Exploiting highly reactive intermediates as opportunities for new amination methodologies: *N*-isocyanates, *O*-isocyanates and carbamoyl nitrenes

By

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Abstract

Nitrogen atoms play a distinctive role in eliciting a host of biological functions. Consequently, the efficient synthesis of nitrogen-containing molecules remains an important challenge for synthetic chemists. In view of these challenges, a variety of new methods for the incorporation of important *N*-containing motifs have been studied. The research efforts described in the present thesis were directed towards the development of novel amination methodologies *via* concerted cycloadditions, hydroamination, cascade reactions of *N*-, and *O*-isocyanates and photocatalytic C–H amination.

In Chapter 2 alkene aminocarbonylation reactions of *N*-isocyanates and cascade reactions of *N*-isocyanates were investigated. Improved conditions for concerted intramolecular alkene aminocarbonylation with *N*-isocyanates were developed. The use of β*N*-benzyl carbazate precursors allowed minimization of *N*-isocyanate dimerization. Diminished dimerization led to higher yields of alkene aminocarbonylation products, to reactivity at lower temperatures, and to an improved scope for a reaction sequence involving alkene aminocarbonylation followed by 1,2-migration of the benzyl group. Furthermore, fine-tuning of the blocking group on the *N*-isocyanate precursor, and base catalysis resulted in room temperature reactivity, consequently minimizing the competing hydroamination pathway. Conditions for milder *N*-isocyanate generation and reactivity enabled new cascade reactions using *N*-isocyanates. Two new cascade processes were reported. First, a one-pot sequence for the synthesis of aza-diketopiperazines involving carbazate acylation with chloroacetyl chloride, S_N2 with a primary amine, *N*-isocyanate formation and cyclization. This approach highlighted that β*N*-acyl carbazates could act as blocked

N-isocyanates, thus allowing a challenging intermolecular S_N2 reaction of a primary amine to proceed while the *N*-isocyanate was "protected", then cyclization once it was deblocked. Control experiments showed that the alternate pathway — *N*-isocyanate substitution then cyclization by intramolecular S_N2 reaction — was not operating. Second, ynone—derived carbazones engaged in a base catalyzed, room temperature substitution / 5-endo-dig cyclization to afford carbamoyl pyrazoles. The ability to use benzyl hydroxylamine as a nucleophile set the stage for subsequent investigations of *O*-isocyanates. Collectively, work in this chapter highlighted that controlled reactivity of amino-isocyanates was possible and provided a broadly applicable approaches to heterocycles possessing the N-N-C-O motif.

In Chapter 3, new *O*-isocyanate reagents were developed. Oxy-carbamate *O*-isocyanate precursors facilitated access to synthetically valuable *N*-oxyureas via substitution reactions with amines. The development of blocked *O*-isocyanate precursors provided controlled reactivity, allowing the first examples of cascade reactions involving *O*-isocyanates. Complex hydroxylamine-derived hydantoins and dihydrouracil compounds were rapidly obtained from α- and β-amino esters, via substitution / intramolecular cyclization cascade reactions. Such reactivity illustrated the convenience of blocked *O*-isocyanates as hydroxylamine derived building blocks. Using allylamines as nucleophiles, the first Cope-type hydroamination of hydroxyureas was also developed. The cycloaddition reactivity of *O*-isocyanates was also assessed. *O*-Isocyanates were investigated as novel uncharched 1,3-dipole equivalents in [3+2] cycloadditions reactions. This enabled the first study of *O*-isocyanate cycloadditions both experimentally and by DFT calculations. This unique cycloaddition strategy allowed access to a novel class of heterocycle—aza-oxonium ylides via intramolecular and intermolecular

cycloadditions with alkenes. This exploratory effort allowed a systematic study of the reactivity of the transient aza-oxonium ylide intermediate, which underwent N–O bond cleavage followed by nitrene C–H insertion, or the formation of β-lactams or isoxazolidinones by varying the structure of the alkene or *O*-isocyanate reagents. Collectively work in this chapter outlines some of the first synthetic uses of *O*-isocyanates. A variety of useful molecules were synthesized incorporating the O-N-C=O motif, or by taking advantage of the lability of the N–O bond for subsequent reactivity.

In Chapter 4, the N–O bond cleavage / nitrene C–H insertion of *O*-isocyanate reagents was assessed. *O*-Isocyanate precursors were developed to act as both isocyanates (carbon electrophiles) and nitrenes (nitrogen electrophiles). Initial efforts were targeted at the cascade reactions of such precursors (e.g. substitution / C-H amination cascade reactions); however, this strategy was abandoned due to competing side reactions. Ultimately, an alternative strategy emerged using the same precursors, but under photocatalysis. While triplet nitrenes had been accessed via energy transfer catalysis using organic azides, hydroxylamine precursors had not previously been studied as nitrene precursors in a photocatalytic context. The combined use of photocatalysis with careful engineering of the precursor enabled C–H amination forming imidazolones and related nitrogen heterocycles from readily accessible hydroxylamine precursors. Preliminary mechanistic results were consistent with the formation of free carbamoyl triplet nitrenes as reactive intermediates.

Overall, the collection of this work demonstrates the broad synthetic utility conferred by developing new reactions with rare amphoteric *N*- and *O*-isocyanate reagents.

Acknowledgements

I have had the pleasure of being a member in the Beauchmin lab for quite some time. I started in the COOP program, and the first taste of organic chemistry research was enough to propel me to drop out of the COOP program and pursue graduate studied directly. I still fondly remember my first day in the lab, even if the smells of the chemical fridge still haunt me! First, I want to thank André for providing a stimulating environment full of good people that anyone would want to work with. Also, André provided me with an optimal balance of freedom to pursue new ideas, while keeping big-picture projects on track and publishing regularly.

I want to specifically thank the following people who I had the pleasure of working with over the years: To the weekend warriors: J-F, I can't think of a better role model to have in the lab. It was great to learn from you and work with you on several projects. You really helped me get started, and constantly challenged me to be a better chemist. Dilan, we worked together in the trenches on the most challenging project I ever undertook. Through the difficulties we kept each other sane! I'm grateful I had your help along the way, as I don't think this project would be possible alone. Meredith, we've had some great ideas for awesome new projects, sadly it seems most of our great ideas relied on smelly norbornene! Nevertheless, we had fun over the years doing some fine detective work, solving tons of unknowns and developing some of the reactions I'm proudest of. Jasper, thanks for your exceptionally hard work, you managed to turn lemons into lemonade with the project I started. It was also awesome having a fellow prog metal-fan in the lab.

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I would also like to thank my supportive wife Laura. It was fun and challenging being busy grad students together. The determination and hard work you poured into your own research drove me to work even harder. I also want to thank my parents for their support over the years, and for not bugging me too much about my research at every family dinner.

Statement and Summary of Contributions

The work presented in this thesis is my own unless specified otherwise. Given that many of the projects presented in thesis were published in various journals, some figures, tables and data have been reproduced with the express permission of the publishers. Many of the projects presented in this thesis were collaborative in nature and I did my best to attribute proper credit to the contributions of my colleagues in the text. :In Chapter 2, the work on aminimide syntheses, after I validated the reactivity, confirmed structural assignment and isolated the first aminimide, Jasper Quartus joined the project and performed the substrate scope / isolations. In Chapter 2, reaction discovery and optimization of aza-DKPs was performed by myself. After validation, I was joined by J.F. Vincent Rocan who aided in the synthesis of several aza-DKPs. In Chapter 3, the work on *O*-isocyanate cascade reactions and substitution reactions, after I validated the reactivity and preliminary survey of reaction scope with a variety of *O*-isocyanate precursors and amines, Dilan Polat and Meredith Allen joined the project, finalized optimization and finished the substrate scope alongside me. In Chapter 3, the work on intramolecular hydroamination, after I validated the reactivity, performed initial optimization and a preliminary survey of reaction scope, Meredith Allen joined the project and helped determine H-bonding reagents and performed at-scale substrate scope synthesis. In Chapter 3, the work on *intermolecular* oxycarbonylation ([3+2] cycloaddition of *O*-isocyanates), after I validated the reactivity and a preliminary survey of reaction scope as well as optimized the reaction, Meredith Allen joined the project to help synthesize new *O*-isocyanate precursors, and test new hypotheses in a combined effort to improve the reactivity. Ultimately at-scale synthesis was divided evenly between lactams and norbornene reactions using *O*-isocyanate precursors which we synthesized in

tandem. DFT was originally performed by me, and later combined with efforts from Meredith Allen. In Chapter 3, the work on *intramolecular* oxycarbonylation ([3+2] cycloadditions of *O*-isocyanates), Meredith and myself simultaneously embarked on synthetic studies of intramolecular reactions using different precursors. I was able to determine with absolute certainty the 4 products from the reaction, 3 of which by X-ray crystallography. The synthetic study described in this thesis was an even contribution from myself and Meredith Allen. In Chapter 4, thermal and metal catalyzed C-H amination reactions were first discovered by me, but I was quickly joined by Dilan Polat. From this point, a combined effort for the synthesis and elucidation of the photoredox reaction was performed.

It is well to remember that most arguments in favor of not trying an experiment are too flimsily based.

- Robert Burns Woodward, **1955**

List of Abreviations

[M] – generic metal
[O] – generic oxidant
$[\alpha]_D^{20}$ – specific rotation at 20°C and 589 nm
°C – degrees Celsius
Å – angstrom
Ac – acetyl
Ar – generic aryl
B3LYP – Becke-3-Lee-Yang-Parr
Bn – benzyl
Boc – *tert*-butyloxycarbonyl
Bt – benzotriazole
Bz – benzoyl
C – carbon
calcd - calculated
CDI – carbonyl diimidazole
cm – centimeter
CSI – chlorosulfonyl isocyanate
CV – cyclic voltammetry
Cy – cyclohexyl
D – dextrorotatory
DCC – *N*,*N'*-dicyclohexylcarbodiimide
DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE – 1,2-dichloroethane
DFT – density functional theory
DMAP – 4-dimethylaminopyridine
DMF – *N*,*N*-dimethylformamide
DMSO – dimethyl sulfoxide
dr – diastereomeric ratio
E – generic electrophile
E – *Ger.*, entgegen
E1cB – elimination unimolecular conjugate base
E_{act} – energy of activation
EDG – electron-donating group
ee – enantiomeric excess
EI – electron impact
EnT – energy transfer
equiv – stoichiometric equivalent
Et – ethyl
E_T – triplet energy
EWG – electron-withdrawing group
FTIR – Fourier transform infrared

FVT – flash vacuum thermolysis
g – gram
h – hour
HA – hydroamination
HRMS – high-resolution mass spectroscopy
Hz – Hertz
hυ – light; electromagnetic radiation
i-Pr – isopropyl
IR – infrared
J – coupling constant
K – equilibrium constant
K – Kelvin
kcal – kilocalorie
L – generic ligand
L – liter, levorotatory
LG – generic leaving group
Lys – lysine
m – meta
M – molar
Me – methyl
MeCN – acetonitrile
mins – minutes
mmol – millimole
mol – mole
MOM – methoxymethyl
n-Bu – *n*-butyl
NMR – nuclear magnetic resonance
NOE – nuclear Overhauser effect
n-Pr – *n*-propyl
Ns – 2-nitrobenzenesulphonyl
Nuc – nucleophile
o – *ortho*
p – para
PCET – proton coupled electron transfer
PG – protecting group
Ph – phenyl
ppm – parts per million
pyr – pyridine
R – generic group
R – *Latin*, *rectus*
Ra-Ni – Raney-Nickel
R_f – retention factor
rt – room temperature
S – *Latin, sinister*

SET – singlet electron transfer
SV – Stern Vollmer
syn – together, same side
syn – 1,5,7-triazabicyclo[4.4.0]dec-5-ene
t-Bu – *tert*-butyl
t-BuOH – *tert*-butanol
temp. – temperature
Tf – trifluoromethanesulfonyl
TFA – trifluoroacetic acid
THF – tetrahydrofuran
THICA – 1,3,5,-trihydroxyisocyanuric acid
TLC – thin-layer chromatography
TMG – 1,1,3,3-tetramethylguanidine
Ts – *para*-toluenesulfonyl
TS – transition state
UV – ultraviolet
vac – vacuum
X – generic halide, generic leaving group
Y – generic leaving group
Z – *Ger.*, zusammen
Δ – thermolysis
δ – chemical shift in parts per million
µm – micrometer
µW – microwave

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Chapter 1

Introduction

Prelude

Synthetic methods generating C–N bonds are central to organic chemistry. The field is too broad to encapsulate, so in lieu of a comprehensive introduction for amination, relevant content will be introduced in detail at the beginning of each chapter. However, to demonstrate the importance of *N*-containing molecules, the bridging tenet of this thesis, a brief historical context of important *N*-containing molecules and the state of industrial reactions pertaining to C–N bond formation will be summarized. A non-exhaustive account of typical C–N bond forming reactions will be presented, with a focus on the development of new reagents and / or precursors that are used to construct C–N bonds.

1.1 On the importance of nitrogen-containing molecules

Since the early 1800s, the synthesis and isolation of nitrogen-containing organic molecules has had a defining impact on the world. Early examples include the natural product, morphine an alkaloid first isolated from poppy extracts in 1804. This nefarious alkaloid fueled the opium wars between England and China in the 1800s, ultimately triggering the collapse of the Qing Dynasty which had ruled for three centuries. On a brighter side of history, in 1820 French chemists isolated quinine from Chincona bark a compound which demonstrated remarkable healing properties against malaria. While attempting to synthesize quinine, Perkin failed spectacularly but instead synthetized mauveine—a series of aromatic amine compounds that spurred the synthetic dye industry. This serendipitous discovery is often credited for the inception of the fashion ($800 billion) and chemical industries ($4 trillion). Around this time, nitration of *N*-atoms provided some of the earliest *stable* high-energy materials. Ultimately, the

deep-seated regret of these discoveries spurred Alfred Nobel to posthumously donate his fortune, which to this day provides the funding for the most competitive and illustrious scientific award—the Nobel prize. Nearly half a century later, chemists at Bayer synthesized and marketed the synthetic aniline based painkiller Paracetamol (Tylenol), which is still among the top 20 most prescribed drugs. In 1928, the β-lactam antibiotic Penicillin was isolated and its use as an antibiotic revolutionized healthcare. In 2009 Gilead developed Remdesevir, which is actively being studied as a treatment for severe cases of COVID-19. From this collection of examples, even to the layperson it is clear that *N*-containing molecules are exceptional.

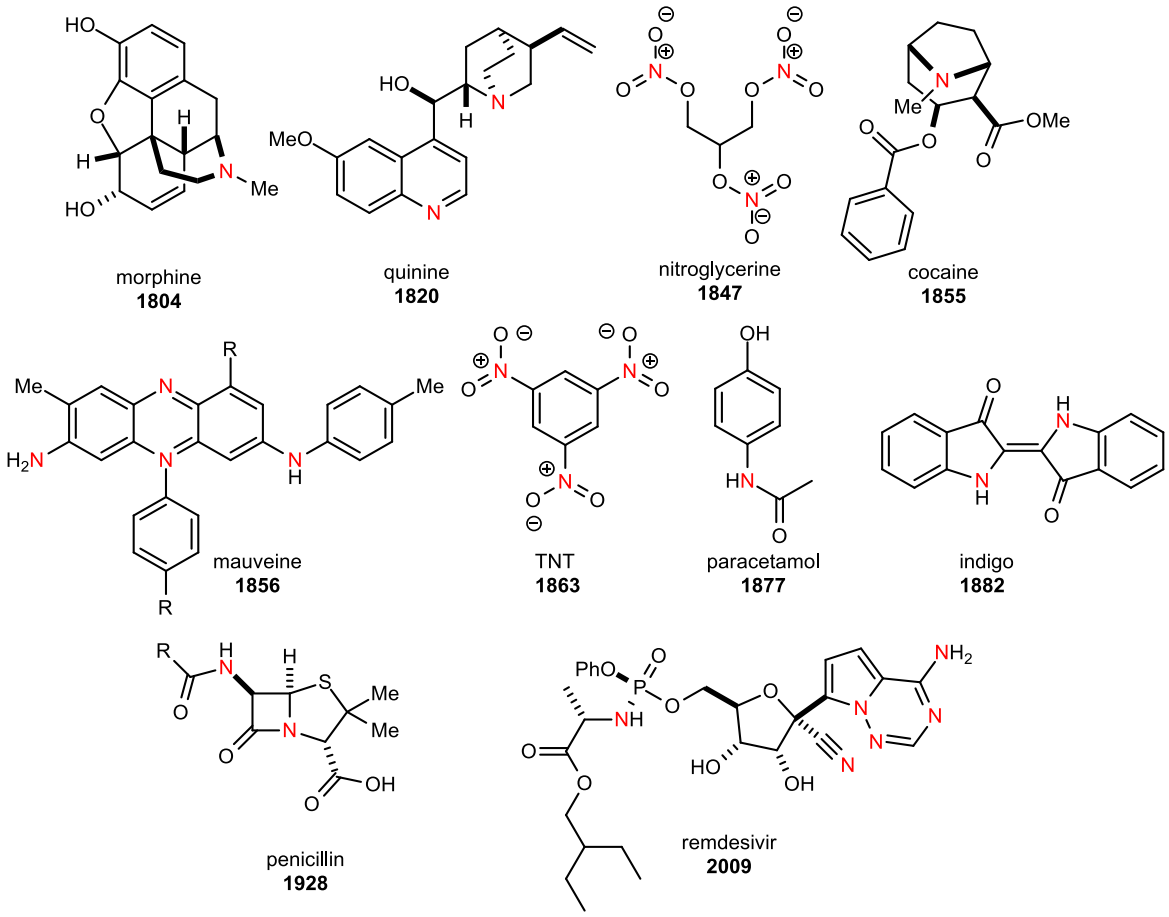


Figure 1 A brief history of some of the world's most important nitrogen containing molecules.

Since these landmark discoveries, the abundance of nitrogen in important medicines and materials has only increased. To put this in perspective, as of 2014, 84% of all small-molecule drugs contained a nitrogen atom, with 59% incorporating an *N*-heterocycle.[1] Unsurprisingly then, a survey of the medicinal chemistry literature reveals that an inordinate amount of reactions reported for the synthesis of active pharmaceutical ingredients (APIs) involve the synthesis or modification of nitrogen atoms.[2,3] Importantly, these preliminary research efforts in the discovery stage were extended to process chemistry, as nearly 25% of all reactions during process

synthesis involve the formation of C–N bonds (**Figure 2**).[4] It comes as no surprise then, that novel synthetic methods to achieve C–N bond formation are intensely researched.

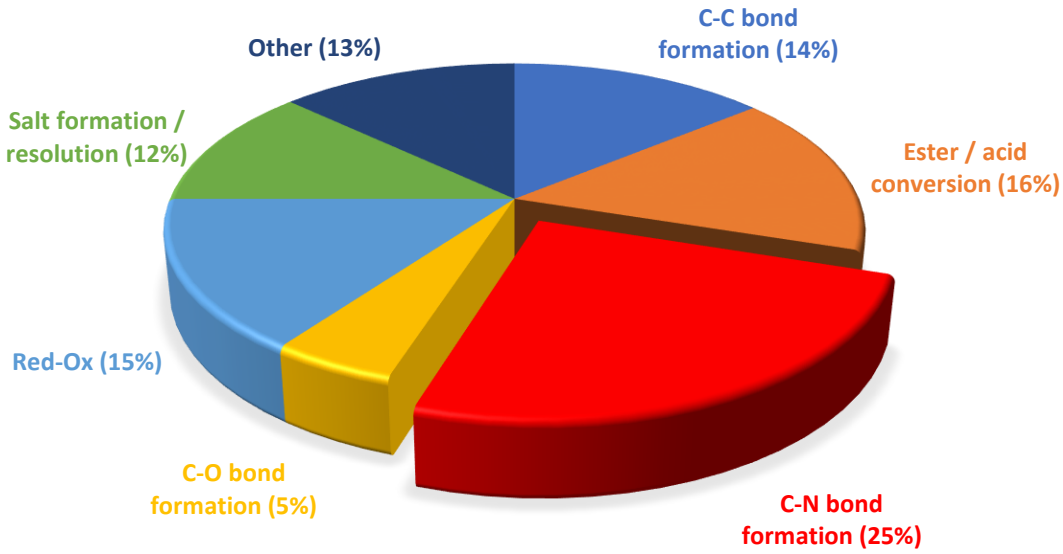


Figure 2 Survey of GMP Bulk Reactions from 1985-2002.

1.2 Classical methodologies for C–N bond formation

Given the variety of *N*-rich pharmaceuticals, a plethora of methods have been developed to construct C–N bonds. While a detailed review of all C–N bond forming reactions remains outside the scope of this thesis, general amination reactions can be categorized as the following: nucleophilic amination, reductive amination, oxidative amination hydroamination and electrophilic amination (**Figure 3**).

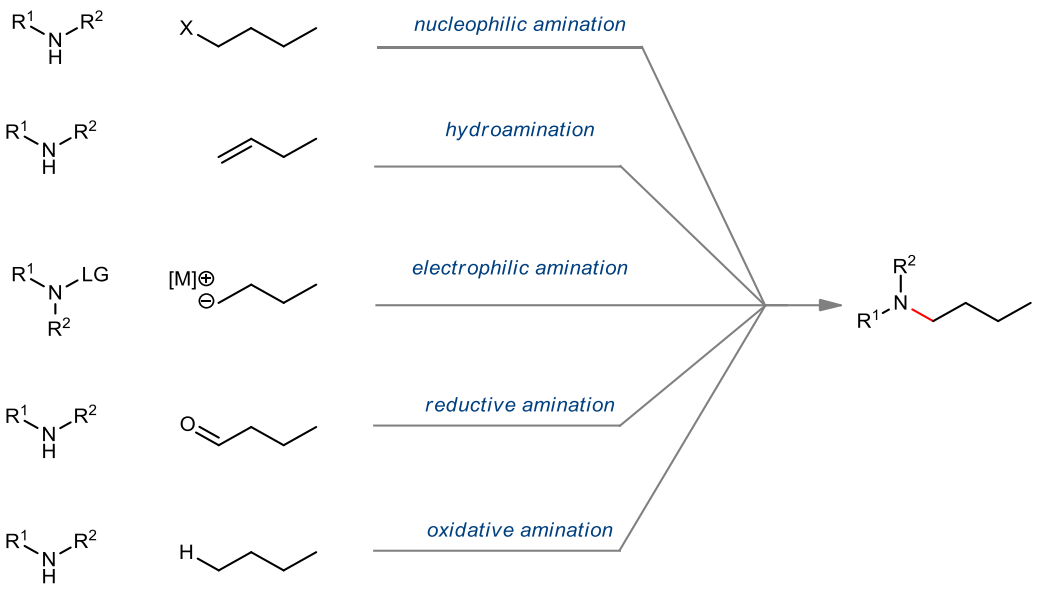


Figure 3 General amination strategies.

Nucleophilic amination reactions rely on classic polar reactivity innate to the atoms involved (*e.g. N*-atom as the nucleophile) and include conventional reactivity such as: S_N2 (Gabriel synthesis), S_N1 (Ritter reaction), S_NAr (Chichibabin reaction), conjugate addition (aza-Michael reaction), *etc.* Nucleophilic amination reactions are often poor reactions with amines, given the tendency of the product of the first nucleophilic substitution to be a more reactive nucleophile, and thus often engage in multiple alkylation / addition. More recently, transition metal catalyzed reactions have bolstered these polar reactions of amine nucleophiles. Most notably, the Buchwald-Hartwig amination,[5] Ullmann coupling,[6] and Chan-Evans-Lam amination[7] have enabled organic chemists to apply the same logical S_N2-type retrosynthetic analyses to π-X systems (even though from a mechanistic perspective these reactions operate very differently). Hydroamination reactions offer direct construction of C–N bonds through the addition of an *N*- and *H*-atom across a π-bond. Hydroamination is among the most efficient methods for

generating amines. Recent Brønsted acid catalyzed,[8] organocatalytic,[9,10] metal catalyzed[11], and radical[12] variants offer mild conditions and enantioselective transformations. Related difunctionalizations of alkenes are also possible using *N*-centered radicals.[13] Electrophilic amination is an example of Umpolung reactivity of nitrogen. A leaving group is covalently bound to the nitrogen; therefore, a nucleophilic atom can perform a substitution reaction on nitrogen with expulsion of the leaving group.[14,15] The inversion of reactivity offers orthogonality and addresses the challenges of poly substitution encountered from conventional nucleophilic aminations. However, the precursors for electrophilic amination are generally unstable and / or challenging to synthesize.[16] Reductive amination is the final major amination subcategory and remains among the most routine methods to prepare amines. While conventional procedures typically used stoichiometric reductants and harsh conditions, emerging catalytic methods provide greener alternatives and enantioselective variants.[17] Unsurprisingly, about a quarter of C-N bond forming reactions performed in the pharmaceutical industry are via reductive amination.[18]

In recent years, the paradigm has shifted to direct C–H amination reactions. C–H amination can be achieved either through the intervention of metal catalysts,[19] and / or through reactive *N*-intermediates (*e.g.* nitrenes,[20] nitreniums,[21] nitrenoids,[22] *N*-centered radicals[23]). Yet, the inherent abundance of C–H bonds perfectly illustrates the dichotomy of reactivity versus selectivity and the challenges this poses to synthetic chemists. A bulk survey of the C–H amination literature clearly establishes that amination still typically occurs at predefined positions, either through intramolecular biases or simply reacting at the most reactive C–H bond. However, new catalysts are constantly emerging to achieve non-native functionality. [24–27]

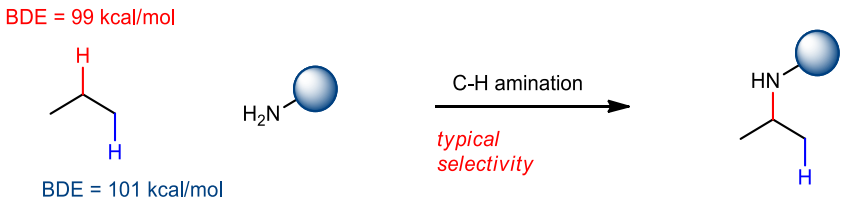


Figure 4 C-H amination offers ideal reactivity, but selectivity is still rather limited.

The above examples are simply the most common amination methods. A variety of rearrangement reactions (Curtius,[28,29] Lossen,[30,31] Beckmann,[32,33] Neber[34,35]), ene-type reactions,[36] and cycloadditions have been developed to enable C–N bond formation. Thus, there are many methods available to introduce a nitrogen atom onto an organic molecule; however, not all methods are suited to the synthesis of a given target molecule. With general amination reactions generally well optimized, methods tailored specifically to structural motifs that are important, but do not possess rich reactivity to access them, are urgently required.

1.3 Research goals

Prior work from our lab in the development of alkene hydroamination reactions led to the serendipitous discovery of alkene aminocarbonylation using *N*-isocyanates. This drew attention to the prevalence of the N-N-C=O motif, which was widely present in marketed pharmaceuticals and agrochemicals (**Figure 5**). Similarly, the O-N-C=O motif was distributed among an array of therapeutics, and bioactive natural products (**Figure 6**).

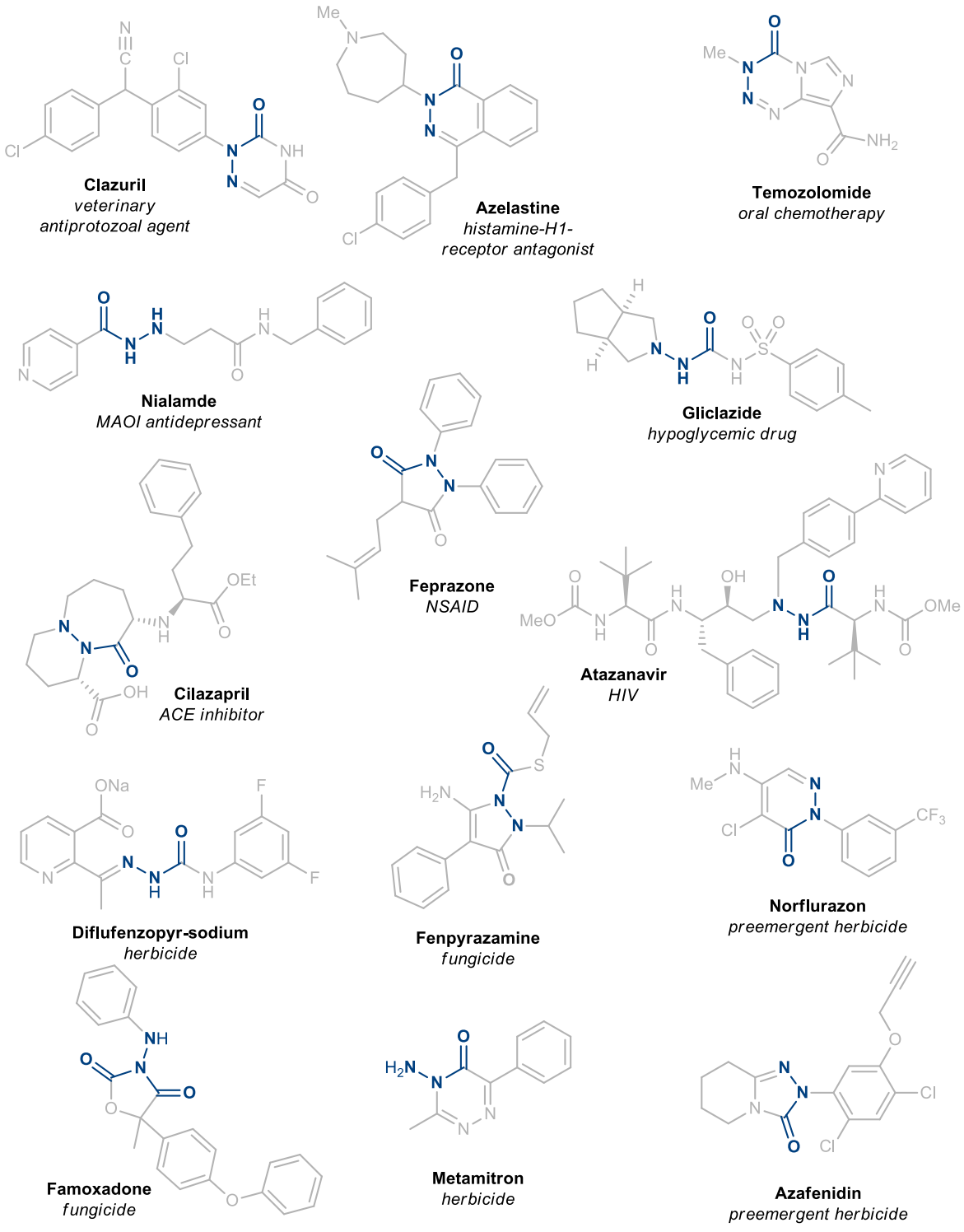


Figure 5 Selected pharmaceuticals and agrochemicals containing the N-N-C-O motif.

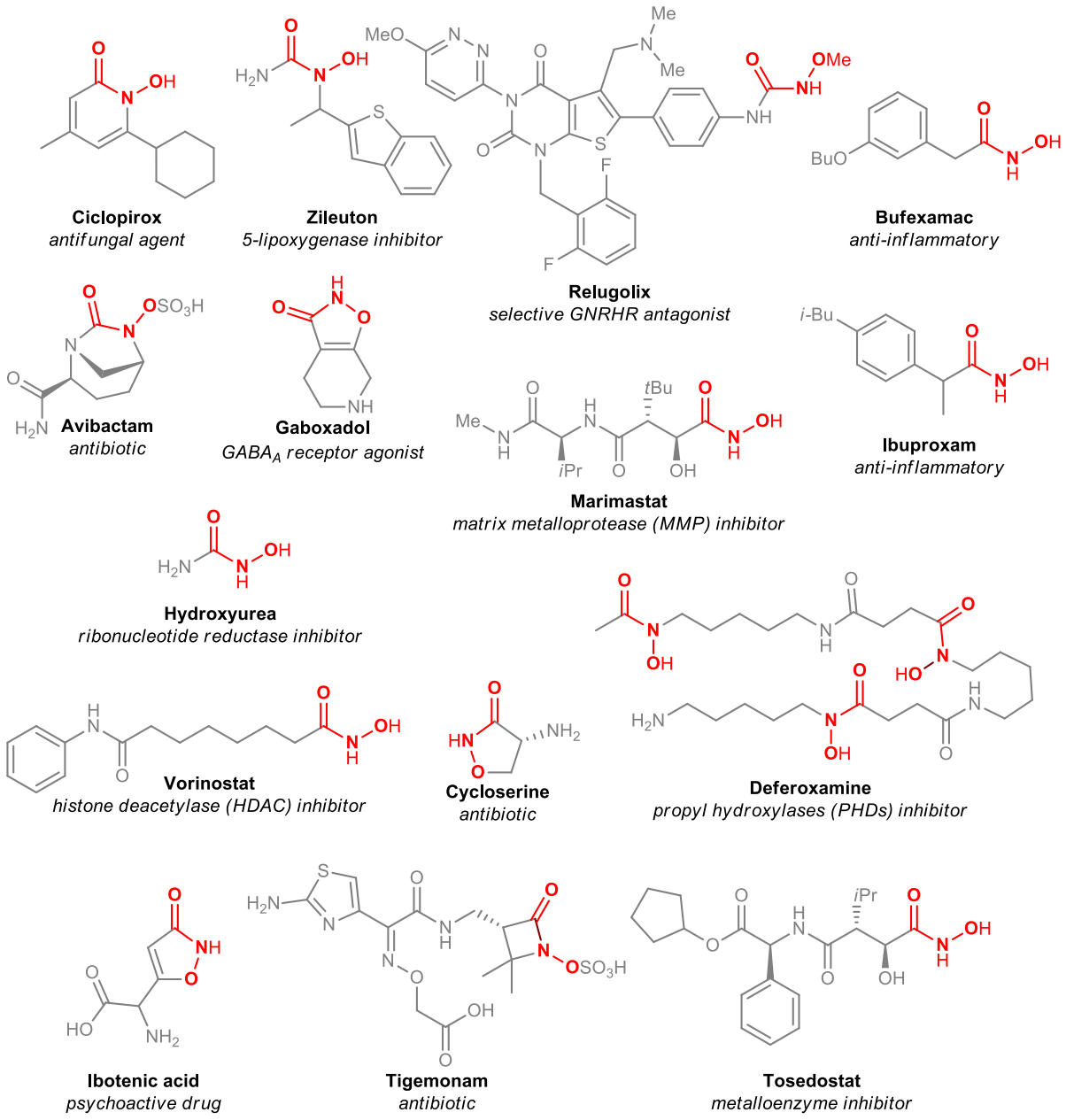


Figure 6 Selected pharmaceuticals and agrochemicals containing the O-N-C-O motif.

Therefore, the motivation of this thesis was to explore new reagents and methods to achieve amination reactions for the synthesis of N-N-C=O and O-N-C=O containing molecules. *N*- and *O*-isocyanates were ideal reagents to achieve efficient synthesis of such molecules but

reports of these reagents were scarce in the literature (**Figure 7**). The development of suitable precursors and conditions to access these highly reactive intermediates ultimately led to their use as versatile synthetic intermediates. A combination of novel cycloadditions, and cascade reactions were developed using these rare amphoteric isocyanates. Chapter 2 focuses on cycloadditions and cascade reactions of *N*-isocyanates. Reactions of *N*-isocyanate led to the origination of *O*-isocyanate reactivity in our lab. Chapter 3 details the discovery, and optimization of *O*-isocyanate precursors / reactivity. Novel cycloadditions and nitrene reactivity disclosed in Chapter 3 conceptually led to our efforts to develop C–H amination reactions with precursors derived from *O*-isocyanate substitution reactions. In Chapter 4, *O*-isocyanates were used to access novel nitrene precursors, and their propensity to undergo C–H amination under photocatalytic activation was evaluated. Notably, this process provided direct access to a variety of important *N*-heterocycles, and extended nitrene reactivity to carbamoyl triplet nitrenes, a class of nitrene that had not been studied previously for C–H amination (**Figure 7**). Collectively, these works enable unorthodox C–N bond formation, enabling access to a variety of important biologically active heterocycles.

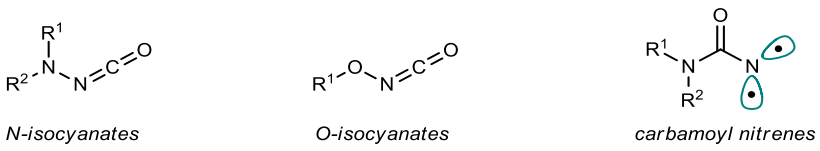


Figure 7 Reactive intermediates for C–N bond formation in this thesis.

Chapter 2

Cycloadditions and cascade reaction of *N*-isocyanates

Prelude

This chapter will focus on efforts to improve and generalize intramolecular aminocarbonylation via [3+2] cycloaddition reactions of *N*-isocyanates with alkenes, and to develop new cascade reactions of *N*-isocyanates. Since reactions with *N*-isocyanates were well underway when I began graduate studies, a thorough literature review is beyond the scope of this document. Moreover, *N*-isocyanates were recently extensively reviewed in a previous thesis by Jean-Francois Vincent Rocan, and later published in a review.[37] Yet, to understand the challenges of developing reactions with *N*-isocyanates, key elements must be introduced that fell outside the general scope of the introduction. These include a non-exhaustive background on *N*-isocyanates, and the initial studies on alkene aminocarbonylation within the research group that both directly and indirectly contributed to these studies.

2.1 Background on *N*-isocyanates

Nitrogen-substituted isocyanates (*N*-isocyanates) are a rare class of isocyanate first discovered in 1927 by Stollé through the Curtius rearrangement of carbamoyl azides (**Figure 8** A).[38] Despite knowledge of their existence for nearly a century, less than 100 reports currently exist describing their generation and reactivity. This is in stark contrast to *C*-isocyanates, which have been the subject of intense research and represent a global industry with a value in the $10s of billions per year.[39] The scarcity of *N*-isocyanate reports is particularly shocking, given the abundance of N–N–C=O containing molecules in marketed pharmaceuticals and agrochemicals. However, a cursory examination of their structure provides a likely explanation for the lack of *N*-isocyanate reports. The additional electron rich *N*-atom leads to amphoteric (ambident)

character and modifies the electronics of the isocyanate through conjugation with the N=C bond.[40,41] This amphoteric character has historically impeded their synthetic development, as dimerization of *N*-isocyanates has been reported to occur at temperatures as low as –40 °C.[37] Of the three unique classes of *N*-isocyanates (**Figure 8** C): amino-isocyanates (β*N* is sp^3), imino-isocyanates (β*N* is sp^2), and amido-isocyanates (β*N*is sp^2), amino isocyanates are the most prone to homodimerization. Therefore, in contrast to *C*-isocyanates which could be purchased from chemical suppliers and used directly from a bottle, *N*-isocyanates must be formed from *precursors* in situ.

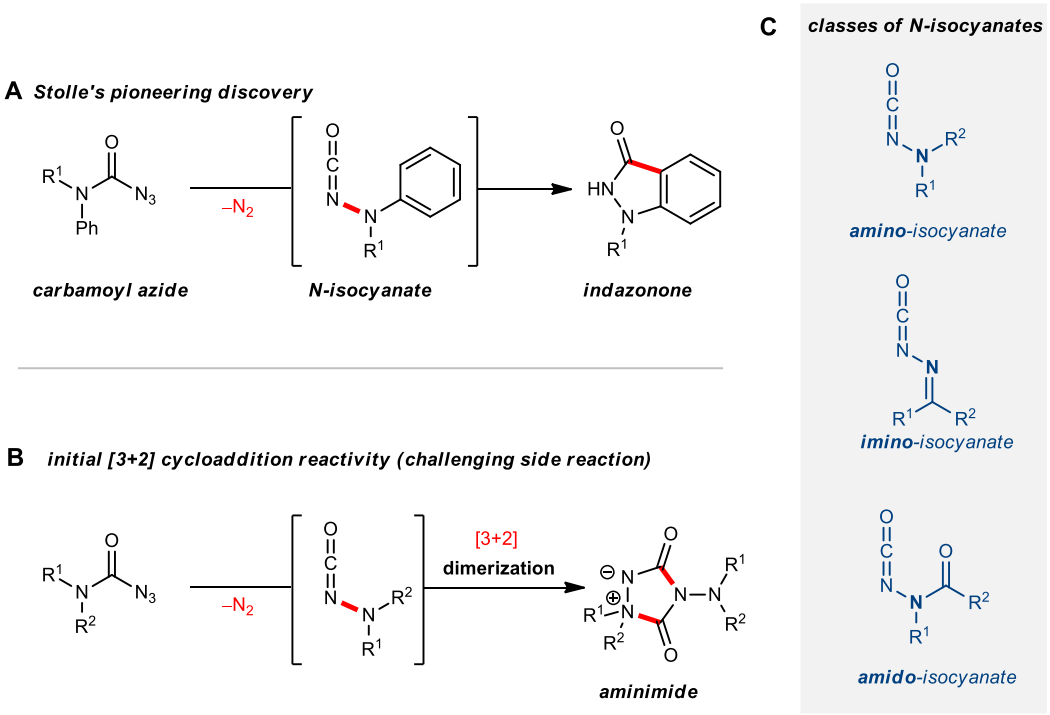


Figure 8 A) First examples of *N*-isocyanates. B) Dimerization as a prevalent side reaction. C) Three classes of *N*-isocyanates.

While early work formed *N*-isocyanates from the Curtius rearrangement of carbamoyl azides, *N*-isocyanates are most easily accessed upon thermolysis of carbazates and semicarbazides or under basic conditions.[37,42–47] This important discovery borrows from decades of thorough studies forming *C*-isocyanates from analogous carbamates and ureas.[48] Thus, *N*-isocyanates can be formed via chemical equilibrium, through the expulsion of an oxygen or nitrogen containing leaving group. For the reverse reaction, this group is a nucleophile (blocking group). Control over the blocking / deblocking equilibrium is achieved via a multitude of factors, including blocking group selection, temperature, concentration, solvent, strength (pKb) of the base, or additives.[49–52]

2.2 Cycloaddition reactions of *N*-isocyanates

Early studies on the formation of amino-isocyanates typically led to the formation of aminimides via [3+2]-cycloaddition dimerization of *N*-isocyanates (**Figure 8**B). However, Lwowski reported the first intermolecular cycloadditions of *N*-isocyanates with various π-systems including alkynes,[53] carbodiimides[54] and *C*-isocyanates (**Figure 9**A).[55] Fundamental insights on *N*-isocyanate reactivity were gained through these preliminary reactions. For example, Lwowski documented better reactivity with electron-poor alkynes (**Figure 9**B).[53] This qualitative assessment suggested that the cycloaddition occurred with the HOMO of the *N*-isocyanate and the LUMO of the alkyne. A regioselective reaction while using methyl propriolate further suggested a HOMO controlled cycloaddition reaction. [53] However, it is crucial to note that no reaction was observed in the absence of an electron withdrawing group. Similar reactivity was observed by Jones[56] when imino-isocyanates were used as intermediates, but the synthetic scope of the reaction was not explored (**Figure 9**C).

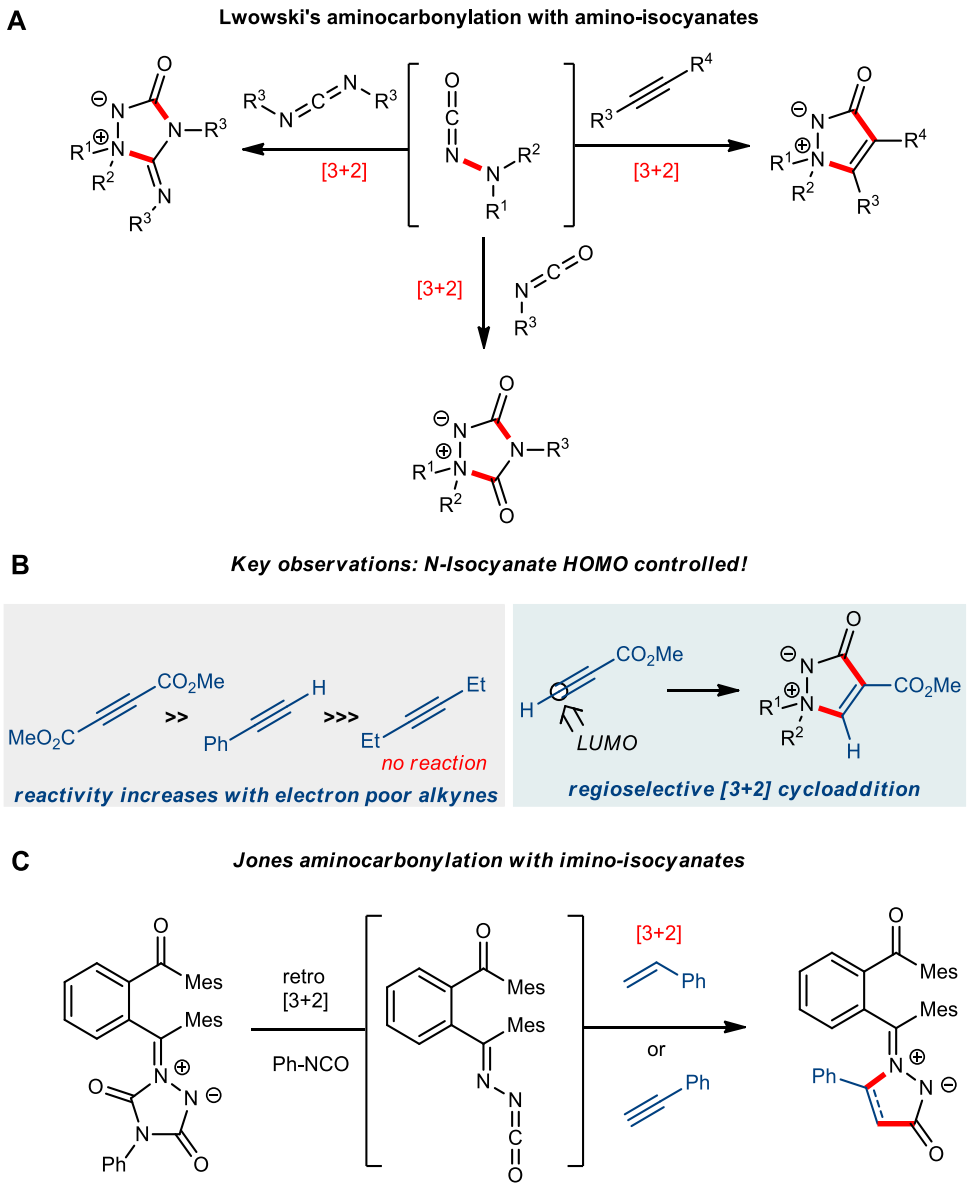


Figure 9 A) First amino-isocyanate [3+2] cycloadditions (non-dimerization). B) Early observations contributing to hypothesis that amino-isocyanate cycloadditions are HOMO controlled. C) First imino-isocyanate [3+2] cycloadditions on alkenes and alkynes.

After these pioneering studies, appearances of *N*-isocyanate cycloadditions in the literature ceased. The first example of amino-isocyanate cycloadditions with alkenes were serendipitously discovered by our lab and reported in 2009—which reinvigorated the study of these rare intermediates.[57] Since the initial report on alkene aminocarbonylation using amino-

isocyanates, our lab has significantly expanded the use of *N*-isocyanates as reagents in aminocarbonylation reactions.[42–46] However, subsequent reports focused on comparatively simple to handle imino-isocyanates, which show a reduced tendency toward dimerization reactions, and have no other competing side reactions (*e.g.* hydroamination). Synthetically, the transition to these imino-isocyanates enabled the development of intermolecular aminocarbonylation reactions, and the synthesis of over 100 azomethine imines. However, it should be noted that the azomethine imine products of imino-isocyanate cycloadditions often required downstream derivatization to become products of interest (pyrazolones, β-amino amides, triazinones *etc.*). On the other hand, alkene aminocarbonylation with amino-isocyanates led directly to saturated *aza*-heterocycles of interest (*e.g. aza*-proline analogues) a driving force behind the desired continued evolution of this project.[58,59]

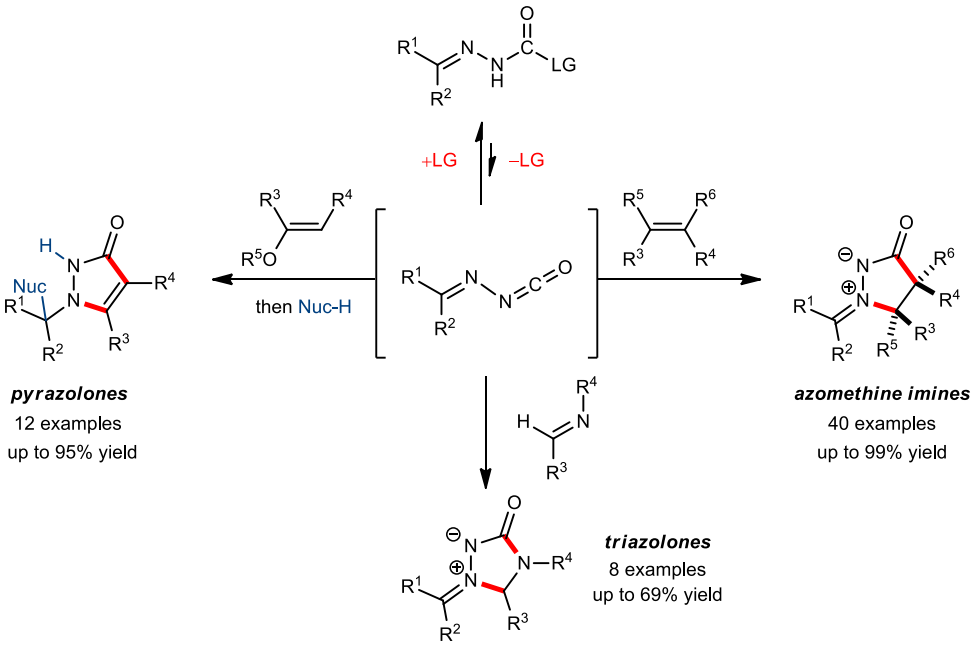


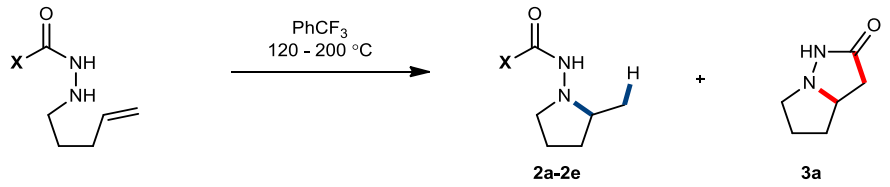
Figure 10 Imino-isocyanate cycloadditions reported by the Beauchemin group since 2012.[42–45]

From a reaction development perspective, amino-isocyanates are the most difficult *N*-isocyanate reagents to work with due to the relatively high nucleophilicity of the β-nitrogen atom. Efforts to expand the intramolecular aminocarbonylation using hydrazine-derived amino-isocyanates was complicated by competing homodimerization of the *N*-isocyanate[37] and intramolecular Cope-type hydroamination[57,60,61] from the *N*-isocyanate precursor. However, it was hoped that a survey of blocked (masked) isocyanate precursors and the accompanying milder conditions could provide increased control of *N*-isocyanate formation,[45] and consequently minimize dimerization and other side reactions. The following strategies were the focus of attempts to improve the reactivity: 1) The development of *N*-isocyanate precursors with more labile leaving groups and base catalyzed *N*-isocyanate formation, 2) The use of β*N*-benzylated carbazates in an aminocarbonylation / 1,2-benzyl shift cascade, and 3) The transacylation of carbazates to enable room temperature reactivity. First, a brief summary of the reaction discovery will be presented to contextualize the work presented in this Chapter.

2.3 First generation aminocarbonylation using *N*-isocyanates: discovery and important observations

During the initial optimization of hydroamination reactivity with hydrazine derivatives, carbazates and semicarbazides produced unexpected compounds in addition to the anticipated hydroamination products (**2a**), which were later identified as aminocarbonylation product **3a** **(Table 1)**.

Table 1 Thermolysis of hydrazine derivatives: hydroamination vs aminocarbonylation.



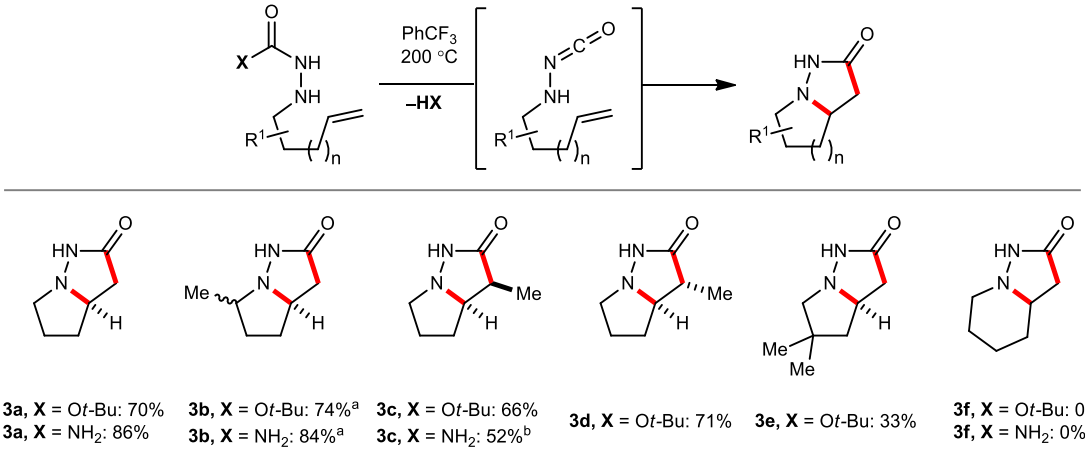
entry	**X**	T (°C)	t (h)	yield (%)
1	Ph	120	18	**2a** (93)
2	*t*-Bu	150	16	**2b** (66)
3	OEt	140	16	**2c**(25) + **3a** (6)
4	OEt	200	0.5	**2a** (13) + **3a** (46)
5	O*t*-Bu	200	0.5	**2d** (0) + **3a** (71)
6	NH_2	150	0.5	**2e** (50) + **3a** (20)[a]
7	NH_2	200	0.25	**2e** (10) + **3a** (85)[a]

Conditions: hydrazide (1 equiv) in $PhCF_3$ (0.05M) at 120-200 °C (mW, sealed tube). Isolated yields are shown unless indicated otherwise. [a] ^1H NMR yield using 1,4-dimethoxybenzene as an internal standard.

A comparative study using various alkenyl-derived carbazates and semicarbazides was performed (**Table 2**). Analysis of the stereochemistry at the distal position of the alkene indicated a stereospecific, syn addition process for compounds **3c** and **3d**. These results suggested a concerted cyclization mechanism, and an amino-isocyanate was suggested as the reactive intermediate. The possibility that an amino-isocyanate would be formed upon thermolysis of carbazate or semicarbazide precursors was consistent with the literature on *N*-isocyanates,[37] and the general cycloaddition reactivity was supported by Lwowski's prior reports of intermolecular amino-isocyanate cycloadditions with other π-systems.[53–55] These encouraging preliminary

results begged to be explored further, but the harsh reaction conditions (200 °C) and narrow substrate scope (*i.e.* entry **3f**) needed to be addressed.

Table 2 Preliminary substrate scope of aminocarbonylation reaction.



Conditions: hydrazide (1 equiv) in $PhCF_3$ (0.05 M) at 200 °C for 0.5 h (mW, sealed tube). Isolated yields are shown unless indicated otherwise. [a] 2: 1 d.r. [b] ^{1}H NMR yield using 1,4-dimethoxybenzene as an internal standard.

2.4 Improving alkene aminocarbonylation: a combined DFT and experimental study

In order to improve this novel aminocarbonylation reaction, a fundamental understanding of the reactivity was required. *N*-Isocyanates are reactive intermediates that are impossible to isolate and study under standard conditions; therefore, density functional theory (DFT) calculations emerged as an ideal strategy to investigate the reaction. The results of exploratory calculations are shown in **Figure 11**. Support for an asynchronous concerted cycloaddition was obtained ($\Delta G^{\ddagger}$ = +19.1 kcal/mol) from the *N*-isocyanate (**Figure 12**). This transition state was surprisingly low, but it indicated that room-temperature reactivity was

possible, provided that the *N*-isocyanate could be generated at lower temperatures. In comparison to the *N*-isocyanate intermediate, the ammonium ylide intermediate predicted to form from the initial cycloaddition was only slightly less stable (ΔG = +2.4 kcal/mol), but the overall reaction after proton transfer was found to be thermodynamically favorable (ΔG = −17.6 kcal/mol). This suggested a highly reversible reaction preceding proton transfer, which could provide a thermodynamic sink for the reaction. Based on these calculations, it was initially hypothesized that generation of the *N*-isocyanate was rate-determining, and that the key to accessing a general aminocarbonylation reaction lied in the development of new aminocarbonylation precursors that could form the *N*-isocyanate under less-forcing conditions. Notably, no additional calculations were performed to probe alternative intermolecular proton transfer pathways, which are likely significantly more facile than the intramolecular proton-transfer process (**Figure 11**, TSB).

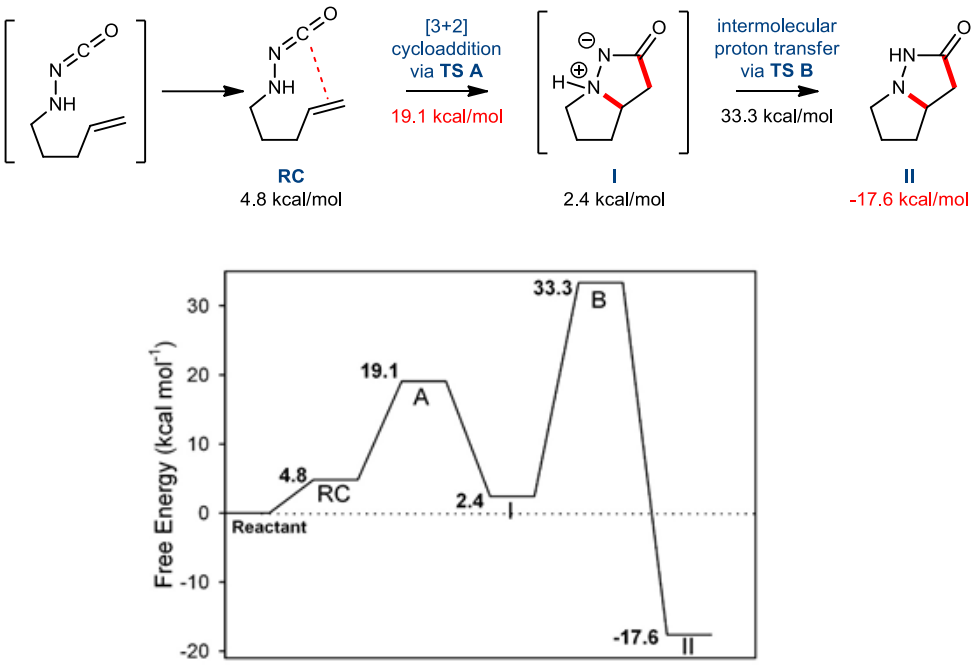


Figure 11 Gibbs free energy (in kcal/mol, 298K, 1 atm) profile for the aminocarbonylation yielding product **II**. To simplify the process, calculations were performed using the amino-isocyanate as reactant. RC = reactant complex between the double bond and the isocyanate.

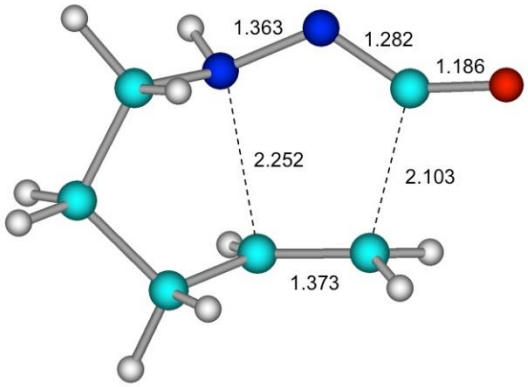
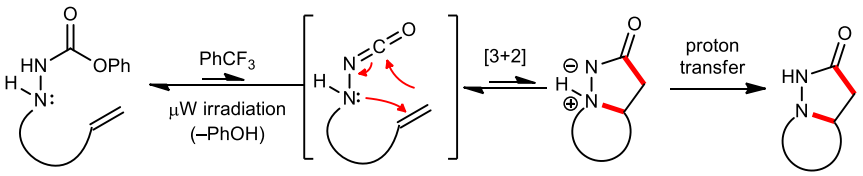


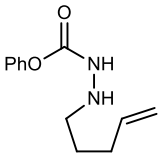
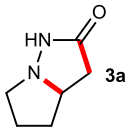
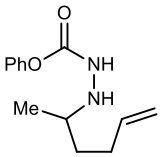
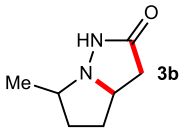
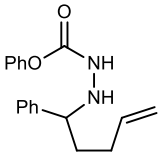
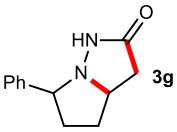
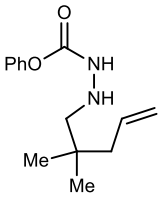
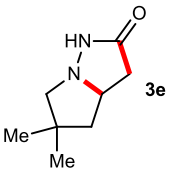
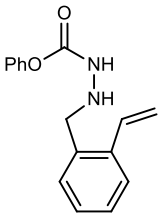
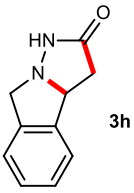
Figure 12 Transition state structure for the intramolecular aminocarbonylation step. The internuclear distances (Å) are shown only for relevant chemical bonds.

2.5 Second generation aminocarbonylation with *N*-isocyanates: Thermolysis and base-catalysis of phenol-blocked carbazates

Insights from these preliminary DFT calculations (**Figure 11**) prompted the synthesis and study of more labile carbazate precursors. Phenol-blocked precursors were obvious candidates, given that *N*-isocyanate could be released under milder heating (90-120 °C),[45] or through recently developed base catalysis.[44] The analogous phenol-blocked substrate **1a** provided a low 28% aminocarbonylation product yield at lower temperature (entry 1). This was in stark contrast to the 70% and 86% yields obtained with *tert*-butyl and ammonia blocked *N*-isocyanates (**Table 2**). *N*-Isocyanate dimer formation was much more problematic at lower temperatures—comprising the bulk of the remaining mass-balance. Indeed, the use of a more labile blocking group such as phenol should facilitate *N*-isocyanate formation at lower temperature; however, it would have no contribution to the subsequent reactivity of the isocyanate (*e.g.* aminocarbonylation versus dimerization). The most likely explanation for the lower yield when using **1a** was that *N*-isocyanate was formed in higher concentration, thus favoring the bimolecular dimerization reaction.

Table 3 Scope of intramolecular alkene aminocarbonylation with *phenol-blocked* carbazates.



entry	substrate		T (°C)	products		yield (%)
1		**1a**	120		**3a**	28
2		**1b**	120		**3b**	70
3		**1c**	120		**3g**	60
4		**1d**	120		**3e**	35
5			120			20[a]
6		**1e**	150		**3h**	50[a]
7			200[b]			75

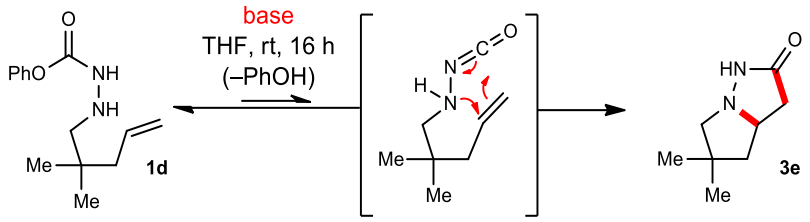
Conditions: carbazate (1 equiv) in $PhCF_3$ (0.05M) at 120-200 °C for 2 h (mW, sealed tube). Isolated yields are shown unless indicated otherwise. [a] ^1H NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [b] 0.5 h.

Yet, under these milder conditions, steric hindrance seemed to impact the aminocarbonylation reaction. Substrates with α-substituents led to higher yielding

aminocarbonylation reactions. This contrasts with initial results, where **3a** and **3b** were formed in similar yields with *t*-BuOH blocked derivatives (**Table 2**). Sterically shielded *N*-isocyanates should be less likely to form dimers, so perhaps the α-substitution is important for blocking dimerization. Notably, a high-yielding, selective aminocarbonylation reaction with Thorpe-Ingold biased substrate (entry 4) was still impossible. The Thorpe-Ingold effect indiscriminately biases both competing cyclizations—aminocarbonylation and hydroamination—and hydroamination can operate at even lower temperatures than *N*-isocyanate formation (80 °C versus 120 °C). Although the development of 2nd generation carbazates did provide some encouraging results (*i.e*. demonstrating reactivity at 120 °C vs 200 °C), the greatly diminished yields due to both competing dimerization and hydroamination presented challenges.

We hypothesized that the competing hydroamination observed with Thorpe-Ingold biased substrates was surmountable, provided that *N*-isocyanate formation could be brought below the onset of hydroamination reactivity (~80 °C). Toward this goal, base catalyzed *N*-isocyanate formation was explored (**Table 4**). Quickly, excitement was generated over traces of aminocarbonylation reactivity observed using catalytic hydride bases at room temperature. However, this was tempered upon exhaustive screening. Ultimately, the best room-temperature conditions were achieved using 1.0 equiv K_3PO_4 (23%) or 0.2 equiv DBU (21%). Despite providing a low yield, this preliminary result proved that it was possible to achieve aminocarbonylation at temperatures far below typical hydroamination conditions—and provided the first validation of theoretical studies suggesting room-temperature aminocarbonylation was possible.

Table 4 Base screen for Thorpe-Ingold room temperature aminocarbonylation



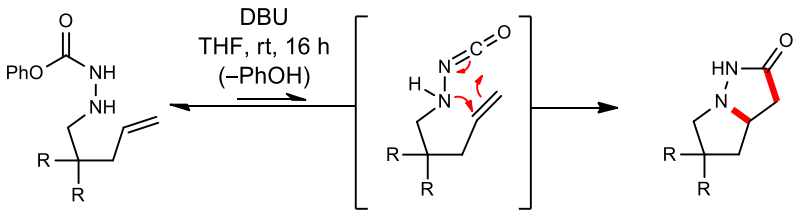
base	equiv.	aminocarbonylation[a] [%]	base	equiv.	aminocarbonylation[a] [%]
-	-	-	K_3PO_4	0.2	-
LiH	0.2	-	K_3PO_4	0.1	-
NaH	0.2	10	TMG	0.2	-
KH	0.2	10	TMG	0.1	-
t-BuOK	1.0	-	DBU	1.0	-
t-BuOK	0.2	-	**DBU**	**0.2**	**21**[b]
t-BuOK	0.1	-	DBU	0.1	12
K_2CO_3	1.0	14	TBD	0.2	16
K_3PO_4	**1.0**	**23**[c]	TBD	0.1	12

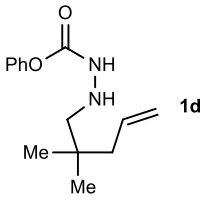
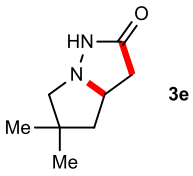
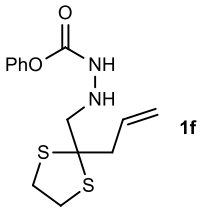
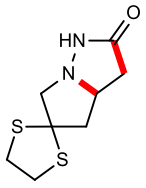
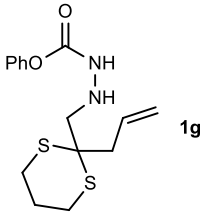
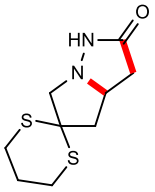
Conditions: carbazate (1 equiv), base (0.1-1.0 equiv) in THF (0.05 M) stirred for 16 h at room temperature. [a] ^{1}H NMR yields using 1,3,5-trimethoxybenzene as internal standard. [b] Isolated yield.

The following trends were noted: when loadings of base increased or when stronger bases were used, the amount of the *N*-isocyanate dimerization by-product increased; however, when the loadings of base were decreased starting material remained. This observation was in line with expectations, since increased base loadings or the use of stronger bases would increase the concentration of *N*-isocyanates in situ and contribute to increased isocyanate dimerization.

Gratifyingly, dimerization was not observed at lower base loadings (e.g., 5 mol% DBU). However, mild heating was required to increase the reaction rate, since 5 mol% DBU at room temperature proved too slow. At 50 °C and with 5 mol% DBU, a selective aminocarbonylation reaction proceeded with the gem-dimethyl carbazate **1d** to yield **3e** in 82% yield.

Table 5 Base catalyzed aminocarbonylation of Thorpe-Ingold biased carbazates.



entry	additive	substrate	products	yield (%)
1	none	 **1d**	 **3e**	<5
2	DBU			82
3	none	 **1f**	 **3i**	<5
4	DBU			81
5	none	 **1g**	 **3j**	<5
6	DBU			83

Conditions: carbazate (1 equiv), DBU (0.05 equiv) in THF (0.05 M) heated for 60 h (oil bath, sealed tube). Isolated yields are shown unless indicated otherwise. nr = no reaction. DBU = 1,8-Diazabicycloundec-7-ene.

This transformation still required long reaction times (60 h), which further highlights the need for a carefully controlled concentration of *N*-isocyanate over the course of this reaction. The mildly basic conditions in THF likely facilitate the slow release of the *N*-isocyanate, while the thermal energy provided from mild heating in conjunction with the conformational restrains of the Thorpe–Ingold effect provide a basis for the intramolecular cycloaddition to occur rather than the intermolecular dimerization. From this point, the scope of the reaction was expanded to a selection of Thorpe–Ingold biased aminocarbonylation substrates (**Table 5**). Pleasingly, the yields remained consistent for these reactions and control experiments confirmed the need for base catalysis. This included the synthesis of substrates possessing 5- and 6- membered thioketals (entries 4 and 6, respectively). Ultimately, by performing the reaction at low temperature and forming the *N*-isocyanate using base catalysis the competing hydroamination reaction could be avoided.

The extension of base catalyzed aminocarbonylation to substrates without a Thorpe-Ingold bias was briefly evaluated (**Figure 13**, see SI for further attempted optimization). Unfortunately, although several bases were able to form the *N*-isocyanate under catalytic or stoichiometric conditions, only a substrate with a larger substituent (**R^1** = Ph, carbazate **1c**) led to a 10% aminocarbonylation yield at room temperature with 1.0 equiv K_3PO_4. This result further supported that steric hindrance near the β-nitrogen of the *N*-isocyanate could minimize dimerization, allowing some aminocarbonylation.

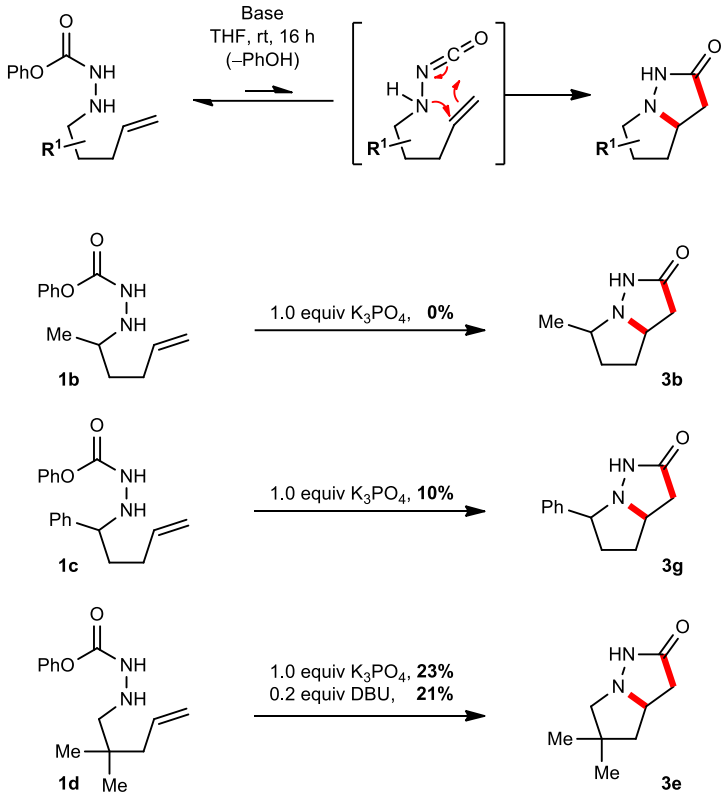


Figure 13 Base catalyzed conditions without Thorpe-Ingold bias.

Overall, simply accessing the *N*-isocyanate at milder temperatures through a blocking group modification was an ineffective strategy to improve aminocarbonylation. However, that is not to say all hope was lost. Reactivity was observed 180 °C lower than initially reported, which encouraged further study, and reactions with Thorpe-Ingold substrates—which had been problematic at 200 °C and 120 °C could be formed in excellent yields at 50 °C.

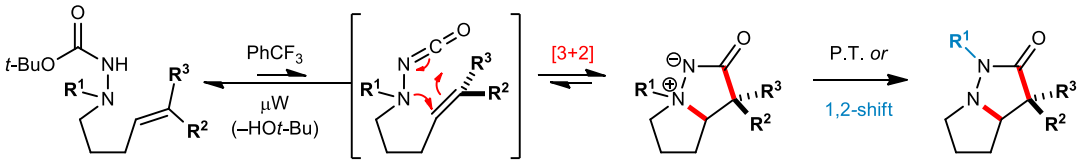
2.6 Third generation aminocarbonylation with *N*-isocyanates: Improved aminocarbonylation and aminimide synthesis with β*N*-alkylated carbazates

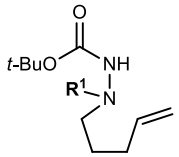
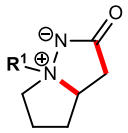
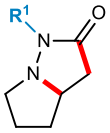
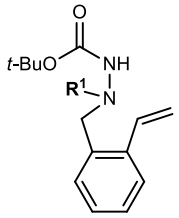
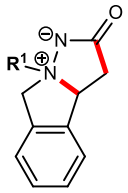
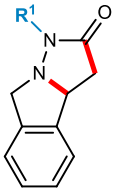
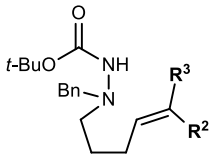
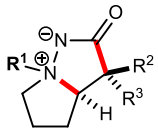
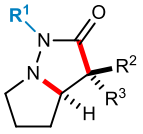
Combining the results of the above study with observations from pioneering work on the generation and reactivity of *N*-isocyanates by Lwowski spurred efforts to improve this aminocarbonylation process. The primary objective was to target new aminocarbonylation precursors and study their reactivity under thermolytic conditions. The propensity of *N*-isocyanates to undergo a competing dimerization reaction precluded the development of the desired low temperature aminocarbonylation reactions. Therefore, minimizing the effects of this side reaction was essential to achieve a more broadly applicable aminocarbonylation reaction. From this point of view, two options were available: 1) increase the reactivity of the *N*-isocyanate towards aminocarbonylation, and / or 2) decrease the reactivity of the *N*-isocyanate towards dimerization. Steric encumbrance surrounding the β-nitrogen appeared to be an important factor in diminishing dimerization in the previously described low temperature aminocarbonylation studies. In addition to α-substituents of the alkyl chain, substitution on the β*N*-atom could provide an alternative method to increase the steric encumbrance around the *N*-isocyanate. Furthermore, assessment of early work from Lwowski showed *N*,*N*-dialkyl isocyanate dimers can undergo cycloreversion and regenerate the reactive *N*-isocyanate. In fact, hindered *N*-isocyanate dimers undergo cycloreversion more readily, regenerating the reactive *N*-isocyanate at temperatures around 100 °C. Therefore, *N*,*N*-dialkyl carbazates emerged as an intriguing class of potential aminocarbonylation reagents. This notion was emboldened by DFT calculations, which predicted a marked increase in the HOMO energy of an *N*-isocyanate possessing *N*,*N*-disubstitution. Reasoning that the *N*-isocyanate [3+2] cycloaddition was HOMO

controlled; this should lead to a more reactive intermediate for alkene cycloadditions. Thus, in either case the properties desired for an improved aminocarbonylation reagent could be met by alkylation of the β-nitrogen. Substituting a hydrogen atom for an alkyl group would require the zwitterionic aminimide generated from the intramolecular [3+2] to undergo a 1,2-alkyl-shift rather than a proton shift. For these reasons, β*N*-benzyl carbazates were first targeted, as benzyl groups undergo relatively facile 1,2-rearrangement upon heating.

The difference in reactivity of monoalkyl carbazates ($\mathbf{R^1}$ = H) and *N*,*N*-dialkyl carbazates ($\mathbf{R^1}$ = alkyl) is presented in **Table 6**. Under standard aminocarbonylation conditions (200 °C), monoalkyl carbazate **1h** provided the aminocarbonylation product **3a** in good yield (**Table 6**, entry 1). In comparison, β*N*-benzyl carbazate **1i** was clearly more reactive, increasing the yield at 200 °C and providing a similar yield of cycloaddition products at 150 °C (**Table 6**, entries 2-3). However, at 150 °C, a 2:1 mixture of **4b**:**3k** was obtained (entry 3). The major product at lower temperatures was the zwitterionic dipole, indicating that 1,2-shift could be rate-determining. Further optimization enabled the aminimide **4b** to be selectively formed in a 1:1 solution of *i*-PrOH/MeCN (entry 4). This was likely through stabilizing H-bonding interactions of the dipole with *i*-PrOH. A direct link between the aminimide and aminocarbonylation products was established by exposing an isolated aminimide to higher temperatures in a non-H-bonding solvent, which induced a quantitative 1,2-shift to the product typically observed in the absence of *i*-PrOH (**Figure 14**). Thus, the proposed mechanism of concerted cycloaddition first forming a zwitterionic intermediate was confirmed.

Table 6 Aminocarbonylation with mono- and *N*,*N*-dialkyl carbazate precursors.



entry	substrate	T (°C)	products & yield (%)	
				
1	R^1 = H (**1h**)	200	0 (**4a**)	74 (**3a**)
2	R^1 = Bn (**1i**)	200	0 (**4b**)	90 (**3k**)
3	R^1 = Bn (**1i**)	150	49 (**4b**)[b]	24 (**3k**)[b]
4	R^1 = Bn (**1i**)	150	89 (**4b**)[c]	0 (**3k**)
5	R^1 = Me (**1j**)	150	57 (93%)[b] (**4c**)[c]	0 (**3l**)
6	R^1 = $(CH_2)_3CHCH_2$ (**1k**)	150	86 (**4d**)[c]	0 (**3m**)
				
7	R^1 = H (**1l**)	200	0 (**4e**)	40 (**3h**)
8	R^1 = Bn (**1m**)	150	71 (**4f**)[c]	0 (**3n**)
				
9	R^2 = Me, R^3 = H (**1n**)	200	0 (**4g**)	44 (**3o**)[b]
10	R^2 = H, R^3 = Me (**1o**)	200	0 (**4h**)	43 (**3p**)[b]

Conditions: carbazate (1 equiv) in $PhCF_3$ (0.05 M) for 0.5 h (mW, sealed tube). Isolated yields are shown unless indicated otherwise. [b] ^1H NMR yield using 1,3,5-trimethoxybenzene as internal standard. [c] 1:1 *i*-PrOH:MeCN.

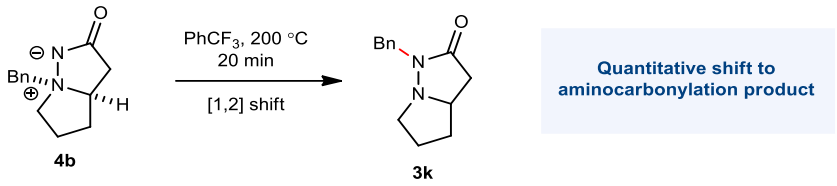


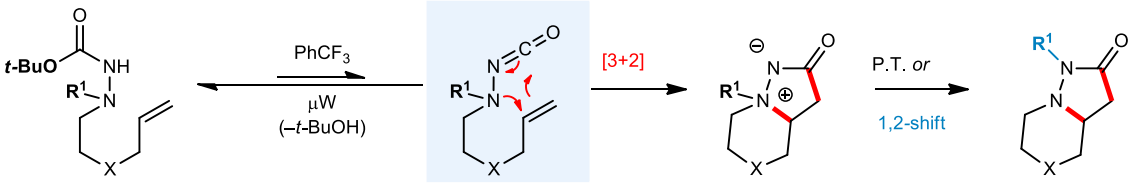
Figure 14 [1,2]-shift observed from aminimide **4b** to aminocarbonylation product **3k**.

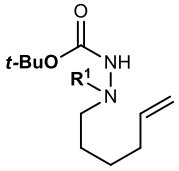
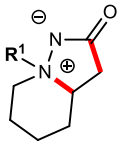
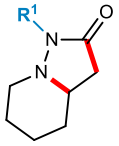
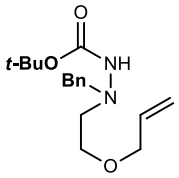
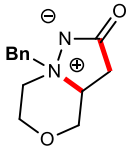
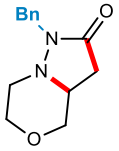
A variety of *N*,*N*-dialkyl carbazates consistently led to higher yields of aminocarbonylation compared to monoalkyl carbazates for terminal olefins (entries 4-8). However, alkene substitution diminished reactivity. β*N*-Benzylated E- and Z-crotyl carbazates **1n** and **1o** cyclized in a stereospecific manner, but only in modest yields (entries 9-10). The lower efficiency encountered with internal alkenes could be rationalized by invoking the stability of the parent aminimide intermediate. DFT calculations indicated that forming this intermediate was already thermodynamically uphill with a terminal alkene (by 2.4 kcal/mol, see **Figure 11**) and would therefore be more endergonic with more stable, internal alkenes. This implied more reversibility for the alkene aminocarbonylation step relative to the 1,2-rearrangement and could allow for other side reactions to compete with the desired reaction sequence. Overall, the data shown in **Table 6** show that aminocarbonylation reactions developed with β*N*-alkyl carbazates were more efficient than analogous reactions with monoalkyl carbazates. This improved reactivity was consistent with the above predictions of β*N*-dialkylation. Although the underlying cause of the improved reactivity was not immediately clear, these promising results demanded further study.

*With the exception of **4b**, Jasper Quartus synthesized the aminimides present in **Table 6** and **Table 7**; Jean Francois synthesized **3o**, **3p**, **3q**, and **3t**.*

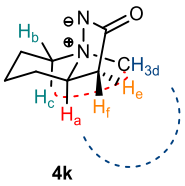
Given the aim of this modification was to broaden aminocarbonylation reactivity, unsuccessful substrates (*e.g.* **3f**, **Table 2**) in the initial survey were attempted with β*N*-benzyl substrates. Results of this study are shown in **Table 7**. Monoalkyl *N*-isocyanate precursor (**1p**) was unable to perform more challenging 6-membered ring-forming cyclizations. Comparatively, β*N*-benzyl precursor **1q** cyclized in nearly quantitative yield to the desired 6,5-bicyclic product at 200 °C (entry 6). The temperature of the reaction was then lowered to 150 °C (entry 7), upon which only the desired product was obtained, albeit in lower yield, with no traces of the aminimide. Encouragingly, β*N*-benzylation could expand the synthesis of 6,5-bicyclic substrates to include morpholine-based bicyclic derivative **3t** (entry 6 and 7) in excellent yield. In this case, generation of **3t** proved optimal at lower temperature (150 °C) and could be obtained in nearly quantitative yield (entry 7). Although β*N*-benzyl precursors seemed to undergo 1,2-shift uncontrollably from the corresponding aminimide, β*N*-methyl precursor **1r** enabled the isolation of the 6,5-aminimide **4k**. From this 6,5-bicyclic aminimide intermediate, meaningful stereochemical insight could be ascertained from NOE analysis (**Figure 15**). NOE signals for the aminimide **4k** reveal a single diastereomer present in the *cis* conformation as would be expected from a concerted [3+2] cycloaddition. These results corroborated with previous studied using *cis*- and *trans*-alkenes which cyclized with retention to form the *syn*-and *anti*-products respectively.[57]

Table 7 Aminocarbonylation forming 6,5-rings with *N*,*N*-dialkyl carbazate precursors.



entry	substrate	T (°C)	products & yield (%)[a]	
				
1	R^1 = H (**1p**)	200	0 (**4i**)	0 (3f)
2	R^1 = Bn (**1q**)	200	0 (**4j**)	99 (3q)
3	R^1 = Bn (**1q**)	150	0 (**4j**)	66 (3q)
4	R^1 = Me (**1r**)	180	70 (**4k**)[b]	0 (3r)
5	R^1 = $(CH_2)_4CHCH_2$ (**1s**)	180	30 (**4l**)[b]	0 (3s)
				
6	(**1t**)	200	0 (**4m**)	82 (**3t**)
7	(**1t**)	150[c]	0 (**4m**)	98 (**3t**)

Conditions: carbazate (1 equiv), in $PhCF_3$ (0.05 M) for 0.5 h (mW, sealed tube). Isolated yields unless noted otherwise. [b] 1:1 iPrOH: MeCN (0.05 M) for 3 h. [c] 6 h



4k

Proton(s)	δ (ppm)	NOESY Interactions
a	3.84	d, e, f, g
b	3.34-3.25	c, f, g
c	3.19-3.10	b, d, g
d	3.14	a, c, e, g
e	2.76	a, d, f, g
f	2.58	a, b, e, g

in red: ring junction proton. in blue: cis methyl substituent. in green: piperidine ring protons. in orange: pyrrolidine ring protons

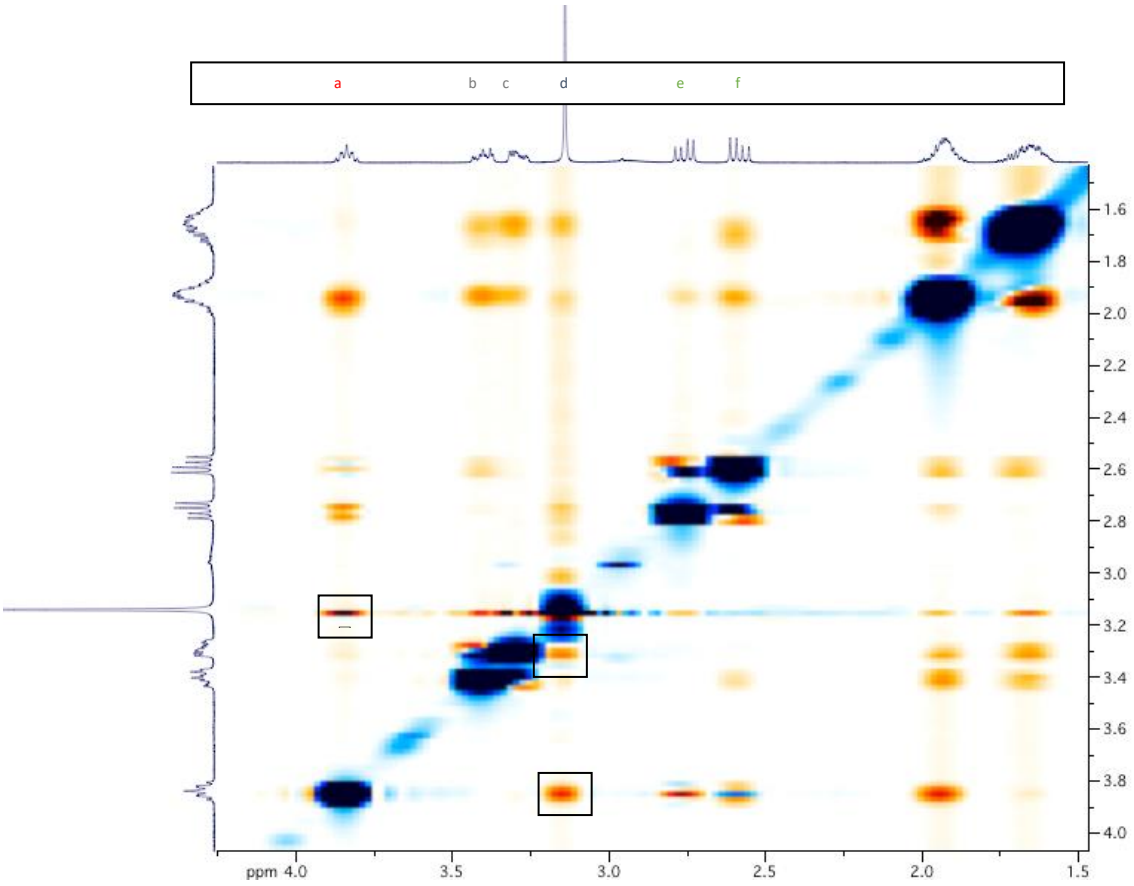
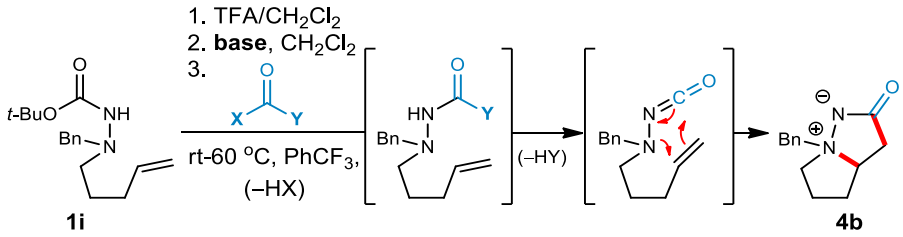


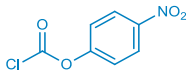
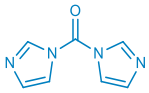
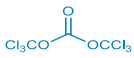
Figure 15 NOESY 2D-NMR spectra for **4k**.

The pursuit of milder aminocarbonylation conditions directed our attention to further modify *N*-isocyanate precursors and attempt new methods of isocyanate formation. Phosgenation of hydrazine was selected given that the subsequent acylation products are known to release isocyanates at room temperature.[37] Unfortunately, the synthesis of unsymmetrical

hydrazines was complicated by inherent chemoselectivity issues to hydrazines (*i.e.* possessing two nucleophilic nitrogen atoms). However, successive nucleophilic substitutions generally occur on the same *N*-atom—producing the desired *N*,*N*-disubstituted derivatives.[62] Fortunately, TFA-induced Boc-deprotection of the β*N*-alkylated carbazate precursors previously synthesized provided the required unsymmetrical hydrazines, which in turn could be treated with phosgene equivalents. These substrates allowed *N*-isocyanate formation under mild conditions, due to the lability of the resultant blocking group following acylation. The results of this study are presented in **Table 8**. *This transacylation study was conducted by Christian Clavette.*

Table 8 Intramolecular aminocarbonylation by transacylation of a *N*,*N*-dialkyl carbazates.



entry	reagent	T (°C)	t (h)	yield (%)
1		rt	1	32
2		rt	1	0
3		rt	12	81
4[a]		rt	1	93

Conditions: carbazate (1 equiv) in 1:1 TFA:CH_2Cl_2 (1 M) for 1 h at rt; then base (10 equiv), and acylating agent (1 equiv) in $PhCF_3$ (0.05 equiv) at rt. ^1H NMR yields using 1,3,5-trimethoxybenzene as an internal standard [a] 5.0 equivalents of DMAP was added to the reaction.

As predicted by DFT, mild *N*-isocyanate formation enabled room temperature aminocarbonylation. Oxalyl chloride provided a modest yield of the desired aminocarbonylation product (entry 1) whereas no product could be observed upon treatment of bisalkyl hydrazine with p-nitrophenyl chloroformate (entry 2). Other phosgene equivalents reacted more effectively. Carbonyldiimidazole (CDI) resulted in an excellent yield of product **4b** at room temperature (entry 3). But triphosgene provided the best yield of the desired product (entry 4). Excess DMAP was used both as a base (given the formation of two equivalents of HCl upon reaction with triphosgene) and as a potential nucleophilic catalyst.

The products obtained were aminimides, since 1,2-benzyl shift could not occur at room temperature. Unlike previous attempts using base catalysis of mono-alkyl carbazates, dimerization seemed to not be an issue with *N*,*N*-dialkyl precursors at room temperature. Therefore, the working hypothesis was that β*N*-dialkylation must be increasing *N*-isocyanate reactivity towards alkenes (through HOMO activation) or diminishing dimerization by sterically hindering the bimolecular reaction. It is unlikely that favoring *N*-isocyanate dimer cycloreversion was responsible for increased yields, given that this typically only occurs above 100 °C.[37]

Although the phosgenation approach enabled room temperature reactivity, this method was somewhat impractical. First, Boc-deprotection with TFA was highly variable and difficult to control. Additionally, the resulting aminimide dipole product was never isolated from this method. The reaction conditions required aquous workup, which rendered isolation of the dipole impossible. Instead, a poor yielding derivatization of the aminimide was performed (*i.e.* 40% yield of the final product over 4-steps). These limitations aside, new routes to *N*,*N*-dialkyl isocyanate precursors are expected to reinvigorate the study of this reaction.[63]

At this point in the study the objectives initially established were achieved, even if the reactivity developed still had some synthetic limitations. Several conclusions regarding the use of β*N*-alkyl carbazates could be made: 1) they are significantly more reactive than their mono-alkyl counterparts under thermolysis; 2) they could expand the substrate scope to include the synthesis of 6,5-bicyclic motifs; 3) tuning of the reaction conditions (H-bonding polar solvent) enabled the selective synthesis of aminimides; and 4) they are capable reacting at room-temperature with suitable *N*-isocyanate precursors. β*N*-Dialkyl substrates allowed the synthesis of experimental probes which were used to prove that the original proposed mechanism of a concerted, *syn* addition of the *N*-isocyanate to the alkene through zwitterionic aminimide intermediates was correct.[57] The relatively limited scope of the intramolecular aminocarbonylation reaction was exacerbated by lengthy and difficult synthesis of the required starting materials.

2.7 Summary and outlook on alkene aminocarbonylation with *N*-isocyanates

A variety of cyclic β-aminocarbonyl motifs can be accessed using novel intramolecular alkene aminocarbonylation reactivity of amino-isocyanate intermediates. Support for the involvement of transient *N*-isocyanates in a 5-membered concerted aminocarbonylation transition state was obtained by DFT calculations, and experimentally by the stereospecificity observed with internal alkenes, and NOE analysis of bicyclic aminimide intermediates. Aminimides are unambiguously intermediates of the cycloaddition, as concluded by their isolation and subsequent 1,2-shift. Several reactions were developed using carbazates as blocked (masked) *N*-isocyanate precursors, allowing the formation of the reactive *N*-isocyanate in situ

upon heating, base catalysis, or a transacylation approach. Complementary methodologies were developed to overcome side reactions, such as hydroamination and *N*-isocyanate dimerization, which were observed depending on the substrate.

Initially, the reaction of βN-H carbazates (LG = O*t*-Bu) and semicarbazides (LG = NH_2) required heating at 200 °C to form the *N*-isocyanate and subsequent pyrazolidinones after aminocarbonylation and proton-transfer steps. DFT calculations suggested the use of hemilabile *N*-isocyanate precursors could improve reactivity. New β*N*-H carbazates (LG = OPh) enabled aminocarbonylation by thermolysis at lower temperatures (ca. 120 °C), albeit in lower yields. Encouragingly, base-catalyzed *N*-isocyanate formation of β*N*-H carbazates occurred at even lower temperatures (rt to 50 °C), which resulted in high yielding aminocarbonylation reactions for substrates containing a Thorpe–Ingold bias. Combining insights from DFT and experimental studies, an alternative approach was developed: the thermolysis of β*N*-alkyl carbazates. Using these substrates in an [3+2] / 1,2-rearrangement sequence typically afforded the desired products in higher yields (up to 99%), and at lower temperatures (from 200 °C to 150 °C). Furthermore, the substrate scope was expanded to include the synthesis of 6,5-bicyclic ring systems, and the corresponding dipolar aminimides. These increased yields were attributed to the minimization of *N*-isocyanate dimerization, or the increased HOMO energy of the β*N*-alkyl *N*-isocyanate. Alternatively, a transacylation sequence of β*N*-alkyl carbazates (Boc cleavage followed by phosgenation) provided a method to form the *N*-isocyanate at lower temperatures and led to room temperature aminocarbonylation reactivity.

Collectively, these results demonstrate the unique reactivity of *N*-isocyanates as reactive intermediates in intramolecular alkene aminocarbonylations. Although a general alkene

aminocarbonylation reaction was still out-of-reach, several strategies and tools to achieve controlled reactivity using these amphoteric intermediates were developed. With a solid understanding of the reaction mechanism, successful optimization of a general aminocarbonylation reaction will be reported in due course. However, future developments ought to focus on intermolecular cycloaddition reactions of amino-isocyanates, as this would lead to improved synthetic diversity and largely deal with the difficulties of starting material synthesis.

2.8 Base catalyzed *N*-isocyanate cascade reactions

Investigations of low temperature aminocarbonylation with phenol-blocked *N*-isocyanate precursors may have largely been unsuccessful; however, conditions for room temperature *N*-isocyanate generation with base catalysis were identified and optimized. Even if the desired cycloaddition could not be optimized at room temperature using β*N*-H precursors, perhaps other reactions of *N*-isocyanates could take advantage of these mild conditions. While cascade reactions of *N*-isocyanates were well-underway in our lab when I started as a graduate student, the following studies represent the first room temperature cascade reactions of *N*-isocyanates developed within our lab (typically reactions were performed using microwave irradiation and high temperatures >150 °C).

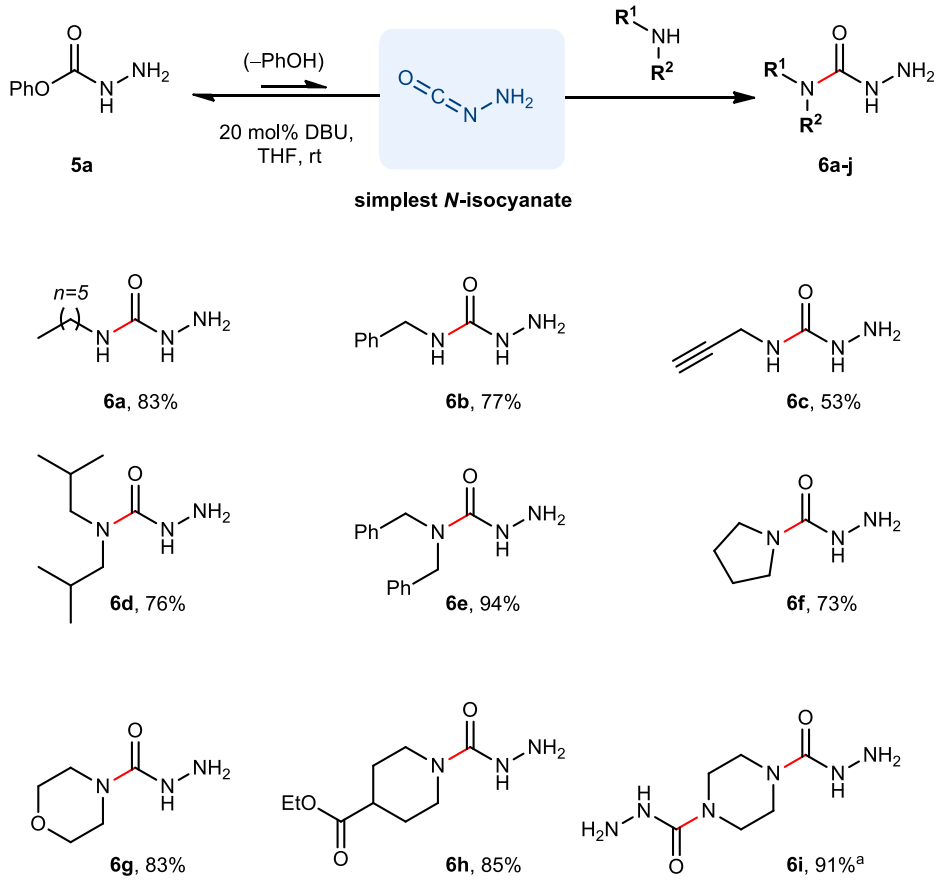
2.9 Improving *N*-isocyanate precursor synthesis

The first reactions of *N*-isocyanates in the group used *t*-butanol as a blocking group. This was convenient, as *t*-butyl carbazate was commercially available. However, as new precursors emerged with more ideal deblocking properties, optimized syntheses of the corresponding precursors lagged significantly. In particular, the synthesis of phenyl carbazate was notoriously arduous, often requiring a full day of work and typically yielding less than 40% product after column chromatography. This slowed the development of reactions with phenol blocked *N*-isocyanates; which, conveniently displayed the most ideal properties for an *N*-isocyanate precursor (*e.g.* low deblocking temperature, susceptibility to base catalysis). Naturally, an improved synthesis of this crucial building block was needed, ideally requiring no column chromatography. Knowing that phenol was the only by-product in this reaction, a reactive crystallization approach was taken to form phenyl carbazate. Toward this goal, water was removed by using hydrazine in a THF solution. Rapidly, petroleum ether was identified as the ideal co-solvent. Phenyl carbonate was dissolved in petroleum ether, and dropwise addition of hydrazine in THF formed crystalline phenyl carbazate upon dropwise addition. Using this procedure, yields over 80% were obtained for phenyl carbazate. Reactions could be run at multi gram scale, thus removing the bottleneck to the development of mild *N*-isocyanate reactions using phenyl carbazate precursors (see SI for detailed experimental set up). *The improved synthesis of phenyl carbazate was developed and optimized with Jean-Francois Vincent Rocan.*

2.10 Base catalyzed reactions of *N*-isocyanates: phenyl carbazate as the simplest *N*-isocyanate

Given that steric shielding on the β*N* appeared to be implicated in reduced dimerization of *N*-isocyanates in cycloaddition studies, we wondered if phenyl carbazate could be used as a simple *N*-isocyanate precursor. While substitution reactions had been reported for imino-isocyanates from our lab;[64] we were curious if more challenging amino-isocyanates could participate in similar reactivity using base catalysis. Previous studies conducted in the context of our alkene aminocarbonylation work showed that bases (*e.g.* catalytic DBU) led to amino-isocyanate formation and cycloaddition / dimerization at room temperature. The same reaction conditions (20 mol% of DBU in THF) were amenable to the generation of NH_2-NCO at room temperature. Using this base catalysis procedure, several semi-carbazides were readily formed at room temperature by combining amines and phenyl carbazate using base catalysis (**Table 9**).

Table 9 Base catalyzed synthesis of unprotected semi-carbazides



Conditions: *O*-phenyl carbazate (1 equiv), amine (1.1 equiv), DBU (0.2 equiv) in THF (0.3 M) stirred at room temperature for 16 h. [a] Reaction with 0.5 equiv amine.

Primary (**6a-c**)and secondary amines (**6d-i**) were tolerated as nucleophiles and even a double substitution reaction was possible using piperazine (**6i**), demonstrating the potential to form polymers. Overall, it was clear that base catalysis of amino-isocyanates was much more successful for nucleophile substitution reactions compared to alkene cycloadditions, as no detectable dimerization or oligomerization was observed in this study. This new reactivity also provides a new route to semi-carbazides that can serve as building blocks for more complex derivatives.[16]

2.11 Room temperature synthesis of aza-DKPs using a novel *N*-isocyanate cascade reaction

Piperazines are an important class of heterocycle, with over 1,200 natural products and 57 pharmaceuticals[1] incorporating a piperazine moiety in their structure. An important subclass of the piperazine family, 2,5-diketopiperazines (DKPs), account for approximately 75% of piperazine-based natural products, unsurprising given that they are cyclic amino acid dimers. In stark contrast, their nitrogen analogues — aza-diketopiperazines (aza-DKPs) — have received significantly less synthetic attention. In fact, very few practical syntheses are available for the formation of these rare heterocycles (**Figure 16**).[65–74] Representative examples include the reaction of *N*-(mesyloxy)malonamide with hydrazines,[68,69] the use of triphosgene and gaseous HCl to form aza-DKPs from N-Boc hydrazides and proline aminoesters,[70] and the solid-phase synthesis from α-aminoesters and *N*-Boc hydrazides.[73,74] Despite this, aza-DKPs possess unique properties as aza-peptide analogues for therapeutic applications *e.g.* replacing the Cα-stereogenic center by a nitrogen atom results in a significant improvement of both the water solubility and the microsomal stability.[75] We perceived that the dearth of viable synthetic methods could be an impediment to the study of their biological properties. Given the integral N–N–C=O motif present in the structure, aza-DKPs were an ideal target for a blocked *N*-isocyanate approach.

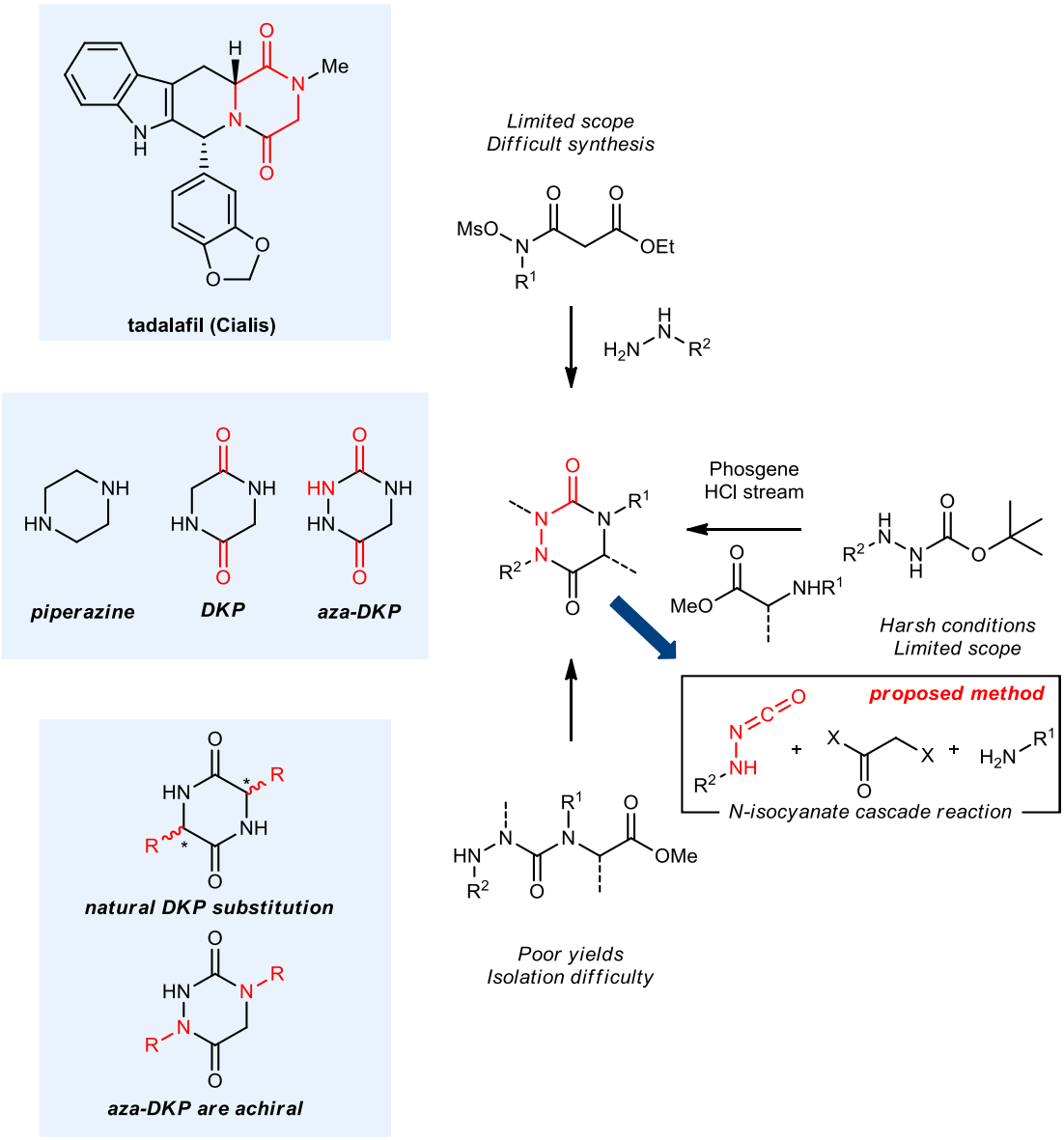


Figure 16 Importance of the piperazine heterocycle in natural products and drugs. Available methods for aza-DKP synthesis at the inception of this project.

At the time of this project, blocked *N*-isocyanate cascade reactions were developed to form saturated nitrogen heterocycles,[76] amino-hydantoins,[77] acyl-pyrazoles,[78] acyl-phthalazinones[78] and 6-azauracils.[78] However, in all these approaches the first step of the reaction sequence involved the generation and reaction of the *N*-isocyanates, and did not take

advantage of the ability of blocked isocyanates to serve as a *hemilabile protecting group*. In order to expand the limits of blocked *N*-isocyanate reaction development, we hoped to design a mild synthesis of aza-DKPs, taking full advantage of the blocked *N*-isocyanate as a latent electrophile. However, at the beginning of our investigations, we were unsure if this level of control would be possible. It was initially reasoned that either strategy outlined in **Figure 17** could allow the formation of aza-DKPs. For example, the final cyclization (step IV) could occur either through addition of the amine on the *N*-isocyanate (path IV-A) or through an intramolecular S_N2 reaction (path IV-B) depending on where the amine adds first (step II-A / III-B respectively).

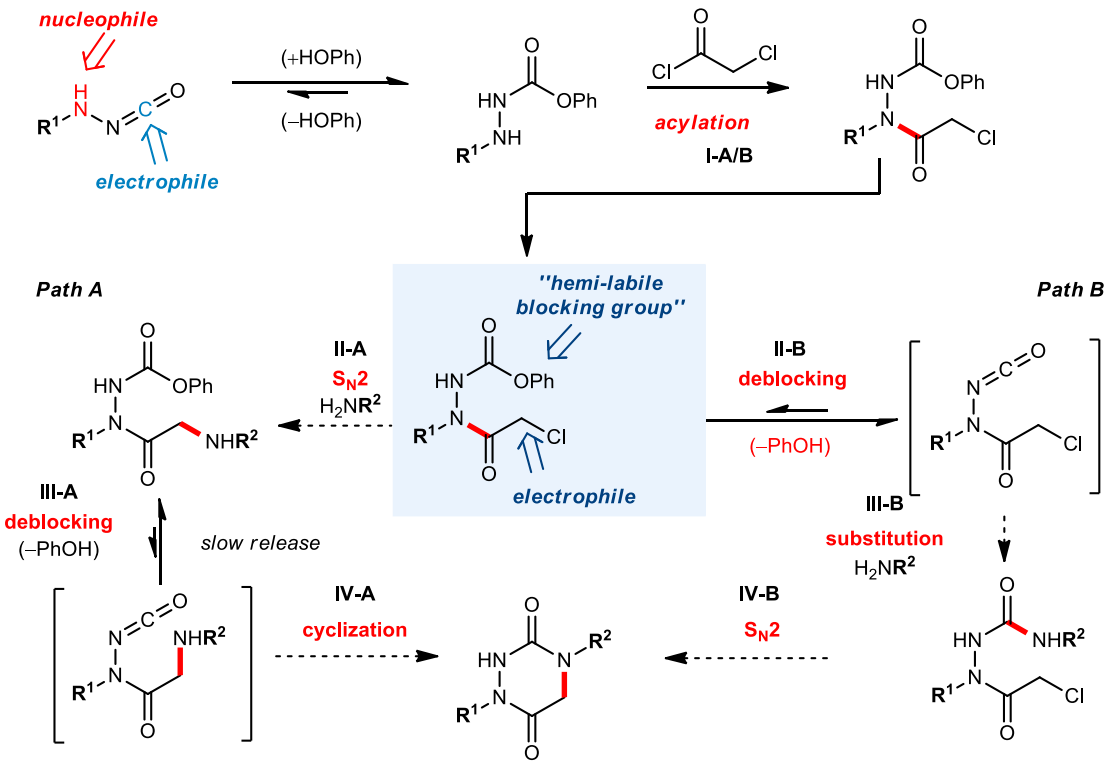
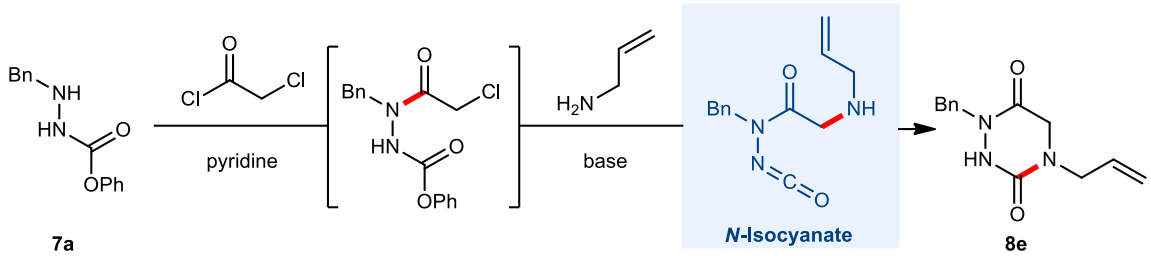


Figure 17 Possible mechanistic routes toward aza-DKP formation (pathway A is likely operating).

Our efforts to optimize this reaction were initiated using a one-pot reaction sequence involving an initial acylation step with chloroacetyl chloride, then addition of primary amine. It was speculated that the amine would be preferentially acylated in the presence of chloroacetyl chloride, so a stepwise approach was chosen. Having previously established that base catalysis allowed *N*-isocyanate generation of phenyl carbazate at room temperature, optimization of a one-pot sequence using *N*-benzyl phenyl carbazate (**7a**) was initiated. Selected optimization results are shown in **Table 10**. Surprisingly, conditions that were developed for room temperature *N*-isocyanate formation (*e.g.* 20 mol% DBU) were ineffective. This provided an early indication that the release of the *N*-isocyanate needed to be carefully controlled in order to follow a preferred reaction sequence (*i.e.* path A) and avoid unproductive pathways since no desired reactivity was observed at room temperature.

Table 10 Optimization of One-Pot Aza-DKP Formation



entry	solvent	amine (equiv)	base	yield (%)[a]
1	THF	1.1	Et_3N	44
2	MeCN	1.1	Et_3N	60
3	CH_2Cl_2	1.1	Et_3N	38
4	DMSO	1.1	Et_3N	35
5	DMF	1.1	Et_3N	33
6	MeCN	1.5	Et_3N	68
7	**MeCN**	**2.0**	**Et_3N**	**75[b]**
8	MeCN	2.0	DMAP	37
9	MeCN	2.0	NMI	46

Conditions: carbazate (1 equiv) stirring at 0 °C in solvent (0.6 M); then pyridine (1.1 equiv), then chloroacetyl chloride (1.05 equiv). The solution was warmed to rt and stirred for 2 h. A solution of amine (1.1-2.0 equiv) and base (2.5 equiv) in solvent (0.6 M) was added to the reaction (final conc.= 0.3 M) and stirred at rt for 24 h. [a] ^{1}H NMR yield based on 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield.

Changing to a weaker bases, such as triethylamine, led to drastic improvements in product yield. Early studies showed that an intermolecular S_N2 reaction was possible in the presence of mild base and occurred with minimal *N*-isocyanate formation. Screening solvents proved that acetonitrile was the optimal solvent for this one-pot sequence, which results in increased yield for the aza-DKP products (entries 1-5). Bases were optimized for each step of the reaction (acylation and amine addition) to ensure that formation of the *N*-isocyanate intermediate was controlled over the course of the entire reaction. Pyridine proved to be an ideal base for the

acylation step, as it appeared to be too weak to form *N*-isocyanates, while triethylamine was optimal for the subsequent steps. Ultimately, the yield was improved by using an excess of the amine nucleophile (2 equiv), signifying a challenging S_N2 reaction.

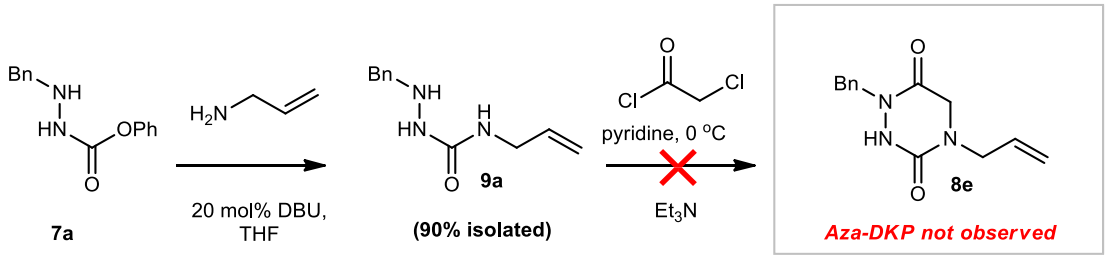
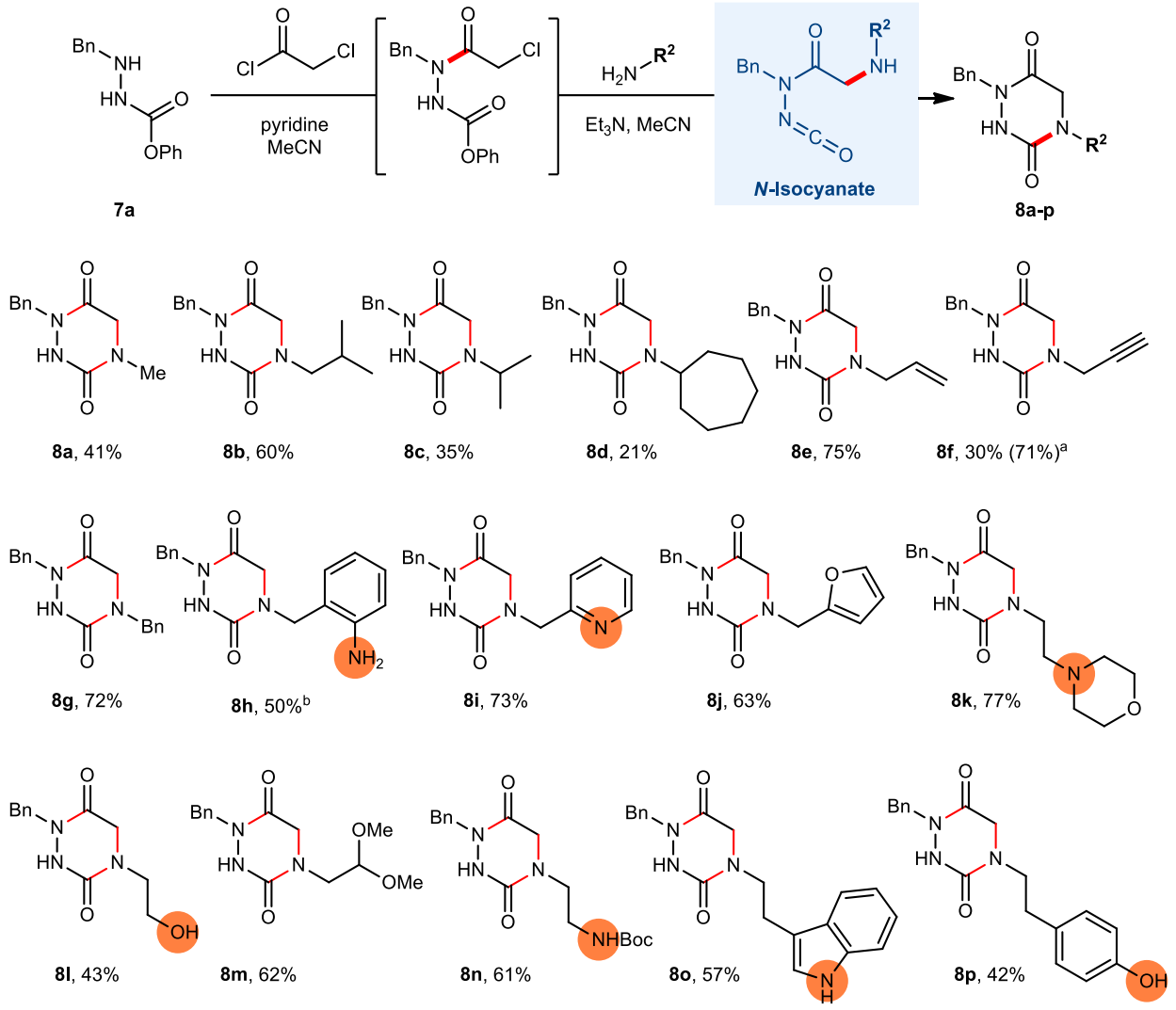


Figure 18 Control experiment verifies the need for controlled deblocking.

Reaction monitoring indicated that the productive pathway for this one-pot sequence likely involved: 1) Acylation using chloroacetyl chloride; 2) Intermolecular S_N2 with a primary amine; 3) Base-induced *N*-isocyanate formation; and 4) Cyclization (**Figure 17**). In contrast, if the *N*-isocyanate formed too early, addition on its electrophilic carbon led to a semicarbazide that could not perform the desired cyclization at room temperature (path B). This observation was verified in a separate control experiment, where **9a** was isolated and submitted to the reaction conditions (**Figure 18**). Overall, this reaction optimization provided a convenient one-pot sequence in which the formation of three C–N bonds could occur sequentially to form the desired product in 75% isolated yield. With optimized conditions in hand, the synthetic scope was surveyed. The reaction was widely tolerant of various nucleophilic / sensitive functional groups, which are highlighted in the tables below.

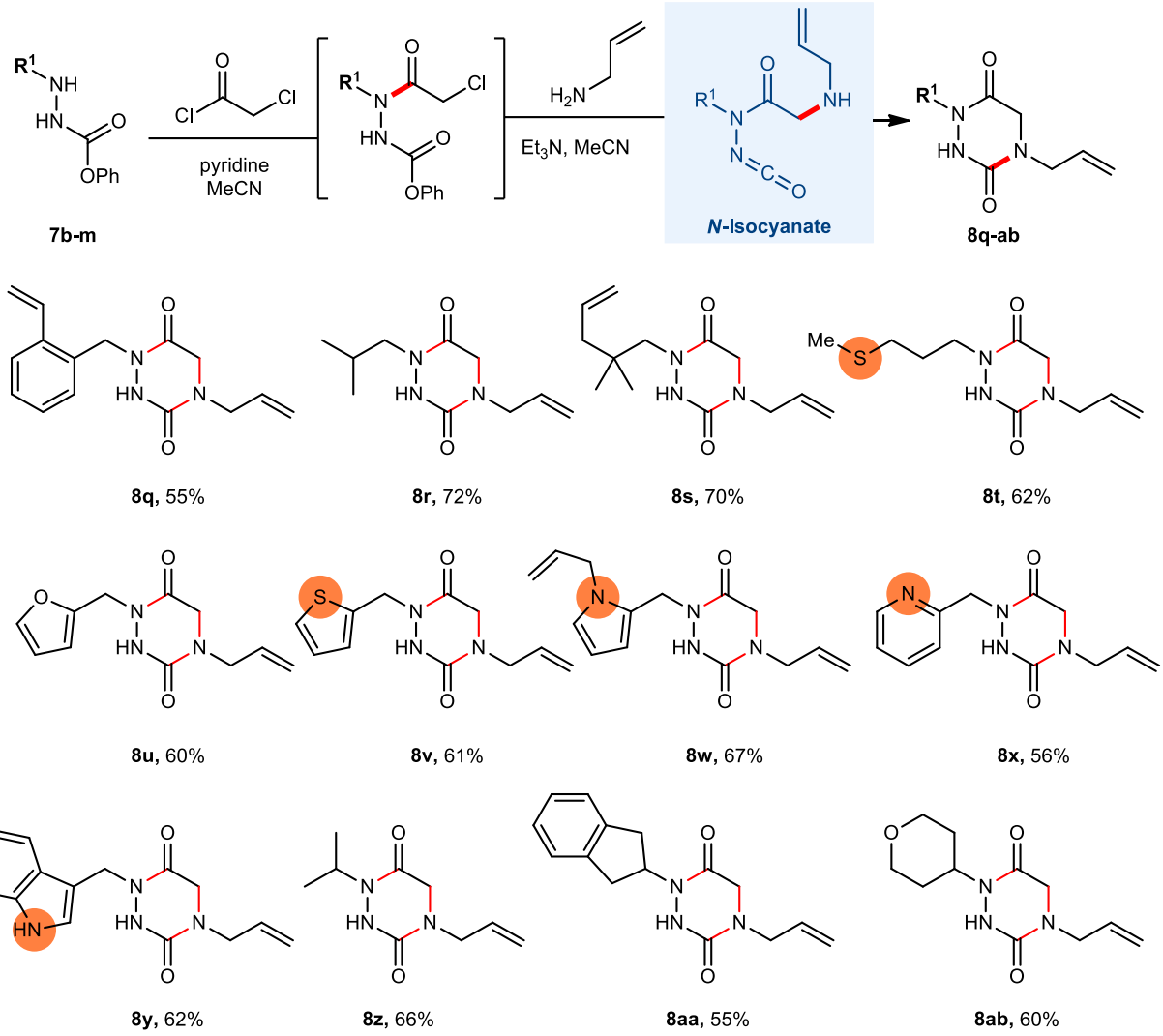
Table 11 One-pot aza-DKP sequence: selected amine scope



Conditions: carbazate (1 equiv) stirring at 0 °C in MeCN (0.6 M); then pyridine (1.1 equiv), then chloroacetyl chloride (1.05 equiv). The solution was warmed to rt and stirred for 2 h. A solution of amine (2 equiv) and Et_3N (2.5 equiv) in MeCN (0.6 M) was added to the reaction (final conc. = 0.3 M) and stirred at rt for 24 h. Isolated yields are shown. [a] Aqueous extraction after acylation then reflux in THF with amine (1.1 equiv) and Et_3N (1.3 equiv). [b] ^1H NMR yield based on 1,3,5-trimethoxybenzene as internal standard.

We first probed the effects of amine structure on reaction efficiency, selected examples are shown in **Table 11**. Typically, ,most aliphatic amines afforded the desired products in 40-70% yield for the three-step reaction cascade. Poorer yields were observed with more bulky branched secondary amines (**8c-d**), which was likely a consequence of a more challenging S_N2 reaction. Benzylic amines reacted in modest to good yields, with chemoselectivity observed for the more nucleophilic nitrogen atom (**8h**). A variety of functional groups were tolerated in high yields: alcohols (**8l**), acetals (**8m**), tertiary amines (**8k**), carbamates (**8n**) and electron rich-(**8o**) and poor-(**8i**) heterocycles. Overall, this approach proved highly versatile to incorporate a variety of substituents at the 4 position of the aza-DKP. All products in **Table 11** were synthesized by me with the exception of **8f**.

Table 12 One-Pot Aza-DKP Sequence: Carbazate Scope

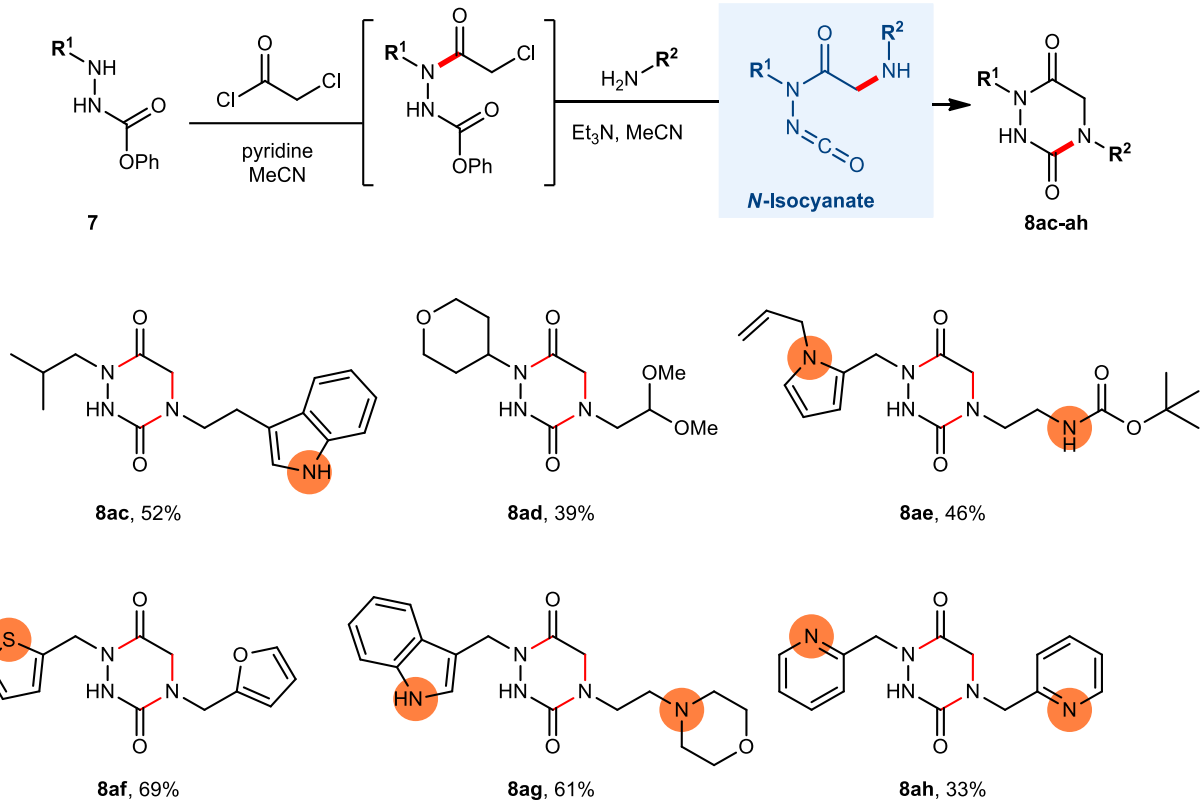


Conditions: carbazate (1 equiv) in MeCN (0.6 M) at 0 °C; then pyridine (1.1 equiv), then chloroacetyl chloride (1.05 equiv). The solution was warmed to rt and stirred for 2 h (16 h for ketone derived carbazates). A solution of amine (2 equiv) and Et_3N (2.5 equiv) in MeCN (0.6 M) was added to the reaction (final conc. = 0.3 M) and stirred at rt for 24 h. Isolated yields are shown.

Naturally, we were next investigated the impact of carbazate substitution on the efficiency of this reaction sequence. The results of this study are shown in **Table 12**. Overall, the yield remained consistent across a broad scope of carbazate precursors using allylamine as a representative nucleophile. The reaction sequence again tolerated the presence of various

functional groups, including alkenes (**8q**, **8s**, **8w**), ethers (**8ab**), thioethers (**8t**) and a free N-H group (**8y**), and electron rich-(**8v**, **8w**, **8y**) and poor-(**8x**) heterocycles. Ketone derived carbazates were obtained but required a lengthier acylation step (16 hours as opposed to 2 hours). Jean-Francois synthesized compounds in Table 12 besides **8q**, **8s**, **8w**, and **8y**. Overall, the results presented in **Table 11** and **Table 12** showed that variation on each reaction partner was well tolerated.

Table 13 One-pot aza-DKP sequence: mixed carbazate and amine scope



Conditions: carbazate (1 equiv) in MeCN (0.6 M) at 0 °C; then pyridine (1.1 equiv), then chloroacetyl chloride (1.05 equiv). The solution was warmed to rt and stirred for 2 h (16 h for ketone derived carbazates). A solution of amine (2 equiv) and Et_3N (2.5 equiv) in MeCN (0.6 M) was added to the reaction (final conc. = 0.3 M) and stirred at rt for 24 h. Isolated yields are shown.

Our last goal was to prove that the sequence was reliable for synthesis of a library of aza-DKPs. To achieve this, we attempted a mix-and-match approach (**Table 13**). Highly functionalized aza-DKPs were formed by reacting complex carbazate precursors with functionalized amines to provide highly decorated aza-DKPs. The yields of the reactions remained preparatively useful considering their exquisite functionality and high heteroatom content (up to 2:3 heteroatom:carbon atoms for entries in **Table 13**). Jean-Francois synthesized **8ad**, **8ae**, and **8af**. Thus, this new methodology was suitable for the synthesis of complex aza-DKPs. We also proved that this sequence was scalable, with a successful gram scale synthesis of allyl substituted aza-DKP.

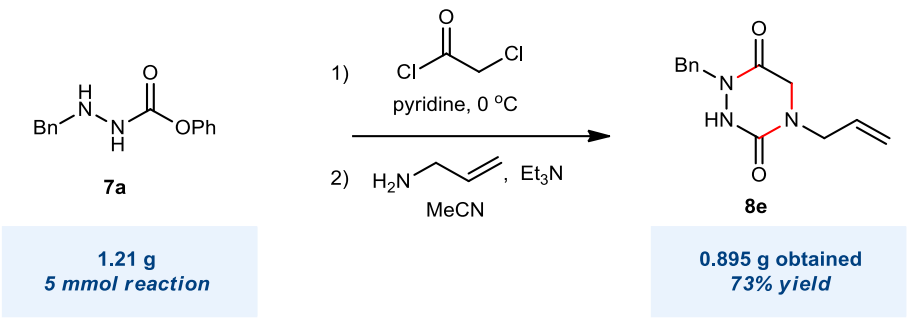


Figure 19 Gram scale synthesis of aza-DKP **8e**.

2.12 Conclusions on the one-pot synthesis of aza-DKPs

In conclusion a mild operationally simple, one-pot sequence for the synthesis of aza-DKPs was developed. This new sequence used readily available, bench-stable carbazates as *N*-isocyanate precursors, chloroacetyl chloride, and primary amines thus allowing for the rapid assembly of structurally diverse aza-DKPs. The success of this reaction was contingent upon the optimization of conditions to ensure slow, controlled formation of the *N*-isocyanate. Ultimately,

aza-DKPs could be formed in a single operation in typical yields from 50-70 % yield (implying an average yield of 80-90 % per elementary C–N bond formation step). Strategically, this sequence was also the first to fully exploit the ability of carbazates to serve as hemi-labile blocked (masked) *N*-isocyanate precursors. Efforts to extend this strategy to access other heterocyclic classes was attempted and preliminary investigations are summarized below (**Figure 20**). This general strategy of *N*-isocyanate precursors as hemi-labile protecting groups was exploited further by other members of the lab for the synthesis of aminopyridazinones,[79] triazinones[80] and indazolones.[81]

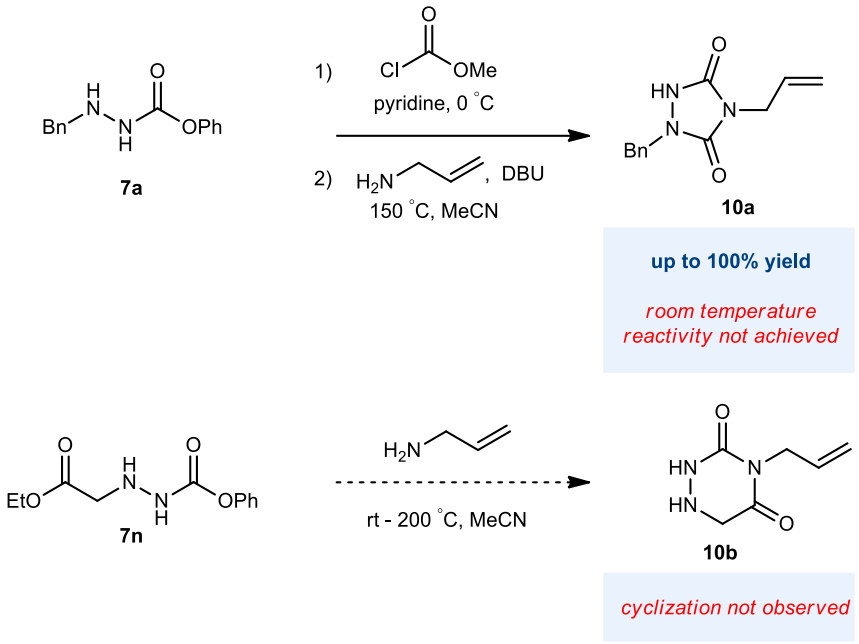


Figure 20 Extensions of the methodology to other *N*-heterocyclic classes.

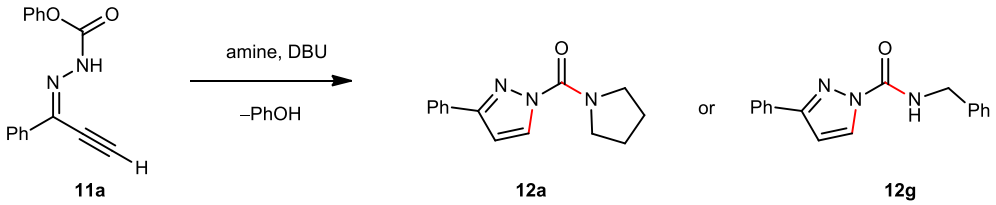
2.13 Base catalyzed synthesis of acyl pyrazoles

My work with imino-isocyanates was brief (1 project), and the bulk of this work was completed while an Honors student in the group. However, the findings stemming from this work

inadvertently set the stage for the next 5 years of my PhD studies; therefore, the work will be summarized below with a focus on how reactions of acyl-pyrazoles led to the discovery of oxygen-substituted isocyanates (*O*-isocyanates), and the first cascade reaction of *O*-isocyanates.

With base catalyzed substitution reactions of *N*-isocyanates established (**Table 9**), and demonstrated proof-of-concept for room temperature cascade reactions with aza-DKPs, subsequent studies focused on the development of new cascade reactions. Cascade reactions thus far had included nucleophile addition to the *N*-isocyanate and subsequent ring-closing via sp^2 addition (alkenes, and esters). Cyclization on *sp*-centers was a natural extension of this cyclization reactivity. We imagined that an ynone-derived carbazone precursor could lead to the synthesis of acyl pyrazoles following a substitution, 5-endo dig cyclization cascade—a novel *sp* addition strategy. The pyrazole core was a desirable synthetic target, given the abundance of pharmaceuticals and agrochemicals incorporating it into their structures.[82] Moreover, methods to form acyl pyrazoles are scarce in the literature, despite their demonstrated bioactivity,[82–87] and broad synthetic utility.[88–95]

Table 14 Preliminary optimization of acyl-pyrazole formation

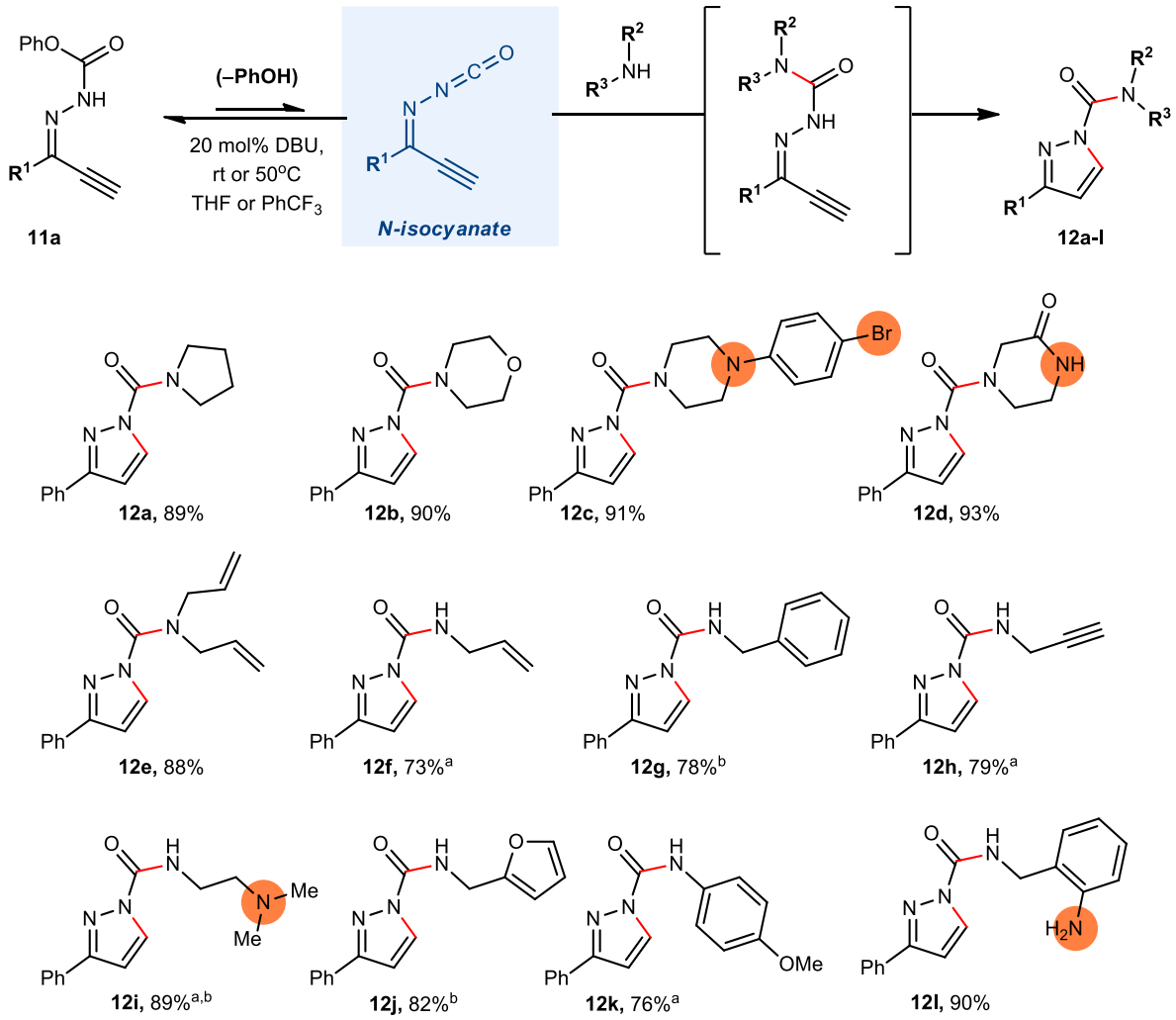


T (°C)	t (h)	solvent	amine	DBU (equiv)	yield (%)
120	6	MeCN	Benzylamine	-	20
175	3	MeCN	Benzylamine	-	40
50	16	$PhCF_3$	Benzylamine	0.1	51
50	16	$PhCF_3$	Pyrrolidine	0.1	59
50	16	$PhCF_3$	Pyrrolidine	0.2	81
r.t.	16	$PhCF_3$	Pyrrolidine	0.2	85
r.t	**16**	**THF**	**Pyrrolidine**	**0.2**	**100** (89)[a]

Conditions: Alkynyl carbazone (1 equiv), amine (1.1 equiv) and DBU (0.1–0.2 equiv.) in solvent (0.3 M) in a sealed tube. ^{1}H NMR yields with 1,3,5-trimethoxybenzene as an internal standard, unless otherwise indicated. [a] Isolated yield.

Reaction optimization of acyl pyrazole formation is presented in **Table 14**. Based on preceding evidence of mild base catalyzed *N*-isocyanate formation, 20 mol% DBU could similarly provide high yields of the desired acyl pyrazole product **12a**. Mild base catalyzed conditions proved essential for the success of this reaction, as the compounds formed were susceptible to decomposition at elevated temperatures that would be required for thermal deblocking of the *N*-isocyanate precursors (>100 °C).

Table 15 Base catalyzed pyrazole synthesis: amine scope

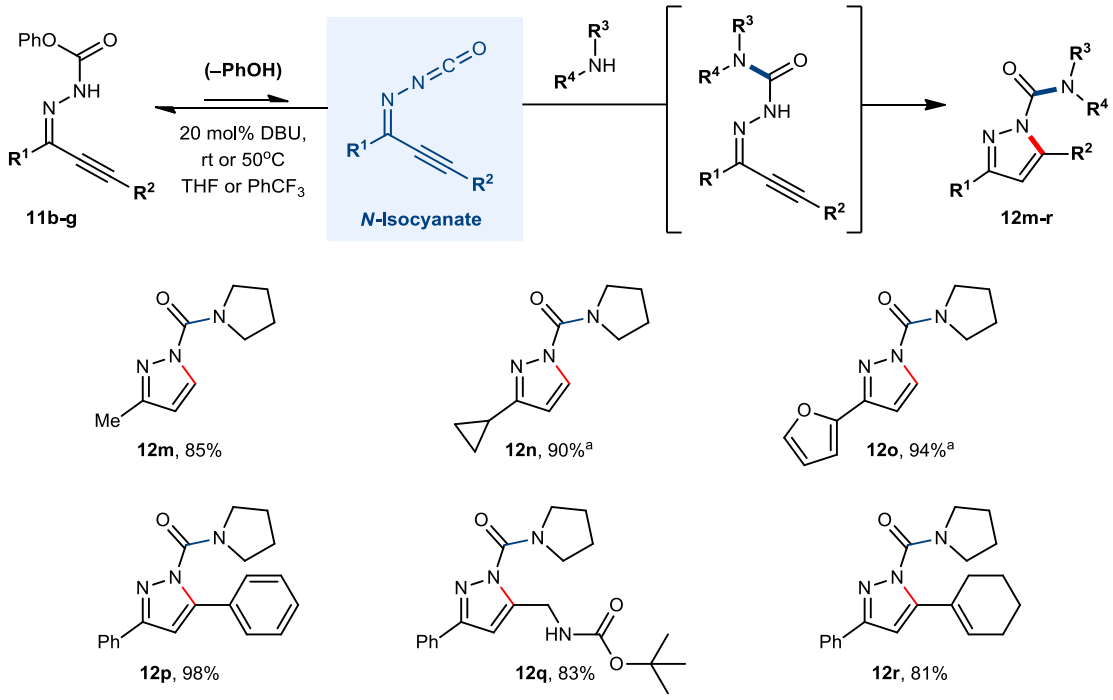


Conditions: alkynyl carbazone (1 equiv), amine (1.1 equiv), DBU (0.2 equiv) in THF (0.3 M) at rt for 16 h. [a] 50 °C. [b] $PhCF_3$ (0.3 M).

With optimized conditions in hand for the synthesis of acyl pyrazoles the scope of amine nucleophiles was studied (**Table 15**). A wide variety of amines proved to be competent partners in this reaction. Cyclic amines including pyrrolidine (**12a**), morpholine (**12b**) and piperazine derivatives (**12c-d**) all cyclized in high yield. The tolerance of halogens and heteroatom-rich functionalities highlight the benefits of mild, transition metal-free reactivity. Anilines were also

effective nucleophiles (**12k**). Given the challenges of aromatic amine substitution reactions on carbamate derivatives, their ability to undergo clean, high yielding substitution in this cascade reaction at 50 °C supports the formation of a reactive *N*-isocyanate intermediate as the participating electrophile.

Table 16 Base catalyzed pyrazole synthesis: carbazone scope



Conditions: alkynyl carbazone (1 equiv), amine (1.1 equiv), DBU (0.2 equiv) in THF at 50 °C for 16 h.
[a]Reaction at room temperature.

In parallel to efforts using different amines the cascade reaction was also performed with several carbazones, using pyrrolidine as a representative nucleophile (**Table 16**). Carbazone (**R^1**) substitution seemed to have almost no effect on reaction yield (**12m-o**). Alkyne substitution (**R^2**) was also well tolerated and allowed the formation of 1,3,5-trisubsituted pyrazoles under similar

conditions (**14p-r**). Finally, the cascade reaction could be scaled-up without an impact on product yield (**Figure 21**).

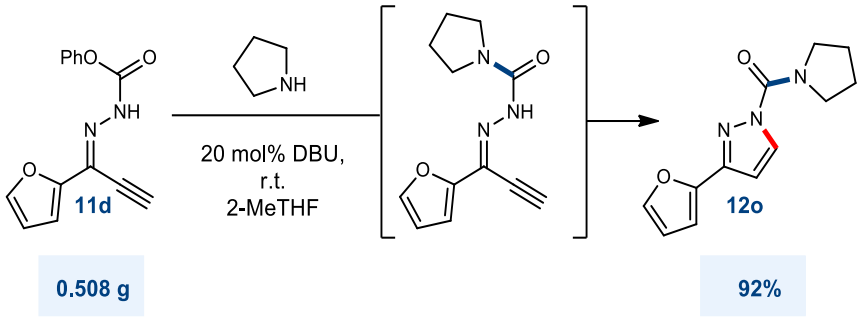


Figure 21 Gram scale synthesis of acyl-pyrazole **12o**

Difficulties were encountered with primary amine derived acyl pyrazoles (*i.e.* **12f**). The products appeared to be labile upon heating or flash-chromatography. Since acyl pyrazole derivatives possessing a free *N*-H were known to act as blocked (masked) *C*-isocyanate precursors,[48] silica gel was treated with Et_3N to ensure stability during product isolation. This suggested that mildly acidic conditions could promote *N*-isocyanate formation from such blocked derivatives. We became interested in this decomposition reaction, and the use of pyrazoles as new acid labile isocyanate precursors. Importantly, the carbamoyl-pyrazoles were isolable, in comparison to analogous highly reactive carbamoyl imidazoles (**Table 8**).

2.14 Initial discovery of blocked *O*-isocyanate reactions

While substitution reactions with hydrazines failed to deliver the desired products, optimization with hydroxylamines proved fruitful. Strategically, if a hydroxylamine nucleophile could participate in this reaction cascade it could act as a blocked oxygen-substituted isocyanate

(*O*-isocyanate). At the time, the reactivity of *O*-isocyanates was a black-box. Despite several contributions to *N*-isocyanates, our group had not considered the potential reactivity of *O*-isocyanates. Upon isolation of the requisite hydroxylamine substituted pyrazole, its ability to undergo substitution and cascade reactions was surveyed. It was rapidly evident that the precursor could enable both clean substitution reactions and even cascade reactions. *The implications of this discovery would be widespread, O-isocyanates would soon become a major research branch in the Beauchemin lab.* The next Chapter will provide a detailed review of *O*-isocyanates and the reactivity developed thus far.

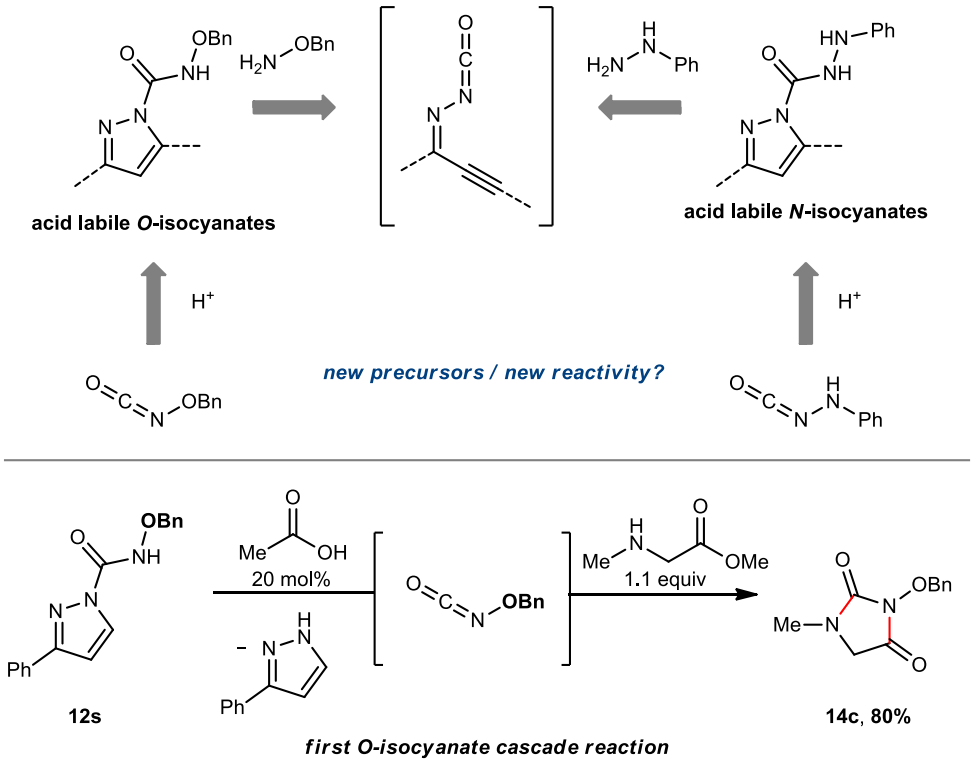


Figure 22 *N*-Isocyanate cascade reaction development leads to study of *O*-isocyanates.

Chapter 3:

A systematic study of *O*-isocyanate reactivity

Prelude

In this chapter, efforts to develop new reactions with *O*-isocyanates will be described. Since *O*-isocyanates were a new direction in our group, a literature survey was necessary both to evaluate the extent to which *O*-isocyanates had been studied previously, and to guide ensuing investigations. The resultant literature survey is presented as the introduction of this chapter. For individuals hoping to develop novel reactions with *O*-isocyanates, this should serve as an ideal reference to learn their fundamental reactivity and history. However, to contextualize original contributions in this thesis within the greater landscape of reported *O*-isocyanate reactions, section 3.3 is the most relevant section to read. This chapter will focus on the optimization of *O*-isocyanate precursors, development of their substitution reactions with nucleophiles, the first examples of *O*-isocyanate cascade reactions and the discovery of their cycloaddition reactivity.

3.1 The synthesis and isolation of *O*-isocyanates: A century of effort

O-Isocyanates are certainly still obscure molecules; yet, their rich history dates back to the early days of organic chemistry. Over nearly a century, chemists struggled to synthesize and isolate *O*-isocyanates, but a variety of methods that could generate *C*-isocyanates have proven ineffective. The earliest reference of these rare intermediates was in 1894. During investigations on nitroparaffins and fulminates, Nef proposed the first isolation of an *O*-isocyanate—a claim that would take nearly 100 years to rightfully be true.[96] Nef obtained a yellow solid from the addition of mercuric chloride to sodium isonitromethane, which was assigned the corresponding *incorrect* structure (**Figure 23**). However, it was later determined by Jones that Nef's salt was more likely a basic mercury salt of formhydroxamic acid.[97] Although erroneous, Nef's structure

must be credited, since it spurred interest in the study of *O*-isocyanates—or as they were originally described in the literature: *the oxime esters of carbon dioxide*.

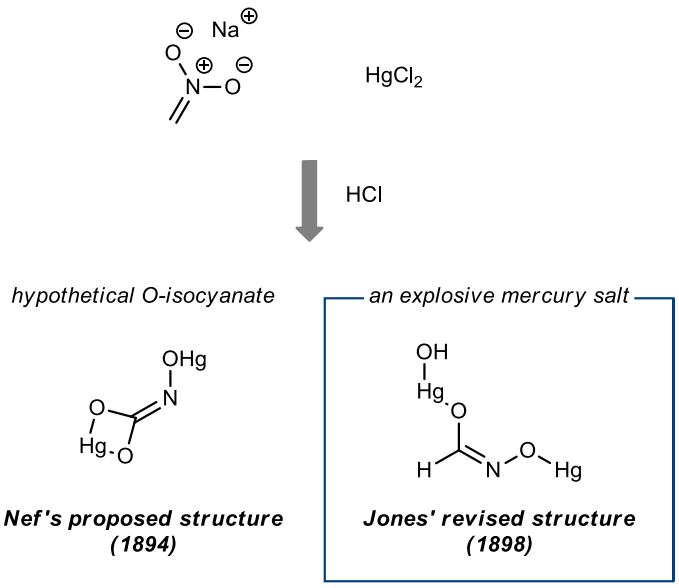


Figure 23 Earliest prediction of *O*-isocyanates stimulates their eventual discovery

Nef's incorrect proposal inspired Jones to investigate the formation of *O*-isocyanates. Around the turn of the 19th century, phosgenation of amines was reported to produce carbamoyl chlorides, which generated the corresponding isocyanates upon treatment with CaO.[98,99] Jones sought to extend this methodology to hydroxylamines, which could deliver a facile synthesis of the corresponding *O*-isocyanates.[97]

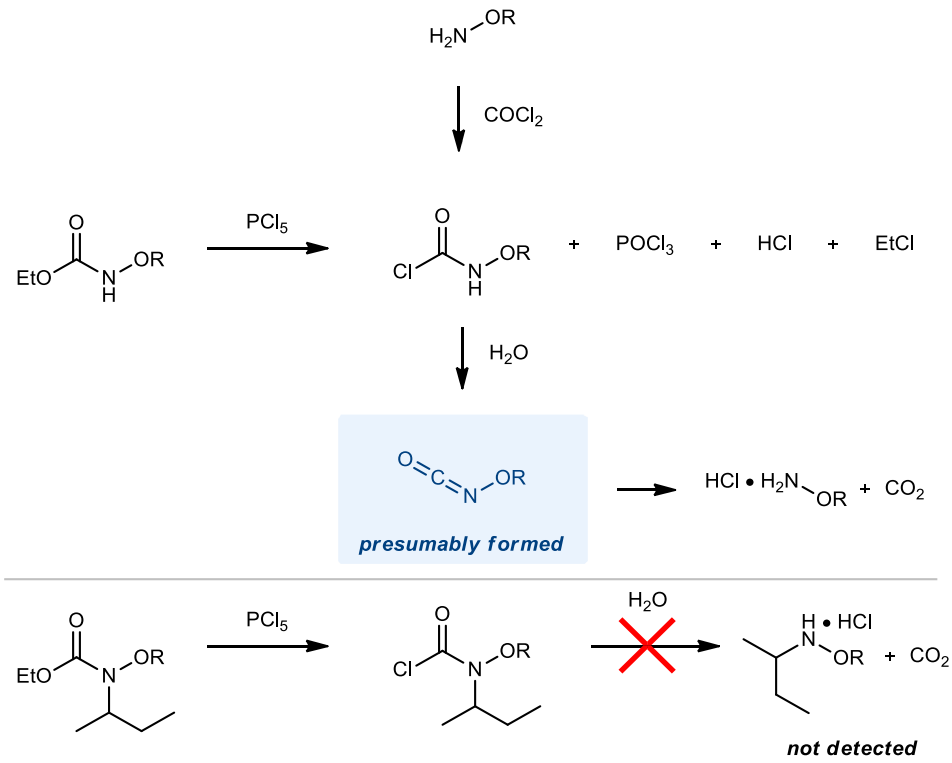


Figure 24 Attempted *O*-isocyanate synthesis by Jones

Jones was decisively unable to isolate *O*-isocyanates using this method, or a variety of iterations (**Figure 24**). It was apparent however, that *O*-isocyanates likely formed from a reaction of the carbamoyl chlorides in water. In analogy to similar reactions forming amines from isocyanates, the hydroxylamine was obtained from a reaction of the carbamoyl chloride in water. Moreover, upon alkylation of the nitrogen, the same decomposition products were not observed, since the formation of an *O*-isocyanate would be impossible. Instead, the carbamoyl chloride starting material was recovered. However, since limited characterization was available for the products of these reactions, it remains somewhat ambiguous to ascribe with certainty what had formed. Yet, it seems highly likely—based on proceeding work by other chemists—that Jones

should be credited with the first *formation* of an *O*-isocyanate, even if it could not be isolated, and no productive reaction was observed or recorded.

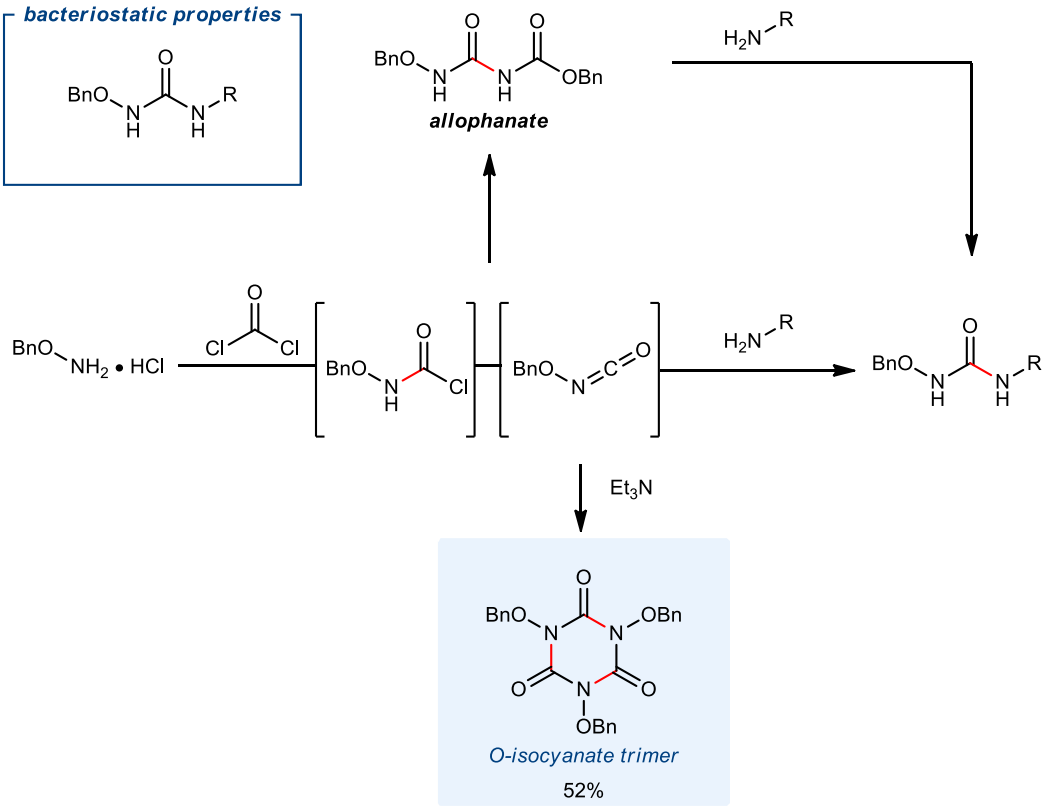


Figure 25 *O*-Isocyanate trimer and allophanate isolation

The study of *O*-isocyanates faded into obscurity over the next decades, until chemists from the National Research Council (NRC) in Canada became interested in the bacteriostatic properties of hydroxylamine derivatives.[100] McKay and collaborators were similarly unsuccessful in the preparation of *O*-isocyanate monomers; however, they were successful in the isolation and characterization of *O*-isocyanate trimers (isocyanuric acids) and allophanates (**Figure 25**). Upon essentially repeating the early investigations of Jones—phosgenation of hydroxylamines—McKay

was able to treat the crude oxyamino carbamoyl chlorides with triethylamine and produce the corresponding *O*-isocyanate trimers.[100] This finally provided compelling evidence that such reactions previously reported by Jones proceeded through *O*-isocyanate intermediates, since the trimer of the *O*-isocyanate monomer was unambiguously assigned. During the preparation of the oxyamino carbamoylchloride, decomposition led to the formation of allophanates. They were able to demonstrate that amine substitution reactions could proceed in good yield, either from the allophanates or from the oxyamino carbamoyl chloride. The allophanates represent a crude, but early example of a masked (blocked) *O*-isocyanates. Arguably, since the allophanates could be isolated, they are more ideal blocked derivatives than some of the early blocked reagents that will be discussed later—but their formation remains questionable.

Between 1961-1962, Staab established that the dissociation of *N*-methoxyimidazolecarboxamides produced *O*-isocyanates (**Figure 26**).[101,102] This method was again ineffective for the preparation and isolation of isocyanate monomers (isocyanuric acid trimerization products were observed); however, Staab was able to prepare a urea via room temperature aminolysis using cyclohexylamine as a nucleophile. Indeed, imidazole blocked isocyanates generally react in a similar fashion to the corresponding free isocyanate. Importantly, when the amide hydrogen was substituted with an alkyl group—rendering dissociation into an *O*-isocyanate impossible—aminolysis was not observed. These early findings were consistent with the formation of an *O*-isocyanate as a reactive intermediate. Arguably, this single example could not provide a solid measure of the reactivity of blocked *O*-isocyanates.

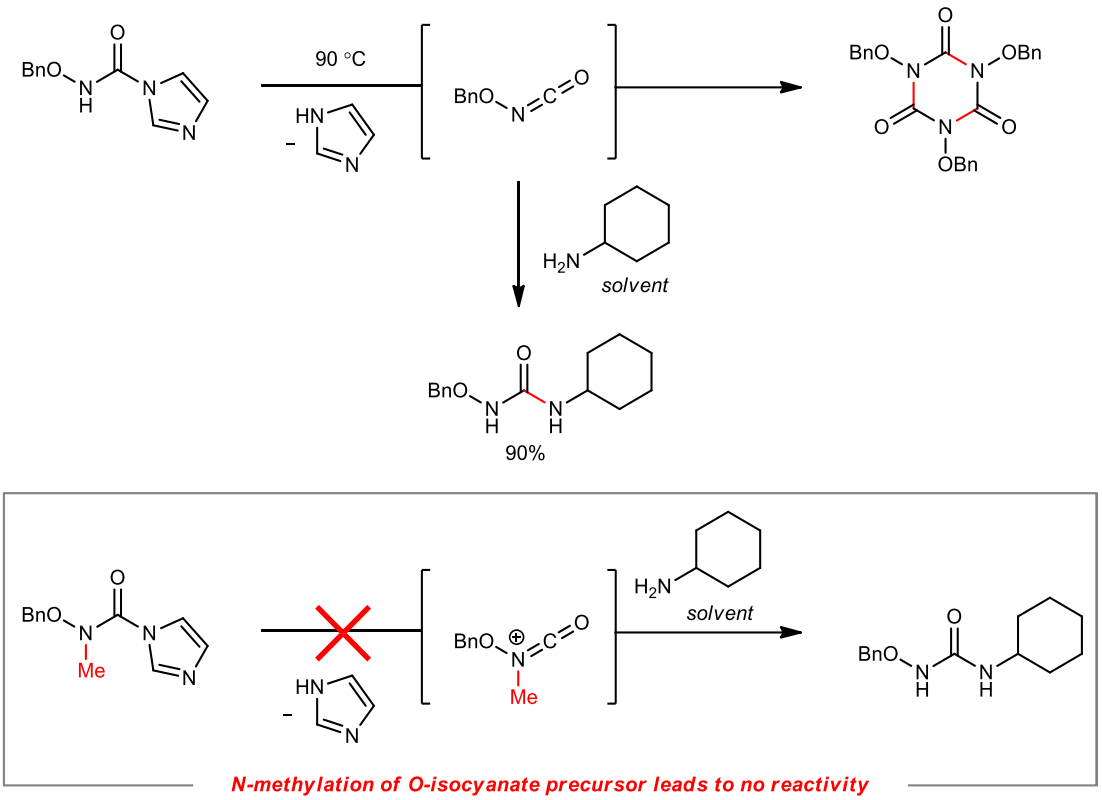


Figure 26 Preliminary investigation of imidazole blocked *O*-isocyanates

In the first conceptually distinct approach to phosgenation / carbamoyl chloride degradation, Hedrick attempted to apply the Wadsworth and Emmons classical isocyanate synthesis to access *O*-isocyanates (**Figure 27**).[103] Although this method had been successful for the preparation / isolation of *C*-isocyanates,[104] it failed in the analogous synthesis of *O*-isocyanates. Hedrick reported a relatively low yield of the trimer, indicating that this reaction was not ideal for the preparation of *O*-isocyanates. It is worth noting that Wadsworth and Emmons were also unable to apply their isocyanate synthesis to *N*-isocyanates and obtained similar yields of the corresponding *N*-isocyanate dimers.[105] Thus, it would appear at first glance, that *O*-

isocyanates are more precarious than *C*-isocyanates and have similar instability to *N*-isocyanates, with potential to be more reactive.

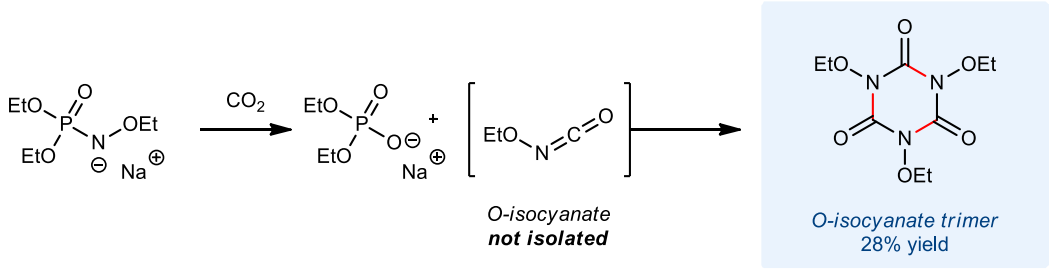


Figure 27 Wadsworth and Emmons isocyanate synthesis does not allow isolation of *O*-isocyanate

While all examples of *O*-isocyanates thus far were alkoxy-derived, Berndt disclosed a retro [3+2] cycloaddition reaction of isoxazolidinone that released hydroxy-*O*-isocyanates (**Figure 28**).[106] Upon heating an isoxazolidinone derivative in benzene, an acidic crystalline product was isolated. Brendt was unable to detect heterocumulene stretches by IR, suggesting that the product was not the monomeric *O*-isocyanate. Rather, mass spectroscopy revealed the compound was likely a dimer of the hydroxy *O*-isocyanate. While a structure of the dimer was not suggested in this publication, a structure resembling the 5-membered hydroxy-oxadiazolidinedione heterocycle seems most likely given the reported acidic nature of the compound and analogous dimerization reactions of *N*-isocyanates (**Figure 8**, B). If the isoxazolidinone was refluxed in *t*-butanol, the *N*-hydroxy carbamate was isolated, thus providing support for an *O*-isocyanate intermediate. Notably, reacting the proposed dimer in *t*-butanol did not provide the same carbamate; and is therefore assumed not to release *O*-isocyanates. This

sharply contrasts with *N*-isocyanate dimers, which reportedly undergo cycloreversion readily to release *N*-isocyanates.[53]

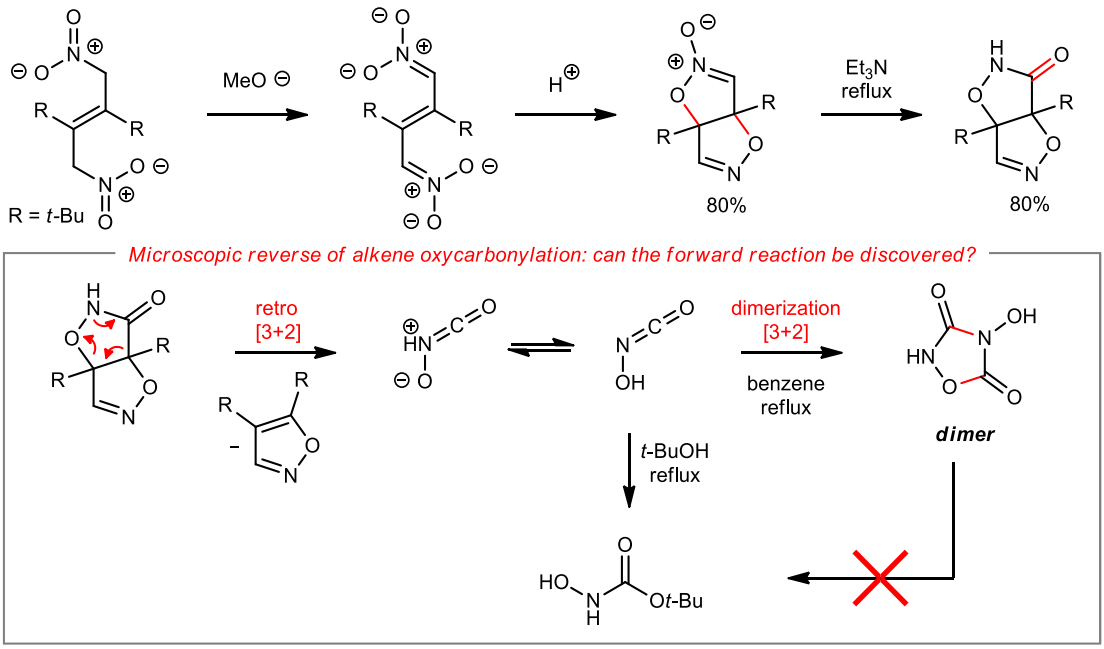


Figure 28 Retro [3+2] cycloaddition provides first hydroxy-*O*-isocyanate

A retro [4+2] cycloaddition strategy similarly failed to isolate *O*-isocyanate monomers, instead delivering only the *O*-isocyanate trimer in low yield (**Figure 29**).[107] Again, the formation of C_{alkyl}-, C_{aryl}-, *O*-, and *N*-isocyanates could be directly compared under these retro cyclization reaction conditions. From the data provided, it could be inferred that *O*-isocyanates are comparatively more reactive than C_{alkyl}-isocyanates at minimum. The fact that even relatively stable C_{aryl}-isocyanate formed urea under such conditions indicates that they were likely too harsh, and unsuitable for the synthesis of capricious intermediates—such as *O*-isocyanates.

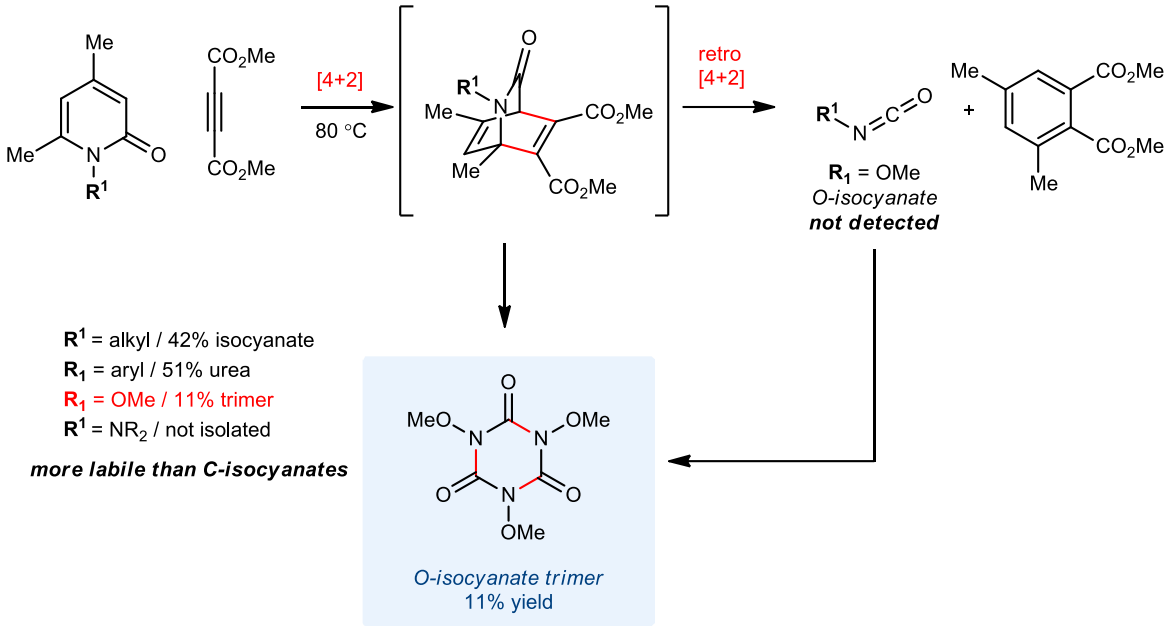


Figure 29 Retro cycloaddition approach to *O*-isocyanates

The observation that both retro [3+2] *and* retro [4+2] reactivity could enable the formation of *O*-isocyanates was striking. Notably, in both cases the formation of *O*-isocyanates was likely driven by the release of an aromatic byproduct. Nevertheless, it suggested that the microscopic reverse of either reaction should be possible, and the lure of novel cycloaddition reactions of *O*-isocyanates was enchanting. However, a thorough review of the literature revealed no examples of the forward reaction *e.g. the cycloaddition of O-isocyanates on any π-system*. This is in stark contrast to the literature of *N*-isocyanates, in which early investigators hastily probed the reactivity of *N*-isocyanates with various π-systems after their discovery.

Finally, in 1983 and 1988—nearly 100 years after the initial proposed isolation of an *O*-isocyanate—Kirilin[108] and Leukel[109] respectively developed the first syntheses and isolation of a

special class of *O*-isocyanate—silyloxy isocyanates (**Figure 30** Isolation of siloxy isocyanates). Kirilin was first to report the synthesis of siloxy isocyanate from a *tris*-TMS protected carbamate derivative (**Figure 30**, A). Upon heating in the presence of TES-Cl, elimination led to the isolation of TMS-protected *O*-isocyanate. It should be noted that a recent attempt to replicate the work of the Kirilin—but with a slightly modified reagent—failed, so the methodology appears somewhat restricted (**Figure 30**, A).[110] While Leukel could also form siloxy isocyanates; in particular, Leukel noted that attempts to extend the synthesis of silyloxy isocyanates to alkoxy isocyanates were unsuccessful (**Figure 30**, B). Subjecting benzyl hydroxylamine to the reaction conditions led to the formation of benzaldehyde. This oxidation could occur from the mechanism proposed below, but the authors offered no proposal. Such silyl derivatives were similarly necessary for the isolation of reactive *amino*-iso(thio)cyanates.[111]

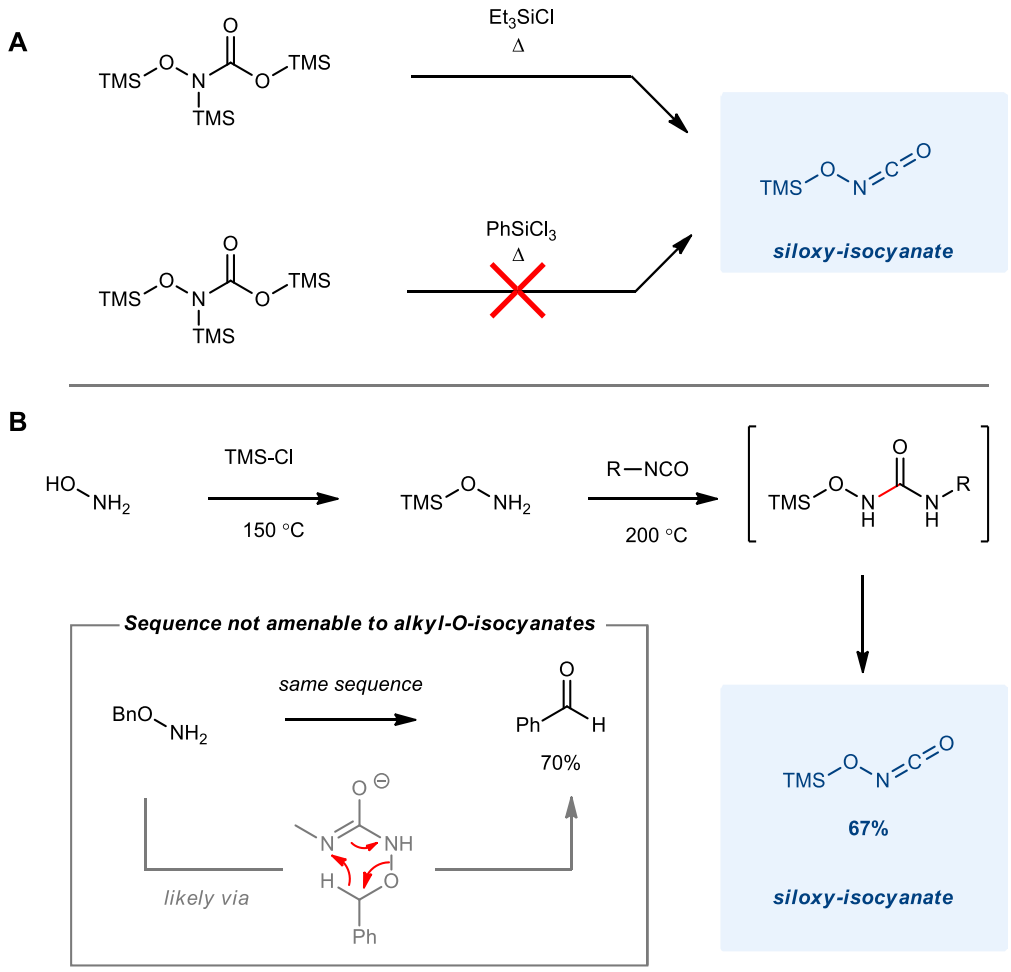


Figure 30 Isolation of siloxy isocyanates.

Thus, synthetic efforts to isolate *O*-isocyanates over nearly 100 years have largely been met with failure. The most likely obstacle is that *O*-isocyanates are simply too prone to trimerization at ambient temperatures to be isolable as monomers. In order to probe the reason for this occurrence, systematic studies on the physiochemical properties of *O*-isocyanates would be necessary. This would require new methods for the formation of *O*-isocyanates and / or technological advancements in the detection of fleeting intermediates.

3.2 Physical and computational studies of *O*-isocyanates

In parallel to synthetic investigations, work began on systematic physical and computational studies of *O*-isocyanates. These efforts were initiated by Lwowski in 1964,[112] and shortly followed by Hafner.[113] Lwowski introduced a new method to form *O*-isocyanates through the Curtius rearrangement of azidoformates (**Figure 31**).[112] Such a transformation was widely believed to be impossible at the time, since azidoformates were "rigid azides"—so called because they did not rearrange upon decomposition. Lwowski was able to show that, although photolysis of rigid azides in hydrocarbon solvents did not lead to rearrangement, photolysis in hydrolytic solvents—such as methanol—gave products derived from the addition of methanol to the corresponding rearranged isocyanates. Hafner later demonstrated that rearrangement did occur in hydrocarbon solvents as well, and a mixture of nitrene and *O*-isocyanate products were obtained. From both studies, rearrangement was but a minor side reaction and nitrene reactivity seemed to dominate.

In continuation of this work, and to better understand the intermediates involved in this supposedly impossible reactivity, Lwowski photolyzed azidoformates in neon-matrices at 4 K.[114] Two products were identified during the photolysis (**Figure 32**). The first product was determined to be an *O*-isocyanate, based on the observance of a characteristic –NCO stretch at 2209 cm^{-1}. The second product, which appeared upon prolonged irradiation, was determined to be a formaldehyde-isocyanic acid molecule pair and was proposed to result from decomposition of the *O*-isocyanate.

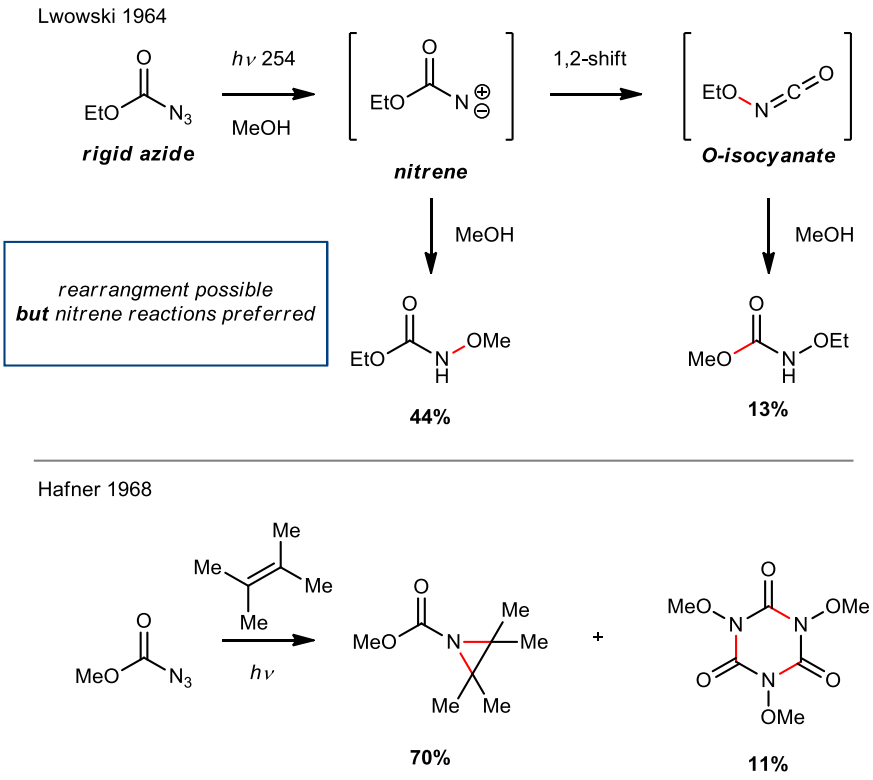


Figure 31 Lwowski dispels the notion of rigid azides and forms *O*-isocyanates by photolysis.

Later, in 1989, Maier and Teles were also able to isolate methoxyisocyanate through the Curtius rearrangement of azidoformates in argon-matrices at 10 K using Lwowski's photolysis conditions(**Figure 32**).[115] From these isolation studies, it was determined that methoxyisocyanate was rather stable (up to 90 K!). They also studied the formation of *O*-isocyanates by flash vacuum pyrolysis (FVP) of methoxy carbamate. Notably, these would form *O*-isocyanates by a different mechanism—thermal deblocking. At 300 °C, conversion was slow and only a small amount of methoxyisocyanate was detected, but above 400 °C substantial decomposition was apparent.

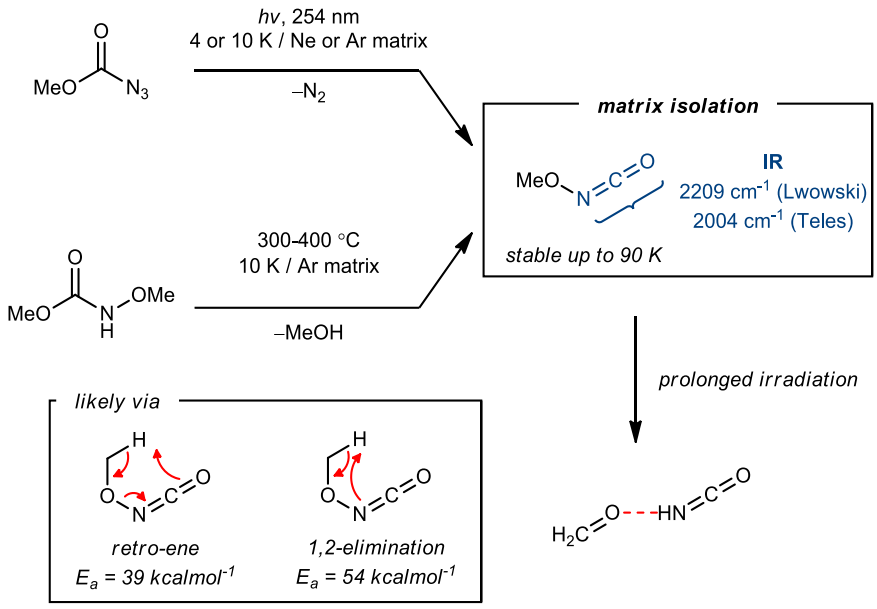


Figure 32 Matrix isolation of methoxy isocyanate via photolysis and thermolysis.

Thus, at least under these FVP conditions, it appeared thermal deblocking was not an effective method to selectively form *O*-isocyanates. The *O*-isocyanate intermediates were similarly assigned by Meyers and Teles, based again on their characteristic –NCO stretch (2204 cm^{-1}). Collectively, the comparatively lower –NCO stretch (~2200 cm^{-1} for methoxy isocyanate versus 2288 cm^{-1} for methyl isocyanate) and the assignment of the –NCO bending motion (518 cm^{-1} for methoxy isocyanate versus 596 cm^{-1} for methyl isocyanate) suggested a high degree of conjugation between the *O*-atom lone pair and the –NCO π-bond. These unique chemical characteristics of *O*-isocyanates highlighted the potential for valuable reactivity. Methoxy-isocyanate was most recently reported in 2017 by IR as the final product after nitrene formation in the Curtius rearrangement of azidoformate (2.8 K in an argon matrix).[116] Thus, from these endeavors studying *O*-isocyanates physically, two methods have emerged which unambiguously

produce *O*-isocyanates: 1,2-rearrangment of azidoformates and thermal deblocking of carbamate derivatives.

More recently, Wentrup studied selected rearrangement reactions of *O*-isocyanates by density functional theory (DFT) calculations.[117] Using the B3LYP/6-311++G(d,p) basis set, he was able to probe the mechanism behind the observance of the CH_2O-HCNO molecule pair following prolonged irradiation of *O*-isocyanates (**Figure 32**).[114,115] While Teles proposed a 1,2-elimination pathway for the observed byproducts, calculations suggested that a retro-ene reaction was lower in energy. Further, Wentrup has shown that H-OCN isomerizes very easily to the thermodynamic isomer H-NCO during collisions with the hot walls of the quartz tube within the FVT apparatus. Regardless of the mechanism, these *O*-isocyanate decomposition pathways would need to be circumvented to develop useful reactions. Fortunately, given their high activation energies, decomposition would likely not be a problem unless forcing conditions were implemented.

The structures of some *O*-isocyanates have been modelled computationally (**Figure 33**). Poppinger and Radom provided the first detailed ab initio molecular orbital studies of *O*-isocyanates in 1978 during their computational survey of various X-NCO isomers.[118] The most stable isomer of the hydroxyl isocyanate adopts a W-shaped planar configuration. This was repeated in the future by Tidwell using a DFT method; a similar but more exaggerated W-shaped structure was found.[119] Hartree-Fock (HF) and DFT modelling of the anionic *O*-isocyanate predicted a linear structure.[120,121] This anionic *O*-isocyanate was even reportedly observed via MS by Bowie.[120] The W-shaped *O*-isocyanates appear primed for [3+2]-cycloadditions, with a structure similar to oximes / nitrones.[122–124] In contrast, the geometry of the anionic *O*-isocyanate appears closer to that of a nitrile oxide.[125] Such structural insight could be imperative in the

design of neutral / anionic cycloaddition reactions. Although preliminary calculations regarding *O*-isocyanates exist, there are by no means detailed DFT studies on their structure, or comparisons of their HOMO-LUMO energies. Such studies would prove helpful for the optimization of future cycloadditions / pericyclic reactions.

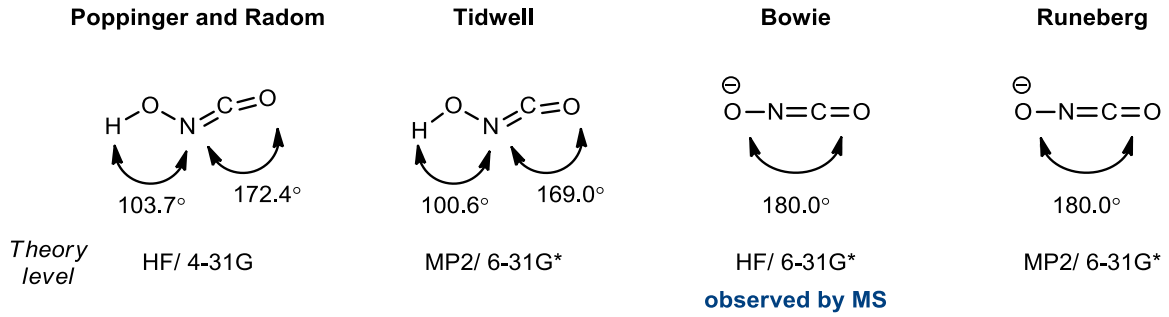


Figure 33 Ab initio molecular structures of some *O*-isocyanates (hydroxy and hydroxide).

3.3 Synthetic applications of *O*-isocyanates

Before our contributions to the study of *O*-isocyanates, their synthetic applications could be categorized as either: 1) Lossen rearrangement / trapping with a nucleophile, or 2) thermal deblocking of a masked *O*-isocyanate / trapping with a nucleophile. The former category will be summarized first. From 1990 to the present, *O*-isocyanates were encountered sporadically through unintentional rearrangement reactivity, primarily during attempted electrophilic amination reactions (**Figure 34**). These results are unsurprising, as the *N*-atom in electrophilic amination reagents is often dually activated / protected.[14,15] This becomes especially problematic for hydroxylamine based electrophilic amination reagents, which are susceptible to Lossen-type rearrangement reactions. The most common protecting groups for *N*-atoms are carbamates[126]—

typically the Boc group[127]—which can produce a *tert*-butoxyisocyanate in the event of a rearrangement reaction. The first example of such reactivity was reported in 1999 by Hanessian.[128] Here, the expected α-amination of β-dicarbonyls from an electrophilic amination precursor was perturbed by the formation of a *tert*-butoxyisocyanate, which was instead alkylated with the β-dicarbonyl nucleophiles. Support for an *O*-isocyanate intermediate was generated by *N*-alkylation of the electrophilic amination precursor, which failed to rearrange to an *O*-isocyanate and generate the same *C*-*C* bond under the reaction conditions (**Figure 34**, A). Moreover, trapping of the *tert*-butoxyisocyanate with benzylamine yielded the expected urea. This work represented the first addition of a *C*-nucleophile to an *O*-isocyanate.

Next, in 2010, Priefer attempted to form hydrazide derivatives through an electrophilic amination using a similar precursor but with amines as nucleophiles.[129] In this case , the products again corresponded to those of a Lossen-type rearrangement, with following amine substitution on the *tert*-butoxyisocyanate (**Figure 34**, B). Nevertheless, the reaction appeared quite general as the yields remained high for a variety of electronically differentiated amines.

In an unfortunate series of communications between 2011 and 2012, Thambidurai attempted nearly the same reaction as Priefer but with a less bulky activating group on the oxygen atom.[130,131] The results could have been predicted to be in accordance with that of Hanessian and Priefer; instead, hydrazide products were reported (**Figure 34**, C). These erroneous reports were corrected in 2015 to provide the proper structures of the products.[132] Overall, while each of these findings were unintentional, they demonstrated that high-yielding reactions of *O*-isocyanates were possible using a Lossen-based rearrangement sequence. These

studies also suggested that reactions with substrates possessing labile N-O bonds are especially problematic but could feasibly enable unique reactivity.

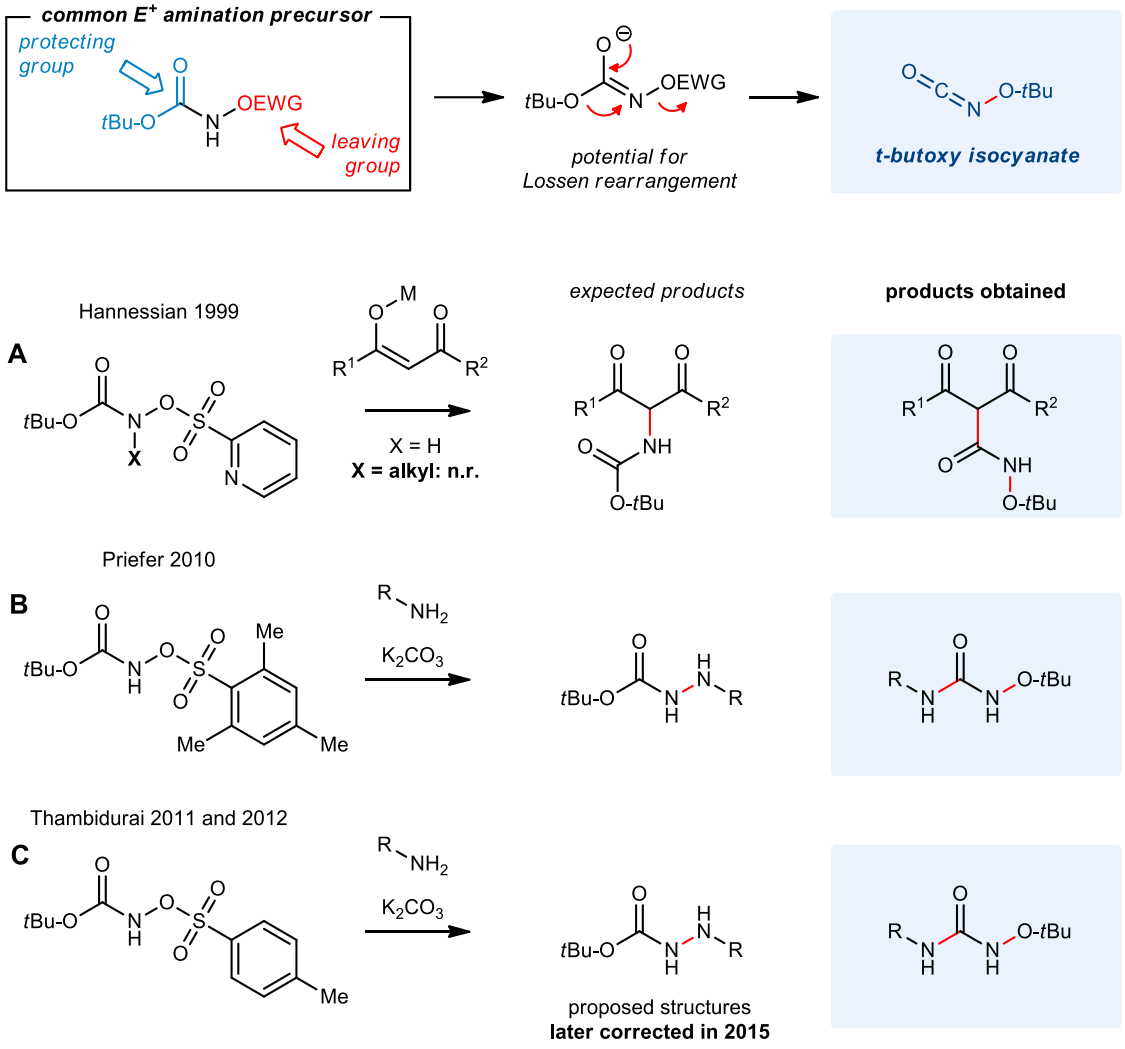


Figure 34 Synthetic applications of unexpected Lossen rearrangements leading to *O*-isocyanates.

The second category of synthetic applications for *O*-isocyanates included deblocking of masked *O*-isocyanate *precursors* and subsequent trapping by a nucleophile. Such reactions of blocked *O*-isocyanates were first seriously considered when a medicinal chemistry program at

Bristol-Myers-Squibb targeted the synthesis of hydroxyurea containing heterocycle (**Figure 35**).[133] Romine and coworkers predicted that an *O*-isocyanate could be a convenient reagent to access the desired synthetic targets. However, it was clear from the literature that such reagents were difficult to handle, and seemingly impossible to prepare. Yet, as Staab had demonstrated a single example of imidazole alkoxyureas undergoing aminolysis;[101,102] they attempted to optimize the reaction, then survey a substrate scope. Strategically, a benzyloxy imidazole precursor was selected, given that the benzyl group could be subsequently removed to provide the free N–OH of the hydroxyurea. Although this blocked *O*-isocyanate reagent could react with a variety of electronically deactivated amines, the desired reaction with anthranilic acid derivatives was unfortunately not possible. In the end, Romine relied on phosgenation of the hydroxylamine, followed by urea bond formation and then cyclization in a subsequent step. Thus, the *O*-isocyanate *precursor* developed seemed unsuited for complex reactions. It was then attractive to assume that an improved *O*-isocyanate precursor could have mitigated these challenges. Moreover, an ideal reagent for the synthesis of hydroxyureas would react efficiently with the N–OH functionality exposed, thus removing the need for subsequent Pd/C hydrogenolysis.

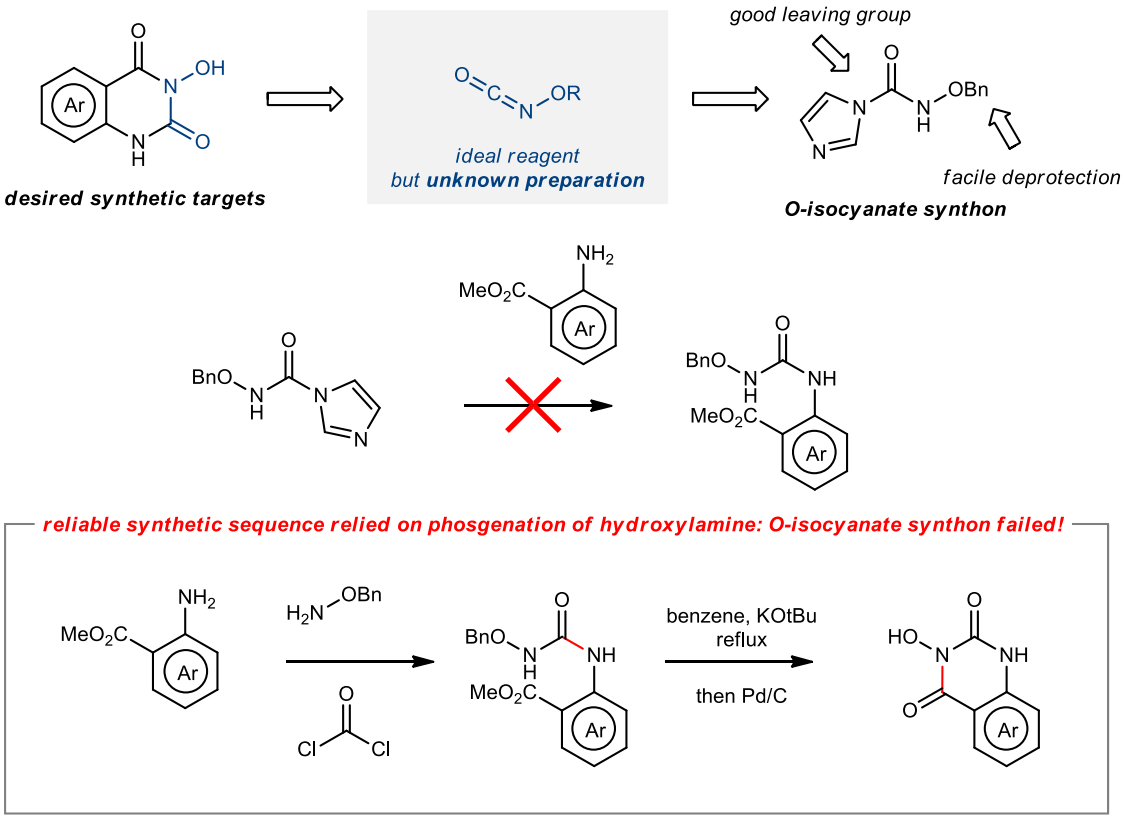


Figure 35 Blocked *O*-isocyanate substitution reactions using CDI.

Five years after the work of Romine, Butula demonstrated that a benzotriazole blocked hydroxy *O*-isocyanate could undergo substitution reactions with a primary amine, directly providing hydroxamic acid derivatives (**Figure 36**).[134] However the reactivity of Butula's blocked *O*-isocyanate was distinctly poor—providing only 34% yield of the desired substitution product. Like Berndt,[106] Butula did not observe formation of the trimer directly from the hydroxy *O*-isocyanate, but it could be obtained via hydrogenolysis of the benzyl protected trimer. Intriguingly, at this time Dupont held several patents on the hydroxy-*O*-isocyanate trimer—1,3,5,-trihydroxyisocyanuric acid (THICA)—but the patents held no mention of its synthesis.

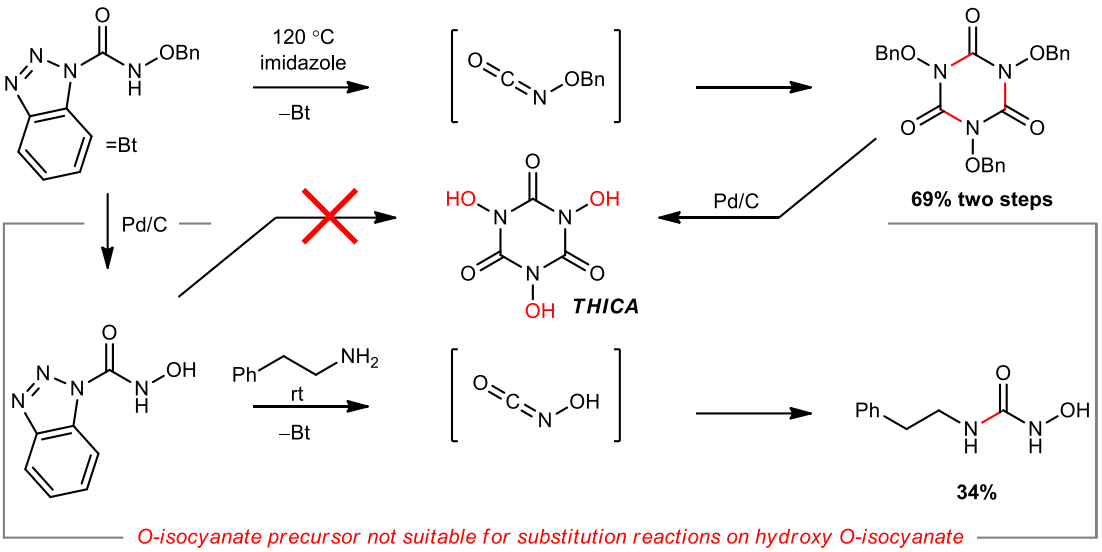


Figure 36 Butula's benzotriazole blocked hydroxy isocyanate precursor.

The final example of blocked *O*-isocyanate reactivity also emerged from industry; Japanese chemists working at Daicel were investigating THICA as a novel HAT catalyst for aeorobic oxidation of alkanes.[135] The catalytic reactivity of THICA was far superior at lower catalyst loadings than other common HAT reagents at the time. However, using a modified version of Staab's procedure,[101,102] they could only form the *O*-isocyanate trimer in 23% isolated yield. To improve upon this, Ishii later optimized the trimerization reaction of *O*-isocyanates using a new blocked derivative (**Figure 37**).[136] In this study, the hydroxylamine was reacted with phenyl chloroformate and a base. Upon thermolysis of the carbamate in the presence of a base, the *O*-isocyanate could be released and trimerization was observed in 82% yield over the two steps. This improved synthesis allowed for THICA to be a viable alternative to NHPI (*N*-hydroxyphthalimide) and its derivatives, as its activity was clearly exceptional in terms of its HAT ability and thermal stability. Most importantly, this was the first study that suggested *O*-

isocyanate *precursor* optimization could prove fruitful in the development of improved *O*-isocyanate reactivity.

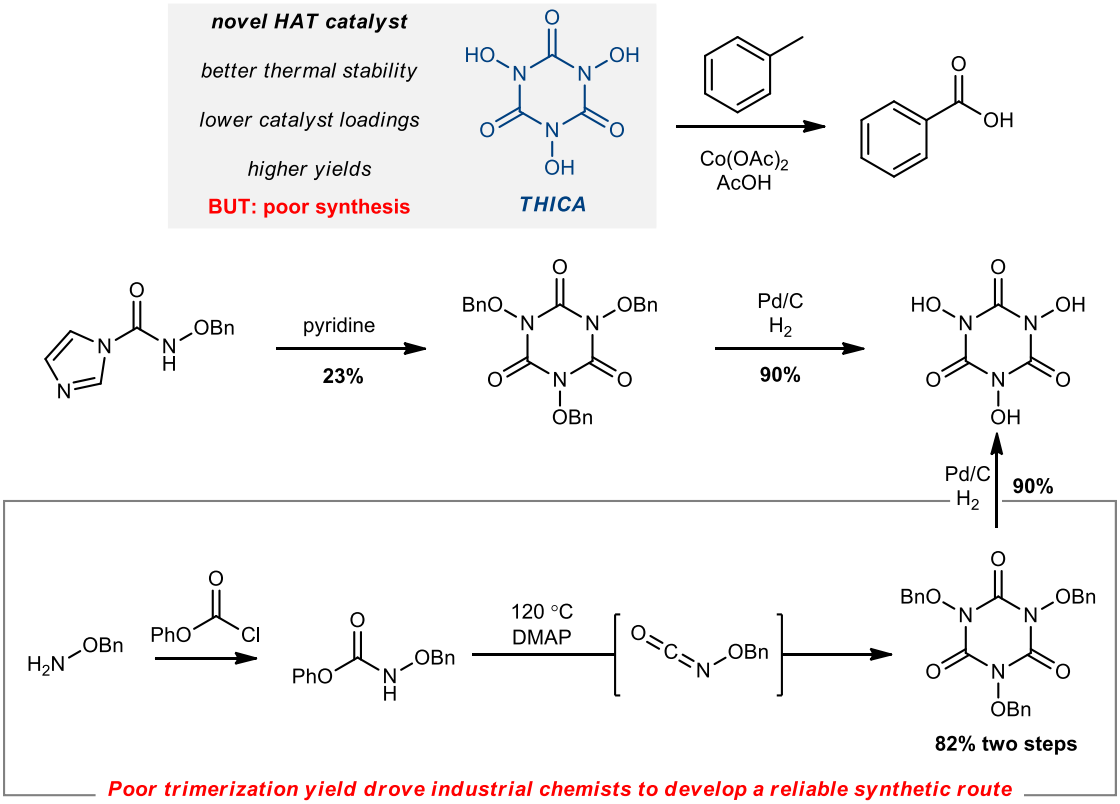


Figure 37 Daicel's optimized route to THICA using blocked *O*-isocyanates.

3.4 Summary and outlook on the known reactivity of *O*-isocyanates

From this survey of the *O*-isocyanate literature, it was clear that considerably less was known regarding the reactivity of *O*-isocyanates compared to *C*-isocyanate or even *N*-isocyanates, which have been studied previously in our lab. *O*-Isocyanates may be rare and rather esoteric molecules, but hopefully this introduction clearly demonstrates that their history traces back to the end of the 19th century, and that a keen interest in their study—in particular from

industrial chemists—was an indication that enabling their use as synthetic intermediates could be broadly useful to the field.

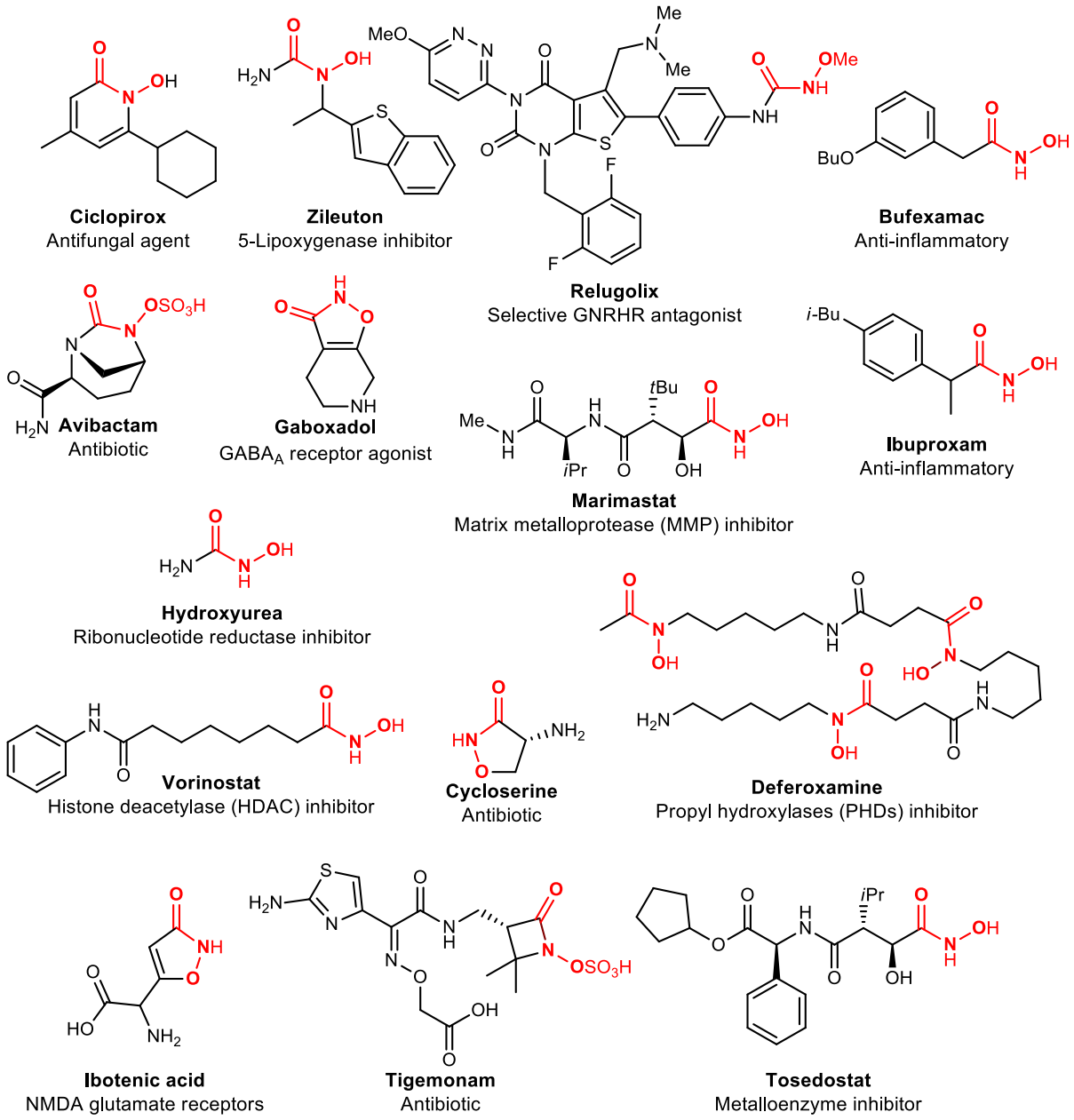


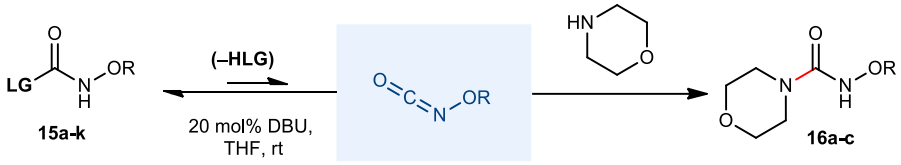
Figure 38 Selected O-N-C=O containing bioactive molecules.

Collectively, these early investigations indicated that *O*-isocyanates could certainly be formed, and that productive reactions were possible. However, their synthetic potential remained largely untapped. Hitherto, aside from nucleophilic trapping and trimerization, other reactions of *O*-isocyanates have gone unreported. Given the well-documented isolation challenges of *O*-isocyanates, a blocking group strategy was an attractive approach to exploit their reactivity. It appeared from Ishii's studies[136] that phenyl carbamates were ideal blocked precursors for *O*-isocyanates, which was reassuring as these were the most ideal reagents to develop new reactions of *N*-isocyanates in our lab.[37] Some nucleophilic addition reactions of alkyl-*O*-isocyanates were quite successful; however, reactions with hydroxy *O*-isocyanates occurred with dramatically lower yields. Ideally, reaction conditions and / or a reagent could be identified to mitigate this challenge, given that hydroxamic acids possess some of the most sought-after bioactivity properties of N-O containing molecules (**Figure 38**). While rearrangement reactions accessing *O*-isocyanates were efficient, the potential for the precursors to act as electrophilic amination reagents in more complex settings presented a barrier. Moreover, this type of reactivity inevitably cannot deliver a direct synthesis of X(C=O)N–OH containing molecules. By and large, the prevalence of the O-N-C=O motif in bioactive molecules provided ample inspiration to generalize the use of *O*-isocyanates in synthesis (**Figure 38**). Therefore, to develop new reactivity of these rare intermediates, a systematic study of *O*-isocyanate precursors was first conducted.

3.5 The pursuit of an ideal *O*-isocyanate precursor

The first course of action was to identify an optimal *O*-isocyanate precursor. Since a blocking approach was targeted, this involved both probing the effects of blocking groups and *O*-atom substituent effects on the reactivity of the *O*-isocyanate. A combined approach was taken, where blocking groups were systematically compared for a variety of *O*-isocyanate derivatives.

Table 17 Screening *O*-isocyanate precursor blocking groups.



entry	precursor	**LG**	**R**	temp (°C)	Time (h)	yield (%)[a]
1	**15a**	PhO	H	70	16	71
2	**15b**	PhO	Et	120	0.5	94
3	**15c**	PhO	Bz	120	2	57 (88)[d]
4	**15d**	*p*-$NO_2C_6H_4O$[b]	H	rt	16	58
5	**15e**	*p*-NO_2 C_6H_4O[b]	Et	rt	16	99
6	**15f**	*p*-NO_2 C_6H_4O[b]	Bz	rt	16	87
7	**15g**	EtO	H	120[c]	16	0[d]
9	**15h**	*i*-Pr_2N	H	70	16	74
10	**15i**	BnO	H	120[c]	16	8[d]
11	**15j**	CF_3CH_2O	H	120[c]	16	4[d]

Conditions: For R = H: precursor (1.1 equiv), morpholine (1.0 equiv), and Et_3N (0.2 equiv) in THF (0.3 M), stir in oil bath overnight. For R = Et: carbamate (1.1 equiv) and morpholine (1.0 equiv) in MeCN (0.2 M), heat in µW to 120 °C. For R = Bz: carbamate (1.0 equiv), morpholine (1.05 equiv) and imidazole (0.1 equiv) in THF (0.2 M), heat in µW at 100 °C for 3 h. [a] Isolated yield. [b] Carbamate (1.0 equiv), morpholine (1.0 equiv), and Et_3N (1.0 equiv) in CH_2Cl_2 (0.08 M), stir at rt overnight. [c] Reactions at 70 and 100 °C result in no formation of product. [d] ^1H NMR yield based on 1,3,5-trimethoxybenzene.

To explore the reactivity of the *O*-isocyanate precursors, we first examined the ability of several blocked derivatives to undergo a simple substitution reaction with morpholine as a representative nucleophile (**Table 17**). Temperatures were screened for each precursor until blocking group release was detected by ^{1}H NMR in the crude spectra. In accordance with the literature on blocked *C*- and *N*-isocyanates,[48,78] the blocking group of the *O*-isocyanate precursor determined the conditions required for the release of the reactive intermediates. Even in this simple reaction system, hydroxy-*O*-isocyanate (R = H, entries 1,4,7-12) required special conditions to achieve a selective reaction. This challenge was anticipated, since the only report in the literature of hydroxy-*O*-isocyanate substitution was poor yielding (**Figure 36**, 34%).[134] Similarly, acyloxy carbamates (R = Bz, entries 3,6) required shorter reaction times and the use of a weaker base (imidazole) to avoid Lossen-type degradation pathways. We predicted challenges with such substrates given the propensity of similarly electronically biased substrates to undergo Lossen rearrangement (**Figure 34**). *These results were performed by Dilan Polat, Meredith Allen and myself.*

Through this survey, phenol emerged as the optimal leaving group for the substitution on *O*-isocyanate precursors. Although *p*-nitrophenol as a leaving group enabled room temperature reactivity and high yields (entry 4-6), the corresponding precursors (**15d-1f**) were too unstable for regular use. Moreover, the syntheses of the *p*-nitrophenol precursors were low yielding, and the exceptionally mild conditions for *O*-isocyanate generation would make the development of future cascade reactions—with differing energetic demands at the various steps—nearly impossible to control. In contrast, phenol-blocked *O*-isocyanates were stable up to 5 years (and counting), were trivial / high yielding to synthesize from cheap and readily available materials

and possessed high reactivity under a *variety* of conditions (**Figure 39**). Further work would encompass studies with hydroxy-, alkoxy-, and acyloxy-substituted carbamates due to the significant differences in reactivity caused by oxygen-substitution. Thus, to study the generality of this amine substitution reaction, various amine nucleophiles were reacted with phenol blocked *O*-isocyanate precursors (**Table 18**).

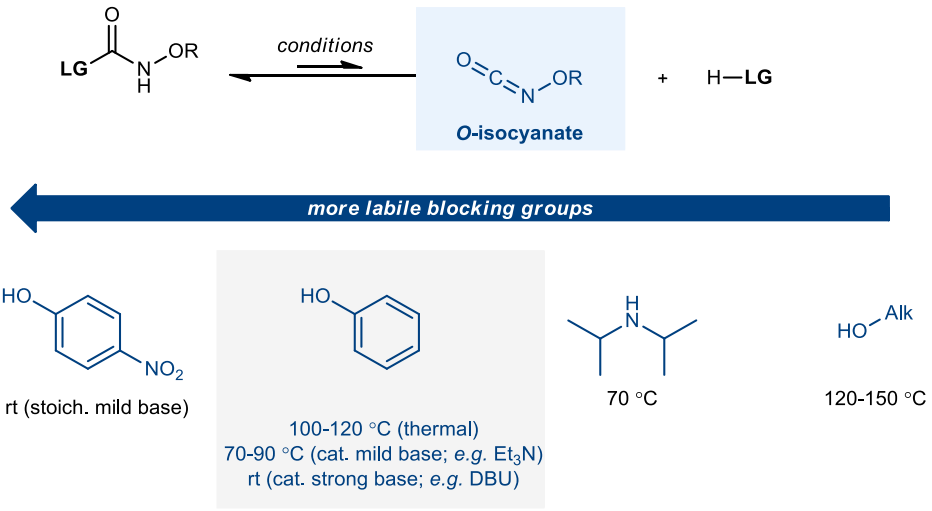


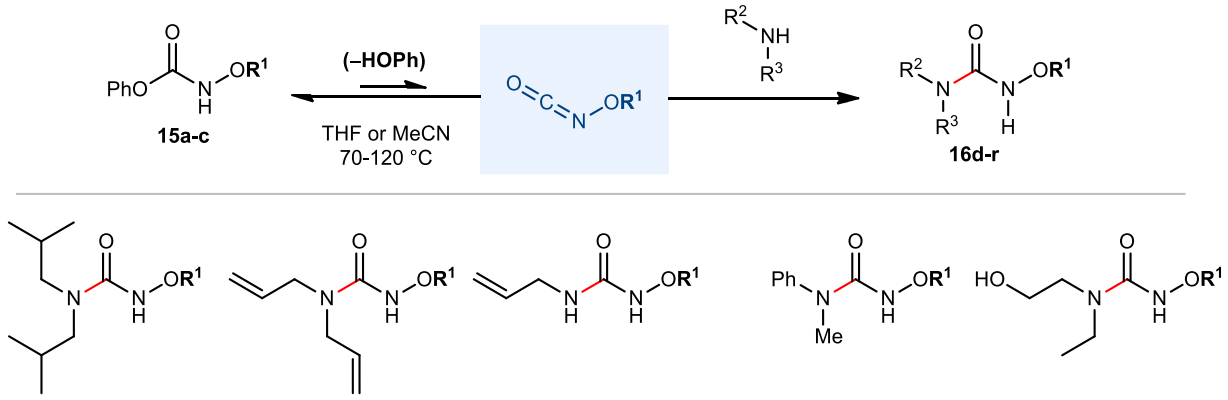
Figure 39 A summary of *O*-isocyanates blocking group reactivity.

3.6 Substitution reactions of *O*-isocyanates—the first step towards cascade reactions

A variety of oxyureas were formed using the reaction of blocked *O*-isocyanates with nitrogen nucleophiles (**Table 18**). Secondary aliphatic amines were competent nucleophiles for all carbamates used (**15a-c**). Primary amines initially led to lower yields under similar conditions; however, using an excess (5 equiv) of the amine improved the yields substantially for hydroxy- and alkoxy-*O*-isocyanates (65-79%). However, primary amines led to decomposition of acyloxy *O*-isocyanate precursors, via a transacylation reaction with the benzoyl group. Despite attempts to

optimize the substitution of anilines, *N*-methylaniline proved a poor reaction partner and led to no substitution under the reaction conditions for the hydroxy-carbamate **15a**. Dimerization of **15a** was likely kinetically favored over aniline addition. The corresponding alkoxy and acyloxy precursors underwent substitution well (40%, 91%), though **16n** was difficult to isolate. The reaction was also chemoselective for *N*-nucleophiles as demonstrated by a selective C–N bond formation with an ethanolamine derivative (**16p-16r**). Having assessed the scope of amine nucleophiles, the substitution on the *O*-isocyanate was probed. The results of this study are shown in **Table 19**. *These results were performed by Dilan Polat and myself.*

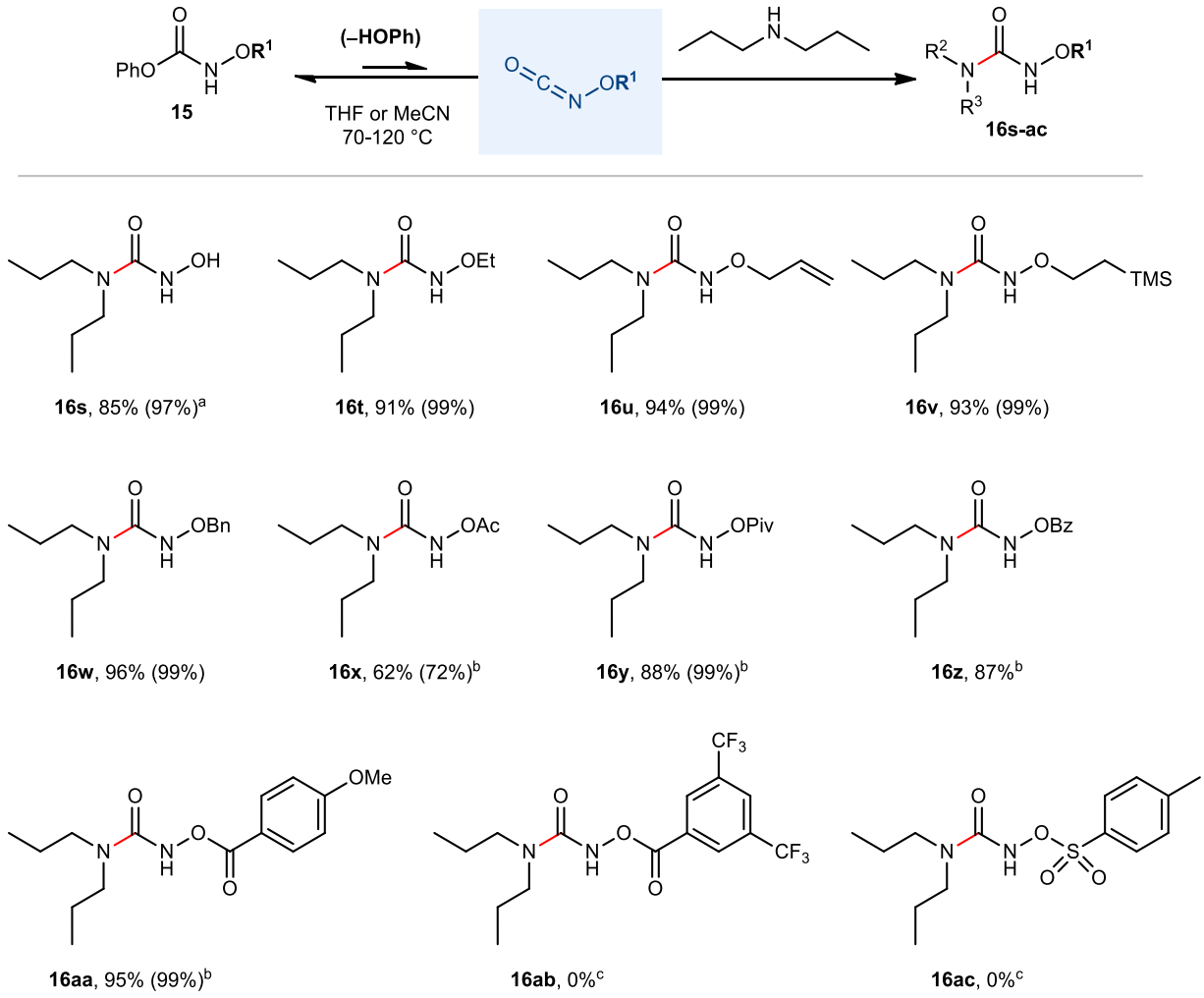
Table 18 Amine substation on blocked *O*-isocyanates: amine scope.



Conditions: For R = H: oxy-carbamate (1.1 equiv), amine (1.0 equiv.), and Et_3N (0.2 equiv) in THF (0.3 M), stir in oil bath at 70 °C overnight. For R = Et: oxy-carbamate (1.1 equiv) and amine (1.0 equiv) in MeCN (0.2 M), heat in µW at 120 °C for 30 min. For R = Bz: oxy-carbamate (1.0 equiv), amine (1.05 equiv) and imidazole (0.1 equiv) in THF (0.2 M), heat in µW at 100 °C for 3 h. Isolated yields are shown. [a] 5 equiv of allylamine used. [b] 1 equiv of Et_3N used.

A variety of carbamates could be used for the substitution, mostly with excellent yields, using di-*n*-propylamine as the nucleophile (**Table 19**). As demonstrated during the leaving group optimization, there was some variability in the yields based on the oxygen substitution. The yield with hydroxy-carbamate **15a** was consistent with previous results (85%). The yields for all alkoxy carbamates (**16t**-**w**) were excellent (>91%). Acyloxy carbamates could react in good to excellent yield (**16x-aa**). However, electron-poor acyloxy and tosyloxy-precursors (**16ab**, **16ac**) underwent degradation via Lossen rearrangements. These results clearly indicated that strong electron-withdrawing groups were required for heterolytic N–O bond cleavage to occur, even at temperatures as high as 120 °C and in the presence of a weak amine base. Overall, the results in **Table 18** and **Table 19** show that variation of each reaction partner was generally well tolerated.

Table 19 Amine substation on blocked *O*-isocyanates: *O*-isocyanate scope.



Conditions: oxy-carbamate (1.05 equiv) and *n*-Pr_2NH (1.0 equiv) in MeCN (0.2 M), heat to 120 °C in µW for 30 min. Isolated yields are shown (^1H NMR yield based on 1,3,5-trimethoxybenzene shown in parentheses). [a] hydroxy-carbamate (1.1 equiv) used, Et_3N (0.2 equiv) added, stirred at 70 °C in oil bath overnight.[b] acyloxy-carbamate (1.0 equiv), amine (1.05 equiv) and imidazole (0.1 equiv) in THF (0.2 M), heat to 100 °C in µW for 1-3 h. [c] Uncontrolled formation of products derived from a Lossen rearrangement was observed.

3.7 Summary of the substitution reactions of *O*-isocyanates

A variety of conditions were developed to achieve selective / high yielding substitution reactions on a variety of *O*-isocyanate precursors. While others had demonstrated some

substitutions on *O*-isocyanates previously, this was the first systematic study encompassing high yielding reactions with hydroxy- and acyloxy *O*-isocyanates. These studies enabled the facile synthesis of *N*-oxyureas, which would serve as the starting point for more complex chemical transformations / cascade reactions. With respect to the aim of synthesizing important *N*-containing molecules, this method provided direct access to important motifs found in pharmaceuticals and agrochemicals **Figure 40**.

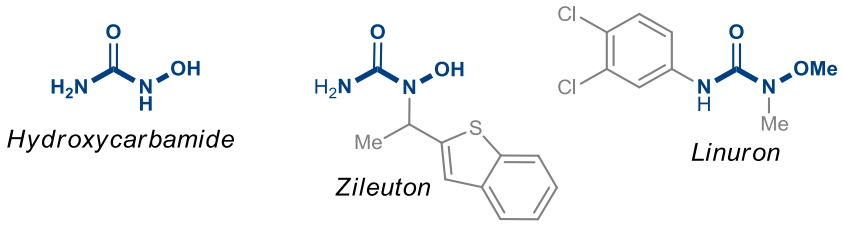


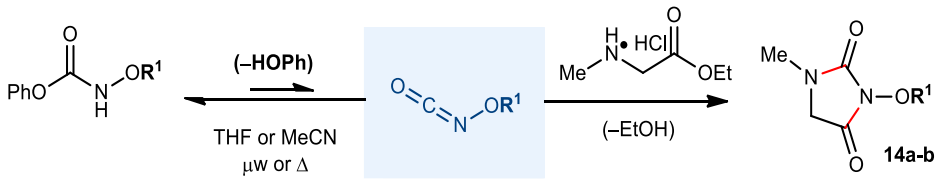
Figure 40 Acyclic O-N-C=O containing pharmaceuticals and agrochemicals.

3.8 Benchmarking the ability of *O*-isocyanates to participate in cascade reactions—hydantoin synthesis

The aim of these studies had always been to develop new reactivity with *O*-isocyanates. With the foundation set on *O*-isocyanate precursor synthesis and substitution reactivity novel chemical transformations could finally be explored. Cascade reactions can rapidly build molecular complexity but had not been explored with *O*-isocyanates. It was logical to probe the competency of *O*-isocyanates in a cascade reaction that had been carried out previously with *N*-isocyanates, since similar challenges for these reagents were present. Such a comparison would provide a relative benchmark of their reactivity. At the time, the synthesis of hydantoins was one of the few *N*-isocyanate cascade reactions developed in our lab.[77] To explore this opportunity and allow

comparison with reactions of blocked *N*-isocyanates, optimization began with the reaction of sarcosine ethyl ester hydrochloride and two masked *O*-isocyanates possessing phenol as a blocking group (**Table 20**).

Table 20 First *O*-isocyanate cascade reaction optimization.



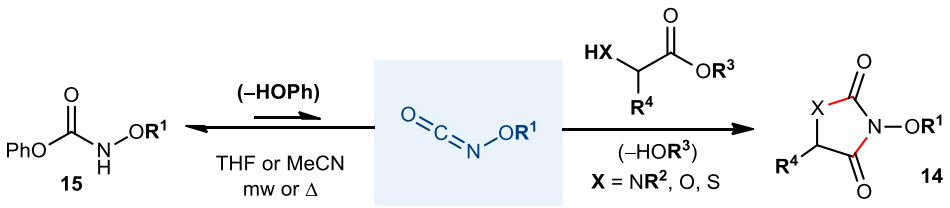
entry	LG	R^1	solvent	temp (°C)	time (h)	yield (%)
1	OPh	H	THF	120 (μw)	6	60 (**14a**)
2	OPh	H	THF	120 (μw)	2	60 (**14a**)
3	OPh	H	THF	70 (oil bath)	16	91 (**14a**)
4	OPh	Me	MeCN	90 (oil bath)	16	54 (**14b**)
5	OPh	Me	MeCN	90 (oil bath)	30	99 (**14b**)
6	OPh	Me	MeCN	120 (μw)	6	99 (**14b**)
7	OPh	Me	MeCN	120 (μw)	2	99 (**14b**)
8	OPh	Me	MeCN	120 (μw)	0.5	90 (**14b**)
9	*p*-NO_2 C_6H_4O	H	THF	70 (oil bath)	16	40 (**14a**)
10	*p*-NO_2 C_6H_4O	H	THF	70 (oil bath)	16	95[a] (**14a**)
11	*p*-NO_2 C_6H_4O	H	THF	70 (oil bath)	16	80[b] (**14a**)

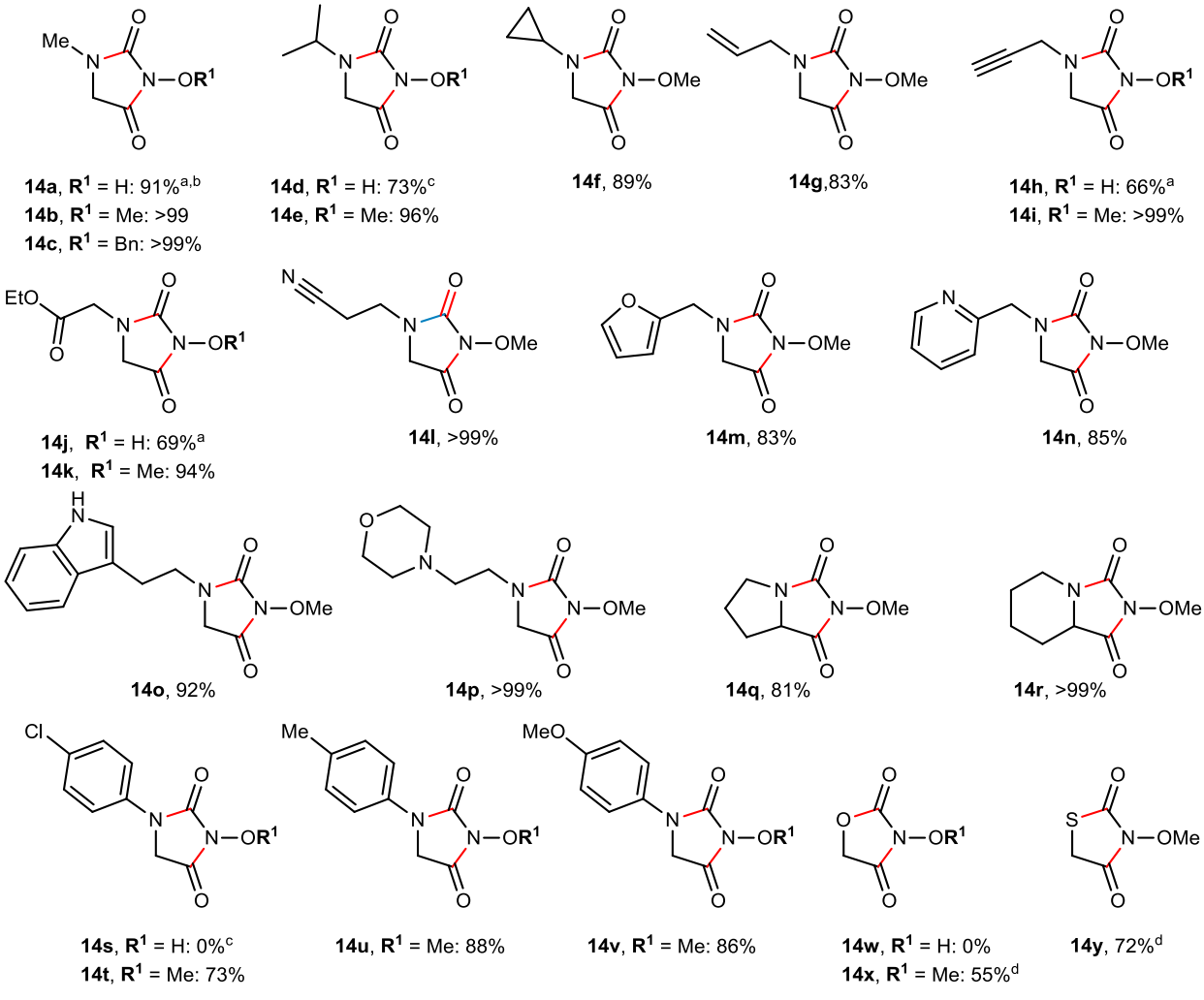
Conditions: carbamate (1 equiv.), sarcosine ethyl ester•HCl (1 equiv.), *i*-Pr_2NEt (1.1 equiv.), solvent (0.3 M). [a] 2.0 equiv. PhOH added. [b] 2.1 equiv. *i*-Pr_2NEt added. Isolated yields are shown. μw: microwave heating.

Encouragingly, formation of the desired heterocycles was observed with both *O*-isocyanate precursors (**Table 20**). Although hydroxy-isocyanate precursor **15a** was more sensitive

than methoxy-isocyanate precursor **15r** under microwave heating conditions (entries 1-2 vs 6-7), changing to milder conventional heating resulted in a significant improvement for the cascade reaction with **15a** (entry 3). In contrast, conventional heating of **15r** required a longer reaction time to form product **14b** efficiently (entries 4-5). The reaction with alkoxy *O*-isocyanate precursors was thus performed using microwave irradiation, allowing a complete reaction within 2 hours at 120 °C (entries 7-8). To probe the influence of blocking groups on this cascade reactivity, *p*-nitrophenyl hydroxycarbamate was tested in the reaction. In the presence of this more labile leaving group the yield of the cascade decreased to 40%, with a fast generation of *p*-nitrophenol and unreacted α-aminoester being observed by ^{1}H NMR. Reasoning that uncontrolled deblocking was occurring, phenol (2 equiv) was added to the reaction. This restored the efficiency of the cascade, likely by acting as a blocking group on the *O*-isocyanate (*e.g.* forming precursor **15a** *in situ*) and ensuring that the concentration of *O*-isocyanate remained low enough to ensure an efficient cascade and prevent side-reactions. Alternatively, reasoning that this reduced efficiency could be due to reversible protonation of the α-aminoester by *p*-nitrophenol, the efficiency of the cascade was restored in the presence excess base (2.1 equiv). Overall, these experiments demonstrated that an *O*-isocyanate precursor that has both a favourable deblocking / blocking profile (equilibrium & rate) and one which releases a “spectator” leaving group was critical for the development of efficient cascade reactions. Thus, although the *p*-nitrophenol reagent **15d** demonstrated good reactivity in early studies of amine substitution (**Table 17**), it was abandoned due to the required use of excess phenol or super-stoichiometric base.

Table 21 Hydantoin synthesis via *O*-isocyanate cascade reaction.



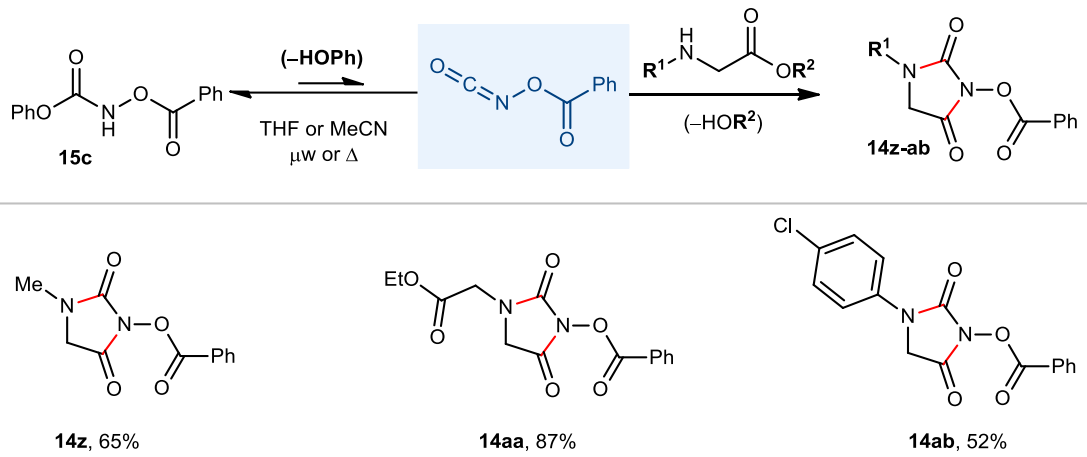


Conditions: carbamate (1 equiv), α-amino ester (1 equiv), *i*-Pr_2NEt (0.1 equiv or 1.1 equiv if the α-amino ester is an HCl salt), in MeCN (0.3 M) at 120 °C for 2 h (μW, sealed tube) unless noted otherwise. Isolated yields are shown. [a] THF, at 70 °C for 16 h (oil bath, sealed tube). [b] Gram scale reaction. [c] THF, at 90 °C for 16 h (oil bath, sealed tube). [d] 5 mol% DBU.

With optimized conditions in hand for both *O*-isocyanate reagents, the scope of the reaction was evaluated (**Table 21**). Small (**14a-c**) and hindered (**14d-f**) *N*-substituted α-aminoesters reacted in high yields to form the corresponding hydantoins. The reaction was remarkably functional group tolerant, with substrates possessing propargyl (**14h-i**), ester (**14j-k**) and cyano (**14l**) heterocyclic (**14m-o**) and saturated Lewis bases (**14p**) cyclizing efficiently. Cyclic α-amino-esters produced the bicyclic derivatives (**14q-r**) in excellent yields. Weakly nucleophilic anilines readily participated in this cascade with **15b**, providing the *N*-aryl hydantoins (**14t-v**) in good yield. As the amine substitution studies predicted, aniline derivatives proved unreactive with hydroxy-*O*-isocyanate precursor **15a**. However, methyl glycolate and thioglycolate engaged in this cascade providing oxygen (**14x**) and sulfur (**14y**) heterocyclic analogues in preparative yields. Alternative conditions were required for preparation of **2v** and **2w**, and this was largely undertaken by Dilan Polat. The use of DBU at higher temperatures proved optimal, likely due to full deprotonation of the alcohol / thiol. In contrast, using conditions optimized for α-aminoesters or lower temperatures with DBU were plagued by competing formation of the *O*-isocyanate trimer. *Entries **14a, 14d, 14h, 14j, 14x** and **14y** were performed by Dilan Polat.*

Perhaps what was most encouraging was the ability to perform controlled cascade reactions with acyloxy-*O*-isocyanate precursor **15c** (**Table 22**). Gratifyingly, this process proceeded *without competition* from a Lossen rearrangement that could arise from N–O bond cleavage and extrusion of benzoate anion, a common reaction reported for similar reagents under basic conditions. The first cascaded reactions of acyloxy-*O*-isocyanates provided access to **14z** -**ab** in modest to excellent yields.

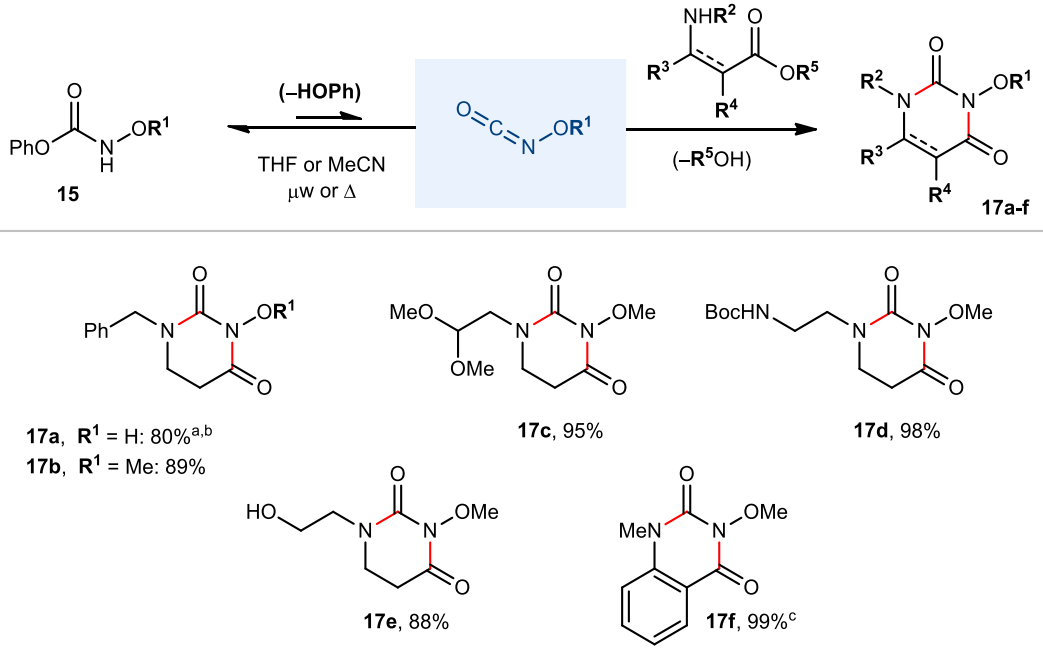
Table 22 Controlled cascade reactions with Lossen-prone *O*-isocyanate precursors.



Conditions: carbamate (1 equiv), α-amino ester (1 equiv), *i*-Pr_2NEt (0.1 equiv or 1.1 equiv if the α-amino ester is an HCl salt) in MeCN (0.3 M) at 90 °C for 2 h (μW, sealed tube). Isolated yields are shown.

Studies then shifted to examine the use of β-aminoesters as substrates (**Table 23**). A single example was reported in the original *N*-isocyanate report and lower yields were observed.[77] In contrast, a variety of 6-membered products were formed in high yields using *O*-isocyanate precursors. From reagent **15a**, the hydroxy-dihydrouracil **17a** was formed on gram-scale in identical yield to the 0.8 mmol reaction. Functional group compatibility was further surveyed, and an acetal (**17c**) a Boc-protected carbamate (**17d**) and an alcohol (**17e**) were tolerated. What was most encouraging from this study, was that the anthranilate derivatives that were targeted in the first blocked *O*-isocyanate report from Romine[133] (**Figure 35**) were amenable in this cascade reaction. Albeit, the reaction required a large excess of the anthranilate and a longer reaction time, likely due to a highly reversible addition on the *O*-isocyanate. *Entry **17a** was performed by Dilan Polat.*

Table 23 Dihydrouracil synthesis via *O*-isocyanate cascade reaction.



Conditions: carbamate (1 equiv), α-amino ester (1 equiv), *i*-Pr_2NEt (0.1 equiv or 1.1 equiv if the α-amino ester is an HCl salt) in MeCN (0.3 M) at 120 °C for 4 h (μW, sealed tube) unless noted otherwise. Isolated yields are shown. [a] 5 mmol scale. [b] THF, at 70 °C for 16 h (oil bath, sealed tube). [c] 5 equiv. anthranilate for 6 h, ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard.

It became a priority at this point to probe *O*-isocyanates were reactive intermediates in these cascade reactions. Although the literature clearly supported the formation of *O*-isocyanates from carbamate derivatives, this is routinely a point of contention between reviewers / readers that are un-engaged in blocked isocyanate research. Further, we felt this was essential to further support the development of new reactions with *O*-isocyanates. A methoxy carbamate derivative possessing an *N*-methyl substituent was subjected to the reaction with sarcosine ethyl ester (**Figure 41**). If the reaction was proceeding through formation of a tetrahedral intermediate via nucleophilic attack on the carbamate, then the *N*-methyl modification should only have a minimal impact on the efficiency of the reaction. In contrast, the

N-H group would be required to form the *O*-isocyanate through elimination of phenol. Therefore, removal of this crucial proton from the substrate should sequester this pathway. When *N*-methyl derivative **1e** was subjected to the reaction product formation was not observed. To account for the steric influence of the *N*-methyl group, the reaction was performed at higher temperatures (up to 175 °C) but phenol was not formed and both starting materials were recovered. Eventually, after prolonged heating at 175 °C the α-amino ester starting material began to decompose. Moreover, the initial phenol doping experiemnts with more labile *O*-isocyanates precursors supported a finely-tuned blocking equilibrium reaction involving *O*-isocyanates (**Table 20**, entry 9-11). Together, these findings were consistent with a reaction that required an *O*-isocyanate reactive intermediate.

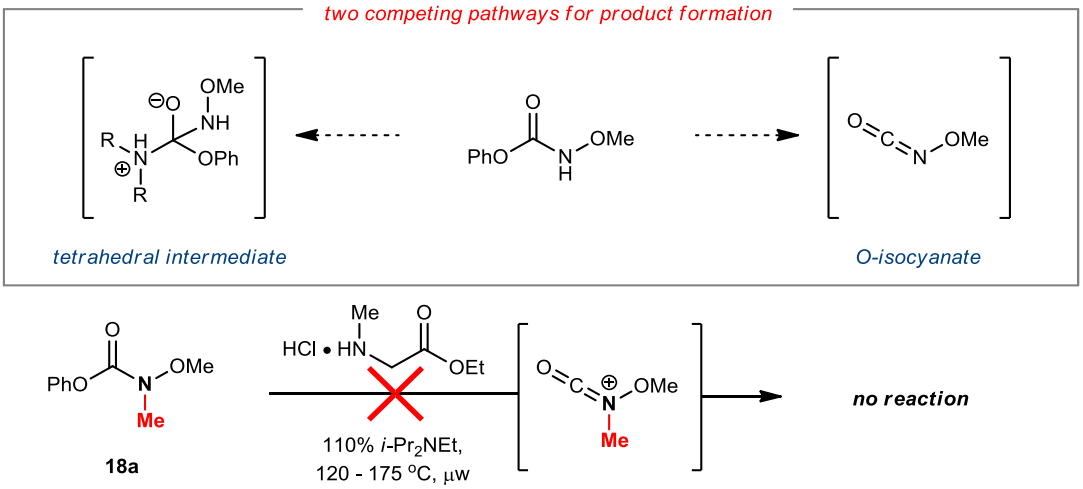


Figure 41 N-Methylation to probe *O*-isocyanate intermediacy.

3.9 Conclusions on the first cascade reaction of *O*-isocyanates

The development of the first *O*-isocyanate cascade reaction was a resounding success. Using phenol as a blocking group, suitable crystalline precursors could conveniently release the

desired *O*-isocyanates *in situ* enabling controlled formation of *O*-isocyanates and mild reaction conditions. These favourable conditions prevented typical side reactions such as trimerization or Lossen rearrangement. A variety of *O*-isocyanates reacted with diverse nucleophiles (*N*-, *O*-, *S*-atom) forming 5- and 6-membered *N*-oxy heterocycles, which are prevalent in pharmaceutical studies (**Figure 42**). Importantly, hydroxamic acid derivatives were synthesized directly in high yields without the need for late stage deprotection. While the products formed were interesting in themselves, simple diversification reactions extensively broadened their usefulness and lead to complex hydroxylamine derivatives (see SI).

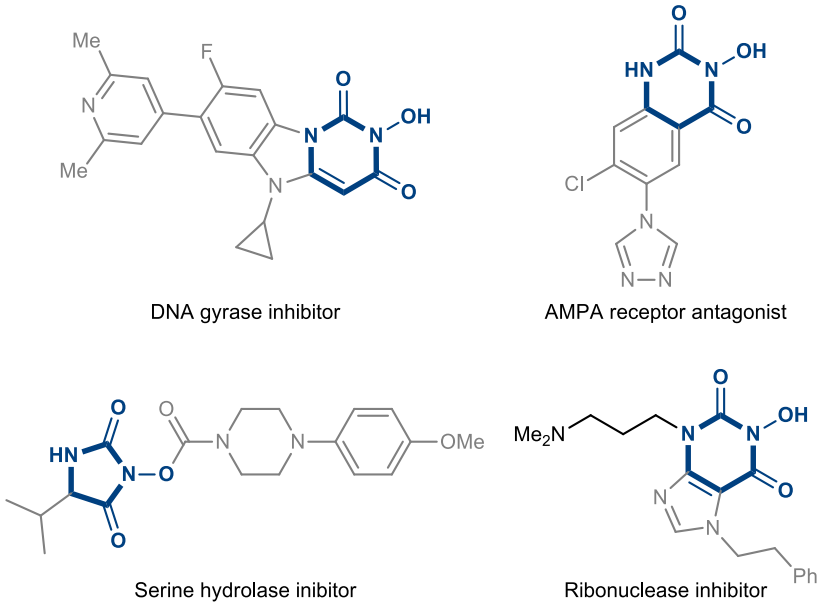


Figure 42 Bioactive *N*-heterocycles resembling the core structures accessible from this new methodology.

3.10 Development of Cope-type hydroamination of hydroxamic acids—a new reaction

With an adequate understanding of *O*-isocyanate reactivity, the goal shifted to the development of new reactions. Experience with metal-free Cope-type hydroaminations using hydroxylamines[9,57,61,137–141] inspired the design of a hydroamination reaction with hydroxamic acids. Our group had been successful performing hydroamination reactions on allylamines via a tethering strategy[10,142–145] and the development of an *O*-isocyanate cascade reaction was an attractive iteration of the pseudo intermolecular reaction (**Figure 43**). However, our experience with Cope-type hydroamination reactions using hydroxylamine derivatives suggested that both the electron-withdrawing nature of the carbonyl group on the nucleophilic nitrogen and the inherent rotamer issues with urea compounds would likely require significantly elevated reaction temperatures for this novel reaction.

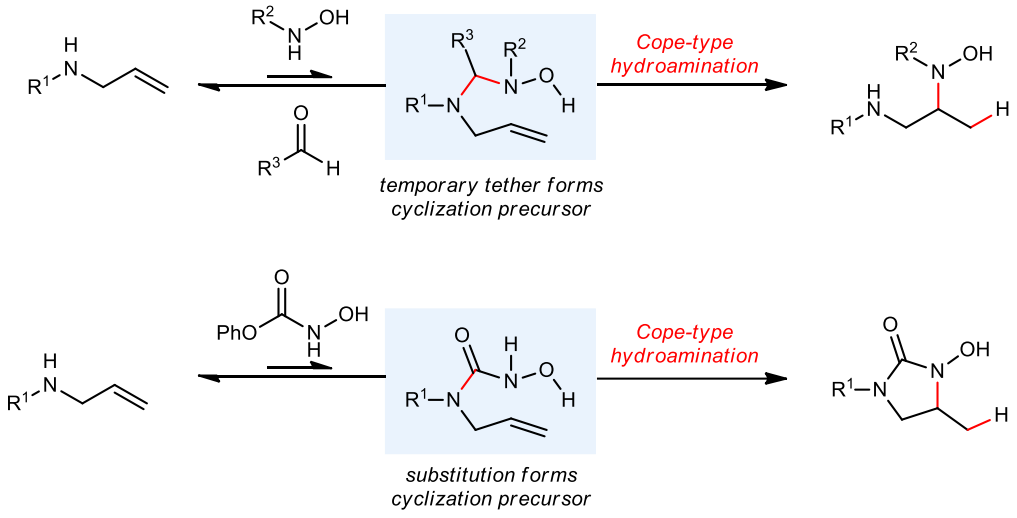
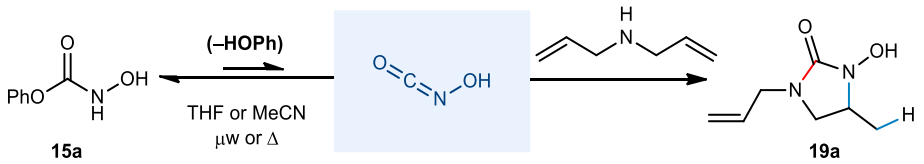


Figure 43 Intramolecular Cope-type hydroamination using hydroxamic acid derivatives.

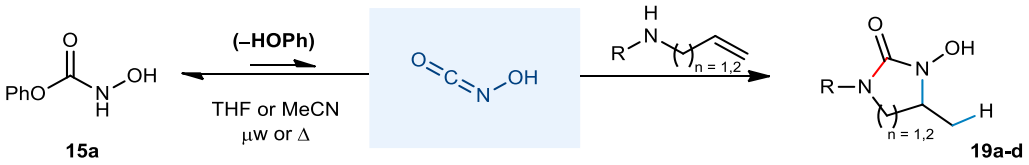
Since rotamer issues were likely to be an issue, diallylamine was selected as a biased amine to conduct initial reaction screening / optimization (**Table 24**). Rapidly, proof-of-concept results were generated that the hydroamination reaction was possible. While the reaction proceeded at relatively mild temperatures, high temperatures were required to increase conversion to the desired product. It was a challenge to pair these forcing conditions with the precarious stability of the hydroxy *O*-isocyanate precursor **15a**, and the *N*-hydroxyurea intermediate. What was more concerning was that small scale probes of substrate scope indicated an uphill battle for unbiased allylamines (**Figure 44**). Ergo, we were correct in our assumption that urea rotamers were going to be an obstacle. Efforts to improve the overall yield of the cyclic products (**19a-d**) by changing to a stepwise sequence (*e.g.* isolating the hydroxyurea intermediates and submitting them to the hydroamination reaction conditions) did not improve this reactivity.

Table 24 Preliminary substation / Cope-type hydroamination optimization.



solvent	time (h)	temp (°C)	additive	concentration (M)	yield (%)
MeCN	2	150	-	0.3	44
MeCN	3	100	-	0.3	29
MeCN	3	120	-	0.3	53
MeCN	3	150	-	0.3	37
MeCN	6	120	-	0.3	42
t-BuOH	**3**	**120**	**-**	**0.3**	**65[a]**
$PhCF_3$	3	120	-	0.3	18
t-BuOH	3	120	-	0.05	58
t-BuOH	3	120	-	1.0	37
t-BuOH	3	120	0.2 eq Et_3N	0.3	40
t-BuOH	3	120	0.2 eq AcOH	0.3	44

Conditions: *N*-hydroxy carbamate (1 equiv), diallyl amine (1.1 equiv), (μw, sealed tube) unless noted otherwise. Isolated yields are shown. ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard. [a] Isolated yield.



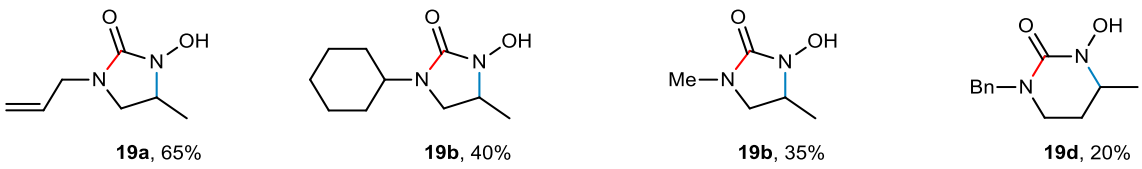
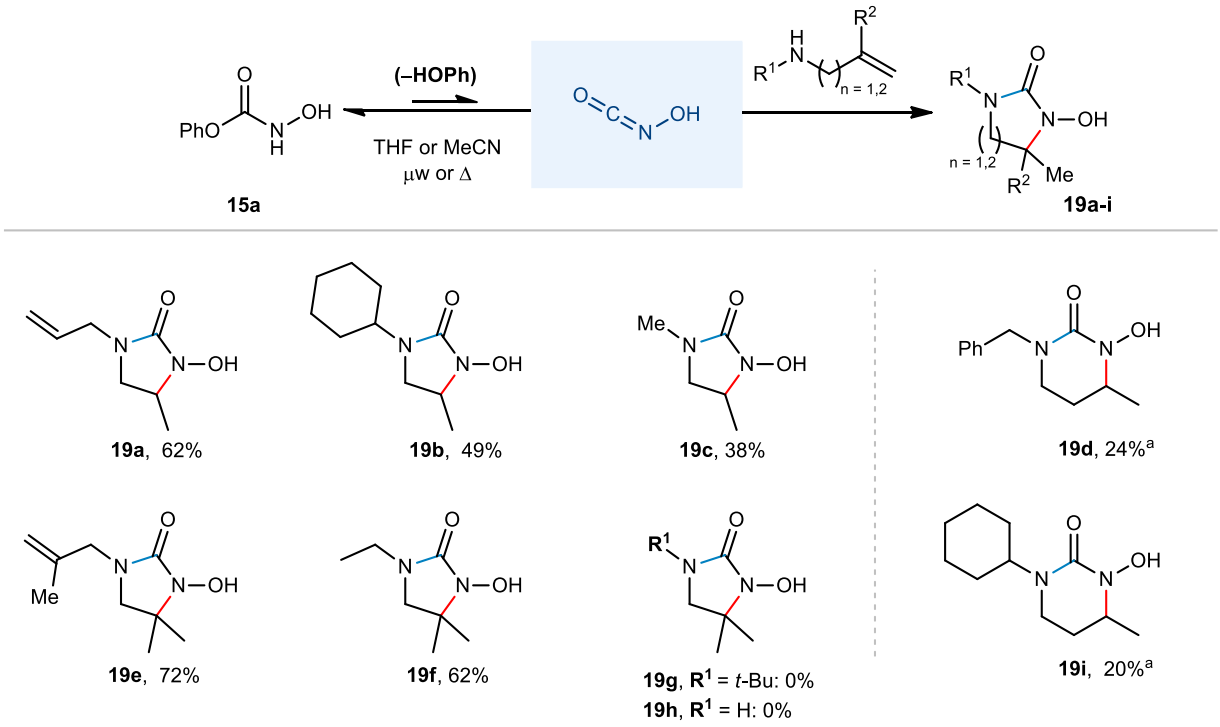


Figure 44 Preliminary substrate scope screen using initial reaction conditions.

At this time in the project's development, Meredith Allen took over the optimization. Given the importance of hydrogen-bonding for difficult Cope-type hydroaminations,[9,143,146] several additives were screened to improve the reactivity. $TfNH_2$ was identified as an effective additive for most substrates, providing marginal improvements in yield. This enabled the cascade reaction with secondary allylamines to proceed with reliably modest yields (**19a-c**). In accordance with the literature of Cope-type hydroaminations, the use of allylamine homologs—that would cyclize thorough a 6-membered transition state—resulted in decreased yields (**19d**, **19i**).[137]

Table 25 Imidazolidinone synthesis via *O*-isocyanate substitution / Cope-type hydroamination cascade reaction



Conditions: *N*-hydroxy carbamate (1 equiv), allylamine (1 equiv), $TfNH_2$ (0.5 equiv), in EtOAc (0.2 M) at 175 °C for 0.3–2.5 h (μW, sealed tube). Isolated yields are shown. [a] ^1H NMR yield based on 1,3,5-trimethoxybenzene.

Reducing the steric bulk of the second substituent on the allylamine results in a slightly lower yield and required an increased reaction time (**19f**), underlining the effects of unfavorable urea

conformers. Cope-type hydroamination on disubstituted alkenes also formed cyclic *N*-oxyurea (**19e**) in good yield.

Several limitations of this reactivity manifested while evaluating the scope of allylamines under optimized conditions (**Table 25**). Sterically bulky amines, such as *N*-*tert*-butyl allylamine, did not undergo the required substitution to furnish the cyclic hydroxamic acid product (**19g**). Or, if substitution was possible, the reverse reaction was simply too favored due to the bulkiness conferred by the *t*-butyl group.[48] Phenyl allylamine could not undergo the required substitution to undergo intramolecular hydroamination. In contrast, allylamine underwent substitution, but did not undergo hydroamination under the optimized reaction conditions (**19h**): this result suggested that only substrates derived from secondary allylamines could access the urea rotamer required for cyclization (*e.g.* with NHOH and allyl groups *s*-cis).

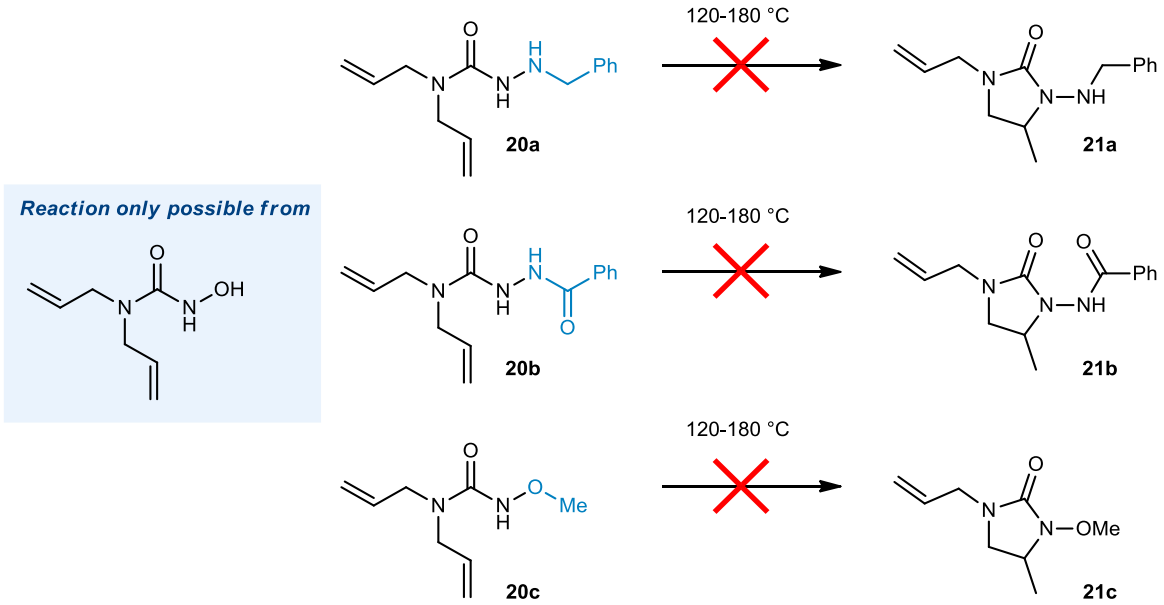


Figure 45 Cope-type hydroamination not possible with hydrazide or alkoxy derivatives.

These synthetic limitations aside, it was interesting that this novel reactivity was not possible with similar hydrazide precursors derived from *N*-isocyanates (**Figure 45**). To showcase that new reactions were possible from *O*-isocyanates, amino- and amido-isocyanates were subjected to the reaction conditions. Despite performing the substitution reaction in excellent yields with the *N*-isocyanate precursors, the subsequent Cope-type hydroamination was not observed, even under more forcing conditions and longer reaction times. To provide experimental support for a concerted Cope-type hydroamination pathway, an *O*-alkyl derivative was subjected to the hydroamination conditions (**Figure 45**). No product was observed, consistent with a Cope-type mechanism since **20c** lacks the hydrogen atom required for the planar, 5-membered transition state.

3.11 Summary on the Cope-type hydroamination of hydroxyureas

Overall, the development of *O*-isocyanate substitution reactions on hydroxy-isocyanate precursors streamlined the synthesis of hydroxyureas. This enabled the development of the first example of Cope-type hydroaminations of hydroxyureas. While it was limited in scope, it highlighted that the study of *O*-isocyanates could lead to the development of new reactivity and provided a new amination method to access important bioactive motifs (**Figure 46**).

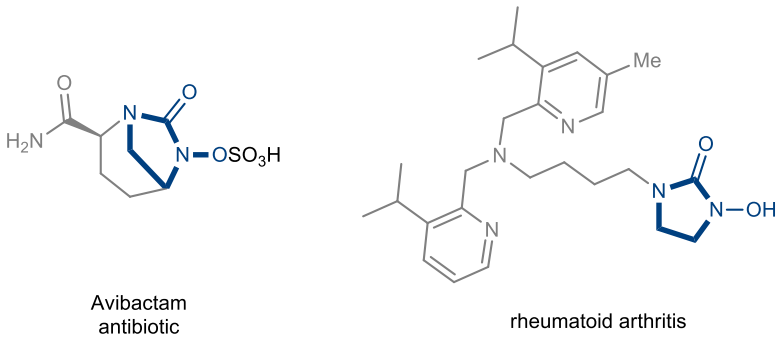


Figure 46 Representative motifs accessible from this novel amination method.

3.12 Cycloadditions of *O*-isocyanates: discovery, optimization and synthetic applications

Around this time, questions were circulating regarding the certainty of an *O*-isocyanate intermediate in these transformations. While the sporadic encounter of *O*-isocyanate trimers in tandem with the *N*-methylation experiment (**Figure 41**) could quell some doubts, these were by no means conclusive. In an ideal setting, access to analytical equipment for the detection of fleeting intermediates *in situ* would provide unambiguous evidence—but such instruments are not available at the University of Ottawa. Alternatively, if we could react these precursors under similar conditions, and in a reaction in which *only* an *O*-isocyanate could participate, then surely this would instill confidence in our hypothesis. Cycloaddition reactivity of *O*-isocyanates was an attractive avenue to achieve this proof, since unlike nucleophilic substitution reactions tetrahedral intermediates would not readily explain the observed products. However, as mentioned in the introduction: no examples of *forward* cycloaddition reactions existed. In truth, the [3+2] cycloreversion reaction forming a hydroxy *O*-isocyanate[106] (see Figure 6) was only found after the literature survey performed for this thesis. Therefore, with the knowledge at the time,

what seemed most likely was that *O*-isocyanates may react like electron deficient *C*-isocyanates *e.g.* [2+2] cycloadditions with alkenes or [4+2] cycloadditions with dienes (**Figure 47**).

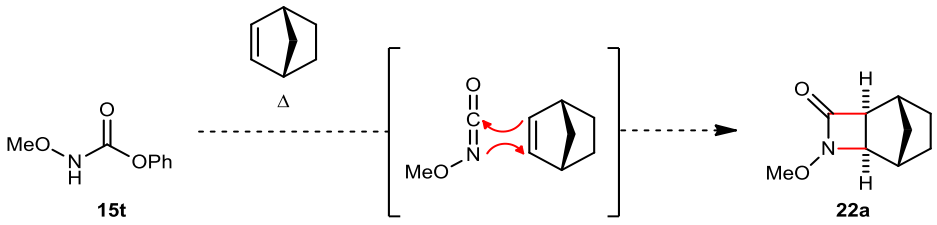


Figure 47 Hypothetical *O*-isocyanate alkene [2+2] cycloaddition reaction

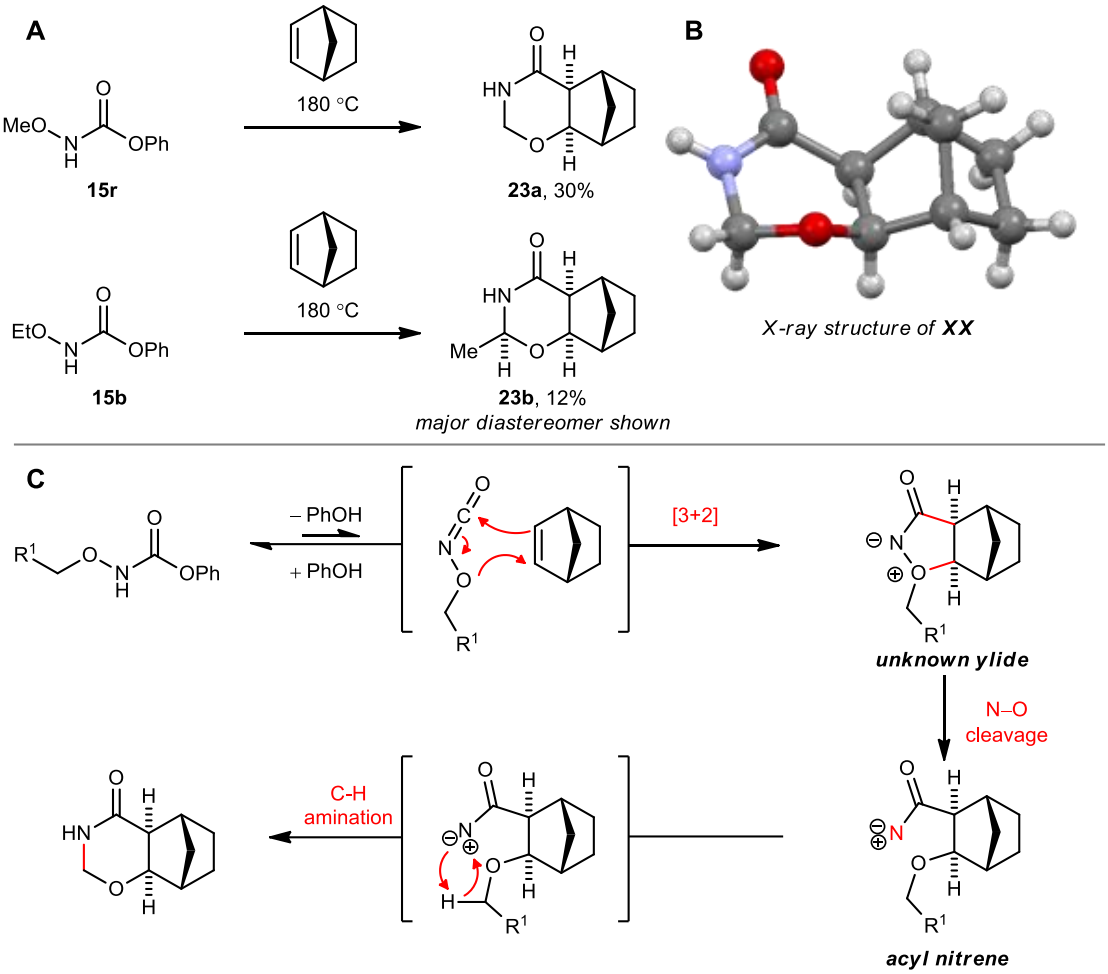


Figure 48 A) Initial discovery of *O*-isocyanate [3+2] cycloaddition. B) X-ray crystallographic structural determination. C) Proposed mechanism for product formation

To probe the reactivity of *O*-isocyanates in cycloadditions, methoxy isocyanate **15r** was reacted in the presence of excess norbornene. This first reaction generated an exciting hit—an unknown bicyclic product in roughly 30% yield. The ^{1}H NMR spectrum possessed clear norbornane peaks and the unsymmetrical norbornane signals indicated the alkene had been difunctionalized. What was striking was that the singlet resonance for the methoxy –OCH_3 (3.82 ppm) had disappeared on the crude ^{1}H NMR spectrum. Instead, a complex multiplet at 4.65 ppm

appeared, indicating a new methylene group. To account for the highly deshielded proton signal, the methylene ought to be linked to two electronegative heteroatoms. Clearly, the product was not the expected [2+2] cycloadduct (**Figure 47**). Based on ^{1}H NMR analysis, the unknown sample was initially ascribed the structure **23a** (**Figure 48**). To further support the formation of this product, other *O*-isocyanate derivatives were subjected to the reaction to see if an analogous structure would be formed. An ethoxy isocyanate precursor **15b** produced a modest yield of a similar looking structure. This time, the deshielded multiplet was a methine, with a clear *dq* resonance at 4.73 ppm indicating a $-CH_3$ was connected to the methine. These two unknowns inextricably provided corroborating evidence for structural determination and hinted that the products were likely formed by a common mechanism.

In tandem to these NMR studies, the unknown sample from the first reaction with **15r** was recrystallized to secure the structural assignment. The product formed monocyclic crystals suitable for X-ray crystal analysis in a mixture of DCM/hexanes. X-Ray crystallography performed by Dr. Bulat Gabidullin ascertained that the product predicted by NMR analysis was correct. The following mechanism was postulated to justify the suggested product (**Figure 48**). This reactivity was particularly captivating for its unorthodox bond disconnection strategy, and unusual intermediates. According to the proposed mechanism, the *O*-isocyanate underwent a [3+2] cycloaddition to form an aza-oxonium ylide intermediate, which then decomposed to an acyl-nitrene intermediate that underwent *selective* C-H amination. Notably, *O*-isocyanates cycloadditions had not been previously reported, the putative aza-oxonium ylide was absent from the literature,[147–149] and the selective C-H amination of acyl-nitrenes (*e.g.* without competing 1,2-rearrangement) was *supposedly impossible*.[150] Therefore, academically, this

reactivity represented the first [3+2] cycloaddition of an *O*-isocyanate, access to a new ylide intermediate and unusual nitrene chemistry; while synthetically, the reaction enabled metal-free alkene oxycarbonylation.[151]

3.13 A quantitative FMO analysis of *N*- and *O*-isocyanates

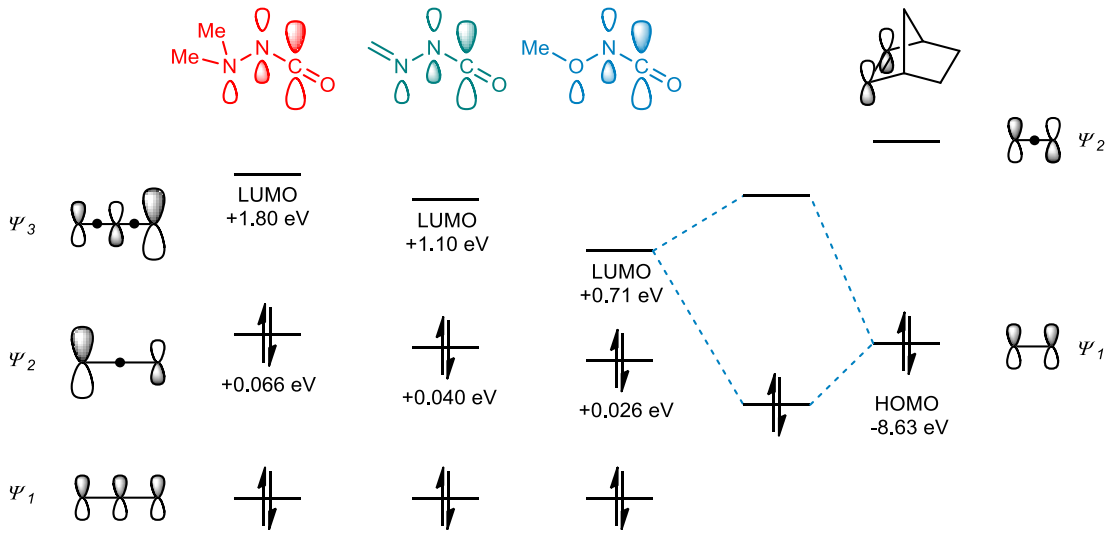


Figure 49 HOMO-LUMO interactions of *N*- and *O*-isocyanates with norbornene. Geometries were optimized using DFT; using B3LYP/6-311+G(2d,p), PCM (acetonitrile). Molecular orbital energies shown were calculated using ωB97XD/cc-pVDZ, PCM (acetonitrile).

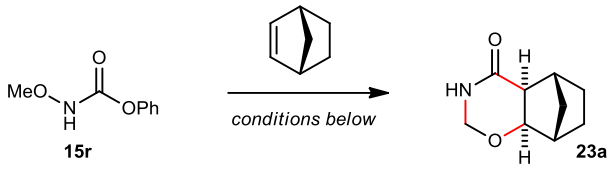
Analysis of the atomic orbitals involved in the cycloaddition could further support the plausibility of such a cycloaddition. While Clavette[152] and Bongers[153] had previously *qualitatively* assessed the cycloaddition of *N*-isocyanates using frontier molecular orbital theory (FMO), the pertinence of a more rigorous *quantitative* assessment became clear. Using DFT, the HOMO-LUMO interactions of amino-, imino-, and oxygen-isocyanates with norbornene could be directly compared. It was immediately clear that *O*-isocyanates had the lowest LUMO energy, and

therefore were primed for cycloaddition reactions due to the smaller HOMO-LUMO gap. As speculated by Clavette,[152] the imino-isocyanate LUMO energy was notably lower than that of the amino-isocyanate. Based on these calculations—and the hypothesis that LUMO energy translated to improved reactivity—*O*-isocyanates should more readily undergo [3+2] cycloadditions than analogous *N*-isocyanates.

3.14 Optimization and synthetic survey of *O*-isocyanate alkene [3+2] cycloaddition

The excitement generated by this initial hit was bolstered by encouraging FMO analysis but was quickly tempered upon reaction optimization (**Table 26**). Although 32% product was formed at 150 °C, only 4% product was observed when the temperature was lowered to 120 °C (entry 1-2). The use of catalytic *i*-Pr_2NEt as a base to catalyze deblocking to form the *O*-isocyanate did not increase the yield of the cycloaddition but did increase the conversion of starting material (entry 3). This provided an early indication that *O*-isocyanate deblocking was likely not rate limiting and that some other process in the proposed mechanism was rate determining. Increasing the temperature to 180 °C led to a marginal improvement in yield but a precipitous decline in remaining starting material (entry 4). We were unable to identify a suitable replacement for acetonitrile through screening various solvents (e.g., entry 5). Ultimately, the yield could only be increased by dramatically increasing the concentration of the alkene reagent (entry 8-9). While the alkene is only involved in the cycloaddition step, the entire preequilibrium preceding C–H amination would certainly be affected by increased alkene concentration (*vide infra*).

Table 26 *O*-Isocyanate [3+2] cycloaddition optimization with norbornene



entry	solvent	temp	time	alkene (eq)	additives	yield (%)	SM (%)
1	MeCN	150	3	10	-	32[a]	24
2	MeCN	120	3	10	-	4	82
3	MeCN	120	3	10	20% *i*-Pr_2NEt	4	63
4	MeCN	180	2	10	-	38	0
5	$PhCF_3$	150	3	10	-	10	75
6	MeCN	180	1	10	-	21	30
7	MeCN	180	2	10	-	45	0
8	MeCN	180	2	30	-	73[a]	0
9	**MeCN**	**180**	**2**	**50**	**-**	**87[a]**	**0**

Conditions: carbamate (1 equiv), norbornene, in solvent (0.2 M) for temperature and time specified (μW, sealed tube). ^1H NMR yield using 1,3,5-trimethoxybenzene as internal standard. [a] Isolated yield.

While using such excess of a reagent presented a limitation, the reactivity was novel enough to warrant further study. Thus, various alkenes were screened to survey the synthetic scope of this new oxycarbonylation reaction (**Figure 50**). Disappointingly, only strained alkenes appeared to provide detectable yields of the anticipated products. Electronically activated dihydrofuran appeared to react but provided a complex mixture of bicyclic products.

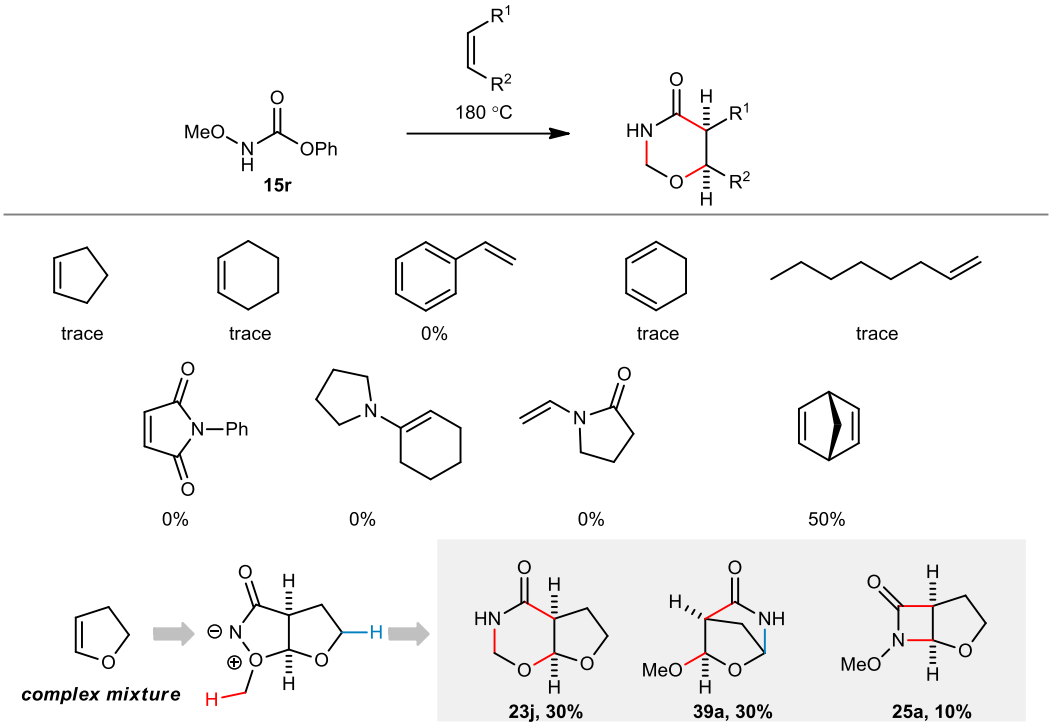


Figure 50 Preliminary alkene survey for *O*-isocyanate [3+2] cycloaddition reaction

Painstaking attempts to isolate all products from the reaction with dihydrofuran were partly successful. Three products were clearly identified, two of which were fully characterized. The first product (**23j**) was the expected product, in accordance with preliminary norbornene reaction. However, the second isolated product had retained the methoxy –OCH_3 signal by ^1H NMR. This meant that either nitrene insertion had occurred elsewhere on the molecule, or it did not occur at all. Ultimately, NMR analysis led to the structural determination of β-lactam **25a**. The third product had also retained the methoxy –OCH_3 signal by ^1H NMR and was most likely **39a**, resulting from nitrene insertion at the ethereal position inside the furan ring. Unfortunately, only partial characterization was achievable due to difficulties in separating it from other by-products. Although a complex mixture of products had formed from the reaction with

dihydrofuran, the products could all convincingly derive from a common [3+2] cycloadduct intermediate. Therefore, the combined yield of these products indicated that the cycloaddition reactivity was quite good with dihydrofuran. This was to be expected, as FMO theory predicted a LUMO controlled cycloaddition (**Figure 49**).

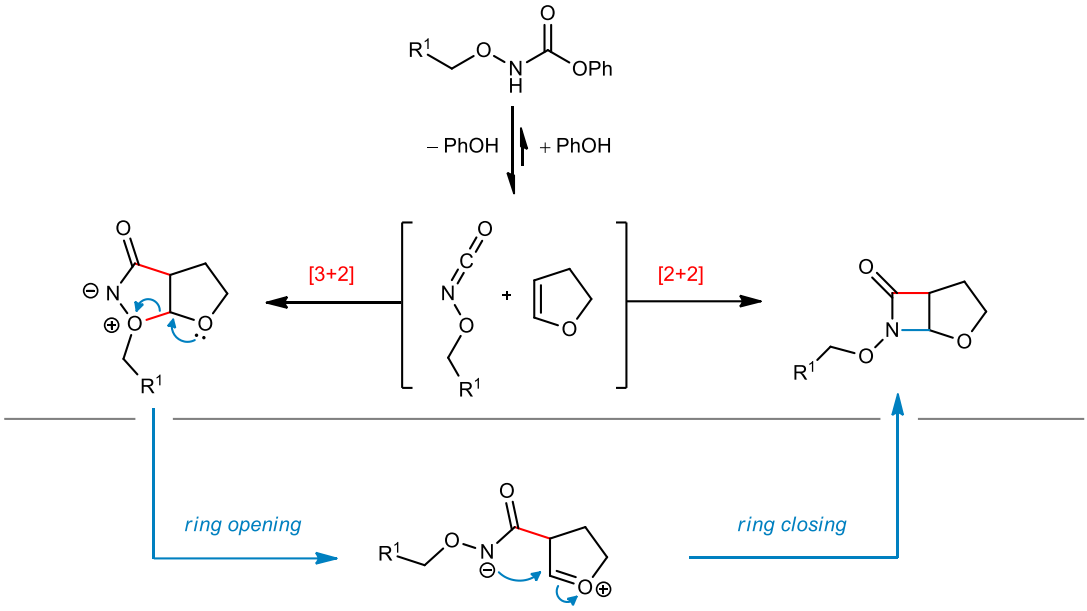


Figure 51 Competing pathways for β-lactam formation: [3+2] cycloaddition versus [2+2] *O*-isocyanate cycloaddition.

The isolation of β-lactam **25a** generated some controversy since two mechanisms could account for its formation (**Figure 51**). Either a [3+2] cycloaddition, ring opening / closing cascade, or a direct [2+2] cycloaddition was possible. However, [2+2] cycloadditions are thermally forbidden and are only rarely observed with exceptionally activated reagents / forcing conditions outside of photochemical reactions. To quantitatively assess the reactivity of the *O*-isocyanate,

an FMO analysis of the hypothetical [2+2] reaction with dihydrofuran was performed (**Figure 52**). Here, *O*-isocyanate **15r** was compared to two reagents that reportedly undergo [2+2] cycloaddition with dihydrofuran. Considering LUMO energy alone, the intermediate LUMO energy of *O*-isocyanates suggested that a [2+2] cycloaddition was possible. However, the higher energy geometric constraints of a [2+2] cycloaddition diminished the likelihood of this pathway (**Figure 53**). Experimental evidence for the [3+2] pathway was eventually obtained (*vide infra*).

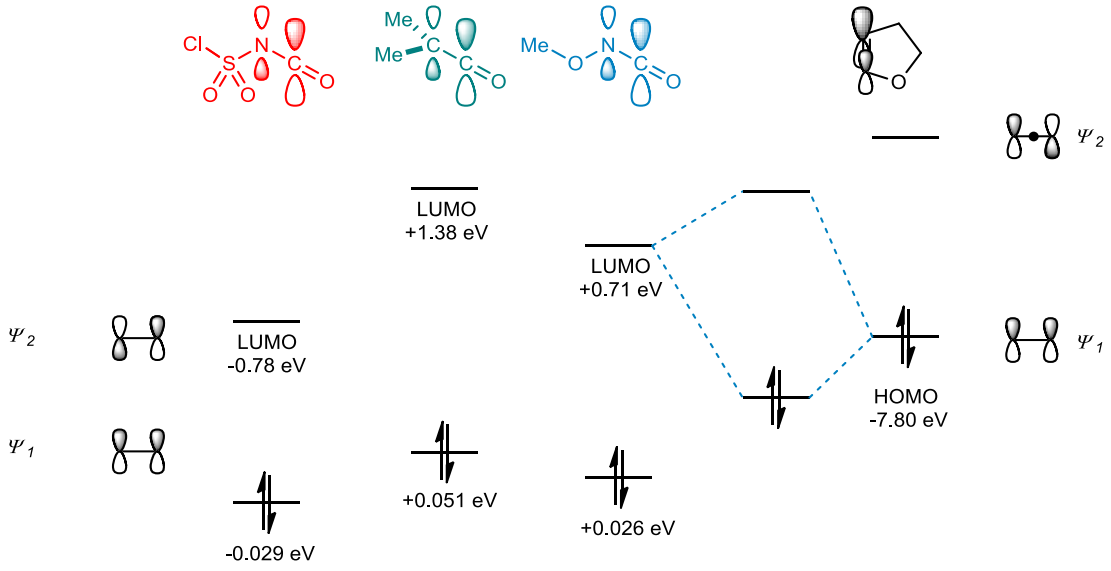


Figure 52 FMO analysis of [2+2] cycloaddition with dihydrofuran. A comparison of *O*-isocyanates to CSI and ketenes. Geometries were optimized using DFT; using B3LYP/6-311+G(2d,p), PCM (acetonitrile). Molecular orbital energies shown were calculated using ωB97XD/cc-pVDZ, PCM (acetonitrile).

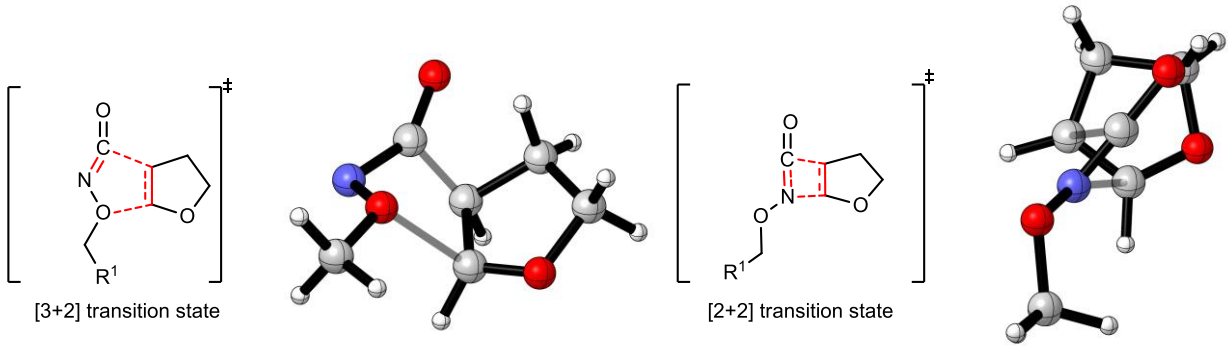
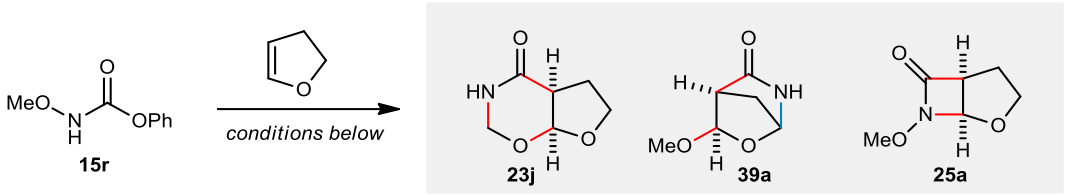


Figure 53 Accepted transition state geometries for conventional [3+2] and [2+2] cycloadditions.

The first objective was to simplify product formation / isolation. Ideally, only a single product would form from this new cycloaddition reaction with enol ethers. Selectivity was readily achieved by reaction optimization (**Table 27**). Screening solvents did not provide an alternative solvent to MeCN (entry 1-3). Reducing the temperature to 150 °C eliminated N–O bond cleavage products **23j** and **39a** (entry 4). Using 10-20 equivalents of dihydrofuran reduced the yield of product (entry 5-6). Continuing to lower the temperature to 120 °C led to poor conversion of starting materials, but a high relative yield of product to phenol produced (entry 7), while quantitative starting material was observed at 90 °C (entry 8). Therefore, we imagined that the sluggish reactivity was due to slow *O*-isocyanate release. When 20% *i*-Pr_2NEt was added, the β-lactam **25a** was formed in nearly quantitative yield. Thus, lower temperatures and base catalysis proved crucial to achieve a selective reaction with enol ethers. The mild conditions under which β-lactams were generated made a [2+2] reaction pathway even more unlikely. Further, that efficient reactions were possible at milder temperatures when N–O bond cleavage / C–H amination were no longer factors indicated that these steps may be rate determining. Indeed, C–H amination was only observed above 150 °C, whereas lactams likely derived from the [3+2]

cycloaddition were observed as low as 90 °C (entry 10). Still, the reaction required a large excess of enol ether to produce synthetically viable yields.

Table 27 β-lactam synthesis through enol ether cycloaddition reaction optimization



entry	solvent	temp	time	alkene (eq)	base	yield (%23j)	yield (%26a)	yield (%25a)
1	MeCN	180	2	30	-	30	30	10
2	$(CH_2Cl)_2$	180	2	30	-	0	0	0
3	$PhCF_3$	180	2	30	-	2	0	0
4	MeCN	150	2	30	-	0	0	70
5	MeCN	150	2	20	-	0	0	55
6	MeCN	150	2	10	-	0	0	30
7	MeCN	120	2	30	-	0	0	15
8	MeCN	90	2	30	-	0	0	0
9	**MeCN**	**120**	**2**	**30**	**20% *i*-Pr_2NEt**	**0**	**0**	**99**
10	MeCN	90	2	30	20% *i*-Pr_2NEt	0	0	35
11	MeCN	120	20	30	-	0	0	40[b]
12	MeCN	120	20	30	20% *i*-Pr_2NEt	0	0	90[b]

Conditions: carbamate (1 equiv), dihydrofuran (10-30 equiv), *i*-Pr_2NEt (0–0.2 equiv), solvent (0.2 M) for temperature and time specified (μW, sealed tube). ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard. [a] Isolated yield. [b] Oil bath, sealed tube.

The combined challenges of these two cycloaddition systems drove our efforts to continue modification of *O*-isocyanate precursors, with the hope that—similar to success with *N*-

isocyanate cycloaddition reactions[45]—a suitable *O*-isocyanate reagent could be identified that would react efficiently with a variety of unbiased alkenes. This would prove a challenge, as this reaction was clearly more complex than the simple cycloadditions with *N*-isocyanates developed previously.

3.15 The pursuit of a second generation oxycarbonylation precursor

At first, we elected to use chemical intuition to develop an improved oxycarbonylation reagent. However, rational design of a precursor for a given reaction was challenging when little was known regarding the mechanism of the desired reaction. Which properties of the *O*-isocyanate needed to be modified drastically changed depending on the rate determining step / thermodynamics of the overall transformation. Moreover, literature support for the key intermediates of this mechanism were tenuous at best. While a traditional kinetic approach would have been ideal, gathering reaction data on these highly reactive intermediates that could not be isolated or even detected was an daunting challenge.

Assessing each step of the putative mechanism (**Figure 48**) resulted in the following predictions / testable hypotheses. 1) Deblocking of the *O*-isocyanate precursors was rate determining: If *O*-isocyanate generation was rate determining, either catalysis of *O*-isocyanate formation (*e.g.* base catalysis) or the use of a different blocked precursor should prove useful. 2) The [3+2] cycloaddition was rate determining: If the cycloaddition presented a barrier, this would require a more activated *O*-isocyanate (lower LUMO), or the use of activated alkenes (higher HOMO). 3) The N–O bond cleavage / nitrene formation was rate determining: If nitrene

formation was rate determining then bestowing the ylide with an alternative, potentially more favourable pathway could lead to improved reactivity. 4) C–H amination was rate determining: If C–H amination was rate determining then the reaction could be improved by increasing the nucleophilicity of the active C–H. *However, this line of thinking was likely too simplistic, as the modification of any parameter perturbs the fine balance governing the overall reactivity. For example, C–H amination may be rate determining for the reaction with norbornene, but with a less activated alkene such as cyclopentene, the cycloaddition may be rate determining.* Nevertheless, each scenario was investigated to the best of our ability with a combined synthetic and computational study (computational abilities were only acquired late in project development).

We first probed the possibility that *O*-isocyanate deblocking was rate determining—or that the blocking group had some deleterious impact on the reactivity. A series of blocked derivatives were screened in the reaction (**Figure 54**). Substrates encompassing a range of deblocking profiles did not lead to improved reactivity. We anticipated that deblocking was not rate determining for this transformation, since during the initial optimization base-catalysis led to a preponderance of *O*-isocyanate trimer and no additional product (**Table 26**). *Thus, it was unlikely that O-isocyanate deblocking was rate limiting for this process.*

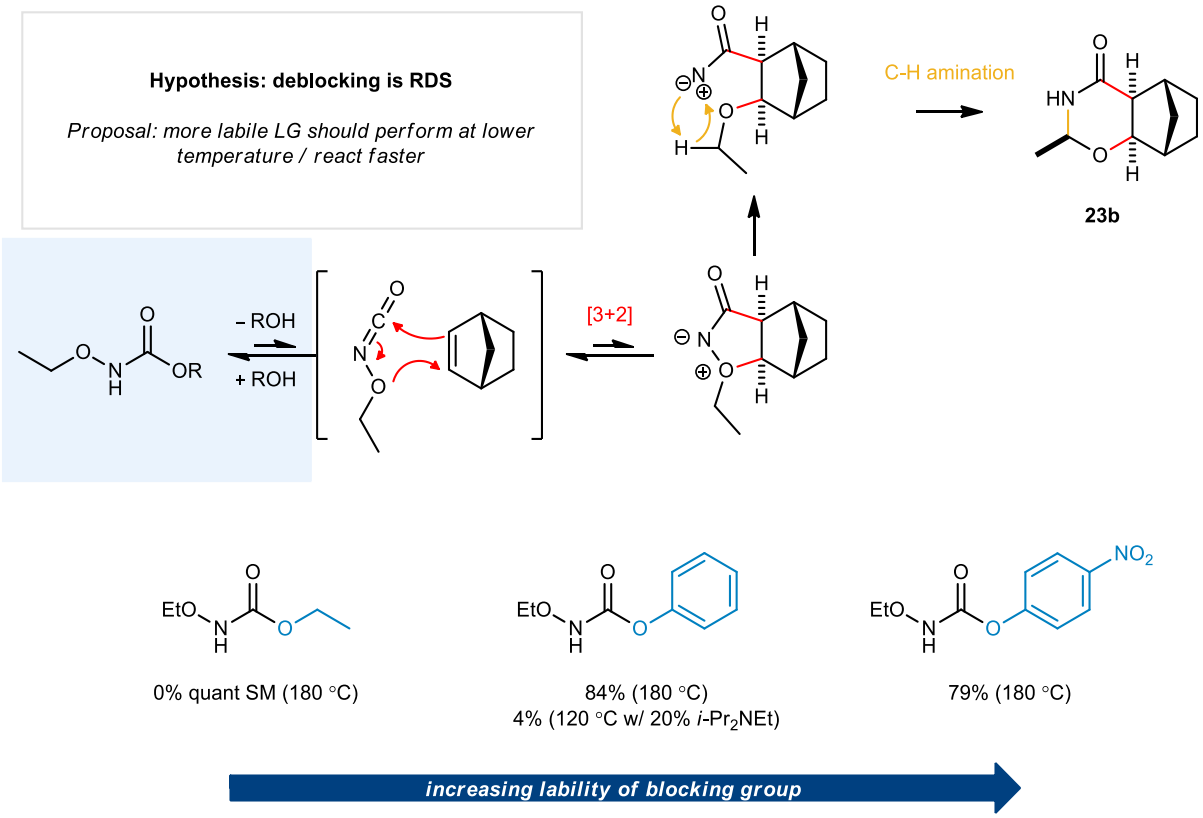


Figure 54 Scenario 1: Investigations of *O*-isocyanate precursor deblocking as RDS.

The next possibility was that the [3+2] cycloaddition was rate determining. From the optimization results this seemed most likely, due to the lack of reactivity for unstrained / unactivated alkenes (**Figure 50**) coupled with the huge excess of alkene required to achieve high yields (**Table 26**). We envisioned two scenarios that could lead to improved reactivity if the cycloaddition was rate determining: 1) the *O*-isocyanate LUMO energy could be lowered through hydrogen bonding or Lewis acid catalysis,[154] or 2) the charged transition state could be stabilized by hydrogen bonding / hyperconjugation.[155]

Theoretically, hydrogen bonding or Lewis acid catalysis could lower the LUMO of the *O*-isocyanate and / or stabilize the nascent charges in the transition state / ylide intermediate. We envisioned two binding modes for internal hydrogen-bonding, either through 5 or 6-membered cyclic structures (**Figure 55**). Ultimately these substrates (**15ac**, **15ad** and **15t**) were ineffective in the transformation and did not lead to product. It was possible that H-bonding / Lewis acid chelation to the *O*-atom diminished the ability of the *O*-atom to engage with the alkene during the cycloaddition.

An alterative approach was to stabilize the positive charges forming in the transition state / aza-oxonouim ylide intermediate. Hyperconjugations via a β-silicon effect was hypothesized to stabilize the aza-oxonium ylide species. Unfortunately, no product corresponding to the cycloaddition was detected when **15ae** was used.

Ultimately, we were unable to truly decouple this step of the reaction from the overall sequence to study it effectively. Yet, the lower LUMO of *O*-isocyanates suggested that the [3+2] cycloaddition should be relatively facile. Thus, we proposed that excess alkene was required to shift the unfavourable equilibrium of cycloadduct forward, and the use of strained alkenes simply made the forward reaction more thermodynamically favoured; rather than a rate determining [3+2] cycloaddition. DFT calculations would later confirm that this step was likely not rate determining (*vide infra*).

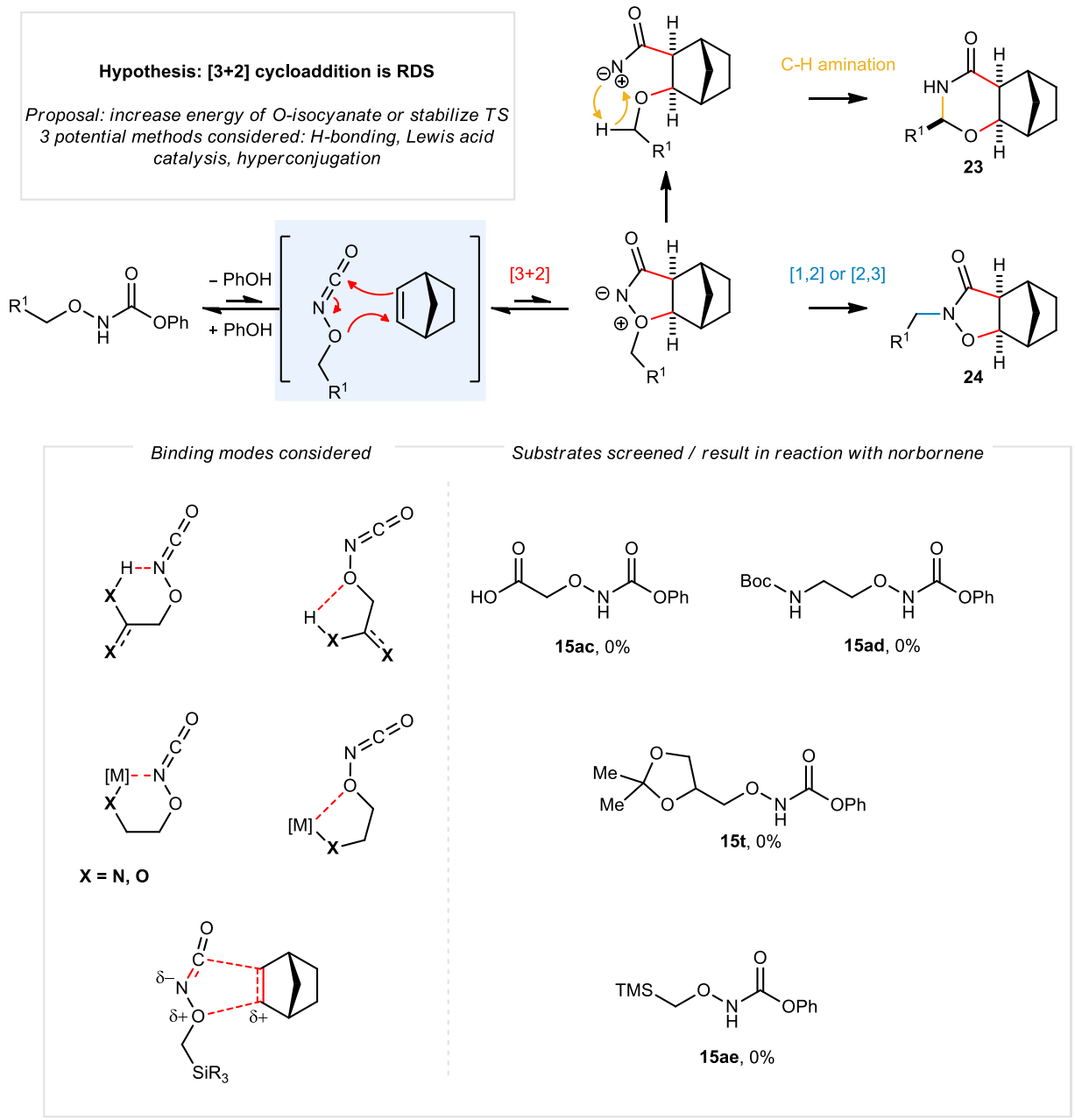


Figure 55 Scenario 2: Investigations of *O*-isocyanate [3+2] cycloadditions as RDS.

We next considered N–O bond cleavage to be rate determining. Admittedly, this seemed unlikely given the fact that various hydroxylamine compounds seem to undergo N–O heterolysis under relatively mild conditions.[156,157] In this system, the *O*-atom bears a positive charge, which

should substantially weaken the N–O bond. Nevertheless, in the unlikely scenario that N–O bond cleavage was rate determining, we sought to design *O*-isocyanate reagents that could avoid N–O bond cleavage by engaging in other chemical reactions. Experience with similar zwitterionic species to the aza-oxonium ylide led us to probe substrates that could undergo 1,2-benzyl shift or [2,3]-sigmatropic rearrangements.[138,158] We reasoned that if N–O bond cleavage was rate determining, *O*-benzyl **15m** or *O*-allyl **15k** substrates could undergo rearrangement from the hypothetical aza-oxonium ylide intermediate. The observance of such rearrangements would also serve as mechanistic evidence for the [3+2] cycloaddition reaction / formation of the elusive aza-oxonium ylide.

Provided these rearrangement pathways were lower in energy than N–O bond cleavage or C–H amination, then perhaps we could *selectively* undergo a [3+2] cycloaddition / rearrangement sequence at lower temperatures. Although *O*-allyl and *O*-benzyl substrates clearly rearranged under the reaction conditions to the corresponding isoxazolones since a mixture of products was observed. Efforts to perform the reaction using milder conditions or with alternative alkenes were unsuccessful. Similar rearrangement studies with *N*-isocyanate ylides (aminimides) required heating above 180 °C to induce the rearrangement (**Figure 14**),[158] so perhaps these rearrangement steps were similar in energy to the N–O cleavage / C–H amination. Since N–O bond cleavage was required to form the acyl nitrene which later undergoes C–H amination, a mixture of products suggested a rapid preequilibrium prior to rate determining irreversible C–H amination, or conversely a rate determining [3+2] cycloaddition with similar energy rearrangement / C-H amination transition state energies.

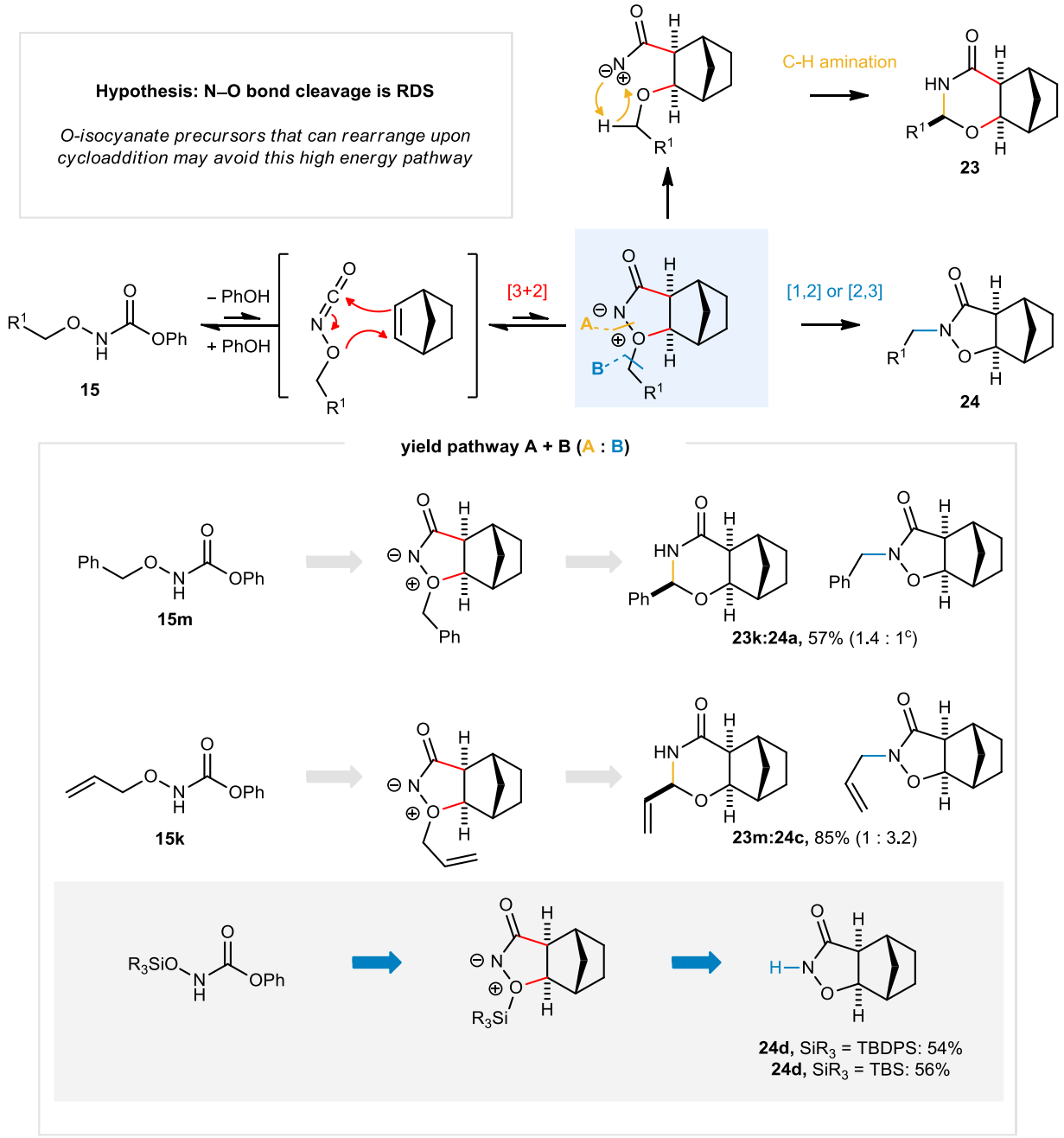


Figure 56 Scenario 3: Investigations of N-O bond cleavage as RDS.

To probe this possibility further we envisioned the use of a siloxy isocyanate in the [3+2] cycloaddition. In accordance with the literature of siloxy deprotections,[159] our hypothesis was

that such a reagent could undergo Si–O cleavage once it had generated the aza-oxonium ylide via [3+2] cycloaddition. When the siloxy isocyanates precursors were subjected to the reaction conditions, the isoxazolones (**24d**) were obtained directly. Unfortunately, these siloxy isocyanate precursors were ineffective with other alkenes or under milder conditions. The [3+2] cycloreversion was reported in the literature to produce the hydroxy-*O*-isocyanate quantitatively via release of an aromatic heterocycle (**Figure 28**).[106] We speculated that the high temperatures of this reaction may have driven the cycloreversion and subsequent dimerization / decomposition of the hydroxy-*O*-isocyanate. Indeed, reactions with siloxy isocyanates required shorter reaction times, as product was not observed when reacted under optimized conditions for alkoxyl isocyanates (2 hours). When reacted for shorter times (15–30 min), higher yields of **24d** were observed. Moreover, isolation and resubmission of **24d** to the reaction proved that **24d** decomposed under the reaction conditions, supporting that the reaction may be reversible when a retro [3+2] reaction is possible (**Figure 57**). Unfortunately, norbornene is volatile and the oligomerization of hydroxy *O*-isocyanate produces no distinguishable peaks by ^{1}H NMR. Ideally, this control reaction should be repeated in CD_3CN, and analyzed by ^{1}H NMR without evaporation of the reaction. *Although inconclusive, collectively these results suggested that N–O bond cleavage was likely not rate determining.*

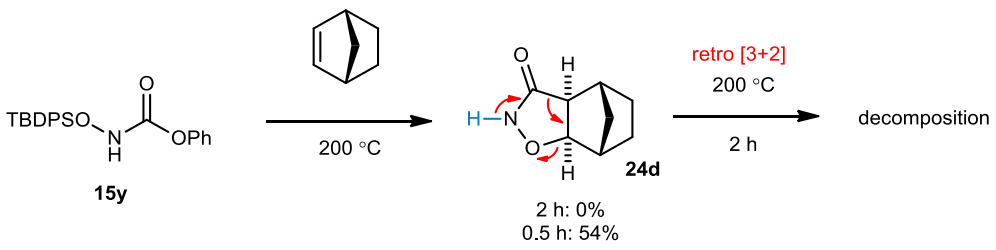


Figure 57 Optimization and reversiblility of siloxyisocyanate [3+2] cycloadditions.

The final possibility we considered was that C–H amination was rate determining. Although nitrenes generally undergo *metal catalyzed* C–H amination at ambient temperatures,[160] uncatalyzed C–H aminations typically require forcing conditions.[161,162] If C–H amination was a challenge, precursors with more hydridic C–H bonds should react more easily. In contrast, *O*-isocyanate precursors with more activated C–H bonds tended to require longer reaction times and higher alkene loadings to react similarly to the most challenging C–H amination substrate. While tentative, it is possible that the increasing steric hindrance inextricably tied to the increasing nucleophilicity of the C–H bond hampered the cycloaddition. This led us to *incorrectly* posit that the C–H amination was not likely rate determining (*vide infra*).

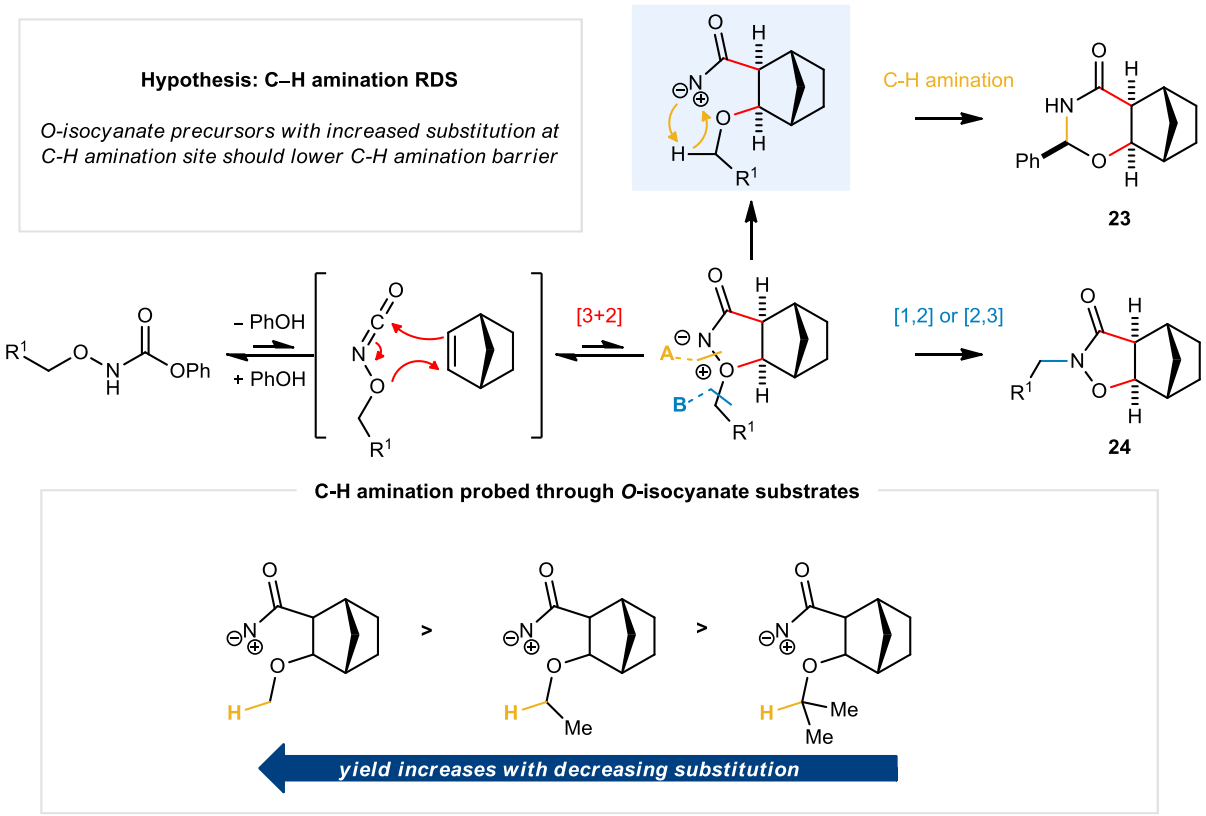


Figure 58 Scenario 4: Investigations of C-H amination as RDS.

Ultimately, we were unable to reliably predict a rate determining step of the transformation through these synthetic studies. This void of crucial information complicated reaction optimization, because it was unclear what the problems were with the reaction that caused such synthetic limitations.

3.16 Computational studies of the reaction mechanism

Our intuitive approach was supplanted by DFT calculations, which were used to isolate and interrogate each step of the reaction. All calculations were performed using B3LYP/6-311+G(2d,p) using a polarizable continuum model (PCM) with acetonitrile as the solvent. The B3LYP functional had been previously found to produce results in accordance with experimental trends of *N*-isocyanate cycloadditions. Calculations commenced with geometry optimizations / harmonic frequency calculations for the key reactive intermediates. This provided a rudimentary understanding of the reactivity based on the relative free energies of the species believed to be involved in this novel transformation (**Figure 59** *top*). From these structures alone, we could confirm that all steps proceeding C–H amination were reversible and given the endothermicity of the aza-oxonium ylide and acyl nitrene compared to the *O*-isocyanate the equilibrium would likely be heavily shifted towards the starting materials. This provided a potential explanation for the necessity of excess alkene, and the incredibly high energy of the nitrene suggested that—in contrast to our initial predictions—the C–H amination could be the rate determining process.

The insight from these preliminary calculations enforced the need to obtain a comprehensive computational analysis of the transformation, including transition state geometries (**Figure 59** *bottom*). The overall reaction coordinate (**Figure 60**) provided a summary

of findings corresponding to the structures in **Figure 59**. A detailed analysis of this computational study in relation to experimental results from synthetic studies will be presented in detail in the order of the reaction sequence. Where possible, these DFT results were contrasted to calculations of intermolecular imino-isocyanate [3+2] cycloadditions to highlight differences that could explain the lack of reactivity observed with *O*-isocyanates.

The aza-oxonium ylide cycloadduct was +6.9 kcal/mol higher in energy than the *O*-isocyanate / norbornene. The relative energies of the *O*-isocyanate / aza-oxonium ylide contrasted sharply to the thermodynamics of related imino-isocyanate [3+2] cycloadditions (**Figure 61**), which were determined to be exothermic processes (−10.9 kcal/mol from the imino-isocyanate / norbornene). Thus, the *O*-isocyanate [3+2] cycloaddition was +17.8 kcal/mol more unfavourable than the imino-isocyanate cycloaddition. Consequently, the products of imino-isocyanate [3+2] cycloadditions—azomethine imines—were readily isolable. In contrast, the predictably unstable aza-oxonium ylides from *O*-isocyanate [3+2] cycloadditions were never detected experimentally.

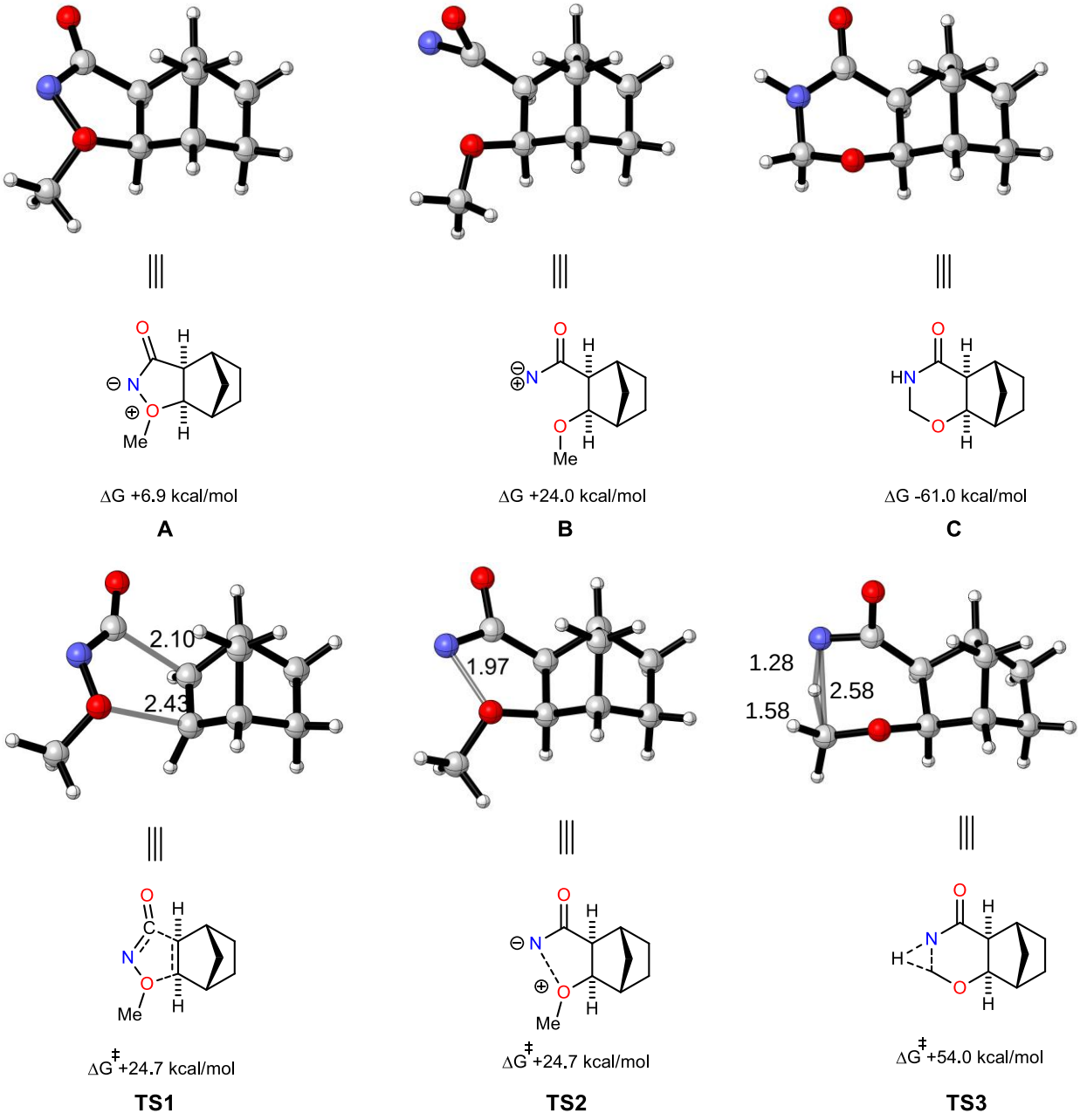


Figure 59 Optimized geometries for key intermediates / transition states of the intermolecular *O*-isocyanate oxycarbonylation reaction. Calculations used B3LYP/6-311+G(2d,p), PCM (acetonitrile). Harmonic frequency calculations ensured energy minima / one imaginary frequency was present for transition states. All Gibbs free energy values are versus the *O*-isocyanate + norbornene.

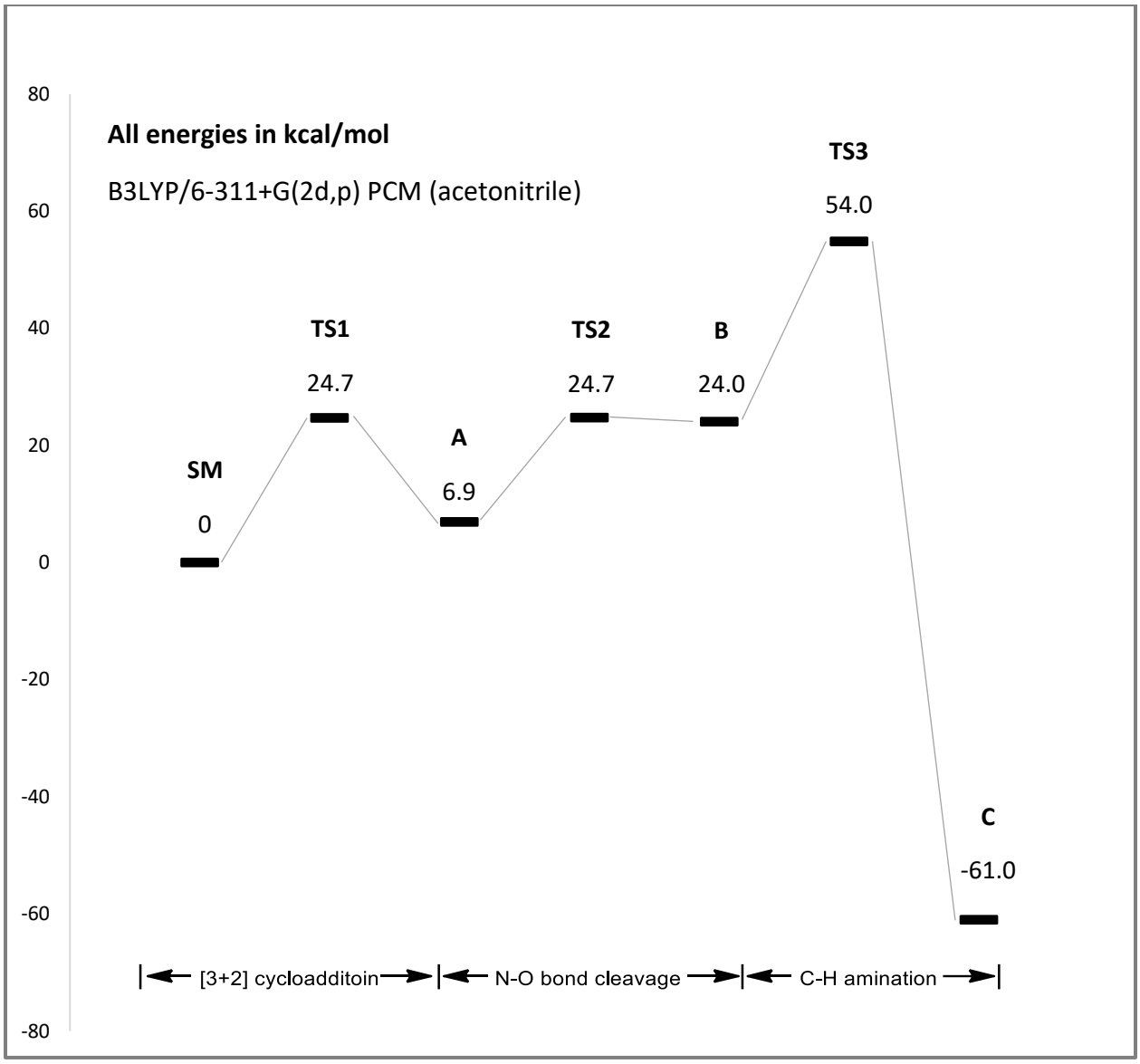


Figure 60 Reaction coordinate for the intermolecular *O*-isocyanate oxycarbonylation reaction

A highly asynchronous [3+2] cycloaddition was predicted **TS1** ($\Delta G^{\ddagger}$ = +24.7 kcal/mol). The predicted asynchronicity of the cycloaddition was in accordance with the regioselectivity observed with vinyl ethers (

The *O*-isocyanate cycloaddition transition state closely resembled the analogous structure for intermolecular imino-isocyanate cycloaddition (**Figure 61**). Both heteroatom isocyanate [3+2] cycloadditions were planar and concerted, though asynchronous in favour of C–C bond formation. The *O*-isocyanate [3+2] cycloaddition was +3.3 kcal/mol lower in energy than the corresponding imino-isocyanate [3+2] cycloaddition.

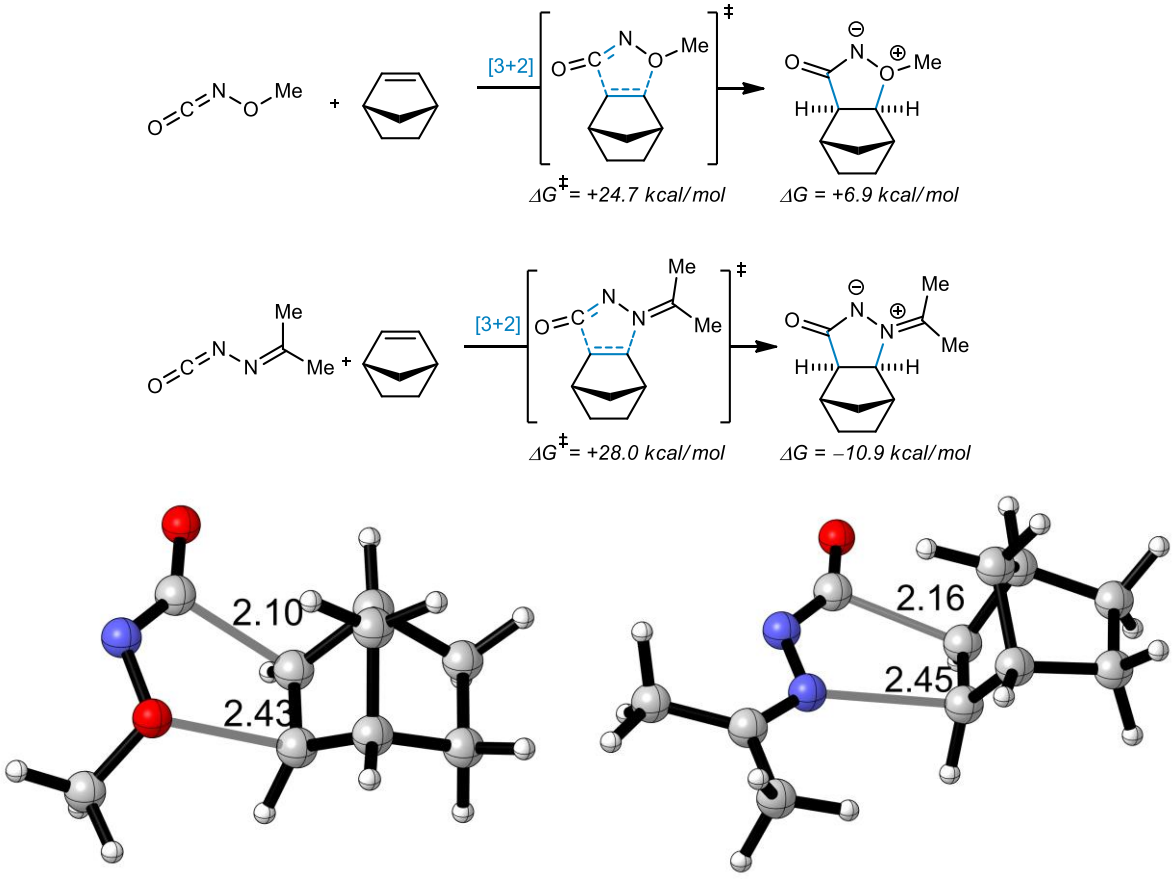


Figure 61 *O*-Isocyanate versus imino-isocyanate cycloaddition TS / thermodynamics

The *O*-isocyanate cycloaddition was slightly more asynchronous than the imino-isocyanate. Expectedly, the isocyanate with the lower LUMO energy also had a lower energy

transition state (**Figure 49**). The issue seemed to be that the cycloaddition produced a product that was incredibly unstable, such that its concentration would be minimal throughout the course of the reaction. This agreed with experimental results, where a large excess of alkene was necessary, and could also explain the lack of reactivity with unstrained / unactivated alkenes. Comparing the thermodynamics of the *O*-isocyanate cycloaddition with norbornene versus cyclopentene clearly demonstrated the additional challenges. Without the release of strain, the [3+2] cycloadduct was +12.9 kcal/mol above the *O*-isocyanate—a highly reversible process. Collectively, these results suggested a kinetically rapid cycloaddition with unfavourable thermodynamics.

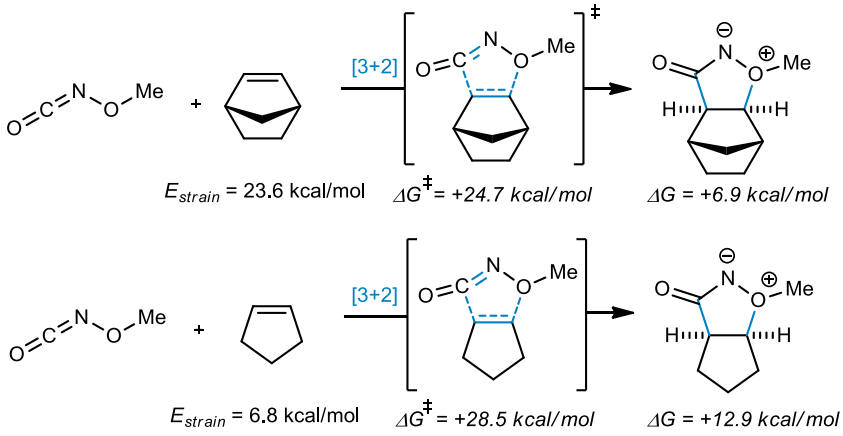
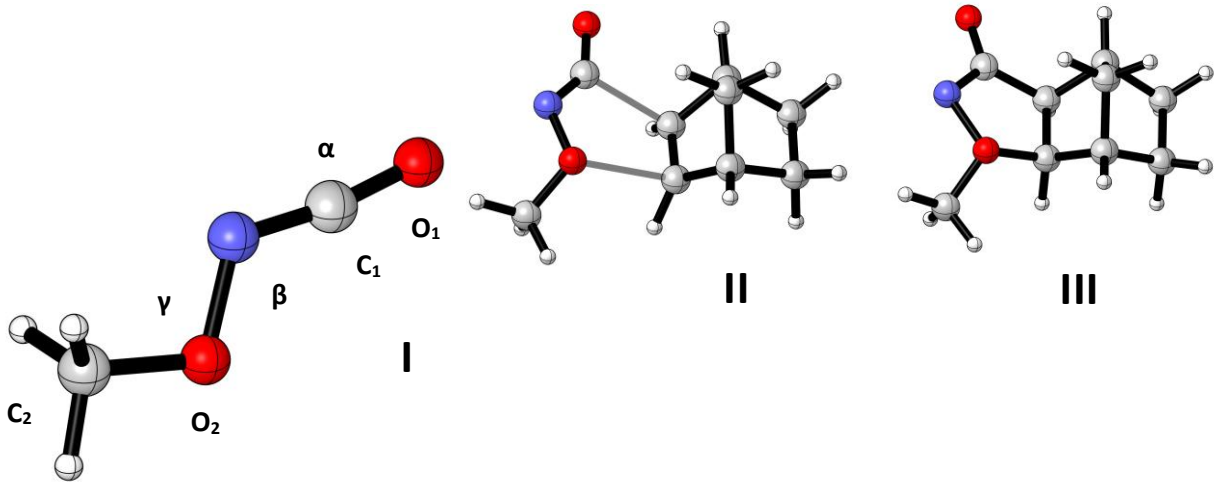


Figure 62 A comparison of norbornene vs cyclopentene [3+2] cycloaddition transition states and thermodynamics

Since the *O*-isocyanate cycloaddition was novel, this led to further studies towards the transition state structure. The transition state was compared to established dipolar cycloadditions to classify the *O*-isocyanate within the propargyl or allyl anion type dipole categories. While electronically biased charged 1,3- dipoles (*e.g.* nitrones, nitrile oxides)

commonly have concerted asynchronous cycloaddition transition state complexes, this was exaggerated for *O*-isocyanates. Additionally, the distortion of the dipole prior to the transition state ($\Delta E_d^{\ddagger}$) was qualitatively assessed using the change in bond angles during the cycloaddition. The distortion of the *O*-isocyanate during cycloaddition, (Δ bond angles α, β, γ) revealed differences to both propargyl and allyl anion type 1,3-dipoles (**Figure 63**). The *O*-isocyanate cycloaddition transition state had minimal distortion of the dipole equivalent based on changes in bond angle β [120.6° (I); 119.8° (II)], similar to allyl anion (bent) type charged dipoles. Although, a large distortion of the *O*-isocyanate moiety before the transition state occurred based on changes in bond angle γ [171.1° (I); 140.9° (II)], common among propargyl anion (linear) type 1,3-dipoles such as azides and nitrile oxides. Another distinguishing feature of propargyl and allyl anion type dipolar cycloadditions, is the shape of the 5-membered transition state (planar and envelope respectively). The calculated planar transition state more closely resembles those of the propargyl anion type 1,3-dipoles. The *O*-isocyanate appeared to be a hybrid of both propargyl and allyl anion type dipoles but exhibited closer similarity to a propargyl anion type dipole.



Bond angles

		I	II	III
C_2-O_2-N	γ	108.4°	109.7°	109.5°
O_2-N-C_1	β	120.6°	119.8°	105.2°
N-C_1-O_1	α	171.1°	140.9°	122.4°

Figure 63 Distortion energy of the intermolecular [3+2] *O*-isocyanate cycloaddition as predicted by Δ bond angles during the transition state.

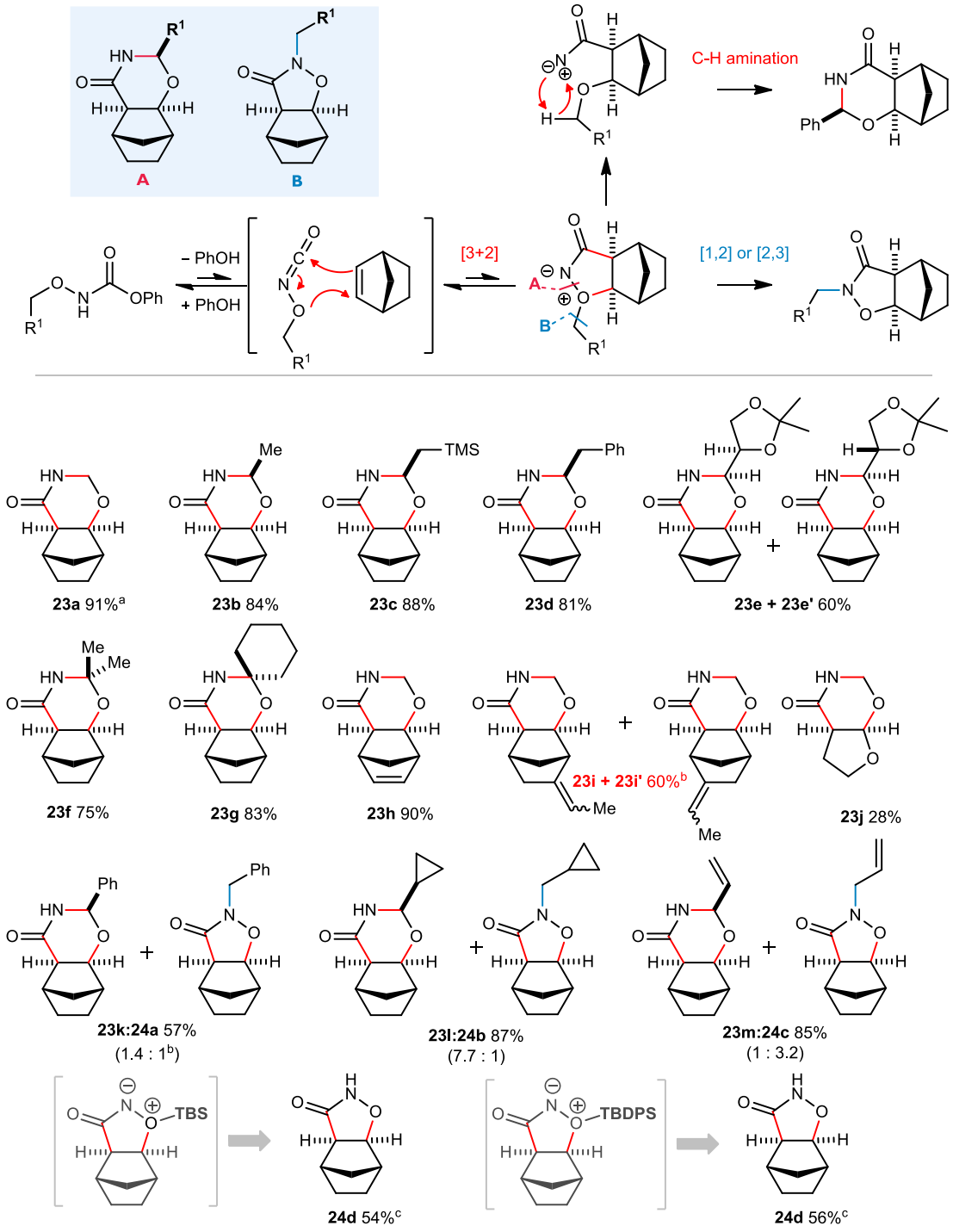
The next intermediate in the suggested mechanism was an acyl nitrene. In accordance with the literature on acyl nitrene species, the singlet nitrene adopted a distinct triangular configuration with a bond angle of 86° along the N–C=O plane. Energetically, the acyl nitrene was even more unstable than the aza-oxonium ylide (+24.0 kcal/mol from the *O*-isocyanate / norbornene). Therefore, an unexpectedly high transition state energy would be required to produce the nitrene (**TS2**). DFT calculations predicated a heterolytic N–O cleavage transition state of $\Delta G^{\ddagger}$ = +24.7 kcal/mol (**TS2**). The incredibly low barrier to revert to the aza-oxonium ylide from the acyl nitrene can be justified in the context of the ylide acting as a *stabilized* nitrene akin to carbonyl ylides,[163] or ammonium ylides.[164] The disparity between the energies of the acyl

nitrene and the final product would demand an exceptionally early transition state for the C–H amination. Indeed, the C–H amination transition state **TS3** ($\Delta G^{\ddagger}$ = 54.0 kcal/mol) closely resembled the acyl nitrene intermediate, and analogous transition state geometries calculated for rhodium catalyzed C–H aminations.[165] Thus, DFT suggested that C–H amination was rate determining. A rate determining C–H amination and an unfavourable equilibrium for the steps leading to the acyl nitrene could account for the limitations observed during optimization and agreed with results of experimental studies.

3.17 Scope of intermolecular oxycabonylation via *O*-isocyanate [3+2] cycloadditions

After extensive optimization, precursor screening and mechanistic studies the reaction was still limited synthetically. Nevertheless, through these investigations a relatively large library of *O*-isocyanate precursors had accumulated, and the scope of the reaction was assessed with these reagents (**Table 28**). Methoxycarbamate precursor (**15r**) provided the product in the highest yield (**23a**, 91%), while isopropyl and cyclohexyl cycloadducts **23f** and **23g** were obtained in 75% and 83% respectively. These results suggested that the cycloaddition was only moderately sensitive to steric hindrance. The reaction proceeded with a variety of 2°-derived *O*-isocyanate precursors (**23b**-**23e**). *O*-Benzyl, *O*-methylcyclopropyl, and *O*-allyl underwent rearrangement to provide a mixture of products (**23k**-**23m**, **24a**-**24c**). Silyl derivatives (**15x** and **15y**) could produce **24d** in a modest yield <60%. Only norbornene derivatives and dihydrofuran were amenable to the reaction (**23h**-**23j**).

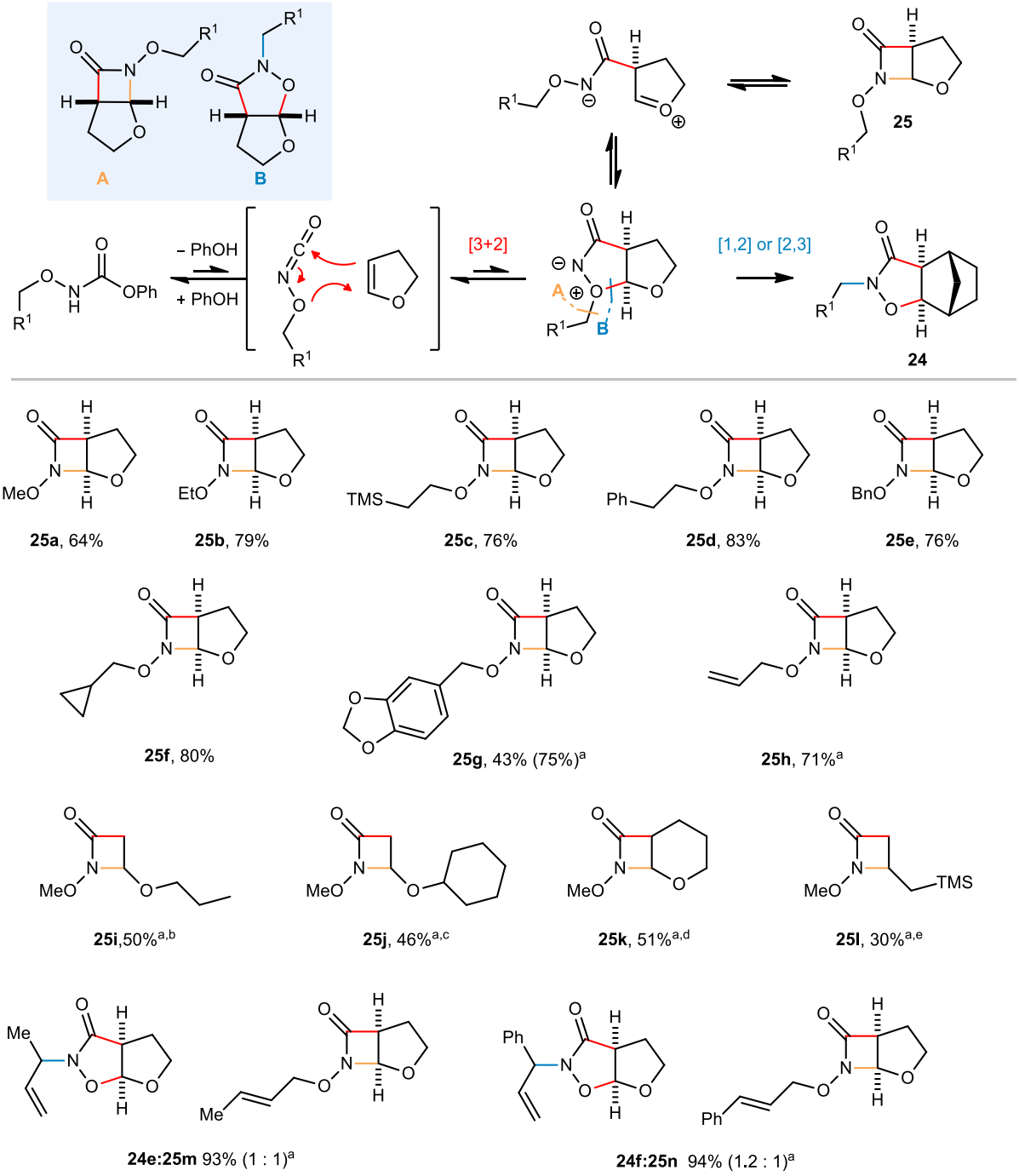
Table 28 Scope of intermolecular oxycarbonylation via *O*-isocyanate [3+2] cycloaddition



Conditions: alkoxycarbamate (1.0 equiv), alkene (50 equiv) in MeCN (0.2 M) at 180 °C for 2 hours (μW, sealed tube). Major diastereomer shown for **23b-23e** (d.r. by ^{1}H NMR are typically ~10:1, see SI for exact values for each entry). [a] 30 equiv alkene used. [b] ^{1}H NMR yields based on 1,3,5-trimethoxybenzene. [c] 0.3 h.

Similarly, the scope of the [3+2] cycloaddition with enol ethers was assessed (**Table 29**). While small scale studies of these compounds were first investigated by myself, these large-scale reactions / isolations were performed by Meredith Allen. The reaction again tolerated a variety of *O*-isocyanate precursors. The yield was unaffected by *O*-isocyanate substitution. Interestingly, *O*-benzyl, *O*-methyl cyclopropyl and *O*-allyl derivatives (**25e**, **25f**, **25h**) did not rearrange under the reaction conditions. However, the rearrangement was ultimately observed with crotyl and cinnamyl derived substrates **24e** and **24f** respectively. The identification of these products provided experimental support for an aza-oxonium ylide formed from [3+2] reaction pathway; however, could also be explained by rearrangement during an ionic stepwise [2+2].

Table 29 Scope of intermolecular [3+2] cycloaddition with enol ethers



Conditions: alkoxycarbamate (1.0 equiv), alkene (20 equiv), *i*-Pr_2NEt (0.20 equiv) in MeCN (0.2 M) at 120 °C for 2.5 hours (µW, sealed tube). [a] ^1H NMR yields based on 1,3,5-trimethoxybenzene. [b] 30 equiv alkene used. [c] 10 equiv alkene used. [d] 100 equiv alkene used. [e] 75 equiv alkene used at 150 °C.

3.18 Summary on the development of intermolecular *O*-isocyanate [3+2] cycloaddition reactions

While an optimal oxycarbonylation precursor was not identified, these foundational studies on their reactivity should provide fertile ground for subsequent investigations. That *O*-isocyanate precursors could lead to divergent reactivity (*e.g.* nitrene C–H amination versus rearrangement) and that enol ethers provided access to β-lactams greatly increased the synthetic utility of this preliminary study. This is highlighted by the variety of *N*-heterocyclic classes attainable from this novel transformation (**Figure 64**). Therefore, further development of this transformation is expected to pay dividends. The focus of subsequent studies ought to be on: 1) trapping the aza-oxonium ylide, 2) tethering strategies to perform pseudo-intramolecular reactions (*vide infra*), or 3) catalysis of the C–H amination step.

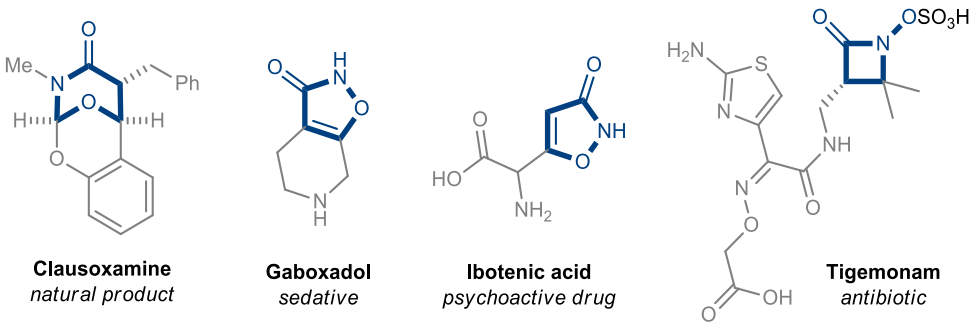


Figure 64 Bioactive *N*-heterocycles theoretically accessible from this methodology

3.19 Intramolecular *O*-isocyanate [3+2] cycloaddition

Conventionally—and when possible—new reactivity is often first studied in controlled intramolecular systems and then extended to intermolecular reactions. Since we had not anticipated this reactivity, we arguably complicated its initial study by having to account for extra variables associated with the initial bimolecular [3+2] cycloaddition. We were curious if some of the limitations encountered, such as the unfavourable equilibrium preceding C–H amination, could be mitigated by an intramolecular approach. However, it was unclear what the product of the intramolecular reaction would be. From the predicted aza-oxonium ylide three products were possible (**Figure 65**). Our combined intuition predicted that **27a** would be a minor product, but we could not agree if **26a** or **28a** would be the major product. **26a** certainly had the most active methylene C–H bond, but the strained product suggested a higher-energy conformationally distorted transition state. In contrast **28a** produced a less strained 5,5-bicyclic system, but its methylene C–H was inactivated.

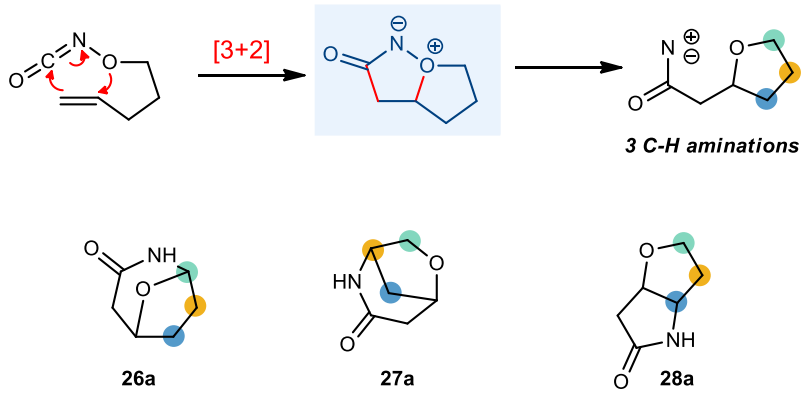


Figure 65 Predicted three products from intramolecular *O*-isocyanate [3+2] cycloaddition

The first reaction generated a complex mixture of products (**Figure 66**). It was immediately clear that this reaction was preferential toward a single product (**26a**), even though several products had also formed. Isolation of each product would prove a significant challenge since the reaction produced a mixture of exceptionally polar constitutional isomers. The isolation of all products was surmounted upon reaction scale-up to 1.0 mmol. The structures were assigned tentatively based on NMR analysis (**Figure 66**). Crystallization of each unknown sample was performed in mixtures of ether / hexanes. X-ray analysis of each unknown unambiguously confirmed the structures—which had been assigned correctly based on ^{1}H NMR analysis. A fourth product was isolated as a clear oil, which was exceptionally less polar than the three isomers. A perplexing singlet in the ^{1}H NMR was eventually clarified by the suggested structure **29a**, which would be formed by the acyl nitrene reacting with acetonitrile and subsequently aromatizing. This indicated that C–H amination could again be rate determining, since intermolecular trapping of the nitrene should be a relatively slow process compared to intramolecular C–H amination. Alternatively, this could suggest that acetonitrile reacts with the ylide and that this adduct is a more stable (conjugated) nitrenoid which performs the C–H amination. This explanation is attractive as it explains the solvent dependence on acetonitrile and also provides some rational to the exquisite selectivity for C–H amination over alteratnive pathways (*e.g.* 1,2-rearrangment).

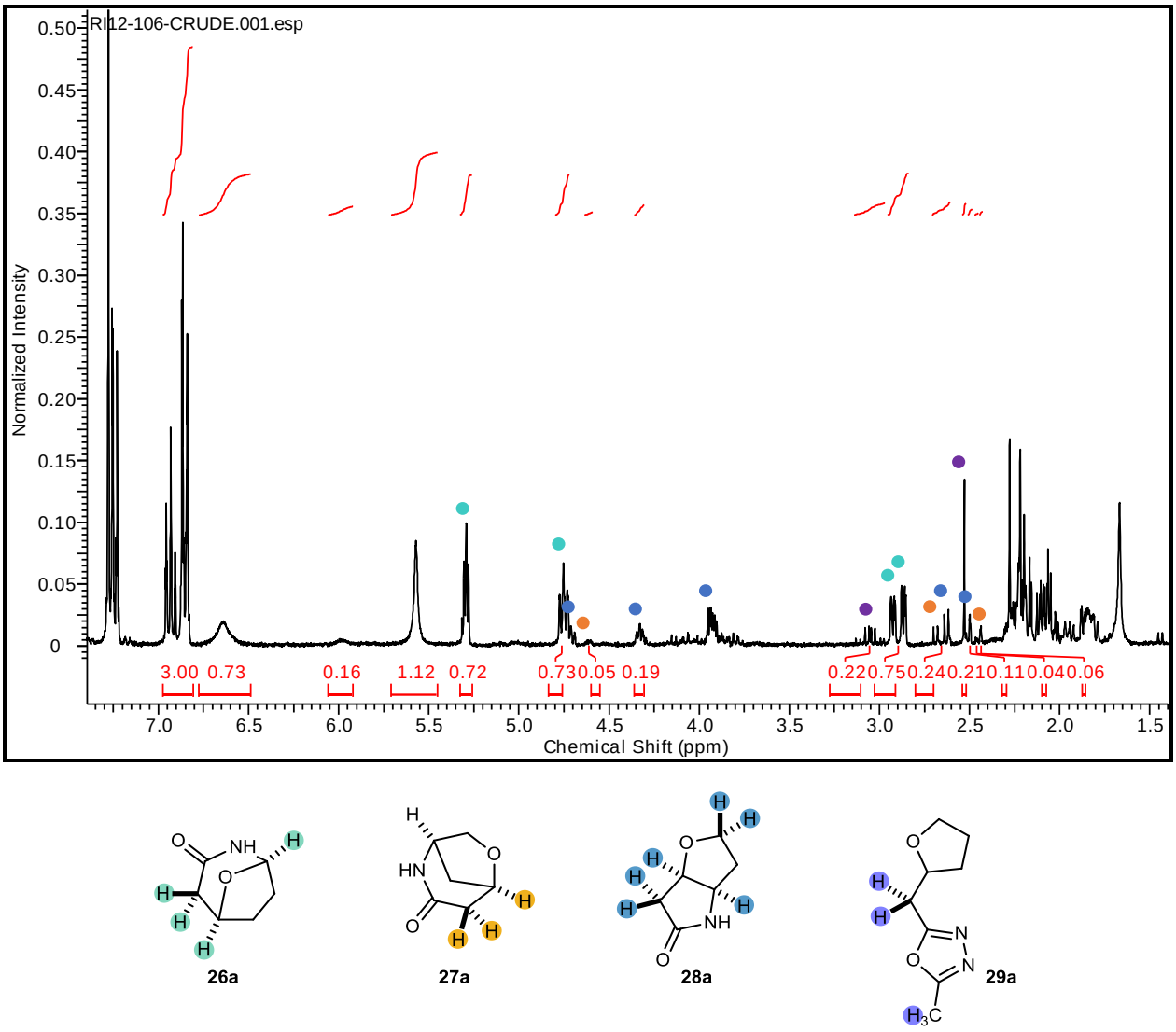


Figure 66 Crude ^{1}H-NMR of intramolecular *O*-isocyanate [3+2] cycloaddition with tentative product assignment based of splitting / ppm.

The combined yield of the cycloadducts and acetonitrile-trapped ylide implied an exceptionally efficient cycloaddition process (essentially quantitative formation of the ylide pre-N–O bond cleavage). Thus, a variety of conditions were screened to improve the *selectivity* of the C–H amination. Unfortunately, we were unable to develop conditions that led to lower

temperatures, or improved selectivity. Even though acetonitrile clearly reacted with the aza-oxonium ylide, no other solvent could be used in its place efficiently.

3.20 Computational study of the intramolecular *O*-isocyanate [3+2] cycloaddition

To probe differences between intermolecular and intramolecular reactivity, DFT was again performed (**Figure 68**). To enable a direct comparison, the relative energies of intermediates and products, as well as transition states for each step were calculated using the B3LYP functional and the 6-311+G(2d,p) basis set. Although the deblocking mechanism of *O*-isocyanate precursor **13a** was not modelled, it was calculated that this step was endergonic by $\Delta H = +8.1$ kcal/mol; yet the entropic driving force renders the process favorable by DFT calculations ($\Delta G = -9.1$ kcal/mol). Henceforth, the energies discussed are relative to the energy of the *O*-isocyanate. The cycloaddition was found to have a transition state energy of +15.9 kcal/mol (**TS1**), 8.8 kcal/mol lower in energy than the intermolecular cycloaddition. The intramolecular cycloaddition was still mildly endergonic ($\Delta G = +1.2$ kcal/mol). The following N–O bond cleavage step (TS2 $\Delta G^{\ddagger} = +21.5$ kcal/mol) forms the highest energy intermediate (acyl nitrene, $\Delta G = 18.6$ kcal/mol). The final C–H insertion step was once again rate determining and required +23.6 kcal/mol for the major product (**TS3**). The observed product distribution was unclear after DFT analysis of nitrene C–H insertion transition state energies for each bicyclic lactam product.

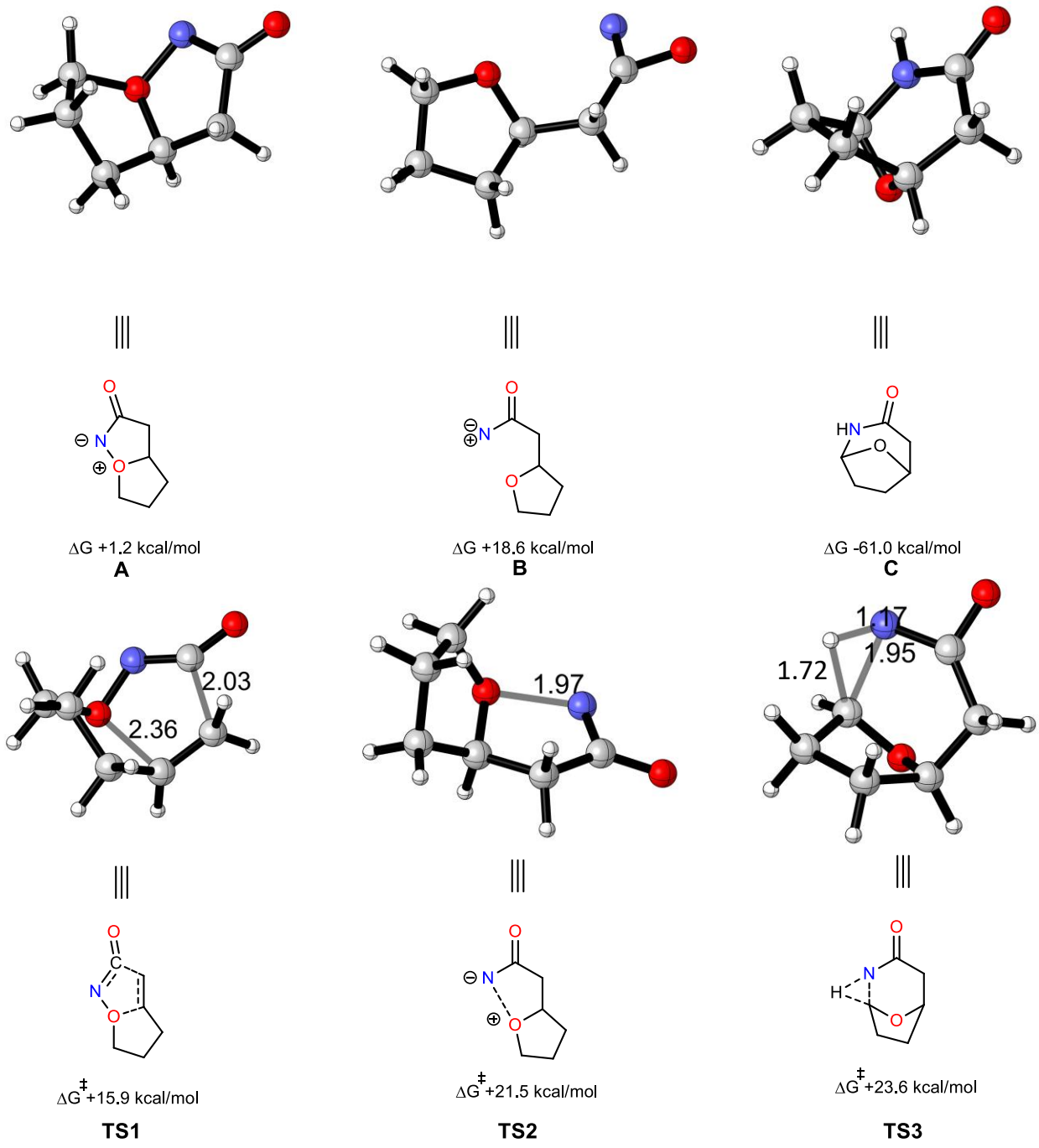


Figure 67 Optimized geometries for key intermediates / transition states of the intramolecular *O*-isocyanate oxycarbonylation reaction. Calculations used B3LYP/6-311+G(2d,p), PCM (acetonitrile). Harmonic frequency calculations ensured energy minima / one imaginary frequency was present for transition states. All Gibbs free energy values are versus the *O*-isocyanate.

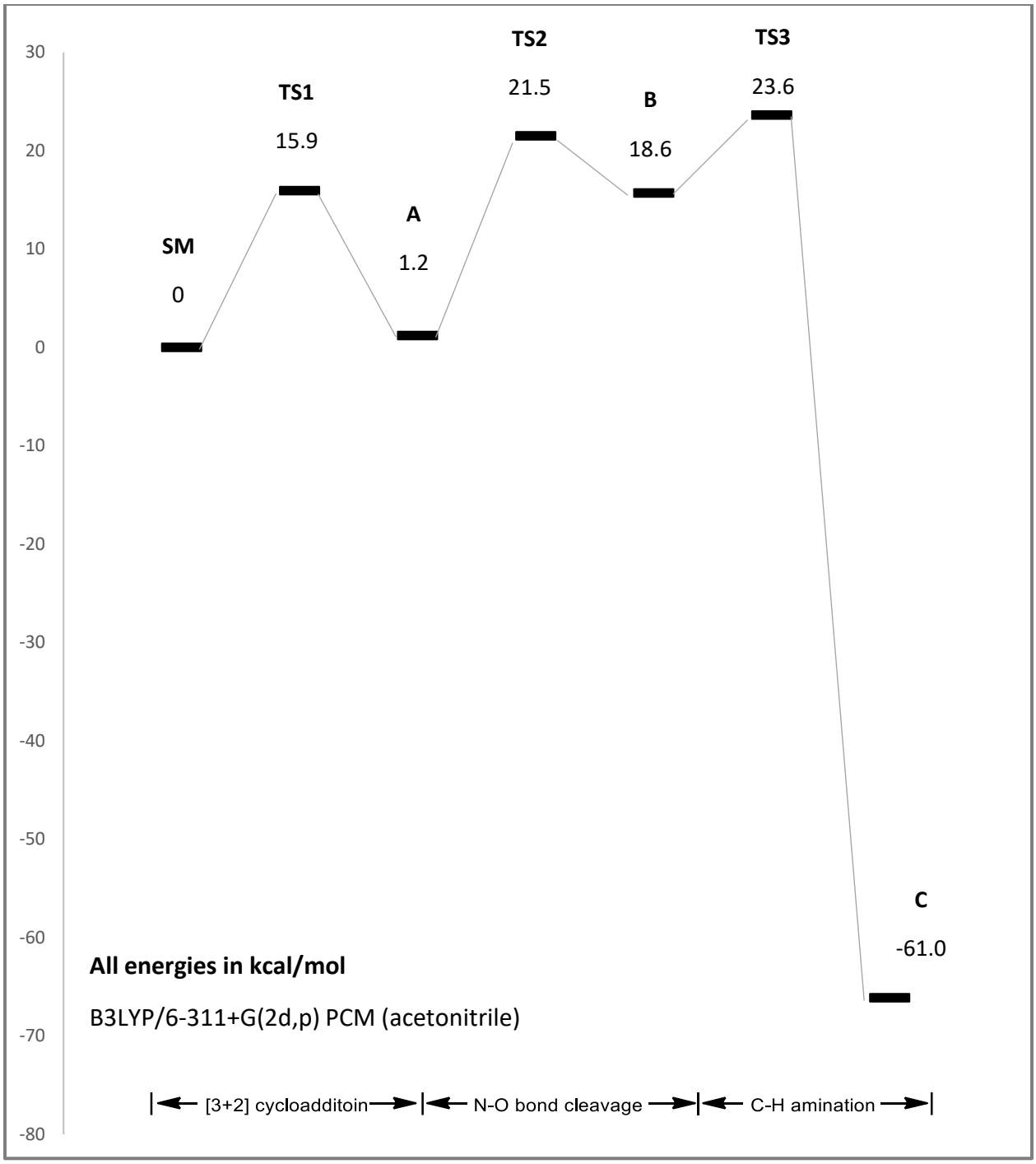


Figure 68 Reaction coordinate for the intramolecular *O*-isocyanate oxycarbonylation reaction.

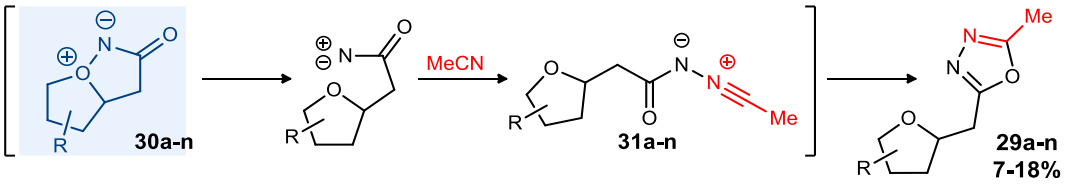


Figure 69 Acetonitrile traps the acyl nitrene proving the intermediacy of an acyl nitrene.

The acetonitrile-nitrene adduct cyclization (**Figure 69**) had previously been studied experimentally in detail.[166] The reaction of acetonitrile with the acyl nitrene and subsequent cyclization to form oxadiazole **29a** was a thermodynamically favourable process, though was clearly not kinetically favourable. Previous work by Jenks[166] found a rapid rate of reaction between acyl nitrenes and acetonitrile (10^5 - 10^6 $M^{-1}s^{-1}$), though, a slower rate of cyclization (10^4 s^{-1}) was observed. This slow rate of oxadiazole formation supports the low yield observed from ylide **31** even with the thermodynamic driving force associated with aromatization.

3.21 Synthetic survey of the intramolecular *O*-isocyanate [3+2] cycloaddition

With a more thorough understanding of the mechanism predicted by DFT, the scope of the transformation was assessed. In general, substitution on the alkyl backbone was well tolerated. Substitution at the terminal position of the alkene led to high yields of the corresponding cycloadducts (**26b**, **26c**). Notably, the *cis* and *trans* methyl-substituted *O*-isocyanates underwent stereospecific cycloadditions to form the corresponding *syn* and *anti* lactam products (**26b**, **26c**) respectively, providing corroborating experimental evidence that the cycloaddition was concerted. Terminal disubstitution on the alkene led to somewhat lower yield (**26d**), whereas substitution at the internal position was well tolerated (**26e**), an expected trend

given the predicted asynchronicity of the cycloaddition. α-Substitution to the oxygen atom was tolerated (**26f**-**26i**); however, basic substituents led to lower yields (**26j**). The *syn* cyclohexyl substrate **13k** underwent cycloaddition readily leading to a high yield of the corresponding tricyclic product (**26k**). The lower yields of α-substituted precursors could be accounted for based on the diastereoselectivity of the cycloaddition (**Figure 70**). Indeed, only a single diastereomer of **30** can form the major product. The isolation of oxadiazoles from **29f** and **29h** in 1:1 / 3:2 mixtures suggested that the cycloaddition was poorly diastereoselective.

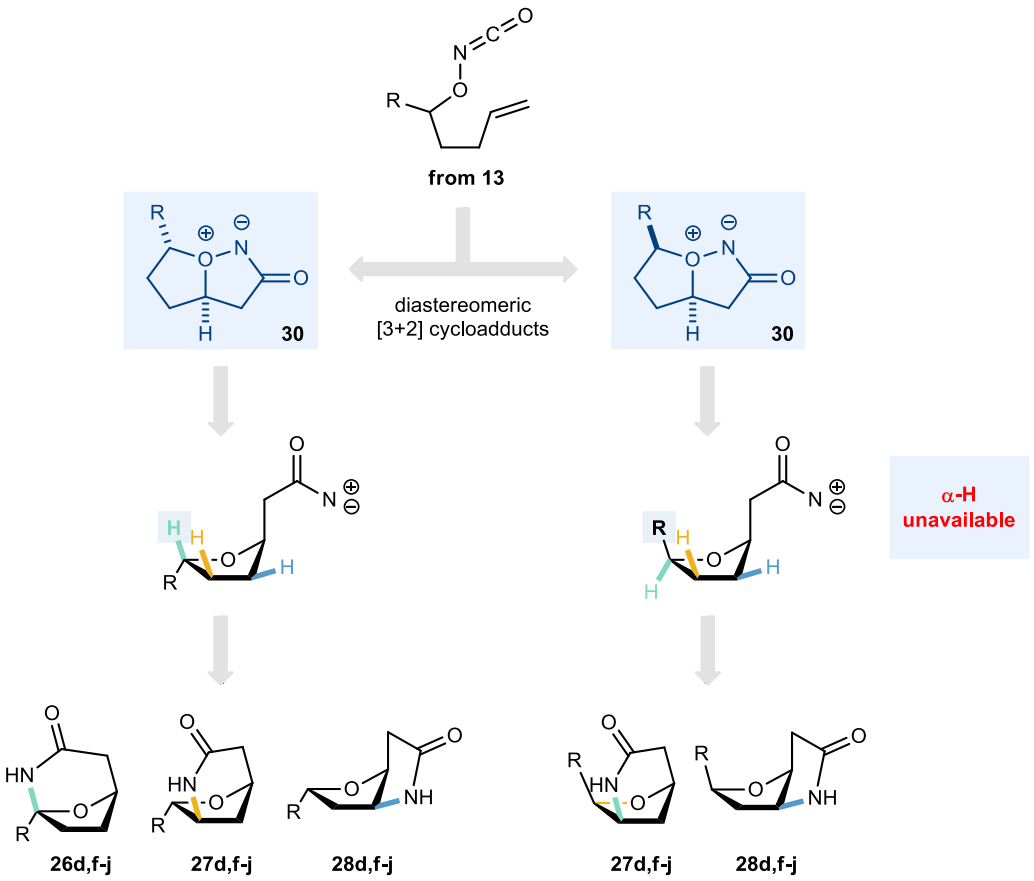


Figure 70 Substitution affects the distribution of products.

Two geminal dimethyl substrates were also tested and led to slightly lower yields relative to the unsubstituted alkyl chain (**26m**, **26n**). In the analogous intramolecular alkene cycloaddition of amino-isocyanates, substrates with a Thorpe-Ingold bias reacted at room temperature and high yields of the products could be obtained as low as 50 °C with catalytic base (unbiased substrates reacted at 120-200 °C)[167] (**Table 3**, **Table 5**). However, the cycloaddition reaction with *O*-isocyanates did not benefit from a Thorpe-Ingold effect and lower temperatures did not lead to product formation. The mechanistic implication of this observation was that the cycloaddition was likely not the rate determining, consistent with the DFT and FMO analyses which suggested a facile [3+2] cycloaddition reaction.

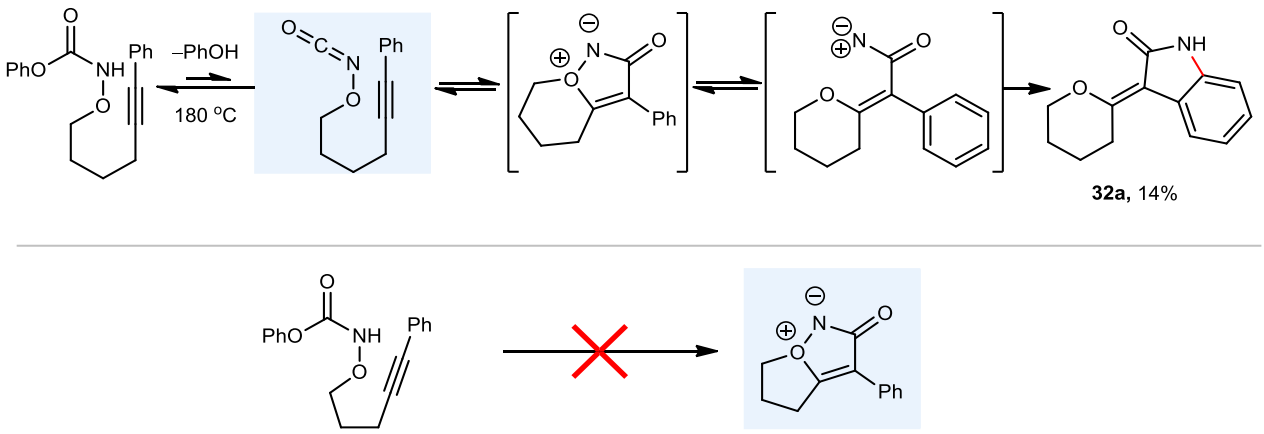


Figure 71 Intramolecular *O*-isocyanate alkyne [3+2] cycloaddition reaction.

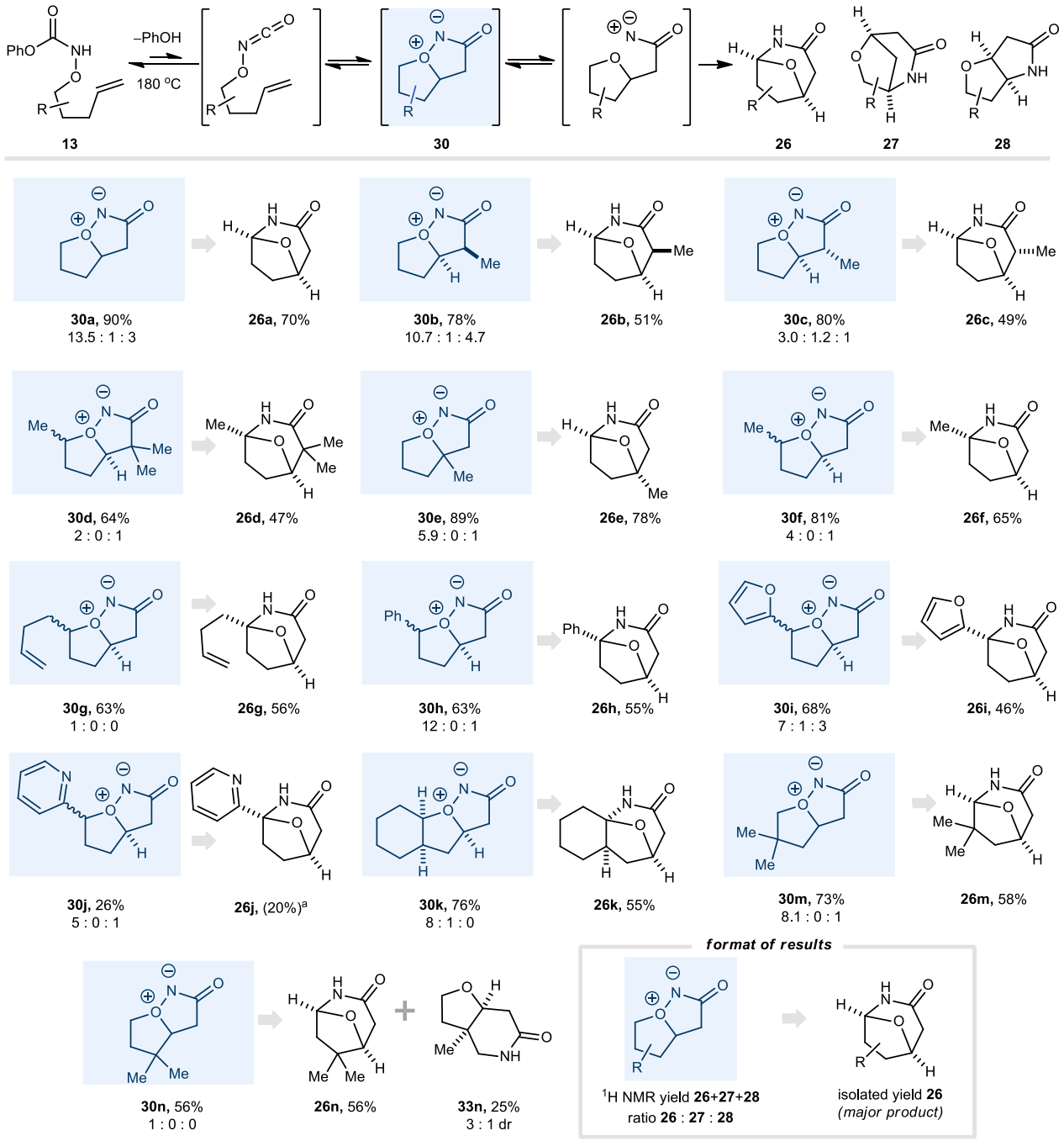
An intramolecular alkyne cycloaddition was attempted. While no examples of intermolecular alkyne cycloaddition were observed (**Figure 50**), the intramolecular reaction provided inklings of reactivity. Although encouraging, our excitement was again tempered after

exhaustive attempts to optimize the reaction failed. Nevertheless, this was the first example of an *O*-isocyanate alkyne [3+2] cycloaddition. Notably, the nitrene underwent a C–H amination on an aryl C(sp^2)-H bond. It is unknown if this was the challenging step of the reaction, since no sp^2 C–H aminations were assessed in the alkene cycloaddition reactions. However, this aryl substituted alkyne was the only feasible substrate to synthesize from an intramolecular cycloaddition reaction perspective. The analogous 5-carbon chain substrate failed to provide any product, likely due to impossible orbital overlap for the planar [3+2] cycloaddition reaction.

3.22 Summary on the intramolecular *O*-isocyanate [3+2] cycloaddition

In summary, these intramolecular reactions clearly demonstrate the strengths and weaknesses of the *O*-isocyanate [3+2] cycloadditions. The unselective C–H amination greatly diminished the synthetic applicability of this transformation, even though the combined yields of cycloadduct-derived products were typically between 70-90%. This reinforced that the cycloaddition step was quite facile, and the readiness that the *O*-isocyanate engaged with unstrained / inactivated alkenes in the intramolecular reaction provided hope that a tethering strategy could be an efficient way to overcome the general lack of synthetic applicability in the intermolecular reaction.

Table 30 Synthetic scope of intramolecular *O*-isocyanate [3+2] cycloaddition reaction



Conditions: carbamate (1.0 equiv) in MeCN (0.05 M) at 180 °C for 4-10 hours (μW, sealed tube). ^{1}H NMR based on 1,3,5-trimethoxybenzene for the inferred yield of common intermediate **5** based on the sum of ^{1}H NMR yields of products **6**, **7**, **8** (ratio **6**:**7**:**8** shown below). The major product **6** was isolated for each entry (isolated yield shown). [a] ^{1}H NMR yield based on 1,3,5-trimethoxybenzene.

3.23 Subtitution / C-H amination cascade project intiation

The *O*-isocyanate cycloaddition work inspired new *O*-isocyanate cascade reactions. We were curious if a suitable precursor could undergo substitution then N–O bond cleavage and subsequent C–H amination. This would require a reagent that could both act as an isocyanate and a nitrene—an elusive synthon (**Figure 72**). Substitution reactions on *O*-isocyanates were developed, but what remained intangible were controlled reactions involving N–O bond cleavage. To achieve this goal, precursors with labile N–O bonds were considered. However, inherent challenges to this reaction would be the ordered reactivity *e.g.* isocyanate reactivity must precede nitrene formation / reactivity. Based on the results of the amine substitution reaction / successful cascade reactions, acyloxy-*O*-isocyanates seemed ideal candidates for further study. Predictably, tosyloxy-*O*-isocyanate precursors proved too unstable and underwent oxa-Lossen rearrangements prior to *O*-isocyanate formation. Reaction screening commenced with precursor **15c** and diisobutyl amine as a biased amine (**Table 31**).

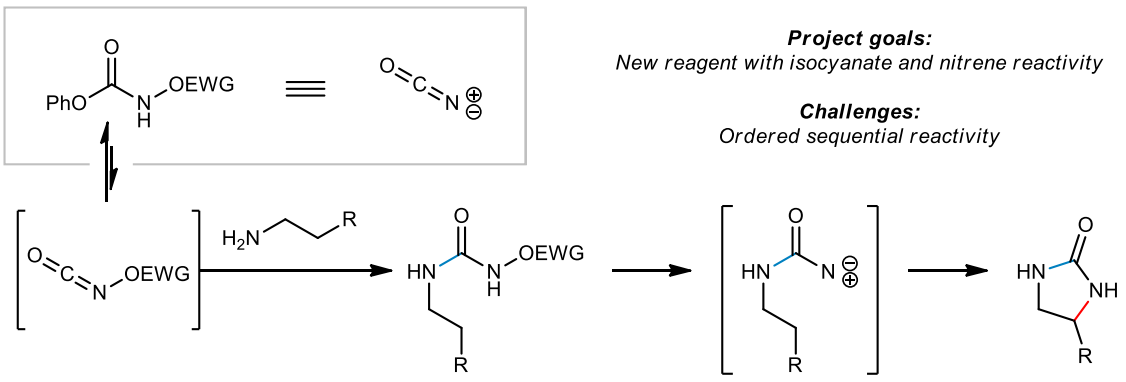
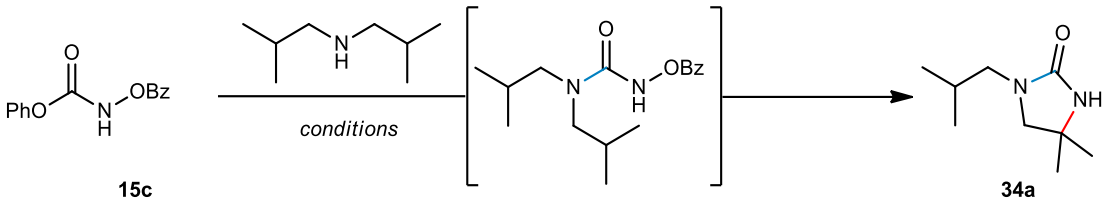


Figure 72 Hypothetical cascade reaction using *O*-isocyanates as a novel isocyanate / nitrene synthon.

Table 31 Selected optimization for thermal substitution / C–H amination cascade reaction.



entry	base	solvent	temp (°C)	time (h)	yield (%)
1	Et_3N	THF	70	15	0
2	*i*-Pr_2NEt	THF	90	15	0
3	*i*-Pr_2NEt	EtOH	90	15	<10
4	*i*-Pr_2NEt	MeCN	90	15	16
5	Et_3N	MeCN	90	20	23
6	K_2CO_3	MeCN	90	20	11
7	*i*-Pr_2NEt	$(CH_2Cl)_2$	90	15	20
8	Et_3N	$(CH_2Cl)_2$	90	15	35
9	Et_3N	$(CH_2Cl)_2$	90	65	73
10	DMAP	$(CH_2Cl)_2$	90	15	7
11	DABCO	$(CH_2Cl)_2$	90	15	12
12	**TMG**	$(CH_2Cl)_2$	**90**	**15**	**62**
13	Imidazole	$(CH_2Cl)_2$	90	15	6
14	DBU	$(CH_2Cl)_2$	90	15	6
15	Pyridine	$(CH_2Cl)_2$	90	15	5
16	Et_3N	$PHCF_3$	120	15	10
19	Imidazole	$(CH_2Cl)_2$	120	15	70
20	Imidazole	$(CH_2Cl)_2$ [Ar]	120	15	65
21	Imidazole	$CDCl_3$	120	15	72
22	Imidazole	$(CH_2Cl)_2$ - sieves	120	15	62

Conditions: phenyl *N*-benzoyloxycarbamate **4b** (1 equiv), diisobutylamine (1 equiv), base (0.2 equiv) in solvent (0.3 M) for temperature and time specified. ^1H NMR yields based on 1,3,5-trimethoxybenzene.

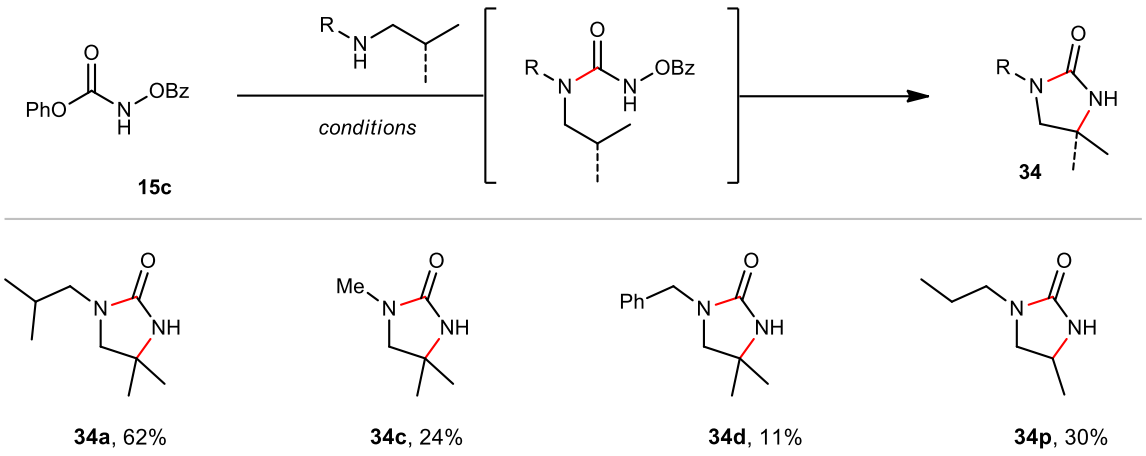


Figure 73 Initial reaction scope for thermal cascade substation / C–H amination.

Quite rapidly, conditions for the substitution / C–H amination cascade reaction were achieved using diisobutylamine as the nucleophile (**Table 31**). However, challenging side reactions were deleterious to product yield. These were chiefly trimerization of the *O*-isocyanate, and interactions of the benzoic acid (released from N-O bond cleavage) with the amine nucleophile. It is possible that the increased incidence of trimerization was the result of the acid / base equilibrium between the amine and the released benzoic acid, which diminished the availability of amine nucleophile to trap the *O*-isocyanate. Therefore, as the substitution / C–H amination proceeded, thus increasing the concentration of benzoic acid, the substitution would become increasingly hampered. This problem was compounded when the amine was changed to an unsymmetrical *N*-methyl isobutylamine. Naturally, the C–H amination was no longer biased to occur regardless of urea conformation. While speculative, it was thought that a slower C–H amination allowed for a more reversible substitution. Ultimately an abundance of amine / benzoic acid salt and trimer was isolated from this reaction. Further attempts to expand the

substrate scope were unsuccessful using a variety of secondary amines (**Figure 73**). Substrate scope expansion and reaction development was achieved by developing a novel strategy for nitrene formation via photocatalysis (see Chapter 4).

Chapter 4:

Photocatalytic C-H amination using hydroxyureas as new amination agents

Prelude

In this chapter, efforts to develop a novel C–H amination reaction is described. Photoredox was a new direction in our group; therefore, the knowledge / equipment required to perform photoredox reactions had to be rapidly acquired (see SI for photoredox reaction set up). Again, a vast literature survey was performed to gauge the state of photoredox chemistry and understand the fundamentals necessary to develop new reactions. A non-exhaustive review of photoredox reactivity will be presented to guide the reader. Since this chapter focuses solely on photocatalytic C–H amination reactions—a relatively rare transformation—previous examples will be described in detail. Optimization of our photocatalytic C–H amination reaction, substrate scope and limitations, attempts to study the mechanism and the attempted extensions of this reactivity to other systems will be described.

4.1 An introduction to photocatalysis: basic photochemistry of $Ru(bpy)_3^{2+}$

Photoredox catalysis has enabled a variety of new bond-forming protocols. However, before such methods can be appreciated, an understanding of the underlying photochemistry is required. Since $Ru(bpy)_3^{2+}$ is a common catalyst for organic transformations, and the optimal catalyst for the C–H amination reaction discussed later, the photochemistry of $Ru(bpy)_3^{2+}$ will be introduced. The basic principles described here can be extended other transition metal photocatalysis with different metal centers or ligands.

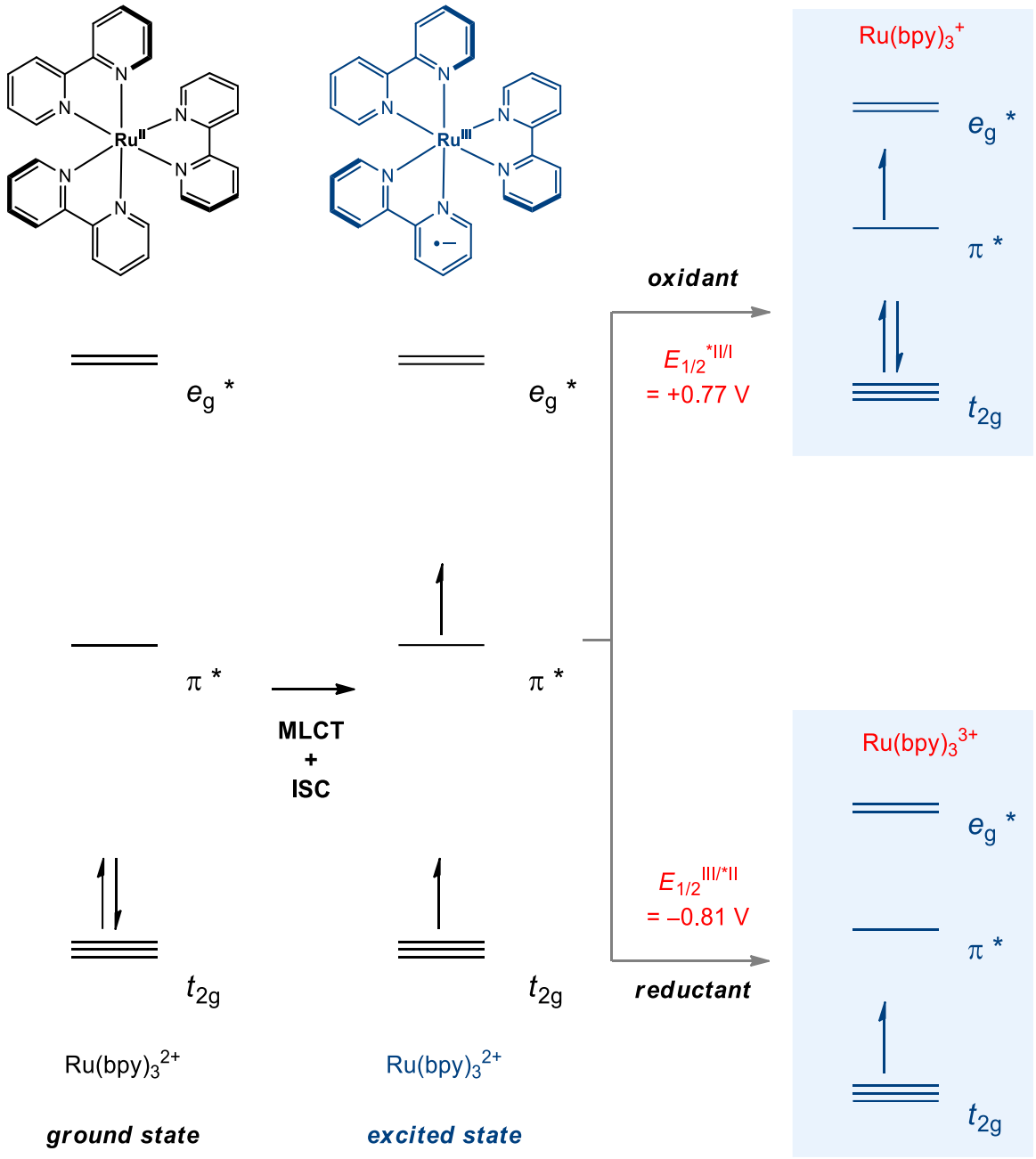


Figure 74 Fundamental MOs involved in $Ru(bpy)_3^{2+}$ photochemistry. Reduction potentials are measured in MeCN as the solvent and versus SCE.

Upon absorption of a photon in the visible region, (λ_{max} = 452 nm for $Ru(bpy)_3^{2+}$) the complex undergoes a metal to ligand charge transfer (MLCT), wherein an electron from one of

the photocatalyst's metal-centered t2g orbitals is excited to a ligand-centered π* orbital (**Figure 74**).[168–170] Thus, during this transition the metal has effectively been oxidized from Ru(II) to Ru(III) and the ligand framework has undergone a single electron reduction to the radial anion species.[171] This initially occupied singlet MLCT state undergoes rapid intersystem crossing (ISC) to the corresponding lower-energy, long-lived reactive triplet MLCT state (665 ns for $*Ru(bpy)_3^{2+}$). Subsequent single electron transfer (SET) reactions occur from the triplet MLCT state. The fact that decay to the singlet ground state is a spin-forbidden process enforces the long triplet lifetime.[172]

The photoexcited complex is both more oxidizing and more reducing than the ground state species. The dual nature of the excited state as both oxidant and reductant can be rationalized based on the molecular orbitals (**Figure 74**). Photoexcitation of $Ru(bpy)_3^{2+}$ generates a lower-energy hole in the t2g orbital; which can accept an electron to oxidize a substrate. Alternately, photoexcitation of $Ru(bpy)_3^{2+}$ generates a higher-energy electron in the π* orbital, which can donate an electron to reduce a substrate.

Consequently, redox transformations of $*Ru(bpy)_3^{2+}$ proceed by oxidative or by reductive quenching of the triplet excited state (**Figure 75**). In an oxidative quench (**Figure 75** -top), $*Ru(bpy)_3^{2+}$ functions as a reductant, reducing an electron acceptor (A) by a SET event. The products of this SET event are the radical anion of A and the oxidized photocatalyst, $Ru(bpy)_3^{3+}$. In turn, the oxidized photocatalyst is a strong oxidant ($E_{1/2}^{III/II}$ = +1.29 V vs SCE) and may accept an electron from some donor (D). The products of this second SET event are the radical cation of D and the Ru(II) ground-state species, thus completing the photocatalytic cycle. Alternately, in a reductive quench (**Figure 75**- bottom), $*Ru(bpy)_3^{2+}$ performs as an oxidant and accepts an

electron from D to give the reduced species $Ru(bpy)_3^+$. This Ru(I) intermediate is a good reductant ($E_{1/2}^{II/I}$ = −1.33 V vs SCE) and can donate an electron to A to replenish the ground-state species, $Ru(bpy)_3^{2+}$.

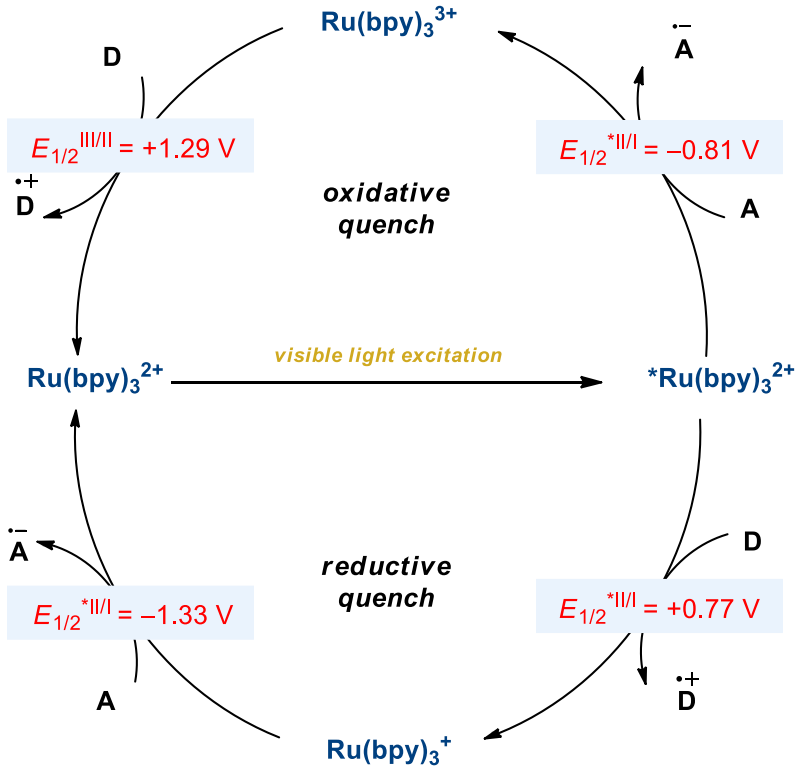


Figure 75 Oxidative versus reductive quenching cycles in $Ru(bpy)_3^{2+}$ photoredox reactions. (D = electron donor, A = electron acceptor).

An alternative activation mode is triplet energy transfer (EnT). Unlike photoredox pathways, which involve SET with organic molecules, a triplet excited state of $Ru(bpy)_3^{2+}$ may otherwise engage in triplet-triplet energy transfer. Here, the decay of $Ru(bpy)_3^{2+}$ from its T_1 to S_0 can promote an acceptor molecule (A) from its S_0 to its T_1.[170] The proclivity of a catalyst to engage

in EnT reactions is based on the difference of triplet excited state energies (ΔE_T) between catalyst and substrate, *e.g.* $\Delta E_T = E_T$ (A) – E_T (Ru^{2+}). For reactions with $\Delta E_T < 0$, EnT is diffusion limited, whereas for reactions with $\Delta E_T > 0$, EnT is generally rate determining.[173] $Ru(bpy)_3^{2+}$ is a modest EnT catalyst (E_T = 49.0 kcal/mol), whereas $Ir(dFppy)_3$ is much higher (E_T = 63.5 kcal/mol). In contrast to photoredox reactions, EnT reactions are relatively understudied in the context of synthetic organic chemistry.

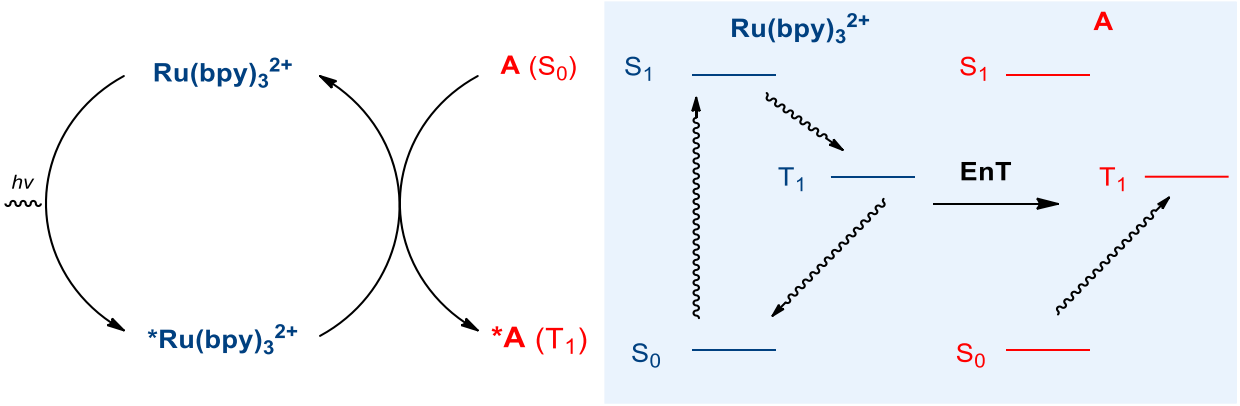


Figure 76 Triplet energy transfer (EnT) from $*Ru(bpy)_3^{2+}$ to an acceptor (A).

4.2 Brief historical context of photoredox catalysis: a synthetic renaissance

The first organic transformation enabled by photoredox catalysis was reported by Kellogg in 1978.[174,175] Using $[Ru(bpy)_3]Cl_2$, Kellogg catalyzed the reduction of sulfonium ions to alkanes / thioethers. Subsequent work by Tanaka[176] and Pac[177–180] extended this catalytic system to a variety of other organic substrates. In 1991 Okada and Oda developed the first reactions with *N*-(acyloxy)phthalimides, which were used as redox-active esters to produce alkyl radicals upon decarboxylative fragmentation.[181] The importance of this seminal study cannot be overstated,

as hundreds of subsequent papers would essentially repeat this work by varying the radical trapping agent / expanding the redox-active esters to other SET-reducible substrates, and also tandem dual catalytic couplings involving the radicals generated. However, despite these encouraging early studies, organic transformations enabled by photoredox catalysis remained a rarity within the synthetic community until the early 2000s. With modern LED technology, the ease-of-access to photoredox reactions likely spurred recent efforts.

4.3 Photocatalytic C–H amination reactions

Since its renaissance, photoredox has emerged as a powerful tool to enable amination reactions. Several reviews document the various new bond disconnection strategies.[23,182,183] Photoredox reactions enable the generation of reactive intermediates under exceptionally mild conditions. This becomes important in the context of C–H amination reactions, which often proceed through high energy *N*-centered radical or nitrene intermediates. Whereas previous methods to access such intermediates typically required harsh UV irradiation, stoichiometric Sn-reductions, or the use of labile chloramine reagents, photoredox offers comparatively benign conditions and has thus been widely adopted by the synthetic community. Photoredox remains a particularly attractive method for amination given the overlap in redox properties between amine reagents / photocatalysts. In general, reactive *N*-species can be generated either through reductive, oxidative or EnT processes. The next section will detail examples of C–H amination using photocatalysis. The first photocatalytic C–H amination was reported in 2014 and despite a recent surge of high impact reports on photocatalytic C–H amination, this topic has not been reviewed.

4.4 Photoredox catalyzed arene C-(sp^2)-H amination

By far, photoredox C–H amination reactions on (hetero)arene π-bonds are the most common. There are essentially two streams of reactivity used to achieve C–H amination of (hetero)arenes: 1) *N*-centered radical / nitrene generation, or 2) arene oxidation to the arene radical cation / trapping with nucleophilic amines.

4.5 Photocatalytic arene C(sp^2)–H amination via *N*-centered radical / nitrene formation

In 2014 Sanford reported the first example of C–H amination (imidation) via photoredox catalysis.[184] Building off prior work by Skell[185,186] / Okada and Oda[181], Sanford engineered a phthalimide redox-active ester to generate *N*-centered radicals (**Figure 77**). Implementing a more electron withdrawing carboxylate group altered the site of reduction from the phthalimide carbonyl to the ester carbonyl. In the proposed mechanism, photoexcitation of $Ir(ppy)_3$ generates the excited state $*Ir(ppy)_3$. SET reduction from $*Ir(ppy)_3$ to the C=O of the trifluoroacetate generates the *N*-centered phthalimidyl radical (PhthN•) and the oxidized catalyst, $Ir(ppy)_3^+$. Addition of PhthN• to the arene dearomatizes the arene forming a neutral radical species, which can be oxidized by the $Ir(ppy)_3^+$ regenerating the catalyst and generating a cationic Wheland intermediate. Rearomatization is driven by deprotonation of the acidic C–H in the Wheland intermediate by the trifluoroacetate anion. Notably, 10 equivalents of the arene reaction partner were necessary and often poor regioselectivity was observed. Predictably, lower yields were often obtained with electron poor aryl reaction partners.

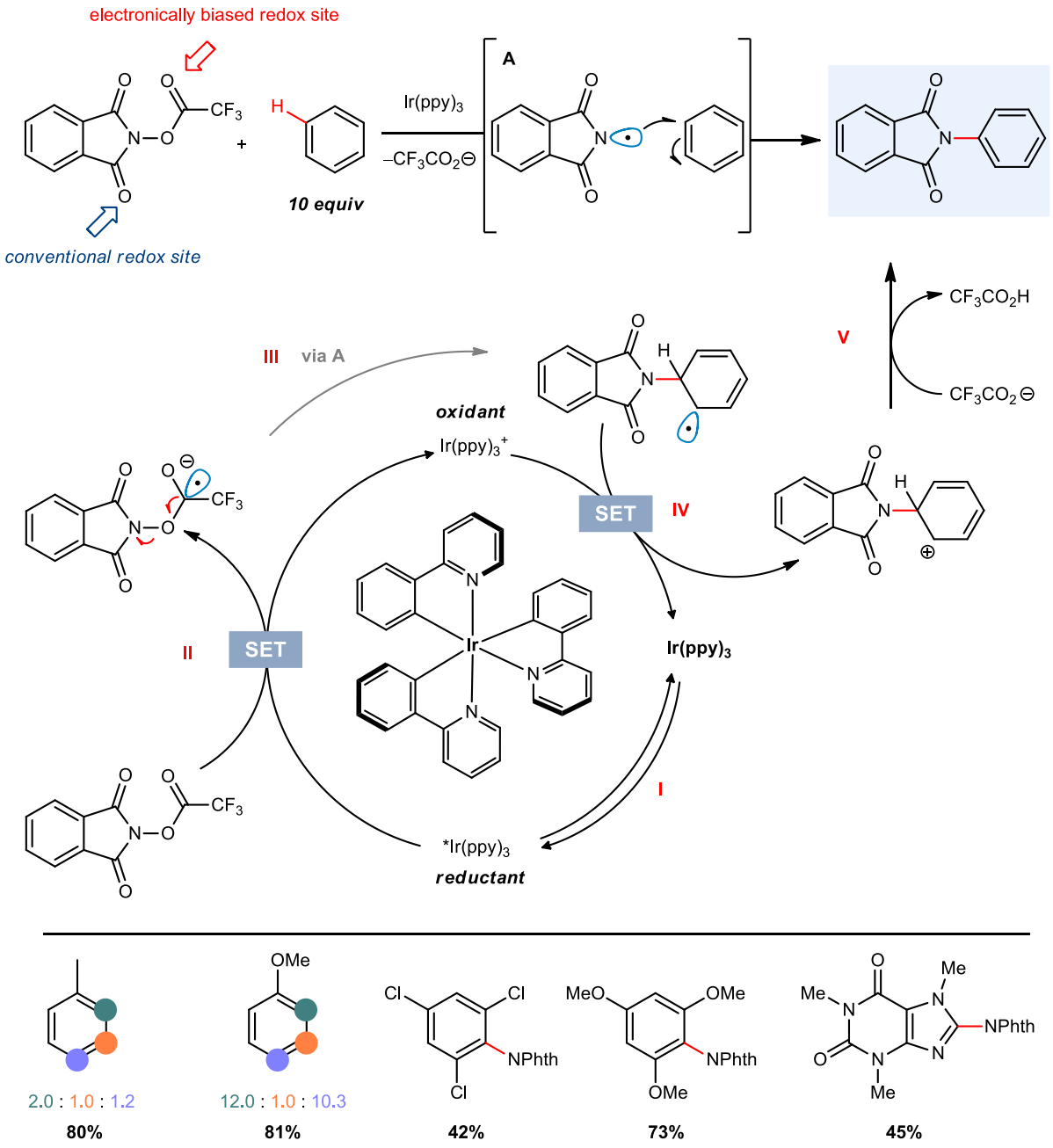


Figure 77 Sanford's pioneering intermolecular arene C–H amination via photoredox catalysis.

Credit must also be attributed to Yu[187] and Lee[188] who disseminated nearly identical work to Sanford only a month after the original publication. Various research groups have since elaborated these studies to incorporate a variety of different amination reagents including

amidyl[189], amino[190,191], iminyl,[192,193] pyridyl,[194–196] and tosylamino[197] *N*-centered radicals. In most cases the mechanism / mode of activation remains unchanged since an initial reductive quench necessarily primes the photocatalyst to subsequently oxidize the resultant neutral aryl radical to the cationic Wheland intermediate. However, the need to prefunctionalize the N-radical precursor to enable *N*-centered radical formation via SET reduction has been circumvented in some cases by deprotonation of an N–H bond and subsequent SET oxidation of the nitrogen anion.[198–200] In turn, the use of additional oxidants were required to oxidize the aryl radical and promote rearomatization, to enable formal cross dehydrogenative C–H amination reactions. As an example, Itami recently demonstrated the cross-dehydrogenative C–H amination of sulfonylimides in the presence of $Ru(bpy)_3^{2+}$ (**Figure 78**).[198] Photoexcited $Ru(bpy)_3^{2+}$ undergoes SET reduction with an excess of IBB, which produces an I-centered radical and $Ru(bpy)_3^{3+}$, a powerful oxidant. $Ru(bpy)_3^{3+}$ oxidizes the sulfonylimide to generate a stabilized *N*-centered radical which undergoes addition to an aryl species. The resultant neutral aryl radical is oxidized by the iodine radical, and subsequent deprotonation leads to rearomatization. While this works avoids prefunctionalization of the aminating reagent, the use of a sulfonylimide and excess oxidant present their own limitations.

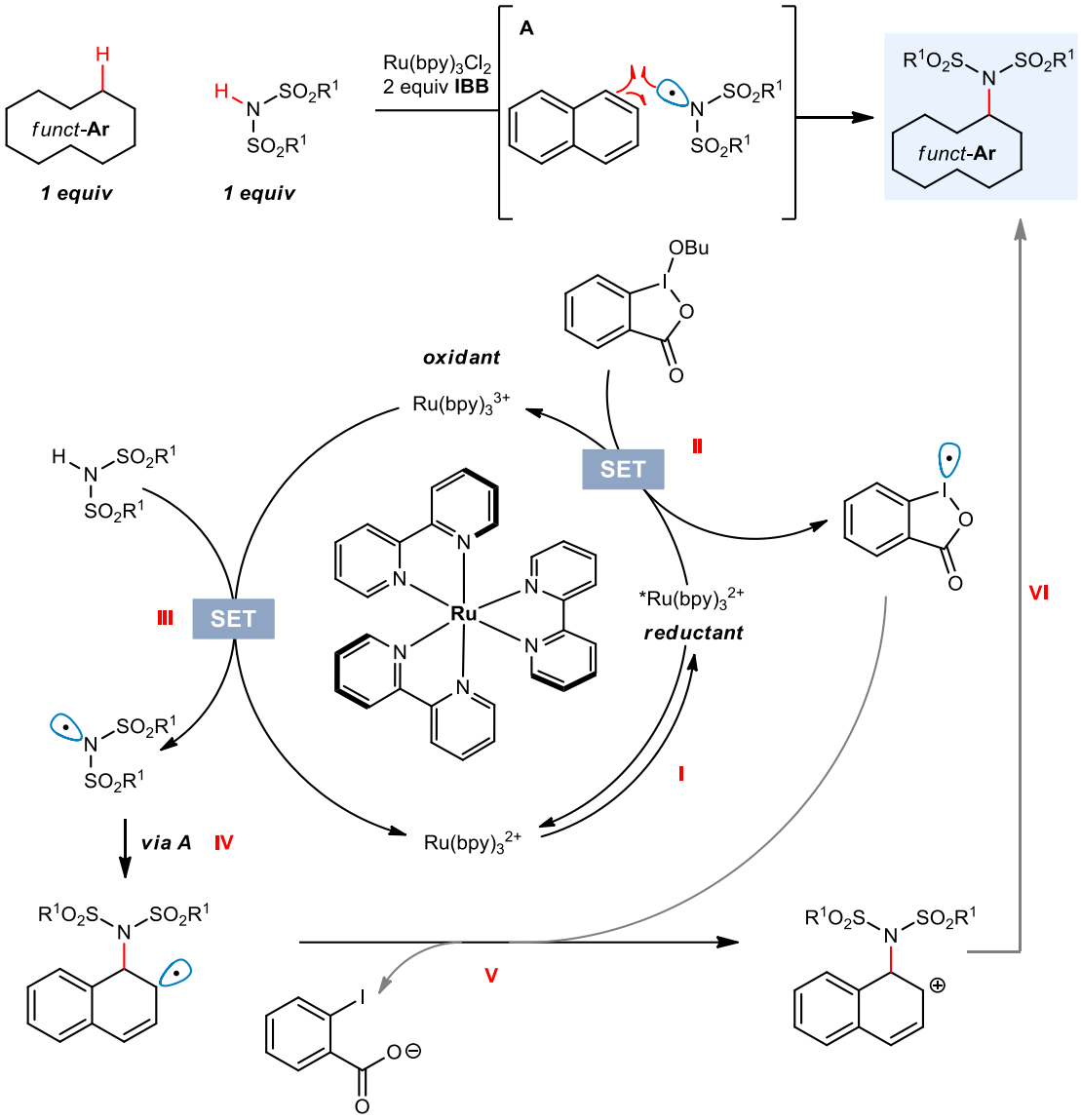


Figure 78 Itami's modified procedure using hypervalent iodine enables cross dehydrogenative coupling

Alternatively, EnT has been used to access nitrenes and *N*-centered radicals from a variety of precursors. In 2015, König reported the triplet sensitized C–H amidation of electron rich heterocycles (**Figure 79**).[201] Using visible light $Ru(bpy)_3^{2+}$ catalysis, triplet sensitization of benzoyl azides resulted in triplet nitrenes. The triplet nitrenes were protonated in the presence of H_3PO_4

to form nitrenium ions, which were used for regioselective intermolecular amidation of electron-rich heteroarenes. Notably, in some instances the oxazoline was formed as the major product.

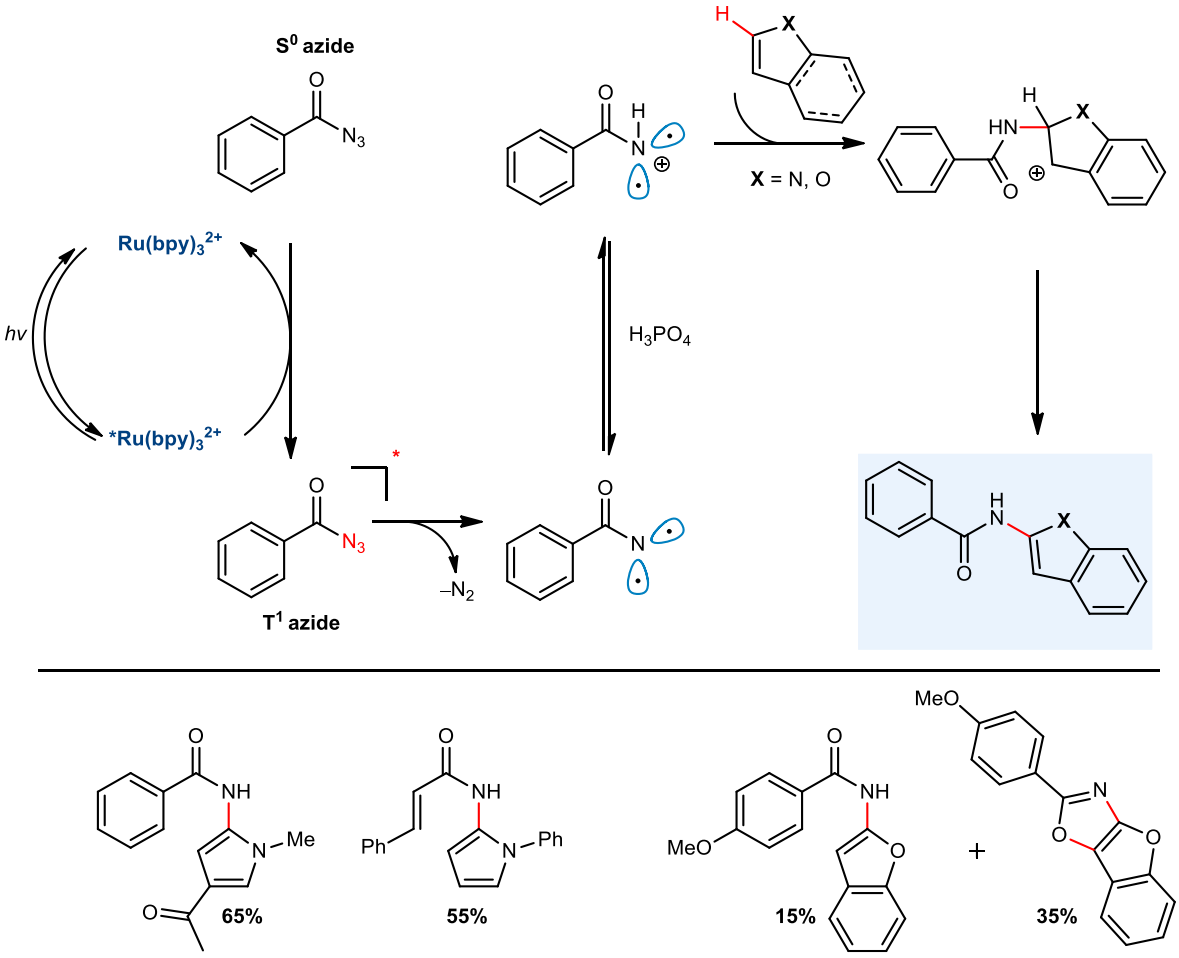


Figure 79 König's energy transfer catalyzed intermolecular C-H amination of activated heteroarenes via triplet nitrenium ions.

In a subsequent report, Li and Lu[202] applied the same conditions developed by König to achieve selective arene C(sp^2)–H amination of *O*-aryl azidoformates (**Figure 80**), even in the presence of highly reactive tertiary benzylic C(sp^3)–H bonds. The fact that the triplet nitrenes did

not undergo C(sp^3)–H amination was striking, especially in the context of the work in this thesis, as well as work by Chang[203]—which presumes triplet nitrene reactivity for C(sp^3)–H amination. The authors proposed a biradical intermediate that underwent a subsequent radical 1,2-hydride shift / rearomatization sequence.

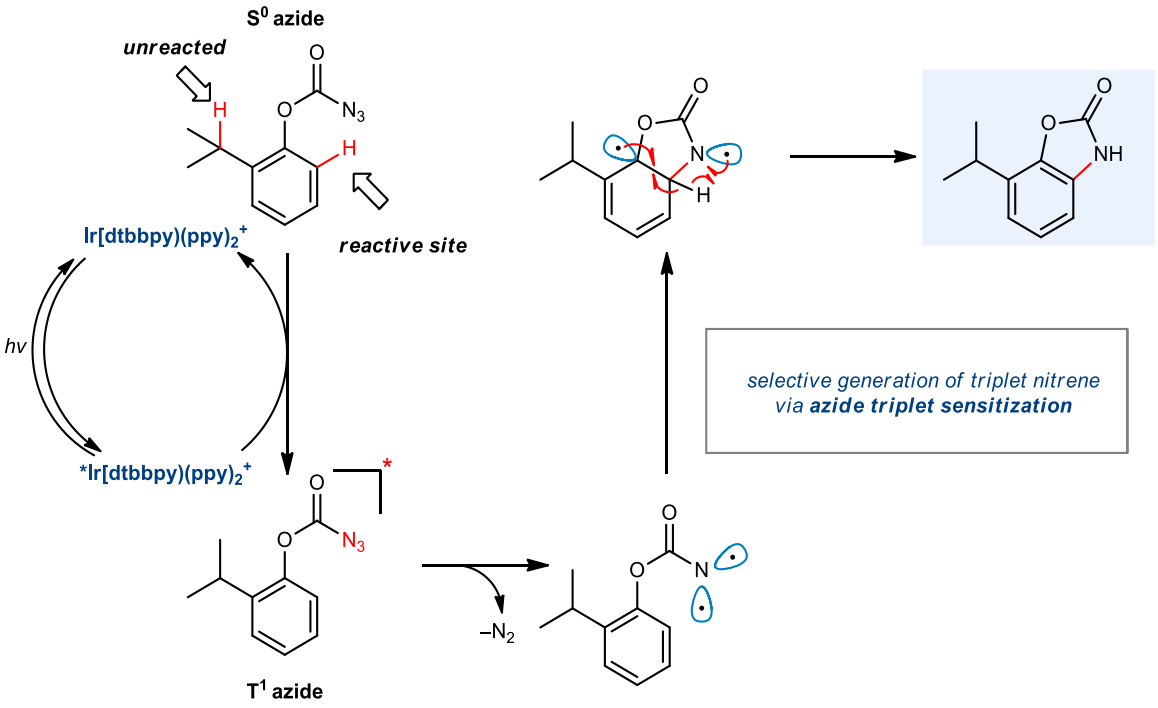


Figure 80 Li and Lu's energy transfer catalyzed intramolecular C-H amination of inactivated arenes via triplet nitrenes.

4.6 Photocatalytic arene C(sp^2)–H amination via arenium formation

An alternate approach to arene C–H amination was introduced by Nicewicz in 2015.[204] Rather than accessing activated N-species, such as *N*-centered radicals or nitrenes, an exceptionally oxidizing organic photocatalyst, *t*-Bu-Mes-Acr ($E_{1/2}$ = +2.15 V) was developed to

oxidize the arene to the arene radical cation (**Figure 81**). This led to highly regioselective aminations of arenes under mild conditions. The catalytic use of TEMPO was required to scavenge for deleterious oxygen radicals (*e.g.* HOO•, and $O_2^{-\bullet}$) which were shown to decompose the acridinium catalyst, starting materials, and products. This work was subsequently extended to include predictive models for the regioselectivity.[205]

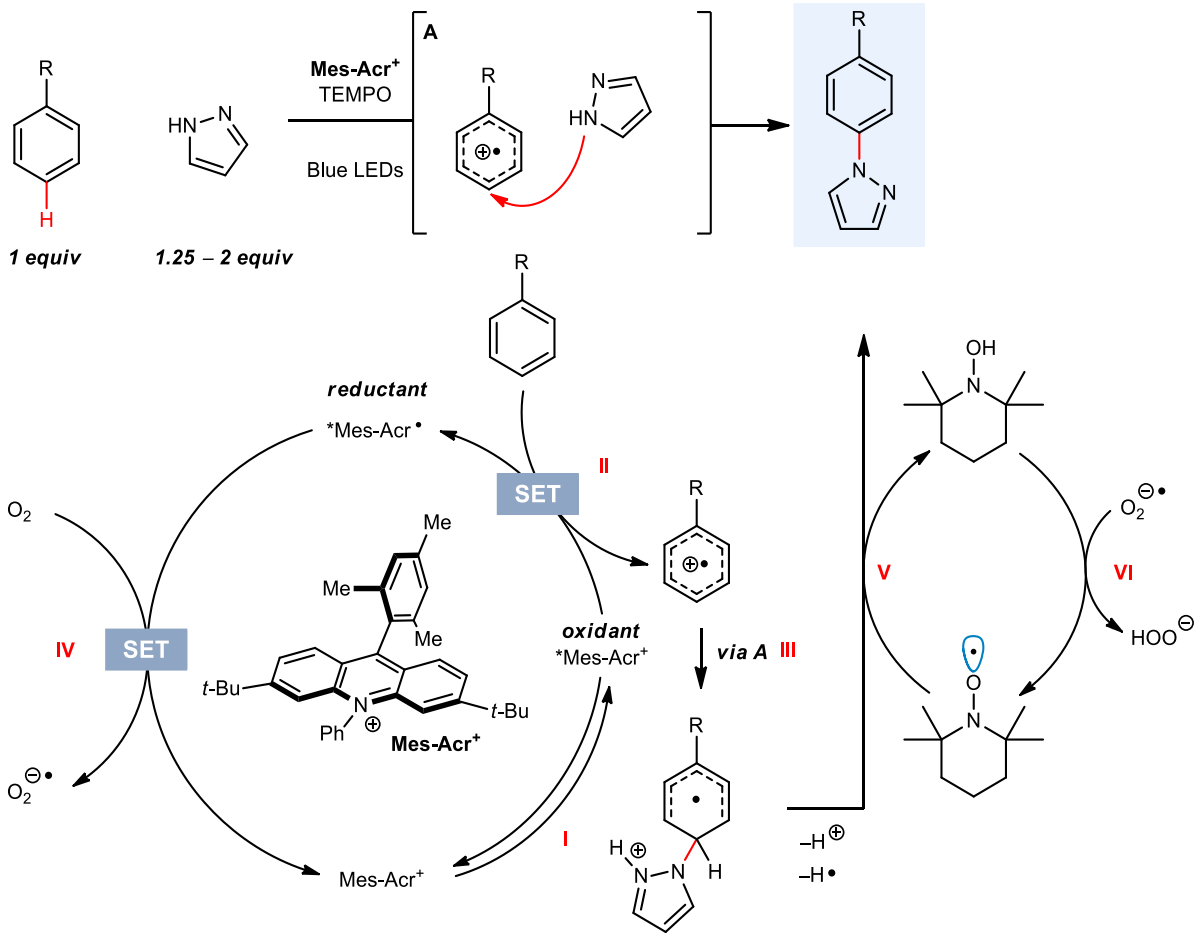


Figure 81 Nicewicz's seminal report on photoredox C-H amination via aryl radical cations

In elaborating this work to alkyl amine nucleophiles, a change in mechanism was proposed.[206] Rather than oxidation of the arene to the arene radical cation, the excited state of the catalyst could oxidize the amine to the amine radical cation. The addition of the arene forms a cyclohexadienyl radical intermediate that can be rearomatized using molecular oxygen. Since several arenes studied possessed similar oxidation potentials to the amine coupling partners, an arene radical cation could also account for the observed reactivity. Stern–Volmer fluorescence quenching analysis determined that insufficiently electron-rich arenes, such as toluene, did not quench the excited state of the photocatalyst, *Mes-Acr. Thus, for neutral arenes, a mechanism involving an amine radical cation seems most likely. For electron-rich arenes, neither reactive intermediate can be excluded since both the amine and the arene quench the acridinium excited state with similar rates. Notably, there was generally very poor regioselectivity between ortho and para C–H amination using alkyl amines as nucleophiles. While the couplings are efficient in some cases, more recent examples with alkyl amines suffer poor selectivity (when not completely biased) and the methodology cannot functionalize electron poor aryl rings.

Since the methyl group of methylarenes were sensitive to oxidative conditions, especially to dioxygen in Nicewicz's photocatalytic system, developing a new strategy for the selective C(sp^2)–H functionalization of methylarenes was urgently required. To improve upon this, photoredox was merged with transition metal catalysis to achieve selective arene C–H amination (**Figure 82**). This work was first reported by Lei[207] and Wu and Tung[208]. In Lei's work, the photocatalyst, Mes-Acr is excited to *Mes-Acr ($E_{1/2}$ +2.06 V) by blue LEDs, which oxidizes methylarenes or biphenyl ($E_{1/2}$ +1.96 V) to the corresponding arene radical cation. The Co (III) catalyst could oxidize the Mes-Acr radical ($E_{1/2}$ –0.49 V) to regenerate the photocatalyst and

simultaneously generate a Co (II) species. The generated arene radical cation was attacked by pyrazole ($E_{1/2}$ +2.27 V). The radical adduct underwent SET with the Co (II) catalyst and quickly lost one proton to generate the amination product. Overall, the catalytic use of cobalt obviated the need for stoichiometric oxidants that were deleterious both for the photocatalysts, reagents and products in Nicewizc's reaction. A similar system was also applied to the direct synthesis of anilines by Wu and Tung.[208]

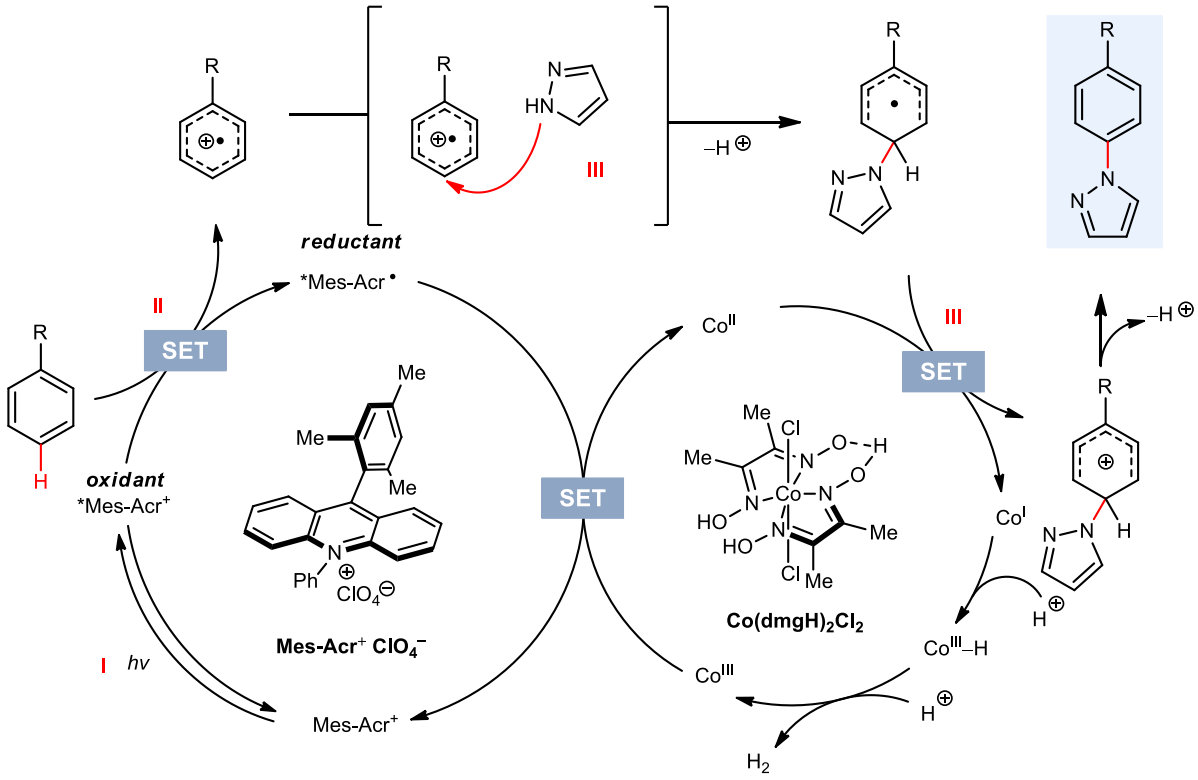


Figure 82 Lei's photocatalytic / cobalt catalyzed C-H amination reaction.

Many challenges of arene C–H amination have been overcome by photocatalysis via distinct mechanistic approaches: 1) *N*-centered radical / nitrene amination or 2) arenium

formation and nucleophilic amine trapping. While selectivity is still a recurring issue in intermolecular reactions, the scope of amine nucleophiles has rapidly expanded, allowing photocatalyzed C–H amination reactions to challenge entrenched methods of C–N bond formation *e.g.* Buchwald-Hartwig amination, Chan-Lam coupling, and Ullmann couplings. The constant development of new highly oxidizing photocatalysts has allowed for key advances in the arenium pathway, however this in inherently limited by the product's susceptibility to degradation from oxidative pathways. On the other hand, new precursors and methodologies to access *N*-centered radicals and nitrenes under mildly reducing conditions has provided some of the most versatile approaches to arene C(sp^2)–H amination.

4.7 Photoredox catalyzed C(sp^2)–H amination of alkenes and hydrazones

In contrast to aromatic C–H amination, the direct C–H amination of non-aromatic π-bonds is scarcely observed. Rather than a lack of reactivity with alkenes / alkynes, photoredox mediated generation of *N*-centered radicals typically undergo alkene hydroamination or difunctionalization. Simply put, the *C*-radicals in alkene / alkyne π-amination that are generated from radical addition are subsequently functionalized, whereas the C-radicals from aromatic π-amination undergo rapid oxidation leading to thermodynamically favored aromatization. Also in contrast to arene reactivity, photocatalytic nitrene generation typically leads to aziridination reactions with alkenes. Thus, while the amination of π-systems has been intensely studied under photocatalytic conditions, C–H amination reactions of alkenes are relatively scarce. However, there are some examples of *formal* C–H amination. Similar to arene C(sp2)-H amination, there

are two general strategies to perform C-H amination: 1) *N*-centered radical / nitrene amination and 2) alkene oxidation to the radical cation / nucleophilic amination.

The first example originated from Yoon's lab in 2013 (**Figure 83**).[209] Yoon reported the EnT catalyzed sensitization of dieneyl azides, which led to the synthesis of pyrroles via formal C–H amination. The actual mechanism of the reaction was proposed to proceed through exergonic energy transfer from the long-lived excited state of *Ru(dtbbpy)$_3^{2+}$ to the dienyl azide (**I**), which produces the triplet nitrene upon expulsion of N_2 (**II**). The triplet nitrene undergoes rapid ring closure to the azirine (**III**), which subsequently slowly rearranges to the corresponding pyrrole products (**IV**). Formally, the reaction represents an intramolecular alkene C–H amination via triplet nitrene. This work was later repeated by Collins using a variety of heteroleptic copper catalysts as the energy transfer catalysts.[210]

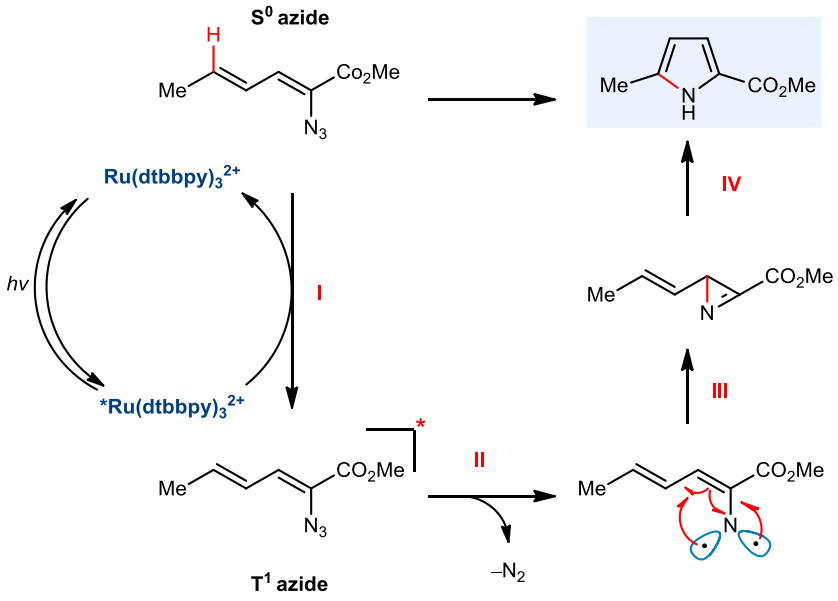


Figure 83 Yoon's EnT catalyzed C-(sp^2)-H amination using dienyl azides.

Yu and Zhu developed the umpolung amination of aldehyde derived hydrazones via SET initiated photoredox catalysis (**Figure 84**).[211] Using a strongly reducing iridium photocatalyst, SET initiated reductive N–O bond cleavage resulted in a sulfonamidyl radical, which could undergo addition across the C(sp^2)–N bond. Oxidation of the resultant N-radical by Ir(IV)$^+$ returns Ir(III) and closes the catalytic cycle of the photocatalyst. Subsequent base-mediated isomerization leads to the formal C(sp^2)–H aminated hydrazones.

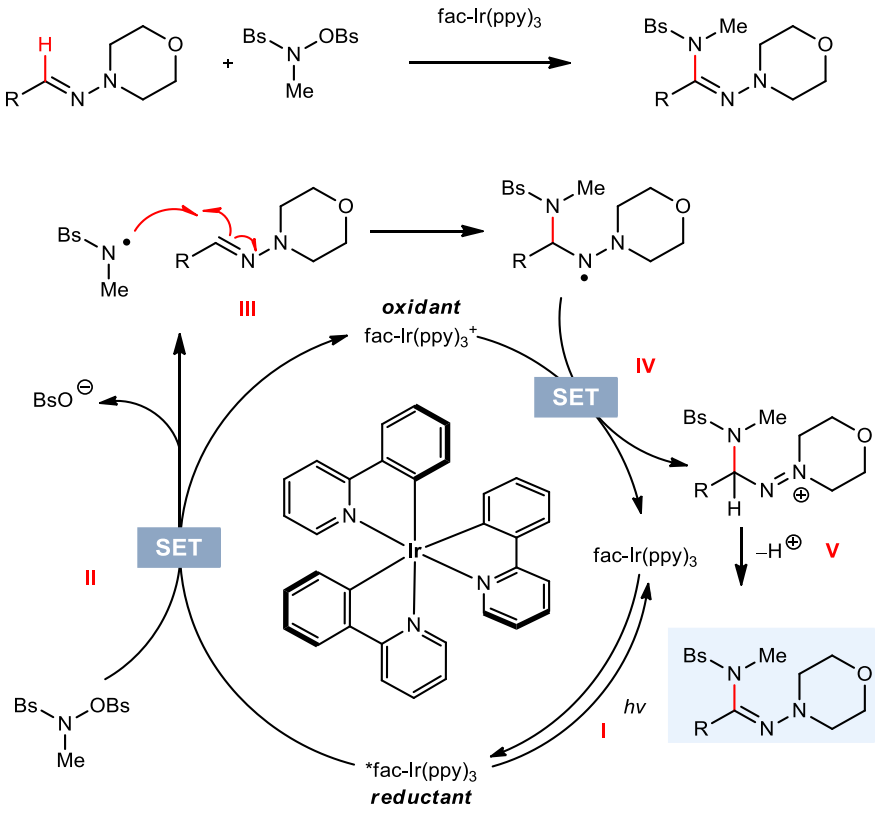


Figure 84 Yu and Zhu's intermolecular C(sp^2)-H amination of hydrazones.

Lei's group also applied their dual cobalt / Mes-Acr^{+} photoredox strategy to the C–H amination of styrene derivatives.[212] Functioning in much the same way as their work on aromatic amination (**Figure 82**), the styrene was first oxidized by strongly oxidizing *Mes-Acr^{+}(**Figure 85**). The aromatic nitrogen nucleophile subsequently underwent addition to the radical cation. Cobalt was reduced by the photocatalyst, closing the catalytic cycle for the photocatalyst and initiating the cobalt cycle. The reaction was limited to styrene derivatives, likely due to the formation of a benzylic radical / carbocation. Only azole-type heterocycles were used as *N*-nucleophiles, likely to avoid unwanted oxidation of electron rich alkyl amine nucleophiles. Indeed aniline, diphenylamine, and dibenzylamine were reported to fail in this system. Notably, there was no stereoselectivity in the alkene products, (*i.e.* *E* : *Z* = 1 : 1).

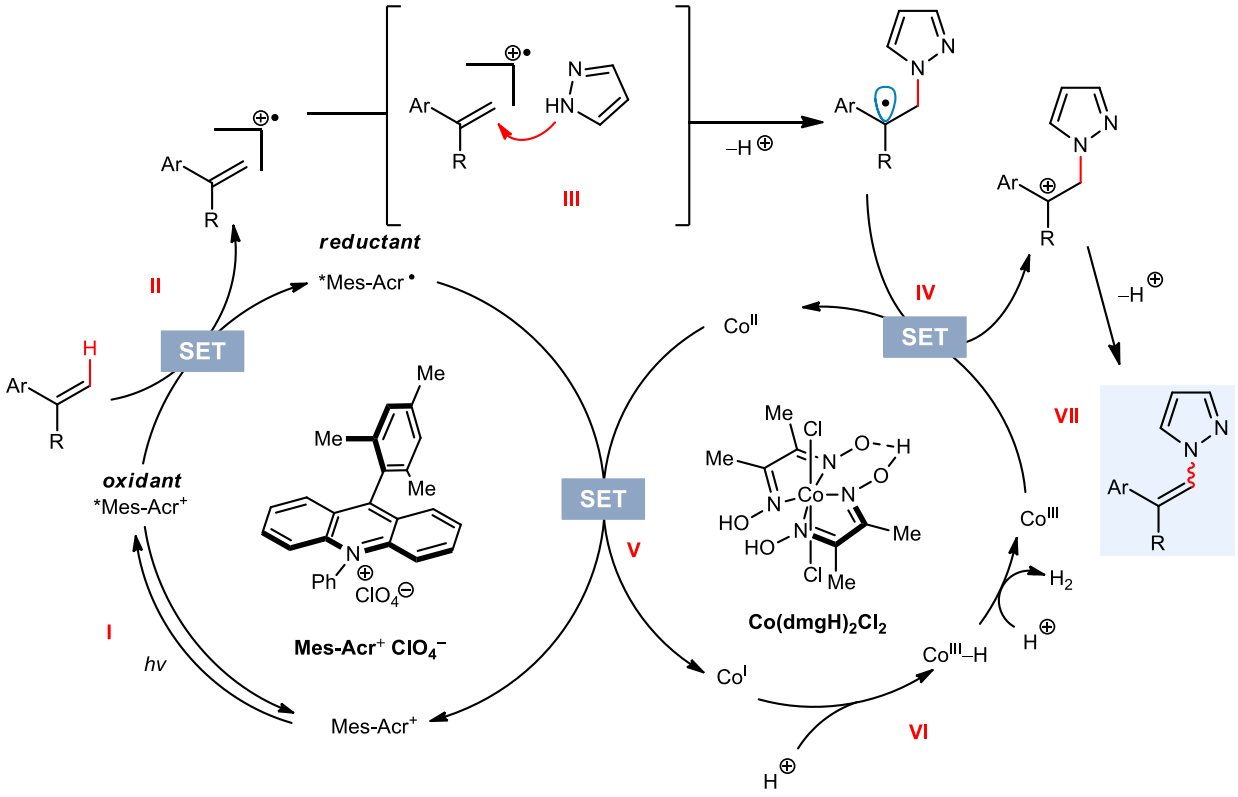


Figure 85 Lei's photocatalytic / cobalt catalyzed C-H amination of styrenes.

This was further explored by He and Guan, where cyano acrylates were C–H aminated using Rose Bengal as an organic photoredox catalyst.[213] Key differences include the lack of metal co-catalyst. Superoxide was invoked to quench the carbon radical, followed by deprotonation with peroxide anion. Surprisingly, the authors claim that no background conjugate addition was observed.

While few examples exist, the initial reactivity on reactive π-systems was quite good. Clearly, future efforts on non-aromatic C(sp^2)-H amination ought to be focused on the amination of unbiased alkenes. However, key challenges to this reactivity will be oxidation of the products *i.e.* enamines, which can be notoriously unstable under photoredox conditions. For these

reasons, this reactivity may be somewhat limited to the synthesis of aromatic heterocycles (**Figure 83**), or rely on the use of *N*-heterocycles as aminating agents (**Figure 85**).

4.8 Photoredox catalyzed C(sp^3)–H amination

Photocatalytic C(sp^3)–H aminations are perhaps the most challenging variant. There are two general pathways to achieve alkane C–H amination via photocatalysis: 1) *N*-centered radical hydrogen atom transfer (HAT) cascade reactions (*e.g.* Hofmann–Löffler–Freytag (HLF)-type cyclizations), or 2) nitrene formation / direct C–H amination. It is important to note that several methods of remote functionalization have been developed through interrupted HLF-aminations.[214]

The first photocatalytic variant of the HLF reaction enabling C(sp^3)–H amination was reported by Yu in 2015 (**Figure 86**).[215] This seminal report laid the groundwork for numerous ensuing publications. First, the excited photocatalyst reduced the *N*-chloroamine to produce the *N*-centered radical and chloride anion. This was followed by 1,5-HAT, and oxidation of the carbon radical by the photocatalyst to produce the carbocation. The carbocation was trapped by the chloride anion to yield the alkyl-chloride with pendant amine. Subsequent addition of NaOH led to C–N bond formation via S_N2. The reliance on *N*-tosyl amines, which are frequently recalcitrant toward deprotection, and the necessity of chloramines as reagents presents synthetic limitation.

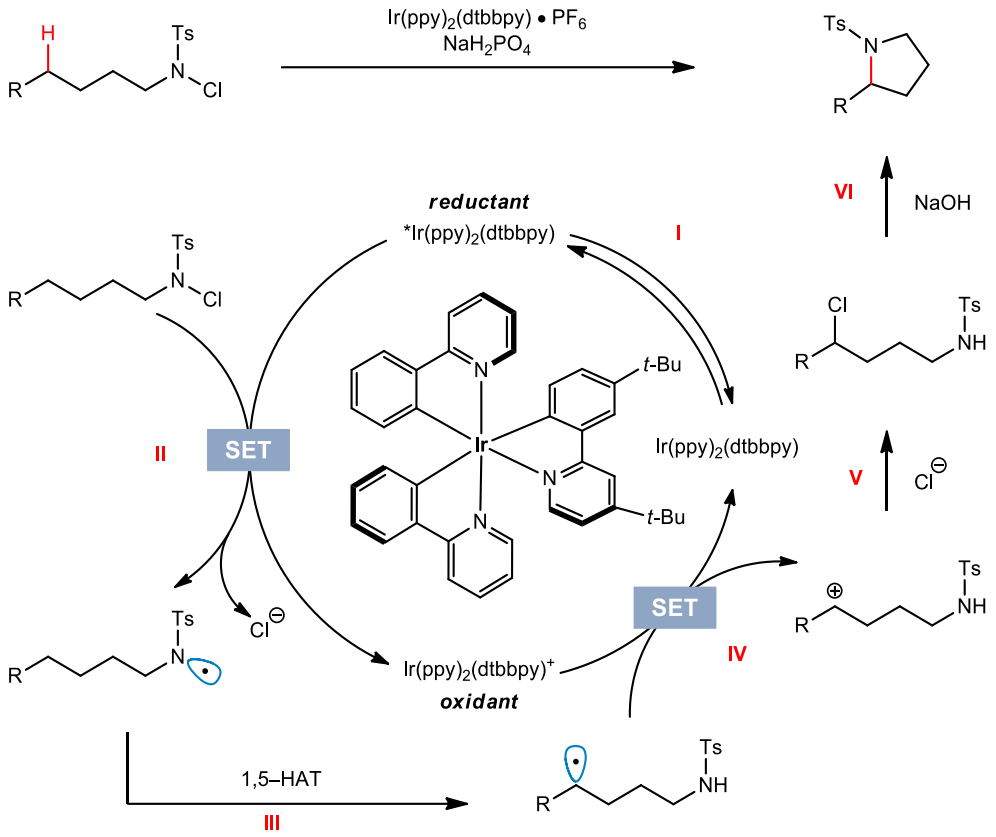


Figure 86 Yu's seminal report on the photoredox HLF reaction.

The method was modified by Reiher and Muñiz to operate from a protected amine (sulfonamide, carbamate, amide) using catalytic iodine (**Figure 87**).[216] Molecular iodine disproportionated in the presence of water to form the active hypoiodite. *N*-Iodination from the hypoiodate led to an intermediate *N*-iodoamine which undergoes homolysis upon blue light irradiation to yield a C-centered radical. This reaction then proceeds analogously to Yu's *N*-chloroamine example. The TPT photocatalyst is present to reoxidize hydrogen iodide to molecular iodine. Yet, in contrast to the pioneering work by Yu, only benzylic amination was reported using this method. This was surprising, as the better nucleofuge of the intermediary benzylic iodide should not have required additional activation by the benzylic position to allow

the internal substitution by the amide nucleophile. However, it is important to note that intramolecular cyclization reported by Yu was only observed after addition of NaOH. Therefore, a better nucleophile was arguably present in Yu's system since full deprotonation of the tosylamide was possible.

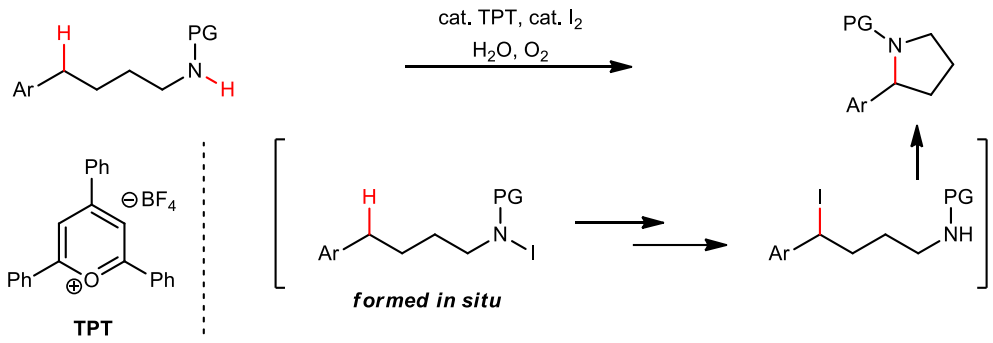


Figure 87 Reiher and Muniz's iodine catalyzed organic-photoredox HLF reaction.

In 2017, Nevado reported a C(sp^3)–H amination of benzylic centers by a 1,5-HAT strategy with an iminyl radical.[217] The amination reactivity was a side reaction of a C–C bond forming reaction (**Figure 88** bottom). Indeed, only 2 examples of benzylic C-H amination were reported in relatively poor yield. Notably, a Thorpe-Ingold bias was also present on the substrate. Therefore, this method was severely limited in comparison to previous examples. However, given that this was a side reaction, little can be inferred regarding the scope of this reactivity.

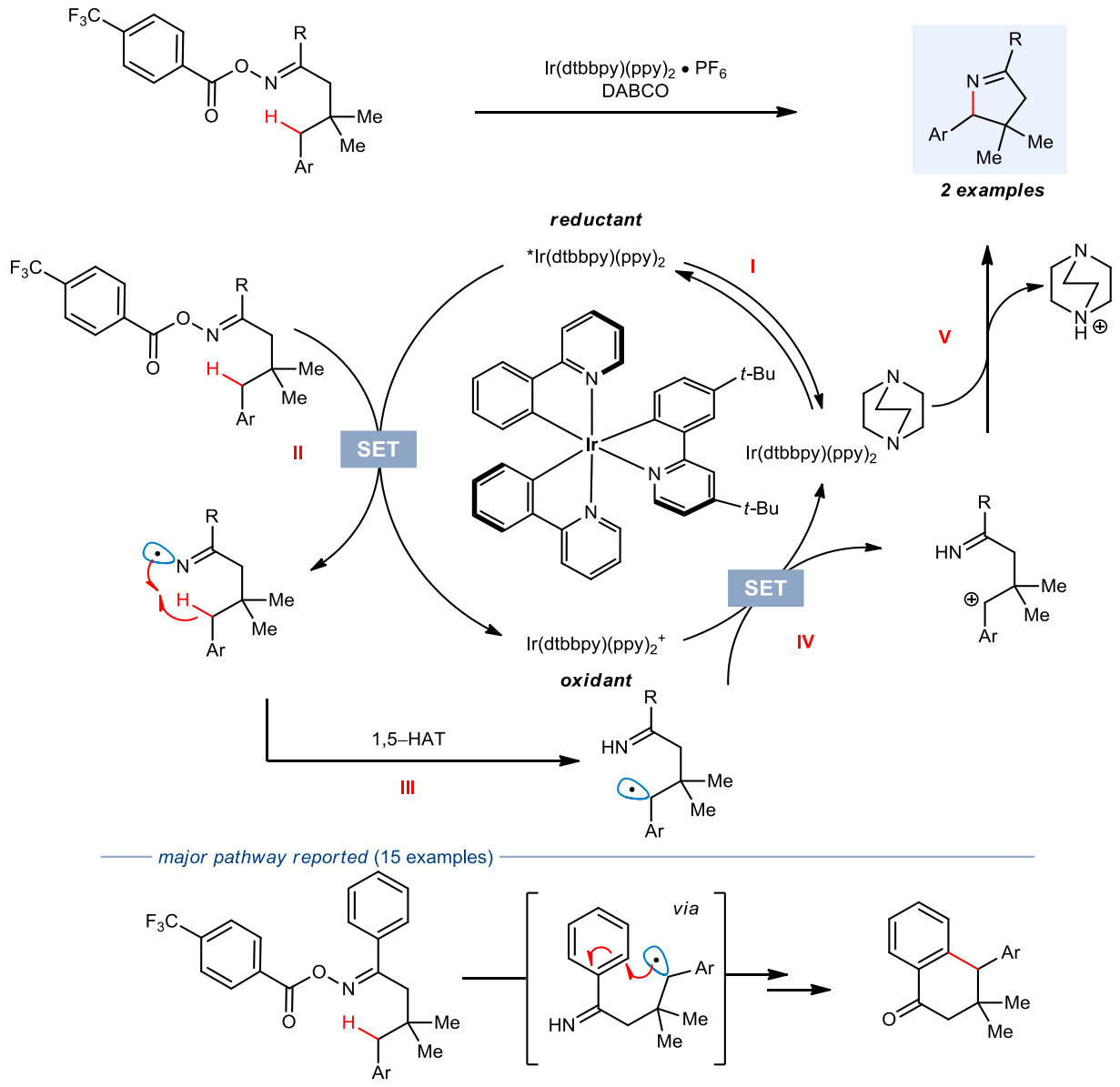


Figure 88 Nevado's C(sp^3)–H amination via 1,5-HAT.

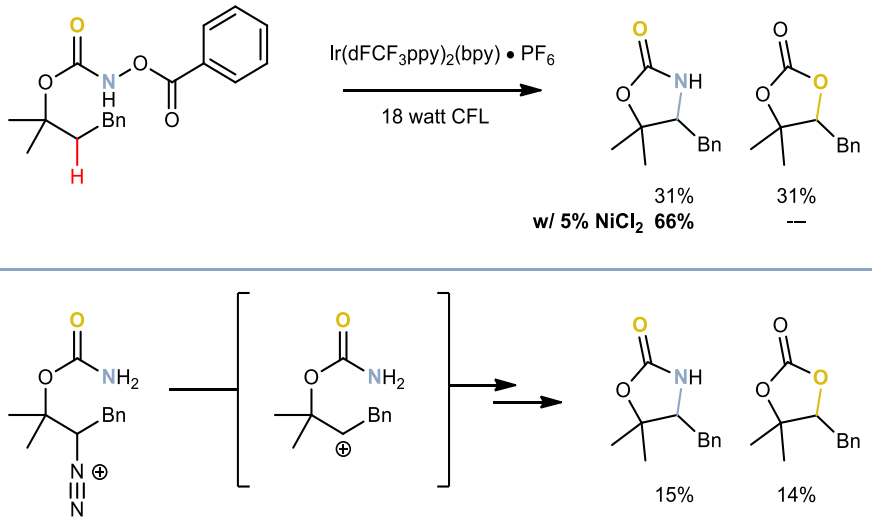


Figure 89 Lu's photoredox C-(sp^3)-H amination via 1,5-HAT of carbamates.

In 2019, Guo reported a C(sp^3)–H amination using carbamates (**Figure 89**).[218] The authors proposed a similar 1,5-HAT mechanism after a reductive SET process to form an *N*-centered radical. At the crux of this proposal was the crucial lack of selectivity for *O*- or *N*-nucleophilicity in the absence of metal additives. Using Zn or Ni as cocatalysts, the authors were able to provide selectivity for either *N*- or C=O-nucleophiles of the carbamate. Moreover, the authors were able to demonstrate via in situ diazo formation that alternative access to a carbocation provided a similar lack of selectivity. Unfortunately, it again appeared that Thorpe-Ingold biased substrates were essential for productive reactions. Despite suggesting a carbocation intermediate, primary C–H bonds were functionalized with relative ease.

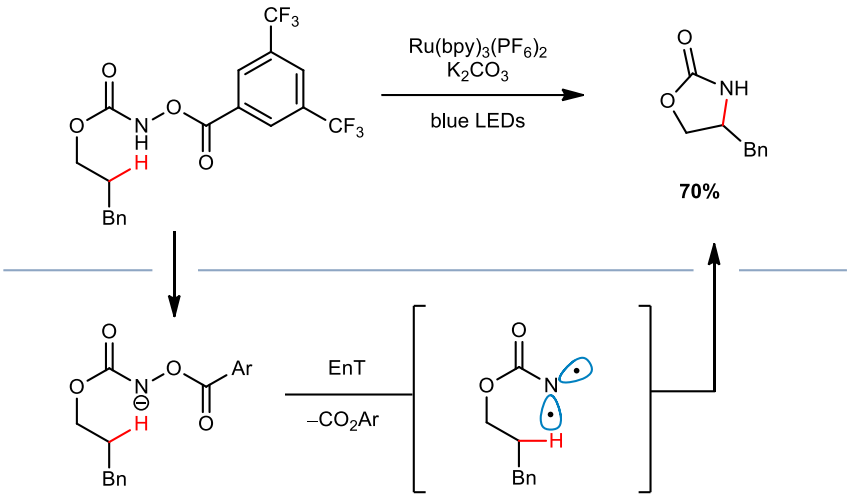


Figure 90 Chang's photocatalytic C(sp^3)-H amination via EnT triplet nitrenes

Recently, Chang reported a similar C(sp^3)–H amination using carbamate and amide hydroxamate precursors; however, support for a completely different mechanism was ultimately found (**Figure 90**).[203] DFT and electrochemical studies were most consistent with an EnT pathway forming triplet nitrenes. The substrates were found to undergo exothermic EnT ($E_{T\ precursor}$ = 40 kcal/mol – $E_{T\ (Ru2+)}$ = 48 kcal/mol) with the excited photocatalyst only when deprotonated, and this was corroborated by Stern-Volmer quenching studies of the precursors in the presence / absence of base. Notably, the reaction did not require Thorpe-Ingold biased substrates, but only reacted at activated (benzylic, allylic or tertiary) C–H bonds in appreciable yields, whereas Guo could even aminate primary C–H bonds. Importantly, Chang reported no issue of *O*- versus *N*-nucleophilicity for the carbamates, or amide precursors, providing a further indication of a reactive nitrene intermediate.

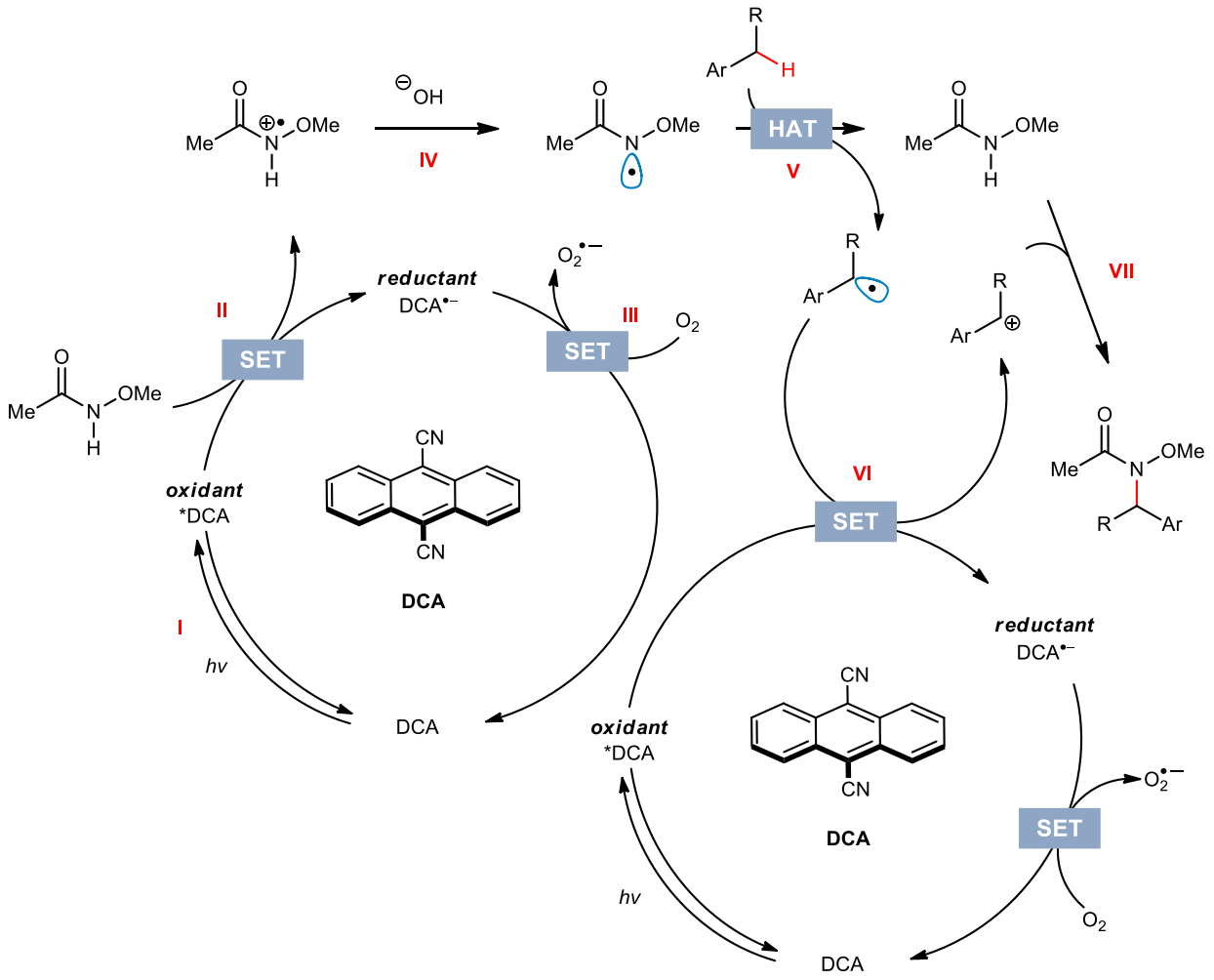


Figure 91 Pandey's pioneering work on intermolecular photoredox C(sp^3)–H amination.

There are also examples of intermolecular C(sp^3)–H amination via photocatalysis. The first example was reported by Pandey in 2015.[219] Pandey developed a metal-free protocol for benzylic C(sp^3)–H bond amidation via cross-dehydrogenative coupling (**Figure 91**). Here, a strongly oxidizing excited-state organic photocatalyst (*DCA), performs SET oxidation of a hydroxamate to form a capto-dative amidyl radical after deprotonation. The capto-dative radical then generates a benzylic radical via HAT. Subsequent oxidation of the benzylic radical to the

carbocation and trapping with the *N*-nucleophilic hydroxamate led to intermolecular benzylic amination.

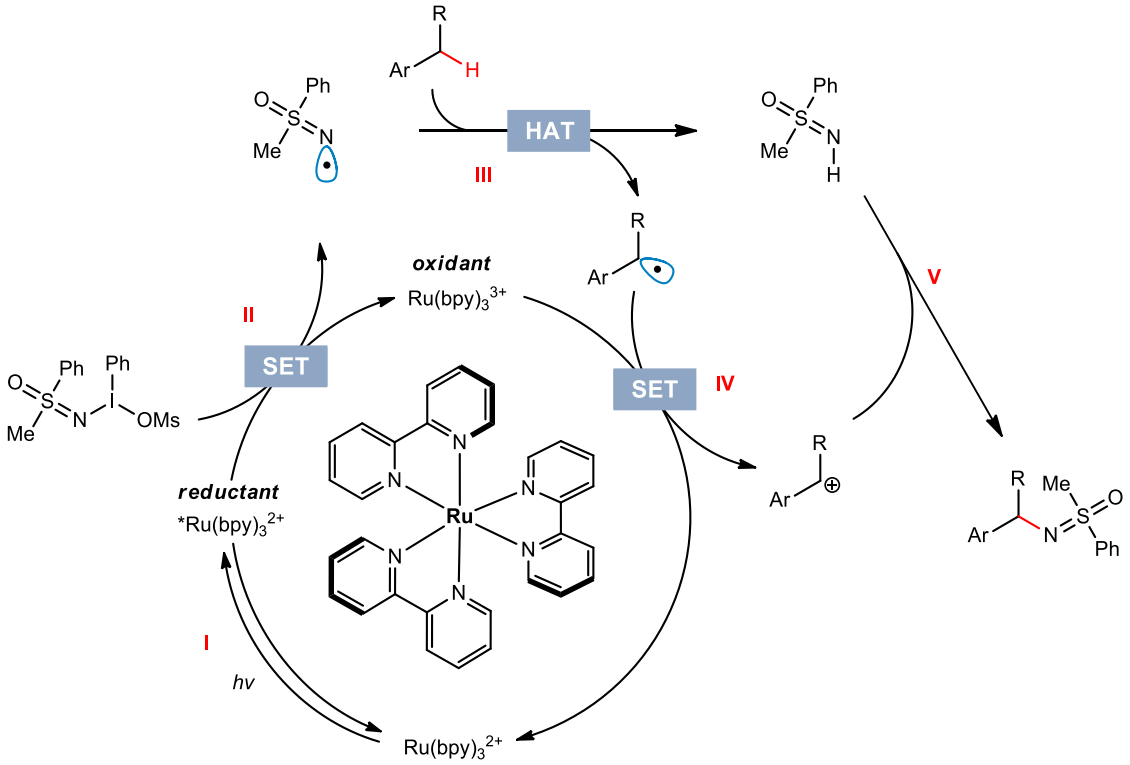


Figure 92 Bolm's photocatalytic intermolecular C(sp^3)–H amination using sulfoximides.

In 2018 Bolm reported the benzylic C(sp^3)–H sulfoximidation operating via a much simpler catalytic cycle (**Figure 92**).[220] Since the reaction is initiated by SET reduction of hypervalent iodine reagent, the photocatalyst is directly primed for a subsequent oxidation of the benzylic radical following HAT. In comparison to work by Pandey (**Figure 91**), the advantages of this simpler catalytic cycle are tempered by the more complex (pre-oxidized) starting material synthesis.

Most photocatalytic C(sp^3)–H aminations proceed via *N*-centered radical pathways. Arguably, these may not be ideal given the propensity of the generated radicals to undergo subsequent undesired side reactions. Indeed, generally Thorpe-Ingold biases were required to

achieve the desired cyclization reactivity. In contrast, Chang recently reported the first photocatalytic C(sp^3)–H amination via a triplet nitrene intermediate, which seemed to overcome substrate scope limitation previously observed. This was likely due to a rapid 1,5-HAT / radical recombination pathway that obviated the need for subsequent oxidation and carbocation trapping. However, the substrates targeted in Chang's study did not fully showcase the development of this novel reactivity, as similar precursors could already undergo high yielding[150] and enantioselective[221] C–H amination using metal catalysis. Currently, only benzylic C(sp^3)–H intermolecular amination reactions are possible. The reliance on benzylic amination is likely a consequence of the lifetime of unstabilized carbocations, which may not exist long enough for bimolecular reactions. It is conceivable that a more concerted process involving a nitrene intermediate could overcome these intermolecular substrate scope limitations.

4.9 Summary and outlook on photocatalytic C–H amination reactions

A variety of new photocatalytic methods are constantly emerging to enable C–H amination reactions. The focus of future studies ought to be on enantioselective variants, and the continued expansion of alkane C(sp^3)–H amination reactions to include the extensive arsenal of *N*-nucleophiles which are available for photocatalytic C(sp^2)–H amination reactions. While *N*-centered radical reactions are becoming quite common, photocatalytic nitrene C–H amination reactions remain rare. Importantly, productive *N*-centered radical amination reactivity seems to frequently require Thorpe-Ingold biases or benzylic C–H centers. The mild conditions offered by photocatalysis coupled with the extraordinary reactivity of nitrenes should provide fertile ground

for the development of useful novel amination chemistries. Moreover, given that many photoredox catalysts are potent photosensitizers, and vice-versa, attention to deciphering the mechanisms of complex photocatalytic reactions is urgently required.

With these challenges in mind, our interest in the development of direct C–H amination via nitrene intermediates from *O*-acyl hydroxureas as precursors began in early 2016. Extensive efforts exhausted all conventional methods for nitrene generation / reactivity (thermolysis, metal catalysis, photolysis) and thus forced the development of a conceptually novel, yet efficient photocatalytic method for nitrene formation (see Supporting Information).

4.10 Project development: Our path to photoredox chemistry

Building on our work on heteroatom-substituted isocyanate cascade reactions,[78] we initially envisioned a reaction in which thermal substitution on an acyloxy *O*-isocyanate followed by α-elimination to a singlet nitrene could lead to nitrogen-rich heterocycles (**Figure 93**). Several competing side reactions impeded the development of this reaction, such as *O*-isocyanate trimerization, pre-emptive N-O bond cleavage, and 1,2-rearrangement followed by *N*-isocyanate dimerization[37] (**Figure 93, I-III**).

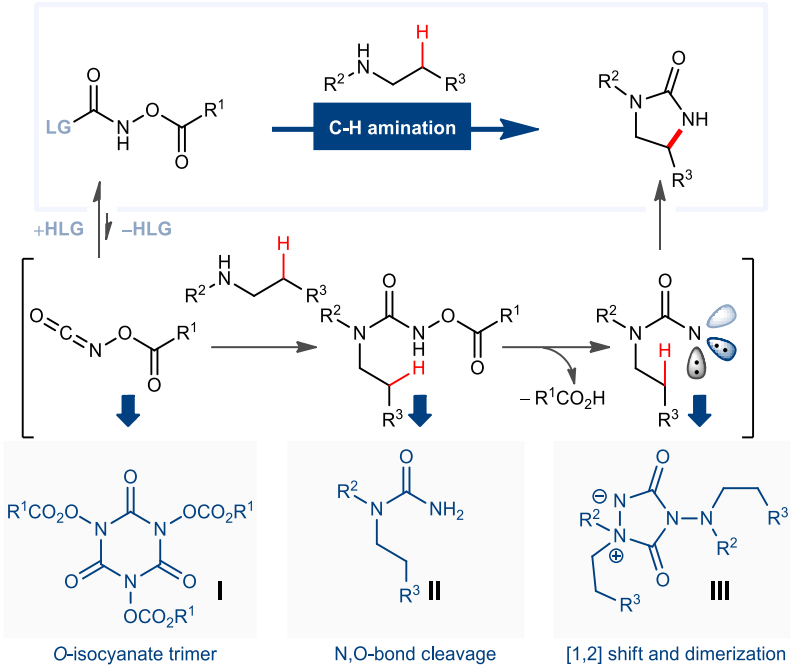


Figure 93 Problematic by-products impeding the desired C-H amination.

However, some side reactions were mitigated when a stepwise approach was undertaken, using the *O*-acyl oxyurea as the starting material (**Table 32, entry 1**). Unfortunately, these conditions were not broadly applicable (**entry 2**) but served as a calibrant for metal-free background reactivity. To minimize the decomposition pathways occurring from thermal activation, transition metal catalyzed nitrene reactions were investigated (**entries 3-6**, see the SI for further experiments). Ultimately, catalysts reported to perform nitrene C–H aminations instead catalyzed the 1,2-rearrangment of the carbamoyl nitrene, leading to *N*-isocyanate dimers (Figure 20, III).[37] Since these 1,2 rearrangements are known to proceed through singlet nitrenes,[161] we hypothesized that selectively accessing the *triplet* nitrene could provide a means to circumvent the 1,2-rearrangment and enable productive C–H amination reactions with free nitrenes. Toward this, we were drawn to photoredox catalysis, intrigued by a report wherein

acyloxy ureas underwent intramolecular aziridination reactions, using an Ir-photoredox catalyst and a proposed single electron transfer (SET)-initiated *N*-centered radical pathway.[222] We had envisioned that an mechanism involving triplet nitrenes could alternatively explain the reactivity observed. In contrast to work by Ren, where a similar aziridination was proposed to proceed via *N*-centered radicals, invoking a triplet nitrene as the reactive intermediate avoids the intermediacy of an unlikely primary carbocation.

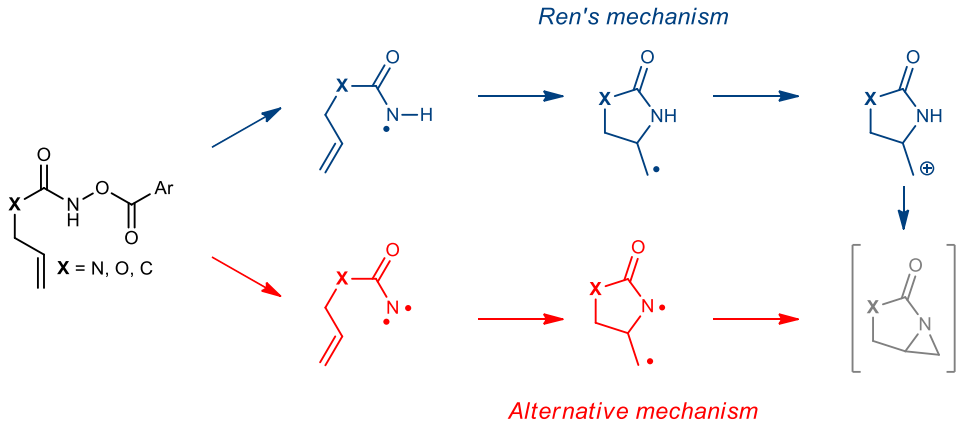
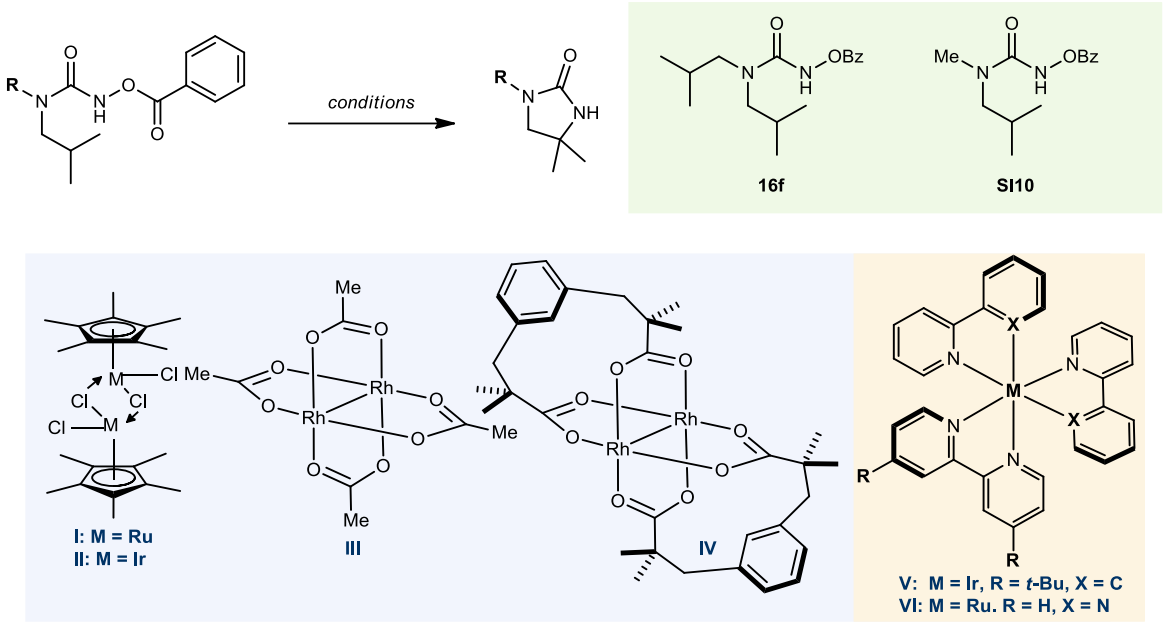


Figure 94 Key differences in proposed reactive intermediates.

Under identical conditions to those of Ren's aziridination, we achieved 60% yield of C–H amination (**entry 7**). Upon screening a variety of conditions, $Ru(bpy)_3(PF_6)_2$ emerged as a uniquely proficient photocatalyst in the presence of triethylamine as a base (**entry 8**).

Table 32 Early optimization of C-H amination using acyl-oxy hydroxurea precursors.



entry	sm	solvent	temp (°C)	base	catalyst	yield (%)
1	**16f**	$(CH_2Cl)_2$	100	TMG	—	**34a**, 86
2	**SI10**	$(CH_2Cl)_2$	120	TMG	—	**34c**, 69
3	**16f**	CH_2Cl_2	rt	K_2CO_3	**I**	**34a**, 16
4	**16f**	CH_2Cl_2	rt	K_2CO_3	**II**	**34a**, 9
5	**16f**	$(CH_2Cl)_2$	rt	K_2CO_3	**III**	**34a**, 10
6	**16f**	$(CH_2Cl)_2$	rt	K_2CO_3	**IV**	**34a**, 0
7[b]	**16f**	MeCN	rt	Et_3N	**V**	**34a**, 60
8[b]	**16f**	MeCN	rt	Et_3N	**VI**	**34a**, 99

[a] Conditions: Starting material (sm) 1a-d (1.0 equiv), base (1.1 equiv), catalyst (2 mol%), solvent (0.2 M), 16 h under argon. [b] 450 nm blue LEDs, rt, 16 h. ^{1}H NMR yields (1,3,5-trimethoxybenzene (TMB) as an internal standard).

4.11 Substrate scope limitations and benzoyl modification

At this point, we investigated the scope of the reaction (**Figure 95**), which revealed systematic issues. The most problematic by-product was identified as **II** (**Figure 93**) seemingly formed from reduction of the N–O bond (ca. 10-20% yield). While the yields were not prohibitively poor, the reduced reactivity even at activated methylenes (**34l**, **34s**) and tertiary positions (**34c**, **34d**) was discouraging. This prompted a return to substrate design, and a systematic probe of the acyl substituent.

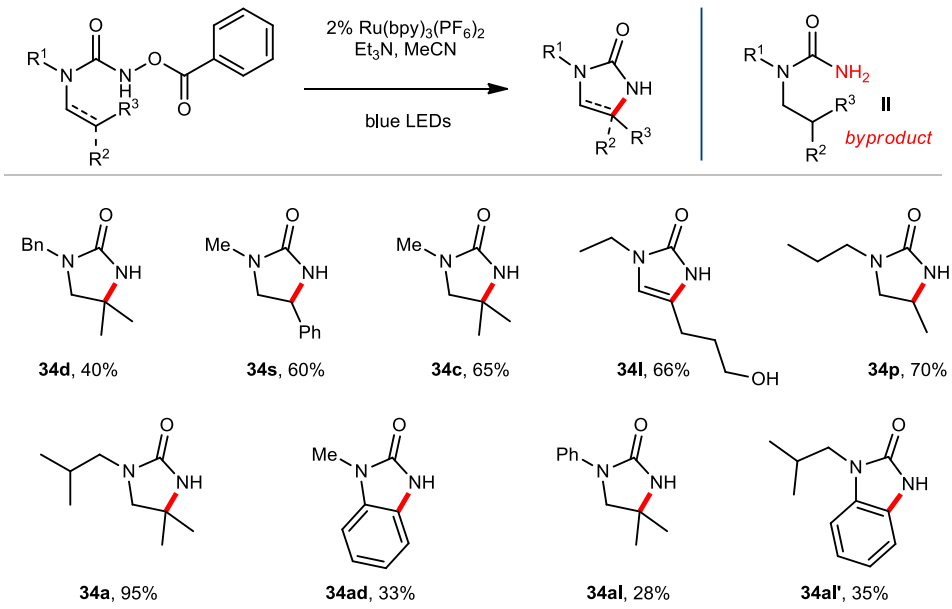


Figure 95 C-H amination using photocatalytic conditions (initial benzoate precursors).

We had reasoned that SET reduction could occur from Ru^{I} ($E_{1/2}$ Ru^{II}*/Ru^{I} = –1.33 V), and that Ru^{I} would be accessible in the presence of triethylamine ($E_{1/2}$ = –0.78 V) as a sacrificial reductant. This could lead to reduction of our *O*-acyl hydroxyureas. *N*-Centered radical formation from SET

reduction could explain the observed C–H amination reactivity. Thus, a variety of *O*-benzoyl hydroxyureas were screened (Scheme X) with the intent on investigating a hypothetical reductive quench of the $Ru(bpy)_3$ photocatalyst. To probe the generality of the effect from *O*-acyl modification, the efficiency of 3°, 2°, and aromatic C–H amination was investigated. From this survey, an unexpected trend emerged where increasing electron donation on the benzoyl substituent led to higher yields for each of C–H amination class surveyed (3°, 2° and aromatic). In contrast to recent work by Chang (**Figure 90**),[203] which clearly demonstrated the effectiveness of the 3,5-*bis*-trifluoromethyl group as an activating group for EnT induced triplet nitrene formation of amide and carbamate precursors, we found the analogous *bis*-trifluoromethyl substrate to be completely ineffective. It would decompose rapidly, even under our milder reaction conditions. This finding was also inconsistent with *N*-centered radical reactivity which relies on an initial SET reduction to generate the radical, such as Lu (**Figure 89**).[218] Expectedly, these approaches consistently employ electron poor aryl redox handles to achieve successful reactions via SET reduction.[189,217] Surprisingly, we found that more electron rich precursors were more effective (**Figure 96**), the implications of this will be discussed more later. Ultimately, a precursor bearing an electron-rich *p*-methoxybenzoate proved to be the most effective, increasing yields of C–H amination by 20-40% for the substrates surveyed.

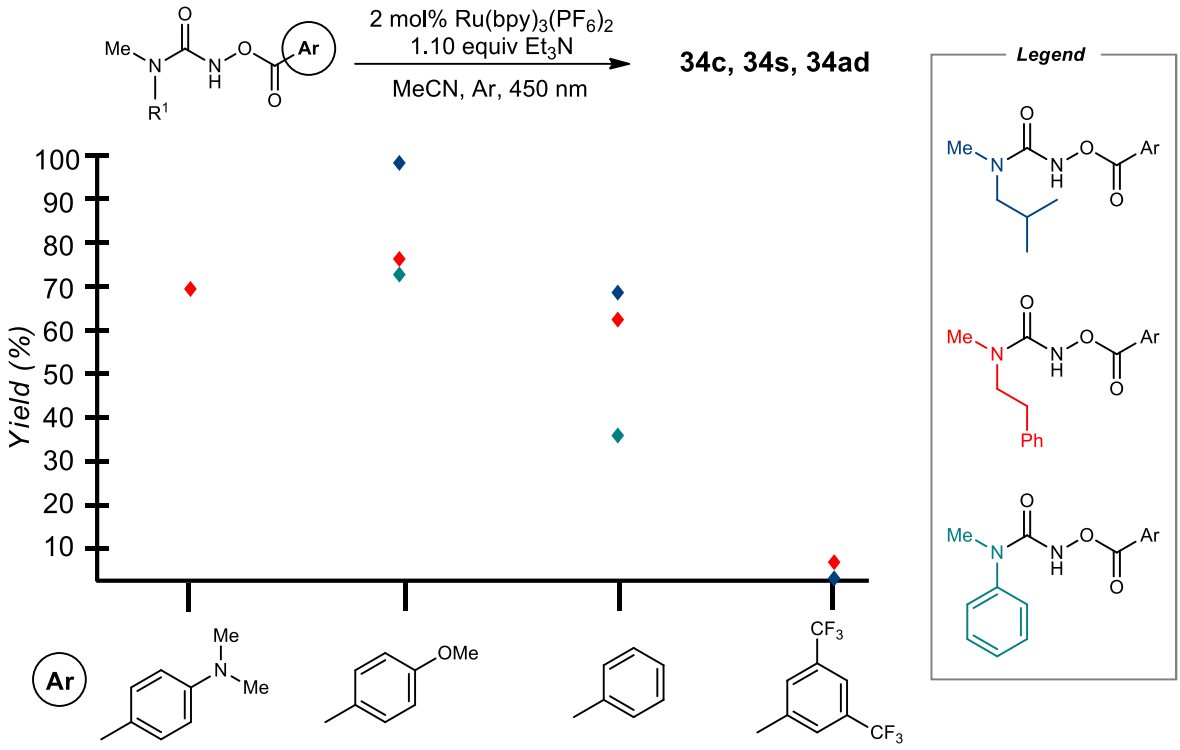
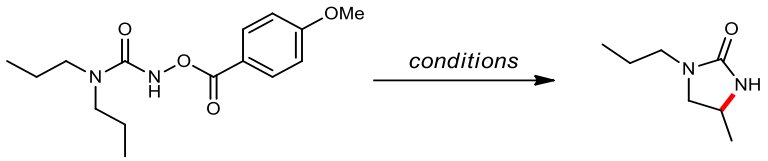


Figure 96 Selected acyl-substituent scan with a variety of C-H amination sites.

4.12 Reaction optimization and synthetic survey with electron rich *p*-methoxy benzoyl precursor

With an optimal precursor in hand, we returned to reaction optimization (**Table 33**). Base or photocatalyst alone were ineffective in promoting the reaction (entry 1-2). Catalyst screening revealed that $Ru(bpy)_3(PF_6)_2$ was still the optimal photocatalyst (entry 3-7). Further screening solvents indicated that MeCN was still the ideal solvent for the reaction, although halogenated solvents were also effective (entry 14-15).

Table 33 Optimization of photocatalytic C-H amination using p-methoxy benzoate precursor.



16aa 34p

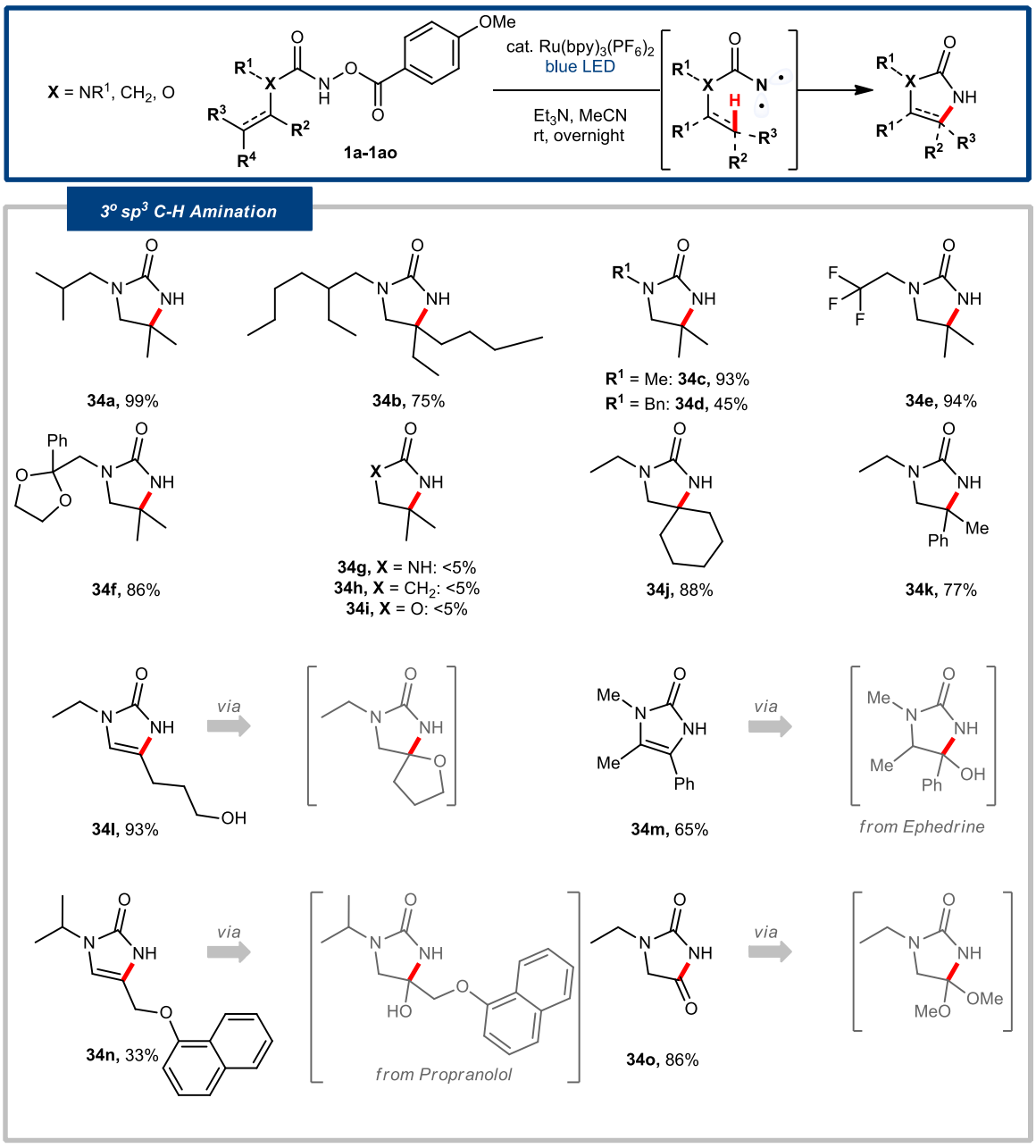
entry	photocatalyst	base	solvent	yield (%)
1	-	Et_3N	MeCN	0
2	$[Ru(bpy)_3](PF_6)_2$	-	MeCN	0
3	**$[Ru(bpy)_3](PF_6)_2$**	**Et_3N**	**MeCN**	**92**
4	$[Ir(ppy)_2(dtbpy)](PF_6)$	Et_3N	MeCN	40
5	$[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)](PF_6)$	Et_3N	MeCN	33
6	$[Ru(bpm)_3]Cl_2$	Et_3N	MeCN	11
7	TPP	Et_3N	MeCN	0
8	$Ir(dFppy)_3$	Et_3N	MeCN	0
9	$[Ru(bpy)_3](PF_6)_2$	Ph_3P	MeCN	17
10	$[Ru(bpy)_3](PF_6)_2$	Et_3N	$PhCF_3$	0
11	$[Ru(bpy)_3](PF_6)_2$	Et_3N	DMSO	57
12	$[Ru(bpy)_3](PF_6)_2$	Et_3N	Dioxane	0
13	$[Ru(bpy)_3](PF_6)_2$	Et_3N	THF	9
14	$[Ru(bpy)_3](PF_6)_2$	Et_3N	$(CH_2Cl)_2$	78
15	$[Ru(bpy)_3](PF_6)_2$	Et_3N	CH_2Cl_2	77

Conditions: 3-(benzoyloxy)-1,1-dipropylurea **1p** (1.00 equiv), photocatalyst (2 mol%), additive (1.10 equiv) in solvent (0.3M) irradiated under inert atmosphere with 450 nm blue LED.

The scope of the reaction was again investigated, and contrary to results obtained with benzoate derivatives, using electron-rich *p*-methoxybenzoates as substrates resulted in amination of 3°, 2° and aromatic C–H bonds (**Table 34**-**Table 36**) in generally higher yields. Expectedly, tertiary C–H bonds were aminated efficiently (**34a-34o**). The method was expanded

beyond saturated heterocycles by targeting C–H amination at α-hydroxy / α-ethereal positions, which led to the corresponding aromatic imidazolones (**34l-34n**). Moreover, a hydantoin heterocycle (**34o**) was also obtained by a targeted C–H amination at an acetal methine C–H. Unfortunately, with these conditions, the *p*-methoxybenzoate precursor was still unable to effect C–H amination using analogous amide and carbamate precursors (**34g-34i**) in acceptable yields.

Table 34 Photocatalytic tertiary C(sp^3)–H amination.

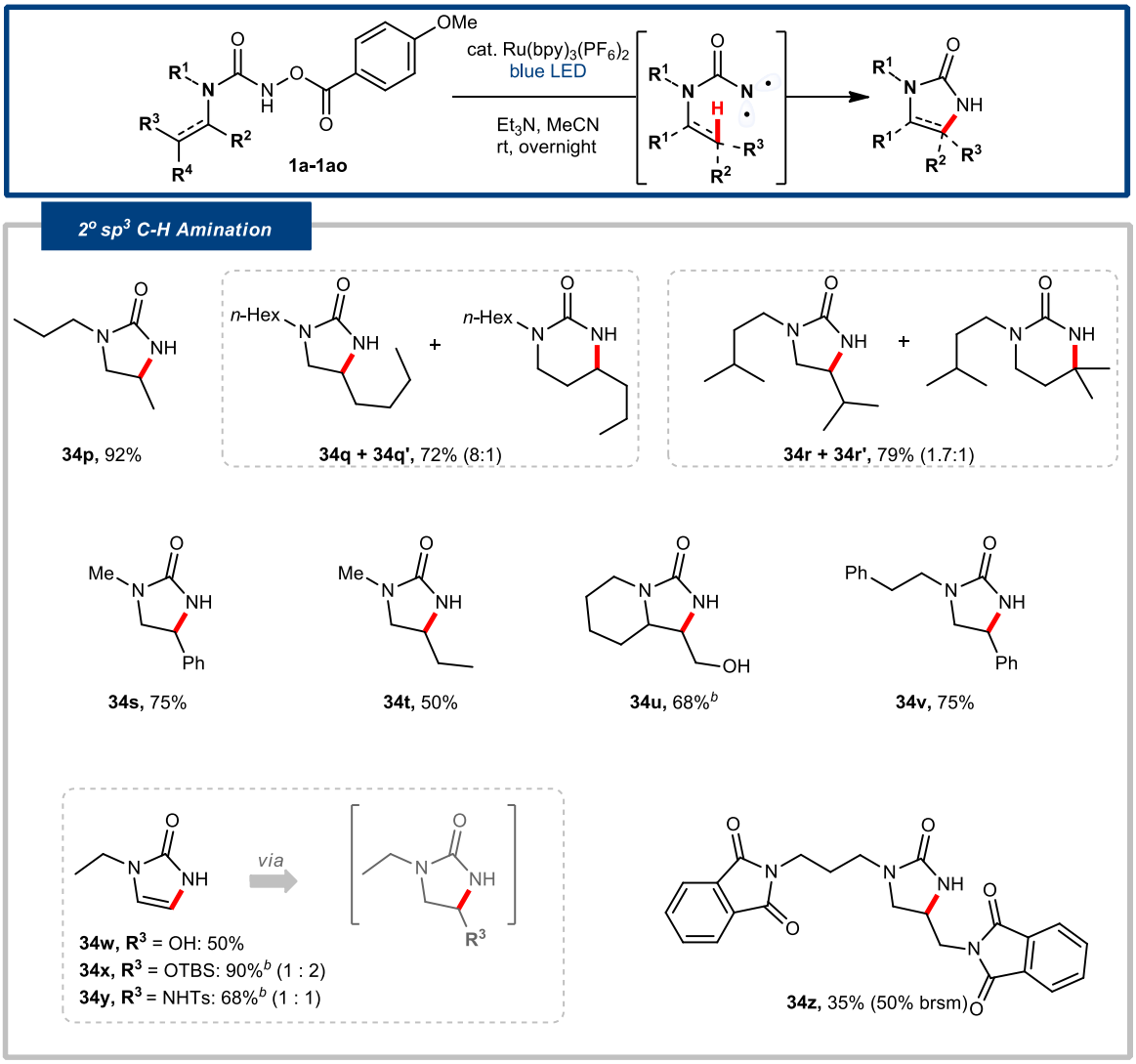


[a] Conditions: **1** (1.0 equiv), Et_3N (1.1 equiv), $Ru(bpy)_3(PF_6)_2$ (0.02 equiv), MeCN (0.2 M), 450 nm blue LEDs, rt, 16 h under argon. [b] ^1H NMR yield (TMB as an internal standard).

Efficient functionalization of unactivated methylenes, which typically show reduced reactivity,[203,223–225] was achieved (**34p**). Notably, formation of 5- and 6-membered rings were

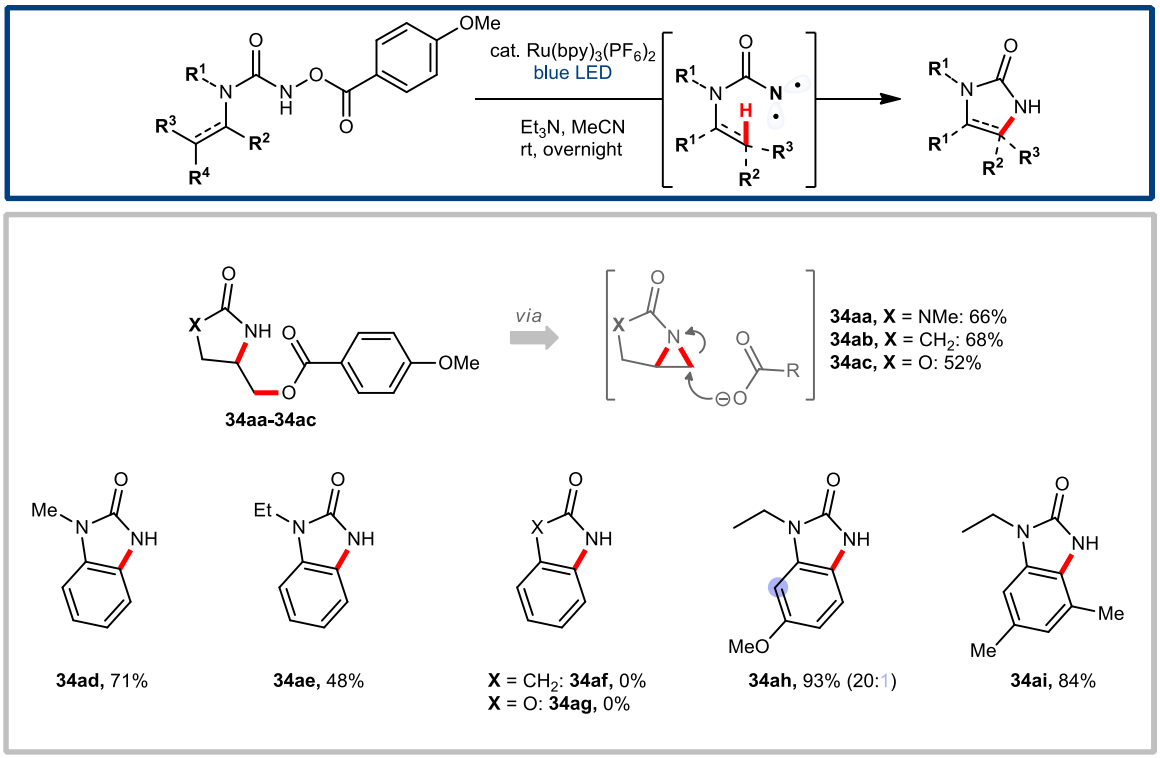
observed in an 8:1 ratio when each position was 2° (**34q**); however, when the 5 position was 2° and the 6 position was 3° (**34r**) the ratio was 1.7:1.[226,227] We found this lack of exquisite selectivity for the 5-position striking. Typically, similar precursors (*e.g.* X-(C=O)-N) undergoing *N*-centered radical based functionalization react with total selectivity for the 5-position.[228] Although, selectivity for 1,6-functionalization can be skewed by different precursors (*i.e.* sulfonamide derivatives),[229,230] the change in regioselectivity can also occur through the involvement of a delocalized π-system at the radical center.[231] So far in the literature, the rare examples of carbamoyl *N*-centered radical C–H functionalization seem to occur with total selectivity for the 5-position.[232] Surprisingly, activated methylenes (*e.g.* benzylic CH_2) did not react better than unactivated methylenes (**34s, 34v** vs **34aa**).

Table 35 Photocatalytic secondary C(sp^3)–H amination.



[a] Conditions: **1** (1.0 equiv), Et_3N (1.1 equiv), $Ru(bpy)_3(PF_6)_2$ (0.02 equiv), MeCN (0.2 M), 450 nm blue LEDs, rt, 16 h under argon. [b] ^1H NMR yield (TMB as an internal standard).

Table 36 Photocatalytic alkene aziridination and C(sp^2)–H amination.

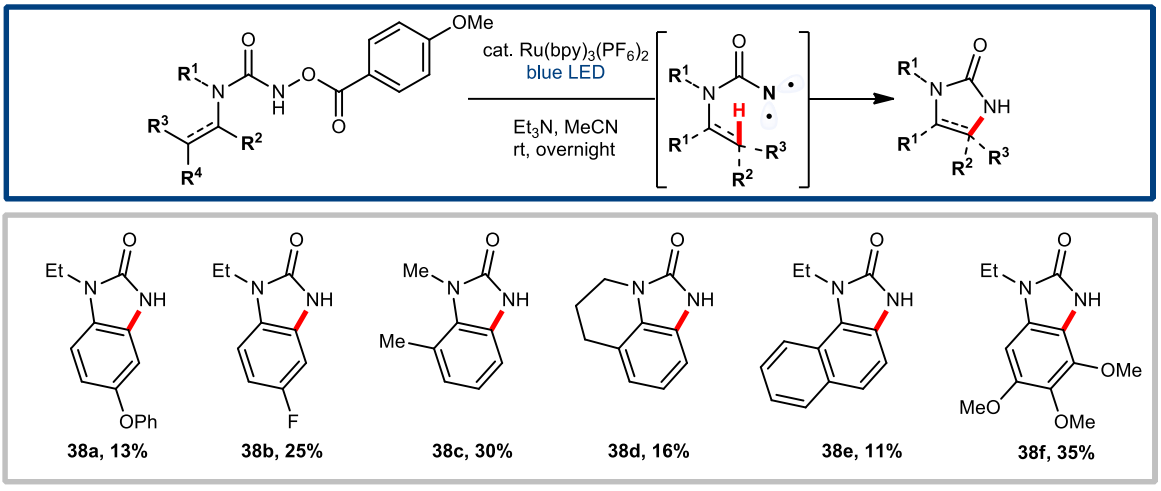


[a] Conditions: **1** (1.0 equiv), Et_3N (1.1 equiv), $Ru(bpy)_3(PF_6)_2$ (0.02 equiv), MeCN (0.2 M), 450 nm blue LEDs, rt, 16 h under argon.

The reaction was not limited to C(sp^3)–H amination; a variety of sp^2 centers were also aminated (**34aa**-**34ai**). Alkenes underwent aziridination, but the released *p*-methoxybenzoate performed a ring opening reaction leading to a formal oxy-amination of the pendant olefin (**34aa**-**34ac**).[233–235] In contrast to the C(sp^3)–H / arene C(sp^2)–H amination reactions, the aziridination reaction delivered the corresponding urea, lactam and carbamate derivatives. Precursors **36ac**-**36ae** undergo aziridination forming **34aa-34ac**, while **15h** and **36ai** cannot undergo aromatic C-H amination to form **34ag** and **34af** respectively. A recent report using azidoformates was capable of both aziridination and aryl C-H amination presumably via triplet nitrenes upon EnT photoexcitation (**Figure 80**).[202] The rate of aziridination from triplet nitrenes is significantly faster

than aliphatic C–H amination, [236,237] and presumably also aryl C-H amination from the substrate scope presented by Lu.[202] The problem in our system seems to lie in the hydroxylamine precursors used, which can also act as phenol blocked *O*-isocyanates. When **15h** was submitted to the reaction, a large amount of phenol was produced indicating that the starting material was susceptible to base catalyzed *O*-isocyanate formation (see Chapter 3). Unfortunately, screening a variety of bases proved unsuccessful for this precursor. For the case of **36ai**, benzyl isocyanate was detected when reacted under optimal conditions. It is possible that the more acidic amide precursor was more susceptible to Lossen-type degradation which lead to 1,2-rearrangement and benzyl-isocyanate formation. Unfortunately, the scope of aromatic C(sp^2)-H was somewhat limited and a variety of urea precursors failed to provide acceptable yield of product (**Table 37**). The yields provided below are the best yields for these substrates and are ^{1}H NMR yields reported from crude reactions.

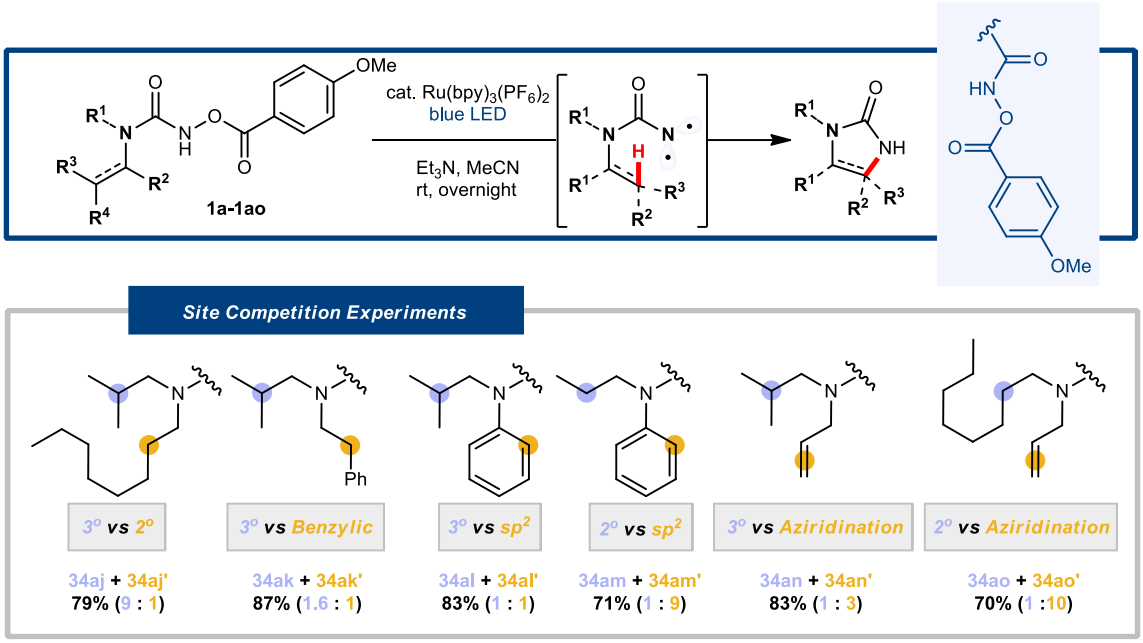
Table 37 Precursors which reacted poorly in optimized photocatalytic conditions.



[a] Conditions: **1** (1.0 equiv), Et_3N (1.1 equiv), $Ru(bpy)_3(PF_6)_2$ (0.02 equiv), MeCN (0.2 M), 450 nm blue LEDs, rt, 16 h under argon. All yields are reported as ^{1}H NMR yields.

Finally, the innate selectivity of the C–H amination was assessed through a series of site-selectivity substrate probes. The results aligned with the reported selectivity of nitrenes: *e.g.* 3° C–H > benzylic C–H ~ ethereal > 2° C–H > 1° C–H.[238] Site competition experiments further demonstrate that alkene aziridination, and aryl C(sp^2)–H amination seem to react more readily than 3° C–H amination consistent with trends of triplet nitrenes in the literature.[202]

Table 38 Site competition experiments for photocatalytic C-H amination.



Conditions: 1 (1.0 equiv), Et_3N (1.1 equiv), $Ru(bpy)_3(PF_6)_2$ (0.02 equiv), MeCN (0.2 M), blue LEDs, rt, 16 h under argon. Product ratios are reported from the crude ^1H NMRs.

4.13 Mechanistic investigations of the photocatalytic C–H amination

The reaction evolved beyond our original synthetic design, to the point where it became unclear how the reaction was operating. At the onset of this project, the reaction was designed to produce nitrenes via thermal degradation, but the intermediate responsible for the C–H

amination under photocatalytic conditions was unknown. While reactions with urea precursors had been largely successful, a seemingly insignificant structural change, *e.g.* substitution of an *N*-methyl for methylene, led to a precipitous decline in yield for C(sp^3)-H insertion (**Figure 97**). These challenges served as a driving force for subsequent mechanistic investigations. Lactam synthesis via C–H amination had only recently been reported in landmark reports via tailored catalysts[150] or enzyme evolution[239] (recently retracted),[240] so the potential to contribute to this competitive area was alluring.

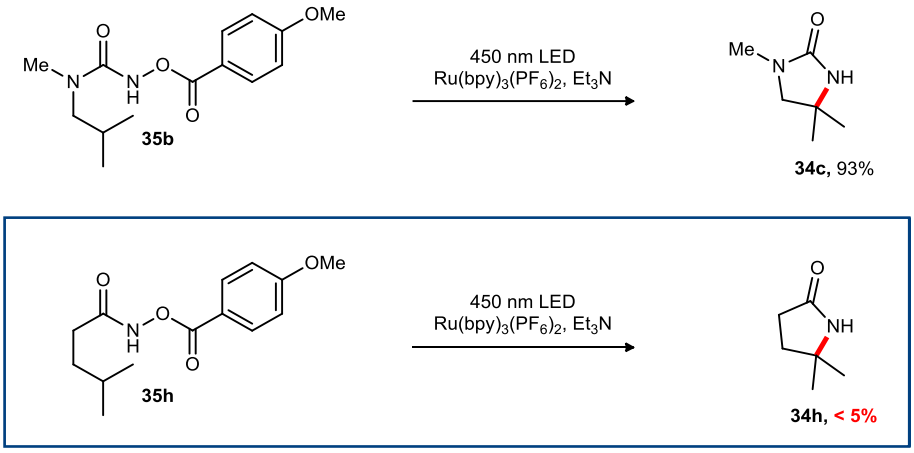


Figure 97 Failure of amination conditions with analogous lactams initiates mechanistic study.

Considering the nature of this photocatalytic reaction, there were three possible intermediates that could account for the C–H amination (**Figure 98**). Gathering support to discern among reactive intermediates proved to be an arduous endeavor and ultimately concrete evidence (*e.g.* direct spectroscopic observation of a given intermediate) was not obtained.

Nevertheless, strong support for a triplet nitrene emerged, and our efforts to ascribe a mechanism for the formation of this triplet nitrene will be described.

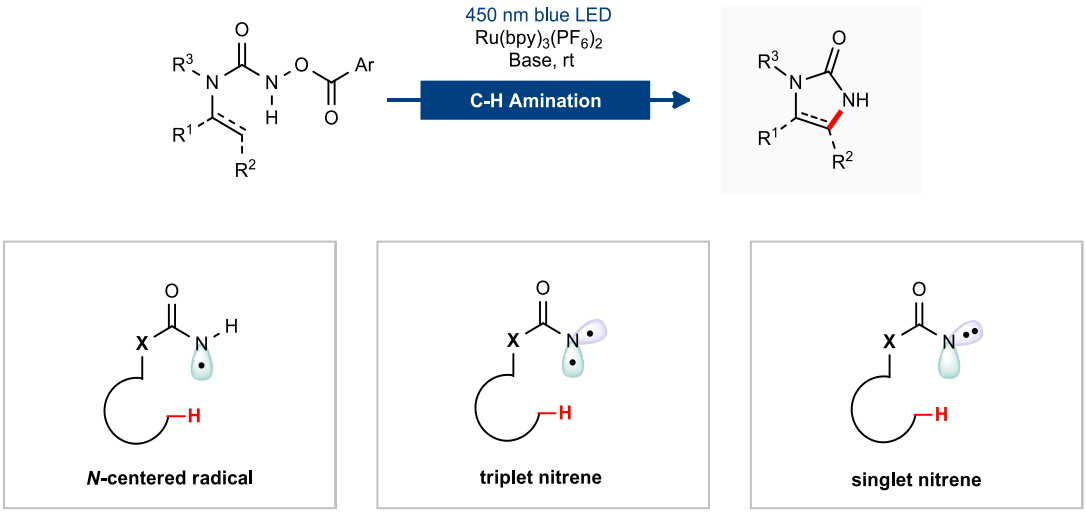


Figure 98 Possible intermediates in the photocatalytic C-H amination.

Given the fact that similar hydroxylamine precursors had formed *N*-centered radicals under photoredox conditions, we first considered similar pathways for *N*-centered radical generation. There are two general strategies to form *N*-centered amidyl radicals photocatalytically from hydroxylamine precursors. In the first example, an electron deficient aryl,[189] or acyl[218,222] substituent bound to the *O*-atom of the hydroxylamine acts as a reducible redox handle via SET. A photocatalyst can donate an electron into the LUMO of these substrates and the resulting radical anion substantially weakens the adjacent N–O bond. Spontaneous homolysis driven by N–O bond weakening delivers the *N*-centered radical. An alternative strategy is the implementation of an oxidative quenching cycle. Typically, a hydroxylamine precursor with

a pendant carboxylic acid is employed.[232] Oxidation of the carboxylate (upon deprotonation) is followed by a similar N–O bond cleavage sequence (**Figure 99**).

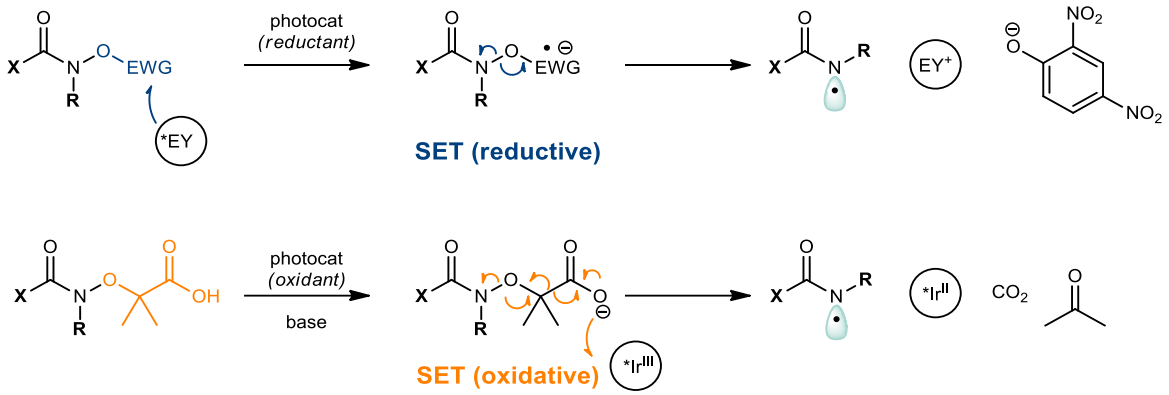


Figure 99 Two methods of *N*-centered (amidly) radical generation via photo(redox)catalysis.

At first glance the acyl-oxy hydroxylamine precursor in our system seemed likely to undergo a similar SET reduction / N-O bond cleavage pathway (**Figure 100**). A mechanism based on literature precedent would operate via: **I**) Excitation of Ru^{II} via blue LED irradiation to its triplet excited state $*Ru^{II}$, **II**) SET oxidation of Et_3N by $*Ru^{II}$ to produce Ru^{I}, **III**) SET reduction of the hydroxylamine precursor by Ru^{I}, **IV**) N–O bond homolytic cleavage, **V**) 1,5 HAT, and then **VI**) SET oxidation of the radical to the carbocation by the amine radical cation, and intramolecular cyclization. Dissecting the elementary steps of this hypothetical mechanism through experimental probes, intermediate trapping and physiochemical studies on the substrates could be used to remove mechanistic possibilities, such as the intermediacy of an *N*-centered radical. We speculated that step **III** could be further assessed through cyclic voltammetry or Stern-

Vollmer quenching, while step **V** could be probed via synthetic probes and additive studies. Step III was already an unlikely scenario given the results of benzoyl modification (**Figure 96**).

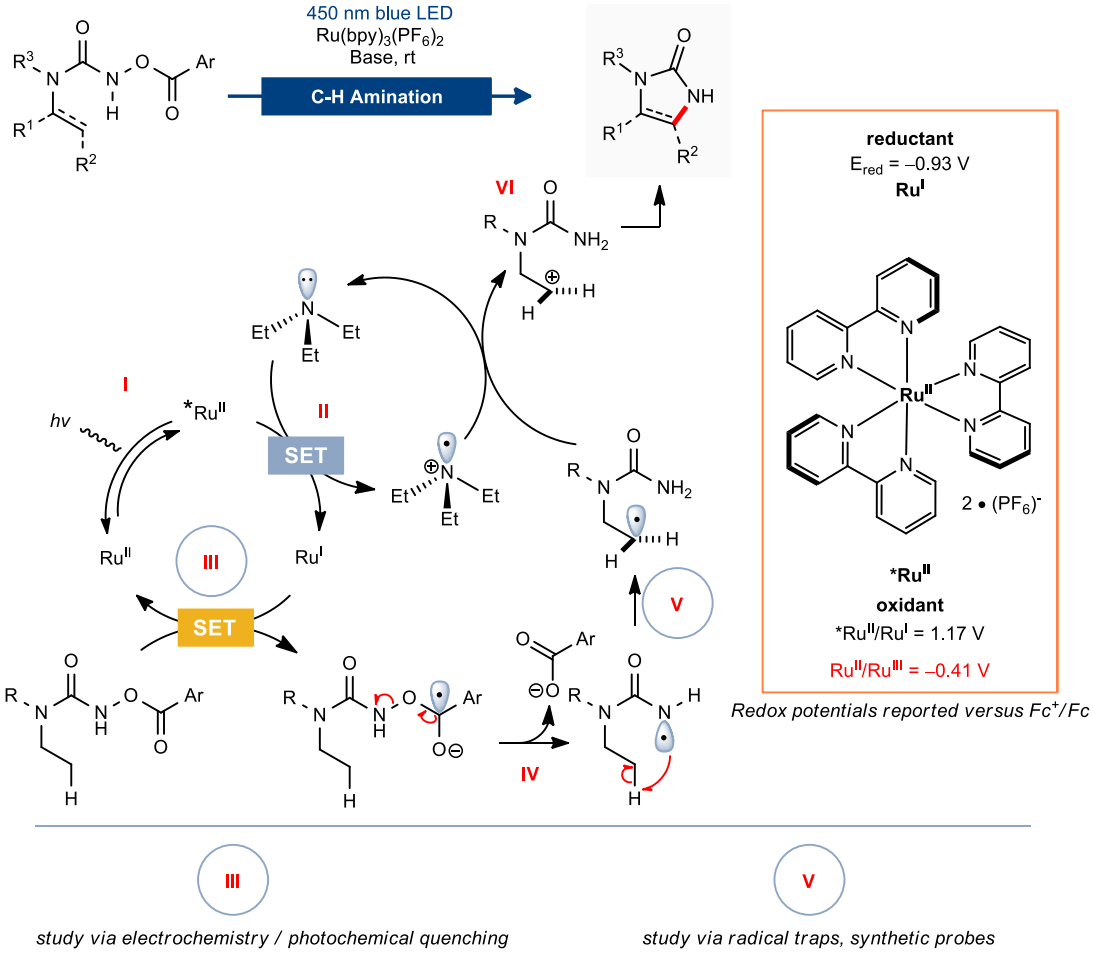


Figure 100 Hypothetical photoredox amination via SET reduction / 1,5-HAT cascade.

4.14 Step III/V mechanistic probes of the hypothetical photoredox amination mechanism

To probe the possibility of such a SET initiated step, reductive and oxidative quenching cyclic voltammetry was performed (see SI for experimental details). Reported measurements for

$Ru(bpy)_3^{2+}$ were converted from SCE to Fc^+/Fc using a reported method.[241,242] Single electron transfer processes were quickly discounted given that electrochemical measurements of precursor **16z** were recorded to be roughly 1.0 V outside the range of $Ru(bpy)_3^{2+}$ for either oxidation ($E_{1/2}$ = +2.15 V) or reduction ($E_{1/2}$ = –1.75 V) versus Fc^+/Fc. For reference, literature consensus suggests that even substrates that lie +/– 0.5 V from a given photocatalyst will not efficiently engage in SET reactions.[173]

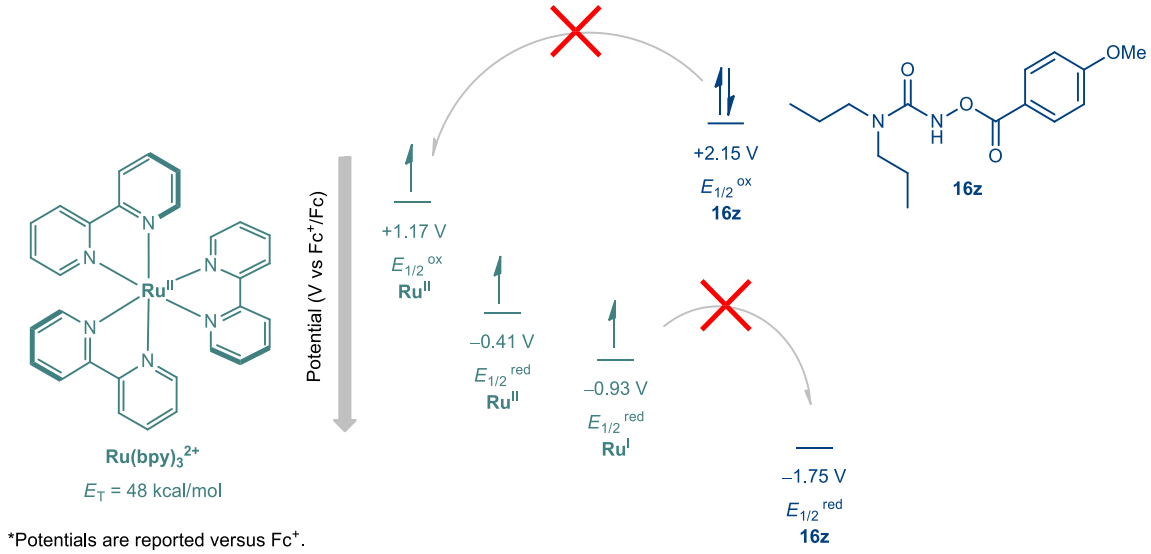


Figure 101 Electrochemical studies of $Ru(bpy)_3$ and precursor **16z**.

Moreover, analysis of early photocatalysts screening with a focus on the electrochemical properties of the photocatalysts did not indicate a process driven by SET-reduction (*e.g.* strongly reducing photocatalysts failed to provide appreciable yields for the C–H amination) (**Table 39**). In fact, the next best yield was achieved with $Ir(ppy)_2(dtbpy)$, which is a worse excited state

reductant than $Ru(bpy)_3$ but possessed a nearly identical triplet energy, indicating the potential for a EnT process. This could indicate that an EnT process was a possible scenario. Thus, single electron reductive processes seemed unlikely for this reaction.

Table 39 Photocatalyst screening with increasing reduction potential of the catalyst excited state.

photocatalyst	E_T	$E_{1/2}^{red}$ (SCE)	$E_{1/2}^{red}$ (Fc+)	$E_{1/2}^{ox}$ (SCE)	$E_{1/2}^{ox}$ (Fc+)	yield
Triphenylpyrylium	53	-0.35	0.05	+2.30	2.7	0%
$[Ru(bpm)_3]Cl_2$	-	-0.91	-0.51	+0.99	1.39	11%
$[Ir(ppy)_2(dtbpy)]PF_6$	49.2	-0.96	-0.56	+0.66	1.06	40%
$[Ru(bpy)_3]PF_{62}$	47.8	-1.33	-0.93	+0.77	1.17	92%
$[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$	61.8	-1.37	-0.97	+1.21	1.61	33%
$Ir(dFppy)_3$	63.5	-2.11	-1.71	-	-	0%

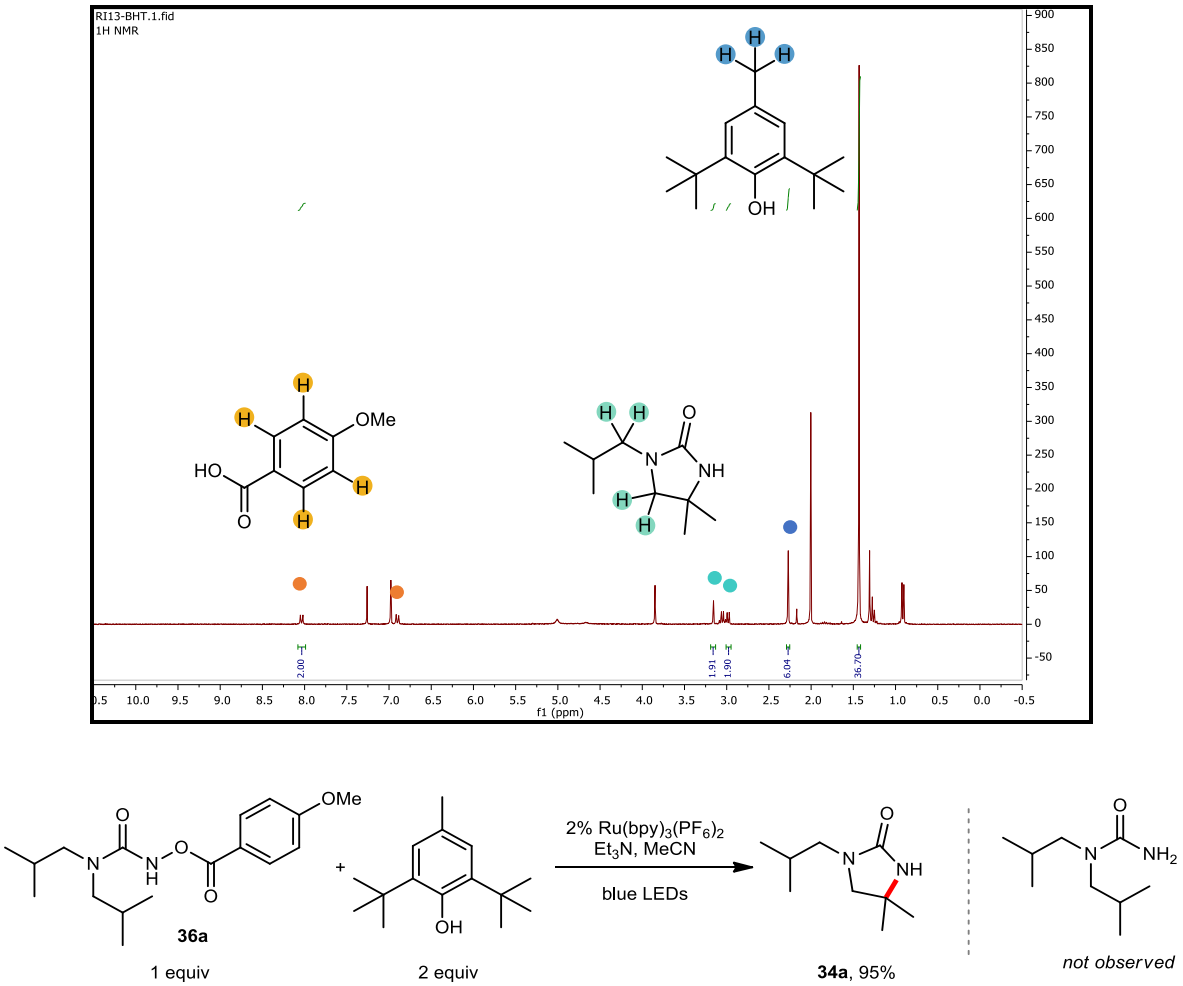


Figure 102 Radical trapping experiments using BHT.

To probe for an *N*-centered radical mechanism, radical trap experiments (BHT, acrylate), substrate modifications (*N*-methylation), and radical clock studies were conducted (vide infra). Radical traps are routinely used to probe for radical mechanisms by intercepting radical intermediates in photocatalytic reactions. The addition of BHT is known to perturb reactions involving 1,5- and 1,6-HAT pathways of *N*-centered radicals but trapping the carbon radical and / or *N*-centered radical.[243–245] The C–H amination reaction with **36a** remained quantitative in the presence of excess BHT (**Figure 102**), which is inconsistent with a *N*-centered radical pathway. To

further rule out a possible radical intermediate, an olefin-trapping experiment was conducted. Several studies have used such traps as probes to support the radical intermediacy induced by electron transfer pathways.[226,227,243] No evidence of alkene addition was observed upon the addition of excess methyl acrylate (**Figure 103**). While these additive studies cannot disprove the presence of radicals on themselves, they form a strong foundation for a case against their intermediacy in this reaction.

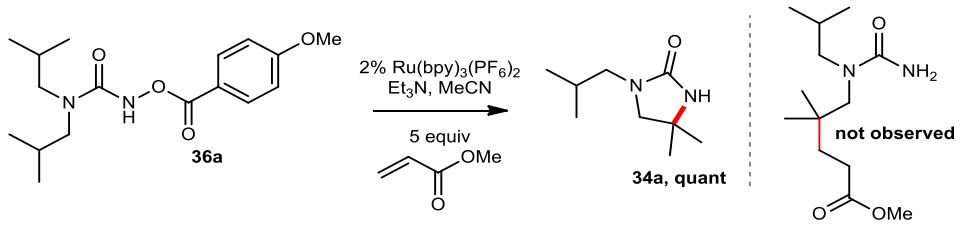
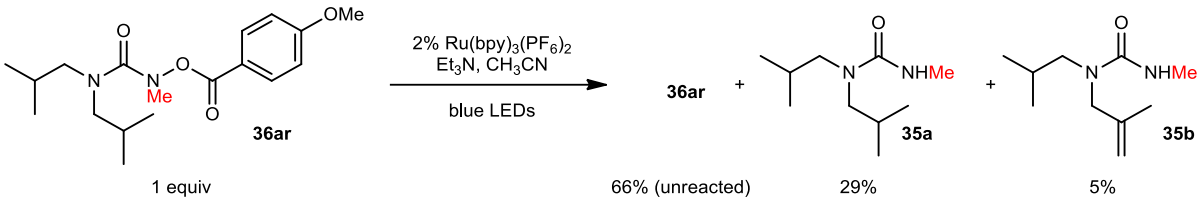


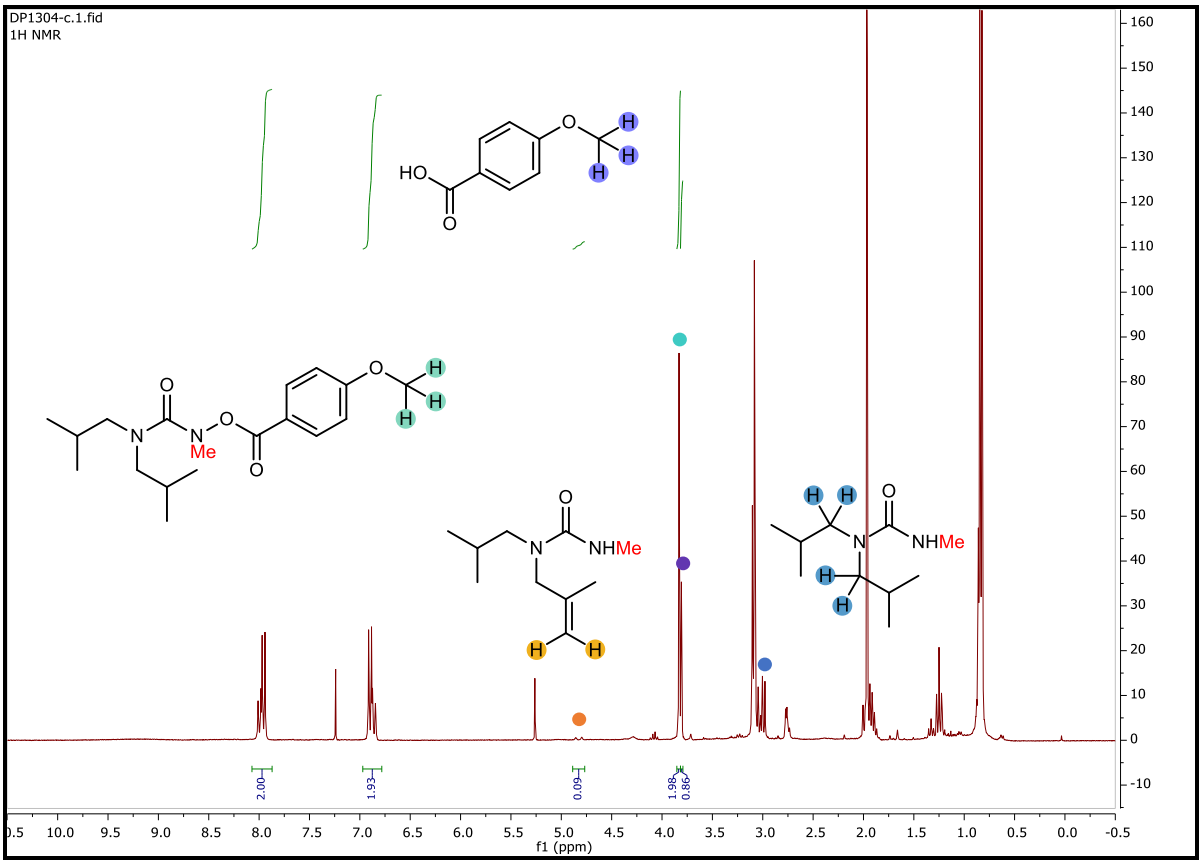
Figure 103 Methyl acrylate probe for radical formation.

A pathway involving an *N*-centered radical initiated via SET-induced N–O bond cleavage was unlikely given the data above in addition to the following observations during early optimization / substrate scope: 1) electron-rich benzoates were required for optimal reactivity, 2) a lack of selectivity for the 5-position, and 3) the isolation of aziridines that would form via unlikely primary carbocations. However, we hoped to further probe this potential mechanism by other experiments aimed to probe whether a SET reduction was likely to lead to product formation. A derivative possessing an *N*-methyl substituent was subjected to the reaction in order to study the effects of *N*-substitution on the transformation. We hypothesized that *N*-methylation would not affect SET reduction significantly. Further, an *N*-centered radical should

not be affected by this structural modification; however, alternative *N*-species such as a nitrene would be unable to form due to this modification. When the *N*-methylated derivative **34ar** was subjected to the reaction, there was no product formation in the crude ^{1}H-NMR after 72 hours (**Figure 104**). Instead, a large amount of starting material (66%) and two ureas, **35a** and **35b** were isolated. These two ureas were presumed to arise from reduction of the precursor via SET. That the precursors could undergo SET reduction, but not undergo C–H amination was inconsistent with a productive SET-induced pathway for product formation. However, it is important to note that conformational changes brought about by this structural modification could have inhibited the C–H amination. We therefore repeated these *N*-methylation experiments with an *N*,*N*-dipropyl precursor, and the analogous carbamate and amide precursors, which all failed to react upon *N*-methylation.

Figure 104 N-methyl probe crude ^{1}H-NMR with products identified.





The crucial lack of C–H amination upon *N*-methylation suggested that the *N*-H was crucial for effective C–H amination, and that SET reduction was not a productive path. Moreover, the isolation of **35b** was important as it clearly demonstrated that even in the presence of a carbocation (required intermediate to form a pendant alkene) there was no cyclization observed; thereby further ruling out the SET-initiated mechanism (**Figure 105**). Various photocatalytic

methods operating via 1,5-HAT of *N*-centered radicals proceed without issue upon *N*-substitution.[189,226,227,232,246,247] Therefore, even if *N*-alkylation would reduce the electrophilicity of the *N*-centered radical somewhat,[248] this modification does not render an *N*-centered amidyl radical unreactive toward 1,5-HAT in previously reported methods. However, if the reaction proceeded through a singlet or triplet nitrene intermediate, this *N*-methylation modification would completely abolish amination reactivity, as was observed (**Figure 106**).

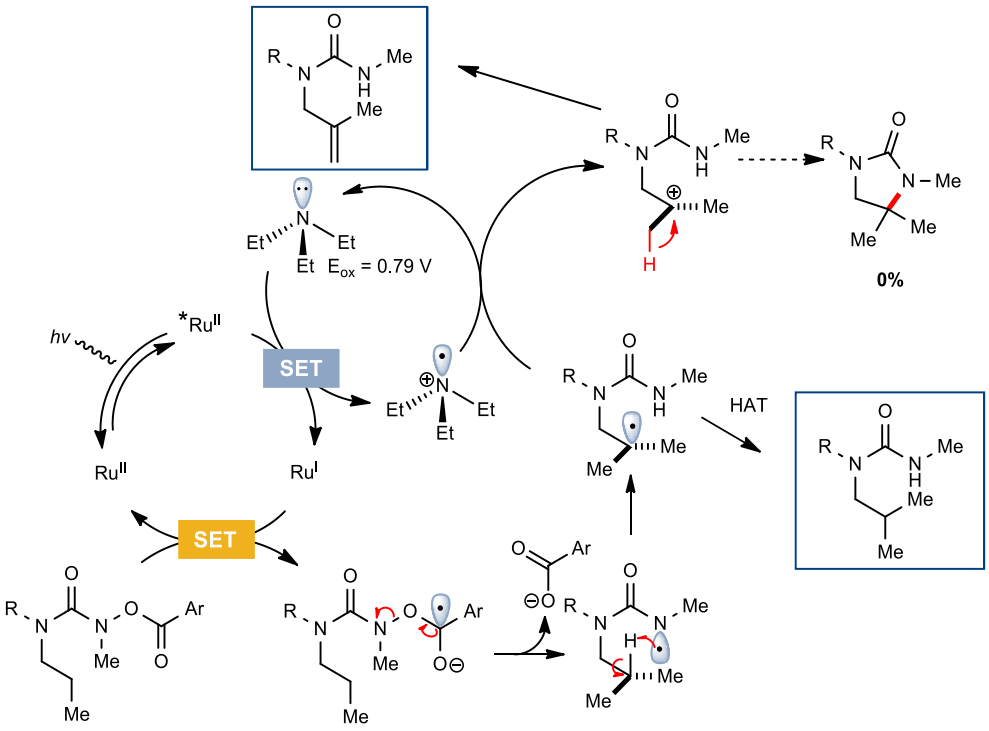


Figure 105 N-Centered radical mechanism with the N-methyl modification.

4.15 Mechanistic probes for singlet versus triplet nitrene reactivity

The lack of reactivity observed upon methylation suggested the intermediacy of a nitrene intermediate; however, nitrenes can perform C–H amination via triplet or singlet states. Triplet nitrenes undergo *stereoselective stepwise* C–H insertion, while singlet nitrenes react via *stereospecific concerted* C–H insertion. Moreover, mechanisms forming nitrenes from hydroxylamine precursors under photocatalytic conditions were unknown at the onset of this study. It seemed logical to first design experiments to ascertain a reactive intermediate (*e.g.* triplet vs singlet nitrene) and then later ascribe a mechanism for its formation.

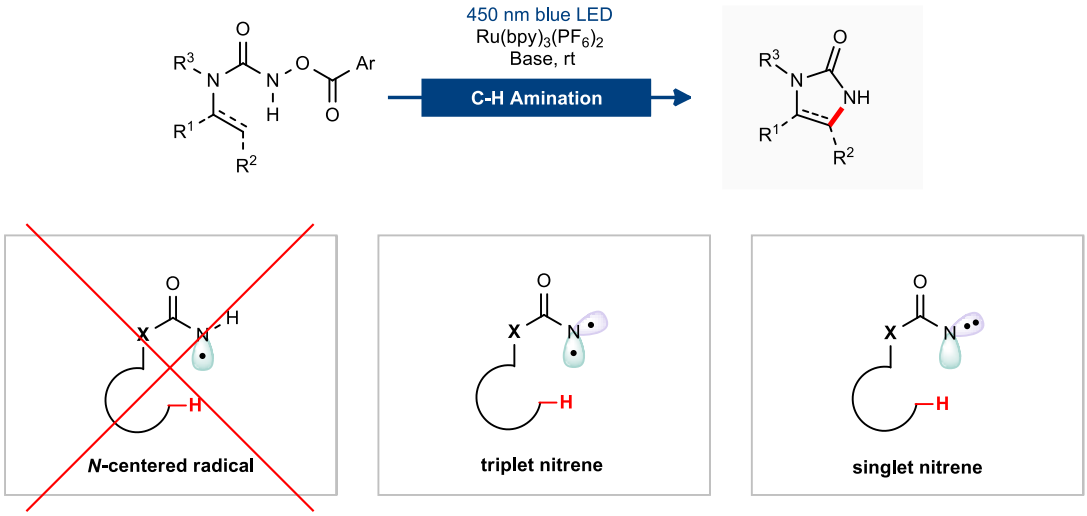


Figure 106 *N*-centered radical not a likely intermediate in the C–H amination.

Thus, to probe for the presence of a singlet or triplet nitrene, an enantioenriched precursor was synthesized and subjected to the reaction. When optically enriched **1as** (92% ee) was used,

the resulting cyclic product **34k** suffered total racemization, (**Figure 107**), thereby ruling out a singlet nitrene. This contrasts to the results of Chang,[203] where an enantioretentive C–H amination via triplet nitrene was proposed, but conforms to the greater literature on non-stereospecific triplet nitrene C–H aminations.[161] It is possible that the more stabilized benzylic radical in our system allowed racemization to occur before radical recombination from the triplet nitrene occurred.

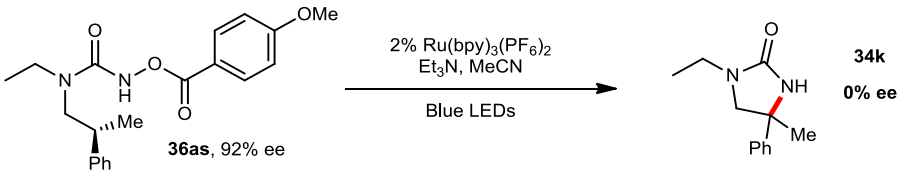


Figure 107 Enantioenriched probe for triplet versus singlet nitrene.

An alkene isomerization study was then conducted using **36at.** If a radical was formed at the allylic carbon, the *Z* stereochemistry of the alkene would be eroded to some extent in the product due to a rapid equilibrium with the more stable *E* geometry. Indeed, metal nitrenes reacting with triplet character lose 10-25% alkene geometry during the allylic C–H amination.[249] Conversely, a concerted amination via singlet nitrene would lead to complete retention of alkene stereochemistry due to the concerted nature of C–H insertion. When **36at** was reacted in the photocatalytic system, nearly 85% retention of the alkene stereochemistry was observed. Thus, the resulting 4:1 ratio of *Z*:*E* alkene in C–H amination products **34ar** and **34as** was most consistent with a rapid stepwise radical recombination through a triplet nitrene (**Figure 108**).[249] Given that

Weaver recently reported thermodynamically uphill photocatalytic alkene isomerization from *E* → *Z* allylamines,[250] we investigated the *E*-alkenyl substrate under the reaction conditions. There was no isomerization from *E*- to *Z*-alkene, indicating that the 4:1 ratio obtained from the reaction of **36at** was likely the result of retention during a rapid radical recombination. It is important to note that the starting material slowly isomerized from Z → E under ambient conditions. Therefore, it is difficult to ascribe certainty between triplet or singlet nitrene from this minimal isomerization. However, the minimal isomerization is inconsistent with a *N*-centered radical

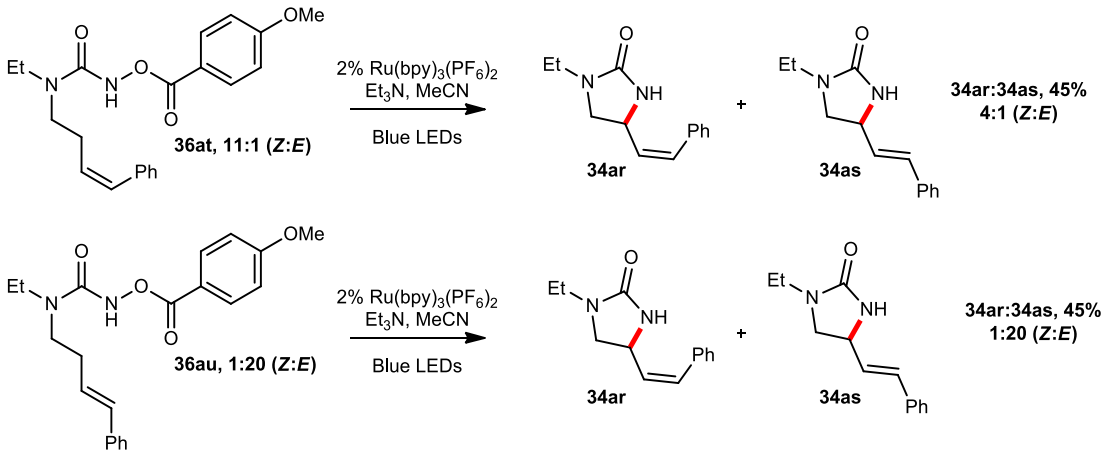


Figure 108 Alkene isomerization study using Z- and E- alkenyl substrates.

Radical clock experiments generally provide compelling evidence for radical intermediates. Despite performing the challenging and lengthy synthesis of the desired probe, **36av** unfortunately did not lead to the cyclized product under the optimized reaction conditions. Instead, *syn* cyclopropane urea (**34at**) was isolated as the major product (**Figure 109**). A minor amount of cyclopropane-ring opened urea was also observed by ^{1}H-NMR (<10%). The limited

observance of ring opening further discounts a singlet nitrene as a potential intermediate but provides little disambiguation between triplet nitrene or *N*-centered radical. Ultimately, these synthetic probes (**26at**-**26av**) could not alone be used to differentiate between an *N*-centered radical or triplet nitrene intermediate; but collectively each entry was inconsistent with a singlet nitrene as a reactive intermediate (**Figure 110**).

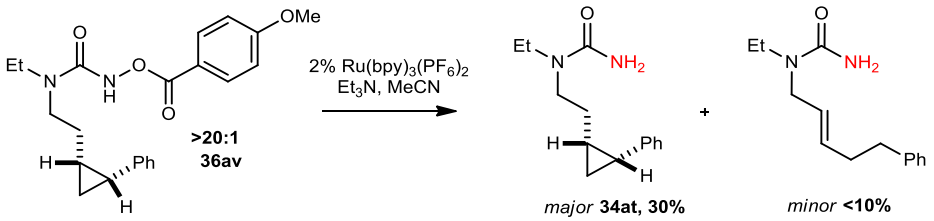


Figure 109 Radical clock experiment is inconclusive.

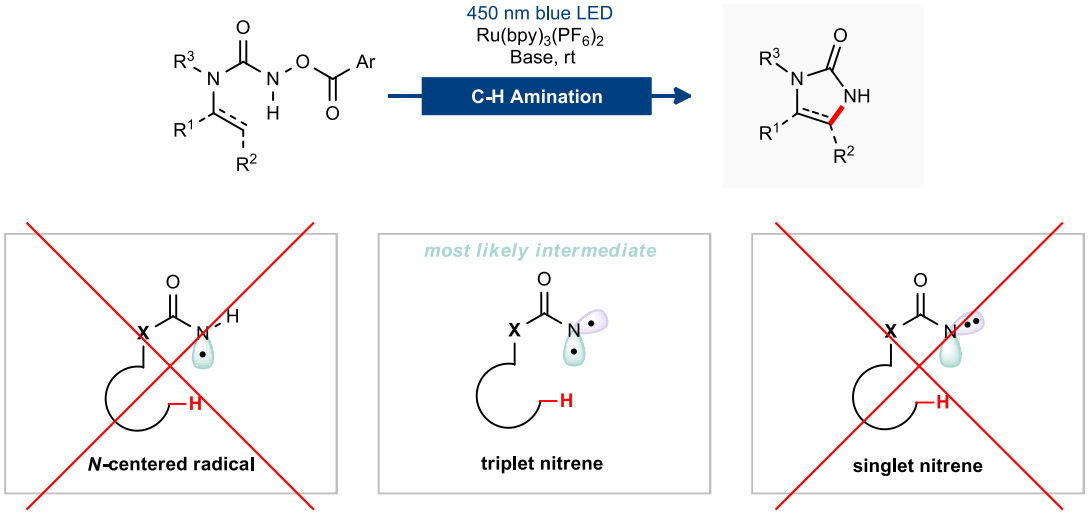


Figure 110 N-Centered radical and singlet nitrene not likely intermediates in the C–H amination.

Taken together, the results of these mechanistic probes were most consistent with a triplet nitrene intermediate; yet, triplet carbamoyl nitrene C–H amination reactions have not been reported in the literature. Therefore, to test if carbamoyl triplet nitrenes could engage in such C(sp^3)–H amination, and to compare the novel hydroxylamine nitrene precursors to conventional nitrene precursors, the reactivity of the parent carbamoyl azide **36aw** was probed (**Figure 111**). Related azidoformates have undergone C(sp^3)–H amination upon photolysis.[251] Under conditions optimized for C–H amination with hydroxylamine precursors, the carbamoyl azide produced only traces of C–H amination. However, when the solvent was changed to DCE, and irradiation was increased for several days the reaction began to produce a low yield of product (**Figure 111**). The poor yield of **34a** with azide precursors indicated that triplet nitrene C(sp^3)–H amination was possible for carbamoyl-triplet nitrenes, but that hydroxylamine-derived precursors were indeed more efficient nitrene precursors under photocatalytic conditions. Similarly, Chang demonstrated azides to be relatively poor precursors for nitrenes via EnT reactions. This peculiar observation was predicted to be due to their high bond reorganization energy originating from structural distortion of the azido moiety from linear to bent upon reaching its triplet state.[203] This crucial experiment demonstrated that triplet nitrenes could undergo intramolecular aliphatic C–H amination reactions, even if such reactivity was not observed in previous studies by Yoon.[209] Collectively, results from experimental probes pointed to a triplet nitrene as the reactive intermediate for this transformation.

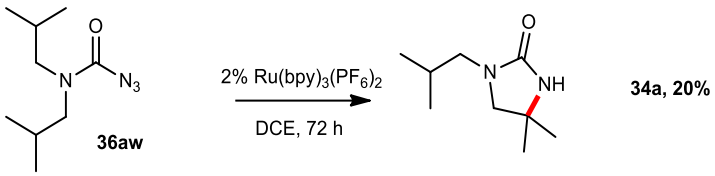


Figure 111 C-H amination observed with **c**arbamoyl azide likely via EnT.

4.16 Two potential mechanisms to access triplet nitrenes via photocatalysis

Even with a triplet nitrene as the most likely intermediate, a mechanism was still required to account for the formation of the triplet nitrene. There were two potential mechanisms hypothesized to produce triplet nitrenes as reactive intermediates: 1) EnT / PCEnT to the substrate to access the triplet nitrene directly; or 2) a two-step, single electron α-elimination initiated by PCET oxidation, followed by SET-reduction to deliver the triplet nitrene. Support for either mechanism will be discussed below.

4.17 Proposed mechanism 1: Energy transfer catalysis

Since Chang reported a proposed EnT reaction to access triplet nitrenes, the likelihood of such a mechanism in our system was assessed with the generated data. The obligatory *N*-H could be explained by invoking the EnT mechanism recently introduced by Chang (**Figure 90**), which required deprotonation of the hydroxamate precursors for exothermic EnT. Although ^{1}H-NMR studies indicated Et_3N did not fully deprotonate the substrate (see SI), control experiments clearly established the need for a base (**Table 33**). DFT calculations (see SI) clearly demonstrated that EnT to the neutral species was exceptionally endergonic (E_T *neutral* = 74 kcal/mol), whereas EnT to the deprotonated precursor was thermodynamically accessible (E_T *anionic* = 53 kcal/mol) for $Ru(bpy)_3^{2+}$ in the excited state (E_T = 48 kcal/mol). Moreover, this could also explain the

success with $[Ir(ppy)_2(dtbpy)]PF_6$ (E_T = 49 kcal/mol) as a catalyst, which possessed the most similar E_T energy to $Ru(bpy)_3^{2+}$ (**Table 39**).

As a probe for the possibility of an EnT reaction pathway, **36a** was irradiated overnight with UVA light, which led to a modest 25% yield. Upon the addition of 20-mol% tetramethylguanidine (TMG) as a base, the yield was increased to 85% (**Figure 112**). The ability of the reaction to proceed in the presence of high energy light alone is an accepted indicator of an EnT pathway.[173,252,253] However, it is important to note that simply because the reaction can occur with UVA alone, does not mean that the milder conditions using blue LEDs and a photocatalyst operate by this same mechanism. This simply confirms that an EnT pathway can productively lead to C-H amination.

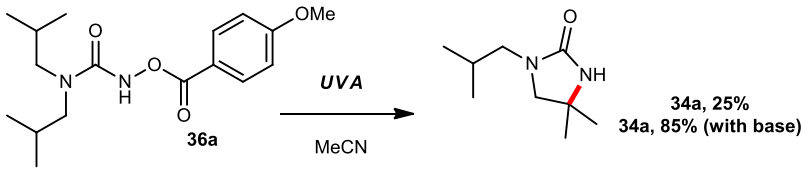


Figure 112 Reactive proceeds using UVA irradiation suggests EnT pathway possible.

Taken together, experimental results were consistent with an EnT pathway towards triplet nitrene formation, but did not completely conform to the mechanism recently introduced by Chang.[203] An important difference between this reaction and the recent report by Chang is the use of a milder organic base (Et_3N, or phosphate versus K_2CO_3), which does not fully deprotonate the nitrene precursor, and the significant differences in precursor effectiveness (*i.e.* the use of

electron rich versus electron poor benzoates). However, these differences could be reconciled by a proton-coupled energy transfer (PCEnT)[254,255] pathway. Such processes are rare but established in the literature and would necessitate the formation of an H-bonded complex between the base (Et_3N or phosphate) and substrate with simultaneous energy transfer and deprotonation. This could account for the requirement of the N–H for C–H amination, even if full deprotonation was not possible. Such concerted processes (*i.e.* PCET) are generally accepted as methods to drive thermodynamically unfavorable deprotonation / sensitization events.[246] There are few examples of EnT reactions involving hydroxylamine precursors, but no examples of PCEnT. Aforementioned, Chang's recent EnT proposal used similar hydroxamate precursors to access triplet nitrenes but required triplet sensitization of the anion followed by N–O bond cleavage. Ultimately, DFT computations supported the formation of a triplet nitrene and benzoate anion from the N–O homolysis of the triplet anion. Since deprotonation was not favourable in our system, it was necessary to rule out alternative potential pathways that were possible via EnT. It has recently been suggested that related hydroxylamine derivatives can undergo direct homolysis of the N–O bond upon EnT.[252] To rule out a direct homolysis of the N–O bond upon triplet sensitization, precursor **36ax** was evaluated in the reaction (**Figure 113**). Homolysis of the N–O bond would be followed by spontaneous decarboxylation to the cumyl radical and would provide an *N*-centered radical intermediate. When **36ax** was subjected to the reaction conditions, quantitative recovery of the carboxylic acid was obtained, along with C–H amination. However, rather than direct homolysis of the N–O bond, if the carbonyl is excited to its triplet state, then a radical pathway towards a triplet nitrene could be hypothesized that also accounts for the observed recovery of carboxylic acid.

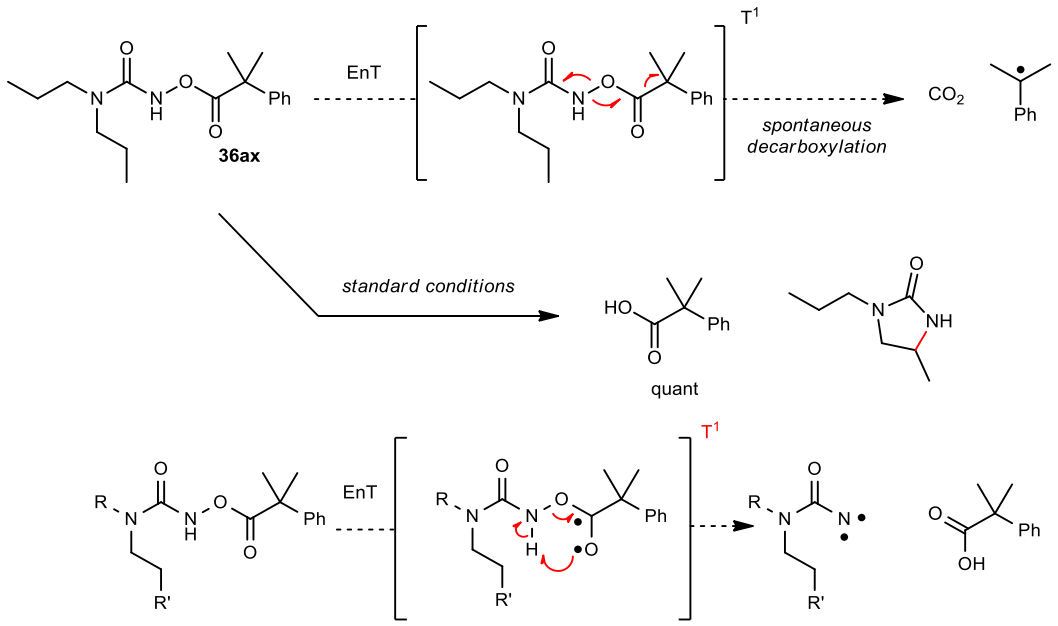


Figure 113 Hypothetical EnT pathways: homolysis or triplet ketyl biradical.

Despite fitting relatively well within the framework of a PCEnT induced triplet nitrene C–H amination, we could not rule out an alternative mechanism which involved a PCET-induced amidyl radical formation / reductive SET-induced N–O bond cleavage sequence forming triplet nitrenes.

4.18 Proposed mechanism 2: single electron α-elimination

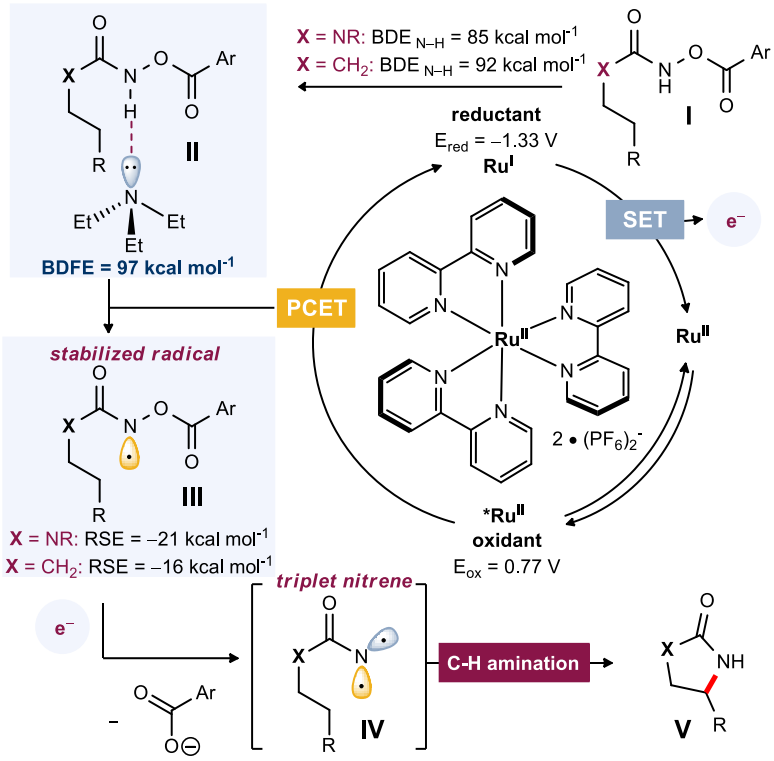


Figure 114 Alternative mechanism invoking sequential PCET oxidation / reduction

Before Chang's report emerged in the literature, the single electron α-elimination mechanism was the preferred hypothesis to account for the generation of triplet nitrenes. Moreover, the mechanism accounted for most of the experimental data / control studies. The proposed mechanism (**Figure 114**) begins with **I** forming H-bonded complex **II**, which undergoes PCET with Ru^{II*} (BDFE = 97 kcal/mol) to produce stabilized radical **III.** To glean stability information on the radical, the radical stabilization energy (RSE) was calculated by DFT at the B3LYP 6-311+G(2d,p) level of theory. An RSE of –21 kcal/mol was calculated for **III** by DFT indicating a substantial degree of stabilization (persistent radical DPPH = –27 kcal/mol). DFT calculations

combined with BDFE data indicated that the PCET oxidation would be a highly exergonic process (ΔG = –12 kcal/mol) and **III** could then undergo SET reduction by Ru^{I} (E_{red} = –1.33 V). Analysis of the putative *N*-centered radical **III** highlights that SET reduction should intuitively be significantly favoured over reduction of **I** ($E_{red(I)}$ = –1.8 V). This hypothesis was substantiated by DFT calculations on the LUMO energies of the *N*-centered radical **III** vs **I**, which clearly indicated that the radical **III** is substantially easier to reduce than starting material **I**. Furthermore, visualization of the LUMO / SOMO orbitals by DFT (see SI) indicated addition to the carbonyl electrophore would be preferred over reduction of the *N*-centered radical to the *N*-anion. Nocera recently calculated the rates of back-electron-transfer (BET)[256] in photochemical PCET reactions of amides, which were nearly diffusion limited processes (*e.g.* the conversion **III** to **IV**). Not only did this invoke a high degree of reversibility in related oxidative processes,[257,258] but they demonstrated that overcoming the reversibility of the initial oxidation was only overcome due to the addition of thiol additives.[256] In the proposed mechanism, rapid BET in the presence of a more suitable electrophore (*e.g.* more polarized π*-orbital / better e-acceptor) should lead to the desired reaction outcome. This not only provides a rationale for the increased rate of conversion observed with the *N*-H vs. *N*-methyl urea precursors, but also justifies the use of *p*-methoxy benzoate precursors to facilitate the careful orchestration of events required to access the triplet nitrene. Reductive N–O bond cleavage from **III** expels the carboxylate via 1-electron α-elimination to provide triplet nitrene **IV** and C-H amination then leads to the urea or lactam products **V**. While such a 1-electron α-elimination process has not been reported to our knowledge, each individual step is well-precedented: 1) PCET is an effective strategy to form amidyl radicals from mildly acidic N-H bonds by an oxidative pathway.[246,259] In this system, the adjacent oxygen atom of the

hydroxylamine derivative should facilitate PCET by: 1) lowering the pKa[260] of the *N*-H bond, and 2) increasing the stability of the generated *N*-radical by a capto-dative effect.[248] 2) Reductive-quenching is efficient to form amidyl radicals by reductive SET-initiated N-O bond cleavage.[189] In addition, precedent for 1-electron α-elimination emerged during the course of this study, with a detailed study on the photogeneration of a Rh_2 nitrenoid from chloramine-T, although synthetic applications were not evaluated.[261]

The kinetics of such a mechanism would hinge on the association equilibrium of the H-bonded complex (**Figure 114**, **II**), and the rates of quenching the complex with the excited photocatalyst. Therefore, to probe the possibility of this mechanism, the solute hydrogen bond acidity was investigated using a reported procedure to determine an approximate equilibrium of the H-bonded complex.[262] Solutions of **36a** and **36h** of 0.01 M in $CDCl_3$ and DMSO-d_6 were prepared. The ^{1}H-NMR spectra were obtained on a 300 MHz NMR.

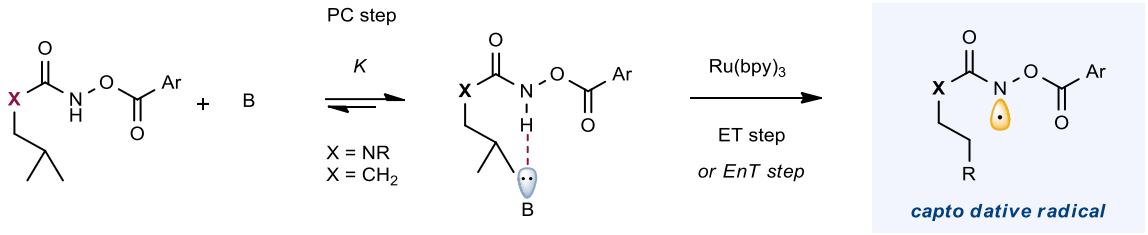


Figure 115 The importance of equilibrium on H-bonded complex for PCET rate.

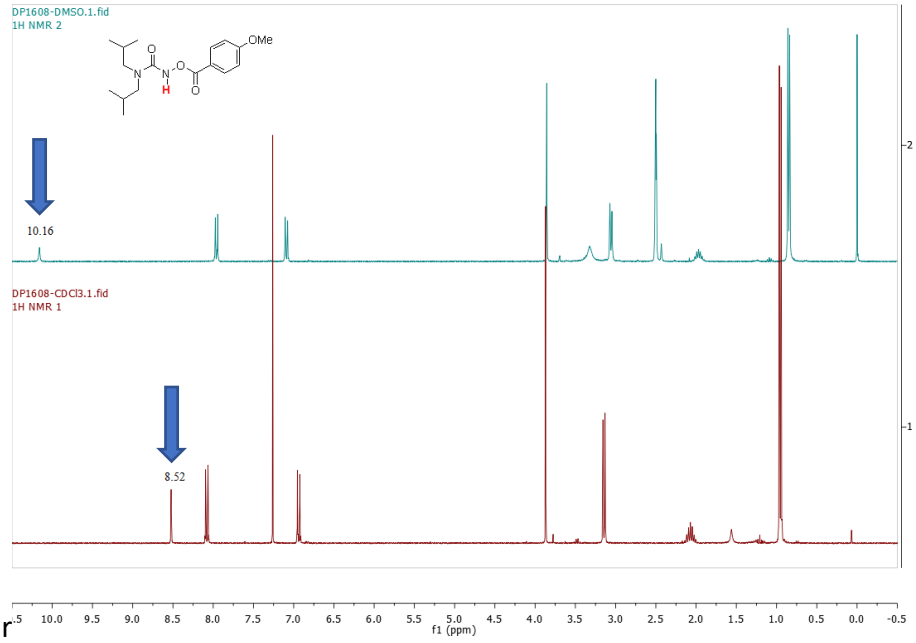


Figure 116 Solute hydrogen bond acidity of **36a**

A= 0.0065+0.133Δδ = 0.0065+0.133∗1.64 = <u>0.224</u>

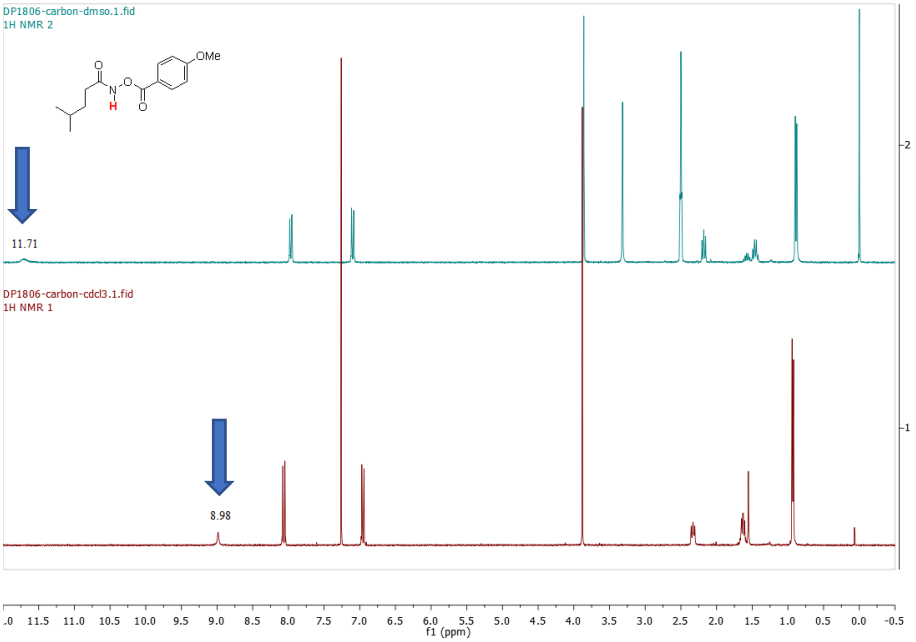


Figure 117 Solute hydrogen bond acidity of **36h**

A= 0.0065+0.133Δδ = 0.0065+0.133∗2.73 = <u>0.370</u>

The compounds were predicted to be relatively poor H-bonding acids, yet the equilibrium constant, (*K*) calculated from the formula (log*K* = (7.354αH2•βH2) – 1.094) for the H-bonded complexes were still calculated to be > 1 suggesting modestly preferential formation of the desired complex in solution. Importantly, these equilibrium studies are equally important in the context of validating the likelihood of a PCEnT reaction, which presumably requires formation of a similar H-bonded complex.

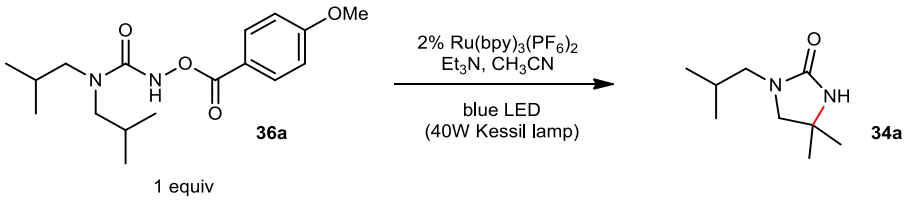
4.19 Alternate mechanisms considered operating via triplet nitrenes

Two recent observations could hugely impact the likelihood of either mechanism. 1) an initial SET-reduction to form a carboxylate base (e.g. *p*-methoxy benzoate) which acts as the active base in the reaction for either PCEnT or PCET, or 2) decomposition of the photocatalyst followed by metal nitrenoid C–H amination. The three alternative mechanisms will be discussed in detail below.

4.20 The potential of an autocatalytic PCET or PCEnT

In order to glean mechanistic insight that could prove helpful in distinguishing between PCEnT, PCET or *N*-centered radical mechanisms, a kinetic study was attempted. The initial goal was to perform a kinetic isotope effect (KIE) study, by deuterating the *N*-H of the hydroxamate. It was first hypothesized that the initial H-bonding / deprotonation event could be rate determining for the hypothetical PCEnT or PCET processes and that a KIE could be used to

substantiate this event. Before a KIE could be obtained using the *N*-D precursor, reliable kinetic data using the *N*-H precursor **36a** was essential. This was a challenge, as the rates of the reaction were highly variable upon initial examination. Even though the shape of the data remained somewhat constant, the slope of the calculated initial rates would change by a factor of 10 if the position of the vial was altered even minimally (expectedly as this was change the path length and absorbance). This was an insurmountable challenge using our standard LED strip light reaction set-up. Ultimately, somewhat repeatable data was obtained by using a 40 W Kessil lamp, and removing aliquots from a large-scale reaction vessel. Notably, the 40 W Kessil lamp produces more heat than the LED strip lights. The data from triplicate runs is presented below (**Figure 118**). However, it is important to note that the 40 W Kessil lamp was not used to evaluate the synthetic scope of the reaction, and often resulted in lower yields for most entries. Ideally, this experiment could be repeated more accurately, though would require technology capable of in situ ^{1}H-NMR monitoring during irradiation (*i.e.* fibre optic cable with blue LED tethered to an NMR probe).[263] Such probes exist, but are not available at the University of Ottawa currently. It appeared that an induction period was present. This led to two hypotheses, 1) the released benzoate from N–O bond cleavage played an active role in the transformation, or 2) the active catalyst was formed during the initial irradiation. We could also not rule out the potential that the induction period was an artefact brought about by a change in rate from mild heating of the reaction by the 40 W light source. It is conceivable that the rate was slower at the beginning because the reaction was approximately 20 °C, whereas quite rapidly the 40 W lamp would heat the vial to 40 °C. Therefore, more studies are needed with careful monitoring of the reaction temperature.



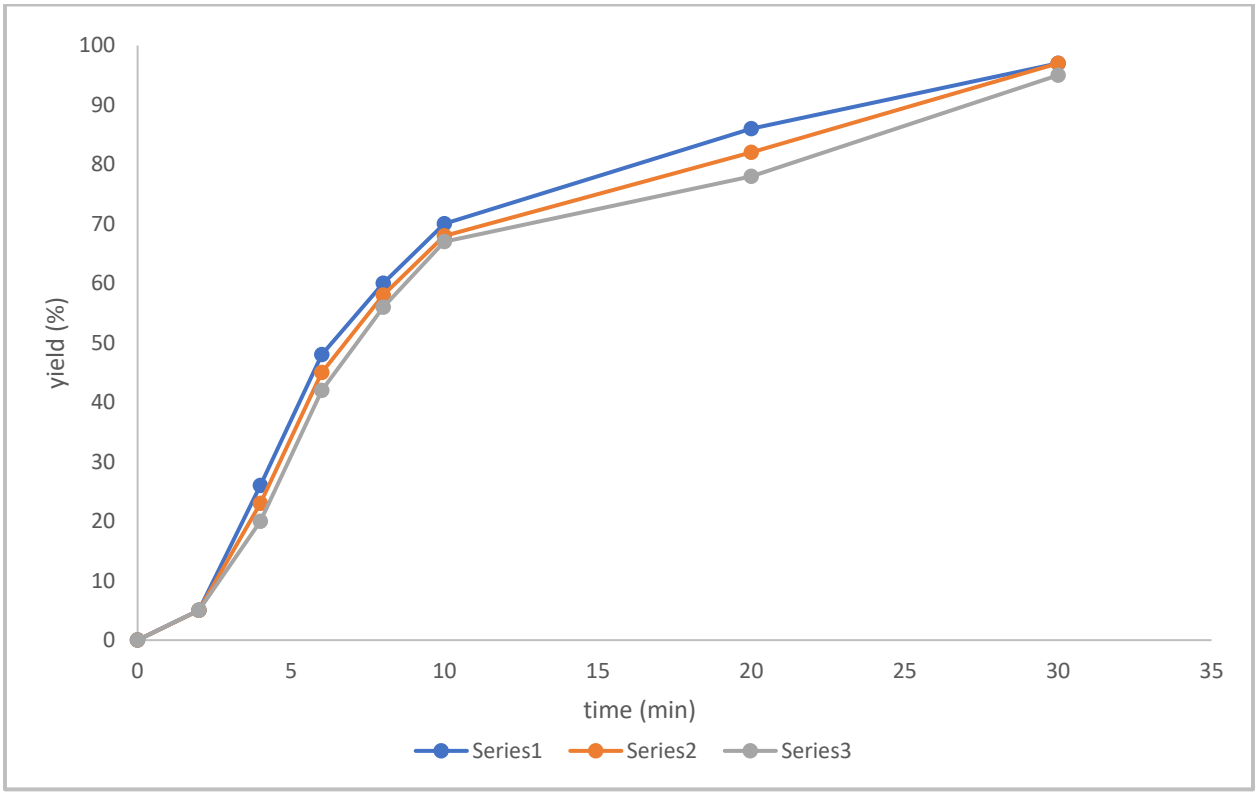


Figure 118 Triplicate runs of a large-scale (1 mmol) photochemical reaction using **36a**. 0.1 mL aliquots were removed at the specified time points, and yields were reported by ^{1}H-NMR versus the released p-methoxy benzoic acid in solution.

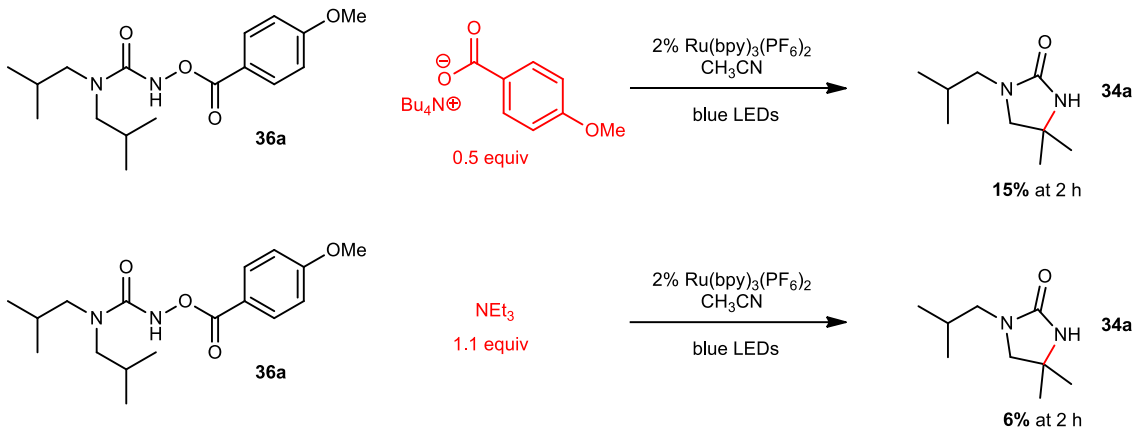


Figure 119 Preliminary difference product conversion using p-methoxy benzoate versus Et_3N.

To probe the potential of the benzoate playing an active role in the C–H amination, a soluble form of the benzoate was synthesized and added to the reaction without Et_3N (**Figure 119**). When comparing the relative conversion of starting material during the first two hours of each reaction (using LED strips), it was clear that the reaction with benzoate base reacted faster. However, repetition of this work is required to ascertain the significance of this finding, given the irreproducibility encountered above and challenges of performing kinetics on photochemical reactions in general. Importantly, carboxylates are regarded as the most exceptional H-bonding bases,[264] which should favorably shift the equilibrium of H-bonded complex by increasing *K* more drastically. This could have implications on increasing the rate of PCEnT or PCET reactions as discussed above.

4.21 $Ru(bpy)_3$ photodegradation and nitrenoid C–H amination

Oft ignored from the synthetic organic community, the precarious stability of the metal complexes typically used in photochemical reactions can lead to alternative mechanisms. It is well documented that Ru^{II}-complexes degrade upon visible light irradiation.[265–274] Indeed, this phenomenon has its applications in emerging therapeutics, and molecular diagnostics.[275] Sterically hindered Ru^{II}-polypyridyl complexes decompose quite rapidly upon photolysis to lose a single bidentate ligand and incorporate two molecules of solvent.[271] In contrast, uncongested complexes such as $Ru(bpy)_3^{2+}$ are generally quite stable. However, $Ru(bpy)_3^{2+}$ has long been known to undergo ligand loss under a variety of conditions,[276] and recent computational investigations have revealed likely excited states for such degradation under milder conditions.[277] In line with this data, ^{1}H-NMR studies in CD_3CN on a 600 MHz instrument clearly demonstrated that the solvated complex [*e.g.* $Ru(bpy)_2(CD_3CN)_2$] was formed to some extent (~10%) even prior to irradiation. Notably, the formation of this complex was only observed by ^{1}H-NMR when Et_3N was also present in the solution, the hydroxamate precursor was not necessary for the formation of $Ru(bpy)_2(CD_3CN)_2$. A substantial increase in photodegraded $Ru(bpy)_3^{2+}$ was not observed after the course of the reaction. Thus, this intriguing observation provides an alternative explanation for the requirement of Et_3N as a base for this transformation, if the formation of $Ru(bpy)_2(MeCN)_2$ was required for product formation through a metal nitrene (**Figure 120**). Considering recent work by Meggers,[278] which demonstrated the ability of chiral $Ru(L)_2(t\text{-}BuCN)_2$ complexes to interact with related cyclic hydroxylamine nitrene precursors and perform enantioselective C–H amination reactions, this potential pathway begs for further investigation. Synthesis and

evaluation of the catalytic efficacy of an authentic sample of $Ru(bpy)_2(MeCN)_2$ would quickly lend credibility or disprove this possible mechanism.

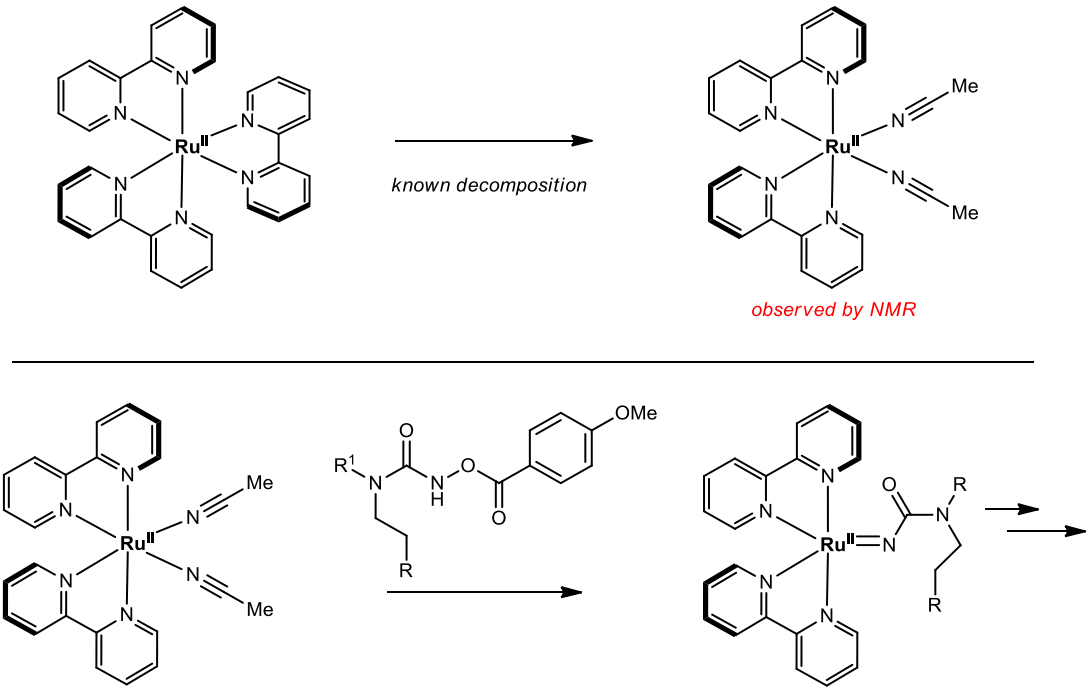


Figure 120 Known decomposition of ruthenium polypyridyl complexes and potential alternative nitrene pathway.

4.22 Preliminary photocatalytic lactam synthesis

With an unknown mechanism, reaction optimization / extension to new systems was challenging. However, working under the hypothesis that the single electron alpha elimination reaction was operating, we attempted to rationally optimize the synthesis of lactams using this method. We hypothesized that formation of lactams was complicated by the susceptibility of the amide starting materials toward premature SET reduction. Cyclic voltammetry experiments

and DFT calculations confirmed that amide substrates were more prone to reduction than the corresponding urea precursors (*e.g.* $E_{1/2}$ = −1.36 V versus Fc^+/Fc for amide **36h** versus −1.78 V versus Fc^+/Fc for urea **36a**). Therefore, it was hypothesized that the use of a different base could lead to improved reactivity. An ideal base would have a higher oxidation potential, and therefore not contribute to the formation of Ru^I, and be a better H-bonding acceptor to promote the hypothetical complexes presumed to be required for PCET or PCEnT mechanisms. Upon screening bases, phosphate bases emerged as ideal candidates. While phosphate bases have demonstrated remarkable ability to induce selective amide *N*-H activation in PCET photoredox reactions,[226,246,257,258,279–283] their use in PCEnT (or EnT) reactions was unknown. As desired, the phosphate base possesses an exceptionally high oxidation potential, which was ~1.0 V outside the range of $Ru(bpy)_3^{2+}$. Therefore, background reduction of the amide substrates by Ru^I, which forms in the presence of Et_3N, would be eliminated. This property is crucial, as it makes a SET reduction pathway via *N*-centered radicals even more unlikely.

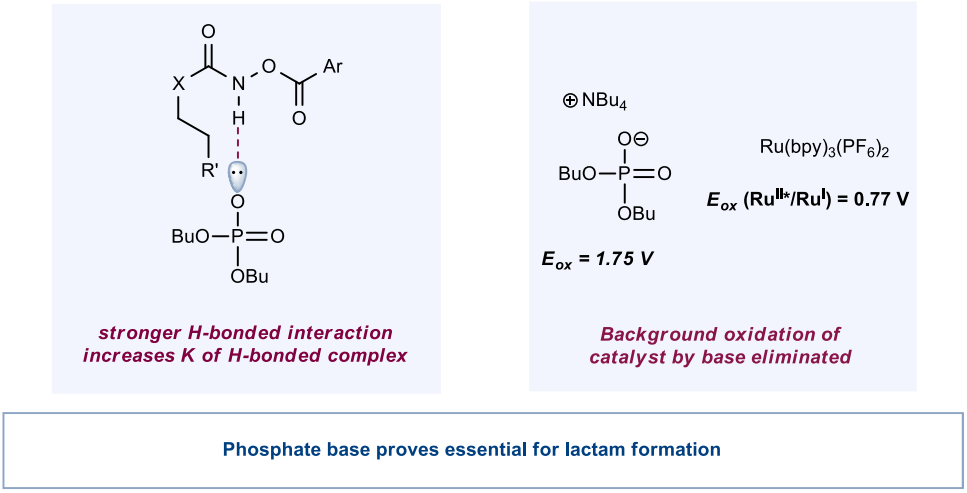
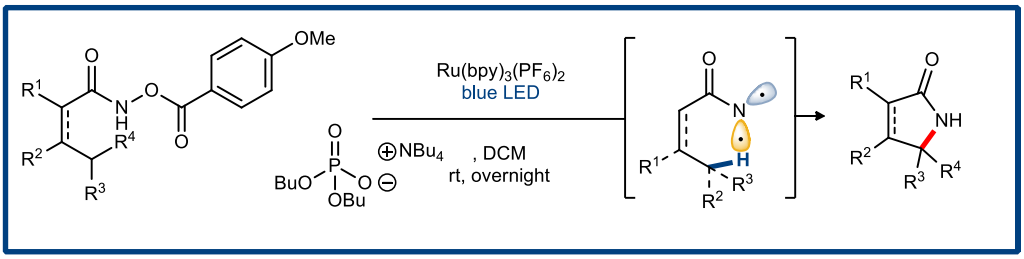
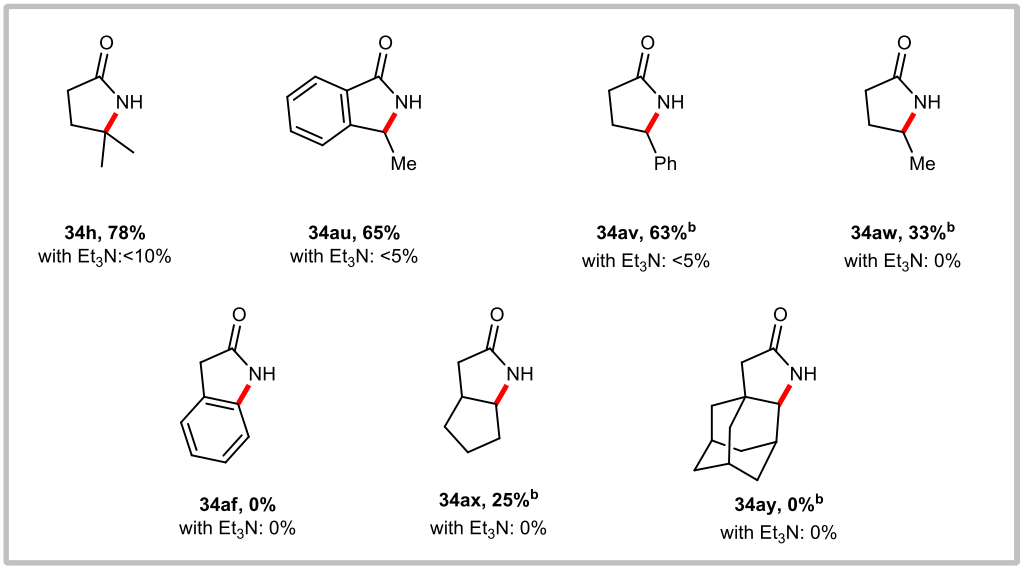


Figure 121 The benefits of phosphate base for lactam C–H amination.

Encouragingly, changing the base from Et_3N to phosphate resulted in significantly improved reactivity for a variety of lactam substrates. Unfortunately, the lactam substrate scope remained somewhat limited to activated C–H bonds compared to the success achieved with urea syntheses (**Table 34**-**Table 36**). However, it is notable that Chang's work was similarly limited to amination of activated C–H bonds (**Figure 90**).[203]

Table 40 Photocatalytic lactam synthesis via C-H amination.





4.23 Summary of the photocatalytic C-H amination

In summary, using a photoredox catalyst, a mild organic base and optimized hydroxamate substrates facilitated efficient amination of 3°, 2°, and aromatic C–H bonds forming a variety of nitrogen heterocycles. Present experimental data fits best with carbamoyl triplet nitrenes as reactive intermediates. The mechanism to form such a carbamoyl nitrene remains elusive, but strong foundational studies have eliminated some pathways and key experiments are currently narrowing in on the sequence.

4.24 Future work and project extensions of new photocatalytic system

Future efforts must be focused on elucidating the mechanism of this reaction. The potential for benzoate to play an active role in the transformation or invoking $Ru(bpy)_2(MeCN)_2$ as an active catalyst that could perform the C–H amination are attractive scenarios. This is especially true for the latter example, which creates the potential for the development of an enantioselective reaction. Not only could this greatly improve the synthetic applicability of the transformation but would provide the first example of enantioselective imidazolone synthesis via C–H amination. The following experiments should prove useful in determining the mechanism: 1) Stern-Volmer quenching studies in the presence of base (Et_3N, benzoate, or phosphate) / without base; 2) Cyclic-Voltammetry studies in the presence of base / without base; 3) LFP and TA-spectroscopy of the hydroxamate versus carbamoyl azide precursors to establish a common reactive intermediate; 4) Full reaction coordinate computational data for potential PCET or PCEnT pathways; and 5) EPR of the presumably stable *N*-centered radical (**Figure 114**, **III**)), which could be generated from the N-chloro species.

While the exact mechanism could not be ascertained, the method was extended to intramolecular reactions of sulfonamide precursors. An excellent yield was obtained in the initial biased substrate (**Figure 122**). This first suggested that the reaction could be general across a range of nitrene precursors. Unfortunately, this reaction quickly demonstrated substrate scope limitations. Reaction optimization, screening and mechanistic investigation of this transformation was undertaken by Jasper Quartus and will be reported in his MSc thesis.

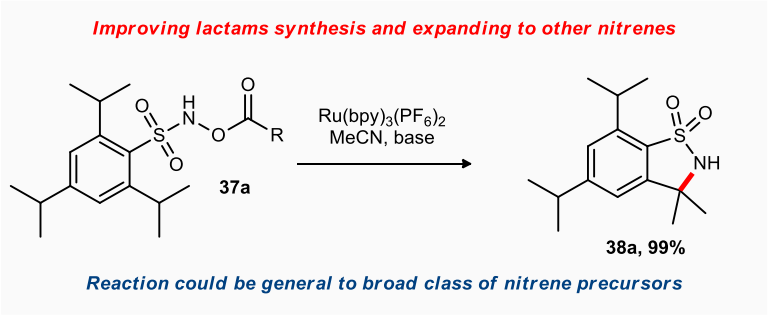


Figure 122 Preliminary reaction using sulfonamide nitrene precursors

The final attempted extension of the reactivity was intermolecular reactions. A variety of new precursors were screened, with the hope of developing a precursor that would release a stable, but reactive enough nitrene to undergo intermolecular reactions Unfortunately, despite much effort, attempts to achieve intermolecular C–H amination were unsuccessful for both C(sp^2)-H and C(sp^3)-H systems. Although C–H amination reactions failed, the intermolecular aziridination reaction exhibited some initial success (**Figure 123**).

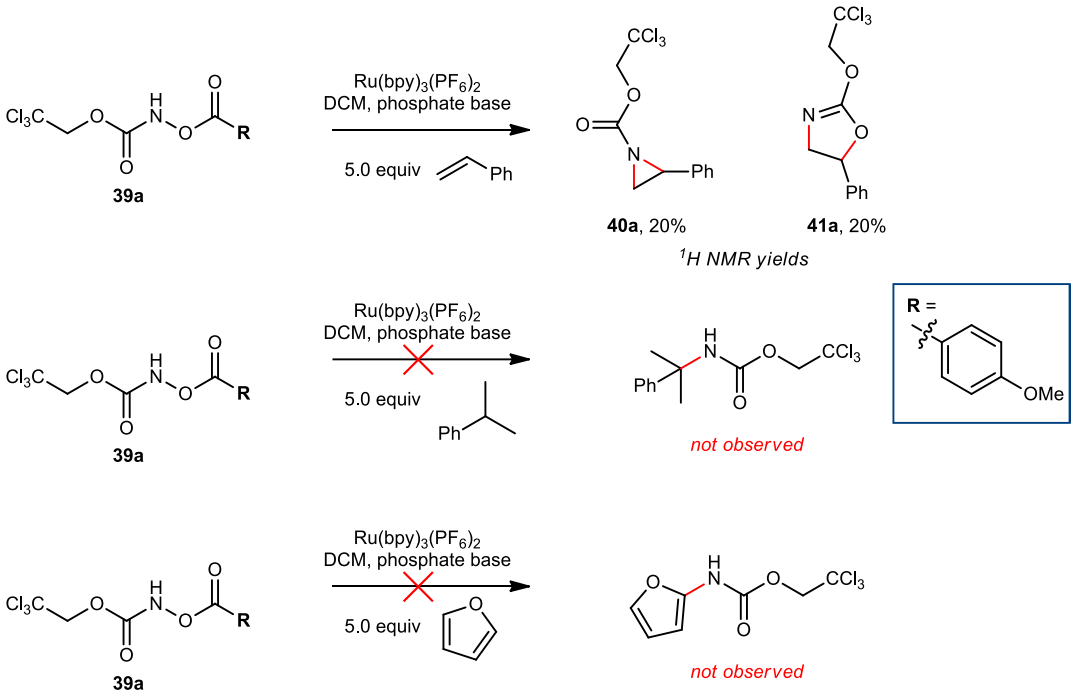


Figure 123 Summary of initial intermolecular investigations using Troc-protected precursors.

Building off seminal work by Lwowski[236,237,251] and the following single photocatalytic variant developed by Yoon,[209] Troc-protected hydroxamate derivatives were selected as precursors to triplet nitrenes. However, using our hydroxamate derivatives only styrene derivatives showed promising reactivity. Moreover, the aziridine products tended to undergo an *N*-acylaziridine to oxazoline rearrangement under the reaction conditions.[284–286] At the present time it is impossible to discount the prospect of an alternative pathway involving *N*-centered radical addition, followed by C=O addition to the carbocation for the formation of such oxazolines.

Chapter 5:

Conclusions and future work

Overall, the work in this thesis clearly demonstrates the synthetic utility of reactive intermediates such as *N*-isocyanates, *O*-isocyanates and nitrenes. In Chapter 2, synthetic applications of *N*-isocyanates were extended to room temperature cascacade reactions forming rare and challenging to access bioactive molecules. Significant insight was gained regarding the nature of the *N*-isocyanatye cycloaddition reactions, which led to improvements in reactivity and milder conditions. However, important challenges still remain, such as the lengthy / arduous synthesis of starting materials required for improved reactivity. In the future, intermolecular reactions using novel methods developed to synthesize β-*N*,*N*-dialkyl *N*-isocyanate precursors should streamline further improvments and applications.

In Chapter 3, *O*-isocyanates were investigated as new synthetic intermediates for cascade reactions and cycloadditions. These foundational studies cemented the use of *O*-isocyanates as viable intermediates to access bioactive O-N-C=O containing heterocycles. More importantly, new reactivity was discovered including metal free Cope-type hydroamination and [3+2] cycloaddition / nitrene C-H amination methodologies. Foundational studies on the novel cycloadditions of *O*-isocyanates led to their use as new uncharged 1,3-dipoles. Future work in this area must overcome the equilibrium challenges associated with the uncharged cycloaddition, which forms several high energy charged intermediates (*e.g. O*-isocyanate, aza-oxonium ylides, nitrenes). Base catalysis of the cycloaddition with enol ethers has enabled the synthesis of β-lactams under mild conditions, clearly demonstrating that the highly reactive aza-oxonium ylides can be harnessed to productive pathways. Continued study of these ylides with new catalysts, with a particular focus on the C–H amination steps should prove fruitful. Important kinetic studies are still required to ensure that DFT computational results reflect

reality. Simple experiments, such as mono-deuteration of the benzylic substrate and analysis of the ratio of C-H : C-D in the product could be informative.

In Chapter 4, photocatalysis was used to develop a novel intramolecular C-H amination reaction using hydroxylamine precursors. From a synthetic perspective, the reaction allowed simple access to imidazolidinones and related heterocycles. Questions remain regarding the mechanism of the transformation. Future work must prioritize mechanistic investigations on the photochemical kinetics of the transformation, which should provide meaningful insight to the mechanism. It is hoped that these crucial mechanistic insights would allow substrate scope expansion, such as better reactivity with lactam and carbamate derivatives. However, given recent publications in this area, the competitiveness / actionalable outcomes from subsequent investigations in this area are important factors for consideration.

Claims to original research and publications from this work

Claims to original research

1. Development of room temperature *N*-isocyanate reactivity (substitutions, cascade reactions, cycloadditions).
2. Mechanistic studies on *N*-isocyanate cycloadditions (isolation of aminimides), 2D NMR confirmation of structure.
3. Discovery of novel masked *O*-isocyanate precursors.
4. Development of conditions for hydroxy, alkoxy, and acyloxy *O*-isocyanate reactivity.
5. Development of the first cascasde reactions of *O*-isocyanates..
6. Discovery of novel Cope-type hydroamination using hydroxyureas.
7. Disovery and development of first *O*-isocyanate cycloaddition reactions.
8. Discovery, development and optimization of β-lactam synthesis from *O*-isocyanate cycloadditions.
9. Discovery of aza-oxonium ylides and their nitrene reactivity.
10. Discovery and development of thermal, metal catalyzed and photocatalytic C-H aminations from hydroxylamine derivatives.
11. Density functional theory calculations on *O*-isocyanate cycloadditions and photocatalytic C-H amination.

Articles from work in this thesis ([†]Authors contributed equally)

[1] **Ivanovich, R. A.**,[†] Vincent-Rocan, J.-F.,[†] Elkaeed, E. B., Beauchemin A. M. One-Pot Synthesis of Aza-Diketopiperazines Enabled by Controlled Reactivity of *N*-Isocyanate Precursors. *Organic Letters,* **2015,** *17*, 4898-4901.

[2] Vincent-Rocan, J.-F., **Ivanovich, R. A.**, Clavette, C., Leckett, K., Bejjiani, J., Beauchemin, A. M. Cascade Reactions of Nitrogen-Substituted Isocyanates: A New Tool in Heterocyclic Chemistry. *Chemical Science,* **2016**, *7*, 315-328. [**Highlighted: OPRD**]

[3] **Ivanovich, R. A.**, Clavette, C., Vincent-Rocan, J.-F., Roveda, J.-G., Gorelsky, S. I., Beauchemin, A. M. Intramolecular Alkene Aminocarbonylation Using Concerted Cycloadditions of Amino-Isocyanates. *Chemistry: A European Journal*, **2016**, *22*, 7906-7916. [**Selected as Hot Paper**]

[4] **Ivanovich, R. A.**, Polat E. D., Beauchemin, A. M. Oxygen-Substituted Isocyanates: Blocked (Masked) Isocyanates Enable Controlled Reactivity. *Advanced Synthesis and Catalysis*, **2017**, *359*, 4289-4293. [**Selected as VIP Paper**]

[5] Allen, M. A.,[†] **Ivanovich, R. A.**,[†] Polat, D. E., Beauchemin, A. M. Synthesis of *N*-Oxyureas by Substitution and Cope-Type Hydroamination Reactions Using *O*-Isocyanate Precursors. *Organic Letters*, **2017**, *19*, 6574-6577.

[6] **Ivanovich, R. A.,**[†] Quartus, J. A. M.,[†] Das Neves, N.; Loiseau, F.; Raymond, M.; Beauchemin, A. M. Aminimide Synthesis Using Concerted Amination Reactions of Alkenes: Scope and Mechanistic Information. *Journal of Organic Chemistry* **2019**, *84*, 9792-9800**.**

[7] **Ivanovich, R. A.,** Polat, D. E., Beauchemin, A. M. Photocatalytic Intramolecular C–H Amination Using *N*-Oxyureas as Nitrene Precursors. *Organic Letters*, **2020**, *22,* 6360–6364.

[8] Allen, M. A.,[†] **Ivanovich, R. A.,**[†] Beauchemin, A. M. *O*-Isocyanates Acting as Uncharged 1,3-Dipole Equivalents in [3+2] Cycloadditions*, Angewandte Chemie International. Edition.* https://doi.org/10.1002/anie.202007942.

[9] Daneshmand, P., Rosca, S., Dalhoff, R., Yin, K., DiPucchio, R., **Ivanovich, R. A.,** Polat, D., Beauchemin, A. M., Schafer, L. A Cyclic Ureate Tantalum Catalyst for Preferential Hydroaminoalkylation with Alkyl Amines. Mechanistic Insights into Substrate Controlled Reactivity. *Journal of the American Chemical Society* https://doi.org/10.1021/jacs.0c04579.

Presentations of work in this thesis

Selected non-peer-reviewed contributions (Asterisks denote presenting author)

[1] **Ivanovich**, **R. A.,*** Vincent-Rocan, J.-F., Beauchemin, A. M. (2014) Cascade Reactions of Nitrogen-Substituted Isocyanates: Synthesis of Acyl-Pyrazoles and Pthalazinones. *25th QOMSBOC.* (Provincial/ Poster)

[2] Vincent-Rocan, J.-F.,* **Ivanovich, R. A.,** Beauchemin, A. M. (2015) Cascade Reactions of Nitrogen-Substituted Isocyanates: A New Tool in Heterocyclic Chemistry. *97th CSC Vancouver.* (International/Oral)

[3] **Ivanovich R. A.,*** Vincent-Rocan, J.-F., Elkaeed, E. B., Beauchemin, A. M. (2015) One-Pot Synthesis of Aza-Diketopiperazines Enabled by Controlled Reactivity of *N*-Isocyanate Precursors. *26th QOMSBOC.* (Provincial/Oral)

[4] **Ivanovich, R. A.,*** Vincent-Rocan, J.-F., Beauchemin, A. M. (2015) Nitrogen-Substituted Isocyanates: A New Tool in Heterocyclic Chemistry. *University of Ottawa Honours Poster Day.* (Institutional/Poster)

[5] **Ivanovich, R. A.,*** Vincent-Rocan, J.-F., Beauchemin, A. M. (2016) Cascade Reactions of Nitrogen-Substituted Isocyanates: A New Tool in Heterocyclic Chemistry. *42nd Spring Symposium in Organic Synthesis: Synthesis Day.* (Institutional/Poster)

[6] Vincent-Rocan, J.-F.,* **Ivanovich, R. A.,** Derasp, J. S., Beauchemin, A. M. (2016) Cascade Reactions of Nitrogen-Substituted Isocyanates: A New Tool in Heterocyclic Chemistry. *ACS San Diego.* (International/Oral)

[7] Polat, D. E.,* **Ivanovich R. A.,** Beauchemin, A. M. (2016) Oxygen-Substituted Isocyanates: New Reagents in Organic Synthesis. *27th QOMSBOC.* (Provincial/Poster)

[8] **Ivanovich, R. A.,**† Polat, D. E.,†* Beauchemin, A. M. (2017) Oxygen-Substituted Isocyanates: New Reagents in Organic Synthesis. *100th CSC Toronto.* (International/Oral)

[9] Allen, M. A.,†* **Ivanovich, R. A.,** † Beauchemin A. M. (2019) Cycloadditions of *O*-Isocyanates: Aza-oxonium ylides as novel nitrene precursors. *102nd CSC Quebec City* (International/Oral)

[10] **Ivanovich, R. A.,*** Polat, D. E., Beauchemin, A. M. (2019) Photoredox Illuminates a Radical Approach to Triplet Nitrenes. *30th QOMSBOC* (Provincial/Oral)

Chapter 6:

Supporting information

General Information

Purification of reaction products was carried out by flash column chromatography using Silicycle silica gel (40-63 µm), unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on aluminum, cut to size. Visualization was accomplished with UV light followed by staining with a potassium permanganate solution and heating.

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 300 MHz and 400 MHz spectrometers at ambient temperature, unless otherwise indicated. Spectral data was reported in ppm using solvent as the reference (CDCl3 at 7.26 ppm, C6D6 at 7.15 ppm or DMSO-*d*6 at 2.50 ppm for ^{1}H NMR and CDCl3 at 77.0 ppm or DMSO-*d*6 at 39.43 for ^{13}C NMR). ^{1}H NMR data was reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, sext. = sextuplet, sept = septuplet, m = multiplet), integration and coupling constant(s) in Hz. Infrared (IR) spectra were obtained with neat thin films on a sodium chloride disk and were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). High-resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70ev at the Ottawa-Carleton Mass Spectrometry Centre.

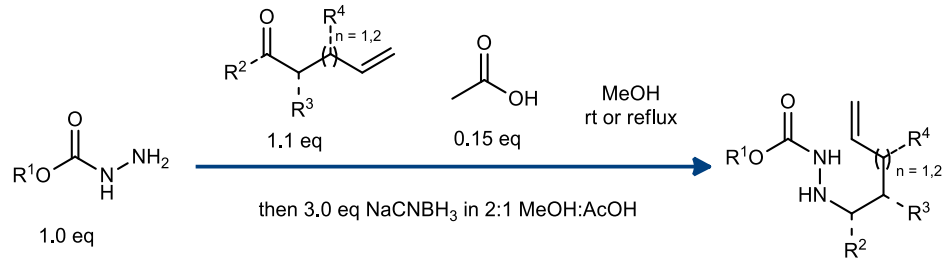
Materials

Unless otherwise noted, all commercially available materials were purchased from commercial sources and used without further purification.

Supporting information for Chapter 2

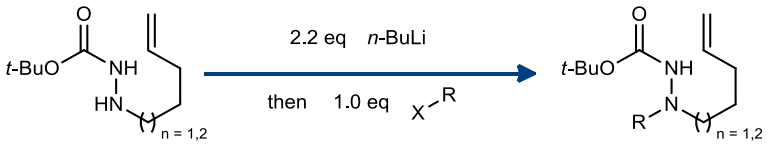
Synthesis of carbazate *N*-isocyanate precursors for intramolecular aminocarbonylation

General Procedure A: (Synthesis of Mono-Alkenyl Hydrazides)



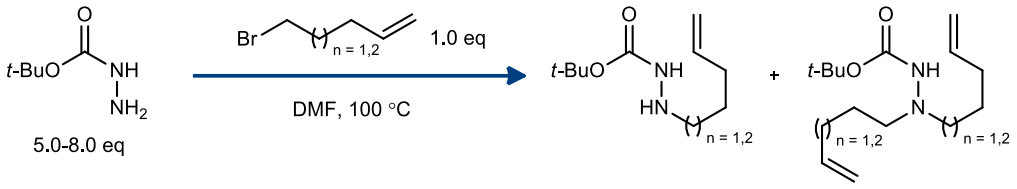
To a flame-dried round bottom flask, the corresponding aldehyde was dissolved in dry methanol (0.3 M) to which the carbazate or semicarbazide (1.00 equiv.) was added. The reaction was stirred under argon until consumption of the aldehyde or ketone was judged to be complete by TLC (30% EtOAc/hexanes). Acetic acid was added to the crude hydrazone reaction solution such that a 2:1 methanol:acetic acid (0.2 M) solution was formed. To this solution was added $NaCNBH_3$ (3.00 equiv) and then allowed to stir at room temperature overnight. Volatiles were then evaporated under reduced pressure and the remaining solution was quenched with a saturated solution of sodium bicarbonate and then gradually basified with 25% NaOH to a pH of 8. The solution was extracted three times with EtOAc, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by silica gel chromatography to give the corresponding pure mono-alkenyl carbazates.

General Procedure B: (Alkylation of Alkenyl Carbazates)

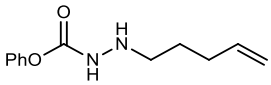


To a flame-dried round bottom flask, the corresponding hydrazide was dissolved in tetrahydrofuran (0.2 M) and cooled to −78 °C under argon. After stirring for 0.25 h, a solution of *n*-butyl lithium in hexanes (2.5 M in hexanes) (2.20 equiv) was added drop-wise and stirred under argon for 0.5 h. Alkyl halide was then added drop-wise (1.00 equiv). The reaction was then allowed to warm up to room temperature and was quenched with MeOH and water. The reaction was concentrated under reduced pressure and the resultant solution was extracted three times with CH_2Cl_2, dried with Na_2SO_4 and filtered. The crude product was concentrated under reduced pressure and then purified by silica gel chromatography with 10% EtOAc/hexanes to give the corresponding pure β*N*-alkylated carbazates.

General Procedure C: (Alkylation / dialkylation of *tert*-Butyl Carbazates)



An alkenyl halide (1.0 equiv) was added to a screw cap pressure vessel with a magnetic stir bar and diluted to 0.3 M using DMF. Following this, the carbazate / hydrazide (5.0-8.0 equiv) was added. The vial was sealed with a screw cap and the mixture was heated at 100 °C in an oil bath for 5 h. The reaction solution was cooled to ambient temperature, and the DMF was removed from the mixture by the addition of ethyl acetate and seven organic phase washes with a 50% brine/H_2O solution. The resulting organic phase was washed with *aq.* saturated NaCl solution, dried with Na_2SO_4, and concentrated under reduced pressure. The mixture was analyzed by ^1H NMR and the product was isolated using silica gel column chromatography. The reaction was found to give the intended monoalkylated carbazate derivatives (at the β-nitrogen), but also low yields of symmetrically dialkenylated carbazates (at the β-nitrogen). Both derivatives were applied in further synthesis.



Phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate (1a): Synthesized according to general procedure **A** using 4-pentenol (1.31 g, 15.2 mmol), and phenylcarbazate (2.10 g, 13.8 mmol) in MeOH (0.3 M)). After condensation was judged to be complete, $NaCNBH_3$ (2.60 g, 41.4 mmol) was added and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% EtOAc/CH_2Cl_2). The title compound was obtained as a white solid (0.712 g, 3.23 mmol, 23% isolated yield).

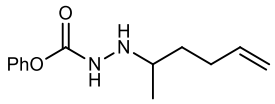
TLC R_f: 0.24 in 5% EtOAc/CH_2Cl_2.

^1H NMR (300 MHz, CDCl3) δ 7.37-7.10 (m, 5H), 6.60 (s, 1H), 5.83 (d, *J* = 10.2 Hz, 1H), 5.06-4.99 (m, 2H), 3.82 (s, 1H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.16-2.09 (m, 2H), 1.61 (q, *J* = 7.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.8 (C), 138.2 (CH), 129.5 (CH), 125.7 (CH), 121.5 (CH), 115.1 (CH_2), 51.4 (CH_2), 31.3 (CH_2), 27.1 (CH_2).

IR (film): 3276, 3081, 2926, 2850, 1900, 1715, 1476, 1266, 1214, 907 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{16}N_2O_2$ $[M]^+$: 220.1212. Found: 220.1219.



Phenyl 2-(hex-5-en-2-yl)hydrazinecarboxylate (1b): Synthesized according to general procedure **A** using hex-5-en-2-one (2.65 g, 27.0 mmol) and phenylcarbazate (3.74 g, 24.6 mmol) in MeOH (0.3 M). After condensation was judged to be complete, $NaCNBH_3$ (4.64 g, 73.8 mmol) was added and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% EtOAc/CH_2Cl_2). The title compound was obtained as a white solid (4.76 g, 83%).

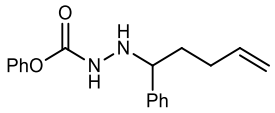
TLC R_f: 0.19 in 2% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.32 (m, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.13-7.10 (m, 2H), 5.85-5.74 (m, 1H), 5.06-4.93 (m, 2H), 3.16-3.05 (m, 1H), 2.22-1.98 (m, 2H), 1.64-1.38 (m, 2H), 1.07 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7 (C), 150.8 (C), 138.3 (CH), 129.4 (CH), 125.5 (CH), 121.4 (CH), 114.8 (CH_2), 54.9 (CH), 33.9 (CH_2), 30.0 (CH_2), 18.4 (CH_3).

IR (film): 2954, 2437, 1733, 1718, 1699, 1662, 1558, 1517, 1338, 1263, 1203, 1164, 995 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O_2$ $[M + H]^+$: 235.1447. Found: 235.1435.



Phenyl 2-(1-phenylpent-4-en-1-yl)hydrazinecarboxylate (1c): Synthesized according to general procedure **A** using 1-phenylpent-4-en-1-one (1.00 g, 6.24 mmol) and phenylcarbazate (0.950 g, 6.24 mmol). After condensation was judged to be complete, $NaCNBH_3$ (1.18 g, 18.7 mmol) was added and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (30% EtOAc/hexanes). The title compound was obtained as a white solid (0.550 g, 30%).

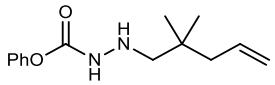
TLC R_f: 0.15 in 30% EtOAc/hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.30 (m, 7H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.10-7.08 (m, 2H), 6.45 (s, 1H), 5.79 (ddt, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.03-4.95 (m, 2H), 4.18-4.14 (m, 1H), 3.93 (s, 1H), 2.04-1.98 (m, 2H), 1.92-1.73 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C), 150.7 (C), 141.3 (C), 137.9 (CH), 129.3 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 125.6 (CH), 121.4 (CH), 115.1 (CH_2), 64.2 (CH), 34.2 (CH_2), 30.1 (CH_2).

IR (film): 3060, 2322, 1718, 1683, 1652, 1558, 1488, 1452, 1263, 1205, 1163, 1026 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{18}H_{20}N_2O_2$ $[M]^+$: 296.1525. Found: 296.1491.



Phenyl 2-(2,2-dimethylpent-4-en-1-yl)hydrazinecarboxylate (1d). Synthesized according to general procedure **A** using 2,2-dimethyl-4-pentenal (0.450 g, 4.00 mmol) and phenylcarbazate (0.552 g, 3.63 mmol). After condensation was judged to be complete, $NaCNBH_3$ (0.684 g, 10.9 mmol) was added and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (4% EtOAc/CH_2Cl_2). The title compound was obtained as a colorless oil (0.800 g, 81%).

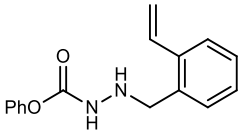
TLC R_f: 0.23 in 4% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.35 (m, 2H), 7.24-7.20 (m, 1H), 7.17-7.14 (m, 2H), 5.94-5-79 (m, 1H), 5.09 (s, 1H), 5.06-5.03 (m, 1H), 2.79 (s, 2H) 2.06 (d, *J* = 7.4 Hz, 2H) 0.96 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7(C), 150.7(C) , 135.0 (CH), 129.3 (CH), 125.5 (CH), 121.4 (CH), 117.4 (CH_2), 61.9 (CH_2), 44.7 (CH_2), 33.9(C), 25.4(CH_3).

IR (film): 3079, 3044, 2492, 2315, 1925, 1706, 1606, 1594, 1367 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{20}N_2O_2$ $[M]^+$: 248.1525. Found: 248.1527.



Phenyl 2-(2-vinylbenzyl)hydrazinecarboxylate (1e): Synthesized according to general procedure **A** by stirring *O*-phenyl carbazate (1.33 g, 8.80 mmol) and 2-vinylbenzaldehyde[4] (1.22 g, 9.23 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (1.66 g, 26.4 mmol) was added and allowed to stir for 16 h. The title compound was purified by column chromatography (2.5% EtOAc/CH_2Cl_2) to yield an amorphous white solid (1.64 g, 70%).

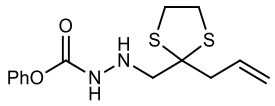
TLC R_f : 0.41 in 2.5% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.62 (m, 1H), 7.13-7.45 (m, 10H), 5.74 (dd, *J* = 17.5, 1.2 Hz, 1H), 5.39 (dd, *J* = 10.9, 1.2 Hz, 1H), 4.20 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5 (C), 150.6 (C), 137.6 (C), 133.9 (CH), 130.6 (CH), 129.4 (CH), 128.2 (CH), 127.8 (CH), 125.8 (CH), 125.6 (CH), 121.4 (CH), 116.4 (CH_2), 83.8 (C), 53.0 (CH_2).

IR (film): 3188, 1683, 1662, 1555, 1266 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{16}H_{16}N_2O_2$ $[M]^+$: 268.1212. Found: 268.1257.



Phenyl 2-((2-allyl-1,3-dithiolan-2-yl)methyl)hydrazinecarboxylate (1f): Synthesized according to general procedure **A** using 2-allyl-1,3-dithiolane-2-carbaldehyde (0.382 g, 2.19 mmol) and phenylcarbazate (0.303 g, 1.99 mmol). After condensation was judged to be complete, $NaCNBH_3$ (0.375 g, 5.97 mmol) was added and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2.5% EtOAc/CH_2Cl_2). The title compound was obtained as a yellow oil (0.500 g, 81%).

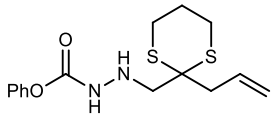
TLC R_f: 0.60 in 2.5% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (t, *J* = 7.8 Hz, 2H), 7.23-7.12 (m, 3H), 5.92 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.23-5.15 (m, 2H), 3.35-3.29 (m, 6H), 2.79 (d, *J* = 7.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5 (C), 150.7 (C), 134.2 (CH), 129.5 (CH), 125.8 (CH), 121.5 (CH), 119.3 (CH_2), 60.7 (CH_2), 45.8 (CH_2), 39.6 (CH_2).

IR (film): 3336, 3217, 1731, 1670, 1652, 1521, 1488, 1473, 1375, 1336, 1263, 1238, 1199 1026 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{18}N_2O_2S_2$ $[M]^+$: 310.0810. Found: 310.0793.



Phenyl 2-((2-allyl-1,3-dithian-2-yl)methyl)hydrazinecarboxylate (1g): Synthesized according to general procedure **A** using 2-allyl-1,3-dithiane-2-carbaldehyde (0.300 g, 1.59 mmol) and phenylcarbazate (0.220 g, 1.45 mmol). After condensation was judged to be complete, $NaCNBH_3$ (0.273 g, 4.35 mmol) was added and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2.5% EtOAc/CH_2Cl_2). The title compound was obtained as an amorphous solid (0.330 g, 70%).

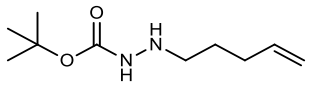
TLC R_f: 0.62 in 2.5% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (t, *J* = 7.9 Hz, 2H), 7.21-7.11 (m, 3H), 6.87 (s, 1H), 5.91 (ddt, *J* = 17.0, 10.0, 7.1 Hz, 1H), 5.19-5.14 (m, 2H), 3.95 (s, 1H), 3.39 (s, 2H), 3.08 (t, *J* = 12.3 Hz, 2H), 2.61 (d, *J* = 7.2 Hz, 4H), 2.01 (dtt, *J* = 13.7, 5.2, 2.7 Hz, 1H), 1.84-1.74 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8 (C), 150.7 (C), 132.0 (CH), 129.5 (CH), 125.8 (CH), 121.5 (CH), 119.2 (CH_2), 54.2 (CH_2), 50.9 (CH_2), 42.8 (CH_2), 26.0 (CH_2), 24.8 (CH_2).

IR (film): 3346, 3045, 2925, 2376, 2227, 1735, 1720, 1662, 1558, 1490, 1444, 1419, 1265, 1225, 1164, 987 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{20}N_2O_2S_2$ $[M]^+$: 324.0966. Found: 324.0914.



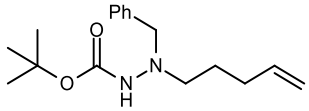
***tert*-Butyl 2-(pent-4-en-1-yl)hydrazinecarboxylate (1h)**. The title compound was synthesized according to general procedure **C** using 5-iodopentene (1.70 g, 8.64 mmol) and *tert*-butyl carbazate (8.27 g, 62.6 mmol) in DMF (29.0 mL). The product was isolated by column chromatography (gradient column with 10% EtOAc/Hexanes to 20% EtOAc/Hexanes after elution of the dialkyl carbazate with R_f = 0.61 in 20% EtOAc/Hexanes, allowing elution of monoalkyl carbazate). The product was obtained as a clear oil (1.30 g, 75% yield).

TLC R_f: 0.28 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.22 (s, 1H), 5.79 (tdd, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (ddd, *J* = 17.1, 3.5, 1.6 Hz, 1H), 4.94 (tdd, *J* = 10.2, 2.1, 1.2 Hz, 1H), 3.93 (s, 1H), 2.83 (t, *J* = 7.2 Hz, 1H), 2.09 (q, *J* = 6.9 Hz, 1H), 1.55−1.52 (m, 1H), 1.44 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8 (C), 138.3 (CH), 114.8 (CH_2), 80.4 (C), 51.5 (CH_2), 31.2 (CH_2), 28.4 (CH_3), 27.0 (CH_2).

^{1}H and ^{13}C NMR are in accordance with those reported in the literature.[17]



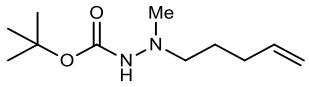
***tert*-Butyl 2-benzyl-2-(pent-4-en-1-yl)hydrazinecarboxylate (1i).** The title compound was synthesized according to general procedure **B** using *tert*-butyl 2-(pent-4-en-1-yl)hydrazinecarboxylate (1.50 g, 7.15 mmol), benyzl bromide (1.22 g, 7.15 mmol), and *n*-BuLi (17.2 mmol) in THF (35.0 mL) at −78 °C. The product was isolated by column chromatography (10% EtOAc/Hexanes). The product was obtained as a clear oil (1.27 g, 61%).

TLC R_f: 0.38 in 10% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.22 (m, 5H), 5.77 (d, *J* = 6.7 Hz, 1H), 5.52−5.34 (m, 1H), 5.02−4.88 (m, 2H), 3.94 (s, 2H), 2.74 (s, 2H), 2.11 (d, *J* = 7.0 Hz, 2H), 1.59 (t, *J* = 7.3 Hz, 2H), 1.37 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8 (C), 138.5 (CH), 137.0 (CH), 129.4 (CH), 128.2 (CH), 127.3 (CH), 114.6 (CH_2), 79.4 (C), 61.5 (CH_2), 55.6 (CH_2), 31.1 (CH_2), 28.3 (CH_3), 26.4 (CH_2).

^{1}H and ^{13}C NMR are in accordance with those reported in the literature.[167]



***tert*-Butyl 2-(pent-4-en-1-yl)-2-methylhydrazinecarboxylate (1j).** The title compound was synthesized following general procedure **B** using *tert*-butyl 2-(pent-4-en-1-yl)hydrazinecarboxylate (1.25 g, 6.25 mmol), methyl iodide (0.887 g, 6.25 mmol), and *n*-BuLi (15.0 mmol) in THF (31.0 mL) at −78 °C. The product was isolated by column chromatography (gradient column with 10% EtOAc/Hexanes to elute spot with TLC R_f = 0.61 in 20% EtOAc/Hexanes, then 20% EtOAc/Hexanes). The product was obtained as a translucent yellow oil (0.209 g, 16%).

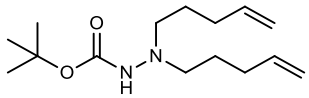
TLC R_f: 0.29 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.41 (s, 1H), 4.97−4.86 (m, 2H), 2.57 (t, *J* = 7.3 Hz, 2H), 2.51 (s, 3H), 2.07−2.02 (m, 2H), 1.52 (quint., *J* = 7.4 Hz, 2H), 1.39 (s, 11H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7 (C), 138.3 (CH), 114.6 (CH_2), 79.7 (C), 59.0 (CH_2), 46.3 (CH_3), 31.2 (CH_2), 28.3 (CH_3), 26.3 (CH_2).

IR (film): 3264, 2978, 1706, 1641, 1454, 1391, 1365, 1245, 1157 cm^{-1}.

HRMS (ESI): exact mass calcd for $C_{11}H_{22}N_2O_2Na^+$ [M + Na^+] 237.1579. Found: 237.1568.



***tert*-Butyl 2,2-di(pent-4-en-1-yl)hydrazinecarboxylate (1k).** The title compound was synthesized according to general procedure **C** using 5-iodopentene (1.70 g, 8.64 mmol) and *tert*-butyl carbazate (8.27 g, 62.6 mmol) in DMF (29.0 mL). The product was isolated by column chromatography (gradient column with 20% EtOAc/Hexanes to 30% EtOAc/Hexanes after elution of the dialkyl carbazate with R_f = 0.61 in 20% EtOAc/Hexanes, allowing elution of monoalkyl carbazate with R_f = 0.28 in 20% EtOAc/Hexanes). The product was obtained as a translucent

yellow oil (0.093 g, 4%). Note: this compound was obtained as a minor side product while forming the corresponding monoalkyl carbazate. Since this dialkyl carbazate was a suitable precursor for aminimide formation it was submitted to the reaction conditions.

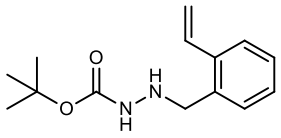
TLC R_f: 0.61 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (tdd, *J* = 6.6, 10.3, 17.0 Hz, 2H), 5.23−4.7 (br. s., 1H), 5.06−4.89 (m, 4H), 2.65 (br. s, 4H), 2.29−1.99 (m, 4H), 1.67−1.53 (m, 4H), 1.44 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C), 138.8 (CH), 114.9 (CH_2), 79.8 (C), 57.9 (CH_2), 31.5(CH_2), 28.7 (CH_3), 26.5 (CH_2).

IR (film): 3276, 3077, 2977, 2932, 2856, 1695, 1640, 1453, 1390, 1365, 1244, 1166 cm^{-1}.

HRMS (ESI): exact mass calcd for $C_{15}H_{28}N_2O_2Na^+$ [M + Na^+] 291.2048. Found: 291.2045.



***tert*-Butyl 2-(2-vinylbenzyl)hydrazinecarboxylate (1l):** Synthesized according to general procedure **A** using 2-vinylbenzaldehyde (0.790 g, 5.98 mmol) and *tert*-butylcarbazate (0.790 g, 5.98 mmol). After condensation was judged to be complete, $NaCNBH_3$ (1.13 g, 17.9 mmol) was added and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (100% CH_2Cl_2 to 2.5% EtOAc/CH_2Cl_2). The title compound was obtained as a white solid (1.43 g, 96%).

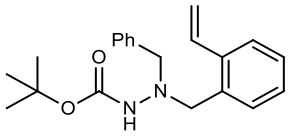
TLC R_f: 0.10 in 100% CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.51 (m, 1H), 7.30-7.21 (m, 3H), 7.14 (dd, *J* = 17.4, 10.9 Hz, 1H), 6.06 (s, 1H), 5.68 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.32 (dd, *J* = 11.0, 1.4 Hz, 1H), 4.11 (s, 1H), 4.05 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5 (C), 137.6 (C), 134.5 (C), 134.2 (CH), 130.6 (CH), 128.0 (CH), 127.8 (CH), 125.8 (CH), 116.1 (CH_2), 80.5 (C), 53.3 (CH_2), 28.4 (C).

IR (film): 3002, 2869, 2380, 2202, 1733, 1712, 1683, 1456, 1446, 1367, 1265, 1151, 1122, 1045, 1008 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{12}N_2O_2$ [M – C_4H_8]$^+$: 192.0893. Found: 192.0917.



***tert*-Butyl 2-benzyl-2-(2-vinylbenzyl)hydrazinecarboxylate (1m).** The title compound was synthesized following general procedure **B** using *tert*-butyl 2-(2-vinylbenzyl)hydrazinecarboxylate (0.689 g, 2.78 mmol), benzyl bromide (0.475 g, 2.78 mmol), and *n*-BuLi (6.66 mmol) in THF (14.0 mL) at −78 °C. The product was isolated by column chromatography (gradient column from 5% EtOAc/Hexanes to 30% EtOAc/Hexanes). The product was obtained as a white powder (0.409 g, 43%).

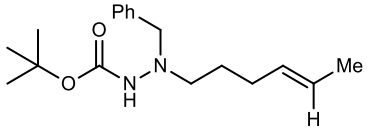
TLC R_f: 0.27 in 10% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.6 Hz, 1H), 7.35−7.19 (m, 9H), 5.65 (d, *J* = 17.3 Hz, 2H), 5.29−5.26 (m, 1H), 5.14 (d, *J* = 0.4 Hz, 1H), 4.15−4.12 (m, 2H), 3.87−3.84 (m, 2H), 1.34 (s, 9H), 1.34 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2 (C), 138.2 (C), 135.2 (CH), 131.2 (CH), 129.6 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 125.9 (CH), 115.6 (CH_2), 80.1 (C), 59.7 (CH_2), 57.4 (CH_2), 28.6 (CH_3) *two aromatic quaternary are overlapped.

IR (film): 3263, 2966, 2927, 2865, 1705, 1628, 1489, 1388, 1362, 1281, 1240, 1141 cm^{-1}.

HRMS (ESI): exact mass calcd for $C_{21}H_{26}N_2O_2Na^+$ [M + Na^+] 361.1892. Found: 361.1900.



(*E*)-*tert*-Butyl 2-benzyl-2-(hex-4-en-1-yl)hydrazinecarboxylate (1n): Synthesized according to general procedure **B** using (*E*)-*tert*-butyl 2-(hex-4-en-1-yl)hydrazinecarboxylate (0.193 g, 0.900 mmol), *n*-BuLi (0.792 mL, 1.98 mmol), and benzyl bromide (0.154 g, 0.900 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (15% EtOAc/hexanes). The title compound was obtained as a clear oil (0.160 g, 59%).

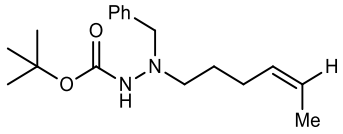
TLC R_f: 0.50 in 20 % EtOAc/hexanes.

^{1}H NMR at 80 °C (300 MHz, $CDCl_3$): δ 7.39-7.14 (m, 5H), 5.36 (s, 2H), 3.82 (s, 2H), 3.08 (s, 2H), 2.68-2.49 (m, 2H), 2.19-2.05 (m, 2H), 1.58-1.20 (s, 12H).

^{13}C NMR at 80 °C (75 MHz, DMSO-d_6): δ 154.6 (C), 138.0 (C), 130.0 (CH), 128.4 (CH), 127.3 (CH), 126.2 (CH), 123.1 (CH), 77.4 (C), 61.1 (CH_2), 55.6 (CH_2), 27.8 (CH_3), 26.4 (CH_2), 23.6 (CH_2), 12.0 (CH_3).

IR (film): 3629, 2960, 1730, 1695, 1683, 1662, 1558, 1458, 1367, 1263, 1172, 1163 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{18}H_{28}N_2O_2$ $[M]^+$: 304.2151. Found: 304.2125.



(*Z*)-*tert*-Butyl 2-benzyl-2-(hex-4-en-1-yl)hydrazinecarboxylate (1o): Synthesized according to general procedure **B** using (*Z*)-*tert*-butyl 2-(hex-4-en-1-yl)hydrazinecarboxylate (0.193 g, 0.900 mmol), *n*-BuLi (0.792 mL, 1.98 mmol), and benzyl bromide (0.154 g, 0.900 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (15% EtOAc/hexanes). The title compound was obtained as a clear oil (0.170 g, 62%).

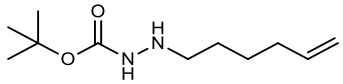
TLC R_f: 0.50 in 20 % EtOAc/hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.17 (m, 5H), 5.54-4.91 (m, 3H), 3.97 (s, 1H), 2.85-2.68 (m, 2H), 2.23-2.10 (m, 2H), 1.65-1.31 (s, 16 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5 (C), 130.3 (CH), 129.4 (CH), 128.2 (CH), 127.2 (CH), 124.1 (CH), 79.7 (C), 57.8 (CH_2), 56.3 (CH_2), 28.4 (CH_3), 27.1 (CH_2), 24.5 (CH_2), 12.6 (CH_3).

IR (film): 2975, 2136, 1828, 1733, 1699, 1662, 1558, 1521, 1475, 1456, 1392, 1367, 1263, 1147 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{18}H_{28}N_2O_2$ $[M]^+$: 304.2151. Found: 304.2151.



***tert*-Butyl 2-(hex-5-en-1-yl)hydrazinecarboxylate (1p):** Synthesized according to general procedure **A** using hex-5-enal (0.719 g, 6.22 mmol) and *tert*-butylcarbazate (0.818 g, 6.22 mmol). After condensation was judged to be complete, $NaCNBH_3$ (1.17 g, 18.7 mmol) was added and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (30% EtOAc/toluene). The title compound was obtained as a clear oil (0.493 g, 37%).

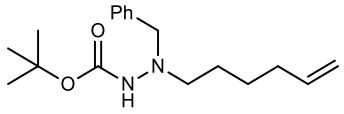
TLC R_f: 0.34 in 30% EtOAc/toluene.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.17 (s, 1H), 5.78 (tdd, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.96 (ddd, *J* = 13.7, 10.9, 1.2 Hz, 2H), 3.64 (s, 1H), 2.82 (t, *J* = 6.6 Hz, 2H), 2.05 (q, *J* = 6.9 Hz, 2H), 1.47-1.36 (m, 13H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7 (C), 138.6 (CH), 114.5 (CH_2), 80.4 (C), 51.9 (CH_2), 33.6 (CH_2), 28.3 (CH_3), 27.7 (CH_2), 26.3 (CH_2).

IR (film): 3321, 3070, 2978, 2930, 2861, 1716, 1641, 1457, 1392, 1368, 1284, 1254, 1155, 1047, 1015, 910 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{13}N_2O$ [M – C_4H_9O]$^+$: 141.1028. Found 141.1022.



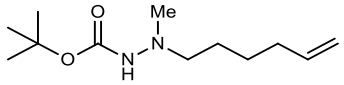
***tert*-Butyl 2-benzyl-2-(hex-5-en-1-yl)hydrazinecarboxylate (1q):** Synthesized according to general procedure **B** using *tert*-butyl 2-(hex-5-en-1-yl)hydrazinecarboxylate (0.493 g, 2.30 mmol), *n*-BuLi (2.02 mL, 5.06 mmol), and benyzl bromide (0.393 g, 2.30 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (13% EtOAc/ toluene). The title compound was obtained as a pale yellow oil (0.583 g, 83%).

TLC R_f: 0.35 in 13% EtOAc/toluene.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 5.79 (tdd, *J* = 17.0 Hz, 10.2 Hz, 6.7 Hz), 4.96 (ddd, *J* = 13.65, 10.92, 1.15 Hz, 2H), 3.97 (s, 2H), 2.76 (s, 2H), 2.03 (q, *J* = 6.9 Hz, 2H), 1.61-1.45 (m, 6H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9 (C), 138.8 (CH), 129.4 (CH), 128.2 (CH), 127.3 (CH), 114.4 (CH_2), 79.7 (C), 77.2 (CH), 61.4 (CH_2), 56.0 (CH_2), 33.6 (CH_2), 28.3 (CH_3), 26.6 (CH_2), 26.3 (CH_2).

IR (film): 3301, 3072, 2977, 2932, 2860, 1695, 1641, 1494, 1450, 1392, 1366, 1247, 1171, 993, 910, 736, 698 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{18}H_{28}N_2O_2$ [M]$^+$: 304.2151. Found: 304.2128.



***tert*-Butyl-2-(hex-5-en-1-yl)-2-methylhydrazinecarboxylate (1r):** The title compound was synthesized following general procedure **B** using *tert*-butyl 2-(hex-5-en-1-yl)hydrazinecarboxylate (1.82 g, 8.49 mmol), methyl iodide (1.20 g, 8.49 mmol), and *n*-BuLi (20.4 mmol) in THF (43.0 mL) at −78 °C. The product was isolated by column chromatography (gradient column with 10% EtOAc/Hexanes to elute spot with TLC R_f = 0.25 in 10% EtOAc/Hexanes, then 20% EtOAc/Hexanes). The product was obtained as a transparent yellow oil (0.433 g, 22%).

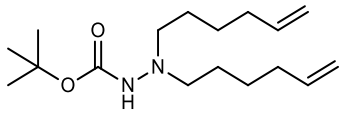
TLC R_f: 0.30 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.38 (s, 1H), 4.94−4.84 (m, 2H), 2.56 (t, *J* = 6.8 Hz, 2H), 2.50 (s, 3H), 2.01−1.95 (m, 2H), 1.43−1.38 (m, 16H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$, 90 °C): δ 154.3 (C), 138.2 (CH), 113.8 (CH_2), 77.4 (C), 57.5 (CH_2), 44.7 (CH_3), 32.4 (CH_2), 27.8 (CH_3), 25.9 (CH_2), 25.4 (CH_2).

IR (film): 3267, 2977, 2932, 2860, 1708, 1640, 1456, 1391, 1365, 1245, 1160 cm^{-1}.

HRMS (ESI): exact mass calcd for $C_{12}H_{24}N_2O_2Na^+$ [M + Na^+] 251.1735. Found: 251.1751.



***tert*-Butyl 2,2-di(hex-5-en-1-yl)hydrazinecarboxylate (1s):** The title compound was synthesized according to general procedure **C** using 6-iodohexene (2.10 g, 10.0 mmol) and *tert*-butyl carbazate (9.52 g, 72.0 mmol) in DMF (33 mL). The product was isolated by column chromatography (gradient column with 20% EtOAc/Hexanes to 30% EtOAc/Hexanes after elution of the dialkyl carbazate with R_f = 0.68 in 20% EtOAc/Hexanes, allowing elution of monoalkyl carbazate with R_f = 0.35 in 20% EtOAc/Hexanes). The product was obtained as a transparent yellow oil (0.116 g, 4%). Note: this compound was obtained as a minor side product while forming the corresponding monoalkyl carbazate. Since this dialkyl carbazate was a suitable precursor for aminimide formation it was submitted to the reaction conditions.

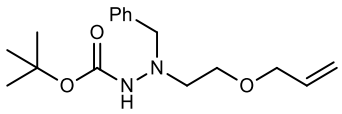
TLC R_f: 0.68 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (tdd, *J* = 6.7, 10.2, 17.0 Hz, 2H), 5.20 (br. s, 1H), 5.06−4.86 (m, 4H), 2.64 (br. s, 4H), 2.04 (q, *J* = 6.9 Hz, 4H), 1.55−1.34 (m, 17H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C), 139.2 (CH), 114.7 (CH_2), 79.8 (C), 58.4 (CH_2), 34.0 (CH_2), 30.0 (CH_2), 28.7 (CH_3), 26.8 (CH_2).

IR (film): 3236, 3076, 2977, 2928, 2856, 1696, 1640, 1456, 1390, 1365, 1245, 1167 cm^{-1}.

HRMS (ESI): exact mass calcd for $C_{17}H_{32}N_2O_2Na^+$ [M + Na^+] 319.2361. Found: 319.2343.



***tert*-Butyl 2-(2-(allyloxy)ethyl)-2-benzylhydrazinecarboxylate (1t):** Synthesized according to general procedure **B** using *tert*-butyl 2-(2-(allyloxy)ethyl)hydrazinecarboxylate (1.04 g, 4.81 mmol), *n*-BuLi (4.23 mL, 10.6 mmol) and benzyl bromide (0.856 g, 4.81 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (25% EtOAc/hexanes). The title compound was obtained as a white solid (0.900 g, 61%).

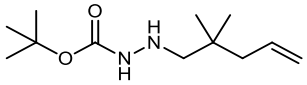
TLC R_f: 0.10 in 10% EtOAc/hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.23 (m, 5H), 5.98-5.84 (m, 2H), 5.31-5.16 (m, 2H), 4.09-3.98 (m, 4H), 3.64-3.60 (m, 2H), 3.06 (s, 2H), 1.41 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 134.7 (CH), 129.4 (CH), 128.2 (CH), 127.4 (CH), 117.0 (CH_2), 72.0 (CH_2), 67.8 (CH_2), 28.3 (CH_3).

IR (film): 3024, 2848, 2352, 1720, 1558, 1490, 1473, 1456, 1390, 1365, 1265, 1247, 1163, 1151, 1081 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{17}H_{26}N_2O_3$ $[M]^+$: 306.1943. Found: 306.1951.



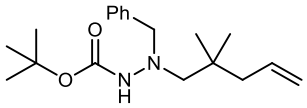
***tert*-Butyl 2-(2,2-dimethylpent-4-en-1-yl)hydrazinecarboxylate** (**1u**). The title compound was synthesized according to general procedure **A** using 2,2-dimethylpent-4-enal (1.19 g, 10.6 mmol) and *tert*-butylcarbazate (1.40 g, 10.6 mmol). After condensation was judged to be complete, $NaCNBH_3$ (1.99 g, 31.8 mmol) was added and allowed to stir overnight. The product was isolated by column chromatography (30% EtOAc/Hexanes). The product was obtained as a clear oil (2.22 g, 92%).

TLC R_f: 0.53 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90−5.76 (m, 1H), 5.06−4.99 (m, 2H), 2.67 (s, 2H), 2.02 (d, *J* = 7.4 Hz, 2H), 1.47 (s, 9H), 0.91 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.5 (C), 137.9 (C), 135.6 (CH), 129.5 (CH), 128.1 (CH), 127.3 (CH), 116.8 (CH_2), 79.6 (C), 66.9 (CH_2), 62.6 (CH_2), 44.7 (CH_2), 35.4 (C), 28.3 (CH_3), 25.6 (CH_3).

^{1}H and ^{13}C NMR are in accordance with those reported in the literature.[167]



***tert*-Butyl 2-benzyl-2-(2,2-dimethylpent-4-en-1-yl)hydrazine-carboxylate** (**1v**). Synthesized according to general procedure **B** using *tert*-butyl 2-(2,2-dimethylpent-4-en-1-yl)hydrazinecarboxylate (1.15 g, 5.00 mmol), benzyl bromide (0.855 g, 5.00 mmol), and *n*-BuLi (12.0 mmol) in THF (25.0 mL) at −78 ° C. Upon completion, the reaction waThe product was isolated by column chromatography (10% EtOAc/Hexanes). The product was obtained as a clear oil (0.573 g, 36%).

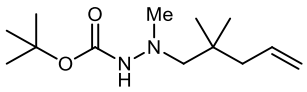
TLC R_f: 0.33 in 10% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.24 (m, 5H), 5.86−5.66 (m, 2H), 5.05−4.97 (m, 2H), 4.03 (s, 2H), 2.72 (s, 2H), 2.06 (d, *J* = 7.5 Hz, 2H), 1.37 (s, 9H), 0.90 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9 (C), 135.1 (CH), 117.1 (CH_2), 80.3 (C), 62.3 (CH_2), 44.7 (CH_2), 33.8 (C), 28.3 (CH_3), 25.3 (CH_3).

IR (film): 2979, 2958, 1718, 1697, 1471, 1456, 1392, 1367, 1247, 1176, 1149, 910, cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{19}H_{30}N_2O_2$ $[M]^+$: 318.2307. Found: 318.2296.



***tert*-Butyl 2-(2,2-dimethylpent-4-en-1-yl)-2-methylhydrazinecarboxylate** (**1w**). The title compound was synthesized following general procedure **B** using *tert*-butyl 2-(2,2-dimethylpent-4-en-1-yl)hydrazinecarboxylate (0.348 g, 1.53 mmol), methyl iodide (0.217 g, 1.53 mmol), and *n*-BuLi (3.82 mmol) in THF (7.6 mL) at −78 ° C. The product was isolated by column chromatography (20% EtOAc/Hexanes). The product was obtained as a transparent yellow oil (0.051 g, 14%).

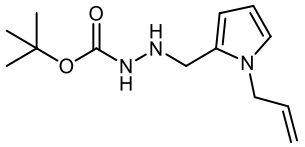
TLC R_f: 0.33 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80−5.70 (m, 1H), 5.63 (s, 1H), 4.98−4.93 (m, 2H), 2.58 (s, 3H), 2.44 (s, 2H), 1.99 (d, *J* = 7.5 Hz, 2H), 1.40 (s, 9H), 0.84 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5 (C), 135.6 (CH), 116.8 (CH_2), 79.7 (C), 69.7 (CH_2), 48.6 (CH_3), 44.7 (CH_2), 35.1 (C), 28.4 (CH_3), 25.6 (CH_3).

IR (film): 2920, 2851, 1733, 1601, 1456, 1376, 1262.

HRMS (ESI): exact mass calcd for $C_{13}H_{26}N_2O_2Na^+$ [M + Na^+] 265.1886. Found: 265.1892.



***tert*-Butyl 2-((1-allyl-1H-pyrrol-2-yl)methyl)hydrazinecarboxylate (1x):** Synthesized according to general procedure **A** using *N*-allyl-pyrrolecarbaldehyde (1.32 g, 9.79 mmol) and *tert*-butyl carbazate (1.45 g, 9.79 mmol). After condensation was judged to be complete, $NaCNBH_3$ (1.85 g, 29.3 mmol) was added and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (15% EtOAc/hexanes). The title compound was obtained as a dark red oil (0.787 g, 32%).

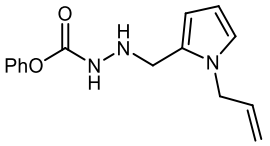
TLC R_f: 0.43 in 20% EtOAc/hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.61 (d, *J* = 2.0 Hz, 1H), 6.18-5.79 (m, 4H), 5.13 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.94 (dd, *J* = 17.0, 1.1 Hz, 1H), 4.58 (d, *J* = 5.0 Hz, 2H), 3.93 (br s, 3H), 1.45 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6 (C), 135.0 (CH), 127.9 (C), 122.0 (CH), 116.0 (CH_2), 110.0 (CH), 107.0 (CH_2), 80.4 (C), 49.1 (CH_2), 47.1 (CH_2), 28.3 (CH_3).

IR (film): 3199, 3033, 2216, 1708, 1599, 1465, 1435, 1388, 1325, 1309, 1288, 1248, 1160, 1144 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{21}N_3O_2$ [$M]^+$: 251.1634. Found: 251.1648.



Phenyl 2-((1-allyl-1*H*-pyrrol-2-yl)methyl)hydrazinecarboxylate (1y): Synthesized according to general procedure **A** by stirring *O*-phenyl carbazate (2.99 g, 19.6 mmol) and 1-allyl-1*H*-pyrrole-2-carbaldehyde (2.65 g, 19.6 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (3.70 g, 58.9 mmol) was added and allowed to stir for 16 h. The title compound was purified by column chromatography (100% CH_2Cl_2 then 5% EtOAc/CH_2Cl_2) to yield an amorphous white solid (3.75 g, 74%).

TLC R_f : 0.33 in 2.5% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.45 (m, 2H), 7.21-7.29 (m, 1H), 7.12-7.21 (m, 2H), 6.70 (dd, *J* = 2.8, 1.9 Hz, 1H), 6.17-6.22 (m, 1H), 6.12-6.17 (m, 1H), 6.02 (ddt, *J* = 17.1, 10.3, 5.2, Hz, 1H), 5.19 (dq, *J* = 10.3, 1.6 Hz, 1H), 4.98 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.64 (dt, *J* = 5.0, 1.7 Hz, 2H), 4.07 (s, 2H).

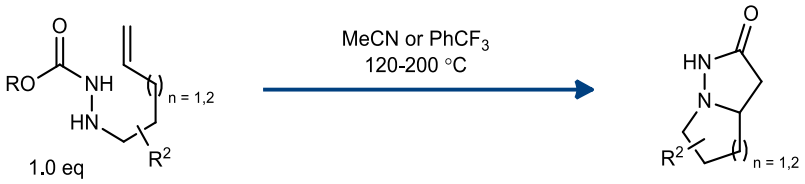
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C), 150.5 (C), 134.9 (CH), 129.3 (CH), 127.2 (C), 125.5 (CH), 122.2 (CH), 121.3 (CH), 116.3 (CH_2), 110.0 (CH), 107.1 (CH), 49.0 (CH_2), 46.7 (CH_2).

IR (film): 3729, 3654, 2981, 1731, 1699, 1539, 1515, 1490, 1460, 1444, 1265, 1203 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{17}N_3O_2$ $[M]^+$: 271.1321. Found: 271.1257.

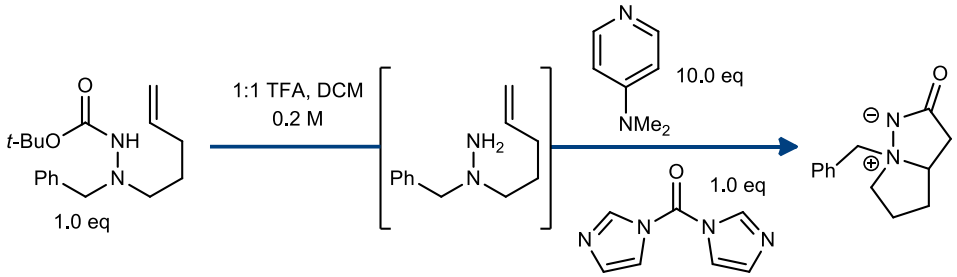
Synthesis of cyclic hydrazides via aminocarbonylation

General Procedure D: (Intramolecular Aminocarbonylation via Thermolysis)



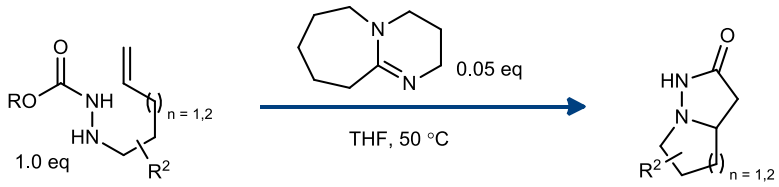
To an oven dried 5-20 mL μw tube, a stir bar was added and the vial was capped with a septum and purged with argon for 5 min. The carbazate (1.00 equiv) dissolved in solvent (acetonitrile or α,α,α-trifluorotoluene, 0.05 M) was added to the sealed tube. The tube was then sealed with a microwave cap and heated for the time specified at the temperature specified. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and then purified by silica gel chromatography to give the corresponding pure aminocarbonylation products.

General Procedure E: (Intramolecular Aminocarbonylation via Transacylation)

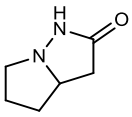


To a flame-dried round bottom flask, β*N*-benzylated carbazates were dissolved in dry dichloromethane (5.0 mL) to which was added TFA (5.0 mL). The solution was stirred for 1 h under argon atmosphere. The solvent was then evaporated and the deprotected hydrazine salt was directly dissolved in α,α,α-trifluorotoluene (0.05 M) to which pyridine or 4-dimethylaminopyridine were added (10 equiv). The corresponding acylating reagent was then added and the reaction was stirred under argon according to the specified time and temperature. The reaction efficiency was measured by ^{1}H-NMR analysis due to instability of the final products.

General Procedure F: (Intramolecular Aminocarbonlyation via Base Catalysis)



To an oven dried 5- 20 mL µw tube, a stir bar was added and the vial was capped with a septum and purged with argon for 5 min. The corresponding carbazate (1.00 equiv) dissolved in THF (0.05 M) was added to the sealed vial. To this solution was added DBU (0.05 equiv). The reaction vessel was sealed with a microwave cap and heated via oil bath at 50 °C for 60 h. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and then purified by silica gel chromatography to give the corresponding pure aminocarbonylation products.



Tetrahydro-1*H*-pyrrolo[1,2-*b*]pyrazol-2(3*H*)-one (3a): Synthesized according to general procedure **D** from phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate (0.051 g, 0.230 mmol) in α,α,α-trifluorotoluene (0.05 M) at 120 °C for 2 h. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (10 % MeOH in CH_2Cl_2). The title compound was obtained as a white solid (0.008 g, 28 %).

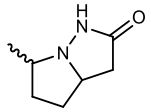
TLC R_f: 0.47 in 10 % MeOH in CH_2Cl_2.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.13-4.01 (m, 1H), 3.11 (td, *J* = 11.1, 6.4 Hz, 1H), 2.88 (td, *J* = 11.0, 6.5 Hz, 1H), 2.64 (dd, *J* = 17.1, 9.3 Hz, 1H), 2.43 (dd, *J* = 17.1, 7.8 Hz, 1H), 2.15-1.97 (m, 2H), 1.85-1.71 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5 (C), 61.9 (CH), 57.9 (CH_2), 37.6 (CH_2), 31.3 (CH_2), 23.7 (CH_2).

IR (film): 3181, 2967, 2873, 1682, 1574, 1422, 1356, 1063, 917 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_{10}N_2O$ $[M]^+$: 126.0793. Found: 126.0813.



Tetrahydro-6-methyl-1*H*-pyrrolo[1,2-*b*]pyrazol-2(3*H*)-one (3b): Synthesized according to general procedure **D** from phenyl 2-(hex-5-en-2-yl)hydrazinecarboxylate (0.228 g, 1.00 mmol) in α,α,α-trifluorotoluene (0.05 M) at 120 °C for 2 h. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (7.5 % MeOH in CH_2Cl_2). The title compound was obtained as a white solid (0.098 g, 70 %)

Diastereoisomer **a**:

TLC R_f: 0.33 in 7.5 % MeOH in CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.49 (s, 1H), 4.04 (ddd, *J* = 13.4, 8.9, 4.3 Hz, 1H), 3.14 (qd, *J* = 13.4, 6.8, 6.6, Hz, 1H), 2.75 (dd, *J* = 17.1, 9.5 Hz, 1H), 2.36 (dd, *J* = 17.1, 4.7 Hz, 1H), 2.17-1.99 (m, 1H), 1.88-1.54 (m, 3H), 1.23 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (C), 62.6 (CH_2), 62.2 (CH_2), 38.8 (CH), 32.4 (CH), 30.2 (CH), 15.9 (CH_3).

IR (film) 3131, 3053, 2967, 2917, 2846, 1699, 1650, 1346, 1284, 1241, 1120 cm-1.

HRMS (EI): Exact mass calcd for $C_7H_{12}N_2O$ $[M]^+$: 140.0950. Found: 140.0949.

Diastereoisomer **b**:

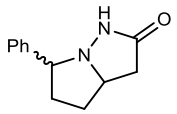
TLC R_f:0.24 in 7.5 % MeOH in CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (s,1H), 4.12 (ddd, *J* = 18.2, 9.3, 5.0 Hz, 1H), 2.95 (td, *J* = 10.5, 5.9 Hz, 1H), 2.60-2.42 (m, 2H), 2.19 (dtd, *J* = 12.8, 8.4, 8.3, 2.5 Hz, 1H), 2.11-1.99 (m, 1H), 1.79-1.65 (m, 1H), 1.61-1.44 (m, 1H), 1.13 (d, *J* = 6.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5 (C), 64.3 (CH), 62.2 (CH), 38.1 (CH_2), 32.3 (CH_2), 29.5 (CH_2), 18.7 (CH_3).

IR (film): 3131, 3053, 2967, 2917, 2846, 1699, 1650, 1346, 1284, 1241, 1120 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{12}N_2O$ $[M]^+$: 140.0950. Found: 140.0949.



6-Phenyltetrahydro-1H-pyrrolo[1,2-b]pyrazol-2(3H)-one (3g): Synthesized according to general procedure **D** from phenyl 2-(1-phenylpent-4-en-1-yl)hydrazinecarboxylate (0.0888 g, 0.300 mmol) in α,α,α-trifluorotoluene (0.05 M) at 120 °C for 2 h. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20% EtOAc/hexanes to 100% EtOAc). The title compound was obtained as a white solid and a mixture of diastereomers (0.0364 g, 60%, 5:1 d.r.).

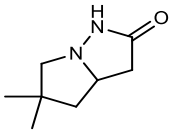
TLC R_f: 0.46 in 20% EtOAc/hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.23 (m, 5H), 7.20-6.53 (m, 1H), 4.40-4.12 (m, 1H), 4.00-3.70 (m, 1H), 2.58 (d, *J* = 9.8 Hz, 2H), 2.44-2.16 (m, 2H), 2.01-1.65 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0 (C), 140.0 (C), 128.6 (CH), 127.8 (CH), 127.2 (CH), 72.7 (CH_2), 62.0 (CH_2), 38.0 (CH_2), 34.1 (CH_2), 30.0 (CH_2).

IR (film): 3124, 2424, 1699, 1668, 1578, 1503, 1423, 1280 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{14}N_2O$ $[M]^+$: 202.1106. Found: 202.1117.



5,5-Dimethyltetrahydro-1H-pyrrolo[1,2-b]pyrazol-2(3H)-one (3e): Synthesized according to general procedure **F** from phenyl 2-(2,2-dimethylpent-4-en-1-yl)hydrazinecarboxylate (0.124 g, 0.500 mmol) and DBU (0.00386, 0.0250 mmol) in THF (0.05 M) at 50 °C for 60 h. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (7.5% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous solid (0.0632 g, 82%).

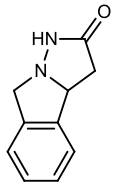
TLC R_f: 0.28 in 7.5% MeOH/CH_2Cl_2.

^{1} H NMR (300 MHz, $CDCl_3$): δ 4.20 (qd, *J* = 9.4, 7.8, 7.8, 7.8 Hz, 1H), 3.04 (dd, J = 9.1, 0.8 Hz, 1H), 2.71-2.55 (m, 2H), 2.48 (dd, *J* = 17.1, 9.5 Hz, 1H), 2.01 (ddd, *J* = 12.9, 7.82, 1.1 Hz, 1H), 1.59 (dd, J = 12.9, 6.8 Hz, 1H), 1.13 (d, *J* = 11.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 73.8 (C), 70.1 (CH2), 61.8 (CH), 46.1 (CH_2), 37.9 (CH_2), 27.6 (CH_3), 27.4 (CH_3).

IR (film): 3174, 2967, 2955, 2936, 2862, 2359, 1716, 1705 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_8H_{14}N_2O$ $[M]^+$: 154.1106. Found: 154.1119.



3,3a-Dihydro-1H-pyrazolo[5,1-a]isoindol-2(8H)-one (3h): Synthesized according to general procedure **D** from phenyl 2-(2-vinylbenzyl)hydrazinecarboxylate (0.134 g, 0.500 mmol) in α,α,α-trifluorotoluene (0.05 M) at 200 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/CH_2Cl_2). The title compound was obtained as a black solid (0.0636 g, 75%).

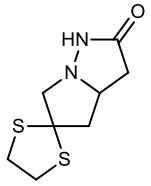
TLC R_f: 0.40 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.28 (dt, *J* = 6.0, 3.2 Hz, 2H), 7.22-7.20 (m, 2H), 5.05 (dd, *J* = 9.1, 5.8 Hz, 1H), 4.42 (d, *J* = 15.0 Hz, 1H), 4.14 (d, *J* = 15.0 Hz, 1H), 2.90 (dd, *J* = 16.8, 9.2 Hz, 1H), 2.73 (dd, *J* = 16.8, 5.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5 (C), 140.8 (C), 137.8 (C), 128.5 (CH), 128.0 (CH), 122.8 (CH), 67.9 (CH), 62.9 (CH_2), 36.6 (CH_2).

IR (film): 3033, 2414, 1689, 1654, 1558, 1506, 1456, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{10}N_2O$ $[M]^+$: 174.0793. Found: 174.0807.



Tetrahydrospiro[[1,3]dithiolane-2,5'-pyrrolo[1,2-b]pyrazol]-2'(1'H)-one (3i): Synthesized according to general procedure **F** from phenyl 2-((2-allyl-1,3-dithiolan-2-yl)methyl)hydrazinecarboxylate (0.155 g, 0.500 mmol) and DBU (0.00386, 0.0250 mmol) in THF (0.05 M) at 50 °C for 60 h. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/CH_2Cl_2). The title compound was obtained as a white solid (0.0876 g, 81%).

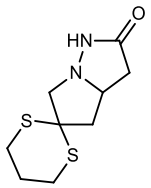
TLC R_f: 0.33 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (s, 1H), 4.23 (qd, *J* = 8.6, 6.5 Hz, 1H), 3.49 (dd, *J* = 10.8, 1.0 Hz, 1H), 3.38-3.24 (m, 5H), 2.74-2.55 (m, 3H), 2.36 (dd, *J* = 13.8, 6.1 Hz, 1H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 174.6 (C), 70.7 (CH_2), 66.2 (C), 61.5 (CH), 49.7 (CH_2), 39.8 (CH_2), 39.5 (CH_2), 37.4 (CH_2).

IR (film): 3105, 2331, 1683, 1554, 1263, 1247 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_8H_{12}N_2OS_2$ $[M]^+$: 216.0391. Found: 216.0403.



Tetrahydrospiro[[1,3]dithiane-2,5'-pyrrolo[1,2-b]pyrazol]-2'(1'H)-one (3j): Synthesized according to general procedure **F** from phenyl 2-((2-allyl-1,3-dithian-2-yl)methyl)hydrazinecarboxylate (0.162 g, 0.500 mmol) and DBU (0.00386, 0.0250 mmol) in THF (0.05 M) at 50 °C for 60 h. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/CH_2Cl_2). The title compound was obtained as a white solid (0.0956 g, 83%). °

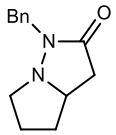
TLC R_f: 0.35 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (s, 1H), 4.42-4.35 (m, 1H), 3.85 (d, *J* = 11.4 Hz, 1H), 3.36 (d, *J* = 11.5 Hz, 1H), 2.97-2.83 (m, 4H), 2.75-2.59 (m, 3H), 2.26 (dd, *J* = 14.0, 5.9 Hz, 1H), 2.08-1.94 (m, 2H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 174.0 (C), 69.8 (CH_2), 62.1 (CH), 52.6 (C) 46.6 (CH_2), 37.3 (CH_2), 29.0 (CH_2), 28.6 (CH_2), 25.0 (CH_2).

IR (film): 3018, 1843, 1701, 1652, 1558, 1510, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{14}N_2OS_2$ $[M]^+$: 230.0548. Found: 230.0571.



1-Benzyltetrahydro-1H-pyrrolo[1,2-b]pyrazol-2(3H)-one (3k): Synthesized according to general procedure **D** from *tert*-butyl 2-benzyl-2-(pent-4-enyl)hydrazinecarboxylate (0.0758 g, 0.261 mmol) in α,α,α-trifluorotoluene (0.05 M) at 200 °C for 0.5 h. The reaction mixture was

concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/CH_2Cl_2). The title compound was obtained as a colorless oil (0.0508 g, 90%).

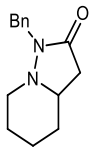
TLC R_f: 0.39 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.18 (m, 5H), 4.71-4.59 (m, 1H), 4.58-4.44 (m, 1H), 4.02-3.87 (m, 1H), 3.06-2.89 (m, 1H), 2.73-2.60 (m, 2H), 2.59-2.43 (m, 1H), 2.13-1.98 (m, 1H), 1.97-1.82 (m, 1H), 1.81-1.59 (m, 2H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 170.8 (C), 136.7 (C), 128.5 (CH), 128.1 (CH), 127.5 (CH), 59.4 (CH), 55.2 (CH_2), 47.7 (CH_2), 37.6 (CH_2), 30.2 (CH_2), 23.7 (CH_2).

IR (film): 3444, 2996, 2588, 2101, 1688, 1396, 1244 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{16}N_2O$ $[M]^+$: 216.1263. Found 216.1261.



1-Benzylhexahydropyrazolo[1,5-a]pyridin-2(1H)-one (3q): Synthesized according to general procedure **D** from *tert*-butyl 2-benzyl-2-(hex-5-en-1-yl)hydrazinecarboxylate (0.0761 g, 0.250 mmol) in α,α,α-trifluorotoluene (0.05 M) at 200 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (70% EtOAc/hexanes). The title compound was obtained as a colorless oil (0.0570 g, 99%).

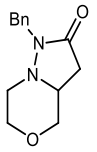
TLC R_f: 0.31 in 70% EtOAc/hexanes.

^{1}H NMR at 115 °C (300 MHz, DMSO-d_6): δ 7.30-7.20 (m, 5H), 4.57 (d, *J* = 15.7 Hz, 1H), 4.36 (d, *J* = 5.7 Hz, 1H), 3.23 (m, 1H), 2.72 (dd, *J* = 9.5 Hz, 5.4 Hz, 2H), 2.48 (m, 1H), 2.15 (dd, *J* = 15.7 Hz, 6.5 Hz, 1H), 1.77-1.68 (m, 1H), 1.61-1.37 (m, 5H).

^{13}C NMR at 115 °C (75 MHz, DMSO-d_6): δ 177.3 (C), 143.0 (C), 133.3 (CH), 132.7 (CH), 132.1 (CH), 64.7 (CH), 56.4 (CH_2), 39.3 (CH_2), 31.9 (CH_2), 28.7 (CH_2), 25.6 (CH_2).

IR (film): 3477, 2937, 2858, 2097, 1678, 1394, 1254 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{18}N_2O$ $[M]^+$: 230.1419. Found 230.1403.



1-Benzyltetrahydro-1H-pyrazolo[5,1-c][1,4]oxazin-2(3H)-one (3t): Synthesized according to general procedure **D** from *tert*-butyl 2-(2-(allyloxy)ethyl)-2-benzylhydrazinecarboxylate (0.0620 g, 0.200 mmol) in α,α,α-trifluorotoluene (0.05 M) 150 °C for 6 h. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/CH_2Cl_2). The title compound was obtained as a white solid (0.0460 g, 98%).

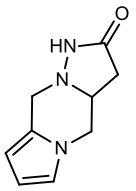
TLC R_f: 0.20 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.21 (m, 5H), 4.71 (d, *J* = 15.3 Hz, 1H), 4.43 (d, *J* = 15.3 Hz, 1H), 3.89-3.85 (m, 1H), 3.76 (dd, *J* = 12.5, 3.1 Hz, 2H), 3.52-3.40 (m, 2H), 3.06-2.89 (m, 2H), 2.75-2.63 (m, 1H), 2.25 (dd, *J* = 16.1, 6.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9 (C), 136.8 (C), 128.5 (CH), 127.9 (CH), 127.6 (CH), 66.0 (CH_2), 65.1 (CH_2), 56.8 (CH), 51.6 (CH_2), 45.8 (CH_2), 31.2 (CH_2).

IR (film): 2957, 1994, 1674, 1405, 1254 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{14}N_2O$ $[M]^+$: 202.1106. Found: 202.1117.



3,3a,4,9-Tetrahydropyrazolo[1,5-a]pyrrolo[1,2-d]pyrazin-2(1H)-one (SI1): Synthesized according to general procedure **D** from phenyl 2-((1-allyl-1*H*-pyrrol-2-yl)methyl)hydrazinecarboxylate (0.163 g, 0.600 mmol) in α,α,α-trifluorotoluene (0.05 M) at 200 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/CH_2Cl_2). The title compound was obtained as a tan solid (0.101 g, 95%).

TLC R_f: 0.37 in 5% MeOH/CH_2Cl_2.

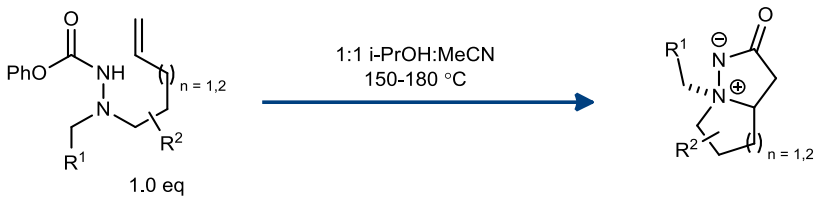
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (d, *J* = 0.3 Hz, 1H), 6.16 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.99-5.98 (m, 1H), 4.24-4.13 (m, 2H), 3.98 (dd, *J* = 12.2, 8.3 Hz, 1H), 3.89-3.83 (m, 1H), 3.68 (br s, 1H), 2.56-2.49 (m, 1H), 2.33-2.23 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6 (C), 124.8 (C), 119.7 (CH), 108.6 (CH), 105.3 (CH), 60.4 (CH), 52.8 (CH_2), 47.5 (CH_2) 34.6 (CH_2).

IR (film): 3238, 2891, 1683, 1662, 1485, 1296, 1266 cm^{-1}.

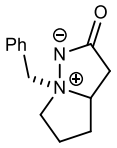
HRMS (EI): Exact mass calcd for $C_9H_{11}N_3O$ $[M]^+$: 177.0902. Found: 177.0902.

Synthesis of aminimides via aminocarbonylation



General Procedure G: Synthesis of Aminimides via Intramolecular Aminocarbonylation.

The carbazate was added to an oven or flame-dried microwave vial with a stir bar. The compound was solubilized using a 1:1 (v:v) mixture of *i*-PrOH and MeCN to achieve a final concentration of 0.05 M, unless otherwise noted. The vial was sealed with a septum and purged with argon. The mixture was heated at 150-180 °C in a microwave reactor for 3 h or wax bath for 15-50 h. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure, and analyzed by ^{1}H NMR. The aminimide product was isolated using silica gel column chromatography, treated with 1% triethylamine.



7-Benzyl-2-oxohexahydro-2H-pyrrolo[1,2-b]pyrazol-7-ium-1-ide (**4b**): The title compound was synthesized according to general procedure **G** using *tert*-butyl 2-benzyl-2-(pent-4-en-1-yl)hydrazinecarboxylate (0.290 g, 1.00 mmol) in a 1:1 (v:v) mixture of *i*-PrOH and MeCN (20.0 mL). The reaction was heated at 150 °C for 3 h. The product was isolated by column chromatography using silica treated with 1% triethylamine (CH_2Cl_2 to remove excess starting material and by products and then 10% MeOH/CH_2Cl_2 to elute the product). The product was obtained as a white-beige powder (0.194 g, 89% yield).

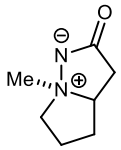
TLC R_f: 0.09 in 10% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61−7.50 (m, 2H), 7.48−7.32 (m, 3H), 4.56 (d, *J* = 12.3 Hz, 1H), 4.34 (d, *J* = 12.3 Hz, 1H), 4.32−4.23 (m, 1H), 3.81−3.67 (m, 1H), 3.56−3.43 (m, 1H), 2.41−2.23 (m, 2H), 2.23−2.08 (m, 2H), 2.02−1.88 (m, 1H), 1.88−1.75 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1 (C), 132.8 (CH), 130.3 (CH), 129.4 (C), 129.1 (CH), 71.2 (CH), 70.1 (CH_2), 67.1 (CH_2), 41.2 (CH_2), 33.1 (CH_2), 23.5 (CH_2).

IR (film): 3378, 2960, 2945, 1610, 1592, 1576, 1396, 1386, 1310, 1277 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{16}N_2ONa^+$ [M + Na^+] 239.1160. Found: 239.1161.



7-Methyl-2-oxohexahydro-2H-pyrrolo[1,2-b]pyrazol-7-ium-1-ide (4c): The title compound was synthesized according to general procedure **G** using *tert*-butyl 2-(pent-4-en-1-yl)-2-methylhydrazinecarboxylate (0.107 g, 0.500 mmol) in a 1:1 (v:v) mixture of *i*-PrOH and MeCN (10.0 mL). The reaction was heated at 150 °C for 3 h. The product was isolated by column chromatography using silica treated with 1% triethylamine (gradient column with 10% MeOH/CH_2Cl_2 to elute spots with R_f>0.15 then 20% MeOH/CH_2Cl_2). The product was obtained as a brown-yellow powder (0.040 g, 57% yield).

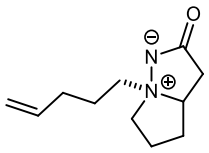
TLC R_f: 0.06 in 10% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15−4.04 (m, 1H), 3.79−3.70 (m, 1H), 3.31 (dt, *J* = 6.1, 10.7 Hz, 1H), 3.19 (s, 3 H), 3.09 (dd, *J* = 9.0, 16.3 Hz, 1H), 2.48 (dd, *J* = 3.1, 16.3 Hz, 1H), 2.43−2.19 (m, 2H), 2.01−1.84 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2 (C), 74.7 (CH), 68.5 (CH_2), 55.2 (CH_3), 40.6 (CH_2), 33.1 (CH_2), 23.9 (CH_2).

IR (film): 3006, 2957, 1582, 1443, 1387, 1301, 1275, 1262 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_7H_{13}N_2O^+$ [M + H^+] 141.1028. Found: 141.1037.



2-Oxo-7-(pent-4-en-1-yl)hexahydro-2H-pyrrolo[1,2-b]pyrazol-7-ium-1-ide (4d): The title compound was synthesized according to general procedure **G** using *tert*-butyl 2,2-di(pent-4-en-1-yl)hydrazinecarboxylate (0.091 g, 0.340 mmol) in a 1:1 (v:v) mixture of *i*-PrOH and MeCN (6.80 mL). The reaction was heated at 150 °C for 3 h. The product was isolated by column chromatography using silica treated with 1% triethylamine (10% MeOH/CH_2Cl_2). The product was obtained as a transparent yellow oil (0.057 g, 86% yield).

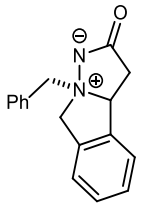
TLC R_f: 0.09 in 10% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69 (tdd, *J* = 6.6, 10.3, 17.0 Hz, 1H), 5.04−4.90 (m, 2H), 4.19 (tt, *J* = 3.6, 9.2 Hz, 1H), 3.71−3.60 (m, 1H), 3.40−3.15 (m, 3H), 3.00 (dd, *J* = 9.3, 16.4 Hz, 1H), 2.41 (dd, *J* = 3.1, 16.5 Hz, 1H), 2.38−2.29 (m, 1H), 2.27−2.13 (m, 1H), 2.10−2.02 (m, 2H), 2.00−1.79 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4 (C), 136.5 (CH), 116.5 (CH_2), 73.2 (CH), 66.9 (CH_2), 66.9 (CH_2), 41.1 (CH_2), 33.0 (CH_2), 30.7 (CH_2), 23.4 (CH_2), 23.1 (CH_2).

IR (film): 1594, 1202 cm^{-1}.

HRMS (ESI): exact mass calcd for $C_{11}H_{18}N_2ONa$ [M + Na^+] 217.1317. Found: 217.1306.



9-Benzyl-2-oxo-3,3a,8,9-tetrahydro-2H-pyrazolo[5,1-a]isoindol-9-ium-1-ide (4f): The title compound was synthesized according to general procedure **G** using *tert*-butyl 2-benzyl-2-(2-vinylbenzyl)hydrazinecarboxylate (0.161 g, 0.476 mmol) in a 1:1 (v:v) mixture of *i*-PrOH and MeCN (9.5 mL). The reaction was heated at 150 °C for 3 h. The product was isolated by column chromatography using silica treated with 1% triethylamine (CH_2Cl_2 to remove excess starting material and by-products and then 10% MeOH/CH_2Cl_2 to elute the product). The product was obtained as a white fluffy powder (0.089 g, 71% yield).

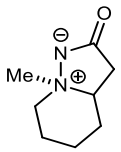
TLC R_f: 0.13 in 10% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 1.7, 7.7 Hz, 2H), 7.54−7.40 (m, 3H), 7.40−7.31 (m, 2H), 7.25−7.17 (m, 1H), 7.17−7.07 (m, 1H), 5.42 (dd, *J* = 1.8, 8.6 Hz, 1H), 5.10 (d, *J* = 14.3 Hz, 1H), 4.98 (d, *J* = 14.3 Hz, 1H), 4.76 (d, *J* = 12.3 Hz, 1H), 4.53 (d, *J* = 12.3 Hz, 1H), 2.50 (dd, *J* = 2.3, 15.6 Hz, 1H), 2.24 (dd, *J* = 8.7, 15.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4 (C), 137.6 (C), 132.9 (CH), 132.7 (C), 130.7 (CH), 129.8 (CH), 129.6 (CH), 129.4 (CH), 129.0 (C), 123.3 (CH), 123.3 (CH), 76.9 (CH), 72.0 (CH_2), 70.5 (CH_2), 39.7 (CH_2).

IR (film): 3041, 2938, 2805, 1599, 1583, 1458, 1372, 1344, 1279 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{17}H_{16}N_2ONa^+$ [M + Na^+] 287.1160. Found: 287.1155.



8-Methyl-2-oxooctahydropyrazolo[1,5-a]pyridin-8-ium-1-ide (4k): The title compound was synthesized according to general procedure **G**, using *tert*-butyl-2-(hex-5-en-1-yl)-2-methylhydrazinecarboxylate (0.114 g, 0.500 mmol) in a 1:1 (v:v) mixture of *i*-PrOH and MeCN (10.0 mL). The reaction was heated at 180 °C for 3 h. The product was isolated by column chromatography using silica treated with 1% triethylamine (gradient column with 10% MeOH/CH_2Cl_2 to elute spots with R_f > 0.15 then 20% MeOH/CH_2Cl_2). The product was obtained as a brown-yellow powder (0.054 g, 70% yield).

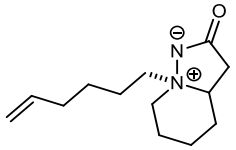
TLC R_f: 0.08 in 10% MeOH/CH_2Cl_2;

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87−3.80 (m, 1H), 3.43−3.37 (m, 1H), 3.32−3.26 (m, 1H), 3.14 (s, 3H), 2.76 (dd, *J* = 15.8, 7.4 Hz, 1H), 2.58 (dd, *J* = 15.8, 8.1 Hz, 1H), 2.01−1.86 (m, 3H), 1.76−1.59 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7 (C), 70.4 (CH), 63.3 (CH_2), 53.9 (CH_3), 38.2 (CH_2), 25.7 (CH_2), 21.1 (CH_2), 18.5 (CH_2).

IR (film): 3258, 2948, 1570, 1451, 1396, 1306, 1231 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_8H_{14}N_2ONa^+$ [M + Na^+] 177.1009. Found: 177.1004.



8-(Hex-5-en-1-yl)-2-oxooctahydropyrazolo[1,5-a]pyridin-8-ium-1-ide (4l). The title compound was synthesized according to general procedure **G** using *tert*-butyl 2,2-di(hex-5-en-1-yl)hydrazinecarboxylate (0.080 g, 0.271 mmol) in a 1:1 (v:v) mixture of *i*-PrOH and MeCN (5.4 mL). The reaction was heated at 180 °C for 3 h. The product was isolated by column chromatography using silica treated with 1% triethylamine (10% MeOH/CH_2Cl_2). The product was obtained as a brown oil (0.018 g, 30% yield).

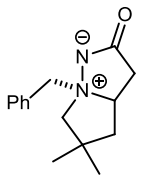
TLC R_f: 0.15 in 10% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79−5.69 (m, 1H), 5.02−4.95 (m, 2H), 4.01−3.98 (m, 1H), 3.45−3.25 (m, 4H), 2.78−2.70 (m, 2H), 2.08 (q, *J* = 7.1 Hz, 2H), 1.99−1.64 (m, 8H), 1.46−1.40 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2 (C), 137.8 (CH), 115.8 (CH_2), 68.7 (CH), 64.2 (CH_2), 60.3 (CH_2), 37.2 (CH_2), 33.5 (CH_2), 26.1 (CH_2), 25.1 (CH_2), 22.7 (CH_2), 20.5 (CH_2), 17.7 (CH_2).

IR (film): 3377, 2927, 1728, 1639, 1574, 1464, 1370, 1271, 1243 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{22}N_2ONa^+$ [M + Na^+] 245.1630. Found: 245.1638.



7-Benzyl-5,5-dimethyl-2-oxohexahydro-2H-pyrrolo[1,2-b]pyrazol-7-ium-1-ide (SI2): The title compound was synthesized according to general procedure **G** using *tert*-butyl 2-benzyl-2-(2,2-dimethylpent-4-en-1-yl)hydrazine-carboxylate (0.146 g, 0.458 mmol) in a 1:1 (v:v) mixture of *i*-PrOH and MeCN (9.2 mL). The reaction mixture was heated at 150 °C for 50 h in a wax bath. The product was isolated by column chromatography using silica treated with 1% triethylamine (CH_2Cl_2 to remove excess starting material and by-products and then 10% MeOH/CH_2Cl_2 to elute the product). The product was obtained as a white-yellow powder (0.019 g, 17% yield).

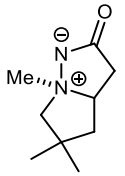
TLC R_f: 0.13 in 10% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.54 (m, 2H), 7.51−7.34 (m, 3H), 4.65 (d, *J* = 12.3 Hz, 1H), 4.52−4.43 (m, 1H), 4.40 (d, *J* = 12.3 Hz, 1H), 3.84−3.66 (m, 2H), 2.26−2.11 (m, 2H), 1.95−1.80 (m, 2H), 1.21 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7 (C), 133.0 (CH), 130.6 (CH), 129.3 (CH), 129.1 (C), 80.0 (CH_2), 71.9 (CH_2), 71.8 (CH), 46.7 (CH_2), 39.2 (CH_2), 38.5 (C), 27.9 (CH_3), 27.7 (CH_3).

IR (film): 3205, 2958, 2919, 2889, 1713, 1588, 1578, 1405, 1214 $cm^{-1.}$

HRMS (ESI): Exact mass calcd for $C_{15}H_{20}N_2ONa$ [M + Na^+] 267.1473. Found: 267.1481.



5,5,7-Trimethyl-2-oxohexahydro-2H-pyrrolo[1,2-b]pyrazol-7-ium-1-ide (SI3): The title compound was synthesized according to general procedure **G** using *tert*-butyl 2-(2,2-dimethylpent-4-en-1-yl)-2-methylhydrazinecarboxylate (0.048 g, 0.200 mmol) in a 1:1 (v:v) mixture of *i*-PrOH and MeCN (4.0 mL). The reaction mixture was heated at 150 °C for 15 h in a

wax bath. The product was isolated by column chromatography using silica treated with 1% triethylamine (gradient column with 10% MeOH/CH_2Cl_2 then 20% MeOH/CH_2Cl_2). The product was obtained as an off-white powder (*m* = 0.030 g, 90% yield).

TLC R_f: 0.11 in 10% MeOH/CH_2Cl_2.

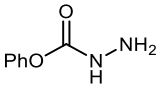
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.30−4.24 (m, 1H), 3.78 (d, *J* = 12.4 Hz, 1H), 3.40 (d, *J* = 12.2 Hz, 1H), 3.19 (s, 3H), 3.04 (dd, *J* = 16.1, 8.5 Hz, 1H), 2.50 (dd, *J* = 16.1, 1.7 Hz, 1H), 2.18 (dd, *J* = 13.2, 7.0 Hz, 1H), 1.98 (dd, *J* = 13.3, 10.7 Hz, 1H), 1.22 (d, *J* = 5.5 Hz, 7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1 (C), 81.3 (CH_2), 75.2 (CH), 57.4 (CH_3), 46.9 (CH_2), 38.9 (C), 38.4 (CH_2), 28.1 (CH_3), 27.6 (CH_3).

IR (film): 3406, 3216, 2958, 2870, 1683, 1588, 1570, 1445, 1396, 1371, 1312, 1269 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_9H_{16}N_2ONa^+$ [M + Na^+] 191.1160. Found: 191.1169.

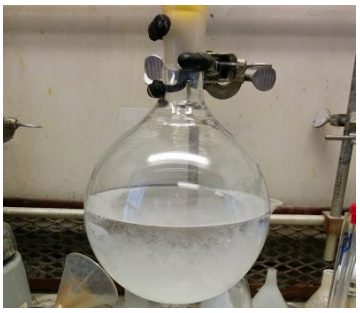
Improved procedure for the synthesis of phenylcarbazate (phenyl hydrazinecarboxylate)



Phenyl hydrazinecarboxylate (**5a**). To a solution of diphenyl carbonate (21.42 g, 100 mmol) (Note 1) in 300 mL of petroleum ether (Note 2) in a 1 L round bottom-flask was added drop-wise 100 mL of hydrazine solution in THF (1 M, 100 mmol) (note 3) using a dripping funnel for 30 minutes at room temperature.

The solution was allowed to stir for an additional 30 minutes at room temperature following the addition of the last drop of hydrazine. The solution was then filtered on a medium-fritted filter funnel.

The remaining crystals in the flask were washed with 100 mL of petroleum ether. 200 mL of petroleum ether was then added to the solution to induce crystallization. The solution was allowed to stand for 30 minutes.



A second filtration was done and the solids were combined and dried on high vacuum (Note 4) for 30 minutes to afford 11.65 g of *O*-phenyl carbazate (Note 5) (77%).

Notes

1. Dipenhyl carbonate (99.0%) was purchased from Alfa Aeasar and used as received
2. Hydrazine solution (1.0 M in THF) was purchased from Sigma-Aldrich and used as received
3. Petroleum ether (ACS reagent grade) was purchased from Fisher Scientific and used as received

M. p.: 109.6-110.2 °C.

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 4.24 (br s, 1.84 H), 4.43 (br s, 0.16 H), 7.08 (d, *J* = 7.6 Hz, 2H), 7.17-7.23 (m, 1H), 7.34-7.41 (m, 2H), 8.13 (br s, 0.08 H), 8.75 (br s, 0.92 H).

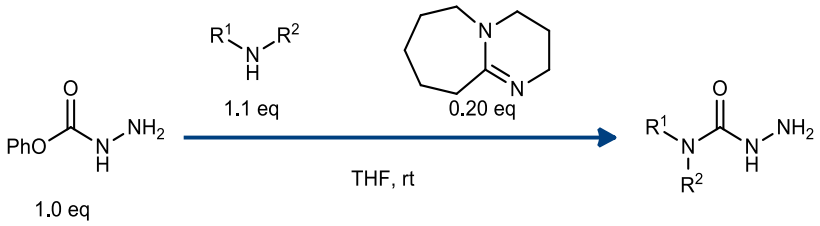
^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 121.6 (CH)(, 124.9 (CH), 129.3 (CH), 151.1 (C), 156.4 (C).

IR (film): 3540, 3461, 3306, 3015, 1764, 1707, 1655, 1593, 1519, 1489, 1370, 1280, 1195, 1161, 1069, 1045, 1005, 940, 911, 834, 784, 714, 687 cm^{-1}.

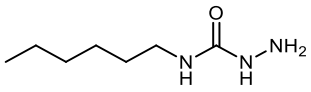
HRMS (ESI): Exact mass calcd for $C_7H_8N_2O_2Na$ $[M+Na]^+$: 175.0483. Found: 175.0862.

Nucleophilic substitution on phenyl carbazate

General procedure H : (Intermolecular Substitution on Blocked Aminoisocyanate)



An oven-dried round bottom flask was charged with a stir bar, phenyl carbazate (1.00 equiv.), an amine (1.10 equiv.), DBU (20 mol%), and THF (0.3 M). The mixture was stirred overnight, concentrated under reduced pressure, and purified by flash column chromatography.



***N*-Hexylhydrazinecarboxamide (6a):** Synthesized according to general procedure **H** using phenyl carbazate (0.152 g, 1.00 mmol), hexylamine (0.15 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (5% CH_3OH/CH_2Cl_2) to yield a white solid (0.132 g, 83%).

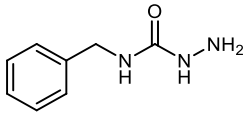
TLC R_f : 0.33 in 5% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.88 (br s, 1H), 6.08 (br s, 1H), 3.66 (br s, 2H), 3.16 (dt, *J* = 7.1, 6.2 Hz, 2H), 1.47 (m, 2H), 1.26 (m, 6H), 0.85 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8 (C), 39.5 (CH_2), 31.4 (CH_2), 30.1 (CH_2), 26.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).

IR (film): 3340, 2926, 2860, 2359, 1661, 1622, 1548, 1463, 1375, 1160 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{17}N_3O$ $[M]^+$: 159.1372. Found: 159.13553.



***N*-Benzylhydrazinecarboxamide (6b):** Synthesized according to general procedure **H** using phenyl carbazate (0.152 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), DBU (0.0300 g, 0.200

mmol), and THF (3.3 mL). The title compound was purified by column chromatography (8% CH_3OH/CH_2Cl_2) to yield an amorphous white solid (0.127 g, 77%).

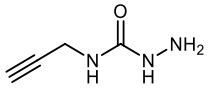
TLC R_f : 0.40 in 8% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 5H), 6.96 (br s, 1H), 6.48 (br s, 1H), 4.40 (d, *J* = 6.1 Hz, 2H), 3.62 (br s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (C), 139.4 (C), 128.4 (CH), 127.2 (CH), 127.0 (CH), 43.3 (CH_2).

IR (film): 3339, 3300, 3194, 2357, 1618, 1555, 1468, 1452, 1265 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_8H_{11}N_3O$ $[M]^+$: 165.0902. Found: 165.09032.



***N*-Propargylhydrazinecarboxamide (6c):** Synthesized according to general procedure **H** using phenyl carbazate (0.152 g, 1.00 mmol), propargylamine (0.070 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (5% CH_3OH/CH_2Cl_2) to yield an amorphous white solid (0.0600 g, 54%).

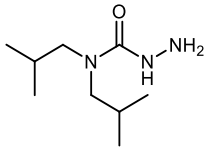
TLC R_f : 0.13 in 5% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.11 (br s, 1 H), 6.60 (br s, 1H), 4.11 (br s, 2H), 3.80 (dd, *J* = 7.1, 2.5 Hz, 2H), 3.01 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 159.7 (C), 82.7 (C), 72.2 (CH), 28.5 (CH_2).

IR (film): 2350, 1710, 1551, 1357, 1337, 1263, 1040 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_4H_7N_3O$ $[M]^+$: 113.0589. Not found. LRMS m/z (relative intensity): 57.1 (7.8%), 55.1(4.6 %), 39.0 (28.4%), 32.0 (73.6%), 32.0 (37.4%), 31.0 (8.1 %), 31.0 (5.3%), 28.0 (100%).



***N*,*N*-Diisobutylhydrazinecarboxamide (6d):** Synthesized according to general procedure **H** using phenyl carbazate (0.152 g, 1.00 mmol), *N*,*N*-diisobutylamine (0.19 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (3% CH_3OH/CH_2Cl_2) to yield an amorphous yellow solid (0.142 g, 76%).

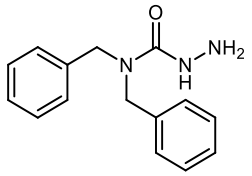
TLC R_f : 0.15 in 5% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75 (br s, 1 H), 3.80 (br s, 2H), 3.02 (d, *J* = 7.5 Hz, 4H), 1.95 (dquint., *J* = 13.8, 6.9 Hz, 2H), 0.88 (d, *J* = 6.7 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5 (C), 55.2 (CH_2), 27.4 (CH_3), 20.1 (CH).

IR (film): 2962, 1713, 1666, 1652, 1616, 1599, 1491, 1265, 1202, 1130 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{21}N_3O$ $[M]^+$: 187.1685. Found: 187.1684.



***N*,*N*-Dibenzylhydrazinecarboxamide (6e):** Synthesized according to general procedure **H** using phenyl carbazate (0.152 g, 1.00 mmol), *N*,*N*-dibenzylamine (0.21 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (3% CH_3OH/CH_2Cl_2) to yield an amorphous yellow solid (0.240 g, 94%).

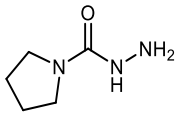
TLC R_f : 0.31 in 3% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 10H), 6.22 (br s, 1H), 4.47 (s, 4H), 3.83 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (C), 140.1 (C), 136.9 (C), 128.7 (CH), 128.2 (CH), 127.9 (CH), 127.4 (CH), 127.0 (CH), 126.7 (CH), 52.9 (CH_2), 49.8 (CH_2).

IR (film): 3317, 3028, 2359, 2336, 1616, 1494, 1452, 1400, 1364, 1261 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{17}N_3O$ $[M]^+$: 255.1372. Found: 255.13965.



Pyrrolidine-1-carbohydrazide (6f): Synthesized according to general procedure **H** using phenyl carbazate (0.152 g, 1.00 mmol), pyrrolidine (0.090 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (8% CH_3OH/CH_2Cl_2) to yield a yellow oil (0.0940 g, 73%).

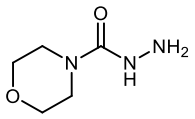
TLC R_f : 0.37 in 8% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94 (br s, 1H), 3.77 (br s, 2H), 3.28 (t, *J* = 6.7 Hz, 4H), 1.86 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8 (C), 45.3 (CH_2), 25.3 (CH_2).

IR (film): 3387, 2978, 2872, 2359, 1616, 1504, 1377 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_5H_{11}N_3O$ $[M]^+$: 129.0902. Found: 129.08920.



Morpholine-4-carbohydrazide (6g): Synthesized according to general procedure **H** using phenyl carbazate (0.152 g, 1.00 mmol), morpholine (0.095 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was obtained by filtration of the solution to yield a white amorphous solid (0.122 g, 84%).

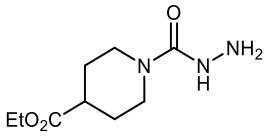
TLC R_f : 0.27 in 8% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.49 (br s, 1H), 3.83 (br s, 2H), 3.64 (t, *J* = 4.7 Hz, 4H), 3.33 (t, *J* = 5.1 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0 (C), 66.3 (CH_2), 43.6 (CH_2).

IR (film): 3344, 2862, 1612, 1506, 1398, 1305, 1269, 1113 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_5H_{11}N_3O_2$ $[M]^+$: 145.0851. Found: 145.08383.



1-Hydrazinocarbonyl-piperidine-4-carboxylic acid ethyl ester (6h): Synthesized according to general procedure **H** using phenyl carbazate (0.152 g, 1.00 mmol), ethyl isonipecotate (0.173 g, 1.10 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (5% CH_3OH/CH_2Cl_2) to yield a white amorphous solid (0.183 g, 85%).

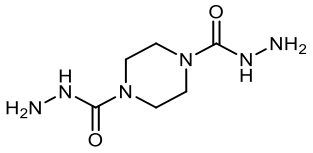
TLC R_f : 0.20 in 5% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 5.92 (br s, 1H), 4.19-4.09 (m, 2H), 3.93-3.77 (m, 2H), 3.67-3.32 (m, 2H), 2.98-2.85 (m, 2H), 2.55-2.41 (m, 1H), 1.96-1.84 (m, 2H), 1.74-1.59 (m, 2H), 1.28-1.18 (m, 3H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 174.3 (C), 159.8 (C), 60.8 (CH_2), 43.2 (CH_2), 40.9 (CH), 27.8 (CH_2), 14.3 (CH_3).

IR (film): 3330, 2952, 1718, 1623, 1606, 1448, 1379, 1313, 1265, 1186, 1164, 1145, 1114, 1095, 1080, 1039 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{17}N_3O_3$ $[M]^+$: 215.1270. Found: 215.1264.



Piperazine-1,4-dicarbohydrazide (6i): Synthesized according to general procedure **H** using phenylcarbazate (0.152 g, 1.00 mmol), ethyl isonipecotate (0.0430 g, 0.500 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound precipitated out of solution to afford the pure compound as an amorphous white solid (0.0930 g, 91%).

^{1}H NMR (300 MHz; DMSO-d_6): δ 7.38 (br s, 2H), 3.72 (br s, 4H), 3.24 (m, 8H).

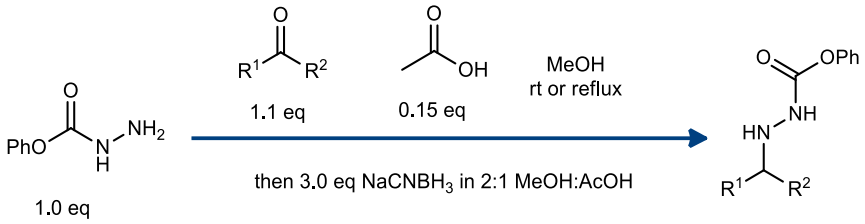
^{13}C NMR (75 MHz; DMSO-d_6): δ 159.6 (C), 43.0 (CH_2).

IR (film): 3002, 1733, 1718, 1662, 1633, 1604, 1448, 1315, 1255, 1184, 1164, 1039 cm^{-1}.

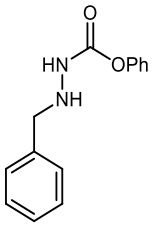
HRMS (EI): Exact mass calcd for $C_{16}H_{12}N_2O_2$ $[M]^+$: 202.1178. Found: 202.1204.

Carbazate starting material synthesis for aza-DKPs

General procedure I : (Reductive amination)



To a solution of the corresponding aldehyde or ketone in MeOH (0.3 M) was added *O*-phenyl carbazate (1.00 equiv). The reaction was carried out at room temperature (aldehyde) or refluxed in MeOH (ketone) until consumption of the aldehyde or ketone was judged complete by TLC. The corresponding crude hydrazones were directly reduced without further purification. *Hydrazone Reduction*: The corresponding hydrazone was diluted in 2:1 MeOH:AcOH (0.2 M) and combined with $NaBH_3CN$ (3 equiv). The reaction mixture was stirred for 16 h. Methanol and excess acetic acid were evaporated and the mixture was dissolved in EtOAc. The pH was increased using saturated sodium bicarbonate solution to reach a pH of 8. The solution was extracted three times with EtOAc and then brine and dried over Na_2SO_4. Volatiles were removed *in-vacuo* and the crude product was purified by column chromatography or filtration.

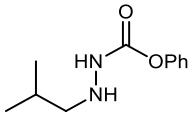


Phenyl 2-benzylhydrazinecarboxylate (7a). Synthesized according to general procedure **I** by stirring phenyl carbazate (0.512 g, 3.37 mmol) and benzaldehyde (0.393 g, 3.7 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (0.696 g, 10.1 mmol) was added and allowed to stir for 16 h. The title compound was purified by column chromatography (5% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.270 g, 33% yield).

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.37-7.32 (m, 7H), 7.21 (s, 1H), 7.12 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.63 (s, 1H), 4.08 (s, 2H), 3.86 (s, 1H).

^{13}C NMR (100 MHz; $CDCl_3$): 155.5 (C), 150.7 (C), 136.8 (C), 129.4 (CH), 129.1 (CH), 128.6 (CH), 127.8 (CH), 125.6 (CH), 121.4 (CH), 55.6 (CH_2).

^{1}H and ^{13}C NMR were in accordance with the literature.



Phenyl 2-isobutylhydrazinecarboxylate (7b): Synthesized according to general procedure **I** by stirring *O*-phenyl carbazate (3.13 g, 20.6 mmol) and isobutyraldehyde (1.49 g, 20.6 mmol) at room temperature in MeOH (0.3M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (3.88 g, 61.8 mmol) was added and allowed to stir for 16 h. The title compound was purified by column chromatography (2.5% EtOAc/CH_2Cl_2 then 10% EtOAc/CH_2Cl_2) to yield an amorphous white solid (3.24 g, 76%).

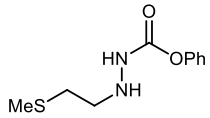
TLC R_f : 0.15 in 100% CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.42 (m, 2H), 7.18-7.25 (m, 1H), 7.11-7.18 (m, 2H), 2.77 (d, *J* = 6.9 Hz, 2H), 1.71-1.89 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6 (C), 129.6 (C), 129.2 (CH), 125.4 (CH), 121.3 (CH), 59.5 (CH_2), 26.7 (CH), 20.4 (CH_3).

IR (film): 3350, 2970, 1718, 1652, 1533, 1490, 1455, 1266, 1238, 1203, 1163 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{16}N_2O_2$ $[M]^+$: 208.1212. Found: 208.1225.



Phenyl 2-(3-(methylthio)propyl)hydrazine-1-carboxylate (7c): Synthesized according to general procedure **I** by stirring *O*-phenyl carbazate (2.68 g, 17.6 mmol) and 3 (methylthio)propanal (1.83 g, 17.6 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (3.31 g, 52.8 mmol) was added and allowed to stir for 16 h. The title compound was purified by column chromatography (80% Hexane/EtOAc) to yield an amorphous white solid (0.200 g, 5%).

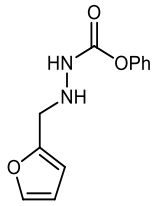
TLC R_f : 0.59 in 50% Hexane/EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.43 (m, 2H), 7.19-7.26 (m, 1H), 7.12-7.19 (m, 2H), 3.13 (t, *J* = 6.9 Hz, 2H), 2.61 (t, *J* = 7.1 Hz, 2H), 2.13 (s, 3H), 1.88 (quin, *J* = 7.02 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5 (C), 150.6 (C), 129.3 (CH), 125.5 (CH), 121.3 (CH), 50.5 (CH_2), 31.7 (CH_2), 27.0 (CH_2), 15.5 (CH_3).

IR (film): 3853, 3836, 3735, 3722, 3712, 3670, 3627, 1874, 1801, 1772, 1733, 1699, 1662, 1647, 1506, 1456, 1361, 1263, 1201, 1163 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{16}N_2O_2S$ $[M]^+$: 240.0932. Found: 111.09289.



Phenyl 2-(furan-2-ylmethyl)hydrazine-1-carboxylate (7d): Synthesized according to general procedure **I** by stirring *O*-phenyl carbazate (2.60 g, 17.1 mmol) and furan-2-carbaldehyde (1.64 g, 17.1 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (3.22 g, 51.3 mmol) was added and allowed to stir for 16 h. The title compound was purified by column chromatography (100% CH_2Cl_2) to yield an amorphous white solid (3.48 g, 87%).

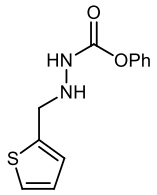
TLC R_f : 0.20 in 100% CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 1.76, 0.8 Hz, 1H), 7.33-7.41 (m, 2H), 7.19-7.26 (m, 1H), 7.11-7.17 (m, 2H), 6.36 (dd, *J* = 3.1, 2.0 Hz, 1H), 6.31 (d, *J* = 2.7 Hz, 1H), 4.11 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 151.3 (C), 150.9 (C), 142.9 (CH), 129.6 (CH), 125.8 (CH), 121.6 (CH), 110.6 (CH), 109.1 (CH), 48.3 (CH_2).

IR (film): 3674, 2364, 1733, 1655, 1506, 1490, 1455, 1265, 1203 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{12}N_2O_3$ $[M]^+$: 232.0848. Found: 232.08262.



Phenyl 2-(thiophen-2-ylmethyl)hydrazine-1-carboxylate (7e): Synthesized according to general procedure **I** by stirring *O*-phenyl carbazate (2.57 g, 16.9 mmol) and thiophene-2-carbaldehyde (1.89 g, 16.9 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (3.18 g, 50.7 mmol) was added and allowed to stir for 16 h. The title compound was purified by column chromatography (80% Hexane/EtOAc) to yield an amorphous white solid (2.63 g, 63%).

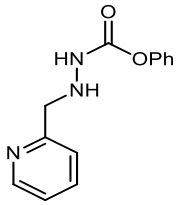
TLC R_f : 0.78 in 50% Hexane/EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.42 (m, 2H), 7.30 (dd, *J* = 5.00, 1.3 Hz, 1H), 7.20-7.26 (m, 1H), 7.12-7.17 (m, 2H), 7.02-7.05 (m, 1H), 6.98-7.02 (m, 1H), 4.32 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (C), 150.5 (C), 140.0 (C), 129.3 (CH), 126.9 (CH), 126.7 (CH), 125.6 (CH), 125.5 (CH), 121.3 (CH), 49.9 (CH_2).

IR (film): 3751, 3687, 1743, 1731, 1696, 1652, 1558, 1533, 1506, 1456, 1266, 1205, 1164 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{12}N_2O_2S$ $[M]^+$: 248.0619. Found: 248.06037.



Phenyl 2-(pyridin-2-ylmethyl)hydrazinecarboxylate (7f): Synthesized according to general procedure **I** by stirring *O*-phenyl carbazate (1.89 g, 17.6 mmol) and picolinaldehyde (2.64 g, 17.6 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (3.32 g, 52.8 mmol) was added and allowed to stir for 16 h. The title compound was filtered after reduction, washed with EtOAc and dried under vacuum to yield an amorphous white solid (2.57 g, 60%).

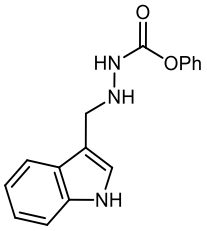
TLC R_f : 0.20 in 2% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (d, *J* = 4.8 Hz, 1H), 7.66 (td, *J* = 7.7, 1.8 Hz, 1H), 7.25-7.38 (m, 3H), 7.17-7.23 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 4.24 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2 (C), 154.7 (C), 148.4 (CH), 136.1 (CH), 129.0 (CH), 124.7 (CH), 121.8 (CH), 121.7 (CH), 121.2 (CH), 112.2 (C), 55.5 (CH_2).

IR (film): 3555, 3024, 2333, 1728, 1683, 1666, 1541, 1498, 1140, 1266, 1201 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{13}N_3O_2$ $[M]^+$: 243.1008. Found: 243.0947.



Phenyl 2-((1*H*-indol-3-yl)methyl)hydrazine-1-carboxylate (7g): Synthesized according to general procedure **I** by stirring *O*-phenyl carbazate (2.27 g, 14.9 mmol) and 1*H*-indole-2-carbaldehyde (2.17 g, 14.9 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (2.81 g, 44.7 mmol) was added and allowed to stir for 16 h. The title compound was filtered after reduction, washed with methanol and dried under vacuum to yield an amorphous white solid (1.48 g, 35%).

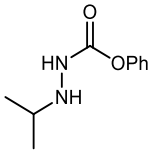
TLC R_f : 0.47 in 50% Hexane/EtOAc.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.14 (d, *J* = 3.9 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.33-7.43 (m, 3H), 7.29 (d, *J* = 2.3 Hz, 1H), 7.17-7.25 (m, 1H), 7.03-7.15 (m, 3H), 6.94-7.03 (m, 1H), 4.74 (d, *J* = 5.0 Hz, 1H), 4.11 (d, *J* = 5.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1 (C), 150.9 (C), 136.2 (C), 129.2 (CH), 127.1 (C), 124.9 (CH_2), 124.1 (CH), 121.6 (CH), 120.9 (CH), 118.7 (CH), 118.3 (CH), 115.1 (CH), 111.3 (C), 111.0 (CH), 46.0 (CH_2).

IR (film): 3726, 3640, 2981, 1676, 1644, 1506, 1456, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{16}H_{15}N_3O_2$ $[M]^+$: 281.1164. Found: 281.1161.



Phenyl 2-isopropylhydrazine-1-carboxylate (7h): Synthesized according to general procedure **I** by refluxing *O*-phenyl carbazate (1.14 g, 19.7 mmol) in acetone (0.3 M) overnight. The crude reaction was concentrated under reduced pressure then diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (3.71 g, 59.1 mmol) was added and allowed to stir for 16 h. The title compound was purified by column chromatography (40% Hexane/EtOAc) to yield an amorphous white solid (1.75 g, 45%).

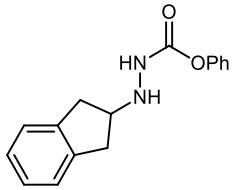
TLC R_f : 0.63 in 50% Hexane/EtOAc.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.03 (d, *J* = 4.1 Hz, 1H), 7.32-7.43 (m, 2H), 7.16-7.24 (m, 1H), 7.04-7.12 (m, 2H), 4.53 (br s, 1H), 3.01-3.14 (m, 1H), 0.96 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 129.3 (C), 129.2 (C), 124.9 (CH), 121.5 (CH), 115.2 (CH), 49.5 (CH), 20.6 (CH_3).

IR (film): 3735, 2970, 2430, 1731, 1705, 1645, 1490, 1456, 1266, 1207, 1164 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{10}H_{14}N_2O_2Na$ $[M]^+$: 217.0953. Found: 217.0953.



Phenyl 2-(2,3-dihydro-1*H*-inden-2-yl)hydrazine-1-carboxylate (7i): Synthesized according to general procedure **I** by stirring *O*-phenyl carbazate (2.50 g, 16.4 mmol) and 1,3-dihydro-2*H*-inden-2-one (2.17 g, 16.4 mmol) at room temperature in MeOH (0.3 M) for 1 h. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (3.10 g, 49.2 mmol) was added and allowed to stir for 16 h. The title compound was filtered after reduction, washed with methanol and dried under vaccum to yield an amorphous white solid (3.69 g, 83%).

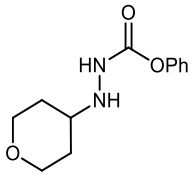
TLC R_f : 0.21 in 80% Hexane/EtOAc.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (d, *J* = 3.9 Hz, 1H), 7.37-7.41 (m, 2H), 7.18-7.24 (m, 3H), 7.09-7.13 (m, 4H), 4.88 (br s, 1H), 3.93 (td, *J* = 6.6, 3.2 Hz, 1H), 2.99 (dd, *J* = 16.4, 6.8 Hz, 2H), 2.80 (dd, *J* = 16.4, 3.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2 (C), 150.9 (C), 141.8 (C), 129.3 (CH), 126.0 (CH), 124.9 (CH), 124.5 (CH), 121.6 (CH), 58.9 (CH), 37.4 (CH_2).

IR (film): 3687, 2989, 2380, 1716, 1683, 1643, 1539, 1521, 1456, 1263, 1201 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{16}H_{16}N_2O_2$ $[M]^+$: 268.1212. Found: 268.12376.



Phenyl 2-(tetrahydro-2*H*-pyran-4-yl)hydrazine-1-carboxylate (7j): Synthesized according to general procedure **I** by refluxing *O*-phenyl carbazate (2.70 g, 17.7 mmol) and tetrahydro-4*H*-pyran-4-one (1.78 g, 17.7 mmol). The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (3.34 g, 53.1 mmol) was added and allowed to stir for 16 h. The title compound was purified by column chromatography (50% Hexane/EtOAc) to yield an amorphous white solid (1.95 g, 47%).

TLC R_f : 0.21 in 50% Hexane/EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.12-7.17 (m, 2H), 4.00 (dt, *J* = 11.6, 3.5 Hz, 2H), 3.42 (td, *J* = 11.4, 2.2 Hz, 2H), 3.14-3.28 (m, 1H), 1.84 (d, *J* = 12.4 Hz, 2H), 1.42-1.58 (m, 2H).

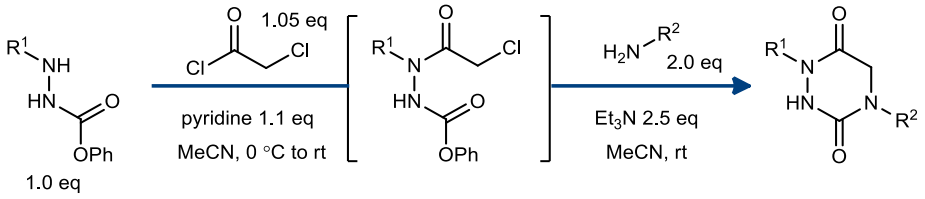
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C), 150.3 (C), 129.0 (CH), 125.2 (CH), 120.9 (CH), 85.7 (CH_2), 55.0 (CH), 30.8 (CH_2).

IR (film): 3753, 2846, 1731, 1718, 1662, 1539, 1456, 1369, 1265, 1240, 1203, 1163, 1093, 1012 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{16}N_2O_3$ $[M]^+$: 236.1161. Found: 236.11563.

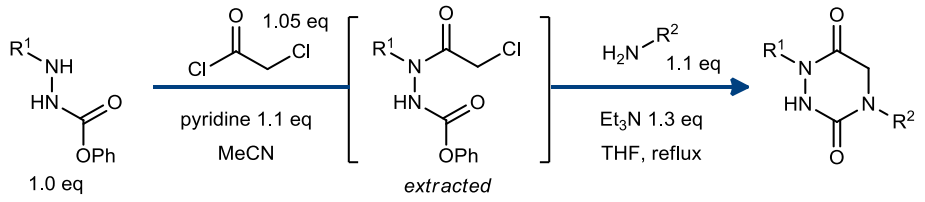
Synthesis of aza-DKPs via *N*-isocyanate cascade reactions

General Procedure J: One pot synthesis of aza-DKPs at room temperature

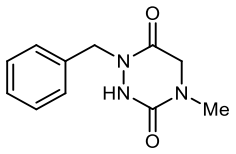


To an oven-dried 10 mL glass vial were added carbazate (1.0 equiv) and MeCN (0.60 M). The solution was allowed to stir in an ice bath until reaching 0 °C. To this solution was added pyridine (1.1 equiv), then chloroacetyl chloride (1.05 equiv). Immediately following the addition of these reagents, the reaction was removed from the ice bath and allowed to stir for 2 h. Subsequently, a solution of amine (2.0 equiv), and triethylamine (2.5 equiv) in MeCN were added to reach a final concentration of 0.30 M. The reaction was allowed to stir overnight at room temperature for 24 h. The reaction contents were concentrated under reduced pressure, and then an aqueous extraction with CH_2Cl_2 and 1.0 M HCl was used to remove excess amine and salts. The combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding aza-DKP.

General Procedure K: Two-step synthesis of aza-DKPs



To an oven-dried 10 mL glass vial were added carbazate (1.0 equiv) and CH_2Cl_2 (0.60 M). The solution was allowed to stir in an ice bath until reaching 0 °C. To this solution was added pyridine (1.1 equiv), then chloroacetyl chloride (1.05 equiv). Immediately following the addition of these reagents, the reaction was removed from the ice bath and allowed to stir for 2 h. The reaction contents were concentrated under reduced pressure, and then an aqueous extraction with CH_2Cl_2 and 1.0 M HCl was used to remove salts. The combined organic layers were dried with Na_2SO_4, then concentrated under reduced pressure. The residue was dissolved in THF (0.30 M), then amine (1.1 equiv), and triethylamine (1.3 equiv) were added. The reaction was refluxed in THF overnight for 16 h. The reaction contents were concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding aza-DKP.



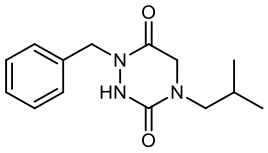
1-Benzyl-4-methyl-1,2,4-triazinane-3,6-dione (8a): Synthesized according to general procedure **J** using methylamine (2.0 M in THF solution, 0.400 mL, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield a white crystalline solid (0.0361 g, 41%).

TLC R_f : 0.61 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.37 (br s, 1H), 7.26-7.38 (m, 5H), 4.66 (s, 2H), 3.89 (s, 2H), 2.73 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2 154.8 (C), 135.8 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 50.3 (CH_2), 48.0 (CH_2), 33.1 (CH_3).
IR (film): 3759, 3600, 3033, 1698, 1654, 1647, 1506, 1488, 1446, 1265 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{13}N_3O_2$ $[M]^+$: 219.1008. Found: 219.1015.



1-Benzyl-4-isobutyl-1,2,4-triazinane-3,6-dione (8b): Synthesized according to general procedure **J** using isobutylamine (0.0585 g, 0.800 mmol). The title compound was purified by column chromatography (30% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0634 g, 60%).

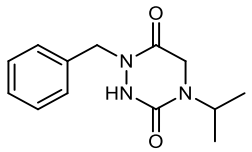
TLC R_f : 0.52 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.28 (br s, 1H), 7.19-7.45 (m, 5H), 4.67 (s, 2H), 3.88 (s, 2H), 3.00 (d, *J* = 7.3 Hz, 2H), 1.83 (dt, *J* = 13.6, 6.8 Hz, 1H), 0.79 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (C), 155.2 (C), 135.9 (C), 128.4 (CH), 127.5 (CH), 127.4 (CH), 52.4 (CH_2), 49.2 (CH_2), 48.2 (CH_2), 26.1 (CH), 19.7 (CH_3).

IR (film): 3710, 2968, 1695, 1650, 1500, 1466, 1423, 1267 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{19}N_3O_2$ $[M]^+$: 261.1477. Found: 261.1481.



1-Benzyl-4-isopropyl-1,2,4-triazinane-3,6-dione (8c): Synthesized according to general procedure **J** using isopropylamine (0.0473 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0346 g, 35%).

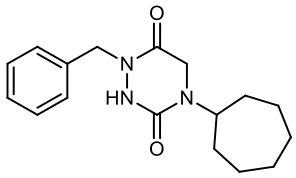
TLC R_f : 0.48 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 7.28-7.42 (m, 1H), 7.02-7.81 (m, 6H), 4.76 (s, 2H), 4.43 (sept, *J* = 6.8 Hz, 1H), 3.78 (s, 2H), 1.15 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5 (C), 155.5 (C), 134.3 (C), 128.8 (CH), 128.5 (CH), 128.3 (CH), 49.4 (CH), 45.0 (CH_2), 43.1 (CH_2), 19.1 (CH_3).

IR (film): 3861, 3749, 2993, 1730, 1683, 1654, 1647, 1506, 1266 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{17}N_3O_2$ $[M]^+$: 247.1321. Found: 247.1316.



1-Benzyl-4-cycloheptyl-1,2,4-triazinane-3,6-dione (8d): Synthesized according to general procedure **J** using cycloheptylamine (0.0906 g, 0.800 mmol). The title compound was purified by column chromatography (30% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0253 g, 21%).

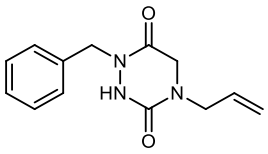
TLC R_f : 0.62 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (br s, 1H), 7.29-7.39 (m, 5H), 4.77 (s, 2H), 4.16 (tt, *J* = 10.3, 4.0 Hz, 1H), 3.83 (s, 2H), 1.48-1.81 (m, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9 (C), 155.1 (C), 133.9 (C), 128.9 (CH), 128.5 (CH), 55.2 (CH), 49.5 (CH_2), 44.4 (CH_2), 32.0 (CH_2), 27.5 (CH_2), 24.9 (CH_2).

IR (film): 3735, 2921, 2916, 2896, 1772, 1733, 1716, 1683, 1650, 1647, 1506, 1455, 1423, 1299, 1263, 1205, 1180 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{17}H_{23}N_3O_2$ $[M]^+$: 301.1790. Found: 301.1835.



4-Allyl-1-benzyl-1,2,4-triazinane-3,6-dione (8e): Synthesized according to general procedure **J** using allylamine (0.0460 g, 0.800 mmol). The title compound was purified by column chromatography (30% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0736 g, 75%).

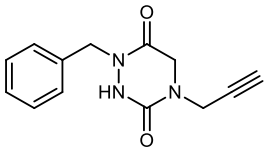
TLC R_f : 0.40 in 30% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (s, 1H), 7.26-7.39 (m, 5H), 5.73 (ddt, *J* = 16.8, 10.5, 6.1 Hz, 1H), 5.14-5.31 (m, 2H), 4.76 (s, 2H), 3.88 (d, *J* = 6.1 Hz, 2H), 3.83 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (C), 155.2 (C), 134.2 (C), 131.4 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 119.3 (CH_2), 49.4 (CH_2), 48.7 (CH_2), 48.4 (CH_2).

IR (film): 3157, 3056, 2939, 1695, 1643, 1608, 1456, 1419, 1303, 1267, 1207, 1186 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{15}N_3O_2$ $[M]^+$: 245.1164. Found: 245.1190.



1-Benzyl-4-(prop-2-yn-1-yl)-1,2,4-triazinane-3,6-dione (8f): Synthesized according to general procedure **K** using propargylamine (0.0242 g, 0.440 mmol). The title compound was purified by column chromatography (30% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0691 g, 71%).

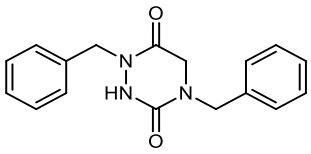
TLC R_f : 0.30 in 30% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.95 (br s, 1H), 7.21-7.29 (m, 5H), 4.70 (s, 2H), 4.02 (d, *J* = 3.5 Hz, 2H), 3.93 (s, 2H), 2.27 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6 (C), 154.7 (C), 134.1 (C), 128.7 (CH), 128.6 (CH), 128.3 (CH), 76.7 (C), 72.4 (CH), 49.4 (CH_2), 48.2 (CH_2), 35.5 (CH_2).

IR (film): 3722, 3687, 3629, 3056, 2221, 1868, 1772, 1730, 1683, 1647, 1506, 1395.

HRMS (EI): Exact mass calcd for $C_{13}H_{13}N_3O_2$ $[M]^+$: 243.1008. Found: 243.1023.



1,4-Dibenzyl-1,2,4-triazinane-3,6-dione (8g): Synthesized according to general procedure **J** using benzylamine (0.0857 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0850 g, 72%).

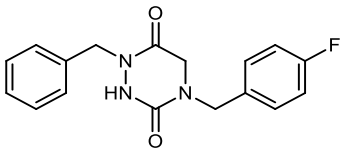
TLC R_f : 0.25 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.39 (m, 10H), 4.81 (s, 2H), 4.51 (s, 2H), 3.88 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7 (C), 155.3 (C), 135.2 (C), 134.2 (C), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 49.9 (CH_2), 49.5 (CH_2), 48.5 (CH_2).

IR (film): 3834, 3735, 3687, 3049, 2322, 1663, 1662, 1642, 1506, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{17}H_{17}N_3O_2$ $[M]^+$: 295.1321. Found: 295.1300.



1-Benzyl-4-(4-fluorobenzyl)-1,2,4-triazinane-3,6-dione (SI5): Synthesized according to general procedure **J** using 4-fluorobenzylamine (0.100 g, 0.800 mmol). The title compound was purified by column chromatography (100% CH_2Cl_2 then 50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0526 g, 42%).

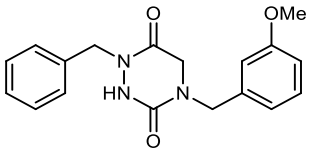
TLC R_f : 0.80 in 100% EtOAc.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.50 (br s, 1H), 7.21-7.35 (m, 7H), 7.11-7.17 (m, 2H), 4.64 (s, 2H), 4.34 (s, 2H), 3.76 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4 (C), 160.3 (C), 154.8 (C), 135.8 (C), 132.95 (C), 130.0 (CH), 129.9 (CH), 128.5 (CH), 127.4 (CH), 115.4 (CH), 115.2 (CH), 48.2 (CH_2), 48.2 (CH_2), 47.9 (CH_2).

IR (film): 3735, 3649, 3004, 2354, 1733, 1683, 1642, 1506, 1455, 1266 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{17}H_{16}FN_3O_2$ $[M]^+$: 313.1227. Found: 313.1206.



1-Benzyl-4-(3-methoxybenzyl)-1,2,4-triazinane-3,6-dione (SI6): Synthesized according to general procedure **J** using 3-methoxybenzylamine (0.102 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 then 2% MeOH/CH_2Cl_2) to yield an amorphous white solid (0.0482 g, 37%).

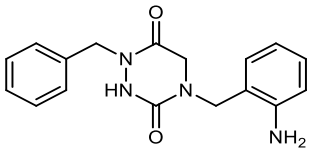
TLC R_f : 0.55 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.53 (br s, 1H), 7.26-7.35 (m, 6H), 6.87-6.80 (m, 3H), 4.68 (s, 2H), 4.37 (s, 2H), 3.79 (s, 2H), 3.73 (s, 3H).

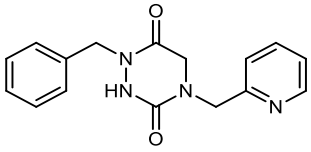
^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4 (C), 159.4 (C), 154.9 (C), 138.3 (C), 135.8 (C), 129.7 (CH), 128.5 (CH), 127.5 (CH), 127.3 (CH), 120.0 (CH), 113.5 (CH), 112.8 (CH), 55.0 (CH_3), 48.5 (CH_2), 48.3 (CH_2), 48.2 (CH_2).

IR (film): 3726, 1791, 1772, 1733, 1684, 1662, 1647, 1488, 1455, 1212 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{18}H_{19}N_3O_3$ $[M]^+$: 325.1426. Found: 325.1442



4-(2-Aminobenzyl)-1-benzyl-1,2,4-triazinane-3,6-dione (8h): Synthesized according to general procedure **J** using 2-aminobenzylamine (0.0977 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 then 2% MeOH/CH_2Cl_2) to yield an amorphous white solid with minor impurities (presumably phenol). TLC Rf = 0.32 in 50% EtOAc/CH_2Cl_2. 50% yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.



1-Benzyl-4-(pyridin-2-ylmethyl)-1,2,4-triazinane-3,6-dione (8i): Synthesized according to general procedure **J** using 2-picolylamine (0.0865 g, 0.800 mmol). The title compound was purified by column chromatography (100% EtOAc then 5% CH_3OH/CH_2Cl_2) to yield an amorphous white solid (0.0870 g, 73%).

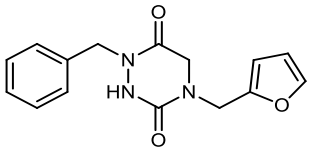
TLC R_f : 0.18 in 5% CH_3OH/CH_2Cl_2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.52 (br s, 1H), 8.46-8.58 (m, 1H), 7.76 (td, *J* = 7.69, 1.86 Hz, 1H), 7.26-7.43 (m, 6H), 7.22 (d, *J* = 7.8 Hz, 1H), 4.70 (s, 2H), 4.51 (s, 2H), 3.99 (s, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4 (C), 156.7 (C), 154.8 (C), 136.8 (C), 135.8 (CH), 128.5 (CH), 127.6 (CH), 127.5 (CH), 122.4 (CH), 121.5 (CH), 50.5 (CH_2), 49.4 (CH_2), 48.2 (CH_2).

IR (film): 3735, 3670, 3035, 2349, 1733, 1683, 1652, 1647, 1525, 1506, 1455, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{16}H_{16}N_4O_2$ $[M]^+$: 296.1273. Found: 296.1266.



1-Benzyl-4-(furan-2-ylmethyl)-1,2,4-triazinane-3,6-dione (8j): Synthesized according to general procedure **J** using furfurylamine (0.0777 g, 0.800 mmol). The title compound was purified by column chromatography (20% EtOAc/CH_2Cl_2 to 50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0719 g, 63%).

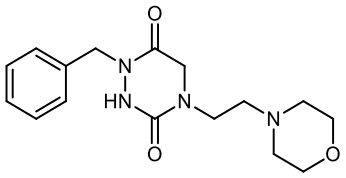
TLC R_f : 0.62 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 1.86, 0.9 Hz, 1H), 7.20-7.40 (m, 5H), 6.42 (dd, *J* = 3.14, 2.0 Hz, 1H), 6.35 (dd, *J* = 3.23, 0.5 Hz, 1H), 4.67 (s, 2H), 4.41 (s, 2H), 3.83 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (C), 155.2 (C), 135.9 (C), 128.4 (CH), 127.5 (CH), 127.4 (CH), 52.4 (CH_2), 49.2 (CH_2), 48.2 (CH_2), 26.1 (CH), 19.7 (CH_3).

IR (film): 3861, 3736, 3649, 1739, 1683, 1652, 1647, 1506, 1456, 1265 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{15}N_3O_3$ $[M]^+$: 285.1113. Found: 285.1115.



1-Benzyl-4-(2-morpholinoethyl)-1,2,4-triazinane-3,6-dione (8k): Synthesized according to general procedure **J** using 4-(2-aminoethyl)morpholine (0.104 g, 0.800 mmol). The title

compound was purified by column chromatography (100% EtOAc/CH_2Cl_2 then 2% CH_3OH/CH_2Cl_2) to yield an amorphous white solid (0.0980 g, 77%).

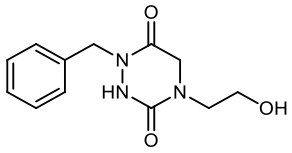
TLC R_f : 0.12 in 2% CH_3OH/CH_2Cl_2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.31 (br s, 1H), 7.22-7.37 (m, 5H), 4.66 (s, 2H), 3.97 (s, 2H), 3.53 (t, *J* = 4.5 Hz, 4H), 3.31 (t, *J* = 6.4 Hz, 2H), 2.29-2.45 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5 (C), 154.7 (C), 135.9 (C), 128.4 (CH), 127.5 (CH), 66.3 (CH_2), 55.4 (CH_2), 53.3 (CH_2), 49.1 (CH_2), 48.1 (CH_2), 42.3 (CH_2).

IR (film): 3735, 2943, 1772, 1733, 1716, 1683, 1647, 1515, 1488, 1456, 1338, 1263, 1244, 1188, 1114, 1070 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{16}H_{22}N_4O_3$ $[M]^+$: 318.1692. Found: 318.1688.



1-Benzyl-4-(2-hydroxyethyl)-1,2,4-triazinane-3,6-dione (8l): Synthesized according to general procedure **J** using ethanolamine (0.0489 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 then 10% MeOH/CH_2Cl_2) to yield an amorphous white solid (0.0430 g, 43%).

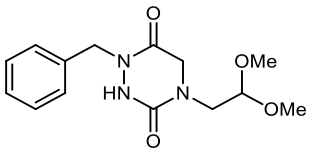
TLC R_f : 0.45 in 10% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz , DMSO-d_6,): δ 9.30 (br s, 1H), 7.24-7.39 (m, 6H), 4.73 (t, *J* = 5.4 Hz, 1H), 4.67 (s, 2H), 3.98 (s, 2H), 3.51 (q, *J* = 5.5 Hz, 2H), 3.25 (t, *J* = 5.8 Hz, 2H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 160.1 (C), 156.0 (C), 133.9 (C), 128.9 (CH), 128.5 (CH), 127.4 (CH), 60.5 (CH_2), 50.3 (CH_2), 49.5 (CH_2), 49.4 (CH).

IR (film): 3683, 3010, 1868, 1739, 1683, 1652, 1533, 1458, 1419, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{15}N_3O_3$ $[M]^+$: 249.1113. Found: 249.1129.



1-Benzyl-4-(2,2-dimethoxyethyl)-1,2,4-triazinane-3,6-dione (8m): Synthesized according to general procedure **J** using aminoacetaldehyde dimethyl acetal (0.0841 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0730 g, 62%).

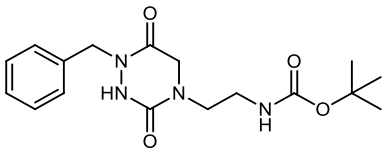
TLC R_f : 0.38 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.45 (br s, 1H), 7.22-7.39 (m, 5H), 4.67 (s, 2H), 4.48 (t, *J* = 5.5 Hz, 1H), 3.96 (s, 2H), 3.23-3.32 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (C), 155.2 (C), 135.9 (C), 128.4 (CH), 127.5 (CH), 127.4 (CH), 52.4 (CH_2), 49.2 (CH_2), 48.2 (CH_2), 26.1 (CH), 19.7 (CH_3).

IR (film): 3735, 2935, 1683, 1662, 1647, 1506, 1456, 1265, 1191, 1118, 1047, 1051 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{19}N_3O_4$ $[M]^+$: 293.1376. Found: 293.1379.



***tert*-Butyl (2-(1-benzyl-3,6-dioxo-1,2,4-triazinan-4-yl)ethyl)carbamate (8n):** Synthesized according to general procedure **J** using *N*-Boc-ethylenediamine (0.128 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0850 g, 61%).

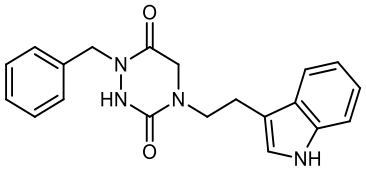
TLC R_f : 0.18 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (br s, 1H), 7.31-7.39 (m, 5H), 4.89 (br s, 1H), 4.78 (s, 2H), 4.00 (s, 2H), 3.40-3.43 (m, 2H), 3.30-3.32 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (C), 155.2 (C), 135.9 (C), 128.4 (CH), 127.5 (CH), 127.4 (CH), 52.4 (CH_2), 49.2 (CH_2), 48.2 (CH_2), 26.1 (CH), 19.7 (CH_3).

IR (film): 3735, 3666, 3461, 1718, 1683, 1588, 1647, 1506, 1436, 1266 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{17}H_{24}N_4O_4$ $[M]^+$: 348.1798. Found: 348.1790.



4-(2-(1H-Indol-3-yl)ethyl)-1-benzyl-1,2,4-triazinane-3,6-dione (8o): Synthesized according to general procedure **J** using tryptamine (0.128 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 then 2% CH_3OH/CH_2Cl_2) to yield an amorphous white solid (0.0795 g, 57%).

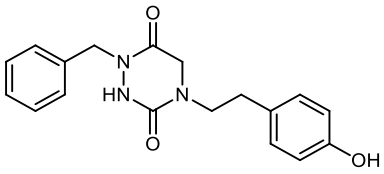
TLC R_f : 0.25 in 2% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (br s, 1H), 7.73 (br s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.26-7.37 (m, 6H), 7.18 (td, *J* = 7.6, 1.1 Hz, 1H), 7.09 (td, *J* = 7.6, 1.1 Hz, 1H), 6.97 (d, *J* = 2.3 Hz, 1H), 4.70 (s, 2H), 3.78 (s, 2H), 3.59 (t, *J* = 7.3 Hz, 2H), 3.02 (t, *J* = 7.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5 (C), 154.7 (C), 136.2 (C), 135.9 (C), 128.4 (CH), 127.4 (CH), 127.1 (C), 122.7 (C), 120.9 (C), 118.3 (C), 118.3 (C), 111.4 (C), 111.1 (CH), 48.7 (CH_2), 48.0 (CH_2), 46.3 (CH_2), 22.6 (CH_2), 19.7 (CH_3).

IR (film): 3735, 3670, 1739, 1683, 1644, 1539, 1506, 1456, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{20}H_{20}N_4O_2$ $[M]^+$: 348.1586. Found: 348.1598.



1-Benzyl-4-(4-hydroxyphenethyl)-1,2,4-triazinane-3,6-dione (8p): Synthesized according to general procedure **J** using tyramine (0.109 g, 0.800 mmol). The title compound precipitated out of solution in 100% CH_2Cl_2 as a white solid to give pure product after aqueous extraction (0.0547 g, 42%).

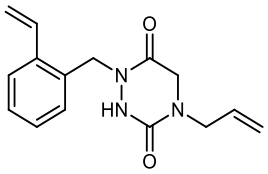
TLC R_f : 0.33 in 5% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.31 (br s, 1H), 9.20 (br s, 1H), 7.32 (s, 3H), 7.22 (s, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 8.4 Hz, 2H), 4.64 (s, 2H), 3.86 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4 (C), 155.7 (C), 154.6 (C), 135.8 (C), 129.5 (CH), 128.9 (C), 128.4 (CH), 127.5 (CH), 127.4 (CH), 115.2 (CH), 48.7 (CH_2), 48.0 (CH_2), 47.2 (CH_2), 31.8 (CH_2).

IR (film): 3853, 3735, 3020, 2347, 1739, 1683, 1648, 1525, 1506, 1456, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{18}H_{19}N_3O_3$ $[M]^+$: 325.1426. Found: 325.1428.



4-Allyl-1-(2-vinylbenzyl)-1,2,4-triazinane-3,6-dione (8q): Synthesized according to general procedure **J** using carbazate **1b** (0.107 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 50% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.0597 g, 55%).

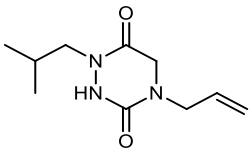
TLC R_f : 0.18 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.38 (s, 1H), 7.56 (s, 1H), 7.26-7.34 (m, 2H), 7.19 (s, 1H), 7.01 (s, 1H), 5.72 (dd, *J* = 17.4, 1.4 Hz, 2H), 5.34 (dd, *J* = 11.1, 1.3 Hz, 1H), 5.16-5.24 (m, 2H), 4.76 (s, 2H), 3.78-3.86 (m, 4H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 160.6 (C), 154.4 (C), 136.0 (C), 133.6 (CH), 132.7 (C), 132.4 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 125.7 (CH), 117.9 (CH_2), 116.7 (CH_2), 48.0 (CH_2), 47.6 (CH_2), 45.9 (CH_2).

IR (film): 3718, 3336, 2993, 1695, 1683, 1662, 1653, 1647, 1636, 1506, 1456, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{17}N_3O_2$ $[M]^+$: 271.1321. Found: 271.1307.



4-Allyl-1-isopropyl-1,2,4-triazinane-3,6-dione (8r): Synthesized according to general procedure **J** using carbazate **1c** (0.0830 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 50% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.0610 g, 72%).

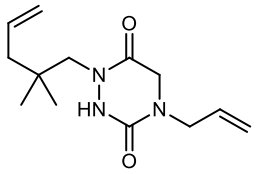
TLC R_f : 0.25 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.30 (br s, 1H), 5.75 (ddt, *J* = 17.6, 9.8, 5.8 Hz, 1H), 5.23-5.16 (m, 2H), 3.82 (dt, *J* = 5.8, 1.4 Hz, 1H), 3.73 (s, 2H), 3.33 (d, *J* = 7.5 Hz, 2H), 2.02 (dq, *J* = 13.6, 7.0 Hz, 1H), 0.82 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 160.3 (C), 154.8 (C), 132.8 (CH), 117.8 (CH_2), 51.6 (CH_2), 48.2 (CH_2), 47.5 (CH_2), 25.7 (CH), 19.5 (CH_3).

IR (film): 3749, 3710, 2960, 2358, 1747, 1733, 1683, 1647, 1489, 1417, 1266 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{17}N_3O_2$ $[M]^+$: 211.1321. Found: 211.1327.



4-Allyl-1-(2,2-dimethylpent-4-en-1-yl)-1,2,4-triazinane-3,6-dione (8s): Synthesized according to general procedure **J** using carbazate **1d** (0.0993 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 30% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.0704 g, 70%).

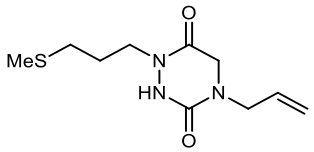
TLC R_f : 0.62 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.17 (s, 1H), 5.69-5.90 (m, 2H), 5.14-5.27 (m, 2H), 4.97-5.10 (m, 2H), 3.82 (d, *J* = 5.7 Hz, 2H), 3.73 (s, 2H), 1.90-2.02 (m, 2H), 0.87 (s, 6H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7 (C), 155.0 (C), 134.8 (CH), 132.9 (CH), 117.6 (CH_2), 54.4 (CH_2), 48.4 (CH_2), 47.5 (CH_2), 44.6 (CH_2), 35.9 (C), 25.1 (CH_3).

IR (film): 3735, 3639, 2966, 1733, 1689, 1647, 1515, 1466, 1267 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{21}N_3O_2$ $[M]^+$: 251.1634. Found: 251.1622.



4-Allyl-1-(3-(methylthio)propyl)-1,2,4-triazinane-3,6-dione (8t): Synthesized according to general procedure **J** using carbazate **1e** (0.0960 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 60% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.0570 g, 62%).

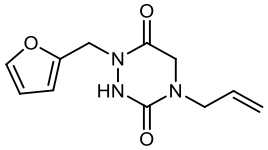
TLC R_f : 0.22 in 60% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.33 (br s, 1H), 5.82-5.68 (m, 1H), 5.23-5.16 (m, 2H), 3.81 (dt, *J* = 5.9, 1.3 Hz, 2H), 3.73 (s, 2H), 3.56 (t, *J* = 7.0 Hz, 2H), 2.43-2.38 (m, 2H), 2.03 (s, 3H), 1.80 (quint, *J* = 7.2 Hz, 2H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 160.3 (C), 154.7 (C), 132.8 (CH), 117.9 (CH_2), 48.1 (CH_2), 47.6 (CH_2), 44.1 (CH_2), 30.1 (CH_2), 25.9 (CH_2), 14.6 (CH_3).

IR (film): 3853, 3735, 1747, 1733, 1718, 1683, 1662, 1647, 1506, 1266 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{17}N_3O_2S$ $[M]^+$: 243.1041. Found: 243.1041.



4-Allyl-1-(furan-2-ylmethyl)-1,2,4-triazinane-3,6-dione (8u): Synthesized according to general procedure **J** using carbazate **1f** (0.0930 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 50% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.0560 g, 60%).

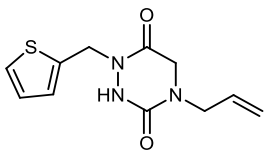
TLC R_f : 0.21 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.38 (br s, 1H), 7.61 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.42 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.36 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.80.-5.66 (m, 1H), 5.19-5.12 (m, 2H), 4.66 (s, 2H), 3.80-3.77 (m, 4H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 160.6 (C), 154.6 (C), 148.8 (C), 142.9 (CH), 132.7 (CH), 117.8 (CH_2), 110.5 (CH), 109.1 (CH), 48.1 (CH_2), 47.6 (CH_2), 41.5 (CH_2).

IR (film): 3735, 2993, 1733, 1683, 1662, 1651, 1647, 1521, 1506, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{13}N_3O_3$ $[M]^+$: 235.0957. Found: 235.0956.



4-Allyl-1-(thiophen-2-ylmethyl)-1,2,4-triazinane-3,6-dione (8v): Synthesized according to general procedure **J** using carbazate **1g** (0.0990 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture

was purified by silica gel column chromatography using 50% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.0610 g, 61%).

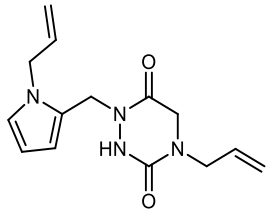
TLC R_f : 0.33 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.14 (br s, 1H), 7.46 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.08 (dd, *J* = 3.4, 1.1 Hz, 1H), 6.98 (dd, *J* = 5.0, 3.4 Hz, 1H), 5.78-5.65 (m, 1H), 5.17-5.10 (m, 2H), 4.81 (s, 2H), 3.79-3.74 (m, 4H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 160.3 (C), 154.6 (C), 137.4 (C), 132.7 (CH), 127.6 (CH), 126.6 (CH), 126.4 (CH), 117.8 (CH_2), 48.1 (CH_2), 47.6 (CH_2), 43.3 (CH_2).

IR (film): 3745, 3735, 3666, 2358, 1733, 1683, 1662, 1655, 1647, 1506, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{13}N_3O_2S$ $[M]^+$: 251.0728. Found: 251.0732.



4-Allyl-1-((1-allyl-1*H*-pyrrol-2-yl)methyl)-1,2,4-triazinane-3,6-dione (8w): Synthesized according to general procedure **J** using carbazate **1h** (0.109 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 50% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.0735 g, 67%).

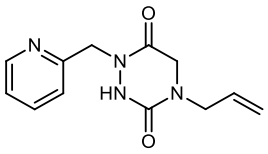
TLC R_f : 0.45 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 6.70 (dd, *J* = 2.6, 1.9 Hz, 1H), 6.14 (dd, *J* = 3.5, 1.8 Hz, 1H), 5.97 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.83-5.94 (m, 1H), 5.66-5.77 (m, 1H), 5.19 (d, *J* = 0.8 Hz, 1H), 5.13-5.17 (m, 1H), 5.05 (dd, *J* = 10.3, 1.7 Hz, 1H), 4.78 (dd, *J* = 17.0, 1.6 Hz, 1H), 4.60 (s, 2H), 4.55 (dt, *J* = 5.0, 1.6 Hz, 2H), 3.77 (dt, *J* = 6.0, 1.2 Hz, 2H), 3.74 (s, 2H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 159.7 (C), 154.2 (C), 135.6 (CH), 132.7 (CH), 125.5 (C), 122.3 (CH), 118.0 (CH_2), 115.5 (CH_2), 110.2 (CH), 106.9 (CH), 48.5 (CH_2), 48.0 (CH_2), 47.6 (CH_2), 40.3 (CH_2).

IR (film): 3733, 3020, 1747, 1716, 1683, 1657, 1647, 1506, 1456, 1398, 1263, 1244, 1186 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{18}N_4O_2$ $[M]^+$: 274.1430. Found: 274.1418.



4-Allyl-1-(pyridin-2-ylmethyl)-1,2,4-triazinane-3,6-dione (8x): Synthesized according to general procedure **J** using carbazate **1i** (0.0970 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 10% MeOH/CH_2Cl_2 to afford the pure compound as a colorless oil (0.0550 g, 56%).

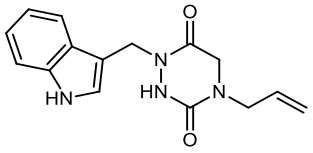
TLC R_f : 0.17 in 10% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.38 (br s, 1H), 8.50-8.47 (m, 1H), 7.76 (td, *J* = 7.7, 1.8 Hz, 1H), 7.27 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.20 (d, *J* = 7.8 Hz 1H), 5.81-5.68 (m, 1H), 5.25-5.15 (m, 2H), 4.75 (s, 2H), 3.82-3.80 (m, 4H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 160.9 (C), 155.1 (C), 154.5 (C), 149.2 (CH), 136.9 (CH), 132.8 (CH), 122.6 (CH), 121.0 (CH), 117.8 (CH_2), 49.8 (CH_2), 48.1 (CH_2), 47.7 (CH_2).

IR (film): 3733, 3610, 3033, 1731, 1706, 1680, 1649, 1642, 1506, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{14}N_4O_2$ $[M]^+$: 246.1117. Found: 246.1115.



1-((1H-Indol-3-yl)methyl)-4-allyl-1,2,4-triazinane-3,6-dione (8y): Synthesized according to general procedure **J** using carbazate **1j** (0.113 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/ CH_2Cl_2) to yield an amorphous white solid (0.0705 g, 62%).

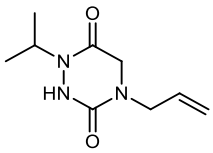
TLC R_f : 0.37 in 50% EtOAc/ CH_2Cl_2.

^{1}H NMR (400 MHz, DMSO-d_6): □ ppm 10.99 (br s, 1H), 9.21 (br s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.27-7.39 (m, 2H), 7.01-7.11 (m, 1H), 6.89-6.99 (m, 1H), 5.55-5.69 (m, 1H), 4.98-5.13 (m, 2H), 4.75 (s, 2H), 3.56-3.75 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1 (C), 155.0 (C), 136.7 (C), 133.1 (CH), 126.8 (C), 126.5 (CH), 121.8 (CH), 119.4 (CH), 119.3 (CH), 118.2 (CH_2), 112.0 (CH), 109.1 (C), 48.6 (CH_2), 47.9 (CH_2), 40.5 (CH), 19.7 (CH_3).

IR (film): 3861, 3735, 3082, 1772, 1739, 1683, 1653, 1533, 1506, 1456, 1266 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{16}N_4O_2$ $[M]^+$: 284.1273. Found: 284.1263.



4-Allyl-1-isopropyl-1,2,4-triazinane-3,6-dione (8z): Synthesized according to general procedure **J** using carbazate **1k** (0.0780 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 16 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 50% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.0520 g, 66%).

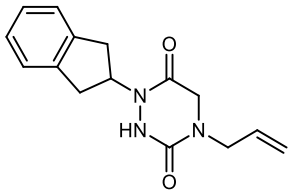
TLC R_f : 0.18 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.07 (br s, 1H), 5.82-5.69 (m, 1H), 5.22-5.14 (m, 2H), 4.60 (sept, *J* = 6.8 Hz, 1H), 3.80 (d, *J* = 5.8 Hz, 2H), 3.68 (s, 2H), 1.14 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 160.8 (C), 155.5 (C), 132.9 (CH), 117.8 (CH_2), 49.4 (CH_2), 47.6 (CH_2), 46.0 (CH_2), 18.5 (CH_3).

IR (film): 3849, 3715, 2946, 2356, 1757, 1744, 1683, 1647, 1489, 1447, 1266 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{15}N_3O_2$ $[M]^+$: 197.1164. Found: 197.1162.



4-Allyl-1-(2,3-dihydro-1*H*-inden-2-yl)-1,2,4-triazinane-3,6-dione (8aa): Synthesized according to general procedure **J** using carbazate **1l** (0.107 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 72 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 30% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.0600 g, 55%).

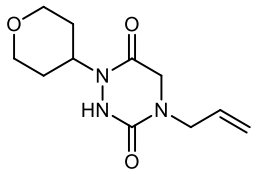
TLC R_f : 0.36 in 30% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.07 (br s, 1H), 5.82-5.69 (m, 1H), 5.22-5.14 (m, 2H), 4.60 (sept, *J* = 6.8 Hz, 1H), 3.80 (d, *J* = 5.8 Hz, 2H), 3.68 (s, 2H), 1.14 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 162.2 (C), 155.4 (C), 140.4 (C), 132.8 (CH), 126.5 (CH), 124.4 (CH), 118.0 (CH), 54.2 (CH), 49.0 (CH_2), 47.8 (CH_2), 34.2 (CH_2).

IR (film): 3851, 3751, 3735, 3649, 3072, 1747, 1733, 1688, 1662, 1647, 1533, 1506, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{17}N_3O_2$ $[M]^+$: 271.1321. Found: 271.1322.



4-Allyl-1-(tetrahydro-2H-pyran-4-yl)-1,2,4-triazinane-3,6-dione (8ab): Synthesized according to general procedure **J** using carbazate **1m** (0.0960 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 16 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 100% EtOAc to afford the pure compound as a white solid (0.0570 g, 60%).

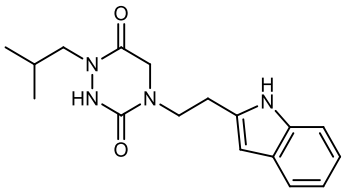
TLC R_f : 0.14 in 100% EtOAc.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.14 (br s, 1H), 5.82-5.69 (m, 1H), 5.22-5.14 (m, 2H), 4.44 (tt, *J* = 12.1, 4.2 Hz, 1H), 3.89 (dd, *J* = 11.2, 4.4 Hz, 2H), 3.80 (dt, *J* = 5.9, 1.3 Hz, 2H), 3.72 (s, 2H), 3.38-3.30 (m, 2H), 1.95 (qd, *J* = 12.4, 4.7 Hz, 2H), 1.43 (dd, *J* = 12.2, 2.3 Hz, 2H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7 (C), 155.4 (C), 132.8 (CH), 117.9 (CH_2), 66.2 (CH_2), 51.5 (CH_2), 48.5 (CH_2), 47.7 (CH_2), 28.6 (CH_2).

IR (film): 3851, 3735, 1730, 1714, 1683, 1655, 1647, 1506, 1265 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{17}N_3O_3$ $[M]^+$: 239.1270. Found: 239.1279.



4-(2-(1H-Indol-2-yl)ethyl)-1-isobutyl-1,2,4-triazinane-3,6-dione (8ac): Synthesized according to general procedure **J** using carbazate **1c** (0.0830 g, 0.400 mmol), tryptamine (0.128 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 3% MeOH/CH_2Cl_2 to afford the pure compound as a white solid (0.0654 g, 52%).

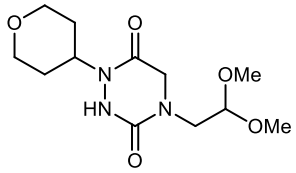
TLC R_f : 0.10 in 3% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (br s, 1H), 8.08 (br s, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.37 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.21 (td, *J* = 7.6, 1.2 Hz, 1H), 7.13 (td, *J* = 7.6, 1.2 Hz, 1H), 7.05 (d, *J* = 2.2 Hz, 1H), 3.80 (s, 2H), 3.65 (t, *J* = 7.3 Hz, 2H), 3.44 (d, *J* = 7.5 Hz, 2H), 3.07 (t, *J* = 7.3 Hz, 2H), 2.00-2.21 (sept, 1H), 0.93 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7 (C), 155.8 (C), 136.3 (C), 127.2 (C), 122.3 (CH), 121.9 (CH), 119.6 (CH), 118.5 (CH), 112.4 (C), 111.3 (CH), 53.1 (CH_2), 49.9 (CH_2), 47.43 (CH_2), 26.3 (CH), 23.4 (CH_2), 19.7 (CH_3).

IR (film): 3865, 3735, 2993, 1733, 1683, 1652, 1647, 1506, 1456, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{17}H_{22}N_4O_2$ $[M]^+$: 314.1743. Found: 314.1753.



4-(2,2-Dimethoxyethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,2,4-triazinane-3,6-dione (8ad): Synthesized according to general procedure **J** using carbazate **1m** (0.0960 g, 0.400 mmol), aminoacetaldehyde dimethyl acetal (0.0840 g, 0.800 mmol). The acylation was allowed to stir for 16 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 3% MeOH/CH_2Cl_2 to afford the pure compound as a white solid (0.0400 g, 35%).

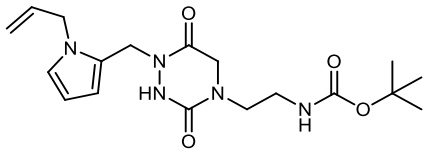
TLC R_f : 0.10 in 3% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.12 (br s, 1H), 4.49 (t, *J* = 5.5 Hz, 1H), 4.45-4.37 (m, 1H), 3.92-3.84 (m, 4H), 3.38-3.26 (m, 10H), 2.04-1.87 (m, 2H), 1.42 (dd, *J* = 12.5, 2.7 Hz, 2H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7 (C), 155.6 (C), 102.0 (CH), 66.2 (CH_2), 53.7 (CH_3), 51.5 (CH), 50.3 (CH_2), 47.0 (CH_2), 28.6 (CH_2).

IR (film): 3735, 3004, 2354, 1730, 1718, 1683, 1653, 1647, 1506, 1423, 1386, 1299, 1266, 1203, 1147, 1126, 1085, 1070, 1051, 1008 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{21}N_3O_5$ $[M]^+$: 287.1481. Found: 287.1456.



***tert*-Butyl(2-(1-((1-allyl-1*H*-pyrrol-2-yl)methyl)-3,6-dioxo-1,2,4-triazinan-4-yl)ethyl) carbamate (8ae):** Synthesized according to general procedure **J** using carbazate **1h** (0.109 g, 0.400 mmol), *N*-Boc ethylenediamine (0.128 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 100% EtOAc to afford the pure compound as a white solid (0.0700 g, 46%).

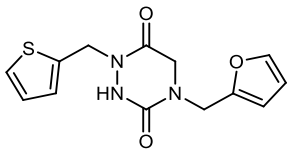
TLC R_f : 0.38 in 100% EtOAc.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.03 (br s, 1H), 6.81 (t, *J* = 5.6 Hz, 1H), 6.69 (dd, *J* = 2.7, 1.8 Hz, 1H), 6.15 (dd, *J* = 3.5, 1.8 Hz, 4H), 5.96 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.93-5.83 (m, 1H), 5.06 (dd, *J* = 10.3, 1.6 Hz, 1H), 4.77 (dd, *J* = 17.1, 1.6 Hz), 4.59-4.55 (m, 4H), 3.86 (s, 2H), 3.22-3.18 (m, 2H), 3.07-3.03 (m, 2H), 1.36 (s, 9H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 159.4 (C), 154.3 (C), 135.6 (CH), 125.5 (C), 122.3 (CH), 115.4 (CH_2), 100.3 (CH), 47.0 (CH_2), 106.9 (CH), 77.7 (C), 48.9 (CH_2), 48.5 (CH_2), 45.3 (CH_2), 40.3 (CH_2), 38.7 (CH_2), 28.2 (CH_3).

IR (film): 3853, 3751, 3735, 3629, 1733, 1683, 1647, 1521, 1394, 1265, 1232, 1151 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{18}H_{27}N_5O_4$ $[M]^+$: 377.2063. Found: 377.2047.



4-(Furan-2-ylmethyl)-1-(thiophen-2-ylmethyl)-1,2,4-triazinane-3,6-dione (8af): Synthesized according to general procedure **J** using carbazate **1g** (0.0973 g, 0.400 mmol), furfurylamine (0.0780 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 50% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.0800 g, 69%).

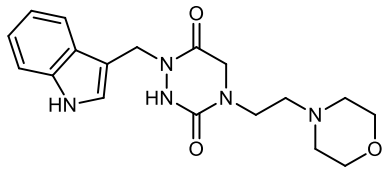
TLC R_f : 0.36 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.56 (br s, 1H), 7.60 (d, *J* = 0.9 Hz, 1H), 7.46 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.07 (d, 3.3 Hz, 1H), 6.98 (dd *J* = 5.1, 3.5 Hz, 1H), 6.50 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.32 (d, *J* = 2.8 Hz, 1H), 4.80 (s, 2H), 4.38 (s, 2H), 3,78 (s, 2H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 160.0 (C), 154.4 (C), 150.0 (C), 142.9 (CH), 137.3 (C), 127.6 (CH), 126.7 (CH), 126.4 (CH), 110.5 (CH), 108.7 (CH), 48.1 (CH_2), 43.3 (CH_2), 41.6 (CH_2).

IR (film): 3853, 3735, 3651, 1772, 1743, 1733, 1683, 1662, 1652, 1555, 1506, 1456, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{13}N_3O_3S$ $[M]^+$: 291.0678. Found: 291.0684.



1-((1H-indol-3-yl)methyl)-4-(2-morpholinoethyl)-1,2,4-triazinane-3,6-dione (8ag): Synthesized according to general procedure **J** using carbazate **1j** (0.113 g, 0.400 mmol), 4-(2-aminoethyl)morpholine (0.104 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 100% EtOAc then 5% CHOH/CH_2Cl_2 to afford the pure compound as a white solid (0.872 g, 61%).

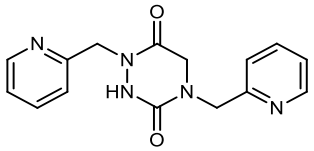
TLC R_f : 0.44 in 5% CHOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (br s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.09-7.23 (m, 4H), 4.94 (s, 2H), 3.99 (s, 2H), 3.56-3.74 (m, 4H), 3.37 (t, *J* = 6.2 Hz, 2H), 2.33-2.58 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6 (C), 154.9 (C), 136.5 (C), 126.3 (C), 125.5 (CH), 123.0 (CH), 120.5 (CH), 119.2 (CH), 111.5 (CH), 108.0 (C), 66.9 (CH_2), 56.1 (CH_2), 53.6 (CH_2), 50.1 (CH_2), 43.2 (CH_2), 41.1 (CH_2).

IR (film): 3751, 3735, 3670, 1683, 1647, 1506, 1455, 1266, 1186, 1116 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{18}H_{23}N_5O_3$ $[M]^+$: 357.1801. Found: 357.1828.



1,4-Bis(pyridin-2-ylmethyl)-1,2,4-triazinane-3,6-dione (8ah): Synthesized according to general procedure **J** using carbazate **1i** (0.0970 g, 0.400 mmol), 2-picolylamine (0.0865 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 50% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.0392 g, 33%).

TLC R_f : 0.36 in 50% EtOAc/ CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (br s, 1H), 8.49-8.61 (m, 2H), 7.62-7.77 (m, 2H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.27 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 7.22 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 4.90 (s, 2H), 4.63 (s, 2H), 4.00 (s, 2H).

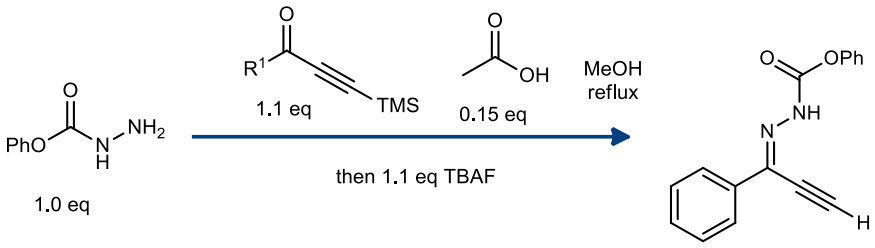
^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5 (C), 155.7 (C), 154.6 (C), 154.5 (C), 149.4 (CH), 149.3 (CH), 137.5 (CH), 137.0 (CH), 123.3 (CH), 122.8 (CH), 122.6 (CH), 122.5 (CH), 51.6 (CH_2), 49.5 (CH_2), 49.2 (CH_2).

IR (film): 3735, 3612, 3043, 1733, 1716, 1683, 1662, 1652, 1506, 1263 cm^{-1}.

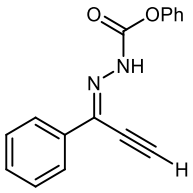
HRMS (EI): Exact mass calcd for $C_{15}H_{15}N_5O_2$ $[M]^+$: 297.1226. Found: 297.1213.

Synthesis of ynone *N*-isocyanate precursors

General procedure L: (Reductive Amination and Silyl-Deprotection Sequence)



An oven-dried round bottomed flask was charged with a stir bar, phenylcarbazate (1.00 equiv.), a ketone (1.10 equiv.), acetic acid (0.150 equiv.), and MeOH (0.3 M). The contents were refluxed for 16 hours. The crude mixture was concentrated under reduced pressure and dissolved in a 99:1 THF:MeOH solution (0.1 M). TBAF (1.10 equiv.) was added dropwise at –78 °C, and the resulting solution was stirred for 15 minutes. The reaction was quenched with a saturated aqueous solution of NH_4Cl and the organic phase was extracted with CH_2Cl_2. The reaction was concentrated under reduced pressure and purification by silica gel column chromatography or recrystallization gave the corresponding hydrazones.



(*E*)-Phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (11a): Synthesized according to general procedure **L** using phenylcarbazate (1.90 g, 12.5 mmol), 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-one[287] (2.78 g, 13.8 mmol), acetic acid (0.113 g, 0.150 mmol), and CH_3OH (42 mL, 0.3 M). TBAF (13.8 mL of a 1 M solution in THF, 13.8 mmol) was added dropwise at -78 °C. The reaction was quenched after 15 minutes and the organic phase was extracted with CH_2Cl_2. The crude mixture was purified by silica gel column chromatography using 40% hexanes/CH_2Cl_2 to afford the pure compound as an amorphous pale yellow solid (2.80 g, 85% over 2 steps).

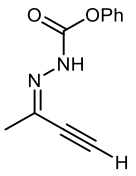
TLC R_f : 0.35 in 40% hexanes/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 9.15 (br s, 1H), 8.00 (dt, *J* = 3.9, 2.8 Hz, 2H), 7.44-7.40 (m, 5H), 7.29-7.24 (m, 3H), 4.09 (s, 1H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 133.7 (C), 130.4 (CH), 129.6 (CH), 128.6 (CH), 126.8 (CH), 126.1 (CH), 121.6 (CH), 93.1 (C), 72.5 (CH).

IR (film): 1770, 1737, 1683, 1481, 1455, 1423, 1363, 1348, 1257, 1249, 1191, 1114 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{16}H_{12}N_2O_2$ $[M]^+$: 264.0899. Found: 264.0895.



(*Z*)-Phenyl-2-(but-3-yn-2-ylidene)hydrazinecarboxylate (11b): Synthesized according to general procedure **L** using phenylcarbazate (1.52 g, 10.0 mmol), 4-(trimethylsilyl)but-3-yn-2-one (1.40 g, 10.0 mmol), and CH_3OH (50 mL, 0.2 M). TBAF (10.0 mL of a 1M solution in THF, 10.0 mmol) was added dropwise at -78 °C. The reaction was quenched after 15 minutes and the organic phase was extracted with CH_2Cl_2. The crude mixture was purified by silica gel column chromatography using CH_2Cl_2 to afford the pure compound as an amorphous pale yellow solid (1.70 g, 84%).

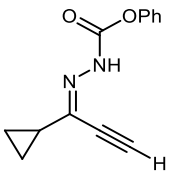
TLC R_f : 0.31 in CH_2Cl_2.

^{1}H NMR (300 MHz; DMSO-d_6): δ 10.40 (br s, 1H), 7.46-7.39 (m, 2H), 7.29-7.23 (m, 1H), 7.21-7.17 (m, 2H), 5.13 (s, 1H), 2.10 (s, 3H).

^{13}C NMR (75 MHz; DMSO-d_6): δ 151.7 (C), 150.4 (C), 129.5 (CH), 125.6 (CH), 121.8 (CH), 93.9 (C), 74.9 (CH), 22.6 (CH_3).

IR (film): 2966, 1755, 1647, 1627, 1593, 1467, 1387, 1265, 1200, 1132, 1109 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{10}N_2O_2$ $[M]^+$: 202.0747. Found: 202.0754.



(*Z*)-Phenyl-2-(1-cyclopropylprop-2-yn-1-ylidene)hydrazinecarboxylate (11c): Synthesized according to general procedure **L** using phenyl carbazate (1.32 g, 8.70 mmol), 1-cyclopropyl-3-(trimethylsilyl)prop-2-yn-1-one[288] (1.59 g, 9.57 mmol), acetic acid (0.113 g, 0.131 mmol), and CH_3OH (30 mL, 0.3 M). TBAF (9.6 mL of a 1 M solution in THF, 9.6 mmol) was added dropwise at -78 °C. The reaction was quenched after 15 minutes and the organic phase was extracted with CH_2Cl_2. The crude mixture was purified by silica gel column chromatography using a gradient of 100% CH_2Cl_2 to 2.5% CH_3OH/CH_2Cl_2 to afford the pure compound as an amorphous white solid (1.32 g, 66% over 3 steps).

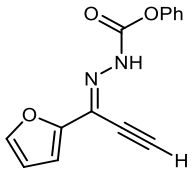
TLC R_f : 0.40 in 2.5% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.77 (br s, 1H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.20 (d, 2H), 3.75 (s, 1H) 2.02-1.99 (m, 1H), 0.90 (ddd, *J* = 9.9, 3.3, 1.2 Hz, 4H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 150.8 (C), 129.6 (CH), 126.0 (CH), 121.5 (CH), 91.3 (C), 71.0 (CH), 16.1 (CH), 6.2 (CH_2).

IR (film): 3244, 2090, 1753, 1733, 1674, 1662, 1505, 1481, 1340, 1199, 1025, 1004 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{12}N_2O_2$ $[M]^+$: 228.0899. Found: 228.0887.



(*E*)-Phenyl-2-(1-(furan-2-yl)prop-2-yn-1-ylidene)hydrazinecarboxylate (11d): Synthesized according to general procedure **L** using phenyl carbazate (0.959 g, 6.31 mmol), 1-furan-3-(trimethylsilyl)prop-2-yn-1-one (1.33 g, 6.94 mmol), acetic acid (0.0570 g, 0.150 mmol), and CH_3OH (21 mL, 0.3 M). TBAF (6.9 mL of a 1 M solution in THF, 6.9 mmol) was added dropwise at -78 °C. The reaction was quenched after 15 minutes and the organic phase was extracted with CH_2Cl_2. The crude mixture was purified by silica gel column chromatography using a gradient of 60% hexanes/CH_2Cl_2 to 40% hexanes/CH_2Cl_2, followed by 100% CH_2Cl_2 to afford the pure compound as an amorphous pale yellow solid (1.39 g, 87% over 2 steps).

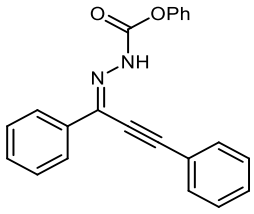
TLC R_f : 0.30 in 40% hexanes/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 9.15 (br s, 1H), 8.00 (dt, *J* = 3.9, 2.8 Hz, 2H), 7.44-7.40 (m, 5H), 7.29-7.24 (m, 3H), 4.09 (s, 1H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 133.7 (C), 130.4 (CH), 129.6 (CH), 128.6 (CH), 126.8 (CH), 126.1 (CH), 121.6 (CH), 93.1 (C), 72.5 (CH).

IR (film): 3004, 2889, 1570, 1541, 1429, 1382, 1371, 1359, 1265, 1253, 1242, 1225, 1199, 1183, 1060, 1037, 1026 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{10}N_2O_3$ $[M]^+$: 254.0691. Found: 254.0723.



(*Z*)-Phenyl 2-(1,3-diphenylprop-2-yn-1-ylidene)hydrazinecarboxylate (11e): Synthesized according to general procedure **L** using phenyl carbazate (1.23 g, 8.12 mmol), 1,3-diphenylprop-2-yn-1-one[289] (1.84 g, 8.93 mmol), acetic acid (0.0730 g, 1.22 mmol), and CH_3OH (30 mL, 0.3 M). The crude mixture was purified by silica gel column chromatography using 5% EtOAc/hexanes to afford the pure compound as a crystalline pale yellow solid (0.911 g, 33%).

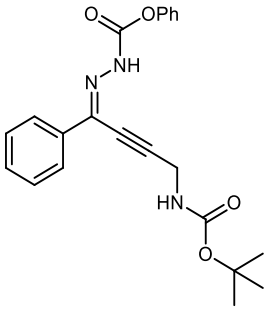
TLC R_f : 0.20 in 10% EtOAc/hexanes.

^{1}H NMR (300 MHz; $CDCl_3$): δ 9.15 (br s, 1H), 8.07-8.05 (m, 2H), 7.66 (m, 2H), 7.48-7.39 (m, 8H), 7.26 (m, 3H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 133.7 (C), 130.4 (CH), 129.6 (CH), 128.6 (CH), 126.8 (CH), 126.1 (CH), 121.6 (CH), 93.1 (C), 72.5 (CH).

IR (film): 3336, 3085, 2198, 1762, 1733, 1716, 1704, 1593, 1506, 1473, 1434, 1357, 1334, 1315, 1307, 1266, 1161 1136, 1070, 1051, 1026, 1002 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{22}H_{16}N_2O_2$ $[M]^+$: 340.1212. Found: 340.1219.



(*Z*)-Phenyl-2-(4-((tert-butoxycarbonyl)amino)-1-phenylbut-2-yn-1-ylidene) hydrazinecarboxylate (11f): Synthesized according to general procedure **L** using phenyl carbazate (0.305 g, 2.00 mmol), *tert*-butyl-(4-oxo-4-phenylbut-2-yn-1-yl)carbamate[289] (0.519 g, 2.00 mmol), and CH_3OH (10 mL, 0.3 M). The crude mixture was purified by silica gel column chromatography using CH_2Cl_2 to afford the pure compound as an amorphous red solid (0.386 g, 49%).

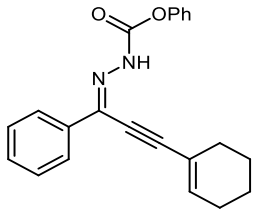
TLC R_f : 0.35 in 40% hexanes/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 9.51 (br s, 1H), 7.96 (ddd, *J* = 5.43, 2.85, 1.29 Hz, 2H), 7.42-7.37 (m, 6H), 7.24 (t, *J* = 7.4 Hz, 3H), 5.17 (s, 1H), 4.23 (d, *J* = 5.71 Hz, 2H), 1.47 (s, 9H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 155.5 (C), 134.0 (C) 130.0 (CH), 129.4 (CH), 128.4 (CH), 126.7 (CH), 125.8 (CH), 121.5 (CH), 102.0 (C), 80.7 (C), 72.2 (C), 31.4 (CH_2), 28.3 (CH_3).

IR (film): 2332, 1689, 1652, 1558, 1508, 1436, 1265, 1195 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{22}H_{23}N_3O_4$ $[M]^+$: 393.1689. Found: 393.1680.



(*Z*)-Phenyl-2-(3-(cyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-ylidene) hydrazinecarboxylate (11g): Synthesized according to general procedure **L** using phenyl carbazate (0.329 g, 2.16 mmol), 3-(cyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-one[290] (0.500 g, 2.38 mmol), acetic acid (0.0200 g, 0.150 mmol), and CH_3OH (7.2 mL, 0.3 M) refluxed at 65 °C. The crude mixture was purified by silica gel column chromatography using 50% hexanes/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.588 g, 79%).

TLC R_f : 0.20 in 50% hexanes/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 9.05 (br s, 1H), 7.98 (m, 2H), 7.43-7.38 (m, 5H), 7.28-7.24 (m, 3H), 6.50 (dt, *J* = 3.9, 2.0 Hz, 1H), 2.34-2.31 (m, 2H), 2.25-2.21 (m, 2H), 1.76-1.65 (m, 4H).

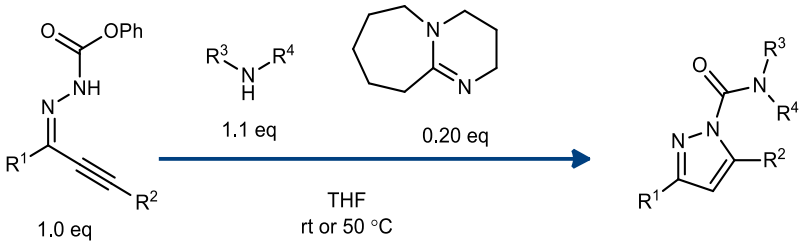
^{13}C NMR (75 MHz; $CDCl_3$): δ 140.4 (C), 130.1 (C), 129.6 (CH), 128.5 (CH), 126.9 (CH), 125.9 (C), 121.7 (C), 119.3 (C), 75.5 (C), 29.0 (CH_2), 26.1 (CH_2), 22.2 (CH_2), 21.3 (CH_2).

IR (film): 2952, 2204, 1766, 1762, 1730, 1718, 1647, 1554, 1506, 1475, 1265, 1186, 1161, 1139 cm^{-1}.

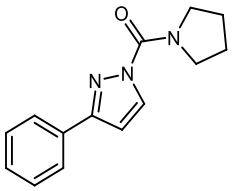
HRMS (EI): Exact mass calcd for $C_{22}H_{20}N_2O_2$ $[M]^+$: 344.1525. Found: 344.1512.

Synthesis of acyl pyrazoles via *N*-isocyanate cascade reactions

General Procedure M: (DBU Catalyzed Synthesis of Acyl Pyrazoles)



An oven-dried round bottom flask was charged with a stir bar, hydrazone (1.00 equiv.), an amine (1.10 equiv.), $PhCF_3$ or THF (0.3 M), and DBU (0.200 equiv.). The reaction was conducted at room temperature or 50 °C. The reaction was concentrated under reduced pressure and purified by silica gel column chromatography to give the corresponding products.



(3-Phenyl-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone (12a): Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.159 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 16 hours. The crude mixture was purified by silica gel column chromatography using 10% hexanes/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.129 g, 89%).

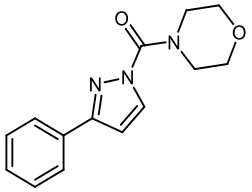
TLC R_f : 0.15 in 10% hexanes/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.30 (d, *J* = 2.8 Hz, 1H), 7.88-7.84 (m, 2H), 7.47-7.34 (m, 4H), 6.69 (d, *J* = 2.8 Hz, 1H), 4.14 (br s, 2H), 3.72 (br s, 2H), 1.99 (br s, 4H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 153.2 (C), 149.6 (C), 132.4 (C), 132.1 (CH), 128.5 (CH), 128.4 (CH) 125.8 (CH), 104.2 (CH), 50.2 (CH_2), 48.8 (CH_2), 26.7 (CH_2), 23.7 (CH_2).

IR (film): 1717, 1670, 1558, 1423, 1265, 1202 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{15}N_3O$ $[M]^+$: 241.1215. Found: 241.1230.



Morpholino(3-phenyl-1H-pyrazol-1-yl)methanone (12b): Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.159 g, 0.600 mmol), morpholine (0.0871 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 16 hours. The crude mixture was purified by silica gel column chromatography using a gradient of CH_2Cl_2 to 5% EtOAc/CH_2Cl_2 to afford the pure compound as a crystalline white solid (0.139 g, 90%).

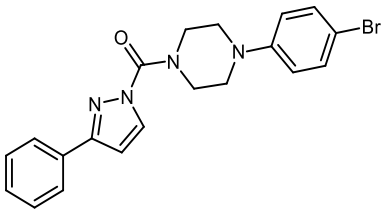
TLC R_f : 0.60 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.18 (d, *J* = 2.8 Hz, 1H), 7.84-7.81 (m, 2H), 7.46-7.37 (m, 3H), 6.69 (d, *J* = 2.8 Hz, 1H), 3.99 (br s, 4H), 3.83 (m, 4H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 154.0 (C), 151.6 (C), 133.6 (CH), 132.4 (C), 129.1 (CH), 129.0 (CH), 126.3 (CH), 105.2 (CH), 67.1 (CH_2), 47.8 (CH_2).

IR (film): 3032, 1683, 1533, 1452, 1426, 1363, 1348, 1301, 1255, 1247, 1188, 1116, 1074, 1045, 1031 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{15}N_3O_2$ $[M]^+$: 257.1164. Found: 257.1136.



(4-(4-Bromophenyl)piperazin-1-yl)(3-phenyl-1H-pyrazol-1-yl)methanone (12c): Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.0795 g, 0.300 mmol), 1-(4-bromophenyl)piperazine (0.0800 g, 0.330 mmol), DBU (0.0090 mL, 0.060 mmol), and THF (1.0 mL) at room temperature for 16 hours. The crude mixture was purified by Et_3N-treated silica gel column chromatography using 10% EtOAc/hexanes to afford the pure compound as an amorphous white solid (0.112 g, 91%).

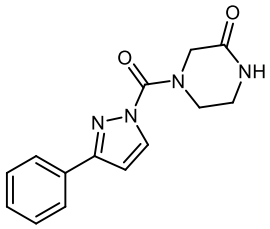
TLC R_f : 0.20 in 10% EtOAc/hexanes.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.20 (d, *J* = 2.8 Hz, 1H), 7.86-7.83 (m, 2H), 7.46-7.42 (m, 2H), 7.40-7.36 (m, 3H), 6.85-6.81 (m, 2H), 6.71 (d, *J* = 2.8 Hz, 1H), 4.12 (br s, 4H), 3.31 (t, *J* = 5.2 Hz, 4H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 153.9 (C), 151.1 (C), 150.1 (C), 133.5 (CH), 132.3 (C), 132.2 (CH), 129.0 (C), 128.9 (CH), 126.2 (CH), 118.3 (CH), 112.8 (C), 105.1 (CH), 49.3 (CH_2), 46.7 (CH_2).

IR (film): 3880, 3768, 1733, 1687, 1662, 1456, 1265 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{20}H_{19}BrN_4O$ $[M]^+$: 410.0742. Found: 410.0753.



4-(3-Phenyl-1H-pyrazole-1-carbonyl)piperazin-2-one (12d): Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.159 g, 0.600 mmol), 2-oxopiperazine (0.0661 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 16 hours. The crude mixture was purified by silica gel column chromatography using 5% CH_3OH/CH_2Cl_2 to afford the pure compound as a crystalline white solid (0.151 g, 93%).

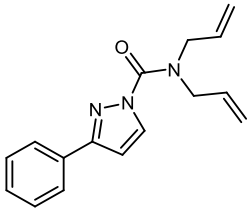
TLC R_f : 0.20 in 5% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.20 (d, *J* = 2.8 Hz, 1H), 7.84-7.82 (m, 2H), 7.46-7.37 (m, 3H), 6.72 (d, *J* = 2.8 Hz, 1H), 6.69 (br s, 1H), 4.67 (br s, 2H), 4.15 (br s, 2H), 3.62 (br s, 2H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 167.1 (C), 154.7 (C), 150.7 (C), 133.3 (CH), 131.8 (C), 129.1 (CH), 128.8 (CH), 126.2 (CH), 105.4 (CH).

IR (film): 3267, 3060, 2900, 1710, 1654, 1537, 1452, 1427, 1352, 1332, 1315, 1249, 1105, 1061, 1034 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{14}N_4O_2$ $[M]^+$: 270.1117. Found: 270.1097.



***N*,*N*-Diallyl-3-phenyl-1H-pyrazole-1-carboxamide (12e):** Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.159 g,

0.600 mmol), diallylamine (0.0800 mL, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 16 hours. The crude mixture was purified by silica gel column chromatography using 20% hexanes/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.141 g, 88%).

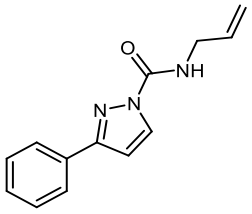
TLC R_f : 0.42 in 20% hexanes/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.22 (d, *J* = 2.8 Hz, 1H), 7.87-7.83 (m, 2H), 7.47-7.34 (m, 4H), 6.70 (d, *J* = 2.8 Hz, 1H), 6.15-5.97 (m, 2H), 5.31-5.25 (m, 4H), 4.27 (s, 4H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 153.4 (C), 151.6 (C), 133.0 (CH), 132.4 (C), 128.7 (CH), 128.6 (CH), 126.0 (CH), 118.2 (CH_2), 104.6 (CH), 116.9 (CH_2), 105.9 (CH), 51.0 (CH_2).

IR (film): 1714, 1654, 1522, 1481, 1424, 1259, 1180 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{16}H_{17}N_3O$ $[M]^+$: 267.1372. Found: 267.1355.



***N*-Allyl-3-phenyl-1H-pyrazole-1-carboxamide (12f):** Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.159 g, 0.600 mmol), allylamine (0.050 mL, 0.66 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at 50 °C for 24 hours. The crude mixture was purified by Et_3N-treated silica gel column chromatography using 20% hexanes/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.100 g, 73%).

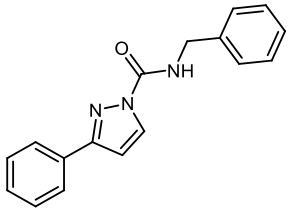
TLC R_f : 0.31 in 20% hexanes/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.27 (d, *J* = 2.8 Hz, 1H), 7.88-7.84 (m, 2H), 7.48-7.36 (m, 4H), 6.73 (d, *J* = 2.8 Hz, 1H), 5.96 (ddt, *J* = 17.2, 10.2, 5.6 Hz, 1H), 5.37-5.21 (m, 2H), 4.12-4.07 (m, 2H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 154.0 (C), 133.5 (C), 132.0 (C), 129.9 (CH), 128.9 (CH), 128.7 (CH), 126.1 (CH), 116.9 (CH_2), 105.9 (CH), 42.7 (CH_2).

IR (film): 1718, 1680, 1651, 1558, 1539, 1423, 1354, 1265 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{13}N_3O$ $[M]^+$: 227.1059. Found: 227.1085.



***N*-Benzyl-3-phenyl-1H-pyrazole-1-carboxamide (12g):** Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.159 g, 0.600 mmol), benzylamine (0.0701 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 24 hours. The crude mixture was purified by Et_3N-treated silica gel column chromatography using 20% hexanes/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.130 g, 78%).

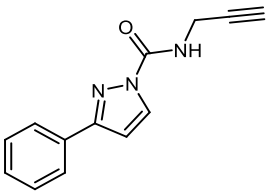
TLC R_f : 0.60 in 20% hexanes/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.27 (d, *J* = 2.8 Hz, 1H), 7.82-7.80 (m, 2H), 7.58 (br s, 1H), 7.43-7.28 (m, 3H), 6.71 (d, *J* = 2.8 Hz, 1H), 4.63 (d, *J* = 6.13 Hz, 2H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 154.1 (C), 149.9 (C), 137.6 (C), 131.9 (CH), 130.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 127.7 (CH), 126.2 (CH), 106.1 (CH), 44.4 (CH_2).

IR (film): 3357, 1716, 1689, 1543, 1500, 1456, 1353, 1284, 1257, 1238, 1080, 1043 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{17}H_{15}N_3O$ $[M]^+$: 277.1215. Found: 277.1217.



3-Phenyl-*N*-(prop-2-yn-1-yl)-1H-pyrazole-1-carboxamide (12h): Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.159 g, 0.600 mmol), propargylamine (0.0363 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at 50 °C for 24 hours. The crude mixture was purified by Et_3N-treated silica gel column chromatography using 40% hexanes/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.100 g, 79%).

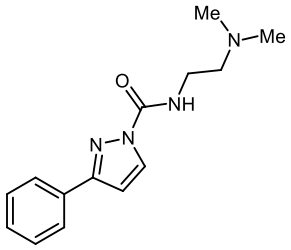
TLC R_f : 0.35 in 40% hexanes/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.26 (d, *J* = 2.8 Hz, 1H), 7.86-7.84 (m, 2H), 7.47-7.37 (m, 4H), 6.73 (d, *J* = 2.8 Hz, 1H), 4.26 (dd, *J* = 5.7, 2.6 Hz, 2H), 2.32 (t, *J* = 2.55, 1H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 154.5 (C), 149.6 (C), 132.0 (C), 130.1 (CH), 129.1 (CH), 128.9 (CH), 126.3 (CH), 106.4 (CH), 78.9 (C), 72.4 (CH), 30.1 (CH_2).

IR (film): 3105, 1739, 1683, 1652, 1554, 1515, 1455, 1339, 1266 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{11}N_3O$ $[M]^+$: 225.0902. Found: 225.0897.



***N*-(2-(Dimethylamino)ethyl)-3-phenyl-1H-pyrazole-1-carboxamide (12i):** Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.159 g, 0.600 mmol), *N,N*-dimethylethylenediamine (0.0582 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and $PhCF_3$ (2.0 mL) at 50 °C for 16 hours. The crude mixture was purified by silica gel column chromatography using a gradient of 10% EtOAc/CH_2Cl_2 to 50% CH_3OH/CH_2Cl_2 to afford the pure compound as a colorless oil (0.138 g, 89%).

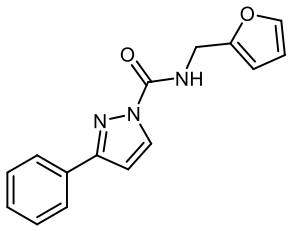
TLC R_f : 0.10 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.25 (d, *J* = 2.7 Hz, 1H), 7.86-7.84 (m, 2H), 7.57 (br s, 1H), 7.45-7.35 (m, 3H), 6.70 (d, *J* = 2.7 Hz, 1H), 3.54 (q, *J* = 6.0 Hz, 2H), 2.56 (t, *J* = 6.2 Hz, 1H), 2.31 (s, 6H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 154.0 (C), 150.1 (C), 132.2 (C), 129.9 (CH), 128.9 (CH), 128.8 (CH), 126.2 (CH), 105.8 (CH), 58.1 (CH_2), 45.4 (CH_3), 38.0 (CH_2).

IR (film): 3023, 1733, 1716, 1683, 1662, 1526, 1455, 1353, 1262 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{18}N_4O$ $[M]^+$: 258.1481. Found: 258.1400.



***N*-(Furan-2-ylmethyl)-3-phenyl-1H-pyrazole-1-carboxamid (12j):** Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.159 g, 0.600 mmol), furfurylamine (0.0641 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and

THF (2.0 mL) at room temperature for 18 hours. The crude mixture was purified by Et_3N-treated silica gel column chromatography using CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.137 g, 82%).

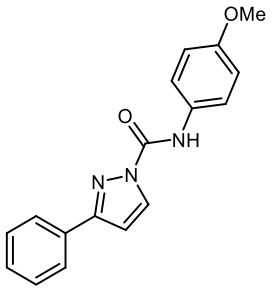
TLC R_f : 0.60 in CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.25 (d, *J* = 2.8 Hz, 1H), 7.83-7.80 (m, 2H), 7.54 (br s, 1H), 7.44-7.36 (m, 4H), 6.70 (d, *J* = 2.8 Hz, 1H), 6.33 (m, 2H) 4.62 (d, *J* = 5.9 Hz, 2H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 154.1 (C), 149.9 (C), 137.6 (C), 131.9 (CH), 130.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 127.7 (CH), 126.2 (CH), 106.1 (CH), 44.4 (CH_2).

IR (film): 3111, 2989, 1716, 1683, 1647, 1444, 1353, 1262, 1238, 1161 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{13}N_3O_2$ $[M]^+$: 267.1008. Found: 267.1023.



***N*-(4-Methoxyphenyl)-3-phenyl-1H-pyrazole-1-carboxamide (12k):** Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.159 g, 0.600 mmol), *p*-methoxyaniline (0.0813 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 16 hours. The crude mixture was purified by Et_3N-treated silica gel column chromatography using 40% hexanes/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.133 g, 76%).

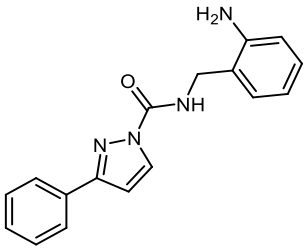
TLC R_f : 0.40 in 40% hexanes/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 9.05 (br s, 1H) 8.34 (d, *J* = 2.8 Hz, 1H), 7.90-7.88 (m, 2H), 7.57-7.53 (m, 2H), 7.49-7.39 (m, 3H), 6.95-6.93 (m, 2H), 6.76 (d, *J* = 2.8 Hz, 1H), 3.82 (s, 3H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 156.9 (C), 154.3 (C), 147.3 (C), 131.9 (C), 130.0 (CH), 129.7 (C), 129.2 (CH), 128.9 (CH), 126.4 (CH), 121.8 (CH), 114.5 (CH), 106.6 (CH), 55.6 (CH_3).

IR (film): 3062, 1733, 1716, 1652, 1596, 1502, 1456, 1419, 1355, 1299, 1247, 1226, 1039 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{17}H_{15}N_3O_2$ $[M]^+$: 293.1164. Found: 293.1213.



***N*-(2-Aminobenzyl)-3-phenyl-1H-pyrazole-1-carboxamide (12l):** Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.159 g, 0.600 mmol), 2-aminobenzylamine (0.0701 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 24 hours. The product precipitated out of solution as an amorphous white solid and was filtrated with Et_2O to give the desired pure product (0.157 g, 90%).

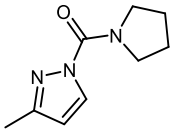
TLC R_f : 0.10 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz; DMSO-d_6): δ 8.67 (br s, 1H), 8.29 (m, 1H), 7.90 (m, 2H), 7.39 (m, 3H), 7.10 (m, 1H), 6.95 (m, 2H), 6.62 (m, 1H), 6.52 (br s, 1H), 4.99 (m, 2H), 4.34 (m, 3H).

^{13}C NMR (75 MHz; DMSO-d_6): δ 158.3 (C), 155.0 (C), 151.4 (C), 137.0 (C), 135.7 (C), 134.6 (CH), 134.1 (CH), 134.0 (CH), 133.3 (CH), 131.2 (CH), 126.6 (C), 121.0 (CH), 120.0 (CH), 111.3 (CH), 45.7 (CH_2).

IR (film): 3002, 1670, 1515, 1455, 1348, 1249, 1184, 1114, 1072, 1031 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{17}H_{16}N_4O$ $[M]^+$: 292.1324. Found: 292.1324.



(3-Methyl-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone (12m): Synthesized according to general procedure **M** using (*Z*)-phenyl-2-(but-3-yn-2-ylidene)hydrazinecarboxylate (0.122 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at 50 °C for 24 hours. The crude mixture was purified by silica gel column chromatography using 3% EtOAc/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.0900 g, 85%).

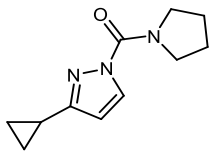
TLC R_f : 0.29 in 3% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.12 (d, *J* = 2.7 Hz, 1H), 6.13 (d, *J* = 2.7 Hz, 1H), 4.06-3.54 (m, 4H), 2.29 (s, 3H), 1.95-1.90 (m, 4H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 151.3 (C), 131.7 (CH), 107.2 (CH), 13.8 (CH_3).

IR (film): 1705, 1663, 1558, 1458, 1437, 1420, 1310, 1265, 1157 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{13}N_3O$ $[M]^+$: 179.1059. Found: 179.1053.



(3-Cyclopropyl-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone (12n): Synthesized according to general procedure **M** using (*Z*)-phenyl-2-(1-cyclopropylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.137 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 16 hours. The crude mixture was purified by Et_3N-treated silica gel column chromatography using 2.5% EtOAc/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.111 g, 90%).

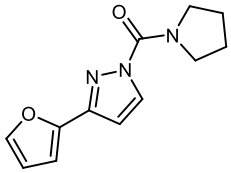
TLC R_f : 0.20 in 2.5% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.10 (d, *J* = 2.7 Hz, 1H), 6.02 (d, *J* = 2.7 Hz, 1H), 3.95 (br s, 2H), 3.64 (br s, 2H), 1.96-1.90 (m, 5H), 0.96-0.91 (m, 2H), 0.79-0.75 (m, 2H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 157.8 (C), 150.8 (C), 131.7 (CH), 104.3 (CH), 50.1 (CH_2), 48.8 (CH_2), 27.0 (CH_2), 24.2 (CH_2), 9.50 (CH_3), 8.3 (CH_2).

IR (film): 3142, 1786, 1699, 1675, 1505,1461, 1331, 1299, 1111, 1009 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{15}N_3O$ $[M]^+$: 205.1215. Found: 205.1248.



(3-(Furan-2-yl)-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone (12o): Synthesized according to general procedure **M** using (*E*)-phenyl-2-(1-(furan-2-yl)prop-2-yn-1-ylidene)hydrazinecarboxylate (0.153 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 16 hours. The crude mixture was purified by Et_3N-treated silica gel column chromatography using 2.5% EtOAc/CH_2Cl_2 to afford the pure compound as an amorphous pale yellow solid (0.131 g, 94%).

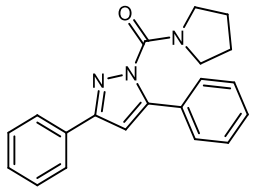
TLC R_f : 0.20 in 2.5% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.23 (d, *J* = 2.8 Hz, 1H), 7.48 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.74 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.48 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.05 (br s, 2H), 3.68 (br s, 2H), 1.95 (br s,4H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 149.9 (C), 148.2 (C), 146.0 (C), 142.7 (CH), 132.2 (CH), 111.6 (CH), 107.4 (CH), 104.5 (CH), 50.3 (CH_2), 48.8 (CH_2), 26.9 (CH_2), 24.1 (CH_2).

IR (film): 2989, 2883, 1674, 1544, 1430, 1386, 1359, 1348, 1267, 1211, 1039 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O_2$ $[M]^+$: 231.1008. Found: 231.0999.



(3,5-Diphenyl-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone (12p): Synthesized according to general procedure **M** using (*Z*)-phenyl 2-(1,3-diphenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.102 g, 0.300 mmol), pyrrolidine (0.0237 g, 0.330 mmol), DBU (0.0090 mL, 0.060 mmol), and THF (1.0 mL) at 50 °C for 16 hours. The crude mixture was purified by Et_3N-treated silica gel column chromatography using 2.5% EtOAc/CH_2Cl_2 to afford the pure compound as a colorless oil (0.100 g, 98%).

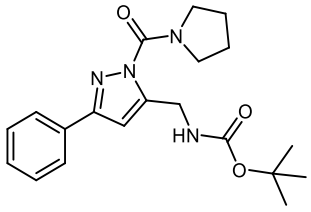
TLC R_f : 0.30 in 2.5% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.90-7.87 (m, 2H), 7.53 (dq, *J* = 6.2, 2.0 Hz, 2H), 7.46-7.34 (m, 6H), 6.76 (s, 1H), 3.63 (t, *J* = 6.7, 2H), 3.56 (t, *J* = 6.5, 2H), 1.91 (m, 4H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 152.3 (C), 150.9 (C), 146.0 (C), 132.6 (C), 130.1 (C), 128.8 (CH) 128.7 (CH) 128.6 (CH) 128.5 (CH) 127.9 (CH), 126.1 (CH), 104.8 (CH), 48.9 (CH_2), 47.5 (CH_2), 26.1 (CH_2), 24.5 (CH_2).

IR (film): 2989, 1670, 1544, 1429, 1419, 1386, 1363, 1348, 1255, 1043, 987 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{20}H_{19}N_3O$ $[M]^+$: 317.1528. Found: 317.1541.



***tert*-Butyl((3-phenyl-1-(pyrrolidine-1-carbonyl)-1H-pyrazol-5-yl)methyl) carbamate (12q):** Synthesized according to general procedure **M** using (*Z*)-phenyl-2-(4-((tert-butoxycarbonyl)amino)-1-phenylbut-2-yn-1-ylidene) hydrazinecarboxylate (0.118 g, 0.300 mmol), pyrrolidine (0.0237 g, 0.330 mmol), DBU (0.0090 mL, 0.060 mmol), and THF (1.0 mL) at 50 °C for 16 hours. The crude mixture was purified by Et_3N-treated silica gel column chromatography using 2.5% EtOAc/CH_2Cl_2 to afford the pure compound as a colorless oil (0.093 g, 83%).

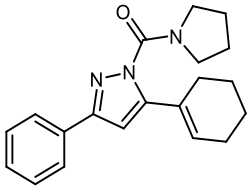
TLC R_f : 0.15 in 2.5% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.82-7.79 (m, 2H), 7.41-7.34 (m, 3H), 6.66 (s, 1H), 5.81 (s, 1H), 4.51 (d, *J* = 6.5 Hz, 2H), 4.00-3.97 (m, 2H), 3.68-3.65 (m, 2H), 1.99-1.95 (m, 4H), 1.43 (s, 9H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 152.3 (C), 150.9 (C), 146.0 (C), 132.6 (C), 130.1 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 126.1 (CH), 104.8 (CH), 48.9 (CH_2), 47.5 (CH_2), 26.1 (CH_2), 24.5 (CH_2).

IR (film): 2989, 1683, 1558, 1444, 1393, 1367, 1353, 1255, 1238, 1195, 1154 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{20}H_{26}N_4O_3$ $[M]^+$: 370.2005. Found: 370.2253.



(5-(Cyclohex-1-en-1-yl)-3-phenyl-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone (12r): Synthesized according to general procedure **M** using (*Z*)-phenyl-2-(3-(cyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-ylidene) hydrazinecarboxylate (0.103 g, 0.300 mmol), pyrrolidine (0.0237 g, 0.330 mmol), DBU (0.0090 mL, 0.060 mmol), and THF (1.0 mL) at 50 °C for 16 hours. The crude mixture was purified by Et_3N-treated silica gel column chromatography using 2.5% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.0783 g, 81%).

TLC R_f : 0.15 in 100% CH_2Cl_2.

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.82-7.79 (m, 2H), 7.41-7.30 (m, 3H), 6.48 (s, 1H), 6.02 (s, 1H), 3.66-3.59 (m, 4H), 2.35-2.31 (m, 2H), 2.21-2.17 (m, 2H), 1.99-1.91 (m, 4H), 1.75 (m, 2H) 1.67 (m, 2H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 151.8 (C), 151.4 (C), 132.9 (C), 128.8 (C), 128.7 (C), 128.3 (CH), 127.9 (CH), 126.0 (CH), 103.2 (CH), 49.0 (CH_2), 47.5 (CH_2), 27.9 (CH_2), 26.25 (CH_2), 25.7 (CH_2), 24.6 (CH_2), 22.7 (CH_2), 21.9 (CH_2).

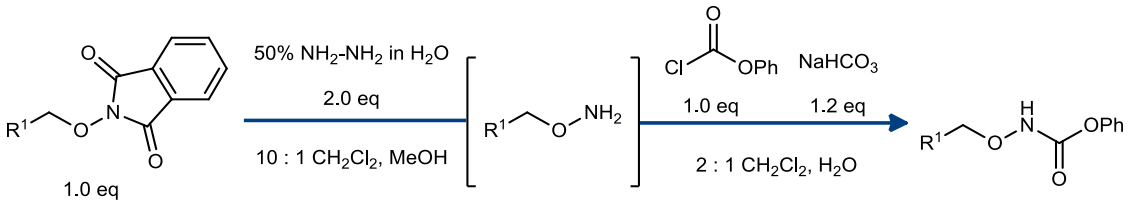
IR (film): 3042, 2221, 1772, 1733, 1697, 1683, 1473, 1446, 1436, 1265, 1188 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{20}H_{23}N_3O$ $[M]^+$: 321.1841. Found: 321.1920.

Supporting information for Chapter 3

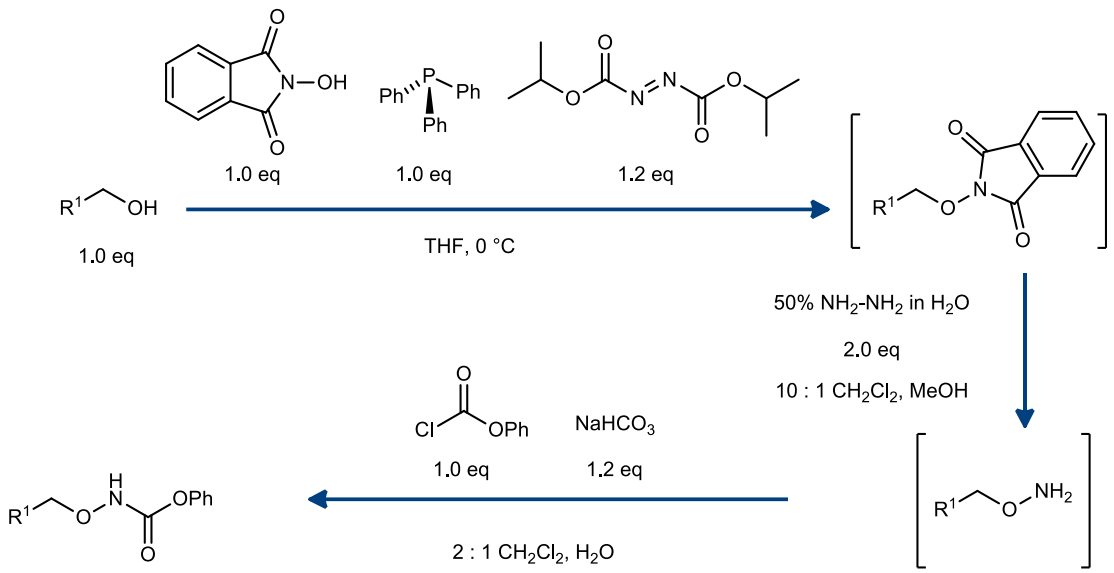
Synthesis of *O*-isocyanate precursors

General Procedure N: Synthesis of alkoxycarbamates



To a round bottom flask charged with a stir bar was added the corresponding *N*-alkoxyphthalimide (1.00 equiv) followed by dilution in CH_2Cl_2:MeOH (10:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added a solution of 50% hydrazine hydrate (2.00 equiv). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the *N*-alkoxyphthalimide. Upon completion, the solution was filtered over a fritted funnel and the filtrate was collected (the white precipitate was discarded). The filtrate was washed with sat. $NaHCO_3$ (x 2) and then brine (x 1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and used in the subsequent step without further purification. To a round bottom flask charged with a stir bar was added the corresponding crude *N*-alkyl hydroxylamine from the previous step (1.00 equiv) followed by dilution with CH_2Cl_2:H_2O (2:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added $NaHCO_3$ (1.20 equiv). After addition of $NaHCO_3$, the solution was allowed to stir at 0 °C for 0.5 h. After 0.5 h passed, phenylchloroformate was added dropwise (1.00 equiv). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the phenylchloroformate. Upon completion, the reaction was extracted using sat. $NaHCO_3$ (x 2) and then brine (x 1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography or recrystallization.

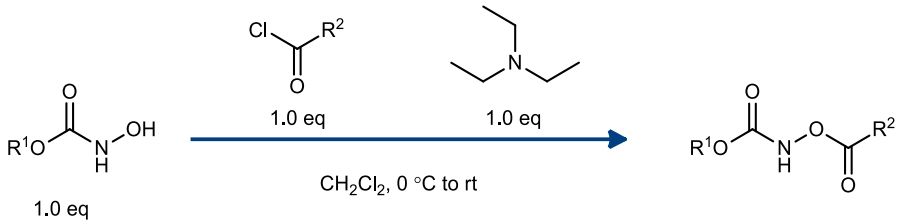
General Procedure O: Express synthesis of *N*-alkoxycarbamates



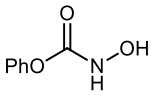
To a round bottom flask charged with a stir bar was added *N*-hydroxyphthalimide (1.00 equiv) followed by dilution in dry THF (0.3 M). PPh_3 (1.00 equiv) and alcohol (1.00 equiv) were added sequentially and the resulting solution was allowed to stir at 0 °C for 0.3 h. DIAD (1.20 equiv) was added dropwise over 1 h, and the mixture was stirred at 0 °C until TLC monitoring indicated completion. Upon completion (by TLC), Et_2O and hexanes were added to the solution, which induced a white precipitate to form upon cooling ($Ph_3P=O$ and DIAD, usually co-crystallize). The precipitate was filtered and discarded and the filtrate, which contained the *N*-alkoxyphthalimide along with minor impurities, was used in the subsequent step without further purification. To a round bottom flask charged with a stir bar was added the corresponding crude *N*-alkoxyphthalimide (1.00 eq) followed by dilution in CH_2Cl_2:MeOH (10:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added a solution of 50% hydrazine hydrate (2.00 eq). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the *N*-alkoxyphthalimide. Upon completion, the solution was filtered over a fritted funnel and the filtrate was collected (the white precipitate was discarded). The filtrate was washed with sat. $NaHCO_3$ (x 2) and then brine (x 1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and used in the subsequent step without further purification. To a round bottom flask charged with a stir bar was added the crude corresponding *N*-alkyl hydroxylamine (1.00 eq) followed by dilution with CH_2Cl_2:H_2O (2:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added $NaHCO_3$ (2.20 eq). After addition of $NaHCO_3$, the solution was allowed to stir at 0 °C for 0.5 h. After 0.5 h passed, phenylchloroformate was added dropwise (1.00 eq). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the phenylchloroformate. Upon completion, the reaction was extracted using sat. $NaHCO_3$ (x 2) and then brine (x 1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The

filtrate was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography or recrystallization.

General Procedure P: Synthesis of acyloxycarbamates



To a round-bottom flask charged with a stir bar was added hydroxycarbamate (1.00 equiv.) then CH_2Cl_2 (0.3 M) and allowed to stir at 0 °C. *Hydroxycarbamates are insoluble and will not always dissolve completely before the next step of the reaction* Upon observing most of the hydroxycarbamate dissolve, Et_3N was added (1.00 equiv.) and finally acyl-chloride was added dropwise (1.00 equiv.). The reaction was allowed to warm gradually to room temperature. Upon completion, H_2O was added and the reaction mixture was extracted. The organic layer was recollected and washed with $NaHCO_3$, and then the organic phase was recollected and washed with brine. The organic phase was dried over Na_2SO_4 (stirring for 15 minutes). Solids were filtered, the filtrate was collected and concentrated under reduced pressure to give the corresponding pure acyloxycarbamates.

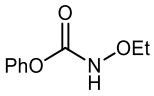


Phenyl *N*-hydroxycarbamate (15a): The title compound was synthesized according to a literature procedure.[291]

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.43-10.15 (br s, 1 H), 9.11-9.03 (br s, 1H), 7.45-7.33 (m, 2H), 7.26-7.17 (m, 1H), 7.14-7.06 (m, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): 155.5 (C), 150.7 (C), 129.4 (CH), 125.1 (CH), 121.6 (CH).

^{1}H and ^{13}C NMR were in accordance with those in the literature.



Phenyl *N*-ethoxycarbamate (15b): The title compound was synthesized according to a literature procedure[291] using phenyl chloroformate (12.6 mL, 0.100 mol), *O*-ethoxylamine hydrochloride

(11.7 g, 0.120 mol), and sodium bicarbonate (18.5 g, 0.220 mol) in H_2O/CH_2Cl_2 (1:1) (0.4 M). The title compound was obtained as a crystalline white solid (14.9 g, 82%).

TLC R_f: 0.73 in 2% MeOH/CH_2Cl_2.

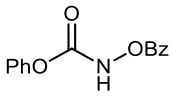
M.p.: 60.5-61.6 ^oC.

^{1}H (300 MHz, $CDCl_3$): δ 7.64-7.57 (br s, 1H), 7.43-7.34 (m, 2H), 7.27-7.20 (m, 1H), 7.19-7.13 (m, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.0 Hz, 3H).

^{13}C (75 MHz, $CDCl_3$): δ 155.3 (C), 150.4 (C), 129.4 (C), 125.8 (CH), 121.3 (CH), 72.7 (CH_2), 13.4 (CH_3).

IR (film): 3204, 2983, 1719, 1588, 1475, 1376, 1251 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_9H_{11}NO_3Na$ [M+Na]+: 204.0637. Found: 204.0647.



Phenyl *N*-benzoyloxycarbamate (15c): The title compound was synthesized according to general procedure **P** using phenyl *N*-hydroxycarbamate (38.3 g, 0.250 mol), Et_3N (34.9 g, 0.250 mol) and benzoyl chloride (29.0 mL, 0.250 mol) in CH_2Cl_2 (0.83 L, 0.30 M). The reaction was allowed to stir at room temperature overnight. Upon completion, H_2O was added and the reaction mixture was extracted with CH_2Cl_2. The organic layer was recollected and washed with $NaHCO_3$, and then the organic phase was recollected again and washed with brine. The organic phase was dried over Na_2SO_4 (stirring for 15 minutes). Solids were filtered and the filtrate was collected and concentrated under reduced pressure to yield an amorphous white solid (61.2 g, 95%).

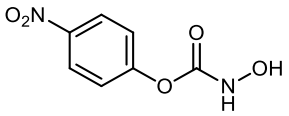
TLC R_f: 0.35 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 2H), 7.66-7.61 (m, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.39-7.34 (m, 2H), 7.25-7.16 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7 (C), 154.7 (C), 150.1 (C), 134.3 (CH), 129.9 (CH), 129.4 (CH), 128.7 (CH), 126.4 (C), 126.1 (CH), 121.2 (CH).

IR (film): 3271, 1770, 1739, 1450, 1229, 1030 cm^{-1}.

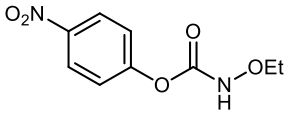
HRMS (ESI): Exact mass calcd for $C_{14}H_{11}NO_4Na$ $[M+Na]^+$: 280.0587. Found 280.0586.



4-Nitrophenyl hydroxycarbamate (15d): The title compound was synthesized according to a literature procedure.[292]

^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.71 (s, 1H), 9.31 (s, 1H), 8.30-8.25 (m, 2H), 7.44-7.38 (m, 2H).

^{1}H and ^{13}C NMR were in accordance with those in the literature.



1-(4-Nitrophenol)-N-(O-ethylhydroxy) carbamate (15e): The title compound was synthesized according to a modified literature procedure[291] using *O*-ethyl hydroxylamine hydrochloride (0.610 g, 6.20 mmol), sodium bicarbonate (0.949 g, 11.3 mmol) and 4-nitrophenyl chloroformate (0.629 g, 3.10 mmol) in CH_2Cl_2 (10 mL, 0.30 M) were stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 and transferred to a separatory funnel, then washed with brine, dried over $MgSO_4$ and filtered. The reaction mixture was concentrated under reduced pressure and recrystallized in diethyl ether. The title compound was obtained as a crystalline white solid (0.356 g, 51%).

TLC R_f: 0.73 in 2% MeOH/CH_2Cl_2.

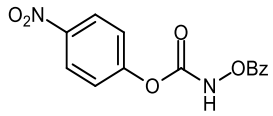
M.p.: 128.9-129.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31-8.25 (m, 2H), 7.75-7.67 (br s, 1H), 7.40-7.34 (m, 4H), 4.07 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): 155.1 (C), 153.9 (C), 145.1 (C), 125.2 (CH), 121.9 (CH), 72.9 (CH_2), 13.3 (CH_3).

IR (film): 3164, 2930, 1755, 1737, 1615, 1519, 1487, 1344 cm^{-1}.

HRMS (EI): Exact mass could not be obtained for the molecular ion. Exact mass calcd for fragment $[C_6H_5NO_3]^+$ (*p*-nitrophenol): 139.0264. Found: 139.0276. Exact mass calcd for fragment $[C_3H_5NO_2]^+$ (ethoxy-isocyanate): 87.0315. Found: 87.0321.



1-(4-Nitrophenol)-N-(O-benzoylhydroxy) carbamate (15f): The title compound was synthesized according to general procedure **P** using 1-(4-nitrophenol)-*N*-hydroxycarbamate (0.198 g, 1.00 mmol), triethylamine (0.14 mL, 1.0 mmol) and benzoyl chloride (0.12 mL, 1.0 mmol) in CH_2Cl_2 (3.3 mL, 0.30 M) were stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 and transferred to a separatory funnel, then washed with brine, dried over $MgSO_4$ and filtered. The reaction mixture was concentrated under reduced pressure and recrystallized in diethyl ether. The title compound as obtained as a crystalline white solid (0.109 g, 36%).

TLC R_f: 0.77 in 2% MeOH/CH_2Cl_2.

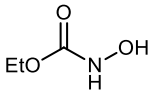
M. p.: 152.3-153.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69-8.63 (br s, 1H), 8.33-8.27 (m, 2H), 8.17-8.12 (m, 2H), 7.72-7.66 (m, 1H), 7.57-7.50 (m, 2H), 7.45-7.39 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5 (C), 154.7 (C), 153.2 (C), 145.5 (C), 134.7 (CH), 130.1 (CH), 128.9 (CH), 126.0 (C), 125.3 (CH), 122.0 (CH).

IR (film): 3167, 1773, 1755, 1520, 1487, 1344 cm^{-1}.

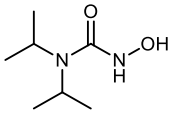
HRMS (EI/ESI): Accurate mass could not be obtained due to the instability of this compound. Exact mass calcd for $C_{24}H_{15}N_3O_9Na$ $[M+Na]^+$ (*O*-benzoyl isocyanurate trimer): 512.0706. Found: 512.0724.



Ethyl hydroxycarbamate (15g): The title compound was synthesized according to a literature procedure using ethyl chloroformate (2.9 mL, 0.030 mol), hydroxylamine hydrochloride (10.4 g, 0.150 mol), and sodium hydroxide (7.20 g, 0.180 mol).[293] The title compound was obtained as a clear and colourless liquid (2.40 g, 76 %) and was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (br s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{1}H and ^{13}C NMR were in accordance with those in the literature.



3-Hydroxy-1,1-diisopropylurea (15h): The title compound was synthesized according to a prep. of *N*, *N*-diethyl hydroxyurea using diisopropylcarbamic chloride (1.64 g, 10 mmol), hydroxylamine hydrochloride (0.879 g, 11.5 mmol), and potassium carbonate (1.45 g, 10.5 mmol) in EtOAc/H_2O (60:1) (1.45 M).[294] The crude reaction mixture was isolated using flash chromatography (30% EtOAc/Hexane then 40% EtOAc/Hexane). The title compound was obtained as an amorphous white solid (0.544 g, 34%).

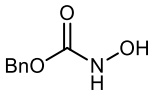
TLC R_f: 0.34 in 40% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (br s, 1H), 6.48 (br s, 1H), 3.77 (sept, *J*= 6.8 Hz, 2H), 1.28 (d, *J* = 6.8 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6 (C), 45.9 (CH), 20.8 (CH_3).

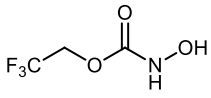
IR (film): 3292, 2964, 2927, 1632, 1493, 1446, 1376, 1367, 1047 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{16}N_2O_2$ $[M]^+$: 160.1212. Found: 160.1208.



Benzyl hydroxycarbamate (15i): The title compound was synthesized according to a literature procedure[291] using benzyl chloroformate (1.43 mL, 10.0 mmol), hydroxylamine hydrochloride (0.777 g, 11.3 mmol), and sodium bicarbonate (1.85 g, 22.0 mmol) in 1.4 : 1 CH_2Cl_2/H_2O (0.5 M). The crude reaction mixture was isolated using flash chromatography (2% MeOH/CH_2Cl_2, then 5% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.998 g, 60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (s, 5H), 7.28 (s, 1H), 6.81 (br s), 5.18 (s, 2H).

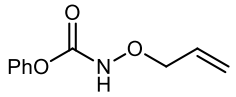


2,2,2-Trifluoroethyl hydroxycarbamate (15j): The title compound was synthesized according to a literature procedure.[295]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (br s, 1H), 6.18 (br s, 1H), 4.56 (q, *J* = 8.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3 (C), 122.6 (q, *J* = 277.3 Hz) (C), 61.5 (q, *J* = 37.1 Hz) (CH_2).

^{1}H and ^{13}C NMR were in accordance with those in the literature.

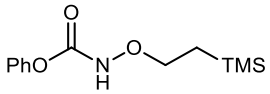


Phenyl allyloxycarbamate (15k): The title compound was synthesized according to a literature procedure.[296]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.42-7.35 (m, 2H), 7.26-7.20 (m, 1H), 7.18-7.13 (m, 2H), 6.02 (ddt, *J*= 17.3, 10.3, 6.4 Hz, 1H), 5.44-5.34 (m, 2H), 4.46 (dt, *J*= 6.4, 1.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C), 150.4 (C), 132.1 (CH), 129.4 (CH), 125.8 (CH), 121.4 (CH), 120.7 (CH_2), 77.9 (CH_2).

^{1}H and ^{13}C NMR were in accordance with those in the literature.



Phenyl 2-(trimethylsilyl)ethoxycarbamate (15l): The title compound was synthesized according to general procedure **N** using *O*-(2-(trimethylsilyl)ethyl)hydroxylamine (5.00 g, 37.5 mmol), and phenyl chloroformate (3.93 mL, 31.3 mmol) in 1 : 1 CH_2Cl_2/H_2O (78 mL, 0.40 M). The reaction was allowed to stir at room temperature overnight. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (78 mL) and extracted from the H_2O. The organic phase was recollected and washed three times using saturated $NaHCO_3$ (25 mL), followed by a single brine wash (25 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (50 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as a clear oil (7.51 g, 95%).

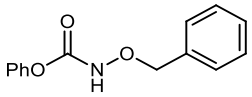
TLC R_f: 0.75 in 20% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (br s, 1H), 7.40-7.35 (m, 2H), 7.25-7.20 (m, 1H), 7.18-7.15 (m, 2H), 4.06-4.01 (m, 2H), 1.09-1.03 (m, 2H), 0.05 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.6 (C), 129.5 (CH), 125.9 (CH), 121.5 (CH), 75.0 (CH_2), 16.8 (CH_2), -1.3 (CH_3).

IR (film): 3273, 2952, 1733, 1593, 1474, 1370, 1248, 1201 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{12}H_{19}NO_3Si$ $[M+Na]^+$: 276.1032. Found: 276.1034.

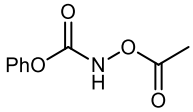


Phenyl benzyloxycarbamate (15m): The title compound was synthesized according to a literature procedure.[136]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (br s, 1H), 7.48-7.37 (m, 7H), 7.28-7.23 (m, 1H), 7.18-7.15 (m, 2H), 4.99 (s, 2H).

^{13}C (100 MHz, $CDCl_3$): δ 155.3 (C), 150.4 (C), 135.2 (C), 129.5 (CH), 129.3 (CH), 128.8 (CH), 128.7 (CH), 125.9 (CH), 121.4 (CH), 78.9 (CH_2).

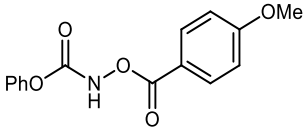
^{1}H and ^{13}C NMR were in accordance with those in the literature.



Phenyl acyloxycarbamate (15n): The title compound was synthesized according to a literature procedure.[297]

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44-8.39 (br s, 1H), 7.41-7.33 (m, 2H), 7.27-7.21 (m, 1H), 7.18-7.10 (m, 2H), 2.23 (s, 3H).

^{1}H and ^{13}C NMR were in accordance with those in the literature.



Phenyl (4-methoxybenzoyl)oxycarbamate (15o): The title compound was synthesized according to general procedure **P** using phenyl *N*-hydroxycarbamate (17.8 g, 0.117 mol), triethylamine (16.4 mL, 0.117 mol) and 4-methoxybenzoyl chloride (20.0 g, 0.117 mol) in CH_2Cl_2 (390 mL, 0.30 M). The reaction was allowed to stir at room temperature overnight. Upon completion the organic phase was washed three times using saturated $NaHCO_3$ (100 mL), followed by a single brine wash (100 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (100 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as a white solid (30.92 g, 92%).

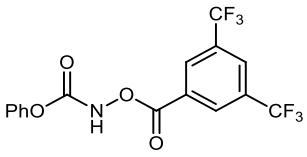
TLC R_f: 0.35 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (br s, 1H), 8.10 (d, *J* = 8.9 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.28-7.20 (m, 3H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5 (C), 164.6 (C), 154.9 (C), 150.3 (C), 132.3 (CH), 129.6 (CH), 126.2 (CH), 121.3 (CH), 118.6 (C), 114.2 (CH), 55.6 (CH_3).

IR (film): 3207, 3020, 2938, 1725, 1605, 1471, 1234 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{13}NO_5Na$ $[M+Na]^+$: 310.0692. Found: 310.0698.



Phenyl (3,5-trifluoromethylbenzoyl)oxycarbamate (15p): The title compound was synthesized according to general procedure **P** using phenyl *N*-hydroxycarbamate (1.02 g, 6.70 mmol), triethylamine (0.93 mL, 6.7 mmol) and 3,5-trifluoromethylbenzoyl chloride (1.21 mL, 6.70 mmol) in CH_2Cl_2 (22 mL, 0.30 M). The reaction was allowed to stir at room temperature overnight. Upon completion, the reaction mixture was diluted with H_2O (5.0 mL) and extracted three times using CH_2Cl_2 (5.0 mL), followed by a single brine wash (5.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (10.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as a white solid (2.63 g, 99%).

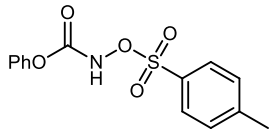
TLC R_f: 0.75 in 20% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.57 (s, 2H), 8.17 (s, 1H), 7.43-7.38 (m, 2H), 7.29-7.18 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 (C), 154.7 (C), 150.1 (C), 132.8 (q, *J* = 34.5 Hz) (C), 130.2 (m) (CH), 129.7 (CH), 128.9 (C), 127.8 (m) (CH), 126.5 (CH), 122.7 (q, *J* = 273.1 Hz) (CH), 121.2 (CH).

IR (film): 3214, 3092, 1780, 1734, 1614, 1591, 1475, 1378, 1279 cm^{-1}.

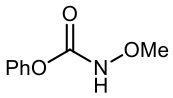
HRMS (EI): Exact mass calcd for $C_{16}H_9F_6NO_4$ $[M]^+$: 393.0436. Found: 393.0450.



Phenyl tosyloxycarbamate (15q): The title compound was synthesized according to a literature procedure.[298]

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 1H), 8.00-7.91 (m, 2H), 7.46-7.11 (m, 5H), 6.95-6.84 (m, 2H), 2.48 (s, 3H).

^{1}H and ^{13}C NMR were in accordance with those in the literature.

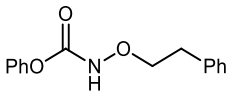


Phenyl methoxycarbamate (15r): The title compound was synthesized according to a literature procedure.[296]

^{1}H (400 MHz, $CDCl_3$): δ 7.88 (br s, 1H), 7.43–7.33 (m, 2H), 7.25–7.21 (m, 1H), 7.19–7.12 (m, 2H), 3.82 (s, 3H).

^{13}C (100 MHz, $CDCl_3$): δ 155.5 (C), 150.3 (C), 129.5 (CH), 125.9 (CH), 121.4 (CH), 64.8 (CH_3).

^{1}H and ^{13}C NMR were in accordance with those in the literature.



Phenyl phenethoxycarbamate (15s): The title compound was synthesized according to general procedure **N** using a two-step deprotection then acylation sequence. First, 2-phenethoxyisoindoline-1,3-dione[299] (2.67 g, 10.0 mmol) and 50% hydrazine hydrate (1.26 mL, 20.0 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. Second, the crude hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.01 g, 12.0 mmol) and phenylchloroformate (1.25 mL, 10.0 mmol) were added at 0 °C and allowed to stir overnight at rt. Upon completion the reaction was extracted using saturated $NaHCO_3$ and then brine. The organic layer was separated and concentrated under reduced pressure. The product was purified by silica gel flash column chomatography in (10% Et_2OAc/Hexanes) to yield the title compound as a white solid (2.31 g, 90%) over two steps.

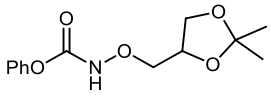
TLC R_f: 0.30 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 0.3 Hz, 1H), 7.40–7.33 (m, 2H), 7.31-7.19 (m, 6H), 7.16–7.11 (m, 2H), 4.20 (t, *J* = 7.1 Hz, 2H), 3.01 (t, *J* = 7.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.4 (C), 137.8 (C), 129.5 (CH), 128.9 (CH), 128.6 (CH), 126.6 (CH), 125.9 (CH), 121.4 (CH), 77.6 (CH_2), 34.6 (CH_2).

IR (film): 3177, 3034, 2958, 2917, 1782, 1601, 1477, 1434, 1265, 1177 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{15}NO_3Na$ $[M+Na]^+$ 280.0950. Found: 280.0935.



Phenyl (2,2-dimethyl-1,3-dioxolan-4-yl)methoxycarbamate (15t): The title compound was synthesized according to general procedure **N** using a two-step deprotection then acylation sequence. First, 2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)isoindoline-1,3-dione[300] (2.77 g, 10.0 mmol) and 50% hydrazine hydrate (1.26 mL, 20.0 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. Second, the crude hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.01 g, 12.0 mmol) and phenylchloroformate (1.25 mL, 10.0 mmol) were added at 0 °C and allowed to stir overnight at rt. Upon completion the reaction was extracted using saturated $NaHCO_3$ and then brine. The organic layer was separated and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography (20% EtOAc/Hexanes) to yield the title compound as clear oil (2.13 g, 80%) over two steps.

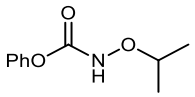
TLC R_f: 0.19 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.38–7.34 (m, 2H), 7.23–7.19 (m, 1H), 7.14–7.12 (m, 2H), 4.41 (quintet, *J* = 5.8 Hz, 1H), 4.09 (dd, *J* = 8.5, 6.5 Hz, 1H), 4.01 (dd, *J* = 5.4, 1.6 Hz, 2H), 3.82 (dd, *J* = 8.5, 6.1 Hz, 1H), 1.44 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5 (C), 150.3 (C), 129.5 (CH), 125.9 (CH), 121.3 (CH), 109.9 (C), 77.3 (CH_2), 73.6 (CH), 66.3 (CH_2), 26.8 (CH_3), 25.3 (CH_3).

IR (film): 3250, 2987, 2936, 1737, 1591, 1475, 1371, 1196, 1160 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{17}NO_5Na$ $[M+Na]^+$ 290.1004. Found: 290.1004.



Phenyl isopropoxycarbamate (15u): The title compound was synthesized according to general procedure **N** using a two-step deprotection then acylation sequence. First, 2-isopropoxyisoindoline-1,3-dione[301] (2.05 g, 10.0 mmol) and 50% hydrazine hydrate (1.26 mL, 20.0 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. Second, the crude hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.01 g, 12.0 mmol) and phenylchloroformate (1.25 mL, 10.0 mmol) were added at 0 °C and allowed to stir overnight at rt. Upon completion the reaction was extracted

using saturated $NaHCO_3$ and then brine. The organic layer was separated and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as clear oil (1.82 g, 88%) over two steps.

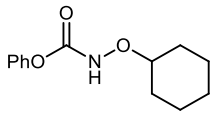
TLC R_f: 0.32 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.37–7.33 (m, 2H), 7.22–7.18 (m, 1H), 7.15–7.13 (m, 2H), 4.16 (sept, *J* = 6.2 Hz, 1H), 1.27 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8 (C), 150.5 (C), 129.4 (CH), 125.8 (CH), 121.4 (CH), 78.5 (CH), 20.5 (CH_3)

IR (film): 3180, 2978, 2909, 1732, 1593, 1482, 1374, 1264, 1202, 1147 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{10}H_{13}NO_3Na$ $[M+Na]^+$ 218.0793. Found: 218.0808.

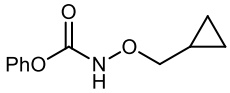


Phenyl cyclohexyloxycarbamate (15v): The title compound was synthesized according to a literature report.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.39–7.31 (m, 2H), 7.23–7.17 (m, 1H), 7.17–7.07 (m, 2H), 3.86 (tt, *J* = 9.3, 3.8 Hz, 1H), 2.06–1.94 (m, 2H), 1.84–1.70 (m, 2H), 1.58–1.53 (m, 1H), 1.50–1.38 (m, 2H), 1.36–1.19 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7 (C), 150.5 (C), 129.4 (CH), 125.7 (CH), 121.4 (CH), 83.8 (CH), 30.5 (CH_2), 25.6 (CH_2), 23.7 (CH_2).

^{1}H and ^{13}C NMR were in accordance with those in the literature.



Phenyl cyclopropylmethoxycarbamate (15w): The title compound was synthesized according to general procedure **N** using a two-step deprotection then acylation sequence. First, 2-(cyclopropylmethoxy)isoindoline-1,3-dione[302] (2.17 g, 10.0 mmol) and 50% hydrazine hydrate (1.26 mL, 20.0 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. Second, the crude hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.01 g, 12.0 mmol) and phenylchloroformate (1.25 mL, 10.0 mmol) were added at 0 °C and allowed to stir overnight at rt. Upon completion the reaction was

extracted using saturated $NaHCO_3$ and then brine. The organic layer was separated and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a white solid (1.82 g, 88%) over two steps.

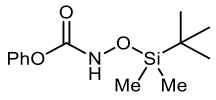
TLC R_f: 0.29 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69–7.63 (m, 1H), 7.38–7.33 (m, 2H), 7.23–7.19 (m, 1H), 7.15–7.13 (m, 2H), 3.78 (d, *J* = 7.3 Hz, 2H), 1.21–1.11 (m, 1H), 0.62–0.58 (m, 2H), 0.33–0.30 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C), 150.4 (C), 129.5 (CH), 125.8 (CH), 121.4 (CH), 81.8 (CH_2), 9.1 (CH), 3.1 (CH_2).

IR (film): 3248, 3064, 2996, 2932, 2876, 1725, 1591, 1472, 1255, 1196 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{11}H_{13}NO_3Na$ $[M+Na]^+$ 230.0793. Found: 230.0813.



Phenyl (*tert*-butyldimethylsilyl)oxycarbamate (15x): The title compound was synthesized according to a modified general procedure **N**. First, $NaHCO_3$ (0.680 g, 8.10 mmol) was diluted in 10 mL of CH_2Cl_2. Then a solution *O*-(*tert*-butyldimethylsilyl)hydroxylamine (0.597 g, 4.05 mmol) in the remaining CH_2Cl_2 (0.25 M) was added dropwise at 0 °C and allowed to stir for 30 min. Phenylchloroformate (0.46 mL, 3.7 mmol) was then added dropwise at 0 °C and allowed to stir overnight at rt. Upon completion, the reaction was diluted with water, then extracted using CH_2Cl_2 twice. The combined organic layers were washed using saturated $NaHCO_3$ and then brine. The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a white solid (1.434 g, 88%).

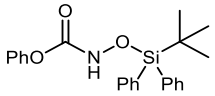
TLC R_f: 0.62 in 15% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): 7.41 – 7.34 (m, 2H), 7.24 – 7.20 (m, 1H), 7.18 – 7.13 (m, 3H), 0.99 (s, 9H), 0.24 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7 (C), 150.5 (C), 129.4 (CH), 125.8 (CH), 121.3 (CH), 25.8 (CH_3), -5.7 (CH_3).

IR (film): 3306, 3242, 2926, 2854, 1727, 1589, 1457, 1360, 1248, 1202 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{21}NO_3SiNa$ $[M+Na]^+$ 290.1188. Found: 290.1211.



Phenyl (*tert*-butyldiphenylsilyl)oxycarbamate (15y): The title compound was synthesized according to a modified general procedure **N**. First, $NaHCO_3$ (0.840 g, 10.0 mmol) was diluted in 40 mL of CH_2Cl_2 (0.25 M). Then a solution *O*-(*tert*-butyldiphenylsilyl)hydroxylamine (1.36 g, 5.00 mmol) in the remaining CH_2Cl_2 (0.25 M) was added dropwise at 0 °C and allowed to stir for 30 min. Phenylchloroformate (0.57 mL, 4.6 mmol) was then added dropwise at 0 °C and allowed to stir overnight at rt. Upon completion, the reaction was diluted with water, then extracted using CH_2Cl_2 twice. The combined organic layers were washed using saturated $NaHCO_3$ and then brine. The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a white solid (1.54 g, 81%).

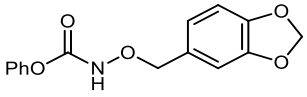
TLC R_f: 0.49 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 8.0, 1.4 Hz, 4H), 7.50–7.45 (m, 2H), 7.43–7.39 (m, 4H), 7.33–7.29 (m, 2H), 7.19–7.17 (m, 1H), 7.16 (s, 1H), 6.96 (d, *J* = 7.7 Hz, 2H), 1.16 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9 (C), 150.5 (C), 135.8 (CH), 131.5 (C), 130.4 (CH), 129.4 (CH), 128.0 (CH), 125.7 (CH), 121.3 (CH), 26.9 (CH_3), 19.2 (C).

IR (film): 3204, 3120, 2954, 2868, 1705, 1425, 1370, 1224, 1198, 1112 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{23}H_{25}NO_3SiNa$ $[M]^+$ 414.1501. Found: 414.1497.



Phenyl benzo[d][1,3]dioxol-5-ylmethoxycarbamate (15z): The title compound was synthesized according to general procedure **O**. To a round bottom flask charged with a stir bar was added *N*-hydroxyphthalimide (2.45 g, 15.0 mmol) followed by dilution in dry THF (0.3 M). PPh_3 (3.93 g, 15.0 mmol) and piperonyl alcohol (2.28 g, 15.0 mmol) were added sequentially and the resulting solution was allowed to stir at 0 °C for 0.3 h. DIAD (3.1 mL, 15.75 mmol) was added dropwise over 1 h, and the mixture was stirred at 0 °C until TLC monitoring indicated completion. Upon completion (by TLC), Et_2O and hexanes were added to the solution, which induced a white precipitate to form upon cooling (Ph_3P=O and DIAD co-crystallize). The precipitate was filtered and the collected solids were discarded. The filtrate, which contained the *N*-alkoxyphthalimide

along with minor impurities, was used in the subsequent step without further purification. Crude NMR spectra are consistent with previous literature reports.[303]

To a round bottom flask charged with a stir bar was added the corresponding crude *N*-alkoxyphthalimide (1.00 eq) followed by dilution in CH_2Cl_2:MeOH (10:1) (0.17 M) and cooled to 0 °C. To this vigorously stirred solution was added a solution of 50% hydrazine hydrate (1.9 mL, 30 mmol). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the *N*-alkoxyphthalimide. Upon completion, the solution is filtered over a fritted funnel and the filtrate is collected (the white precipitate is discarded). The filtrate is extracted with sat. $NaHCO_3$ (x 2) and then brine (x 1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and used in the subsequent step without further purification.
To a round bottom flask charged with a stir bar was added $NaHCO_3$ (2.77 g, 33.0 mmol) followed by dilution with CH_2Cl_2:H_2O (1:1) (0.25 M) and cooled to 0 °C. To this vigorously stirred solution was added the crude corresponding *N*-alkyl hydroxylamine (1.00 eq) and was allowed to stir at 0 °C for 0.5 h. After 0.5 h passed, phenylchloroformate (2.06 mL, 16.5 mmol) was added dropwise. The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the phenylchloroformate. Upon completion, the reaction was extracted using sat. $NaHCO_3$ (x 2) and then brine (x 1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and isolated using recrystallization with ether and hexanes. The product was isolated as white crystals (1.28 g, 30% yield over 3 steps).

M.p.: 113.8-114.1 °C.

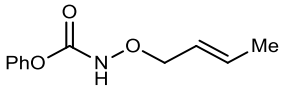
TLC R_f: 0.58 in 40% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (br s, 1H), 7.43 – 7.33 (m, 2H), 7.25 – 7.20 (m, 1H), 7.19 – 7.12 (m, 2H), 6.94 (d, *J* = 1.6 Hz, 1H), 6.90 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 5.98 (s, 2H), 4.87 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (C), 150.33 (C), 148.1 (C), 147.9 (C), 129.4 (CH), 128.8 (CH), 125.8 (CH), 123.3 (CH), 121.3 (CH), 109.7 (CH), 108.3 (CH), 101.2 (CH_2), 78.7 (CH_2).

IR (film): 3293, 2919, 2851, 1720, 1593, 1473, 1441, 1362, 1251, 1203, 1036 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{13}NO_5Na$ $[M+Na]^+$ 310.0691. Found: 310.0710.



(*E*)-Phenyl but-2-en-1-yloxycarbamate (15aa):The title compound was synthesized according to general procedure **N** using a two-step deprotection then acylation sequence. First, (E)-2-(but-2-en-1-yloxy)isoindoline-1,3-dione[304] (1.24 g, 5.70 mmol) and 50% hydrazine hydrate (0.70 mL, 11 mmol) in CH_2Cl_2:MeOH (10:1) (0.17 M) were stirred overnight at 0 °C to rt. The crude hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. Second, the crude hydroxylamine was diluted in CH_2Cl_2:H_2O (1:1) (0.25 M) and $NaHCO_3$ (1.05 g, 12.54 mmol) and phenylchloroformate (0.80 mL, 6.3 mmol) were added at 0 °C and allowed to stir overnight at rt. Upon completion the reaction was extracted using saturated $NaHCO_3$ and then brine. The organic layer was separated and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography (30% EtOAc/Hexanes) to yield the title compound as a white solid (0.639 g, 54%) over two steps.

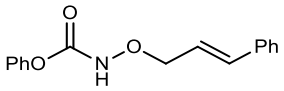
TLC R_f: 0.65 in 40% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (br s, 1H), 7.40 – 7.31 (m, 2H), 7.24 – 7.17 (m, 1H), 7.17 – 7.10 (m, 2H), 5.93 – 5.77 (m, 1H), 5.66 (dddd, *J* = 15.2, 6.8, 5.3, 1.6 Hz, 1H), 4.37 (dt, *J* = 6.8, 1.0 Hz, 2H), 1.75 (ddt, *J* = 6.4, 1.8, 1.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2 (C), 150.4 (C), 133.9 (CH), 129.4 (CH), 125.8 (CH), 124.8 (CH), 121.3 (CH), 77.6 (CH_2), 17.9 (CH_3).

IR (film): 2983, 2939, 1734, 1438, 1371, 1235, 1205, 1163, 1094, 1043 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{11}H_{13}NO_3Na$ $[M+Na]^+$ 230.0793. Found: 230.0768.



(*E*)-Phenyl cinnamyloxycarbamate (15ab): The title compound was synthesized according to general procedure **N** using a two-step deprotection then acylation sequence. First, 2-(cinnamyloxy)isoindoline-1,3-dione[305] (4.19 g, 15.0 mmol) and 50% hydrazine hydrate (1.90 mL, 30.0 mmol) in CH_2Cl_2:MeOH (10:1) (0.17 M) were stirred overnight at 0 °C to rt. The crude hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. Second, the crude hydroxylamine was diluted in CH_2Cl_2:H_2O (1:1) (0.25 M) and $NaHCO_3$ (2.772 g, 33.0 mmol) and phenylchloroformate (2.10 mL, 16.5 mmol) were added at 0 °C and allowed to stir overnight at rt. Upon completion the reaction was extracted using saturated $NaHCO_3$ and then brine. The organic layer was separated and concentrated under

reduced pressure. The product was purified by silica gel flash column chromatography (20% EtOAc/Hexanes) to yield the title compound as a white solid (3.56 g, 88%) over two steps.

TLC R_f: 0.61 in 40% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (br s, 1H), 7.46 – 7.27 (m, 7H), 7.25 – 7.18 (m, 1H), 7.18 – 7.09 (m, 2H), 6.72 (d, *J* = 15.9 Hz, 1H), 6.38 (dt, *J* = 15.9, 6.8 Hz, 1H), 4.62 (dd, *J* = 6.8, 1.1 Hz, 2H).

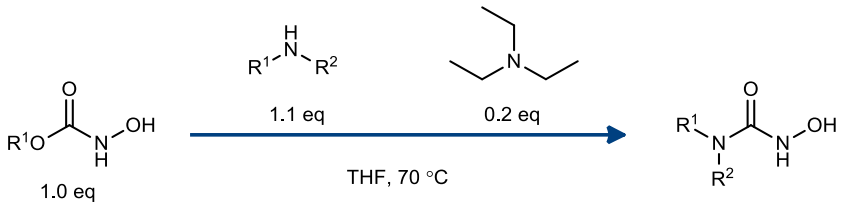
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (C), 150.3 (C), 136.3 (CH), 136.0 (C), 129.4 (CH), 128.6 (CH), 128.3 (CH), 126.7 (CH), 125.8 (CH), 122.7 (CH), 121.3 (CH), 77.6 (CH_2).

IR (film): 3027, 2928, 2853, 1730, 1593, 1490, 1472, 1453, 1238, 1202, 1163, 1086, 967 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{15}NO_3Na$ $[M+Na]^+$ 292.0950. Found: 292.0966.

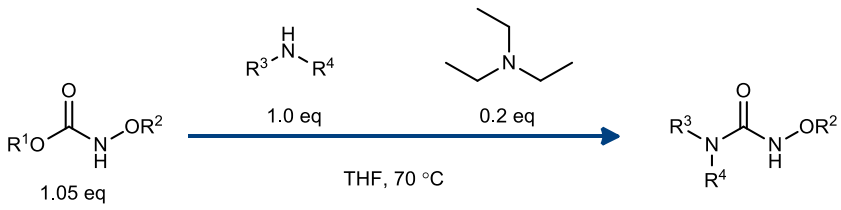
Synthesis of *N*-oxyureas via *O*-isocyanate nucleophilic subsitution

General Procedure Q: Substitution of hydroxycarbamates



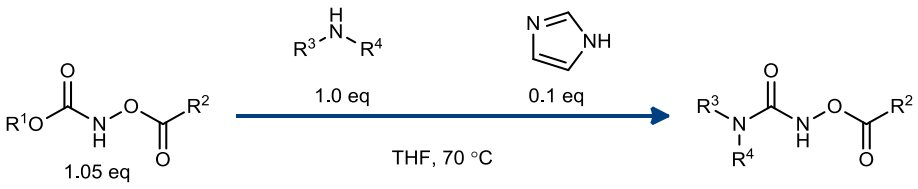
To a 5 mL microwave vial charged with a stir bar was added the phenyl *N*-hydroxycarbamate (1.10 equiv.) then THF (0.3 M), to which was added triethylamine (0.20 equiv.) and the corresponding amine (1.00 equiv.). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via conventional (oil bath) heating. Solvent was removed under reduced pressure and the products were then purified by silica gel chromatography to give the corresponding pure hydroxyureas.

General Procedure R: Substitution of alkoxycarbamates

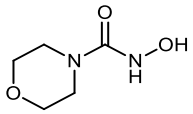


To a 5 mL microwave vial charged with a stir bar was added the phenyl *N*-alkoxycarbamate (1.05 equiv.) then MeCN (0.3 M), to which was added the corresponding amine (1.00 equiv.). The vial was sealed with a microwave cap and heated for 30 min °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, washed twice with 1 M NaOH, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding pure ethoxyureas.

General Procedure S: Substitution of acyloxycarbamates



To a 5 mL microwave vial charged with a stir bar was added the phenyl *N*-acyloxycarbamate (1.00 equiv.) then THF (0.2 M), to which was added the corresponding amine (1.05 equiv.) and then imidazole (0.10 equiv.). The vial was sealed with a microwave cap and heated for 1-3 hours at 100 °C via microwave irradiation. The reaction mixture diluted with EtOAc and transferred to a separatory funnel, was washed twice with 1 M NaOH, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding pure acyloxyureas. In some cases, a higher degree of purity was needed after the extraction and the products could easily be recrystallized or purified by silica gel chromatography.



1-Morpholin-3-hydroxy-urea (16a): The title compound was synthesized using a modified general procedure **Q** using phenyl *N*-hydroxycarbamate (0.754 g, 4.93 mmol), DIPEA (0.013 mL, 0.20 mmol) and morpholine (0.43 mL, 5.0 mmol) in THF (17 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath. The reaction mixture was concentrated under reduced pressure and recrystallized in Et_2O/Hexane. The title compound was obtained as a crystalline white solid (0.511 g, 72%).

TLC R_f: 0.73 in 2% MeOH/CH_2Cl_2.

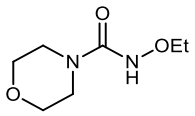
M. p.: 172.0-172.7 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.09-9.06 (br s, 1H), 8.07-8.04 (br s, 1H), 3.54-3.49 (m, 4H), 3.24-3.19 (m, 4H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 159.7(C), 65.8 (CH_2), 43.6 (CH_2).

IR (film): 3303, 3163, 1773, 1519, 1487 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_5H_{10}N_2O_5$ $[M]^+$: 146.0691. Found: 146.0688.



1-Morpholin-3-ethoxy-urea (16b): The title compound was synthesized according to general procedure **R** using phenyl *N*-ethoxycarbamate (0.901 g, 1.05 mmol) and morpholine (0.087 g, 1.0 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over $MgSO_4$, filtered. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (3% MeOH/CH_2Cl_2 then 10% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous yellowish solid (0.174 g, 94%).

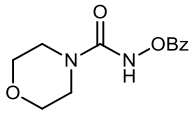
TLC R_f: 0.35 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-6.82 (br s, 1H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.73-3.64 (m, 4H), 3.45-3.37 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2 (C), 71.8 (CH_2), 66.4 (CH_2), 44.0 (CH_2), 13.5 (CH_3).

IR (film): 3165, 1773, 1518, 1487, 1451, 1253 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_7H_{14}N_2O_3Na$ $[M+Na]^+$: 197.0902. Found: 197.0902.



***N*-(Benzoyloxy)morpholine-4-carboxamide (16c):** The title compound was synthesized according to general procedure **S** using phenyl *N*-benzoyloxycarbamate (0.257 g, 1.00 mmol), and diisobutylamine (0.18 mL, 1.05 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h at 120 °C. Upon completion, a small amount of Hexane was added to the crude reaction resulting in a precipitate that was filtered and subsequently washed with a small amount of ether. The title compound was obtained as an off-white amorphous solid (0.156 g, 57 %).

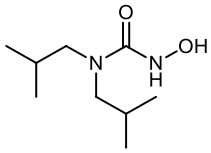
TLC R_f: 0.18 in 50% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67-8.29 (br s, 1H), 8.16-8.08 (m, 2H), 7.69-7.60 (m, 1H), 7.55-7.46 (m, 2H), 3.80-3.69 (m, 4H), 3.59-3.50 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7 (C), 157.2 (C), 134.2 (CH), 129.9 (CH), 128.7 (CH), 126.9 (C), 66.3 (CH_2), 44.2 (CH_2).

IR (film): 3162, 3075, 2980, 2960, 2916, 2841, 1752, 1663, 1507, 1424, 1239 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_7H_{14}N_2O_3Na$ $[M+Na]^+$: 273.0851. Found: 273.0866.



1,1-Diisobutyl-3-hydroxy-urea (16d): The title compound was synthesized according to general procedure **Q** using phenyl *N*-hydroxycarbamate (0.842 g, 5.50 mmol), triethylamine (0.14 mL, 1.0 mmol) and diisobutylamine (0.87 mL, 5.0 mmol) in THF (17 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.785 g, 84%).

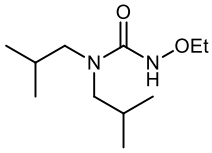
TLC R_f: 0.54 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65-6.61 (br s, 1H), 6.60-6.52 (br s, 1H), 3.07 (d, *J* = 7.6 Hz, 4H), 1.99 (sept, *J* = 7.5 Hz, 2H), 0.92 (d, *J* = 6.7 Hz, 12H).

^{13}C (75 MHz, $CDCl_3$): δ 162.0 (C), 54.4 (CH_2), 27.1 (CH), 20.1 (CH_3).

IR (film): 3365, 3295, 1699, 1496, 1276 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{20}N_2O_2$: 188.1525. Found: 188.1515.



1,1-Diisobutyl-3-ethoxy-urea (16e): The title compound was synthesized according to general procedure **R** using phenyl *N*-ethoxycarbamate (0.901 g, 1.05 mmol) and diisobutylamine (0.129 g, 1.00 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The title compound was obtained as an amorphous white solid (0.211 g, 98%).

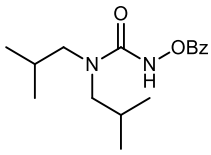
TLC R_f: 0.65 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08-7.05 (br s, 1H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.03 (d, *J* = 7.6 Hz, 4H), 2.04-1.92 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 12H).

^{13}C (75 MHz, $CDCl_3$): δ 159.7 (C), 71.8 (CH_2), 55.1 (CH_2), 27.3 (CH), 20.2 (CH), 13.6 (CH).

IR (film): 3197, 2957, 1636, 1520, 1410, 1383 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{11}H_{24}N_2O_2Na$ $[M+Na]^+$: 239.1736. Found: 239.1729.



3-(Benzoyloxy)-1,1-diisobutylurea (16f): The title compound was synthesized according to general procedure **S** using phenyl *N*-benzoyloxycarbamate (0.257 g, 1.00 mmol), and diisobutylamine (0.18 mL, 1.05 mmol) and imidazole (0.007 g, 0.10 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h. The reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.260 g, 89%).

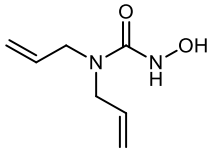
TLC R_f: 0.35 in 40% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (br s, 1H), 8.11 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.62-7.58 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 3.14 (d, *J* = 7.6 Hz, 4H), 2.16-1.97 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3 (C), 158.1 (C), 134.1 (C), 130.0 (CH), 128.7 (CH), 127.3 (CH), 55.1 (CH_2), 27.3 (CH), 20.3 (CH_3).

IR (film): 3125, 2958, 2872, 1760, 1655, 1482, 1417, 1236 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{24}N_2O_3Na$ $[M+Na]^+$: 315.1685. Found: 315.1700.



1,1-Diallyl-3-hydroxy-urea (16g): The title compound was synthesized according to general procedure **Q** using phenyl *N*-hydroxycarbamate (0.168 g, 1.00 mmol), triethylamine (0.03 mL, 0.2 mmol) and diallylamine (0.097 mg, 1.0 mmol) in THF (3.3 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. The reaction mixture was

concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.098 g, 63%).

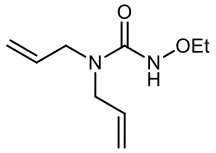
TLC R_f: 0.53 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86-6.80 (br s, 1H), 6.69 (d, *J* = 3.1 Hz, 1H), 5.86-5.72 (m, 2H), 5.27-5.18 (m, 4H), 3.89 (dt, *J* = 5.5, 1.5 Hz, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5 (C), 132.8 (CH), 117.5 (CH_2), 49.0 (CH_2).

IR (film): 3246, 2915, 1640, 1471, 1414, 1281 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{14}N_2O_2$ $[M]^+$: 156.0899. Found: 156.0914.



1,1-Diallyl-3-ethoxy-urea (16h): The title compound was synthesized according to general procedure **R** using phenyl *N*-ethoxycarbamate (0.901 g, 1.05 mmol) and diallylamine (0.097 g, 1.0 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The title compound was obtained as a yellow oil (0.158 g, 86%).

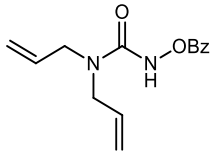
TLC R_f: 0.26 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-7.11 (br s, 1H), 5.85-5.74 (m, 2H), 5.52-5.18 (m, 4H), 3.91 (q, *J* = 7.1Hz, 2H), 3.86 (dt, *J* = 5.6, 1.4 Hz, 4H), 1.24 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3 (C), 133.4 (CH), 117.3 (CH_2), 71.8 (CH_2), 49.1 (CH_2), 13.5 (CH_3).

IR (film): 3228, 2979, 1643, 1471, 1283 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{16}N_2O_2$ $[M]^+$: 184.1212. Found 184.1240.



1,1-Diallyl-3-(benzoyloxy)urea (16i): The title compound was synthesized according to general procedure **S** using phenyl *N*-benzoyloxycarbamate (0.257 g, 1.00 mmol), and diallylamine (0.13 mL, 1.05 mmol) and imidazole (0.007 g, 0.10 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated via microwave irradiation for 3 h. The reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.232 g, 89%).

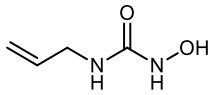
TLC R_f: 0.35 in 30% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (br s, 1H), 8.11 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.61 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.46 (tt, *J* = 7.6, 1.4 Hz, 2H), 5.86 (ddt, *J* = 17.2, 10.4, 5.3 Hz, 2H), 5.35-5.27 (m, 4H), 3.97 (dt, *J* = 5.4, 1.4 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9 (C), 157.8 (C), 134.1 (C), 132.7 (CH), 130.0 (CH), 128.6 (CH), 127.2 (CH), 117.8 (CH_2), 49.3 (CH_2).

IR (film): 3226, 3078, 2959, 1759, 1662, 1600, 1484, 1235 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{14}H_{16}N_2O_3H$ $[M+H]^+$: 261.1239. Found: 261.1214.



1-Allyl-3-hydroxy-urea (16j): The title compound was synthesized according to a modified general procedure **Q** using phenyl *N*-hydroxycarbamate (0.306 g, 2.00 mmol), triethylamine (0.006 g, 0.2 mmol) and allylamine (0.75 mL, 10 mmol) in THF (6.7 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (3% MeOH/CH_2Cl_2 then 10% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.156 g, 67%).

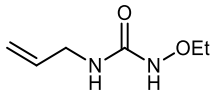
TLC R_f: 0.10 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.57 (d, *J* = 1.2 Hz, 1H), 8.33-8.31 (br s, 1H), 6.82-6.74 (br s, 1H), 5.88-5.74 (m, 1H), 5.13-4.98 (m, 2H), 3.70-3.63 (m, 2H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3 (C), 136.5 (CH), 114.4 (CH_2), 41.0 (CH_2).

IR (film): 3310, 3161, 2853, 1592, 1519, 1488, 1345 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_4H_8N_2O_2$ $[M]^+$: 116.0586. Found 116.0607.



1-Allyl-3-ethoxy-urea (16k): The title compound was synthesized according to a modified general procedure **R** using phenyl *N*-ethoxycarbamate (0.901 g, 1.05 mmol) and allylamine (0.37 mL, 5.0 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The title compound was obtained as a white solid (0.113 g, 79%).

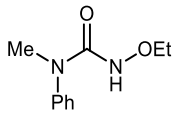
TLC R_f: 0.47 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07-6.96 (br s, 1H), 5.98-5.74 (m, 2H), 5.33-5.12 (m, 2H), 3.98-3.85 (m, 4H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0 (C), 134.5 (CH), 115.9 (CH_2), 71.9 (CH_2), 41.9 (CH_2), 13.7 (CH_3).

IR (film): 3164, 2971, 1669, 1650, 1529, 1441, 1364 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_{12}N_2O_2$ $[M]^+$: 144.0899. Found: 144.0900.



3-Ethoxy-1-methyl-1-phenylurea (16n): The title compound was synthesized according to a modified general procedure **R** using phenyl *N*-ethoxycarbamate (0.901 g, 1.05 mmol), *N*-methylaniline (0.107 g, 1.00 mmol) and imidazole (0.006 g, 0.2 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (3% MeOH/CH_2Cl_2 then 10% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous yellowish solid (0.055 g, 24%).

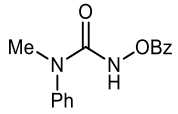
TLC R_f: 0.84 in CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.37 (m, 2H), 7.33-7.27 (m, 1H), 7.24-7.19 (m, 2H), 7.00-6.97 (br s, 1H), 3.83 (q, *J* = 6.9 Hz, 2H), 3.24 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2 (C), 141.9 (C), 129.9 (CH), 127.7 (CH), 126.9 (CH), 71.8 (CH_2), 37.4 (CH_3), 13.3 (CH_3).

IR (film): 3409, 2980, 1747, 1669, 1603, 1507, 1202 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{10}H_{14}N_2O_2Na$ $[M+Na]^+$: 217.0953. Found: 217.0943.



3-(Benzoyloxy)-1-methyl-1-phenylurea (16o): The title compound was synthesized according to general procedure **S** using phenyl *N*-benzoyloxycarbamate (0.257 g, 1.00 mmol), and *N*-methylaniline (0.13 mL, 1.05 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 6 h at 120 °C. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (10% EtOAc/Hexane then 40% EtOAc/Hexane). The title compound was obtained as an amorphous white solid (0.232 g, 91%).

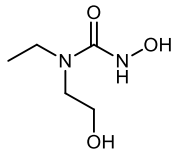
TLC R_f: 0.40 in 50% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (br s, 1H), 8.07-8.04 (m, 2H), 7.62-7.57 (m, 1H), 7.51-7.35 (m, 7H), 3.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8 (C), 157.1 (C), 141.4 (C), 134.0 (C), 130.4 (CH), 130.0 (CH), 128.7 (CH), 128.6 (CH), 127.2 (CH), 127.1 (CH), 38.0 (CH_3).

IR (film): 3125, 2958, 2873, 1760, 1655, 1483, 1452, 1237 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{14}N_2O_3Na$ $[M+Na]^+$: 293.0902. Found: 293.0900.



1-Ethyl-3-hydroxy-1-(2-hydroxyethyl)urea (16p): The title compound was synthesized according to general procedure **Q** using phenyl *N*-hydroxycarbamate (0.842 g, 5.50 mmol), triethylamine (0.14 mL, 1.0 mmol) and 2-(ethylamino)ethanol (0.446 g, 5.00 mmol) in THF (17 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via oil bath heating. The

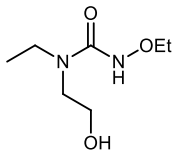
reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH_2Cl_2 then 5% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous yellowish solid (0.671 g, 91%).
TLC R_f: 0.10 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, *J* = 1.8 Hz, 1H), 7.88 (d, *J* = 2.2 Hz, 1H), 4.87 (t, *J* = 5.1 Hz, 1H), 3.47 (q, *J* = 5.7 Hz, 2H), 3.24-3.16 (m, 4H), 1.00 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 160.1 (C), 59.9 (CH_2), 48.0 (CH_2), 41.4 (CH_2), 13.3 (CH_3).

IR (film): 3164, 2931, 1773, 1615, 1519, 1344 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_5H_{12}N_2O_3$ $[M]^+$: 148.0848. Found: 148.0845.



3-Ethoxy-1-ethyl-1-(2-hydroxyethyl)urea (16q): The title compound was synthesized according to general procedure **R** using phenyl *N*-ethoxycarbamate (0.901 g, 1.05 mmol) and 2-(ethylamino)ethanol (0.089 g, 1.0 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The title compound was obtained as a yellowish solid (0.155 g, 88%).

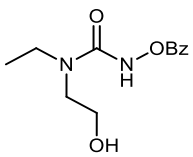
TLC R_f: 0.26 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36-8.28 (br s, 1H), 3.87 (q, *J* = 7.0 Hz, 2H), 3.80-3.74 (m, 2H), 3.37-3.26 (m, 4H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4 (C), 71.4 (CH_2), 61.4 (CH_2), 48.5 (CH_2), 41.8 (CH_2), 13.5 (CH_3), 13.0 (CH_3).

IR (film): 3383, 3275, 2976, 1625, 1518, 1487, 1382 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_7H_{16}N_2O_3Na$ $[M+Na]^+$: 199.1059. Found: 199.1064.



3-(Benzoyloxy)-1-ethyl-1-(2-hydroxyethyl)urea (16r): The title compound was synthesized according to general procedure **S** using phenyl *N*-benzoyloxycarbamate (0.257 g, 1.00 mmol), and *N*-ethylethanolamine (0.10 mL, 1.05 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 6 h at 120 °C. The reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.159 g, 63%).

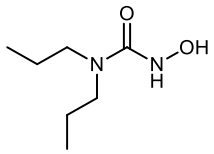
TLC R_f: 0.28 in 50% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66-9.65 (br s, 1H), 8.12-8.08 (m, 2H), 7.62-7.56 (m, 1H), 7.48-7.43 (m, 2H), 3.84 (t, *J* = 4.8 Hz, 2H), 3.47 (t, *J* = 4.8 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 2H), 3.20 (br s, 1H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C), 159.1 (C), 134.0 (C), 130.0 (CH), 128.7 (CH), 127.6 (CH), 62.2 (CH_2) 48.7 (CH_2) 42.7 (CH_2) 13.2 (CH_3).

IR (film): 3355, 3156, 2987, 2916, 1726, 1655, 1464, 1448, 1268, 1236 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{12}H_{16}N_2O_4H$ $[M+H]^+$: 253.1188. Found: 253.1161.



3-Hydroxy-1,1-dipropylurea (16s): The title compound was synthesized according to general procedure **Q** using phenyl *N*-hydroxycarbamate (0.101 g, 0.660 mmol), triethylamine (0.0121 g, 0.120 mmol) and dipropylamine (0.0607 g, 0.060 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (3% MeOH/CH_2Cl_2 then 12% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.081 g, 85%).

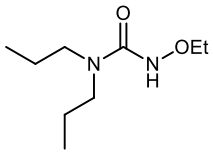
TLC R_f: 0.18 in 50% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.64 (br s, 1H), 6.58 (br s, 1H), 3.19-3.15 (m, 4H), 1.63-1.54 (m, 4H), 0.91 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4 (C), 48.4 (CH_2), 21.3 (CH_2), 11.2 (CH_3).

IR (film): 3274, 2959, 2931, 2875, 1613, 1498, 1376, 1250, 1094 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{16}N_2O_2$ $[M]^+$: 160.1212. Found: 160.1209.



3-Ethoxy-1,1-dipropylurea (16t): The title compound was synthesized according to general procedure **R** using phenyl *N*-ethoxycarbamate (0.181 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.1 mmol) in MeCN (5.0 mL, 0.20 M). The reaction was heated via microwave irradiation for 20 min at 120 °C. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as a clear oil (0.171 g, 91%).

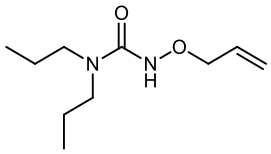
TLC R_f: 0.44 in 20% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (br s, 1H), 3.91 (q, *J* = 7.0 Hz, 2H), 3.13 (t, *J* = 7.7 Hz, 4H), 1.57 (ap sext, *J* = 7.6 Hz, 4H), 1.24 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4 (C), 71.9 (CH_2), 49.1 (CH_2), 21.7 (CH_2), 13.7 (CH_3), 11.4 (CH_3).

IR (film): 3216, 2964, 2933, 2875, 1725, 1644, 1478, 1243 cm^{-1}.

HRMS (EI): Exact mass could not be obtained for the molecular ion. Exact mass calcd for fragment $[C_2H_6NO]^+$ (*O*-ethylhydroxylamine): 60.0449. Found: 60.0440, Exact mass calcd for fragment $[C_7H_{14}NO]^+$ (*N,N*-dipropyl carbamoyl): 128.1075. Found: 128.1056.



3-(Allyloxy)-1,1-dipropylurea (16u): The title compound was synthesized according to general procedure **R** using phenyl allyloxycarbamate (0.193 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.1 mmol) in MeCN (5.0 mL, 0.20 M). The reaction was heated via microwave irradiation for 20 min. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.188 g, 94%).

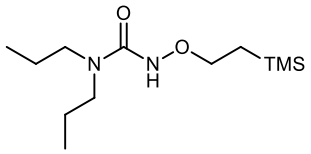
TLC R_f: 0.43 in 20% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (br s, 1H), 5.97 (ddt, *J* = 17.1, 10.5, 6.4 Hz, 1H), 5.33-5.24 (m, 2H), 4.34 (dt, *J* = 6.3, 1.1 Hz, 2H), 3.11 (t, *J* = 7.7 Hz, 4H), 1.55 (ap sext, *J* = 7.6 Hz, 4H), 0.87 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1 (C), 133.1 (CH), 119.7 (CH_2), 77.2 (CH_2), 48.9 (CH_2), 21.6 (CH_2), 11.4 (CH_3).

IR (film): 3219, 2962, 2927, 2873, 1644, 1481, 1405, 1379, 1244 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{10}H_{20}N_2O_2Na$ $[M+Na]^+$: 223.1423. Found: 223.1394.



1,1-Dipropyl-3-(2-(trimethylsilyl)ethoxy)urea (16v): The title compound was synthesized according to general procedure **R** using phenyl 2-(trimethylsilyl)ethoxycarbamate (0.253 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.05 mmol) in MeCN (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 20 min. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.242 g, 93%).

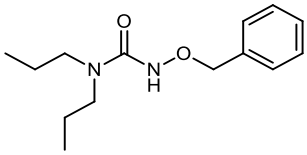
TLC R_f: 0.38 in 20% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (br s, 1H), 3.91-3.87 (m, 2H), 3.11 (dd, *J* = 8.4, 7.0 Hz, 4H), 1.55 (ap sext, *J* = 7.6 Hz, 4H), 1.01-0.97 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 6H), -0.05 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4 (C), 74.1 (CH_2), 49.1(CH_2), 21.7 (CH_2), 16.9 (CH_2), 11.5 (CH_3), 1.28 (CH_3).

IR (film): 3192, 2959, 2929, 2875, 1636, 1518, 1490, 1405, 1426 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{12}H_{28}N_2O_2SiNa$ $[M+Na]^+$: 283.1818. Found: 283.1821.



3-(Benzyloxy)-1,1-dipropylurea (16w): The title compound was synthesized according to general procedure **R** using phenyl benzyloxycarbamate (0.243 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.05 mmol) in MeCN (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 20 min. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.240 g, 96%).

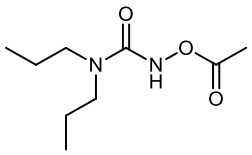
TLC R_f: 0.39 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.30 (m, 5H), 6.96 (br s, 1H), 4.87 (s, 2H), 3.08 (t, *J* = 7.7 Hz, 4H), 1.51 (ap sext, *J* = 7.6 Hz, 4H), 0.84 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0 (C), 136.3 (C), 129.3 (CH), 128.6 (CH), 128.5 (C), 78.1 (CH_2), 49.0 (CH_2), 21.6 (CH_2), 11.4 (CH_3).

IR (film): 3203, 3064, 3033, 2958, 2928, 2872, 1648, 1505, 1473, 1455, 1413, 1239 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{22}N_2O_2$ $[M]^+$: 250.1681. Found: 250.1664.



3-Acetoxy-1,1-dipropylurea (16x): The title compound was synthesized according to general procedure **S** using phenyl acetoxycarbamate (0.195 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.05 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.125 g, 62%).

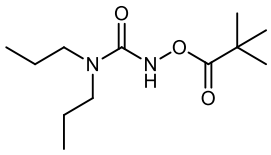
TLC R_f: 0.42 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (br s, 1H), 3.17 (t, *J* = 7.6 Hz, 4H), 2.19 (s, 3H), 1.57 (ap sext, *J* = 7.5, 4H), 0.89 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1 (C), 157.5 (C), 48.9 (CH_2), 21.4 (CH_2), 18.6 (CH_3), 11.3 (CH_3).

IR (film): 3162, 2964, 2936, 2877, 1782, 1655, 1478, 1376 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{18}N_2O_3$ $[M]^+$: 202.1317. Found: 202.1324.



3-(Pivaloyloxy)-1,1-dipropylurea (16y): The title compound was synthesized according to general procedure **S** with slight modification, phenyl pivaloyloxycarbamate (0.237 g, 1.00 mmol) was formed *in situ* following general procedure **P** and used without purification, to which was added dipropylamine (0.14 mL, 1.1 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h at 120 °C. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.215 g, 88%) over two steps.

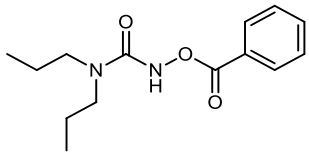
TLC R_f: 0.66 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H), 3.19 (t, *J* = 7.7 Hz, 4H), 1.61 (ap sext, *J* = 7.5 Hz, 4H), 1.31 (s, 9H), 0.91 (t, *J* = 7.4, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0 (C), 157.6 (C), 48.9 (CH_2), 38.4 (C), 27.1 (CH_3), 21.4 (CH_2), 11.3 (CH_3).

IR (film): 3231, 2964, 2936, 2874, 1773, 1659, 1478, 1241 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{24}N_2O_3$ $[M]^+$: 244.1787. Found: 244.1791.



3-(Benzoyloxy)-1,1-dipropylurea (16z): The title compound was synthesized according to general procedure **S** using phenyl *N*-benzoyloxycarbamate (0.257 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.1 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h at 120 °C. Upon completion, the reaction mixture

was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.230 g, 87%).

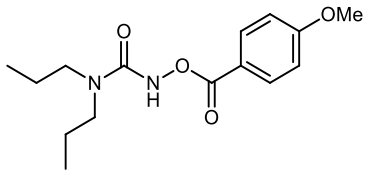
TLC R_f: 0.40 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (br s, 1H), 8.12-8.08 (m, 2H), 7.62-7.56 (m, 1H), 7.44 (tt, *J* = 7.5, 1.3 Hz, 2H), 3.24 (t, *J* = 7.6 Hz, 4H), 1.64 (ap sext, *J* = 7.5 Hz, 4H), 0.92 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2 (C), 157.6 (C), 134.0 (C), 129.9 (CH), 128.6 (CH), 127.3 (C), 49.0 (CH_2), 21.4 (CH_2), 11.3 (CH_3).

IR (film): 3213, 2963, 2931, 2874, 1781, 1762, 1647, 1510, 1483, 1378 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{20}N_2O_3$ $[M]^+$: 264.1474. Found: 264.1453.



3-((4-Methoxybenzoyl)oxy)-1,1-dipropylurea (16aa): The title compound was synthesized according to general procedure **S** using phenyl (4-methoxybenzoyl)oxycarbamate (0.287 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.1 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 1 h at 120 °C. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.280 g, 95%).

TLC R_f: 0.33 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.07-8.04 (m, 2H), 6.93-6.91 (m, 2H), 3.23 (t, *J* = 7.6 Hz, 4H), 1.64 (ap sext, 7.5 Hz, 4H), 0.92 (t, *J* = 7.4 Hz, 6H).

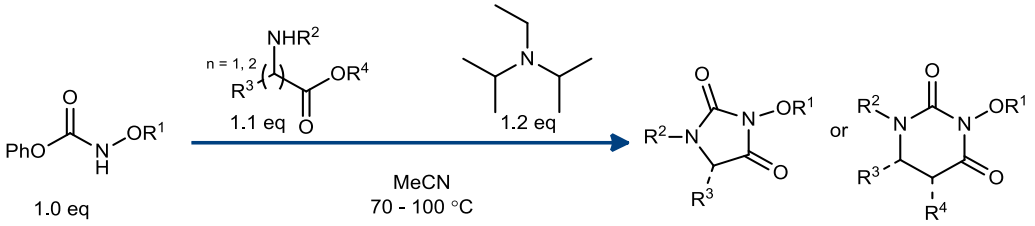
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C), 164.3 (C), 157.8 (C), 132.2 (CH), 119.5 (C), 114.1 (CH), 55.6 (CH_3), 49.1 (CH_2), 21.6 (CH_2), 11.4 (CH_3).

IR (film): 3218, 2963, 2933, 2874, 1748, 1666, 1604, 1509, 1463, 1238, 1165 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{22}N_2O_4$ $[M]^+$: 294.1580. Found: 294.1595.

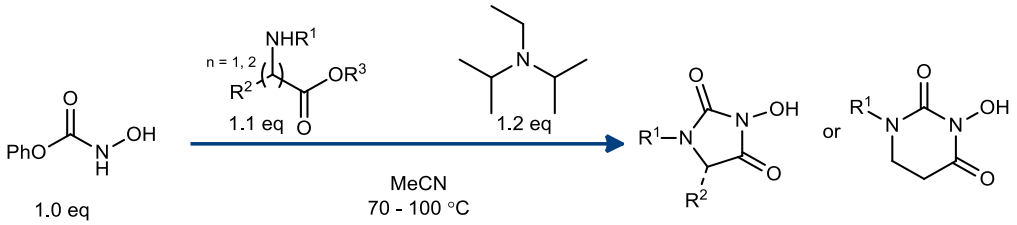
Synthesis of hydantoins and dihydrouracils via *O*-isocyanate cascade reactions

General Procedure T: Synthesis of alkoxy-hydantoins and dihydrouracils



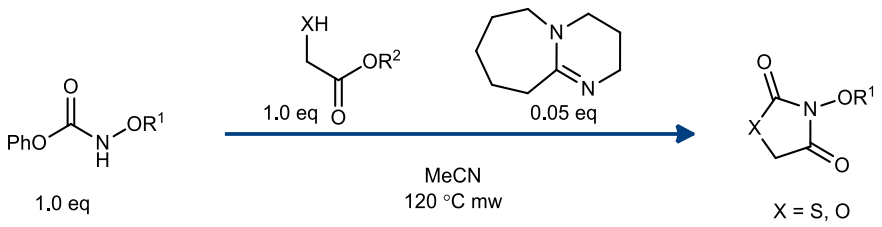
To a 5 mL microwave vial charged with a stir bar was added the corresponding α- or β-aminoester (1.00 equiv) then acetonitrile (0.3 M), to which was added *i*-Pr_2NEt (0.05 equiv, 1.10 equiv for aminoester hydrochlorides), and finally the *N*-alkoxycarbamate (1.00 equiv). The vial was sealed with a microwave cap and heated for 2 h or 4 h at the temperature specified (90-120 °C) via microwave irradiation. The crude products were then purified by silica gel chromatography to give the corresponding pure alkoxy-hydantoins and dihydrouracils.

General Procedure U: Synthesis of hydroxy-hydantoins and dihydrouracils)

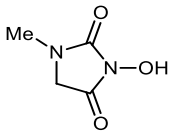


To a 5 mL microwave vial charged with a stir bar was added the corresponding α- or β-aminoester (1.10 equiv) then THF (0.3 M), to which was added *i*-Pr_2NEt (1.20 equiv), and finally the *N*-hydroxycarbamate (1.00 equiv). The vial was sealed with a microwave cap and heated for 16 h at the temperature specified (70-100 °C) via conventional (oil bath) heating. The crude products were then purified by silica gel chromatography to give the corresponding pure hydroxy-hydantoins and dihydrouracils.

General Procedure V: Synthesis of alkoxyoxazolidine-2,4-dione and alkoxythiazolidine-2,4-diones



To a 5 mL microwave vial charged with a stir bar was added the corresponding ester (1.00 equiv) then acetonitrile (0.3 M), to which was added DBU (0.05 equiv), and finally the *N*-alkoxycarbamate (1.00 equiv). The vial was sealed with a microwave cap and heated for 2 h at the temperature specified (120 °C) via microwave irradiation. The crude products were then purified by silica gel chromatography to give the corresponding pure alkoxy-oxazolidine/ thiazolidines.



3-Hydroxy-1-methylimidazolidine-2,4-dione (14a): Synthesized according to general procedure **U** using sarcosine ethyl ester hydrochloride (0.153 g, 1.00 mmol), phenyl hydroxycarbamate (0.168 g, 1.10 mmol) and *i*-Pr_2NEt (0.155 g, 1.20 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C in an oil bath. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (1% MeOH/CH_2Cl_2 then 10% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.118 g, 91%).

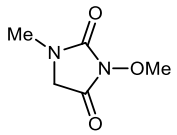
TLC R_f: 0.07 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 2H), 3.02 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1 (C), 154.5 (C), 49.8 (CH_2), 30.3 (CH_3).

IR (film): 2881, 1725, 1717, 1272 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_4H_6N_2O_3$ $[M]^+$: 130.0378. Found: 130.0377.



3-Methoxy-1-methylimidazolidine-2,4-dione (14b): Synthesized according to general procedure **T** using sarcosine ethyl ester hydrochloride (0.123 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.114 g, 0.880 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (10% EtOAc/CH_2Cl_2). The title compound was obtained as a clear oil (0.114 g, >99%).

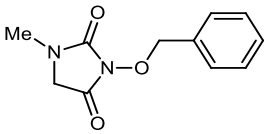
TLC R_f: 0.25 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.98 (s, 3H), 3.85 (s, 2H), 3.00 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9 (C), 152.8 (C), 65.3 (CH_3), 49.7 (CH_2), 30.7 (CH_3).

IR (film): 3674, 3103, 2923, 1787, 1735, 1558, 1440, 1363, 1276, 1246, 1176 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_5H_8N_2O_3$ $[M]^+$: 144.0535. Found: 144.0533.



3-(Benzyloxy)-1-methylimidazolidine-2,4-dione (14c): Synthesized according to general procedure **T** using sarcosine ethyl ester hydrochloride (0.0614 g, 0.400 mmol), phenyl benzyloxycarbamate (0.0972 g, 0.400 mmol) and *i*-Pr_2NEt (0.0568 g, 0.44 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH_2Cl_2 then 10% EtOAc/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.0873 g, >99%).

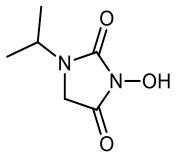
TLC R_f: 0.52 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58- 7.47 (m, 2H), 7.45-7.33 (m, 3H), 5.14 (s, 2H), 3.80 (s, 2H), 2.98 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1 (C), 153.1 (C), 133.5 (C), 129.8 (CH), 129.3 (CH), 128.5 (CH), 79.4 (CH_2), 49.6 (CH_2), 30.1 (CH_3).

IR (film): 3450, 2470, 1791, 1736, 1558, 1506, 1446, 1244, 1085 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{12}N_2O_3$ $[M]^+$: 220.0848. Found: 220.0845.



3-Hydroxy-1-isopropylimidazolidine-2,4-dione (14d): Synthesized according to general procedure **U** using *N*-(ethoxycarbonylmethyl)-*N*-isopropylammonium chloride (0.145 g, 0.800 mmol), phenyl hydroxycarbamate (0.135 g, 0.880 mmol) and *i*-Pr_2NEt (0.124 g, 0.960 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 90 °C in an oil bath. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (2% MeOH/CH_2Cl_2). The title compound was obtained as a brown oil (0.092 g, 73%).

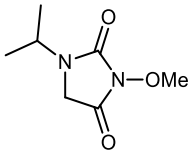
TLC R_f: 0.30 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.33 (spt, *J* = 6 Hz, 1H), 3.83 (s, 2H), 1.21 (d, *J* = 6Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8 (C), 154.1 (C), 44.2 (CH_2), 43.1 (CH_3), 19.9 (CH_3).

IR (film): 2891, 2158, 1735, 1717, 1513, 1236 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_{10}N_2O_3$ $[M]^+$: 158.0691. Found: 158.0689.



1-Isopropyl-3-methoxyimidazolidine-2,4-dione (14e): Synthesized according to general procedure **T** using ethyl 2-(isopropylamino)acetate hydrochloride (0.145 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.114 g, 0.880 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH_2Cl_2 then 7.5% EtOAc/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.132 g, 96%).

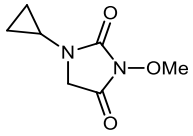
TLC R_f: 0.25 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.32 (spt, *J* = 6.8 Hz, 1H), 3.95 (s, 3H), 3.74 (s, 2H), 1.18 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.4 (C), 151.9 (C), 65.3 (CH_3), 43.9 (CH), 42.9 (CH_2), 19.9 (CH_3).

IR (film): 2921, 1784, 1730, 1683, 1448, 1417, 1266, 1238, 1078 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{12}N_2O_3$ $[M]^+$: 172.0848. Found: 172.0849.



1-Cyclopropyl-3-methoxyimidazolidine-2,4-dione (14f): Synthesized according to general procedure **T** using ethyl 2-(cyclopropylamino)acetate (0.115 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (5% EtOAc/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.121 g, 89%).

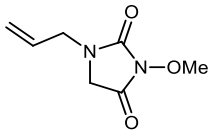
TLC R_f: 0.60 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (s, 3H), 3.82 (s, 2H), 2.69-2.57 (m, 1H), 0.92-0.72 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0 (C), 152.9 (C), 65.3 (CH_3), 48.5 (CH_2), 25.3 (CH), 5.7 (CH_2).

IR (film): 2864, 1843, 1778, 1733, 1683, 1647, 1558, 1506, 1448, 1264, 1112 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{10}N_2O_3$ $[M]^+$: 170.0691. Found: 170.0699.



1-Allyl-3-methoxyimidazolidine-2,4-dione (14g): Synthesized according to general procedure **T** using ethyl 2-(allylamino)acetate (0.115 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (5% EtOAc/CH_2Cl_2). The title compound was obtained as clear oil (0.113 g, 83%).

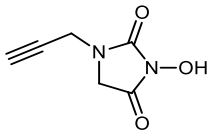
TLC R_f: 0.55 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.73 (dd, *J* = 10.2, 17.0 Hz, 1H), 5.31-5.20 (m, 2H), 4.00-3.93 (m, 5H), 3.78 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.2 (C), 152.5 (C), 131.0 (CH), 120.0 (CH_2), 65.4 (CH_3), 47.2 (CH_2), 45.7 (CH_2).

IR (film): 3105, 1787, 1733, 1558, 1454, 1417, 1266, 1232, 1188 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{10}N_2O_3$ $[M]^+$: 170.0691. Found: 170.0729.



3-Hydroxy-1-(prop-2-yn-1-yl)imidazolidine-2,4-dione (14h): Synthesized according to general procedure **U** using ethyl 2-(prop-2-yn-1-ylamino)acetate (0.113 g, 0.800 mmol), phenyl hydroxycarbamate (0.135 g, 0.880 mmol) and *i*-Pr_2NEt (0.124 g, 0.960 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C in an oil bath. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (1% MeOH/CH_2Cl_2 then 5% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.081g, 66%).

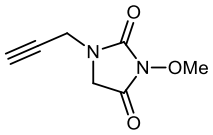
TLC R_f: 0.10 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 4.13 (d, *J* = 3 Hz, 2H), 3.97 (s, 2H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 165.2 (C), 154.0 (C), 77.8 (CH_2), 75.7 (C), 47.0 (CH_2), 34.2 (CH).

IR (film): 2997, 2142, 1734, 1647, 1562 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_6N_2O_3$ $[M]^+$: 154.0378. Found: 154.0378.



3-Methoxy-1-(prop-2-yn-1-yl)imidazolidine-2,4-dione (14i): Synthesized according to general procedure **T** using ethyl 2-(prop-2-yn-1-ylamino)acetate (0.113 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH_2Cl_2 then 10% EtOAc/CH_2Cl_2). The title compound was obtained as clear oil (0.122 g, >99%).

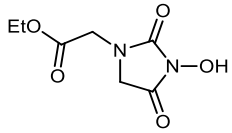
TLC R_f: 0.39 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 4.14 (d, *J* = 2.5 Hz, 2H), 3.98 (s, 2H), 3.83 (s, 3H), 3.38 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3 (C), 152.1 (C), 77.6 (CH), 75.8 (C), 64.8 (CH_3), 47.3 (CH_2), 32.3 (CH_2).

IR (film): 1816, 1749, 1733, 1662, 1558, 1505, 1446, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_8N_2O_3$ $[M]^+$: 168.0535. Found: 168.0539.



Ethyl 2-(3-hydroxy-2,4-dioxoimidazolidin-1-yl)acetate (14j): Synthesized according to general procedure **U** using diethyl 2,2'-azanediyldiacetate (0.151 g, 0.800 mmol), phenyl hydroxycarbamate (0.135 g, 0.880 mmol) and *i*-Pr_2NEt (0.124 g, 0.960 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 90 °C in an oil bath. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (1% MeOH/CH_2Cl_2 then 5% MeOH/CH_2Cl_2). The title compound was obtained as a brown oil (0.141g, 69%).

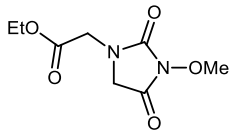
TLC R_f: 0.23 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.33 (q, *J* = 6 Hz, 2H), 4.14 (s, 2H), 4.06 (s, 2H), 1.21 (d, *J* = 6Hz, 3H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 168.3 (C), 165.9 (C), 155.0 (C), 61.9 (CH_2), 48.4 (CH_2), 44.1 (CH_2), 13.9 (CH_3).

IR (film): 2842, 1740, 1701, 1684, 1562 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{10}N_2O_5$ $[M]^+$: 202.0590. Found: 202.0592.



Ethyl 2-(3-methoxy-2,4-dioxoimidazolidin-1-yl)acetate (14k): Synthesized according to general procedure **T** using diethyl 2,2'-azanediyldiacetate (0.151 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using

flash chromatography (10% EtOAc/CH_2Cl_2). The title compound was obtained as clear oil (0.163 g, 94%).

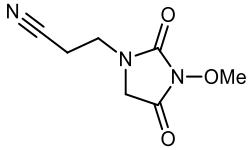
TLC R_f: 0.28 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.21 (q, *J* = 7.3 Hz, 2H), 4.11 (s, 2 H), 4.01-3.95 (m, 5H), 1.27 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0 (C), 164.0 (C), 153.2 (C), 65.4 (CH_3), 62.0 (CH_2), 48.4 (CH_2), 44.0 (CH_2), 14.1 (CH_3).

IR (film): 3647, 1733, 1683, 1662, 1558, 1506, 1466, 1262 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_8H_{12}N_2O_3$ $[M]^+$: 216.0746. Found: 216.0743.



3-(3-Methoxy-2,4-dioxoimidazolidin-1-yl)propanenitrile (14l): Synthesized according to general procedure **T** using ethyl 2-((2-cyanoethyl)amino)acetate (0.125 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (30% EtOAc/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.147 g, >99%).

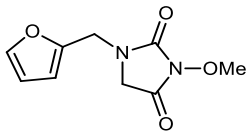
TLC R_f: 0.18 in 30% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.04 (s, 2H), 3.97 (s, 3H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.69 (t, *J* = 6.4 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (C), 152.8 (C), 117.4 (C), 65.6 (CH_3), 48.8 (CH_2), 39.8 (CH_2), 17.4 (CH_2).

IR (film): 2804, 1868, 1791, 1735, 1700, 1653, 1558, 1606, 1264 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_9N_3O_3$ $[M]^+$: 183.0644. Found: 183.0651.



1-(Furan-2-ylmethyl)-3-methoxyimidazolidine-2,4-dione (14m): Synthesized according to general procedure **T** using ethyl 2-((furan-2-ylmethyl)amino)acetate (0.147 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (5% EtOAc/CH_2Cl_2). The title compound was obtained as a dark yellow oil (0.139 g, 83%).

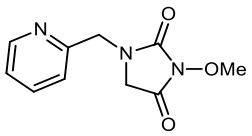
TLC R_f: 0.58 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 0.8, 1.7 Hz, 1H), 6.37-6.27 (m, 2H), 4.52 (s, 2H), 3.97 (s, 3H), 3.80 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1 (C), 152.5 (C), 148.3 (C), 143.2 (CH), 110.7 (CH_2), 109.6 (CH_2), 65.4 (CH_3), 47.5 (CH_2), 39.6 (CH_2).

IR (film): 3550, 2955, 2415, 1788, 1772, 1735, 1716, 1647, 1542, 1240, 1085 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{10}N_2O_4$ $[M]^+$: 210.0641. Found: 210.0633.



3-Methoxy-1-(pyridin-2-ylmethyl)imidazolidine-2,4-dione (14n): Synthesized according to general procedure **T** using ethyl 2-((pyridin-2-ylmethyl)amino)acetate (0.155 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (30% EtOAc/CH_2Cl_2 then 5% CH_3OH/CH_2Cl_2). The title compound was obtained as a dark yellow oil (0.150 g, 85%).

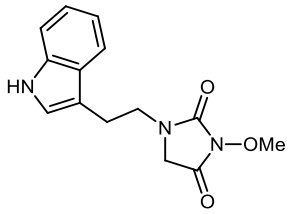
TLC R_f: 0.22 in 5% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56-8.47 (m, 1H), 7.67 (dt, *J* = 1.7, 7.7 Hz, 1H), 7.29-7.14 (m, 2H), 4.62 (s, 2H), 3.99-3.92 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5 (C), 154.8 (C), 153.2 (C), 149.7 (CH), 137.2 (CH), 123.0 (CH), 122.4 (CH), 65.4 (CH_3), 48.3 (CH_2), 48.2 (CH_2).

IR (film): 3524, 2935, 2402, 1733, 1706, 1555, 1539, 1489, 1254, 1191 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{11}N_3O_3$ $[M]^+$: 221.0800. Found: 221.0804.



1-(2-(1*H*-Indol-3-yl)ethyl)-3-methoxyimidazolidine-2,4-dione (14o): Synthesized according to general procedure **T** using ethyl 2-((2-(1H-indol-3-yl)ethyl)amino)acetate (0.0986 g, 0.400 mmol), phenyl methoxycarbamate (0.0669 g, 0.400 mmol) and *i*-Pr_2NEt (0.0026 g, 0.020 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (30% EtOAc/CH_2Cl_2 then 2.5% CH_3OH/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.101 g, 92%).

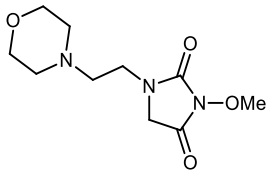
TLC R_f: 0.44 in 2.5% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (br s, 1H), 7.63-7.56 (m, 1H), 7.39 (td, *J* = 0.9, 8.1 Hz, 1H), 7.26-7.20 (m, 1H), 7.18-7.12 (m, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 3H), 3.74 (t, *J* = 7.0 Hz, 2H), 3.63 (s, 2H), 3.09 (dt, *J* = 0.8, 7.0 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3 (C), 152.7 (C), 136.3 (C), 127.0 (C), 122.5 (CH), 121.9 (CH), 119.8 (CH), 118.3 (CH), 112.0 (C), 111.5 (CH), 65.3 (CH_3), 48.3 (CH_2), 43.7 (CH_2), 23.9 (CH_2).

IR (film): 3569, 2931, 1818, 1733, 1706, 1679, 1647, 1263, 1220, 1010 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{12}N_3O_3$ $[M]^+$: 273.1113. Found: 273.1069.



3-Methoxy-1-(2-morpholinoethyl)imidazolidine-2,4-dione (14p): Synthesized according to general procedure **T** using ethyl 2-((2-morpholinoethyl)amino)acetate (0.0865 g, 0.400 mmol), phenyl methoxycarbamate (0.0669 g, 0.400 mmol) and *i*-Pr_2NEt (0.0026 g, 0.020 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and

purified using flash chromatography (10% EtOAc/CH_2Cl_2 then 5% CH_3OH/CH_2Cl_2). The title compound was obtained as a clear oil (0.0972 g, >99%).

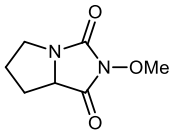
TLC R_f: 0.33 in 5% CH_3OH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.05-3.86 (m, 5H), 3.68 (br s, 4H), 3.51 (t, *J* = 5.9 Hz, 2H), 2.50 (br s, 3H), 2.57 (br s., 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5 (C), 152.9 (C), 67.0 (CH_2), 65.4 (CH_3), 56.3 (CH_2), 53.5 (CH_2), 48.3 (CH_2), 39.3 (CH_2).

IR (film): 3514, 2864, 1789, 1792, 1733, 1652, 1455, 1263 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{17}N_3O_4$ $[M]^+$: 243.1219. Found: 243.1226.



2-Methoxytetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (14q): Synthesized according to general procedure **T** using methyl pyrrolidine-2-carboxylate hydrochloride (0.133 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.114 g, 0.880 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH_2Cl_2 then 10% EtOAc/CH_2Cl_2). The title compound was obtained as a clear oil (0.110 g, 81%).

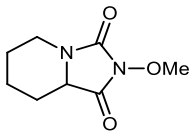
TLC R_f: 0.31 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.05 (dd, *J* = 7.3, 9.5 Hz, 1H), 3.97 (s, 3H), 3.66 (td, *J* = 7.9, 11.2 Hz, 1H), 3.30 (ddd, *J* = 4.2, 8.3, 11.2 Hz, 1 H), 2.38-2.27 (m, 1H), 2.21-2.10 (m, 1H), 2.10-1.98 (m, 1H), 1.80-1.66 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3 (C), 156.3 (C), 65.2 (CH_3), 61.0 (CH), 45.6 (CH_2), 27.6 (CH_2), 26.5 (CH_2).

IR (film): 2935, 1865, 1791, 1731, 1718, 1668, 1558, 1392, 1257, 1224 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{10}N_2O_3$ $[M]^+$: 170.0691. Found: 170.0693.



2-Methoxytetrahydroimidazo[1,5-*a*]pyridine-1,3(2*H*,5*H*)-dione (14r): Synthesized according to general procedure **T** using methyl piperidine-2-carboxylate (0.126 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH_2Cl_2 then 10% EtOAc/CH_2Cl). The title compound was obtained as a clear oil (0.147 g, >99%).

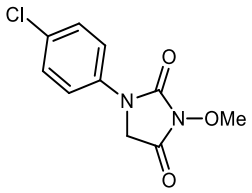
TLC R_f: 0.30 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17-4.03 (m, 1H), 3.94 (s, 3H), 3.73 (dd, *J* = 4.2, 11.9 Hz, 1H), 2.79 (dt, *J* = 3.5, 12.8 Hz, 1H), 2.20 (dd, *J* = 3.1, 12.7 Hz, 1H), 2.05-1.91 (m, 1H), 1.80-1.66 (m, 1H), 1.51-1.27 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2 (C), 150.7 (C), 65.3 (CH_3), 55.7 (CH), 39.4 (CH_2), 27.5 (CH_2), 24.9 (CH_2), 22.5 (CH_2).

IR (film): 3647, 2360, 1890, 1855, 1780, 1737, 1683, 1558, 1521, 1446, 1276 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_8H_{12}N_2O_3$ $[M]^+$: 184.0848. Found: 184.0861.



1-(4-Chlorophenyl)-3-methoxyimidazolidine-2,4-dione (14t): Synthesized according to general procedure **T** using ethyl 2-((4-chlorophenyl)amino)acetate (0.167 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in CH_2Cl_2 and then recrystallized in CH_2Cl_2/hexanes. The solid was then filtered and washed with Et_2O to give pure product. The title compound was obtained as a crystalline tan solid (0.141 g, 73%).

TLC R_f: 0.13 in 100% CH_2Cl_2.

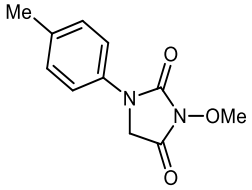
M.p.: 192.2-193.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56-7.46 (m, 2H), 7.43-7.34 (m, 2H), 4.27 (s, 2H), 4.06 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3 (C), 150.2 (C), 135.7 (C), 130.3 (C), 129.5 (CH), 119.3 (CH), 65.6 (CH_3), 47.7 (CH_2).

IR (film): 2921, 1789, 1743, 1729, 1683, 1496, 1436, 1406, 1298, 1184, 1093 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_9ClN_2O_3$ $[M]^+$: 240.0302. Found: 240.0302.



3-Methoxy-1-(*p*-tolyl)imidazolidine-2,4-dione (14u): Synthesized according to general procedure **T** using ethyl 2-(*p*-tolylamino)acetate (0.118 g, 0.610 mmol), phenyl methoxycarbamate (0.102 g, 0.610 mmol) and *i*-Pr_2NEt (0.0039 g, 0.030 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in CH_2Cl_2 and then recrystallized in CH_2Cl_2/hexanes. The solid was then filtered and washed with Et_2O to give pure product. The title compound was obtained as an amorphous white solid (0.118 g, 88%).

TLC R_f: 0.15 in 100% CH_2Cl_2.

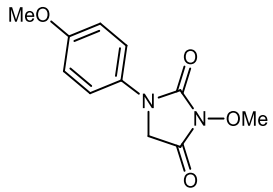
M.p.: 172.6-173.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.37 (m, 2H), 7.24-7.17 (m, 2H), 4.26 (s, 2H), 4.06 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9 (C), 150.3 (C), 134.8 (C), 134.5 (C), 129.9 (CH), 118.4 (CH), 65.5 (CH_3), 47.9 (CH_2), 20.8 (CH_3).

IR (film): 3197, 2956, 1791, 1735, 1683, 1647, 1616, 1558, 1515, 1436, 1404, 1363, 1184, 1107 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{12}N_2O_3$ $[M]^+$: 220.0848. Found: 220.0854.



3-methoxy-1-(4-methoxyphenyl)imidazolidine-2,4-dione (14v): Synthesized according to general procedure **T** using ethyl 2-((4-methoxyphenyl)amino)acetate (0.167 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in CH_2Cl_2 and then recrystallized in CH_2Cl_2/hexanes. The solid was then filtered and washed with Et_2O to give pure product. The title compound was obtained as a crystalline tan solid (0.163 g, 86%).

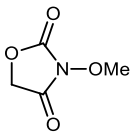
TLC R_f: 0.10 in 100% CH_2Cl_2. M.p 183.7-184.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.36 (m, 2H), 7.00-6.88 (m, 2H), 4.26 (s, 2H), 4.06 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9 (C), 157.1 (C), 150.4 (C), 130.4 (C), 120.6 (CH), 114.7 (CH), 65.5 (CH_3), 55.5 (CH_3), 48.3 (CH_2).

IR (film): 3601, 1772, 1733, 1652, 1516, 1261, 1199, 1056 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{12}N_2O_4$ $[M]^+$: 236.0797. Found: 236.0805.



3-Methoxyoxazolidine-2,4-dione (14x): Synthesized according to general procedure **V** using ethyl 2-hydroxyacetate (0.0833 g, 0.800 mmol), phenyl methoxycarbamate (0.066 g, 0.40 mmol) and DBU (0.006 g, 0.05 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (30% EtOAc/hexanes then 40% EtOAc/hexanes). The title compound was obtained as an amorphous white solid (0.030 g, 55%).

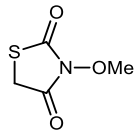
TLC R_f: 0. 38 in 100% CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.74 (s, 2H), 4.04 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0 (C), 151.0 (C), 66.2 (CH_2), 65.5 (CH_3).

IR (film): 2956, 1772, 1757, 1259, 1122 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_4H_5NO_4Na$ $[M+Na]^+$: 154.0111. Found: 154.0116.



3-Methoxythiazolidine-2,4-dione (14y): Synthesized according to general procedure **V** using methyl thioglycolate (0.0.849 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and DBU (0.006 g, 0.05 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (30% EtOAc/hexanes then 40% EtOAc/hexanes). The title compound was obtained as a yellow oil (0.090 g, 72%).

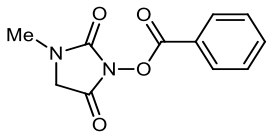
TLC R_f: 0. 50 in 100% CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99 (s, 3H), 3.90 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8 (C), 164.9 (C), 64.8 (CH_2), 29.8 (CH_3).

IR (film): 2896, 2827,1713, 1697, 1192 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_4H_5NO_3S$ $[M]^+$: 146.9990. Found: 147.0013.



3-Methyl-2,5-dioxoimidazolidin-1-yl benzoate (14z): Synthesized according to general procedure **T** using sarcosine ethyl ester hydrochloride (0.0614 g, 0.400 mmol), phenyl benzoyloxycarbamate (0.103 g, 0.400 mmol) and *i*-Pr_2NEt (0.0568 g, 0.440 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 90 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH_2Cl_2 then 10% EtOAc/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.061g, 65%).

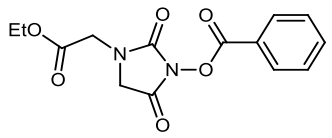
TLC R_f: 0.50 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18-8.06 (m, 2H), 7.66 (tt, *J* = 1.2, 7.5 Hz, 1H), 7.55-7.44 (m, 2H), 4.04 (s, 2H), 3.05 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4 (C), 162.6 (C), 151.7 (C), 134.9 (CH), 130.7 (CH), 128.9 (CH), 125.2 (C), 50.0 (CH_2), 30.4 (CH_3).

IR (film): 3444, 2988, 1755, 1735, 1718, 1690, 1597, 1422, 1406, 1398, 1284, 1083 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{10}N_2O_4$ $[M]^+$: 234.0641. Found: 234.0627.



3-(2-Ethoxy-2-oxoethyl)-2,5-dioxoimidazolidin-1-yl benzoate (14aa): Synthesized according to general procedure **T** using diethyl 2,2'-azanediyldiacetate (0.151 g, 0.400 mmol), phenyl benzoyloxycarbamate (0.103 g, 0.400 mmol) and *i*-Pr_2NEt (0.0026 g, 0.020 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 90 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH_2Cl_2 then 10% EtOAc/CH_2Cl_2). The title compound was obtained as clear oil (0.107 g, 87%).

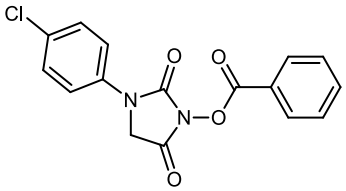
TLC R_f: 0.60 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26-8.10 (m, 2H), 7.69 (tt, *J* = 1.2, 7.5 Hz, 1H), 7.58-7.46 (m, 2H), 4.36-4.07 (m, 6H), 1.32 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8 (C), 163.2 (C), 162.3 (C), 134.9 (CH), 130.6 (CH), 128.8 (CH), 125.0 (C), 62.0 (CH_3), 48.7 (CH_2), 44.2 (CH_2), 14.1 (CH_3).

IR (film): 3180, 2999, 1760, 1733, 1725, 1680, 1497, 1433, 1306, 1098 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{14}N_2O_6$ $[M]^+$: 306.0852. Found: 306.0849.



3-(4-Chlorophenyl)-2,5-dioxoimidazolidin-1-yl benzoate (14ab): Synthesized according to general procedure **T** using ethyl 2-((4-chlorophenyl)amino)acetate (0.0855 g, 0.400 mmol), phenyl benzoyloxycarbamate (0.103 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in CH_2Cl_2 and then recrystallized in CH_2Cl_2/hexanes. The solid was

then filtered and washed with Et_2O to give pure product. The title compound was obtained as an amorphous white solid (0.138 g, 52%).

TLC R_f: 0.13 in 100% CH_2Cl_2.

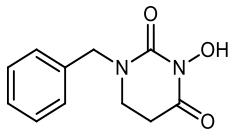
M.p.: 213.3-214.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24-8.13 (m, 2H), 7.76-7.67 (m, 1H), 7.61-7.47 (m, 4H), 7.46-7.33 (m, 2H), 4.49 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.4 (C), 161.7 (C), 149.1 (C), 135.6 (C), 135.1 (C), 130.7 (CH), 129.6 (CH), 128.9 (CH), 124.8 (C), 119.5 (CH), 48.1 (CH_2).

IR (film): 3335, 2884, 1758, 1733, 1718, 1622, 1597, 1335, 1306 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{16}H_{11}ClN_2O_4$ $[M]^+$: 330.0407. Found: 330.0406.



1-Benzyl-3-hydroxydihydropyrimidine-2,4(1*H*,3*H*)-dione (17a): Synthesized according to general procedure **U** using ethyl 3-(benzylamino)propanoate (0.842 g, 5.50 mmol), phenyl hydroxycarbamate (1.03 g, 5.00 mmol) and *i*-Pr_2NEt (1.05 mL, 6.00 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 100 °C in an oil bath. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (10% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.868 g, 80%).

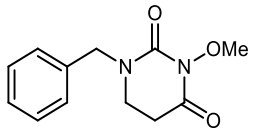
TLC R_f: 0.16 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.21 (m, 5H), 4.62 (s, 2H), 3.29 (t, *J* = 6Hz, 2H), 2.72 (t, *J* = 6 Hz, 2H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 152.7 (C), 135.6 (CH), 128.9 (CH), 128.1 (CH), 51.5 (CH_2), 39.9 (CH_2), 30.9 (CH_2).

IR (film): 3090, 2889, 2075, 174, 1719, 1563, 1506, 1471, 1272 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{12}N_2O_3$ $[M]^+$: 220.0848. Found: 220.0858.



1-Benzyl-3-methoxydihydropyrimidine-2,4(1*H*,3*H*)-dione (17b): Synthesized according to general procedure **T** using ethyl 3-(benzylamino)propanoate (0.166 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 4 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH_2Cl_2 then 10% EtOAc/CH_2Cl_2). The title compound was obtained as a clear oil (0.209 g, 89%).

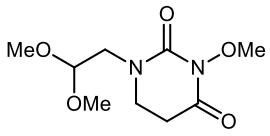
TLC R_f: 0.23 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.28 (m, 5H), 4.64 (s, 2H), 3.95 (s, 3H), 3.26 (t, *J* = 6.8 Hz, 2H), 2.71 (t, *J* = 6.7 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1 (C), 151.6 (C), 135.8, (C), 128.9 (CH), 128.2 (CH), 64.3 (CH_3), 51.4 (CH_2), 39.9 (CH_2), 31.5 (CH_2).

IR (film): 3396, 2935, 2460, 1773, 1706, 1630, 1558, 1539, 1488, 1191 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{14}N_2O_3$ $[M]^+$: 234.1004. Found: 234.1001.



1-(2,2-Dimethoxyethyl)-3-methoxydihydropyrimidine-2,4(1*H*,3*H*)-dione (17c): Synthesized according to general procedure **T** using methyl 3-((2,2-dimethoxyethyl)amino)propanoate (0.153 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 4 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH_2Cl_2 then 30% EtOAc/CH_2Cl_2). The title compound was obtained as a clear oil (0.176 g, 95%).

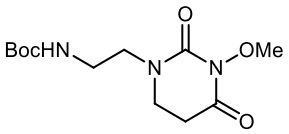
TLC R_f: 0.33 in 30% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.50 (t, *J* = 5.2 Hz, 1H), 3.90 (s, 3H), 3.53-3.45 (m, 4H), 3.45-3.41 (m, 6H), 2.73 (t, *J* = 6.8 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5 (C), 151.5 (C), 103.1 (CH), 64.2 (CH_3), 55.1 (CH_3), 50.0 (CH_2), 42.6 (CH_2), 31.8 (CH_2).

IR (film): 3186, 2942, 2680, 1773, 1709, 1631, 1488, 1436, 1286, 1109 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{16}N_2O_5$ $[M]^+$: 232.1059. Found: 232.1021.



***tert*-Butyl (2-(3-methoxy-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)ethyl)carbamate (17d):** Synthesized according to general procedure **T** using methyl 3-((2-((*tert*-butoxycarbonyl)amino)ethyl)amino)propanoate (0.197 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 4 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH_2Cl_2 then 30% EtOAc/CH_2Cl_2). The title compound was obtained as a clear oil (0.225 g, 98%).

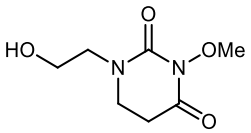
TLC R_f: 0.18 in 30% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.97 (br s, 1H), 3.87 (s, 3 H), 3.57-3.49 (m, 2H), 3.42 (t, *J* = 6.7 Hz, 2H), 3.34 (q, *J* = 5.7 Hz, 2H), 2.78 (t, *J* = 6.7 Hz, 2H), 1.37 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3 (C), 156.2 (C), 151.7 (C), 79.6 (C), 64.1 (CH_3), 47.7 (CH_2), 41.1 (CH_2), 38.3 (CH_2), 31.5 (CH_2), 28.3 (CH_3).

IR (film): 3333, 2385, 1730, 1697, 1683, 1515, 1367, 1272, 1247, 1191, 1161 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{21}N_3O_5$ $[M]^+$: 287.1481. Exact mass calcd for $C_8H_{12}N_3O_5$ $[M - C_4H_9]^+$: 230.0777. Found: 231.0859.



1-(2-Hydroxyethyl)-3-methoxydihydropyrimidine-2,4(1*H*,3*H*)-dione (17e): Synthesized according to general procedure **T** using methyl 3-((2-hydroxyethyl)amino)propanoate (0.118 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr_2NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 4 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH_2Cl_2 then 30% EtOAc/CH_2Cl_2). The title compound was obtained as a clear oil (0.132 g, 88%).

TLC R_f: 0.18 in 30% EtOAc/CH_2Cl_2.

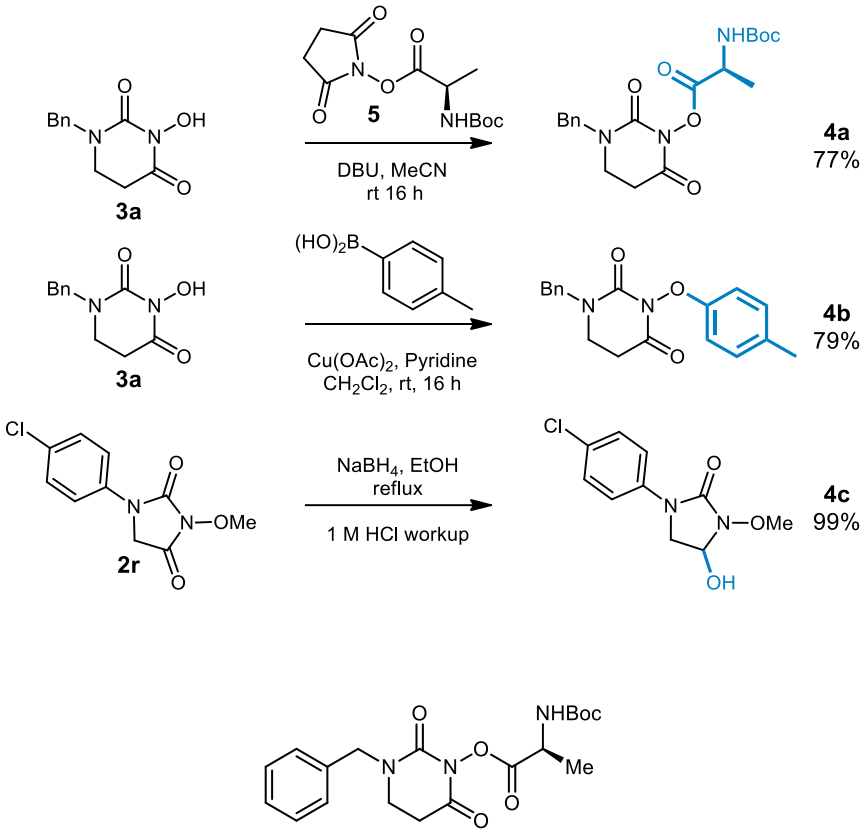
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H), 3.81 (t, *J* = 5.1 Hz, 2H), 3.62-3.54 (m, 2H), 3.53-3.46 (m, 2H), 2.78 (t, *J* = 6.8 Hz, 2H), 2.70 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6 (C), 151.9 (C), 64.2 (CH_3), 60.7 (CH_2), 50.9 (CH_2), 42.2 (CH_2), 31.5 (CH_2).

IR (film): 3301, 2671, 2027, 1735, 1699, 1652, 1558, 1276, 1197, 1053 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{12}N_2O_4$ $[M]^+$: 188.0797. Found: 188.0801.

Derivitization of hydantoin and dihydrouracils products



(*S*)-3-Benzyl-2,6-dioxotetrahydropyrimidin-1(2H)-yl2-((tert-butoxycarbonyl)amino)propanoate (SI7): To a vial charged with a magnetic stir bar were added hexahydro-3-hydroxy-1-benzyl-1,3-diazine-2,4-dione (0.215 g, 0.980 mmol) and Boc-Ala-OSu (0.143 g, 0.500 mmol) and a catalytic amount of DBU in acetonitrile (0.30 M). The reaction was stirred 24 h at r.t. Water was added and the reaction was extracted with DCM, washed with brine, dried over $MgSO_4$ filtered and concentred under reduced pressure and purified using flash chromatography (5% MeOH/DCM). The title compound was obtained as an amorphous white solid (0.150 g, 77%).

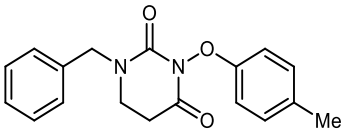
TLC R_f: 0.08 in 100% CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.22 (m, 5H), 5.10-5.00 (br s, 1H), 4.76-4.64 (m, 1H), 4.63-4.52 (m, 2H), 3.37-3.25 (m, 2H), 2.85-2.65 (m, 2H), 1.56 (t, *J* = 3Hz, 3H), 1.43 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0 (C), 163.8 (C), 150.3 (C), 150.2 (C), 135.5 (CH), 135.4 (CH), 129.0 (CH), 128.2 (CH), 128.0 (CH), 77.2 (CH_2), 51.5 (CH_2), 51.4 (CH_2), 39.8 (CH), 31.2 (CH_3), 28.3 (CH_3).

IR (film): 2827, 1792, 1772, 1684, 1653, 1558, 1506, 1272 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{19}H_{25}N_3O_6Na$ $[M+Na]^+$: 414.1641. Found: 414.1657.



1-Benzyl-3-(p-tolyloxy)dihydropyrimidine-2,4(1H,3H)-dione (SI8): To a vial charged with a magnetic stir bar were added hexahydro-3-hydroxy-1-benzyl-1,3-diazine-2,4-dione (0.111 g, 0.500 mmol), CuCl (0.0908 g, 0.500 mmol, freshly activated 4 Å molecular sieves (~25 mg), and 4-methylphenylboronic acid (0.136 g, 1.00 mmol). DCM was added (0.30 M) was added followed by pyridine (0.044 g, 0.55 mmol). The reaction was open to the atmosphere during 16 h. The reaction was filtered over silica gel and the solvent was removed under reduced pressure and purified using flash chromatography (1% MeOH/DCM). The title compound was obtained as a brown oil (0.123 g, 79%).

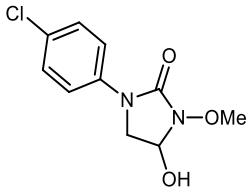
TLC R_f: 0. 19 in 100% CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.29 (m, 5H), 7.15-7.09 (m, 2H), 7.00-6.95 (m, 2H), 4.65 (s, 2H) 3.36 (t, *J* = 6 Hz, 2H), 2.80 (t, *J* = 6Hz 2H), 2.31 (3H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1 (C), 156.8 (C) 151.4 (CH), 135.7 (CH), 133.4 (CH), 129.9 (CH), 129.0 (CH), 128.2 (CH), 113.9 (CH), 51.6 (CH), 39.9 (CH), 31.6 (CH), 20.6 (CH_3).

IR (film): 2987, 1743, 1700, 1558, 1506, 1472, 1277, 1205 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{18}H_{18}N_2O_3$ $[M]^+$: 310.1317. Found: 310.1318.



1-(4-Chlorophenyl)-4-hydroxy-3-methoxyimidazolidin-2-one (SI9): To a round bottom flask charged with a magnetic stir bar were added 1-(4-chlorophenyl)-3-methoxyimidazolidine-2,4-dione (0.120 g, 0.500 mmol), ethanol (0.30 M), and then $NaBH_4$ (0.029 g, 0.75 mmol). The reaction was refluxed for 16 h. Upon completion, the reaction was concentrated under reduced pressure to remove the ethanol, and then the crude concentrate was dissolved in CH_2Cl_2. The compound was extracted using 1 M HCl. The organic phase was dried over Na_2SO_4 and then concentrated under reduced pressure to give the pure product as a white solid (0.121 g, 99%).

TLC R_f: 0. 15 in 100% CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.46 (m, 2H), 7.33-7.29 (m, 2H), 5.40 (dd, *J* = 5.9, 3.0 Hz, 1H), 3.91 (s, 3H), 3.84 (dd, *J* = 9.9, 5.9 Hz, 1H), 3.62 (dd, *J* = 9.9, 3.0 Hz, 1H), 3.47 (s, 1H).

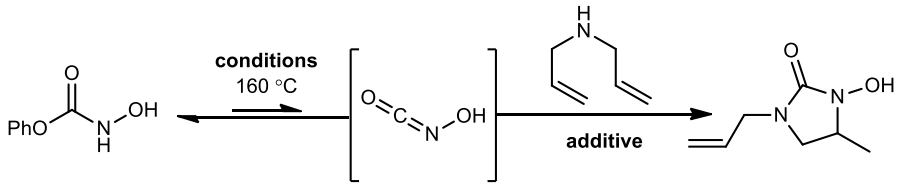
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8 (C) 137.6 (CH), 129.2 (CH), 129.1 (C), 119.2 (CH), 78.8 (CH), 64.7 (CH_3), 48.8 (CH_2).

IR (film): 3350, 2987, 1743, 1556, 1526, 1373, 1250, 1205 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{18}H_{18}N_2O_3$ $[M]^+$: 242.0458. Found: 242.0463.

Optimization of Cope-type hydroamination using *N*-hydroxyureas

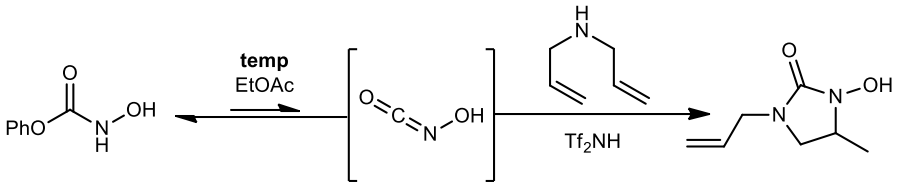
Table 41: Additive survey for cascade substitution-hydroamination reaction



Entry	Conditions	Additive (equiv.)	^{1}H NMR yield vs. PhOH (%)
1	A	-	66
2	A	*i*Pr$_2$NEt (0.05)	63
3	A	DBU (0.25)	6
4	A	DBU (1.0)	0
5	B	NaCNBH$_3$ (1.0)	4
6	A	Diphenylurea (1.0)	17
7	A	Tf$_2$NH (1.0)	18
8	A	TsNH$_2$ (1.0)	66
9	A	Nitroaniline (1.0)	64
10	A	TfNH$_2$ (1.0)	77
11	A	TfNH$_2$ (0.1)	71
12	A	TfNH$_2$ (0.25)	73
13	**A**	**TfNH$_2$ (0.5)**	**78**
14	A	TfNH$_2$ (1.5)	70
15	A	TfNH$_2$ (2.0)	65

Conditions A: Phenyl *N*-hydroxycarbamate **15a** (1.0 equiv.), diallylamine (1.0 equiv.) in EtOAc (0.2M), 160 C, 1h
Conditions B: Phenyl *N*-hydroxycarbamate **15a** (1.0 equiv.), diallylamine (1.0 equiv.) in *i*PrOH (0.2M), 160 C, 1h

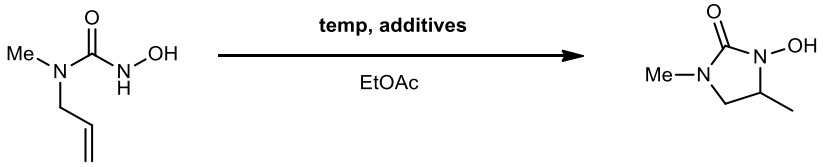
Table 42: Temperature requirements for hydroamination



Entry	Temp (°C)	PhOH formation (%)	^{1}H NMR yield (%)[b]
1	75	25	0
2	100	51	0
3	125	86	trace
4	150	100	28
5	**175**	**90 (no SM)**	**60**

Conditions: Phenyl *N*-hydroxycarbamate **15a** (1.0 equiv.), diallylamine (1.0 equiv.), $TfNH_2$ (0.5 equiv.) in EtOAc (0.2M), 1h

Table 43: Non-cascade hydroamination optimization

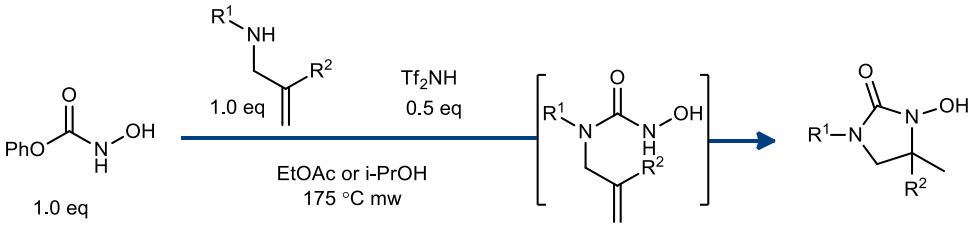


Entry	Additive (equiv.)	temp (°C)	Time (h)	^{1}H NMR yield (%)[b]
1	-	175	1	32
2	PhOH (1.0)	175	1	41
3	$TfNH_2$ (0.5)	175	1	40
4	PhOH (1.0), $TfNH_2$ (0.5)	175	1	36
5	PhOH (1.0), $TfNH_2$ (0.5)	150	2	34
6	PhOH (1.0), $TfNH_2$ (0.5)	175	2	48

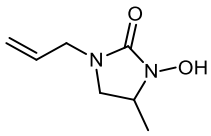
Conditions: hydroxyurea (1.0 equiv.) in EtOAc (0.2M) (Isolated yield for cascade hydroamination is 38% after 2.5 h)

Synthesis of imidazolidinones via Cope type hydroamination cascade reaction

General Procedure W: Cascade substitution/hydroamination of *N*-oxyureas



To an oven-dried microwave vial was weighed the allylamine (1.00 equiv.). Phenyl hydroxycarbamate (1.00 equiv.), trifluoromethanesulfonamide (0.50 equiv.), EtOAc (0.2 M), and a stir bar were added. The vial was sealed with a microwave cap, purged with argon, and heated to 175 °C via microwave irradiation for 20 min- 2.5 h. The reaction mixture was then concentrated under reduced pressure. Purification was performed by flash chromatography.



1-Allyl-3-hydroxy-4-methylimidazolidin-2-one (19a): The title compound was synthesized according to general procedure **W** using phenyl *N*-hydroxycarbamate (0.061 g, 0.400 mmol), diallylamine (0.039 g, 0.400 mmol), and trifluoromethanesulfonamide (0.030 g, 0.200 mmol) in EtOAc (2.0 mL, 0.20 M). The vial was sealed with a microwave cap, purged, then heated for 1 h at 175 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (50% EtOAc/Hexane then 100% EtOAc). The title compound was obtained as an amorphous white solid (0.039 g, 62%).

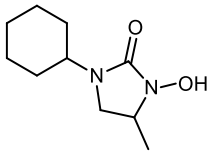
TLC R_f: 0.57 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (br s, 1H), 5.72 (ddt, *J* = 17.6, 9.8, 6.1 Hz, 1H), 5.23-5.18 (m, 2H), 3.91 (ddt, *J* = 15.4, 5.9, 1.5 Hz, 1H), 3.72 (ddt, *J* = 15.4, 6.3, 1.3 Hz, 1H), 3.59 (ddt, *J* = 9.5, 7.7, 6.1 Hz, 1H), 3.35 (dd, *J* = 8.7, 7.7 Hz, 1H), 2.82 (dd, *J* = 9.5, 8.7 Hz, 1H), 1.33 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2 (C), 132.2 (CH), 118.4 (CH_2), 55.4 (CH), 47.8 (CH_2), 46.7 (CH_2), 16.7 (CH_3).

IR (film): 3198, 2973, 2898, 1690, 1490, 1449, 1258, 977 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{12}N_2O_2$ $[M]^+$: 156.0899. Found: 156.0918.



1-Cyclohexyl-3-hydroxy-4-methylimidazolidin-2-one (19b): The title compound was synthesized according to general procedure **W** using phenyl *N*-hydroxycarbamate (0.061 g, 0.400 mmol), *N*-cyclohexylallylamine (0.056 g, 0.400 mmol), and trifluoromethanesulfonamide (0.030 g, 0.200 mmol) in EtOAc (2.0 mL, 0.20 M). The vial was sealed with a microwave cap, purged, then heated for 20 min at 175 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (65% EtOAc/Hexane then 75% EtOAc/Hexane). The title compound was obtained as an amorphous white solid (0.039 g, 49%).

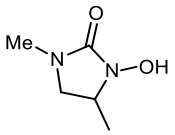
TLC R_f: 0.34 in 75% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (br s, 1H), 3.72 (tt, *J* = 11.6, 3.8 Hz, 1H), 3.51 (ddq, *J* = 9.5, 7.7, 6.1 Hz, 1H), 3.33 (dd, *J* = 8.5, 7.7 Hz, 1H), 2.81 (dd, *J* = 9.5, 8.5 Hz, 1H), 1.81-1.64 (m, 5H), 1.39-1.24 (m, 7H), 1.12-1.01 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8 (C), 55.9 (CH), 51.6 (CH), 44.0 (CH_2), 30.2 (CH_2), 29.8 (CH_2), 25.4 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 16.7 (CH_3).

IR (film): 3189, 2924, 2853, 1690, 1484, 1436, 1254 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{18}N_2O_2$ $[M]^+$: 198.1368. Found: 198.1348.



3-Hydroxy-1,4-dimethylimidazolidin-2-one (19c): The title compound was synthesized according to general procedure **W** using phenyl *N*-hydroxycarbamate (0.061 g, 0.400 mmol), *N*-methylallylamine (0.028 g, 0.400 mmol), and trifluoromethanesulfonamide (0.030 g, 0.200 mmol) in EtOAc (2.0 mL, 0.20 M). The vial was sealed with a microwave cap, purged, then heated for 2.5 h at 175 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (65% EtOAc/Hexane then 100% EtOAc). The title compound was obtained as an amorphous white solid (0.020 g, 38%).

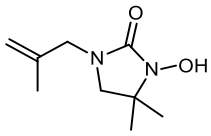
TLC R_f: 0.12 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (br s, 1H), 3.58 (ddq, *J* = 9.5, 7.7, 6.1 Hz, 1H), 3.38 (dd, *J* = 8.5, 7.7 Hz, 1H), 2.85 (dd, *J* = 9.5, 8.5 Hz, 1H), 2.82 (s, 3H), 1.30 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7 (C), 55.3 (CH), 50.5 (CH), 31.1 (CH_3), 16.7 (CH_3).

IR (film): 3196, 2906, 1694, 1497, 1404, 1261, 1015 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_5H_{10}N_2O_2$ $[M]^+$: 130.0742. Found: 130.0758.



3-Hydroxy-4,4-dimethyl-1-(2-methylallyl)imidazolidin-2-one (19e): The title compound was synthesized according to general procedure **W** using phenyl *N*-hydroxycarbamate (0.061 g, 0.400 mmol), bis(2-methyl)allylamine (0.050 g, 0.400 mmol), and trifluoromethanesulfonamide (0.030 g, 0.200 mmol) in EtOAc (2.0 mL, 0.20 M). The vial was sealed with a microwave cap, purged, then heated for 1 h at 175 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (60% EtOAc/Hexane). The title compound was obtained as an amorphous white solid (0.054 g, 72%).

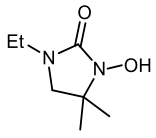
TLC R_f: 0.62 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (br s, 1H), 4.90-4.84 (m, 2H), 3.75 (s, 2H), 2.95 (s, 2H), 1.69 (s, 3H), 1.30 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0 (C), 140.2 (C), 113.4 (CH_2), 59.4 (C), 53.9 (CH_2), 50.1 (CH_2), 22.7 (CH_3), 19.9 (CH_3).

IR (film): 3199, 2988, 2969, 2916, 2854, 1686, 1482, 1317, 948 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{16}N_2O_2$ $[M]^+$: 184.1212. Found: 184.1187.



1-Ethyl-3-hydroxy-4,4-dimethylimidazolidin-2-one (19f): The title compound was synthesized according to general procedure **W** using phenyl *N*-hydroxycarbamate (0.061 g, 0.400 mmol), *N*-

ethyl(2-methyl)allylamine (0.040 g, 0.400 mmol), and trifluoromethanesulfonamide (0.030 g, 0.200 mmol) in EtOAc (2.0 mL, 0.20 M). The vial was sealed with a microwave cap, purged, then heated for 1 h at 175 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (60% EtOAc/Hexane then 100% EtOAc). The title compound was obtained as an amorphous white solid (0.039 g, 62%).

TLC R_f: 0.43 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (br s, 1H), 3.27 (q, *J* = 7.3 Hz, 2H), 3.03 (t, *J* = 7.3 Hz, 2H), 1.30 (s, 1H), 1.10 (s, 1H).

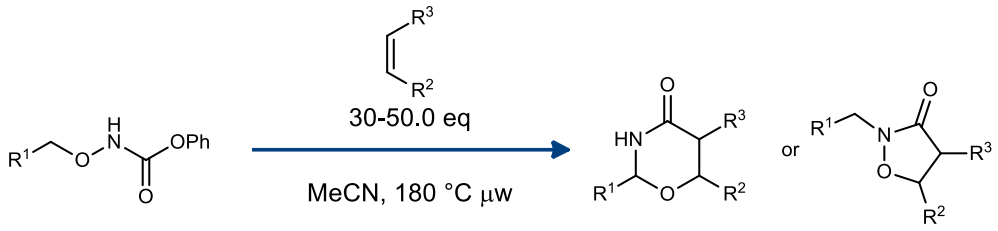
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (C), 59.5 (C), 53.6 (CH_2), 38.4 (CH_2), 22.4 (CH_3), 12.3 (CH_3).

IR (film): 3178, 2970, 2930, 2856, 1694, 1451, 1441, 1236, 1089, 796 cm^{-1}.

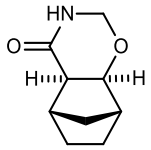
HRMS (EI): Exact mass calcd for $C_7H_{14}N_2O_2$ $[M]^+$: 158.1055. Found: 158.1076.

Synthesis of oxazinones via *O*-isocyanate [3+2] cycloadditions on strained alkenes

General procedure X: Synthesis of oxo-azabicyclooctanones via *O*-isocyanate cycloaddition



To a clean dry microwave vial charged with a stir bar was added the corresponding *N*-alkoxycarbamate (1.00 equiv) followed by alkene (50.0 equiv) and then MeCN (0.1 M). The vial was sealed and Argon was bubbled through the solution for 10 min. The reaction vessel was heated at 180 °C via microwave irradiation for 0.5–8 h. Upon completion, the reaction was concentrated via rotary evaporation and the product was isolated using silica-gel flash column chromatography.



Hexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (23a): The title compound was synthesized according to general procedure **X** using phenyl methoxycarbamate (0.167 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a white solid (0.152 g, 91% yield).

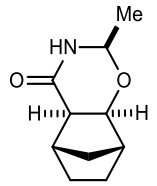
TLC R_f: 0.15 in 100% EtOAc

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 4.65 (qd, *J* = 9.5, 3.8 Hz, 2H), 3.95 (d, *J* = 6.9 Hz, 1H), 2.85 (t, *J* = 1.2 Hz, 1H), 2.38 (dd, *J* = 2.8, 1.0 Hz, 1H), 2.23 (dd, *J* = 6.9, 1.4 Hz, 1H), 1.64–1.51 (m, 3H), 1.27–1.08 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4 (C), 82.6 (CH), 72.4 (CH_2), 50.1 (CH), 42.4 (CH), 39.7 (CH), 34.2 (CH_2), 28.6 (CH_2), 24.3 (CH_2).

IR (film): 3262, 2956, 2875, 1658, 1621, 1471, 1368, 1314, 1223, 1135 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{13}NO_2$ $[M]^+$ 167.0946. Found: 167.0926.



2-Methylhexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (23b): The title compound was synthesized according to general procedure **X** using phenyl ethoxycarbamate (0.181 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as an off-white solid in a 9:1 mixture of diastereoisomers (0.152 g, 84% yield).

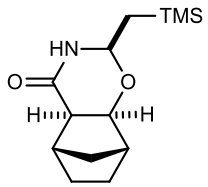
TLC R_f: 0.16 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H), 4.73 (qd, *J* = 5.6, 2.0 Hz, 1H), 3.95 (d, *J* = 6.8 Hz, 1H), 2.84 (d, *J* = 1.6 Hz, 1H), 2.37 (d, *J* = 3.1 Hz, 1H), 2.16 (dd, *J* = 6.9, 1.2 Hz, 1H), 1.65–1.51 (m, 3H), 1.32 (d, *J* = 5.6 Hz, 3H), 1.20–1.09 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (C), 81.9 (CH), 78.2 (CH), 49.3 (CH), 42.4 (CH), 39.5 (CH), 34.2 (CH_2), 28.7 (CH_2), 24.3 (CH_2), 20.9 (CH_3).

IR (film): 3166, 3070, 2958, 2873, 1660, 1485, 1450, 1403, 1298, 1147 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{15}NO_2$ $[M]^+$ 181.1103. Found: 181.1073.



2-((Trimethylsilyl)methyl)hexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (23c): The title compound was synthesized according to general procedure **X** using phenyl 2-(trimethylsilyl)ethoxycarbamate (0.253 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and

MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a white solid in a 9:1 mixture of diastereoisomers (0.223 g, 88% yield).

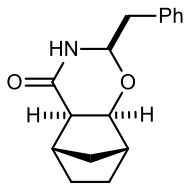
TLC R_f: 0.27 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (s, 1H), 4.72 (ddd, *J* = 7.5, 5.3, 2.2 Hz, 1H), 3.92 (d, *J* = 6.9 Hz, 1H), 2.86 (d, *J* = 1.7 Hz, 1H), 2.36 (d, *J* = 2.4 Hz, 1H), 2.17 (dd, *J* = 6.9, 1.2 Hz, 1H), 1.62–1.56 (m, 3H), 1.26–1.10 (m, 4H), 1.03–0.89 (m, 2H), 0.07 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6 (C), 81.9 (CH), 80.4 (CH), 49.3 (CH), 42.5 (CH), 39.5 (CH), 34.3 (CH_2), 28.7 (CH_2), 24.3 (CH_2), 24.1 (CH_2), -0.8 (CH_3).

IR (film): 3163, 2955, 2873, 1651, 1406, 1349, 1246, 1222, 1102 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{23}NO_2SiNa$ $[M+Na]^+$ 276.1396. Found: 276.1371.



2-Benzylhexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (23d): The title compound was synthesized according to general procedure **X** using phenyl phenethoxycarbamate (0.257 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as an off-white solid in a 15:1 mixture of diastereoisomers (0.208 g, 81% yield).

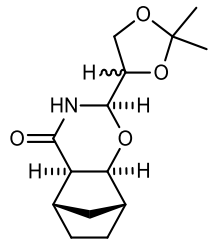
TLC R_f: 0.20 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.25 (m, 3H), 7.22–7.18 (m, 2H), 6.24 (s, 1H), 4.84 (ddd, *J* = 7.1, 5.4, 1.7 Hz, 1H), 3.97 (d, *J* = 6.8 Hz, 1H), 3.07 (dd, *J* = 13.9, 5.4 Hz, 1H), 2.83 (dt, *J* = 0.8, 0.4 Hz, 1H), 2.71 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.42–2.41 (m, 1H), 2.18–2.16 (m, 1H), 1.65–1.51 (m, 3H), 1.24–1.19 (m, 1H), 1.15–1.10 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3 (C), 134.3 (C), 129.5 (CH), 129.0 (CH), 127.4 (CH), 81.9 (CH), 81.8 (CH), 49.6 (CH), 42.5 (CH), 41.3 (CH_2), 39.7 (CH), 34.2 (CH_2), 28.8 (CH_2), 24.1 (CH_2).

IR (film): 3178, 2954, 2875, 1664, 1399, 1309, 1221, 1173, 1148, 1113 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{16}H_{19}NO_2$ $[M]^+$ 257.1416. Found: 257.1449.



2-(2,2-Dimethyl-1,3-dioxolan-4-yl)hexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (23e + 23e'): The title compound was synthesized according to general procedure **X** using phenyl (2,2-dimethyl-1,3-dioxolan-4-yl)methoxycarbamate (0.267 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (50% EtOAc/Hexanes → 100% EtOAc). The product was isolated as an off-white solid in a 7:1:7:1 (A:B:C:D) mixture of diastereoisomers (0.182 g, 63% yield).

TLC R_f: 0.23 in 50% EtOAc/Hexanes

(2e A) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.53 (s, 1H), 4.48 (dd, *J* = 7.6, 1.3 Hz, 1H), 4.05 (dd, *J* = 9.0, 6.1 Hz, 1H), 3.98-3.86 (m, 3H), 2.85-2.83 (m, 1H), 2.36 (d, *J* = 3.0 Hz, 1H), 2.22 (d, *J* = 6.6 Hz, 1H), 1.61–1.50 (m, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 1.26–1.18 (m, 1H), 1.13–1.07 (m, 2H).

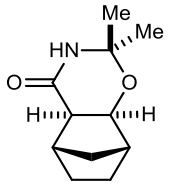
(2e C) ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.39 (s, 1H), 4.86 (dd, *J* = 3.7, 1.4 Hz, 1H), 4.20 (td, *J* = 6.1, 3.8 Hz, 1H), 3.98 (dd, *J* = 6.1, 3.8 Hz, 3H), 2.85–2.85 (m, 1H), 2.36 (d, *J* = 2.7 Hz, 1H), 2.23 (d, *J* = 6.0 Hz, 1H), 1.60–1.51 (m, 3H), 1.45 (d, *J* = 4.9 Hz, 3H), 1.32 (s, 3H), 1.26–1.19 (m, 1H), 1.17–1.08 (m, 2H).

(2e A) ^{13}C NMR (100 MHz, $CDCl_3$): 170.5 (C), 110.3 (C), 82.1 (CH), 81.9 (CH), 76.2 (CH), 66.2 (CH_2), 50.0 (CH), 42.5 (CH), 39.7 (CH), 34.2 (CH_2), 28.9 (CH_2), 27.0 (CH_3), 25.0 (CH_3), 23.9 (CH_2).

(2e C) ^{13}C NMR (100 MHz, $CDCl_3$): 171.2 (C), 110.0 (C), 82.1 (CH), 80.3 (CH), 74.5 (CH), 63.9 (CH_2), 49.9 (CH), 42.5 (CH), 39.8 (CH), 34.3 (CH_2), 28.8 (CH_2), 26.2 (CH_3), 24.1 (CH_3), 23.9 (CH_2).

IR (film): 3189, 2982, 2908, 2897, 1655, 1481, 1402, 1373, 1220, 1144 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{21}NO_4Na$ $[M+Na]^+$ 267.1471. Found:.267.1475.



2,2-Dimethylhexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (23f): The title compound was synthesized according to general procedure **X** using phenyl isopropoxycarbamate (0.195 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a white solid (0.146 g, 75% yield).

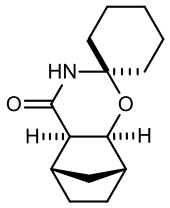
TLC R_f: 0.16 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (br. s, 1H), 4.09 (d, *J* = 6.5 Hz, 1H), 2.83 (d, *J* = 1.6 Hz, 1H), 2.30 (d, *J* = 2.5 Hz, 1H), 2.15 (dd, *J* = 6.5, 1.4 Hz, 1H), 1.67–1.56 (m, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.30–1.09 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8 (C), 83.0 (C), 76.9 (C), 48.2 (CH), 42.6 (CH), 40.1 (CH), 33.9 (CH_2), 29.5 (CH_3), 28.9 (CH_2), 26.8 (CH_3), 24.3 (CH_2).

IR (film): 3162, 2873, 1651, 1481, 1407, 1224, 1183, 1144 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{17}NO_2Na$ $[M+Na]^+$ 218.1157. Found: 218.1144.



Hexahydrospiro[5,8-methanobenzo[*e*][1,3]oxazine-2,1'-cyclohexan]-4(3*H*)-one (23g): The title compound was synthesized according to general procedure **X** using phenyl cyclohexyloxycarbamate (0.235 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a white solid (0.195 g, 83% yield).

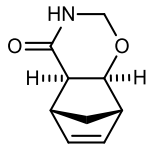
TLC R_f: 0.25 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46–6.46 (m, 1H), 4.03 (d, *J* = 6.6 Hz, 1H), 2.83–2.83 (m, 1H), 2.31–2.30 (m, 1H), 2.17 (dd, *J* = 6.5, 1.3 Hz, 1H), 1.99–1.94 (m, 1H), 1.73–1.69 (m, 2H), 1.65–1.43 (m, 9H), 1.34–1.28 (m, 1H), 1.26–1.21 (m, 1H), 1.17–1.09 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8 (C), 83.7 (C), 76.0 (CH), 48.7 (CH), 42.6 (CH), 40.1 (CH), 38.0 (CH_2), 35.5 (CH_2), 34.0 (CH_2), 28.8 (CH_2), 24.9 (CH_2), 24.3 (CH_2), 22.4 (CH_2), 21.8 (CH_2).

IR (film): 3159, 2913, 2872, 1658, 1477, 1404, 1228, 1143, 1117 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{21}NO_2$ $[M]^+$ 235.1572. Found: 235.1551.



4a,5,8,8a-Tetrahydro-2H-5,8-methanobenzo[e][1,3]oxazin-4(3H)-one (23h): The title compound was synthesized according to general procedure **X** using phenyl methoxycarbamate (0.167 g, 1.00 mmol), norbornadiene (2.76 g, 30.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (30% EtOAc/Hexanes → 50% EtOAc/Hexanes → 100% EtOAc). The product was isolated as a white solid (0.080 g, 54% yield).

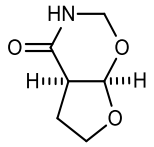
TLC R_f: 0.40 in 100% EtOAc

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 1H), 6.32 (dd, *J* = 5.7, 3.0 Hz, 1H), 6.06 (dd, *J* = 5.7, 3.2 Hz, 1H), 4.78 – 4.64 (m, 2H), 3.99 (dt, *J* = 6.9, 1.1 Hz, 1H), 3.41 (ddt, *J* = 3.2, 1.6, 0.8 Hz, 1H), 3.04 – 2.97 (m, 2H), 2.20 (dd, *J* = 6.9, 2.1 Hz, 1H), 1.72 (dt, *J* = 9.2, 1.6 Hz, 1H), 1.56 (dt, *J* = 9.1, 1.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (C), 140.0 (CH), 133.8 (CH), 79.0 (CH), 72.8 (CH_2), 48.0 (CH), 44.9 (CH_2), 44.6 (CH), 44.6 (CH).

IR (film): 3231, 2916, 2854, 1665, 1624, 1469, 1367, 1321, 1270, 1080 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_9H_{11}NO_2$ $[M+Na]^+$ 188.0687. Found: 188.0680.



Tetrahydro-2*H*-furo[3,2-*e*][1,3]oxazin-4(3*H*)-one (23j): The title compound was synthesized according to general procedure **X** using phenyl methoxycarbamate (0.167 g, 1.00 mmol), 2,3,-dihydrofuran (2.10 g, 30 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc→5% MeOH/CH_2Cl_2). The product was isolated as an off-white solid (0.041 g, 28% yield).

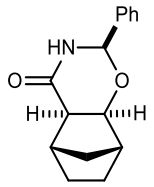
TLC R_f: 0.15 in 5% MeOH/CH_2Cl_2

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (s, 1H), 5.45 (d, *J* = 5.4 Hz, 1H), 4.84 (dd, *J* = 9.4, 2.9 Hz, 1H), 4.70 (dd, *J* = 9.4, 2.7 Hz, 1H), 4.11 (td, *J* = 8.2, 4.9 Hz, 1H), 3.88 (q, *J* = 7.9 Hz, 1H), 2.96 (td, *J* = 9.1, 5.3 Hz, 1H), 2.40 (dddd, *J* = 12.5, 9.9, 7.4, 5.0 Hz, 1H), 2.16 (dq, *J* = 12.7, 8.1 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 171.2 (C), 101.2 (CH), 68.6 (CH_2), 67.8 (CH_2), 45.4 (CH), 28.9 (CH_2).

IR (film): 3198, 2973, 2875, 1656, 1453, 1374, 1263, 1209 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_6H_9NO_3$ $[M]^+$ 143.0582. Found: 143.0586.



2-Phenylhexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (23k): The title compound was synthesized according to general procedure **X** using phenyl benzyloxycarbamate (0.243 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as an off-white solid in a 15:1 mixture of diastereoisomers (0.097 g, 40% yield).

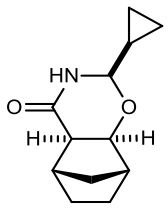
TLC R_f: 0.32 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.37 (m, 5H), 6.51 (s, 1H), 5.55 (d, *J* = 1.8 Hz, 1H), 4.12 (d, *J* = 6.9 Hz, 1H), 2.89 (d, *J* = 1.4 Hz, 1H), 2.46 (d, *J* = 3.1 Hz, 1H), 2.29 (dd, *J* = 6.9, 1.0 Hz, 1H), 1.72 (dt, *J* = 10.3, 1.8 Hz, 1H), 1.65–1.54 (m, 2H), 1.29–1.23 (m, 1H), 1.19–1.14 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2 (C), 137.5 (C), 129.9 (CH), 129.0 (CH), 126.5 (CH), 83.0 (CH), 82.2 (CH), 49.5 (CH), 42.6 (CH), 39.8 (CH), 34.4 (CH_2), 28.8 (CH_2), 24.2 (CH_2).

IR (film): 3156, 2954, 2870, 1648, 1476, 1398, 1353, 1297, 1222, 1172 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{17}NO_2$ $[M]^+$ 243.1259. Found: 243.1286.



2-Cyclopropylhexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (23l): The title compound was synthesized according to general procedure **X** using phenyl cyclopropylmethoxycarbamate (0.207 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a white solid in a 5:1 mixture of diastereoisomers (0.159 g, 77% yield).

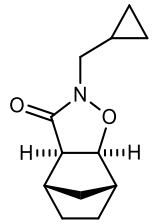
TLC R_f: 0.19 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (s, 1H), 3.90–3.88 (m, 2H), 2.85–2.83 (s, 1H), 2.42 (d, *J* = 3.4 Hz, 1H), 2.15 (dd, *J* = 6.8, 1.1 Hz, 1H), 1.63–1.50 (m, 4H), 1.25–1.18 (m, 2H), 1.14–1.08 (m, 2H), 1.03 (tt, *J* = 7.8, 4.6 Hz, 1H), 0.65–0.56 (m, 2H), 0.48–0.43 (m, 1H), 0.35–0.31 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3 (C), 85.8 (CH), 82.0 (CH), 49.5 (CH), 42.5 (CH), 39.6 (CH), 34.2 (CH_2), 28.8 (CH_2), 24.2 (CH_2), 15.1 (CH), 2.4 (CH_2), 1.3 (CH_2).

IR (film): 3171, 2950, 2873, 1652, 1471, 1392, 1368, 1296, 1099 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{17}NO_2$ $[M]^+$ 207.1259. Found: 207.1238.



2-(Cyclopropylmethyl)hexahydro-4,7-methanobenzo[*d*]isoxazol-3(2*H*)-one (24b): The title compound was synthesized according to general procedure **X** using phenyl cyclopropylmethoxycarbamate (0.207 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a clear oil (0.020 g, 10% yield).

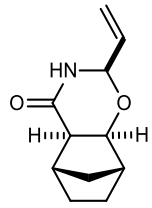
TLC R_f: 0.56 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74–3.66 (m, 2H), 3.64 (d, *J* = 3.4 Hz, 1H), 2.66 (dt, *J* = 3.2, 1.5 Hz, 1H), 2.58 (dd, *J* = 3.2, 1.4 Hz, 1H), 2.48 (dd, *J* = 4.1, 1.3 Hz, 1H), 1.69–1.49 (m, 3H), 1.22–1.19 (m, 2H), 1.15–1.01 (m, 3H), 0.62–0.54 (m, 2H), 0.28–0.24 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (C), 80.6 (CH_2), 63.4 (CH), 52.1 (CH), 36.5 (CH), 35.5 (CH), 30.9 (CH_2), 27.3 (CH_2), 24.7 (CH_2), 9.7 (CH), 3.5 (CH_2), 3.0 (CH_2).

IR (film): 2960, 2877, 2252, 1759, 1660, 1454, 1375, 1210, 1114 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{17}NO_2$ $[M]^+$ 207.1259. Found: N/A.



2-Vinylhexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (23m): The title compound was synthesized according to general procedure **X** using phenyl allyloxycarbamate (0.193 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as an off-white solid in a 10:1 mixture of diastereoisomers (0.044 g, 23% yield).

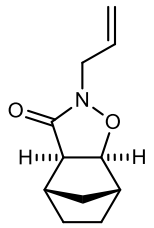
TLC R_f: 0.18 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (s, 1H), 5.79 (ddd, *J* = 17.3, 10.4, 6.2 Hz, 1H), 5.47 (dt, *J* = 17.3, 0.9 Hz, 1H), 5.38 (dt, *J* = 10.4, 0.8 Hz, 1H), 5.04 (dt, *J* = 6.2, 1.0 Hz, 1H), 4.01 (d, *J* = 6.9 Hz, 1H), 2.85–2.83 (m, 1H), 2.41 (d, *J* = 3.5 Hz, 1H), 2.21 (dd, *J* = 6.9, 1.2 Hz, 1H), 1.63–1.53 (m, 3H), 1.25–1.20 (m, 1H), 1.16–1.10 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3 (C), 133.7 (CH), 120.6 (CH_2), 82.0 (CH), 81.9 (CH), 49.6 (CH), 42.5 (CH), 39.7 (CH), 34.2 (CH_2), 28.7 (CH_2), 24.2 (CH_2).

IR (film): 3162, 2920, 2851, 1655, 1468, 1400, 1299, 1072 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{15}NO_2$ $[M]^+$ 193.1103. Found: 193.1127.



2-Allylhexahydro-4,7-methanobenzo[*d*]isoxazol-3(2*H*)-one (24c): The title compound was synthesized according to general procedure **X** using phenyl allyloxycarbamate (0.193 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a clear oil (0.120 g, 62% yield).

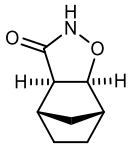
TLC R_f: 0.58 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.26 (dq, *J* = 17.1, 1.4 Hz, 1H), 5.19 (dq, *J* = 10.2, 1.3 Hz, 1H), 4.39 (dt, *J* = 7.7, 1.2 Hz, 1H), 4.11–4.00 (m, 2H), 2.74 (d, *J* = 7.6 Hz, 1H), 2.67–2-65 (m, 1H), 2.49 (d, *J* = 3.4 Hz, 1H), 1.61–1.46 (m, 3H), 1.24–1.20 (m, 1H), 1.20–1.12 (m, 1H), 1.06–0.97 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8 (C), 131.2 (CH), 118.8 (CH_2), 82.6 (CH), 52.7 (CH), 46.9 (CH_2), 42.8 (CH), 39.5 (CH), 32.9 (CH_2), 27.5 (CH_2), 22.3 (CH_2).

IR (film): 3415, 3083, 2965, 2877, 1667, 1447, 1411, 1331, 1252, 1047, 974 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{15}NO_2$ $[M]^+$ 193.1103. Found: 193.1090.



Hexahydro-4,7-methanobenzo[*d*]isoxazol-3(2*H*)-one (24d): The title compound was synthesized according to general procedure **X** using phenyl (*tert*-butyldiphenylsilyl)oxycarbamate (0.391 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 0.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a white solid (0.083 g, 54% yield).

TLC R_f: 0.20 in 100% EtOAc

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.55 (d, *J* = 7.7 Hz, 1H), 2.74 (d, *J* = 7.6 Hz, 1H), 2.68 (d, *J* = 2.6 Hz, 1H), 2.54 (d, *J* = 4.3 Hz, 1H), 1.77–1.73 (m, 1H), 1.62–1.49 (m, 2H), 1.30–1.18 (m, 3H), 1.06–1.00 (m, 1H).

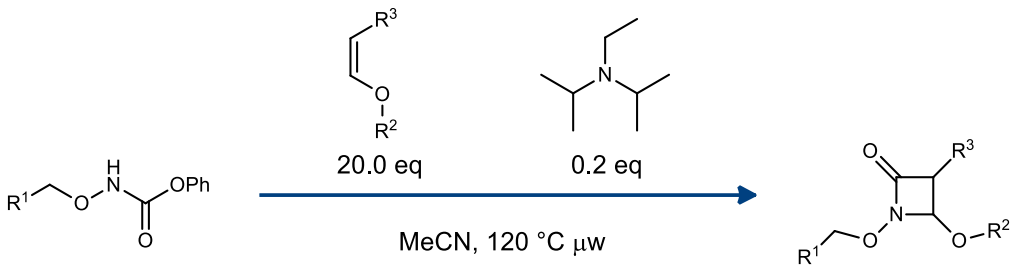
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4 (C), 85.8 (CH), 52.3 (CH), 43.1 (CH), 39.2 (CH), 33.0 (CH), 27.6 (CH_2), 22.3 (CH_2)

IR (film): 2966, 2869, 2741, 1673, 1633, 1359, 1297, 1034, 997, cm^{-1}.

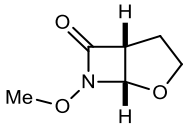
HRMS (EI): Exact mass calcd for $C_8H_{11}NO_2$ $[M]^+$ 153.0790. Found: 153.0807.

Synthesis of β-lactams via *O*-isocyanate [3+2] cycloadditions on enol ethers

General procedure Y: Base catalyzed synthesis of β-lactams via O-isocyanate cycloaddition



To a clean dry microwave vial charged with a stir bar was added the corresponding *N*-alkoxycarbamate (1.00 equiv) followed by vinyl ether (20.0 equiv) and *i*-Pr_2NEt (0.20 equiv) then MeCN (0.1 M). The vial was sealed and Argon was bubbled through the solution for 10 min. The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion, the reaction was concentrated via rotary evaporation and the product was isolated using silica-gel flash column chromatography.



***cis*-7-Methoxy-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (25a):** The title compound was synthesized according to general procedure **Y** using phenyl methoxycarbamate (0.334 g, 2.00 mmol) followed by 2,3-dihydrofuran (3.0 mL, 40 mmol) and *i*-Pr_2NEt (0.052 g, 0.40 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (60% EtOAc/Hexanes). The product was isolated as a pale yellow oil (0.183 g, 64% yield).

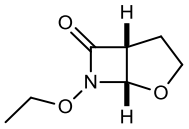
TLC R_f: 0.29 in 60% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77 (d, *J* = 3.0 Hz, 1H), 4.26 (ddt, *J* = 9.5, 8.1, 0.7 Hz, 1H), 3.98 (ddd, *J* = 12.0, 9.5, 5.6 Hz, 1H), 3.85 (d, *J* = 0.7 Hz, 3H), 3.44 (ddt, *J* = 8.4, 3.0, 0.7 Hz, 1H), 2.21 (ddq, *J* = 13.1, 5.5, 0.7 Hz, 1H), 1.79 (dddd, *J* = 13.1, 12.0, 8.6, 7.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6 (C), 90.9 (CH), 66.8 (CH_2), 64.3 (CH_3), 51.5 (CH), 24.9 (CH_2).

IR (film): 2983, 2888, 1669, 1642, 1488, 1442, 1364, 1256, 1219, 1064 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_9NO_3$ $[M]^+$ 143.0582. Found: 143.0573.



***cis*-7-Ethoxy-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (25b):** The title compound was synthesized according to general procedure **Y** using phenyl ethoxycarbamate (0.362 g, 2.00 mmol) followed by 2,3-dihydrofuran (3.0 mL, 40 mmol) and *i*-Pr_2NEt (0.052 g, 0.40 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (45% EtOAc/Hexanes). The product was isolated as a pale yellow oil (0.248 g, 79% yield).

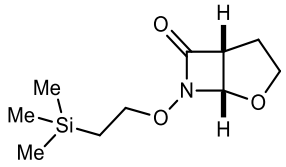
TLC R_f: 0.32 in 40% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (d, *J* = 3.0 Hz, 1H), 4.25 (ddq, *J* = 9.6, 8.2, 0.7 Hz, 1H), 4.05 (ddddd, *J* = 16.6, 9.5, 7.1, 2.5, 0.7 Hz, 2H), 3.96 (ddd, *J* = 12.0, 9.5, 5.5 Hz, 1H), 3.44 (dd, *J* = 8.6, 2.9 Hz, 1H), 2.21 (ddt, *J* = 13.2, 5.6, 0.8 Hz, 1H), 1.87 – 1.70 (m, 1H), 1.29 (td, *J* = 7.1, 0.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3 (C), 91.2 (CH), 72.5 (CH_2), 66.8 (CH_2), 51.3 (CH), 24.9 (CH_2), 14.0 (CH_3).

IR (film): 2978, 2892, 1656, 1614, 1510, 1383, 1280, 1120, 1046 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{11}NO_3$ $[M]^+$ 157.0739. Found: 157.0748.



***cis*-7-(2-(Trimethylsilyl)ethoxy)-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (25c):** The title compound was synthesized according to general procedure **Y** using phenyl 2-(trimethylsilyl)ethoxycarbamate (0.507 g, 2.00 mmol) followed by 2,3-dihydrofuran (3.0 mL, 40 mmol) and *i*-Pr_2NEt (0.052 g, 0.40 mmol) then MeCN (0.1 M). The reaction vessel was heated at

120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (30% EtOAc/Hexanes). The product was isolated as a pale yellow oil (0.348 g, 76% yield).

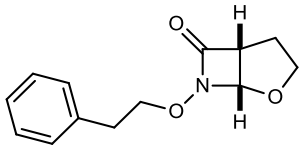
TLC R_f: 0.45 in 40% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (d, *J* = 3.0 Hz, 1H), 4.25 (ddt, *J* = 9.5, 8.1, 0.7 Hz, 1H), 4.13 – 3.99 (m, 2H), 3.96 (ddd, *J* = 12.0, 9.8, 5.9 Hz, 1H), 3.44 (ddt, *J* = 8.4, 3.1, 0.6 Hz, 1H), 2.21 (ddt, *J* = 13.1, 5.6, 0.7 Hz, 1H), 1.78 (ddt, *J* = 13.1, 12.0, 8.3 Hz, 1H), 1.09 – 1.00 (m, 2H), 0.03 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3 (C), 91.2 (CH), 74.9 (CH_2), 66.8 (CH_2), 51.3 (CH), 24.8 (CH_2), 17.3 (CH_2), -1.2 (CH_3), -1.5 (CH_3).

IR (film): 2951, 2882, 1766, 1500, 1442, 1362, 1250, 1214, 1069, 1039 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{10}H_{19}NO_3SiNa$ $[M+Na]^+$ 252.1032. Found: 252.1049.



***cis*-7-Phenethoxy-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (25d):** The title compound was synthesized according to general procedure **Y** using phenyl phenethoxycarbamate (0.515 g, 2.00 mmol) followed by 2,3-dihydrofuran (3.0 mL, 40 mmol) and *i*-Pr_2NEt (0.052 g, 0.40 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (40% EtOAc/Hexanes). The product was isolated as an off-white solid (0.386 g, 83% yield).

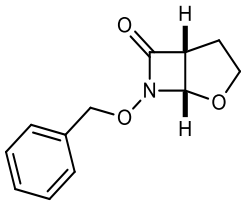
TLC R_f: 0.30 in 40% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.29 (m, 2H), 7.25 – 7.21 (m, 3H), 5.70 (d, *J* = 3.1 Hz, 1H), 4.33 – 4.11 (m, 3H), 3.97 (ddd, *J* = 12.0, 9.5, 5.6 Hz, 1H), 3.43 (dd, *J* = 8.4, 3.1 Hz, 1H), 3.00 (t, *J* = 7.3 Hz, 2H), 2.21 (dd, *J* = 13.2, 5.6 Hz, 1H), 1.78 (ddt, *J* = 13.1, 11.9, 8.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2 (C), 137.1 (C), 128.9 (CH), 128.6 (CH), 126.6 (CH), 91.3 (CH), 77.4 (CH_2), 66.8 (CH_2), 51.3 (CH), 35.0 (CH_2), 24.9 (CH_2).

IR (film): 3026, 2946, 2880, 1768, 1495, 1453, 1362, 1066, 1046 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{15}NO_3Na$ $[M+Na]^+$ 256.0950. Found: 256.0959.



***cis*-7-(Benzyloxy)-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (25e):** The title compound was synthesized according to general procedure **Y** using *N*-benzyloxycarbamate (0.486 g, 2.00 mmol) followed by 2,3-dihydrofuran (3.0 mL, 40 mmol) and *i*-Pr_2NEt (0.052 g, 0.40 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (40% EtOAc/Hexanes). The product was isolated as an off-white solid (0.335 g, 76% yield).

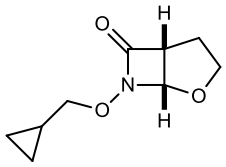
TLC R_f: 0.34 in 40% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.29 (m, 5H), 5.42 (d, *J* = 3.0 Hz, 1H), 4.98 (s, 2H), 4.14 (ddd, *J* = 9.5, 8.1, 0.7 Hz, 1H), 3.79 (ddd, *J* = 12.0, 9.5, 5.5 Hz, 1H), 3.36 (dd, *J* = 8.4, 3.0 Hz, 1H), 2.12 (dd, *J* = 13.1, 5.5 Hz, 1H), 1.70 (ddt, *J* = 13.1, 12.0, 8.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3 (C), 135.0 (C), 129.0 (CH), 128.6 (CH), 91.6 (CH), 78.4 (CH_2), 66.8 (CH_2), 51.4 (CH), 24.9 (CH_2). * One CH peak is overlapped.

IR (film): 3030, 2985, 2881, 1766, 1686, 1498, 1442, 1362, 1234, 1214, 1067 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{12}H_{13}NO_3Na$ $[M+Na]^+$ 242.0793. Found: 242.0785.



***cis*-7-(Cyclopropylmethoxy)-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (25f):** The title compound was synthesized according to general procedure **Y** using phenyl cyclopropylmethoxycarbamate (0.207 g, 1.00 mmol) followed by 2,3-dihydrofuran (1.5 mL, 20 mmol) and *i*-Pr_2NEt (0.026 g, 0.20 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure

and the product was isolated using silica gel flash column chromatography (45% EtOAc/Hexanes→100% EtOAc). The product was isolated as a pale yellow oil (0.146 g, 80% yield).

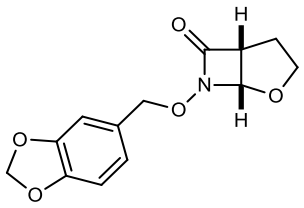
TLC R_f: 0.30 in 45% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (d, *J* = 3.0 Hz, 1H), 4.24 (dd, *J* = 9.5, 8.1 Hz, 1H), 3.96 (ddd, *J* = 12.0, 9.5, 5.5 Hz, 1H), 3.81 (d, *J* = 7.3 Hz, 2H), 3.44 (dd, *J* = 8.3, 3.0 Hz, 1H), 2.21 (dd, *J* = 13.0, 5.6 Hz, 1H), 1.78 (ddt, *J* = 13.1, 12.0, 8.3 Hz, 1H), 1.15 (dddd, *J* = 15.3, 8.0, 4.0, 2.7 Hz, 1H), 0.70 – 0.56 (m, 2H), 0.38 – 0.26 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2 (C), 91.4 (CH), 81.6 (CH_2), 66.8 (CH_2), 51.4 (CH), 24.9 (CH_2), 9.5 (CH), 3.4 (CH_2), 3.1 (CH_2).

IR (film): 3082, 2949, 2878, 1765, 1686, 1469, 1363, 1218, 1067 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_9H_{13}NO_3Na$ $[M+Na]^+$ 206.0793. Found: 206.0817.



***cis*-7-(benzo[d][1,3]dioxol-5-ylmethoxy)-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (25g):** The title compound was synthesized according to general procedure **Y** using phenyl benzo[d][1,3]dioxol-5-ylmethoxycarbamate (0.574 g, 2.00 mmol) followed by 2,3-dihydrofuran (3.0 mL, 40 mmol) and *i*-Pr_2NEt (0.052 g, 0.40 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (50% EtOAc/Hexanes). Analysis of the mixture indicated 75% conversion to the product (by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard). Isolation using silica gel flash column chromatography was attempted under a variety of conditions, but this product proved prone to degradation. The product was isolated as a pale yellow oil (0.226 g, 43% yield).

TLC R_f: 0.21 in 40% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, *J* = 1.7 Hz, 1H), 6.87 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 5.98 (s, 2H), 5.48 (d, *J* = 3.1 Hz, 1H), 4.88 (s, 1H), 4.18 (dd, *J* = 9.5, 8.2 Hz, 1H), 3.85 (ddd, *J* = 12.2, 9.6, 5.6 Hz, 1H), 3.40 (dd, *J* = 8.2, 3.0 Hz, 1H), 2.16 (dd, *J* = 13.2, 5.4 Hz, 1H), 1.73 (ddt, *J* = 13.1, 12.0, 8.2 Hz, 1H).

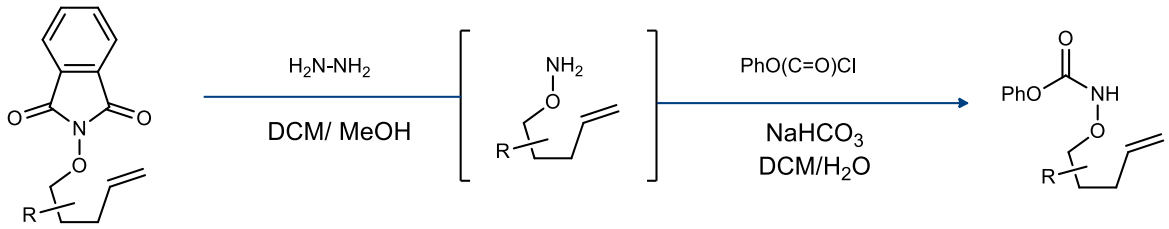
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4 (C), 149.6 (C), 148.3 (C), 143.0 (C), 141.1 (CH), 123.2 (CH), 108.2 (CH), 101.3 (CH_2), 91.6 (CH), 78.4 (CH_2), 66.8 (CH_2), 51.5 (CH), 24.9 (CH_2).

IR (film): 3115, 2998, 2883, 1766, 1662, 1605, 1500, 1441, 1379, 1361, 1250, 1214, 1038 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{13}NO_5Na$ $[M+Na]^+$ 286.0691. Found: 286.0686.

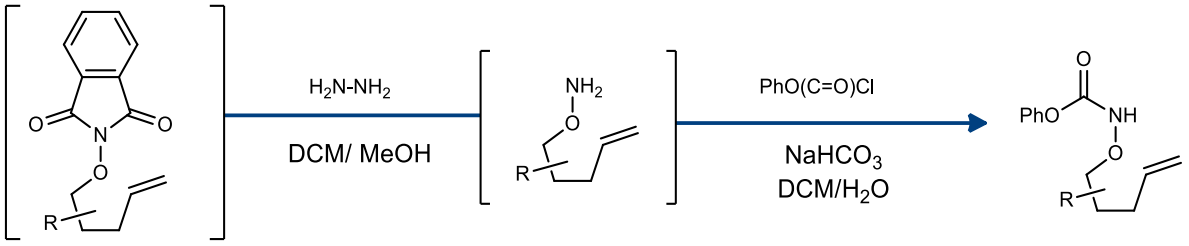
Synthesis of *O*-isocyanate precursors for intramolecular [3+2] cycloadditions

General procedure Z: Synthesis of *N*-alkoxycarbamates

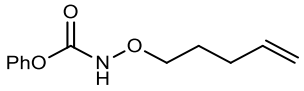


To a round bottom flask charged with a stir bar was added the corresponding *N*-alkoxyphthalimide (1.00 eq) followed by dilution in CH_2Cl_2:MeOH (10:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added a solution of 50% hydrazine hydrate (2.00 eq). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the *N*-alkoxyphthalimide. Upon completion, the solution was filtered over a fritted funnel and the filtrate was collected (the white precipitate was discarded). The filtrate was extracted with sat. $NaHCO_3$ (x 2) and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and used in the subsequent step without further purification. To a round bottom flask charged with a stir bar was added the corresponding crude *N*-alkyl hydroxylamine from the previous step (1.00 eq) followed by dilution with CH_2Cl_2:H_2O (2:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added $NaHCO_3$ (2.20 eq). After addition of $NaHCO_3$, the solution was allowed to stir at 0 °C for 0.5 h. After 0.5 h passed, phenylchloroformate was added dropwise (1.00 eq). The solution was allowed to stir at rt. The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the phenylchloroformate. Upon completion, the reaction was extracted using sat. $NaHCO_3$ (x 2) and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography or recrystallization.

General procedure AA: Express Synthesis of *N*-alkoxycarbamates



Phthalimide synthesis as seen in general procedure A. Upon completion (by TLC), Et_2O and hexanes were added to the solution, which induced a white precipitate to form upon cooling (Ph_3P=O and DIAD, usually co-crystallize). The precipitate was filtered and discarded and the filtrate, which contained the *N*-alkoxyphthalimide along with minor impurities, was used in the subsequent step without further purification. Phthalimide deprotection was completed using a modified literature procedure. To a round bottom flask charged with a stir bar was added the corresponding crude *N*-alkoxyphthalimide (1.00 eq) followed by dilution in CH_2Cl_2:MeOH (10:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added a solution of 50% hydrazine hydrate (2.00 eq). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the *N*-alkoxyphthalimide. Upon completion, the solution was filtered over a fritted funnel and the filtrate was collected (the white precipitate was discarded). The filtrate was extracted with sat. $NaHCO_3$ (x 2) and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and used in the subsequent step without further purification. To a round bottom flask charged with a stir bar was added the crude corresponding *N*-alkyl hydroxylamine (1.00 eq) followed by dilution with CH_2Cl_2:H_2O (2:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added $NaHCO_3$ (2.20 eq). After addition of $NaHCO_3$, the solution was allowed to stir at 0 °C for 0.5 h. After 0.5 h passed, phenylchloroformate was added dropwise (1.00 eq). The solution was allowed to stir at rt. The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the phenylchloroformate. Upon completion, the reaction was extracted using sat. $NaHCO_3$ (x 2) and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography or recrystallization.



Phenyl pent-4-en-1-yloxycarbamate (13a): The title compound was synthesized according to general procedure **Z** using a two-step deprotection then acylation sequence. First, 2-(pent-4-en-1-yloxy)isoindoline-1,3-dione (1.62 g, 7.00 mmol) and 50% hydrazine hydrate (0.90 mL, 14 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(pent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(pent-4-en-1-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.29 g, 15.4 mmol) and phenylchloroformate (0.88 mL, 7.0 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes → 20% EtOAc/Hexanes) to yield the title compound as a colourless oil (1.41 g, 91%) over two steps.

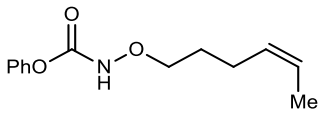
TLC R_f: 0.41 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.41-7.34 (m, 2H), 7.26-7.20 (m, 1H), 7.18-7.13 (m, 2H), 5.83 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.09-4.97 (m, 2H), 3.99 (t, *J* = 6.6 Hz, 2H), 2.22-2.15 (m, 2H), 1.84-1.74 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.4 (C), 137.7 (CH), 129.5 (CH), 125.8 (CH), 121.4 (CH), 115.3 (CH_2), 76.6 (CH_2), 29.9 (CH_2), 27.1 (CH_2).

IR (film): 3282, 3075, 2924, 1730, 1639, 1591, 1471, 1333, 1215, 1200, 1162, 1089 cm^{-1}..

HRMS (ESI): Exact mass calcd for $C_{12}H_{15}NO_3$ $[M+Na]^+$ 244.0939. Found: 244.0950.



(Z)-Phenyl hex-4-en-1-yloxycarbamate (13b): The title compound was synthesized according to general procedure **AA** using a three-step Mitsunobu, deprotection then acylation sequence. First, (Z)-hex-4-en-1-ol (1.50 g, 15.0 mmol), *N*-hydroxyphthalimide (2.45 g, 15.0 mmol), triphenylphosphine (3.93 g, 15.0 mmol), and diisopropyl azodicarboxylate (3.10 mL, 15.8 mmol) in THF (0.3 M) were stirred at 0 °C. Upon completion, hexanes and Et_2O were added to the solution leading to precipitation of Ph_3P=O and DIAD-H_2 which was removed by filtration. The filtrate containing the(Z)-2-(hex-4-en-1-yloxy)isoindoline-1,3-dione and minor impurities was

used in the subsequent step without further purification. The crude (Z)-2-(hex-4-en-1-yloxy)isoindoline-1,3-dione was diluted in CH_2Cl_2:MeOH (10:1) (0.3 M) and 50% hydrazine hydrate (1.9 mL, 30 mmol) was added at 0 °C and allowed to stir overnight at rt. The (Z)-O-(hex-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The (Z)-O-(hex-4-en-1-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (2.77 g, 33.0 mmol) and phenylchloroformate (2.06 mL, 16.5 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a colourless oil (1.542 g, 44%) over three steps.

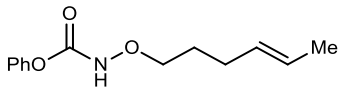
TLC R_f: 0.78 in 50% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.40-7.35 (m, 2H), 7.25-7.21 (m, 1H), 7.18-7.14 (m, 2H), 5.54-5.46 (m, 1H), 5.43-5.35 (m, 1H), 3.98 (t, *J* = 6.6Hz, 2H), 2.17 (ap q, *J* = 7.3 Hz, 2H), 1.76 (ap quin, *J* = 6.7 Hz, 2H), 1.62 (ddt, *J* = 6.7, 1.6, 0.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5 (C), 150.4 (C), 129.4 (CH), 129.3 (CH), 125.8 (CH), 124.9 (CH), 121.3 (CH), 76.7 (CH_2), 27.7 (CH_2), 23.08 (CH_2), 12.7 (CH_3).

IR (film): 3265, 3012, 2937, 1731, 1592, 1475, 1456, 1198, 1091 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{17}NO_3$ $[M+Na]^+$ 258.1106. Found: 258.1111.



(E)-Phenyl hex-4-en-1-yloxycarbamate (13c): The title compound was synthesized according to general procedure **Z** using a two-step deprotection then acylation sequence. First, (E)-2-(hex-4-en-1-yloxy)isoindoline-1,3-dione (0.936 g, 3.80 mmol) and 50% hydrazine hydrate (0.48 mL, 7.6 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude(E)-O-(hex-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude(E)-O-(hex-4-en-1-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (0.702 g, 8.36 mmol) and phenylchloroformate (0.52 mL, 4.18 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.614 g, 68%) over two steps.

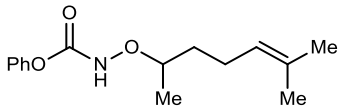
TLC R_f: 0.78 in 50% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.41-7.34 (m, 2H), 7.26-7.20 (m, 1H), 7.17-7.13 (m, 2H), 5.53-5.37 (m, 2H), 3.97 (t, *J* = 6.6 Hz, 2H), 2.14-2.05 (m, 2H), 1.74 (quint, *J* = 6.7 Hz, 2H), 1.65 (d, *J* = 5.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (C), 150.5 (C), 130.1 (CH), 129.4 (CH), 125.81 (CH), 125.79 (CH), 121.3 (CH), 76.7 (CH_2), 28.7 (CH_2), 27.8 (CH_2), 17.9 (CH_3).

IR (film): 3266, 3019, 2935, 1729, 1592, 1475, 1454, 1198, 1091 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{17}NO_3$ $[M+Na]^+$ 258.1106. Found: 258.1093.



Phenyl (6-methylhept-5-en-2-yl)oxycarbamate (13d): The title compound was synthesized according to general procedure **AA** using a three-step Mitsunobu, deprotection then acylation sequence. First, 6-methylhept-5-en-2-ol (3.00 mL, 19.7 mmol), *N*-hydroxyphthalimide (3.21 g, 19.7 mmol), triphenylphosphine (5.17 g, 19.7 mmol), and diisopropyl azodicarboxylate (4.08 mL, 20.7 mmol) in THF (0.3 M) were stirred at 0 °C. Upon completion, hexanes and Et_2O were added to the solution leading to precipitation of Ph_3P=O and DIAD-H_2 which was removed by filtration. The filtrate containing the 2-((6-methylhept-5-en-2-yl)oxy)isoindoline-1,3-dione and minor impurities was used in the subsequent step without further purification. The crude 2-((6-methylhept-5-en-2-yl)oxy)isoindoline-1,3-dione was diluted in CH_2Cl_2:MeOH (10:1) (0.3 M) and 50% hydrazine hydrate (2.53 mL, 39.4 mmol) was added at 0 °C and allowed to stir overnight at rt. The crude *O*-(hex-5-en-2-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(6-methylhept-5-en-2-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (3.64 g, 43.3 mmol) and phenylchloroformate (2.47 mL, 19.7 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (5% EtOAc/Hexanes → 15% EtOAc/Hexanes) to yield the title compound as a colourless oil (2.58 g, 50%) over three steps.

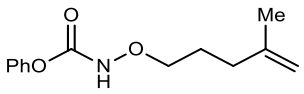
TLC R_f: 0.46 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.40-7.35 (m, 2H), 7.25-7.20 (m, 1H), 7.18-7.14 (m, 2H), 5.15-5.09 (m, 1H), 4.01 (sextet, *J* = 6.2 Hz, 1H), 2.15-2.08 (m, 2H), 1.80 (s, 1H), 1.69 (d, *J* = 1.1 Hz, 3H), 1.61 (d, *J* = 0.2 Hz, 3H), 1.55-1.47 (m, 1H), 1.29 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9 (C), 150.6 (C), 132.2 (C), 129.5 (CH), 125.9 (CH), 123.9 (CH), 121.5 (CH), 82.2 (CH), 34.8 (CH_2), 25.8 (CH_3), 24.1 (CH_2), 18.6 (CH_3), 17.8 (CH_3).

IR (film): 3268, 2927, 2856, 1735, 1592, 1475, 1454, 1375, 1199, 1069 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{21}NO_3$ $[M+Na]^+$ 286.1394. Found: 286.1419.



Phenyl (4-methylpent-4-en-1-yl)oxycarbamate (13e): The title compound was synthesized according to general procedure **AA** using a three-step Mitsunobu, deprotection then acylation sequence. First, 4-methylpent-4-en-1-ol (0.542 g, 5.41 mmol), *N*-hydroxyphthalimide (0.883 g, 5.41 mmol), triphenylphosphine (1.42 g, 5.41 mmol), and diisopropyl azodicarboxylate (1.12 mL, 5.68 mmol) in THF (0.3 M) were stirred at 0 °C. Upon completion, hexanes and Et_2O were added to the solution leading to precipitation of $Ph_3P=O$ and DIAD-H_2 which was removed by filtration. The filtrate containing the 2-((4-methylpent-4-en-1-yl)oxy)isoindoline-1,3-dione and minor impurities was used in the subsequent step without further purification. The crude 2-((4-methylpent-4-en-1-yl)oxy)isoindoline-1,3-dione was diluted in CH_2Cl_2:MeOH (10:1) (0.3 M) and 50% hydrazine hydrate (0.67 mL, 11 mmol) was added at 0 °C and allowed to stir overnight at rt. The crude *O*-(4-methylpent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(4-methylpent-4-en-1-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.00 g, 11.9 mmol) and phenylchloroformate (0.75 mL, 6.0 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.892 g, 70%) over three steps.

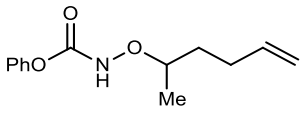
TLC R_f: 0.75 in 50% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.41-7.34 (m, 2H), 7.26-7.20 (m, 1H), 7.18-7.13 (m, 2H), 4.76-4.73 (m, 1H), 4.73-4.70 (m, 1H), 3.98 (t, *J* = 6.6 Hz, 2H), 2.14 (dd, *J* = 8.5, 7.0 Hz, 2H), 1.88-1.79 (m, 2H), 1,74 (td, *J* = 1.3, 0.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.4 (C), 144.8 (C), 129.4 (CH), 125.8 (CH), 121.3 (CH), 110.4 (CH2), 76.8 (CH2), 33.8 (CH2), 25.9 (CH2), 22.4 (CH3)

IR (film): 3265, 3073, 2938, 1731, 1649, 1592, 1476, 1456, 1198, 1023 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{17}NO_3$ $[M+Na]^+$ 258.1106. Found: 258.1090.



Phenyl hex-5-en-2-yloxycarbamate (13f): The title compound was synthesized according to general procedure **Z** using a two-step deprotection then acylation sequence. First, 2-(hex-5-en-2-yloxy)isoindoline-1,3-dione (4.26 g, 17.36 mmol) and 50% hydrazine hydrate (2.22 mL, 34.72 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(hex-5-en-2-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(hex-5-en-2-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (3.21 g, 38.2 mmol) and phenylchloroformate (2.17 mL, 17.36 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a colourless oil (3.81 g, 93%) over two steps.

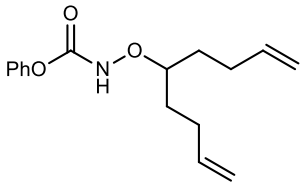
TLC R_f: 0.15 in 10% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.38-7.33 (m, 2H), 7.23-7.18 (m, 1H), 7.18-7.12 (m, 2H), 5.82 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.07-4.93 (m, 2H), 4.01 (sextet, *J* = 6.2 Hz, 1H), 2.19 (q, *J* = 7.2 Hz, 2H), 1.84-1.72 (m, 1H), 1.62-1.50 (m, 1H), 1.27 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0 (C), 150.6 (C), 138.2 (CH), 129.5 (CH), 125.9 (CH), 121.5 (CH), 115.0 (CH_2), 82.0 (CH), 33.9 (CH_2), 29.7 (CH_2), 18.6 (CH_3).

IR (film): 3273, 2974, 2936, 1725, 1640, 1592, 1490, 1464, 1374, 1188, 1081 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{17}NO_3$ $[M+Na]^+$ 258.1116. Found: 258.1106.



Phenyl nona-1,8-dien-5-yloxycarbamate (13g): The title compound was synthesized according to general procedure **Z** using a two-step deprotection then acylation sequence. First, 2-(nona-1,8-dien-5-yloxy)isoindoline-1,3-dione (2.29 g, 8.04 mmol) and 50% hydrazine hydrate (1.05 mL, 16.9 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(nona-

1,8-dien-5-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(nona-1,8-dien-5-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.48 g, 17.6 mmol) and phenylchloroformate (1.1 mL, 8.8 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes→ 18% EtOAc/Hexanes) to yield the title compound as a colourless oil (1.65 g, 87%).

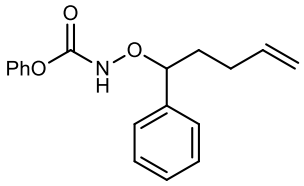
TLC R_f: 0.83 in 50% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (br s, 1H), 7.41-7.34 (m, 2H), 7.25-7.20 (m, 1H), 7.18-7.13 (m, 2H), 5.84 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 2H), 5.05 (ap dq, *J* = 17.1, 3.5, 2H), 4.98 (ddt, *J* = 10.2, 2.0, 1.2 Hz, 2H), 3.92 (tt, *J* = 6.6, 5.3 Hz, 1H), 2.21 (dtt, *J* = 8.1, 6.8, 1.4 Hz, 4H), 1.84-1.61 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.4 (C), 138.2 (CH), 129.4 (CH), 125.8 (CH), 121.4 (CH), 114.9 (CH_2), 85.2 (CH), 31.5 (CH_2), 29.4 (CH_2).

IR (film): 3272, 2074, 2937, 1734, 1639, 1592, 1487, 1451, 1359, 1198, 1085 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{21}NO_3$ $[M+Na]^+$ 298.1419. Found: 298.1406.



Phenyl (1-phenylpent-4-en-1-yl)oxycarbamate (13h): The title compound was synthesized according to general procedure **Z** using a two-step deprotection then acylation sequence. First, 2-((1-phenylpent-4-en-1-yl)oxy)isoindoline-1,3-dione (0.715 g, 2.34 mmol) and 50% hydrazine hydrate (0.30 mL, 4.68 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(1-phenylpent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(1-phenylpent-4-en-1-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (0.432 g, 5.15 mmol) and phenylchloroformate (0.29 mL, 2.34 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified by recrystallization (Et_2O/ Hexanes) to yield the title compound as a crystalline solid (0.694 g, 99%) over two steps.

M.p.: 69.9-70.2 °C.

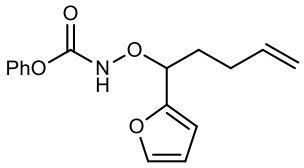
TLC R_f: 0.43 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.34 (m, 8H), 7.22 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.12-7.10 (m, 2H), 5.84 (ddt, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.07-4.97 (m, 2H), 4.87 (dd, *J* = 7.2, 6.2 Hz, 1H), 2.30-2.07 (m, 3H), 1.87-1.77 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (C), 150.5 (C), 140.0 (C), 137.8 (CH), 129.5 (CH), 128.9 (CH), 128.7 (CH), 127.3 (CH), 125.9 (CH), 121.5 (CH), 115.4 (CH_2), 88.0 (CH), 34.6 (CH_2), 29.9 (CH_2).

IR (film): 3249, 3062, 2944, 1720, 1482, 1258, 1204, 1162, 1097 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{18}H_{19}NO_3$ $[M+Na]^+$ 320.1241. Found: 320.1263.



Phenyl (1-(furan-2-yl)pent-4-en-1-yl)oxycarbamate (13i): The title compound was synthesized according to general procedure **Z** using a two-step deprotection then acylation sequence. First, 2-((1-(furan-2-yl)pent-4-en-1-yl)oxy)isoindoline-1,3-dione (1.97 g, 6.63 mmol) and 50% hydrazine hydrate (0.85 mL, 13 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(1-(furan-2-yl)pent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(1-(furan-2-yl)pent-4-en-1-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.23 g, 14.6 mmol) and phenylchloroformate (0.83 mL, 6.6 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a pale yellow solid (1.65 g, 87%).

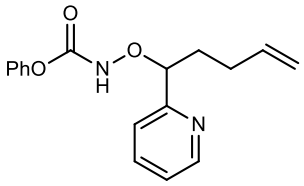
TLC R_f: 0.29 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.45 (m, 1H), 7.45-7.43 (m, 1H), 7.37-7.32 (m, 2H), 7.22-7.18 (m, 1H), 7.12-7.08 (m, 2H), 6.41 (dt, *J* = 3.2, 0.4 Hz, 1H), 6.38 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.81 (ddt, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.05-4.96 (m, 2H), 4.87 (dd, *J* = 8.6, 5.0 Hz, 1H), 2.22-2.12 (m, 3H), 2.03-1.94 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1 (C), 152.2 (C), 150.4 (C), 143.1 (CH), 137.4 (CH), 129.4 (CH), 125.8 (CH), 121.3 (CH), 115.4 (CH_2), 110.3 (CH), 109.9 (CH), 80.2 (CH), 30.7 (CH_2), 29.6 (CH_2).

IR (film): 3283, 3119, 2924, 1730, 1639, 1591, 1469, 1332, 1246, 1204, 1151, 1015 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{17}NO_4$ $[M+Na]^+$ 310.1050. Found: 310.1055.



Phenyl (1-(pyridin-2-yl)pent-4-en-1-yl)oxycarbamate (13j). The title compound was synthesized according to general procedure **Z** using a two-step deprotection then acylation sequence. First, 2-((1-(pyridin-2-yl)pent-4-en-1-yl)oxy)isoindoline-1,3-dione (0.840 g, 2.72 mmol) and 50% hydrazine hydrate (0.35 mL, 5.44 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(1-(pyridin-2-yl)pent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(1-(pyridin-2-yl)pent-4-en-1-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (0.502 g, 5.98 mmol) and phenylchloroformate (0.34 mL, 2.7 mmol) were added at 0 °C and allowed to stir for 12 h. After stirring for 12 h, the reaction vessel was cooled in the fridge overnight. A white precipitate formed and was filtered over a fritted funnel to yield the title compound as an amorphous white solid (0.781 g, 96% over two steps).

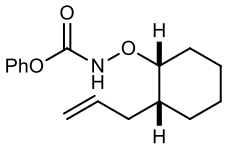
TLC R_f: 0.37 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, *J* = 4.6 Hz, 1H), 7.99 (s, 1H), 7.74 (td, *J* = 7.7, 1.6 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.36-7.31 (m, 2H), 7.28-7.25 (m, 1H), 7.22-7.16 (m, 1H), 7.11-7.07 (m, 2H), 5.83 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.07-4.93 (m, 3H), 2.34-1.85 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (C), 155.3 (C), 150.5 (C), 149.3 (CH), 137.7 (CH), 137.2 (CH), 129.5 (CH), 125.9 (CH), 123.3 (CH), 121.9 (CH), 121.5 (CH), 115.5 (CH_2), 87.9 (CH), 33.9 (CH_2), 29.7 (CH_2).

IR (film): 3091, 2914, 1756, 1594, 1516, 1491, 1435, 1343, 1244, 1203, 1166, 1084 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{17}H_{18}N_2O_3$ $[M+Na]^+$ 321.1212. Found: 321.1215



***syn*-Phenyl (2-allylcyclohexyl)oxycarbamate (13k):** The title compound was synthesized according to general procedure **AA** using a three-step Mitsunobu, deprotection then acylation sequence. First, *trans*-2-allylcyclohexanol (1.08 g, 7.67 mmol), *N*-hydroxyphthalimide (1.25 g,

7.67 mmol), triphenylphosphine (2.01 g, 7.67 mmol), and diisopropyl azodicarboxylate (1.6 mL, 8.06 mmol) in THF (0.3 M) were stirred at 0 °C. Upon completion, hexanes and Et_2O were added to the solution leading to precipitation of Ph_3P=O and DIAD-H_2 which was removed by filtration. The filtrate containing the *cis*-2-Allylcyclohexyl)oxy)isoindoline-1,3-dione and minor impurities was used in the subsequent step without further purification. The crude *cis*-2-Allylcyclohexyl)oxy)isoindoline-1,3-dione was diluted in CH_2Cl_2:MeOH (10:1) (0.3 M) and 50% hydrazine hydrate (0.40 mL, 6.2 mmol) was added at 0 °C and allowed to stir overnight at rt. The crude *cis*-*O*-2-allylcyclohexyl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *cis*-*O*-2-allylcyclohexyl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (0.575 g, 6.84 mmol) and phenylchloroformate (0.43 mL, 3.4 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (4% EtOAc/Toluene) to yield the title compound as a pale yellow oil (0.332 g, 16%) over three steps.

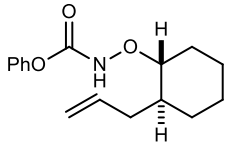
TLC R_f: 0.77 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (br s, 1H), 7.41-7.34 (m, 2H), 7.25-7.19 (m, 1H), 7.18-7.13 (m, 2H), 5.86 (ddt, *J* = 17.1, 10.1, 7.2 Hz, 1H), 5.09-4.97 (m, 2H), 4.06 (dt, *J* = 5.4, 2.7 Hz, 1H), 2.37 (dtt, *J* = 13.9, 6.7, 1.2 Hz, 1H), 2.15-2.05 (m, 2H), 1.74-1.61 (m, 3H), 1.53-1.30 (m, 5H),

^{13}C NMR (150 MHz, $CDCl_3$): 155.6 (C), 150.4 (C), 137.5 (CH), 129.4 (CH), 125.8 (CH), 121.4 (CH), 115.9 (CH_2), 83.6 (CH), 40.1 (CH), 35.9 (CH_2), 28.0 (CH_2), 26.9 (CH_2), 24.7 (CH_2), 21.0 (CH_2).

IR (film): 3249, 3070, 2919, 1855, 1755, 1729, 1637, 1590, 1478, 1252, 1209, 1090 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{21}NO_3$ $[M+Na]^+$ 298.1419. Found: 298.1404.



***anti*-Phenyl (2-allylcyclohexyl)oxycarbamate (13l):** The title compound was synthesized according to general procedure **Z** using a two-step deprotection then acylation sequence. First, *trans*-2-((2-allylcyclohexyl)oxy)isoindoline-1,3-dione (0.175 g, 0.613 mmol) and 50% hydrazine hydrate (0.08 mL, 1.2 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *trans*-*O*-(2-allylcyclohexyl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *trans*-*O*-(2-allylcyclohexyl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (0.113 g, 1.35 mmol) and phenylchloroformate (0.09 mL, 0.67 mmol) were added at 0 °C and allowed to stir

overnight at rt. The product was purified by recrystallization in ether/hexanes to yield the title compound as a off-white crystals (0.110 g, 65%).

M.p.: 84.0-84.3 °C.

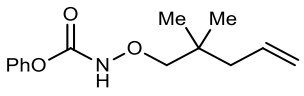
TLC R_f: 0.88 in 50% EtOAc/Hexanes

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (br s, 1H), 7.40-7.35 (m, 2H), 7.24-7.20 (m, 1H), 7.17-7.14 (m, 2H), 5.84 (dddd, *J* = 16.9, 10.1, 7.9, 6.6 Hz, 1H), 5.06-4.99 (m, 2H), 3.57 (td, *J* = 14.0, 5.5 Hz, 1H), 2.60 (dt, *J* = 14.0, 5.5 Hz, 1H), 2.27-2.21 (m, 1H), 2.03 (dt, *J* = 14.9, 8.0 Hz, 1H), 1.88-1.77 (m, 2H), 1.66-1.51 (m, 2H), 1.38 (tdd, *J* = 12.4, 10.4, 3.5 Hz, 1H), 1.30-1.13 (m, 2H), 1.07-0.96 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 155.8 (C), 150.4 (C), 136.9 (CH), 129.4 (CH), 125.8 (CH), 121.4 (CH), 116.1 (CH_2), 87.8 (CH), 40.7 (CH), 36.7 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 25.0 (CH_2), 24.3 (CH_2).

IR (film): 3262, 3071, 2931, 2857, 1720, 1642, 1594, 1482, 1255, 1207, 1160, 1097 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{21}NO_3$ $[M+Na]^+$ 298.1419. Found: 298.1412.



Phenyl (2,2-dimethylpent-4-en-1-yl)oxycarbamate (13m): The title compound was synthesized according to general procedure **Z** using a two-step deprotection then acylation sequence. First, 2-((2,2-dimethylpent-4-en-1-yl)oxy)isoindoline-1,3-dione (1.63 g, 6.30 mmol) and 50% hydrazine hydrate (0.80 mL, 13 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(2,2-dimethylpent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(2,2-dimethylpent-4-en-1-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.16 g, 13.9 mmol) and phenylchloroformate (0.87 mL, 6.9 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (1.5% *i*-PrOH/Toluene) to yield the title compound as a pale yellow oil (1.04 g, 66%).

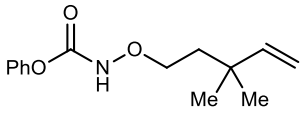
TLC R_f: 0.57 in 25% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.40-7.35 (m, 2H), 7.25-7.21 (m, 1H), 7.18-7.14 (m, 2H), 5.91-5.77 (m, 1H), 5.07-5.02 (m, 2H), 3.72 (s, 2H), 2.08 (dt, *J* = 7.5, 1.1 Hz, 2H), 0.97 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C), 150.4 (C), 134.7 (CH), 129.4 (CH), 125.8 (CH), 121.4 (CH), 117.6 (CH_2), 85.43 (CH_2), 43.5 (CH_2), 34.5 (C), 24.3 (CH_3).

IR (film): 3279, 3073, 2959, 1732, 1638, 1593, 1472, 1364, 1199, 1094 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{14}H_{19}NO_3$ $[M+Na]^+$ 272.1263. Found: 272.1266.



Phenyl (3,3-dimethylpent-4-en-1-yl)oxycarbamate (13n): The title compound was synthesized according to general procedure **Z** using a two-step deprotection then acylation sequence. First, 2-((3,3-dimethylpent-4-en-1-yl)oxy)isoindoline-1,3-dione (2.07 g, 8.00 mmol) and 50% hydrazine hydrate (1.03 mL, 16.00 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(3,3-dimethylpent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(3,3-dimethylpent-4-en-1-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.48 g, 17.6 mmol) and phenylchloroformate (1.00 mL, 8.00 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (5% EtOAc/Hexanes → 20% EtOAc/Hexanes) to yield the title compound as a colourless oil (1.93 g, 97%) over two steps.

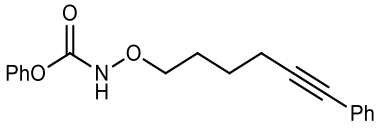
TLC R_f: 0.35 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (br s, 1H), 7.40-7.35 (m, 2H), 7.25-7.20 (m, 1H), 7.18-7.13 (m, 2H), 5.80 (dd, *J* = 17.8, 10.4 Hz, 1H), 4.98-4.92 (m, 2H), 3.97 (t, *J* = 7.3 Hz, 2H), 1.71 (t, *J* = 7.3 Hz, 2H), 1.05 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.5 (C), 147.6 (CH), 129.6 (CH), 125.9 (CH), 121.5 (CH), 111.1 (CH_2), 74.8 (CH), 39.8 (CH_2), 35.7 (C), 27.2 (CH_3).

IR (film): 3253, 3065, 2951, 2862, 1725, 1639, 1588, 1465, 1437, 1353, 1185 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{14}H_{19}NO_3$ $[M+Na]^+$ 272.1245. Found: 272.1263.



Phenyl (6-phenylhex-5-yn-1-yl)oxycarbamate (XX): The title compound was synthesized according to general procedure Z using a two-step deprotection then acylation sequence. First, 2-(6-phenylhex-5-yn-1-yloxy)isoindoline-1,3-dione (3.00 g, 9.39 mmol) and 50% hydrazine hydrate (1.20 mL, 18.8 mmol) in CH_2Cl_2:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(hex-5-yn-1-yl)hydroxylamine obtained from this phthalimide deprotection was

used in the subsequent step without further purification. The crude *O*-(6-phenylhex-5-yn-1-yl)hydroxylamine was diluted in CH_2Cl_2:H_2O (2:1) (0.3 M) and $NaHCO_3$ (0.946 g, 11.3 mmol) and phenylchloroformate (1.17 mL, 9.39 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes → 20% EtOAc/Hexanes) to yield the title compound as a colourless oil (2.90 g, 80%) over two steps.

TLC R_f: 0.18 in 10% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.39-7.33 (m, 4H), 7.27-7.21 (m, 5H), 7.15-7.13 (m, 2H), 4.02 (t, 2H), 2.47 (t, 2H), 1.88-1.83 (m, 2H), 1.77-1.71 (m, 2H)

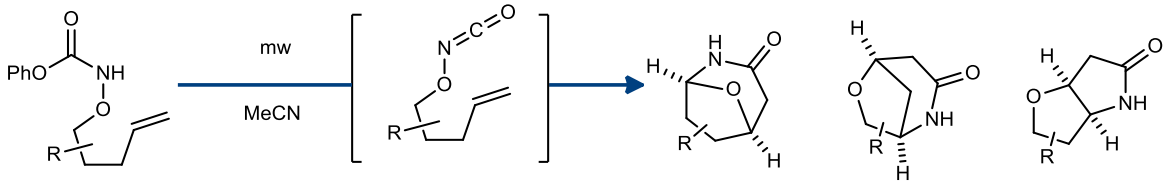
^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.4 (C), 131.6 (CH), 129.5 (CH), 128.2 (CH), 127.6 (CH), 125.8 (CH), 123.9 (C), 121.4 (CH), 89.6 (C), 81.2 (C), 76.7 (CH), 27.1 (CH_2), 25.1 (CH_2), 19.1 (CH_2).

IR (film): 3259, 3054, 2948, 2799, 1724, 1640, 1599, 1461, 1430, 1352, 1189 cm^{-1}.

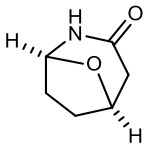
HRMS (ESI): Exact mass calcd for $C_{19}H_{19}NO_3Na$ $[M+Na]^+$ 332.1263. Found: 332.1260.

Synthesis of azabicyclooctanones via intramolecular *O*-isocyanate [3+2] cycloadditions

General procedure BB: Microwave heating of oxo-azabicyclooctanon



To a clean dry microwave vial charged with a stir bar was added the corresponding *N*-alkoxycarbamate followed by dilution with MeCN (0.05 M). The vial was sealed and Argon was bubbled through the solution for 10 min. The reaction vessel was heated at 180-200 °C via microwave irradiation for 3 – 10 h. Upon completion, the reaction was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography.



8-Oxa-2-azabicyclo[3.2.1]octan-3-one (26a): The title compound was synthesized following general procedure **BB** using phenyl pent-4-en-1-yloxycarbamate (0.221, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 3 h. The product was purified using silica-gel flash column chromatography (100% EtOAc) to yield the title compound as a white solid (0.089 g, 70%).

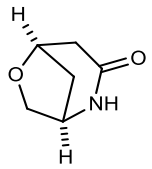
TLC R_f: 0.10 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (br s, 1H), 5.25 (t, *J* = 3.9 Hz, 1H), 4.71 (ddd, *J* = 7.4, 5.7, 1.5 Hz, 1H), 2.84 (ddd, *J* = 17.5, 5.6, 2.0 Hz, 1H), 2.22-2.12 (m, 3H), 2.09-1.97 (m, 1H), 1.85-1.75 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0 (C), 82.7 (CH), 73.7 (CH), 40.8 (CH_2), 36.2 (CH_2), 27.8 (CH_2).

IR (film): 3227, 2920, 2850, 1627, 1467, 1441, 1397, 1359, 1290, 1151, 1073 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_9NO_2$ $[M]^+$ 127.0633. Found: 127.0634.



6-Oxa-2-azabicyclo[3.2.1]octan-3-one (27a): The title compound was synthesized following general procedure **BB** using phenyl pent-4-en-1-yloxycarbamate (0.221, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 3 h. The product was purified using silica-gel flash column chromatography (100% EtOAc → 5% MeOH/CH_2Cl_2 → 10% MeOH/CH_2Cl_2) to yield the title compound as a white solid (0.006 g, 5%).

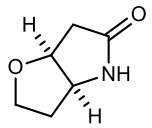
TLC R_f: 0.15 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (br s, 1H), 4.56 (dt, *J* = 5.4, 2.7 Hz, 1H), 4.03 (dd, *J* = 8.3, 1.1 Hz, 1H), 3.92-3.86 (m, 1H), 3.81 (dd, *J* = 8.3, 2.7 Hz, 1H), 2.58 (dt, *J* = 18.0, 1.7 Hz, 1H), 2.43 (dd, *J* = 18.1, 2.5 Hz, 1H), 2.09-1.97 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 171.0 (C), 76.9 (CH_2), 72.8 (CH), 52.4 (CH), 41.8 (CH_2), 35.3 (CH_2).

IR (film): 3447, 2953, 2919, 2851, 2156, 1653, 1458, 1375, 1299 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_9NO_2$ $[M]^+$ 127.0633. Found: 127.0612.



Tetrahydro-2H-furo[3,2-b]pyrrol-5(3H)-one (28a): The title compound was synthesized following general procedure **BB** using phenyl pent-4-en-1-yloxycarbamate (0.221, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 3 h. The product was purified using silica-gel flash column chromatography (100% EtOAc → 5% MeOH/CH_2Cl_2) to yield the title compound as a white solid (0.020 g, 15%).

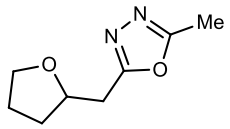
TLC R_f: 0.21 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65 (br s, 1H), 4.67-4.63 (m, 1H), 4.28 (td, *J* = 5.7, 1.5 Hz, 1H), 3.88 (td, *J* = 5.5, 2.9 Hz, 2H), 2.60 (dd, *J* = 18.2, 6.8 Hz, 1H), 2.40 (ddd, *J* = 18.2, 1.3, 0.6 Hz, 1H), 2.07-1.89 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7 (C), 77.9 (CH), 66.5 (CH), 58.7 (CH_2), 38.0 (CH_2), 34.0 (CH_2).

IR (film): 3166, 3075, 2943, 2875, 1673, 1439, 1386, 1308, 1236, 1187, 1061 cm^{-1}..

HRMS (EI): Exact mass calcd for $C_6H_9NO_2$ $[M]^+$ 127.0633. Found: 127.0633.



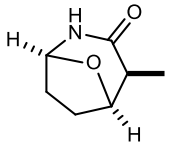
2-Methyl-5-((tetrahydrofuran-2-yl)methyl)-1,3,4-oxadiazole (29a): The title compound was synthesized following general procedure **BB** using phenyl pent-4-en-1-yloxycarbamate (0.221, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 3 h. The product was purified using silica-gel flash column chromatography (100% EtOAc to yield the title compound as a clear oil (0.016 g, 10%).

TLC R_f: 0.55 in 100% EtOAc

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (quintet, *J* = 6.5 Hz, 1H), 3.88 (dt, *J* = 8.3, 6.8 Hz, 1H), 3.78-3.72 (m, 1H), 3.00 (qd, *J* = 16.3, 6.4 Hz, 2H), 2.49-2.47 (m, 3H), 2.13-2.05 (m, 1H), 1.94-1.87 (m, 2H), 1.70-1.63 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8 (C), 164.0 (C), 76.0 (CH), 68.4 (CH_2), 31.8 (CH_2), 31.3 (CH_2), 25.7 (CH_2), 11.1 (CH_3).

IR (film): 1678, 1531, 1444, 1372, 1223, 1022, 929 cm^{-1}.
HRMS (EI): Exact mass calcd for $C_8H_{12}N_2O_2$ $[M]^+$ 168.0899. Found: 168.0900.



4-Methyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (26b): The title compound was synthesized following general procedure **BB** using (Z)-phenyl hex-4-en-1-yloxycarbamate (0.235g, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (100% EtOAc → 1% MeOH/CH_2Cl_2) to yield the title compound as a white solid (0.072g, 51%).

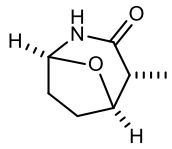
TLC R_f: 0.24 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.36 (br s, 1H), 5.25 (q, *J* = 2.5 Hz, 1H), 4.54 (ddd, *J* = 6.3, 4.8, 2.7 Hz, 1H), 2.89 (*J* = 7.7, 6.9, 5.2 Hz, 1H), 2.13-1.92 (m, 4H), 1.13 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4 (C), 83.5 (CH), 78.5 (CH), 42.5 (CH), 35.9 (CH_2), 21.8 (CH_2), 10.7 (CH_3).

IR (film): 3294, 3178, 2954, 1651, 1471, 1409, 1353, 1279, 1249, 1073 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{11}NO_2$ $[M]^+$ 141.0790. Found: 141.0765



4-Methyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (26c): The title compound was synthesized following general procedure **BB** using (E)-phenyl hex-4-en-1-yloxycarbamate (0.235 g, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (100% EtOAc) to yield the title compound as a white solid (0.069 g, 49%).

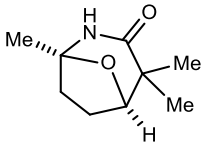
TLC R_f: 0.16 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.42 (br s, 1H), 5.23 (dd, *J* = 4.2, 3.4 Hz, 1H), 4.38 (dd, *J* = 8.1, 1.4 Hz, 1H), 2.30-1.94 (m, 4H), 1.83-1.73 (m, 1H), 1.38 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6 (C), 82.8 (CH), 79.3 (CH), 46.2 (CH), 35.7 (CH_2), 27.4 (CH_2), 17.9 (CH_3).

IR (film): 3223, 2977, 2875, 1732, 1656, 1621, 1471, 1441, 1372, 1295, 1253, 1060 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{11}NO_2$ $[M]^+$ 141.0790. Found: 141.0800.



1,4,4-Trimethyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (26d): The title compound was synthesized following general procedure **BB** using phenyl (6-methylhept-5-en-2-yl)oxycarbamate (0.235, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (50% EtOAc/Hexanes → 100% EtOAc) to yield the title compound as a white solid (0.079 g, 47%).

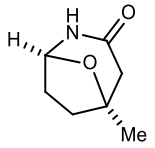
TLC R_f: 0.29 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.03 (br. s, 1H), 4.10 (dd, *J* = 7.4, 2.0 Hz, 1H), 2.12-1.97 (m, 3H), 1.85-1.79 (m, 1H), 1.53 (s, 3H), 1.34 (s, 3H), 1.09 (s, 3H).

^{13}C NMR (100 M9Hz, $CDCl_3$): δ 176.2 (C), 90.5 (C), 83.7 (CH), 44.0 (CH), 40.7 (CH_2), 27.3 (CH_3), 24.4 (CH_2), 23.4 (CH_3), 20.2 (CH_3).

IR (film): 3171, 3053, 2981, 2919, 1655, 1476, 1437, 1397, 1316, 1203, 1138 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{15}NO_2$ $[M]^+$ 169.1103. Found: 169.1106.



5-Methyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (26e): The title compound was synthesized following general procedure **BB** using phenyl (4-methylpent-4-en-1-yl)oxycarbamate (0.235 g, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 6 h. The product was purified using silica-gel flash column chromatography (100% EtOAc → 1% MeOH/CH_2Cl_2) to yield the title compound as a pale yellow solid (0.110 g, 78%).

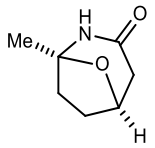
TLC R_f: 0.13 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (br s, 1H), 5.26 (td, *J* = 3.5, 1.1 Hz, 1H), 2.59 (ddd, *J* = 17.3, 2.6, 0.8 Hz, 1H), 2.32 (d, *J* = 17.3 Hz, 1H), 2.22-2.10 (m, 2H), 2.00-1.93 (m, 1H), 1.83 (tdd, *J* = 12.8, 4.7, 2.5 Hz, 1H), 1.47 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3 (C), 82.3 (CH), 80.5 (C), 46.7 (CH_2), 37.1 (CH_2), 34.0 (CH_2), 20.6 (CH_3).

IR (film): 3166, 2974, 2873, 1651, 1471, 1442, 1320, 1303, 1197, 1061 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{11}NO_2$ $[M]^+$ 141.0790. Found: 141.0777.



1-Methyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (26f): The title compound was synthesized following general procedure **BB** using phenyl hex-5-en-2-yloxycarbamate (0.235, 1.00 mmol) in

MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (100% EtOAc) to yield the title compound as a white solid (0.092 g, 65%).

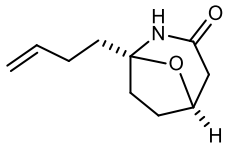
TLC R_f: 0.13 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (br s, 1H), 4.69 (dd, *J* = 7.3, 5.8 Hz, 1H), 2.78 (ddd, *J* = 17.4, 5.4, 1.6 Hz, 1H), 2.33-2.16 (m, 3H), 1.90-1.77 (m, 2H), 1.57 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (C), 89.8 (C), 74.1 (CH), 41.4 (CH_2), 40.1 (CH_2), 29.6 (CH_2), 23.4 (CH_3).

IR (film): 3458, 3175, 2920, 2850, 1637, 1435, 1393, 1359, 1305, 1160, 1015 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{11}NO_2$ $[M]^+$ 141.0790. Found: 141.0805.



1-(But-3-en-1-yl)-8-oxa-2-azabicyclo[3.2.1]octan-3-one (26g): The title compound was synthesized following general procedure **BB** using phenyl nona-1,8-dien-5-yloxycarbamate (0.275 g, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 3 h. The product was purified using silica-gel flash column chromatography (50% EtOAc/Hexanes → 70% EtOAc/Hexanes → 100% EtOAc) to yield the title compound as a white solid (0.101 g, 56%).

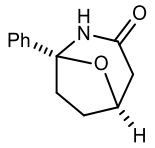
TLC R_f: 0.18 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 (br s, 1H), 5.85 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.08 (ap dd, *J* = 17.1, 1.6 Hz, 1H), 5.02 (ap dt, *J* = 10.2, 1.4 Hz, 1H), 4.71 (ddd, *J* = 7.6, 5.6, 1.1 Hz, 1H), 2.80 (ddd, *J* = 17.4, 5.5, 1.7 Hz, 1H), 2.33-2.14 (m, 5H), 1.95-1.78 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2 (C), 137.3 (CH), 115.6 (CH_2), 91.8 (C), 73.8 (CH), 40.2 (CH_2), 39.8 (CH_2), 35.8 (CH_2), 28.9 (CH_2), 27.9 (CH_2).

IR (film): 3178, 3068, 2954, 2874, 1654, 1459, 1435, 1397, 1310, 1245, 1170, 1002 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{15}NO_2$ $[M]^+$ 181.1103. Found: 181.1086.



1-Phenyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (26h): The title compound was synthesized following general procedure **BB** using phenyl pent-4-en-1-yloxycarbamate (0.235, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (50% EtOAc/Hexanes → 100% EtOAc) to yield the title compound as a white solid (0.111 g, 55%).

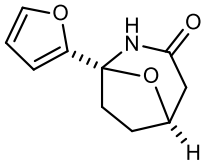
TLC R_f: 0.15 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.50 (m, 2H), 7.43-7.37 (m, 3H), 6.28 (br s, 1H), 4.88 (ddd, *J* = 7.5, 5.6, 1.6 Hz, 1H), 2.91 (ddd, *J* = 17.4, 5.5, 1.6 Hz, 1H), 2.66 (ddd, *J* = 12.0, 9.2, 2.7 Hz, 1H), 2.45-2.36 (m, 1H), 2.33-2.22 (m, 2H), 1.98-1.90 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (C), 139.0 (C), 129.3 (CH), 129.0 (CH), 125.3 (CH), 92.2 (C), 74.3 (CH), 41.0 (CH_2), 40.4 (CH_2), 29.0 (CH_2).

IR (film): 3450, 3175, 2960, 2919, 2850, 1637, 1435, 1393, 1332, 1325, 1160 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{13}NO_2$ $[M]^+$ 203.0946. Found: 203.0921.



1-(Furan-2-yl)-8-oxa-2-azabicyclo[3.2.1]octan-3-one (26i): The title compound was synthesized following general procedure **BB** using phenyl pent-4-en-1-yloxycarbamate (0.144, 0.500 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (100% EtOAc → 5% MeOH/CH_2Cl_2) to yield the title compound as a white solid (0.045 g, 46%).

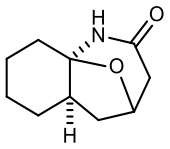
TLC R_f: 0.16 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.93 (br s, 1H), 6.57 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.42 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.86-4.83 (m, 1H), 2.90 (ddd, *J* = 17.4, 5.4, 1.5 Hz, 1H), 2.56-2.39 (m, 3H), 2.27 (dd, *J* = 17.4, 0.5 Hz, 1H), 1.97-1.90 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1 (C), 150.2 (C), 143.5 (CH), 110.9 (CH), 108.8 (CH), 88.1 (C), 74.7 (CH), 40.6 (CH_2), 39.9 (CH_2), 28.7 (CH_2).

IR (film): 3167, 3066, 2913, 1657, 1501, 1465, 1392, 1311, 1219, 1159, 1072 cm^{-1}..

HRMS (EI): Exact mass calcd for $C_{10}H_{11}NO_3$ $[M]^+$ 193.0739. Found: 193.0743.



Octahydro-4,9a-epoxybenzo[b]azepin-2(1H)-one (26k): The title compound was synthesized following general procedure **BB** using *cis*-phenyl (2-allylcyclohexyl)oxycarbamate (0.275 g, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 10 h. The product was purified using silica-gel flash column chromatography (90% EtOAc) to yield the title compound as a white solid (0.100 g, 55%).

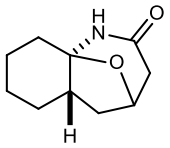
TLC R_f: 0.23 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.38 (br s, 1H), 4.69 (ddd, *J* = 7.6, 4.7, 2.4 Hz, 1H), 2.75 (dddd *J* = 17.1, 4.9, 1.5, 0.8 Hz, 1H), 2.26-2.14 (m, 3H), 1.95 (ddd, *J* = 12.4, 7.6, 2.4 Hz, 1H), 1.82 (ddt, *J* = 12.7, 7.9, 1.3 Hz, 1H), 1.75-1.62 (m, 3H), 1.54-1.40 (m, 2H), 1.20-1.03 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (C), 90.0 (C), 72.7 (CH), 47.5 (CH), 41.0 (CH_2), 36.6 (CH_2), 32.9 (CH_2), 32.5 (CH_2), 24.5 (CH_2), 21.6 (CH_2).

IR (film): 3156, 3047, 2924, 2829, 1669, 1473, 1441, 1392, 1328, 1252, 1089 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{15}NO_2$ $[M]^+$ 181.1103. Found: 181.1103.



Octahydro-4,9a-epoxybenzo[b]azepin-2(1H)-one (26l): The title compound was synthesized following general procedure **BB** using *trans*-Phenyl (2-allylcyclohexyl)oxycarbamate (0.106 g, 0.38 mmol) in MeCN (0.05 M) at 200 °C for 6 h. The product was purified using silica-gel flash column chromatography (100% EtOAc) to yield the title compound as a white solid (0.018 g, 26%).

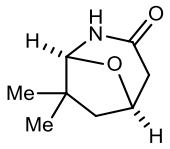
TLC R_f: 0.21 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (br s, 1H), 4.67 (ddd, *J* = 7.3, 4.8, 1.9 Hz, 1H), 2.74 (dd, *J* = 17.2, 4.8 Hz, 1H), 2.20 (t, *J* = 9.6 Hz, 2H), 2.16 (d, *J* = 17.1 Hz, 1H), 1.94 (ddd, *J* = 13.0, 7.6, 2.3 Hz, 1H), 1.81 (dd, *J* = 13.0, 8.0 Hz, 1H), 1.70 (ddd, *J* = 13.0, 5.7, 2.8 Hz, 1H), 1.64 (tt, *J* = 15.3, 2.5 Hz, 2H), 1.54-1.44 (m, 2H), 1.17 (dddt, *J* = 12.3, 10.7, 9.8, 2.7 Hz, 1H), qd (qd, *J* = 12.3, 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8 (C), 90.0 (C), 72.6 (CH), 47.4 (CH), 41.0 (CH_2), 36.6 (CH_2), 32.7 (CH_2), 32.5 (CH_2), 24.5 (CH_2), 21.6 (CH_2).

IR (film): 3155, 3047, 2924, 2849, 1669, 1441, 1392, 1372, 1328, 1254, 1090 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{15}NO_2$ $[M]^+$ 181.1103. Found: 181.1089.



7,7-Dimethyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (26m): The title compound was synthesized following general procedure **BB** using phenyl (2,2-dimethylpent-4-en-1-yl)oxycarbamate (0.249 g, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 6 h. The product was purified using silica-gel flash column chromatography (90% EtOAc/Hexanes → 100% EtOAc → 1% MeOH/CH_2Cl_2 → 5% MeOH/CH_2Cl_2) to yield the title compound as a white solid (0.090 g, 58%).

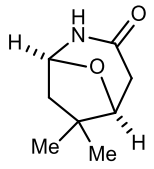
TLC R_f: 0.23 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.43 (br s, 1H), 4.67 (ddd, *J* = 7.7, 5.3, 1.9 Hz, 1H), 4.58 (d, *J* = 3.4 Hz, 1H), 2.84 (ddd, *J* = 17.3, 5.4, 1.8, 0.7 Hz, 1H), 2.17 (dd, *J* = 17.3, 0.7 Hz, 1H), 2.04 (ddd, *J* = 12.8, 7.9, 1.5 hz, 1H), 1.51 (dd, *J* = 12.9, 1.9 Hz, 1H), 1.18 (s, 3H), 1.12 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (C), 90.1 (CH), 74.2 (CH), 47.4 (C), 43.3 (CH_2), 41.2 (CH_2), 28.6 (CH_3), 23.5 (CH_3).

IR (film): 3249, 2962, 2871, 1662, 1636, 1457, 1412, 1387, 1356, 1281, 1079 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_8H_{13}NO_2$ $[M]^+$ 155.0946. Found: 155.0944.



6,6-Dimethyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (26n): The title compound was synthesized following general procedure **BB** using phenyl pent-4-en-1-yloxycarbamate (0.125, 0.500 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (100% EtOAc) to yield the title compound as a white solid (0.043g, 56%).

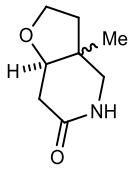
TLC R_f: 0.32 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (br s, 1H), 5.19 (t, *J* = 3.9 Hz, 1H), 4.12 (d, *J* = 6.0 Hz, 1H), 2.72 (dd, *J* = 17.9, 6.0 Hz, 1H), 2.44 (d, *J* = 17.9 Hz, 1H), 1.95 (dq, *J* = 12.8, 6.8 Hz, 2H), 1.18 (s, 3H), 1.17 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3 (C), 84.2 (CH), 83.6 (CH), 51.5 (CH_2), 40.4 (C), 35.7 (CH_2), 32.1 (CH_3), 25.4 (CH_3).

IR (film): 3231, 2958, 2869, 1639, 1467, 1411, 1356, 1309, 1276, 1129, 1042 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_8H_{13}NO_2$ $[M+Na]^+$ 178.0851. Found: 178.0844.



3a-Methylhexahydrofuro[3,2-c]pyridin-6(2H)-one (33n): The title compound was synthesized following general procedure **BB** using phenyl pent-4-en-1-yloxycarbamate (0.125, 0.500 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (100% EtOAc → 5% MeOH/ CH_2Cl_2→ 10% MeOH/ CH_2Cl_2) to yield the title compound as a white solid (0.019 g, 25%, 3:1 diastereomeric mixture).

TLC R_f: 0.08 in 100% EtOAc.

Major diastereomer

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.74 (s, 1H), 3.94 (ddd, *J* = 8.7, 7.8, 3.2 Hz, 1H), 3.79 (dd, *J* = 4.7, 3.3 Hz, 1H), 3.64 (td, *J* = 9.1, 6.4 Hz, 1H), 3.14 (dd, *J* = 13.1, 4.3 Hz, 1H), 3.02 (dd, *J* = 13.0, 2.9 Hz, 1H),

2.55 (dd, *J* = 16.1, 3.2 Hz, 1H), 2.46 (dd, *J* = 16.1, 4.9 Hz, 1H), 1.95 (ddd, *J* = 12.2, 9.3, 7.8 Hz, 1H), 1.74 (ddd, *J* = 12.2, 6.4, 3.2 Hz, 1H), 1.16 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.1 (C), 82.7 (CH), 66.4 (CH_2), 49.6 (CH_2), 42.0 (C), 38.7 (CH_2), 36.3 (CH_2), 23.8 (CH_3).

Minor diastereomer (1H is overlapped)

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.53 (s, 1H), 4.12-4.00 (m, 2H), 3.62 (dd, *J* = 12.4, 5.8 Hz, 1H), 3.28 (dd, *J* = 11.5, 3.9 Hz, 1H), 2.75 (dd, *J* = 17.0, 5.9 Hz, 1H), 2.40 (dd, *J* = 16.8, 12.5 Hz, 1H), 1.83-1.80 (m, 2H), 1.02 (s, 3H).

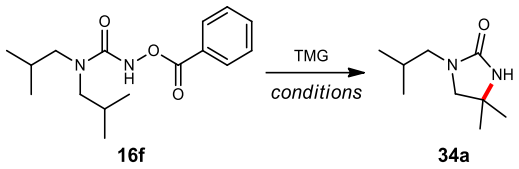
^{13}C NMR (150 MHz, $CDCl_3$): δ 171.6 (C), 79.2 (CH), 67.6 (CH_2), 50.6 (CH_2), 39.2 (C), 36.8 (CH_2), 34.7 (CH_2), 16.1 (CH_3).

IR (film): 3240, 2954, 2868, 1653, 1482, 1454, 1383, 1314, 1267, 1212, 1060 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_8H_{13}NO_2$ $[M]^+$ 155.0946. Found: 155.0937.

Extended optimization efforts for imidazolidinone synthesis via C-H amination

Table 44 Thermal C-H amination of **16f** via microwave irradiation

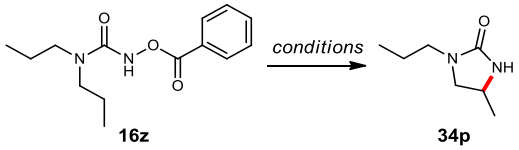


16f **34a**

Entry	Solvent	Temp °C	Time h	%**34a**
1	$(CH_2Cl)_2$	100	1	66
2	$(CH_2Cl)_2$	**100**	**2**	**83**
3	$(CH_2Cl)_2$	150	3	67
4	$CHCl_3$	90	2	0

Conditions: 3-(benzoyloxy)-1,1-diisobutylurea **16f** (1.00 equiv), TMG (0.10 equiv) in solvent (0.30 M) stir under microwave irradiation. NMR yields are shown using 1,3,5-trimethoxybenzene as an internal standard.

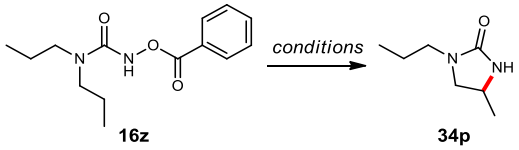
Table 45 Thermal C-H amination of**16z**



Entry	Additive	Solvent	Temp °C	Time h	%**34p**
1	TMG	$(CH_2Cl)_2$	90	15	20
2	TMG	$CHCl_3$	90	15	13
3	TMG	$PHCF_3$	90	15	<10
4	TMG	DMSO	90	15	0
5	TMG	EtOH - sieves	90	15	25
6	TMG	MeCN	90	15	18
7	TMG	Monoglyme	90	15	0
8	TMG	Diglyme	90	15	0
9	TMG	$PhCF_3$	150	15	26
10	TMG	DMSO	150	15	0
11	TMG	DMF	150	15	0
12	**TMG**	**Diglyme**	**150**	**15**	**69**
13	TMG	Dichlorobenzene	150	15	0
14	Benzoic acid	$CHCl_3$	90	15	0
15	Phosphazene	$CHCl_3$	90	15	27
16	AIBN	MeCN	90	15	0
17	-	MeCN	90	15	0
18	-	DMSO	90	15	0
19	-	$PhCF_3$	90	15	0
20	-	EtOH - sieves	90	15	30
21	-	EtOH	90	15	30
22	-	MeOH	90	15	0
23	-	*i*-PrOH	90	15	15
24	-	*t*-BuOH	90	15	0

Conditions: 3-(benzoyloxy)-1,1-dipropylurea **16z** (1.00 equiv), additive (0.10 equiv) in solvent (0.30 M) stir in oil bath. NMR yields are shown using 1,3,5-trimethoxybenzene as an internal standard.

Table 46 Thermal C-H amination of **16z** via microwave irradiation



Entry	Additive (equiv)	Solvent	Temp °C	%**34p**
1	**TMG (0.10)**	$(CH_2Cl)_2$	**120**	**60**
2	DBU (0.10)	$(CH_2Cl)_2$	120	52
3	**Et_3N (0.10)**	$(CH_2Cl)_2$	**120**	**60**
4	*i*-Pr_2NEt (0.10)	$(CH_2Cl)_2$	120	57
5	TMG (0.10)	$(CH_2Cl)_2$	90	14
6	DMAP (0.10)	$(CH_2Cl)_2$	120	14
7	$BF_3.OEt_2$ (1.00)	MeCN	100	0
8	$PhI(OAc)_2$ (1.20)	MeCN	120	0
9	HCl (g) (excess)	MeCN	120	0

Conditions: 3-(benzoyloxy)-1,1-dipropylurea **16z** (1.00 equiv), additive in solvent (0.30 M) stir under microwave irradiation. NMR yields are shown using 1,3,5-trimethoxybenzene as an internal standard.

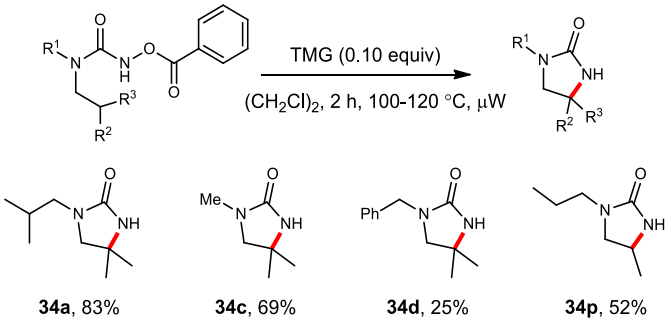
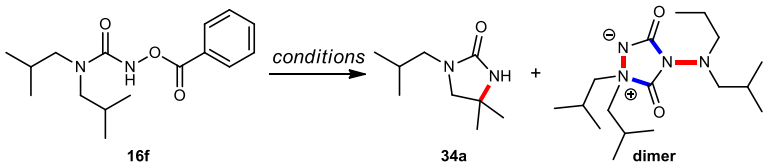


Figure 124 Preliminary scope of thermal C-H amination (sequential) via microwave irradiation

Table 47 Metal catalyzed C-H amination of **16f**



Entry	Metal (mol%)	Base (equiv)	Solvent	Temp °C	Time	%**16f**	%**34a**	%dimer
1	$[IrCp^*Cl_2]_2$ (2.5)	K_2CO_3 (1.5)	CH_2Cl_2	rt	3	0	16	20
2	**$[IrCp^*Cl_2]_2$ (2.5)**	**CsOAc (1.5)**	**CH_2Cl_2**	**rt**	**3**	**0**	**20**	**33**
3	$[IrCp^*Cl_2]_2$ (2.5)	Imidazole (1.5)	CH_2Cl_2	rt	16	100	0	0
4	$[IrCp^*Cl_2]_2$ (2.5)	CsOAc (0.2)	CH_2Cl_2	rt	3	0	17	20
5	$[IrCp^*Cl_2]_2$ (0.5)	CsOAc (0.2)	CH_2Cl_2	rt	3	0	21	15
6	$[IrCp^*Cl_2]_2$ (0.5)	CsOAc (5.0)	CH_2Cl_2	rt	3	0	18	14
7	$[IrCp^*Cl_2]_2$ (0.5)	CsOAc (0.2)	THF	rt	13	72	11	3
8	$[IrCp^*Cl_2]_2$ (0.5)	CsOAc (0.2)	$PhCF_3$	rt	13	0	27	18
9	$[IrCp^*Cl_2]_2$ (0.5)	CsOAc (0.2)	MeCN	rt	13	37	11	6
10	$[IrCp^*Cl_2]_2$ (0.5)	CsOAc (0.2)	DMSO	rt	13	60	0	0
11	$[IrCp^*Cl_2]_2$ (0.5)	KOAc (0.2)	CH_2Cl_2	rt	3	24	21	11
12	$[IrCp^*Cl_2]_2$ (0.5)	NaOAc (0.2)	CH_2Cl_2	rt	3	25	19	10
13	$[IrCp^*Cl_2]_2$ (0.5)	MgO (0.2)	CH_2Cl_2	rt	3	15	7	7
14	$[IrcodCl_2]_2$ (2.5)	CsOAc (1.5)	CH_2Cl_2	rt	16	100	0	0
15	$[IrcodCl_2]_2$ (2.5)	CsOAc (1.5)	MeOH	rt	16	40	24	0
16	$[IrcodCl_2]_2$ (2.5)	CsOAc (0.2)	CH_2Cl_2	rt	16	0	17	20
17	$[RhCp^*Cl_2]_2$ (2.5)	K_2CO_3 (1.5)	MeOH	rt	16	0	5	0
18	$[RhCp^*Cl_2]_2$ (2.5)	CsOAc (1.5)	MeOH	rt	16	0	0	0
19	$[RhCp^*Cl_2]_2$ (2.5)	Cs_2OAc_3 (1.5)	MeOH	rt	16	0	7	0
20	$[RhCp^*Cl_2]_2$ (2.5)	*t*-BuOK (1.5)	MeOH	rt	16	0	13	0
21	$[RhCp^*Cl_2]_2$ (2.5)	*t*-BuOK (1.5)	MeOH	rt	16	0	0	0
22	$[RhCp^*Cl_2]_2$ (2.5)	*t*-BuOK (1.5)	*i*-PrOh	rt	16	0	0	0
23	$[RhOAc]_2$ (5.0)	K_2CO_3 (1.5)	CH_2Cl_2	rt	16	0	10	
24[a]	$[RhOAc]_2$ (5.0)	Imidazole (1.5)	$(CH_2Cl)_2$	90	16		37	
25	$[Rhesp_2]_2$ (5.0)	K_2CO_3 (1.5)	$(CH_2Cl)_2$	rt	16	100	0	0

Conditions: 3-(benzoyloxy)-1,1-diisobutylurea **16f** (1.00 equiv), metal, base in solvent (0.3M) stir at r.t.. [a]Cascade reaction with 80% of SM converted. NMR yield are shown using 1,3,5-trimethoxybenzene as an internal standard.

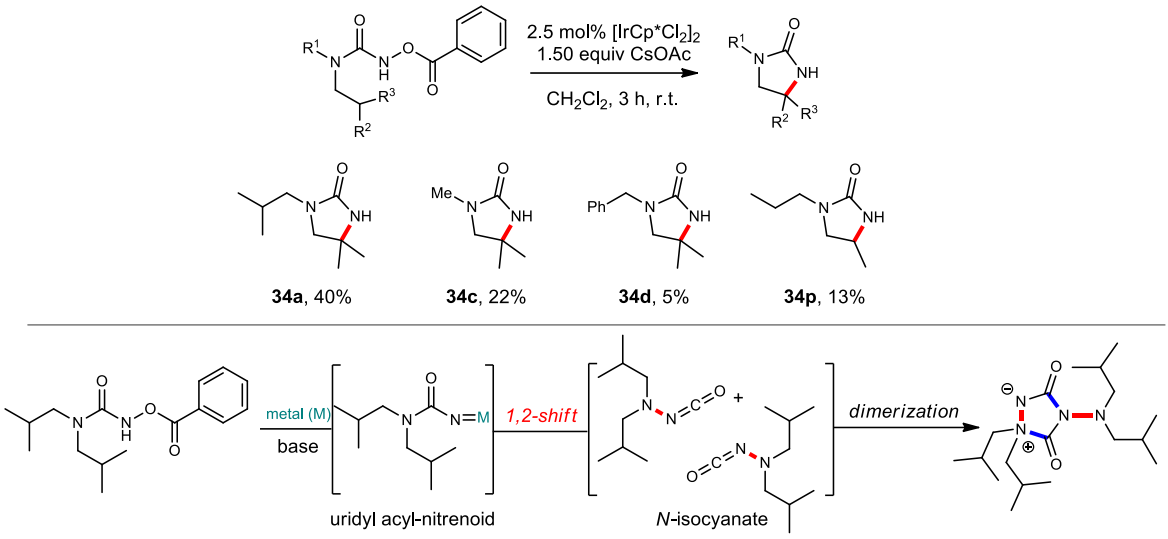
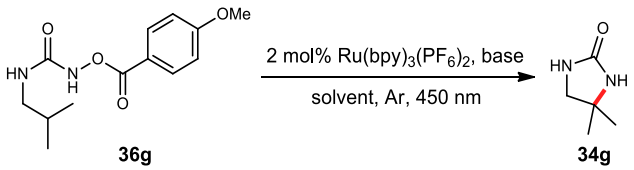


Figure 125 Preliminary scope of metal catalyzed C-H amination / mechanism for dimerization

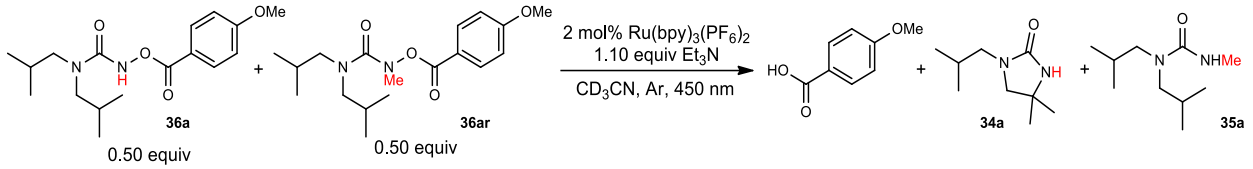
Table 48 Optimization of photocatalytic C-H amination using **36g**

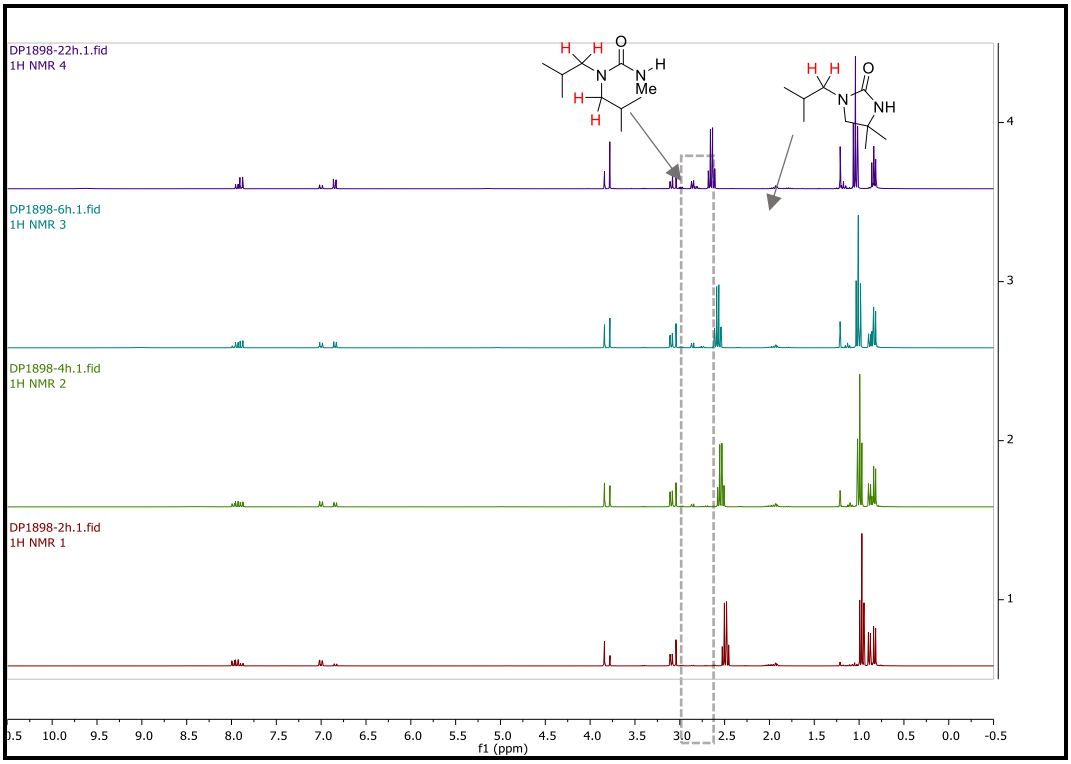


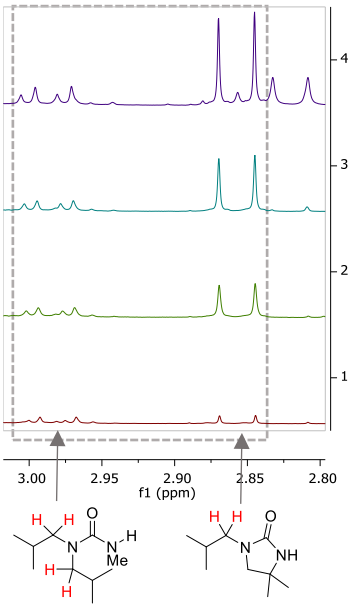
Entry	Base (equiv)	Solvent	Temp °C	%Product
1	Et_3N (1.10 equiv)	MeCN	r.t.	0
2	Phosphate (5 mol%)	CH_2Cl_2	r.t.	18
3	Phosphate (5 mol%)	CH_2Cl_2	40	45
4	Phosphate (5 mol%)	CH_2Cl_2	60	50
5	Phopshate (5 mol%)	CH_2Cl_2	80	17

Conditions: 1-isobutyl-3-((4-methoxybenzoyl)oxy)urea **36g** (1.00 equiv), photocatalyst (2 mol%), additive (1.10 equiv) in solvent (0.3M) irradiated under inert atmosphere with 450 nm blue LED.

Figure 126 Single reaction vessel competition experiment using **36a** and **36ar**





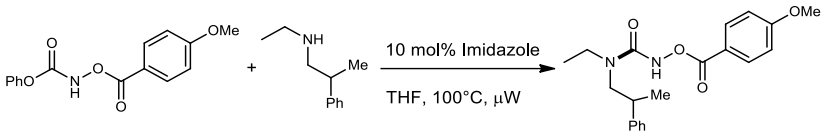


Time (h)	%SM	%Acid	%C-H Activation	%Urea
2	84	16	2	>1
4	63	37	13	4
6	52	48	22	6
22	29	71	33	8

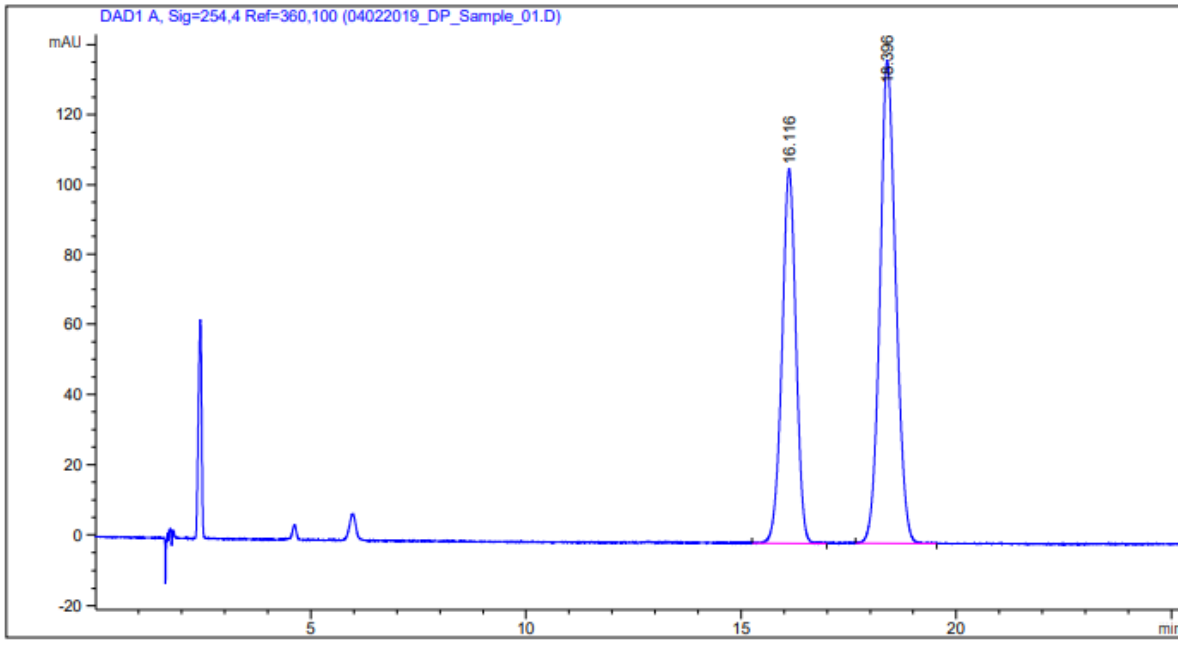
We directly compared the conversion of **36a** and **36ar** by allowing the two precursors to react simultaneously in the same reaction vessel. When we compared the conversion of **36a** and its *N*-methylated derivative **36ar** by NMR we noted a substantial discrepancy in the conversion to **34a** (from **36a**) versus **35a** (from **36ar**). We believe that this is due to the requisite *N*-H on **36a**, which can be deprotonated and allows for EnT to occur or allows a PCEnT process. If this reaction was simply arising from SET reduction, the discrepancy between **36a** and **36ar** conversion should not be as large, since their reduction potentials should ultimately be similar (this was affirmed by calculating and comparing their LUMO energies by DFT, which were nearly identical). We find this peculiar difference in kinetics between **36a** and **36ar** is wholly consistent with the necessity to deprotonate the precursor for EnT.

HPLC studies to determine ee

Figure 127 HPLC spectrum of **36k**

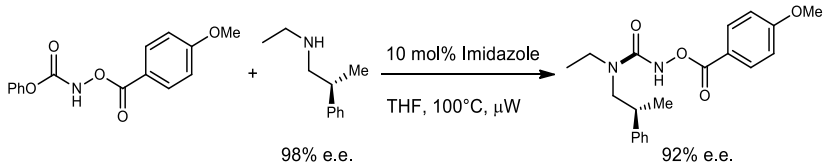


Sample Info : SFC IB, 5% *MeOH 200 bar/60 degC, colTemp 40 degC, 2.0 mL/min



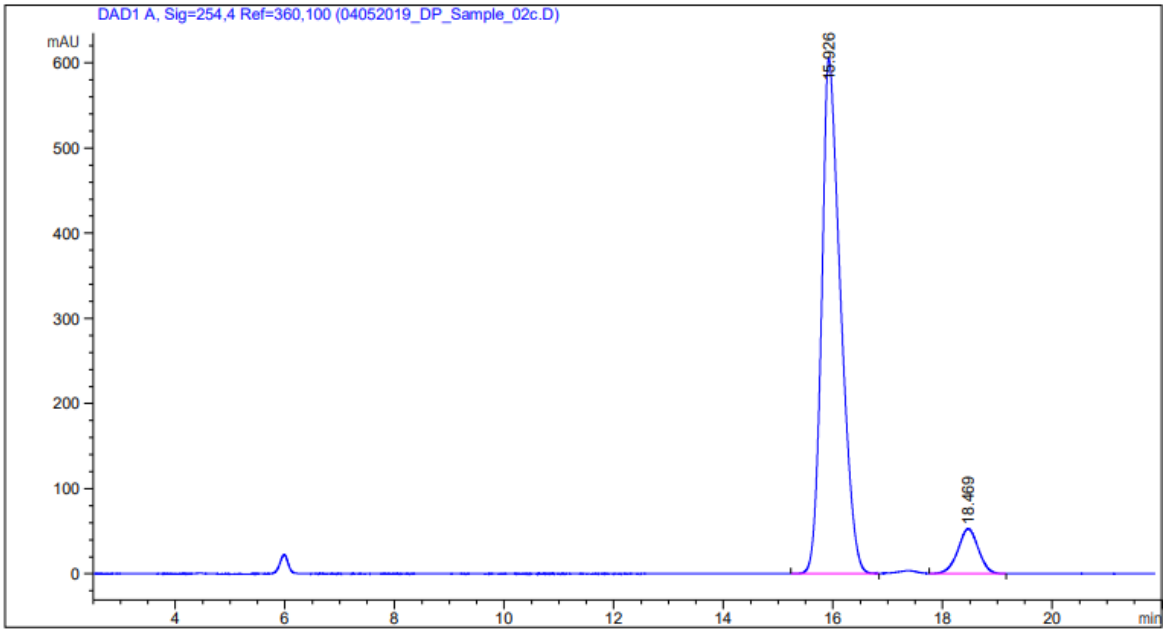
#	Time	Area	Height Width	%
1	16.116	2402.9	106.9	40.4366
2	18.396	3539.2	137.9	59.5634

Figure 128 HPLC spectrum of enantioenriched **36as**



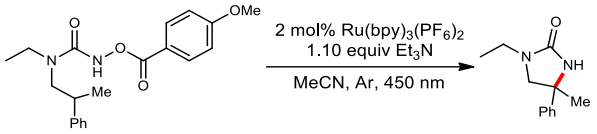
98% e.e. 92% e.e.

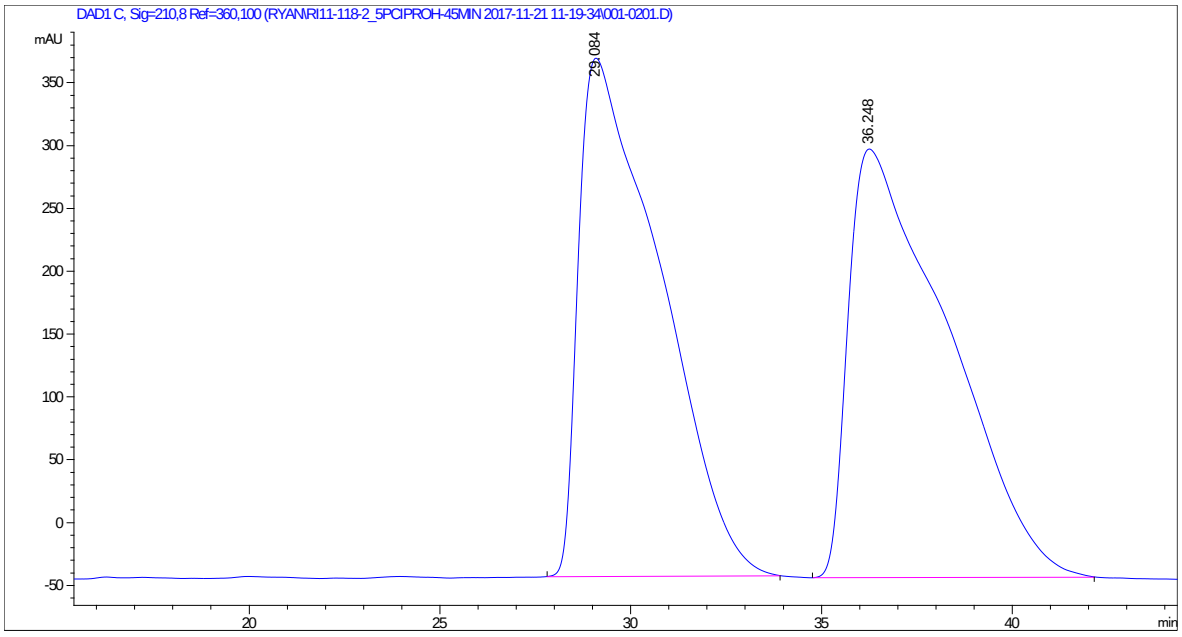
Sample Info : SFC IB, 5% *MeOH 200 bar/60 degC, colTemp 40 degC, 2.0 mL/min



#	Time	Area	Height Width	%
1	15.926	14526.3	604.9	91.3709
2	18.469	1371.9	52.9	8.6291

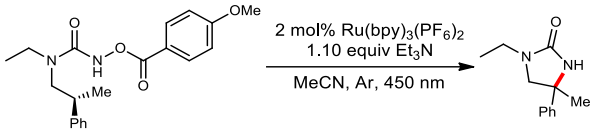
Figure 129 HPLC spectrum of **34k** from photocatalytic C-H amination of **36k**

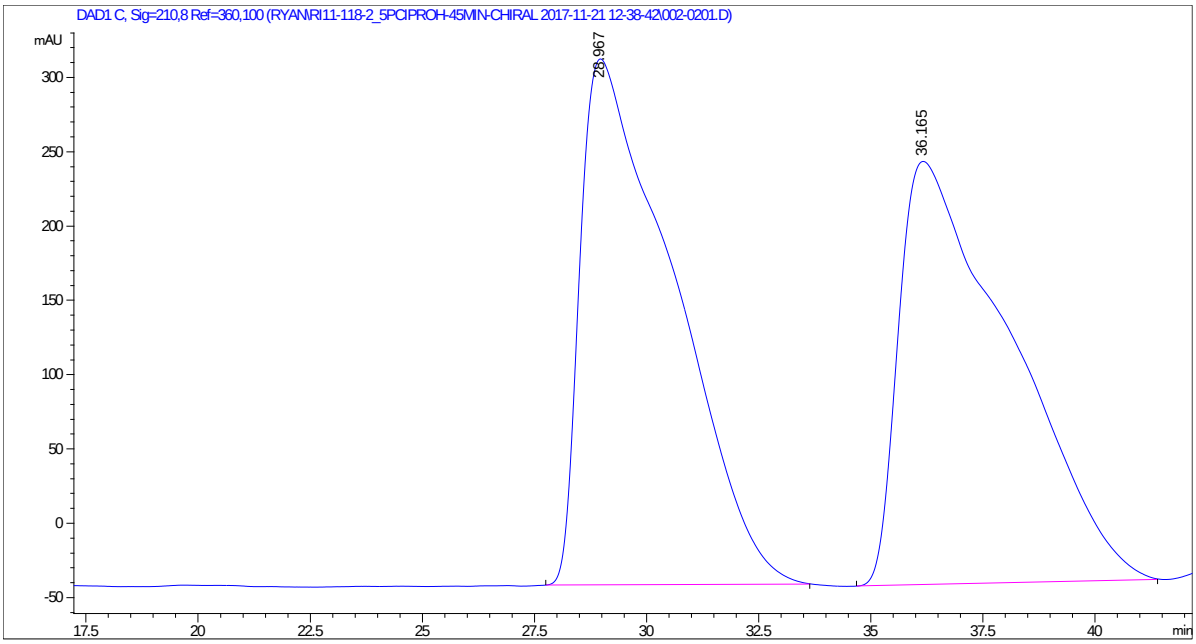




#	Time	Area	Height Width	%
1	29.084	61505.5	412.4	49.893
2	36.248	61769.7	341	50.107

Figure 130 HPLC spectrum of **34k** from photocatalytic C-H amination of enantioenriched **36as**



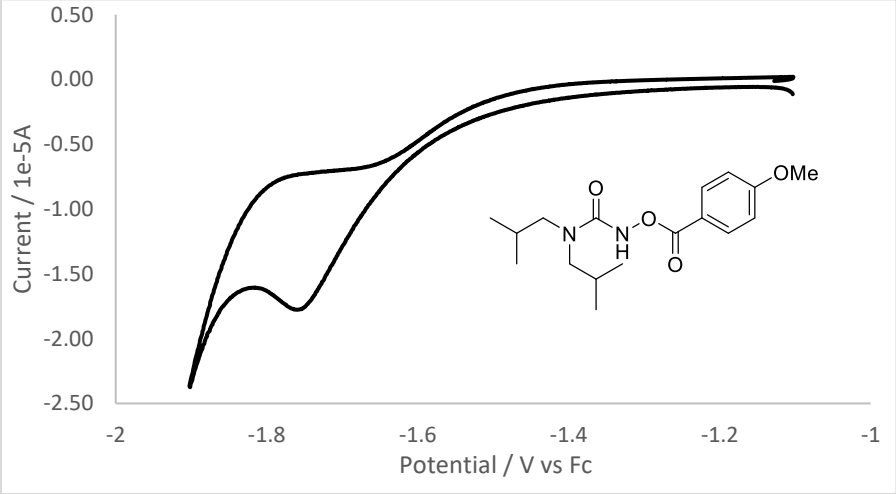


#	Time	Area	Height Width	%
1	28.967	51326.1	354	50.790
2	36.165	49730.3	284.8	49.210

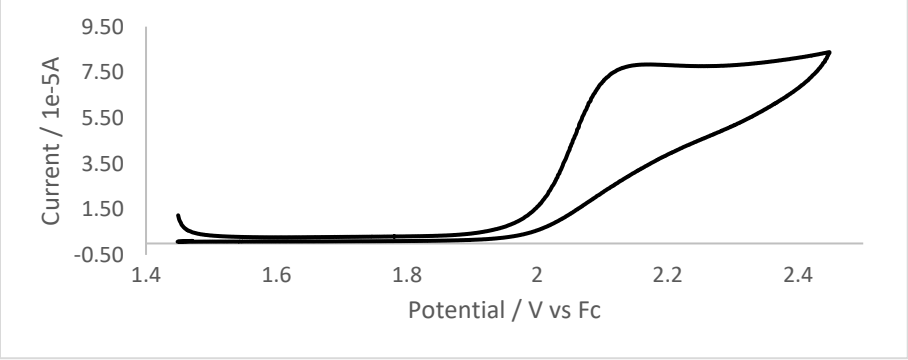
Cyclic voltammetry studies of C-H amination precursors

Cyclic voltammetry was performed using a Princeton Applied Research Versastat 3 potentiostat employing a glass cell and platinum auxiliary wires for the counter and pseudo-reference electrodes, where a 1.6 mm platinum disk electrode was used for the working electrode. The measurements were carried out in CH_3CN solutions (dried by J. C. Meyer solvent system and stored over molecular sieves) containing 0.1 M tetrabutylammonium hexafluorophosphate (Sigma Aldrich) as supporting electrolyte with a scan rate of 100 mV/s. The experiments were referenced to the Fc/Fc^+ redox couple of ferrocene (Sigma Aldrich).

Figure 131 Cyclic voltammetry of **36a**

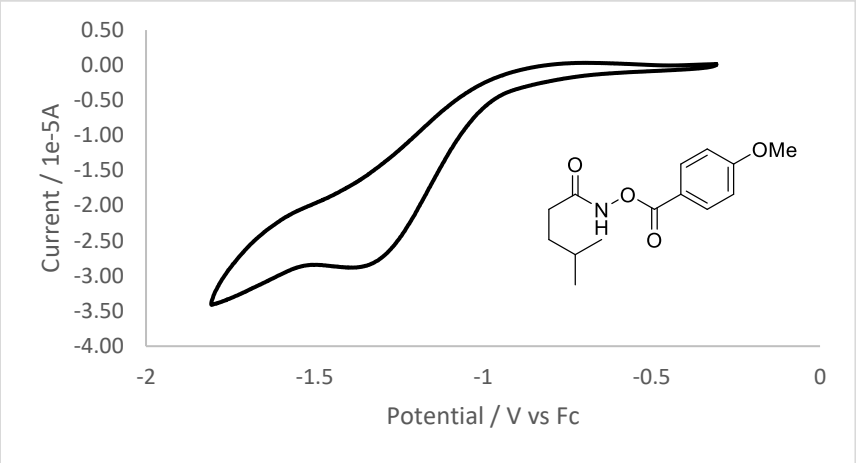


Irreversible reduction at -1.75V vs Fc^+/Fc.

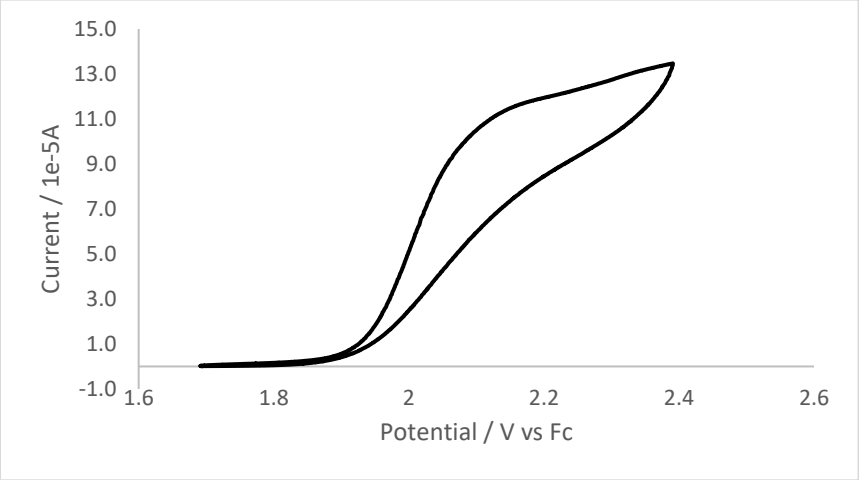


Irreversible oxidation at +2.15V vs Fc^+/Fc.

Figure 132 Cyclic voltammetry of **36h**

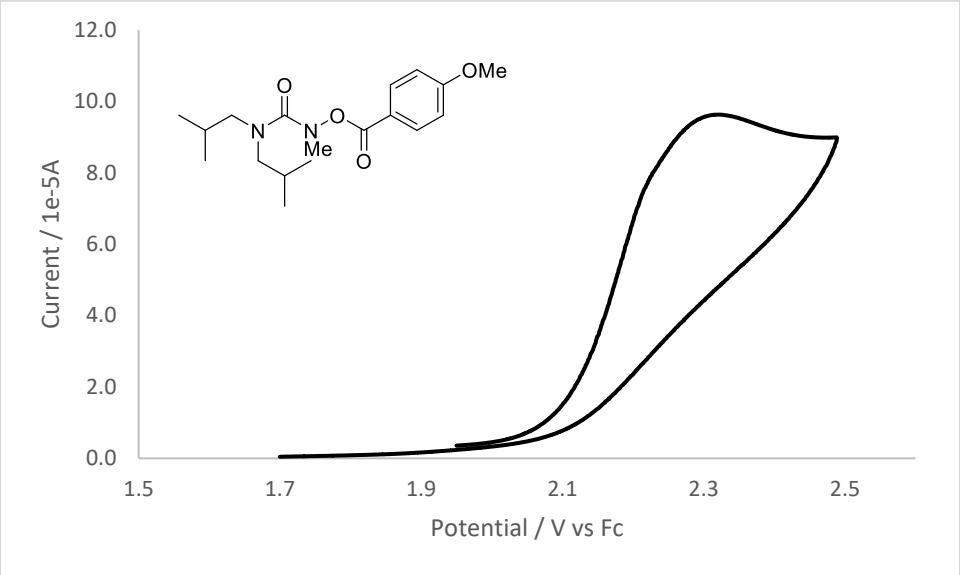


Irreversible reduction at -1.36 vs Fc^{+}/Fc



Irreversible oxidation at +2.13 vs Fc^{+}/Fc

Figure 133 Cyclic voltammetry of **36ar**

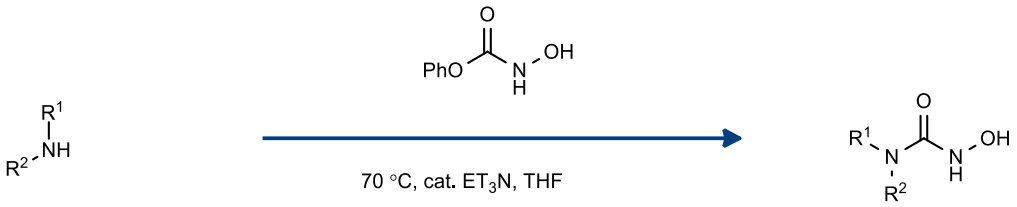


Irreversible oxidation at +2.30 vs Fc^{+}/Fc

No reduction was observed at potential -2.3 V vs Fc^{+}/Fc.

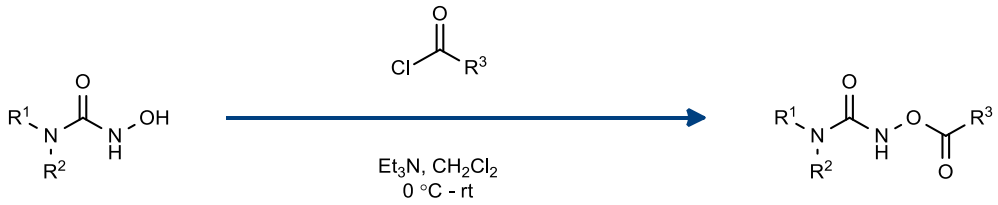
Synthesis of benzoyl *N*-oxyureas for initial reaction screening

General Procedure CC: Substitution of N-hydroxycarbamates



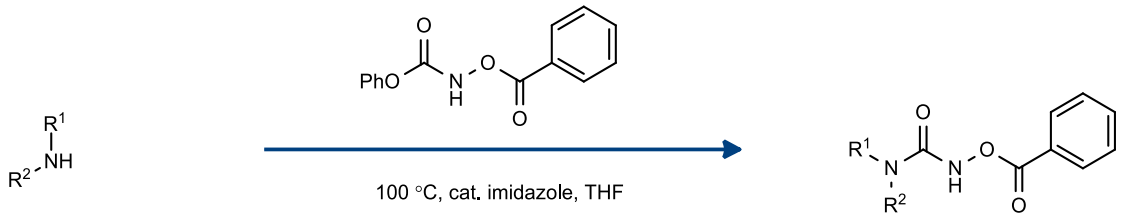
To a 5.0 mL microwave vial charged with a stir bar was added the phenyl *N*-hydroxycarbamate (1.10 equiv.), then THF (0.30 M), to which was added triethylamine (0.20 equiv.) and the corresponding amine (1.00 equiv.). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via conventional (oil bath) heating. Solvent was removed under reduced pressure and the products were then purified by silica gel chromatography to give the corresponding pure hydroxyureas.

General Procedure DD: Synthesis of *N*-oxycarbamates via urea acylation

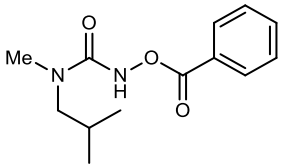


To a roundbottom flask charged with a stir bar was added *N*-hydroxycarbamate (1.00 equiv.) then CH_2Cl_2 (0.30 M) and allowed to stir at 0 °C. *Hydroxycarbamates are insoluble and will not always dissolve completely before the next step of the reaction* Upon observing most of the hydroxycarbamate dissolve, Et_3N was added (1.00 equiv.) and finally the acyl chloride was added dropwise (1.00 equiv.). The reaction was allowed to warm gradually to room temperature. Upon completion, H_2O was added and the reaction mixture was extracted with CH_2Cl_2. The organic layer was recollected and washed with a saturated $NaHCO_3$ solution, and then the organic phase was recollected and washed with brine. The organic phase was dried over Na_2SO_4 (stirring for 15 minutes). Solids were filtered and the filtrate was collected and concentrated under reduced pressure to give the corresponding pure acyloxycarbamates.

General Procedure EE: Synthesis of *N*-oxycarbamates via *O*-isocyanate substitution



To a 5 mL microwave vial charged with a stir bar was added the phenyl benzoyloxycarbamate (1.00 equiv.), then THF (0.2 M), to which was added the corresponding amine (1.05 equiv.) and then imidazole (0.10 equiv.). The vial was sealed with a microwave cap and heated for 1-3 hours at 100 ^{o}C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH and once with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding pure acyloxyureas. In some cases, a higher degree of purity was needed after the extraction and the products could be recrystallized or purified by silica gel chromatography.



3-(Benzoyloxy)-1-isobutyl-1-methylurea (SI10): The title compound was synthesized according to general procedure **EE** using phenyl benzoyloxycarbamate (1.29 g, 5.00 mmol), and *N*-methylisobutylamine (0.60 mL, 5.0 mmol) and imidazole (0.034 g, 0.50 mmol) in THF (16.7 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (30% EtOAc/Et_2O) to yield the title compound as a colourless oil (1.05 g, 84%).

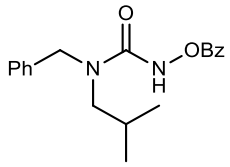
TLC R_f: 0.30 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54-8.43 (br s., 1H), 8.17-8.10 (m, 2H), 7.67-7.58 (m, 1H), 7.53-7.44 (m, 2H), 3.17 (d, *J* = 7.7 Hz, 2H), 3.02 (s, 3H), 2.04-1.97 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C), 157.9 (C), 134.0 (CH), 129.9 (CH), 128.6 (CH), 127.1 (C), 56.6 (CH_2), 34.6 (CH), 27.2 (CH), 20.0 (CH).

IR (film): 3269, 2657, 1747, 167, 1489, 1243 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{18}N_2O_3Na$ $[M+Na]^+$: 273.1317. Found: 273.1302.



3-(Benzoyloxy)-1-benzyl-1-isobutylurea (SI11): The title compound was synthesized according to general procedure **EE** using phenyl benzoyloxycarbamate (0.630 g, 2.45 mmol), and *N*-benzyl-2-methylpropan-1-amine (0.400 g, 2.45 mmol) and imidazole (0.017 g, 0.25 mol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 4 h at 100 °C. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in hexanes and then recrystallized in Et_2O/hexanes. The solid was then filtered and washed with hexanes to give pure product. The title compound was obtained as a crystalline white solid (0.763 g, 78%).

M.p.: 140.1-140.4 °C.

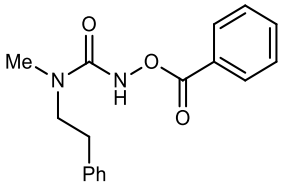
TLC R_f: 0.55 in 25% EtOAc/Hexanes.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.50-8.40 (1H, br. s.), 8.18-8.08 (2H, m), 7.67-7.57 (1H, m), 7.53-7.27 (7H, m), 4.61 (2H, s), 3.20 (2H, d, *J*=6 Hz), 2.09 (1H, sept, *J*=6 Hz), 0.99 (6H, d, *J*=6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C), 158.3 (C), 136.4 (C), 134.0 (CH), 129.9 (CH), 128.9 (CH), 128.6 (CH), 127.8 (CH), 127.1 (CH), 127.0 (C), 54.6 (CH2), 50.6 (CH2), 27.3 (CH), 20.2 (CH_3).

IR (film): 3106, 2955, 1756, 1645, 1495, 1232 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{19}H_{22}N_2O_3Na$ $[M+Na]^+$: 349.1528. Found: 349.1515.



3-(Benzoyloxy)-1-methyl-1-phenethylurea (SI12): The title compound was synthesized according to general procedure **EE** using phenyl benzoyloxycarbamate (0.772 g, 3.00 mmol), and *N*-methyl-2-phenylethanamine (0.406 mg, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (16.7 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (20% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.841 g, 95%).

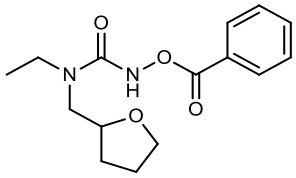
TLC R_f: 0.35 in 33% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.11-8.08 (m, 2H), 7.63-7.57 (m, 1H), 7.48-7.43 (m, 2H), 7.33-7.28 (m, 2H), 7.23-7.19 (m, 3H), 3.56 (t, *J* = 7.4 Hz, 2H), 2.92-2.88 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9 (C), 157.7 (C), 138.7 (C), 134.1 (C), 130.1 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 127.3 (C), 126.8 (CH), 51.5 (CH2), 34.9 (CH_3), 34.3 (CH_2).

IR (film): 3257, 3071, 3027, 2948, 1750, 1672, 1485, 1253, 1079 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{17}H_{18}N_2NaO_3^+$ $[M+Na]^+$: 321.1210. Found: 321.1215.

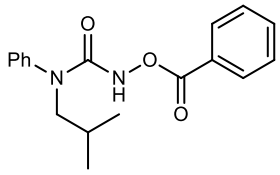


3-(benzoyloxy)-1-ethyl-1-((tetrahydrofuran-2-yl)methyl)urea (SI13): Synthesized according to general procedure **EE** using N-ethyltetrahydrofurfurylamine (1.03 g, 8.000 mmol), phenyl benzoyloxycarbamate (2.06 g, 8.00 mmol) and imidazole (0.0545 g, 0.800 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 100 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (10% EtOAc/CH_2Cl_2). The title compound was obtained as clear oil (1.49 g, 64%).

^{1}H NMR (300 MHz; $CDCl_3$): δ 10.25-10.14 (1H, br. s.), 8.17-8.09 (2H, m), 7.64-755 (1H, m), 7.51-7.41 (2H, m), 4.17-4.04 (2H, m), 3.96-8.82 (1H, m), 3.59-3.42 (3H, m), (1H, sept, *J*= 6 Hz), 2.08-1.88 (3H, m), 1.72-1.56 (1H, m), 1.18 (3H, t, $_J$=9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3 (C), 158.7 (C), 133.5 (CH), 129.9 (CH), 128.4 (CH), 127.7 (C), 79.3 (CH), 68.5 (CH_2), 50.3 (CH_2), 43.7 (CH_2), 28.6 (CH_2), 25.9 (CH_2), 12.8 (CH).

HRMS (ESI): Exact mass calcd for $C_{15}H_{20}N_2O_4Na$ $[M+Na]^+$: 315.1321. Found: 315.1303.



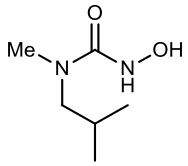
3-(benzoyloxy)-1-isobutyl-1-phenylurea (SI14): Synthesized according a modified general procedure **EE** using N-isobutylaniline (0.877 g, 5.90 mmol), phenyl benzoyloxycarbamate (1.2850 g, 5.00 mmol) and imidazole (0.0340 g, 0.500 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 6 h at 100 °C via microwave irradiation. The reaction

mixture was concentrated under reduced pressure and isolated using flash chromatography (10% AcOEt/hexanes). The title compound was obtained as an amorphous white solid (1.2174g, 78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11-8.05 (2H, m), 8.02-7.98 (1H, br. s.), 7.64-7.57 (1H, m), 7.54-7.38 (7H, m), 3.57 (2H, d, *J*=6 Hz), 1.82 (1H, sept, *J*=6 Hz), 0.95 (6H, d, *J*=6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9 (C), 157.1 (C), 139.9 (C), 134.0 (CH), 130.2 (CH), 129.9 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127 (C), 57.3 (CH_2), 26.9 (CH), 19.9 (CH).

HRMS (ESI): Exact mass calcd for $C_{18}H_{20}N_2O_3Na$ $[M+Na]^+$: 335.1372. Found: 335.1374.



1-Isobutyl-1-methyl-3-hydroxyurea (SI15.5): The title compound was synthesized according to general procedure **CC** using phenyl *N*-hydroxycarbamate (0.841 g, 5.50 mmol), and *N*-methylisobutylamine (0.436 g, 5.00 mmol) and Et_3N (0.14 mL, 1.0 mmol) in THF (16.6 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.530 g, 73%).

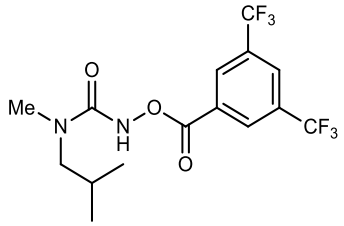
TLC R_f: 0.12 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07-6.95 (br s, 1H), 6.86-6.77 (br s, 1H), 3.09 (d, *J* = 7.6 Hz, 2H), 2.89 (s, 3H), 2.02-1.86 (m, 1H), 0.90 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8 (C), 56.2 (CH_2), 34.1 (CH_3), 27.2 (CH), 19.9 (CH_3).

IR (film): 3220, 2956, 1615, 1521, 1386, 1287, 1108 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_{14}N_2O_2$ [M]+: 146.1055. Found: 146.1040.



3-((3,5-Bistrifuoromethylbenzoyl)oxy)-1-isobutyl-1-methylurea (SI15): The title compound was synthesized according to general procedure **DD** using the pure 1-isobutyl-1-methyl-3-hydoxyurea (0.530 g, 3.60 mmol) was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (0.50 mL, 3.60 mmol) followed immediately by dropwise addition of 3,5-bis(trifluoromethyl)benzoyl chloride (0.65 mL, 3.60 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x1), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude which was purified by flash column chromatography (20% EtOAc/Hexanes). The title compound was obtained as an amorphous white solid (0.831 g, 60%).

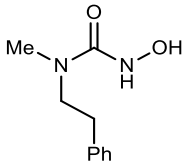
TLC R_f: 0.94 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58-8.56 (br s, 2H), 8.43-8.41 (br s, 1H), 8.14-8.11 (br s, 1H), 3.17 (d, *J* = 7.4 Hz, 2H), 3.03 (s, 3H), 2.07-1.95 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7 (C), 157.3 (C), 132.5 (C, q, *J* = 23 Hz), 130.0 (CH, m), 129.5 (C), 127.3 (CH, m), 122.6 (C, d, *J* = 203 Hz), 56.6 (CH_2), 34.6 (CH), 27.1 (CH), 19.9 (CH_3).

IR (film): 2697, 1767, 1664, 1221, 1127, 697 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{16}N_2O_3F_6Na$ $[M+Na]^+$: 409.0963. Found: 409.0983.



1-Methyl-1-phenethyl-3-hydroxyurea (SI16.5): The title compound was synthesized according to general procedure **CC** using phenyl *N*-hydroxycarbamate (0.337 g, 2.20 mmol), and *N*-methyl-*N*-phenethylamine (0.270 g, 2.20 mmol) and Et_3N (0.6 mL, 0.4 mmol) in THF (6.0 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (1% MeOH/CH_2Cl_2 → 5% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.321 g, 83%).

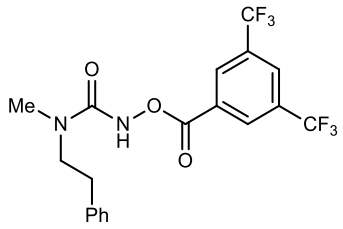
TLC R_f: 0.15 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.30 (m, 2H), 7.29-7.23 (m, 1H), 7.22-7.18 (m, 2H), 6.43-6.38 (br s, 1H), 6.30-6.23 (br s, 1H), 3.52 (t, *J* = 7.1 Hz, 2H), 2.90-2.83 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5 (C), 138.5 (C), 128.9 (CH), 128.8 (CH), 126.9 (CH), 50.6 (CH_2), 34.1 (CH_2), 33.9 (CH_3).

IR (film): 3326, 3023, 2924, 1645, 1491, 1390, 1296 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{10}H_{14}N_2O_2Na$ $[M+Na]^+$: 217.0948. Found: 217.0926.



3-((3,5-Bistrifuoromethylbenzoyl)oxy)-1-methyl-1-phenethylurea (SI16): The title compound was synthesized according to the general procedure **DD** using the pure 1-methyl-1-phenethyl-3-hydroxyurea (0.321 g, 1.66 mmol) was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (0.23 mL, 1.66 mmol) followed immediately by dropwise addition of 3,5-bis(trifluoromethyl)benzoyl chloride (0.30 mL, 1.66 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x1), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude which was purified by flash column chromatography (20% EtOAc/Hexanes). The title compound was obtained as an amorphous white solid (0.370 g, 46%).

TLC R_f: 0.97 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.53 (br s, 2H), 8.14-8.11 (br s, 1H), 8.10-8.06 (br s, 1H), 7.38-7.32 (m, 2H), 7.30-7.23 (m, 3H), 3.60 (t, *J* = 7.2 Hz, 2H), 2.96-2.89 (m, 5H).

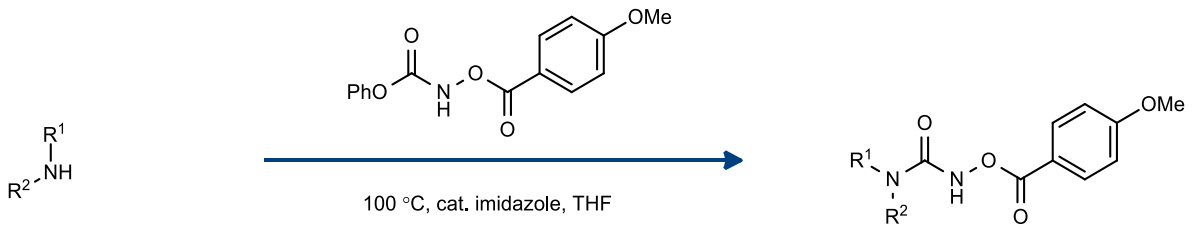
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3 (C), 157.0 (C), 138.4 (C), 132.5 (C, q, *J*= 26 Hz), 130.0 (CH), 129.5 (C), 128.9 (CH), 128.8 (CH), 127.3 (CH, m), 126.8 (CH), 122.7 (C, d, *J*= 203 Hz), 51.3 (CH_2), 34.7 (CH), 34.1 (CH_2).

IR (film): 3208, 1774, 1670, 1497, 1279, 1121 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_9H_{16}F_6N_2O_3Na$ $[M+Na]^+$: 457.0963. Found: 457.0954.

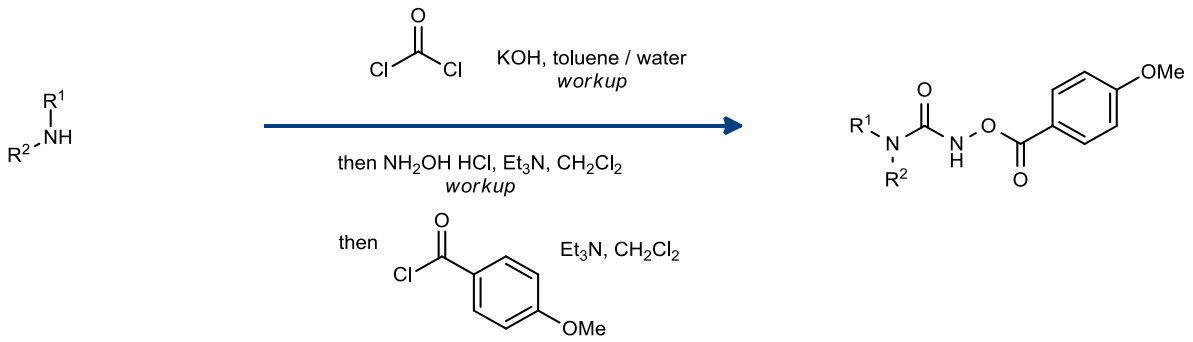
Synthesis of *p*-methoxybenzoate C-H amination precursors

General Procedure FF: Substitution on phenyl (4-methoxybenzoyl)oxycarbamate



To a 5 mL microwave vial charged with a stir bar was added the phenyl (4-methoxybenzoyl)oxycarbamate (1.00 equiv.), then THF (0.2 M), to which was added the corresponding amine (1.05 equiv.) and then imidazole (0.10 equiv.). The vial was sealed with a microwave cap and heated for 1-3 hours at 100 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH and once with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding pure acyloxyureas. In some cases, a higher degree of purity was needed after the extraction and the products could be recrystallized or purified by silica gel chromatography.

General Procedure GG: Synthesis of N-oxyureas via carbamoyl chloride formation



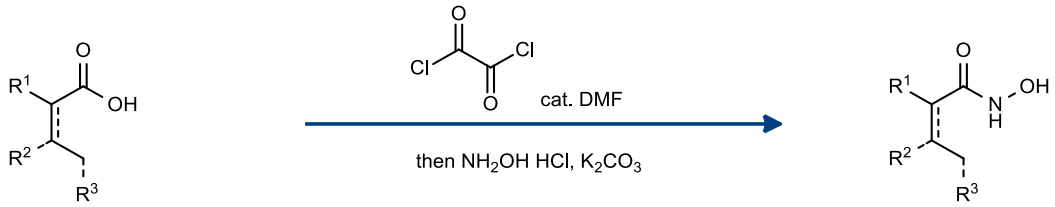
To a clean 50 mL round bottom flask charged with a stir bar was added the amine (1.00 equiv.) then PhMe (0.8 M) to which was added KOH pellets (1.00 equiv.) and water (2.9 M). A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes at 0 °C. Phosgene (15% in toluene) (2.30 equiv.) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously.

The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon competition, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude carbamoyl chloride which was used in the next step without further purification.

To the crude carbamoyl chloride was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added hydroxylamine hydrochloride (1.00 equiv.), and followed immediately by Et_3N (2.00 equiv.). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x1), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-hydroxyurea, which could be used in the next step without further purification.

To the crude *N*-hydroxyurea was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (1.00 equiv.) followed immediately by addition of *p*-methoxybenzoylchloride (1.00 equiv.). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x1), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-oxyurea which was be recrystallized or purified by silica gel chromatography.

General Procedure HH: Synthesis of hydroxamic acids

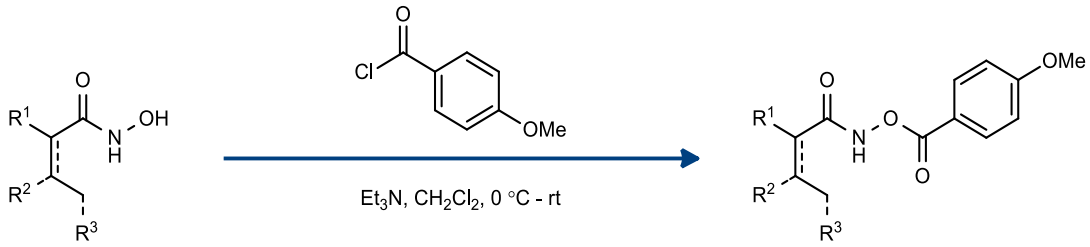


To a clean 50 mL round bottom flask charged with a stir bar was added the carboxylic acid (1.00 equiv.), then CH_2Cl_2 (0.07 M) and cooled to 0 °C. To this was added oxalyl chloride (2.00 equiv.) and DMF (2 drops) and the reaction was allowed to stir for an additional 2.5 to 4 hours at room temperature. Upon completion, the crude reaction was evaporated under reduced pressure to provide the crude hydroxamic acid which was used in the next step without further purification.

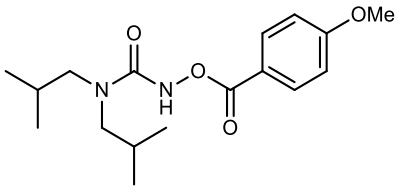
To a clean 50 mL round bottom flask charged with a stir bar was added the hydroxylamine hydrochloride (1.20 equiv.), then a 2:1 mixture of EtOAc and H_2O (0.08 M) and cooled to 0 °C. To this was added K_2CO_3 (2.00 equiv.) and the crude hydroxamic acid was added dropwise. The

reaction was allowed to stir for 12 hours at room temperature. Upon completion, the reaction was separated and extracted twice with EtOAc (20 mL x2). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-oxyurea which was be recrystallized or purified by silica gel chromatography.

General Procedure II: Synthesis of *p*-methoxybenzoylhydroxamic acid



To a clean 50 mL round bottom flask charged with a stir bar was added the pure hydroxamic acid (1.00 equiv.), then CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (1.00 equiv.) followed immediately by portionwise addition of *p*-methoxybenzoylchloride (1.00 equiv.). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x2), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-*p*-methoxybenzoylhydroxamic acid which was be recrystallized or purified by silica gel chromatography.



1-Diisobutyl-3-((4-methoxybenzoyl)oxy)urea (36a): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and N,N-diisobutylamine (0.388 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (20% EtOAc/hexanes) to yield the title compound as an amorphous off-white solid (0.940 g, 97%).

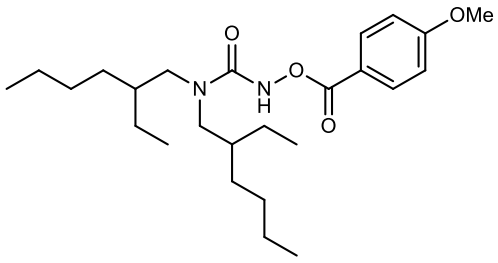
TLC R_f: 0.28 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (br s, 1H), 8.07-8.04 (m, 2H), 6.93-6.90 (m, 2H), 3.84 (s, 3H), 3.12 (d, *J* = 7.6 Hz, 4H), 2.04 (dquintet, *J* = 13.7, 6.9 Hz, 2H), 0.93 (d, *J* = 6.7 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C), 164.3 (C), 158.3 (C), 132.2 (CH), 119.5 (C), 114.1 (CH), 55.5 (CH_3), 55.0 (CH_2), 27.2 (CH), 20.2 (CH_3).

IR (film): 3186, 2954, 2870, 1748, 1655, 1605, 1509, 1484, 1316, 1242 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{17}H_{26}N_2NaO_4^+$ $[M+Na]^+$: 345.1785. Found: 345.1799.



3-((4-Methoxybenzoyl)oxy)-1,1-bis(2-methylhexyl)urea (36b): The title compound was synthesized according to a modified general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.639 g, 3.00 mmol), and bis(2-ethylhexyl)amine (0.640 g, 2.65 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (10% EtOAc/hexanes) to yield the title compound as an amorphous off-white solid (0.917 g, 85%).

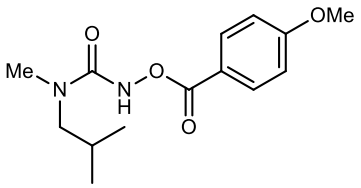
TLC R_f: 0.40 in 10% EtOAc/Hexanes.

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.21-10.18 (br s, 1H), 7.99-7.91 (m, 2H), 7.14-7.04 (m, 2H), 3.86 (s, 3H), 3.21-3.01 (m, 4H), 1.76-1.58 (m, 2H), 1.36-1.12 (m, 16H), 0.94-0.76 (m, 12H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 165.5 (C), 163.4 (C), 158.4 (C), 131.9 (CH), 120.4 (C), 114.7 (CH), 56.1 (CH), 49.5 (CH_2), 49.5 (CH_2), 37.1 (CH), 30.2 (CH_2), 28.6 (CH_2), 23.6 (CH_2), 23.0 (CH_2), 14.4 (CH_3), 11.0 (CH_3).

IR (film): 3177, 2959, 2925, 1756, 1658, 1509, 1241 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{25}H_{42}N_2NaO_4^+$ $[M+Na]^+$: 457.3043. Found: 457.3058.



1-Isobutyl-3-((4-methoxybenzoyl)oxy)-1-methylurea (36c): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N*-methyl-isobutylamine (0.262 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (10% EtOAc/Hexanes → 33% EtOAc/Hexanes) to yield the title compound as an amorphous white solid (0.800 g, 95%).

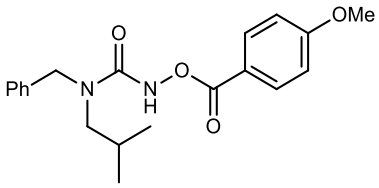
TLC R_f: 0.36 in 40% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50-8.37 (br s, 1H), 8.12-7.99 (m, 2H), 7.04-6.86 (m, 2H), 3.85 (s, 3H), 3.14 (d, *J* = 10.7 Hz, 2H), 2.98 (s, 3H), 1.98 (dquintet, *J* = 13.8, 6.9 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9 (C), 164.3 (C), 158.1 (C), 132.2 (CH), 119.5 (C), 114.1 (CH), 56.7 (CH_3) 55.6 (CH_3), 51.4 (CH_2), 34.9 (CH_2), 27.4 (CH), 20.1 (CH_3).

IR (film): 3158, 3005, 2959, 1751, 1663, 1604, 1507, 1315, 1249, 1159 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{14}H_{20}N_2NaO_4^+$ $[M+Na]^+$: 303.1315. Found: 303.1325.



1-Benzyl-1-isobutyl-3-((4-methoxybenzoyl)oxy)urea (36d): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and benzyl-2-methylpropan-1-amine (0.490 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (20% EtOAc/hexanes) to yield the title compound as an amorphous off-white solid (0.930 g, 87%).

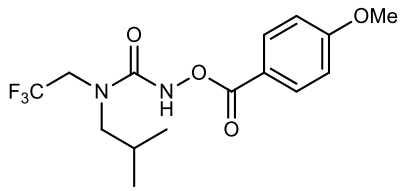
TLC R_f: 0.28 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (br s, 1H), 8.06 (d, *J* = 9.0 Hz, 2H), 7.40-7.30 (m, 6H), 6.93 (d, *J* = 9.0 Hz, 2H), 4.59 (s, 2H), 3.86 (s, 3H), 3.17 (d, *J* = 7.5 Hz, 2H), 2.07 (dquintet, *J* = 13.7, 6.9 Hz, 1H), 0.97 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C), 164.2 (C), 158.5 (C), 136.5 (C), 132.1 (CH), 129.0 (CH), 127.8 (CH), 127.1, (CH), 119.4 (C), 113.9 (CH), 55.5 (CH_3), 54.6 (CH_2), 27.4 (CH), 20.2 (CH_3).

IR (film): 3116, 2959, 2840, 1751, 1647, 1603, 1509, 1419, 1315, 1238 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{20}H_{24}N_2NaO_4^+$ $[M+Na]^+$: 379.1628. Found: 379.1634.



1-Isobutyl-3-((4-methoxybenzoyl)oxy)-1-(2,2,2-trifluoroethyl)urea (36e): The title compound was synthesized according to general procedure **GG** using *N*-propylaniline (1.55 g, 10.0 mmol), toluene (0.8 M), KOH pellets (0.561 g, 10.0 mmol), and water (2.9 M) at 0 °C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (16.4 mL, 23 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon competition, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude isobutyl(2,2,2-trifluoroethyl)carbamic chloride which was used in the next step without further purification.

To the crude isobutyl(2,2,2-trifluoroethyl)carbamic chloride was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added hydroxylamine hydrochloride (0.691 g, 10.0 mmol), and followed immediately by Et_3N (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x1), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude N-propylanilinehydroxyurea, which could be used in the next step without further purification.

To the crude 3-hydroxy-1-isobutyl-1-(2,2,2-trifluoroethyl)urea was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (1.39 mL, 10.0 mmol) followed immediately by addition

of p-methoxybenzoylchloride (1.70 g, 10.0 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x1), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 1-isobutyl-3-((4-methoxybenzoyl)oxy)-1-(2,2,2-trifluoroethyl)urea which was purified by recrystallization with Et_2O to yield a white crystalline solid (2.43 g, 70% over 3 steps).

TLC R_f: 0.57 in 33% EtOAc/Hexanes.

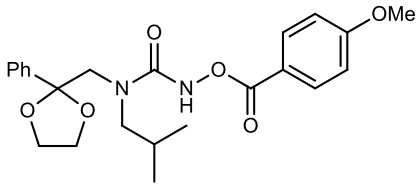
M.p.: 105.8-106.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (br s, 1H), 8.07 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 4.01 (q, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.26 (d, *J* = 7.7 Hz, 2H), 2.13 (dsept, *J* = 13.7, 6.9 Hz, 1H), 0.99 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4 (C), 164.4 (C), 158.1 (C), 132.2 (CH), 124.5 (q, *J* = 278 Hz, C), 118.9 (C), 114.0 (CH), 55.5 (CH_3), 55.3 (CH_2), 48.1 (q, *J* = 34 Hz, CH_2), 27.1 (CH), 19.9 (CH_3).

IR (film): 3144, 2971, 2889, 2360, 1749, 1660, 1606, 1249, 1160, 1143 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{19}F_3N_2NaO_4$ $[M+Na]^+$: 371.1188. Found: 371.1195.



1-Isobutyl-1-(2-phenyl-1,3-dioxolan-2-yl)isobutyl-3-((4-methoxybenzoyl)oxy)urea (36f): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.574 g, 2.00 mmol), and isobutylamine (0.470 g, 2.00 mmol) and imidazole (0.014 g, 0.20 mmol) in THF (6.6 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (10% EtOAc/Hexanes). The title compound was obtained as an amorphous pale orange solid (0.770 g, 90%).

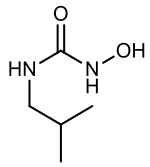
TLC R_f: 0.24 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.28-10-21 (br s, 1H), 8.16-8.07 (m, 2H), 7.58-7.51 (m, 2H), 7.45-7.32 (m, 3H), 7.00-6.90 (m, 2H), 4.30-4.23 (m, 2H), 3.96-3.85 (m, 5H), 3.75-3.65 (br s, 2H), 3.33-3.21 (d, *J*= 6.9 Hz, 2H), 2.18-2.01 (m, 1H), 0.88 (d, *J*= 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8 (C), 163.9 (C), 159.5 (C), 139.9 (C), 132.0 (CH), 128.8 (CH), 128.5 (CH), 125.7 (CH), 119.9 (C), 113.8 (CH), 110.6 (C), 65.4 (CH_2), 56.7 (CH_2), 55.4 (CH), 54.0 (CH_2), 26.8 (CH), 20.1 (CH_3).

IR (film): 3221, 2941, 1740, 1691, 1468, 1257 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{23}H_{28}N_2O_6Na^+$ $[M+Na]^+$: 451.1845. Found: 451.1825.



1-Isobutyl-3-hydroxyurea (36.5g): The title compound was synthesized according to a modified general procedure **CC** using phenyl *N*-hydroxycarbamate (0.765 g, 5.00 mmol), and *N*-isobutylamine (2.48 mL, 25.0 mmol) and Et_3N (0.14 mL, 1.0 mmol) in THF (16.6 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/CH_2Cl_2 then 7% MeOH/CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.380 g, 58%).

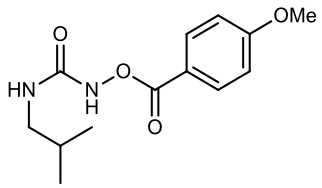
TLC R_f: 0.28 in 10% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.52 (d, *J*= 1.2 Hz, 1H), 8.21 (br s, 1H), 6.61 (t, *J*= 6.2 Hz, 1H), 2.86 (t, *J*= 6.9 Hz, 2H), 1.78-1.65 (m, 1H), 0.82 (d, *J*= 6.7 Hz, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.0 (C), 46.7 (CH_2), 28.9 (CH), 20.4 (CH_3).

IR (film): 3389, 3123, 2955, 2871, 1617, 1549, 1424 cm^{-1}.

HRMS (EI): Despite multiple attempts to obtain an accurate mass using both ESI and EI, one could not be obtained for this compound. However, this product was a precursor to **1g**, for which all characterization was obtained, thereby clearly demonstrating this to be the desired product.



3-((4-Methoxybenzoyl)oxy)-1-isobutylurea (36g): The title compound was synthesized according to general procedure **DD** using 1-isobutyl-3-hydroxyurea (0.330 g, 2.50 mmol) was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (0.35 mL, 0.40 mmol) mmol) followed immediately by addition of p-methoxybenzoylchloride (0.427 g, 2.50 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x1), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated vacuo and purified by recrystallization with Et_2O to yield a white crystalline solid (0.548 g, 82%).

TLC R_f: 0.21 in 2% MeOH/CH_2Cl_2.

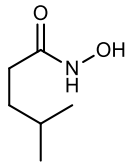
M.p.: 139.7-140.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.68-9.60 (br s, 1H), 7.98 (d, *J*= 8.9 Hz, 2H), 7.09 (d, *J*= 8.9 Hz, 2H), 7.04 (t, *J*= 6.0 Hz, 1H), 3.84 (s, 3H), 2.86 (t, *J*= 6.4 Hz, 2H), 1.80-1.63 (m, 1H), 0.81 (d, *J*= 6.7 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 165.5 (C), 164.1 (C), 159.3 (C), 132.2 (CH), 120.2 (C), 114.7 (CH), 56.1 (CH), 47.0 (CH_2), 28.8 (CH), 20.4 (CH_3).

IR (film): 3304, 2959, 1748, 1663, 1571, 1510, 1249 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{18}N_2O_4Na$ $[M+Na]^+$: 289.1165. Found: 289.1176.

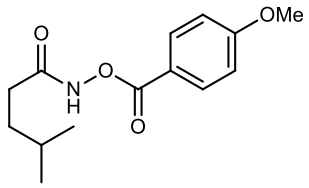


***N*-Hydroxy-4-methylpentanamide (36.5h):** The title compound was synthesized according to general procedure **HH** using 4-methylpentanoyl chloride (1.35 g, 10.0 mmol) and hydroxylamine hydrochloride (0.694 g, 10.0 mmol) and $NaHCO_3$ (1.85 g, 22.0 mmol) in 2 : 1 CH_2Cl_2 : H_2O (0.30 M). Upon completion, the reaction mixture was concentrated in vacuo and isolated using flash chromatography (50% EtOAc/ Hexanes) to yield the title compound as a white solid (1.13 g, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (br s, 2H), 2.18-2.13 (m, 2H), 1.62-1.49 (m, 3H), 0.90 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1 (C), 34.2 (CH_2), 31.0 (CH_2), 27.7 (CH), 22.2 (CH_3).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[306]



***N*-((4-Methoxybenzoyl)oxy)-4-methylpentanamide (36h):** The title compound was synthesized according to general procedure **II** using *N*-hydroxy-4-methylpentanamide (0.656 g, 5.00 mmol) and 4-methoxybenzoyl chloride (0.853 g, 5.00 mmol) and triethylamine (0.70 mL, 5.0 mmol) in CH_2Cl_2 (0.30 M). Upon completion the reaction mixture was extracted with saturated $NaHCO_3$ three times (10 mL x 3) followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (20.0 mL). The filtrate was collected, and concentrated in vacuo and isolated using flash chromatography (50% EtOAc/Hexanes) to yield the title compound as a white solid (1.12 g, 82% yield).

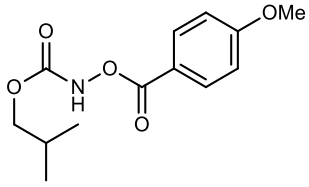
TLC R_f: 0.71 in 50% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (br s, 1H), 8.03 (d, *J*= 9.0 Hz, 2H), 6.93 (d, *J*= 9.0 Hz, 2H), 3.85 (s, 3H), 2.30 (t, *J*= 7.4 Hz, 2H), 1.67-1.57 (m, 4H), 0.90 (d, *J*= 6.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (C), 164.8 (C), 164.4 (C), 132.2 (CH), 118.9 (C), 114.0 (CH), 55.5 (CH_3), 33.9 (CH_2), 31.2 (CH_2) 27.7 (CH), 22.2 (CH_3).

IR (film): 3147, 2959, 1759, 1657, 1603, 1509, 1248, 1167, 1024 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{14}H_{19}NO_4Na$ $[M+Na]^+$: 288.1210. Found: 288.1212.



Isobutyl (4-methoxybenzoyl)oxycarbamate (36i): Isobutyl hydroxycarbamate was synthesized according to general procedure **HH** using isobutyl chloroformate (1.30 mL, 10.0 mmol) and hydroxylamine hydrochloride (0.694 g, 10.0 mmol) and $NaHCO_3$ (1.85 mL, 22.0 mmol) in 2 : 1 CH_2Cl_2 : H_2O (0.30 M). Upon completion, the reaction mixture was concentrated in vacuo to

provide the crude isobutyl hydroxycarbamate which was used in the next step without further purification.

The title compound was synthesized according to general procedure **II** using the crude isobutyl hydroxycarbamate (0.666 g, 5.00 mmol) to this was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (0.70 mL, 5.0 mmol) followed immediately by addition of *p*-methoxybenzoylchloride (0.853 g, 5.00 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion the reaction mixture was extracted with saturated $NaHCO_3$ three times (10 mL x 3) followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (20.0 mL). The filtrate was collected, and concentrated in vacuo and isolated using flash chromatography (15% EtOAc/Hexanes) to yield the title compound as a clear oil (1.17 g, 88% yield).

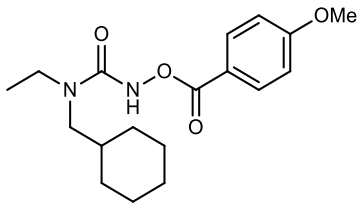
TLC R_f: 0.70 in 33% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (br s, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 3.98 (d, *J* = 6.6 Hz, 2H), 3.86 (s, 3H), 1.96 (dquintet, *J* = 13.4, 6.7 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (C), 164.4 (C), 157.0 (C), 132.2 (CH), 118.9 (C), 114.1 (CH), 72.7 (CH_2), 55.6 (CH_3), 27.9 (CH), 18.9 (CH_3)

IR (film): 3147, 2960, 1759, 1656, 1603, 1509, 1459, 1248, 1167 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{17}NO_5Na^+$ $[M+Na]^+$: 290.1005. Found: 290.1004.



3-((4-Methoxybenzoyl)oxy)-1-cyclohexylmethyl-1-ethylurea (36j): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.861 g, 3.00 mmol), and *N*-(cyclohexylmethyl)-*N*-ethylamine (0.555 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated vacuo and isolated using silica plug (15% EtOAc/Hexanes → 50% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.653 g, 54%).

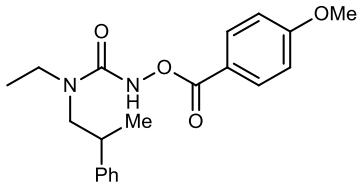
TLC R_f: 0.30 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.21-10.14 (br s, 1H), 8.00-7.91 (m, 2H), 7.14-7.05 (m, 2H), 3.85 (s, 3H), 3.25 (q, *J*= 7.0 Hz, 2H), 3.05 (d, *J*= 6.9 Hz, 2H), 1.74-1.45 (m, 6H), 1.27-1.12 (m, 3H), 1.08 (t, *J*= 7.0 Hz, 3H), 0.98-0.80 (m, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 165.2 (C), 163.6 (C), 157.2 (C), 131.4 (CH), 119.8 (C), 114.3 (CH), 55.6 (CH), 51.4 (CH_2), 41.2 (CH_2), 36.2 (CH), 30.2 (CH_2), 26.1 (CH_2), 25.4 (CH_2), 13.0 (CH_3).

IR (film): 3251, 2923, 2850, 1741, 1660, 1604, 1248, 1164 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{21}H_{34}N_2O_4Na$ $[M+Na]^+$: 401.2417. Found: 401.2423.



1-Ethyl-3-((4-methoxybenzoyl)oxy)-1-(2-phenylpropyl)urea (36k): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N*-ethyl-2-phenylpropan-1-amine (0.490 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated vacuo and isolated using silica plug (20% EtOAc/Hexanes → 40% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.919 g, 86%).

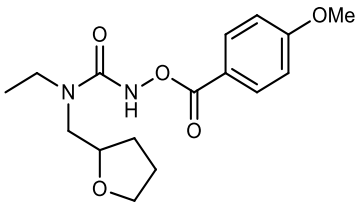
TLC R_f: 0.19 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (br s, 1H), 8.11-7.99 (m, 2H), 7.35-7.27 (m, 2H), 7.27-7.17 (m, 3H), 6.98-6.86 (m, 2H), 3.85 (s, 3H), 3.58 (dd, *J* = 6.4, 13.6 Hz, 1H), 3.27-3.11 (m, 3H), 2.96 (qd, *J* = 7.2, 14.6 Hz, 1H), 1.35-1.27 (m, 3H), 1.18-1.03 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4 (C), 164.2 (C), 157.7 (C), 144.0 (C), 132.1 (CH), 128.8 (CH), 127.3 (CH), 126.8 (CH), 119.4 (C), 113.9 (CH), 55.5 (CH_3), 54.6 (CH_2), 42.6 (CH_2), 38.8 (CH), 18.6 (CH_3), 12.9 (CH_3).

IR (film): 3216, 2966, 1747, 1668, 1604, 1509, 1454, 1245, 1167 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{20}H_{24}N_2NaO_4^+$ [M+Na]$^+$: 379.1628. Found: 379.1634.



1-Ethyl-3-((4-methoxybenzoyl)oxy)-1-((tetrahydrofuran-2-yl)methyl)urea (36l): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N*-((tetrahydrofuran-2-yl)methyl)ethanamine (0.388 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (20% EtOAc/Hexanes) to yield the title compound as a clear oil (0.580 g, 59%).

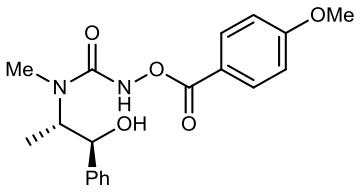
TLC R_f: 0.34 in 50% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (br s, 1H), 8.05 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 4.10-4.02 (m, 2H), 3.86-3.81 (m, 4H), 3.50-3.26 (m, 4H), 2.02-1.90 (m, 3H), 1.63-1.58 (m, 1H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2 (C), 164.0 (C), 156.0 (C), 132.1 (CH), 120.1 (C), 113.9 (CH), 79.5 (CH), 68.6 (CH_2), 55.5 (CH_3), 54.6 (CH_2), 43.8 (CH_2), 28.8 (CH_2), 26.1 (CH_2), 13.0 (CH_3).

IR (film): 3192, 2962, 1685, 1604, 1566, 1245, 1067 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{22}N_2NaO_5^+$ [M+Na]$^+$: 345.1421. Found: 345.1426.



1-(2-Hydroxy-2-phenylethyl)-3-((4-methoxybenzoyl)oxy)-1-methylurea (36m): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.861 g, 3.00 mmol), and (−)-(1*R*,2*S*)-ephedrine (0.495 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted

with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated vacuo and isolated using flash chromatography (20% EtOAc/Hexanes → 50% EtOAc/Hexanes) to yield the title compound as a colourless oil (1.16 g, 97%).

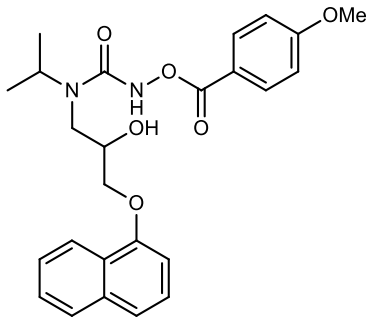
TLC R_f: 0.30 in 20% EtOAc/Hexanes.

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.53-8.83 (br s, 1H), 8.10-8.01 (m, 2H), 7.43-7.25 (m, 5H), 6.98-6.89 (m, 2H), 4.84 (d, *J* = 3.2 Hz, 1H), 4.36 (qd, *J* = 6.8, 3.0 Hz, 1H), 3.86 (s, 3H), 3.62-3.01 (br s, 1H), 2.51 (s, 3H), 1.20 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6 (C), 164.2 (C), 159.5 (C), 132.2 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.6 (CH), 119.6 (CH), 119.8 (C), 114.3 (CH), 77.7 (CH), 57.5 (CH), 55.6 (CH), 30.7 (CH), 13.4 (CH_3).

IR (film): 3251, 2923, 2850, 1741, 1660, 1604, 1248, 1164 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{21}H_{34}N_2O_4Na$ $[M+Na]^+$: 401.2417. Found: 401.2423.



1-(2-Hydroxy-3-(naphthalen-1-yloxy)propyl)-1-isopropyl-3-((4-methoxybenzoyl)oxy)urea (36n): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.861 g, 3.00 mmol), and propranolol (0.778 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (12.0 mL, 0.25 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using flash chromatography (40% Et_2O/Toluene) to yield the title compound as a white solid (0.855 g, 60%).

TLC R_f: 0.22 in 20% Et_2O/Toluene.

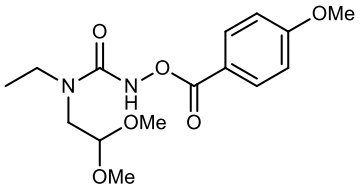
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.85-9.73 (br s, 1H), 8.26-8.16 (m, 2H), 8.12-8.03 (m, 2H), 7.87-7.78 (m, 1H), 7.56-7.44 (m, 3H), 7.42-7.34 (m, 1H), 6.97-6.90 (m, 2H), 6.86-6.80 (m, 1H), 4.57-4.36 (m,

2H), 4.17 (qd, *J* = 9.5, 6.0 Hz, 2H), 3.86 (s, 3H), 3.68 (dd, *J* = 15.8, 9.0 Hz, 1H), 3.52 (dd, *J* = 15.7, 2.2 Hz, 1H), 1.28 (app dd, *J* = 24.1, 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C), 164.1 (C), 159.7 (C), 153.8 (C), 134.6 (C), 132.2 (CH), 127.8 (CH), 126.7 (CH), 125.9 (CH), 125.6 (CH), 125.5 (C), 121.6 (CH), 121.2 (CH), 119.7 (C), 114.0 (CH), 105.7 (CH), 72.4 (CH), 69.9 (CH_2), 55.6 (CH_3), 47.8 (CH), 45.6 (CH_2), 21.2 (CH), 20.0 (CH_3).

IR (film): 3205, 2973, 1742, 1633, 1604, 1509, 1249 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{25}H_{28}N_2O_6Na^+$ $[M+Na]^+$: 475.1845. Found: 475.1823.



1-(2,2-Dimethoxyethyl)-1-ethyl-3-((4-methoxybenzoyl)oxy)urea (36o): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N*-ethyl-2,2-dimethoxyethanamine (0.399 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (30% EtOAc/Hexanes → 40% EtOAc/Hexanes) to yield the title compound as a clear oil (0.979 g, 99%).

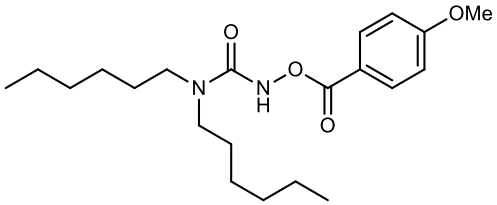
TLC R_f: 0.40 in 40% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.63 (s, 1H), 8.05 (d, *J* = 8.6 Hz, 2H), 6.93-6.90 (m, 2H), 4.46 (t, *J* = 5.3 Hz, 1H), 3.84 (s, 3H), 3.50 (s, 6H), 3.36-3.45 (m, 4H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3 (C), 163.9 (C), 158.6 (C), 132.0 (CH), 119.8 (C), 113.9 (CH), 104.4 (CH), 55.6 (CH_3), 55.5 (CH_3), 49.4 (CH_2), 43.3 (CH_2), 13.4 (CH_3).

IR (film): 3216, 2943, 1740, 1686, 1466, 1247, 1169, 1068 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{22}N_2NaO_6^+$ $[M+Na]^+$: 349.1370. Found: 349.1376.



1,1-Dihexyl-3-((4-methoxybenzoyl)oxy)urea (36q): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N,N*-dihexylamine (0.555 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using silica column chromatography (10% EtOAc/Hexanes → 20% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.840 g, 74%).

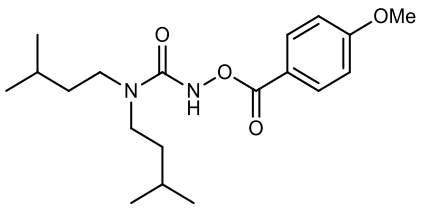
TLC R_f: 0.24 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (br s, 1H), 8.06 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.24 (t, *J* = 7.7 Hz, 4H), 1.62-1.58 (m, 4H), 1.32-1.27 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C), 164.3 (C), 157.7 (C), 132.2 (CH), 119.5 (C), 114.0 (CH), 55.6 (CH_3), 47.5 (CH_2), 31.7 (CH_2), 28.3 (CH_2), 26.7 (CH_2), 22.7 (CH_2), 14.2 (CH_3).

IR (film): 3156, 2955, 2930, 2856, 1753, 1652, 1509, 1486, 1264 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{21}H_{34}N_2NaO_4^+$ $[M+Na]^+$: 401.2411. Found: 401.2416.



1,1-Diisopentyl-3-((4-methoxybenzoyl)oxy)urea (36r): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N,N*-diisopentylamine (0.472 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using

silica column chromatography (15% EtOAc/Hexanes → 30% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.800 g, 79%).

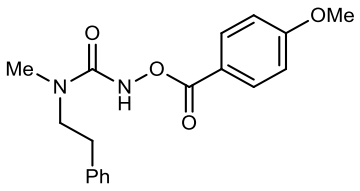
TLC R_f: 0.38 in 33% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (br s, 1H), 8.06 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.26 (t, *J* = 7.9 Hz, 4H), 1.63-1.54 (m, 2H), 1.54-1.47 (m, 4H), 0.93 (d, *J* = 6.5 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C), 164.3 (C), 157.5 (C), 132.2 (CH), 119.5 (C), 114.1 (CH), 55.6 (CH_3), 45.8 (CH_2), 37.1 (CH_2), 26.2 (CH), 22.6 (CH_3).

IR (film): 3263, 2953, 2868, 1745, 1655, 1604, 1510, 1249, 1166 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{19}H_{30}N_2NaO_4^+$ $[M+Na]^+$: 373.2098. Found: 373.2103.



3-((4-Methoxybenzoyl)oxy)-1-methyl-1-phenethylurea (36s): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N*-methyl-2-phenylethanamine (0.406 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (30% EtOAc/Hexanes → 40% EtOAc/Hexanes) to yield the title compound as an amorphous off-white solid (0.896 g, 91%).

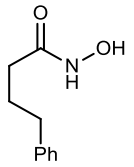
TLC R_f: 0.22 in 33% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (br s, 1H), 8.07 (d, *J* = 9.0 Hz, 2H), 7.34-7.21 (m, 5H), 6.94 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.56 (t, *J* = 7.4 Hz, 2H), 2.93-2.89 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6 (C), 164.3 (C), 157.9 (C), 138.7 (C), 132.2 (CH), 129.0 (CH), 128.9 (CH), 126.7 (CH), 119.4 (C), 114.0 (CH), 55.6 (CH_3), 51.4 (CH_2), 34.9 (CH_3), 34.3 (CH_2).

IR (film): 3302, 3065, 2972, 2934, 1737, 1702, 1602, 1508, 1456 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{18}H_{20}N_2NaO_4^+$ $[M+Na]^+$: 351.1315. Found: 351.1321.

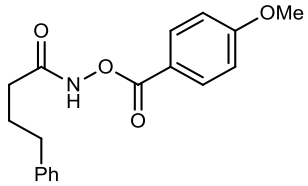


***N*-Hydroxy-4-phenylbutanamide (36.5t):** The title compound was synthesized according to a literature procedure.[150]

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.49-10.17 (br s, 1H), 8.85-8.49 (br s, 1H), 7.33-7.24 (m, 2H), 7.23-7.13 (m, 3H), 2.59-2.52 (m, 2H), 2.01-1.91 (m, 2H), 1.84-1.71 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (C), 142.1 (C), 128.8 (CH), 126.3 (CH), 35.1 (CH_2), 32.3 (CH_2), 27.5 (CH_2) (one Cquart is missing).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.



***N*-((4-Methoxybenzoyl)oxy)-4-phenylbutanamide (36t):** The title compound was synthesized according to general procedure **II** using *N*-hydroxy-4-phenylbutanamide (0.940 g, 5.25 mmol), CH_2Cl_2 (0.30 M) at 0 °C. To this was added Et_3N (0.70 mL, 5.0 mmol) followed immediately by portionwise addition of *p*-methoxybenzoylchloride (0.853 g, 5.00 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x2), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure and the crude product isolated using flash column chromatography (33 % EtOAc/Hexanes) to yield the title compound as an amorphous white solid (1.55 g, 98%).

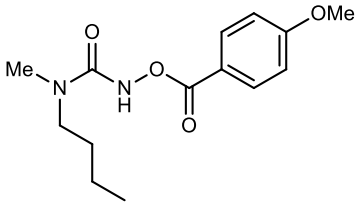
TLC R_f: 0.15 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.63-10.08 (br s, 1H), 8.88-8.49 (m, 2H), 7.39-7.22 (m, 2H), 7.23-7.11 (m, 2H), 2.60-2.52 (m, 2H), 2.01-1.91 (m, 2H), 1.84-1.71 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7 (C), 164.4 (C), 141.2 (C), 132.2 (CH), 128.6 (CH), 128.5 (CH), 126.1 (CH), 118.7 (C), 114.1 (CH), 55.6 (CH), 34.9 (CH_2), 32.2 (CH_2), 26.5 (CH_2).

IR (film): 3119, 3018, 2943, 1752, 1648, 1506, 1253 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{18}H_{19}NO_4Na$ $[M+Na]^+$: 336.1212. Found: 336.1219.



3-((4-Methoxybenzoyl)oxy)-1-butyl-1-methylurea (36u): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.861 g, 3.00 mmol), and *N*-methylbutylamine (0.262 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using flash chromatography (25% EtOAc/Hexanes) to yield the title compound as a yellow oil (0.466 g, 55%).

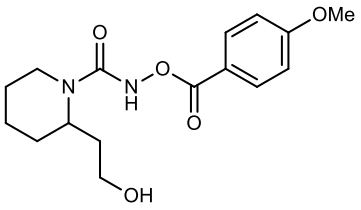
TLC R_f: 0.16 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45-8.42 (br s, 1H), 8.12-8.06 (m, 2H), 6.98-6.92 (m, 2H), 3.88 (s, 3H), 3.37-3.30 (m, 2H), 3.00 (s, 3H), 1.66-1.54 (m, 2H), 1.43-1.30 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6 (C), 164.1 (C), 157.8 (C), 132.0 (CH), 119.3 (C), 113.9 (CH), 55.4 (CH), 48.8 (CH_2), 33.9 (CH_3), 29.7 (CH_2), 19.9 (CH_2), 13.8 (CH_3).

IR (film): 3213, 2956, 2870, 1752, 1649, 1503, 1244, 1074 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{14}H_{20}N_2O_4Na$ $[M+Na]^+$: 303.1321. Found: 303.1298.



2-(2-Hydroxyethyl)-*N*-((4-methoxybenzoyl)oxy)piperidine-1-carboxamide (36v): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and 2-(piperidin-2-yl)ethanol (0.388 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (50% EtOAc/Hexanes → 40% EtOAc/DCM) to yield the title compound as a white foam (0.919 g, 95%).

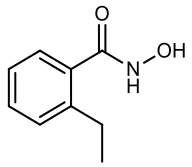
TLC R_f: 0.40 in 40% EtOAc/DCM.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (br s, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 4.37-4.10 (m, 2H), 3.84 (s, 3H), 3.77-3.67 (m, 2H), 2.77-2.67 (m, 2H), 2.11-2.02 (m, 1H), 1.82-1.78 (m, 1H), 1.67-1.49 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C), 164.3 (C), 158.2 (C), 132.2 (CH), 119.7 (C), 114.0 (CH), 58.4 (CH_2), 55.6 (CH_3), 47.0 (CH), 38.5 (CH_2), 31.3 (CH_2), 29.2 (CH_2), 25.5 (CH_2), 19.3 (CH_2).

IR (film): 3372, 3146, 2938, 1742, 1653, 1603, 1508, 1420, 1247, 1166 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{22}N_2NaO_5^+$ $[M+Na]^+$: 345.1421. Found: 345.1426.

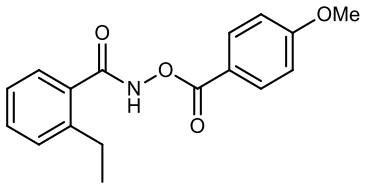


2-Ethyl-*N*-hydroxybenzamide (36.5w): The title compound was synthesized according to a literature procedure.[150]

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87-8.09 (br s, 2H), 7.47-7.38 (m, 1H), 7.38-7.29 (m, 2H), 7.26-7.19 (m, 1H), 2.81 (q, *J*= 7.4 Hz, 2H), 1.24 (t, *J*= 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8 (C), 143.3 (C), 131.3 (C), 131.0 (CH), 129.6 (CH), 127.3 (CH), 125.8 (CH), 26.2 (CH_2), 15.7 (CH_3).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.



2-Ethyl-*N*-((4-methoxybenzoyl)oxy)benzamide (36w): The title compound was synthesized according to the general procedure **II** using 2-ethyl-*N*-hydroxybenzamide (0.520 g, 3.15 mmol), CH_2Cl_2 (0.30 M) at 0 °C. To this was added Et_3N (0.42 mL, 3.0 mmol) followed immediately by portionwise addition of *p*-methoxybenzoylchloride (0.516 g, 3.00 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x2), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure and the crude product isolated using flash column

chromatography (20 % EtOAc/Hexanes) to yield the title compound as an amorphous white solid (0.592 g, 67%).

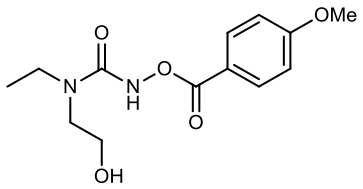
TLC R_f: 0.21 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.36-9.27 (br s, 1H), 8.15-8.07 (m, 2H), 7.55 (dd, *J*= 7.6, 1.2 Hz, 1H), 7.48-7.42 (m, 1H), 7.36-7.30 (m, 1H), 7.29-7.22 (m, 1H), 7.00-6.94 (m, 2H), 3.90 (s, 3H), 2.87 (q, *J*= 7.5 Hz, 2H), 1.28 (t, *J*= 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9 (C), 164.5 (C), 143.9 (C), 132.3 (CH), 131.4 (CH), 131.3 (C), 127.7 (CH), 125.8 (CH), 118.6 (CH), 114.1 (CH), 55.6 (CH), 26.3 (CH_2), 16.0 (CH_3).

IR (film): 3138, 2957, 1751, 1653, 1505, 1252 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{17}H_{17}NO_4Na$ $[M+Na]^+$: 322.1056. Found: 322.1056.



1-Ethyl-1-(2-hydroxyethyl)-3-((4-methoxybenzoyl)oxy)urea (36x): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and 2-(ethylamino)ethanol (0.267 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (50% EtOAc/Hexanes → 40% EtOAc/DCM) to yield the title compound as a white solid (0.788 g, 93%).

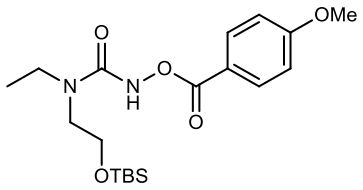
TLC R_f: 0.20 in 40% EtOAc/DCM.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (br s, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H), 3.81 (t, *J* = 4.8 Hz, 2H), 3.45 (t, *J* = 4.8 Hz, 2H), 3.37 (q, *J* = 7.1 Hz, 2H), 3.14 (br s, 1H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C), 164.1 (C), 159.1 (C), 132.1 (CH), 119.6 (C), 113.9 (CH), 62.2 (CH_2), 55.6 (CH_3), 48.8 (CH_2), 42.7 (CH_2), 13.2 (CH_3).

IR (film): 3404, 3181, 2864, 1720, 1678, 1600, 1514, 1475, 1325, 1262, 1246, 1172 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{18}N_2NaO_5^+$ $[M+Na]^+$: 305.1108. Found: 305.1113.



3-((4-Methoxybenzoyl)oxy)-1-ethyl-1-(2-(tert-butyldimethylsilyloxy)ethyl)urea (36y): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.574 g, 2.00 mmol), and 2-((tert-butyldimethylsilyl)oxy)-*N*-ethylethan-1-amine (0.406 g, 2.00 mmol) and imidazole (0.014 g, 0.20 mmol) in THF (10.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using flash chromatography (20% Et_2O/Toluene) to yield the title compound as a colourless oil (0.463 g, 58%).

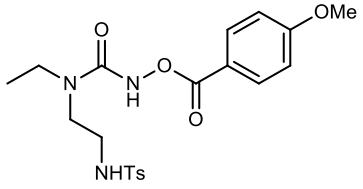
TLC R_f: 0.17 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34-9.29 (br s, 1H), 8.10-8.03 (m, 2H), 6.96-6.90 (m, 2H), 3.87 (s, 3H), 3.83 (t, *J*= 4.8 Hz, 2H), 3.49 (t, *J*= 4.7 Hz, 2H), 3.41 (q, *J*= 7.0 Hz, 2H), 1.2 (t, *J*= 7.1 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5 (C), 163.8 (C), 158.9 (C), 132.0 (CH), 120.1 (C), 113.7 (CH), 63.1 (CH_2), 55.4 (CH), 48.9 (CH_2), 42.6 (CH_2), 25.9 (CH), 18.4 (C), 13.2 (CH_3), -5.6 (CH).

IR (film): 3186, 2933, 1743, 1686, 1253, 1064, 834, 780 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{19}H_{32}N_2O_5SiNa$ $[M+Na]^+$: 419.1978. Found: 419.1959.



***N*-(2-(1-Ethyl-3-((4-methoxybenzoyl)oxy)ureido)ethyl)-4-methylbenzenesulfonamide (36z):** The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.861 g, 3.00 mmol), and *N*-(2-ethylamino)ethyl-4-methylbenzenesulfonamide (0.726 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using

1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The title compound was purified by recrystallization using Et_2O to yield a crystalline pale brown solid (0.563 g, 43%).

TLC R_f: 0.09 in 20% EtOAc/Hexanes.

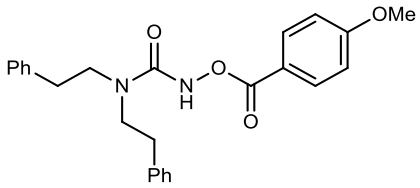
M.p.: 168.7-169.3°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.37-10.23 (br s, 1H), 8.00-7.91 (m, 2H), 7.74-7.57 (m, 3H), 7.48-7.33 (m, 2H), 7.14-7.01 (m, 2H), 3.84 (s, 3H), 3.29-3.17 (m, 4H), 2.90-2.80 (m, 2H), 2.38 (s, 3H), 1.04 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 165.1 (C), 163.6 (C), 157.0 (C), 142.7 (C), 137.3 (C), 131.5 (CH), 129.7 (CH), 126.5 (CH), 119.6 (C), 114.3 (CH), 55.6 (CH), 45.5 (CH_2), 41.4 (CH_2), 41.0 (CH_2), 21.0 (CH_3).

IR (film): 3223, 3081, 2983, 1671, 1595, 1337, 1163 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{20}H_{25}N_3O_6SNa$ [M+Na]$^+$: 458.1362. Found: 458.1344.



3-((4-Methoxybenzoyl)oxy)-1,1-diphenethylurea (36aa): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N,N*-diphenethylamine (0.676 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (20% EtOAc/Hexanes) to yield the title compound as a white solid (0.880 g, 70%).

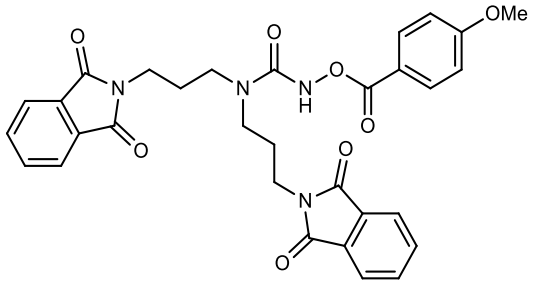
TLC R_f: 0.31 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (br s, 1H), 8.09-8.06 (m, 2H), 7.35-7.19 (m, 10H), 6.96-6.93 (m, 2H), 3.87 (s, 3H), 3.43 (t, *J* = 7.5 Hz, 4H), 2.89 (t, *J* = 7.4 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5 (C), 164.3 (C), 157.7 (C), 138.7 (C), 132.2 (CH), 128.93 (CH), 128.90 (CH), 126.8 (CH), 119.4 (C), 114.1 (CH), 55.6 (CH_3), 50.1 (CH_2), 34.7 (CH_2).

IR (film): 3209, 2931, 1744, 1673, 1604, 1475, 1247, 1166 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{25}H_{26}N_2NaO_4^+$[M+Na]$^+$: 441.1785. Found: 441.1790.



1,1-Bis(3-(1,3-dioxoisoindolin-2-yl)propyl)-3-((4-methoxybenzoyl)oxy)urea (36ab): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N,N*-diphenethylamine (1.17 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (gradient: 50% EtOAc/Hexanes → 100% EtOAc) to yield the title compound as a white foam (1.45 g, 83%).

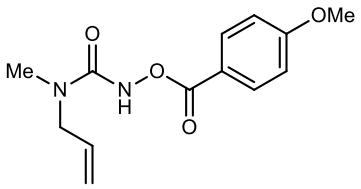
TLC R_f: 0.75 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (br s, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 7.84-7.78 (m, 4H), 7.73-7.67 (m, 4H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.76 (t, *J* = 6.8 Hz, 4H), 3.42 (t, *J* = 7.3 Hz, 4H), 2.02 (quintet, *J* = 7.1 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4 (C), 166.5 (C), 164.1 (C), 157.9 (C), 134.0 (CH), 132.0 (CH), 123.3 (CH), 119.3 (C), 113.9 (CH), 55.5 (CH), 44.8 (CH_2), 35.5 (CH_2), 27.4 (CH_2).

IR (film): 2939, 1694, 1604, 1389, 1244, 1167, 1025 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{31}H_{28}N_4O_8Na^+$ $[M+Na]^+$: 607.1805. Found: 607.1791.



1-Allyl-3-((4-methoxybenzoyl)oxy)-1-methylurea (36ac): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.511 g, 1.78 mmol), and *N*-methylallylamine (0.17 mL, 1.78 mmol) and imidazole (0.012 g, 0.18 mmol) in THF (9.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and

rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using silica plug (20% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.376 g, 80%).

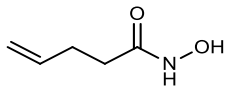
TLC R_f: 0.11 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46-8.43 (br s, 1H), 8.11-8.05 (m, 2H), 6.99-6.93 (m, 2H), 5.93-5.78 (m, 1H), 5.35-5.26 (m, 2H), 3.97 (dt, *J*= 5.3, 1.6 Hz, 2H), 3.88 (s, 3H), 3.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6 (C), 164.2 (C), 157.0 (C), 132.3 (CH), 132.1 (CH), 119.3 (C), 117.5 (CH_2), 114.0 (CH), 55.5 (CH), 51.3 (CH_2), 34.2 (CH).

IR (film): 3184, 3010, 1744, 1651, 1506, 1238 cm^{-1}.

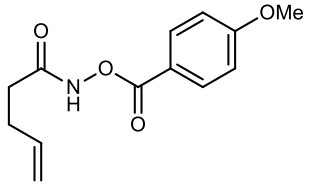
HRMS (ESI): Exact mass calcd for $C_{13}H_{16}N_2O_4Na$ $[M+Na]^+$: 287.1008. Found: 287.1014.



***N*-Hydroxypent-4-enamide (36.5ad)**: The title compound was synthesized according to a literature procedure.[307]

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.46-10.25 (br s, 1H), 878-8.57 (br s, 1H), 5.78 (ddt, *J*= 17.0, 10.4, 6.4 Hz, 1H), 5.08-4.91 (m, 2H), 2.29-.217 (m, 2H), 2.08-1.97 (m, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 168.4 (C), 137.5 (CH), 115.2 (CH_2), 31.5 (CH_2), 29.0 (CH_2).



***N*-((4-Methoxybenzoyl)oxy)pent-4-enamide (36ad):** The title compound was synthesized according to general procedure **II** using *N*-hydroxypent-4-enamide (1.15 g, 10.0 mmol), and *p*-methoxybenzoyl chloride (1.71 g, 10.0 mmol), and Et_3N (1.39 mL, 10.0 mmol) in CH_2Cl_2 (0.30 M) at 0 °C to rt. Upon completion the reaction was extracted three times using sat. $NaHCO_3$ (10.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (50.0 mL). The filtrate was collected, concentrated in vacuo to yield the title compound as a white solid (2.49 g, 99%).

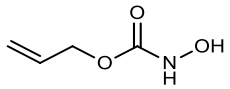
TLC R_f: 0.27 in 33% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.85 (ddt, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.13-5.03 (m, 2H), 3.87 (s, 3H), 2.48-2.41 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7 (C), 164.4 (C), 136.4 (CH), 132.2 (CH), 131.7 (CH), 118.7 (C), 116.1 (CH_2), 114.1 (C), 55.6 (CH_3), 32.4 (CH_2), 28.9 (CH_2).

IR (film): 3186, 2971, 2840, 1759, 1663, 1604, 1506, 1419, 1248, 1168 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{15}NO_4Na$ $[M+Na]^+$: 272.0897. Found: 272.0899.



Allylhydroxycarbamate (36.5ae): The title compound was synthesized according to a literature procedure.[308]

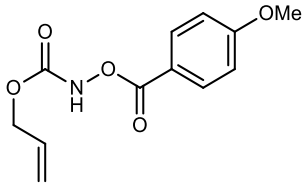
TLC R_f: 0.27 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.69-9.57 (br s, 1H), 8.73-8.70 (br s, 1H), 5.95-5.85 (m, 1H), 5.31-5.16 (m, 2H), 4.50 (dt, *J*= 5.3, 1.5 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5 (C), 133.5 (CH), 117.2 (CH_2), 64.4 (CH_2).

IR (film): 3272, 2947, 1699, 1456, 1260, 1110 cm^{-1}.

HRMS (ESI): Despite multiple attempts to obtain an accurate mass using both ESI and EI, one could not be obtained for this compound. However, this product was a precursor to **1ai**, for which all characterization was obtained, thereby clearly demonstrating this to be the desired product.



Allyl (4-methoxybenzoyl)oxycarbamate (36ae): The title compound was synthesized according to general procedure **II** using allyl hydroxycarbamate (1.17 g, 10.0 mmol), and *p*-methoxybenzoyl chloride (1.71 g, 10.0 mmol), and Et_3N (1.39 mL, 10.0 mmol) in CH_2Cl_2 (0.30 M) at 0 °C to rt. Upon completion the reaction was extracted three times using sat. $NaHCO_3$ (10.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (50.0 mL). The filtrate was collected, concentrated in vacuo and isolated using silica gel column chromatography (solvent system) to yield the title compound as a white solid (2.20 g, 88%).

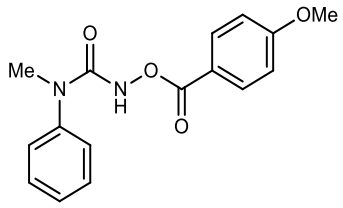
TLC R_f: 0.54 in 33% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.06-7.98 (m, *J* = 9.0 Hz, 2H), 6.97-6.88 (m, *J* = 9.0 Hz, 2H), 5.97-5.85 (m, 1H), 5.37-5.19 (m, 2H), 4.68 (td, *J* = 1.4, 5.7 Hz, 2H), 3.85 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5 (C), 164.4 (C), 156.4 (C), 132.1 (CH), 131.4 (CH), 118.9 (CH_2), 118.8 (C), 114.0 (CH), 67.1 (CH_2), 55.5 (CH).

IR (film): 3199, 2953, 2844, 1754, 1718, 1602, 1492, 1238 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{12}H_{13}NO_5Na$ [M+Na]+: 274.0696. Found: 274.0691.



3-((4-Methoxybenzoyl)oxy)-1-methyl-1-phenylurea (36af): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N*-methyl aniline (0.325 mL, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (30% EtOAc/hexanes) to yield the title compound as an amorphous off-white solid (0.896 g, 91%).

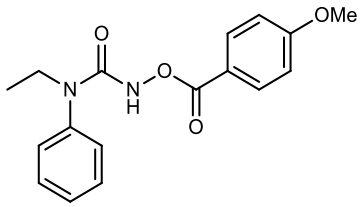
TLC R_f: 0.22 in 33% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (br s, 1H), 8.03-7.99 (m, 2H), 7.49-7.36 (m, 5H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6 (C), 164.3 (C), 157.2 (C), 141.5 (C), 132.2 (CH), 130.4 (CH), 128.5 (CH), 127.2, (CH), 119.4 (C), 114.0 (CH), 55.6 (CH_3), 38.0 (CH_3).

IR (film): 3307, 2936, 1693, 1596, 1453, 1249 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{16}N_2NaO_4^+$ $[M+Na]^+$ 323.1011. Found: 323.1108.



3-((4-Methoxybenzoyl)oxy)-1-ethyl-1-phenylurea (36ag): The title compound was synthesized according general procedure **GG** using *N*-ethylaniline (1.26 mL, 10.0 mmol), toluene (0.8 M), KOH pellets (0.561 g, 10.0 mmol), and water (2.9 M) at 0 °C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (16.4 mL, 23.0 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon competition, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-ethylanilinecarbamoyl chloride which was used in the next step without further purification.
To the crude *N*-ethylanilinecarbamoyl chloride was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added hydroxylamine hydrochloride (0.695 g, 10.0 mmol), and followed immediately by Et_3N (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-ethylanilinehydroxyurea, which could be used in the next step without further purification.
To the crude *N*-ethylanilinehydroxyurea (1.53 g, 8.53 mmol) was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (1.19 mL, 8.53 mmol) followed immediately by dropwise addition of *p*-methoxybenzoylchloride (1.45 g, 8.53 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 3-((4-methoxybenzoyl)oxy)-1-ethyl-1-phenylurea which was purified by flash column chromatography (10 % Et_2O/Toluene) to yield a colourless oil (1.93 g, 62% over 3 steps).

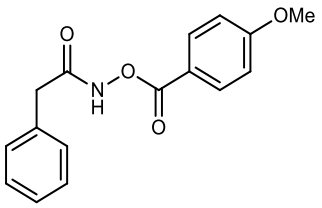
TLC R_f: 0.23 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.00 (m, 2H), 7.97-7.95 (br s, 1H), 7.53-7.46 (m, 2H), 7.44-7.37 (m, 3H), 6.96-6.90 (m, 2H), 3.86 (s, 3H), 3.77 (q, *J*= 7.2 Hz, 2H), 1.17 (t, *J*= 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4 (C), 164.1 (C), 156.6 (C), 138.5 (C), 132.0 (CH), 130.2 (CH), 128.4 (CH), 119.2 (C), 113.9 (CH), 55.5 (CH), 45.0 (CH_2), 13.3 (CH_3).

IR (film): 3302, 2972, 1737, 1701, 1602, 1508, 1646, 1168 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{17}H_{18}N_2O_4Na$ $[M+Na]^+$: 337.1165. Found: 337.1194.



***N*-((4-Methoxybenzoyl)oxy)-2-phenylacetamide (36ai):** *N*-hydroxy-2-phenylacetamide was synthesized according to general procedure **HH** using phenylacetyl chloride (1.55 g, 10.0 mmol) and hydroxylamine hydrochloride (0.695 g, 10.0 mmol) and $NaHCO_3$ (1.85 g, 22.0 mmol) in 2 : 1 CH_2Cl_2 : H_2O (0.30 M). The reaction allowed to stir at room temperature overnight; the following day a substantial amount of white solid had precipitated out of solution. The white solid was collected over a fritted funnel and used directly in the subsequent step without further purification. The title compound was synthesized using the general procedure **II** using the crude hydroxamic acid was dissolved in CH_2Cl_2 (0.30 M, sparingly soluble). To the crude solution of phenylacetyl hydroxamic acid was added 4-methoxybenzoyl chloride (1.71 g, 10.0 mmol) and triethylamine (1.39 mL, 10.0 mmol). Upon completion the reaction mixture was extracted with saturated $NaHCO_3$ three times (10 mL x 3) followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (20 mL). The filtrate was collected, and concentrated in vacuo and isolated using flash chromatography (50% EtOAc/Hexanes) to yield the title compound as a white solid (2.51 g, 88% yield over two steps).

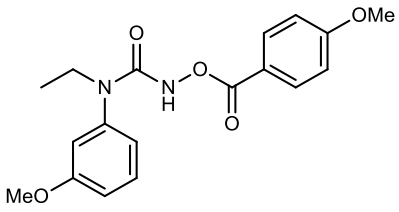
TLC R_f: 0.57 in 50% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (br s, 1H), 8.04-8.01 (m, 2H), 7.41-7.31 (m, 5H), 6.94 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.73 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7 (C), 164.7 (C), 164.6 (C), 133.2 (C), 132.3 (CH), 129.5 (CH), 129.2 (CH), 127.8 (CH), 118.7 (C), 114.2 (CH), 55.7 (CH), 41.9 (CH_2)

IR (film): 3162, 2963, 1753, 1669, 1600, 1501, 12050, 1025 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{15}NO_4Na^+$ $[M+Na]^+$: 308.0899. Found: 308.0897.



1-Ethyl-3-((4-methoxybenzoyl)oxy)-1-(3-methoxyphenyl)urea (36aj): The title compound was synthesized according general procedure **GG** using *N*-ethyl-3-methoxyaniline (1.51 g, 10.0 mmol), toluene (0.8 M), KOH pellets (0.561 g, 10.0 mmol), and water (2.9 M) at 0 °C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (16.4 mL, 23.0 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon competition, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-ethyl(3-methoxyphenyl)carbamic chloride which was used in the next step without further purification.

To the crude ethyl(3-methoxyphenyl)carbamic chloride was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added hydroxylamine hydrochloride (0.695 g, 10.0 mmol), and followed immediately by Et_3N (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 1-ethyl-3-hydroxy-1-(3-methoxyphenyl)urea, which could be used in the next step without further purification.

To the crude 1-ethyl-3-hydroxy-1-(3-methoxyphenyl)urea was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (1.39 mL, 10.0 mmol) followed immediately by addition of *p*-methoxybenzoylchloride (1.70 g, 10.0 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 1-ethyl-3-((4-methoxybenzoyl)oxy)-1-(3-methoxyphenyl)urea which was purified by flash column chromatography (20 % EtOAc/Hexanes) to yield a light pink solid (2.60 g, 76% over 3 steps).

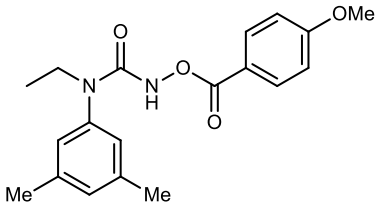
TLC R_f: 0.15 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (br s, 1H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 6.97-6.89 (m, 5H), 3.84 (s, 3H), 3.82 (s, 3H), 3.73 (q, *J* = 7.1 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6 (C), 164.3 (C), 161.0 (C), 156.8 (C), 140.8 (C), 132.2 (CH), 131.0 (CH), 120.5 (CH), 119.4 (C), 114.5 (CH), 114.04 (CH), 113.94 (CH), 55.6 (CH_3), 45.2 (CH_2), 13.5 (CH_3).

IR (film): 3294, 2940, 2842, 2360, 1748, 1701, 1601, 1446, 1286, 1246, 1209, 1172 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{18}H_{20}N_2O_5Na$ $[M+Na]^+$: 367.1291. Found: 367.1270.



1-(3,5-Dimethylphenyl)-1-ethyl-3-((4-methoxybenzoyl)oxy)urea (36ak): The title compound was synthesized according to general procedure **GG** using *N*-ethyl-3,5-dimethylaniline (1.49 g, 10.0 mmol), toluene (0.8 M), KOH pellets (0.561 g, 10.0 mmol), and water (2.9 M) at 0 °C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (16.4 mL, 23.0 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon competition, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude (3,5-dimethylphenyl)(ethyl)carbamic chloride which was used in the next step without further purification.

To the crude (3,5-dimethylphenyl)(ethyl)carbamic chloride was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added hydroxylamine hydrochloride (0.695 g, 10.0 mmol), and followed immediately by Et_3N (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 1-(3,5-dimethylphenyl)-1-ethyl-3-hydroxyurea, which could be used in the next step without further purification.

To the crude 1-(3,5-dimethylphenyl)-1-ethyl-3-hydroxyurea was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (1.39 mL, 10.0 mmol) followed immediately by dropwise addition of *p*-methoxybenzoylchloride (1.70 g, 10.0 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 1-(3,5-dimethylphenyl)-1-ethyl-3-((4-methoxybenzoyl)oxy)urea which was purified by flash column chromatography (20% EtOAc/Hexanes → 40% EtOAc/Hexanes) to yield a colourless oil (2.74 g, 80% over 3 steps).

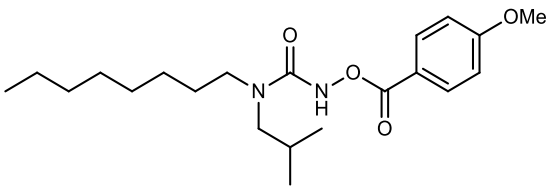
TLC R_f: 0.21 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02-7.98 (m, 2H), 7.97 (br s, 1H), 7.00 (d, *J* = 0.6 Hz, 1H), 6.96 (d, *J* = 0.5 Hz, 2H), 6.91-6.88 (m, 2H), 3.83 (d, *J* = 3.6 Hz, 3H), 3.70 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 6H), 1.13 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5 (C), 164.1 (C), 156.7 (C), 140.0 (C), 139.3 (C), 132.1 (CH), 130.3 (CH), 125.8 (CH), 119.3 (C), 113.9 (CH), 55.5 (CH_3), 45.0 (CH_2), 21.2 (CH_3), 13.4 (CH_3).

IR (film): 2970, 1744, 1695, 1602, 1510, 1454, 1310, 1245, 1167, 1062 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{19}H_{22}N_2O_4Na$ $[M+Na]^+$: 365.1458. Found: 365.1477.



3-((4-Methoxybenzoyl)oxy)-1-isobutyl-1-octylurea (36al): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.861 g, 3.00 mmol), and *N*-isobutyloctylamine (0.555 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using silica plug (20% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.957 g, 84%).

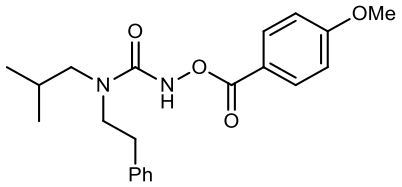
TLC R_f: 0.54 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.21-10.13 (br s, 1H), 8.01-7.91 (m, 2H) 7.15-7.03 (m, 2H), 3.85 (s, 3H), 3.23-3.14 (m, 2H), 3.03 (d, *J*= 7.4 Hz, 2H), 2.01-1.84 (m, 1H), 1.57-1.45 (m, 2H), 1.32-1.18 (m, 10H), 0.89-0.81 (m, 9H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 165.2 (C), 163.5 (C), 157.4 (C), 131.4 (CH), 119.8 (C), 114.3 (CH), 55.6 (CH), 53.0 (CH_2), 46.4 (CH_2), 31.2 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 27.4 (CH_2), 26.7 (CH), 26.2 (CH_2), 22.1 (CH_2), 19.8 (CH), 13.9 (CH_3).

IR (film): 3230, 2924, 2854, 1750, 1669, 1605, 1510, 1248 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{21}H_{34}N_2O_4Na$ [M+Na]$^+$: 401.2417. Found: 401.2423.



1-Isobutyl-3-((4-methoxybenzoyl)oxy)-1-phenethylurea (36am): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and 2-(ethylamino)ethanol (0.532 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (10% EtOAc/Hexanes → 30% EtOAc/Hexanes) to yield the title compound as a white solid (1.06 g, 95%).

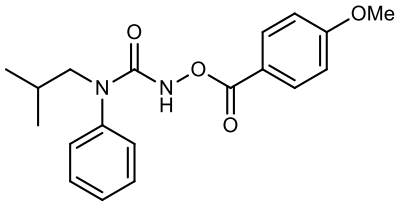
TLC R_f: 0.80 in 40% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (br s, 1H), 8.06 (d, *J* = 9.0 Hz, 2H), 7.38-7.15 (m, 5H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H), 3.50 (t, *J* = 7.7 Hz, 2H), 3.00 (d, *J* = 7.6 Hz, 2H), 2.92 (t, *J* = 7.7 Hz, 2H), 1.99 (dsextet, *J* = 13.7, 6.9 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C), 164.2 (C), 157.8 (C), 138.7 (C), 132.1 (CH), 128.8 (CH), 128.7 (CH), 126.6 (CH), 119.3 (C), 113.9 (CH), 55.5 (CH), 55.1 (CH_2), 50.0 (CH_2), 34.2 (CH_2), 27.6 (CH), 20.1 (CH_3).

IR (film): 3181, 2957, 1744, 1649, 1603, 1509, 1244, 1168 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{21}H_{26}N_2NaO_4^+$ [M+Na]$^+$: 393.1784. Found: 393.1790.



3-((4-Methoxybenzoyl)oxy)-1-isobutyl-1-phenylurea (36an): The title compound was synthesized according to general procedure **GG** using *N*-isobutylaniline (1.07 g, 7.20 mmol), toluene (0.8 M), KOH pellets (0.389 g, 7.20 mmol), and water (2.9 M) at 0 °C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (11.8 mL, 23.0 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon competition, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-isobutylanilinecarbamoyl chloride which was used in the next step without further purification.

To the crude *N*-isobutylanilinecarbamoyl chloride was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added hydroxylamine hydrochloride (0.500 g, 7.20 mmol), and followed immediately by Et_3N (1.00 mL, 14.4 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-isobutylanilinehydroxyurea, which could be used in the next step without further purification.

To the crude *N*-isobutylanilinehydroxyurea (1.38 g, 6.63 mmol) was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (0.92 mL, 6.63 mmol) followed immediately by dropwise addition of *p*-methoxybenzoylchloride (1.13 g, 6.63 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x1), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 3-((4-methoxybenzoyl)oxy)-1-isobutyl-1-phenylurea which was purified by recrystallization with Et_2O to yield a white crystalline solid (1.23 g, 36% over 3 steps).

TLC R_f: 0.34 in 20% EtOAc/Hexanes.

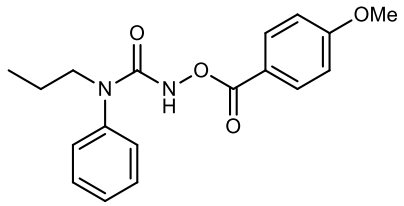
M.p.: 137.0-137.7°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-8.00 (m, 2H), 7.98-7.96 (br s, 1H), 7.53-7.46 (m, 2H), 7.45-7.37 (m, 3H), 6.96-6.90 (m, 2H), 3.87 (s, 3H), 3.57 (d, *J*= 7.4 Hz, 2H), 1.87-1.75 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5 (C), 164.1 (C), 157.3 (C), 140.0 (C), 132.1 (CH), 130.2 (CH), 128.5 (CH), 128.2 (CH), 119.2 (C), 113.9 (CH), 57.2 (CH_2), 55.5 (CH), 26.9 (CH), 19.9 (CH).

IR (film): 2960, 1741, 1709, 1604, 1490, 1246, 1173, 1053 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{19}H_{22}N_2O_4Na$ $[M+Na]^+$: 365.1478. Found: 365.1501.



3-((4-Methoxybenzoyl)oxy)-1-phenyl-1-propylurea (36ao): The title compound was synthesized according to general procedure **GG** using *N*-propylaniline (0.812 g, 6.00 mmol), toluene (0.8 M), KOH pellets (0.336 g, 6.00 mmol), and water (2.9 M) at 0 °C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (9.8 mL, 14 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon competition, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-propylanilinecarbamoyl chloride which was used in the next step without further purification.
To the crude *N*-propylanilinecarbamoyl chloride was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added hydroxylamine hydrochloride (0.417 g, 6.00 mmol), and followed immediately by Et_3N (1.67 mL, 12.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x1), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-propylanilinehydroxyurea, which could be used in the next step without further purification.
To the crude *N*-propylanilinehydroxyurea (0.927 g, 5.45 mmol) was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (0.76 mL, 5.45 mmol) followed immediately by dropwise addition of *p*-methoxybenzoylchloride (1.06 g, 5.45 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with

$NaHCO_3$ (5.0 mL x1), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 3-((4-methoxybenzoyl)oxy)-1-phenyl-1-propylurea which was purified by recrystallization with Et_2O to yield a white crystalline solid (0.935 g, 48% over 3 steps).

TLC R_f: 0.40 in 20% EtOAc/Hexanes.

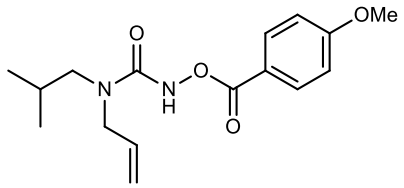
M.p.: 118.3-119.4°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-7.99 (m, 2H), 7.98-7.95 (br s, 1H), 7.54-7.46 (m, 2H), 7.45-7.37 (m, 3H), 6.97-6.89 (m, 2H), 3.87 (s, 3H), 3.71-3.66 (m, 2H), 1.59 (dq, *J*= 14.9, 7.5 Hz, 2H), 0.93 (t, *J*= 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5 (C), 164.2 (C), 156.9 (C), 139.7 (C), 132.1 (CH), 130.2 (CH), 128.6 (CH), 128.3 (CH), 119.2 (C), 113.9 (CH), 55.5 (CH), 51.7 (CH_2), 21.2 (CH_2), 11.0 (CH_3).

IR (film): 3291, 2913, 1748, 1716, 1605, 1490, 1247, 1175 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{18}H_{20}N_2O_4Na$ $[M+Na]^+$: 351.1321. Found: 351.1347.



1-Allyl-1-isobutyl-3-((4-methoxybenzoyl)oxy)urea (36ap): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N*-isobutylprop-2-en-1-amine (0.340 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (10% EtOAc/Hexanes → 20% EtOAc/Hexanes) to yield the title compound as a white solid (0.919 g, 95%).

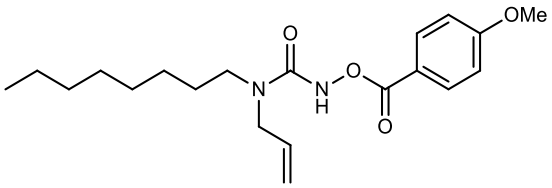
TLC R_f: 0.22 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (br s, 1H), 8.08-8.05 (m, 2H), 6.95-6.92 (m, 2H), 5.92-5.81 (m, 1H), 5.37-5.30 (m, 2H), 3.95 (td, *J* = 3.4, 1.7 Hz, 2H), 3.86 (d, *J* = 5.3 Hz, 3H), 3.16 (d, *J* = 7.5 Hz, 2H), 1.98 (dsextet, *J* = 13.7, 6.8 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C), 164.2 (C), 158.2 (C), 132.7 (CH), 132.1 (CH), 119.3 (C), 117.5 (CH_2), 113.9 (CH), 55.5 (CH_3), 55.1 (CH_2), 49.9 (CH_2), 27.5 (CH), 20.1 (CH_3).

IR (film): 3277, 2953, 1739, 1685, 1463, 1253, 1024 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{22}N_2O_4Na^+$ $[M+Na]^+$: 329.1491. Found: 329.1477.



1-Allyl-3-((4-methoxybenzoyl)oxy)-1-octylurea (36aq): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N*-allyloctan-1-amine (0.508 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (10% EtOAc/Hexanes → 20% EtOAc/Hexanes) to yield the title compound as a white solid (0.870 g, 80%).

TLC R_f: 0.28 in 20% EtOAc/Hexanes.

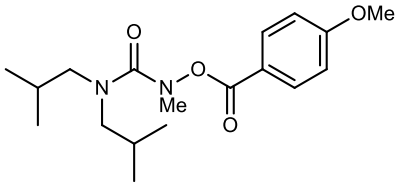
^{1}H NMR (400 MHz, $CDCl_3$):) δ 8.47 (s, 1H), 8.05 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 5.85 (ddt, *J* = 17.3, 10.3, 5.2 Hz, 1H), 5.35-5.27 (m, 2H), 3.92 (dt, *J* = 5.2, 1.6 Hz, 2H), 3.84 (s, 3H), 3.30 (t, *J* = 7.6 Hz, 2H), 1.60 (s, 3H), 1.28-1.25 (m, 11H), 0.85 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C), 164.2 (C), 157.8 (C), 132.9 (CH), 132.1 (CH), 119.3 (C), 117.4 (CH_2), 113.9 (CH), 55.5 (CH_3), 49.5 (CH_2), 47.8 (CH_2), 31.8 (CH_2), 29.34 (CH_2), 29.22 (CH_2), 28.2 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

IR (film): 3270, 2922, 2854, 1737, 1692, 1601, 163, 1251 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{20}H_{30}N_2O_4Na^+$ $[M+Na]^+$: 385.2099. Found: 385.2103.

Synthesis of mechanistic probes



3-((4-Methoxybenzoyl)oxy)-1,1-diisobutyl-3-methylurea (36ar): The title compound was synthesized according to general procedure **GG** using *N*,*N*-diisobutylamine (1.75 mL, 10.0 mmol),

toluene (0.8 M), NaOH pellets (0.400 g, 10.0 mmol), and water (2.9 M) at 0 °C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (16.4 mL, 23.0 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon competition, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N,N*-diisobutylaminecarbamoyl chloride which was used in the next step without further purification.

To the crude *N,N*-diisobutylaminecarbamoyl chloride was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added hydroxylamine hydrochloride (0.835 g, 10.0 mmol), and followed immediately by Et_3N (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N,N*-diisobutylaminehydroxyurea, which could be used in the next step without further purification.

To the crude *N,N*-diisobutylaminehydroxyurea (1.77 g, 8.80 mmol) was added CH_2Cl_2 (0.30 M) and cooled to 0 °C. To this was added Et_3N (1.23 mL, 8.80 mmol) followed immediately by dropwise addition of *p*-methoxybenzoylchloride (1.19 mL, 8.80 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x1), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 3-((4-methoxybenzoyl)oxy)-1,1-diisobutyl-3-methylurea which was purified by flash column chromatography (10 % EtOAc/Hexanes) to yield a colourless oil (0.760 g, 23% over 3 steps).

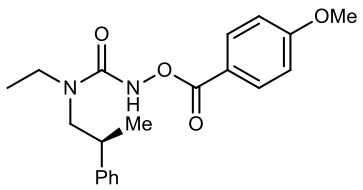
TLC R_f: 0.65 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04-7.97 (m, 2H), 6.98-6.90 (m, 2H), 3.88 (s, 3H), 3.17-3.09 (m, 7H), 1.98 (dt, *J*= 13.8, 7 Hz, 2H), 0.88 (d, *J*= 6.9 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0 (C), 163.9 (C), 163.3 (C), 131.7 (CH), 120.3 (C), 113.9 (CH), 55.5 (CH), 54.6 (CH_2), 40.1 (CH), 26.4 (CH), 20.0 (CH_3).

IR (film): 2655, 1692, 1622, 1534, 1332, 1261 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{18}H_{28}N_2O_4Na$ $[M+Na]^+$: 359.1947. Found: 359.1957.



(S)-1-Ethyl-3-((4-methoxybenzoyl)oxy)-1-(2-phenylpropyl)urea (36as): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and (S)-*N*-ethyl-2-phenylpropan-1-amine (0.490 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated vacuo and isolated using silica plug (20% EtOAc/Hexanes → 40% EtOAc/Hexanes) to yield the title compound as a (0.950 g, 89%).

TLC R_f: 0.19 in 20% EtOAc/Hexanes.

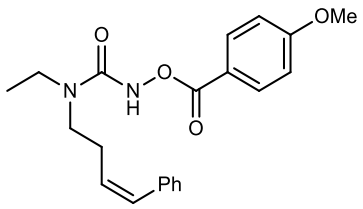
$[\alpha]_D^{26°C}$: 45.5 (C= 0.1 M in CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (br s, 1H), 8.11-7.99 (m, 2H), 7.35-7.27 (m, 2H), 7.27-7.17 (m, 3H), 6.98-6.86 (m, 2H), 3.85 (s, 3H), 3.58 (dd, *J* = 6.4, 13.6 Hz, 1H), 3.27-3.11 (m, 3H), 2.96 (qd, *J* = 7.2, 14.6 Hz, 1H), 1.35-1.27 (m, 3H), 1.18-1.03 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4 (C), 164.2 (C), 157.7 (C), 144.0 (C), 132.1 (CH), 128.8 (CH), 127.3 (CH), 126.8 (CH), 119.4 (C), 113.9 (CH), 55.5 (CH_3), 54.6 (CH_2), 42.6 (CH_2), 38.8 (CH), 18.6 (CH_3), 12.9 (CH_3).

IR (film): 3216, 2966, 1747, 1668, 1604, 1509, 1454, 1245, 1167 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{20}H_{24}N_2NaO_4^+$ $[M+Na]^+$: 379.1628. Found: 379.1634.



(*Z*)-1-Ethyl-3-((4-methoxybenzoyl)oxy)-1-(4-phenylbut-3-en-1-yl)urea (36at): The title compound was synthesized according to general procedure **FF** using phenyl (4-

methoxybenzoyl)oxycarbamate (0.861 g, 3.00 mmol), and (*Z*)-*N*-ethyl-4-phenylbut-3-en-1-amine (0.525 g, 3.00 mmol) and imidazole (0.020 g, 0.30 mmol) in THF (10 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated vacuo and isolated using flash chromatography (20% EtOAc/hexanes) to yield the title compound as a clear oil yield (0.890 g, 80%).

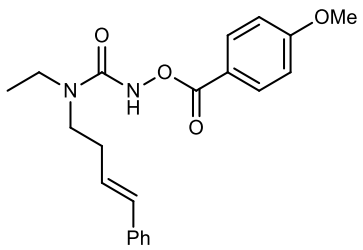
TLC R_f: 0.14 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (br s, 1H), 8.06 (d, *J* = 9.1 Hz, 2H), 7.34-7.30 (m, 2H), 7.26-7.19 (m, 3H), 6.92 (d, *J* = 9.1 Hz, 2H), 6.57 (d, *J* = 11.6 Hz, 1H), 5.67 (dt, *J* = 11.6, 7.4 Hz, 1H), 3.85 (s, 3H), 3.39 (dd, *J* = 8.0, 6.8 Hz, 2H), 3.28 (q, *J* = 7.2 Hz, 2H), 2.63 (qd, *J* = 7.4, 1.5 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C), 164.2 (C), 157.5 (C), 137.1 (C), 132.1 (CH), 131.8 (CH), 128.6 (CH), 128.3 (CH), 128.0 (CH), 126.9 (CH), 119.3 (C), 114.0 (CH), 55.5 (CH_3), 46.6 (CH_2), 41.8 (CH_2), 27.4 (CH_2), 13.3 (CH_3).

IR (film): 2931, 1746, 1668, 1602, 1477, 1245, 1165 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{21}H_{24}N_2NaO_4^+$ $[M+Na]^+$: 391.1658. Found: 391.1620.



(*E*)-1-Ethyl-3-((4-methoxybenzoyl)oxy)-1-(4-phenylbut-3-en-1-yl)urea (36au): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.565 g, 1.97 mmol), and (*E*)-N-ethyl-4-phenylbut-3-en-1-amine (0.289 g, 1.97 mmol) and imidazole (0.014 g, 0.20 mmol) in THF (6.5 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated vacuo and isolated using flash chromatography (30% EtOAc/Hexanes) to yield the title compound as a yellow oil (0.307 g, 42%).

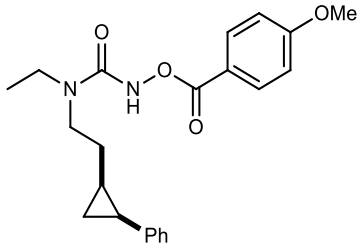
TLC R_f: 0.37 in 40% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53-8.49 (br s, 1H), 8.11-8.04 (m, 2H), 7.38-7.26 (m, 4H), 7.24-7.17 (m, 2H), 6.96-6.90 (m, 2H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.20 (dt, *J* = 15.8, 7.1 Hz), 3.87 (s, 3H), 3.48-3.34 (m, 4H), 2.56 (qd, *J* = 7.3, 1.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8 (C), 164.4 (C), 157.6 (C), 137.4 (C), 132.8 (CH), 132.2 (CH), 128.7 (CH), 127.4 (CH), 126.3 (CH), 126.3 (CH), 119.4 (C), 114.1 (CH), 55.6 (CH), 47.1 (CH_2), 42.4 (CH_2), 32.2 (CH_2), 13.6 (CH_3).

IR (film): 3222, 2931, 1745, 1670, 1603, 1478, 1245 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{21}H_{24}N_2O_4Na^+$ $[M+Na]^+$: 391.1634. Found: 391.1658.



1-Ethyl-3-((4-methoxybenzoyl)oxy)-1-(2-2-phenylcyclopropyl)ethyl)urea (36av): The title compound was synthesized according to general procedure **FF** using phenyl (4-methoxybenzoyl)oxycarbamate (0.330 g, 1.15 mmol), and *N*-ethyl-2-phenylcyclopropyl)ethanamine (0.220 g, 1.15 mmol) and imidazole (0.008 g, 0.15 mmol) in THF (4 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using flash chromatography (33% EtOAc/hexanes) to yield the title compound as a clear oil yield (0.210 g, 48%).

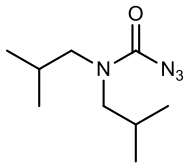
TLC R_f: 0.30 in 33% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.9 Hz, 2H), 7.89 (s, 1H), 7.27-7.20 (m, 4H), 7.14-7.10 (m, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.22-2.94 (m, 4H), 2.21 (td, *J* = 8.5, 6.1 Hz, 1H), 1.61-1.52 (m, 1H), 1.32-1.20 (m, 1H), 1.15-1.07 (m, 1H), 1.02-0.97 (m, 3H), 0.81 (q, *J* = 5.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (C), 164.2 (C), 157.2 (C), 138.5 (C), 132.1 (CH), 128.8 (CH), 128.2 (CH), 126.0 (CH), 119.5 (C), 113.9 (CH), 55.5 (CH_3), 45.7 (CH_2), 41.7 (CH_2), 27.1 (CH_2), 20.8 (CH), 16.4 (CH), 13.1 (CH_3), 9.1 (CH_2).

IR (film): 2934, 1750, 1667, 1601, 1511, 1450, 1242, 1162 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{22}H_{26}N_2NaO_4^+$ $[M+Na]^+$: 405.1790. Found: 405.1788.



1-Ethyl-3-((4-methoxybenzoyl)oxy)-1-(2-2-phenylcyclopropyl)ethyl)urea (36 aw): To a clean 50 mL round bottom flask charged with a stir bar was added the carbamoyl chloride (1.91 g, 10 mmol), then acetone (1 M) and cooled to 0 °C. To this was added sodium azide (1.95 g, 3.00 equiv.) and and the reaction was allowed to stir overnight. Upon completion, the crude reaction was evaporated under reduced pressure to remove the acetone. The crude carbamoyl azide was then extracted using CH_2Cl_2 and water to remove excess sodium azide. The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using flash chromatography (100% toluene) to yield the title compound as a clear oil yield (0.990 g, 50%).

TLC R_f: 0.22 in 100% Toluene.

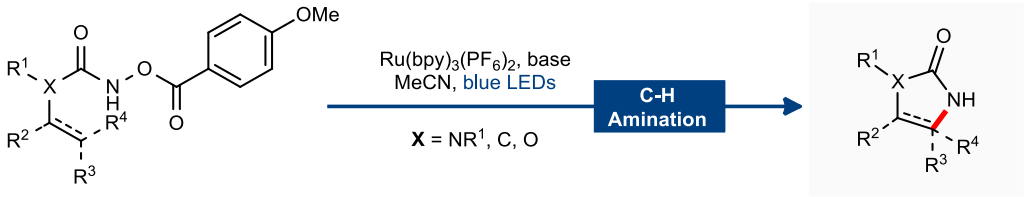
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.11 (dd, *J* = 7.6, 1.3 Hz, 2H), 2.99 (dd, *J* = 7.6, 1.2 Hz, 2H), 1.93 (qq, *J* = 13.7, 6.9 Hz, 2H), 0.85 (ddd, *J* = 6.7, 2.8, 1.5 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9 (C), 55.4 (CH_2), 54.7 (CH_2), 27.4 (CH), 26.7 (CH), 19.9 (CH_3), 19.8 (CH_3).

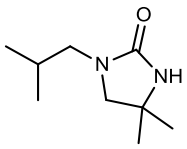
HRMS (EI): Exact mass calcd for $C_9H_{18}N_4O$ $[M]^+$: 198.1481. Found: 198.1485.

Synthesis of imidazolidinones via photocatalytic C-H amination

General Procedure JJ: Photoinduced C-H amination of *N*-oxyureas.



To a 8 mL Kimax glass vial charged with a stir bar was added the *N*-oxyurea (1.00 equiv.), then MeCN (0.2m), to which was added tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (2 mol%), and then base triethylamine (1.10 equiv.) or tetrabutylammonium dibutylphosphate (5 mol%). The vial was closed with Teflon screw cap and was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by silica gel chromatography.



1-Isobutyl-4,4-dimethylimidazolidin-2-one (34a): The title compound was synthesized according to general procedure **JJ** using 1,1-diisobutyl-3-((4-methoxybenzoyl)oxy)urea (0.161 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.080 g, 95%).

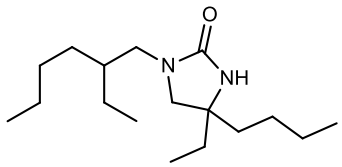
TLC R_f: 0.30 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.34 (br. s, 1H), 3.14 (s, 2H), 2.96 (d, *J* = 7.5 Hz, 2H), 1.89-1.76 (m, 1H), 1.29 (s, 6H), 0.90 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4 (C), 58.7 (CH_2), 52.1 (C), 50.9 (CH_2), 28.6 (CH_3), 27.1 (CH), 20.1 (CH_3).

IR (film): 3208, 3074, 2955, 2871, 1683, 1488, 1448, 1295, 1240 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{18}N_2O$ $[M]^+$: 170.1419. Found: 170.1407.



4-Butyl-4-methyl-1-(2-ethylhexyl)imidazolidin-2-one1-isobutyl-4,4-dimethylimidazolidin-2-one (34b): The title compound was synthesized according to general procedure **JJ** using 3-((4-methoxybenzoyl)oxy)-1,1-bis(2-ethylhexyl)urea (0.196 g, 0.450 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (60% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.095 g, 75% as a 1:1 diastereoisomers mixt).

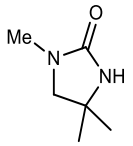
TLC R_f: 0.21 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (300 MHz, DMSO-d_6): δ 6.37-6.34 (br s, 1H), 3.02-2.99 (m, 2H), 2.91-2.86 (m, 2H), 1.51-1.33 (m, 5H), 1.32-1.11 (m, 14H), 0.91-0.75 (m, 14H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 160.6 (C), 56.0 (C), 56.0 (C), 54.0 (CH_2), 53.9 (CH_2), 46.2 (CH_2), 38.7 (CH_2), 38.7 (CH_2), 37.0 (CH_2), 36.9 (CH), 31.8 (CH_2), 31.8 (CH_2), 30.1 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 25.3 (CH_2), 23.5 (CH_2), 23.5 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 14.0 (CH), 13.9 (CH), 10.5 (CH_3), 10.5 (CH_3), 7.7 (CH_3), 7.7 (CH_3).

IR (film): 3196, 3069, 2967, 2893, 1685, 1441, 1118 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{30}N_2O^+$ $[M]^+$: 282.2671. Found: 282.2655.



1,4,4-Trimethylimidazolidin-2-one (34c): The title compound was synthesized according to general procedure **JJ** using 1-isobutyl-3-((4-methoxybenzoyl)oxy)-1-methylurea (0.140 g, 0.500 mmol), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.060 g, 93%).

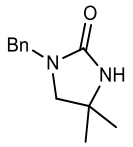
TLC R_f: 0.16 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.57 (br. s, 1H), 3.13 (s, 2H), 2.77 (s, 3H), 1.28 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5 (C), 60.7 (CH_2), 51.9 (C), 30.6 (CH_3), 28.6 (CH_3).

IR (film): 3540, 3475, 3224, 2955, 2927, 2846, 1673, 1502, 1446, 1405, 1305 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_{12}N_2O$ $[M]^+$: 128.0950. Found: 128.0945.



1-Benzyl-4,4-dimethylimidazolidin-2-one (34d): The title compound was synthesized according to general procedure **JJ** using 1-benzyl-1-isobutyl-3-((4-methoxybenzoyl)oxy)urea (0.190 g, 0.500 mmol), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.051 g, 50%).

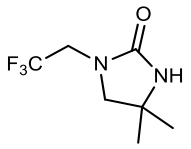
TLC R_f: 0.35 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 5H), 4.50 (br s, 1H), 4.35 (s, 2H), 3.00 (s, 2H), 1.24 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9 (C), 137.2 (C), 128.6 (CH), 128.0 (CH), 127.4 (CH), 57.4 (CH_2), 52.0 (C), 47.4 (CH_2), 28.5 (CH_3).

IR (film): 3201, 3069, 2962, 2861, 1688, 1492, 1437, 1363, 1299 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{16}N_2$ $[M]^+$: 204.1263. Found: 204.1252.



4,4-Dimethyl-1-(2,2,2-trifluoroethyl)imidazolidin-2-one (34e): The title compound was synthesized according to general procedure **JJ** using 1-isobutyl-3-((4-methoxybenzoyl)oxy)-1-(2,2,2-trifluoroethyl)urea (0.174 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (30% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.092 g, 94%).

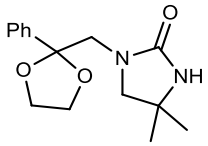
TLC R_f: 0.45 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.87 (br s, 1H), 3.78 (q, *J* = 9.1 Hz, 2H), 3.30 (s, 2H), 1.32 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3 (C), 124.7 (q, *J* = 278 Hz, C), 59.0 (CH_2), 52.5 (C), 45.4 (q, *J* = 34 Hz, CH_2), 28.4 (CH_3).

IR (film): 3223, 3082, 2976, 1697, 1446, 1416, 1313, 1265, 1221, 1149 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{11}N_2OF_3$ $[M]^+$: 196.0823. Found: 196.0807.



4,4-Dimethyl-1-((2-phenyl-1,3-dioxolan-2-yl)methyl)imidazolidin-2-one (34f): The title compound was synthesized according to general procedure **JJ** using 1-isobutyl-1-(2-phenyl-1,3-dioxolan-2-yl)isobutyl-3-((4-methoxybenzoyl)oxy)urea (0.214 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.118 g, 86%).

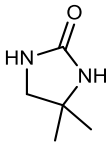
TLC R_f: 0.13 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.46 (m, 2H), 7.41-7.30 (m, 3H), 4.19-4.10 (br s, 1H), 4.09-4.00 (m, 2H), 3.91-3.79 (m, 2H), 3.58 (s, 2H), 3.23 (s, 2H), 1.20 (s, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 160.8 (C), 140.3 (C), 128.3 (CH), 128. (CH), 109.7 (C), 64.7 (CH_2), 59.6 (CH_2), 51.8 (C), 50.5 (CH_2), 28.3 (CH_3).

IR (film): 3197, 3070, 2967, 2893, 1685, 1442, 1243, 1023 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{20}N_2O_3Na^+$ $[M+Na]^+$: 299.1372. Found: 299.1394.



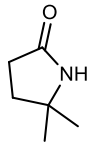
4,4-Dimethylimidazolidin-2-one (34g): The title compound was synthesized according to a modified general procedure **JJ** using 1-isobutyl-3-((4-methoxybenzoyl)oxy)urea (0.133 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), tetrabutylammonium dibutyl phosphate (0.026 g, 5 mol%) in CH_2Cl_2 (5.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and heated in a water bath at 60 °C overnight. Upon completion, the reaction was diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and

concentrated under reduced pressure. The title compound was purified by column chromatography (5% MeOH/CH_2Cl_2 + 1% Et_3N) to yield a clear oil (0.013 g, 22%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.94-4.62 (br s, 2H), 3.23 (s, 2H), 1.31 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9 (C), 55.3 (C), 54.0 (CH_2), 28.4 (CH_3).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[309]

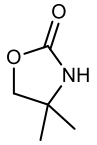


5,5-Dimethylpyrrolidin-2-one (34h): The title compound was synthesized according to general procedure **JJ** using *N*-((4-methoxybenzoyl)oxy)-4-methylpentanamide (0.265 g, 1.00 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.017 g, 2 mol%), triethylamine (0.026 g, 5 mol%) in CH_2Cl_2 (5.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 → 100% EtOAc) to yield a clear oil (0.088 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (s, 1H), 2.41 (dd, *J* = 8.4, 7.6 Hz, 2H), 1.93 (t, *J* = 8.0 Hz, 2H), 1.28 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1 (C), 56.7 (C), 35.5 (CH_2), 30.8 (CH_2), 29.3 (CH_3).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[150]



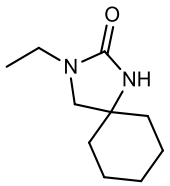
4,4-Dimethyloxazolidin-2-one (34i): The title compound was synthesized according to general procedure **JJ** using isobutyl ((4-methoxybenzoyl)oxy)carbamate (0.134 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), tetrabutylammonium dibutyl phosphate (0.011 g, 5 mol%) in CH_2Cl_2 (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The

vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (20% EtOAc/CH_2Cl_2 → 100% EtOAc) to yield a clear oil (0.014 g, 24%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.21-5.00 (br s, 1H), 4.09 (s, 2H), 1.37 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (C), 77.1 (C), 55.4 (CH_2), 27.7 (CH_3).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[203]



3-Ethyl-1,3-diazaspiro[4.5]decan-2-one (34j): The title compound was synthesized according to general procedure **JJ** using 3-((4-Methoxybenzoyl)oxy)-1-cyclohexylmethyl-1-ethylurea (0.167 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.22 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (40% EtOAc/Hexanes) to yield an amorphous white solid (0.080 g, 88%).

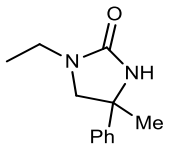
TLC R_f: 0.39 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.65-6.60 (br s, 1H), 3.08-3.01 (m, 4H), 1.62-1.21 (m, 10H), 0.97 (t, *J*= 7.2 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 159.9 (C), 54.5 (CH_2), 53.6 (C), 37.3 (CH_2), 37.1 (CH_2), 24.9 (CH_2), 22.1 (CH_2), 12.6 (CH_3).

IR (film): 3202, 2926, 2853, 1677, 1489, 1330, 1258, 1198 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{18}N_2O$ $[M]^+$: 182.1419. Found: 182.1413.



1-Ethyl-4-methyl-4-phenylimidazolidin-2-one (34k): The title compound was synthesized according to general procedure **JJ** using 1-ethyl-3-((4-methoxybenzoyl)oxy)-1-(2-phenylpropyl)urea (0.163 g, 0.500 mmol), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.079 g, 77%).

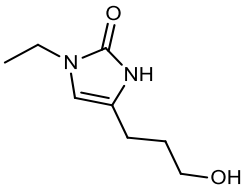
TLC R_f: 0.42 in 30% EtOAc/CH_2Cl_2

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.27 (m, 5H), 4.69-4.68 (m, 1H), 3.45 (q, *J* = 10.0 Hz, 2H), 3.39-3.17 (m, 2H), 1.68 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8 (C), 145.9 (C), 128.8 (CH), 127.4 (CH), 124.9 (CH), 58.9 (CH_2), 57.2 (C), 37.9 (CH_2), 28.6 (CH_3), 12.8 (CH_3).

IR (film): 3194, 3069, 2969, 2925, 2854, 1679, 1493, 1444, 1299, 1283, 1089 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{16}N_2O$ $[M]^+$: 204.1263. Found: 204.1237.



1-Ethyl-4-(3-hydroxypropyl)-1*H*-imidazol-2(3*H*)-one (34l): The title compound was synthesized according to general procedure **JJ** using 1-ethyl-3-((4-methoxybenzoyl)oxy)-1-((tetrahydrofuran-2-yl)methyl)urea (0.161 g, 0.500 mmol), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times

with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The majority of the product was found to dissolve in the aqueous phase, and so the aqueous phase was collected, and concentrated under reduced pressure. The combined organic and aqueous phases were purified by column chromatography (50% EtOAc/CH_2Cl_2 → 5% MeOH/CH_2Cl_2) to yield an amorphous white solid (0.079 g, 93%).

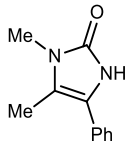
TLC R_f: 0.06 in 50% EtOAc/CH_2Cl_2; 0.53 in 10% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.63 (s, 1H), 5.91 (br. s, 1H), 3.74 (s, 1H), 3.68-3.56 (m, 4H), 2.50 (t, *J* = 6.9 Hz, 2H), 1.81-1.72 (m, 2H), 1.27-1.20 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2 (C), 122.6 (C), 106.3 (CH), 60.9 (CH_2), 37.8 (CH_2), 31.8 (CH_2), 21.7 (CH_2), 14.9 (CH_3).

IR (film): 3271, 2962, 1683, 1428, 1351, 1242, 1047 cm^{-1}.

HRMS (EI): Despite multiple attempts to obtain an accurate mass using both ESI and EI, one could not be obtained for this compound. However, C^{13} peaks at 122.6 and 106.3 ppm align with known structures and provides solid evidence for structural assignment. Moreover, this product is formed in analogy to **34m**, **34n** and **34v**.

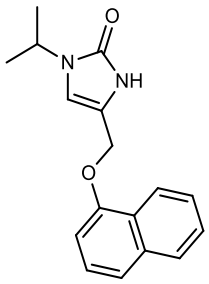


1,5-Dimethyl-4-phenyl-1H-imidazol-2(3H)-one (34m): The title compound was synthesized according to general procedure **JJ** using 1-(2-hydroxy-2-phenylethyl)-3-((4-methoxybenzoyl)oxy)-1-methylurea (0.167 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the product precipitated from solution and was collected by filtration to yield an amorphous white solid (0.047 g, 50%) the filtrate was evaporated to reveal product in solution which could be purified by silica column chromatography (50% EtOAc/CH_2Cl_2 → 5% CH_3OH/ CH_2Cl_2) (0.020 g, 18%). The combined isolated yield is therefore 0.067 g, 71%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 7.32 (d, *J* = 39.5 Hz, 6H), 3.24 (s, 3H), 2.22 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4 (C), 131.0 (C), 129.1 (CH), 127.0 (CH), 126.5 (CH), 117.7 (C), 116.4 (C), 27.2 (CH_3), 9.8 (CH_3)

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[310]



1-Ethyl-4-((naphthalen-1-yloxy)methyl)-1H-imidazol-2(3H)-one (34n): The title compound was synthesized according to general procedure **JJ** using 1-(2-hydroxy-3-(naphthalen-1-yloxy)propyl)-1-isopropyl-3-((4-methoxybenzoyl)oxy)urea (0.158 g, 0.350 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.006 g, 2 mol%), triethylamine (0.039 g, 0.385 mmol) in MeCN (1.75 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the product precipitated from solution and was collected by filtration to yield an amorphous white solid (0.035 g, 35%) the filtrate was evaporated to reveal an additional product in solution which could coeluted with *p*-methoxybenzoic acid upon silica column chromatography (50% EtOAc/CH_2Cl_2 → 5% CH_3OH/ CH_2Cl_2) (0.020 g, 18%). The combined isolated yield is therefore 0.067 g, 71%.

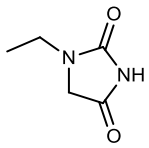
TLC R_f: 0.07 in 50% EtOAc/CH_2Cl_2; 0.45 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (600 MHz, DMSO-d_6): δ 10.36-10.35 (m, 1H), 8.17-8.15 (m, 1H), 7.88-7.86 (m, 1H), 7.54-7.43 (m, 5H), 7.09-7.08 (m, 1H), 6.78-6.78 (m, 1H), 4.92 (d, *J* = 5.4 Hz, 2H), 4.19 (dt, *J* = 0.8, 0.4 Hz, 1H), 1.25-1.21 (m, 6H).

^{13}C NMR (151 MHz, DMSO-d_6): δ 154.0 (C), 153.4 (C), 134.5 (C), 127.9 (CH), 127.0 (CH), 126.6 (CH), 125.7 (CH), 125.5 (C), 122.3 (CH), 120.7 (CH), 116.7 (C), 108.8 (CH), 106.2 (CH), 62.1 (CH_2), 43.7 (CH), 22.3 (CH_3).

IR (film): 3292, 3227, 2952, 2878, 1681, 1577, 1491, 1453, 1394 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{17}H18N_2O_2$ $[M]^+$: 282.1368. Found: 282.1378.

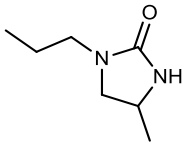


1-Ethylimidazolidine-2,4-dione (34o): The title compound was synthesized according to general procedure **JJ** using 1-(2,2-dimethoxyethyl)-1-ethyl-3-((4-methoxybenzoyl)oxy)urea (0.148 g, 0.500 mmol), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure and then purified by column chromatography (50% EtOAc/CH_2Cl_2 → 5% CH_3OH/ CH_2Cl_2) to yield an amorphous white solid (0.055 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 3.91 (s, 2H), 3.43 (q, *J* = 7.3 Hz, 2H), 1.19 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4 (C), 156.0 (C), 50.2 (CH_2), 37.2 (CH_2), 12.9 (CH_3).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[311]



4-Methyl-1-propylimidazolidin-2-one (34p): The title compound was synthesized according to general procedure **JJ** using 3-((4-methoxybenzoyl)oxy)-1,1-dipropylurea (0.147 g, 0.500 mmol), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.059 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.065 g, 92%).

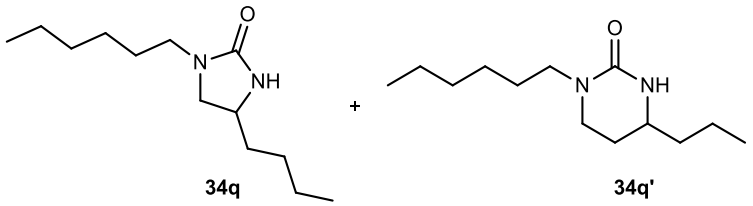
TLC R_f: 0.15 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13-4.23 (br s, 1H), 3.84-3.68 (m, 1H), 3.50 (t, *J*= 8.5 Hz, 1H), 3.25 – 3.01 (m, 2H), 2.94 (dd, *J* =8.5, 6.3 Hz, 1H), 1.50 (h, *J* =7.4 Hz, 1H), 1.22 (d, *J*= 6.1 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (C), 52.3 (CH), 45.6 (CH_2), 45.0 (CH_2), 21.6 (CH_2), 20.9 (CH_3), 11.3 (CH_3).

IR (film): 3327, 2973, 2866, 1666, 1381, 1045 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{14}N_2$ $[M]^+$: 142.1106. Found: 142.1124.



34q 34q'

1-Hexyl-4-butyl-imidazol-2-one (34q) and 1-hexyl-4-propyltetrahydropyrimidin-2(1H)-one (34q'): The title compound was synthesized according to general procedure **JJ** using 3-((4-methoxybenzoyl)oxy)-1,1-dihexylurea (0.189 g, 0.500 mmol), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.059 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compounds were purified by column chromatography (97:2:1 CH_2Cl_2/iPrOH/AcOH) to yield an inseparable mixture as a colourless oil (0.051 g, 72%).

TLC R_f: 0.18 in 2% MeOH/CH_2Cl_2.

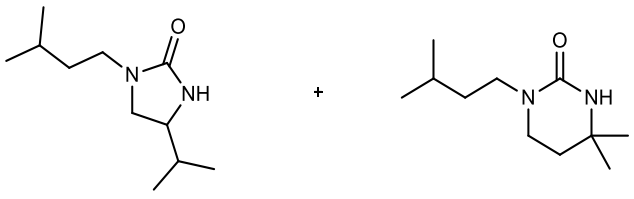
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50-6.40 (br s, 1H), 6.08-5.99 (br s, 1H), 3.53-3.26 (m, 3H), 3.21-2.90 (m, 3H), 2.89-2.83 (m, 1H), 1.47-1.14 (m, 1H), 0.90-0.81 (m, 8H).

Compound **34q**: **^{13}C NMR (100 MHz, DMSO-d_6):** δ 161.3 (C), 49.9 (CH2), 49.1 (CH), 42.5 (CH_2), 35.3 (CH_2), 30.9 (CH_2), 27.0 (CH_2), 25.9 (CH_2), 22.1 (CH_2), 22.0 (CH_2), 22.0 (CH_2), 13.9 (CH_3), 13.9 (CH_3).

Compound **34q'**: **^{13}C NMR (100 MHz, DMSO-d_6):** δ 155.1 (C), 49.8 (CH), 46.2 (CH_2), 43.3 (CH_2), 37.8 (CH_2), 31.1 (CH_2), 28.1 (CH_2), 27.3 (CH_2), 27.1 (CH_2), 26.0 (CH_2), 18.0 (CH_2), 14.0 (CH_3).
(one carbon is missing due to overlap with compound A).

IR (film): 3213, 2956, 2923, 2856, 1687, 1449, 1261 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{26}N_2O$ $[M]^+$: 226.2045. Found: 226.2030.



34r 34r'

1-Isopentyl-4-isopropylimidazolidin-2-one (34r) and 1-isopentyl-4-isopropylimidazolidin-2-one (34r'): The title compound was synthesized according to general procedure **JJ** using 1,1-diisopentyl-3-((4-methoxybenzoyl)oxy)urea (0.175 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compounds were purified by column chromatography (96:3:1 CH_2Cl_2/iPrOH/AcOH) to yield an inseparable mixture as a colourless oil (0.078 g, 79%).

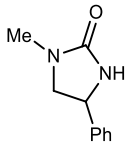
TLC R_f: 0.51 in 50% EtOAc/$CH2Cl_2$.

^{1}H NMR (300 MHz, DMSO-d_6): δ 6.55-6.50 (br s, 1H), 6.08-6.02 (br s, 1H), 3.29-2.88 (m, 10H), 1.66-1.58 (m, 2H), .56-1.41 (m, 4H), 1.38-1.22 (m, 6H), 1.09 (s, 6H), 0.91-0.77 (m, 27H).

^{13}C (100 MHz, DMSO-d_6): δ 161.4 (C), 154.7 (C), 54.9 (CH), 49.3 (C), 47.8 (CH2), 44.4 (CH2), 41.5 (CH2), 40.8 (CH2), 36.0 (CH2), 35.9 (CH2), 34.3 (CH2), 32.7 (CH), 29.0 (CH), 25.4 (CH), 25.2 (CH), 22.5 (CH), 22.4 (CH), 22.3 (CH), 18.2 (CH_3), 17.7 (CH_3).

IR (film): 3210, 2956, 2870, 1685, 1644, 1459, 1261 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{22}N_2O$ $[M]^+$: 198.1732. Found: 198.1716.



1-Methyl-4-phenylimidazolidin-2-one (34s): The title compound was synthesized according to general procedure **JJ** using 3-((4-methoxybenzoyl)oxy)-1-methyl-1-phenethylurea (0.164 g, 0.500 mmol), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (40% EtOAc/Hexanes → 100% EtOAc) to yield a white solid (0.067 g, 75%).

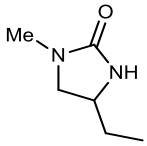
TLC R_f: 0.29 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 4.77 (br. s, 1H), 4.72 (ddd, *J* = 8.8, 7.4, 1.5 Hz, 1H), 3.76 (t, *J* = 8.8 Hz, 1H), 3.20 (dd, *J* = 8.8, 7.4 Hz, 1H), 2.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (C), 141.7 (C), 129.0 (CH), 128.3 (CH), 126.2 (CH), 56.2 (CH_2), 53.8 (CH), 30.7 (CH_3).

IR (film): 3198, 3083, 2919, 2852, 1681, 1500, 1440, 1403, 1252 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{12}N_2O$ $[M]^+$: 176.0950. Found: 176.0974.



1-Methyl-4-ethyl-imidazol-2-one (34t): The title compound was synthesized according to general procedure **JJ** using 3-((4-methoxybenzoyl)oxy)-1-butyl-1-methylurea (0.140 g, 0.500 mmol), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4,

filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (96:3:1 CH_2Cl_2/iPrOH/AcOH) to yield an amorphous white solid (0.032 g, 50%).

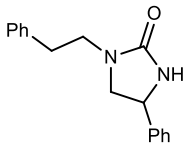
TLC R_f: 0.36 in 2% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.64-4.28 (br s, 1H), 3.64-3.46 (m, 2H), 3.03 (dd, *J* = 8, 6.1 Hz, 1H), 2.78 (s, 3H), 1.61-1.56 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (C), 52.9 (CH_2), 51.1 (CH), 30.5 (CH), 28.6 (CH_2), 9.6 (CH_3).

IR (film): 3203, 2960, 1683, 1507, 1311, 161, 1231 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_{12}N_2O$ $[M]^+$: 128.0950. Found: 128.0946.



Phenethyl-4-phenylimidazolidin-2-one (34v): The title compound was synthesized according to general procedure **JJ** using 3-((4-methoxybenzoyl)oxy)-1,1-diphenethylurea (0.209 g, 0.500 mmol), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (40% EtOAc/Hexanes) to yield a white solid (0.100 g, 75%).

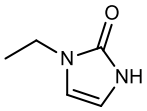
TLC R_f: 0.50 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.19 (m, 10H), 4.73 (br. s, 1H), 4.68 (ddd, *J* = 8.8, 7.1, 1.4 Hz, 1H), 3.68 (t, J = 8.8 Hz, 1H), 3.56-3.43 (m, 2H), 3.14 (dd, *J* = 8.8, 7.1 Hz, 1H), 2.85 (t, *J* = 7.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7 (C), 141.7 (C), 139.0 (C), 129.0 (CH), 128.9 (C), 128.6 (CH), 128.3 (CH), 126.5 (CH), 126.2 (CH), 54.2 (CH_2), 53.9 (CH), 44.9 (CH_2), 34.5 (CH_2).

IR (film): 3216, 3083, 3028, 2917, 2854, 1680, 1490, 1452, 1360, 1318, 1255 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{17}H_{18}N_2O$ $[M]^+$: 266.1419. Found: 233.1431.



1-Ethyl-1*H*-imidazol-2(3*H*)-one (34w): The title compound was synthesized according to general procedure **JJ** using 1-ethyl-1-(2-hydroxyethyl)-3-((4-methoxybenzoyl)oxy)urea (0.141 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 → 5% MeOH/CH_2Cl_2) to yield a white solid (0.028 g, 50%).

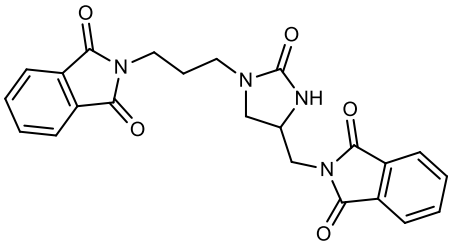
TLC R_f: 0.07 in 50% EtOAc/CH_2Cl_2; 0.45 in 5% MeOH/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 6.29 (t, *J* = 2.6 Hz, 1H), 6.20 (t, *J* = 2.5 Hz, 1H), 3.67 (q, *J* = 7.3 Hz, 2H), 1.30 (t, *J* = 7.3 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3 (C), 110.8 (CH), 108.0 (CH), 37.9 (CH_2), 14.8 (CH_3).

IR (film): 3200, 2929, 1663, 1455, 1258, 1088 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_5H_8N_2O$ $[M]^+$: 112.0637. Found: 112.0618.



2-(3-(4-((1,3-Dioxoisoindolin-2-yl)methyl)-2-oxoimidazolidin-1-yl)propyl)isoindoline-1,3-dione (34z): The title compound was synthesized according to general procedure **JJ** using 1,1-bis(3-(1,3-dioxoisoindolin-2-yl)propyl)-3-((4-methoxybenzoyl)oxy)urea (0.292 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to

remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 → 100% EtOAc) to yield a white solid (0.078 g, 36%).

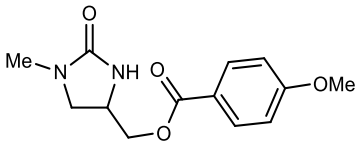
TLC R_f: 0.16 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (ddd, *J* = 13.4, 5.5, 3.0 Hz, 4H), 7.70 (ddd, *J* = 14.6, 5.5, 3.0 Hz, 4H), 4.74 (s, 1H), 3.98 (dq, *J* = 9.0, 4.8 Hz, 1H), 3.90 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.78 (dd, *J* = 14.0, 4.7 Hz, 1H), 3.68 (td, *J* = 7.3, 3.2 Hz, 2H), 3.56 (t, *J* = 8.8 Hz, 1H), 3.34 (dd, *J* = 9.0, 5.6 Hz, 1H), 3.25-3.12 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (C), 138.2 (C), 161.1 (C), 134.3 (CH), 133.9 (CH), 131.1 (C), 131.7 (C), 123.6 (CH), 123.2 (CH), 49.3 (CH), 48.6 (CH_2), 41.1 (CH_2), 40.9 (CH_2), 35.4 (CH2), 26.6 (CH_2).

IR (film): 3200, 2864, 1693, 1387, 1258, 1027 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{23}H_{20}N_4O_5Na$ $[M+Na]^+$: 455.1325. Found: 455.1331.



(1-Methyl-2-oxoimidazolidin-4-yl)methyl 4-methoxybenzoate (34aa): The title compound was synthesized according to general procedure **JJ** using 1-allyl-3-((4-methoxybenzoyl)oxy)-1-methylurea (0.132 g, 0.50 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.057 g, 0.55 mmol) in CH_2Cl_2 (5.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL). The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 → 30% EtOAc/CH_2Cl_2) to yield a white solid (0.089 g, 66%).

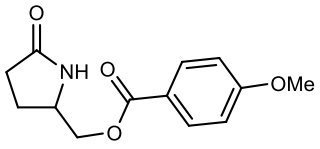
TLC R_f: 0.51 in 2% MeOH/CH_2Cl_2

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.94 (m, 2H), 6.97-6.91 (m, 2H), 4.68-4.58 (br s, 1H), 4.41-4.35 (dd, *J* = 11.1, 4.8 Hz, 1H), 4.26-4.20 (dd, *J* = 11.2, 7.1 Hz, 1H), 4.09-4.00 (m, 1H), 3.88 (s, 3H), 3.62 (t, *J* = 9.0 Hz, 3H), 3.26 (dd, *J* = 9.0, 5.5 Hz, 1H), 2.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C), 163.7 (C), 161.5 (C), 131.7 (CH), 121.8 (C), 113.8 (CH), 66.2 (CH_2), 55.5 (CH), 49.8 (CH_2), 48.4 (CH), 30.5 (CH_3).

IR (film): 3200, 2942, 2866, 1699, 1600, 1444, 1252 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{14}N_2O_2$ $[M]^+$: 264.1110. Found: 264.1080.



(5-Oxopyrrolidin-2-yl)methyl 4-methoxybenzoate (34ab): The title compound was synthesized according to general procedure **JJ** using *N*-((4-methoxybenzoyl)oxy)pent-4-enamide (0.249 g, 1.00 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.017 g, 2 mol%), tetrabutylammonium dibutyl phosphate (0.022 g, 5 mol%) in CH_2Cl_2 (5.0 mL, 0.2 M) in a 8 mL

Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL). The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 → 100% EtOAc) to yield a white solid (0.169 g, 68%).

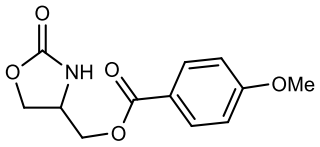
TLC R_f: 0.12 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.12 (br s, 1H), 4.40 (dd, *J* = 11.2, 3.7 Hz, 1H), 4.11 (dd, *J* = 11.2, 7.2 Hz, 1H), 4.04-3.98 (m, 1H), 3.84 (s, 3H), 2.45-2.26 (m, 3H), 1.95-1.86 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9 (C), 166.0 (C), 163.7 (C), 131.7 (CH), 121.8 (C), 113.8 (CH), 67.2 (CH_2), 55.5 (CH_3), 53.0 (CH), 29.5 (CH_2), 23.4 (CH_2).

IR (film): 3168, 3079, 2965, 2841, 1680, 1605, 1511, 1461, 1383, 1252 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{15}NO_4Na$ $[M]^+$: 272.0899. Found: 272.0904.



(2-Oxooxazolidin-4-yl)methyl 4-methoxybenzoate (34ac): The title compound was synthesized according to general procedure **JJ** using allyl (4-methoxybenzoyl)oxycarbamate (0.126 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.057 g, 0.55 mmol) in CH_2Cl_2 (5.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL). The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 → 100% EtOAc) to yield a white solid (0.065 g, 52%).

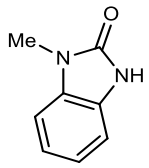
TLC R_f: 0.32 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.79 (br s, 1H), 4.59-4.55 (m, 1H), 4.44-4.41 (m, 1H), 4.31-4.22 (m, 3H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1 (C), 164.0 (C), 159.4 (C), 132.0 (CH), 121.5 (C), 114.0 (CH), 67.2 (CH_2), 65.3 (CH_2), 55.6 (CH_3), 51.5 (CH).

IR (film): 3277, 2941, 2840, 1750, 1706, 1603, 1580, 1511, 1417, 1281, 1251 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{13}NO_5$ $[M]^+$: 251.0794. Found: 251.0799.

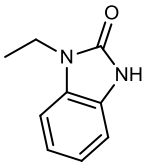


1-Methyl-1H-benzo[d]imidazol-2(3H)-one (34ad): The title compound was synthesized following general procedure **JJ** using 3-((4-methoxybenzoyl)oxy)-1-methyl-1-phenylurea (0.240 g, 0.800 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.014 g, 2 mol%), triethylamine (0.089 g, 0.88 mmol) in MeCN (4.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (10% EtOAc/Hexanes → 50% EtOAc/Hexanes) to yield a white solid (0.085 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (s, 1H), 7.11-7.05 (m, 3H), 6.98-6.95 (m, 1H), 3.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0 (C), 131.1 (C), 128.0 (C), 121.8 (CH), 121.5 (CH), 109.7 (CH), 107.8 (CH), 27.0 (CH_3).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[312]



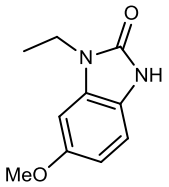
1-Ethyl-1,3-dihydro-benzoimidazol-2-one (34ae): The title compound was synthesized according to general procedure **JJ** using 3-((4-methoxybenzoyl)oxy)-1-ethyl-1-phenylurea (0.157 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate

(3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.039 g, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.49-10.20 (br s, 1H), 7.19-6.96 (m, 4H), 3.98 (q, *J*= 7.2 Hz, 2H), 1.38 (t, *J*= 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5 (C), 130.0 (C), 128.1 (C), 121.4 (CH), 121.2 (CH), 109.7 (CH), 107.7 (CH), 35.6 (CH_2), 13.6 (CH_3).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[313]



1-Ethyl-5-methoxy-1H-benzo[d]imidazol-2(3H)-one (34ah): The title compound was synthesized according to general procedure **JJ** using 1-ethyl-3-((4-methoxybenzoyl)oxy)-1-(3-methoxyphenyl)urea (0.276 g, 0.800 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.014 g, 2 mol%), triethylamine (0.089 g, 0.88 mmol) in MeCN (4.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na2SO4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (40% EtOAc/CH_2Cl_2) to yield a white solid (0.143 g, 93%).

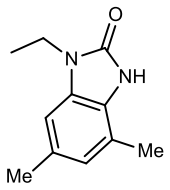
TLC R_f: 0.33 in 50% EtOAc/CH_2Cl_2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (d, *J* = 0.3 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 3.90 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9 (C), 155.5 (C), 131.1 (C), 122.2 (C), 109.9 (CH), 106.7 (CH), 95.3 (CH), 56.1 (CH_3), 35.8 (CH_2), 13.7 (CH_3).

IR (film): 2978, 2934, 1681, 1629, 1609, 1493, 1447, 1396, 1223, 1081 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{12}N_2O_2$ $[M]^+$: 192.0899. Found: 192.0876.



1-Ethyl-4,6-dimethyl-1H-benzo[d]imidazol-2(3H)-one (34ai): The title compound was synthesized according to general procedure **JJ** using 1-(3,5-dimethylphenyl)-1-ethyl-3-((4-methoxybenzoyl)oxy)urea (0.273 g, 0.80 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.014 g, 2 mol%), triethylamine (0.089 g, 0.88 mmol) in MeCN (4.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the product precipitated out of solution and was collected over a fritted funnel (0.128 g, 84%).

TLC R_f: 0.42 in 50% EtOAc/CH_2Cl_2.

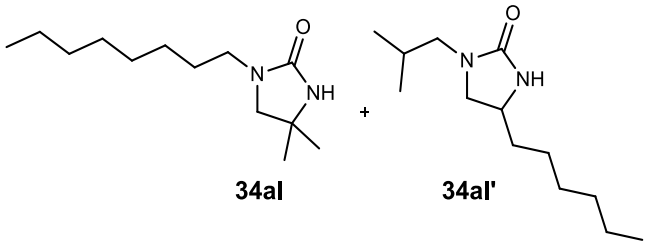
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.04 (br s, 1H), 6.68 (s, 1H), 6.65 (s, 1H), 3.90 (q, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 2.35 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7 (C), 130.8 (C), 129.8 (C), 125.0 (C), 123.3 (CH), 119.1 (C), 105.9 (CH), 35.6 (CH_2), 21.5 (CH_3), 16.2 (CH_3), 13.7 (CH_3).

IR (film): 2978, 1687, 1459, 1396, 1280 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{14}N_2O$ $[M]^+$: 190.1106. Found: 190.1120.

Site competition experiments for photocatalytic C-H amination



34al **34al'**

1-Octyl-4,4-dimethylimidazolidin-2-one (34al) and 4-hexyl-1-isobutylimidazolidin-2-one (34al'): The title compound was synthesized according to general procedure **JJ** using 3-((4-methoxybenzoyl)oxy)-1-isobutyl-1-octylurea (0.189 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.057 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (30% EtOAc/Hexanes) to yield a colourless oil (0.077 g, 68%).

TLC R_f: 0.48 in 50% EtOAc/CH_2Cl_2.

1-Octyl-4,4-dimethylimidazolidin-2-one (34al):

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.36-6.33 (br s, 1H), 3.03-2.97 (m, 4H), 1.42-1.35 (m, 3H, 2aj and 2aj'), 1.30-1.18 (m, 13H, 2aj and 2aj'), 1.15 (s, 6H), 0.85 (app t, *J*= 6.9 Hz, 4H, 2aj and 2aj'), 0.81 (app dd, *J*= 6.6, 2.4 Hz, 2H, 2aj and 2aj').

^{13}C NMR (100 MHz, DMSO-d_6): δ 160.3 (C), 57.1 (CH_2), 51.1 (C), 42.2 (CH_2), 31.2 (CH_2), 28.6 (CH_2), 28.6 (CH), 28.0 (CH), 27.0 (CH_2), 26.1 (CH_2), 22.1 (CH_2), 13.9 (CH_3).

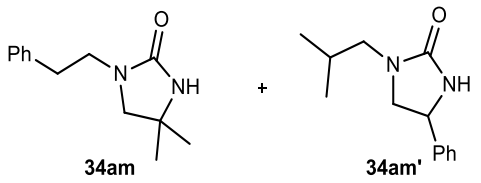
4-Hexyl-1-isobutylimidazolidin-2-one (34al'):

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.46-6.44 (br s, 1H), 3.52-3.46 (m, 1H), 3.43-3.38 (m, 2H), 2.89-2.85 (m, 1H), 2.83-2.74 (m, 2H), 1.81-1.71 (m, 1H), 1.42-1.35 (m, 3H, , 2aj and 2aj'), 1.30-1.18 (m, 13H, , 2aj and 2aj'), 0.85 (app t, *J*= 6.9 Hz, 4H, , 2aj and 2aj'), 0.81 (app dd, *J*= 6.6, 2.4 Hz, 2H, , 2aj and 2aj').

^{13}C NMR (100 MHz, DMSO-d_6): δ 161.4, 50.6, 50.3, 49.1, 35.7, 26.4, 24.7, 22.0, 20.0, 19.9, 13.9 (one carbon is missing due to overlap).

IR (film): 3202, 2917, 2852, 1686, 1457, 1303, 1240 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{26}N_2O$ $[M]^+$: 226.2045. Found: 226.2020.



4,4-Dimethyl-1-phenethylimidazolidin-2-one (34am) and 1-Isobutyl-4-phenylimidazolidin-2-one (34am'): The title compound was synthesized according to general procedure **JJ** using 1-isobutyl-3-((4-methoxybenzoyl)oxy)-1-phenethylurea (0.185 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (gradient 20% EtOAc/Hexanes → 40% EtOAc/Hexanes) to yield a white solid (0.037 g, 37%).

4,4-Dimethyl-1-phenethylimidazolidin-2-one (34am): as an amorphous white solid (0.037 g, 37%).

TLC R_f: 0.13 in 30% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.19 (m, 5H), 4.31 (s, 1H), 3.44 (dd, *J* = 7.9, 6.8 Hz, 2H), 3.02 (s, 2H), 2.83 (t, *J* = 7.4 Hz, 2H), 1.21 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9 (C), 139.3 (C), 128.9 (CH), 128.6 (CH), 126.5 (CH), 58.6 (CH_2), 52.1 (C), 44.8 (CH_2), 34.6 (CH_2), 28.5 (CH_3).

IR (film): 3202, 3069, 2967, 2956, 2857, 1683, 1489, 1452, 1365, 1302 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O$ $[M]^+$: 218.1419. Found: 218.1396.

1-Isobutyl-4-phenylimidazolidin-2-one (34am'): as amorphous white solid (0.059 g, 50%).

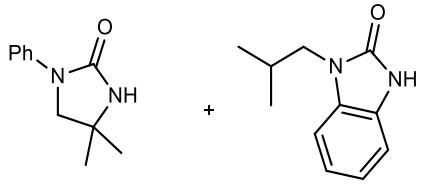
TLC R_f: 0.28 in 30% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.29 (m, 5H), 4.77-4.73 (m, 2H), 3.79 (t, *J* = 9.0 Hz, 1H), 3.22 (dd, *J* = 8.8, 7.3 Hz, 1H), 3.09-2.95 (m, 2H), 1.82 (dquintet, *J* = 13.7, 6.9 Hz, 1H), 0.91 (dd, *J* = 6.7, 4.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (C), 141.9 (C), 129.1 (CH), 128.3 (CH), 126.2 (CH), 54.4 (CH_2), 54.0 (CH), 51.2 (CH_2), 27.1 (CH), 20.16 (CH_3).

IR (film): 3200, 3082, 2953, 1682, 1491, 1449, 1255 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O$ $[M]^+$: 218.1419. Found: 218.1404.



34an **34an'**

4,4-Dimethyl-1-phenylimidazolidin-2-one (34an) and 1-isobutyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (34an'): The title compound was synthesized according to general procedure **JJ** using 3-((4-methoxybenzoyl)oxy)-1-isobutyl-1-phenylurea (0.171 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.057 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compounds were purified by column chromatography (10% EtOAc/CH_2Cl_2 → 20% EtOAc/CH_2Cl_2).

4,4-Dimethyl-1-phenyl-2-imidazolidinone (34an): as a white solid (0.039 g, 41%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.51 (m, 2H), 7.39-7.30 (m, 2H), 7.10-7.02 (m, 1H), 4.61-5.43 (br s, 1H), 3.66 (s, 2H), 1.41 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2 (C), 140.2 (C), 128.8 (CH), 122.5 (CH), 117.7 (CH), 58.2 (CH_2), 51.3 (C), 28.6 (CH_3).

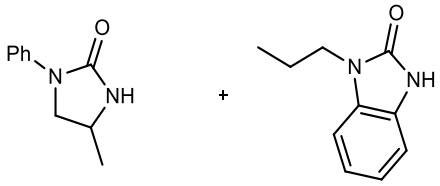
The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[314]

1-Isobutyl-1,3-dihydro-benzoimidazol-2-one (34an'): as a pink solid (0.033 g, 35%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92-8.83 (br s, 1H), 7.13-7.05 (m, 3H), 7.02-6.97 (m, 1H), 3.70 (d, *J* = 7.5 Hz, 2H), 2.33-2.17 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8 (C), 130.8 (C), 127.9 (C), 121.3 (CH), 121.1 (CH), 109.5 (CH), 108.1 (CH), 48.3 (CH_2), 27.9 (CH), 20.1 (CH_3).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[315]



34o **34o'**

4-Methyl-1-phenylimidazolidin-2-one (34ao) and 1-propyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (34ao'): The title compound was synthesized according to general procedure **JJ** using 3-((4-methoxybenzoyl)oxy)-1-phenyl-1-propylurea (0.164 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.057 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compounds were purified by column chromatography (10% EtOAc/CH_2Cl_2 → 20% EtOAc/CH_2Cl_2).

4-Methyl-1-phenylimidazolidin-2-one (34ao): as a yellow solid (0.009 g, 10%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.51 (m, 2H), 7.39-7.31 (m, 2H), 7.10-7.02 (m, 1H), 4.87-4.79 (br s, 1H), 4.08-3.90 (m, 2H), 3.50 (dd, *J* = 8.3, 7.7 Hz, 1H), 1.36 (d, *J* = 5.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8 (C), 140.1 (C), 128.8 (CH), 122.7 (CH), 117.8 (CH), 52.5 (CH_2), 44.8 (CH), 21.7 (CH_3).

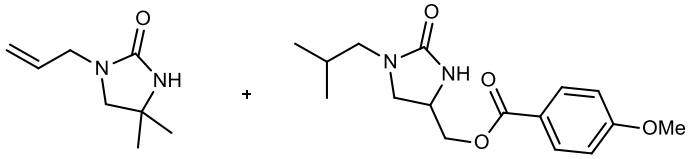
The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[314]

1-Propyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (34ao'): as a yellow solid (0.056 g, 63%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.69-10.36 (br s, 1H), 7.20-6.97 (m, 4H), 3.93-3.84 (m, 2H), 1.83 (apt sxt, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8 (C), 130.4 (C), 128.0 (C), 121.3 (CH), 121.1 (CH), 109.7 (CH), 107.9 (CH), 42.4 (CH_2), 21.7 (CH_2), 11.3 (CH).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[316]



34ap **34ap'**

1-Allyl-4,4-dimethylimidazolidin-2-one (34ap) and (1-isobutyl-2-oxoimidazolidin-4-yl)methyl 4-methoxybenzoate (34ap'): The title compound was synthesized according to general procedure **JJ** using 1-allyl-1-isobutyl-3-((4-methoxybenzoyl)oxy)urea (0.306 g, 1.00 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.017 g, 2 mol%), triethylamine (0.111 g, 0.55 mmol) in MeCN (5.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compounds were isolated as a mixture by column chromatography (20% EtOAc/CH_2Cl_2 → 40% EtOAc/CH_2Cl_2), white solid (59%, 1.8 : 1 (**34ap** : **34ap'**)).

TLC R_f: 0.30 in 50% EtOAc/CH_2Cl_2.

1-Allyl-4,4-dimethylimidazolidin-2-one (34ap):

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.19-5.12 (m, 2H), 4.50 (br s, 1H), 3.76 (dt, *J* = 6.0, 1.4 Hz, 2H), 3.09 (s, 2H), 1.27 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (C), 133.5 (CH), 117.4 (CH_2), 57.7 (CH_2), 52.0 (C), 46.1 (CH_2), 28.5 (CH_3).

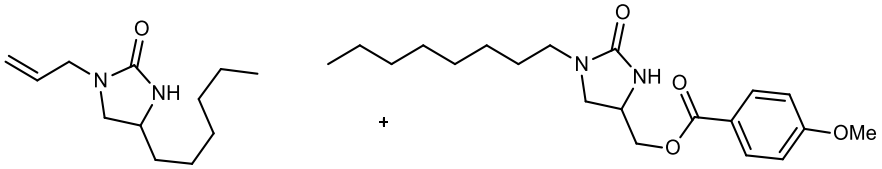
The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[314]

1-Isobutyl-2-oxoimidazolidin-4-yl)methyl 4-methoxybenzoate (34ap'):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 5.07 (br s, 1H), 4.33 (dd, *J* = 11.1, 4.9 Hz, 1H), 4.19 (dd, *J* = 11.1, 7.0 Hz, 1H), 4.05-3.98 (m, 1H), 3.84 (s, 3H), 3.57 (t, *J* = 9.1 Hz, 1H), 3.22 (dd, *J* = 9.2, 5.3 Hz, 1H), 2.97 (qd, *J* = 12.5, 7.5 Hz, 2H), 1.84 (tt, *J* = 13.8, 6.9 Hz, 1H), 0.88 (dd, *J* = 6.7, 3.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0 (C), 163.7 (C), 161.7 (C), 131.8 (CH), 121.9 (C), 113.8 (CH), 66.4 (CH_2), 55.5 (CH_3), 51.0 (CH_2), 48.6 (CH), 48.0 (CH_2), 26.9 (CH), 20.0 (CH_3).

IR (film): 3210, 2950, 1681, 1604, 1450, 1254, 1113 cm^{-1}.



34aq **34aq'**

1-Allyl-4-hexylimidazolidin-2-one (34aq) and (1-octyl-2-oxoimidazolidin-4-yl)methyl 4-methoxybenzoate (34aq'): The title compounds were synthesized according to general procedure **JJ** using 1-allyl-3-((4-methoxybenzoyl)oxy)-1-octylurea (0.362 g, 1.00 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.017 g, 2 mol%), triethylamine (0.111 g, 0.55 mmol) in MeCN (5.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compounds co-eluted upon flash column chromatography (20% EtOAc/CH_2Cl_2 → 40% EtOAc/CH_2Cl_2), (0.175 g, 48% yield) white solid (10 : 1 (**34aq** : **34aq'**)).

TLC R_f = 0.41 in 100% EtOAc.

1-Allyl-4-hexylimidazolidin-2-one (34aq):

^{1}H NMR (400 MHz, $CDCl_3$): (300 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.1, 10.1, 6.0 Hz, 1H), 5.20-5.13 (m, 2H), 4.45 (br s, 1H), 3.82-3.69 (m, 2H), 3.63-3.61 (m, 1H), 3.01-2.94 (m, 1H), 1.53-1.44 (m, 10H), 0.90-0.88 (m, 3H).

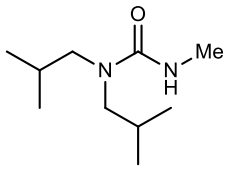
^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3 (C), 133.4 (CH), 117.5 (CH_2), 50.5 (CH_2), 50.1 (CH), 46.2 (CH_2), 36.0 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 25.5 (CH_2), 22.5 (CH_2), 14.1 (CH_3).

(1-Octyl-2-oxoimidazolidin-4-yl)methyl 4-methoxybenzoate (34aq'):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 4.67 (br s, 1H), 4.33 (dd, *J* = 11.1, 4.8 Hz, 1H), 4.20 (dd, *J* = 11.1, 6.9 Hz, 1H), 4.03-3.99 (m, 1H), 3.85 (s, 3H), 3.58 (t, *J* = 9.0 Hz, 1H), 3.45 (s,), 3.24-3.12 (m, 3H), 1.29-1.23 (m, 12H), 0.87-0.84 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0 (C), 163.7 (C), 161.4 (C), 131.8 (CH), 121.8 (C), 113.8 (CH), 66.3 (CH_2), 55.5 (CH_3), 48.6 (CH), 47.4 (CH_2), 43.4 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.6 (CH_2), 26.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

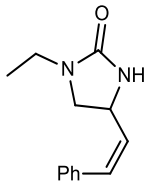
IR (film): 3205, 2920, 2855, 1681, 1605, 1455, 1255, 1118 cm^{-1}.



1,1-diisobutyl-3-methylurea (35a): The title compound was synthesized according general procedure **D** using diisobutylamine (0.87 mL, 5.0 mmol), toluene (0.8 M), KOH pellets (0.280 g, 5.00 mmol), and water (2.9 M) at 0 °C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (8.2 mL, 11.5 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon competition, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-diisobutylcarbamoyl chloride which was used in the next step without further purification.
To the crude *N*-diisobutylcarbamoyl chloride was added CH_2Cl_2 (0.3 M) and cooled to 0 °C. To this was added methylamine hydrochloride (0.338 g, 5.00 mmol), and followed immediately by Et_3N (1.39 mL, 10.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with $NaHCO_3$ (5.0 mL x1), and then brine (5.0 mL x1). The organic phase was collected and dried with Na_2SO_4. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure which was purified by flash column chromatography (30% EtOAc/Hexanes → 70% EtOAc/Hexanes) to yield a colourless oil (0.507 g, 54% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33-4.20 (br s, 1H), 3.2 (d, *J* = 7.5 Hz, 2H), 2.79 (d, *J* = 4.7 Hz, 4H), 2.08-1.78 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0 (C), 55.7 (CH_2), 27.7 (CH), 27.0 (CH), 20.4 (CH_3).



(Z)-1-Ethyl-4-styrylimidazolidin-2-one (34ar): The title compound was synthesized according to general procedure **JJ** using (*E*)-1-ethyl-3-((4-methoxybenzoyl)oxy)-1-(4-phenylbut-3-en-1-yl)urea (0.074 g, 0.20 mmol), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.003 g, 2 mol%), triethylamine (0.022 g, 0.22 mmol) in MeCN (1.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Analysis of the crude NMR revealed a 4:1 ratio of Z:E olefin totaling 64%. The title compound was purified by column chromatography (5% MeOH/CH_2Cl_2 + 1% Et_3N) to yield a clear oil (0.026 g, 45%).

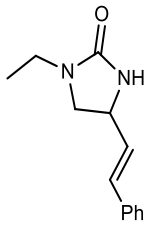
TLC R_f: 0.23 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (600 MHz, DMSO-d_6): δ 7.40-7.37 (m, 2H), 7.32-7.28 (m, 3H), 6.73 (br s, 1H), 6.60 (d, *J* = 11.5 Hz, 1H), 5.67 (dd, *J* = 11.5, 9.3 Hz, 1H), 4.46-4.42 (m, 1H), 3.62 (t, *J* = 8.6 Hz, 1H), 3.13 (dq, *J* = 13.9, 7.0 Hz, 1H), 3.07-3.01 (m, 2H), 1.01 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, DMSO-d_6): δ 161.6 (C), 136.3 (C), 133.1 (CH), 131.5 (CH), 129.06 (CH), 128.88 (CH), 127.9 (CH), 50.4 (CH), 47.4 (CH_2), 37.9 (CH_2), 13.1 (CH_3).

IR (film): 3230, 2922, 2857, 1680, 1486, 1449, 1243 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{21}H_{24}N_2O_4Na$ $[M]^+$: 391.1634. Found: 391.1620.



(*E*)-1-Ethyl-4-styrylimidazolidin-2-one (34as): The title compound was synthesized according to general procedure **JJ** using (*E*)-1-ethyl-3-((4-methoxybenzoyl)oxy)-1-(4-phenylbut-3-en-1-yl)urea (0.074 g, 0.20 mmol), tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate (0.003 g, 2 mol%), triethylamine (0.022 g, 0.22 mmol) in MeCN (1.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (5% MeOH/CH_2Cl_2 + 1% Et_3N) to yield a clear oil (0.013 g, 22%).

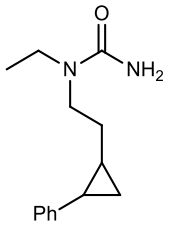
TLC R_f: 0.23 in 10% EtOAc/CH_2Cl_2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.24 (m, 5H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.19 (dd, *J* = 15.8 Hz, 7.7 Hz, 1H), 4.56-4.46 (br s, 1H), 4.32 (app q, *J* = 7.7 Hz, 1H), 3.65 (t, *J* = 8.7 Hz, 1H), 3.37-3.16 (m, 3H), 1.13 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5 (C), 136.9 (C), 136.1 (CH), 132.4 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 127.0 (CH), 52.7 (CH), 50.7 (CH_2), 38.1 (CH_2), 12.8 (CH_3).

IR (film): 3232, 2925, 2852, 1680, 1485, 1449, 1247 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{16}N_2O$ $[M]^+$: 216.1263. Found: 216.1250.



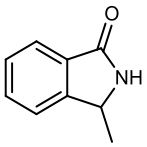
1-Ethyl-1-(2-(2-phenylcyclopropyl)ethyl)urea (34at): The title compound was synthesized according to general procedure **JJ** using 1-ethyl-3-((4-methoxybenzoyl)oxy)-2-phenylcyclopropyl)ethyl)urea (0.115 g, 0.30 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.005 g, 2 mol%), triethylamine (0.033 g, 0.33 mmol) in MeCN (1.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (100% EtOAc) to yield a clear oil (0.021 g, 30%).

TLC R_f: 0.14 in 100% EtOAc.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (t, *J* = 7.7 Hz, 2H), 7.20 (t, *J* = 8.2 Hz, 3H), 4.42 (s, 1H), 2.86-2.81 (m, 1H), 2.22-2.18 (m, 1H), 1.66-1.61 (m, 1H), 1.13-0.97 (m, 7H), 0.82 (t, *J* = 5.4 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 158.2 (C), 138.4 (C), 128.7 (CH), 128.3 (CH), 126.1 (CH), 46.3 (CH_2), 42.0 (CH_2), 26.9 (CH_2), 20.7 (CH), 16.3 (CH), 13.2 (CH_3), 8.9 (CH_2).

HRMS (EI): Exact mass calcd for $C_{14}H_{20}N_2O$ $[M]^+$: 232.1576. Found: 232.1578.



3-Methylisoindolin-1-one (34au): The title compound was synthesized according to general procedure **JJ** using 2-ethyl-N-((4-methoxybenzoyl)oxy)benzamide (0.150 g, 0.50 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), tetrabutylammonium dibutyl phosphate (0.011 g, 5 mol%) in CH_2Cl_2 (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was diluted in CH_2Cl_2 (5.0 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid.

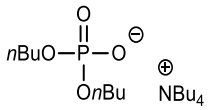
The organic phase was collected, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.048 g, 65%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.58 (td, *J* = 7.5, 1.2 Hz, 1H), 7.52 – 7.40 (m, 2H), 6.73-6.57 (br s, 1H), 4.70 (q, J = 6.7 Hz, 1H), 1.51 (d, J = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7 (C), 149.0 (C), 132.1 (CH), 131.6 (C), 128.3 (CH), 124.0 (CH), 122.3 (CH), 52.6 (CH), 20.5 (CH_3).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.[150]

Synthesis of tetrabutylammonium dibutyl phosphate base



Tetrabutylammonium dibutyl phosphate (SI17): The title compound was synthesized according to a literature procedure.[279]

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (q, *J* = 6.6 Hz, 4H), 3.44-3.31 (m, 8H), 1.75-1.52 (m, 12H), 1.51-1.29 (m, 12H), 0.99 (t, *J* = 7.3 12H), 0.89 (t, *J* = 7.3 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 64.7 (CH_2), 59.0 (CH_2), 33.3 (CH_2), 24.3 (CH_2), 19.0 (CH_2), 19.3 (CH_2), 14.0 (CH_3), 13.8 (CH_3).

^{31}P NMR (121 MHz, CDCl3): δ -2.26 (s).

The ^{1}H NMR and ^{13}C NMR is in agreement with previous reports.

DFT studies

Density functional theory (DFT) calculations have been performed using WebMO (G09). Optimized molecular geometries were calculated using the B3LYP[317] exchange-correlation functional. The 6-311+G(2d,p) basis set was used for calculations. Vibrational frequency calculations were performed to ensure that the stationary points and to calculate vibrational zero point energy. The unscaled frequencies were used for calculating enthalpies and BDEs (at 298 K and 1 atm).

DFT studies on the Cope-type hydroamination reaction (5 vs 6 membered rings)

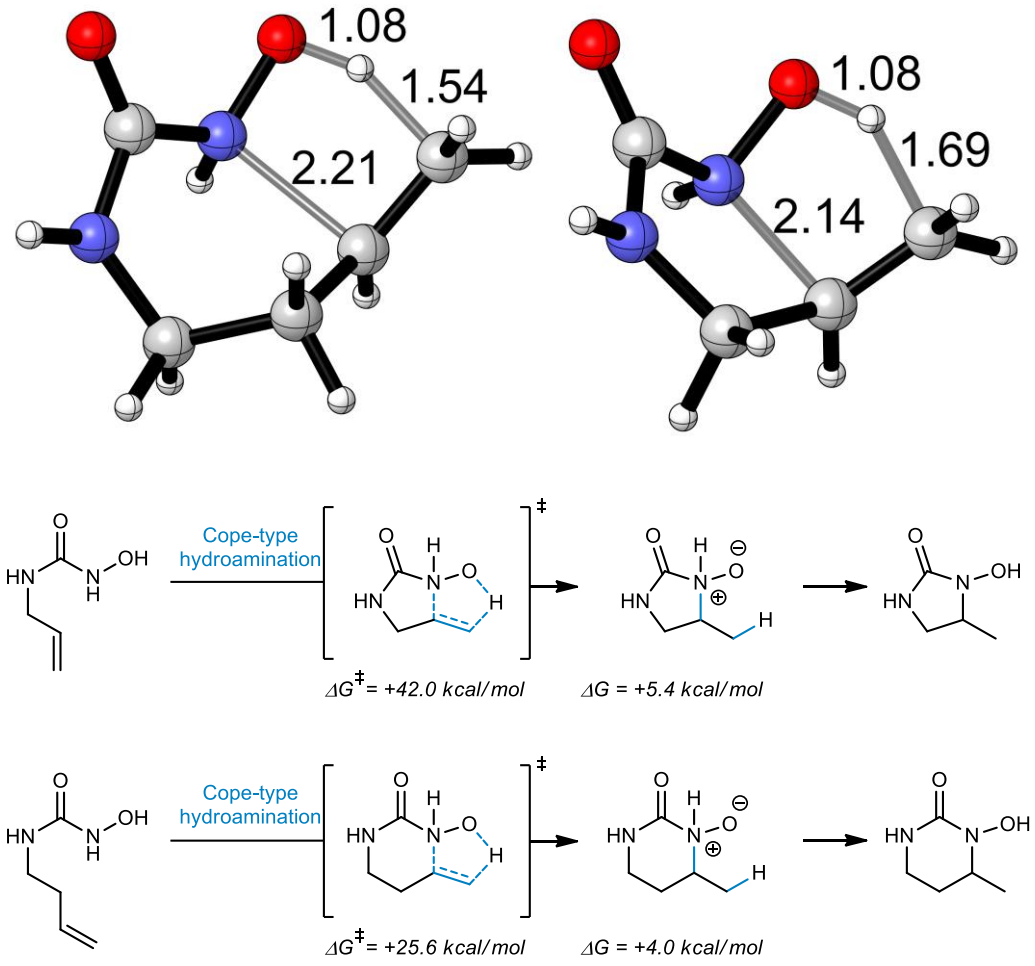
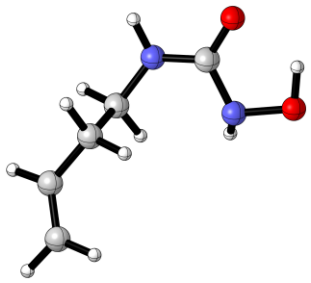


Figure 134 Transition state geometries for 5- and 6-membered Cope-type hydroaminations.

The reaction was studied *post facto* by DFT to provide support for the concerted cyclization pathways and to attempt to understand the limited reactivity in the homoallylic system (**Figure 134**). DFT predicted that the transition state for the 6-membered cyclization was in fact lower than the 5-membered transition state ($\Delta\Delta G^{\ddagger}$ = 16.4 kcal/mol). While this was unintuitive based on observed yields, this made sense from a structural standpoint. Orbital overlap required to form the 5-membered product was complicated by the planarity enforced by the urea and thus

required a highly strained conformer to enter the transition state. Therefore, it was speculated that the lower yield of cyclization for 6-membered Cope-type hydroaminations was due to the increased number of unfavorable conformational isomers inherent to the longer alkyl chain.

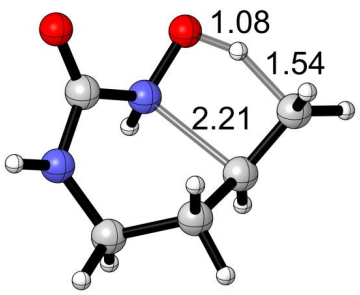


Quantity	Value
Job History	42431,42446,42450,42468
Route	#N B3LYP/6-31G(d) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Connectivi
Stoichiometry	$C_5H_{10}N_2O_2$
Symmetry	C1
Basis	6-31G(d)
RB3LYP Energy	-456.442559678 Hartree
ZPE	0.157973 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-456.274313 Hartree
Enthalpy	-456.273368 Hartree
Free Energy	-456.321393 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.542905
3	6	0	1.396874	0.000000	2.102604
4	6	0	1.923480	0.977089	2.843268
5	1	0	2.942735	0.925353	3.217496

6	1	0	1.351649	1.864384	3.109107
7	1	0	2.007604	-0.871436	1.860069
8	1	0	-0.555010	0.873756	1.902099
9	1	0	-0.539574	-0.895555	1.882117
10	7	0	-1.335987	-0.080720	-0.590910
11	6	0	-2.249782	0.922116	-0.663184
12	7	0	-1.786897	2.216576	-0.374499
13	8	0	-2.751799	3.200416	-0.727985
14	1	0	-3.498980	2.634630	-1.037451
15	1	0	-0.917647	2.468751	-0.840474
16	8	0	-3.443666	0.747459	-0.939593
17	1	0	-1.752484	-1.000113	-0.669087
18	1	0	0.563441	-0.857693	-0.379296
19	1	0	0.512187	0.891964	-0.374695

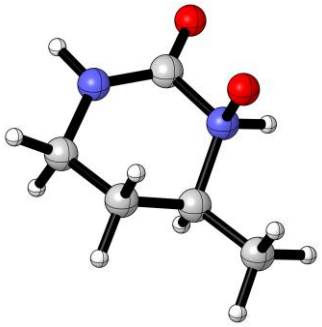


Quantity	Value
Job History	42431,42432,42433,42435,42437,42438,42439,42440,42442
Route	#N B3LYP/6-31G(d) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Connectivi
Stoichiometry	$C_5H_{10}N_2O_2$
Symmetry	C1
Basis	6-31G(d)
RB3LYP Energy	-456.403818613 Hartree
ZPE	0.155377 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-456.240279 Hartree
Enthalpy	-456.239335 Hartree
Free Energy	-456.281173 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	7	0	0.000000	0.000000	1.468401
3	6	0	1.132818	0.000000	2.227592
4	7	0	2.234723	0.631786	1.549635
5	8	0	3.449922	0.399168	2.051683

6	1	0	3.838182	-0.387869	1.069964
7	1	0	2.065192	1.602674	1.282350
8	8	0	1.226889	-0.488115	3.342457
9	1	0	-0.771222	-0.476043	1.920243
10	6	0	1.115318	-0.888602	-0.584860
11	6	0	2.476697	-0.274527	-0.454684
12	6	0	3.676099	-0.932802	-0.120773
13	1	0	4.578936	-0.596343	-0.633068
14	1	0	3.627701	-2.012934	0.030258
15	1	0	2.564670	0.707857	-0.919833
16	1	0	1.081619	-1.882158	-0.122185
17	1	0	0.904393	-1.025132	-1.656154
18	1	0	-0.981372	-0.363115	-0.312162
19	1	0	0.100402	1.022112	-0.385560

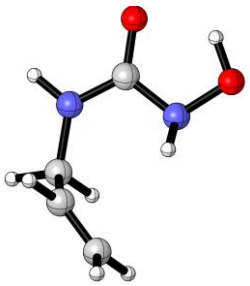


Quantity	Value
Job History	42431,42447
Route	#N B3LYP/6-31G(d) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Connectivi
Stoichiometry	$C_5H_{10}N_2O_2$
Symmetry	C1
Basis	6-31G(d)
RB3LYP Energy	-456.444359093 Hartree
ZPE	0.162329 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-456.273536 Hartree
Enthalpy	-456.272592 Hartree
Free Energy	-456.314953 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	7	0	0.000000	0.000000	1.470518
3	6	0	1.064986	0.000000	2.289452
4	7	0	2.354965	-0.427478	1.643783

5	8	0	2.425763	-1.790820	1.789264
6	1	0	3.086780	0.043531	2.200998
7	6	0	2.500862	0.033508	0.194476
8	6	0	1.309999	-0.555210	-0.551887
9	1	0	1.346253	-1.641199	-0.433976
10	1	0	1.380537	-0.316933	-1.616856
11	1	0	2.441126	1.129500	0.221935
12	6	0	3.856368	-0.416199	-0.328696
13	1	0	3.941226	-1.502556	-0.256850
14	1	0	4.672342	0.040729	0.242748
15	1	0	3.966198	-0.113529	-1.374400
16	8	0	1.068336	0.230403	3.485963
17	1	0	-0.868899	0.239948	1.933774
18	1	0	-0.849802	-0.599543	-0.337948
19	1	0	-0.157293	1.028394	-0.350370

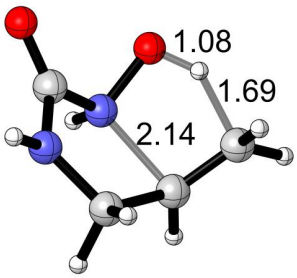


Quantity	Value
Job History	42431,42432,42433,42435,42437,42438,42439,42440,42442,42445,42448,42452
Route	#N B3LYP/6-31G(d) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Connectivi
Stoichiometry	$C_4H_8N_2O_2$
Symmetry	C1
Basis	6-31G(d)
RB3LYP Energy	-417.129307114 Hartree
ZPE	0.129270 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-416.991118 Hartree
Enthalpy	-416.990174 Hartree
Free Energy	-417.034137 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	7	0	0.000000	0.000000	1.464681
3	6	0	1.098555	0.000000	2.260580
4	7	0	2.333507	-0.033800	1.595973

5	8	0	3.406969	-0.234374	2.506831
6	1	0	2.927390	-0.257634	3.368917
7	1	0	2.398257	-0.750210	0.873079
8	8	0	1.061040	0.079096	3.495777
9	1	0	-0.879197	0.064871	1.958378
10	6	0	0.408891	-1.327404	-0.593871
11	6	0	1.387565	-1.475545	-1.489791
12	1	0	1.637549	-2.447151	-1.906703
13	1	0	1.964610	-0.625805	-1.850529
14	1	0	-0.155471	-2.192618	-0.247036
15	1	0	-1.022144	0.246794	-0.303919
16	1	0	0.653646	0.799154	-0.369839

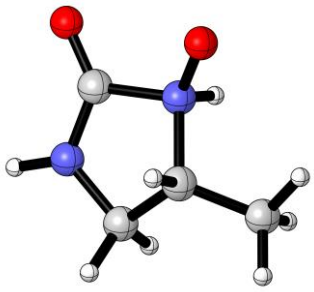


Quantity	Value
Job History	42437,42438,42439,42440,42442,42445,42448,42453,42461,42462,42466
Route	#N B3LYP/6-31G(d) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Connectivi
Stoichiometry	$C_4H_8N_2O_2$
Symmetry	C1
Basis	6-31G(d)
RB3LYP Energy	-417.06127852 Hartree
ZPE	0.125587 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-416.928691 Hartree
Enthalpy	-416.927747 Hartree
CPU time	216.5 sec

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	7	0	0.000000	0.000000	1.479527
3	6	0	1.161194	0.000000	2.184955
4	7	0	2.219765	0.515627	1.307565
5	8	0	3.286322	-0.362601	1.479101

6	1	0	3.146978	-0.932056	0.575977
7	1	0	2.669489	1.556614	1.555421
8	6	0	1.413732	-0.083693	-0.583751
9	6	0	2.211263	-1.183022	-0.809778
10	1	0	1.771496	-2.190420	-0.884301
11	1	0	3.032813	-1.036562	-1.512136
12	1	0	1.620975	0.830714	-1.132324
13	8	0	1.302451	-0.441273	3.306932
14	1	0	-0.801278	-0.402593	1.953048
15	1	0	-0.636563	-0.830361	-0.354745
16	1	0	-0.465298	0.947076	-0.322505



Quantity	Value
Job History	42431,42432,42433,42435,42437,42438,42439,42440,42442,42445,42448,42454
Route	#N B3LYP/6-31G(d) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Connectivi
Stoichiometry	$C_4H_8N_2O_2$
Symmetry	C1
Basis	6-31G(d)
RB3LYP Energy	-417.126204388 Hartree
ZPE	0.132511 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-416.986203 Hartree
Enthalpy	-416.985259 Hartree
Free Energy	-417.025476 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	7	0	0.000000	0.000000	1.463327
3	6	0	1.209722	0.000000	2.041408
4	7	0	2.232836	-0.019664	0.876945

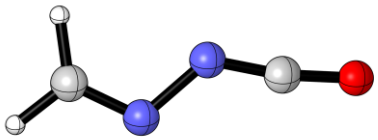
5	8	0	3.348726	-0.730448	1.120955
6	1	0	2.450765	0.982535	0.708016
7	6	0	1.412435	-0.507113	-0.311966
8	6	0	2.036465	-0.081978	-1.624727
9	1	0	1.508364	-0.543662	-2.464533
10	1	0	2.001072	1.005903	-1.753781
11	1	0	3.079855	-0.409869	-1.645356
12	1	0	1.452809	-1.592400	-0.188186
13	8	0	1.548090	0.013213	3.199834
14	1	0	-0.841520	0.082038	2.019729
15	1	0	-0.770175	-0.669457	-0.388873
16	1	0	-0.177115	1.008322	-0.394198

DFT calculations for FMO analysis of π-systems

Density functional theory (DFT) calculations have been performed using WebMO (G09). Optimized molecular geometries were calculated using the B3LYP[317] exchange-correlation functional. The 6-311+G(2d,p) basis set was used for calculations. Natural bond orbital (NBO) calculations were used to determing HOMO and LUMO energies. For NBO calculations the w-B97XD[318] functional was used with the CC-pVDZ basis set using MeCN as solvent (PCM). The results of the NBO calculations are summarized in the table below. Input orientations and calculation history are provided.

Table 49 NBO calculations for π-systems.

	Reagent	HOMO	LUMO
Job#		Hartree	Hartree
42535	*N*,*N*-dimethylaminoisocyanate	-0.23619	-0.03058
42527	imino-isocyanate	-0.28787	-0.05198
42521	methoxy isocyanate	-0.26592	-0.0693
42539	chlorosulfonyl isocyanate	-0.34403	-0.1123
42611	dimethyl ketene	-0.29133	0.05087
42524	dihydrofuran	-0.29001	0.10831
42526	norbornene	-0.24479	-0.00067

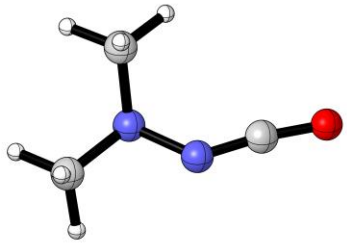


Natural bond orbital calculation of imino isocyanate

Quantity	Value
Job History	22765,42517,42525,42527,42592
Route	#N wB97XD/cc-pVDZ SP GFINPUT POP=(FULL,NBORead) SCRF=(PCM,Solvent=Acet
Stoichiometry	$C_2H_2N_2O$
Symmetry	CS
Basis	CC-pVDZ
RwB97XD Energy	-262.009023684 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	7	0	0.000000	0.000000	1.271314
3	7	0	1.283784	0.000000	1.826054
4	6	0	1.585176	0.000000	3.001726
5	8	0	2.041211	0.000000	4.076690
6	1	0	0.906391	0.000000	-0.601115
7	1	0	-0.970030	0.000000	-0.482521

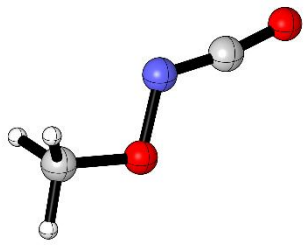


Natural bond orbital calculation of *N*,*N*-dimethylamino isocyanate

Quantity	Value
Job History	22763,22764,42516,42523,42528,42535
Route	#N wB97XD/cc-pVDZ SP GFINPUT POP=(FULL,NBORead) SCRF=(PCM,Solvent=Acet
Stoichiometry	$C_3H_6N_2O$
Symmetry	C1
Basis	CC-pVDZ
RwB97XD Energy	-302.525336073 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	7	0	0.000000	0.000000	1.465922
3	6	0	1.359619	0.000000	2.018766
4	1	0	1.309749	-0.058329	3.106102
5	1	0	1.869380	-0.888072	1.646175
6	1	0	1.927874	0.892404	1.726314
7	7	0	-0.715481	1.141838	1.903222
8	6	0	-0.954744	1.589725	2.994940
9	8	0	-1.263184	2.146867	3.984813
10	1	0	0.536358	0.861014	-0.419652
11	1	0	0.482398	-0.918697	-0.331716
12	1	0	-1.028352	0.007557	-0.357468

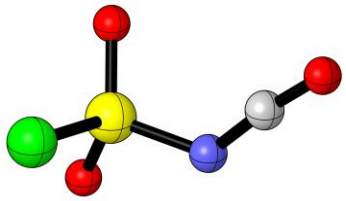


Natural bond orbital calculation of methoxy isocyanate

Quantity	Value
Job History	19109,19111,19274,42519,42519,42521,42590
Route	#N wB97XD/cc-pVDZ SP GFINPUT POP=(FULL,NBORead) SCRF=(PCM,Solvent=Acet
Stoichiometry	$C_2H_3NO_2$
Symmetry	CS
Basis	CC-pVDZ
RwB97XD Energy	-283.053186089 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.435514
3	7	0	1.338375	0.000000	1.879588
4	6	0	1.598149	0.000000	3.073548
5	8	0	2.019023	0.000000	4.162682
6	1	0	-1.054984	0.000000	-0.267469
7	1	0	0.488155	0.896739	-0.383991
8	1	0	0.488155	-0.896739	-0.383991

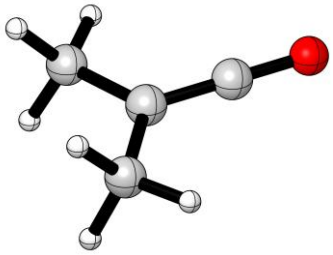


Natural bond orbital calculation of chlorosulfonyl isocyanate

Quantity	Value
Job History	42532,42537,42539
Route	#N wB97XD/cc-pVDZ SP GFINPUT POP=(FULL,NBORead) SCRF=(PCM,Solvent=Acet
Stoichiometry	$CClNO_3S$
Symmetry	C1
Basis	CC-pVDZ
RwB97XD Energy	-1176.74230102 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	0.000000	0.000000	0.000000
2	7	0	0.000000	0.000000	1.655870
3	6	0	0.982944	0.000000	2.389359
4	8	0	1.828642	-0.005466	3.169220
5	8	0	-1.299994	-0.440173	-0.403165
6	8	0	1.200698	-0.592104	-0.515924
7	17	0	0.103081	2.038563	-0.392823

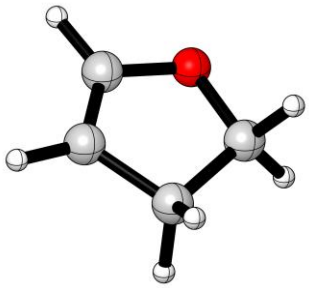


Natural bond orbital calculation of dimethylketene

Quantity	Value
Job History	42608,42609
Route	#N wB97XD/cc-pVDZ SP GFINPUT POP=(FULL,NBORead) SCRF=(PCM,Solvent=Acet
Stoichiometry	C_4H_6O
Symmetry	C1
Basis	CC-pVDZ
RwB97XD Energy	-231.167432385 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.763886	1.306635	-0.000021
3	6	0	0.000076	2.613318	0.000011
4	1	0	0.662462	3.479102	0.000055
5	1	0	-0.642406	2.678141	-0.883460
6	1	0	-0.642438	2.678078	0.883463
7	6	0	2.070310	1.306604	-0.000004
8	8	0	3.243537	1.306618	0.000020
9	1	0	0.662335	-0.865824	-0.000010
10	1	0	-0.642485	-0.064751	0.883474
11	1	0	-0.642518	-0.064756	-0.883450

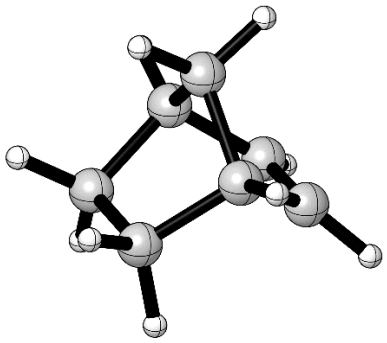


Natural bond orbital calculation of dihydrofuran

Quantity	Value
Job History	19116,19363,42524,42602
Route	#N wB97XD/cc-pVDZ SP GFINPUT POP=(FULL,NBORead) SCRF=(PCM,Solvent=Acet
Stoichiometry	C_4H_6O
Symmetry	C1
Basis	CC-pVDZ
RwB97XD Energy	-231.163399011 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.456611
3	6	0	1.310412	0.000000	1.845246
4	6	0	2.195920	-0.131871	0.864674
5	6	0	1.452420	-0.286833	-0.443402
6	1	0	1.566524	-1.295000	-0.856141
7	1	0	1.782759	0.415517	-1.212369
8	1	0	3.266933	-0.172540	0.984702
9	1	0	1.464615	0.095107	2.910229
10	1	0	-0.719027	-0.749447	-0.327180
11	1	0	-0.339187	0.986769	-0.323251



Natural bond orbital calculation of norbornene

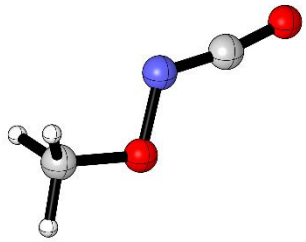
Quantity	Value
Job History	19110,19114,19263,19266,42526
Route	#N wB97XD/cc-pVDZ SP GFINPUT POP=(FULL,NBORead) SCRF=(PCM,Solvent=Acet
Stoichiometry	C_7H_{10}
Symmetry	C1
Basis	CC-pVDZ
RwB97XD Energy	-272.663613911 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.520152
3	6	0	1.273813	0.000000	1.923714
4	6	0	2.149056	0.000164	0.680810
5	6	0	1.988240	-1.419626	0.038819
6	6	0	0.501498	-1.419736	-0.432368
7	1	0	0.430681	-1.532361	-1.516434
8	1	0	-0.088859	-2.214997	0.024034
9	1	0	2.670532	-1.532350	-0.806560
10	1	0	2.208038	-2.214816	0.752024
11	6	0	1.269673	0.836175	-0.276009

12	1	0	1.170208	1.876623	0.037657
13	1	0	1.599528	0.793079	-1.317249
14	1	0	3.181564	0.317269	0.817853
15	1	0	1.638844	-0.109763	2.937358
16	1	0	-0.882068	-0.109734	2.138759
17	1	0	-0.923165	0.316834	-0.482490

DFT studies on the intermolecular *O*-isocyanate [3+2] cycloaddition

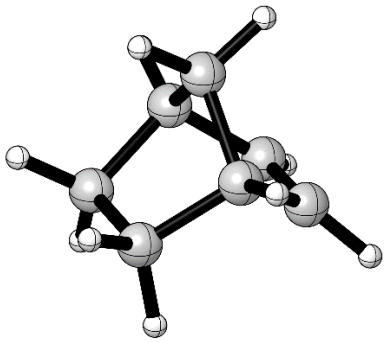


Vibrational frequency calculation of methoxy *O*-isocyanate

Quantity	Value
Job History	19109,19111,36670
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_2H_3NO_2$
Symmetry	CS
Basis	6-311+G(2d,p)
RB3LYP Energy	-283.227246979 Hartree
ZPE	0.053744 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-283.167925 Hartree
Enthalpy	-283.166981 Hartree
Free Energy	-283.202468 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.435514
3	7	0	1.338375	0.000000	1.879588
4	6	0	1.598149	0.000000	3.073548
5	8	0	2.019023	0.000000	4.162682
6	1	0	-1.054984	0.000000	-0.267469
7	1	0	0.488155	0.896739	-0.383991
8	1	0	0.488155	-0.896739	-0.383991



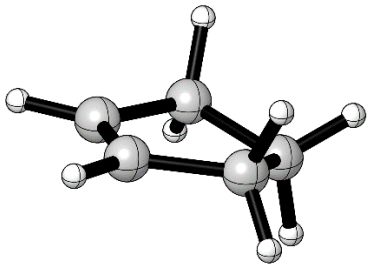
Vibrational frequency calculation of norbornene

Quantity	Value
Job History	19110,19114,19263
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	C_7H_{10}
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-272.806569479 Hartree
ZPE	0.152051 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-272.649278 Hartree
Enthalpy	-272.648334 Hartree
Free Energy	-272.683038 Hartree

Input orientation:

Center Atomic Atomic Coordinates (Angstroms)

Number	Number	Type	X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.520152
3	6	0	1.273813	0.000000	1.923714
4	6	0	2.149056	0.000164	0.680810
5	6	0	1.988240	-1.419626	0.038819
6	6	0	0.501498	-1.419736	-0.432368
7	1	0	0.430681	-1.532360	-1.516435
8	1	0	-0.088859	-2.214997	0.024034
9	1	0	2.670532	-1.532350	-0.806560
10	1	0	2.208038	-2.214816	0.752024
11	6	0	1.269674	0.836175	-0.276009
12	1	0	1.170209	1.876623	0.037657
13	1	0	1.599530	0.793079	-1.317249
14	1	0	3.181564	0.317268	0.817854
15	1	0	1.638844	-0.109763	2.937358
16	1	0	-0.882068	-0.109734	2.138759
17	1	0	-0.923164	0.316834	-0.482491



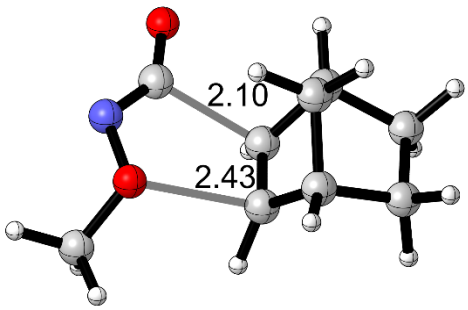
Vibrational frequency calculation of cyclopentene

Quantity	Value
Job History	41863
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	C_5H_8
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-195.387788186 Hartree
ZPE	0.116001 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-195.267113 Hartree
Enthalpy	-195.266169 Hartree
Free Energy	-195.299210 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.510004

3	6	0	1.232619	0.000000	2.011978
4	6	0	2.287540	0.000032	0.931583
5	6	0	1.477113	0.313272	-0.352756
6	1	0	1.829756	-0.248327	-1.218670
7	1	0	1.574624	1.374573	-0.592234
8	1	0	2.778087	-0.979799	0.876797
9	1	0	3.080742	0.730559	1.113188
10	1	0	1.473316	-0.036470	3.068327
11	1	0	-0.910204	-0.036469	2.097659
12	1	0	-0.312680	-0.979850	-0.381887
13	1	0	-0.694422	0.730498	-0.424228



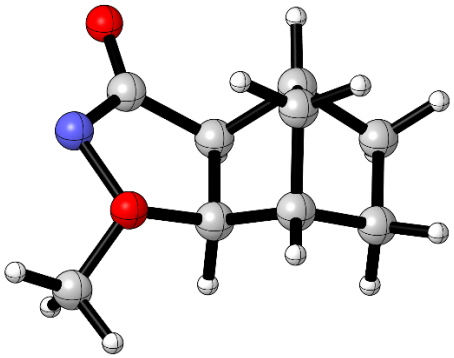
Vibrational frequency calculation of *O*-isocyanate norbornene [3+2] TS

Quantity	Value
Job History	19152,19153,19154,19157,19273
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_9H_{13}NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-556.016741749 Hartree
ZPE	0.207661 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-555.798161 Hartree
Enthalpy	-555.797217 Hartree
Free Energy	-555.846134 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.371954

3	6	0	1.421297	0.000000	1.844463
4	6	0	1.898064	-1.474664	1.557500
5	6	0	1.931644	-1.536221	0.001667
6	6	0	1.469525	-0.105783	-0.412819
7	6	0	2.132192	0.741567	0.690362
8	1	0	3.216692	0.628177	0.726151
9	1	0	1.878099	1.801015	0.643924
10	1	0	1.681822	0.163064	-1.444849
11	1	0	2.942820	-1.727265	-0.362473
12	1	0	1.279566	-2.310145	-0.404700
13	1	0	2.890495	-1.614583	1.989373
14	1	0	1.234530	-2.216443	2.002678
15	1	0	1.599411	0.338348	2.862223
16	8	0	-0.753609	2.291994	1.639856
17	7	0	-0.955771	2.681356	0.319622
18	6	0	-0.559080	1.928262	-0.630501
19	8	0	-0.398870	1.934343	-1.814671
20	6	0	-1.989534	2.385932	2.367408
21	1	0	-2.368347	3.407977	2.333427
22	1	0	-2.730598	1.697457	1.956160
23	1	0	-1.741313	2.111787	3.391205
24	1	0	-0.846173	-0.221545	2.006813
25	1	0	-0.808245	-0.425764	-0.582640



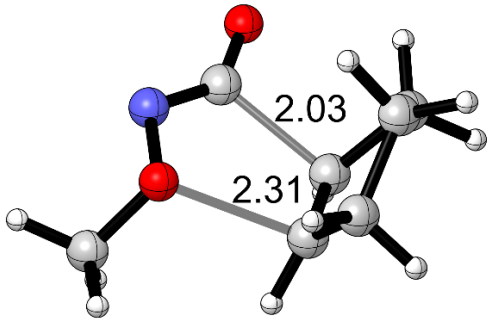
Vibrational frequency calculation of norbornene aza-oxonium ylide

Quantity	Value
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_9H_{13}NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-556.05227638 Hartree
ZPE	0.212701 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-555.829746 Hartree
Enthalpy	-555.828802 Hartree
Free Energy	-555.874492 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000

2	6	0	0.000000	0.000000	1.525032
3	6	0	1.470073	0.000000	1.921831
4	6	0	1.993106	-1.417352	1.567153
5	6	0	2.061459	-1.398616	0.007211
6	6	0	1.512488	0.000410	-0.345081
7	6	0	2.093503	0.856314	0.798841
8	1	0	3.183950	0.848391	0.825305
9	1	0	1.748044	1.890815	0.795973
10	1	0	1.719570	0.329534	-1.361243
11	1	0	3.090693	-1.501648	-0.339977
12	1	0	1.477052	-2.198811	-0.449421
13	1	0	2.979518	-1.561885	2.008174
14	1	0	1.345512	-2.206619	1.953583
15	1	0	1.655011	0.303093	2.950768
16	8	0	-0.619740	1.352150	1.860807
17	7	0	-1.156398	2.034953	0.597723
18	6	0	-0.744337	1.272554	-0.412582
19	8	0	-0.957173	1.570024	-1.603335
20	6	0	-1.662708	1.323960	2.881145
21	1	0	-1.960036	2.355496	3.034866
22	1	0	-2.495420	0.718247	2.529642
23	1	0	-1.205874	0.910629	3.776737
24	1	0	-0.625297	-0.741558	2.014765
25	1	0	-0.524401	-0.850161	-0.436789



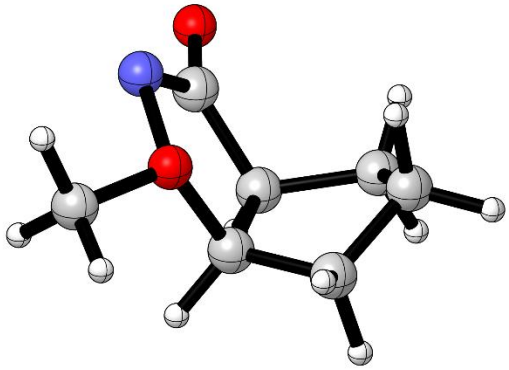
Vibrational frequency calculation of *O*-isocyanate cyclopentene [3+2] TS

Quantity	Value
Job History	41907,41912,41914,41918,41920,41922,41926
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_7H_{11}NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-478.593502355 Hartree
ZPE	0.171874 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-478.412110 Hartree
Enthalpy	-478.411166 Hartree
Free Energy	-478.456322 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.381658
3	6	0	1.394570	0.000000	1.936698
4	6	0	2.275797	0.297564	0.700234
5	6	0	1.432522	-0.205478	-0.492607
6	1	0	1.639608	0.322288	-1.427845
7	1	0	1.604358	-1.275628	-0.673333
8	1	0	3.260519	-0.173945	0.759541
9	1	0	2.429211	1.379868	0.614697
10	1	0	1.532606	0.694906	2.771298
11	1	0	1.595688	-1.010069	2.329164
12	8	0	-0.552768	2.224948	1.701170
13	7	0	-0.694284	2.705486	0.400610
14	6	0	-0.371427	1.917040	-0.568659
15	8	0	-0.211632	1.973373	-1.761408
16	6	0	-1.794170	2.375059	2.410597
17	1	0	-2.084337	3.429140	2.437081
18	1	0	-2.585121	1.782693	1.938464
19	1	0	-1.595675	2.014463	3.421770
20	1	0	-0.872457	-0.185896	1.997724
21	1	0	-0.850934	-0.375168	-0.563226



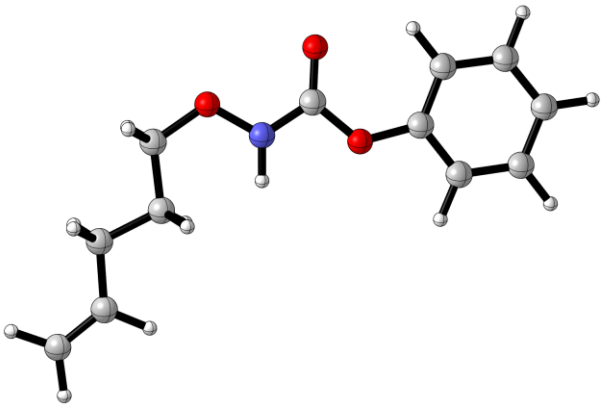
Vibrational frequency calculation of cyclopentene aza-oxonium ylide

Quantity	Value
Job History	19152,19153,19154,19157,19273,19279,41853,41857
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_7H_{11}NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-478.623442032 Hartree
ZPE	0.176706 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-478.437725 Hartree
Enthalpy	-478.436781 Hartree
Free Energy	-478.481042 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.519774
3	6	0	1.444254	0.000000	1.986986
4	6	0	2.210503	0.647399	0.822307
5	6	0	1.488545	0.106344	-0.423328
6	1	0	1.613063	0.734073	-1.305736
7	1	0	1.864389	-0.888563	-0.671601
8	1	0	3.272882	0.403644	0.834549
9	1	0	2.121611	1.735757	0.874539
10	1	0	1.576490	0.492696	2.950974
11	1	0	1.745810	-1.044939	2.108182
12	8	0	-0.605309	1.368833	1.840195
13	7	0	-1.250179	1.980525	0.596231
14	6	0	-0.843690	1.213059	-0.411834
15	8	0	-1.127895	1.460660	-1.598509
16	6	0	-1.560013	1.379936	2.941847
17	1	0	-1.851897	2.415430	3.078402
18	1	0	-2.413645	0.756005	2.684713
19	1	0	-1.029204	1.005335	3.813306
20	1	0	-0.655951	-0.723302	1.996421
21	1	0	-0.481114	-0.884202	-0.416704



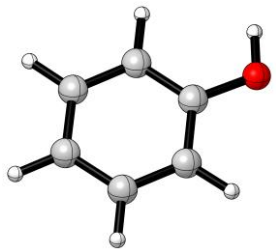
Vibrational frequency calculation of 13a

Quantity	Value
Job History	19214
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_{12}H_{15}NO_3$
Symmetry	CS
Basis	6-311+G(2d,p)
RB3LYP Energy	-746.881977202 Hartree
ZPE	0.250696 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-746.618441 Hartree
Enthalpy	-746.617497 Hartree
Free Energy	-746.673094 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.519800
3	6	0	1.442830	0.000000	2.043423
4	6	0	1.518077	0.000000	3.553568
5	6	0	2.643438	0.000000	4.259699
6	1	0	2.628250	0.000000	5.343094
7	1	0	3.619173	0.000000	3.783264
8	1	0	0.568896	0.000000	4.085048
9	1	0	1.970070	-0.875005	1.650291
10	1	0	1.970070	0.875005	1.650291
11	1	0	-0.512092	0.886473	1.906733
12	1	0	-0.512092	-0.886473	1.906733
13	8	0	-1.289841	0.000000	-0.687176
14	7	0	-2.412575	0.000000	0.137801
15	6	0	-3.615875	0.000000	-0.461466
16	8	0	-4.559811	0.000000	0.533155
17	6	0	-5.936292	0.000000	0.335227
18	6	0	-6.663003	0.000000	1.525250
19	6	0	-8.050444	0.000000	1.487534
20	6	0	-8.719390	0.000000	0.265399
21	6	0	-7.982528	0.000000	-0.912845
22	6	0	-6.587899	0.000000	-0.895612
23	1	0	-6.025656	0.000000	-1.813581
24	1	0	-8.491065	0.000000	-1.869673
25	1	0	-9.801875	0.000000	0.234069
26	1	0	-8.607910	0.000000	2.416368
27	1	0	-6.129478	0.000000	2.467404
28	8	0	-3.815775	0.000000	-1.658404
29	1	0	-2.293760	0.000000	1.137794
30	1	0	0.516779	-0.887115	-0.371517
31	1	0	0.516779	0.887115	-0.371517



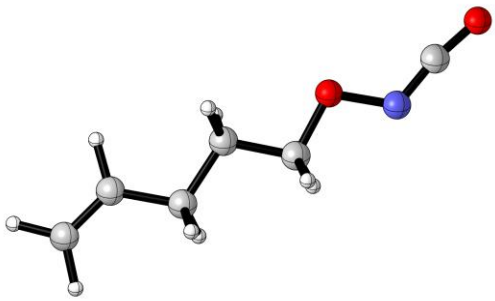
Vibrational frequency calculation of phenol

Quantity	Value
Job History	19218,19219
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	C_6H_6O
Symmetry	CS
Basis	6-311+G(2d,p)
RB3LYP Energy	-307.573334305 Hartree
ZPE	0.104166 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-307.463641 Hartree
Enthalpy	-307.462697 Hartree
Free Energy	-307.498157 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.393615
3	6	0	1.214068	0.000000	2.074250
4	6	0	2.417853	0.000000	1.375714

5	6	0	2.406337	0.000000	-0.018321
6	6	0	1.195394	0.000000	-0.709196
7	1	0	1.203151	0.000000	-1.792445
8	8	0	3.557200	0.000000	-0.761735
9	1	0	4.326186	0.000000	-0.177020
10	1	0	3.362293	0.000000	1.909354
11	1	0	1.230816	0.000000	3.157737
12	1	0	-0.934234	0.000000	1.941098
13	1	0	-0.938148	0.000000	-0.542444



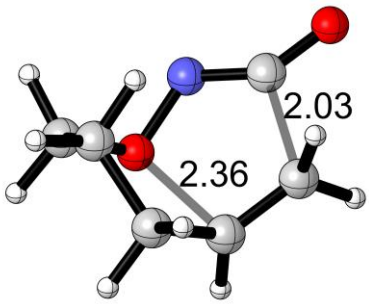
Vibrational frequency calculation of alkenyl *O*-isocyanate

Quantity	Value
Job History	19169,19207
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_6H_9NO_2$
Symmetry	CS
Basis	6-311+G(2d,p)
RB3LYP Energy	-439.295655139 Hartree
ZPE	0.143157 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-439.142736 Hartree
Enthalpy	-439.141791 Hartree
Free Energy	-439.189420 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.516415

3	6	0	1.422913	0.000000	2.085365
4	6	0	1.451869	0.000000	3.597291
5	6	0	2.551647	0.000000	4.340235
6	1	0	3.543178	0.000000	3.897894
7	1	0	2.501382	0.000000	5.422158
8	1	0	0.485713	0.000000	4.097286
9	1	0	1.965454	-0.875118	1.711269
10	1	0	1.965454	0.875118	1.711269
11	1	0	-0.543339	0.879253	1.875334
12	1	0	-0.543339	-0.879253	1.875334
13	8	0	-1.376863	0.000000	-0.413734
14	7	0	-1.415713	0.000000	-1.824845
15	6	0	-2.492747	0.000000	-2.405468
16	8	0	-3.423352	0.000000	-3.108198
17	1	0	0.493719	-0.889289	-0.403578
18	1	0	0.493719	0.889289	-0.403578



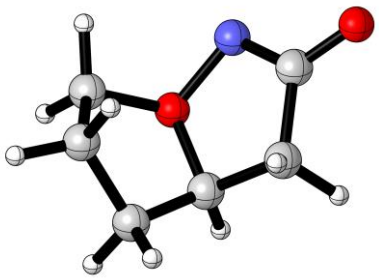
Vibrational frequency calculation of intramolecular *O*-isocyanate [3+2] TS

Quantity	Value
Job History	19156,19161(19161),19178(19161),19181,19202,19206
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_6H_9NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-439.276351257 Hartree
ZPE	0.145014 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-439.123342 Hartree
Enthalpy	-439.122398 Hartree
Free Energy	-439.164019 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	2.357787

3	6	0	1.445360	0.000000	2.498434
4	6	0	2.086834	0.611686	1.266785
5	6	0	1.500984	-0.051058	0.003803
6	1	0	1.833227	-1.089312	-0.049824
7	1	0	1.882802	0.465021	-0.881669
8	1	0	1.906664	1.688628	1.245616
9	1	0	3.169088	0.467163	1.306212
10	1	0	1.712792	0.519538	3.418258
11	1	0	1.692555	-1.058018	2.595598
12	7	0	-0.543156	1.247478	2.627766
13	6	0	-1.060368	1.939949	1.678221
14	6	0	-0.726302	1.151147	-0.157518
15	1	0	-1.779903	1.074937	-0.395720
16	1	0	-0.224815	2.049303	-0.501034
17	8	0	-1.690970	2.945371	1.530932
18	1	0	-0.530999	-0.942056	0.066385



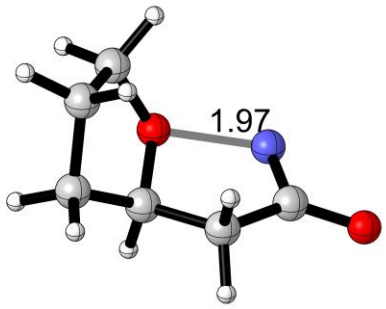
Vibrational frequency calculation of intramolecular oxonium ylide

Quantity	Value
Job History	19156,19213
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_6H_9NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-439.30380681 Hartree
ZPE	0.148877 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-439.147423 Hartree
Enthalpy	-439.146479 Hartree
Free Energy	-439.187483 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.550343
3	6	0	1.417531	0.000000	2.028476

4	6	0	2.223572	0.461317	0.833369
5	6	0	1.471941	-0.167323	-0.349908
6	1	0	1.721547	-1.225382	-0.438696
7	1	0	1.698657	0.316369	-1.299353
8	1	0	2.230789	1.550522	0.768814
9	1	0	3.255285	0.117365	0.896729
10	1	0	1.435492	0.642030	2.901464
11	1	0	1.614017	-1.035488	2.299480
12	7	0	-0.773969	1.198894	2.080771
13	6	0	-1.155844	1.889522	1.007846
14	6	0	-0.669897	1.312691	-0.323789
15	1	0	-1.522382	1.180863	-0.989015
16	1	0	0.009998	2.031885	-0.784384
17	8	0	-1.842508	2.924262	1.084230
18	1	0	-0.611072	-0.863740	-0.243236



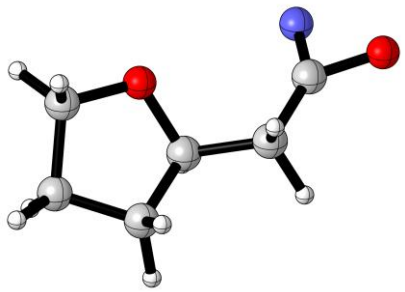
Vibrational frequency calculation of intramolecular N-O bond cleavate TS

Quantity	Value
Job History	19156,19213,19225,19232,19235,19238,19245,42645
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_6H_9NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-439.269013937 Hartree
ZPE	0.146399 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-439.115139 Hartree
Enthalpy	-439.114195 Hartree
Free Energy	-439.155139 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.445073
3	6	0	1.359481	0.000000	1.950671

4	6	0	2.266066	0.192973	0.736376
5	6	0	1.421073	-0.388578	-0.406806
6	1	0	1.510428	-1.476148	-0.434366
7	1	0	1.695199	-0.000617	-1.388105
8	1	0	2.468728	1.252929	0.570873
9	1	0	3.222600	-0.315811	0.853045
10	1	0	1.450774	0.794201	2.692147
11	1	0	1.532958	-0.962133	2.439760
12	7	0	-1.390407	1.389060	1.579903
13	6	0	-1.452710	1.956838	0.408086
14	6	0	-0.430902	1.388366	-0.498827
15	1	0	-0.832061	1.349726	-1.513989
16	1	0	0.409826	2.090032	-0.509805
17	8	0	-2.356769	2.874232	0.239780
18	1	0	-0.740000	-0.737351	-0.314518



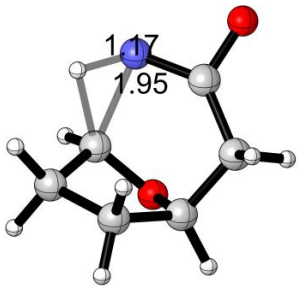
Vibrational frequency calculation of intramolecular acyl nitrene

Quantity	Value
Job History	19156,19216,19253
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_6H_9NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-439.274398208 Hartree
ZPE	0.145786 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-439.119635 Hartree
Enthalpy	-439.118691 Hartree
Free Energy	-439.164381 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.438124

3	6	0	1.359558	0.000000	1.932841
4	6	0	2.256392	-0.213415	0.713724
5	6	0	1.417386	0.390319	-0.417497
6	1	0	1.677525	0.005724	-1.403584
7	1	0	1.520358	1.478875	-0.434275
8	1	0	3.228828	0.265535	0.827337
9	1	0	2.419551	-1.279211	0.539125
10	1	0	1.551926	0.964191	2.412548
11	1	0	1.453542	-0.788540	2.681027
12	6	0	-1.083459	0.948445	-0.501220
13	6	0	-2.446517	0.563875	-0.091257
14	7	0	-3.075013	-0.270031	0.605769
15	8	0	-3.624161	1.065649	-0.402193
16	1	0	-1.080622	0.993322	-1.595102
17	1	0	-0.909036	1.966705	-0.138851
18	1	0	-0.224055	-1.015762	-0.347915



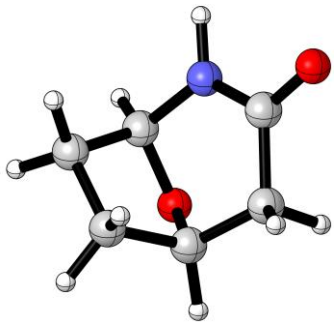
Vibrational frequency calculation of intramolecular C-H amination TS

Quantity	Value
Job History	19172,23163,23164,23165,23167,23168,23169,23170,23171,23172,23173,23174,23175,23176
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_6H_9NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-439.262129294 Hartree
ZPE	0.141355 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-439.114120 Hartree
Enthalpy	-439.113176 Hartree
Free Energy	-439.151765 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.462777

3	6	0	1.367194	0.000000	1.829689
4	6	0	2.007745	-1.105833	0.891899
5	6	0	1.207409	-0.868729	-0.418980
6	1	0	0.874184	-1.817952	-0.860719
7	1	0	1.825637	-0.353757	-1.185485
8	1	0	1.827528	-2.128414	1.309544
9	1	0	3.103517	-0.990664	0.754262
10	7	0	2.100317	1.774452	1.479583
11	6	0	1.181926	2.169017	0.418955
12	6	0	0.137277	1.462588	-0.402952
13	1	0	0.383787	1.573659	-1.490064
14	1	0	-0.812899	2.025117	-0.266075
15	8	0	1.280879	3.463331	0.553783
16	1	0	2.811919	0.842551	1.432287
17	1	0	1.459402	-0.166042	2.936665
18	1	0	-0.955510	-0.414940	-0.308459



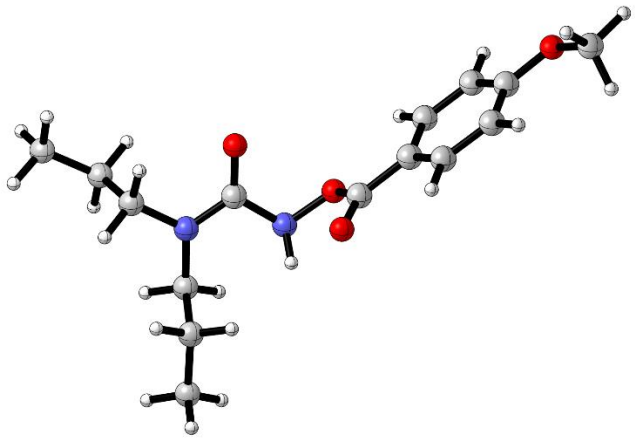
Vibrational frequency calculation of major product 26a

Quantity	Value
Job History	19172
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_6H_9NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-439.41409112 Hartree
ZPE	0.151141 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-439.255824 Hartree
Enthalpy	-439.254880 Hartree
Free Energy	-439.294778 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.444724

3	6	0	1.376322	0.000000	1.759556
4	6	0	1.943044	-1.145286	0.905776
5	6	0	1.075150	-1.049111	-0.376140
6	1	0	0.615169	-2.008579	-0.610687
7	1	0	1.652032	-0.737390	-1.247334
8	1	0	1.783235	-2.094454	1.419218
9	1	0	3.010180	-1.030760	0.717343
10	7	0	1.943736	1.300139	1.389828
11	6	0	1.565697	1.988413	0.271808
12	6	0	0.350389	1.418096	-0.456487
13	1	0	0.546984	1.465310	-1.529112
14	1	0	-0.482835	2.095350	-0.250613
15	8	0	2.128297	3.004981	-0.095159
16	1	0	2.760649	1.648412	1.871572
17	1	0	1.489421	-0.138489	2.833825
18	1	0	-1.001656	-0.282855	-0.319934



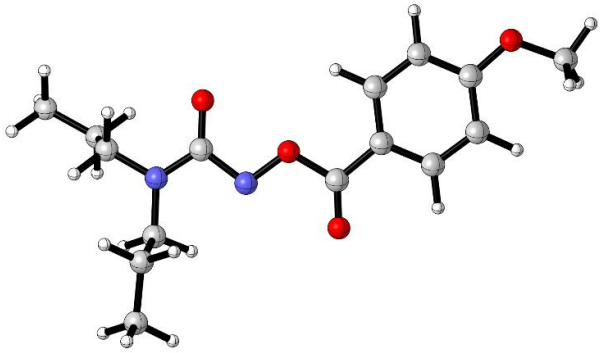
Vibrational frequency of **16z**

Quantity	Value
Job History	20370,20385,37254,37256,40582
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Basis	6-311+G(2d,p)
RB3LYP Energy	-995.546488834 Hartree
ZPE	0.359200 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-995.164753 Hartree
Enthalpy	-995.163809 Hartree
Free Energy	-995.242439 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.432224
3	6	0	1.183856	0.000000	2.085138
4	6	0	2.433916	0.001153	1.456067
5	6	0	3.585120	0.001332	2.228635
6	6	0	3.519575	-0.000618	3.623707
7	6	0	2.260242	-0.001332	4.244469
8	6	0	1.108261	-0.000827	3.485685
9	1	0	0.132897	0.000084	3.955443
10	1	0	2.187256	0.000507	5.323079
11	6	0	4.781127	0.006717	4.380493
12	8	0	5.896918	0.050575	3.913319
13	8	0	4.566769	-0.082665	5.736446
14	7	0	5.738994	-0.024985	6.519091
15	6	0	6.109635	1.327536	6.813344
16	8	0	5.374201	2.265570	6.533386
17	7	0	7.286710	1.440592	7.471586
18	6	0	8.107298	0.297135	7.888463
19	1	0	8.564971	0.561239	8.844482
20	1	0	7.455273	-0.554478	8.087730
21	6	0	9.202361	-0.085642	6.886945
22	6	0	10.056578	-1.247440	7.395331
23	1	0	10.830572	-1.508891	6.671335
24	1	0	10.552125	-0.991239	8.335581
25	1	0	9.448750	-2.139028	7.570814
26	1	0	8.749588	-0.351457	5.926531
27	1	0	9.834914	0.786040	6.696256
28	6	0	7.754372	2.783462	7.833989
29	1	0	8.845564	2.775186	7.779251
30	1	0	7.393986	3.482671	7.080371
31	6	0	7.300322	3.232989	9.224962
32	6	0	7.838154	4.619893	9.579063
33	1	0	7.503627	4.927736	10.571774
34	1	0	8.931601	4.633687	9.577120
35	1	0	7.494507	5.372096	8.863826
36	1	0	6.207430	3.235682	9.255078
37	1	0	7.635539	2.505619	9.970688
38	1	0	6.465460	-0.532652	6.019176
39	1	0	4.554037	0.002910	1.746703
40	1	0	2.517199	0.002177	0.379126
41	1	0	-1.046656	-0.000115	-0.292206
42	1	0	0.489787	0.894243	-0.390436
43	1	0	0.489964	-0.894242	-0.390303



Vibrational frequency of 16z radical

Quantity	Value
Job History	20370,20385,37254,37256,37262,37918,37924,40580
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_{15}H_{21}N_2O_4$(2)
Symmetry	C1
Basis	6-311+G(2d,p)
UB3LYP Energy	-994.897469537 Hartree
ZPE	0.345825 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-994.529155 Hartree
Enthalpy	-994.528211 Hartree
Free Energy	-994.607363 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000

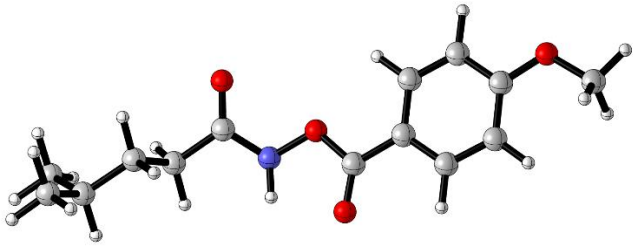
2	8	0	0.000000	0.000000	1.433319
3	6	0	1.180029	0.000000	2.087334
4	6	0	2.432270	-0.000042	1.459080
5	6	0	3.581012	0.000109	2.231527
6	6	0	3.513957	0.000449	3.628938
7	6	0	2.251920	0.000141	4.248712
8	6	0	1.102275	0.000029	3.488243
9	1	0	0.126073	-0.000077	3.955997
10	1	0	2.177308	-0.000396	5.326875
11	6	0	4.773627	0.000731	4.376796
12	8	0	5.887718	0.000080	3.930605
13	8	0	4.518235	0.001432	5.766537
14	7	0	5.636782	0.004070	6.523536
15	6	0	5.225394	-0.011077	7.889625
16	8	0	4.057880	-0.067216	8.268736
17	7	0	6.299620	0.044579	8.719248
18	6	0	7.699296	0.112199	8.270771
19	1	0	8.294802	-0.410877	9.022457
20	1	0	7.803498	-0.436386	7.338025
21	6	0	8.210684	1.545103	8.101867
22	6	0	9.693195	1.579160	7.729952
23	1	0	10.039733	2.607003	7.606027
24	1	0	10.307106	1.111617	8.504498
25	1	0	9.879097	1.049666	6.791727
26	1	0	7.616680	2.038248	7.327299
27	1	0	8.047615	2.102393	9.029053
28	6	0	6.051758	0.065835	10.162910
29	1	0	6.848302	0.653788	10.623421
30	1	0	5.108061	0.581604	10.338005
31	6	0	6.005606	-1.335205	10.782879
32	6	0	5.766103	-1.280142	12.291890
33	1	0	5.739741	-2.284855	12.718416
34	1	0	6.558452	-0.723387	12.799526
35	1	0	4.814797	-0.794375	12.524707
36	1	0	5.212278	-1.909157	10.297508
37	1	0	6.946560	-1.853296	10.574884
38	1	0	4.550552	0.000008	1.750804
39	1	0	2.516054	-0.000131	0.382245
40	1	0	-1.046705	0.000533	-0.291425
41	1	0	0.490416	0.894223	-0.389182
42	1	0	0.489496	-0.894740	-0.389198

Vibrational frequency of H-atom

Quantity	Value
Job History	20371,20372
Route	#N B3LYP/6-311+G(2d,p) OPT FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=C
Stoichiometry	H(2)
Symmetry	OH
Basis	6-311+G(2d,p)
UB3LYP Energy	-0.502177020841 Hartree
ZPE	0.000000 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-0.500761 Hartree
Enthalpy	-0.499817 Hartree
Free Energy	-0.512831 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	0.000000	0.000000	0.000000



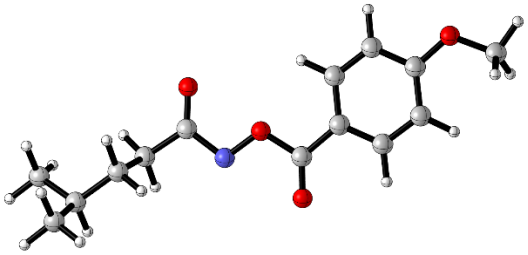
Vibrational frequency of 36h

Quantity	Value
Job History	20370,23453,23465,23475,43197,43199,43200
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_{14}H_{19}NO_4$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-900.848191837 Hartree
ZPE	0.313090 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-900.515112 Hartree
Enthalpy	-900.514168 Hartree
Free Energy	-900.587179 Hartree

Input orientation:

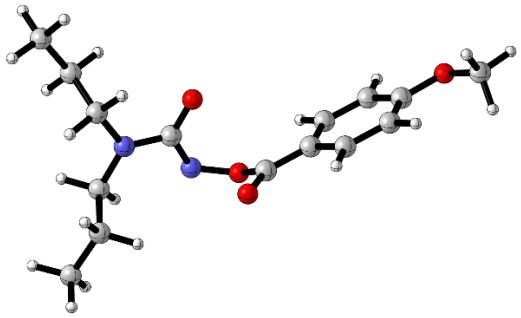
Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.432488
3	6	0	1.183246	0.000000	2.084958
4	6	0	2.433339	-0.000998	1.455466

5	6	0	3.584850	0.000545	2.227149
6	6	0	3.518197	0.002396	3.622355
7	6	0	2.259107	0.001652	4.244269
8	6	0	1.107581	0.000830	3.485905
9	1	0	0.132244	0.001129	3.955581
10	1	0	2.186121	0.003003	5.323061
11	6	0	4.777573	0.012235	4.377362
12	8	0	5.898884	0.018895	3.913350
13	8	0	4.565548	0.009506	5.730537
14	7	0	5.761918	-0.016691	6.465634
15	6	0	5.737598	0.640001	7.670672
16	8	0	4.708463	1.038367	8.190357
17	6	0	7.104442	0.743914	8.317405
18	1	0	7.865008	0.266773	7.694283
19	1	0	7.048533	0.176776	9.249499
20	6	0	7.480931	2.207841	8.595924
21	6	0	8.866346	2.391900	9.238061
22	6	0	9.217220	3.882917	9.306828
23	1	0	10.216273	4.032273	9.723774
24	1	0	9.193432	4.343815	8.315987
25	1	0	8.506826	4.420260	9.943071
26	6	0	8.962656	1.750791	10.627580
27	1	0	9.952101	1.917582	11.060609
28	1	0	8.223786	2.186300	11.307994
29	1	0	8.796896	0.671832	10.598722
30	1	0	9.603455	1.904233	8.587801
31	1	0	7.456505	2.762005	7.651985
32	1	0	6.718836	2.654983	9.241476
33	1	0	6.567514	0.030681	5.846898
34	1	0	4.553641	0.000885	1.744967
35	1	0	2.516132	-0.002115	0.378450
36	1	0	-1.046614	-0.001082	-0.292134
37	1	0	0.489258	0.894823	-0.389817
38	1	0	0.490999	-0.893881	-0.389454



Vibrational frequency of 36h radical

Quantity	Value
Job History	20370,23453,23465,23475,43197,43199
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_{14}H_{18}NO_4$(2)
Symmetry	C1
Basis	6-311+G(2d,p)
UB3LYP Energy	-900.18925328 Hartree
ZPE	0.299774 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-899.869514 Hartree
Enthalpy	-899.868570 Hartree
Free Energy	-899.942308 Hartree



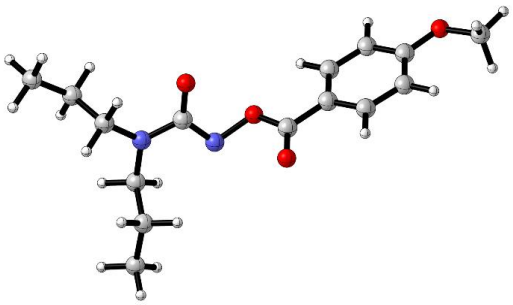
Vibrational frequency of anionic **16z** (triplet)

Quantity	Value
Job History	20370,20385,37254,37256,40582,43019,43020
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_{15}H_{21}N_2O_4(1-,3)$
Symmetry	C1
Basis	6-311+G(2d,p)
UB3LYP Energy	-994.974027916 Hartree
ZPE	0.341705 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-994.609506 Hartree
Enthalpy	-994.608561 Hartree
Free Energy	-994.687569 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.420378

3	6	0	1.225533	0.000000	2.062304
4	6	0	2.469280	0.000479	1.421119
5	6	0	3.642919	-0.000588	2.160257
6	6	0	3.631793	-0.001551	3.593625
7	6	0	2.339968	-0.005045	4.216482
8	6	0	1.184496	-0.001859	3.470272
9	1	0	0.217364	-0.000929	3.961681
10	1	0	2.270869	-0.005158	5.296346
11	6	0	4.848408	0.013788	4.296652
12	8	0	6.028770	0.043437	3.905808
13	8	0	4.647484	-0.201347	5.773641
14	7	0	5.393370	0.468680	6.662058
15	6	0	5.771025	1.787333	6.277628
16	8	0	5.053174	2.512801	5.586500
17	7	0	6.922369	2.205208	6.866145
18	6	0	7.774887	1.347822	7.695737
19	1	0	8.182560	1.972893	8.495102
20	1	0	7.153627	0.587423	8.165783
21	6	0	8.919198	0.680846	6.926767
22	6	0	9.820781	-0.139594	7.850241
23	1	0	10.628445	-0.614700	7.289638
24	1	0	10.275366	0.488626	8.621394
25	1	0	9.256634	-0.929038	8.354529
26	1	0	8.496072	0.039428	6.149381
27	1	0	9.511310	1.446417	6.416206
28	6	0	7.343315	3.593182	6.667764
29	1	0	8.435577	3.613071	6.679063
30	1	0	7.018221	3.910776	5.677052
31	6	0	6.791582	4.551822	7.727859
32	6	0	7.277432	5.985243	7.510770
33	1	0	6.875032	6.656025	8.272746
34	1	0	8.368456	6.045486	7.557005
35	1	0	6.964786	6.365255	6.534236
36	1	0	5.699372	4.517452	7.697953
37	1	0	7.092506	4.204811	8.721242
38	1	0	4.595405	0.001528	1.645579
39	1	0	2.534652	0.001799	0.340683
40	1	0	-1.045121	0.000739	-0.303846
41	1	0	0.492981	0.891299	-0.400936
42	1	0	0.491691	-0.892029	-0.401027



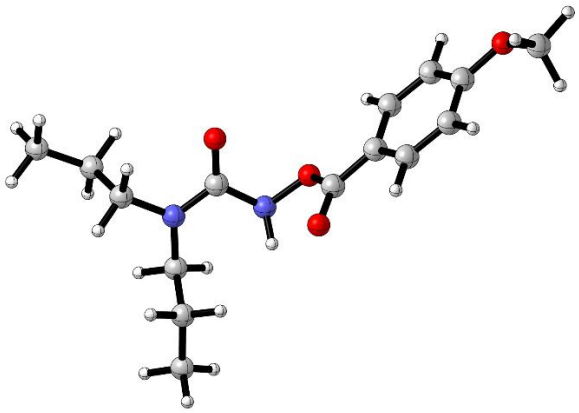
Vibrational frequency of anionic **16z** (singlet)

Quantity	Value
Job History	20370,20385,37254,37256,40582,43019
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_{15}H_{21}N_2O_4(1-)$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-995.061093687 Hartree
ZPE	0.344749 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-994.693880 Hartree
Enthalpy	-994.692936 Hartree
Free Energy	-994.772062 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.429579

3	6	0	1.193395	0.000000	2.079474
4	6	0	2.438607	-0.001272	1.446001
5	6	0	3.596413	-0.003518	2.215222
6	6	0	3.545116	-0.001282	3.608358
7	6	0	2.288144	0.002276	4.230191
8	6	0	1.127967	0.001261	3.478645
9	1	0	0.155783	0.000614	3.956061
10	1	0	2.224446	0.002283	5.309582
11	6	0	4.827985	-0.007007	4.373619
12	8	0	5.918917	-0.105368	3.835797
13	8	0	4.617541	0.100680	5.683493
14	7	0	5.785415	-0.084789	6.543622
15	6	0	6.091123	1.109692	7.087416
16	8	0	5.592991	2.232155	6.808632
17	7	0	7.083996	1.030095	8.072871
18	6	0	7.731178	-0.224666	8.431400
19	1	0	8.048944	-0.151385	9.477738
20	1	0	6.991795	-1.024706	8.379711
21	6	0	8.944140	-0.596679	7.567180
22	6	0	9.602193	-1.899484	8.023811
23	1	0	10.463654	-2.150393	7.400409
24	1	0	9.951809	-1.826671	9.058075
25	1	0	8.900168	-2.736882	7.971156
26	1	0	8.619192	-0.685348	6.527711
27	1	0	9.677122	0.216243	7.602062
28	6	0	7.663274	2.254310	8.605278
29	1	0	8.751248	2.130740	8.665631
30	1	0	7.467954	3.060267	7.898422
31	6	0	7.128008	2.651589	9.987315
32	6	0	7.800695	3.912991	10.530447
33	1	0	7.407480	4.182677	11.513369
34	1	0	8.880993	3.773052	10.632426
35	1	0	7.639937	4.765119	9.863504
36	1	0	6.047389	2.805377	9.913457
37	1	0	7.278954	1.823171	10.687660
38	1	0	4.562959	-0.006631	1.728251
39	1	0	2.516791	-0.001050	0.368387
40	1	0	-1.046342	0.000235	-0.294727
41	1	0	0.490583	0.893603	-0.392484
42	1	0	0.490249	-0.893632	-0.392994



Vibrational frequency of neutral **16z** (triplet)

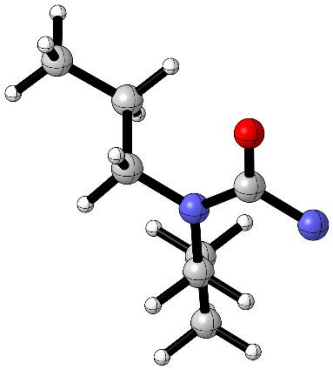
Quantity	Value
Job History	20370,20385,37254,37256,40582,41038
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_{15}H_{22}N_2O_4$(3)
Symmetry	C1
Basis	6-311+G(2d,p)
UB3LYP Energy	-995.430848351 Hartree
ZPE	0.354867 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-995.052591 Hartree
Enthalpy	-995.051647 Hartree
Free Energy	-995.133360 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.436900
3	6	0	1.166266	0.000000	2.100749
4	6	0	2.461378	0.005115	1.509784
5	6	0	3.569028	-0.000460	2.295943
6	6	0	3.449079	-0.021306	3.769763
7	6	0	2.120582	-0.011091	4.350101
8	6	0	1.031883	-0.002317	3.550334
9	1	0	0.030354	0.004056	3.962299
10	1	0	2.010879	-0.011265	5.424540
11	6	0	4.640415	-0.052328	4.551526
12	8	0	5.795718	-0.059294	4.117061
13	8	0	4.385191	-0.116292	5.927892
14	7	0	5.541363	-0.013103	6.720695
15	6	0	5.864064	1.346022	7.026460
16	8	0	5.098636	2.264610	6.759079
17	7	0	7.039155	1.495478	7.685278
18	6	0	7.899255	0.378127	8.091807
19	1	0	8.358193	0.655194	9.043628
20	1	0	7.276751	-0.494299	8.295757
21	6	0	8.996322	0.030478	7.079531
22	6	0	9.895550	-1.099988	7.580933
23	1	0	10.669438	-1.337723	6.848651
24	1	0	10.393130	-0.824100	8.514581
25	1	0	9.320534	-2.011179	7.766427
26	1	0	8.542618	-0.253192	6.124661
27	1	0	9.596297	0.923146	6.880353
28	6	0	7.460378	2.849767	8.059204
29	1	0	8.551306	2.879811	8.004535
30	1	0	7.076090	3.543169	7.312022
31	6	0	6.992029	3.272412	9.454051
32	6	0	7.480538	4.674737	9.818800
33	1	0	7.137340	4.962681	10.814545
34	1	0	8.572842	4.727651	9.814904
35	1	0	7.108916	5.419892	9.110188
36	1	0	5.899752	3.235938	9.484443
37	1	0	7.353248	2.551392	10.193822
38	1	0	6.292577	-0.489910	6.226318
39	1	0	4.559526	0.006211	1.866185
40	1	0	2.569699	0.015607	0.433697

41	1	0	-1.046159	-0.003428	-0.290631
42	1	0	0.490562	0.896900	-0.379926
43	1	0	0.496673	-0.893641	-0.379849



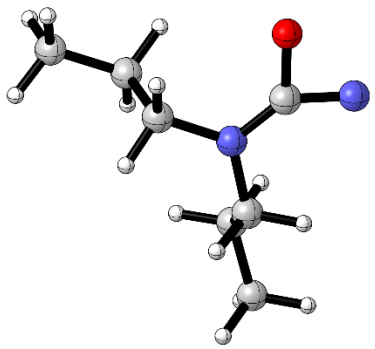
Vibrational frequency of nitrene **16z** (triplet)

Quantity	Value
Job History	20370,20382,20416,37250,37252,40581
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_7H_{14}N_2O(3)$
Symmetry	C1
Basis	6-311+G(2d,p)
UB3LYP Energy	-459.965682017 Hartree
ZPE	0.206760 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-459.746817 Hartree
Enthalpy	-459.745872 Hartree
Free Energy	-459.798765 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

1	6	0	0.000000	0.000000	0.000000
2	7	0	0.000000	0.000000	1.468465
3	6	0	1.145661	0.000000	2.181806
4	7	0	2.352798	0.059300	1.497850
5	8	0	1.222740	-0.049254	3.421474
6	6	0	-1.271939	-0.081637	2.194852
7	6	0	-1.739250	1.249206	2.797444
8	6	0	-3.046827	1.079813	3.571886
9	1	0	-3.373004	2.032427	3.993667
10	1	0	-3.846953	0.709902	2.925146
11	1	0	-2.929283	0.372255	4.396797
12	1	0	-0.959848	1.631707	3.459886
13	1	0	-1.870488	1.983650	1.999354
14	1	0	-2.016280	-0.465075	1.495448
15	1	0	-1.150136	-0.817936	2.992649
16	6	0	-0.483845	1.309907	-0.625523
17	6	0	-0.438238	1.247577	-2.152846
18	1	0	-0.786135	2.185740	-2.588891
19	1	0	0.578516	1.068560	-2.512060
20	1	0	-1.074680	0.445561	-2.535754
21	1	0	-1.504859	1.521799	-0.298124
22	1	0	0.143554	2.128639	-0.262033
23	1	0	1.015018	-0.215869	-0.335465
24	1	0	-0.630951	-0.831314	-0.327450



Vibrational frequency of nitrene **16z** (singlet)

Quantity	Value
Job History	20370,20382,20416,37250,37252,40581,40847,42883,42886
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_7H_{14}N_2O$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-459.951776226 Hartree
ZPE	0.207153 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-459.732259 Hartree
Enthalpy	-459.731315 Hartree
Free Energy	-459.784642 Hartree

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000

2	7	0	0.000000	0.000000	1.471179
3	6	0	1.153932	0.000000	2.103188
4	7	0	2.422072	0.038088	1.899005
5	8	0	1.445369	-0.059049	3.376245
6	6	0	-1.249390	-0.105714	2.245158
7	6	0	-1.798805	1.230541	2.749653
8	6	0	-3.084161	1.037103	3.555337
9	1	0	-3.465538	1.995015	3.913537
10	1	0	-3.866084	0.572542	2.948692
11	1	0	-2.913474	0.398888	4.426410
12	1	0	-1.039661	1.715119	3.369685
13	1	0	-1.986407	1.894905	1.903053
14	1	0	-1.975466	-0.601775	1.598385
15	1	0	-1.065283	-0.772674	3.090245
16	6	0	-0.456683	1.314364	-0.632464
17	6	0	-0.374801	1.256610	-2.158511
18	1	0	-0.708375	2.197121	-2.600564
19	1	0	0.649631	1.074242	-2.493637
20	1	0	-1.004815	0.458065	-2.559168
21	1	0	-1.484051	1.530568	-0.329074
22	1	0	0.166132	2.128714	-0.251845
23	1	0	1.017006	-0.234178	-0.323152
24	1	0	-0.637527	-0.824471	-0.330241

---

*BDE calculation for carbamoyl precursor **16z***
BDE = [ΔH(radical) + ΔH(hydrogen)] – ΔH(precursor)
BDE = [-994.528211+ (-0.499817)]– (-995.163809)
BDE = 0.135781 Hartree
BDE = 85.2 kcal/mol

BDE for the urea derived substrates was calculated to be 85.2 kcal/mol

*BDE calculation for amide precursor **36h***
BDE = [ΔH(radical) + ΔH(hydrogen)] – ΔH(precursor)
BDE = [-899.868570 + (-0.499817)]– (-900.514168)
BDE = 0.145781 Hartree
BDE = 91.5 kcal/mol

BDE for the amide derived substrates was calculated to be 91.5 kcal/mol

*E_T calculation from neutral **16z***
$E_T = T^1 – S^0$
E_T = -995.133360– -995.242439
$E_T = 0.109079$
E_T = 68.4 kcal/mol

Energy transfer (EnT) to the neutral urea precursor was calculated to be 68.4 kcal/mol

*E_T calculation from anionic **16z***
$E_T = T^1 – S^0$
E_T = -994.687569 – -994.772062
$E_T = 0.084493$
E_T = 53.0 kcal/mol

Energy transfer (EnT) to the neutral urea precursor was calculated to be 53.0 kcal/mol

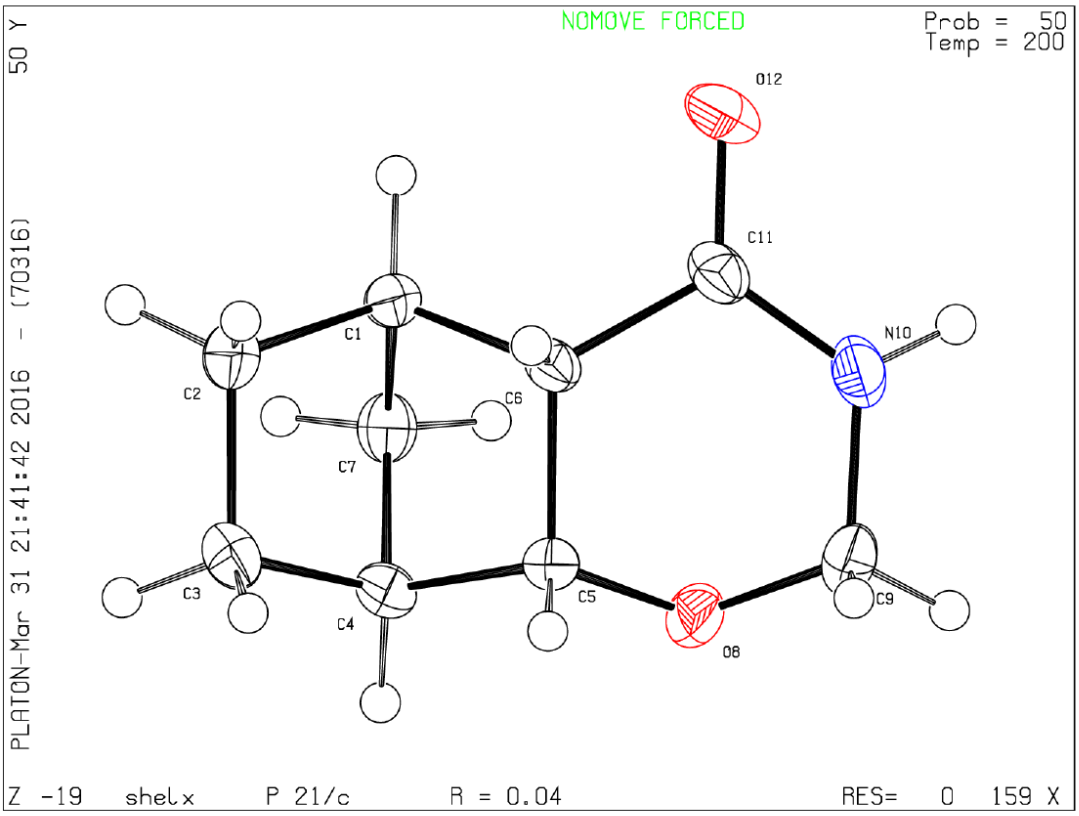
Triplet vs singlet nitrene energy from **16z**
$\Delta G = T^1 – S^0$
ΔG = -459.798765 *– (*-459.784642)
ΔG = -0.014123
ΔG = -8.9 kcal/mol

Triplet nitrene was calculated to be 8.9 kcal/mol lower in energy to the singlet nitrene

BDFE were calculated using the formula: Formal BDFE (kcal/mol) = 2.3RTpKa +23.06E + 54.9 (MeCN).

X-ray structures

Structure **23a** determination via X-ray analysis (CCDC deposition #: 1949773)



Bond precision: C-C = 0.0017 A Wavelength=0.71073

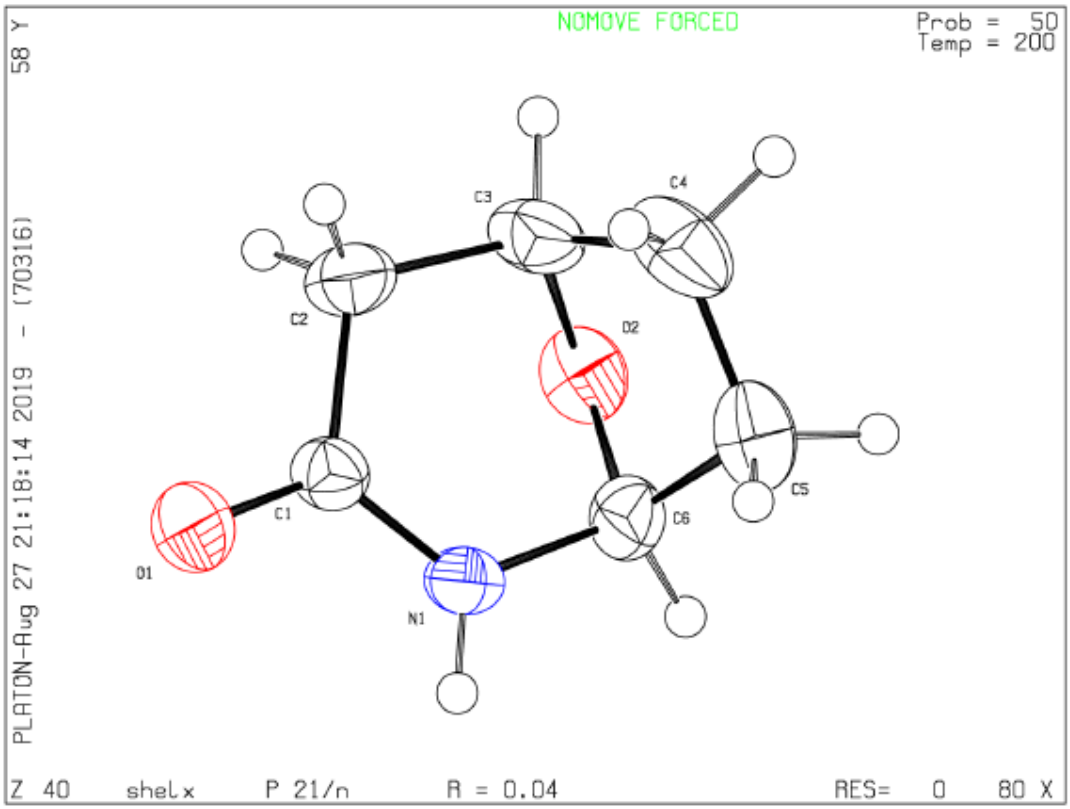
Cell: a=13.2954(6) b=6.5562(3) c=9.7000(4)
alpha=90 beta=108.393(2) gamma=90

Temperature: 200 K

	Calculated	Reported
Volume	802.33(6)	802.33(6)
Space group	P 21/c	P 21/c
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C9 H13 N O2	?
Sum formula	C9 H13 N O2	C9 H13 N O2
Mr	167.20	167.20
Dx,g cm-3	1.384	1.384
Z	4	4
Mu (mm-1)	0.098	0.098
F000	360.0	360.0
F000'	360.17	
h,k,lmax	17,8,12	17,8,12
Nref	2004	1999
Tmin,Tmax	0.961,0.992	0.694,0.746

```
Tmin'              0.935
Correction method= # Reported T Limits: Tmin=0.694
Tmax=0.746 AbsCorr = MULTI-SCAN
Data completeness= 0.998       Theta(max)= 28.317
R(reflections)= 0.0416( 1581)     wR2(reflections)= 0.1096( 1999)
S = 1.042             Npar= 113
```

Structure 26a determination via X-ray analysis (CCDC deposition #: 1949772)



Bond precision: C-C = 0.0019 A Wavelength=0.71073

Cell: a=10.1308(10) b=6.2598(6) c=10.9357(11)
alpha=90 beta=115.193(2) gamma=90

Temperature: 200 K

	Calculated	Reported
Volume	627.54(11)	627.54(11)
Space group	P 21/n	P 21/n
Hall group	-P 2yn	-P 2yn
Moiety formula	C6 H9 N O2	?
Sum formula	C6 H9 N O2	C6 H9 N O2
Mr	127.14	127.14
Dx,g cm-3	1.346	1.346
Z	4	4
Mu (mm-1)	0.101	0.101
F000	272.0	272.0
F000'	272.14	
h,k,lmax	14,8,15	14,8,14
Nref	1848	1696
Tmin,Tmax	0.933,0.989	0.602,0.746
Tmin'	0.933	

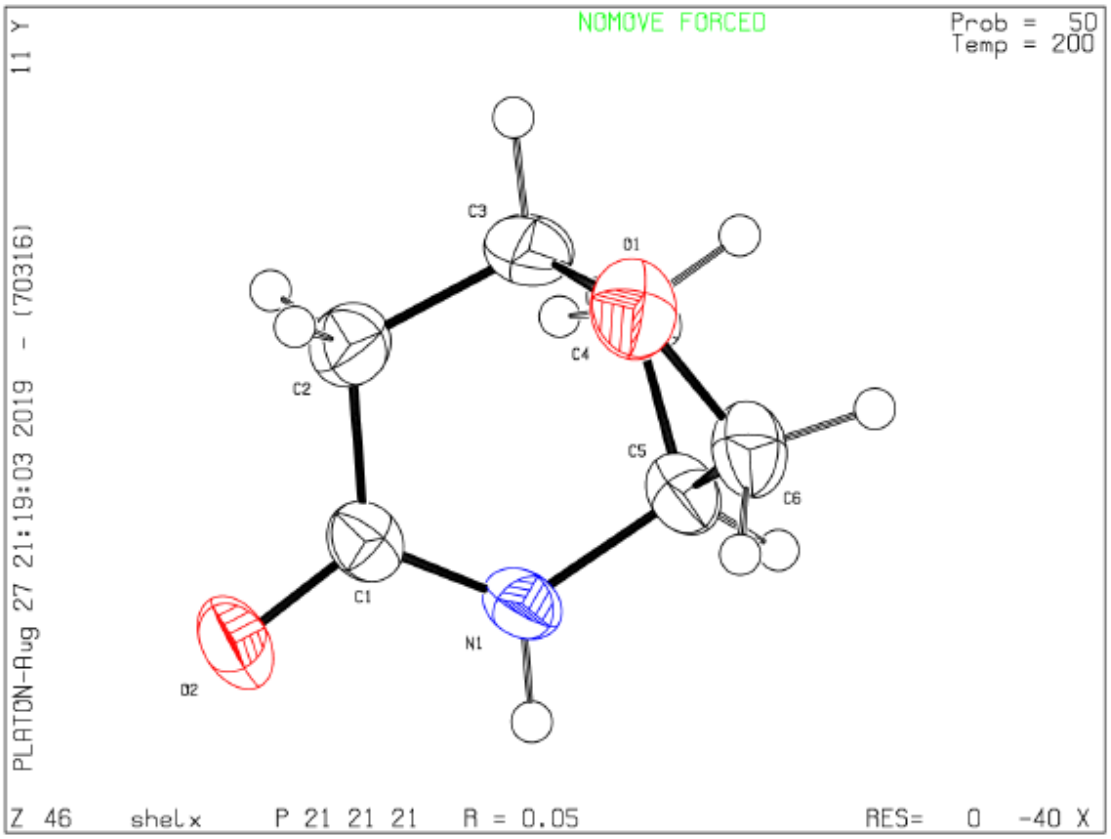
Correction method= # Reported T Limits: Tmin=0.602
Tmax=0.746 AbsCorr = MULTI-SCAN

Data completeness= 0.918 Theta(max)= 30.148

R(reflections)= 0.0403(1377) wR2(reflections)= 0.1098(1696)

S = 1.036 Npar= 86

Structure **27a** determination via X-ray analysis (CCDC deposition #: 1949771)



Bond precision: C-C = 0.0030 A Wavelength=0.71073

Cell: a=6.5435(3) b=9.2647(6) c=10.1612(6)
alpha=90 beta=90 gamma=90

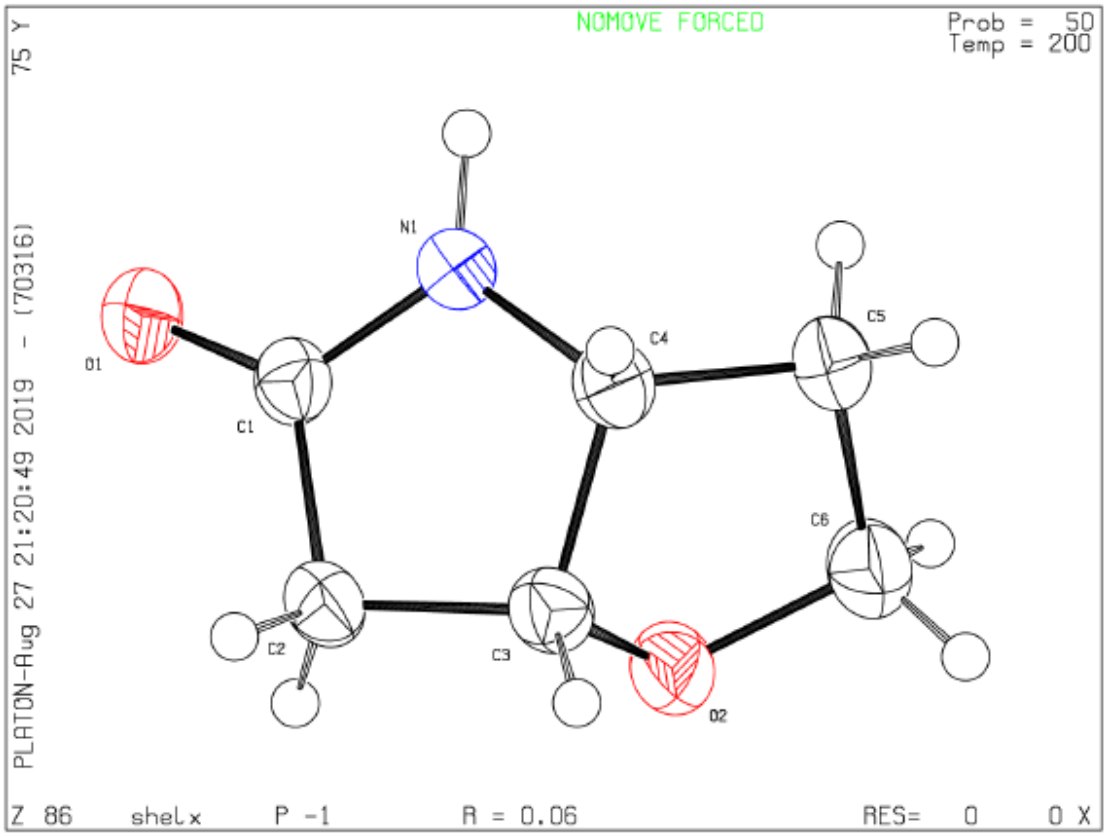
Temperature: 200 K

	Calculated	Reported
Volume	616.01(6)	616.01(6)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C6 H9 N O2	?
Sum formula	C6 H9 N O2	C6 H9 N O2
Mr	127.14	127.14
Dx,g cm-3	1.371	1.371
Z	4	4
Mu (mm-1)	0.103	0.103
F000	272.0	272.0
F000'	272.14	
h,k,lmax	12,18,19	11,17,19
Nref	4722[2675]	3752
Tmin,Tmax	0.976,0.995	0.632,0.749
Tmin'	0.974	

Correction method= # Reported T Limits: Tmin=0.632
Tmax=0.749 AbsCorr = MULTI-SCAN

```
Data completeness= 1.40/0.79   Theta(max)= 43.677
R(reflections)= 0.0510( 1535)     wR2(reflections)= 0.1284( 3752)
S = 0.982             Npar= 86
```

Structure **28a** determination via X-ray analysis (CCDC deposition #: 1949770)



Bond precision: C-C = 0.0036 A Wavelength=0.71073
Cell: a=4.461(2) b=7.110(3) c=9.569(4)
alpha=90.794(5) beta=96.326(5) gamma=96.411(5)
Temperature: 200 K

	Calculated	Reported
Volume	299.7(2)	299.7(2)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C6 H9 N O2	?
Sum formula	C6 H9 N O2	C6 H9 N O2
Mr	127.14	127.14
Dx,g cm-3	1.409	1.409
Z	2	2
Mu (mm-1)	0.106	0.106
F000	136.0	136.0
F000'	136.07	
h,k,lmax	6,9,13	6,9,13
Nref	1639	1436
Tmin,Tmax	0.967,0.994	0.602,0.746
Tmin'	0.960	

Correction method= # Reported T Limits: Tmin=0.602
Tmax=0.746 AbsCorr = MULTI-SCAN

```
Data completeness= 0.876       Theta(max)= 29.311
R(reflections)= 0.0581( 1138)     wR2(reflections)= 0.1619( 1436)
S = 1.077             Npar= 87
```

References

1 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.

2 D. G. Brown and J. Boström, *J. Med. Chem.*, 2016, **59**, 4443–4458.

3 J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337–2347.

4 R. W. Dugger, J. A. Ragan and D. H. B. Ripin, *Org. Process Res. Dev.*, 2005, **9**, 253–258.

5 P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, **116**, 12564–12649.

6 C. Sambiagio, S. P. Marsden, A. J. Blacker and P. C. McGowan, *Chem. Soc. Rev.*, 2014, **43**, 3525–3550.

7 M. J. West, J. W. B. Fyfe, J. C. Vantourout and A. J. B. Watson, *Chem. Rev.*, 2019, **119**, 12491–12523.

8 J.-S. Lin, P. Yu, L. Huang, P. Zhang, B. Tan and X.-Y. Liu, *Angew. Chemie Int. Ed.*, 2015, **54**, 7847–7851.

9 A. R. Brown, C. Uyeda, C. A. Brotherton and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2013, **135**, 6747–6749.

10 M. J. MacDonald, D. J. Schipper, P. J. Ng, J. Moran and A. M. Beauchemin, *J. Am. Chem. Soc.*, 2011, **133**, 20100–20103.

11 L. Huang, M. Arndt, K. Gooßen, H. Heydt and L. J. Gooßen, *Chem. Rev.*, 2015, **115**, 2596–2697.

12 A. J. Musacchio, B. C. Lainhart, X. Zhang, S. G. Naguib, T. C. Sherwood and R. R. Knowles, *Science (80-.).*, 2017, **355**, 727 LP – 730.

13 X.-W. Lan, N.-X. Wang and Y. Xing, *European J. Org. Chem.*, 2017, **2017**, 5821–5851.

14 E. Erdik and M. Ay, *Chem. Rev.*, 1989, **89**, 1947–1980.

15 M. Corpet and C. Gosmini, *Synthesis (Stuttg).*, 2014, **46**, 2258–2271.

16 E. Ciganek, *Org. React.*, 2009, 1–366.

17 R. P. Tripathi, S. S. Verma and J. P. and V. K. Tiwari, *Curr. Org. Chem.*, 2008, 12, 1093–1115.

18 O. I. Afanasyev, E. Kuchuk, D. L. Usanov and D. Chusov, *Chem. Rev.*, 2019, **119**, 11857–11911.

19 Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247–9301.

20 H. Hayashi and T. Uchida, *European J. Org. Chem.*, 2020, **2020**, 909–916.

21 S. Maiti, M. T. Alam, A. Bal and P. Mal, *Adv. Synth. Catal.*, 2019, **361**, 4401–4425.

22 H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417.

23 T. Xiong and Q. Zhang, *Chem. Soc. Rev.*, 2016, **45**, 3069–3087.

24 C. K. Prier, R. K. Zhang, A. R. Buller, S. Brinkmann-Chen and F. H. Arnold, *Nat. Chem.*, 2017, **9**, 629.

25 S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller and M. Christina White, *Nat. Chem.*, 2015, **7**, 987.

26 M. Huang, J. Paretsky and J. M. Schomaker, *ChemCatChem*, , DOI:10.1002/cctc.202000336.

27 J. R. Clark, K. Feng, A. Sookezian and M. C. White, *Nat. Chem.*, 2018, **10**, 583–591.

28 A. K. Ghosh, A. Sarkar and M. Brindisi, *Org. Biomol. Chem.*, 2018, **16**, 2006–2027.

29 A. K. Ghosh, M. Brindisi and A. Sarkar, *ChemMedChem*, 2018, **13**, 2351–2373.

30 *Compr. Org. Name React. Reagents*, 2010, 1772–1776.

31 M. Thomas, J. Alsarraf, N. Araji, I. Tranoy-Opalinski, B. Renoux and S. Papot, *Org. Biomol. Chem.*, 2019, **17**, 5420–5427.

32 *Compr. Org. Name React. Reagents*, 2010, 288–295.

33 A. H. Blatt, *Chem. Rev.*, 1933, **12**, 215–260.

34 M. J. Hatch and D. J. Cram, *J. Am. Chem. Soc.*, 1953, **75**, 38–44.

35 *Compr. Org. Name React. Reagents*, 2010, 2017–2021.

36 H. Bao and U. K. Tambar, *J. Am. Chem. Soc.*, 2012, **134**, 18495–18498.

37 J.-F. Vincent-Rocan and A. M. Beauchemin, *Synthesis (Stuttg).*, 2016, **48**, 3625–3645.

38 R. Stollé, H. Nieland and M. Merkle, *J. für Prakt. Chemie*, 1927, **117**, 185–210.

39 C. Six and F. Richter, *Ullmann's Encyclopedia of Industrial Chemistry*, 2012.

40 W. Reichen, *Chem. Rev.*, 1978, **78**, 569–588.

41 C. Wentrup and J. J. F. and R. Koch, *Curr. Org. Chem.*, 2011, 15, 1745–1759.

42 A. Bongers, I. Ranasinghe, P. Lemire, A. Perozzo, J.-F. Vincent-Rocan and A. M. Beauchemin, *Org. Lett.*, 2016, **18**, 3778–3781.

43 A. Bongers, C. Clavette, W. Gan, S. I. Gorelsky, L. Betit, K. Lavergne, T. Markiewicz, P. J.

Moon, N. Das Neves, N. K. Obhi, A. B. Toderian and A. M. Beauchemin, *J. Org. Chem.*, 2017, **82**, 1175–1194.

44 K. Lavergne, A. Bongers, L. Betit and A. M. Beauchemin, *Org. Lett.*, 2015, **17**, 3612–3615.

45 C. Clavette, W. Gan, A. Bongers, T. Markiewicz, A. B. Toderian, S. I. Gorelsky and A. M. Beauchemin, *J. Am. Chem. Soc.*, 2012, **134**, 16111–16114.

46 W. Gan, P. J. Moon, C. Clavette, N. Das Neves, T. Markiewicz, A. B. Toderian and A. M. Beauchemin, *Org. Lett.*, 2013, **15**, 1890–1893.

47 J. Shao, X. Liu, K. Shu, P. Tang, J. Luo, W. Chen and Y. Yu, *Org. Lett.*, 2015, **17**, 4502–4505.

48 E. Delebecq, J.-P. Pascault, B. Boutevin and F. Ganachaud, *Chem. Rev.*, 2013, **113**, 80–118.

49 Z. W. Wicks, *Prog. Org. Coatings*, 1975, **3**, 73–99.

50 D. A. Wicks and Z. W. Wicks, *Prog. Org. Coatings*, 1999, **36**, 148–172.

51 D. A. Wicks and Z. W. Wicks, *Prog. Org. Coatings*, 2001, **41**, 1–83.

52 M. S. Rolph, A. L. J. Markowska, C. N. Warriner and R. K. O'Reilly, *Polym. Chem.*, 2016, **7**, 7351–7364.

53 W. J. S. Lockley and W. Lwowski, *Tetrahedron Lett.*, 1974, **15**, 4263–4266.

54 W. Lwowski, S. Kanemasa, R. A. Murray, V. T. Ramakrishnan, T. K. Thiruvengadam, K. Yoshida and A. Subbaraj, *J. Org. Chem.*, 1986, **51**, 1719–1723.

55 H. H. Gibson, K. Weissinger, A. Abashawl, G. Hall, T. Lawshae, K. LeBlanc, J. Moody and W. Lwowski, *J. Org. Chem.*, 1986, **51**, 3858–3861.

56 D. W. Jones, *J. Chem. Soc. Chem. Commun.*, 1982, 766–768.

57 J.-G. Roveda, C. Clavette, A. D. Hunt, S. I. Gorelsky, C. J. Whipp and A. M. Beauchemin, *J. Am. Chem. Soc.*, 2009, **131**, 8740–8741.

58 C. Proulx, D. Sabatino, R. Hopewell, J. Spiegel, Y. García Ramos and W. D. Lubell, *Future Med. Chem.*, 2011, **3**, 1139–1164.

59 A. J. Kasznel, T. Harris, N. J. Porter, Y. Zhang and D. M. Chenoweth, *Chem. Sci.*, 2019, **10**, 6979–6983.

60 F. Loiseau, C. Clavette, M. Raymond, J.-G. Roveda, A. Burrell and A. M. Beauchemin, *Chem. Commun.*, 2011, **47**, 562–564.

61 A. M. Beauchemin, *Org. Biomol. Chem.*, 2013, **11**, 7039–7050.

62 A. Bredihhin and U. Mäeorg, *Org. Lett.*, 2007, **9**, 4975–4977.

63 D. E. Polat, D. D. Brzezinski and A. M. Beauchemin, *Org. Lett.*, 2019, **21**, 4849–4852.

64 K. Garland, W. Gan, C. Depatie-Sicard and A. M. Beauchemin, *Org. Lett.*, 2013, **15**, 4074–4077.

65 D. Maume, J.-C. Lancelot and M. Robba, *J. Heterocycl. Chem.*, 1979, **16**, 1217–1222.

66 J.-C. Lancelot and D. M. Et MaxRobba, *J. Heterocycl. Chem.*, 1981, **18**, 743–746.

67 T. J. Schwan, *J. Heterocycl. Chem.*, 1983, **20**, 547–549.

68 R. V Hoffman and N. K. Nayyar, *J. Org. Chem.*, 1995, **60**, 5992–5994.

69 R. V Hoffman, M. M. Reddy, C. M. Klumas and F. Cervantes-Lee, *J. Org. Chem.*, 1998, **63**, 9128–9130.

70 A. Obreza and U. Urleb, *Synth. Commun.*, 2003, **33**, 1011–1018.

71 A. Bolognese, G. Correale, M. Manfra, A. Esposito, E. Novellino and A. Lavecchia, *J. Med. Chem.*, 2008, **51**, 8148–8157.

72 C. B. Bourguet, C. Proulx, S. Klocek, D. Sabatino and W. D. Lubell, *J. Pept. Sci.*, 2010, **16**, 284–296.

73 D. Bonnet, J.-F. Margathe, S. Radford, E. Pflimlin, S. Riché, P. Doman, M. Hibert and A. Ganesan, *ACS Comb. Sci.*, 2012, **14**, 323–334.

74 P. Regenass, J.-F. Margathe, A. Mann, J. Suffert, M. Hibert, N. Girard and D. Bonnet, *Chem. Commun.*, 2014, **50**, 9657–9660.

75 P. Regenass, D. Bosc, S. Riché, P. Gizzi, M. Hibert, L. Karmazin, A. Ganesan and D. Bonnet, *J. Org. Chem.*, 2017, **82**, 3239–3244.

76 C. Clavette, J.-F. Vincent Rocan and A. M. Beauchemin, *Angew. Chemie Int. Ed.*, 2013, **52**, 12705–12708.

77 J.-F. Vincent-Rocan, C. Clavette, K. Leckett and A. M. Beauchemin, *Chem. – A Eur. J.*, 2015, **21**, 3886–3890.

78 J.-F. Vincent-Rocan, R. A. Ivanovich, C. Clavette, K. Leckett, J. Bejjani and A. M. Beauchemin, *Chem. Sci.*, 2016, **7**, 315–328.

79 J. S. Derasp, J.-F. Vincent-Rocan and A. M. Beauchemin, *Org. Lett.*, 2016, **18**, 658–661.

80 M. A. Dahab, J. S. Derasp and A. M. Beauchemin, *Synlett*, 2017, **13**, 456–460.

81 E. B. Elkaeed, J. An and A. M. Beauchemin, *J. Org. Chem.*, 2017, **82**, 9890–9897.

82 S. Fustero, M. Sánchez-Roselló, P. Barrio and A. Simón-Fuentes, *Chem. Rev.*, 2011, **111**, 6984–7034.

83 J. B. Wright, W. E. Dulin and J. H. Markillie, *J. Med. Chem.*, 1964, **7**, 102–105.

84 C. C. Cheng, E. F. Elslager, L. M. Werbel and W. R. Leopold, *J. Med. Chem.*, 1986, **29**, 1544–1547.

85 I. A. Schepetkin, A. I. Khlebnikov and M. T. Quinn, *J. Med. Chem.*, 2007, **50**, 4928–4938.

86 D. Catarzi, V. Colotta, F. Varano, D. Poli, L. Squarcialupi, G. Filacchioni, K. Varani, F. Vincenzi, P. A. Borea, D. Dal Ben, C. Lambertucci and G. Cristalli, *Bioorg. Med. Chem.*, 2013, **21**, 283–294.

87 K. Otrubova, S. Chatterjee, S. Ghimire, B. F. Cravatt and D. L. Boger, *Bioorg. Med. Chem.*, 2019, **27**, 1693–1703.

88 G. Meng, R. Szostak and M. Szostak, *Org. Lett.*, 2017, **19**, 3596–3599.

89 F. Franco, S. Meninno, M. Benaglia and A. Lattanzi, *Chem. Commun.*, 2020, **56**, 3073–3076.

90 X.-Q. Dong, X. Fang, H.-Y. Tao, X. Zhou and C.-J. Wang, *Chem. Commun.*, 2012, **48**, 7238–7240.

91 B. Tan, G. Hernández-Torres and C. F. Barbas III, *Angew. Chemie Int. Ed.*, 2012, **51**, 5381–5385.

92 M. Hori, A. Sakakura and K. Ishihara, *J. Am. Chem. Soc.*, 2014, **136**, 13198–13201.

93 T.-Z. Li, Y. Jiang, Y.-Q. Guan, F. Sha and X.-Y. Wu, *Chem. Commun.*, 2014, **50**, 10790–10792.

94 S. Agrawal, N. Molleti and V. K. Singh, *Chem. Commun.*, 2015, **51**, 9793–9796.

95 Y. Kuang, K. Wang, X. Shi, X. Huang, E. Meggers and J. Wu, *Angew. Chemie Int. Ed.*, 2019, **58**, 16859–16863.

96 J. U. Nef, *Justus Liebigs Ann. Chem.*, 1894, **280**, 263–291.

97 L. W. Jones and L. Neuffer, *J. Am. Chem. Soc.*, 1917, **39**, 652–659.

98 L. Gattermann and G. Schmidt, *Berichte der Dtsch. Chem. Gesellschaft*, 1887, **20**, 858–

862.

99 L. Gattermann and G. Schmidt, *Berichte der Dtsch. Chem. Gesellschaft*, 1887, **20**, 118–121.

100 A. F. McKay, D. L. Garmaise, G. Y. Paris and S. Gelblum, *Can. J. Chem.*, 1960, **38**, 343–358.

101 H. A. Staab, *Angew. Chemie Int. Ed. English*, 1962, **1**, 351–367.

102 H. A. Staab and W. Benz, *Angew. Chemie*, 1961, **73**, 657.

103 R. T. Major and R. J. Hedrick, *J. Org. Chem.*, 1965, **30**, 1268–1270.

104 W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, 1962, **84**, 1316–1317.

105 W. S. Wadsworth and W. D. Emmons, *J. Org. Chem.*, 1967, **32**, 1279–1285.

106 A. Berndt, *Tetrahedron Lett.*, 1970, **11**, 173–176.

107 U. Heep, *Tetrahedron*, 1975, **31**, 77–80.

108 V. D. Sheludjakov, A. B. Dmitriev, A. D. Kirilin and E. A. Chernyshev, *Zh. Obs. Khim*, 1983, **53**, 706.

109 W. Mormann and G. Leukel, *Synthesis (Stuttg).*, 1988, **1988**, 990–992.

110 A. D. Kirilin, L. O. Belova, M. V Pletneva, N. A. Golub, P. A. Storozhenko and N. I. Kirilina, *Mendeleev Commun.*, 2017, **27**, 99–100.

111 N. Wiberg and G. Hübler, *Z. Naturforsch*, 1978, **33**, 575–582.

112 W. Lwowski, R. DeMauriac, T. W. Mattingly and E. Scheiffele, *Tetrahedron Lett.*, 1964, **5**, 3285–3288.

113 R. Puttner, W. Kaiser and K. Hafner, *Tetrahedron Lett.*, 1968, **9**, 4315–4316.

114 R. E. Wilde, T. K. K. Srinivasan and W. Lwowski, *J. Am. Chem. Soc.*, 1971, **93**, 860–863.

115 J. H. Teles and G. Maier, *Chem. Ber.*, 1989, **122**, 745–748.

116 H. Li, Z. Wu, D. Li, H. Wan, J. Xu, M. Abe and X. Zeng, *Chem. Commun.*, 2017, **53**, 4783–4786.

117 R. Koch, J. J. Finnerty and C. Wentrup, *J. Org. Chem.*, 2011, **76**, 6024–6029.

118 D. Poppinger and L. Radom, *J. Am. Chem. Soc.*, 1978, **100**, 3674–3685.

119 M. A. McAllister and T. T. Tidwell, *J. Chem. Soc. Perkin Trans. 2*, 1994, 2239–2248.

120 R. J. Waugh, P. C. H. Eichinger, R. A. J. O'Hair, J. C. Sheldon, J. H. Bowie and R. N. Hayes, *Rapid Commun. Mass Spectrom.*, 1989, **3**, 151–152.

121 P. Pyykkö and N. Runeberg, *J. Mol. Struct. THEOCHEM*, 1991, **234**, 269–277.

122 J. Hamer and A. Macaluso, *Chem. Rev.*, 1964, **64**, 473–495.

123 H. M. I. Osborn, N. Gemmell and L. M. Harwood, *J. Chem. Soc. Perkin Trans. 1*, 2002, 2419–2438.

124 P. N. Confalone and E. M. Huie, *Org. React.*, 2004, 1–173.

125 F. Heaney, *European J. Org. Chem.*, 2012, **2012**, 3043–3058.

126 K. Jarowicki and P. Kocienski, *J. Chem. Soc. Perkin Trans. 1*, 2001, 2109–2135.

127 U. Ragnarsson and L. Grehn, *RSC Adv.*, 2013, **3**, 18691–18697.

128 S. Hanessian and S. Johnstone, *J. Org. Chem.*, 1999, **64**, 5896–5903.

129 J. G. Krause, B. D. Leskiw, M. L. Emery, M. E. McGahan, M. P. McCourt and R. Priefer, *Tetrahedron Lett.*, 2010, **51**, 3568–3570.

130 T. Baburaj and S. Thambidurai, *Synlett*, 2011, **22**, 1993–1996.

131 T. Baburaj and S. Thambidurai, *Tetrahedron Lett.*, 2012, **53**, 2292–2294.

132 T. Baburaj and S. Thambidurai, *Synlett*, 2015, **26**, 1137.

133 J. L. Romine, S. W. Martin, N. A. Meanwell and J. R. Epperson, *Synthesis (Stuttg).*, 1994, **1994**, 846–850.

134 I. Butula and M. J.-M. Takač, *Croat. Chem. Acta*, 2000, **73**, 569–574.

135 N. Hirai, N. Sawatari, N. Nakamura, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 2003, **68**, 6587–6590.

136 N. Hirai, T. Kagayama, Y. Tatsukawa, S. Sakaguchi and Y. Ishii, *Tetrahedron Lett.*, 2004, **45**, 8277–8280.

137 N. J. Cooper and D. W. Knight, *Tetrahedron*, 2004, **60**, 243–269.

138 J. Bourgeois, I. Dion, P. H. Cebrowski, F. Loiseau, A.-C. Bédard and A. M. Beauchemin, *J. Am. Chem. Soc.*, 2009, **131**, 874–875.

139 J. Moran, S. I. Gorelsky, E. Dimitrijevic, M.-E. Lebrun, A.-C. Bédard, C. Séguin and A. M. Beauchemin, *J. Am. Chem. Soc.*, 2008, **130**, 17893–17906.

140 A. M. Beauchemin, J. Moran, M.-E. Lebrun, C. Séguin, E. Dimitrijevic, L. Zhang and S. I. Gorelsky, *Angew. Chemie Int. Ed.*, 2008, **47**, 1410–1413.

141 X. Peng, B. M. K. Tong, H. Hirao and S. Chiba, *Angew. Chemie Int. Ed.*, 2014, **53**, 1959–1962.

142 N. Guimond, M. J. MacDonald, V. Lemieux and A. M. Beauchemin, *J. Am. Chem. Soc.*, 2012, **134**, 16571–16577.

143 S.-B. Zhao, E. Bilodeau, V. Lemieux and A. M. Beauchemin, *Org. Lett.*, 2012, **14**, 5082–5085.

144 M. J. MacDonald, C. R. Hesp, D. J. Schipper, M. Pesant and A. M. Beauchemin, *Chem. – A Eur. J.*, 2013, **19**, 2597–2601.

145 C. R. Hesp, M. J. MacDonald, M. M. Zahedi, D. A. Bilodeau, S.-B. Zhao, M. Pesant and A. M. Beauchemin, *Org. Lett.*, 2015, **17**, 5136–5139.

146 M.-E. Lebrun, J. Y. Pfeiffer and A. M. Beauchemin, *Synlett*, 2009, **2009**, 1087–1090.

147 M. Ochiai, S. Yamane, M. M. Hoque, M. Saito and K. Miyamoto, *Chem. Commun.*, 2012, **48**, 5280–5282.

148 R. Poe, K. Schnapp, M. J. T. Young, J. Grayzar and M. S. Platz, *J. Am. Chem. Soc.*, 1992, **114**, 5054–5067.

149 J. Escudero, V. Bellosta and J. Cossy, *Angew. Chemie Int. Ed.*, 2018, **57**, 574–578.

150 S. Y. Hong, Y. Park, Y. Hwang, Y. B. Kim, M.-H. Baik and S. Chang, *Science (80-.).*, 2018, **359**, 1016 LP – 1021.

151 T. Gracza, *Stereoselective Synth. Drugs Nat. Prod.*, 2013, 1–20.

152 C. Clavette, 2015.

153 A. Bongers, 2017.

154 H. Sardon, A. C. Engler, J. M. W. Chan, J. M. García, D. J. Coady, A. Pascual, D. Mecerreyes, G. O. Jones, J. E. Rice, H. W. Horn and J. L. Hedrick, *J. Am. Chem. Soc.*, 2013, **135**, 16235–16241.

155 J. B. Lambert, Y. Zhao, R. W. Emblidge, L. A. Salvador, X. Liu, J.-H. So and E. C. Chelius, *Acc. Chem. Res.*, 1999, **32**, 183–190.

156 P. G. Gassman and G. D. Hartman, *J. Chem. Soc. Chem. Commun.*, 1972, 853–854.

157 A. A. Tabolin and S. L. Ioffe, *Chem. Rev.*, 2014, **114**, 5426–5476.

158 R. A. Ivanovich, J. A. M. Quartus, N. Das Neves, F. Loiseau, M. Raymond and A. M. Beauchemin, *J. Org. Chem.*, 2019, **84**, 9792–9800.

159 R. D. Crouch, *Tetrahedron*, 2013, **69**, 2383–2417.

160 B. Darses, R. Rodrigues, L. Neuville, M. Mazurais and P. Dauban, *Chem. Commun.*, 2017, **53**, 493–508.

161 C. Wentrup, *Angew. Chemie Int. Ed.*, 2018, **57**, 11508–11521.

162 G. Dequirez, V. Pons and P. Dauban, *Angew. Chemie Int. Ed.*, 2012, **51**, 7384–7395.

163 A. Padwa, *Acc. Chem. Res.*, 1991, **24**, 22–28.

164 L. Roiser, K. Zielke and M. Waser, *Asian J. Org. Chem.*, 2018, **7**, 852–864.

165 E. Azek, M. Khalifa, J. Bartholoméüs, M. Ernzerhof and H. Lebel, *Chem. Sci.*, 2019, **10**, 718–729.

166 V. Desikan, Y. Liu, J. P. Toscano and W. S. Jenks, *J. Org. Chem.*, 2007, **72**, 6848–6859.

167 R. A. Ivanovich, C. Clavette, J.-F. Vincent-Rocan, J.-G. Roveda, S. I. Gorelsky and A. M. Beauchemin, *Chem. – A Eur. J.*, 2016, **22**, 7906–7916.

168 S. Campagna, F. Puntoriero, F. Nastasi, G. Bergamini and V. Balzani, eds. V. Balzani and S. Campagna, Springer Berlin Heidelberg, Berlin, Heidelberg, 2007, pp. 117–214.

169 K. Kalyanasundaram, *Coord. Chem. Rev.*, 1982, **46**, 159–244.

170 C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363.

171 J. K. McCusker, *Acc. Chem. Res.*, 2003, **36**, 876–887.

172 D. O. Cowan and R. L. Drisko, eds. D. O. Cowan and R. L. Drisko, Springer US, Boston, MA, 1976, pp. 205–266.

173 F. Strieth-Kalthoff, M. J. James, M. Teders, L. Pitzer and F. Glorius, *Chem. Soc. Rev.*, 2018, **47**, 7190–7202.

174 D. M. Hedstrand, W. H. Kruizinga and R. M. Kellogg, *Tetrahedron Lett.*, 1978, **19**, 1255–1258.

175 T. J. Van Bergen, D. M. Hedstrand, W. H. Kruizinga and R. M. Kellogg, *J. Org. Chem.*, 1979, **44**, 4953–4962.

176 S. Fukuzumi, S. Koumitsu, K. Hironaka and T. Tanaka, *J. Am. Chem. Soc.*, 1987, **109**, 305–316.

177 C. Pac, Y. Miyauchi, O. Ishitani, M. Ihama, M. Yasuda and H. Sakurai, *J. Org. Chem.*, 1984, **49**, 26–34.

178 C. Pac, M. Ihama, M. Yasuda, Y. Miyauchi and H. Sakurai, *J. Am. Chem. Soc.*, 1981, **103**, 6495–6497.

179 O. Ishitani, S. Yanagida, S. Takamuku and C. Pac, *J. Org. Chem.*, 1987, **52**, 2790–2796.

180 O. Ishitani, C. Pac and H. Sakurai, *J. Org. Chem.*, 1983, **48**, 2941–2942.

181 K. Okada, K. Okamoto, N. Morita, K. Okubo and M. Oda, *J. Am. Chem. Soc.*, 1991, **113**, 9401–9402.

182 J.-R. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, *Chem. Soc. Rev.*, 2016, **45**, 2044–2056.

183 M. D. Kärkäs, *ACS Catal.*, 2017, **7**, 4999–5022.

184 L. J. Allen, P. J. Cabrera, M. Lee and M. S. Sanford, *J. Am. Chem. Soc.*, 2014, **136**, 5607–5610.

185 U. Lüning and P. S. Skell, *Tetrahedron*, 1985, **41**, 4289–4302.

186 J. C. Day, N. Govindaraj, D. S. McBain, P. S. Skell and J. M. Tanko, *J. Org. Chem.*, 1986, **51**, 4959–4963.

187 Q. Qin and S. Yu, *Org. Lett.*, 2014, **16**, 3504–3507.

188 H. Kim, T. Kim, D. G. Lee, S. W. Roh and C. Lee, *Chem. Commun.*, 2014, **50**, 9273–9276.

189 J. Davies, T. D. Svejstrup, D. Fernandez Reina, N. S. Sheikh and D. Leonori, *J. Am. Chem. Soc.*, 2016, **138**, 8092–8095.

190 T. D. Svejstrup, A. Ruffoni, F. Juliá, V. M. Aubert and D. Leonori, *Angew. Chemie Int. Ed.*, 2017, **56**, 14948–14952.

191 A. Ruffoni, F. Juliá, T. D. Svejstrup, A. J. McMillan, J. J. Douglas and D. Leonori, *Nat. Chem.*, 2019, **11**, 426–433.

192 X.-D. An and S. Yu, *Org. Lett.*, 2015, **17**, 2692–2695.

193 H. Jiang, X. An, K. Tong, T. Zheng, Y. Zhang and S. Yu, *Angew. Chemie Int. Ed.*, 2015, **54**, 4055–4059.

194 W. S. Ham, J. Hillenbrand, J. Jacq, C. Genicot and T. Ritter, *Angew. Chemie Int. Ed.*, 2019, **58**, 532–536.

195 J. Hillenbrand, W. S. Ham and T. Ritter, *Org. Lett.*, 2019, **21**, 5363–5367.

196 S. L. Rössler, B. J. Jelier, P. F. Tripet, A. Shemet, G. Jeschke, A. Togni and E. M. Carreira, *Angew. Chemie Int. Ed.*, 2019, **58**, 526–531.

197 T. W. Greulich, C. G. Daniliuc and A. Studer, *Org. Lett.*, 2015, **17**, 254–257.

198 E. Ito, T. Fukushima, T. Kawakami, K. Murakami and K. Itami, *Chem*, 2017, **2**, 383–392.

199 T. Yamaguchi, E. Yamaguchi and A. Itoh, *Org. Lett.*, 2017, **19**, 1282–1285.

200 Y. Moon, E. Jang, S. Choi and S. Hong, *Org. Lett.*, 2018, **20**, 240–243.

201 E. Brachet, T. Ghosh, I. Ghosh and B. König, *Chem. Sci.*, 2015, **6**, 987–992.

202 Y. Zhang, X. Dong, Y. Wu, G. Li and H. Lu, *Org. Lett.*, 2018, **20**, 4838–4842.

203 H. Jung, H. Keum, J. Kweon and S. Chang, *J. Am. Chem. Soc.*, , DOI:10.1021/jacs.0c00868.

204 N. A. Romero, K. A. Margrey, N. E. Tay and D. A. Nicewicz, *Science (80-.).*, 2015, **349**, 1326 LP – 1330.

205 K. A. Margrey, J. B. McManus, S. Bonazzi, F. Zecri and D. A. Nicewicz, *J. Am. Chem. Soc.*, 2017, **139**, 11288–11299.

206 K. A. Margrey, A. Levens and D. A. Nicewicz, *Angew. Chemie Int. Ed.*, 2017, **56**, 15644–15648.

207 L. Niu, H. Yi, S. Wang, T. Liu, J. Liu and A. Lei, *Nat. Commun.*, 2017, **8**, 14226.

208 Y.-W. Zheng, B. Chen, P. Ye, K. Feng, W. Wang, Q.-Y. Meng, L.-Z. Wu and C.-H. Tung, *J. Am. Chem. Soc.*, 2016, **138**, 10080–10083.

209 S. O. Scholz, E. P. Farney, S. Kim, D. M. Bates and T. P. Yoon, *Angew. Chemie Int. Ed.*, 2016, **55**, 2239–2242.

210 C. Minozzi, A. Caron, J.-C. Grenier-Petel, J. Santandrea and S. K. Collins, *Angew. Chemie Int. Ed.*, 2018, **57**, 5477–5481.

211 M. Zhang, Y. Duan, W. Li, P. Xu, J. Cheng, S. Yu and C. Zhu, *Org. Lett.*, 2016, **18**, 5356–5359.

212 H. Yi, L. Niu, C. Song, Y. Li, B. Dou, A. K. Singh and A. Lei, *Angew. Chemie Int. Ed.*, 2017, **56**, 1120–1124.

213 J.-R. Xin, Y.-H. He and Z. Guan, *Org. Chem. Front.*, 2018, **5**, 1684–1688.

214 J. Heng and S. Armido, *CCS Chem.*, 2020, **1**, 38–49.

215 Q. Qin and S. Yu, *Org. Lett.*, 2015, **17**, 1894–1897.

216 P. Becker, T. Duhamel, C. J. Stein, M. Reiher and K. Muñiz, *Angew. Chemie Int. Ed.*, 2017, **56**, 8004–8008.

217 W. Shu and C. Nevado, *Angew. Chemie Int. Ed.*, 2017, **56**, 1881–1884.

218 Q. Guo, X. Ren and Z. Lu, *Org. Lett.*, 2019, **21**, 880–884.

219 G. Pandey and R. Laha, *Angew. Chemie Int. Ed.*, 2015, **54**, 14875–14879.

220 H. Wang, D. Zhang and C. Bolm, *Angew. Chemie Int. Ed.*, 2018, **57**, 5863–5866.

221 Y. Park and S. Chang, *Nat. Catal.*, 2019, **2**, 219–227.

222 X. Ren, Q. Guo, J. Chen, H. Xie, Q. Xu and Z. Lu, *Chem. – A Eur. J.*, 2016, **22**, 18695–18699.

223 S. Huh, S. Y. Hong and S. Chang, *Org. Lett.*, 2019, **21**, 2808–2812.

224 C. G. Espino, K. W. Fiori, M. Kim and J. Du Bois, *J. Am. Chem. Soc.*, 2004, **126**, 15378–15379.

225 M. Kim, J. V Mulcahy, C. G. Espino and J. Du Bois, *Org. Lett.*, 2006, **8**, 1073–1076.

226 G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu and R. R. Knowles, *Nature*, 2016, **539**, 268.

227 J. C. K. Chu and T. Rovis, *Nature*, 2016, **539**, 272–275.

228 L. M. Stateman, K. M. Nakafuku and D. A. Nagib, *Synthesis (Stuttg).*, 2018, **50**, 1569–1586.

229 M. A. Short, J. M. Blackburn and J. L. Roizen, *Angew. Chemie Int. Ed.*, 2018, **57**, 296–299.

230 A. L. G. Kanegusuku, T. Castanheiro, S. K. Ayer and J. L. Roizen, *Org. Lett.*, 2019, **21**, 6089–6095.

231 M. Nechab, S. Mondal and M. P. Bertrand, *Chem. – A Eur. J.*, 2014, **20**, 16034–16059.

232 S. P. Morcillo, E. M. Dauncey, J. H. Kim, J. J. Douglas, N. S. Sheikh and D. Leonori, *Angew. Chemie Int. Ed.*, 2018, **57**, 12945–12949.

233 E. J. Alexanian, C. Lee and E. J. Sorensen, *J. Am. Chem. Soc.*, 2005, **127**, 7690–7691.

234 G.-S. Liu, Y.-Q. Zhang, Y.-A. Yuan and H. Xu, *J. Am. Chem. Soc.*, 2013, **135**, 3343–3346.

235 H. Lei, J. H. Conway, C. C. Cook and T. Rovis, *J. Am. Chem. Soc.*, 2019, **141**, 11864–11869.

236 W. Lwowski and F. P. Woerner, *J. Am. Chem. Soc.*, 1965, **87**, 5491–5492.

237 W. Lwowski, *Angew. Chemie Int. Ed. English*, 1967, **6**, 897–906.

238 K. W. Fiori, C. G. Espino, B. H. Brodsky and J. Du Bois, *Tetrahedron*, 2009, **65**, 3042–3051.

239 I. Cho, Z.-J. Jia and F. H. Arnold, *Science (80-.).*, 2019, **364**, 575 LP – 578.

240 I. Cho, Z.-J. Jia and F. H. Arnold, *Science (80-.).*, 2020, **367**, 155 LP – 155.

241 D. M. Peloquin, D. R. Dewitt, S. S. Patel, J. W. Merkert, B. T. Donovan-Merkert and T. A. Schmedake, *Dalt. Trans.*, 2015, **44**, 18723–18726.

242 G. Ragazzon, C. Schäfer, P. Franchi, S. Silvi, B. Colasson, M. Lucarini and A. Credi, *Proc. Natl. Acad. Sci.*, 2018, **115**, 9385 LP – 9390.

243 W. Yuan, Z. Zhou, L. Gong and E. Meggers, *Chem. Commun.*, 2017, **53**, 8964–8967.

244 X. Bao, Q. Wang and J. Zhu, *Nat. Commun.*, 2019, **10**, 769.

245 Y.-R. Gu, X.-H. Duan, L. Chen, Z.-Y. Ma, P. Gao and L.-N. Guo, *Org. Lett.*, 2019, **21**, 917–920.

246 E. C. Gentry and R. R. Knowles, *Acc. Chem. Res.*, 2016, **49**, 1546–1556.

247 D.-F. Chen, J. C. K. Chu and T. Rovis, *J. Am. Chem. Soc.*, 2017, **139**, 14897–14900.

248 J. Hioe, D. Šakić, V. Vrček and H. Zipse, *Org. Biomol. Chem.*, 2015, **13**, 157–169.

249 S. M. Paradine and M. C. White, *J. Am. Chem. Soc.*, 2012, **134**, 2036–2039.

250 K. Singh, S. J. Staig and J. D. Weaver, *J. Am. Chem. Soc.*, 2014, **136**, 5275–5278.

251 W. Lwowski and T. W. Mattingly, *J. Am. Chem. Soc.*, 1965, **87**, 1947–1958.

252 T. Patra, S. Mukherjee, J. Ma, F. Strieth-Kalthoff and F. Glorius, *Angew. Chemie Int. Ed.*, 2019, **58**, 10514–10520.

253 E. R. Welin, C. Le, D. M. Arias-Rotondo, J. K. McCusker and D. W. C. MacMillan, *Science (80-.).*, 2017, **355**, 380 LP – 385.

254 E. R. Young, J. Rosenthal and D. G. Nocera, *Chem. Sci.*, 2012, **3**, 455–459.

255 C. Drolen, E. Conklin, S. J. Hetterich, A. Krishnamurthy, G. A. Andrade, J. L. Dimeglio, M. I. Martin, L. K. Tran, G. P. A. Yap, J. Rosenthal and E. R. Young, *J. Am. Chem. Soc.*, 2018, **140**, 10169–10178.

256 S. Ruccolo, Y. Qin, C. Schnedermann and D. G. Nocera, *J. Am. Chem. Soc.*, 2018, **140**, 14926–14937.

257 G. J. Choi and R. R. Knowles, *J. Am. Chem. Soc.*, 2015, **137**, 9226–9229.

258 D. C. Miller, G. J. Choi, H. S. Orbe and R. R. Knowles, *J. Am. Chem. Soc.*, 2015, **137**, 13492–13495.

259 S. Zheng, Á. Gutiérrez-Bonet and G. A. Molander, *Chem*, 2019, **5**, 339–352.

260 F. G. Bordwell, H. E. Fried, D. L. Hughes, T. Y. Lynch, A. V Satish and Y. E. Whang, *J. Org. Chem.*, 1990, **55**, 3330–3336.

261 A. Das, A. G. Maher, J. Telser and D. C. Powers, *J. Am. Chem. Soc.*, 2018, **140**, 10412–10415.

262 M. H. Abraham, R. J. Abraham, J. Byrne and L. Griffiths, *J. Org. Chem.*, 2006, **71**, 3389–3394.

263 D. Lehnherr, Y. Ji, A. J. Neel, R. D. Cohen, A. P. J. Brunskill, J. Yang and M. Reibarkh, *J. Am. Chem. Soc.*, 2018, **140**, 13843–13853.

264 S. J. Pike, J. J. Hutchinson and C. A. Hunter, *J. Am. Chem. Soc.*, 2017, **139**, 6700–6706.

265 L. Zayat, C. Calero, P. Alborés, L. Baraldo and R. Etchenique, *J. Am. Chem. Soc.*, 2003, **125**, 882–883.

266 B. S. Howerton, D. K. Heidary and E. C. Glazer, *J. Am. Chem. Soc.*, 2012, **134**, 8324–8327.

267 M. H. Al-Afyouni, T. N. Rohrabaugh, K. F. Al-Afyouni and C. Turro, *Chem. Sci.*, 2018, **9**, 6711–6720.

268 M. Dickerson, B. Howerton, Y. Bae and E. C. Glazer, *J. Mater. Chem. B*, 2016, **4**, 394–408.

269 E. Wachter, B. S. Howerton, E. C. Hall, S. Parkin and E. C. Glazer, *Chem. Commun.*, 2014, **50**, 311–313.

270 Q.-X. Zhou, Y. Zheng, T.-J. Wang, Y.-J. Chen, K. Li, Y.-Y. Zhang, C. Li, Y.-J. Hou and X.-S. Wang, *Chem. Commun.*, 2015, **51**, 10684–10686.

271 J. D. Knoll, B. A. Albani, C. B. Durr and C. Turro, *J. Phys. Chem. A*, 2014, **118**, 10603–10610.

272 L. Salassa, C. Garino, G. Salassa, R. Gobetto and C. Nervi, *J. Am. Chem. Soc.*, 2008, **130**, 9590–9597.

273 C. Mari, V. Pierroz, S. Ferrari and G. Gasser, *Chem. Sci.*, 2015, **6**, 2660–2686.

274 N. Karaoun and A. K. Renfrew, *Chem. Commun.*, 2015, **51**, 14038–14041.

275 A. Li, C. Turro and J. J. Kodanko, *Chem. Commun.*, 2018, **54**, 1280–1290.

276 J. Van Houten and R. J. Watts, *J. Am. Chem. Soc.*, 1976, **98**, 4853–4858.

277 A. Soupart, F. Alary, J.-L. Heully, P. I. P. Elliott and I. M. Dixon, *Inorg. Chem.*, 2018, **57**, 3192–3196.

278 Z. Zhou, S. Chen, Y. Hong, E. Winterling, Y. Tan, M. Hemming, K. Harms, K. N. Houk and E. Meggers, *J. Am. Chem. Soc.*, 2019, **141**, 19048–19057.

279 Q. Zhu, D. E. Graff and R. R. Knowles, *J. Am. Chem. Soc.*, 2018, **140**, 741–747.

280 G. Qiu and R. R. Knowles, *J. Am. Chem. Soc.*, 2019, **141**, 16574–16578.

281 S. T. Nguyen, Q. Zhu and R. R. Knowles, *ACS Catal.*, 2019, **9**, 4502–4507.

282 L. Q. Nguyen and R. R. Knowles, *ACS Catal.*, 2016, **6**, 2894–2903.

283 C. B. Roos, J. Demaerel, D. E. Graff and R. R. Knowles, *J. Am. Chem. Soc.*, 2020, **142**, 5974–5979.

284 T. Nishiguchi, H. Tochio, A. Nabeya and Y. Iwakura, *J. Am. Chem. Soc.*, 1969, **91**, 5835–5841.

285 D. Ferraris, W. J. Drury, C. Cox and T. Lectka, *J. Org. Chem.*, 1998, **63**, 4568–4569.

286 D. R. Williams, C. M. Rojas and S. L. Bogen, *J. Org. Chem.*, 1999, **64**, 736–746.

287 D. M. Arnold, M. G. LaPorte, S. M. Anderson and P. Wipf, *Tetrahedron*, 2013, **69**, 7719–7731.

288 B. Willy, F. Rominger and T. J. J. Müller, *Synthesis (Stuttg).*, 2008, **2008**, 293–303.

289 R. J. Cox, D. J. Ritson, T. A. Dane, J. Berge, J. P. H. Charmant and A. Kantacha, *Chem. Commun.*, 2005, 1037–1039.

290 J. P. Waldo and R. C. Larock, *Org. Lett.*, 2005, **7**, 5203–5205.

291 A. O. Stewart and D. W. Brooks, *J. Org. Chem.*, 1992, **57**, 5020–5023.

292 J. J. Higgin, G. I. Yakovlev, V. A. Mitkevich, A. A. Makarov and R. T. Raines, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 409–412.

293 K.-H. Ng, A. S. C. Chan and W.-Y. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 12862–12864.

294 J. Huang, Z. Zou, D. B. Kim-Shapiro, S. K. Ballas and S. B. King, *J. Med. Chem.*, 2003, **46**, 3748–3753.

295 D.-F. Lu, C.-L. Zhu, Z.-X. Jia and H. Xu, *J. Am. Chem. Soc.*, 2014, **136**, 13186–13189.

296 Q. Wang, J. An, H. Alper, W.-J. Xiao and A. M. Beauchemin, *Chem. Commun.*, 2017, **53**, 13055–13058.

297 L. C. Dias, L. S. Farina and M. A. B. Ferreira, *J. Brazilian Chem. Soc.* , 2013, 24, 184–190.

298 G. M. STEINBERG and J. BOLGER, *J. Org. Chem.*, 1956, **21**, 660–662.

299 D.-K. Kim, J. Gam, Y.-W. Kim, J. Lim, H.-T. Kim and K. H. Kim, *J. Med. Chem.*, 1997, **40**, 2363–2373.

300 H. Baji, M. Flammang, T. Kimny, F. Gasquez, P. L. Compagnon and A. Delcourt, *Eur. J. Med. Chem.*, 1995, **30**, 617–626.

301 Q.-A. Sun, Z.-H. Lu, X.-Q. Pu, H.-L. Hu, J. Zhang and X.-J. Yang, *European J. Org. Chem.*, 2018, **2018**, 3920–3927.

302 S. D. Barrett, A. J. Bridges, D. T. Dudley, A. R. Saltiel, J. H. Fergus, C. M. Flamme, A. M. Delaney, M. Kaufman, S. LePage, W. R. Leopold, S. A. Przybranowski, J. Sebolt-Leopold, K. Van Becelaere, A. M. Doherty, R. M. Kennedy, D. Marston, W. A. Howard, Y. Smith, J. S. Warmus and H. Tecle, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 6501–6504.

303 M.-Z. Wang, H. Xu, T.-W. Liu, Q. Feng, S.-J. Yu, S.-H. Wang and Z.-M. Li, *Eur. J. Med. Chem.*, 2011, **46**, 1463–1472.

304 J. N. Kim, K. M. Kim and E. K. Ryu, *Synth. Commun.*, 1992, **22**, 1427–1432.

305 C. Alamillo-Ferrer, J. M. Curle, S. C. Davidson, S. C. C. Lucas, S. J. Atkinson, M. Campbell, A. R. Kennedy and N. C. O. Tomkinson, *J. Org. Chem.*, 2018, **83**, 6728–6740.

306 P. Dubé, N. F. F. Nathel, M. Vetelino, M. Couturier, C. L. Aboussafy, S. Pichette, M. L. Jorgensen and M. Hardink, *Org. Lett.*, 2009, **11**, 5622–5625.

307 H. Lei and T. Rovis, *J. Am. Chem. Soc.*, 2019, **141**, 2268–2273.

308 T. J. Donohoe, M. J. Chughtai, D. J. Klauber, D. Griffin and A. D. Campbell, *J. Am. Chem. Soc.*, 2006, **128**, 2514–2515.

309 M. Leung, J.-L. Lai, K.-H. Lau, H. Yu and H.-J. Hsiao, *J. Org. Chem.*, 1996, **61**, 4175–4179.

310 G. Holzmann, B. Krieg, H. Lautenschläger and P. Konieczny, *J. Heterocycl. Chem.*, 1979, **16**, 983–991.

311 A. S. Sigachev, A. N. Kravchenko, P. A. Belyakov, O. V Lebedev and N. N. Makhova, *Russ. Chem. Bull.*, 2006, **55**, 865–872.

312 K. Ando, T. Kobayashi and N. Uchida, *Org. Lett.*, 2015, **17**, 2554–2557.

313 P. Liu, Z. Wang and X. Hu, *European J. Org. Chem.*, 2012, **2012**, 1994–2000.

314 T. H. Kim and G.-J. Lee, *J. Org. Chem.*, 1999, **64**, 2941–2943.

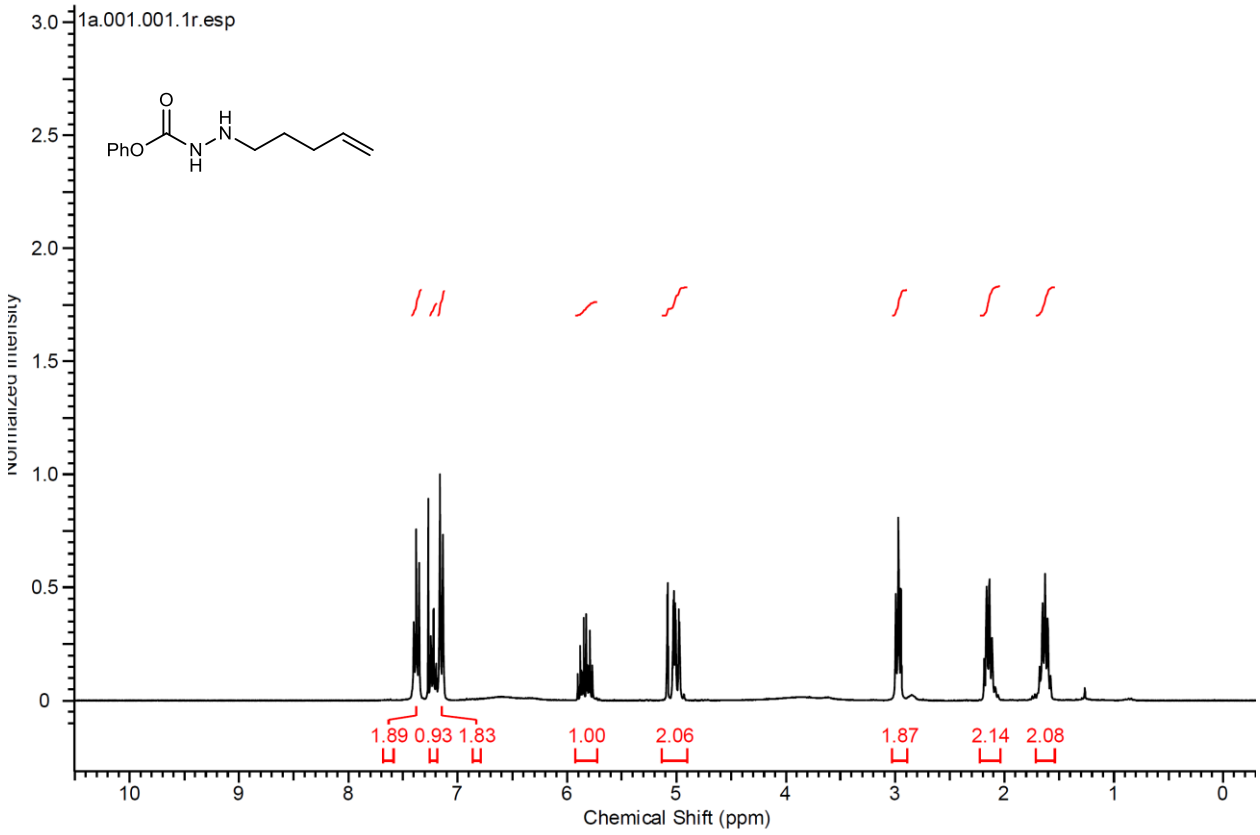
315 G. Vernin, H. Domlog, C. Siv, J. Metzger and A. K. El-Shafei, *J. Heterocycl. Chem.*, 1981, **18**, 85–89.

316 I. Tapia, L. Alonso-Cires, P. L. López-Tudanca, R. Mosquera, L. Labeaga, A. Innerárity and A. Orjales, *J. Med. Chem.*, 1999, **42**, 2870–2880.

317 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648–5652.

318 N. Mardirossian and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, 2014, **16**, 9904–9924.

NMR Spectra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PhO
O
H
N
N
H
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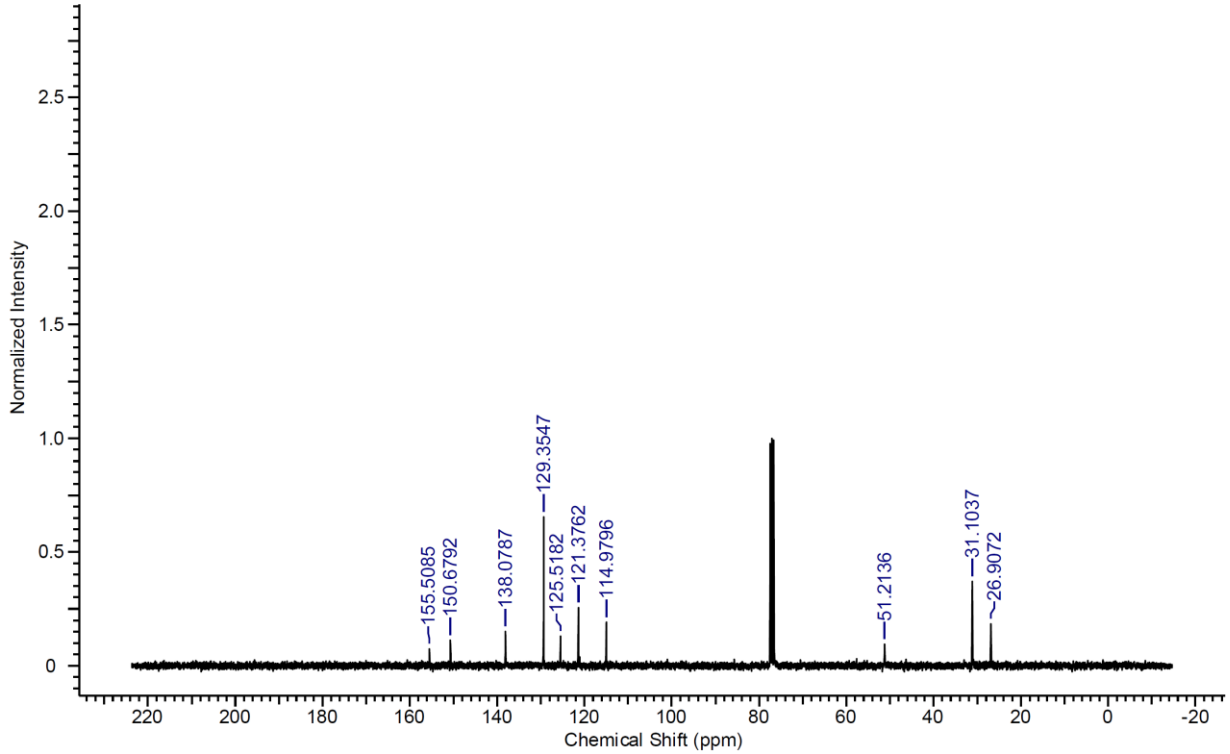
1.83
1.00
2.06
1.87
2.14
2.08
Chemical Shift (ppm)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51.2136
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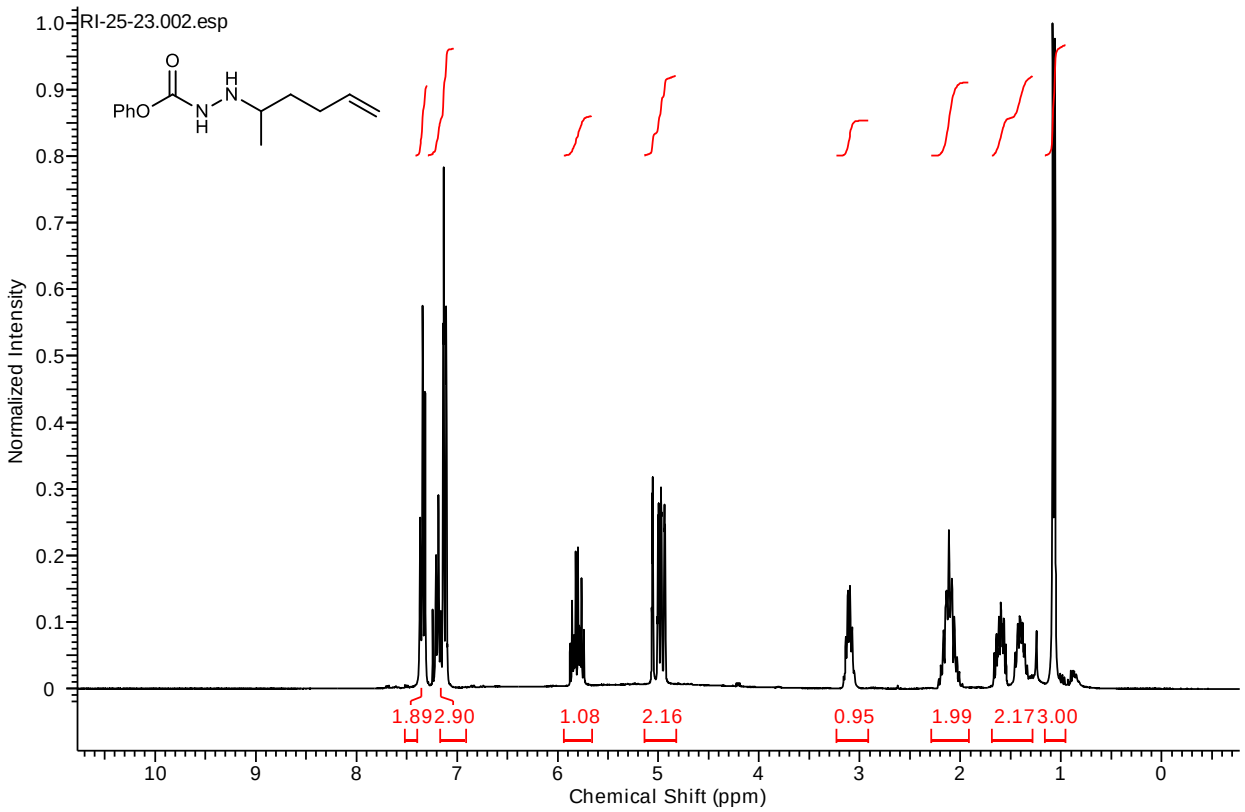
26.9072
Chemical Shift (ppm)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1.08
2.16
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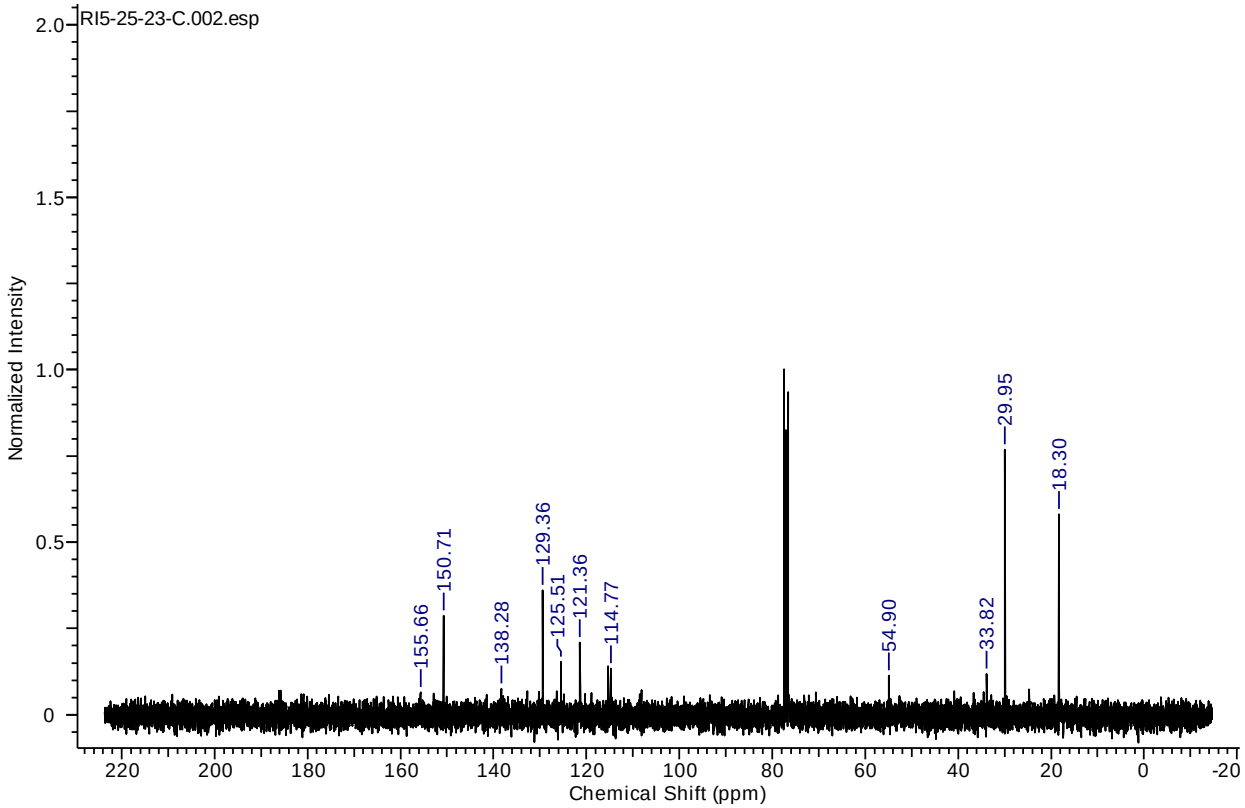
1.99
2.17
3.00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Chemical Shift (ppm)
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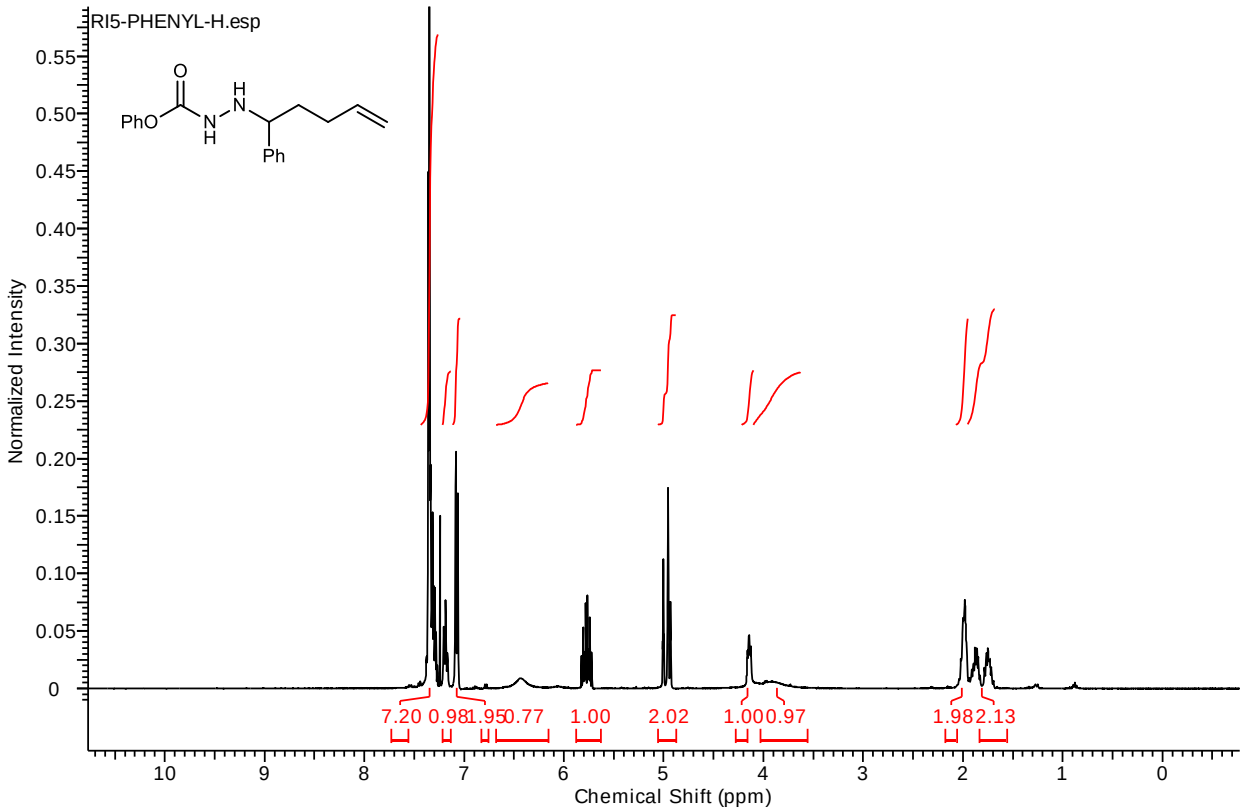
125.51
121.36
114.77
54.90
33.82
29.95
18.30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Normalized Intensity
Chemical Shift (ppm)
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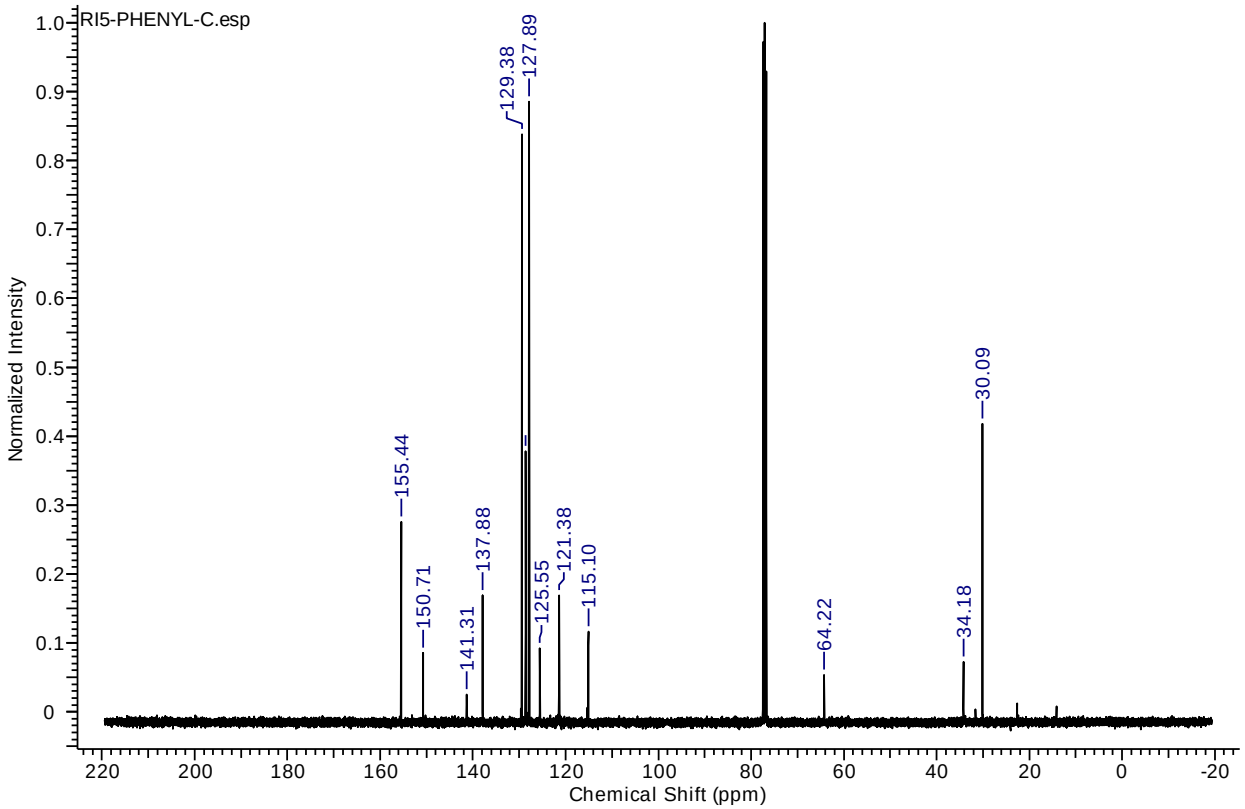
0.98
1.95
0.77
1.00
2.02
1.00
0.97
1.98
2.13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Normalized Intensity
Chemical Shift (ppm)
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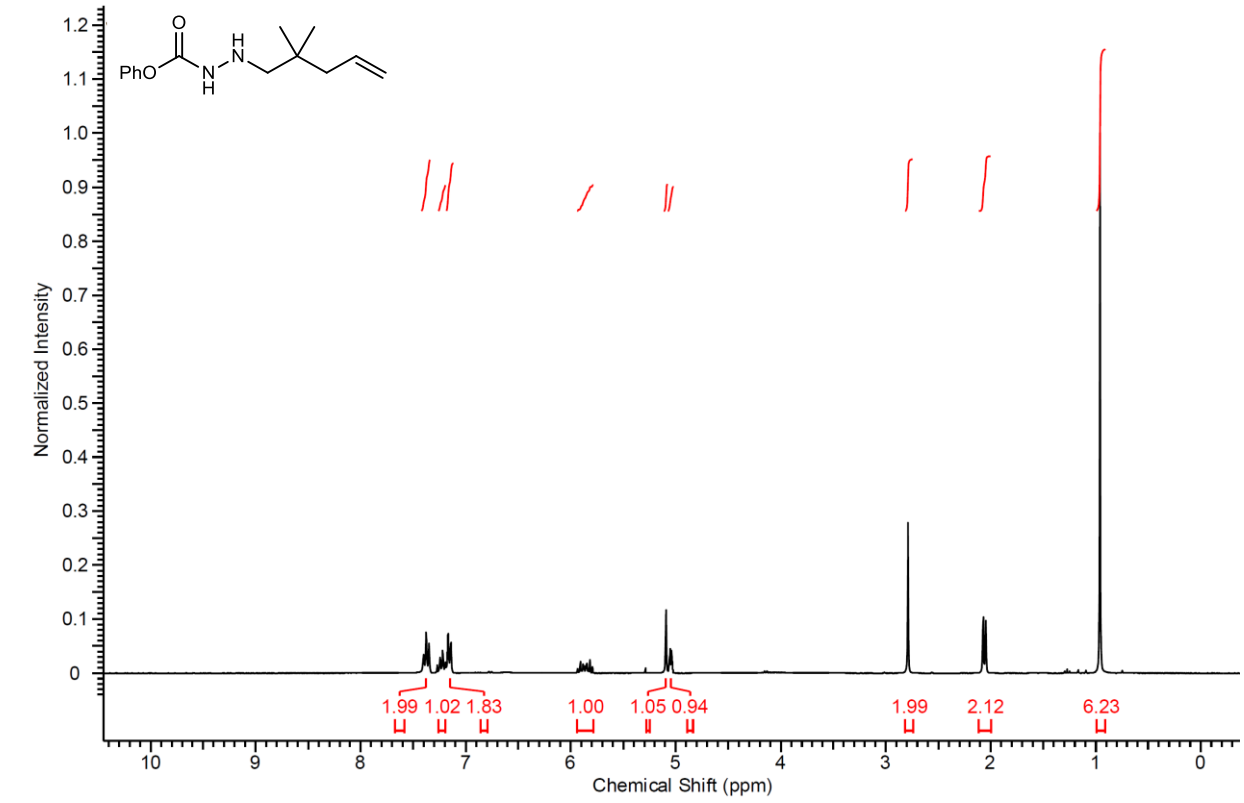
129.38
127.89
125.55
121.38
115.10
64.22
34.18
30.09


PhO
O
N
H
N
H
Normalized Intensity
Chemical Shift (ppm)
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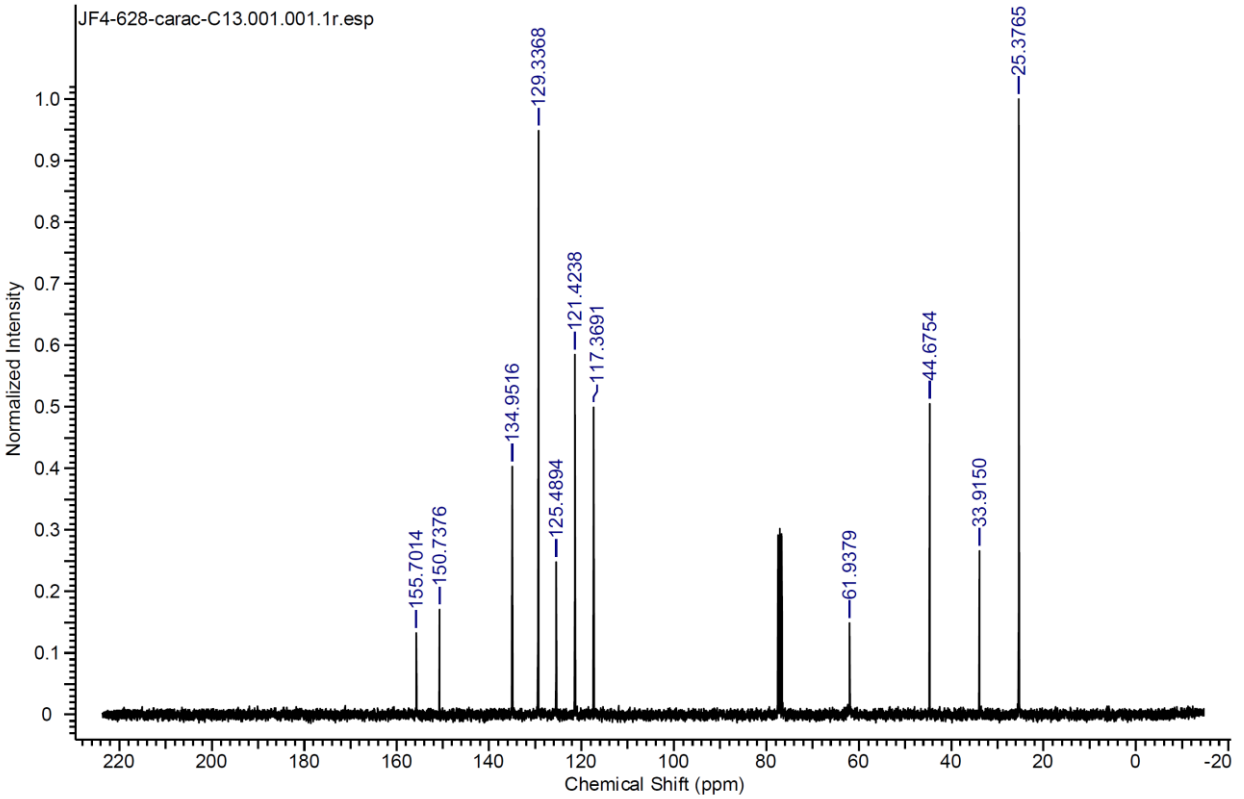
1.02
1.83
1.00
1.05
0.94
1.99
2.12
6.23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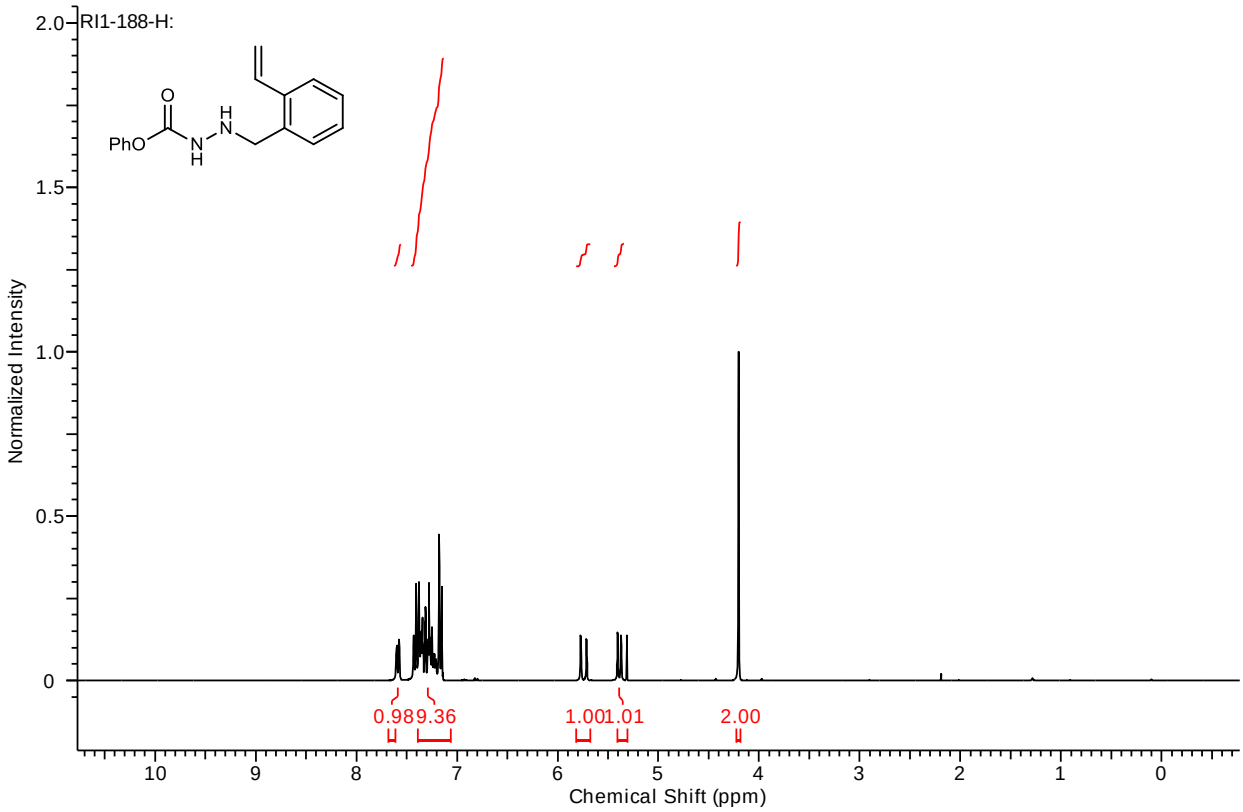
25.3765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O
PhO
N
H
H
N
Normalized Intensity
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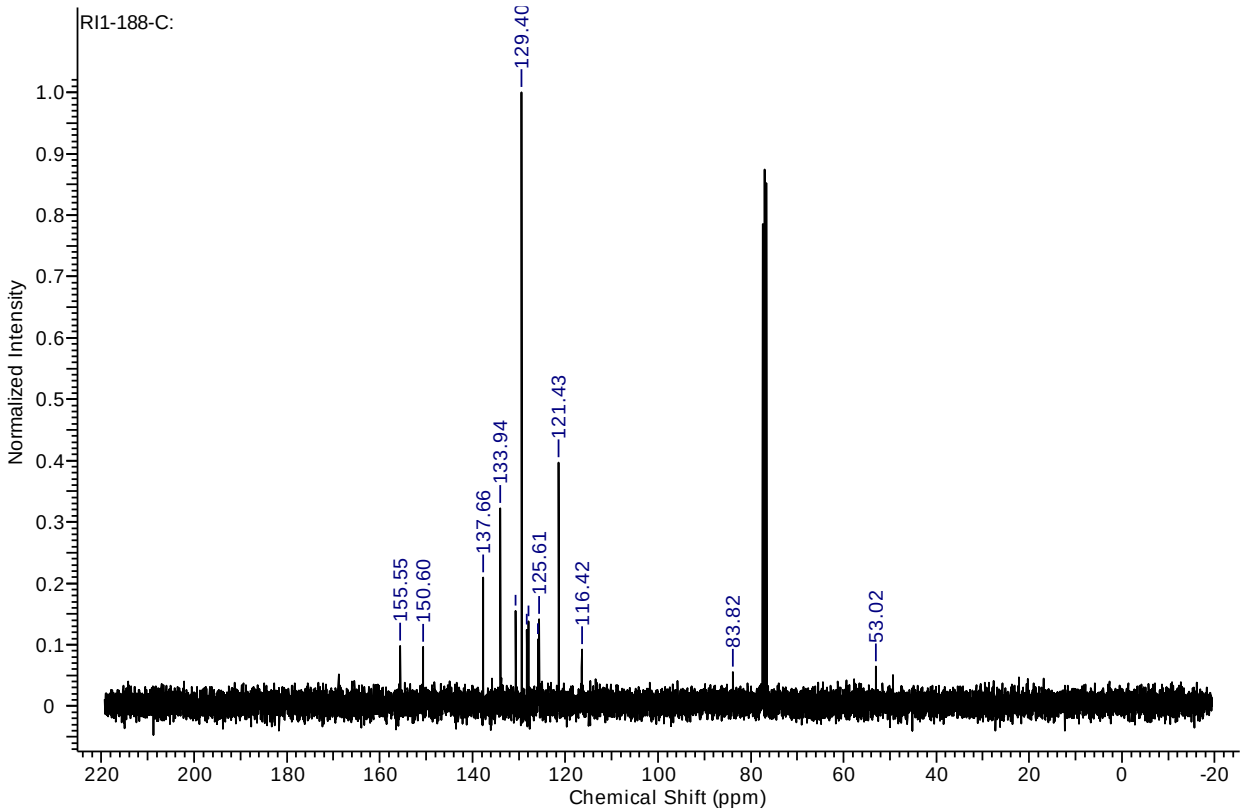
1.0
0.5
0
0.98
9.36
1.00
1.01
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)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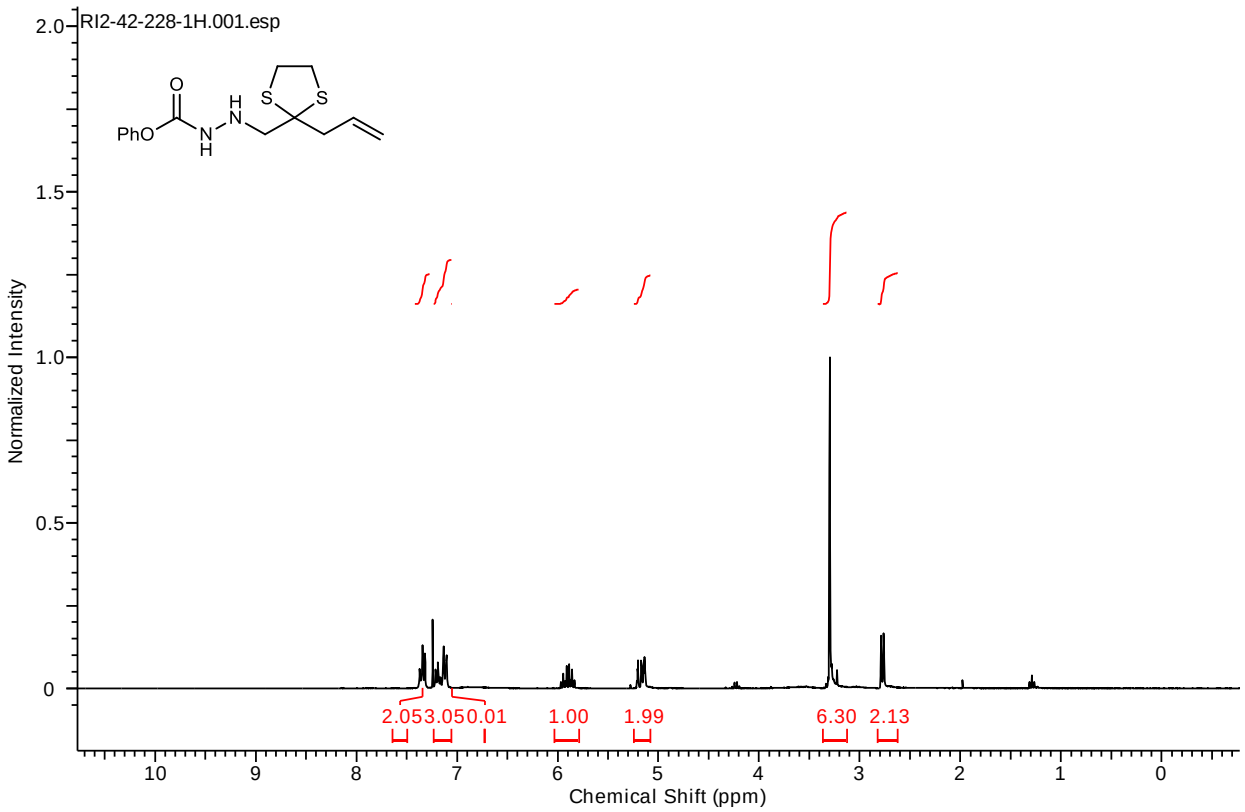
133.94
137.66
121.43
155.55
150.60
125.61
116.42
83.82
53.02
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)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O
H
N
N
H
S
S
Normalized Intensity
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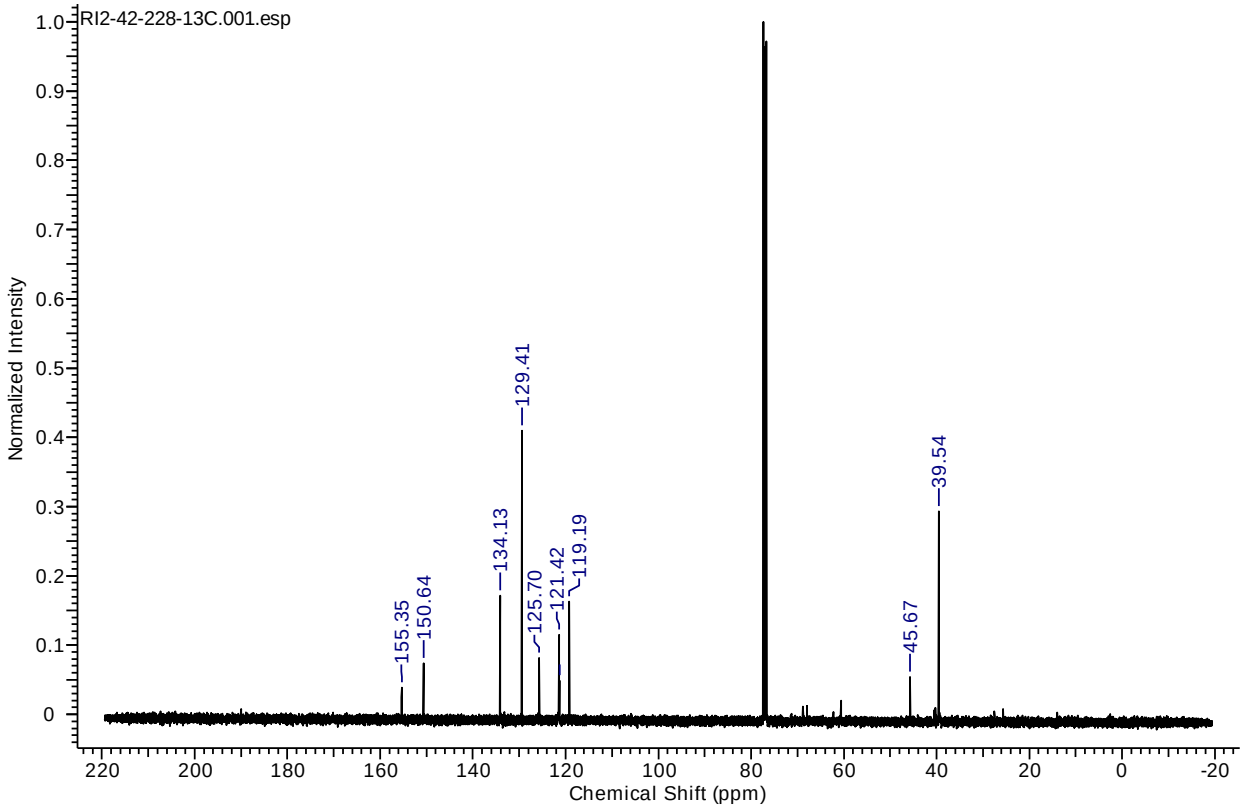
1.00
1.99
6.30
2.13
Chemical Shift (ppm)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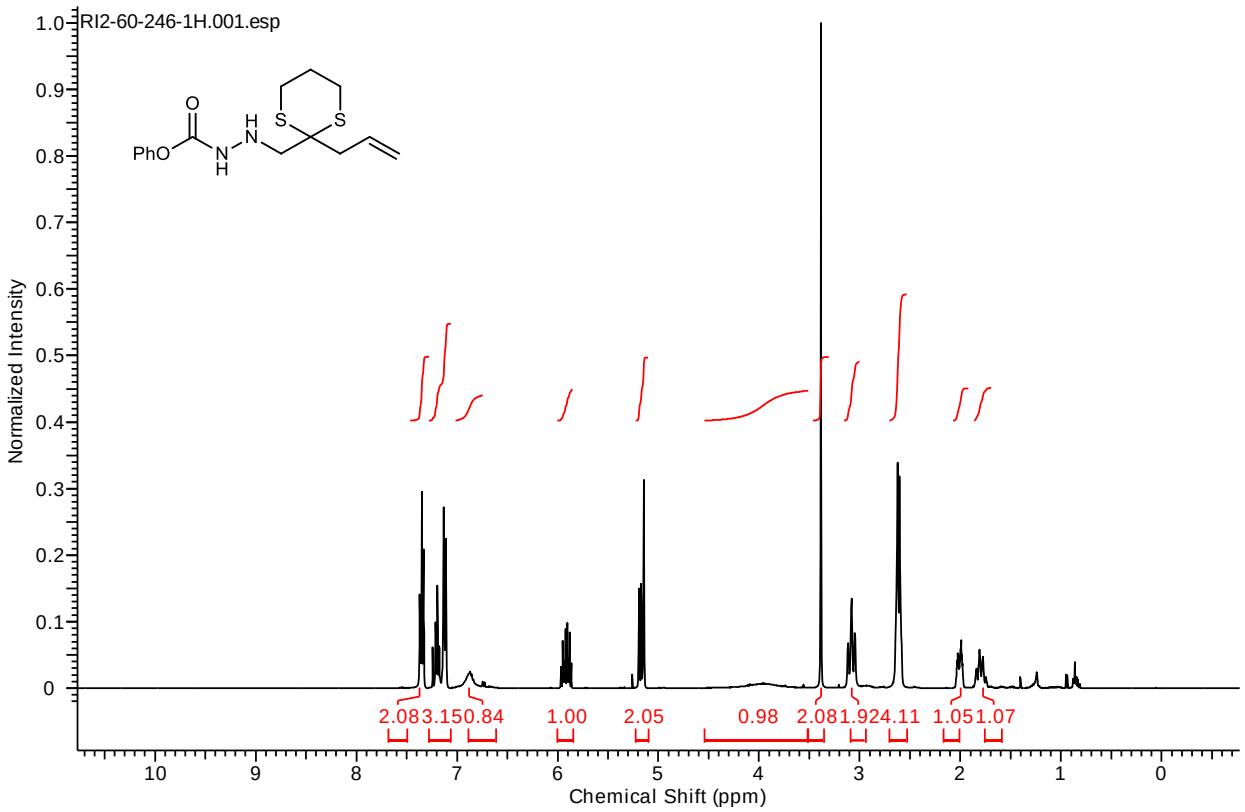
129.41
125.70
121.42
119.19
45.67
39.54
Chemical Shift (ppm)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Normalized Intensity
Chemical Shift (ppm)
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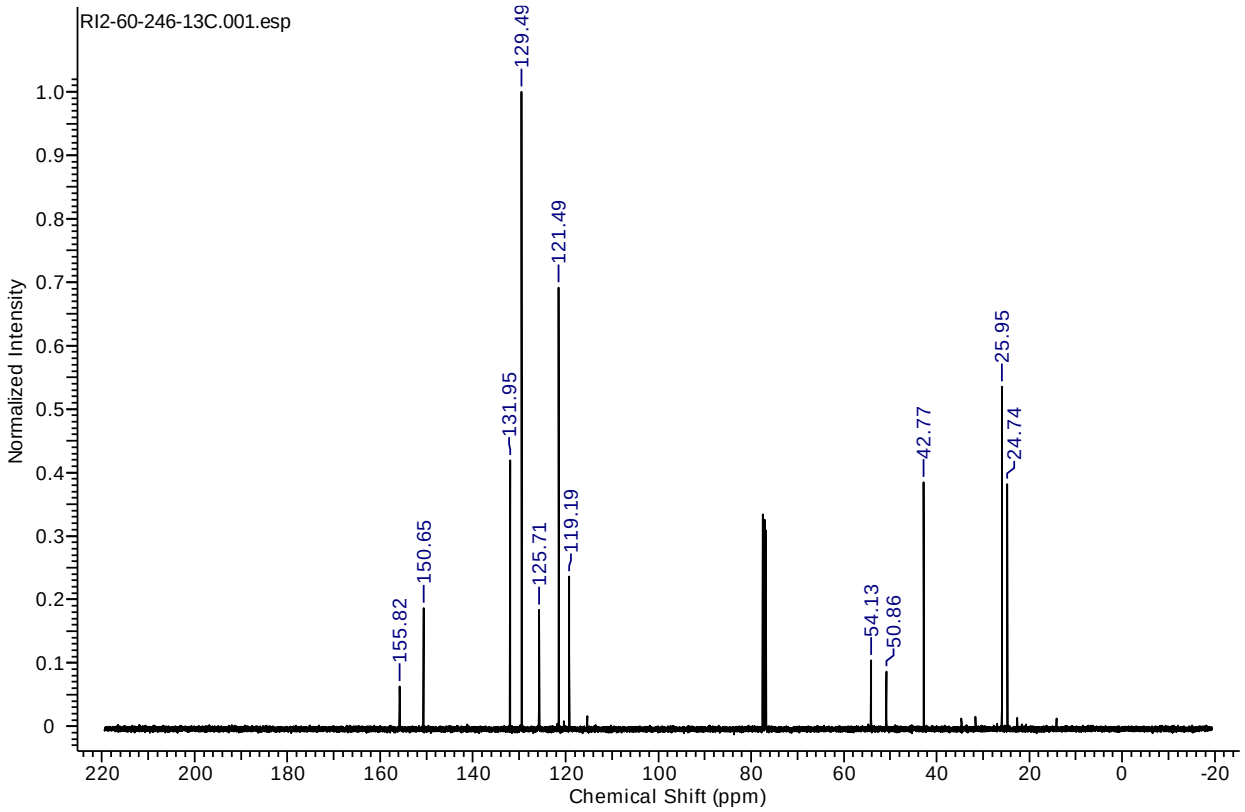
1.00
2.05
0.98
2.08
1.92
4.11
1.05
1.07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Normalized Intensity
Chemical Shift (ppm)
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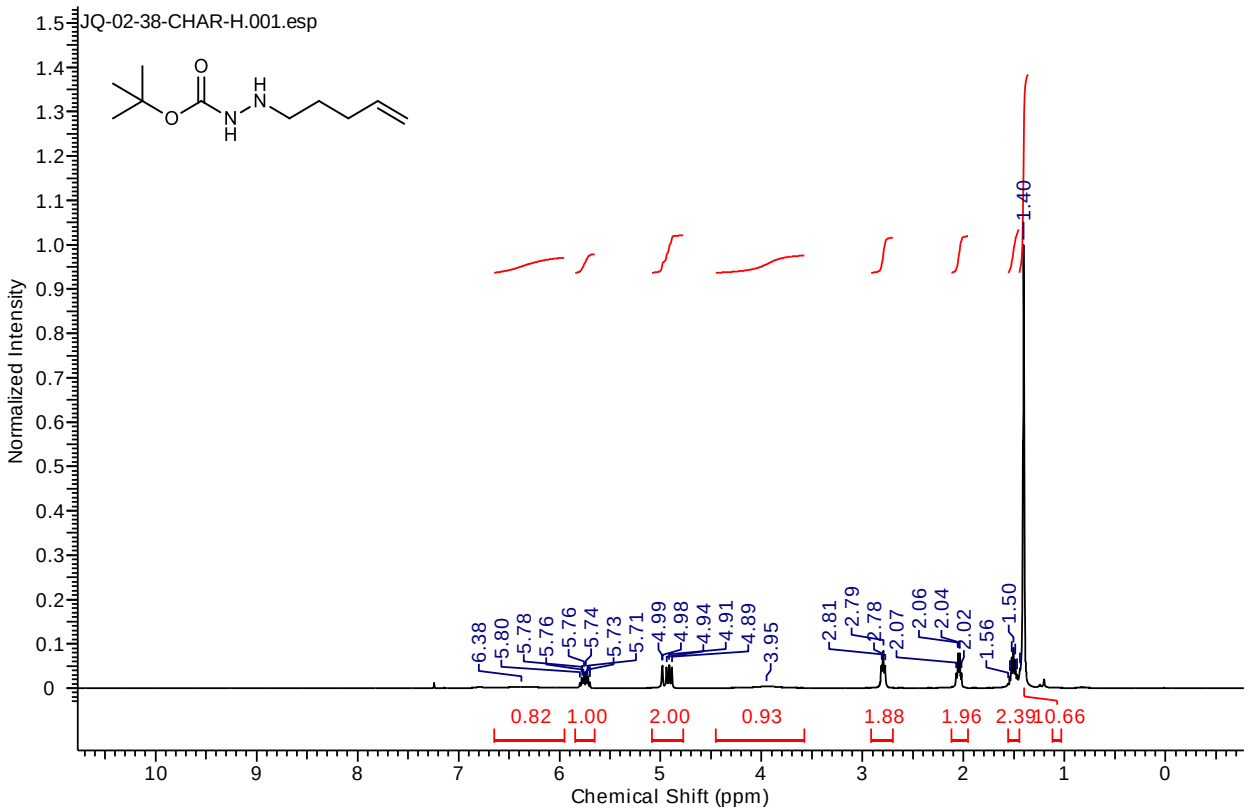
125.71
121.49
119.19
54.13
50.86
42.77
25.95
24.74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Normalized Intensity
Chemical Shift (ppm)
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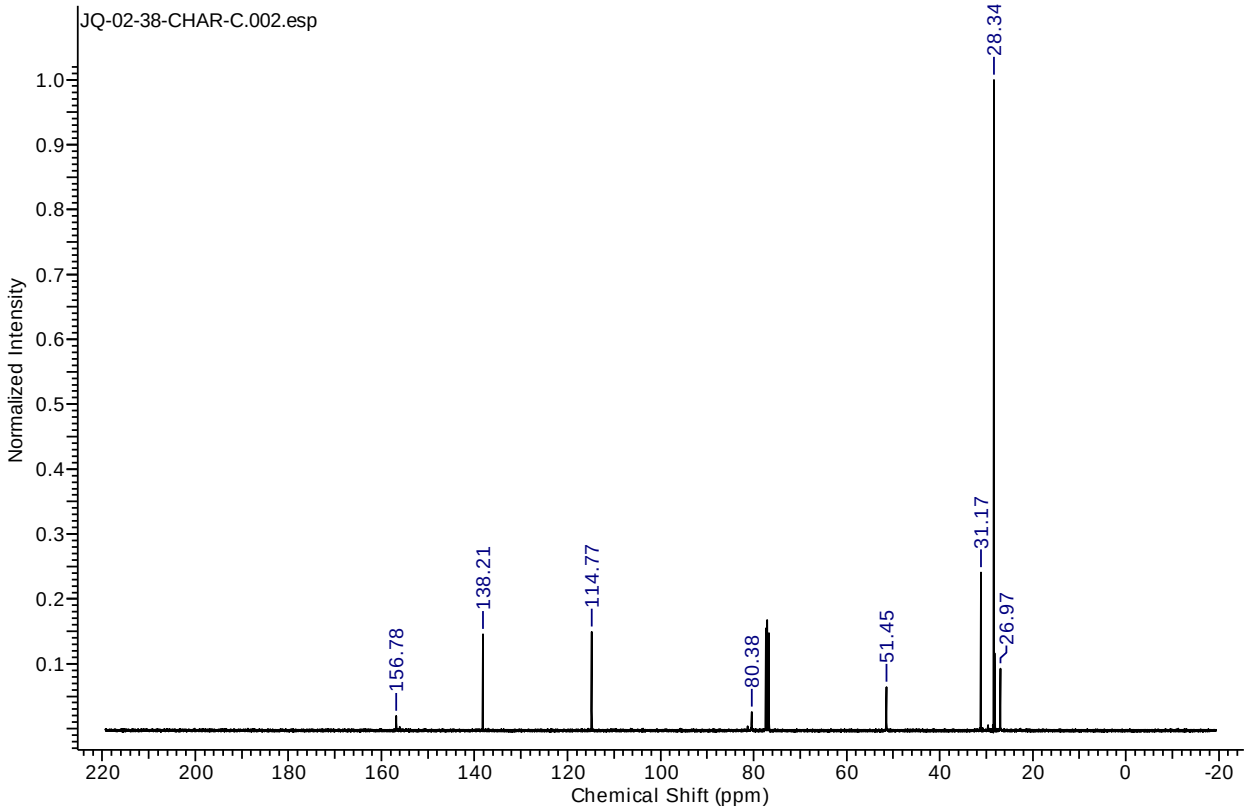
5.80
5.78
5.76
5.74
5.73
5.71
4.99
4.98
4.94
4.91
4.89
3.95
2.81
2.79
2.78
2.07
2.06
2.04
2.02
1.56
1.50
1.40
0.82
1.00
2.00
0.93
1.88
1.96
2.39
10.66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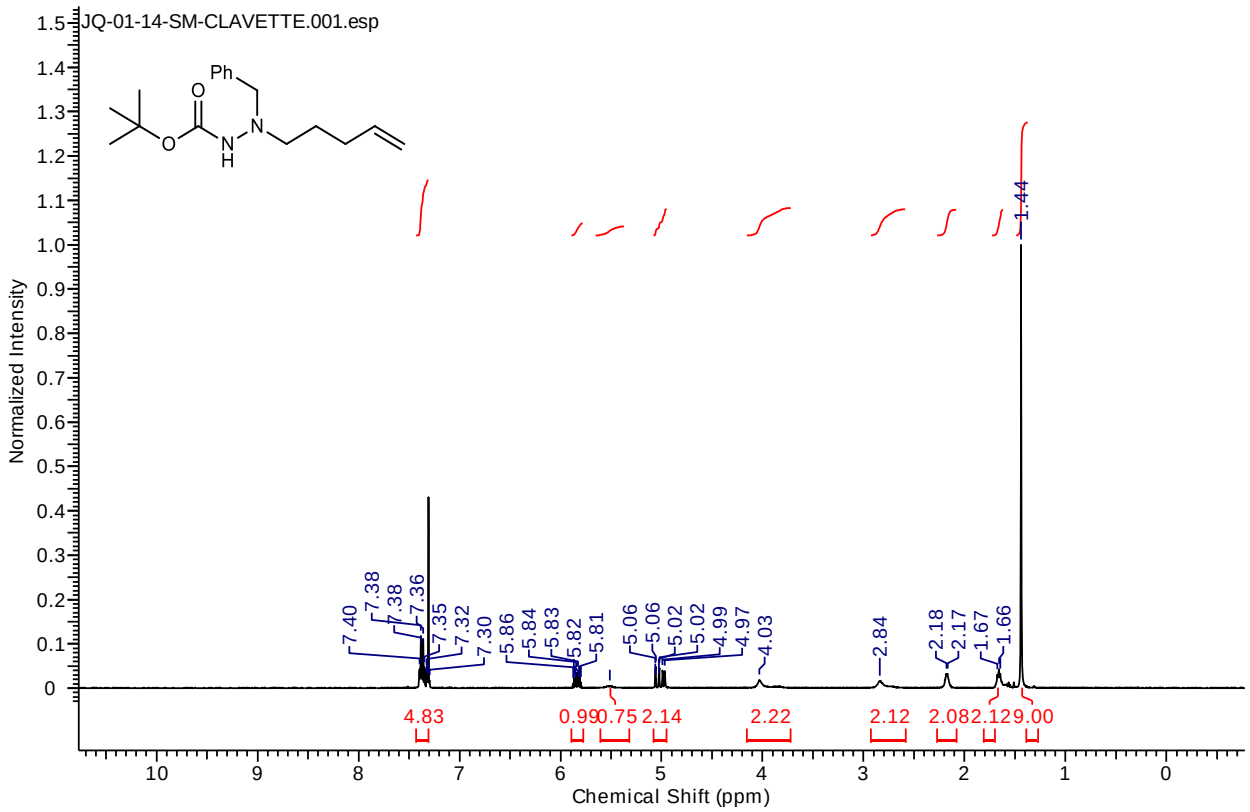
28.34
26.97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Ph
O
O
N
N
H
Normalized Intensity
Chemical Shift (ppm)
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7.38
7.38
7.36
7.35
7.32
7.30
5.86
5.84
5.83
5.82
5.81
5.06
5.06
5.02
5.02
4.99
4.97
4.03
2.84
2.18
2.17
1.67
1.66
1.44
4.83
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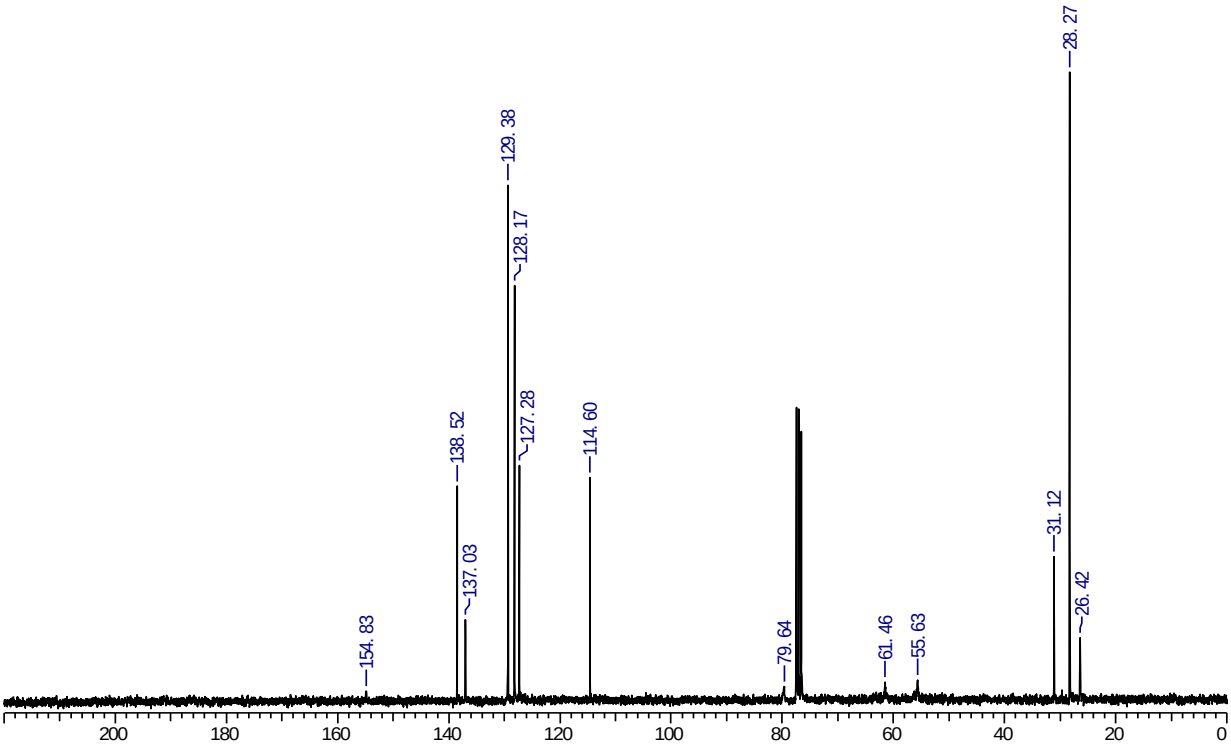
2.22
2.12
2.08
2.12
9.00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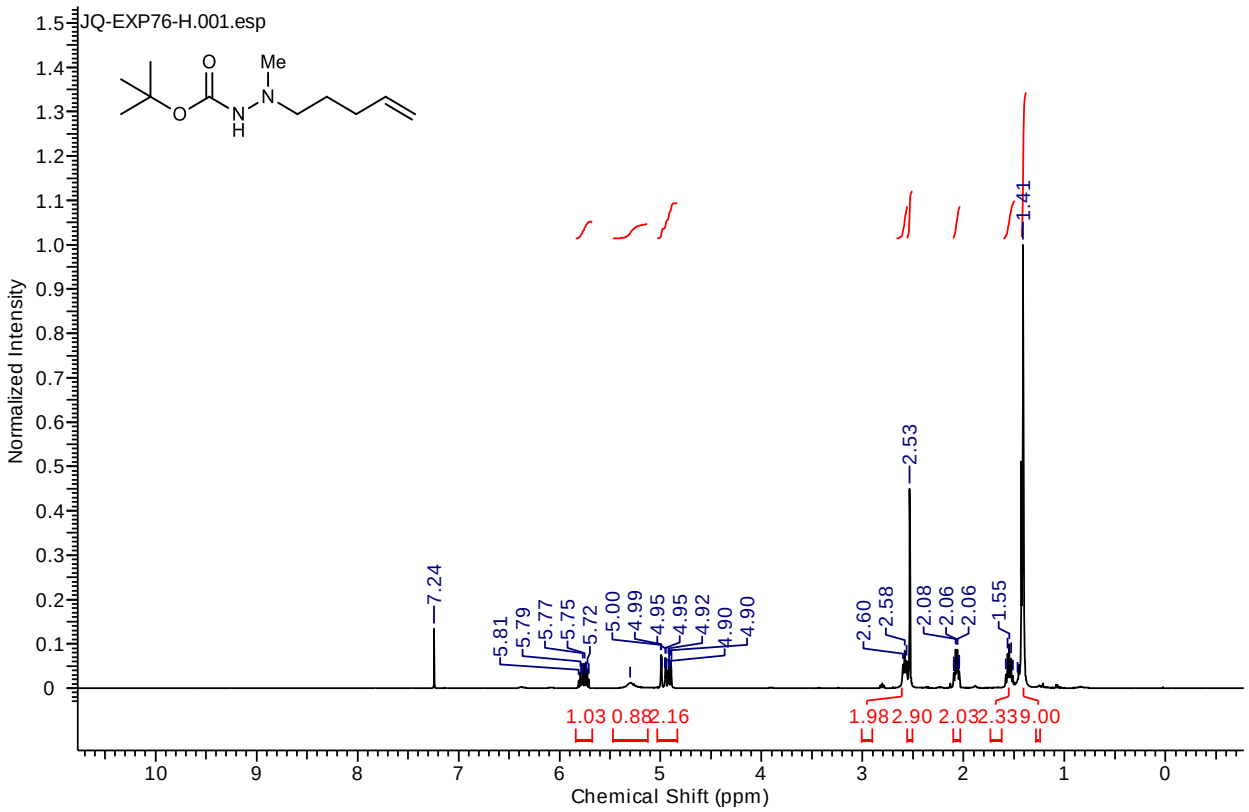
31.12
28.27
26.42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O
O
N
H
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Chemical Shift (ppm)
7.24
5.81
5.79
5.77
5.75
5.72
5.00
4.99
4.95
4.95
4.92
4.90
4.90
2.60
2.58
2.53
2.08
2.06
2.06
1.55
1.41
1.03
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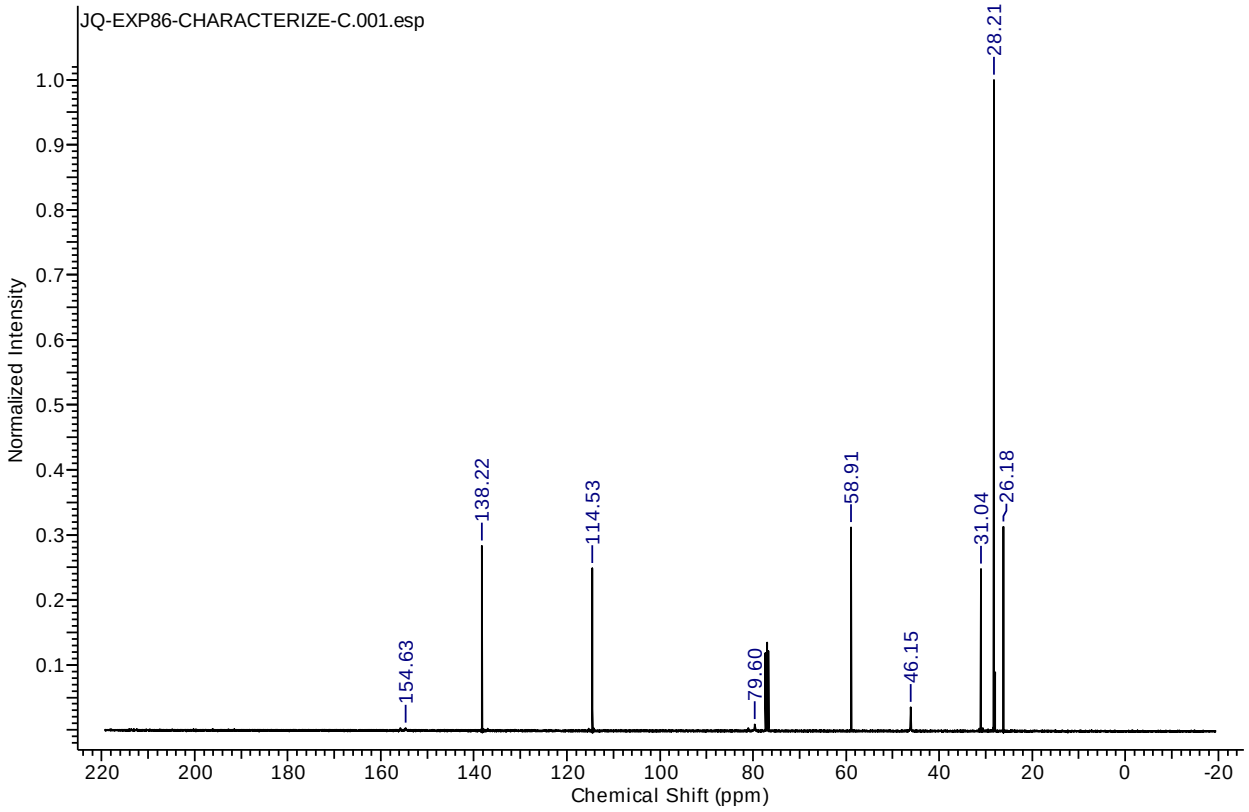
2.16
1.98
2.90
2.03
2.33
9.00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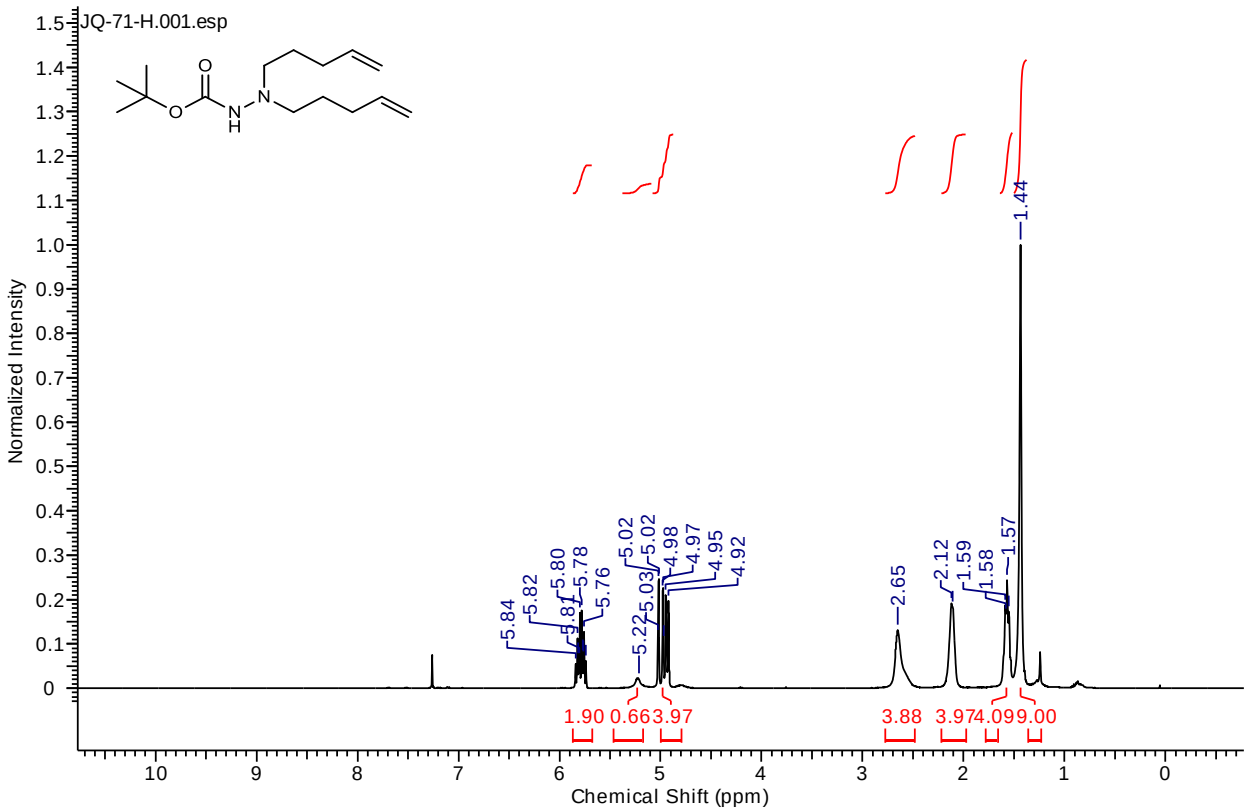
28.21
26.18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Chemical Shift (ppm)
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5.82
5.80
5.78
5.76
5.22
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5.02
5.03
4.98
4.97
4.95
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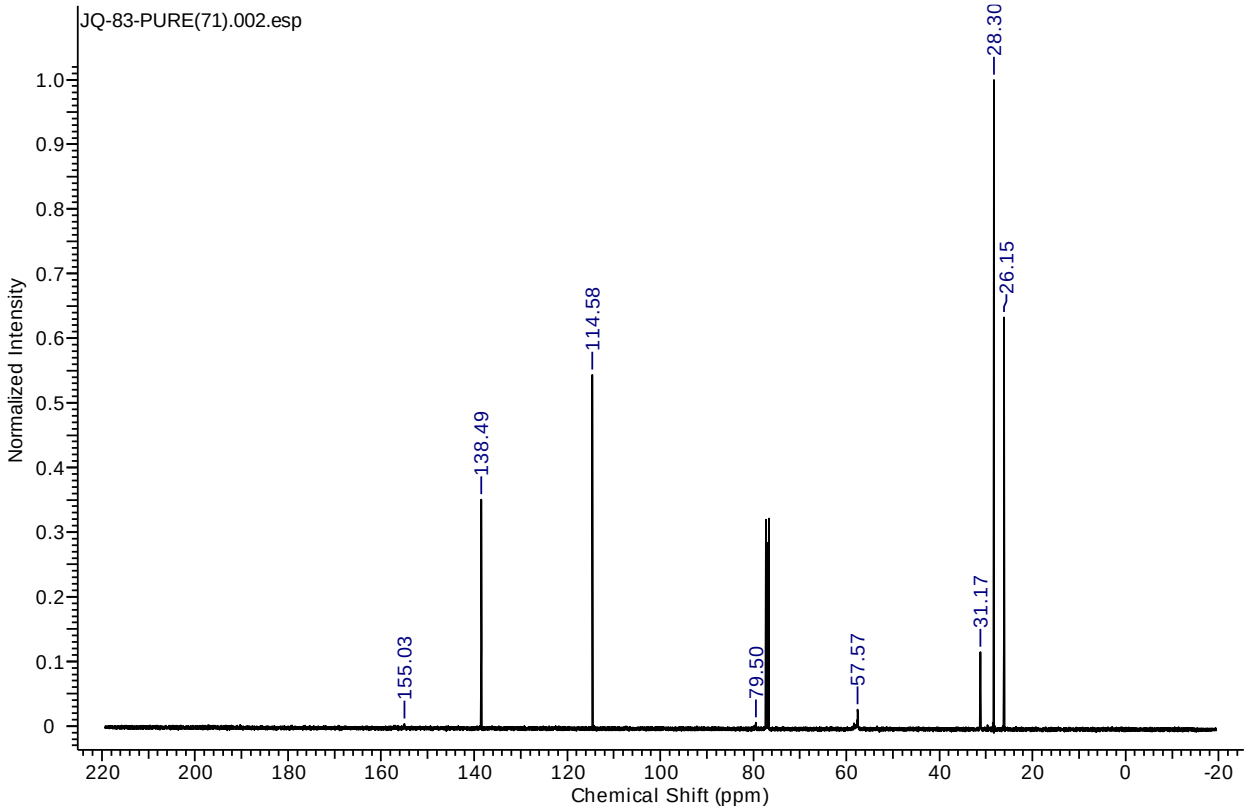
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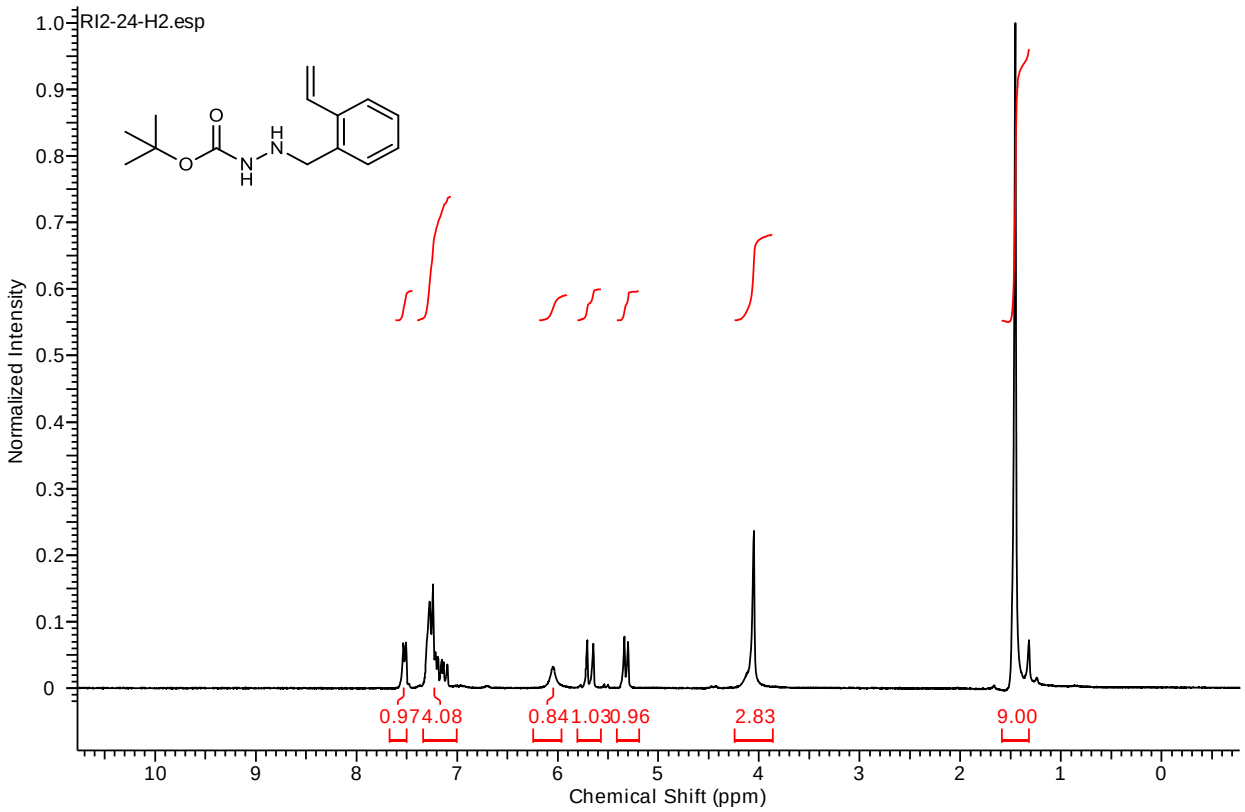
28.30
26.15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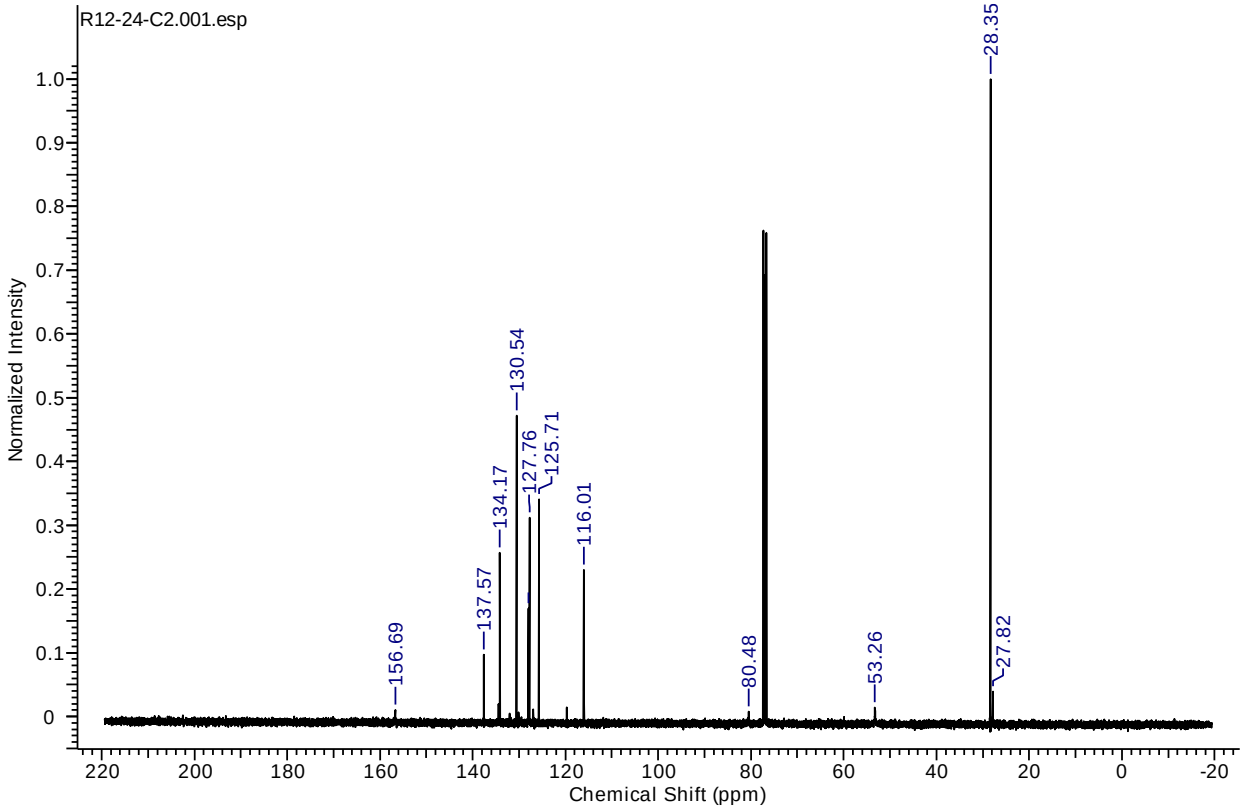
4.08
0.84
1.03
0.96
2.83
9.00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Normalized Intensity
Chemical Shift (ppm)
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125.71
134.17
116.01
137.57
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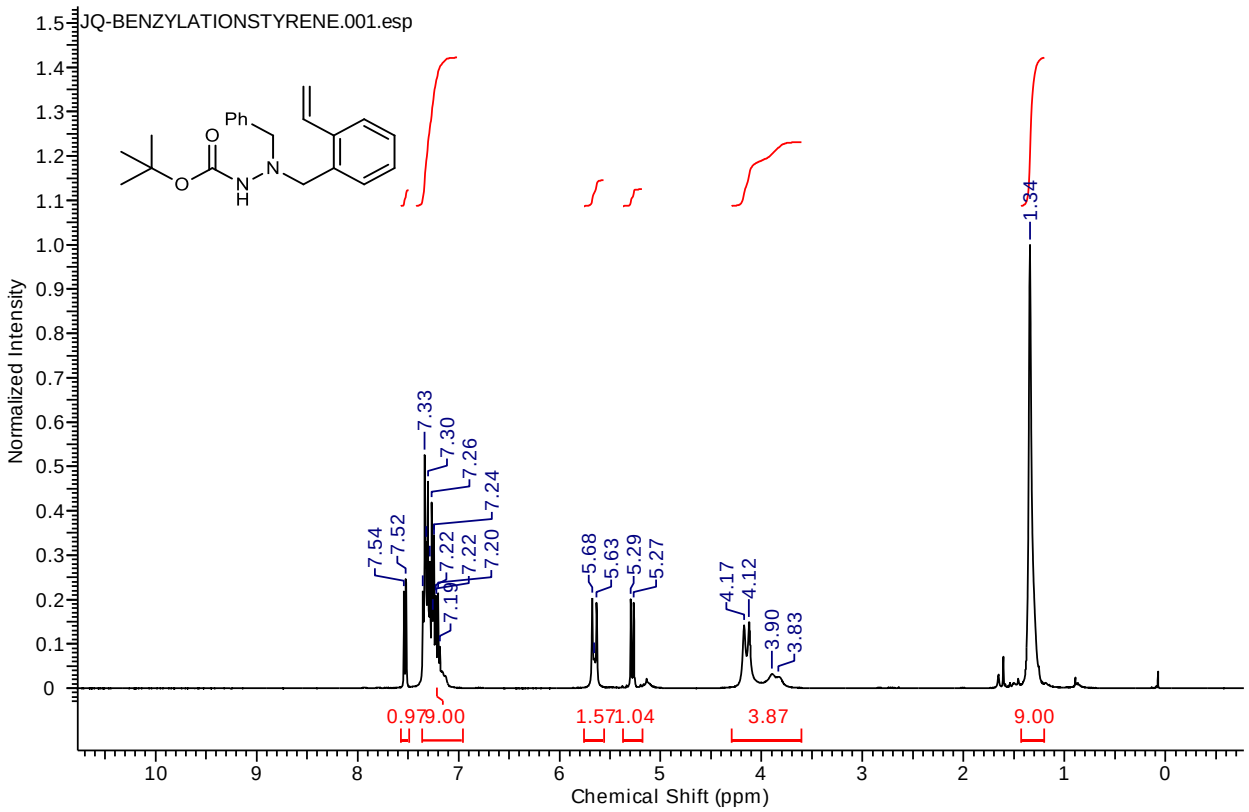
80.48
53.26
27.82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Chemical Shift (ppm)
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7.52
7.33
7.30
7.26
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7.22
7.20
7.19
5.68
5.63
5.29
5.27
4.17
4.12
3.90
3.83
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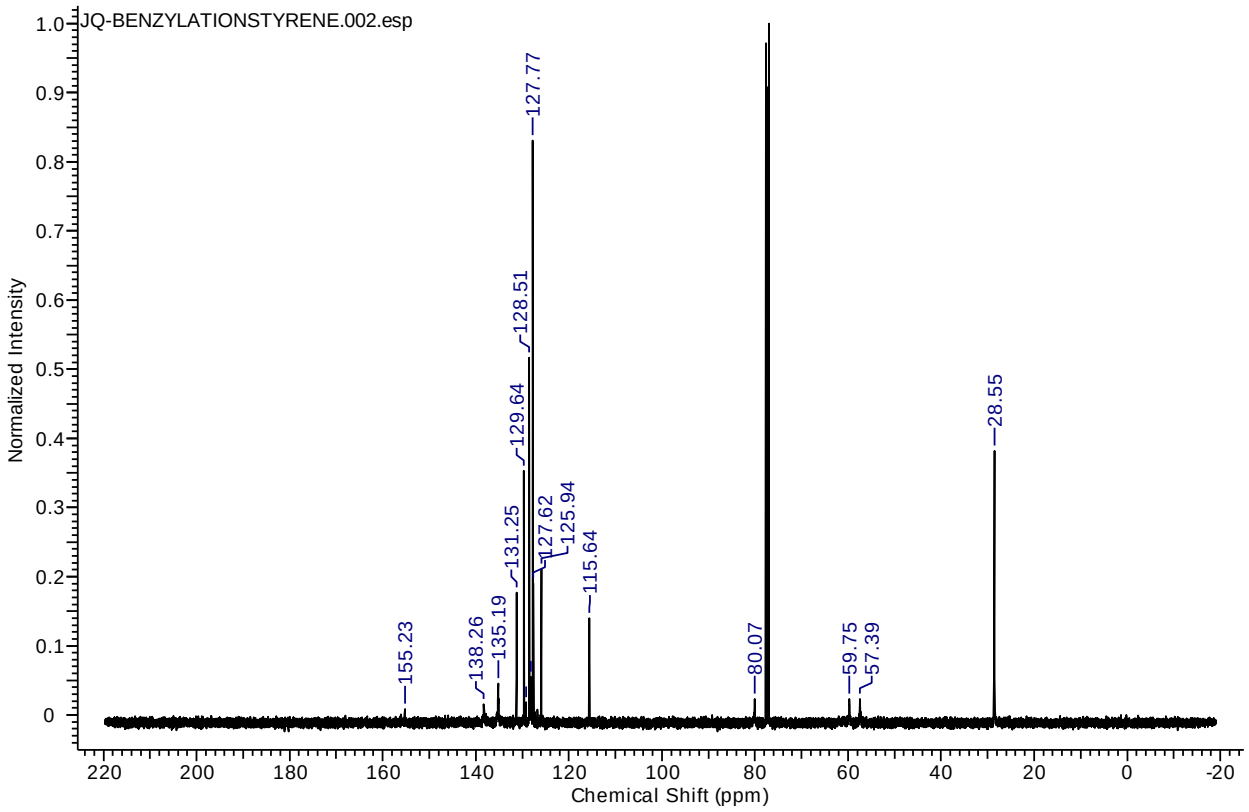
9.00
1.57
1.04
3.87
9.00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131.25
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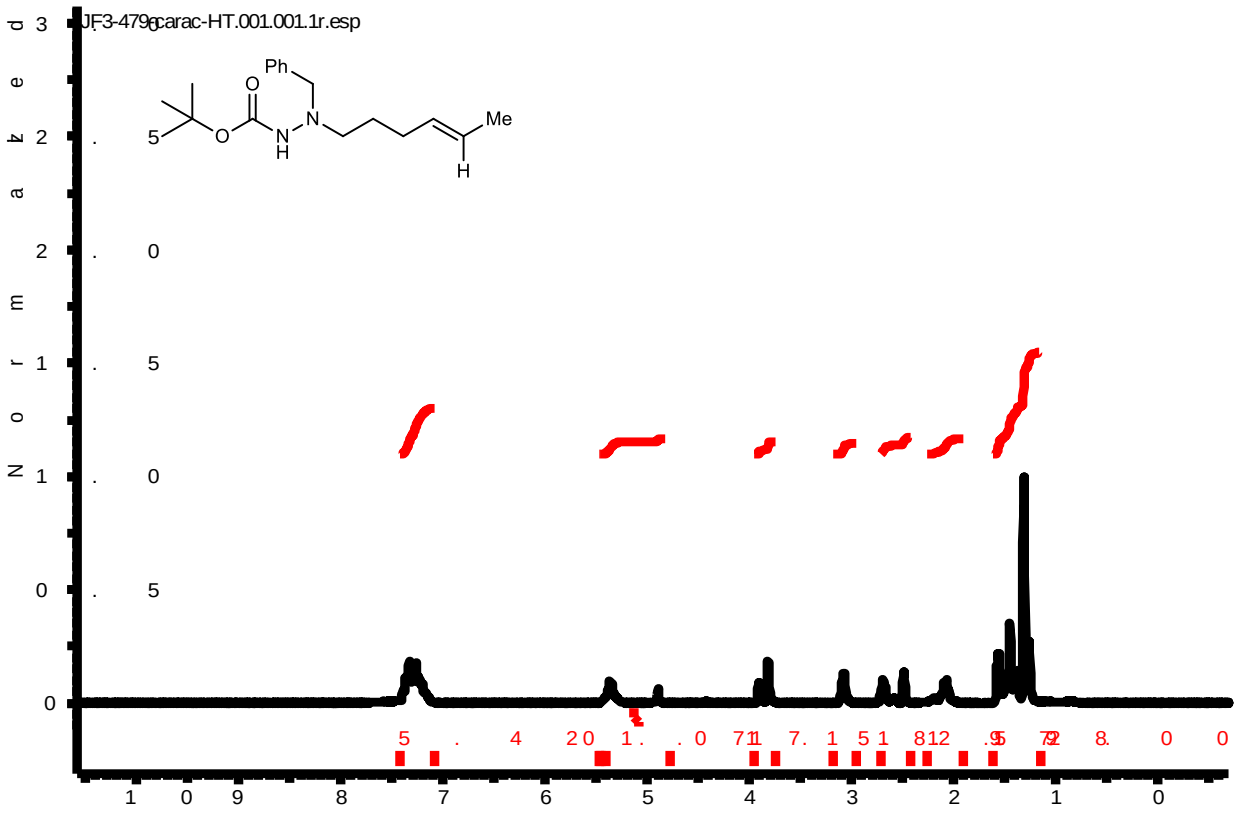
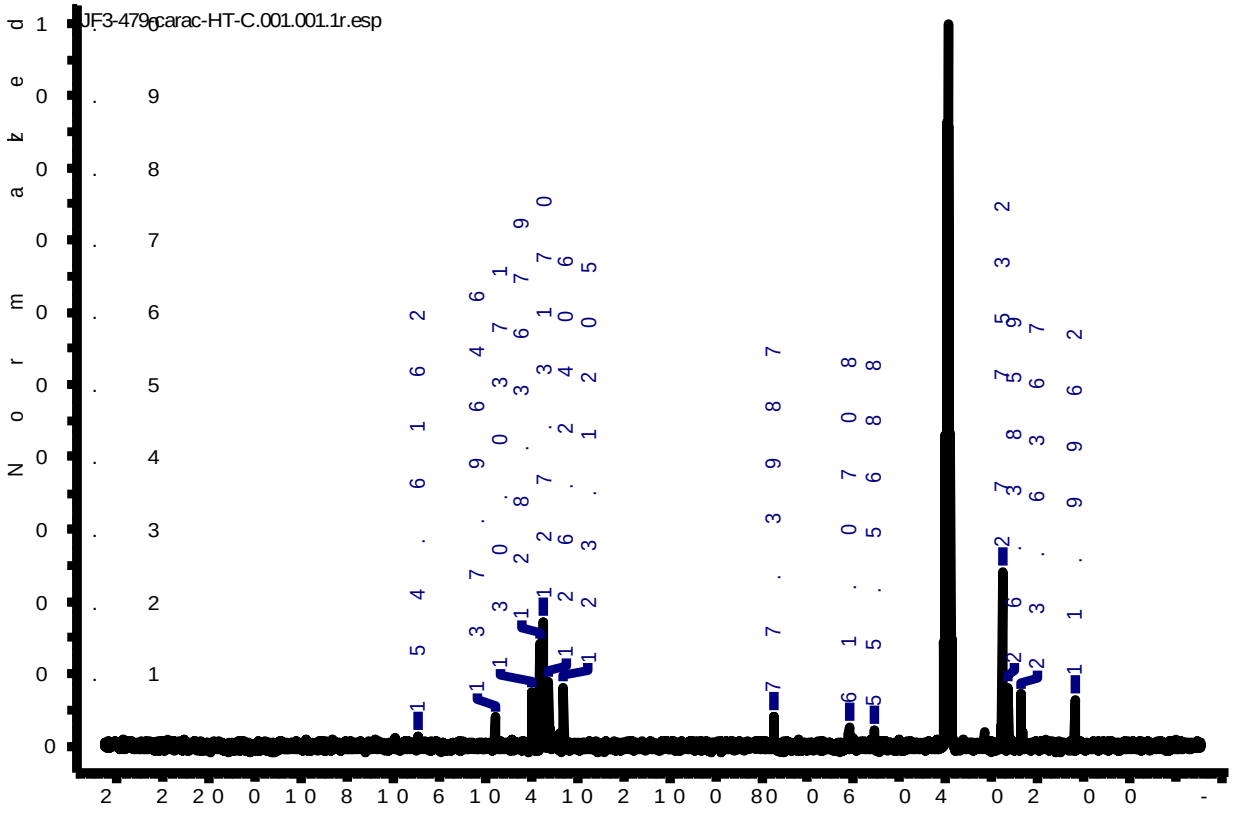
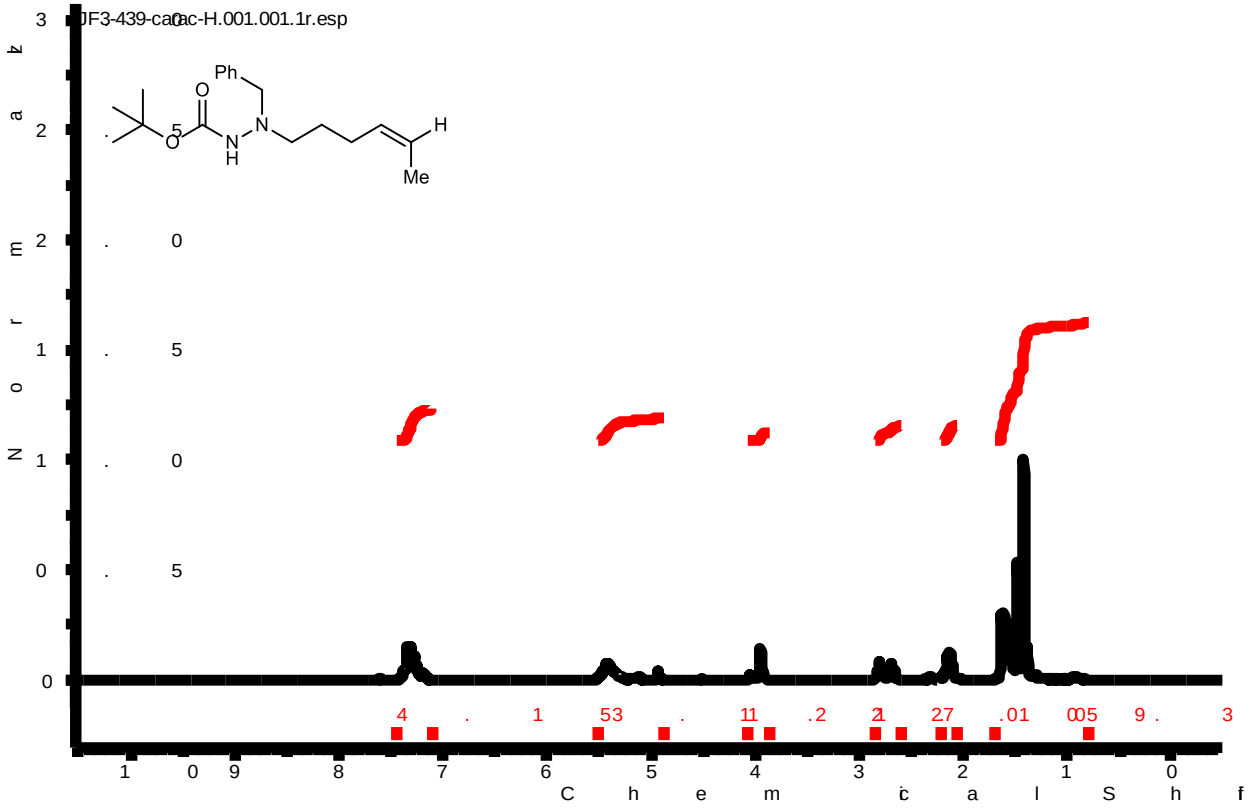
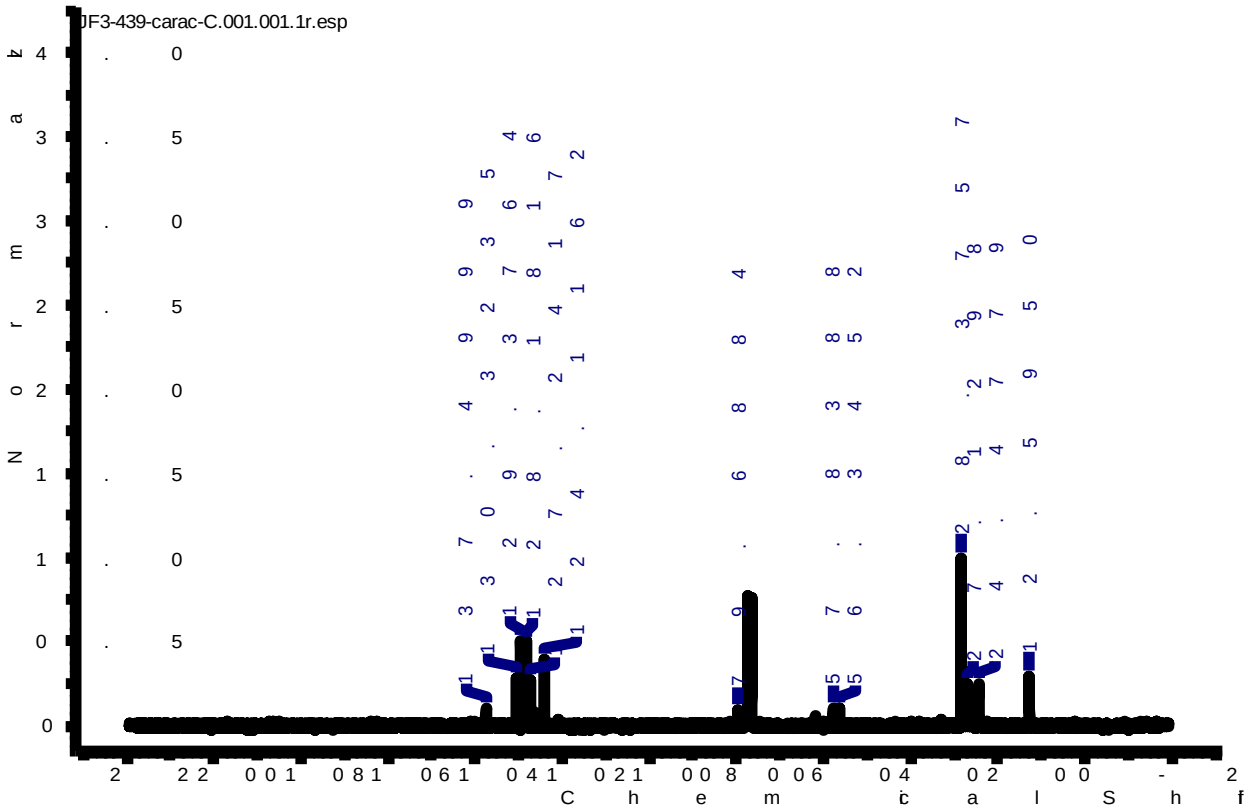
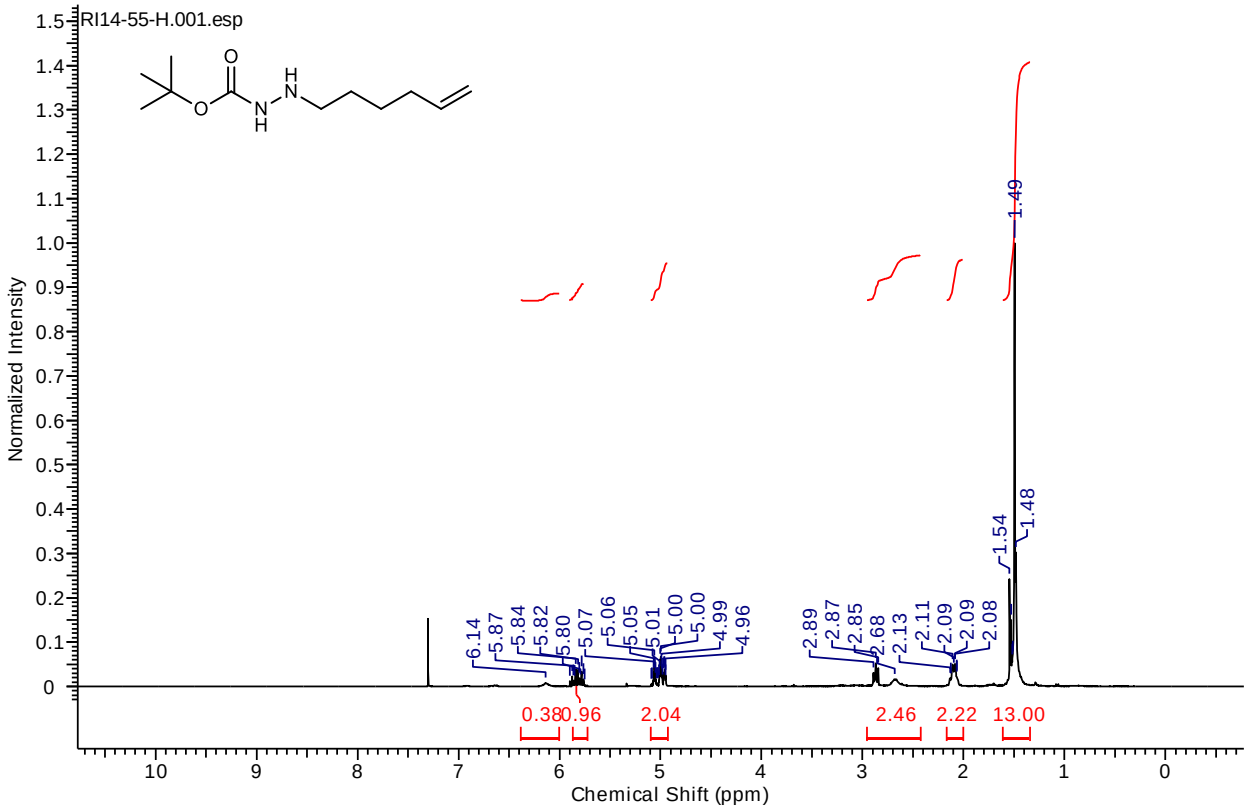
127.77
127.62
125.94
115.64
80.07
59.75
57.39
28.55

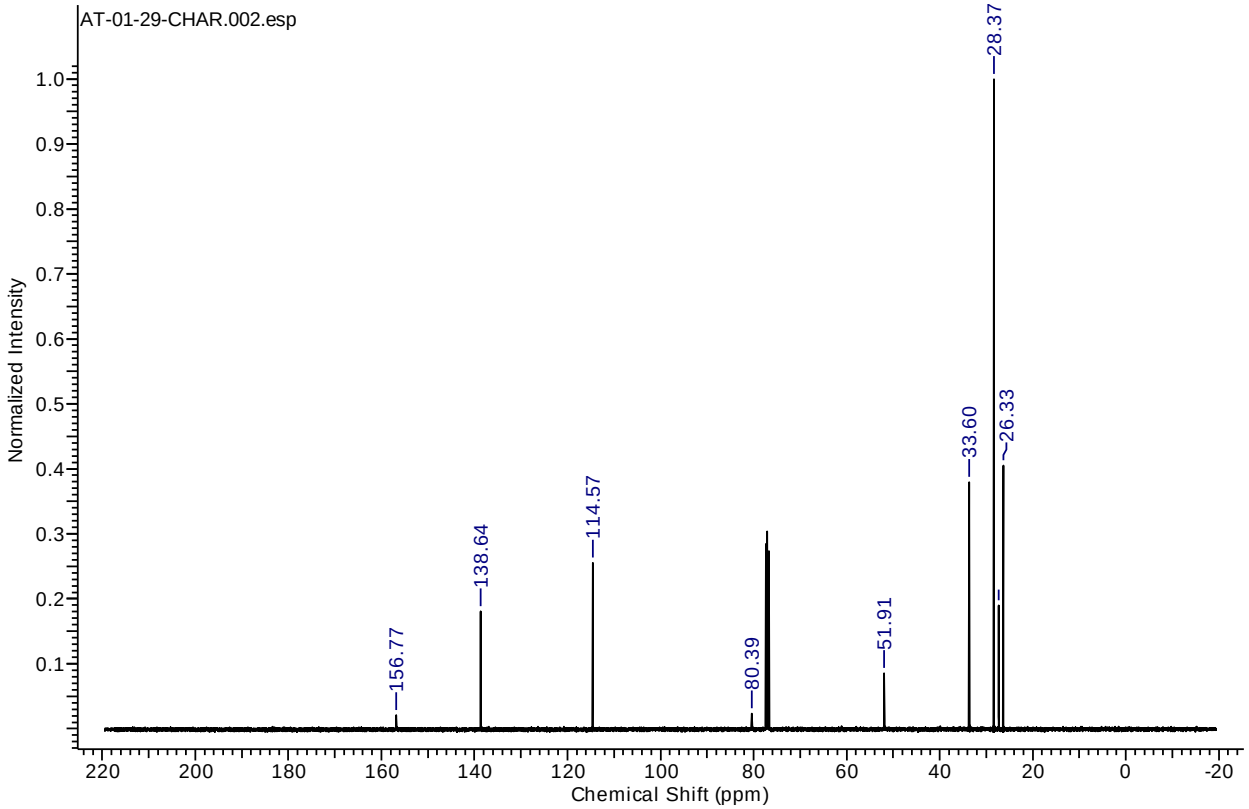

JF3-479carac-HT.001.001.1r.esp
Normalized
Ph
O
N
Me
O
N
H
H

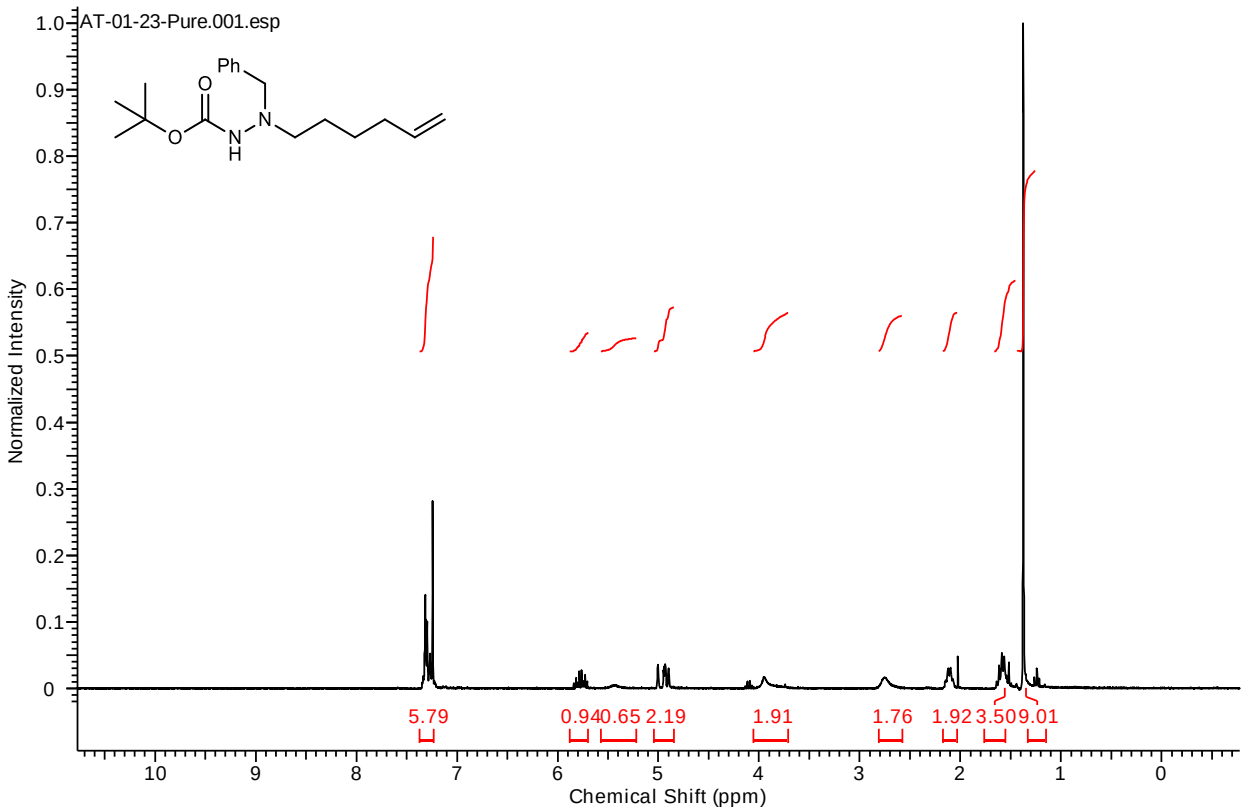

JF3-479carac-HT-C.001.001.1r.esp
Normalized

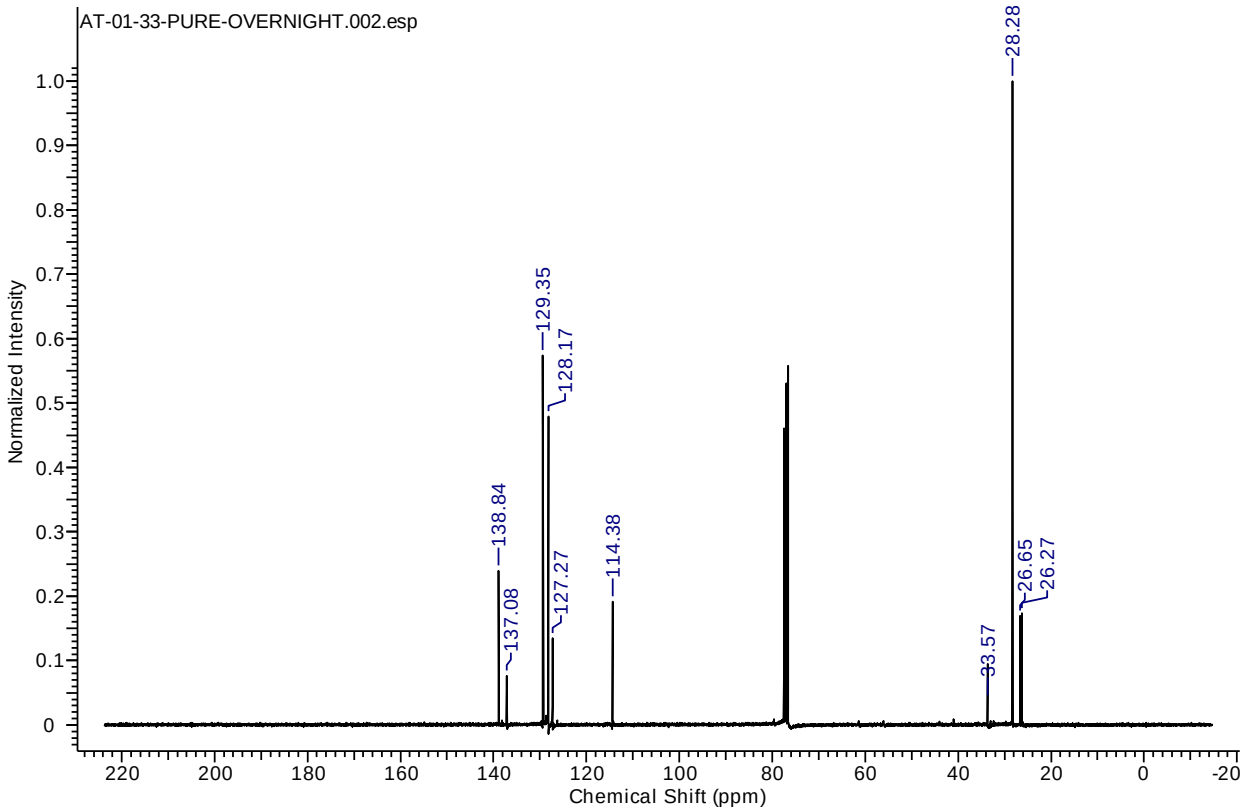

JF3-439-carac-H.001.001.1r.esp
Ph
O
O
N
N
H
H
Me
Normalized
Chemical Shift

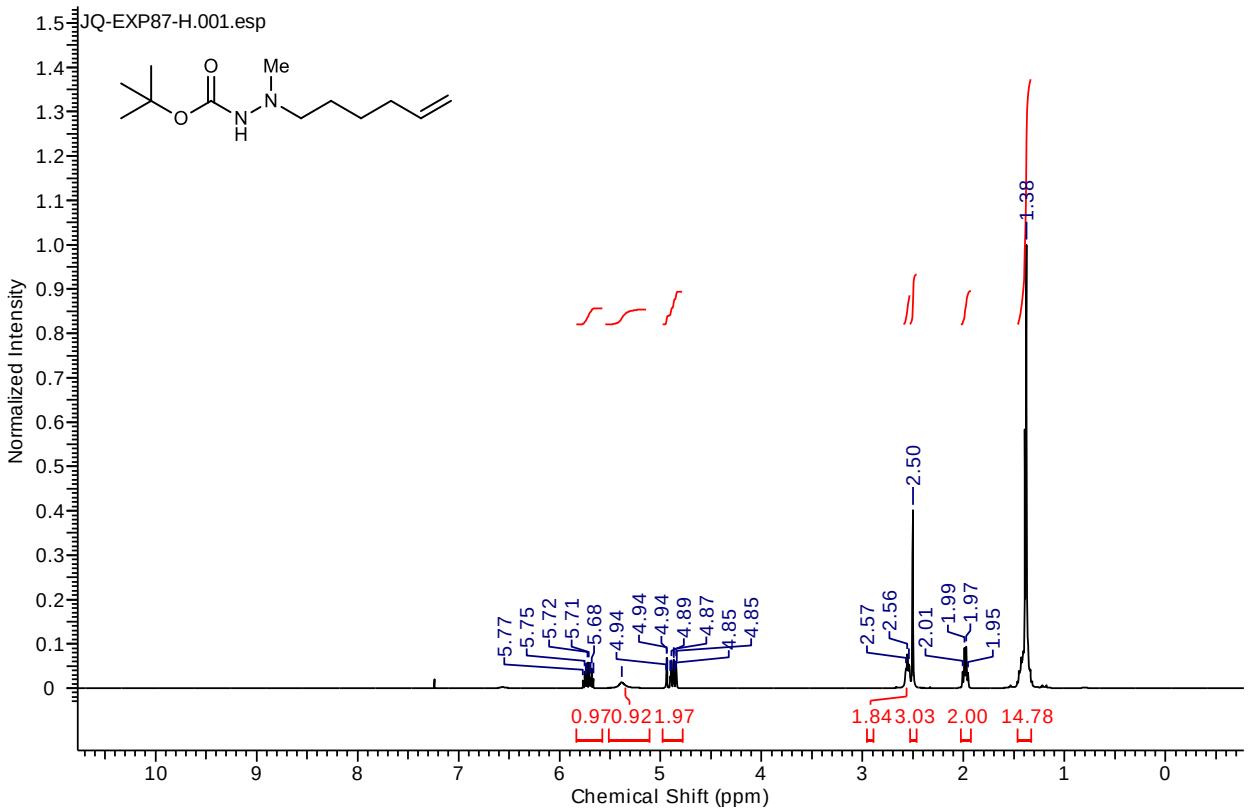

JF3-439-carac-C.001.001.1r.esp
Normalized
Chemical Shift

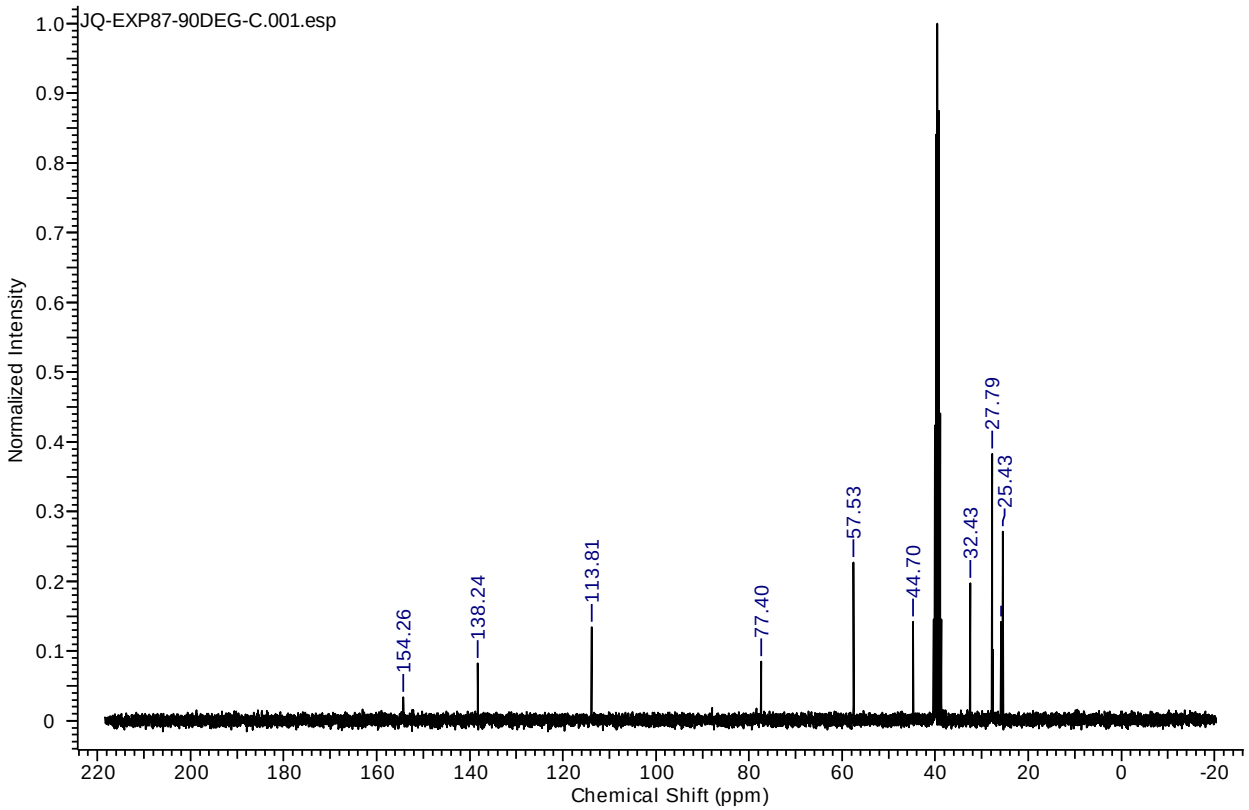

RI14-55-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
6.14
5.87
5.84
5.82
5.80
5.07
5.06
5.05
5.01
5.00
5.00
4.99
4.96
2.89
2.87
2.85
2.68
2.13
2.11
2.09
2.09
2.08
1.54
1.49
1.48
0.38
0.96
2.04
2.46
2.22
13.00

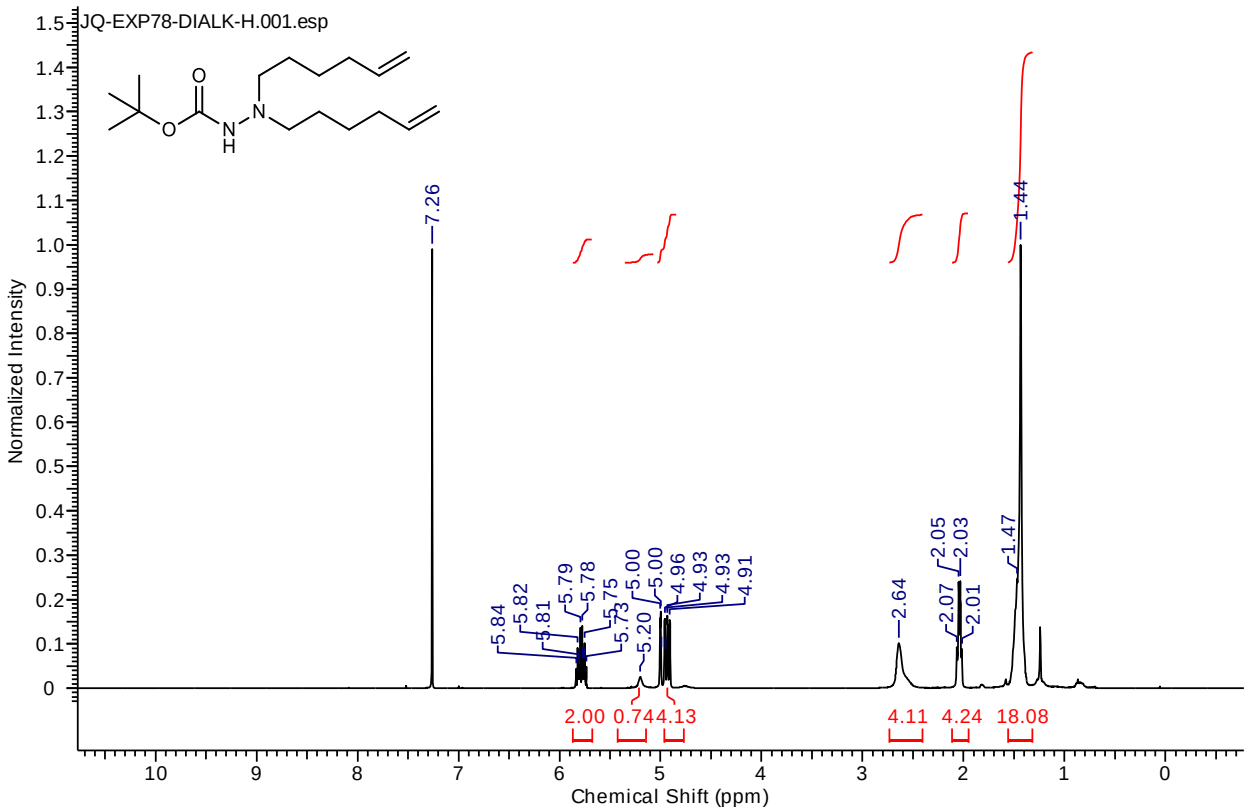

AT-01-29-CHAR.002.esp
Normalized Intensity
Chemical Shift (ppm)
28.37
33.60
26.33
114.57
138.64
156.77
80.39
51.91

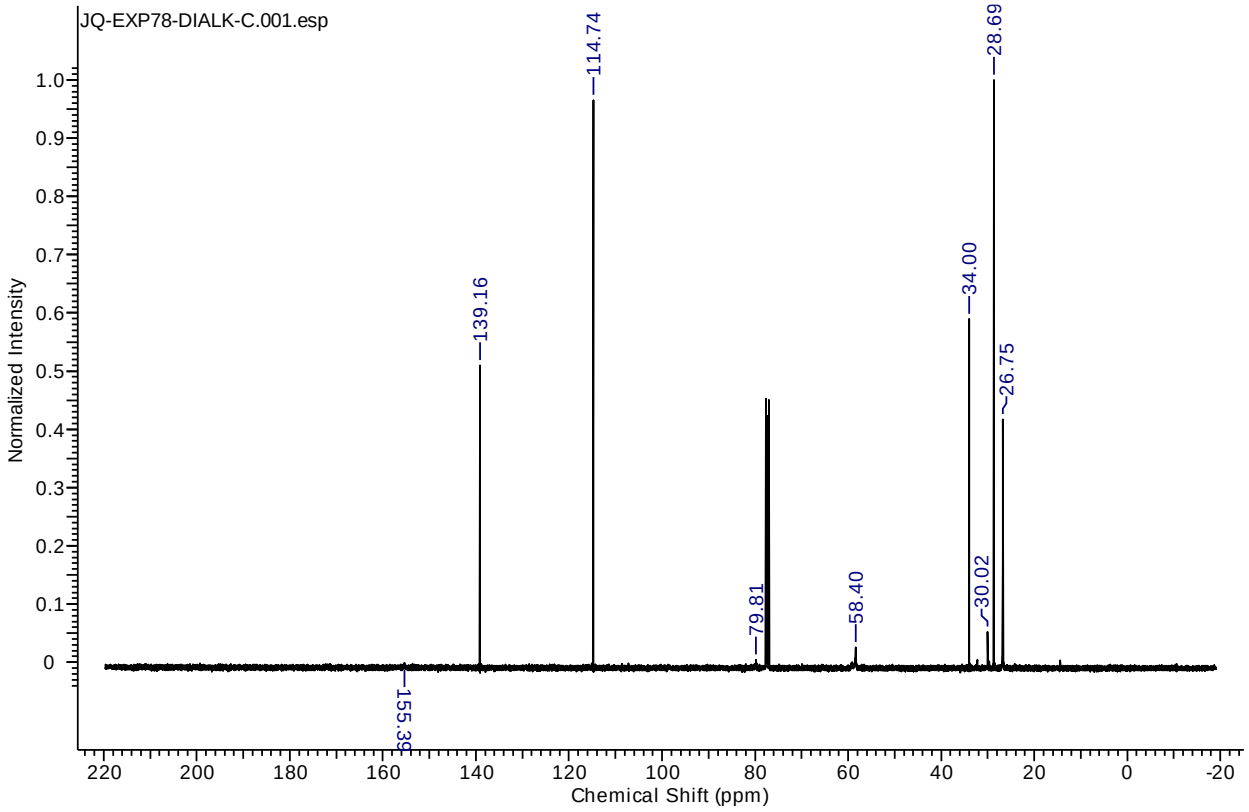

AT-01-23-Pure.001.esp
Ph
O
O
N
N
H
Normalized Intensity
5.79
0.94
0.65
2.19
1.91
1.76
1.92
3.50
9.01
Chemical Shift (ppm)

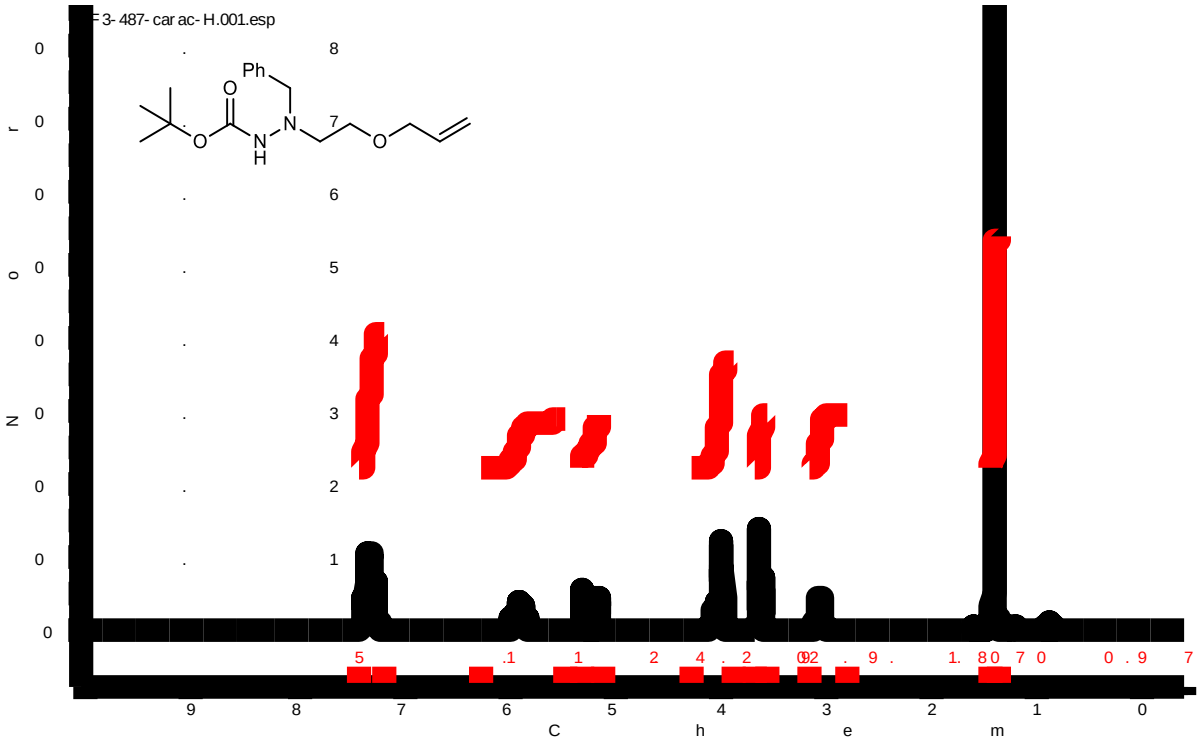

AT-01-33-PURE-OVERNIGHT.002.esp
28.28
129.35
128.17
138.84
137.08
127.27
114.38
26.65
26.27
33.57
Normalized Intensity
Chemical Shift (ppm)

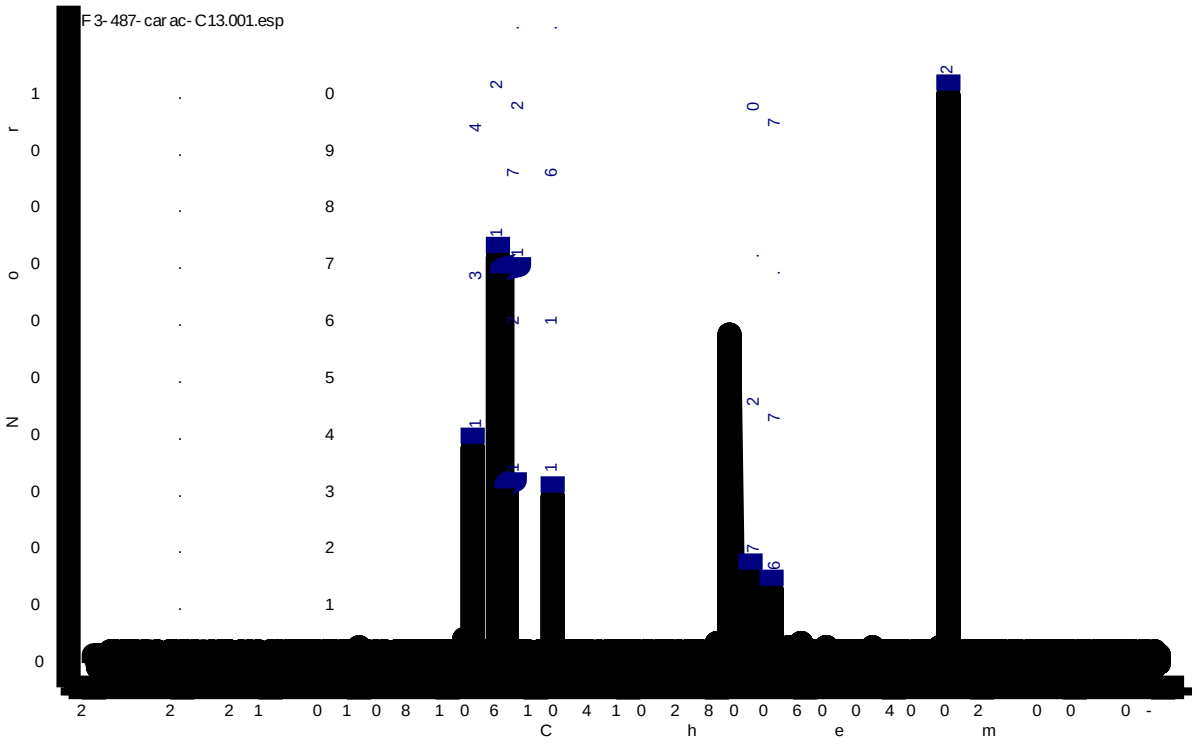

JQ-EXP87-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
5.77
5.75
5.72
5.71
5.68
4.94
4.94
4.94
4.89
4.87
4.85
4.85
2.57
2.56
2.50
2.01
1.99
1.97
1.95
1.38
0.97
0.92
1.97
1.84
3.03
2.00
14.78

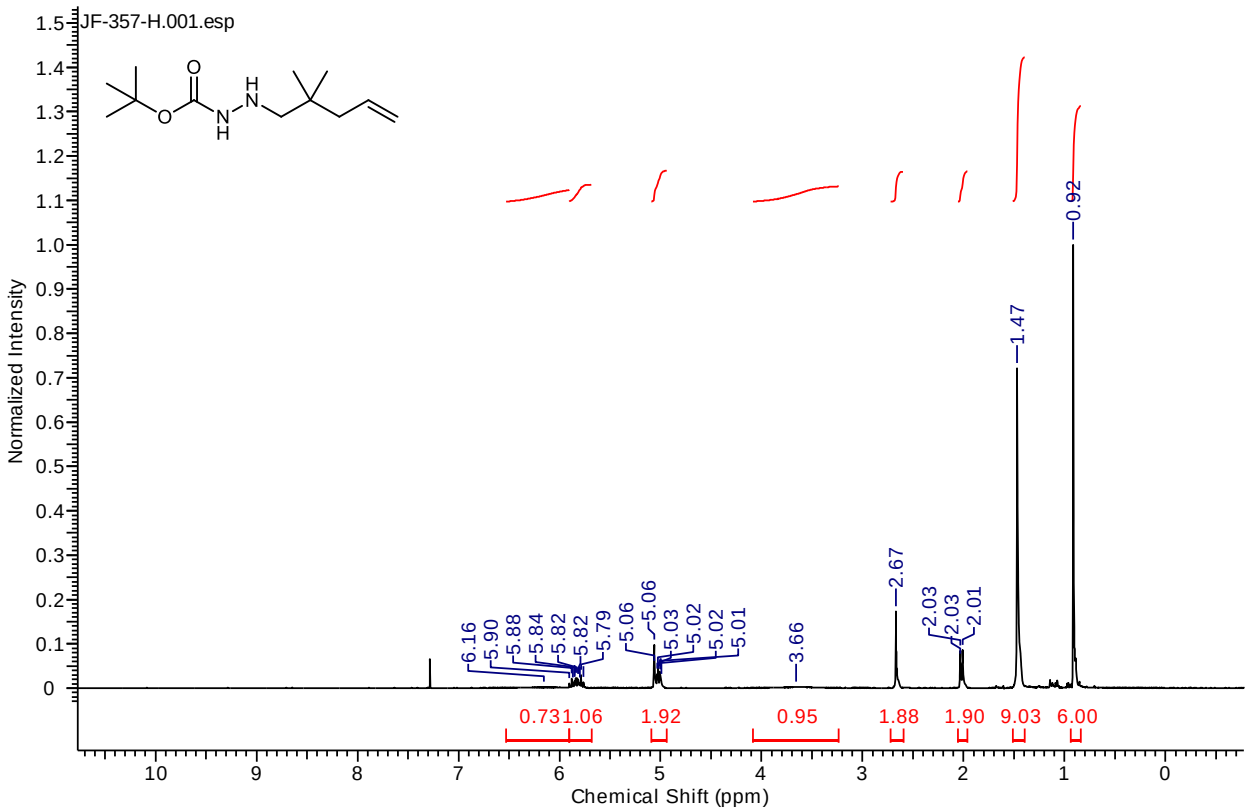

JQ-EXP87-90DEG-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
154.26
138.24
113.81
77.40
57.53
44.70
32.43
27.79
25.43

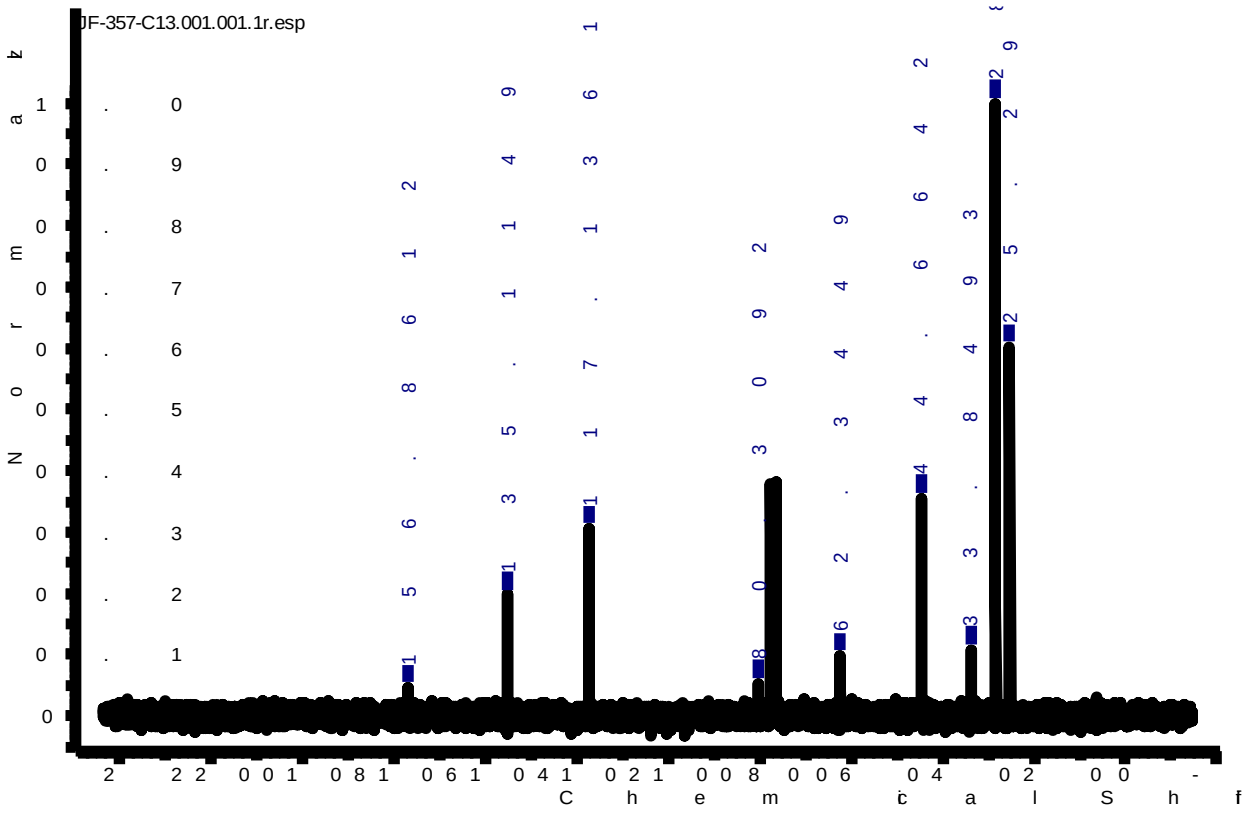

JQ-EXP78-DIALK-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
7.26
5.84
5.82
5.81
5.79
5.78
5.75
5.73
5.20
5.00
5.00
4.96
4.93
4.93
4.91
2.64
2.07
2.05
2.03
2.01
1.47
1.44
2.00
0.74
4.13
4.11
4.24
18.08

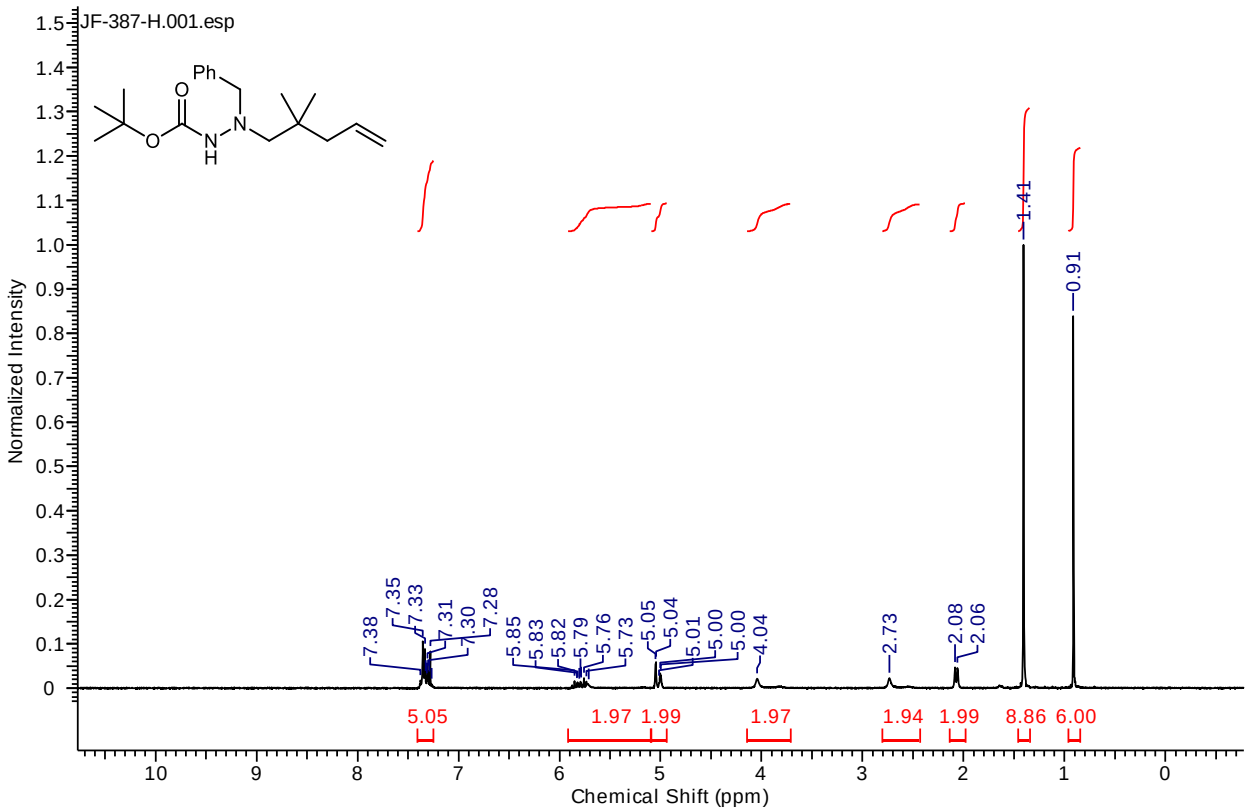

JQ-EXP78-DIALK-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
155.39
139.16
114.74
79.81
58.40
34.00
30.02
28.69
26.75

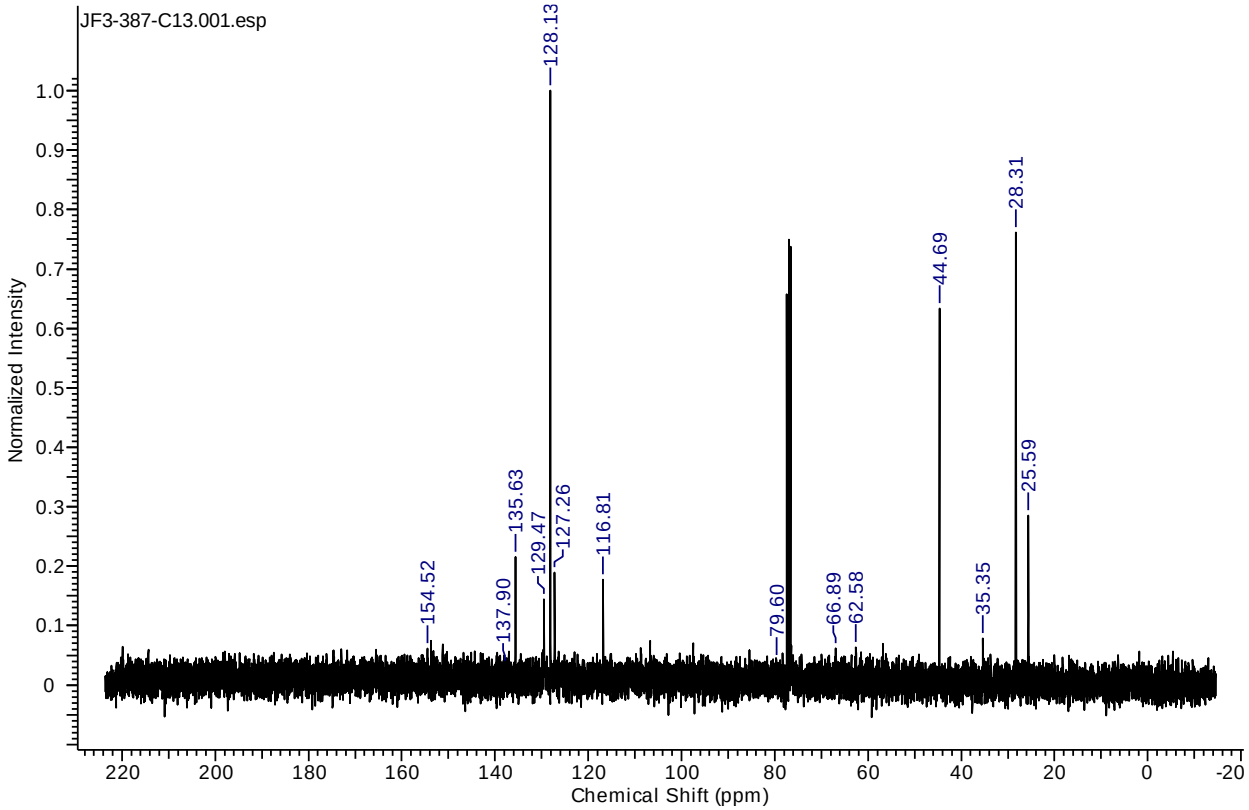

F3-487-carac-H.001.esp
Ph
O
N
N
H
O
O
Chem

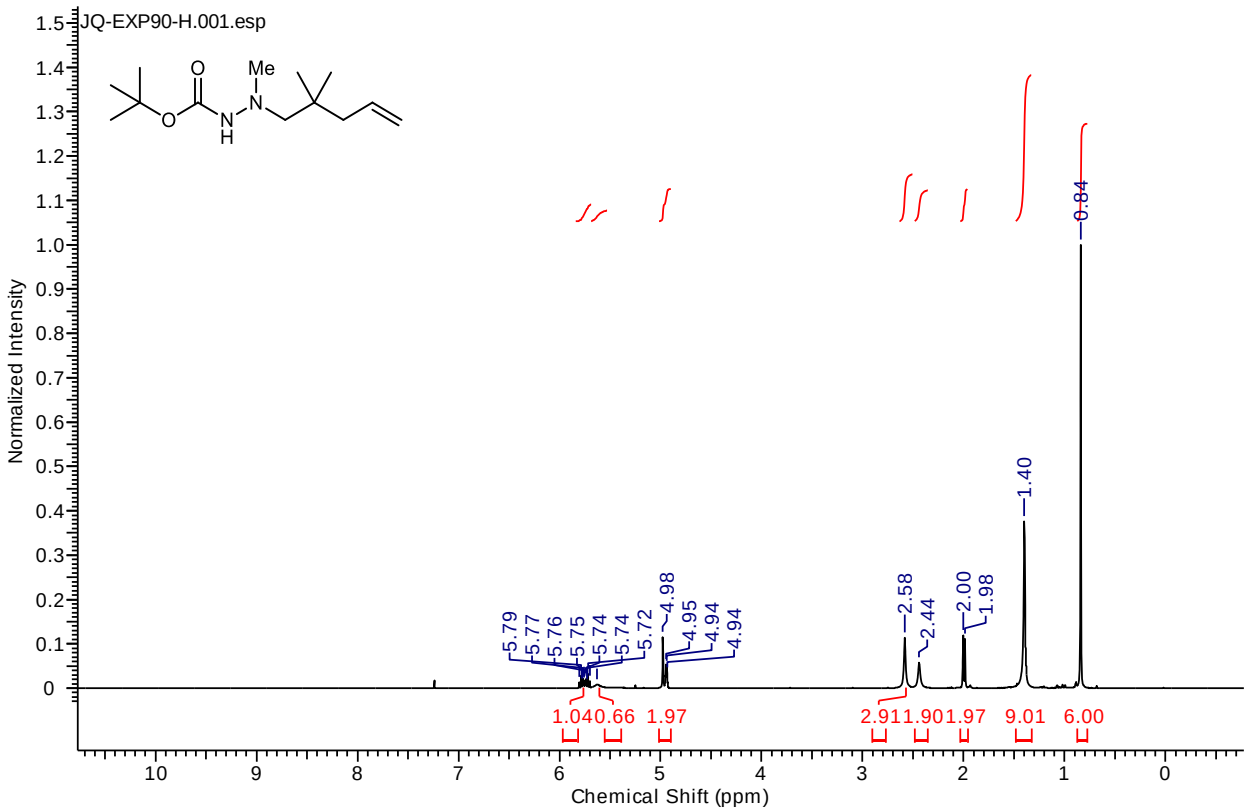

F3-487-carac-C13.001.esp
Chem

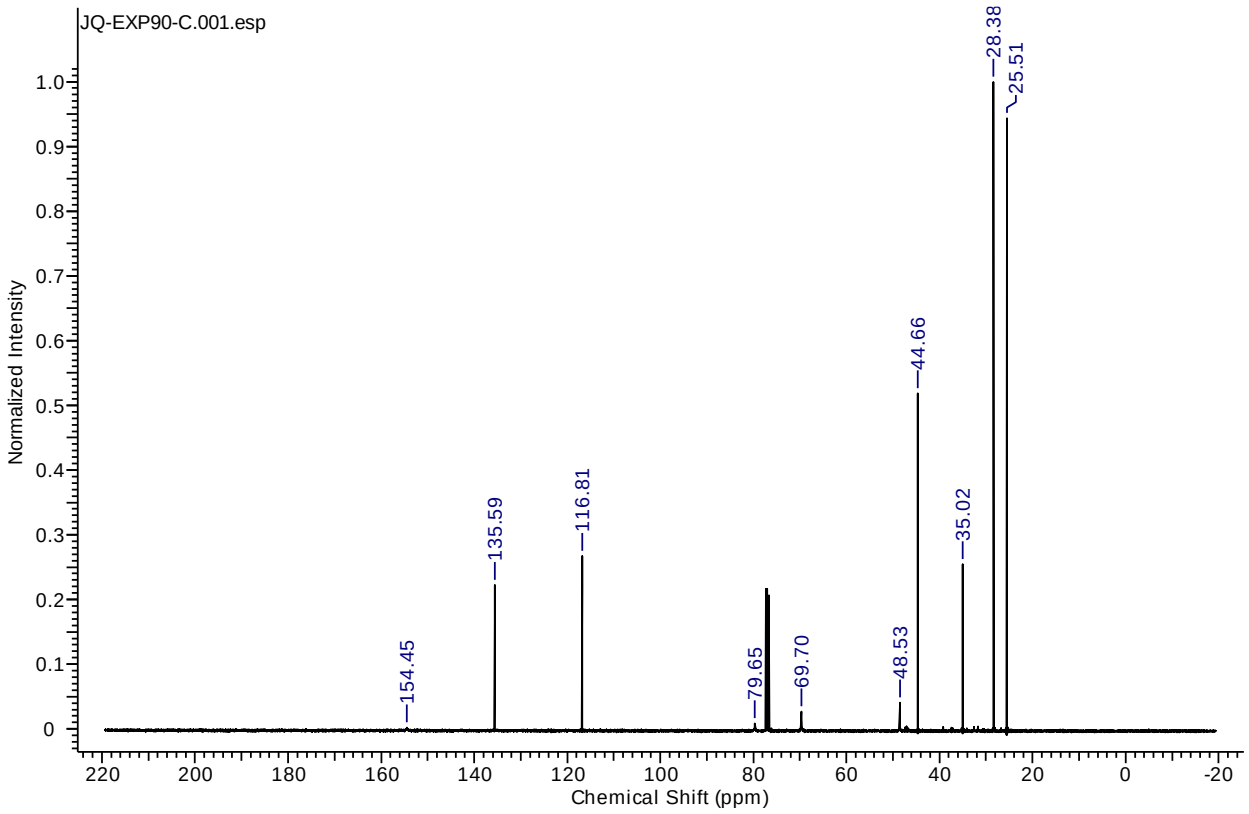

JF-357-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
6.16
5.90
5.88
5.84
5.82
5.82
5.79
5.06
5.06
5.03
5.02
5.02
5.01
3.66
2.67
2.03
2.03
2.01
1.47
0.92
0.73
1.06
1.92
0.95
1.88
1.90
9.03
6.00

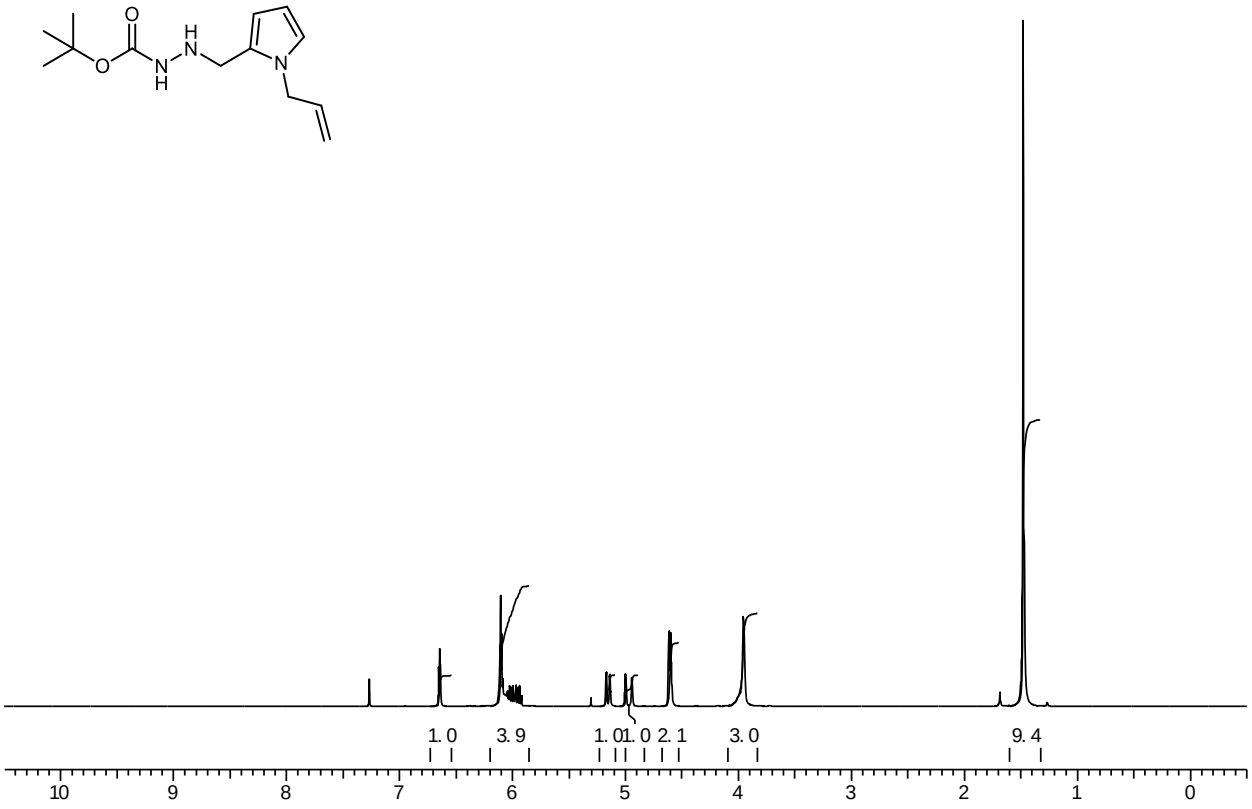

JF-357-C13.001.001.1r.esp
Normalized
ChemicalShift

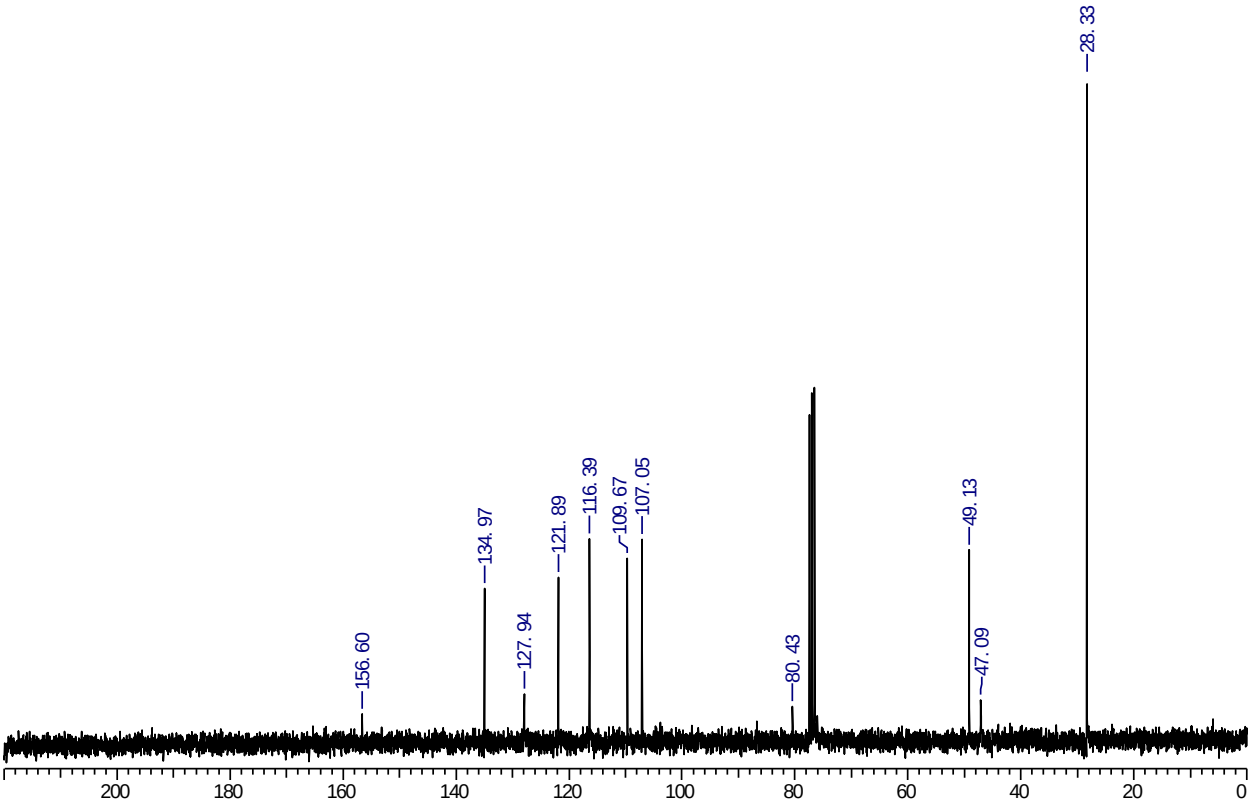

JF-387-H.001.esp
Ph
O
N
N
H
O
Normalized Intensity
Chemical Shift (ppm)
7.38
7.35
7.33
7.31
7.30
7.28
5.85
5.83
5.82
5.79
5.76
5.73
5.05
5.04
5.01
5.00
5.00
4.04
2.73
2.08
2.06
1.41
0.91
5.05
1.97
1.99
1.97
1.94
1.99
8.86
6.00

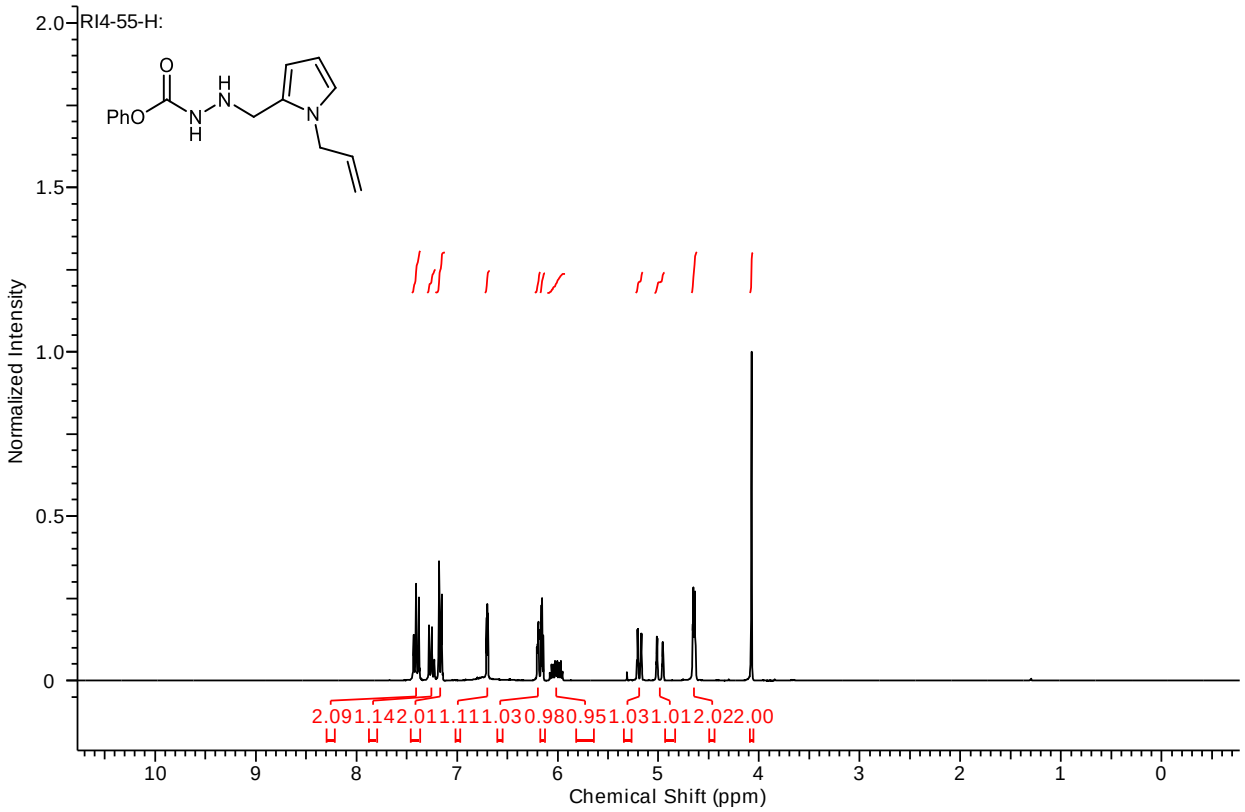

JF3-387-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
128.13
135.63
129.47
127.26
116.81
154.52
137.90
79.60
66.89
62.58
44.69
35.35
28.31
25.59

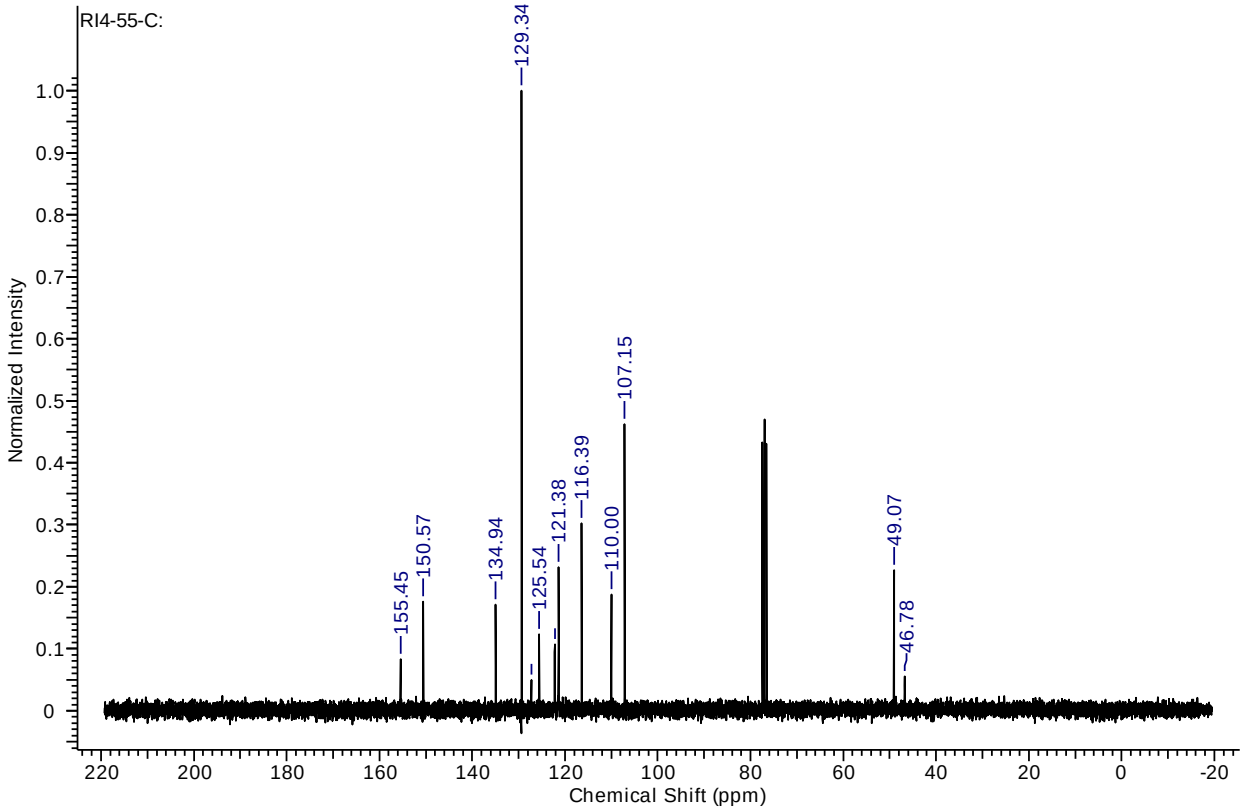

JQ-EXP90-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
5.79
5.77
5.76
5.75
5.74
5.74
5.72
4.98
4.95
4.94
4.94
2.58
2.44
2.00
1.98
1.40
0.84
1.04
0.66
1.97
2.91
1.90
1.97
9.01
6.00

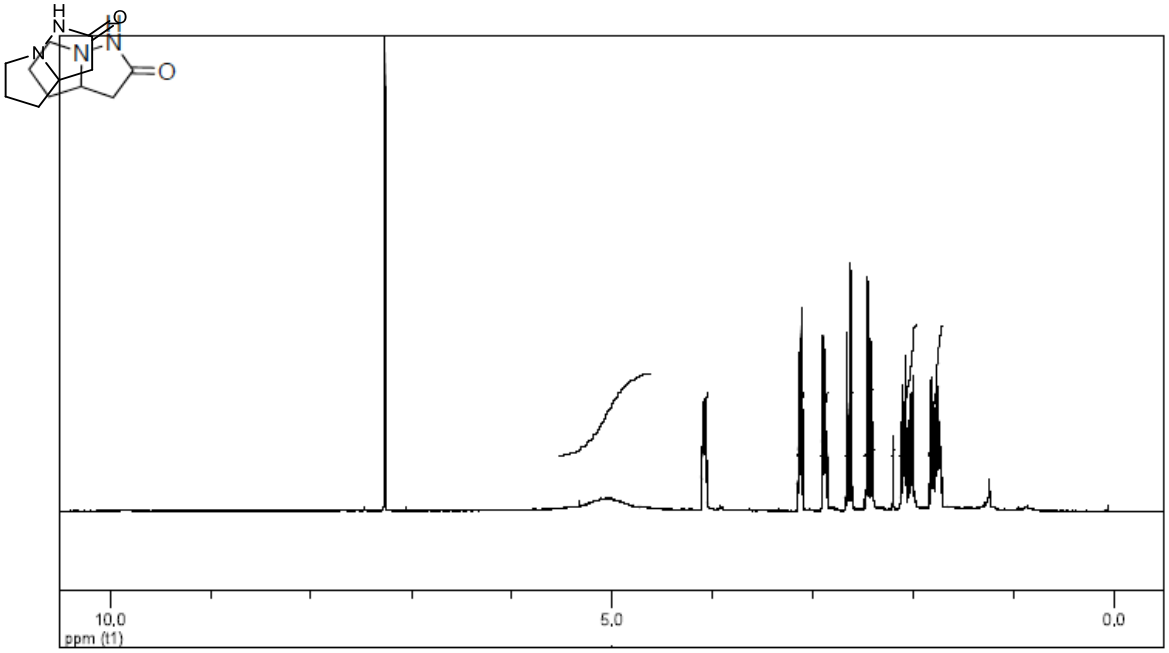

JQ-EXP90-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
154.45
135.59
116.81
79.65
69.70
48.53
44.66
35.02
28.38
25.51

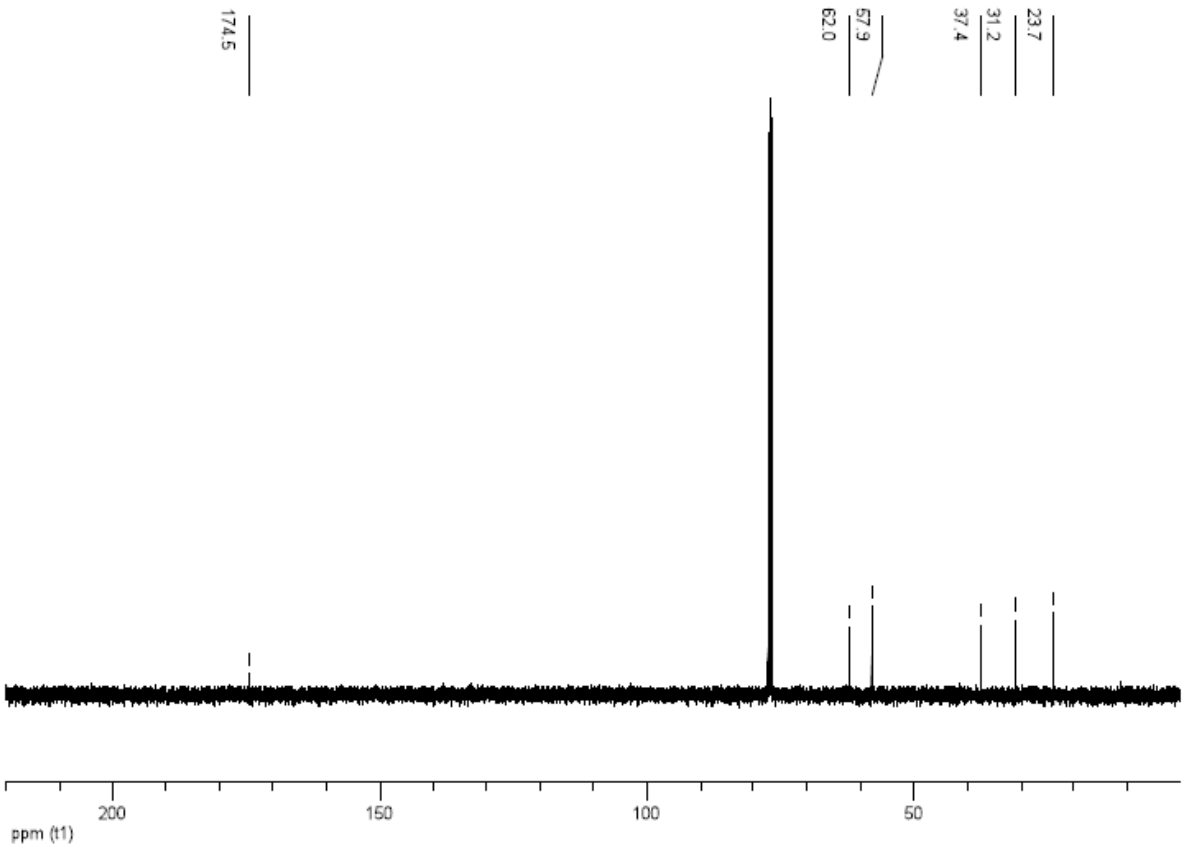

1.0
3.9
1.0
1.0
2.1
3.0
9.4
10
9
8
7
6
5
4
3
2
1
0

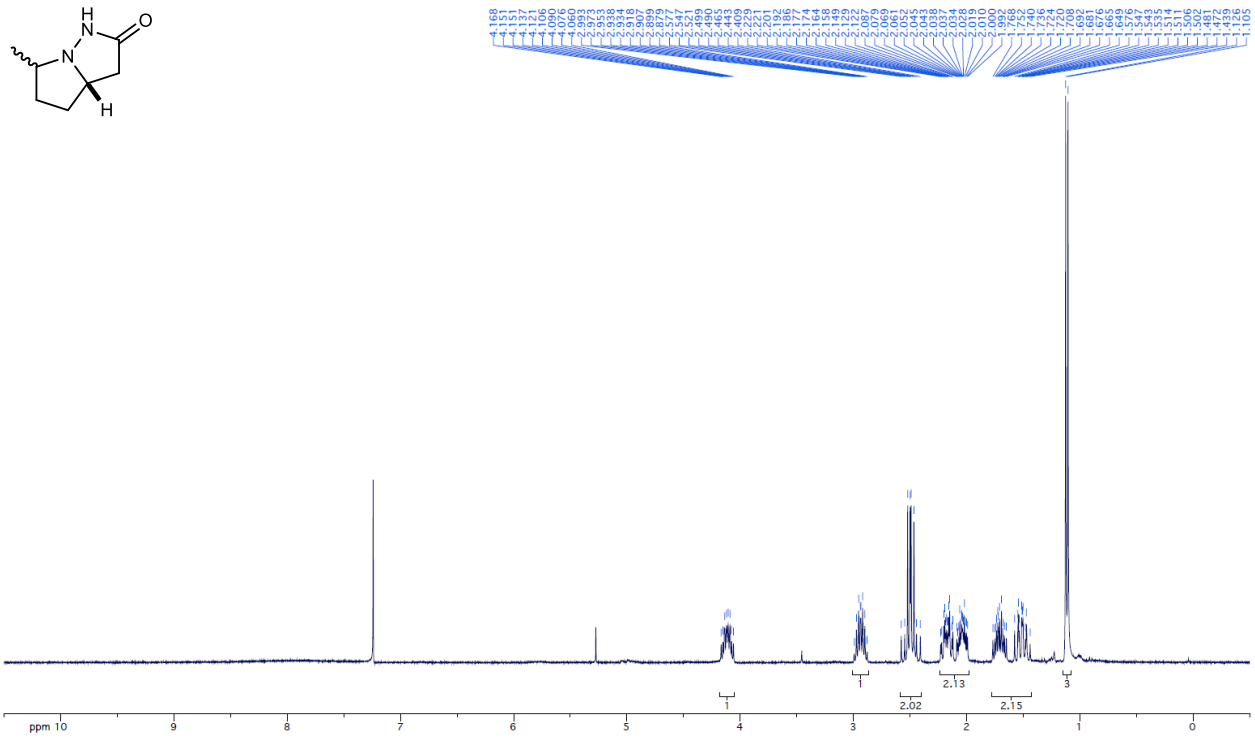

28.33
156.60
134.97
127.94
121.89
116.39
109.67
107.05
80.43
49.13
47.09
200
180
160
140
120
100
80
60
40
20
0

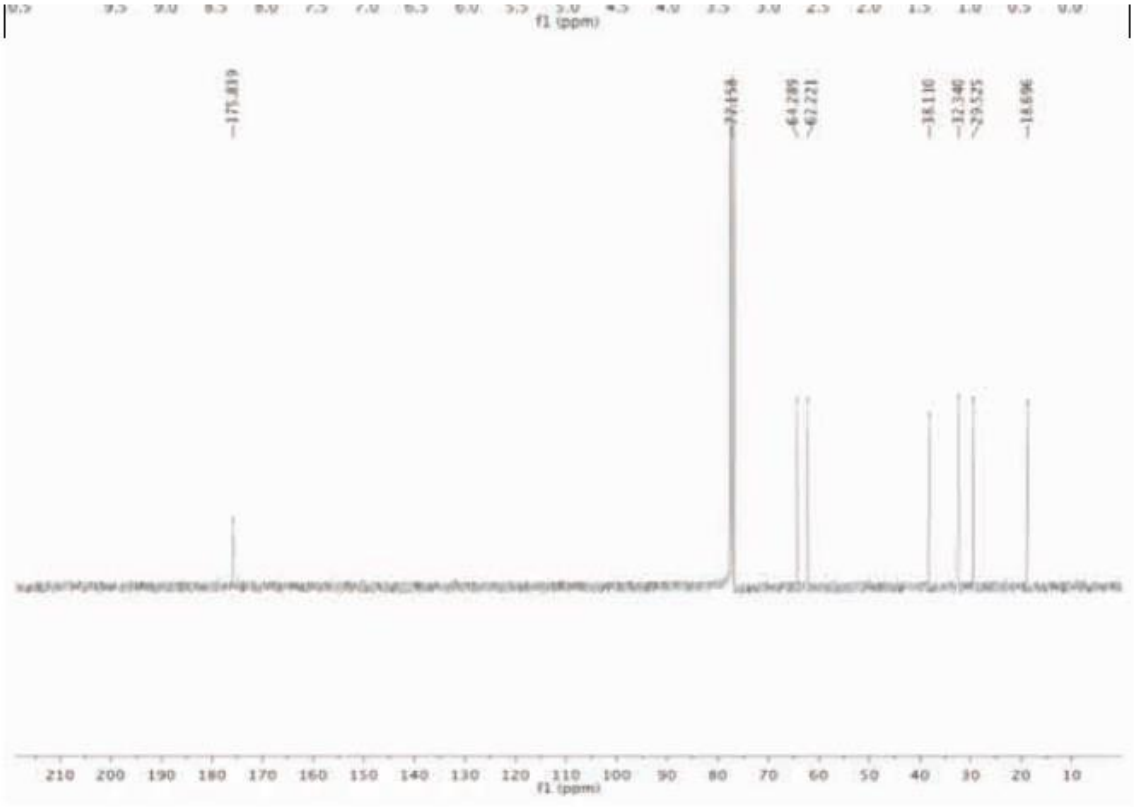

RI4-55-H:
PhO
O
H
N
N
H
N
Normalized Intensity
2.09 1.14 2.01 1.11 1.03 0.98 0.95 1.03 1.01 2.02 2.00
Chemical Shift (ppm)

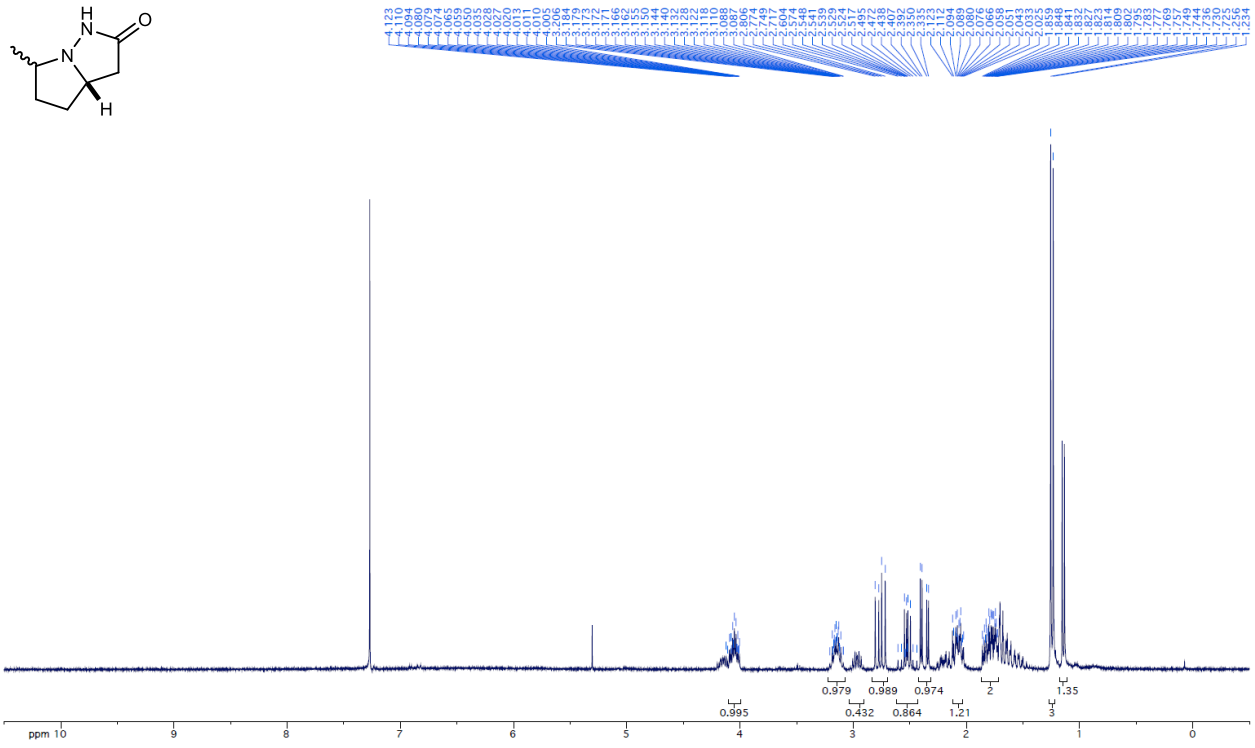

RI4-55-C:
129.34
155.45
150.57
134.94
125.54
121.38
116.39
110.00
107.15
49.07
46.78
Normalized Intensity
Chemical Shift (ppm)

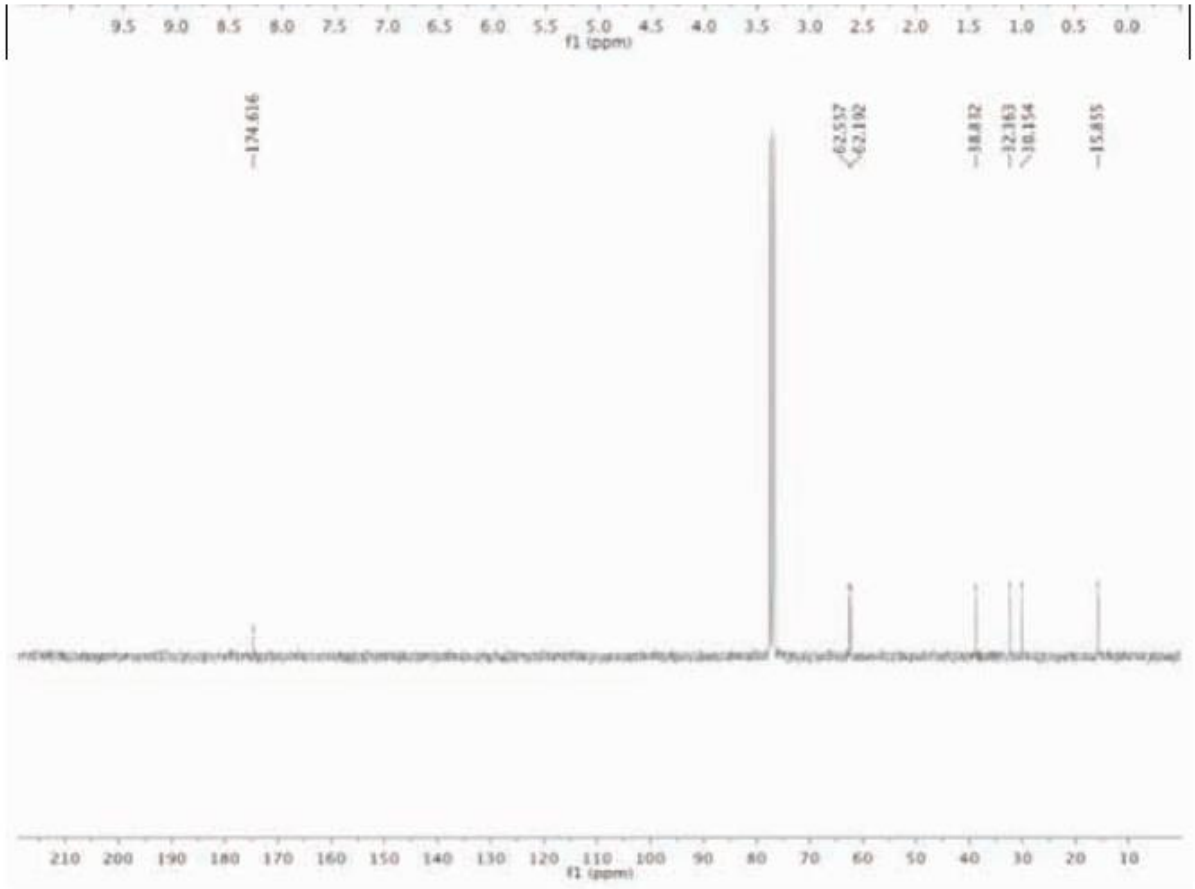

H
N
O
N
N
N
O
10,0
ppm (t1)
5,0
0,0

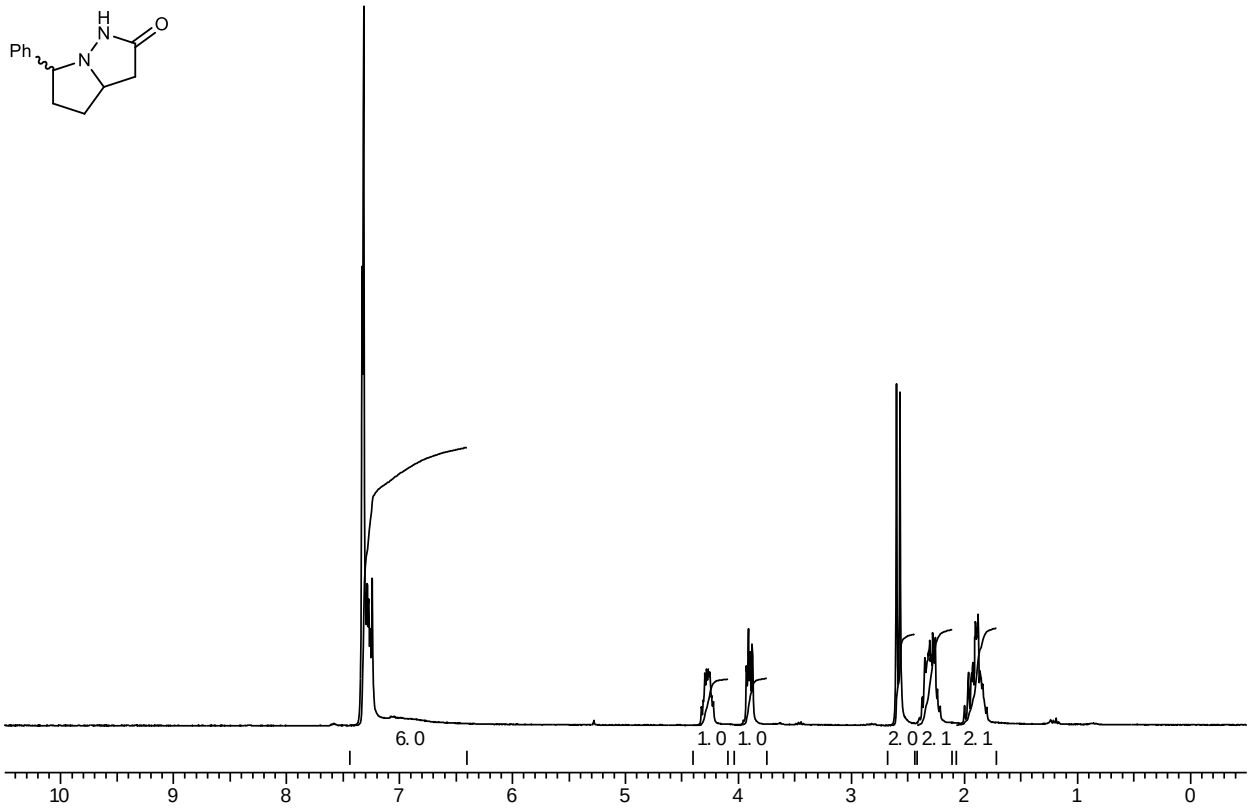

174.5
62.0
57.9
37.4
31.2
23.7
200
150
100
50
ppm (t1)

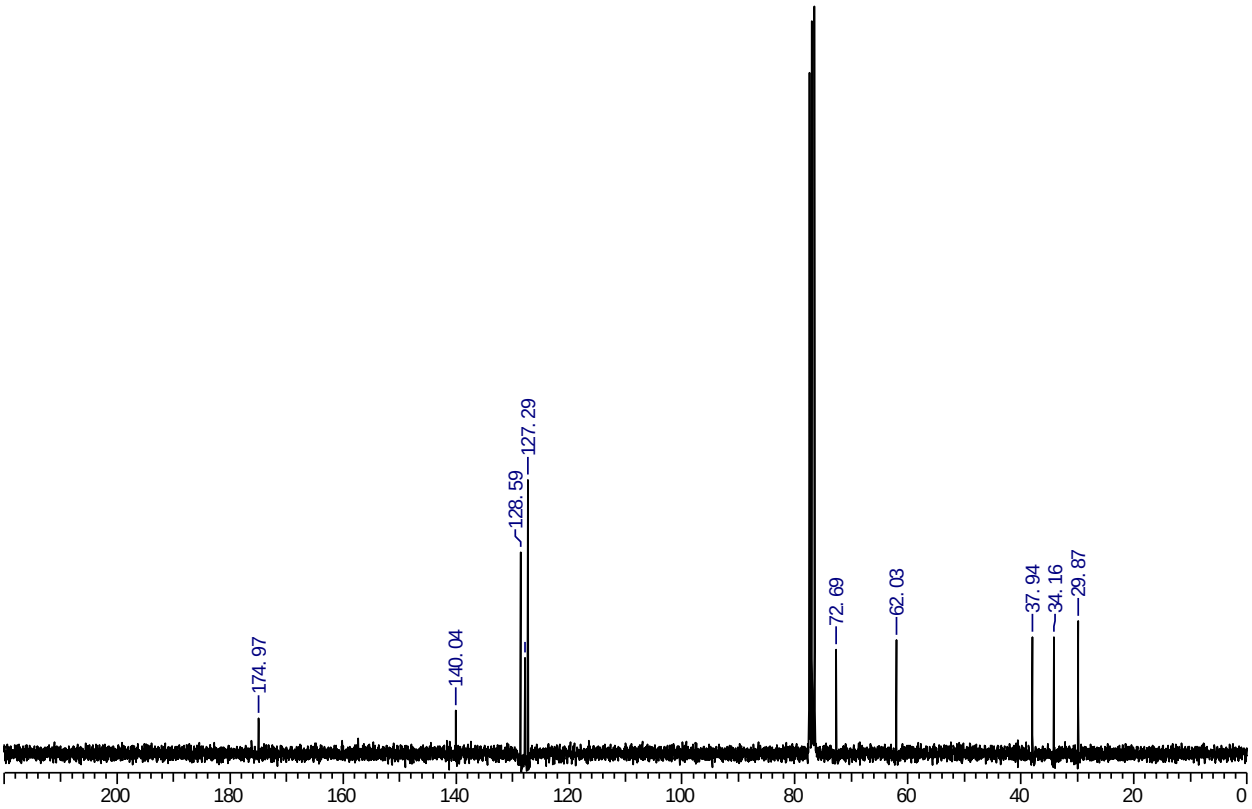

ppm 10
9
8
7
6
5
4
3
2
1
0
1
2.02
2.13
2.15
3

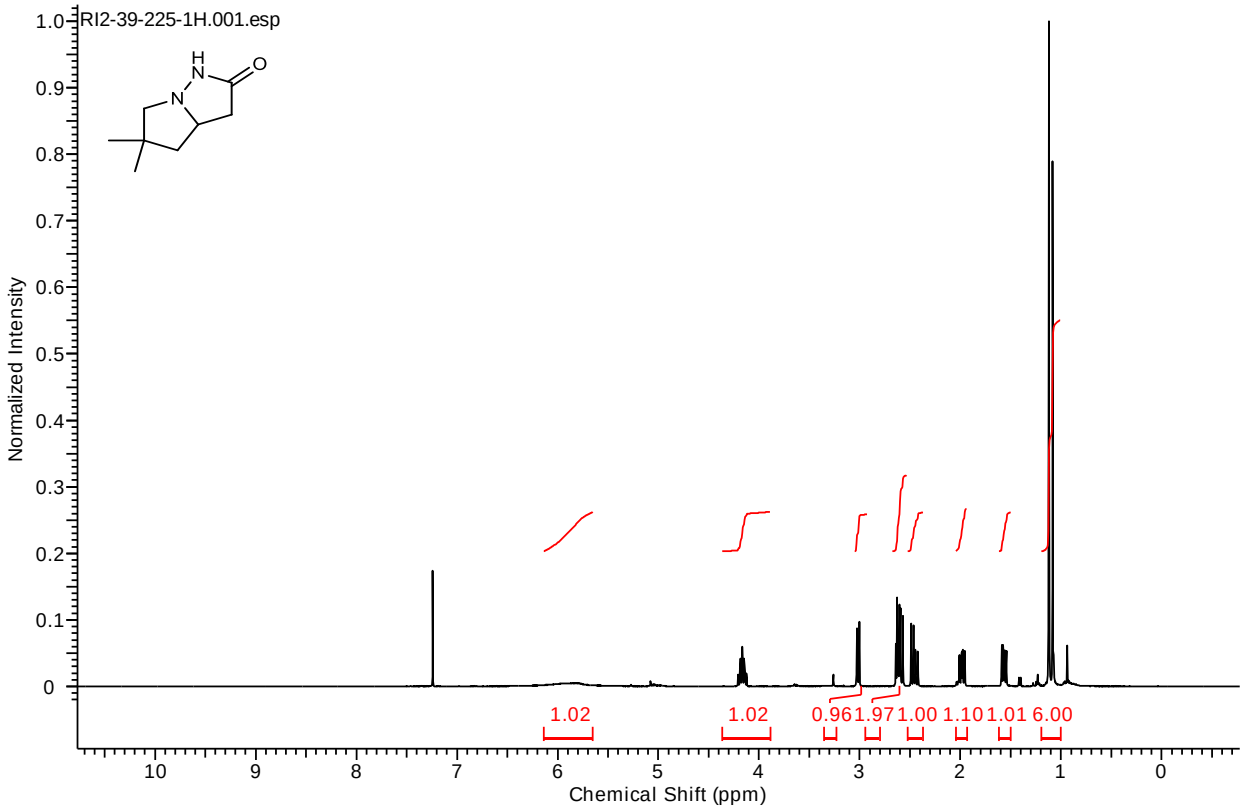

f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

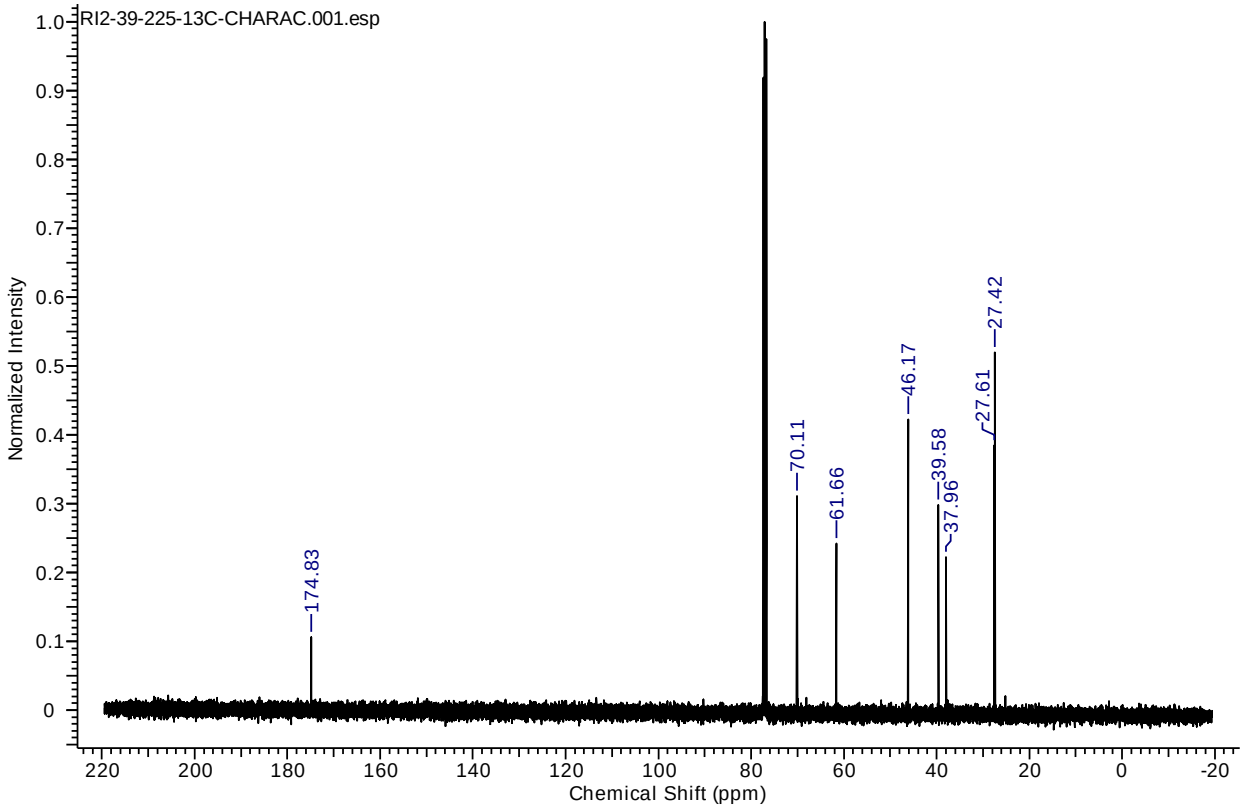

0.979
0.989
0.974
2
1.35
0.995
0.432
0.864
1.21
3
ppm 10
9
8
7
6
5
4
3
2
1
0

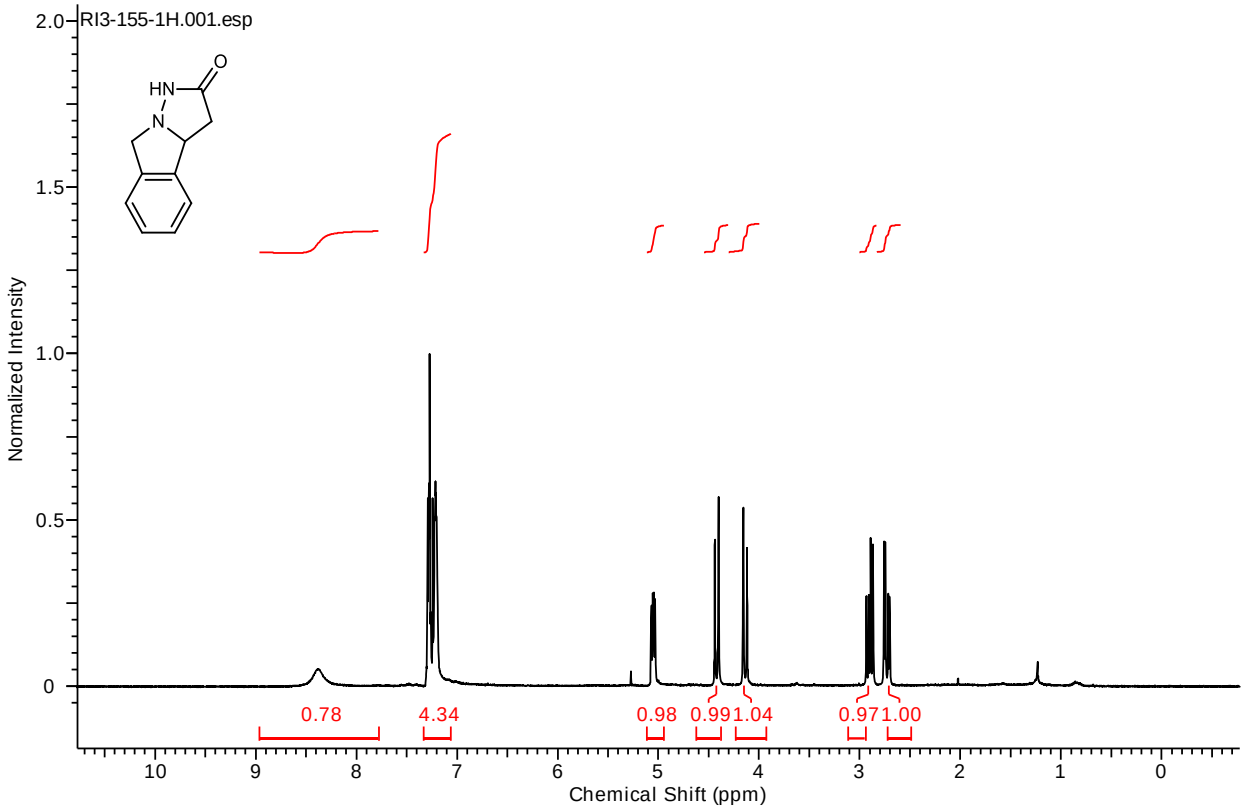

f1 (ppm)
174.616
62.557
62.192
38.832
32.363
30.154
15.855
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

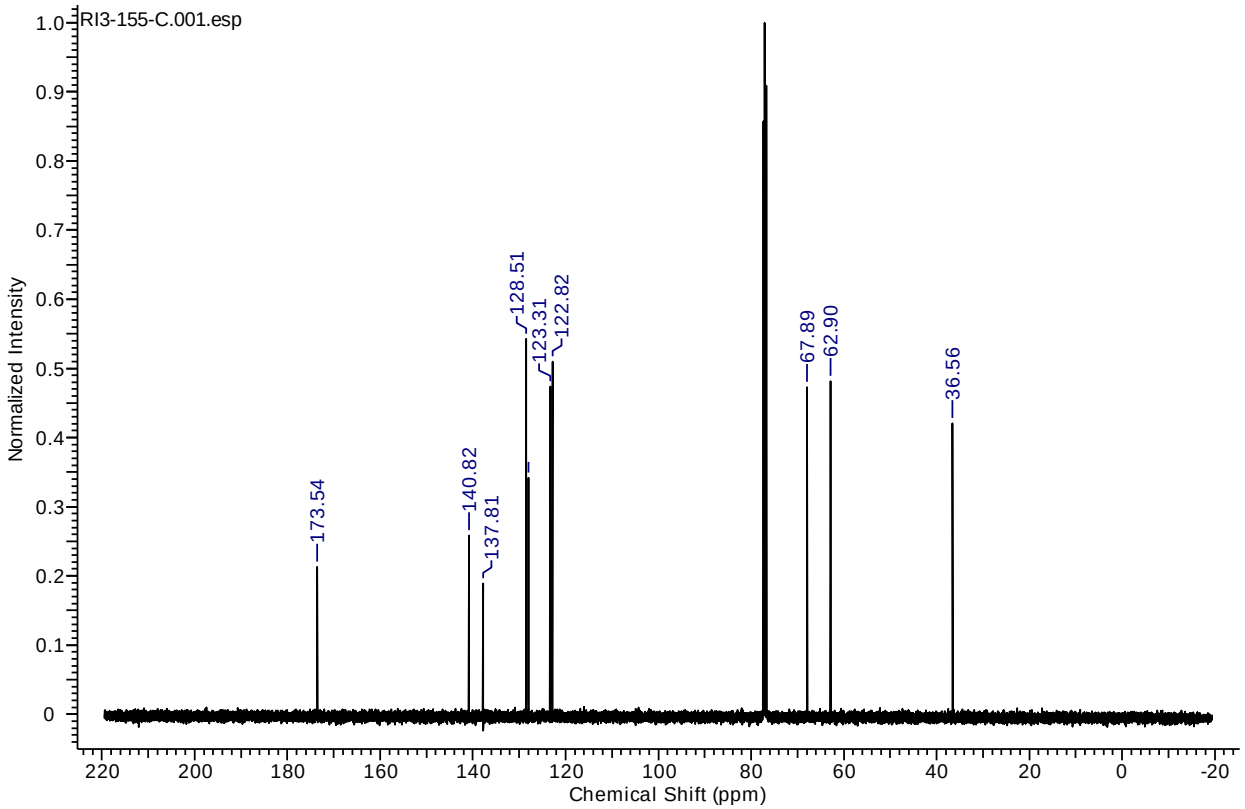

Ph
N
N
H
O
6.0
1.0
1.0
2.0
2.1
2.1
10
9
8
7
6
5
4
3
2
1
0

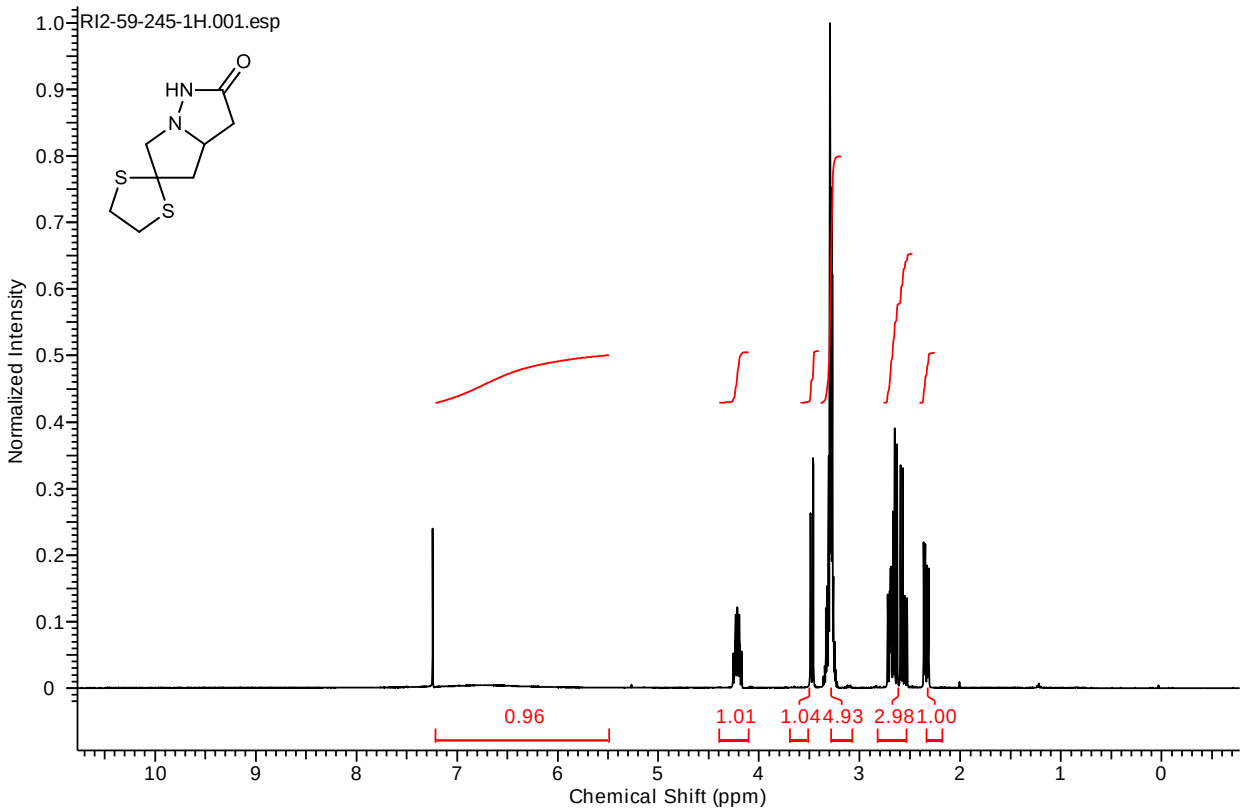

174.97
140.04
128.59
127.29
72.69
62.03
37.94
34.16
29.87
200
180
160
140
120
100
80
60
40
20
0

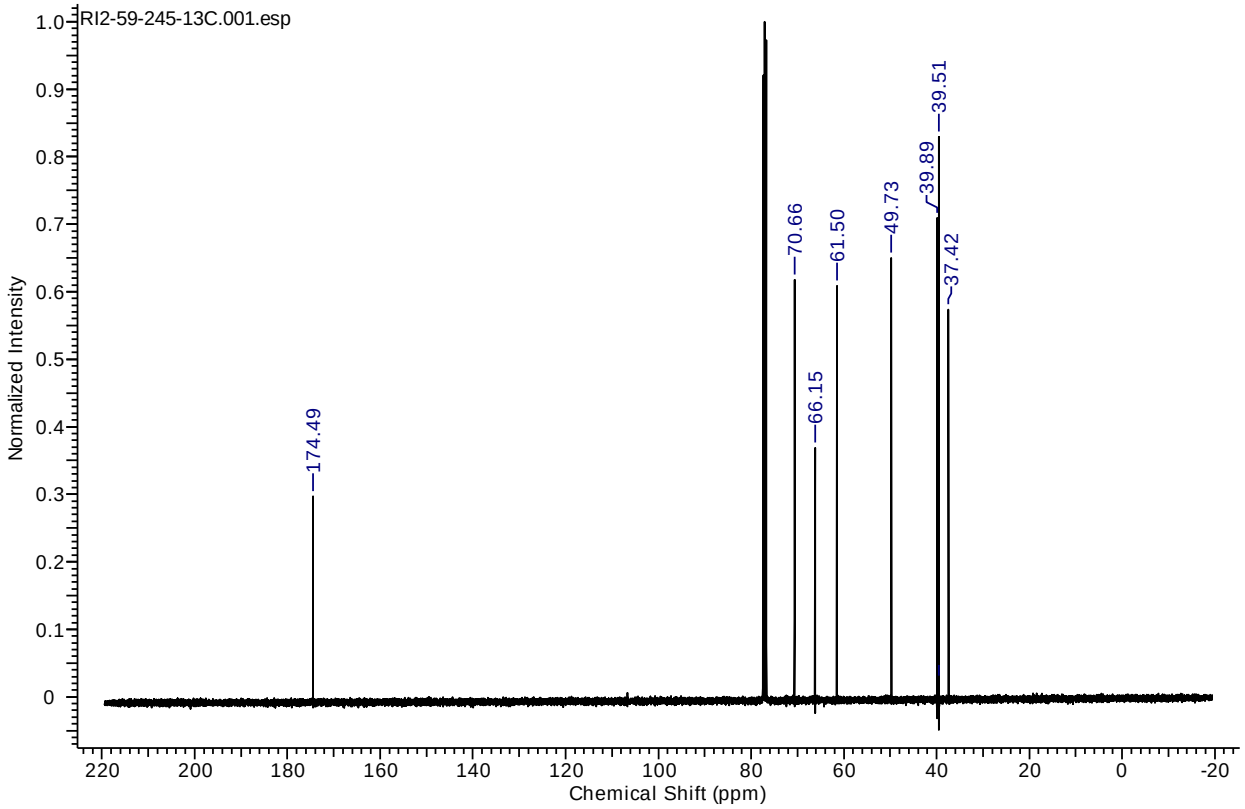

RI2-39-225-1H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.02
1.02
0.96
1.97
1.00
1.10
1.01
6.00

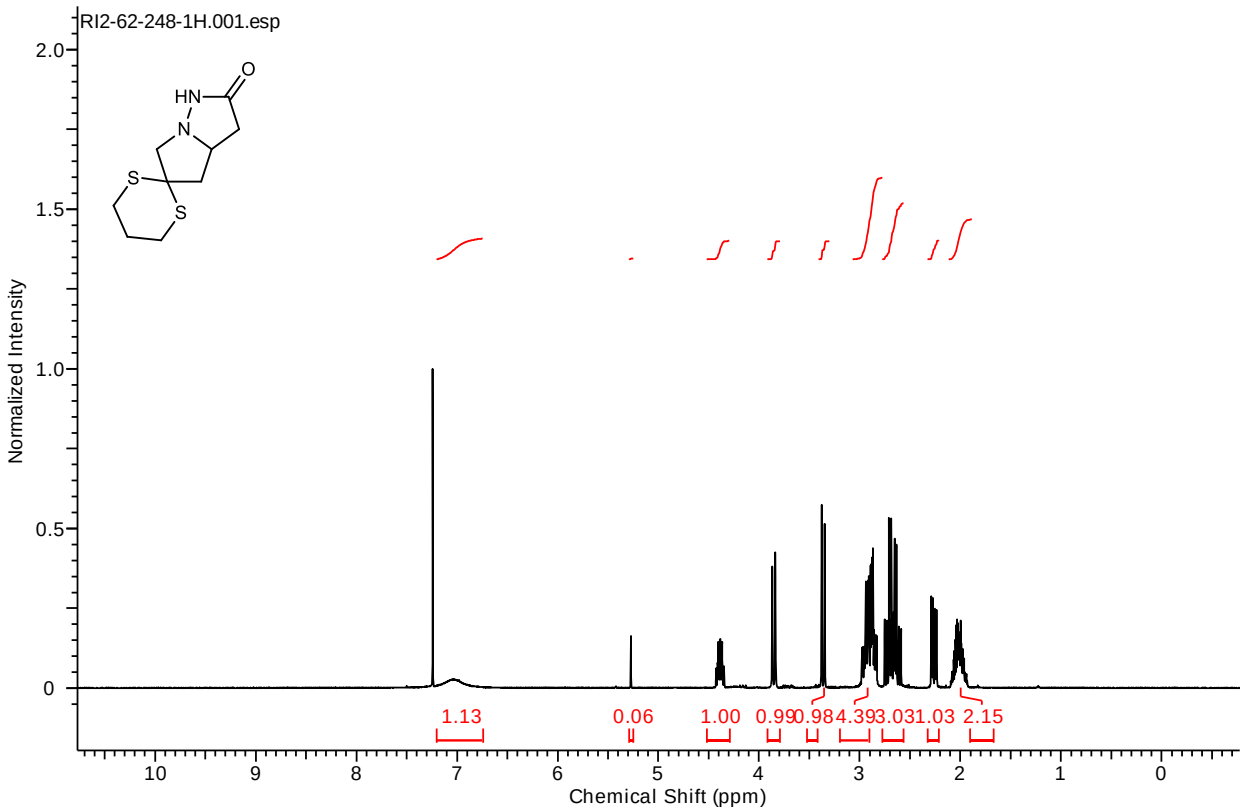

RI2-39-225-13C-CHARAC.001.esp
Normalized Intensity
Chemical Shift (ppm)
174.83
70.11
61.66
46.17
39.58
37.96
27.61
27.42

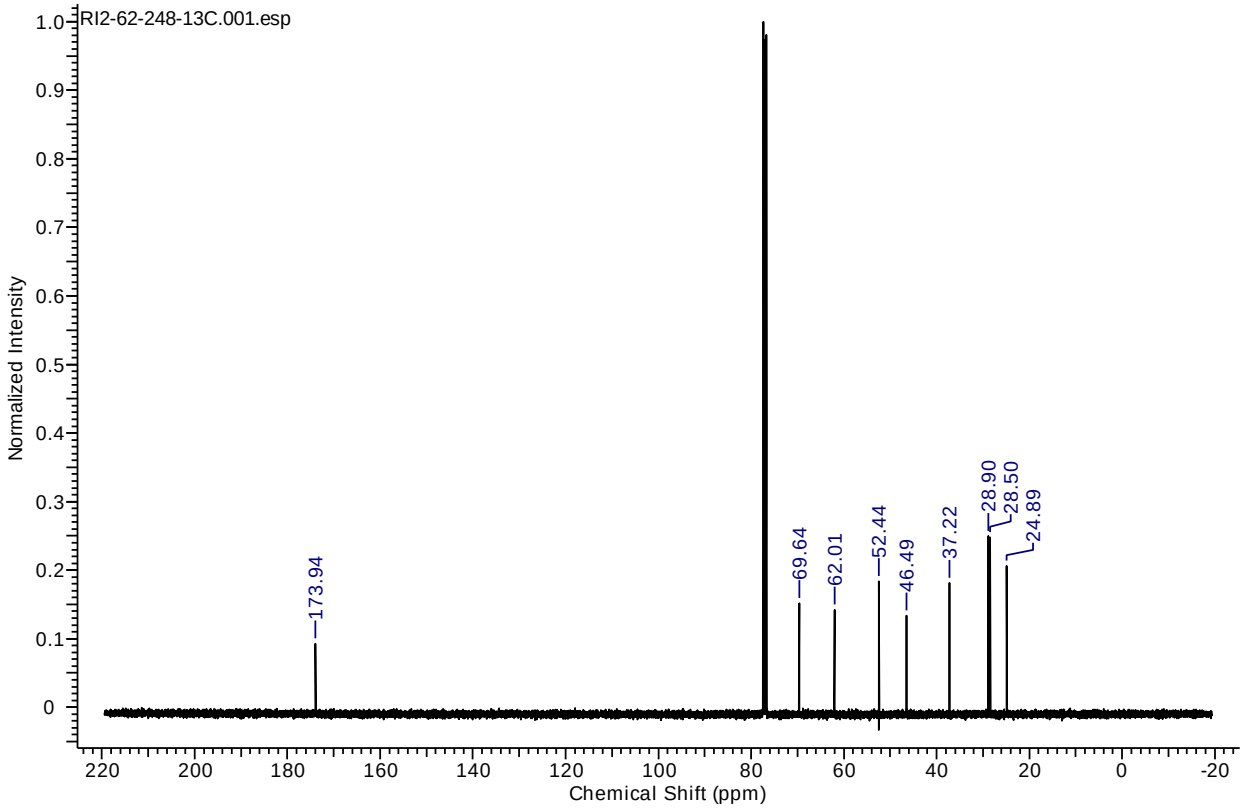

RI3-155-1H.001.esp
HN
N
O
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.78
4.34
0.98
0.99
1.04
0.97
1.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

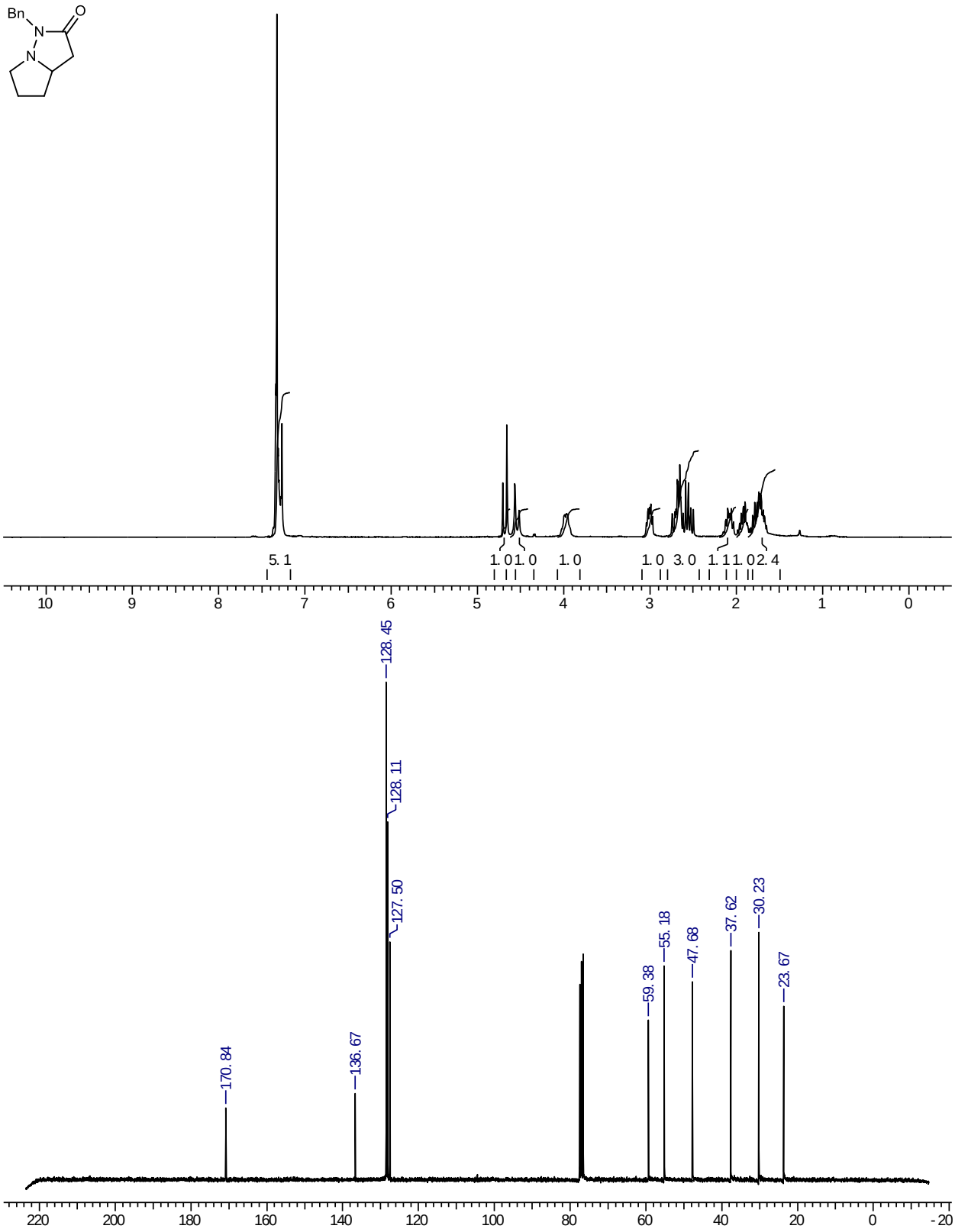

RI3-155-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
173.54
140.82
137.81
128.51
123.31
122.82
67.89
62.90
36.56
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

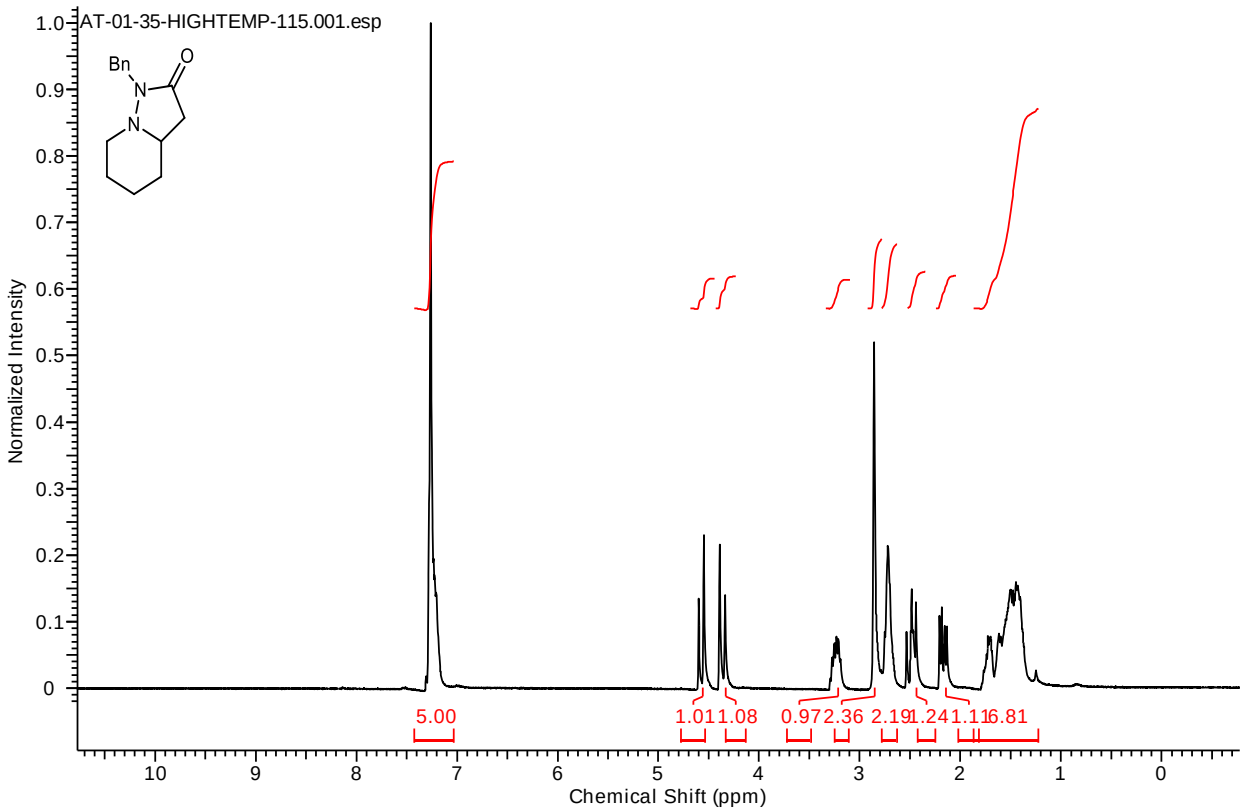

RI2-59-245-1H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.96
1.01
1.04
4.93
2.98
1.00

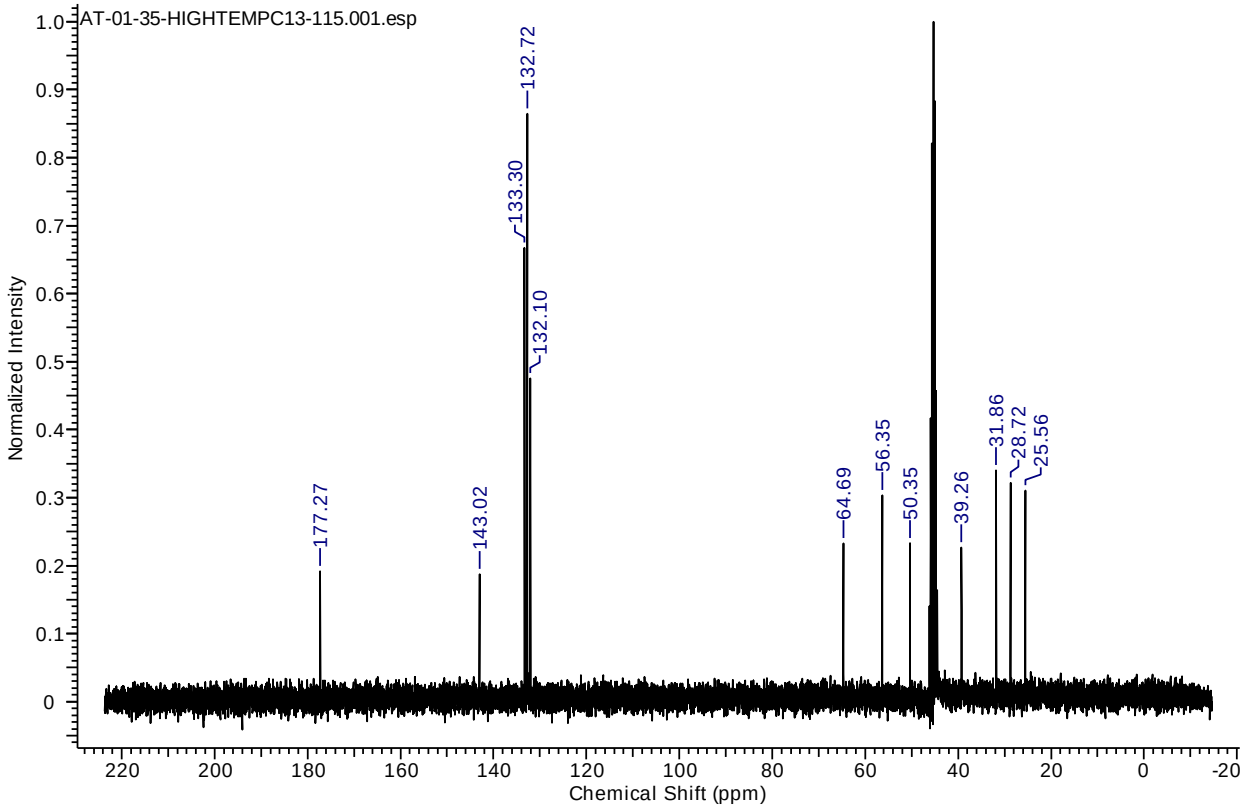

RI2-59-245-13C.001.esp
Normalized Intensity
Chemical Shift (ppm)
174.49
70.66
66.15
61.50
49.73
39.89
39.51
37.42

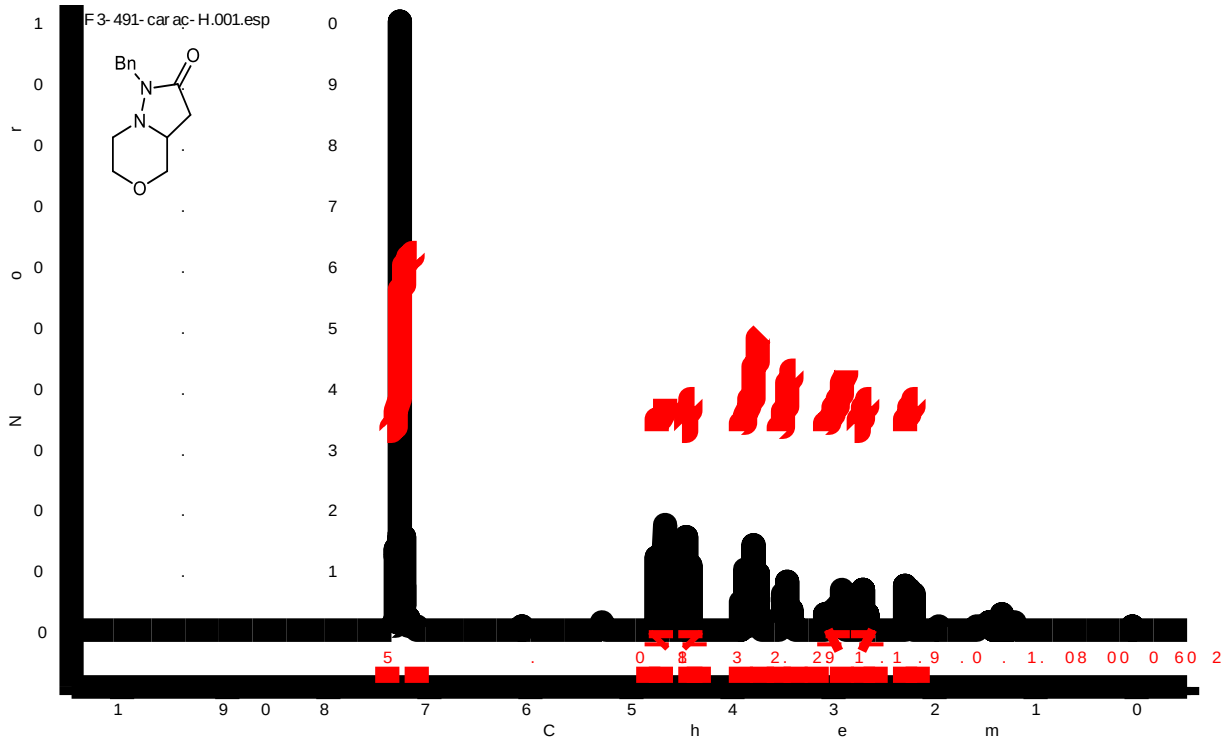

RI2-62-248-1H.001.esp
HN
O
N
S
S
Normalized Intensity
Chemical Shift (ppm)
1.13
0.06
1.00
0.99
0.98
4.39
3.03
1.03
2.15

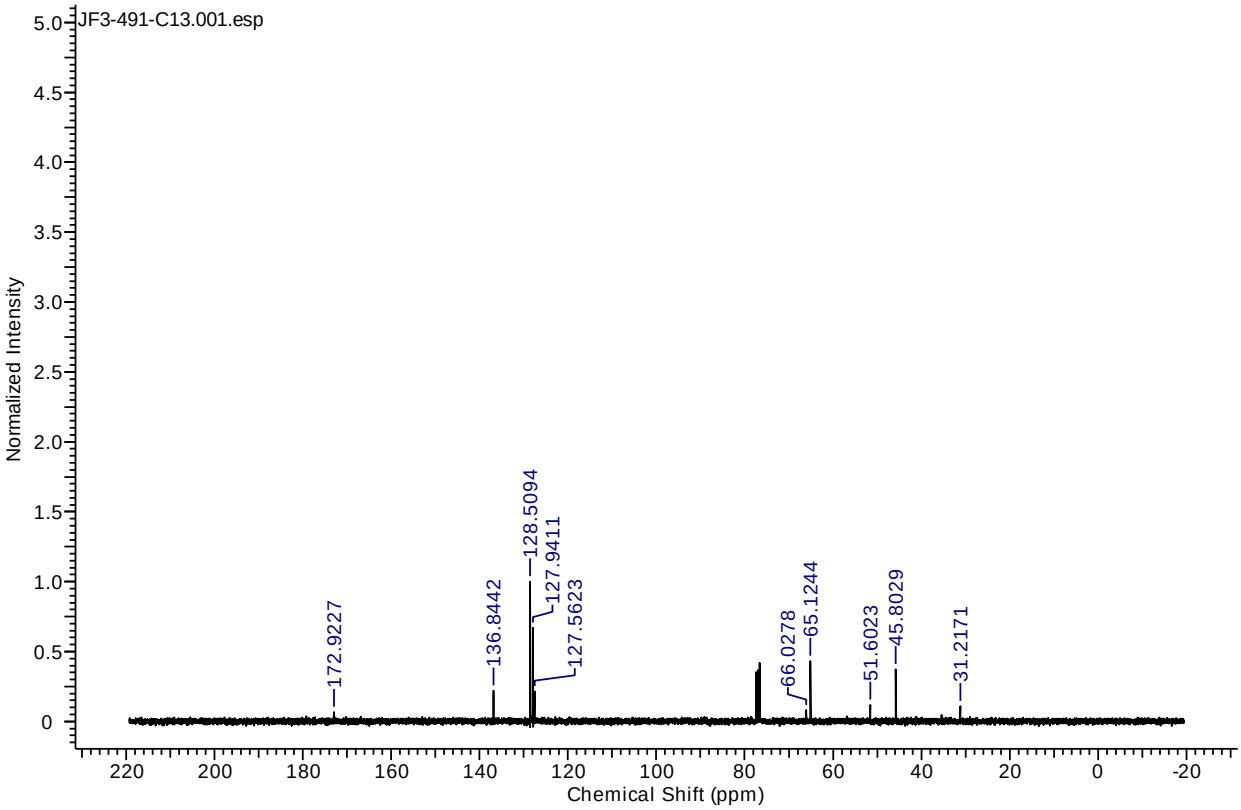

RI2-62-248-13C.001.esp
Normalized Intensity
Chemical Shift (ppm)
173.94
69.64
62.01
52.44
46.49
37.22
28.90
28.50
24.89

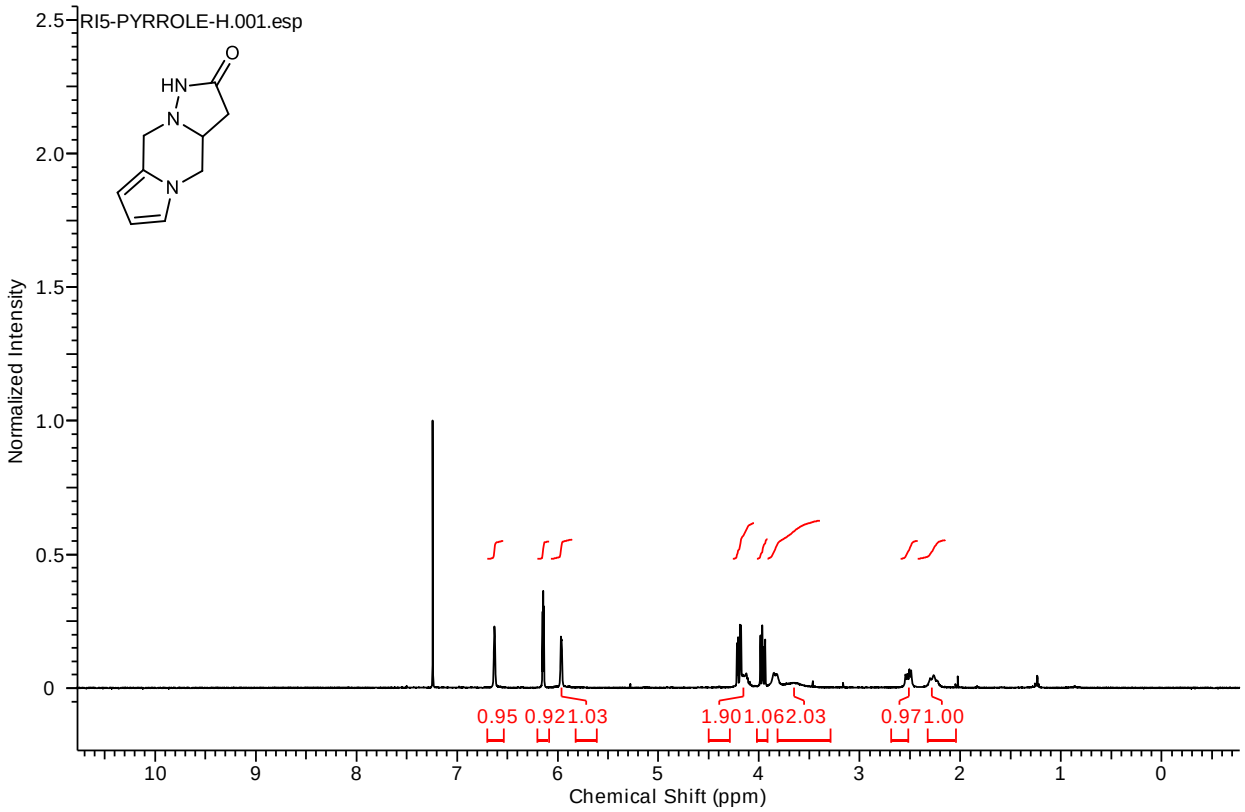

Bn
N
N
O
5.1
1.0
1.0
1.0
1.0
3.0
1.1
1.0
2.4
10
9
8
7
6
5
4
3
2
1
0
128.45
128.11
127.50
170.84
136.67
59.38
55.18
47.68
37.62
30.23
23.67
220
200
180
160
140
120
100
80
60
40
20
0
-20

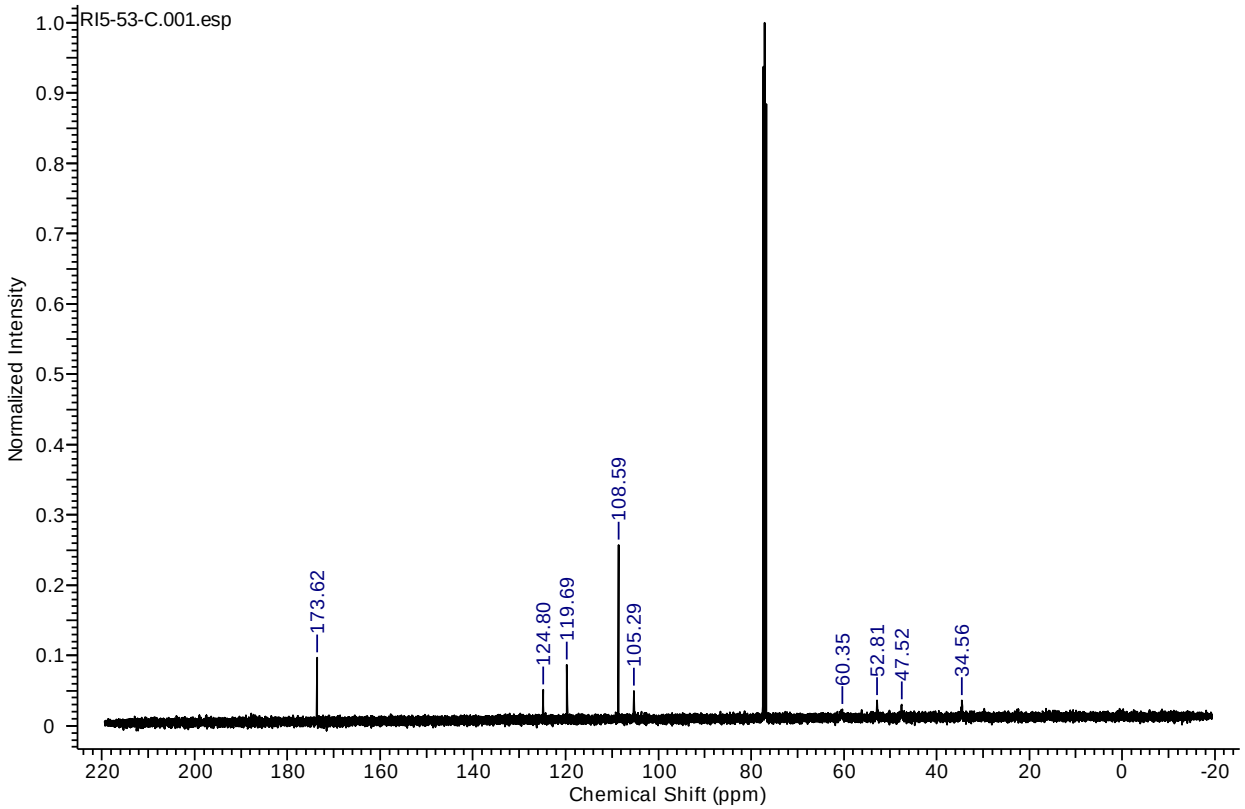

AT-01-35-HIGHTEMP-115.001.esp
Bn
O
N
N
Normalized Intensity
Chemical Shift (ppm)
5.00
1.01
1.08
0.97
2.36
2.19
1.24
1.11
6.81

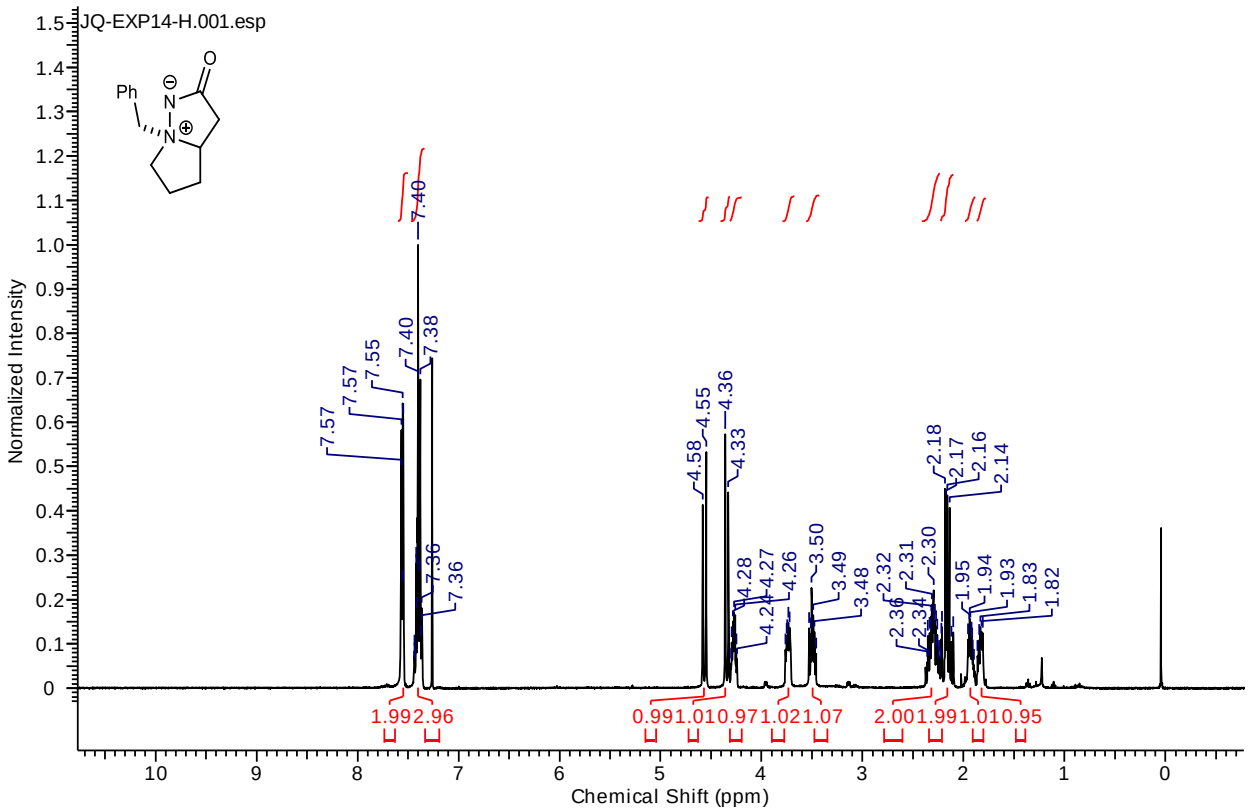

AT-01-35-HIGHTEMPC13-115.001.esp
Normalized Intensity
Chemical Shift (ppm)
177.27
143.02
133.30
132.72
132.10
64.69
56.35
50.35
39.26
31.86
28.72
25.56

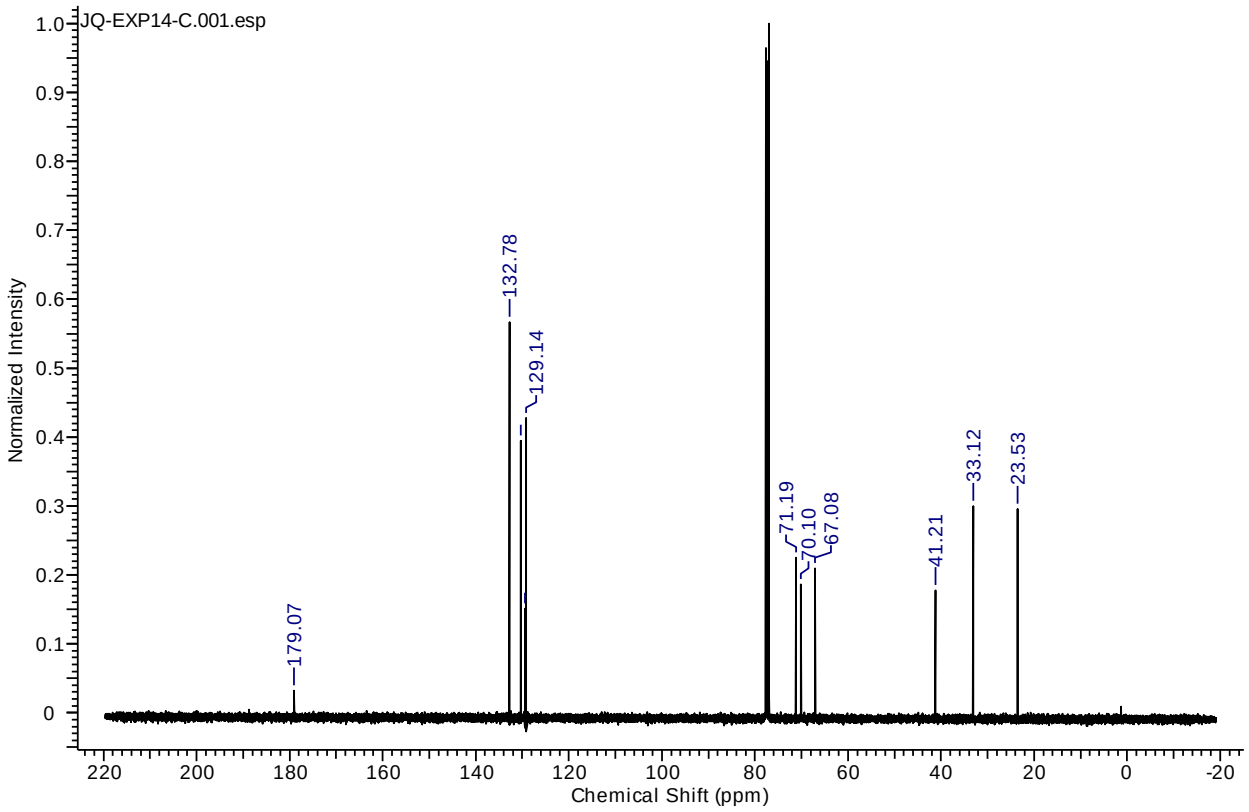

JF3-491-carac-H.001.esp
Bn
O
N
N
O
Normalized Intensity
Chemical Shift (ppm)

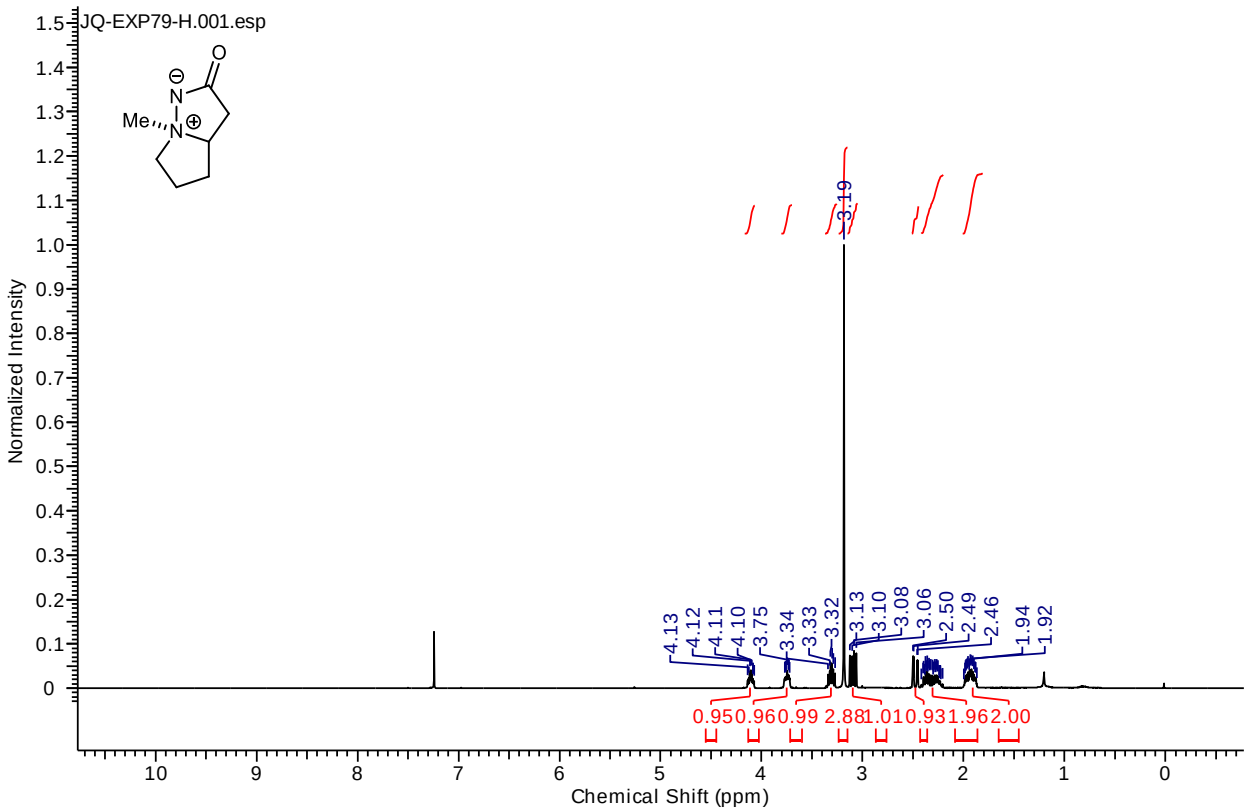

JF3-491-C13.001.esp
172.9227
136.8442
128.5094
127.9411
127.5623
66.0278
65.1244
51.6023
45.8029
31.2171
Normalized Intensity
Chemical Shift (ppm)

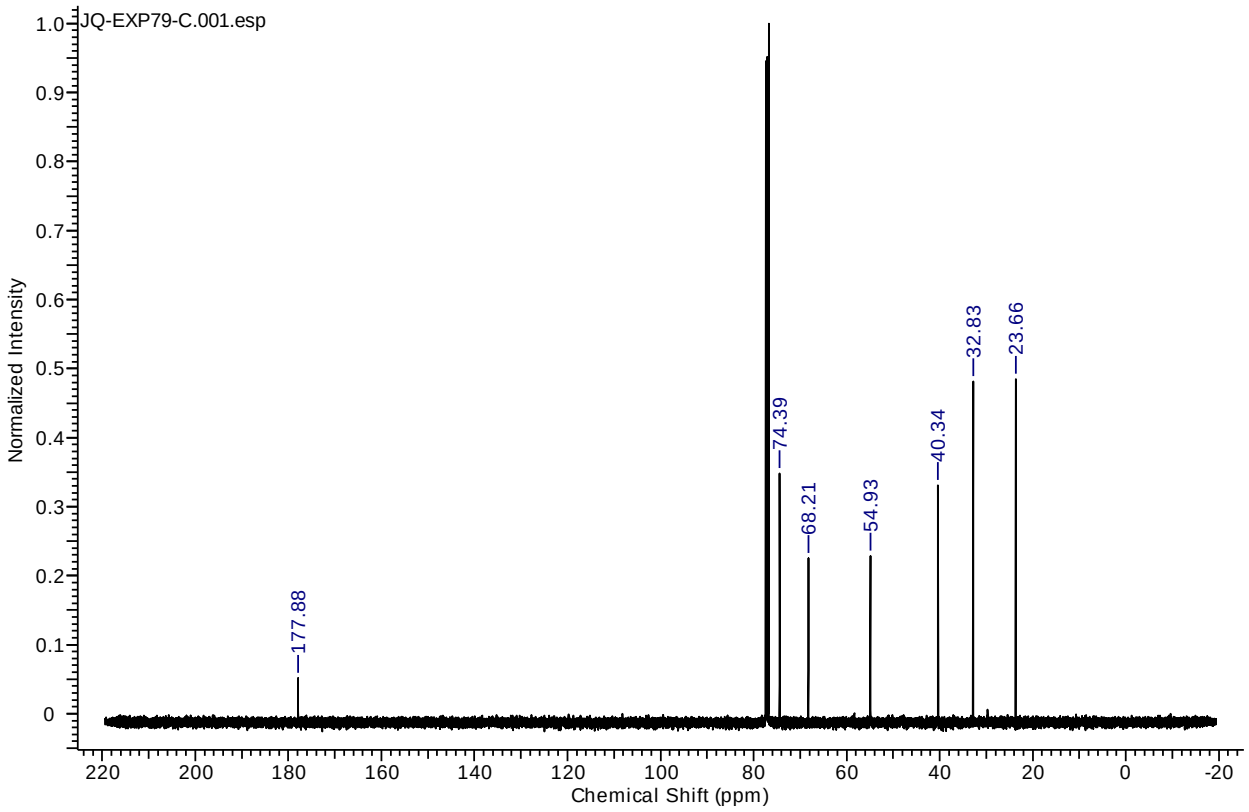

RI5-PYRROLE-H.001.esp
HN
O
N
N
Normalized Intensity
Chemical Shift (ppm)
0.95 0.92 1.03
1.90 1.06 2.03
0.97 1.00

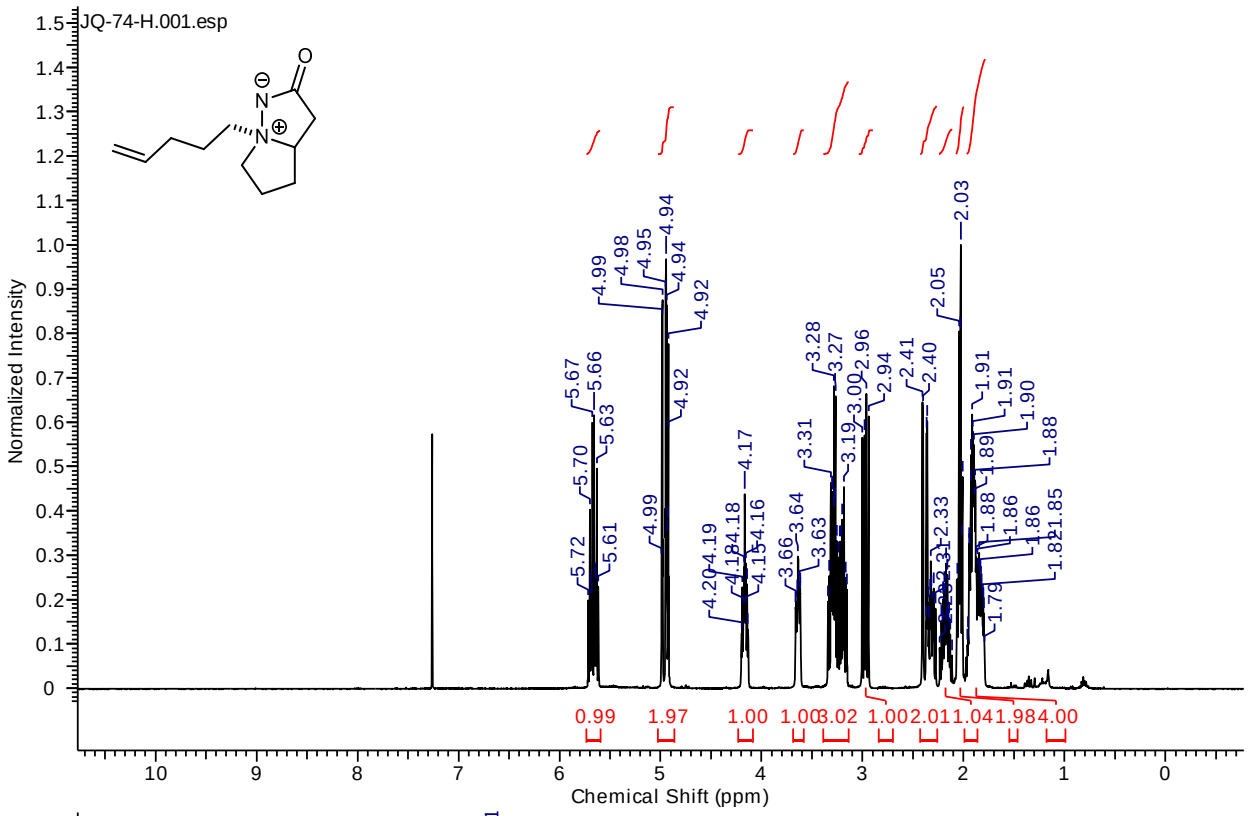

RI5-53-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
173.62
124.80
119.69
108.59
105.29
60.35
52.81
47.52
34.56

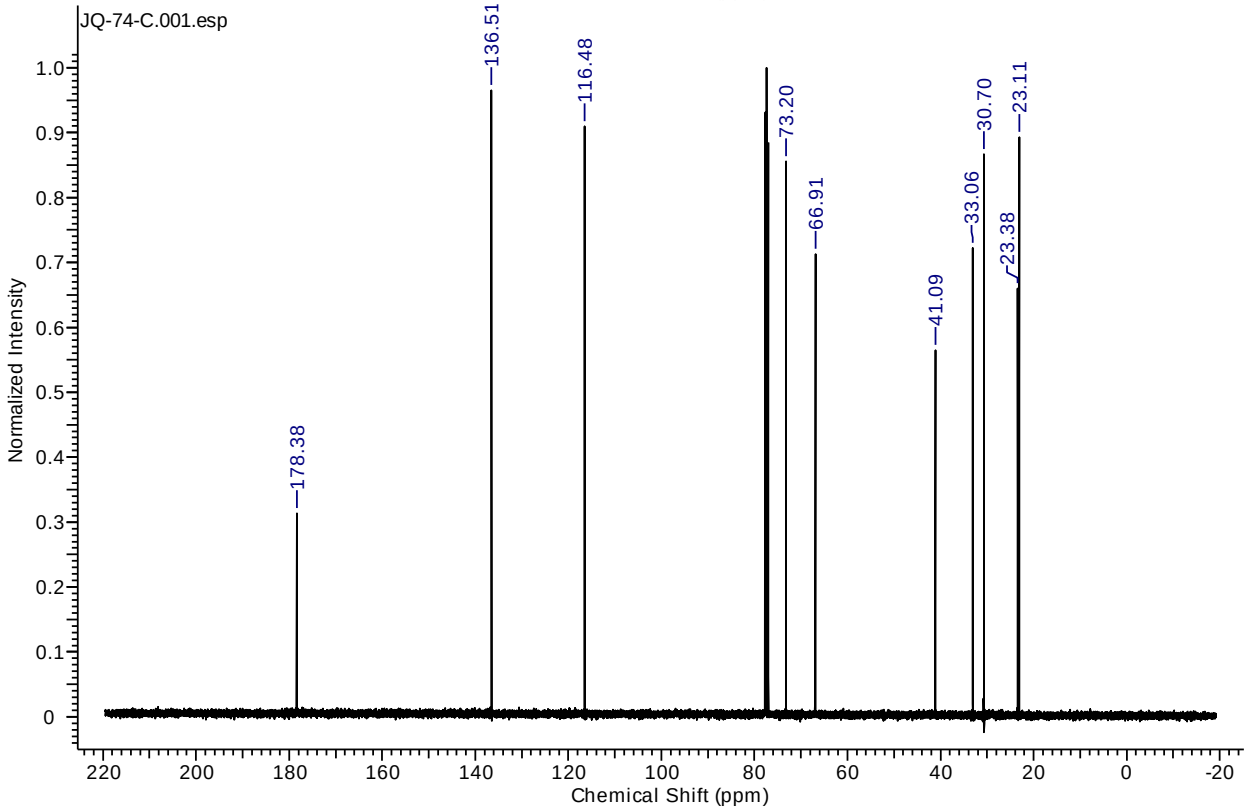

JQ-EXP14-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
7.57
7.57
7.55
7.40
7.40
7.38
7.36
7.36
4.58
4.55
4.36
4.33
4.28
4.27
4.26
3.50
3.49
3.48
2.32
2.31
2.30
2.18
2.17
2.16
2.14
1.95
1.94
1.93
1.83
1.82
1.99
2.96
0.99
1.01
0.97
1.02
1.07
2.00
1.99
1.01
0.95

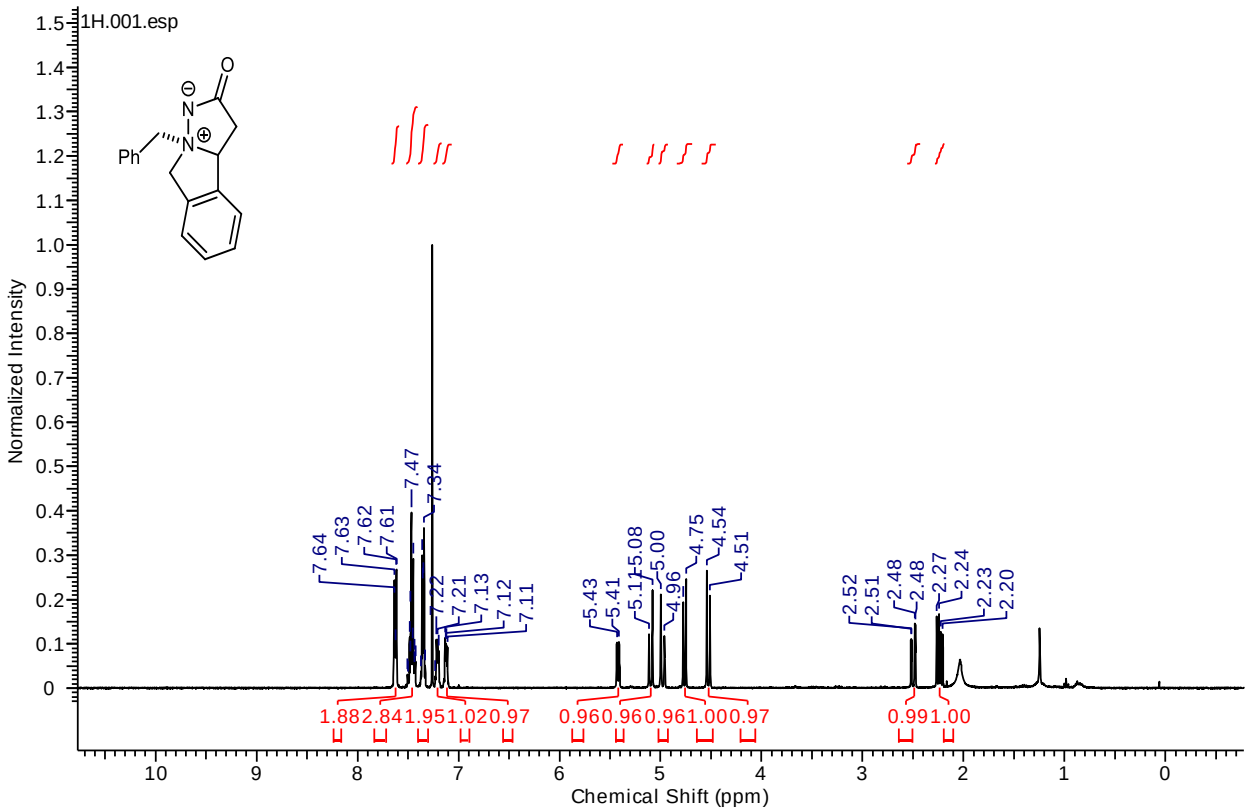

JQ-EXP14-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
179.07
132.78
129.14
71.19
70.10
67.08
41.21
33.12
23.53

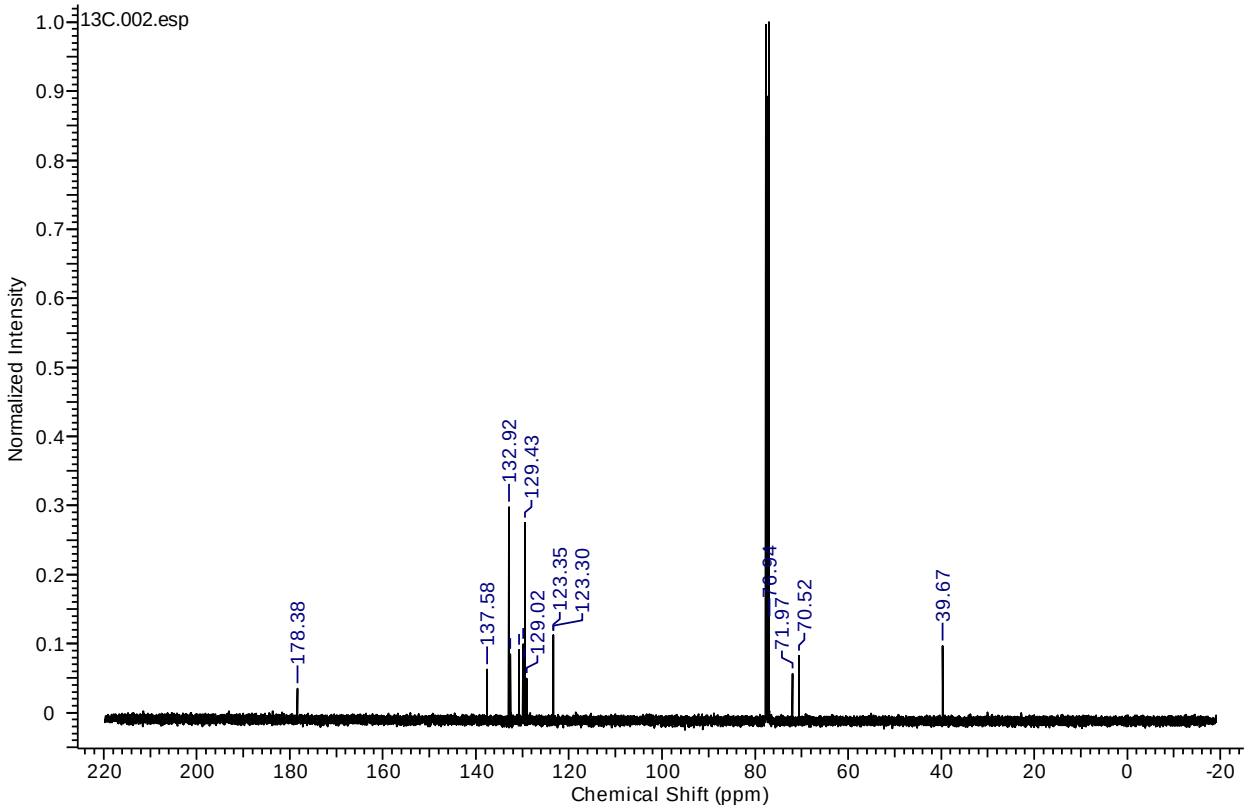

JQ-EXP79-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
4.13
4.12
4.11
4.10
3.75
3.34
3.33
3.32
3.19
3.13
3.10
3.08
3.06
2.50
2.49
2.46
1.94
1.92
0.95 0.96 0.99 2.88 1.01 0.93 1.96 2.00

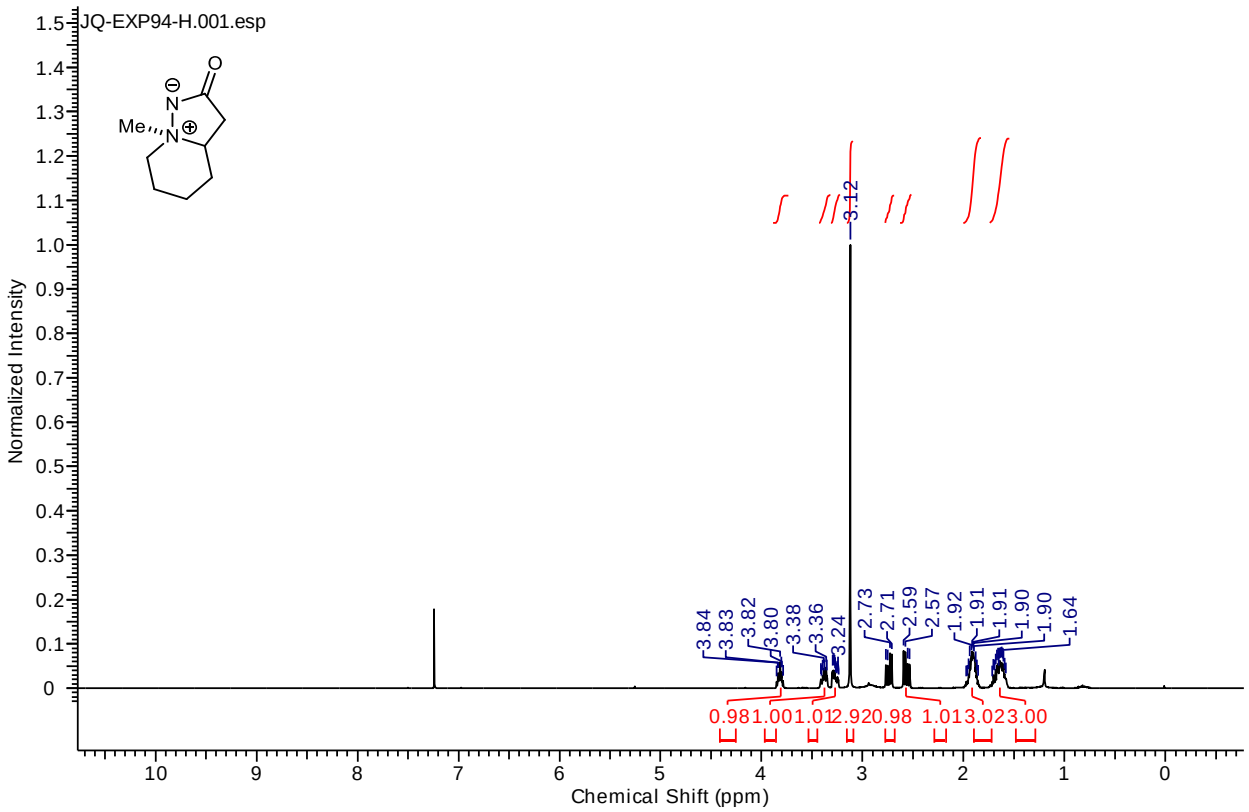

JQ-EXP79-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
177.88
74.39
68.21
54.93
40.34
32.83
23.66

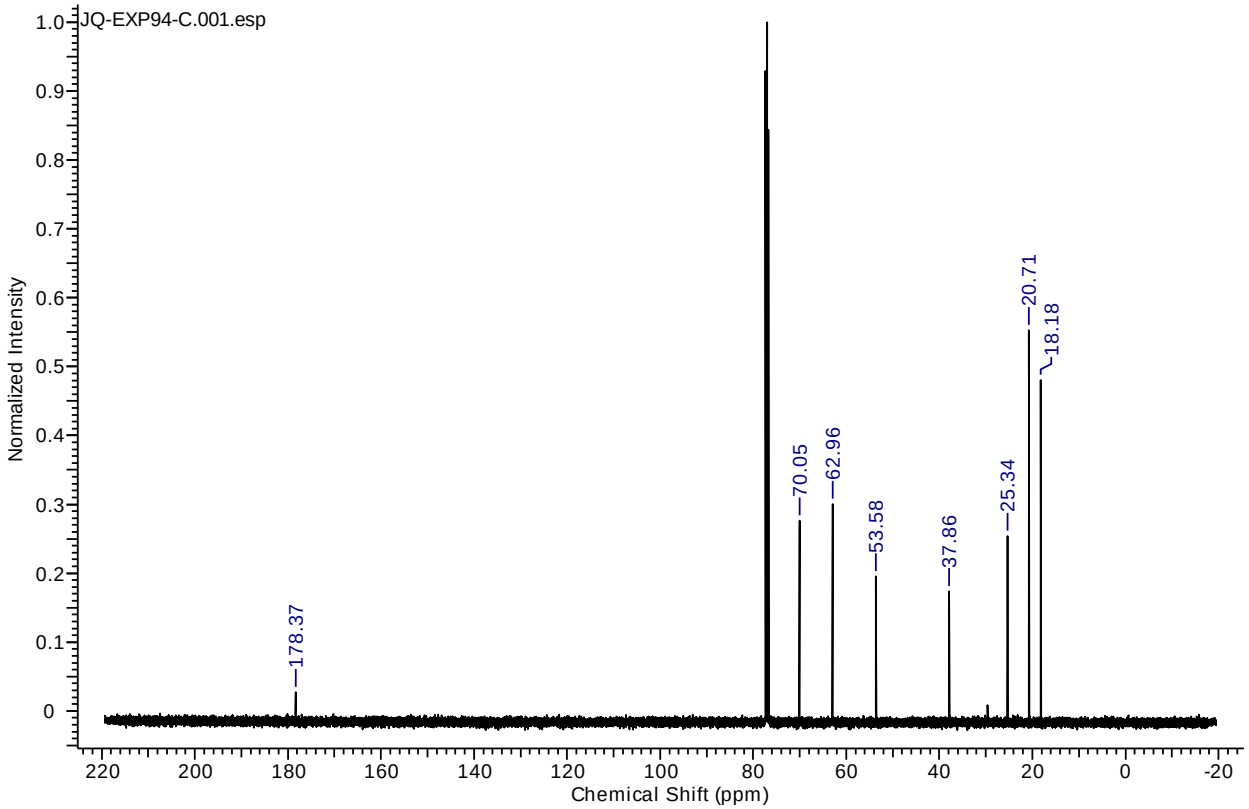

JQ-74-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
5.72
5.67
5.66
5.63
5.61
5.70
4.99
4.99
4.98
4.95
4.94
4.94
4.92
4.92
4.20
4.19
4.18
4.17
4.16
4.15
3.66
3.64
3.63
3.31
3.28
3.27
3.19
3.00
2.96
2.94
2.41
2.40
2.33
2.05
2.03
1.91
1.91
1.90
1.89
1.88
1.88
1.86
1.86
1.85
1.82
1.79
0.99
1.97
1.00
1.00
3.02
1.00
2.01
1.04
1.98
4.00

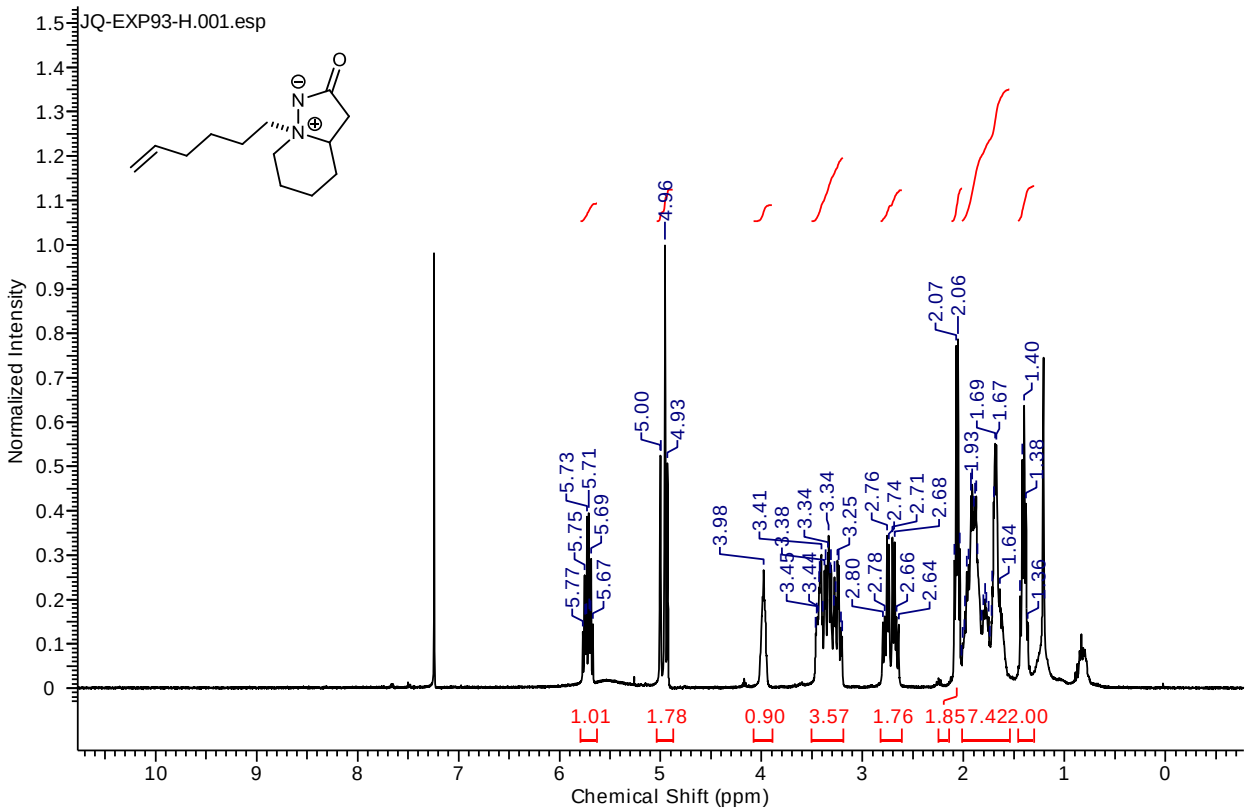

JQ-74-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
178.38
136.51
116.48
73.20
66.91
41.09
33.06
30.70
23.38
23.11

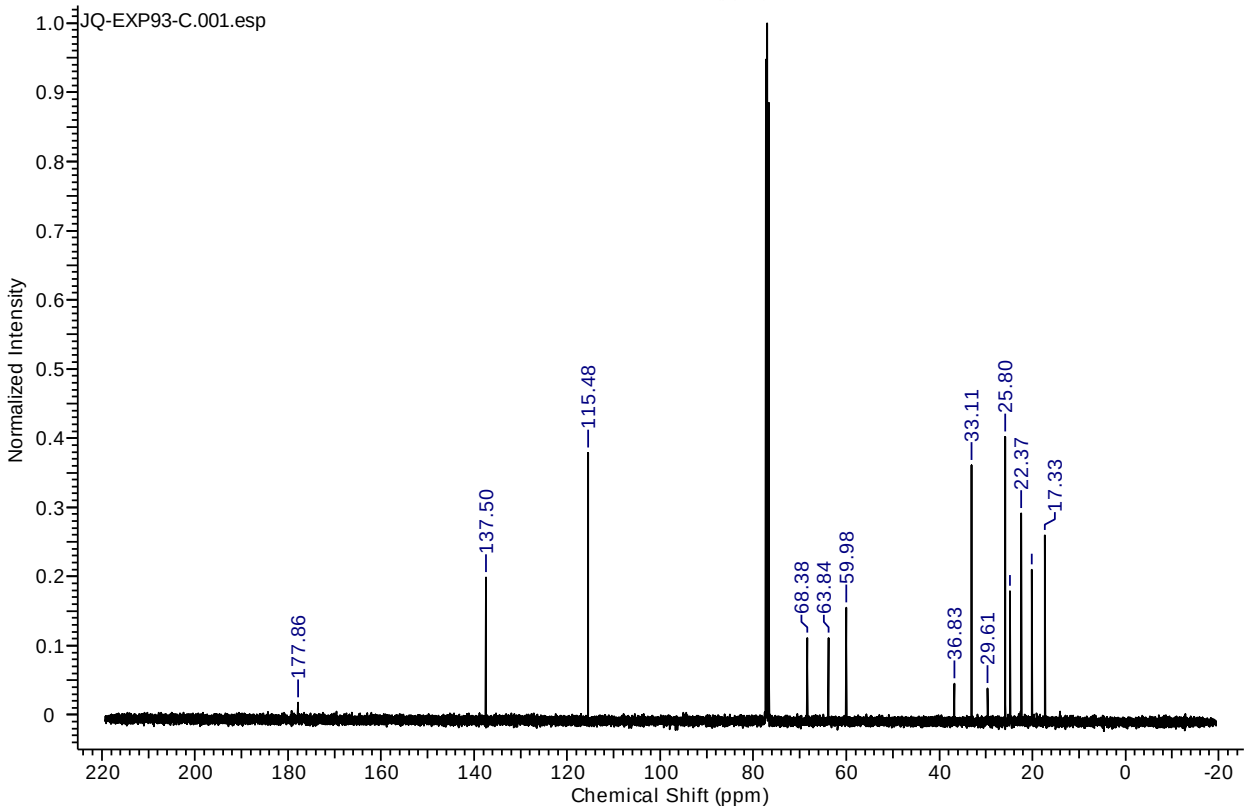

1H.001.esp
Ph
Normalized Intensity
7.64
7.63
7.62
7.61
7.47
7.34
7.22
7.21
7.13
7.12
7.11
5.43
5.41
5.11
5.08
5.00
4.96
4.75
4.54
4.51
2.52
2.51
2.48
2.48
2.27
2.24
2.23
2.20
1.88 2.84 1.95 1.02 0.97
0.96 0.96 0.96 1.00 0.97
0.99 1.00
Chemical Shift (ppm)

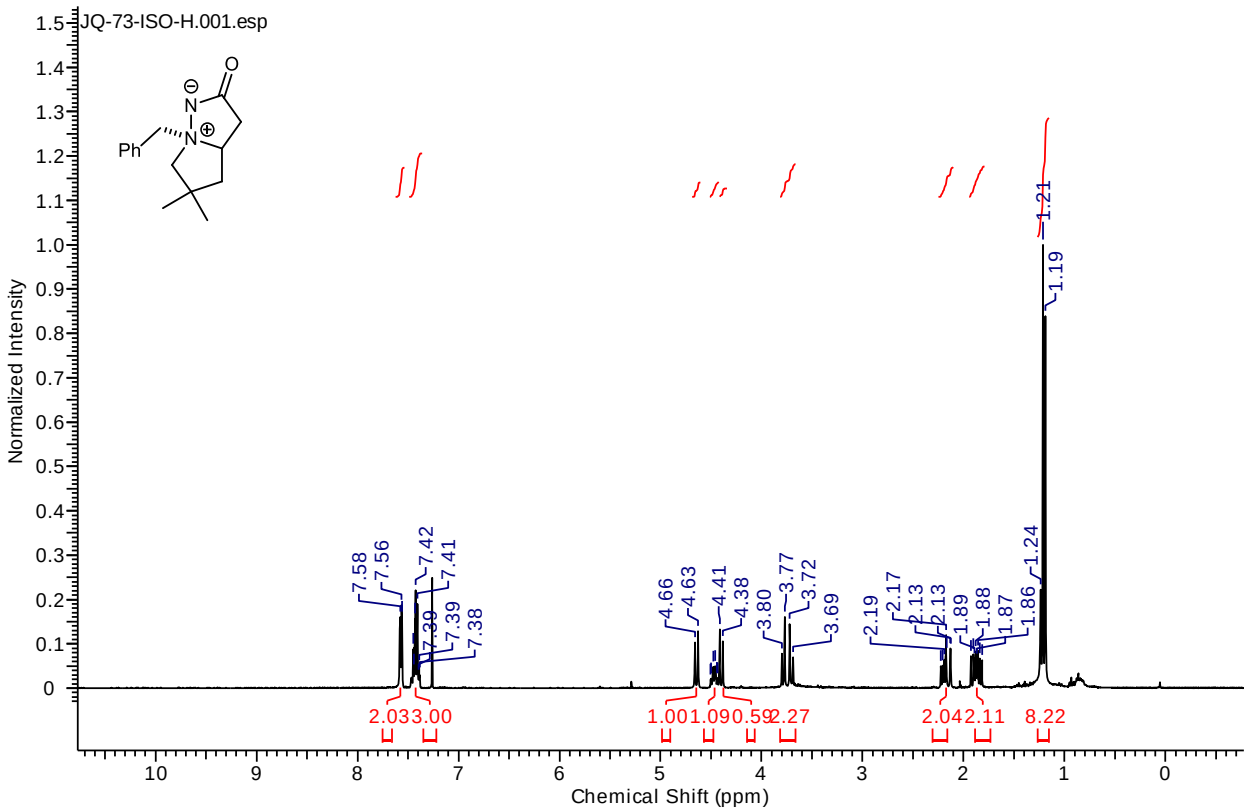

13C.002.esp
Normalized Intensity
178.38
137.58
132.92
129.43
129.02
123.35
123.30
78.94
77.97
70.52
39.67
Chemical Shift (ppm)

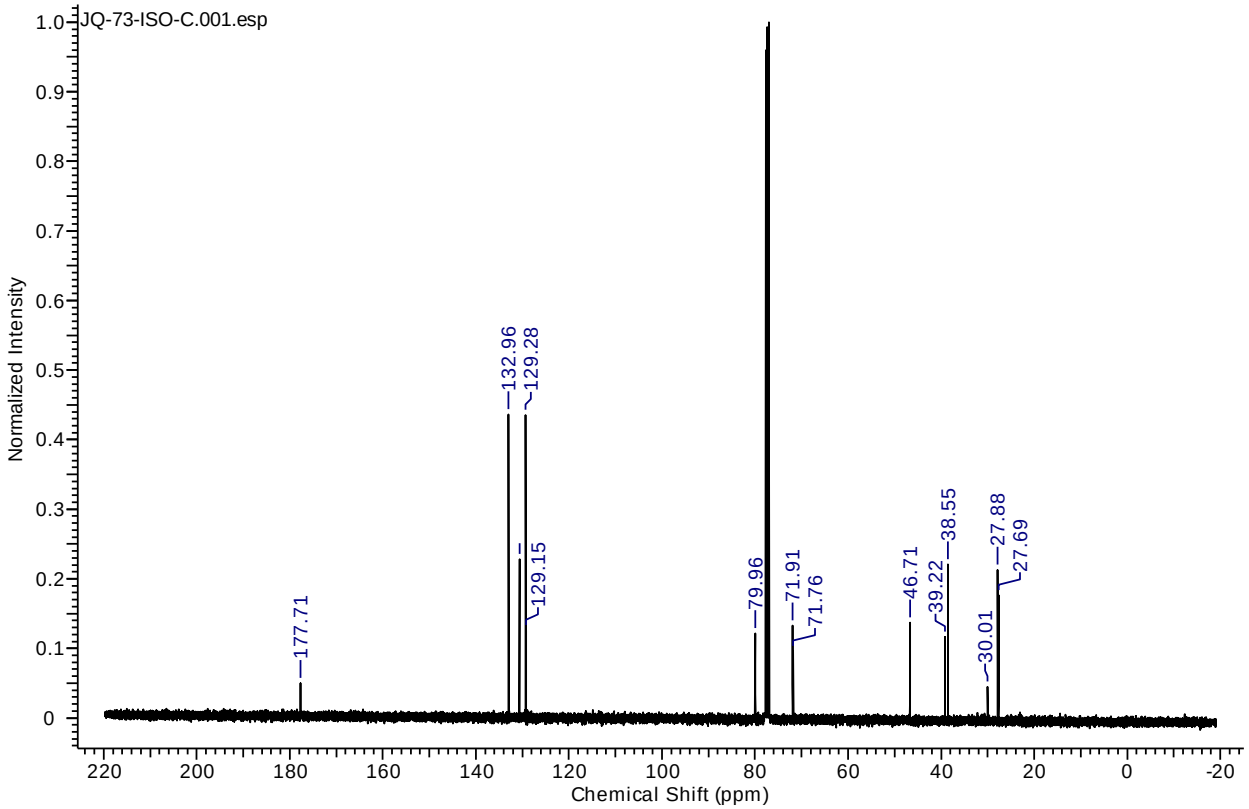

JQ-EXP94-H.001.esp
Me
O
Normalized Intensity
Chemical Shift (ppm)
3.84
3.83
3.82
3.80
3.38
3.36
3.24
3.12
2.73
2.71
2.59
2.57
1.92
1.91
1.91
1.90
1.90
1.64
0.98 1.00 1.01 2.92 0.98 1.01 3.02 3.00

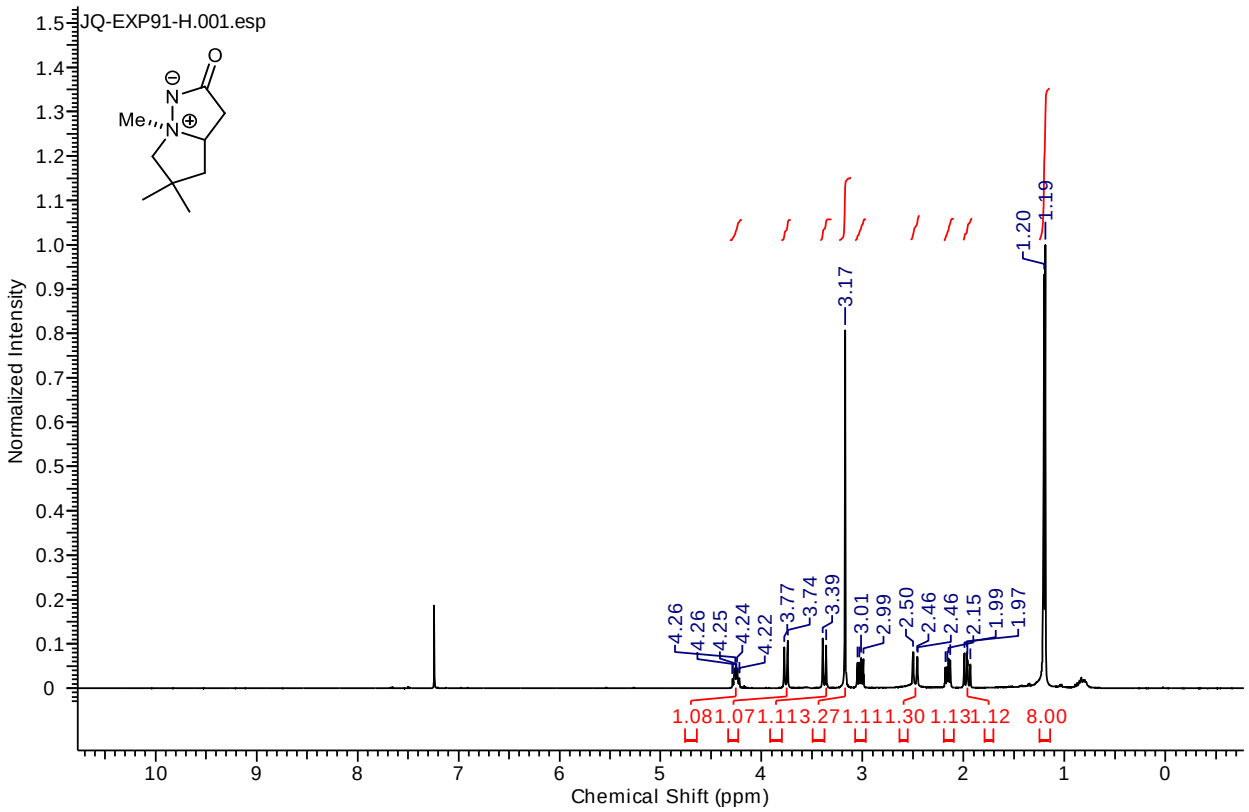

JQ-EXP94-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
178.37
70.05
62.96
53.58
37.86
25.34
20.71
18.18

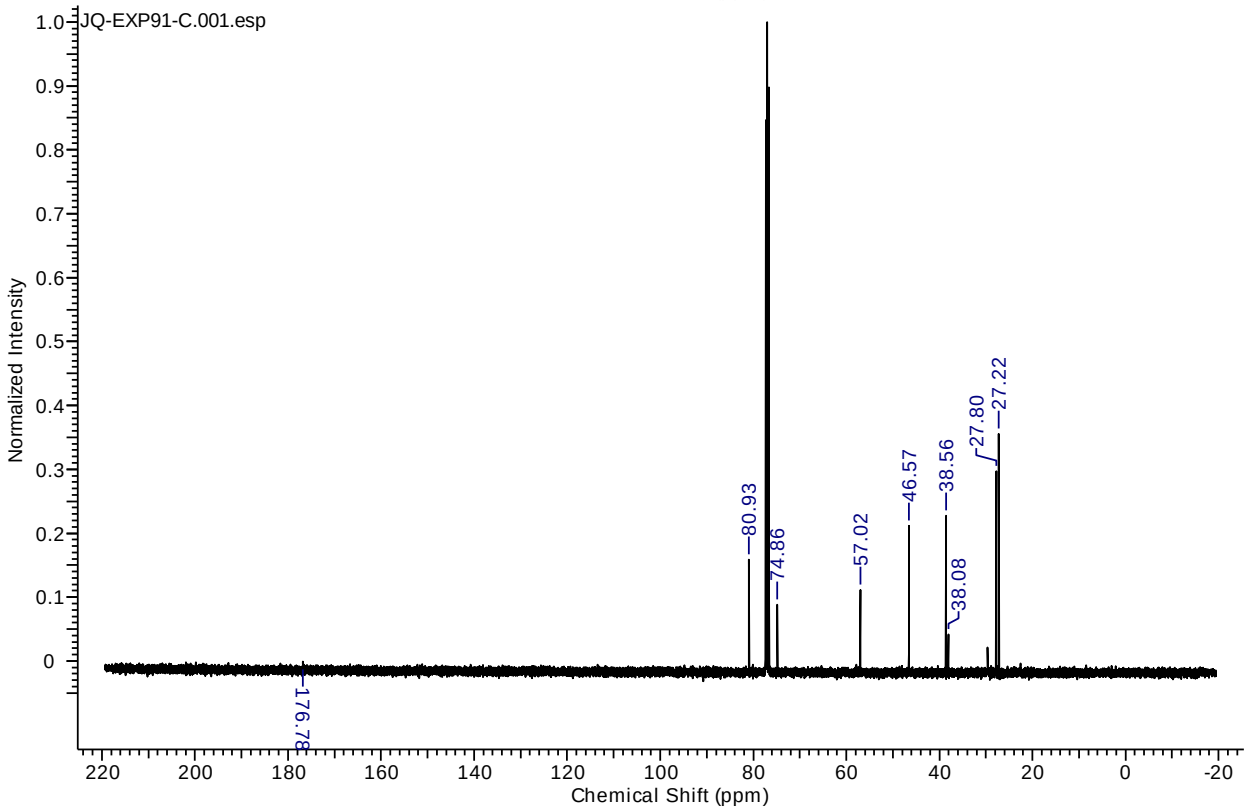

JQ-EXP93-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
5.77
5.75
5.73
5.71
5.69
5.67
5.00
4.96
4.93
3.98
3.41
3.38
3.34
3.25
2.80
2.78
2.76
2.74
2.71
2.68
2.66
2.64
2.07
2.06
1.93
1.69
1.67
1.64
1.40
1.38
1.36
1.01
1.78
0.90
3.57
1.76
1.85
7.42
2.00

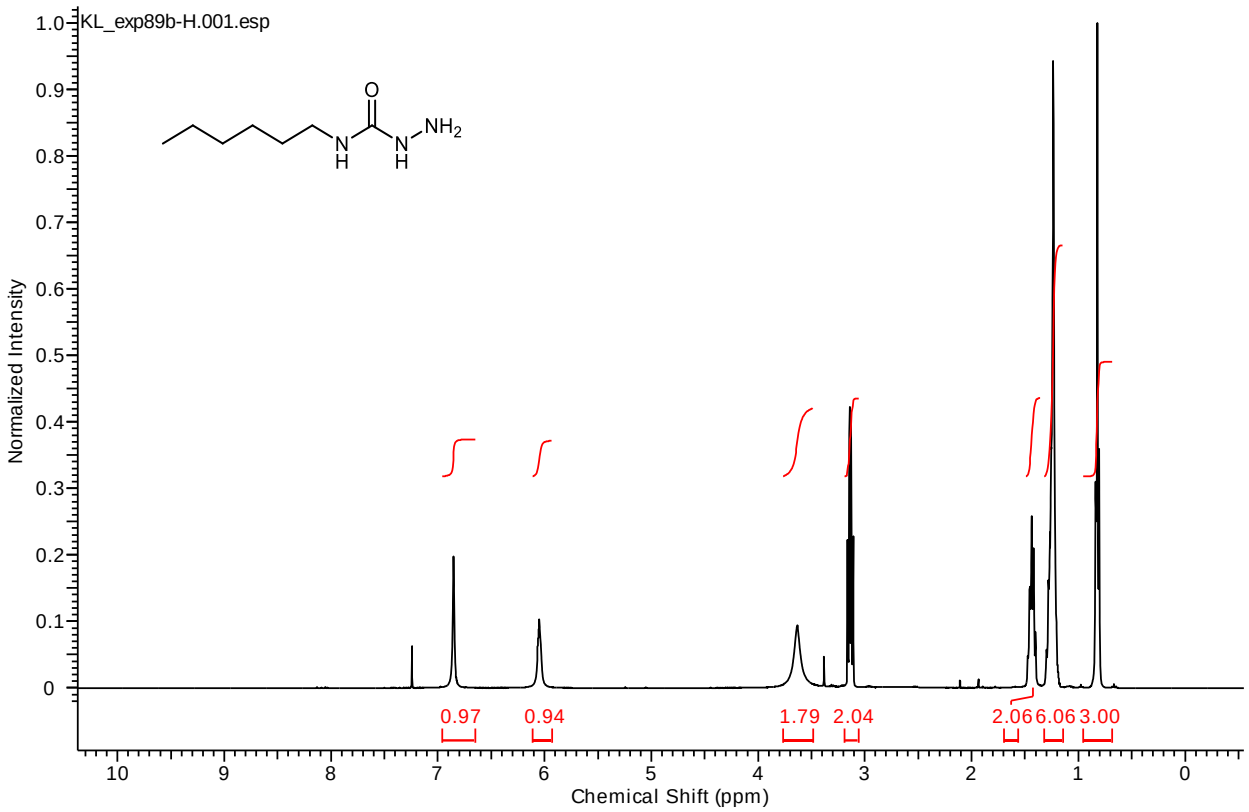

JQ-EXP93-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
177.86
137.50
115.48
68.38
63.84
59.98
36.83
33.11
29.61
25.80
22.37
17.33

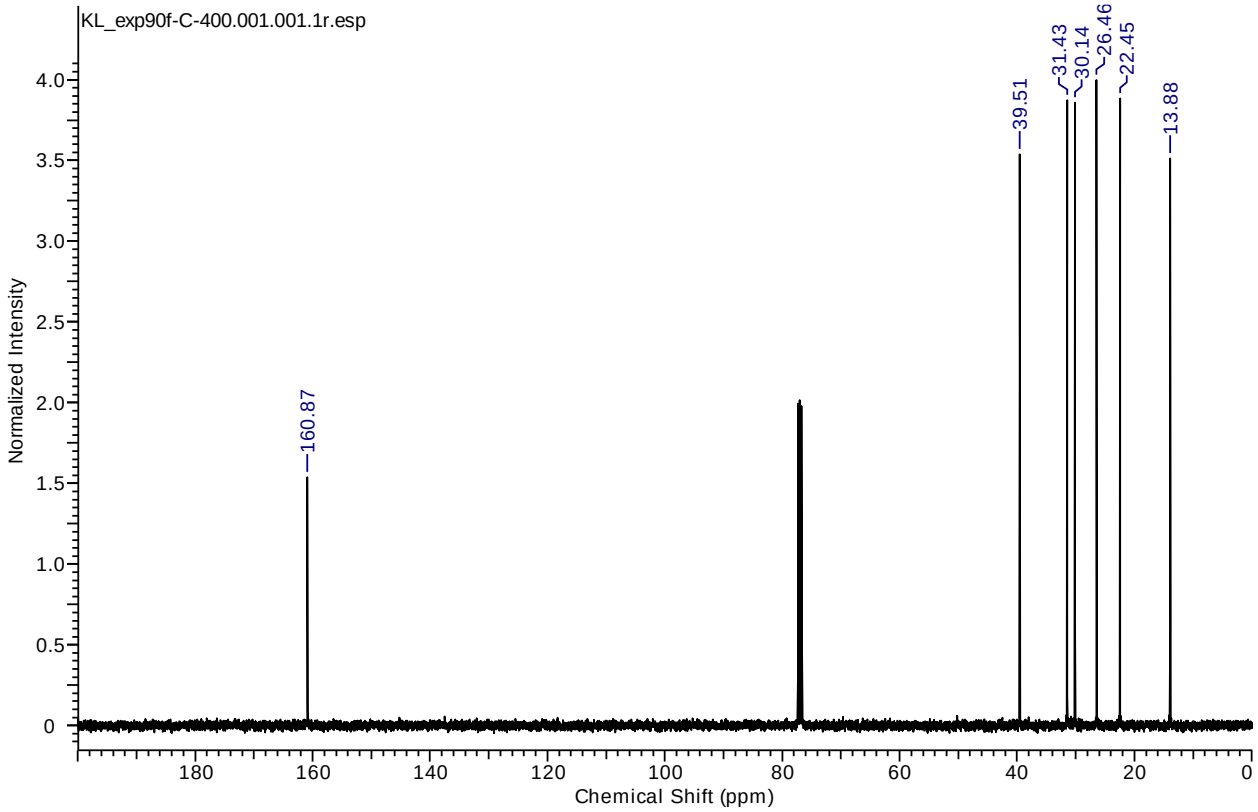

JQ-73-ISO-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
7.58
7.56
7.42
7.41
7.39
7.38
4.66
4.63
4.41
4.38
3.80
3.77
3.72
3.69
2.19
2.17
2.13
2.13
1.89
1.88
1.87
1.86
1.24
1.21
1.19
2.03
3.00
1.00
1.09
0.59
2.27
2.04
2.11
8.22

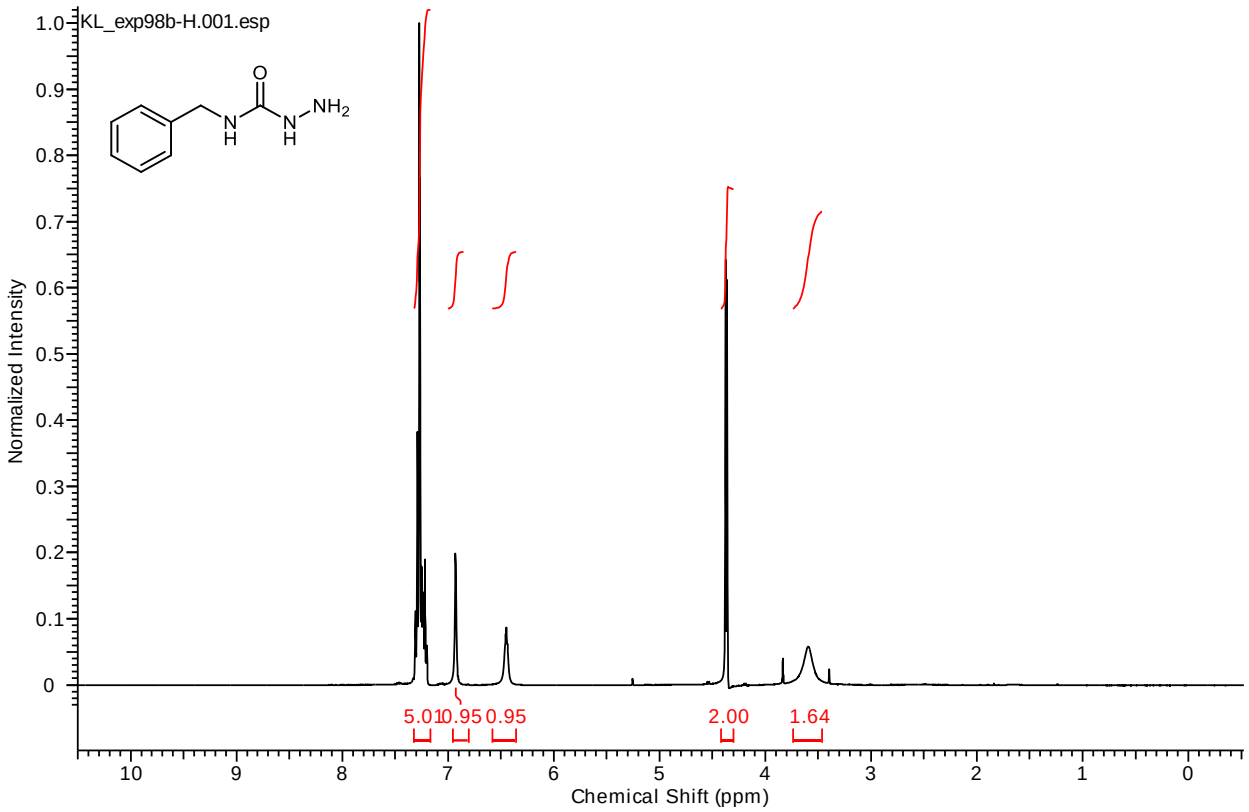

JQ-73-ISO-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
177.71
132.96
129.28
129.15
79.96
71.91
71.76
46.71
39.22
38.55
30.01
27.88
27.69

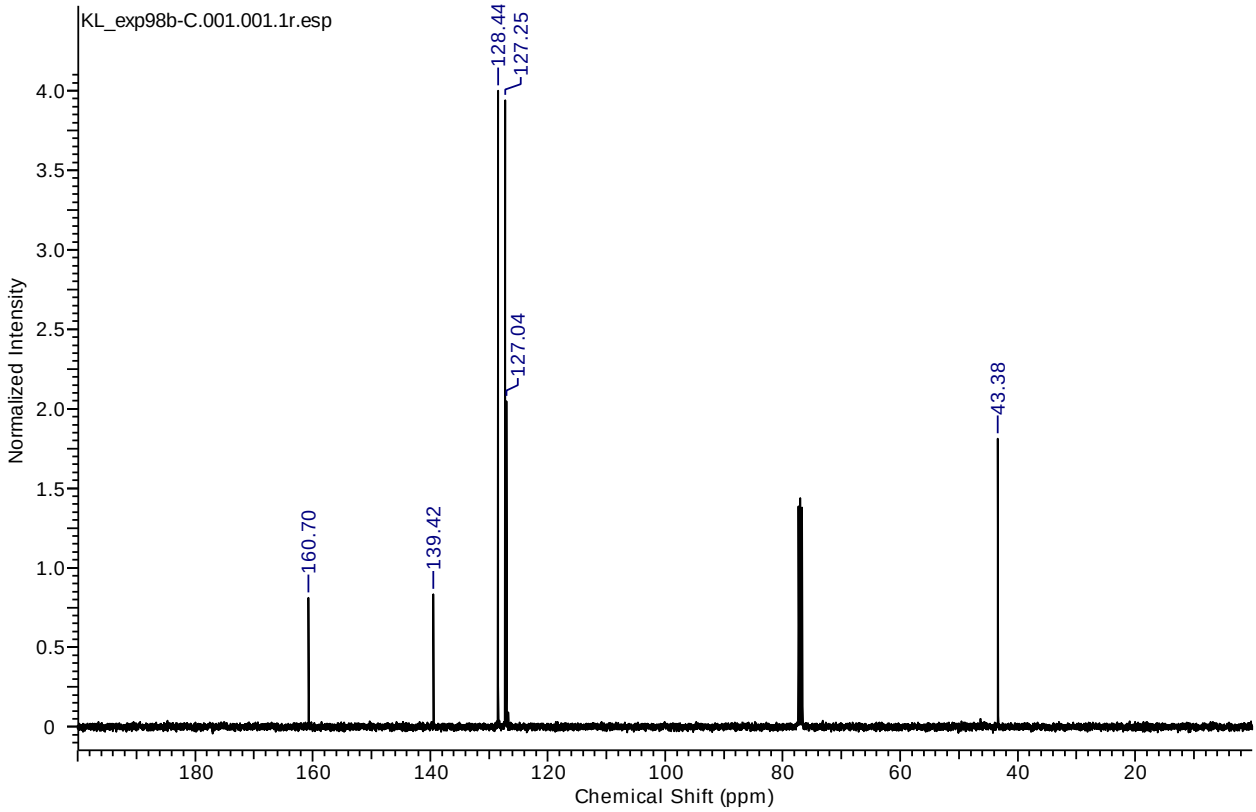

JQ-EXP91-H.001.esp
Me
Normalized Intensity
Chemical Shift (ppm)
4.26
4.26
4.25
4.24
4.22
3.77
3.74
3.39
3.17
3.01
2.99
2.50
2.46
2.46
2.15
1.99
1.97
1.20
1.19
1.08
1.07
1.11
3.27
1.11
1.30
1.13
1.12
8.00

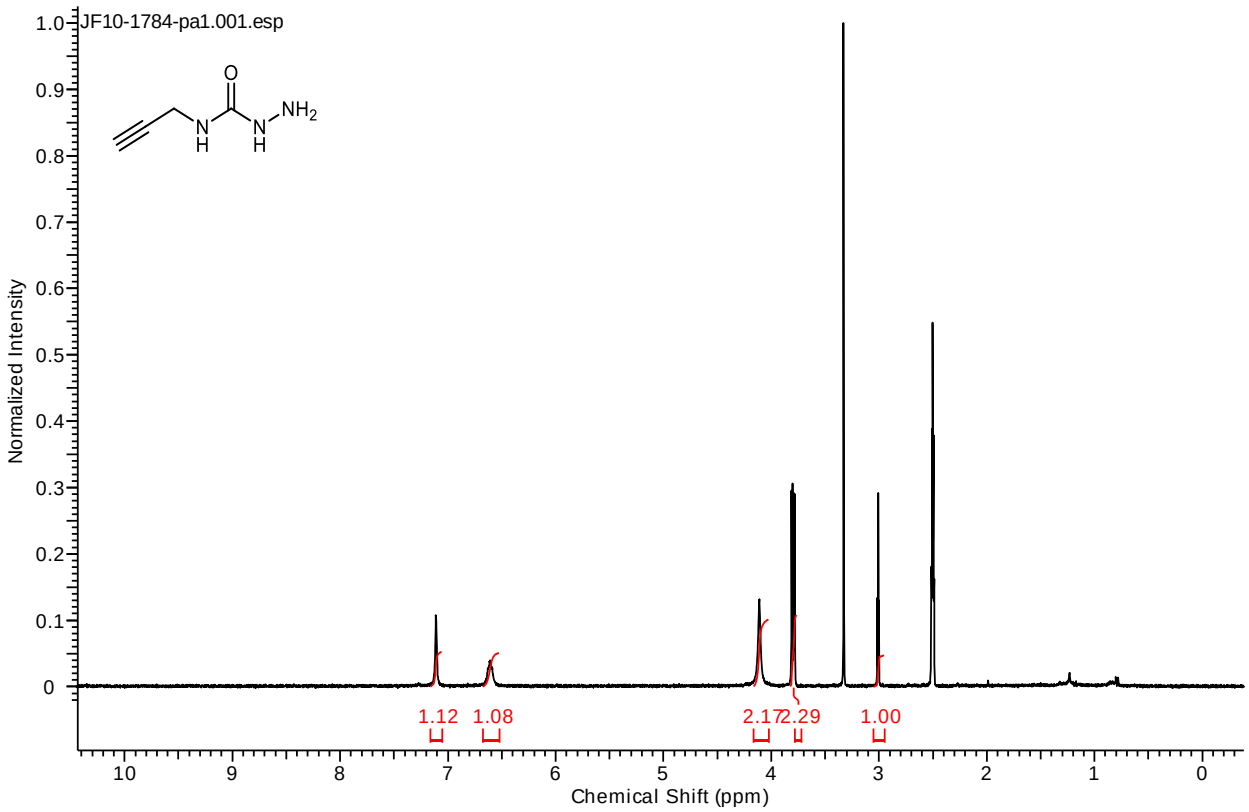

JQ-EXP91-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
176.78
80.93
74.86
57.02
46.57
38.56
38.08
27.80
27.22

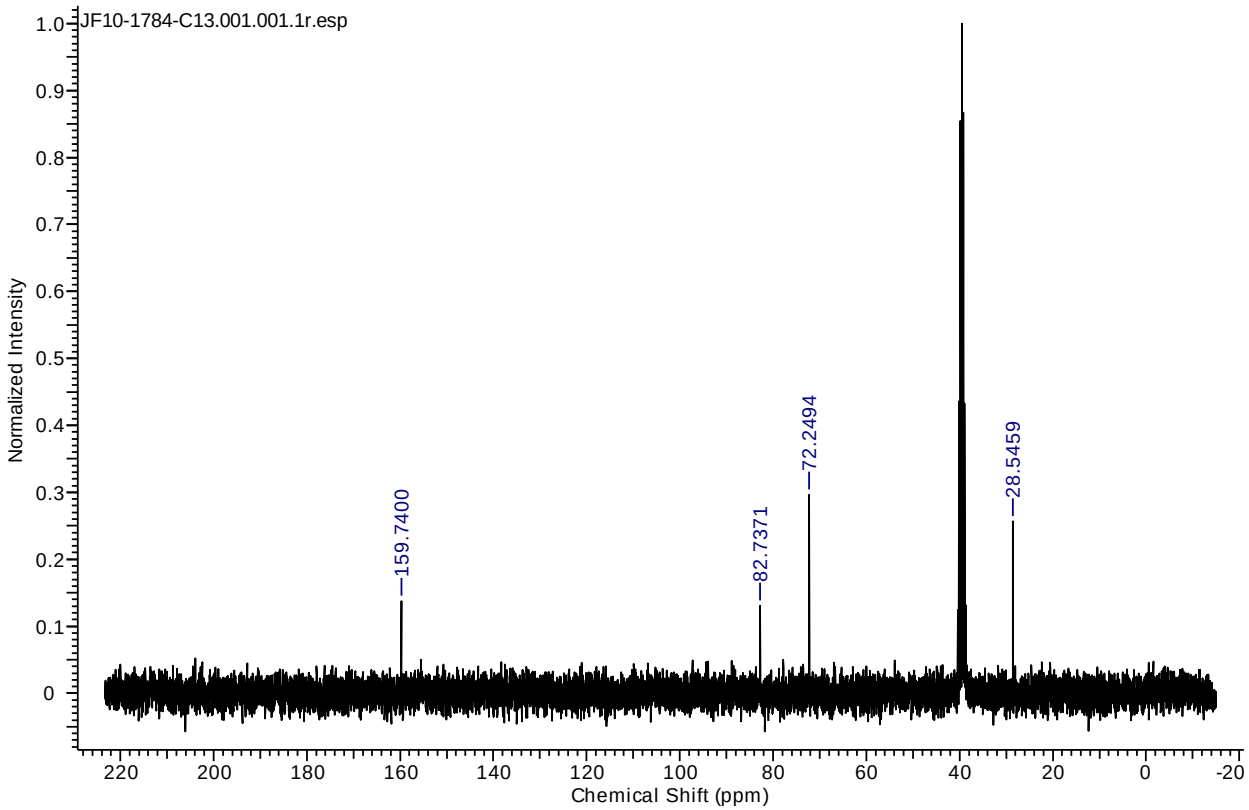

KL_exp89b-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.97
0.94
1.79
2.04
2.06
6.06
3.00

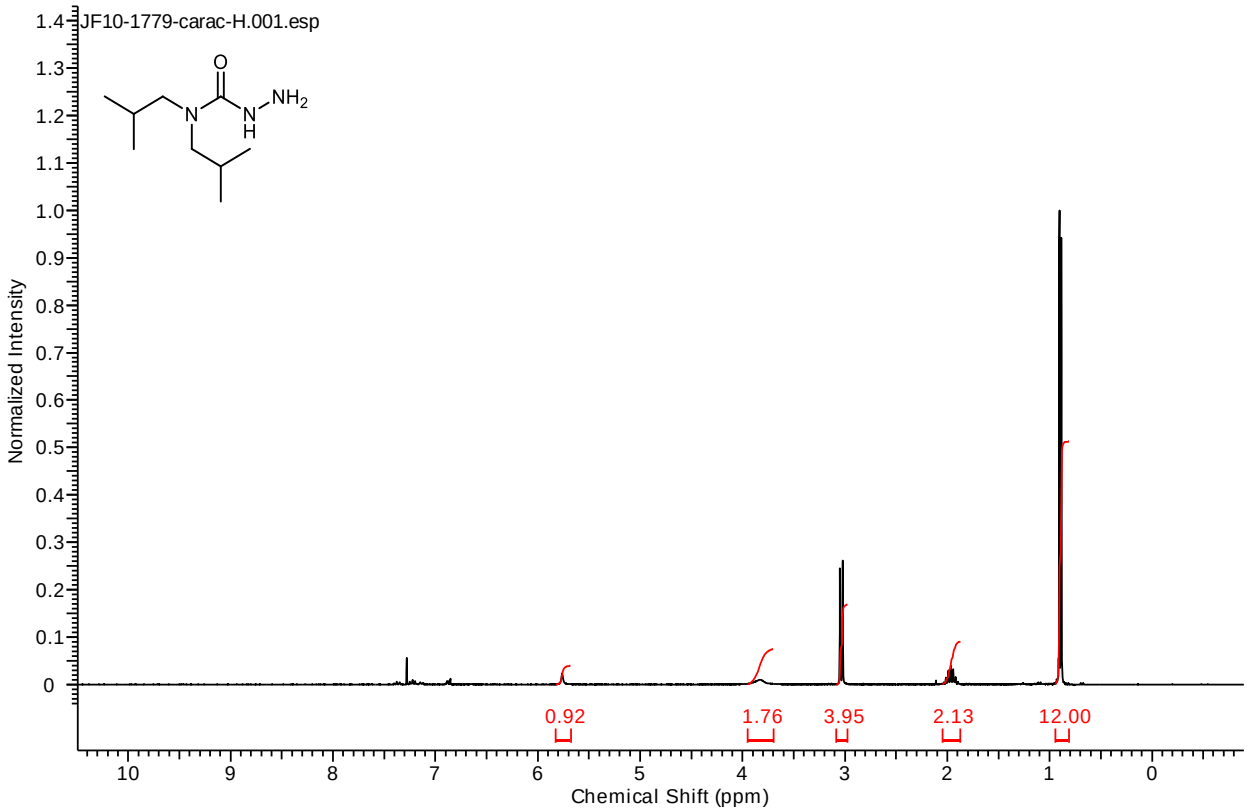

KL_exp90f-C-400.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
160.87
39.51
31.43
30.14
26.46
22.45
13.88

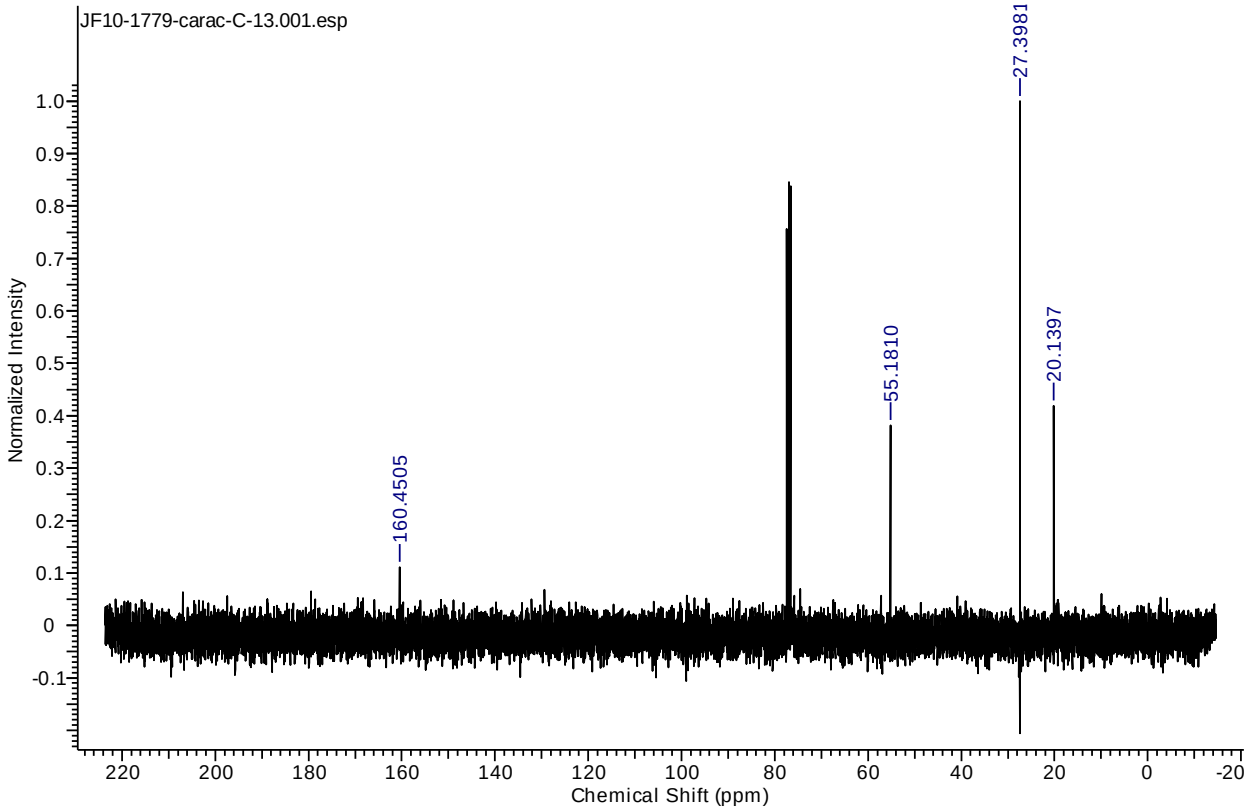

KL_exp98b-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
5.01
0.95
0.95
2.00
1.64

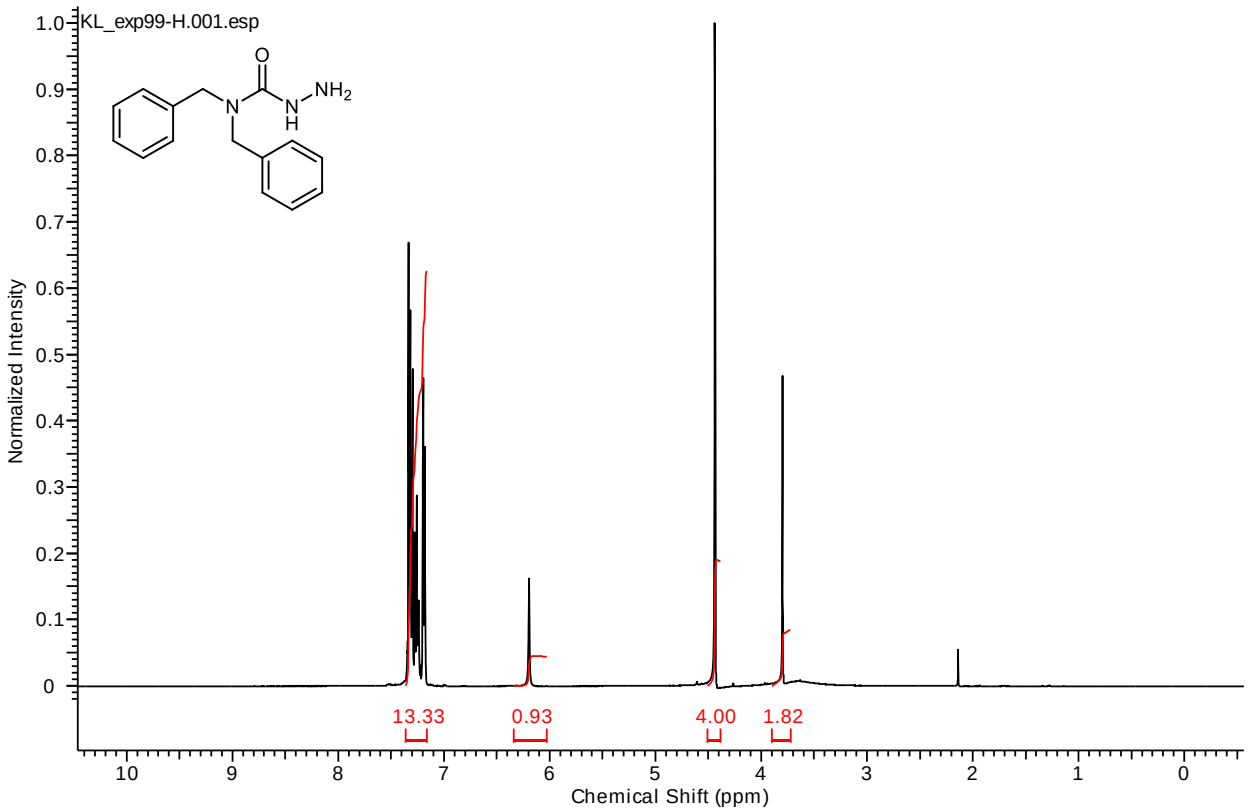

KL_exp98b-C.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
128.44
127.25
127.04
160.70
139.42
43.38

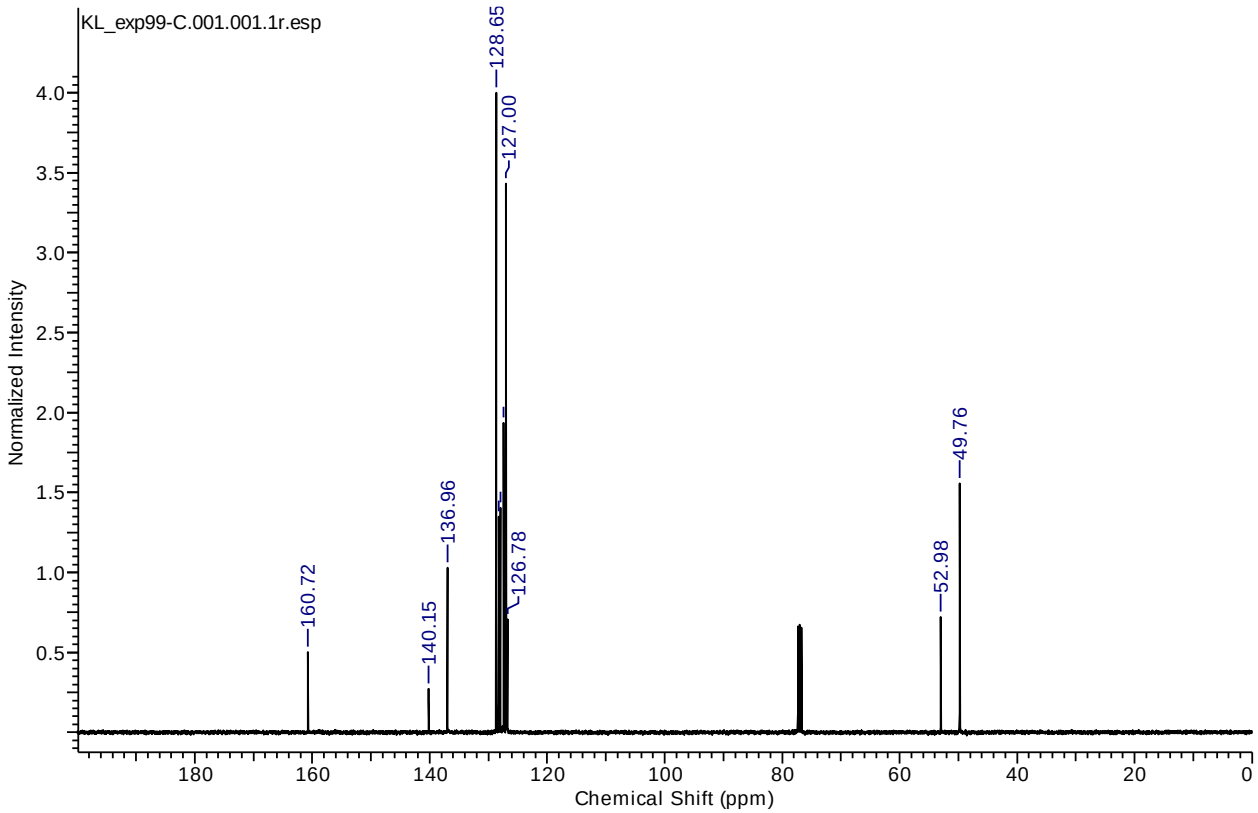

JF10-1784-pa1.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.12
1.08
2.17
2.29
1.00

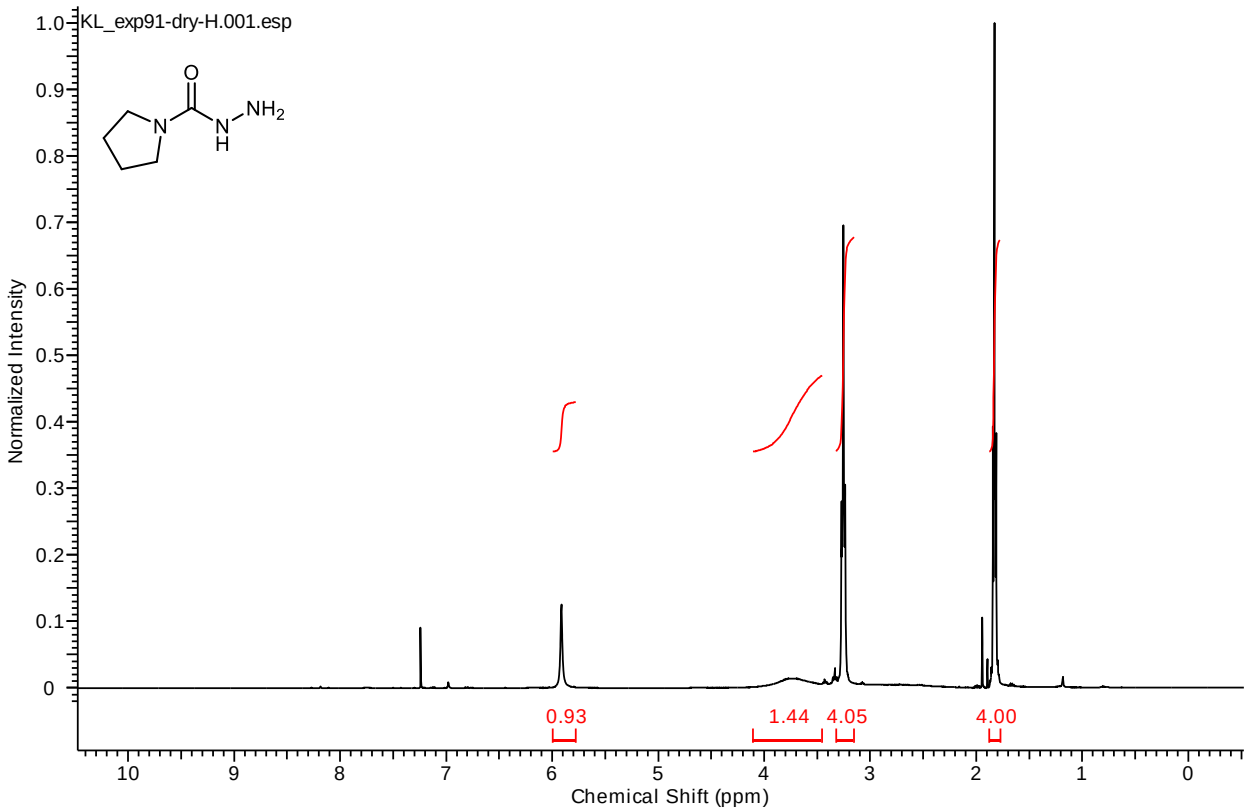

JF10-1784-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
159.7400
82.7371
72.2494
28.5459

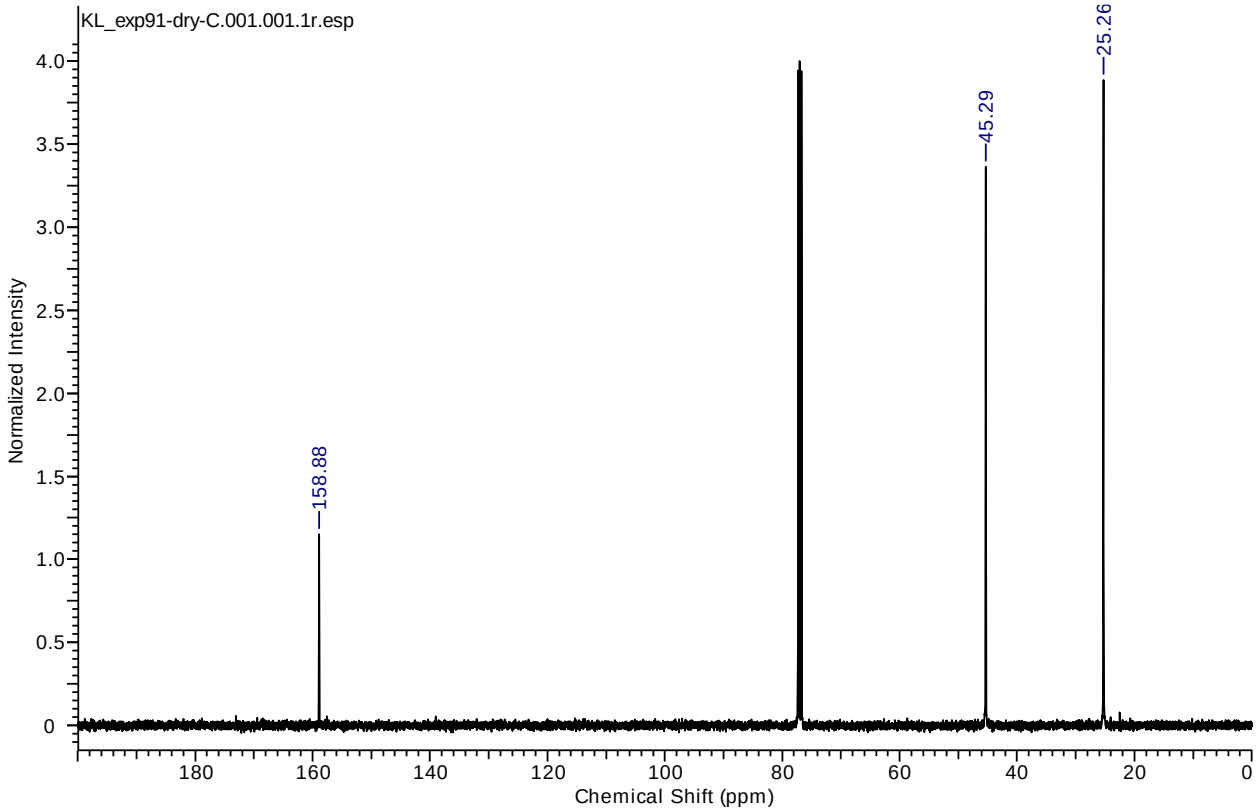

JF10-1779-carac-H.001.esp
O
N
N
H
NH2
Normalized Intensity
0.92
1.76
3.95
2.13
12.00
Chemical Shift (ppm)

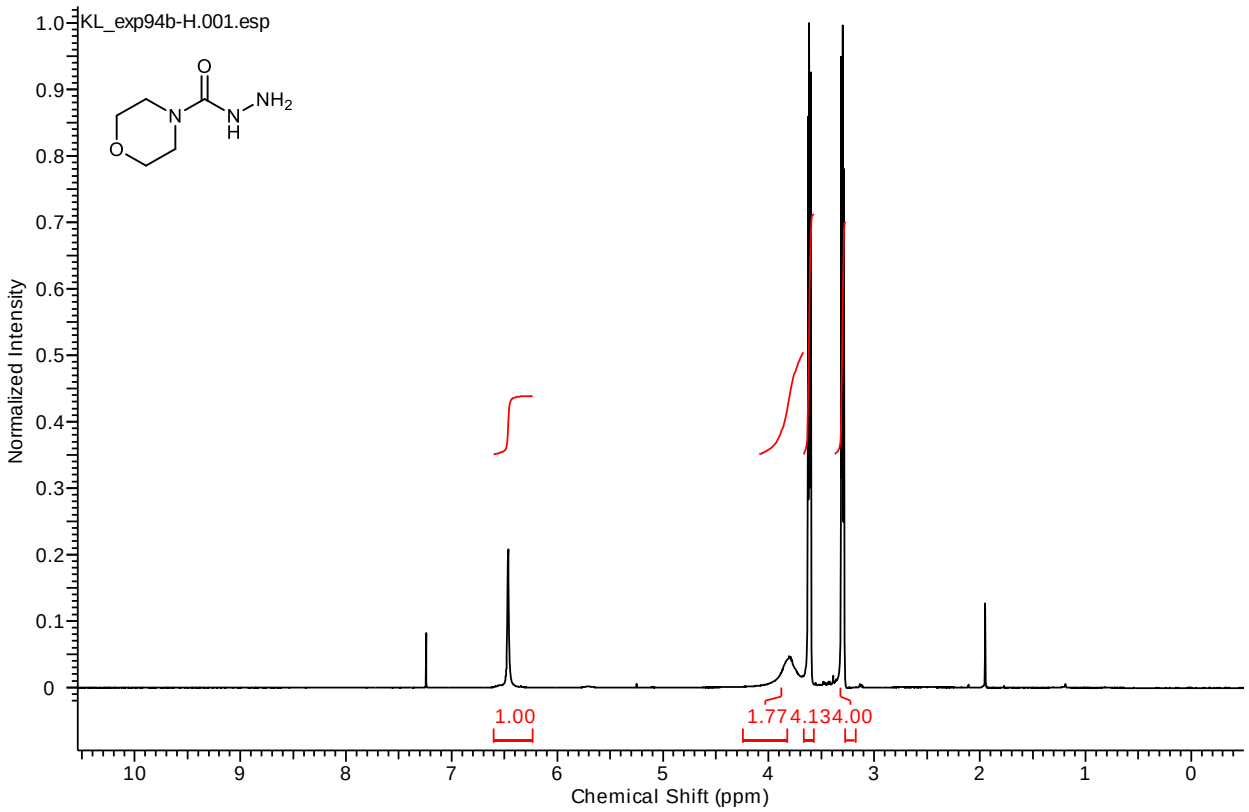

JF10-1779-carac-C-13.001.esp
160.4505
55.1810
27.3981
20.1397
Normalized Intensity
Chemical Shift (ppm)

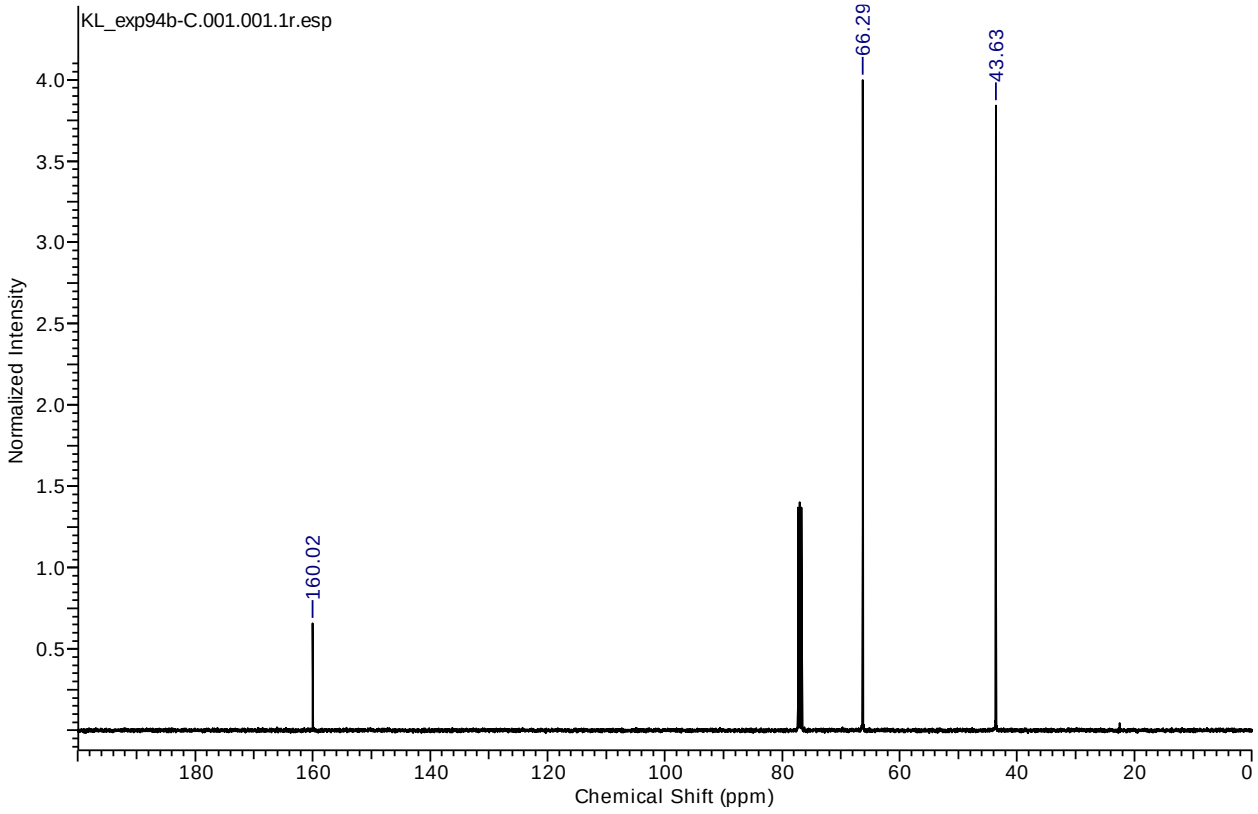

KL_exp99-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
13.33
0.93
4.00
1.82

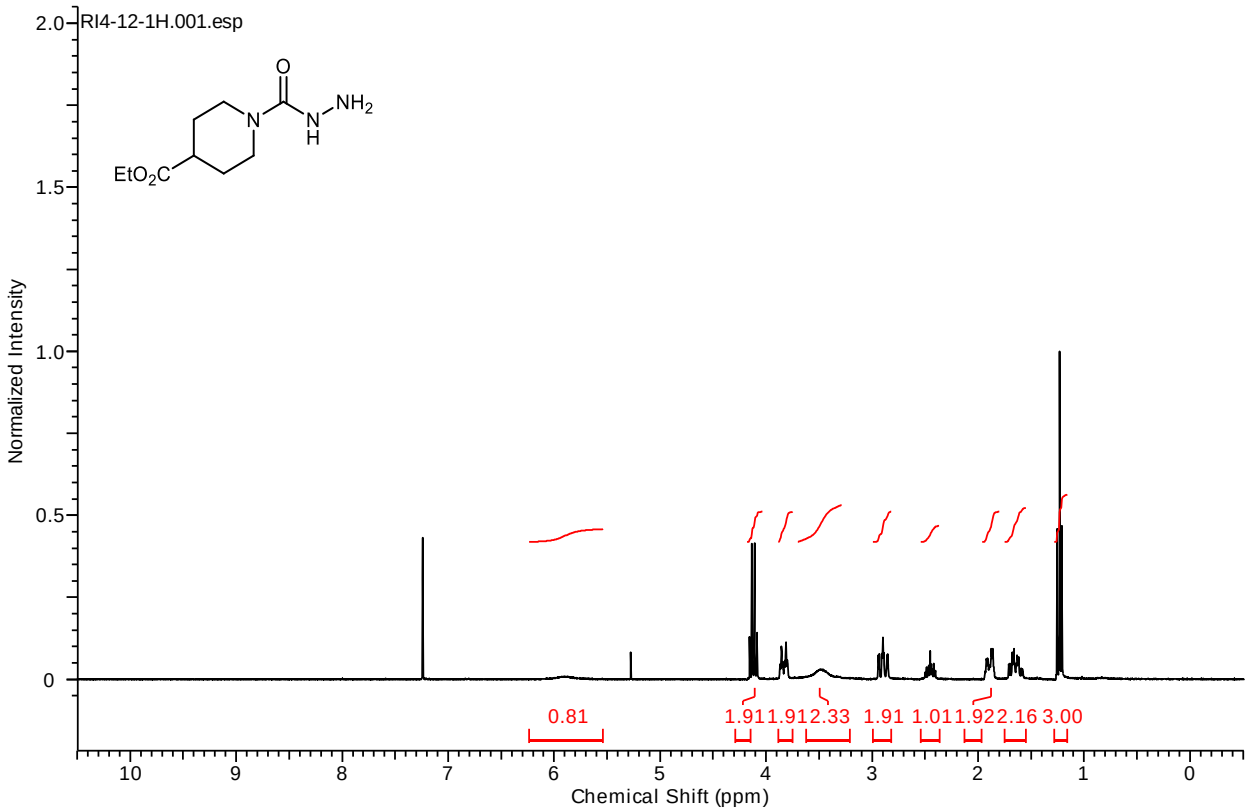

KL_exp99-C.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
160.72
140.15
136.96
128.65
127.00
126.78
52.98
49.76

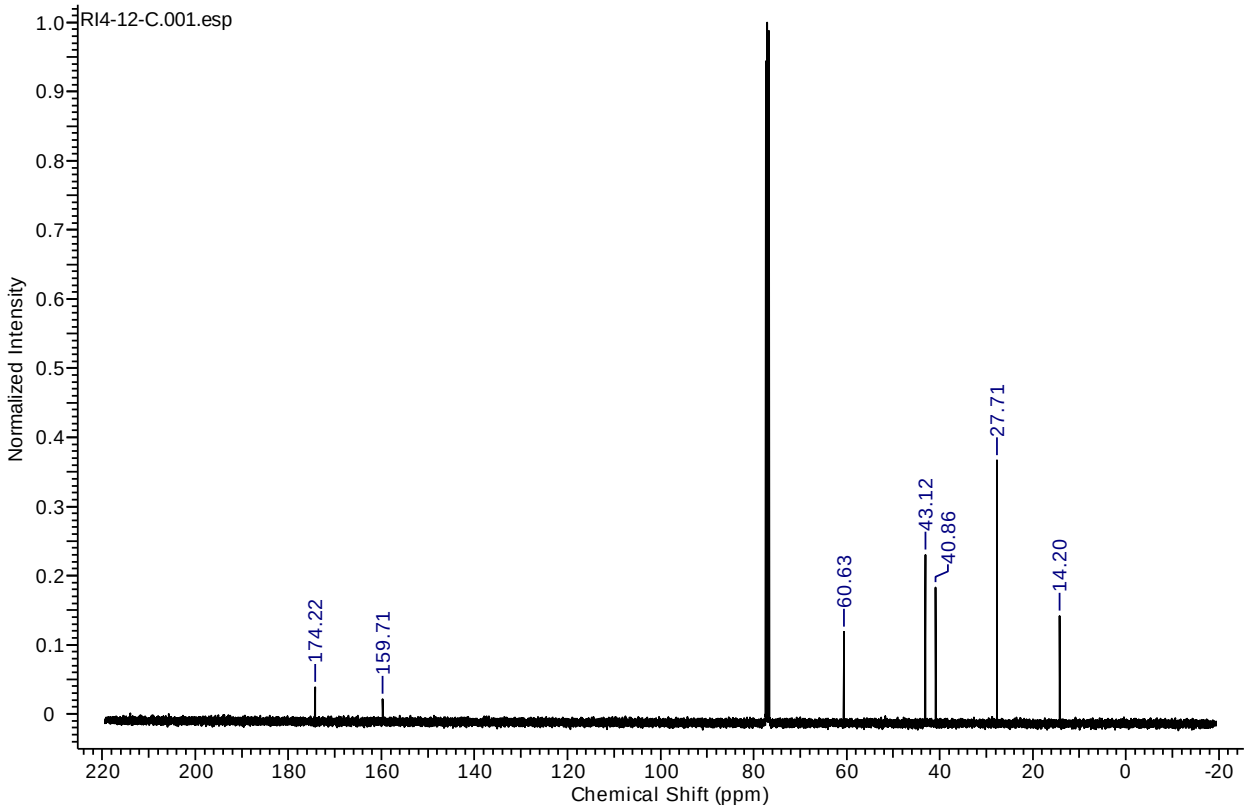

KL_exp91-dry-H.001.esp
O
N
N
H
NH2
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.93
1.44
4.05
4.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

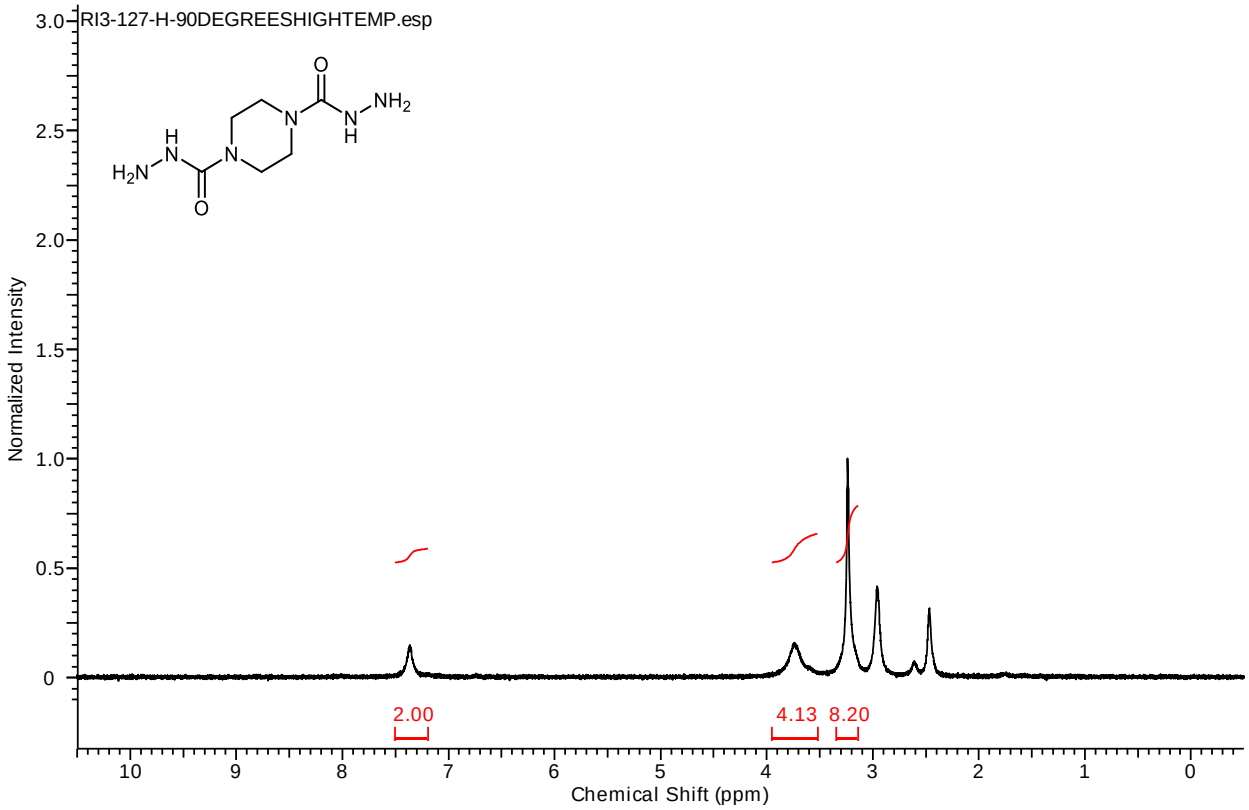

KL_exp91-dry-C.001.001.1r.esp
158.88
45.29
25.26
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

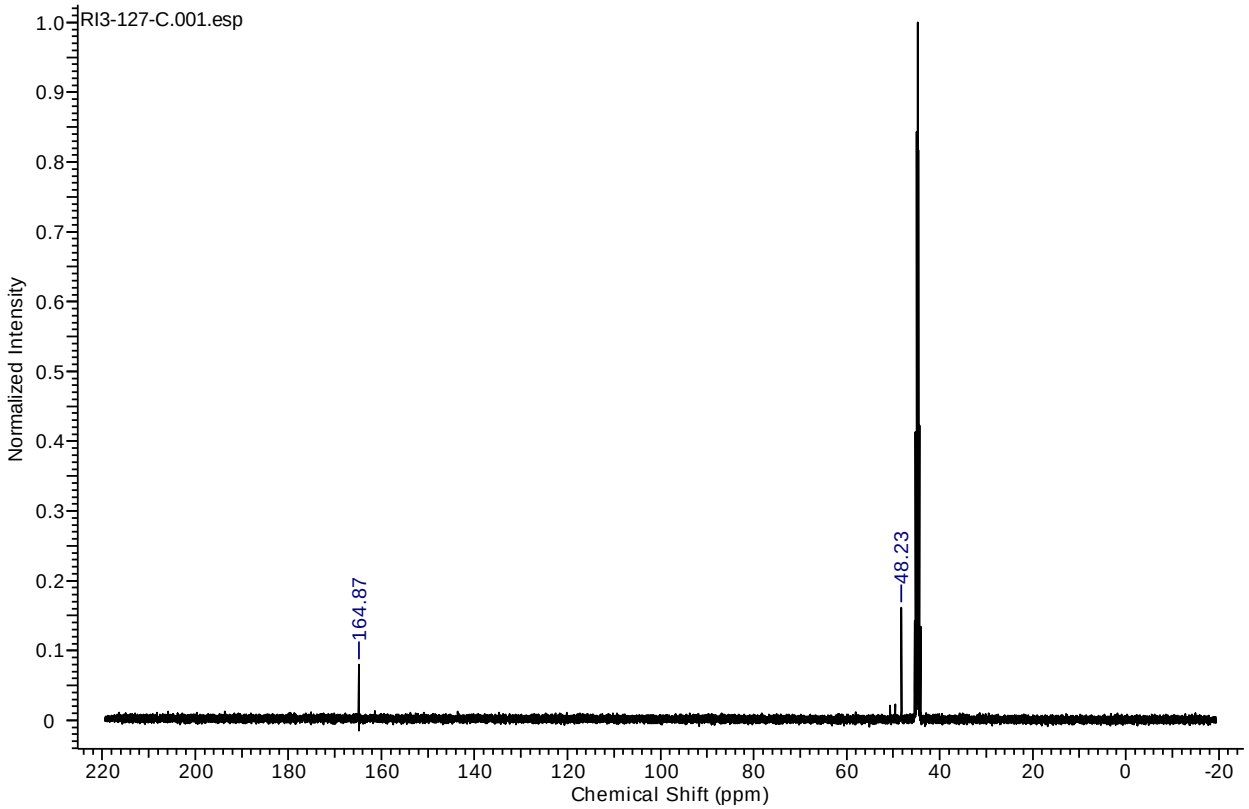

KL_exp94b-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
1.77
4.13
4.00

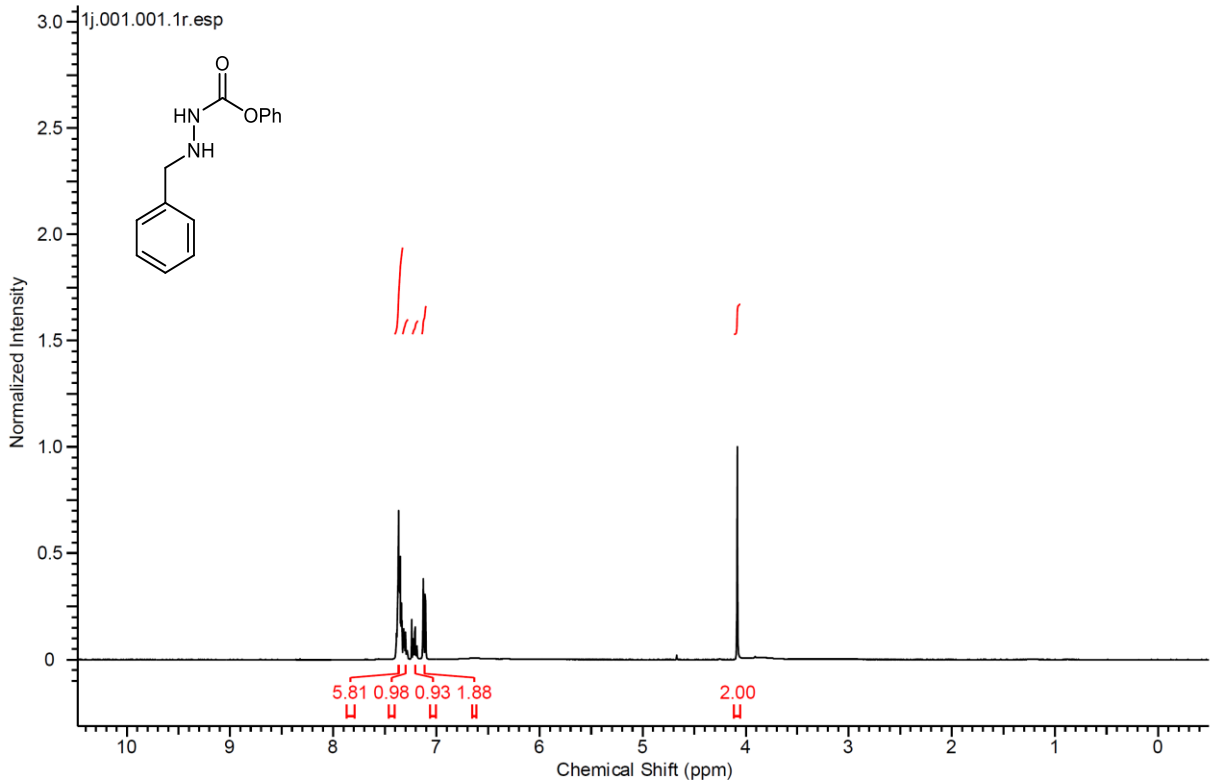

KL_exp94b-C.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
160.02
66.29
43.63

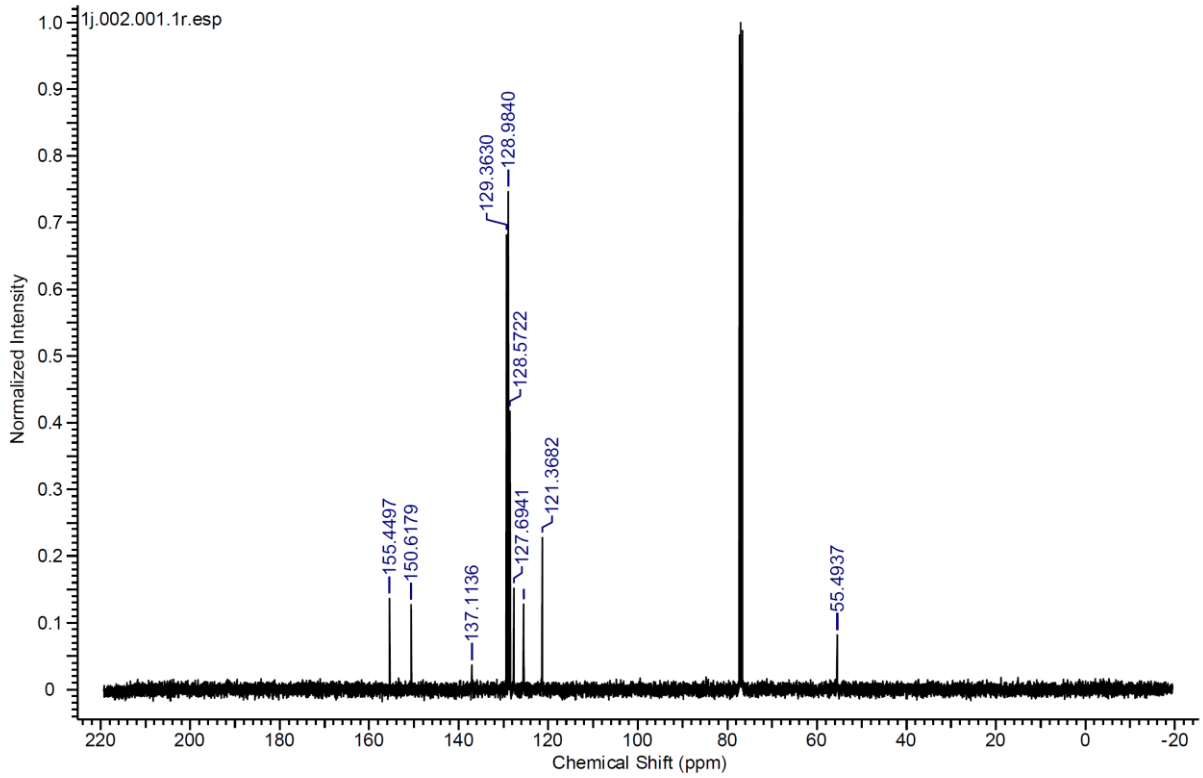

RI4-12-1H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.81
1.91
1.91
2.33
1.91
1.01
1.92
2.16
3.00

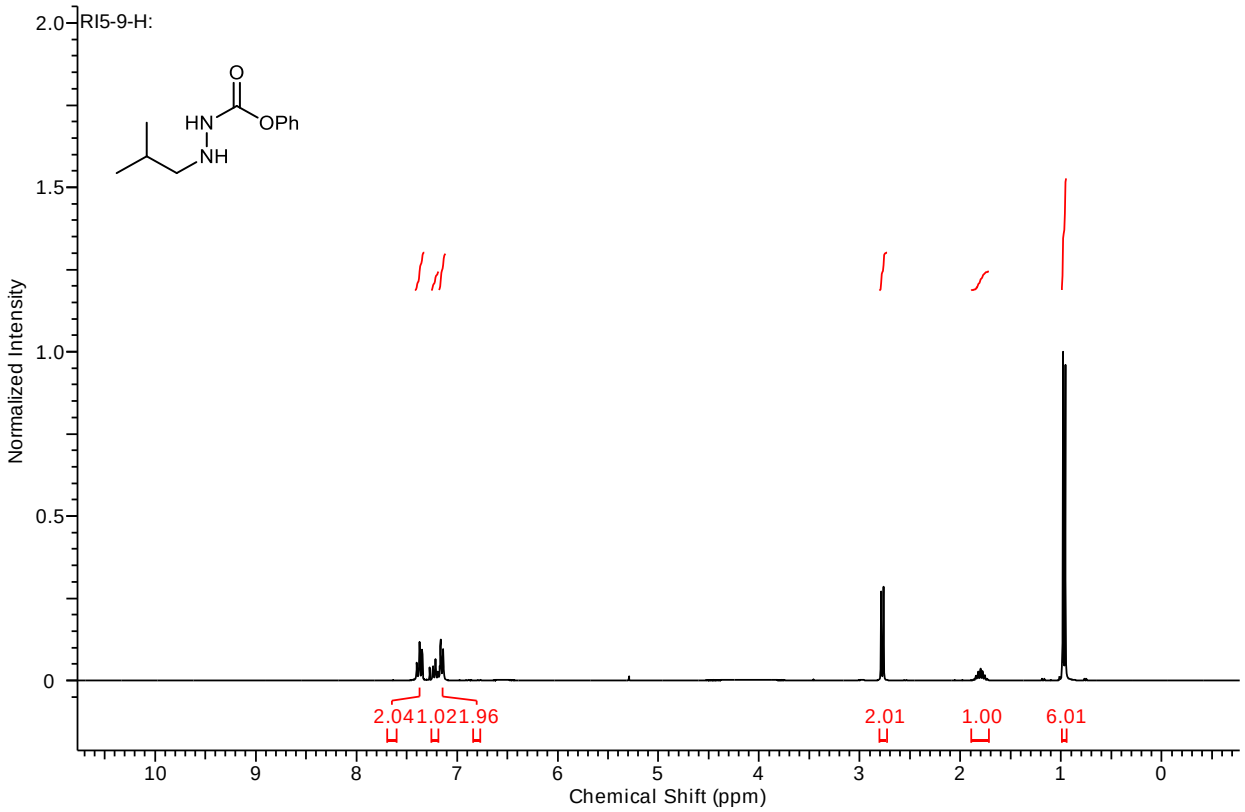

RI4-12-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
174.22
159.71
60.63
43.12
40.86
27.71
14.20

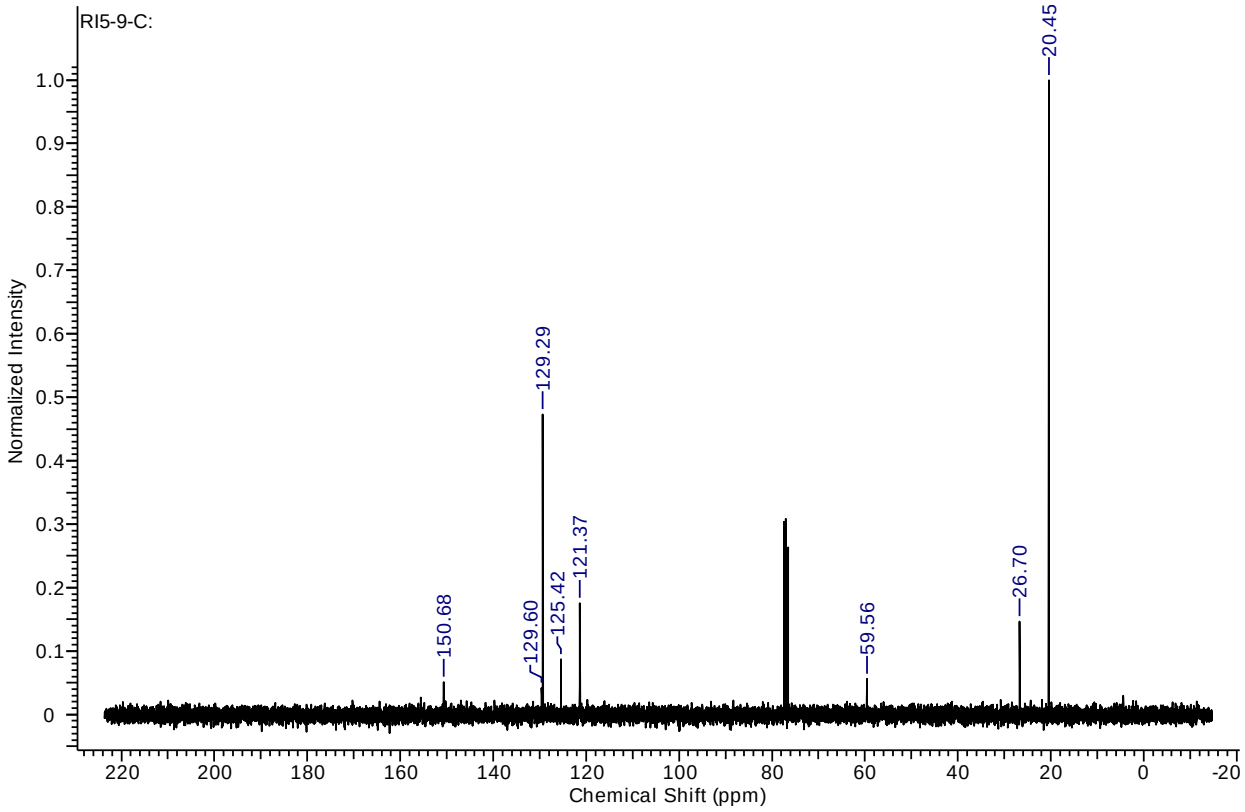

RI3-127-H-90DEGREESHIGHTEMP.esp
Normalized Intensity
Chemical Shift (ppm)
2.00
4.13
8.20

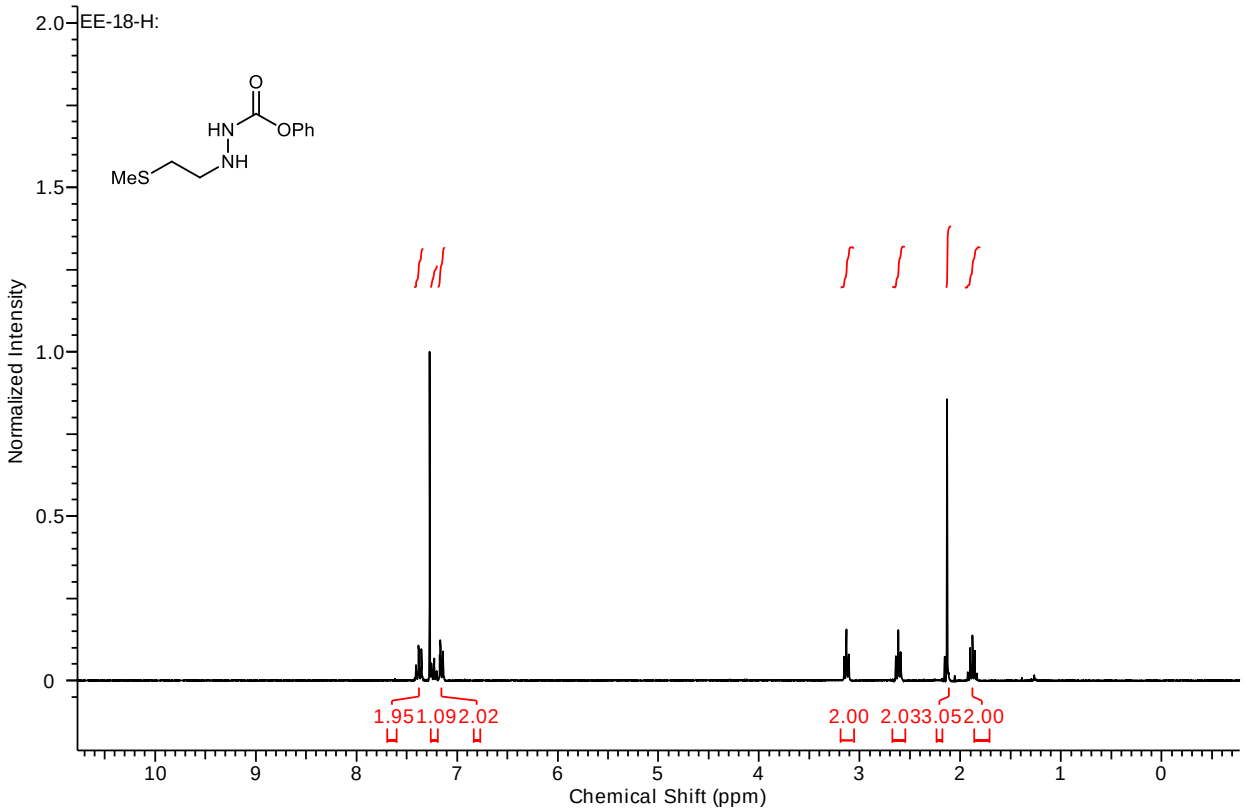

RI3-127-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
164.87
48.23

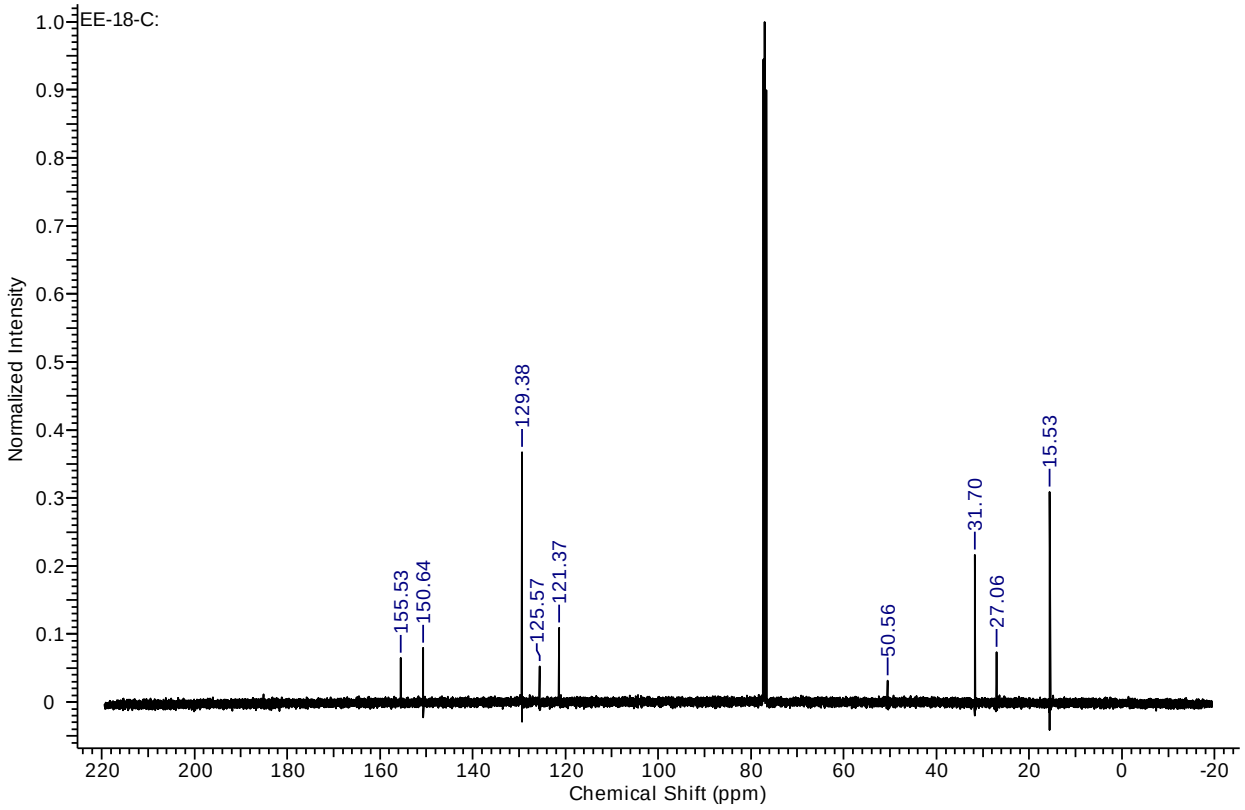

1j.001.001.1r.esp
O
HN
OPh
NH
Normalized Intensity
5.81 0.98 0.93 1.88
2.00
Chemical Shift (ppm)

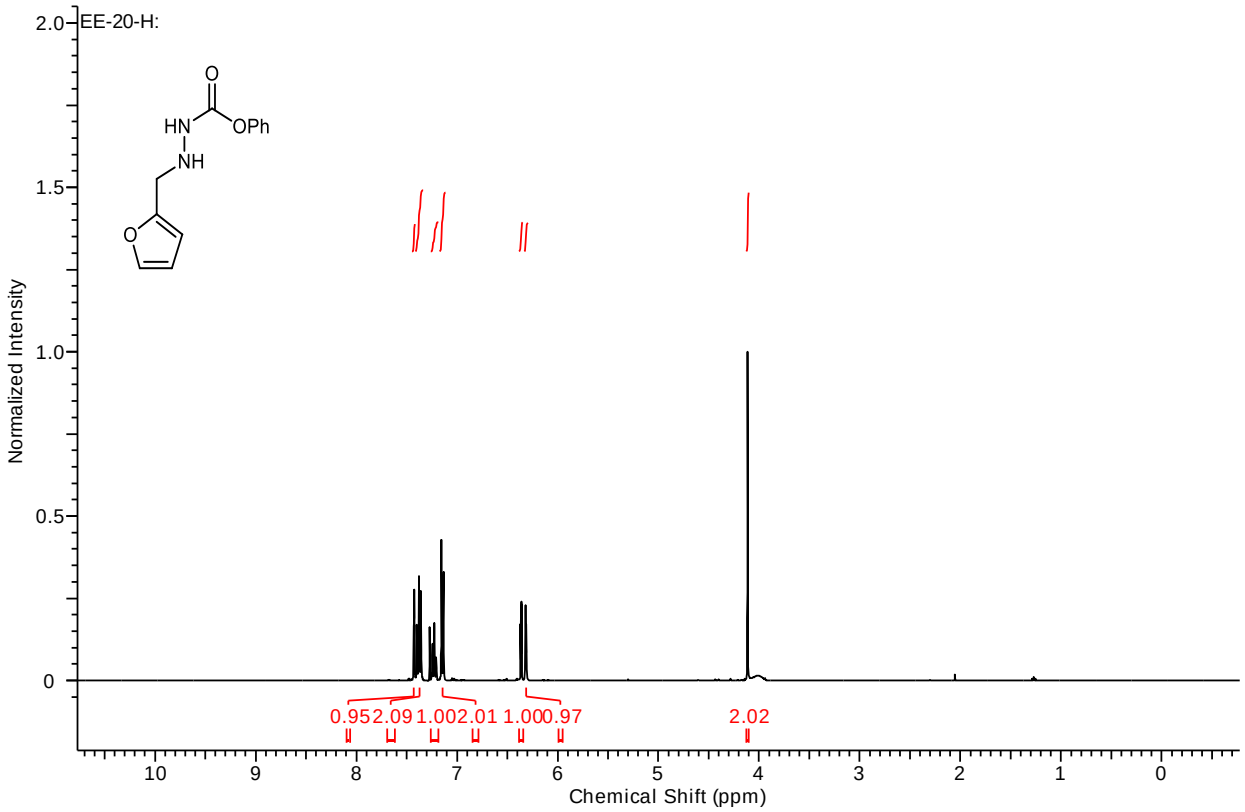

1j.002.001.1r.esp
Normalized Intensity
129.3630
128.9840
128.5722
121.3682
127.6941
155.4497
150.6179
137.1136
55.4937
Chemical Shift (ppm)

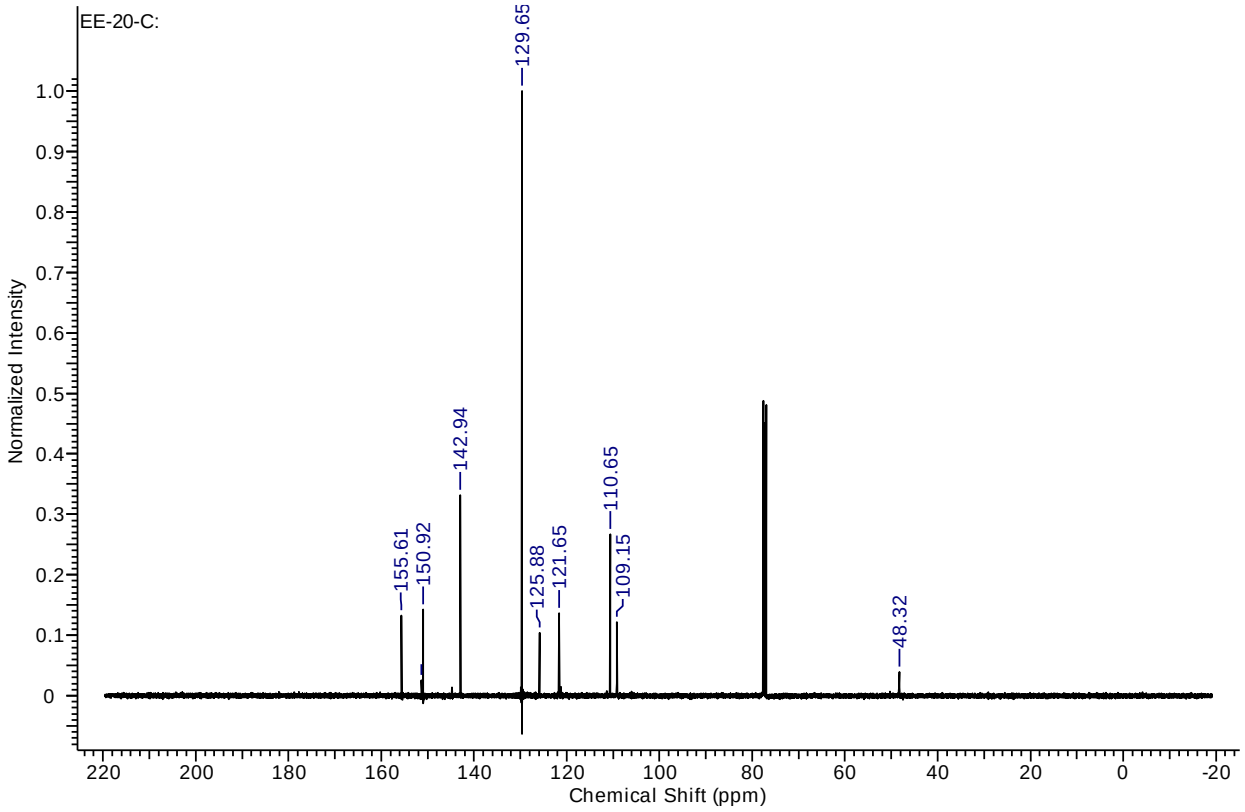

RI5-9-H:
O
HN
OPh
NH
Normalized Intensity
2.0
1.5
1.0
0.5
0
2.04
1.02
1.96
2.01
1.00
6.01
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

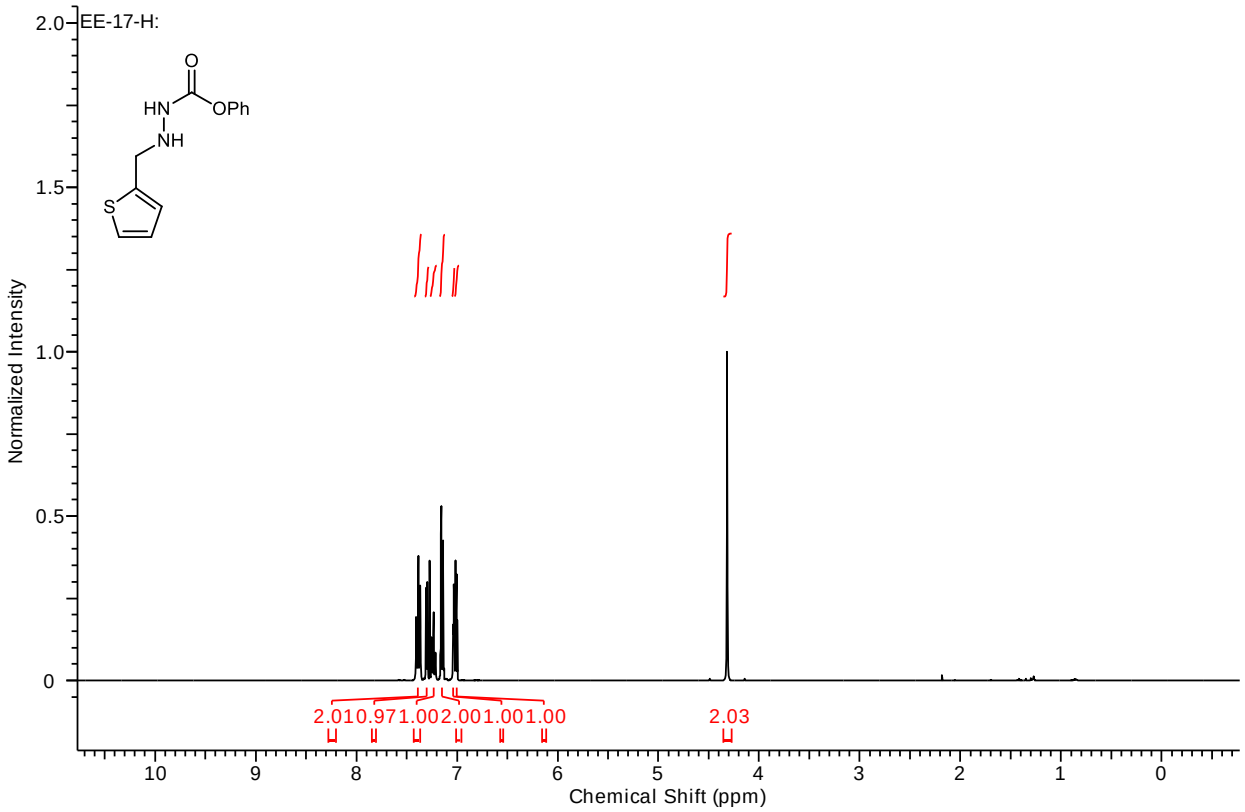

RI5-9-C:
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
150.68
129.60
129.29
125.42
121.37
59.56
26.70
20.45
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

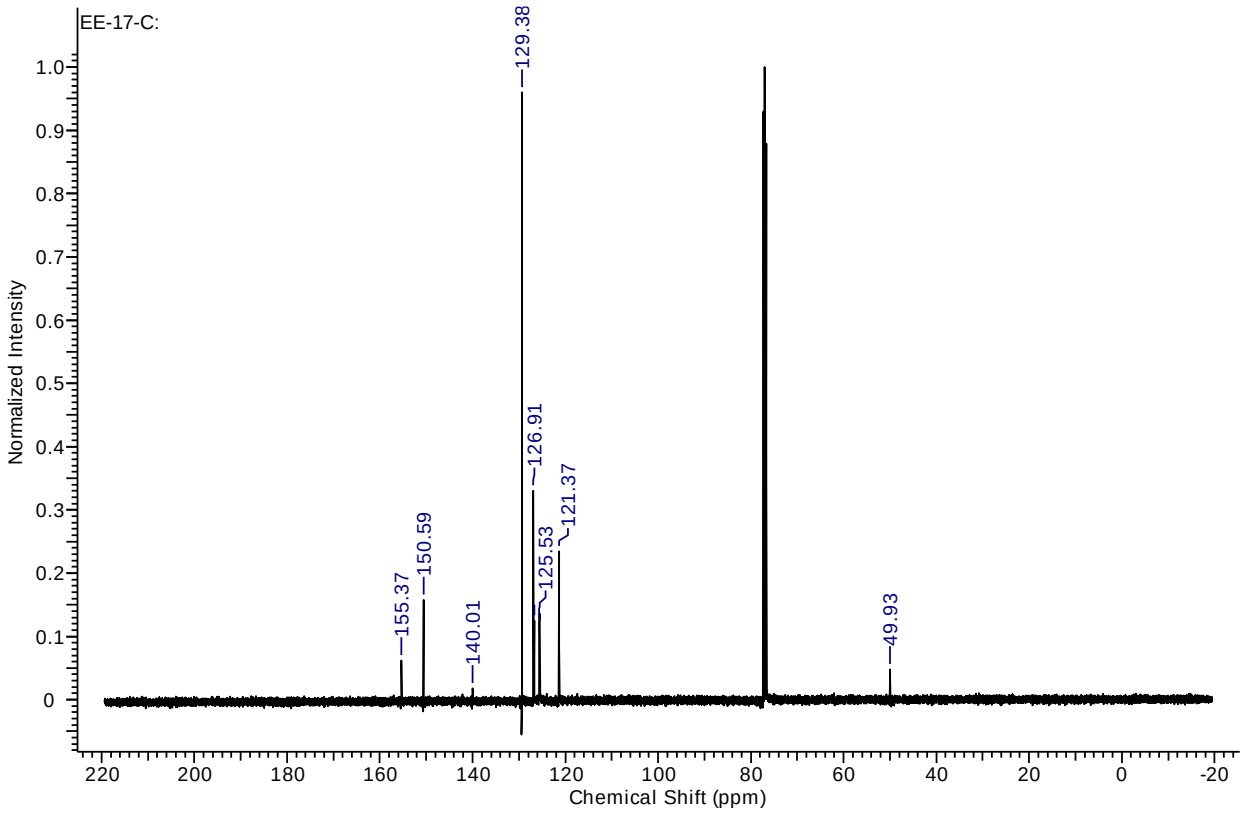

EE-18-H:
O
HN
OPh
NH
MeS
Normalized Intensity
1.95
1.09
2.02
2.00
2.03
3.05
2.00
Chemical Shift (ppm)

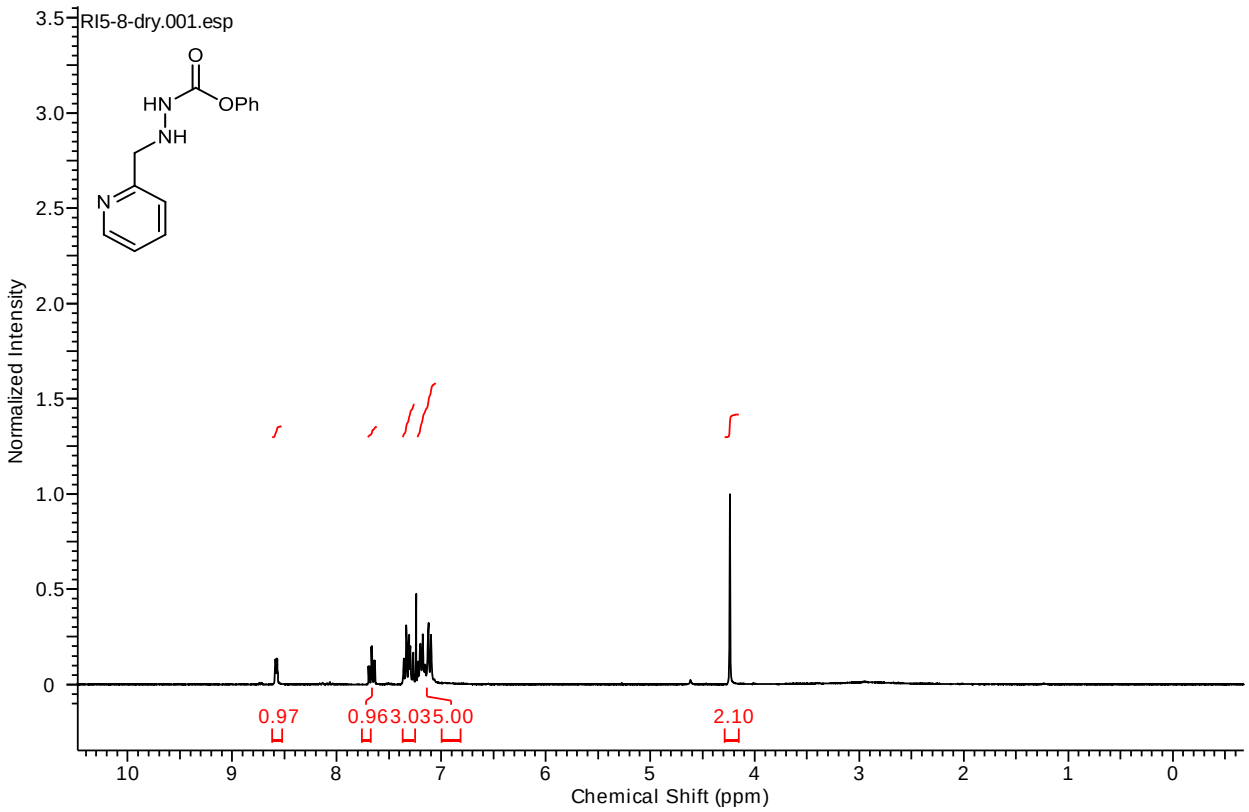

EE-18-C:
Normalized Intensity
155.53
150.64
129.38
125.57
121.37
50.56
31.70
27.06
15.53
Chemical Shift (ppm)

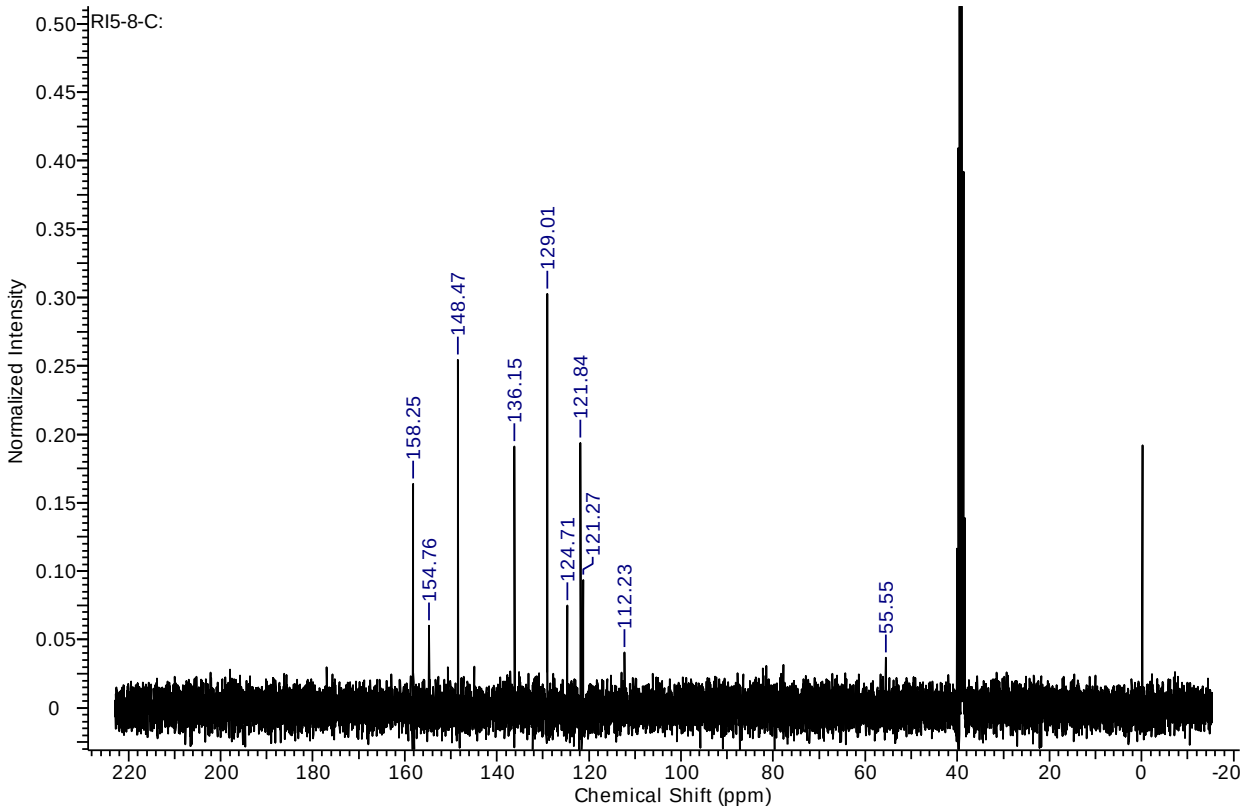

EE-20-H:
O
HN
OPh
NH
O
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.95
2.09
1.00
2.01
1.00
0.97
2.02
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

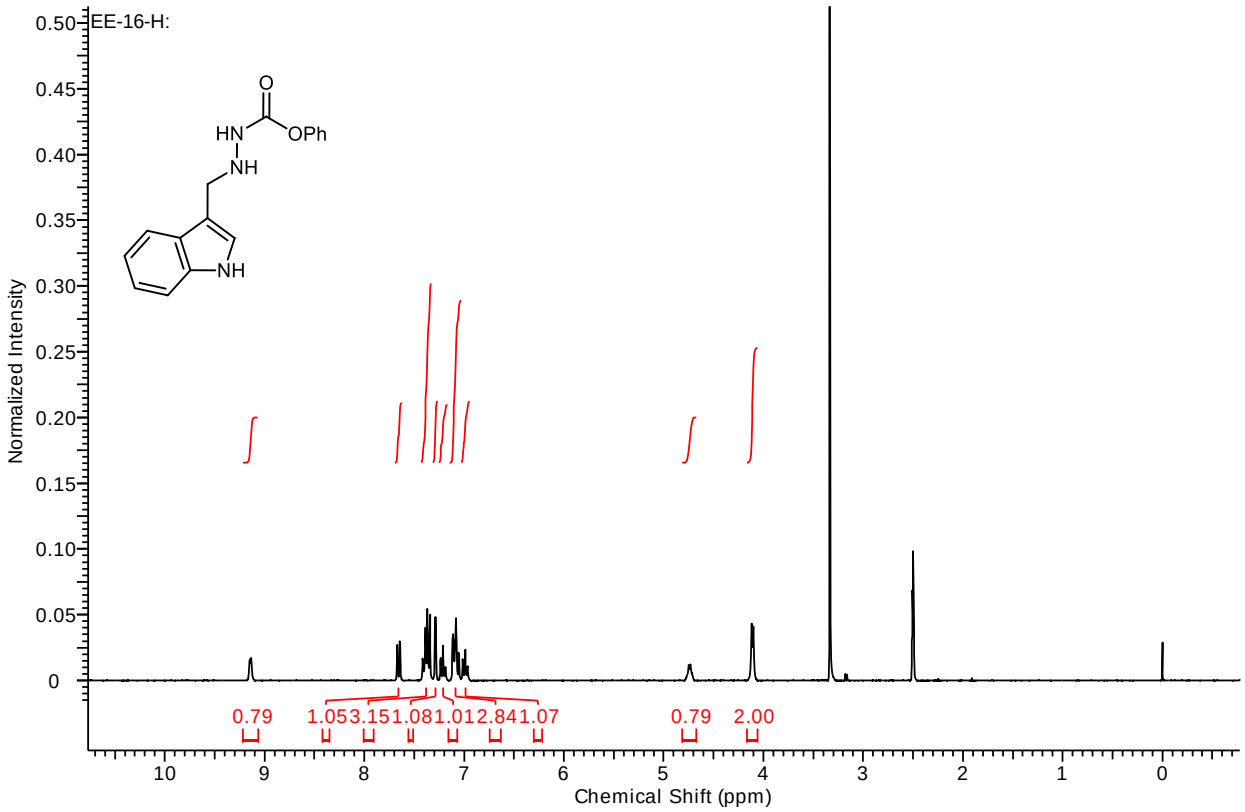

EE-20-C:
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
129.65
142.94
155.61
150.92
125.88
121.65
110.65
109.15
48.32
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

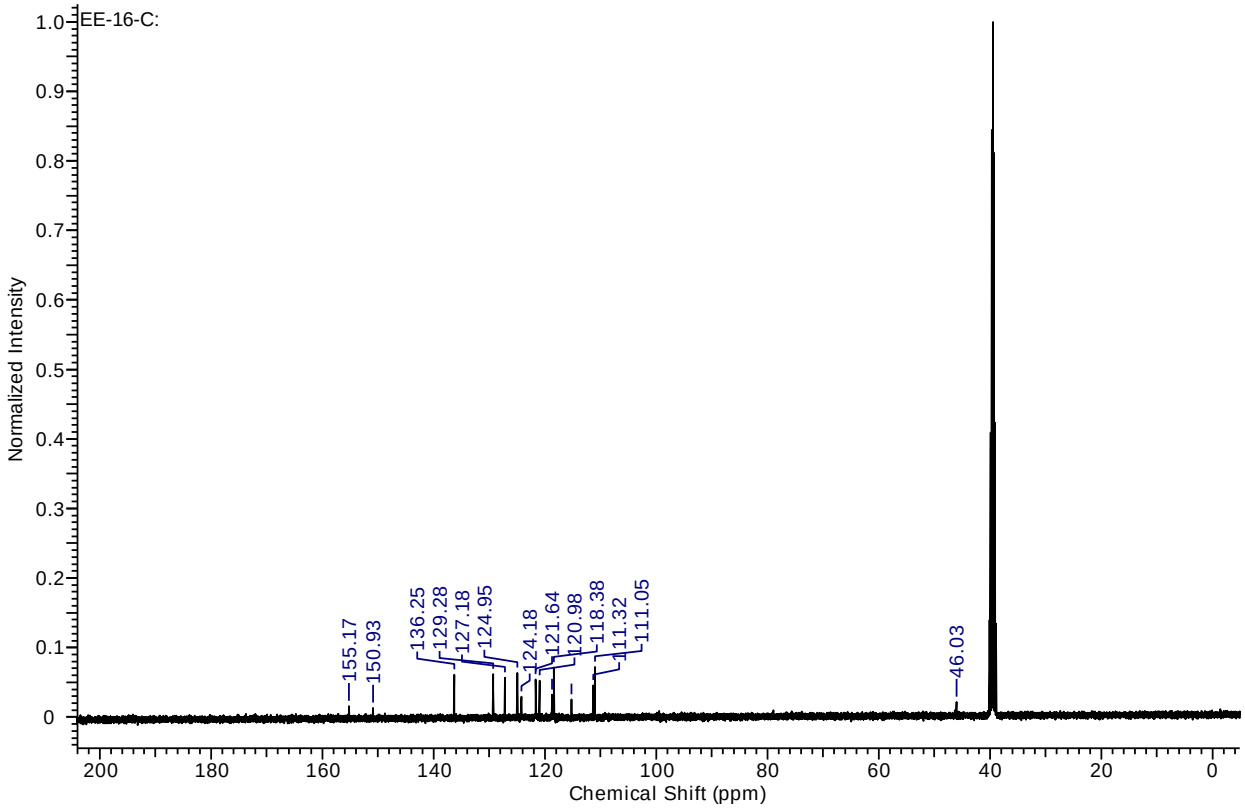

EE-17-H:
O
HN
OPh
NH
S
Normalized Intensity
2.0
1.5
1.0
0.5
0
2.01
0.97
1.00
2.00
1.00
1.00
2.03
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

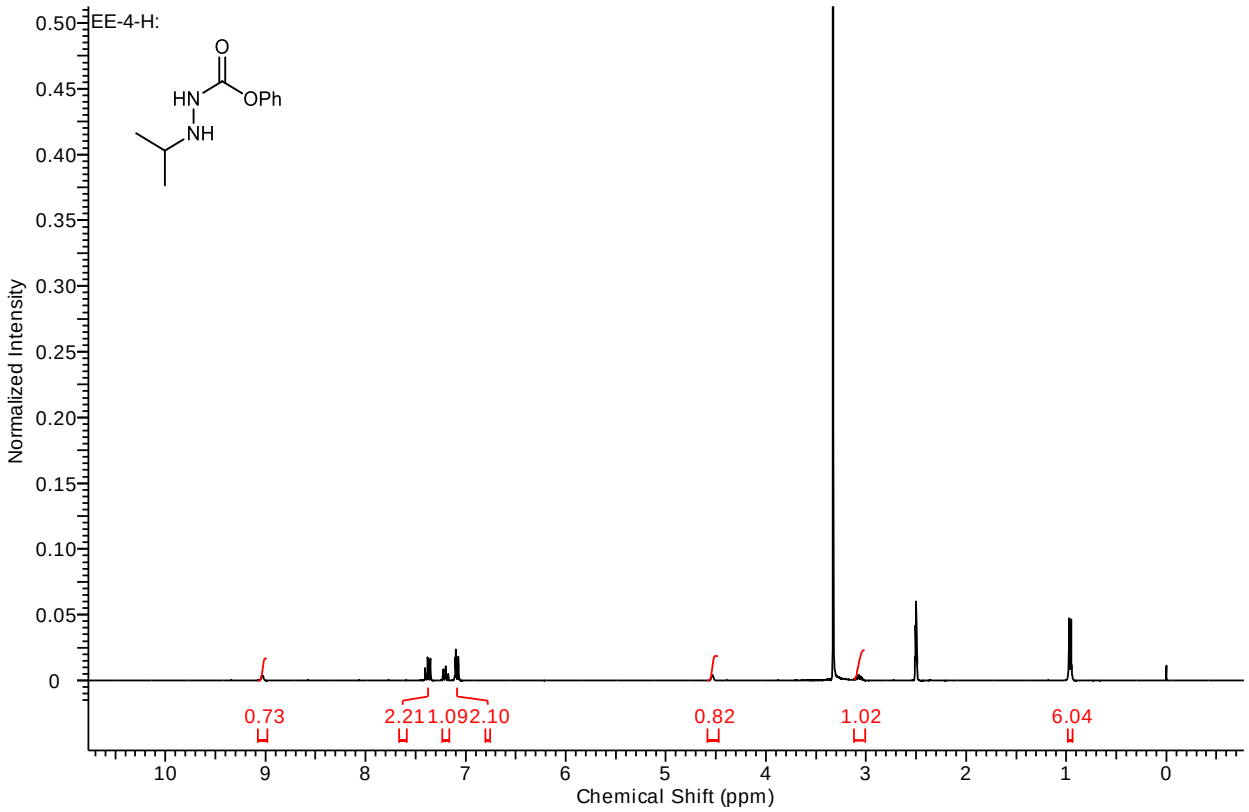

EE-17-C:
129.38
126.91
121.37
125.53
155.37
150.59
140.01
49.93
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

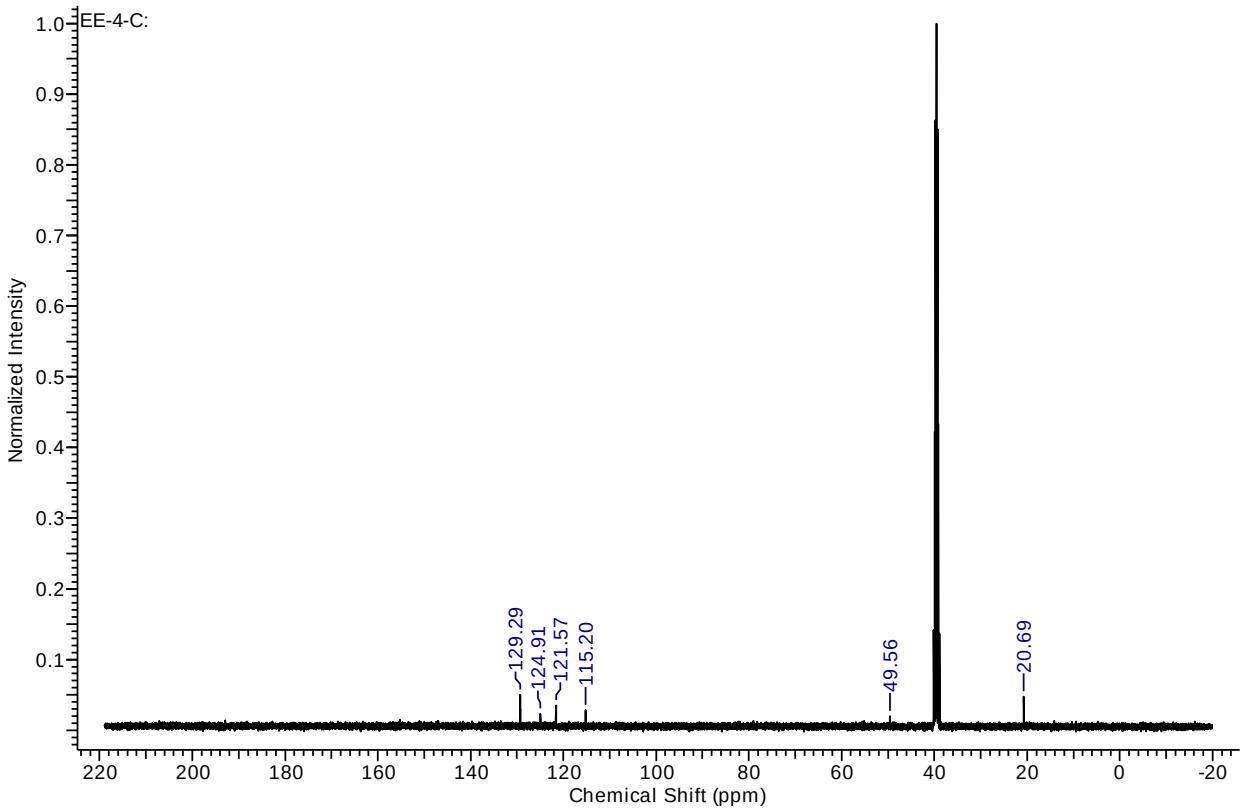

RI5-8-dry.001.esp
O
HN
OPh
NH
N
Normalized Intensity
0.97
0.96
3.03
5.00
2.10
Chemical Shift (ppm)

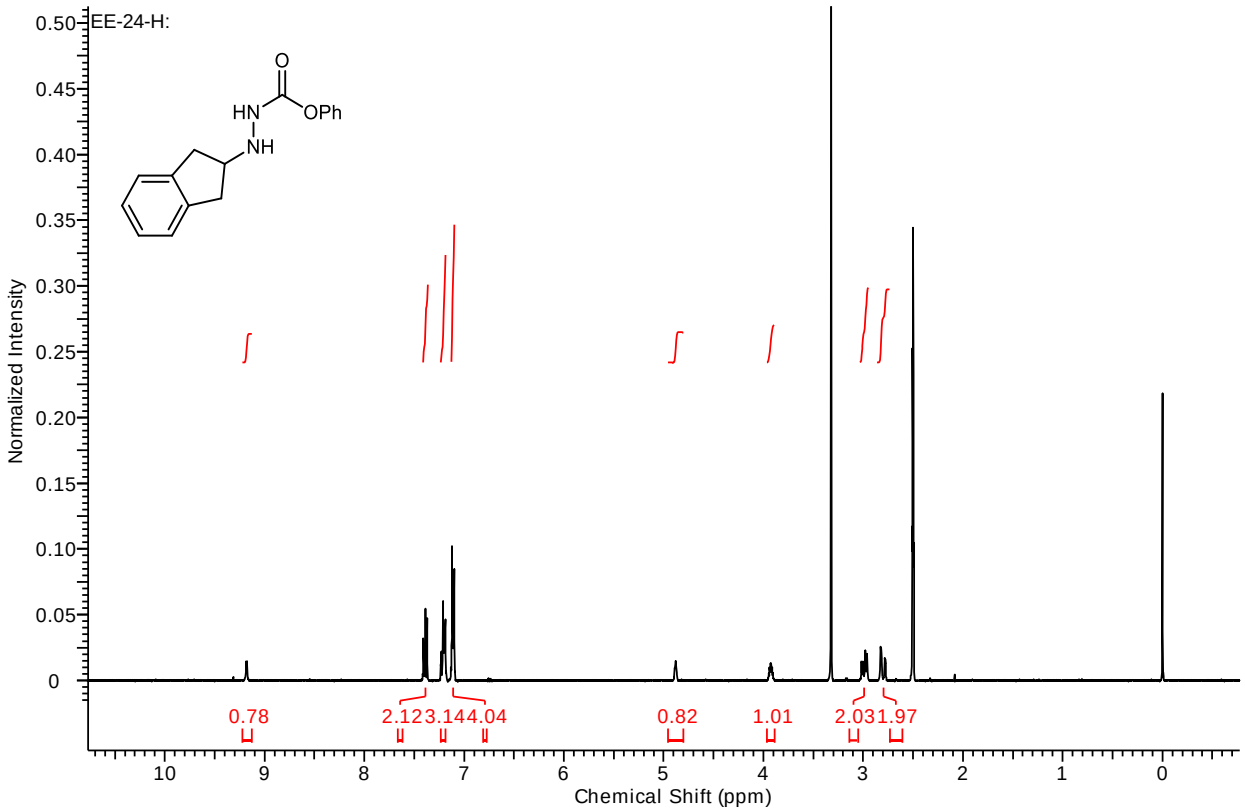

RI5-8-C:
Normalized Intensity
158.25
154.76
148.47
136.15
129.01
124.71
121.84
121.27
112.23
55.55
Chemical Shift (ppm)

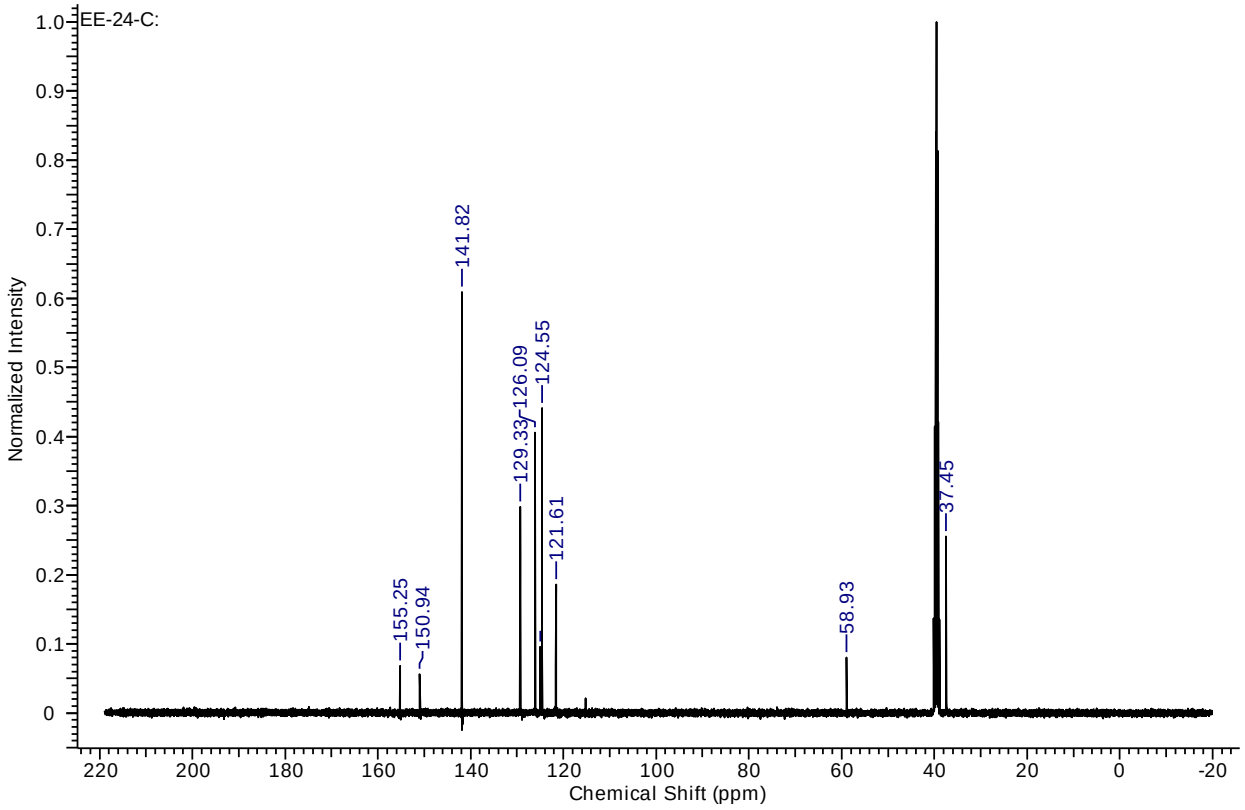

EE-16-H:
O
HN
OPh
NH
NH
Normalized Intensity
0.79
1.05
3.15
1.08
1.01
2.84
1.07
0.79
2.00
Chemical Shift (ppm)

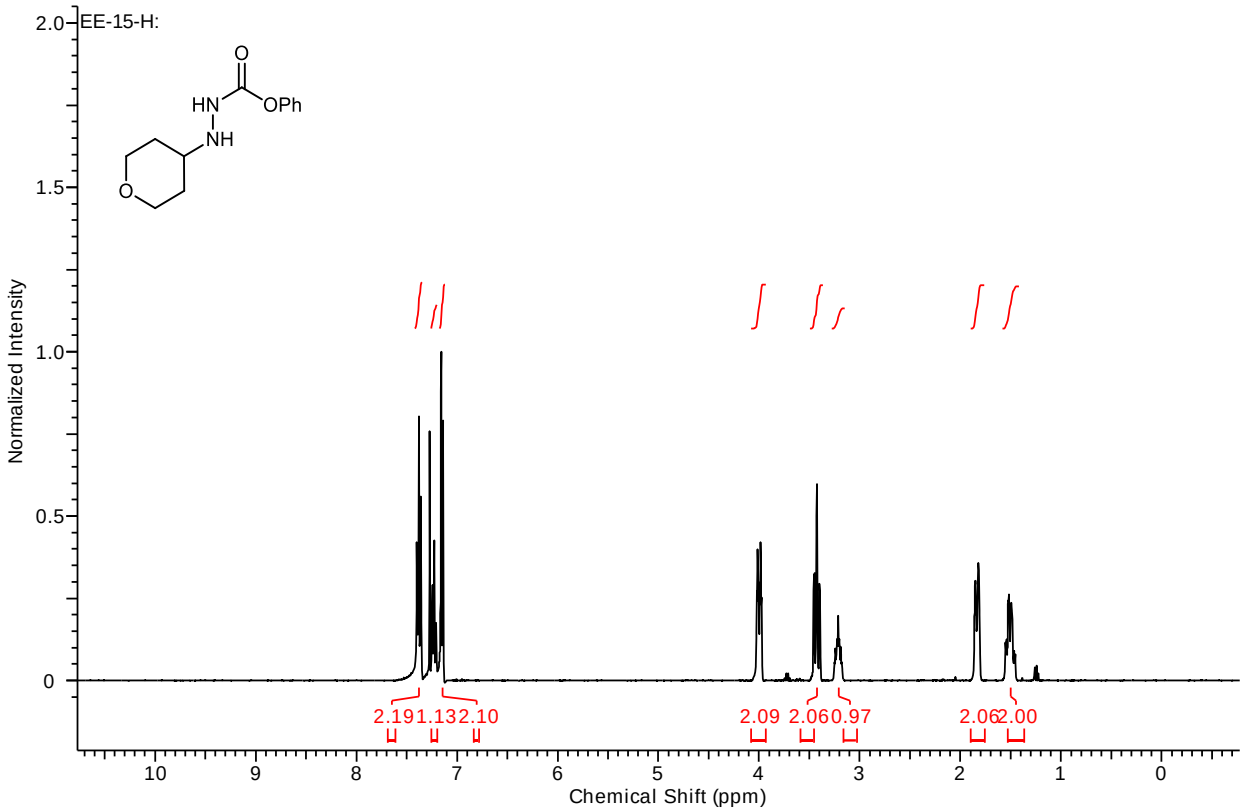

EE-16-C:
Normalized Intensity
155.17
150.93
136.25
129.28
127.18
124.95
124.18
121.64
120.98
118.38
111.32
111.05
46.03
Chemical Shift (ppm)

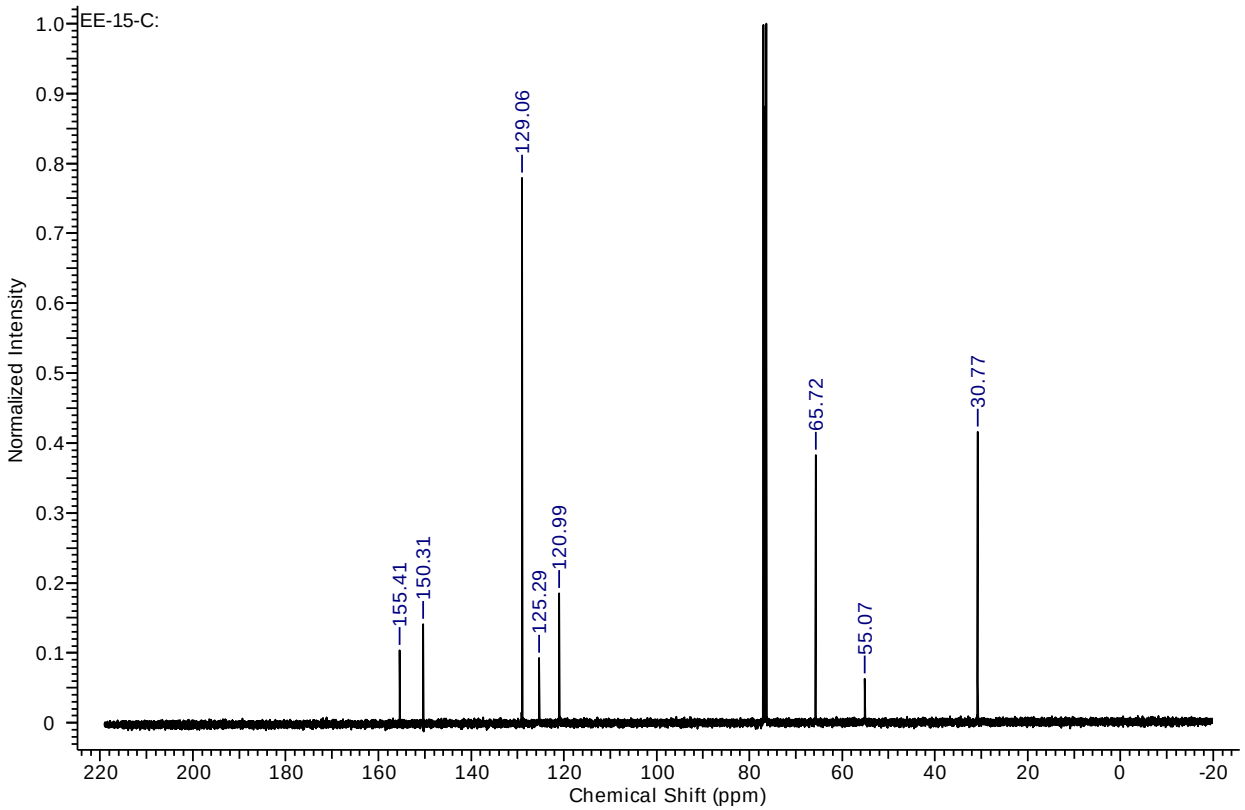

EE-4-H:
O
HN
OPh
NH
Normalized Intensity
0.73
2.21
1.09
2.10
0.82
1.02
6.04
Chemical Shift (ppm)

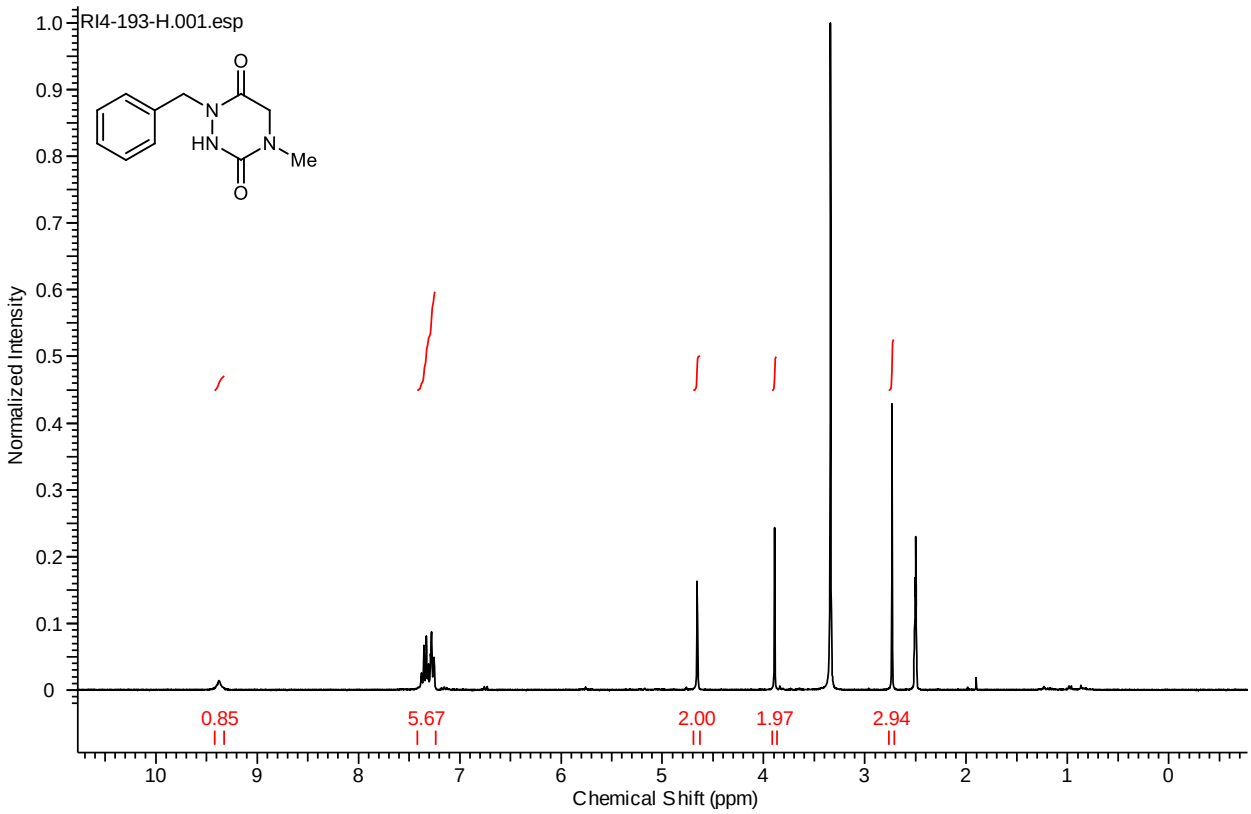

EE-4-C:
Normalized Intensity
129.29
124.91
121.57
115.20
49.56
20.69
Chemical Shift (ppm)

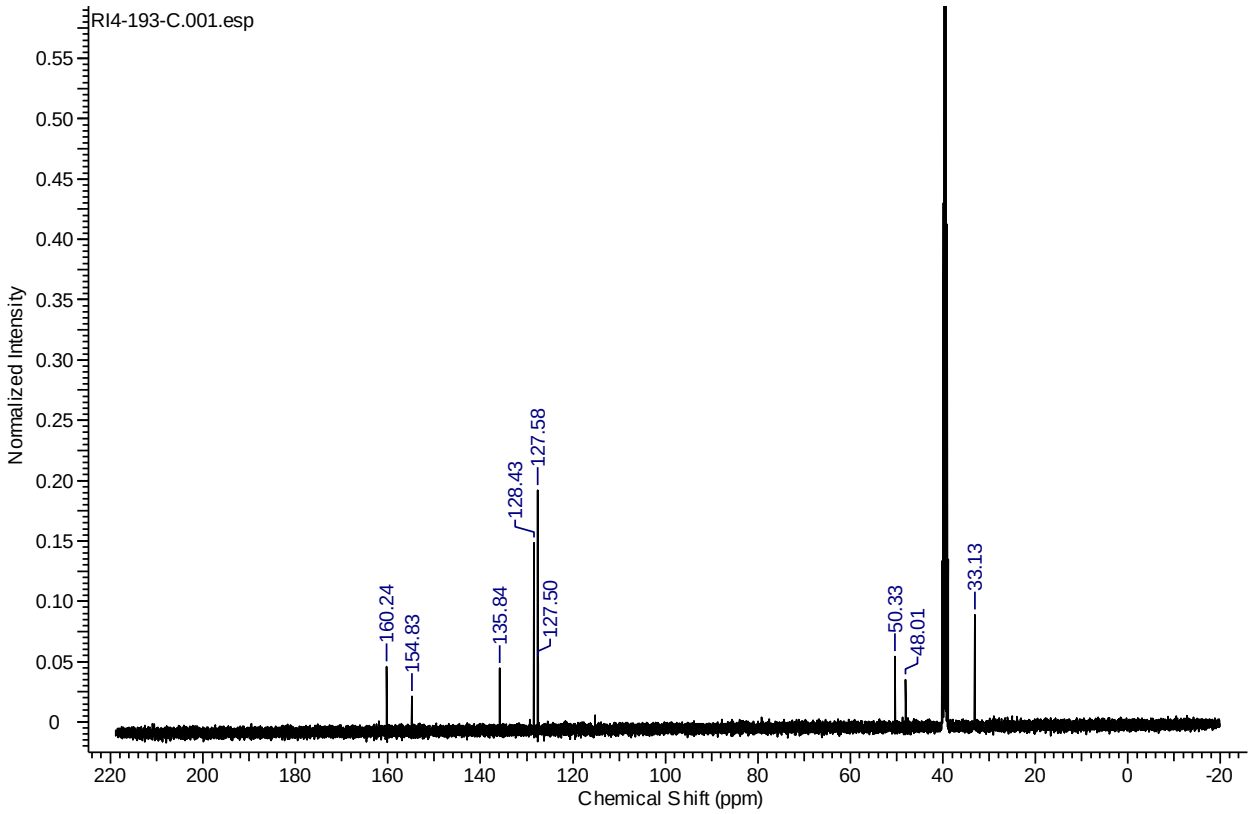

EE-24-H:
HN
NH
O
OPh
Normalized Intensity
0.78
2.12
3.14
4.04
0.82
1.01
2.03
1.97
Chemical Shift (ppm)

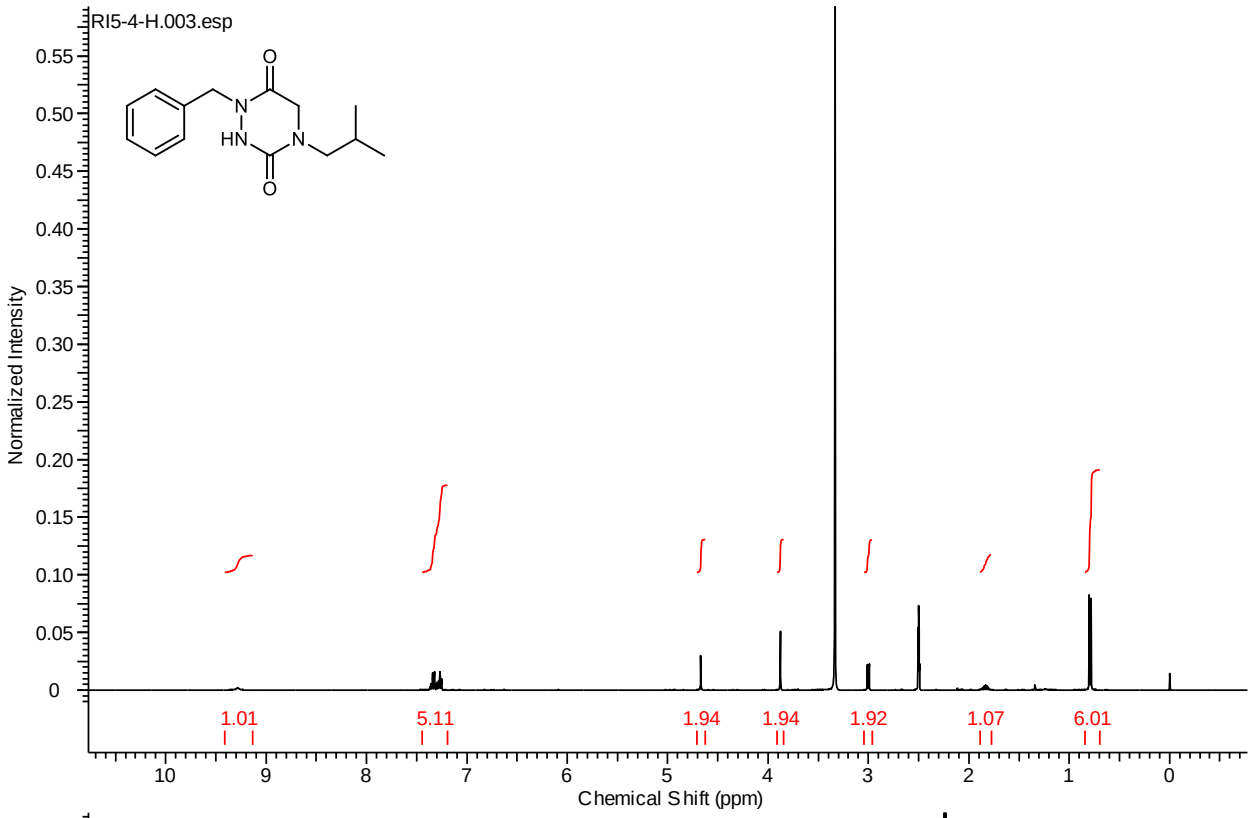

EE-24-C:
Normalized Intensity
155.25
150.94
141.82
129.33
126.09
124.55
121.61
58.93
37.45
Chemical Shift (ppm)

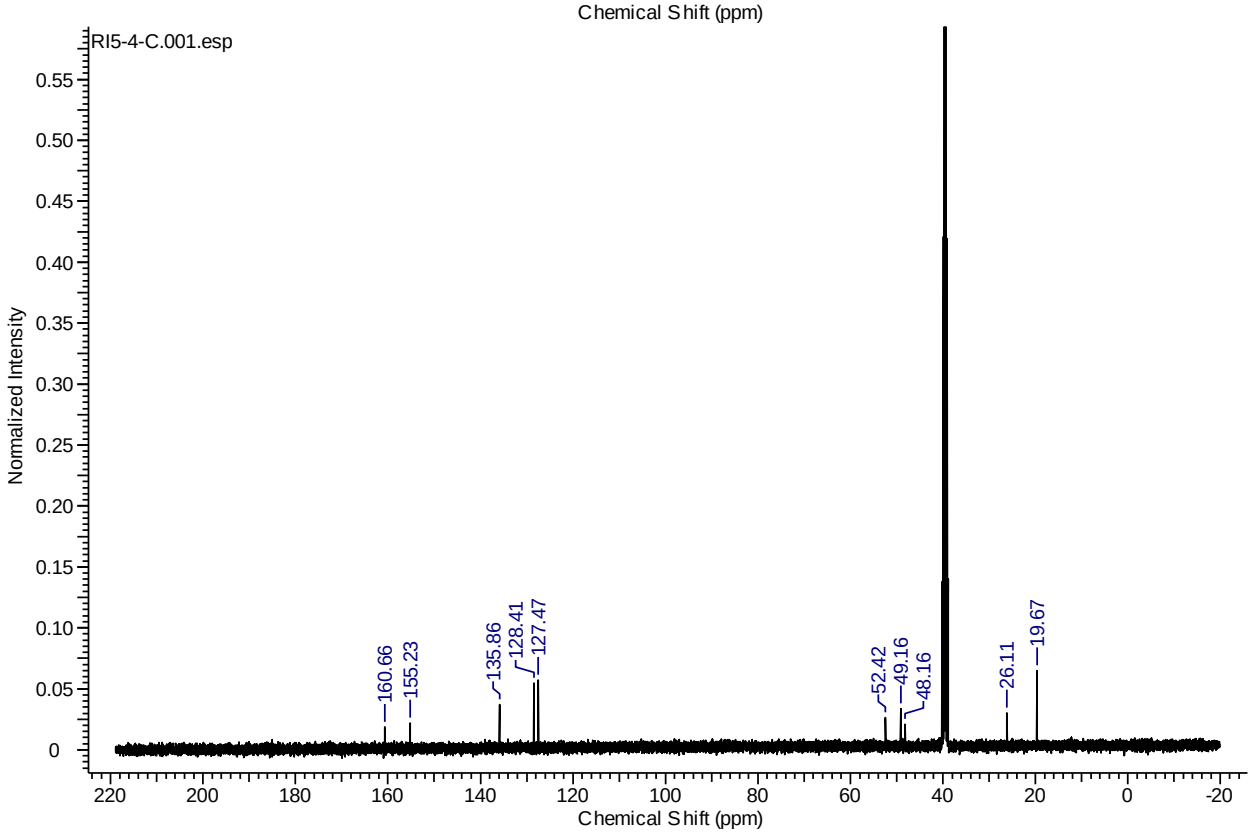

EE-15-H:
O
HN
OPh
NH
O
Normalized Intensity
2.0
1.5
1.0
0.5
0
2.19
1.13
2.10
2.09
2.06
0.97
2.06
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

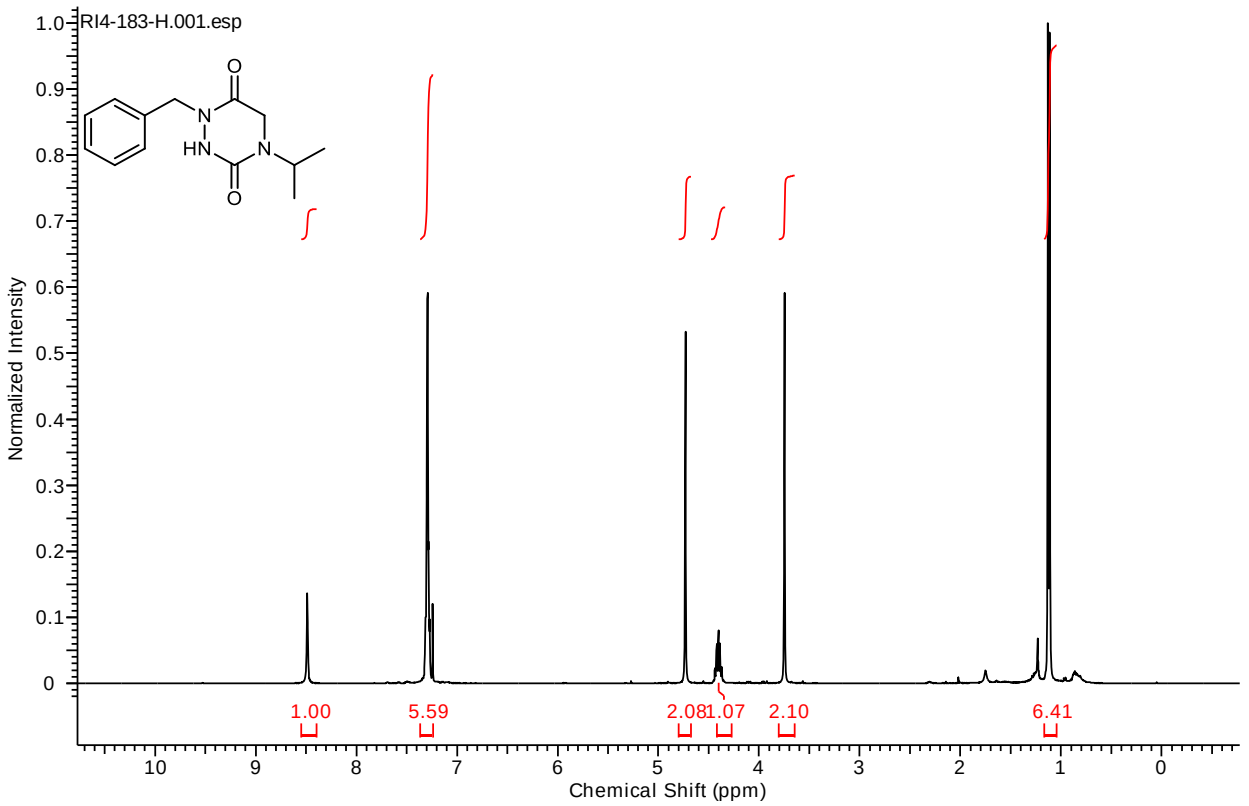

EE-15-C:
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
155.41
150.31
129.06
125.29
120.99
65.72
55.07
30.77
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

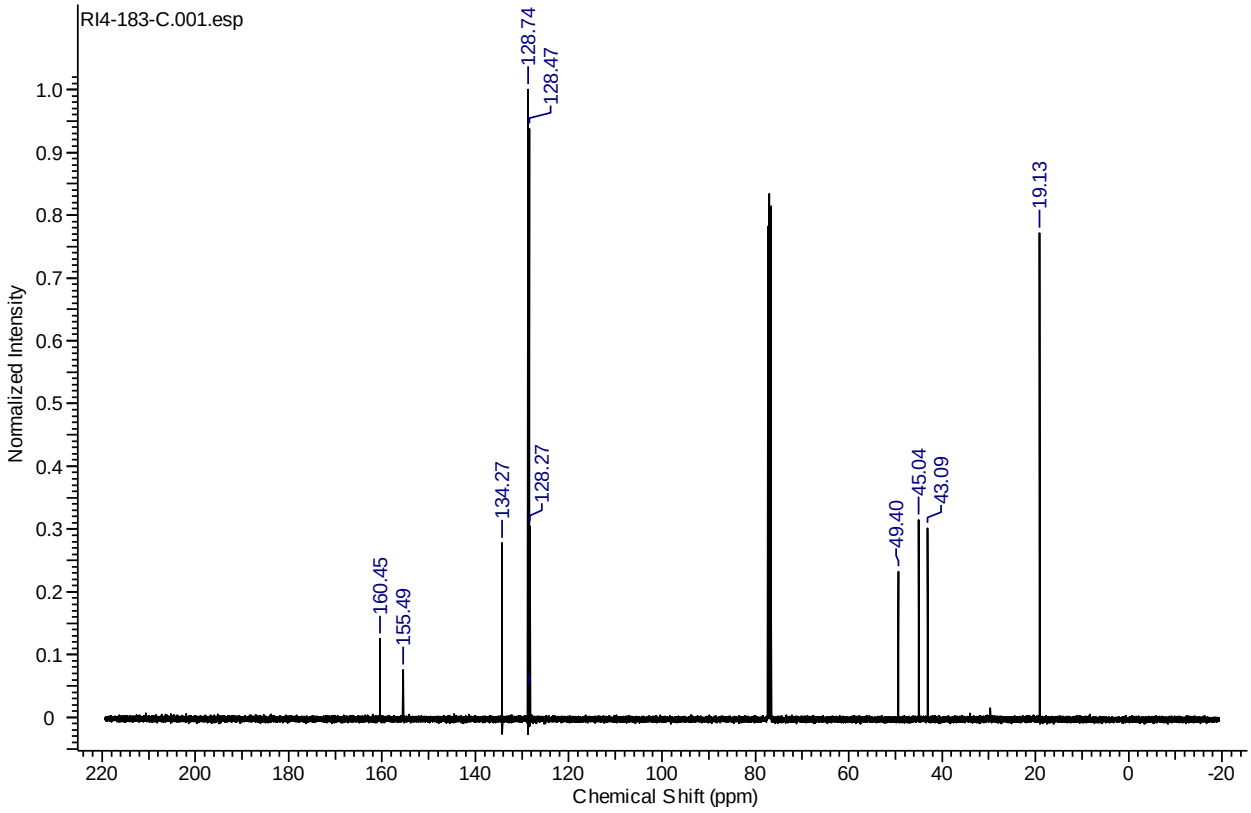

RI4-193-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.85
5.67
2.00
1.97
2.94
Me

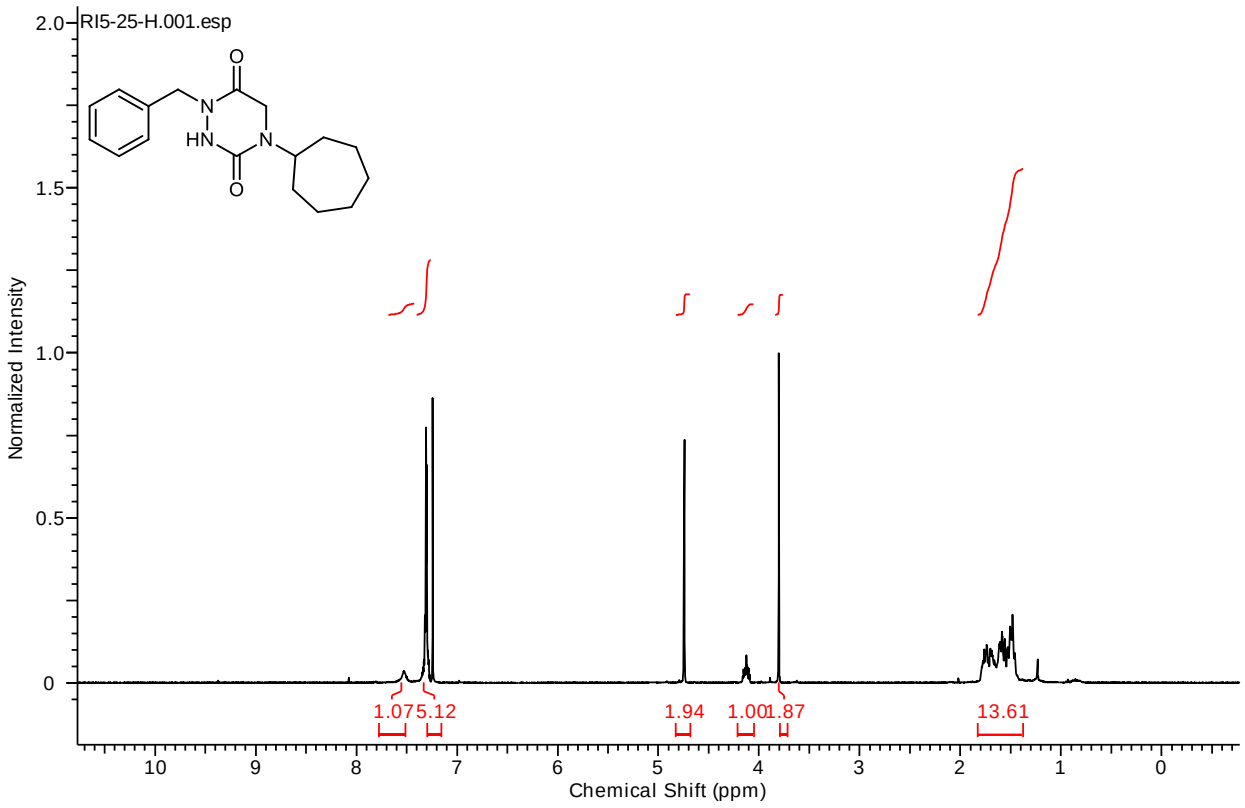

RI4-193-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
160.24
154.83
135.84
128.43
127.58
127.50
50.33
48.01
33.13

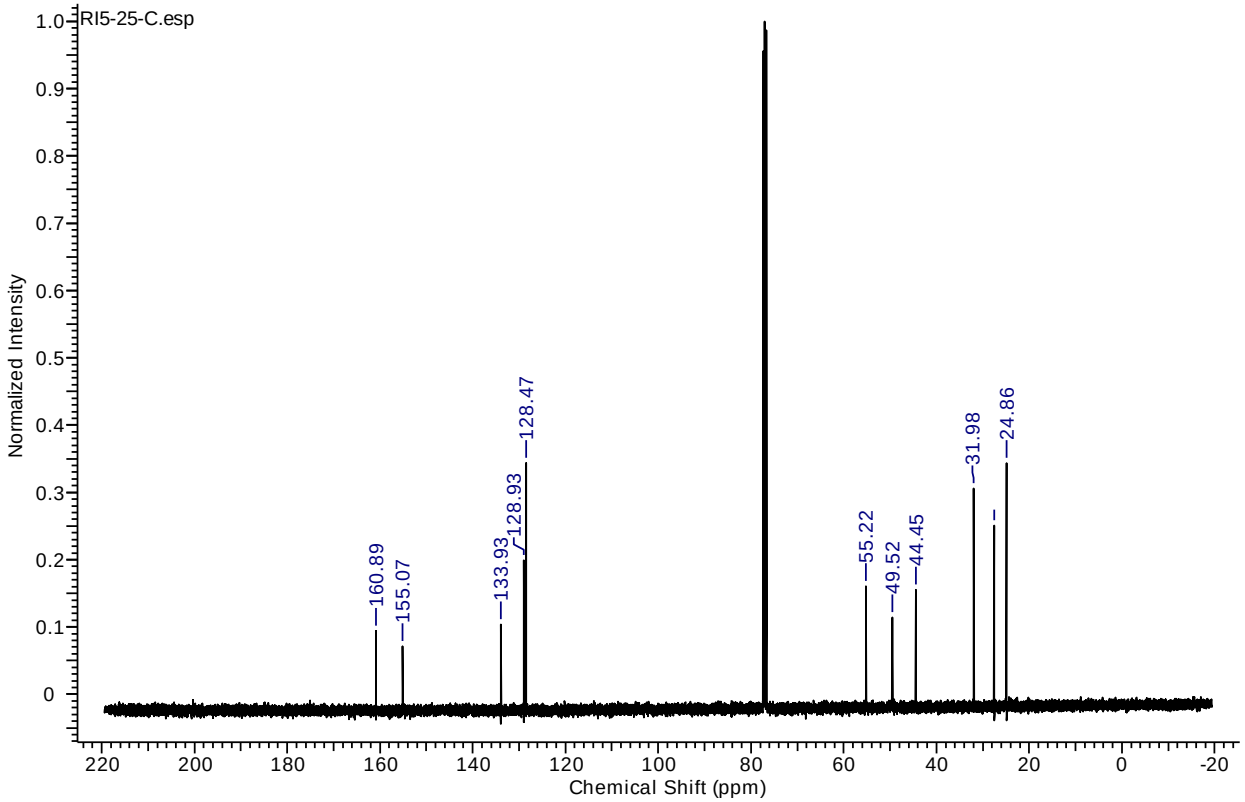

RI5-4-H.003.esp
Normalized Intensity
Chemical Shift (ppm)
1.01
5.11
1.94
1.94
1.92
1.07
6.01

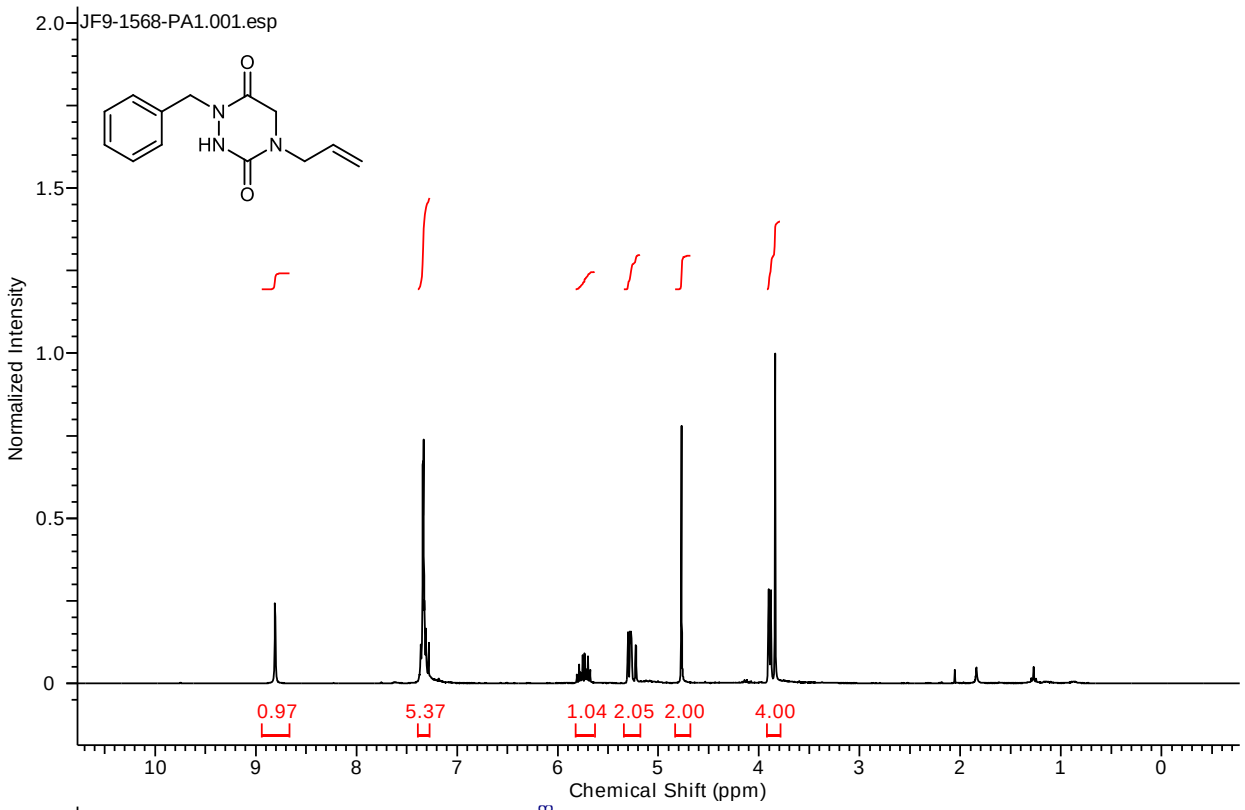

RI5-4-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
160.66
155.23
135.86
128.41
127.47
52.42
49.16
48.16
26.11
19.67

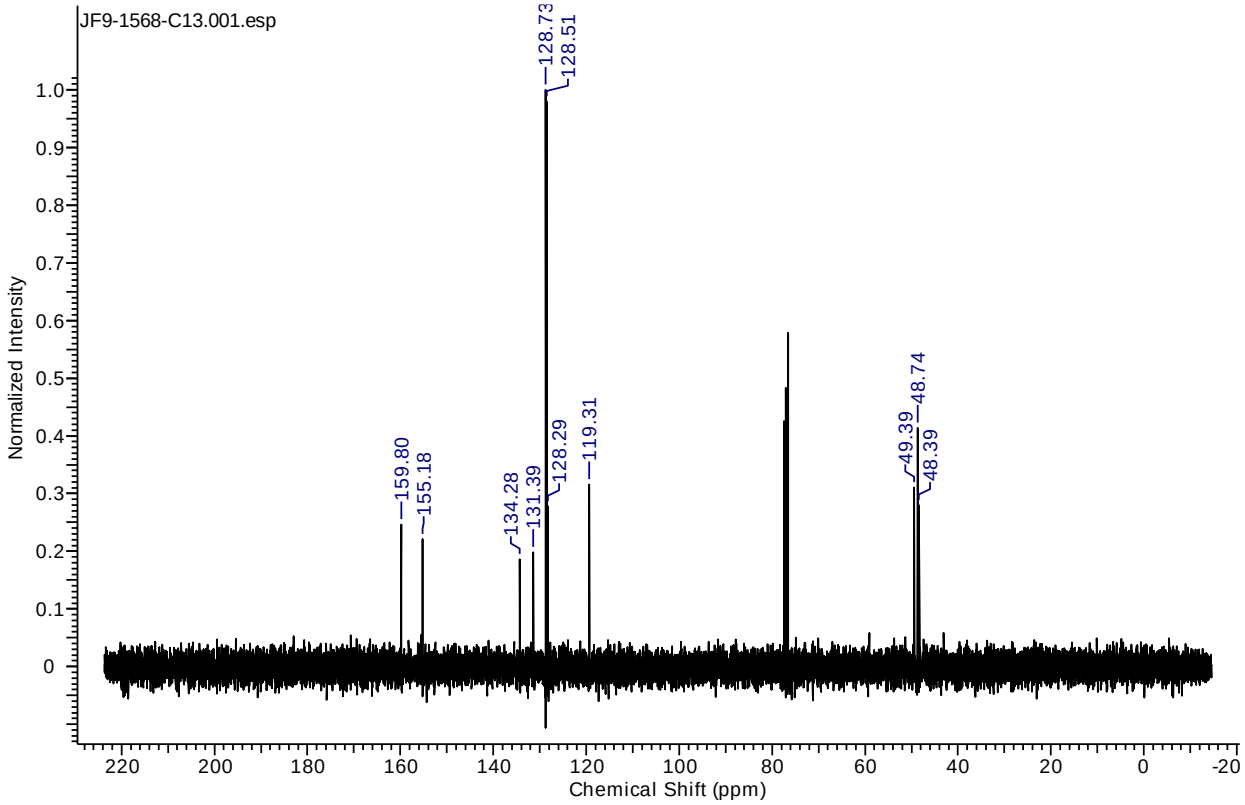

RI4-183-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
5.59
2.08
1.07
2.10
6.41

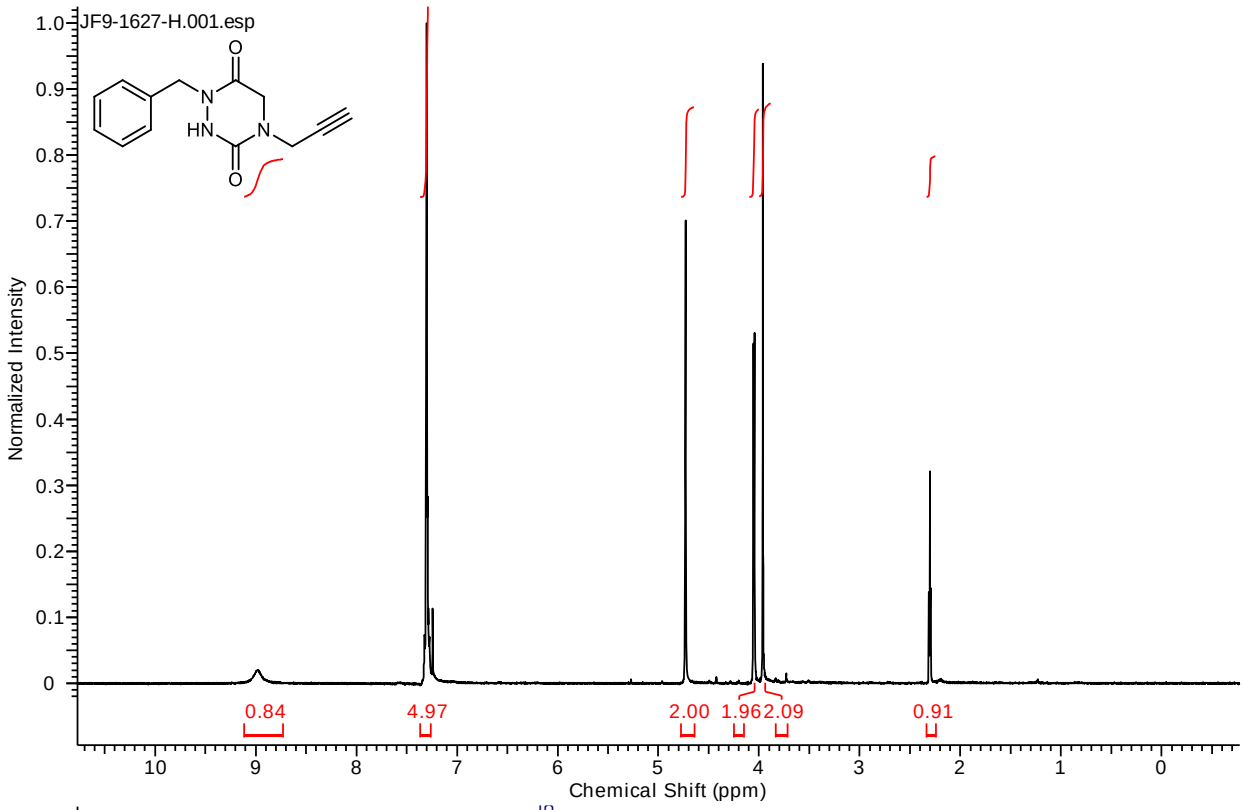

RI4-183-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
128.74
128.47
128.27
134.27
160.45
155.49
49.40
45.04
43.09
19.13

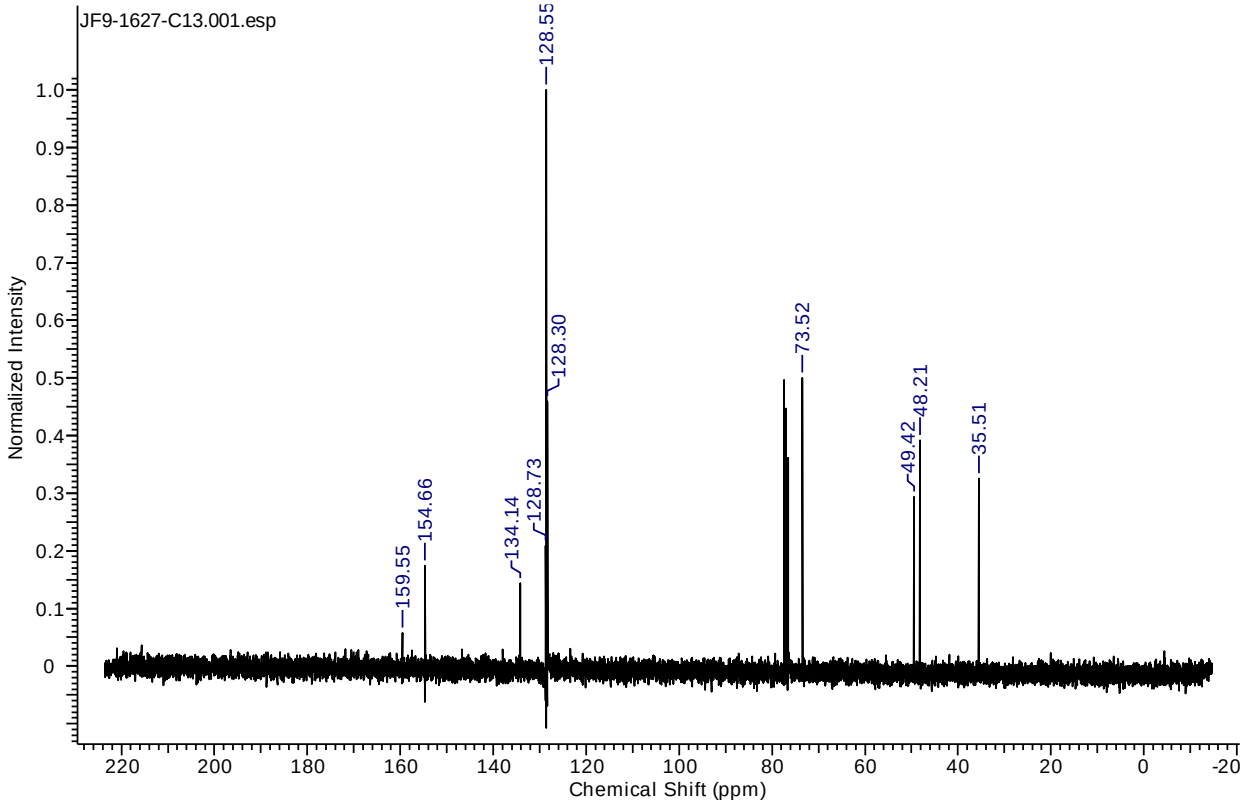

RI5-25-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.07
5.12
1.94
1.00
1.87
13.61

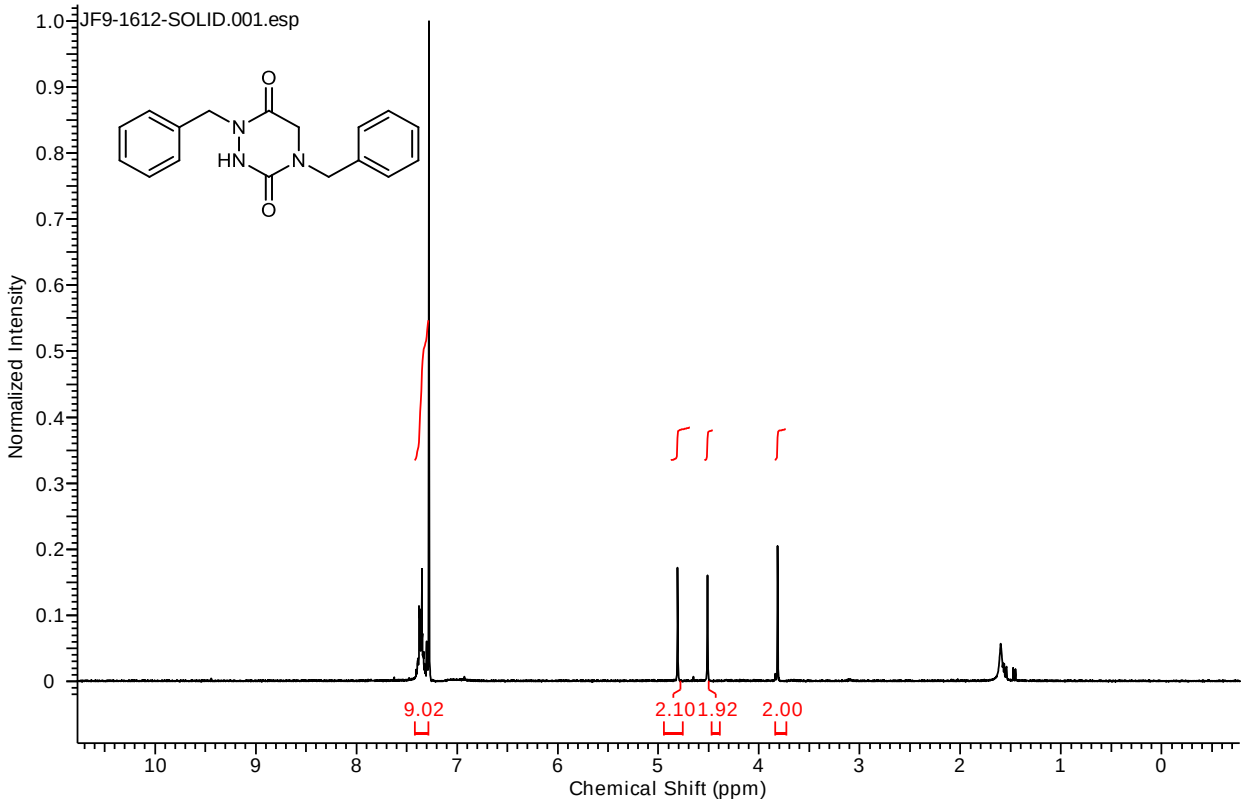

RI5-25-C.esp
Normalized Intensity
Chemical Shift (ppm)
160.89
155.07
133.93
128.93
128.47
55.22
49.52
44.45
31.98
24.86

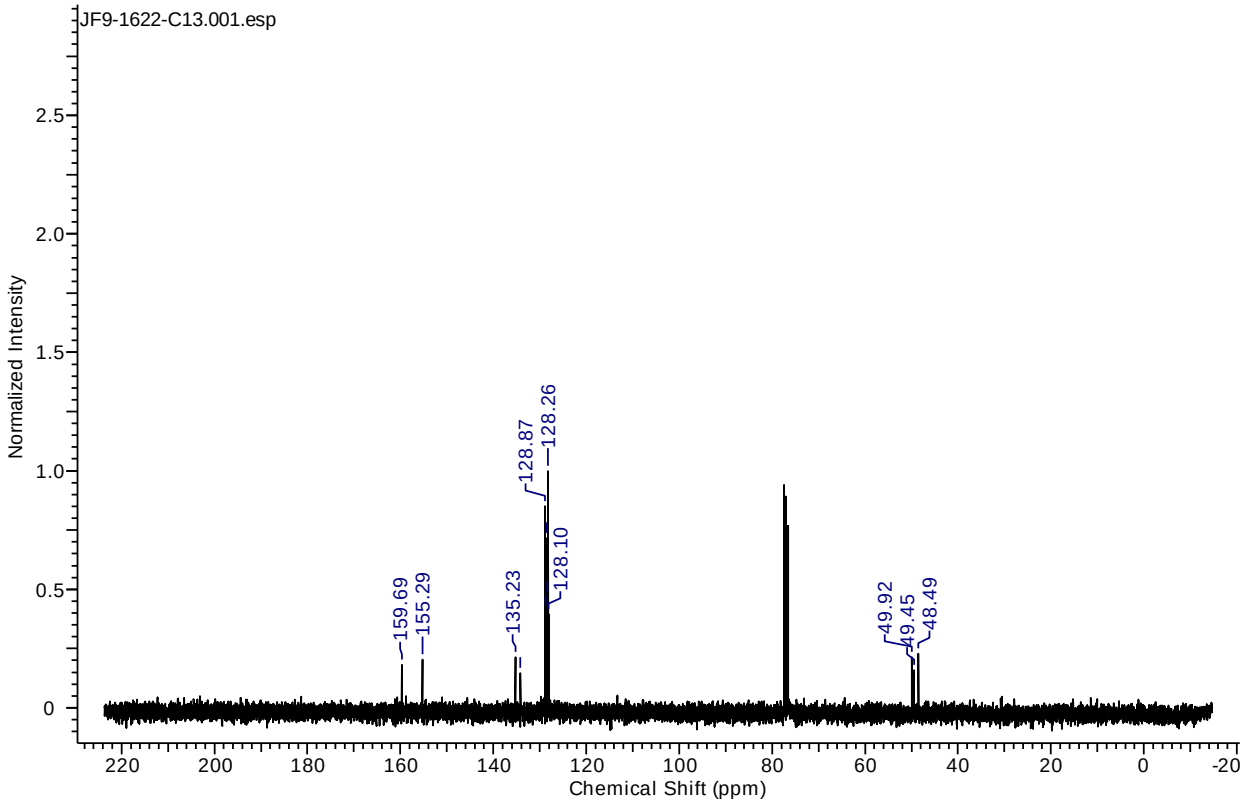

JF9-1568-PA1.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.97
5.37
1.04
2.05
2.00
4.00

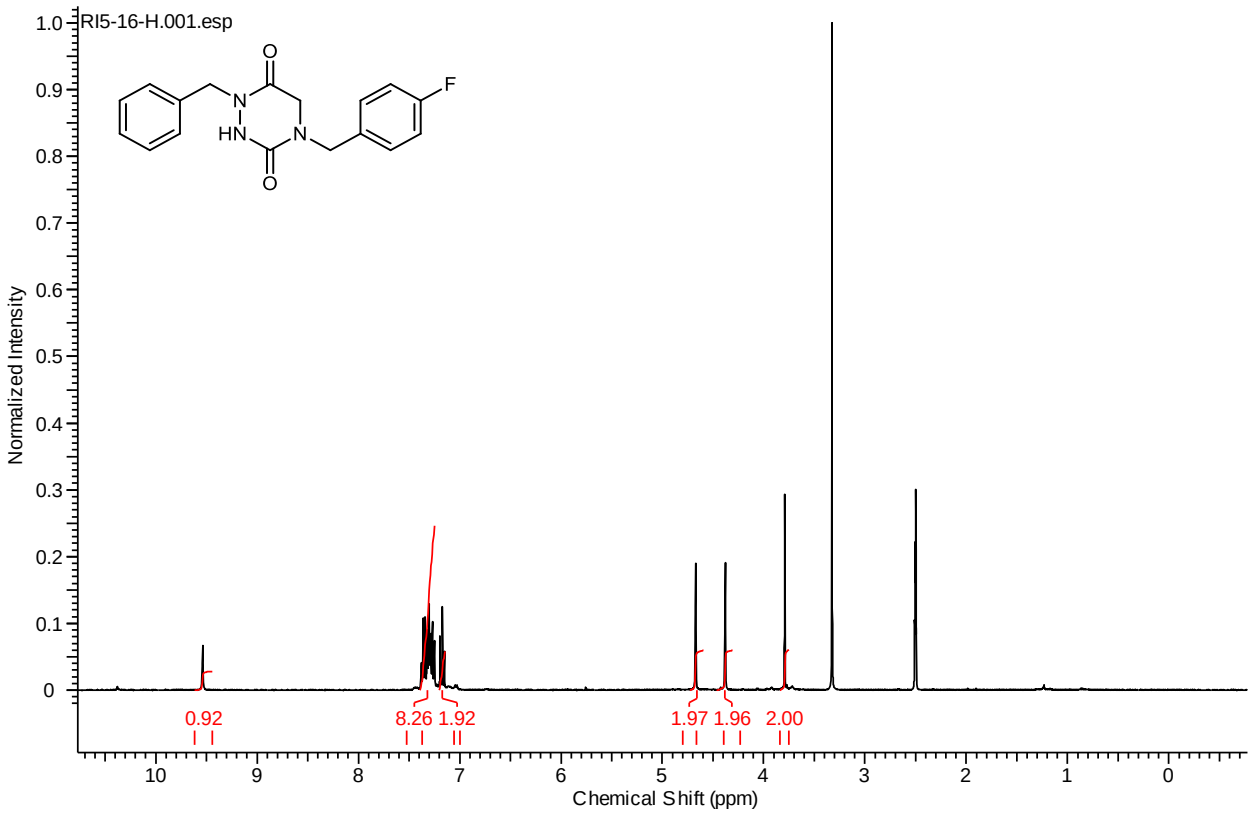

JF9-1568-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
128.73
128.51
159.80
155.18
134.28
131.39
128.29
119.31
49.39
48.74
48.39

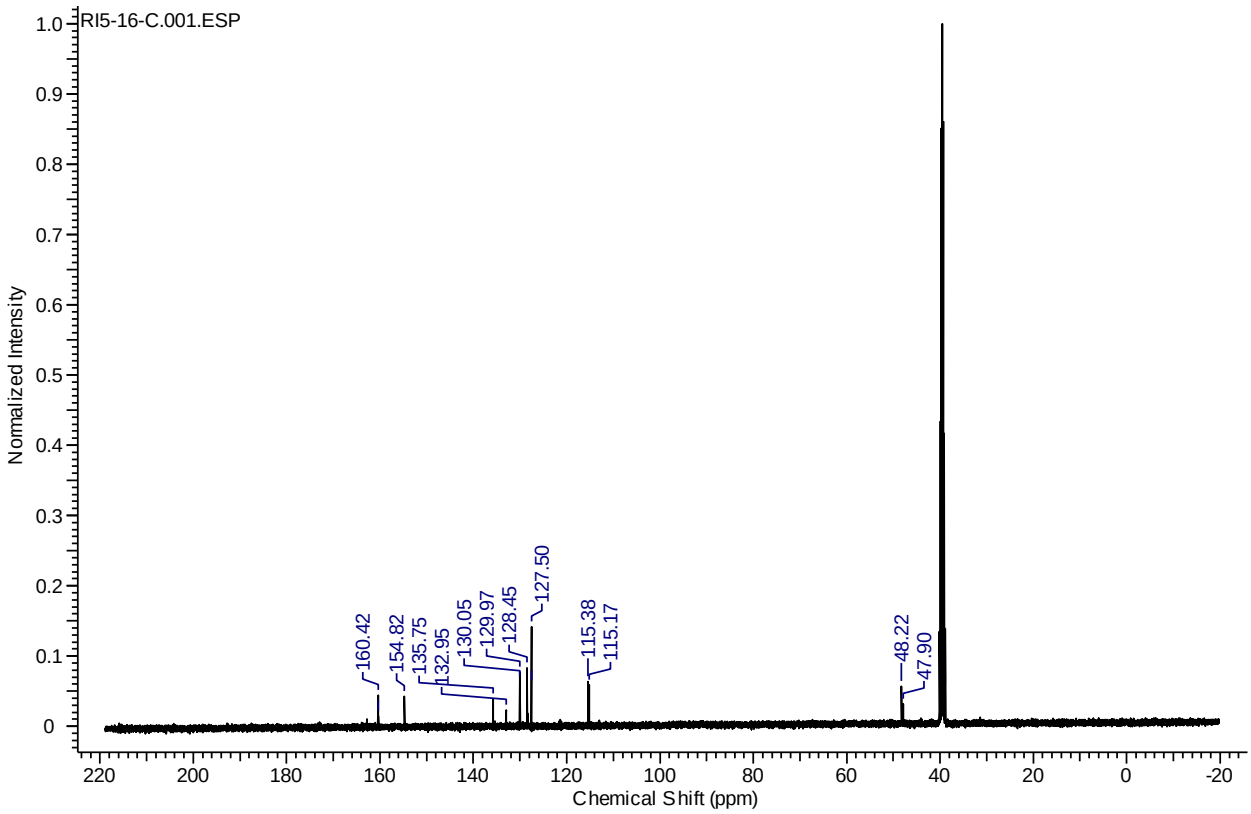

JF9-1627-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.84
4.97
2.00
1.96
2.09
0.91

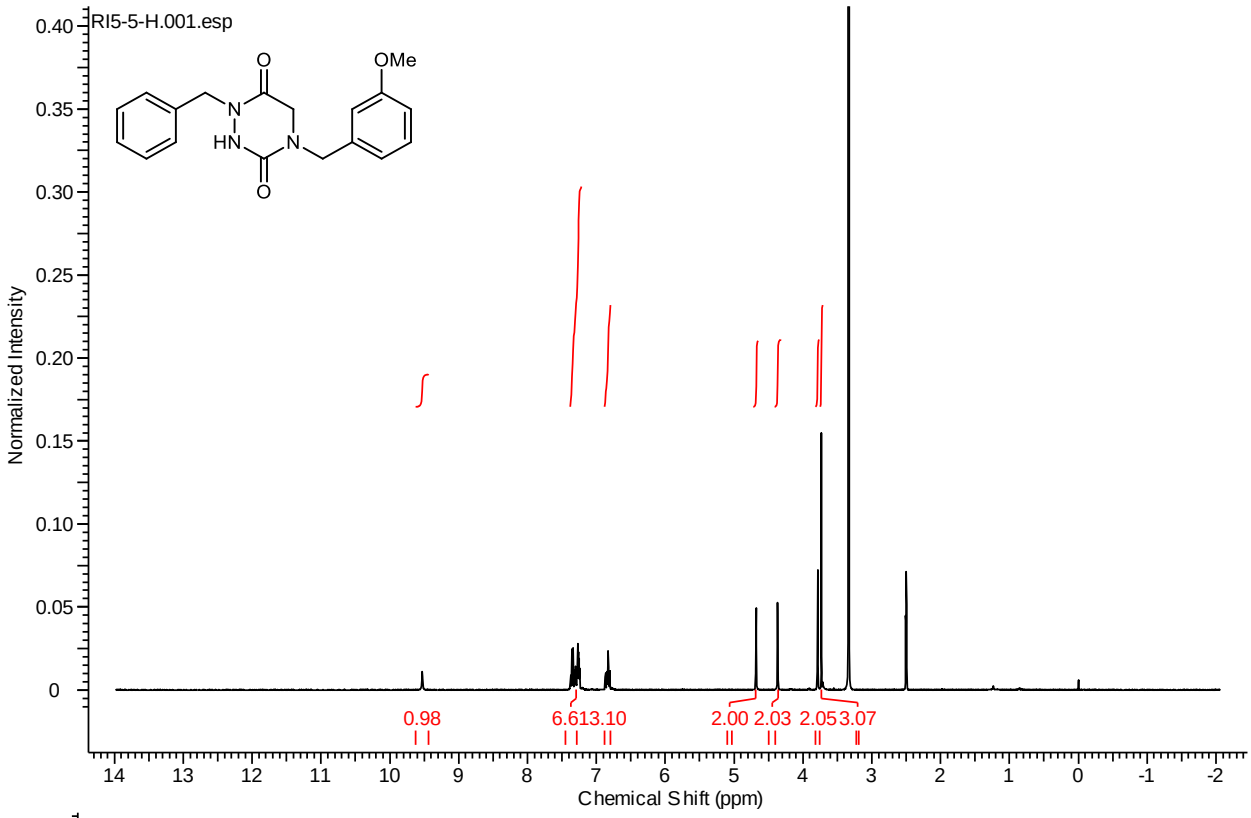

JF9-1627-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
128.55
128.30
73.52
49.42
48.21
35.51
159.55
154.66
134.14
128.73

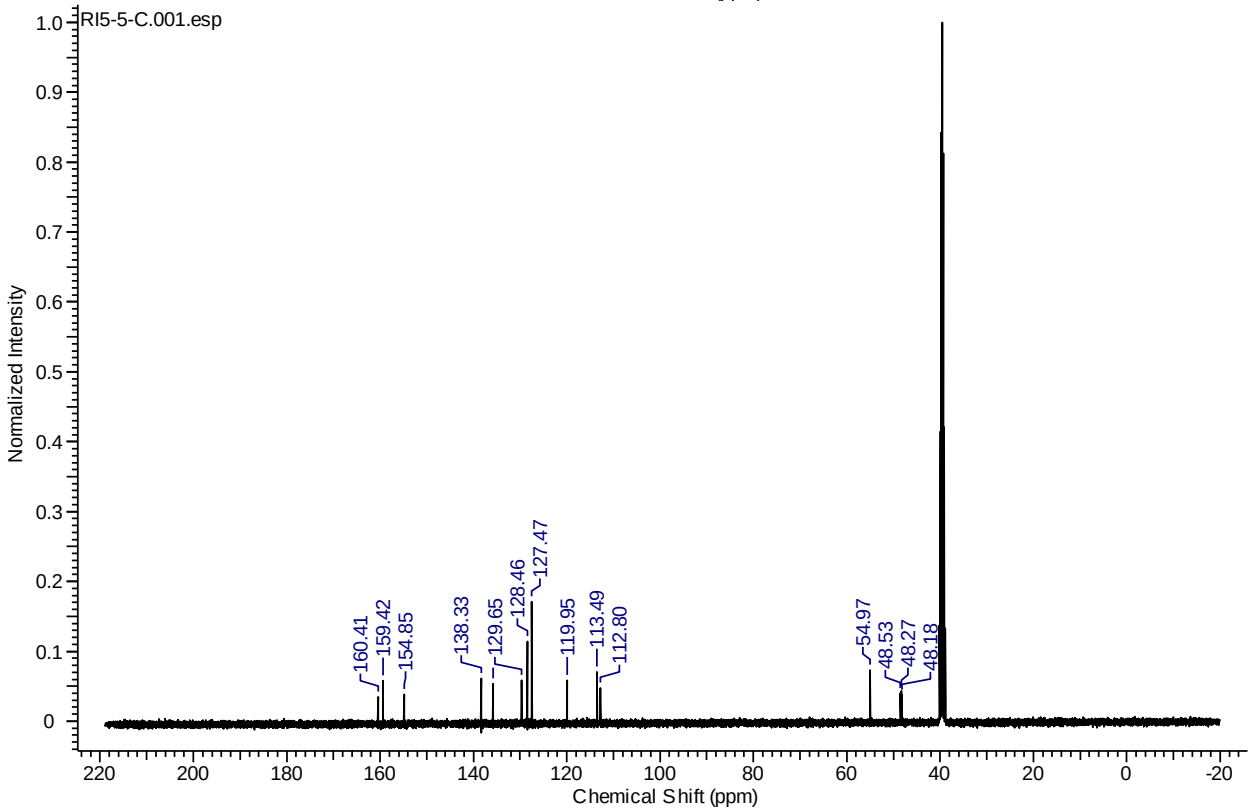

JF9-1612-SOLID.001.esp
Normalized Intensity
Chemical Shift (ppm)
9.02
2.10
1.92
2.00

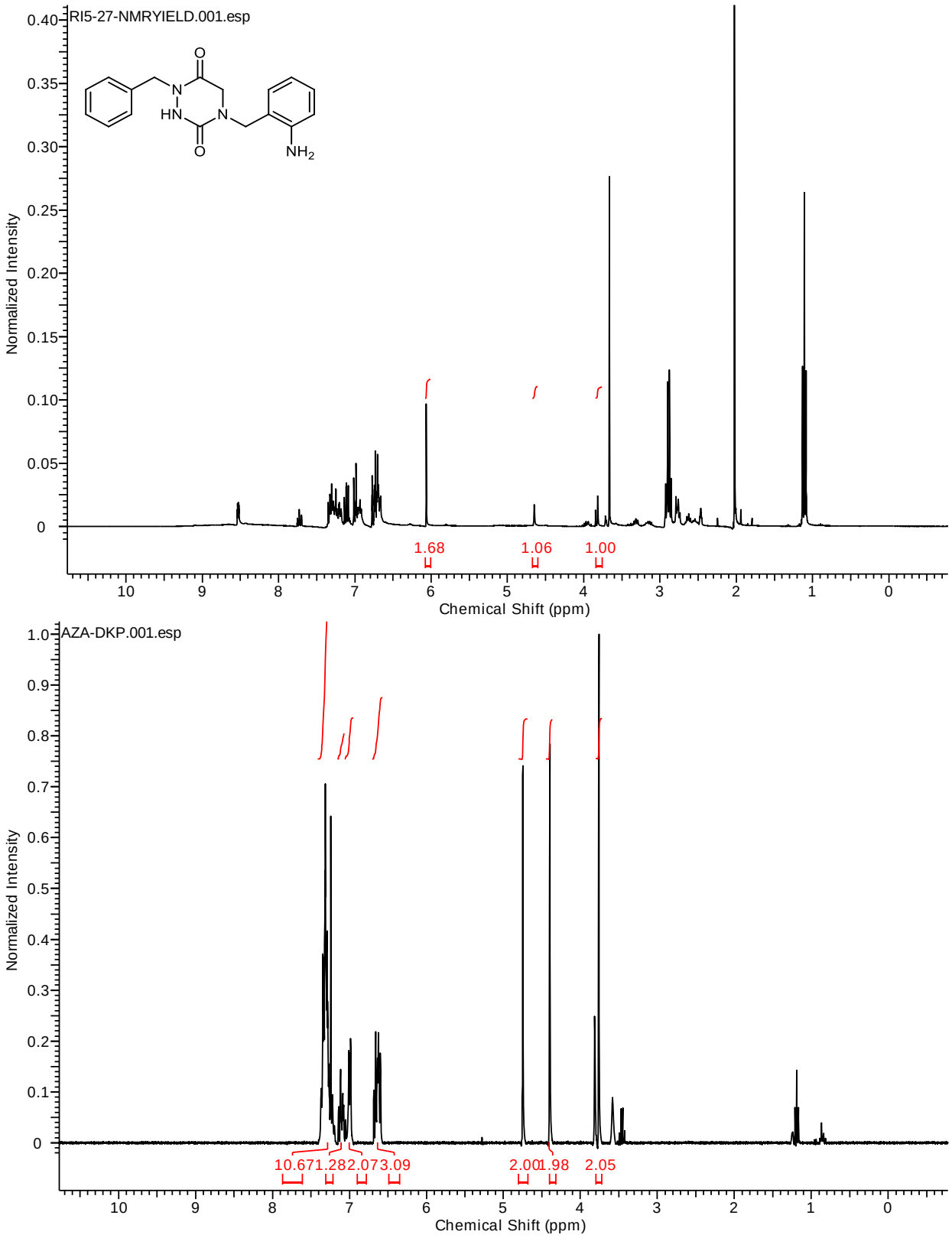

JF9-1622-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
159.69
155.29
135.23
128.87
128.26
128.10
49.92
49.45
48.49


RI5-16-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.92
8.26
1.92
1.97
1.96
2.00

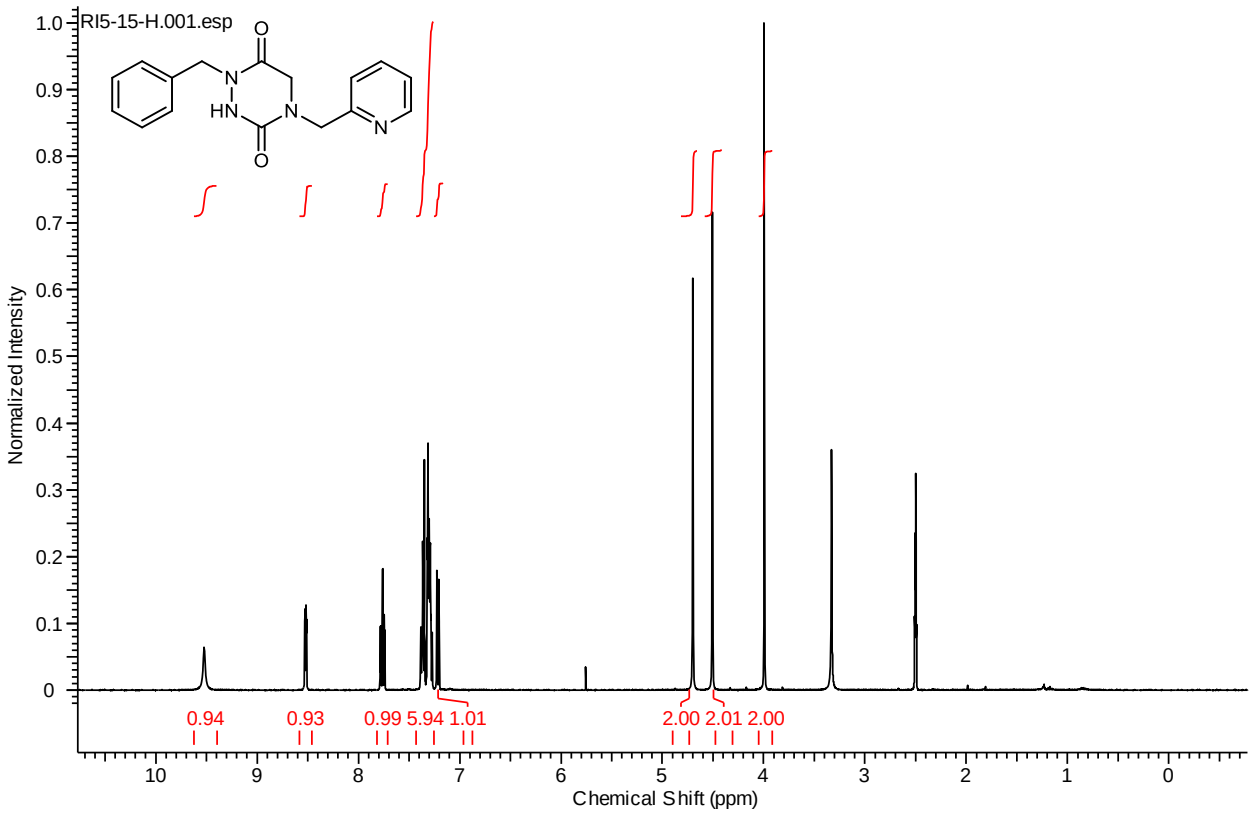

RI5-16-C.001.ESP
Normalized Intensity
Chemical Shift (ppm)
160.42
154.82
135.75
132.95
130.05
129.97
128.45
127.50
115.38
115.17
48.22
47.90

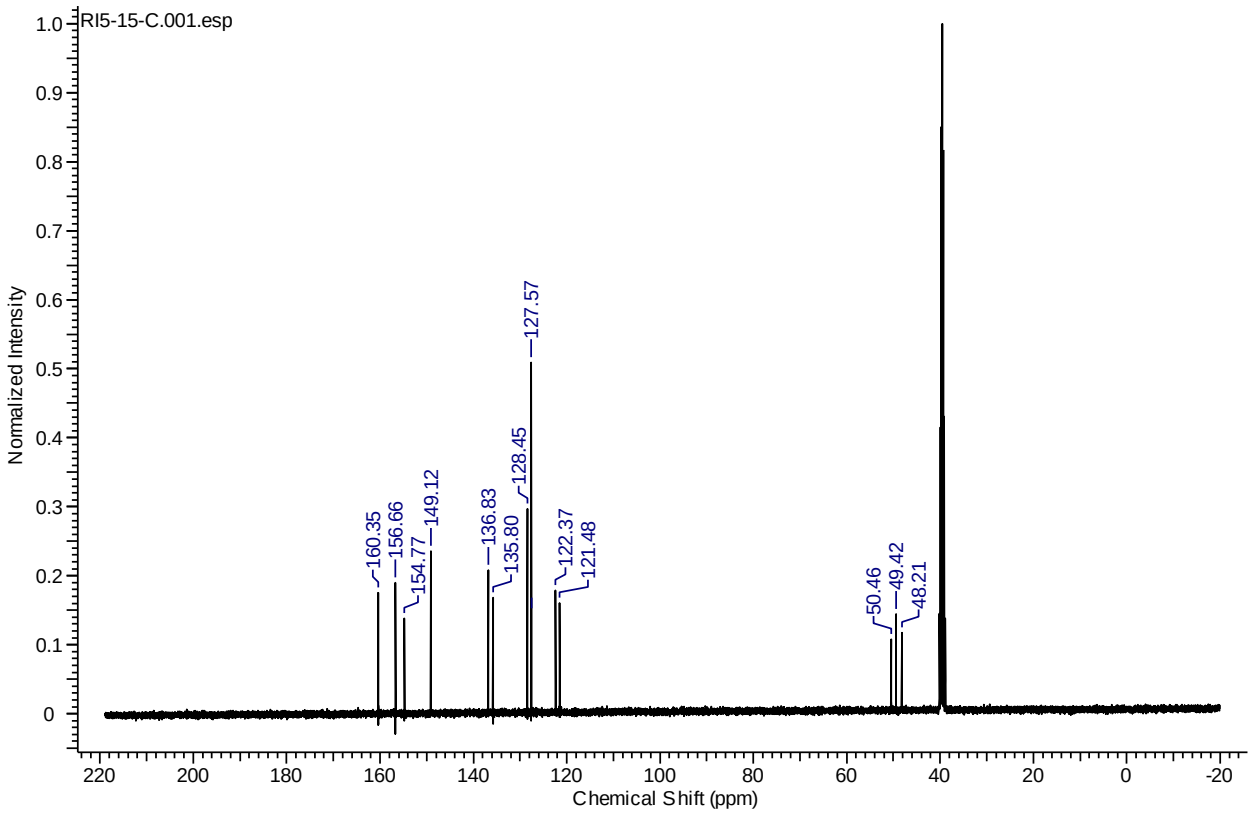

RI5-5-H.001.esp
OMe
O
N
HN
N
O
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.98
6.61
3.10
2.00
2.03
2.05
3.07
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

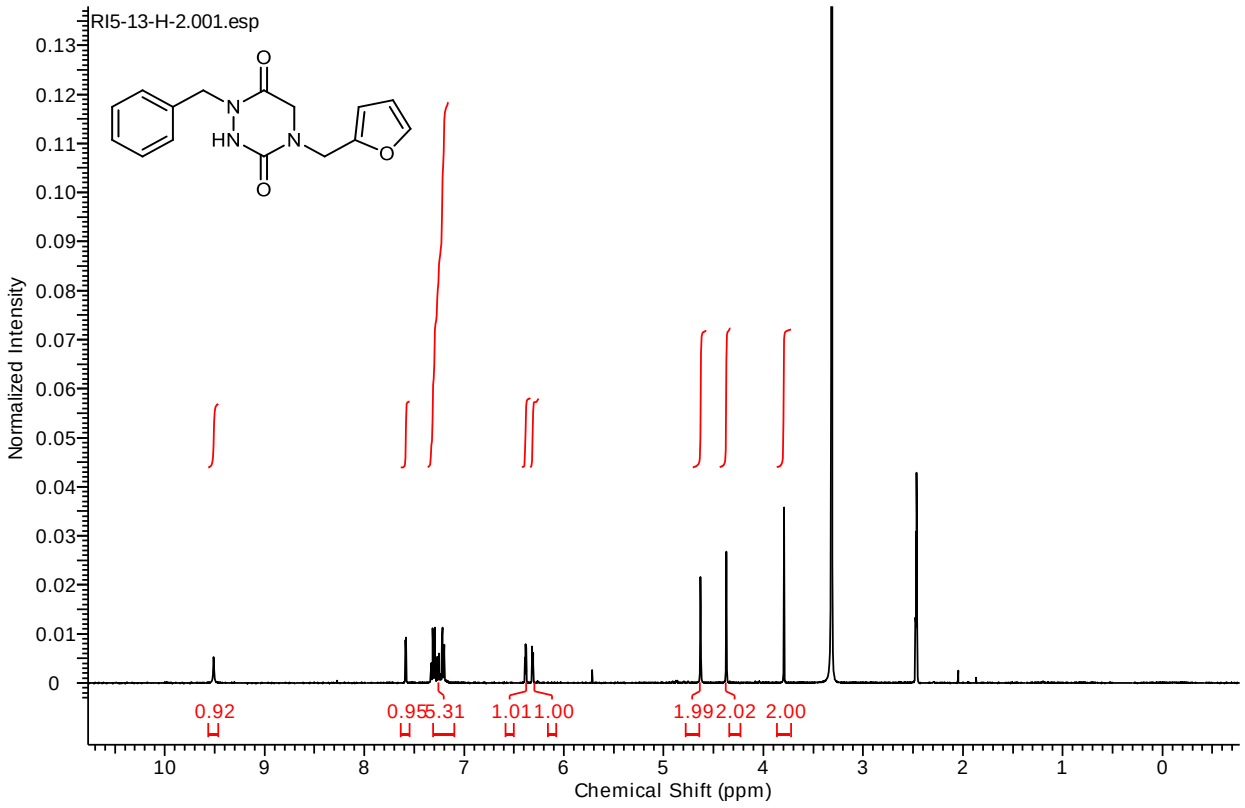

RI5-5-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.41
159.42
154.85
138.33
129.65
128.46
127.47
119.95
113.49
112.80
54.97
48.53
48.27
48.18
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

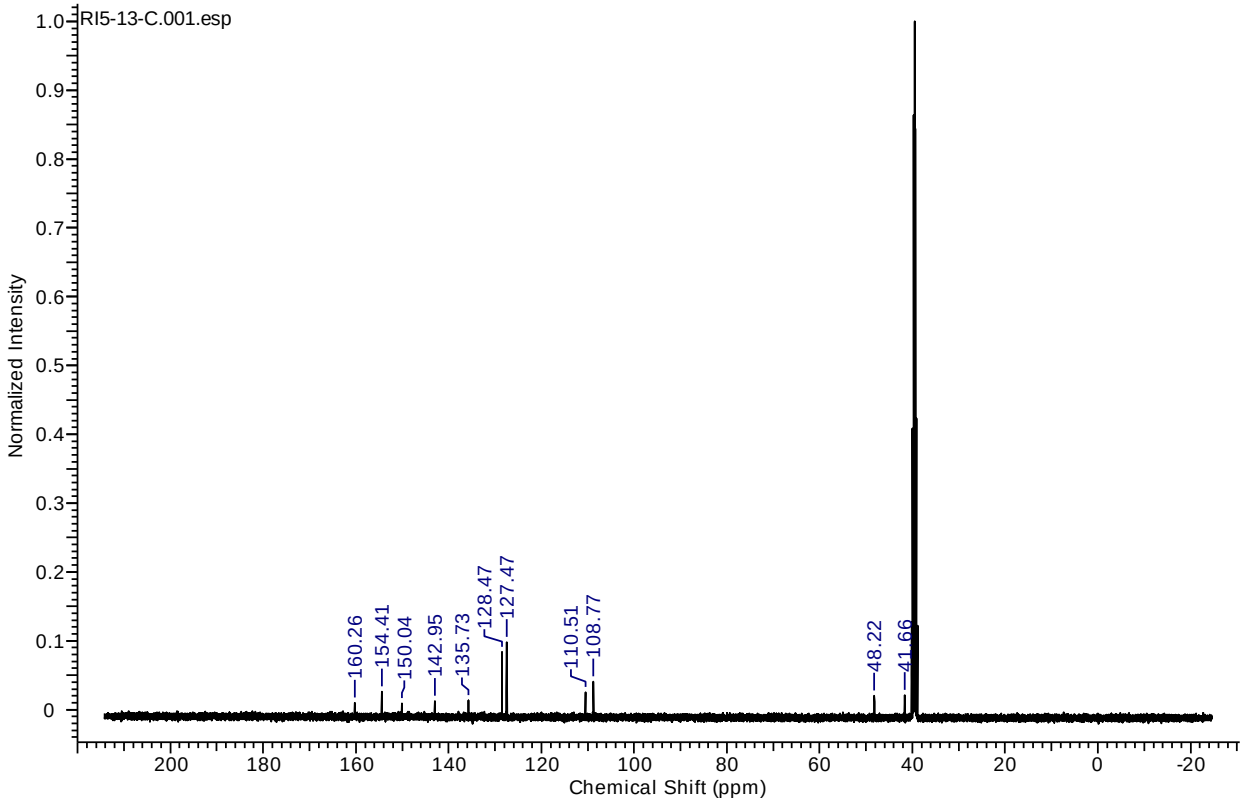


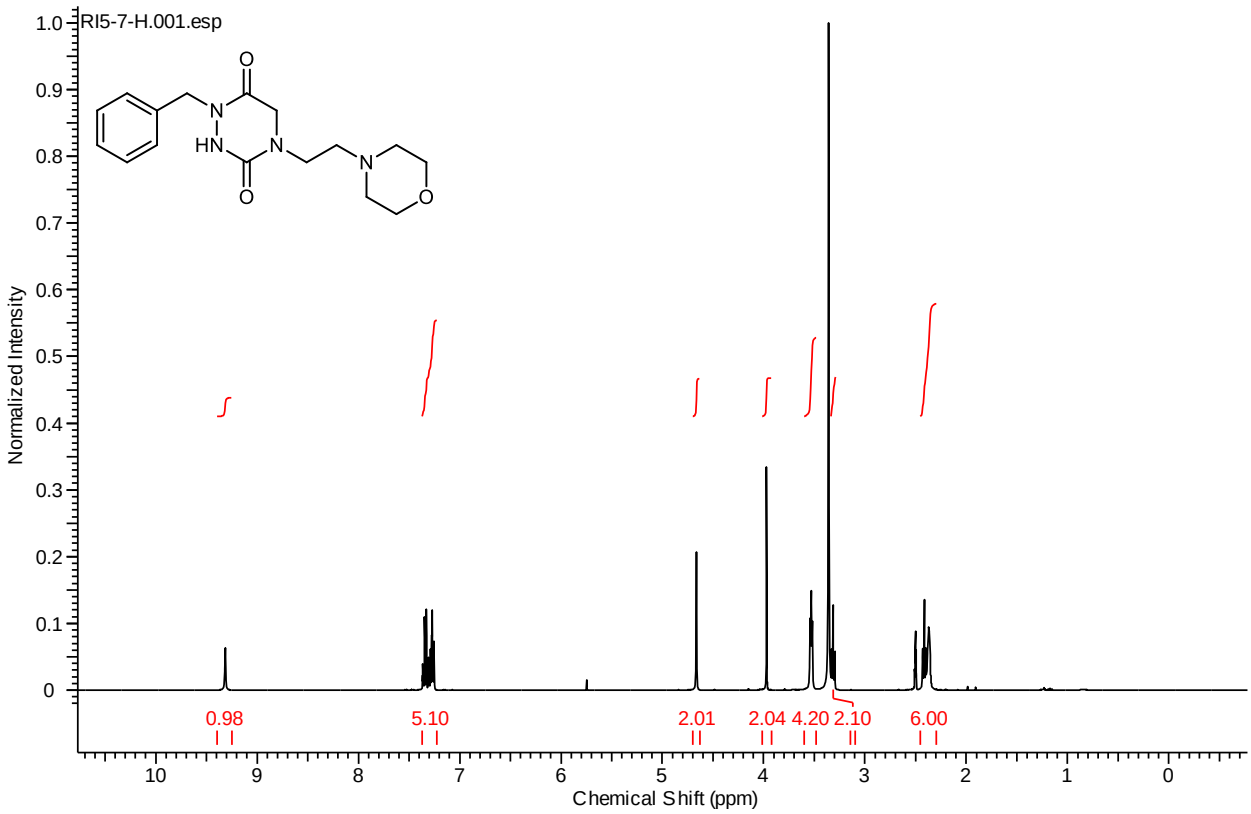
37.8 mg TMB used standard. Top spectra is NMR yield. Bottom spectra is isolation attempt.

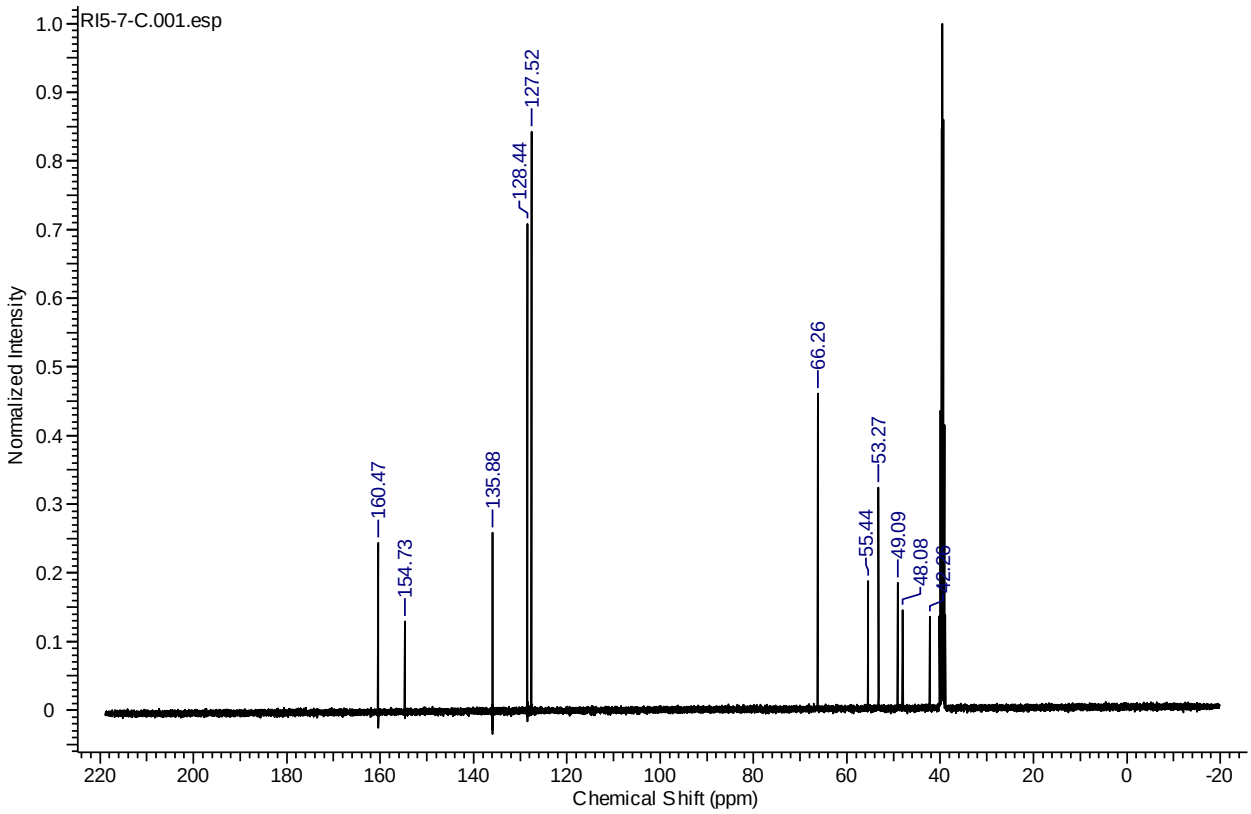

RI5-15-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.94
0.93
0.99
5.94
1.01
2.00
2.01
2.00

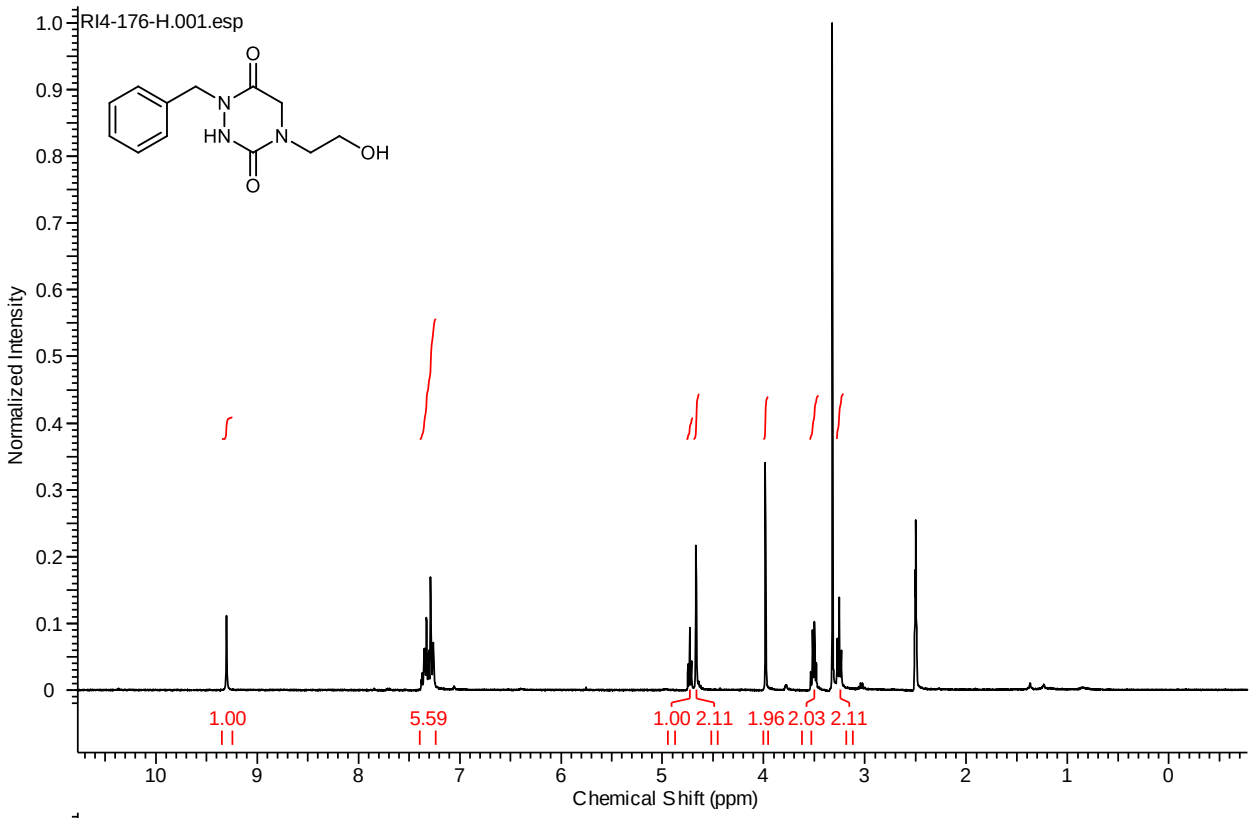

RI5-15-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
160.35
156.66
154.77
149.12
136.83
135.80
128.45
127.57
122.37
121.48
50.46
49.42
48.21

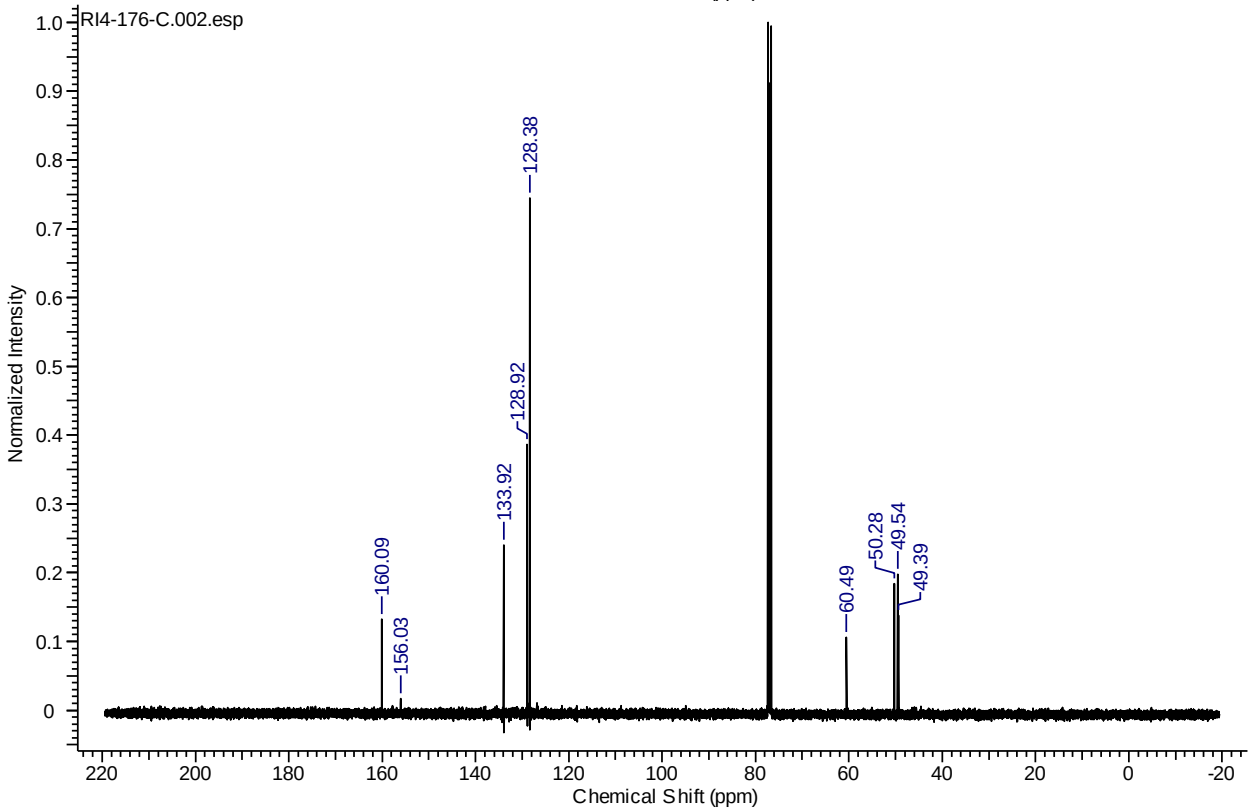

RI5-13-H-2.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.92
0.95
5.31
1.01
1.00
1.99
2.02
2.00

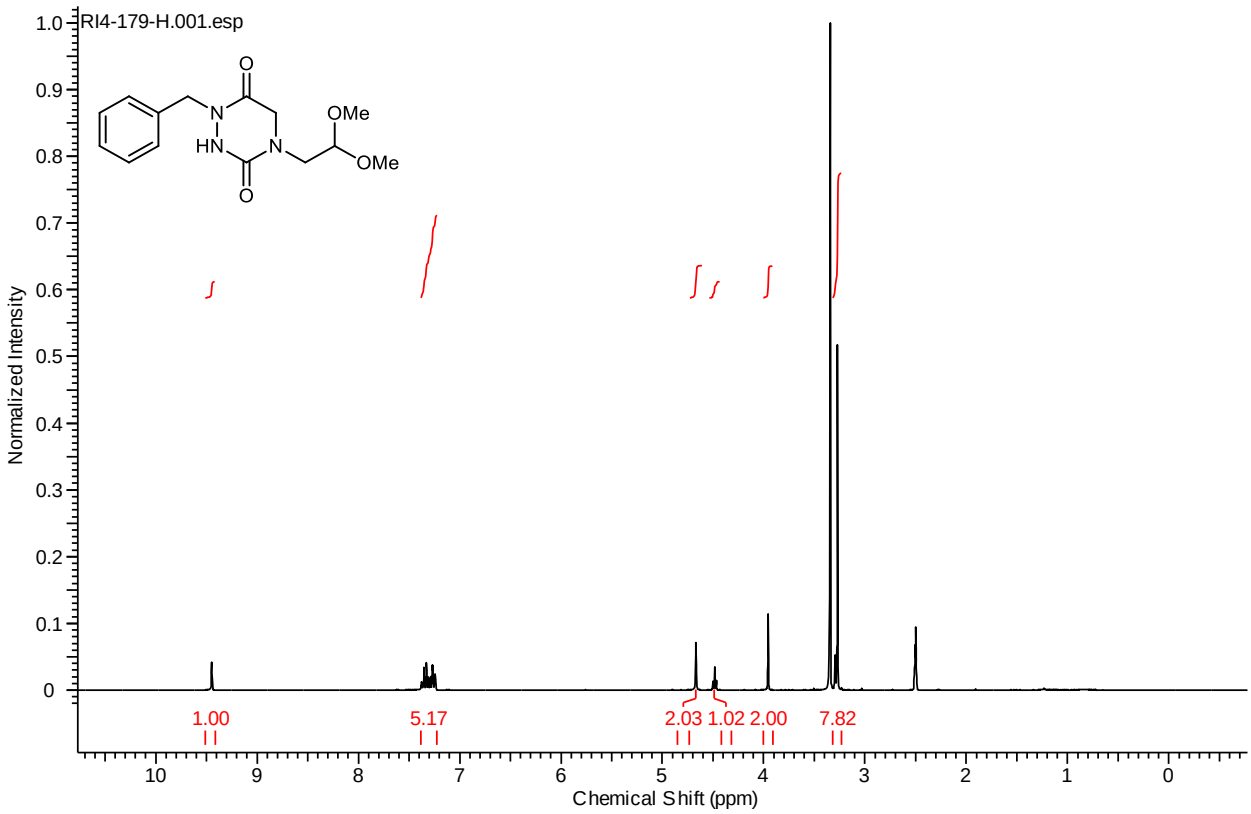

RI5-13-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
160.26
154.41
150.04
142.95
135.73
128.47
127.47
110.51
108.77
48.22
41.66

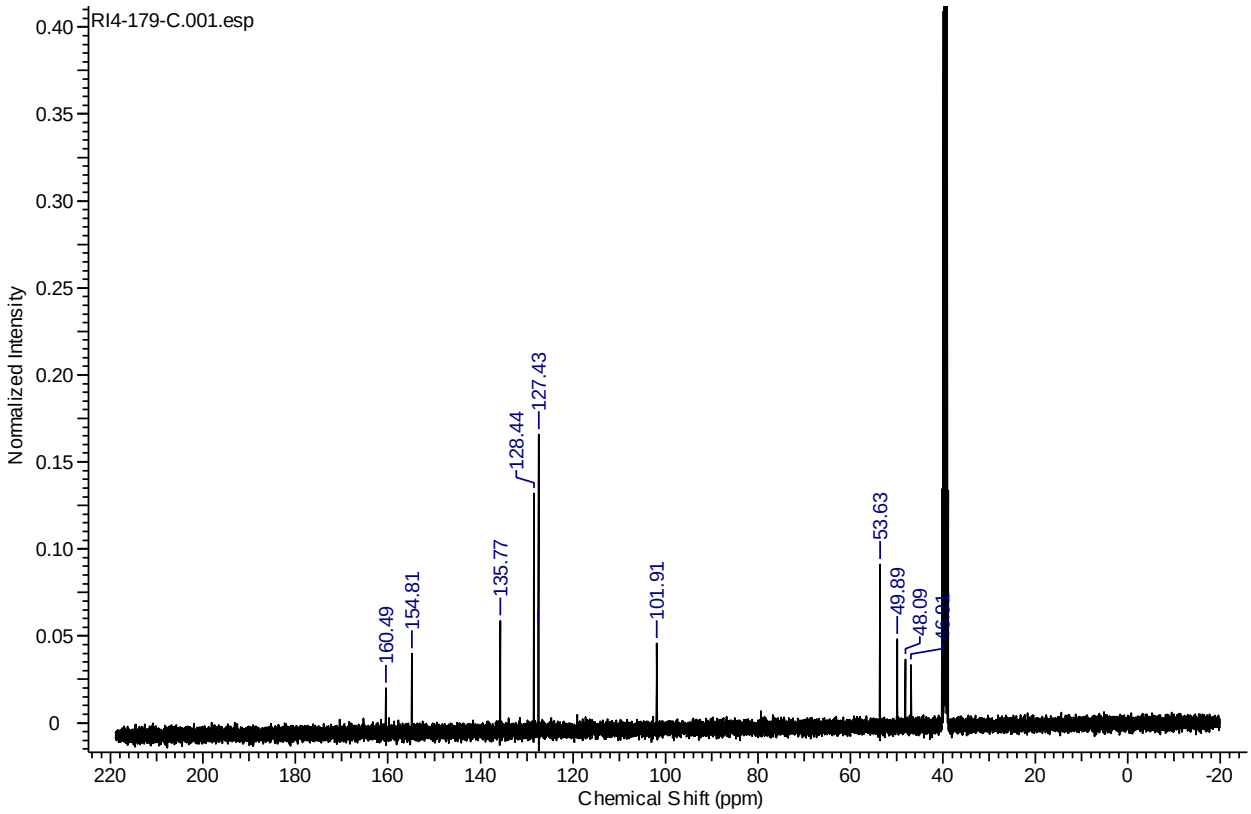

RI5-7-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.98
5.10
2.01
2.04
4.20
2.10
6.00

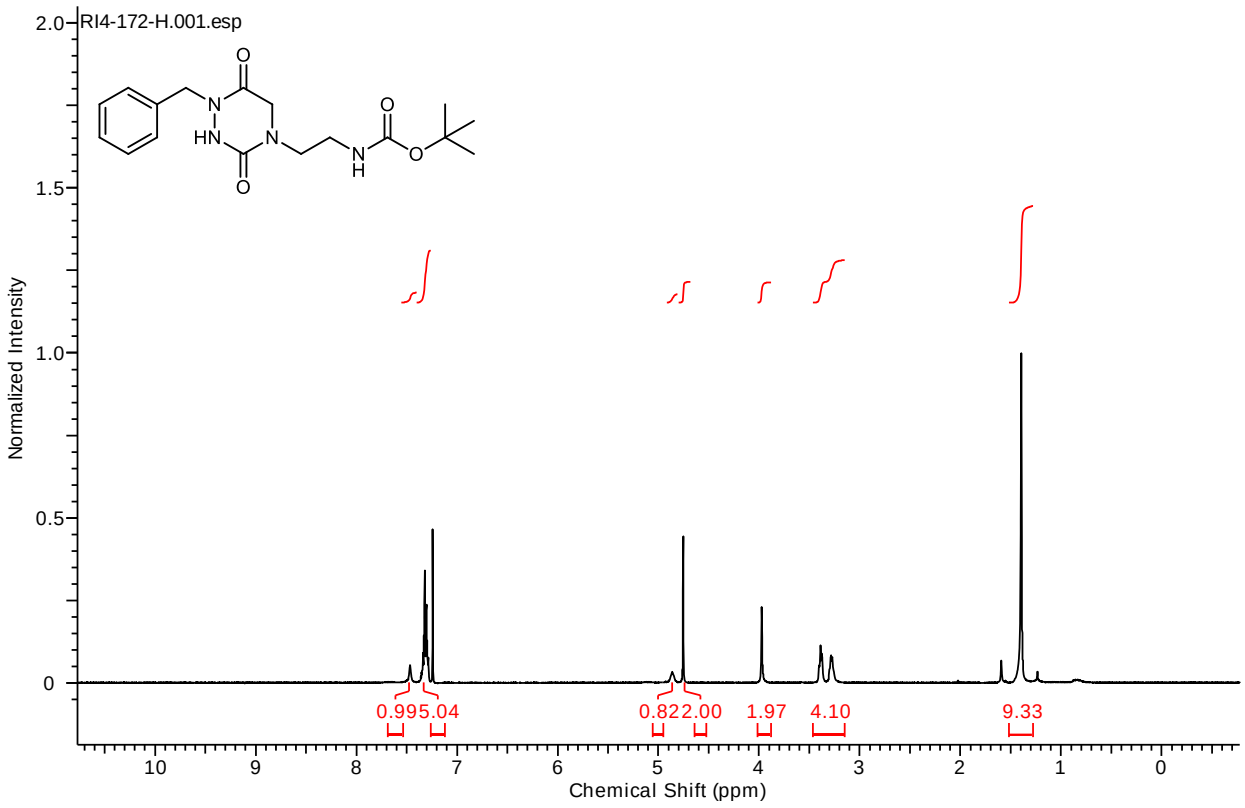

RI5-7-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
160.47
154.73
135.88
128.44
127.52
66.26
55.44
53.27
49.09
48.08

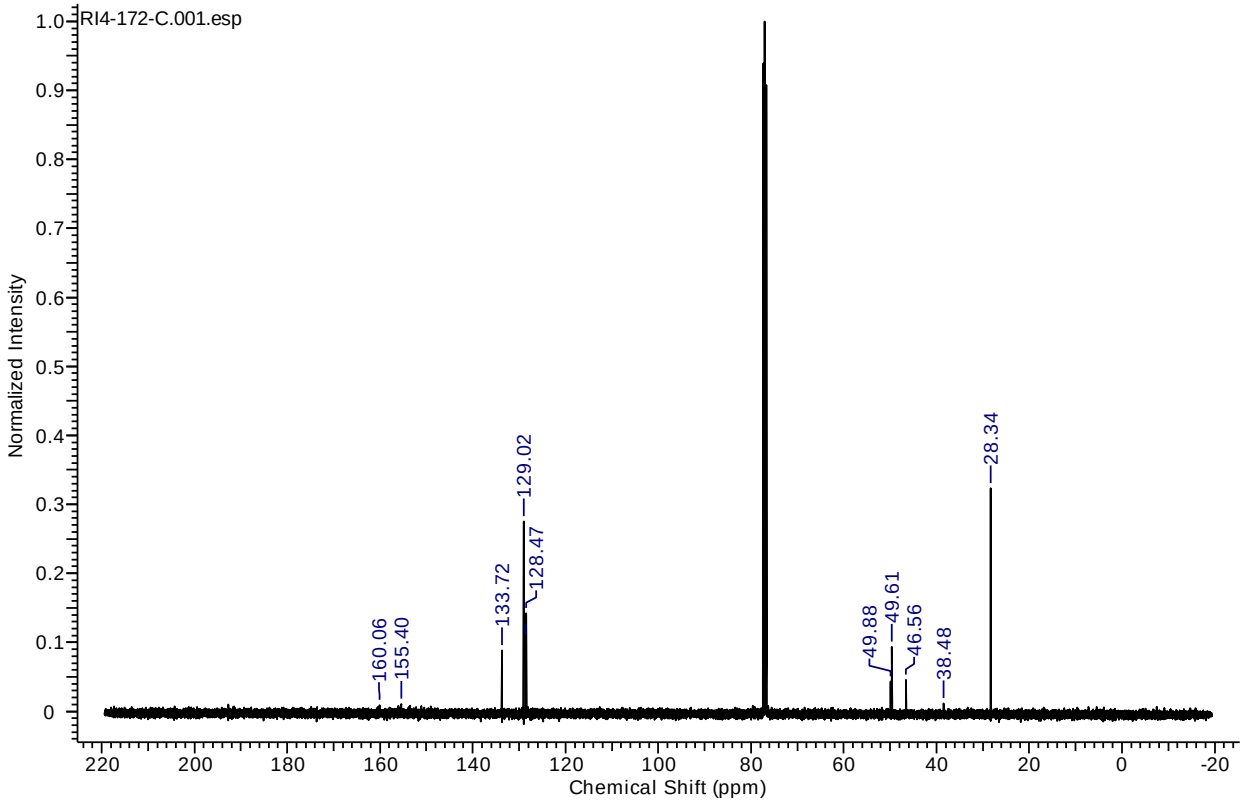

RI4-176-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
5.59
1.00 2.11
1.96 2.03 2.11
O
N
HN
N
OH
O

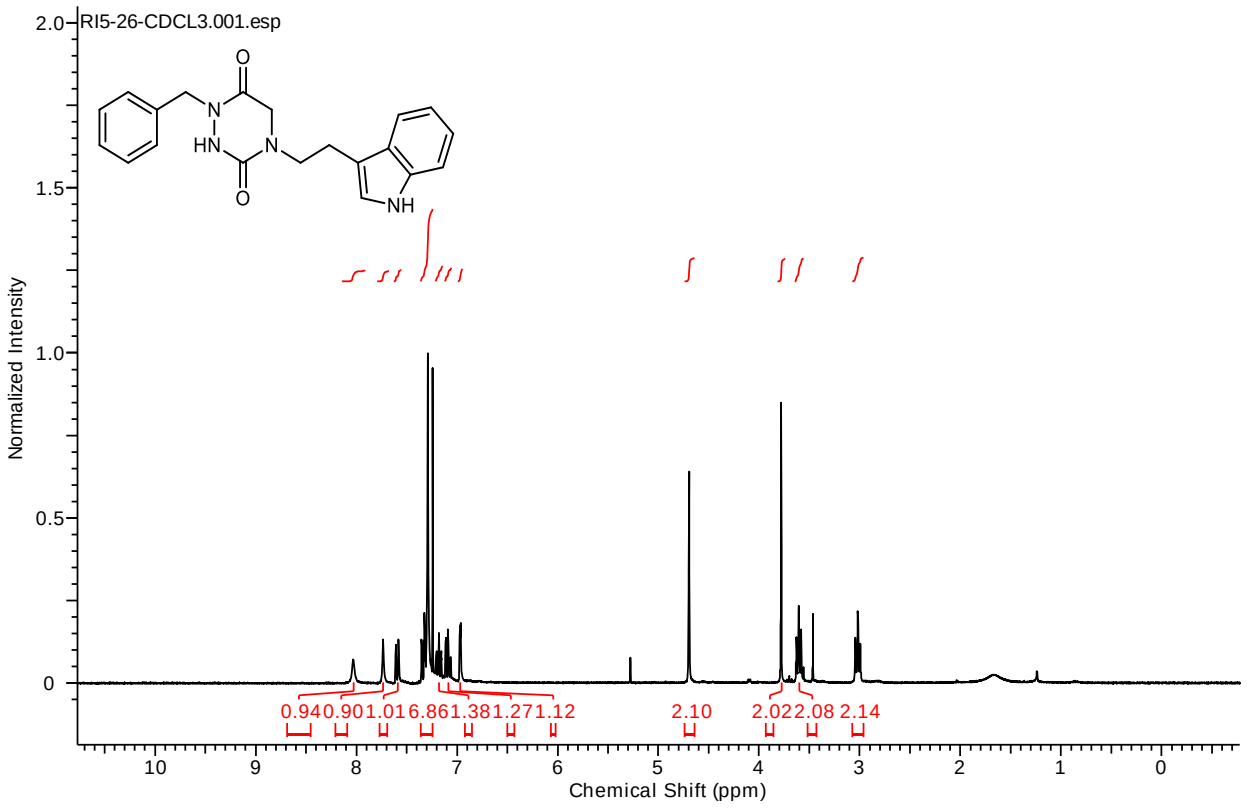

RI4-176-C.002.esp
Normalized Intensity
Chemical Shift (ppm)
160.09
156.03
133.92
128.92
128.38
60.49
50.28
49.54
49.39

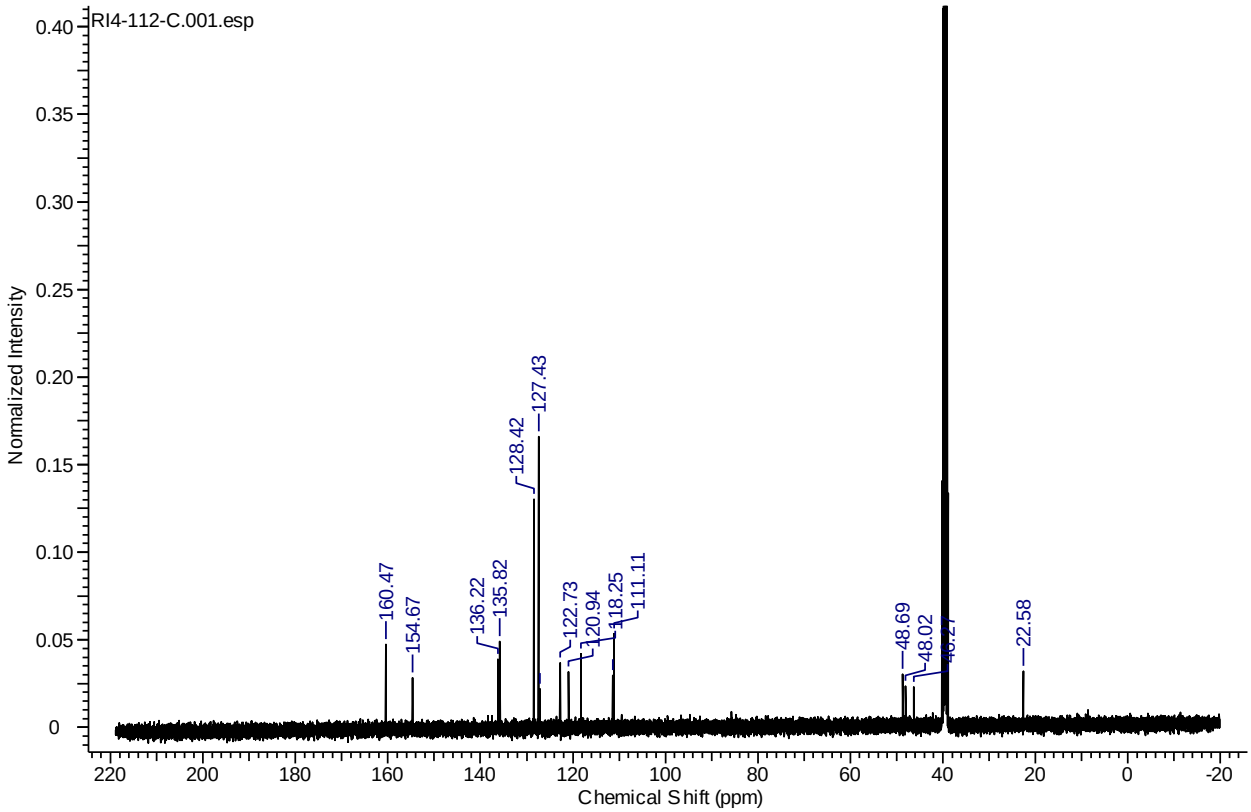

RI4-179-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
5.17
2.03
1.02
2.00
7.82
OMe
OMe
N
HN
N
O
O

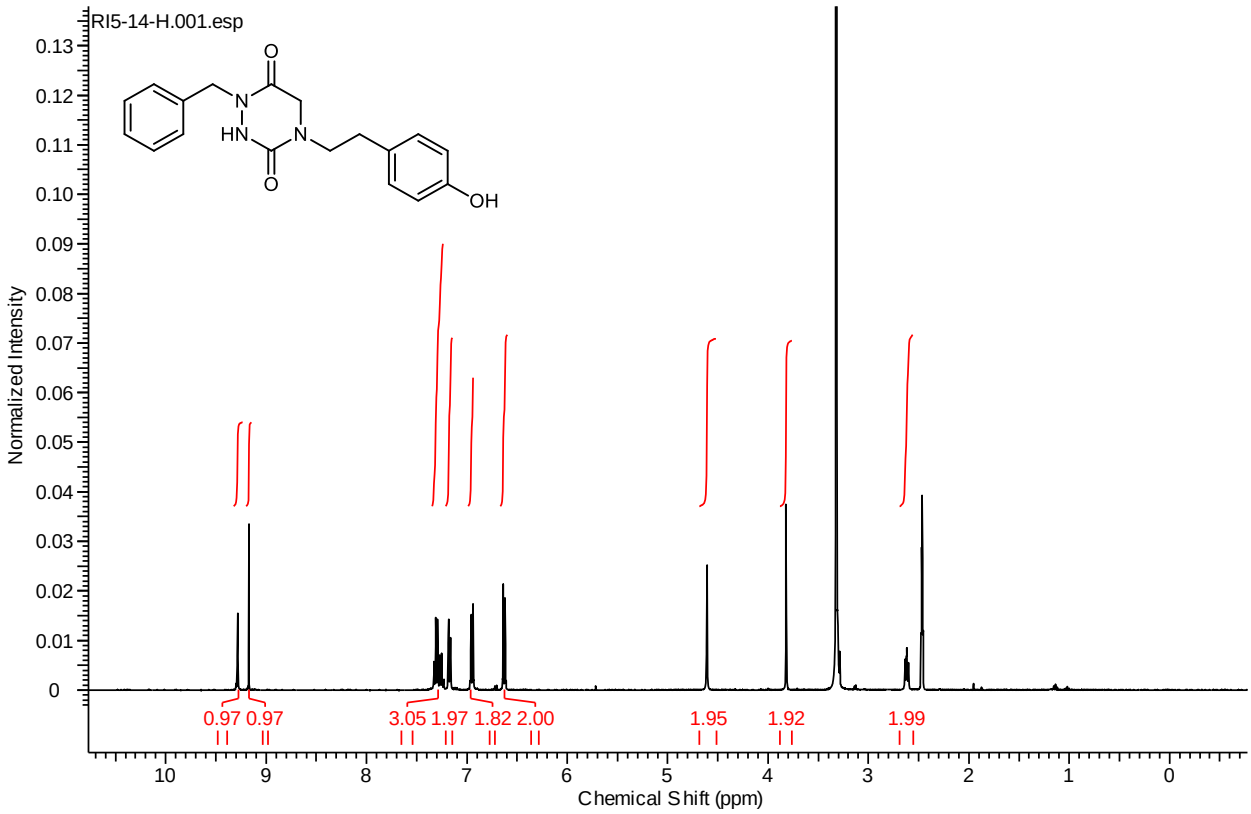

RI4-179-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
160.49
154.81
135.77
128.44
127.43
101.91
53.63
49.89
48.09

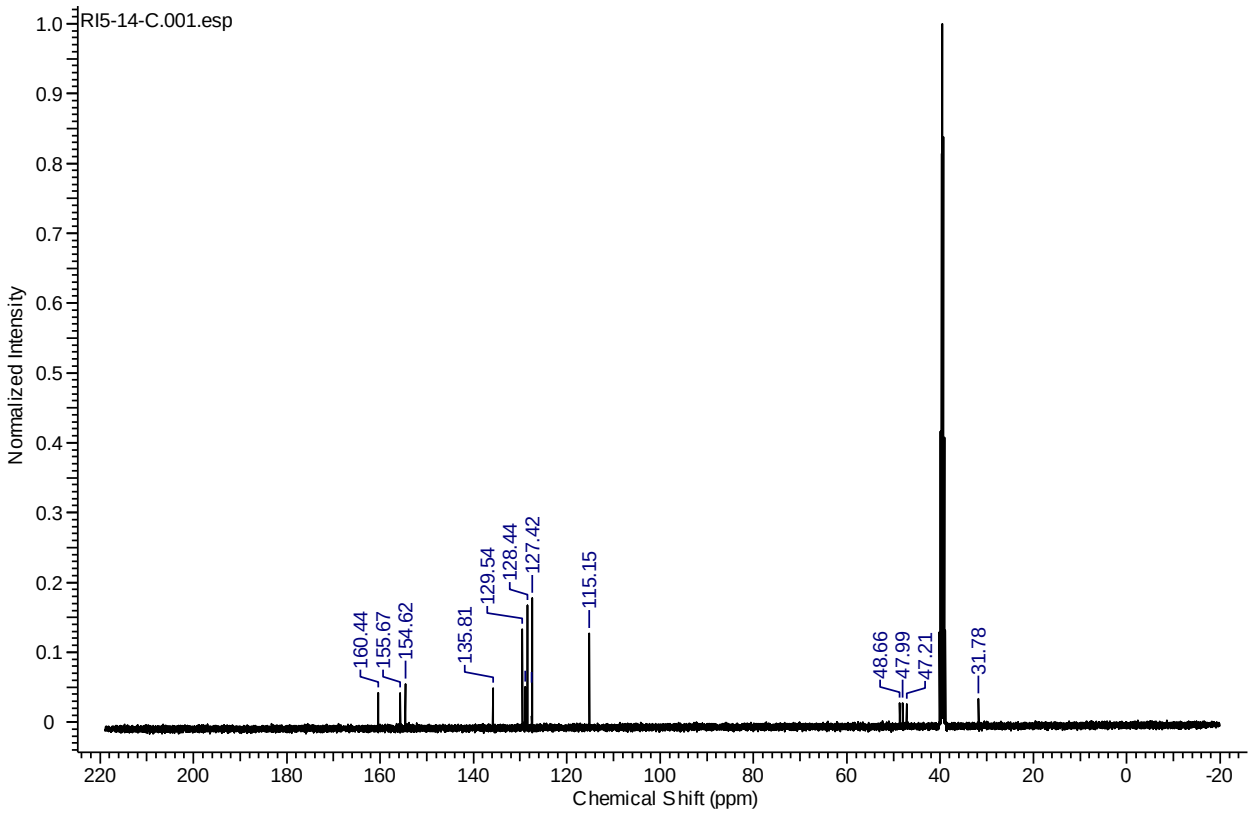

RI4-172-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.99
5.04
0.82
2.00
1.97
4.10
9.33

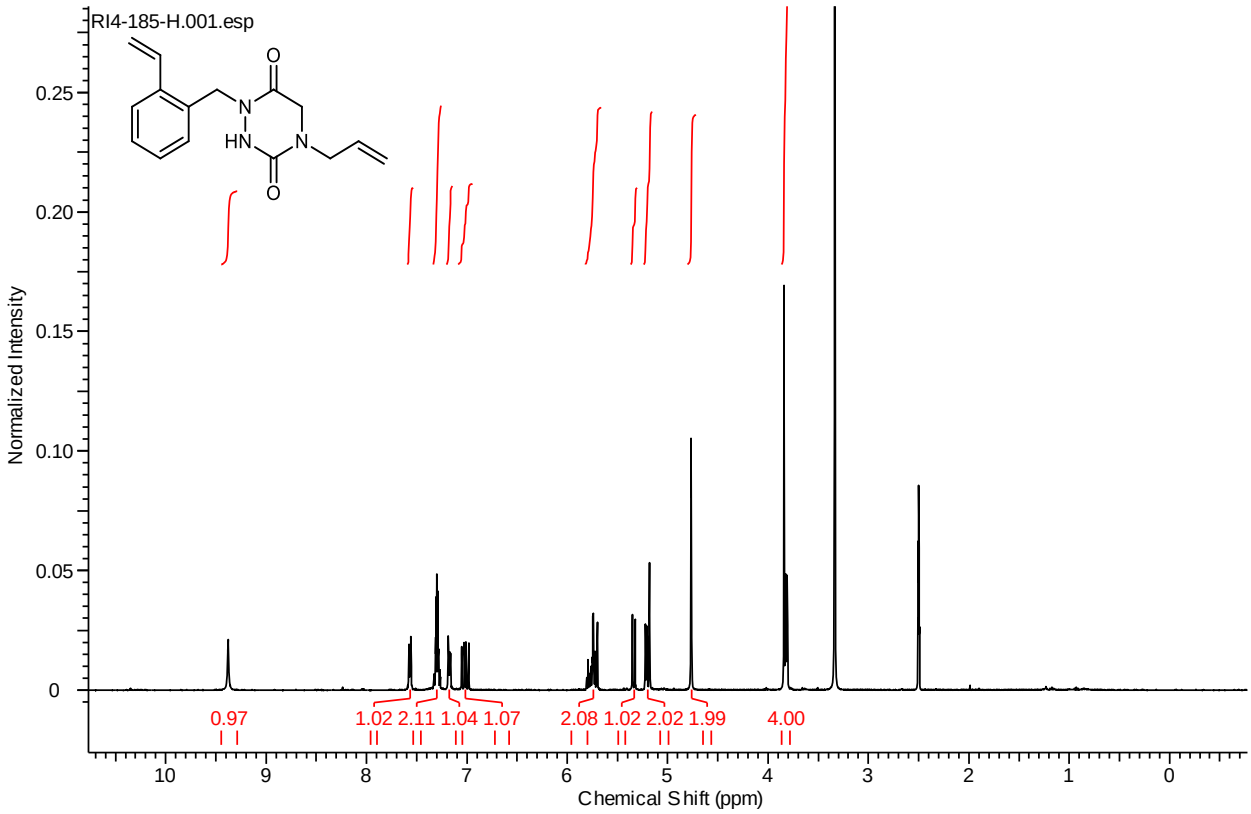

RI4-172-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
160.06
155.40
133.72
129.02
128.47
49.88
49.61
46.56
38.48
28.34

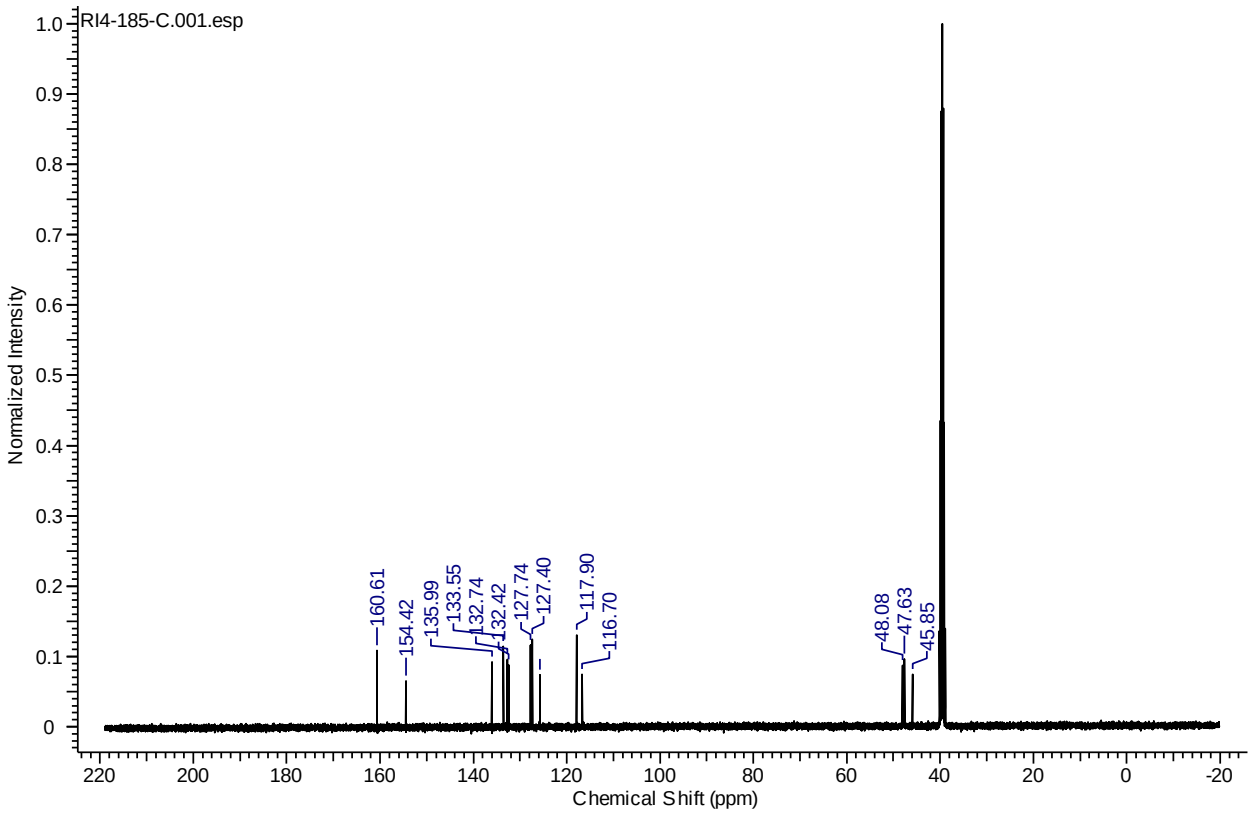

RI5-26-CDCL3.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.94 0.90 1.01 6.86 1.38 1.27 1.12
2.10
2.02 2.08 2.14

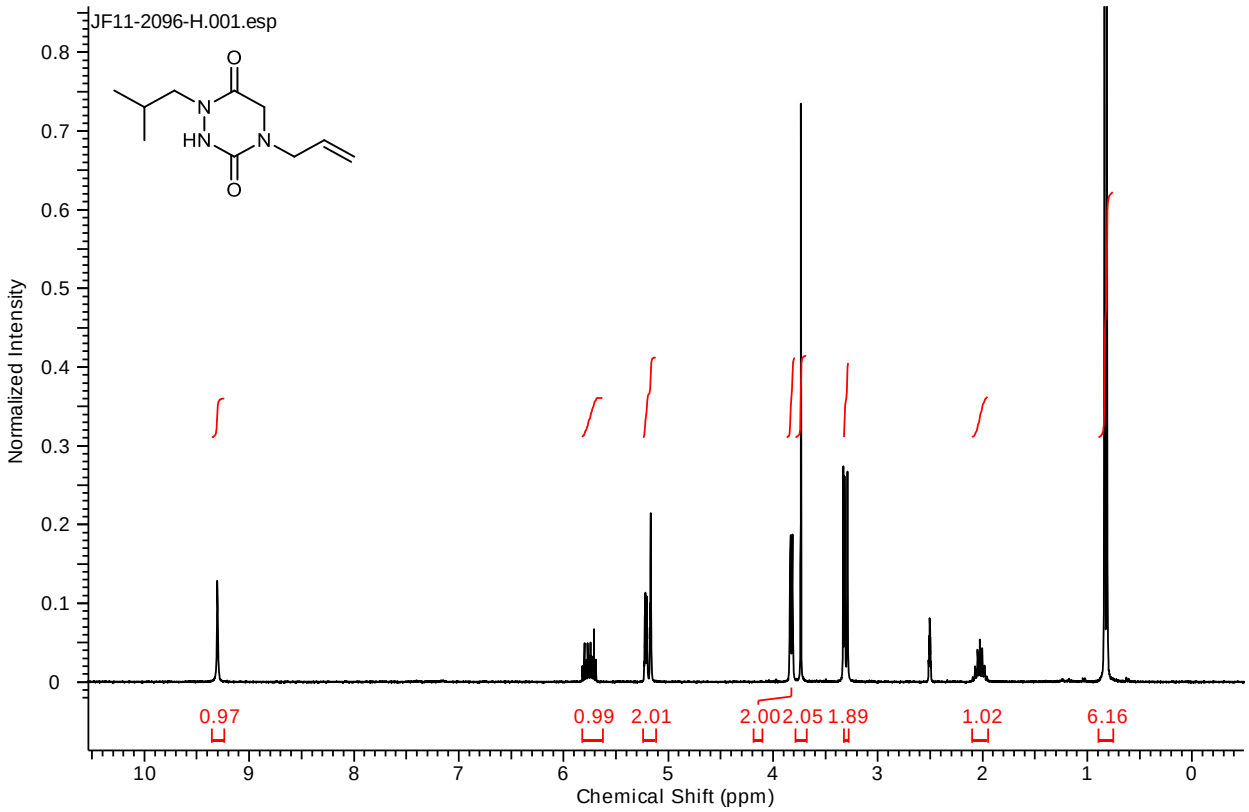

RI4-112-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
160.47
154.67
136.22
135.82
128.42
127.43
122.73
120.94
118.25
111.11
48.69
48.02
22.58

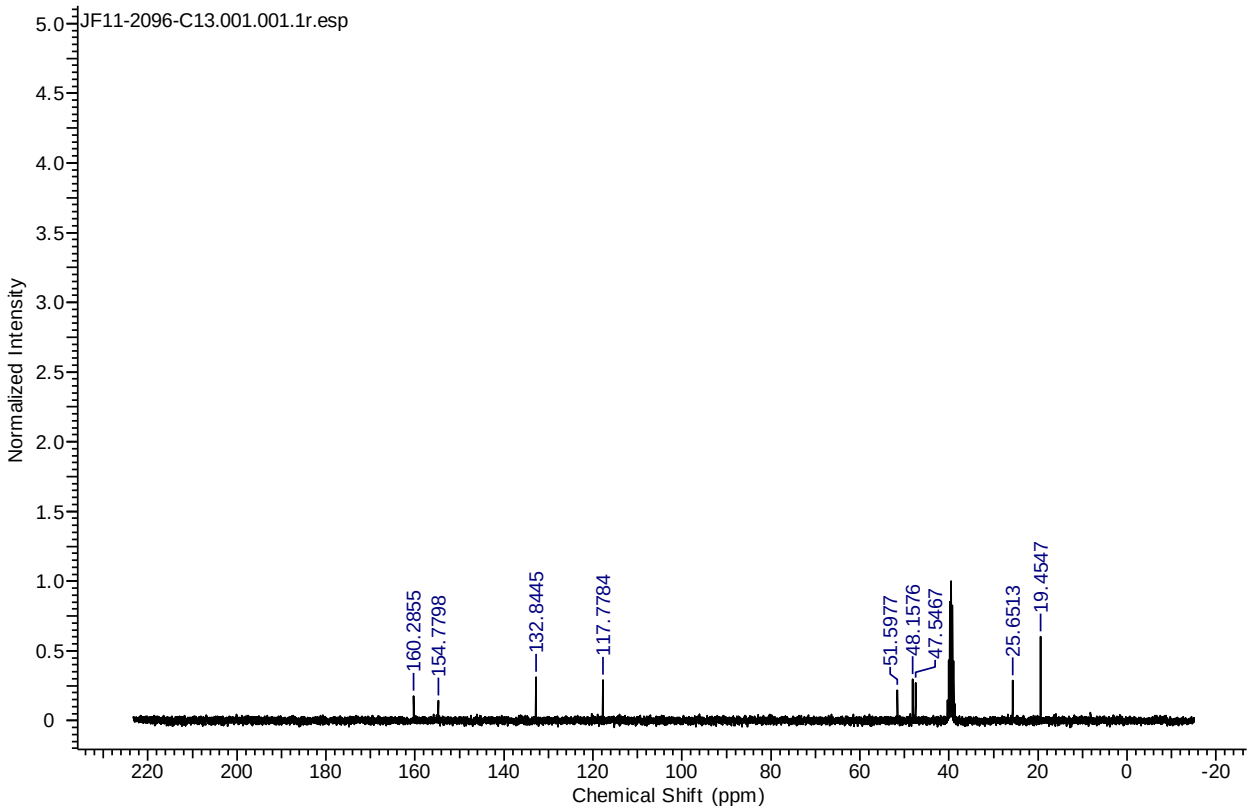

RI5-14-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.97 0.97
3.05 1.97 1.82 2.00
1.95
1.92
1.99
OH

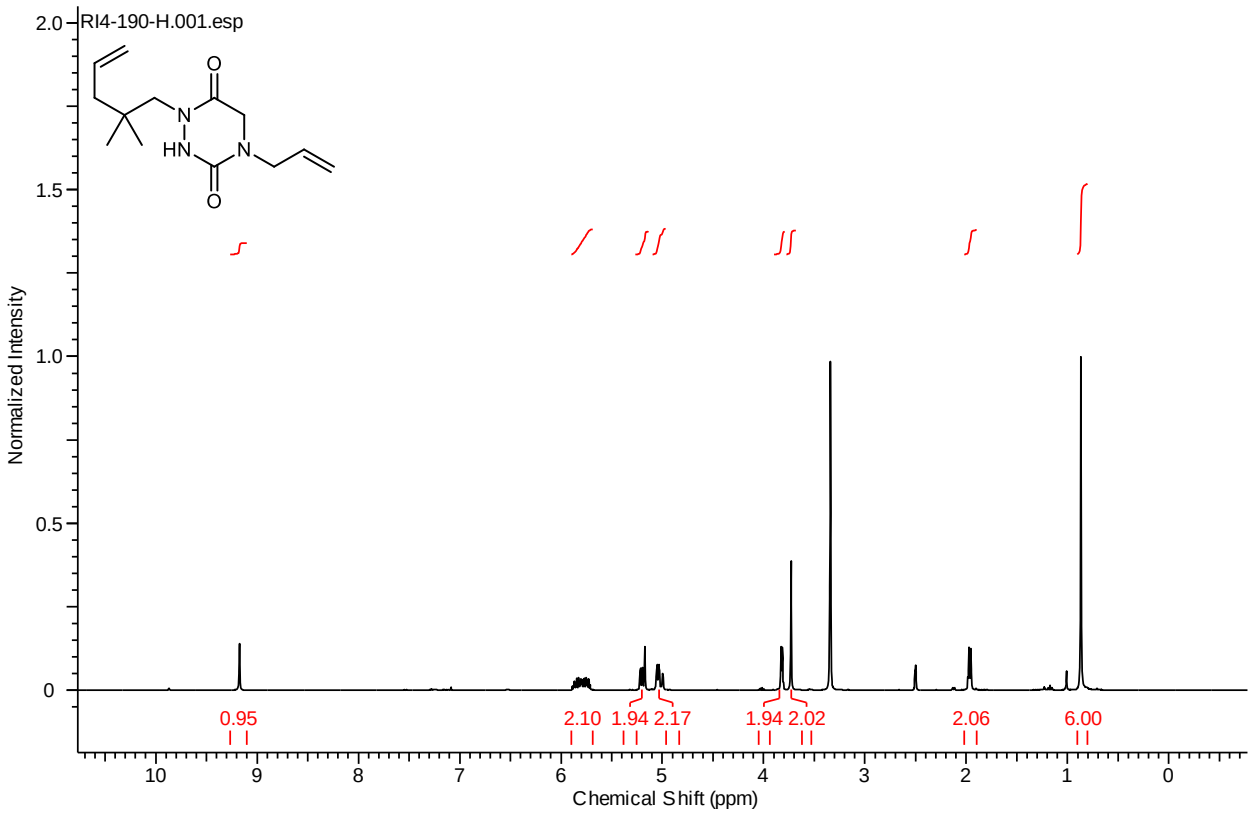

RI5-14-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
160.44
155.67
154.62
135.81
129.54
128.44
127.42
115.15
48.66
47.99
47.21
31.78

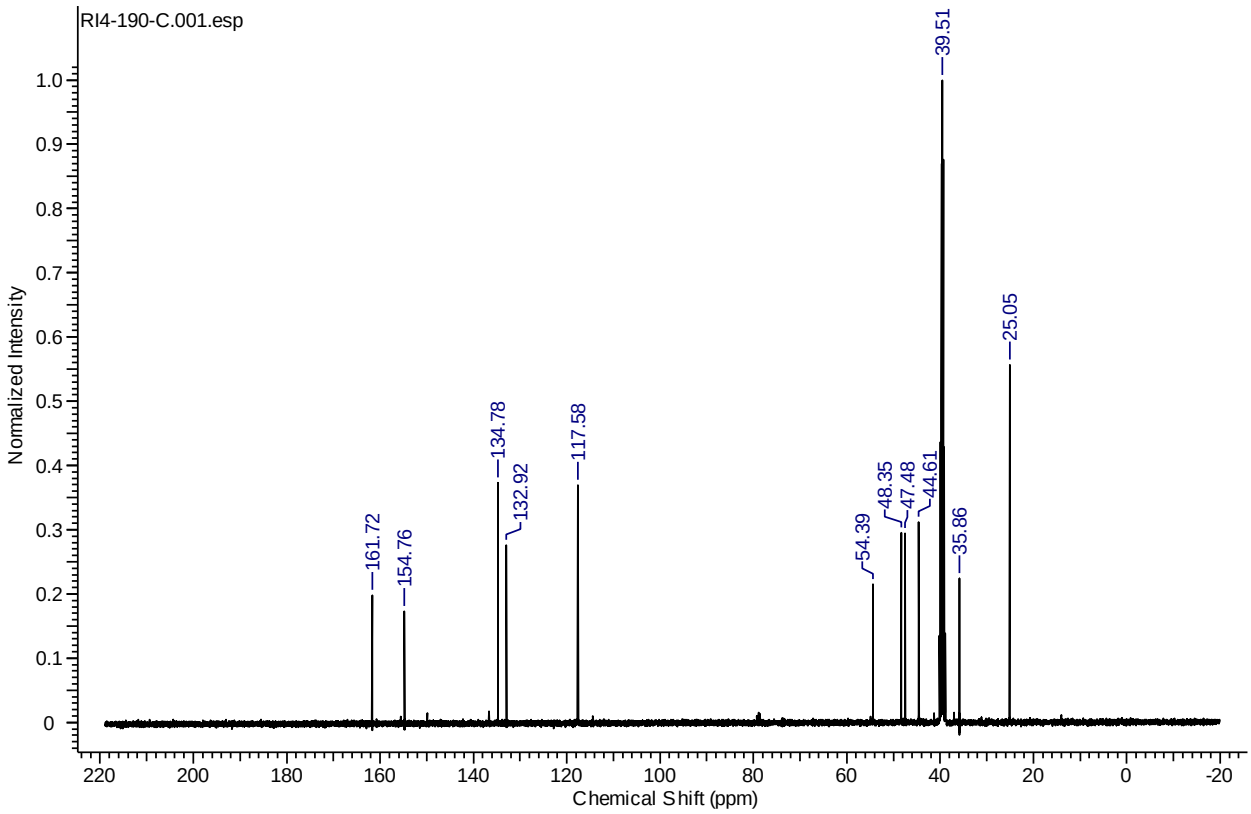

RI4-185-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.97
1.02 2.11 1.04 1.07
2.08 1.02 2.02 1.99
4.00

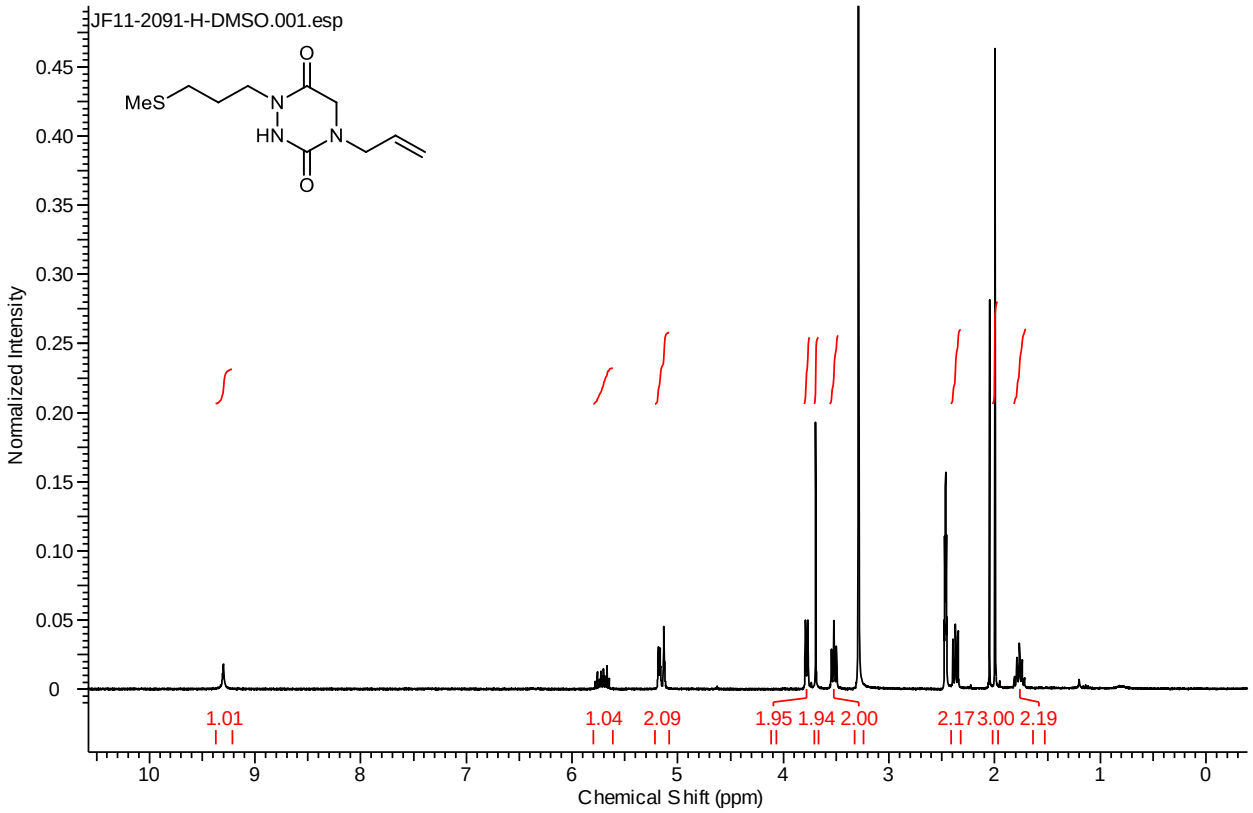

RI4-185-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
160.61
154.42
135.99
133.55
132.74
132.42
127.74
127.40
117.90
116.70
48.08
47.63
45.85

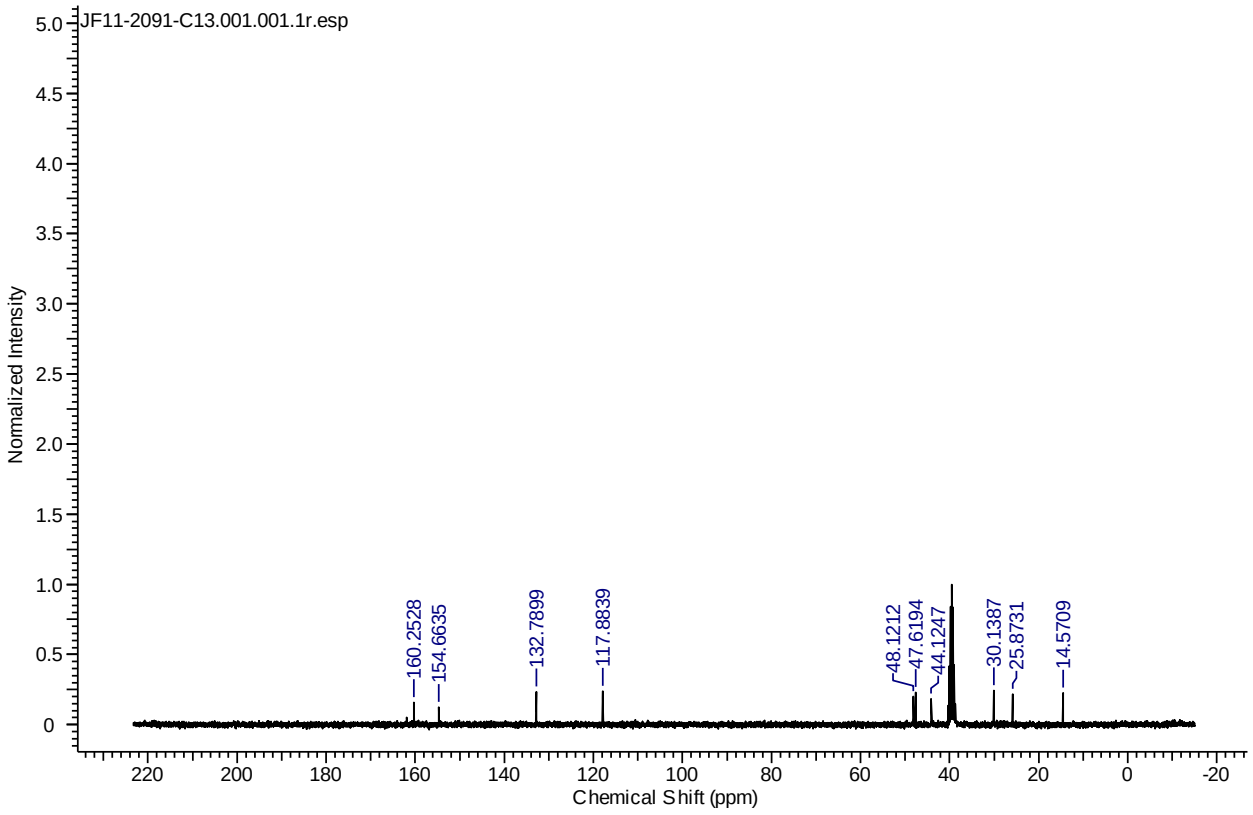

JF11-2096-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.97
0.99
2.01
2.00
2.05
1.89
1.02
6.16

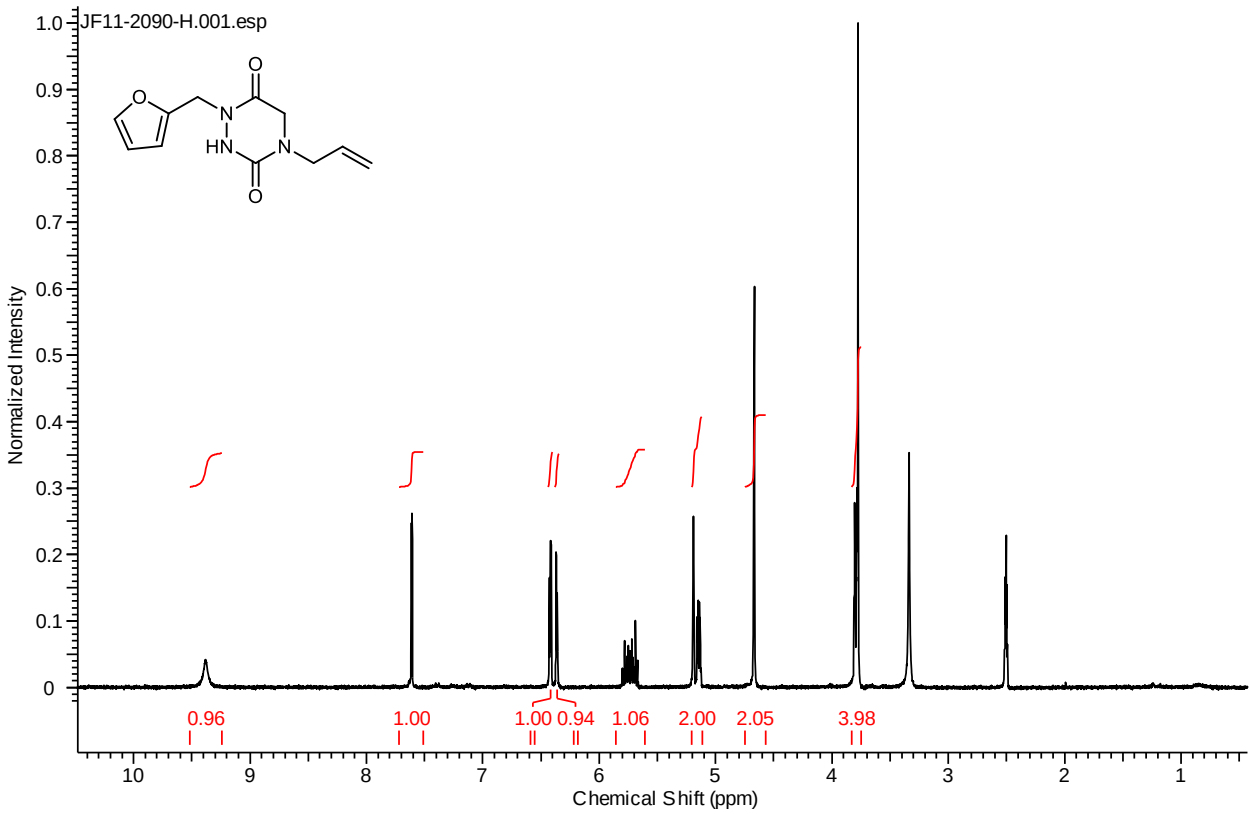

JF11-2096-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
160.2855
154.7798
132.8445
117.7784
51.5977
48.1576
47.5467
25.6513
19.4547

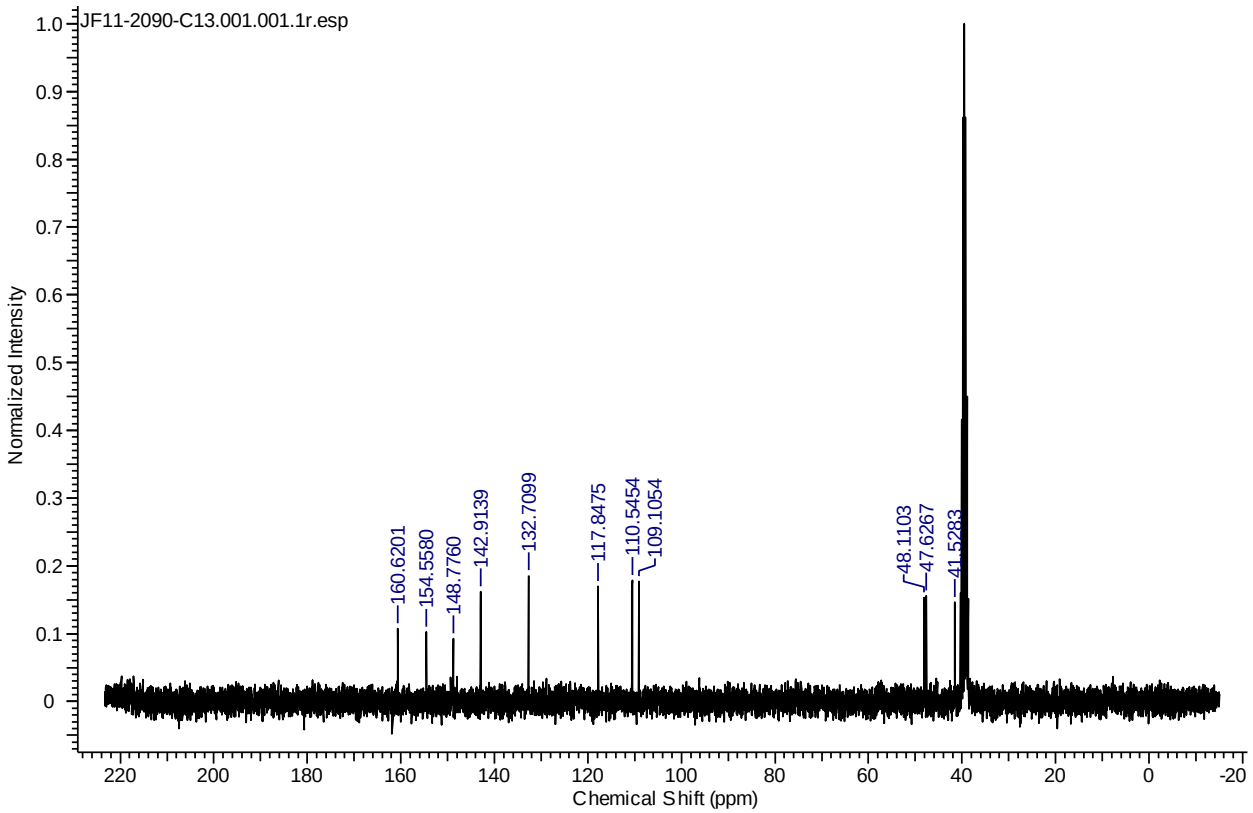

RI4-190-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.95
2.10
1.94
2.17
1.94
2.02
2.06
6.00

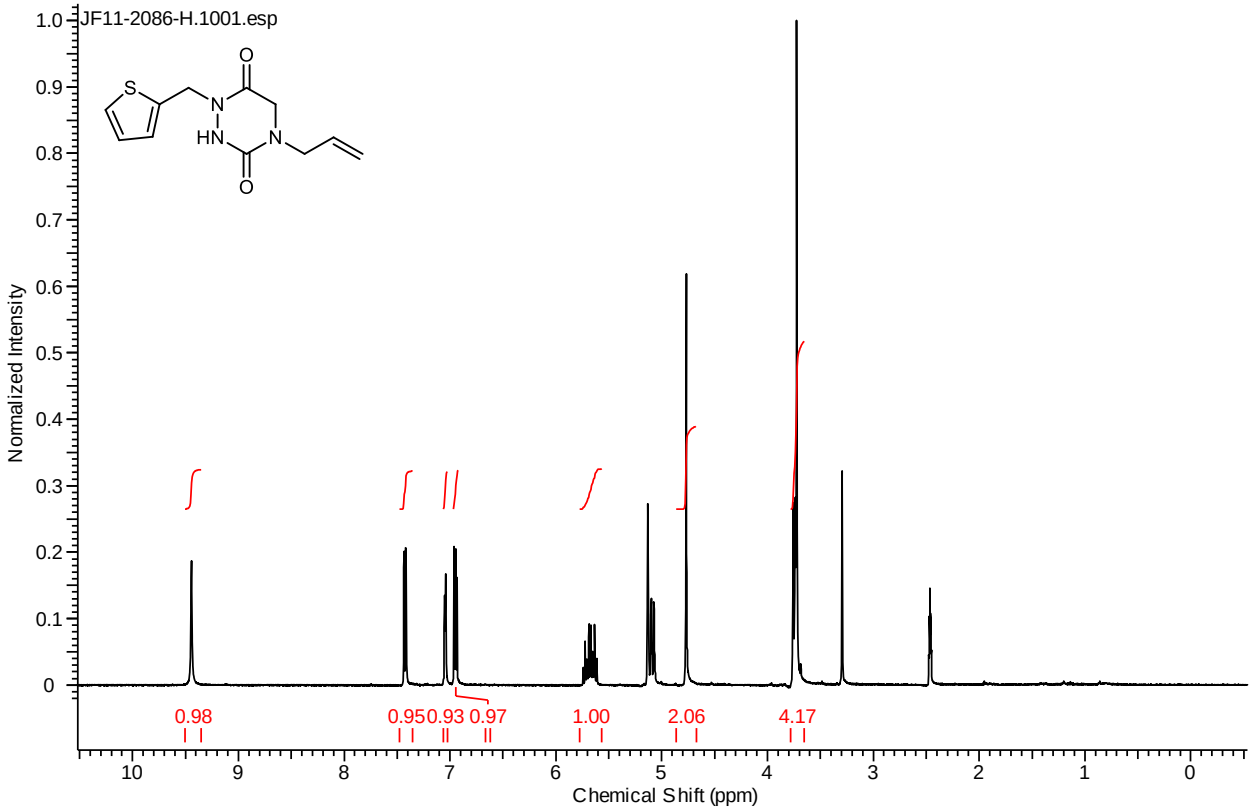

RI4-190-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
161.72
154.76
134.78
132.92
117.58
54.39
48.35
47.48
44.61
39.51
35.86
25.05

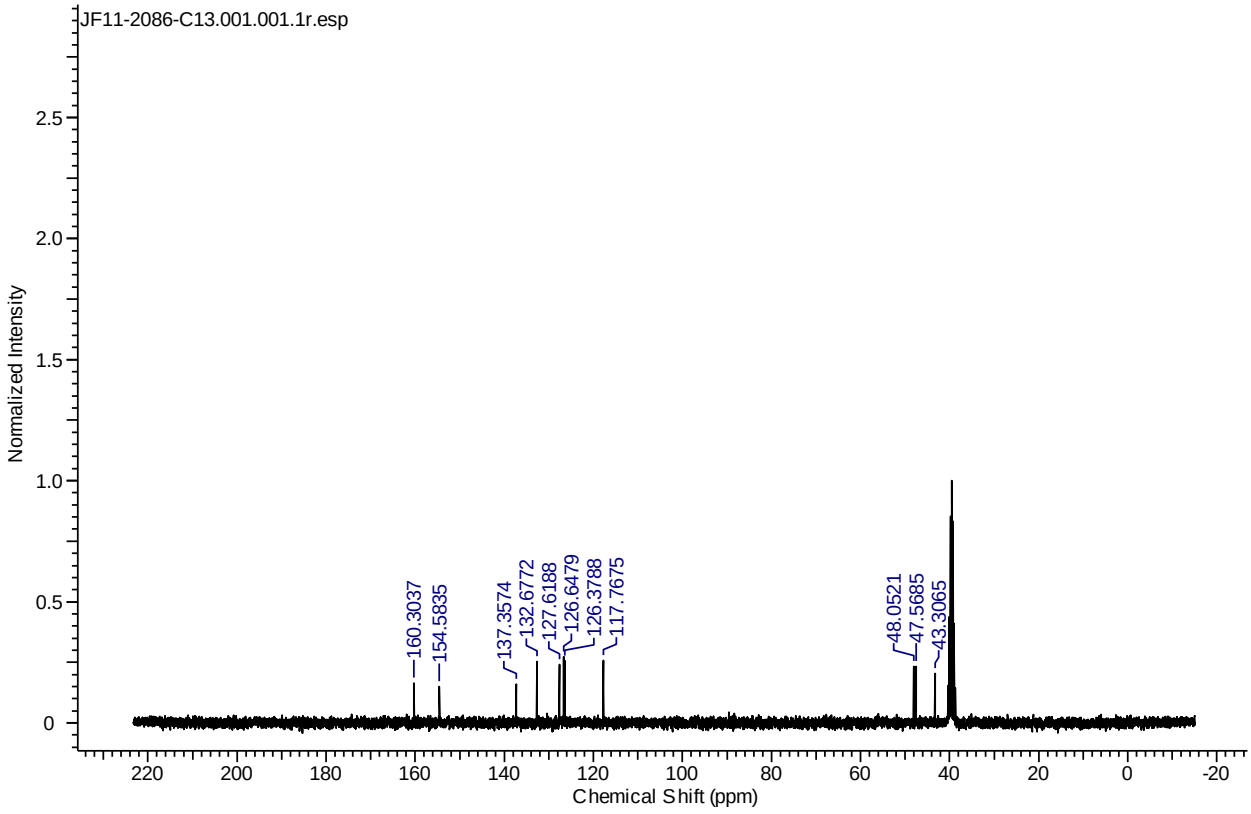

JF11-2091-H-DMSO.001.esp
MeS
N
HN
N
O
O
O
Normalized Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
1.01
1.04
2.09
1.95
1.94
2.00
2.17
3.00
2.19
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

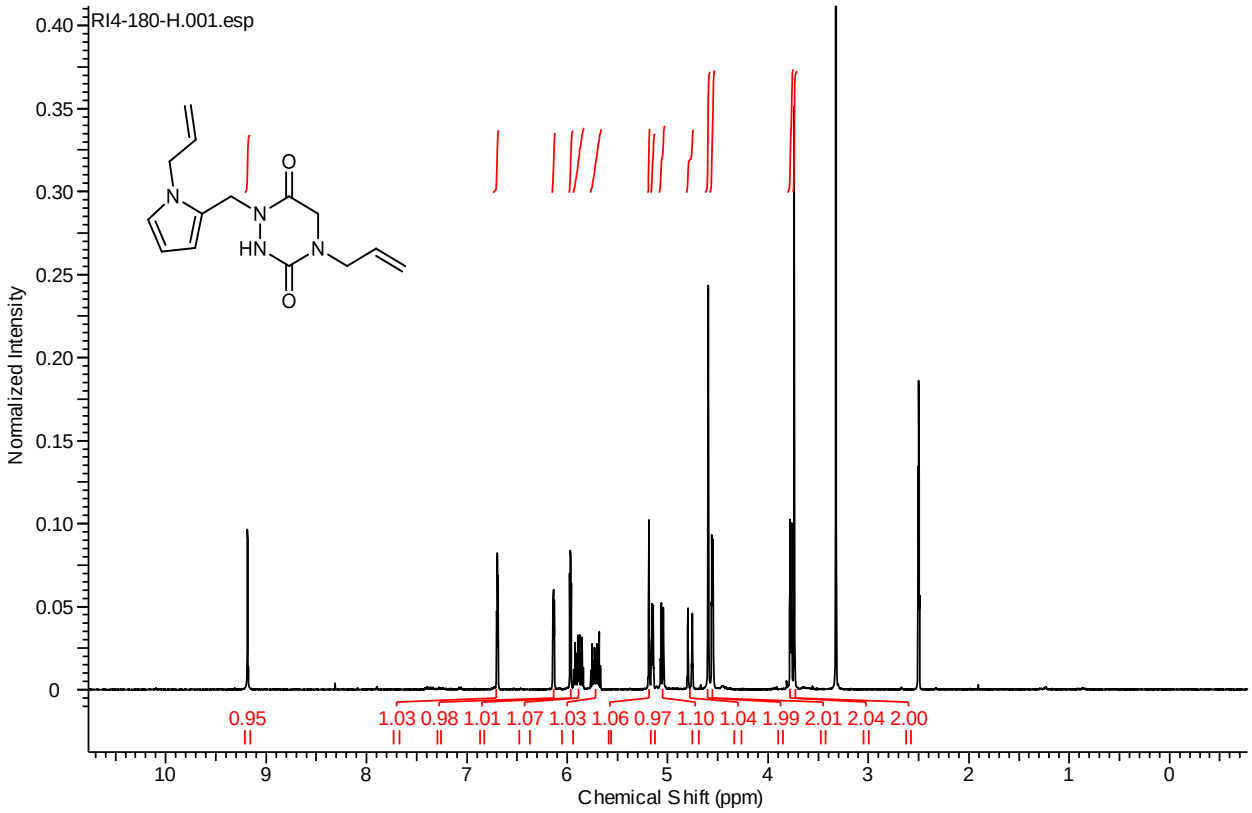

JF11-2091-C13.001.001.1r.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
160.2528
154.6635
132.7899
117.8839
48.1212
47.6194
44.1247
30.1387
25.8731
14.5709
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

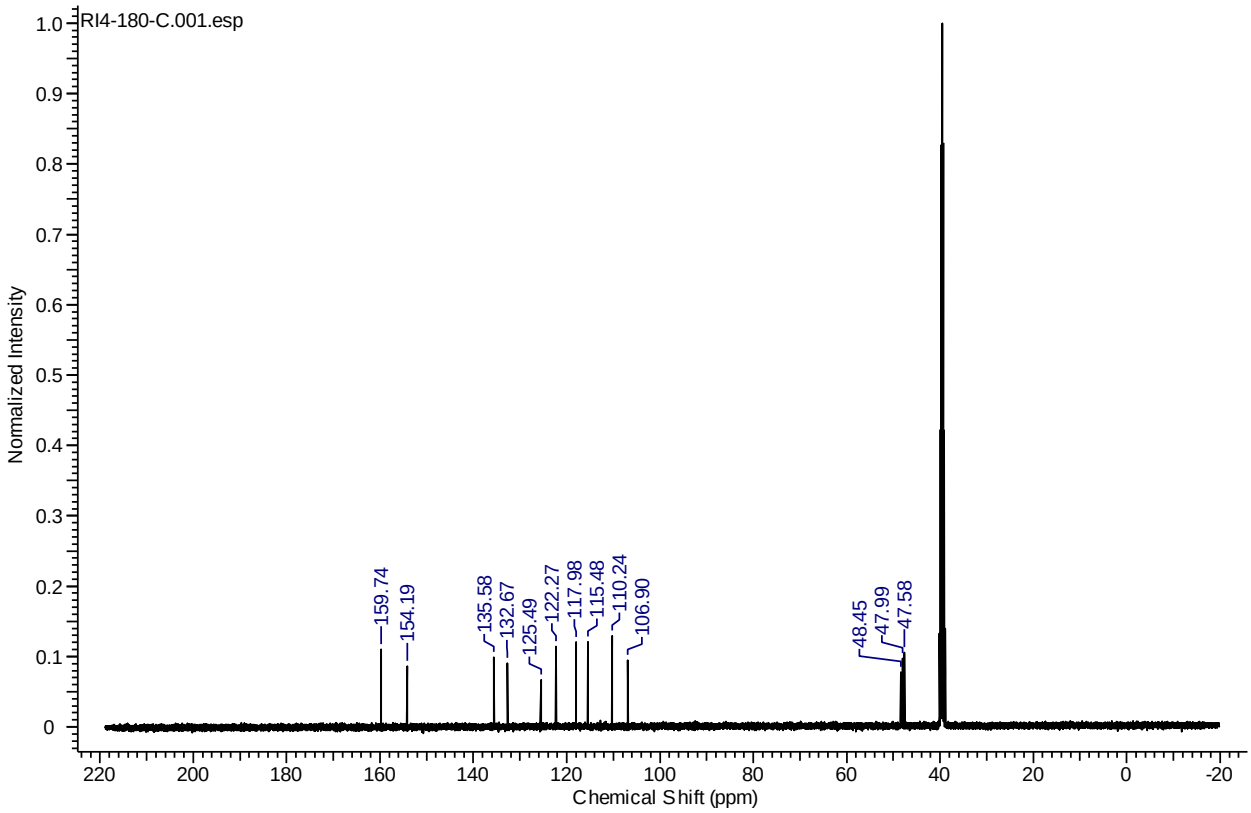

JF11-2090-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.96
1.00
1.00
0.94
1.06
2.00
2.05
3.98

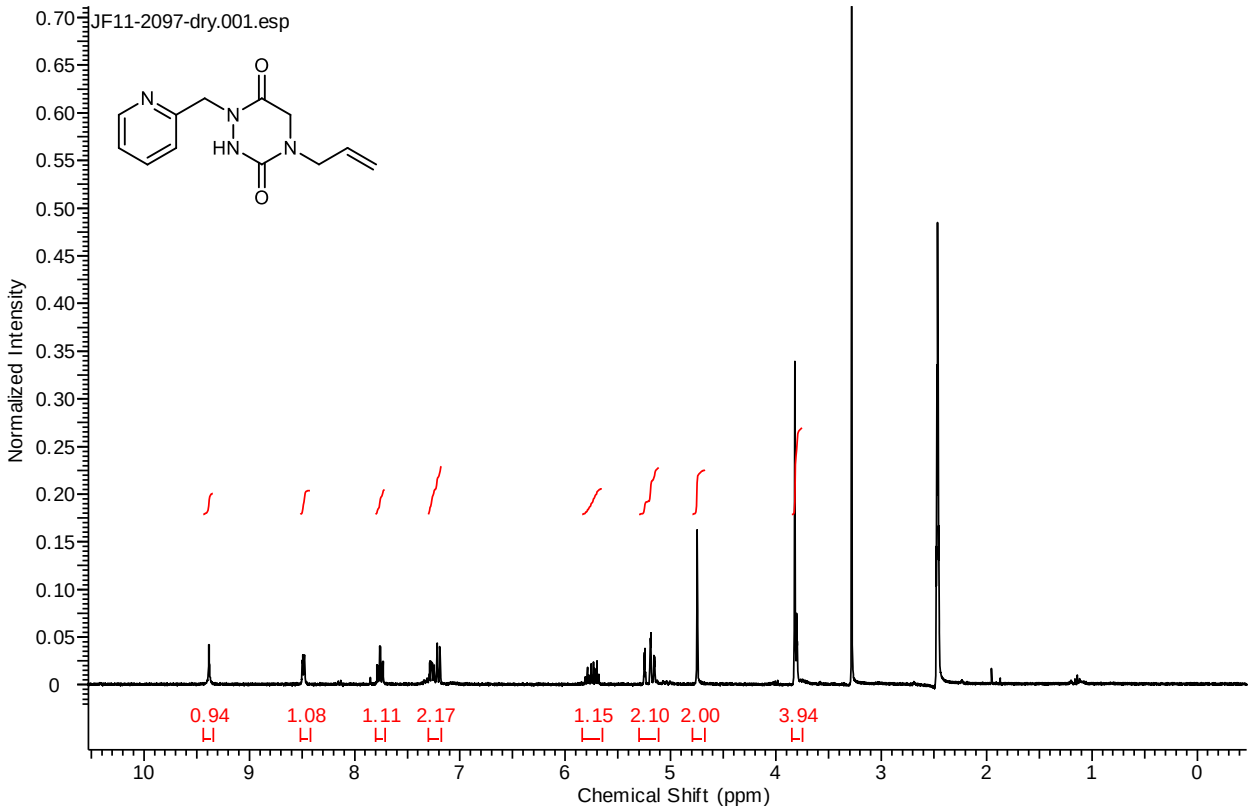

JF11-2090-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
160.6201
154.5580
148.7760
142.9139
132.7099
117.8475
110.5454
109.1054
48.1103
47.6267
41.5283

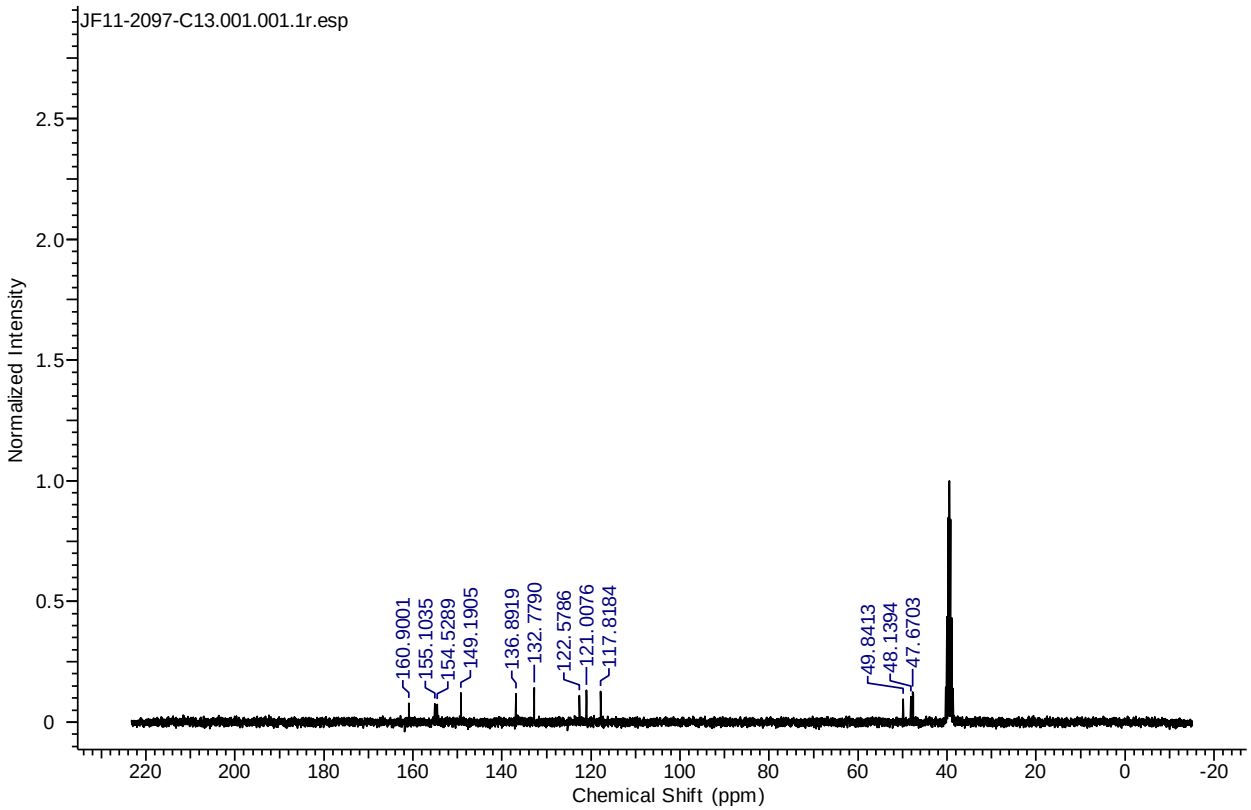

JF11-2086-H.1001.esp
Normalized Intensity
Chemical Shift (ppm)
0.98
0.95
0.93
0.97
1.00
2.06
4.17

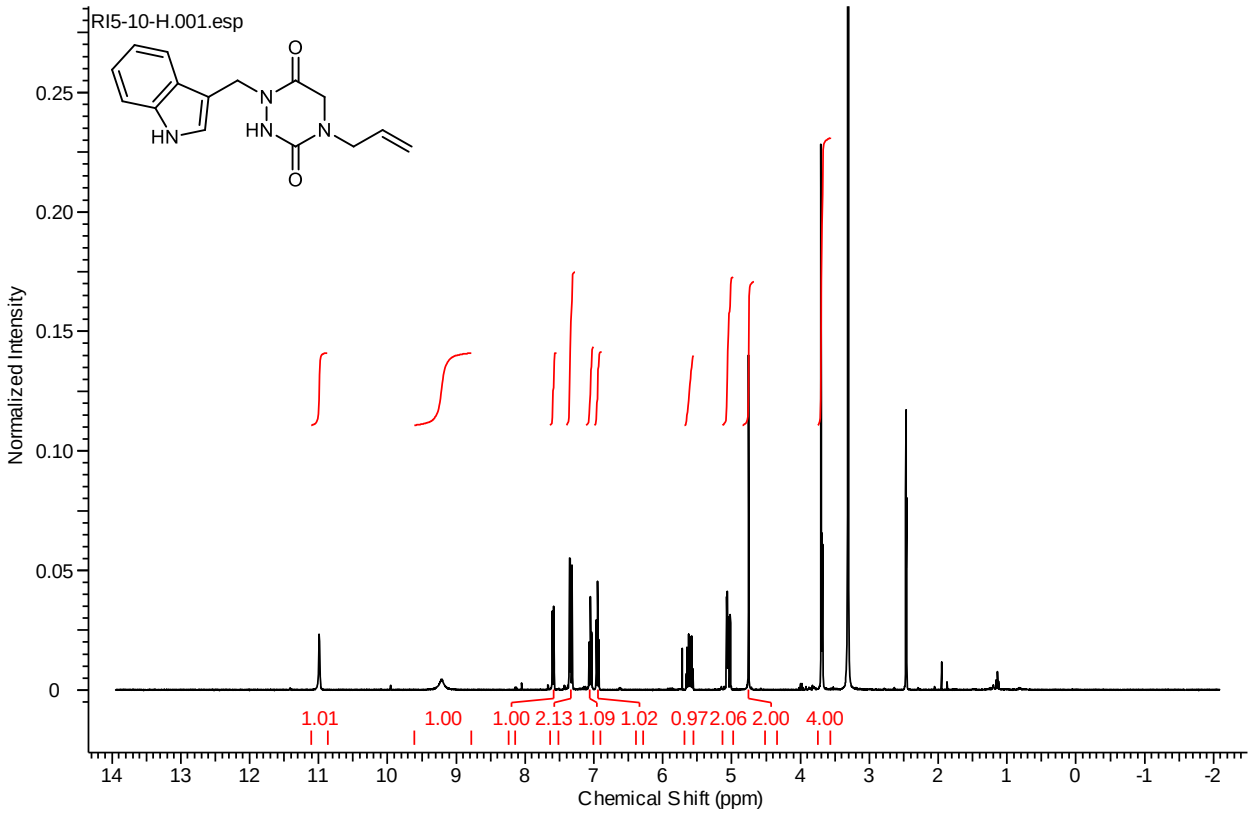

JF11-2086-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
160.3037
154.5835
137.3574
132.6772
127.6188
126.6479
126.3788
117.7675
48.0521
47.5685
43.3065

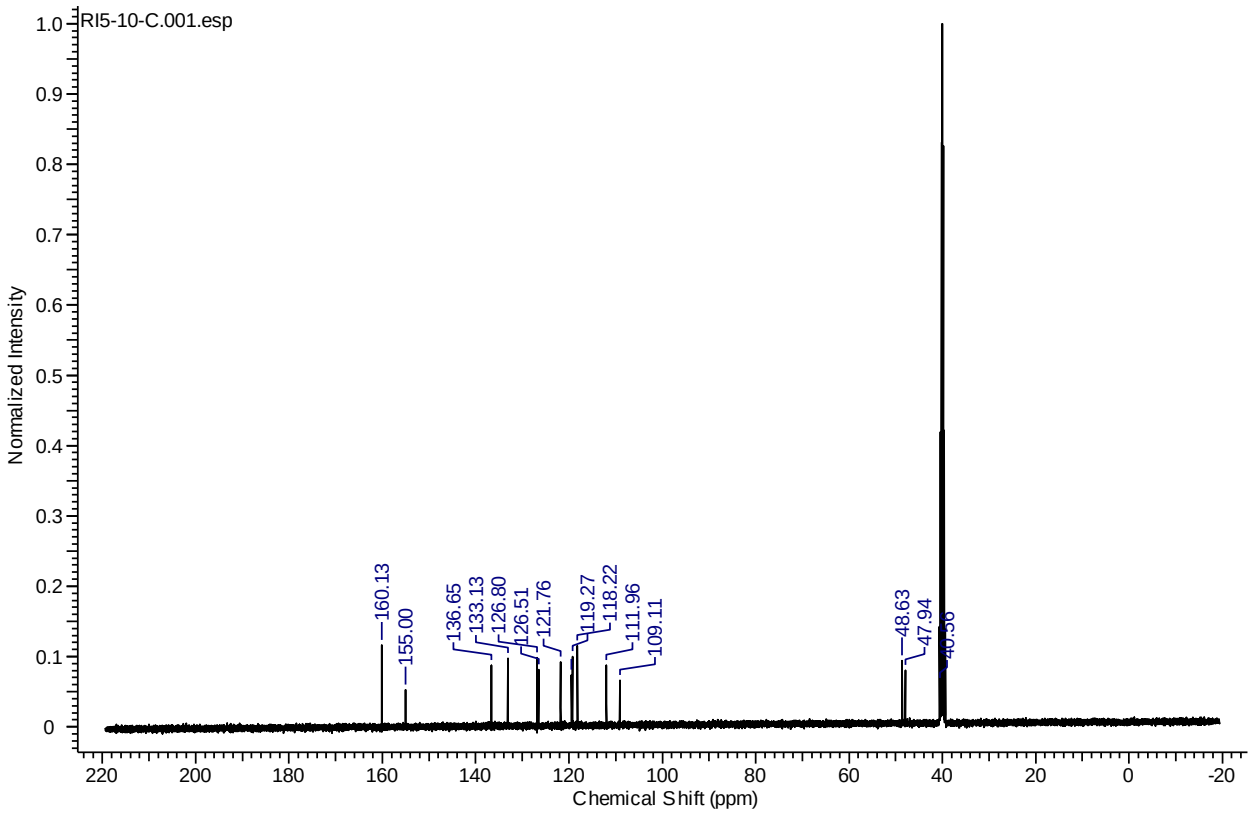

RI4-180-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.95
1.03 0.98 1.01 1.07 1.03 1.06 0.97 1.10 1.04 1.99 2.01 2.04 2.00

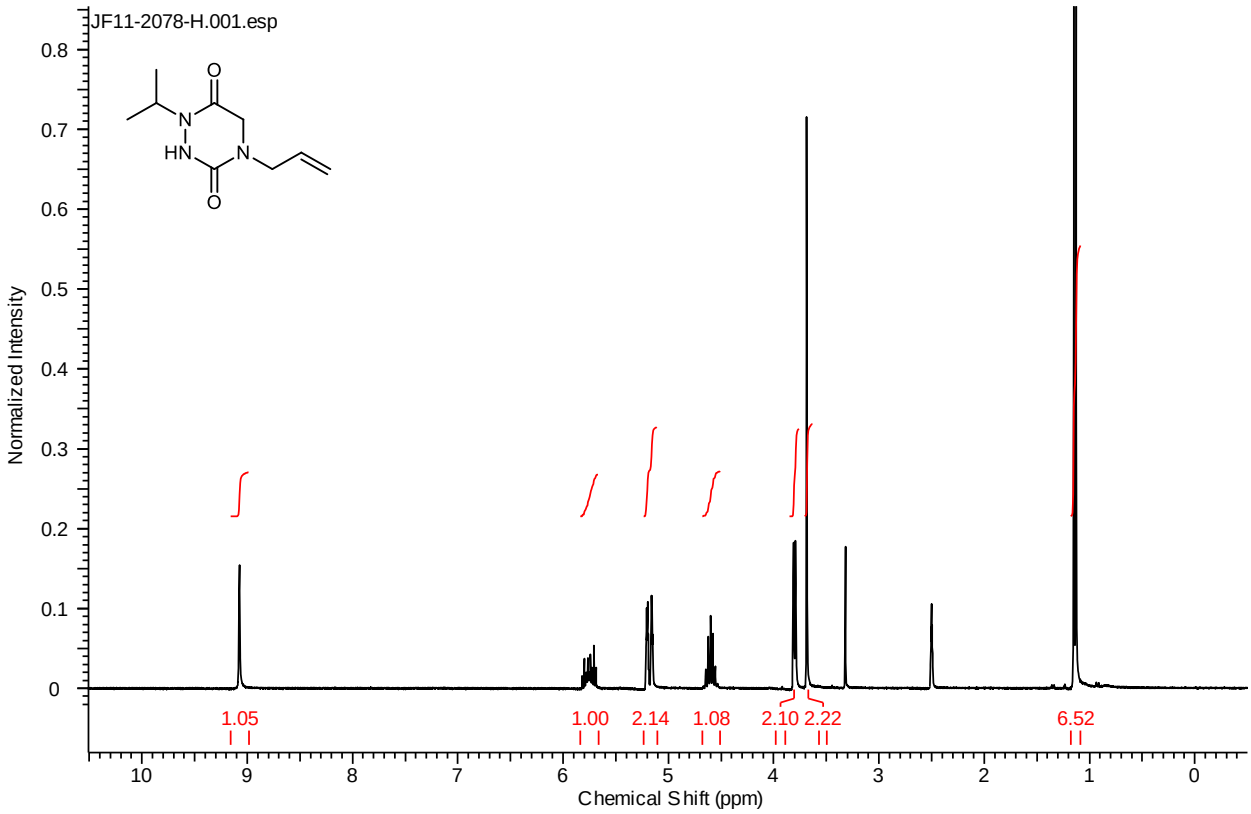

RI4-180-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
159.74
154.19
135.58
132.67
125.49
122.27
117.98
115.48
110.24
106.90
48.45
47.99
47.58

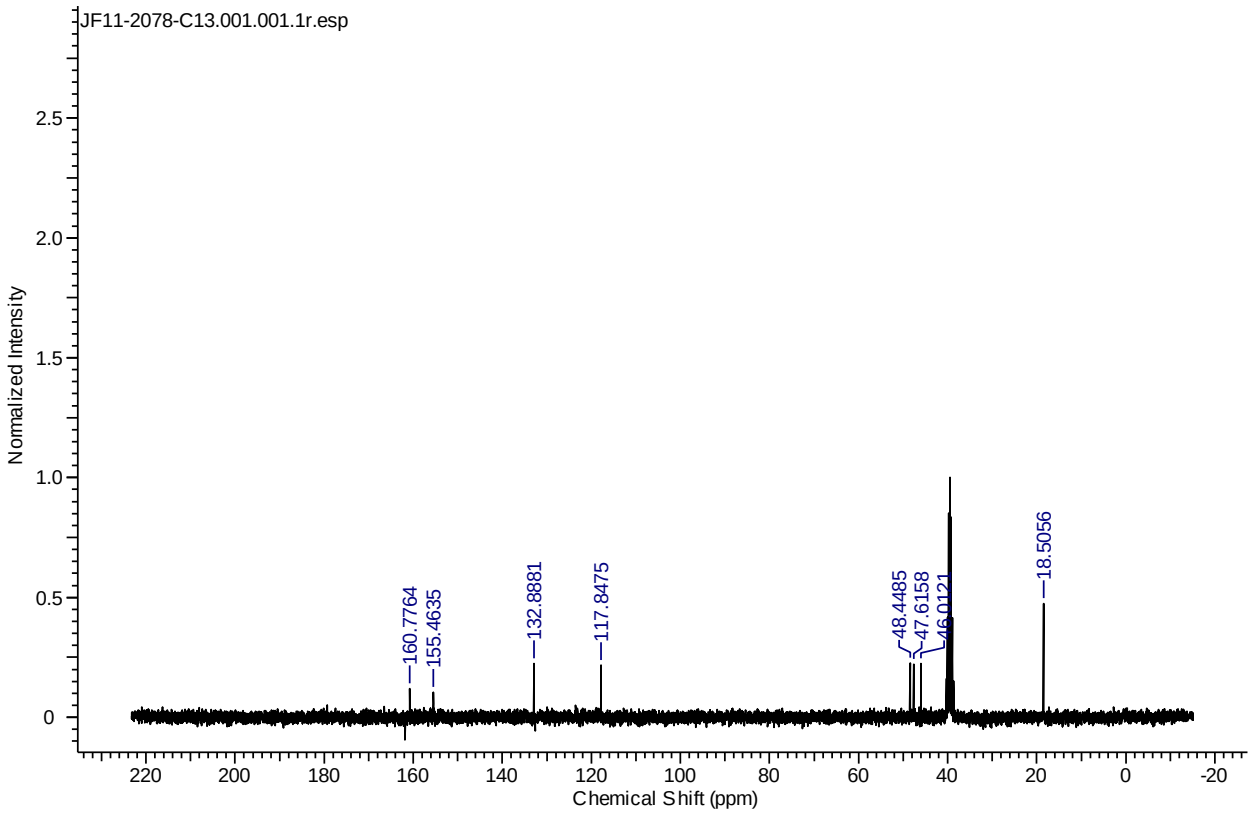

JF11-2097-dry.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.94
1.08
1.11
2.17
1.15
2.10
2.00
3.94

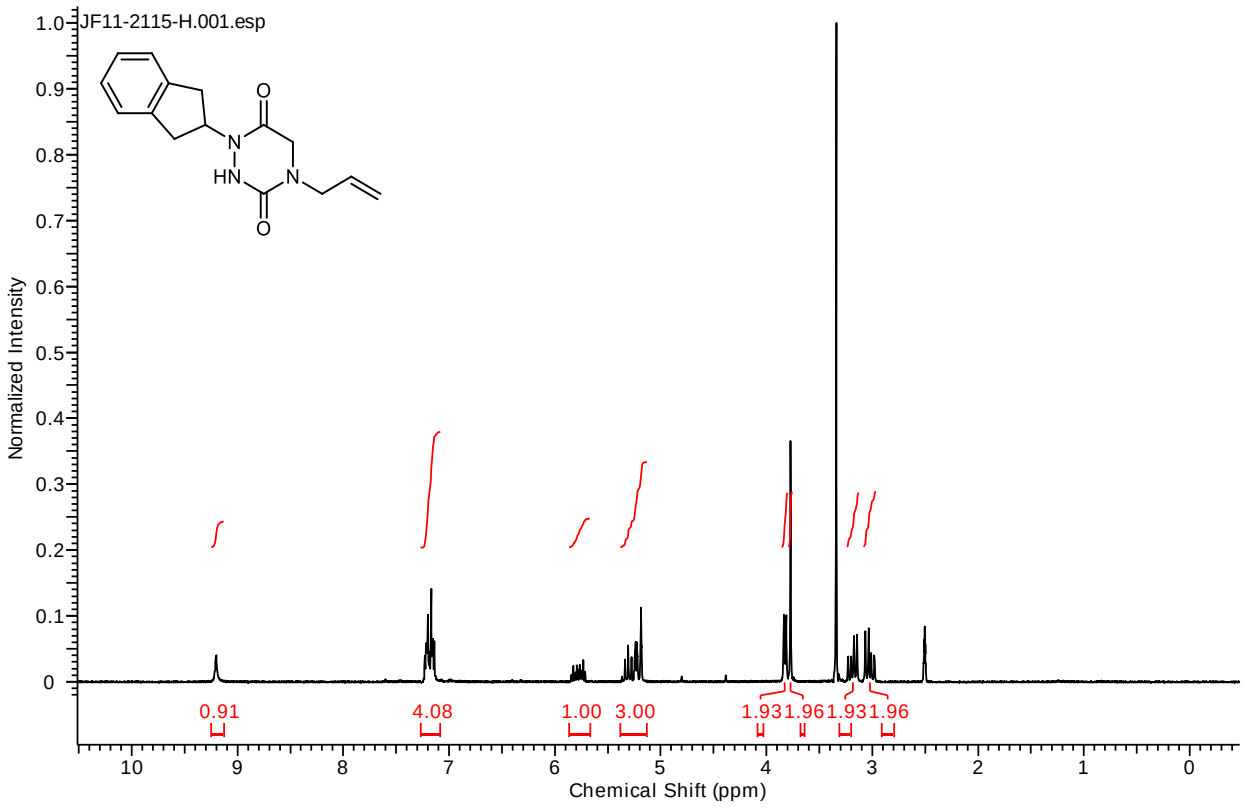

JF11-2097-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
160.9001
155.1035
154.5289
149.1905
136.8919
132.7790
122.5786
121.0076
117.8184
49.8413
48.1394
47.6703

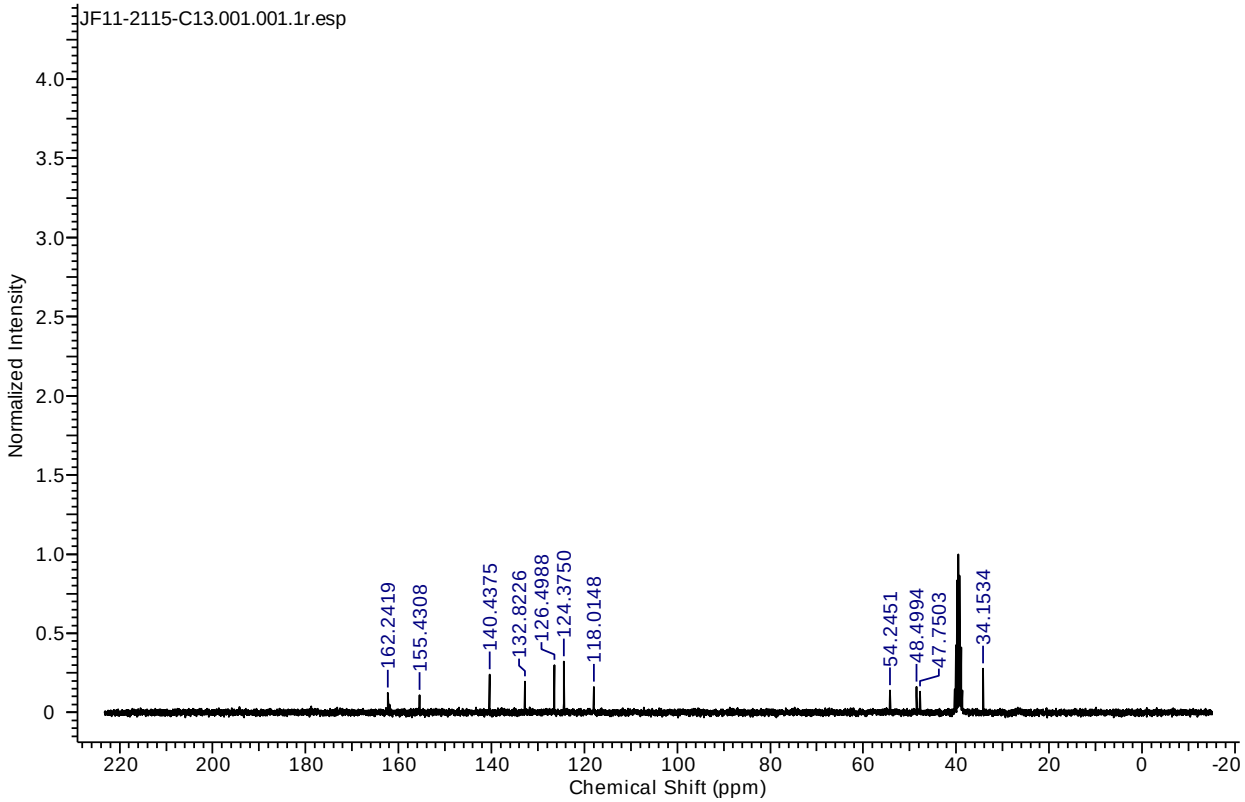

RI5-10-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.01
1.00
1.00
2.13
1.09
1.02
0.97
2.06
2.00
4.00

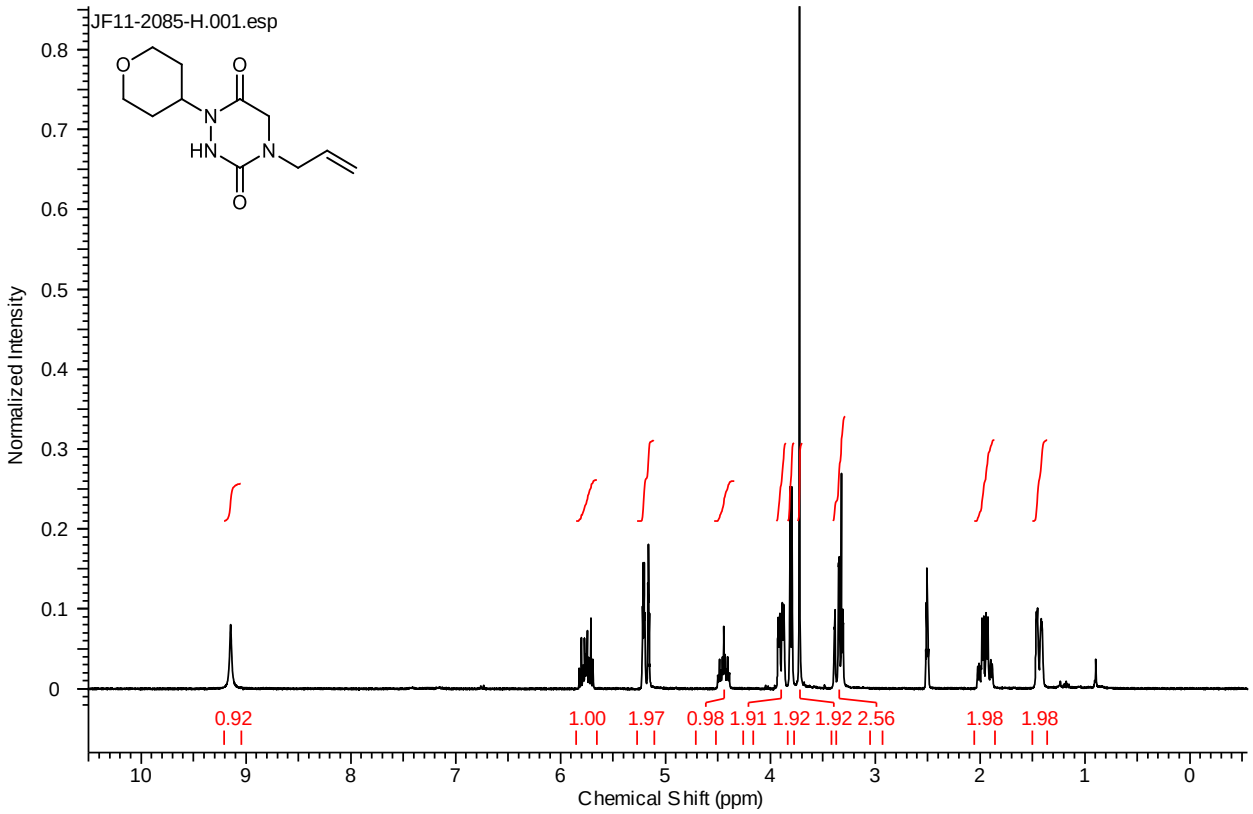

RI5-10-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
160.13
155.00
136.65
133.13
126.80
126.51
121.76
119.27
118.22
111.96
109.11
48.63
47.94
40.56

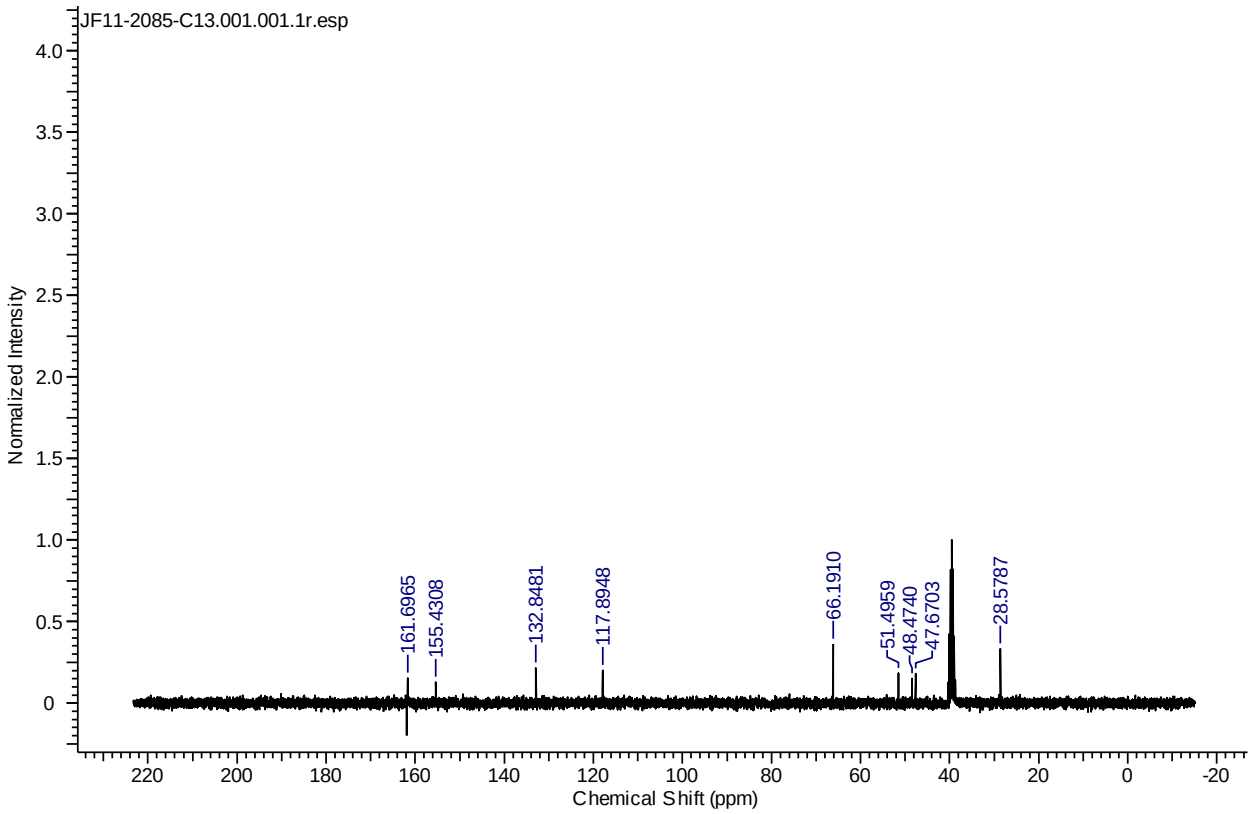

JF11-2078-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.05
1.00
2.14
1.08
2.10
2.22
6.52

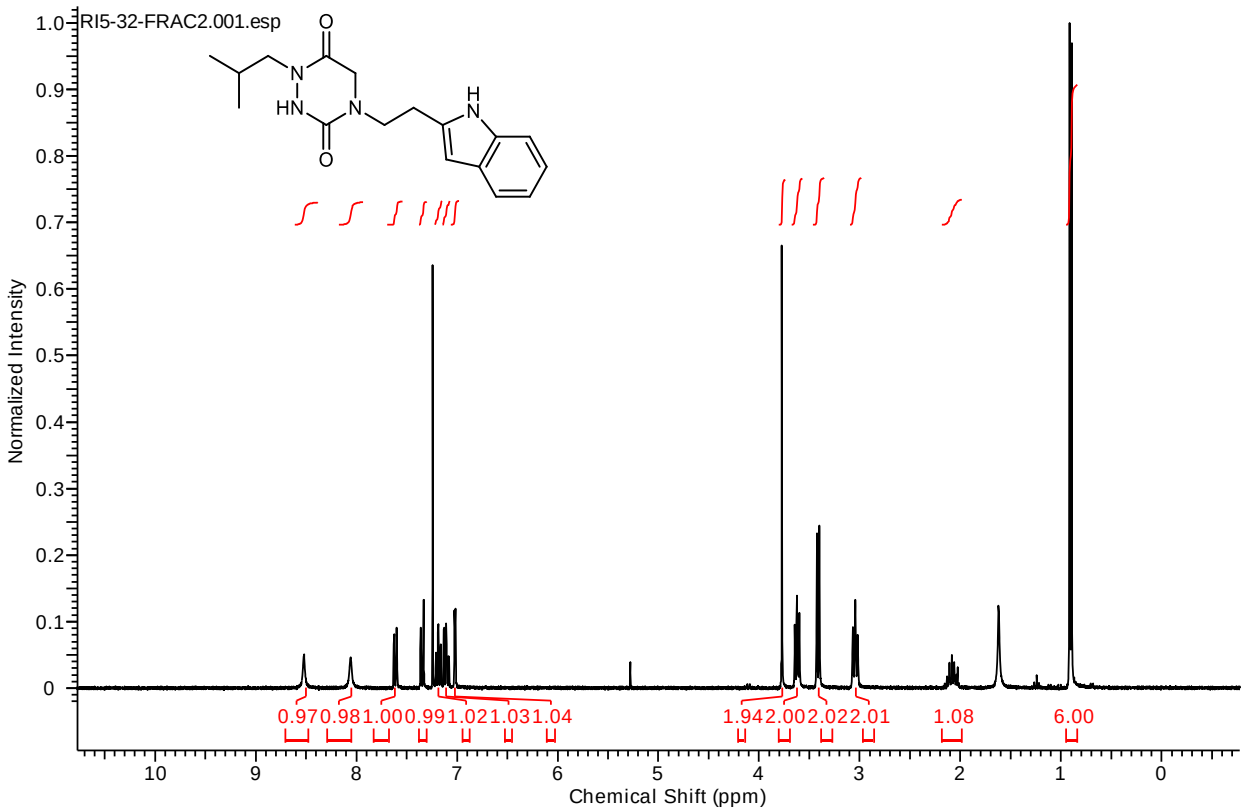

JF11-2078-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
160.7764
155.4635
132.8881
117.8475
48.4485
47.6158
46.0121
18.5056

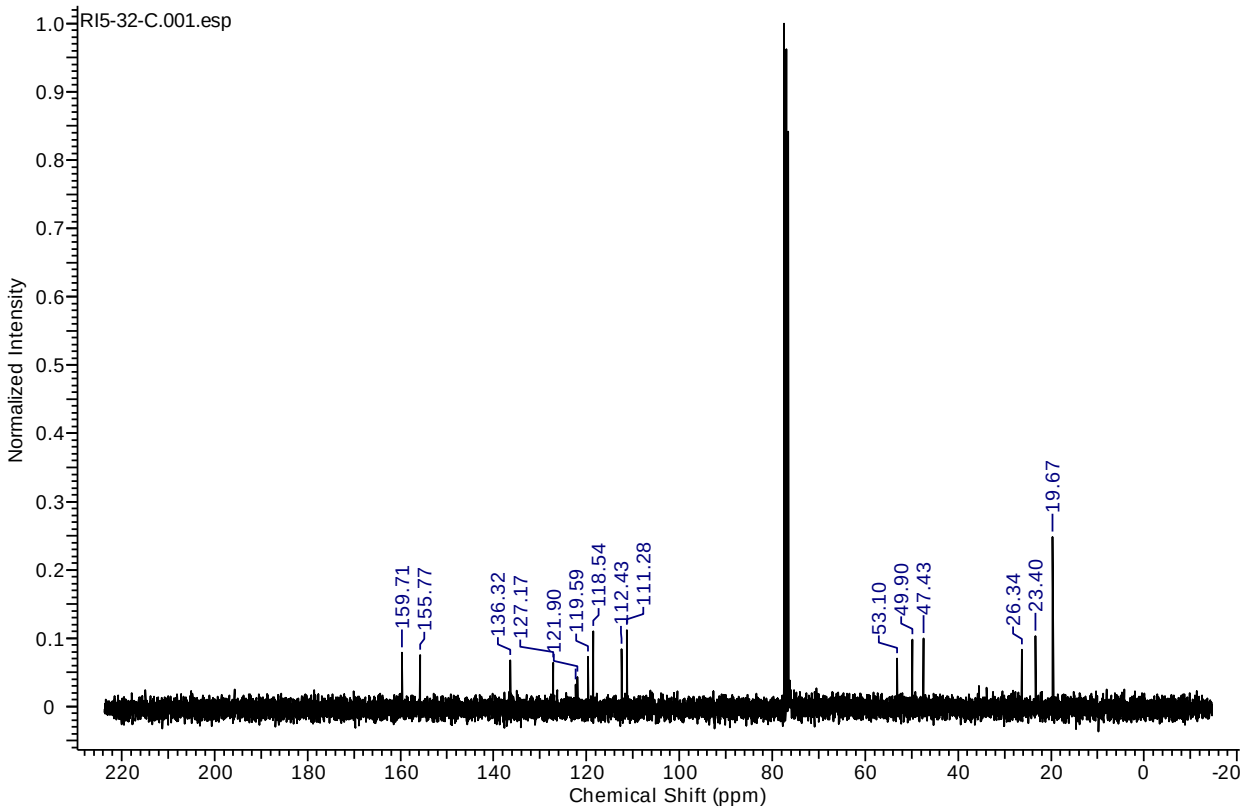

JF11-2115-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.91
4.08
1.00
3.00
1.93
1.96
1.93
1.96

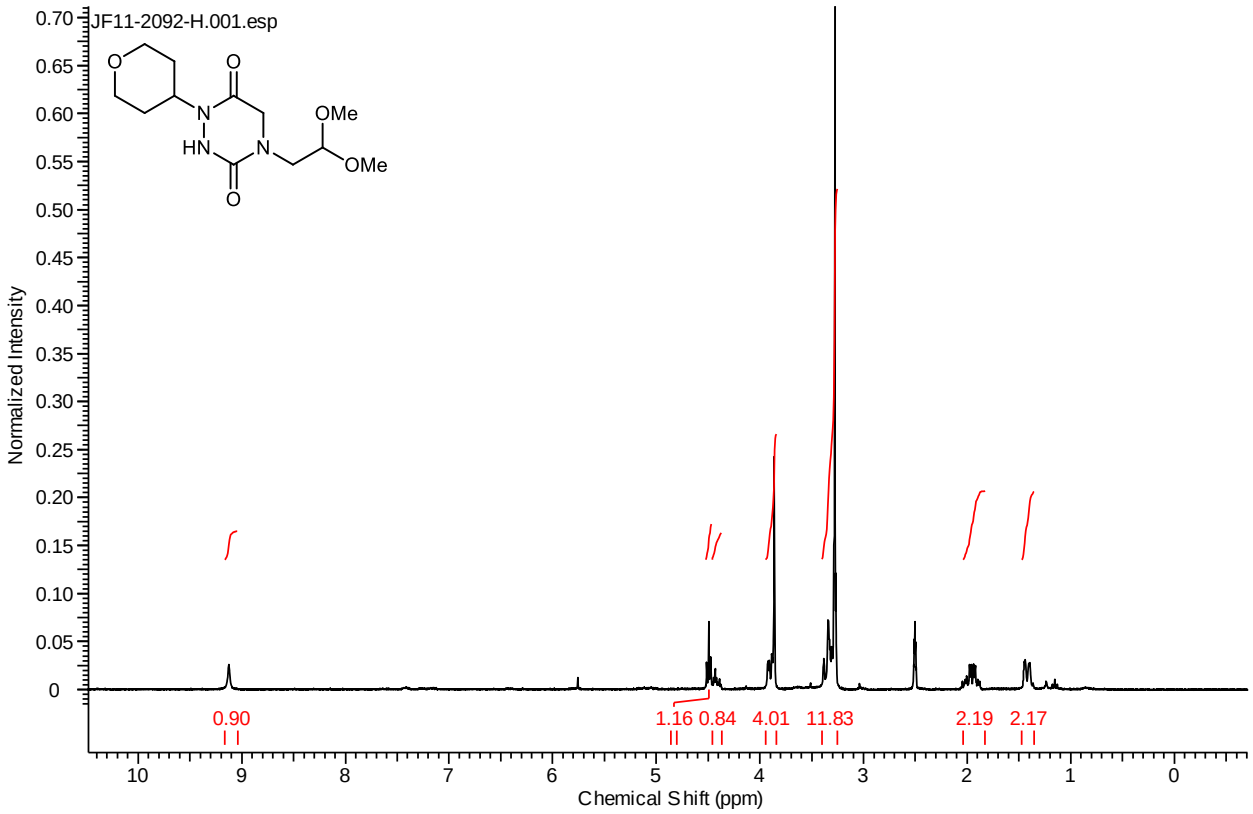

JF11-2115-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
162.2419
155.4308
140.4375
132.8226
126.4988
124.3750
118.0148
54.2451
48.4994
47.7503
34.1534

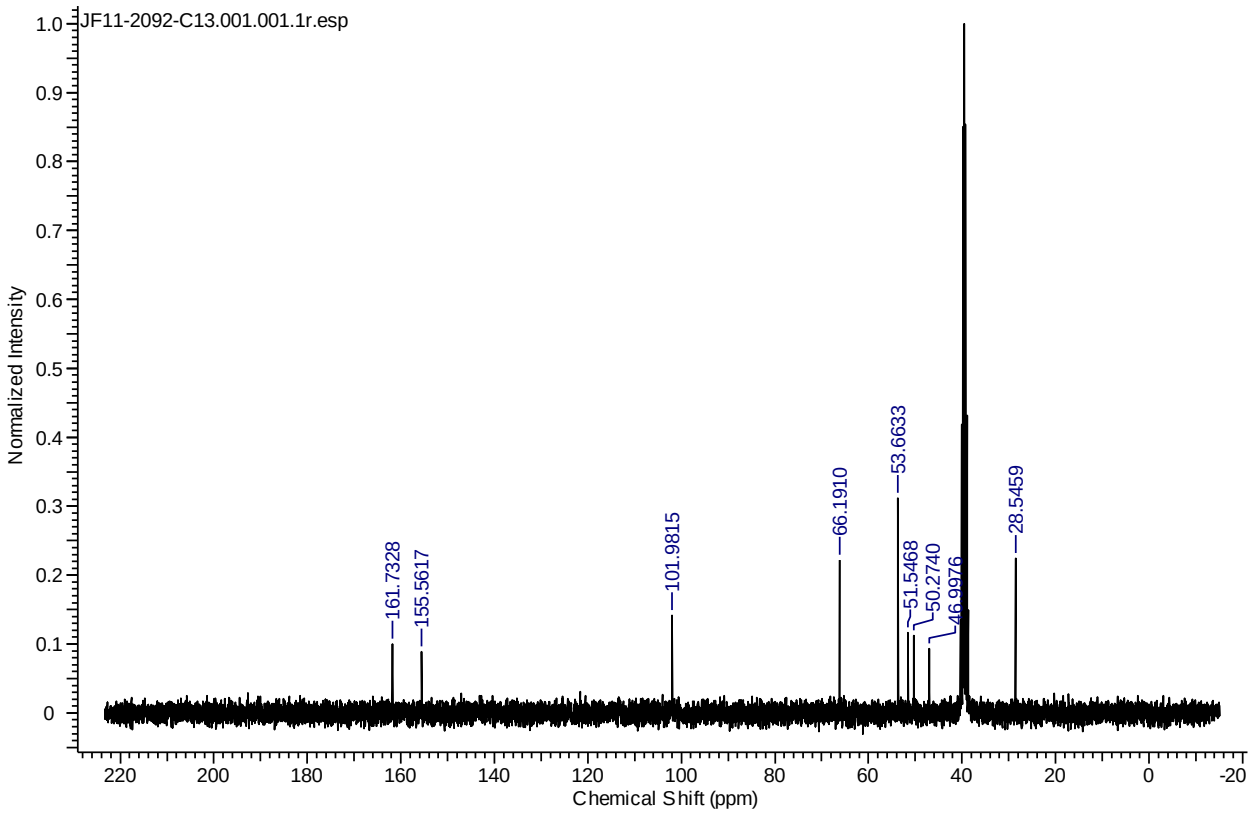

JF11-2085-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.92
1.00
1.97
0.98
1.91
1.92
1.92
2.56
1.98
1.98

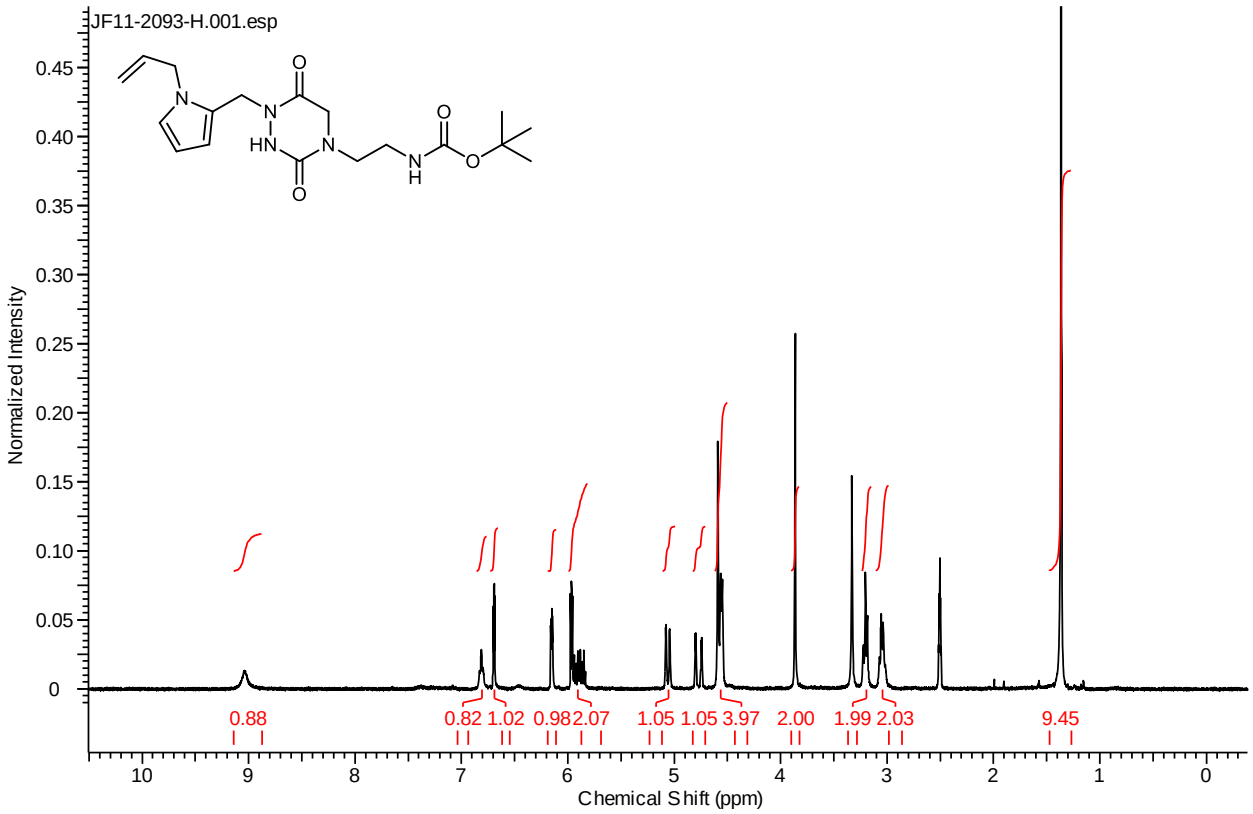

JF11-2085-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
161.6965
155.4308
132.8481
117.8948
66.1910
51.4959
48.4740
47.6703
28.5787

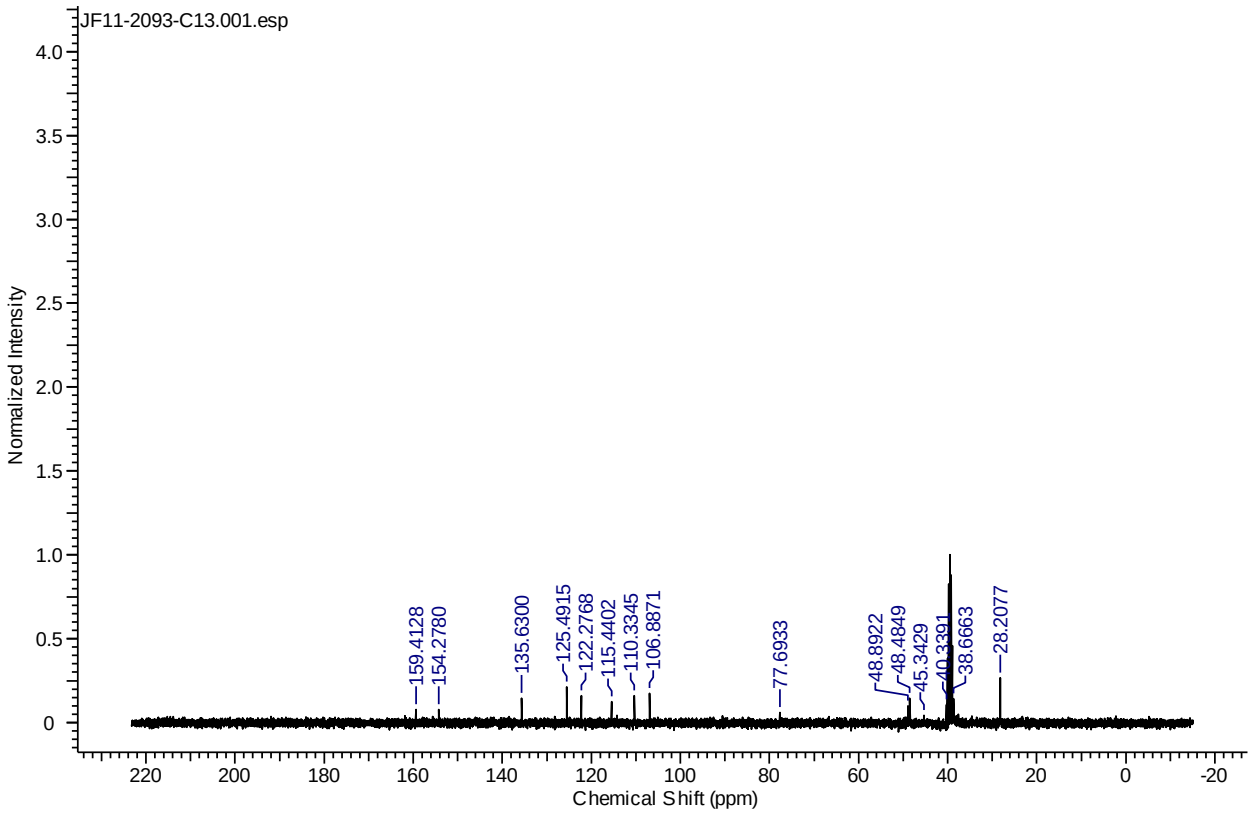

RI5-32-FRAC2.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.97 0.98 1.00 0.99 1.02 1.03 1.04
1.94 2.00 2.02 2.01
1.08
6.00

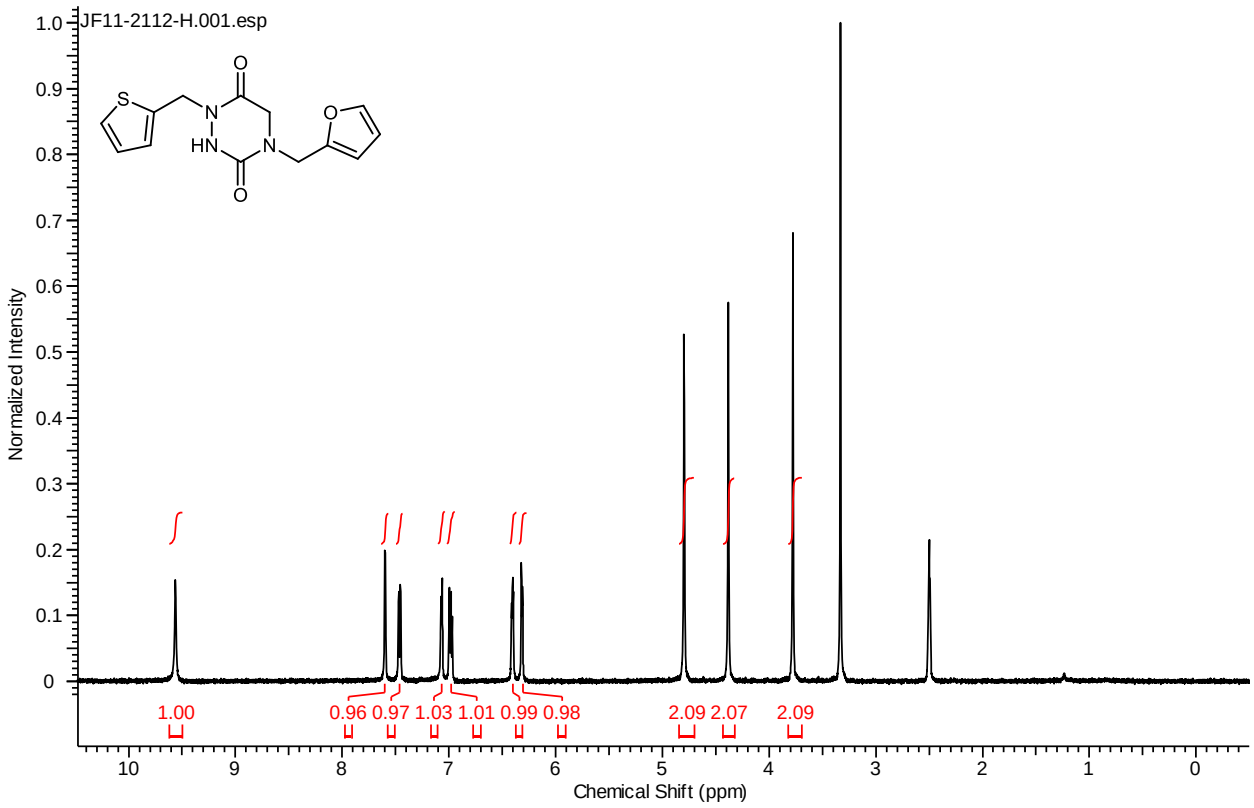

RI5-32-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
159.71
155.77
136.32
127.17
121.90
119.59
118.54
112.43
111.28
53.10
49.90
47.43
26.34
23.40
19.67

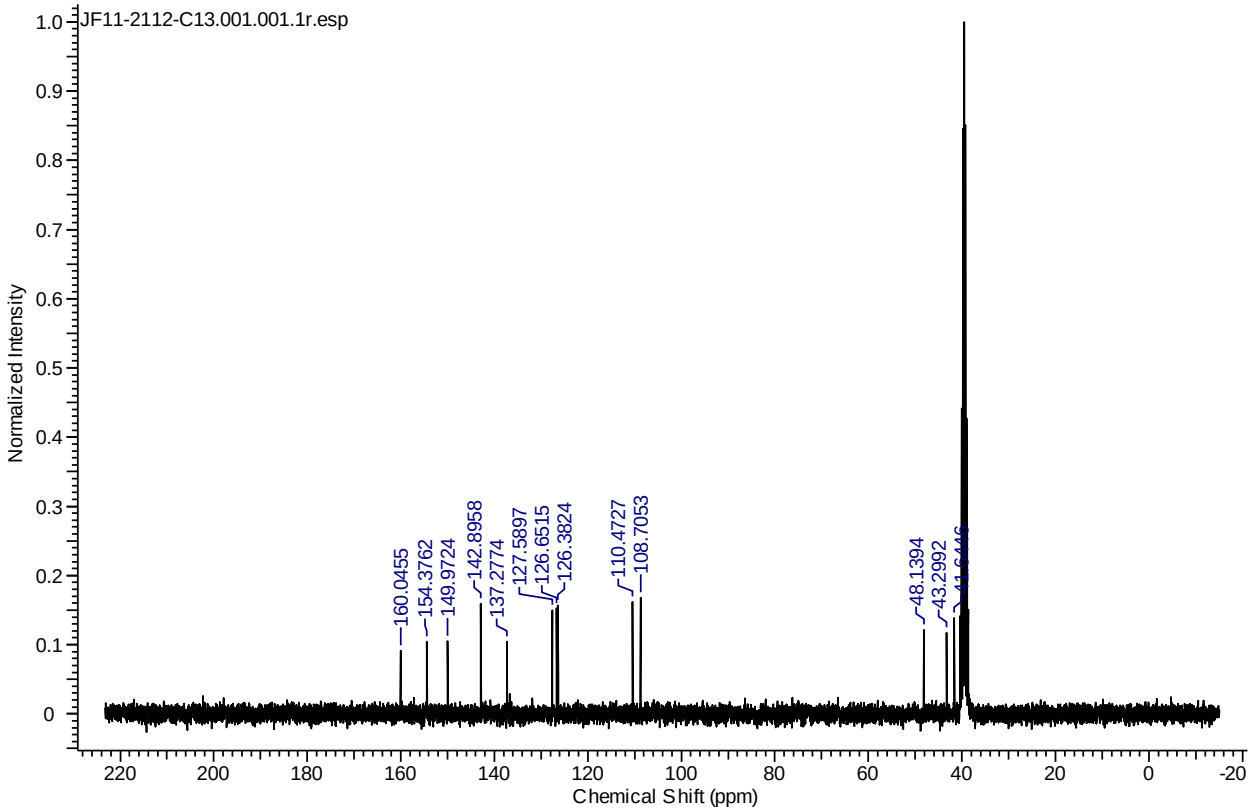

JF11-2092-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.90
1.16
0.84
4.01
11.83
2.19
2.17

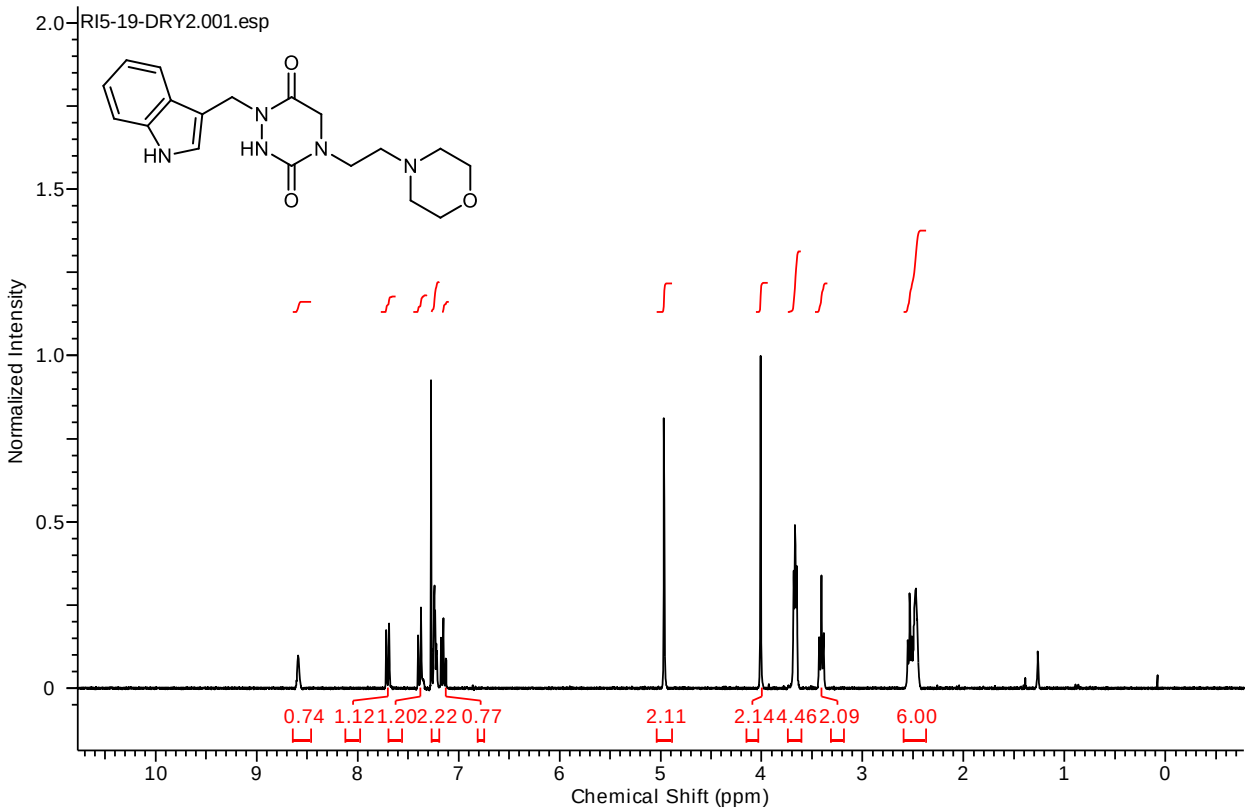

JF11-2092-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
161.7328
155.5617
101.9815
66.1910
53.6633
51.5468
50.2740
46.9976
28.5459

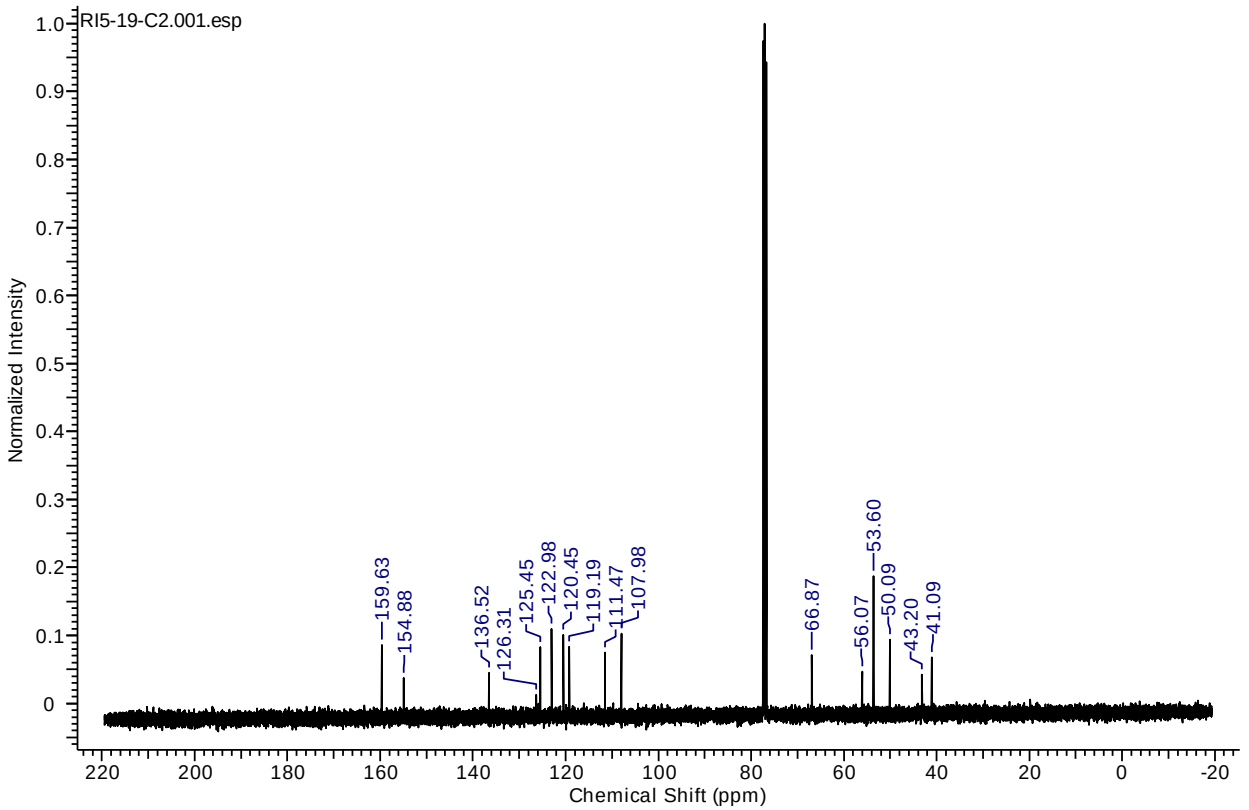

JF11-2093-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.88
0.82
1.02
0.98
2.07
1.05
1.05
3.97
2.00
1.99
2.03
9.45

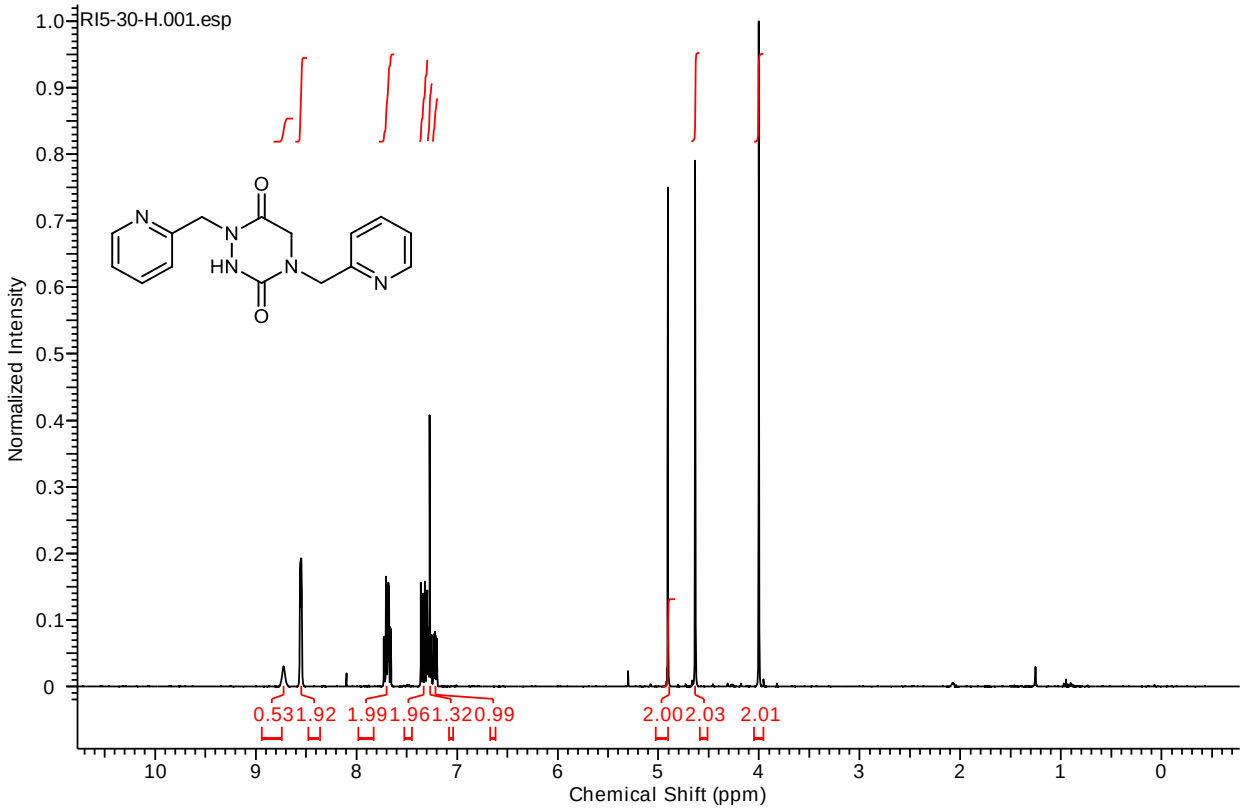

JF11-2093-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
159.4128
154.2780
135.6300
125.4915
122.2768
115.4402
110.3345
106.8871
77.6933
48.8922
48.4849
45.3429
40.3391
38.6663
28.2077

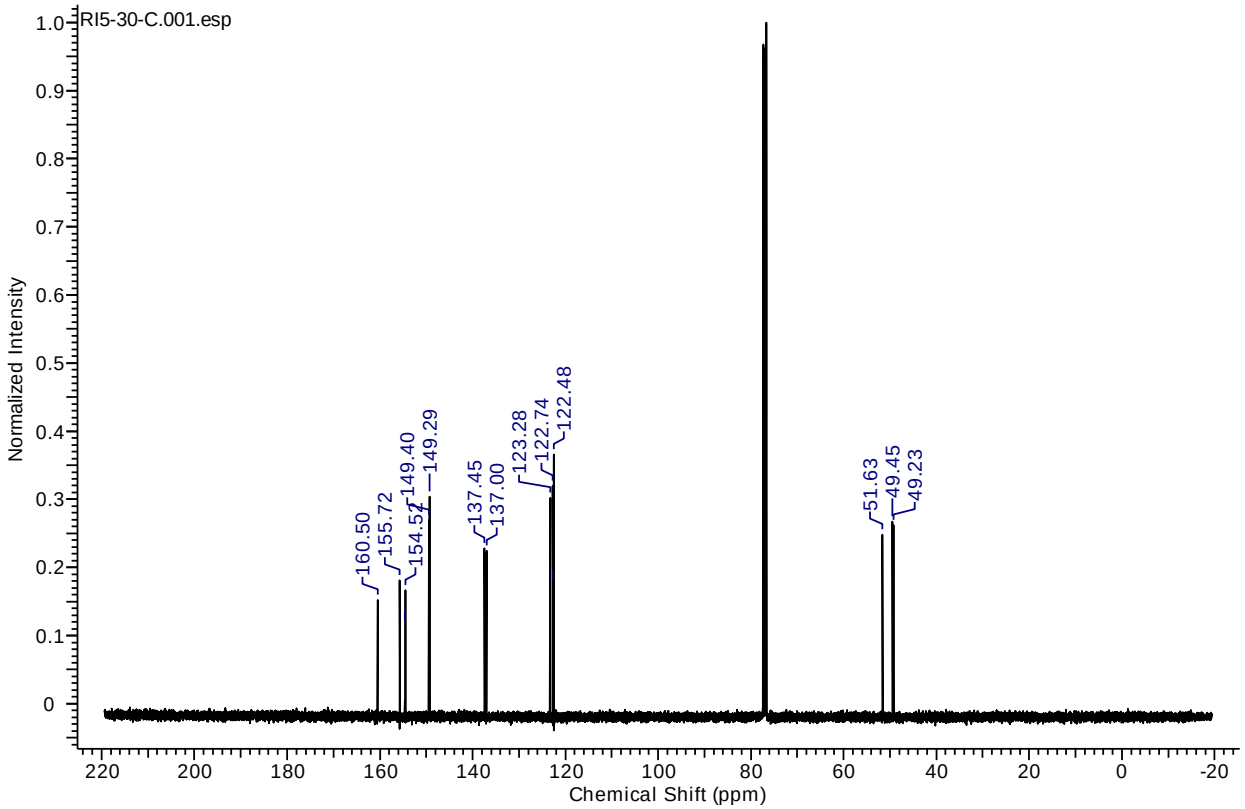

JF11-2112-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
0.96 0.97 1.03 1.01 0.99 0.98
2.09 2.07 2.09

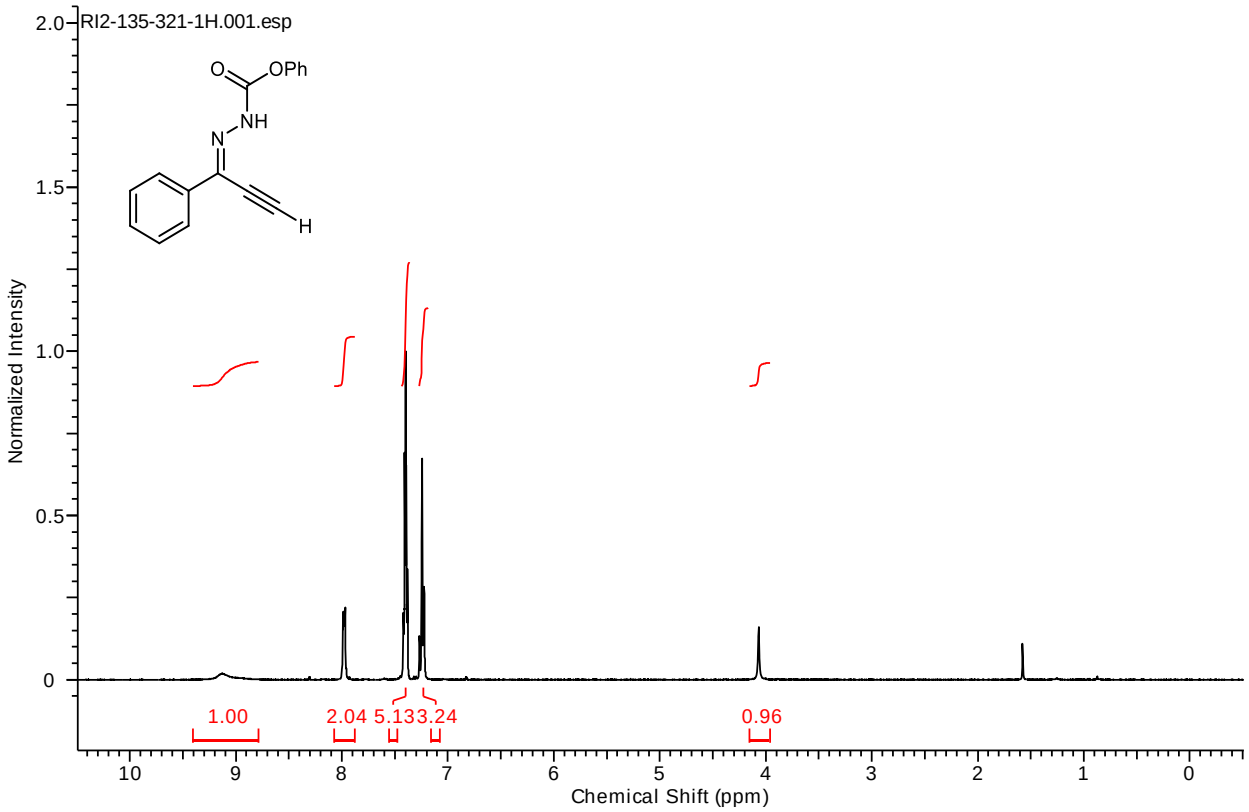

JF11-2112-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
160.0455
154.3762
149.9724
142.8958
137.2774
127.5897
126.6515
126.3824
110.4727
108.7053
48.1394
43.2992

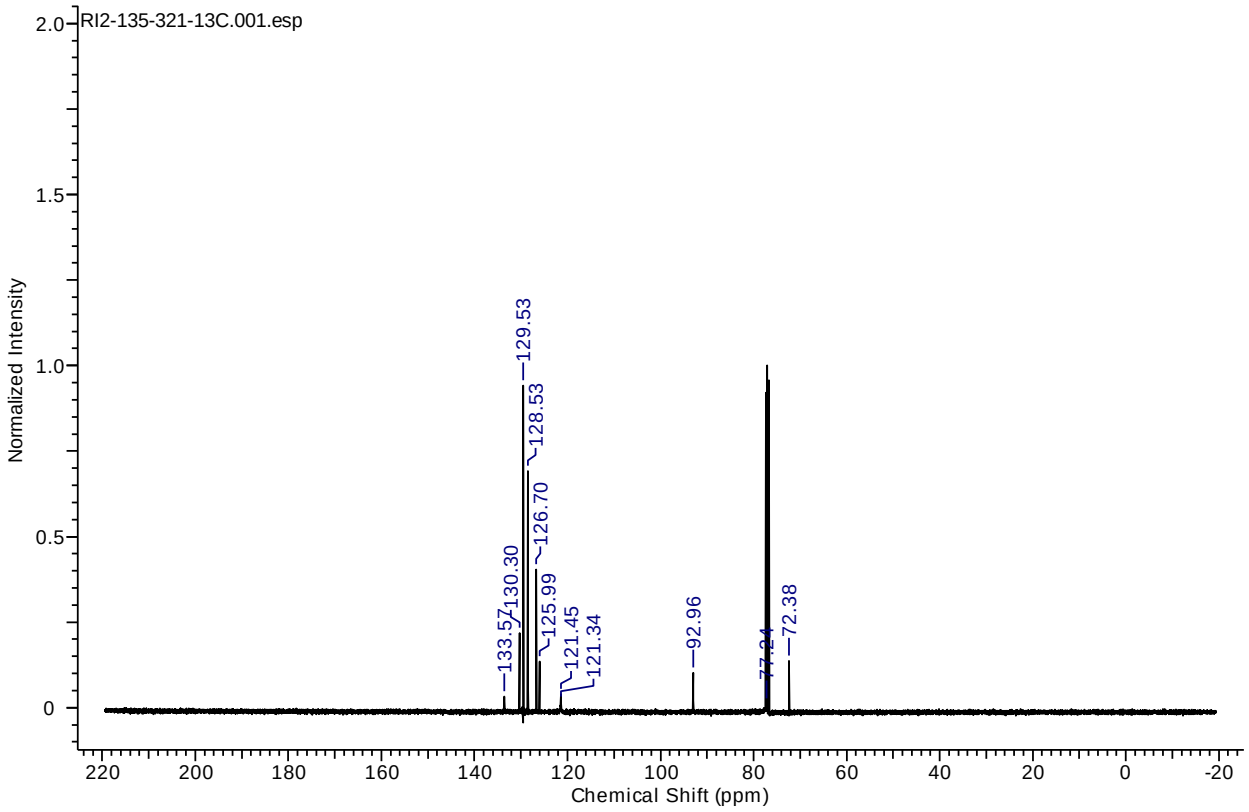

RI5-19-DRY2.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.74
1.12
1.20
2.22
0.77
2.11
2.14
4.46
2.09
6.00

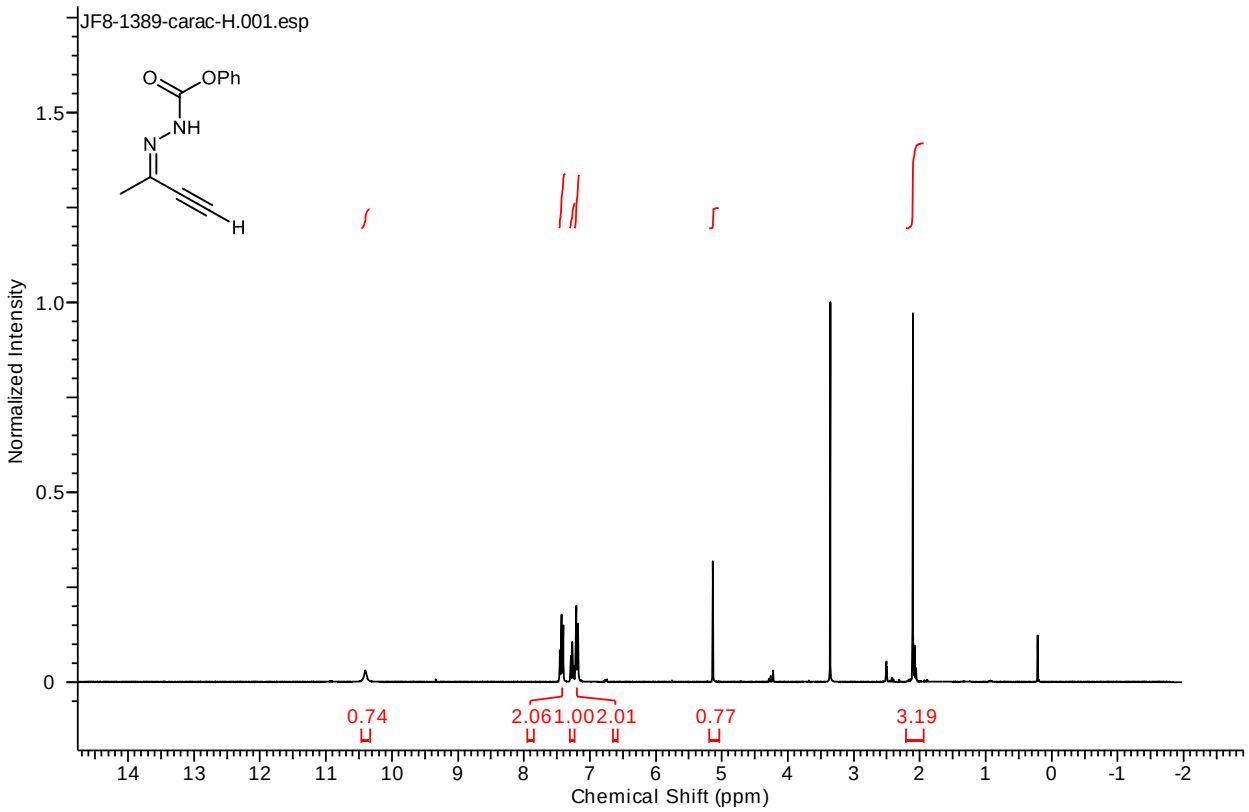

RI5-19-C2.001.esp
Normalized Intensity
Chemical Shift (ppm)
159.63
154.88
136.52
126.31
125.45
122.98
120.45
119.19
111.47
107.98
66.87
56.07
53.60
50.09
43.20
41.09

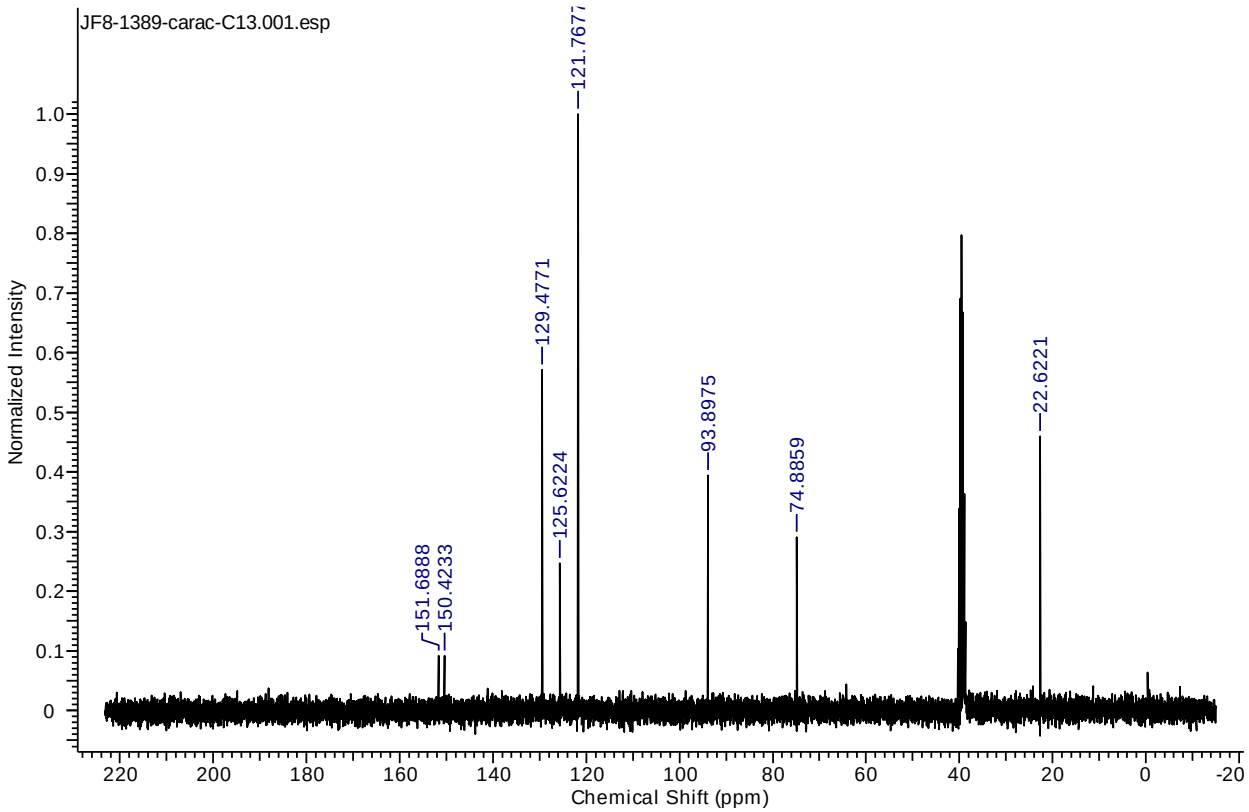

RI5-30-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.53 1.92 1.99 1.96 1.32 0.99 2.00 2.03 2.01

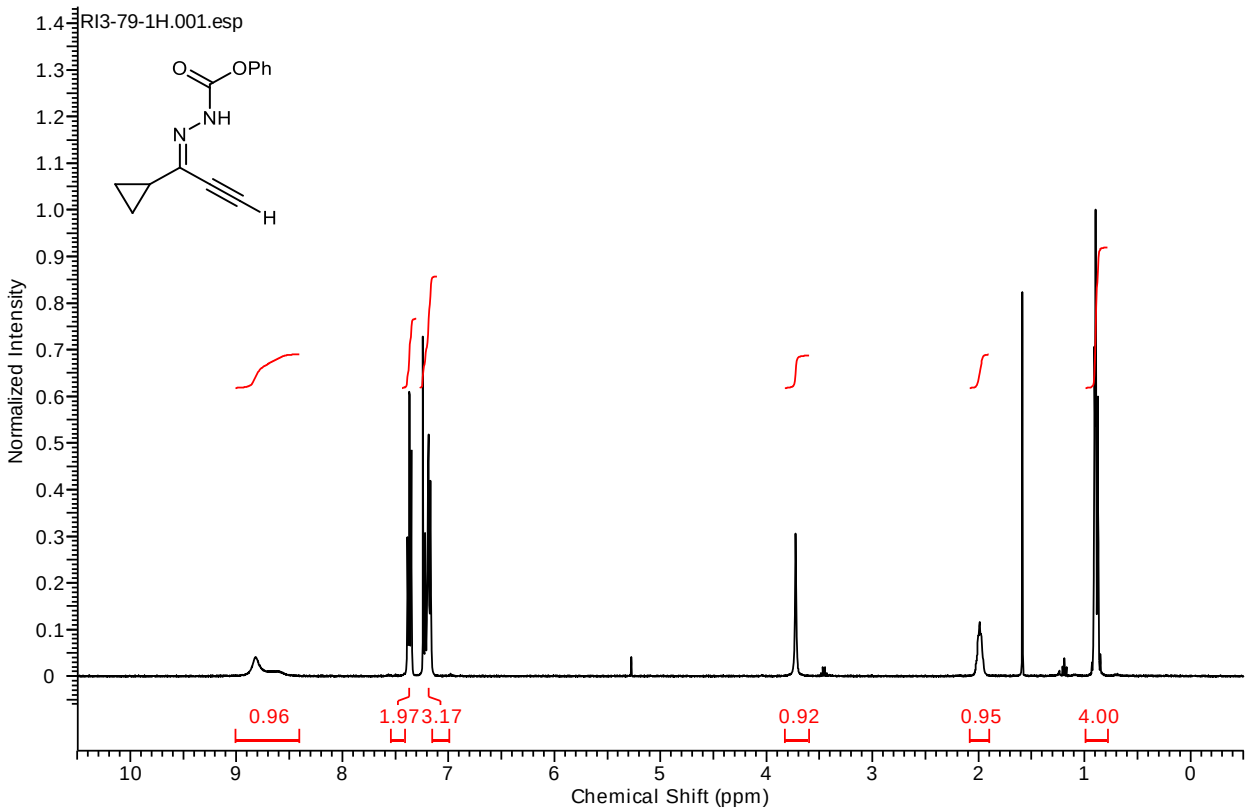

RI5-30-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
160.50
155.72
154.52
149.40
149.29
137.45
137.00
123.28
122.74
122.48
51.63
49.45
49.23

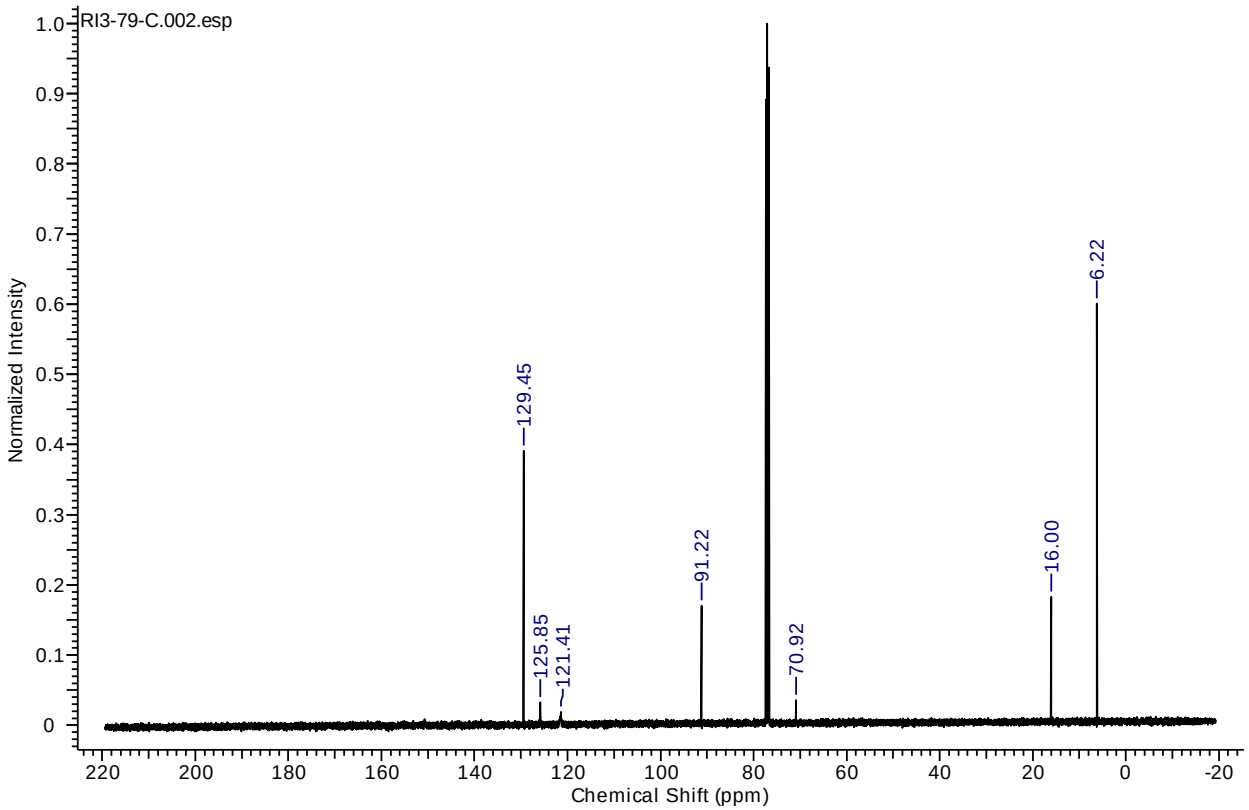

RI2-135-321-1H.001.esp
O
OPh
NH
N
H
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.00
2.04
5.13
3.24
0.96
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

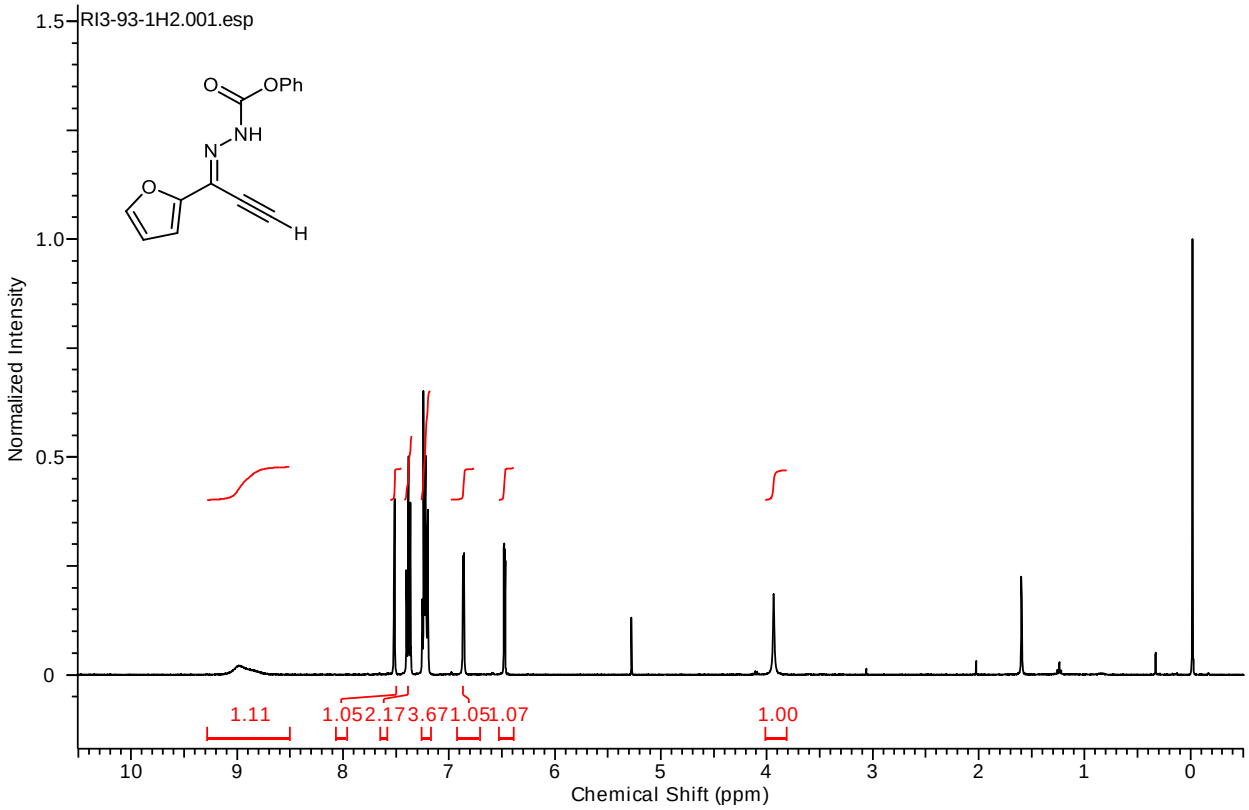

RI2-135-321-13C.001.esp
Normalized Intensity
2.0
1.5
1.0
0.5
0
133.57
130.30
129.53
128.53
126.70
125.99
121.45
121.34
92.96
77.24
72.38
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

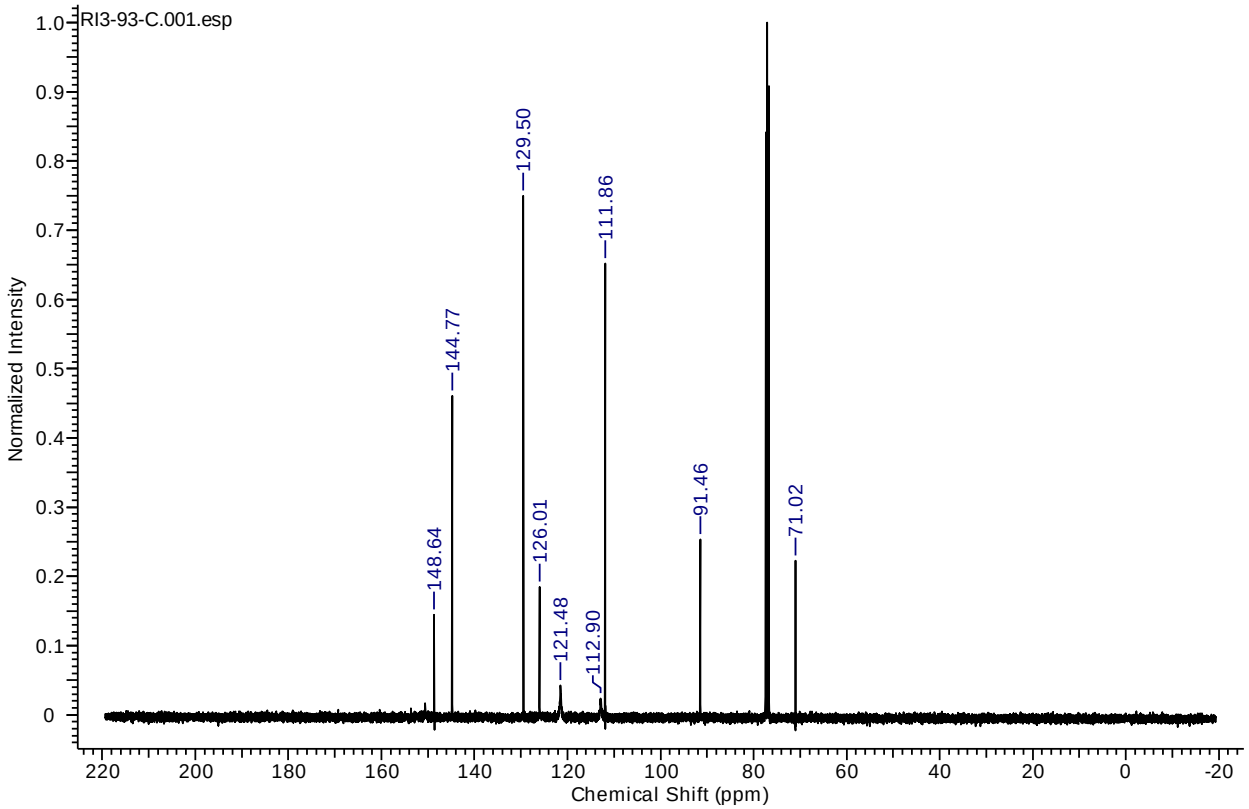

JF8-1389-carac-H.001.esp
O
OPh
NH
N
H
Normalized Intensity
1.5
1.0
0.5
0
0.74
2.06
1.00
2.01
0.77
3.19
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

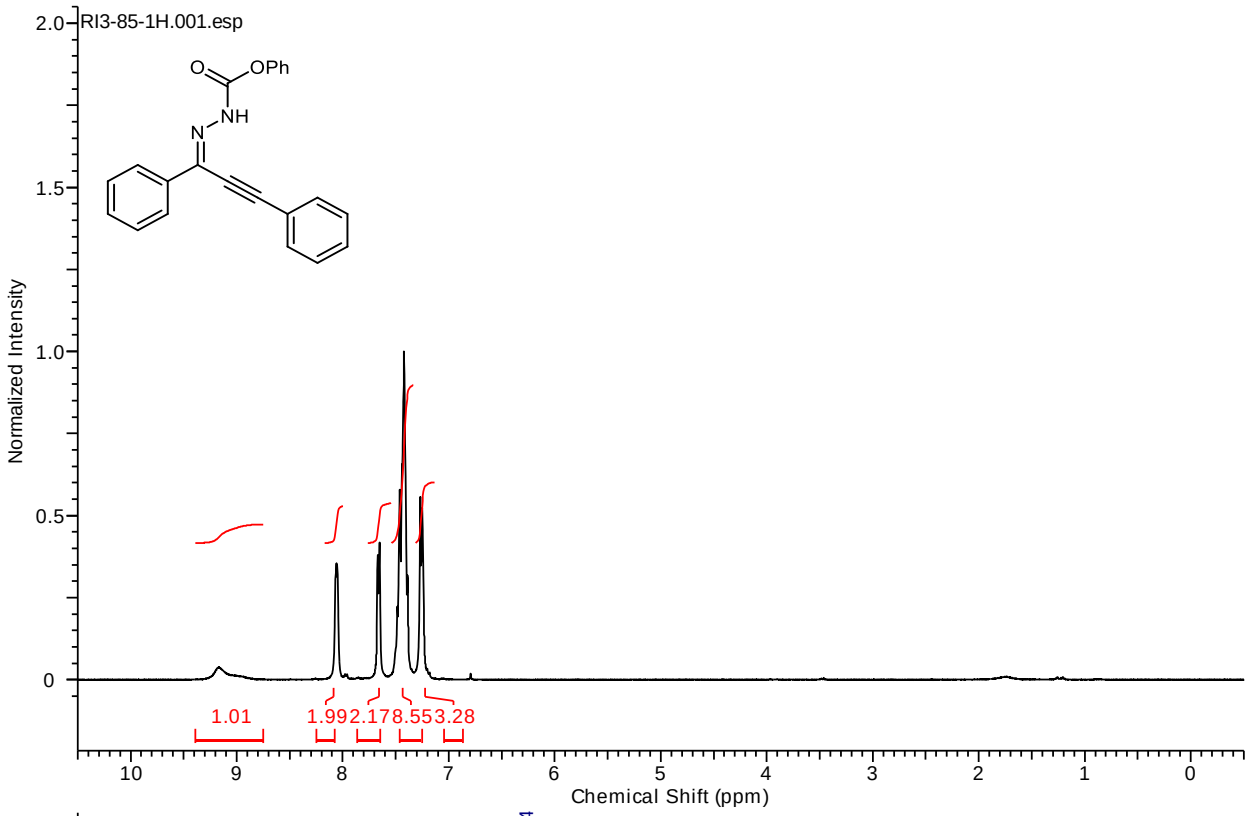

JF8-1389-carac-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
151.6888
150.4233
129.4771
125.6224
121.7677
93.8975
74.8859
22.6221
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

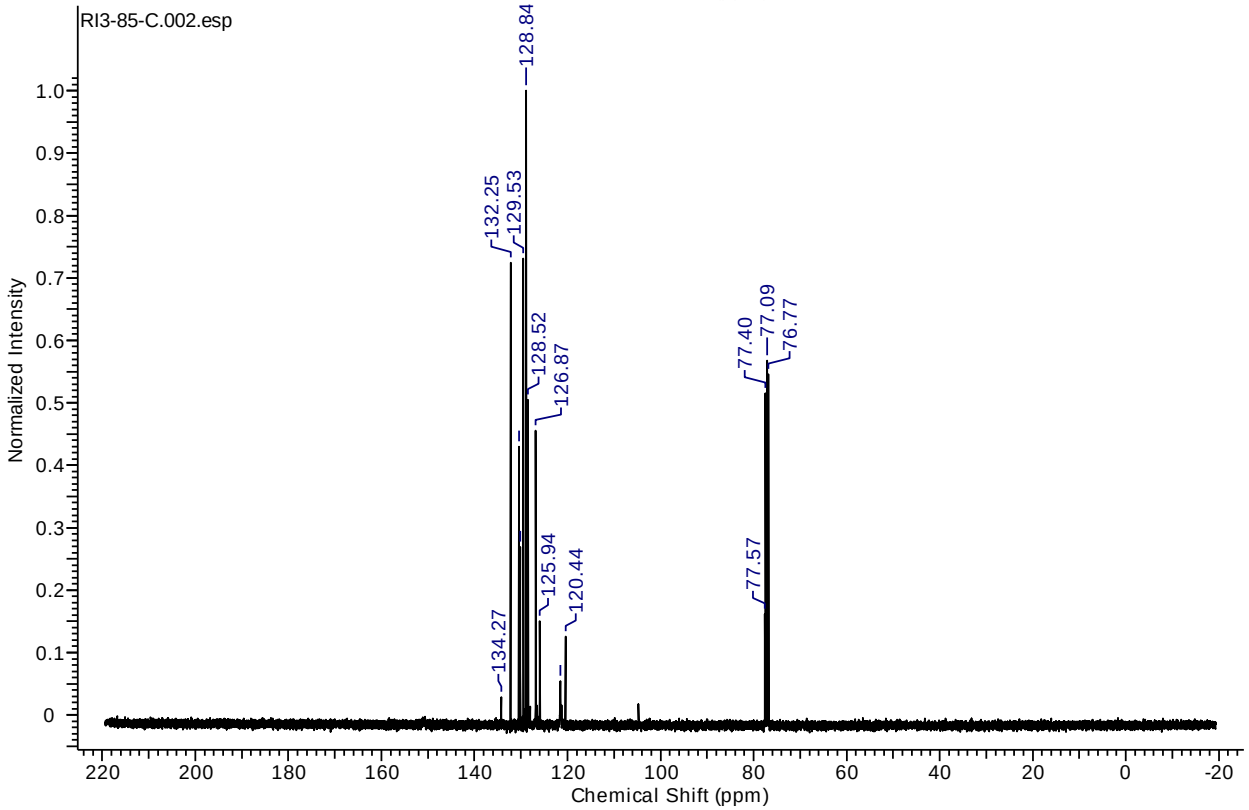

RI3-79-1H.001.esp
O
OPh
NH
N
H
Normalized Intensity
0.96
1.97
3.17
0.92
0.95
4.00
Chemical Shift (ppm)

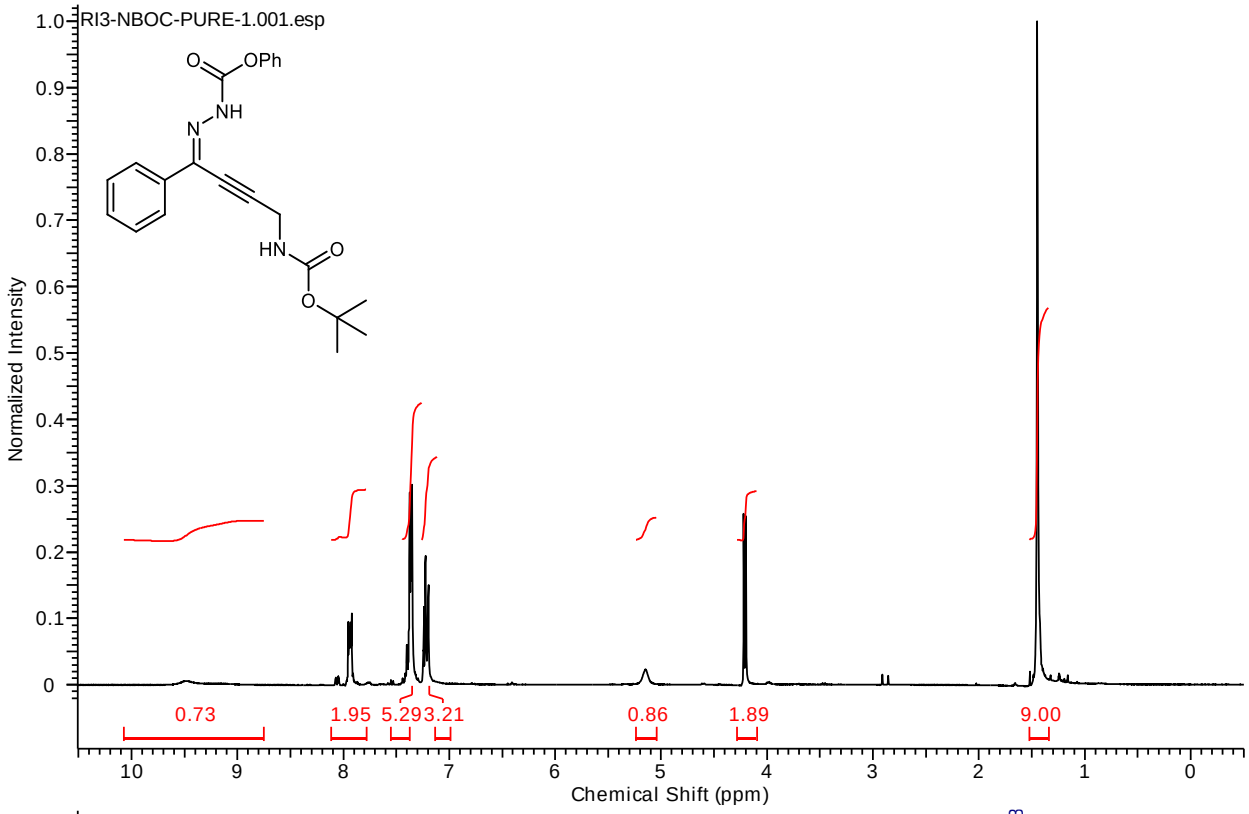

RI3-79-C.002.esp
Normalized Intensity
129.45
125.85
121.41
91.22
70.92
16.00
6.22
Chemical Shift (ppm)

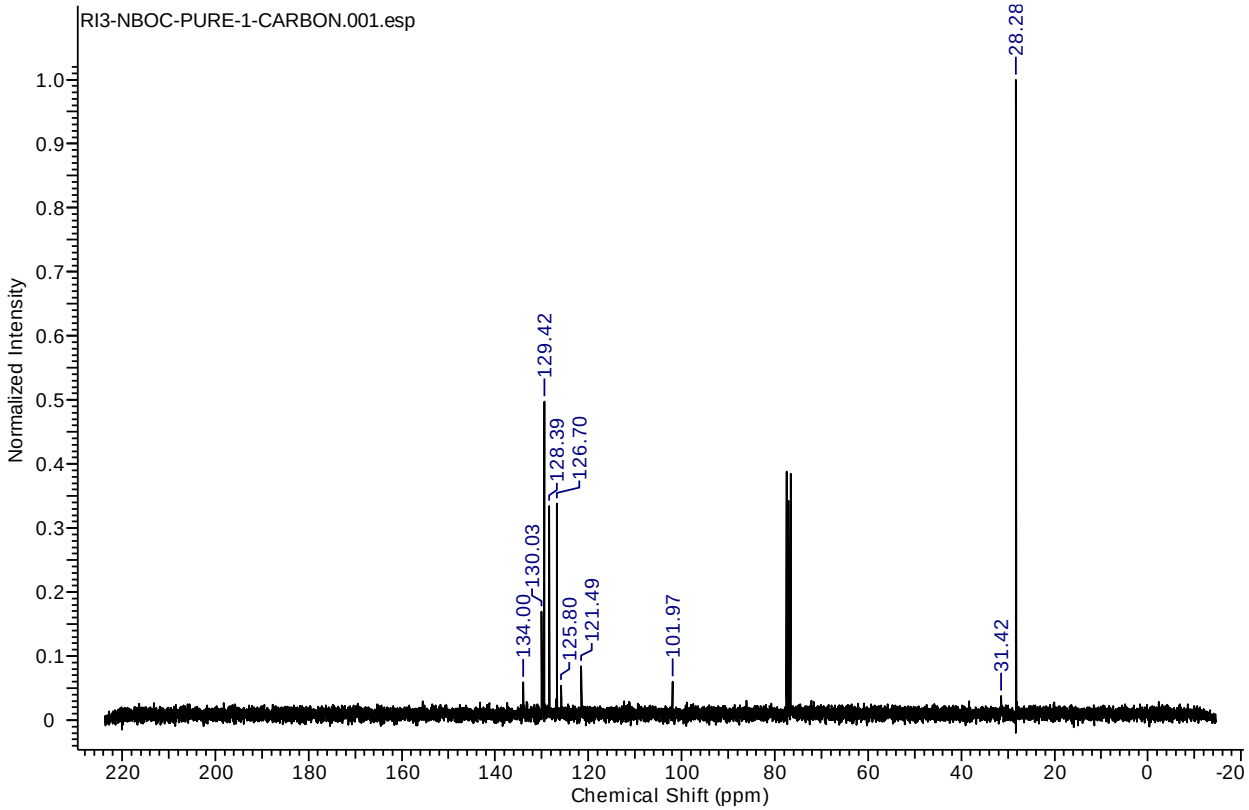

RI3-93-1H2.001.esp
O
OPh
NH
N
O
H
Normalized Intensity
1.5
1.0
0.5
0
1.11
1.05
2.17
3.67
1.05
1.07
1.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

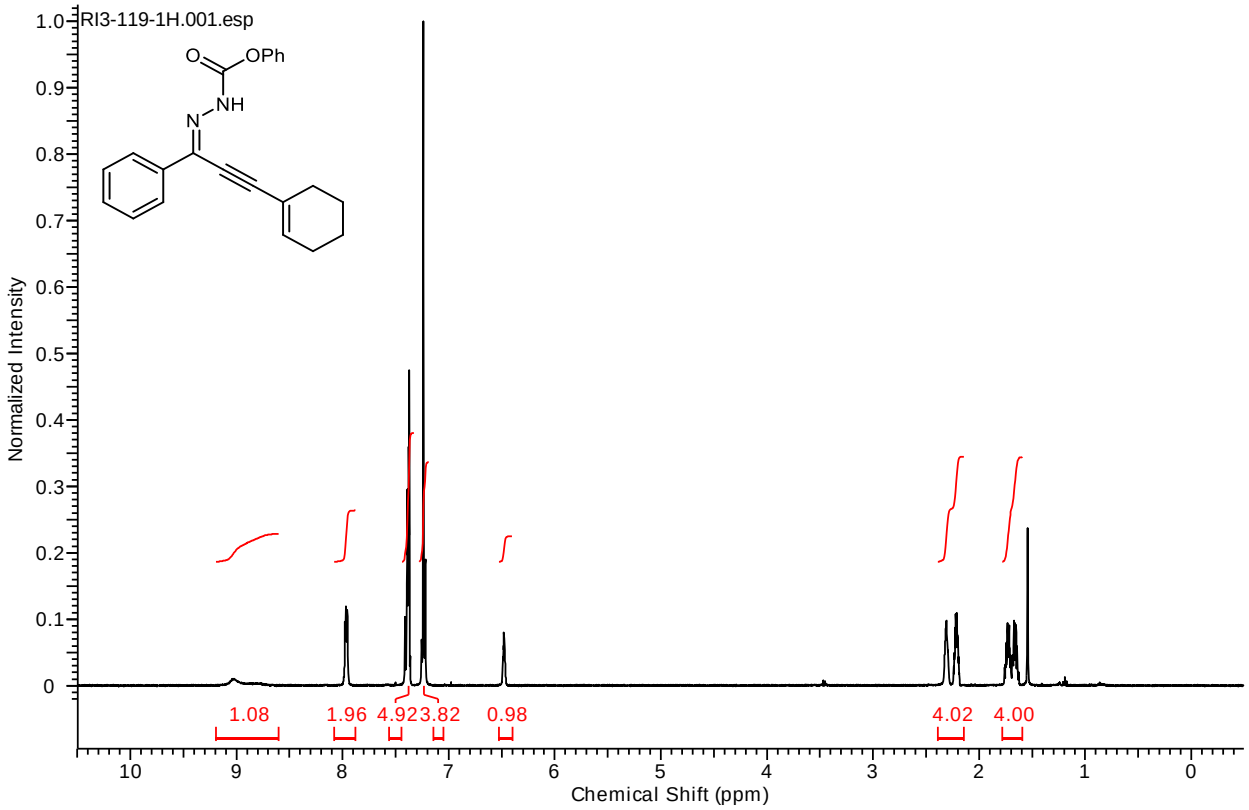

RI3-93-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
148.64
144.77
129.50
126.01
121.48
112.90
111.86
91.46
71.02
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

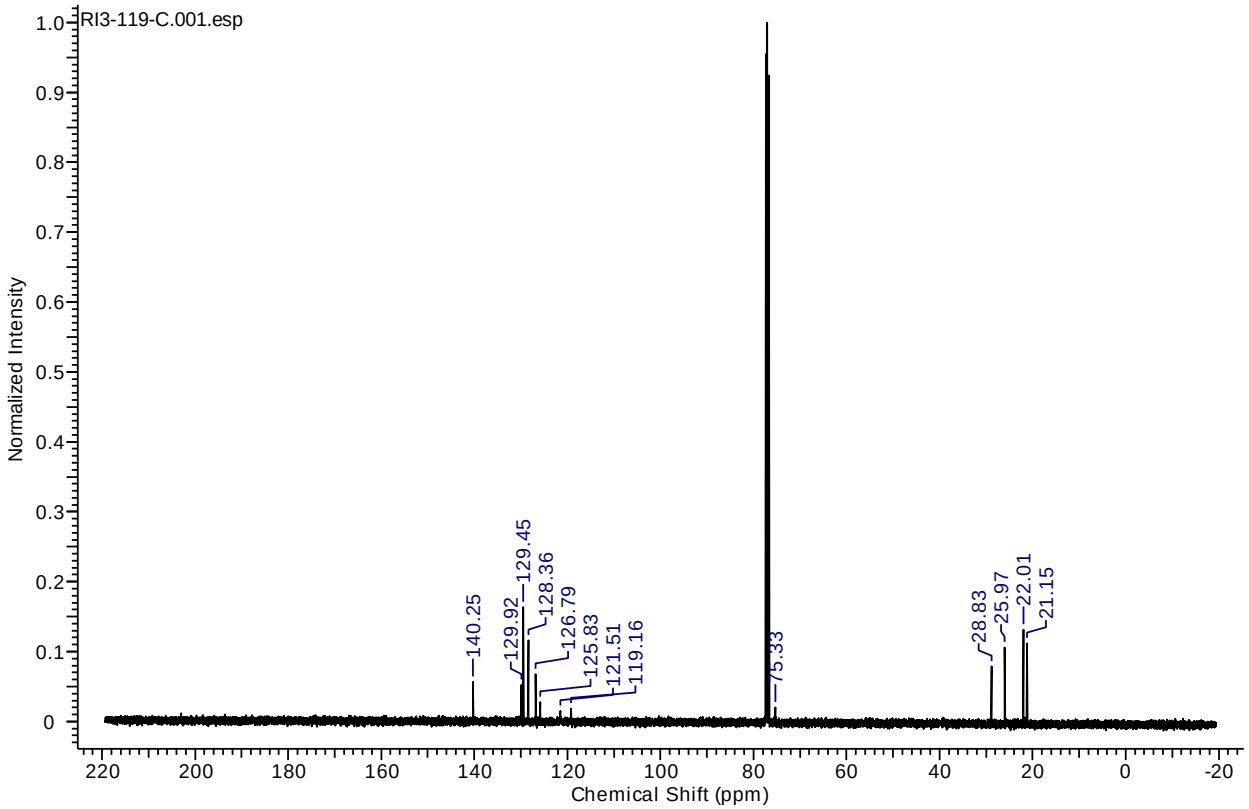

RI3-85-1H.001.esp
O
OPh
NH
N
Normalized Intensity
1.01
1.99
2.17
8.55
3.28
Chemical Shift (ppm)

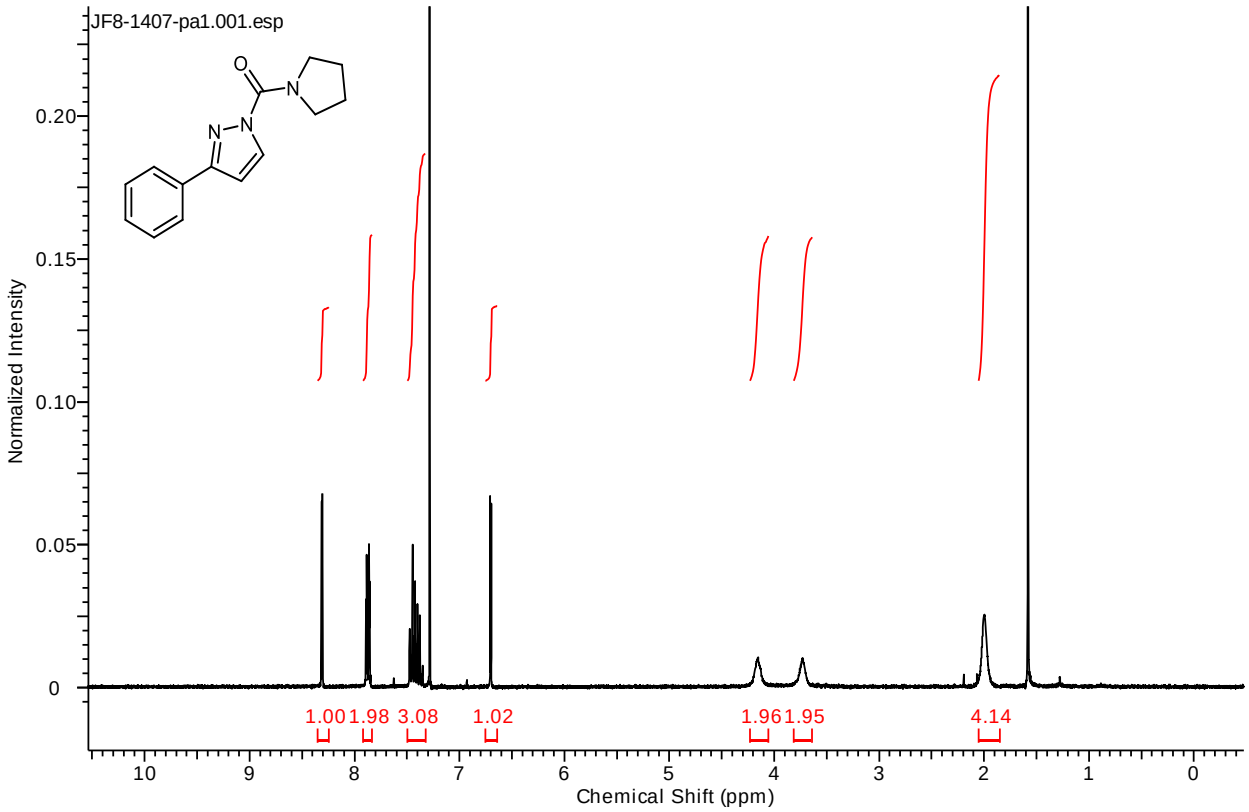

RI3-85-C.002.esp
128.84
132.25
129.53
128.52
126.87
77.40
77.09
76.77
125.94
120.44
77.57
134.27
Normalized Intensity
Chemical Shift (ppm)

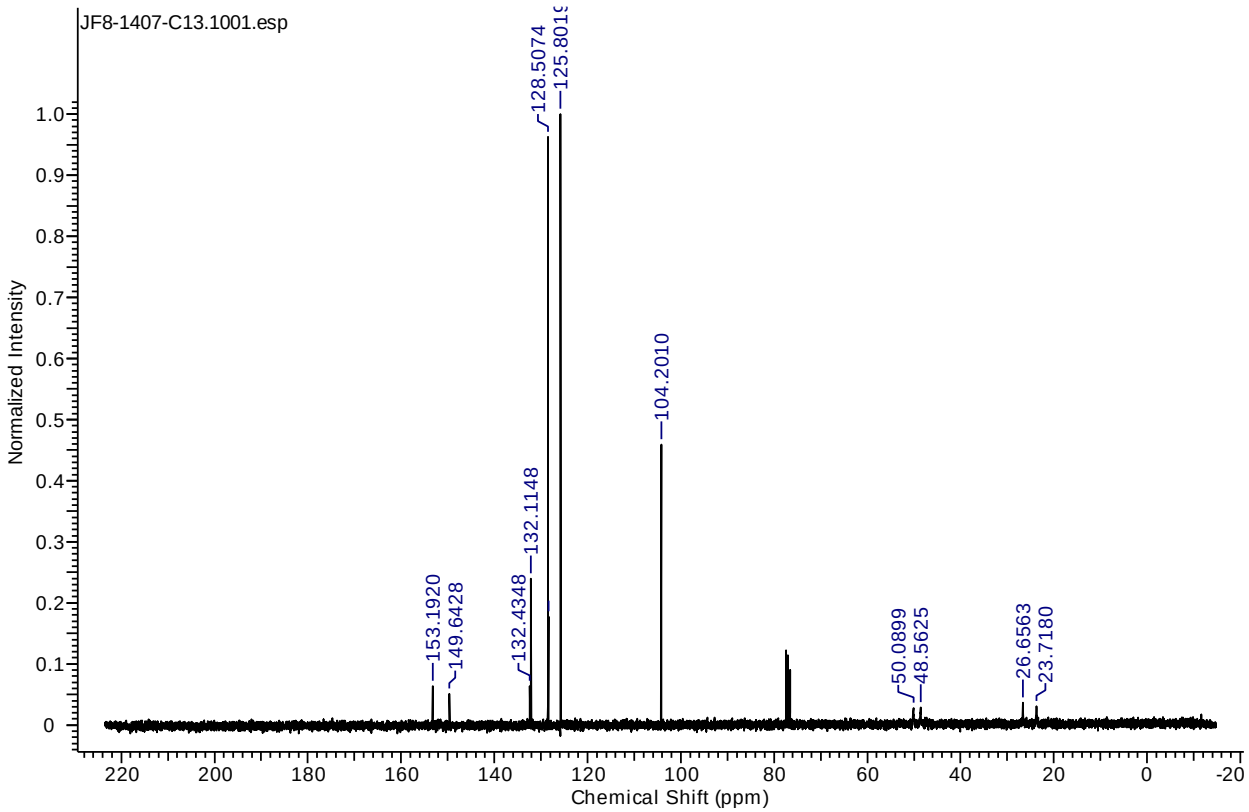

RI3-NBOC-PURE-1.001.esp
O
OPh
NH
N
HN
O
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.73
1.95
5.29
3.21
0.86
1.89
9.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

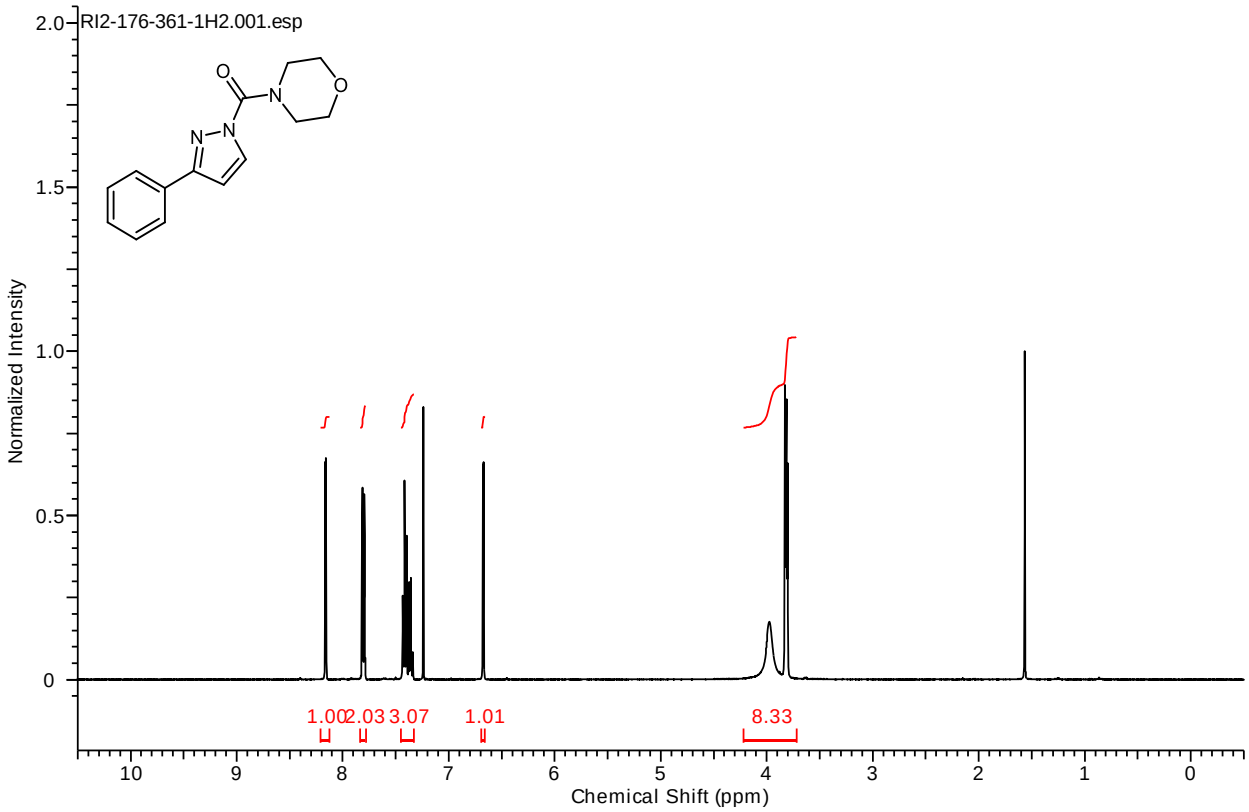

RI3-NBOC-PURE-1-CARBON.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
28.28
129.42
128.39
126.70
130.03
134.00
125.80
121.49
101.97
31.42
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

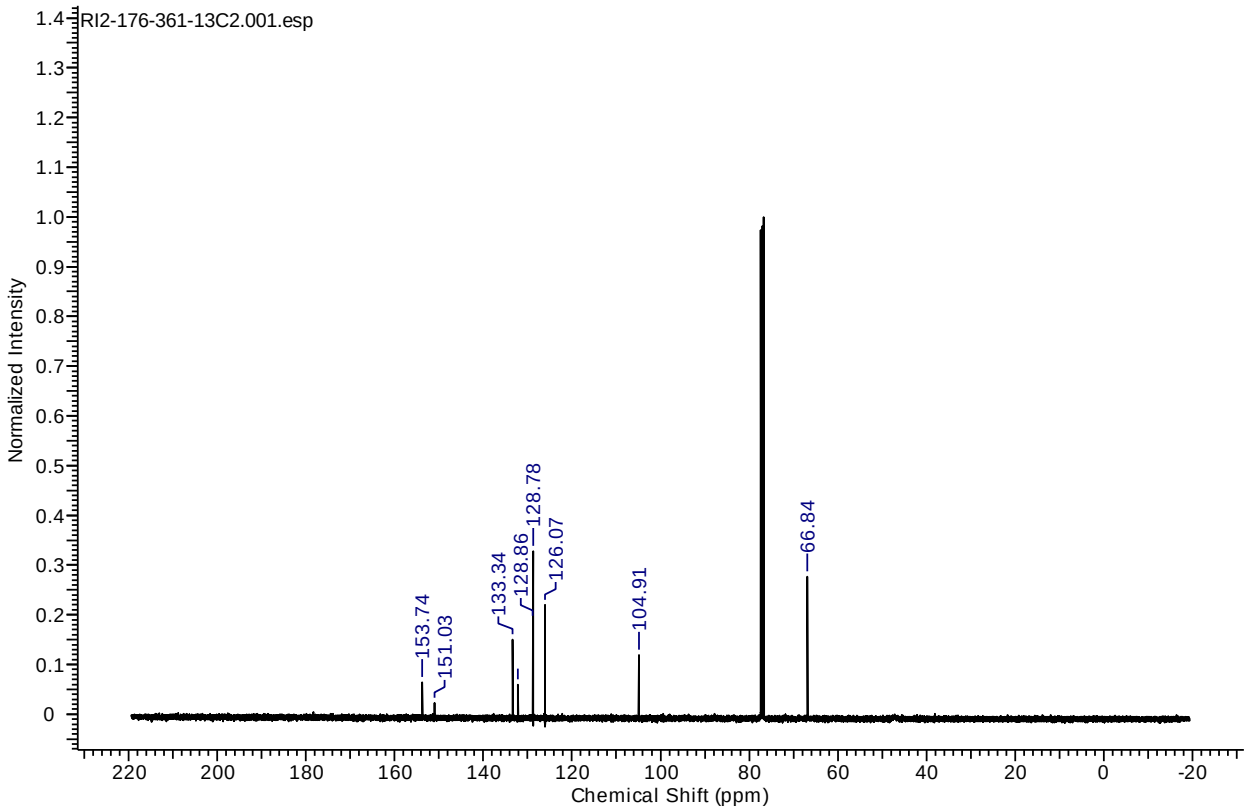

RI3-119-1H.001.esp
O
OPh
NH
N
Normalized Intensity
1.08
1.96
4.92
3.82
0.98
4.02
4.00
Chemical Shift (ppm)

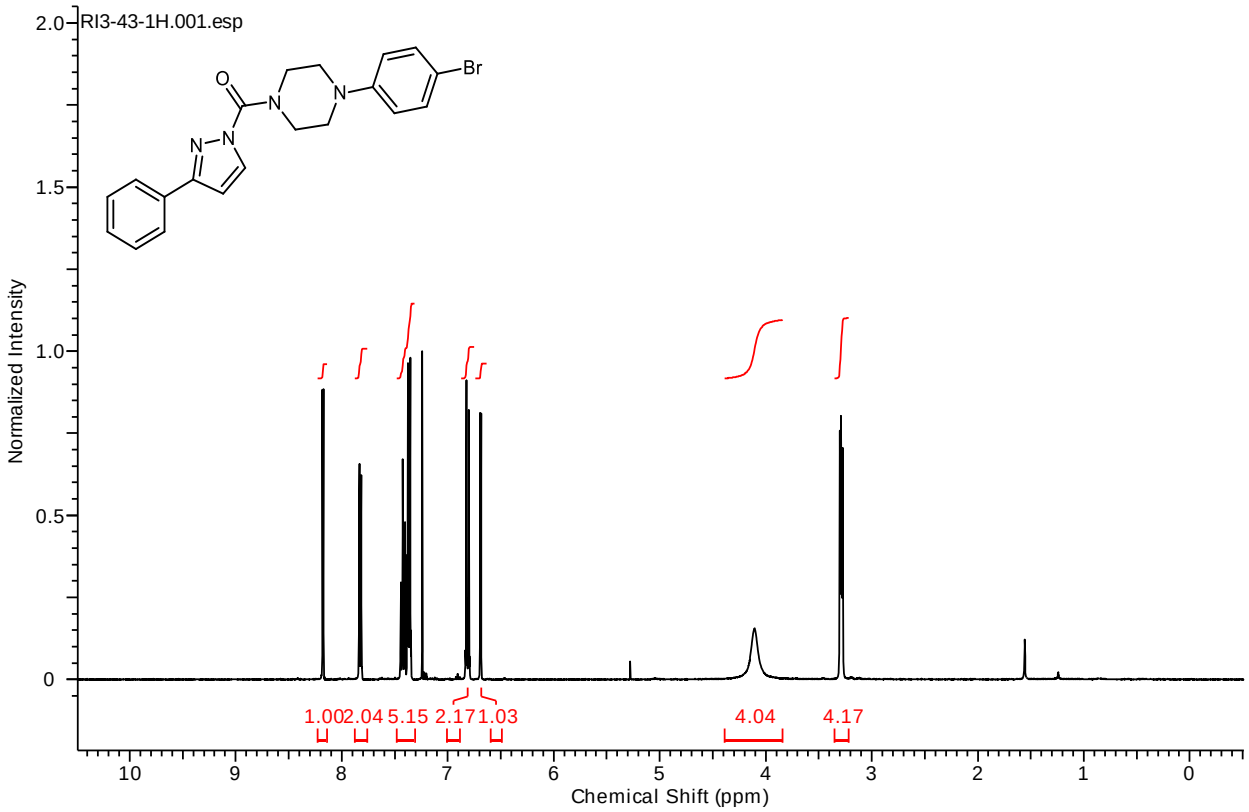

RI3-119-C.001.esp
Normalized Intensity
140.25
129.92
129.45
128.36
126.79
125.83
121.51
119.16
75.33
28.83
25.97
22.01
21.15
Chemical Shift (ppm)

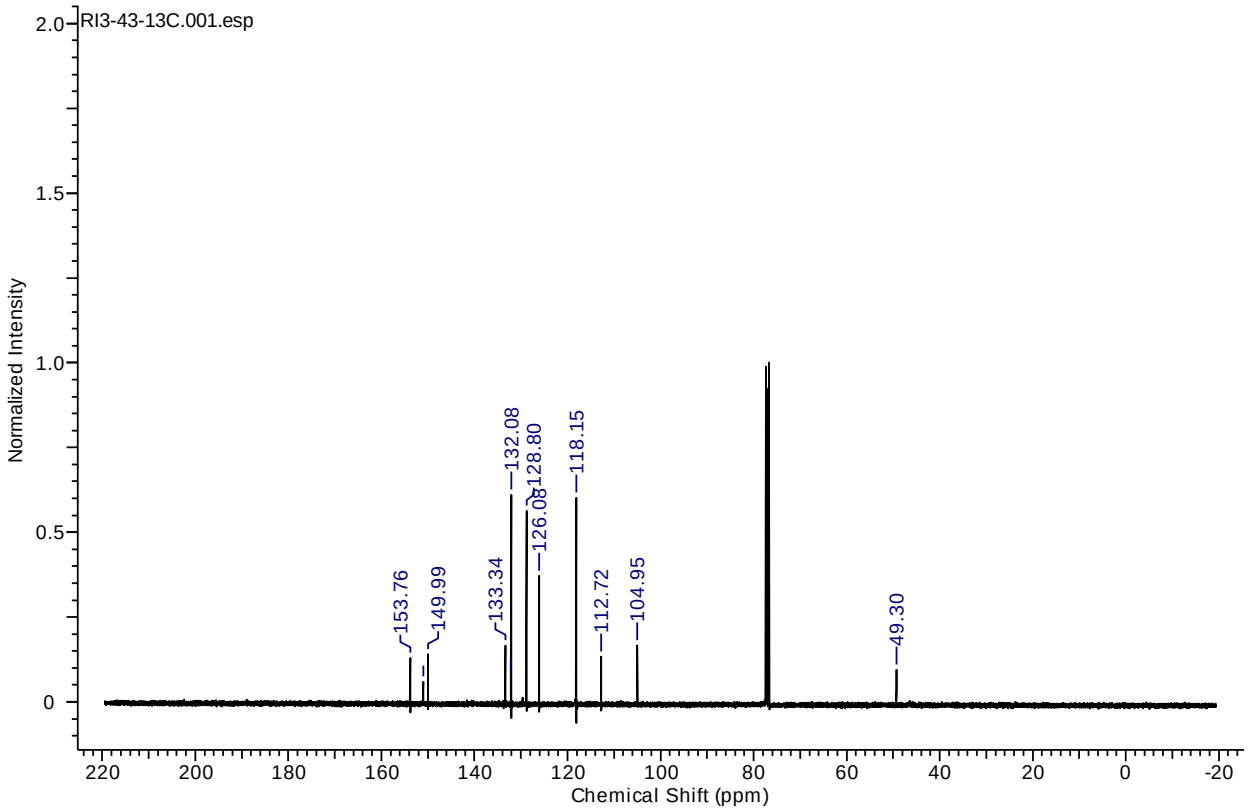

JF8-1407-pa1.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00 1.98 3.08 1.02 1.96 1.95 4.14

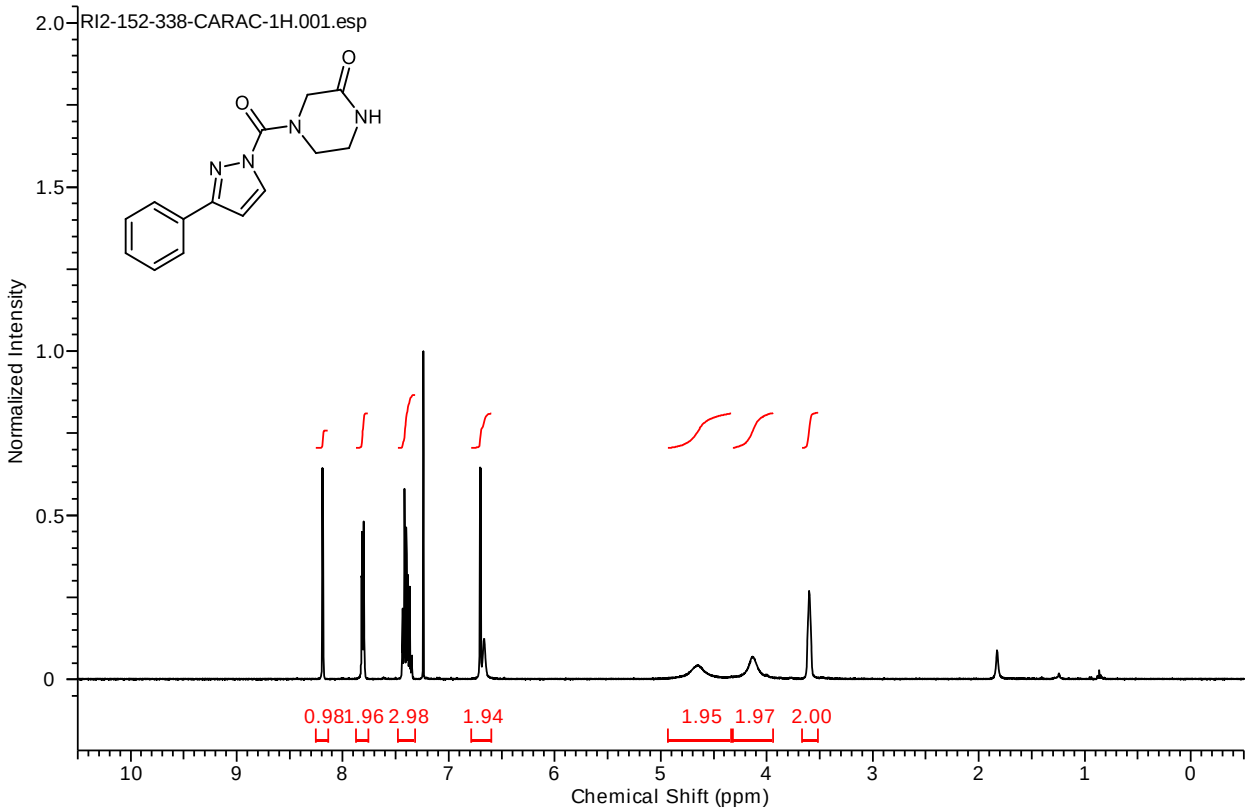

JF8-1407-C13.1001.esp
Normalized Intensity
Chemical Shift (ppm)
128.5074
125.8015
104.2010
153.1920
149.6428
132.4348
132.1148
50.0899
48.5625
26.6563
23.7180

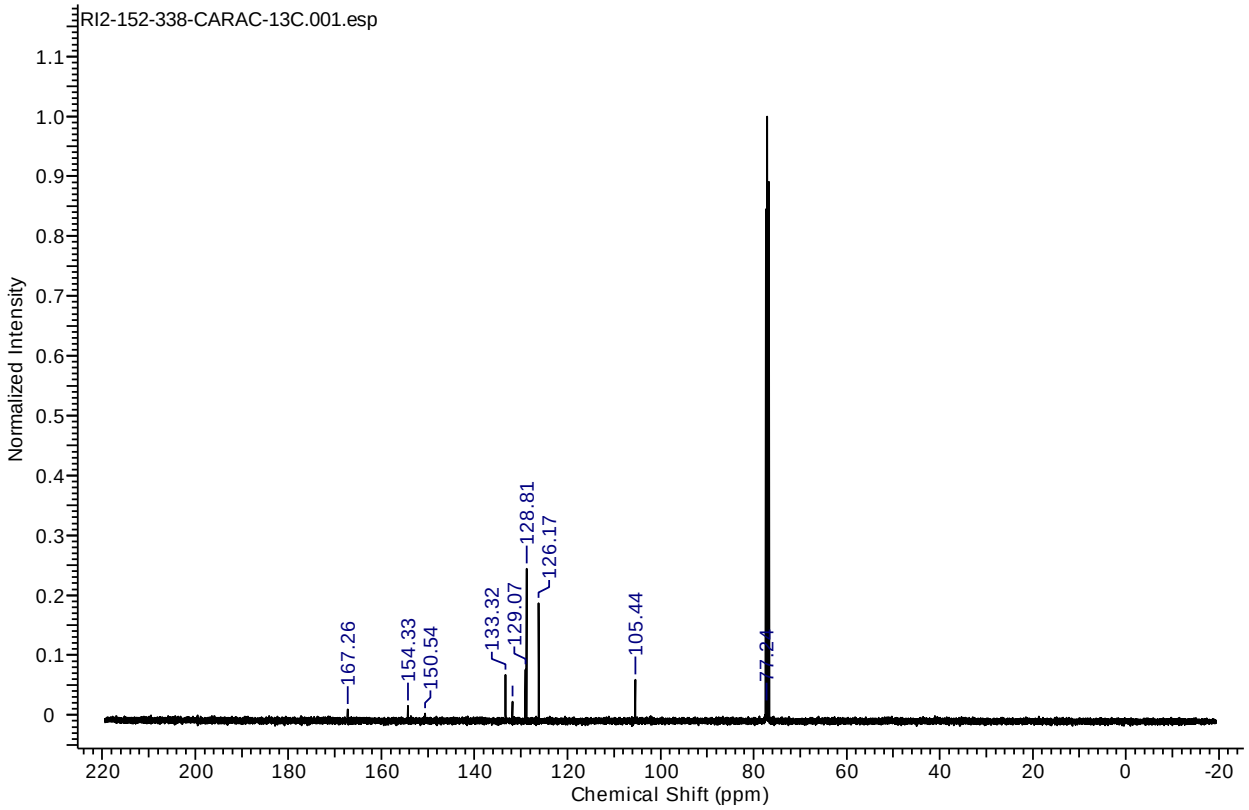

RI2-176-361-1H2.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
2.03
3.07
1.01
8.33

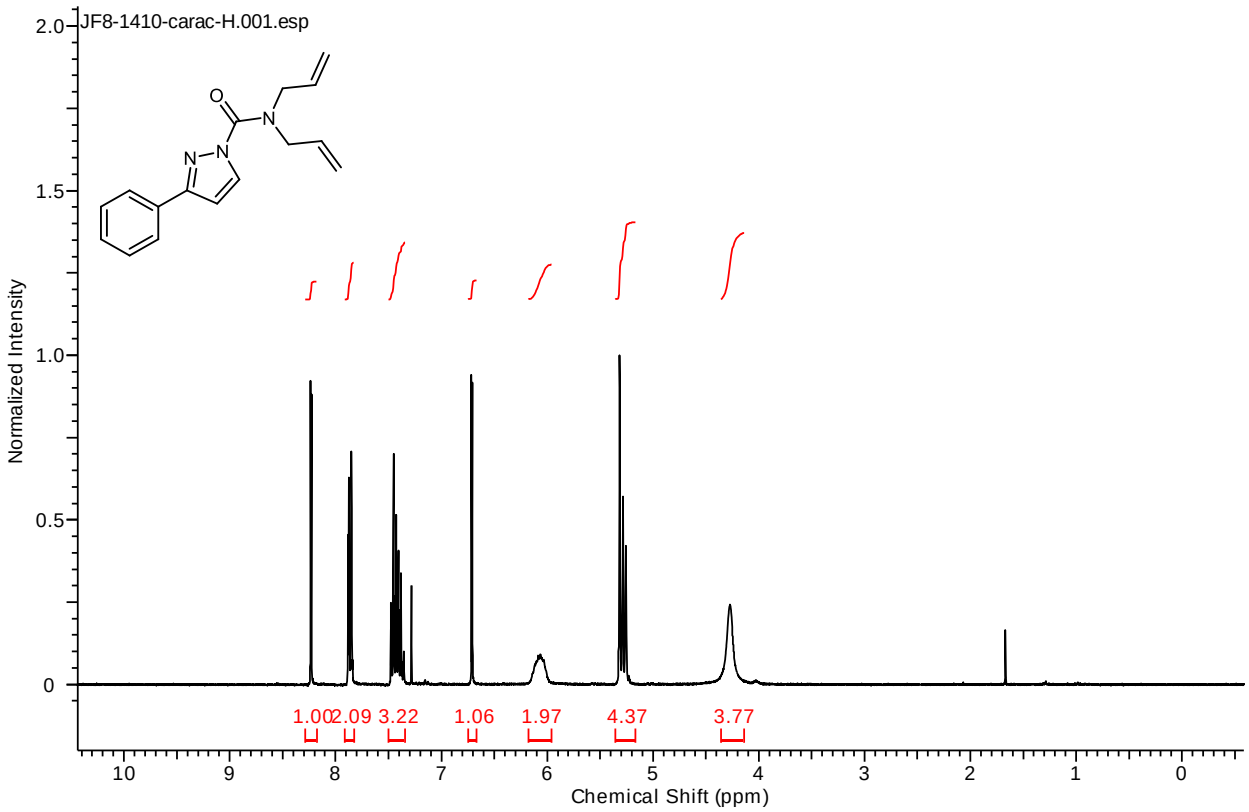

RI2-176-361-13C2.001.esp
Normalized Intensity
Chemical Shift (ppm)
153.74
151.03
133.34
128.86
128.78
126.07
104.91
66.84

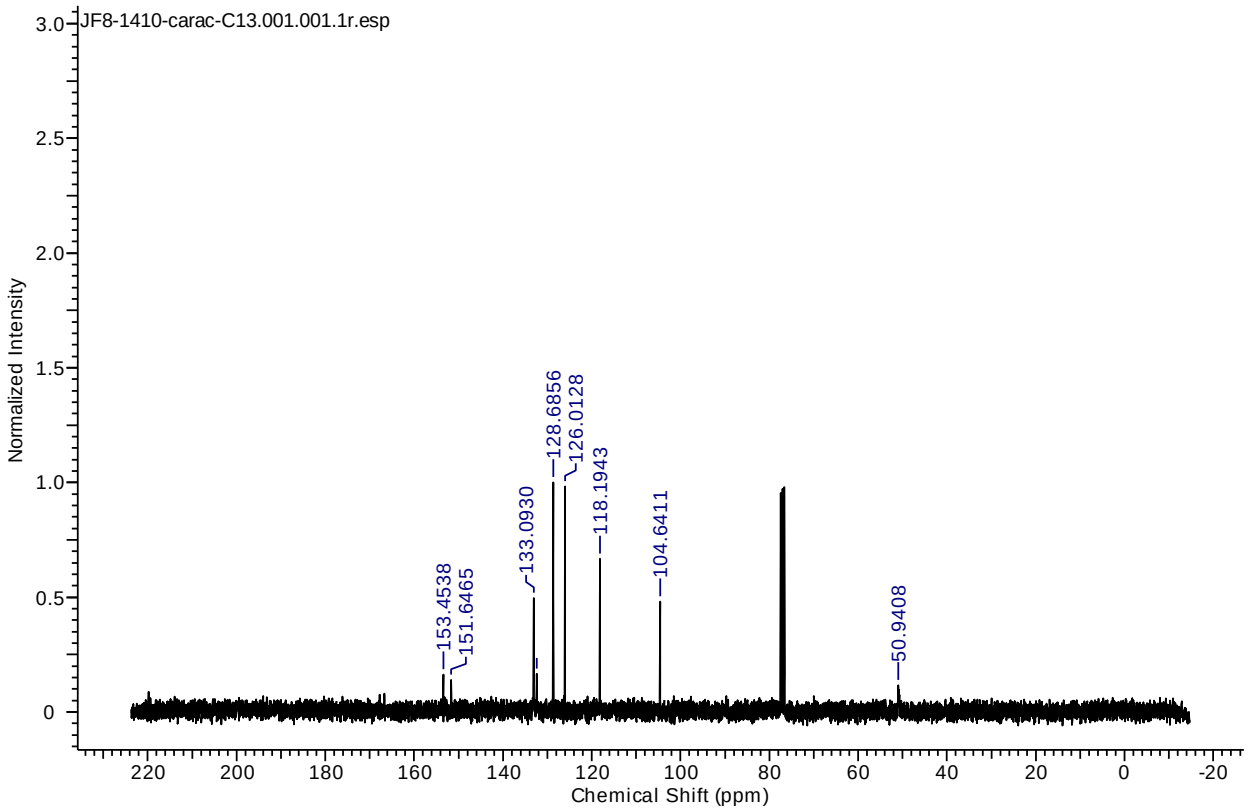

RI3-43-1H.001.esp
Br
O
N
N
N
N
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.00
2.04
5.15
2.17
1.03
4.04
4.17
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

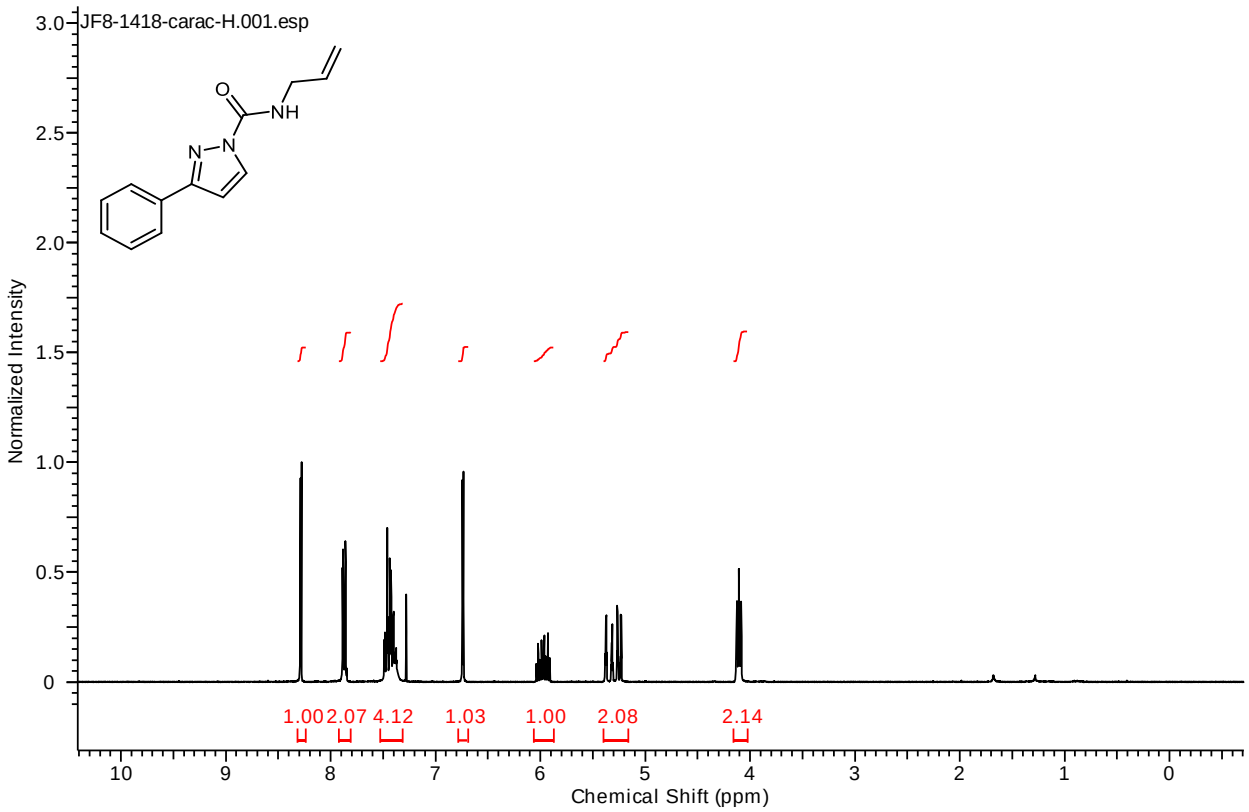

RI3-43-13C.001.esp
Normalized Intensity
2.0
1.5
1.0
0.5
0
153.76
149.99
133.34
132.08
128.80
126.08
118.15
112.72
104.95
49.30
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

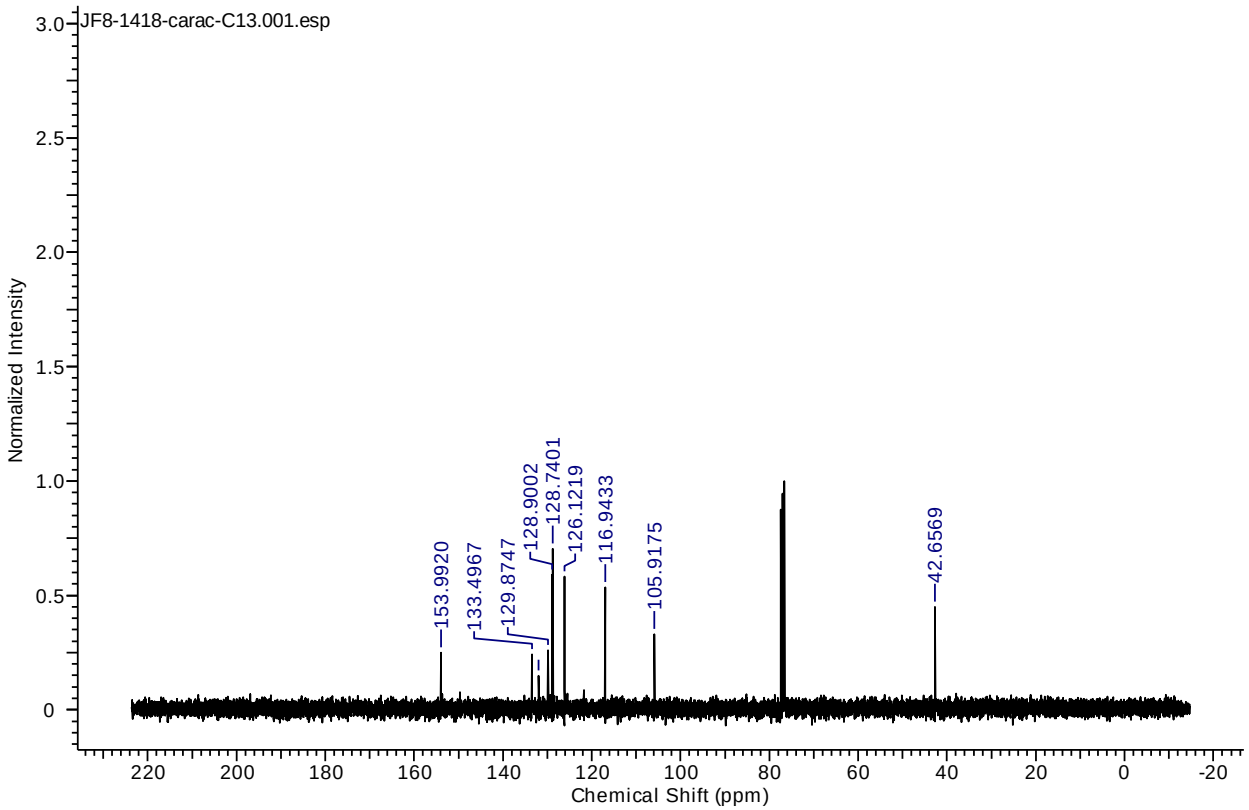

RI2-152-338-CARAC-1H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.98 1.96 2.98 1.94 1.95 1.97 2.00

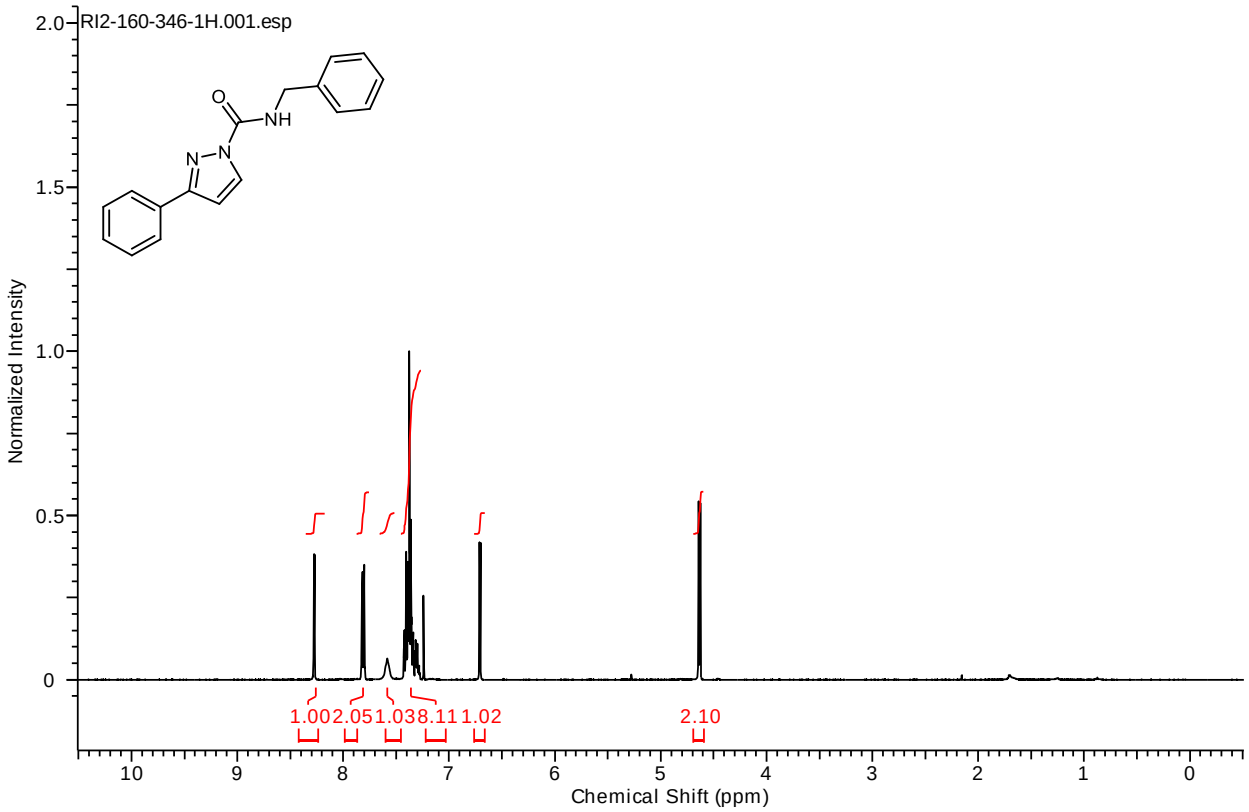

RI2-152-338-CARAC-13C.001.esp
Normalized Intensity
Chemical Shift (ppm)
167.26
154.33
150.54
133.32
129.07
128.81
126.17
105.44
77.24

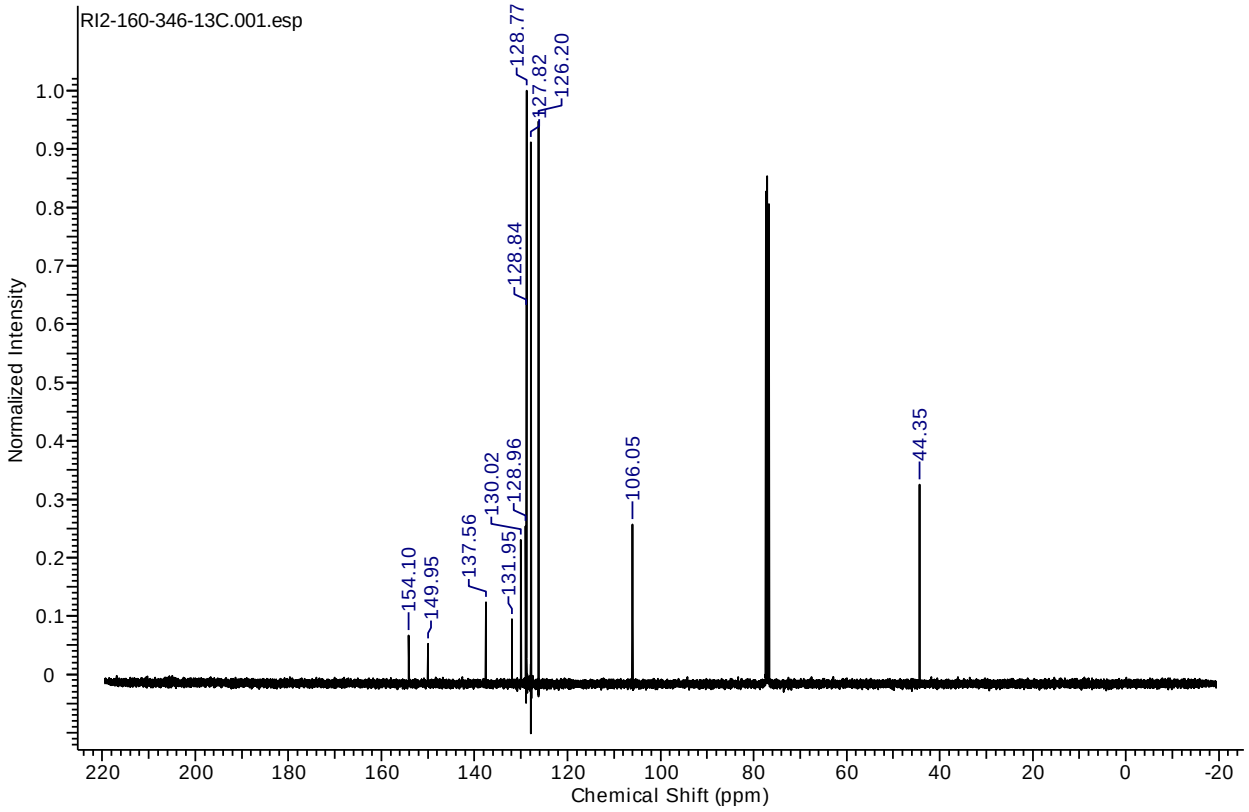

JF8-1410-carac-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
2.09
3.22
1.06
1.97
4.37
3.77

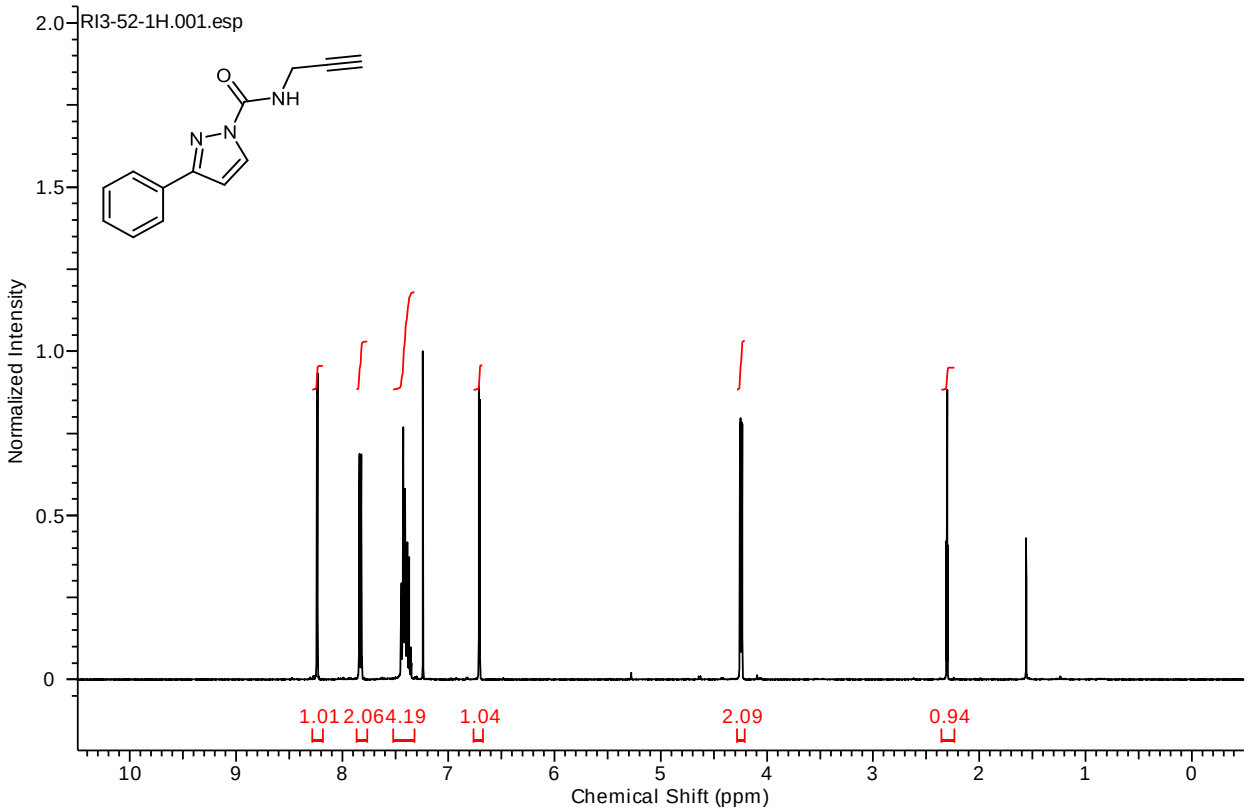

JF8-1410-carac-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
153.4538
151.6465
133.0930
128.6856
126.0128
118.1943
104.6411
50.9408

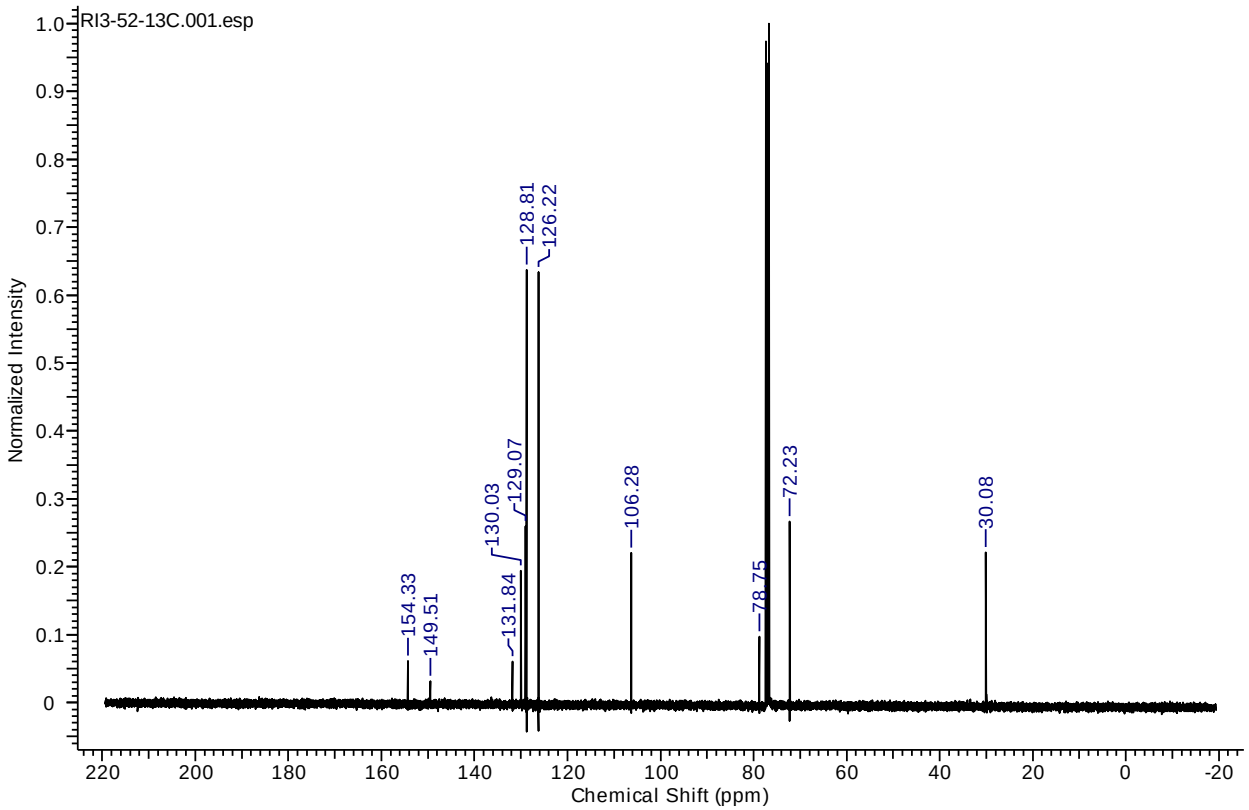

JF8-1418-carac-H.001.esp
O
NH
N
N
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
1.00 2.07 4.12 1.03 1.00 2.08 2.14
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

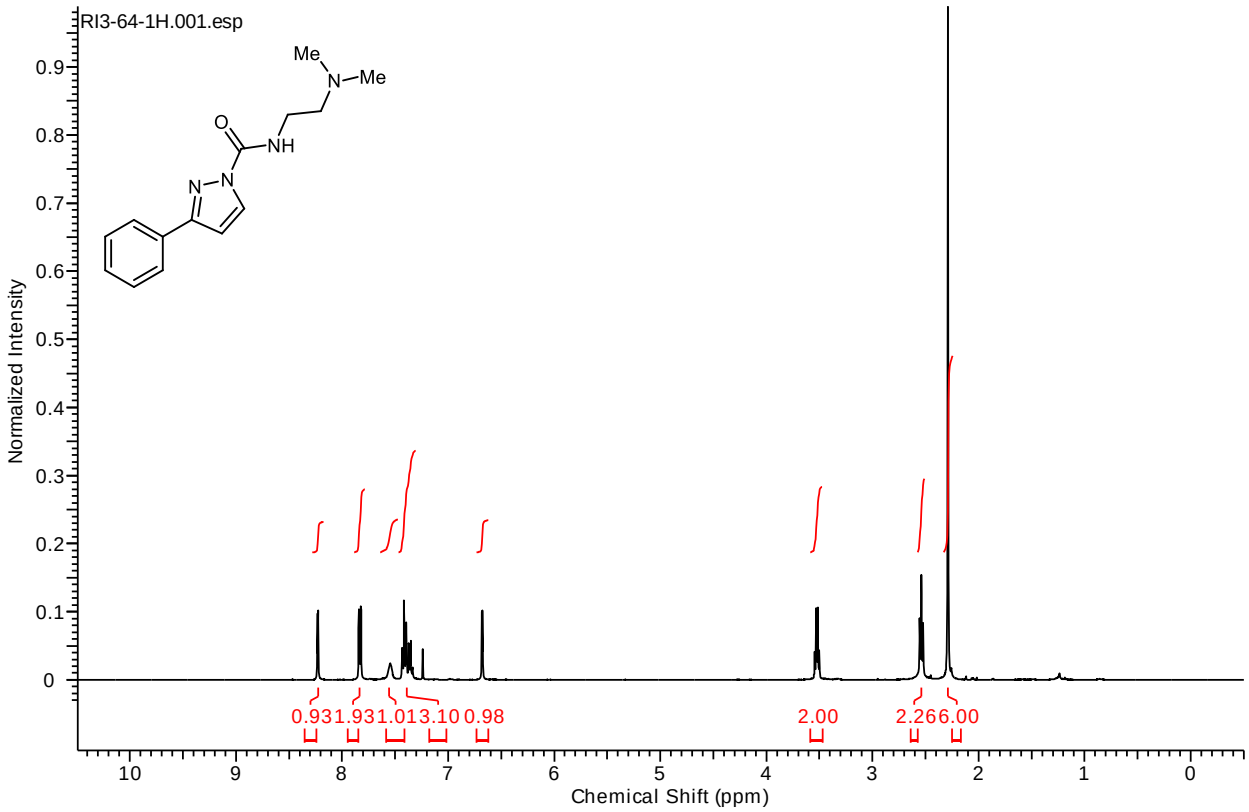

JF8-1418-carac-C13.001.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
153.9920
133.4967
129.8747
128.9002
128.7401
126.1219
116.9433
105.9175
42.6569
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

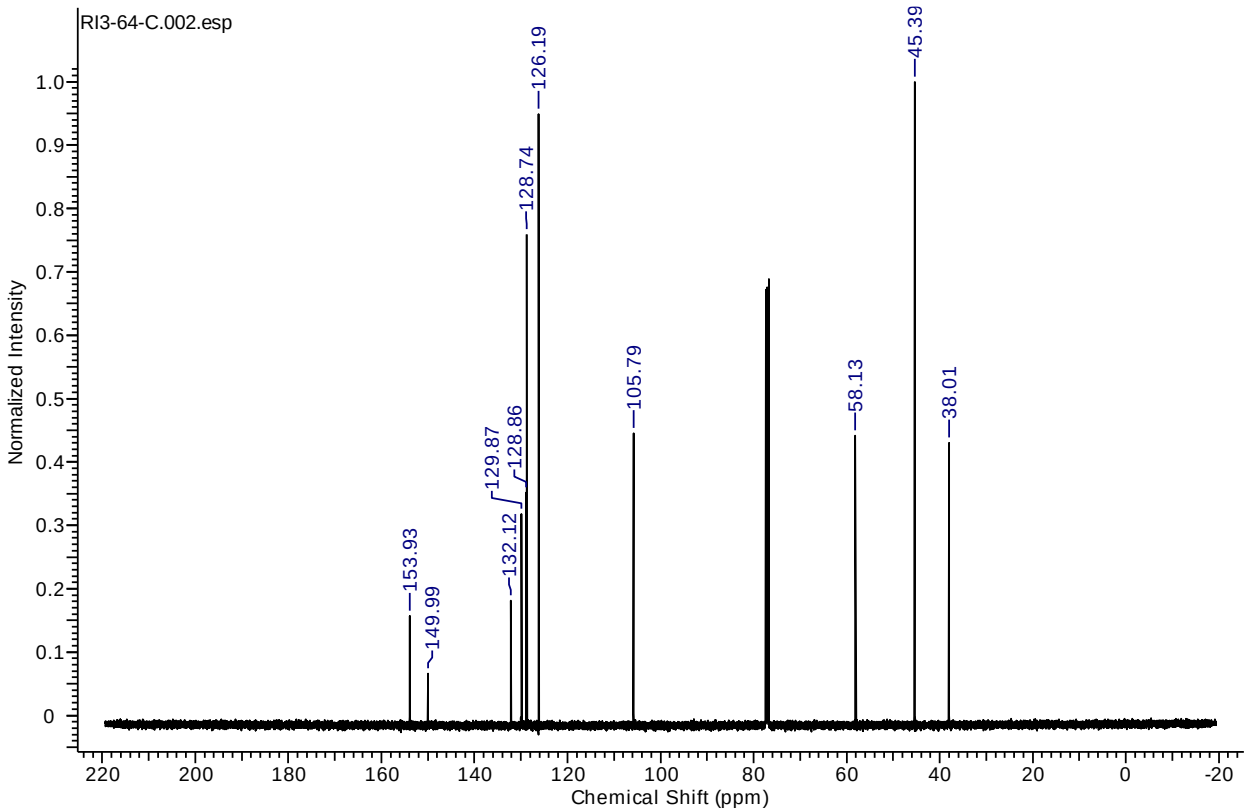

RI2-160-346-1H.001.esp
O
NH
N
N
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.00
2.05
1.03
8.11
1.02
2.10
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

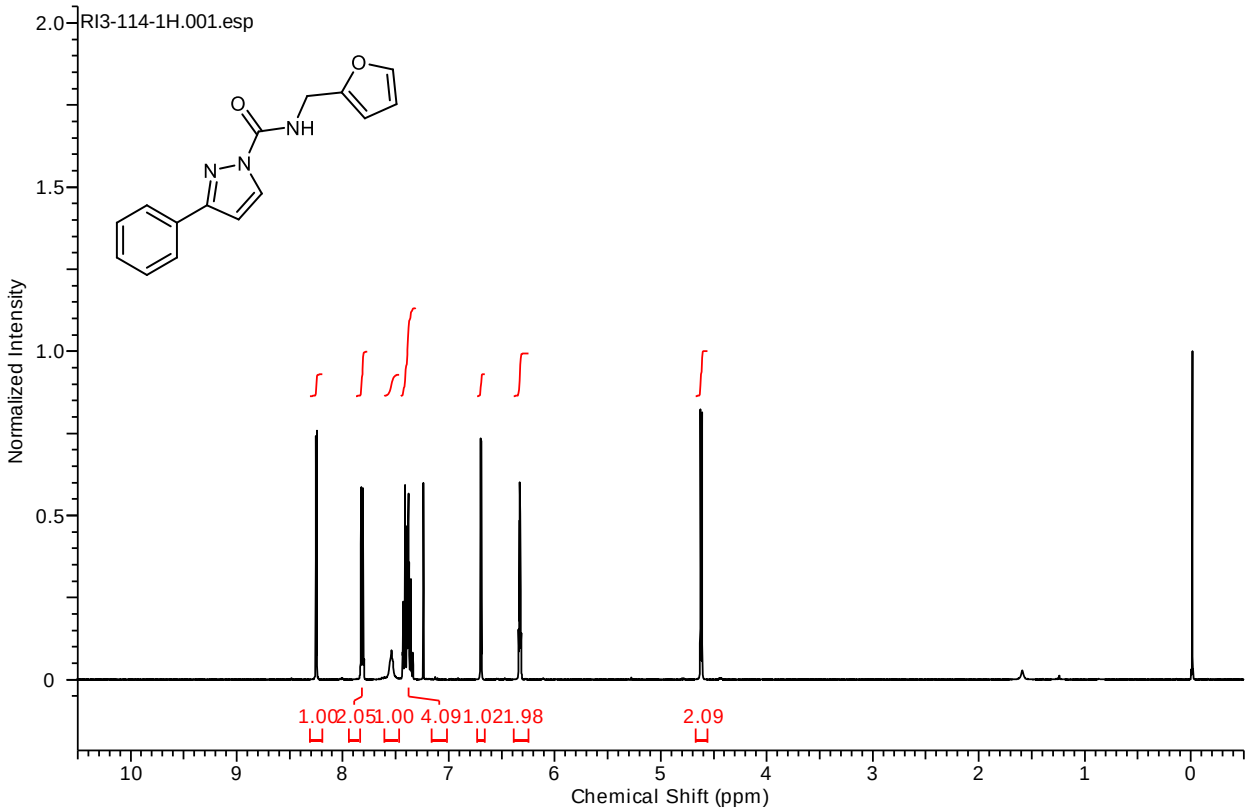

RI2-160-346-13C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
128.77
127.82
126.20
128.84
130.02
128.96
131.95
137.56
154.10
149.95
106.05
44.35
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

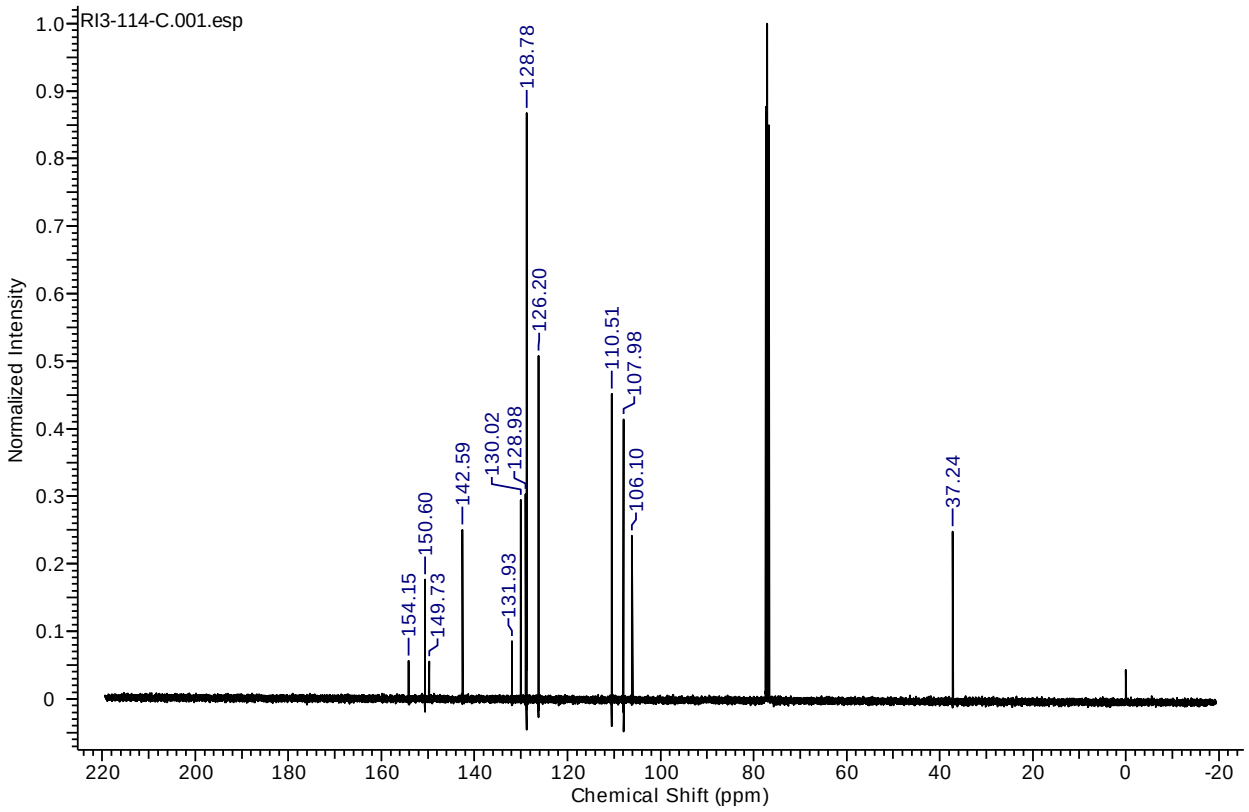

RI3-52-1H.001.esp
O
NH
N
N
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.01
2.06
4.19
1.04
2.09
0.94
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

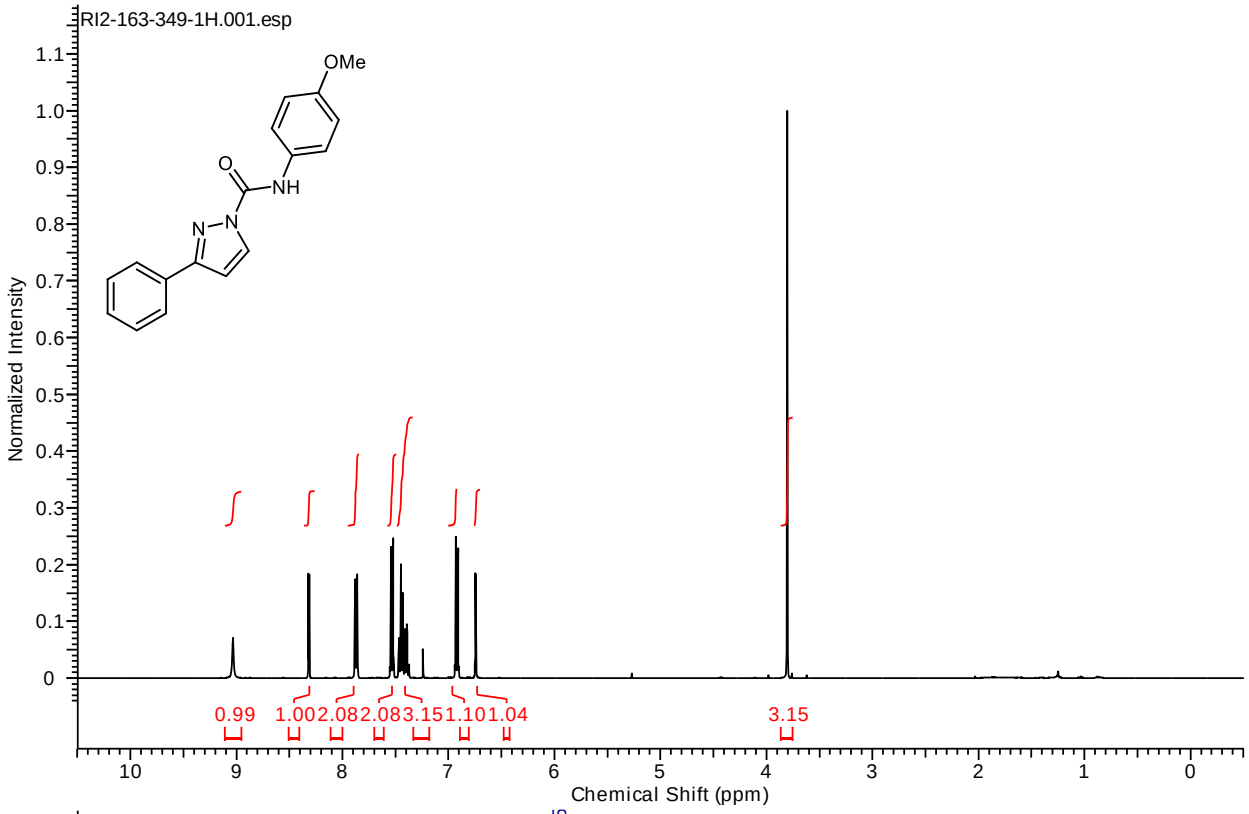

RI3-52-13C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
154.33
149.51
131.84
130.03
129.07
128.81
126.22
106.28
78.75
72.23
30.08
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

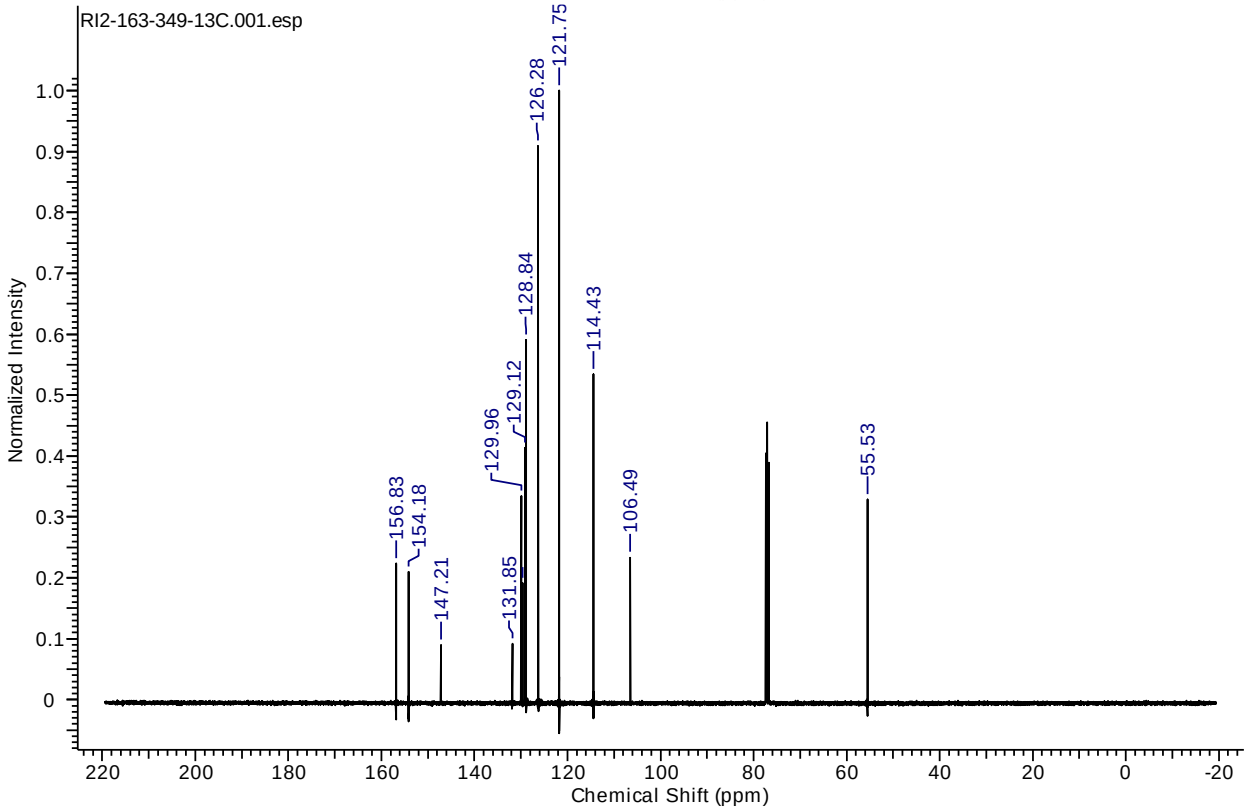

RI3-64-1H.001.esp
Me
N
Me
O
NH
N
N
Normalized Intensity
0.93
1.93
1.01
3.10
0.98
2.00
2.26
6.00
Chemical Shift (ppm)

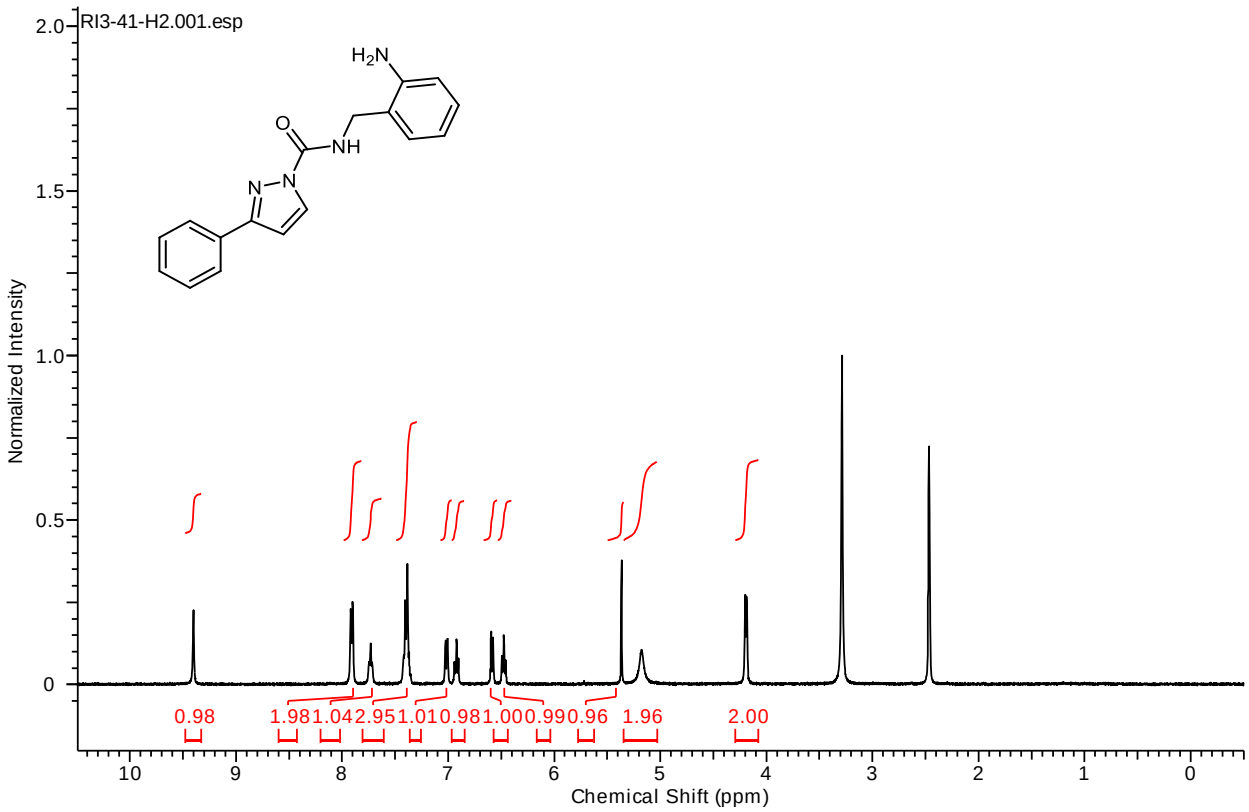

RI3-64-C.002.esp
153.93
149.99
132.12
129.87
128.86
128.74
126.19
105.79
58.13
45.39
38.01
Normalized Intensity
Chemical Shift (ppm)

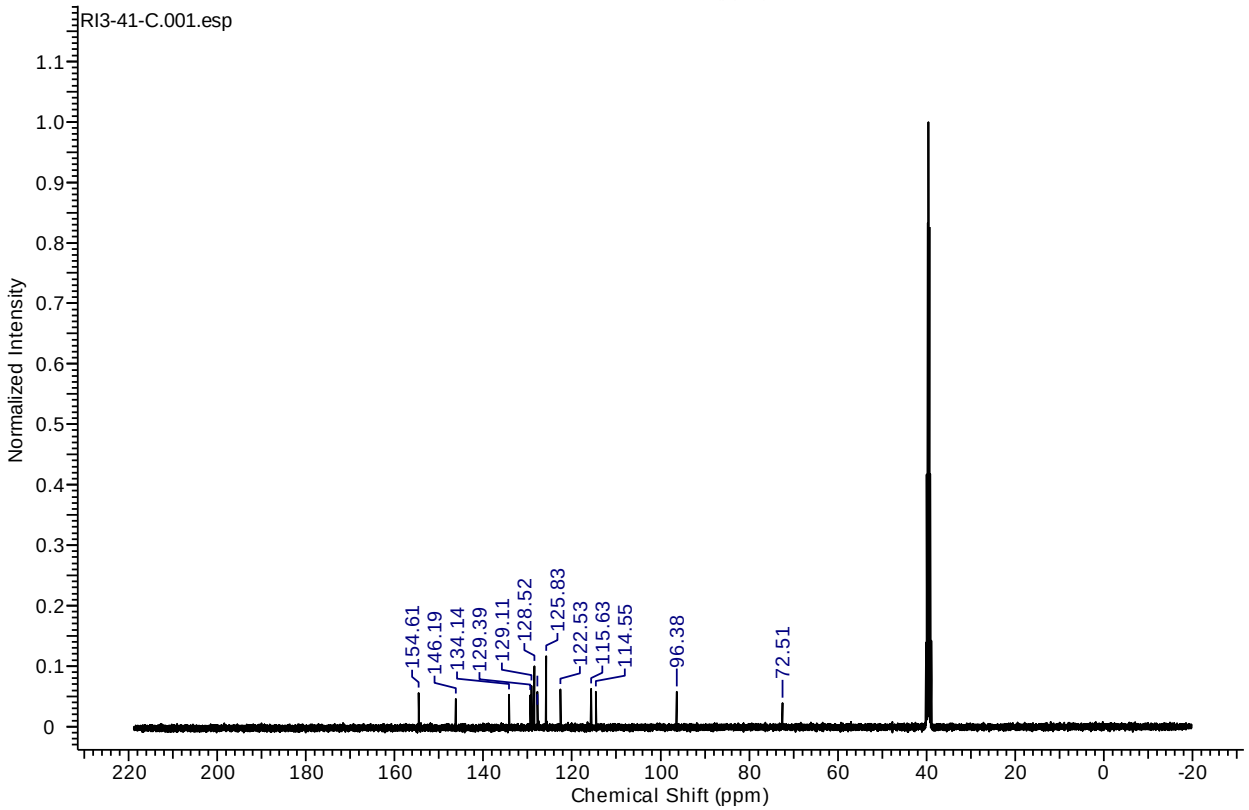

RI3-114-1H.001.esp
O
NH
O
N
N
Normalized Intensity
1.00
2.05
1.00
4.09
1.02
1.98
2.09
Chemical Shift (ppm)

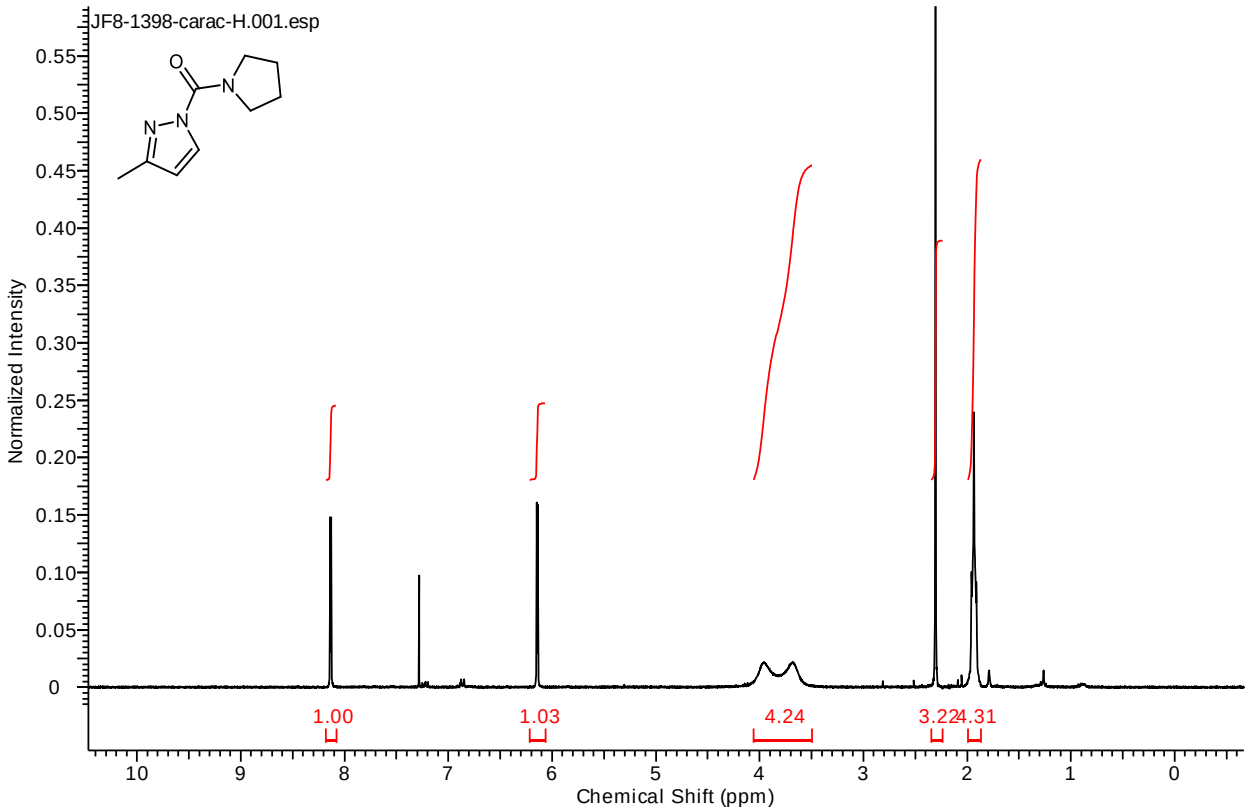

RI3-114-C.001.esp
154.15
150.60
149.73
142.59
131.93
130.02
128.98
128.78
126.20
110.51
107.98
106.10
37.24
Normalized Intensity
Chemical Shift (ppm)

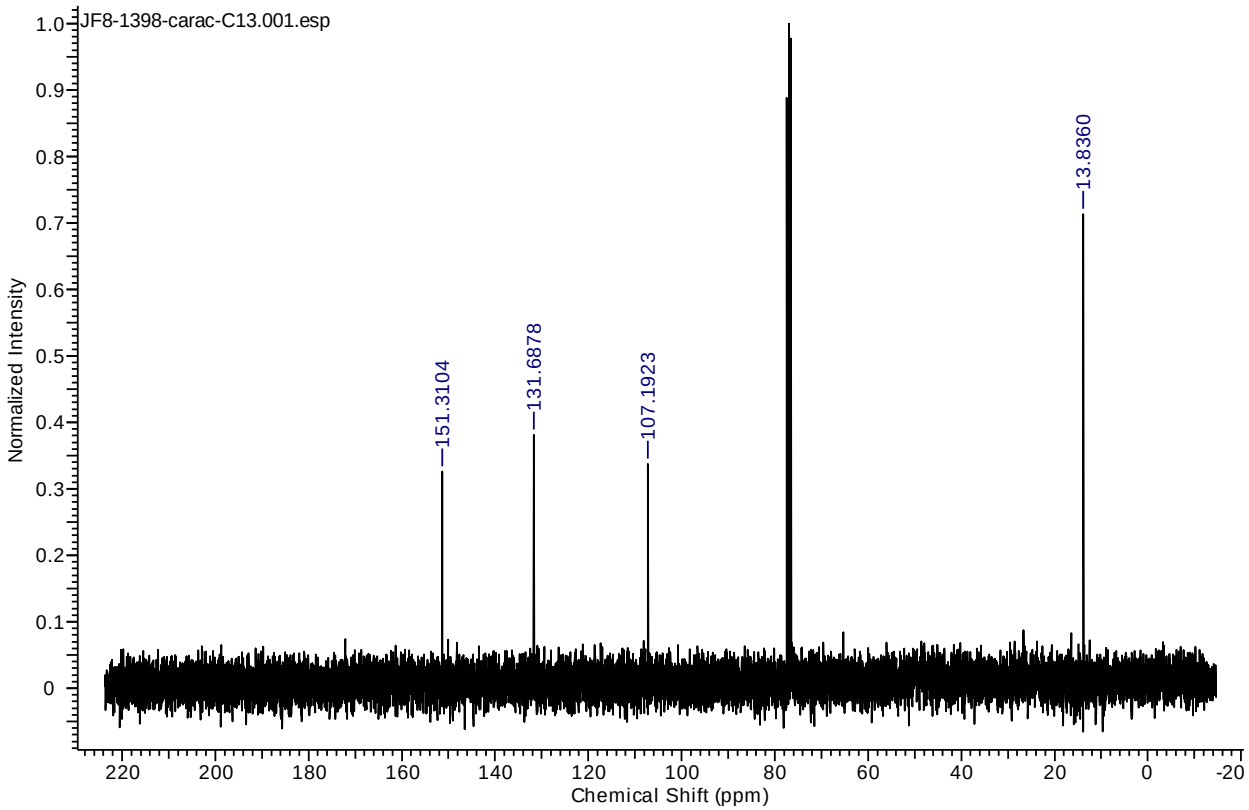

RI2-163-349-1H.001.esp
OMe
O
NH
N
N
Normalized Intensity
0.99
1.00
2.08
2.08
3.15
1.10
1.04
3.15
Chemical Shift (ppm)

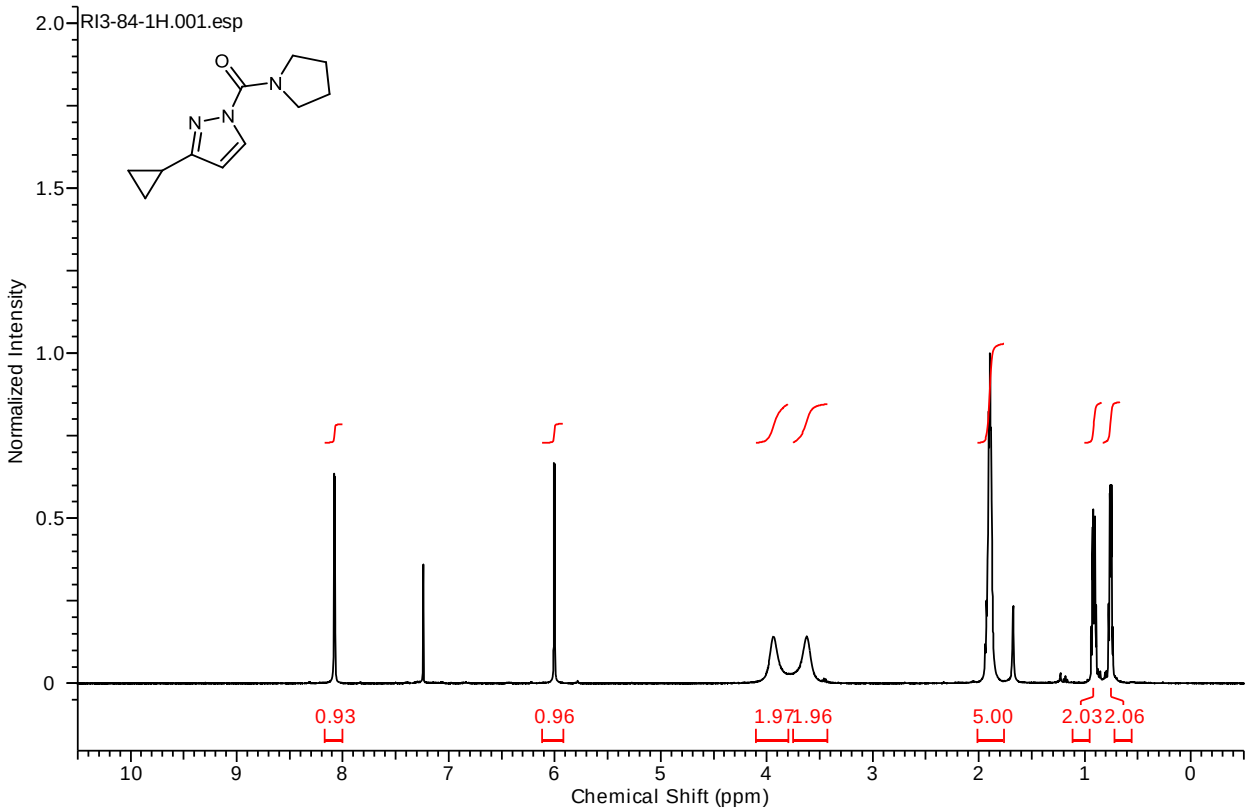

RI2-163-349-13C.001.esp
156.83
154.18
147.21
131.85
129.96
129.12
128.84
126.28
121.75
114.43
106.49
55.53
Normalized Intensity
Chemical Shift (ppm)

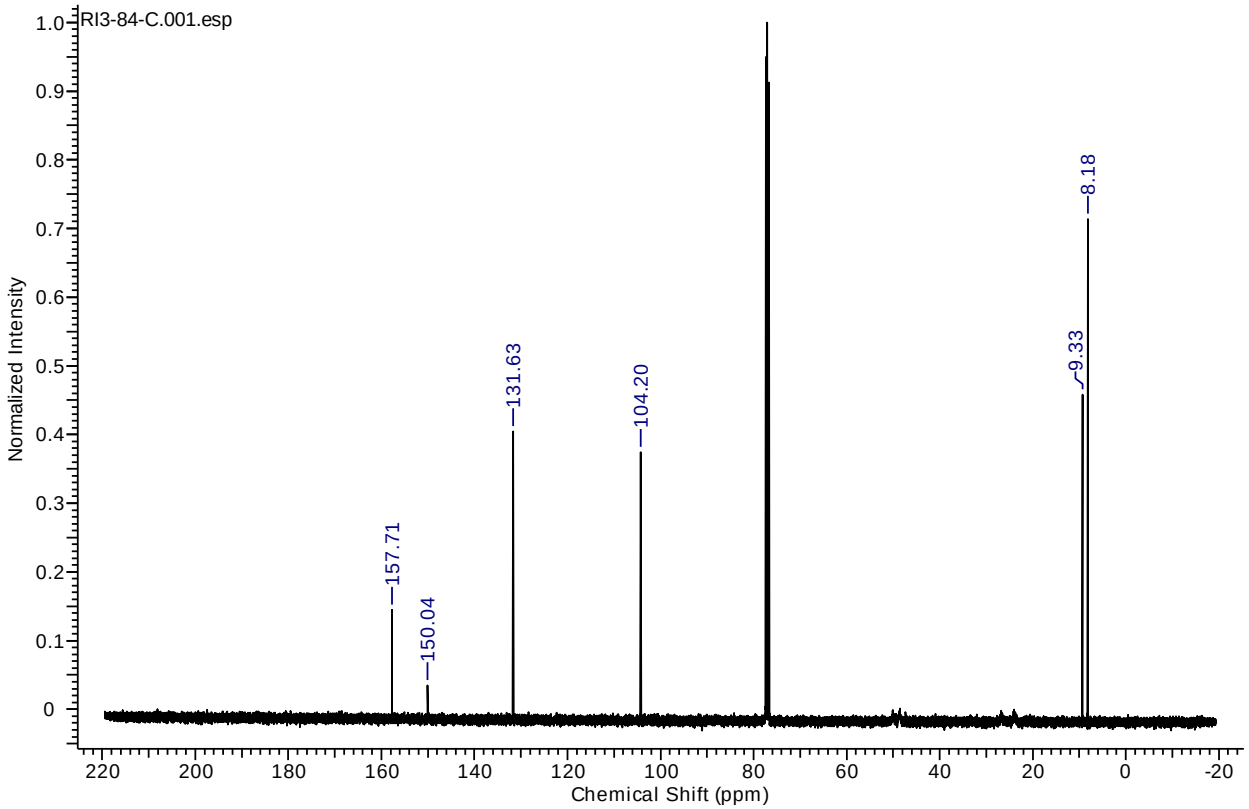

RI3-41-H2.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.98
1.98
1.04
2.95
1.01
0.98
1.00
0.99
0.96
1.96
2.00

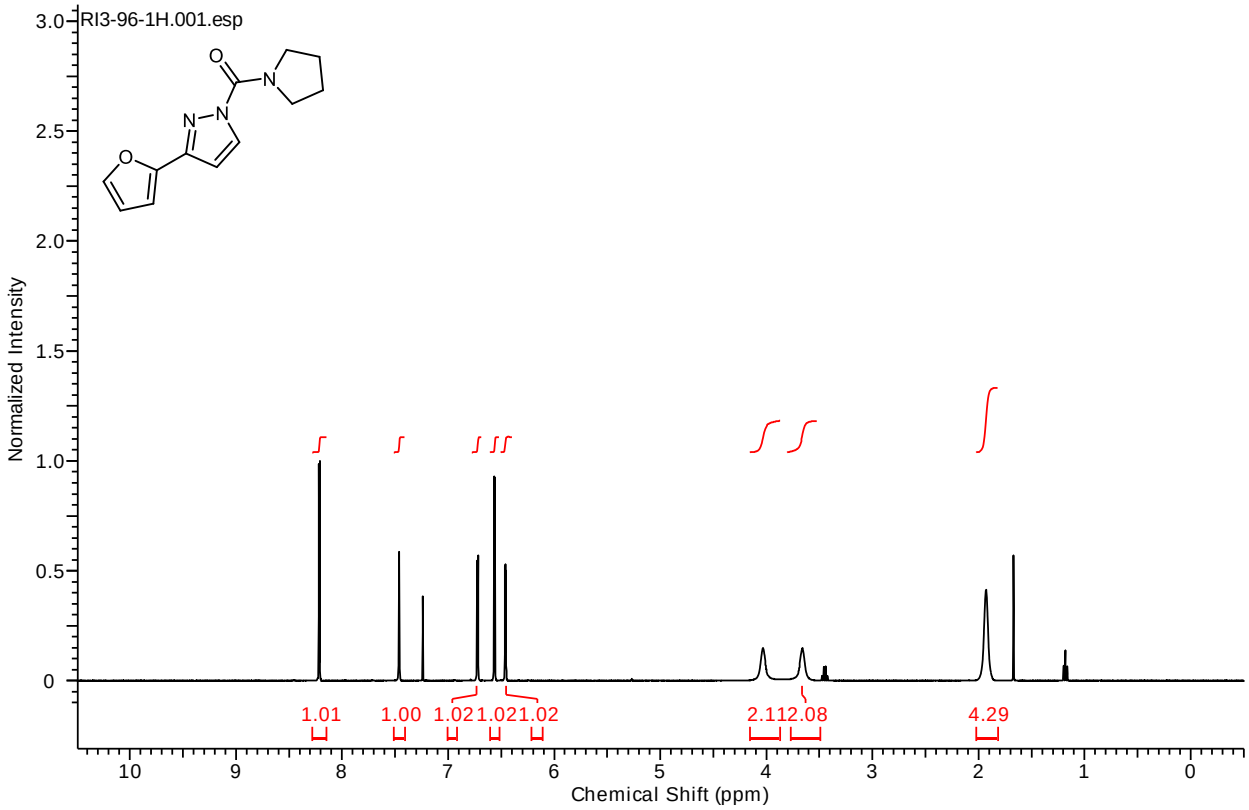

RI3-41-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
154.61
146.19
134.14
129.39
129.11
128.52
125.83
122.53
115.63
114.55
96.38
72.51

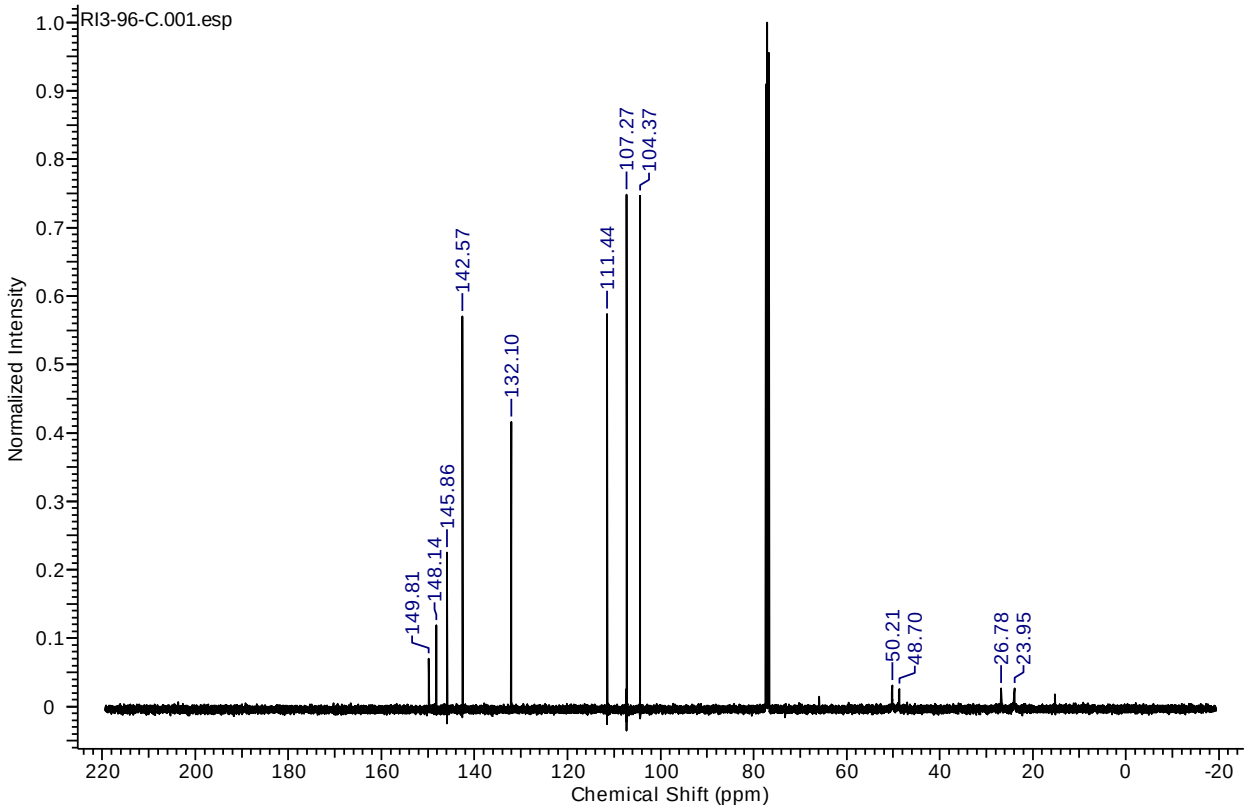

JF8-1398-carac-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
1.03
4.24
3.22
4.31

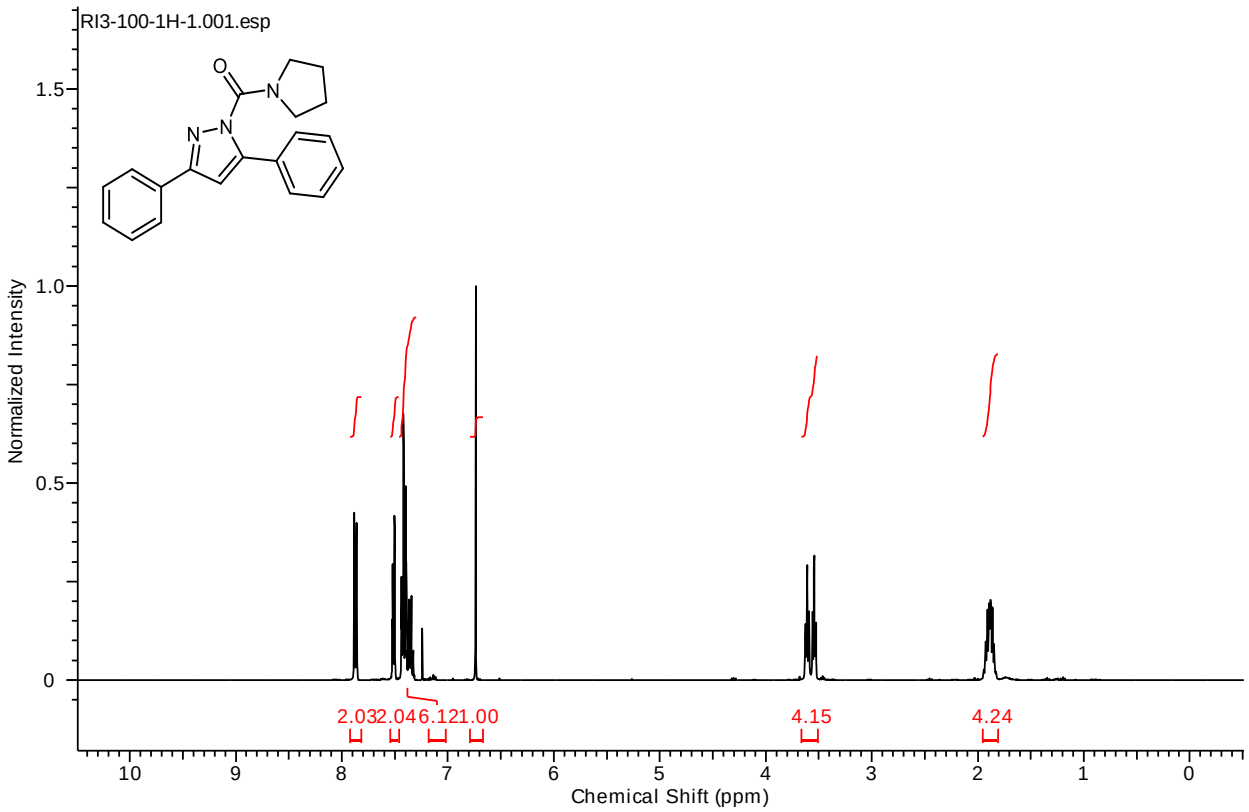

JF8-1398-carac-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
151.3104
131.6878
107.1923
13.8360

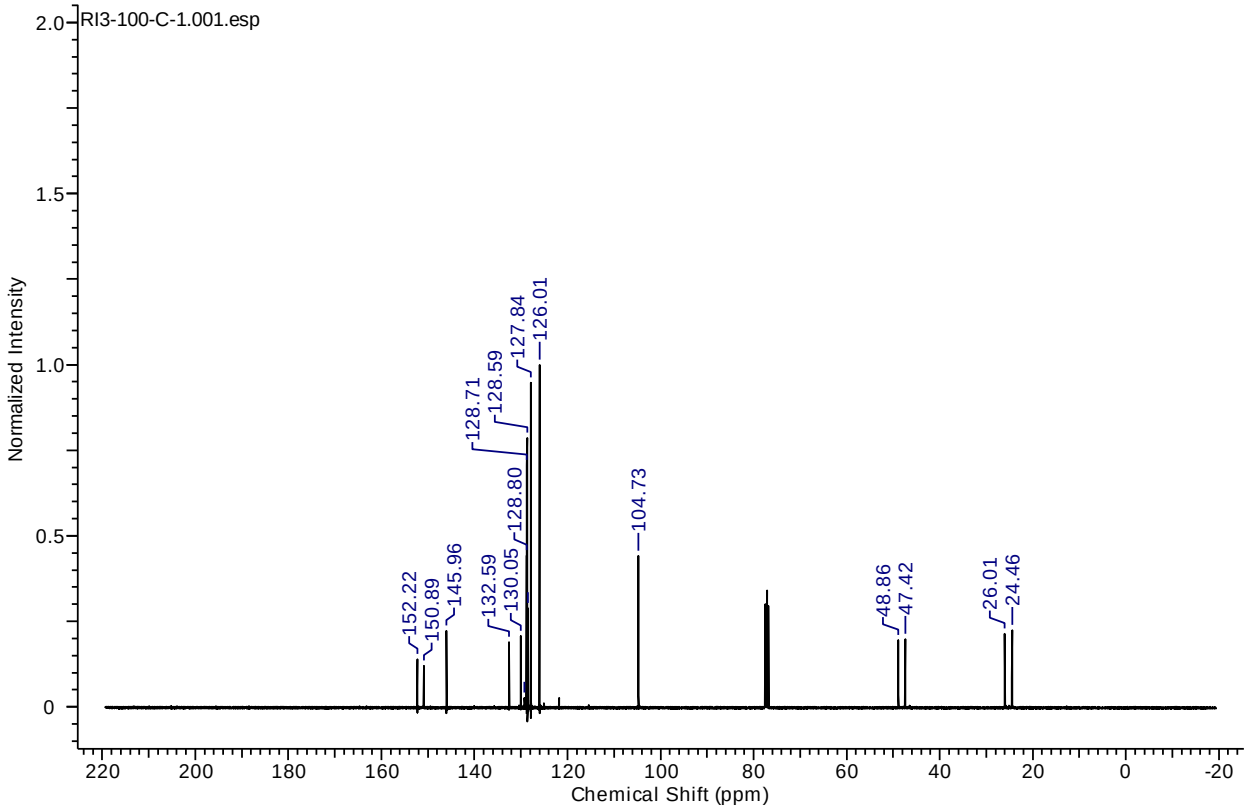

RI3-84-1H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.93
0.96
1.97
1.96
5.00
2.03
2.06

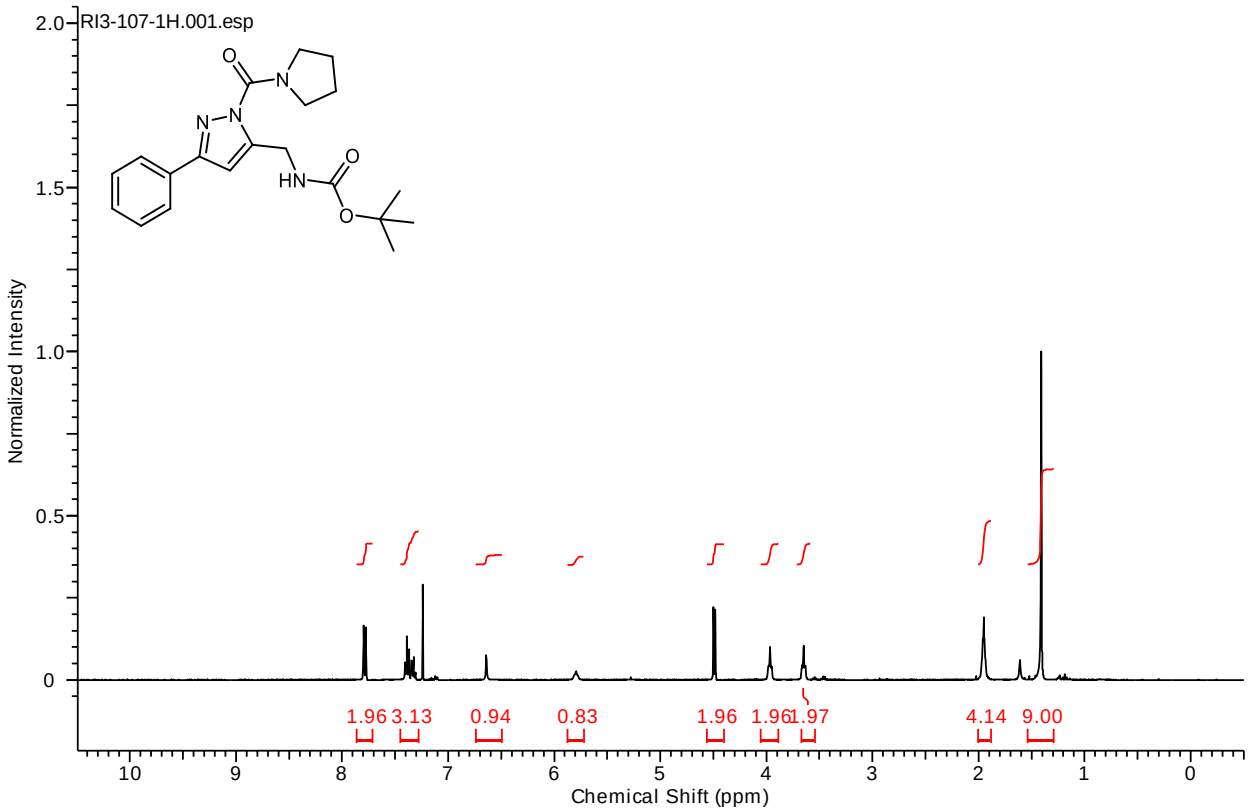

RI3-84-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
157.71
150.04
131.63
104.20
9.33
8.18

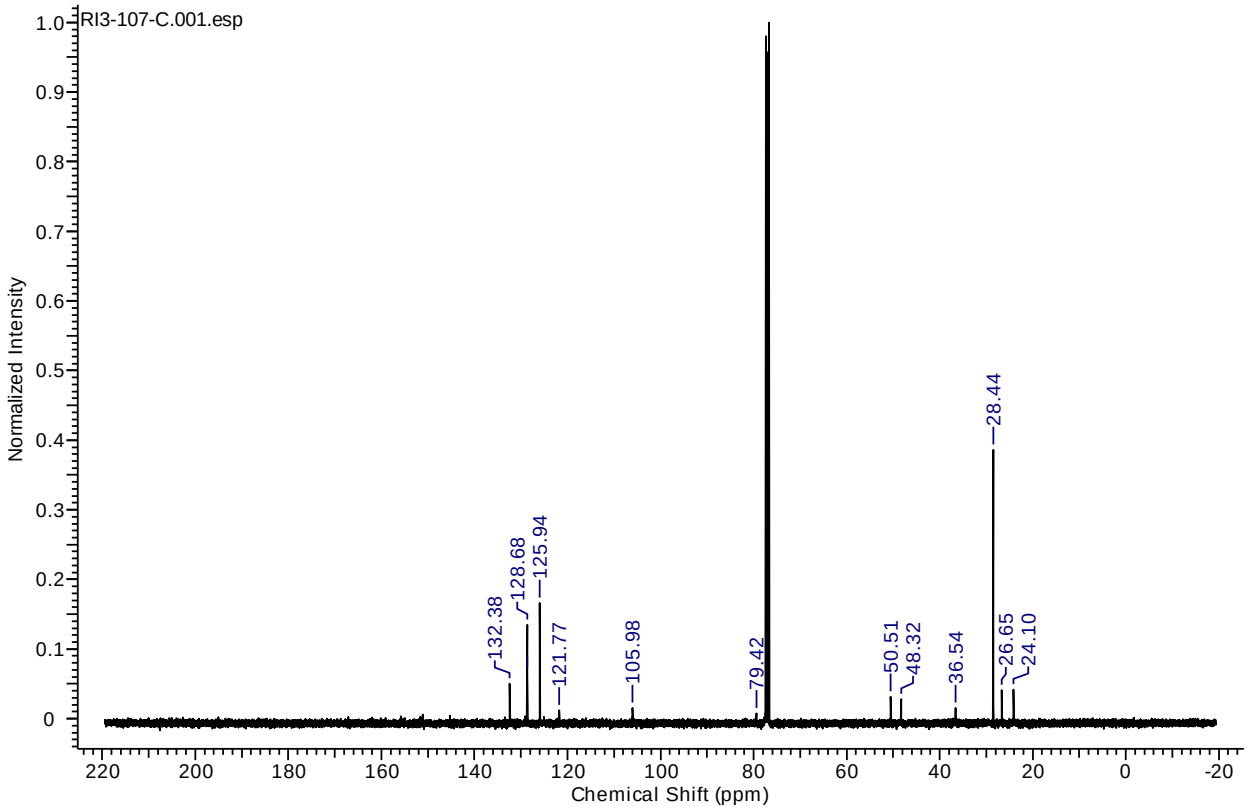

RI3-96-1H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.01
1.00
1.02
1.02
1.02
2.11
2.08
4.29

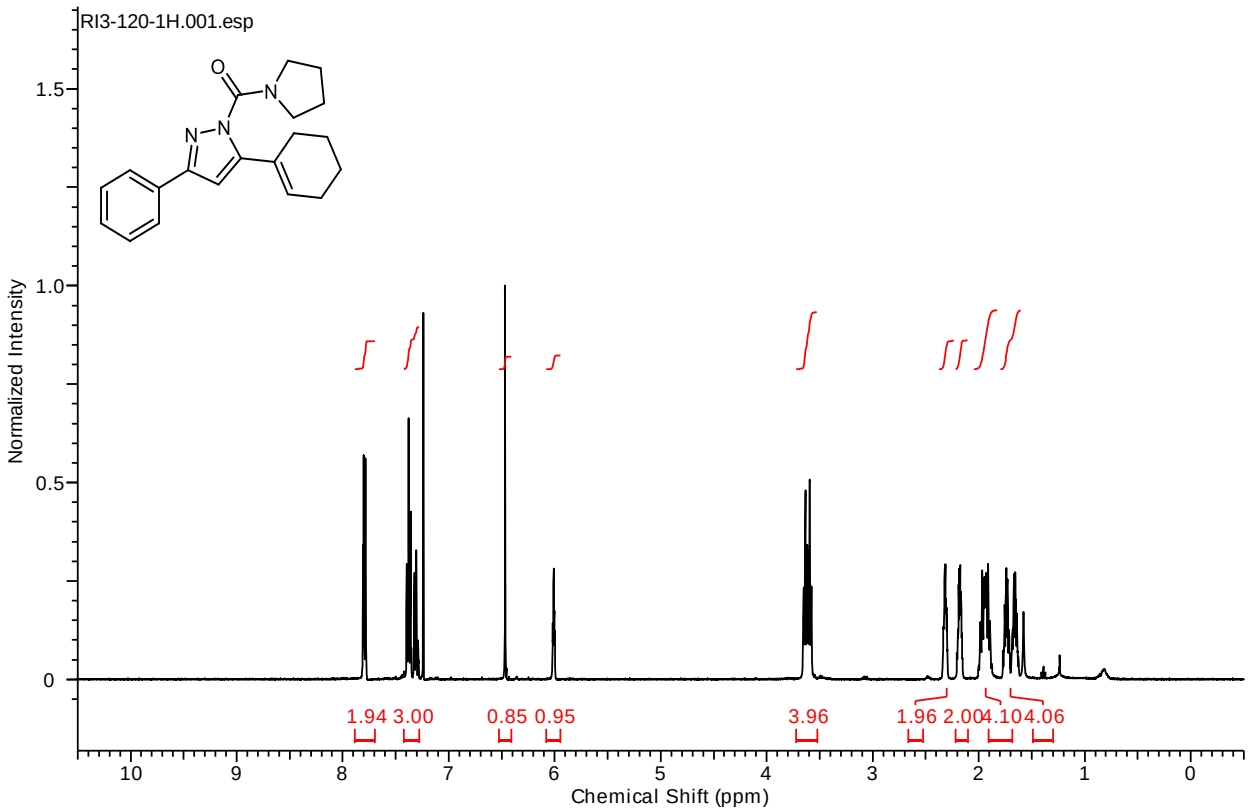

RI3-96-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
149.81
148.14
145.86
142.57
132.10
111.44
107.27
104.37
50.21
48.70
26.78
23.95

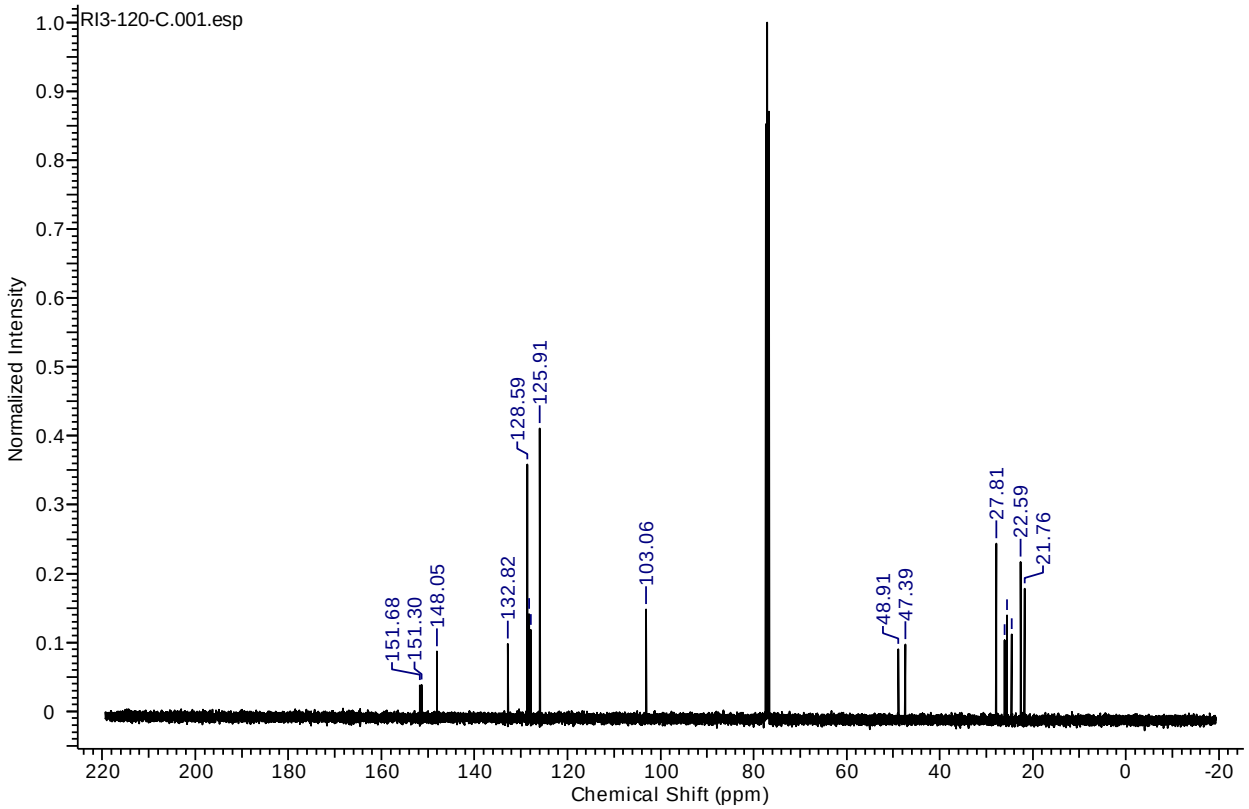

RI3-100-1H-1.001.esp
Normalized Intensity
Chemical Shift (ppm)
2.03
2.04
6.12
1.00
4.15
4.24

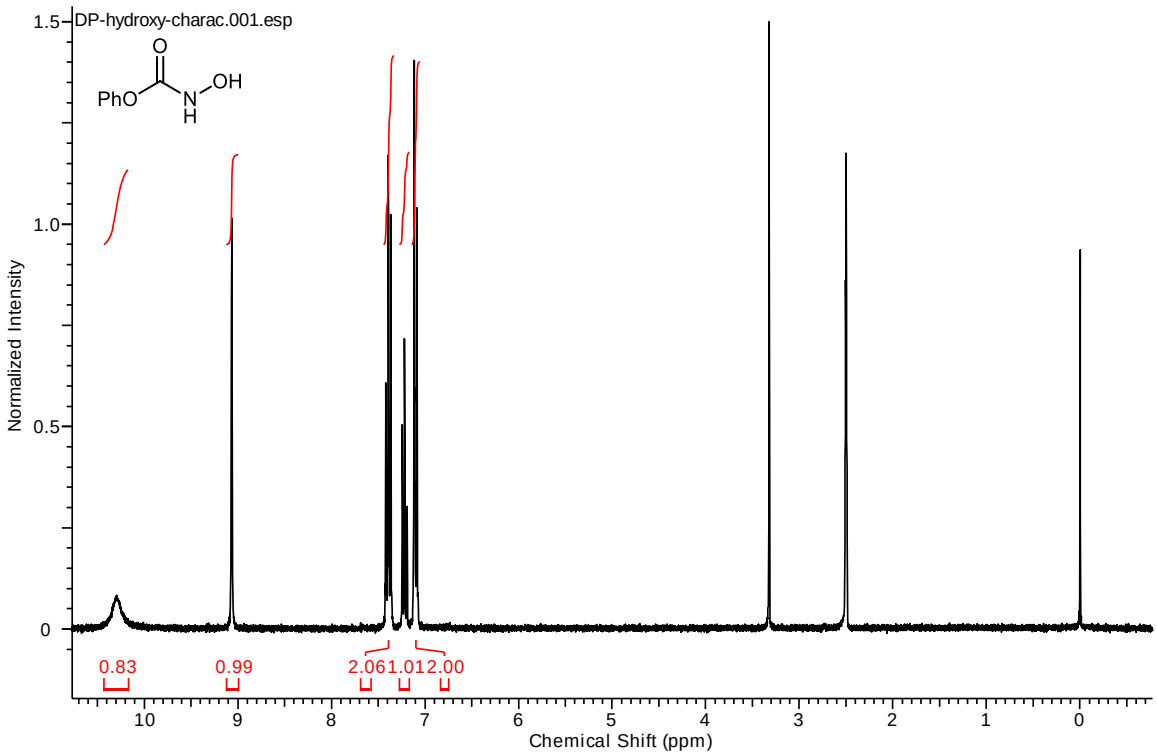

RI3-100-C-1.001.esp
Normalized Intensity
Chemical Shift (ppm)
152.22
150.89
145.96
132.59
130.05
128.80
128.71
128.59
127.84
126.01
104.73
48.86
47.42
26.01
24.46

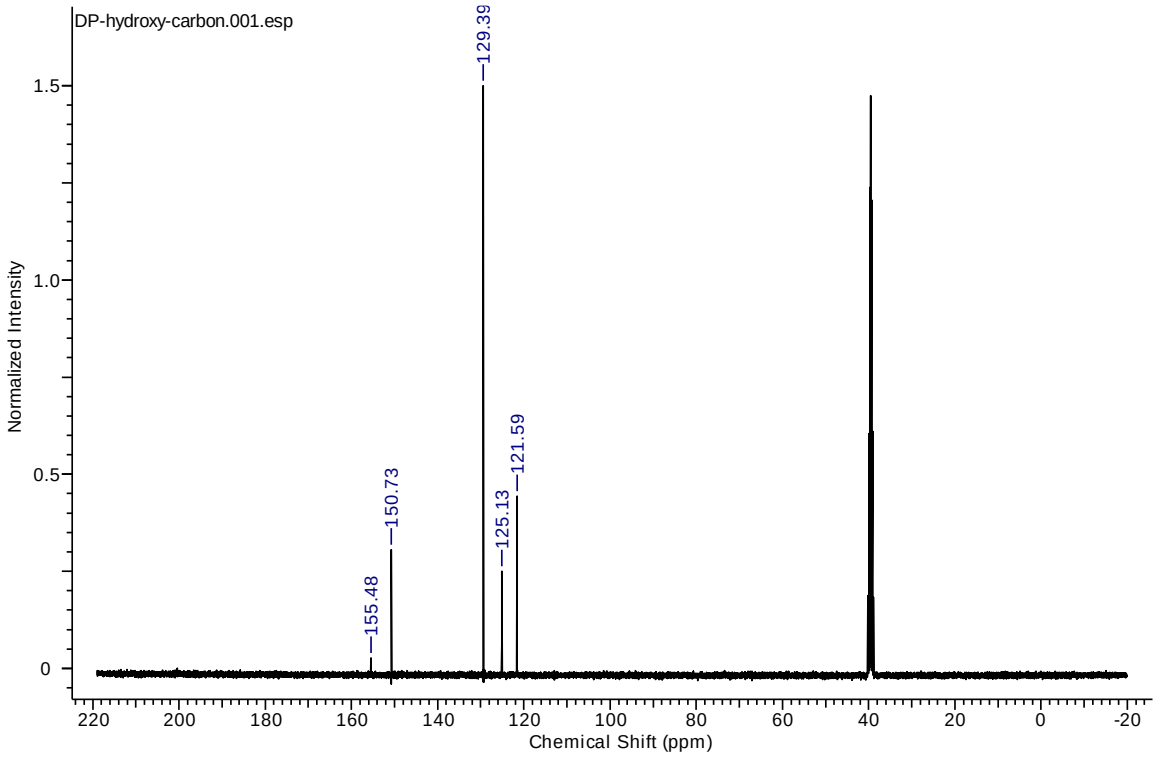

RI3-107-1H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.96 3.13 0.94 0.83 1.96 1.96 1.97 4.14 9.00

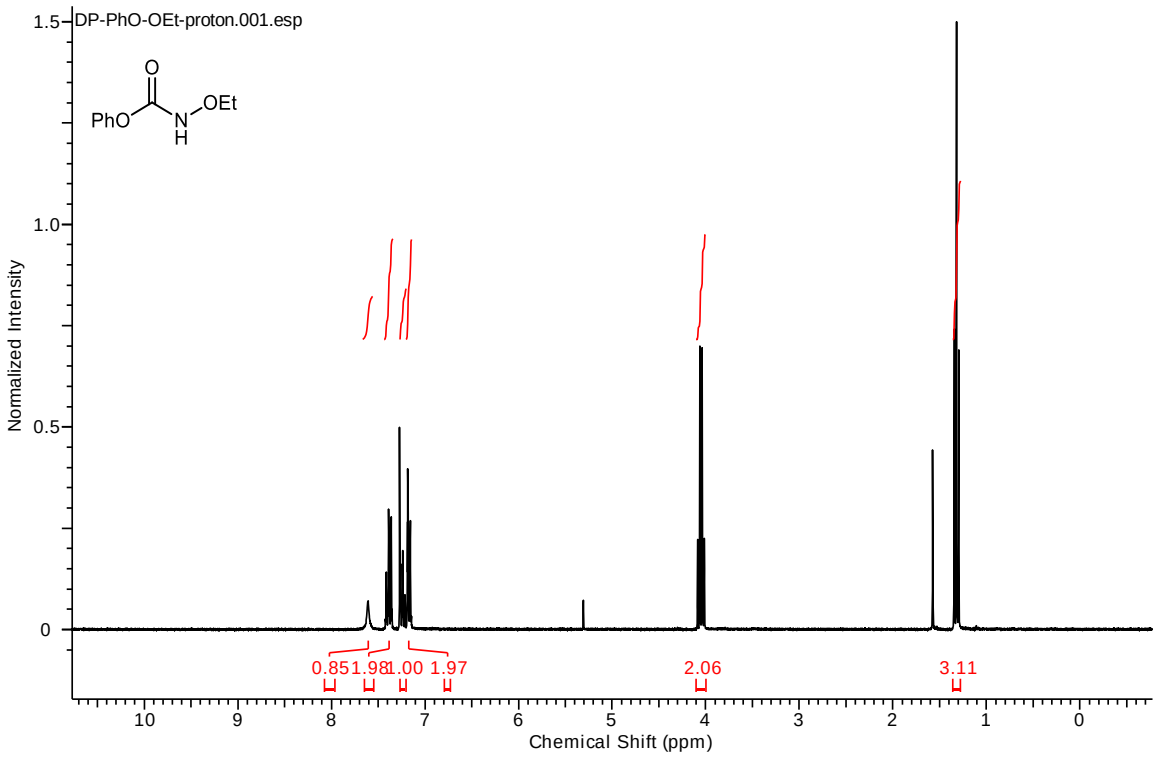

RI3-107-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
132.38
128.68
125.94
121.77
105.98
79.42
50.51
48.32
36.54
28.44
26.65
24.10

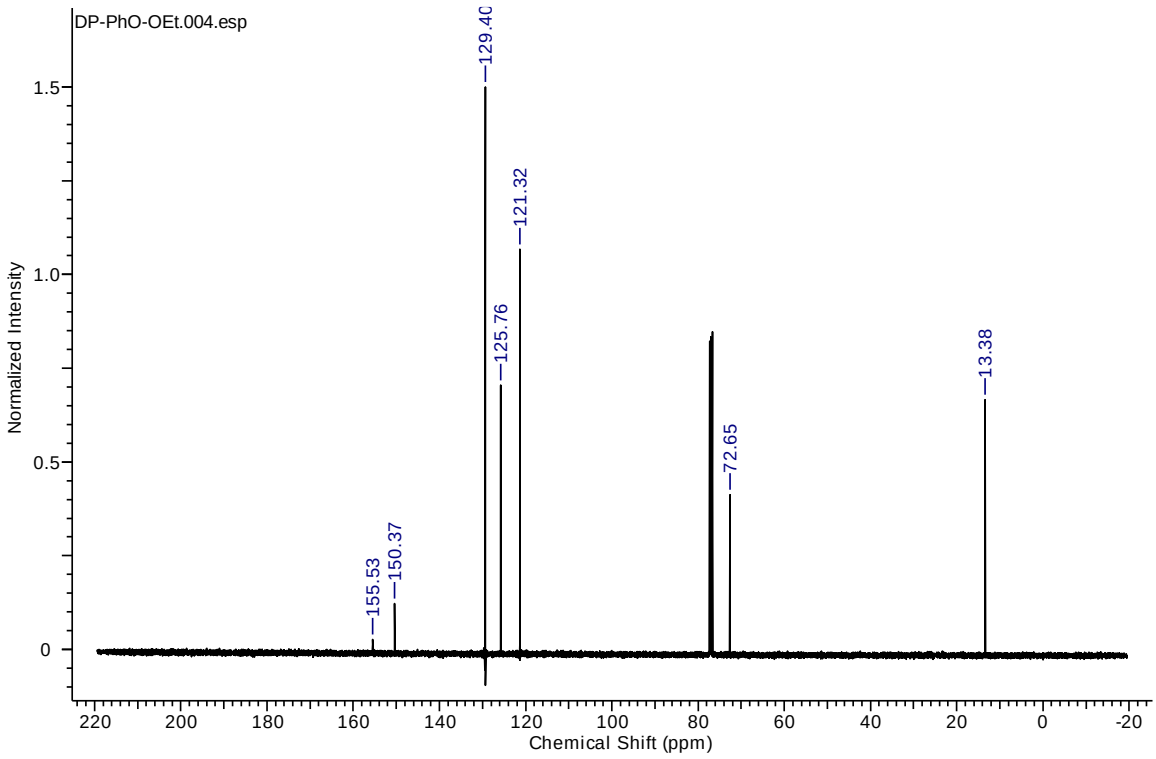

RI3-120-1H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.94 3.00 0.85 0.95 3.96 1.96 2.00 4.10 4.06

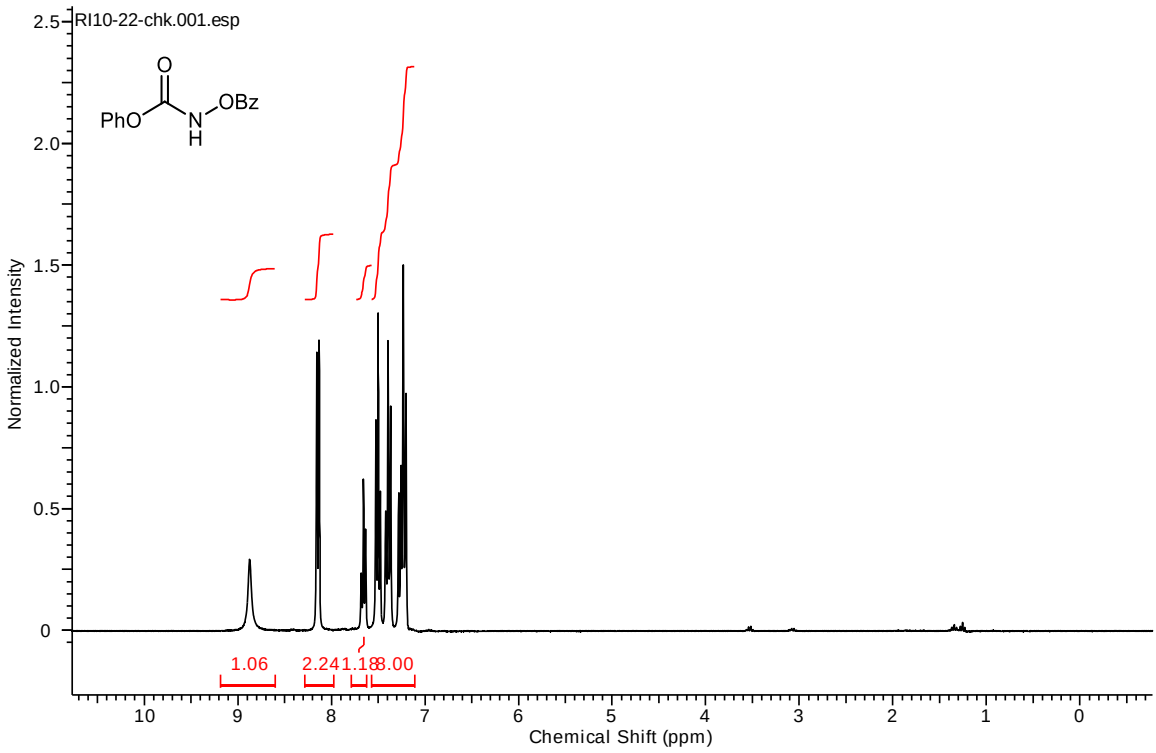

RI3-120-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
151.68
151.30
148.05
132.82
128.59
125.91
103.06
48.91
47.39
27.81
22.59
21.76

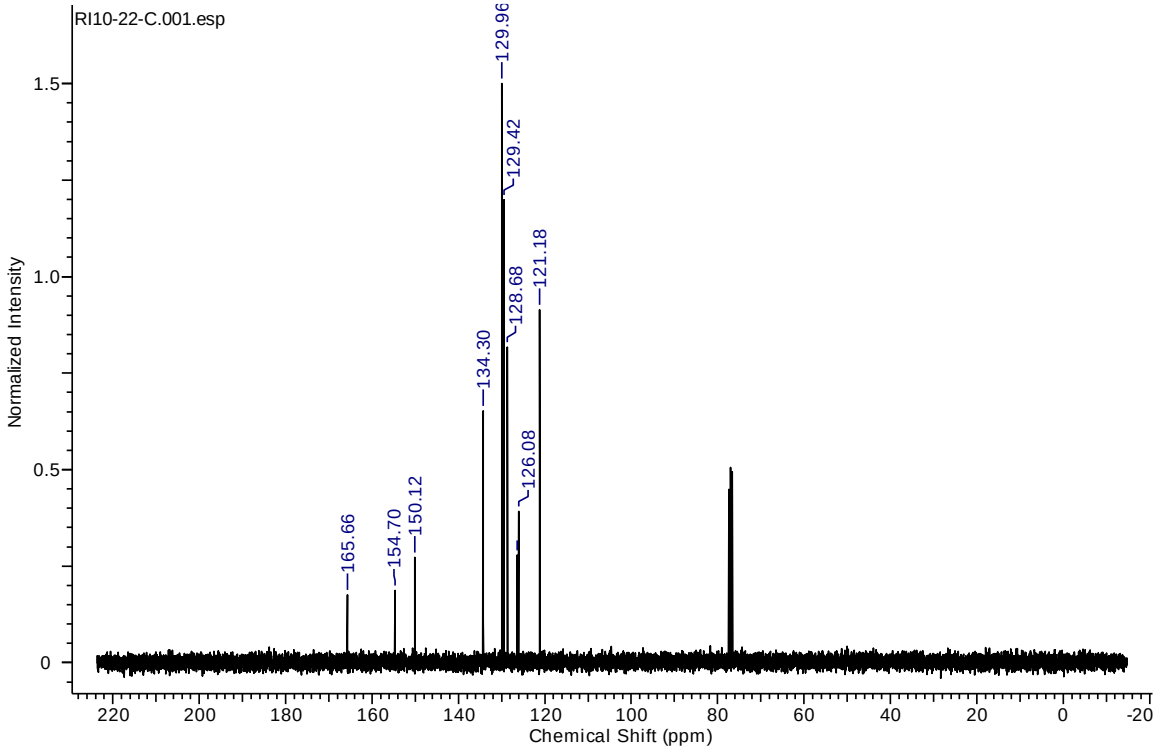

DP-hydroxy-charac.001.esp
O
PhO
N
H
OH
Normalized Intensity
1.5
1.0
0.5
0
0.83
0.99
2.06
1.01
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

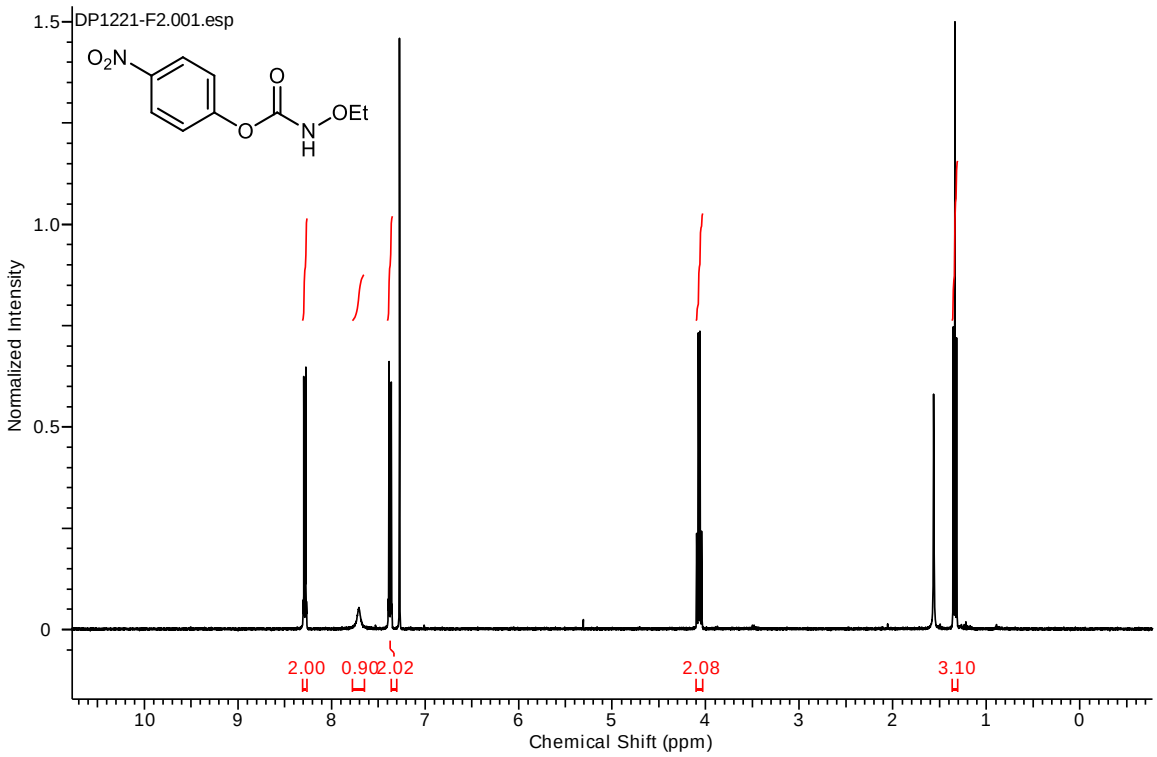

DP-hydroxy-carbon.001.esp
Normalized Intensity
1.5
1.0
0.5
0
129.39
150.73
155.48
125.13
121.59
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

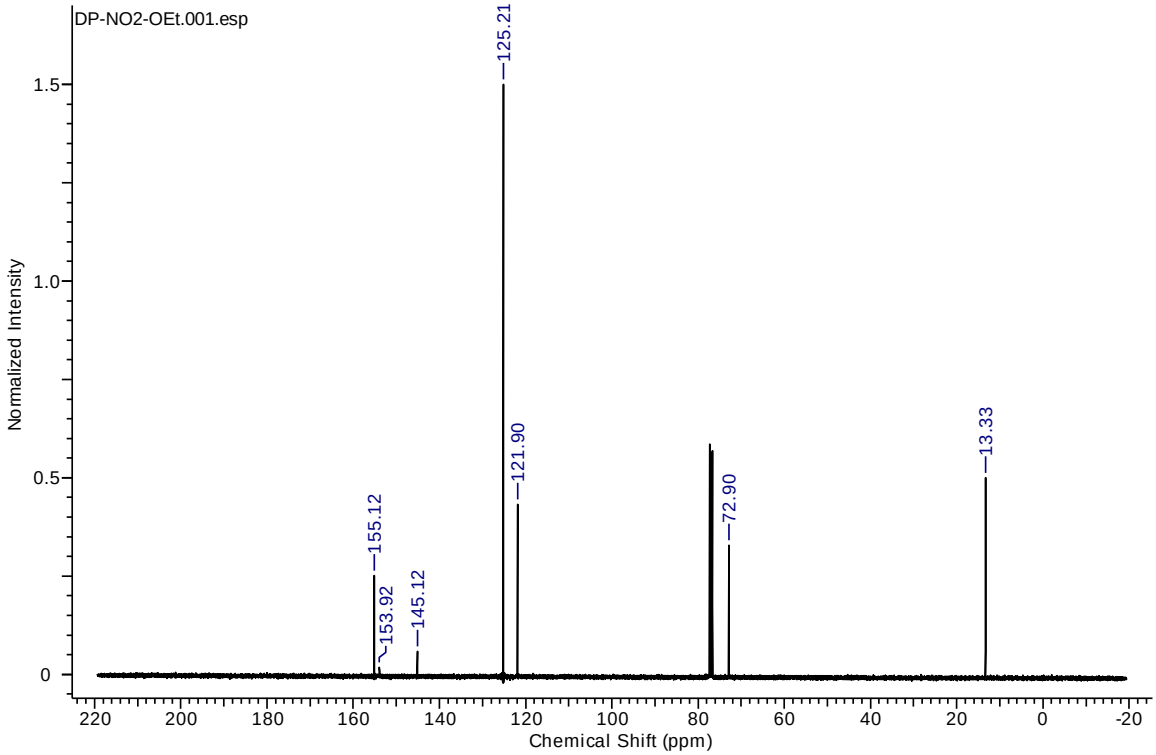

DP-PhO-OEt-proton.001.esp
PhO
O
N
H
OEt
Normalized Intensity
1.5
1.0
0.5
0
0.85
1.98
1.00
1.97
2.06
3.11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

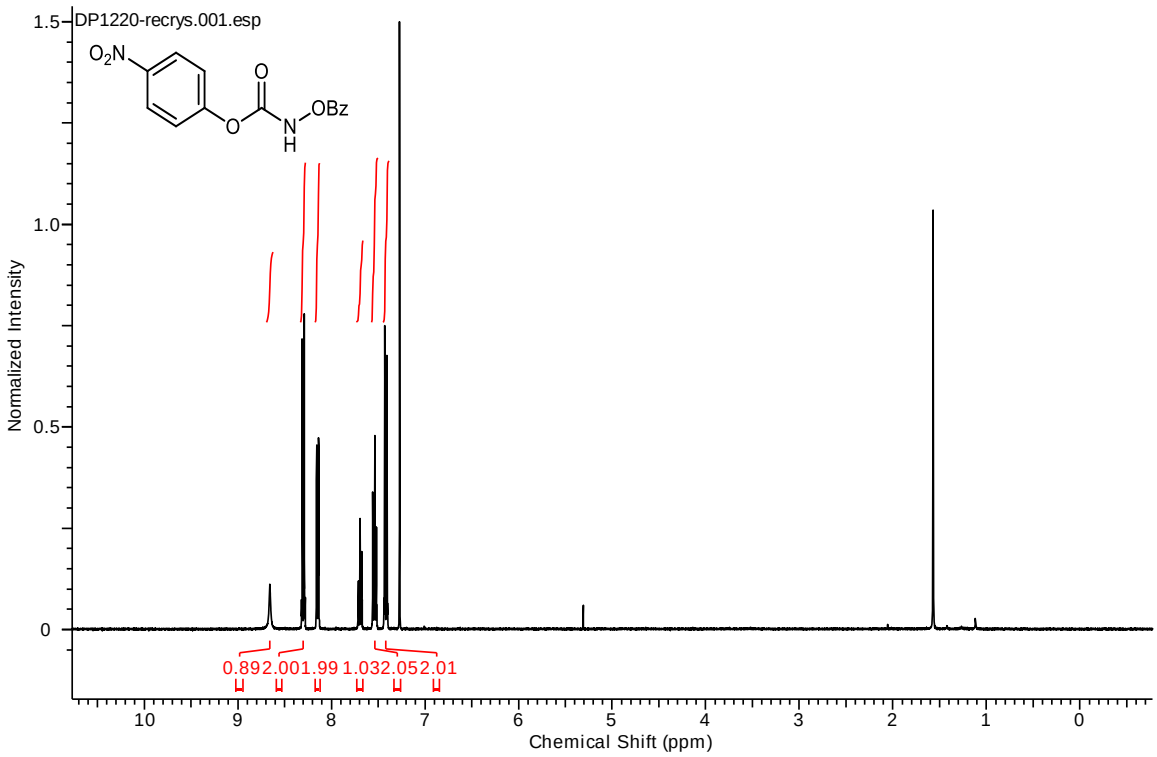

DP-PhO-OEt.004.esp
Normalized Intensity
1.5
1.0
0.5
0
129.40
121.32
125.76
72.65
13.38
155.53
150.37
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

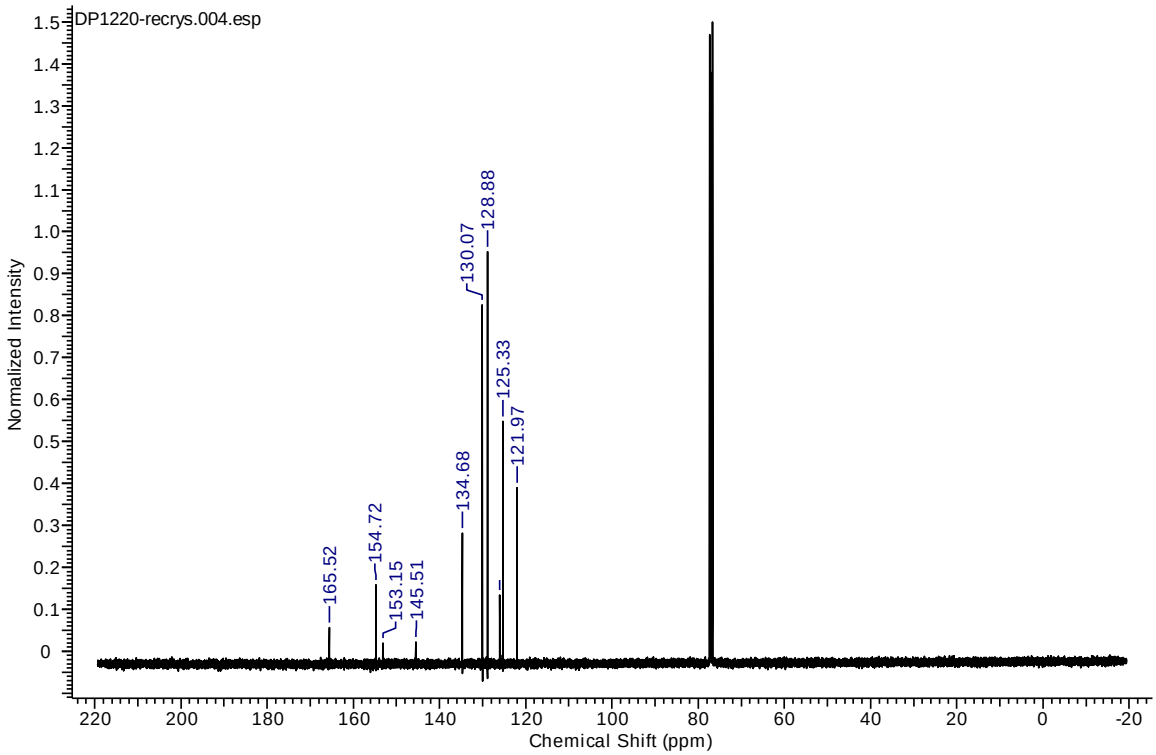

RI10-22-chk.001.esp
PhO
O
N
H
OBz
Normalized Intensity
1.06
2.24
1.18
8.00
Chemical Shift (ppm)

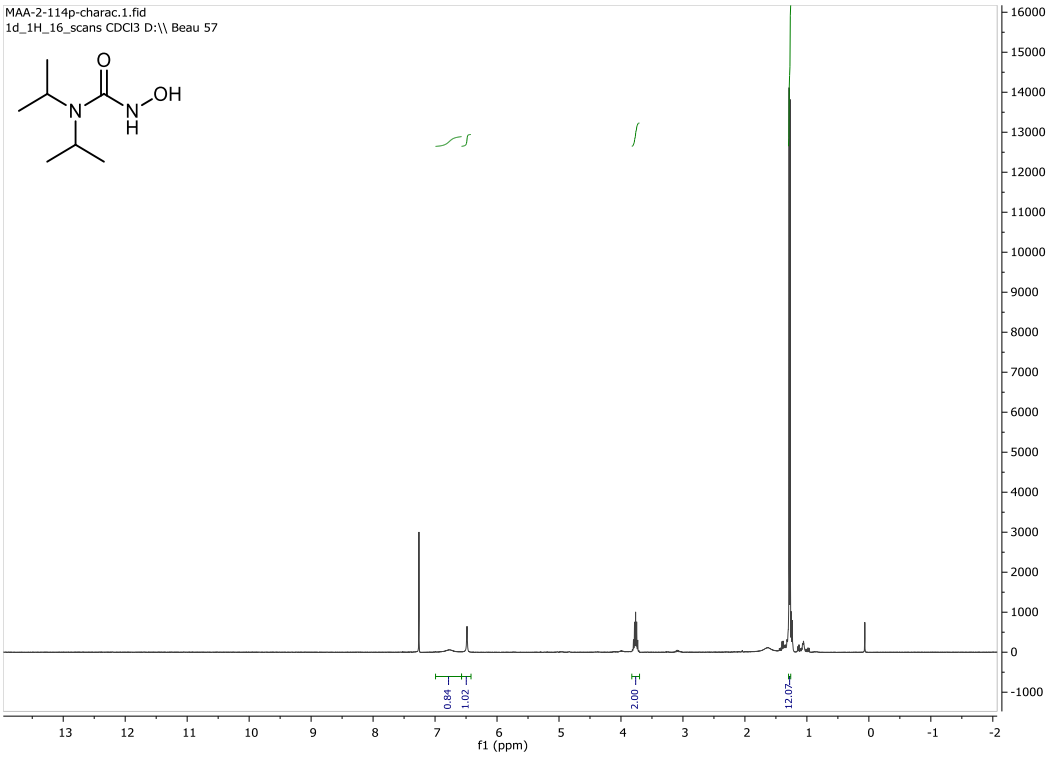

RI10-22-C.001.esp
129.96
129.42
128.68
121.18
134.30
126.08
165.66
154.70
150.12
Normalized Intensity
Chemical Shift (ppm)

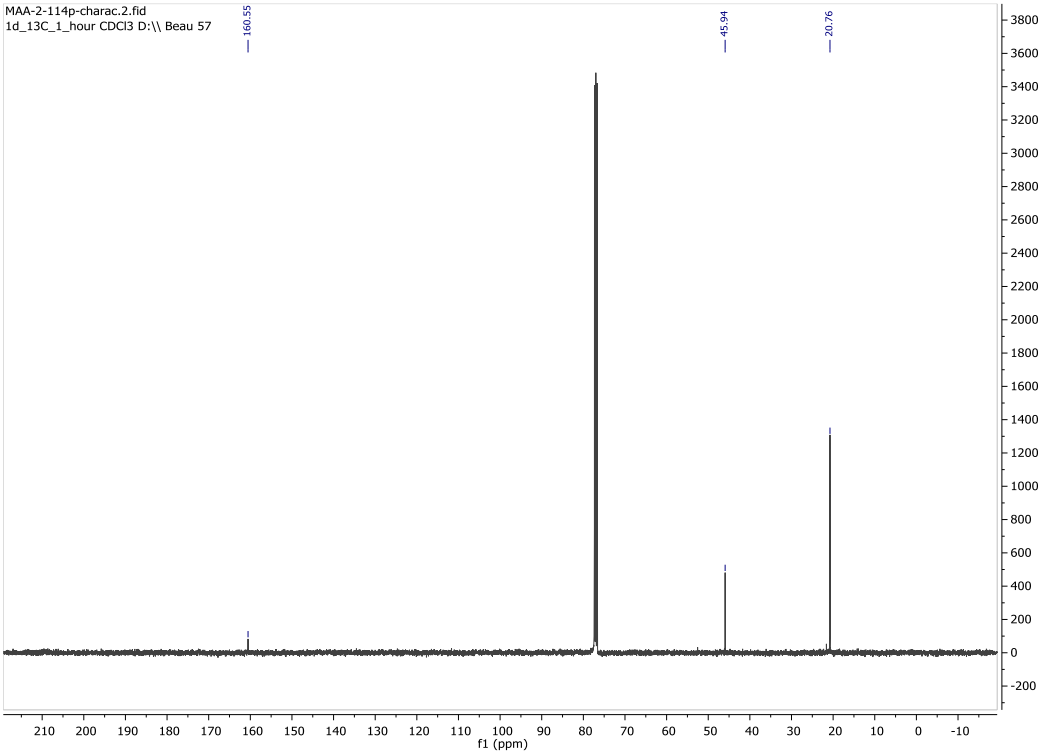

DP1221-F2.001.esp
O_2N
O
O
N
H
OEt
Normalized Intensity
1.5
1.0
0.5
0
2.00
0.90
2.02
2.08
3.10
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

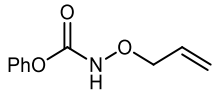

DP-NO2-OEt.001.esp
Normalized Intensity
1.5
1.0
0.5
0
125.21
121.90
155.12
153.92
145.12
72.90
13.33
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

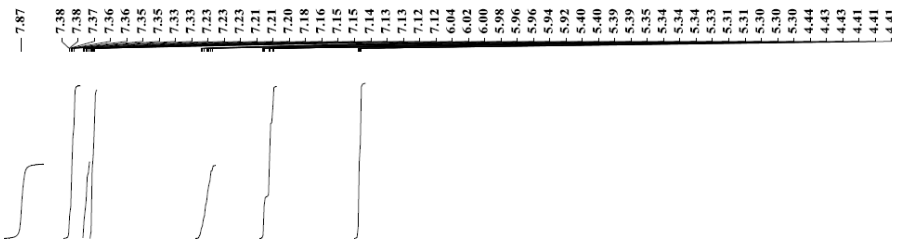

DP1220-recrys.001.esp
O2N
O
O
N
H
OBz
Normalized Intensity
0.89
2.00
1.99
1.03
2.05
2.01
Chemical Shift (ppm)

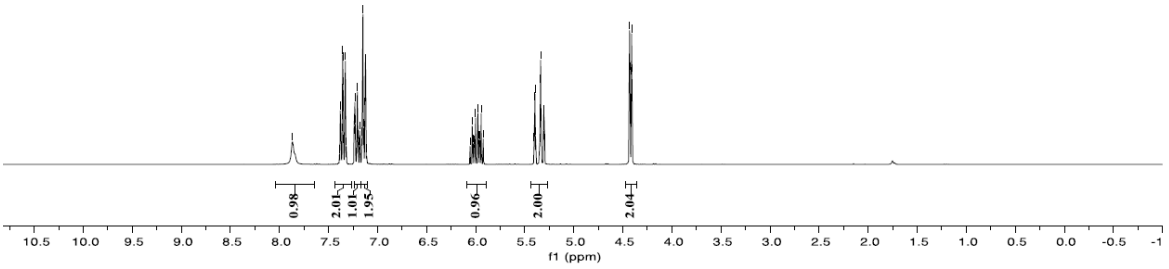

DP1220-recrys.004.esp
Normalized Intensity
165.52
154.72
153.15
145.51
134.68
130.07
128.88
125.33
121.97
Chemical Shift (ppm)

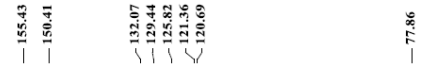

MAA-2-114p-charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 57
O
N
N
H
OH
0.84
1.02
2.00
12.07
f1 (ppm)

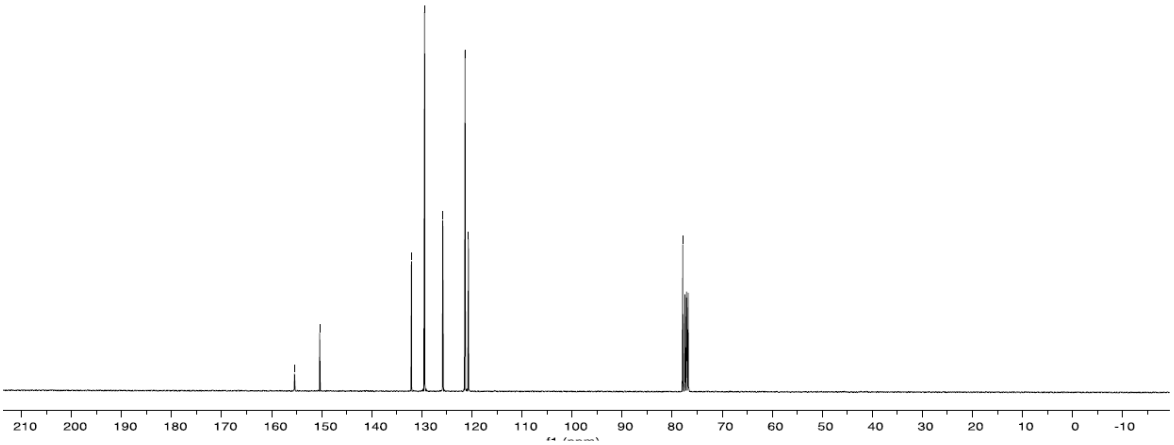

MAA-2-114p-charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 57
160.55
45.94
20.76
f1 (ppm)

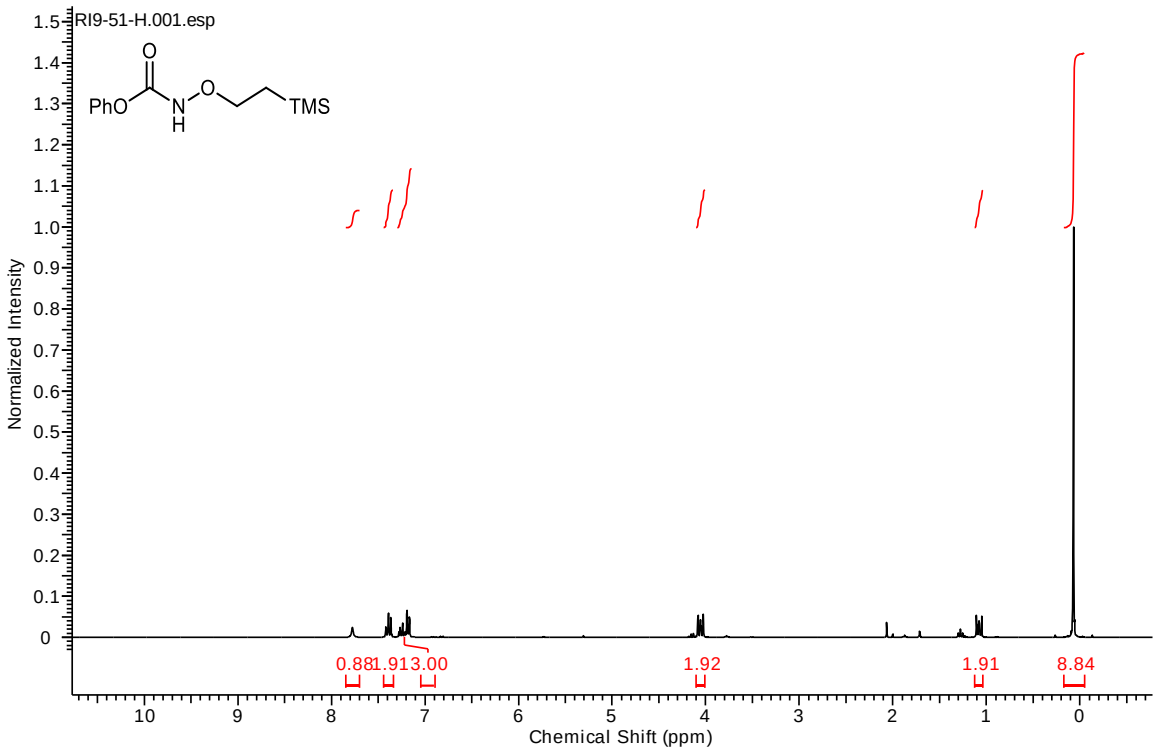

O
PhO
N
H
O

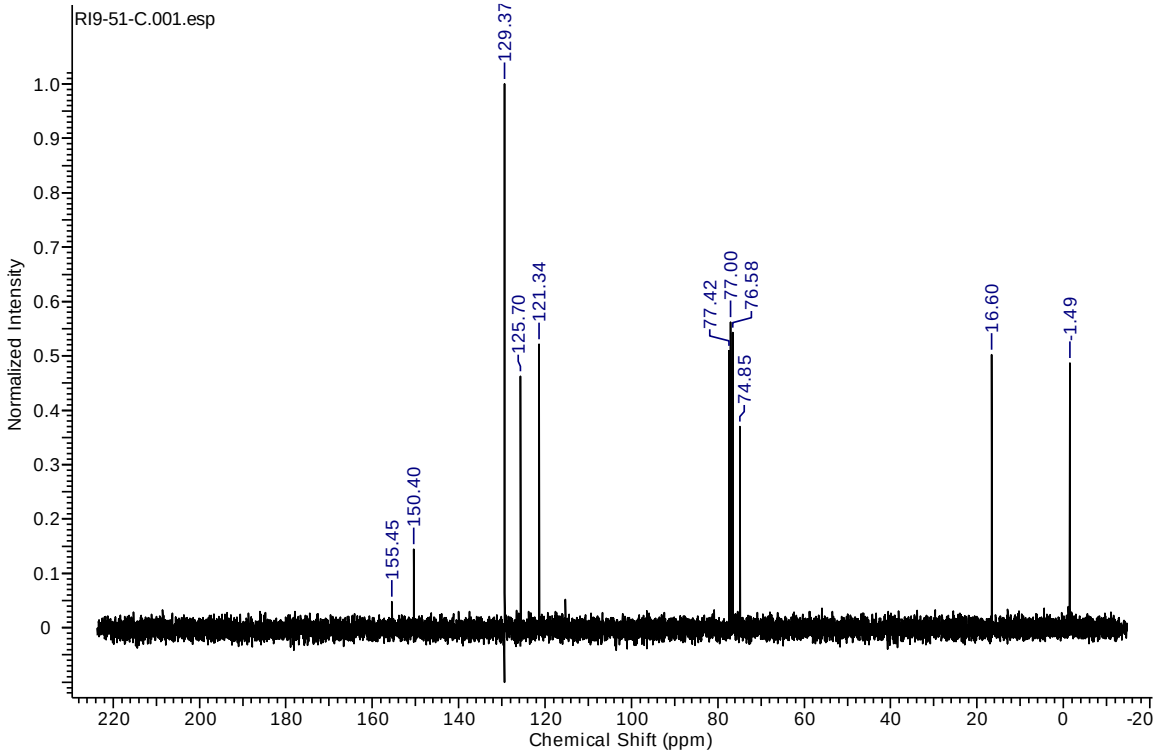

7.87
7.38
7.38
7.37
7.36
7.36
7.35
7.35
7.33
7.33
7.23
7.23
7.23
7.21
7.21
7.20
7.18
7.16
7.15
7.15
7.14
7.13
7.13
7.12
7.12
6.04
6.02
6.00
5.98
5.96
5.96
5.94
5.92
5.40
5.40
5.39
5.39
5.35
5.34
5.34
5.33
5.31
5.31
5.30
5.30
5.30
4.44
4.43
4.43
4.41
4.41
4.41

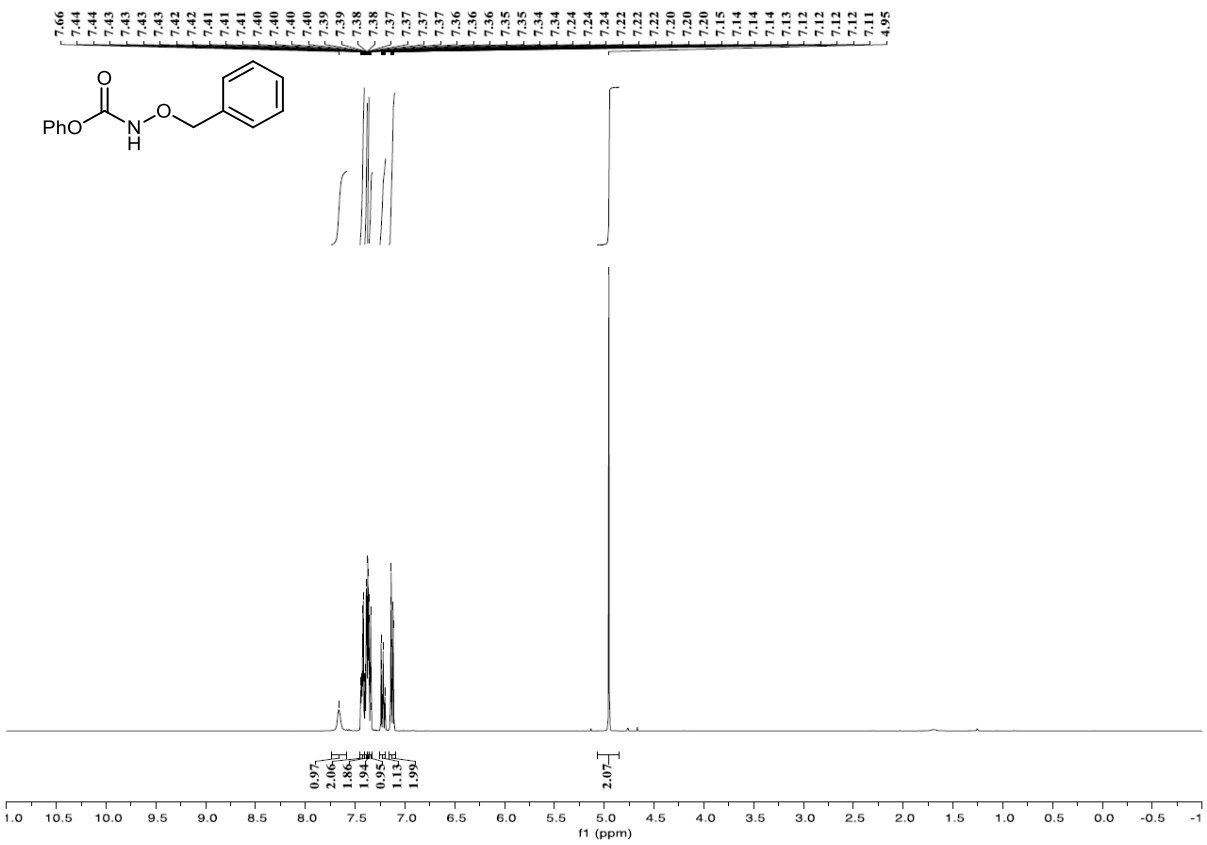

0.98
2.01
1.01
1.95
0.96
2.00
2.04
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

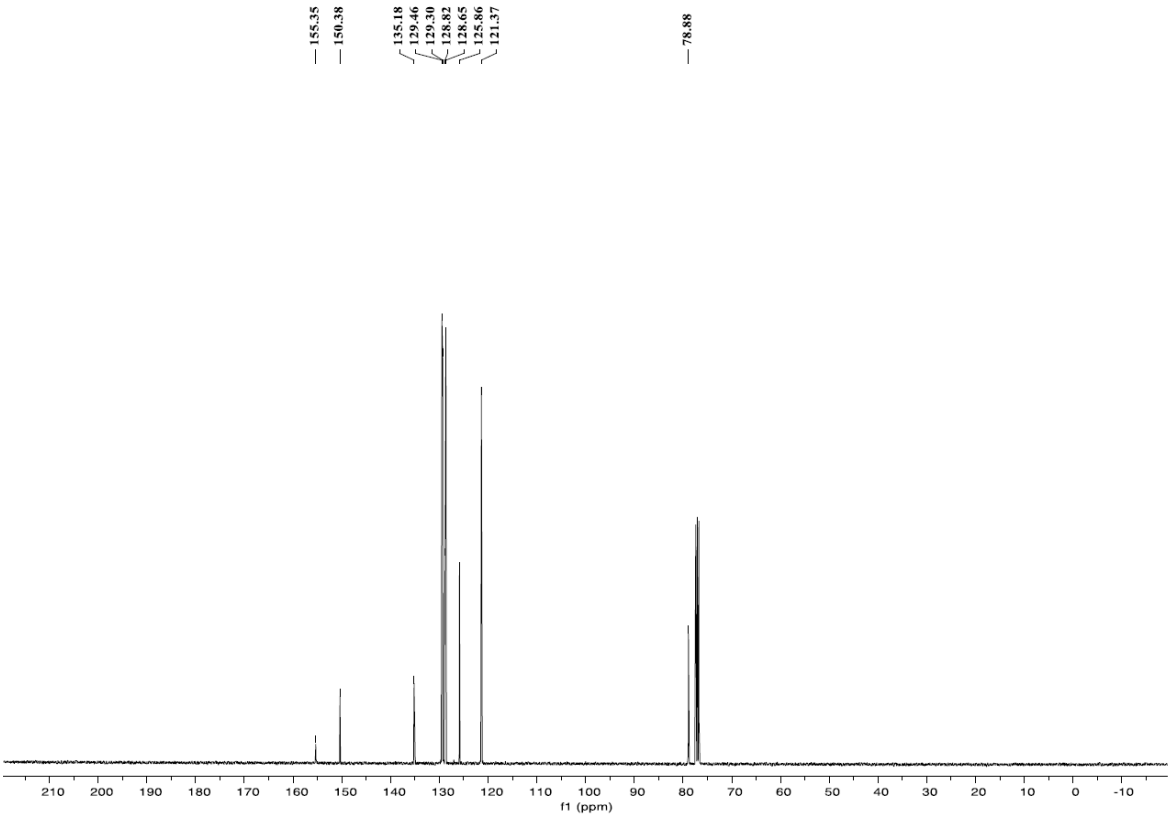

155.43
150.41
132.07
129.44
125.82
121.36
120.69
77.86

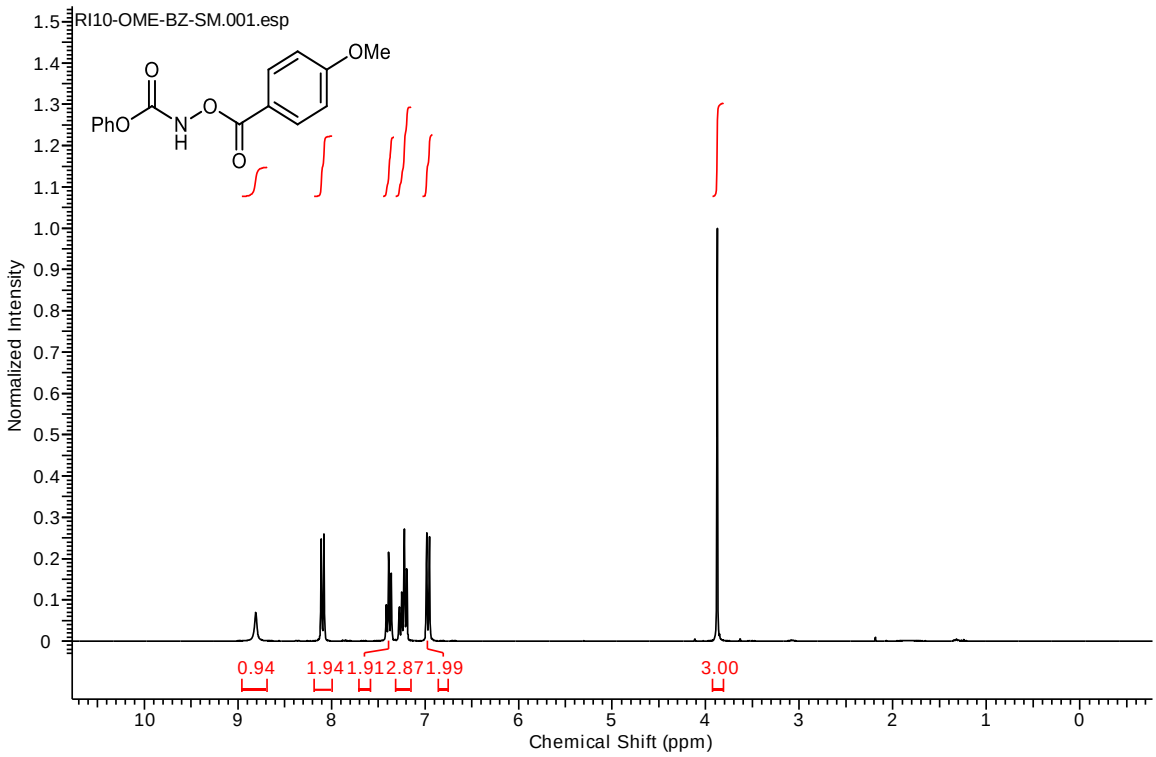

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

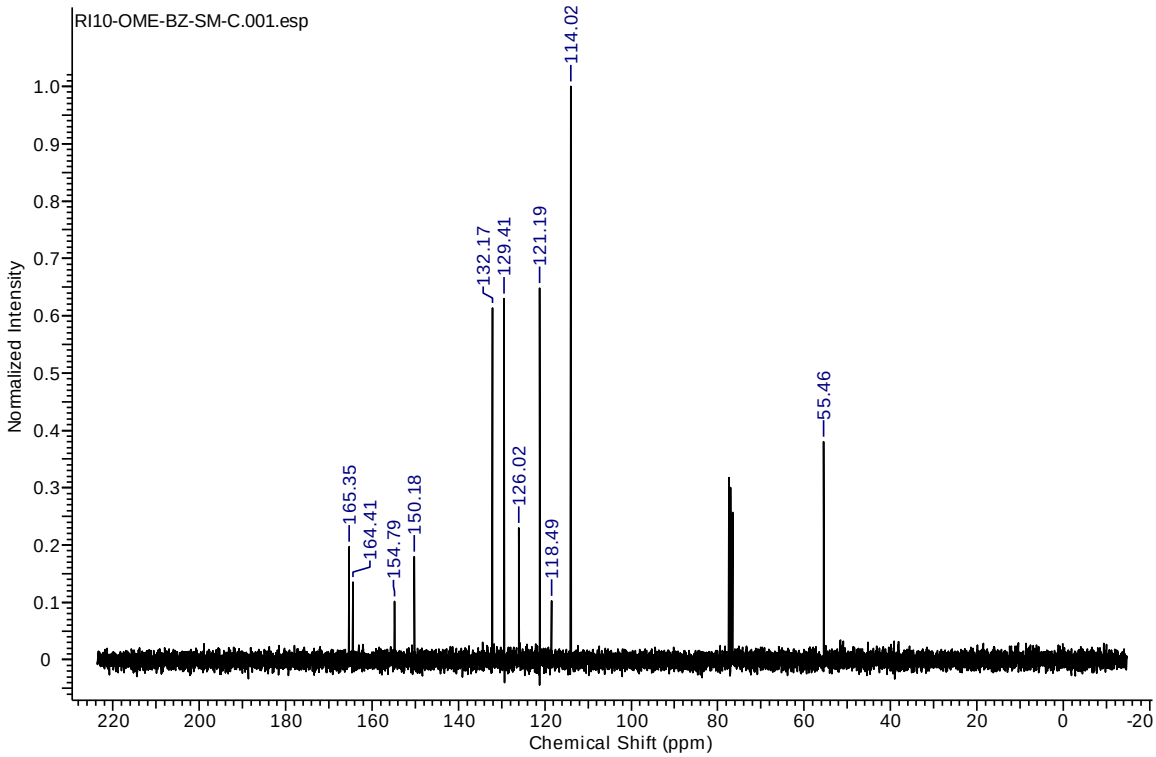

RI9-51-H.001.esp
PhO
O
N
H
O
TMS
Normalized Intensity
0.88
1.91
3.00
1.92
1.91
8.84
Chemical Shift (ppm)

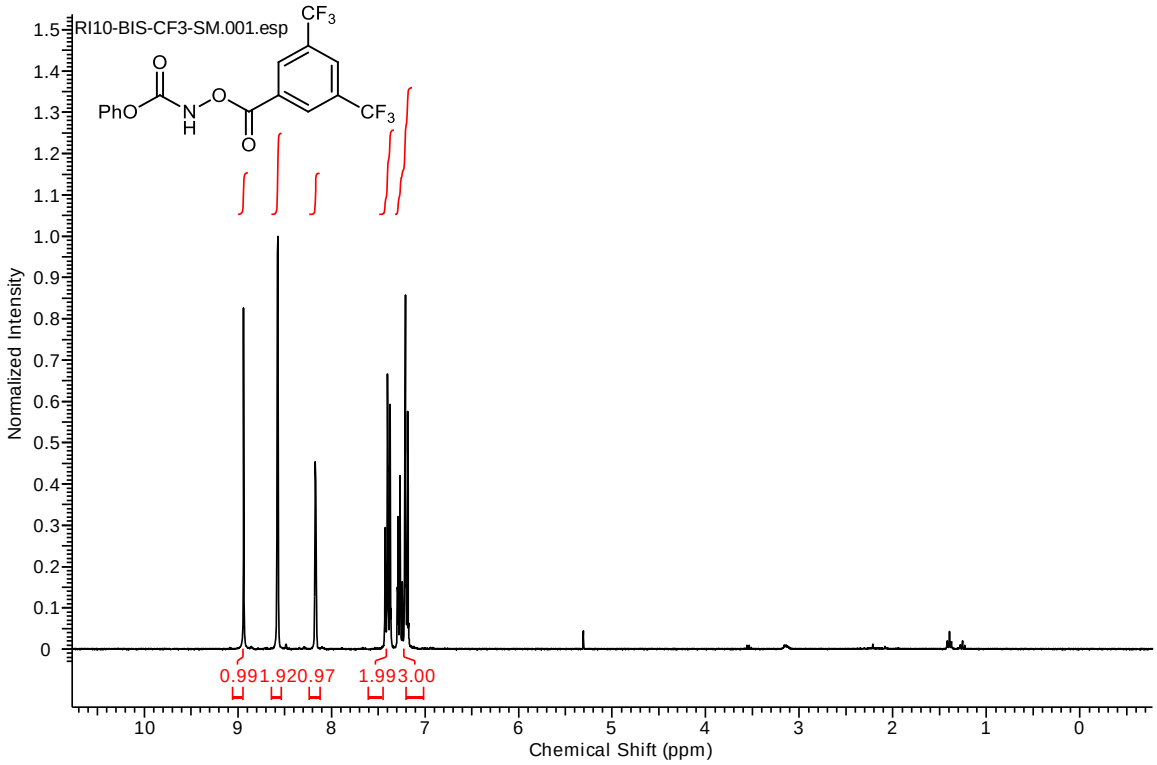

RI9-51-C.001.esp
129.37
125.70
121.34
77.42
77.00
76.58
74.85
155.45
150.40
16.60
-1.49
Normalized Intensity
Chemical Shift (ppm)

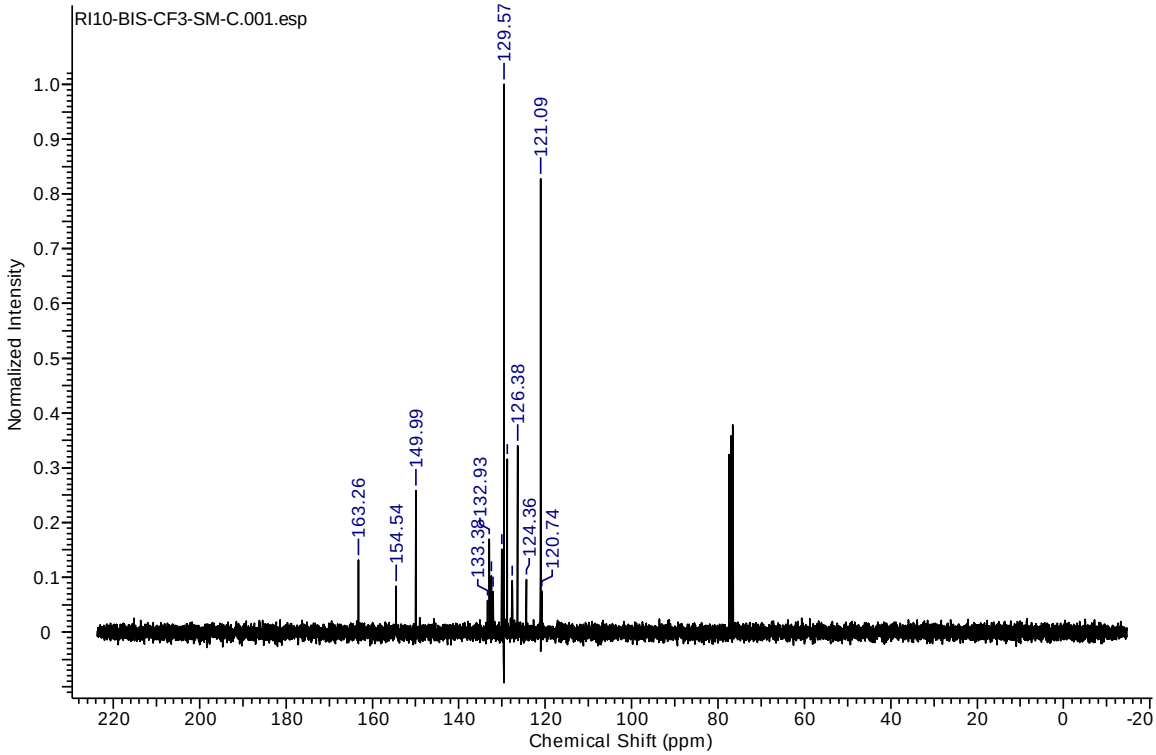

7.66 7.44 7.44 7.43 7.43 7.43 7.43 7.42 7.42 7.41 7.41 7.41 7.40 7.40 7.40 7.40 7.39 7.39 7.38 7.38 7.37 7.37 7.37 7.37 7.36 7.36 7.36 7.35 7.35 7.34 7.34 7.24 7.24 7.24 7.22 7.22 7.20 7.20 7.20 7.15 7.14 7.14 7.14 7.13 7.12 7.12 7.12 7.12 7.11 4.95
PhO
O
N
H
O
0.97 2.06 1.86 1.94 0.95 1.13 1.99 2.07
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

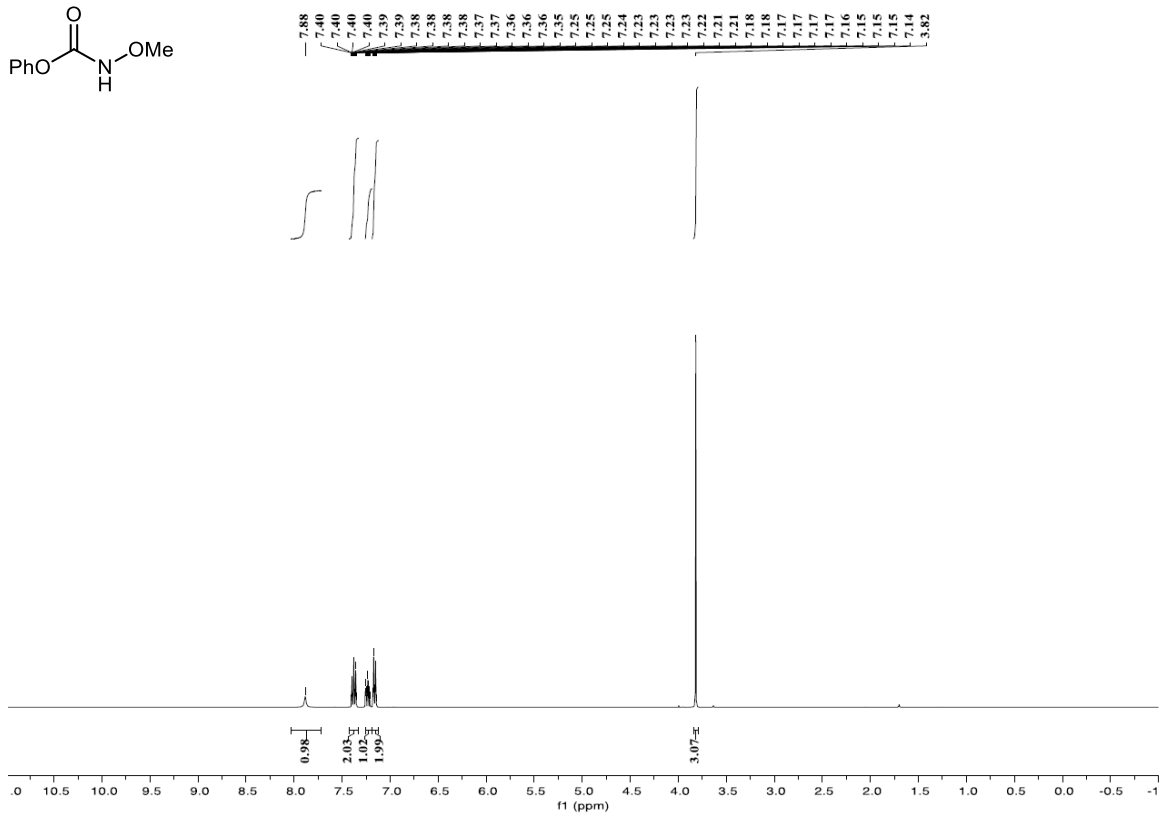

155.35 150.38 135.18 129.46 129.30 128.82 128.65 125.86 121.37 78.88
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

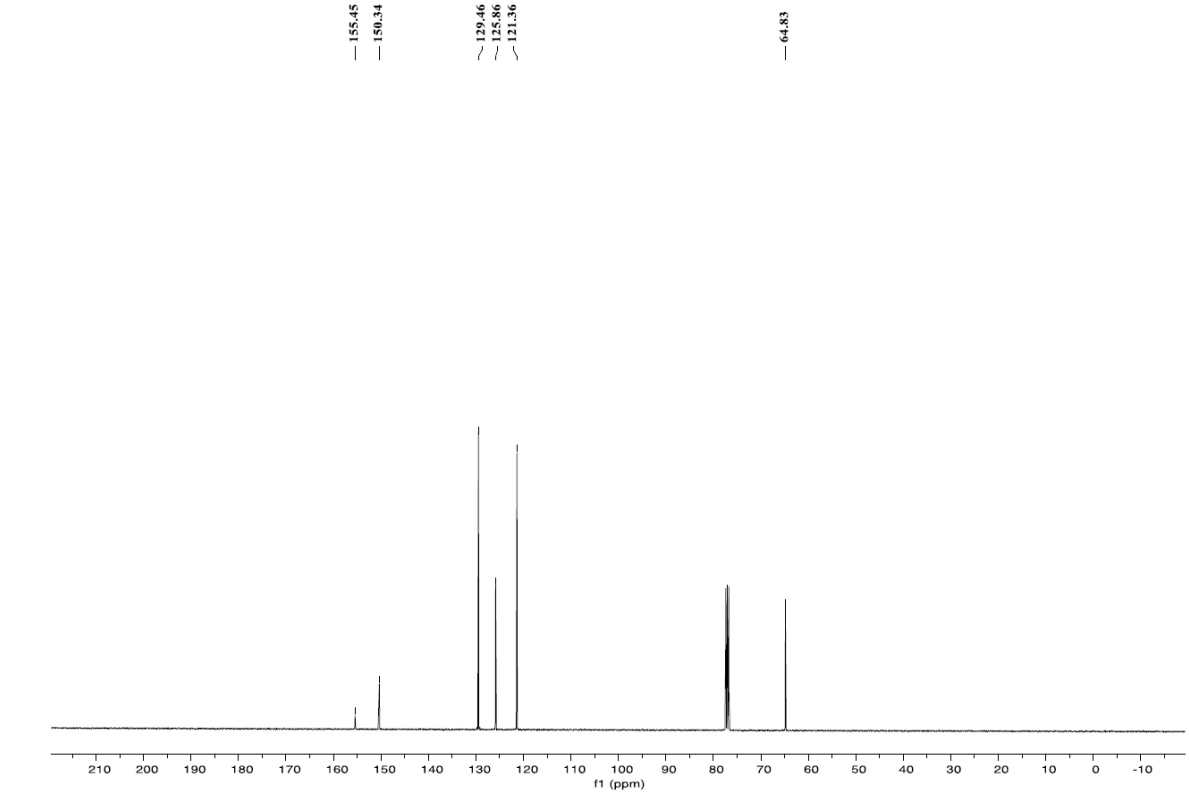

RI10-OME-BZ-SM.001.esp
OMe
PhO
N
H
O
O
O
O
Normalized Intensity
0.94
1.94
1.91
2.87
1.99
3.00
Chemical Shift (ppm)

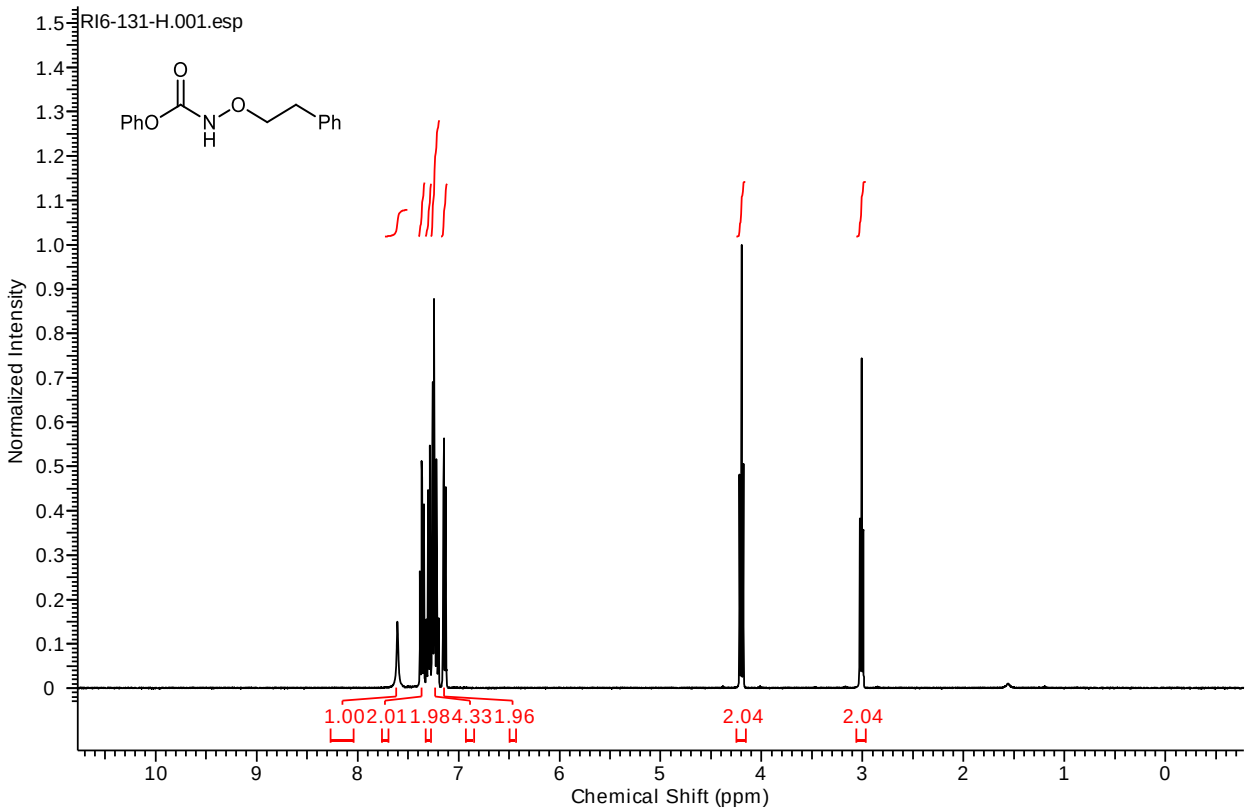

RI10-OME-BZ-SM-C.001.esp
114.02
132.17
129.41
121.19
55.46
165.35
164.41
154.79
150.18
126.02
118.49
Normalized Intensity
Chemical Shift (ppm)

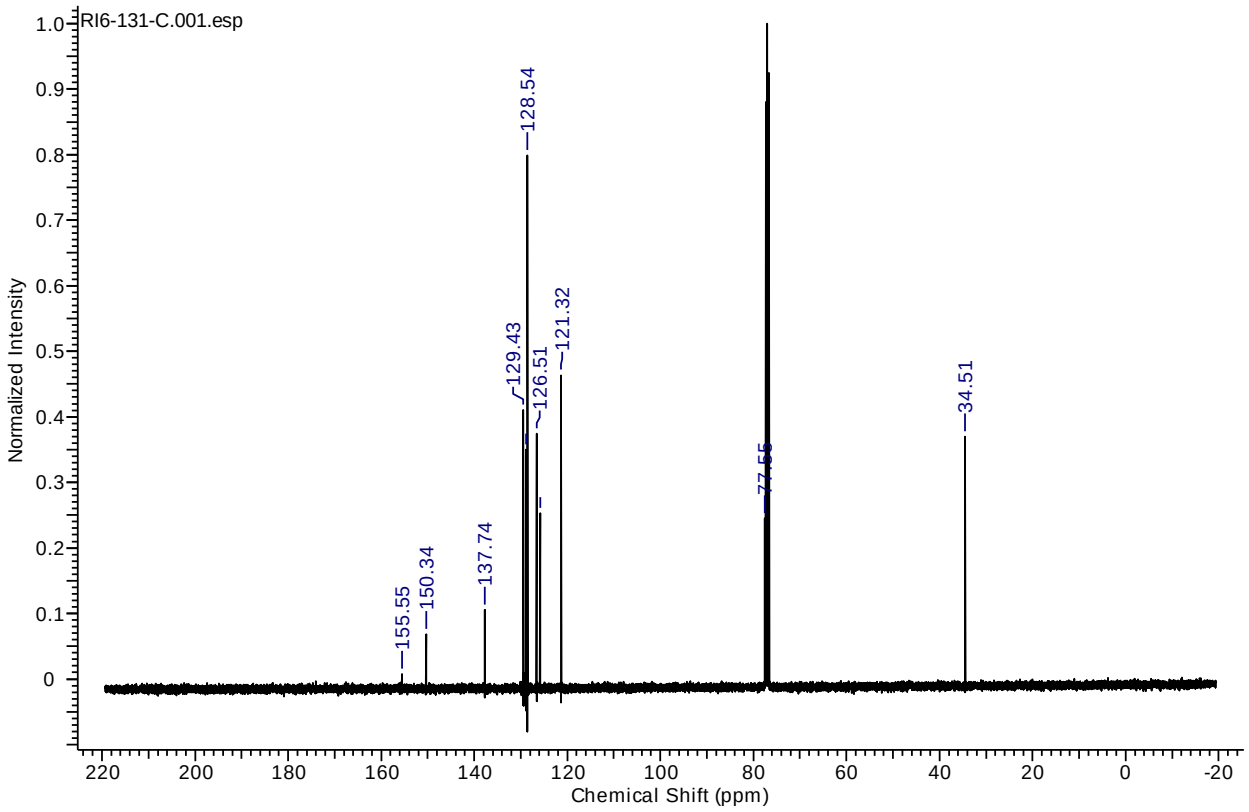

RI10-BIS-CF3-SM.001.esp
CF3
PhO
O
N
H
O
O
CF3
Normalized Intensity
0.99
1.92
0.97
1.99
3.00
Chemical Shift (ppm)

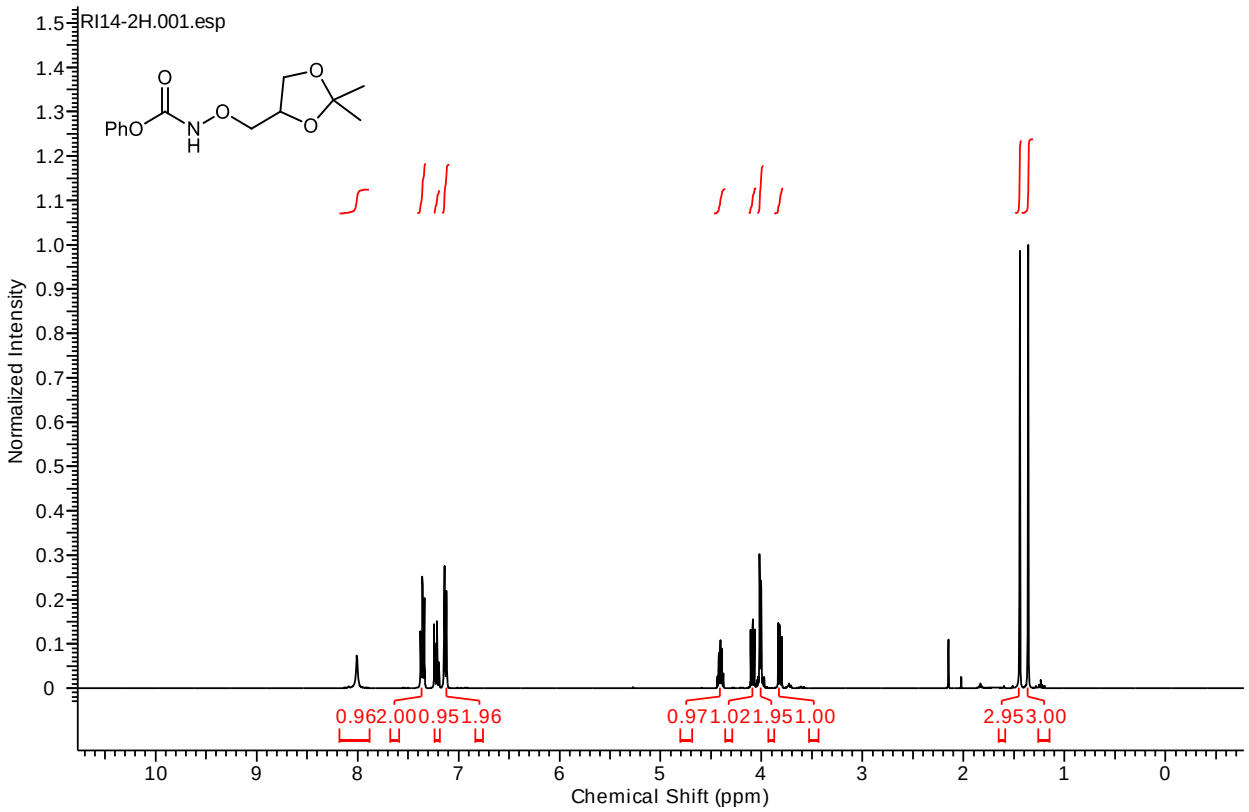

RI10-BIS-CF3-SM-C.001.esp
129.57
121.09
126.38
149.99
163.26
154.54
132.93
133.38
124.36
120.74
Normalized Intensity
Chemical Shift (ppm)

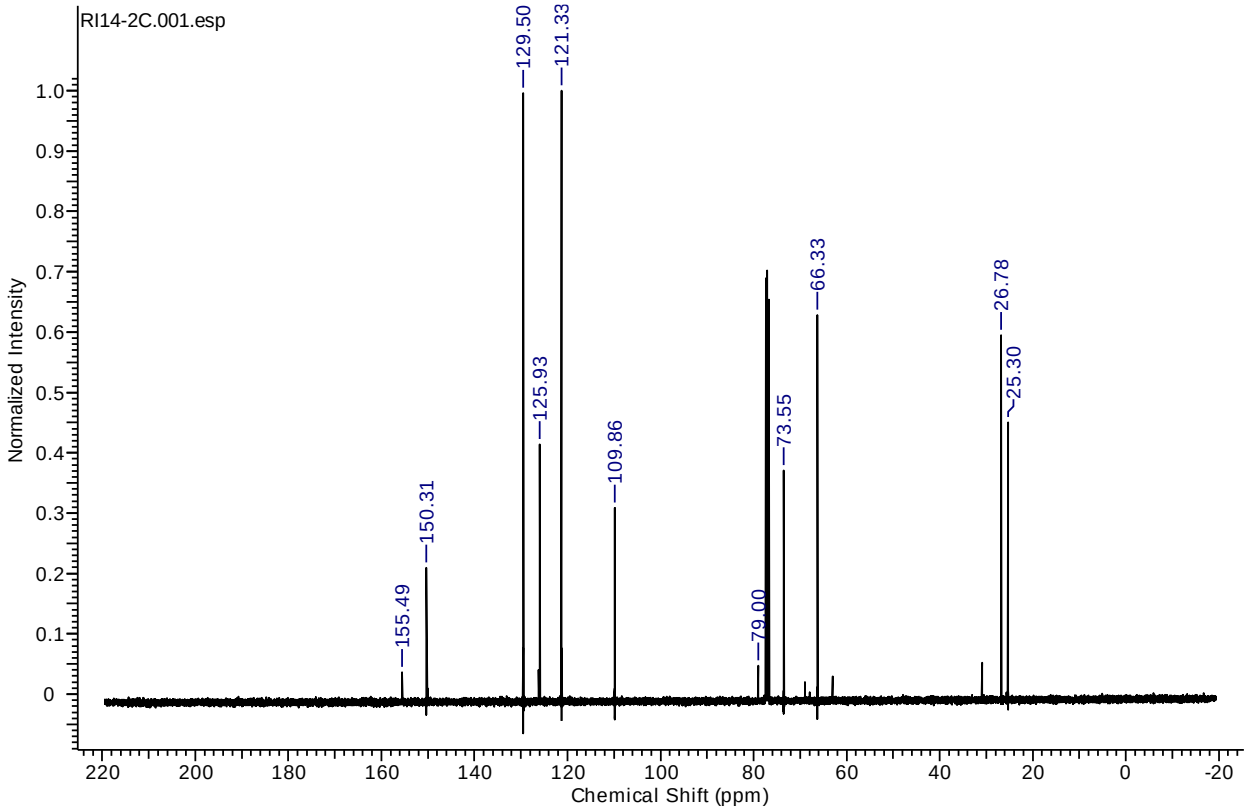

PhO
O
N
H
OMe
7.88
7.40
7.40
7.40
7.40
7.39
7.39
7.38
7.38
7.38
7.38
7.37
7.37
7.36
7.36
7.36
7.35
7.25
7.25
7.25
7.24
7.23
7.23
7.23
7.23
7.22
7.21
7.21
7.18
7.18
7.17
7.17
7.17
7.17
7.16
7.15
7.15
7.15
7.14
3.82
0.98
2.03
1.02
1.99
3.07
f1 (ppm)

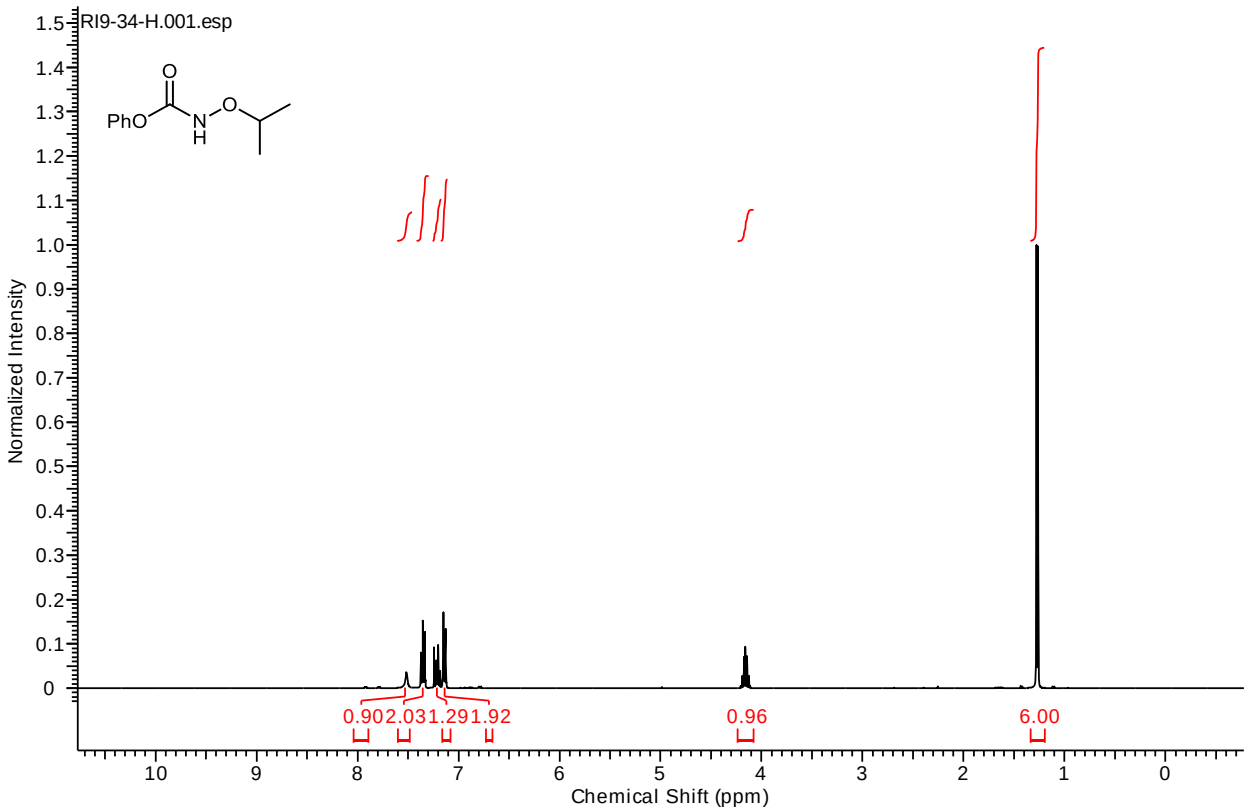

155.45
150.34
129.46
125.86
121.36
64.83
f1 (ppm)

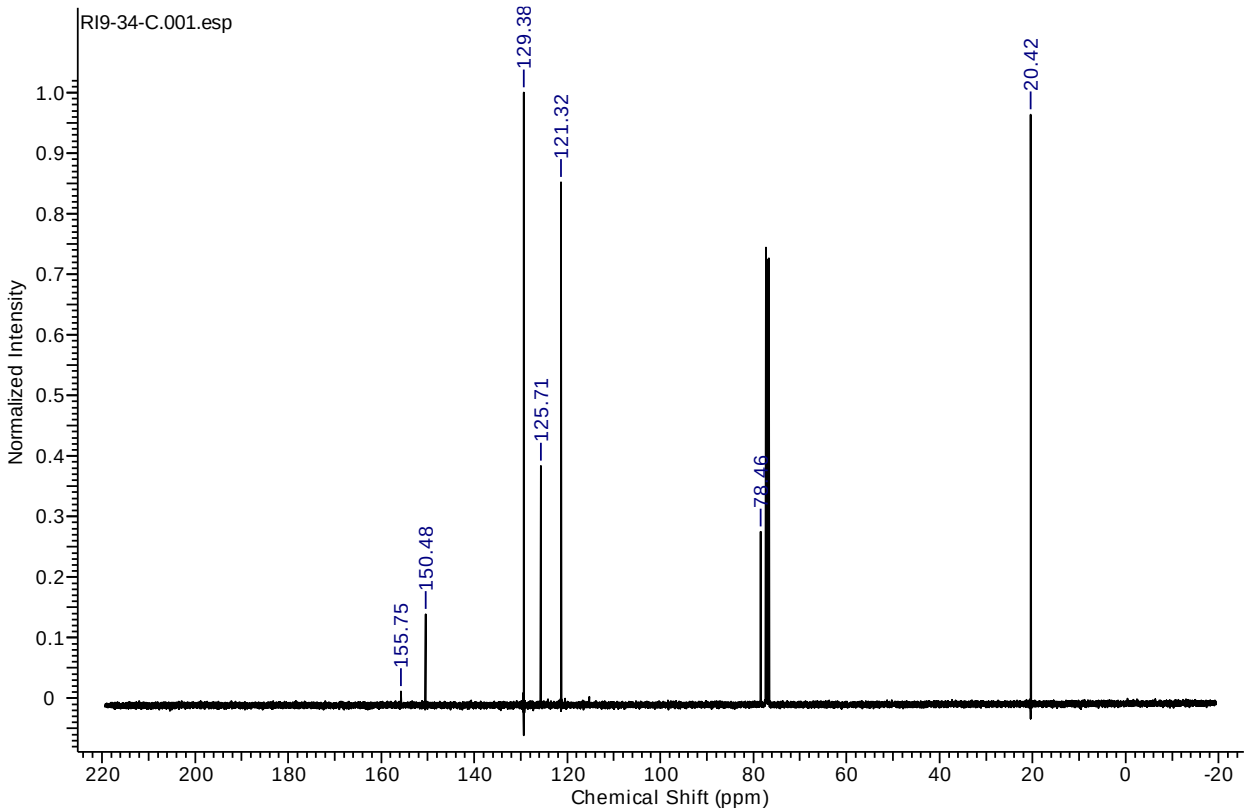

RI6-131-H.001.esp
PhO
O
N
H
O
Ph
Normalized Intensity
1.00
2.01
1.98
4.33
1.96
2.04
2.04
Chemical Shift (ppm)

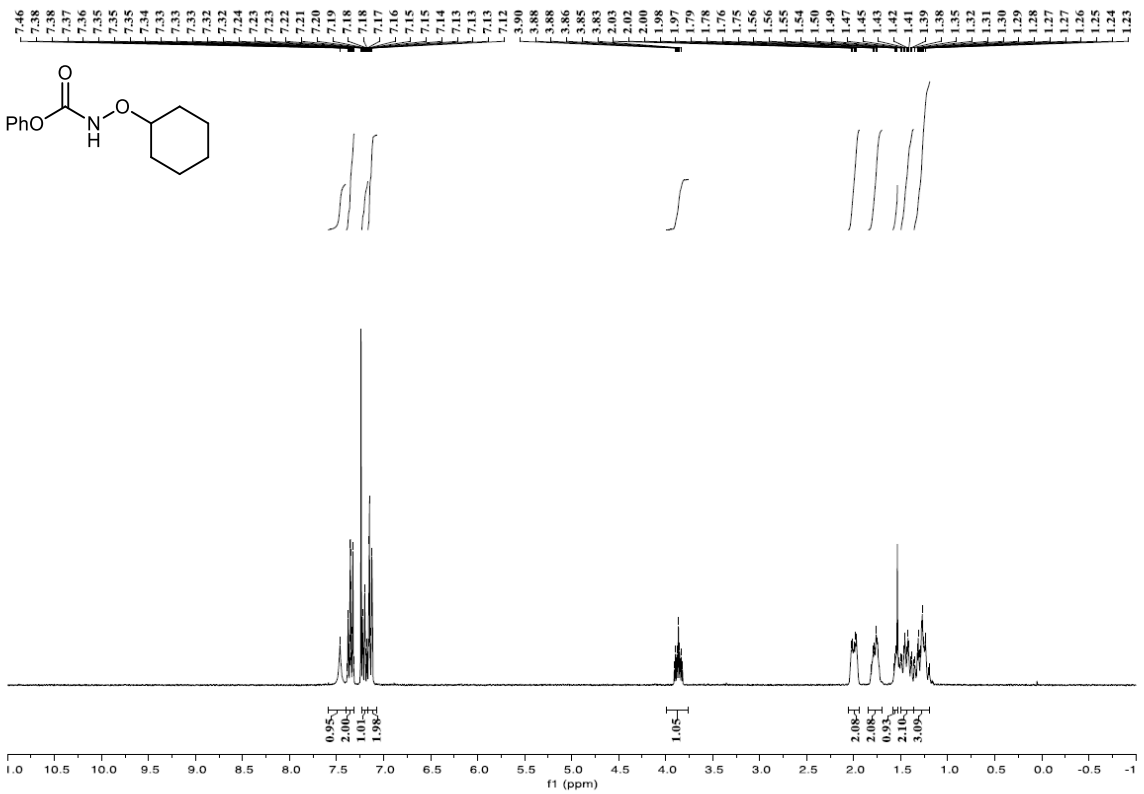

RI6-131-C.001.esp
128.54
129.43
126.51
121.32
77.55
34.51
137.74
150.34
155.55
Normalized Intensity
Chemical Shift (ppm)

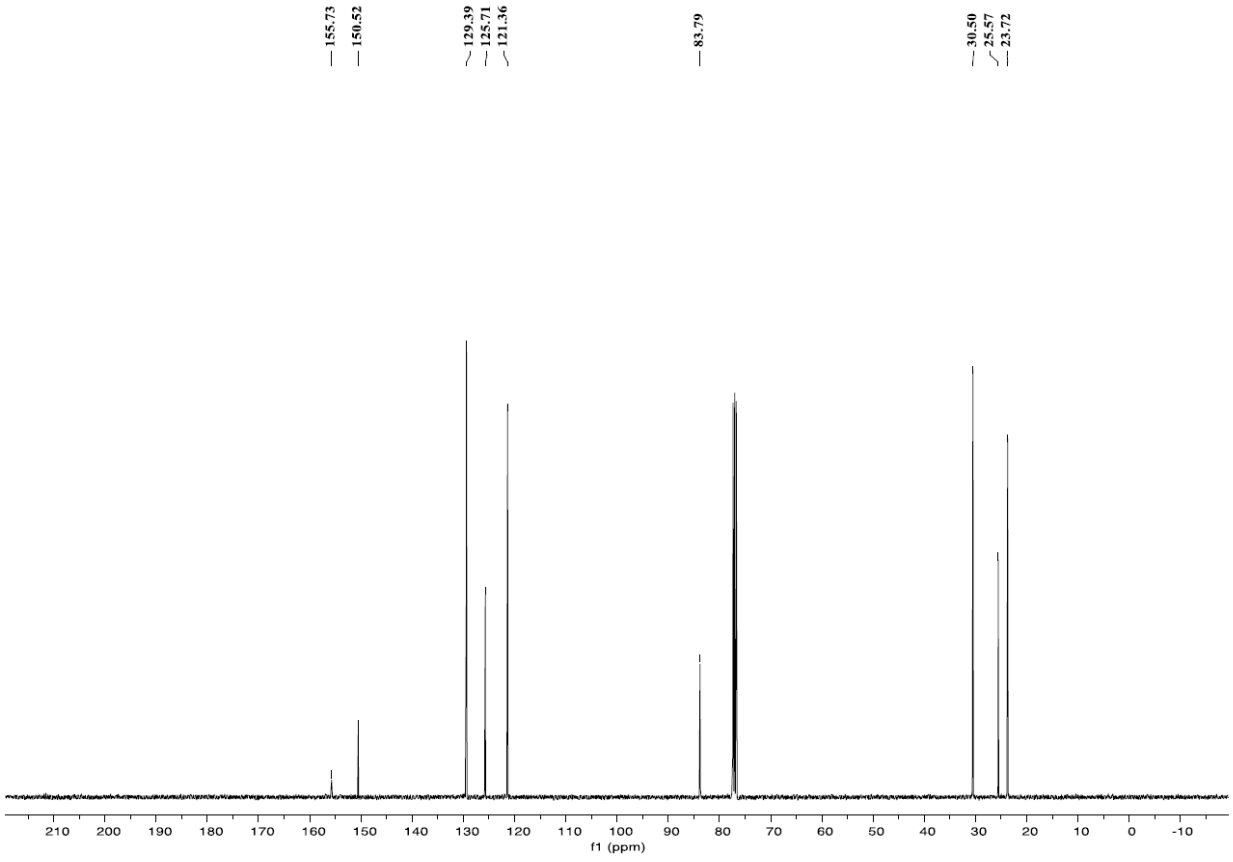

RI14-2H.001.esp
PhO
O
N
H
O
O
O
Normalized Intensity
0.962.000.951.96
0.971.021.951.00
2.953.00
Chemical Shift (ppm)

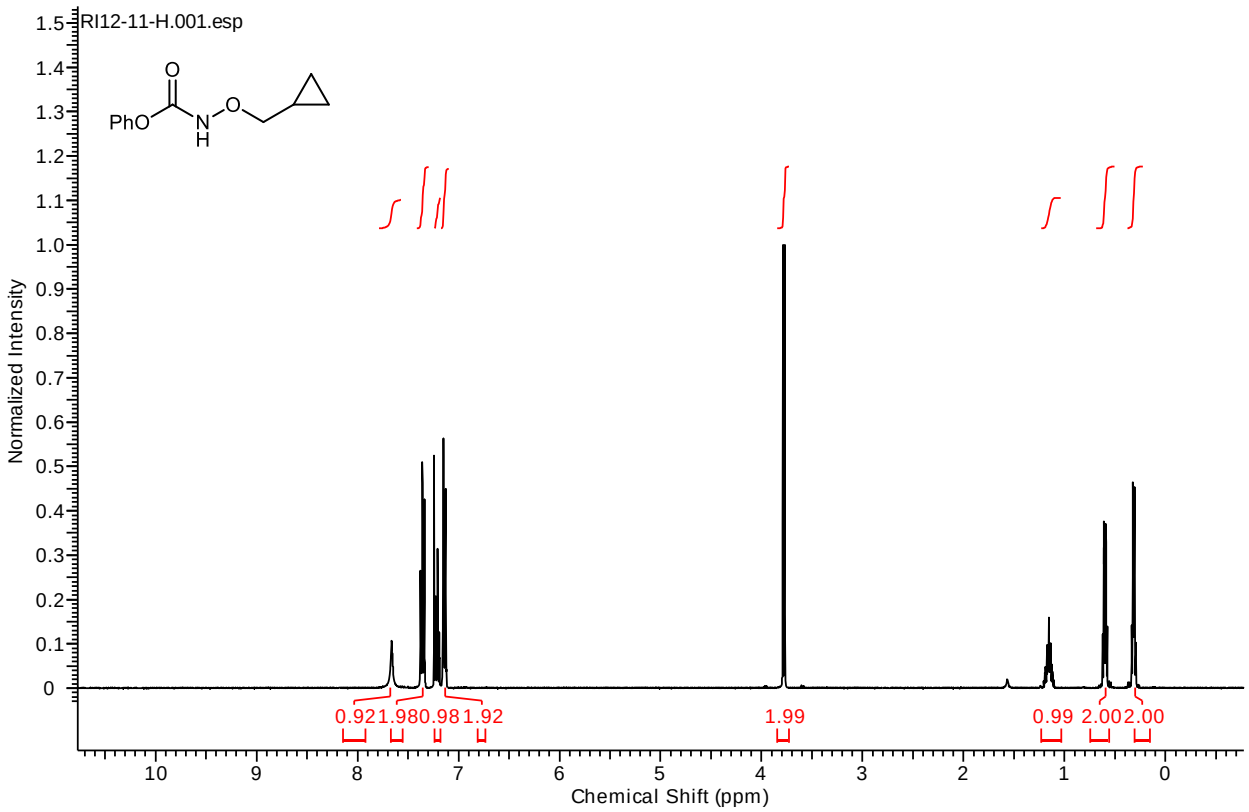

RI14-2C.001.esp
129.50
121.33
125.93
109.86
155.49
150.31
79.00
73.55
66.33
26.78
25.30
Normalized Intensity
Chemical Shift (ppm)

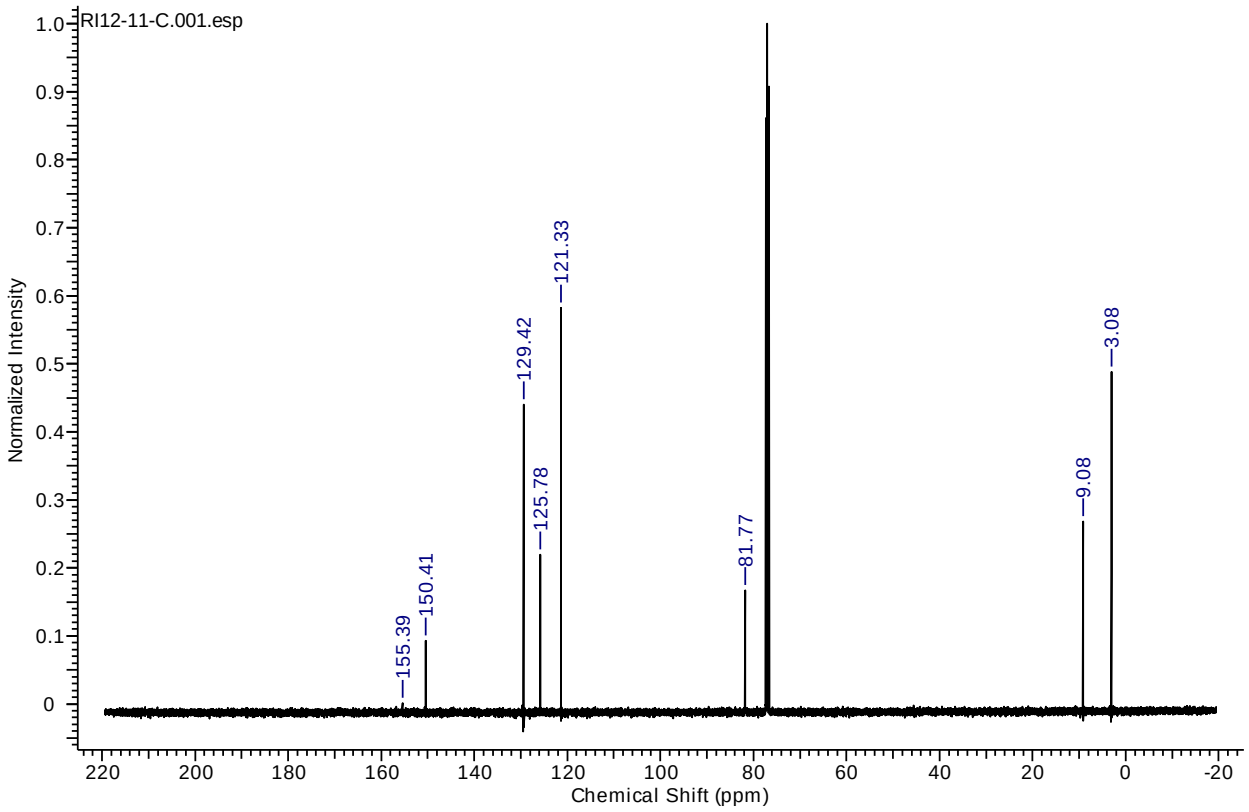

RI9-34-H.001.esp
PhO
O
N
H
O
Normalized Intensity
0.90
2.03
1.29
1.92
0.96
6.00
Chemical Shift (ppm)

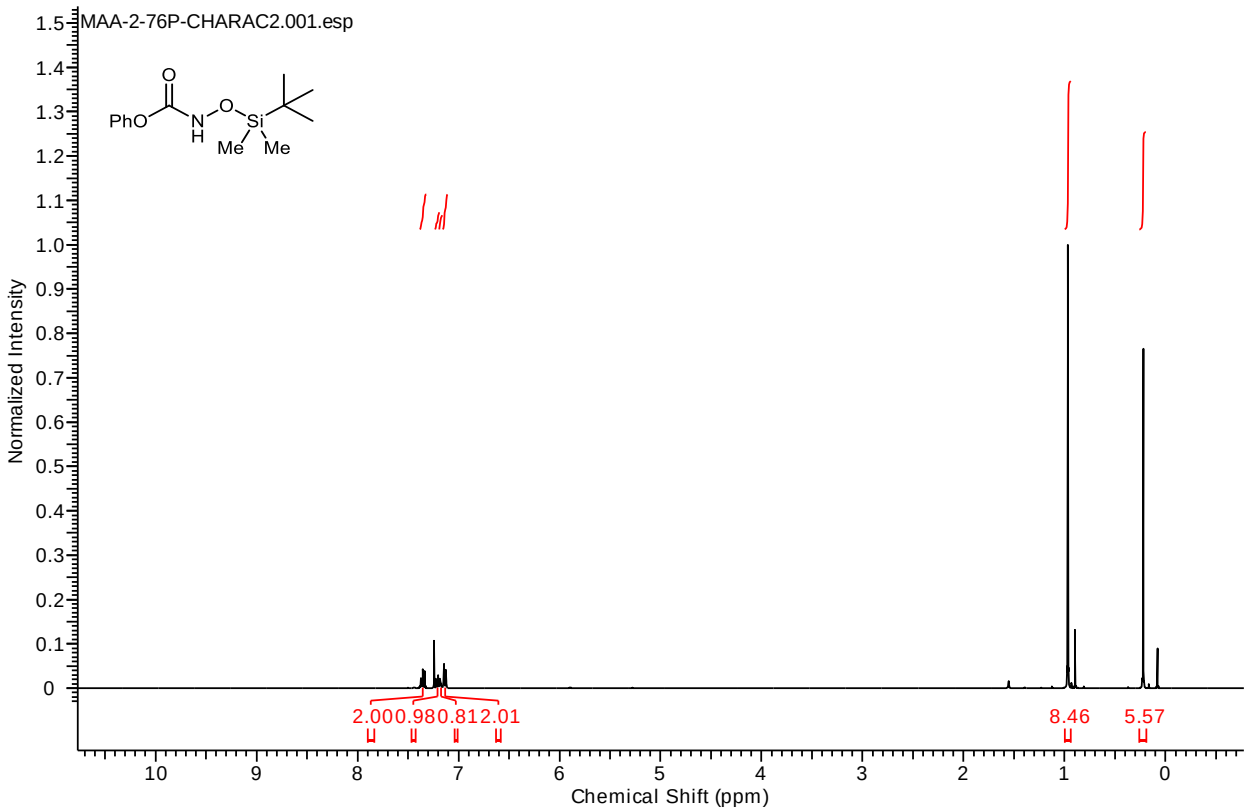

RI9-34-C.001.esp
129.38
121.32
125.71
78.46
150.48
155.75
20.42
Normalized Intensity
Chemical Shift (ppm)

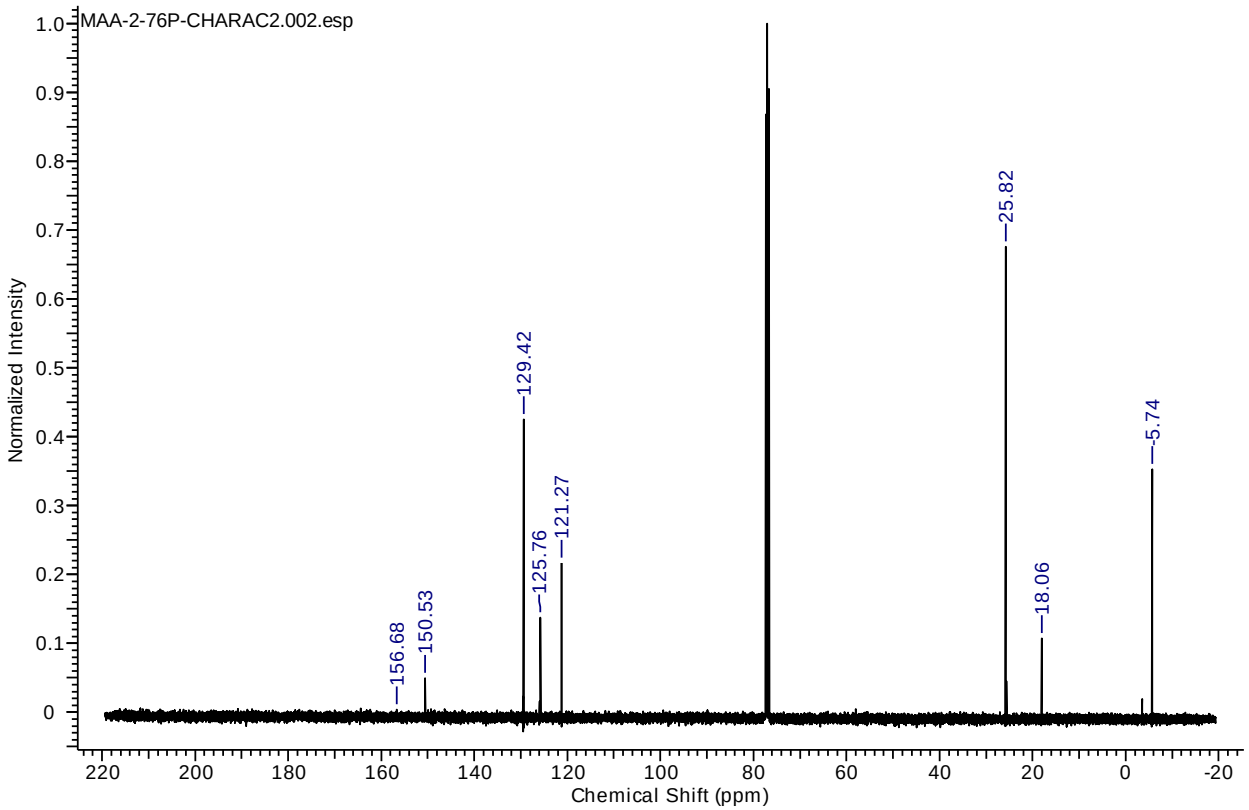

PhO
O
N
H
O
f1 (ppm)

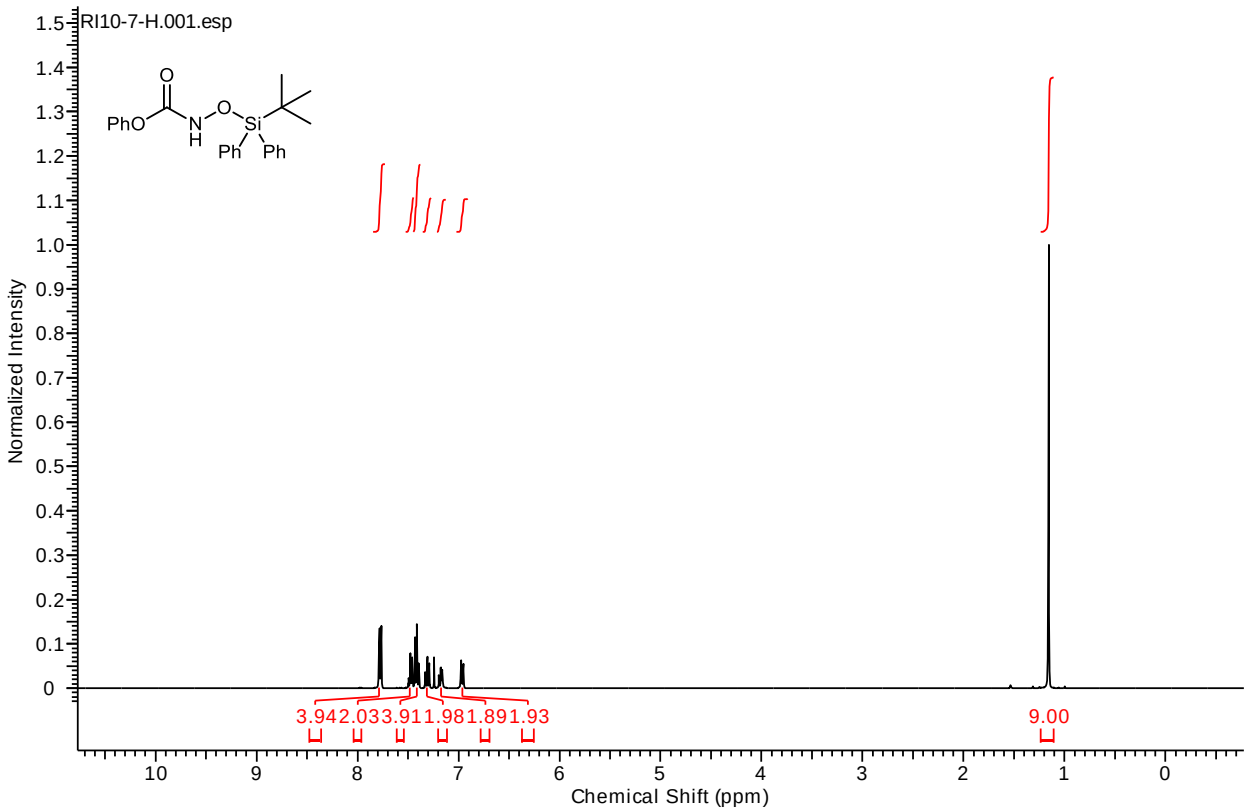

155.73
150.52
129.39
125.71
121.36
83.79
30.50
25.57
23.72
f1 (ppm)

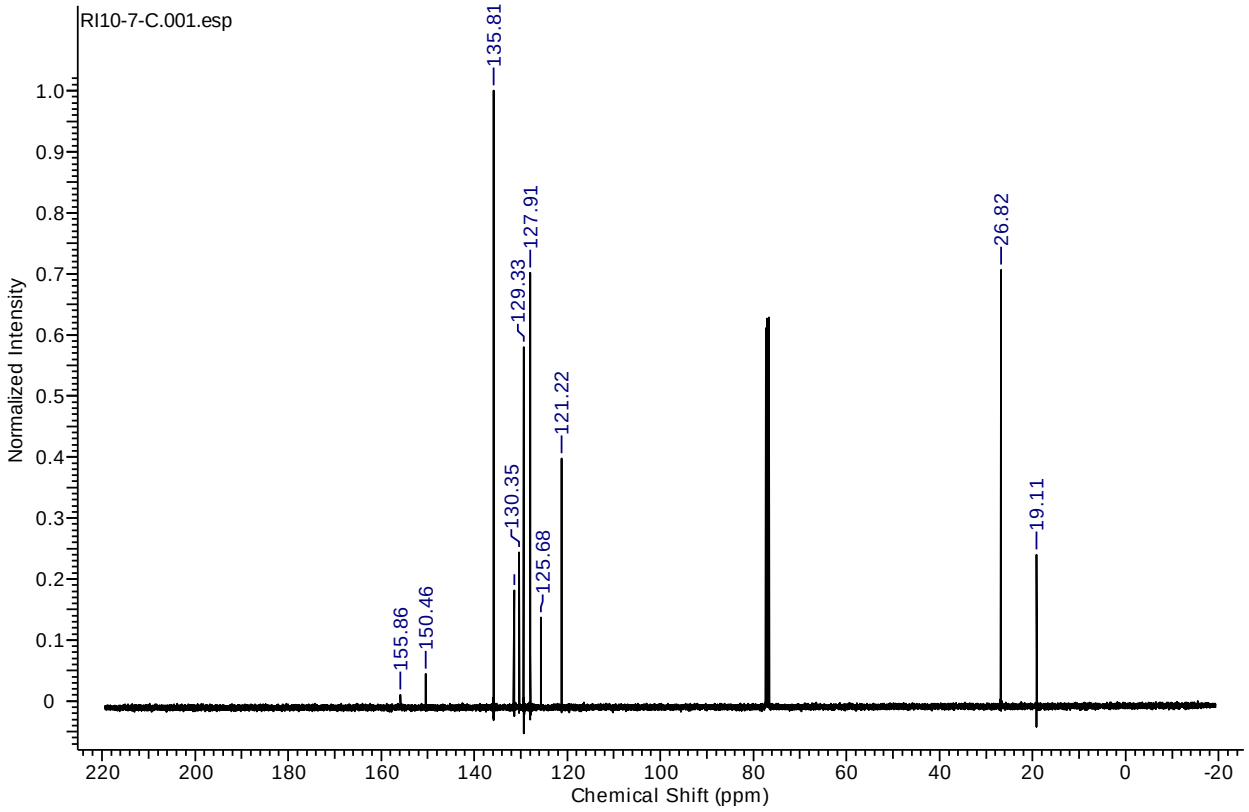

RI12-11-H.001.esp
PhO
O
N
H
O
Normalized Intensity
0.92 1.98 0.98 1.92
1.99
0.99 2.00 2.00
Chemical Shift (ppm)

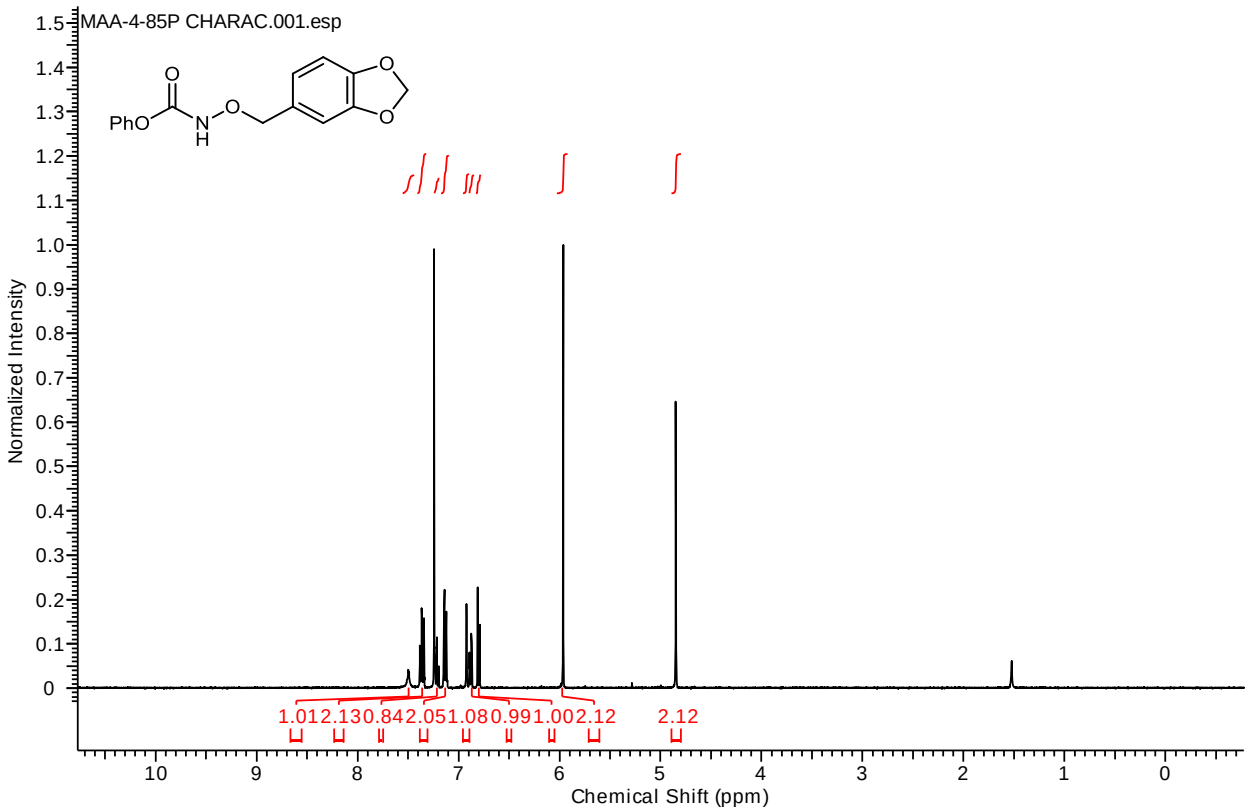

RI12-11-C.001.esp
Normalized Intensity
155.39
150.41
129.42
125.78
121.33
81.77
9.08
3.08
Chemical Shift (ppm)

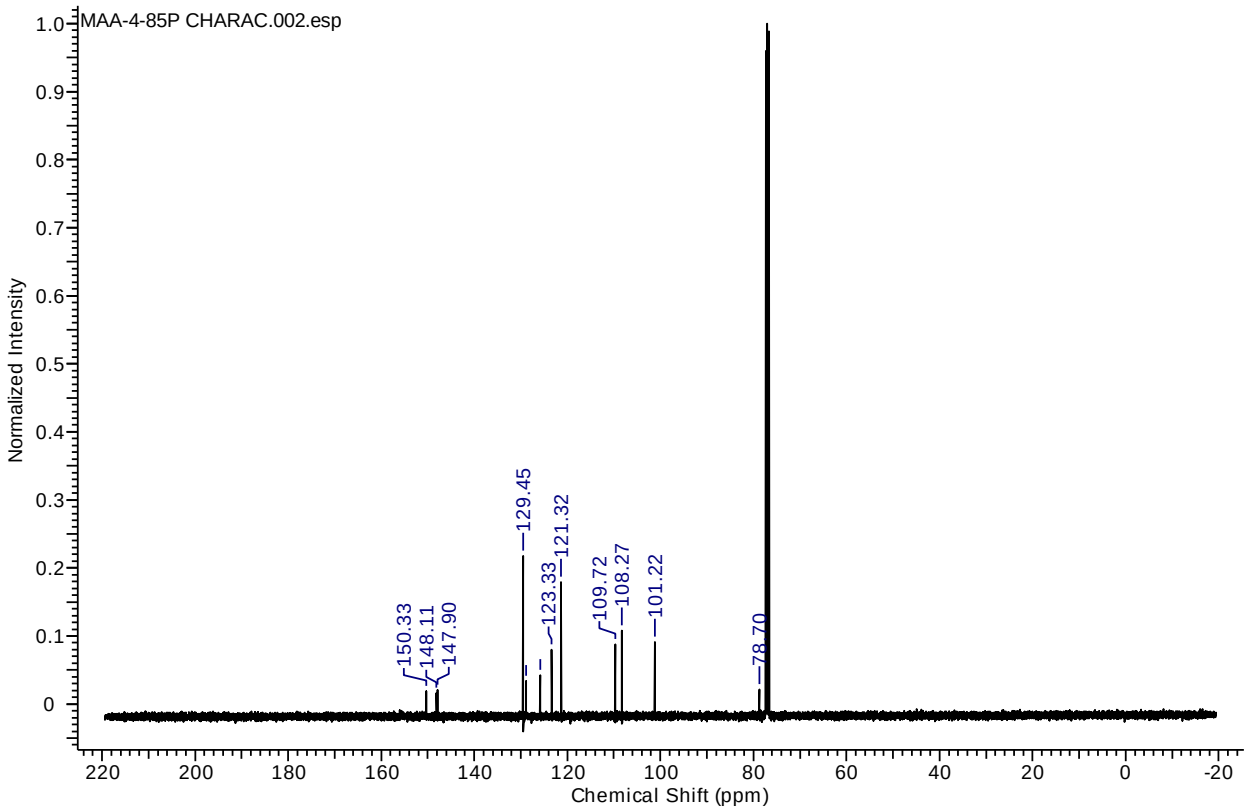

MAA-2-76P-CHARAC2.001.esp
PhO
O
N
H
O
Si
Me
Me
Normalized Intensity
2.00
0.98
0.81
2.01
8.46
5.57
Chemical Shift (ppm)

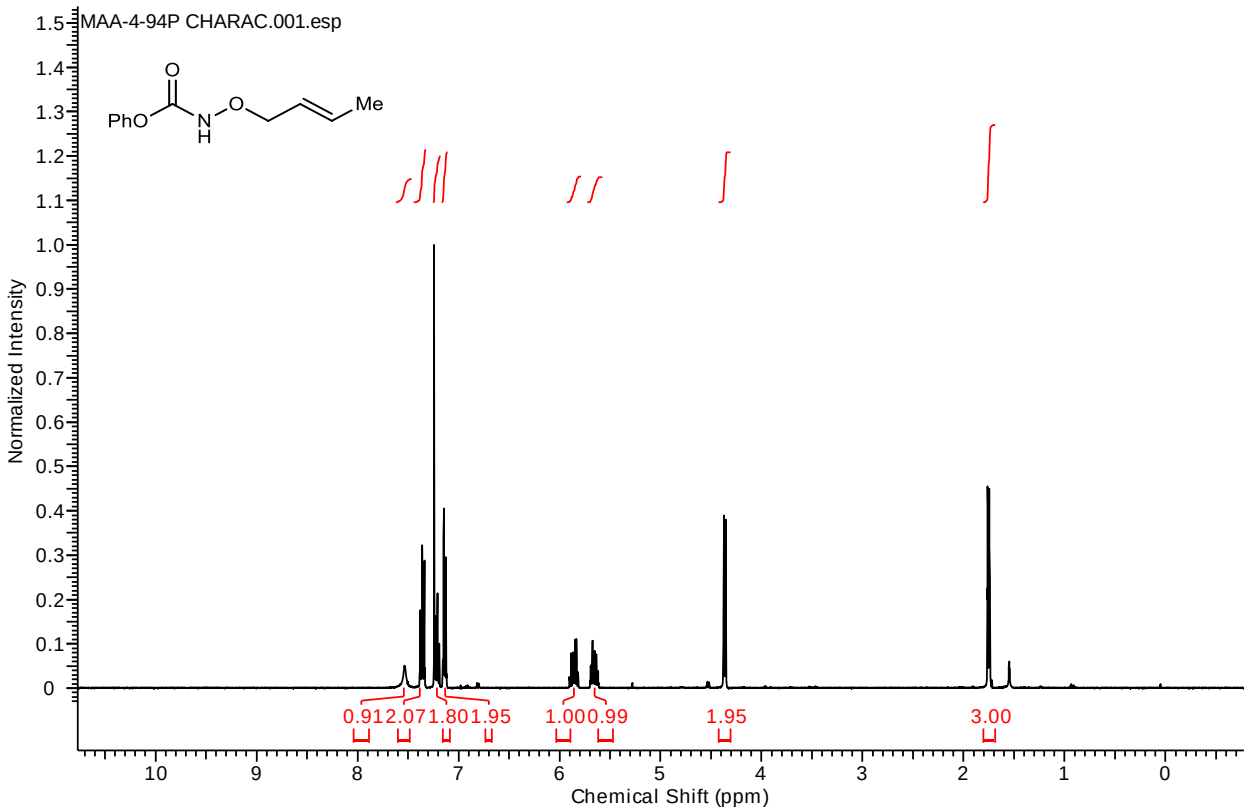

MAA-2-76P-CHARAC2.002.esp
Normalized Intensity
156.68
150.53
129.42
125.76
121.27
25.82
18.06
5.74
Chemical Shift (ppm)

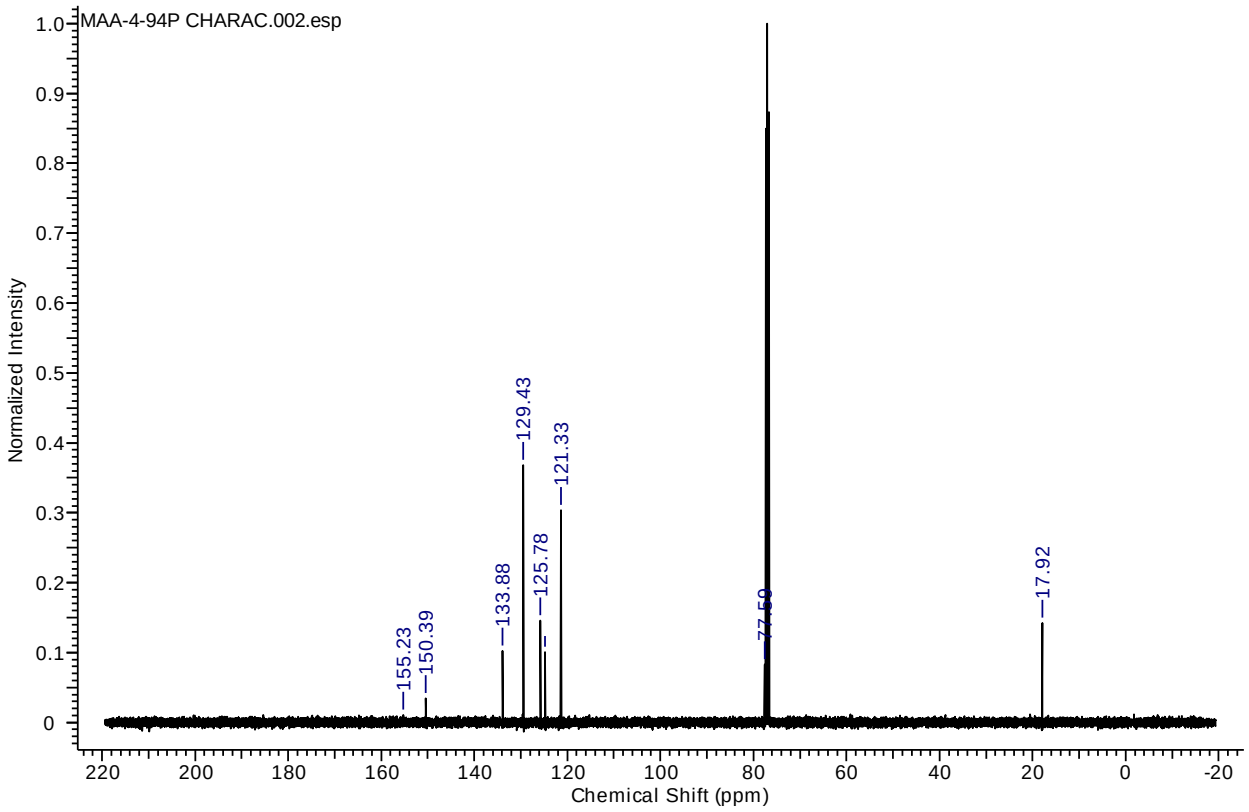

RI10-7-H.001.esp
PhO
O
N
H
O
Si
Ph
Ph
Normalized Intensity
3.94
2.03
3.91
1.98
1.89
1.93
9.00
Chemical Shift (ppm)

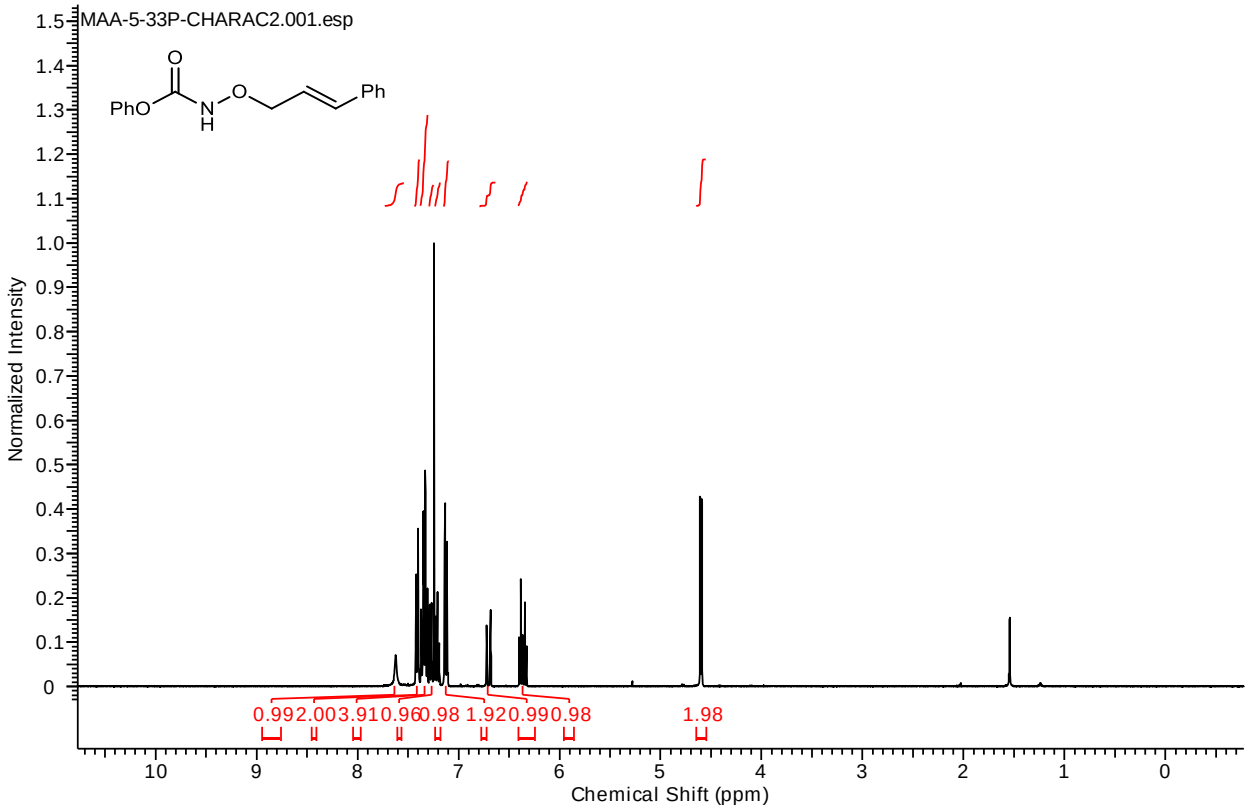

RI10-7-C.001.esp
135.81
129.33
127.91
121.22
130.35
125.68
155.86
150.46
26.82
19.11
Normalized Intensity
Chemical Shift (ppm)

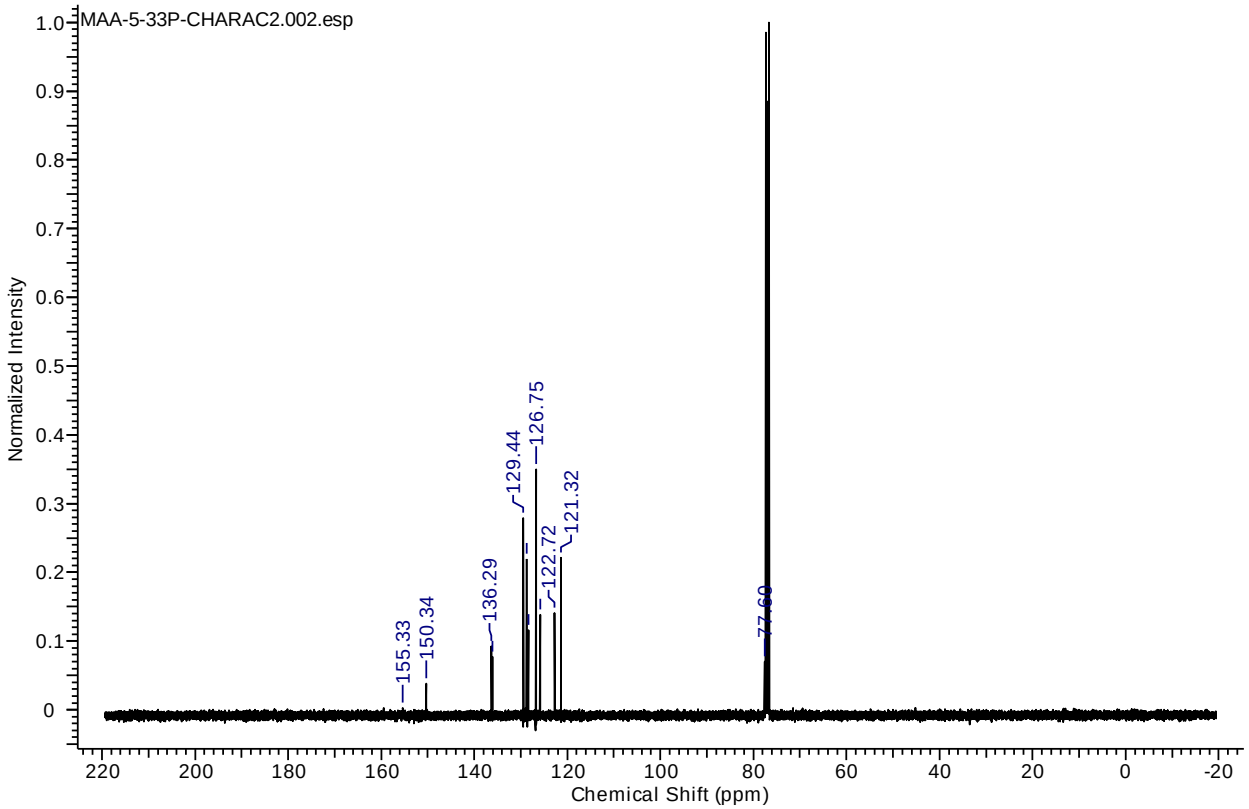

MAA-4-85P CHARAC.001.esp
PhO
O
N
H
O
O
O
Normalized Intensity
1.01
2.13
0.84
2.05
1.08
0.99
1.00
2.12
2.12
Chemical Shift (ppm)

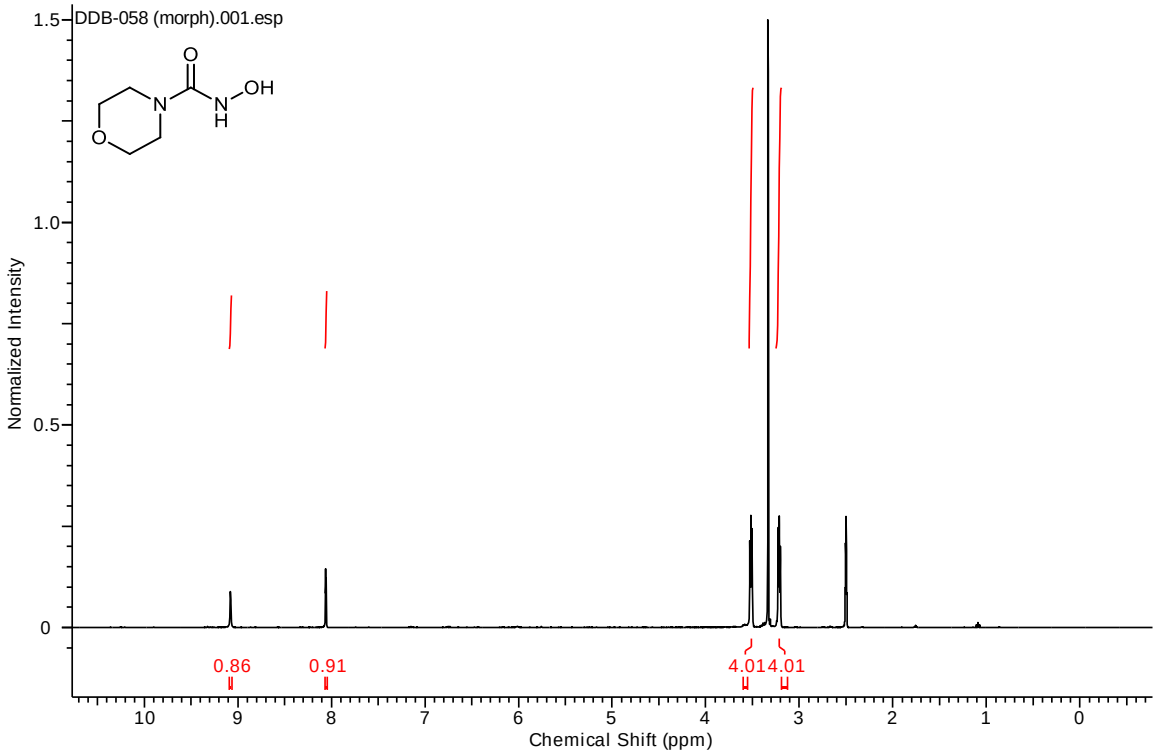

MAA-4-85P CHARAC.002.esp
Normalized Intensity
150.33
148.11
147.90
129.45
123.33
121.32
109.72
108.27
101.22
78.70
Chemical Shift (ppm)

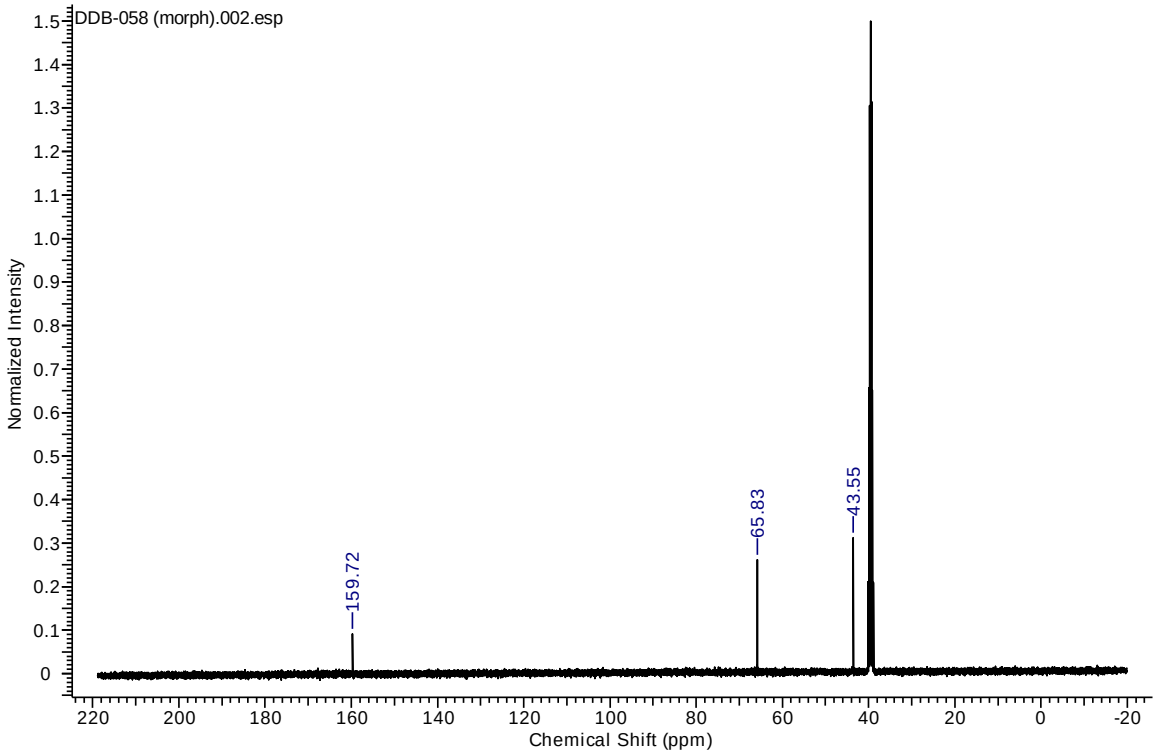

MAA-4-94P CHARAC.001.esp
O
PhO
N
H
O
Me
Normalized Intensity
0.91
2.07
1.80
1.95
1.00
0.99
1.95
3.00
Chemical Shift (ppm)

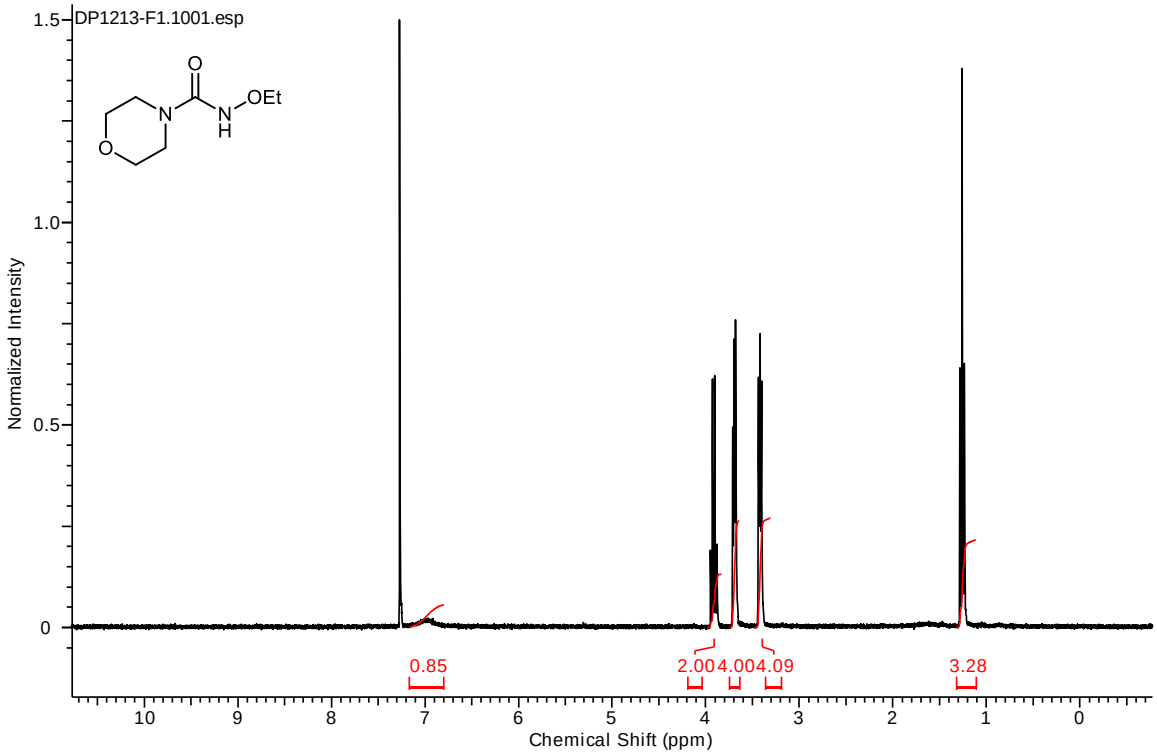

MAA-4-94P CHARAC.002.esp
155.23
150.39
133.88
129.43
125.78
121.33
77.59
17.92
Normalized Intensity
Chemical Shift (ppm)

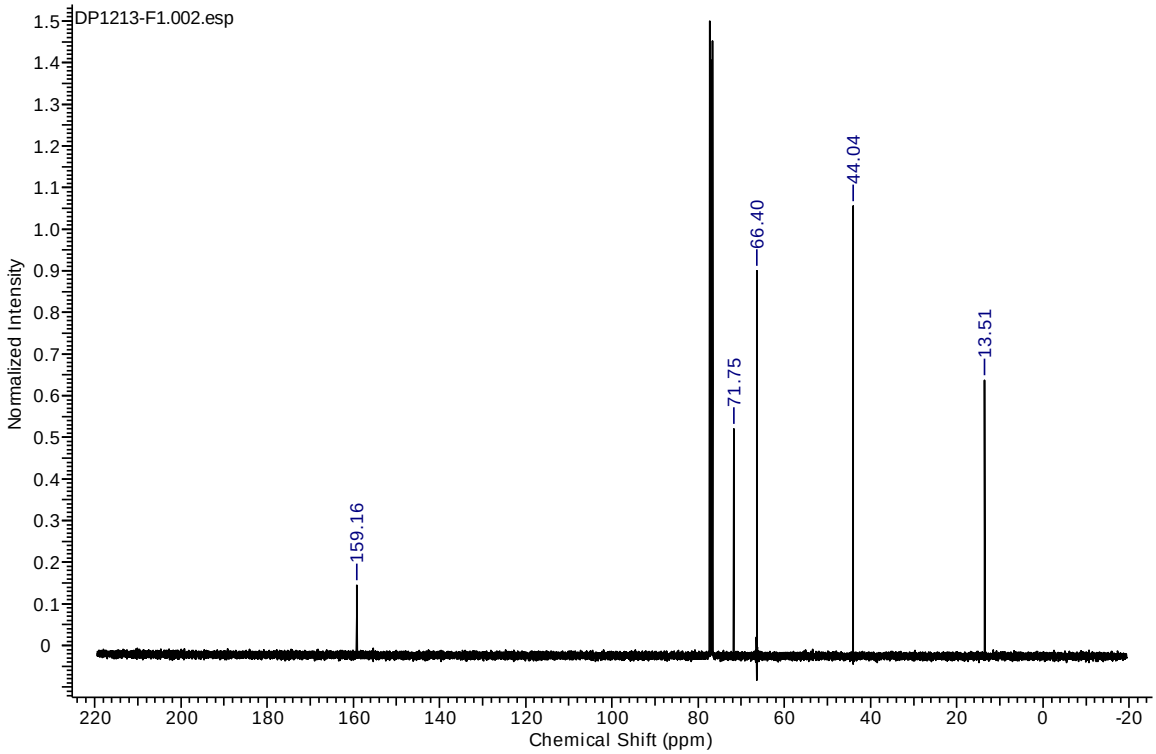

MAA-5-33P-CHARAC2.001.esp
PhO
O
N
H
O
Ph
Normalized Intensity
0.99
2.00
3.91
0.96
0.98
1.92
0.99
0.98
1.98
Chemical Shift (ppm)

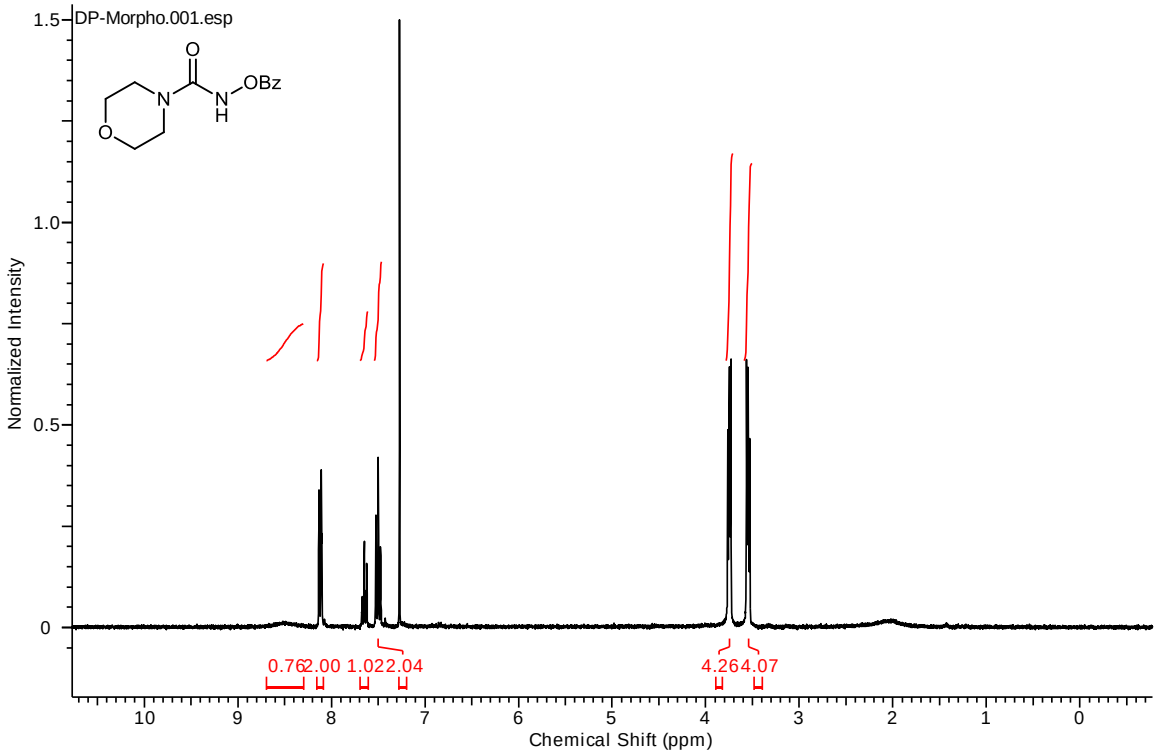

MAA-5-33P-CHARAC2.002.esp
Normalized Intensity
155.33
150.34
136.29
129.44
126.75
122.72
121.32
77.00
Chemical Shift (ppm)

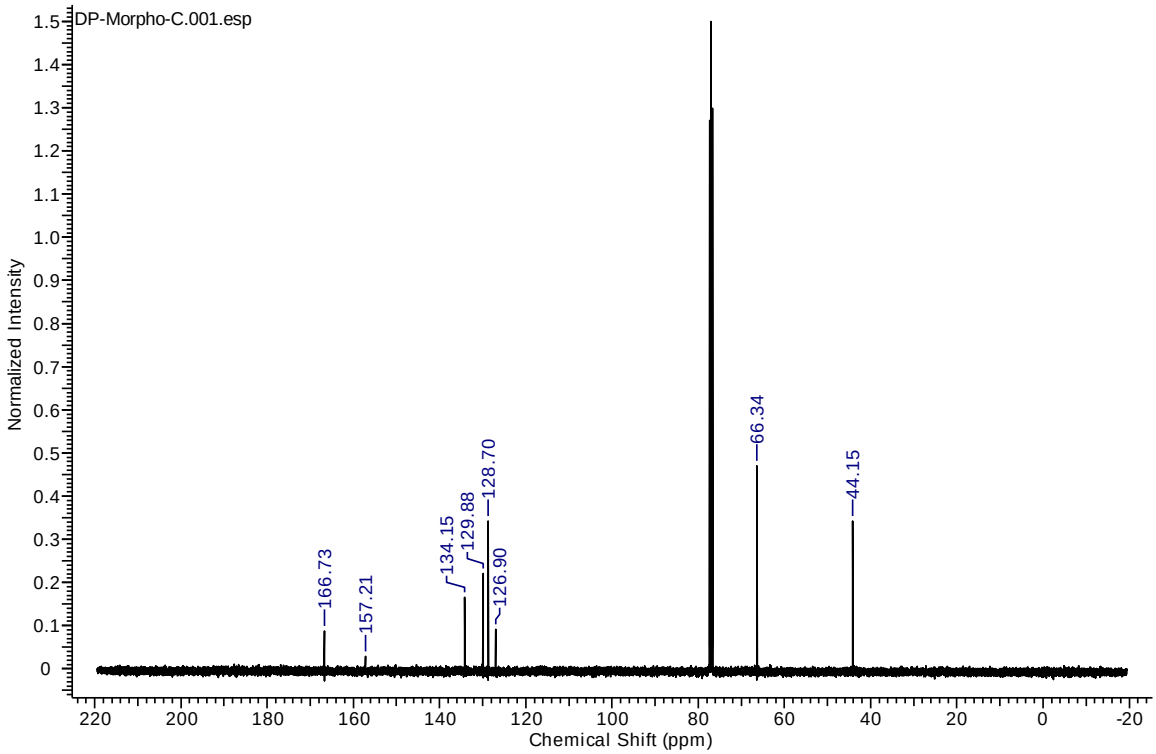

DDB-058 (morph).001.esp
O
N
OH
N
H
O
Normalized Intensity
1.5
1.0
0.5
0
0.86
0.91
4.01
4.01
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

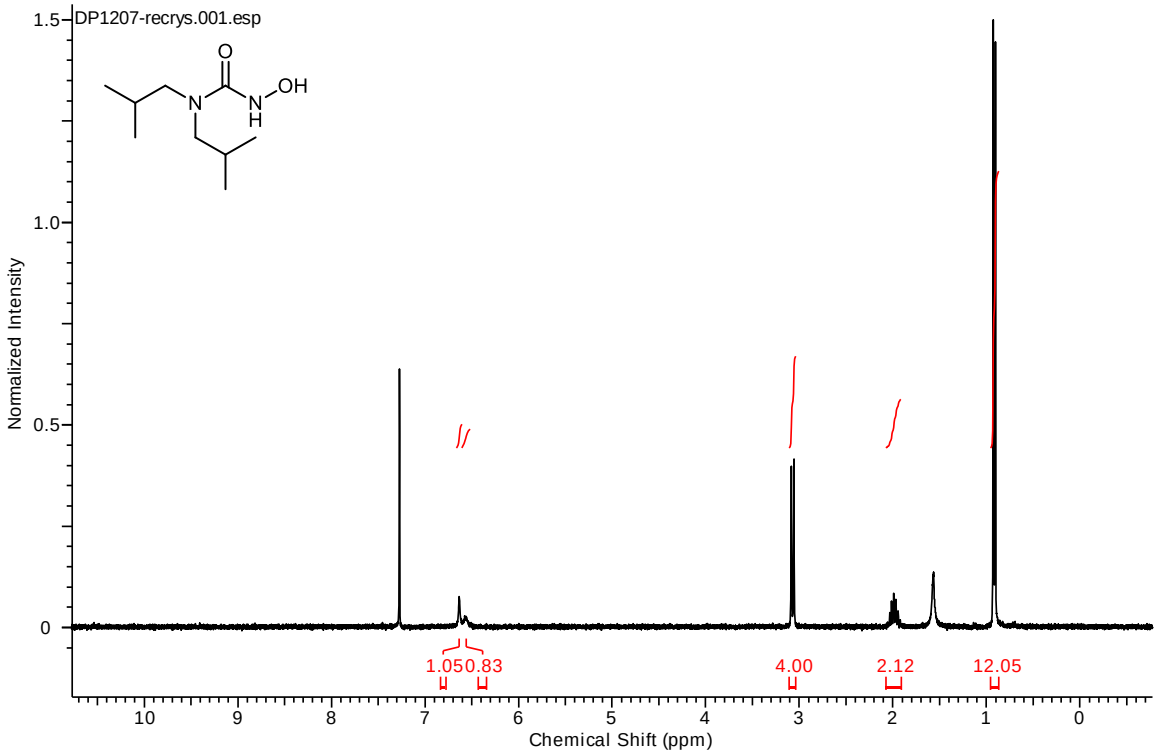

DDB-058 (morph).002.esp
Normalized Intensity
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
159.72
65.83
43.55
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

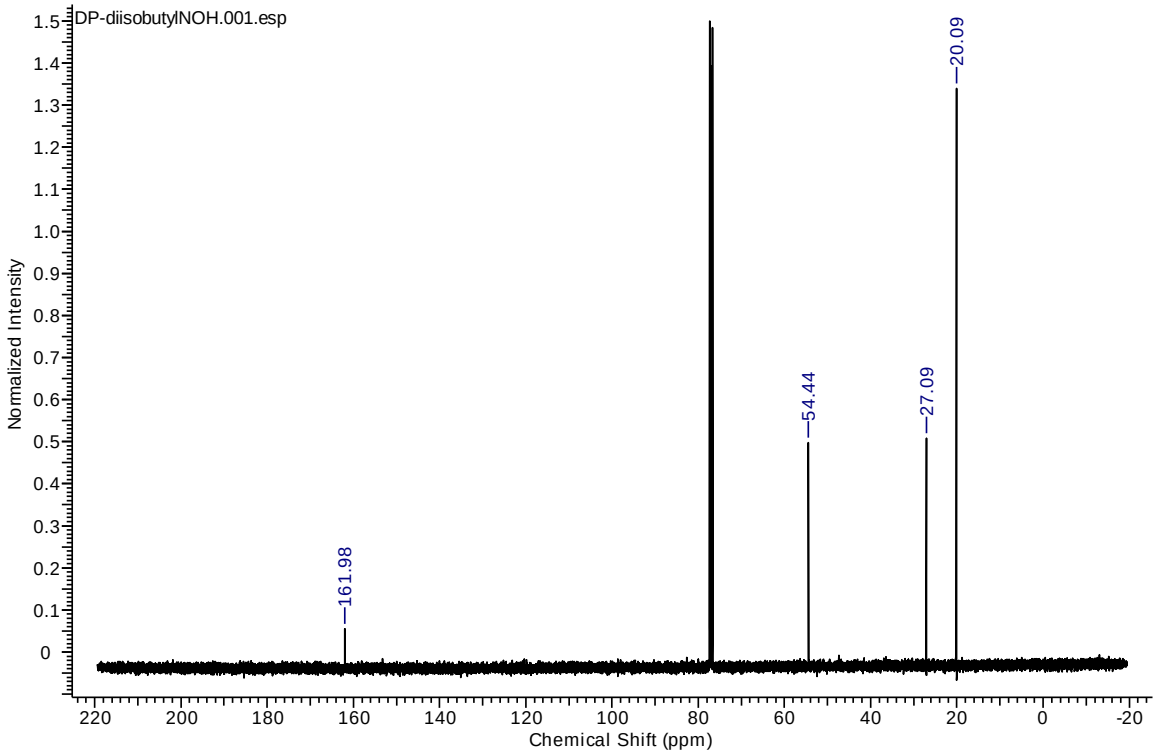

DP1213-F1.1001.esp
O
N
N
H
OEt
O
Normalized Intensity
0.85
2.00
4.00
4.09
3.28
Chemical Shift (ppm)

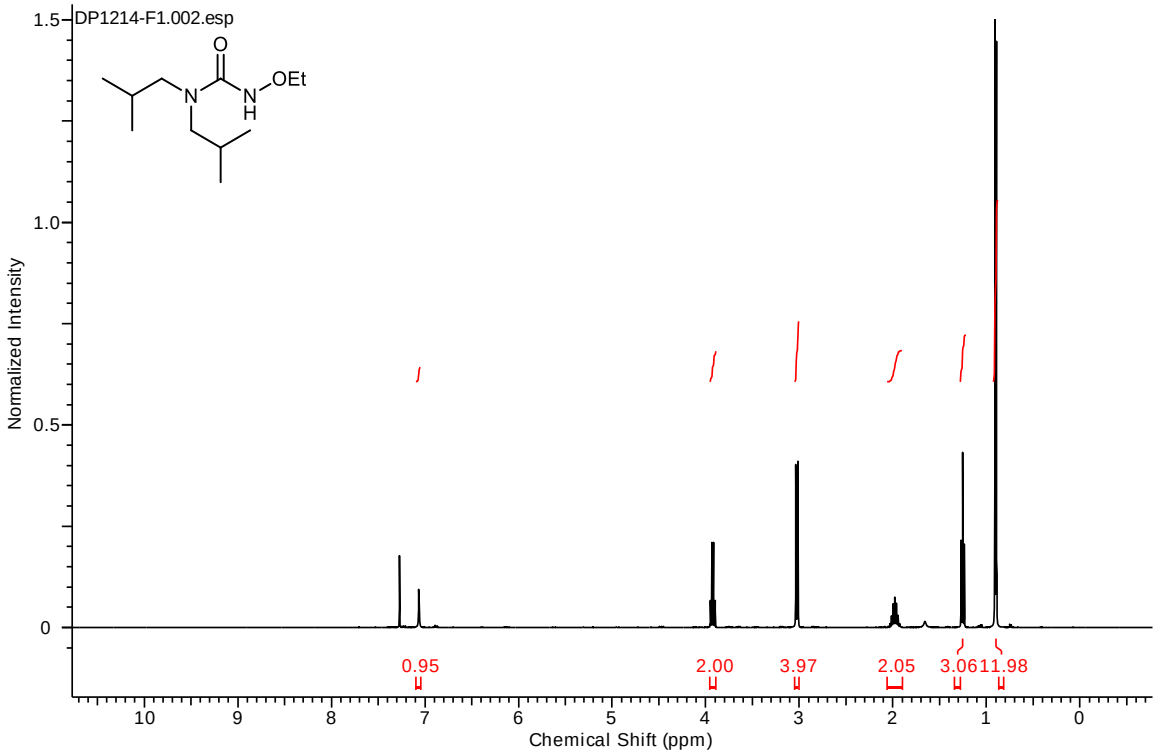

DP1213-F1.002.esp
159.16
71.75
66.40
44.04
13.51
Normalized Intensity
Chemical Shift (ppm)

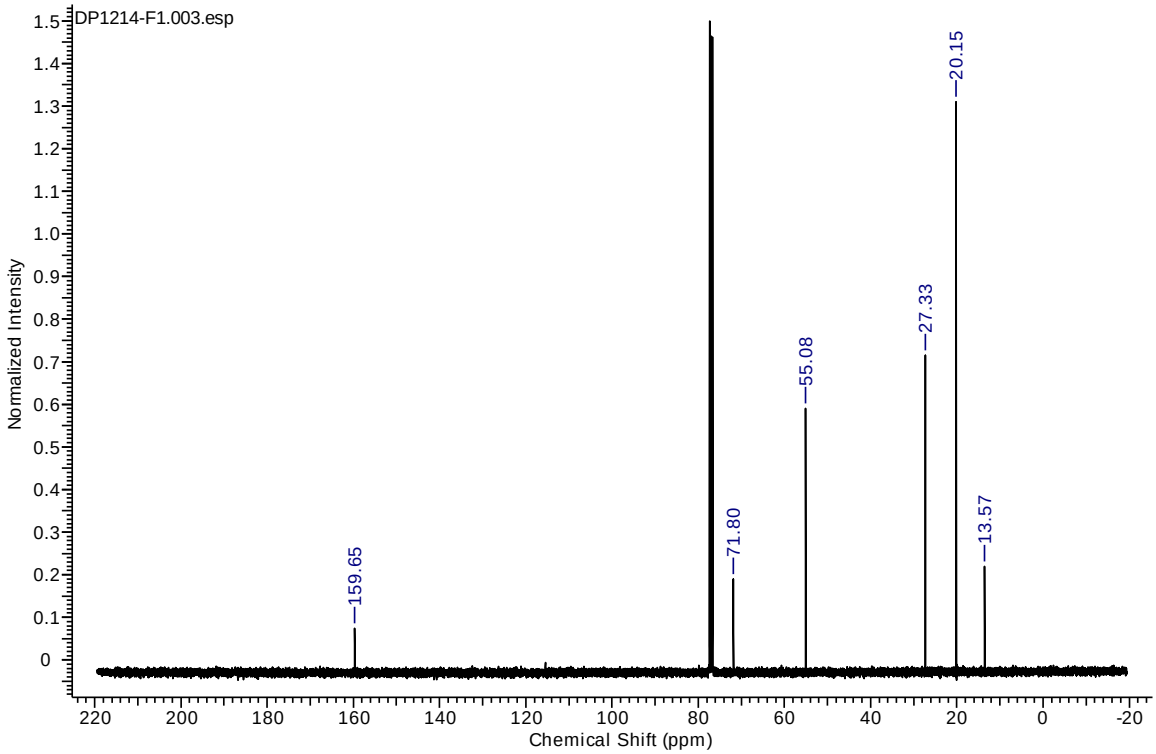

DP-Morpho.001.esp
O
N
N
H
OBz
O
Normalized Intensity
1.5
1.0
0.5
0
0.76
2.00
1.02
2.04
4.26
4.07
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

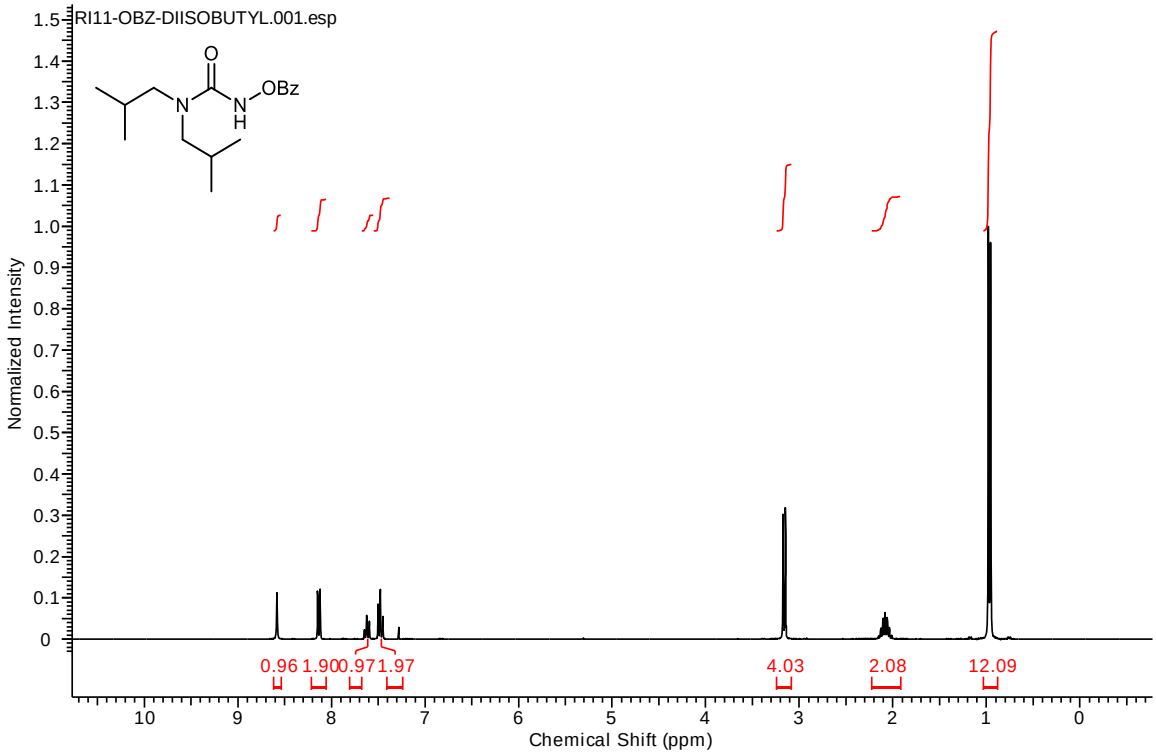

DP-Morpho-C.001.esp
Normalized Intensity
166.73
157.21
134.15
129.88
128.70
126.90
66.34
44.15
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

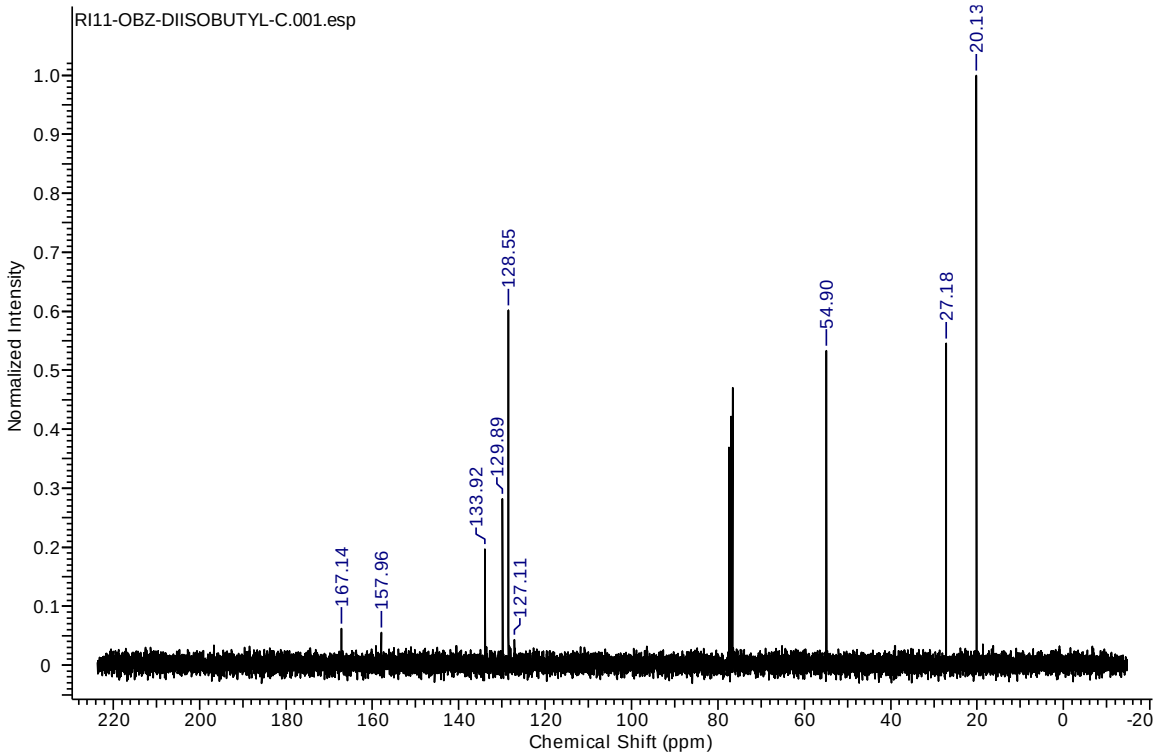

DP1207-recrys.001.esp
O
N
N
H
OH
Normalized Intensity
1.05
0.83
4.00
2.12
12.05
Chemical Shift (ppm)

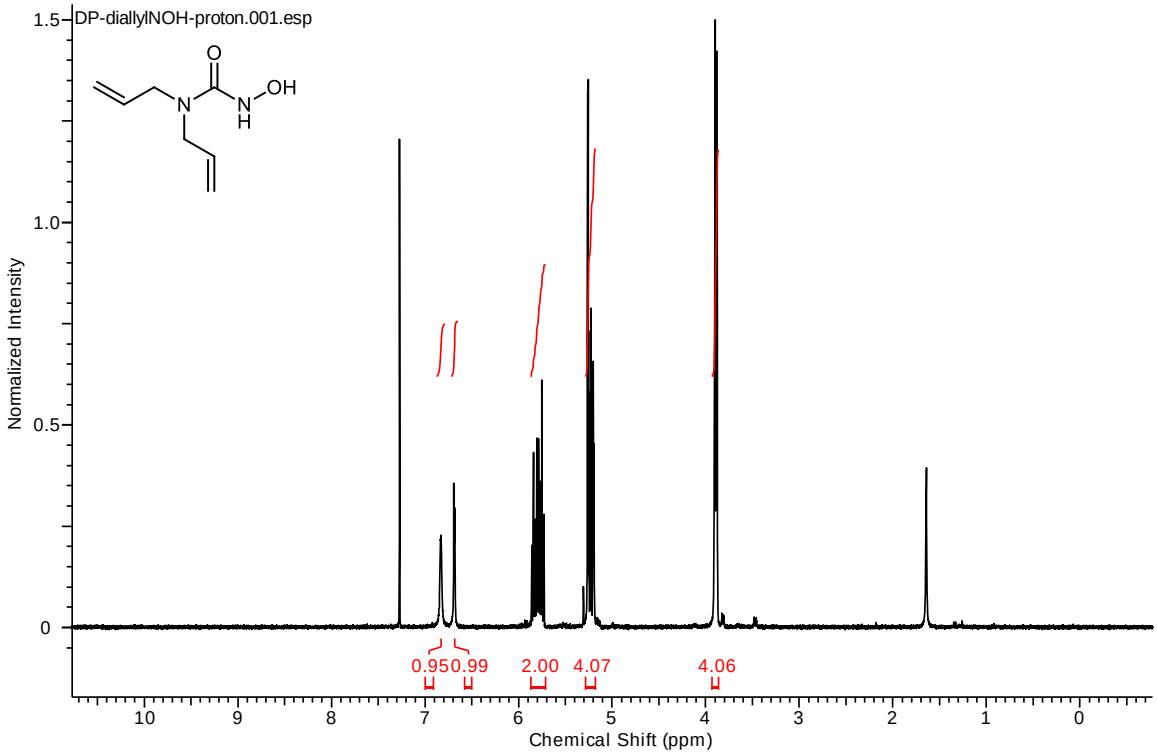

DP-diisobutylNOH.001.esp
161.98
54.44
27.09
20.09
Normalized Intensity
Chemical Shift (ppm)

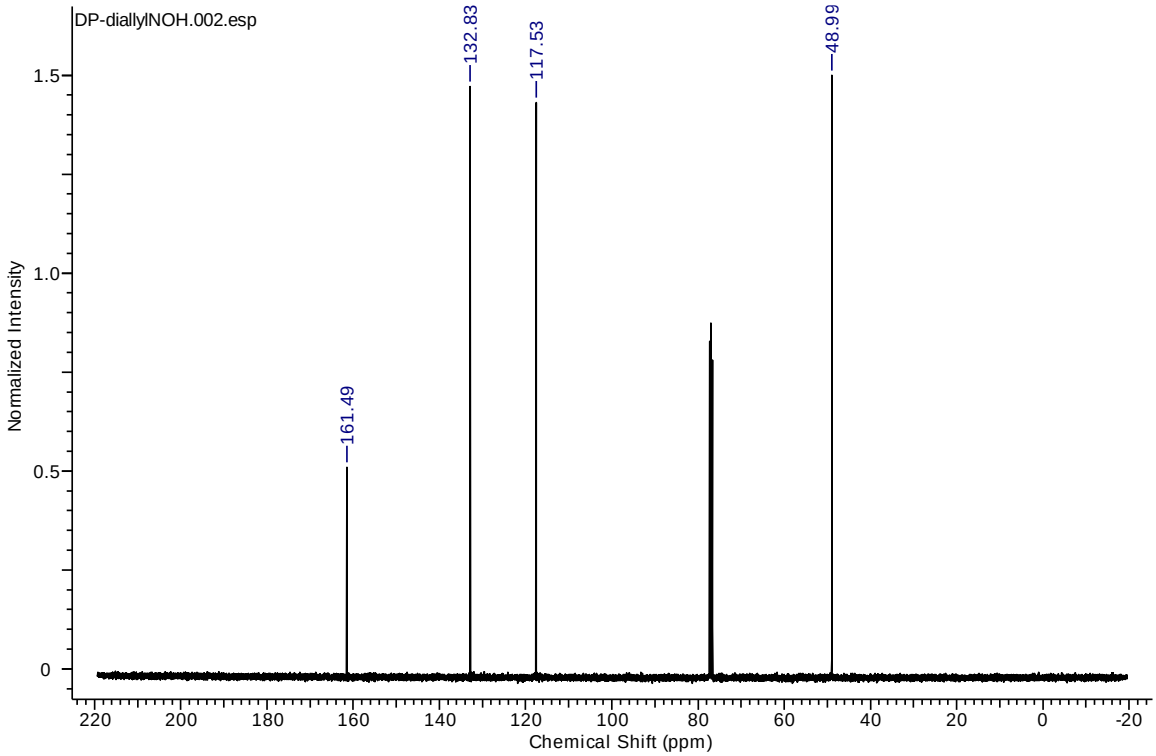

DP1214-F1.002.esp
O
N
N
H
OEt
Normalized Intensity
1.5
1.0
0.5
0
0.95
2.00
3.97
2.05
3.06
11.98
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

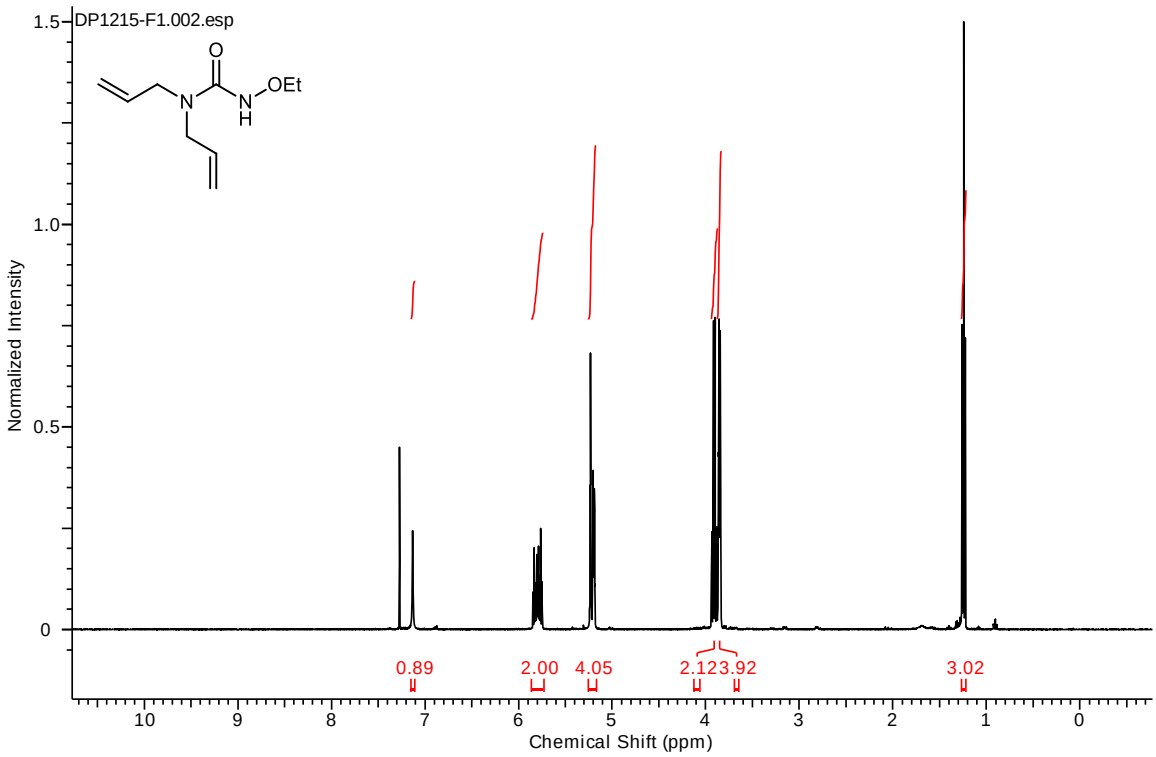

DP1214-F1.003.esp
Normalized Intensity
159.65
71.80
55.08
27.33
20.15
13.57
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

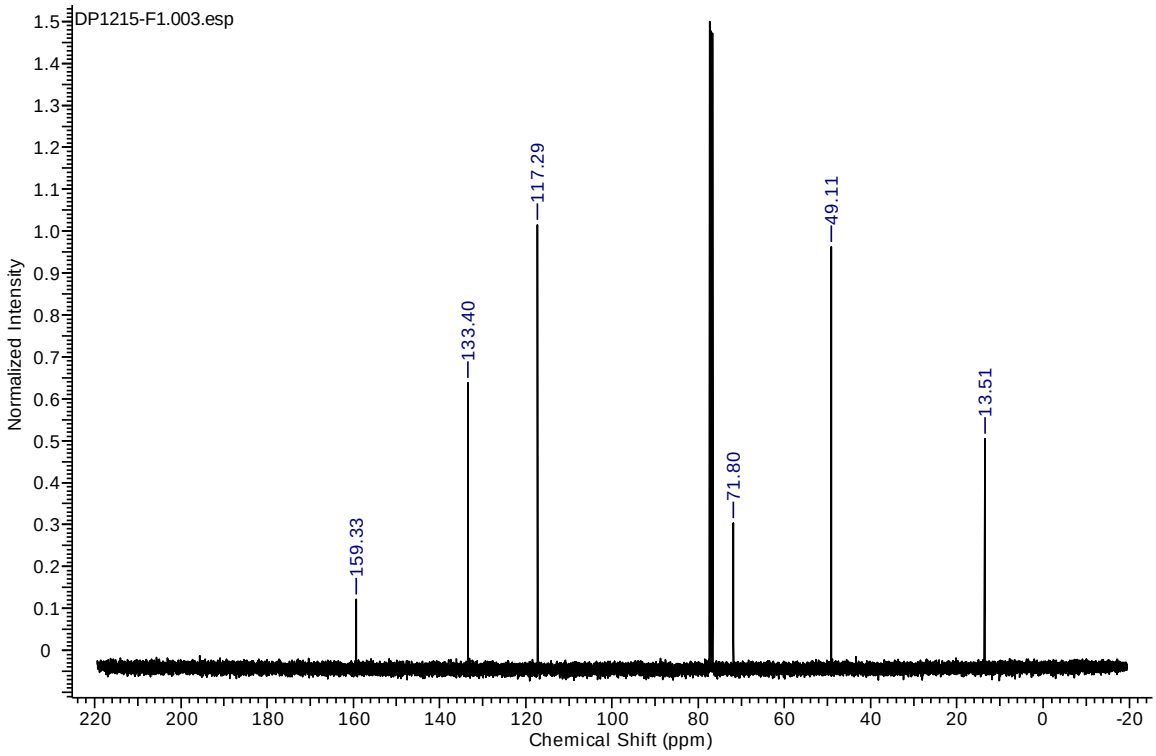

RI11-OBZ-DIISOBUTYL.001.esp
O
N
N
H
OBz
Normalized Intensity
0.96
1.90
0.97
1.97
4.03
2.08
12.09
Chemical Shift (ppm)

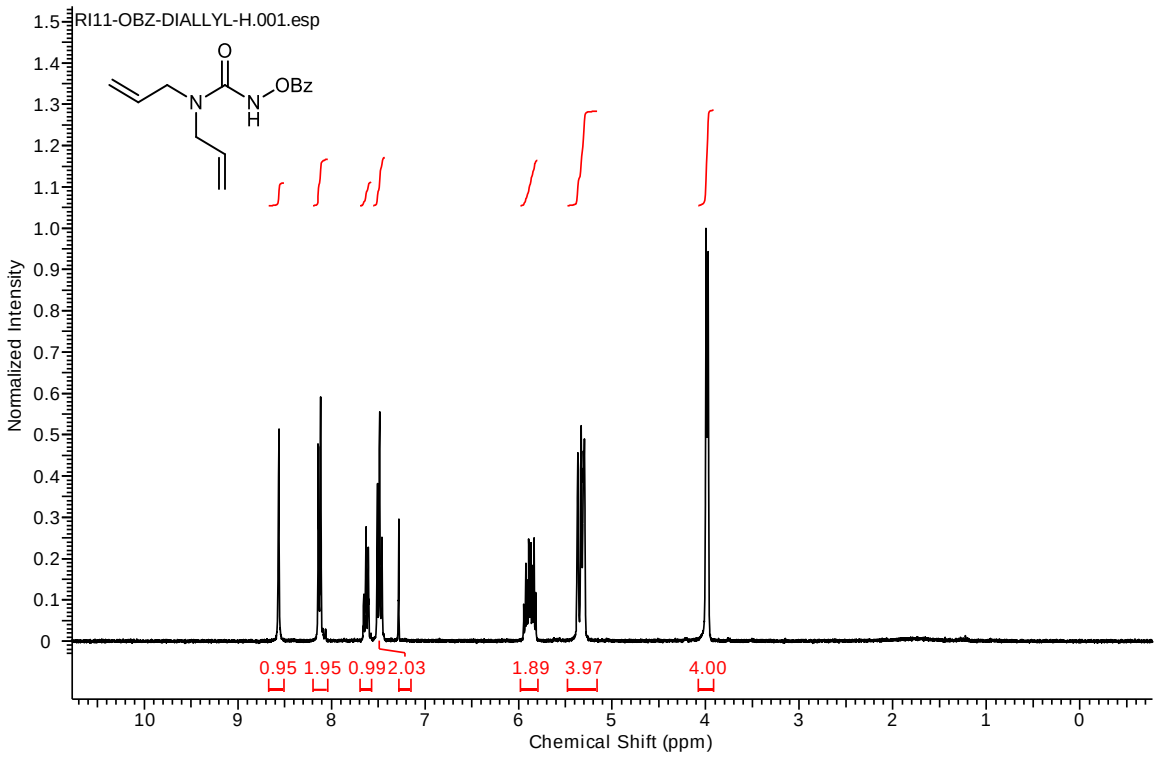

RI11-OBZ-DIISOBUTYL-C.001.esp
Normalized Intensity
167.14
157.96
133.92
129.89
128.55
127.11
54.90
27.18
20.13
Chemical Shift (ppm)

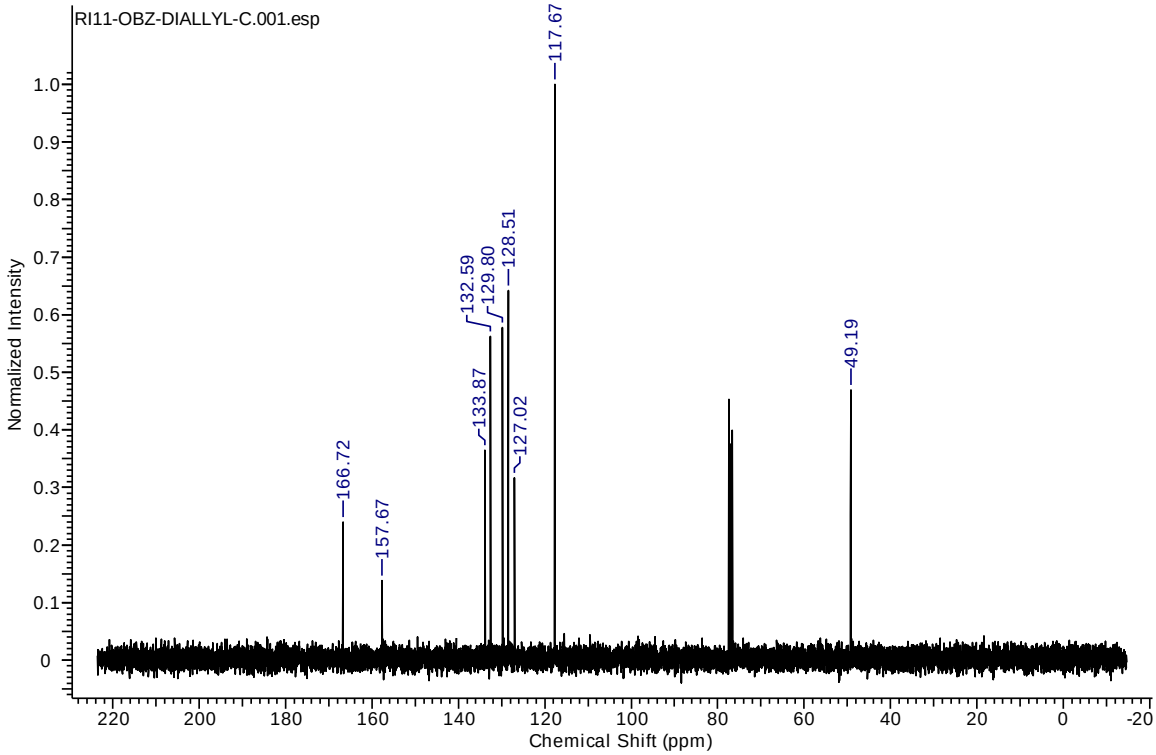

DP-diallylNOH-proton.001.esp
O
N
N
H
OH
Normalized Intensity
1.5
1.0
0.5
0
0.95
0.99
2.00
4.07
4.06
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

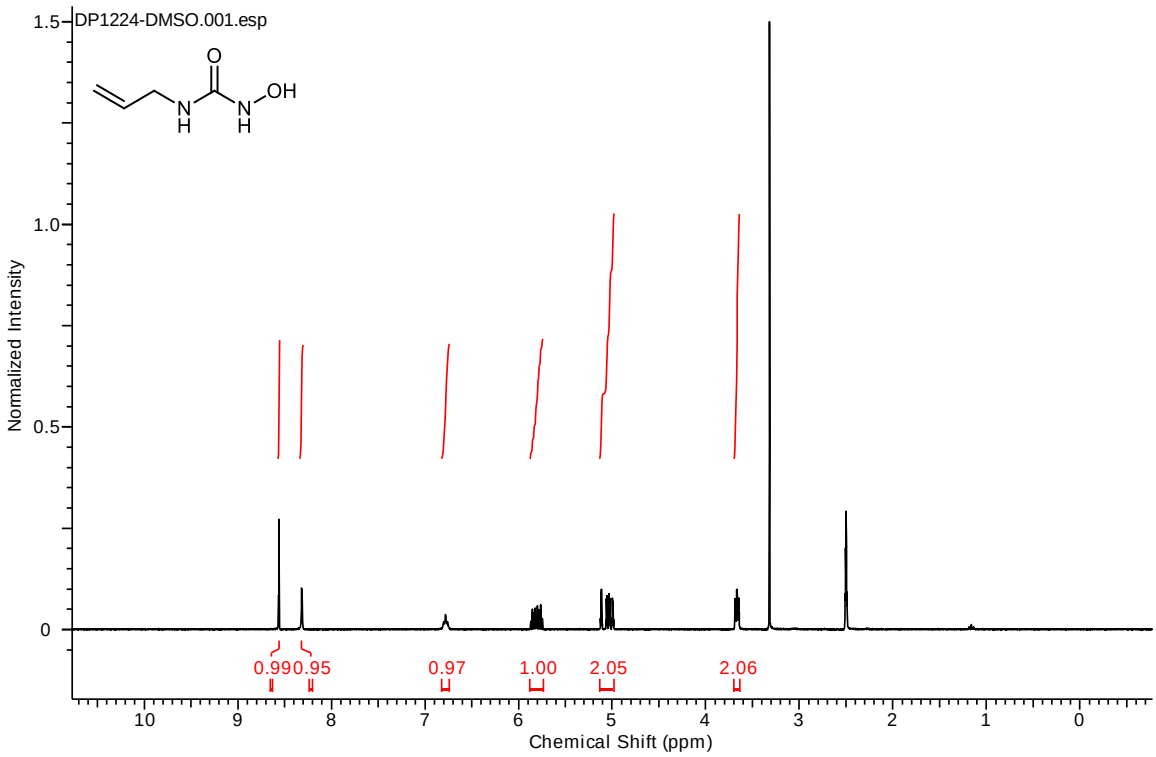

DP-diallylNOH.002.esp
132.83
117.53
48.99
161.49
Normalized Intensity
1.5
1.0
0.5
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

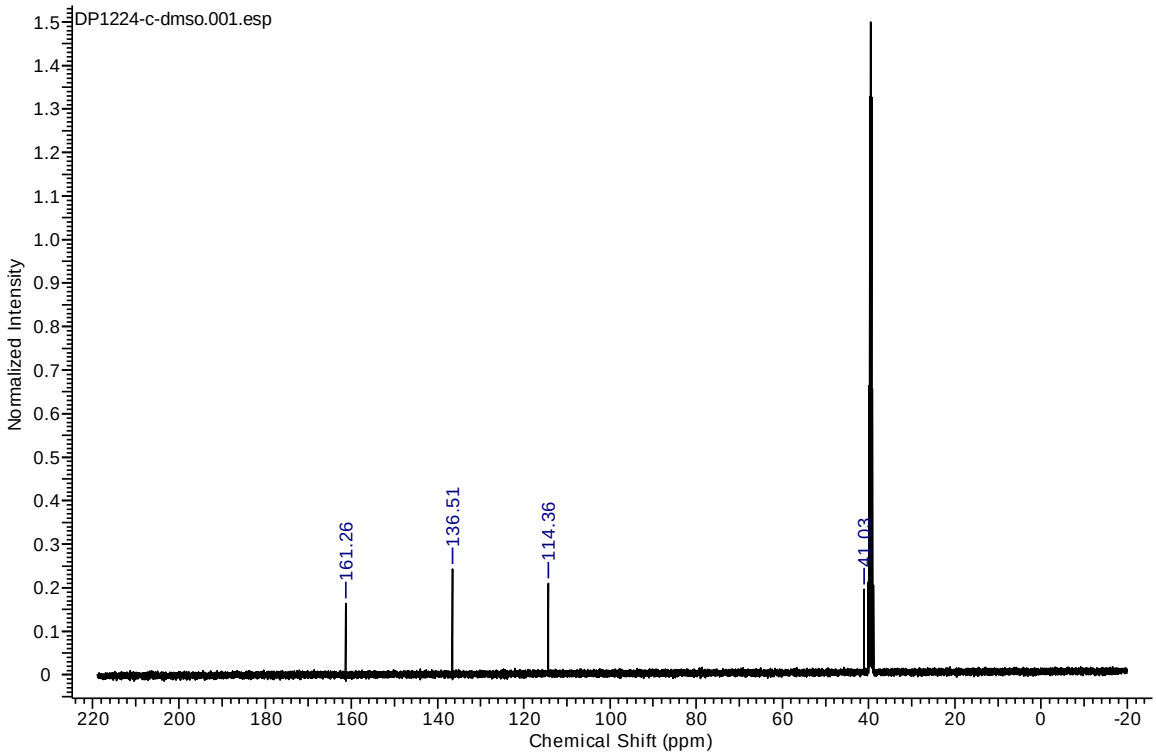

DP1215-F1.002.esp
O
N
N
H
OEt
Normalized Intensity
1.5
1.0
0.5
0
0.89
2.00
4.05
2.12
3.92
3.02
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

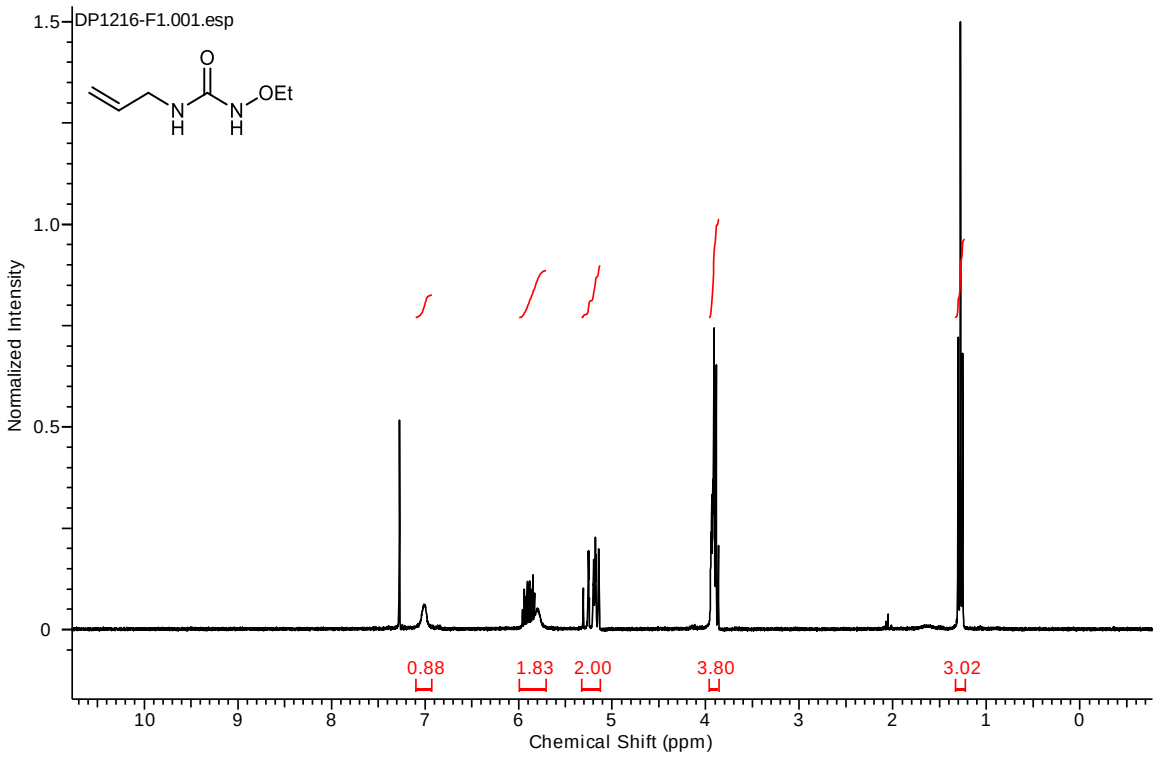

DP1215-F1.003.esp
Normalized Intensity
159.33
133.40
117.29
71.80
49.11
13.51
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

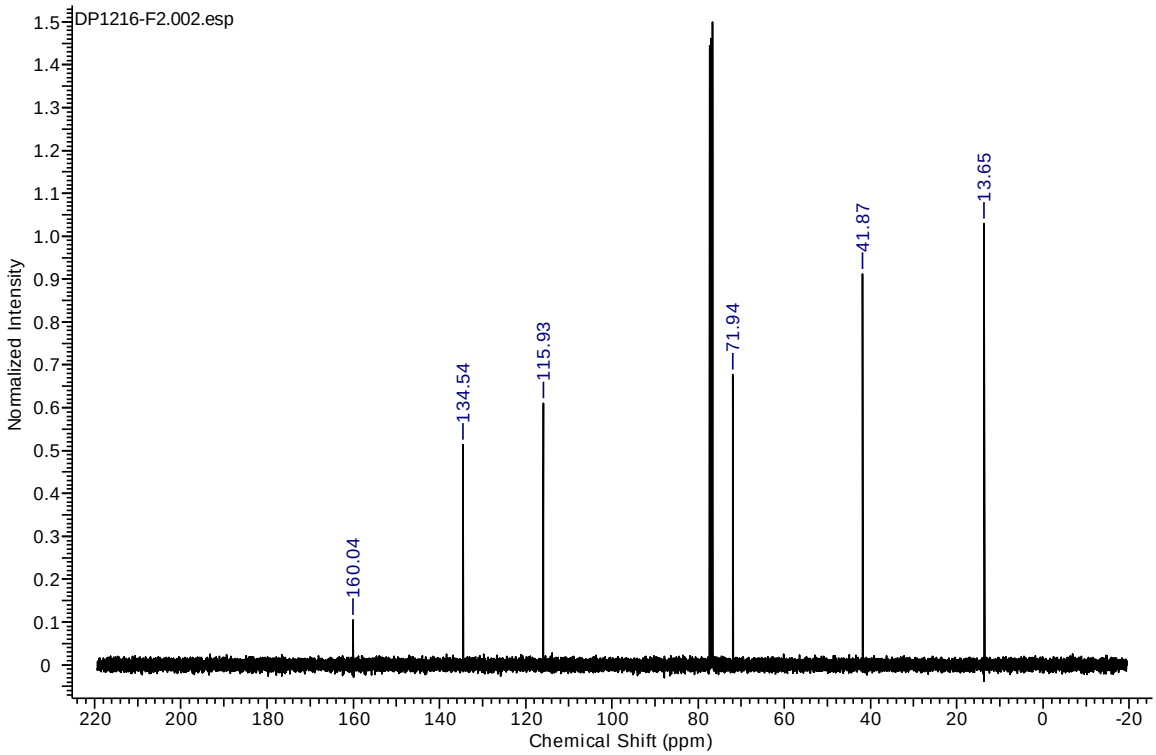

RI11-OBZ-DIALLYL-H.001.esp
O
N
N
H
OBz
Normalized Intensity
0.95
1.95
0.99
2.03
1.89
3.97
4.00
Chemical Shift (ppm)

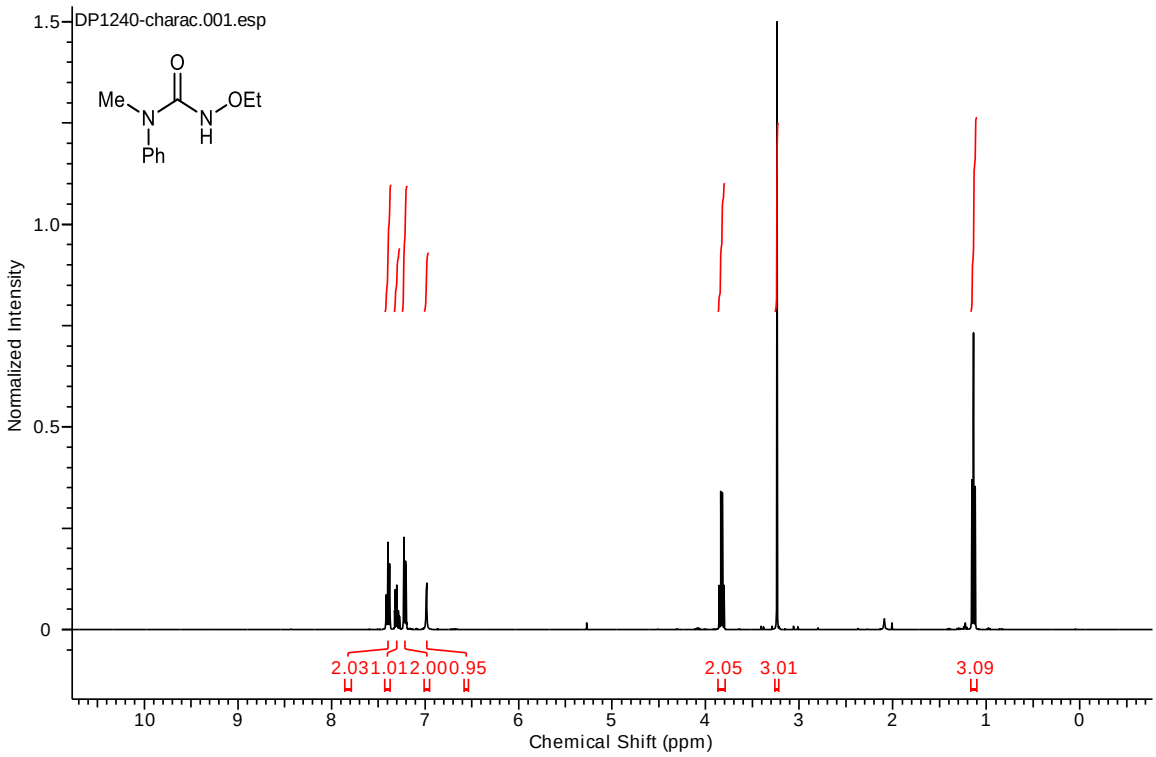

RI11-OBZ-DIALLYL-C.001.esp
117.67
132.59
129.80
128.51
133.87
127.02
49.19
166.72
157.67
Normalized Intensity
Chemical Shift (ppm)

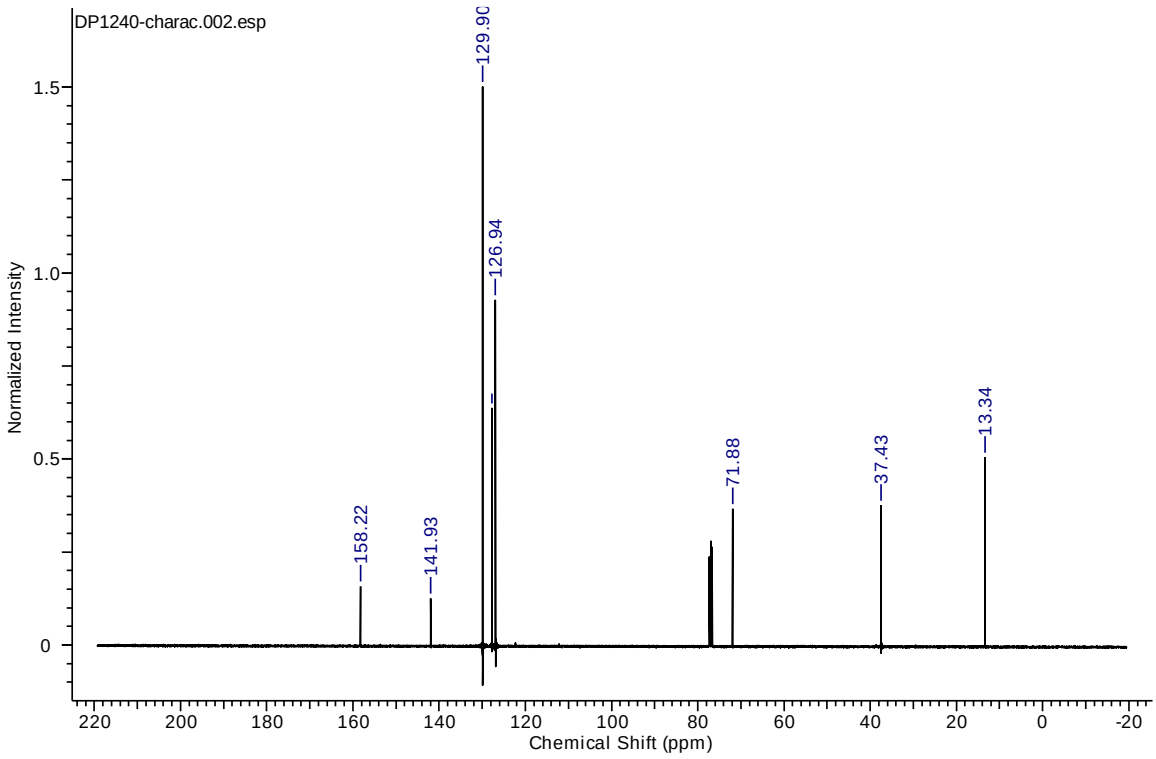

DP1224-DMSO.001.esp
O
N
H
N
H
OH
Normalized Intensity
0.99
0.95
0.97
1.00
2.05
2.06
Chemical Shift (ppm)

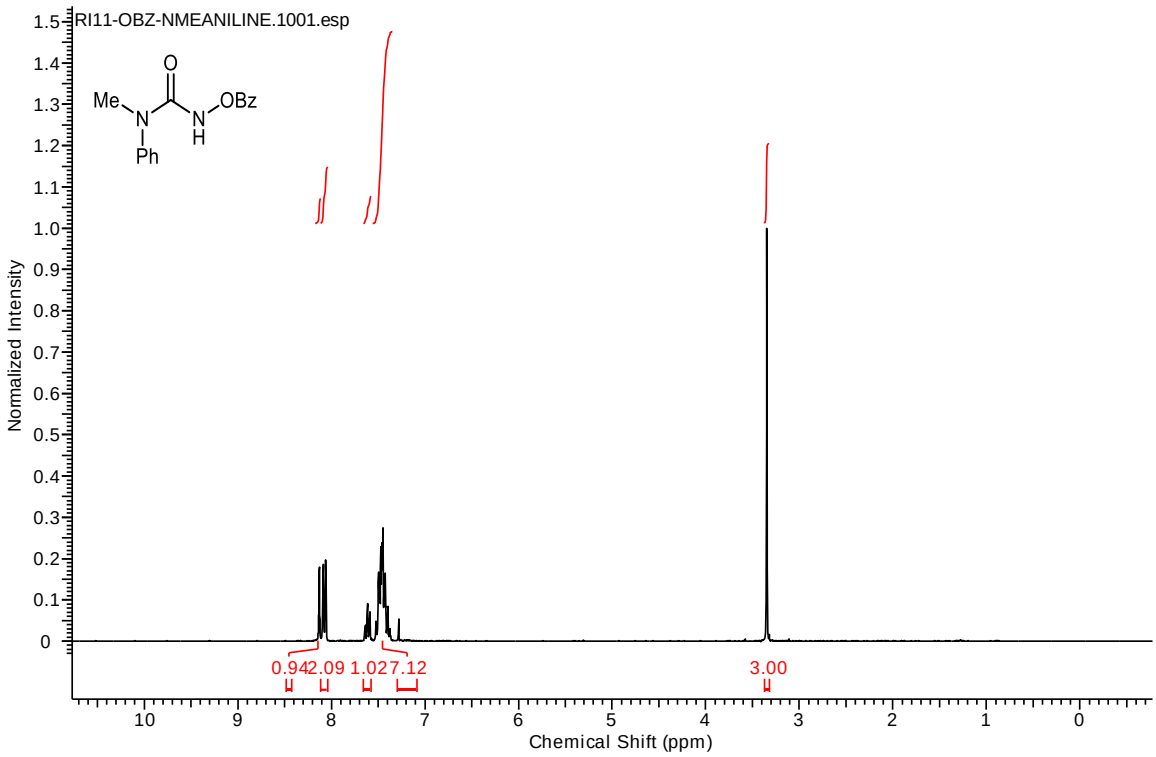

DP1224-c-dmso.001.esp
Normalized Intensity
161.26
136.51
114.36
41.03
Chemical Shift (ppm)

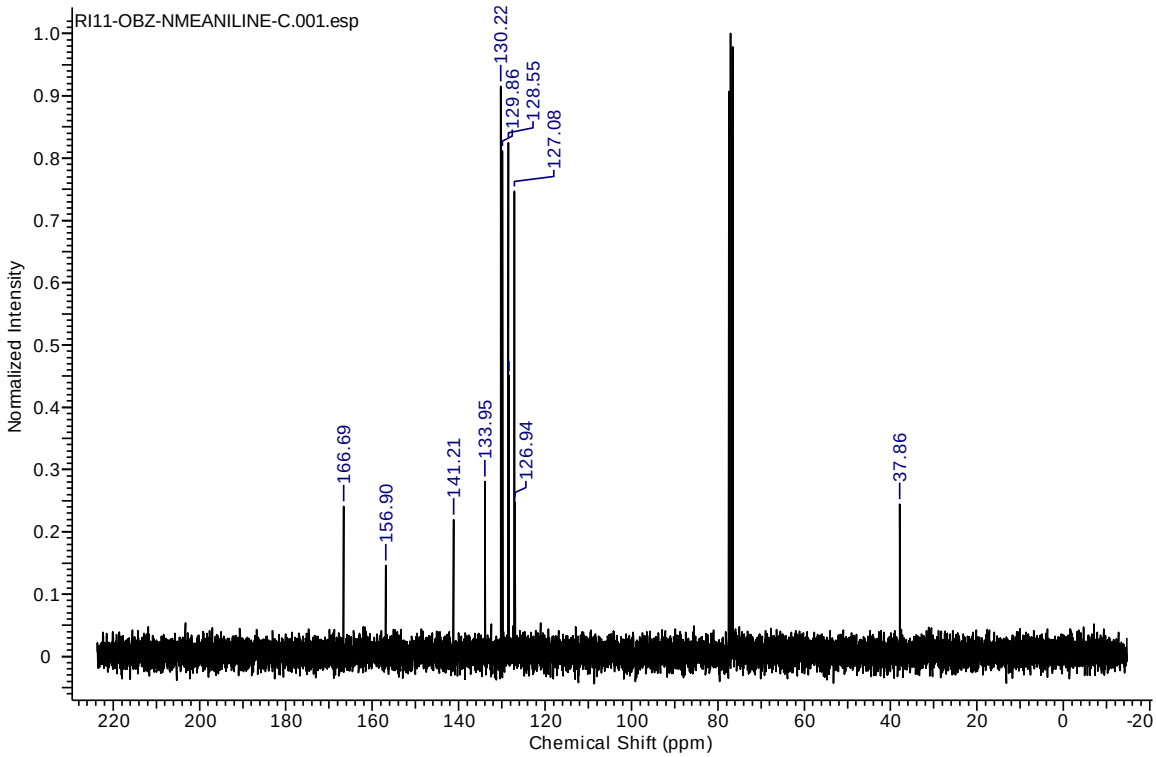

DP1216-F1.001.esp
O
OEt
N
H
N
H
Normalized Intensity
1.5
1.0
0.5
0
0.88
1.83
2.00
3.80
3.02
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

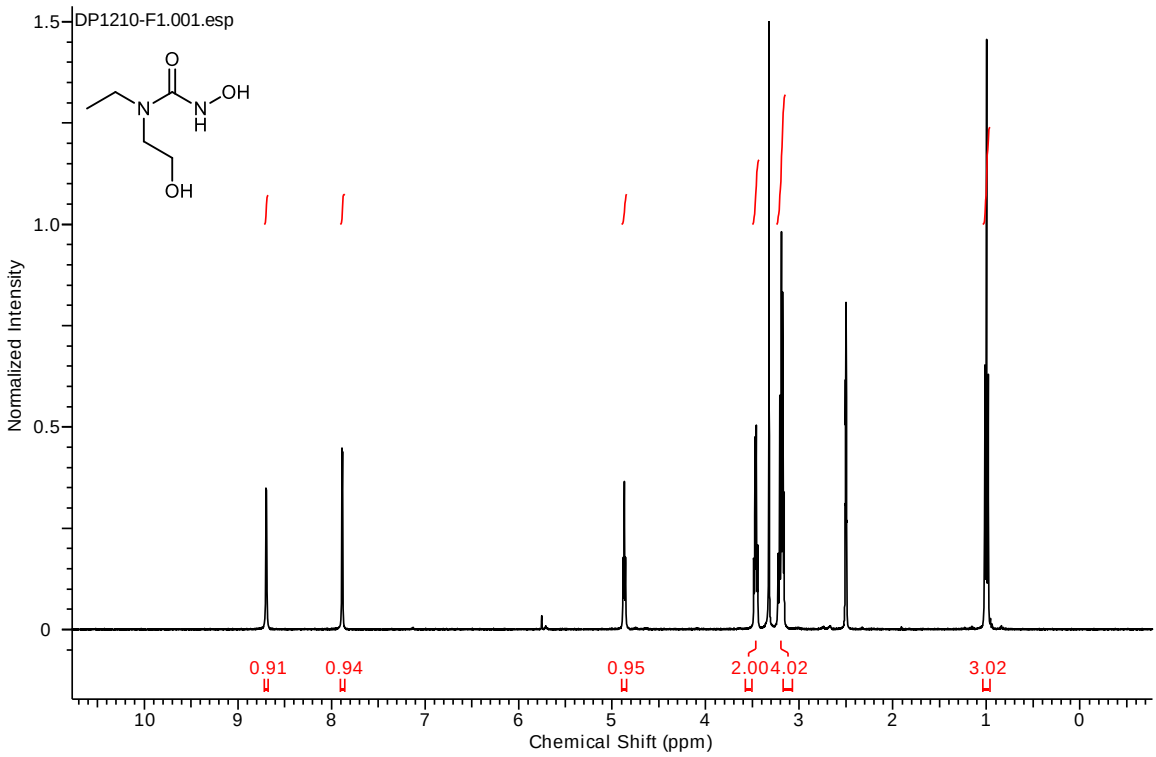

DP1216-F2.002.esp
Normalized Intensity
160.04
134.54
115.93
71.94
41.87
13.65
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

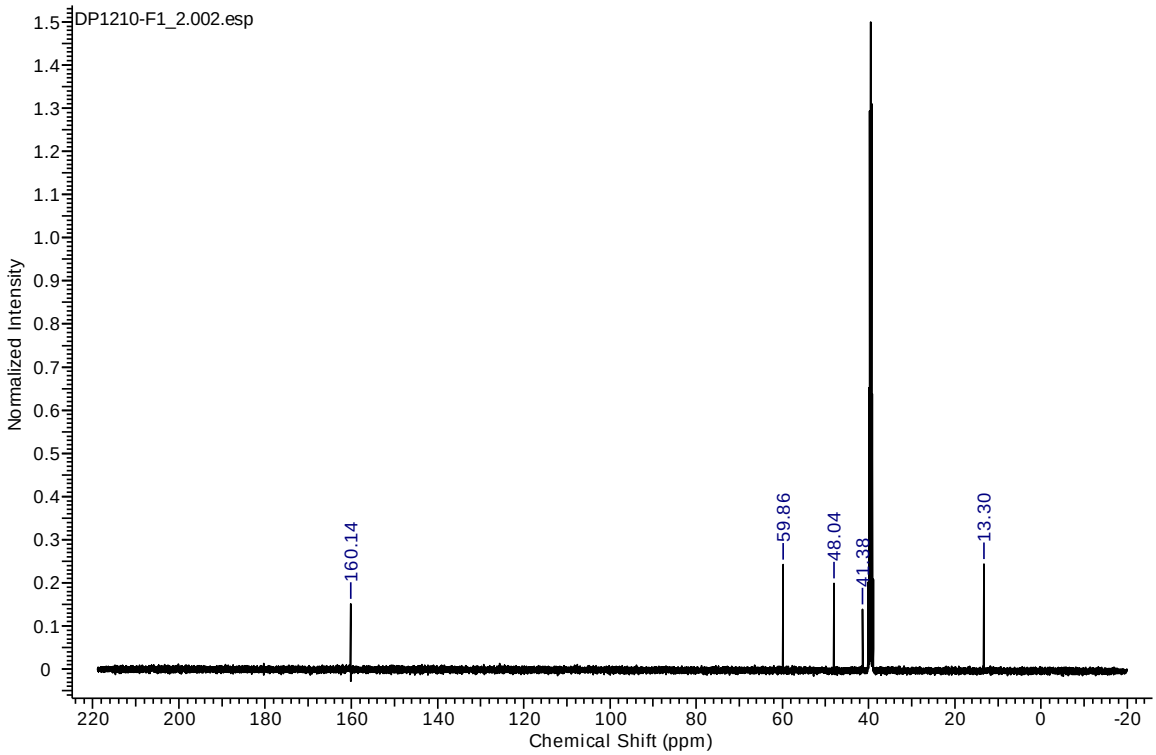

DP1240-charac.001.esp
Me
N
O
N
H
OEt
Ph
Normalized Intensity
1.5
1.0
0.5
0
2.03
1.01
2.00
0.95
2.05
3.01
3.09
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

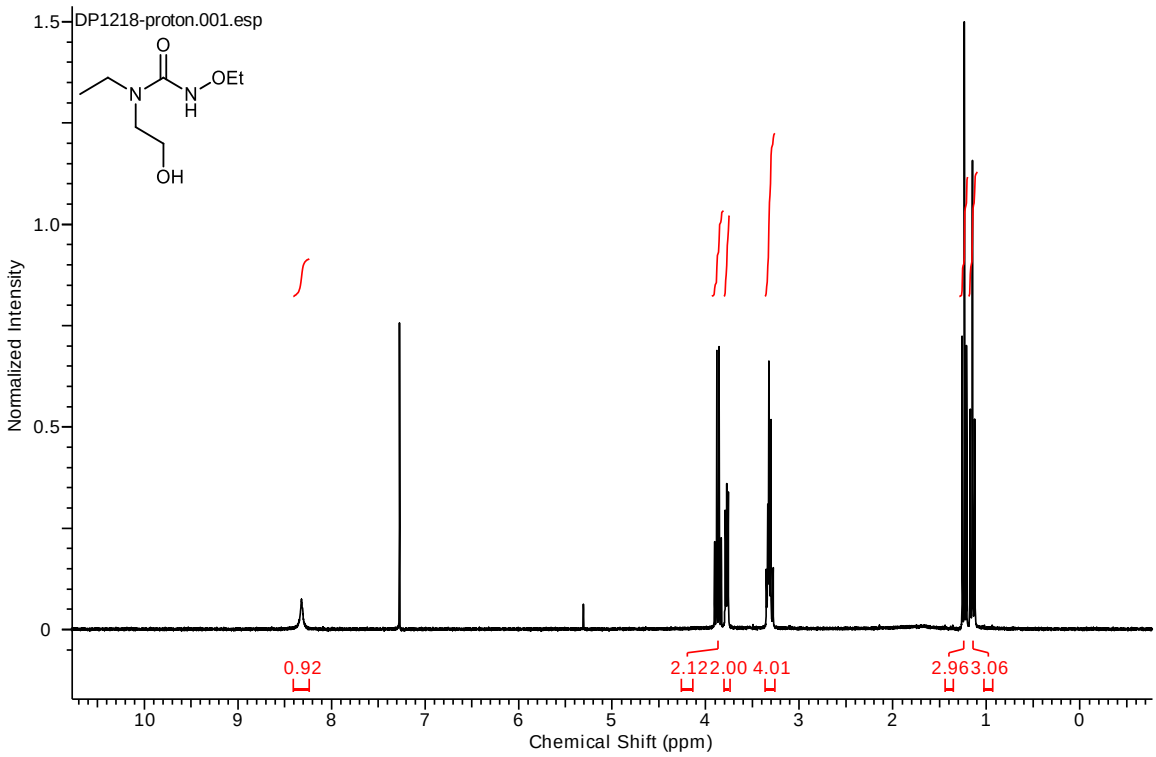

DP1240-charac.002.esp
129.90
126.94
158.22
141.93
71.88
37.43
13.34
Normalized Intensity
1.5
1.0
0.5
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

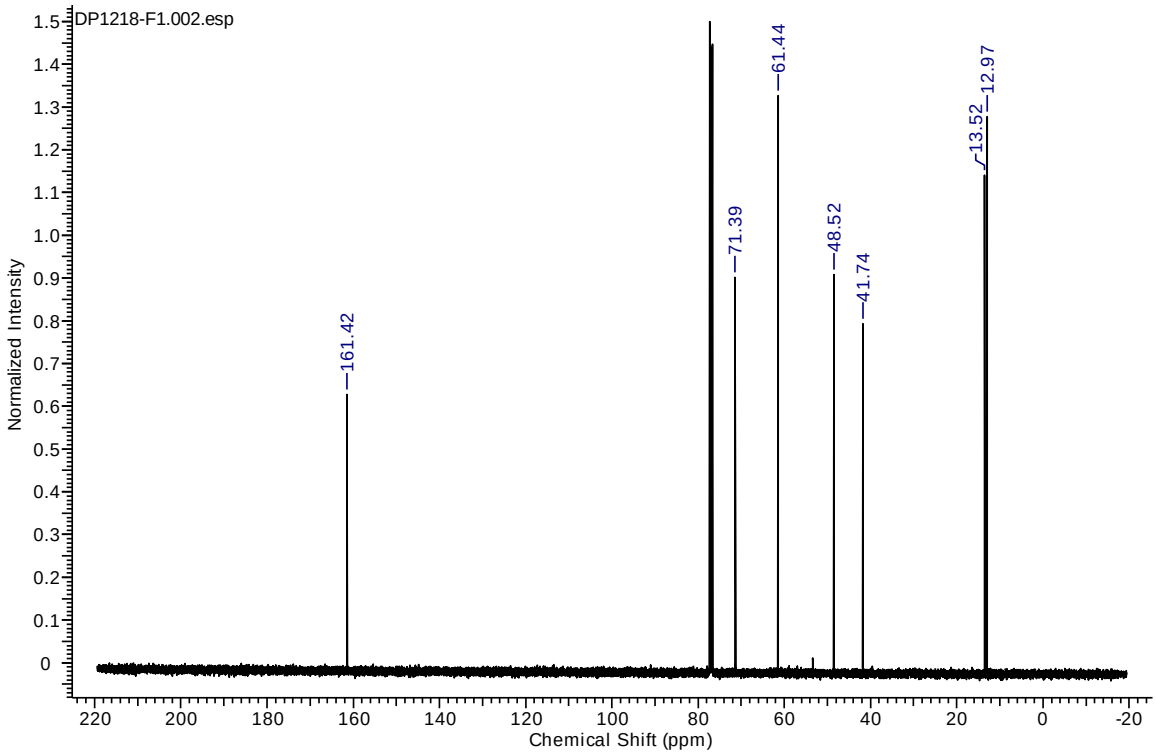

RI11-OBZ-NMEANILINE.1001.esp
Me
N
Ph
O
N
H
OBz
Normalized Intensity
0.94
2.09
1.02
7.12
3.00
Chemical Shift (ppm)

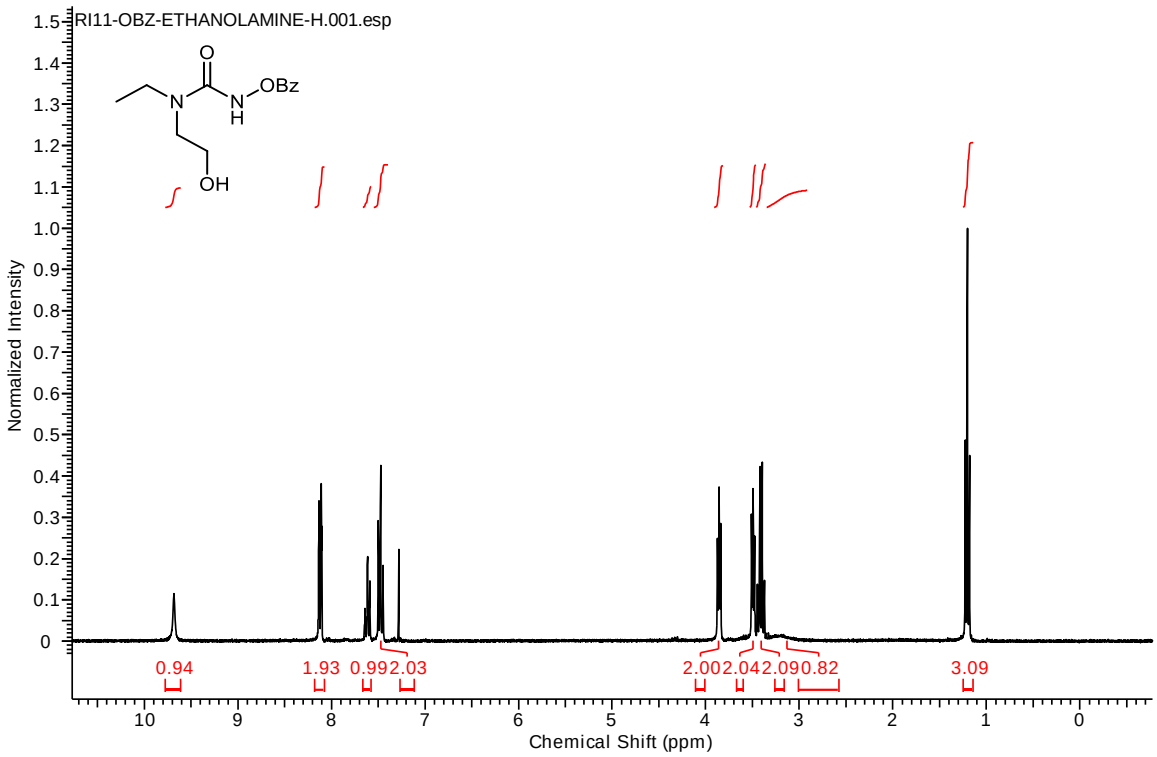

RI11-OBZ-NMEANILINE-C.001.esp
130.22
129.86
128.55
127.08
166.69
156.90
141.21
133.95
126.94
37.86
Normalized Intensity
Chemical Shift (ppm)

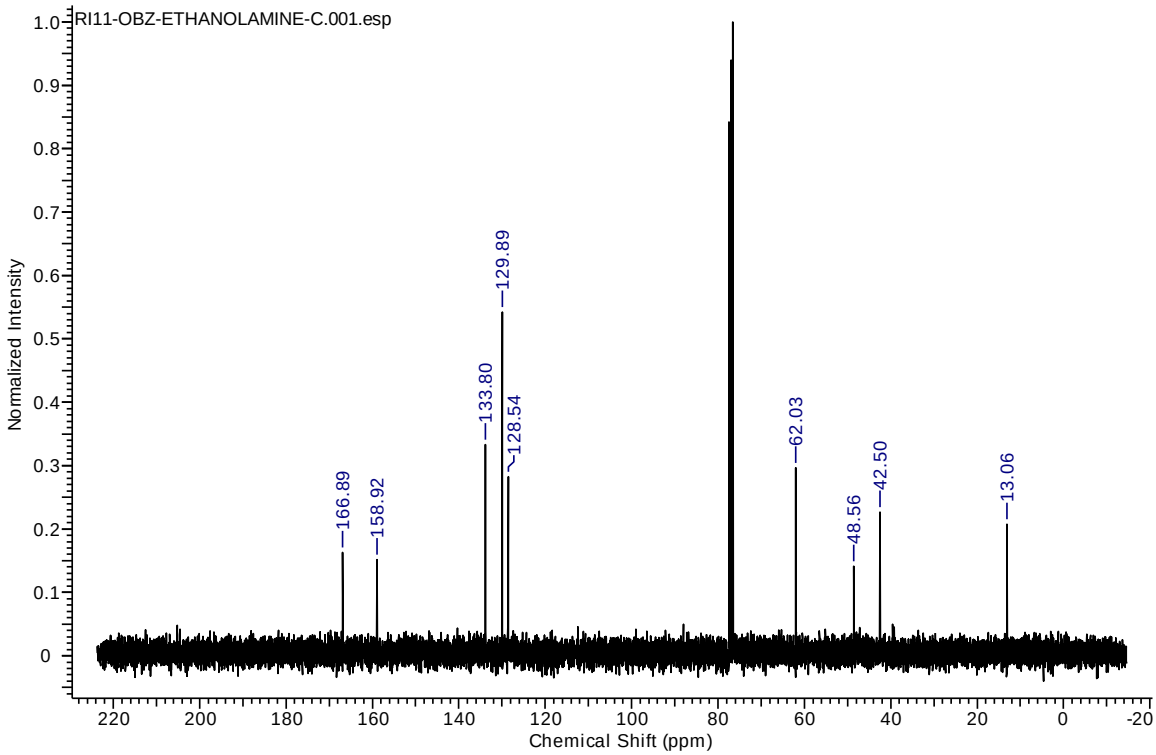

DP1210-F1.001.esp
O
N
N
H
OH
OH
Normalized Intensity
1.5
1.0
0.5
0
0.91
0.94
0.95
2.00
4.02
3.02
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

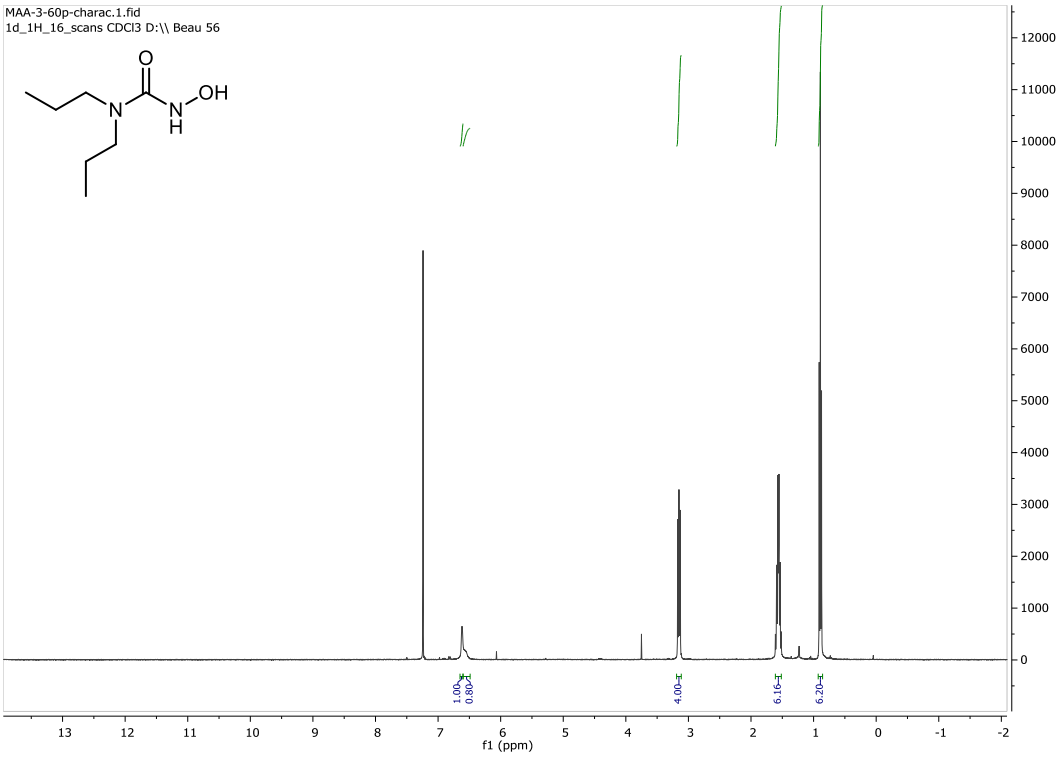

DP1210-F1_2.002.esp
Normalized Intensity
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.14
59.86
48.04
41.38
13.30
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

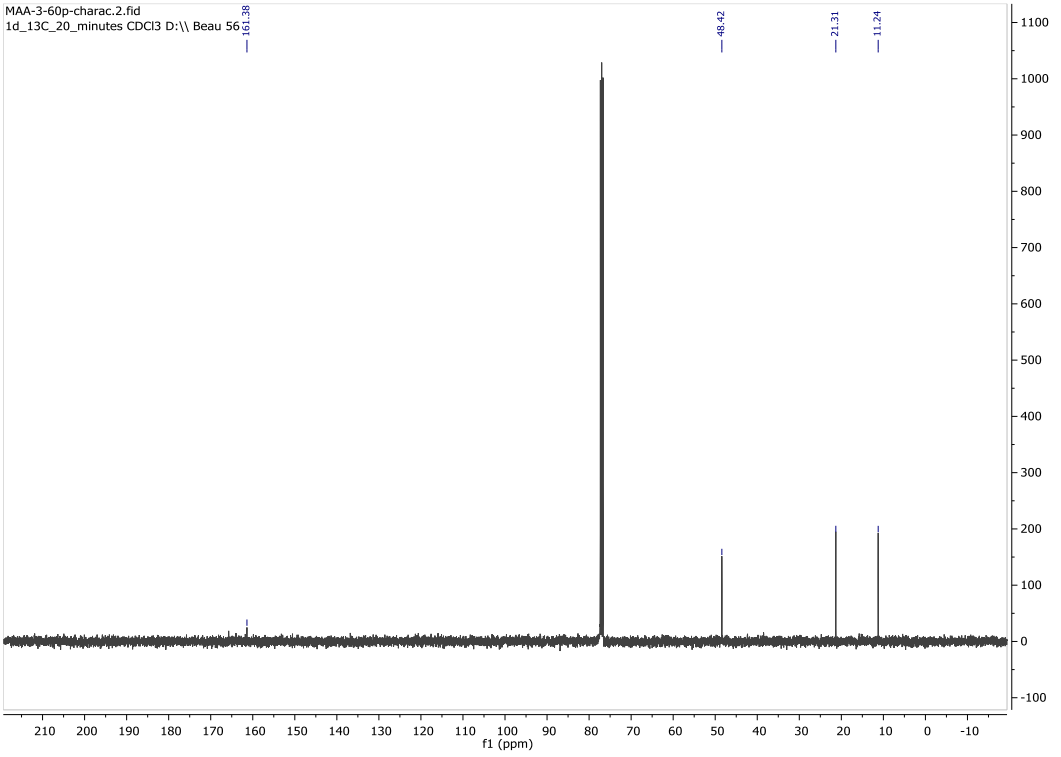

DP1218-proton.001.esp
O
N
N
H
OEt
OH
Normalized Intensity
1.5
1.0
0.5
0
0.92
2.12
2.00
4.01
2.96
3.06
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

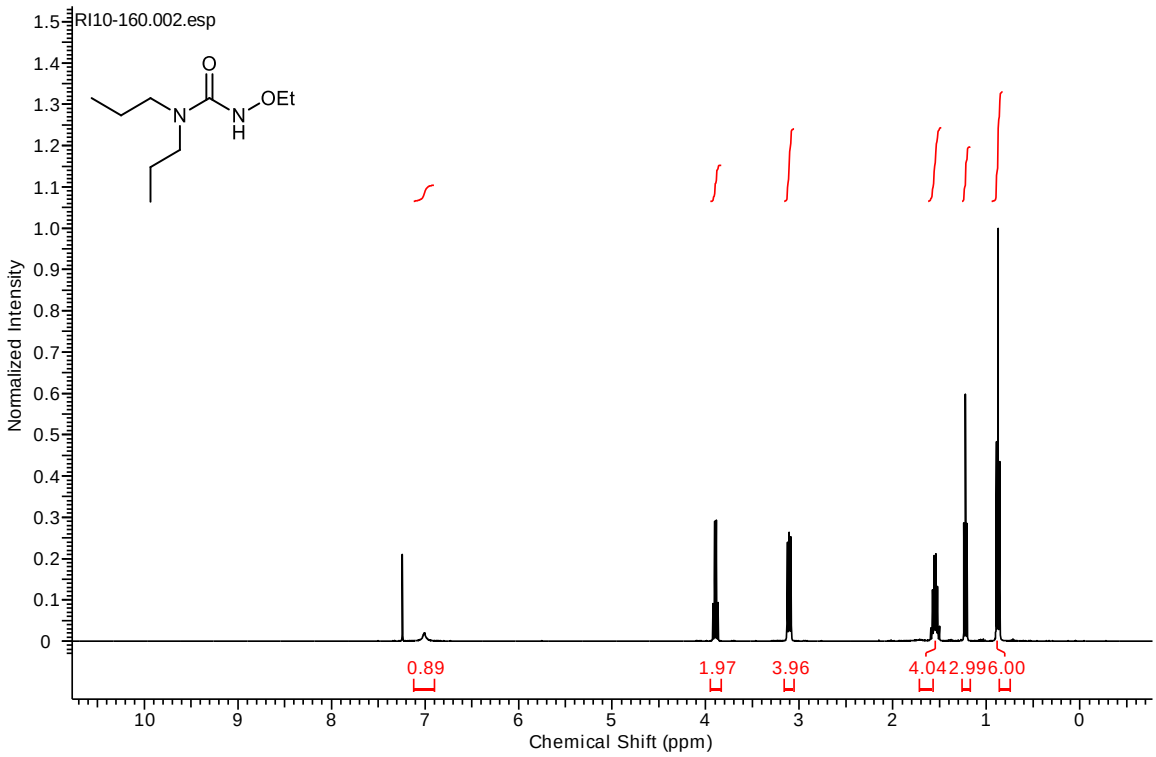

DP1218-F1.002.esp
Normalized Intensity
161.42
71.39
61.44
48.52
41.74
13.52
12.97
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

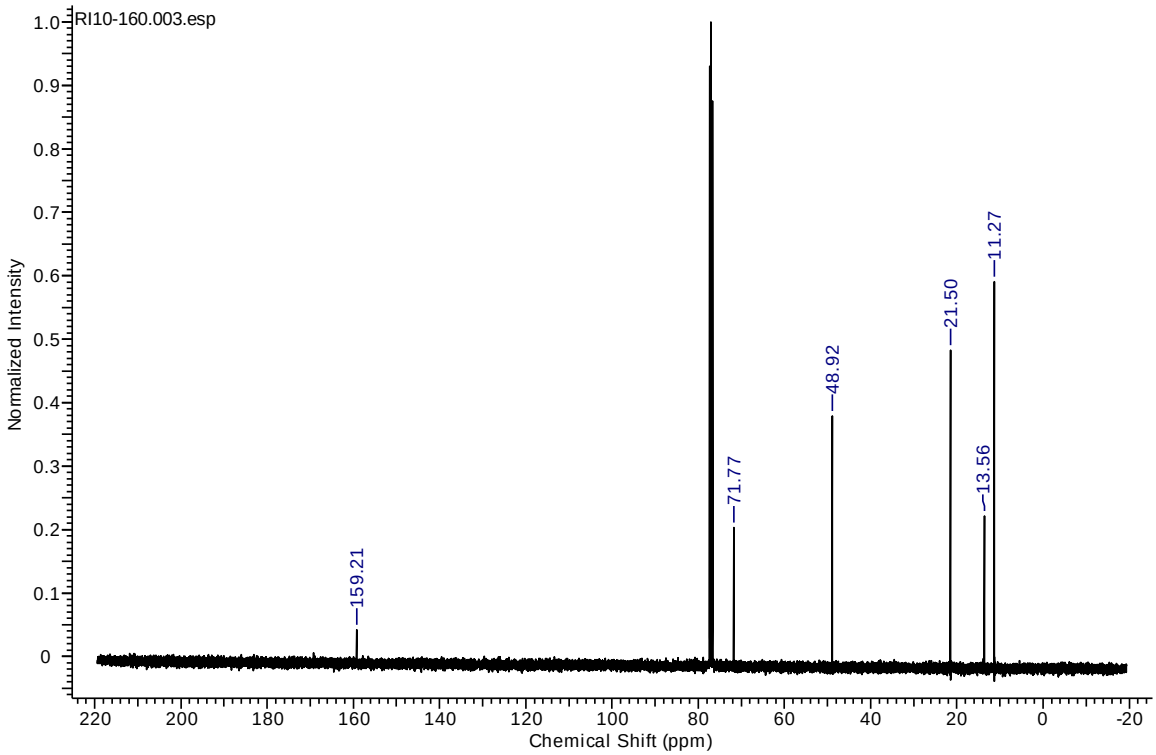

RI11-OBZ-ETHANOLAMINE-H.001.esp
O
N
N
H
OBz
OH
Normalized Intensity
0.94
1.93
0.99
2.03
2.00
2.04
2.09
0.82
3.09
Chemical Shift (ppm)

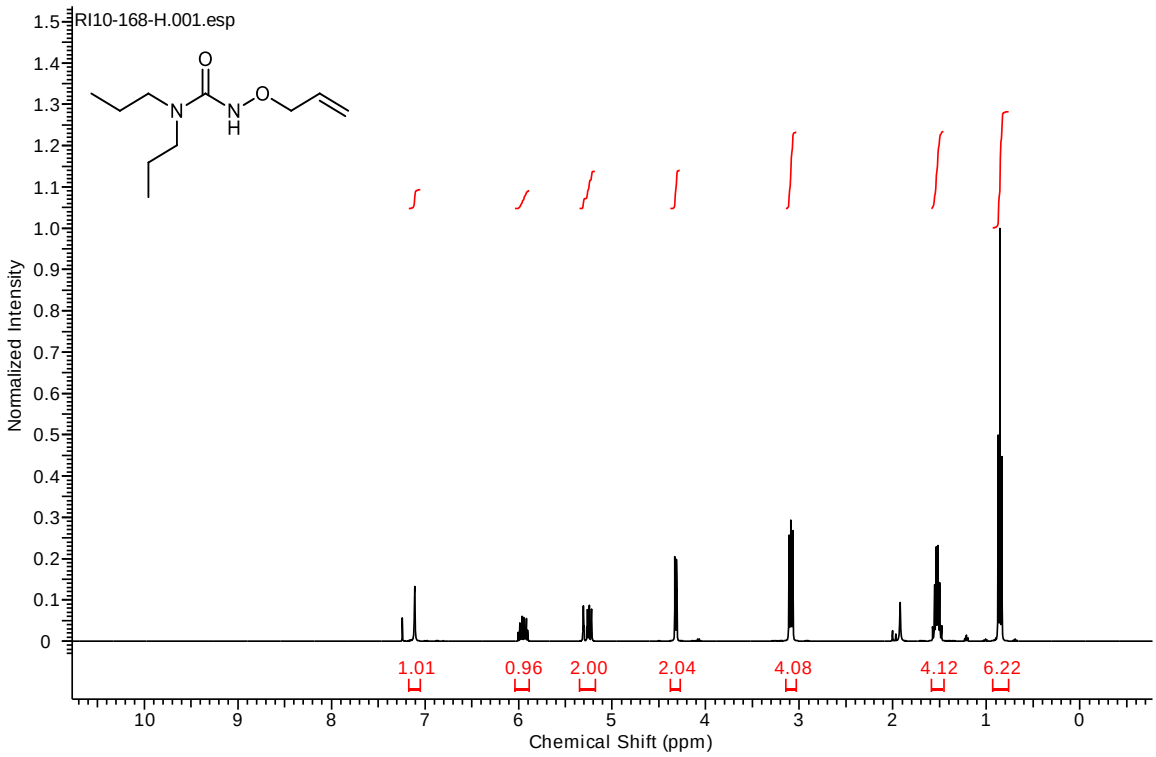

RI11-OBZ-ETHANOLAMINE-C.001.esp
Normalized Intensity
166.89
158.92
133.80
129.89
128.54
62.03
48.56
42.50
13.06
Chemical Shift (ppm)

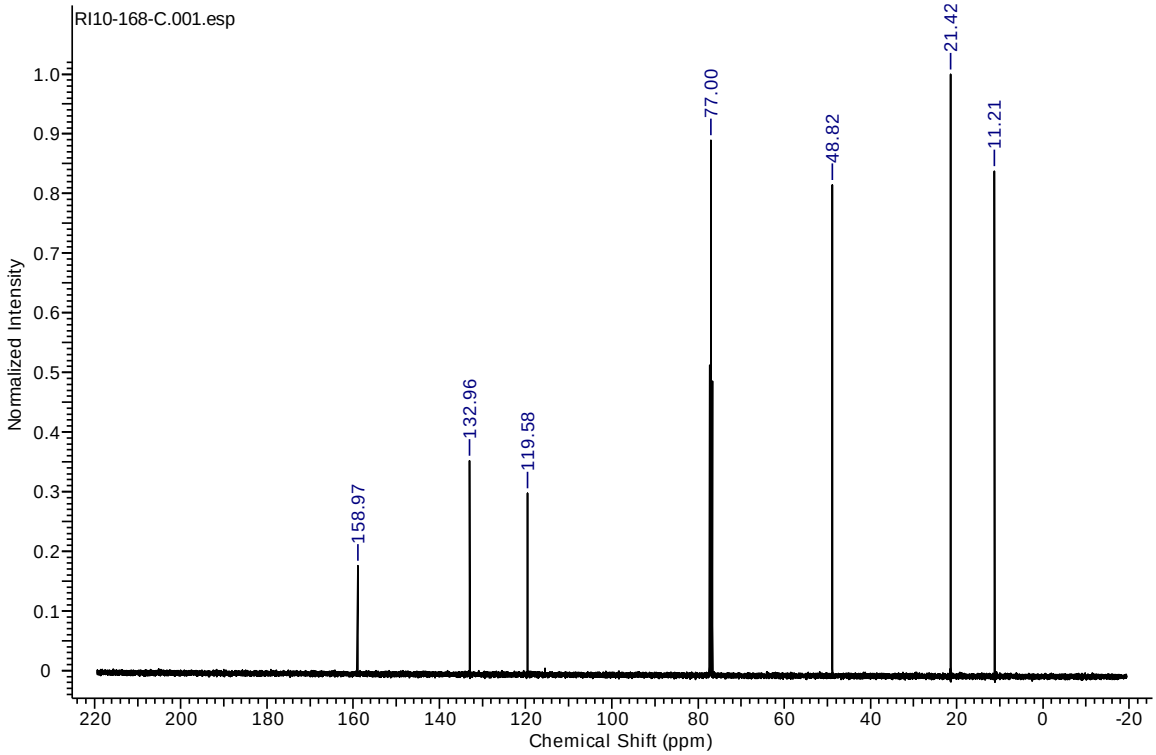

MAA-3-60p-charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 56
O
N
N
H
OH
1.00
0.80
4.00
6.16
6.20
f1 (ppm)

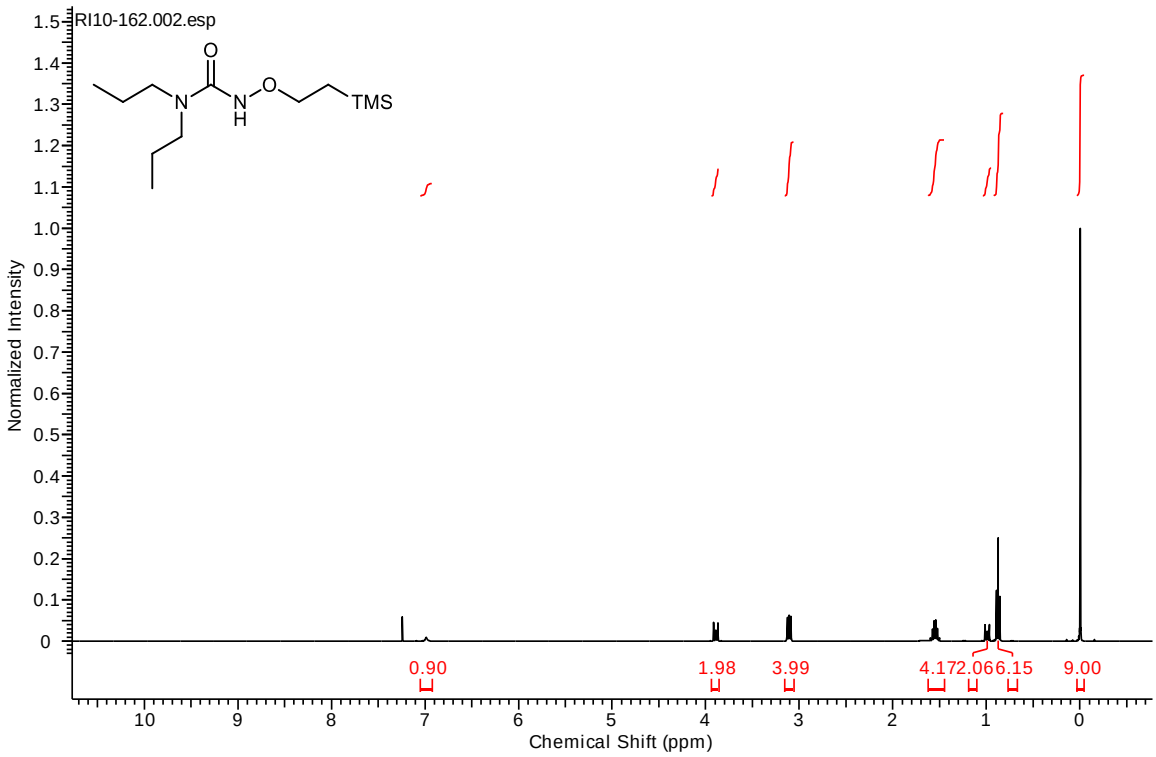

MAA-3-60p-charac.2.fid
1d_13C_20_minutes CDCl3 D:\\ Beau 56
161.38
48.42
21.31
11.24
f1 (ppm)

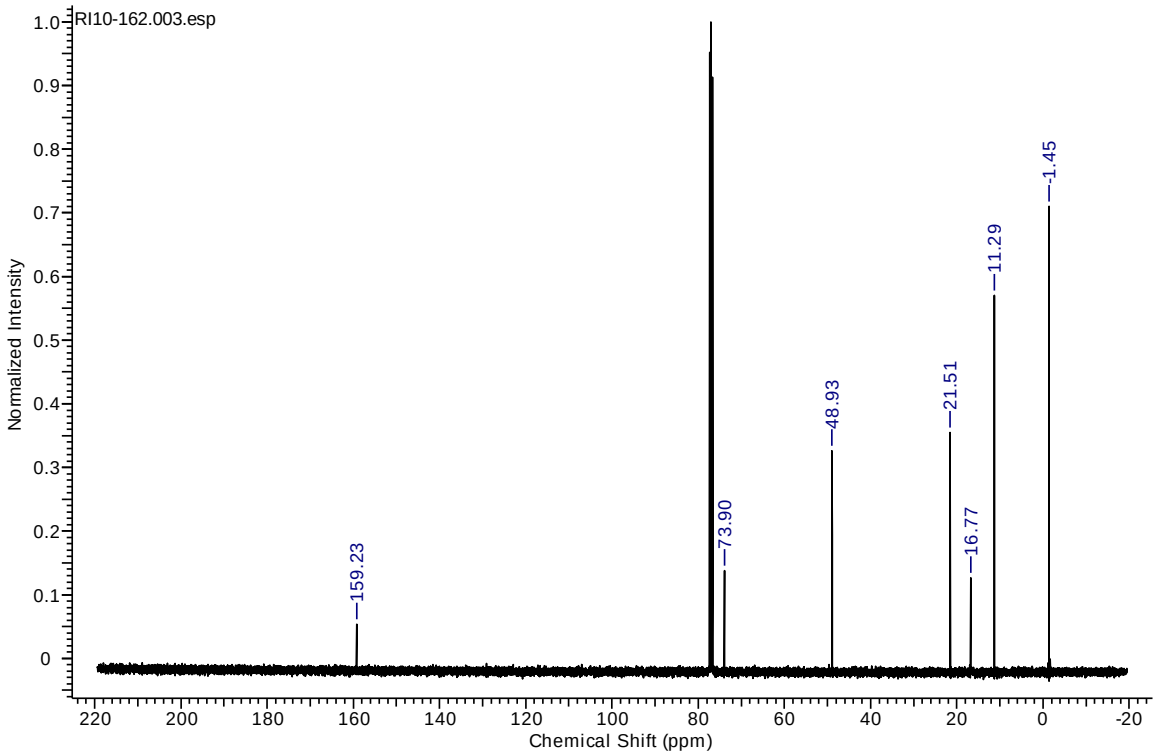

RI10-160.002.esp
O
N
N
H
OEt
Normalized Intensity
0.89
1.97
3.96
4.04
2.99
6.00
Chemical Shift (ppm)

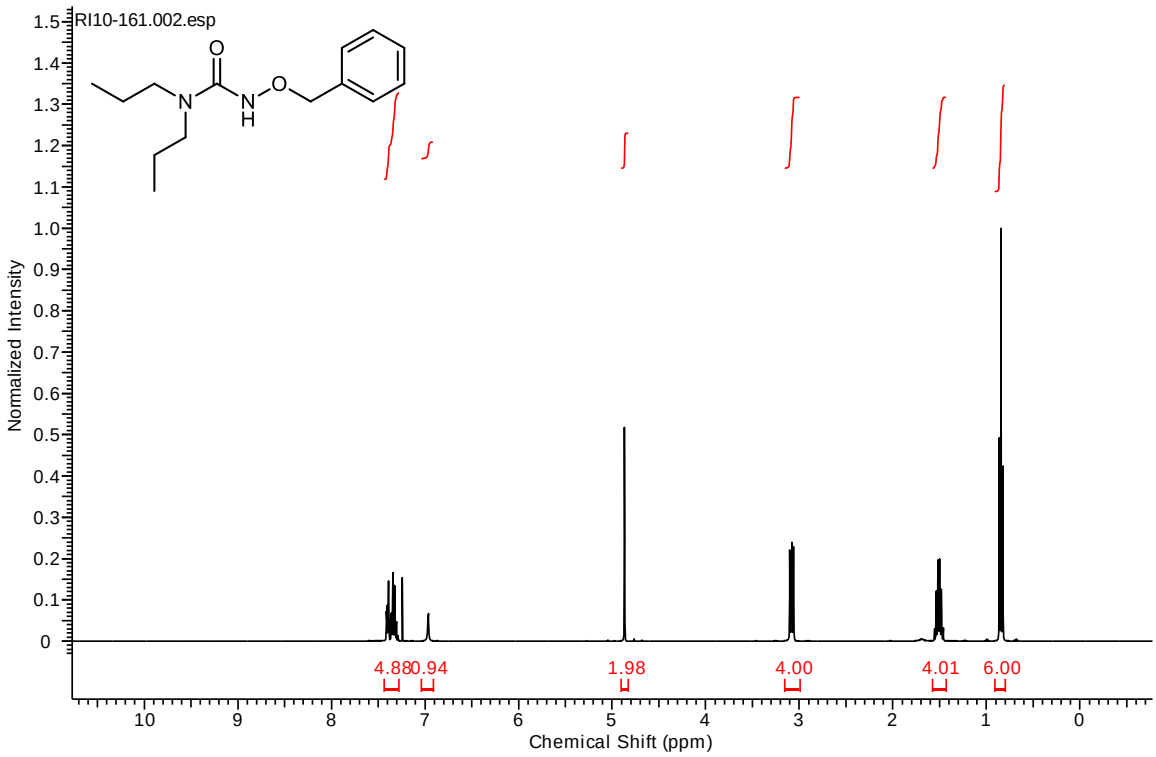

RI10-160.003.esp
Normalized Intensity
159.21
71.77
48.92
21.50
13.56
11.27
Chemical Shift (ppm)

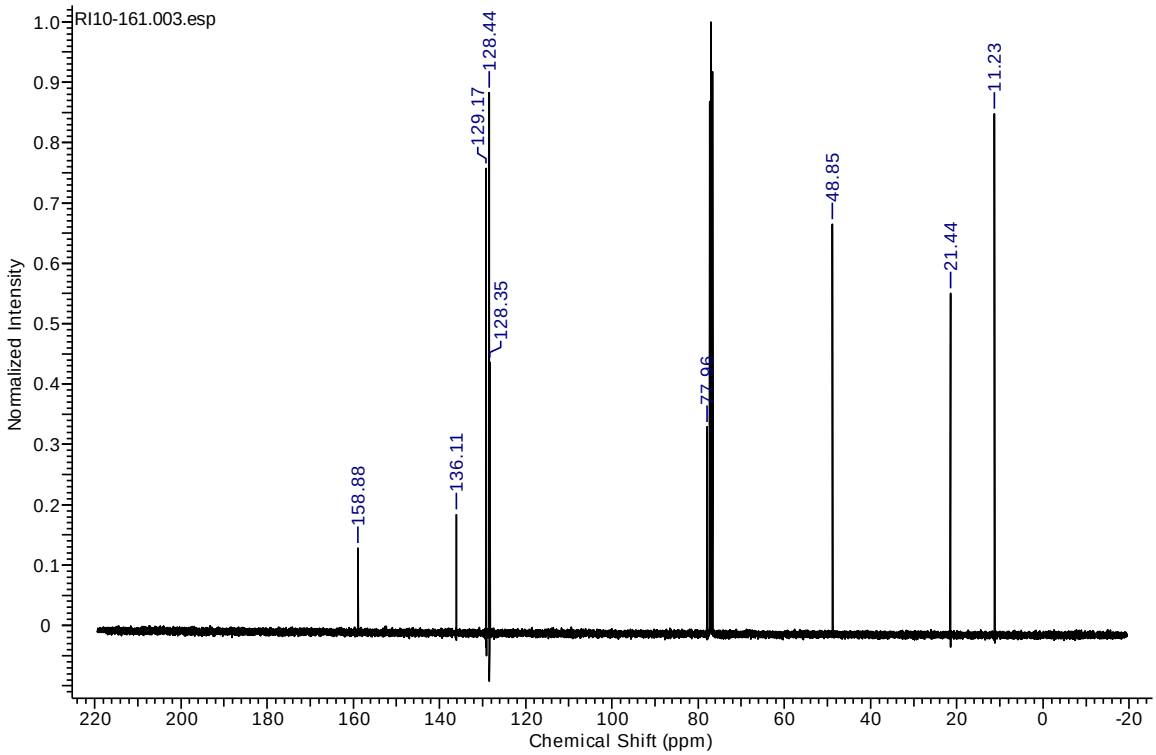

RI10-168-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.01
0.96
2.00
2.04
4.08
4.12
6.22

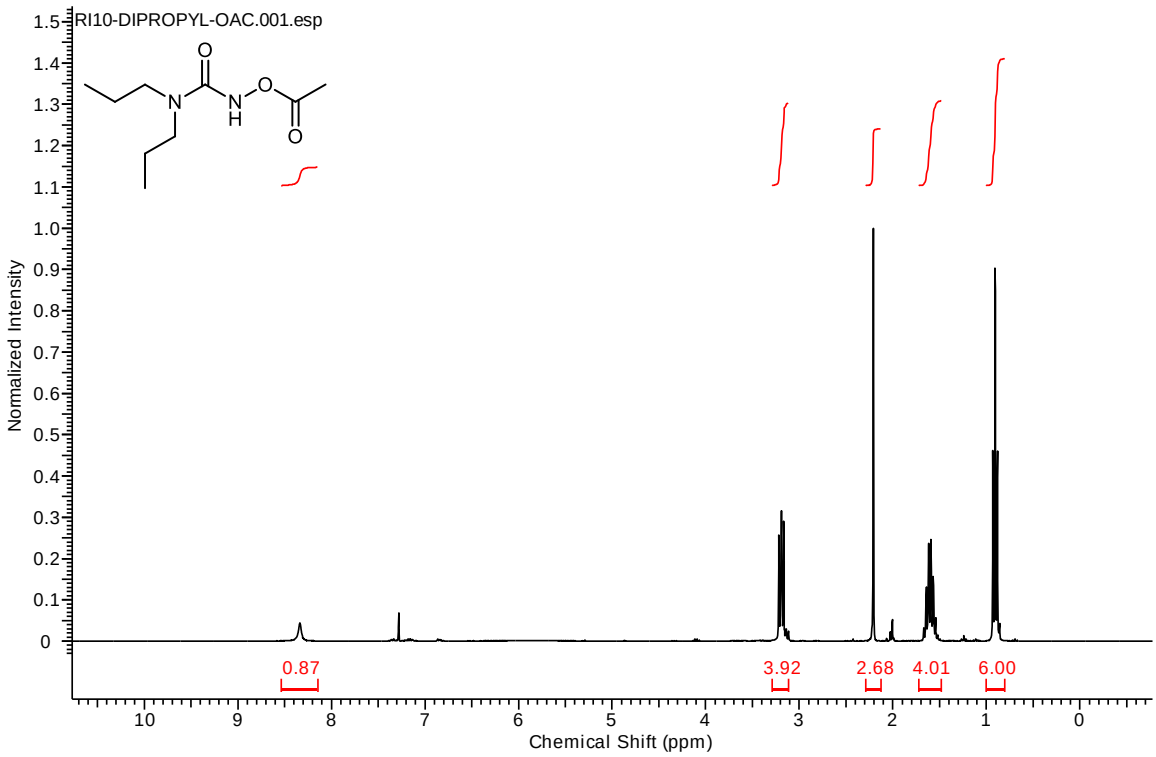

RI10-168-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
158.97
132.96
119.58
77.00
48.82
21.42
11.21

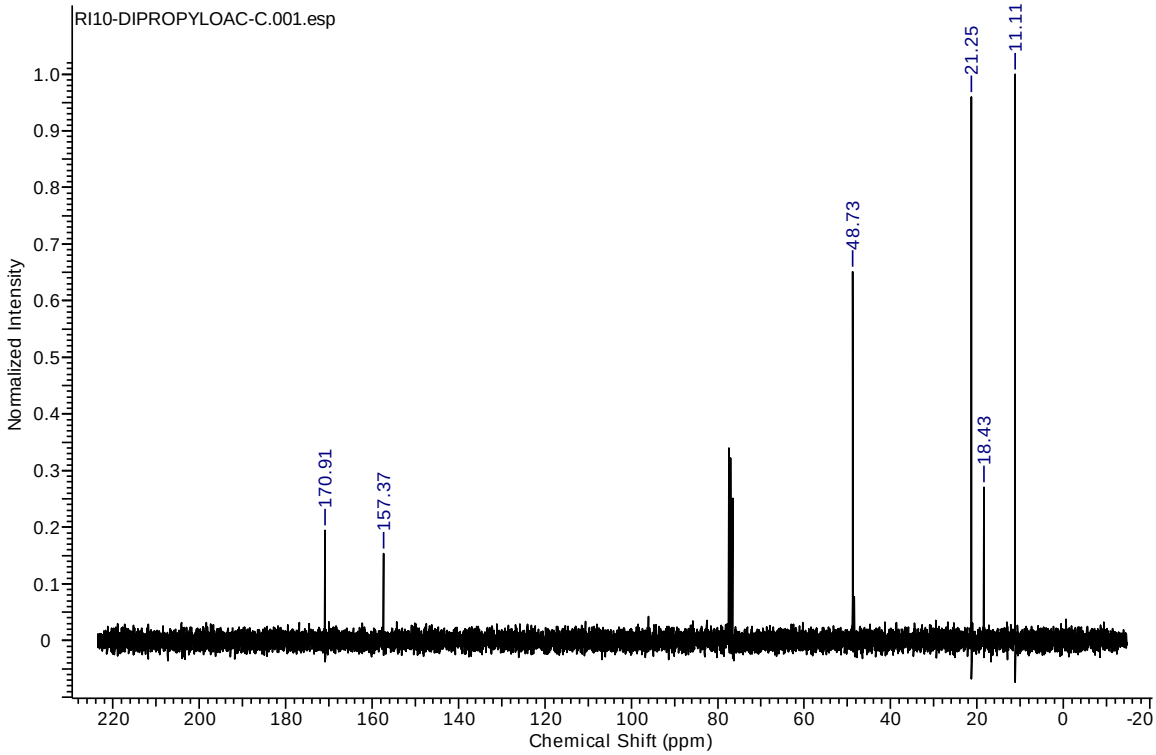

RI10-162.002.esp
O
N
O
N
H
TMS
Normalized Intensity
0.90
1.98
3.99
4.17
2.06
6.15
9.00
Chemical Shift (ppm)

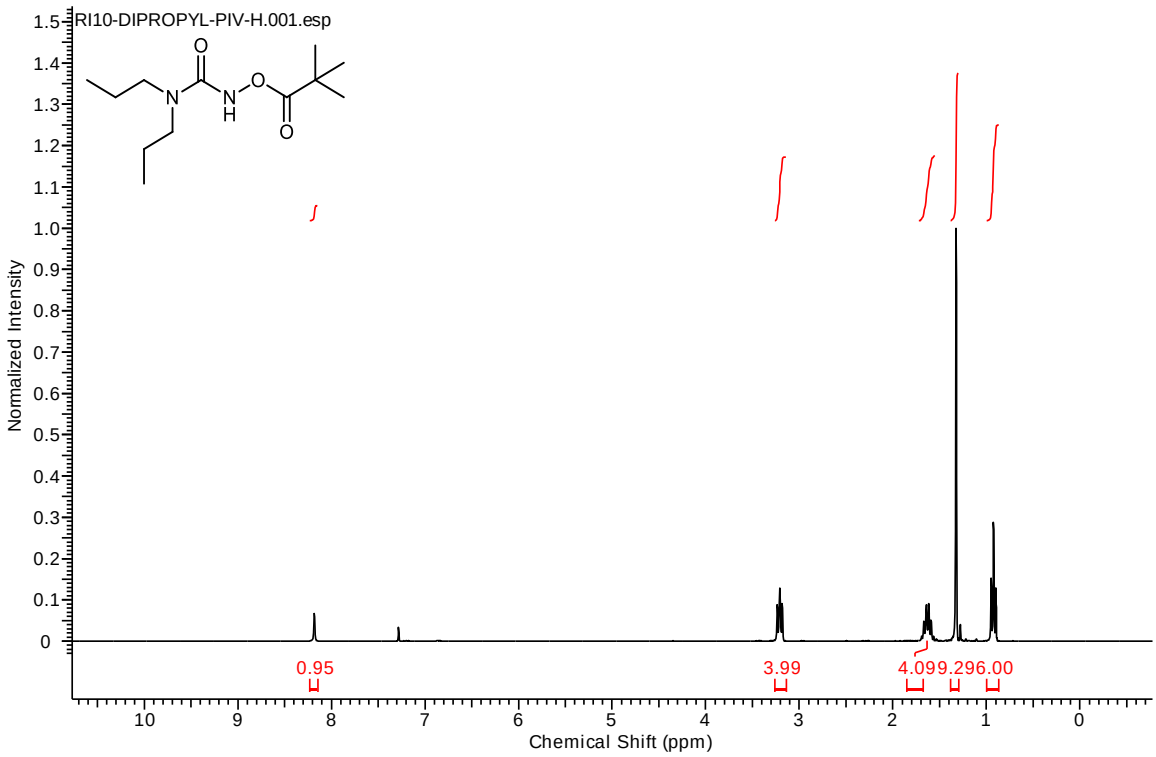

RI10-162.003.esp
Normalized Intensity
159.23
73.90
48.93
21.51
16.77
11.29
1.45
Chemical Shift (ppm)

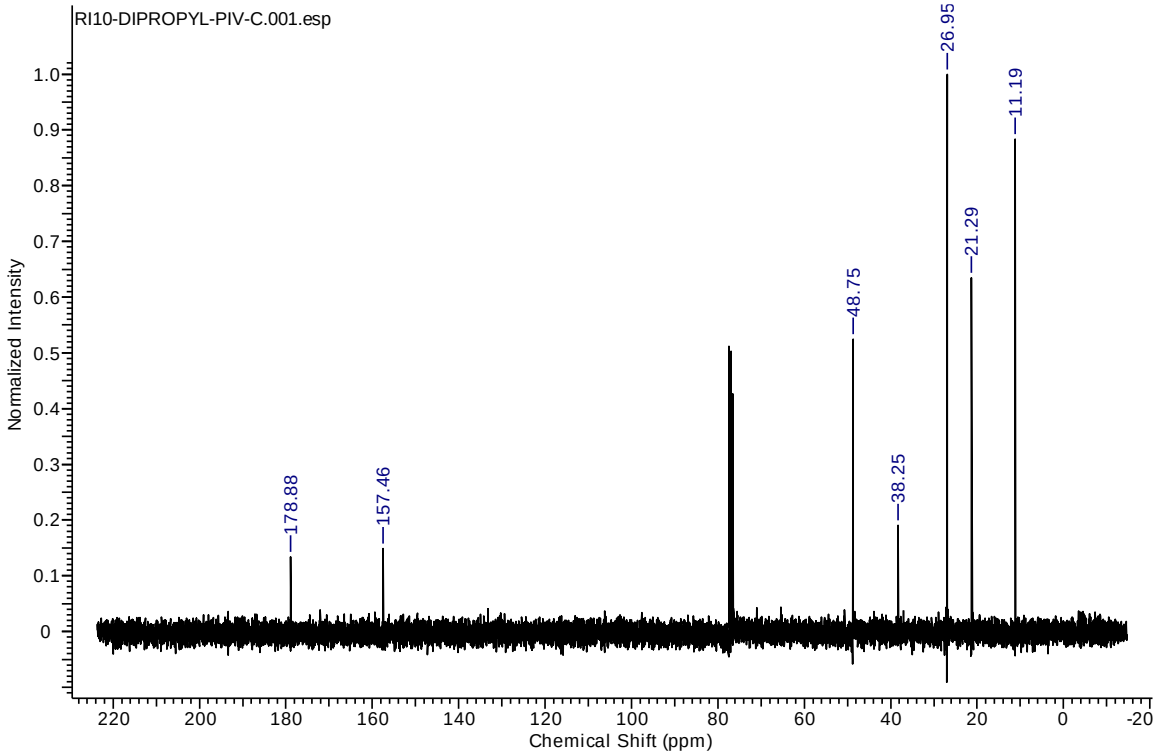

RI10-161.002.esp
Normalized Intensity
Chemical Shift (ppm)
4.88
0.94
1.98
4.00
4.01
6.00

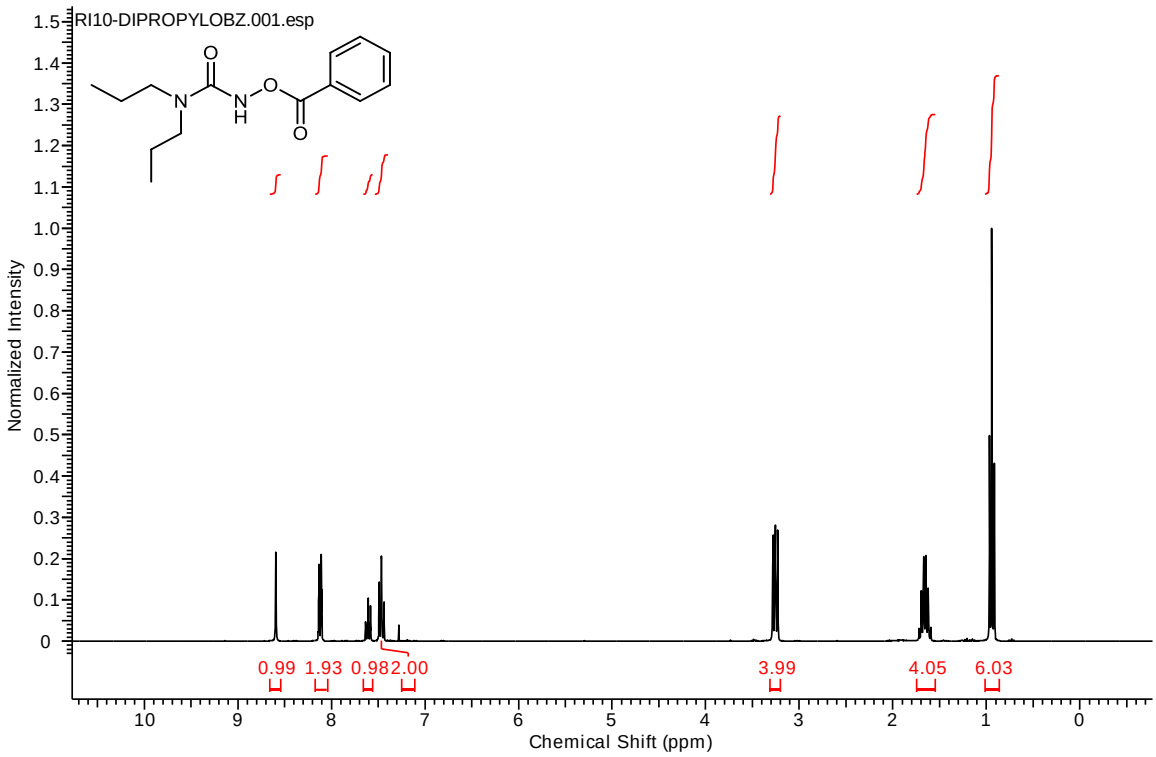

RI10-161.003.esp
Normalized Intensity
Chemical Shift (ppm)
158.88
136.11
129.17
128.44
128.35
77.06
48.85
21.44
11.23

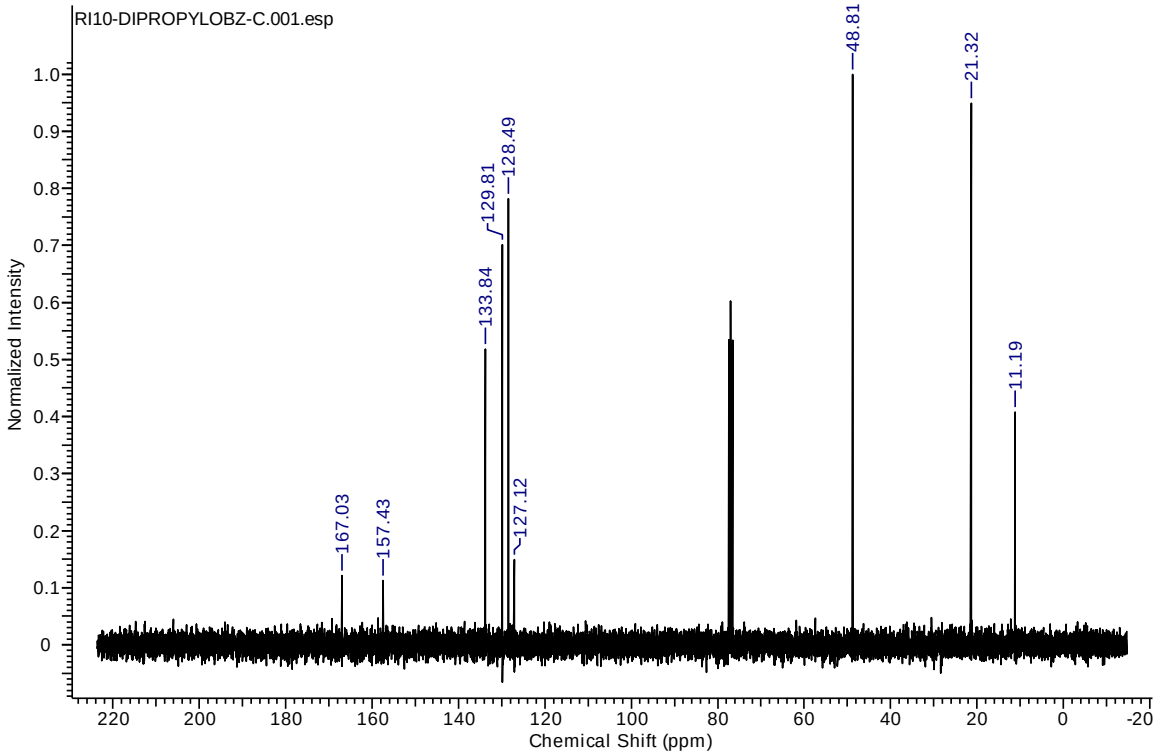

RI10-DIPROPYL-OAC.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.87
3.92
2.68
4.01
6.00

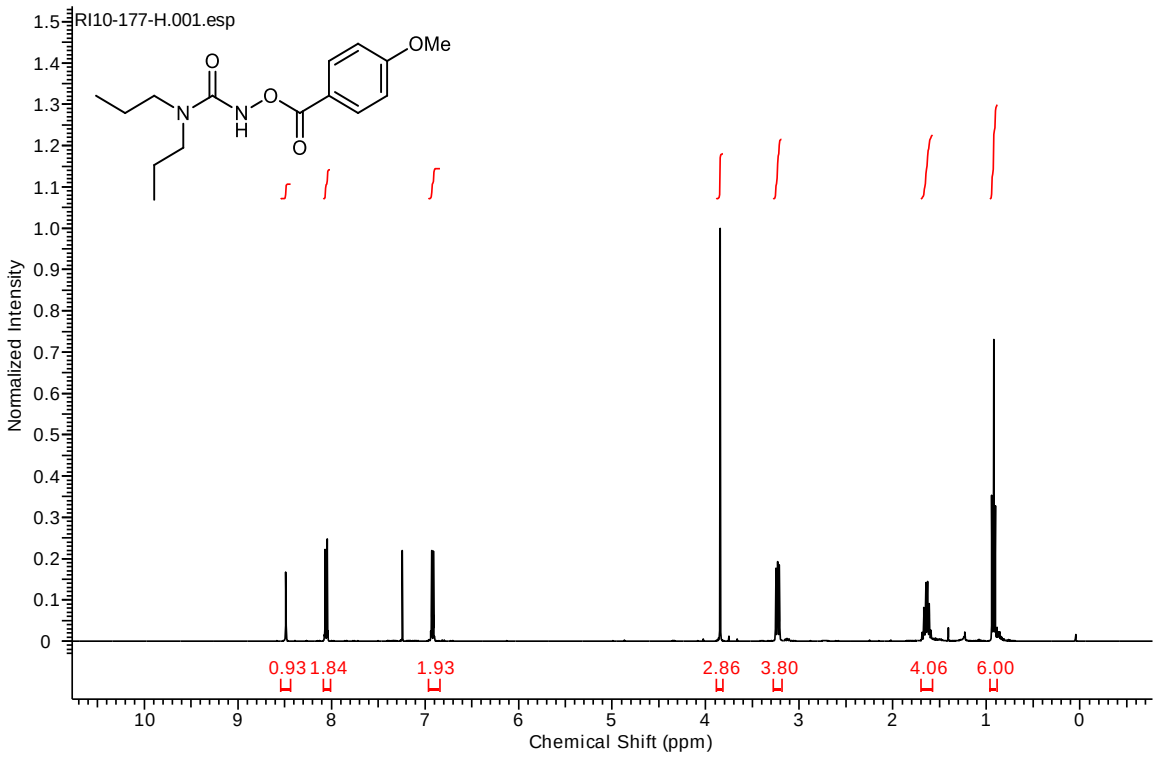

RI10-DIPROPYLOAC-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
170.91
157.37
48.73
21.25
18.43
11.11

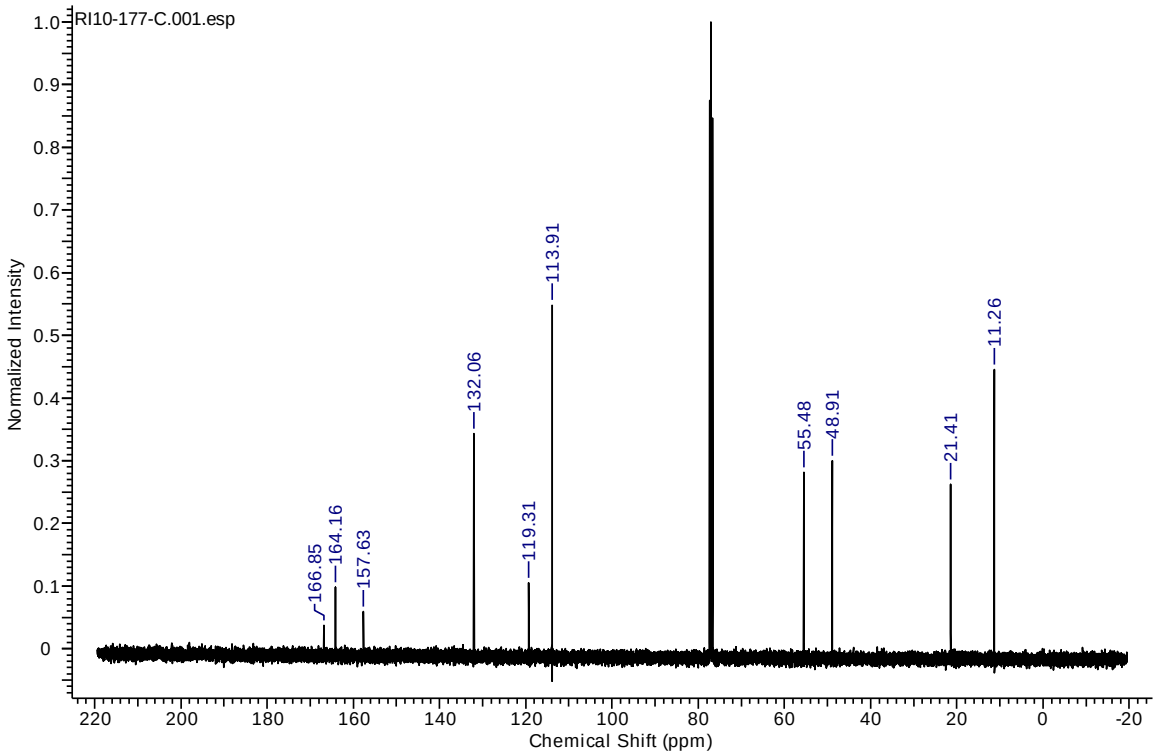

RI10-DIPROPYL-PIV-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.95
3.99
4.09
9.29
6.00

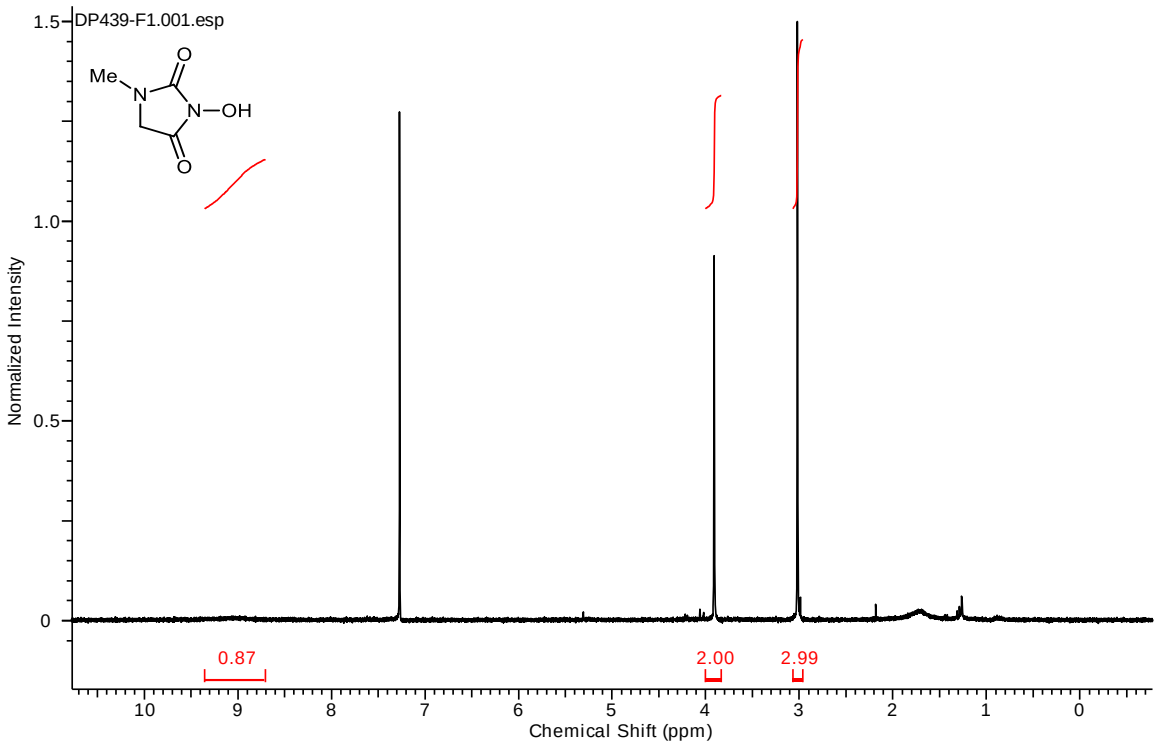

RI10-DIPROPYL-PIV-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
178.88
157.46
48.75
38.25
26.95
21.29
11.19

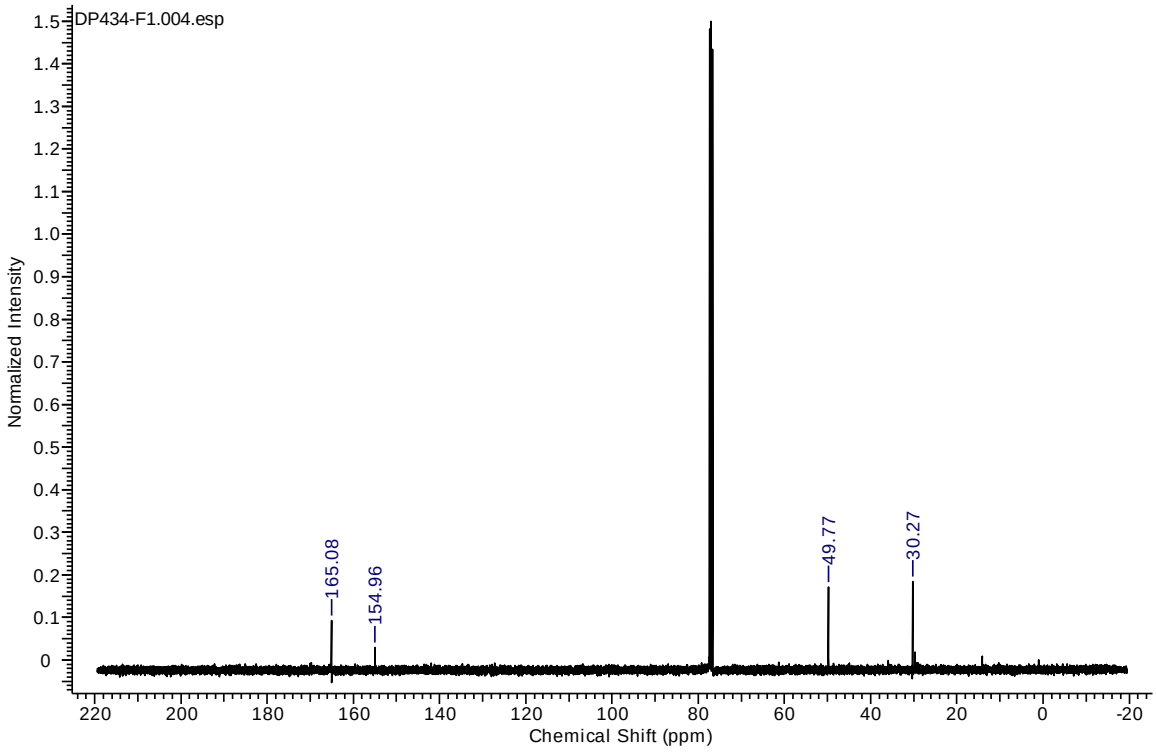

RI10-DIPROPYLOBZ.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.99
1.93
0.98
2.00
3.99
4.05
6.03

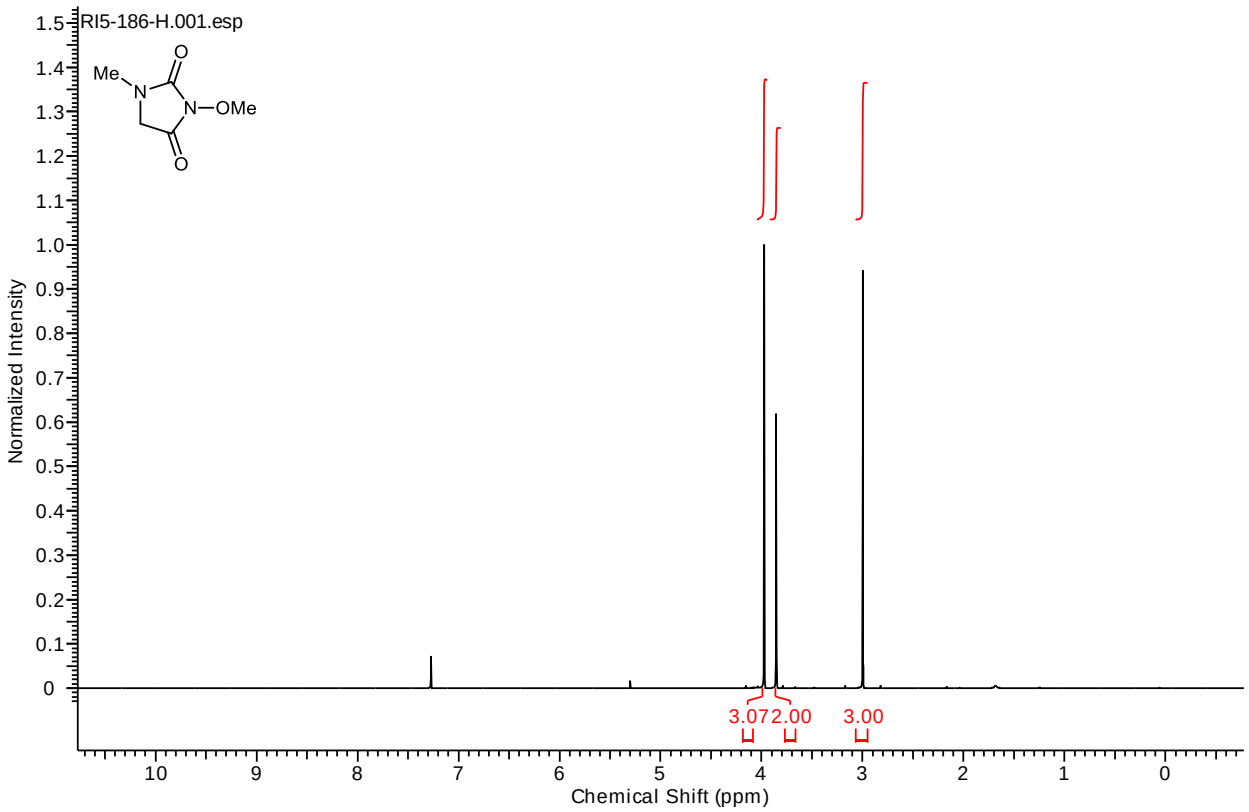

RI10-DIPROPYLOBZ-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
167.03
157.43
133.84
129.81
128.49
127.12
48.81
21.32
11.19

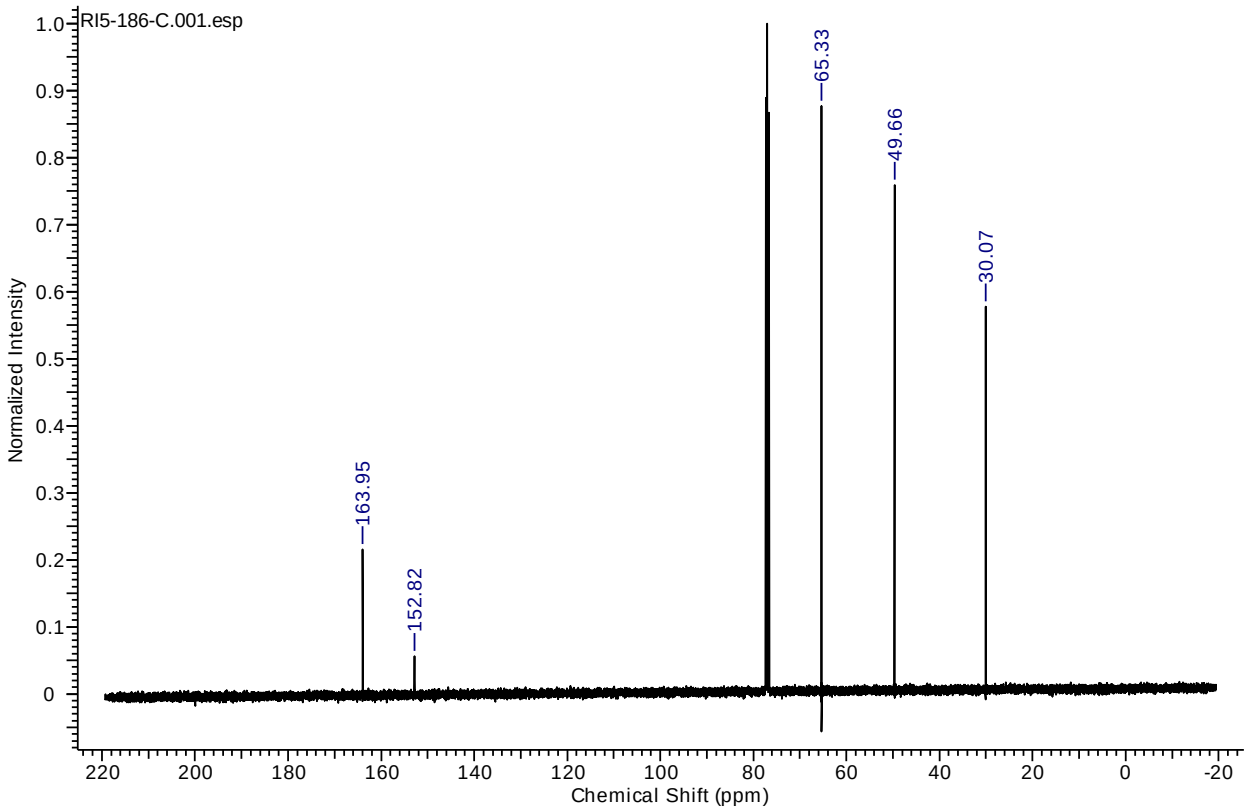

RI10-177-H.001.esp
OMe
O
N
N
H
O
O
Normalized Intensity
0.93
1.84
1.93
2.86
3.80
4.06
6.00
Chemical Shift (ppm)

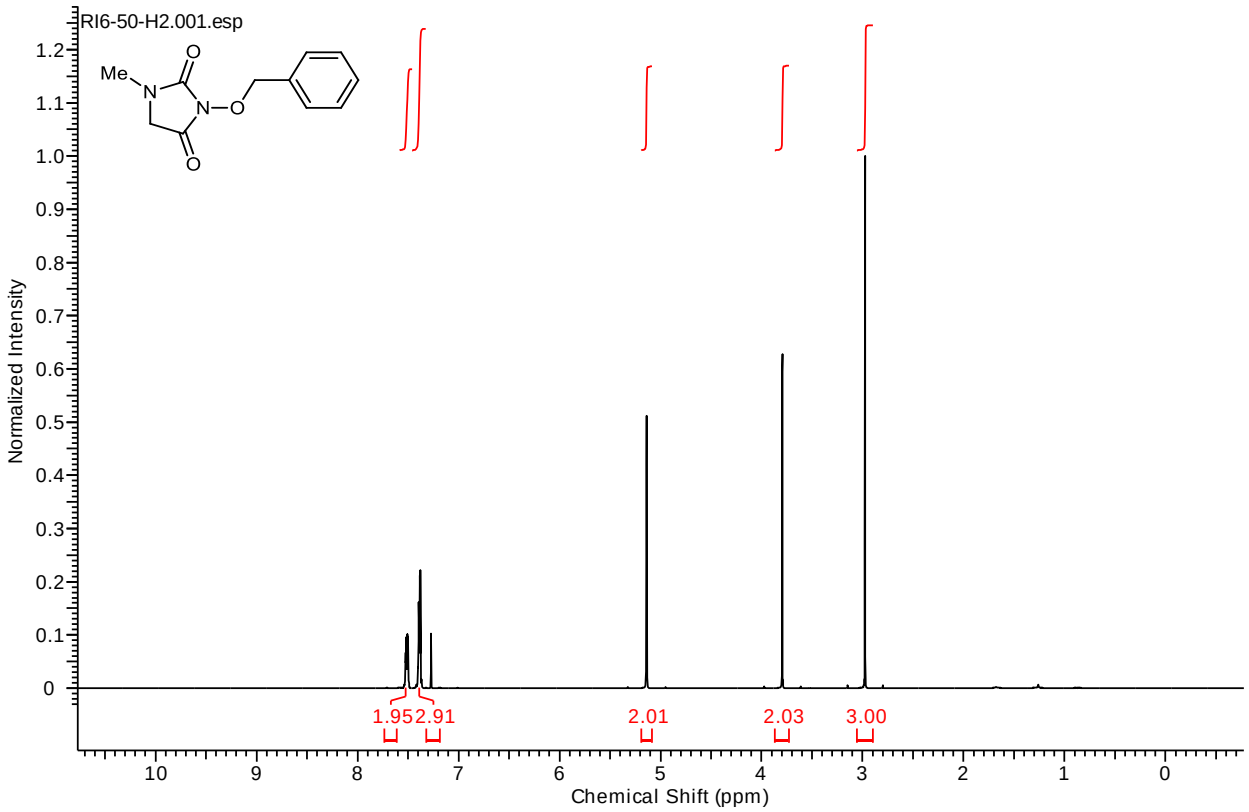

RI10-177-C.001.esp
Normalized Intensity
166.85
164.16
157.63
132.06
119.31
113.91
55.48
48.91
21.41
11.26
Chemical Shift (ppm)

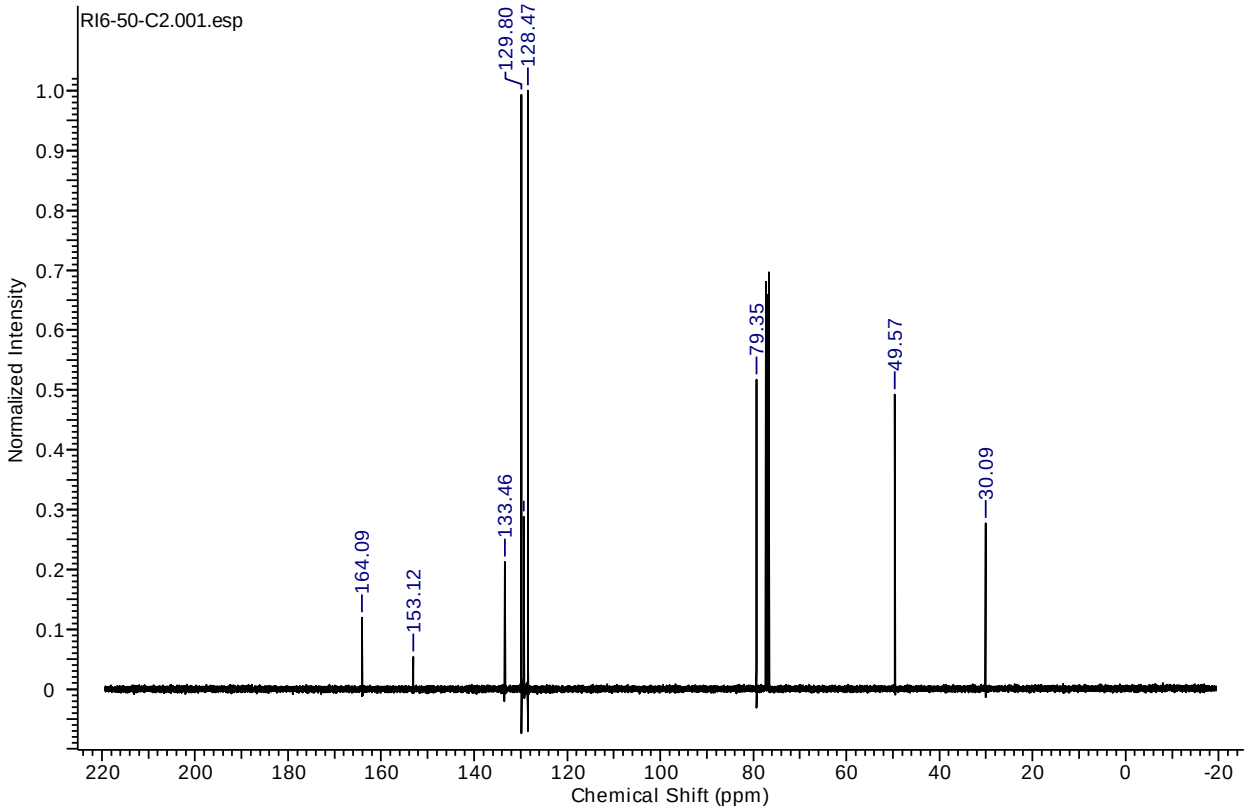

DP439-F1.001.esp
Me
N
O
O
N—OH
O
Normalized Intensity
1.5
1.0
0.5
0
0.87
2.00
2.99
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

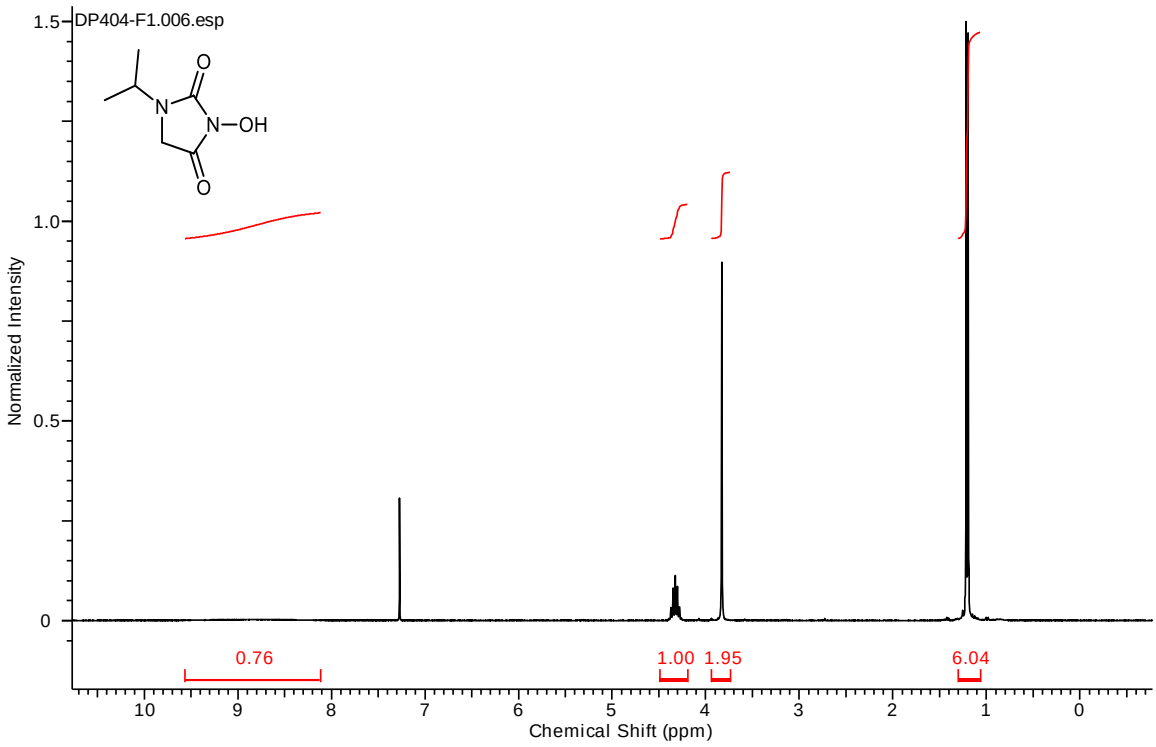

DP434-F1.004.esp
Normalized Intensity
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
165.08
154.96
49.77
30.27
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

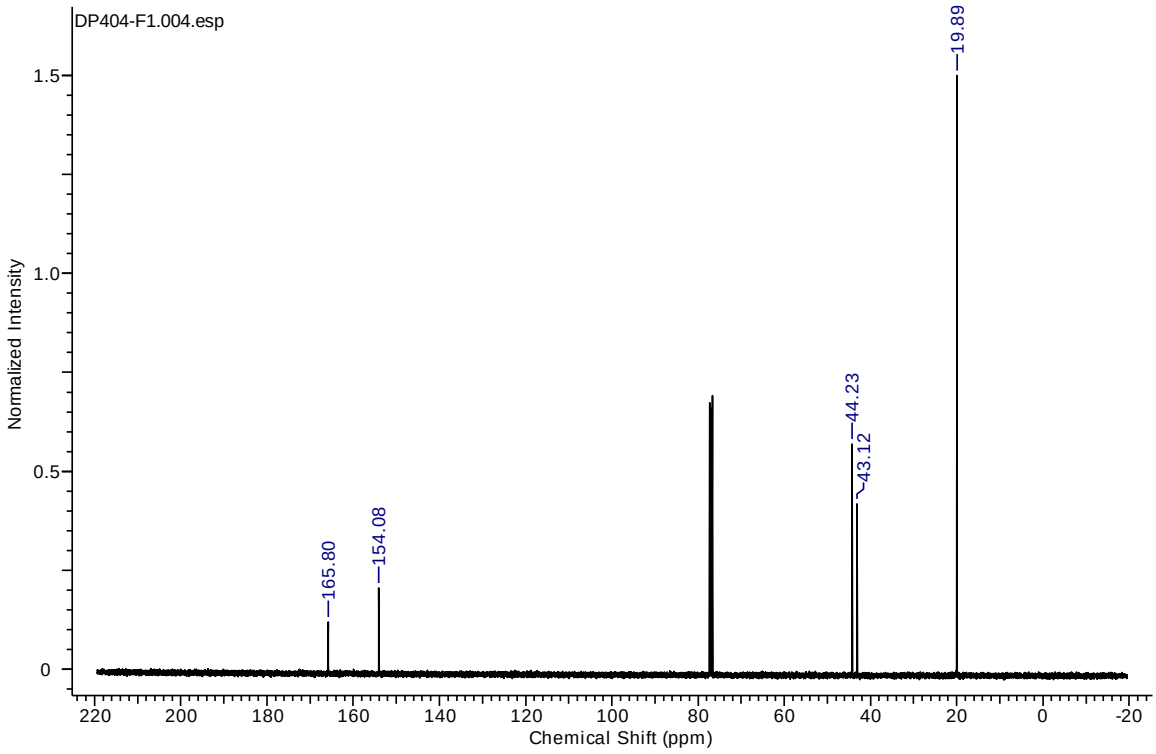

RI5-186-H.001.esp
Me
N
O
N—OMe
O
Normalized Intensity
3.07
2.00
3.00
Chemical Shift (ppm)

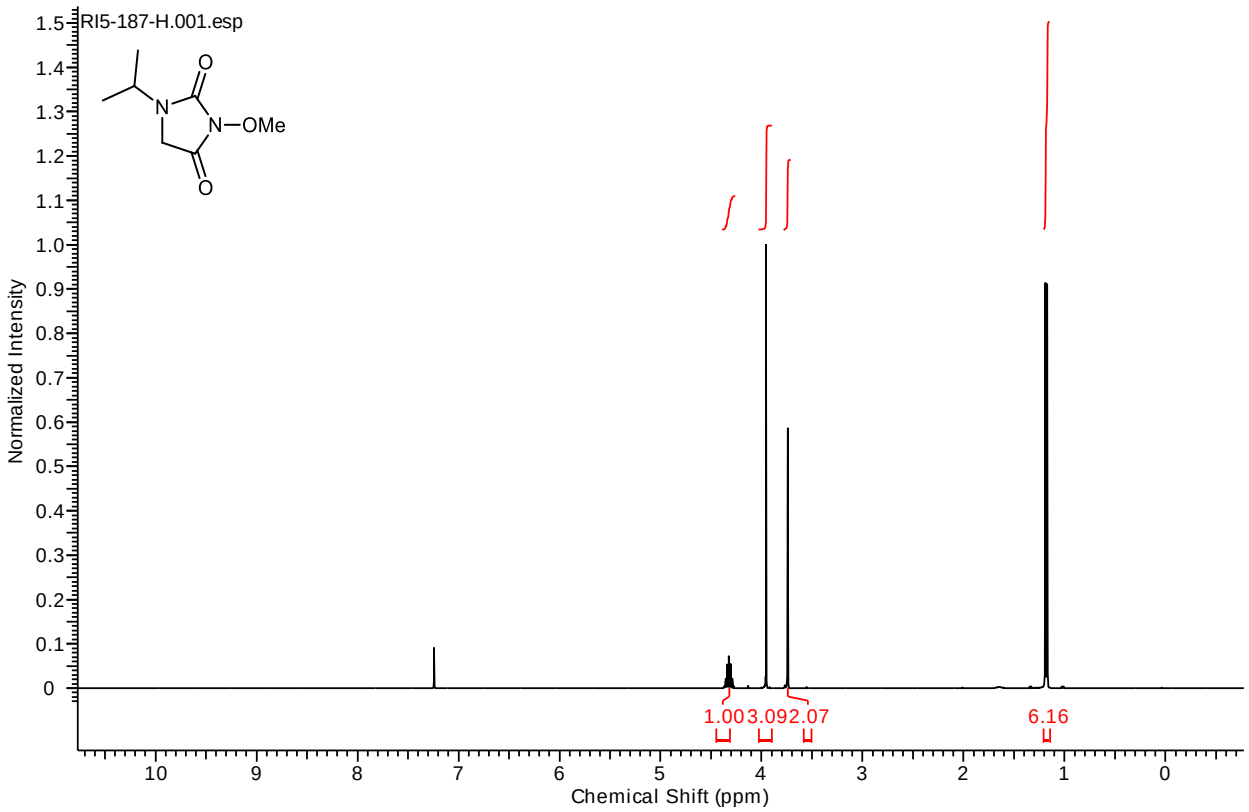

RI5-186-C.001.esp
163.95
152.82
65.33
49.66
30.07
Normalized Intensity
Chemical Shift (ppm)

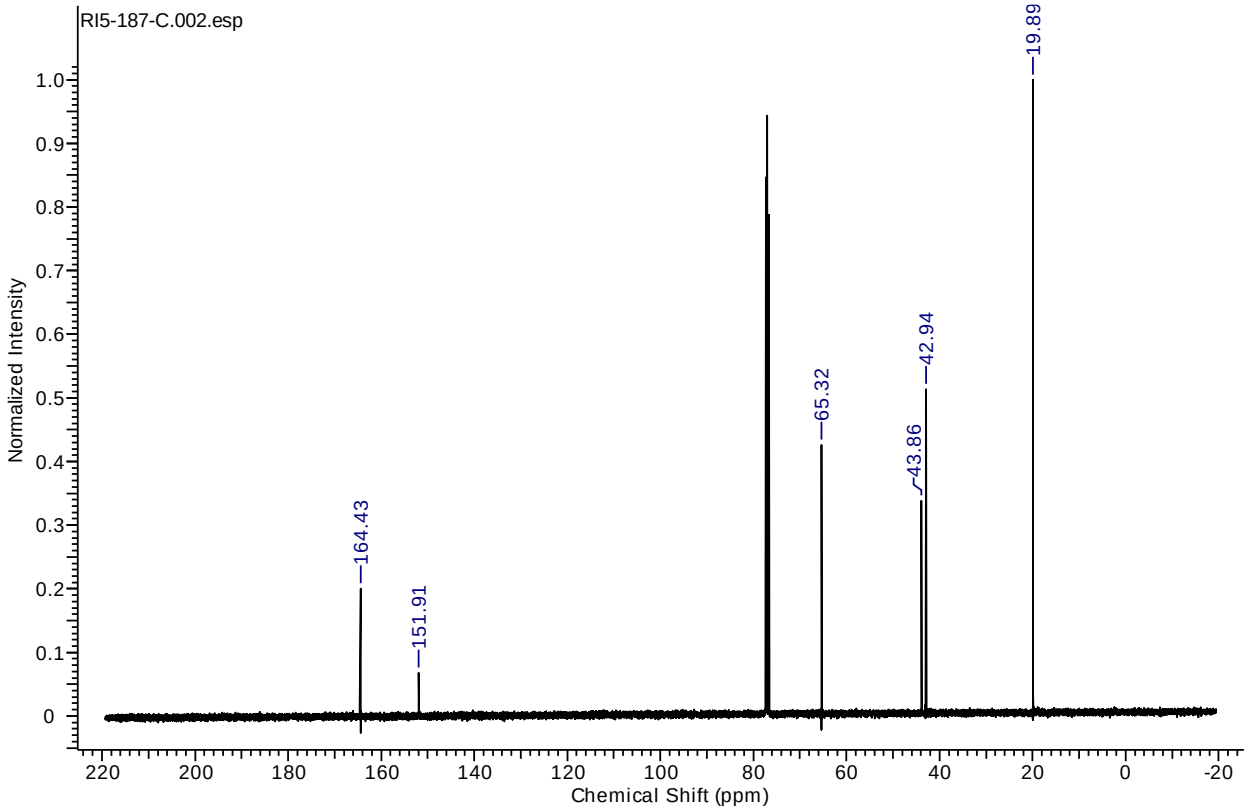

RI6-50-H2.001.esp
Me
N
O
N
O
N
O
O
Normalized Intensity
1.95
2.91
2.01
2.03
3.00
Chemical Shift (ppm)

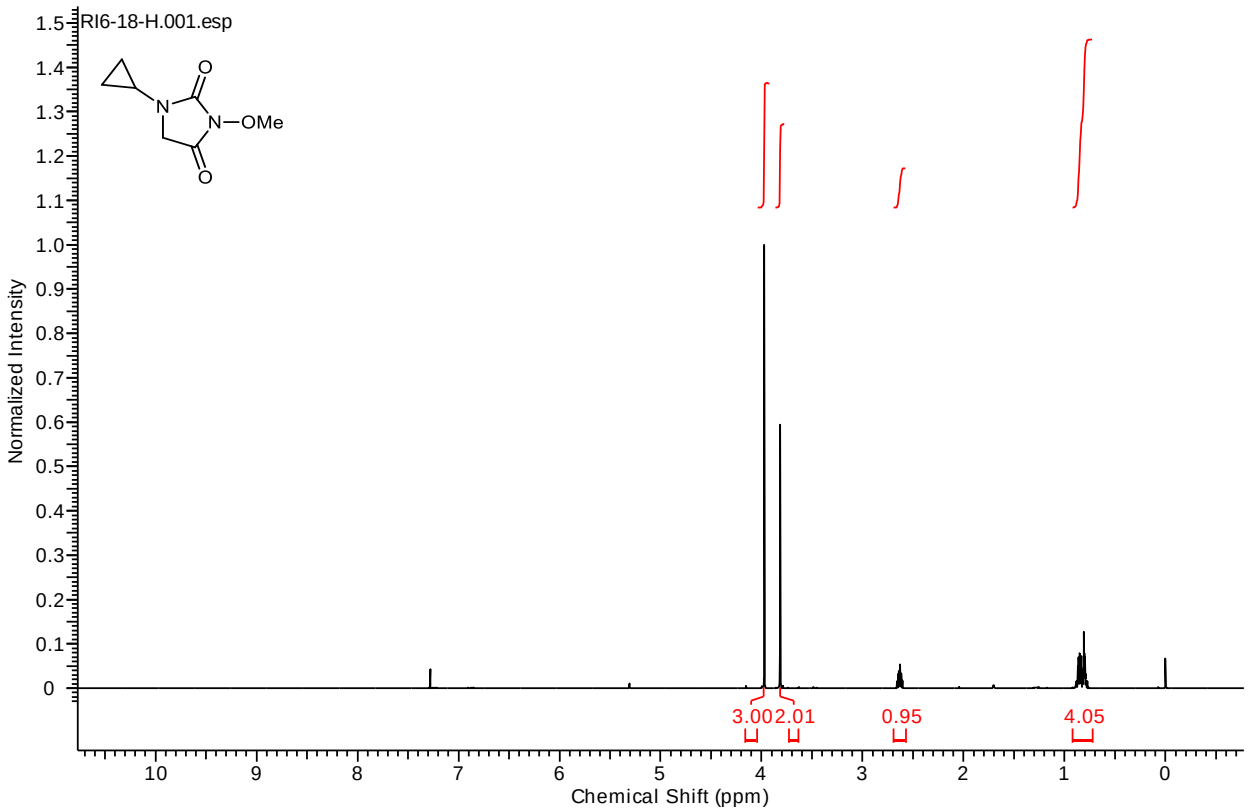

RI6-50-C2.001.esp
129.80
128.47
164.09
153.12
133.46
79.35
49.57
30.09
Normalized Intensity
Chemical Shift (ppm)

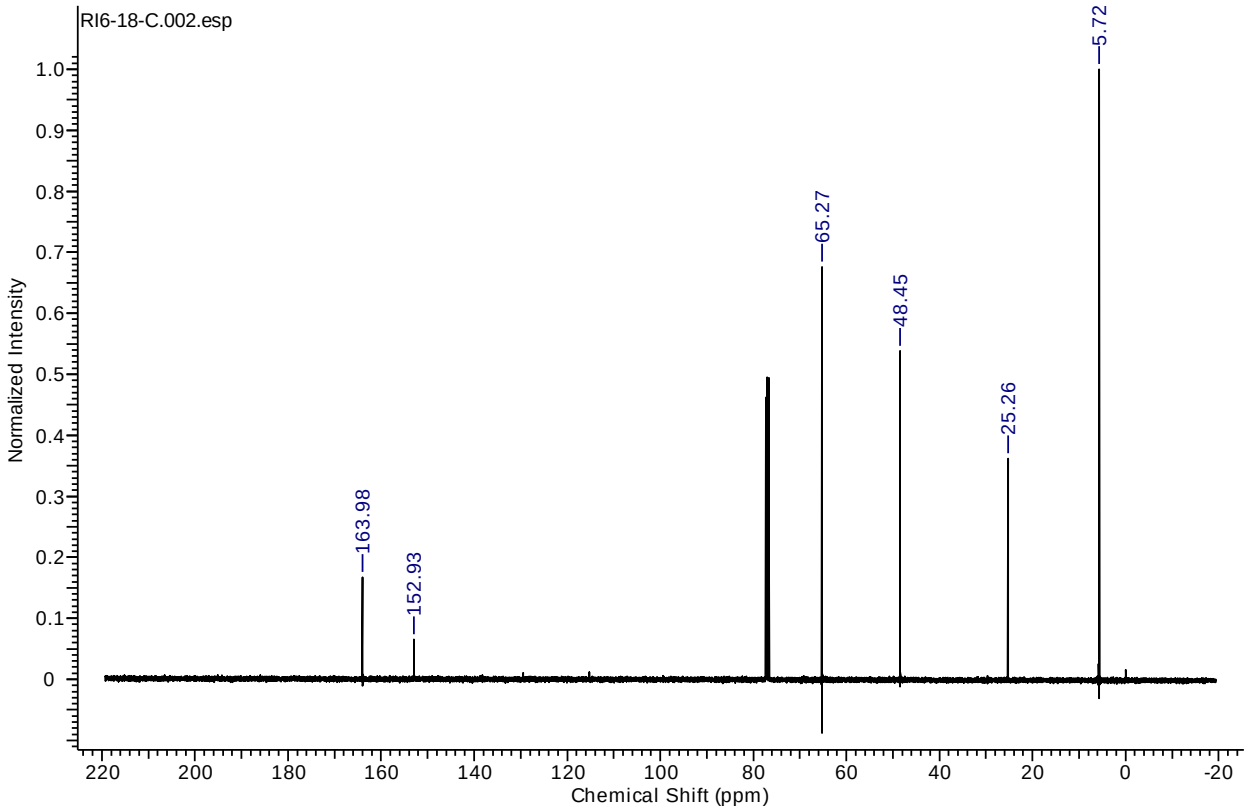

DP404-F1.006.esp
O
N
N—OH
O
Normalized Intensity
1.5
1.0
0.5
0
0.76
1.00
1.95
6.04
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

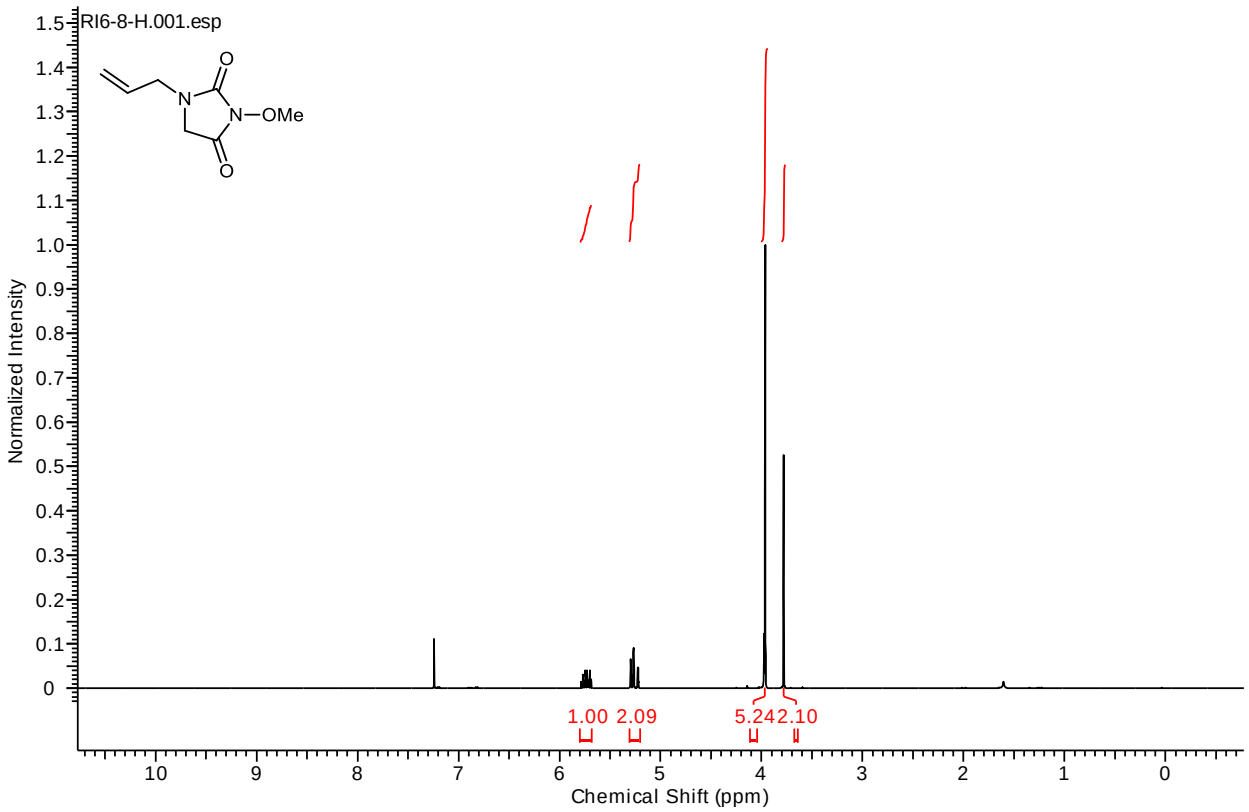

DP404-F1.004.esp
19.89
44.23
43.12
165.80
154.08
Normalized Intensity
1.5
1.0
0.5
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

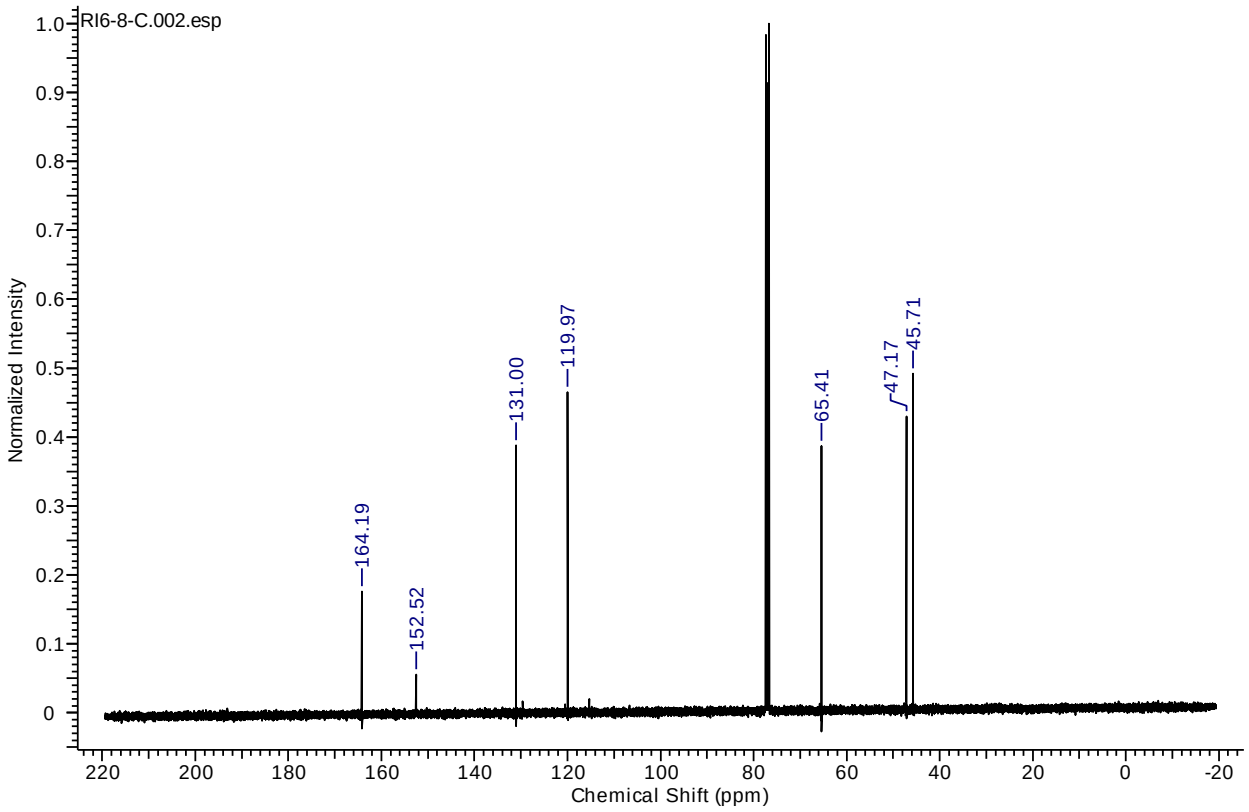

RI5-187-H.001.esp
O
N
N—OMe
O
Normalized Intensity
1.00
3.09
2.07
6.16
Chemical Shift (ppm)

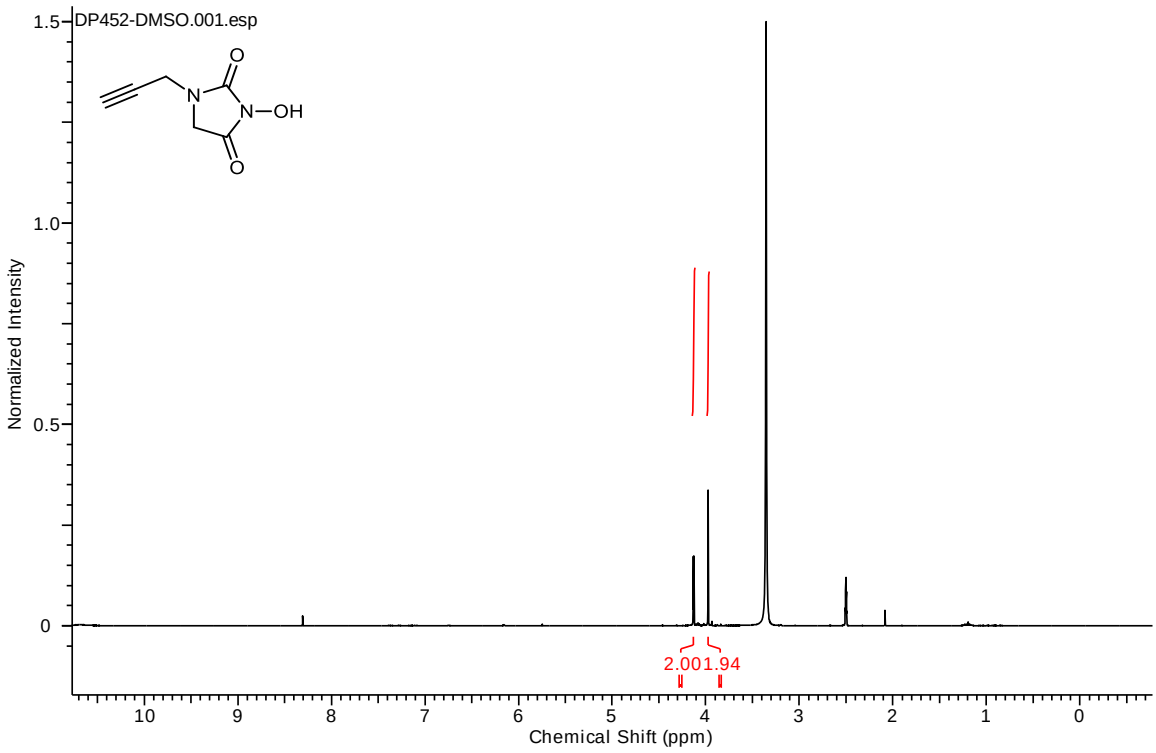

RI5-187-C.002.esp
Normalized Intensity
164.43
151.91
65.32
43.86
42.94
19.89
Chemical Shift (ppm)

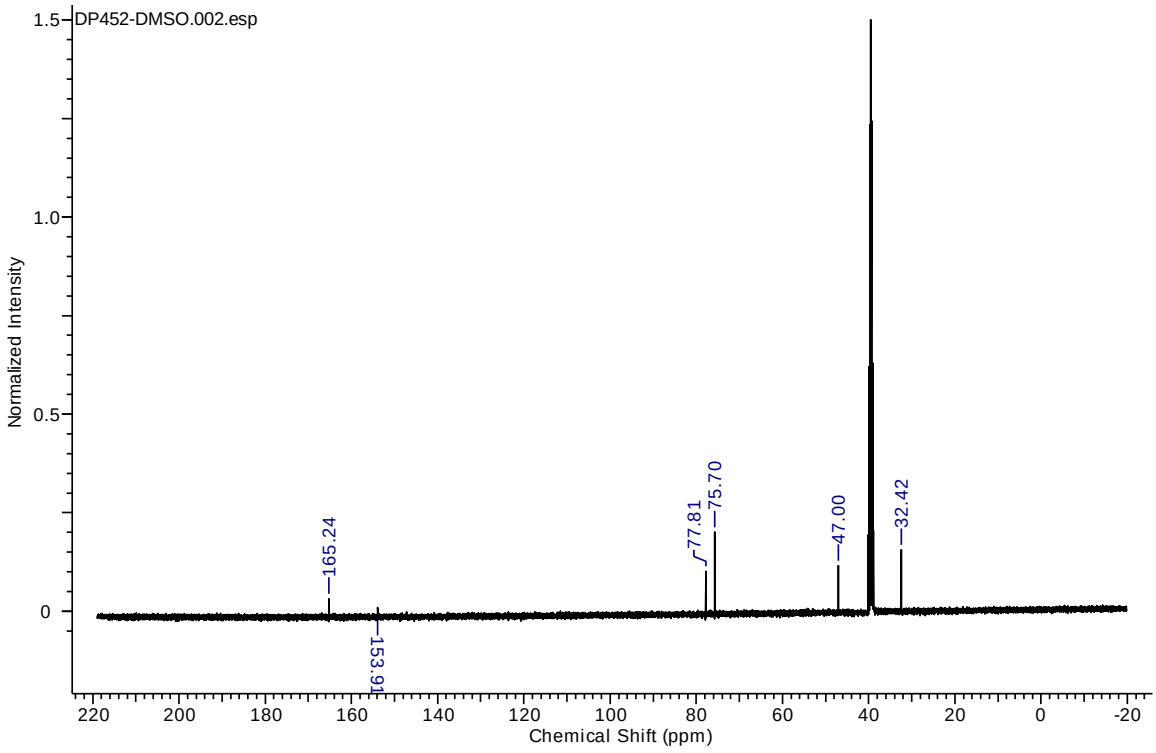

RI6-18-H.001.esp
O
N
N—OMe
O
Normalized Intensity
3.00
2.01
0.95
4.05
Chemical Shift (ppm)

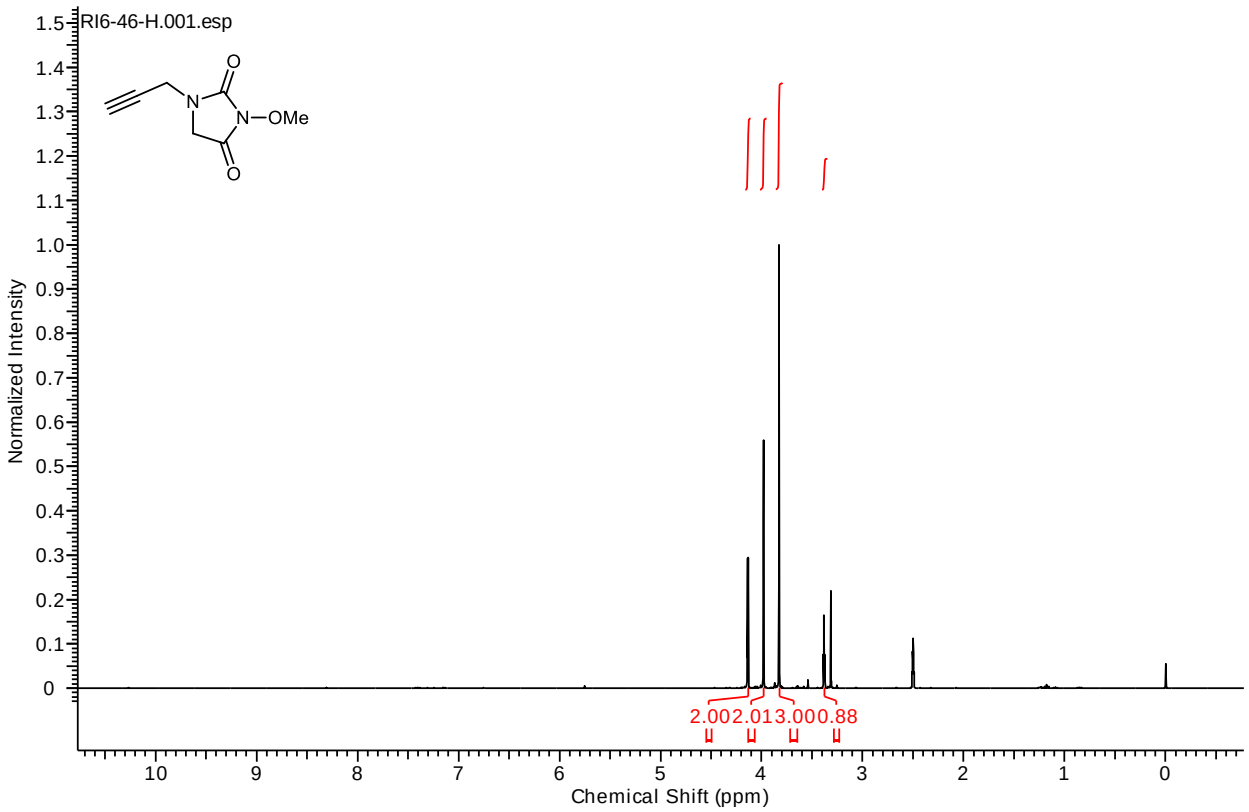

RI6-18-C.002.esp
163.98
152.93
65.27
48.45
25.26
5.72
Normalized Intensity
Chemical Shift (ppm)

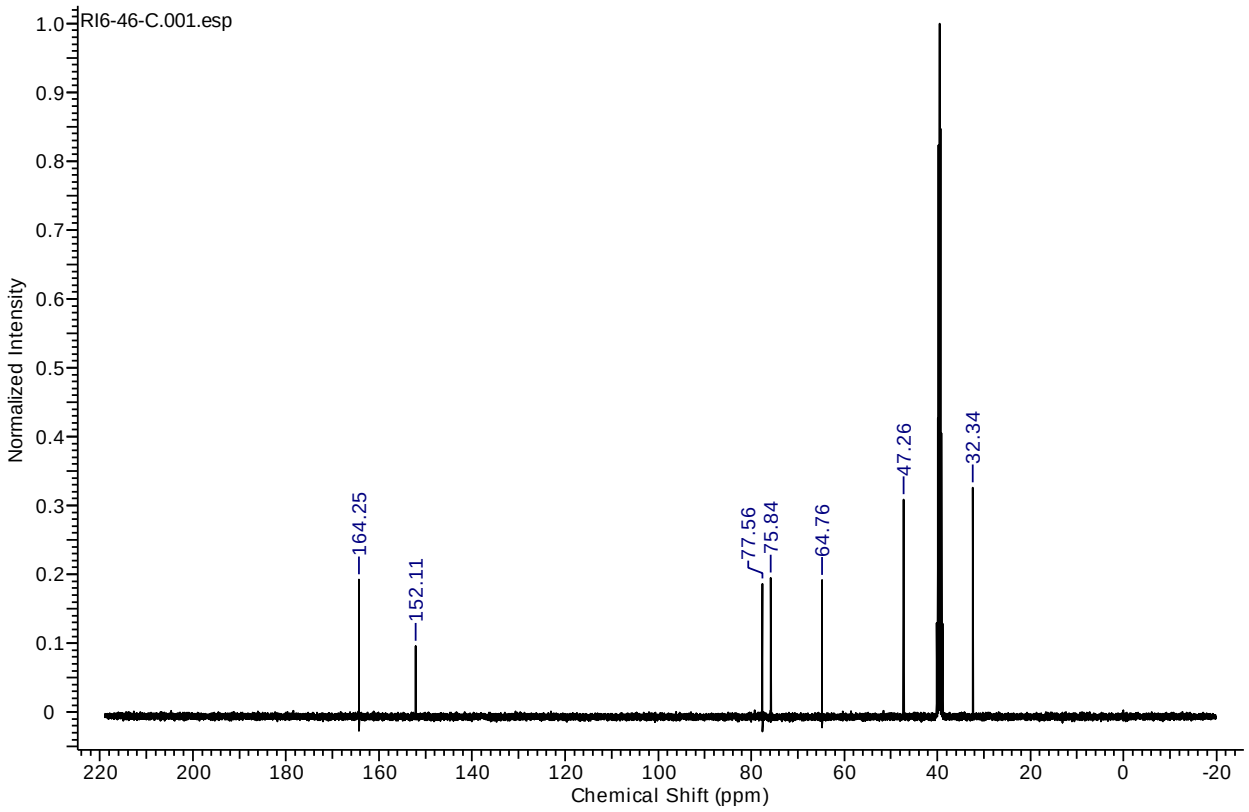

RI6-8-H.001.esp
N
O
N—OMe
O
Normalized Intensity
1.00 2.09 5.24 2.10
Chemical Shift (ppm)

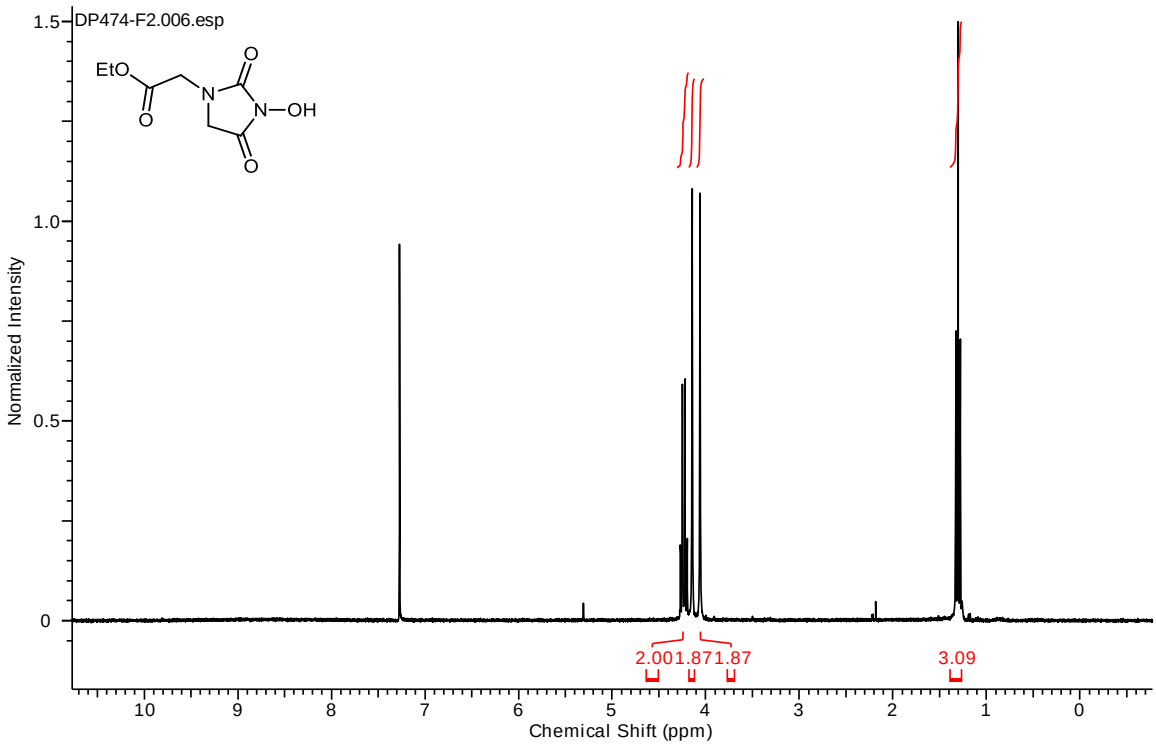

RI6-8-C.002.esp
Normalized Intensity
164.19
152.52
131.00
119.97
65.41
47.17
45.71
Chemical Shift (ppm)

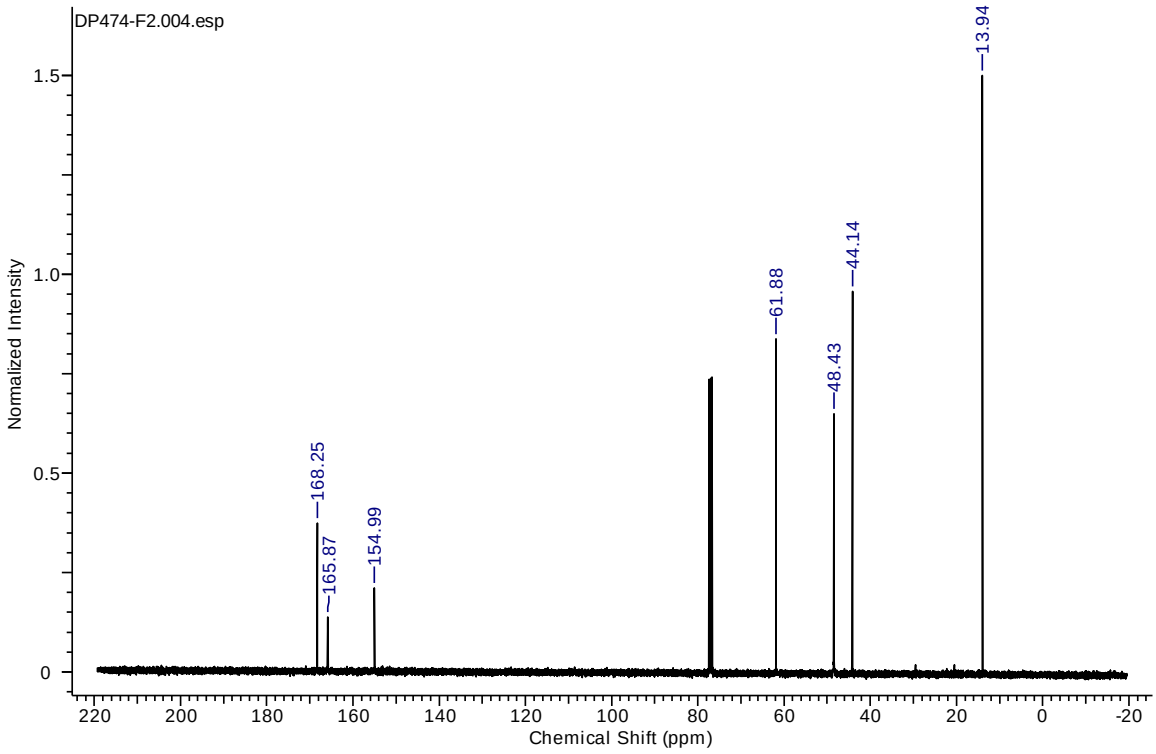

DP452-DMSO.001.esp
O
N
N—OH
O
1.5
1.0
0.5
0
Normalized Intensity
2.00
1.94
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

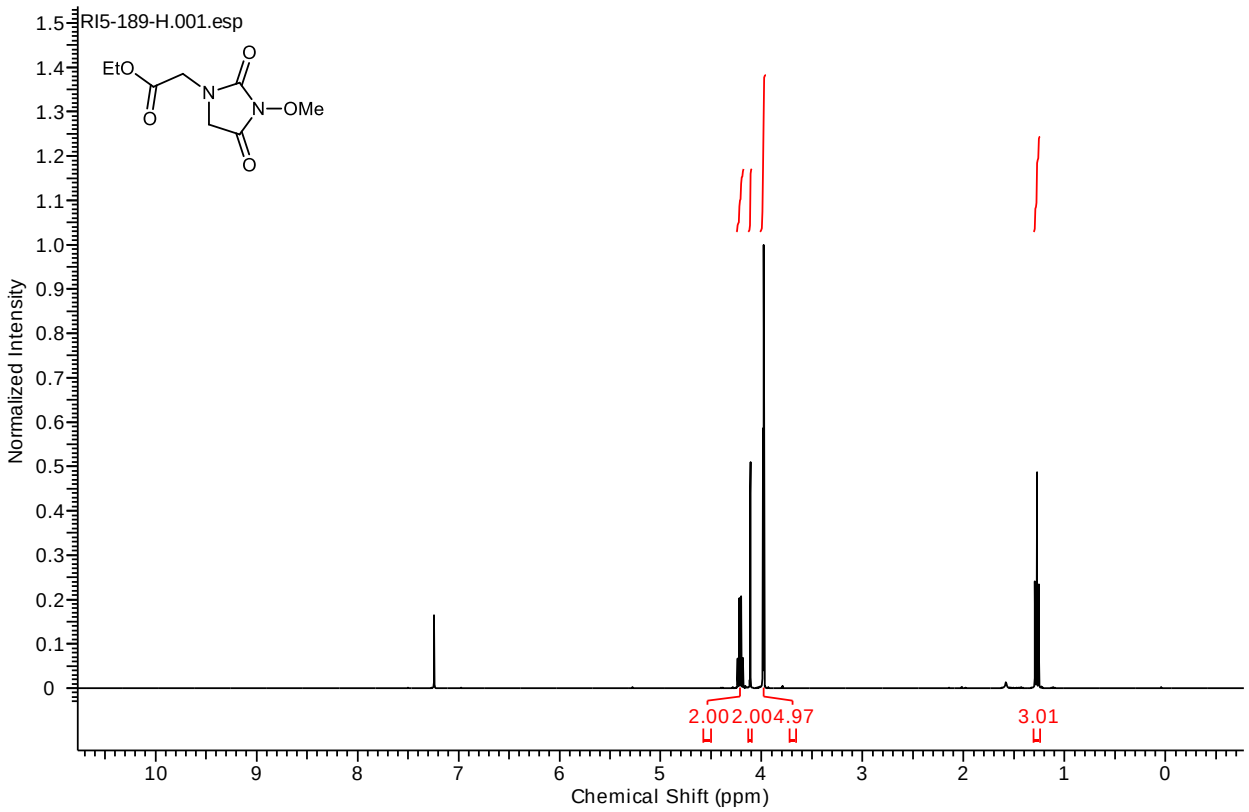

DP452-DMSO.002.esp
1.5
1.0
0.5
0
Normalized Intensity
165.24
153.91
77.81
75.70
47.00
32.42
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

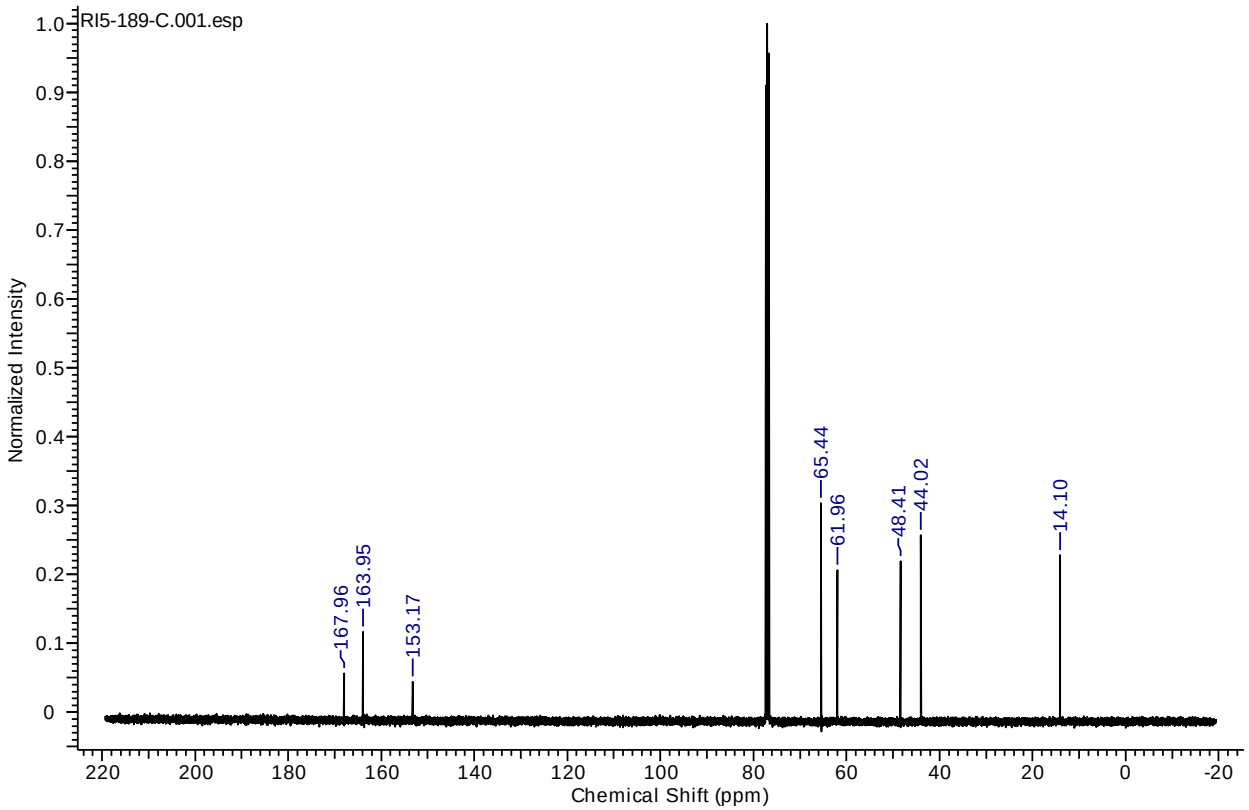

RI6-46-H.001.esp
O
N
N—OMe
O
Normalized Intensity
2.00
2.01
3.00
0.88
Chemical Shift (ppm)

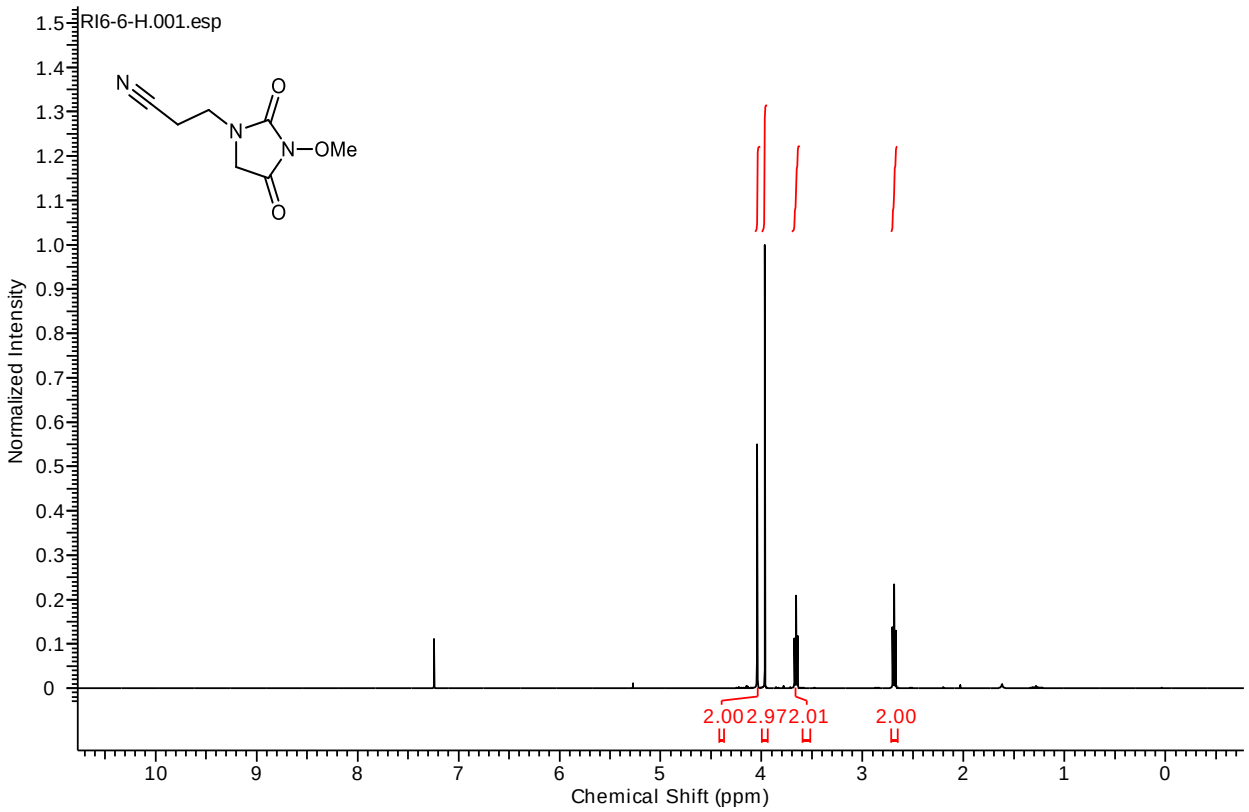

RI6-46-C.001.esp
Normalized Intensity
164.25
152.11
77.56
75.84
64.76
47.26
32.34
Chemical Shift (ppm)

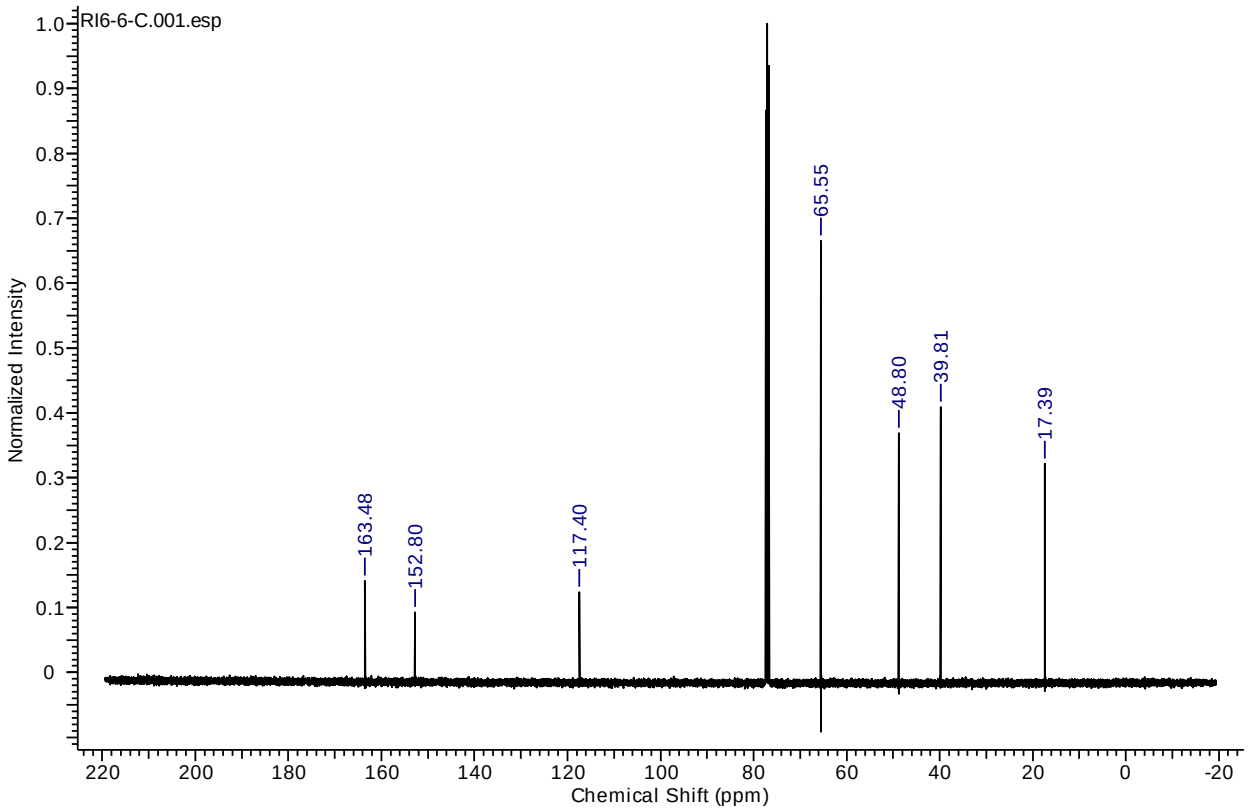

DP474-F2.006.esp
EtO
O
O
N
O
N—OH
O
Normalized Intensity
1.5
1.0
0.5
0
2.00
1.87
1.87
3.09
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

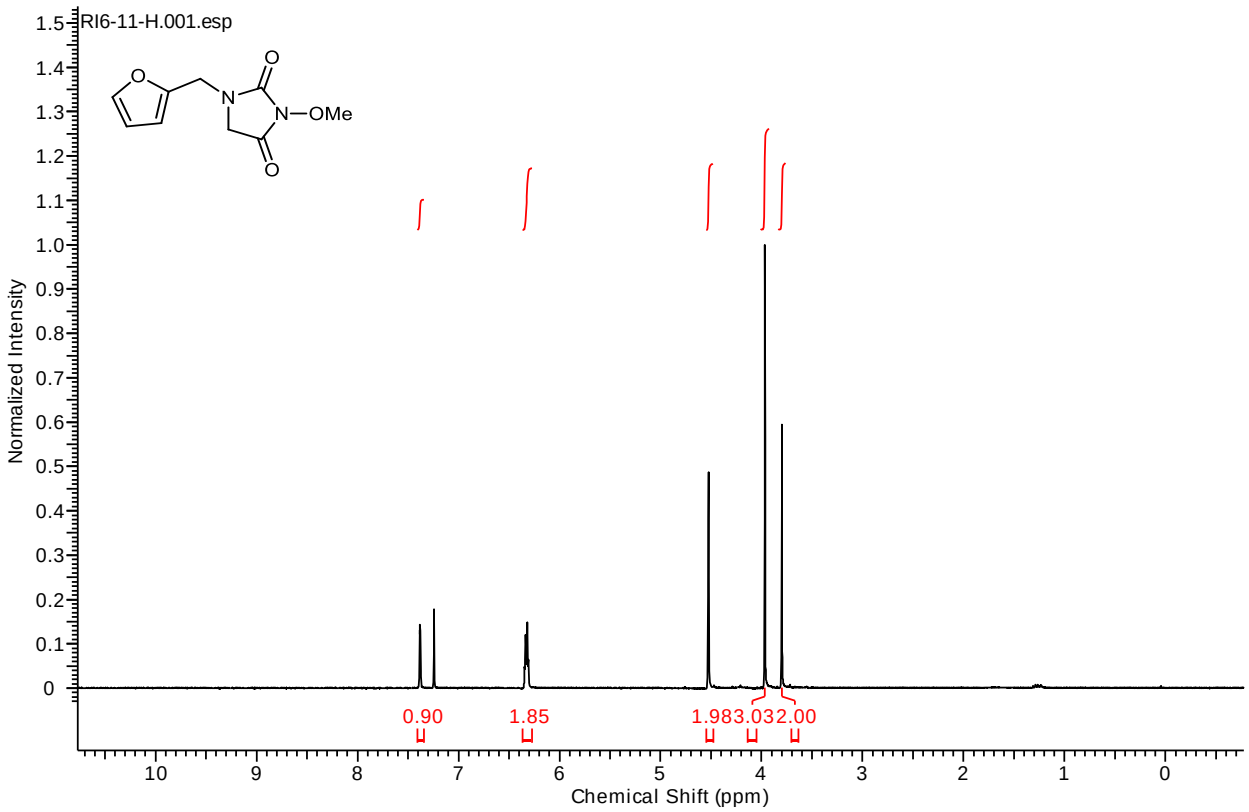

DP474-F2.004.esp
Normalized Intensity
1.5
1.0
0.5
0
168.25
165.87
154.99
61.88
48.43
44.14
13.94
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

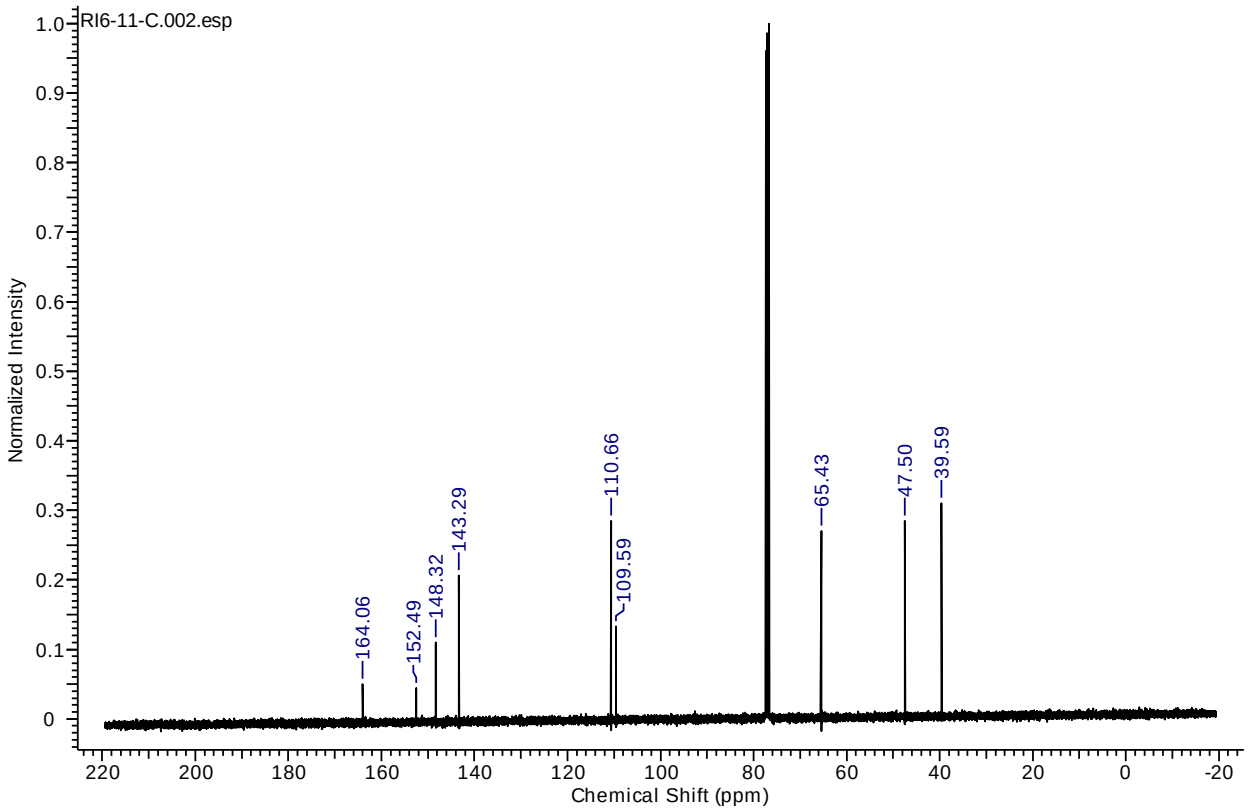

RI5-189-H.001.esp
EtO
O
O
N
O
N—OMe
O
Normalized Intensity
2.00
2.00
4.97
3.01
Chemical Shift (ppm)

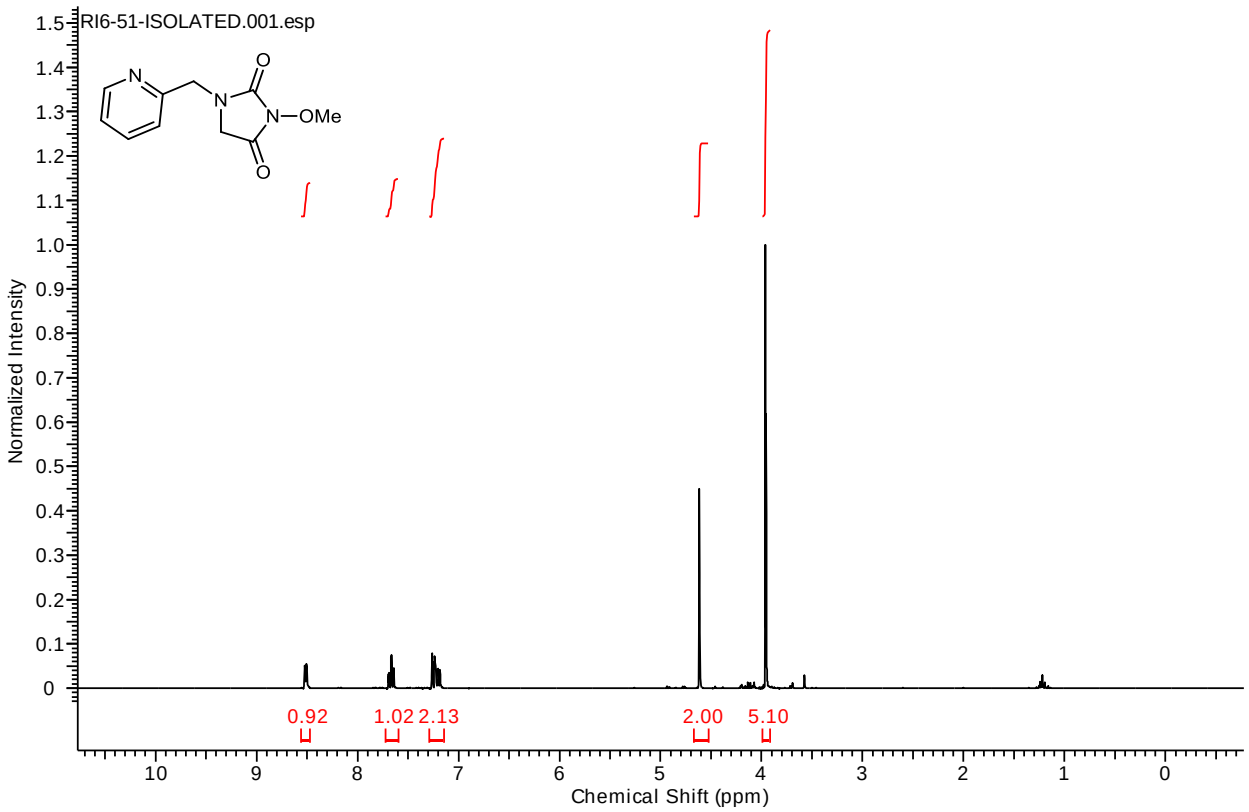

RI5-189-C.001.esp
Normalized Intensity
167.96
163.95
153.17
65.44
61.96
48.41
44.02
14.10
Chemical Shift (ppm)

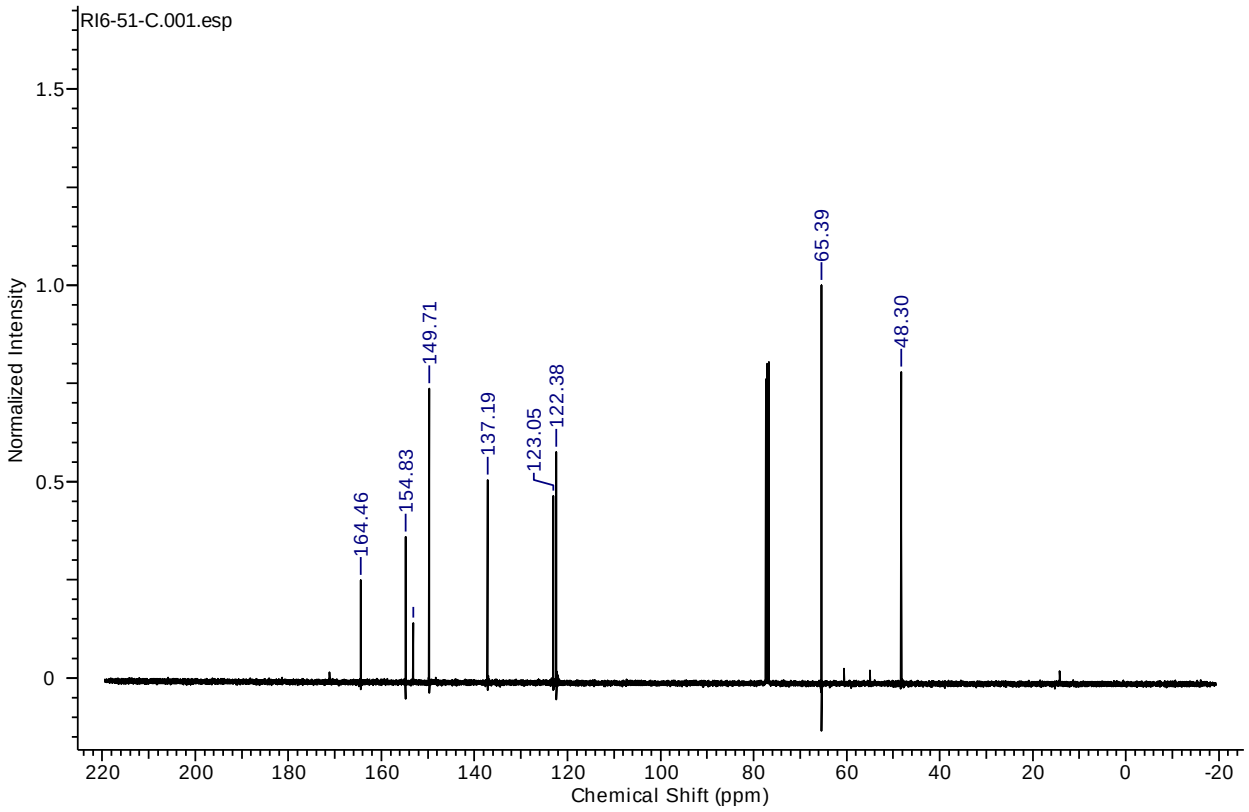

RI6-6-H.001.esp
N
O
N
N—OMe
O
Normalized Intensity
2.00
2.97
2.01
2.00
Chemical Shift (ppm)

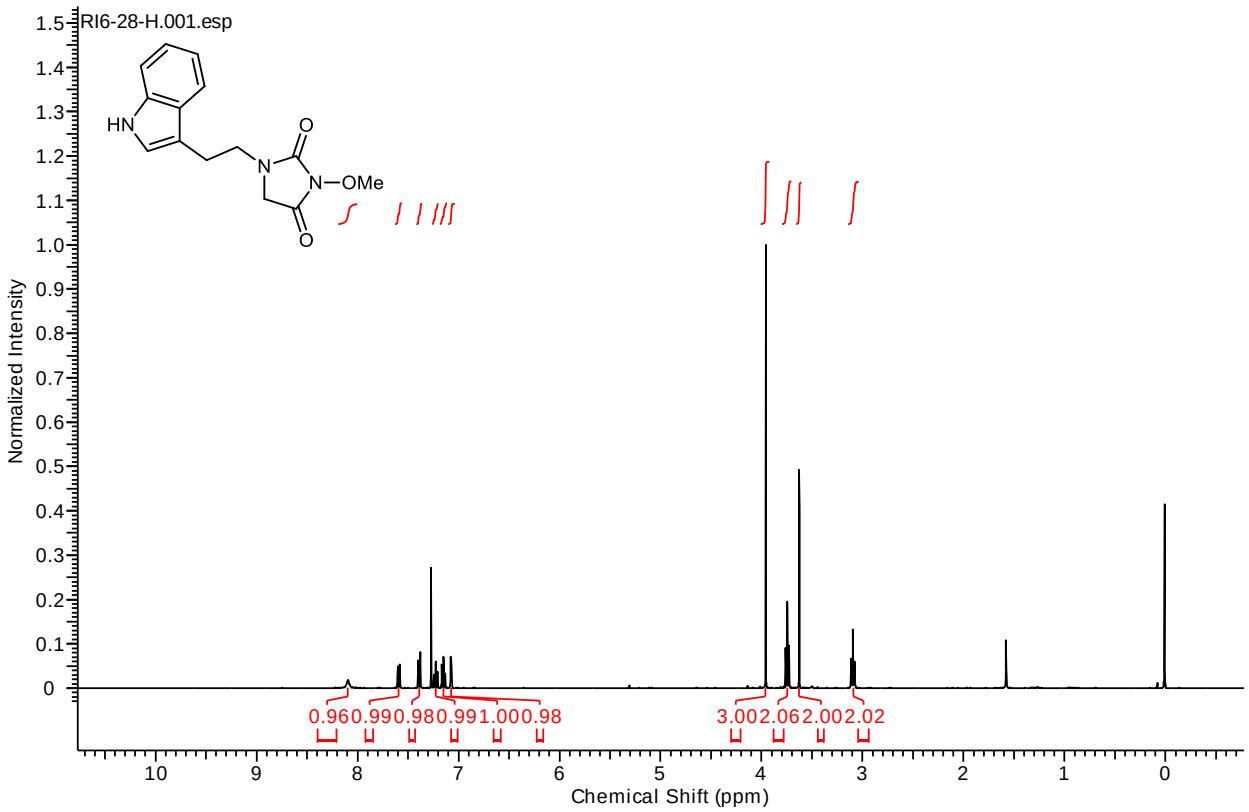

RI6-6-C.001.esp
163.48
152.80
117.40
65.55
48.80
39.81
17.39
Normalized Intensity
Chemical Shift (ppm)

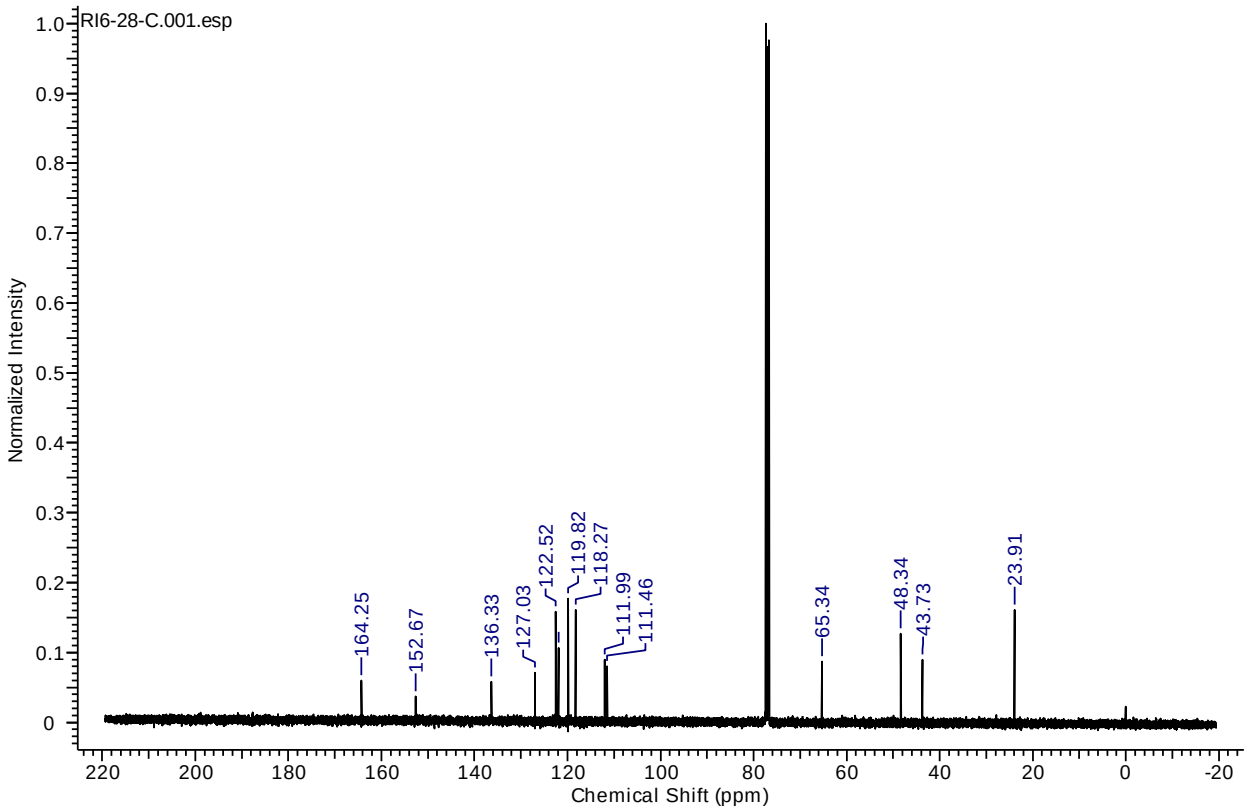

RI6-11-H.001.esp
O
N
N—OMe
O
O
Normalized Intensity
0.90
1.85
1.98
3.03
2.00
Chemical Shift (ppm)

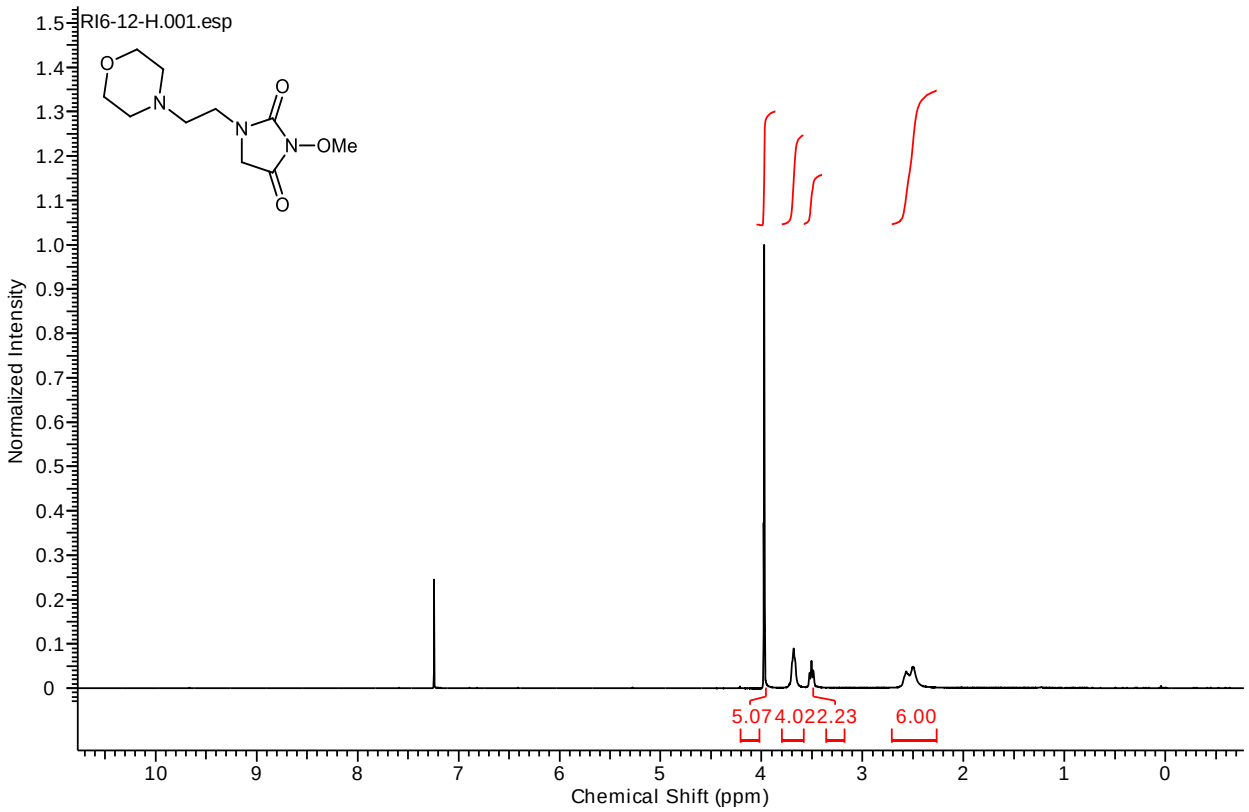

RI6-11-C.002.esp
Normalized Intensity
164.06
152.49
148.32
143.29
110.66
109.59
65.43
47.50
39.59
Chemical Shift (ppm)

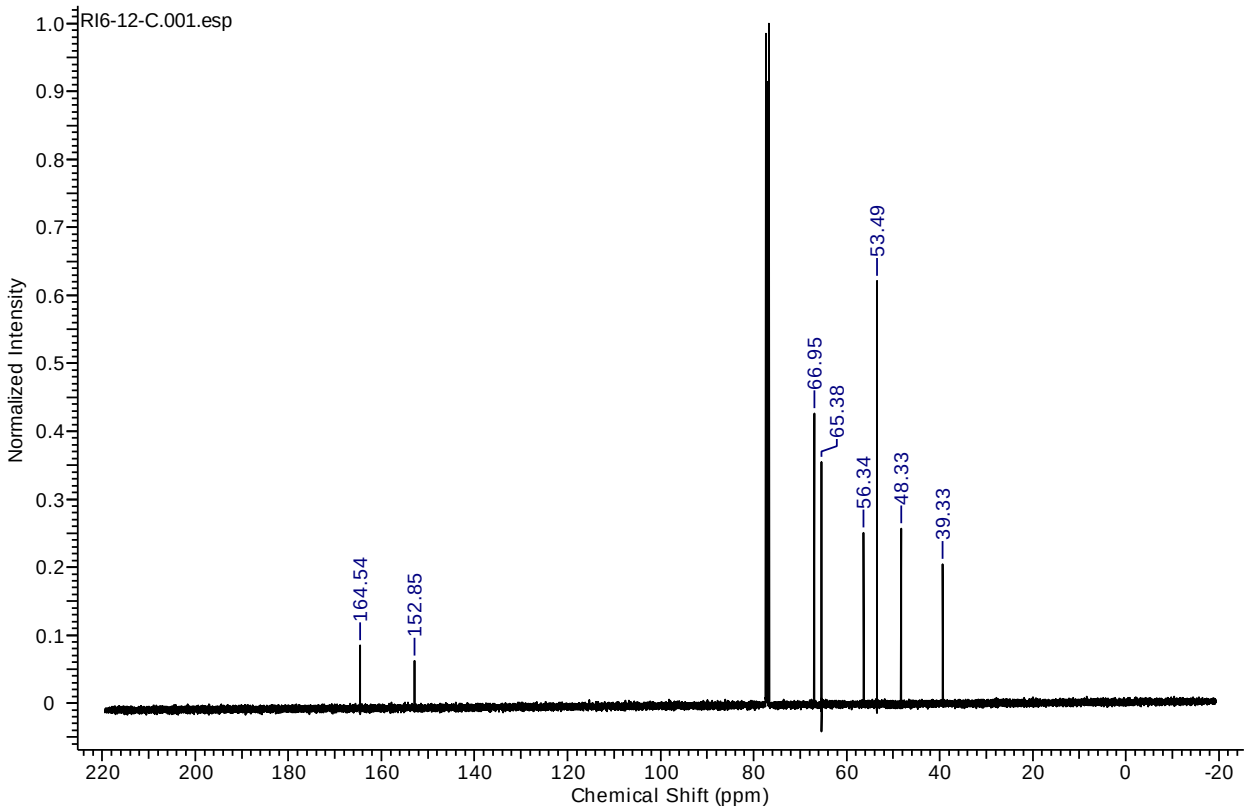

RI6-51-ISOLATED.001.esp
N
N
O
N—OMe
O
Normalized Intensity
0.92
1.02
2.13
2.00
5.10
Chemical Shift (ppm)

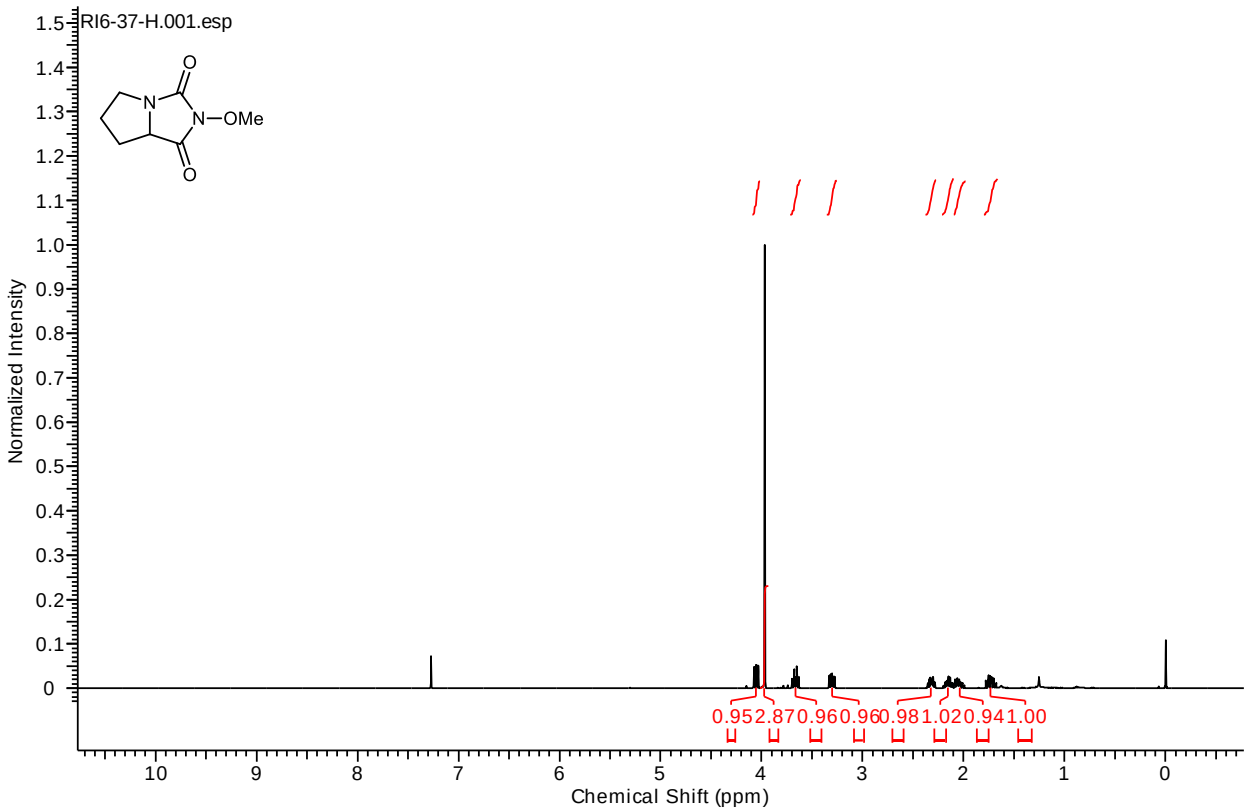

RI6-51-C.001.esp
Normalized Intensity
164.46
154.83
149.71
137.19
123.05
122.38
65.39
48.30
Chemical Shift (ppm)

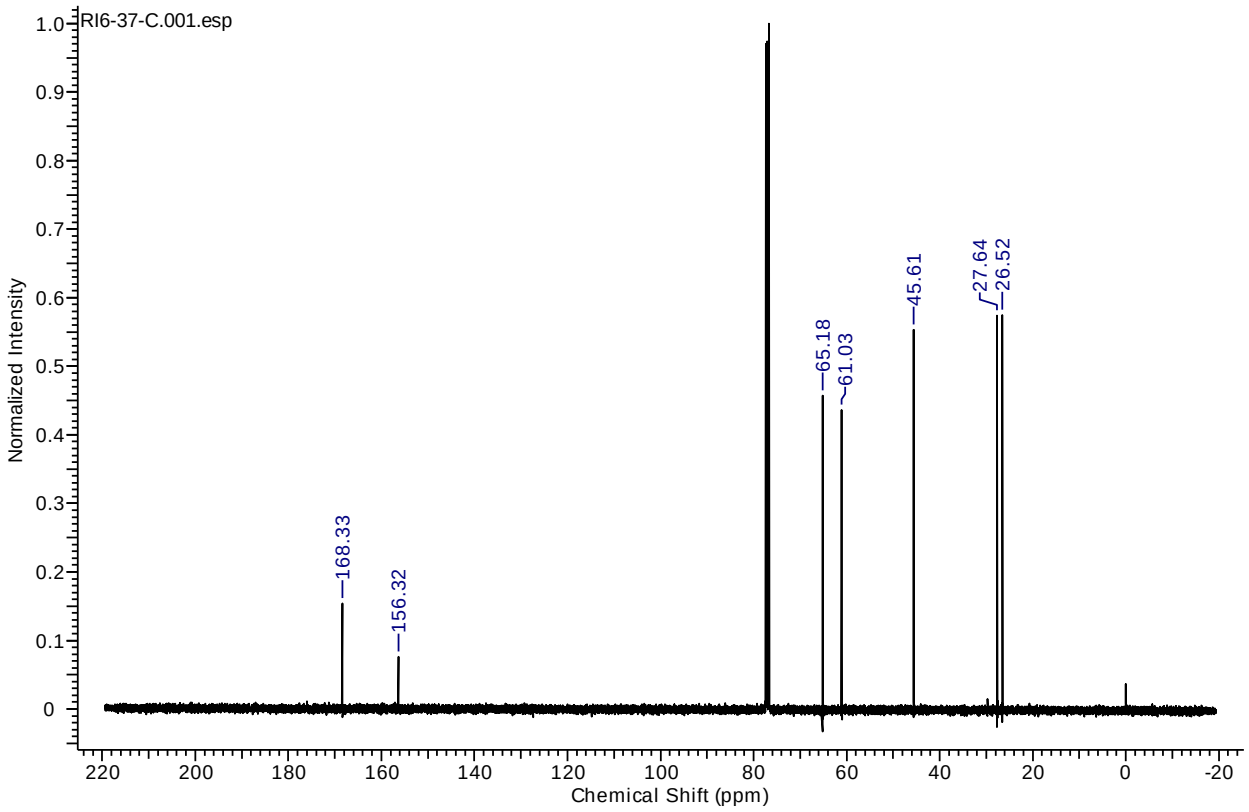

RI6-28-H.001.esp
HN
O
N
N—OMe
O
Normalized Intensity
0.960.990.980.991.000.98
3.002.062.002.02
Chemical Shift (ppm)

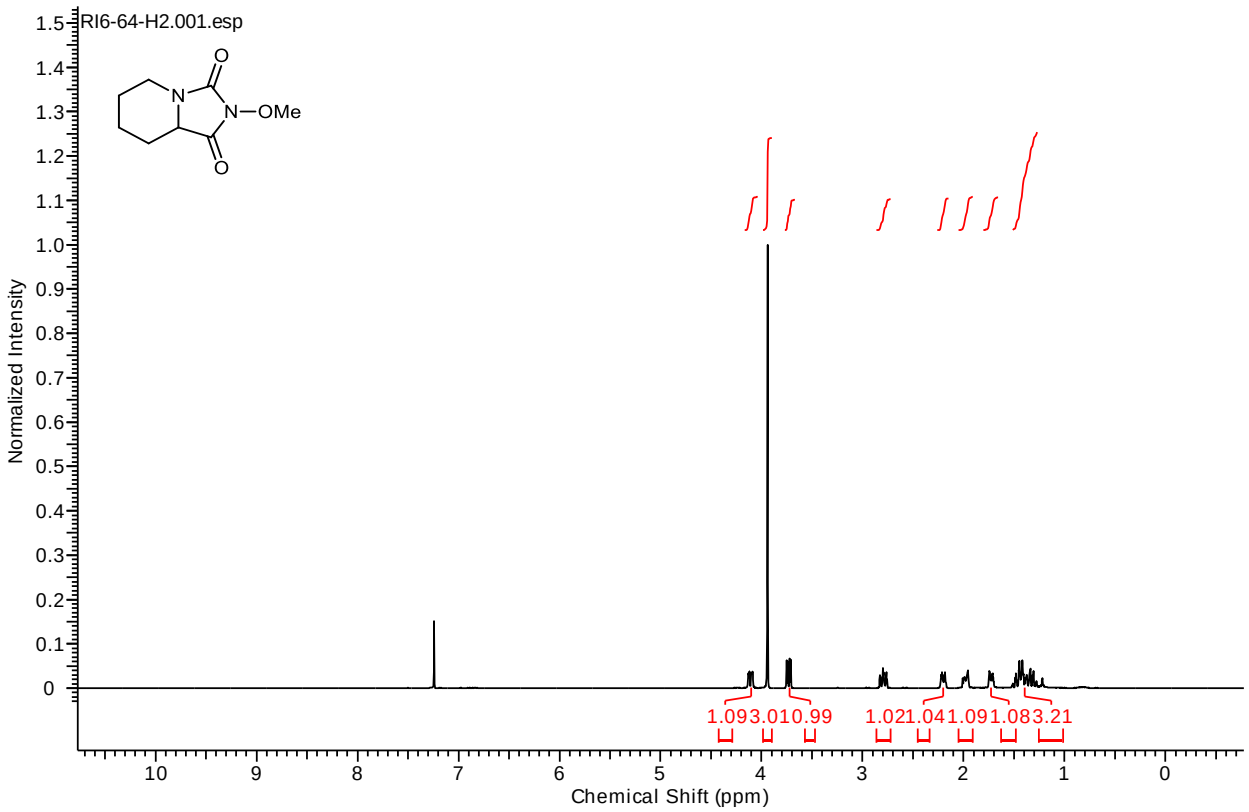

RI6-28-C.001.esp
Normalized Intensity
164.25
152.67
136.33
127.03
122.52
119.82
118.27
111.99
111.46
65.34
48.34
43.73
23.91
Chemical Shift (ppm)

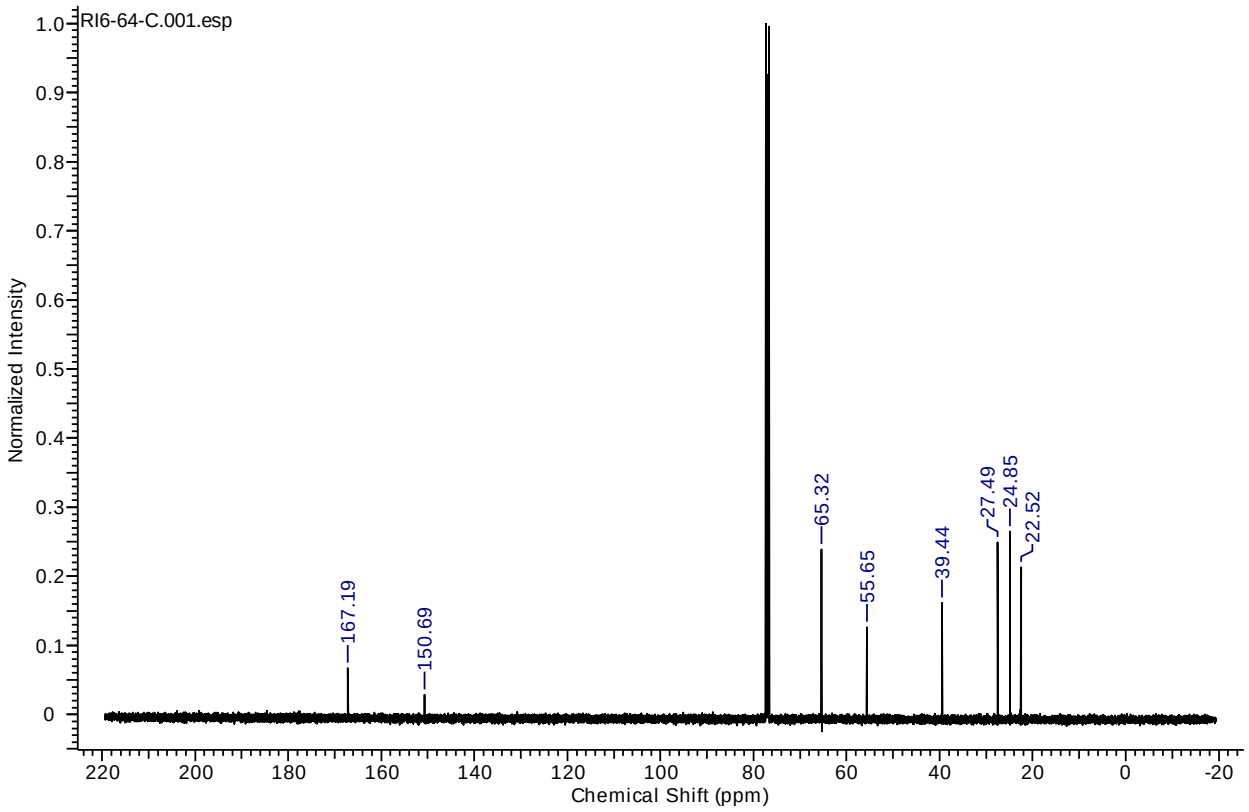

RI6-12-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
5.07
4.02
2.23
6.00
N
O
N
N
O
N—OMe
O

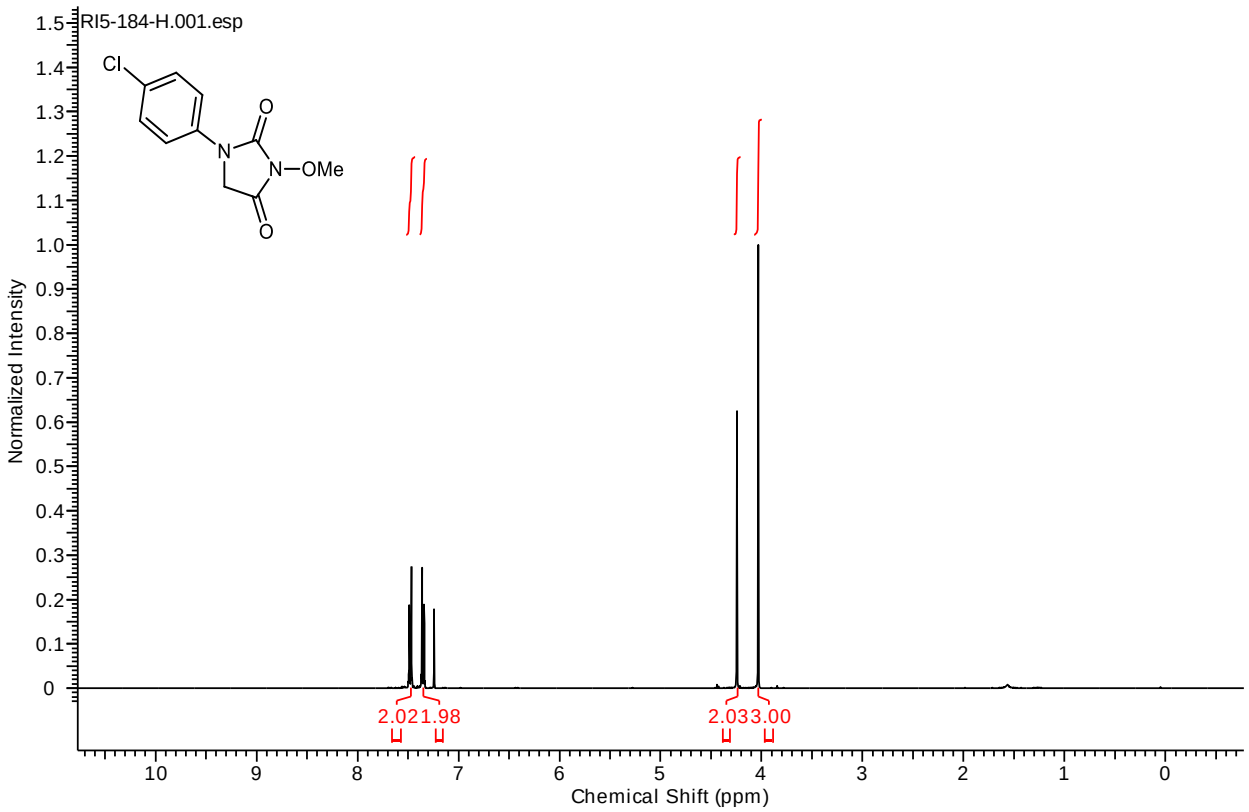

RI6-12-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
164.54
152.85
66.95
65.38
56.34
53.49
48.33
39.33

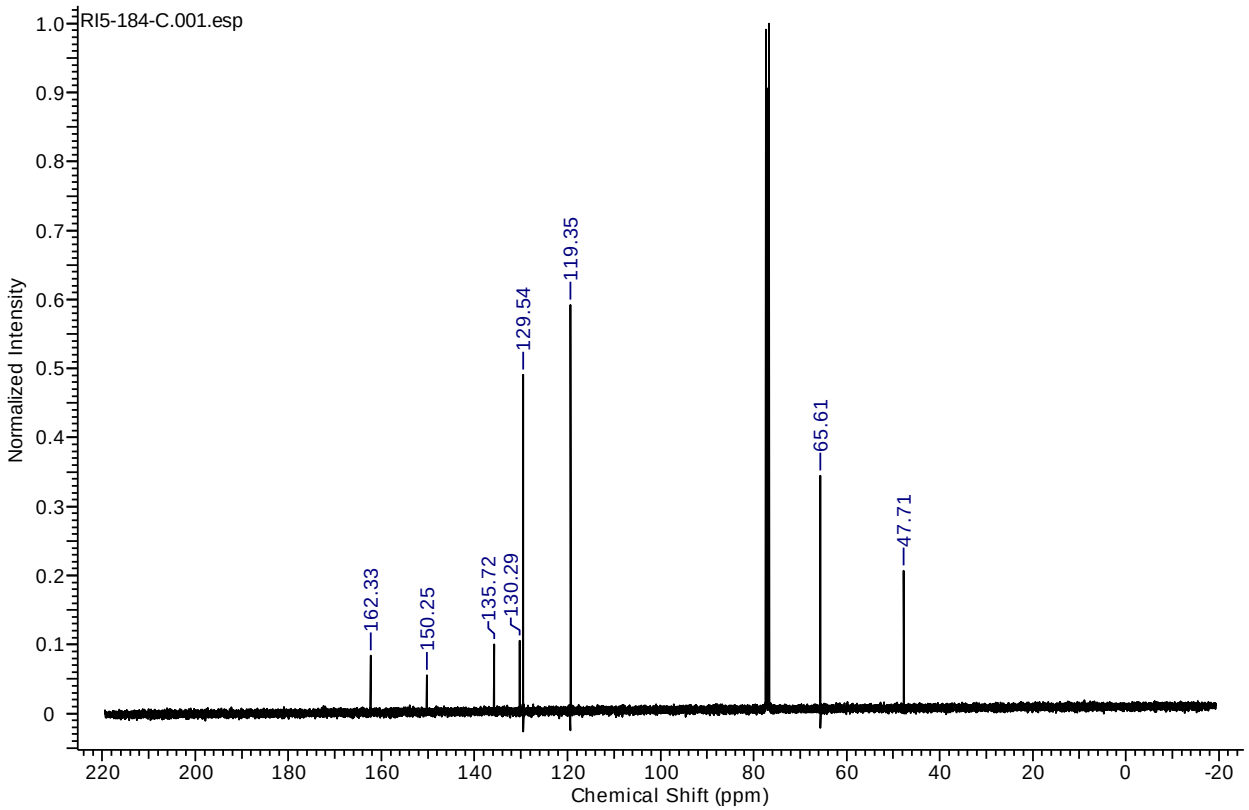

RI6-37-H.001.esp
O
N
N—OMe
O
Normalized Intensity
0.952.870.960.960.981.020.941.00
Chemical Shift (ppm)

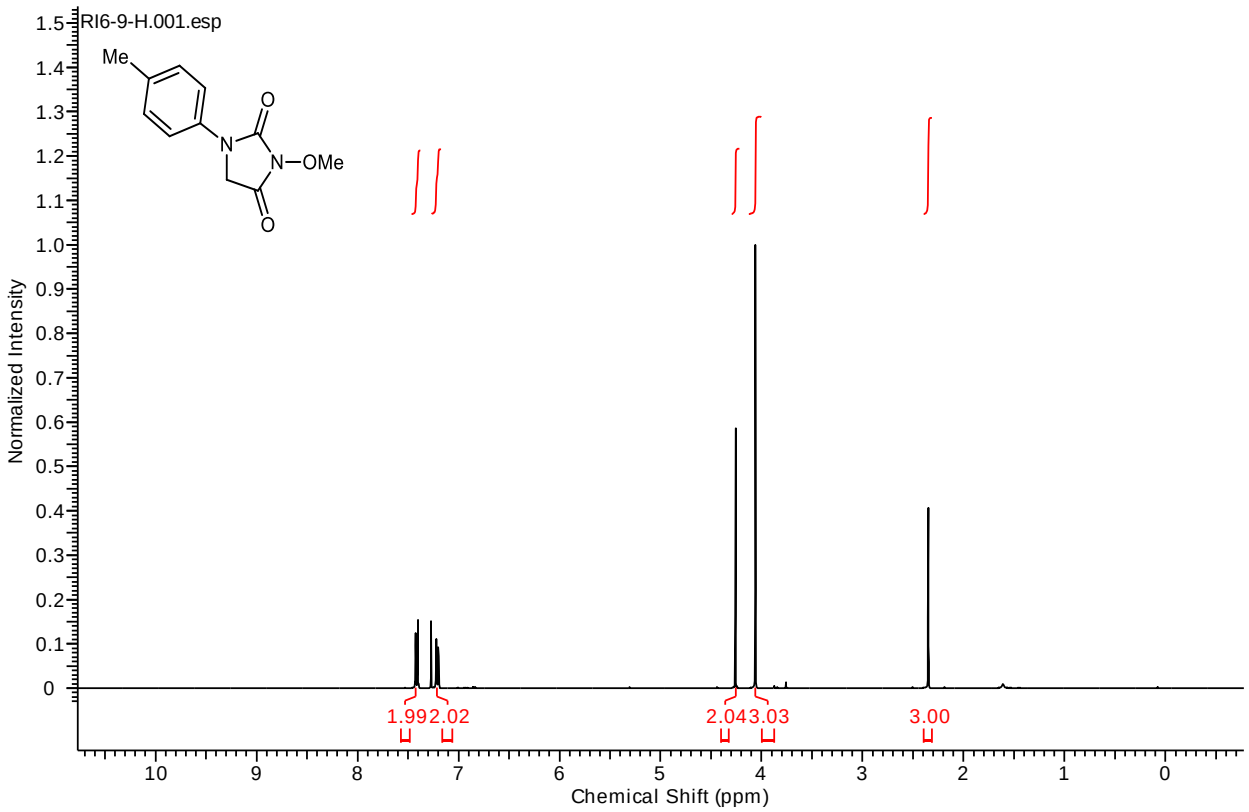

RI6-37-C.001.esp
168.33
156.32
65.18
61.03
45.61
27.64
26.52
Normalized Intensity
Chemical Shift (ppm)

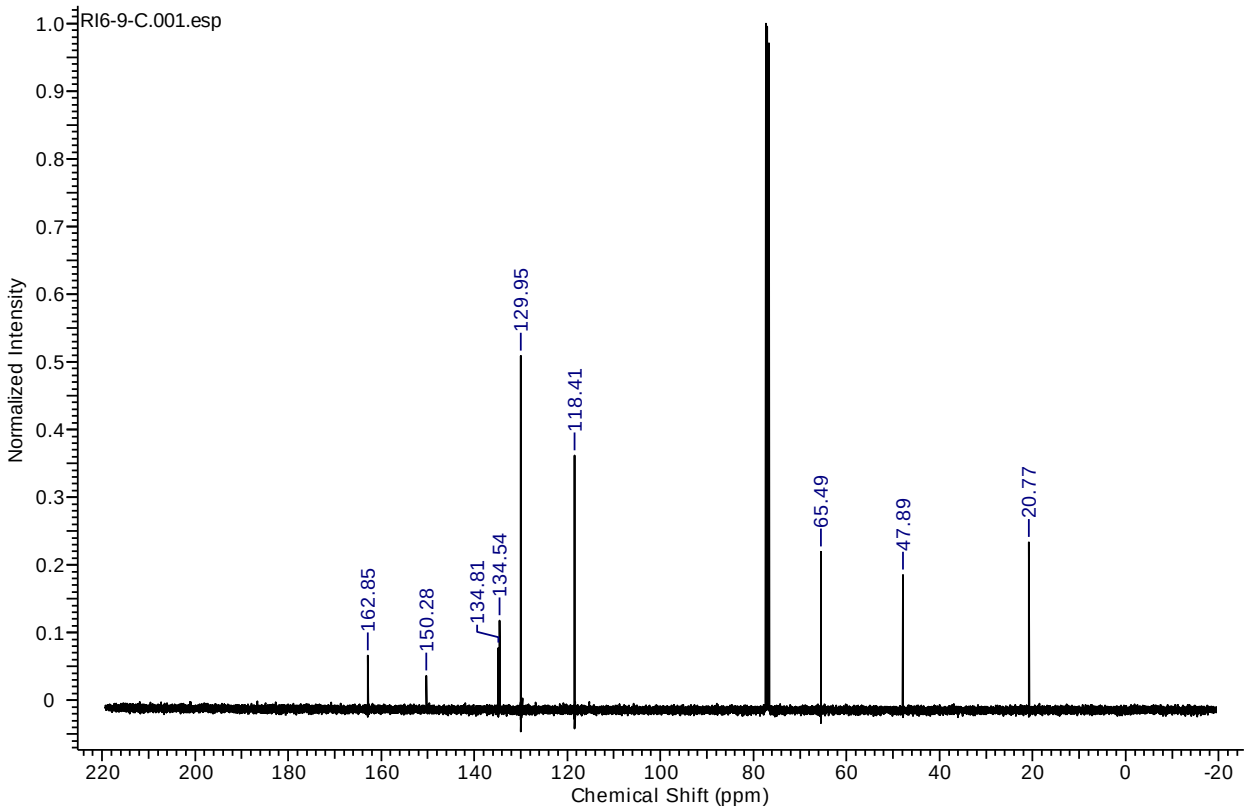

RI6-64-H2.001.esp
O
N
N—OMe
O
Normalized Intensity
1.09
3.01
0.99
1.02
1.04
1.09
1.08
3.21
Chemical Shift (ppm)

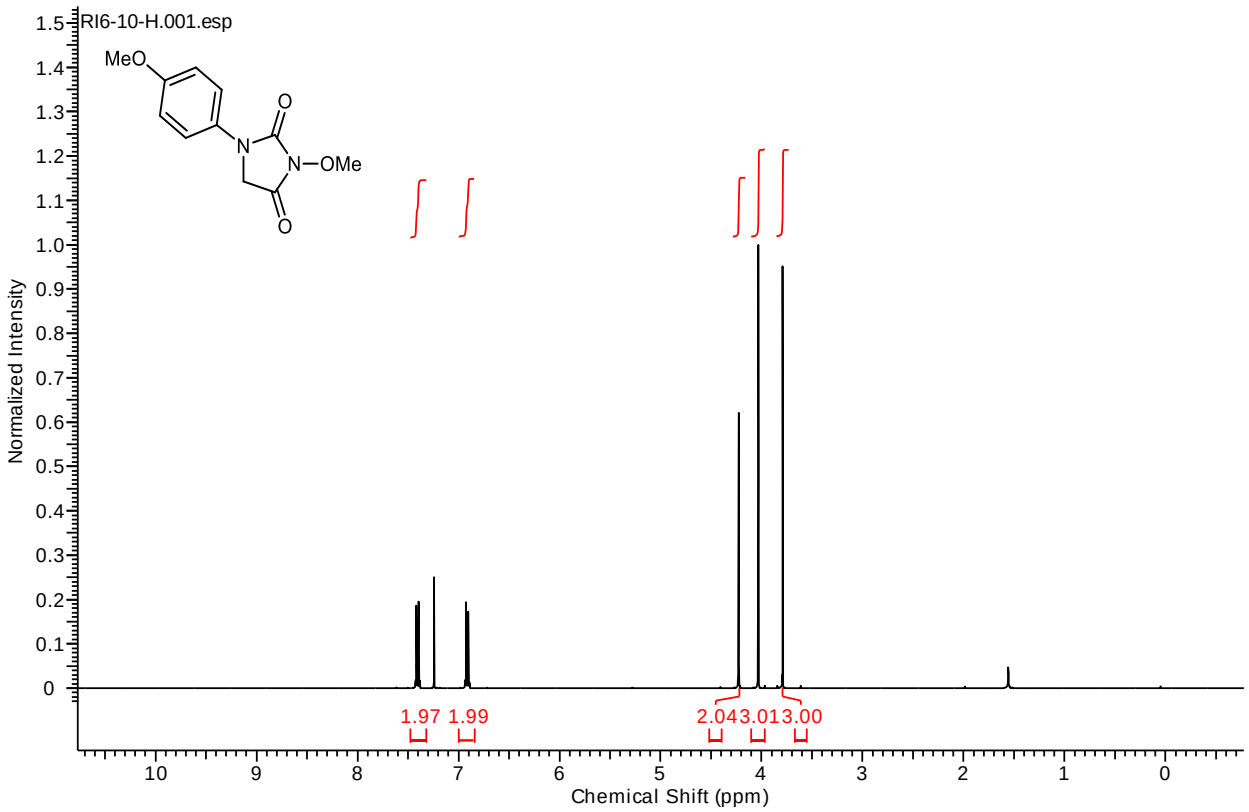

RI6-64-C.001.esp
Normalized Intensity
167.19
150.69
65.32
55.65
39.44
27.49
24.85
22.52
Chemical Shift (ppm)

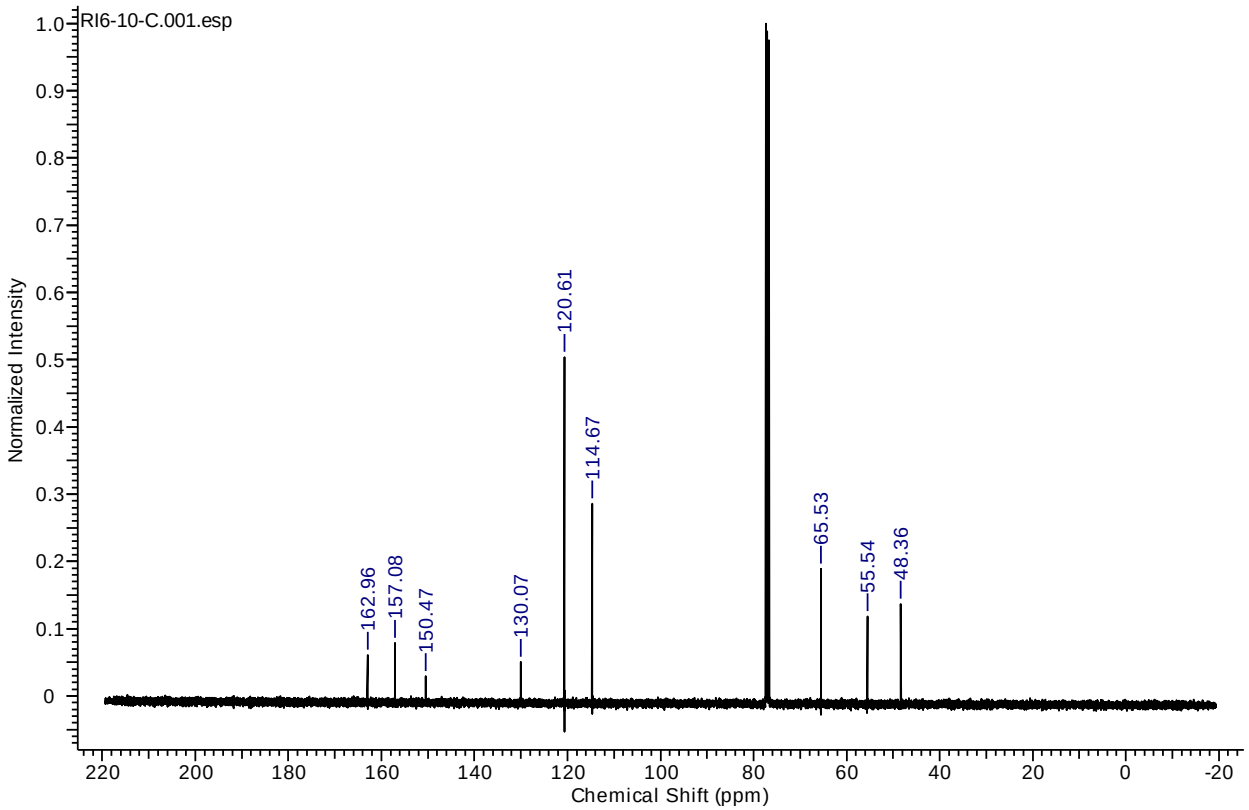

RI5-184-H.001.esp
Cl
O
N
N—OMe
O
Normalized Intensity
2.02
1.98
2.03
3.00
Chemical Shift (ppm)

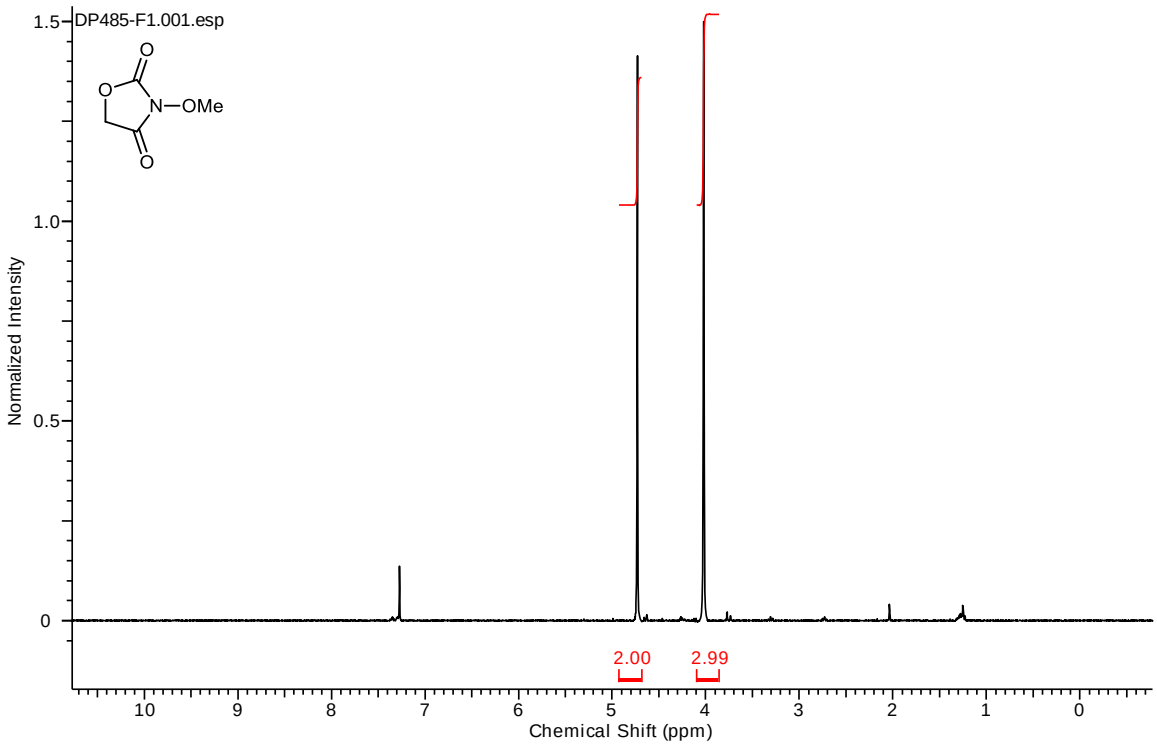

RI5-184-C.001.esp
Normalized Intensity
162.33
150.25
135.72
130.29
129.54
119.35
65.61
47.71
Chemical Shift (ppm)

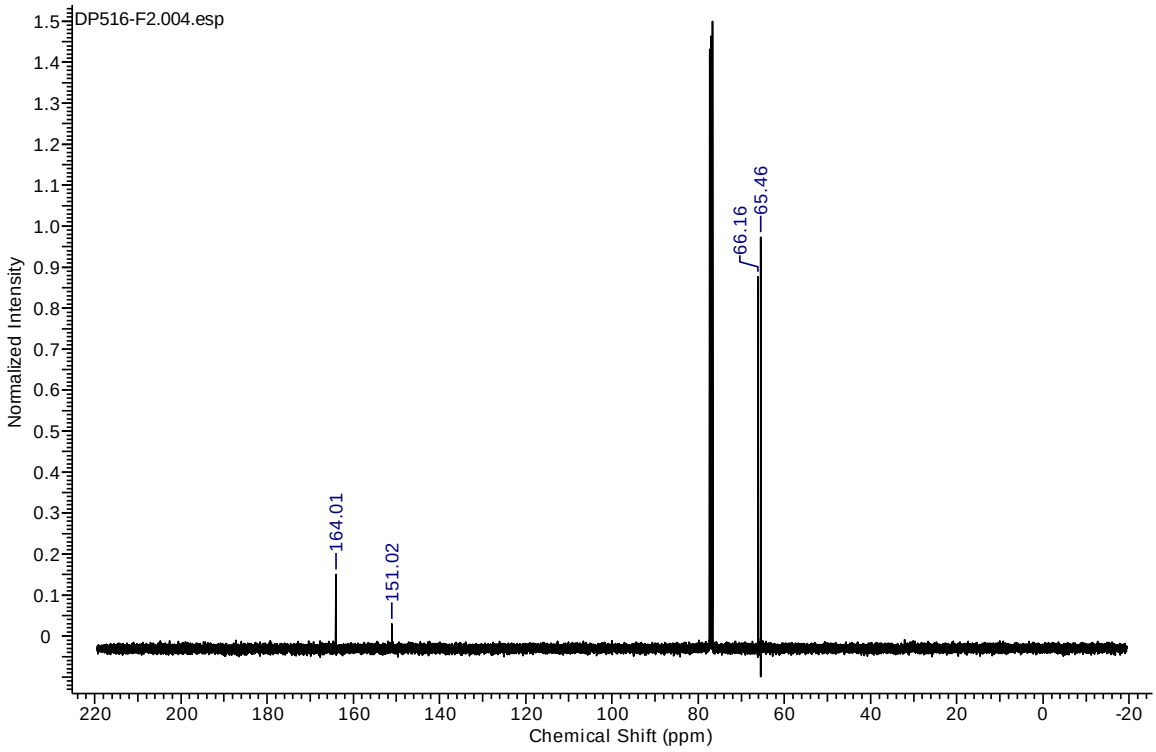

RI6-9-H.001.esp
Me
O
N
N—OMe
O
Normalized Intensity
1.99
2.02
2.04
3.03
3.00
Chemical Shift (ppm)

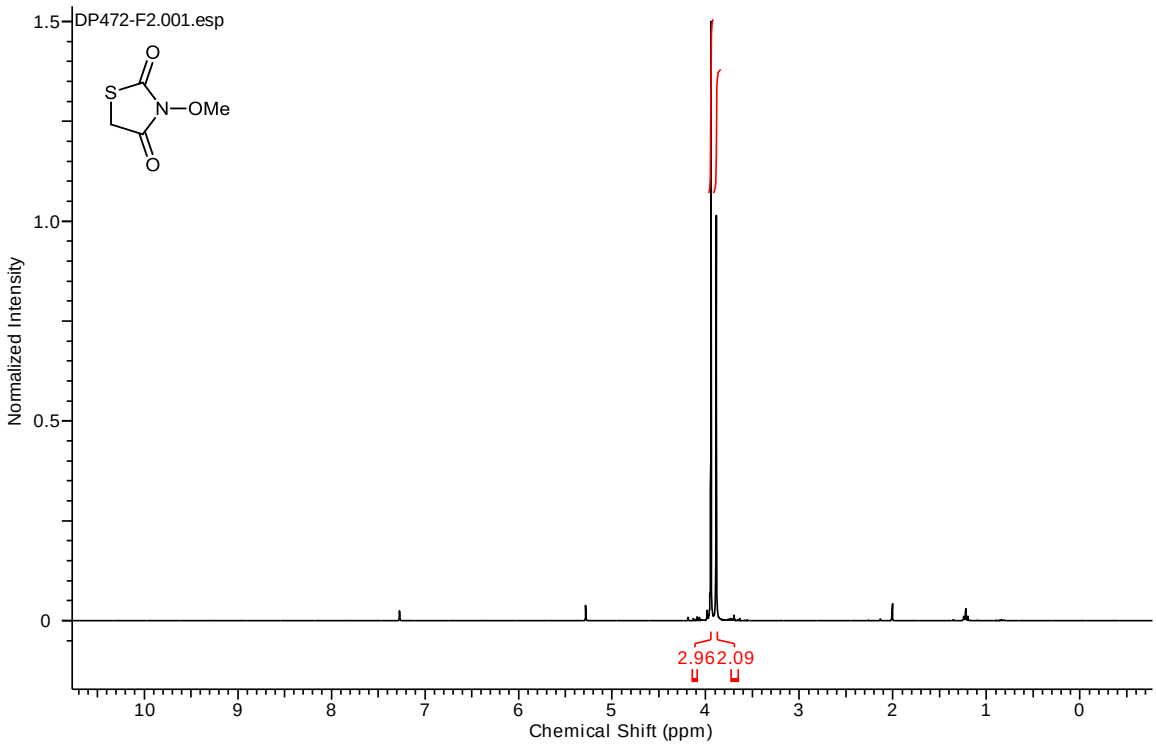

RI6-9-C.001.esp
Normalized Intensity
162.85
150.28
134.81
134.54
129.95
118.41
65.49
47.89
20.77
Chemical Shift (ppm)

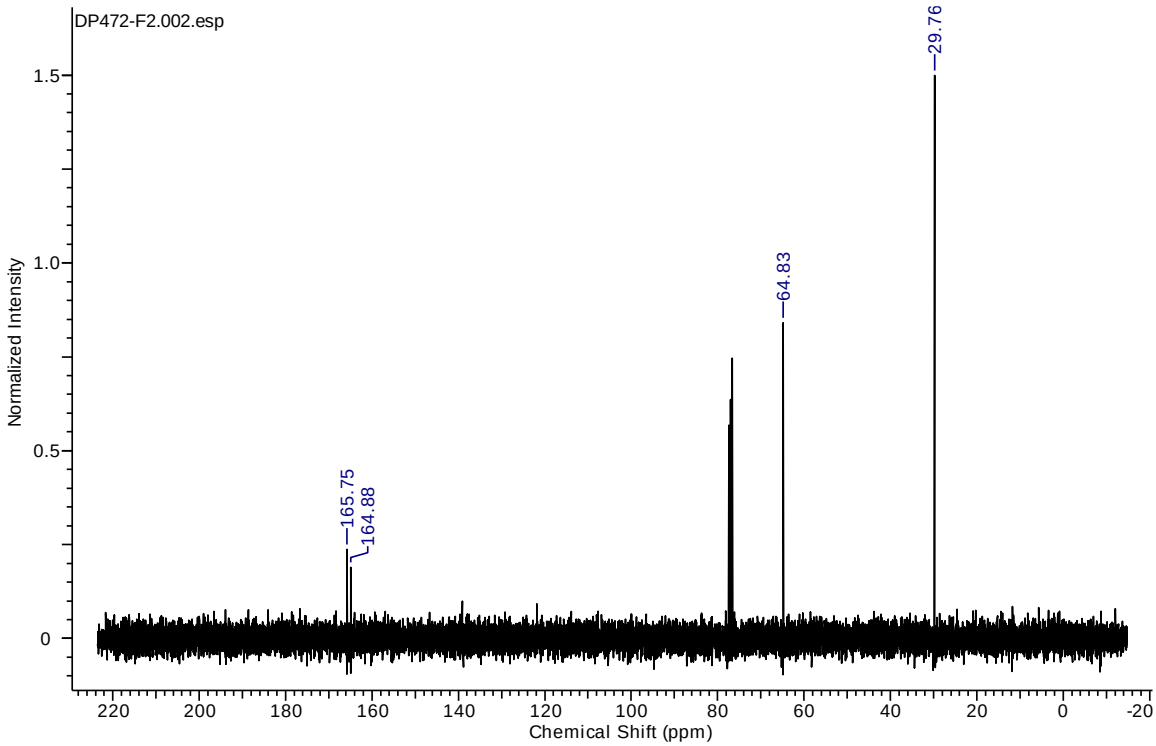

RI6-10-H.001.esp
MeO
O
N
N—OMe
O
Normalized Intensity
1.97 1.99
2.04 3.01 3.00
Chemical Shift (ppm)

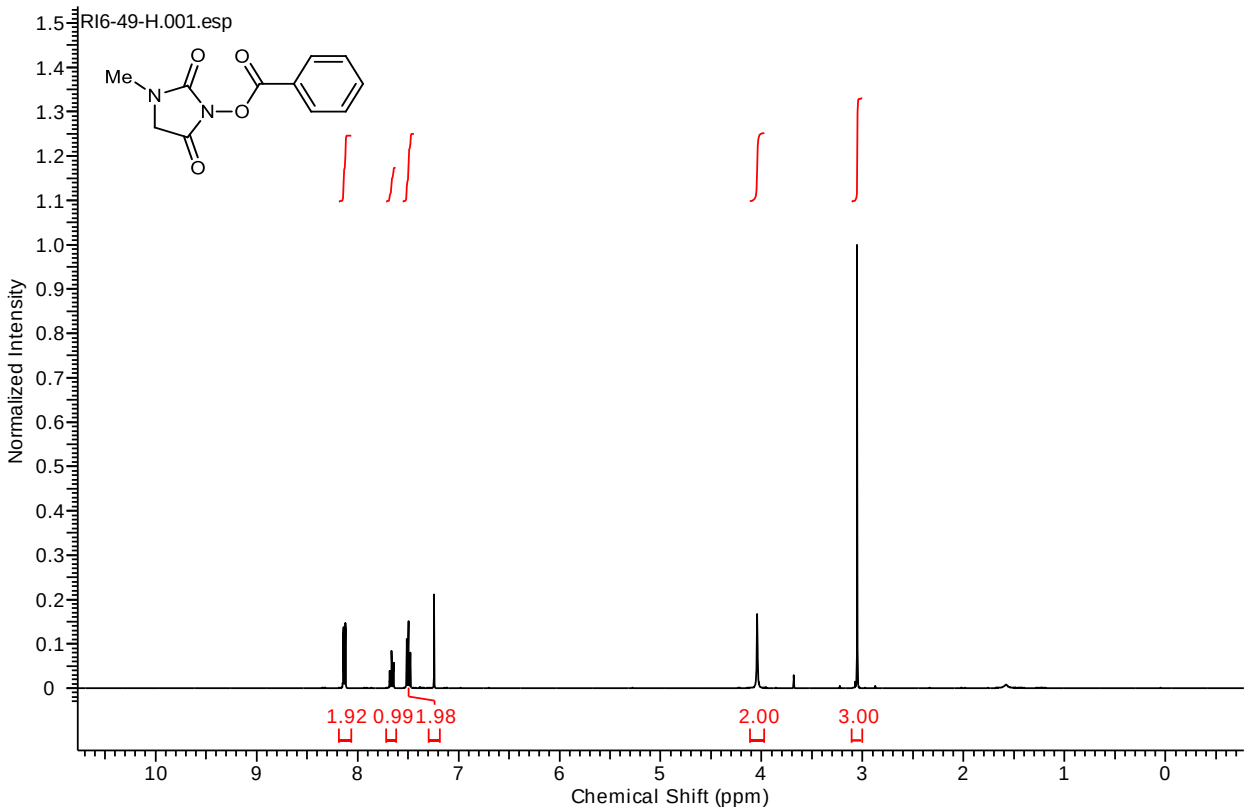

RI6-10-C.001.esp
Normalized Intensity
162.96
157.08
150.47
130.07
120.61
114.67
65.53
55.54
48.36
Chemical Shift (ppm)

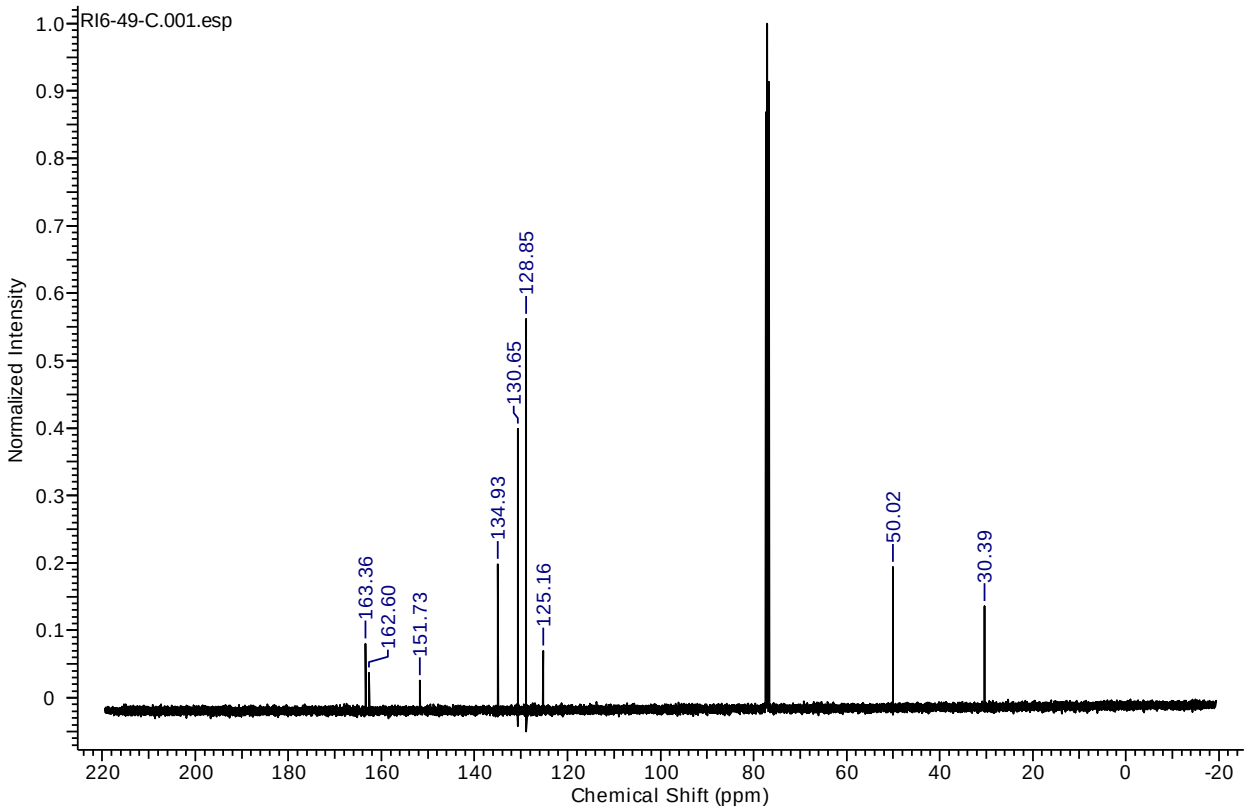

DP485-F1.001.esp
O
O
N—OMe
O
Normalized Intensity
1.5
1.0
0.5
0
2.00
2.99
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

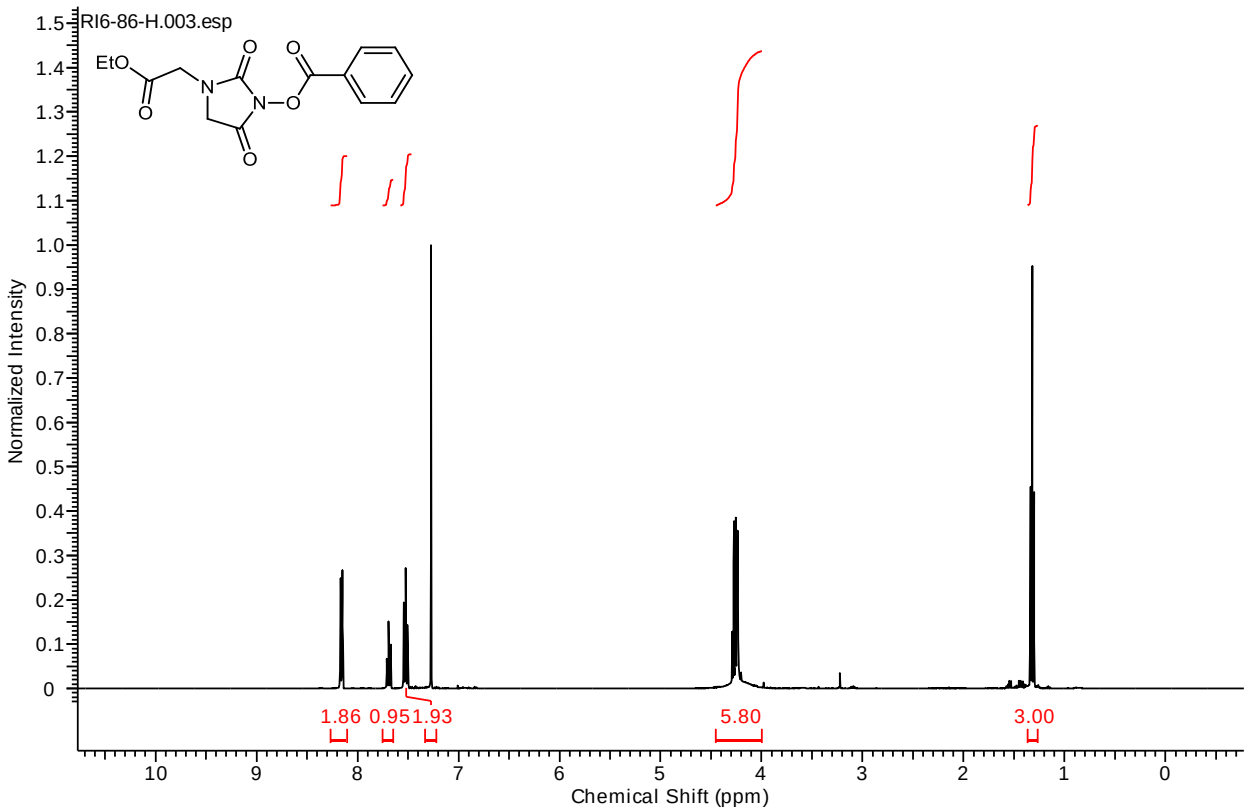

DP516-F2.004.esp
Normalized Intensity
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
164.01
151.02
66.16
65.46
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

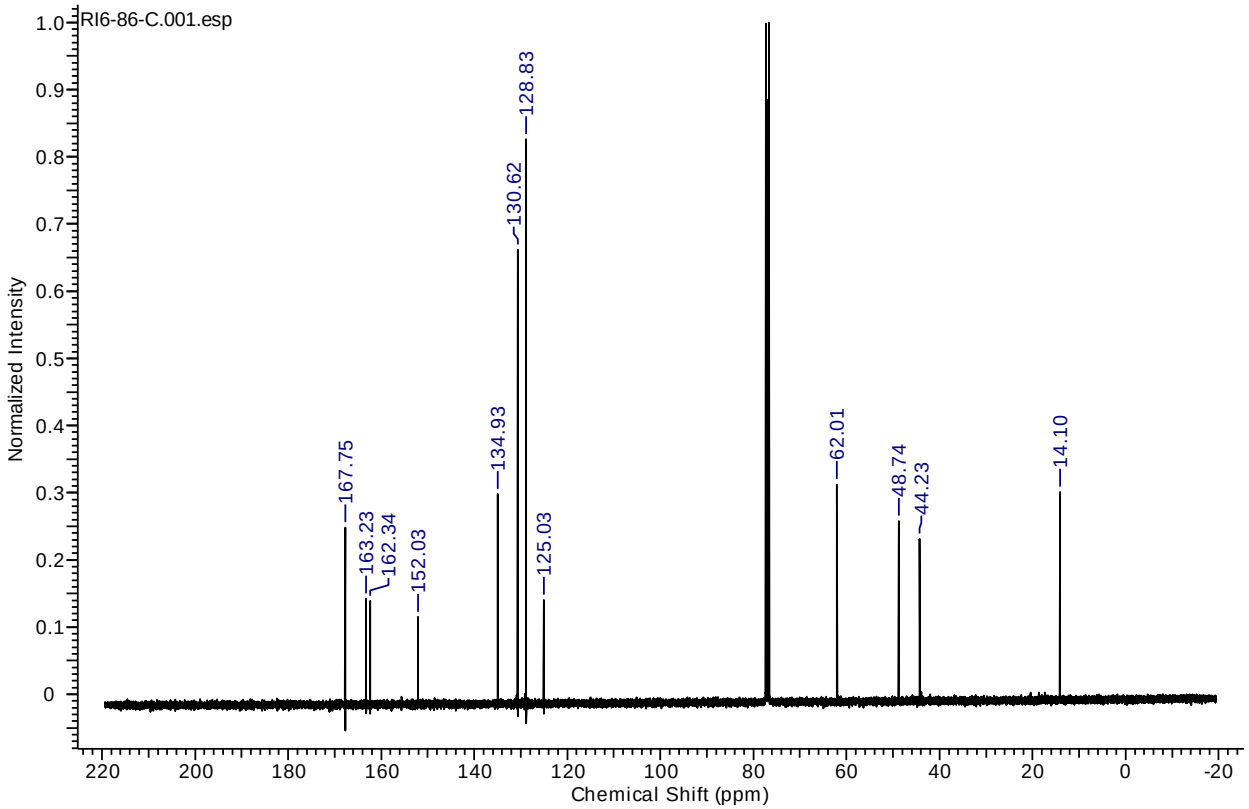

DP472-F2.001.esp
O
S
N—OMe
O
1.5
1.0
0.5
0
Normalized Intensity
2.96
2.09
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

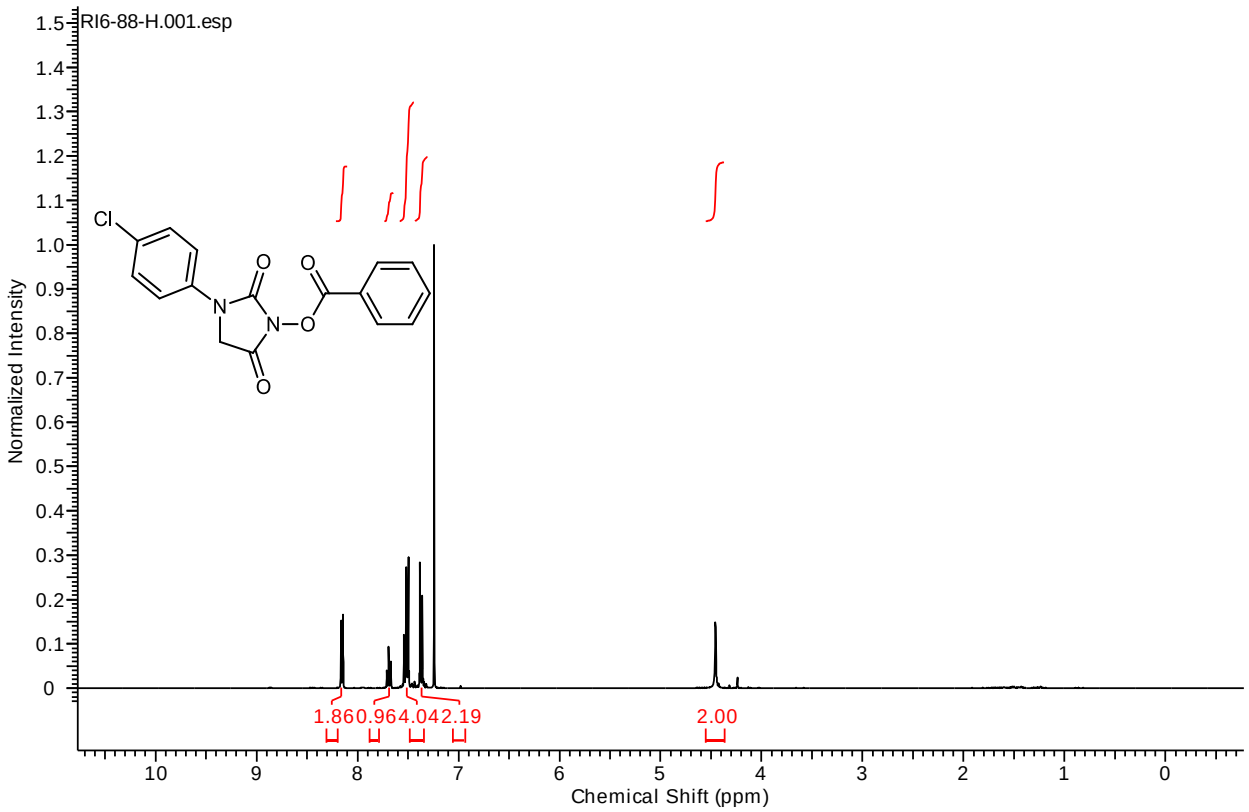

DP472-F2.002.esp
29.76
64.83
165.75
164.88
1.5
1.0
0.5
0
Normalized Intensity
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

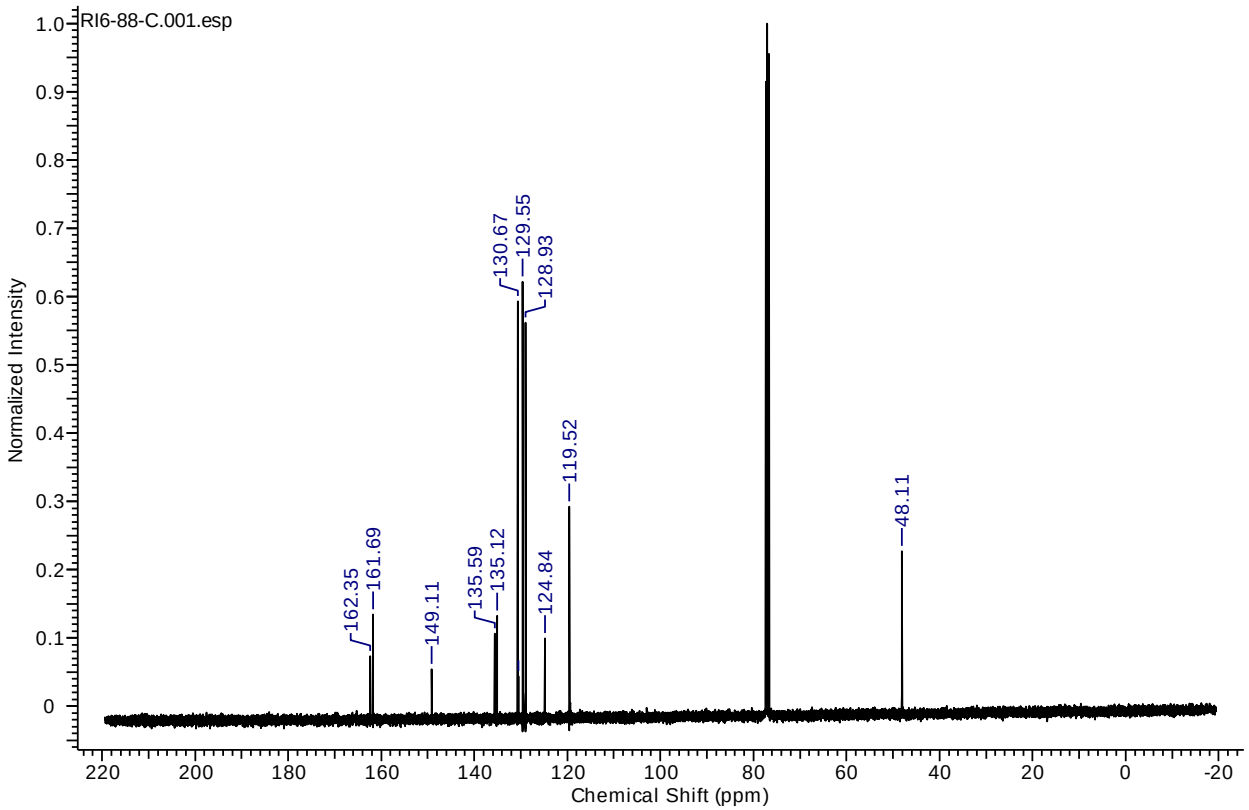

RI6-49-H.001.esp
Me
N
O
O
N
O
O
O
Normalized Intensity
1.92
0.99
1.98
2.00
3.00
Chemical Shift (ppm)

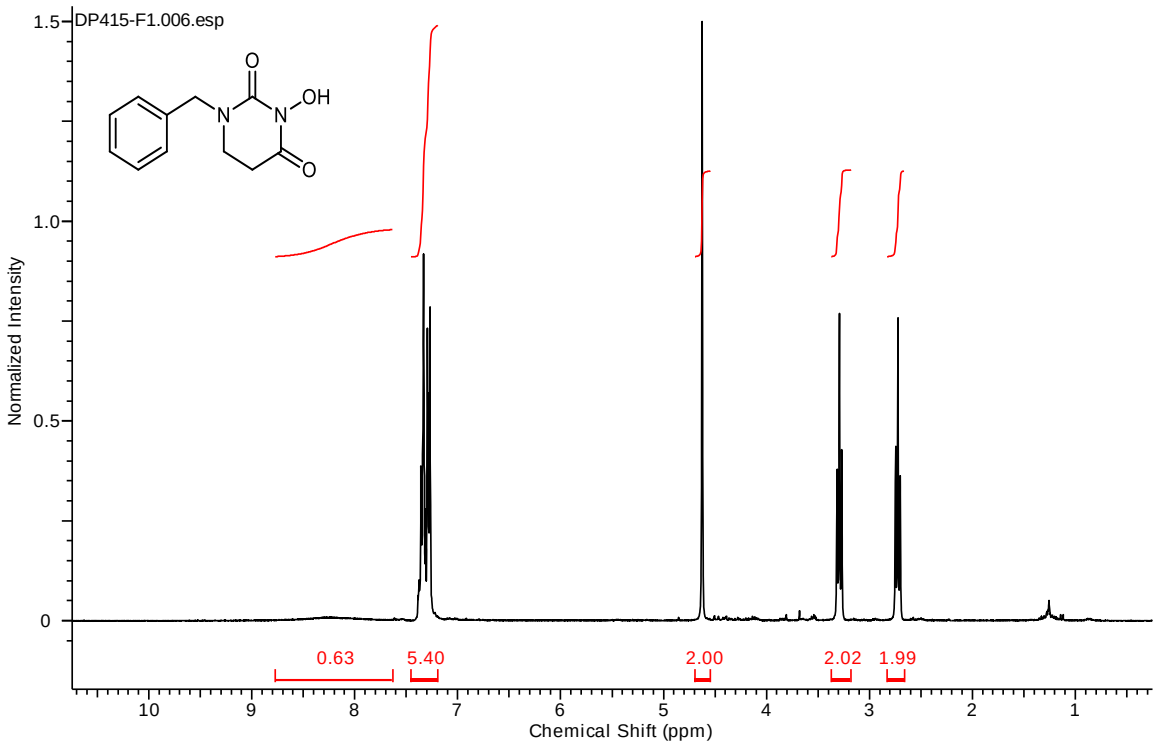

RI6-49-C.001.esp
Normalized Intensity
163.36
162.60
151.73
134.93
130.65
128.85
125.16
50.02
30.39
Chemical Shift (ppm)

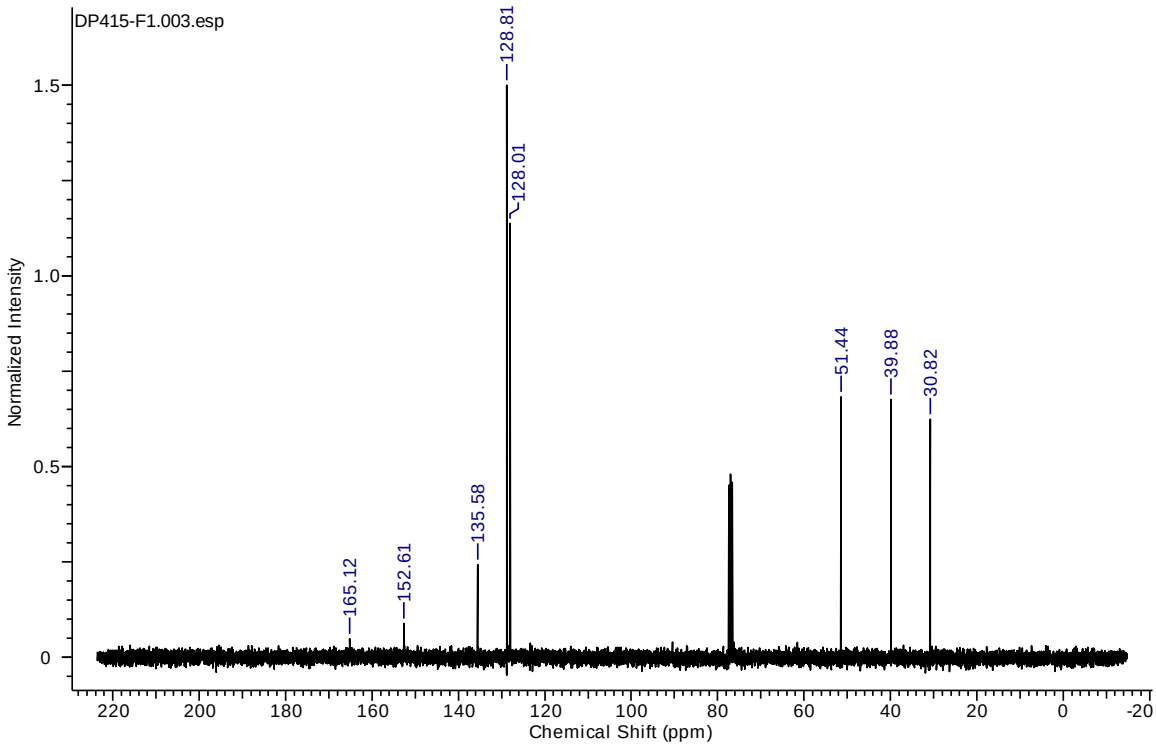

RI6-86-H.003.esp
EtO
O
O
N
O
N
O
O
O
Normalized Intensity
1.86
0.95
1.93
5.80
3.00
Chemical Shift (ppm)

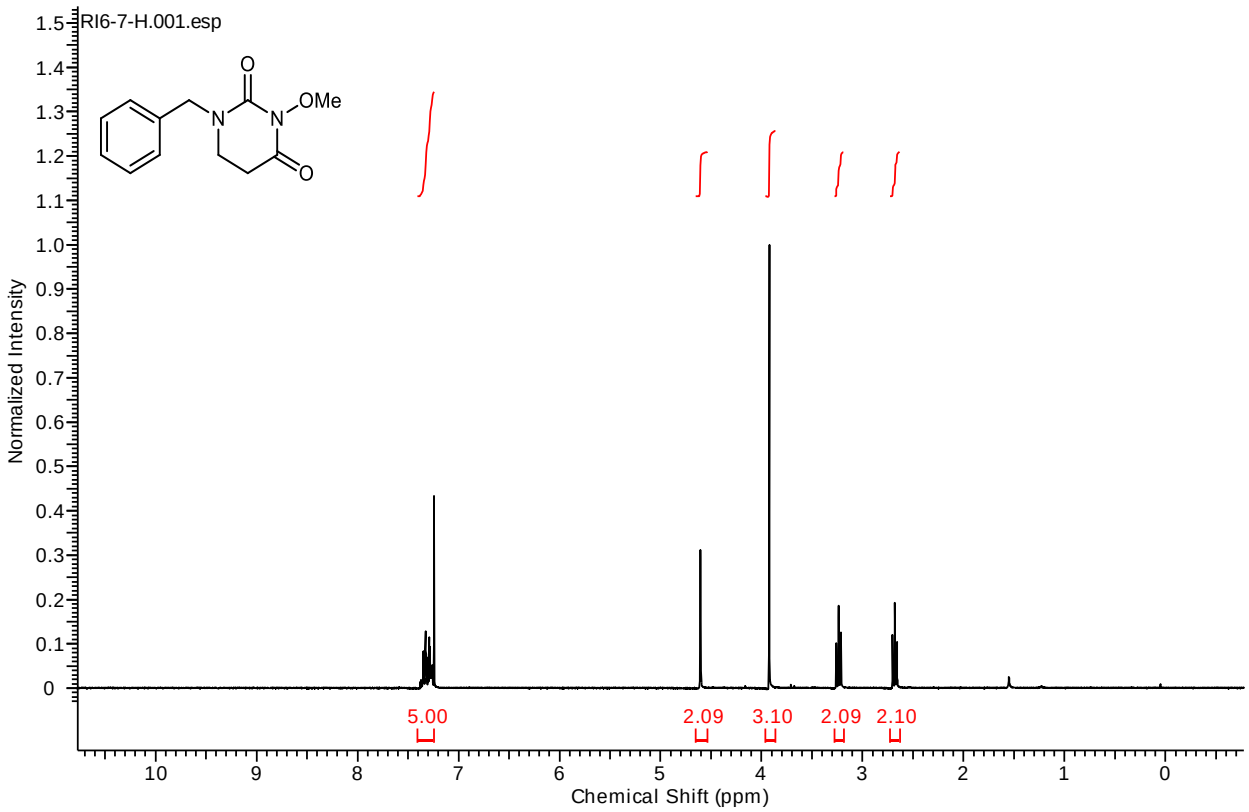

RI6-86-C.001.esp
Normalized Intensity
167.75
163.23
162.34
152.03
134.93
130.62
128.83
125.03
62.01
48.74
44.23
14.10
Chemical Shift (ppm)

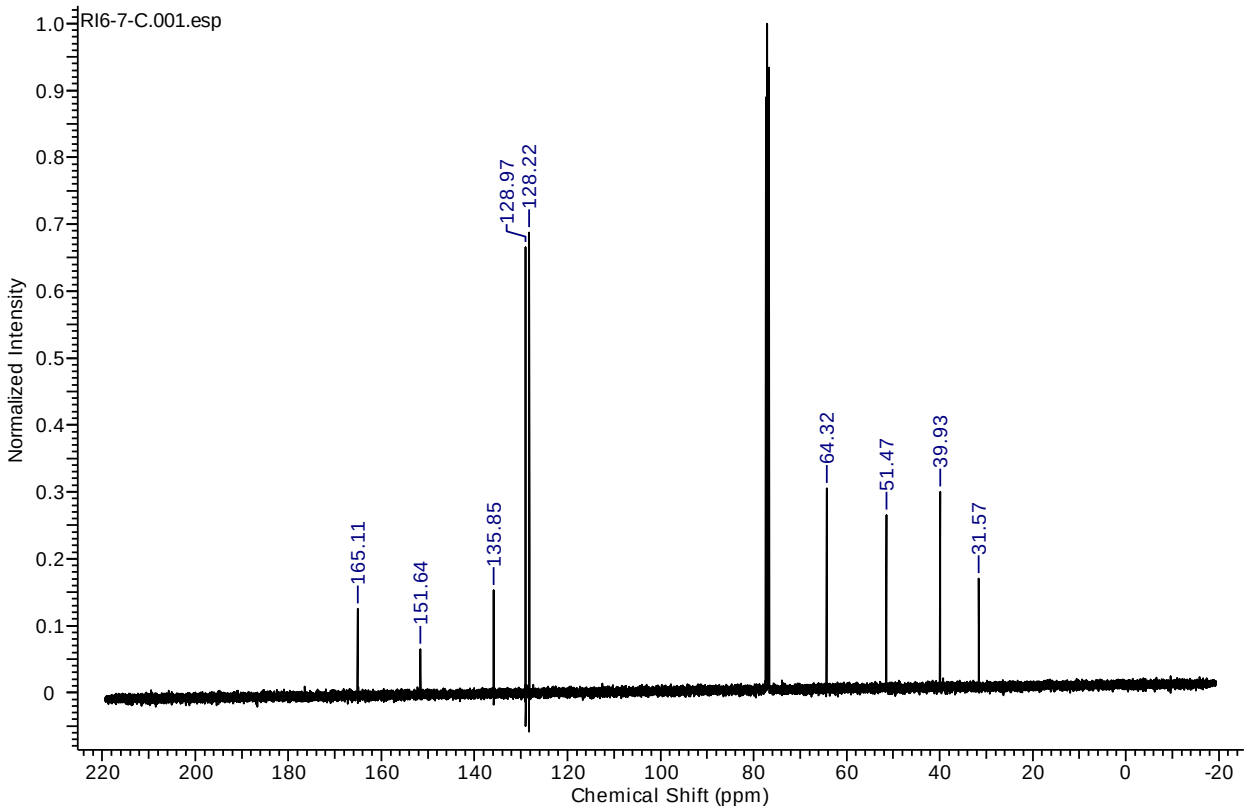

RI6-88-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.86
0.96
4.04
2.19
2.00
Cl
N
O
N
O
O
O

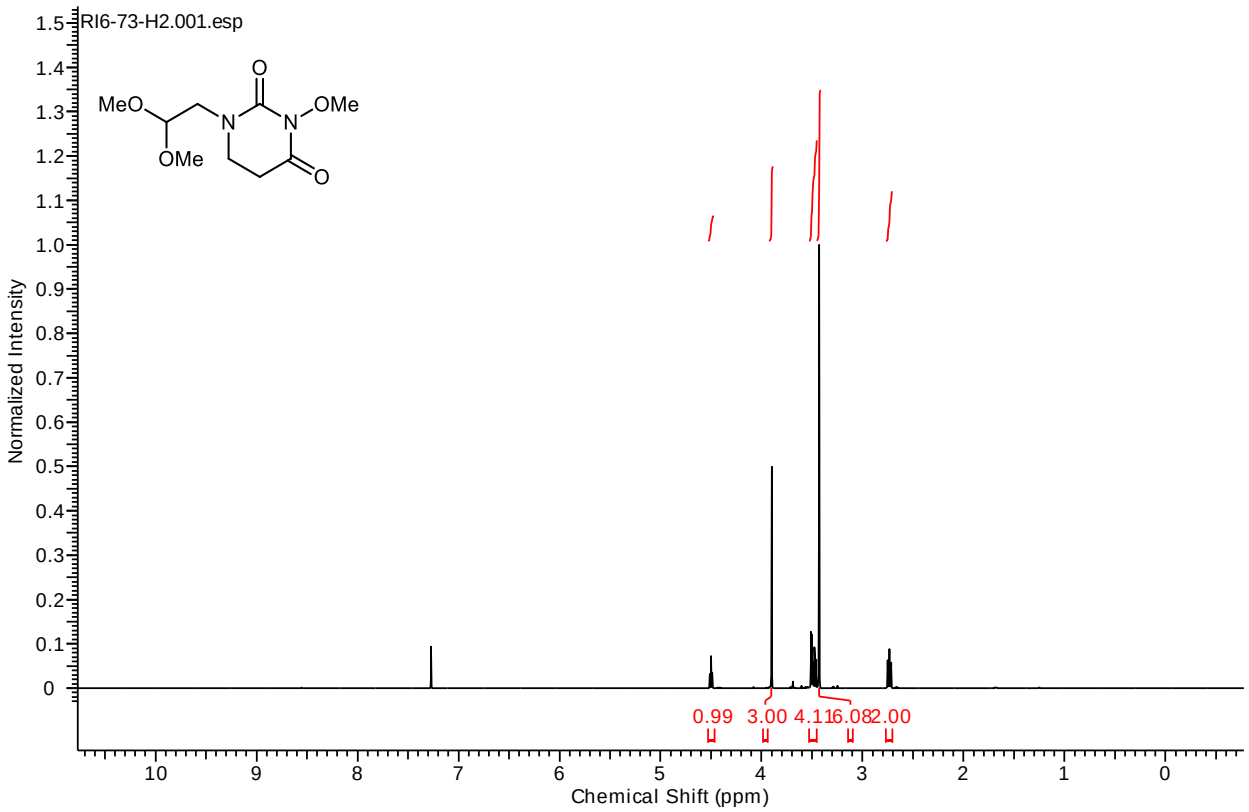

RI6-88-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
162.35
161.69
149.11
135.59
135.12
130.67
129.55
128.93
124.84
119.52
48.11

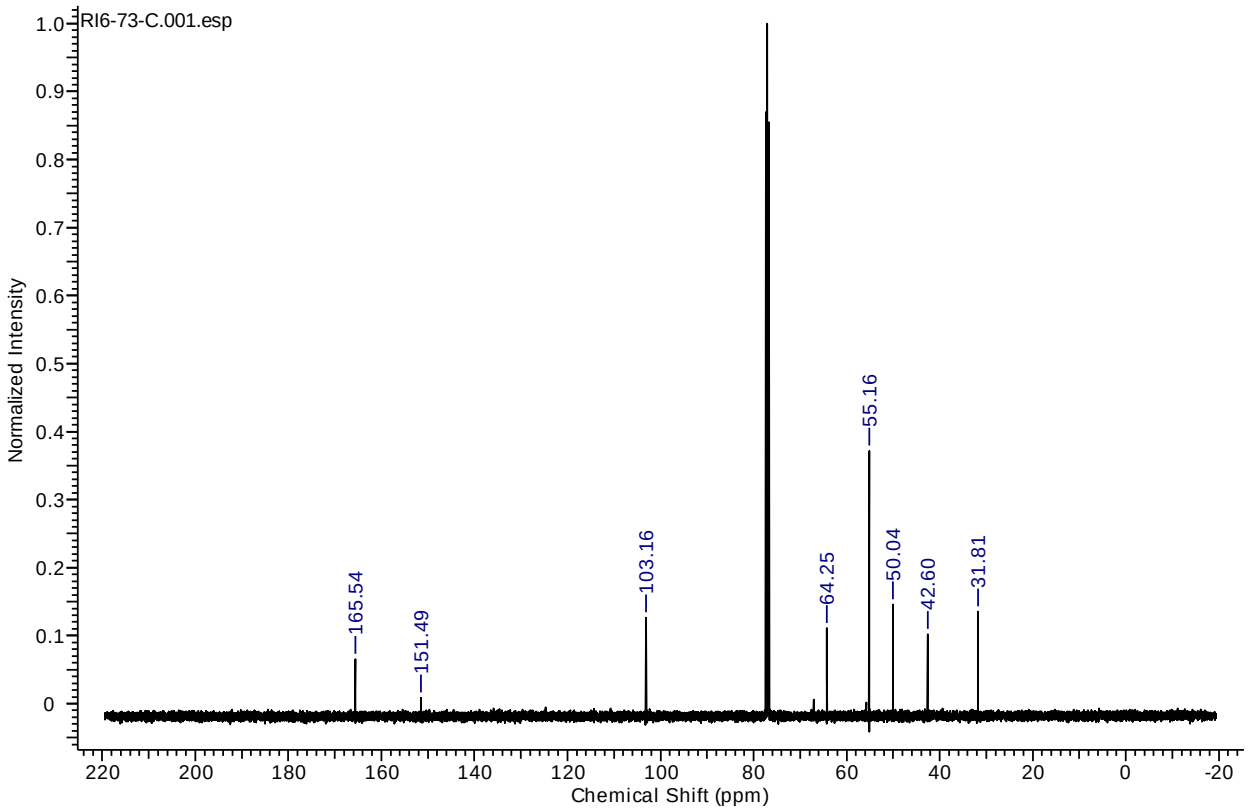

DP415-F1.006.esp
O
OH
N
N
O
Normalized Intensity
1.5
1.0
0.5
0
0.63
5.40
2.00
2.02
1.99
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

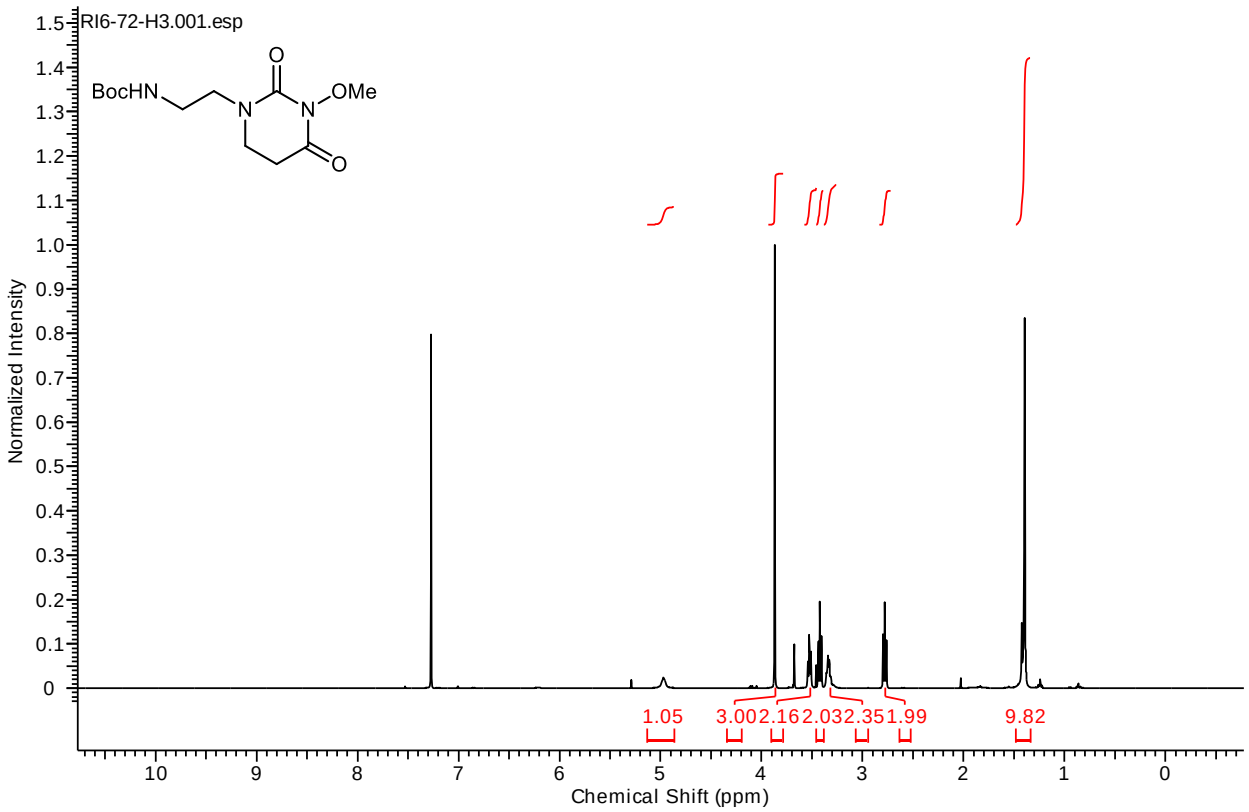

DP415-F1.003.esp
128.81
128.01
51.44
39.88
30.82
165.12
152.61
135.58
Normalized Intensity
1.5
1.0
0.5
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

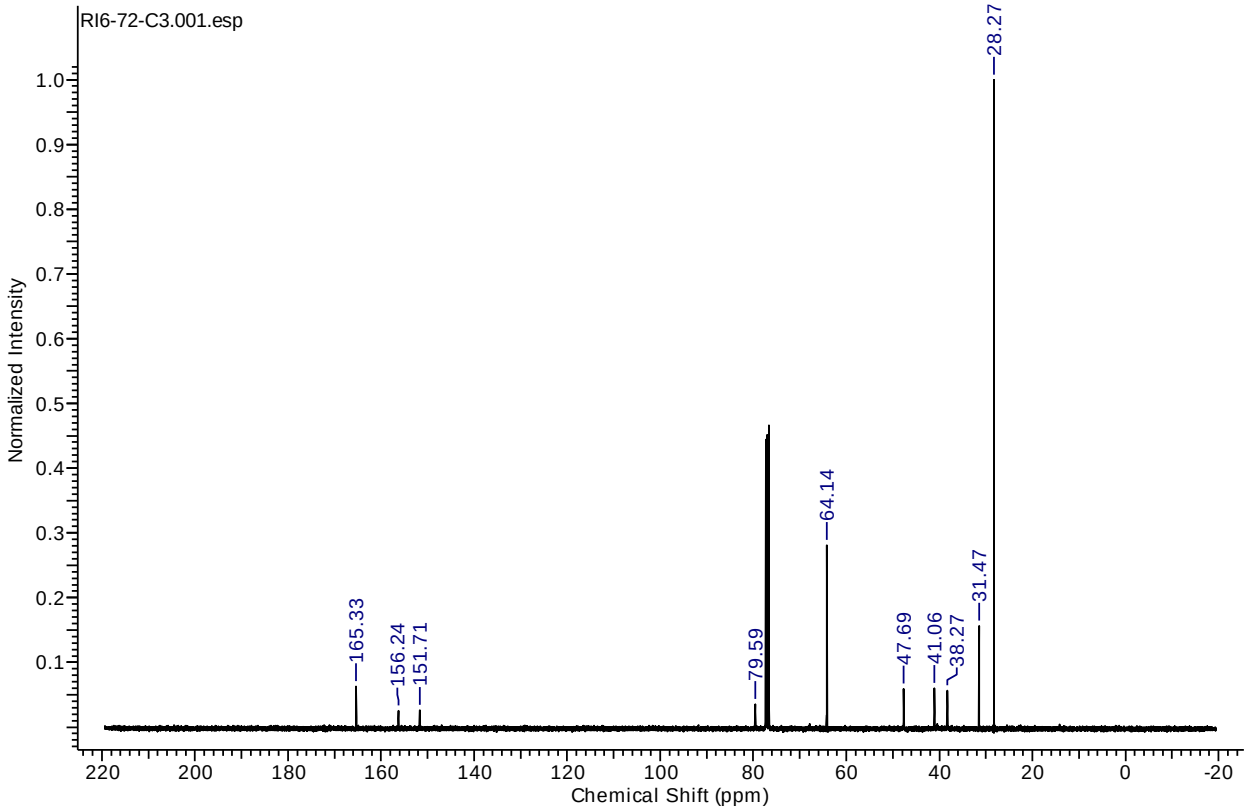

RI6-7-H.001.esp
O
N
N
OMe
O
Normalized Intensity
5.00
2.09
3.10
2.09
2.10
Chemical Shift (ppm)

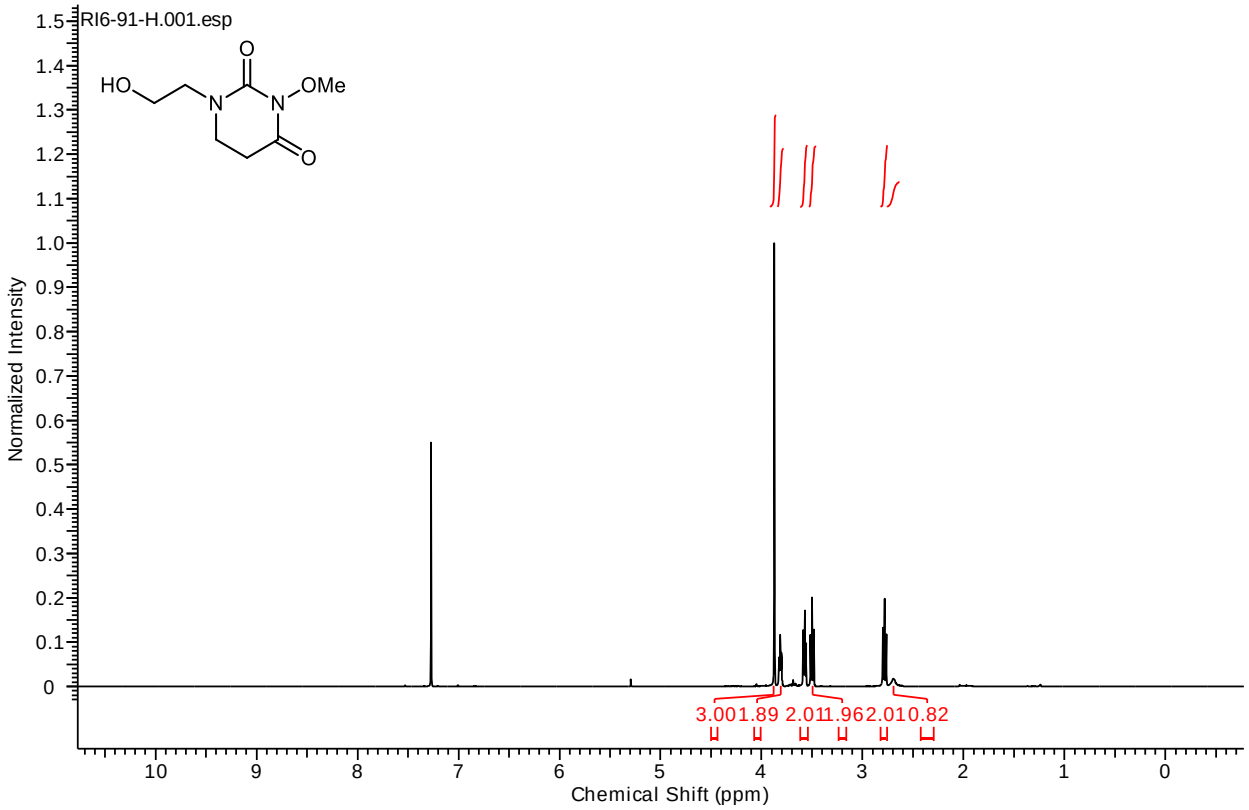

RI6-7-C.001.esp
165.11
151.64
135.85
128.97
128.22
64.32
51.47
39.93
31.57
Normalized Intensity
Chemical Shift (ppm)

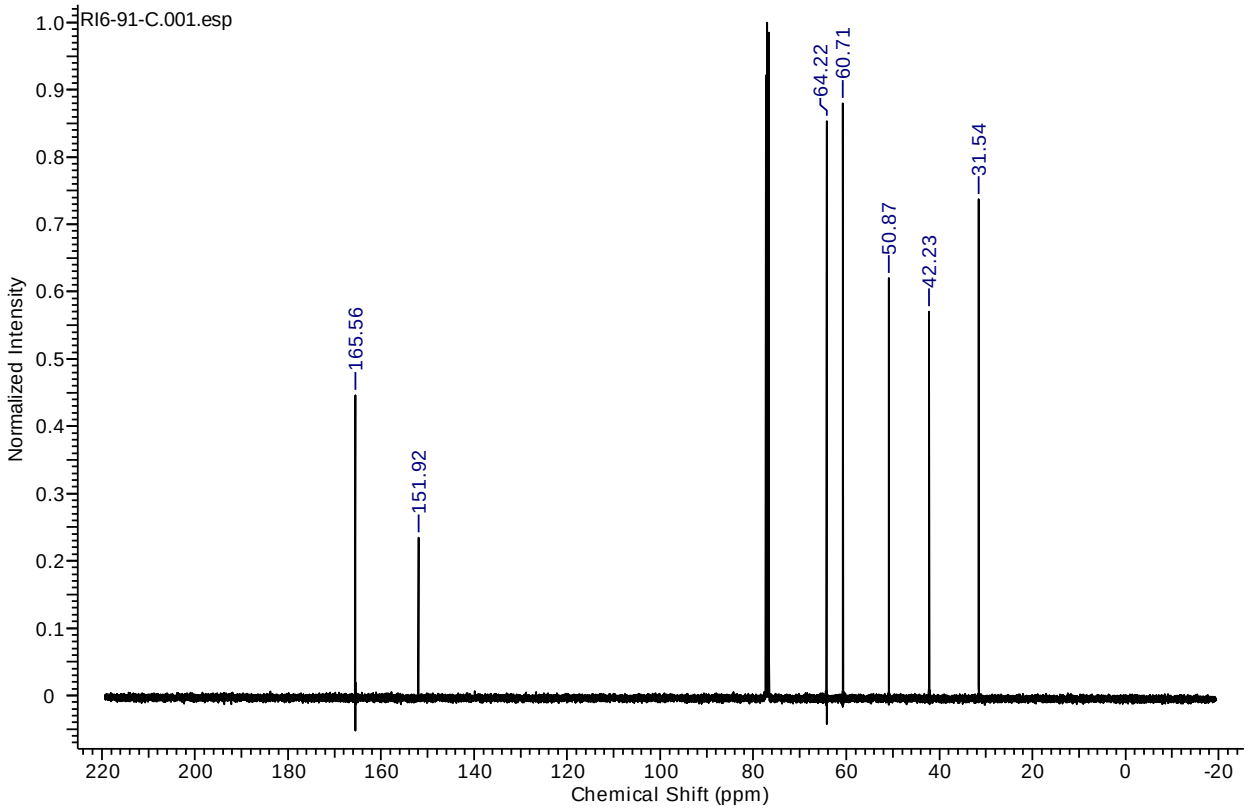

RI6-73-H2.001.esp
MeO
OMe
N
N
OMe
OMe
O
O
Normalized Intensity
0.99
3.00
4.11
6.08
2.00
Chemical Shift (ppm)

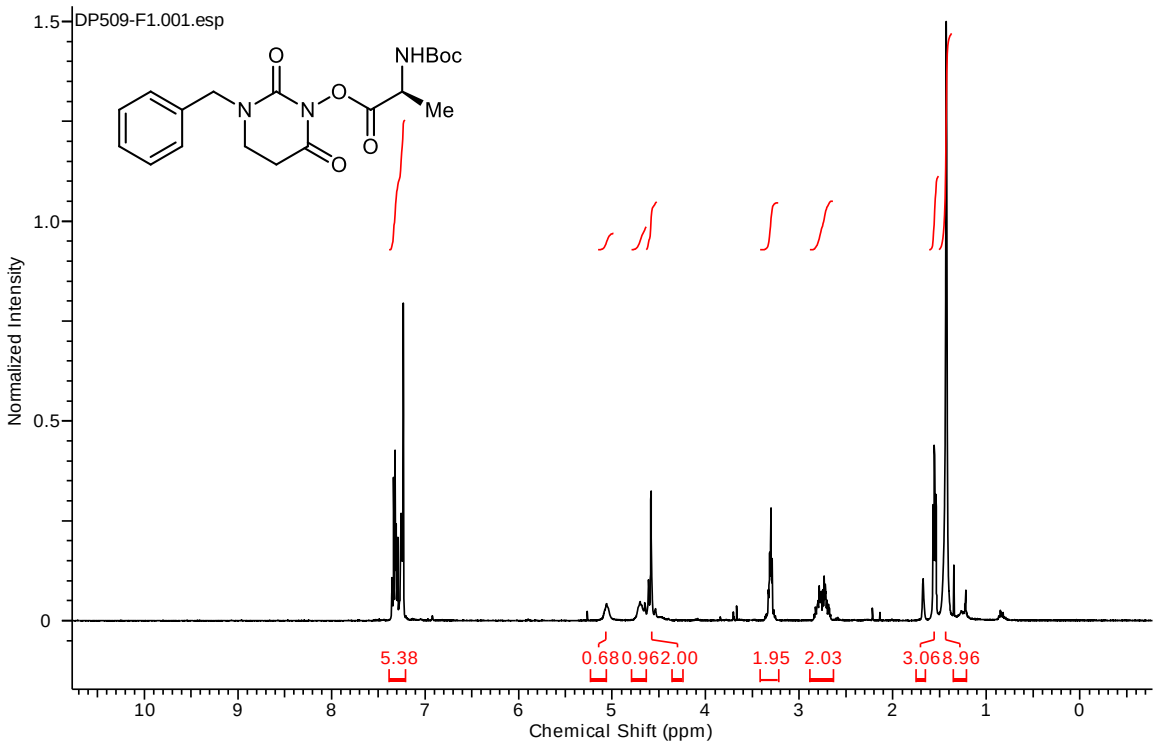

RI6-73-C.001.esp
Normalized Intensity
165.54
151.49
103.16
64.25
55.16
50.04
42.60
31.81
Chemical Shift (ppm)

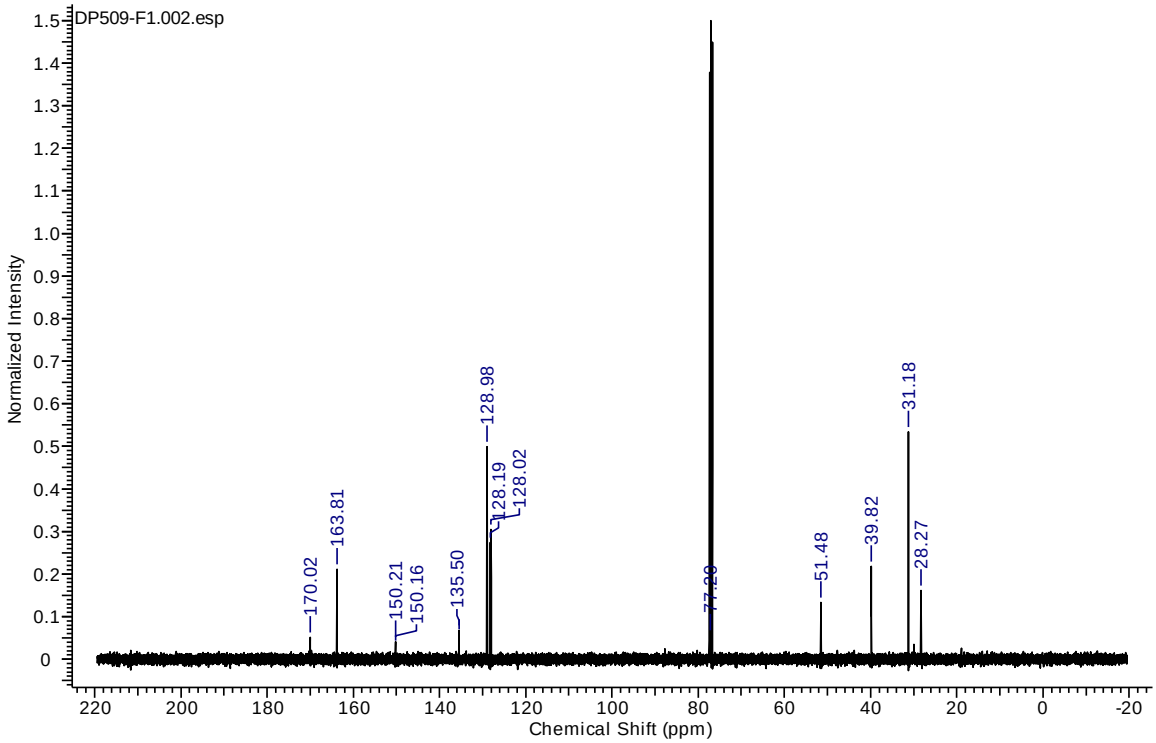

RI6-72-H3.001.esp
BocHN
N
N
OMe
O
O
O
Normalized Intensity
1.05
3.00
2.16
2.03
2.35
1.99
9.82
Chemical Shift (ppm)

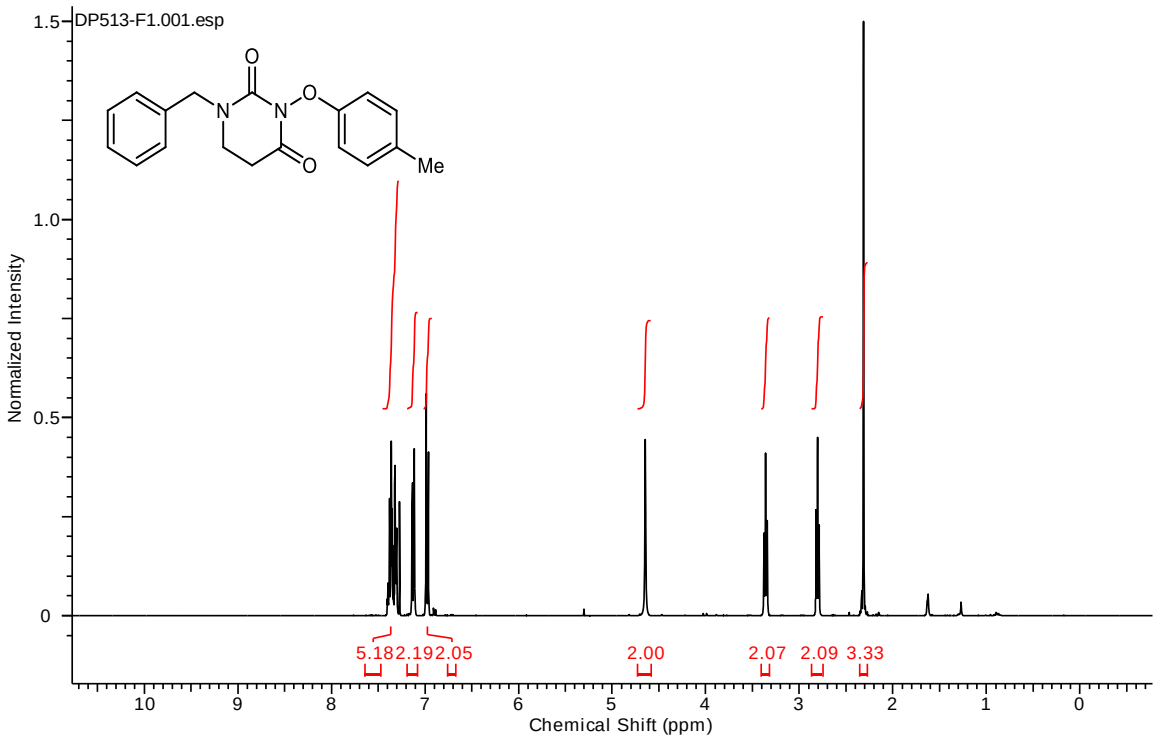

RI6-72-C3.001.esp
28.27
64.14
165.33
156.24
151.71
79.59
47.69
41.06
38.27
31.47
Normalized Intensity
Chemical Shift (ppm)

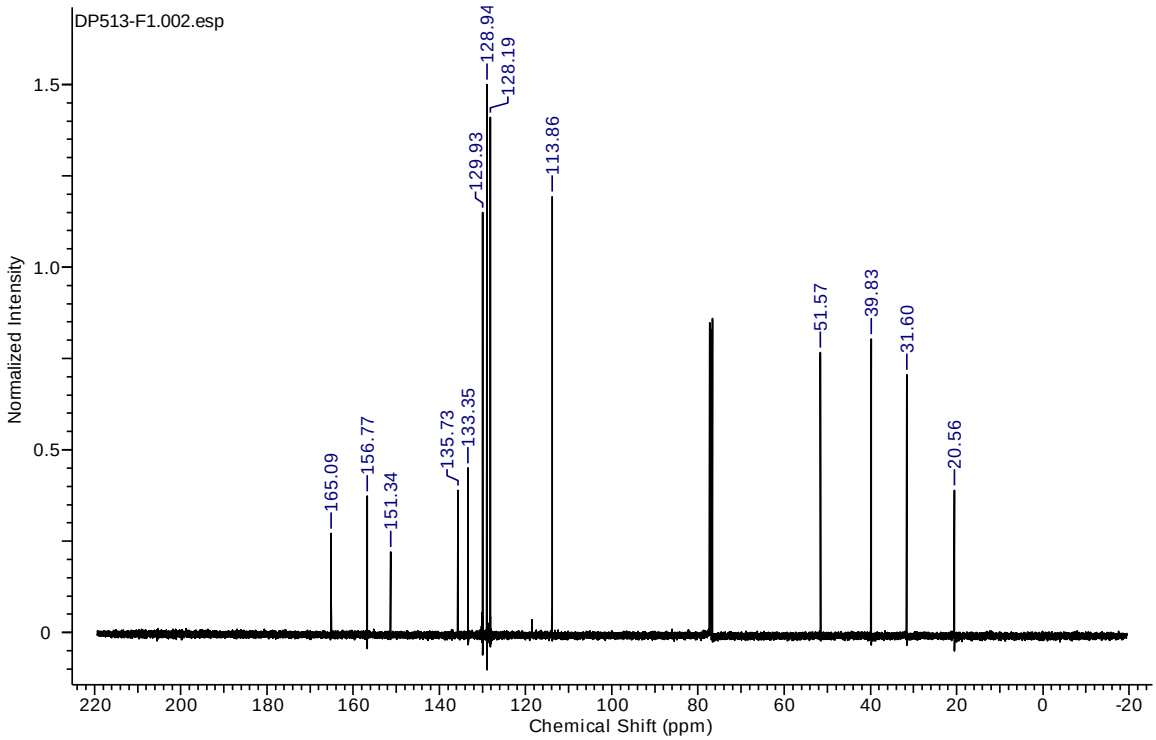

RI6-91-H.001.esp
HO
N
O
N
OMe
O
Normalized Intensity
3.00 1.89 2.01 1.96 2.01 0.82
Chemical Shift (ppm)

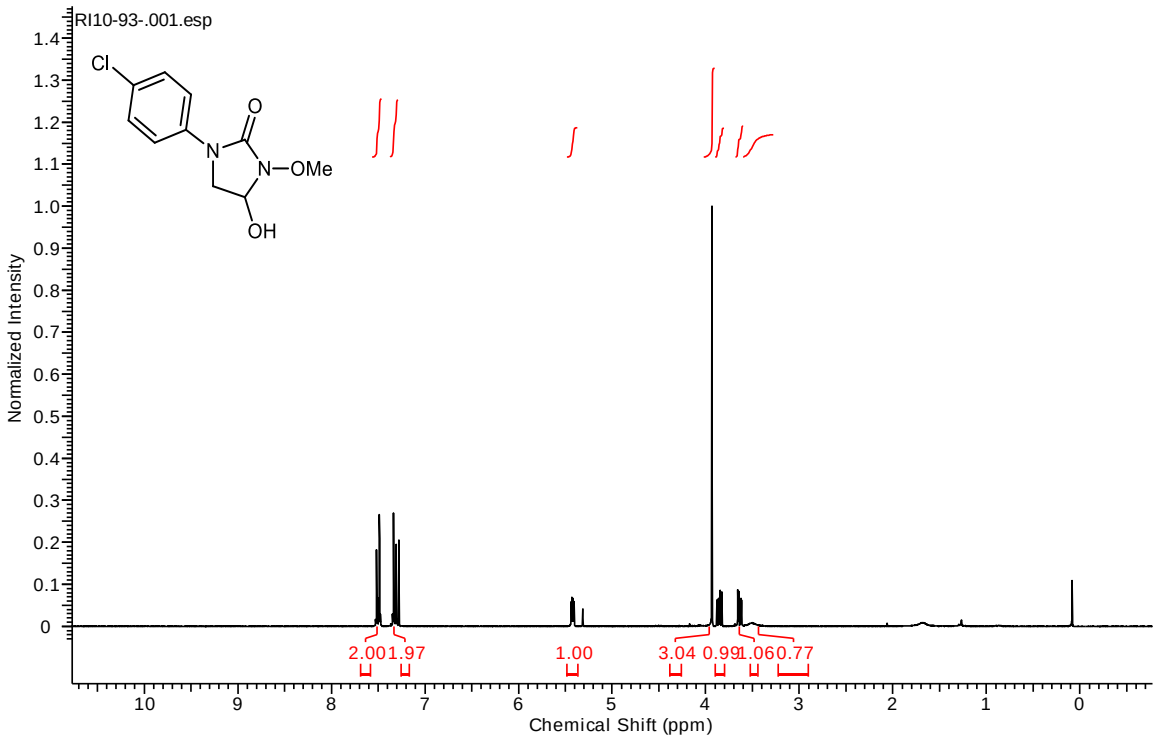

RI6-91-C.001.esp
165.56
151.92
64.22
60.71
50.87
42.23
31.54
Normalized Intensity
Chemical Shift (ppm)

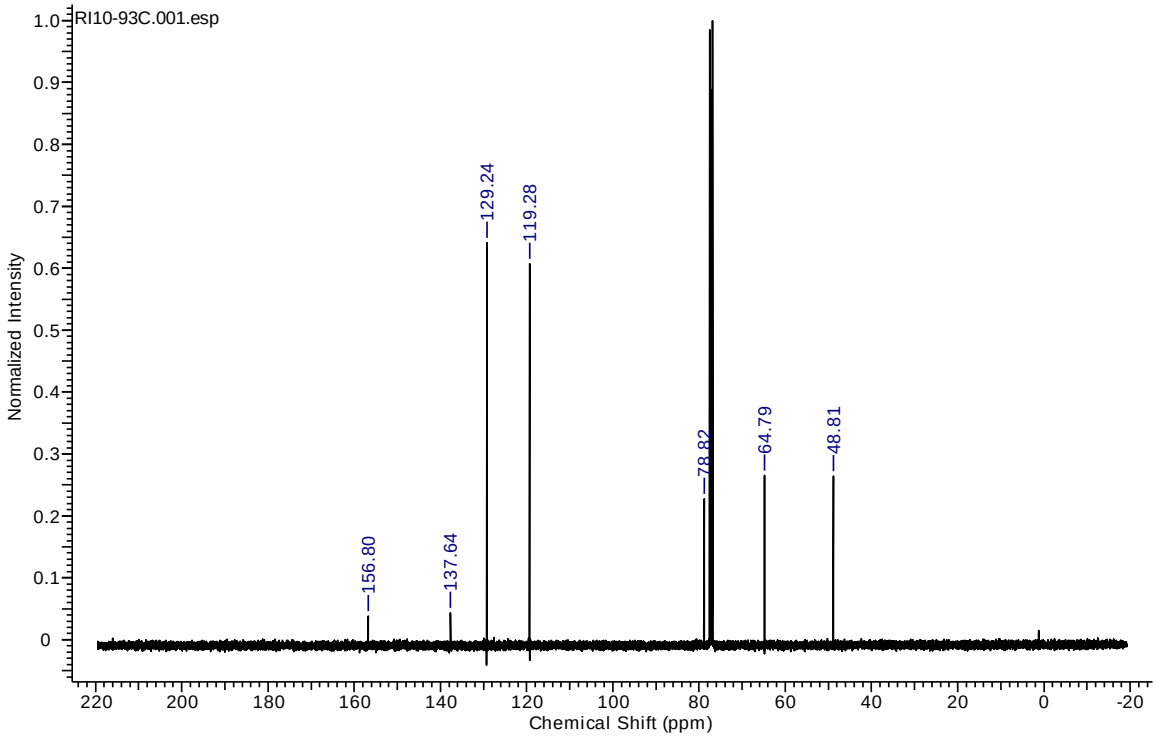

DP509-F1.001.esp
NHBoc
Me
Normalized Intensity
Chemical Shift (ppm)
5.38
0.68
0.96
2.00
1.95
2.03
3.06
8.96

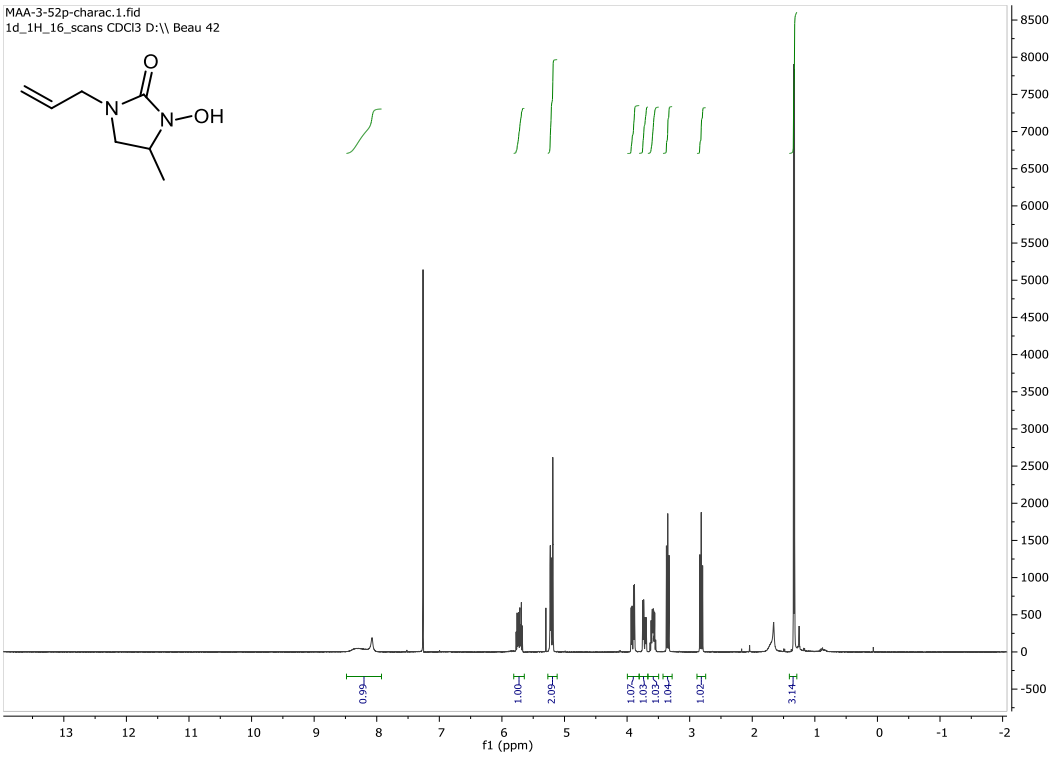

DP509-F1.002.esp
Normalized Intensity
Chemical Shift (ppm)
170.02
163.81
150.21
150.16
135.50
128.98
128.19
128.02
77.29
51.48
39.82
31.18
28.27

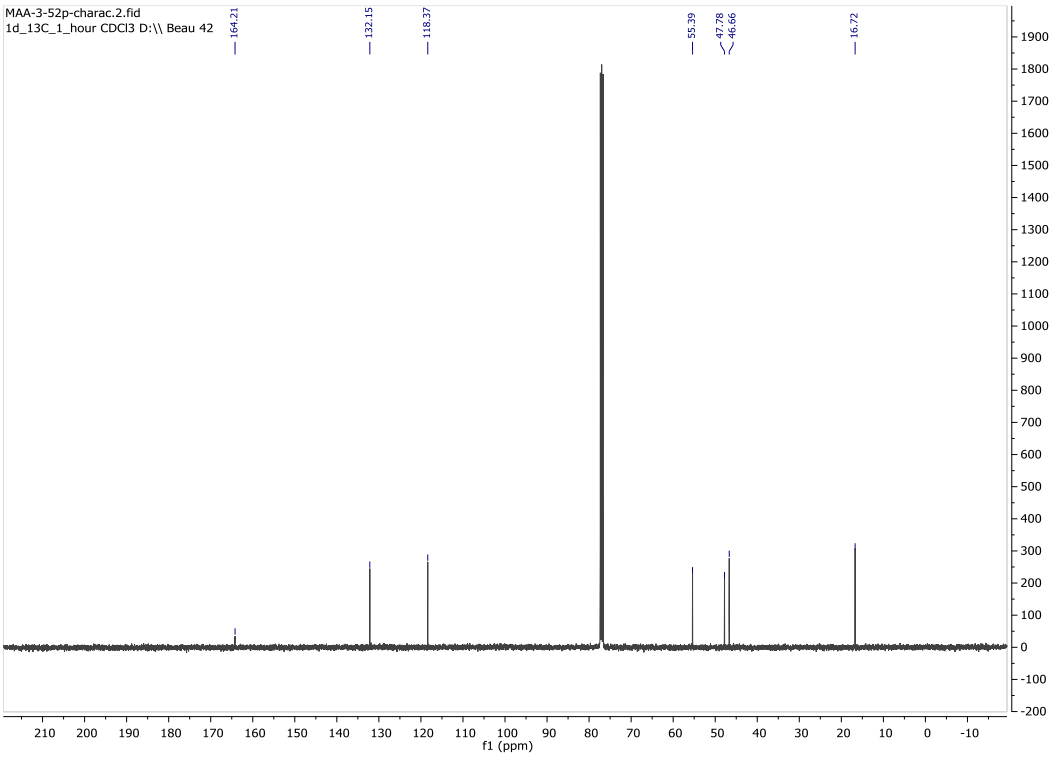

DP513-F1.001.esp
Normalized Intensity
Chemical Shift (ppm)
5.18
2.19
2.05
2.00
2.07
2.09
3.33
Me

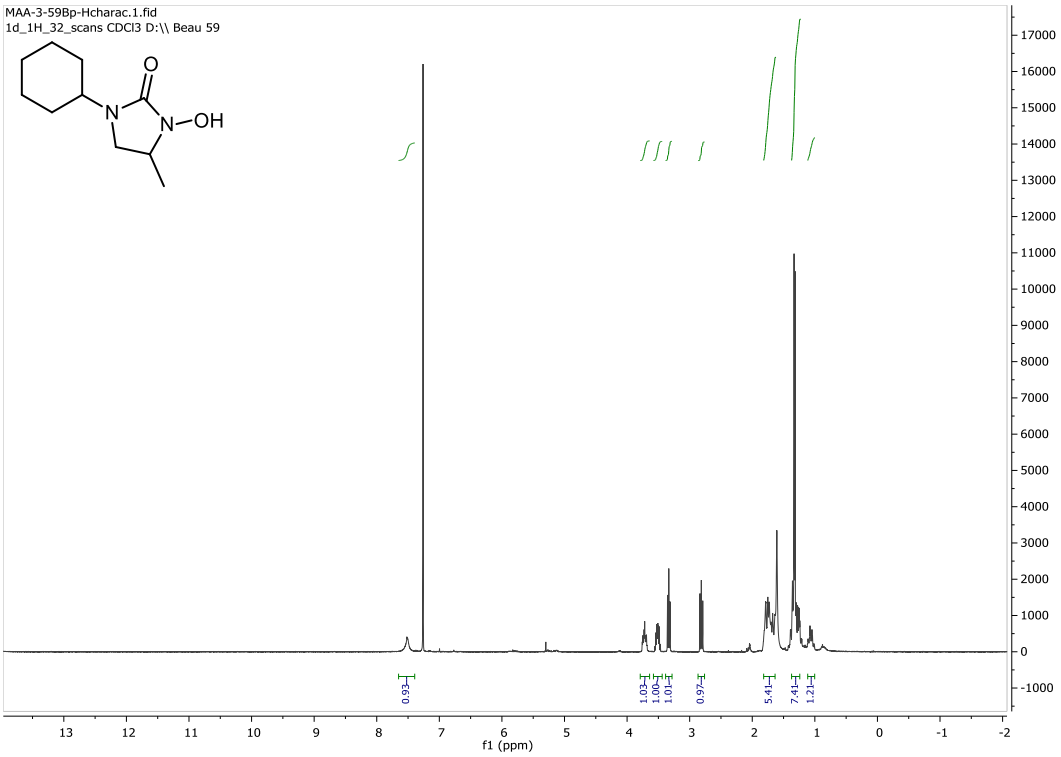

DP513-F1.002.esp
Normalized Intensity
Chemical Shift (ppm)
165.09
156.77
151.34
135.73
133.35
129.93
128.94
128.19
113.86
51.57
39.83
31.60
20.56

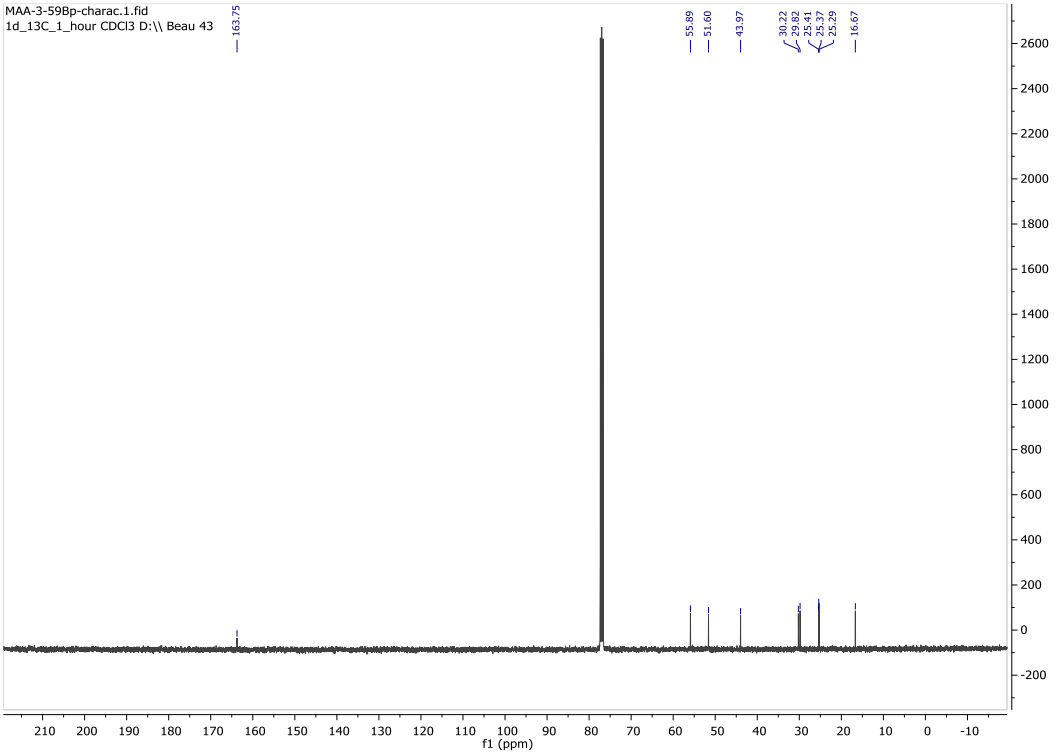

RI10-93-.001.esp
Cl
O
N
N—OMe
OH
Normalized Intensity
2.00 1.97
1.00
3.04 0.99 1.06 0.77
Chemical Shift (ppm)

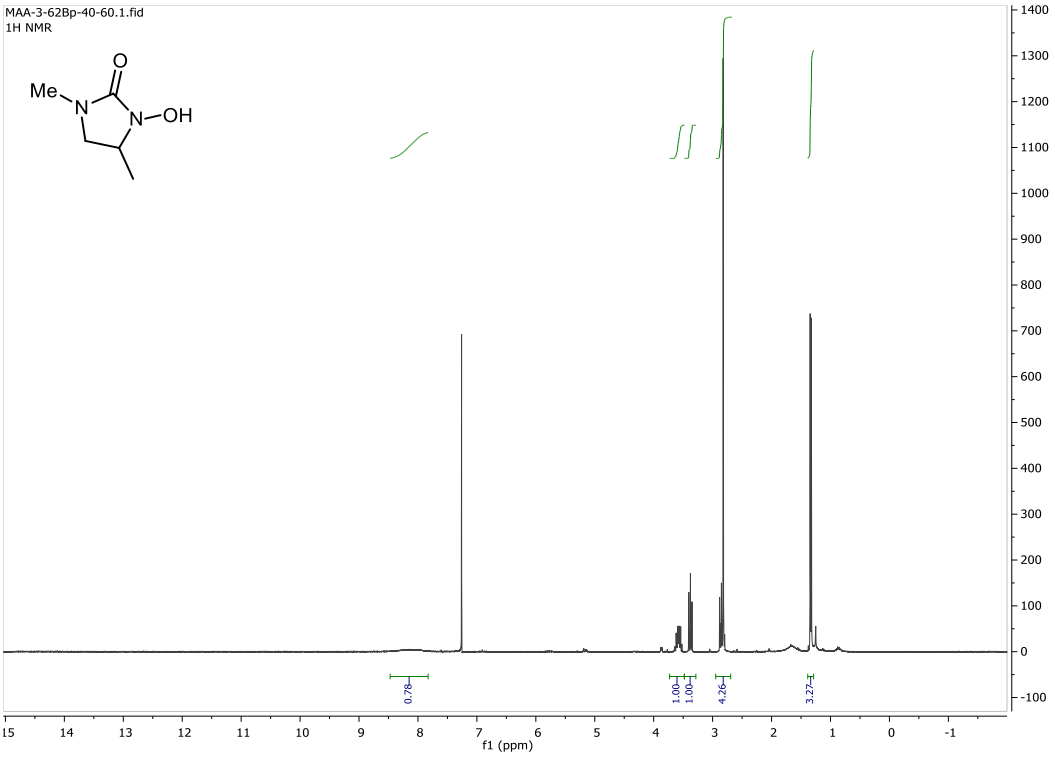

RI10-93C.001.esp
Normalized Intensity
156.80
137.64
129.24
119.28
78.82
64.79
48.81
Chemical Shift (ppm)

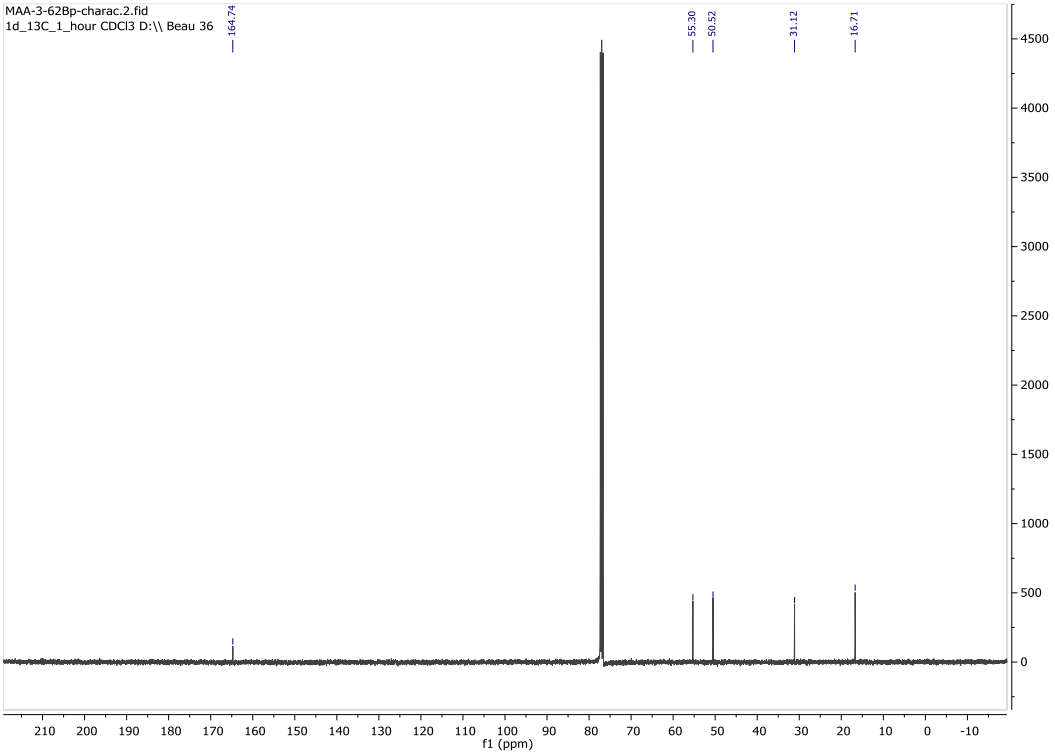

MAA-3-52p-charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 42
O
N
N
OH
0.99
1.00
2.09
1.07
1.03
1.03
1.04
1.02
3.14
f1 (ppm)

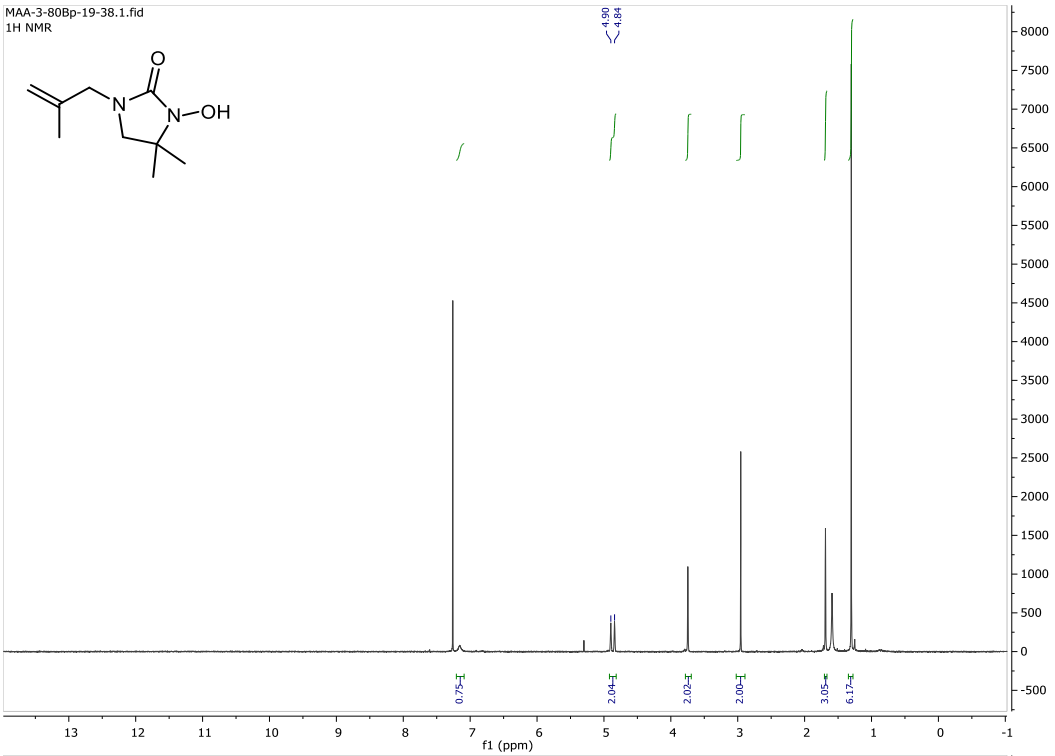

MAA-3-52p-charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 42
164.21
132.15
118.37
55.39
47.78
46.66
16.72
f1 (ppm)

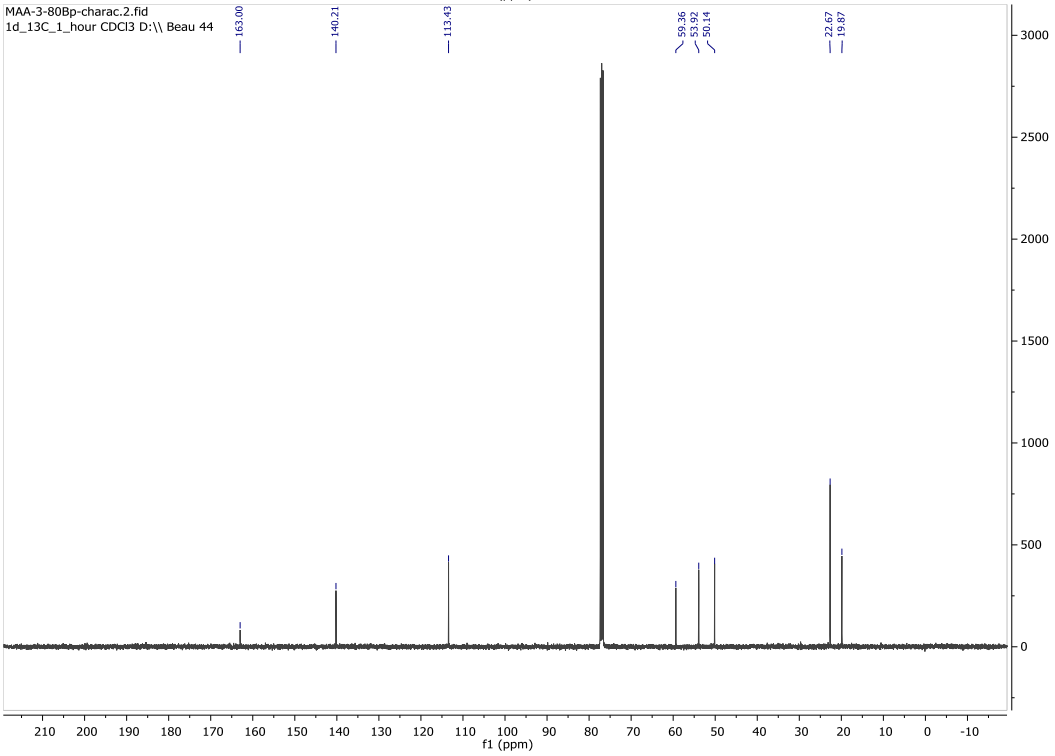

MAA-3-59Bp-Hcharac.1.fid
1d_1H_32_scans CDCl3 D:\\ Beau 59
O
N
N
OH
0.93
1.03
1.00
1.01
0.97
5.41
7.41
1.21
f1 (ppm)

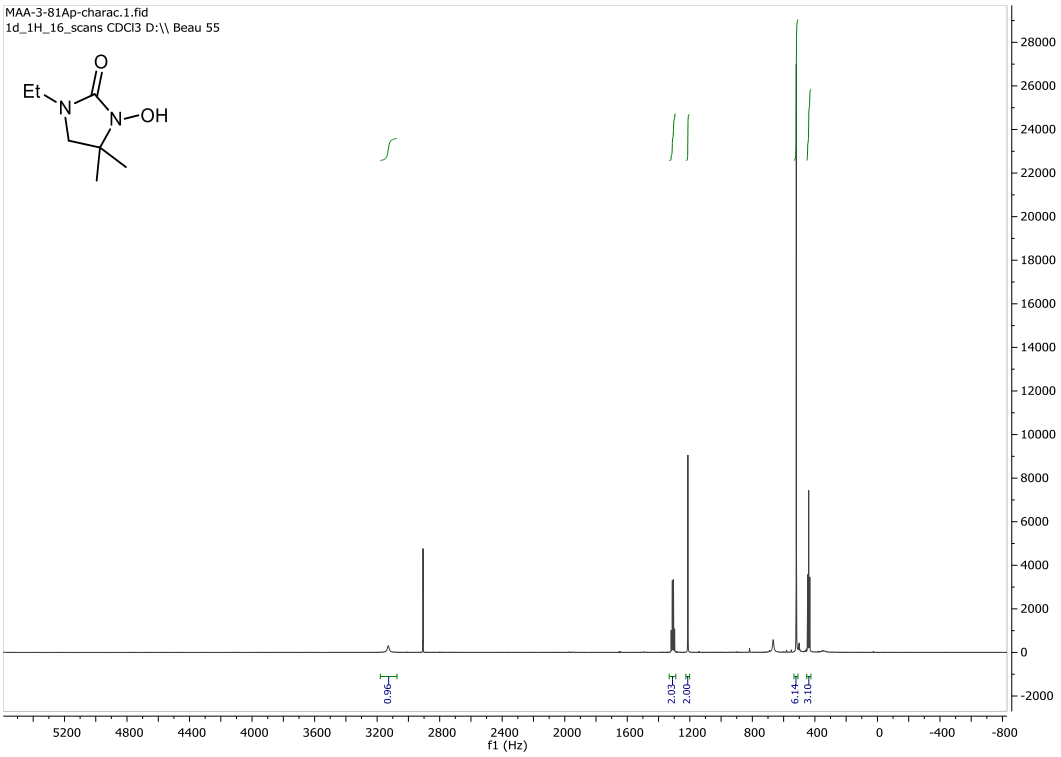

MAA-3-59Bp-charac.1.fid
1d_13C_1_hour CDCl3 D:\\ Beau 43
163.75
55.89
51.60
43.97
30.22
29.82
25.41
25.37
25.29
16.67
f1 (ppm)

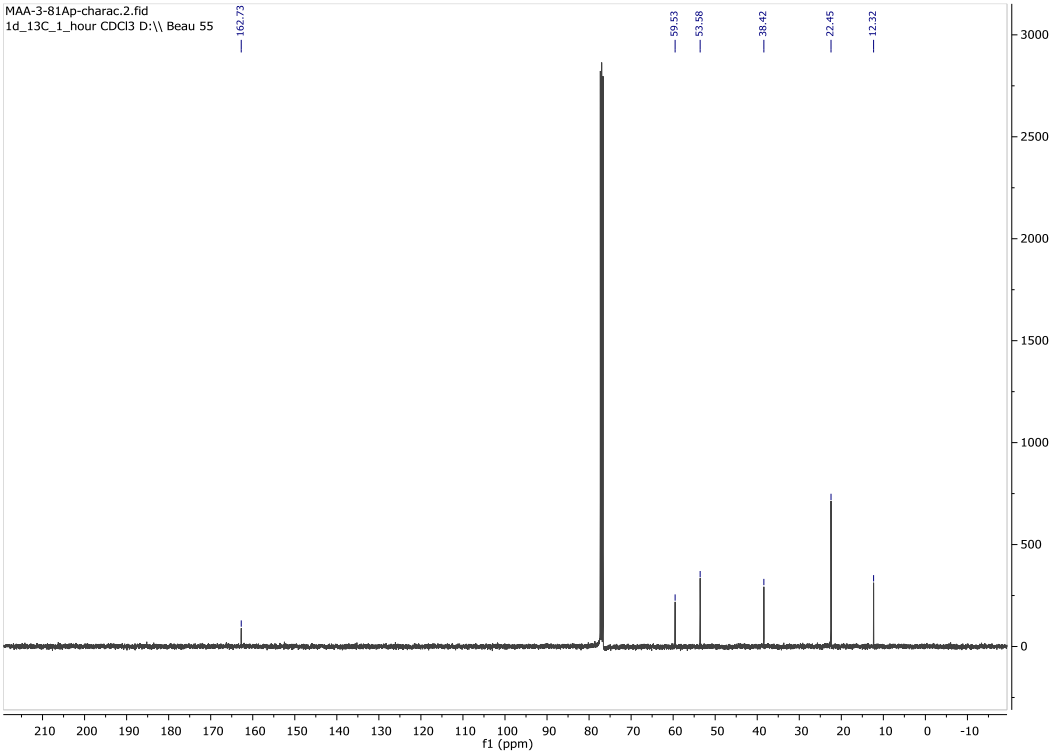

MAA-3-62Bp-40-60.1.fid
1H NMR
Me
N
O
N
OH
0.78
1.00
1.00
4.26
3.27
f1 (ppm)

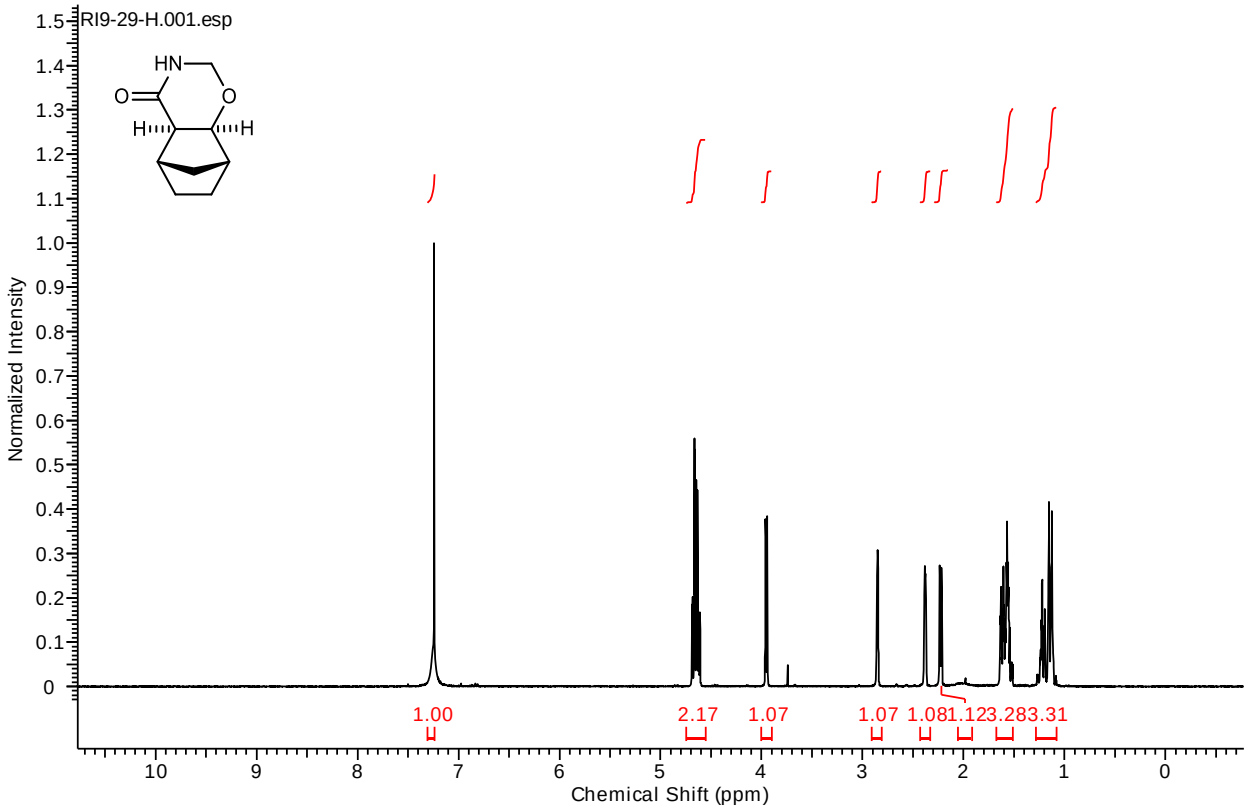

MAA-3-62Bp-charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 36
164.74
55.30
50.52
31.12
16.71
f1 (ppm)

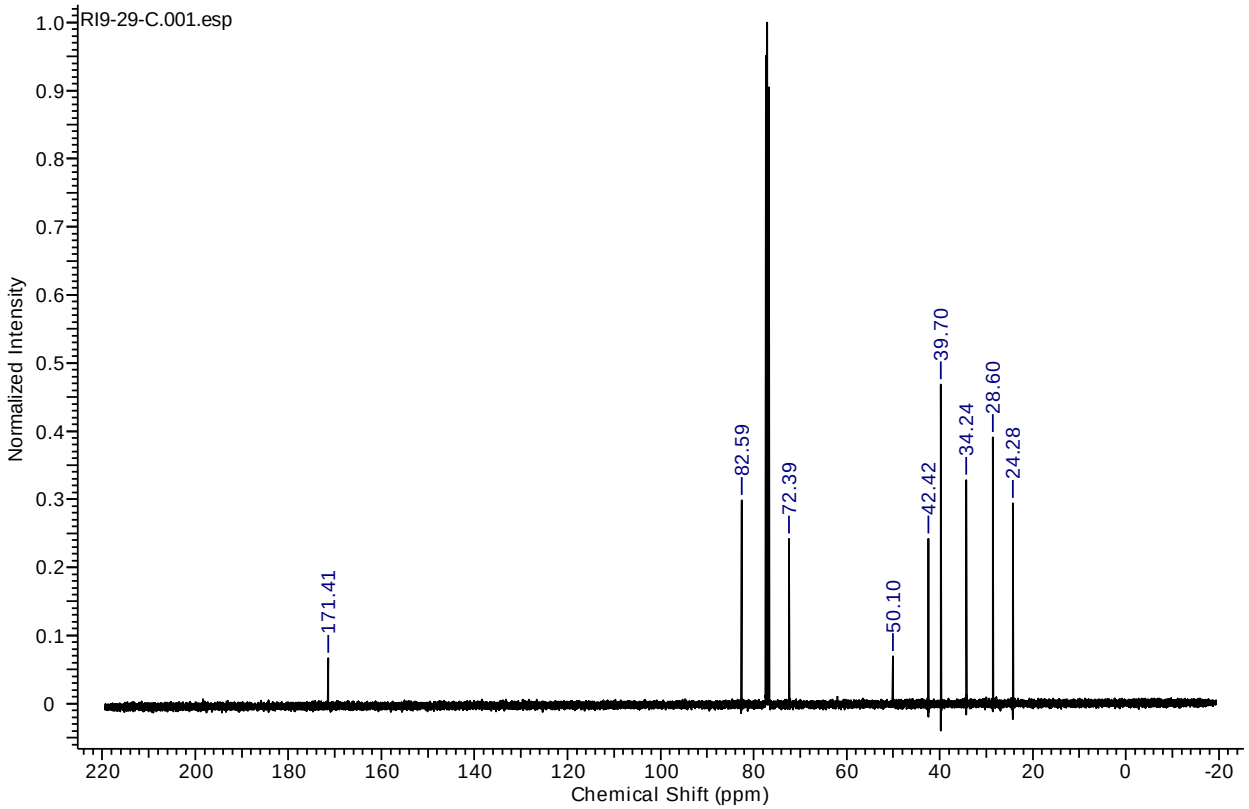

MAA-3-80Bp-19-38.1.fid
1H NMR
O
N
N
OH
4.90
4.84
0.75
2.04
2.02
2.00
3.05
6.17
f1 (ppm)

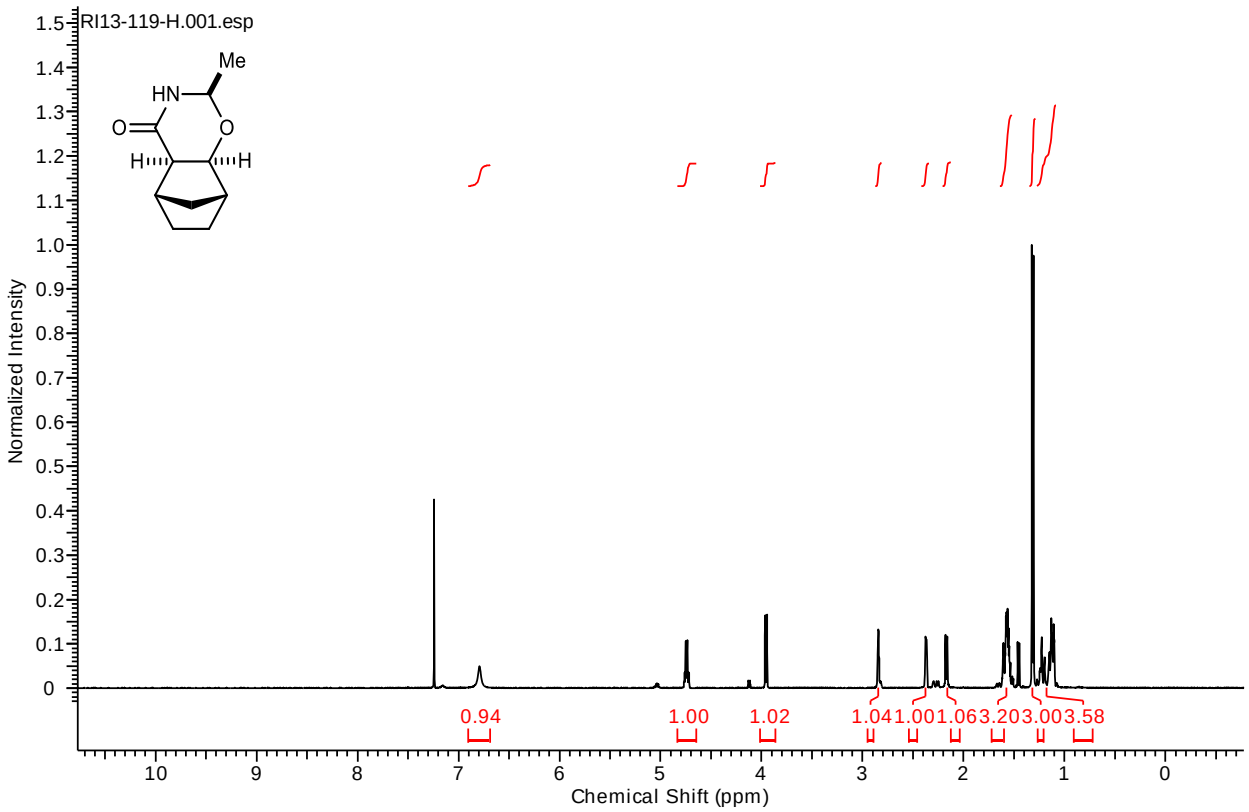

MAA-3-80Bp-charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 44
163.00
140.21
113.43
59.36
53.92
50.14
22.67
19.87
f1 (ppm)

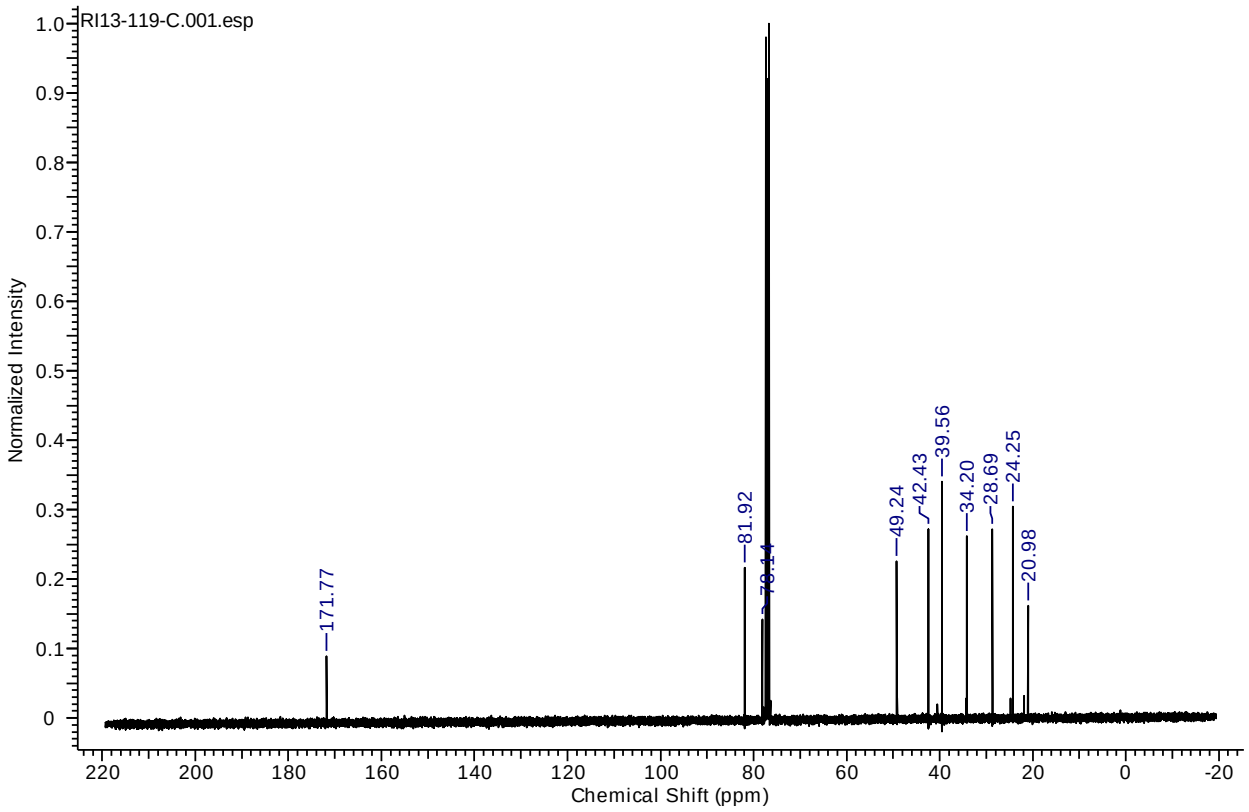

MAA-3-81Ap-charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 55
Et
N
O
N
OH
0.96
2.03
2.00
6.14
3.10
f1 (Hz)

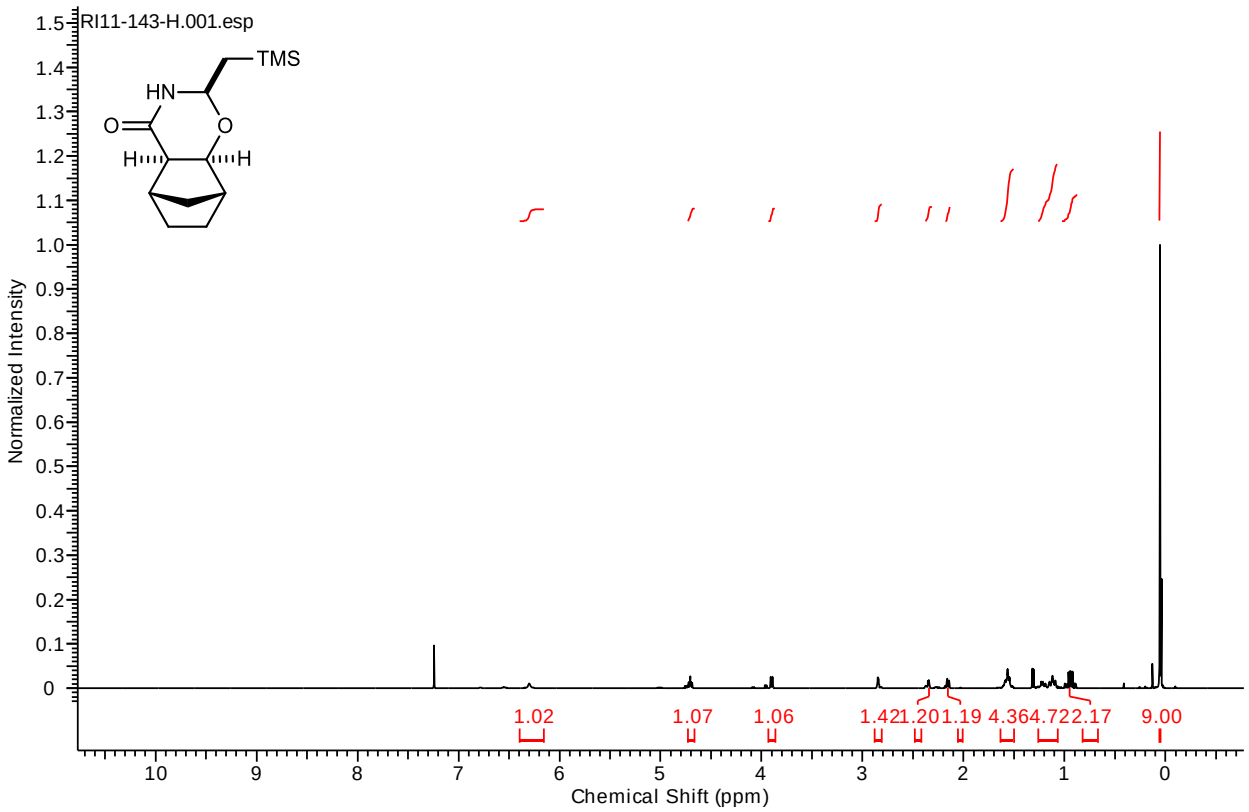

MAA-3-81Ap-charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 55
162.73
59.53
53.58
38.42
22.45
12.32
f1 (ppm)

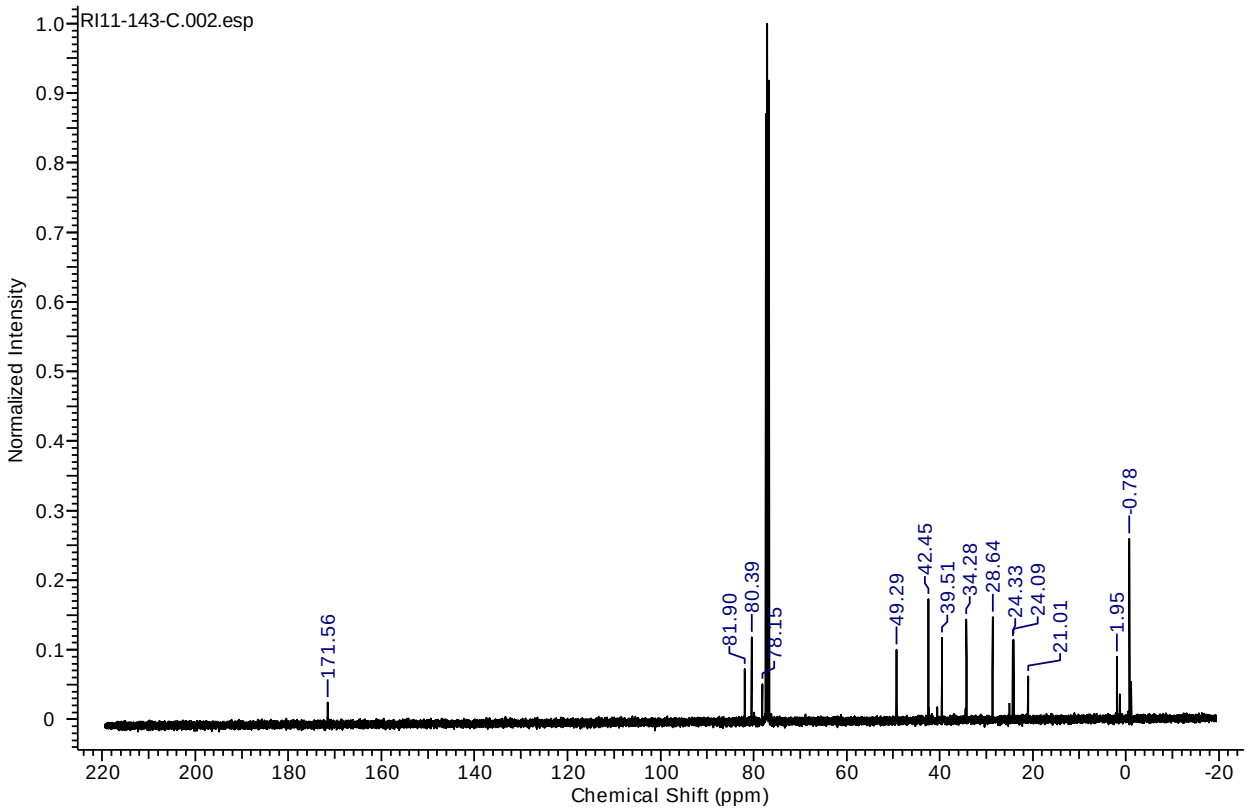

RI9-29-H.001.esp
HN
O
O
H
H
Normalized Intensity
1.00
2.17
1.07
1.07
1.08
1.12
3.28
3.31
Chemical Shift (ppm)

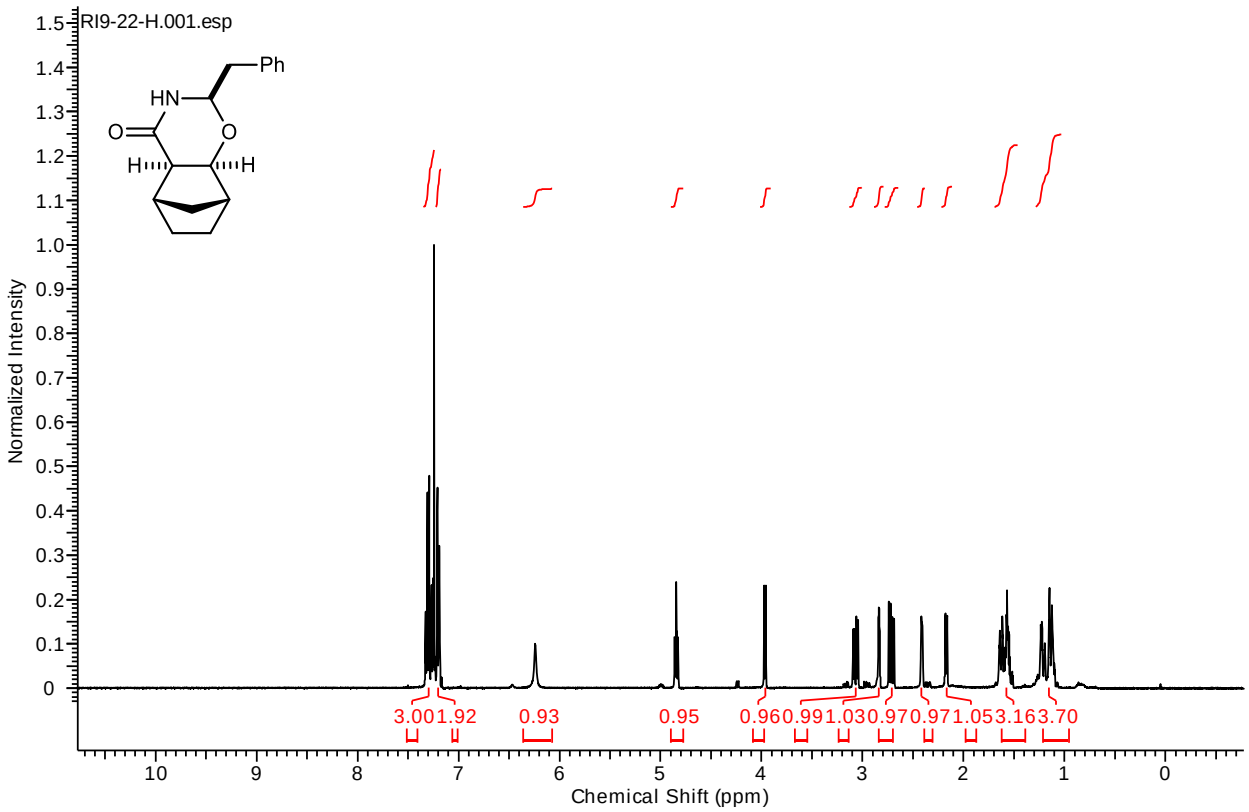

RI9-29-C.001.esp
Normalized Intensity
171.41
82.59
72.39
50.10
42.42
39.70
34.24
28.60
24.28
Chemical Shift (ppm)

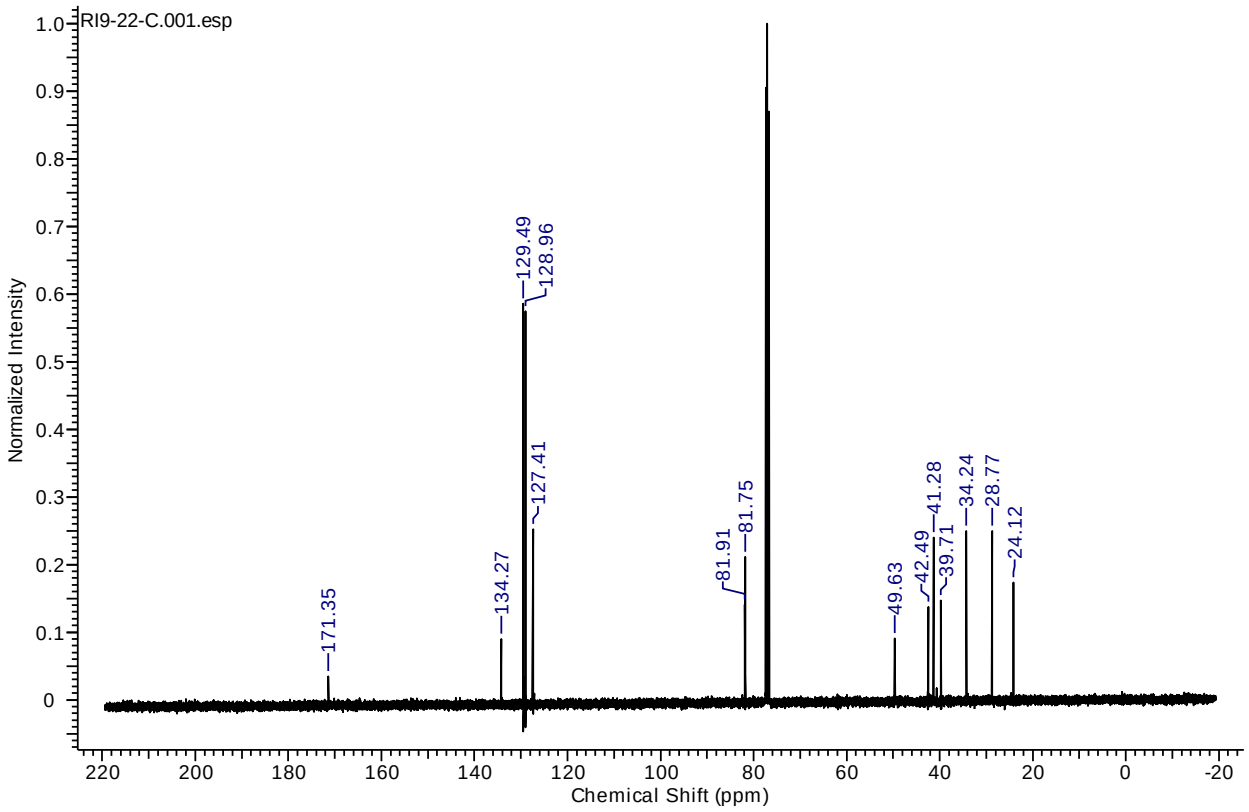

RI13-119-H.001.esp
Me
HN
O
O
H
H
Normalized Intensity
0.94
1.00
1.02
1.04
1.00
1.06
3.20
3.00
3.58
Chemical Shift (ppm)

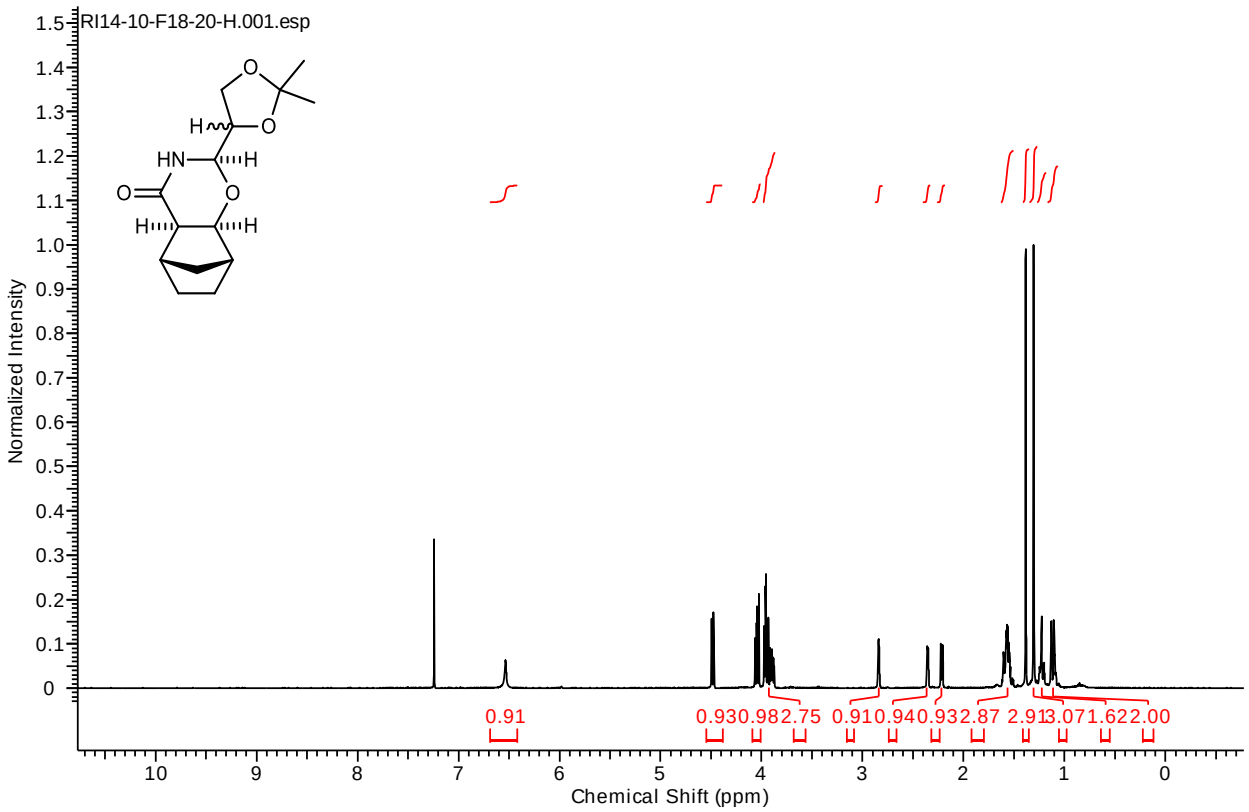

RI13-119-C.001.esp
Normalized Intensity
171.77
81.92
79.14
49.24
42.43
39.56
34.20
28.69
24.25
20.98
Chemical Shift (ppm)

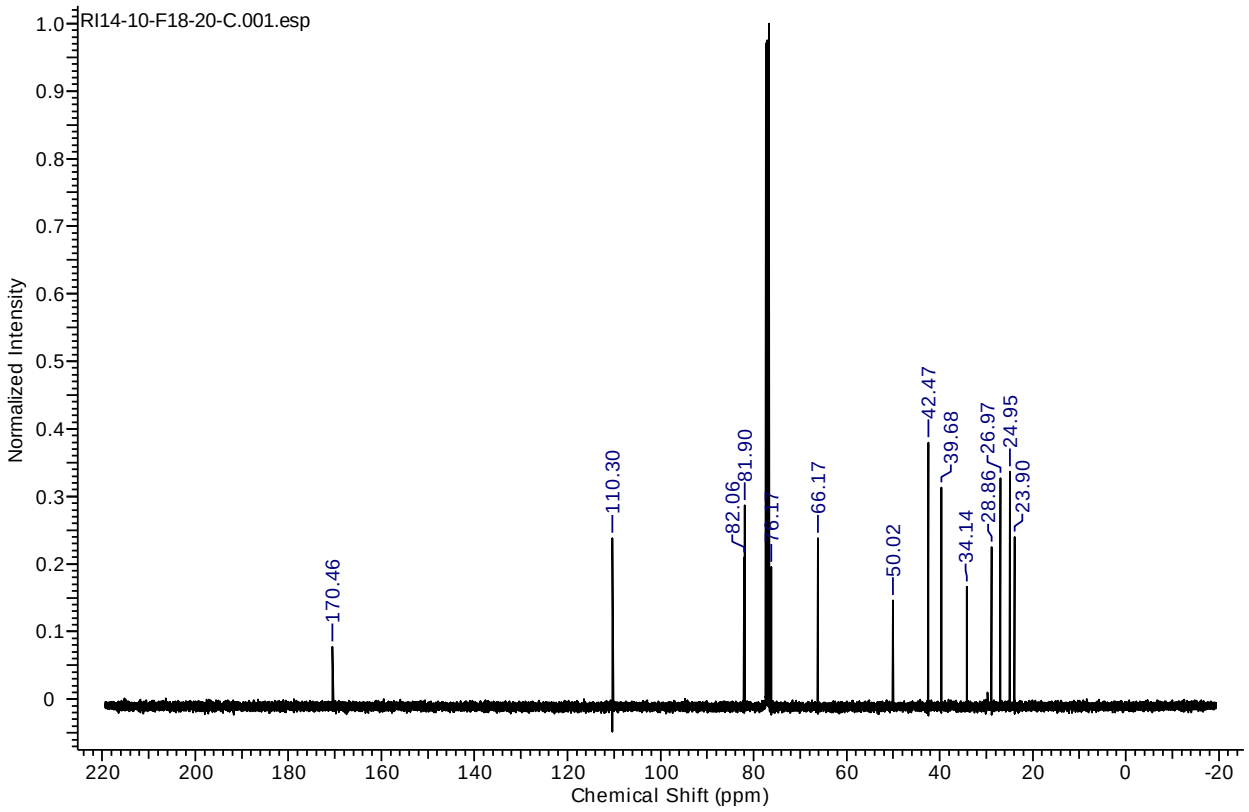

RI11-143-H.001.esp
TMS
HN
O
O
H
H
Normalized Intensity
1.02
1.07
1.06
1.42
1.20
1.19
4.36
4.72
2.17
9.00
Chemical Shift (ppm)

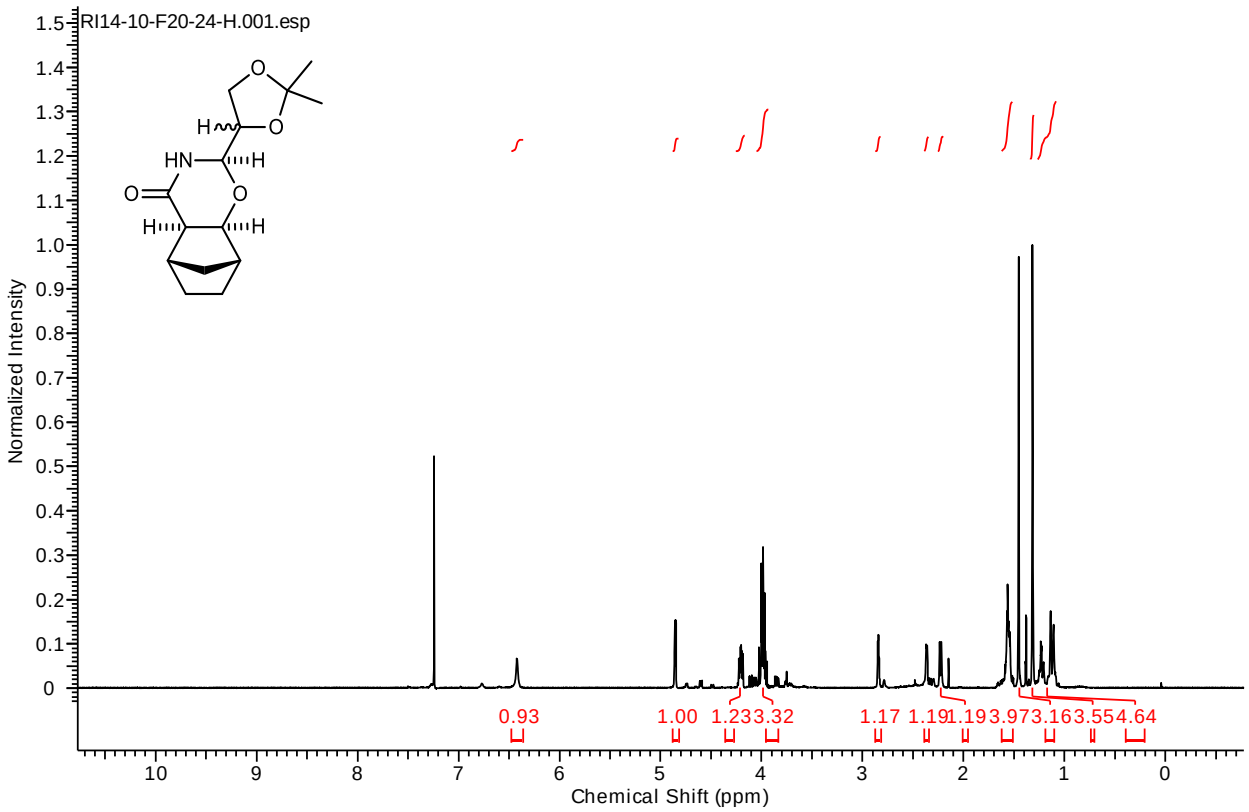

RI11-143-C.002.esp
Normalized Intensity
171.56
81.90
80.39
78.15
49.29
42.45
39.51
34.28
28.64
24.33
24.09
21.01
1.95
-0.78
Chemical Shift (ppm)

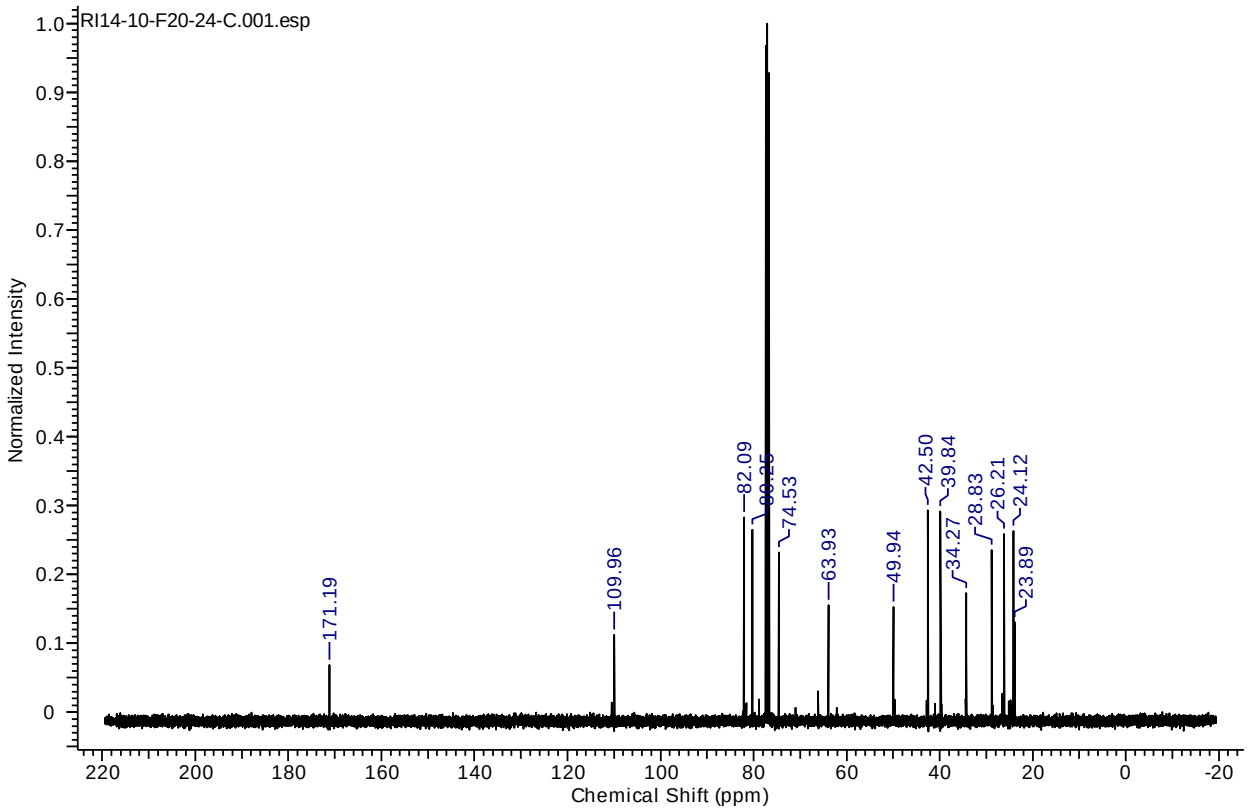

RI9-22-H.001.esp
Ph
HN
O
O
H
H
Normalized Intensity
3.00
1.92
0.93
0.95
0.96
0.99
1.03
0.97
0.97
1.05
3.16
3.70
Chemical Shift (ppm)

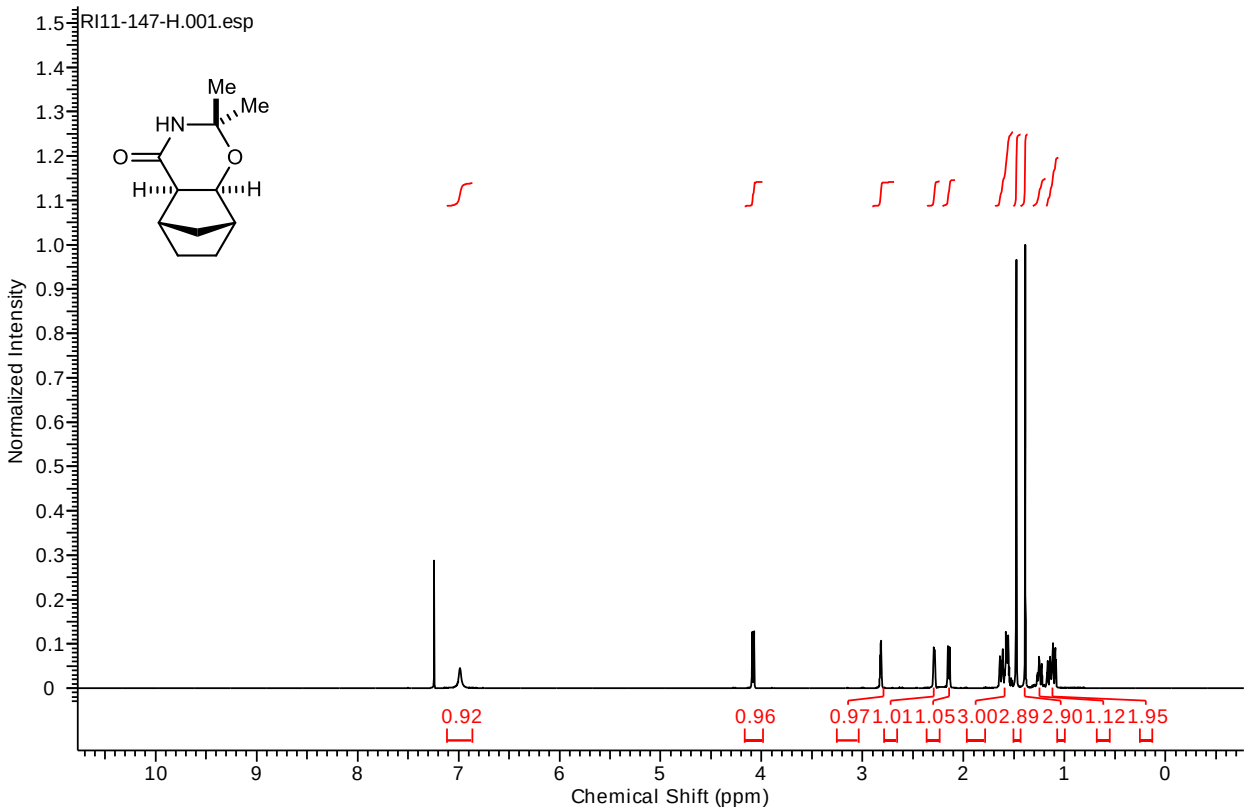

RI9-22-C.001.esp
Normalized Intensity
171.35
134.27
129.49
128.96
127.41
81.91
81.75
49.63
42.49
41.28
39.71
34.24
28.77
24.12
Chemical Shift (ppm)

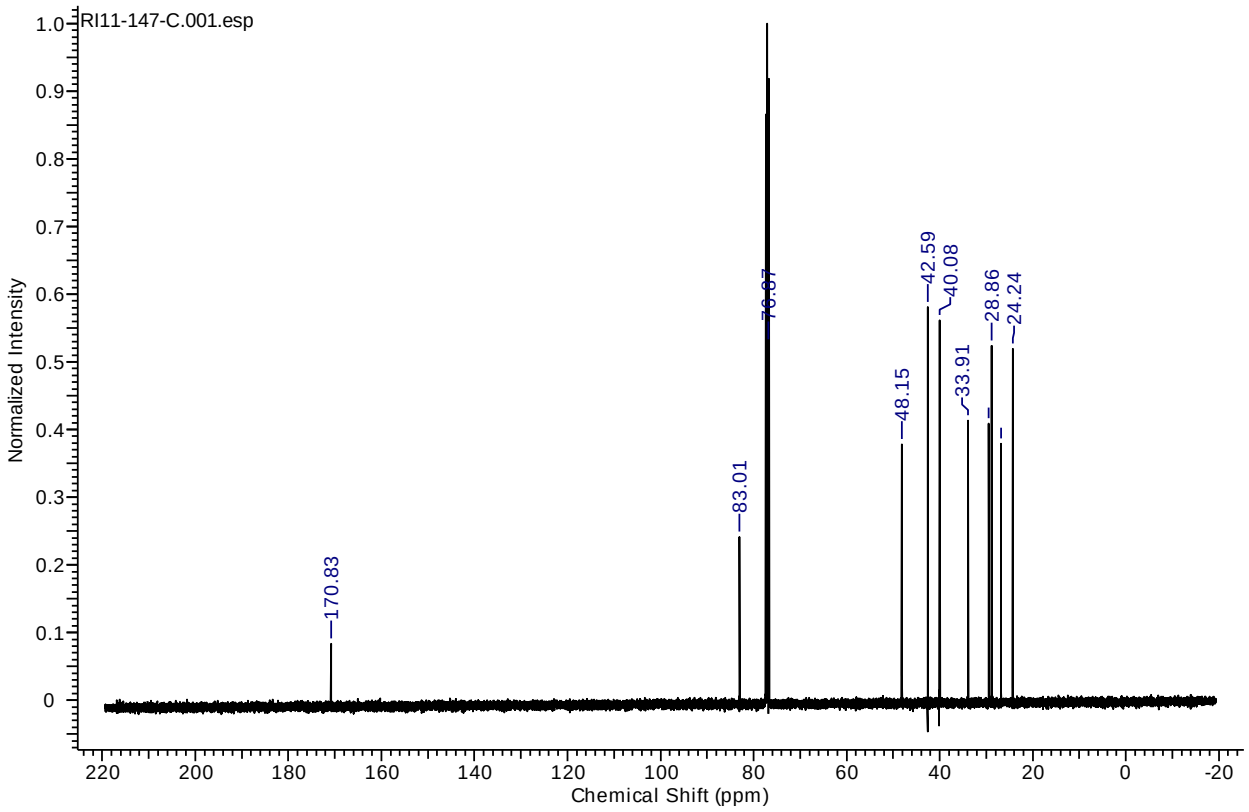

RI14-10-F18-20-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.91
0.93
0.98
2.75
0.91
0.94
0.93
2.87
2.91
3.07
1.62
2.00

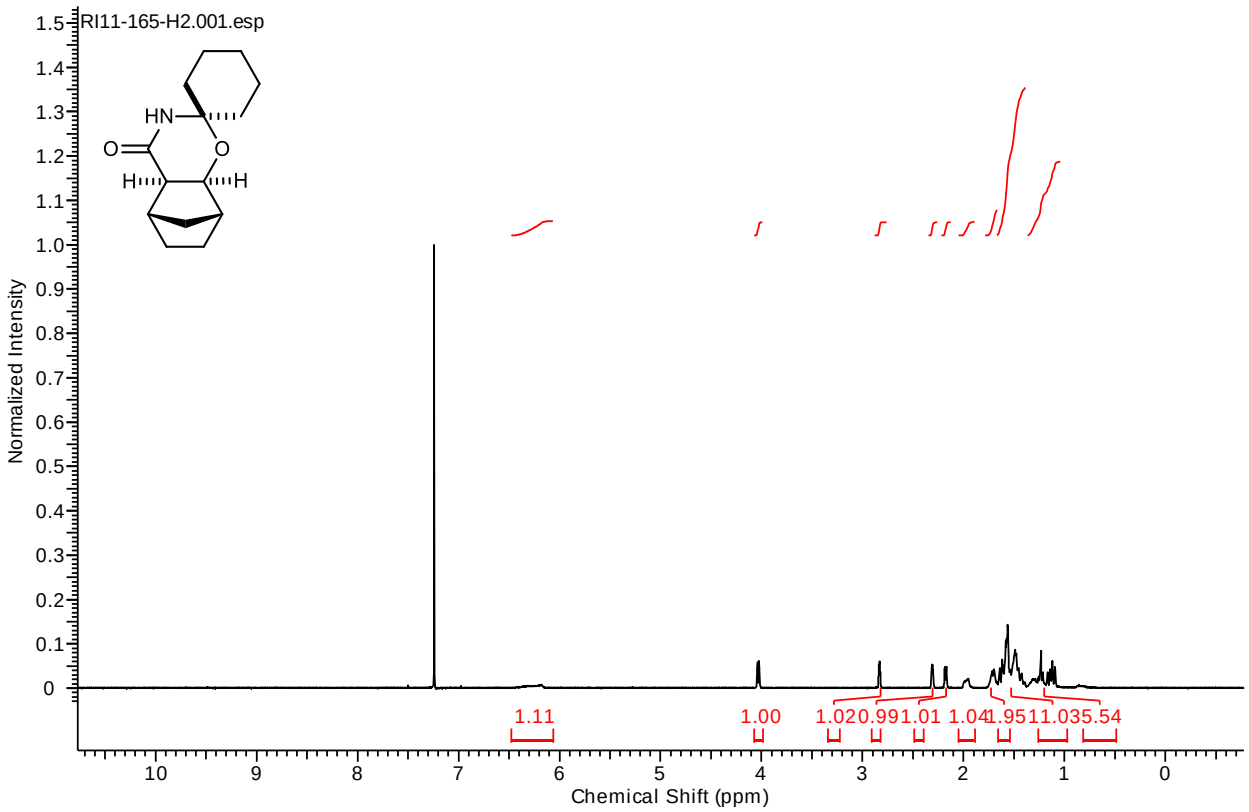

RI14-10-F18-20-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
170.46
110.30
82.06
81.90
76.17
66.17
50.02
42.47
39.68
34.14
28.86
26.97
24.95
23.90

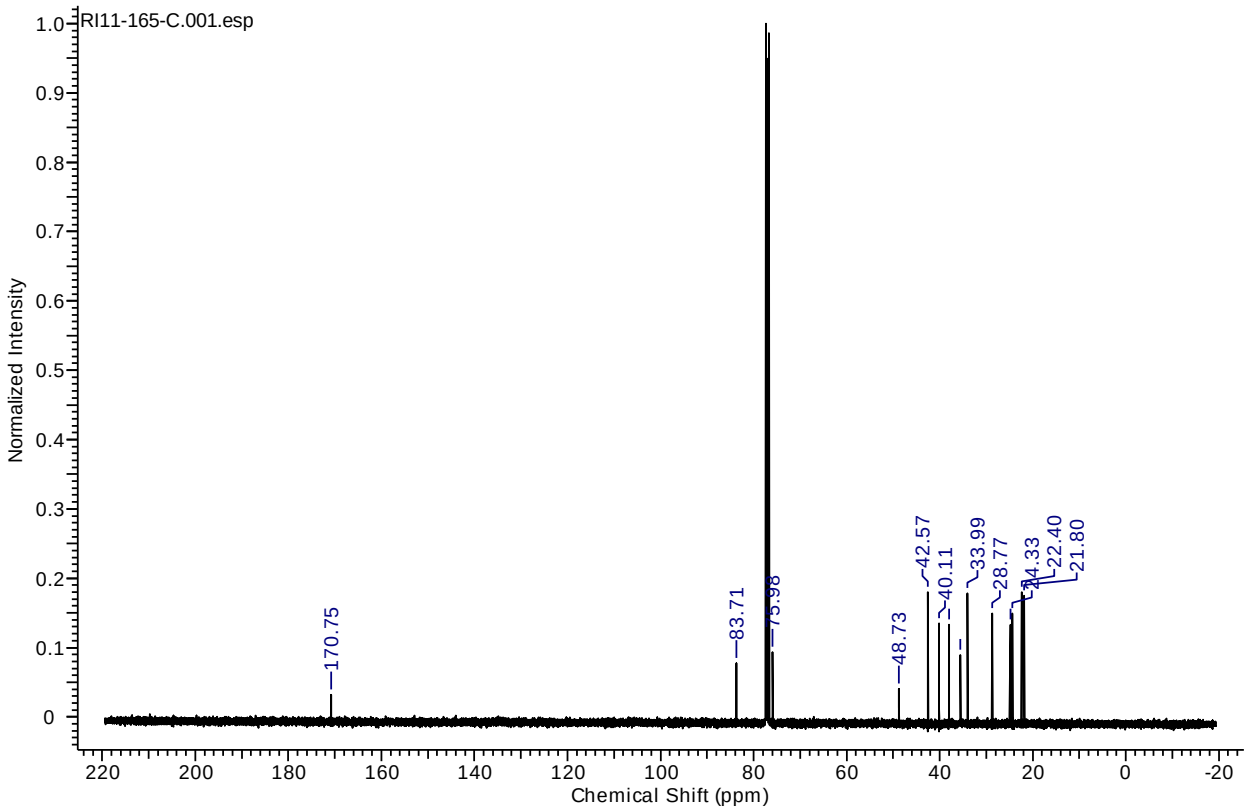

RI14-10-F20-24-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.93
1.00
1.23
3.32
1.17
1.19
1.19
3.97
3.16
3.55
4.64

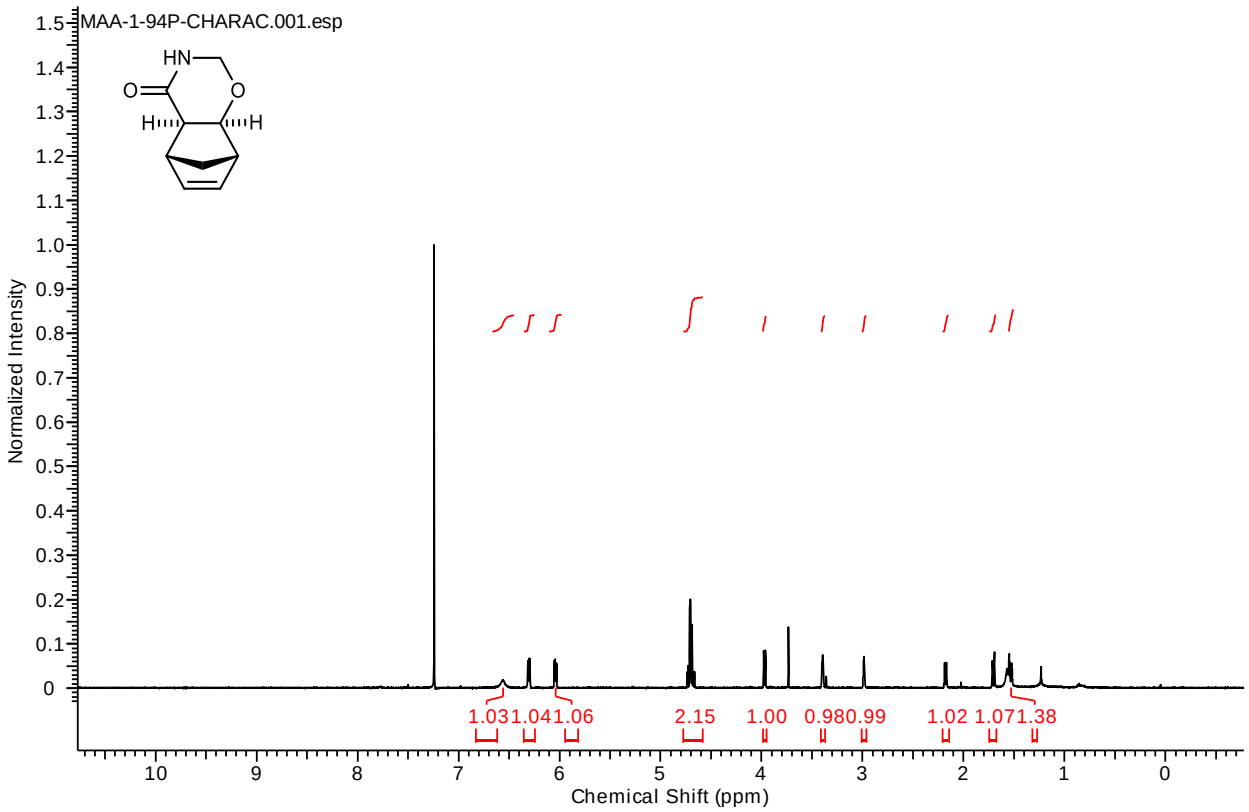

RI14-10-F20-24-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
171.19
109.96
82.09
80.45
74.53
63.93
49.94
42.50
39.84
34.27
28.83
26.21
24.12
23.89

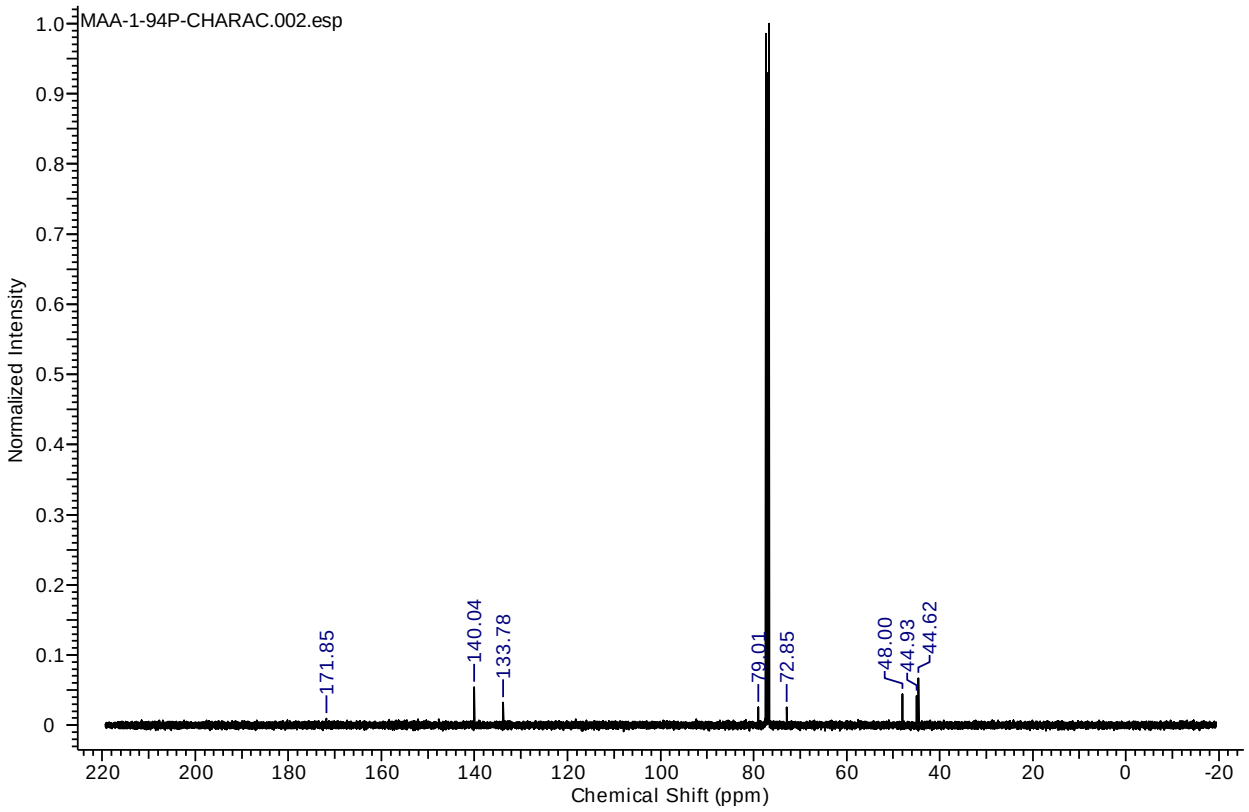

RI11-147-H.001.esp
Me
Me
HN
O
O
H
H
Normalized Intensity
0.92
0.96
0.97
1.01
1.05
3.00
2.89
2.90
1.12
1.95
Chemical Shift (ppm)

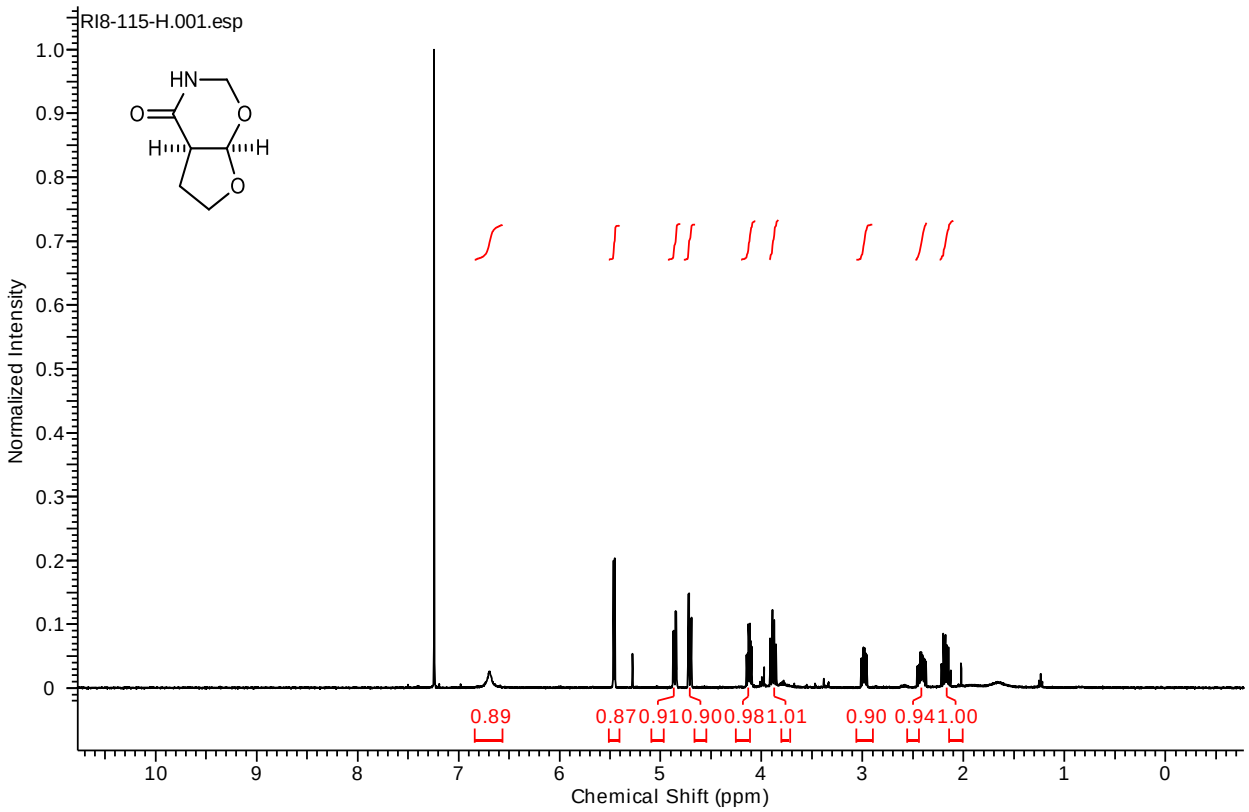

RI11-147-C.001.esp
Normalized Intensity
170.83
83.01
76.67
48.15
42.59
40.08
33.91
28.86
24.24
Chemical Shift (ppm)

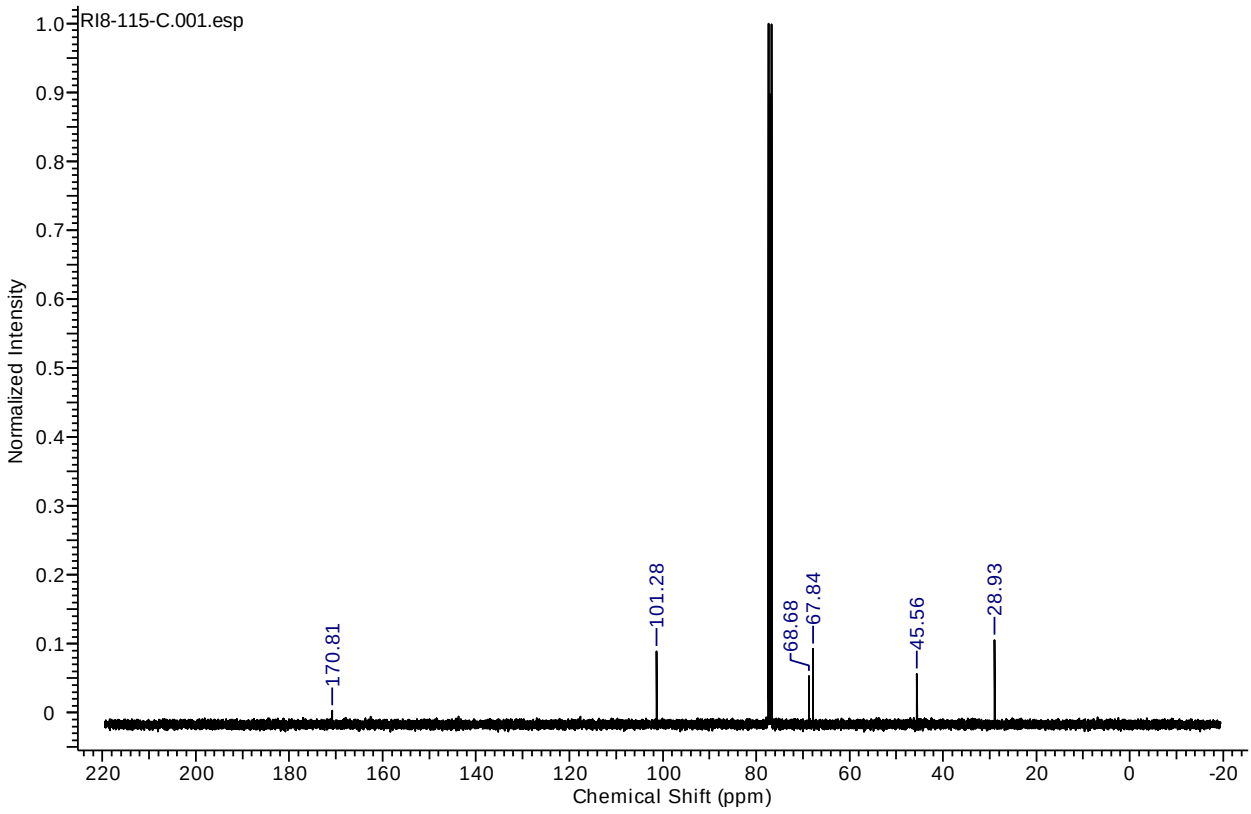

RI11-165-H2.001.esp
HN
O
O
H
H
Normalized Intensity
1.11
1.00
1.02
0.99
1.01
1.04
1.95
11.03
5.54
Chemical Shift (ppm)

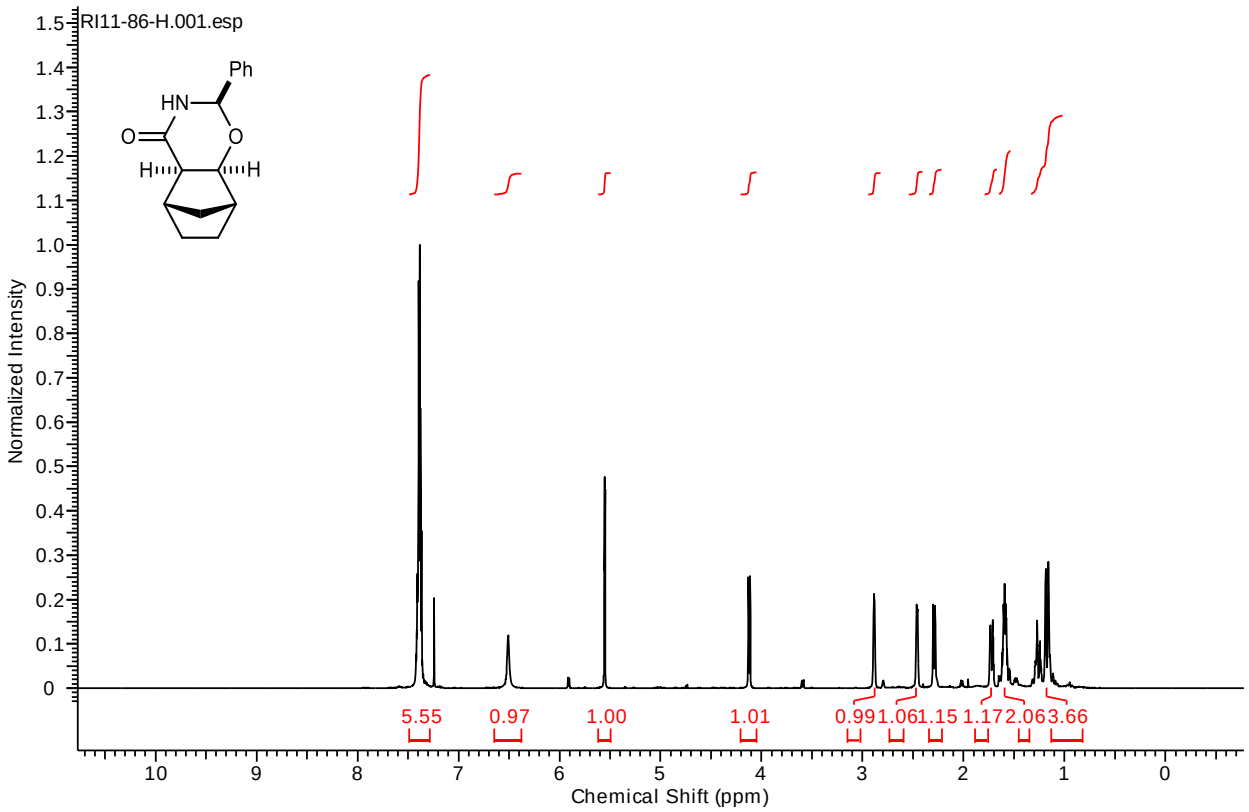

RI11-165-C.001.esp
Normalized Intensity
170.75
83.71
75.98
48.73
42.57
40.11
33.99
28.77
24.33
22.40
21.80
Chemical Shift (ppm)

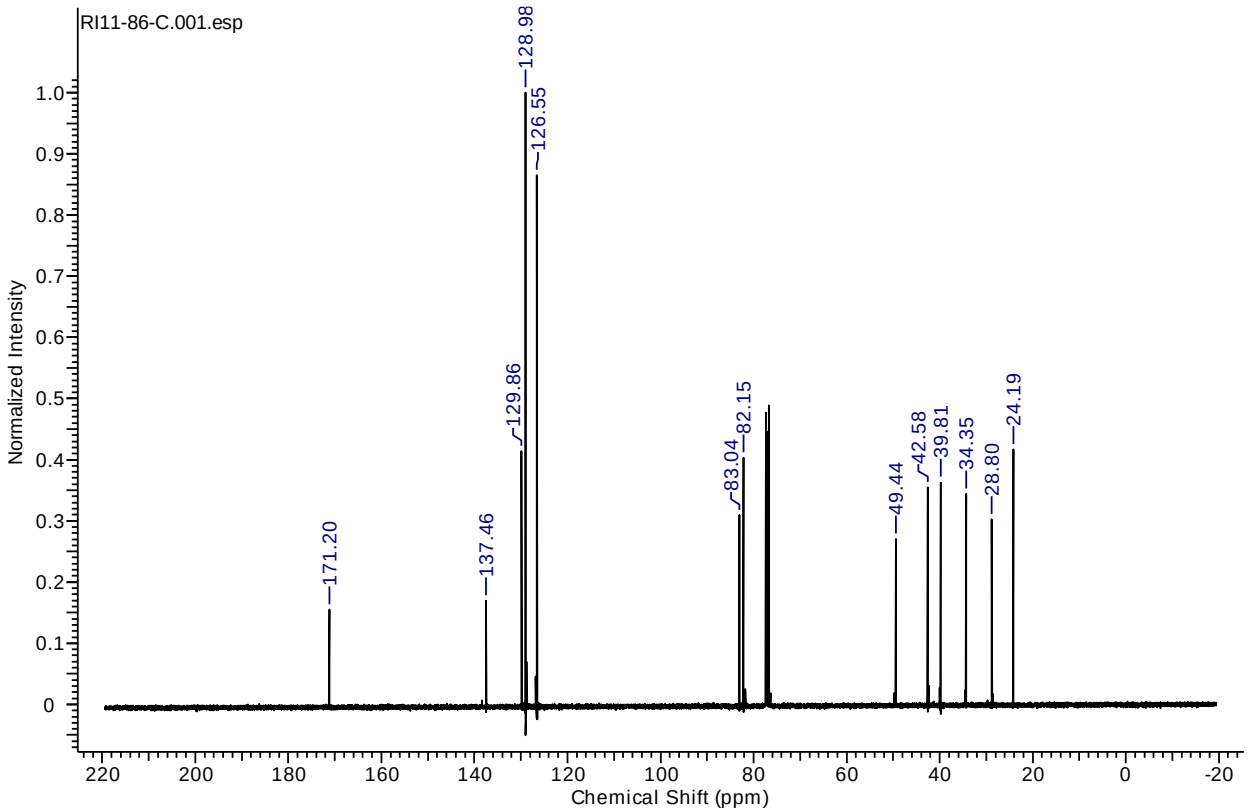

MAA-1-94P-CHARAC.001.esp
HN
O
O
H
H
Normalized Intensity
1.031.041.06
2.15
1.00
0.980.99
1.02 1.071.38
Chemical Shift (ppm)

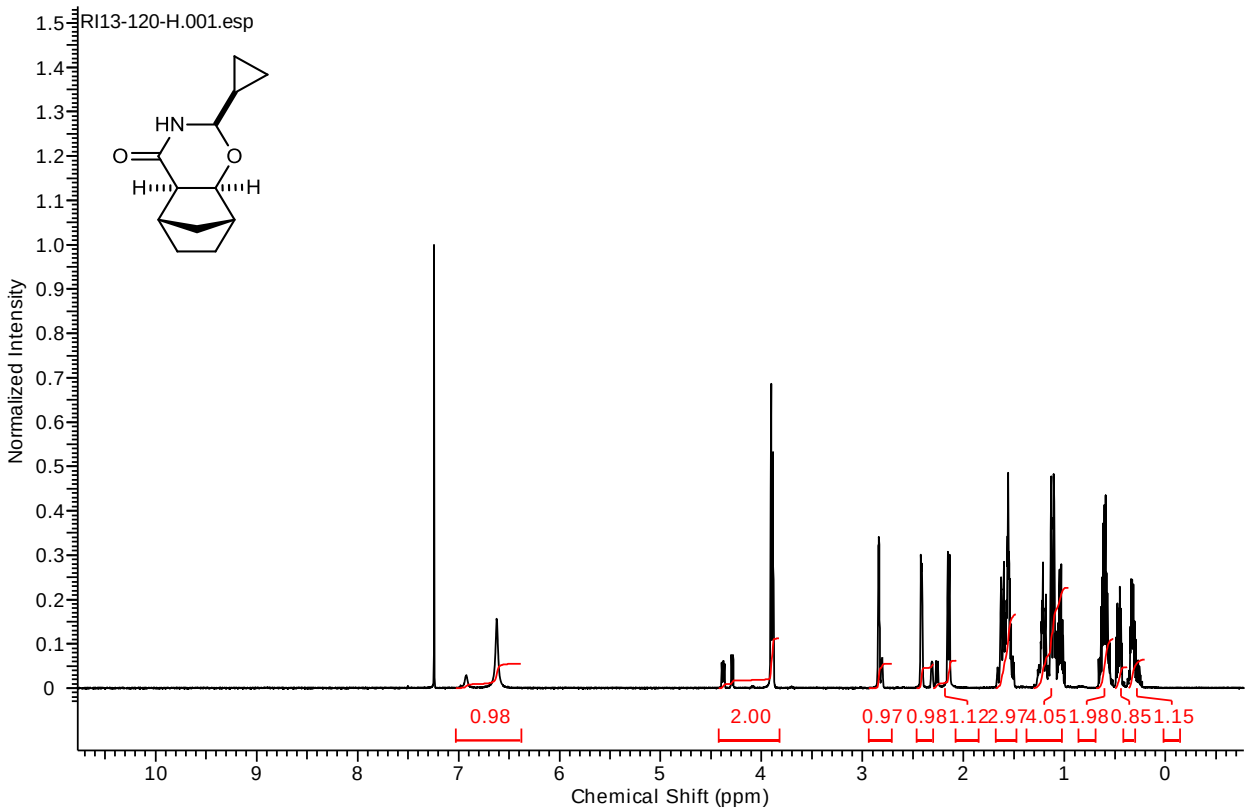

MAA-1-94P-CHARAC.002.esp
Normalized Intensity
171.85
140.04
133.78
79.01
72.85
48.00
44.93
44.62
Chemical Shift (ppm)

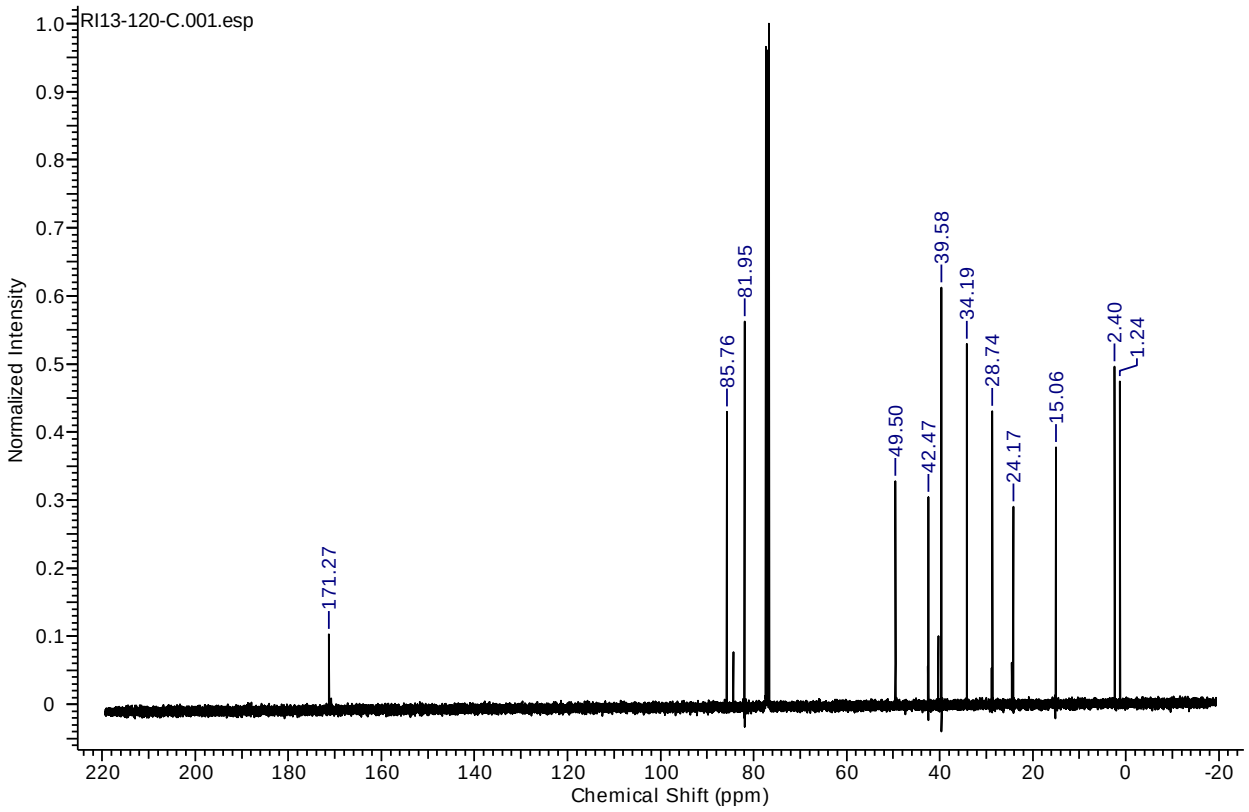

RI8-115-H.001.esp
HN
O
O
H
H
O
Normalized Intensity
0.89
0.87
0.91
0.90
0.98
1.01
0.90
0.94
1.00
Chemical Shift (ppm)

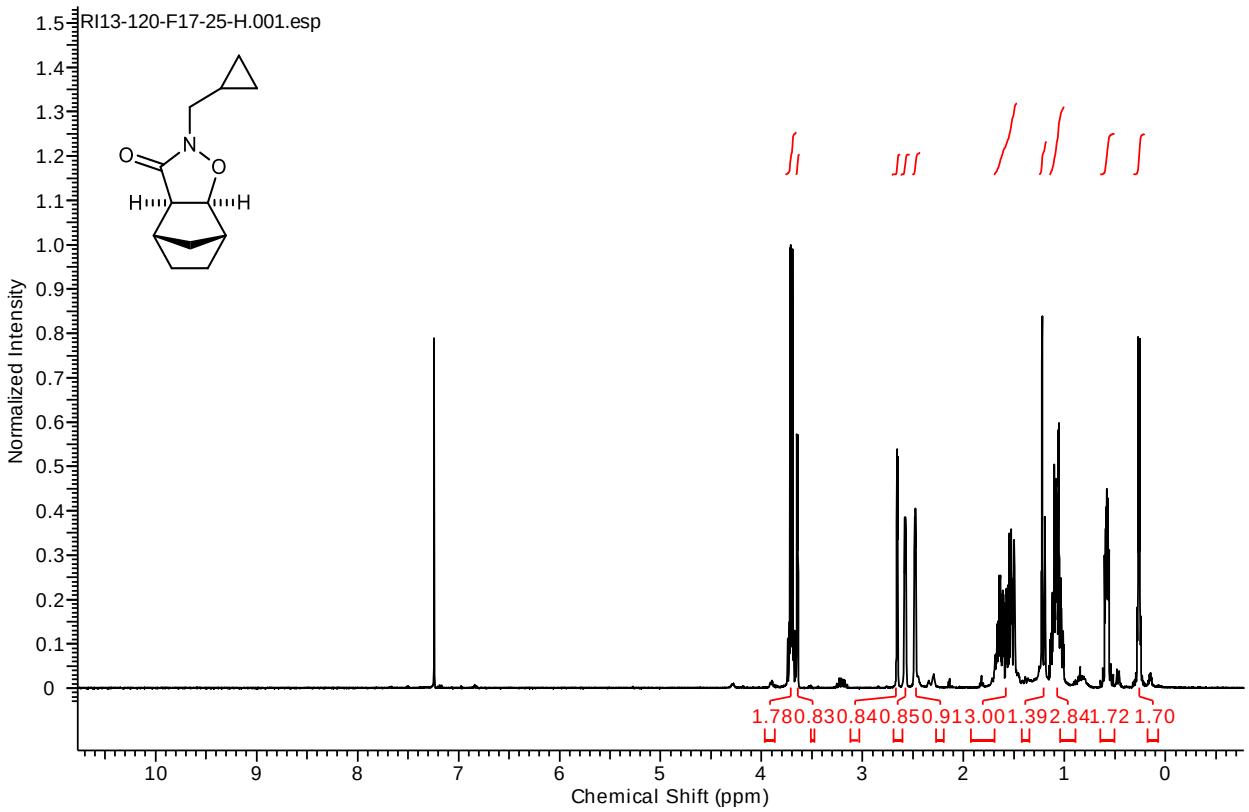

RI8-115-C.001.esp
Normalized Intensity
170.81
101.28
68.68
67.84
45.56
28.93
Chemical Shift (ppm)

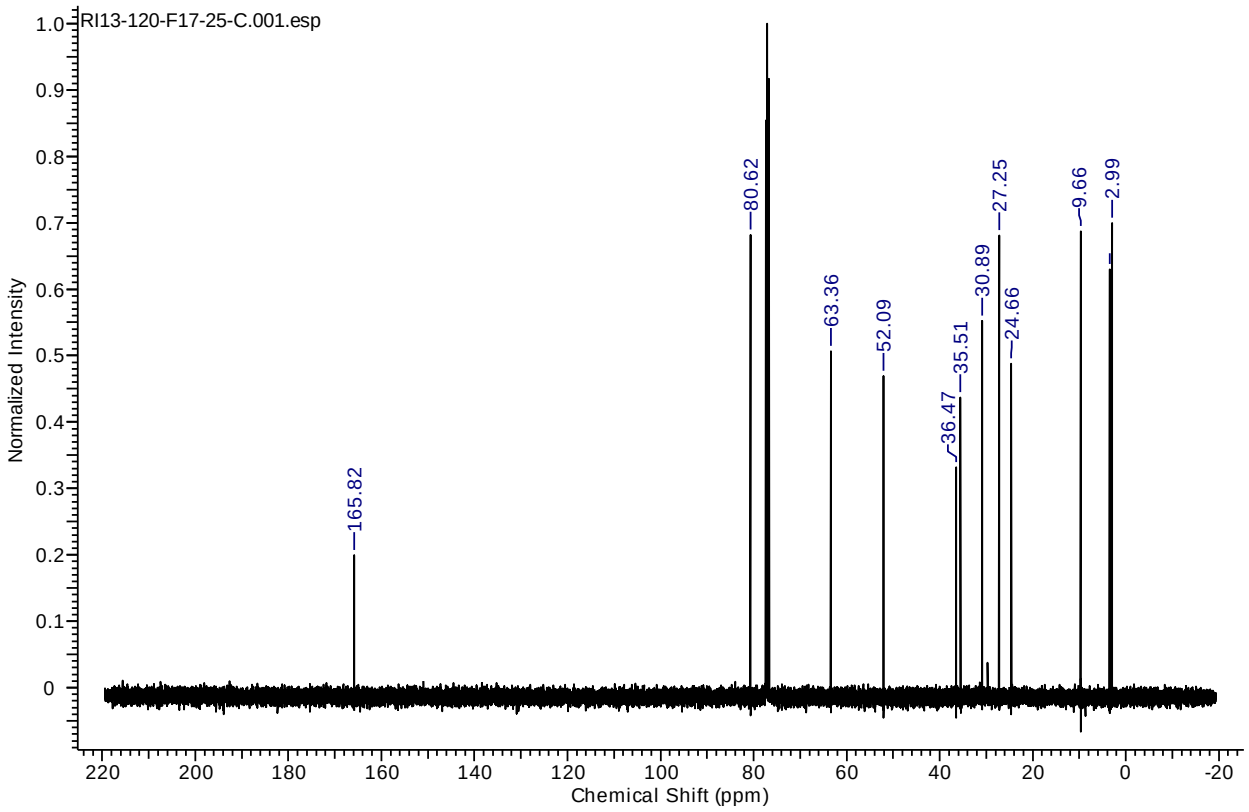

RI11-86-H.001.esp
Ph
HN
O
O
H
H
Normalized Intensity
5.55
0.97
1.00
1.01
0.99
1.06
1.15
1.17
2.06
3.66
Chemical Shift (ppm)

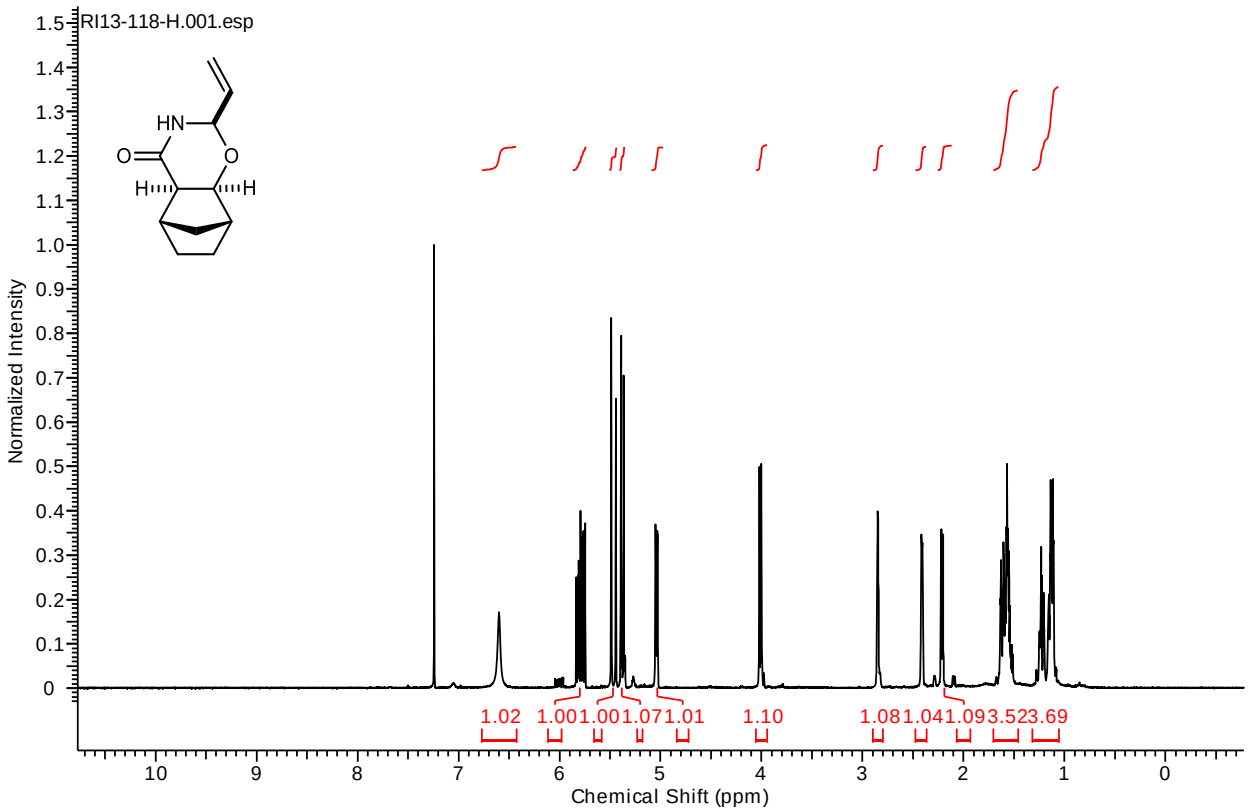

RI11-86-C.001.esp
128.98
126.55
129.86
171.20
137.46
83.04
82.15
49.44
42.58
39.81
34.35
28.80
24.19
Normalized Intensity
Chemical Shift (ppm)

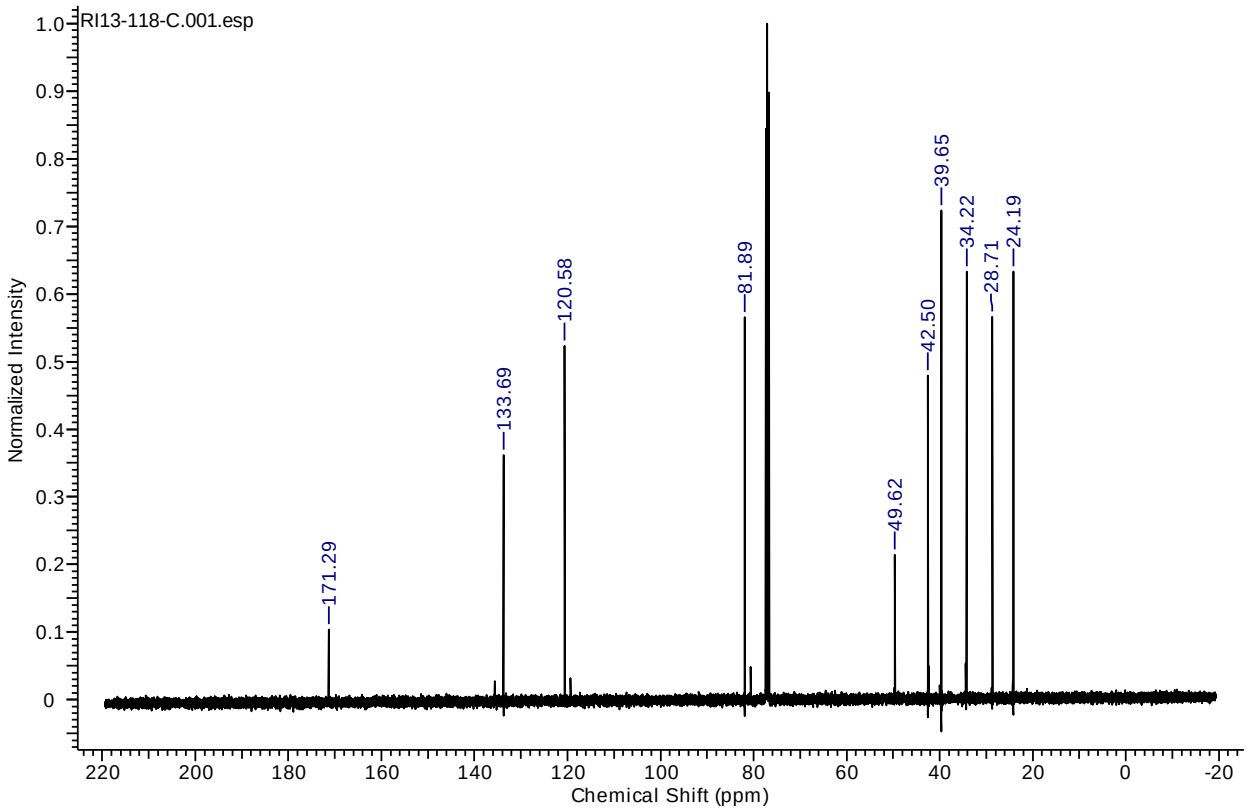

RI13-120-H.001.esp
HN
O
O
H
H
Normalized Intensity
0.98
2.00
0.97
0.98
1.12
2.97
4.05
1.98
0.85
1.15
Chemical Shift (ppm)

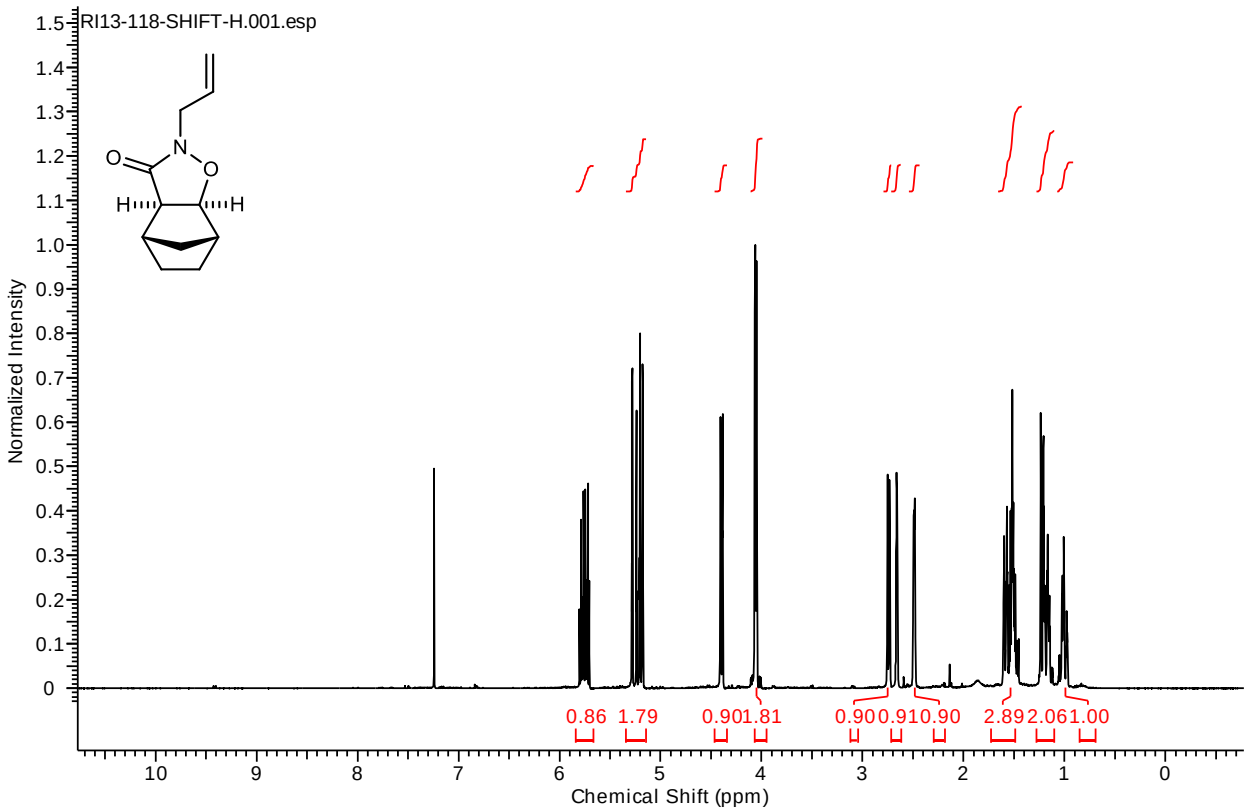

RI13-120-C.001.esp
Normalized Intensity
171.27
85.76
81.95
49.50
42.47
39.58
34.19
28.74
24.17
15.06
2.40
1.24
Chemical Shift (ppm)

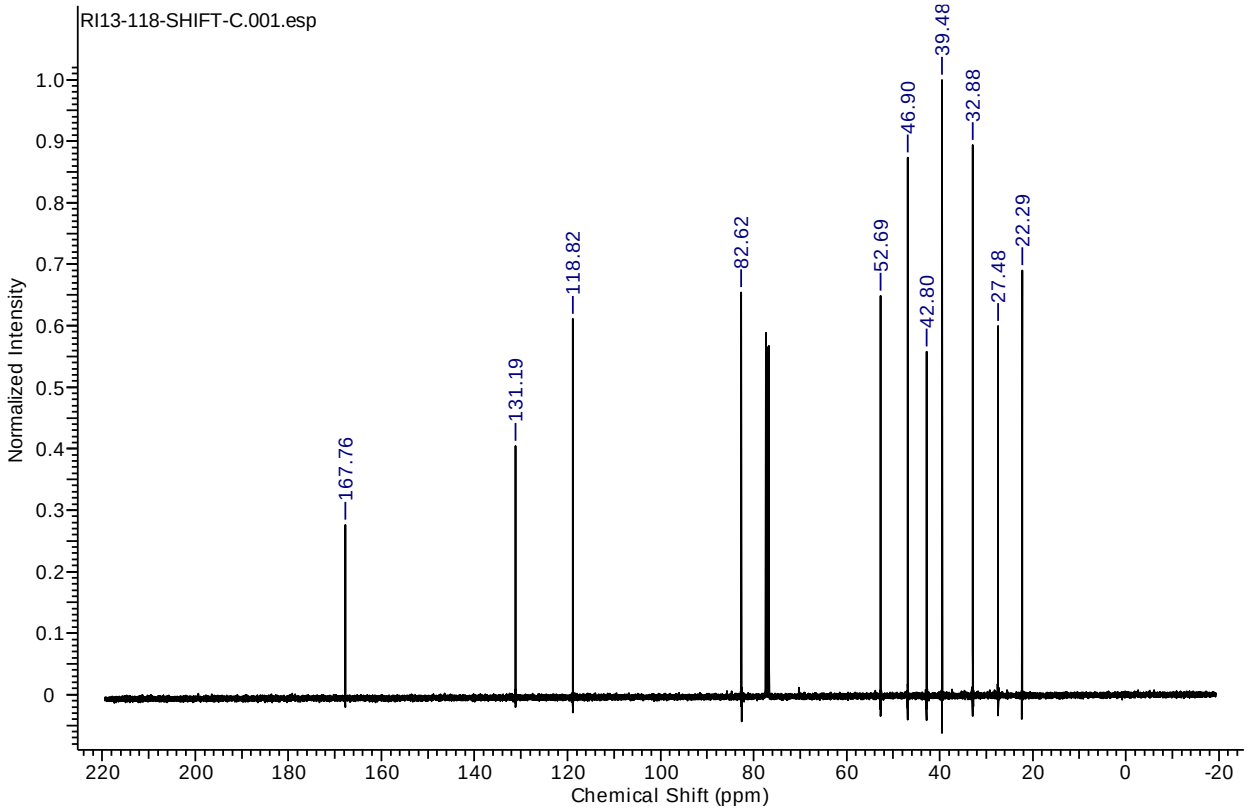

RI13-120-F17-25-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.78 0.83 0.84 0.85 0.91 3.00 1.39 2.84 1.72 1.70

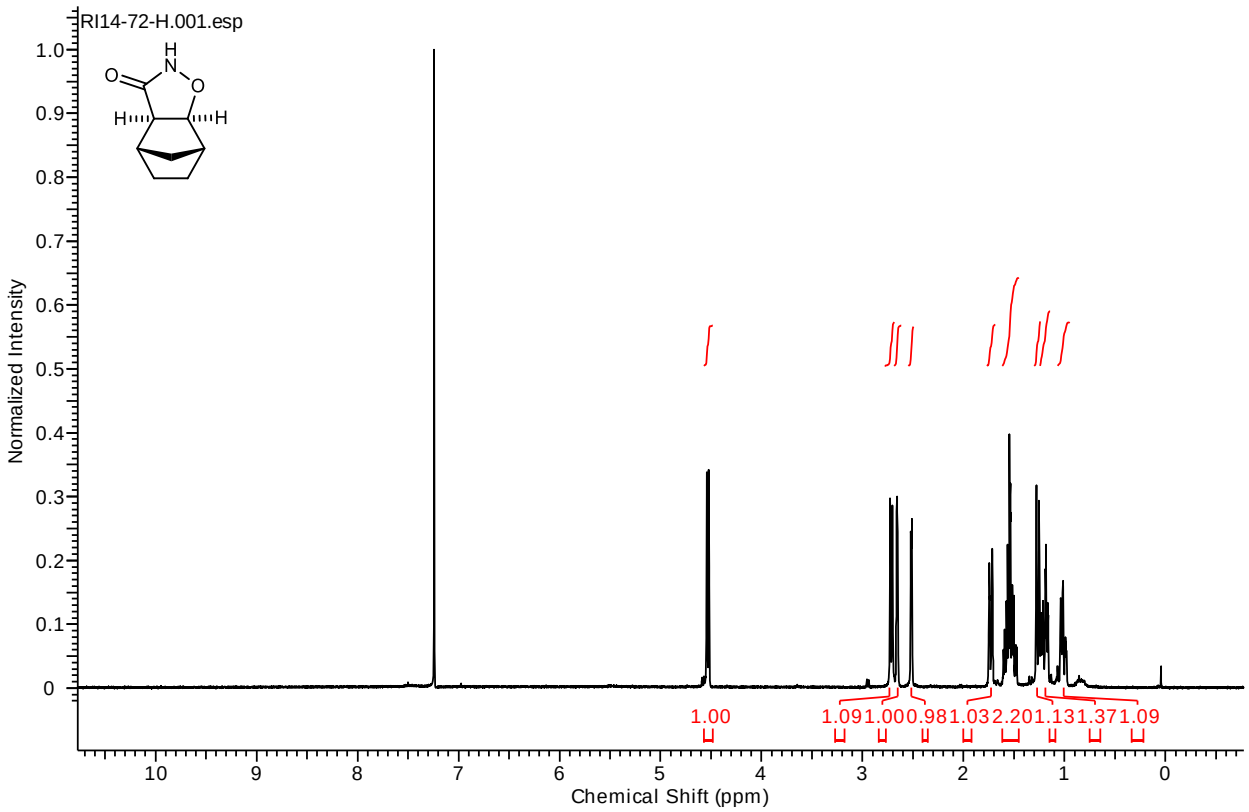

RI13-120-F17-25-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
165.82
80.62
63.36
52.09
36.47
35.51
30.89
27.25
24.66
9.66
2.99

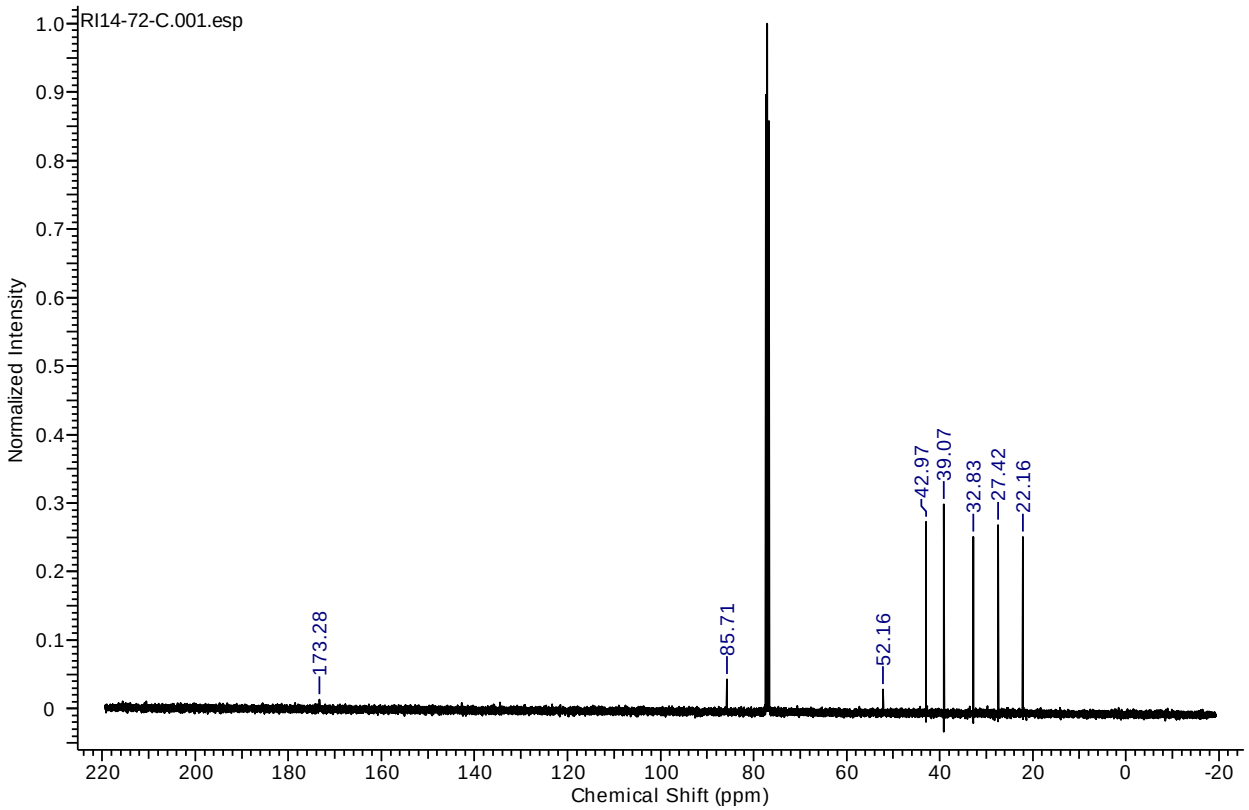

RI13-118-H.001.esp
HN
O
O
H
H
Normalized Intensity
Chemical Shift (ppm)
1.02
1.00
1.00
1.07
1.01
1.10
1.08
1.04
1.09
3.52
3.69

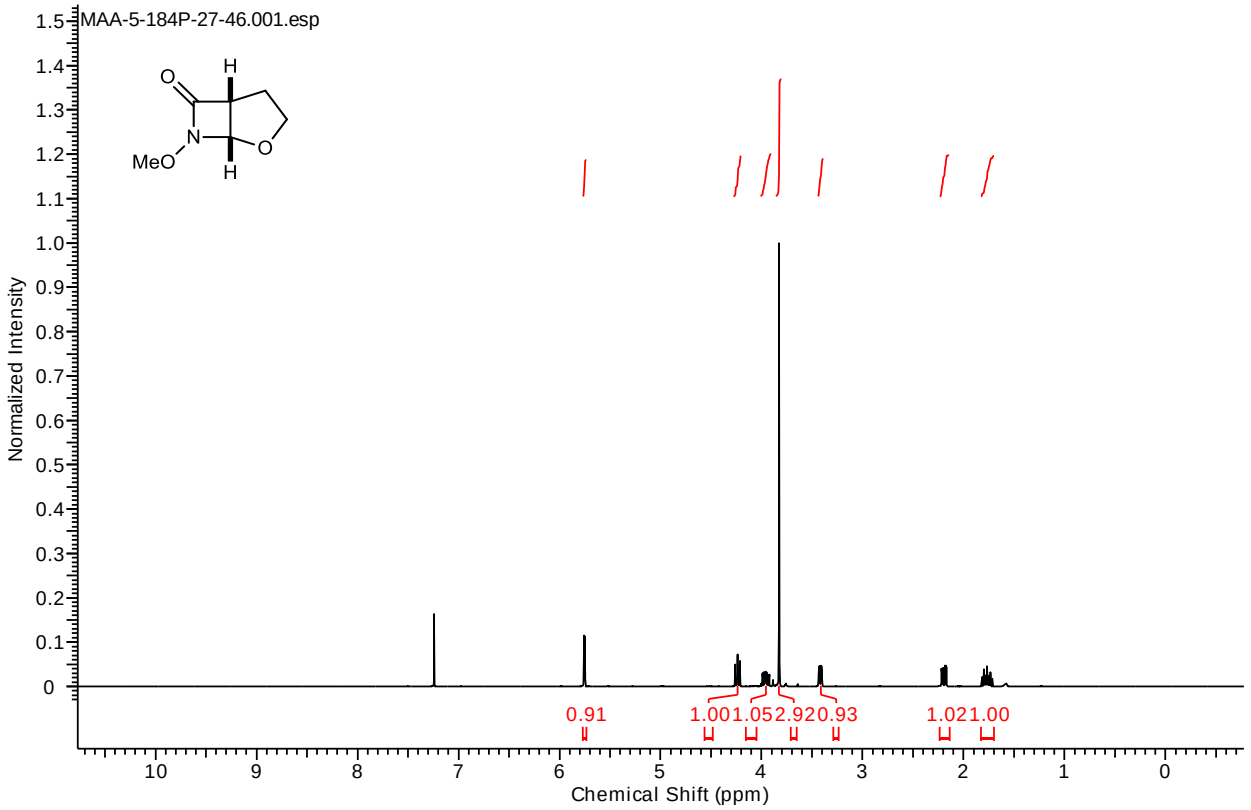

RI13-118-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
171.29
133.69
120.58
81.89
49.62
42.50
39.65
34.22
28.71
24.19

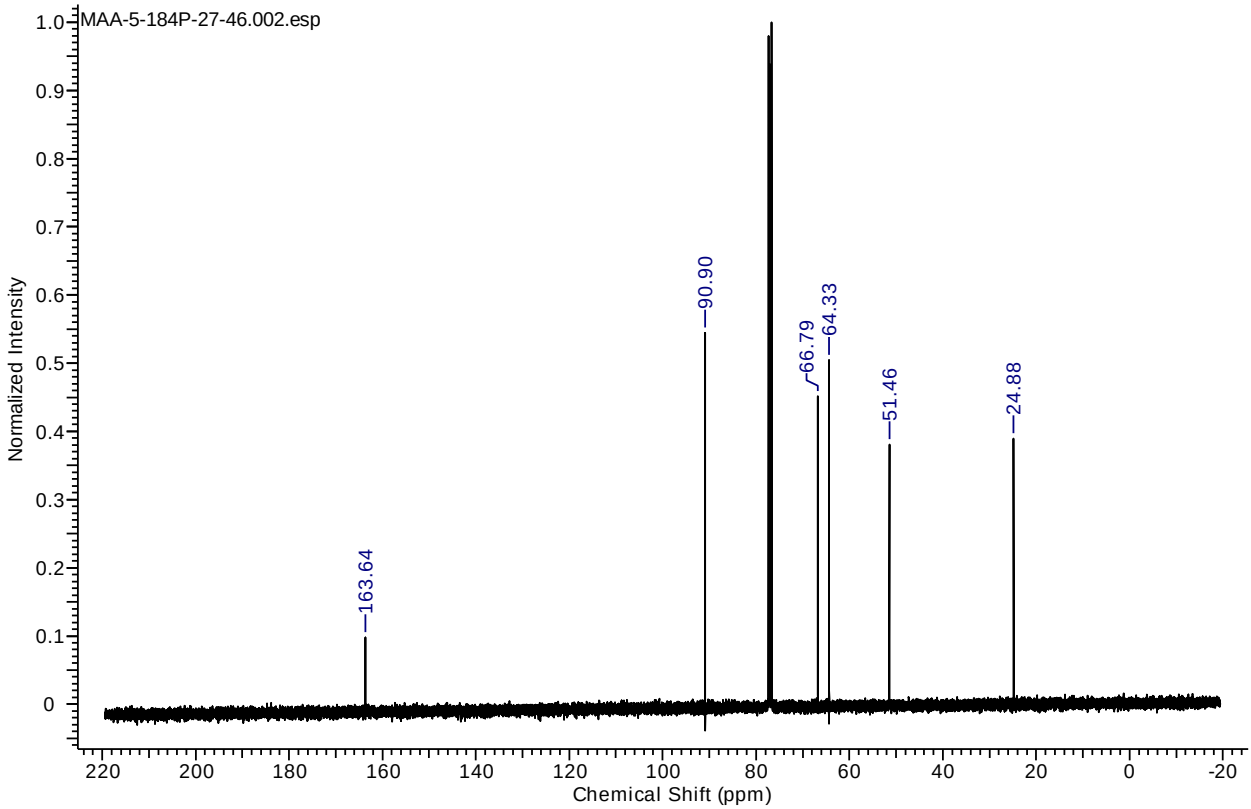

RI13-118-SHIFT-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.86 1.79 0.90 1.81 0.90 0.91 0.90 2.89 2.06 1.00

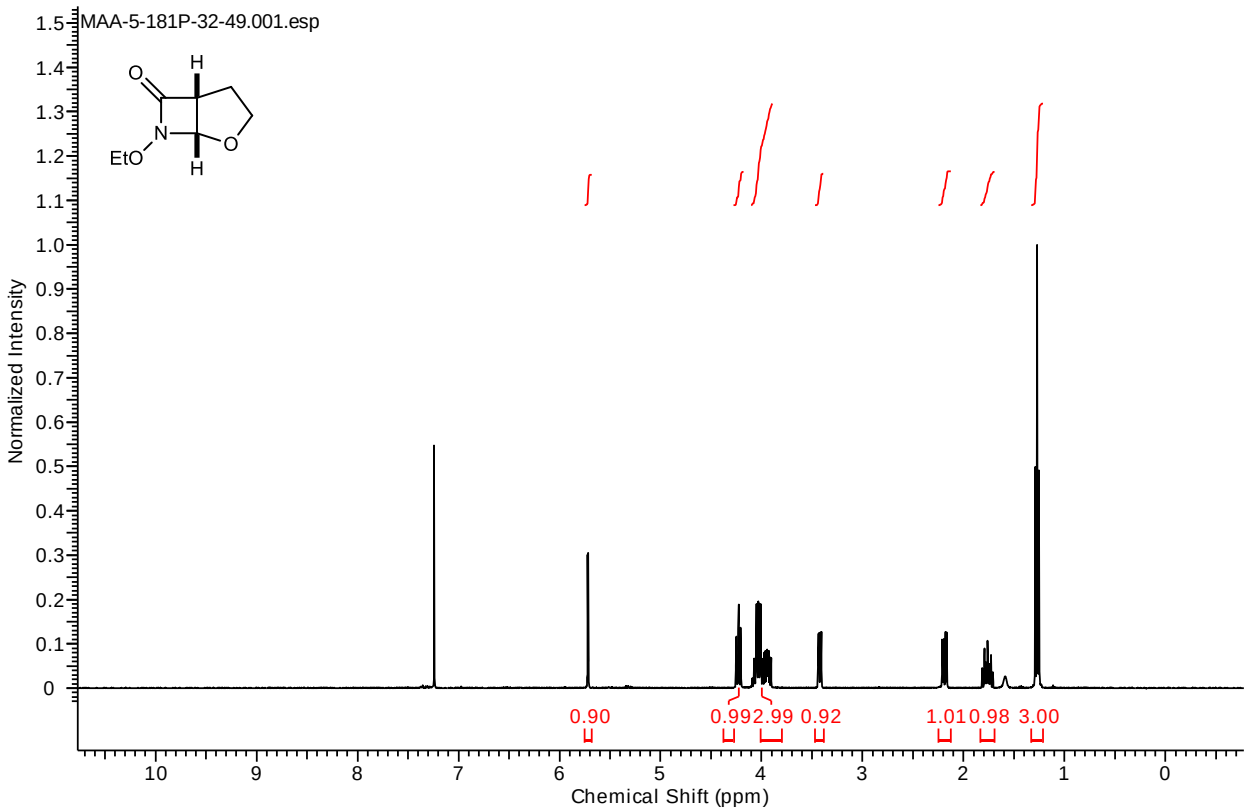

RI13-118-SHIFT-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
167.76
131.19
118.82
82.62
52.69
46.90
42.80
39.48
32.88
27.48
22.29

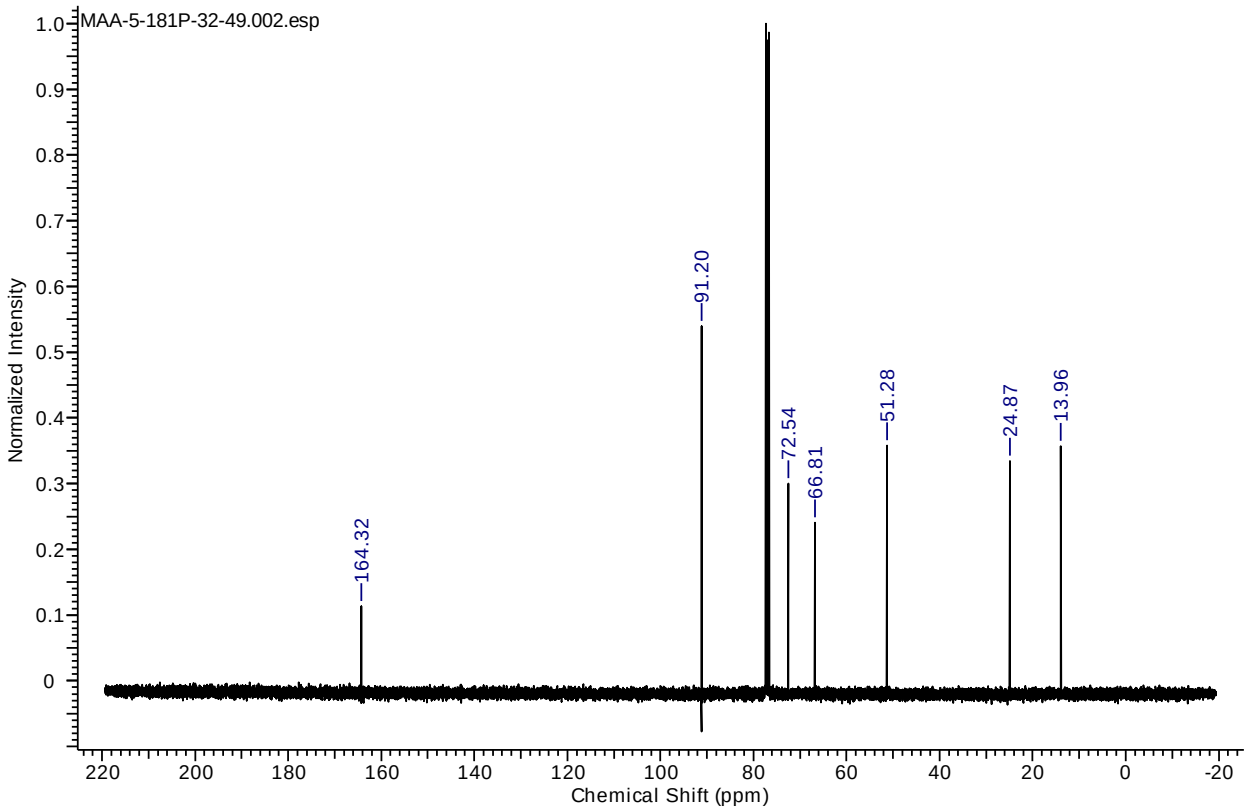

RI14-72-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
1.09
1.00
0.98
1.03
2.20
1.13
1.37
1.09

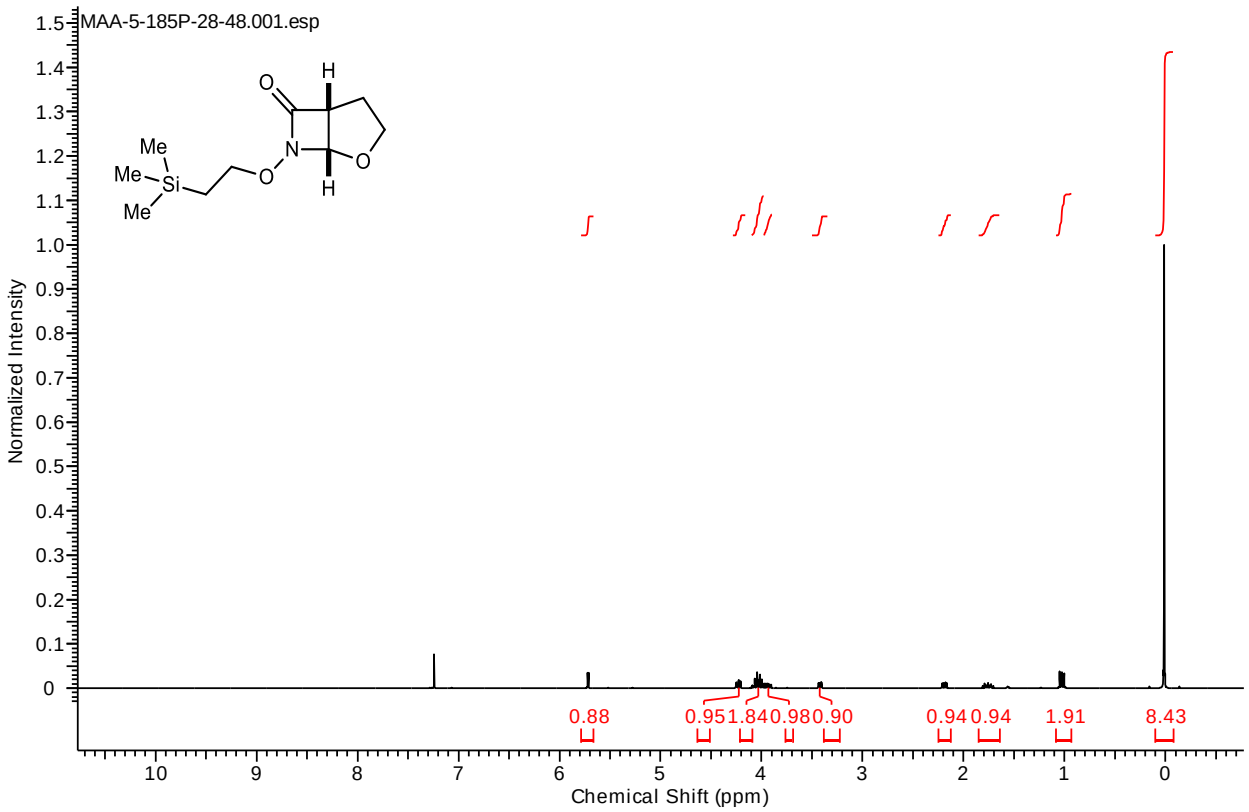

RI14-72-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
173.28
85.71
52.16
42.97
39.07
32.83
27.42
22.16

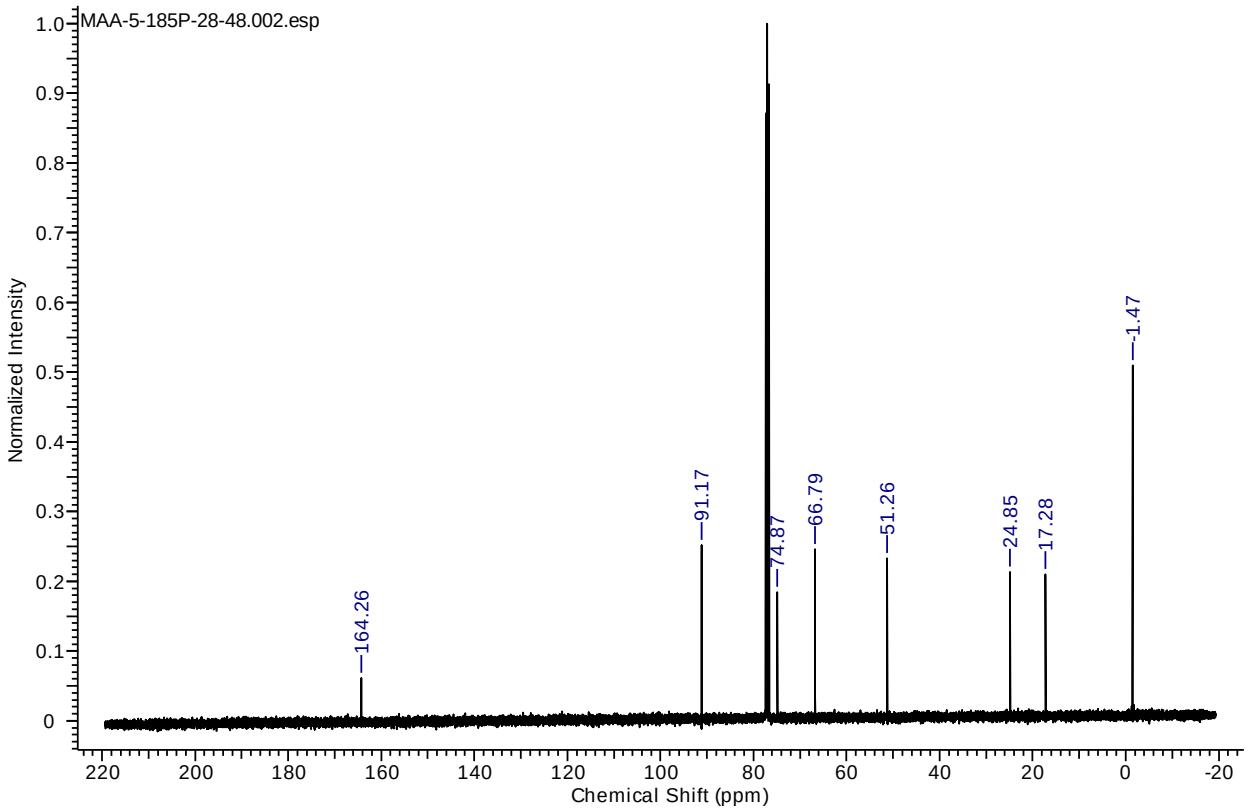

MAA-5-184P-27-46.001.esp
O
H
N
MeO
O
H
Normalized Intensity
0.91
1.00
1.05
2.92
0.93
1.02
1.00
Chemical Shift (ppm)

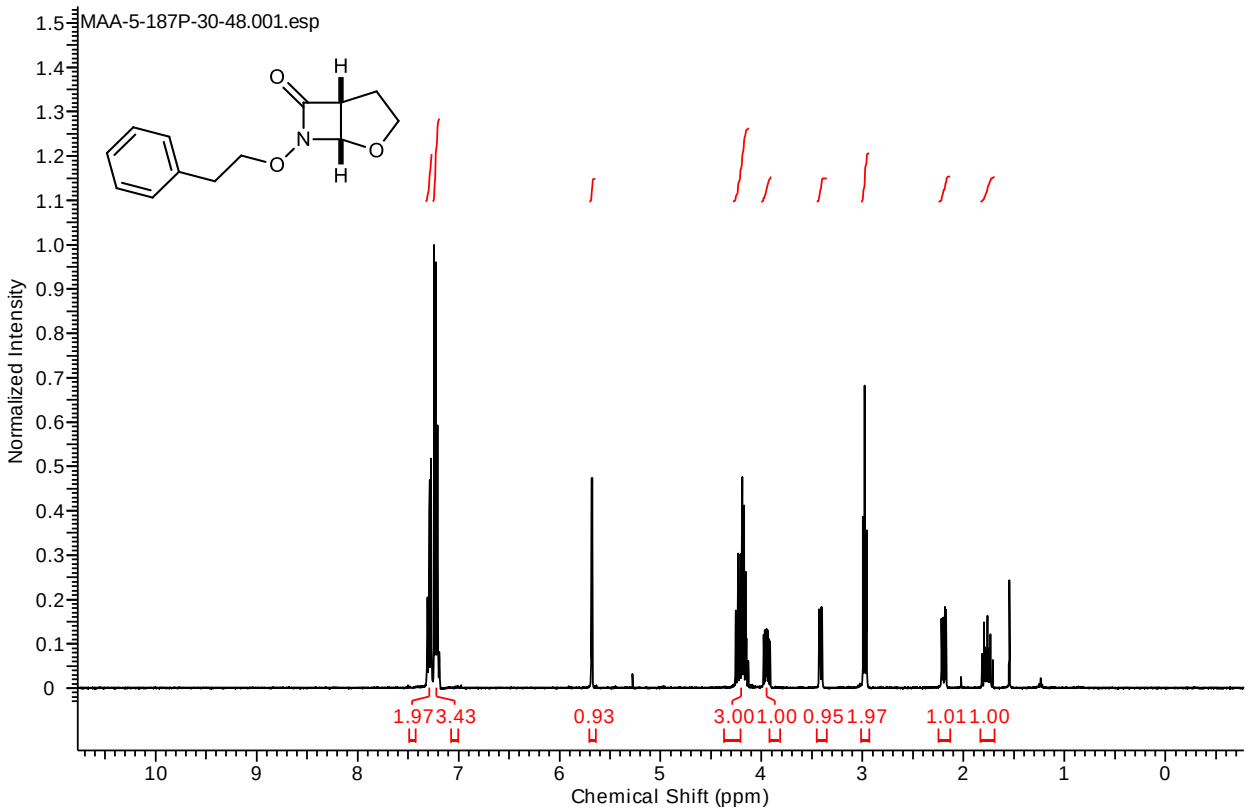

MAA-5-184P-27-46.002.esp
Normalized Intensity
163.64
90.90
66.79
64.33
51.46
24.88
Chemical Shift (ppm)

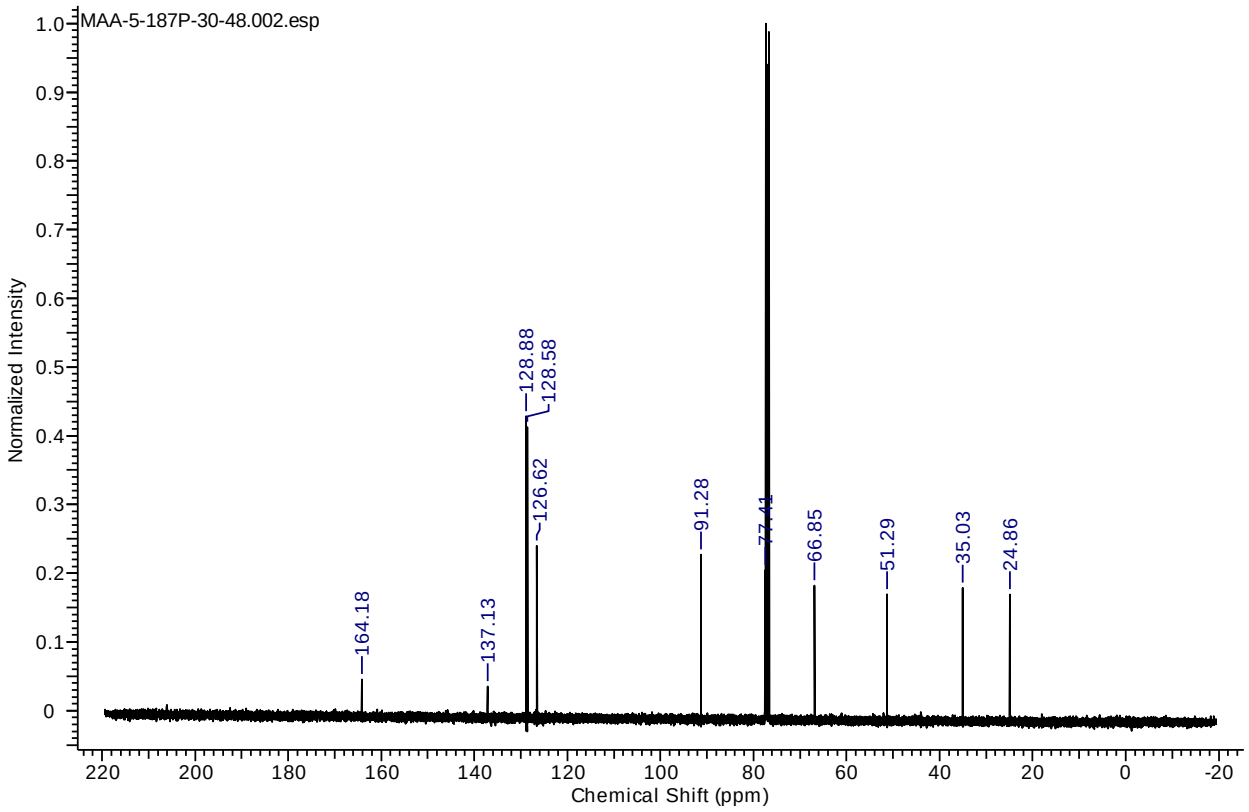

MAA-5-181P-32-49.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.90
0.99
2.99
0.92
1.01
0.98
3.00

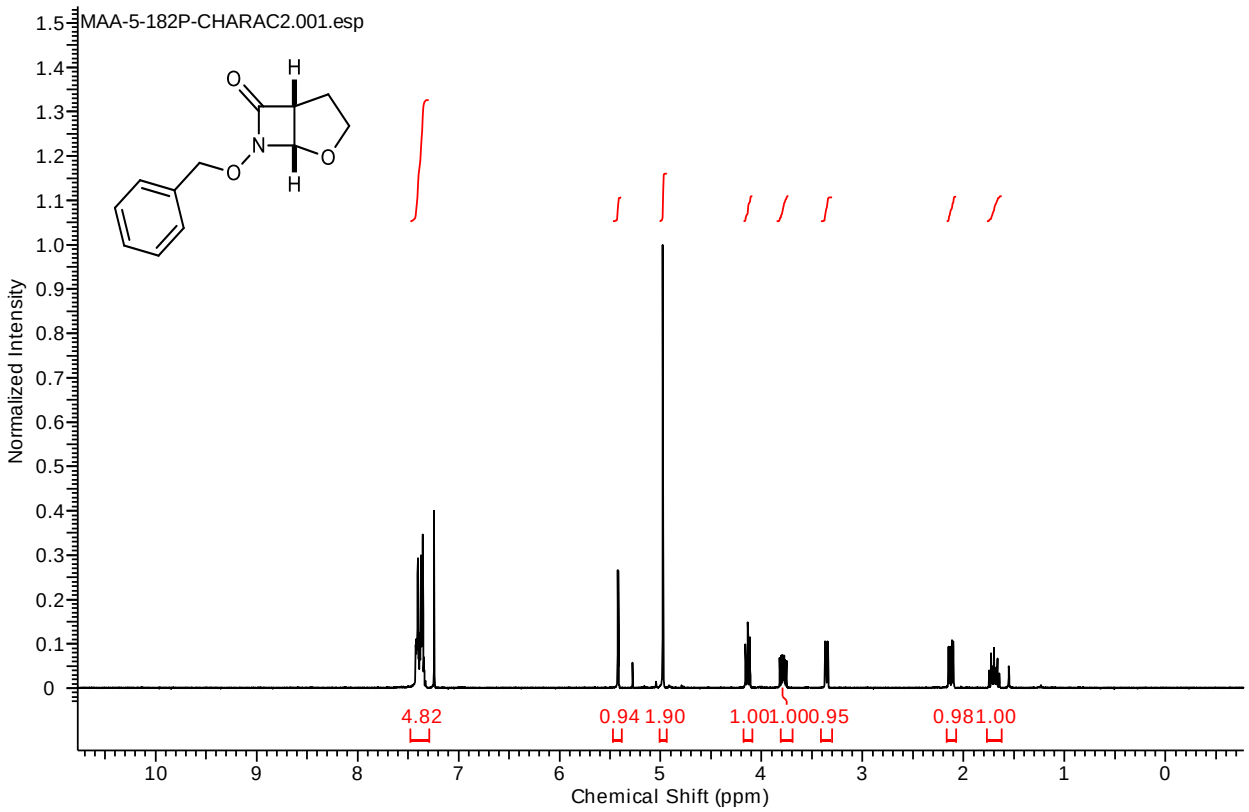

MAA-5-181P-32-49.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.32
91.20
72.54
66.81
51.28
24.87
13.96

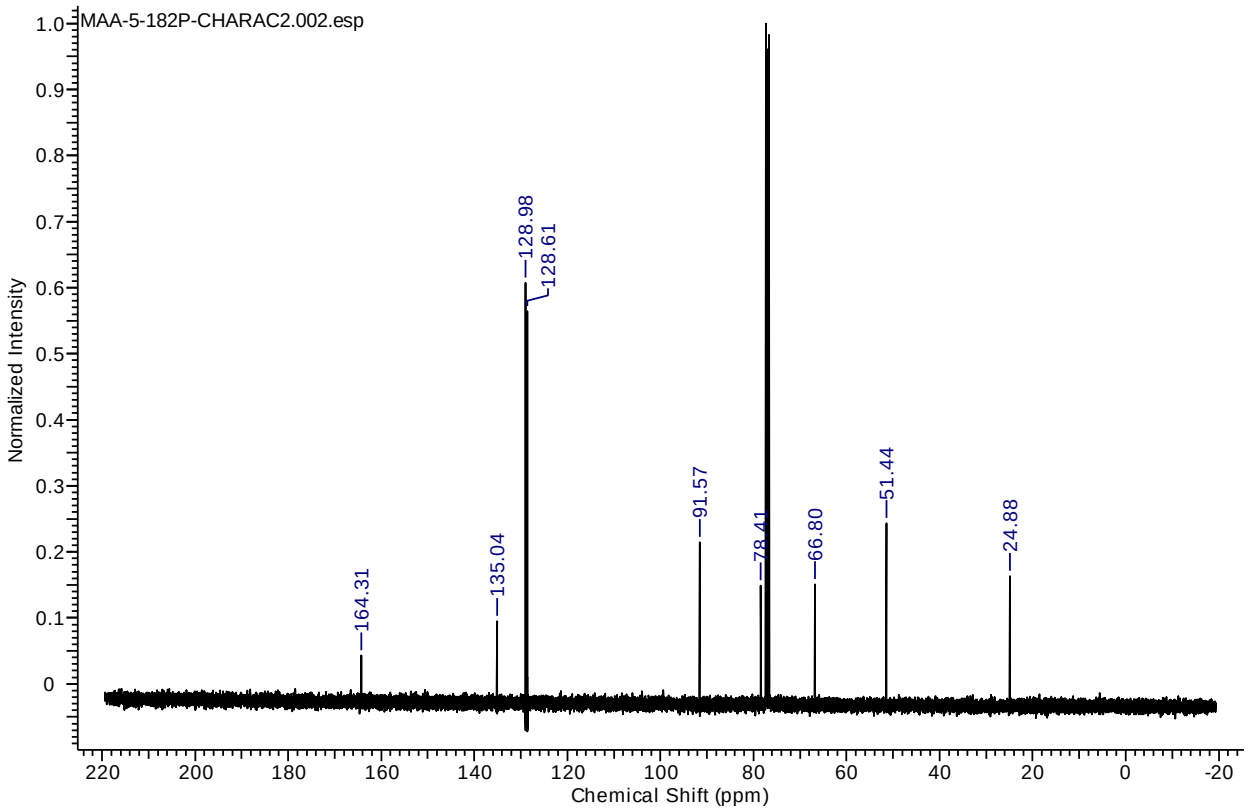

MAA-5-185P-28-48.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.88
0.95
1.84
0.98
0.90
0.94
0.94
1.91
8.43

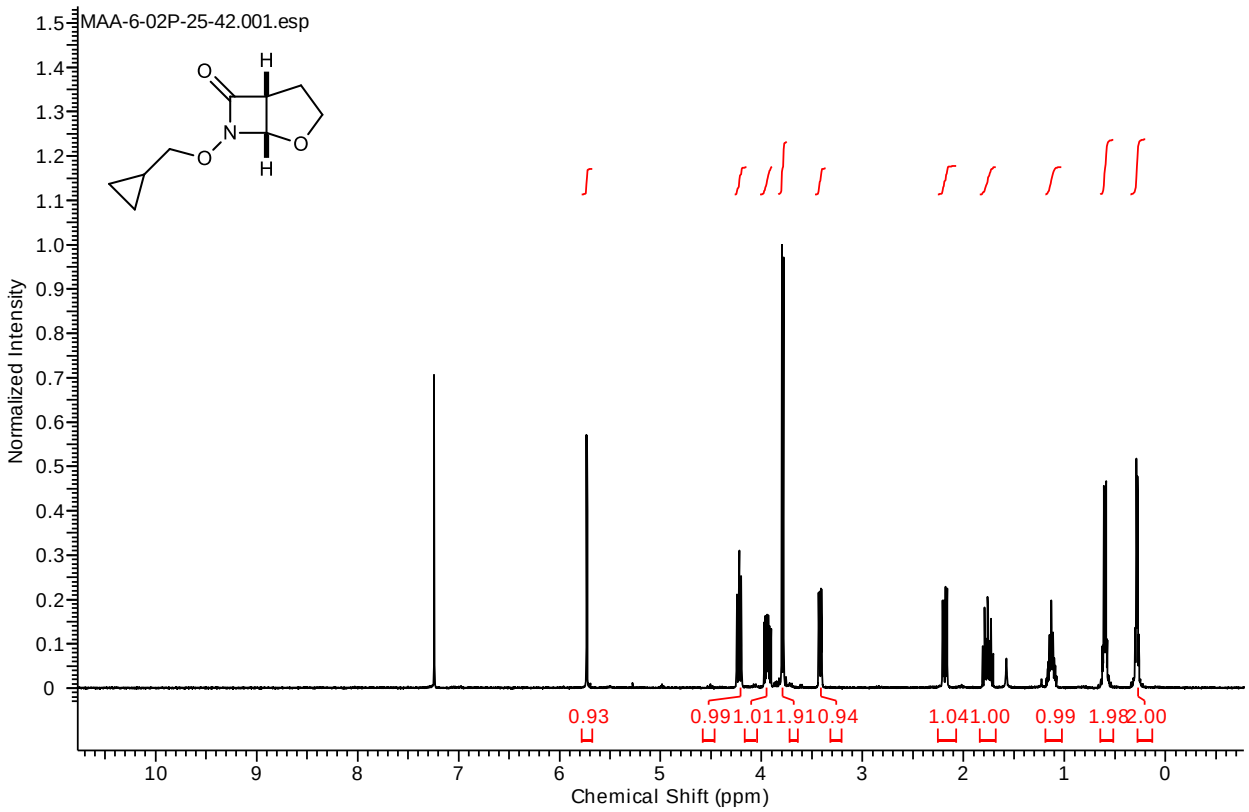

MAA-5-185P-28-48.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.26
91.17
74.87
66.79
51.26
24.85
17.28
-1.47

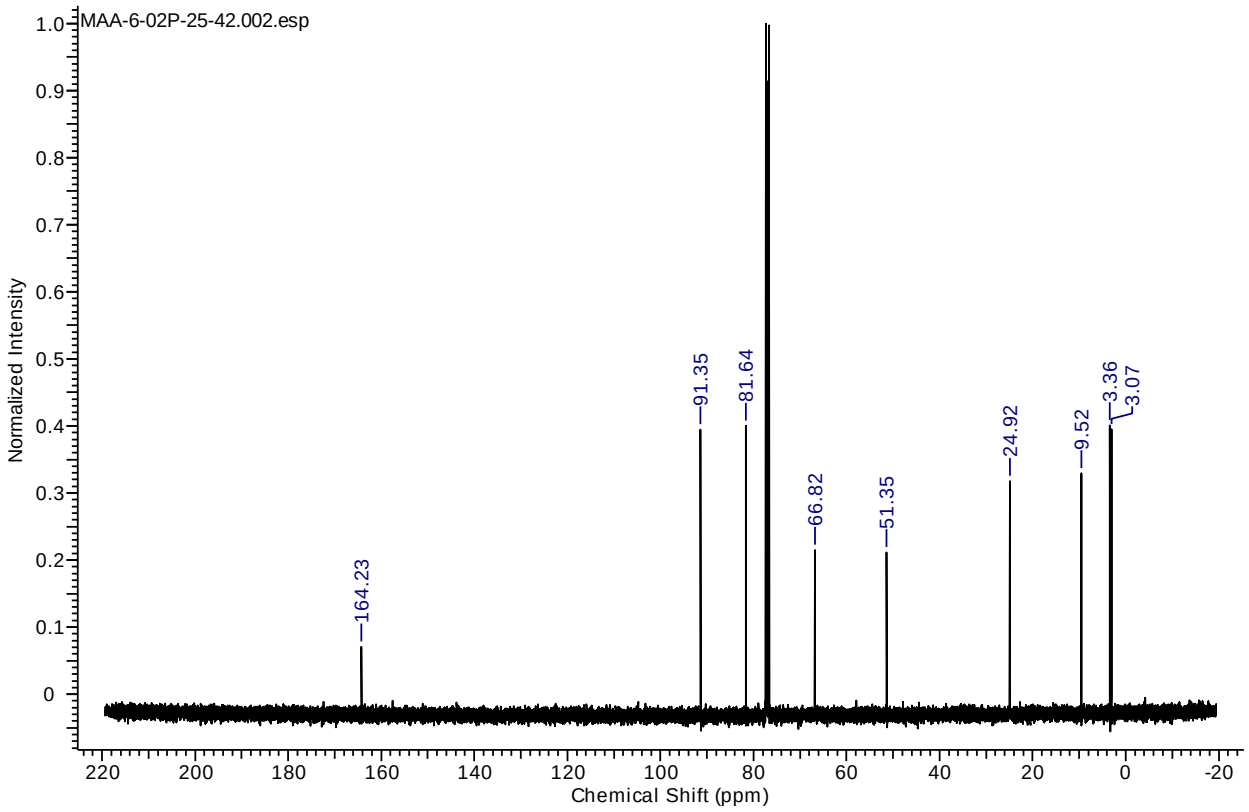

MAA-5-187P-30-48.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.97 3.43
0.93
3.00 1.00 0.95 1.97
1.01 1.00

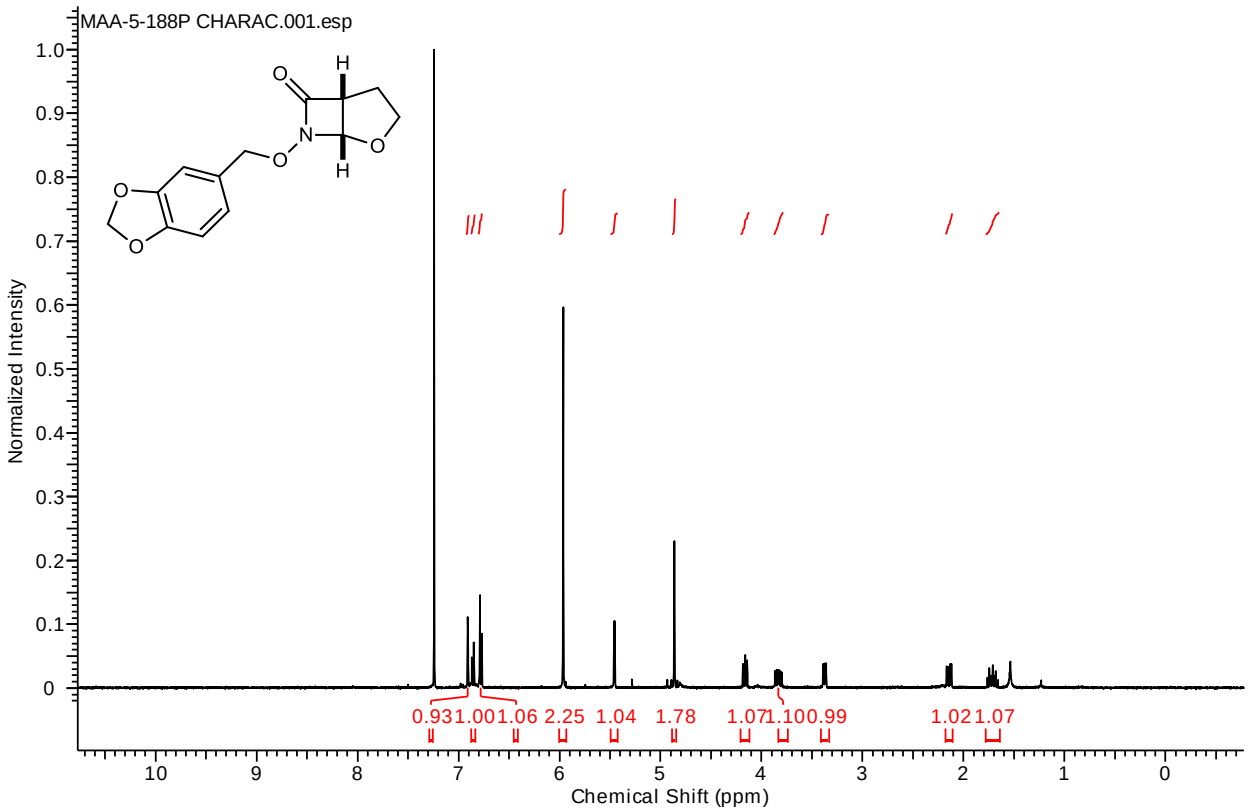

MAA-5-187P-30-48.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.18
137.13
128.88
128.58
126.62
91.28
77.41
66.85
51.29
35.03
24.86

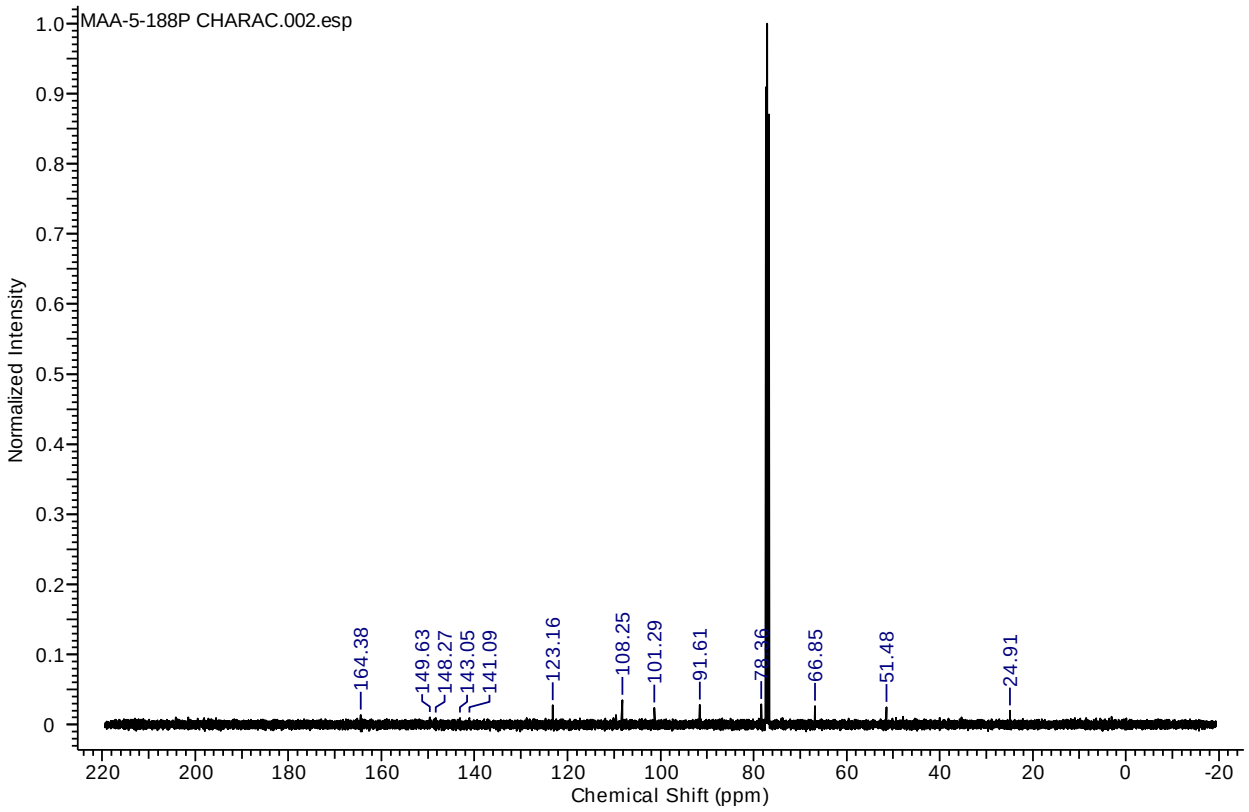

MAA-5-182P-CHARAC2.001.esp
Normalized Intensity
Chemical Shift (ppm)
4.82
0.94
1.90
1.00
1.00
0.95
0.98
1.00

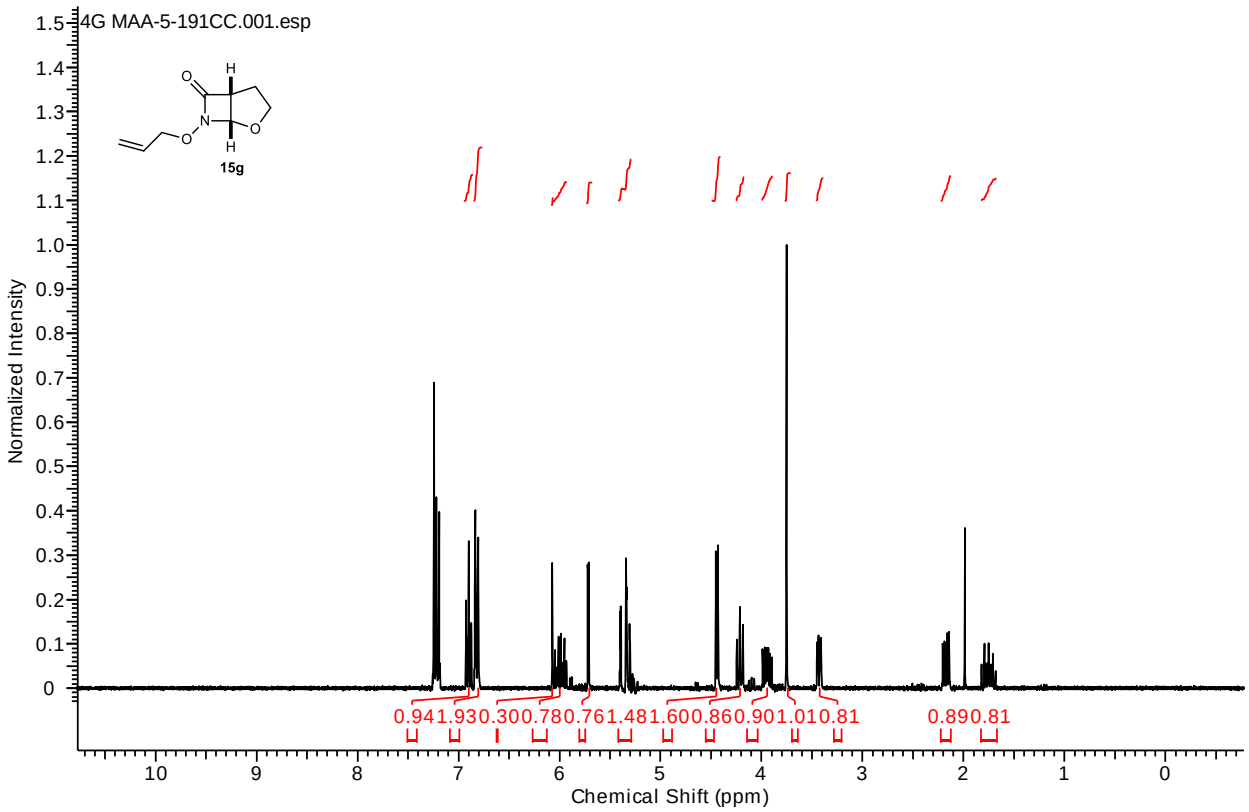

MAA-5-182P-CHARAC2.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.31
135.04
128.98
128.61
91.57
78.41
66.80
51.44
24.88

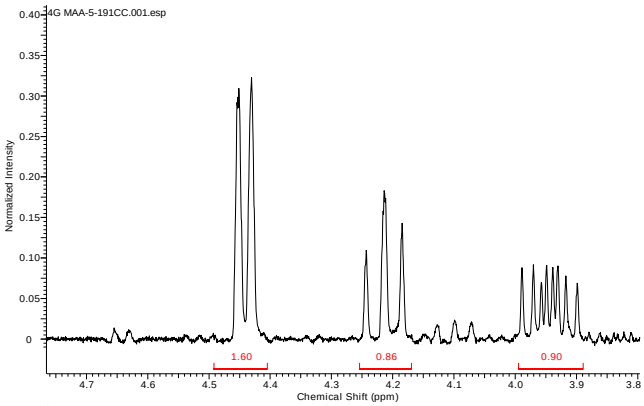

MAA-6-02P-25-42.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.93
0.99
1.01
1.91
0.94
1.04
1.00
0.99
1.98
2.00

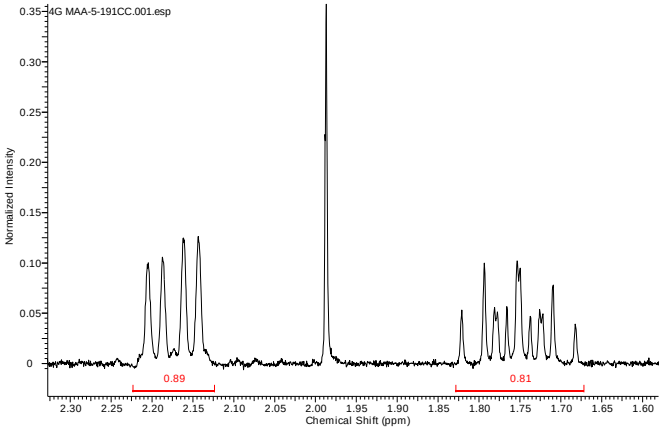

MAA-6-02P-25-42.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.23
91.35
81.64
66.82
51.35
24.92
9.52
3.36
3.07

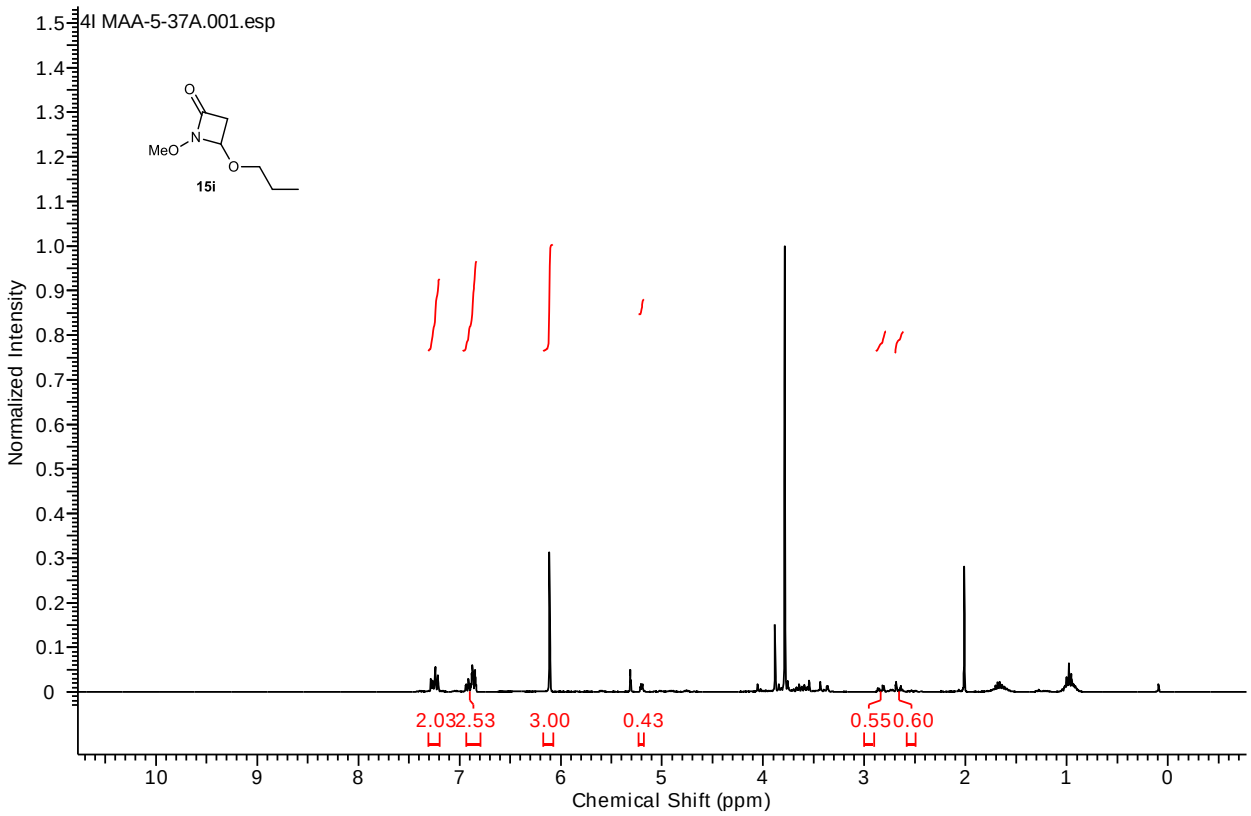

MAA-5-188P CHARAC.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.93 1.00 1.06 2.25 1.04 1.78 1.07 1.10 0.99 1.02 1.07

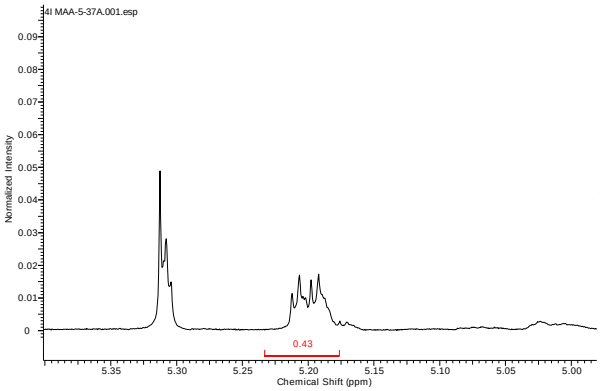

MAA-5-188P CHARAC.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.38
149.63
148.27
143.05
141.09
123.16
108.25
101.29
91.61
78.36
66.85
51.48
24.91

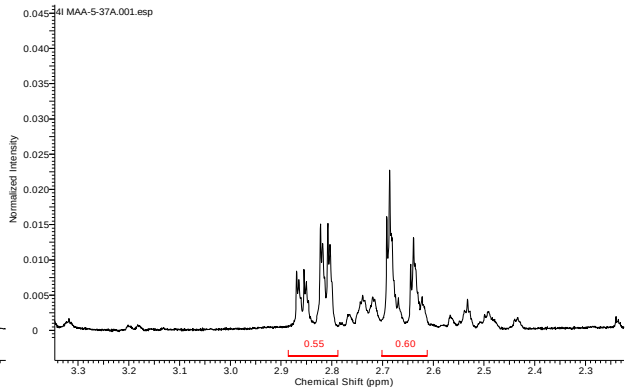

4G MAA-5-191CC.001.esp
15g
Normalized Intensity
Chemical Shift (ppm)
0.941.930.300.780.761.481.600.860.901.010.81
0.890.81

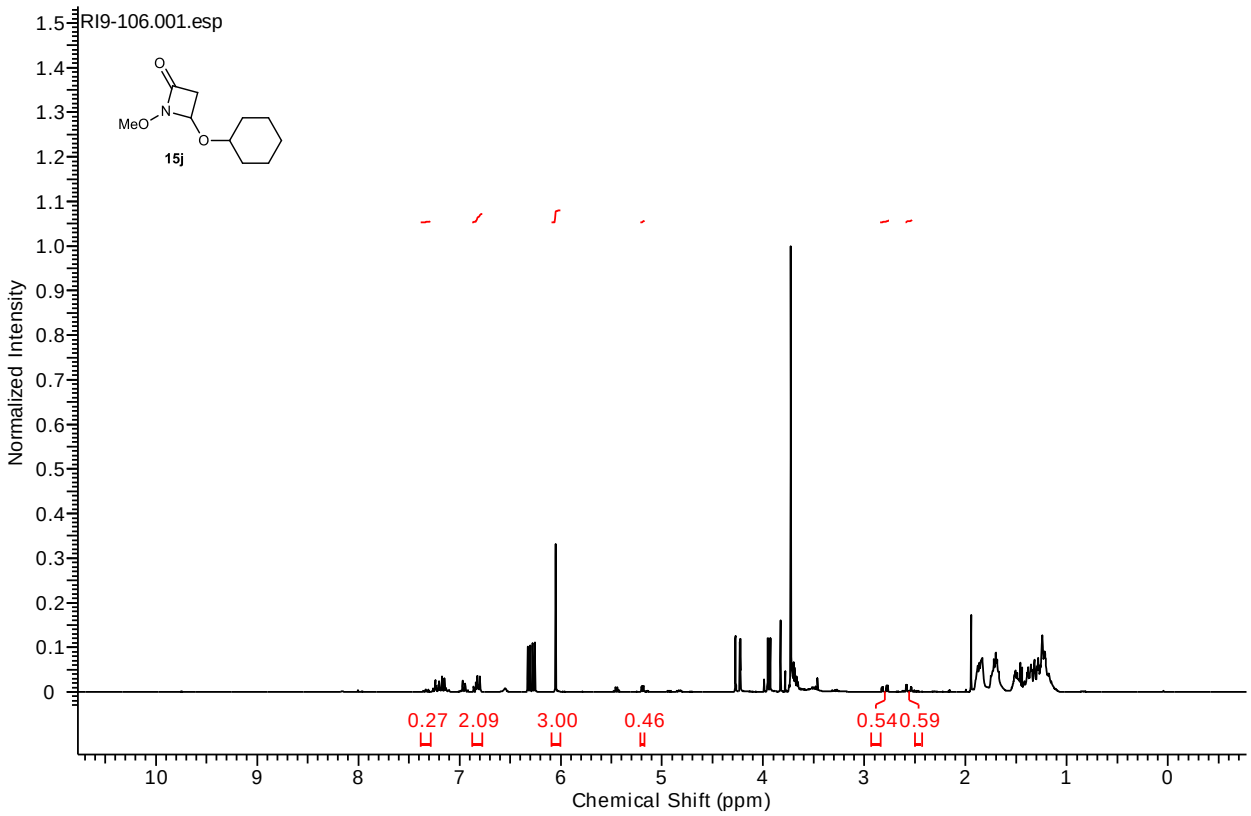

4G MAA-5-191CC.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.60
0.86
0.90

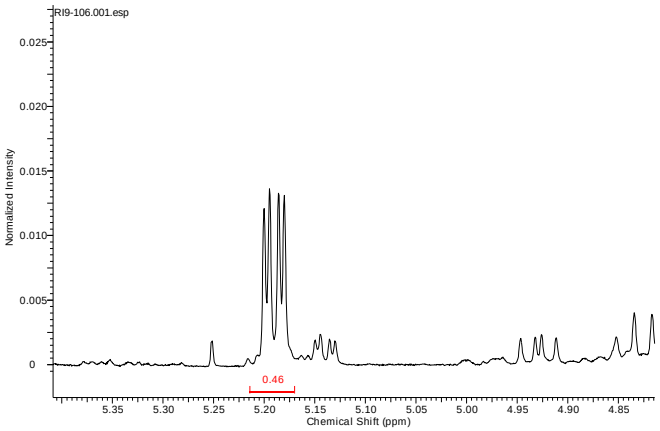

4G MAA-5-191CC.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.89
0.81

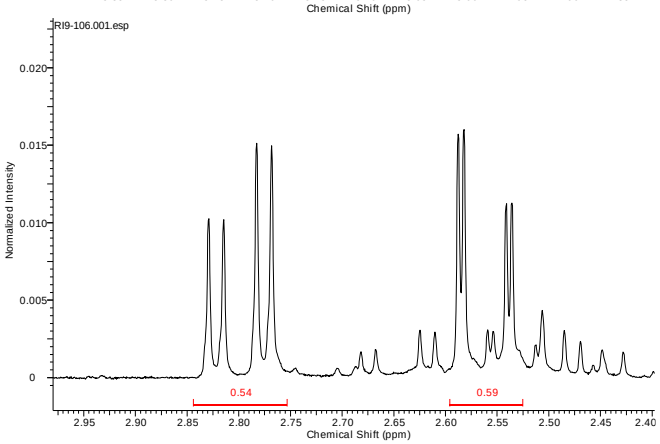

4I MAA-5-37A.001.esp
MeO
N
O
O
15i
Normalized Intensity
Chemical Shift (ppm)
2.03
2.53
3.00
0.43
0.55
0.60

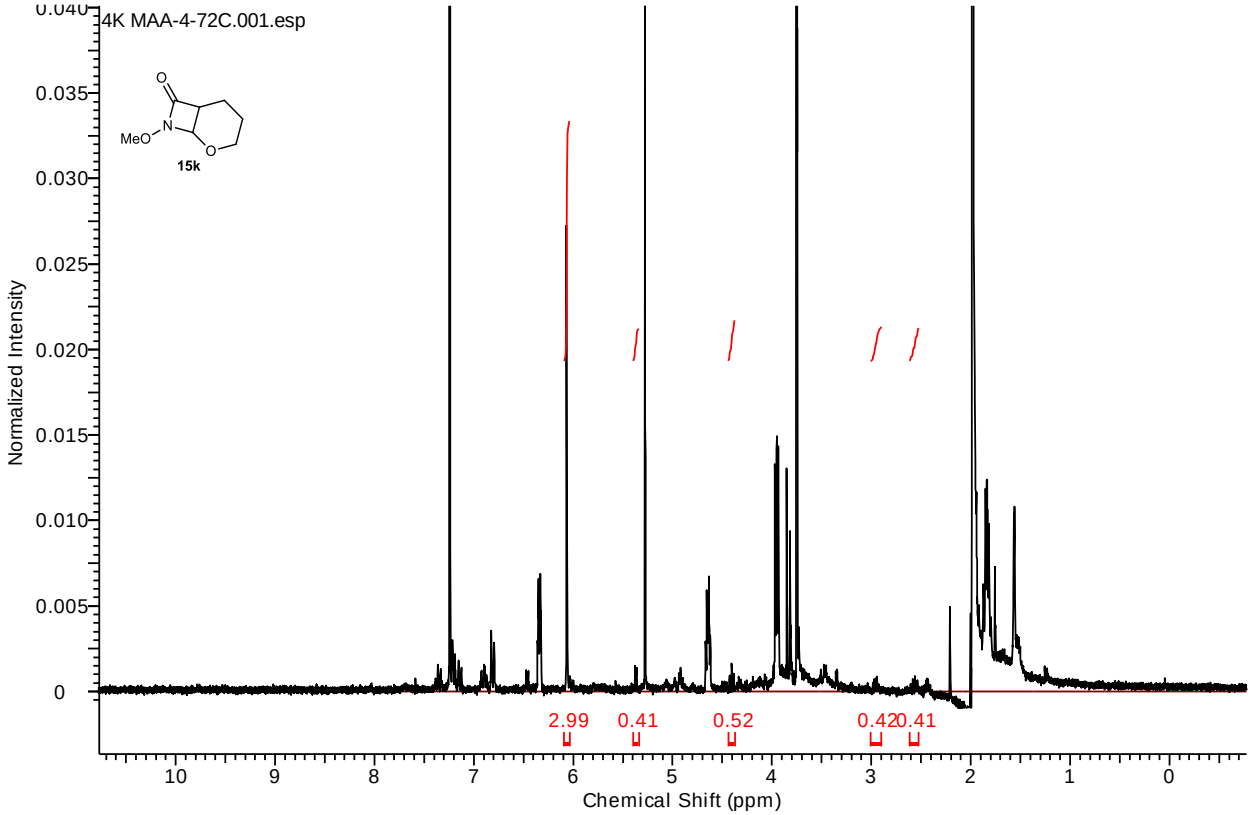

4I MAA-5-37A.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.43

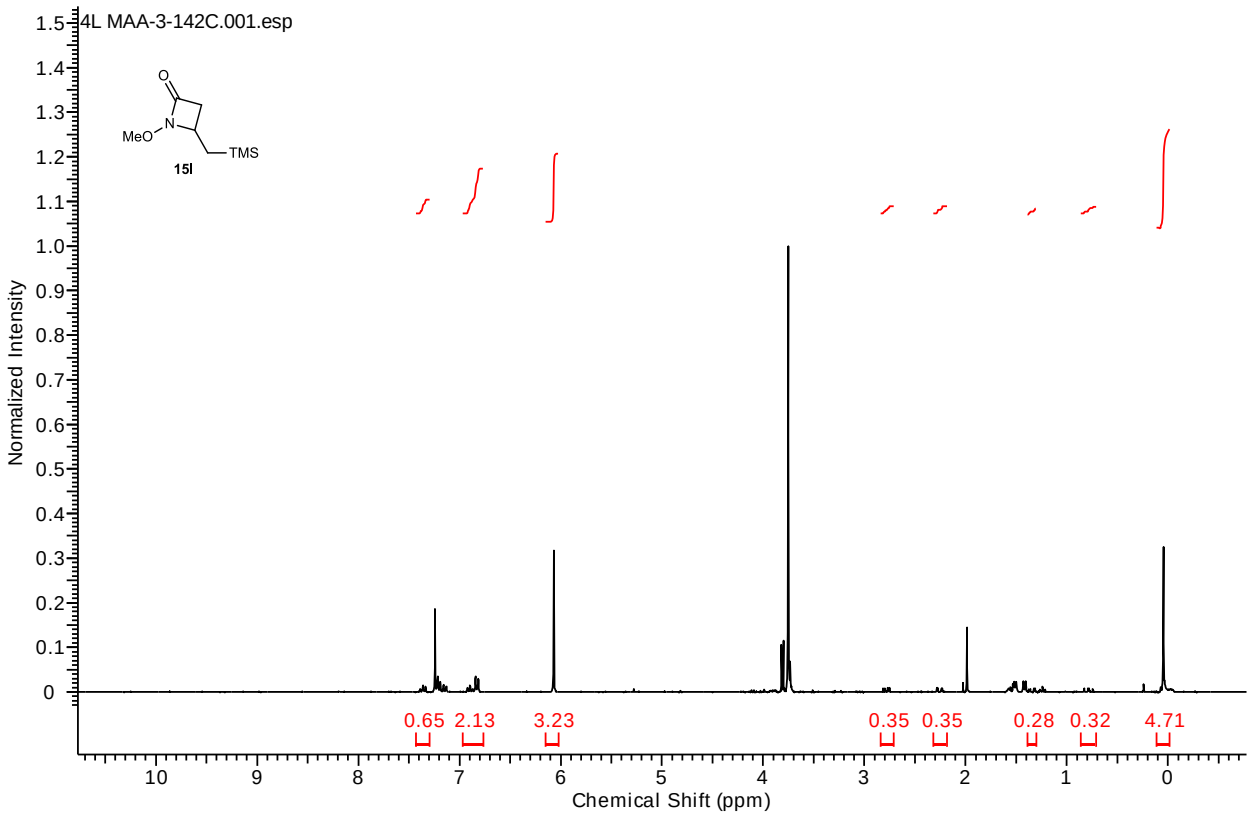

4I MAA-5-37A.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.55
0.60

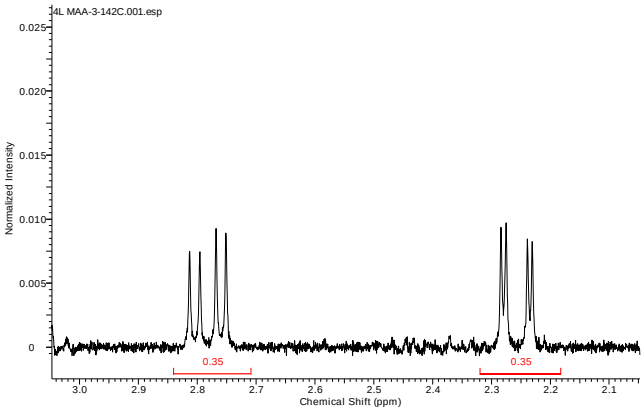

RI9-106.001.esp
MeO
N
O
O
15j
Normalized Intensity
Chemical Shift (ppm)
0.27
2.09
3.00
0.46
0.54
0.59

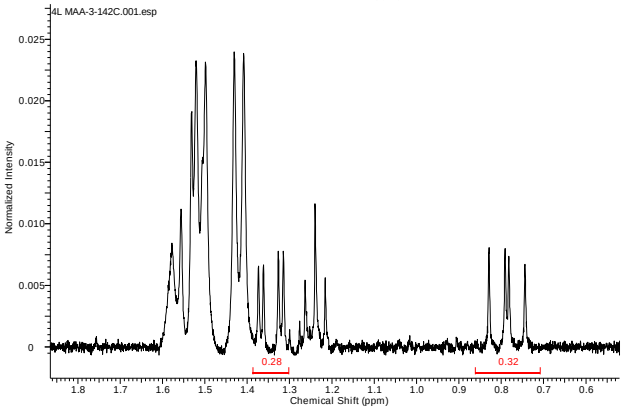

RI9-106.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.46

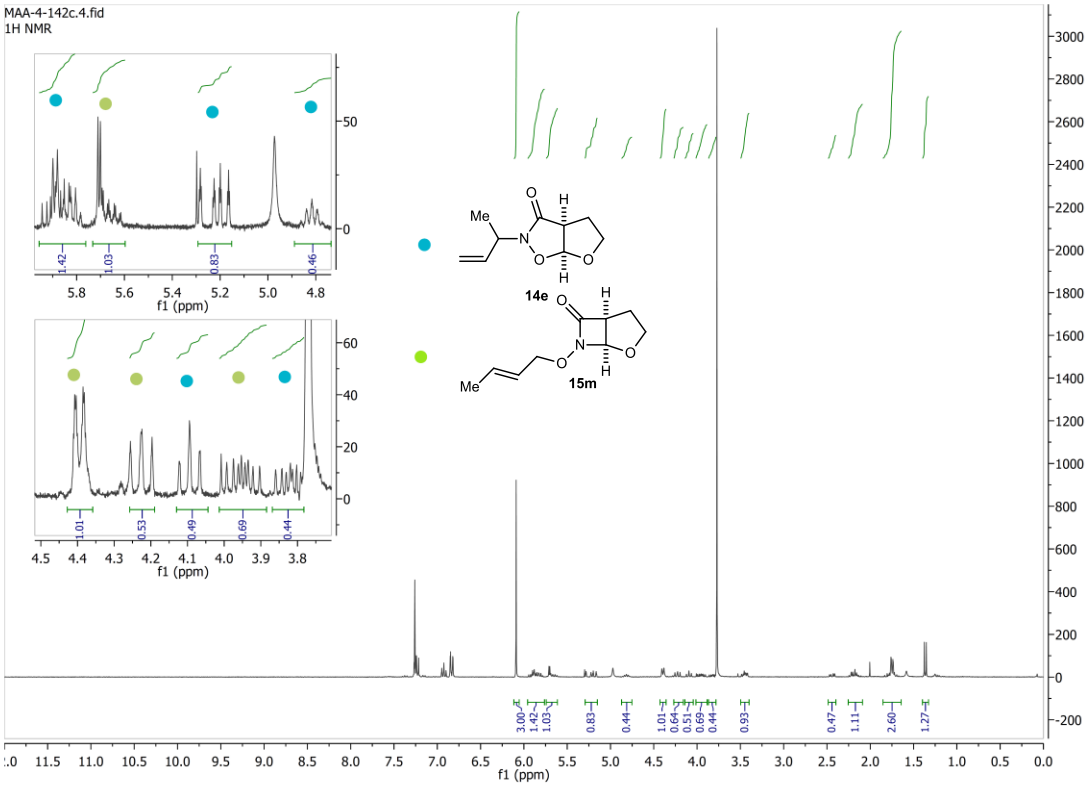

RI9-106.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.54
0.59

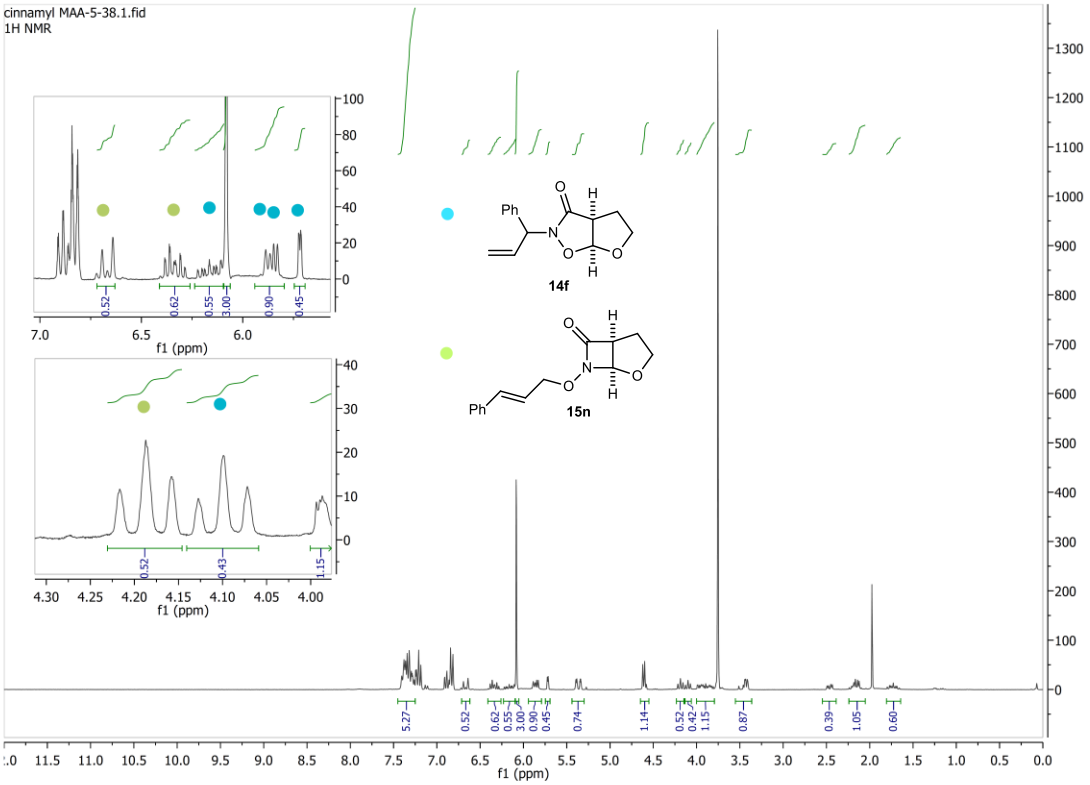

4K MAA-4-72C.001.esp
MeO
N
O
O
15k
Normalized Intensity
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0
2.99
0.41
0.52
0.42
0.41
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

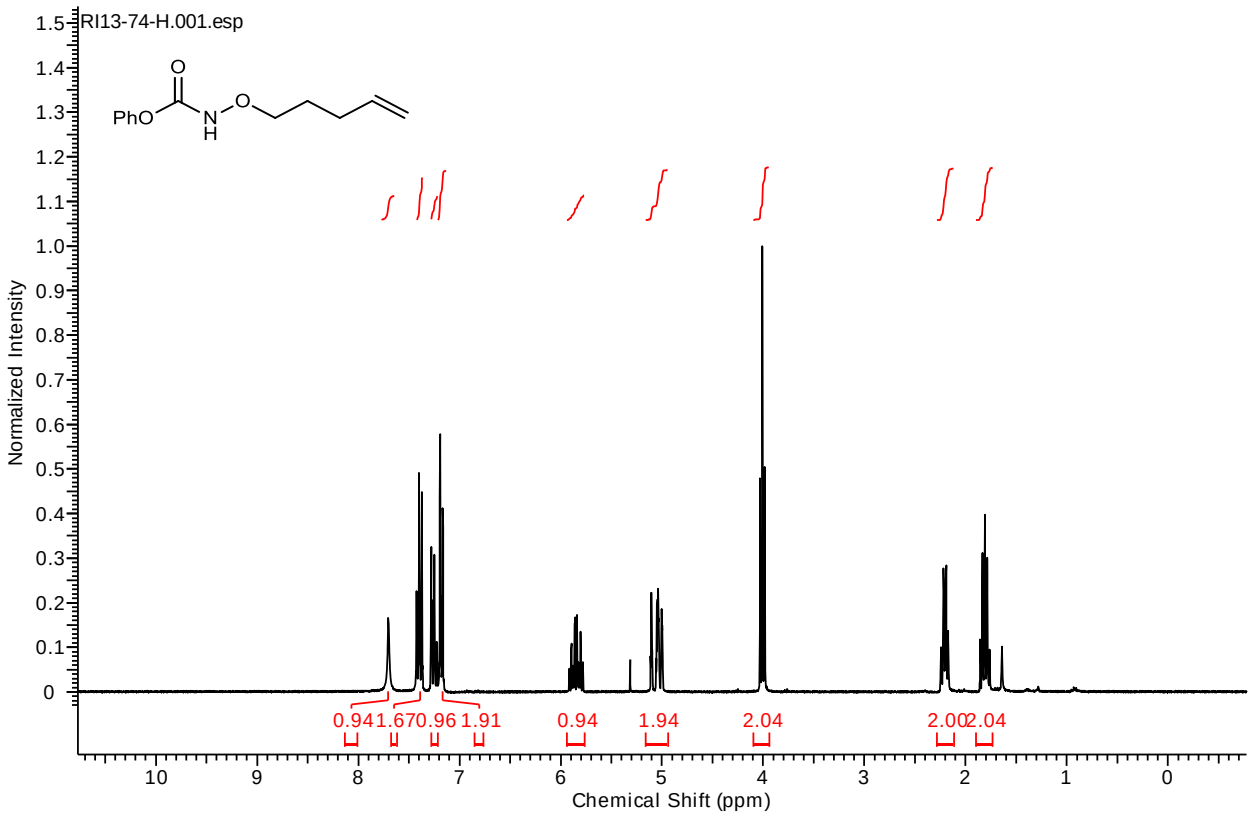

4L MAA-3-142C.001.esp
O
N
MeO
TMS
15l
Normalized Intensity
0.65 2.13 3.23 0.35 0.35 0.28 0.32 4.71
Chemical Shift (ppm)

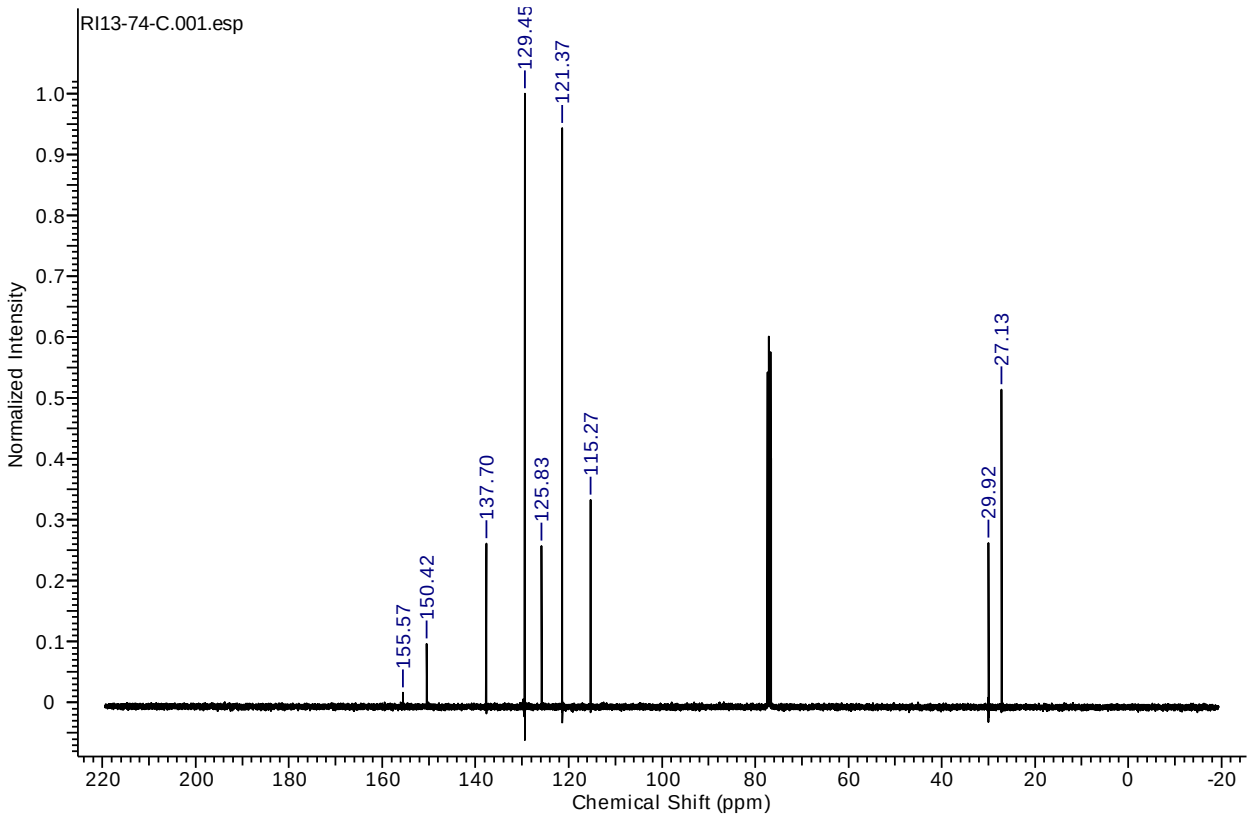

4L MAA-3-142C.001.esp
Normalized Intensity
0.35
0.35
Chemical Shift (ppm)

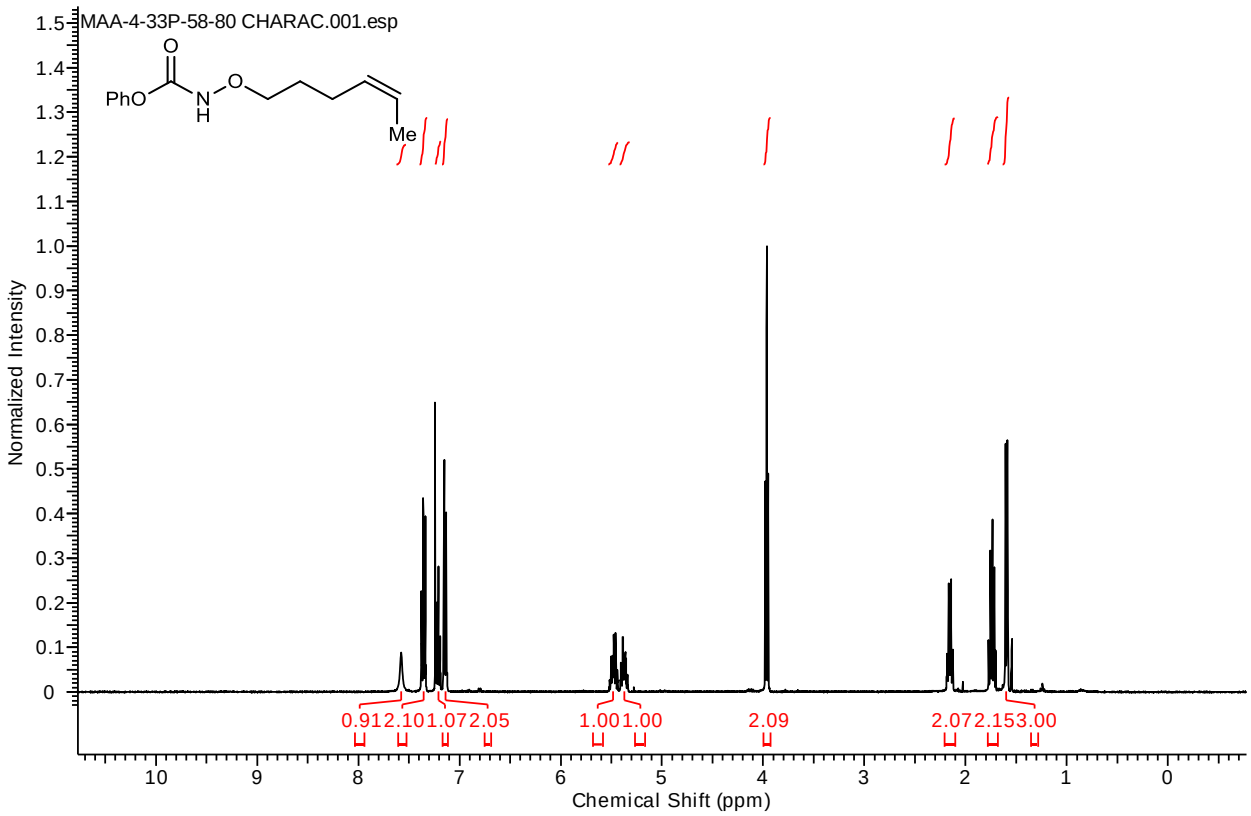

4L MAA-3-142C.001.esp
Normalized Intensity
0.28
0.32
Chemical Shift (ppm)

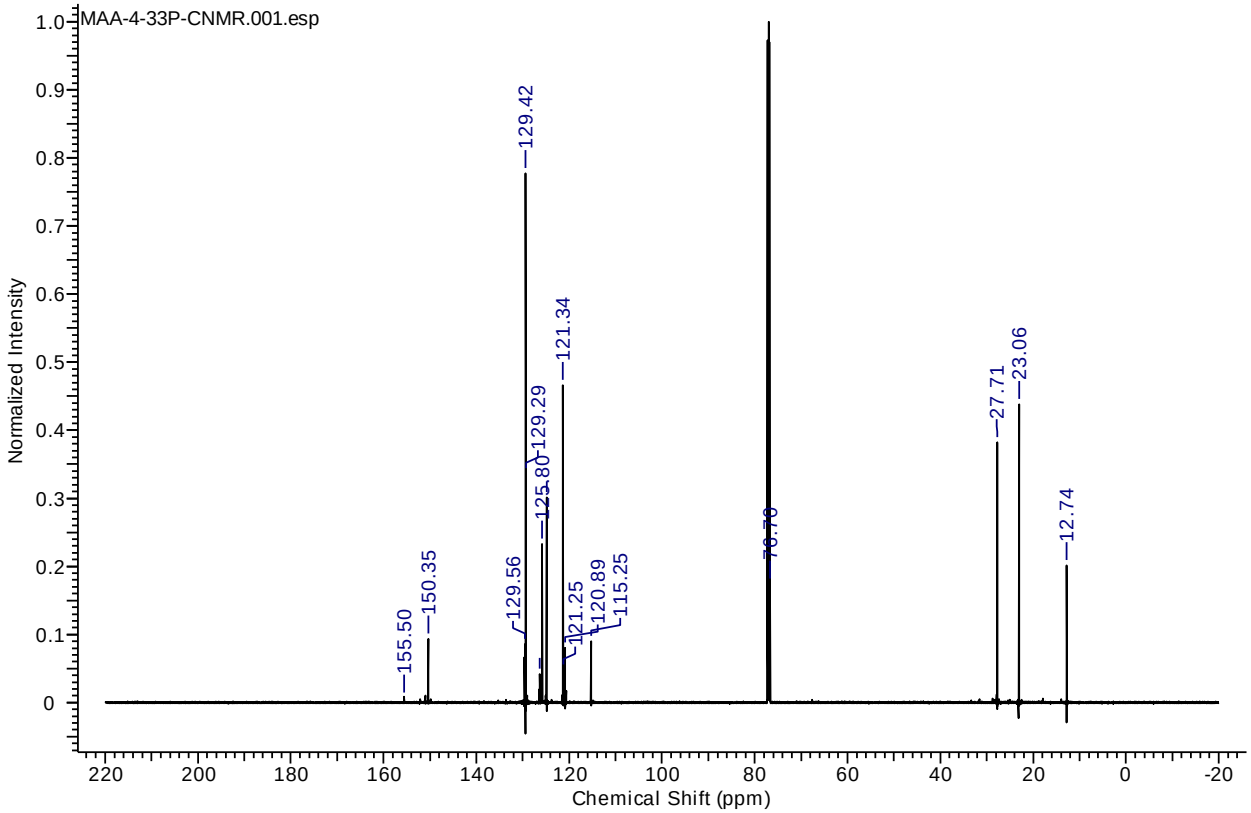

MAA-4-142c.4.fid
1H NMR
14e
15m
f1 (ppm)

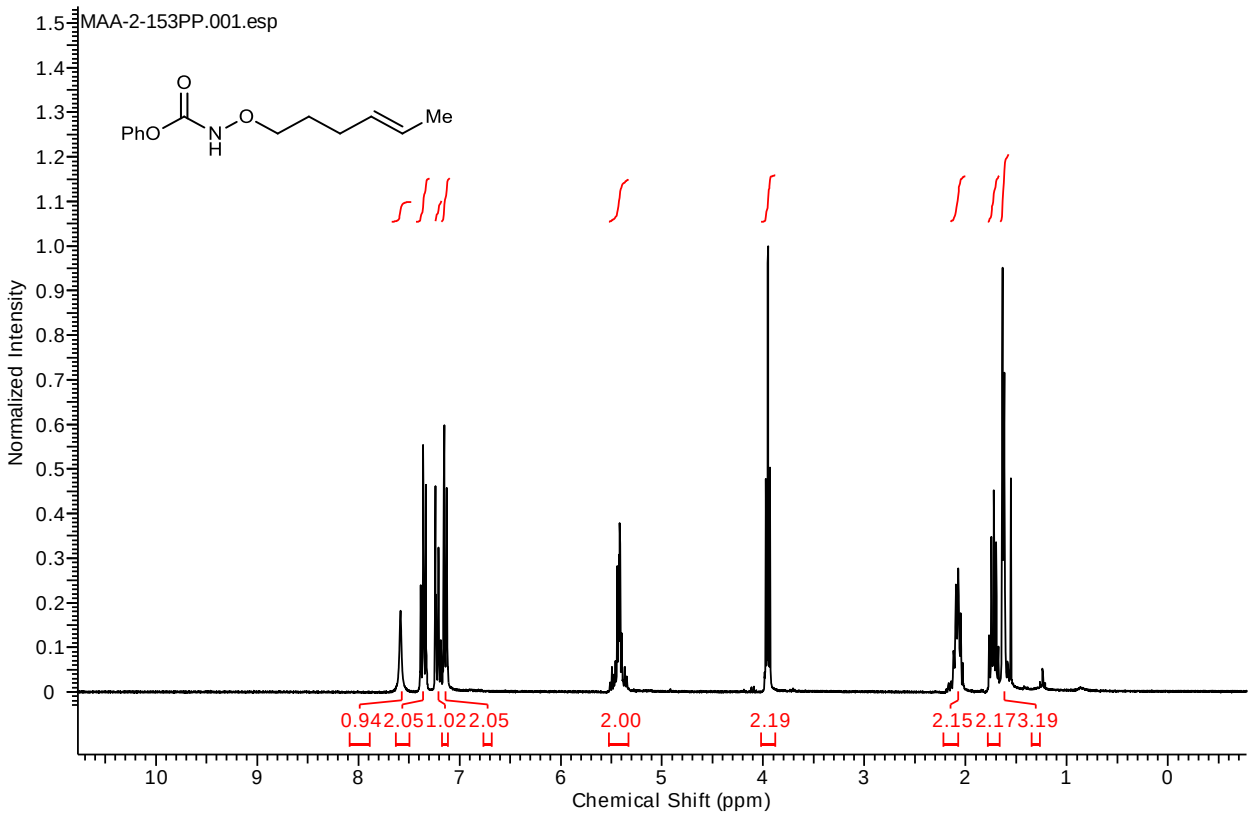

cinnamyl MAA-5-38.1.fid
1H NMR
14f
15n
f1 (ppm)

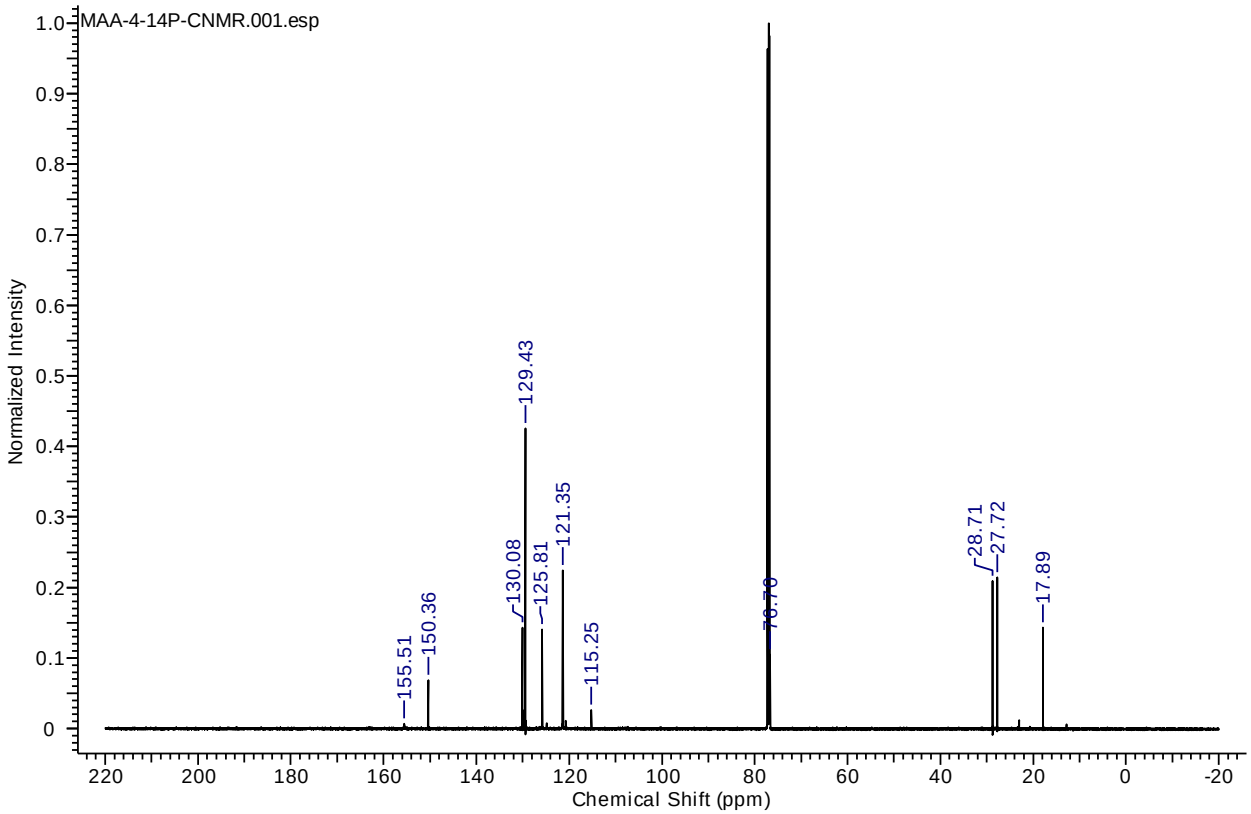

RI13-74-H.001.esp
PhO
O
N
H
O
Normalized Intensity
0.94
1.67
0.96
1.91
0.94
1.94
2.04
2.00
2.04
Chemical Shift (ppm)

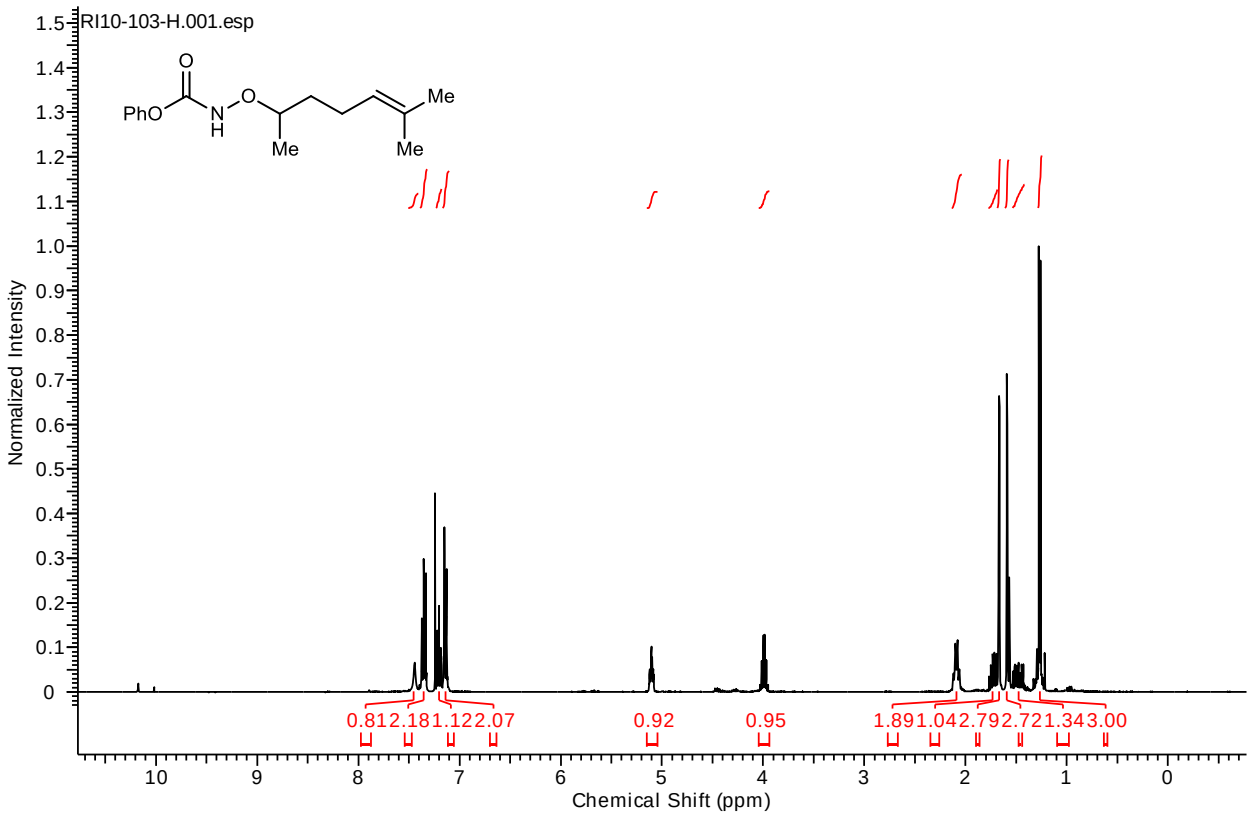

RI13-74-C.001.esp
129.45
121.37
137.70
125.83
115.27
155.57
150.42
29.92
27.13
Normalized Intensity
Chemical Shift (ppm)

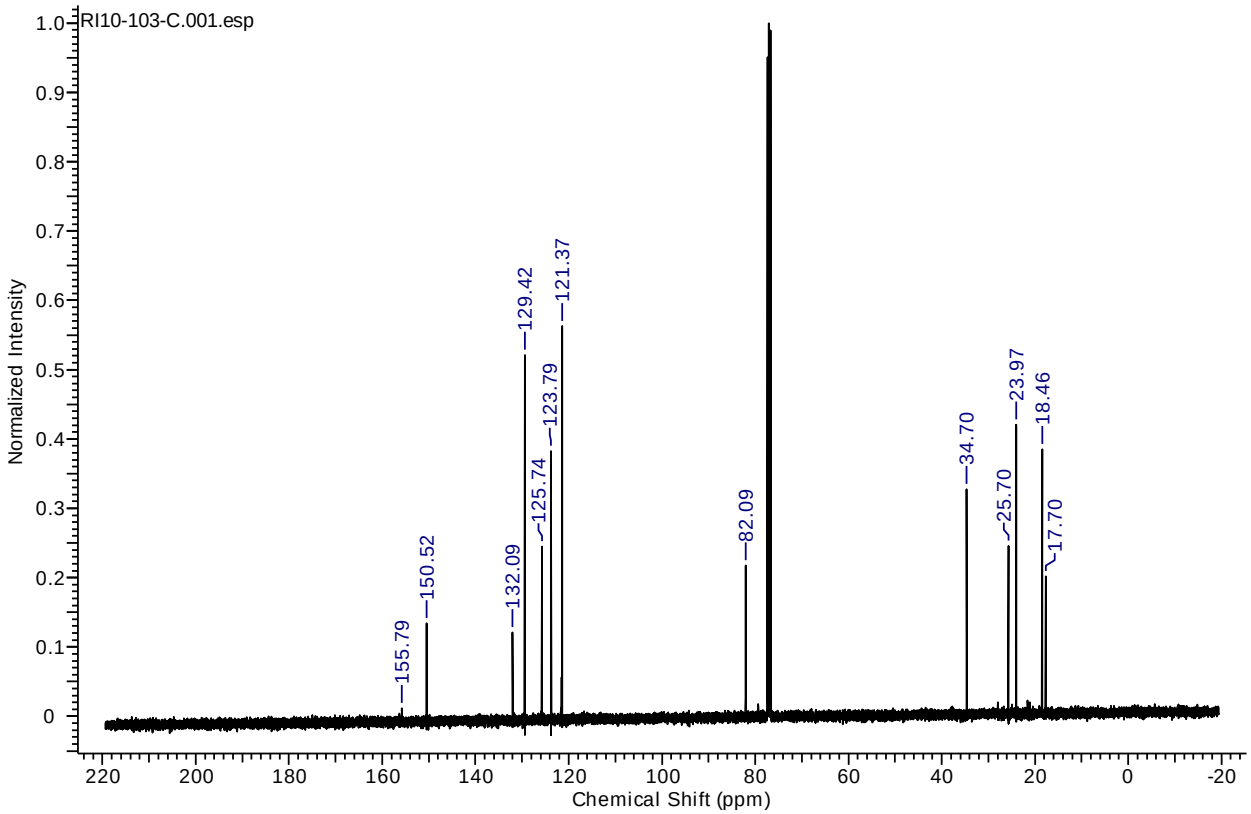

MAA-4-33P-58-80 CHARAC.001.esp
PhO
O
N
H
O
Me
Normalized Intensity
0.912.101.072.05
1.001.00
2.09
2.072.153.00
Chemical Shift (ppm)

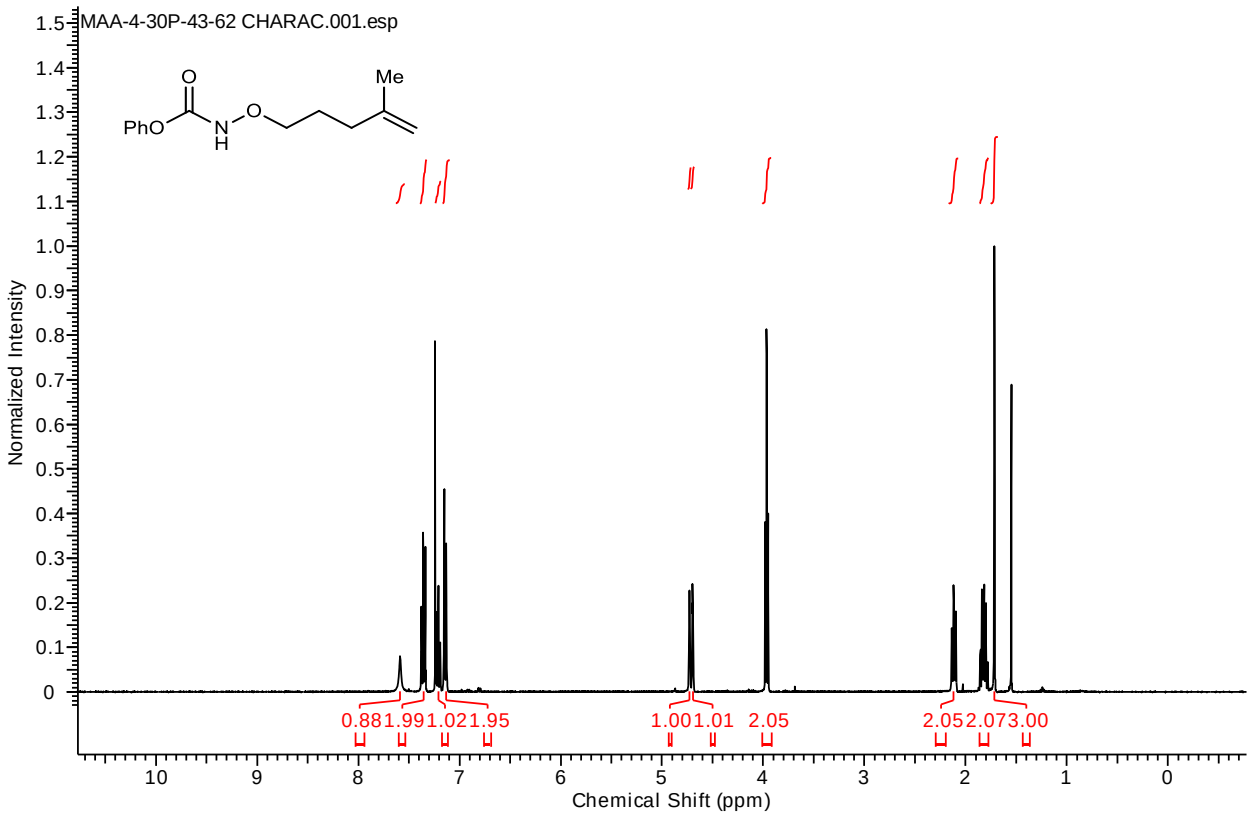

MAA-4-33P-CNMR.001.esp
Normalized Intensity
129.42
121.34
129.29
125.80
155.50
150.35
129.56
121.25
120.89
115.25
76.76
27.71
23.06
12.74
Chemical Shift (ppm)

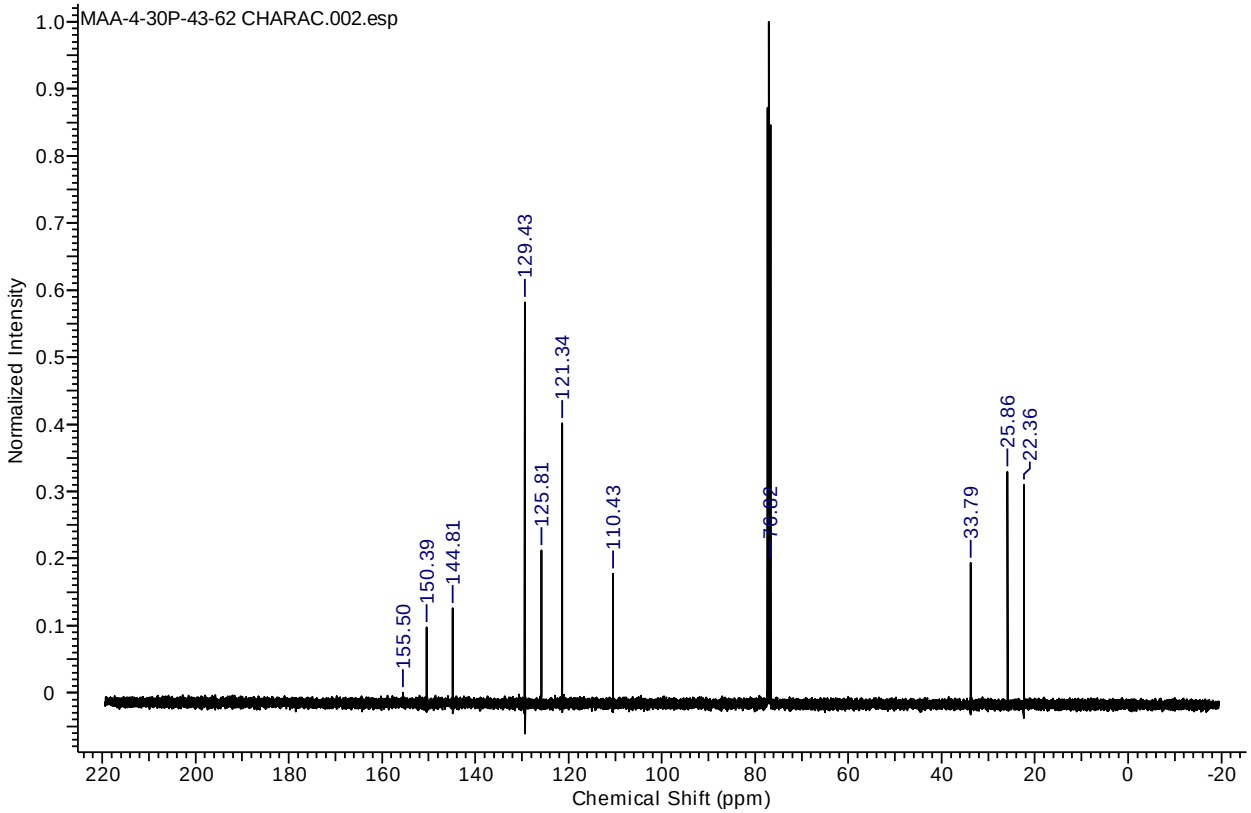

MAA-2-153PP.001.esp
PhO
O
N
H
O
Me
Normalized Intensity
0.94
2.05
1.02
2.05
2.00
2.19
2.15
2.17
3.19
Chemical Shift (ppm)

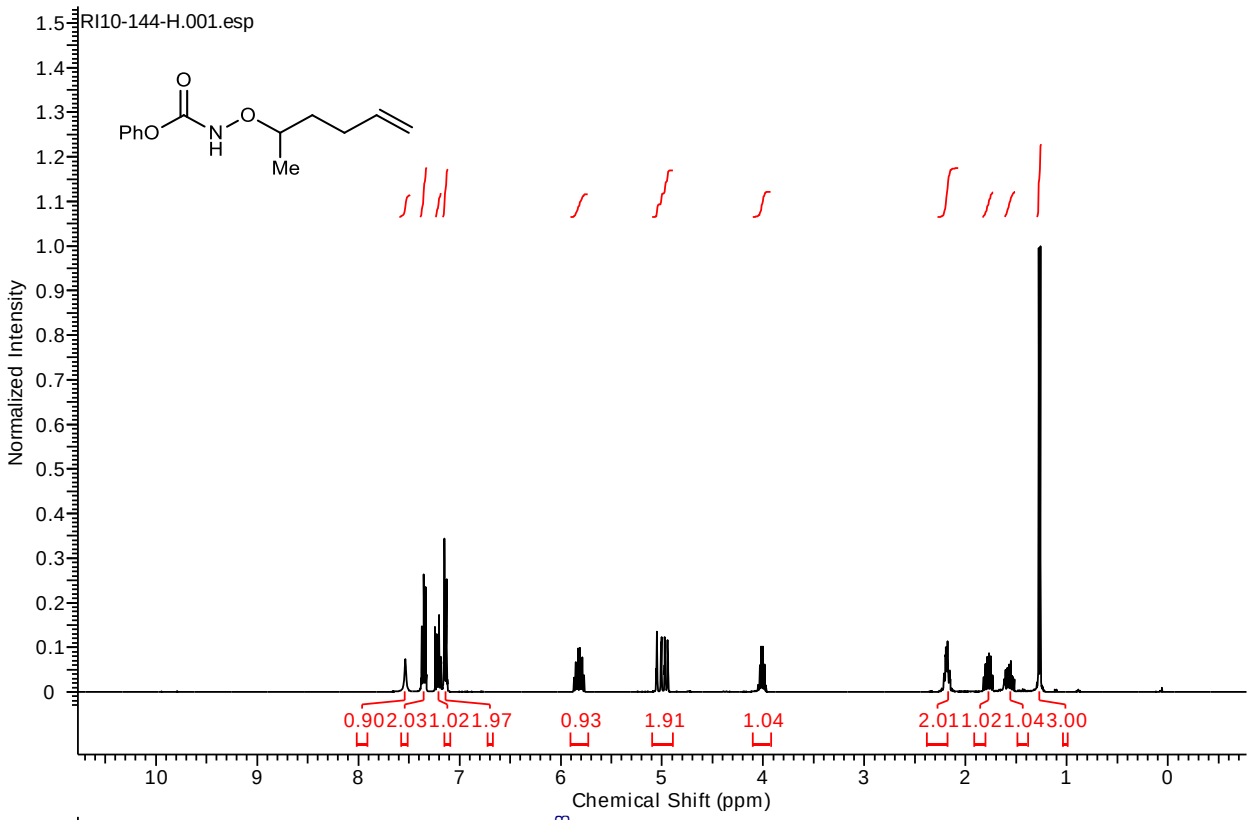

MAA-4-14P-CNMR.001.esp
Normalized Intensity
155.51
150.36
130.08
129.43
125.81
121.35
115.25
76.70
28.71
27.72
17.89
Chemical Shift (ppm)

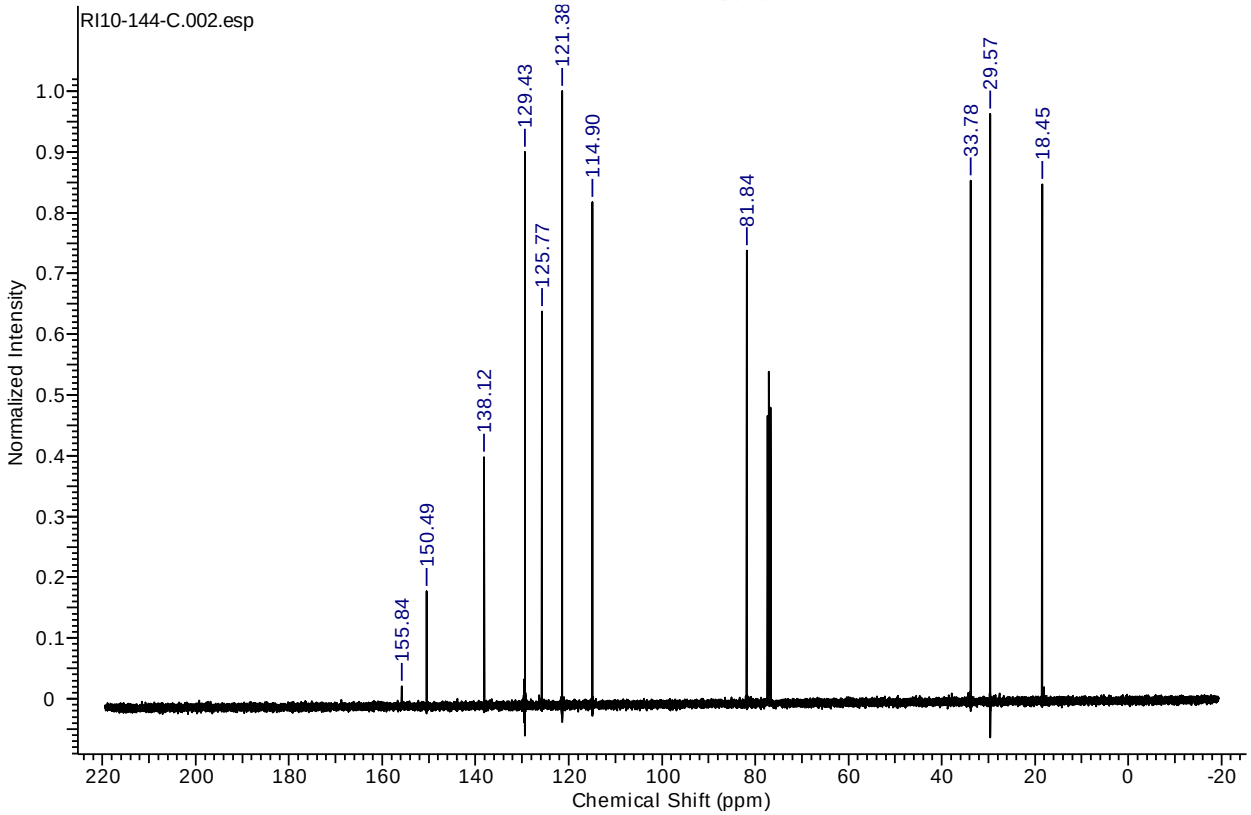

RI10-103-H.001.esp
PhO
O
N
H
O
Me
Me
Me
Normalized Intensity
0.81
2.18
1.12
2.07
0.92
0.95
1.89
1.04
2.79
2.72
1.34
3.00
Chemical Shift (ppm)

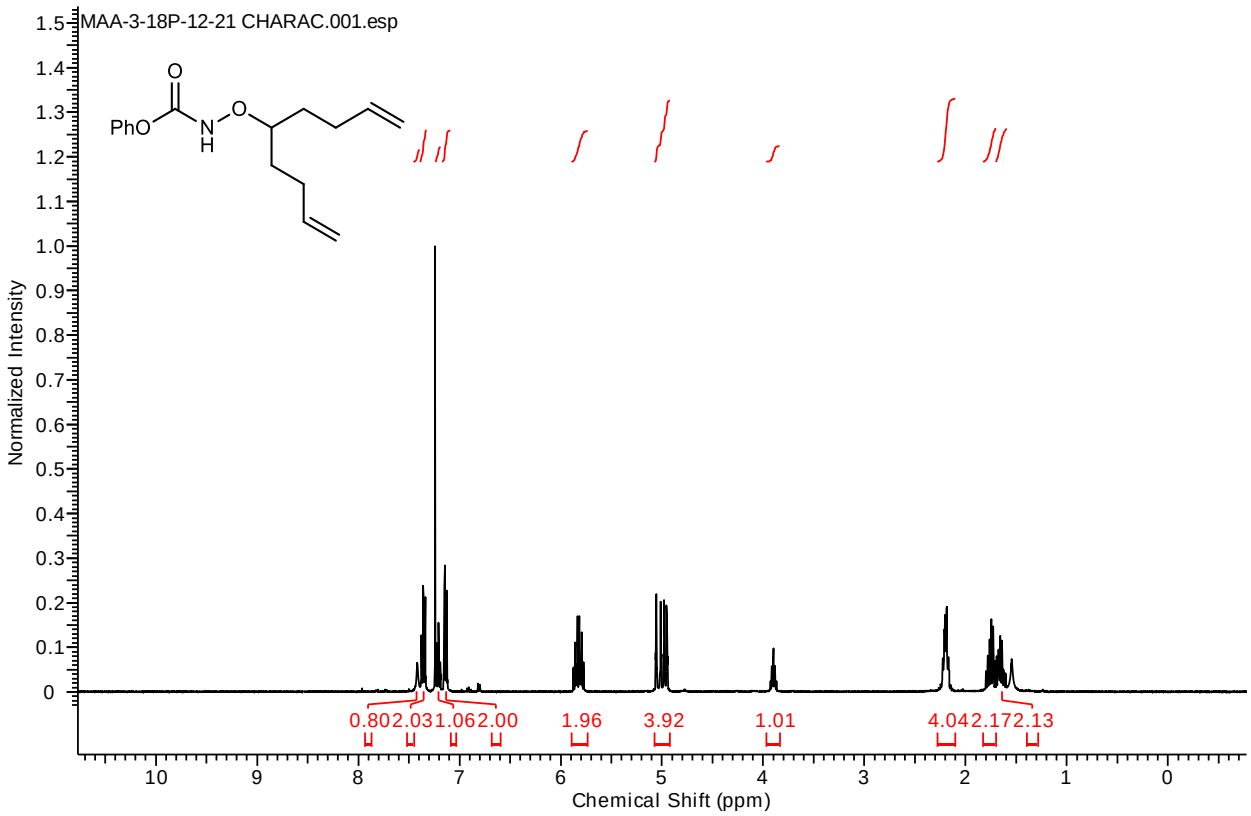

RI10-103-C.001.esp
Normalized Intensity
155.79
150.52
132.09
129.42
125.74
123.79
121.37
82.09
34.70
25.70
23.97
18.46
17.70
Chemical Shift (ppm)

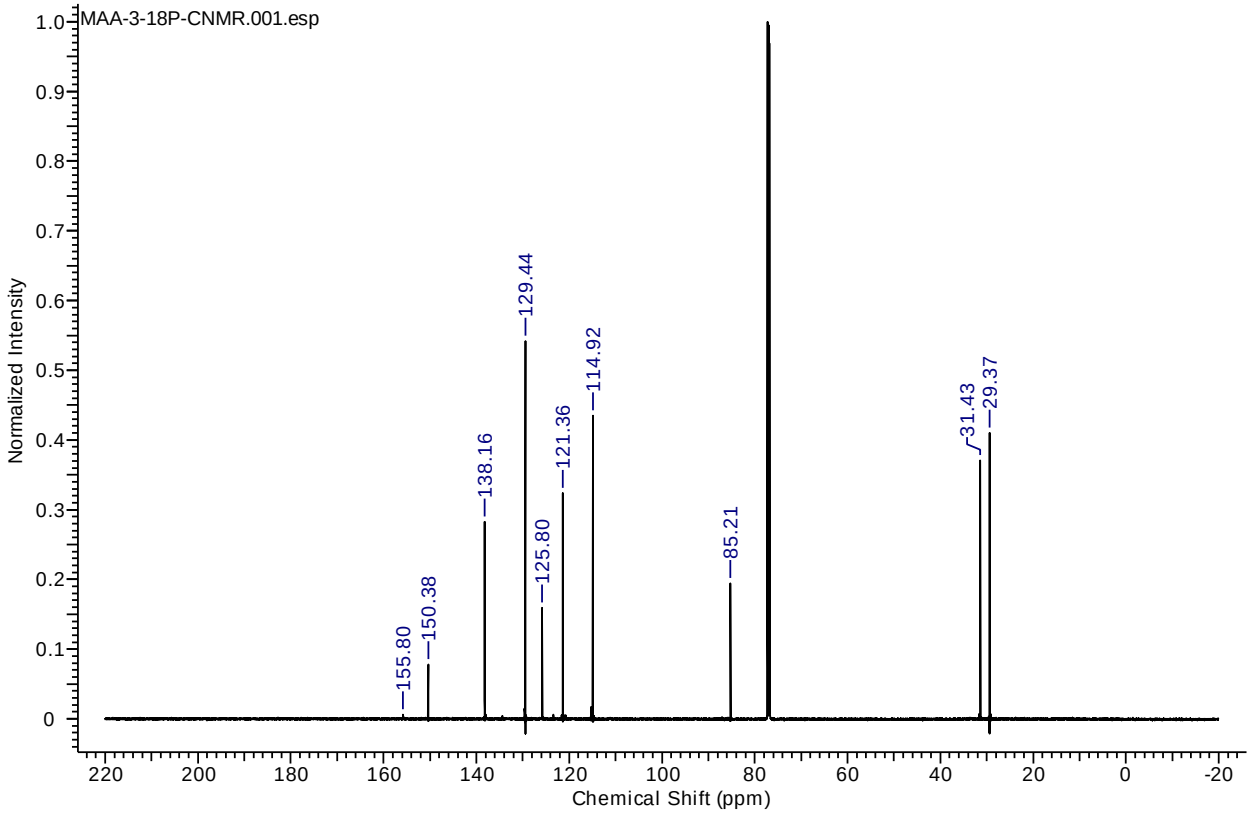

MAA-4-30P-43-62 CHARAC.001.esp
O
Me
PhO
N
H
O
Normalized Intensity
0.881.991.021.95
1.001.01
2.05
2.052.073.00
Chemical Shift (ppm)

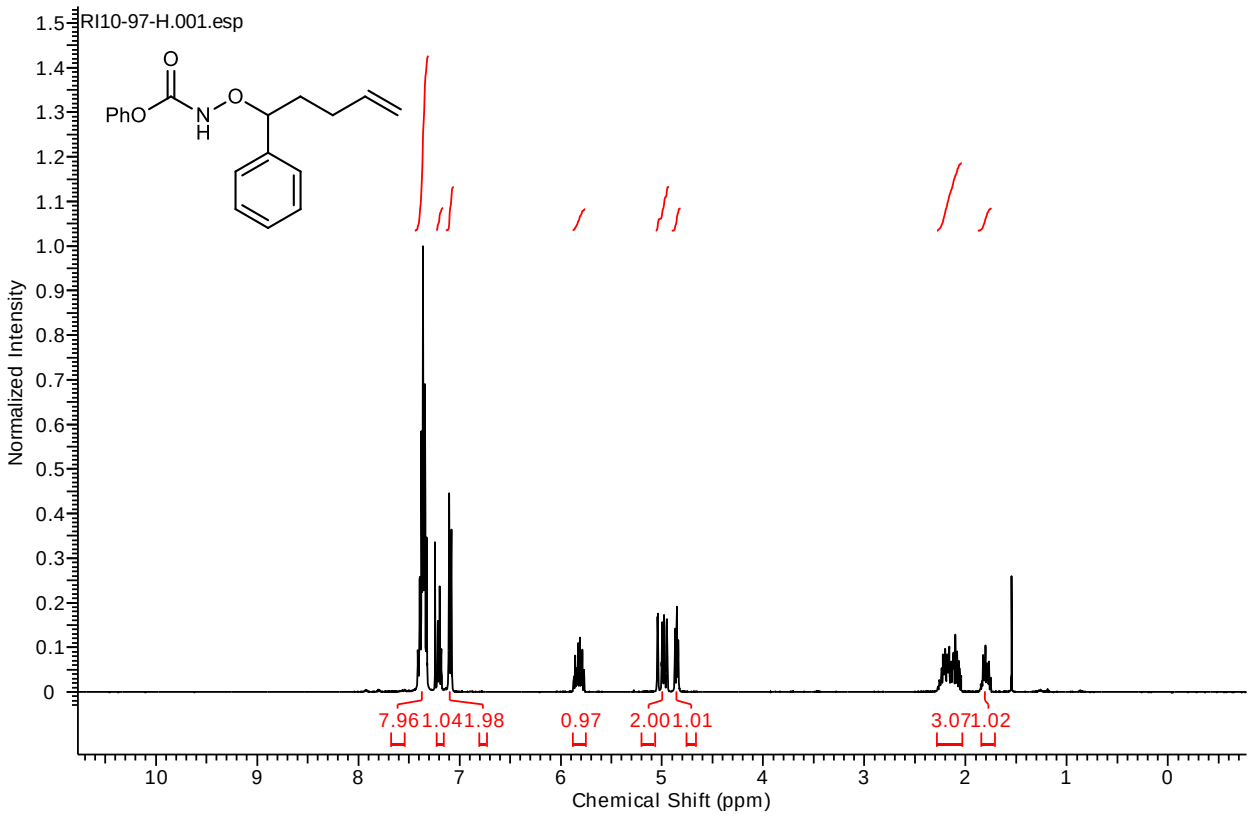

MAA-4-30P-43-62 CHARAC.002.esp
Normalized Intensity
155.50
150.39
144.81
129.43
125.81
121.34
110.43
76.62
33.79
25.86
22.36
Chemical Shift (ppm)

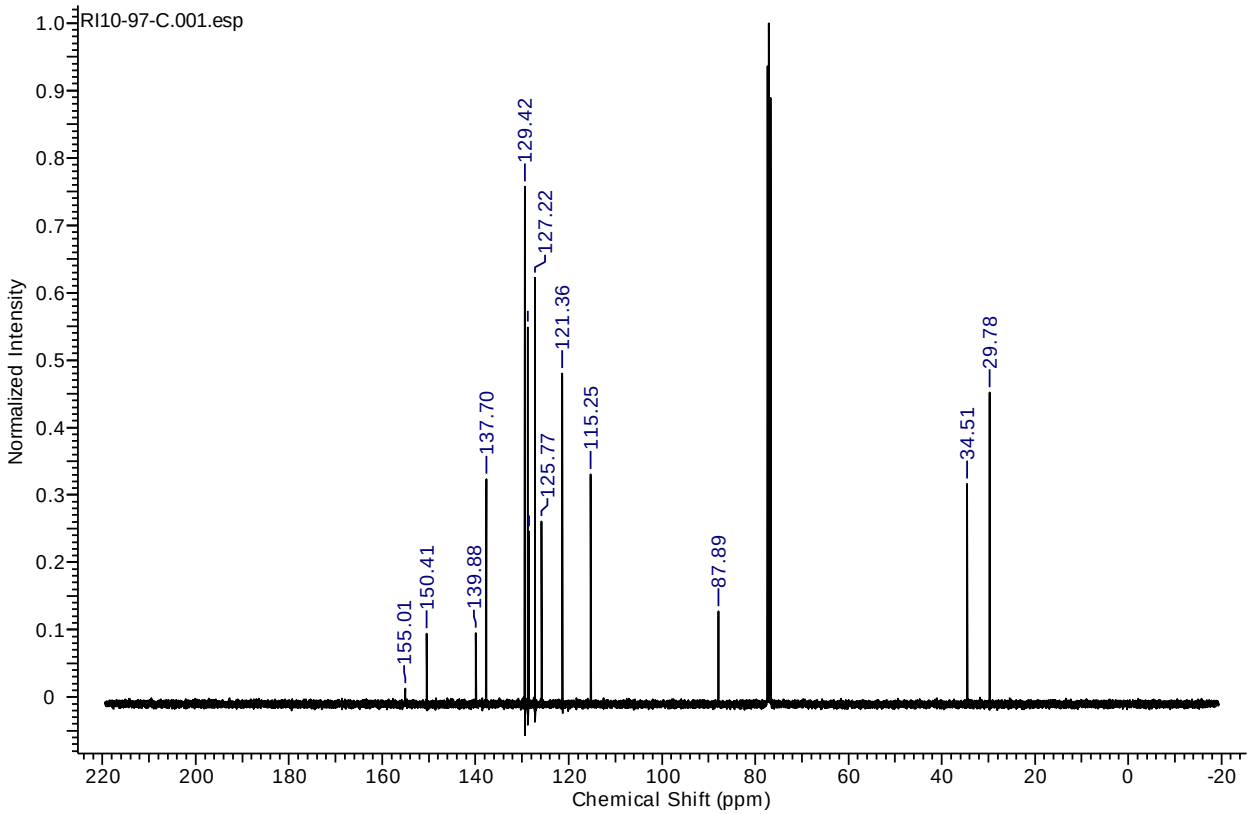

RI10-144-H.001.esp
PhO
O
N
H
O
Me
Normalized Intensity
0.90
2.03
1.02
1.97
0.93
1.91
1.04
2.01
1.02
1.04
3.00
Chemical Shift (ppm)

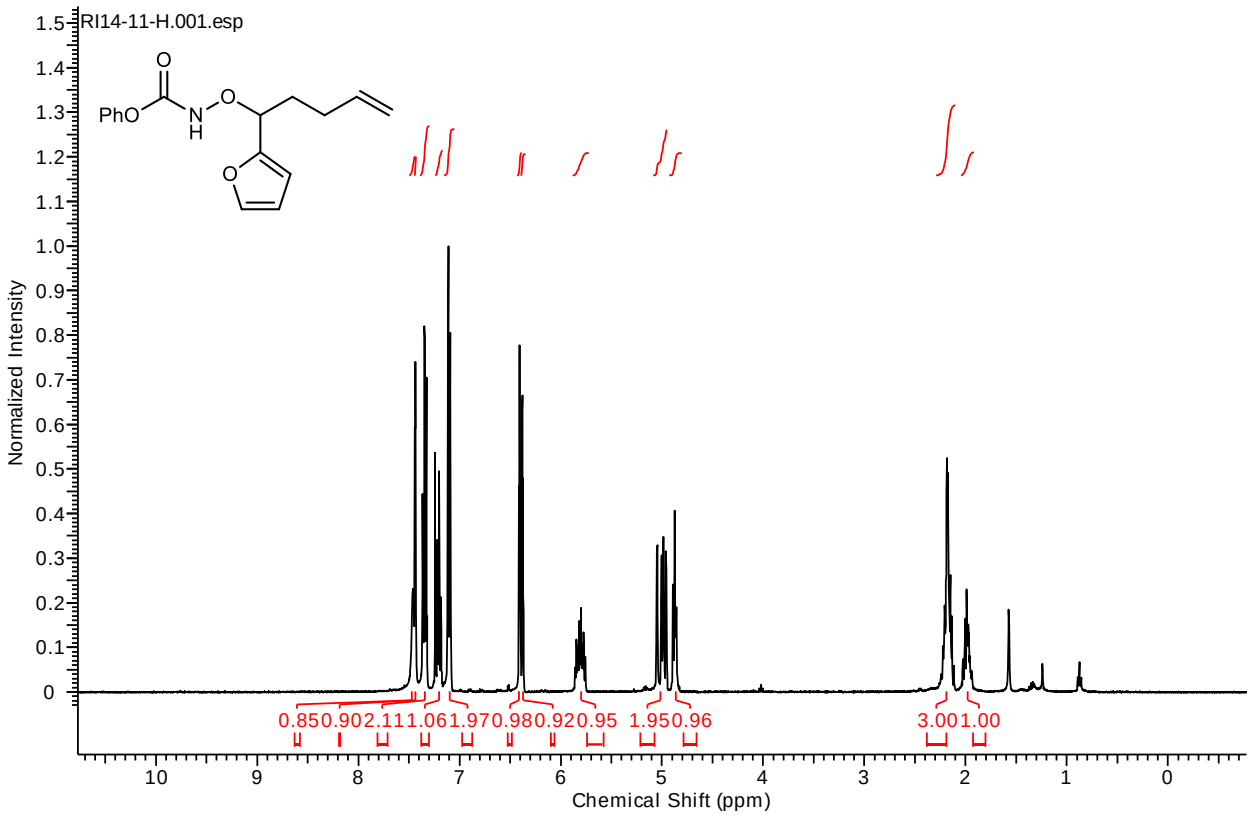

RI10-144-C.002.esp
155.84
150.49
138.12
129.43
125.77
121.38
114.90
81.84
33.78
29.57
18.45
Normalized Intensity
Chemical Shift (ppm)

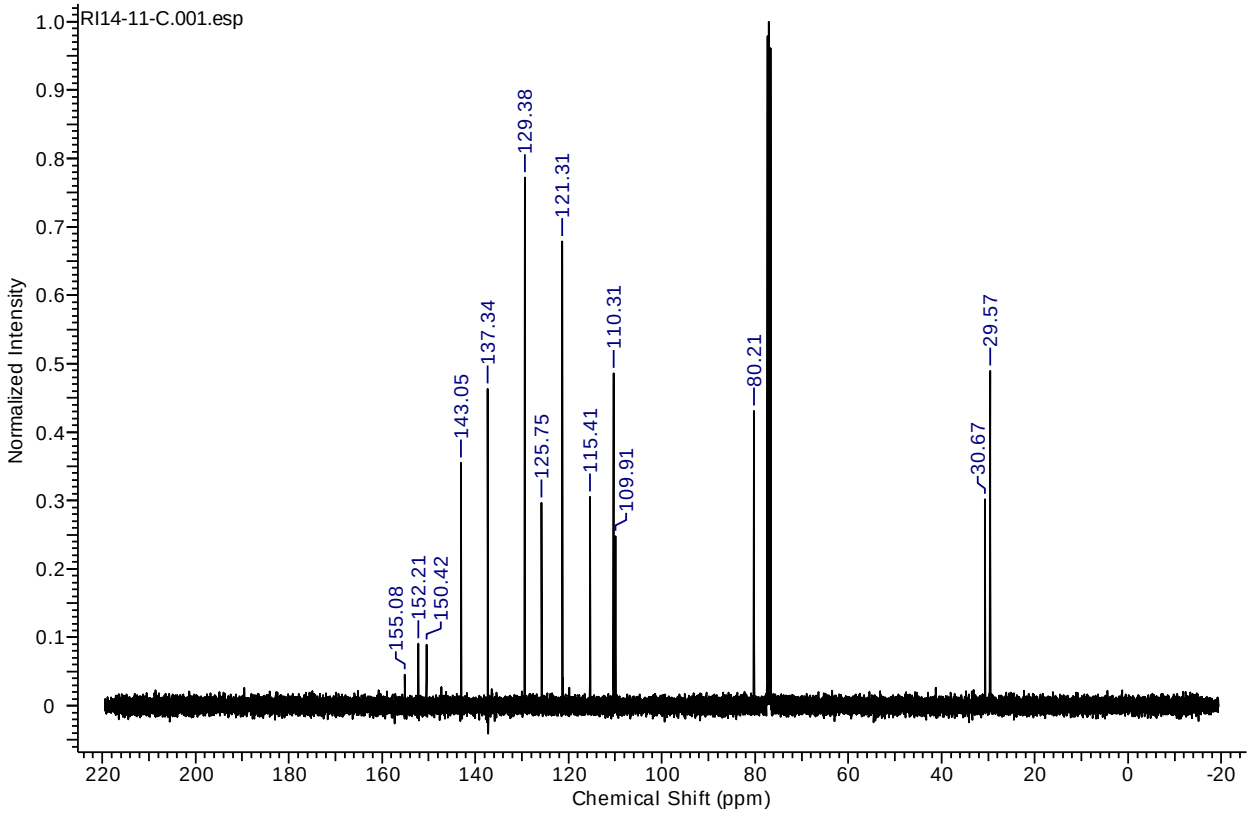

MAA-3-18P-12-21 CHARAC.001.esp
PhO
O
N
H
O
Normalized Intensity
0.80
2.03
1.06
2.00
1.96
3.92
1.01
4.04
2.17
2.13
Chemical Shift (ppm)

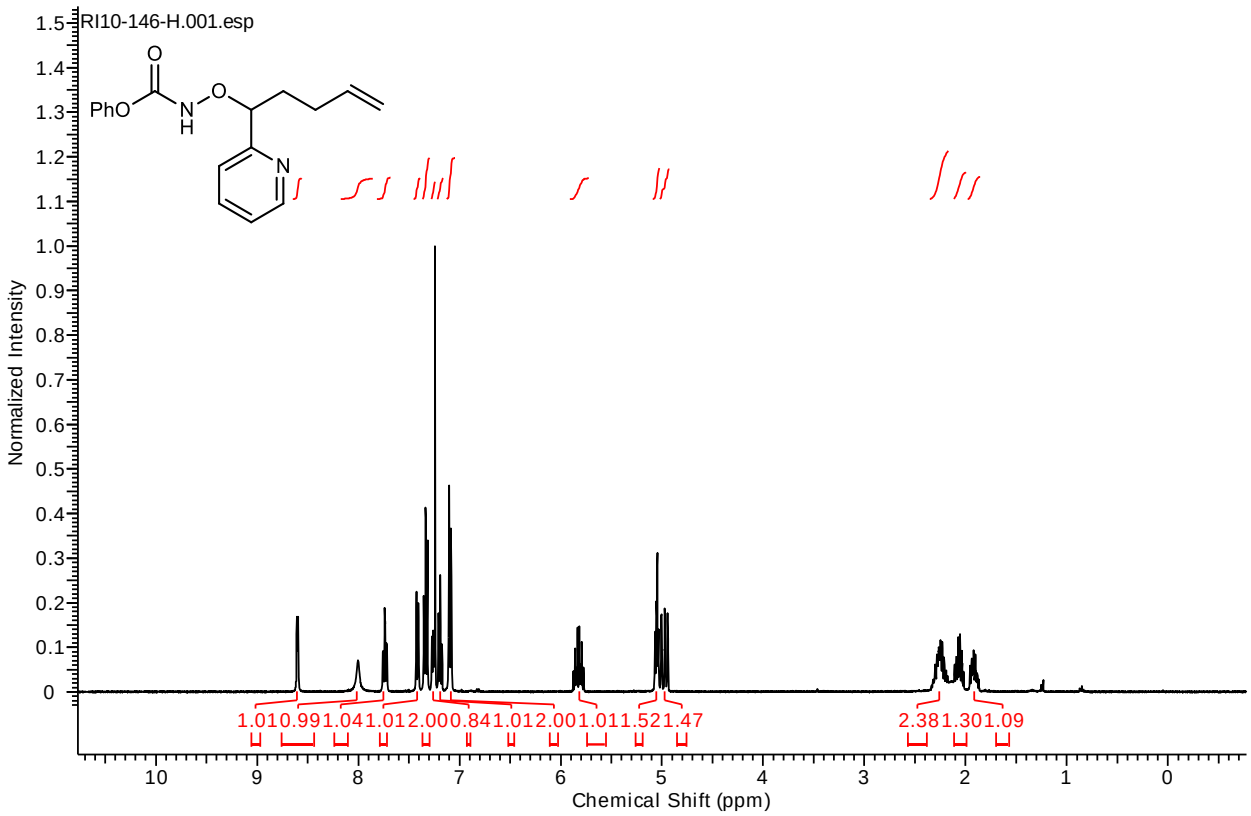

MAA-3-18P-CNMR.001.esp
Normalized Intensity
155.80
150.38
138.16
129.44
125.80
121.36
114.92
85.21
31.43
29.37
Chemical Shift (ppm)

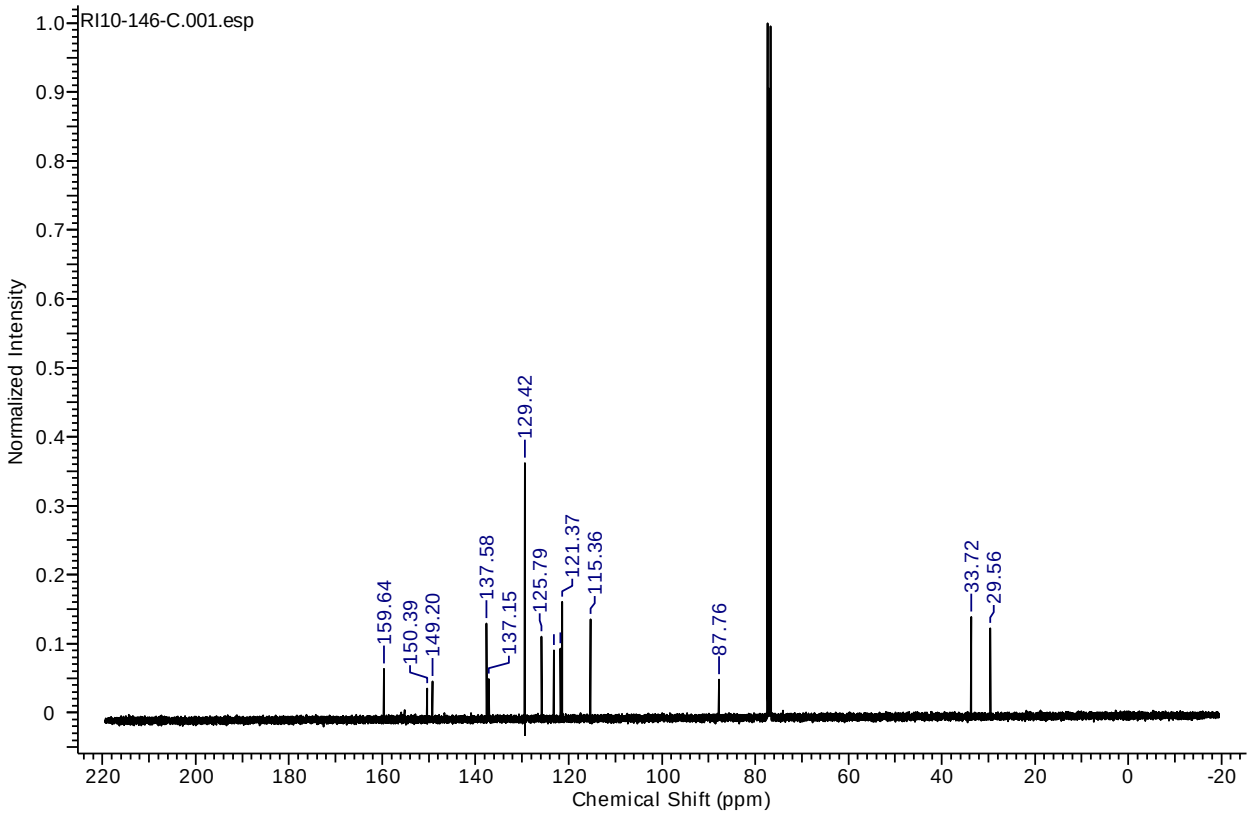

RI10-97-H.001.esp
PhO
O
N
H
O
Normalized Intensity
Chemical Shift (ppm)
7.96
1.04
1.98
0.97
2.00
1.01
3.07
1.02

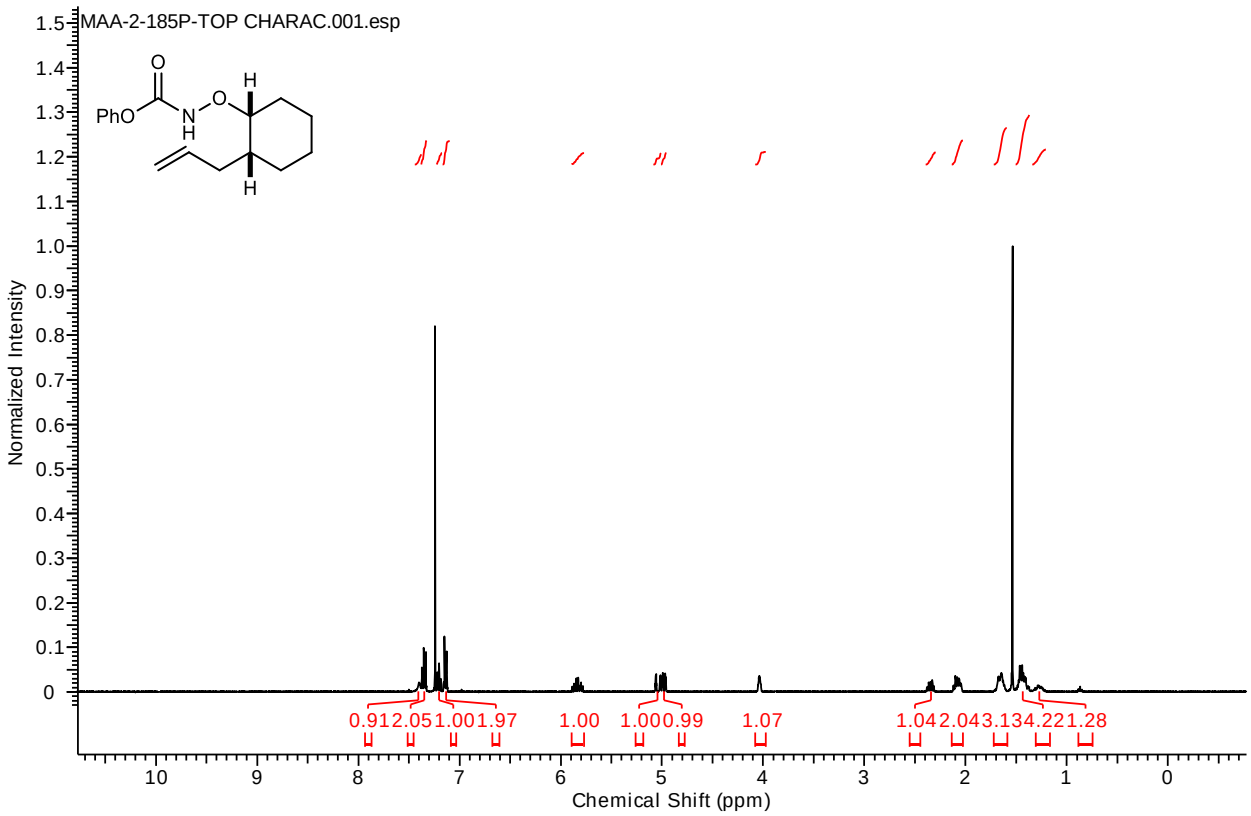

RI10-97-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
155.01
150.41
139.88
137.70
129.42
127.22
125.77
121.36
115.25
87.89
34.51
29.78

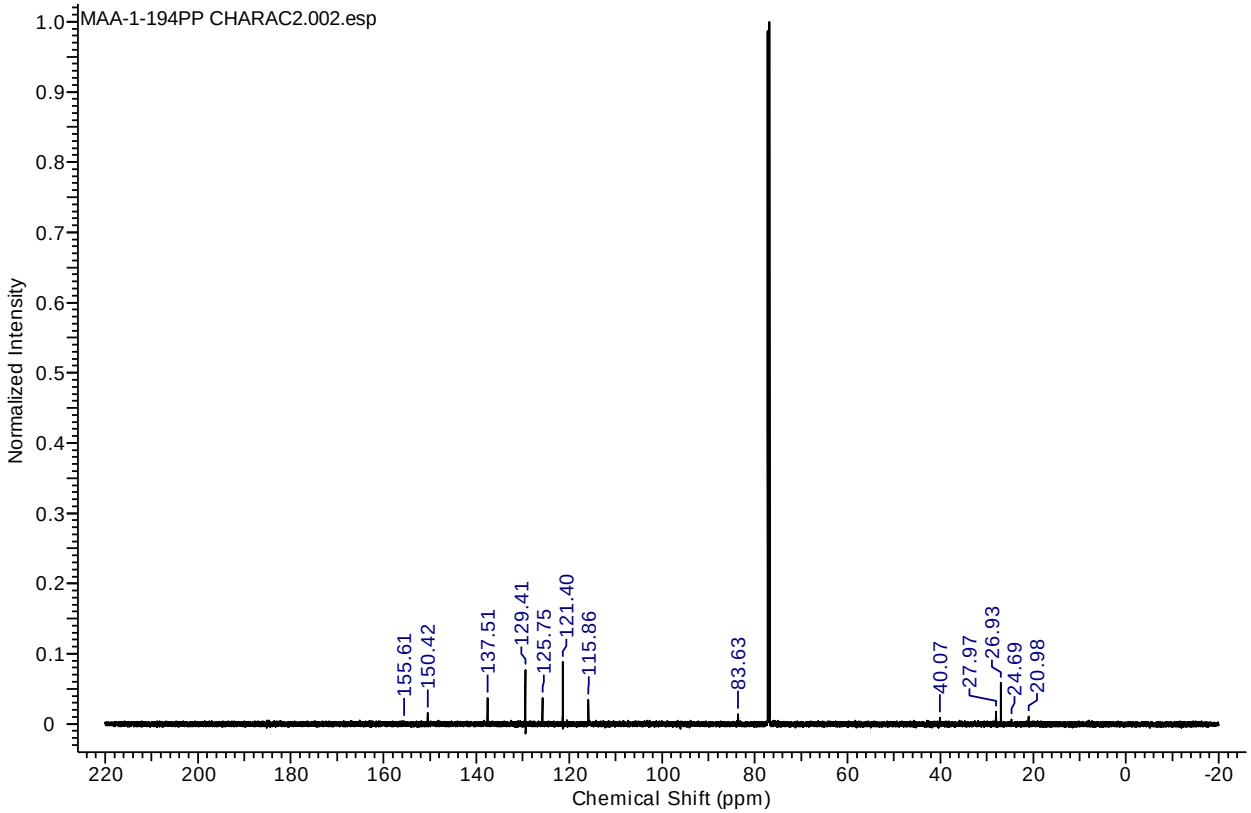

RI14-11-H.001.esp
PhO
O
N
H
O
O
Normalized Intensity
0.85 0.90 2.11 1.06 1.97 0.98 0.92 0.95 1.95 0.96
3.00 1.00
Chemical Shift (ppm)

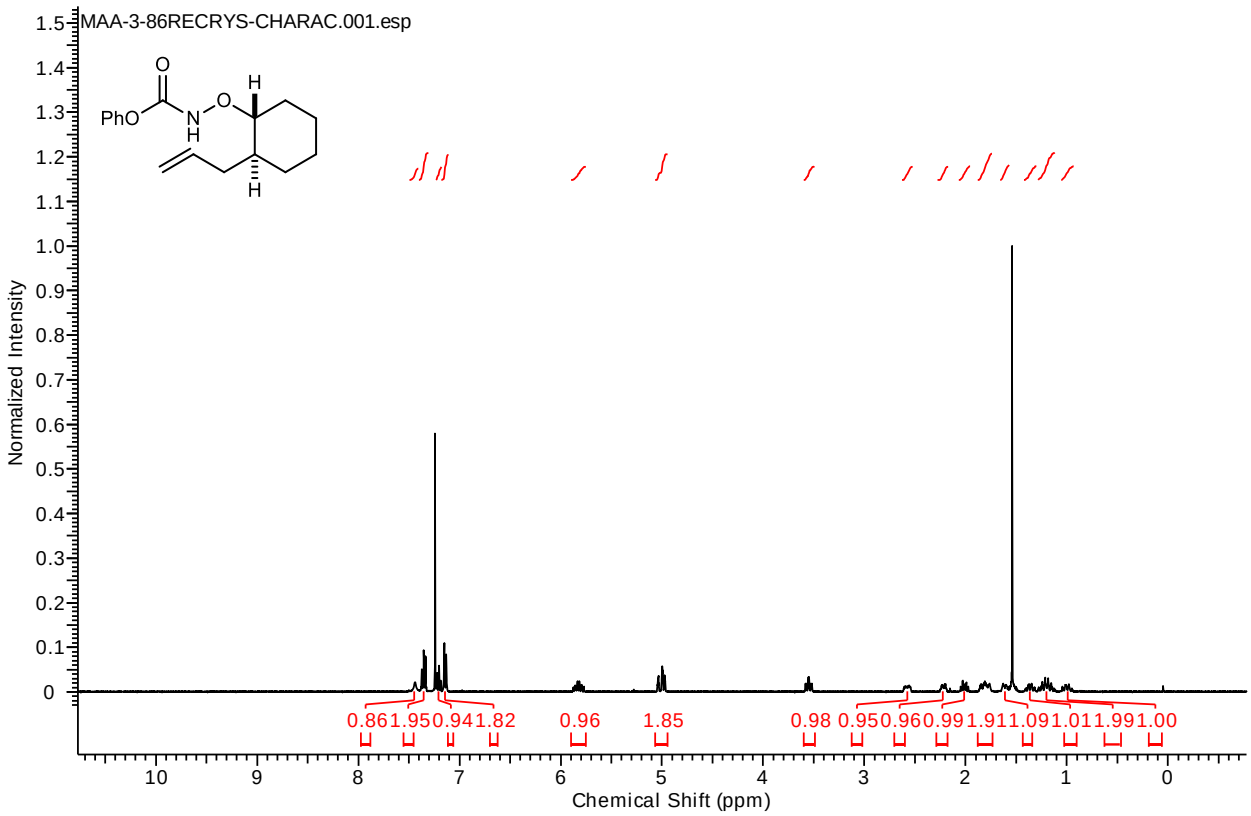

RI14-11-C.001.esp
155.08
152.21
150.42
143.05
137.34
129.38
125.75
121.31
115.41
110.31
109.91
80.21
30.67
29.57
Normalized Intensity
Chemical Shift (ppm)

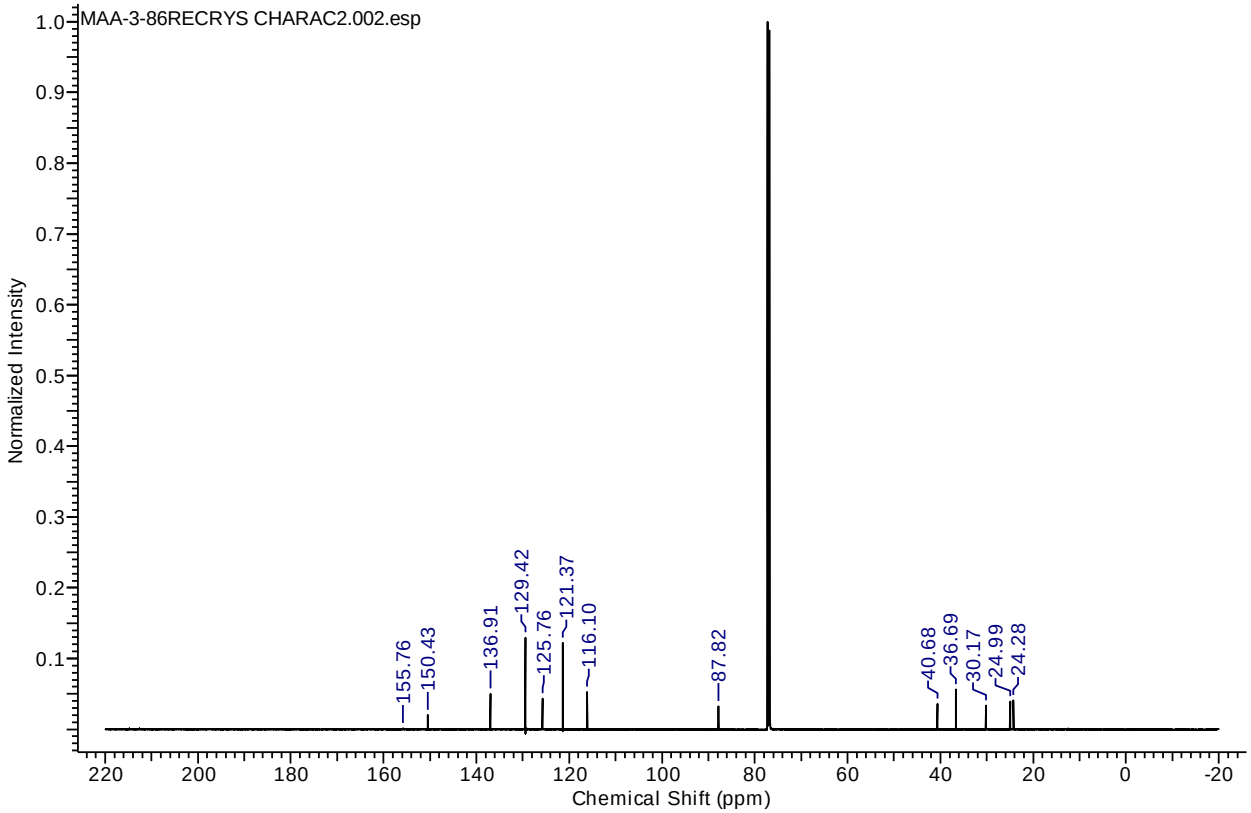

RI10-146-H.001.esp
PhO
O
N
H
O
N
Normalized Intensity
1.010.991.041.012.000.841.012.001.011.521.47
2.381.301.09
Chemical Shift (ppm)

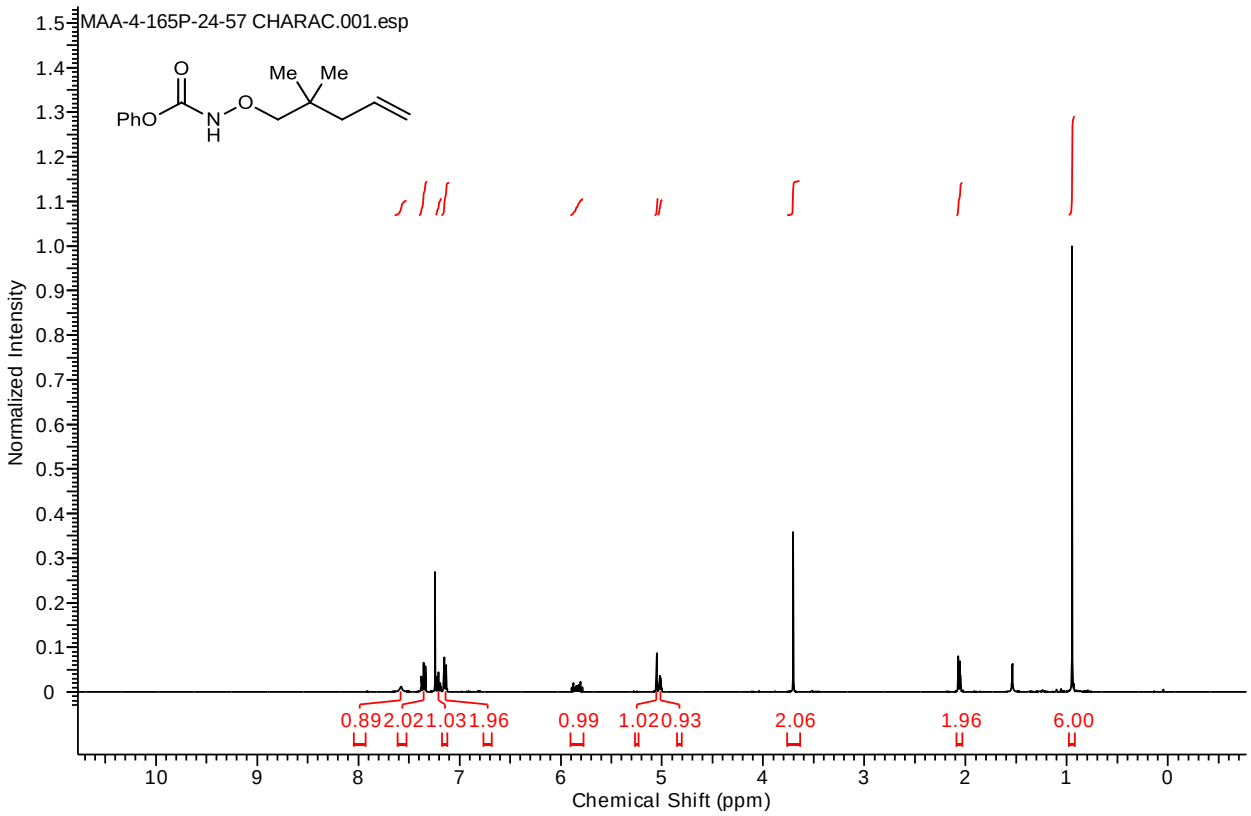

RI10-146-C.001.esp
Normalized Intensity
159.64
150.39
149.20
137.58
137.15
129.42
125.79
121.37
115.36
87.76
33.72
29.56
Chemical Shift (ppm)

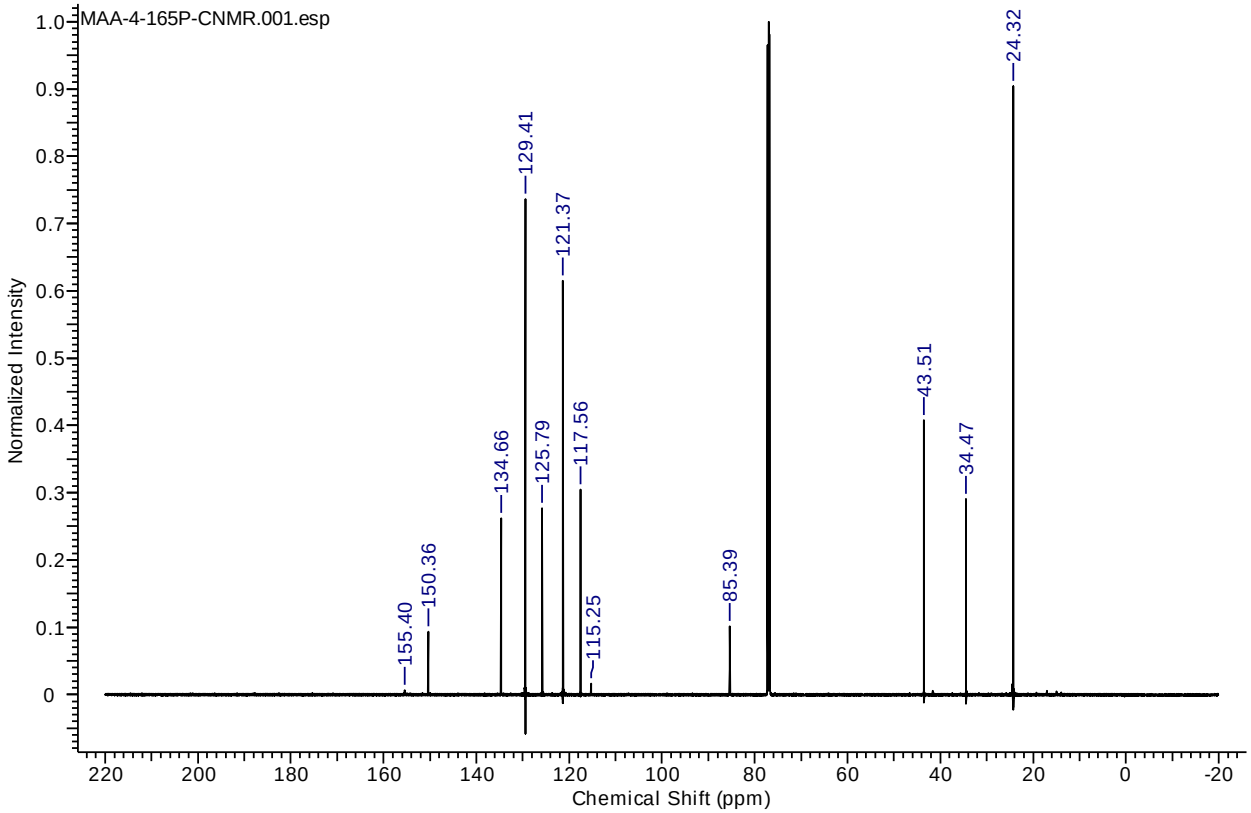

MAA-2-185P-TOP CHARAC.001.esp
PhO
O
N
H
O
H
H
Normalized Intensity
0.91
2.05
1.00
1.97
1.00
1.00
0.99
1.07
1.04
2.04
3.13
4.22
1.28
Chemical Shift (ppm)

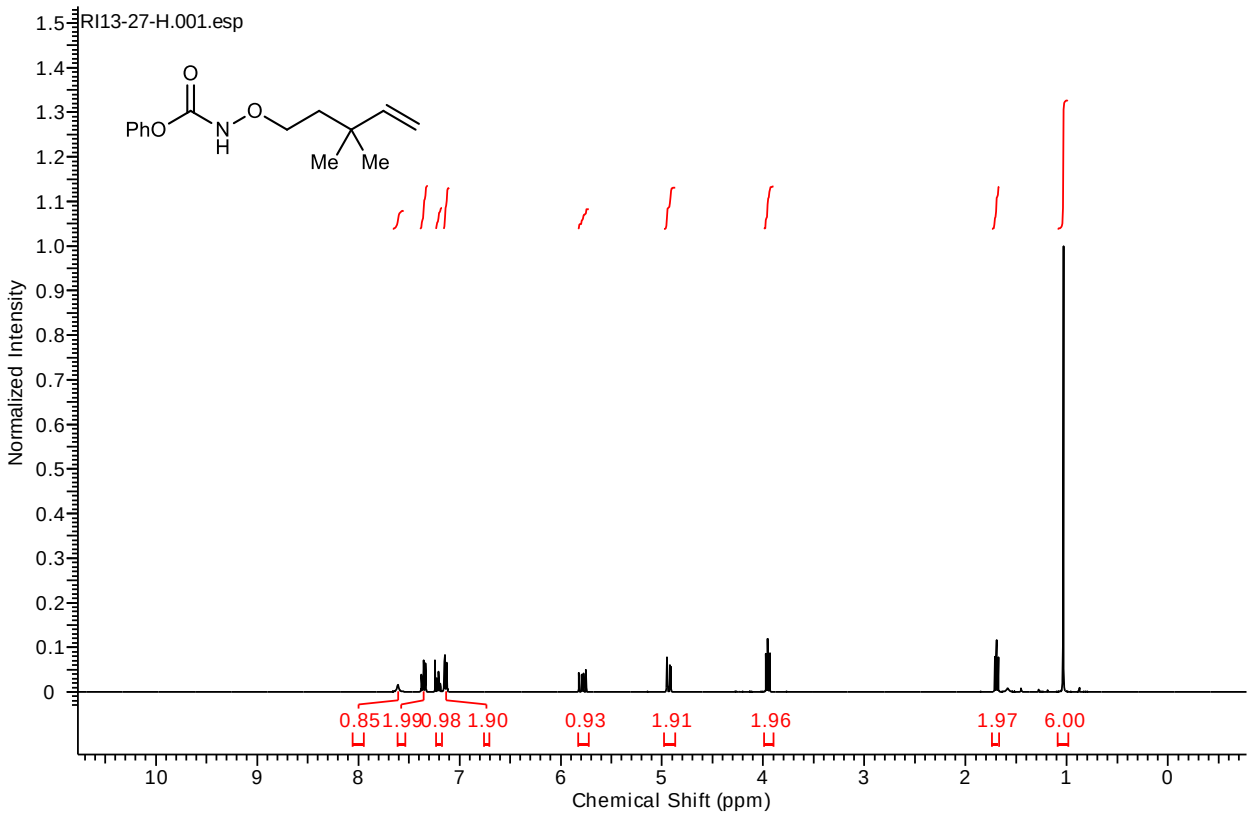

MAA-1-194PP CHARAC2.002.esp
Normalized Intensity
155.61
150.42
137.51
129.41
125.75
121.40
115.86
83.63
40.07
27.97
26.93
24.69
20.98
Chemical Shift (ppm)

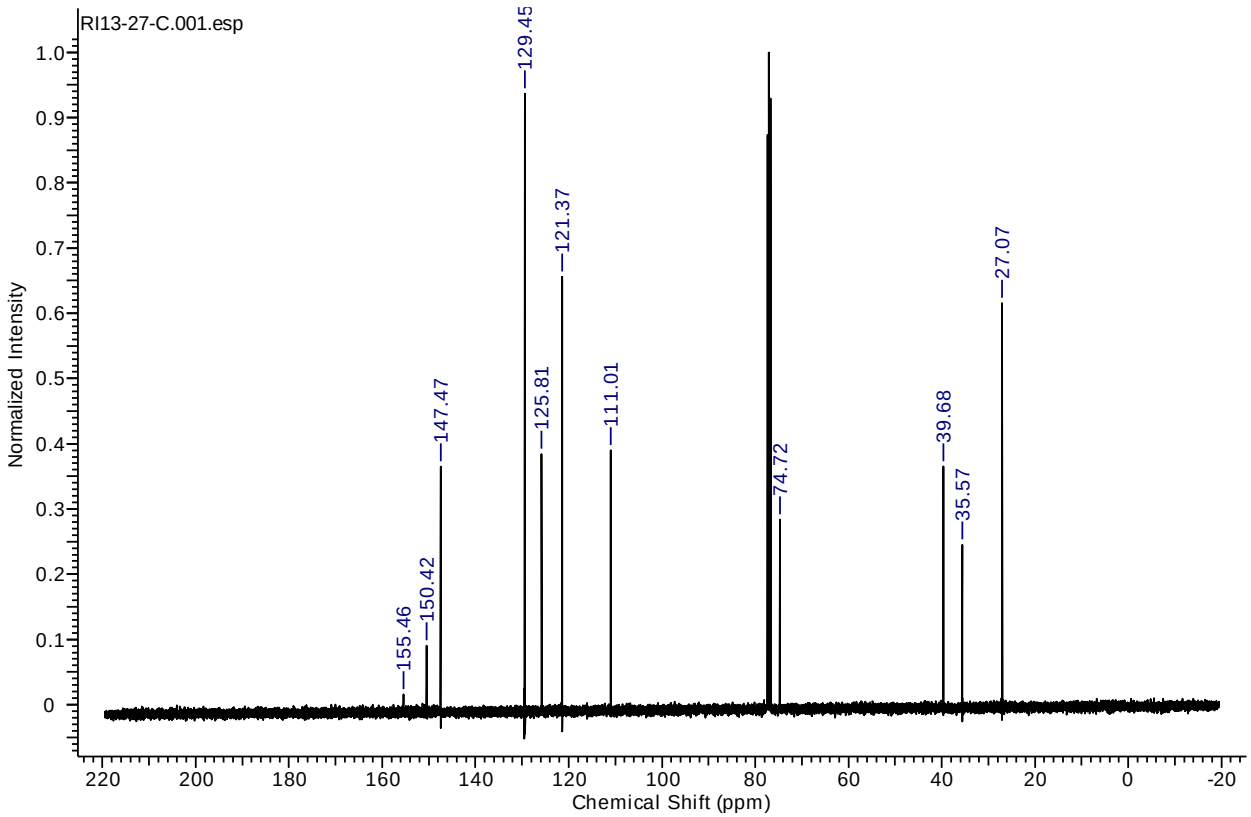

MAA-3-86RECRYS-CHARAC.001.esp
PhO
O
N
H
O
H
H
Normalized Intensity
0.86 1.95 0.94 1.82
0.96
1.85
0.98 0.95 0.96 0.99 1.91 1.09 1.01 1.99 1.00
Chemical Shift (ppm)

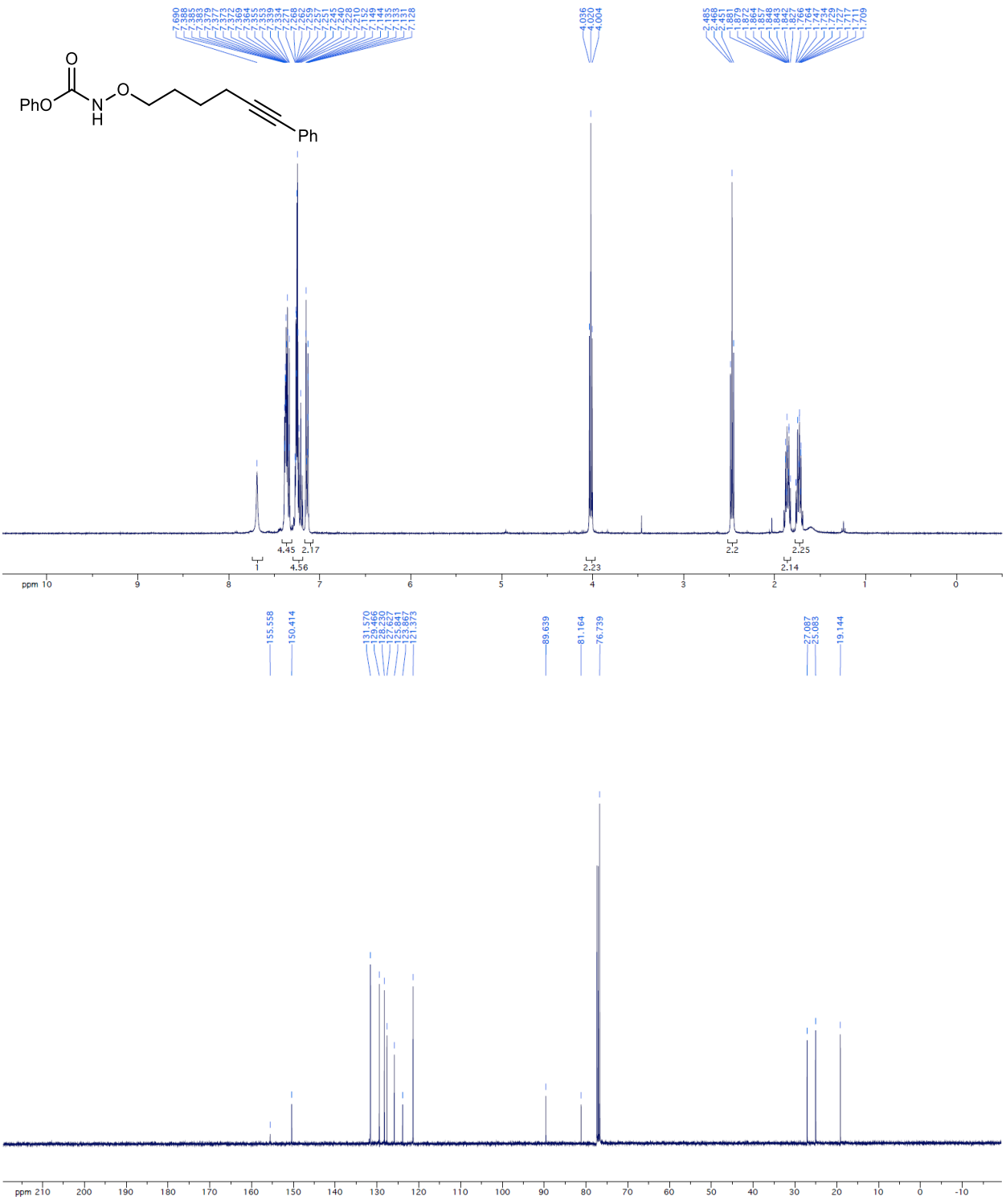

MAA-3-86RECRYS CHARAC2.002.esp
Normalized Intensity
155.76
150.43
136.91
129.42
125.76
121.37
116.10
87.82
40.68
36.69
30.17
24.99
24.28
Chemical Shift (ppm)

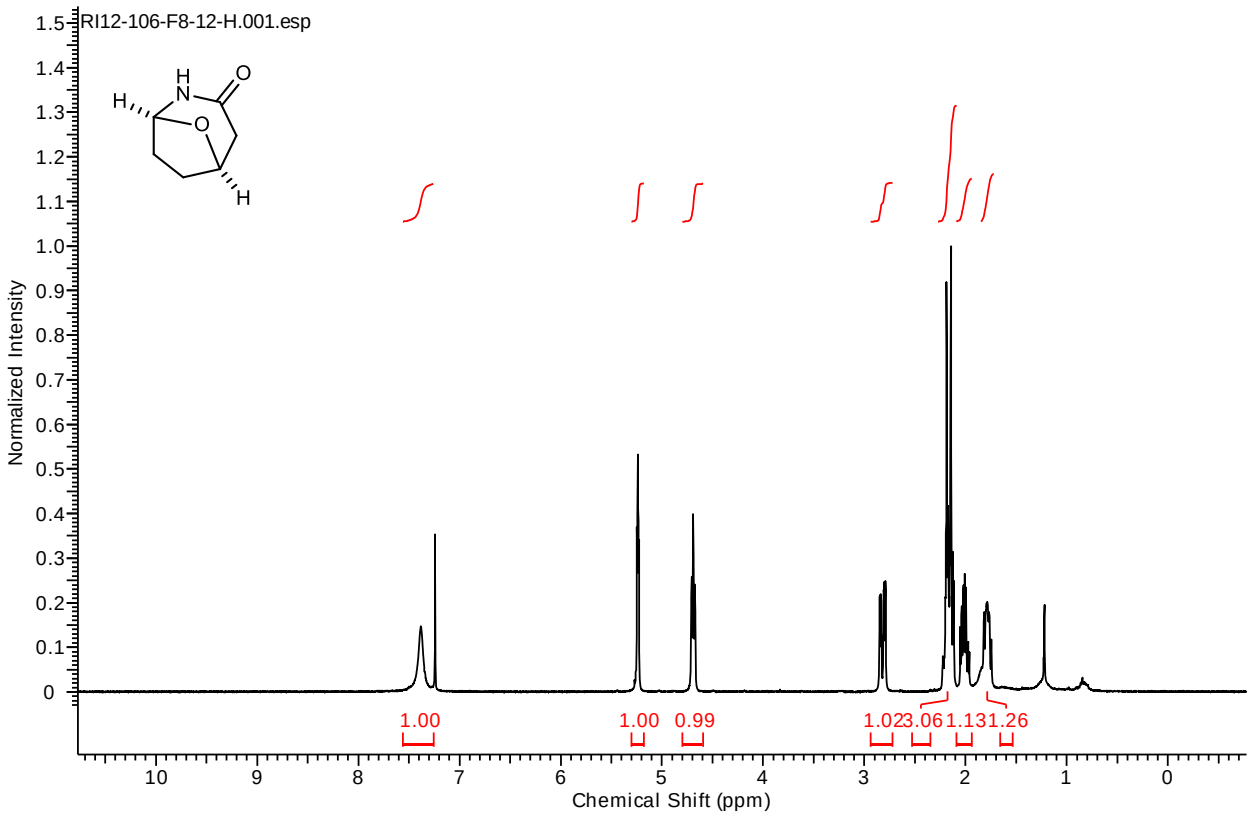

MAA-4-165P-24-57 CHARAC.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.89
2.02
1.03
1.96
0.99
1.02
0.93
2.06
1.96
6.00

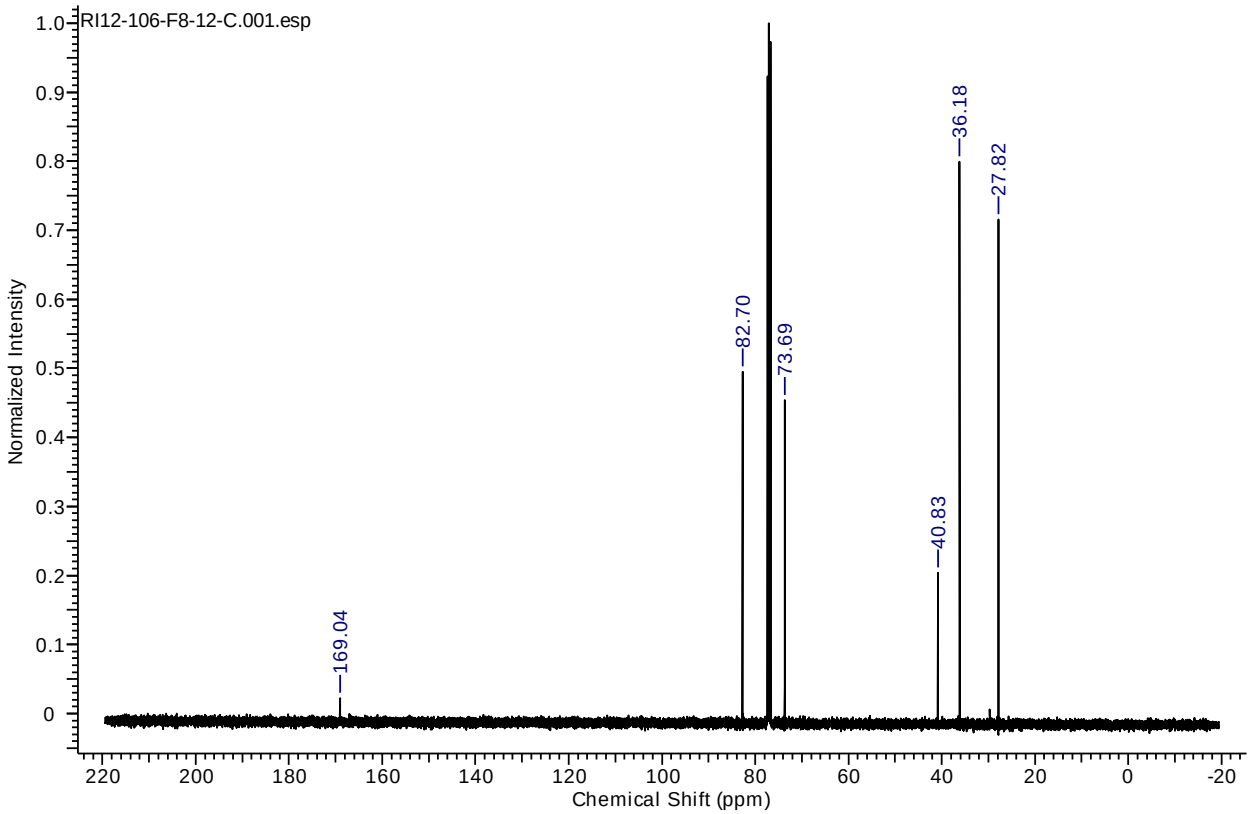

MAA-4-165P-CNMR.001.esp
Normalized Intensity
Chemical Shift (ppm)
155.40
150.36
134.66
129.41
125.79
121.37
117.56
115.25
85.39
43.51
34.47
24.32

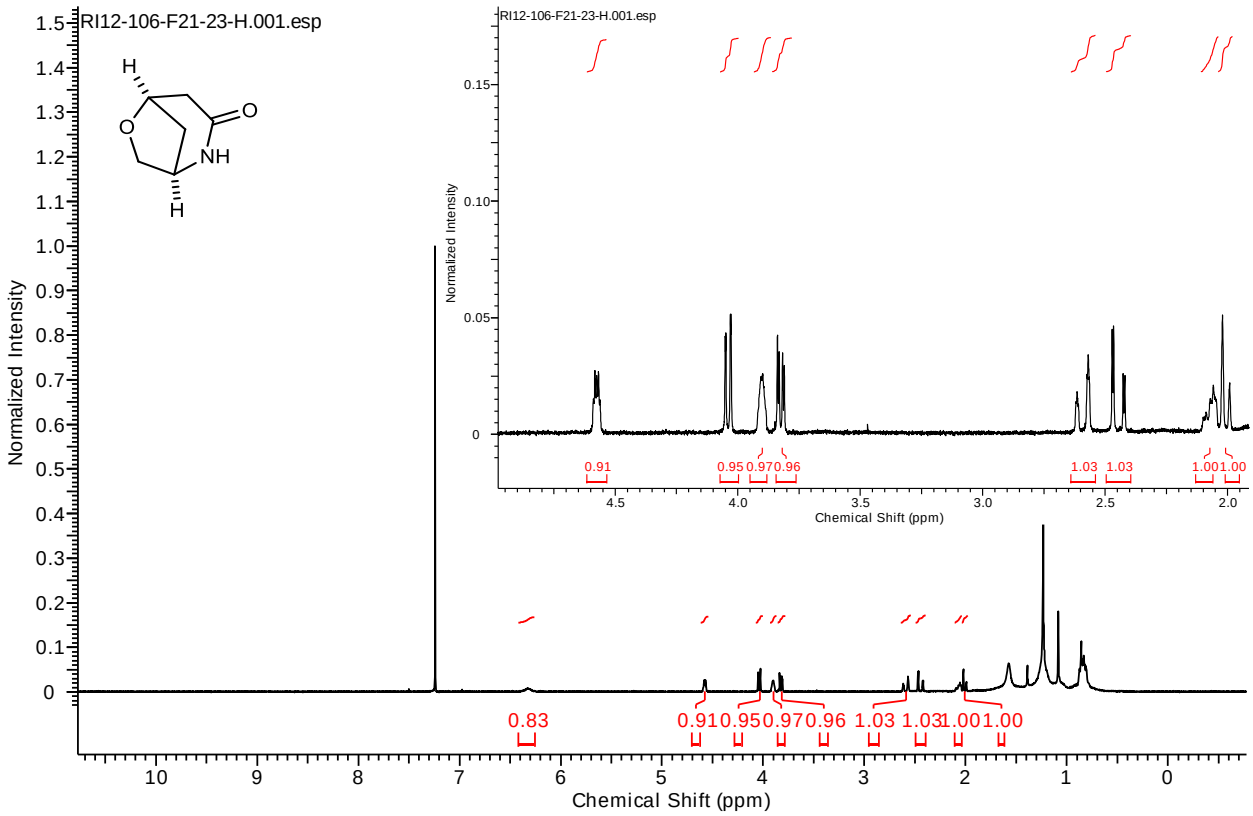

RI13-27-H.001.esp
PhO
O
N
H
O
Me
Me
Normalized Intensity
0.85
1.99
0.98
1.90
0.93
1.91
1.96
1.97
6.00
Chemical Shift (ppm)

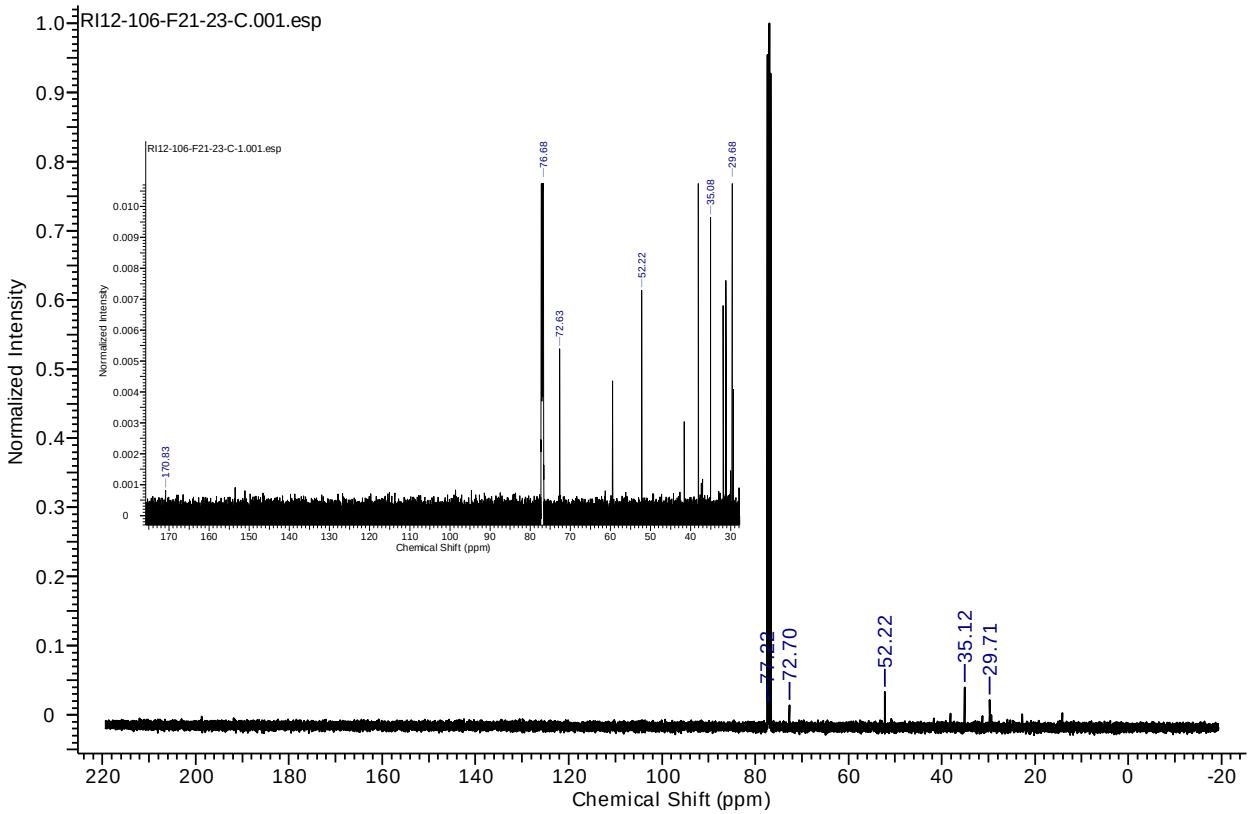

RI13-27-C.001.esp
155.46
150.42
147.47
129.45
125.81
121.37
111.01
74.72
39.68
35.57
27.07
Normalized Intensity
Chemical Shift (ppm)

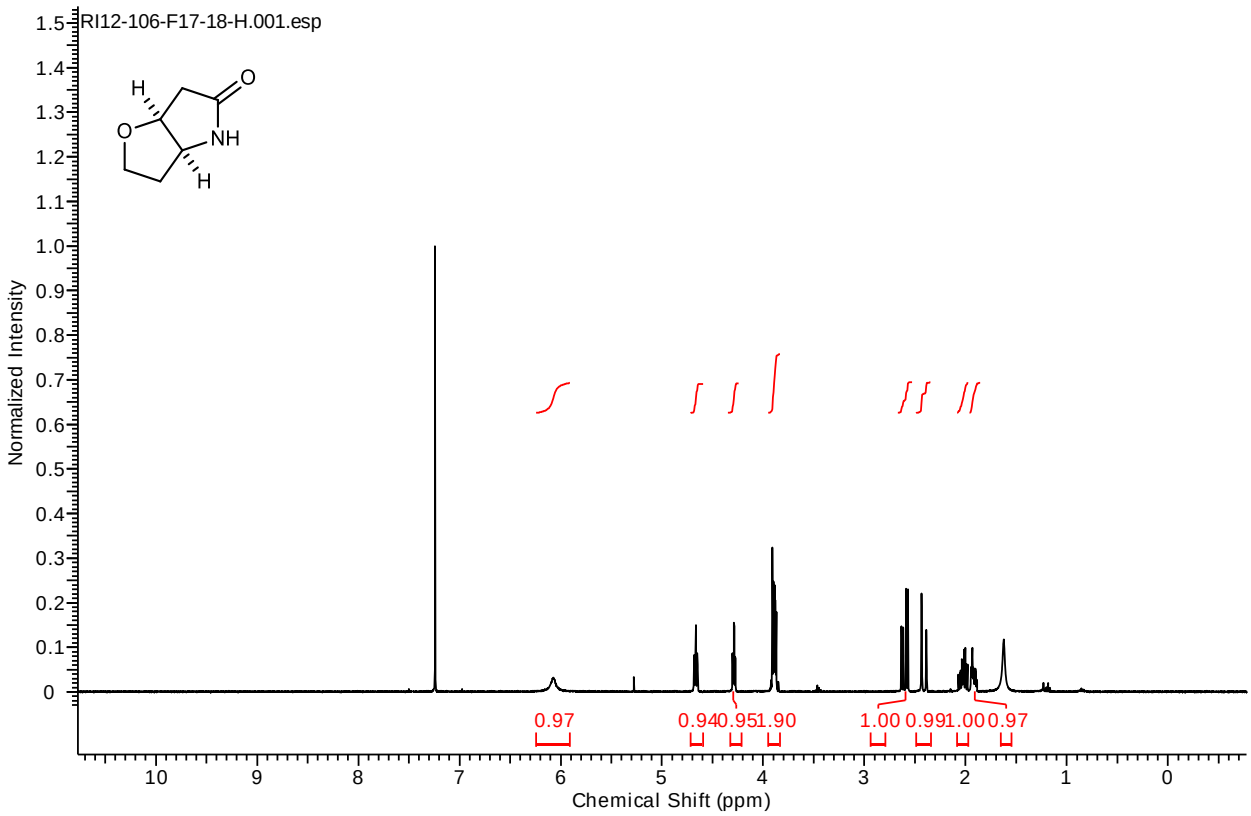

PhO
O
N
H
O
Ph
7.690
7.688
7.385
7.383
7.379
7.377
7.373
7.372
7.369
7.364
7.355
7.353
7.339
7.334
7.271
7.268
7.262
7.259
7.257
7.251
7.245
7.240
7.228
7.210
7.152
7.149
7.144
7.135
7.133
7.131
7.128
4.036
4.020
4.004
2.485
2.468
2.451
2.881
2.872
2.864
2.857
2.848
2.843
2.842
2.827
1.766
1.764
1.747
1.734
1.729
1.727
1.717
1.711
1.709
4.45
2.17
4.56
2.23
2.2
2.25
2.14
ppm 10
9
8
7
6
5
4
3
2
1
0
155.558
150.414
131.570
130.466
128.230
127.847
127.644
123.867
121.373
89.639
81.164
76.739
27.087
25.083
19.144
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

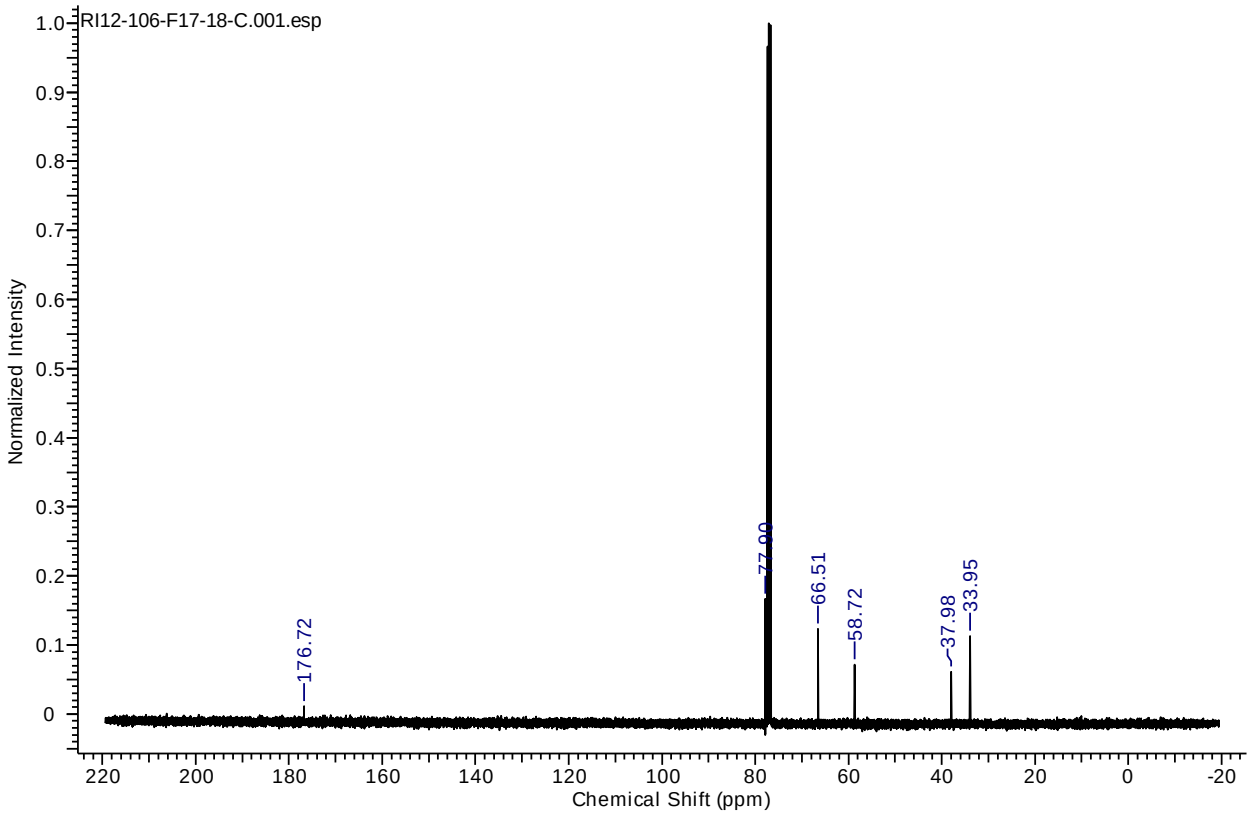

RI12-106-F8-12-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
1.00
0.99
1.02
3.06
1.13
1.26

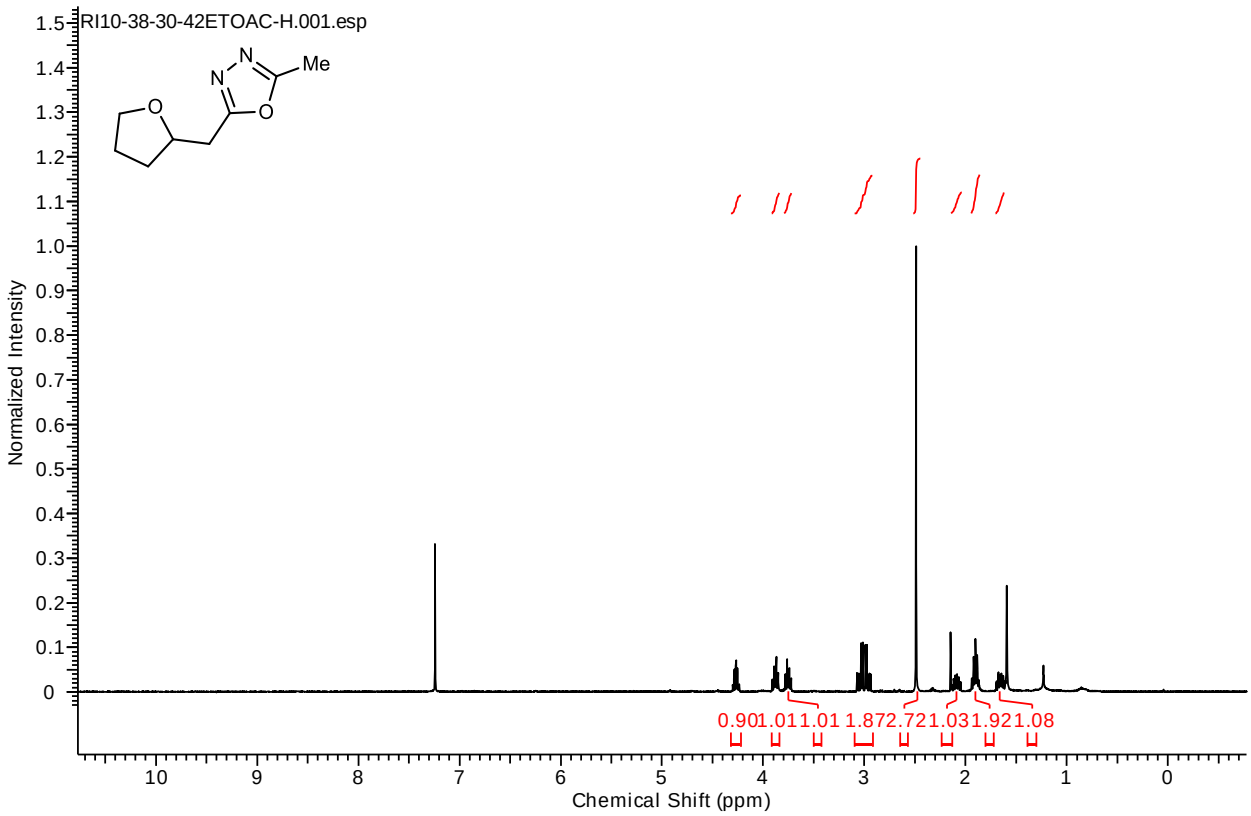

RI12-106-F8-12-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
169.04
82.70
73.69
40.83
36.18
27.82

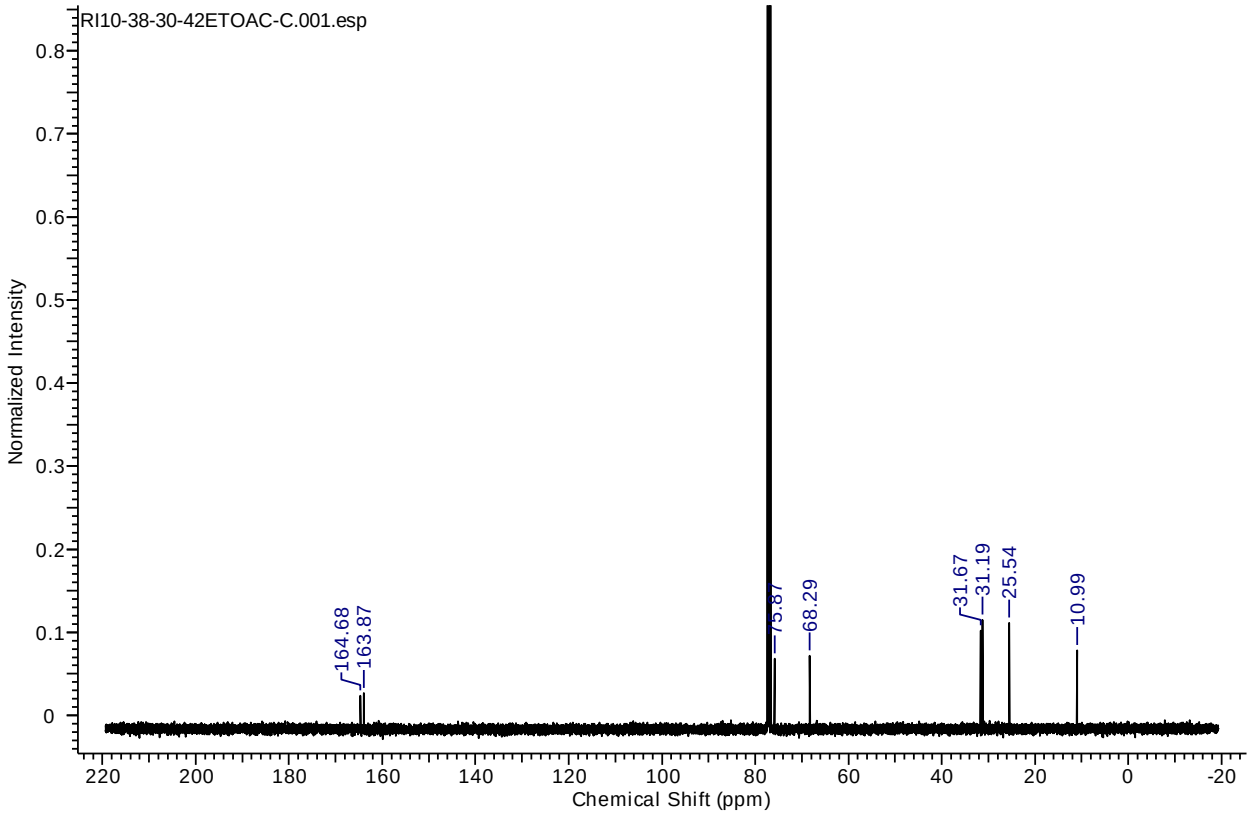

RI12-106-F21-23-H.001.esp
H
O
O
NH
H
Normalized Intensity
Chemical Shift (ppm)
0.83
0.91
0.95
0.97
0.96
1.03
1.03
1.00
1.00

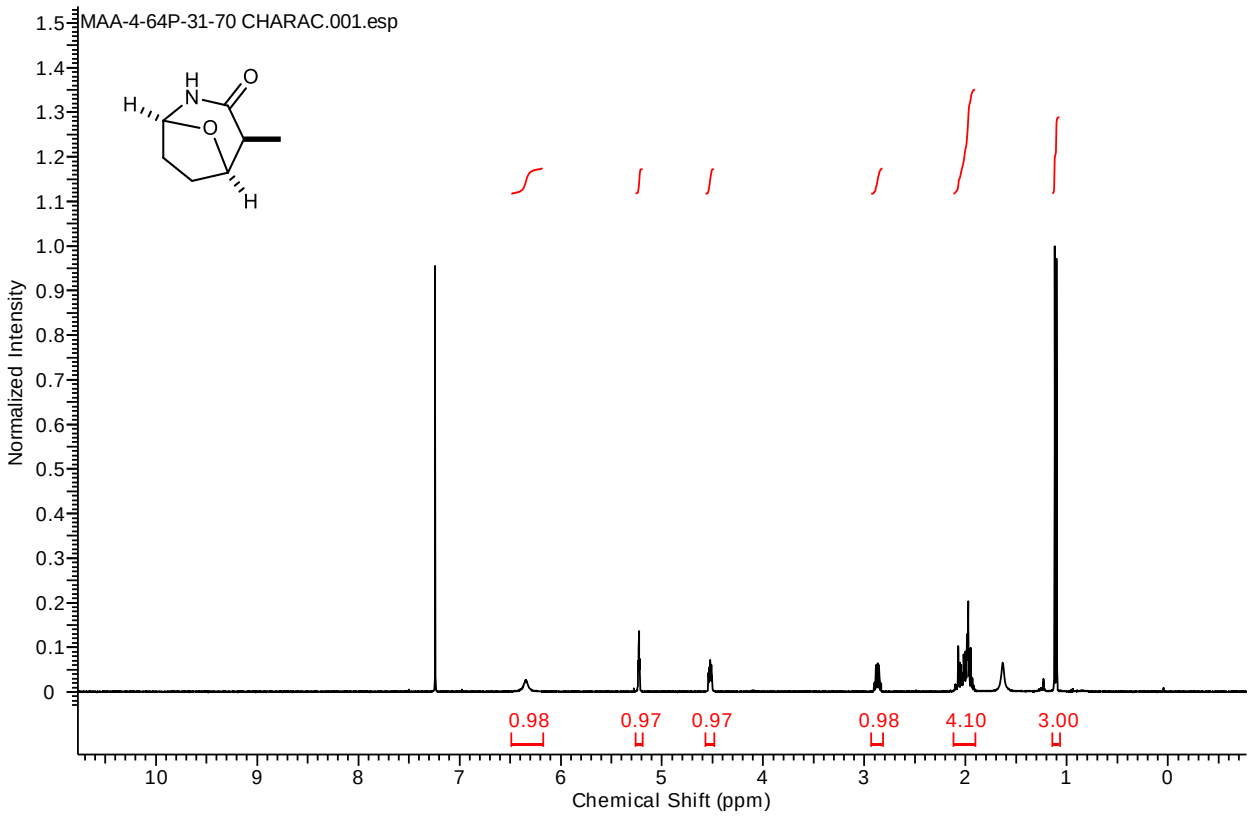

RI12-106-F21-23-C.001.esp
RI12-106-F21-23-C-1.001.esp
Normalized Intensity
Chemical Shift (ppm)
170.83
76.68
72.63
52.22
35.08
29.68
77.32
72.70
52.22
35.12
29.71

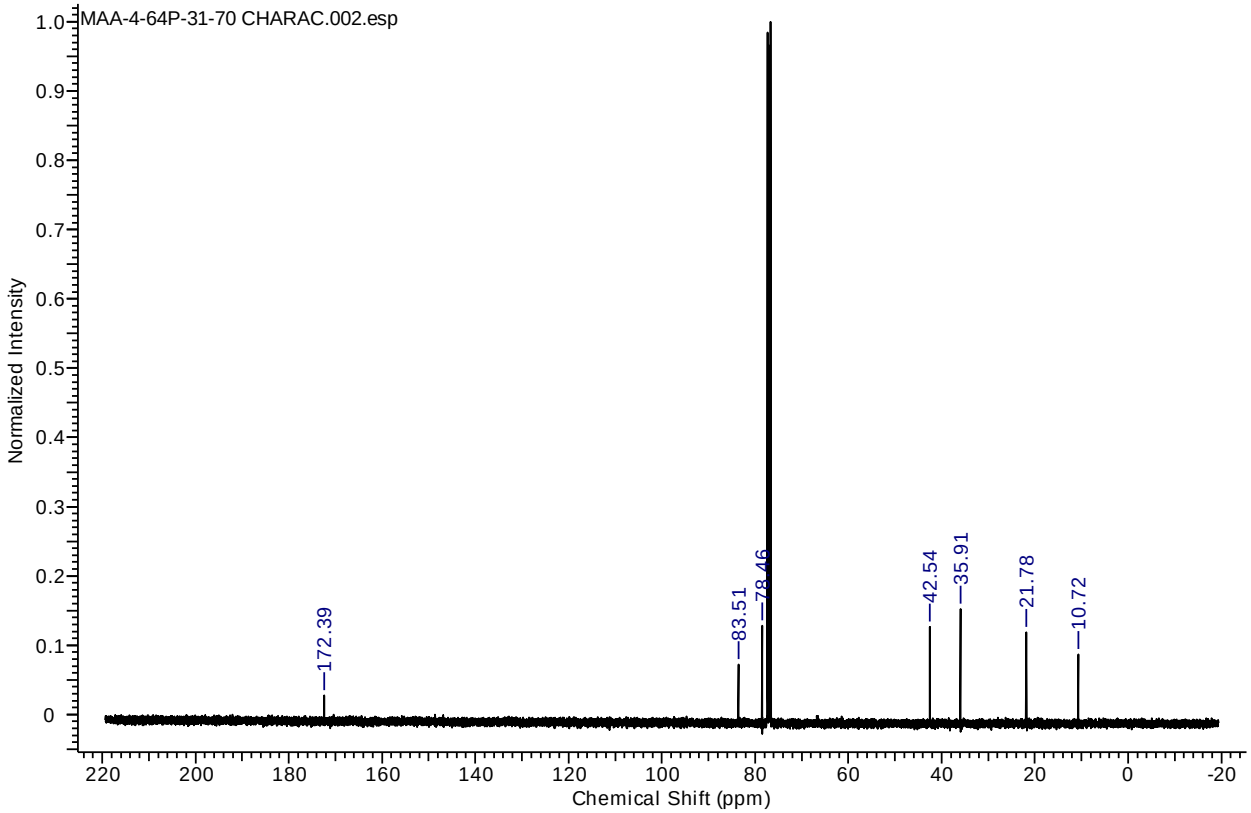

RI12-106-F17-18-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.97
0.94
0.95
1.90
1.00
0.99
1.00
0.97

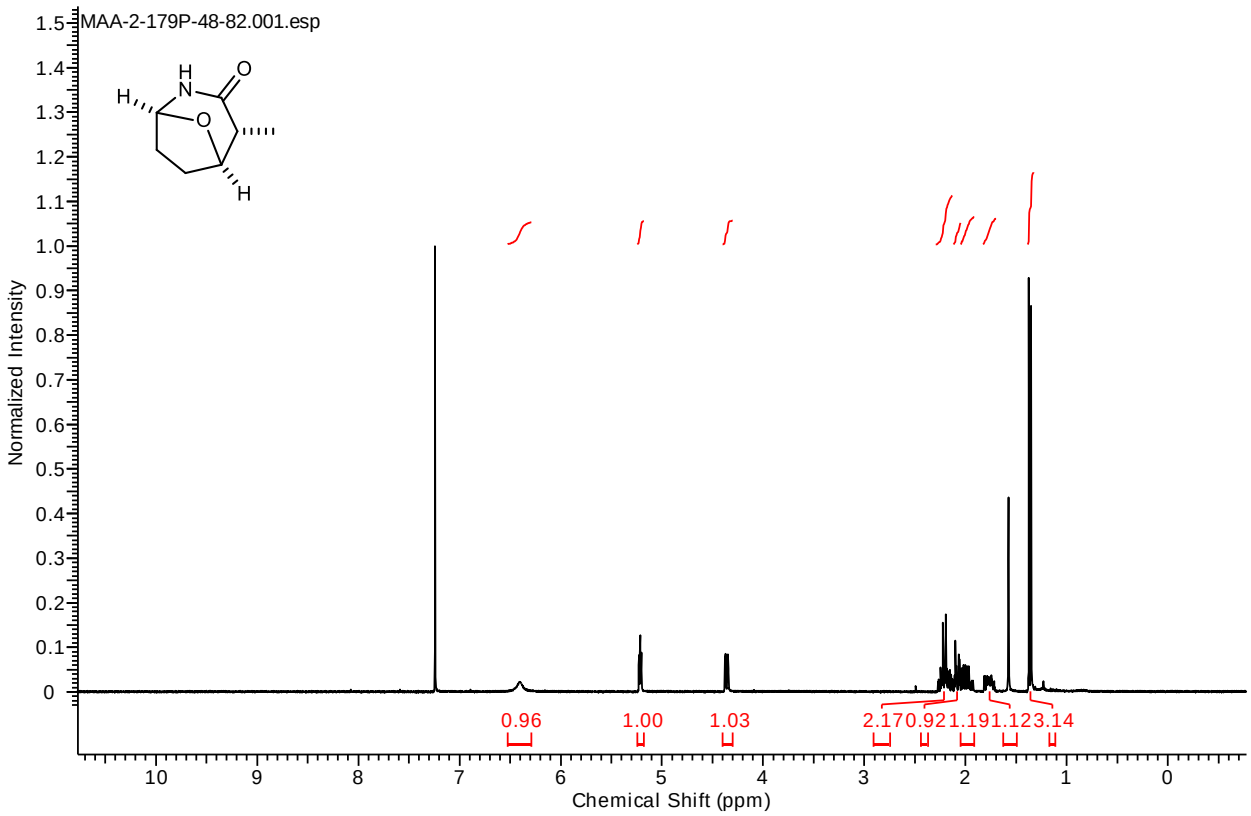

RI12-106-F17-18-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
176.72
77.00
66.51
58.72
37.98
33.95

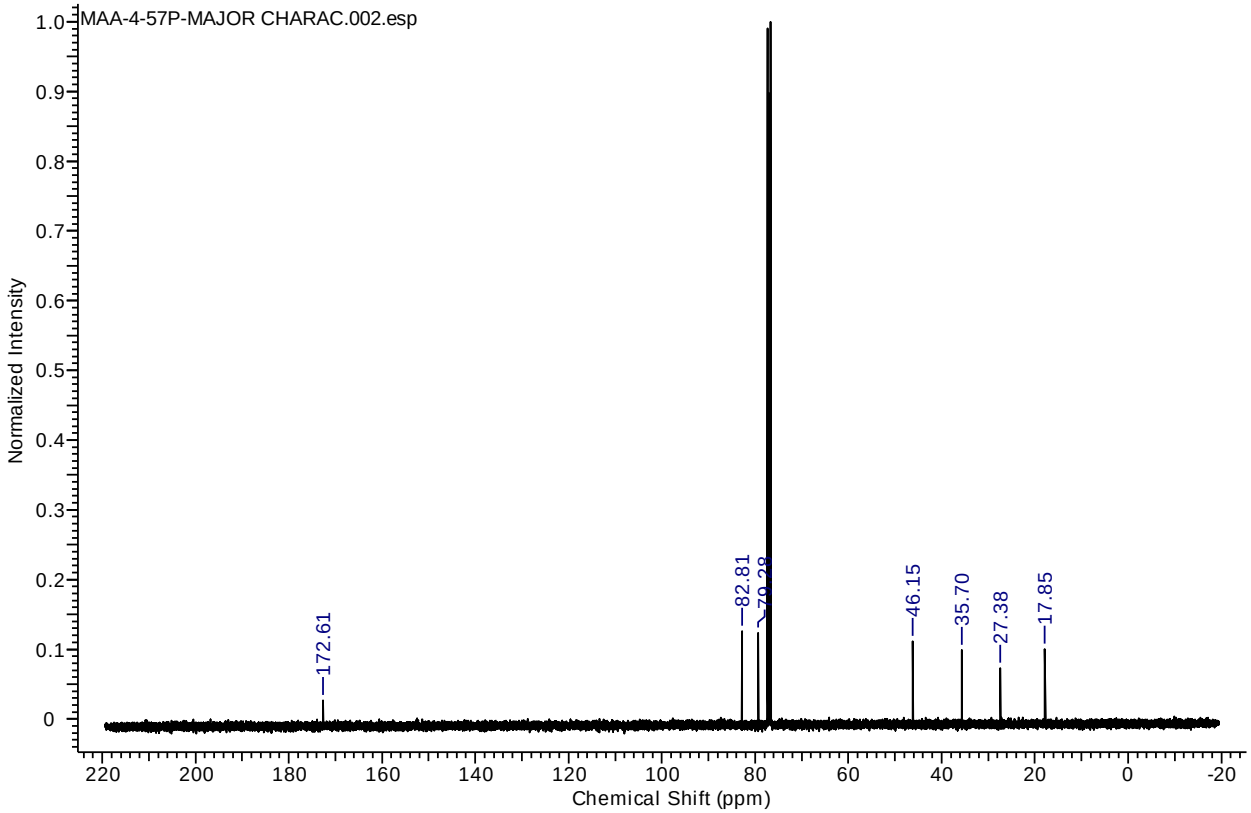

RI10-38-30-42ETOAC-H.001.esp
Me
N
N
O
O
Normalized Intensity
0.90
1.01
1.01
1.87
2.72
1.03
1.92
1.08
Chemical Shift (ppm)

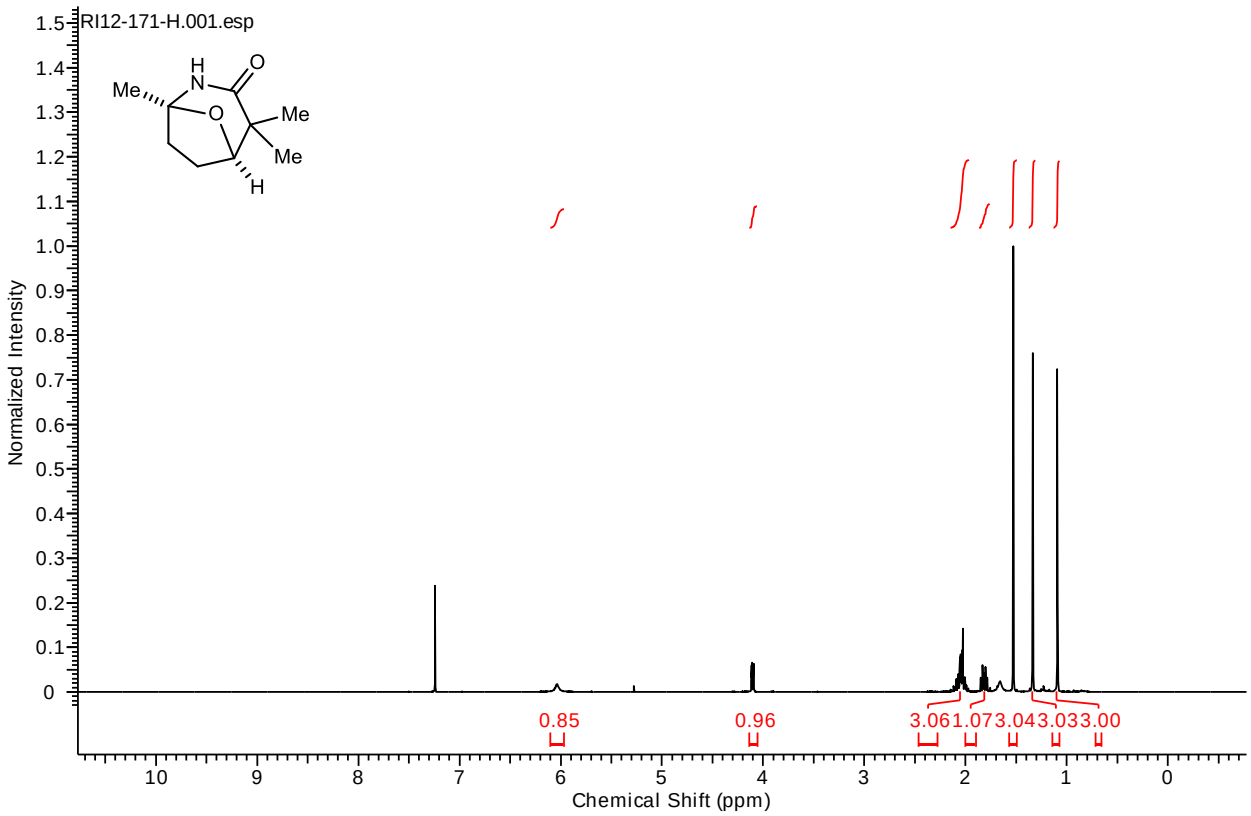

RI10-38-30-42ETOAC-C.001.esp
Normalized Intensity
164.68
163.87
75.87
68.29
31.67
31.19
25.54
10.99
Chemical Shift (ppm)

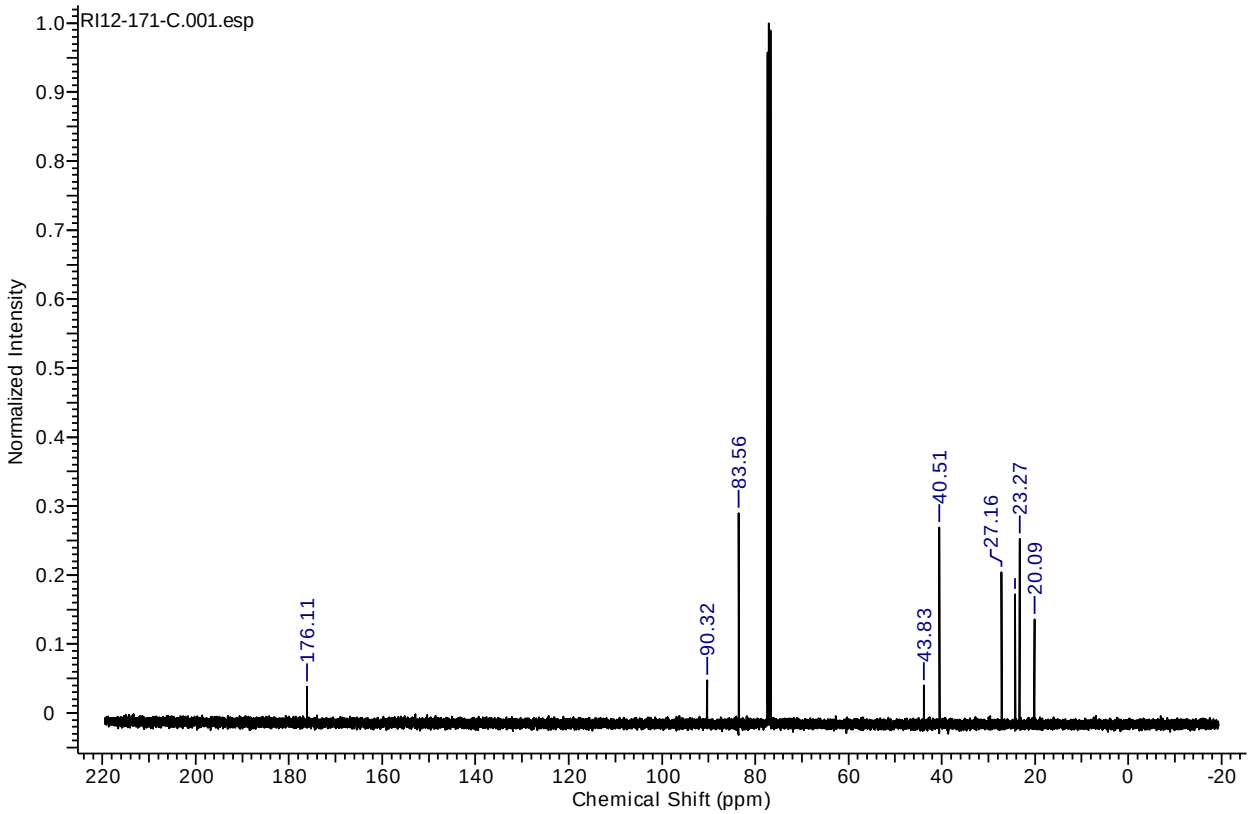

MAA-4-64P-31-70 CHARAC.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.98
0.97
0.97
0.98
4.10
3.00

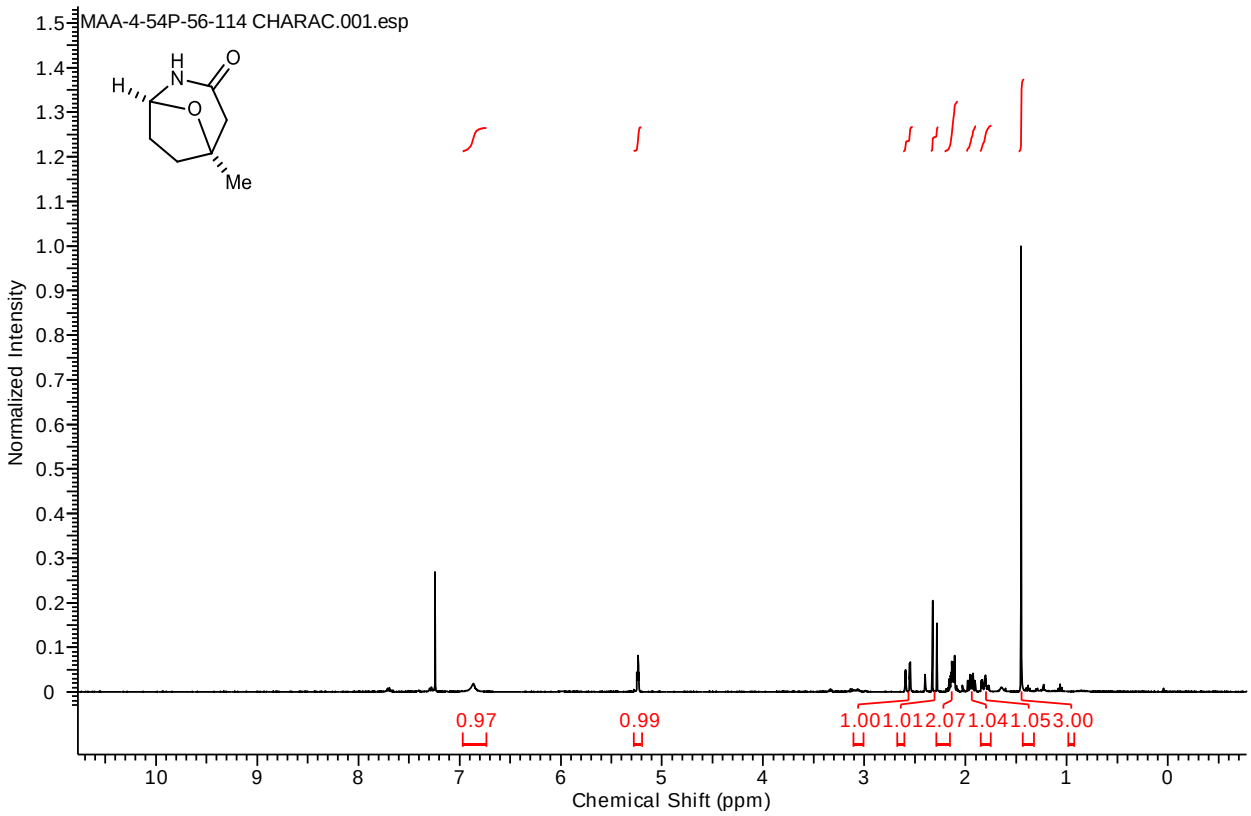

MAA-4-64P-31-70 CHARAC.002.esp
Normalized Intensity
Chemical Shift (ppm)
172.39
83.51
78.46
42.54
35.91
21.78
10.72

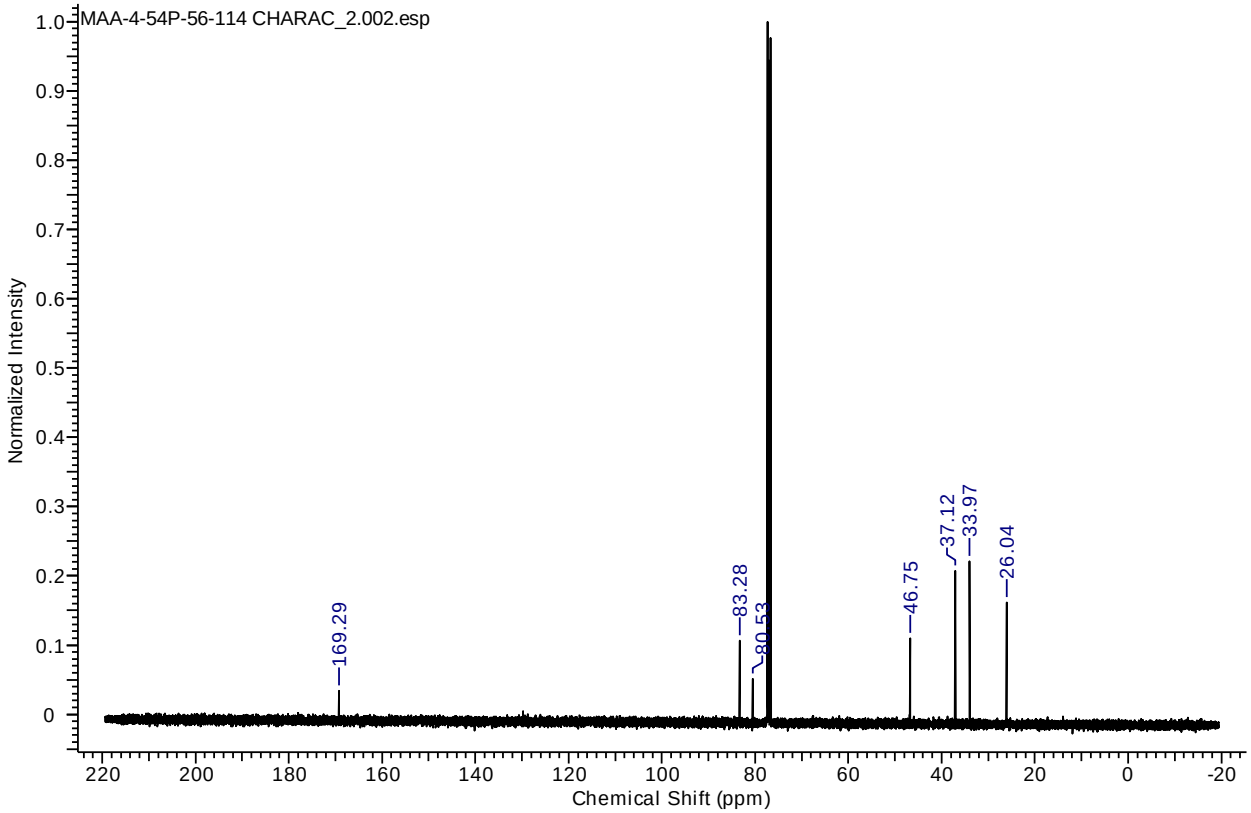

MAA-2-179P-48-82.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.96
1.00
1.03
2.17
0.92
1.19
1.12
3.14

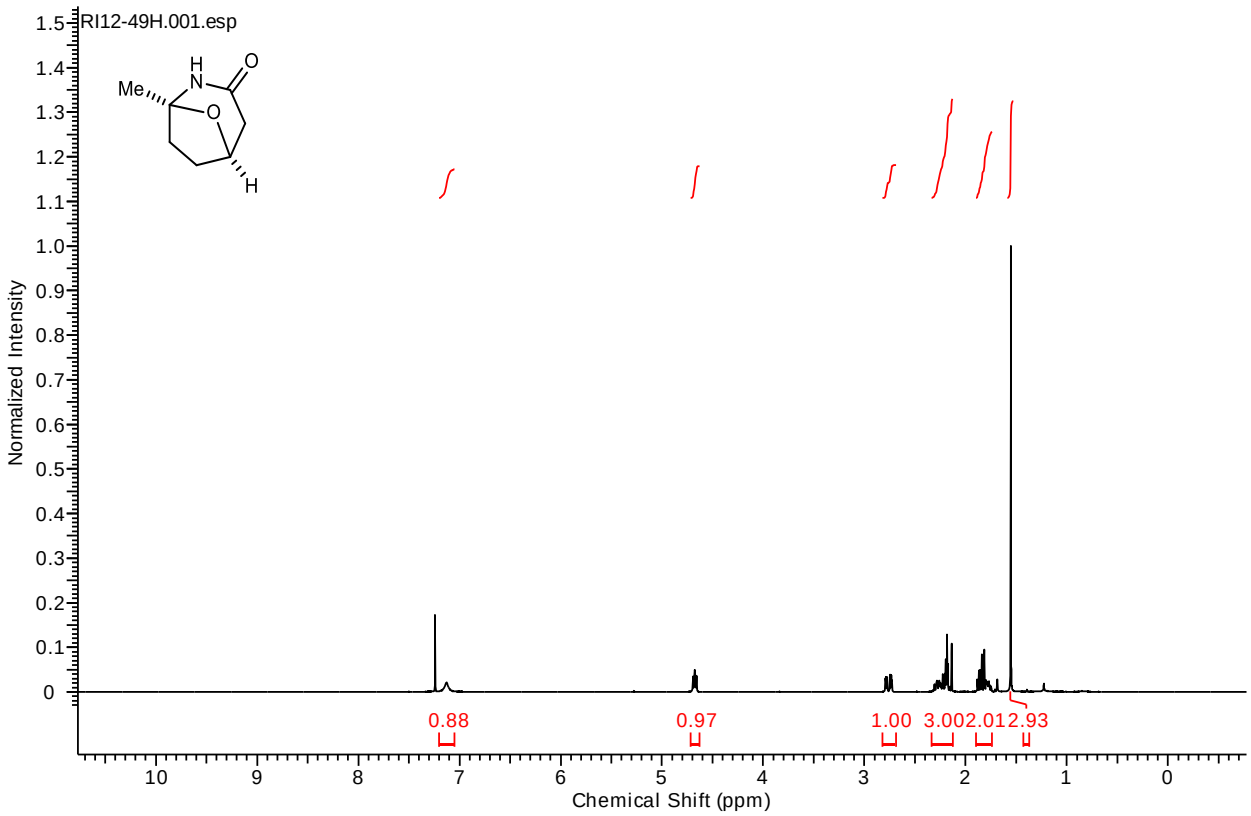

MAA-4-57P-MAJOR CHARAC.002.esp
Normalized Intensity
Chemical Shift (ppm)
172.61
82.81
79.28
46.15
35.70
27.38
17.85

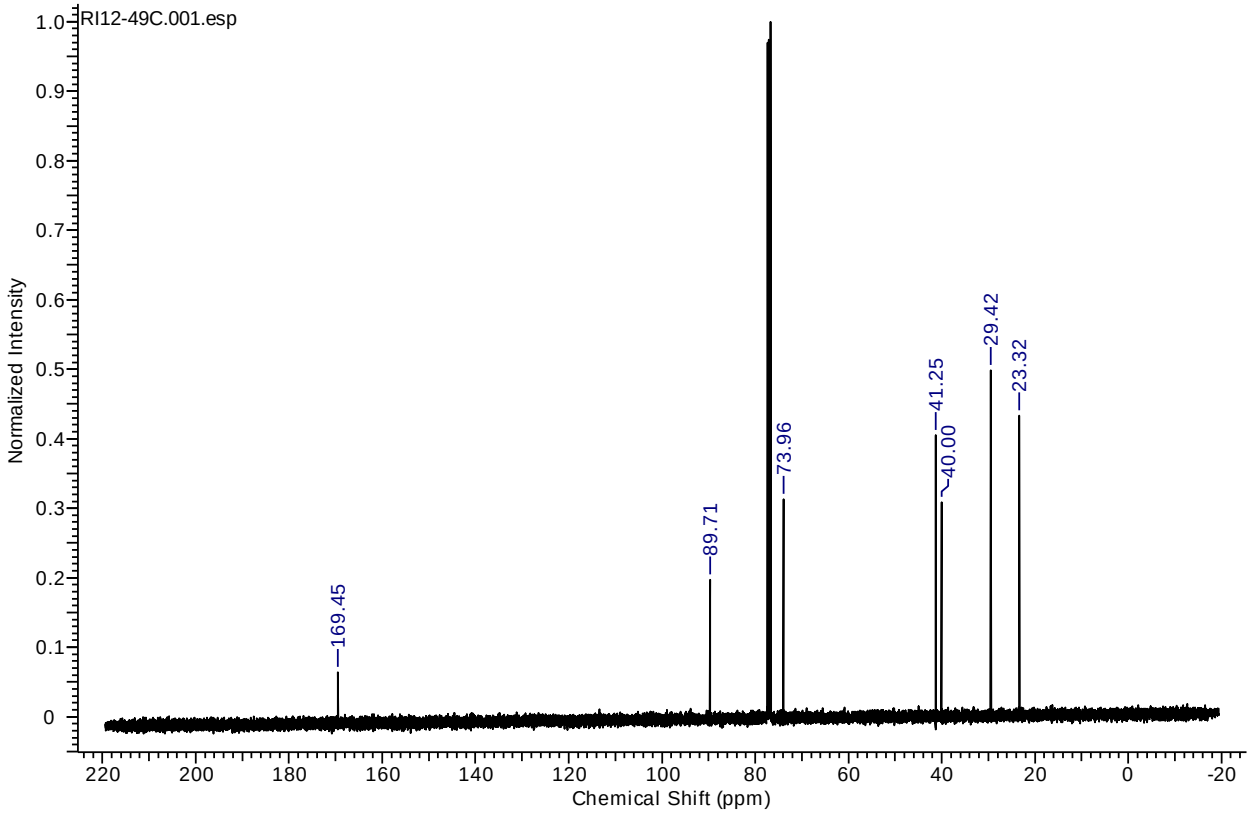

RI12-171-H.001.esp
Me
H
N
O
O
Me
Me
H
Normalized Intensity
0.85
0.96
3.06
1.07
3.04
3.03
3.00
Chemical Shift (ppm)

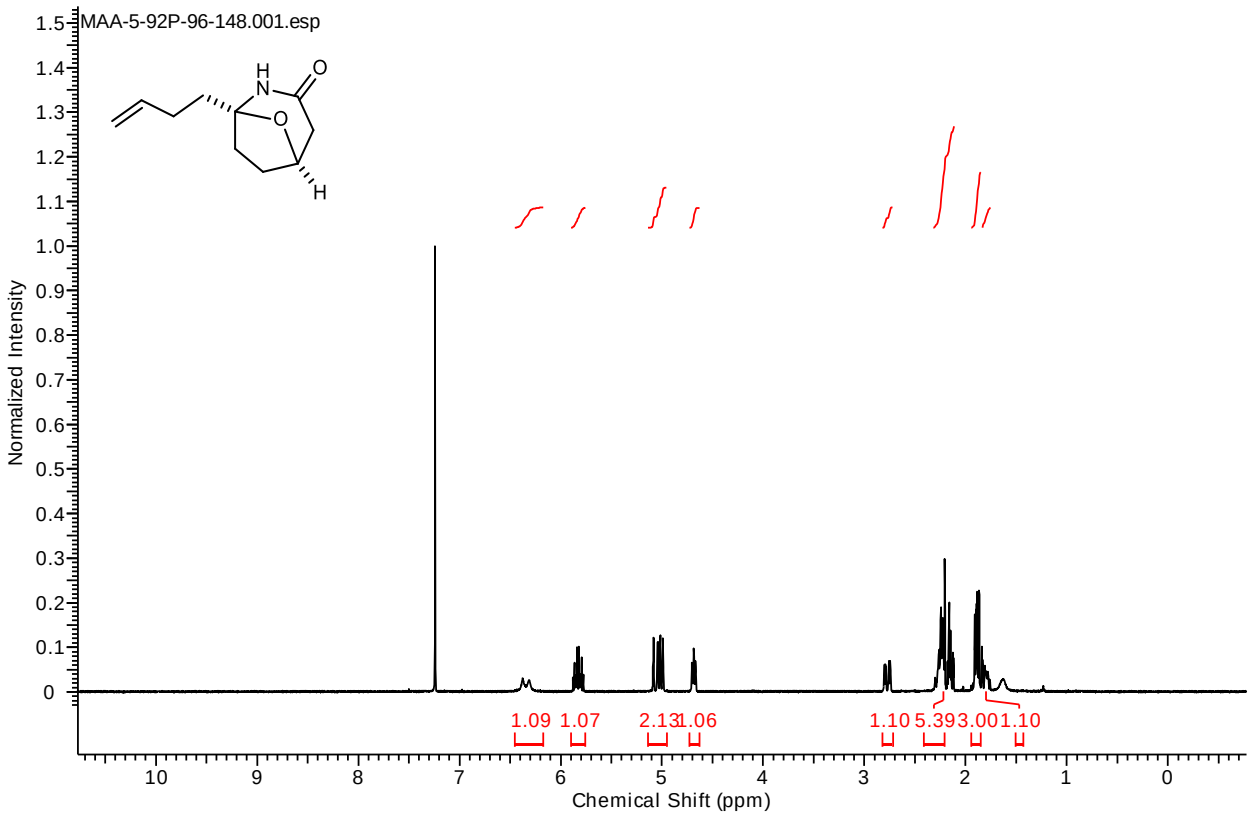

RI12-171-C.001.esp
Normalized Intensity
176.11
90.32
83.56
43.83
40.51
27.16
23.27
20.09
Chemical Shift (ppm)

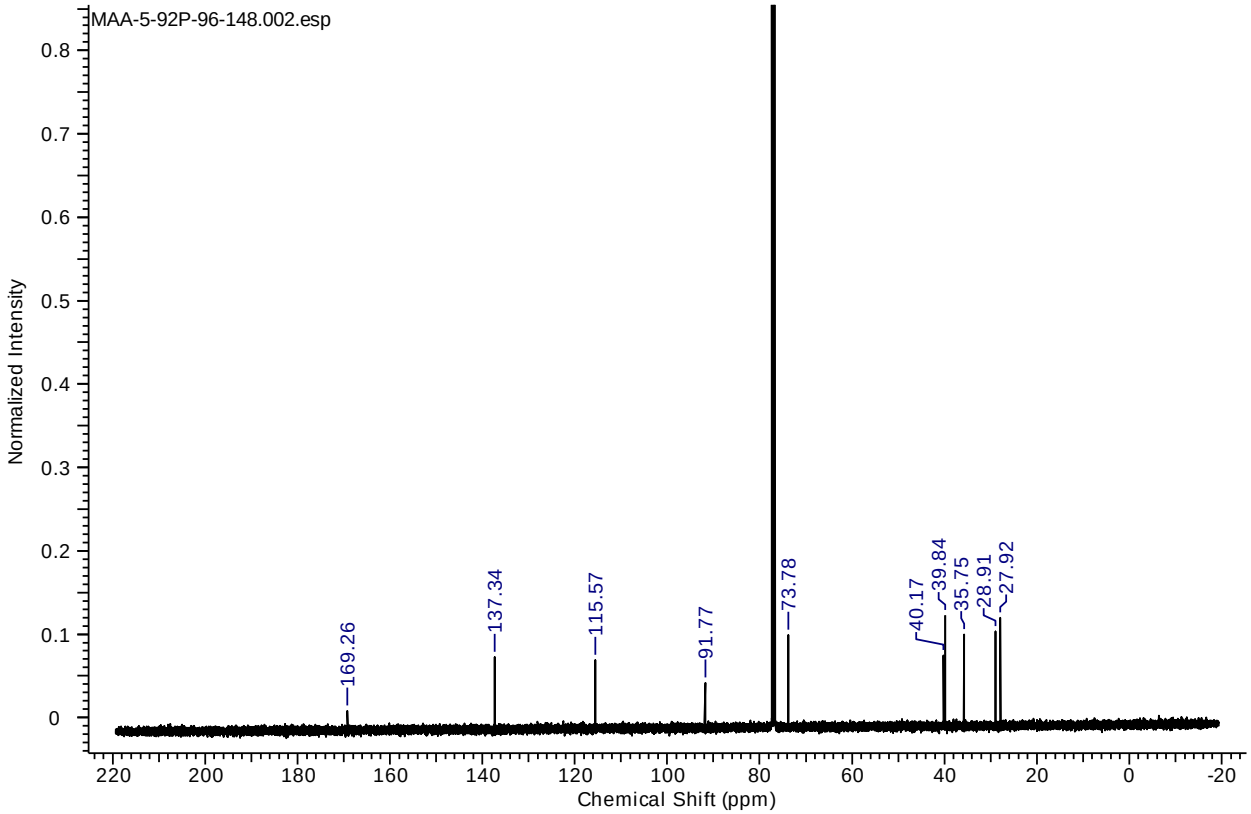

MAA-4-54P-56-114 CHARAC.001.esp
H
N
O
H
O
Me
Normalized Intensity
0.97
0.99
1.00
1.01
2.07
1.04
1.05
3.00
Chemical Shift (ppm)

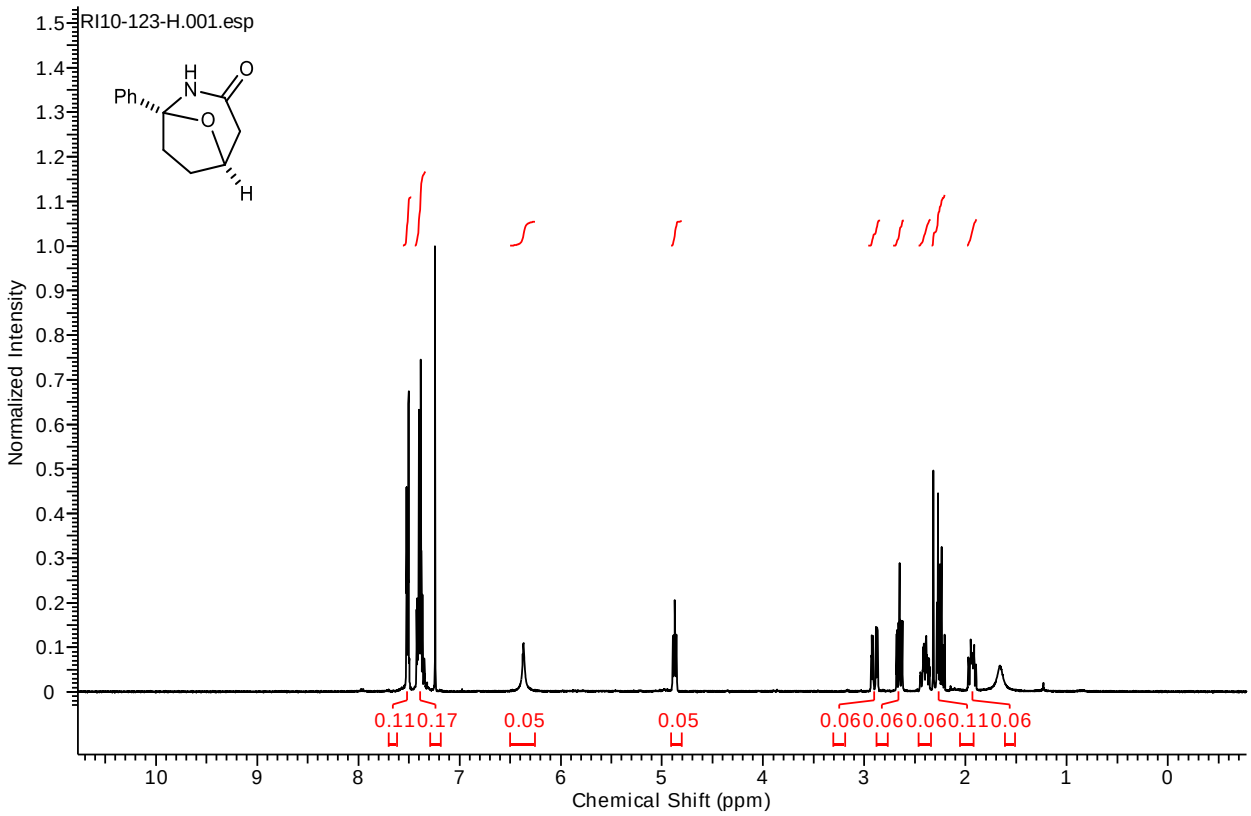

MAA-4-54P-56-114 CHARAC_2.002.esp
169.29
83.28
80.53
46.75
37.12
33.97
26.04
Normalized Intensity
Chemical Shift (ppm)

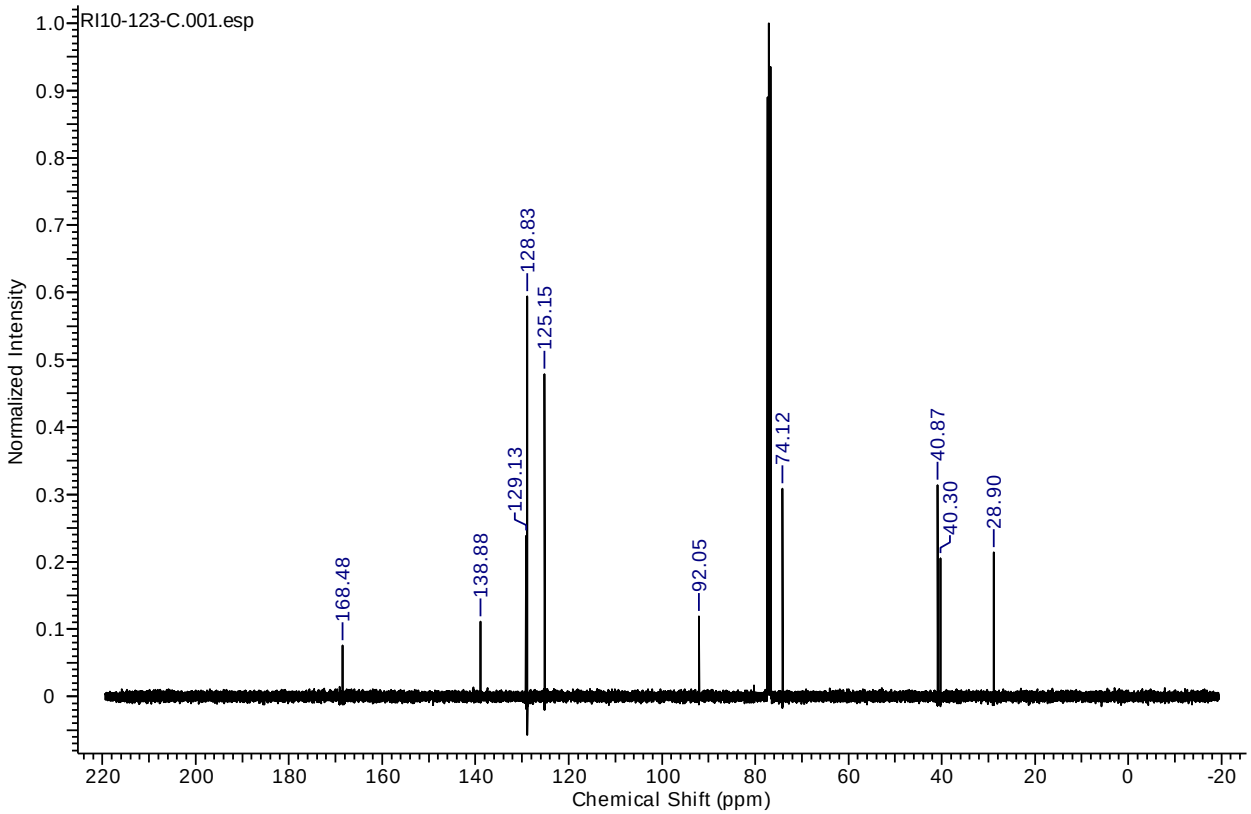

RI12-49H.001.esp
Me
H
N
O
O
H
Normalized Intensity
0.88
0.97
1.00
3.00
2.01
2.93
Chemical Shift (ppm)

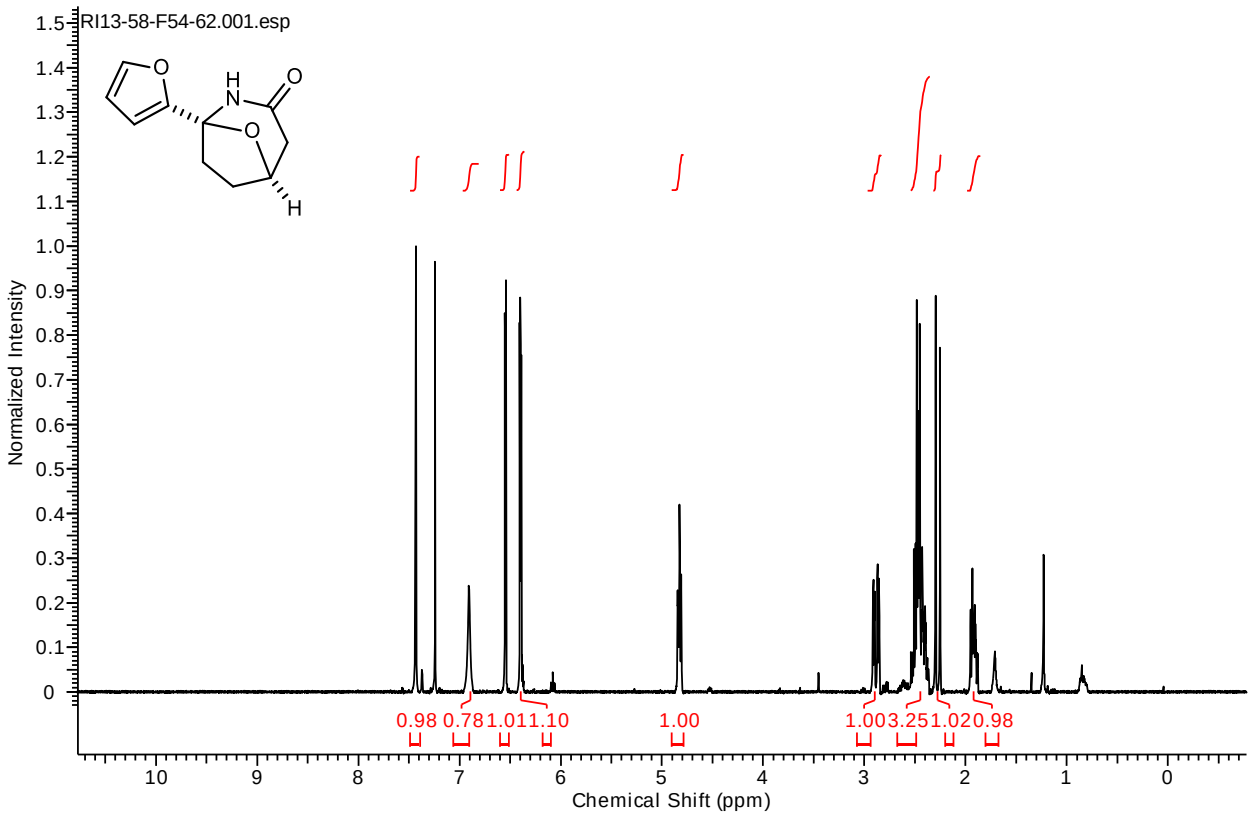

RI12-49C.001.esp
Normalized Intensity
169.45
89.71
73.96
41.25
40.00
29.42
23.32
Chemical Shift (ppm)

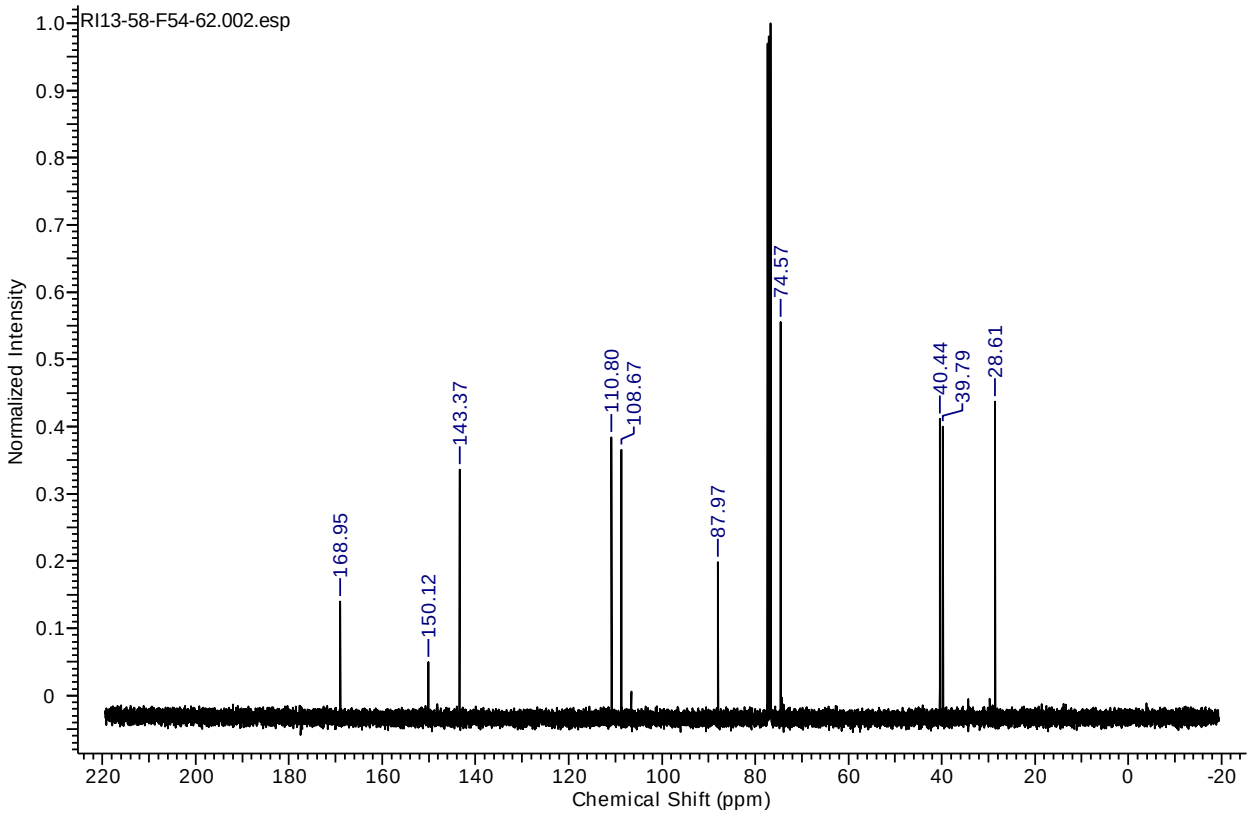

MAA-5-92P-96-148.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.09
1.07
2.13
1.06
1.10
5.39
3.00
1.10

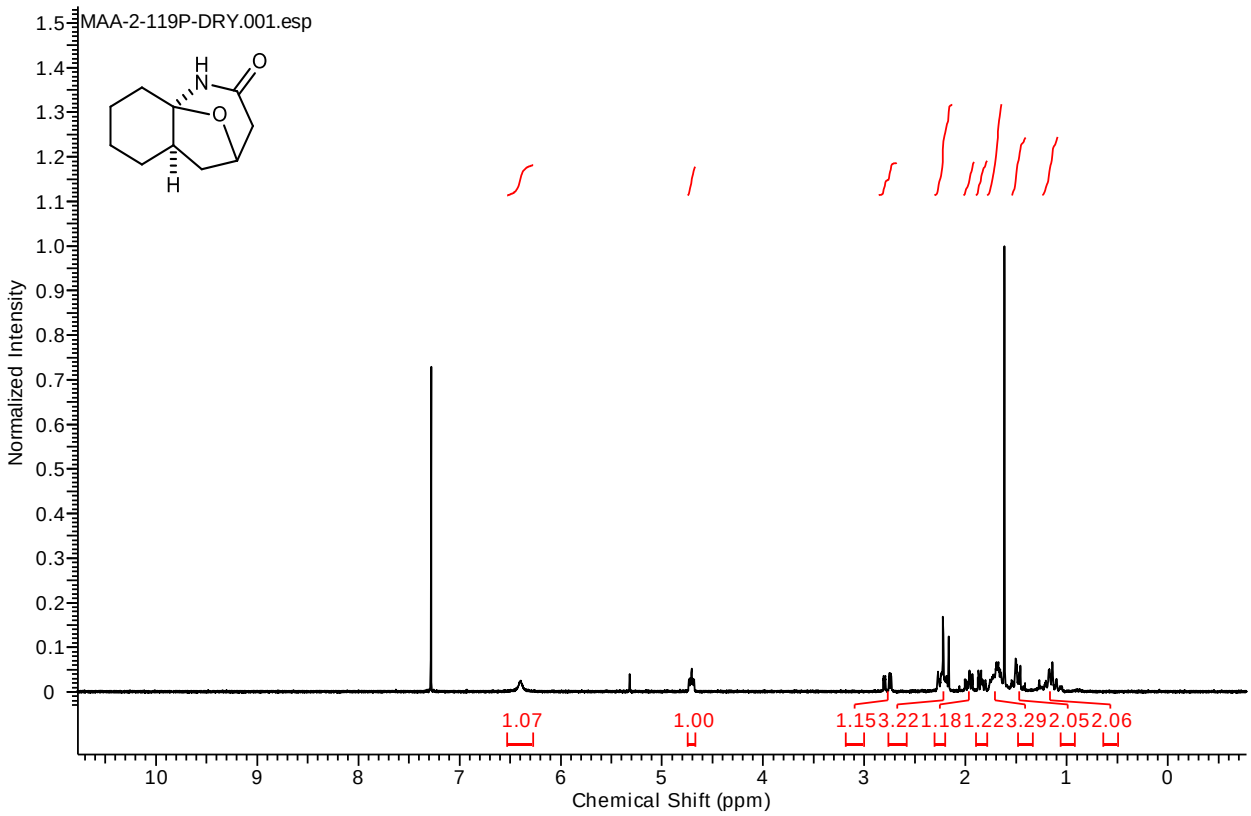

MAA-5-92P-96-148.002.esp
Normalized Intensity
Chemical Shift (ppm)
169.26
137.34
115.57
91.77
73.78
40.17
39.84
35.75
28.91
27.92

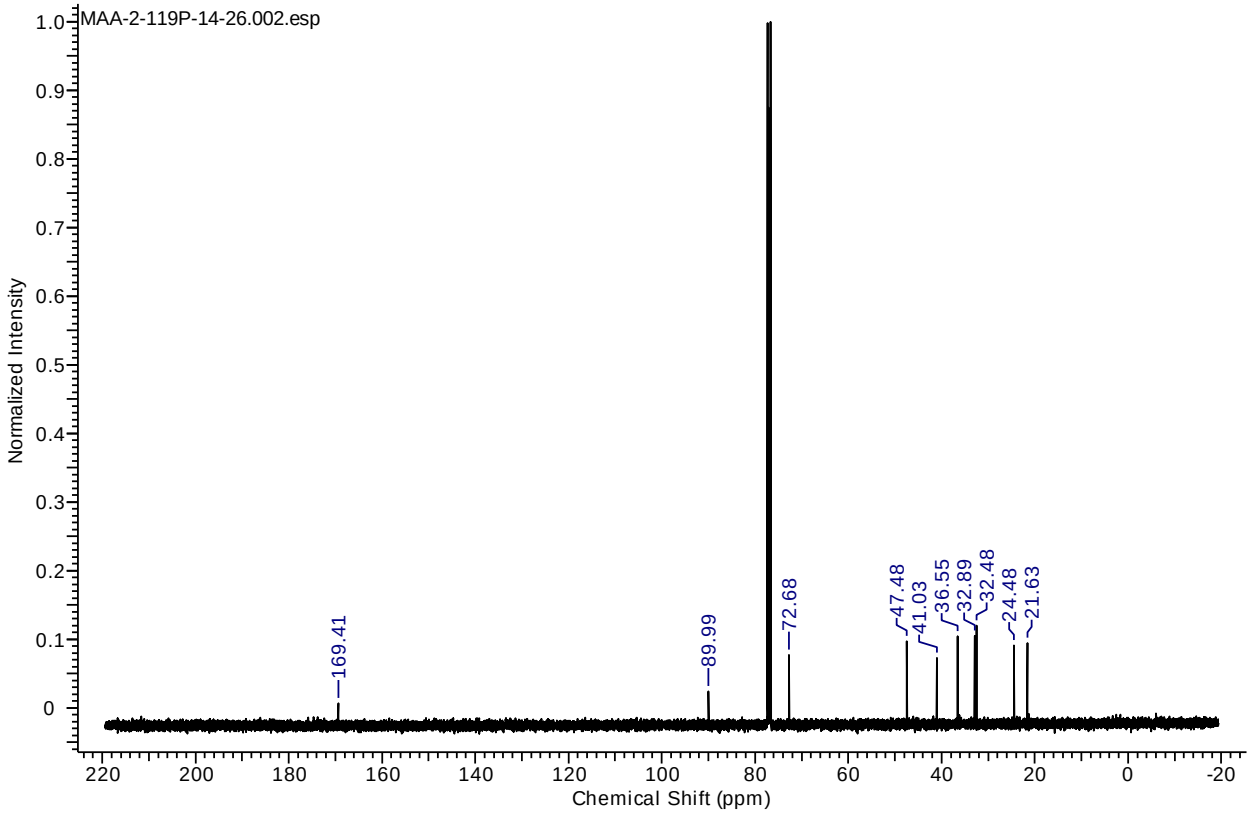

RI10-123-H.001.esp
Ph
H
N
O
O
H
Normalized Intensity
0.11
0.17
0.05
0.05
0.06
0.06
0.06
0.11
0.06
Chemical Shift (ppm)

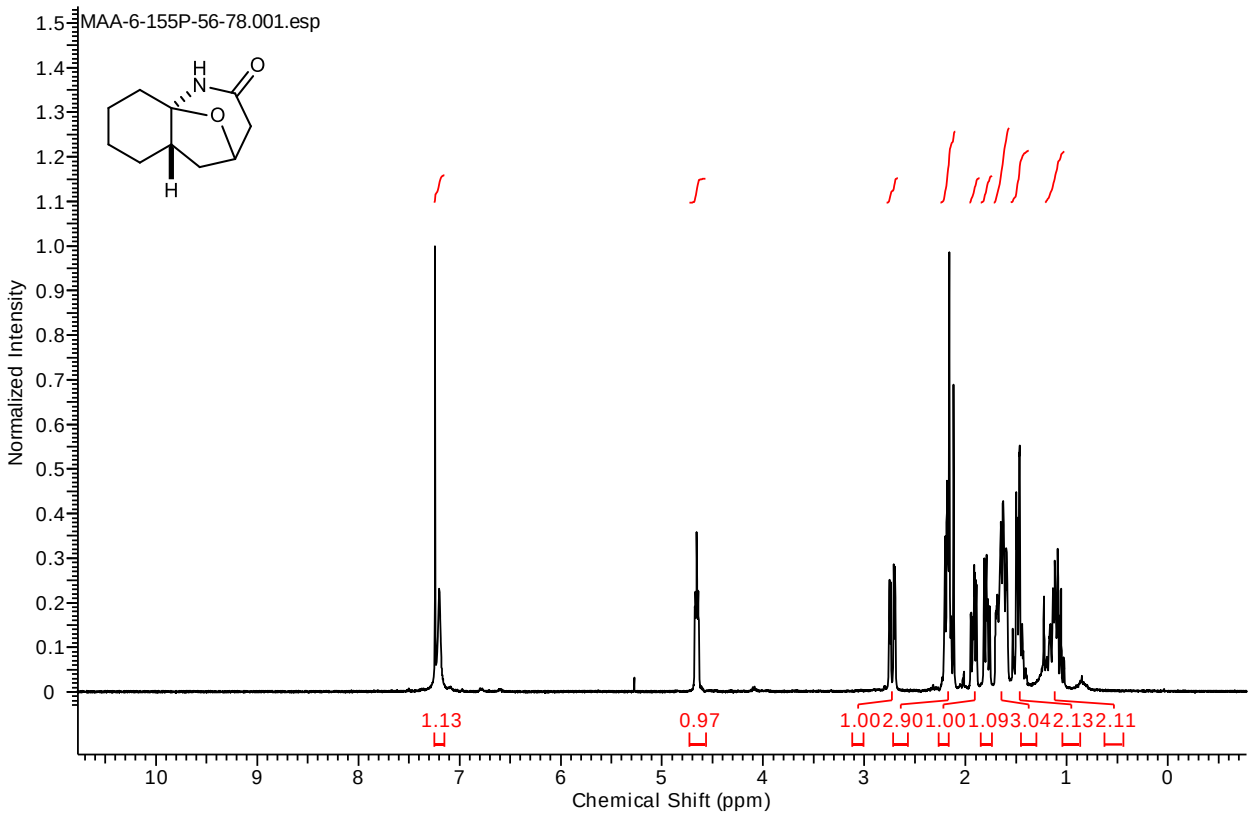

RI10-123-C.001.esp
Normalized Intensity
168.48
138.88
129.13
128.83
125.15
92.05
74.12
40.87
40.30
28.90
Chemical Shift (ppm)

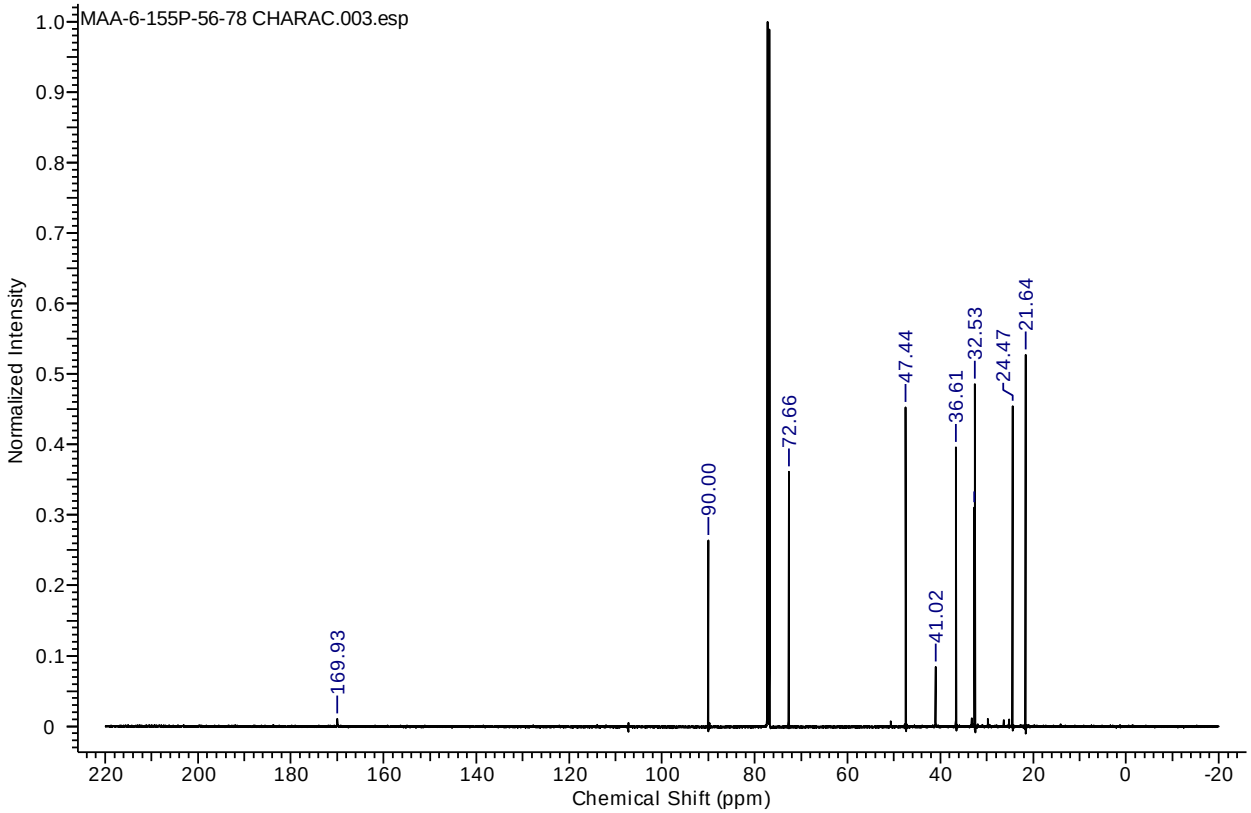

RI13-58-F54-62.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.98 0.78 1.01 1.10 1.00 1.00 3.25 1.02 0.98

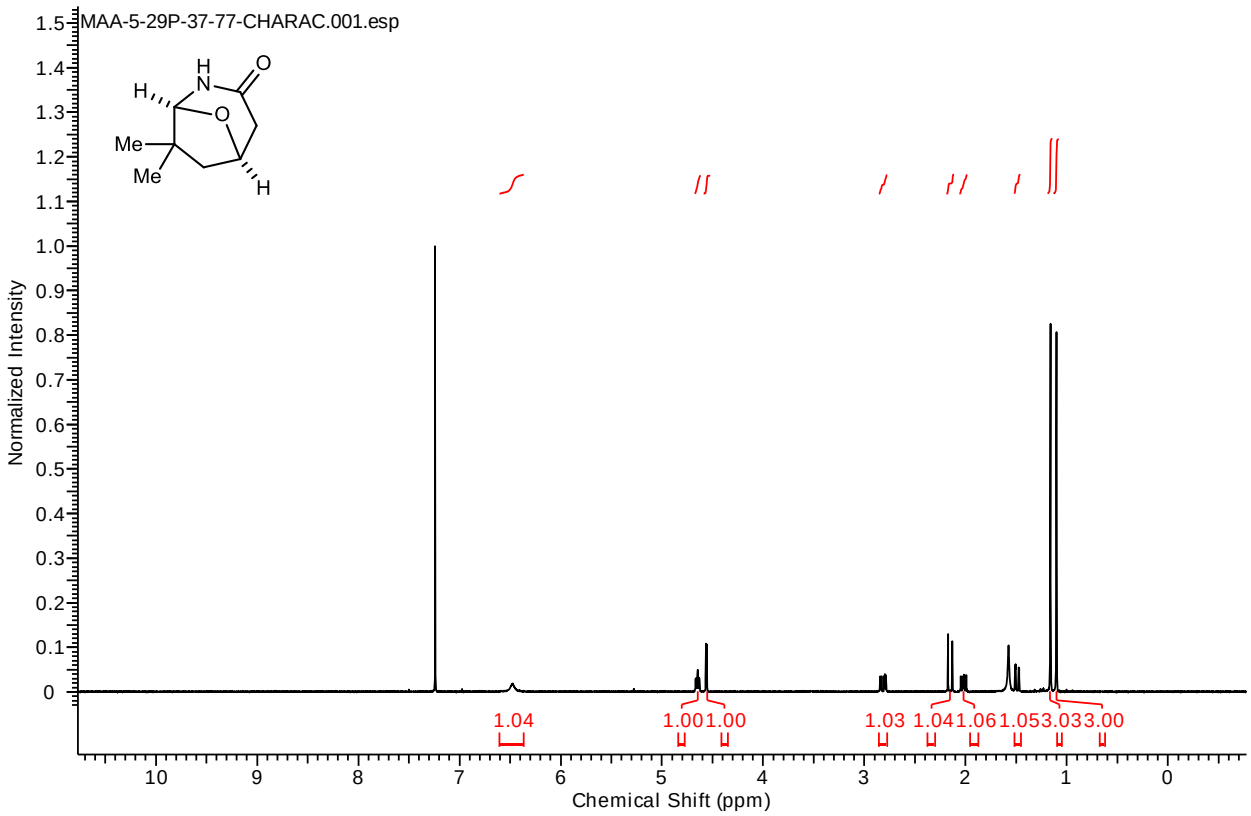

RI13-58-F54-62.002.esp
Normalized Intensity
Chemical Shift (ppm)
168.95
150.12
143.37
110.80
108.67
87.97
74.57
40.44
39.79
28.61

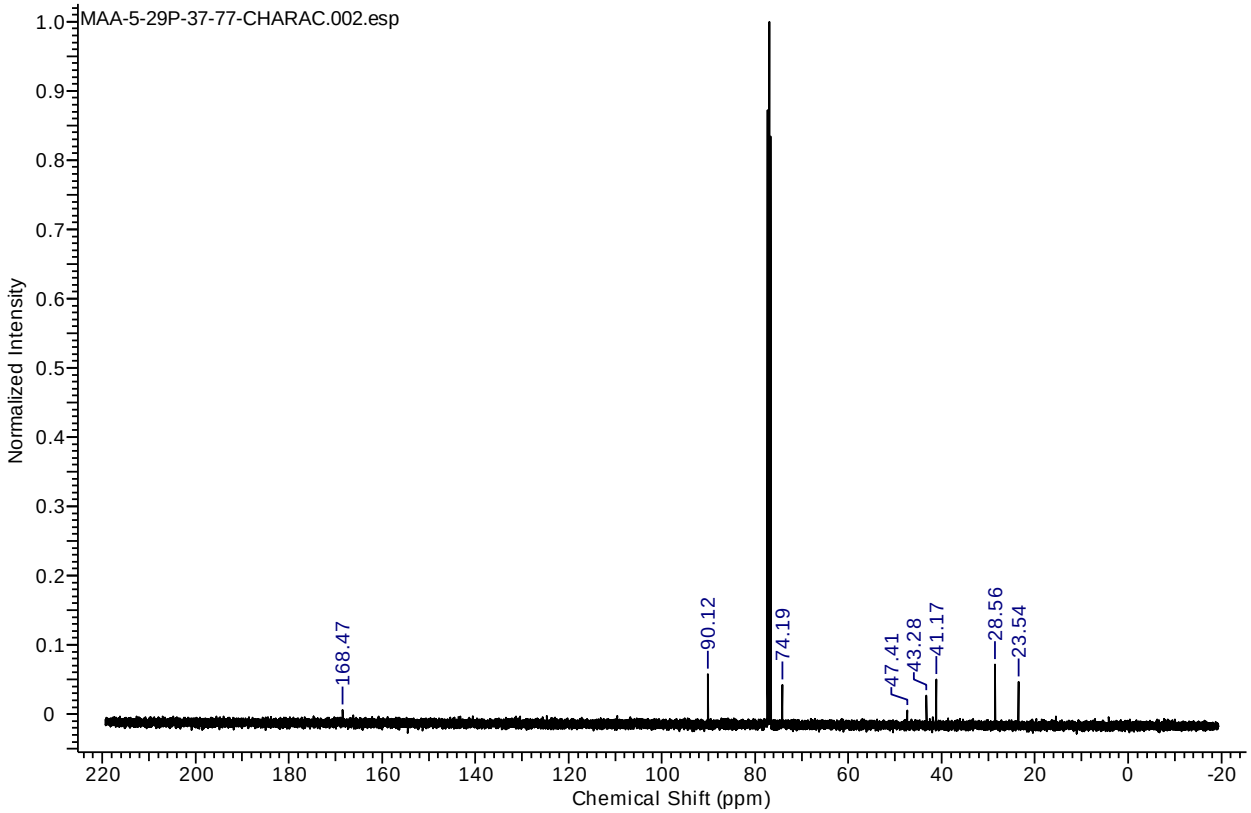

MAA-2-119P-DRY.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.07
1.00
1.15
3.22
1.18
1.22
3.29
2.05
2.06

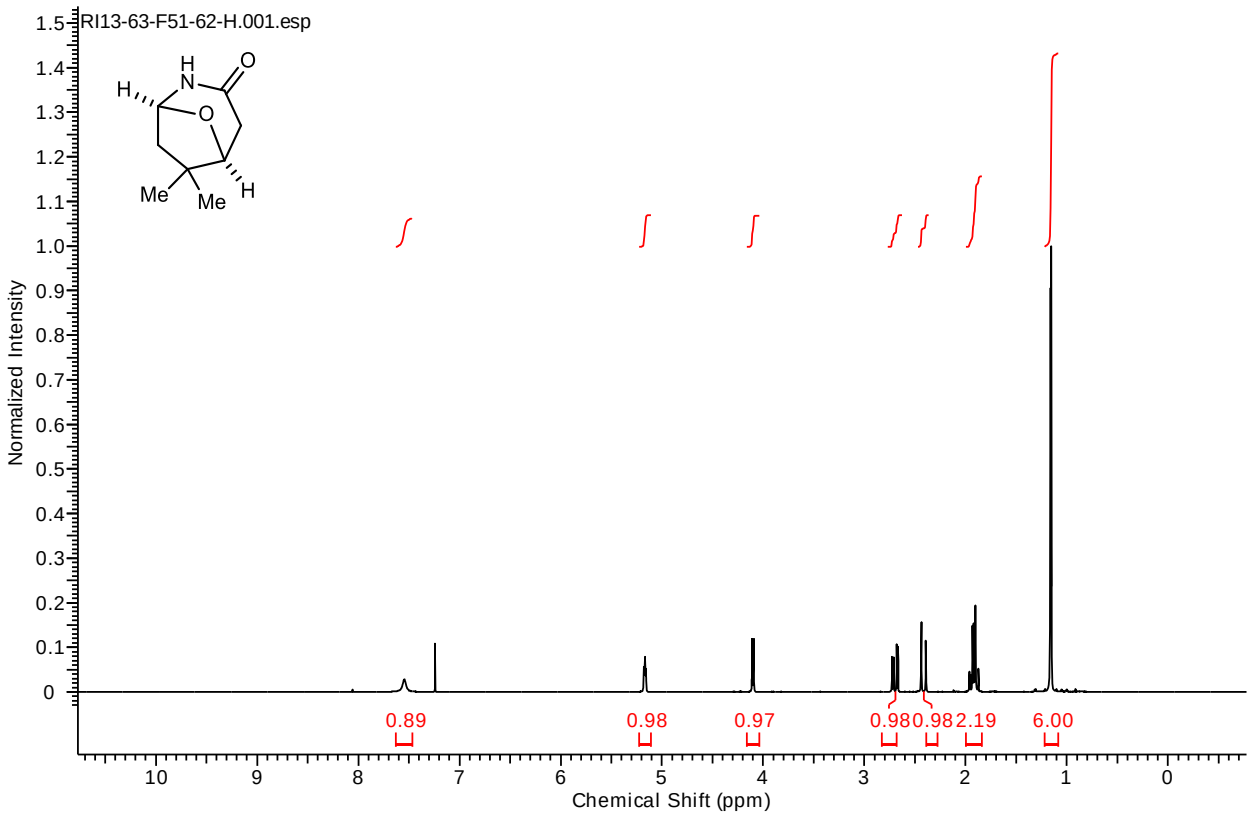

MAA-2-119P-14-26.002.esp
Normalized Intensity
Chemical Shift (ppm)
169.41
89.99
72.68
47.48
41.03
36.55
32.89
32.48
24.48
21.63

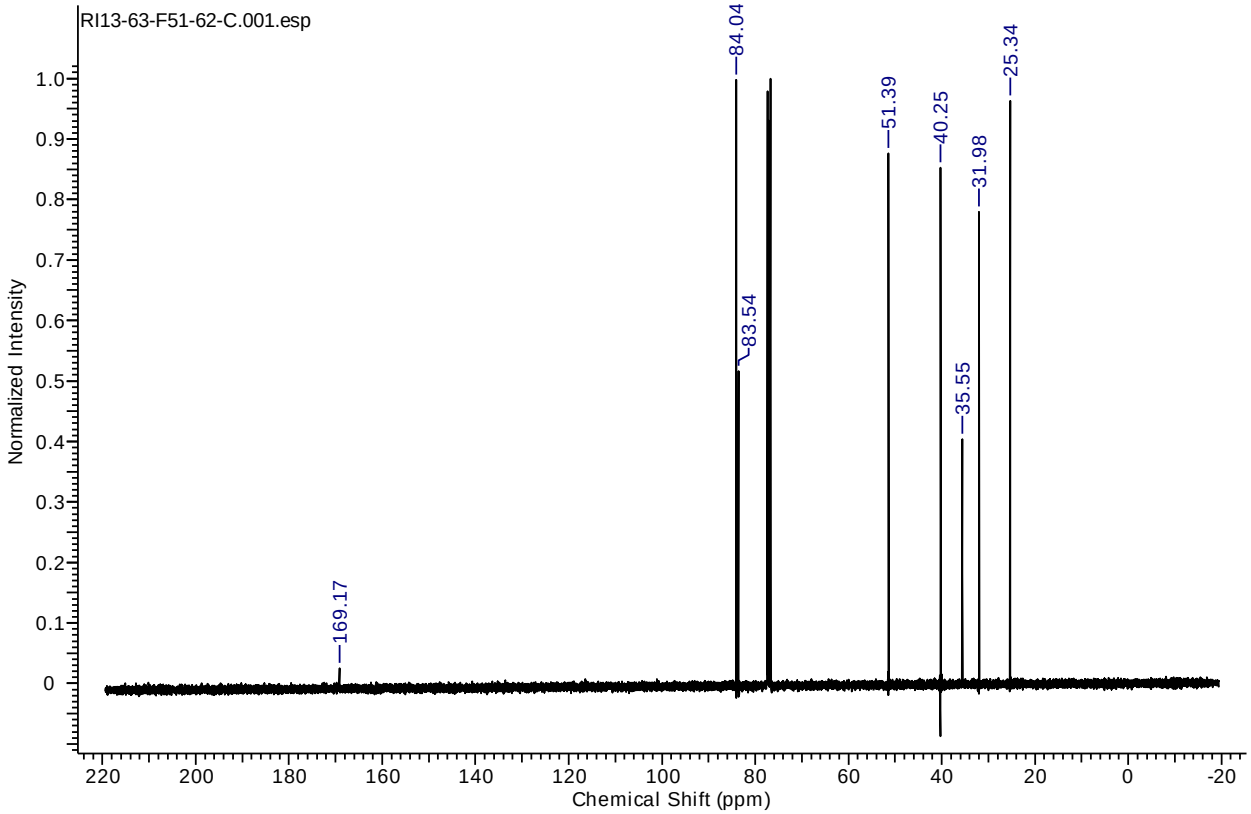

MAA-6-155P-56-78.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.13
0.97
1.00
2.90
1.00
1.09
3.04
2.13
2.11

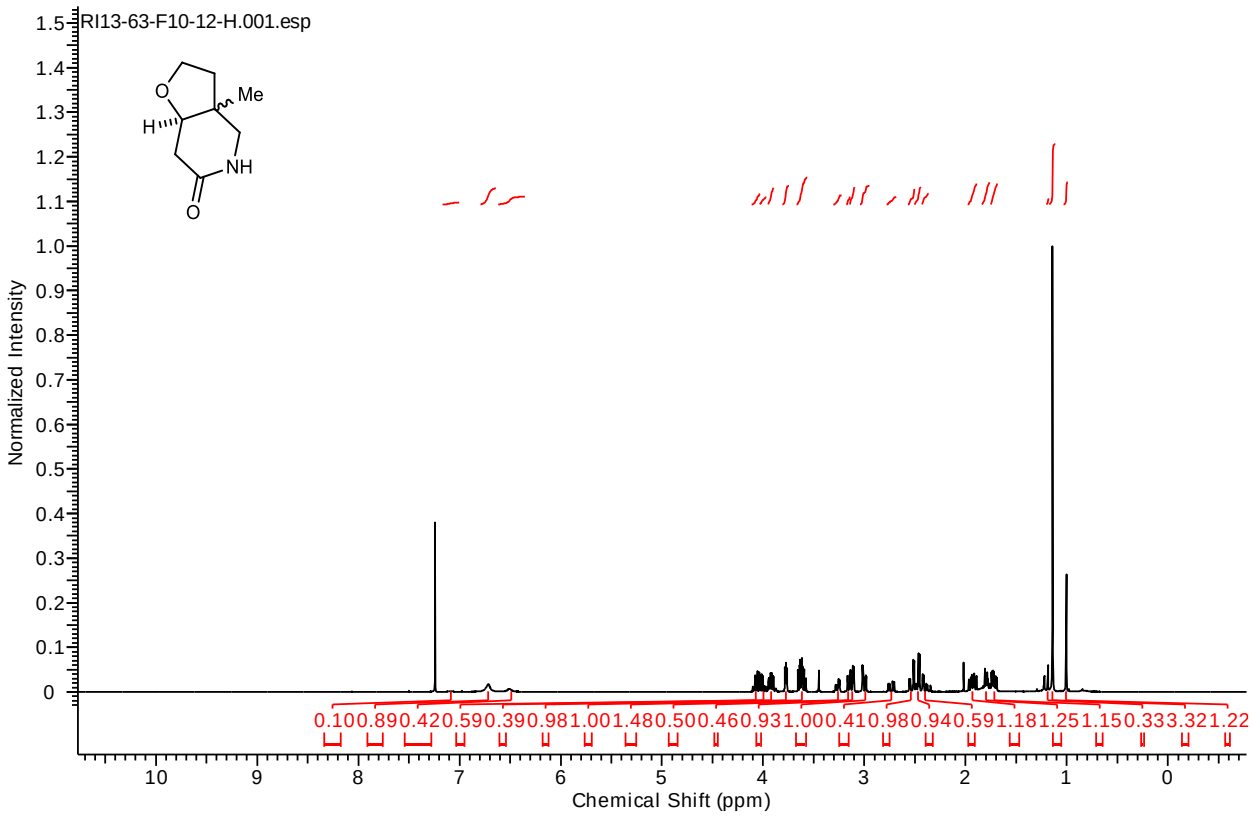

MAA-6-155P-56-78 CHARAC.003.esp
Normalized Intensity
Chemical Shift (ppm)
169.93
90.00
72.66
47.44
41.02
36.61
32.53
24.47
21.64

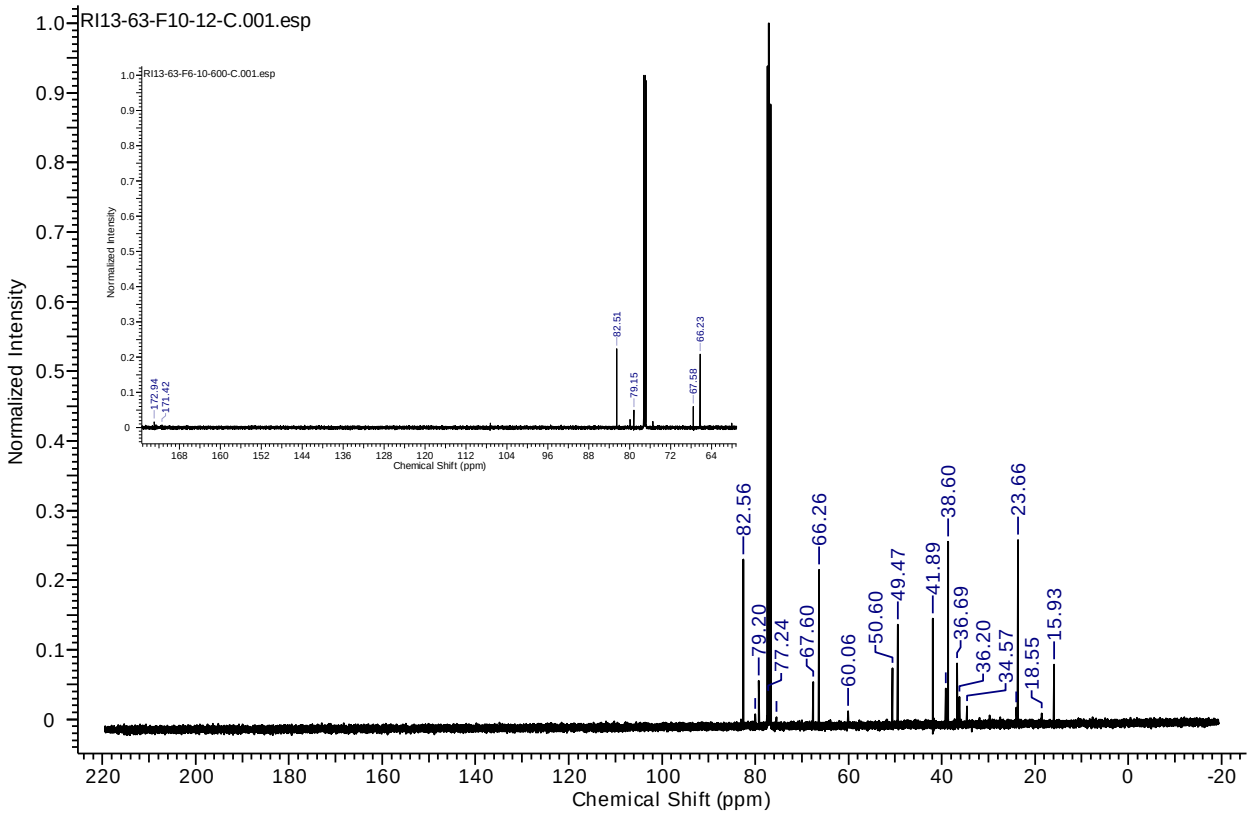

MAA-5-29P-37-77-CHARAC.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.04
1.00
1.00
1.03
1.04
1.06
1.05
3.03
3.00

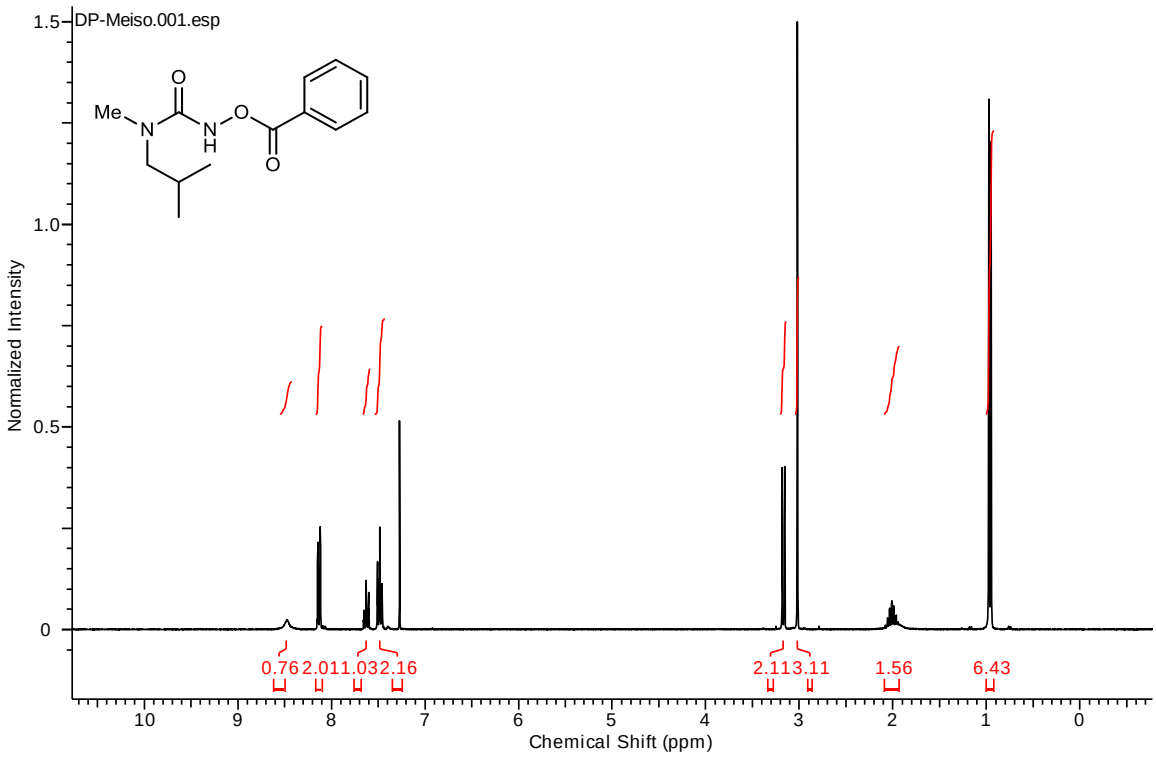

MAA-5-29P-37-77-CHARAC.002.esp
Normalized Intensity
Chemical Shift (ppm)
168.47
90.12
74.19
47.41
43.28
41.17
28.56
23.54

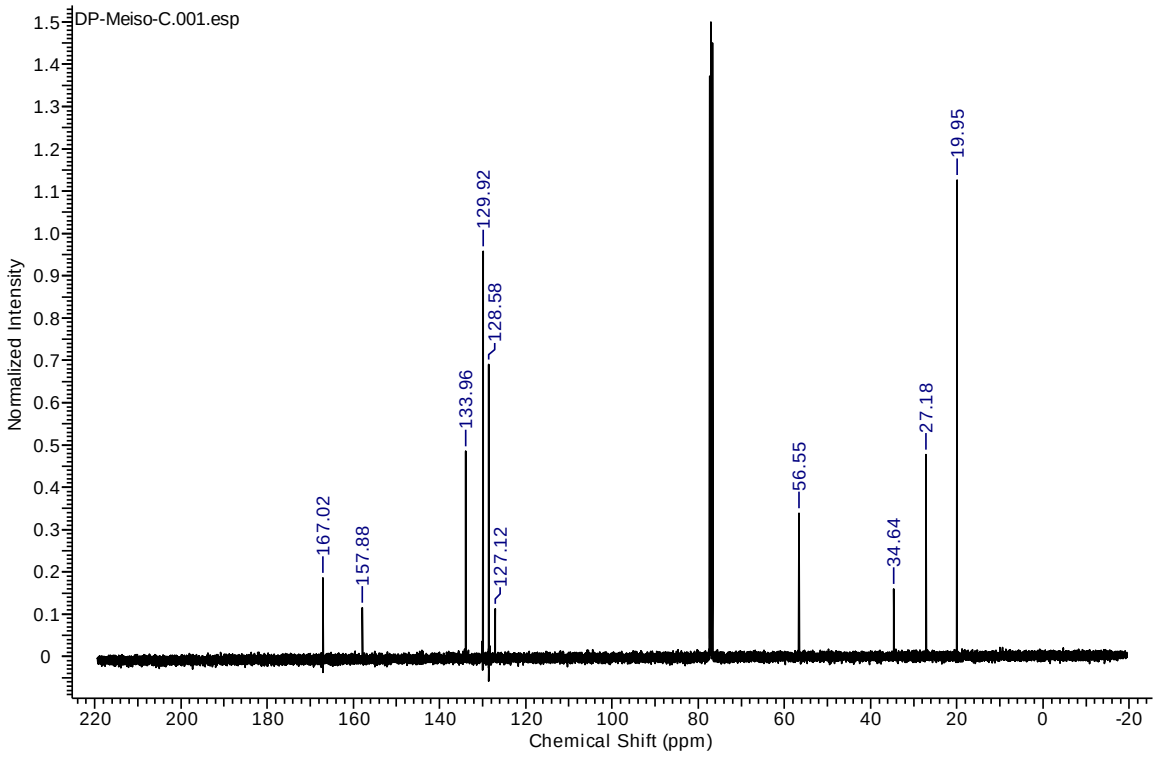

RI13-63-F51-62-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.89
0.98
0.97
0.98
0.98
2.19
6.00

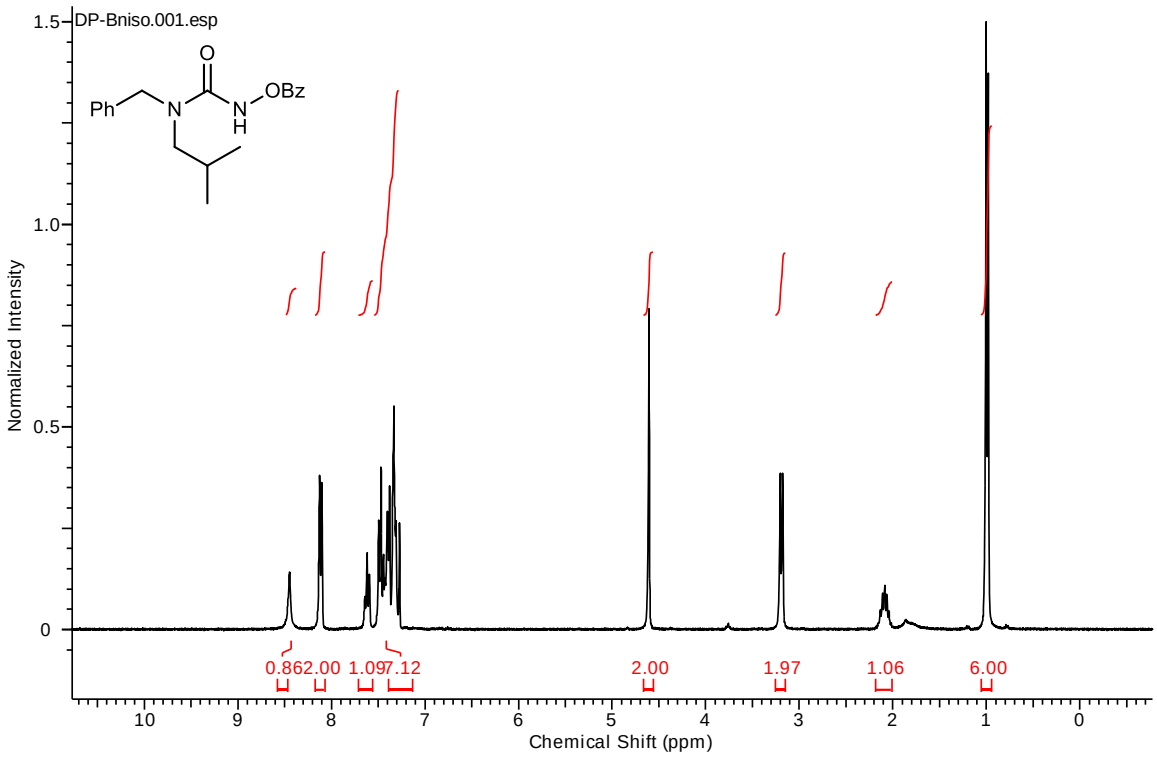

RI13-63-F51-62-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
84.04
83.54
51.39
40.25
35.55
31.98
25.34
169.17

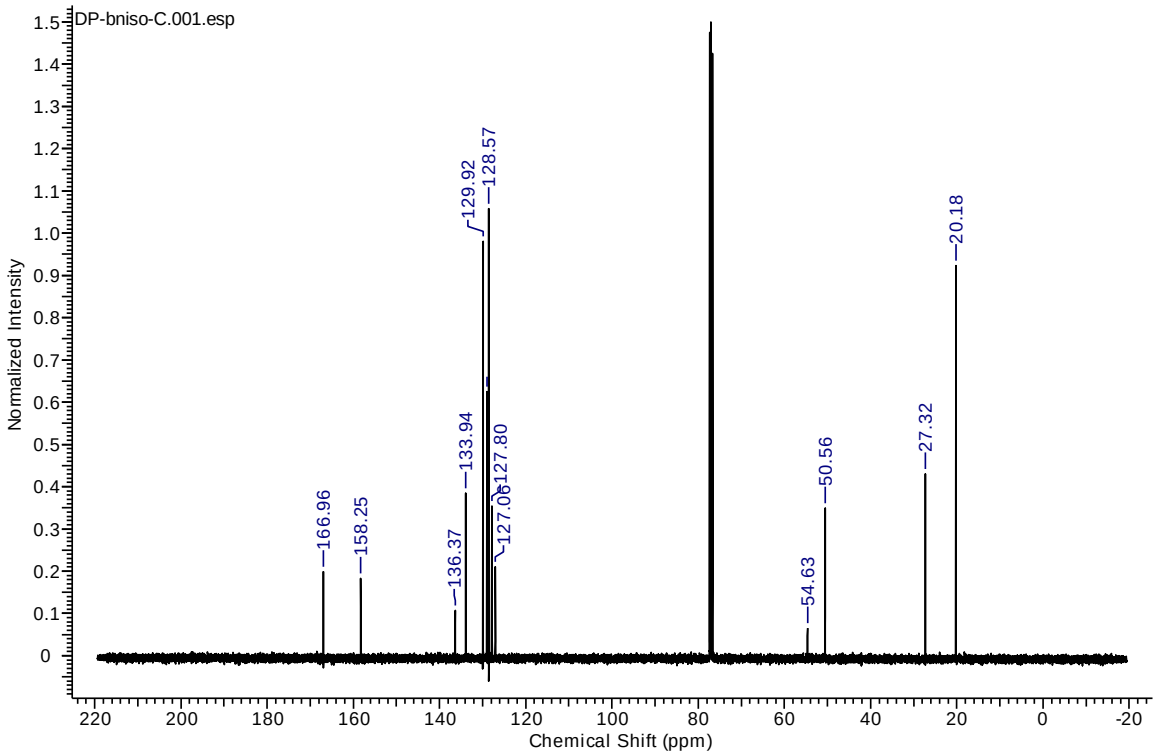

RI13-63-F10-12-H.001.esp
Me
H
O
NH
O
Normalized Intensity
0.100.890.420.590.390.981.001.480.500.460.931.000.410.980.940.591.181.251.150.333.321.22
Chemical Shift (ppm)

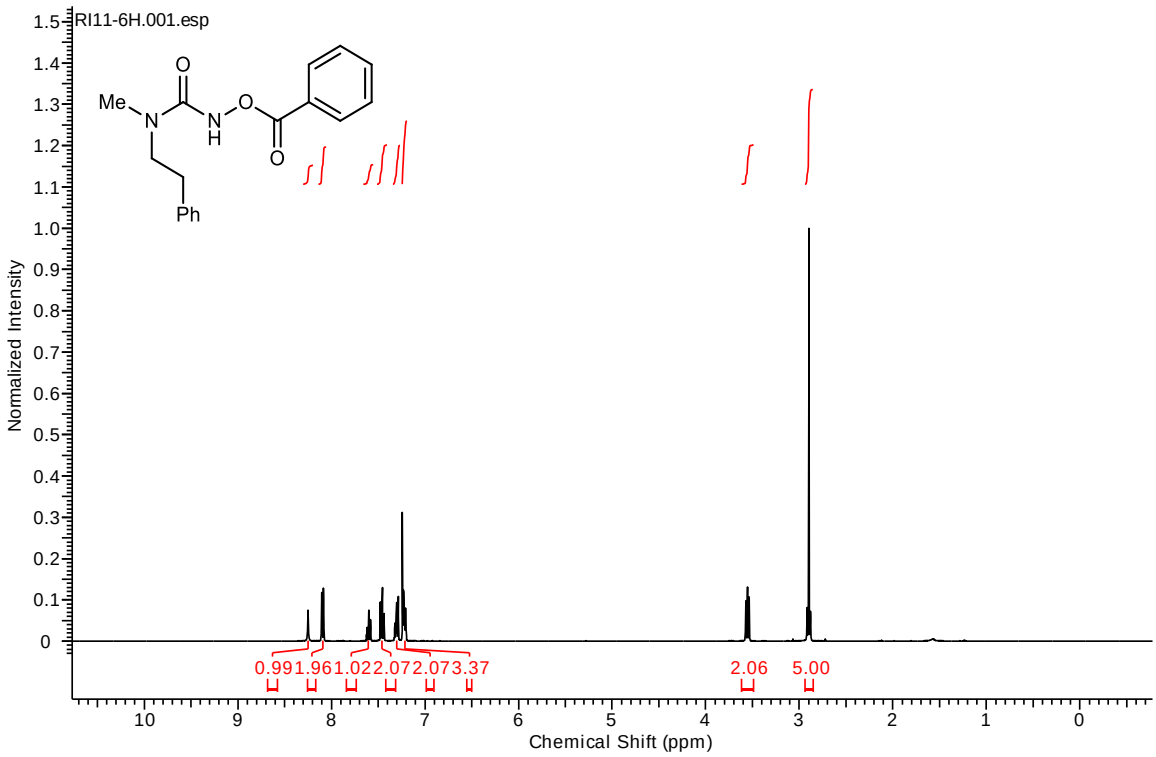

RI13-63-F10-12-C.001.esp
RI13-63-F6-10-600-C.001.esp
Normalized Intensity
172.94
171.42
82.51
79.15
67.58
66.23
Chemical Shift (ppm)
Normalized Intensity
82.56
79.20
77.24
67.60
66.26
60.06
50.60
49.47
41.89
38.60
36.69
36.20
34.57
23.66
18.55
15.93
Chemical Shift (ppm)

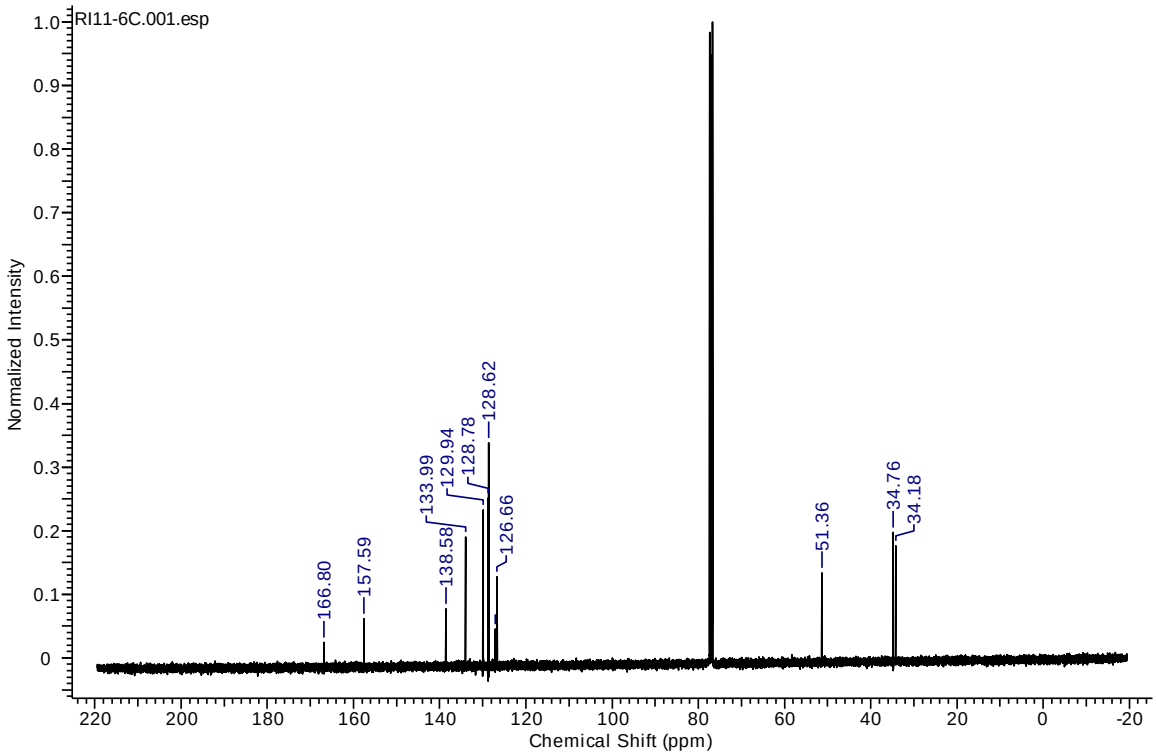

DP-Meiso.001.esp
Me
N
O
N
H
O
O
Normalized Intensity
1.5
1.0
0.5
0
0.76
2.01
1.03
2.16
2.11
3.11
1.56
6.43
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

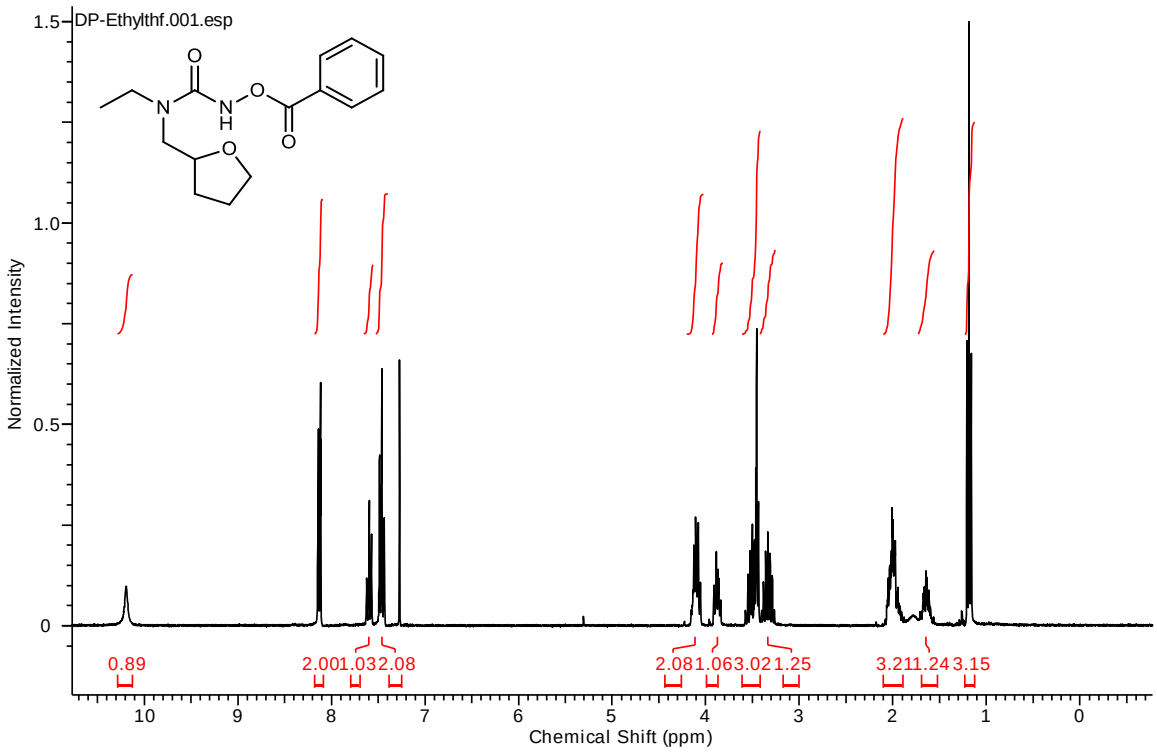

DP-Meiso-C.001.esp
Normalized Intensity
167.02
157.88
133.96
129.92
128.58
127.12
56.55
34.64
27.18
19.95
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

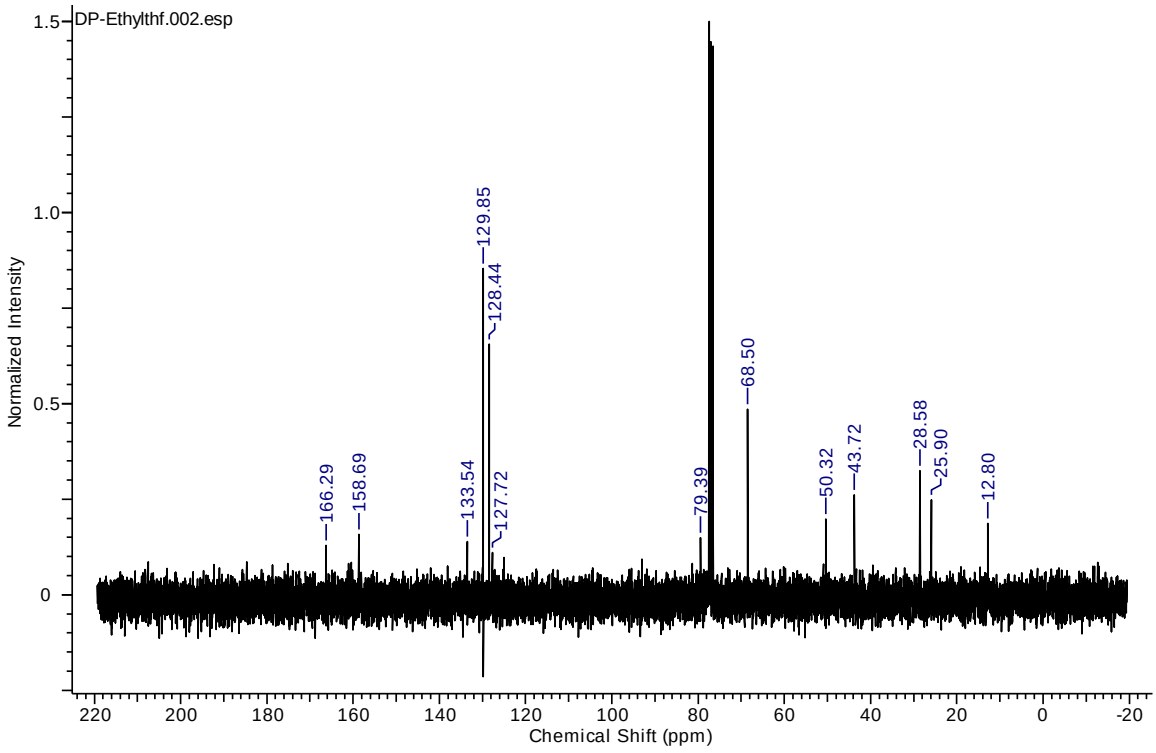

DP-Bniso.001.esp
O
Ph
N
N
H
OBz
Normalized Intensity
0.86
2.00
1.09
7.12
2.00
1.97
1.06
6.00
Chemical Shift (ppm)

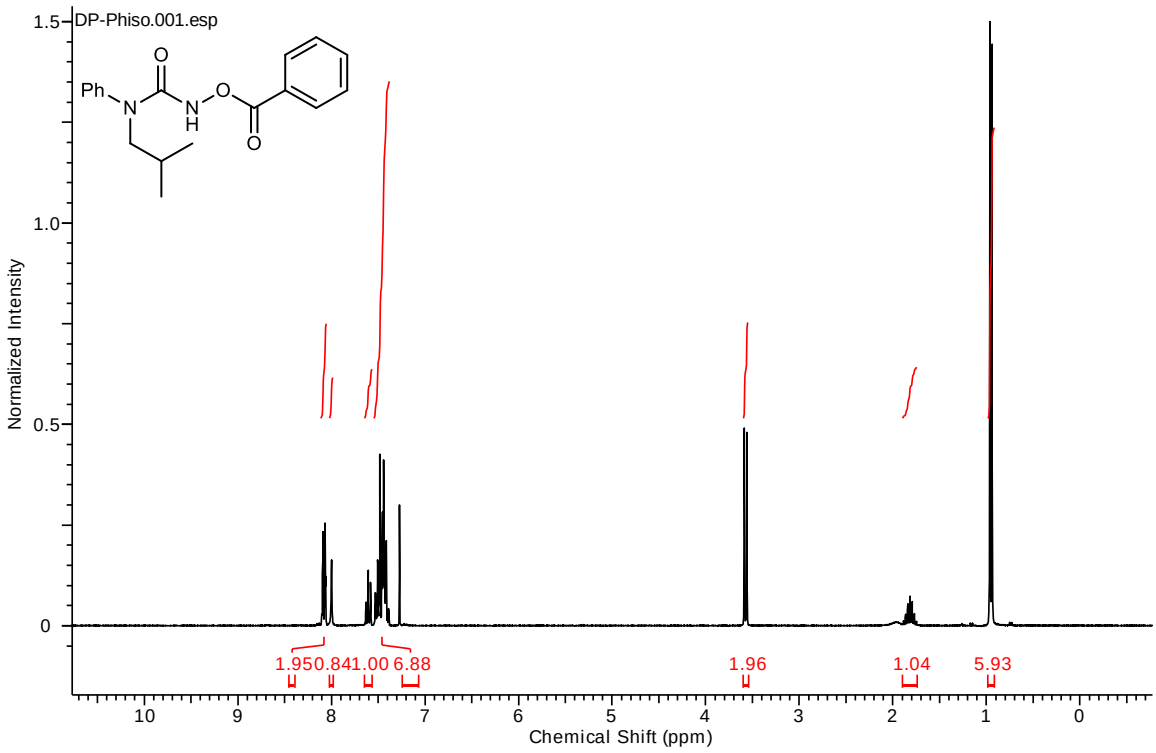

DP-bniso-C.001.esp
Normalized Intensity
166.96
158.25
136.37
133.94
129.92
128.57
127.80
127.05
54.63
50.56
27.32
20.18
Chemical Shift (ppm)

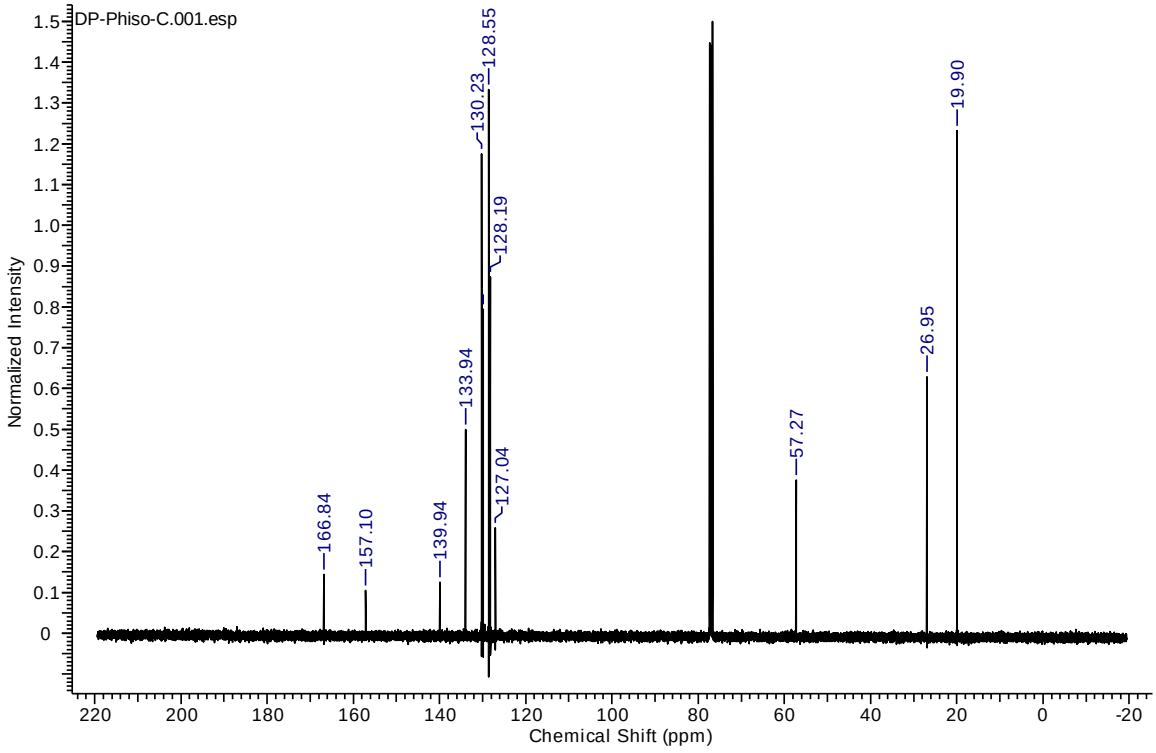

RI11-6H.001.esp
Me
N
O
N
H
O
O
Ph
Normalized Intensity
0.99
1.96
1.02
2.07
2.07
3.37
2.06
5.00
Chemical Shift (ppm)

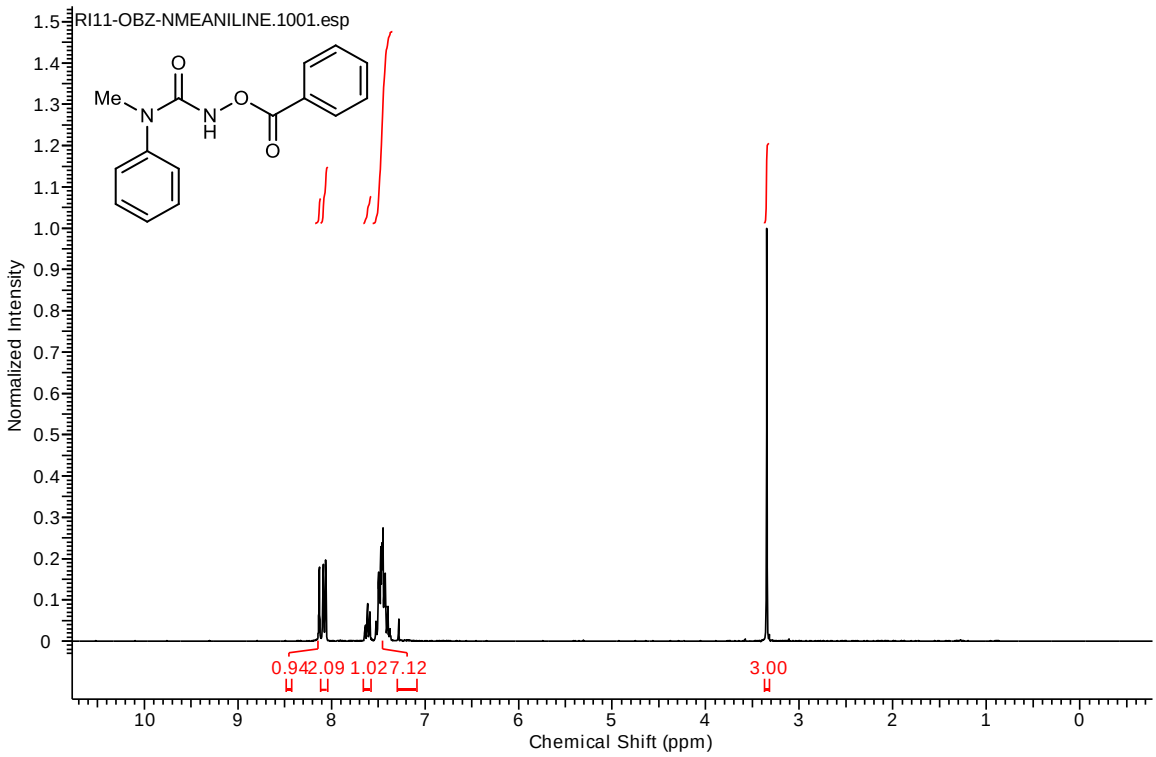

RI11-6C.001.esp
Normalized Intensity
166.80
157.59
133.99
129.94
128.78
128.62
126.66
138.58
51.36
34.76
34.18
Chemical Shift (ppm)

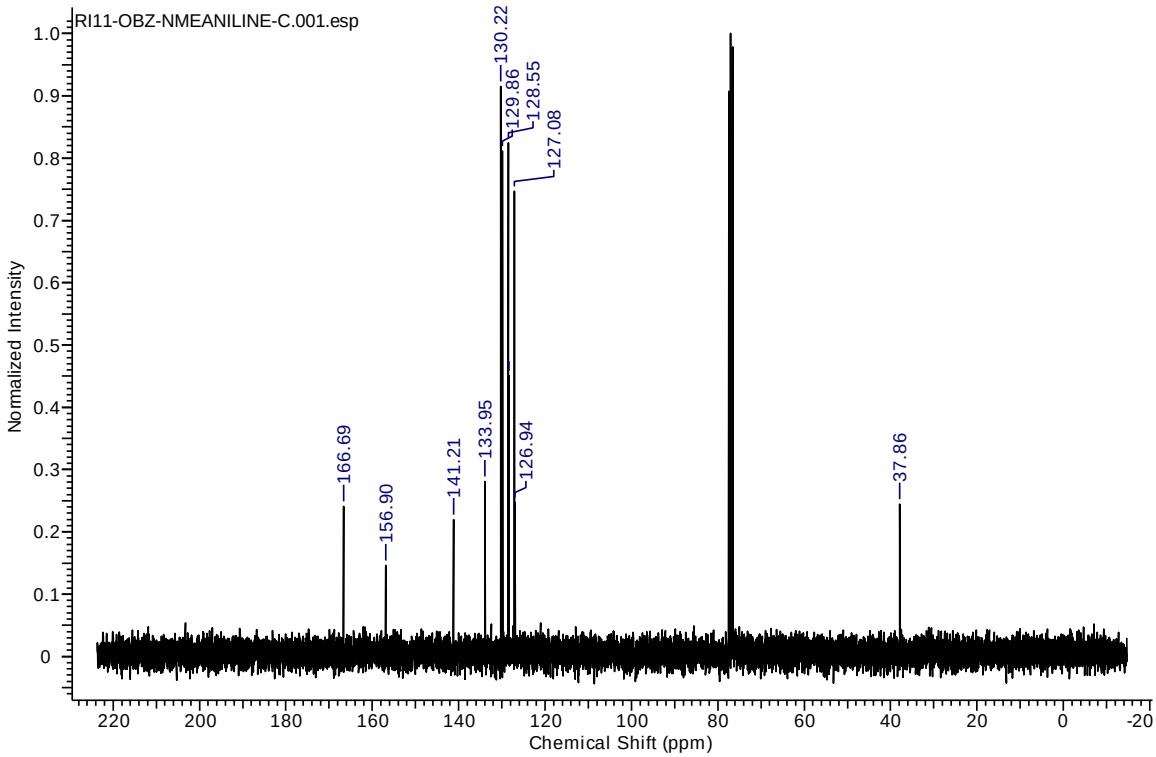

DP-Ethylthf.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.89
2.00
1.03
2.08
2.08
1.06
3.02
1.25
3.21
1.24
3.15

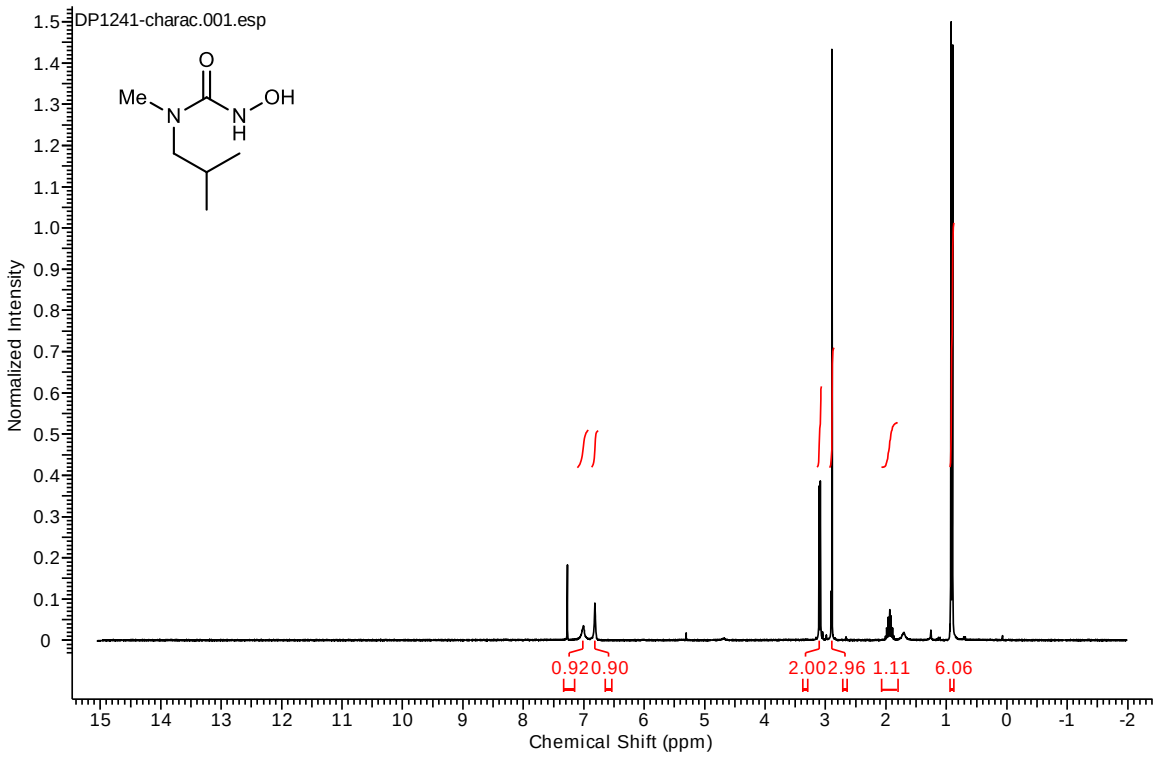

DP-Ethylthf.002.esp
Normalized Intensity
Chemical Shift (ppm)
166.29
158.69
133.54
129.85
128.44
127.72
79.39
68.50
50.32
43.72
28.58
25.90
12.80

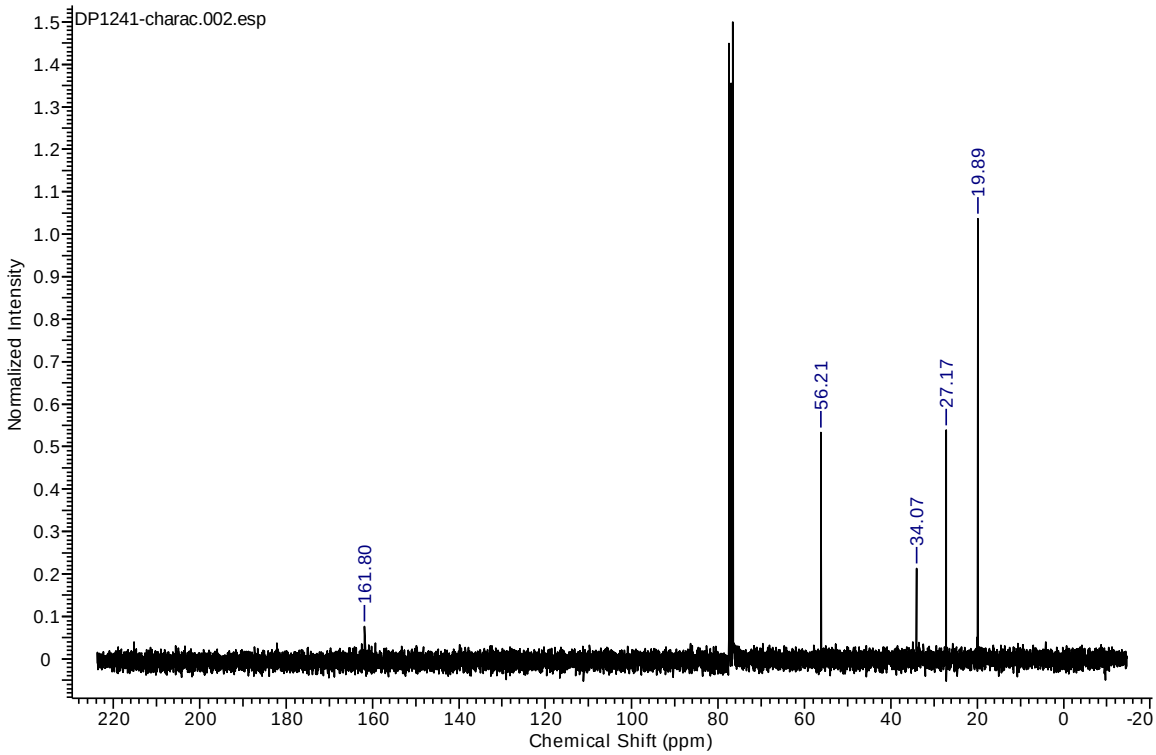

DP-Phiso.001.esp
Ph
N
O
N
H
O
O
Normalized Intensity
1.95
0.84
1.00
6.88
1.96
1.04
5.93
Chemical Shift (ppm)

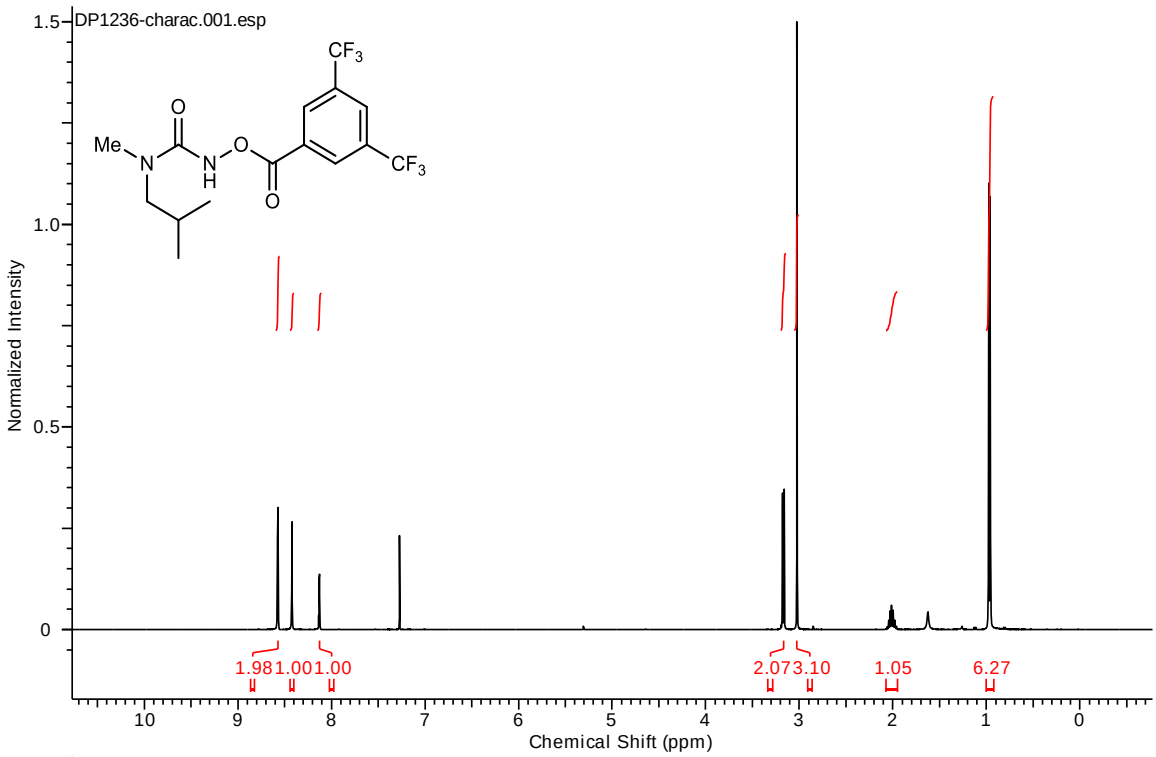

DP-Phiso-C.001.esp
166.84
157.10
139.94
133.94
130.23
128.55
128.19
127.04
57.27
26.95
19.90
Normalized Intensity
Chemical Shift (ppm)

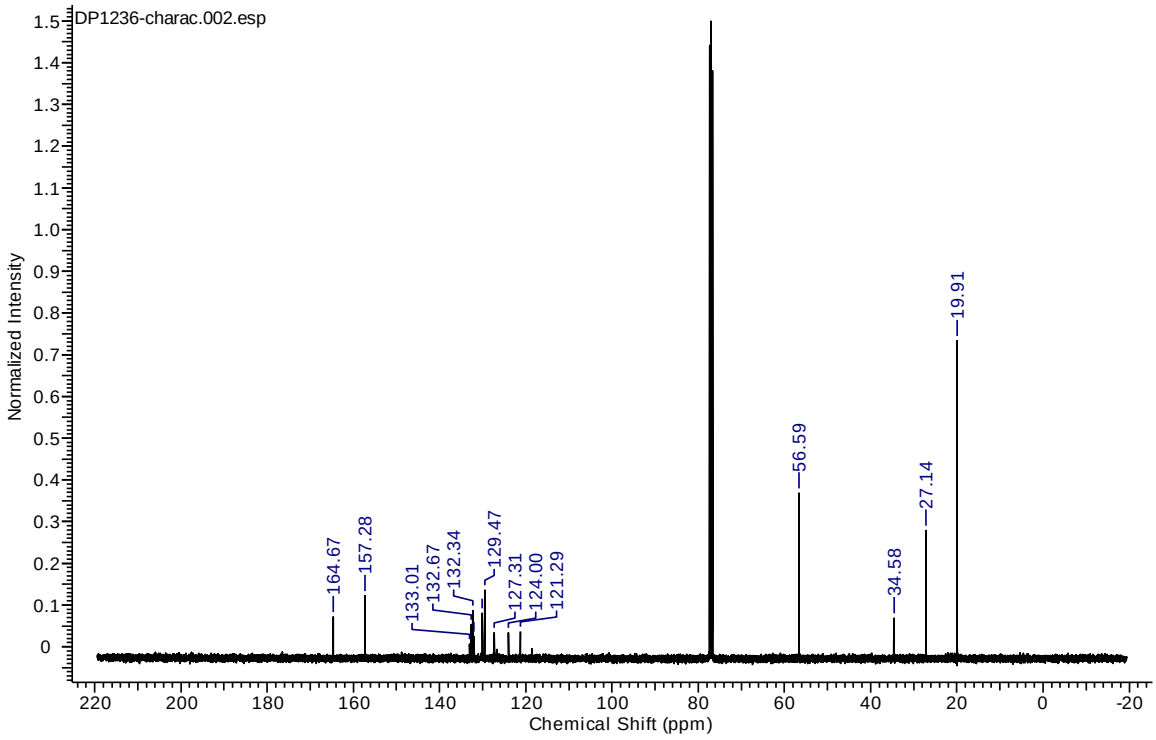

RI11-OBZ-NMEANILINE.1001.esp
Me
N
O
N
H
O
O
Normalized Intensity
0.94
2.09
1.02
7.12
3.00
Chemical Shift (ppm)

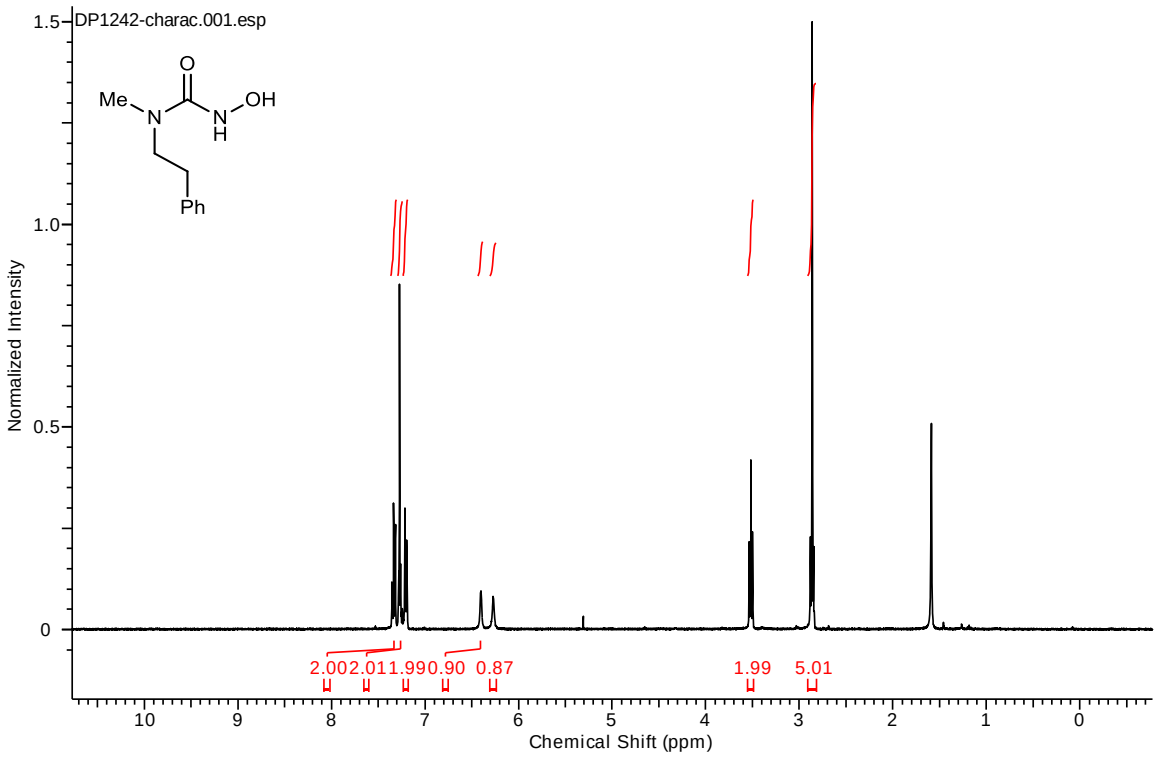

RI11-OBZ-NMEANILINE-C.001.esp
130.22
129.86
128.55
127.08
166.69
156.90
141.21
133.95
126.94
37.86
Normalized Intensity
Chemical Shift (ppm)

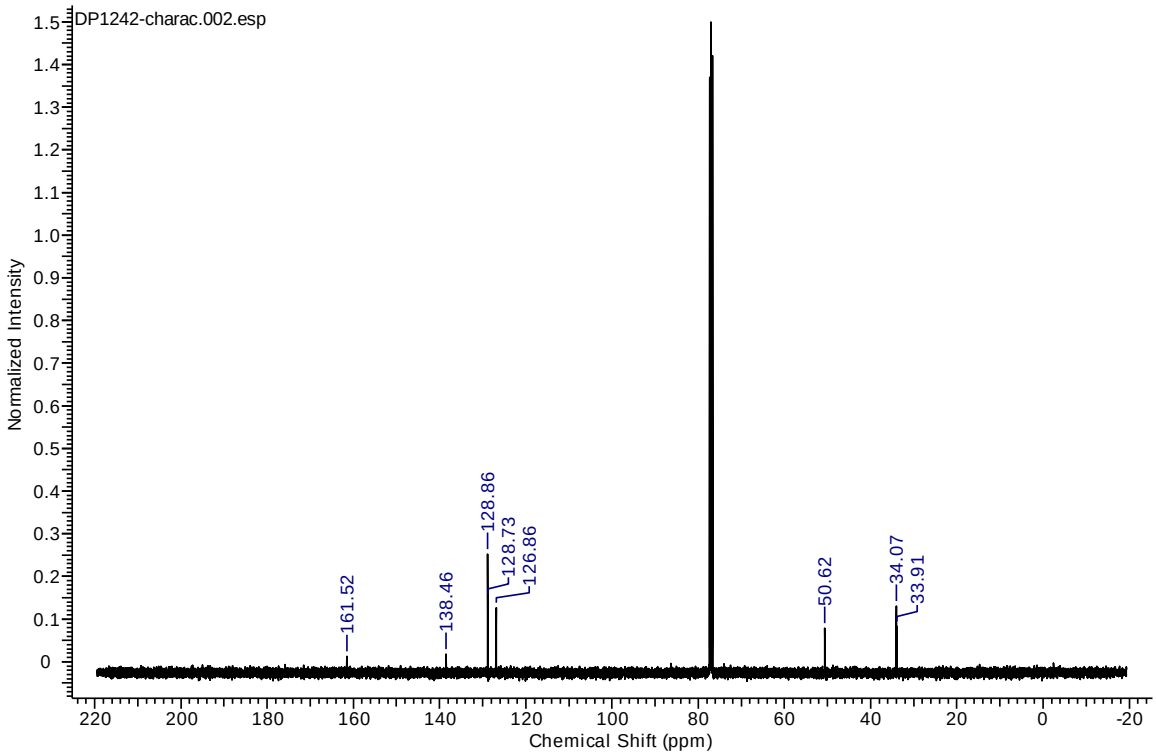

DP1241-charac.001.esp
Me
N
O
N
H
OH
Normalized Intensity
0.92
0.90
2.00
2.96
1.11
6.06
Chemical Shift (ppm)

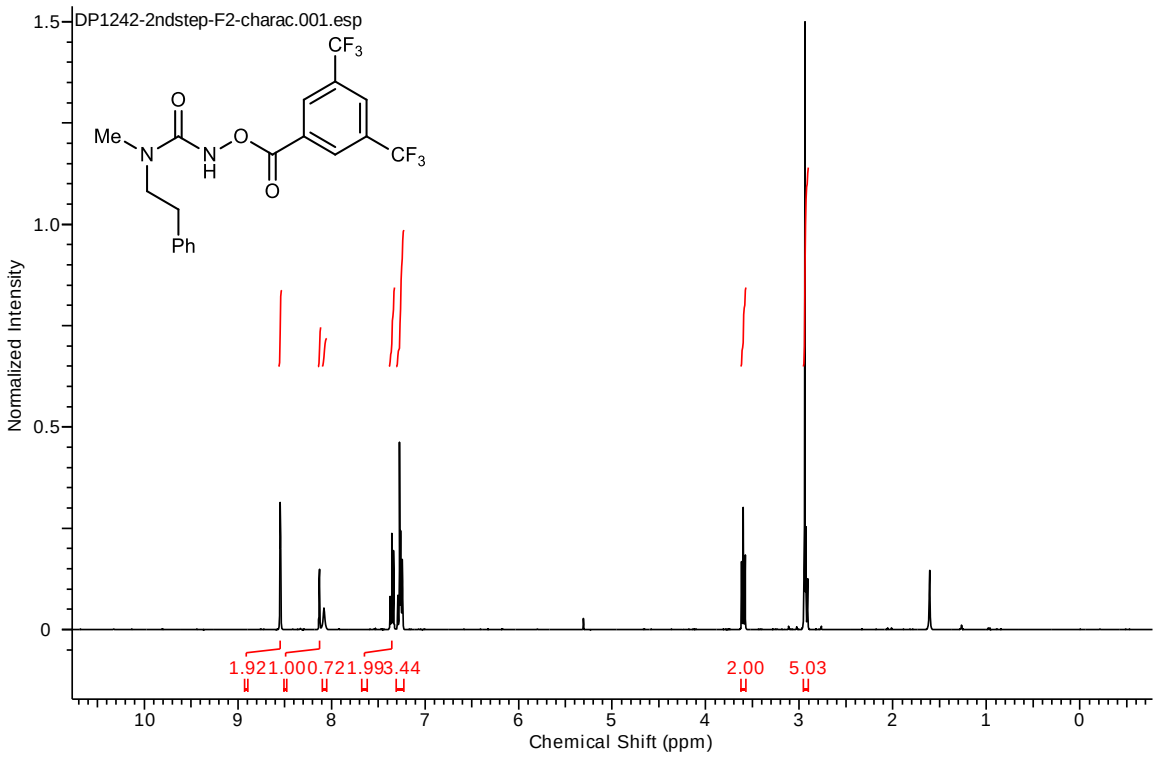

DP1241-charac.002.esp
Normalized Intensity
161.80
56.21
34.07
27.17
19.89
Chemical Shift (ppm)

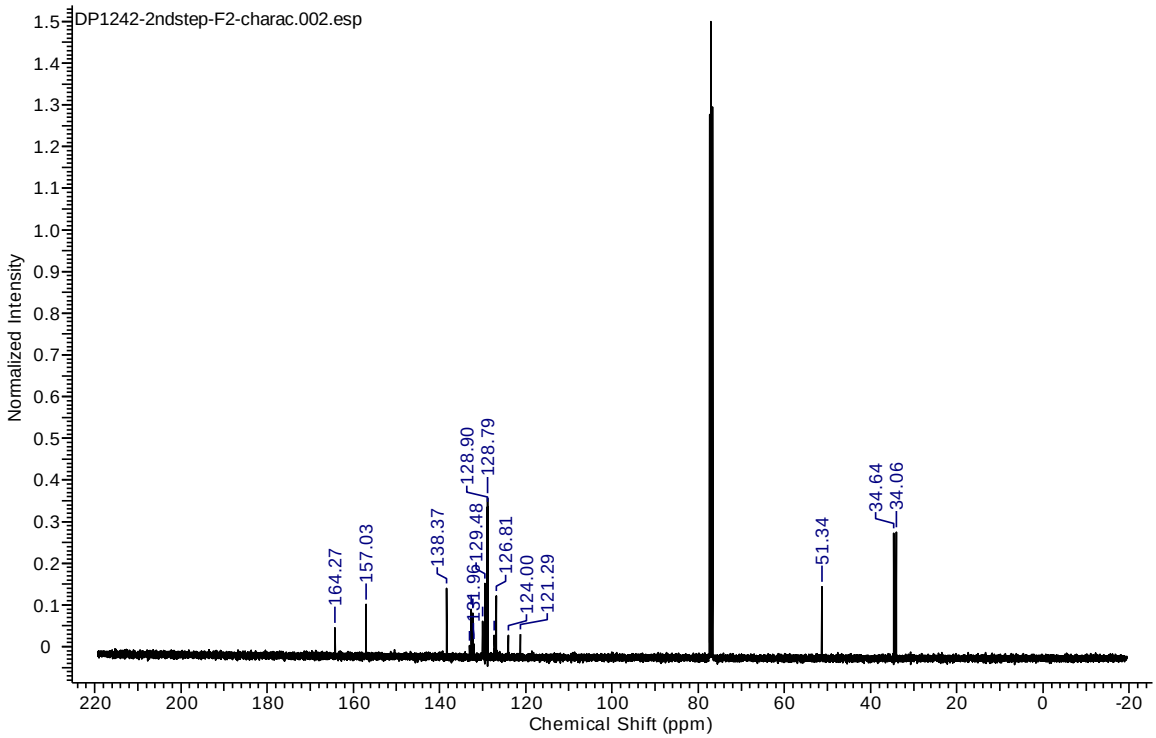

DP1236-charac.001.esp
CF3
O
Me
N
O
N
H
O
CF3
O
Normalized Intensity
1.5
1.0
0.5
0
1.98
1.00
1.00
2.07
3.10
1.05
6.27
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

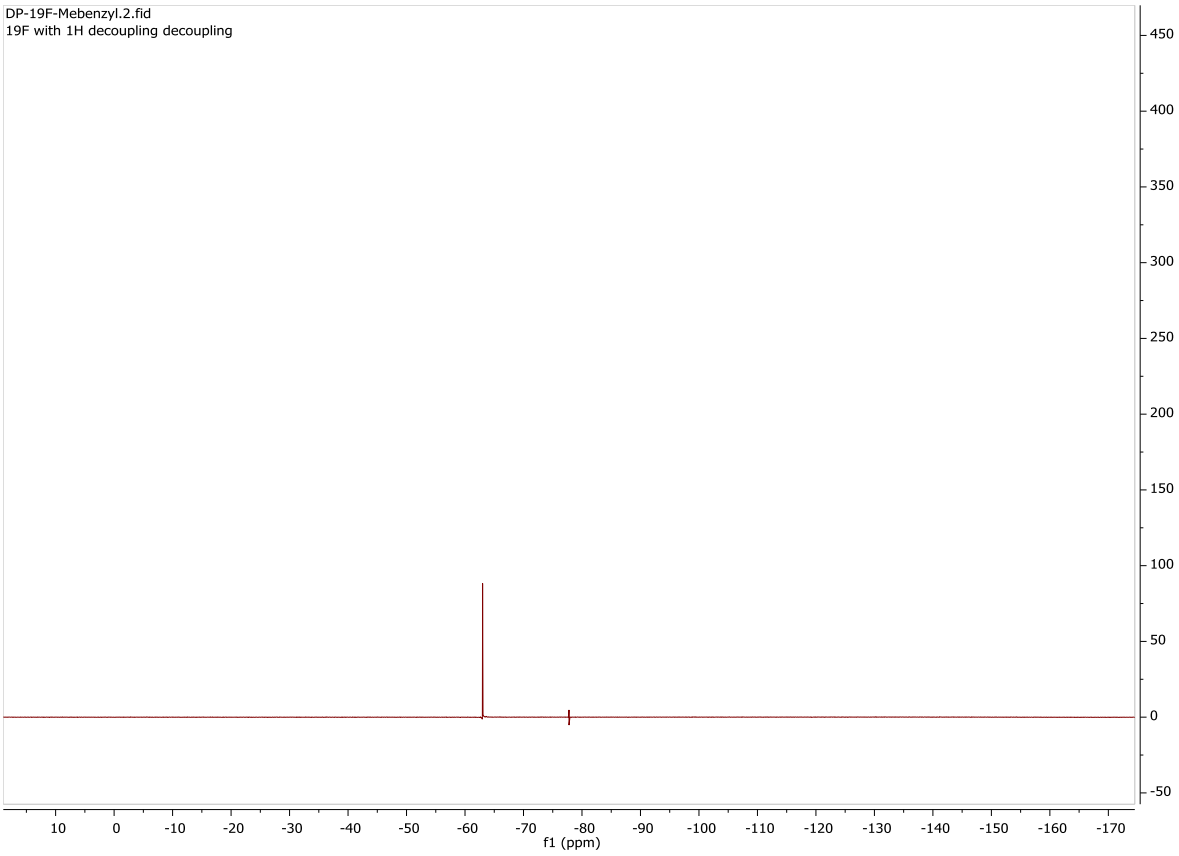

DP1236-charac.002.esp
Normalized Intensity
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
164.67
157.28
133.01
132.67
132.34
129.47
127.31
124.00
121.29
56.59
34.58
27.14
19.91
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

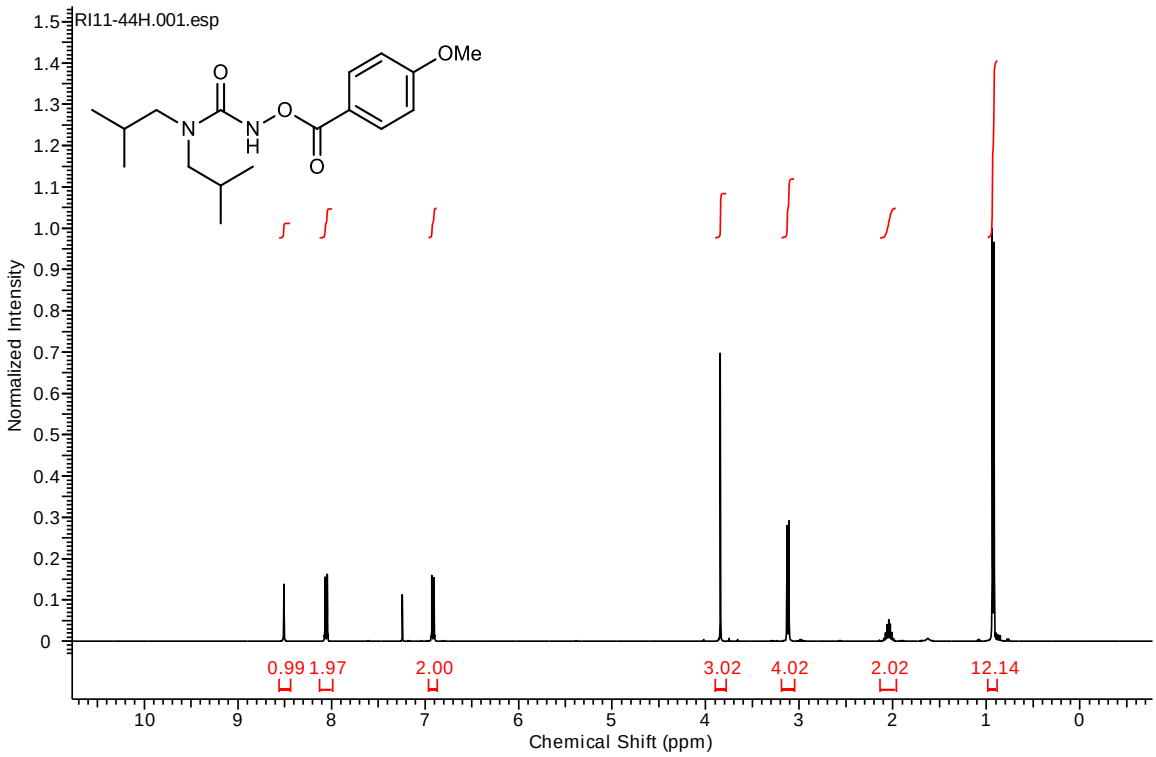

DP1242-charac.001.esp
Me
N
O
N
H
OH
Ph
Normalized Intensity
Chemical Shift (ppm)
2.00
2.01
1.99
0.90
0.87
1.99
5.01

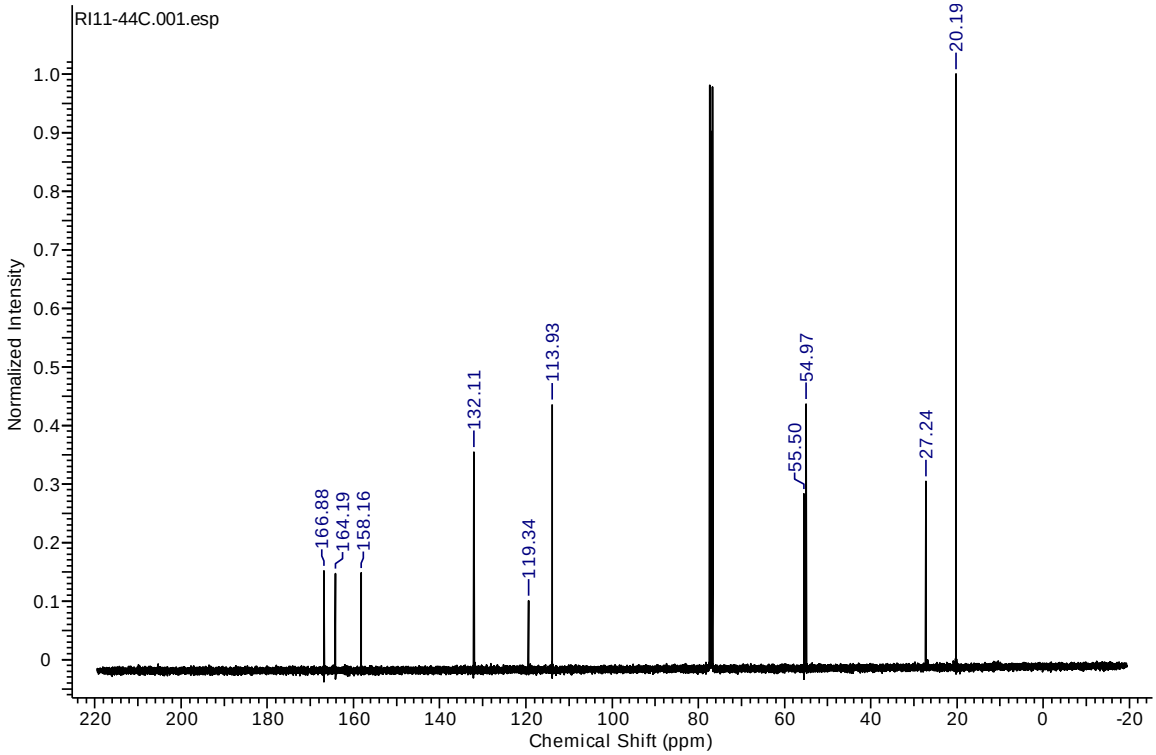

DP1242-charac.002.esp
Normalized Intensity
Chemical Shift (ppm)
161.52
138.46
128.86
128.73
126.86
50.62
34.07
33.91

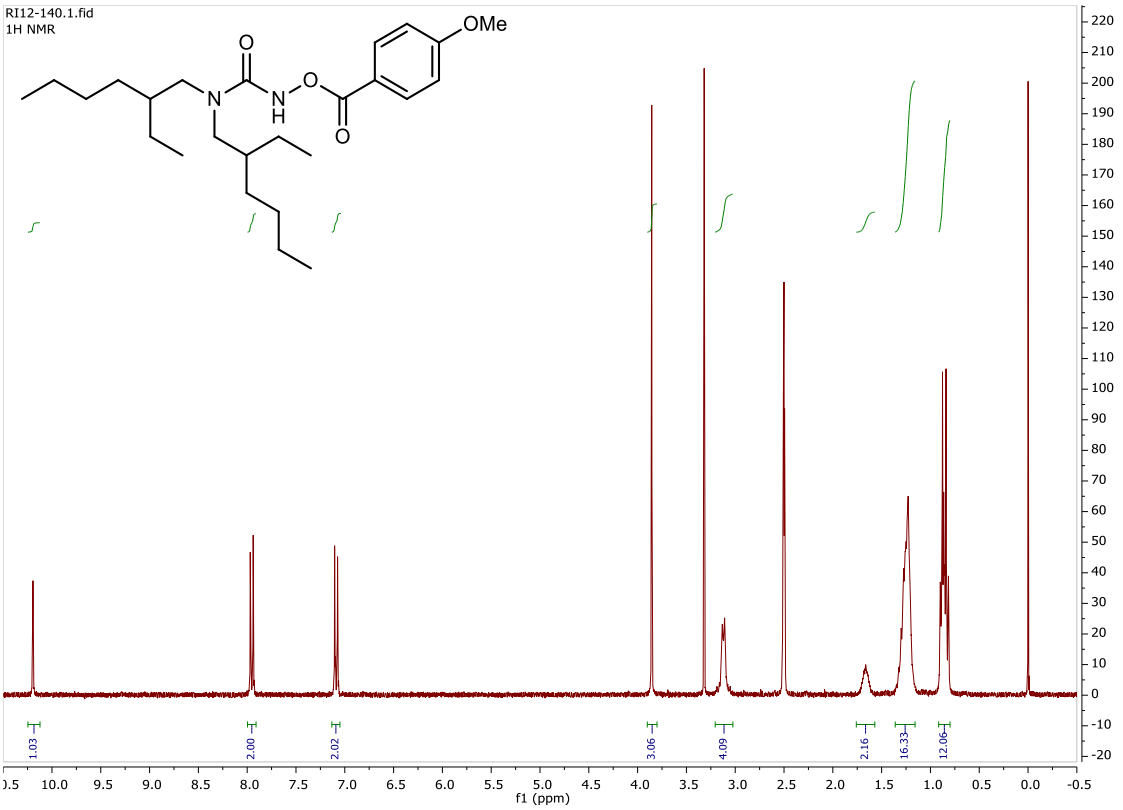

DP1242-2ndstep-F2-charac.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.92
1.00
0.72
1.99
3.44
2.00
5.03

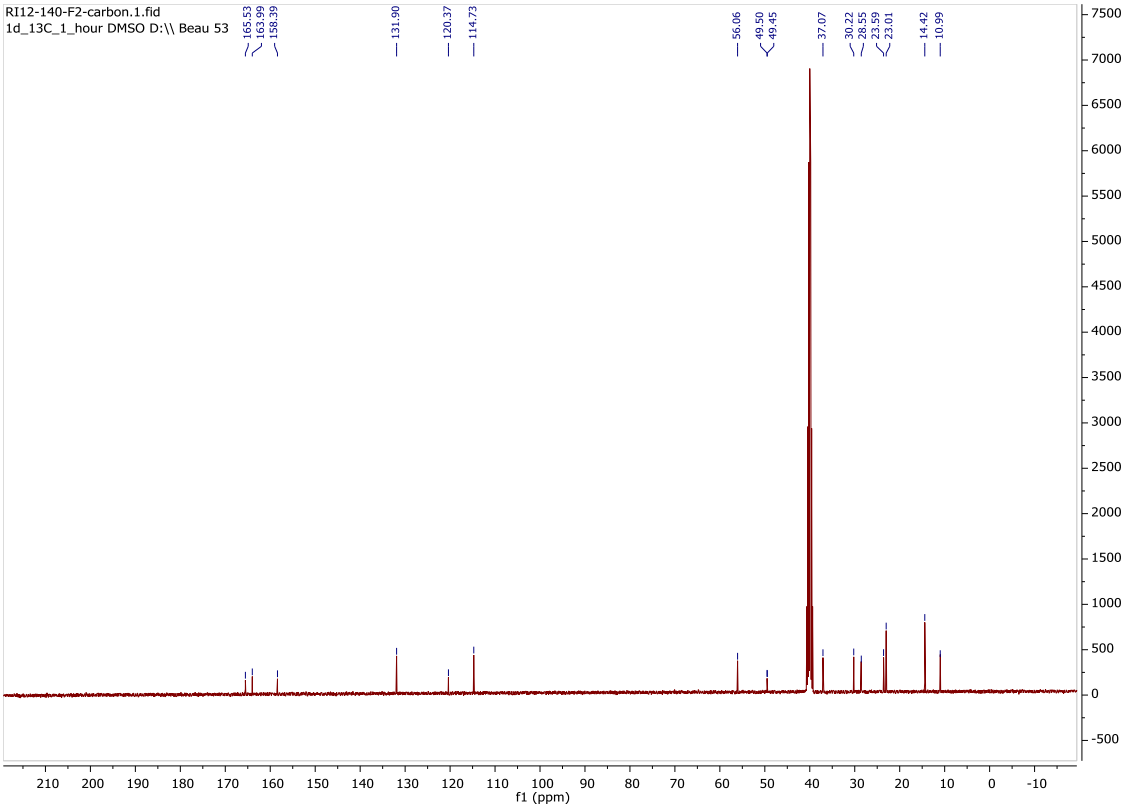

DP1242-2ndstep-F2-charac.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.27
157.03
138.37
129.48
128.90
128.79
126.81
124.00
121.29
51.34
34.64
34.06

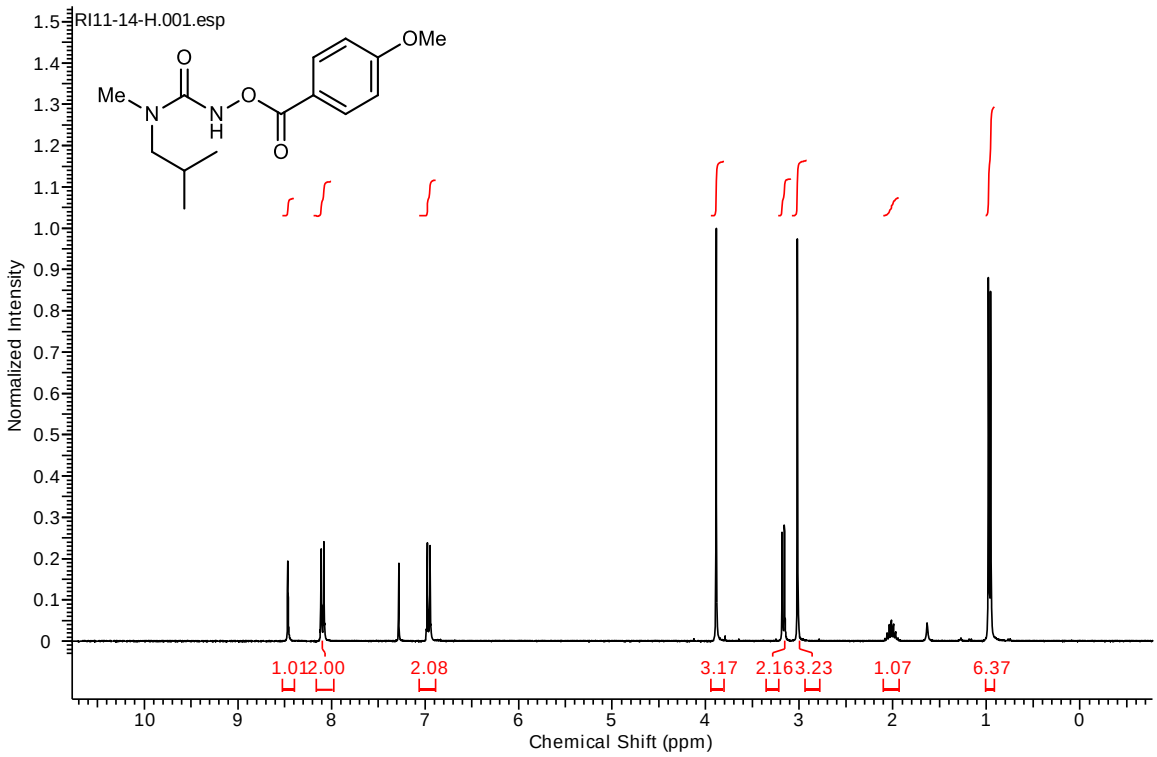

DP-19F-Mebenzyl.2.fid
19F with 1H decoupling decoupling
450
400
350
300
250
200
150
100
50
0
-50
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
f1 (ppm)

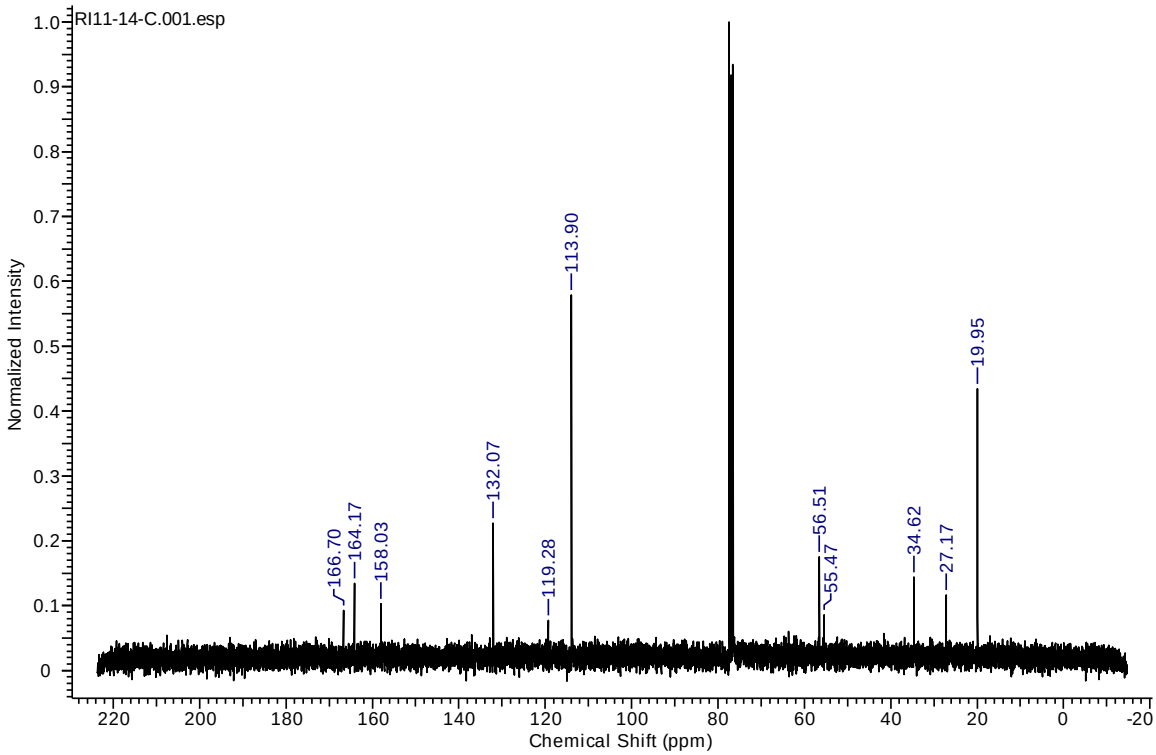

RI11-44H.001.esp
OMe
O
N
N
H
O
O
Normalized Intensity
0.99
1.97
2.00
3.02
4.02
2.02
12.14
Chemical Shift (ppm)

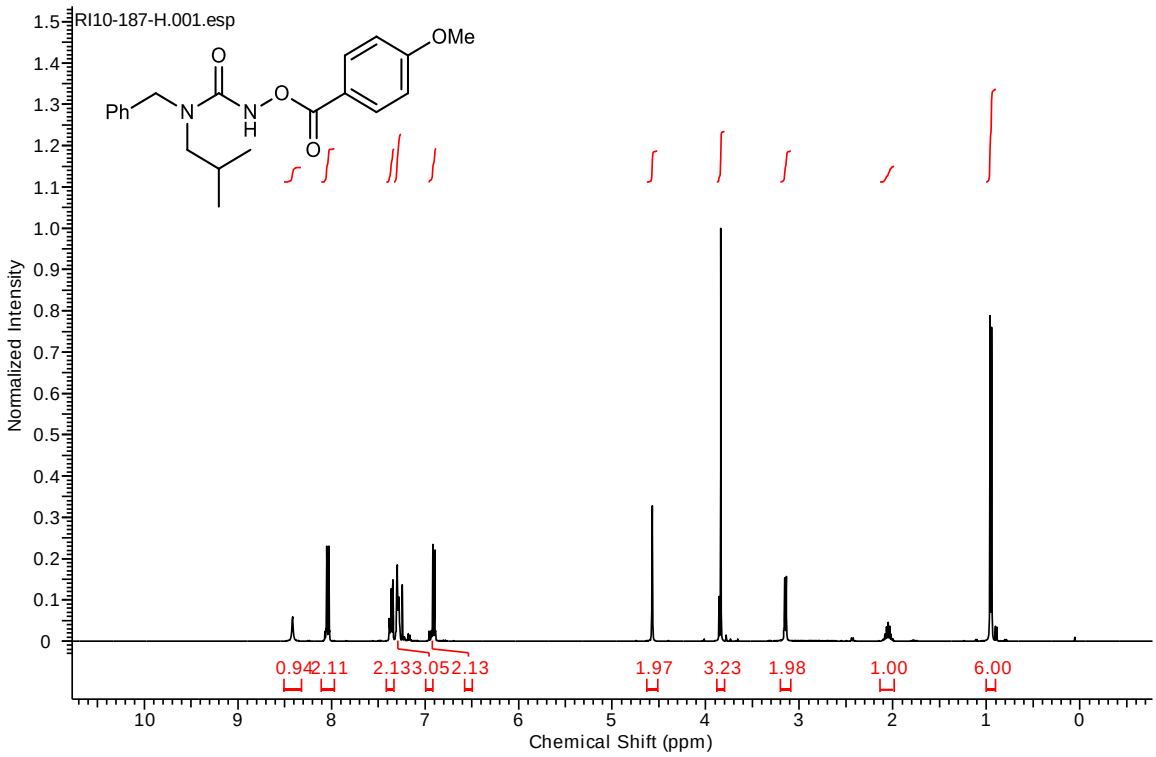

RI11-44C.001.esp
166.88
164.19
158.16
132.11
119.34
113.93
55.50
54.97
27.24
20.19
Normalized Intensity
Chemical Shift (ppm)

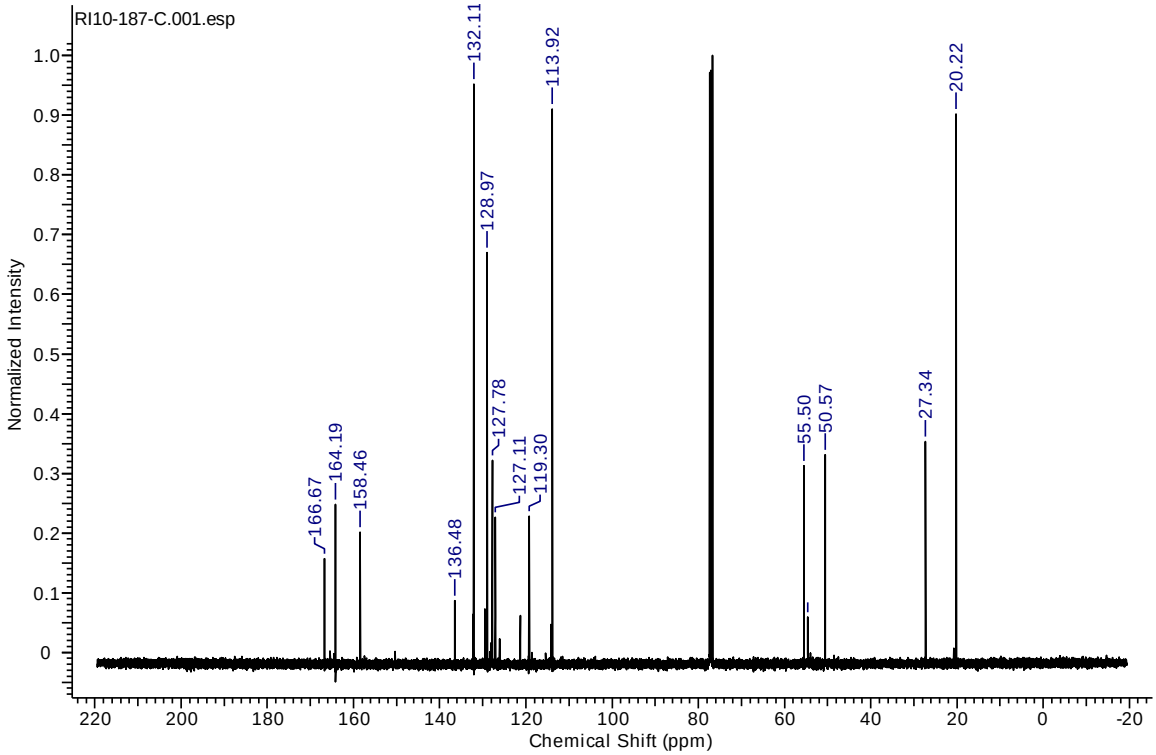

RI12-140.1.fid
1H NMR
OMe
O
N
N
H
O
O
1.03
2.00
2.02
3.06
4.09
2.16
16.33
12.06
f1 (ppm)

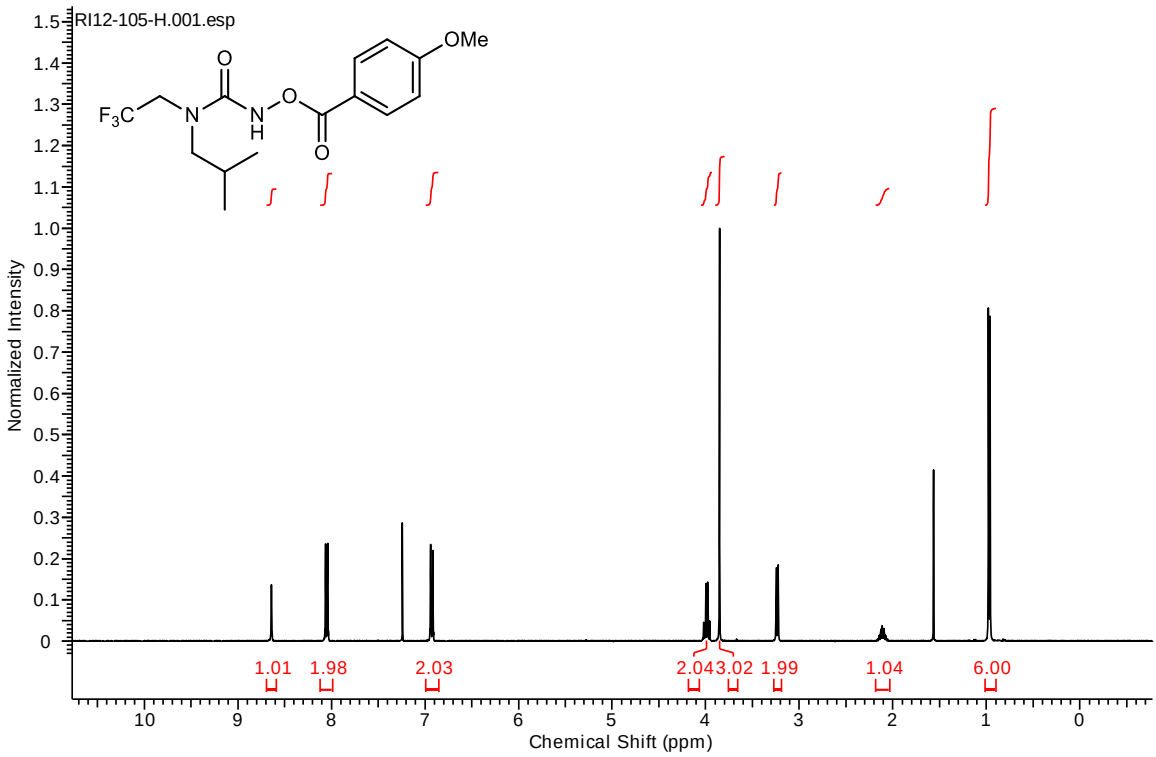

RI12-140-F2-carbon.1.fid
1d_13C_1_hour DMSO D:\\ Beau 53
165.53
163.99
158.39
131.90
120.37
114.73
56.06
49.50
49.45
37.07
30.22
28.55
23.59
23.01
14.42
10.99
f1 (ppm)

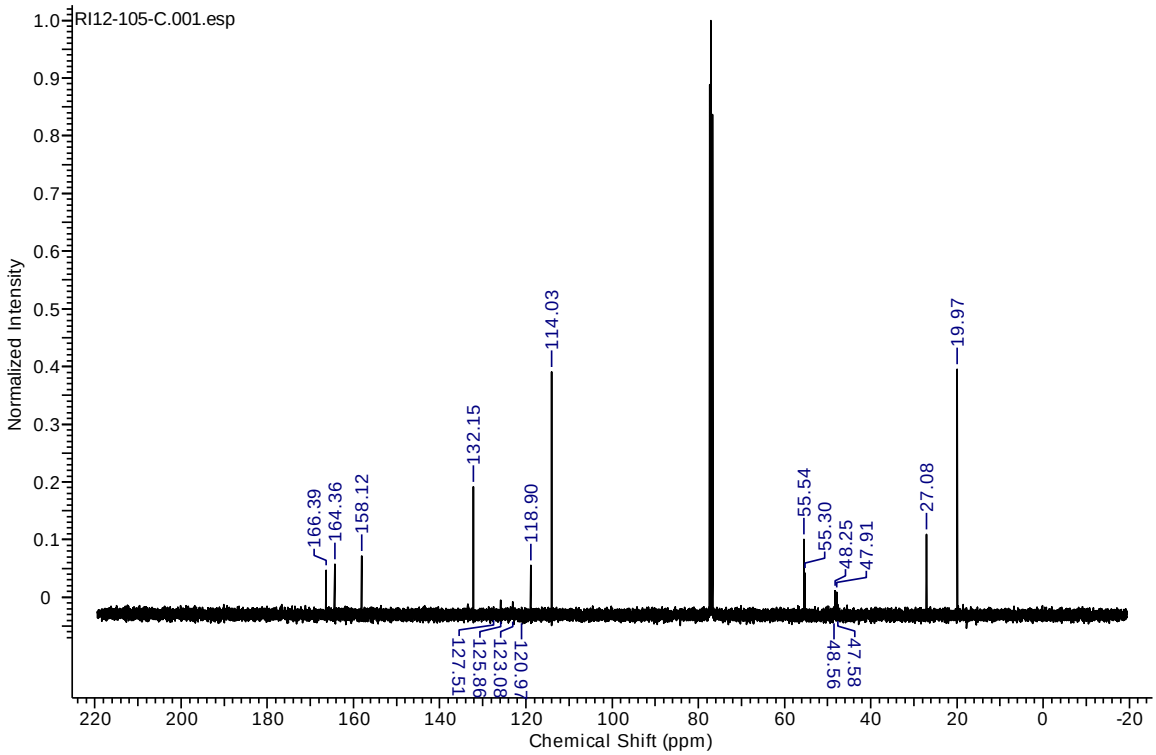

RI11-14-H.001.esp
OMe
Me
N
O
N
H
O
O
Normalized Intensity
1.01
2.00
2.08
3.17
2.16
3.23
1.07
6.37
Chemical Shift (ppm)

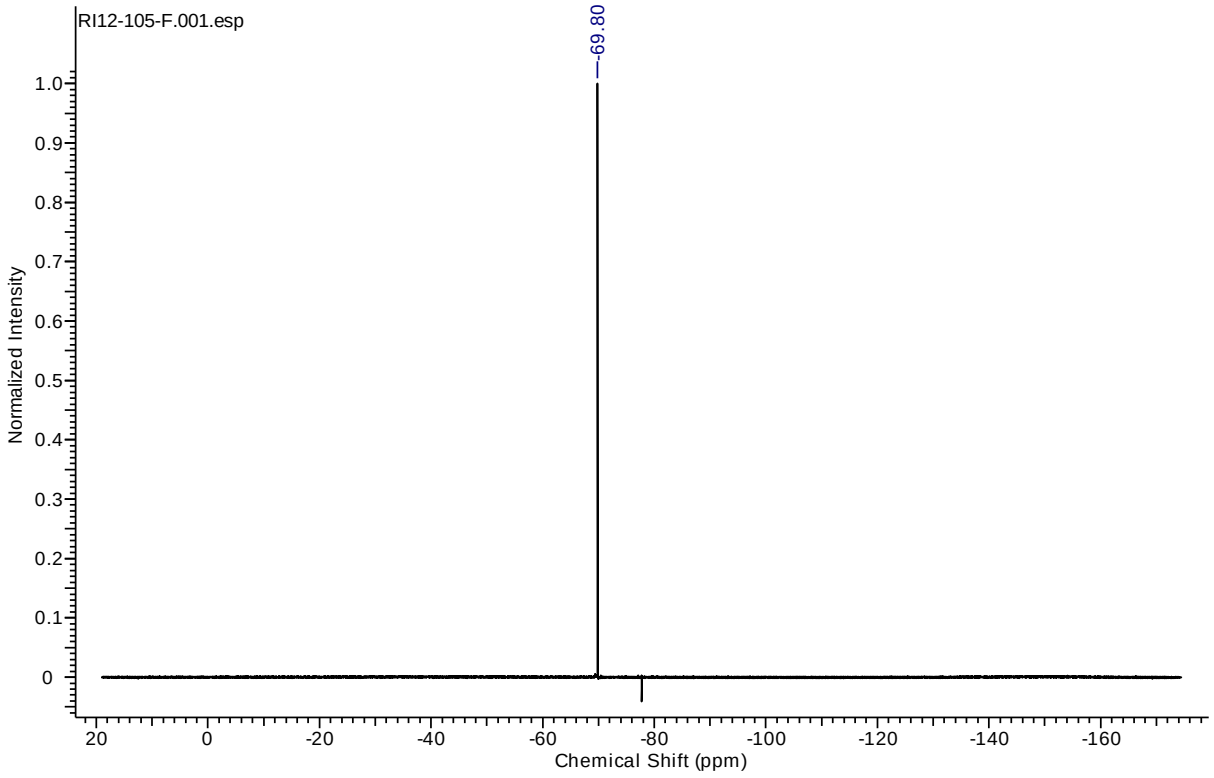

RI11-14-C.001.esp
Normalized Intensity
166.70
164.17
158.03
132.07
119.28
113.90
56.51
55.47
34.62
27.17
19.95
Chemical Shift (ppm)

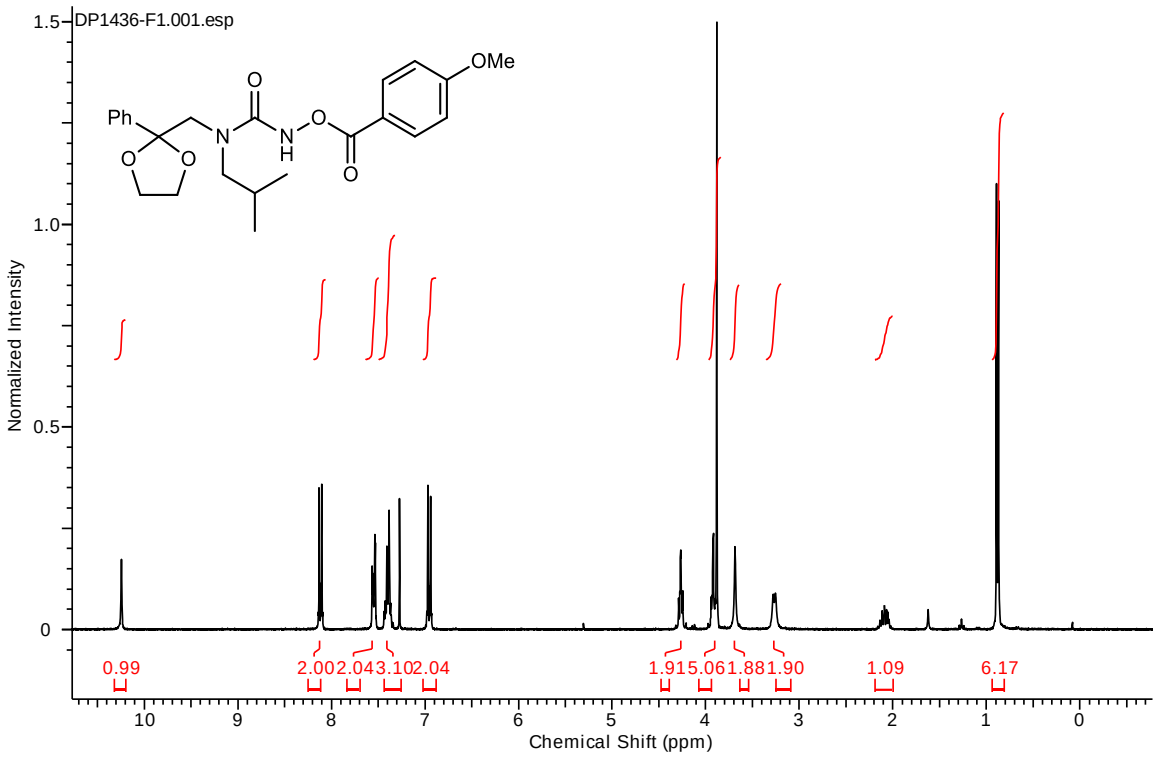

RI10-187-H.001.esp
OMe
O
Ph
N
N
H
O
O
Normalized Intensity
0.94
2.11
2.13
3.05
2.13
1.97
3.23
1.98
1.00
6.00
Chemical Shift (ppm)

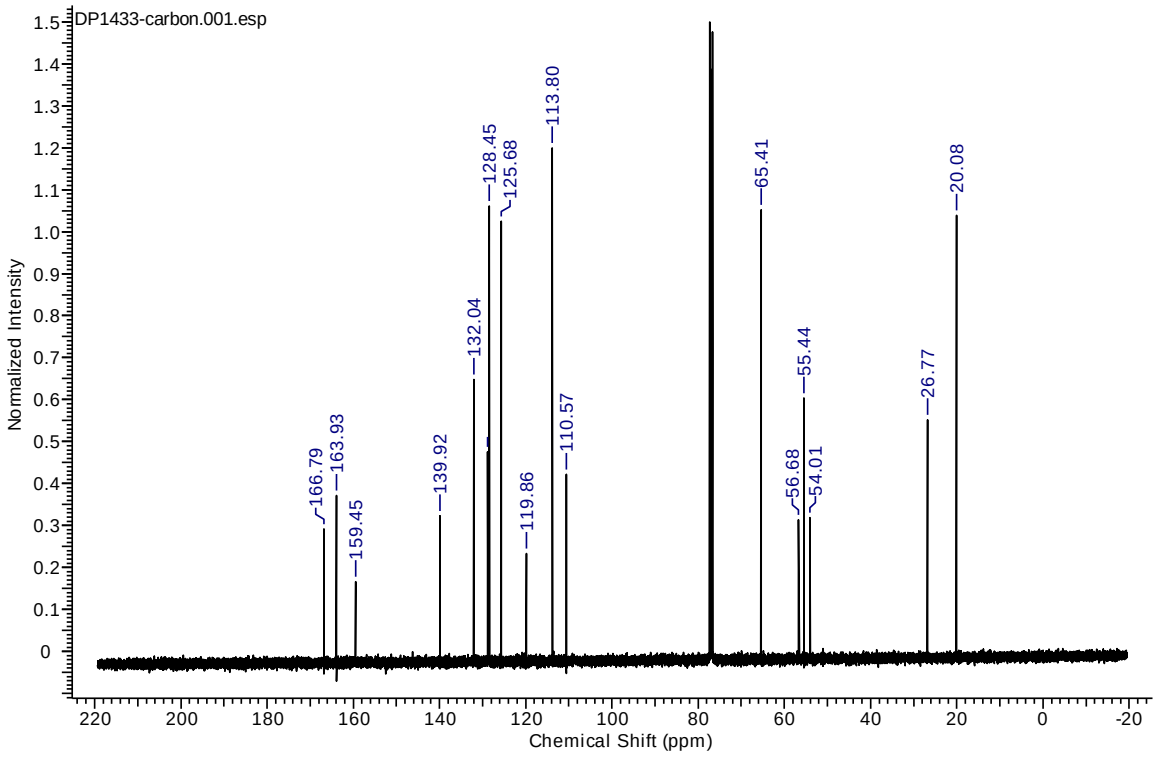

RI10-187-C.001.esp
132.11
113.92
128.97
20.22
127.78
127.11
119.30
55.50
50.57
27.34
166.67
164.19
158.46
136.48
Normalized Intensity
Chemical Shift (ppm)

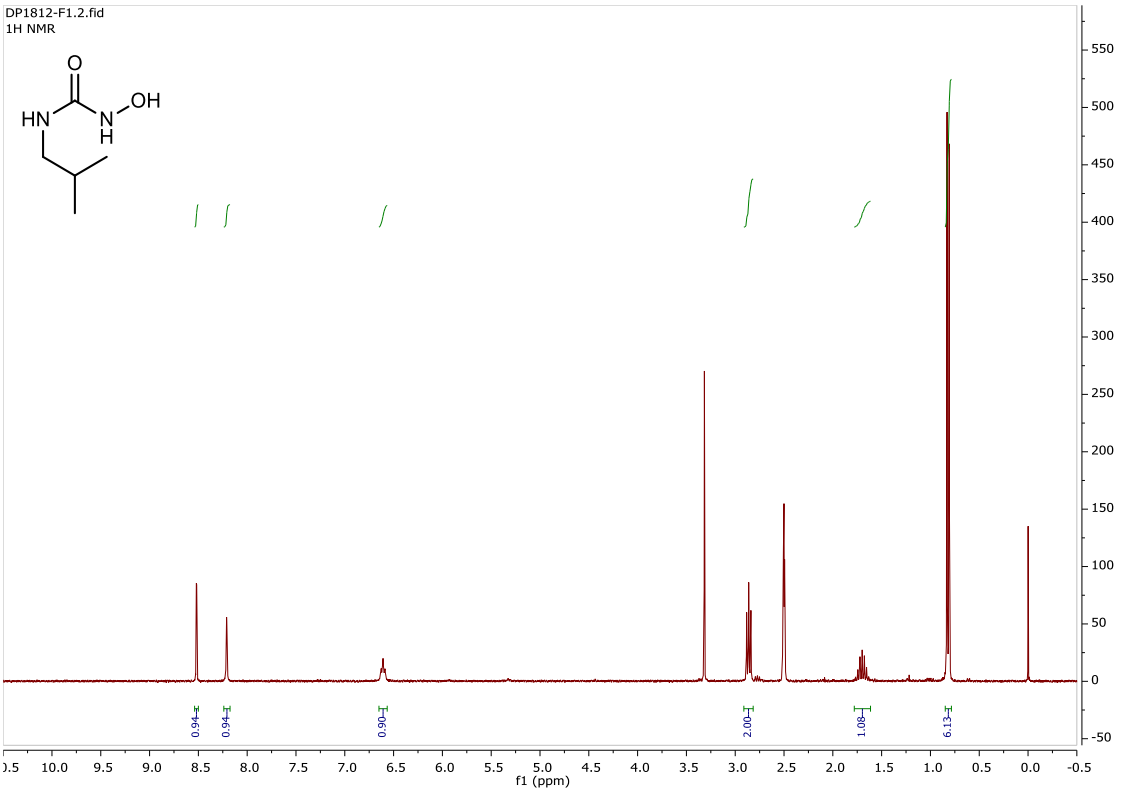

RI12-105-H.001.esp
OMe
O
O
N
N
H
O
O
F3C
Normalized Intensity
Chemical Shift (ppm)
1.01
1.98
2.03
2.04
3.02
1.99
1.04
6.00

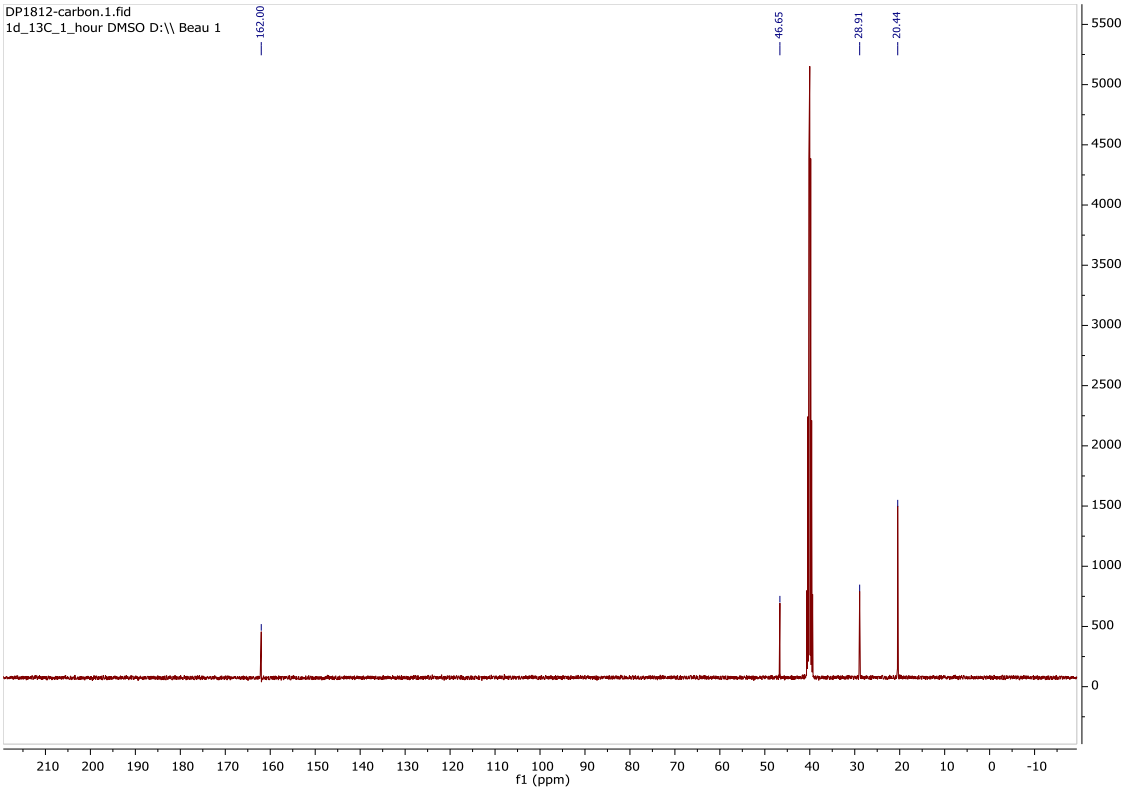

RI12-105-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
166.39
164.36
158.12
132.15
118.90
114.03
55.54
55.30
48.25
47.91
27.08
19.97
127.51
125.86
123.08
120.97
48.56
47.58

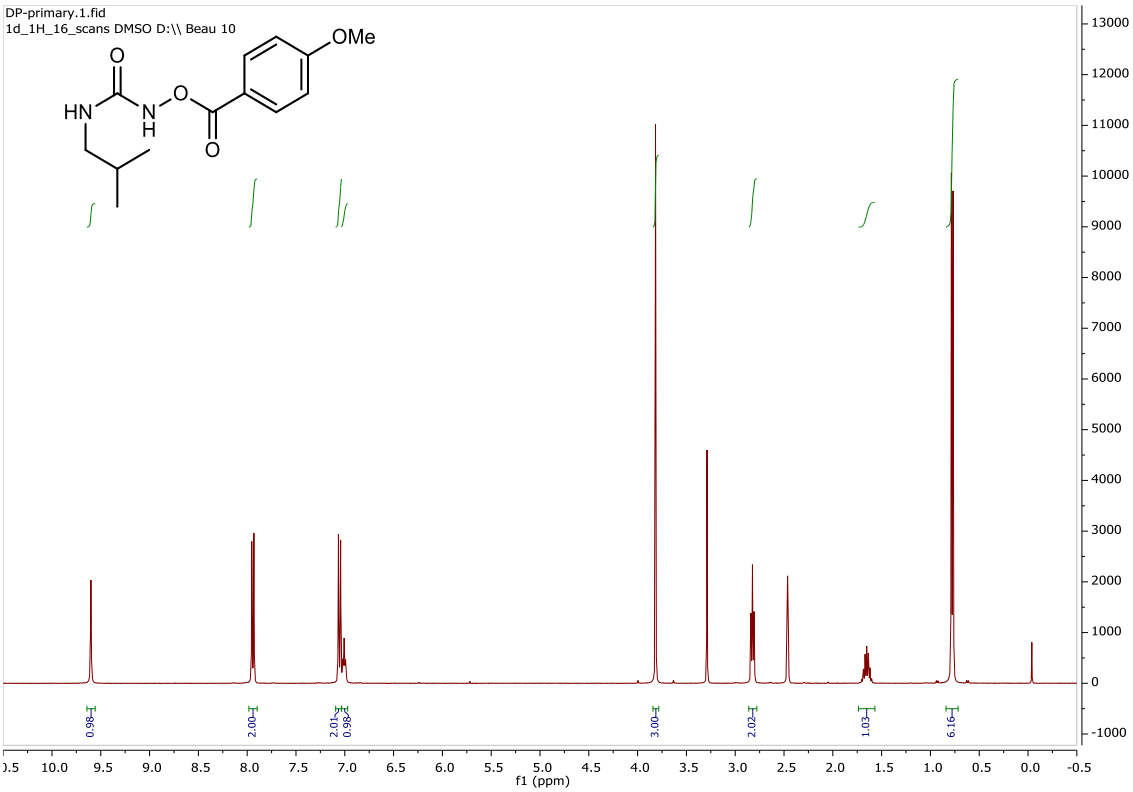

RI12-105-F.001.esp
-69.80
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
20
0
-20
-40
-60
-80
-100
-120
-140
-160
Chemical Shift (ppm)

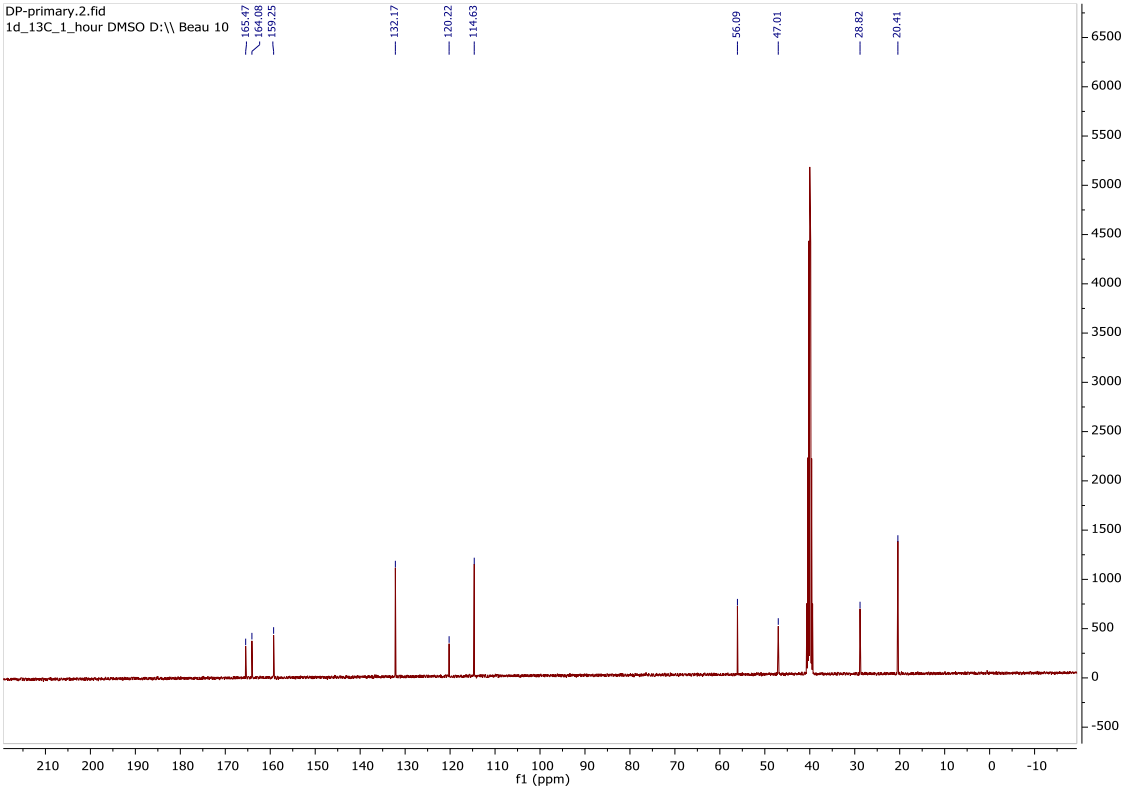

DP1436-F1.001.esp
Ph
O
O
N
O
N
H
O
O
OMe
Normalized Intensity
Chemical Shift (ppm)
0.99
2.00
2.04
3.10
2.04
1.91
5.06
1.88
1.90
1.09
6.17

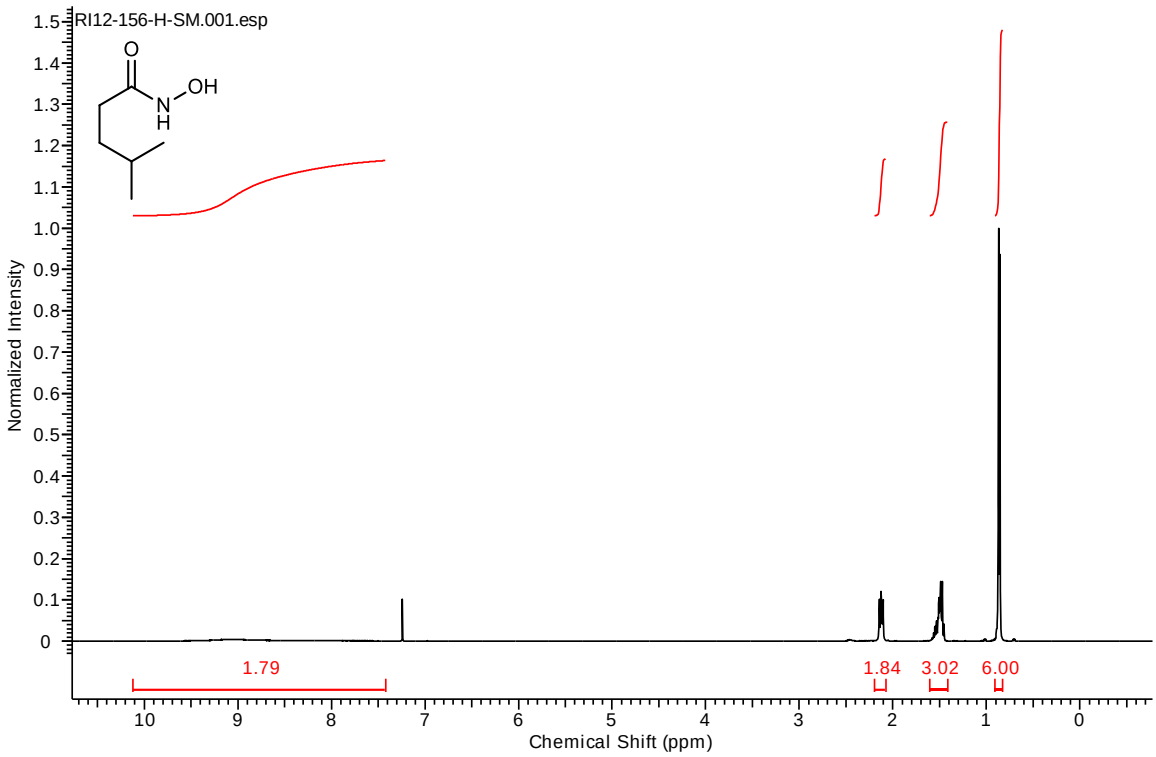

DP1433-carbon.001.esp
Normalized Intensity
Chemical Shift (ppm)
166.79
163.93
159.45
139.92
132.04
128.45
125.68
119.86
113.80
110.57
65.41
56.68
55.44
54.01
26.77
20.08

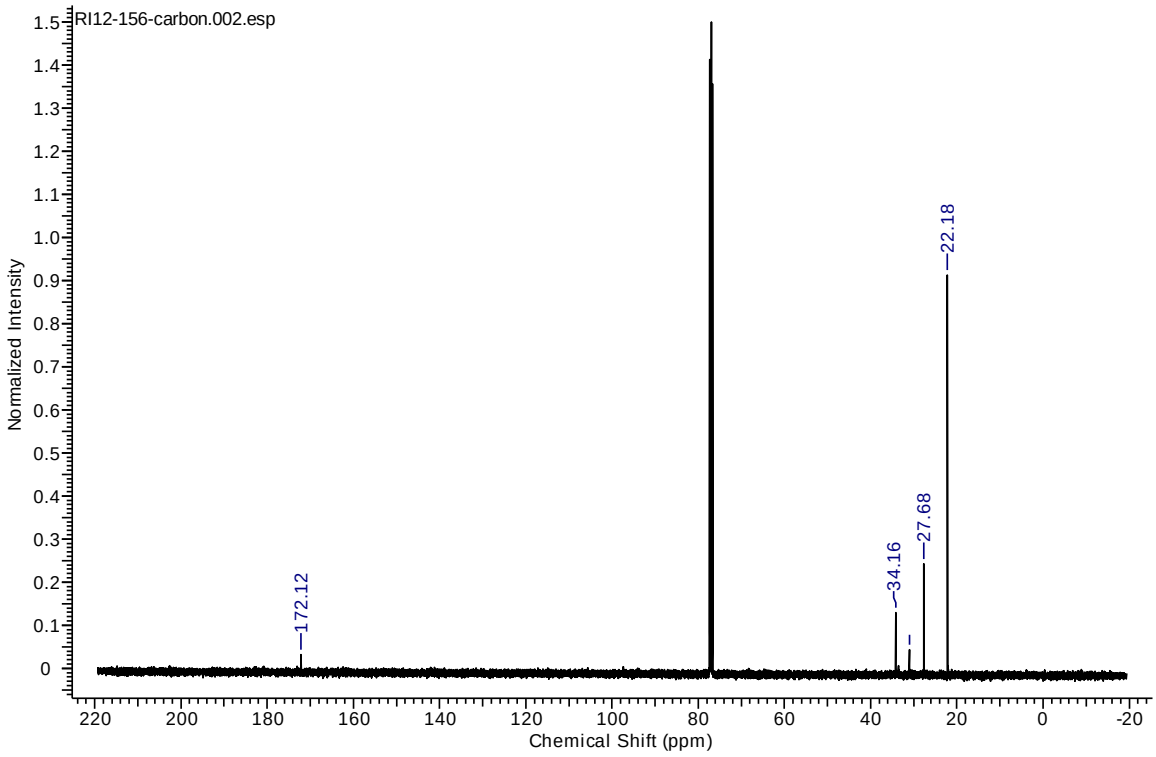

DP1812-F1.2.fid
1H NMR
O
HN
N
H
OH
0.94
0.94
0.90
2.00
1.08
6.13
f1 (ppm)

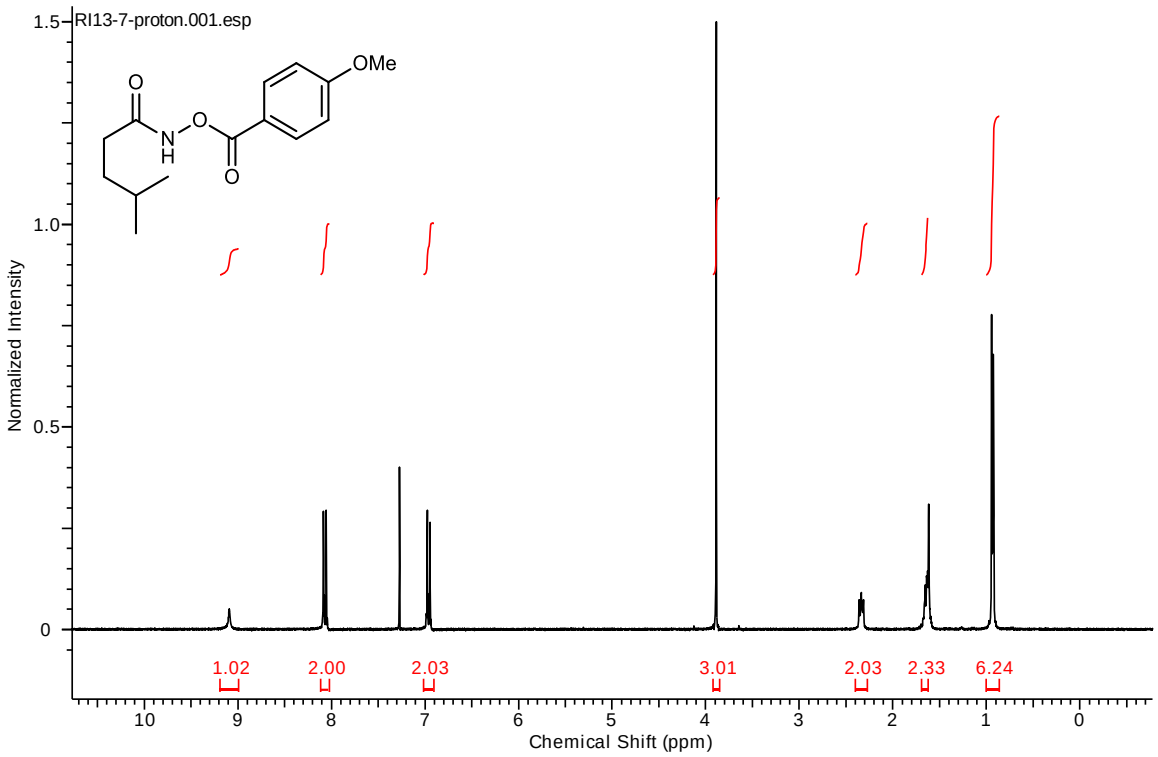

DP1812-carbon.1.fid
1d_13C_1_hour DMSO D:\\ Beau 1
162.00
46.65
28.91
20.44
f1 (ppm)

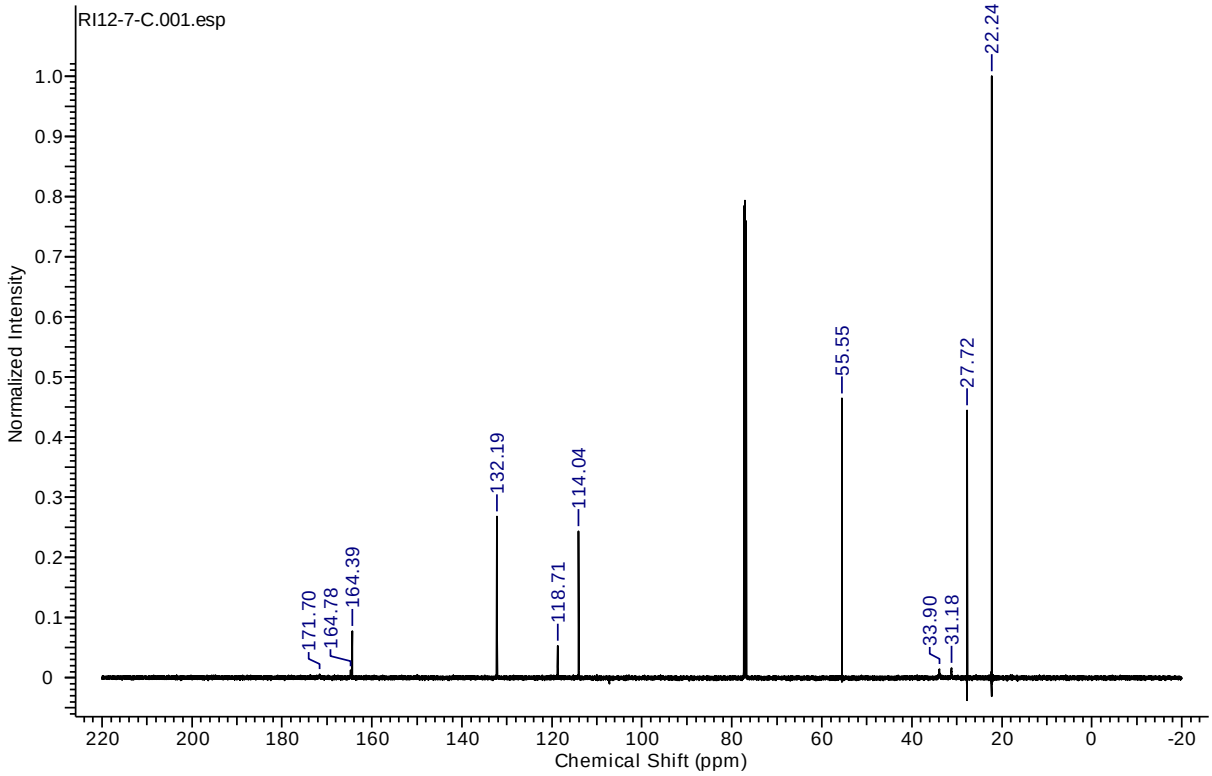

DP-primary.1.fid
1d_1H_16_scans DMSO D:\\ Beau 10
OMe
HN
N
H
O
O
O
O
0.98
2.00
2.01
0.98
3.00
2.02
1.03
6.16
f1 (ppm)

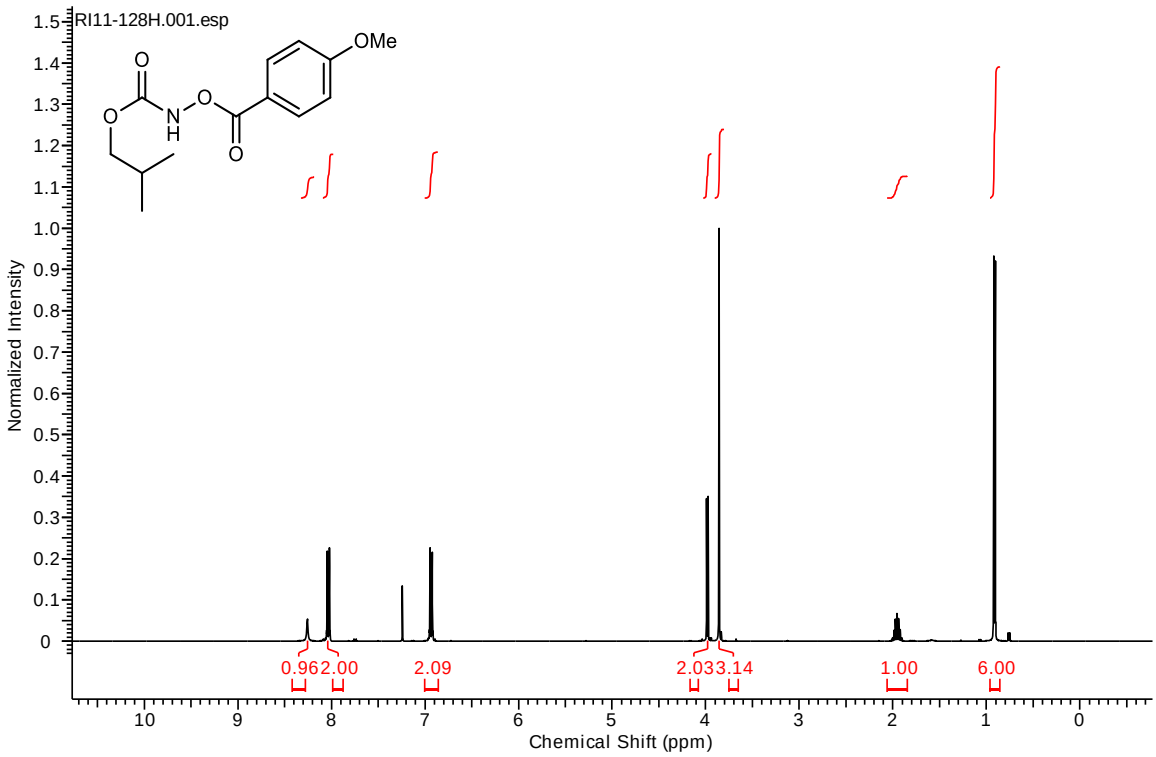

DP-primary.2.fid
1d_13C_1_hour DMSO D:\\ Beau 10
165.47
164.08
159.25
132.17
120.22
114.63
56.09
47.01
28.82
20.41
f1 (ppm)

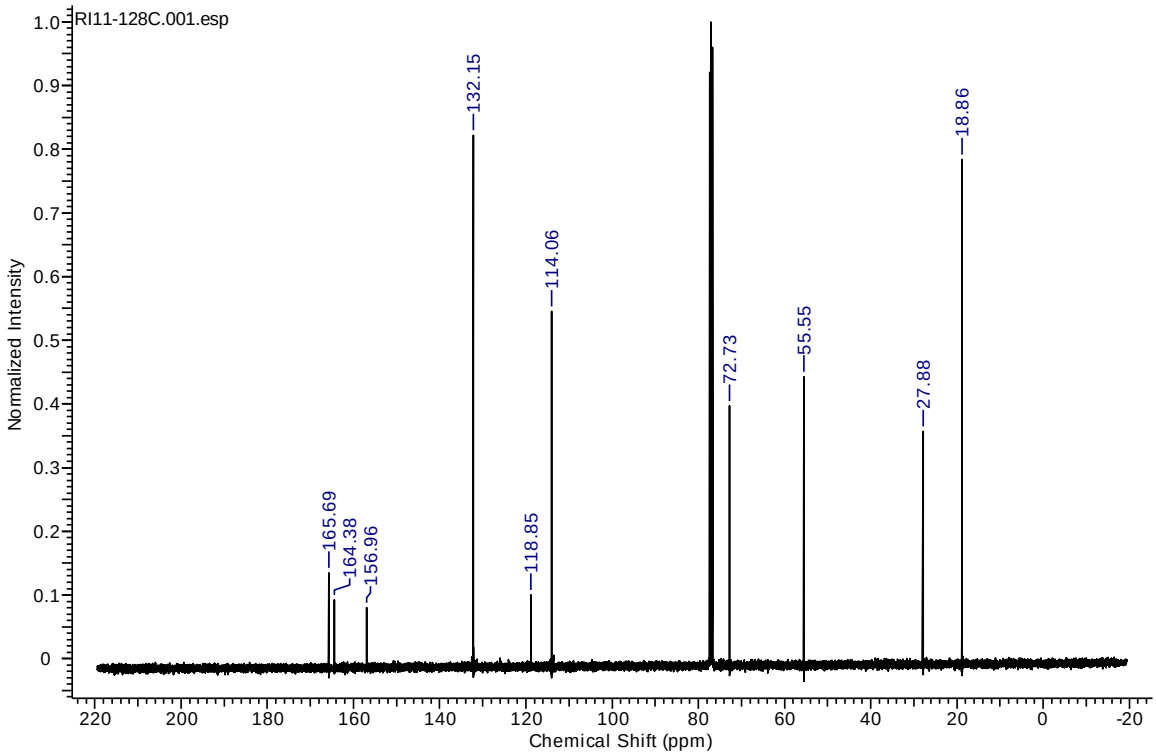

RI12-156-H-SM.001.esp
O
N
H
OH
Normalized Intensity
1.79
1.84
3.02
6.00
Chemical Shift (ppm)

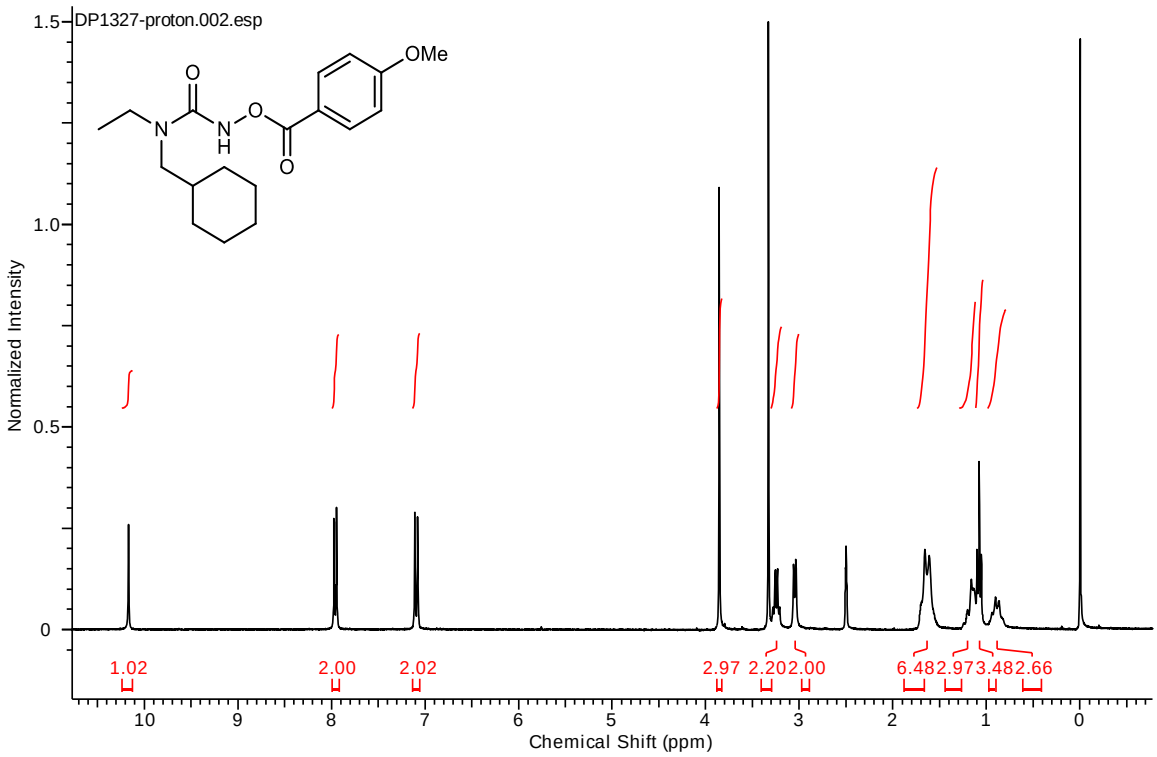

RI12-156-carbon.002.esp
Normalized Intensity
172.12
34.16
27.68
22.18
Chemical Shift (ppm)

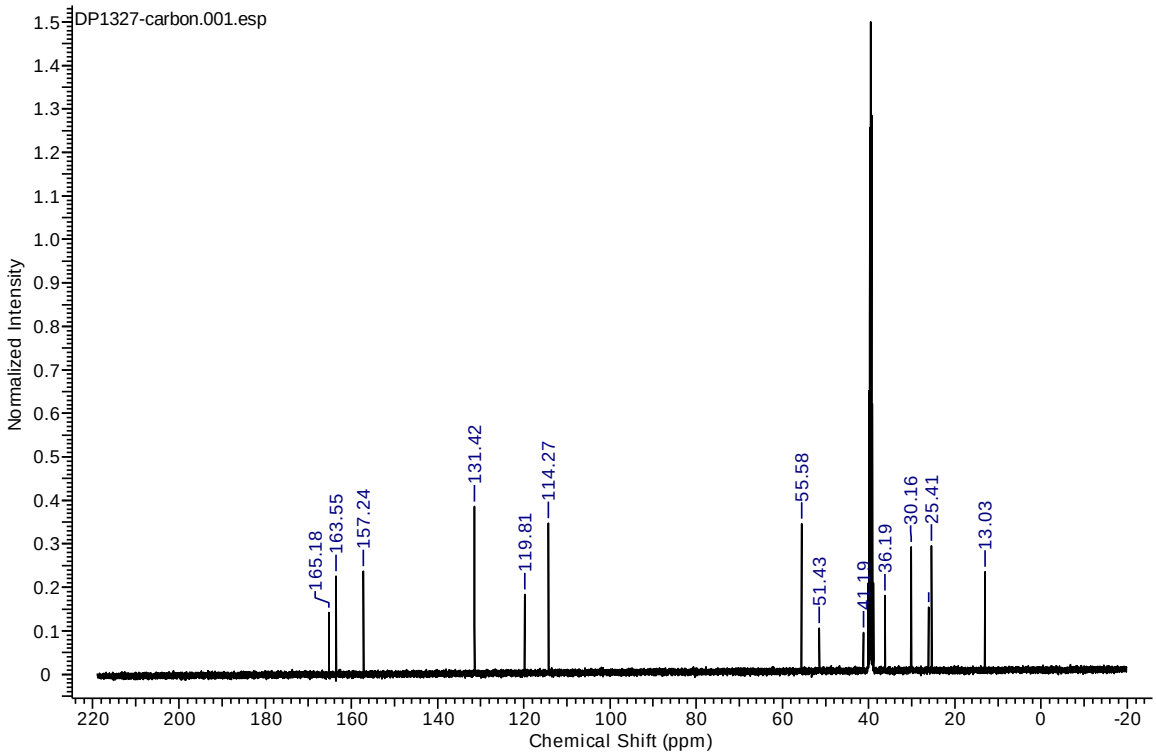

RI13-7-proton.001.esp
OMe
O
N
H
O
O
Normalized Intensity
1.5
1.0
0.5
0
1.02
2.00
2.03
3.01
2.03
2.33
6.24
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

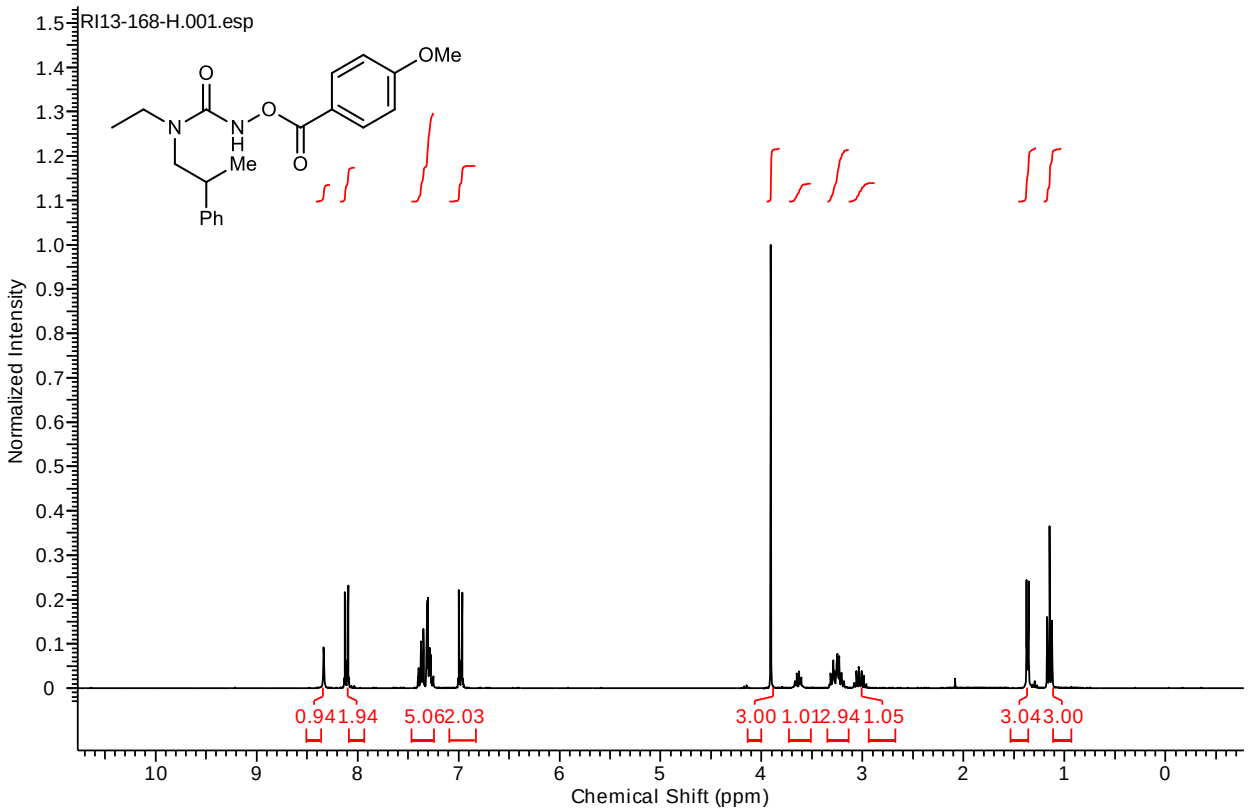

RI12-7-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
171.70
164.78
164.39
132.19
118.71
114.04
55.55
33.90
31.18
27.72
22.24
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

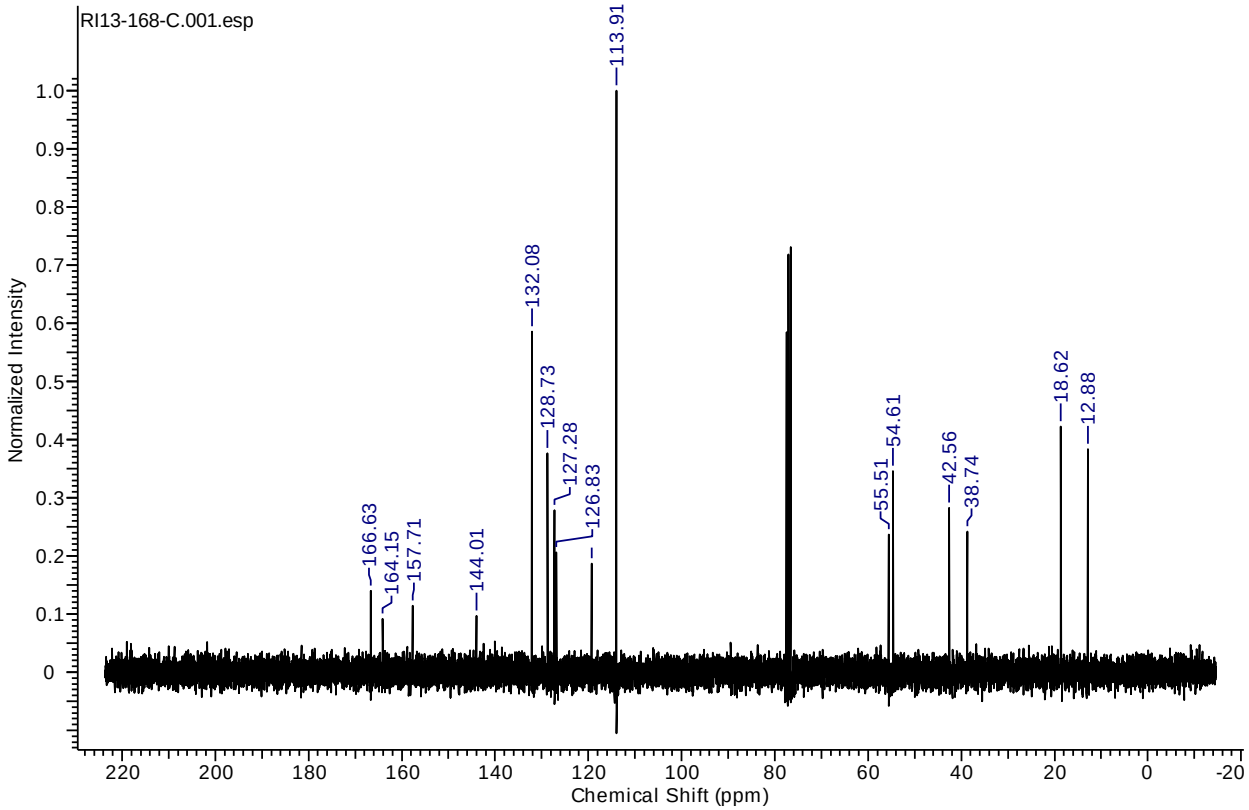

RI11-128H.001.esp
OMe
O
N
H
O
O
O
Normalized Intensity
0.96
2.00
2.09
2.03
3.14
1.00
6.00
Chemical Shift (ppm)

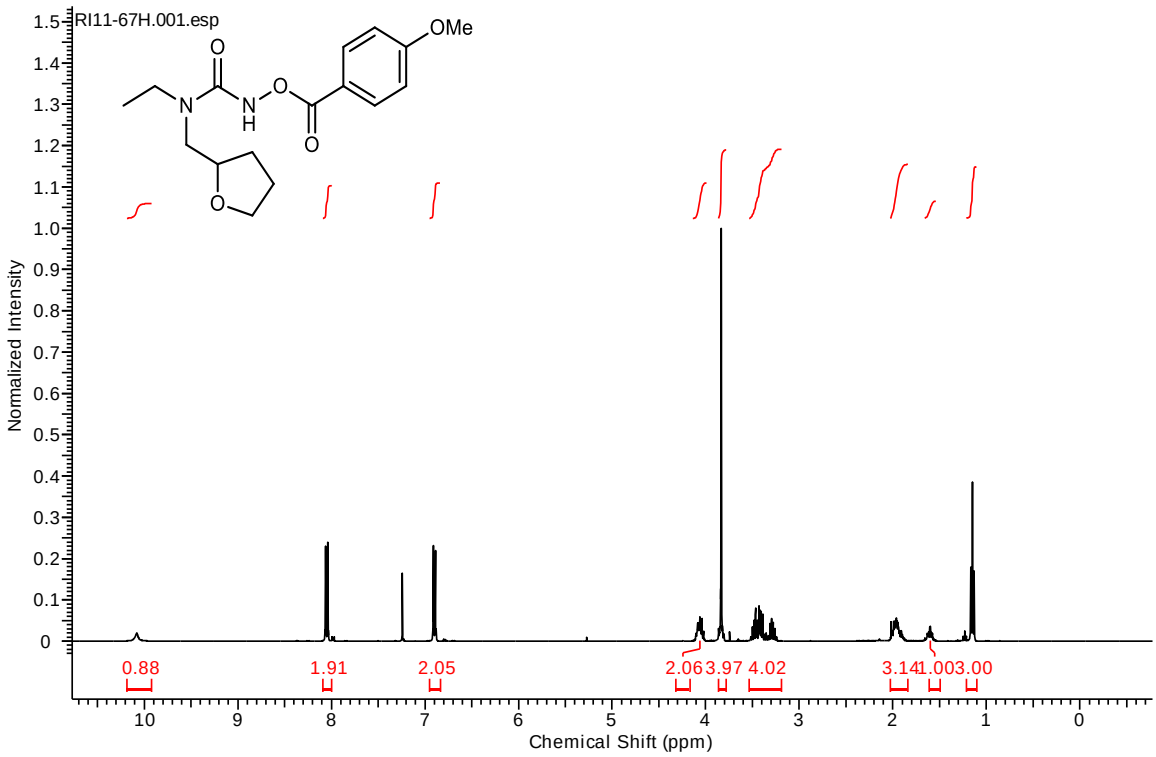

RI11-128C.001.esp
132.15
114.06
72.73
55.55
27.88
18.86
165.69
164.38
156.96
118.85
Normalized Intensity
Chemical Shift (ppm)

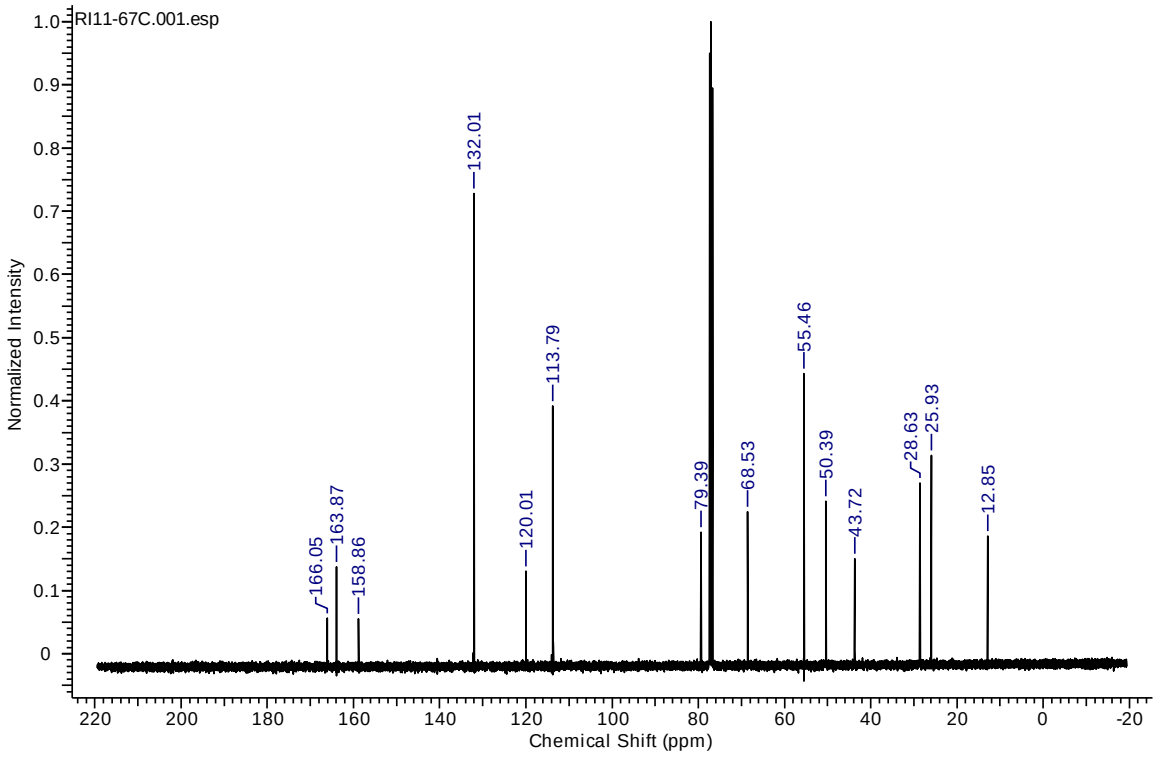

DP1327-proton.002.esp
OMe
O
N
O
N
H
O
Normalized Intensity
1.02
2.00
2.02
2.97
2.20
2.00
6.48
2.97
3.48
2.66
Chemical Shift (ppm)

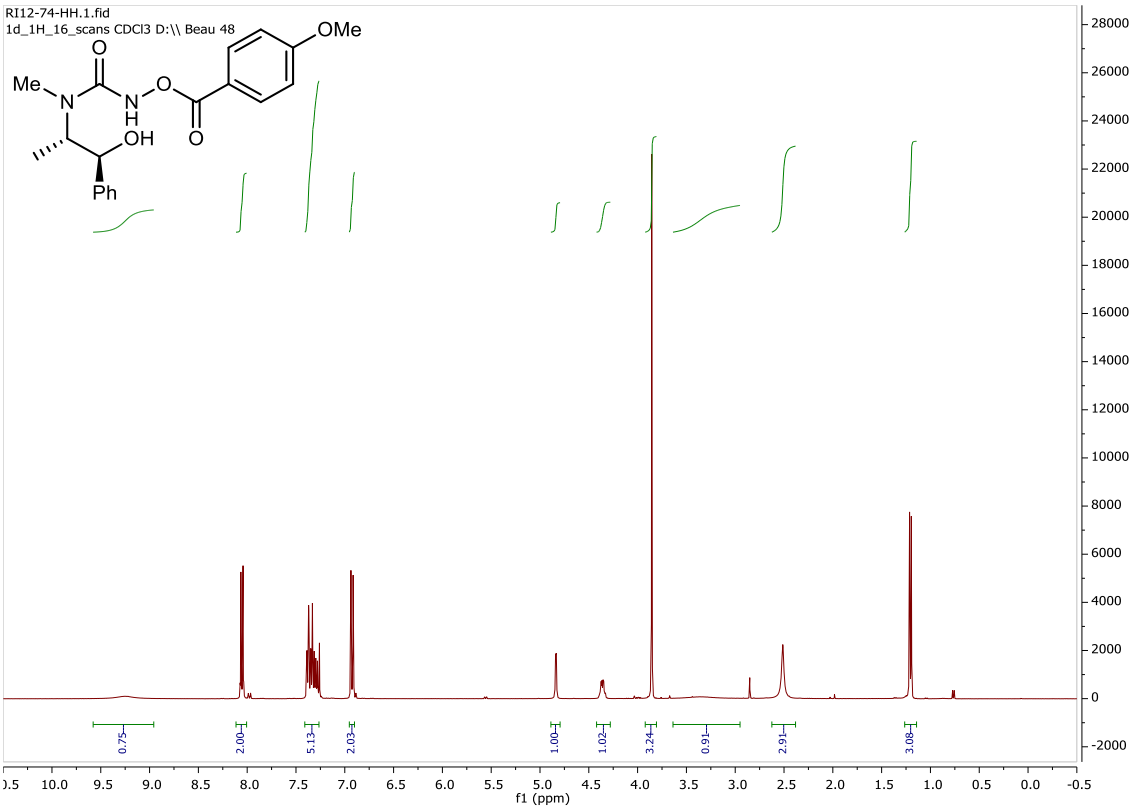

DP1327-carbon.001.esp
Normalized Intensity
165.18
163.55
157.24
131.42
119.81
114.27
55.58
51.43
41.19
36.19
30.16
25.41
13.03
Chemical Shift (ppm)

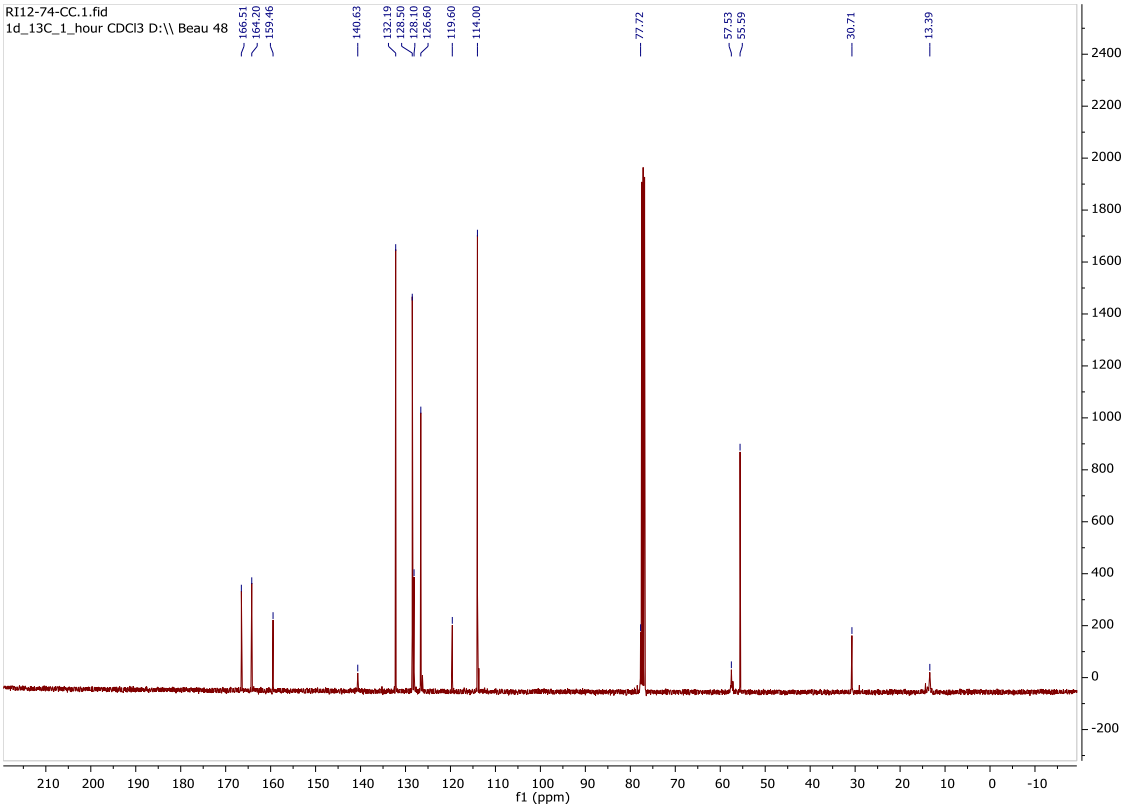

RI13-168-H.001.esp
OMe
O
N
O
N
H
Me
O
Ph
Normalized Intensity
0.94 1.94 5.06 2.03 3.00 1.01 2.94 1.05 3.04 3.00
Chemical Shift (ppm)

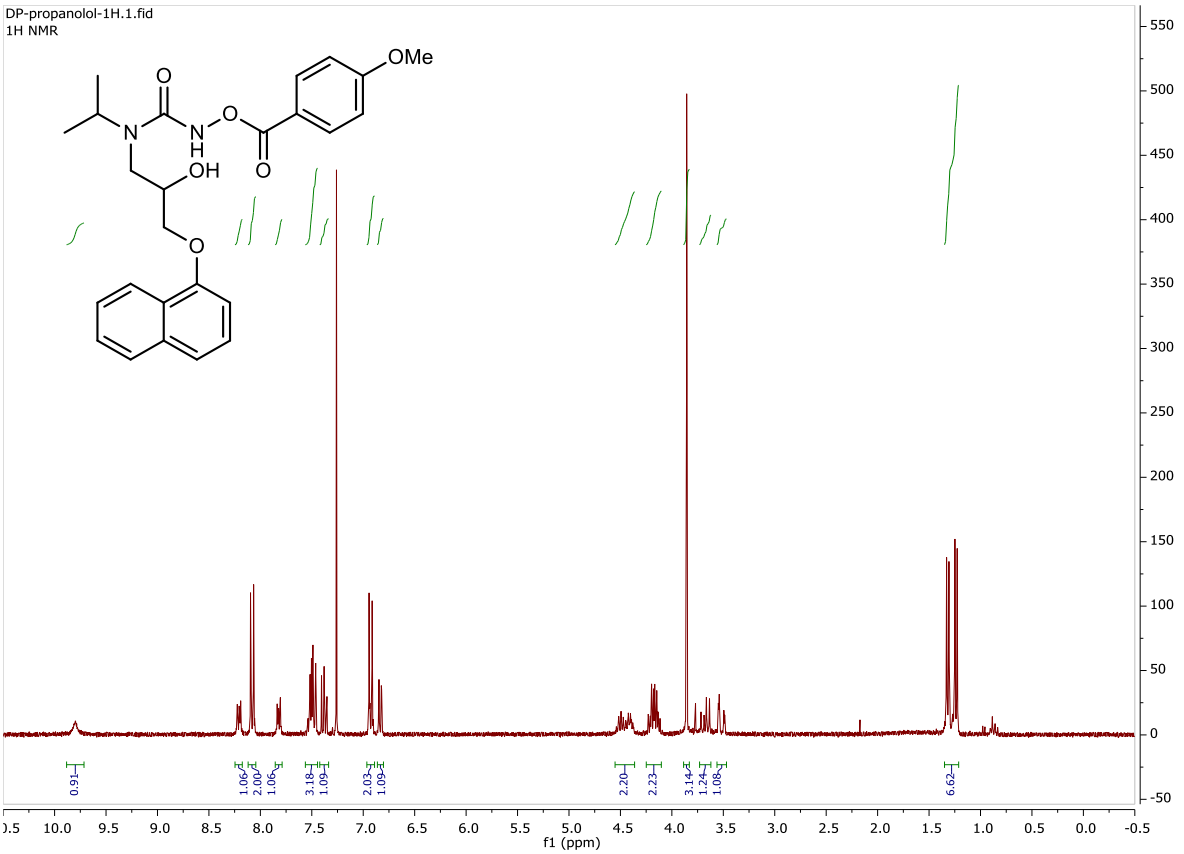

RI13-168-C.001.esp
Normalized Intensity
166.63
164.15
157.71
144.01
132.08
128.73
127.28
126.83
113.91
55.51
54.61
42.56
38.74
18.62
12.88
Chemical Shift (ppm)

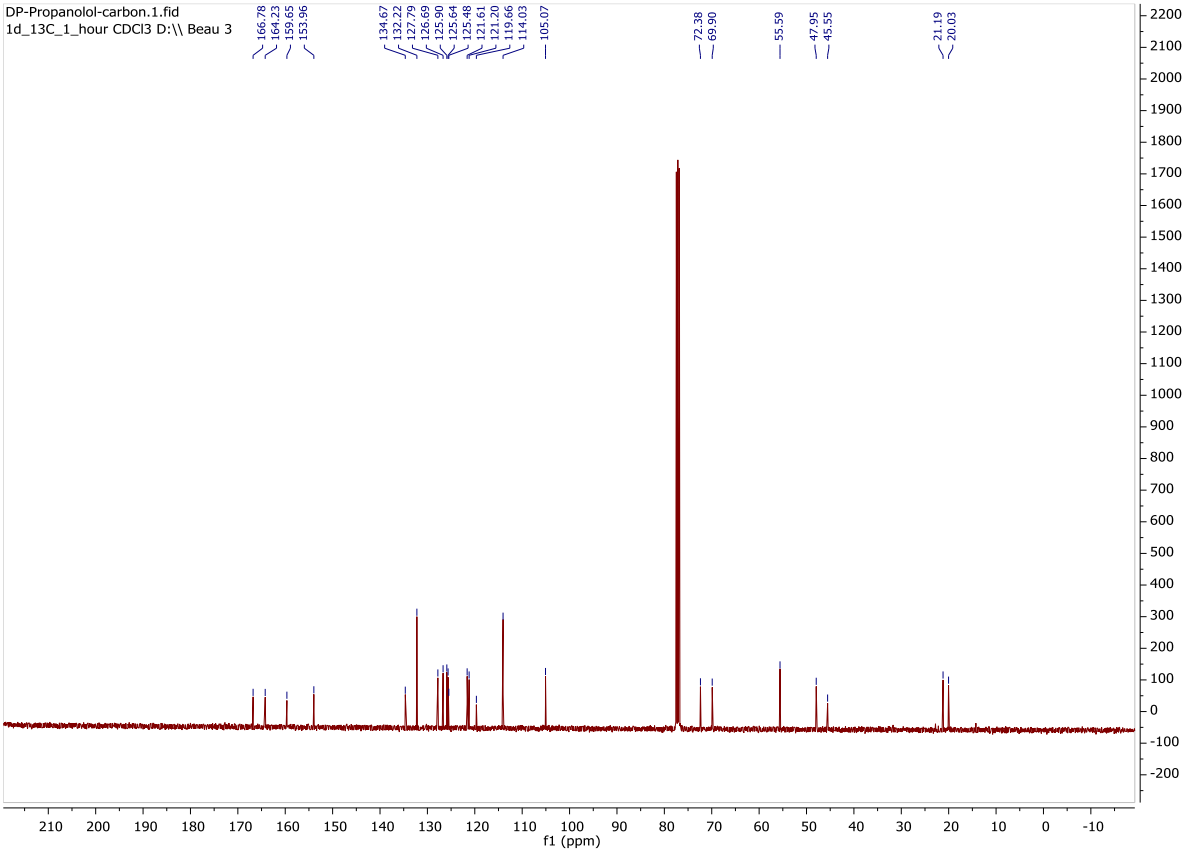

RI11-67H.001.esp
OMe
O
N
N
H
O
O
O
Normalized Intensity
0.88
1.91
2.05
2.06
3.97
4.02
3.14
1.00
3.00
Chemical Shift (ppm)

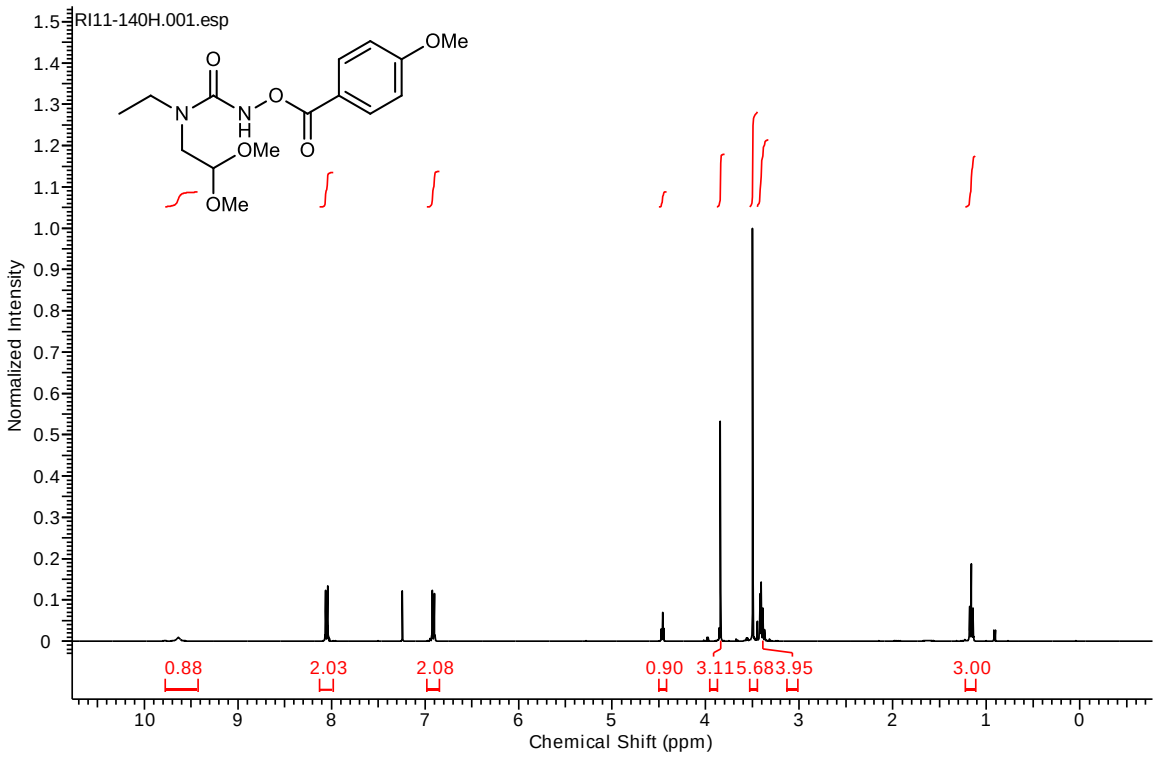

RI11-67C.001.esp
Normalized Intensity
166.05
163.87
158.86
132.01
120.01
113.79
79.39
68.53
55.46
50.39
43.72
28.63
25.93
12.85
Chemical Shift (ppm)

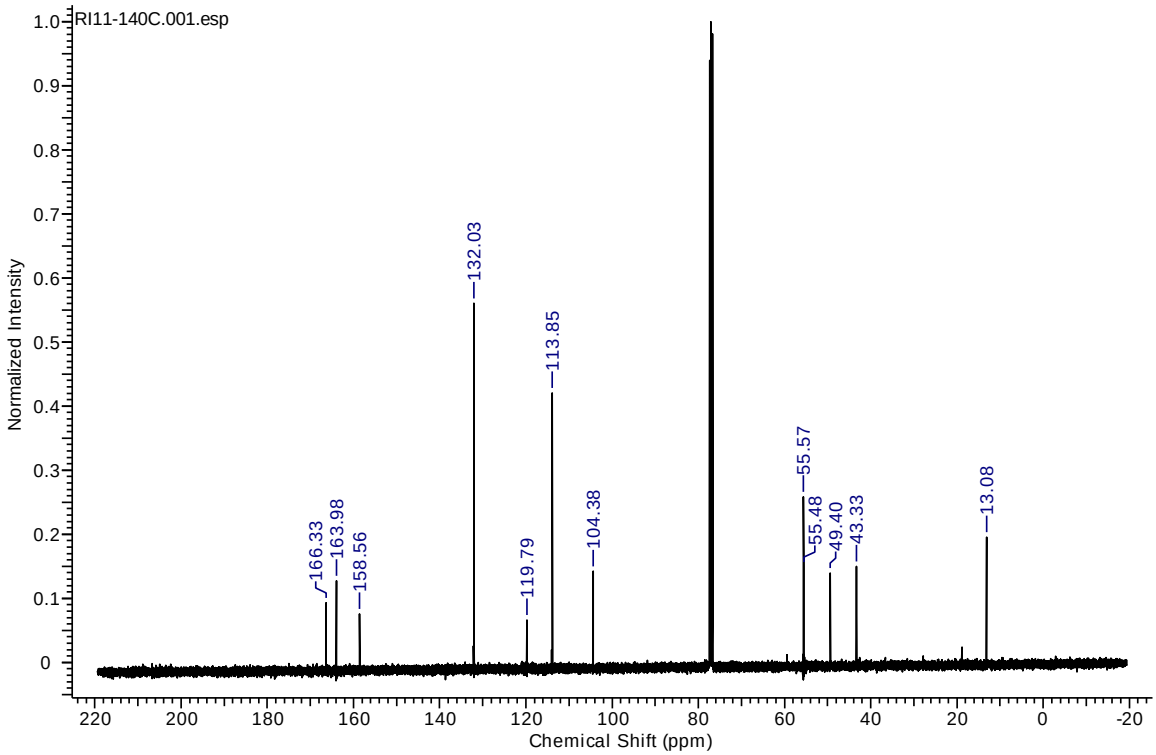

RI12-74-HH.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 48
OMe
O
Me
N
O
N
H
O
OH
O
Ph
0.79
2.00
5.13
2.03
1.00
1.02
3.24
0.91
2.91
3.08
f1 (ppm)

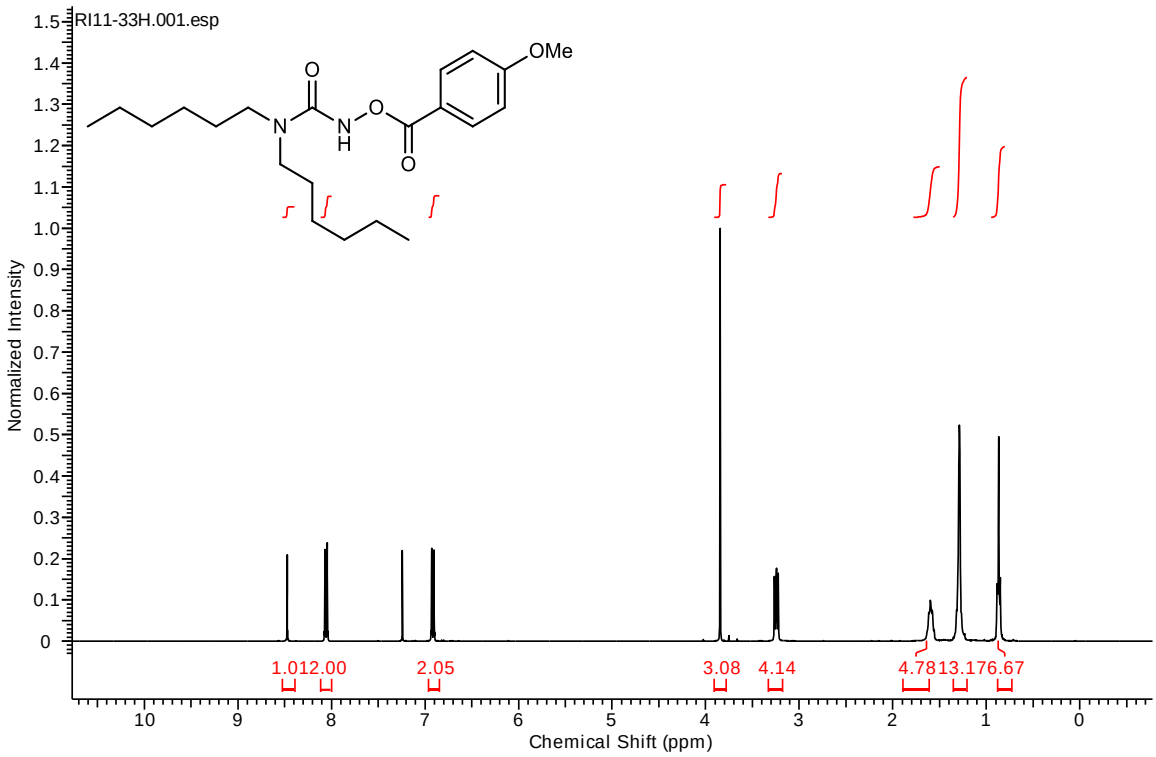

RI12-74-CC.1.fid
1d_13C_1_hour CDCl3 D:\\ Beau 48
166.51
164.20
159.46
140.63
132.19
128.50
128.10
126.60
119.60
114.00
77.72
57.53
55.59
30.71
13.39
f1 (ppm)

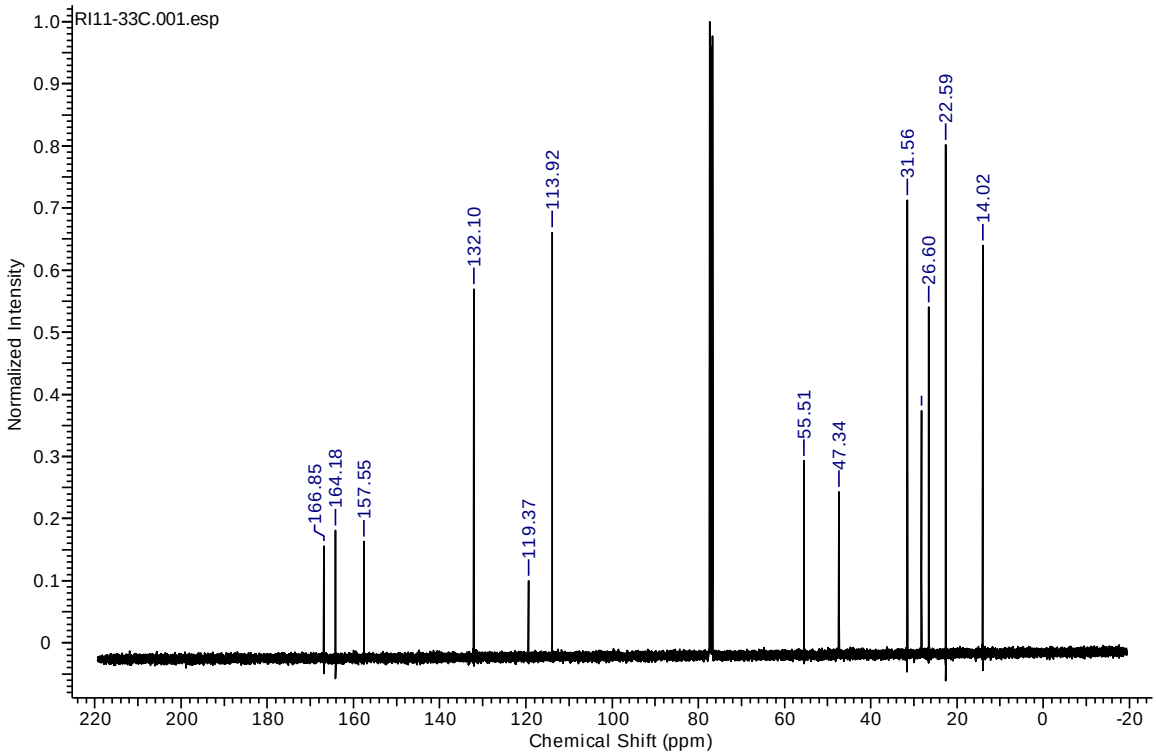

DP-propanolol-1H.1.fid
1H NMR
OMe
O
N
N
H
O
OH
O
O
0.91
1.06
2.00
1.06
3.18
1.09
2.03
1.09
2.20
2.23
3.14
1.24
1.08
6.62
f1 (ppm)

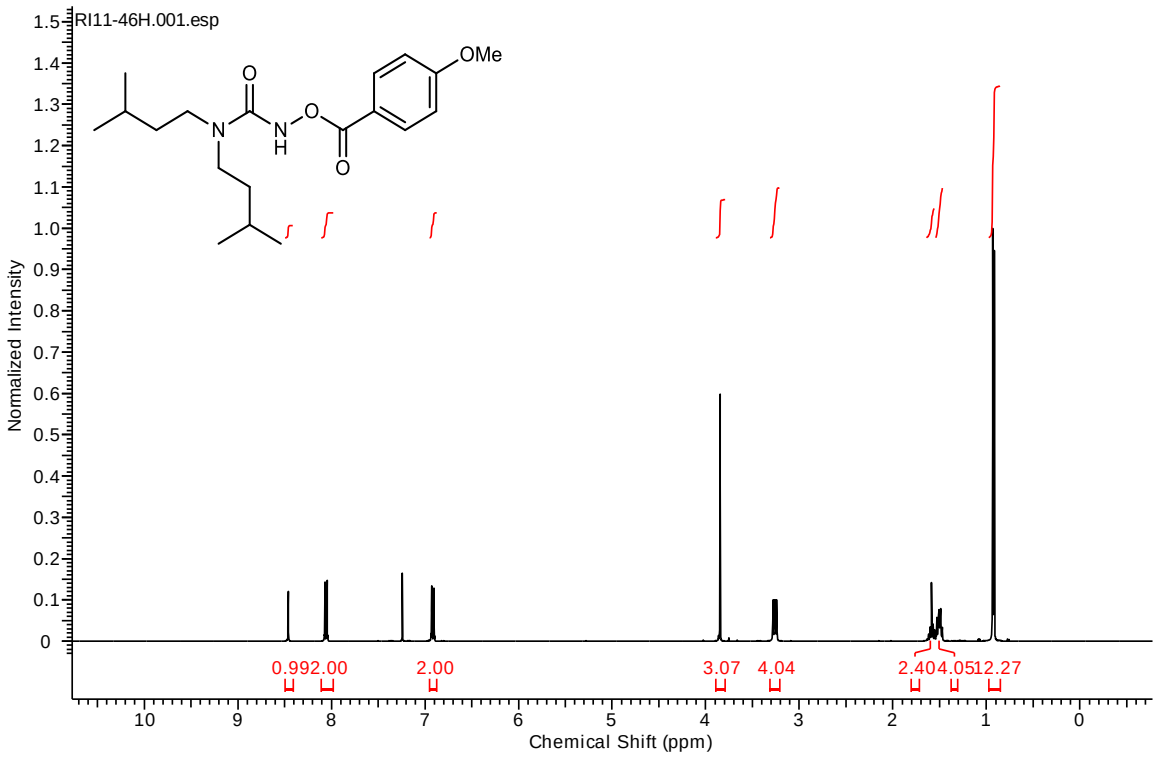

DP-Propanolol-carbon.1.fid
1d_13C_1_hour CDCl3 D:\\ Beau 3
166.78
164.23
159.65
153.96
134.67
132.22
127.79
126.69
125.90
125.64
125.48
121.61
121.20
119.66
114.03
105.07
72.38
69.90
55.59
47.95
45.55
21.19
20.03
f1 (ppm)

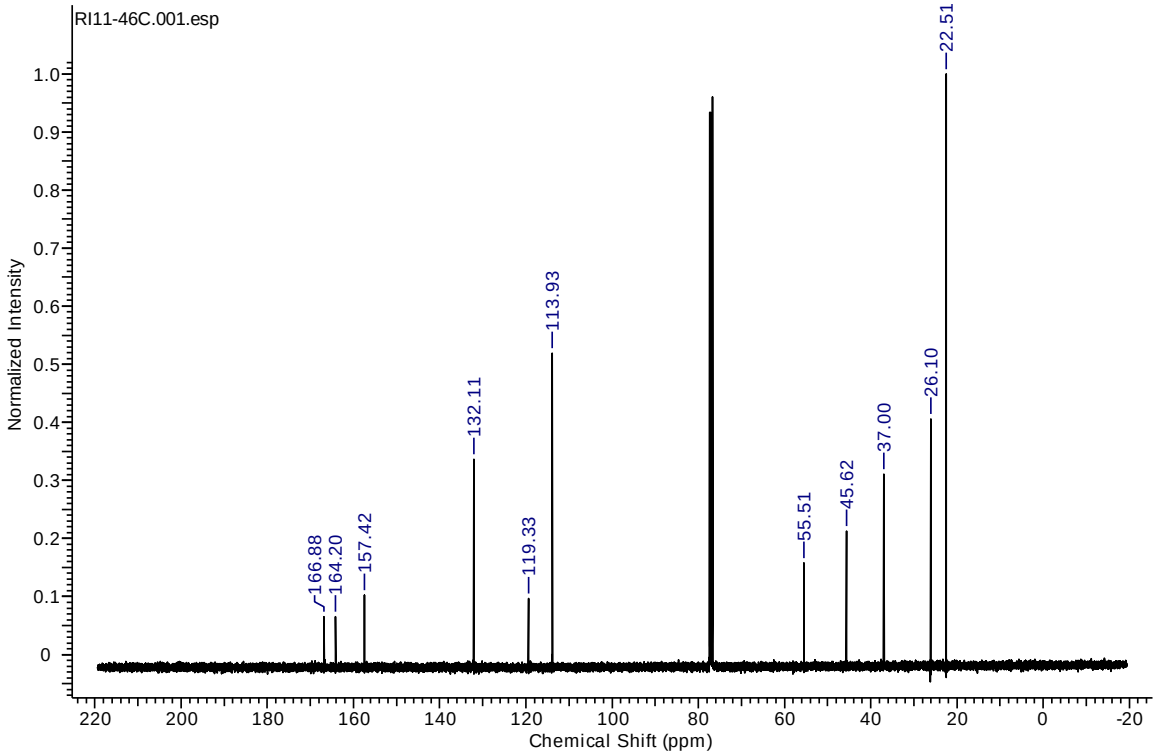

RI11-140H.001.esp
OMe
O
N
N
H
O
O
OMe
OMe
Normalized Intensity
0.88
2.03
2.08
0.90
3.11
5.68
3.95
3.00
Chemical Shift (ppm)

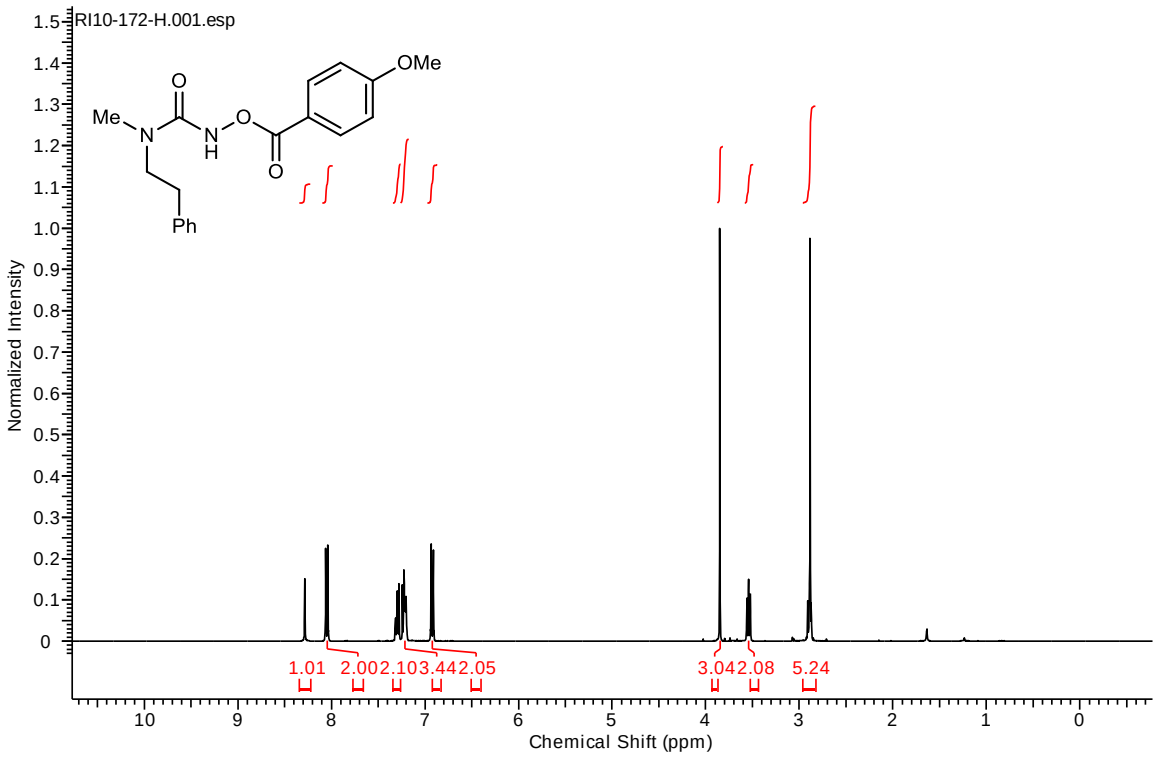

RI11-140C.001.esp
Normalized Intensity
166.33
163.98
158.56
132.03
119.79
113.85
104.38
55.57
55.48
49.40
43.33
13.08
Chemical Shift (ppm)

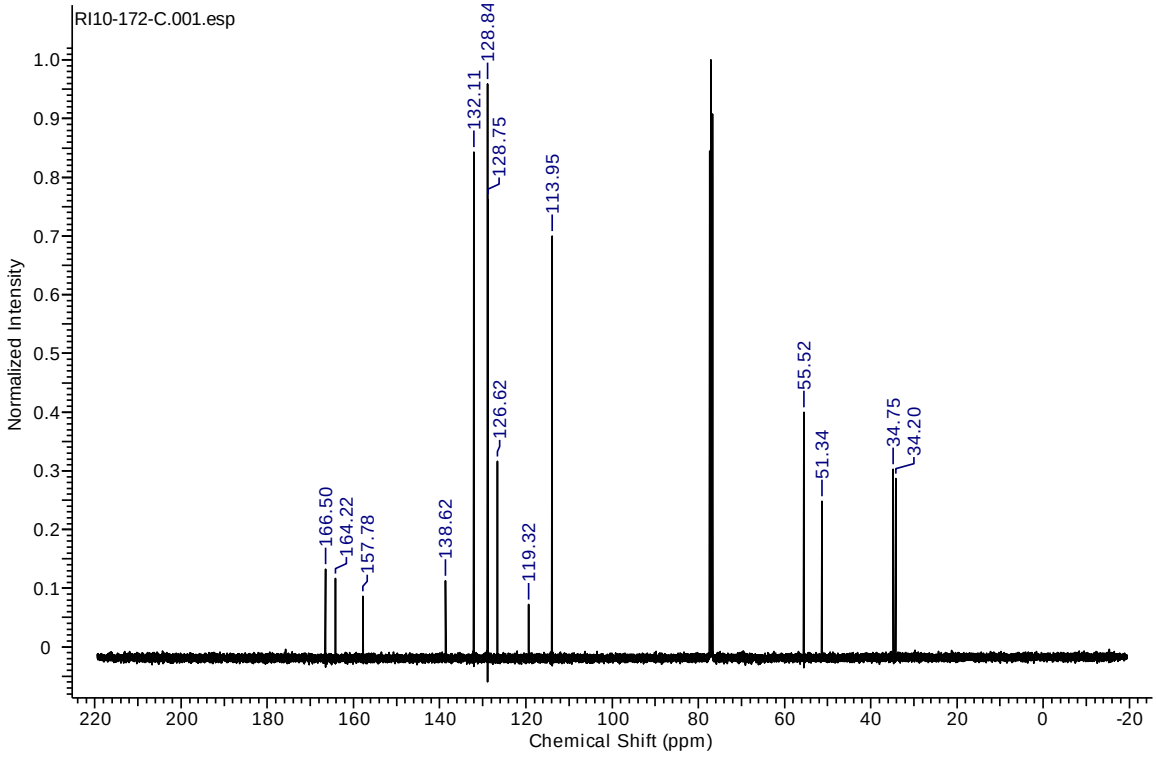

RI11-33H.001.esp
OMe
O
N
O
N
H
O
O
Normalized Intensity
1.01
2.00
2.05
3.08
4.14
4.78
13.17
6.67
Chemical Shift (ppm)

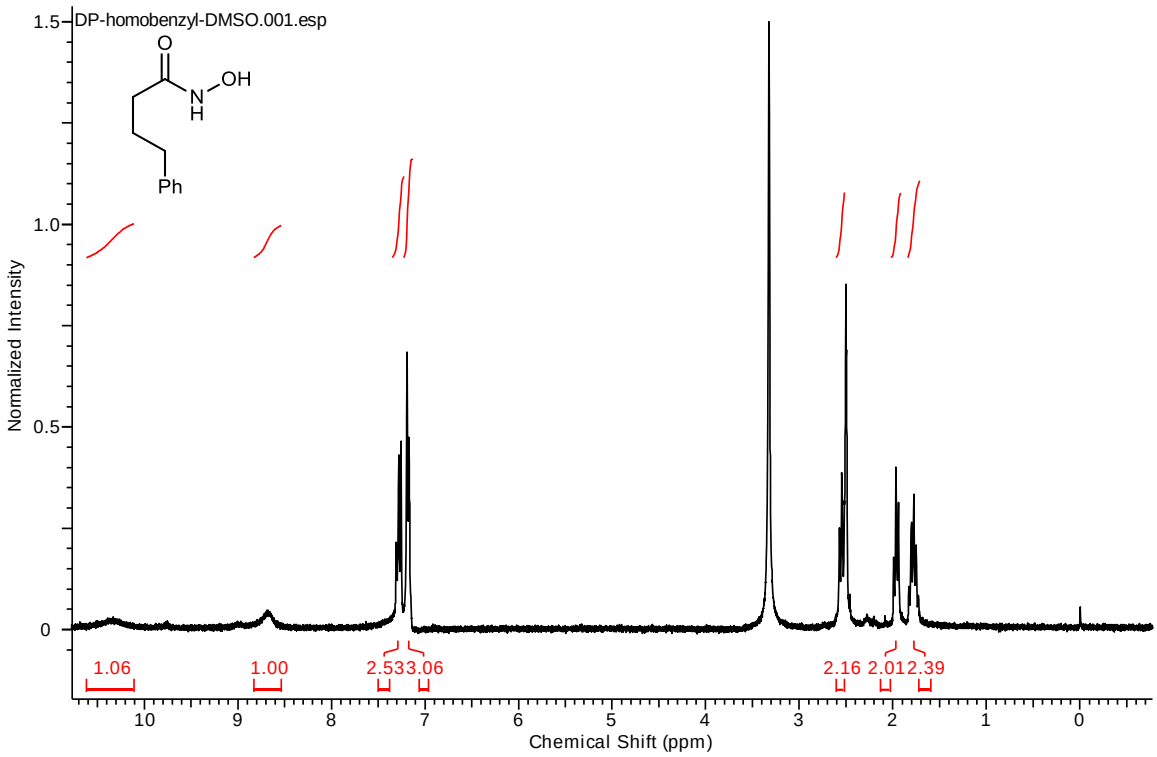

RI11-33C.001.esp
166.85
164.18
157.55
132.10
119.37
113.92
55.51
47.34
31.56
26.60
22.59
14.02
Normalized Intensity
Chemical Shift (ppm)

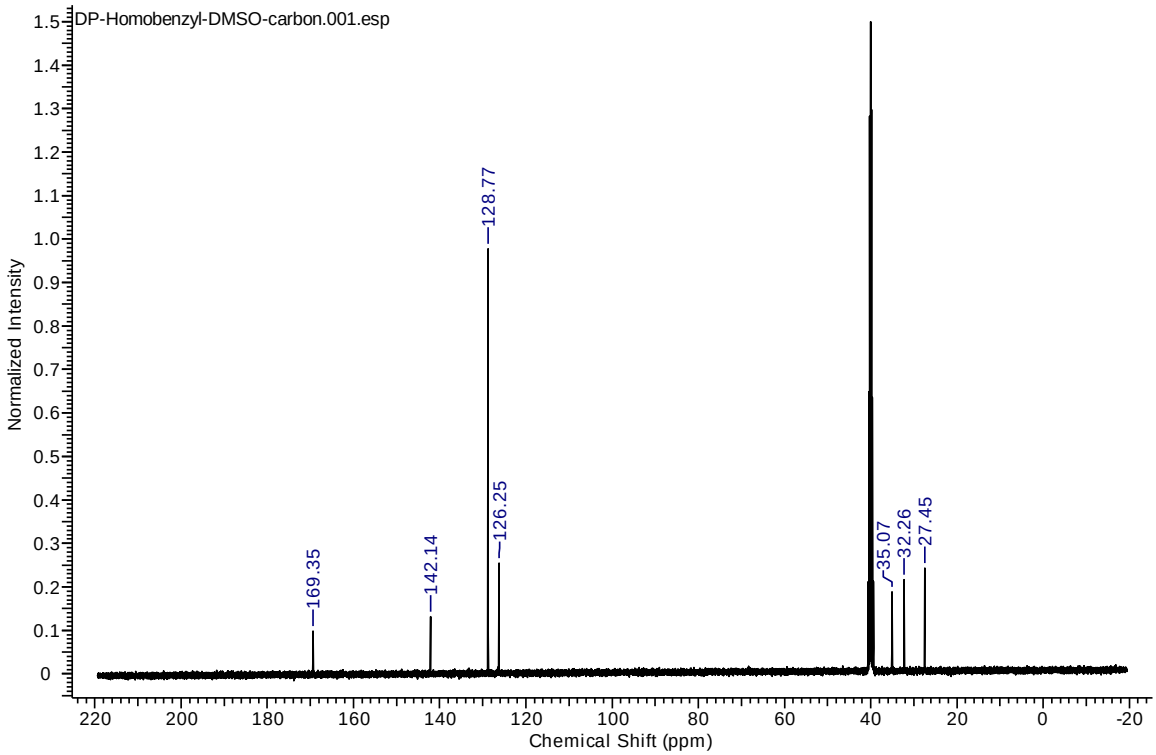

RI11-46H.001.esp
OMe
O
N
N
H
O
O
Normalized Intensity
0.99
2.00
2.00
3.07
4.04
2.40
4.05
12.27
Chemical Shift (ppm)

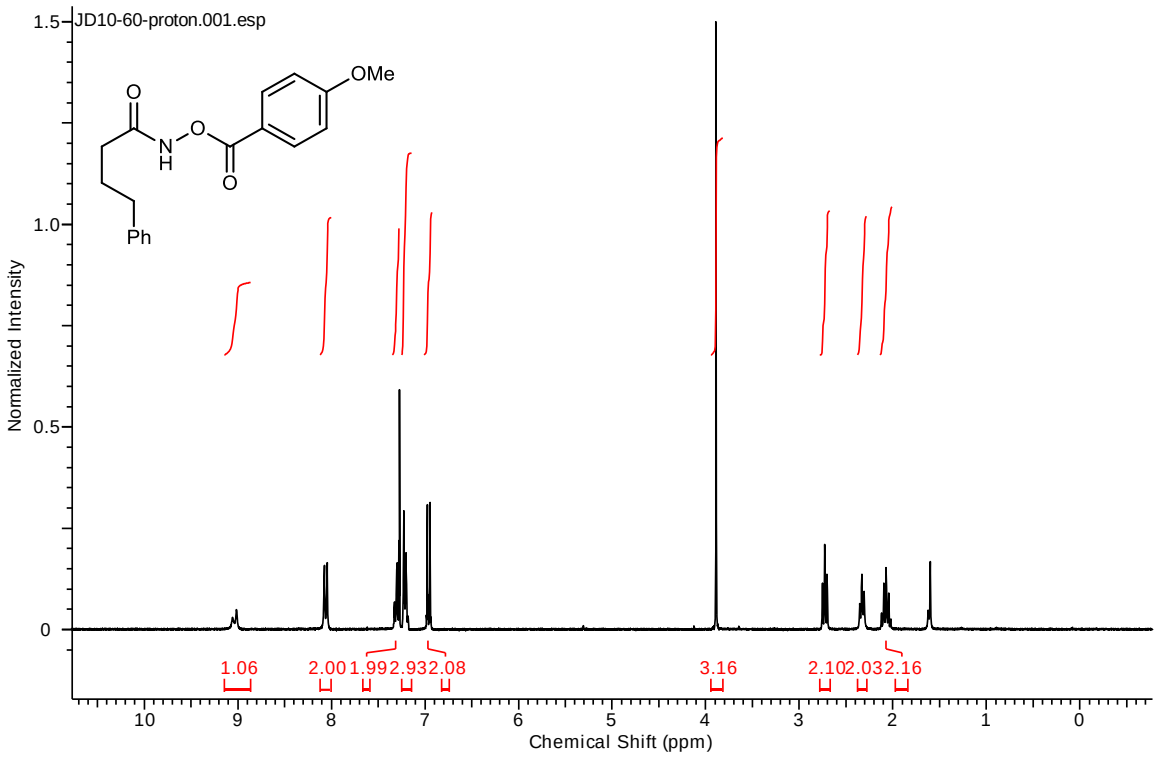

RI11-46C.001.esp
166.88
164.20
157.42
132.11
119.33
113.93
55.51
45.62
37.00
26.10
22.51
Normalized Intensity
Chemical Shift (ppm)

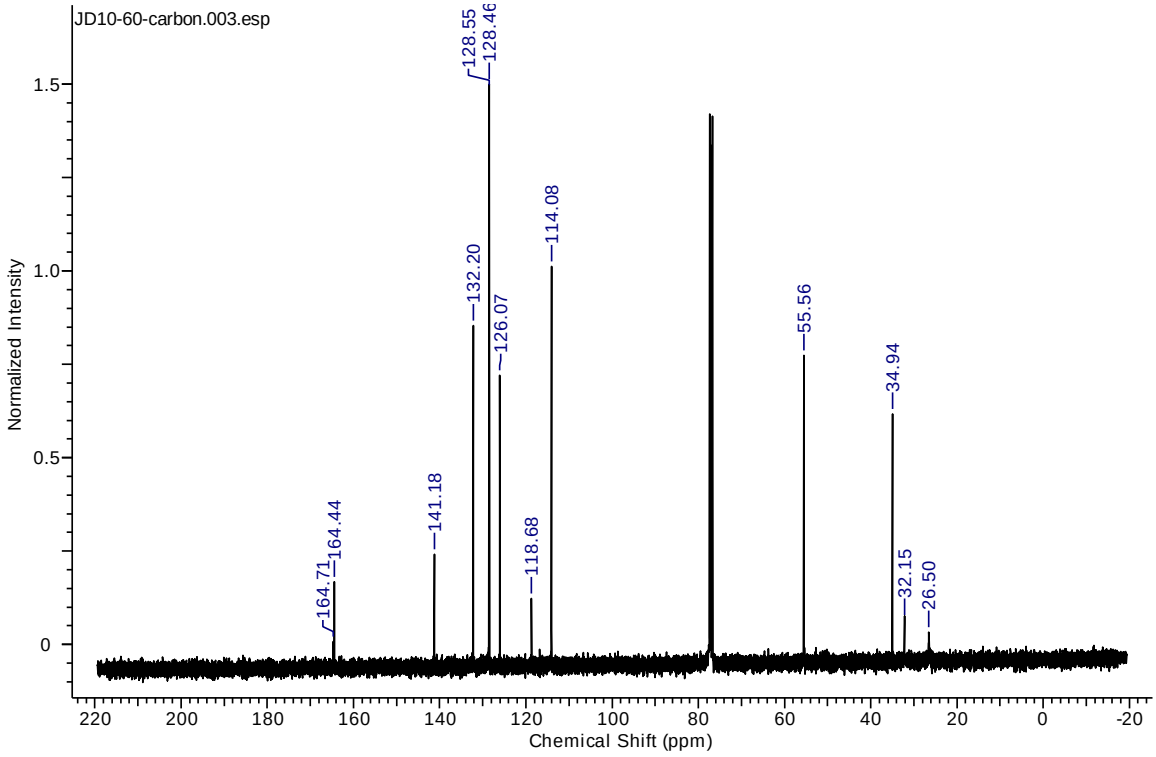

RI10-172-H.001.esp
OMe
Me
N
O
N
H
O
O
Ph
Normalized Intensity
1.01
2.00
2.10
3.44
2.05
3.04
2.08
5.24
Chemical Shift (ppm)

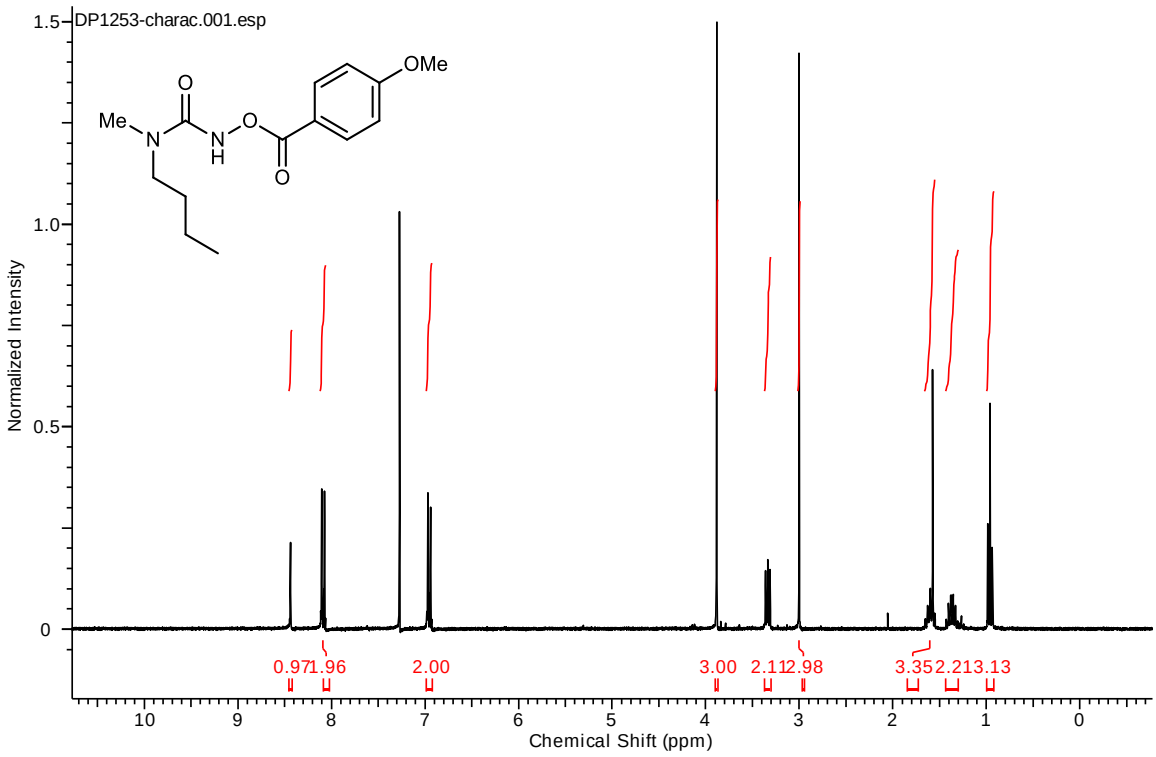

RI10-172-C.001.esp
166.50
164.22
157.78
138.62
132.11
128.84
128.75
126.62
119.32
113.95
55.52
51.34
34.75
34.20
Normalized Intensity
Chemical Shift (ppm)

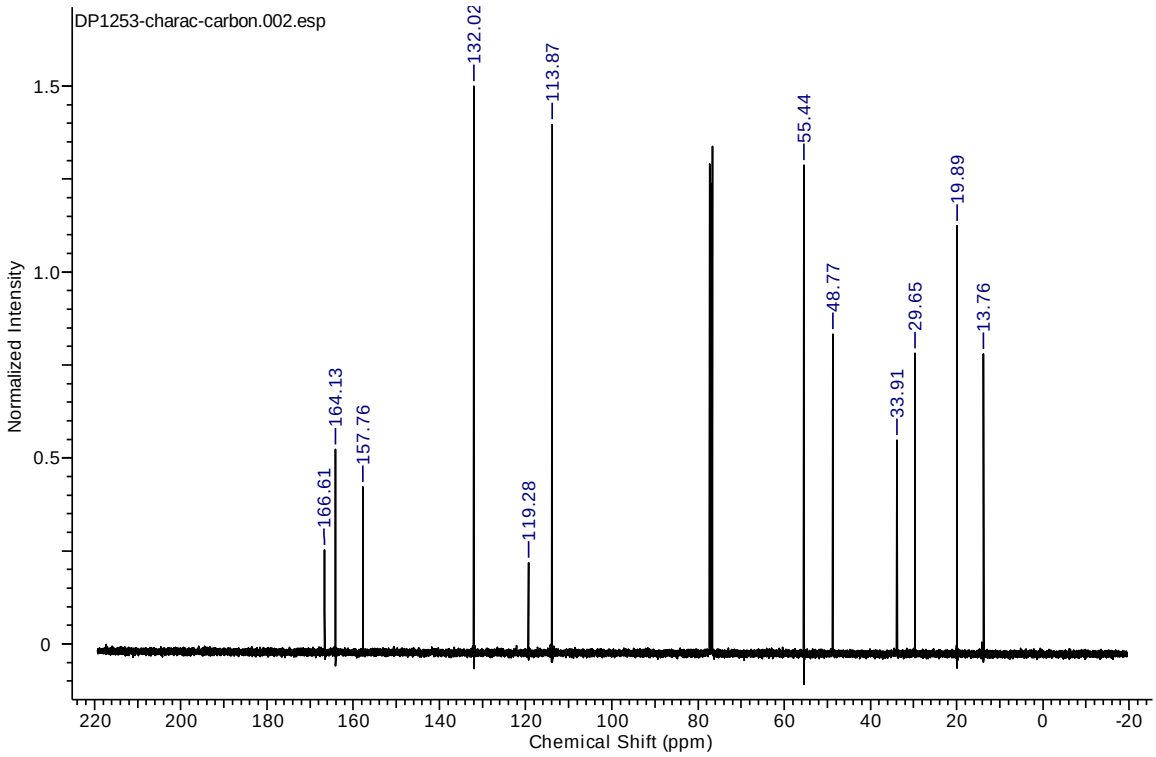

DP-homobenzyl-DMSO.001.esp
O
N
H
OH
Ph
Normalized Intensity
1.5
1.0
0.5
0
1.06
1.00
2.53
3.06
2.16
2.01
2.39
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

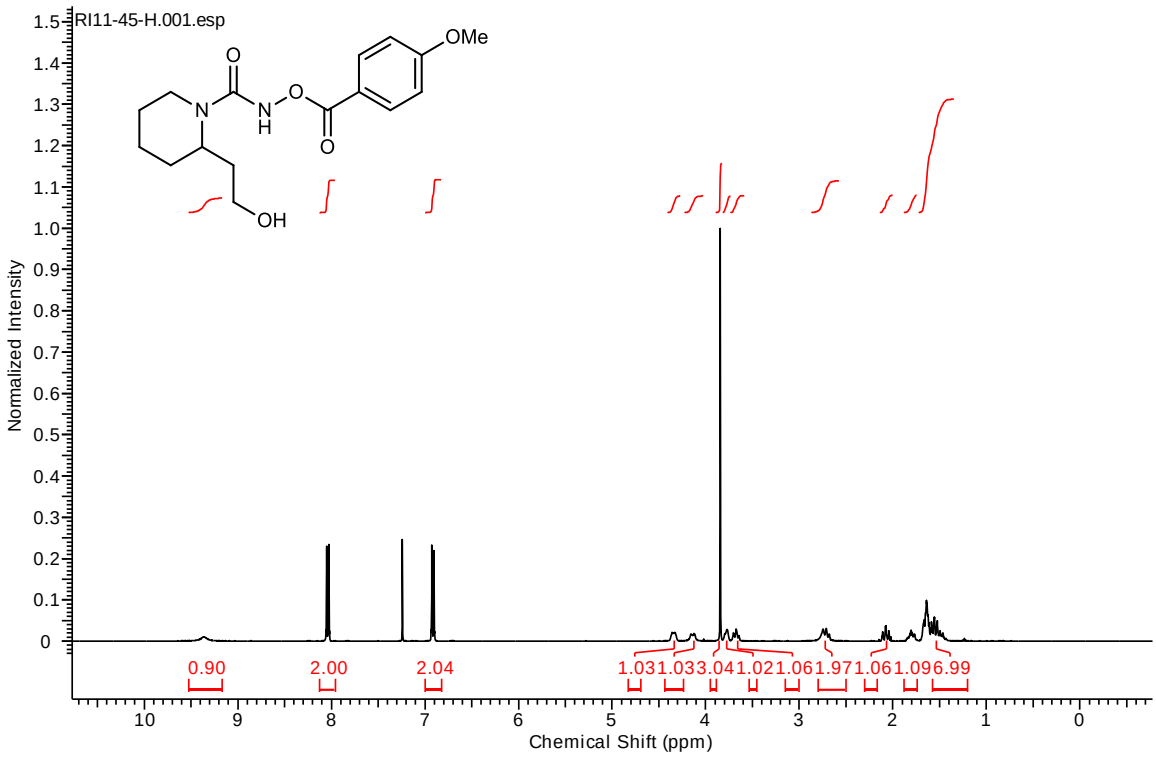

DP-Homobenzyl-DMSO-carbon.001.esp
Normalized Intensity
128.77
126.25
169.35
142.14
35.07
32.26
27.45
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

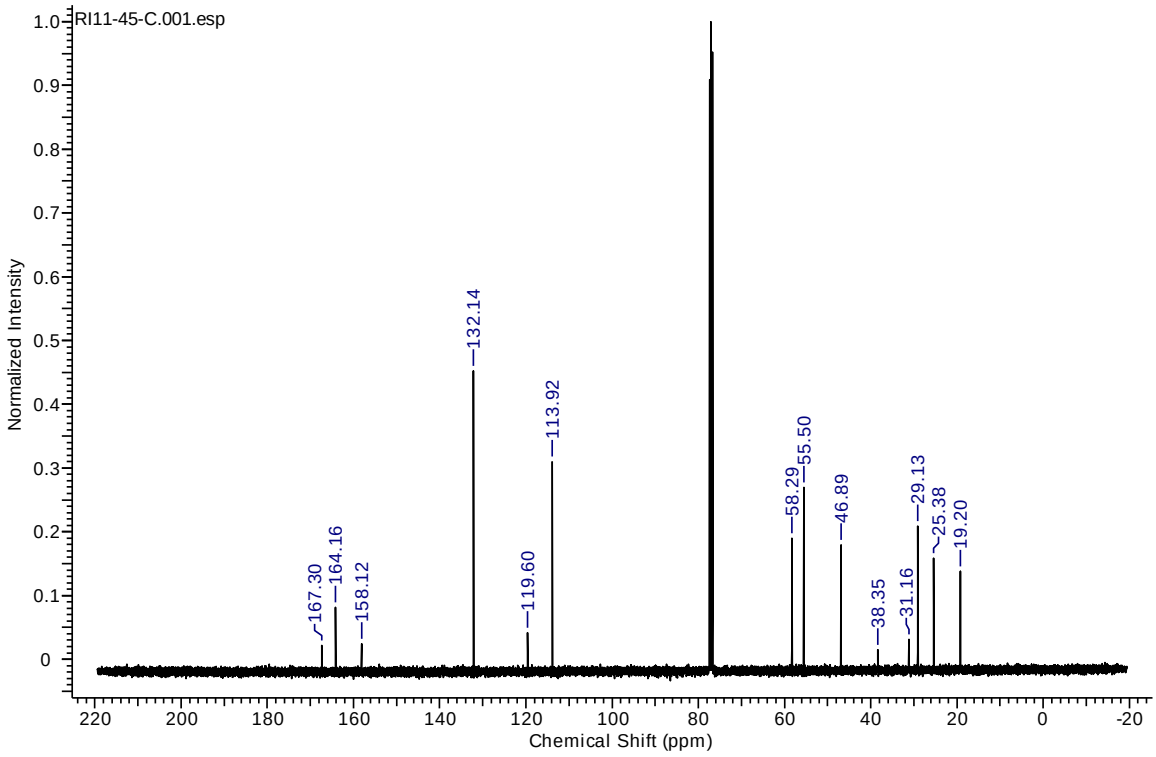

JD10-60-proton.001.esp
OMe
O
N
H
O
O
Ph
Normalized Intensity
1.5
1.0
0.5
0
1.06
2.00
1.99
2.93
2.08
3.16
2.10
2.03
2.16
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

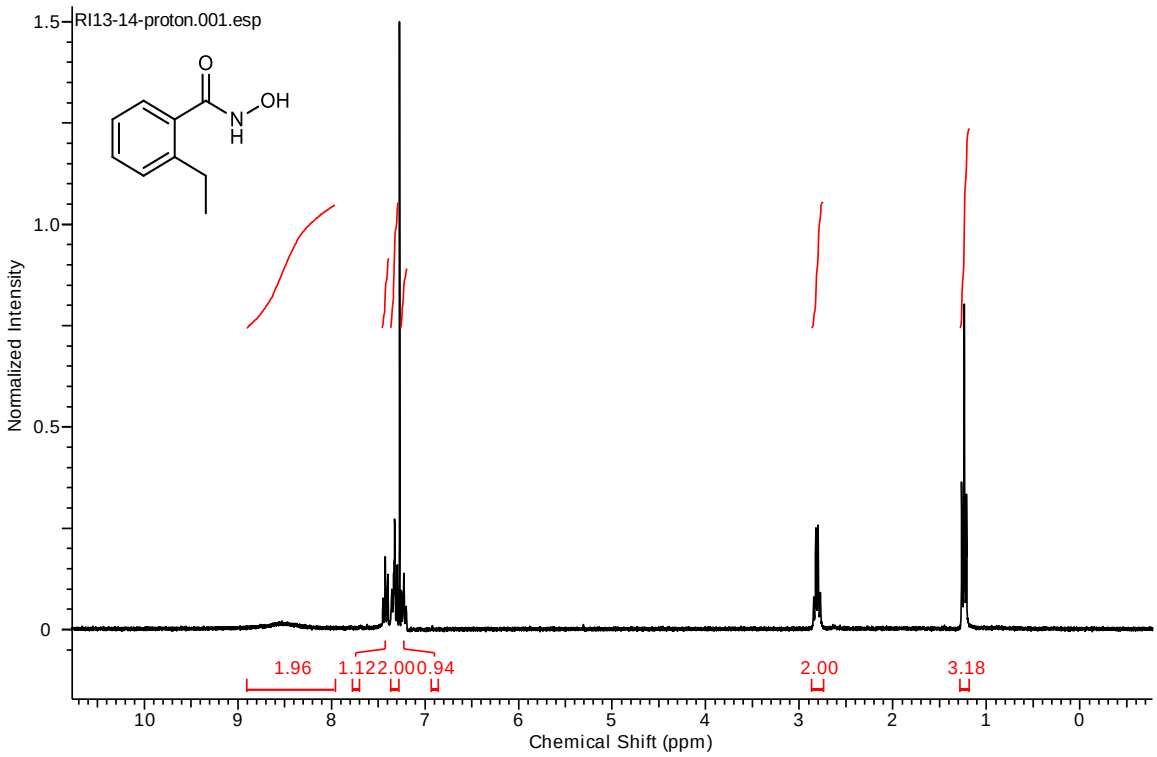

JD10-60-carbon.003.esp
Normalized Intensity
1.5
1.0
0.5
0
128.55
128.46
132.20
126.07
114.08
55.56
34.94
164.71
164.44
141.18
118.68
32.15
26.50
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

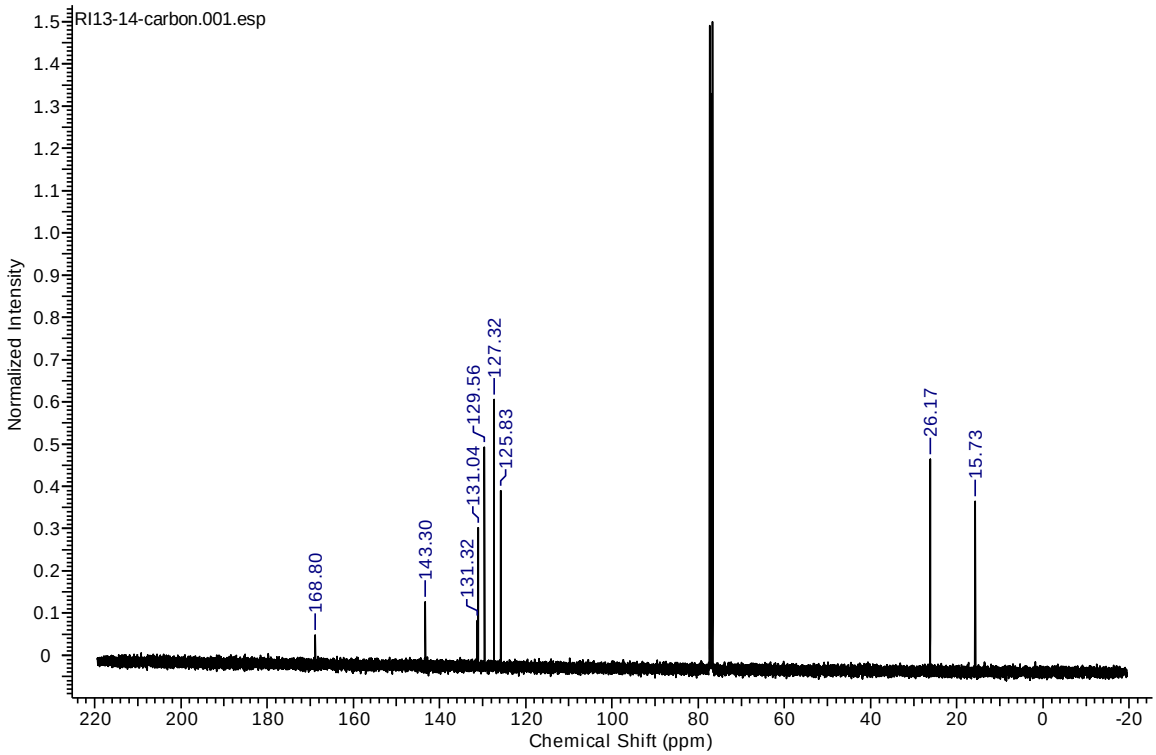

DP1253-charac.001.esp
OMe
Me
N
O
N
H
O
O
Normalized Intensity
0.97
1.96
2.00
3.00
2.11
2.98
3.35
2.21
3.13
Chemical Shift (ppm)

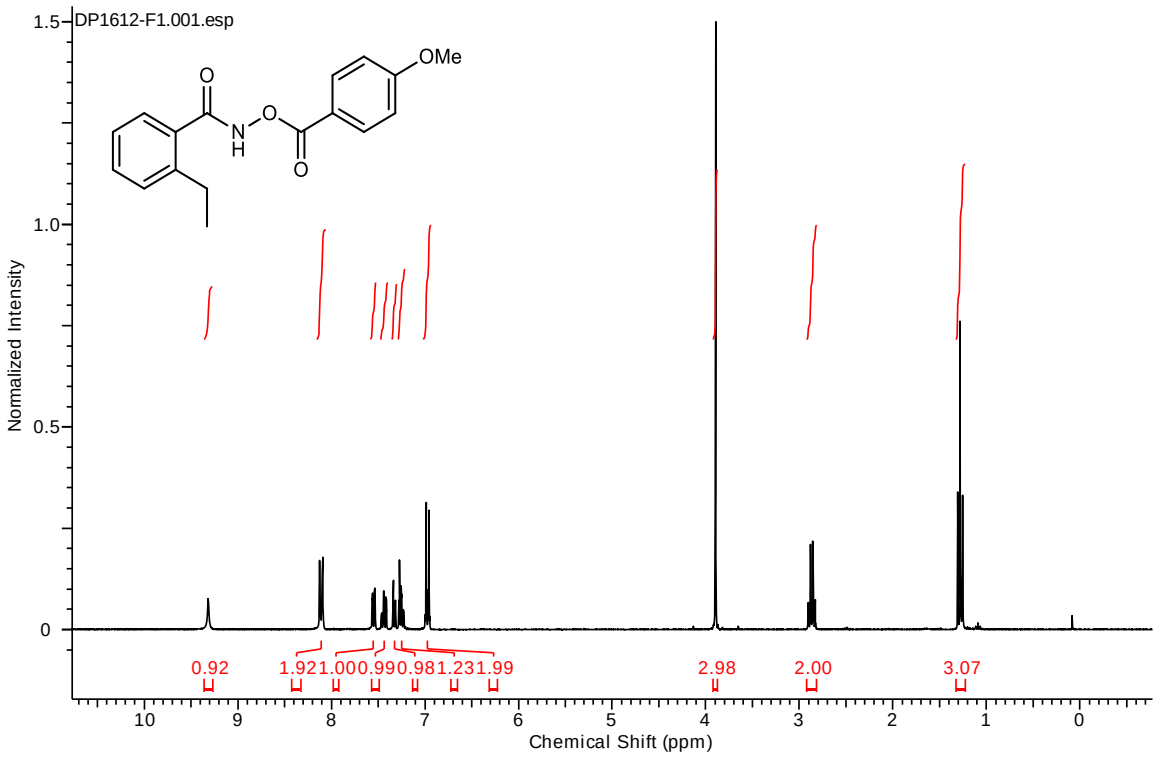

DP1253-charac-carbon.002.esp
132.02
113.87
55.44
19.89
48.77
29.65
33.91
13.76
164.13
166.61
157.76
119.28
Normalized Intensity
Chemical Shift (ppm)

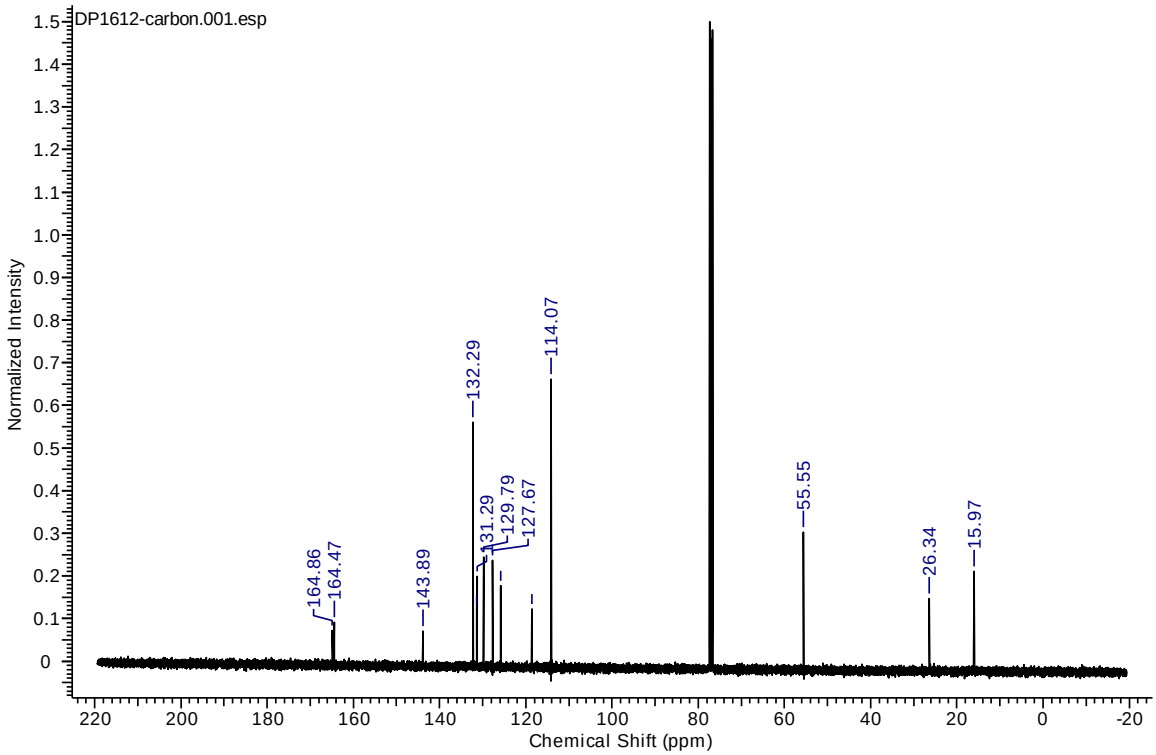

RI11-45-H.001.esp
OMe
O
N
N
H
O
O
OH
Normalized Intensity
0.90
2.00
2.04
1.03
1.03
3.04
1.02
1.06
1.97
1.06
1.09
6.99
Chemical Shift (ppm)

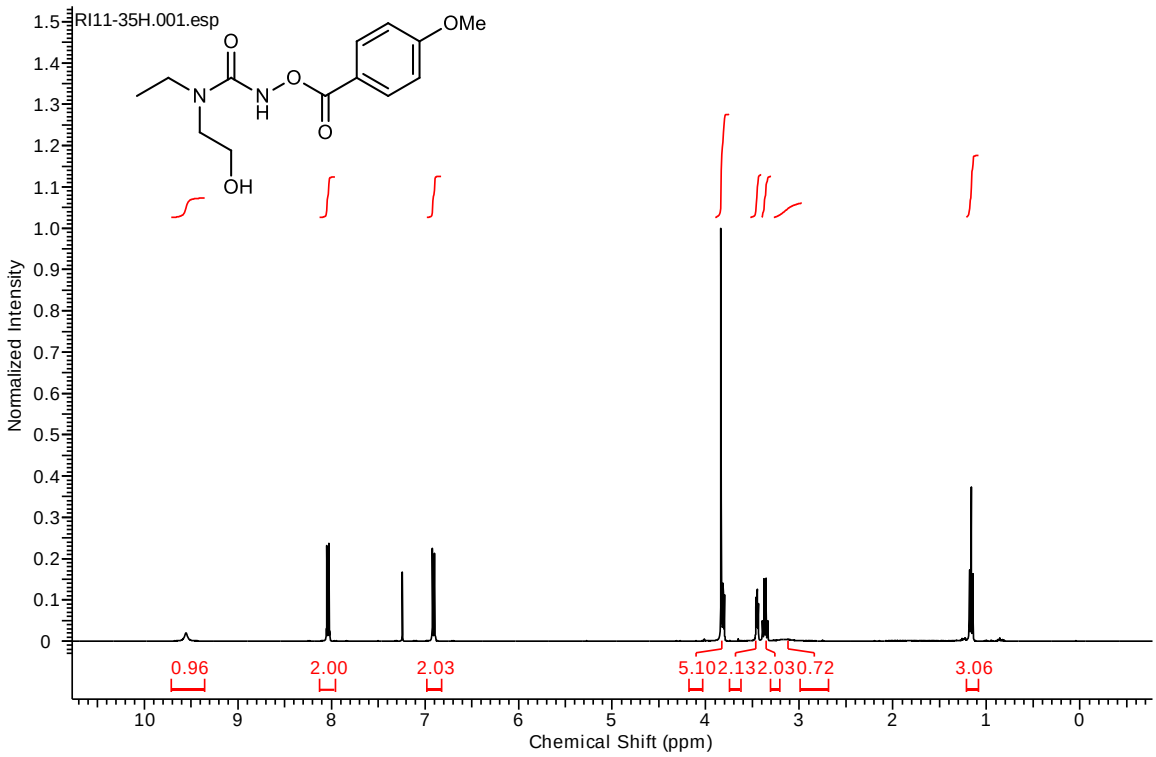

RI11-45-C.001.esp
Normalized Intensity
167.30
164.16
158.12
132.14
119.60
113.92
58.29
55.50
46.89
38.35
31.16
29.13
25.38
19.20
Chemical Shift (ppm)

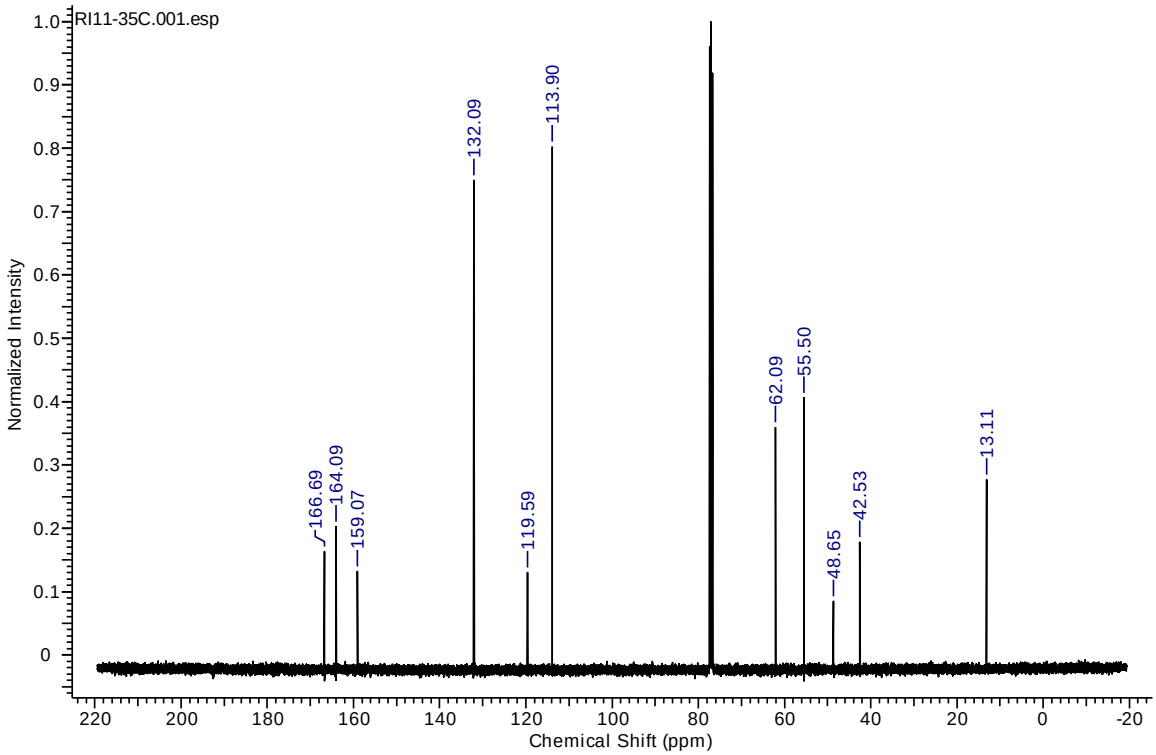

RI13-14-proton.001.esp
O
N
H
OH
Normalized Intensity
1.96
1.12
2.00
0.94
2.00
3.18
Chemical Shift (ppm)

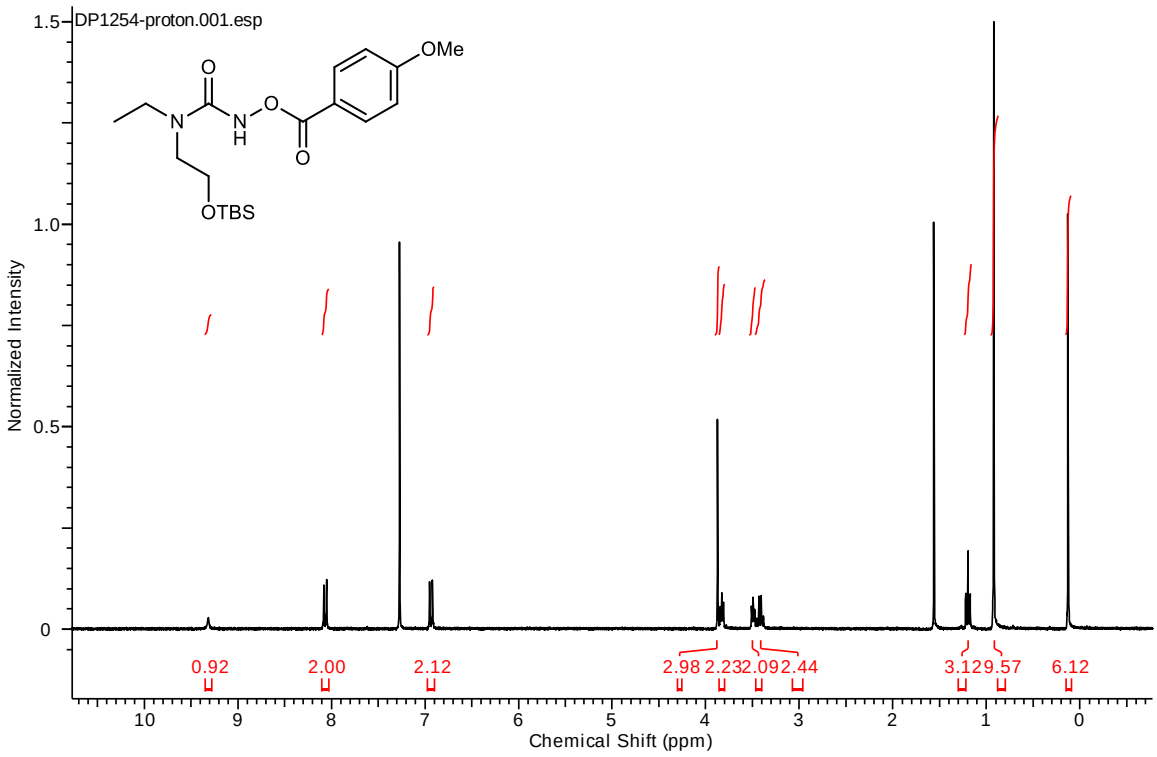

RI13-14-carbon.001.esp
Normalized Intensity
168.80
143.30
131.32
131.04
129.56
127.32
125.83
26.17
15.73
Chemical Shift (ppm)

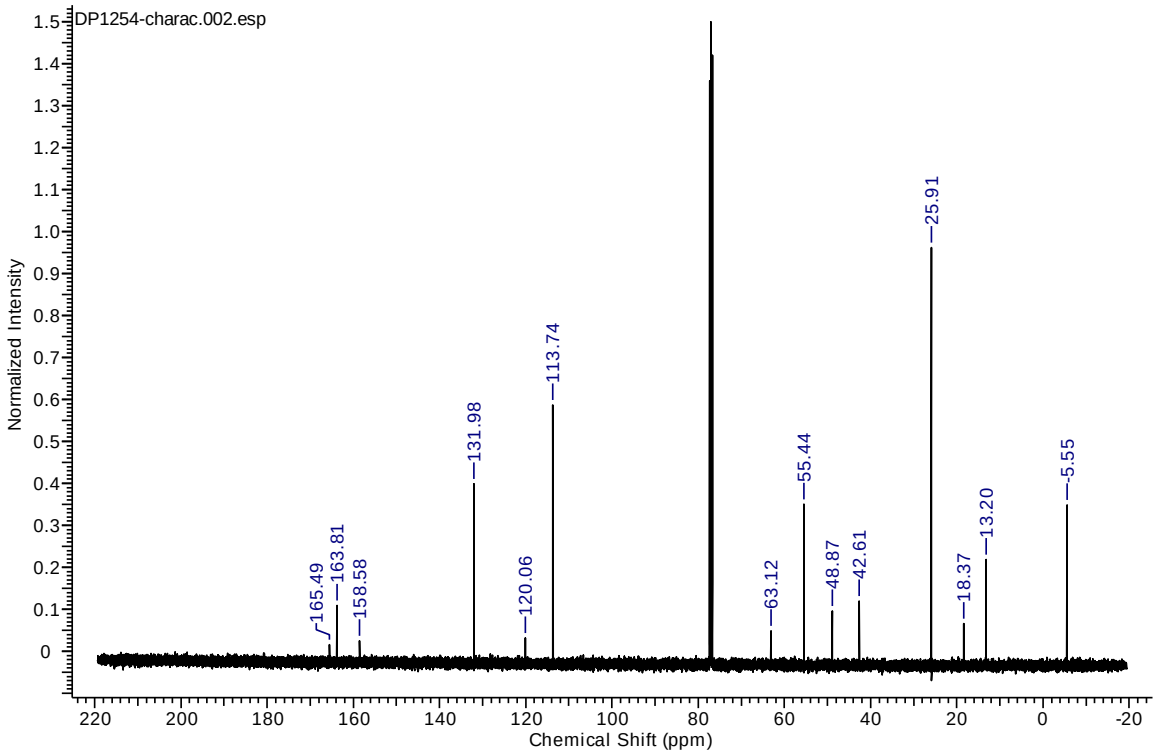

DP1612-F1.001.esp
OMe
O
N
H
O
O
Normalized Intensity
0.92
1.92
1.00
0.99
0.98
1.23
1.99
2.98
2.00
3.07
Chemical Shift (ppm)

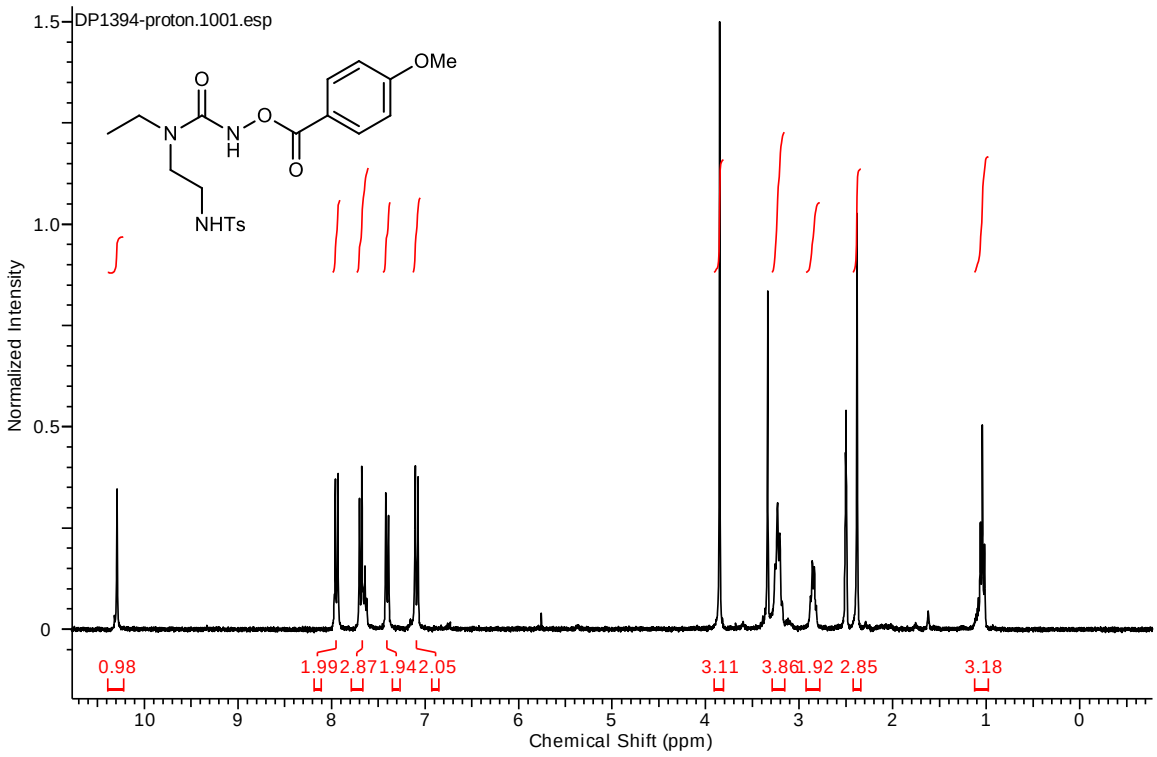

DP1612-carbon.001.esp
Normalized Intensity
164.86
164.47
143.89
132.29
131.29
129.79
127.67
114.07
55.55
26.34
15.97
Chemical Shift (ppm)

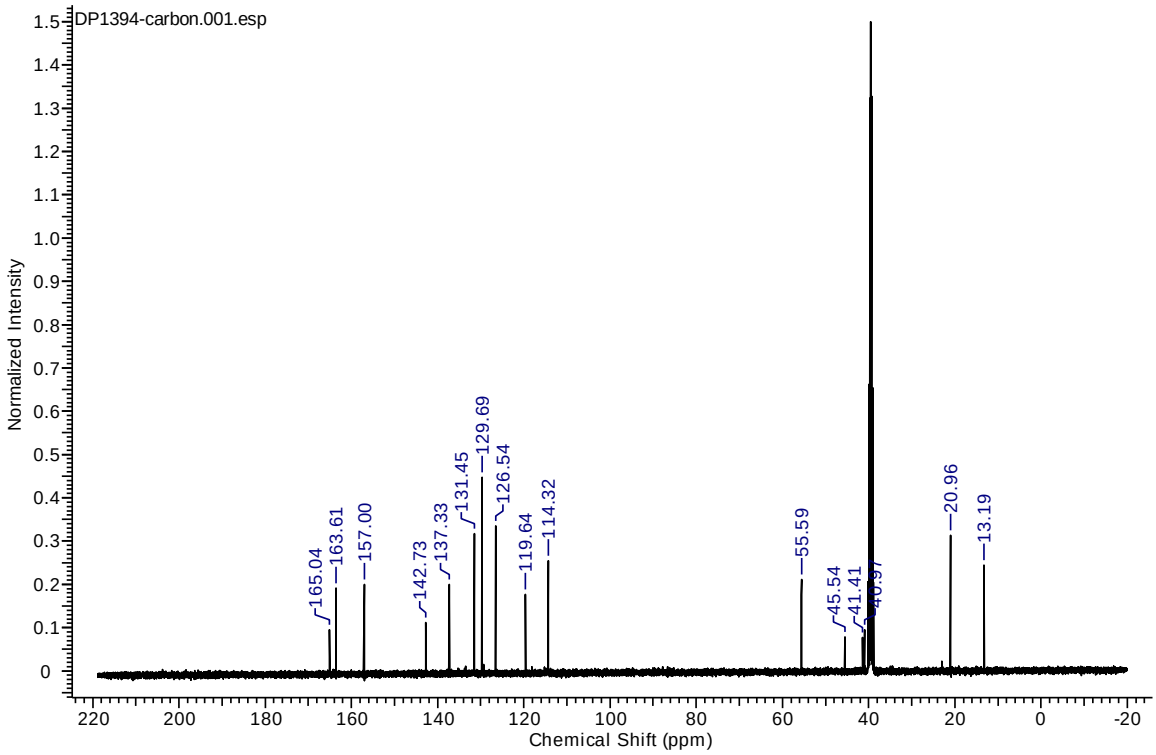

RI11-35H.001.esp
OMe
O
N
O
N
H
O
O
OH
Normalized Intensity
Chemical Shift (ppm)
0.96
2.00
2.03
5.10
2.13
2.03
0.72
3.06

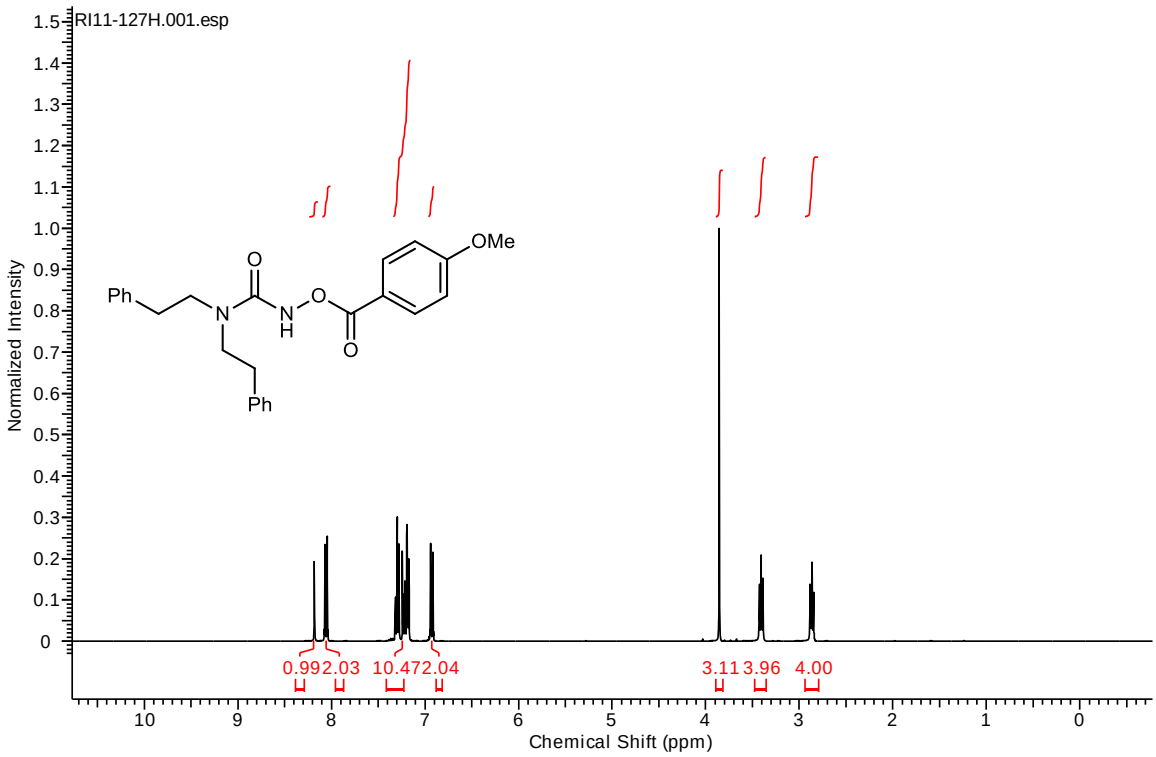

RI11-35C.001.esp
Normalized Intensity
Chemical Shift (ppm)
166.69
164.09
159.07
132.09
119.59
113.90
62.09
55.50
48.65
42.53
13.11

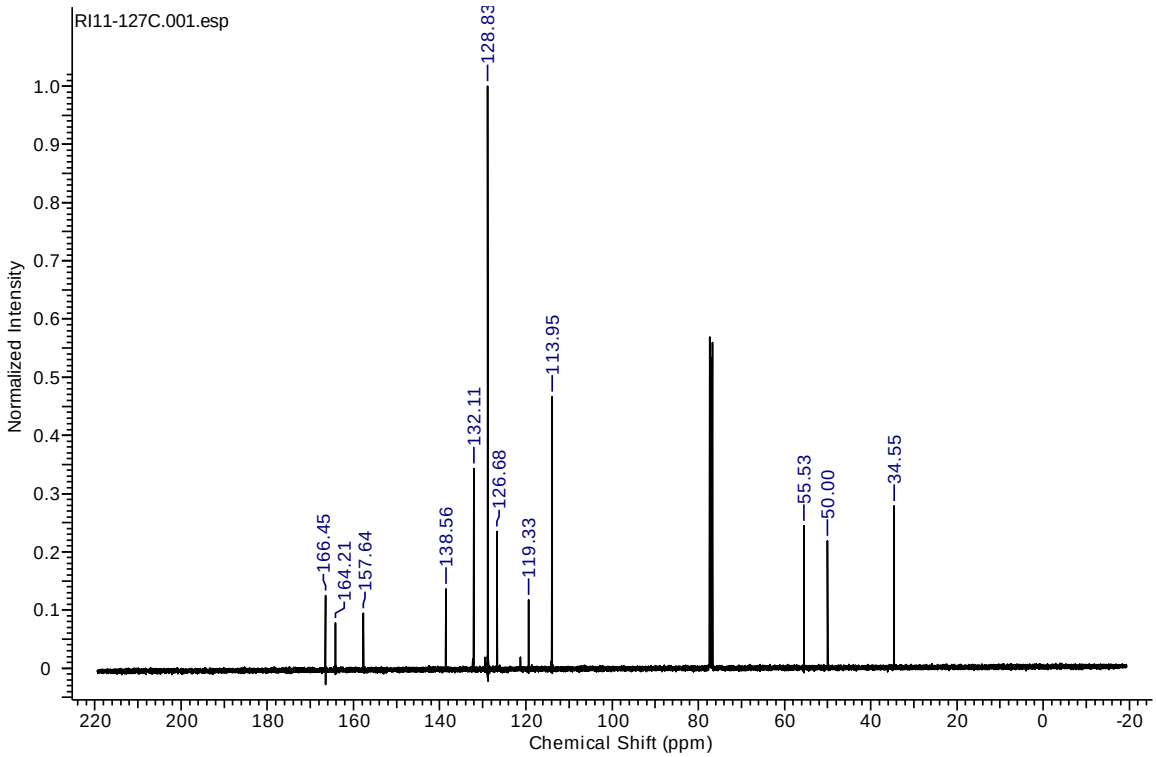

DP1254-proton.001.esp
OMe
O
N
O
N
H
O
O
OTBS
Normalized Intensity
1.5
1.0
0.5
0
0.92
2.00
2.12
2.98
2.23
2.09
2.44
3.12
9.57
6.12
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

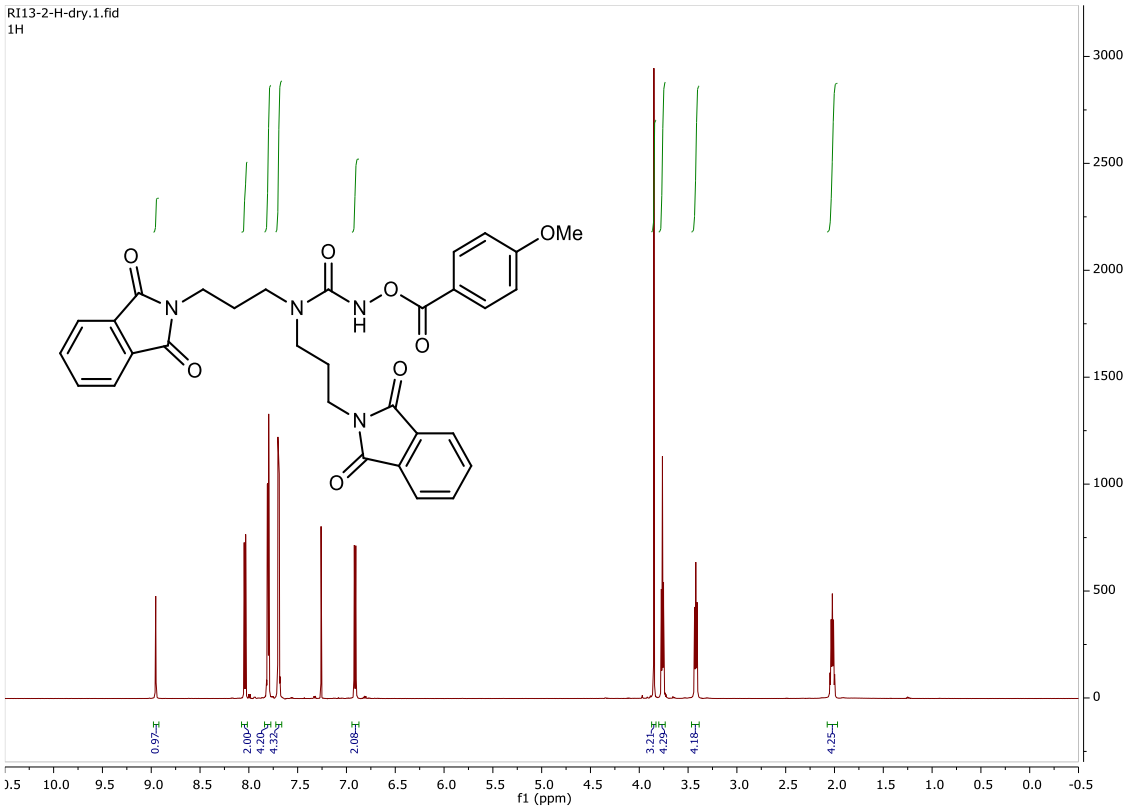

DP1254-charac.002.esp
Normalized Intensity
165.49
163.81
158.58
131.98
120.06
113.74
63.12
55.44
48.87
42.61
25.91
18.37
13.20
-5.55
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

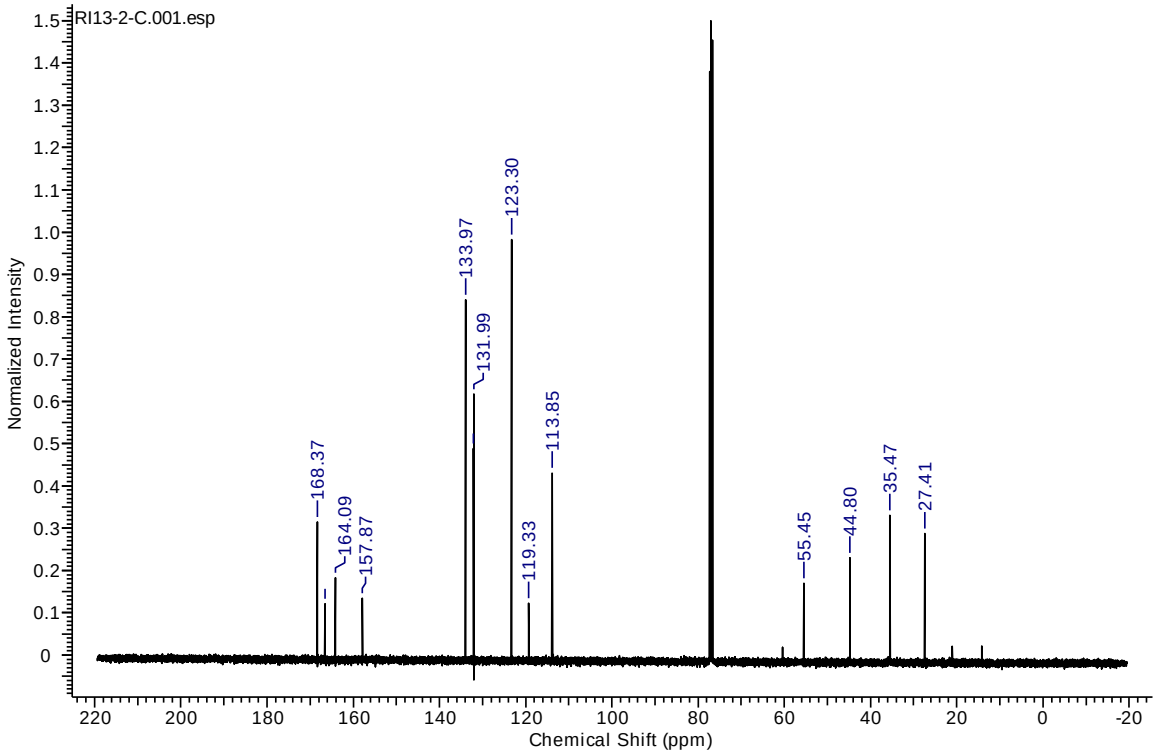

DP1394-proton.1001.esp
OMe
O
N
O
N
H
O
NHTs
Normalized Intensity
1.5
1.0
0.5
0
0.98
1.99
2.87
1.94
2.05
3.11
3.86
1.92
2.85
3.18
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

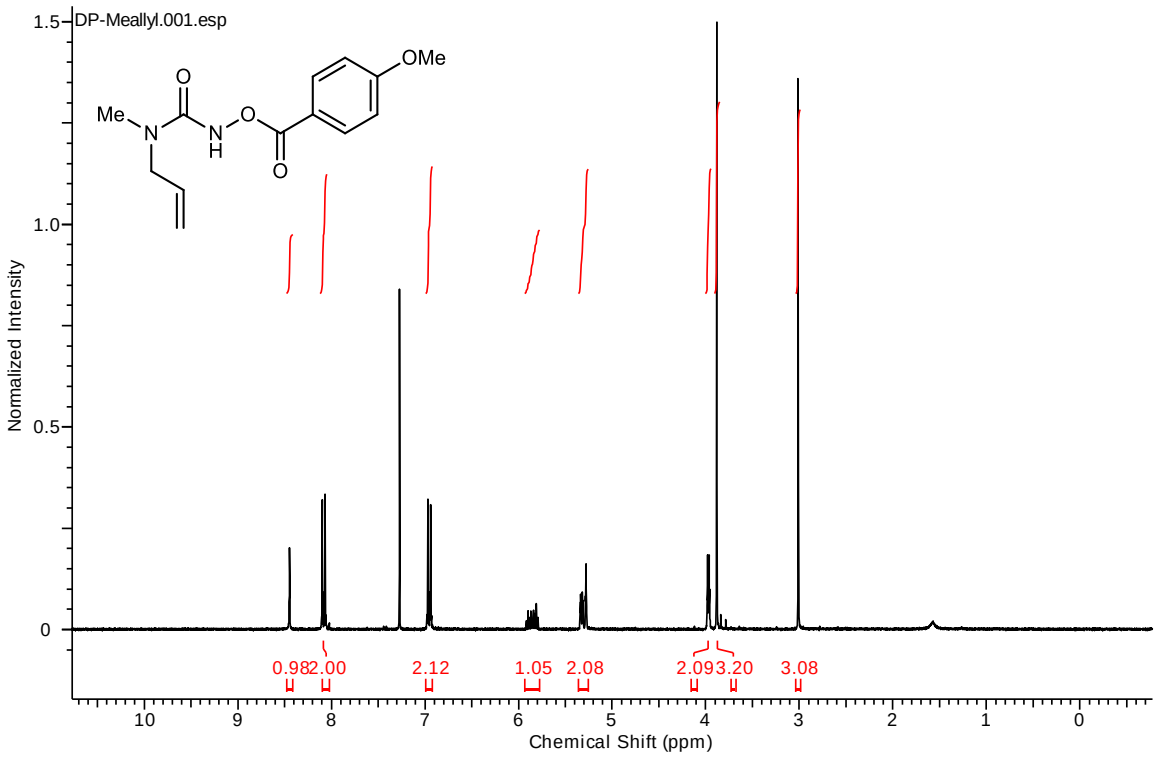

DP1394-carbon.001.esp
Normalized Intensity
165.04
163.61
157.00
142.73
137.33
131.45
129.69
126.54
119.64
114.32
55.59
45.54
41.41
40.97
20.96
13.19
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

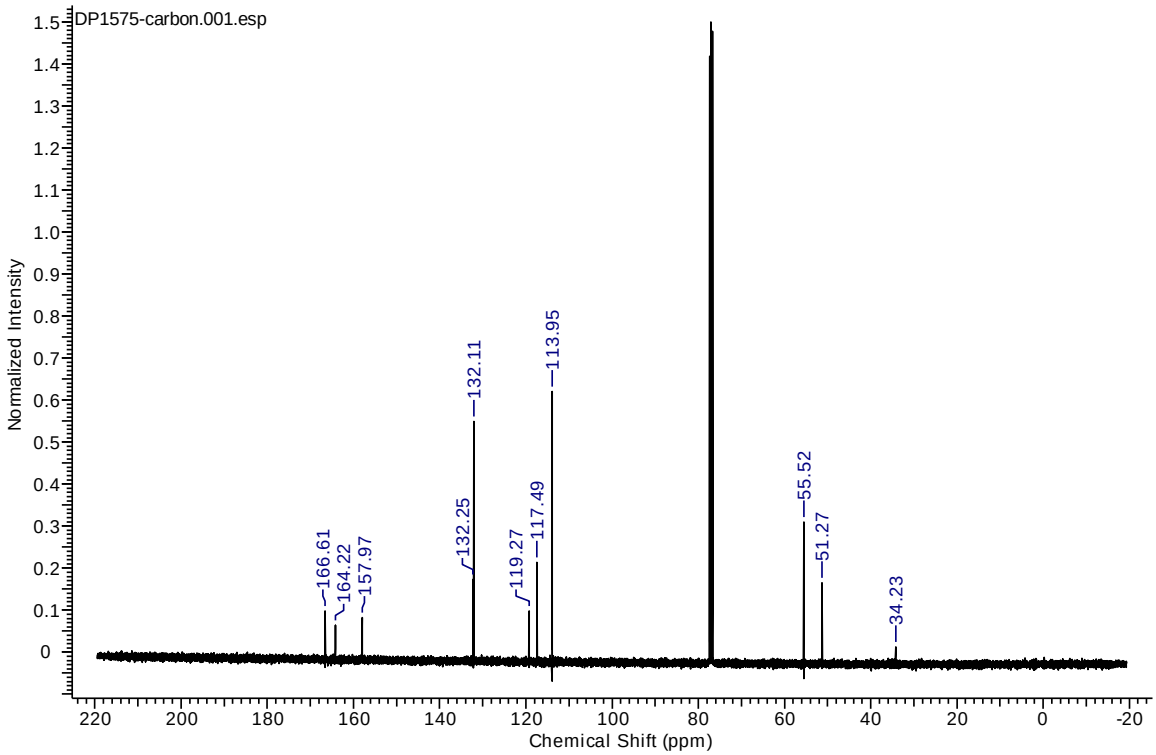

RI11-127H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.99
2.03
10.47
2.04
3.11
3.96
4.00
OMe
Ph
Ph
O
N
H
O
O
O

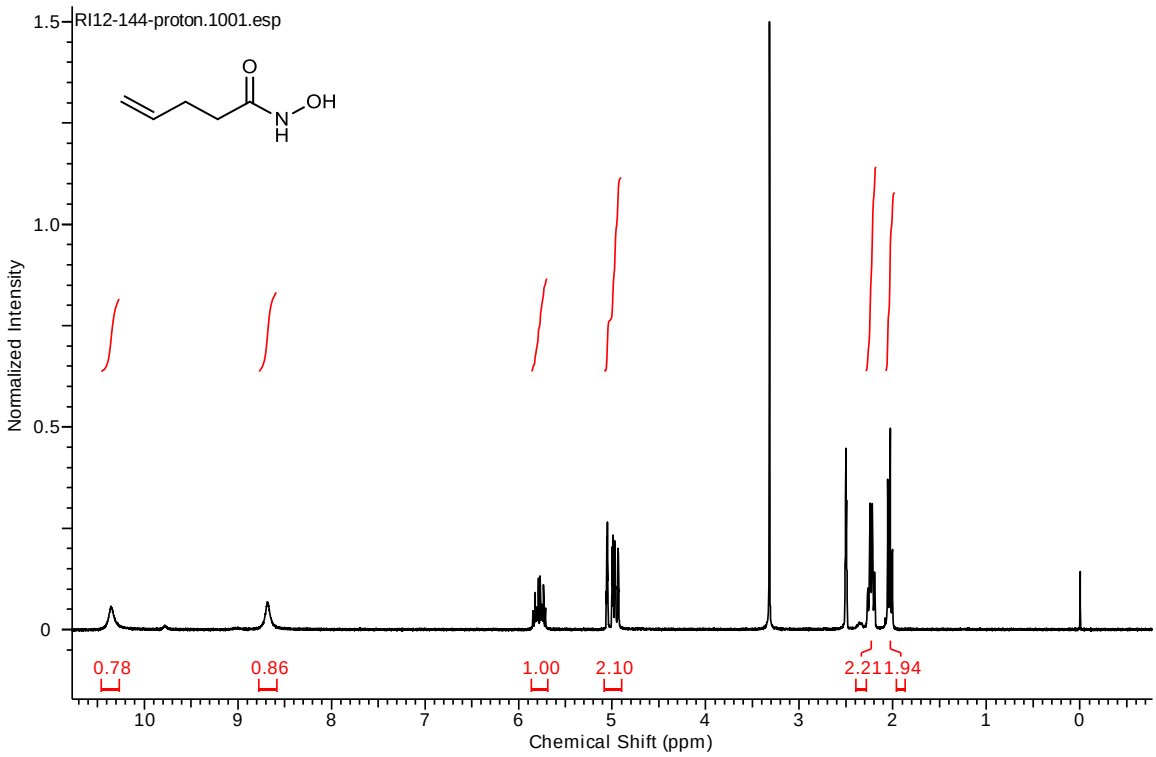

RI11-127C.001.esp
Normalized Intensity
Chemical Shift (ppm)
166.45
164.21
157.64
138.56
132.11
128.83
126.68
119.33
113.95
55.53
50.00
34.55

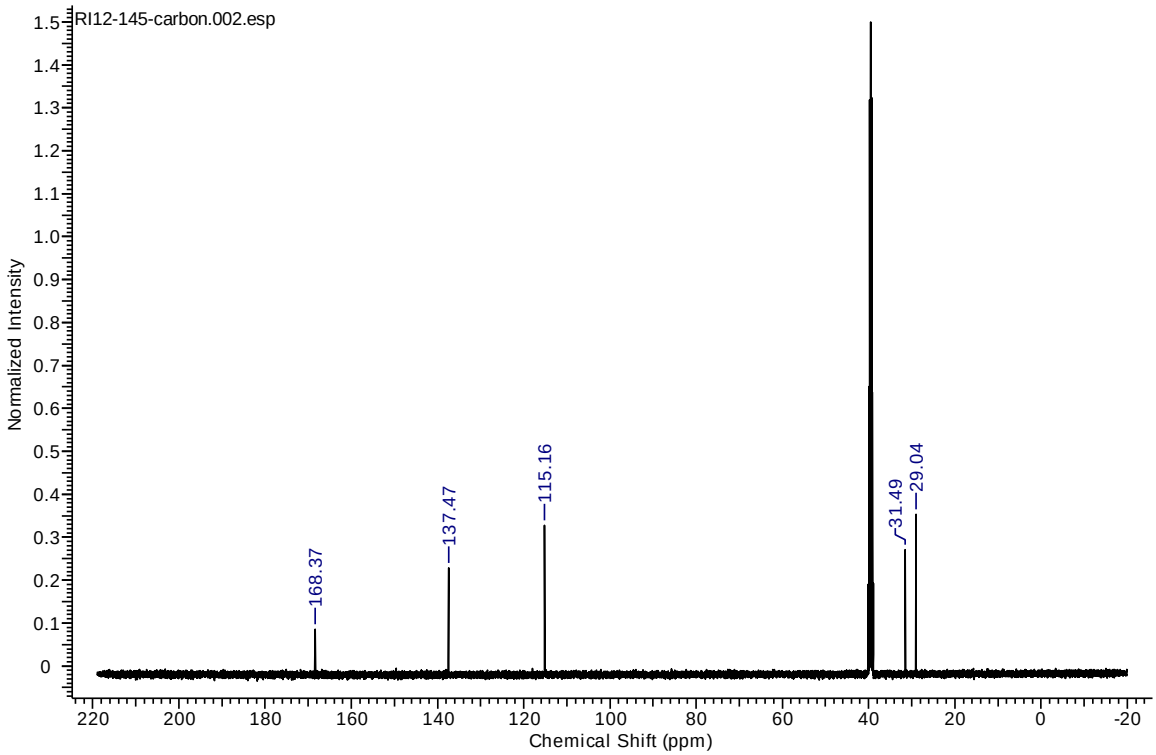

RI13-2-H-dry.1.fid
1H
OMe
f1 (ppm)

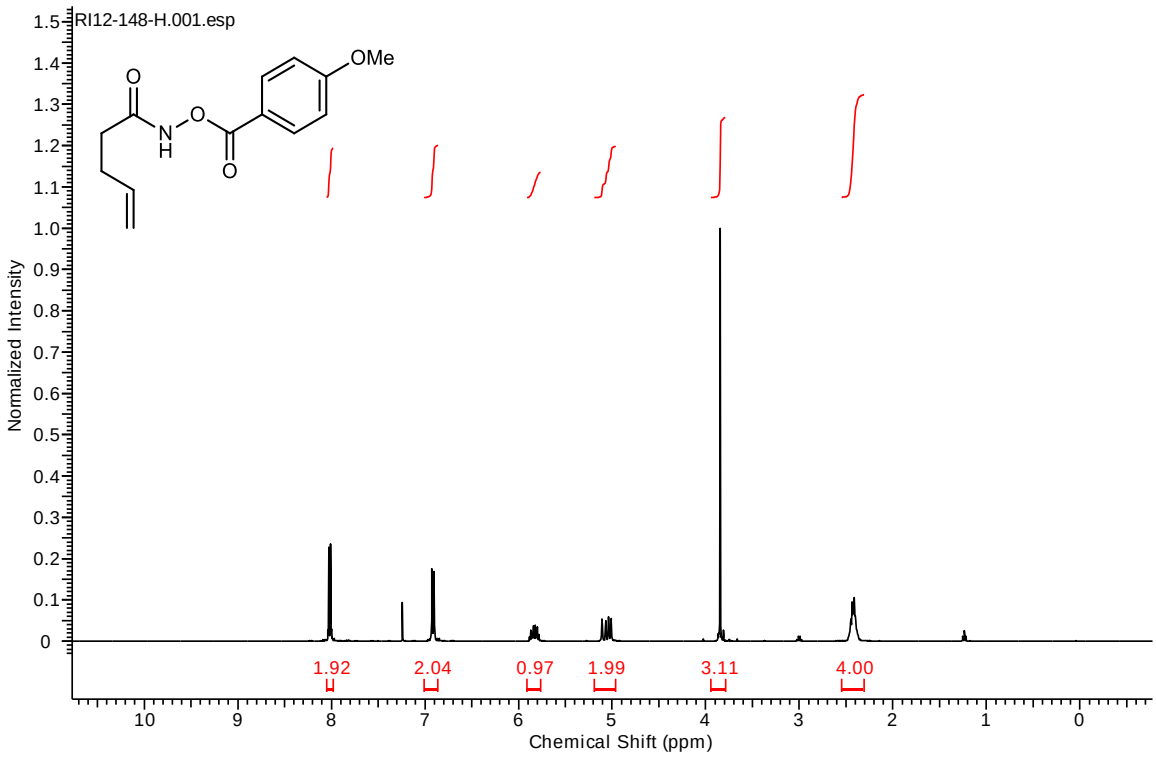

RI13-2-C.001.esp
Normalized Intensity
168.37
164.09
157.87
133.97
131.99
123.30
119.33
113.85
55.45
44.80
35.47
27.41
Chemical Shift (ppm)

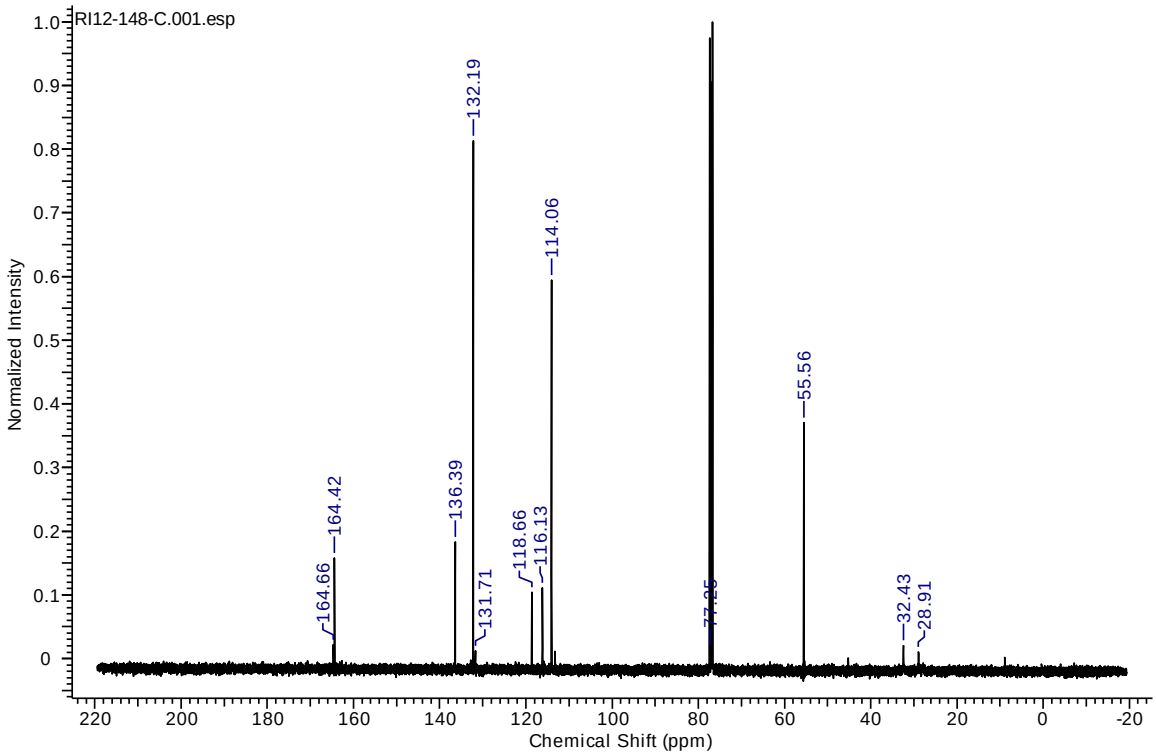

DP-Meallyl.001.esp
OMe
Me
N
O
N
H
O
O
Normalized Intensity
0.98
2.00
2.12
1.05
2.08
2.09
3.20
3.08
Chemical Shift (ppm)

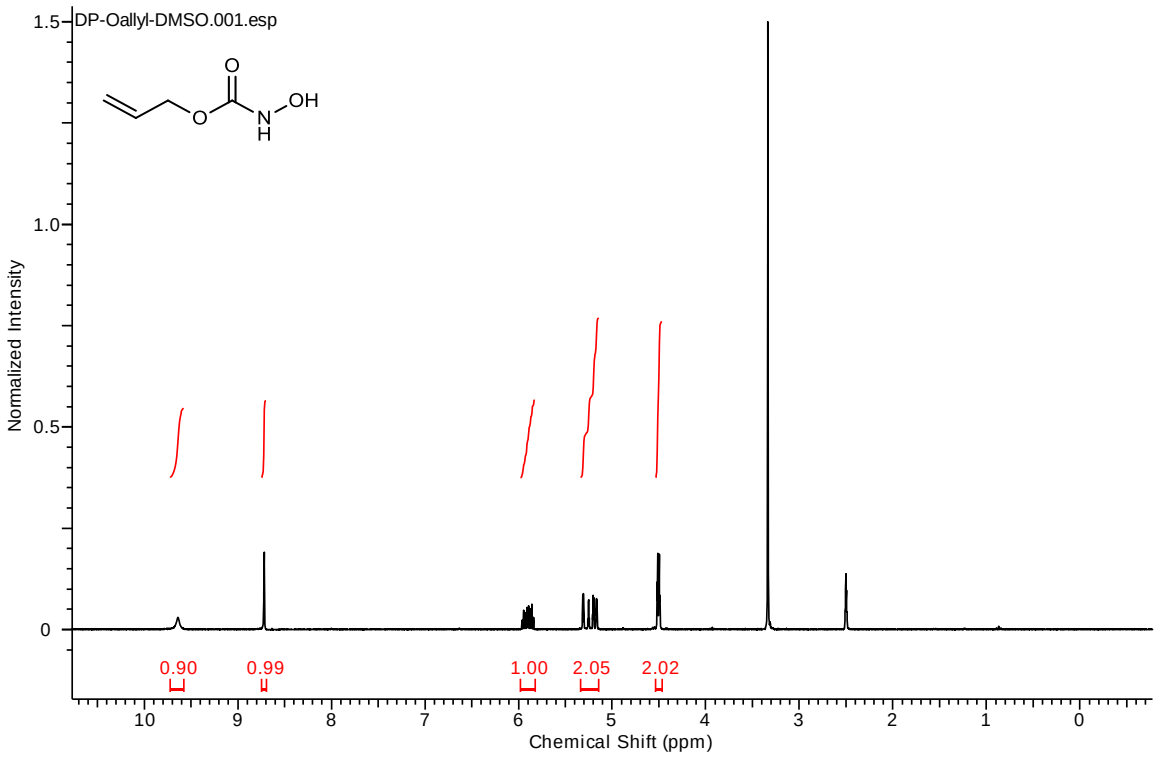

DP1575-carbon.001.esp
Normalized Intensity
166.61
164.22
157.97
132.25
132.11
119.27
117.49
113.95
55.52
51.27
34.23
Chemical Shift (ppm)

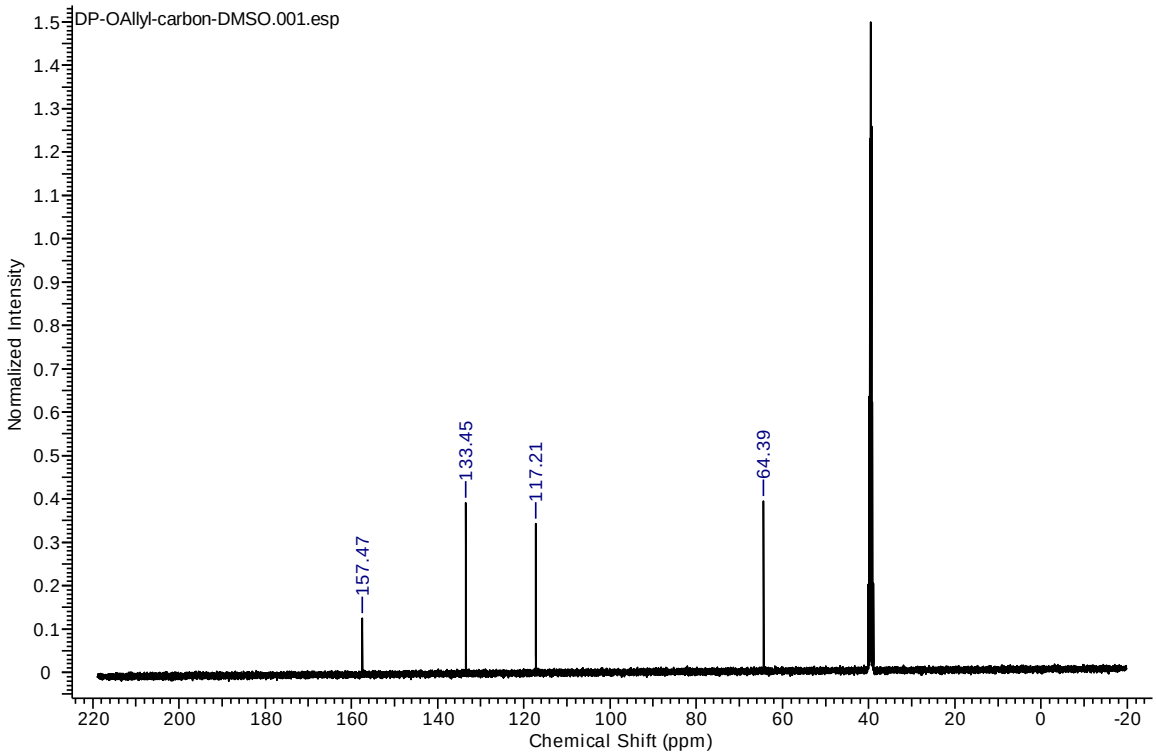

RI12-144-proton.1001.esp
O
N
H
OH
Normalized Intensity
1.5
1.0
0.5
0
0.78
0.86
1.00
2.10
2.21
1.94
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

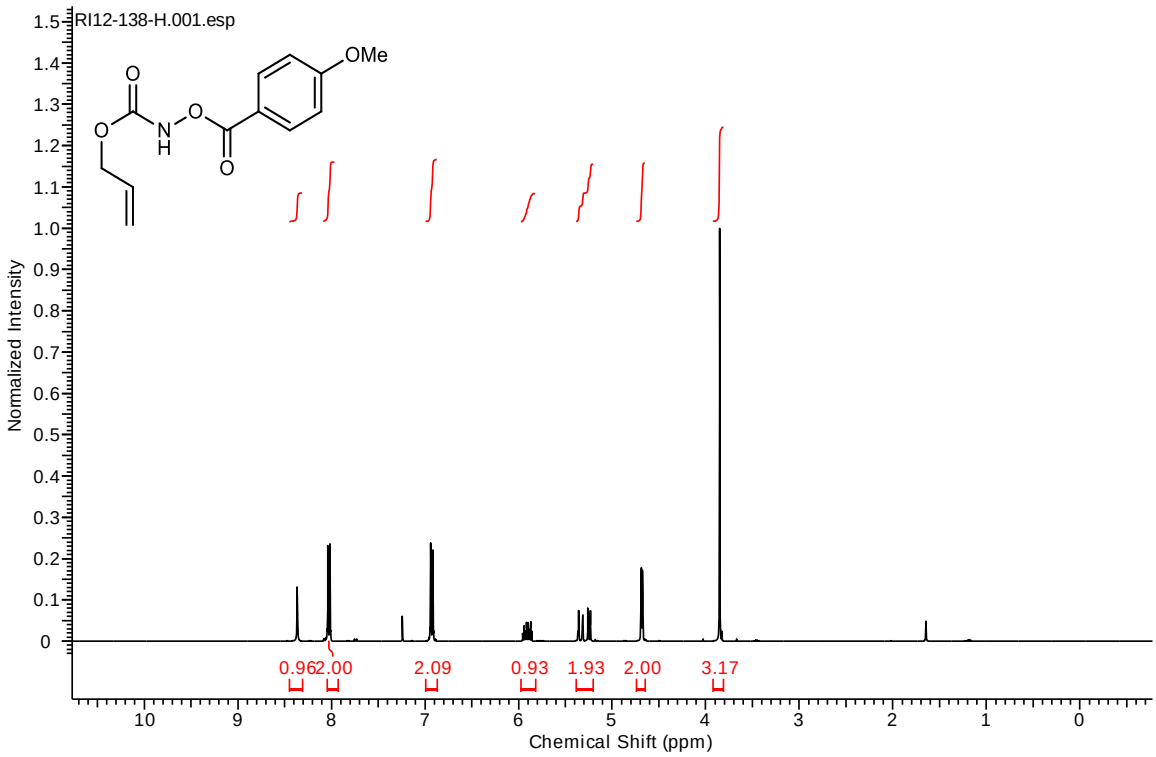

RI12-145-carbon.002.esp
Normalized Intensity
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
168.37
137.47
115.16
31.49
29.04
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

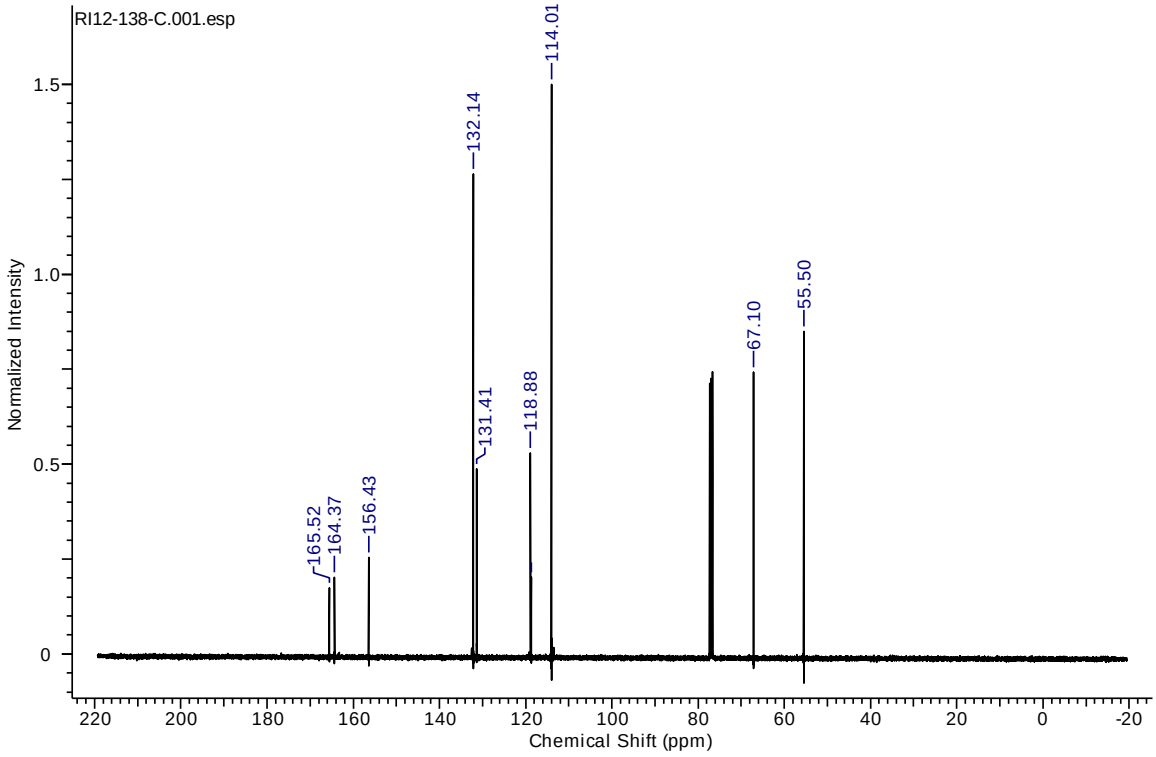

RI12-148-H.001.esp
OMe
O
N
H
O
O
Normalized Intensity
1.92
2.04
0.97
1.99
3.11
4.00
Chemical Shift (ppm)

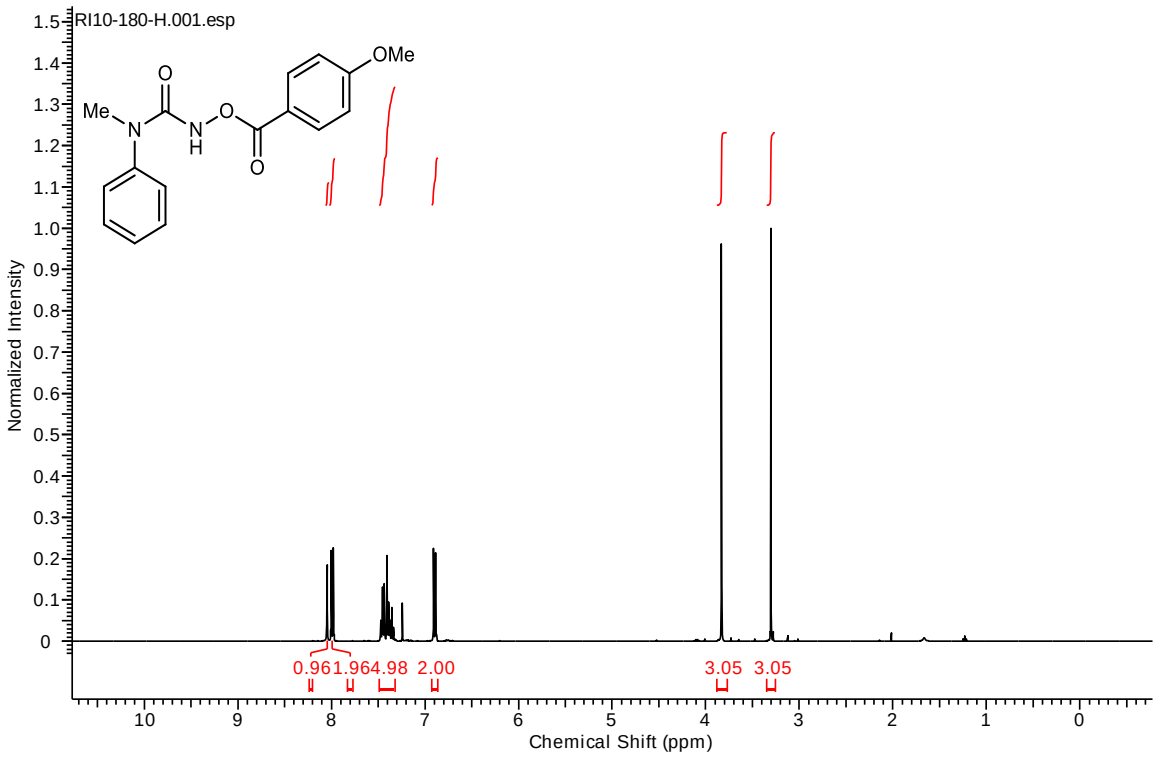

RI12-148-C.001.esp
132.19
114.06
55.56
164.42
136.39
118.66
116.13
164.66
131.71
77.05
32.43
28.91
Normalized Intensity
Chemical Shift (ppm)

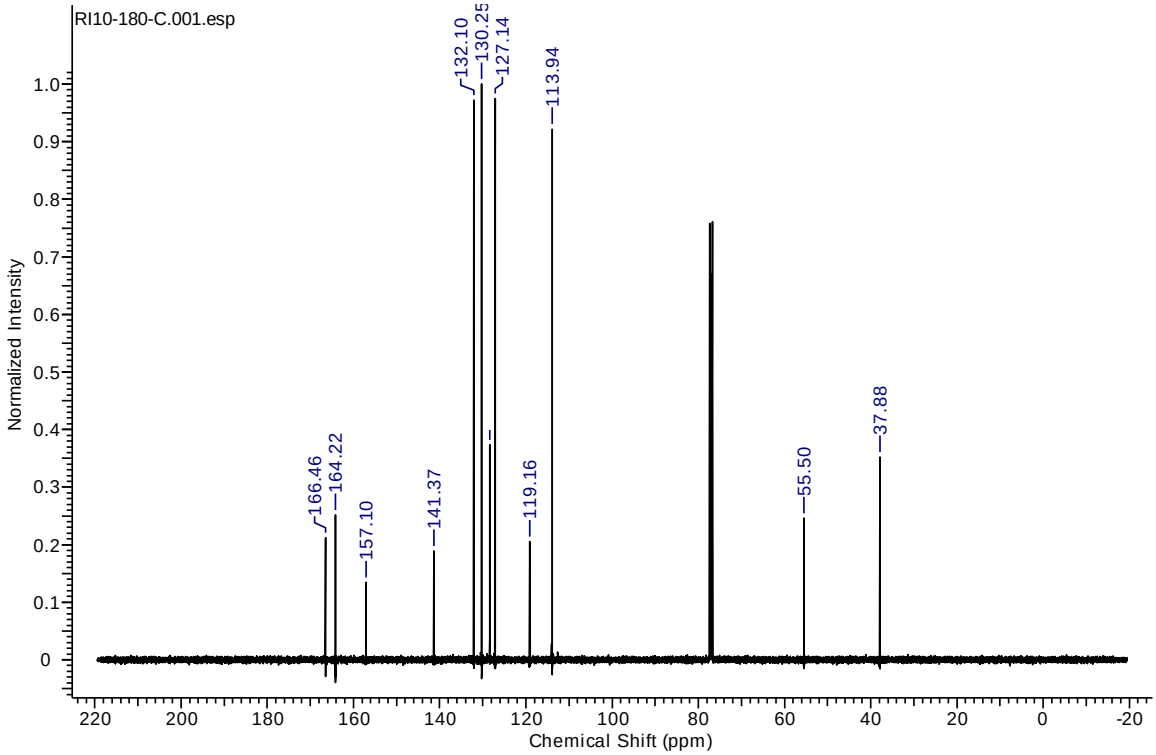

DP-Oallyl-DMSO.001.esp
O
O
N
H
OH
Normalized Intensity
1.5
1.0
0.5
0
0.90
0.99
1.00
2.05
2.02
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

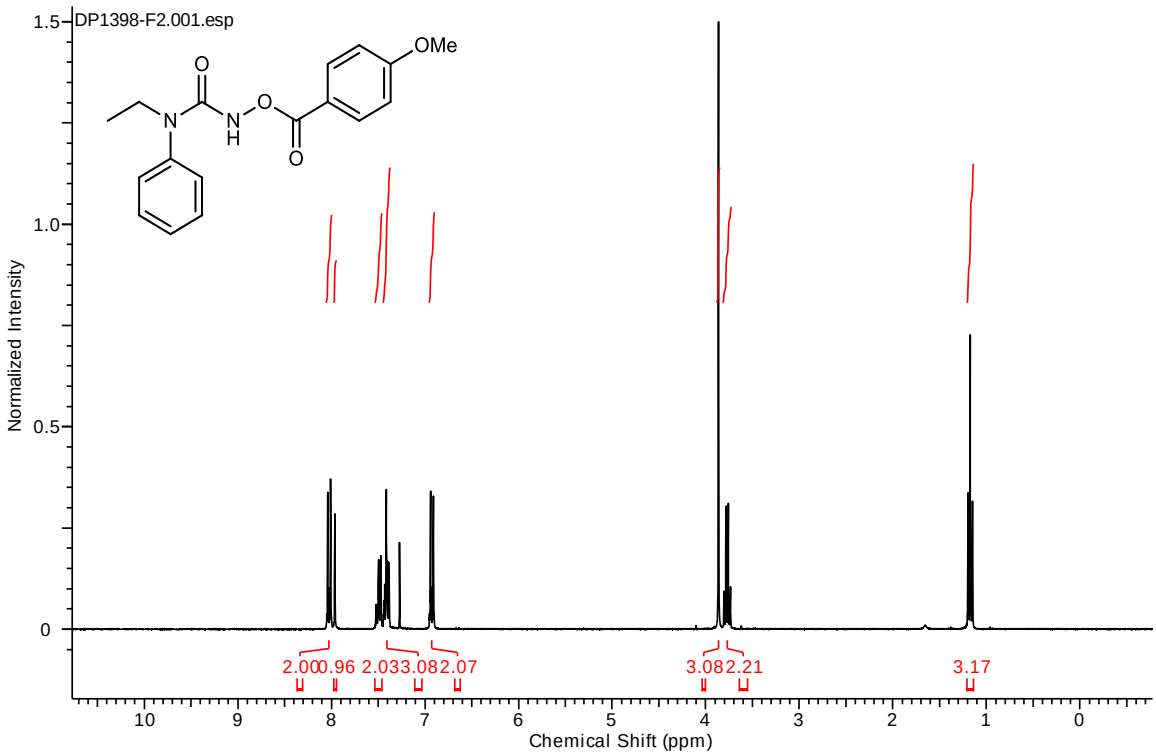

DP-OAllyl-carbon-DMSO.001.esp
Normalized Intensity
157.47
133.45
117.21
64.39
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

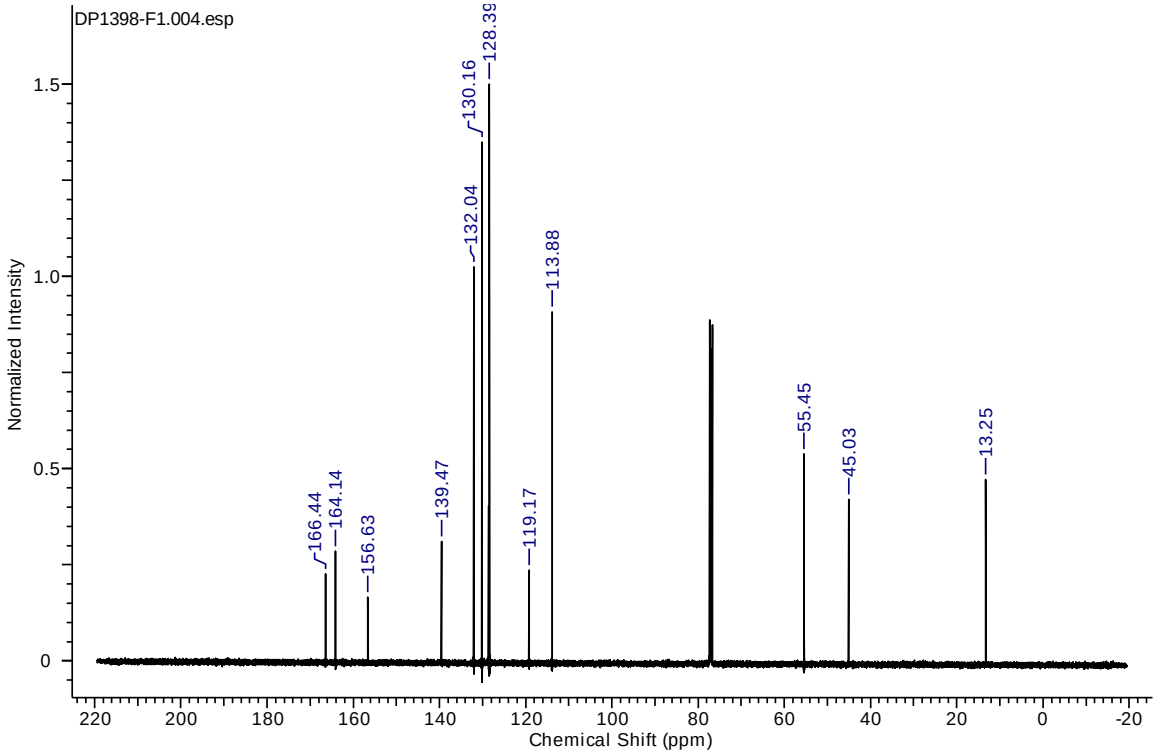

RI12-138-H.001.esp
OMe
O
O
N
H
O
O
O
Normalized Intensity
0.96
2.00
2.09
0.93
1.93
2.00
3.17
Chemical Shift (ppm)

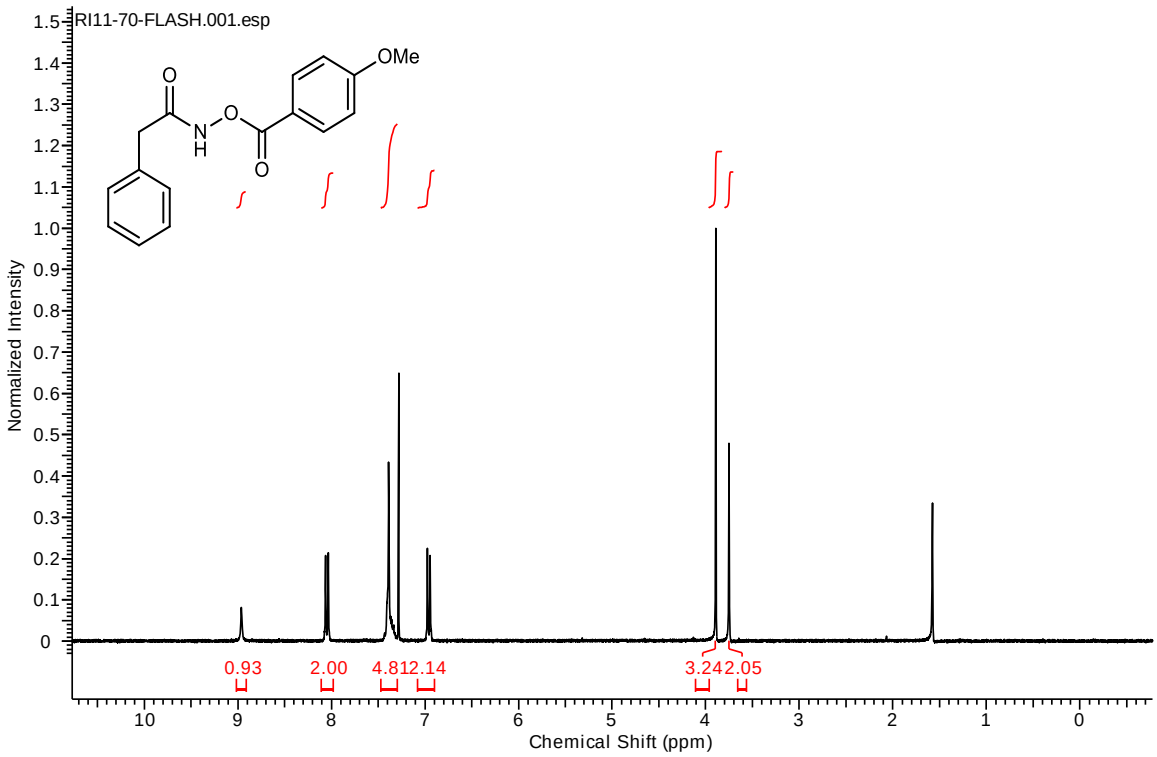

RI12-138-C.001.esp
114.01
132.14
131.41
118.88
67.10
55.50
165.52
164.37
156.43
Normalized Intensity
Chemical Shift (ppm)

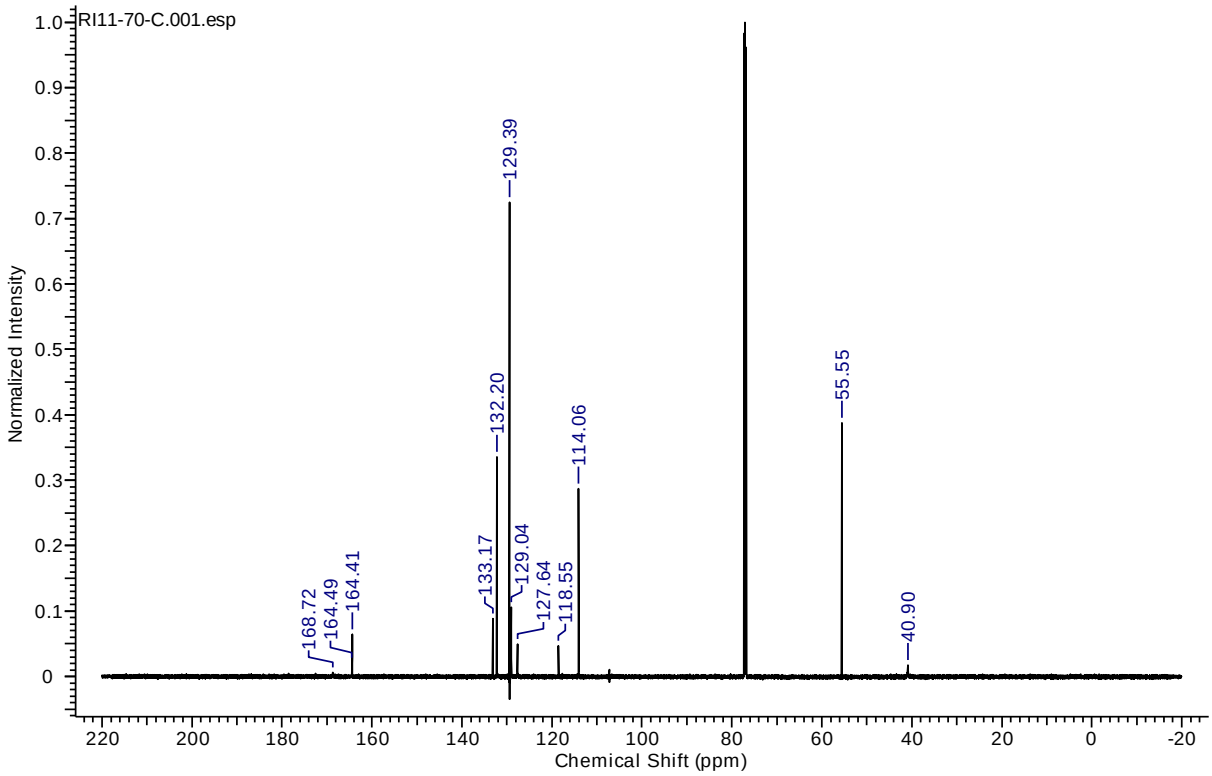

RI10-180-H.001.esp
OMe
Me
N
O
N
H
O
O
Normalized Intensity
0.96
1.96
4.98
2.00
3.05
3.05
Chemical Shift (ppm)

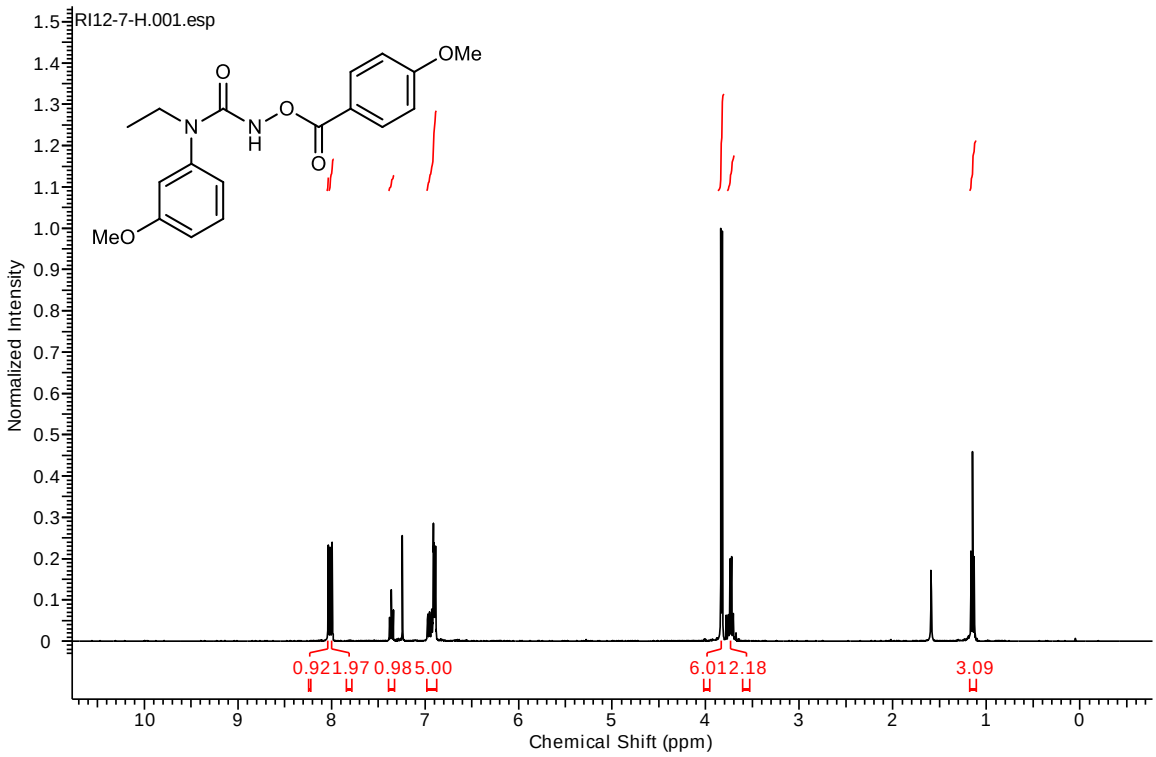

RI10-180-C.001.esp
132.10
130.25
127.14
113.94
166.46
164.22
157.10
141.37
119.16
55.50
37.88
Normalized Intensity
Chemical Shift (ppm)

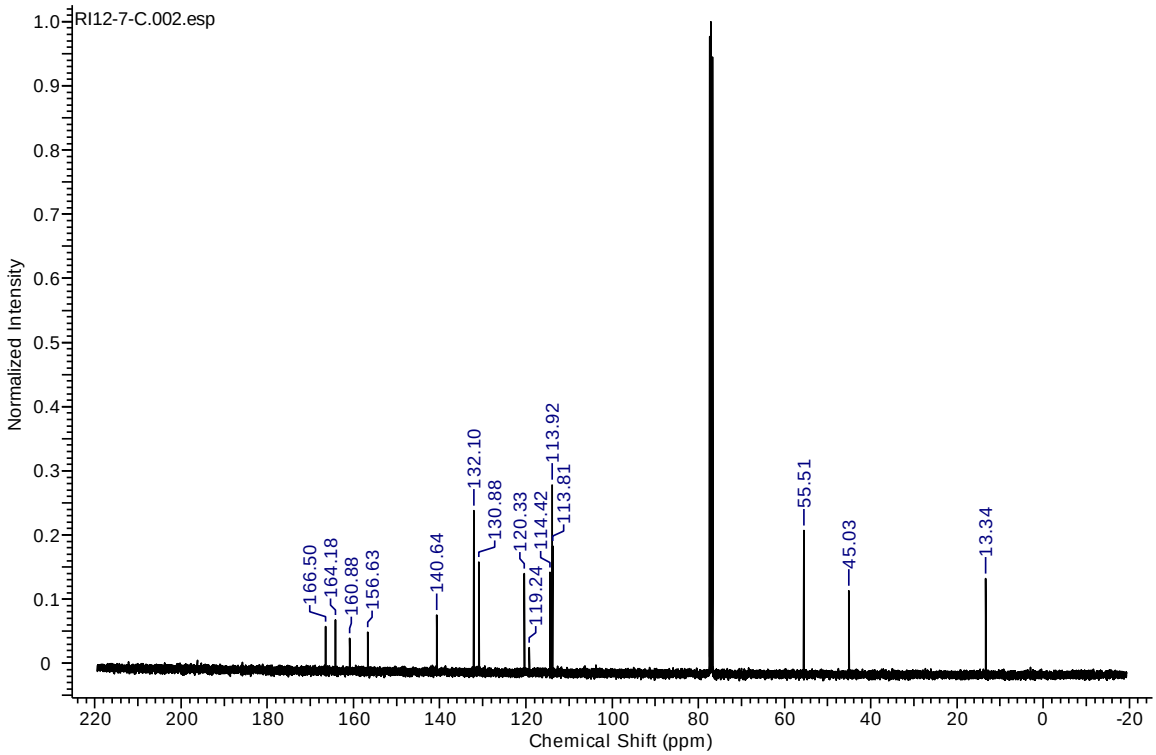

DP1398-F2.001.esp
OMe
O
N
O
N
H
O
O
Normalized Intensity
1.5
1.0
0.5
0
2.00
0.96
2.03
3.08
2.07
3.08
2.21
3.17
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

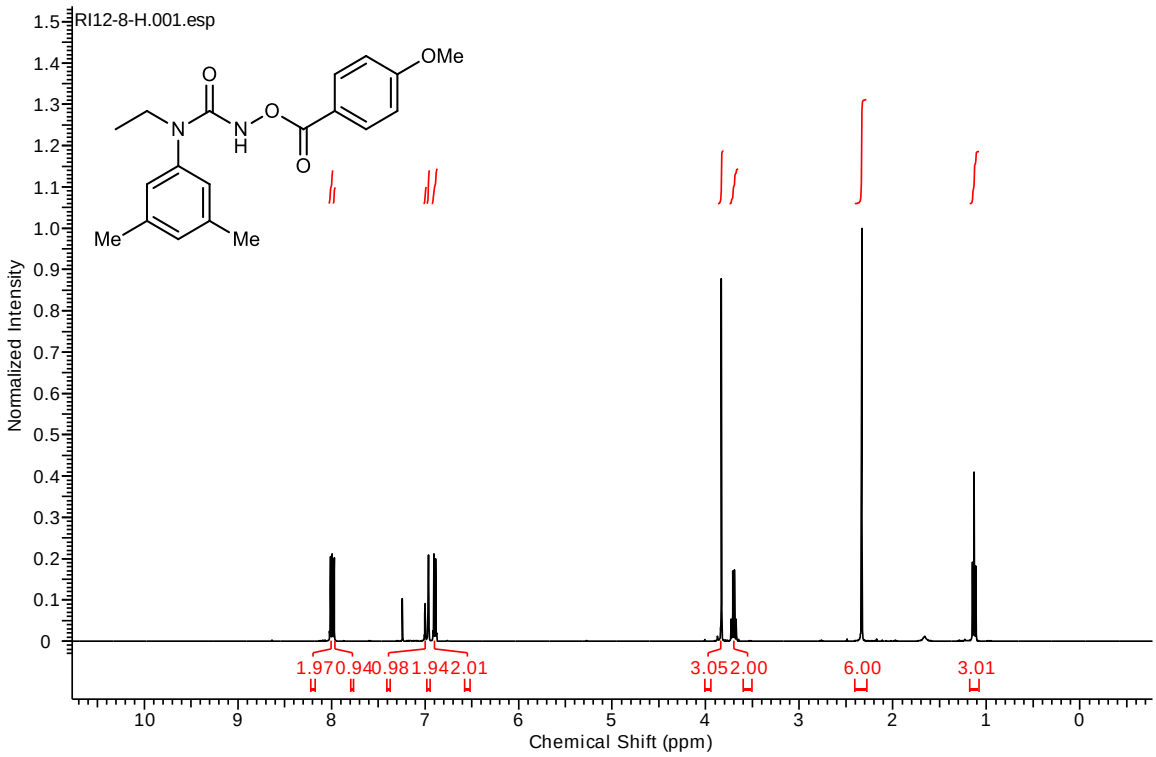

DP1398-F1.004.esp
Normalized Intensity
1.5
1.0
0.5
0
166.44
164.14
156.63
139.47
132.04
130.16
128.39
119.17
113.88
55.45
45.03
13.25
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

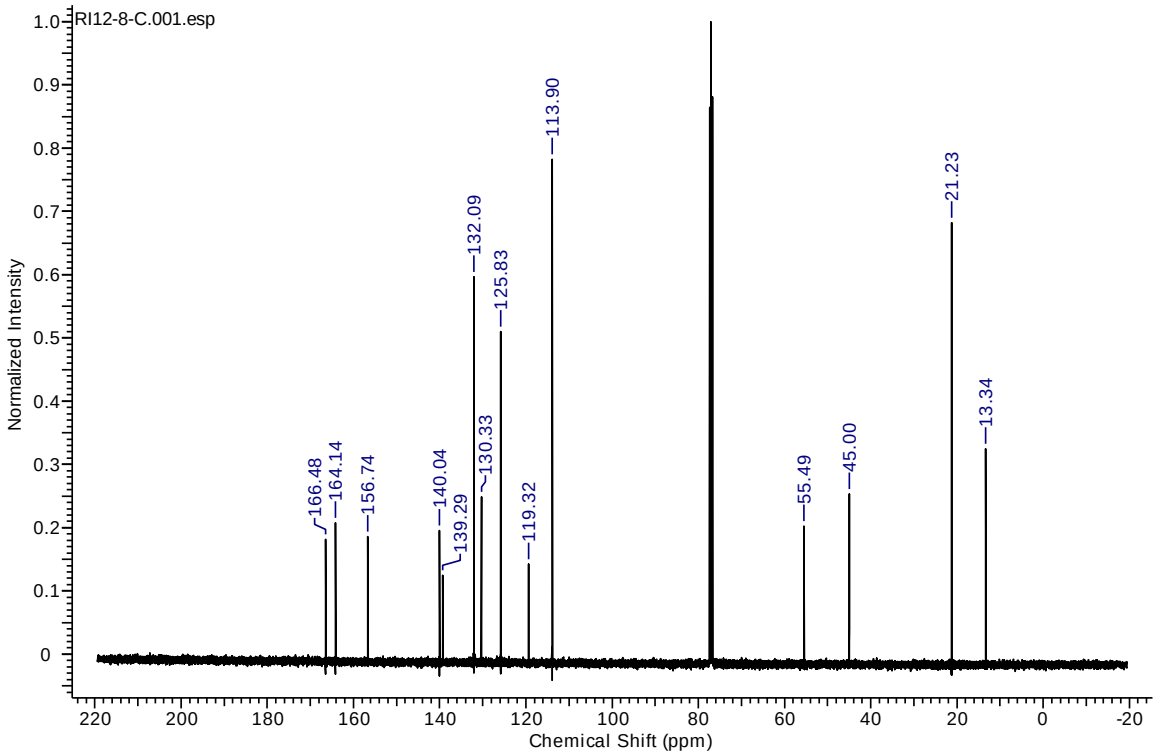

RI11-70-FLASH.001.esp
OMe
O
N
H
O
O
Normalized Intensity
0.93
2.00
4.81
2.14
3.24
2.05
Chemical Shift (ppm)

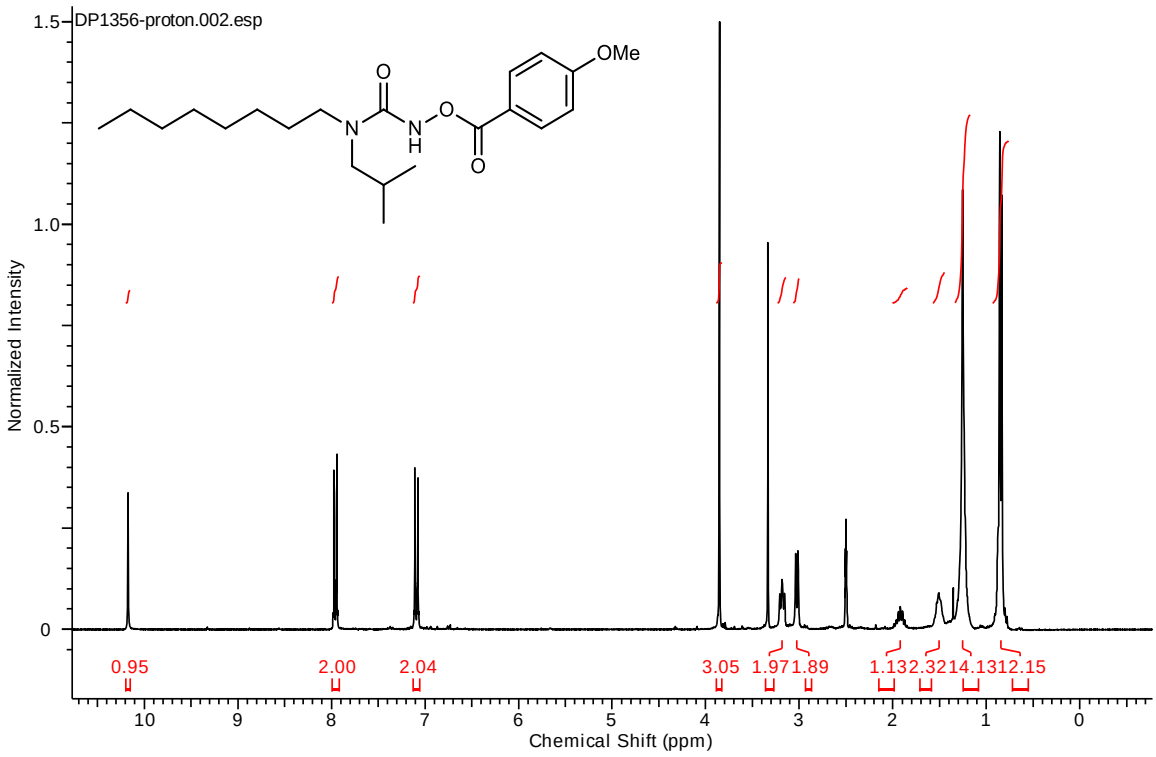

RI11-70-C.001.esp
Normalized Intensity
168.72
164.49
164.41
133.17
132.20
129.39
129.04
127.64
118.55
114.06
55.55
40.90
Chemical Shift (ppm)

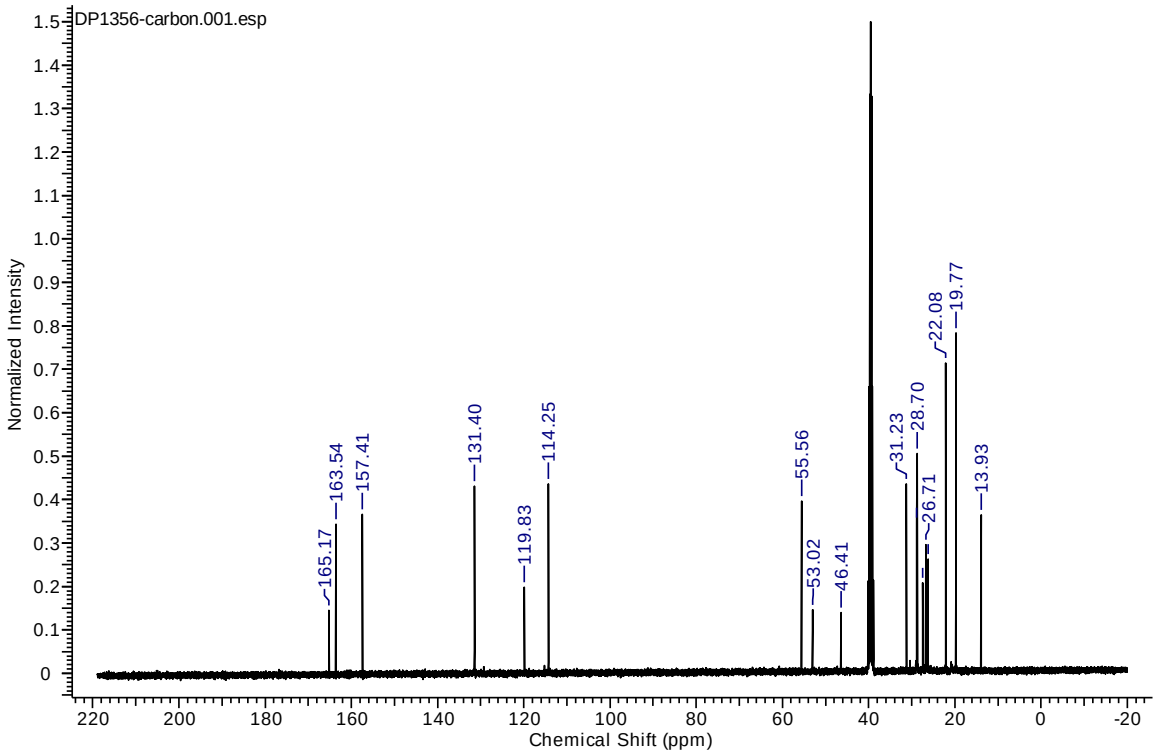

RI12-7-H.001.esp
OMe
MeO
Normalized Intensity
0.92
1.97
0.98
5.00
6.01
2.18
3.09
Chemical Shift (ppm)

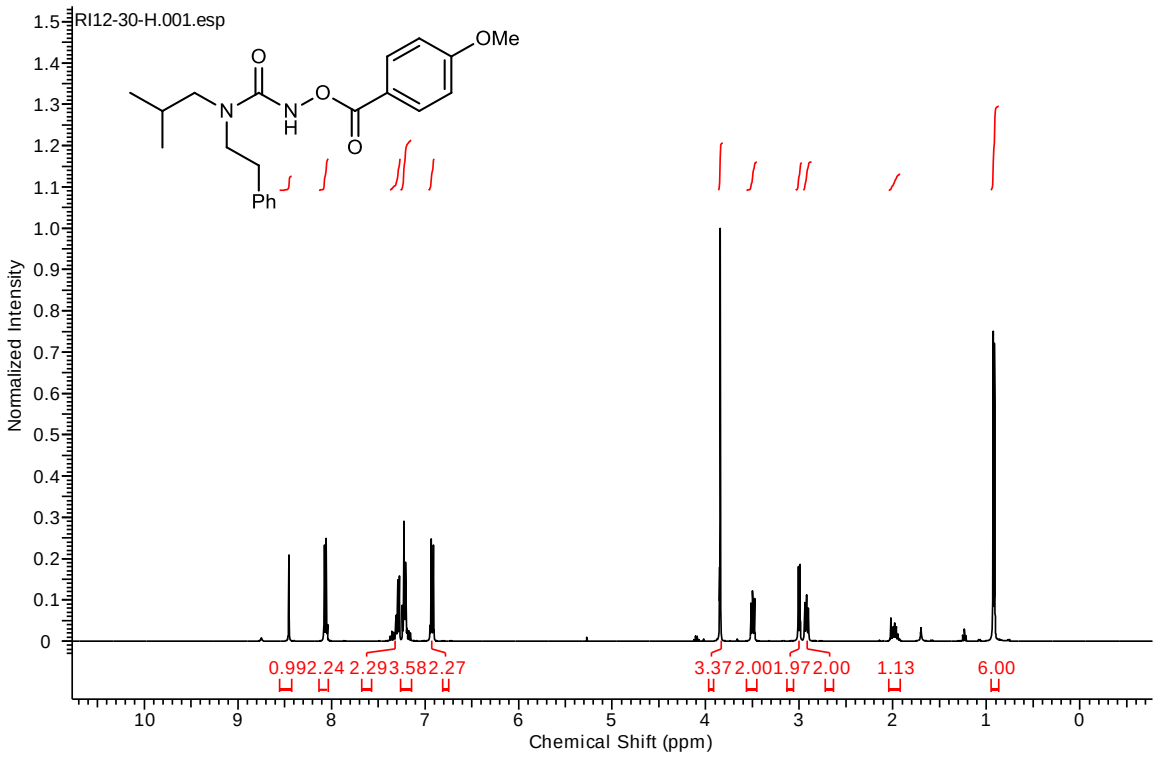

RI12-7-C.002.esp
Normalized Intensity
166.50
164.18
160.88
156.63
140.64
132.10
130.88
120.33
119.24
114.42
113.92
113.81
55.51
45.03
13.34
Chemical Shift (ppm)

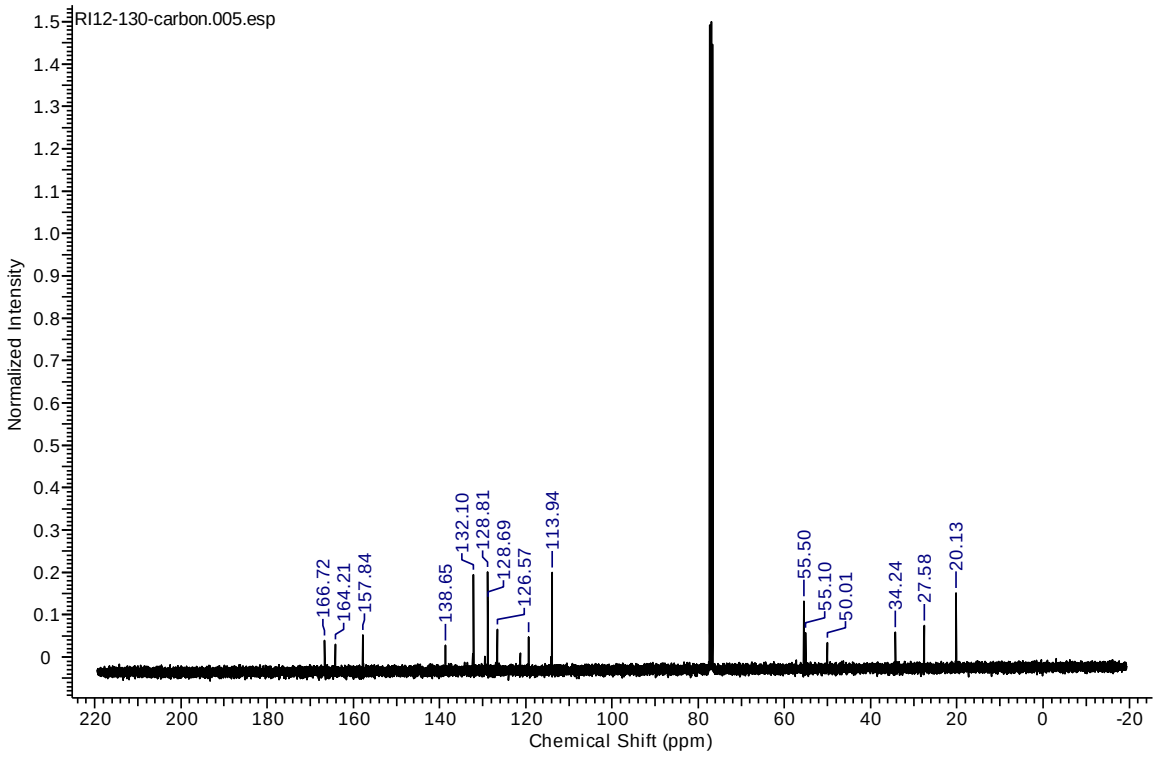

RI12-8-H.001.esp
OMe
O
N
O
N
H
O
Me
Me
Normalized Intensity
1.97
0.94
0.98
1.94
2.01
3.05
2.00
6.00
3.01
Chemical Shift (ppm)

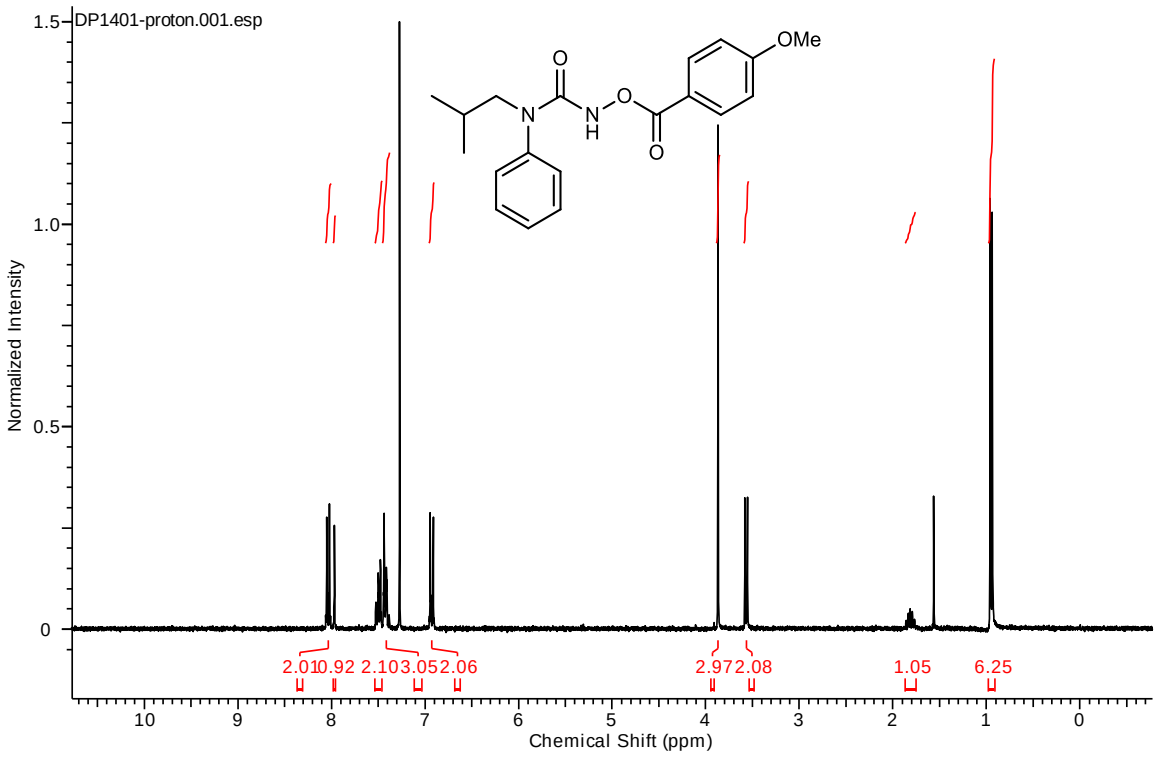

RI12-8-C.001.esp
166.48
164.14
156.74
140.04
139.29
132.09
130.33
125.83
119.32
113.90
55.49
45.00
21.23
13.34
Normalized Intensity
Chemical Shift (ppm)

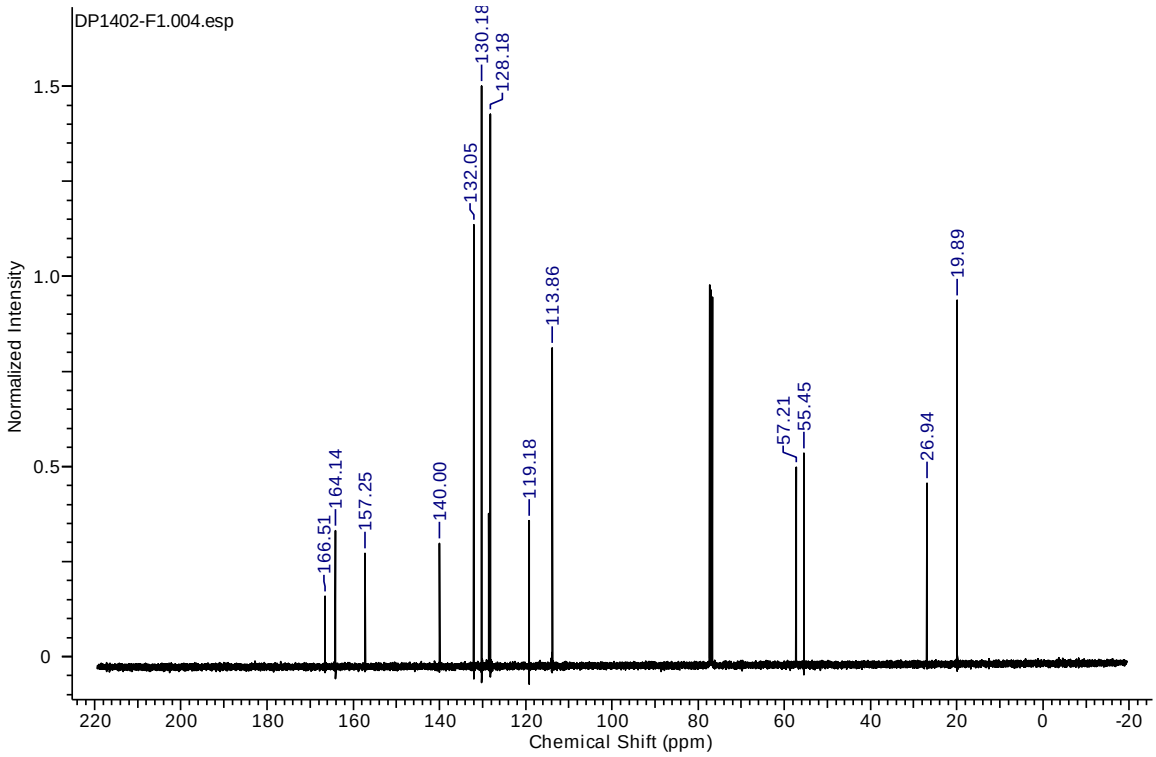

DP1356-proton.002.esp
OMe
O
N
N
H
O
O
Normalized Intensity
0.95
2.00
2.04
3.05
1.97
1.89
1.13
2.32
14.13
12.15
Chemical Shift (ppm)

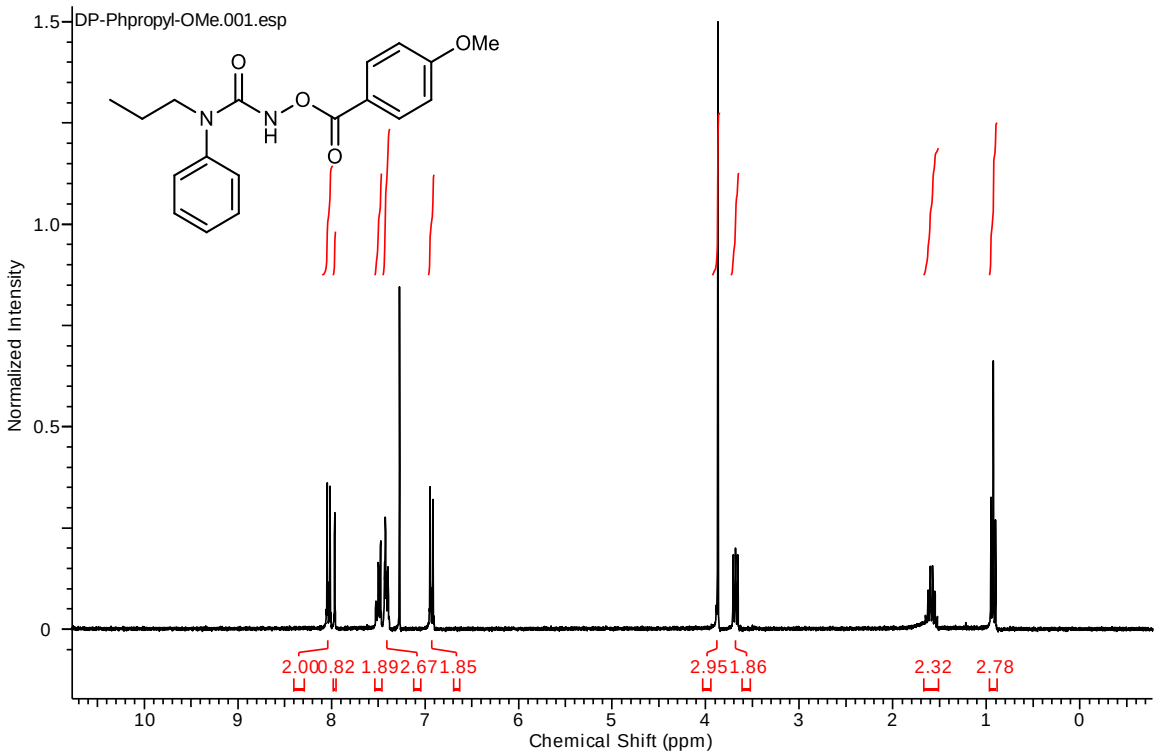

DP1356-carbon.001.esp
Normalized Intensity
165.17
163.54
157.41
131.40
119.83
114.25
55.56
53.02
46.41
31.23
28.70
26.71
22.08
19.77
13.93
Chemical Shift (ppm)

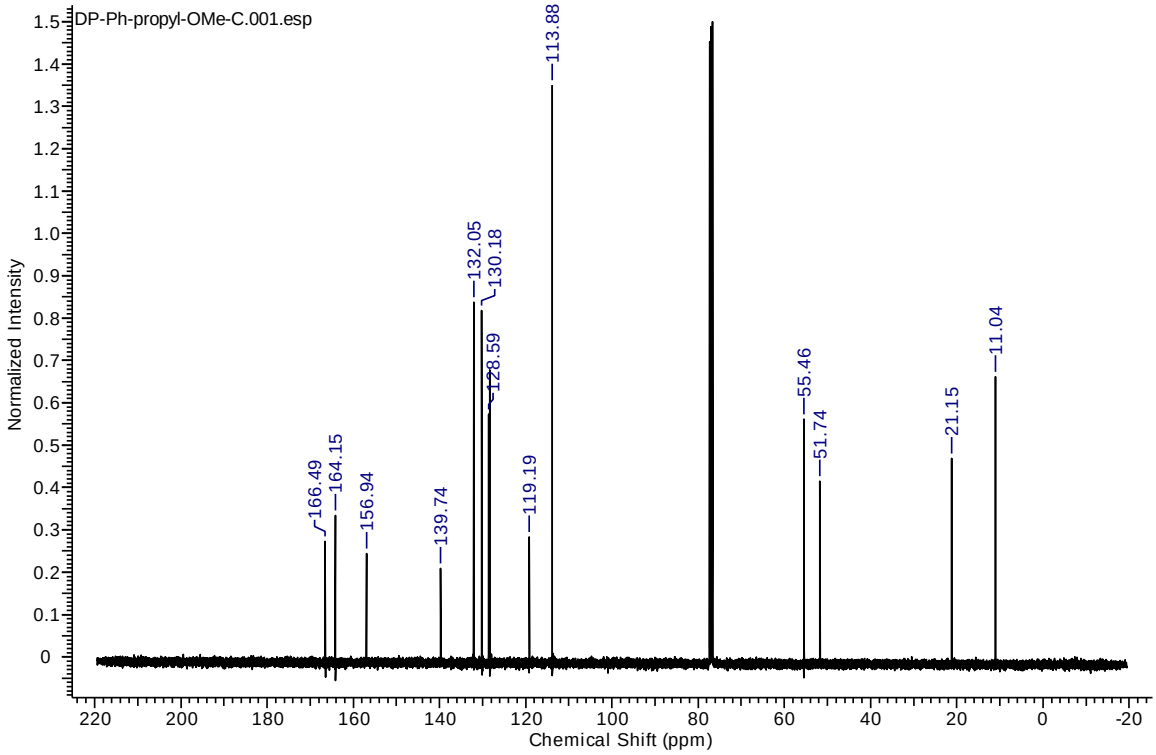

RI12-30-H.001.esp
OMe
O
N
N
H
O
O
Ph
Normalized Intensity
0.992.24 2.293.582.27
3.372.001.972.00
1.13
6.00
Chemical Shift (ppm)


RI12-130-carbon.005.esp
Normalized Intensity
166.72
164.21
157.84
138.65
132.10
128.81
128.69
126.57
113.94
55.50
55.10
50.01
34.24
27.58
20.13
Chemical Shift (ppm)

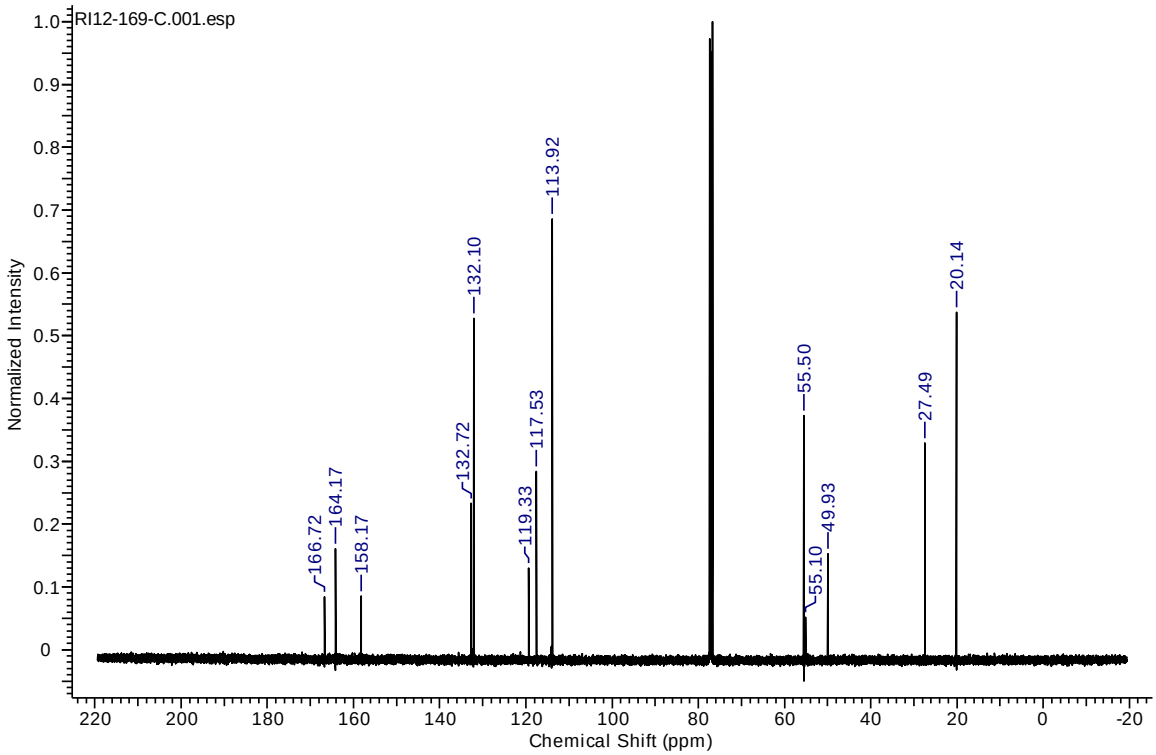

DP1401-proton.001.esp
OMe
O
N
N
H
O
O
O
Normalized Intensity
1.5
1.0
0.5
0
2.01
0.92
2.10
3.05
2.06
2.97
2.08
1.05
6.25
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

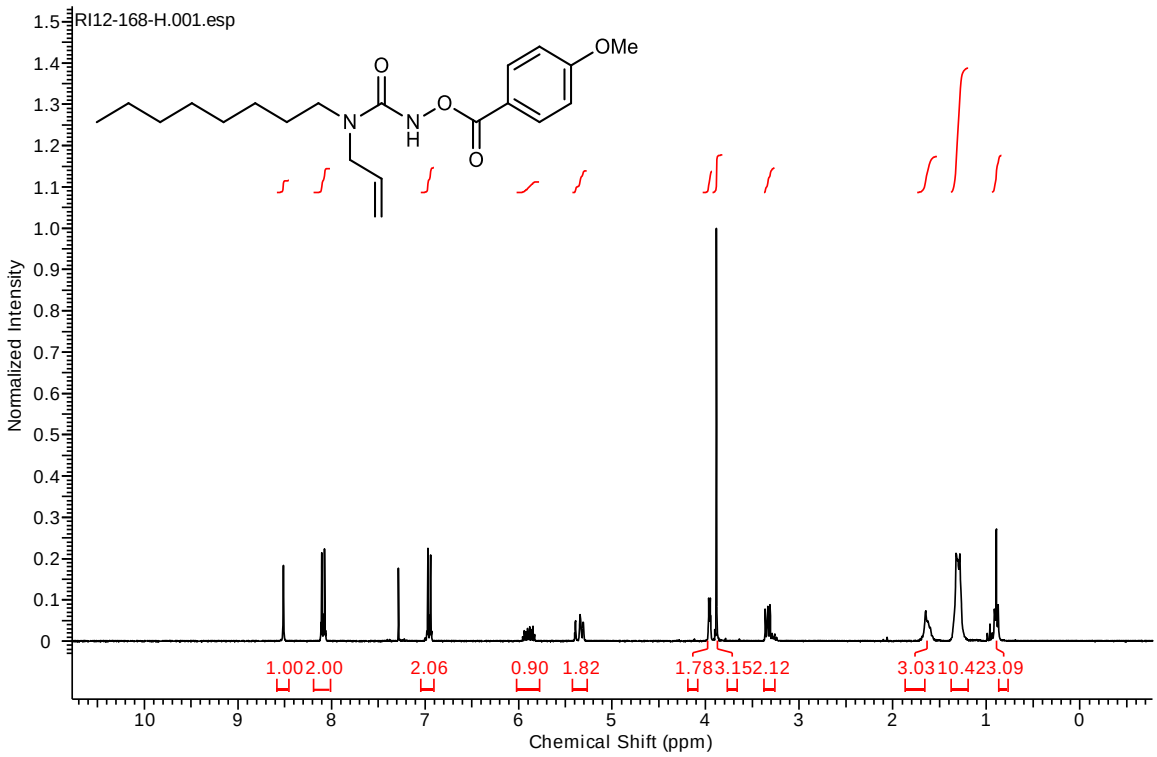

DP1402-F1.004.esp
Normalized Intensity
1.5
1.0
0.5
0
166.51
164.14
157.25
140.00
132.05
130.18
128.18
119.18
113.86
57.21
55.45
26.94
19.89
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

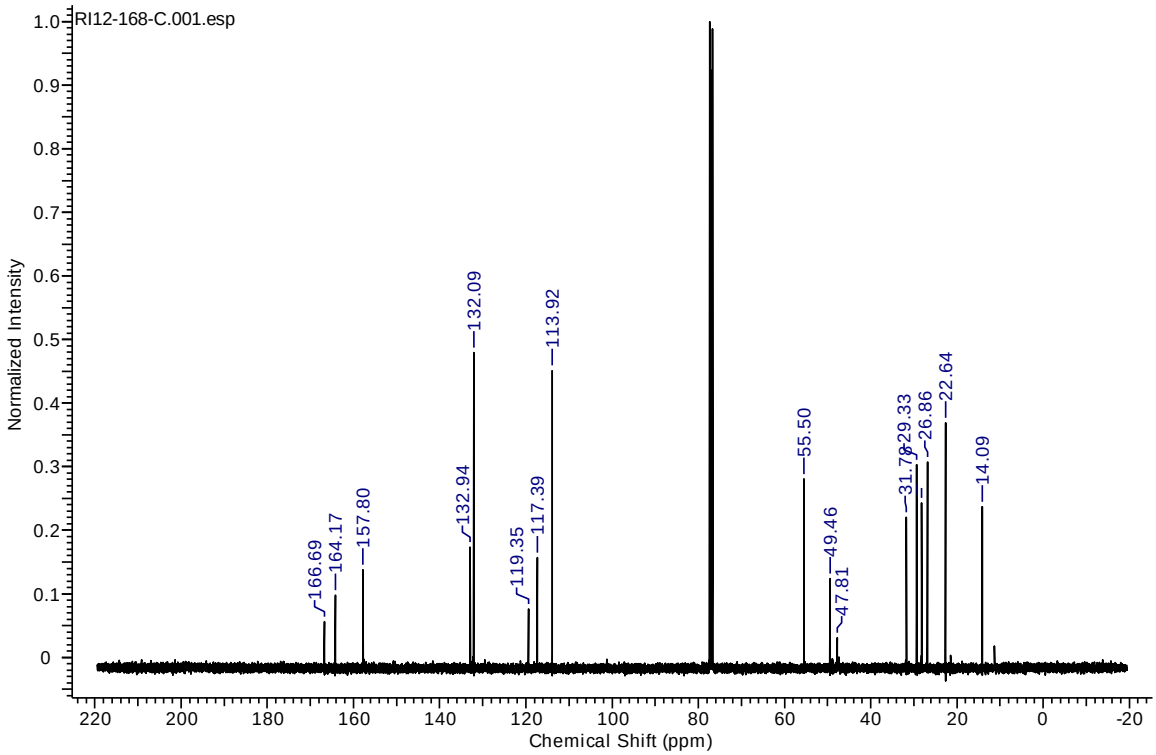

DP-Phpropyl-OMe.001.esp
OMe
O
N
O
N
H
O
O
Normalized Intensity
1.5
1.0
0.5
0
2.00
0.82
1.89
2.67
1.85
2.95
1.86
2.32
2.78
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

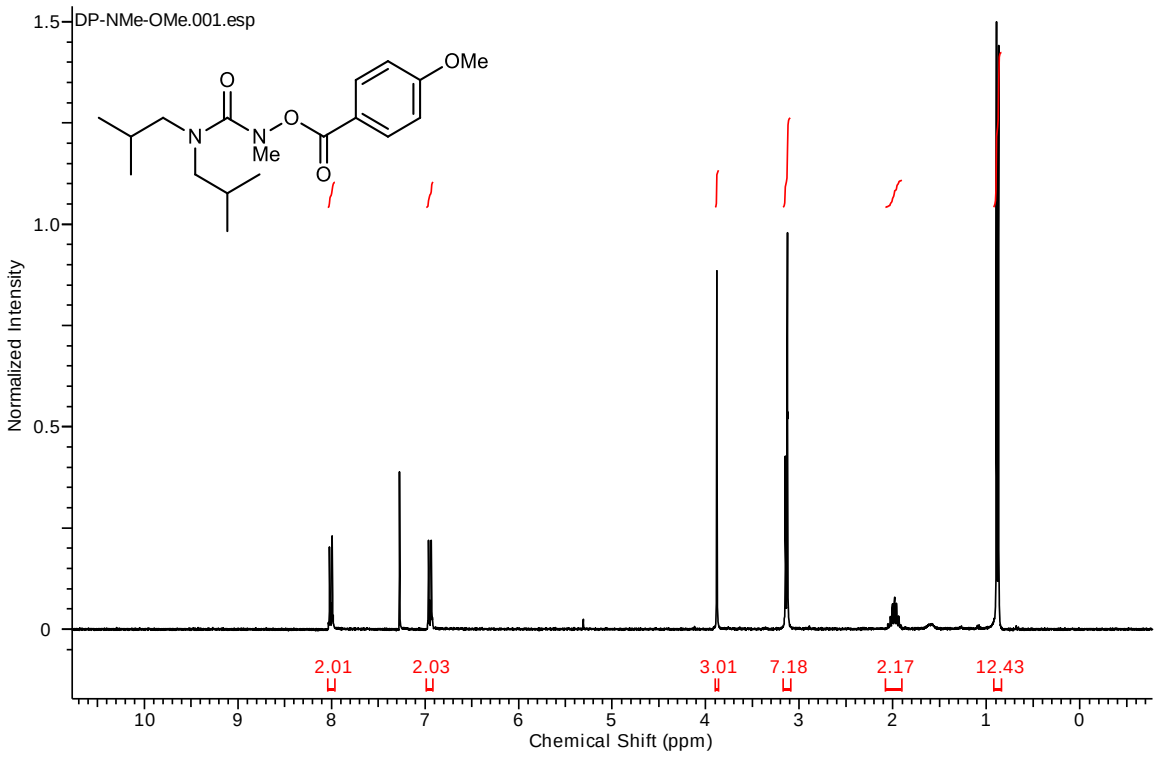

DP-Ph-propyl-OMe-C.001.esp
Normalized Intensity
166.49
164.15
156.94
139.74
132.05
130.18
128.59
119.19
113.88
55.46
51.74
21.15
11.04
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

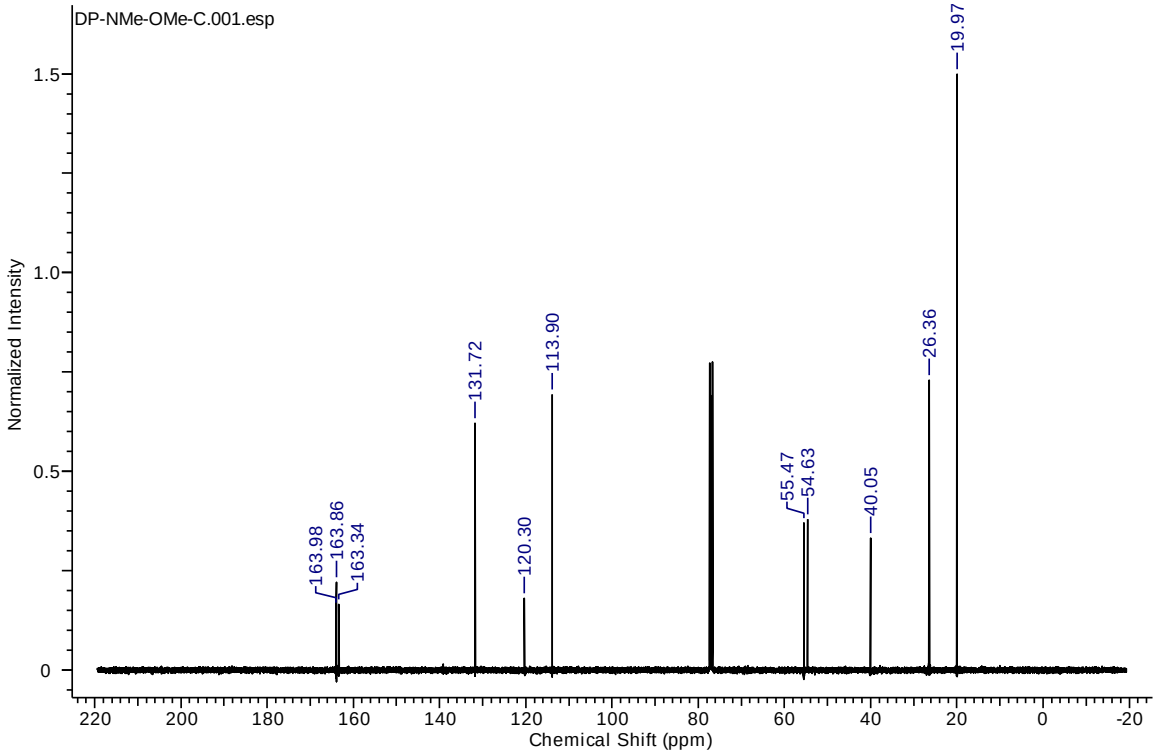
RI12-169-H.001.esp
OMe
O
N
N
H
O
O
Normalized Intensity
0.99 1.90 1.96 0.91 1.84 1.85 2.97 1.94 1.00 6.00
Chemical Shift (ppm)

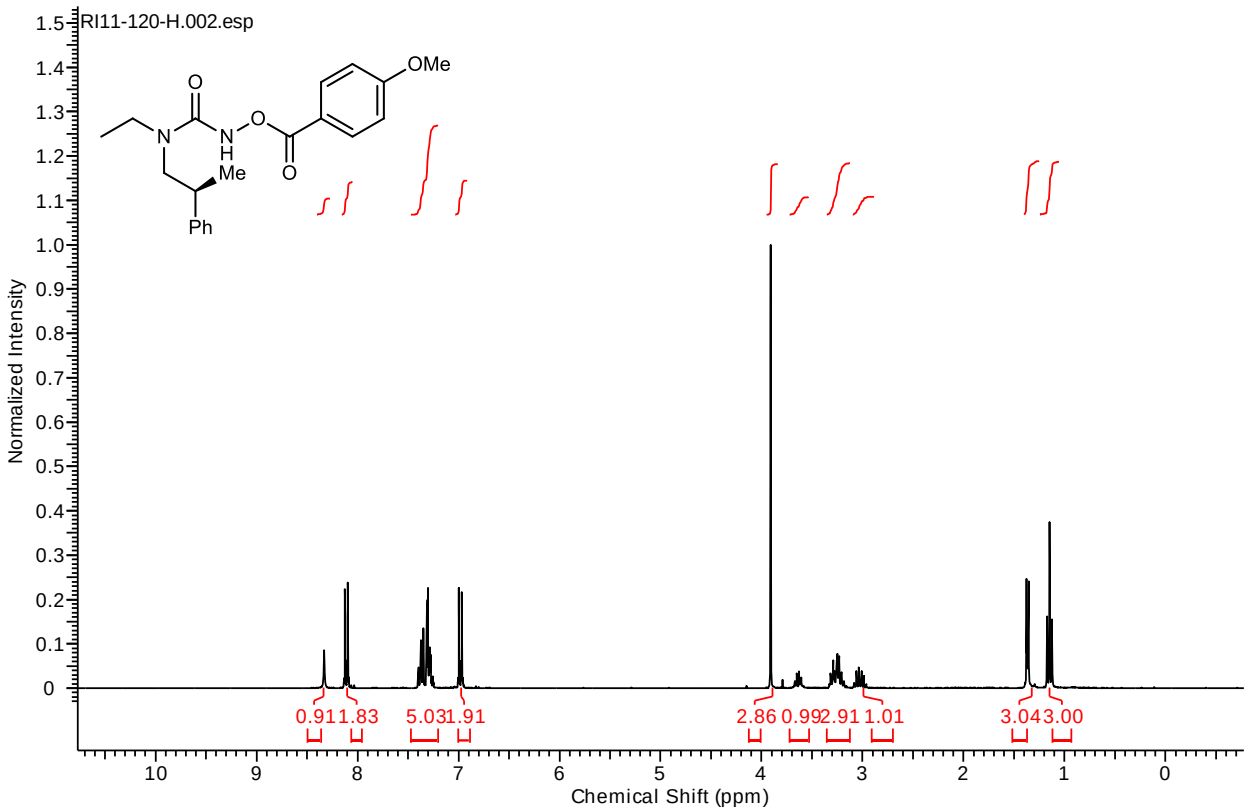

RI12-169-C.001.esp
Normalized Intensity
166.72
164.17
158.17
132.72
132.10
119.33
117.53
113.92
55.50
55.10
49.93
27.49
20.14
Chemical Shift (ppm)

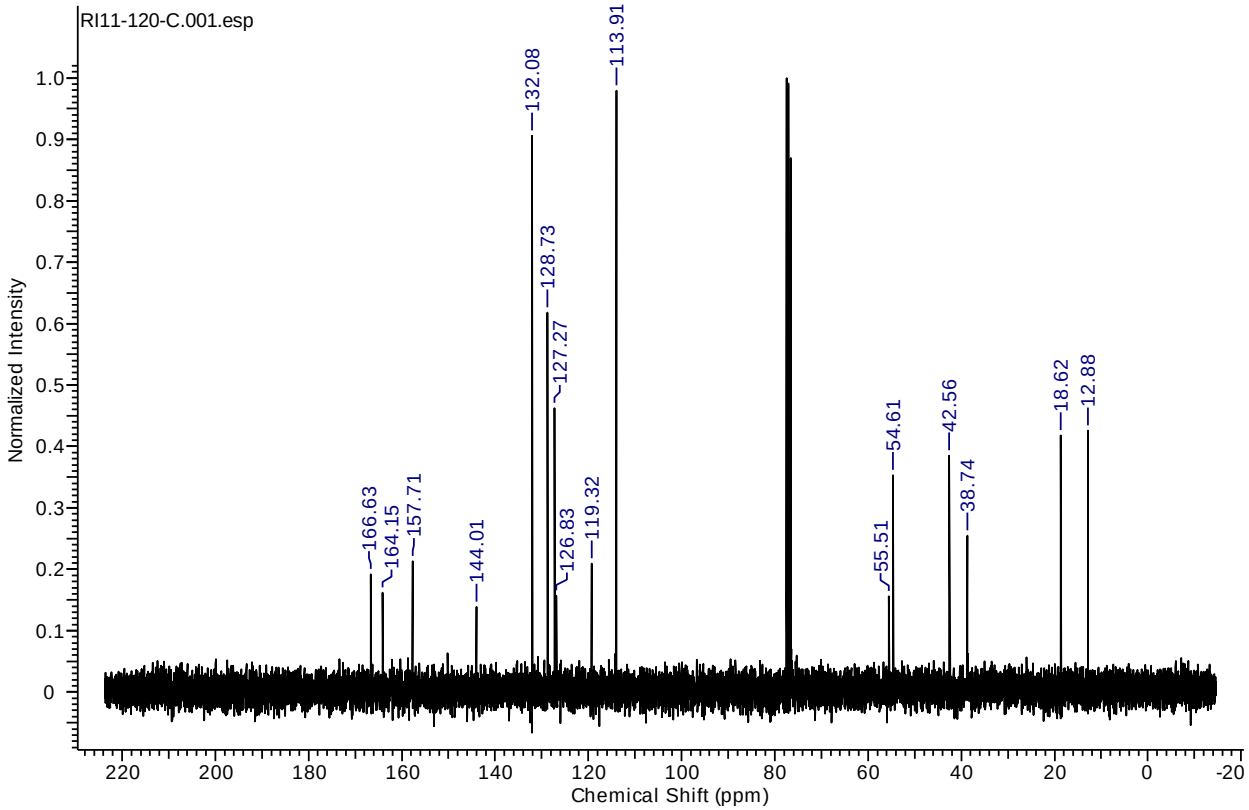

RI12-168-H.001.esp
OMe
O
N
O
N
H
O
O
Normalized Intensity
1.00
2.00
2.06
0.90
1.82
1.78
3.15
2.12
3.03
10.42
3.09
Chemical Shift (ppm)

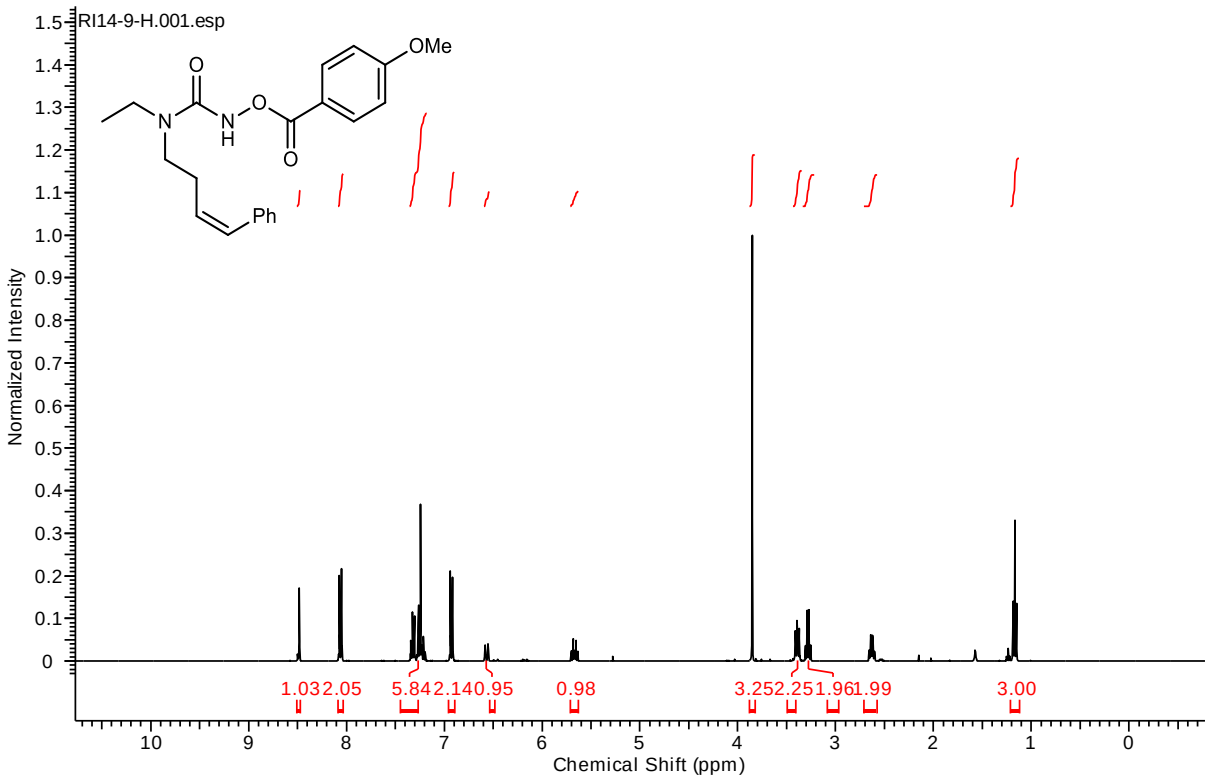

RI12-168-C.001.esp
Normalized Intensity
166.69
164.17
157.80
132.94
132.09
119.35
117.39
113.92
77.00
55.50
49.46
47.81
31.79
29.33
26.86
22.64
14.09
Chemical Shift (ppm)

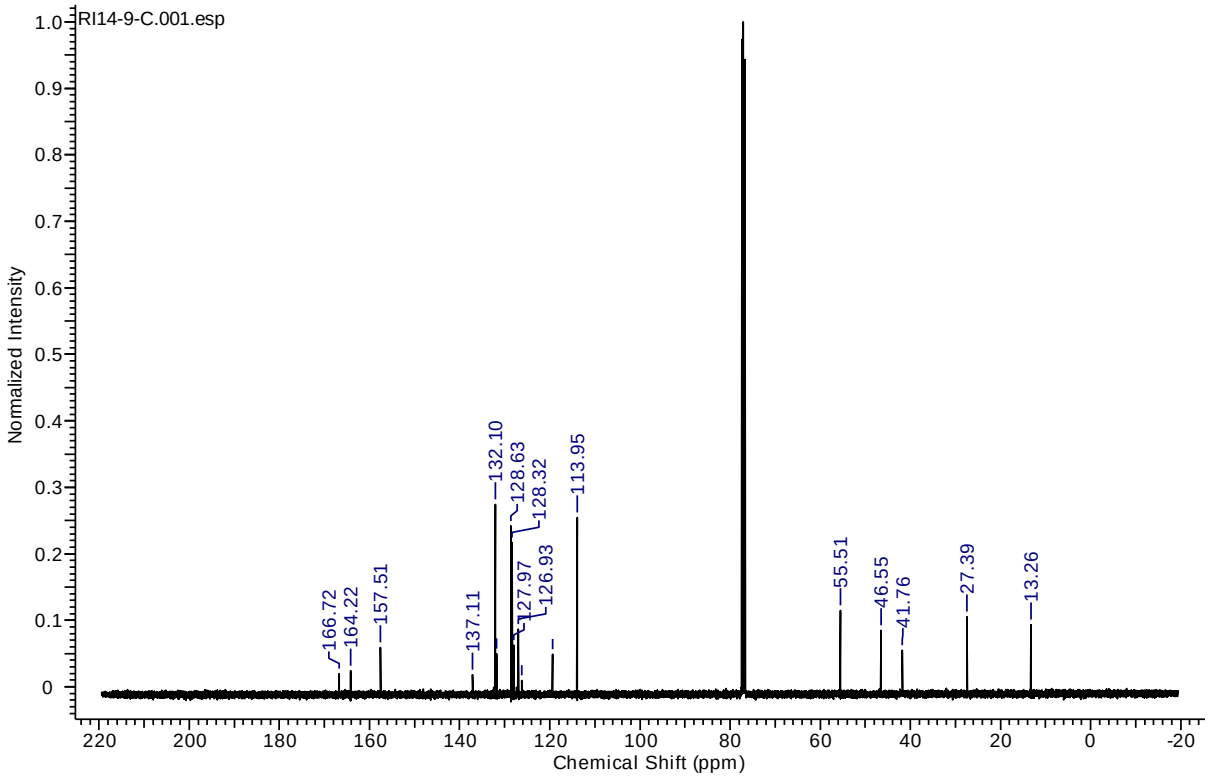

DP-NMe-OMe.001.esp
OMe
O
N
N
O
Me
O
Normalized Intensity
1.5
1.0
0.5
0
2.01
2.03
3.01
7.18
2.17
12.43
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

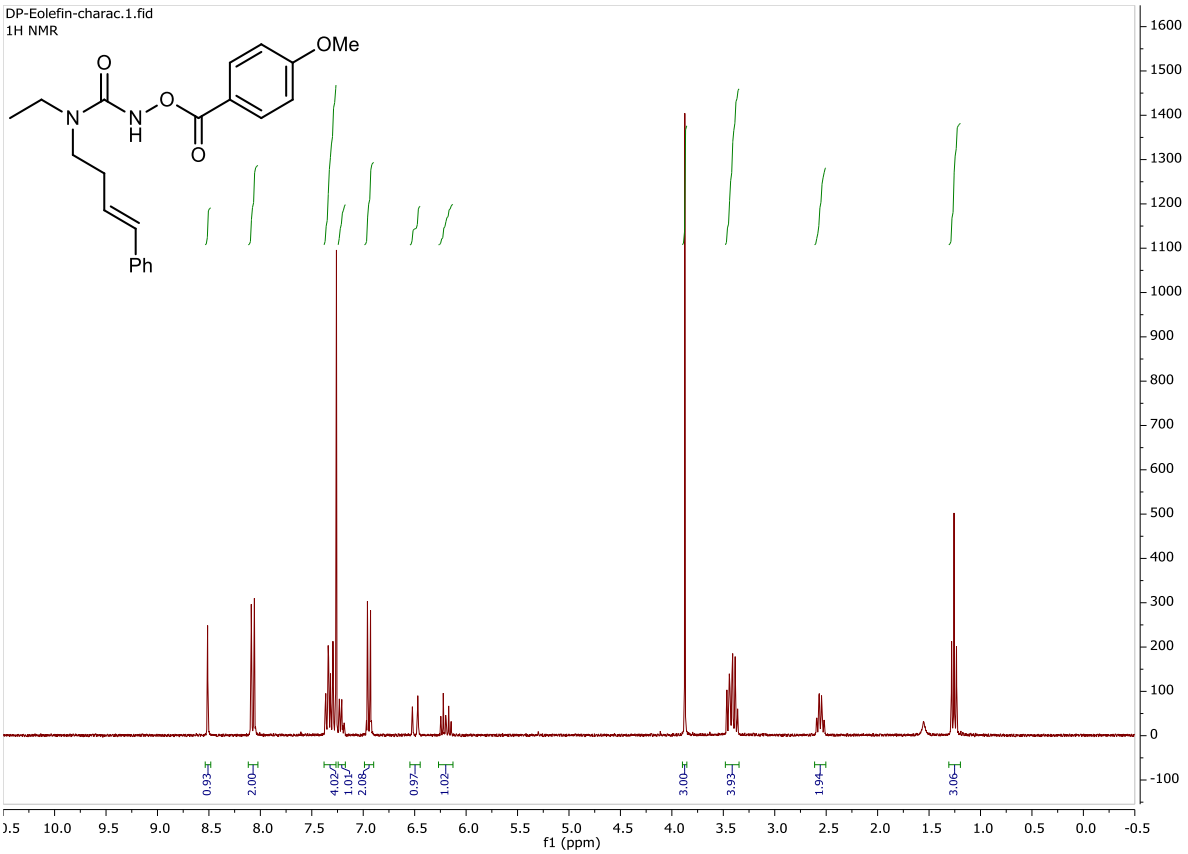

DP-NMe-OMe-C.001.esp
Normalized Intensity
1.5
1.0
0.5
0
163.98
163.86
163.34
131.72
120.30
113.90
55.47
54.63
40.05
26.36
19.97
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

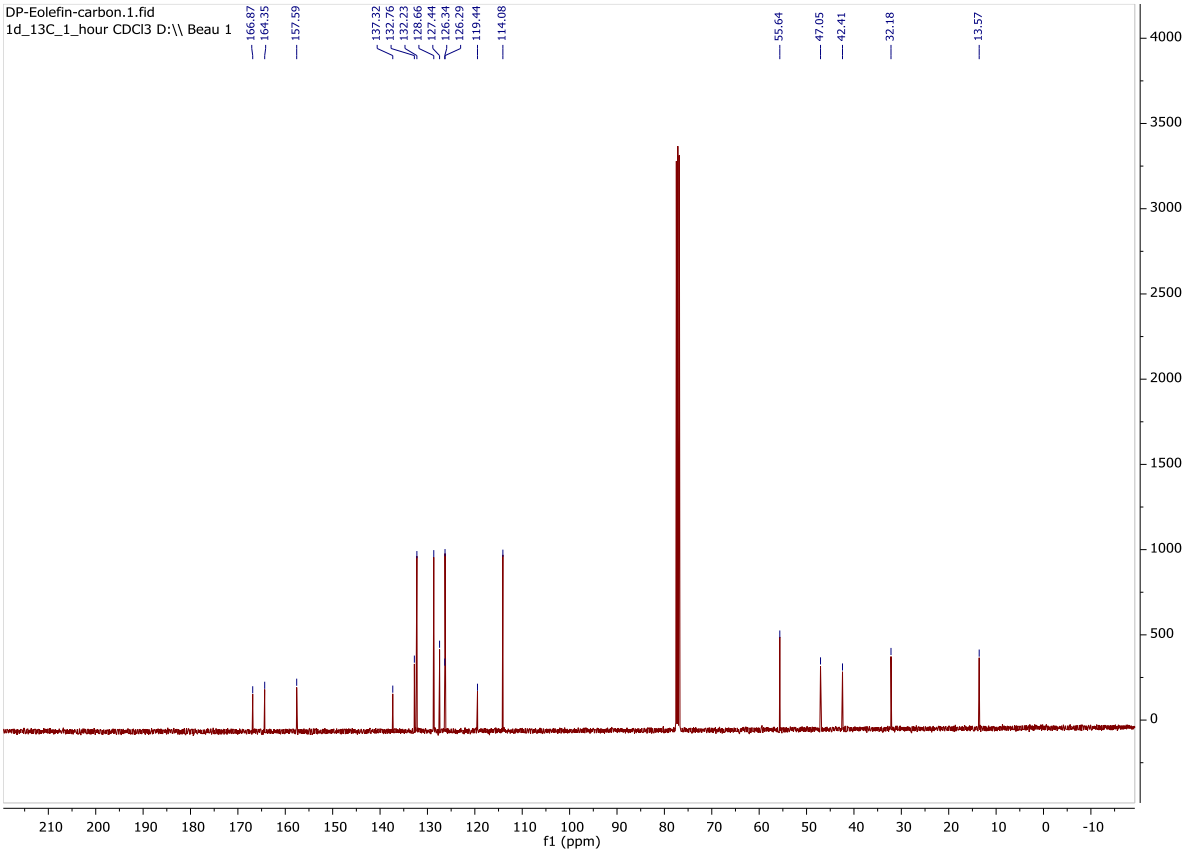

RI11-120-H.002.esp
OMe
O
N
N
H
Me
O
O
O
Ph
Normalized Intensity
0.91 1.83 5.03 1.91 2.86 0.99 2.91 1.01 3.04 3.00
Chemical Shift (ppm)

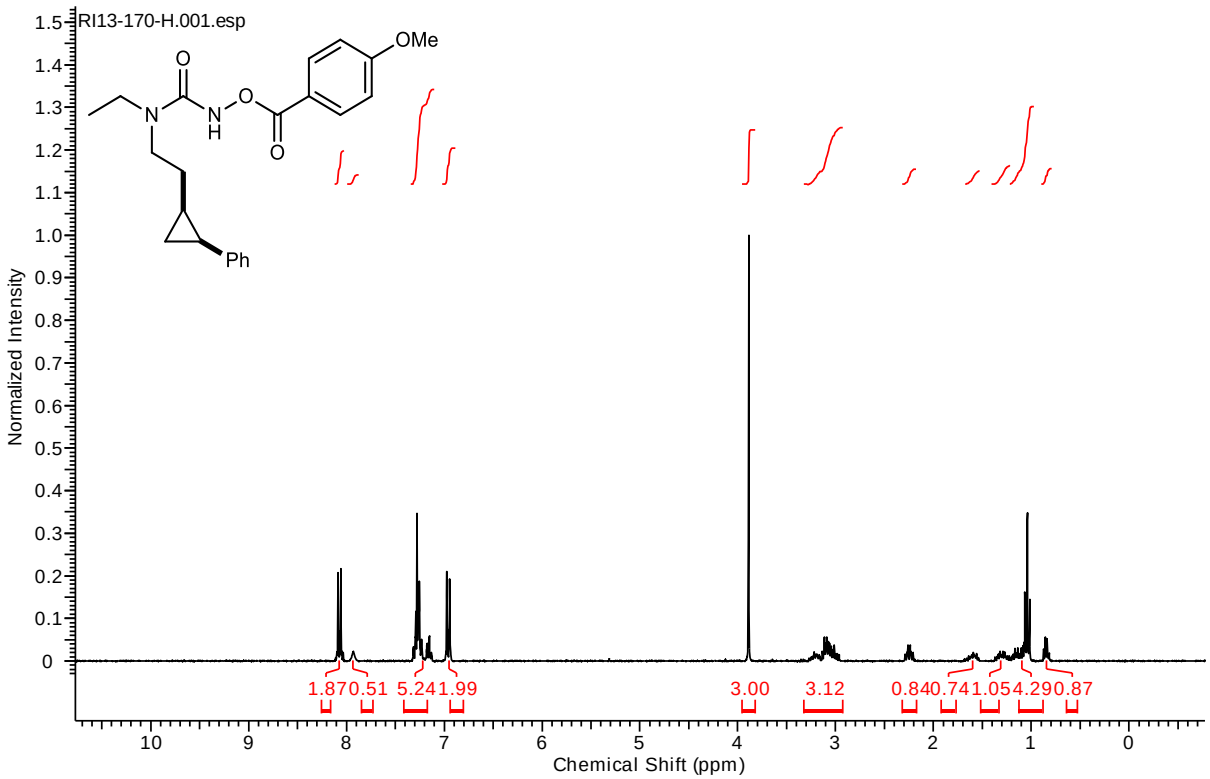

RI11-120-C.001.esp
166.63
164.15
157.71
144.01
132.08
128.73
127.27
126.83
119.32
113.91
55.51
54.61
42.56
38.74
18.62
12.88
Normalized Intensity
Chemical Shift (ppm)

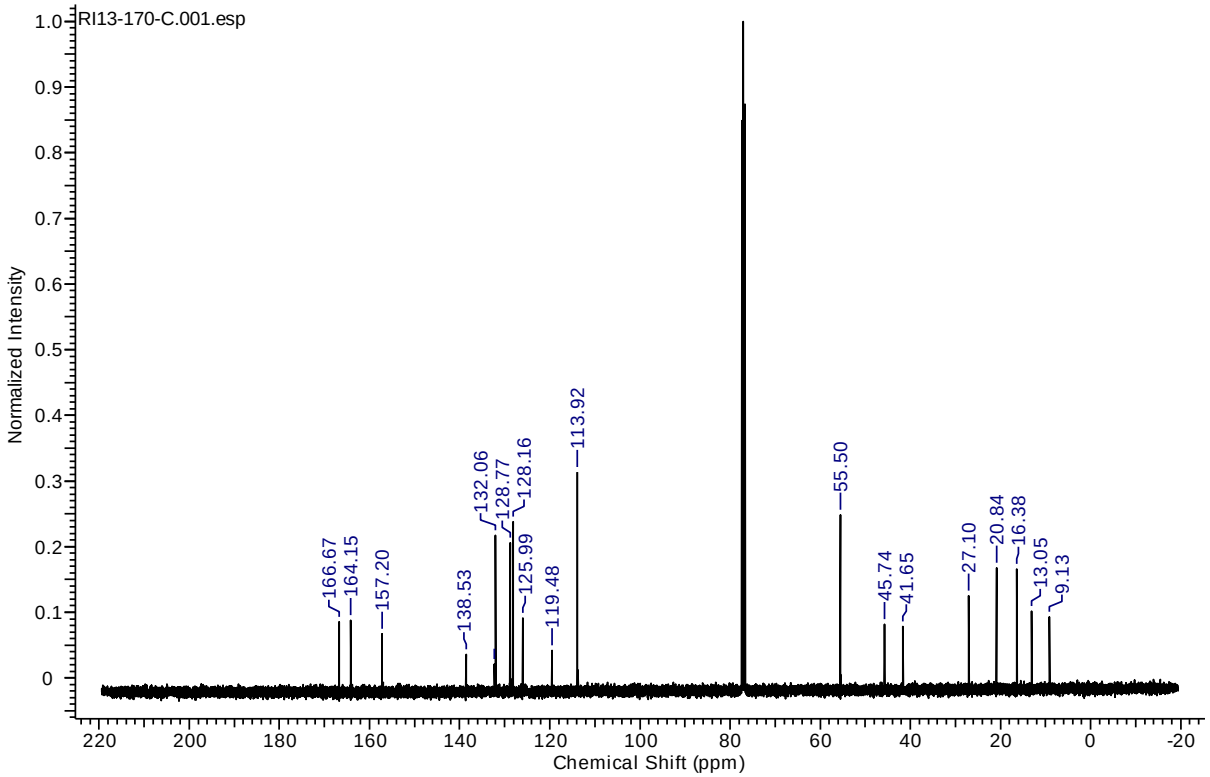

RI14-9-H.001.esp
OMe
O
N
N
H
O
O
Ph
Normalized Intensity
1.03
2.05
5.84
2.14
0.95
0.98
3.25
2.25
1.96
1.99
3.00
Chemical Shift (ppm)

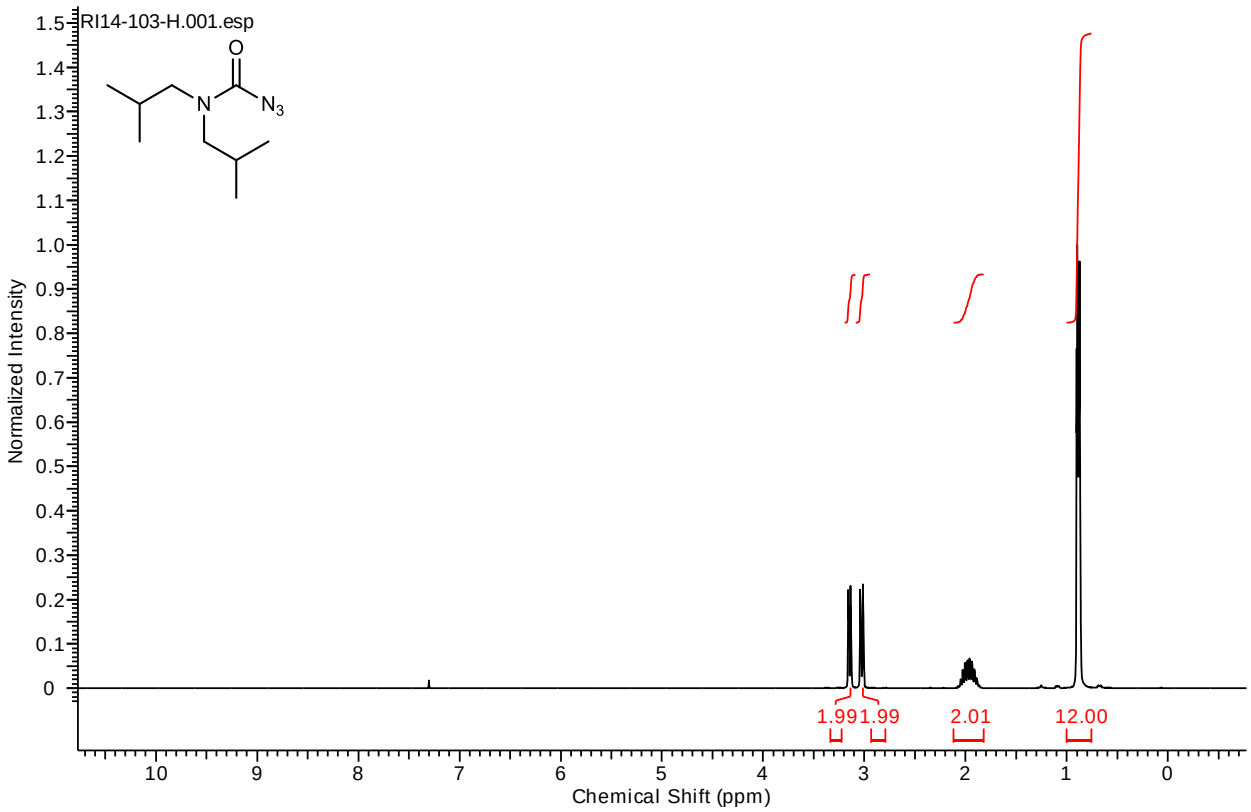

RI14-9-C.001.esp
Normalized Intensity
166.72
164.22
157.51
137.11
132.10
128.63
128.32
127.97
126.93
113.95
55.51
46.55
41.76
27.39
13.26
Chemical Shift (ppm)

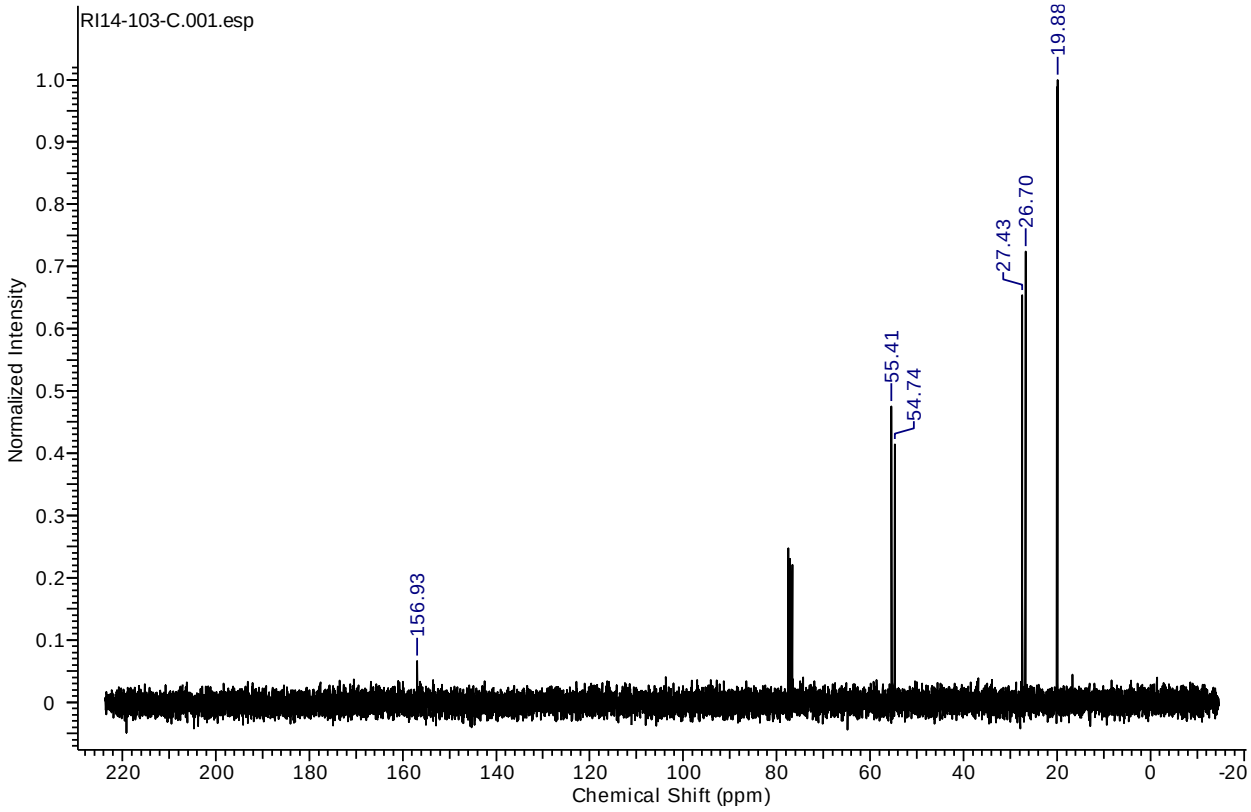

DP-Eolefin-charac.1.fid
1H NMR
OMe
O
N
O
N
H
O
Ph
0.93
2.00
4.02
1.01
2.08
0.97
1.02
3.00
3.93
1.94
3.06
f1 (ppm)

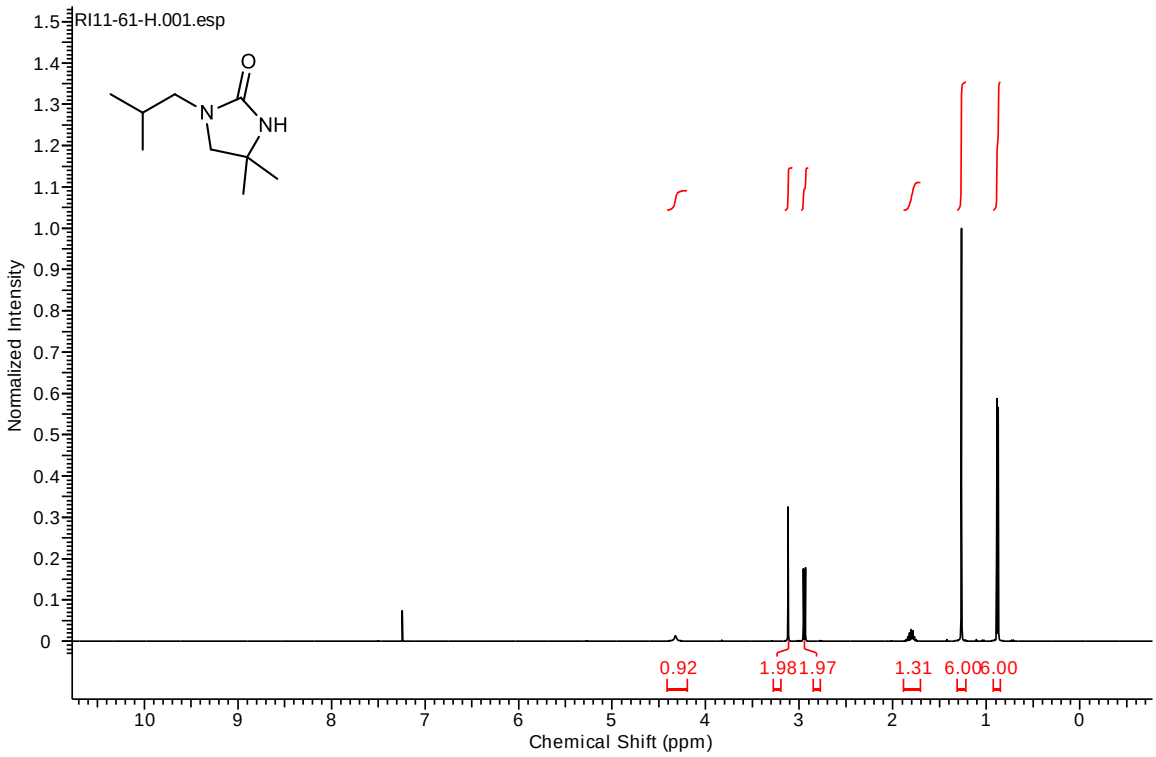

DP-Eolefin-carbon.1.fid
1d_13C_1_hour CDCl3 D:\\ Beau 1
166.87
164.35
157.59
137.32
132.76
132.23
128.66
127.44
126.34
126.29
119.44
114.08
55.64
47.05
42.41
32.18
13.57
f1 (ppm)

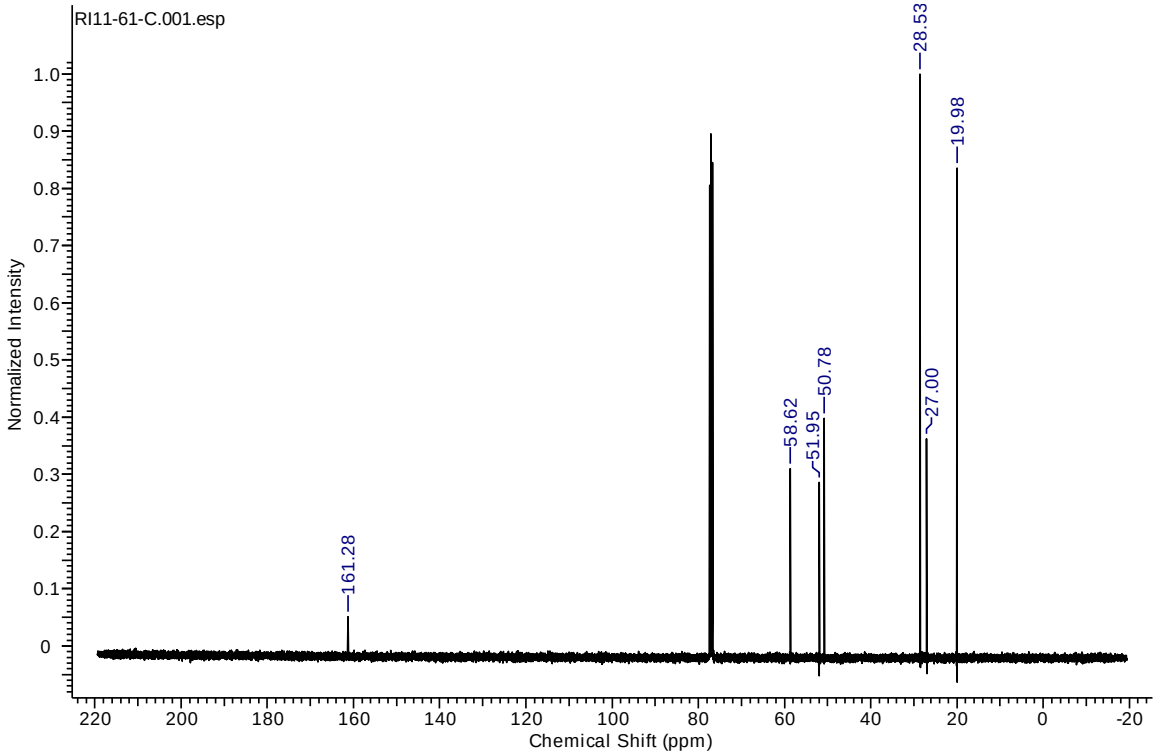

RI13-170-H.001.esp
OMe
O
N
N
H
O
O
Ph
Normalized Intensity
1.87
0.51
5.24
1.99
3.00
3.12
0.84
0.74
1.05
4.29
0.87
Chemical Shift (ppm)

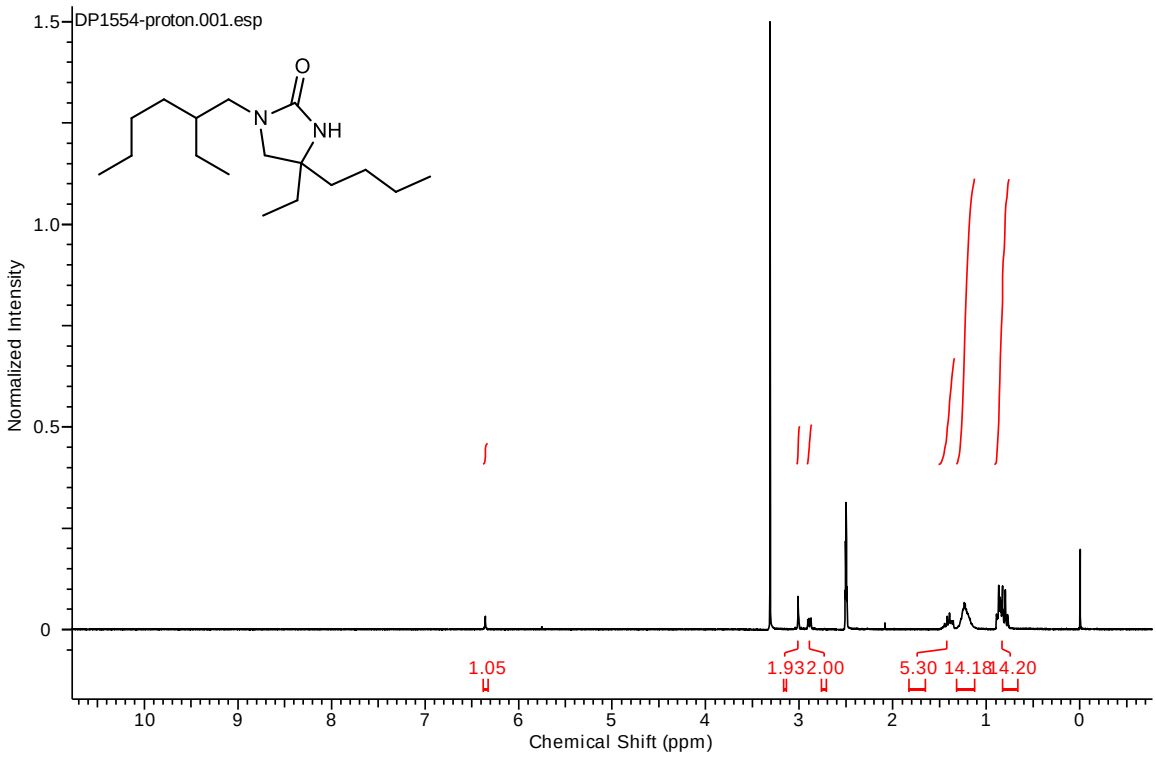

RI13-170-C.001.esp
Normalized Intensity
166.67
164.15
157.20
138.53
132.06
128.77
128.16
125.99
119.48
113.92
55.50
45.74
41.65
27.10
20.84
16.38
13.05
9.13
Chemical Shift (ppm)

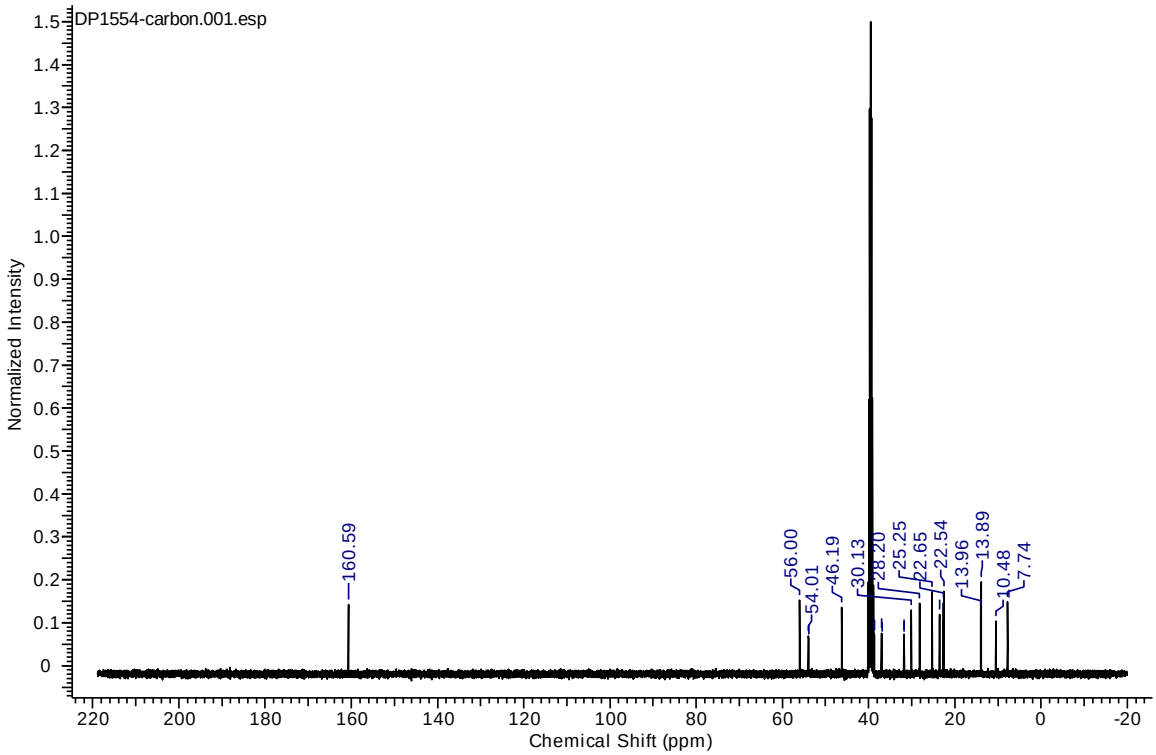

RI14-103-H.001.esp
O
N
N3
Normalized Intensity
1.99
1.99
2.01
12.00
Chemical Shift (ppm)

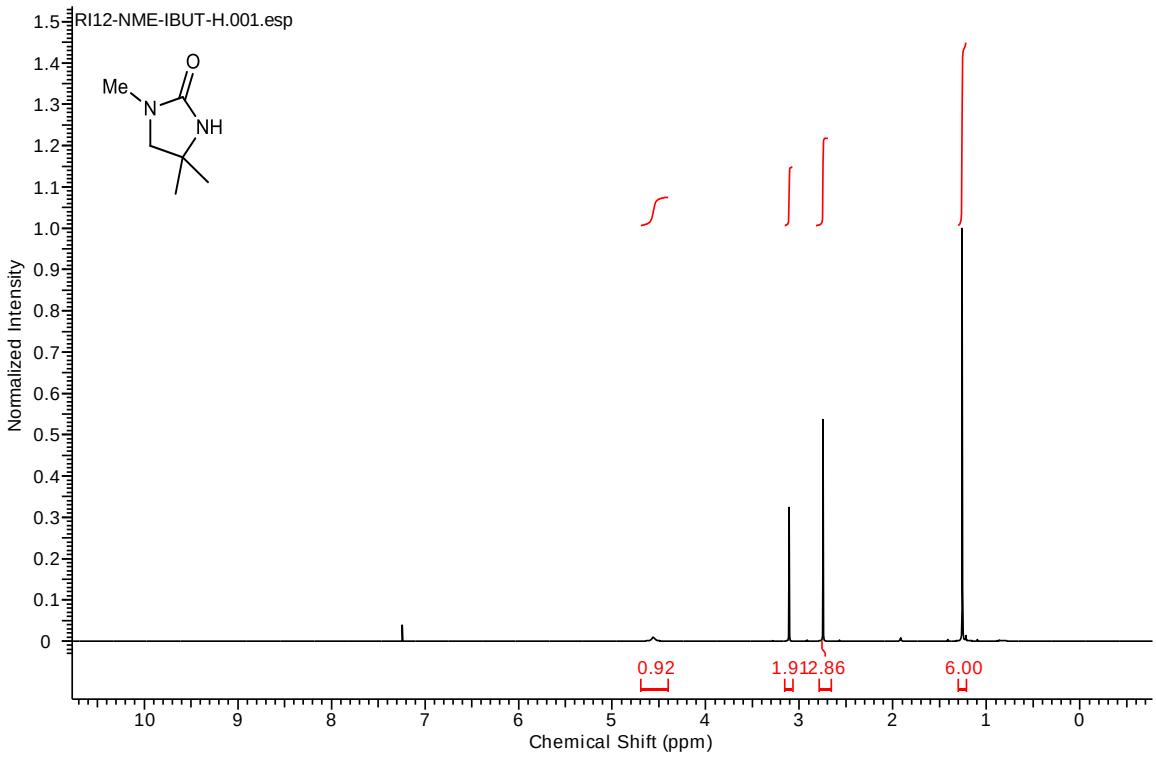

RI14-103-C.001.esp
19.88
26.70
27.43
55.41
54.74
156.93
Normalized Intensity
Chemical Shift (ppm)

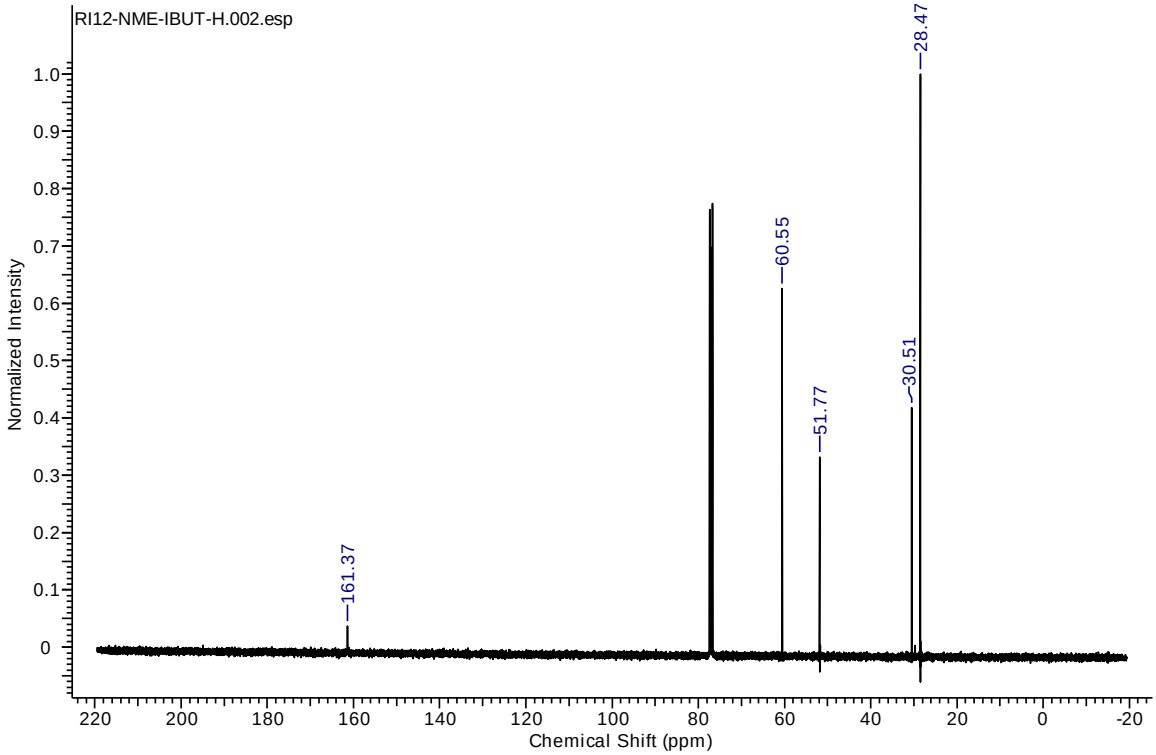

RI11-61-H.001.esp
O
N
NH
Normalized Intensity
Chemical Shift (ppm)
0.92
1.98
1.97
1.31
6.00
6.00

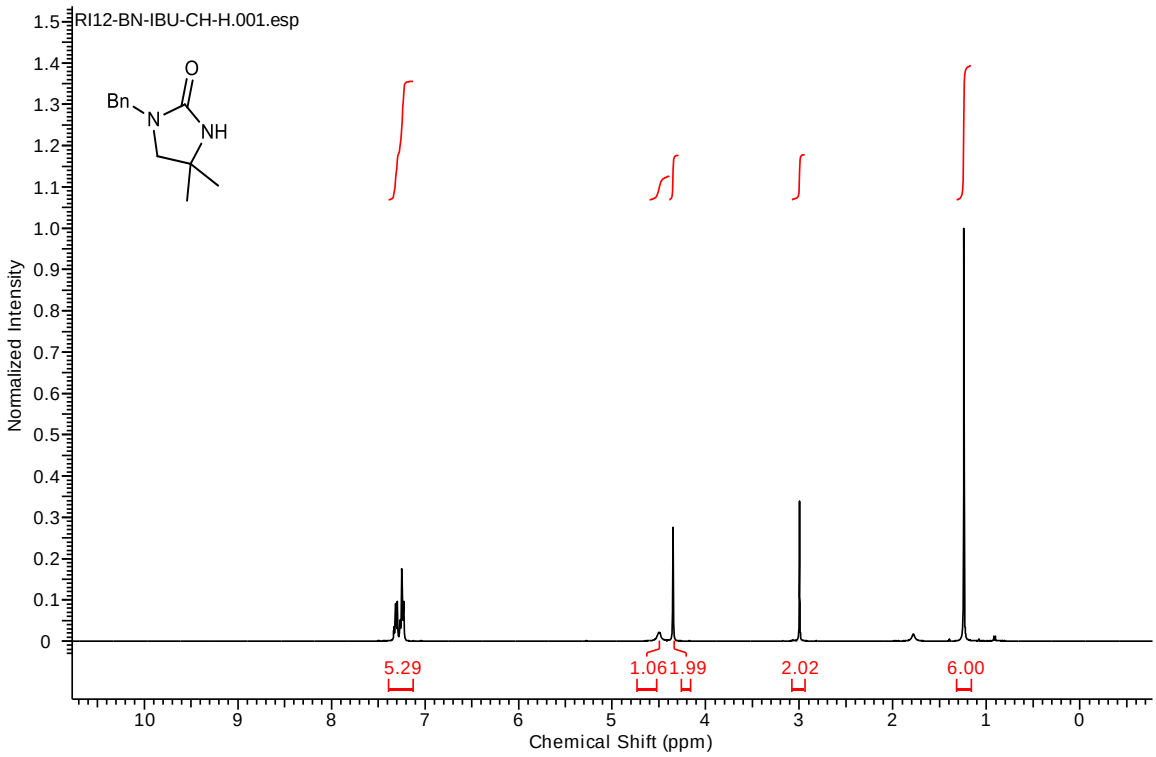

RI11-61-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
161.28
58.62
51.95
50.78
28.53
27.00
19.98

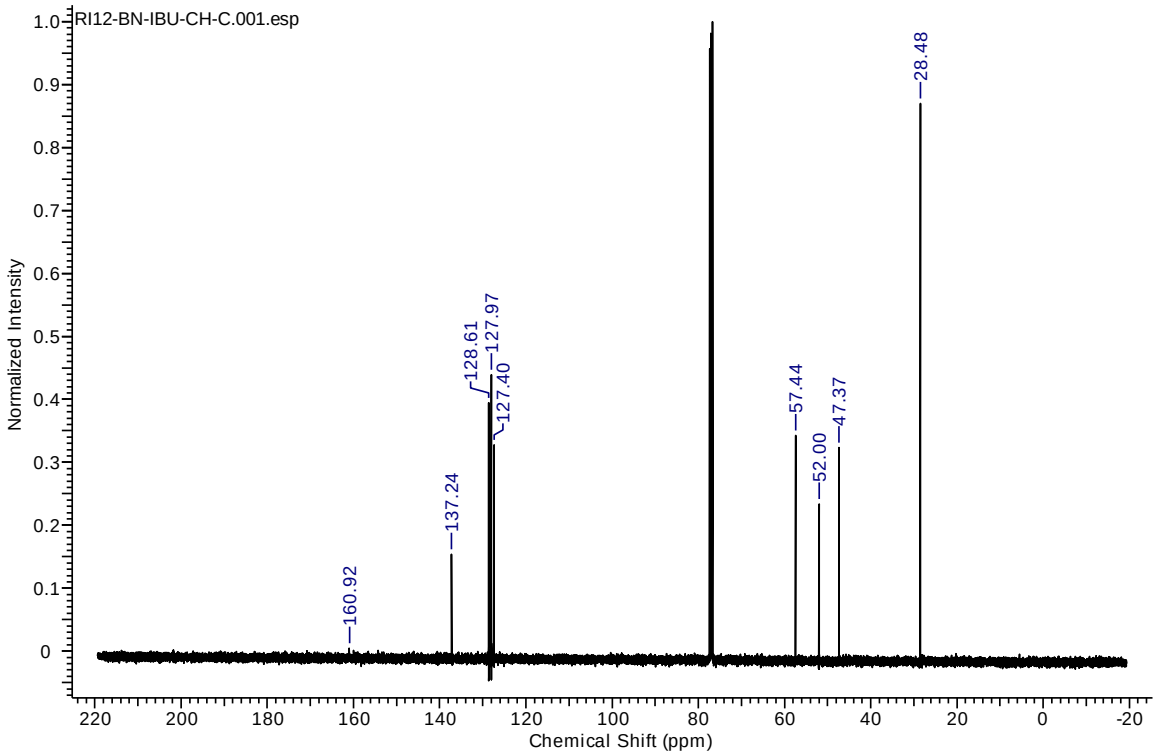

DP1554-proton.001.esp
O
N
NH
Normalized Intensity
1.05
1.93
2.00
5.30
14.18
14.20
Chemical Shift (ppm)

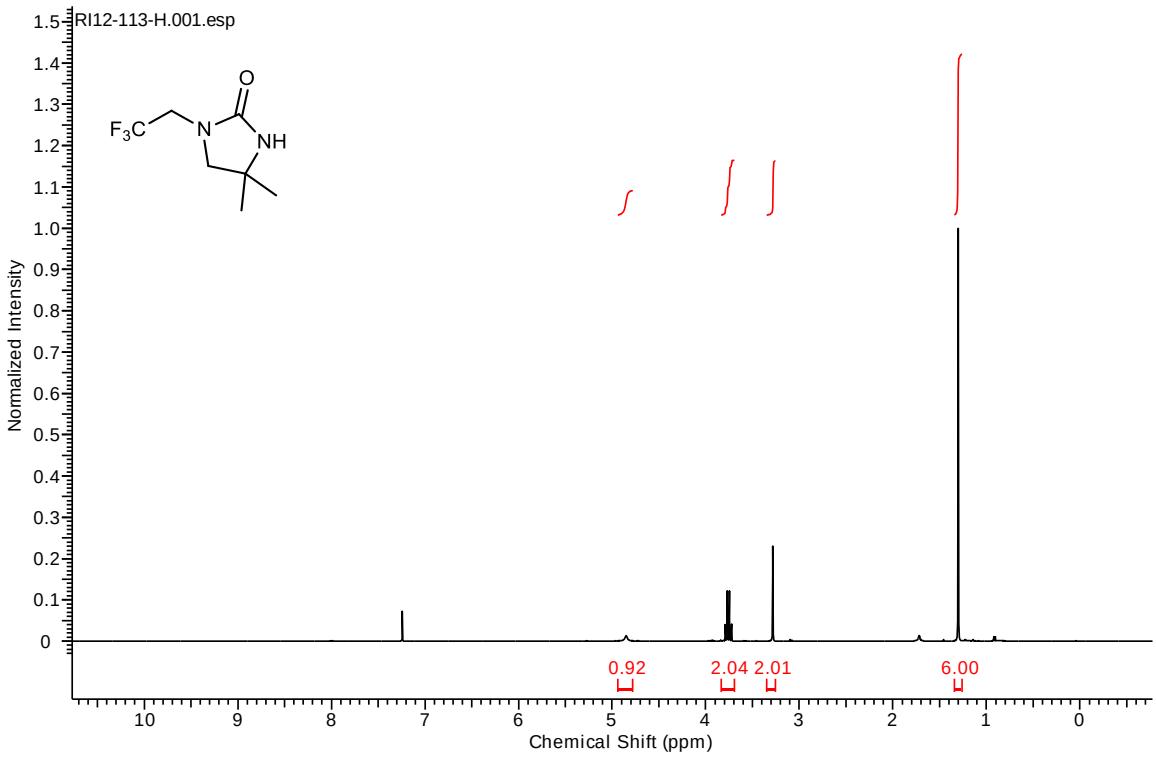

DP1554-carbon.001.esp
Normalized Intensity
160.59
56.00
54.01
46.19
30.13
28.20
25.25
22.65
22.54
13.96
13.89
10.48
7.74
Chemical Shift (ppm)

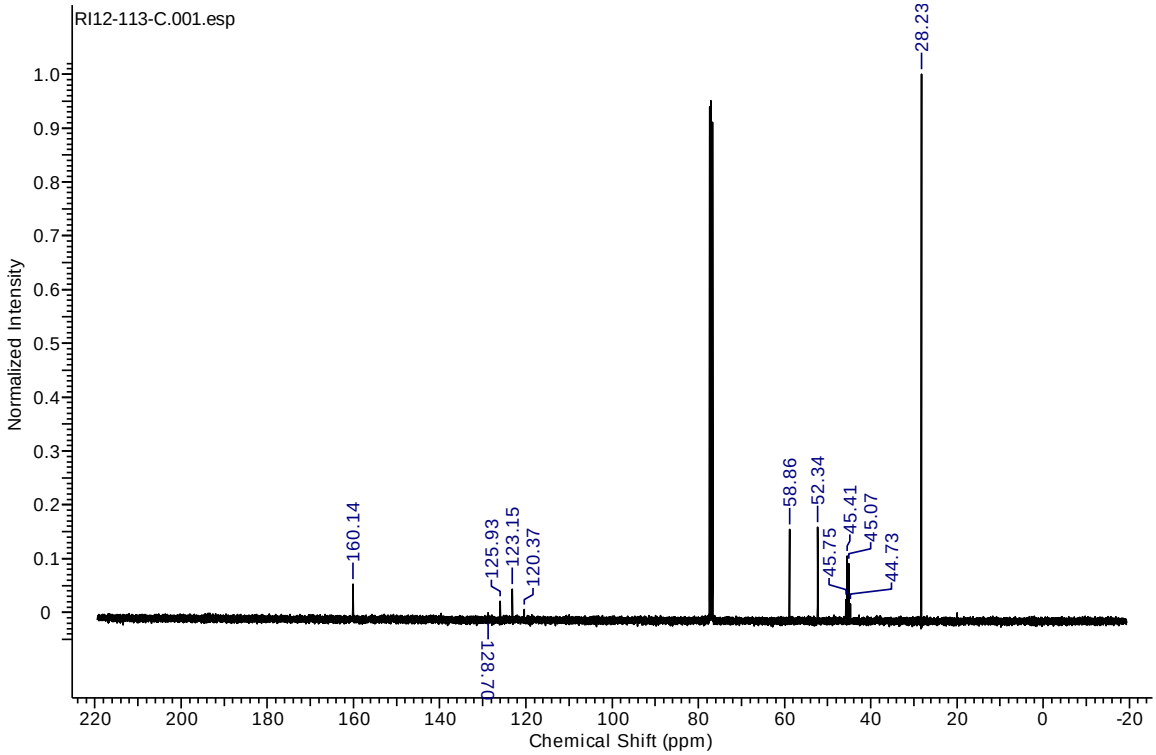

RI12-NME-IBUT-H.001.esp
Me
N
O
NH
Normalized Intensity
0.92
1.91
2.86
6.00
Chemical Shift (ppm)

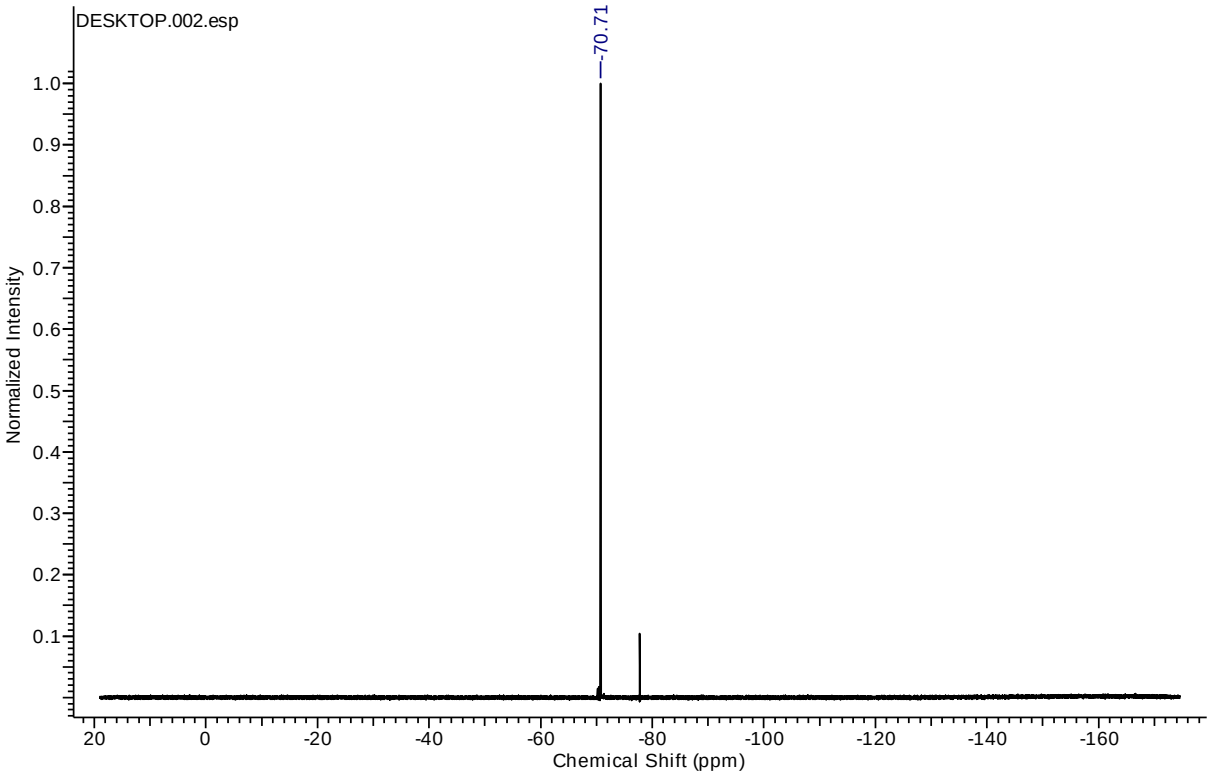

RI12-NME-IBUT-H.002.esp
Normalized Intensity
161.37
60.55
51.77
30.51
28.47
Chemical Shift (ppm)

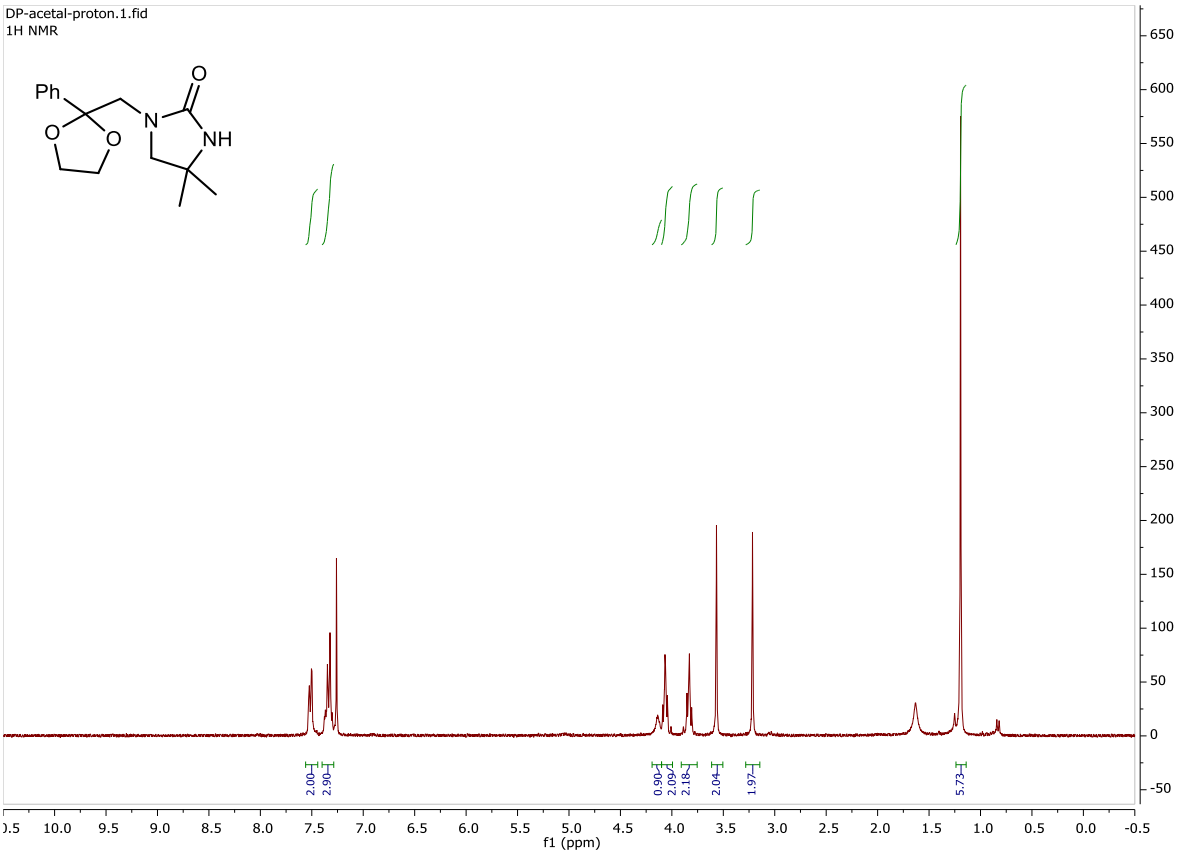

RI12-BN-IBU-CH-H.001.esp
Bn
N
O
NH
Normalized Intensity
5.29
1.06
1.99
2.02
6.00
Chemical Shift (ppm)

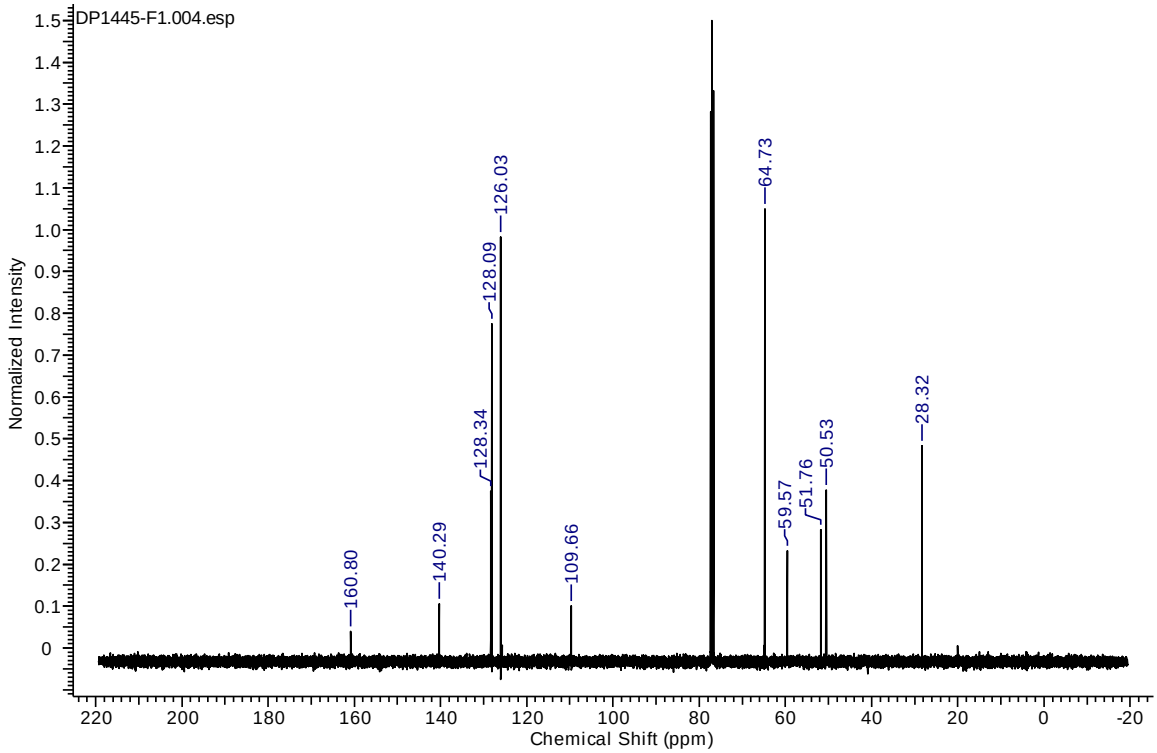

RI12-BN-IBU-CH-C.001.esp
Normalized Intensity
160.92
137.24
128.61
127.97
127.40
57.44
52.00
47.37
28.48
Chemical Shift (ppm)

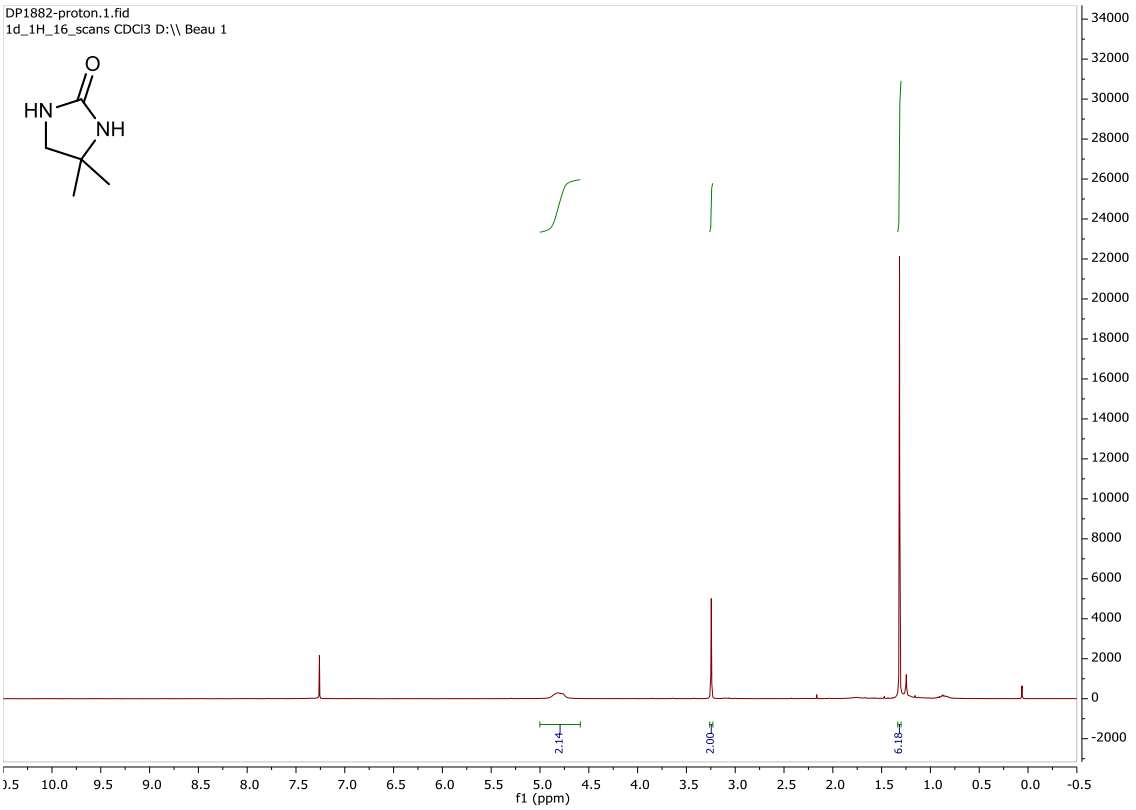

RI12-113-H.001.esp
O
F3C
N
NH
Normalized Intensity
0.92
2.04
2.01
6.00
Chemical Shift (ppm)

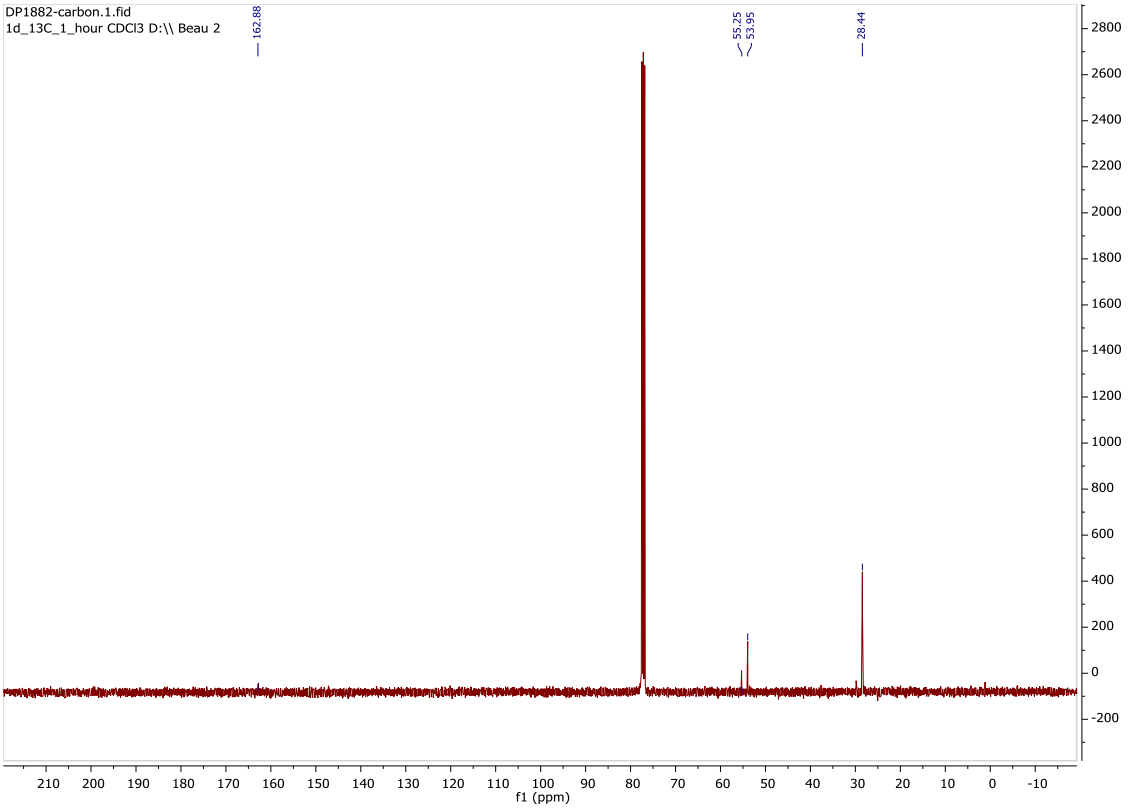

RI12-113-C.001.esp
28.23
160.14
125.93
123.15
120.37
128.70
58.86
52.34
45.75
45.41
45.07
44.73
Normalized Intensity
Chemical Shift (ppm)

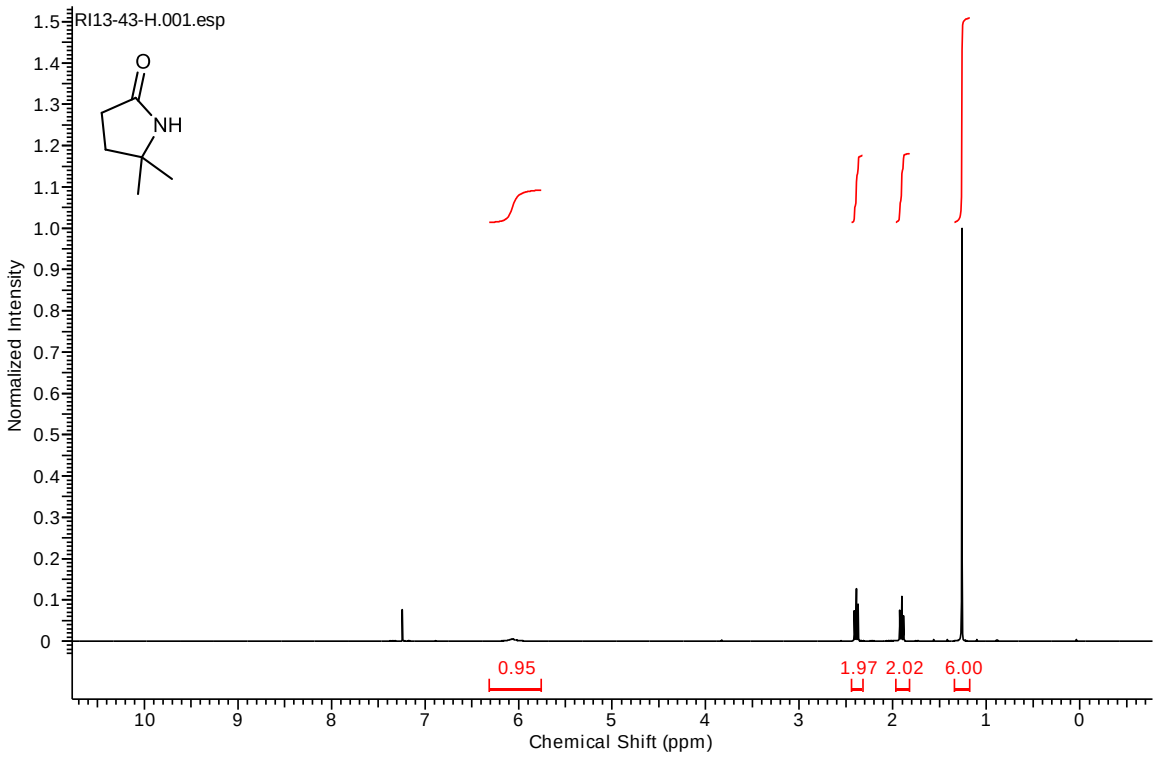

DESKTOP.002.esp
-70.71
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
Chemical Shift (ppm)

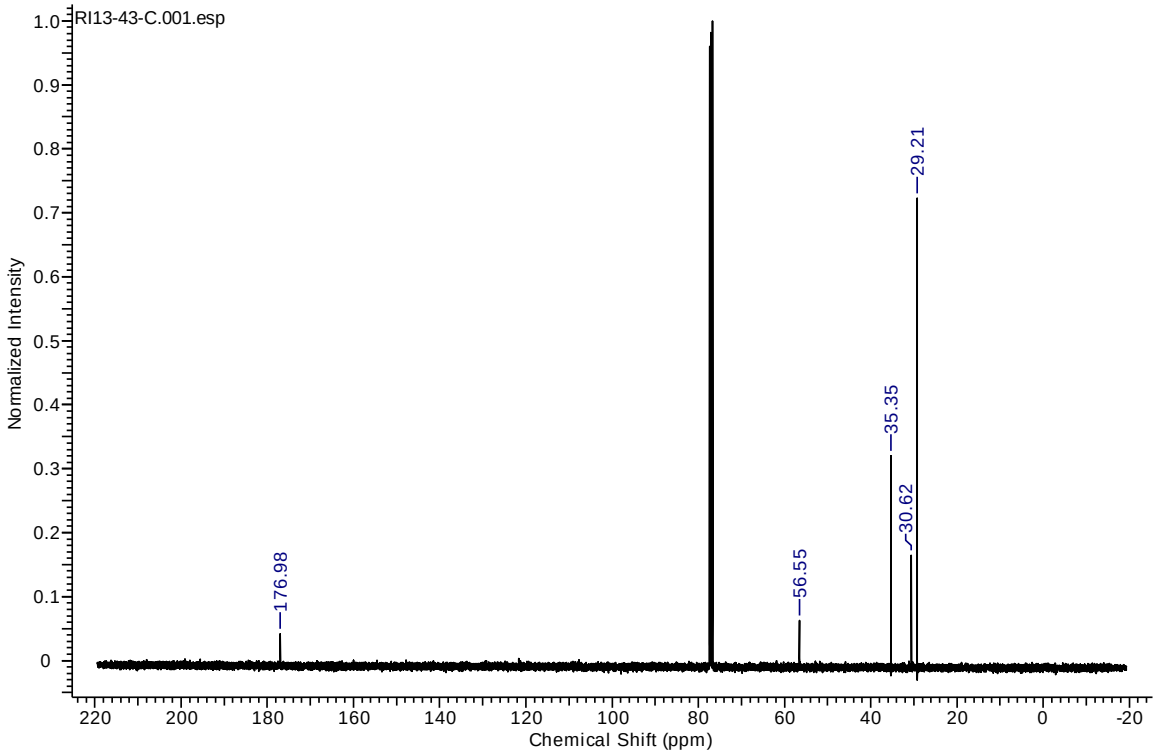

DP-acetal-proton.1.fid
1H NMR
Ph
O
O
O
N
NH
2.00
2.90
0.90
2.09
2.18
2.04
1.97
5.73
f1 (ppm)

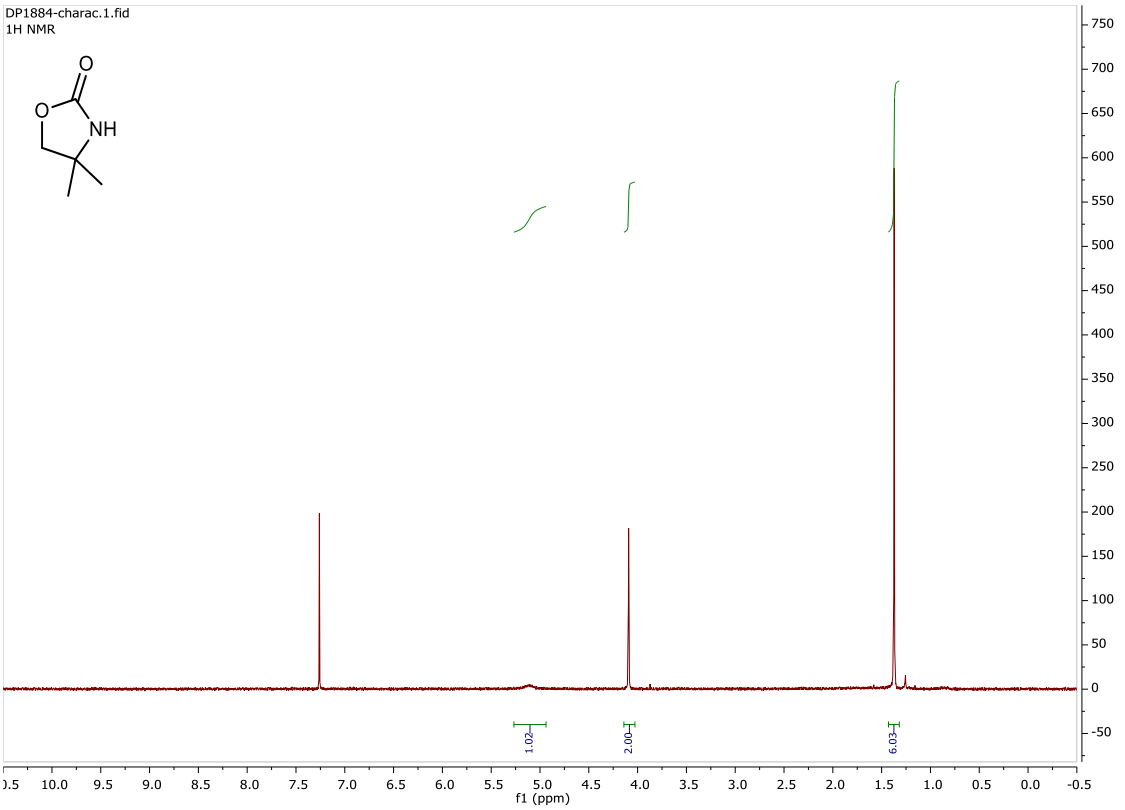

DP1445-F1.004.esp
Normalized Intensity
160.80
140.29
128.34
128.09
126.03
109.66
64.73
59.57
51.76
50.53
28.32
Chemical Shift (ppm)

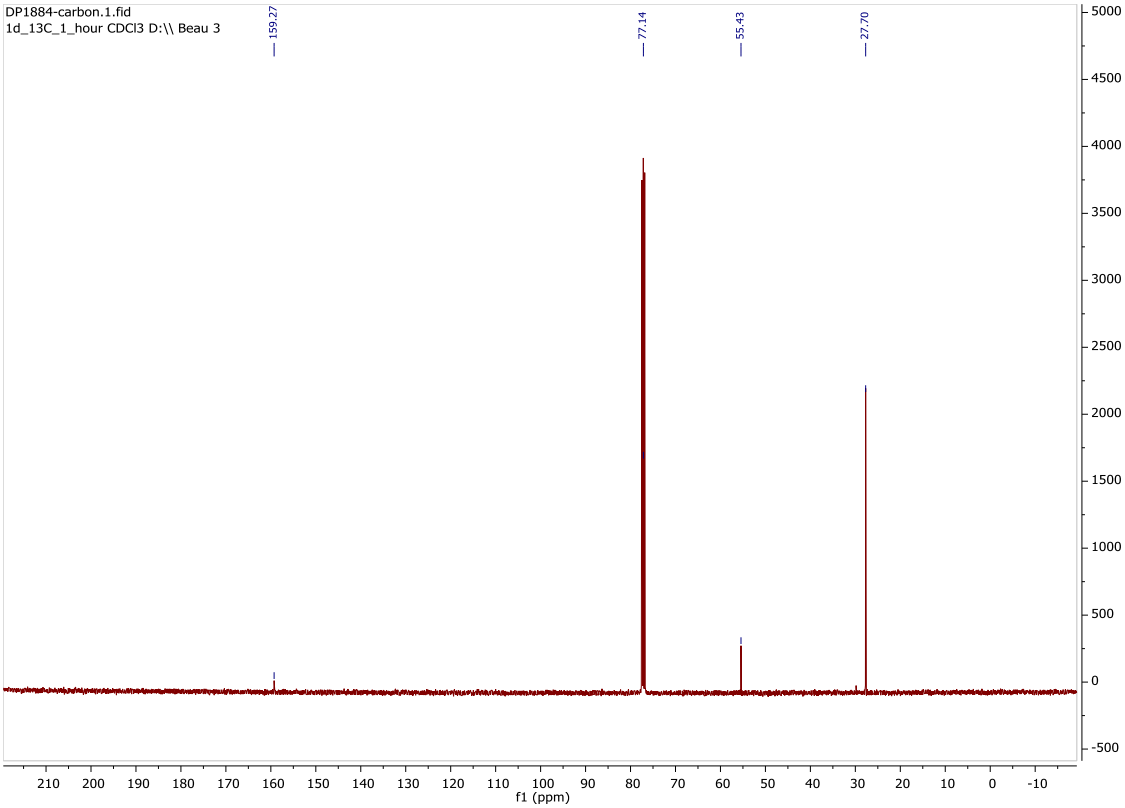

DP1882-proton.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 1
O
HN
NH
2.14
2.00
6.18
f1 (ppm)

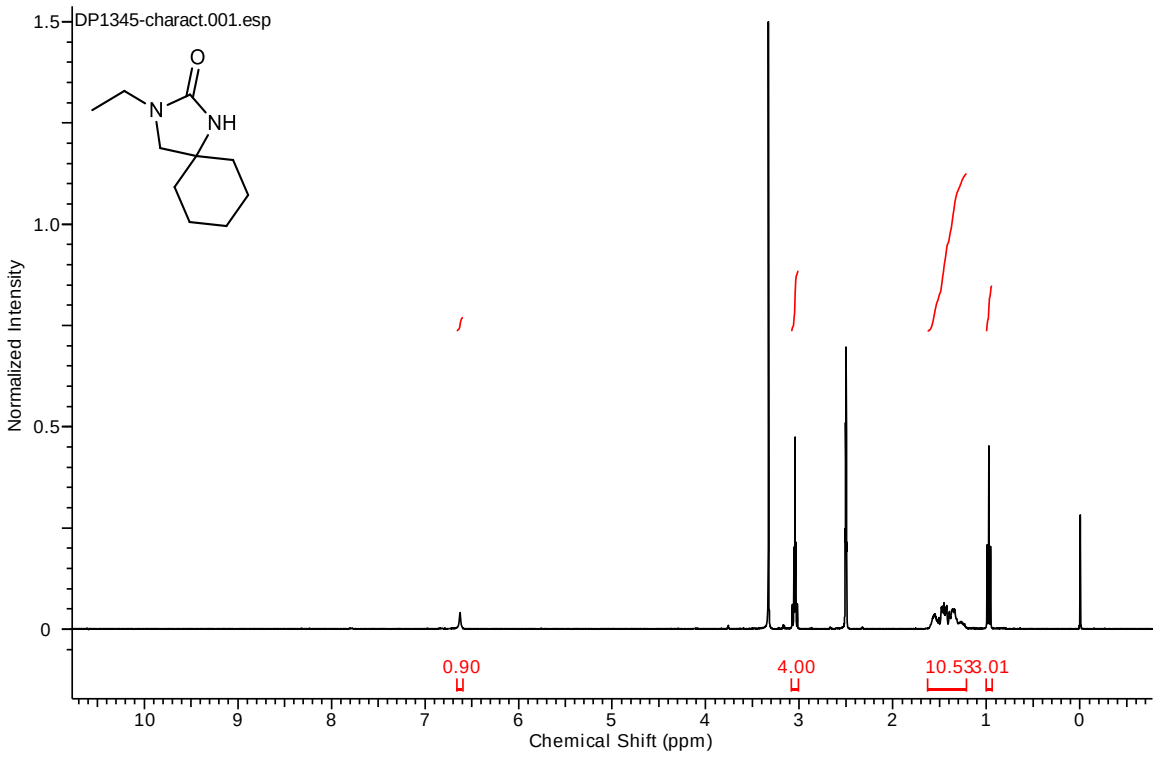

DP1882-carbon.1.fid
1d_13C_1_hour CDCl3 D:\\ Beau 2
162.88
55.25
53.95
28.44
f1 (ppm)

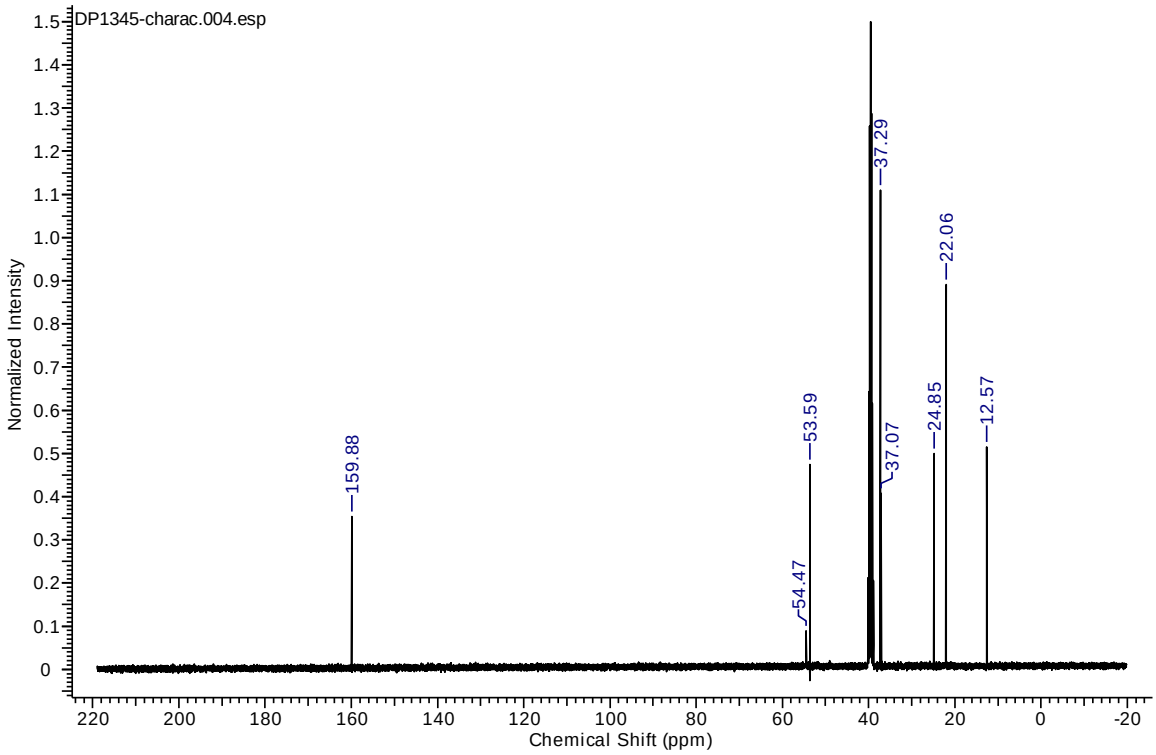

RI13-43-H.001.esp
O
NH
Normalized Intensity
0.95
1.97
2.02
6.00
Chemical Shift (ppm)

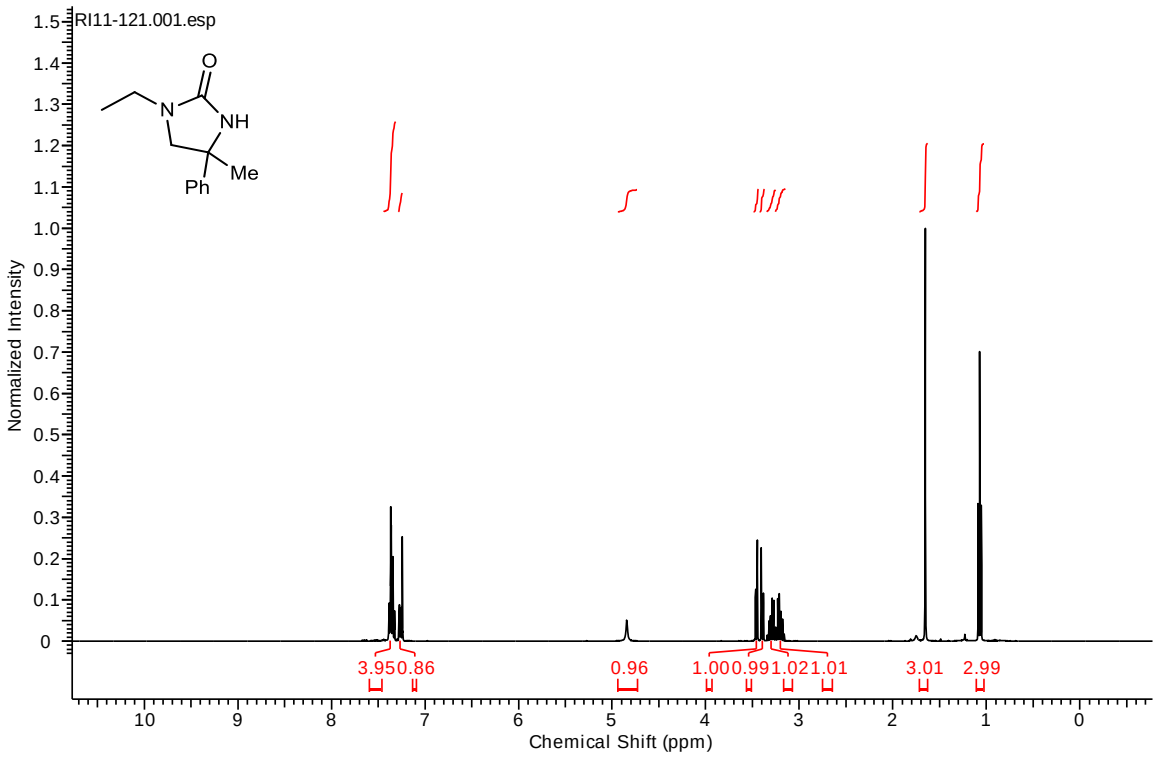

RI13-43-C.001.esp
Normalized Intensity
176.98
56.55
35.35
30.62
29.21
Chemical Shift (ppm)

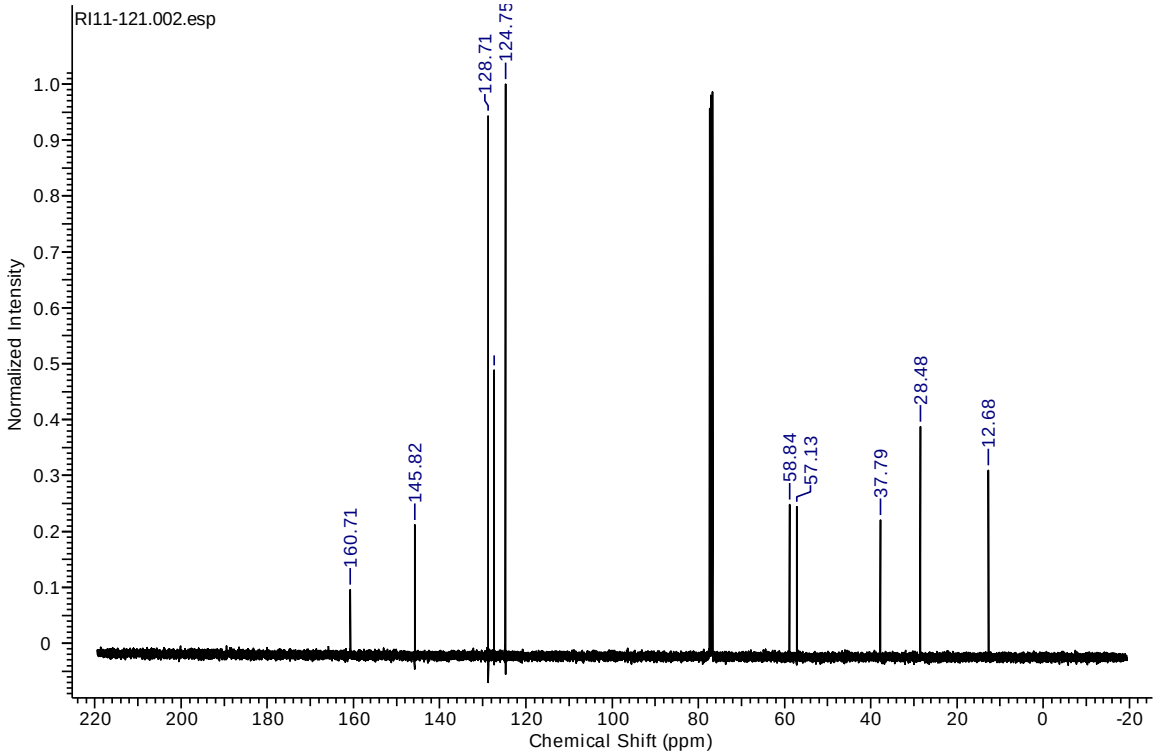

DP1884-charac.1.fid
1H NMR
O
O
NH
1.02
2.00
6.03
f1 (ppm)

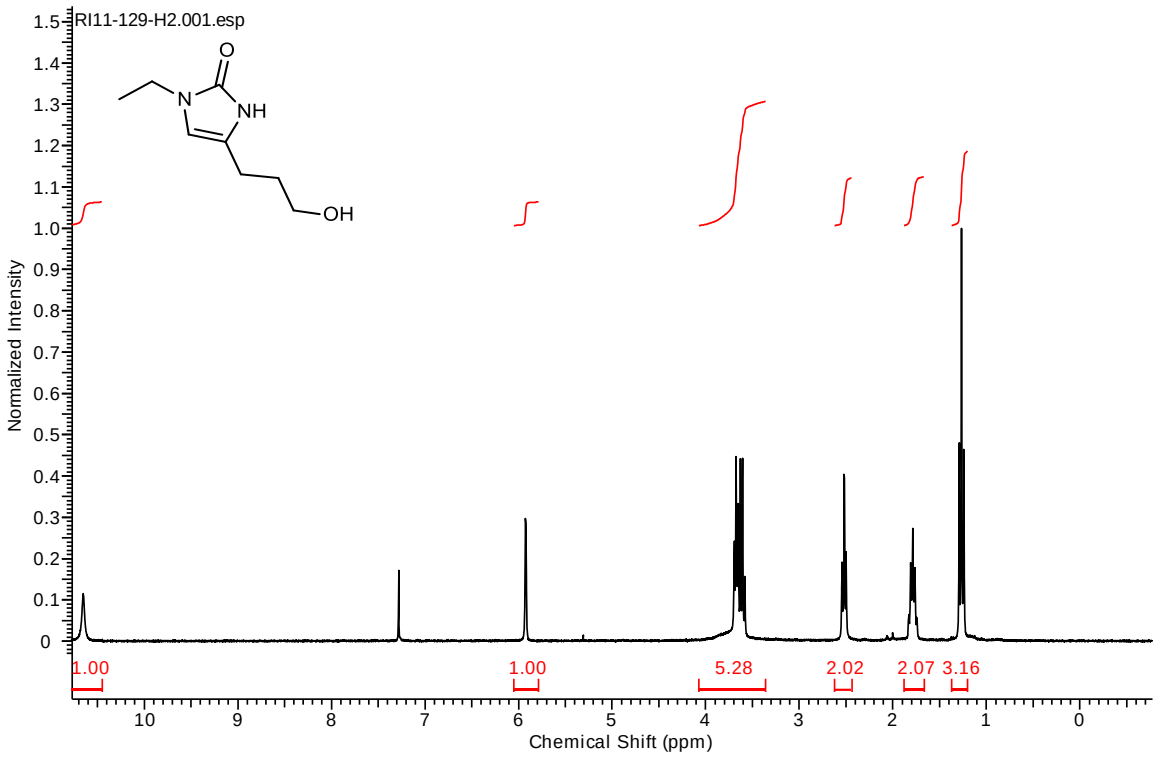

DP1884-carbon.1.fid
1d_13C_1_hour CDCl3 D:\\ Beau 3
159.27
77.14
55.43
27.70
f1 (ppm)

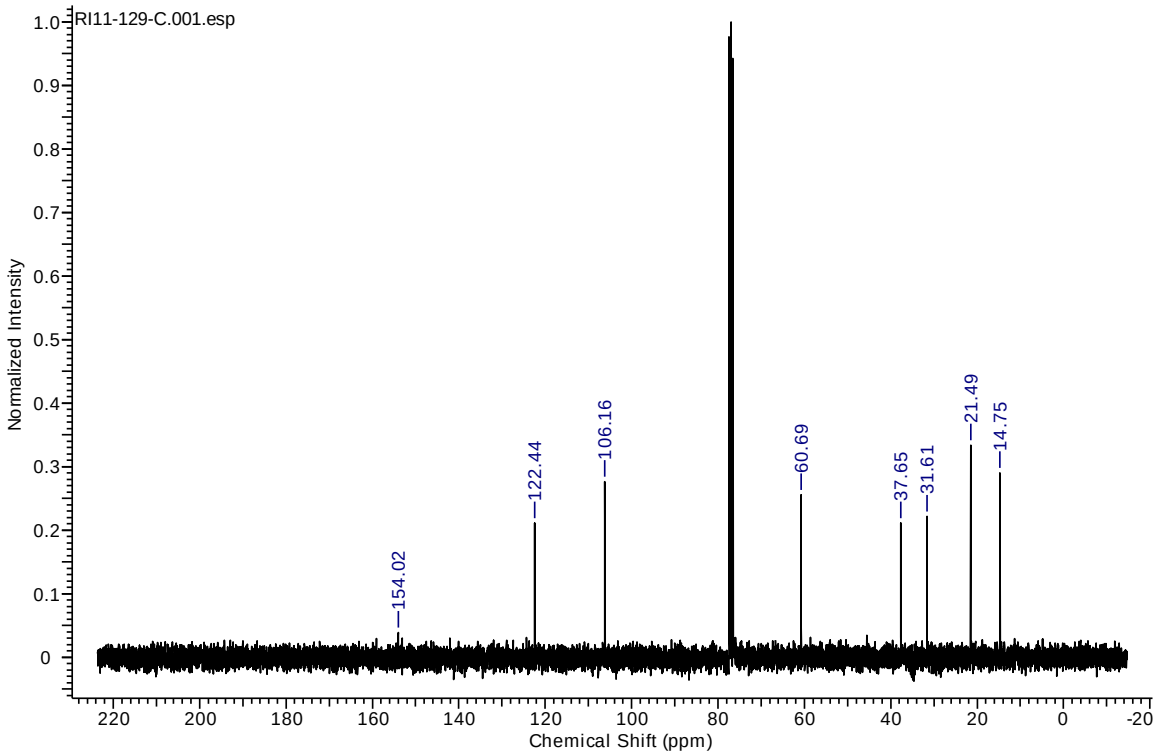

DP1345-charact.001.esp
O
N
NH
Normalized Intensity
0.90
4.00
10.53
3.01
Chemical Shift (ppm)

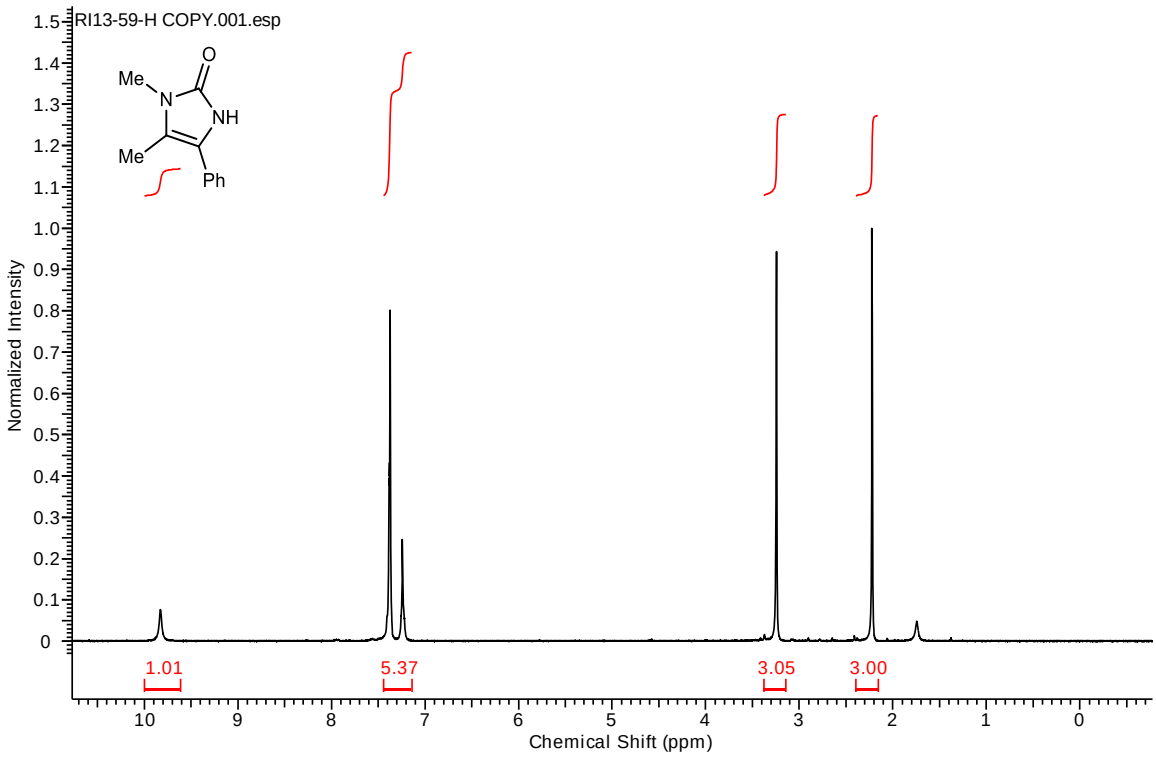

DP1345-charac.004.esp
Normalized Intensity
159.88
54.47
53.59
37.29
37.07
24.85
22.06
12.57
Chemical Shift (ppm)

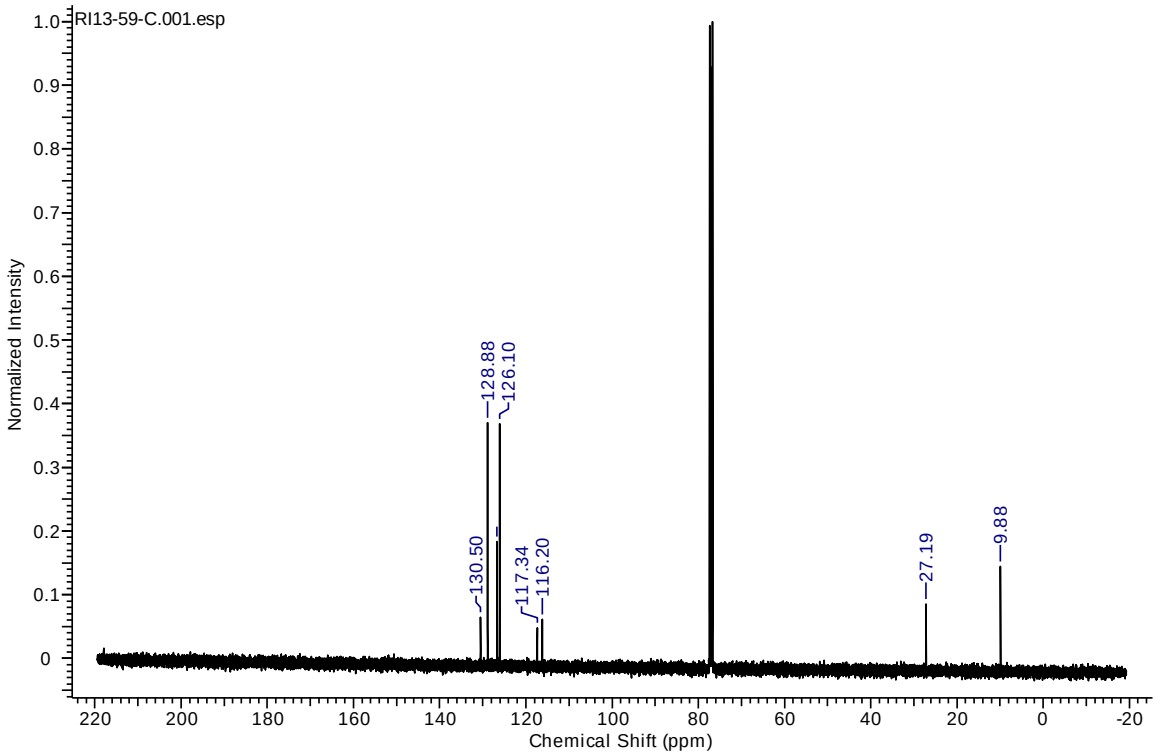

RI11-121.001.esp
O
N
NH
Me
Ph
Normalized Intensity
3.95
0.86
0.96
1.00
0.99
1.02
1.01
3.01
2.99
Chemical Shift (ppm)

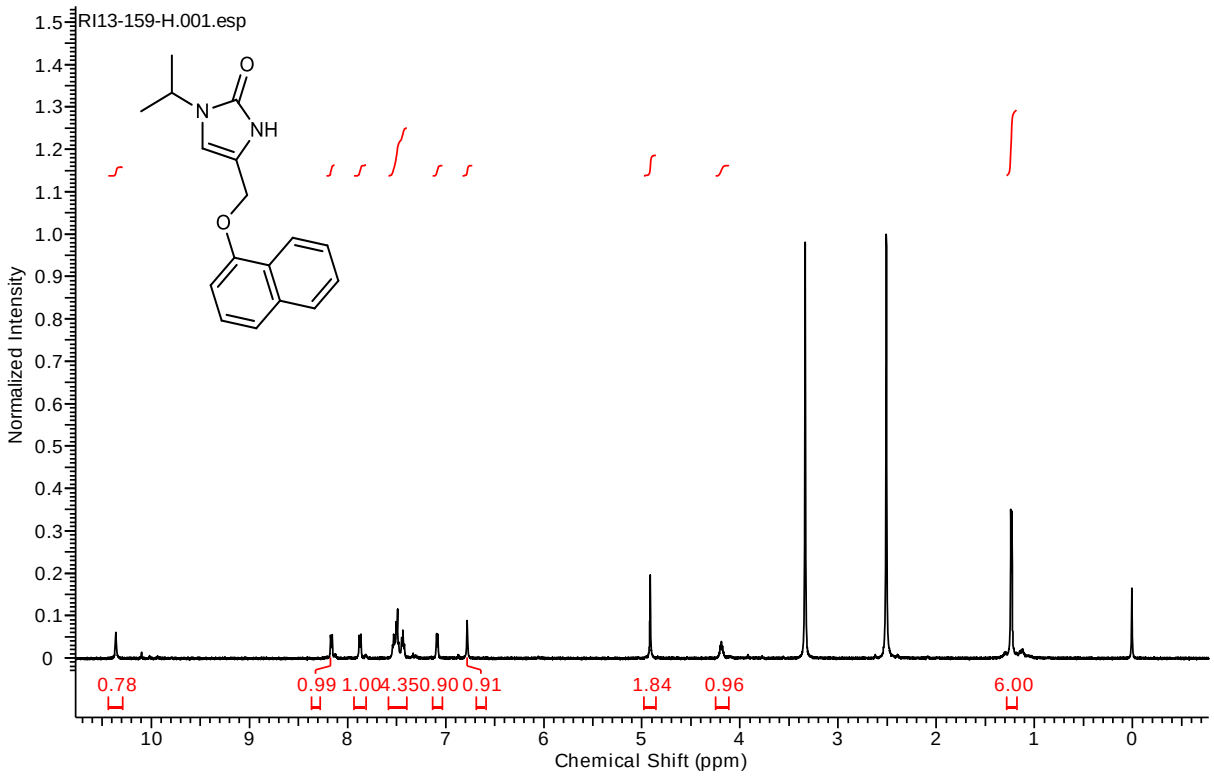

RI11-121.002.esp
128.71
124.75
160.71
145.82
58.84
57.13
37.79
28.48
12.68
Normalized Intensity
Chemical Shift (ppm)

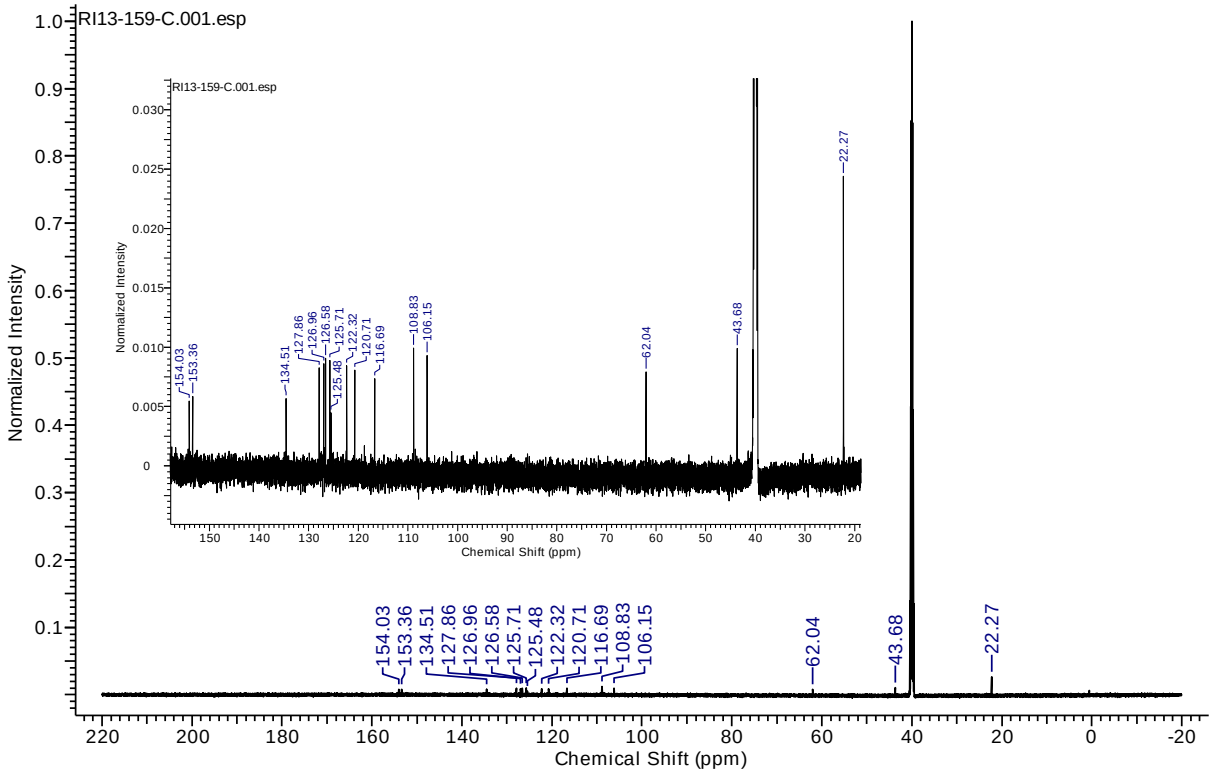

RI11-129-H2.001.esp
O
N
NH
OH
Normalized Intensity
1.00
1.00
5.28
2.02
2.07
3.16
Chemical Shift (ppm)

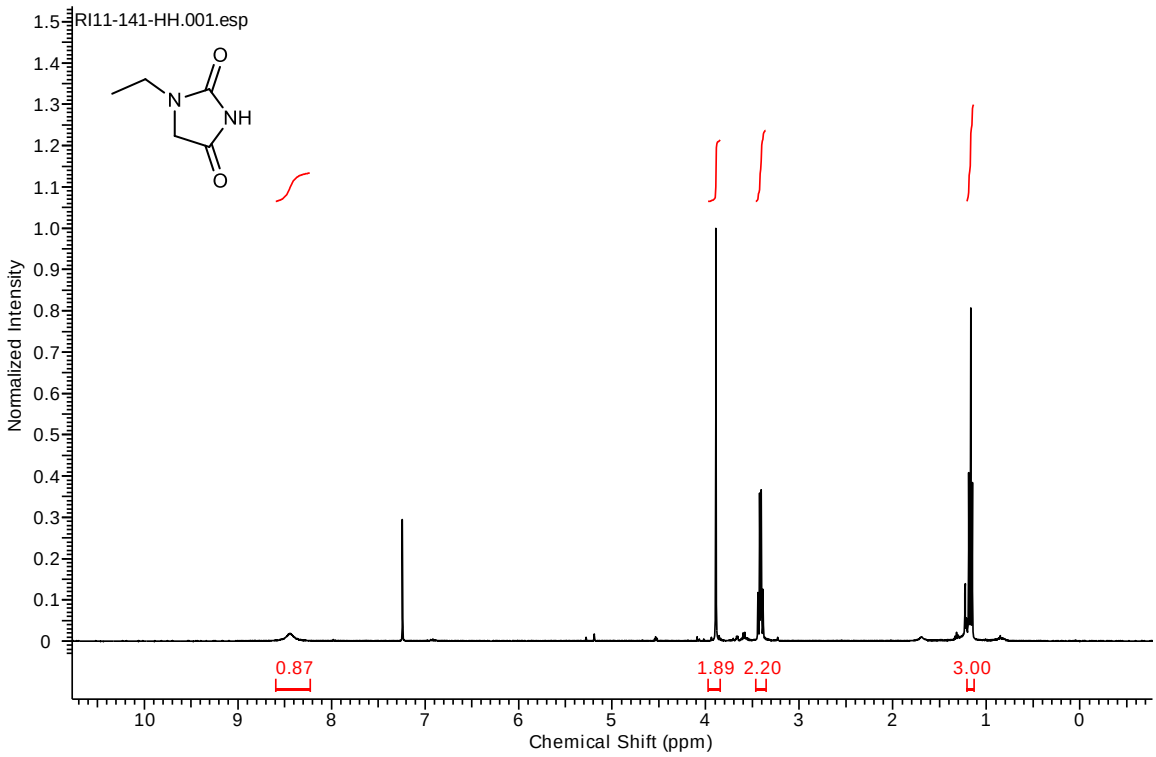

RI11-129-C.001.esp
Normalized Intensity
154.02
122.44
106.16
60.69
37.65
31.61
21.49
14.75
Chemical Shift (ppm)

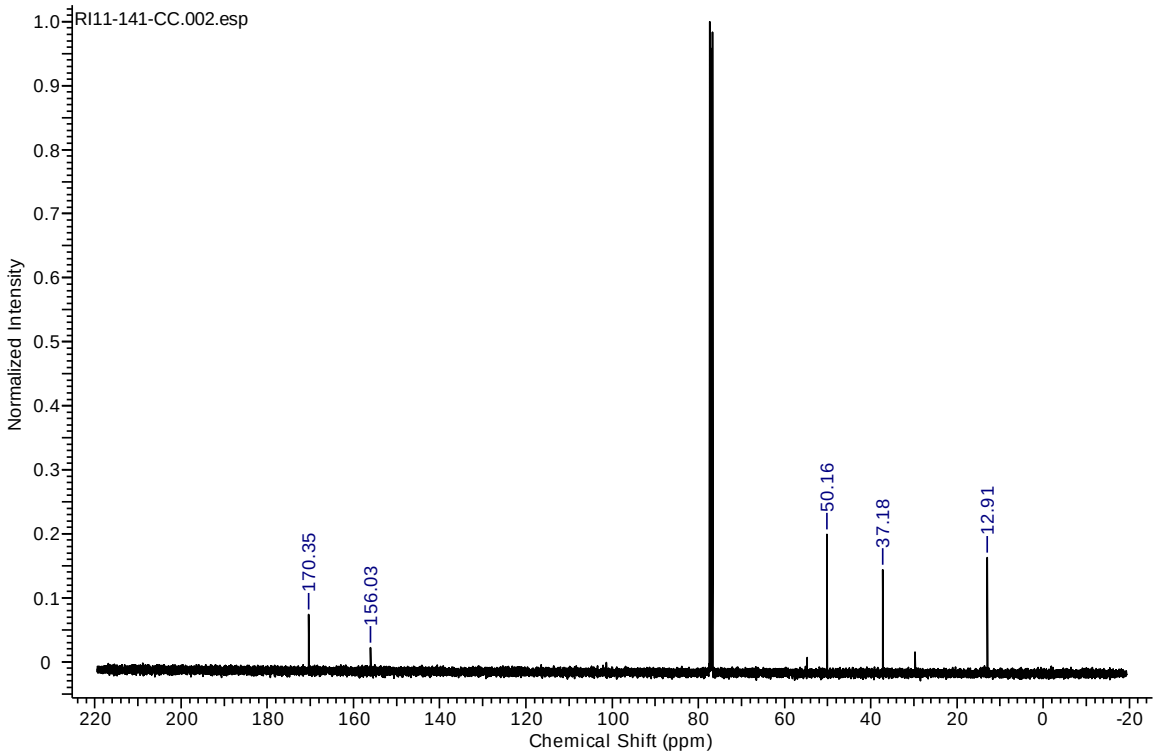

RI13-59-H COPY.001.esp
Me
N
O
NH
Me
Ph
Normalized Intensity
1.01
5.37
3.05
3.00
Chemical Shift (ppm)

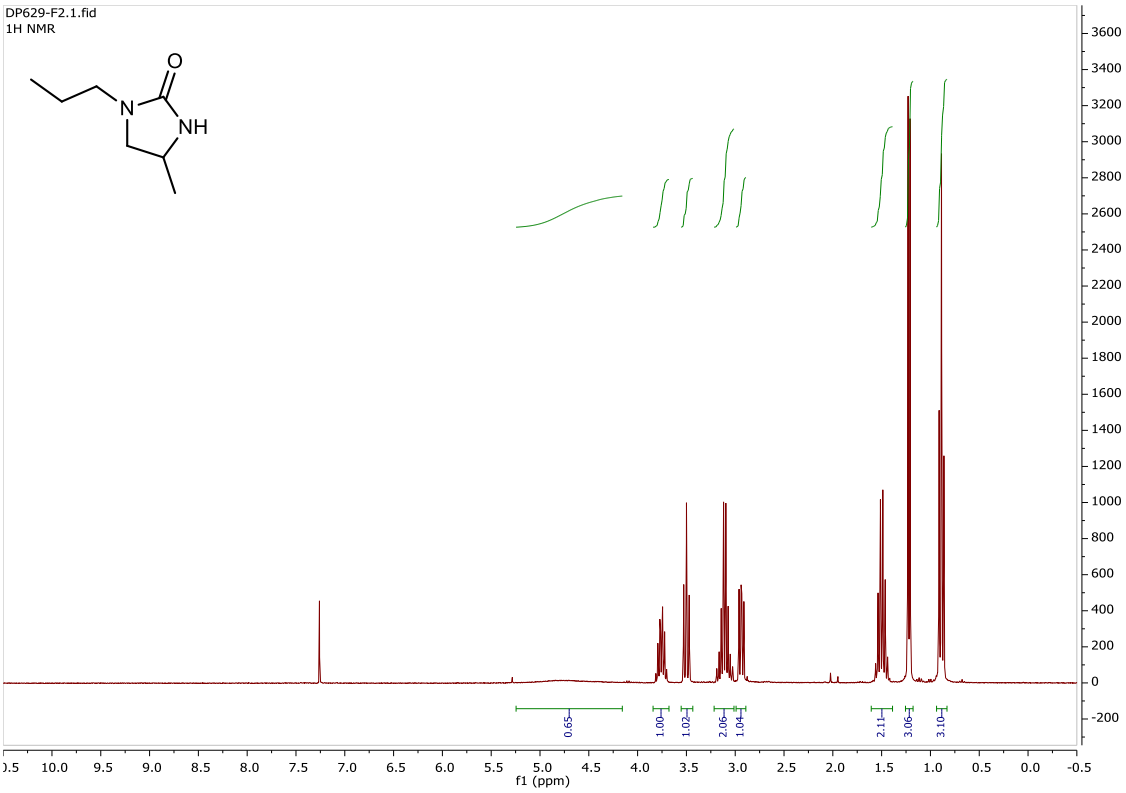

RI13-59-C.001.esp
Normalized Intensity
128.88
126.10
130.50
117.34
116.20
27.19
9.88
Chemical Shift (ppm)

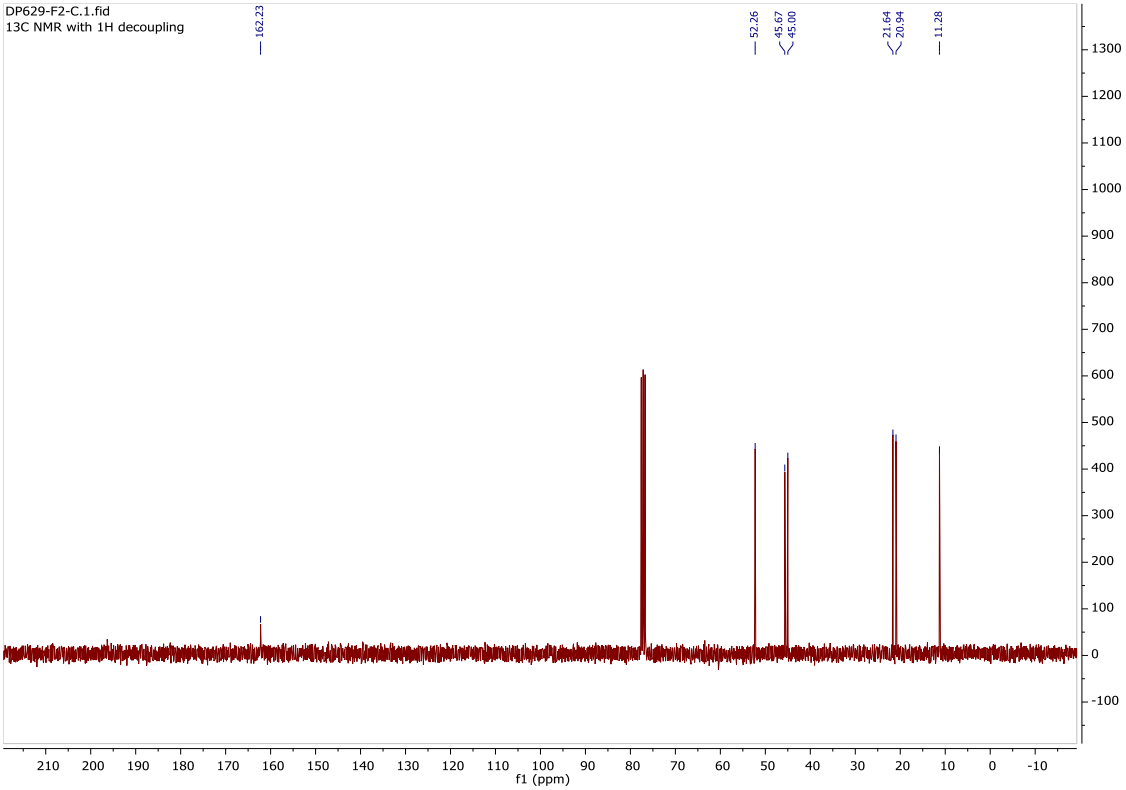

RI13-159-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.78
0.99
1.00
4.35
0.90
0.91
1.84
0.96
6.00

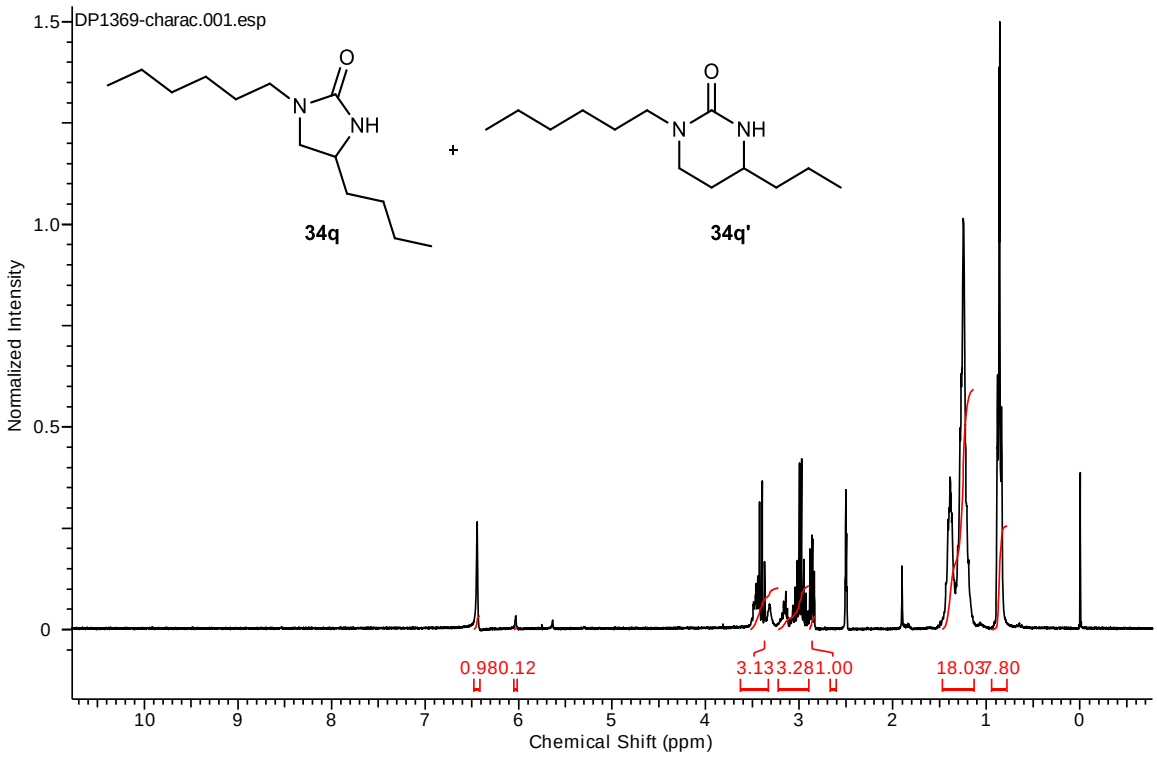

RI13-159-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
154.03
153.36
134.51
127.86
126.96
126.58
125.71
125.48
122.32
120.71
116.69
108.83
106.15
62.04
43.68
22.27

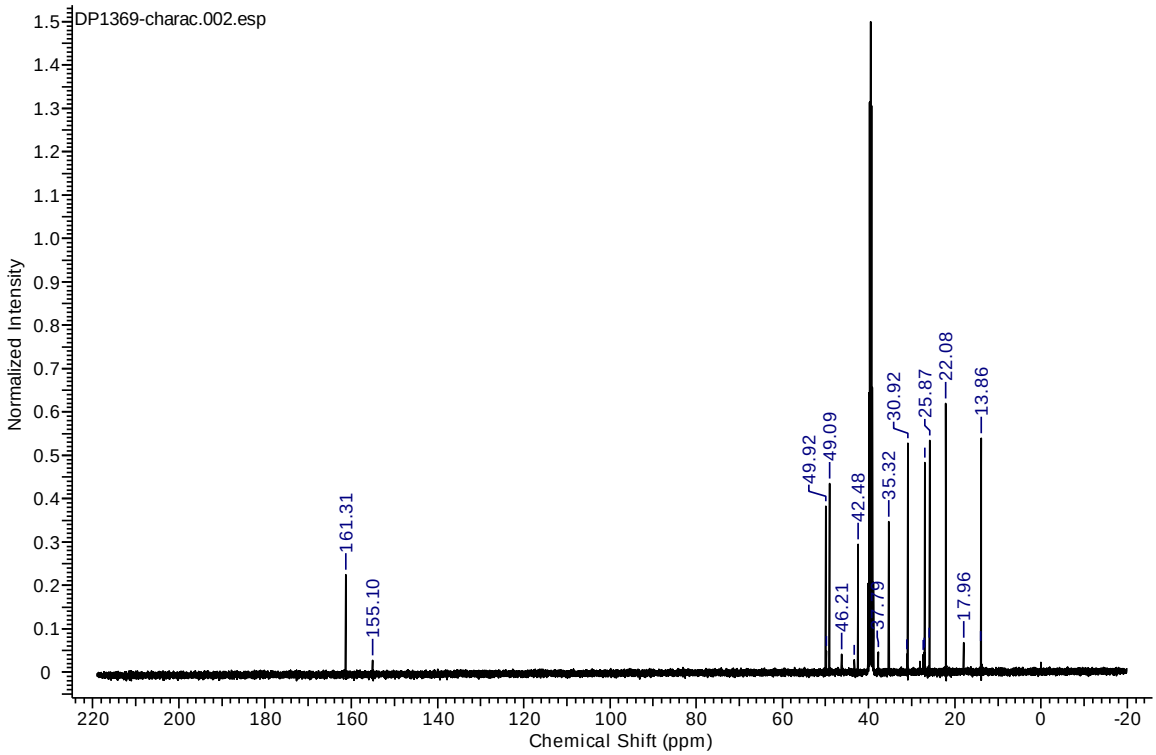

RI11-141-HH.001.esp
O
N
NH
O
Normalized Intensity
0.87
1.89
2.20
3.00
Chemical Shift (ppm)

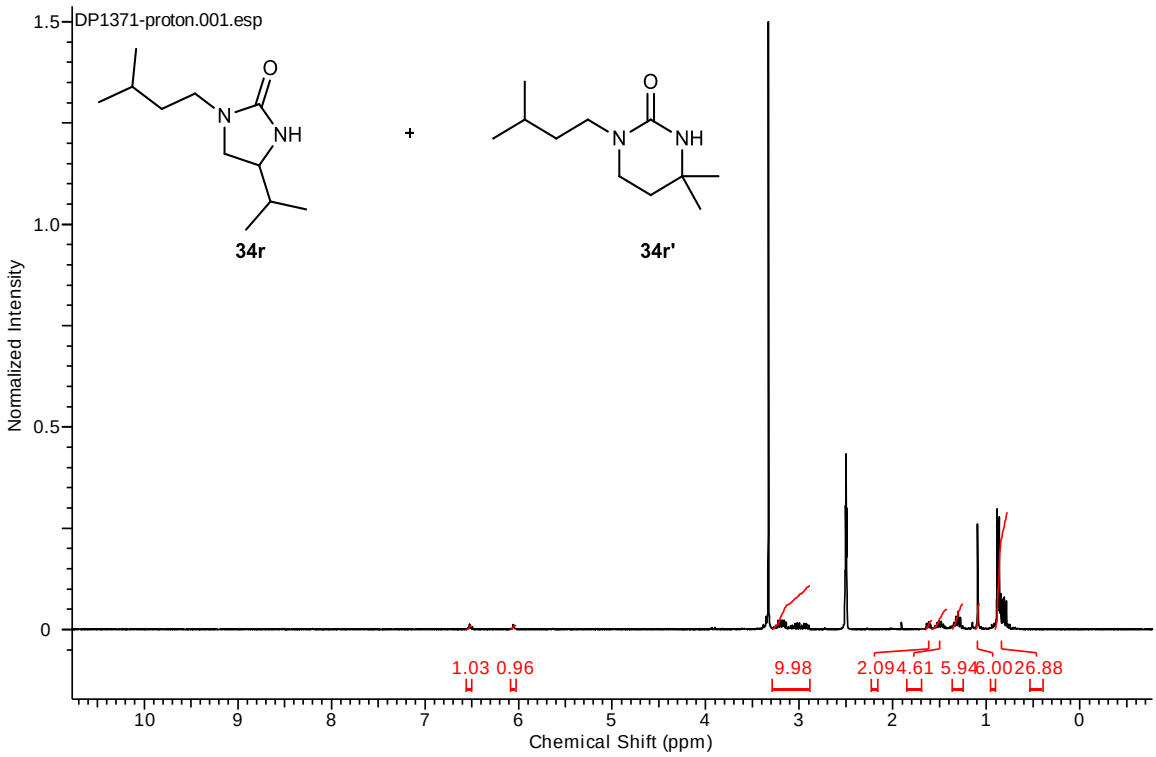

RI11-141-CC.002.esp
Normalized Intensity
170.35
156.03
50.16
37.18
12.91
Chemical Shift (ppm)

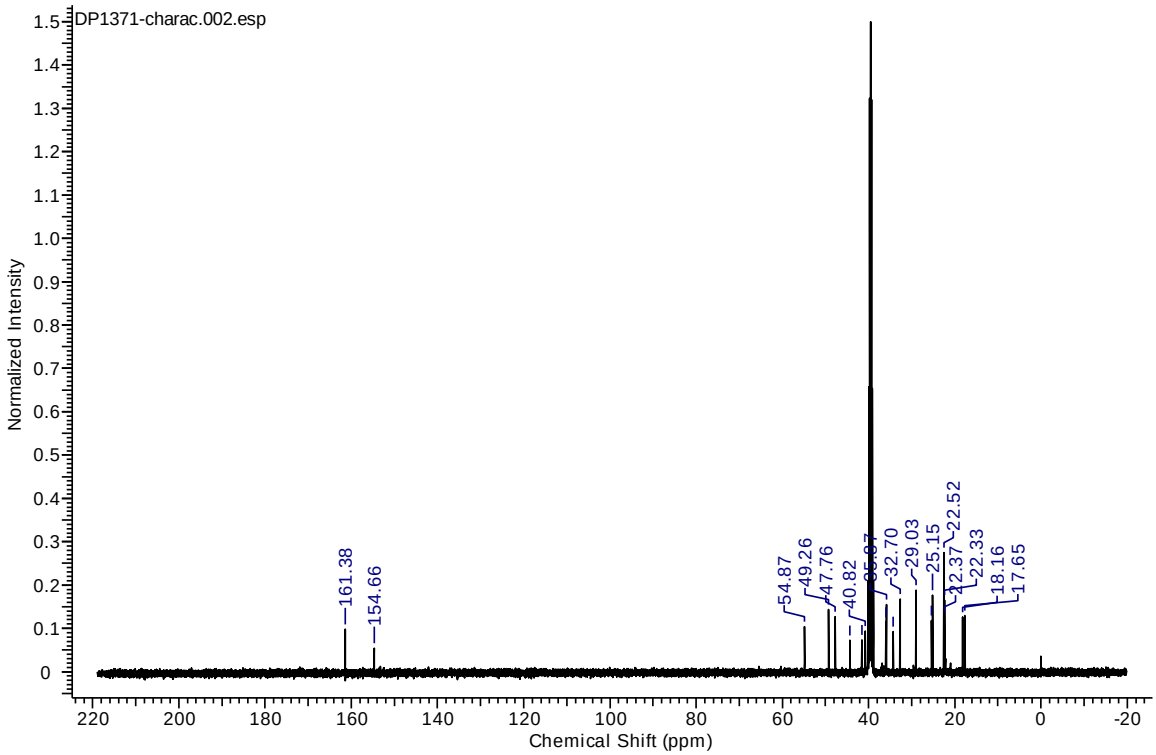

DP629-F2.1.fid
1H NMR
O
N
NH
0.65
1.00
1.02
2.06
1.04
2.11
3.06
3.10
f1 (ppm)

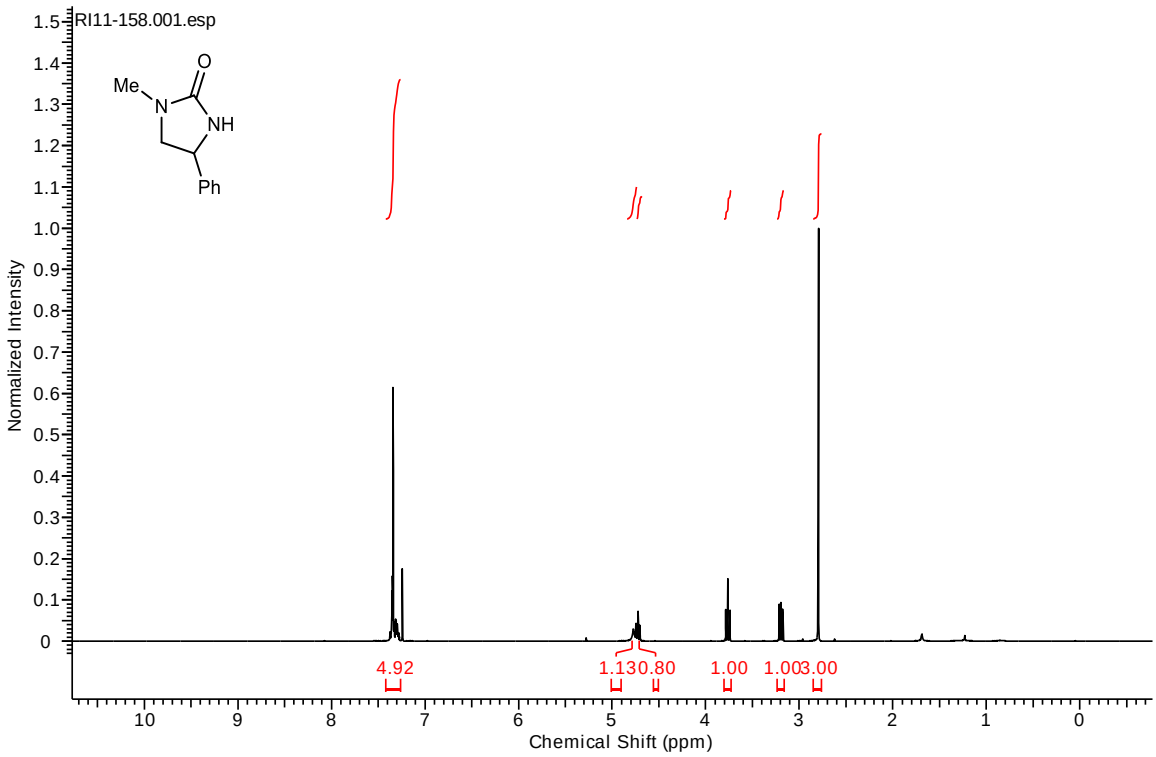

DP629-F2-C.1.fid
13C NMR with 1H decoupling
162.23
52.26
45.67
45.00
21.64
20.94
11.28
f1 (ppm)

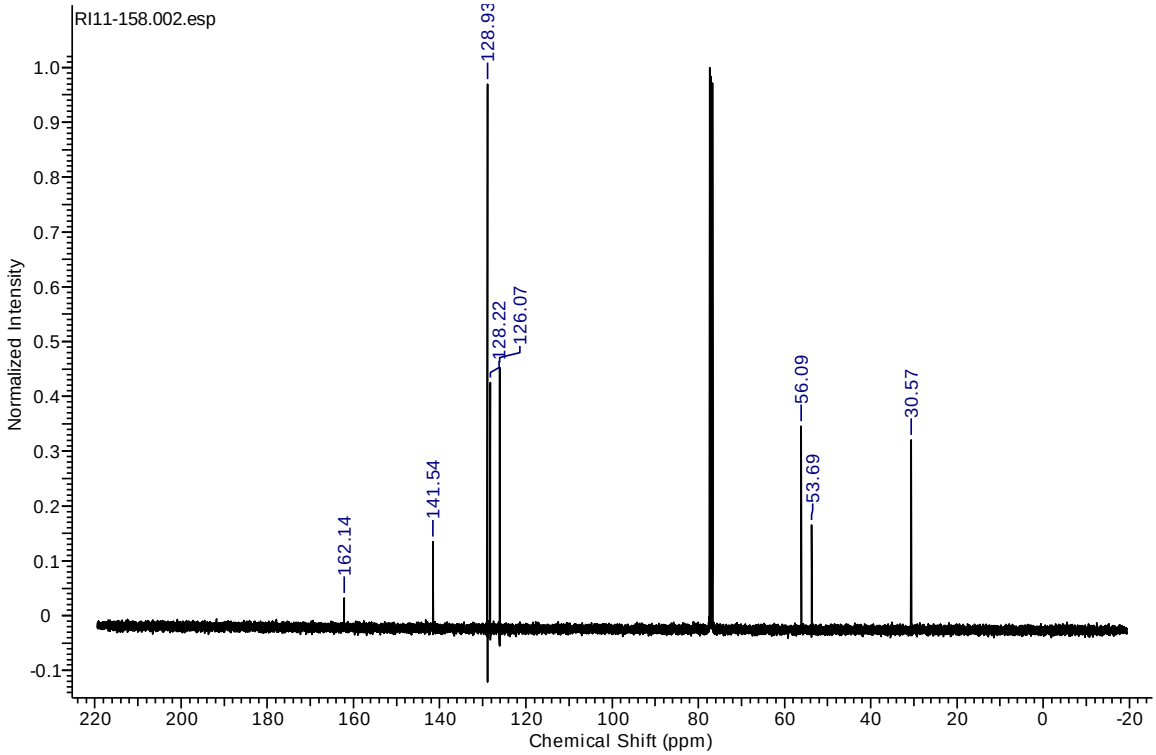

DP1369-charac.001.esp
34q
34q'
Normalized Intensity
Chemical Shift (ppm)
0.98
0.12
3.13
3.28
1.00
18.03
7.80

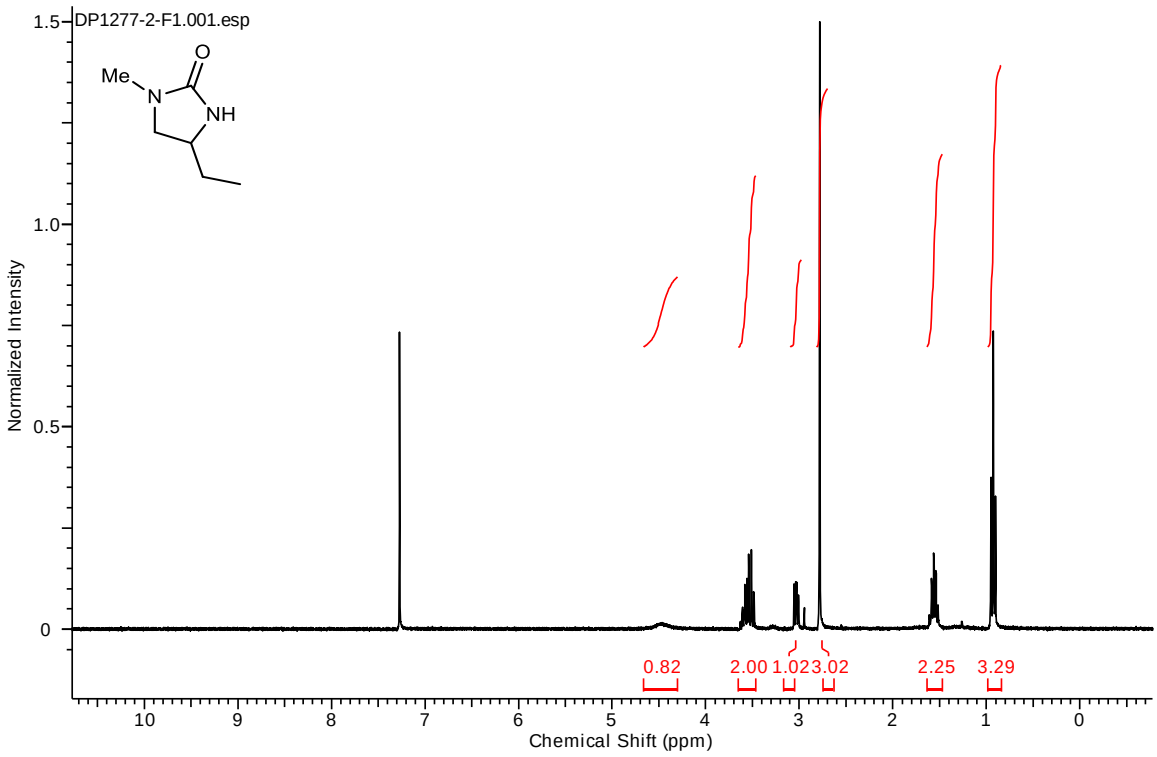

DP1369-charac.002.esp
Normalized Intensity
Chemical Shift (ppm)
161.31
155.10
49.92
49.09
46.21
42.48
37.79
35.32
30.92
25.87
22.08
17.96
13.86

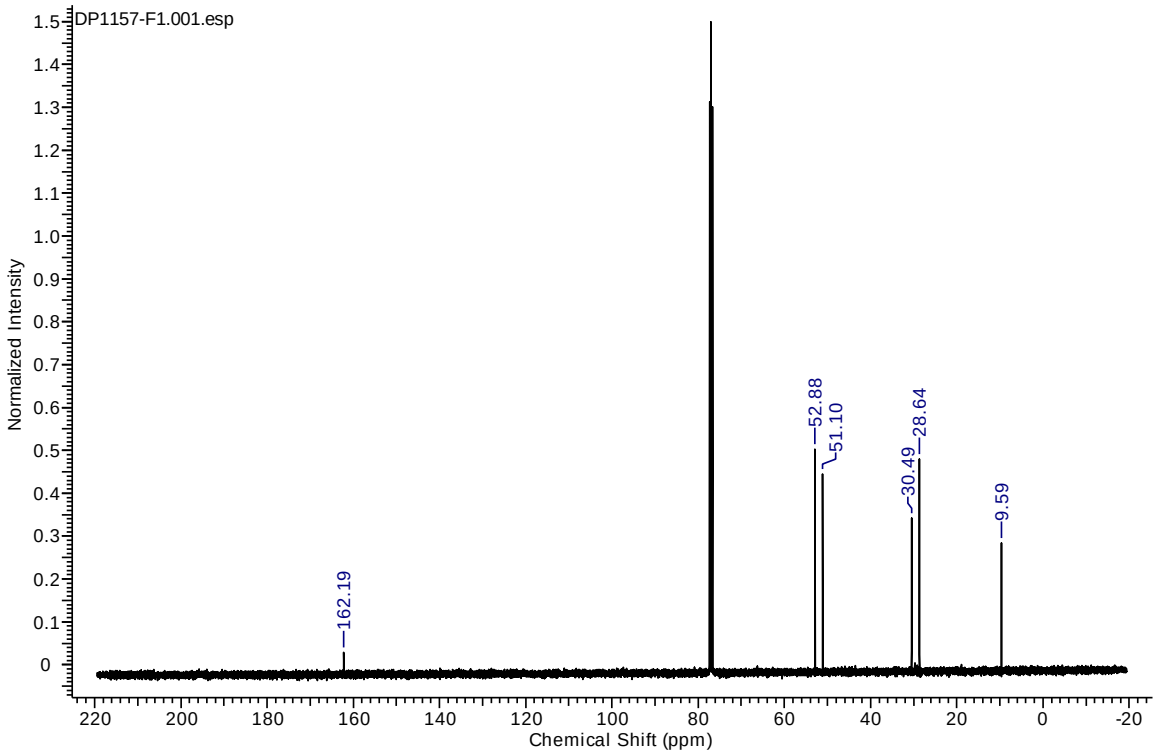

DP1371-proton.001.esp
34r
34r'
Normalized Intensity
Chemical Shift (ppm)
1.03 0.96
9.98
2.09 4.61 5.94 6.00 26.88

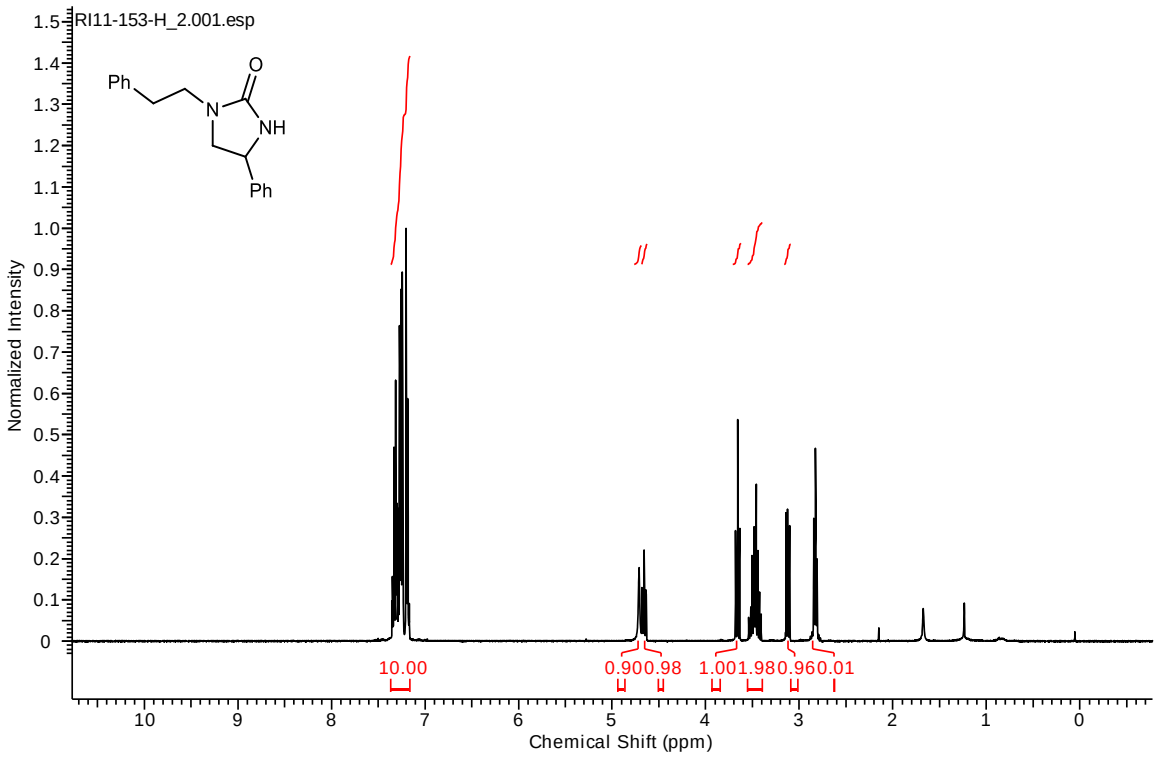

DP1371-charac.002.esp
Normalized Intensity
Chemical Shift (ppm)
161.38
154.66
54.87
49.26
47.76
40.82
32.70
29.03
25.15
22.52
22.37
22.33
18.16
17.65

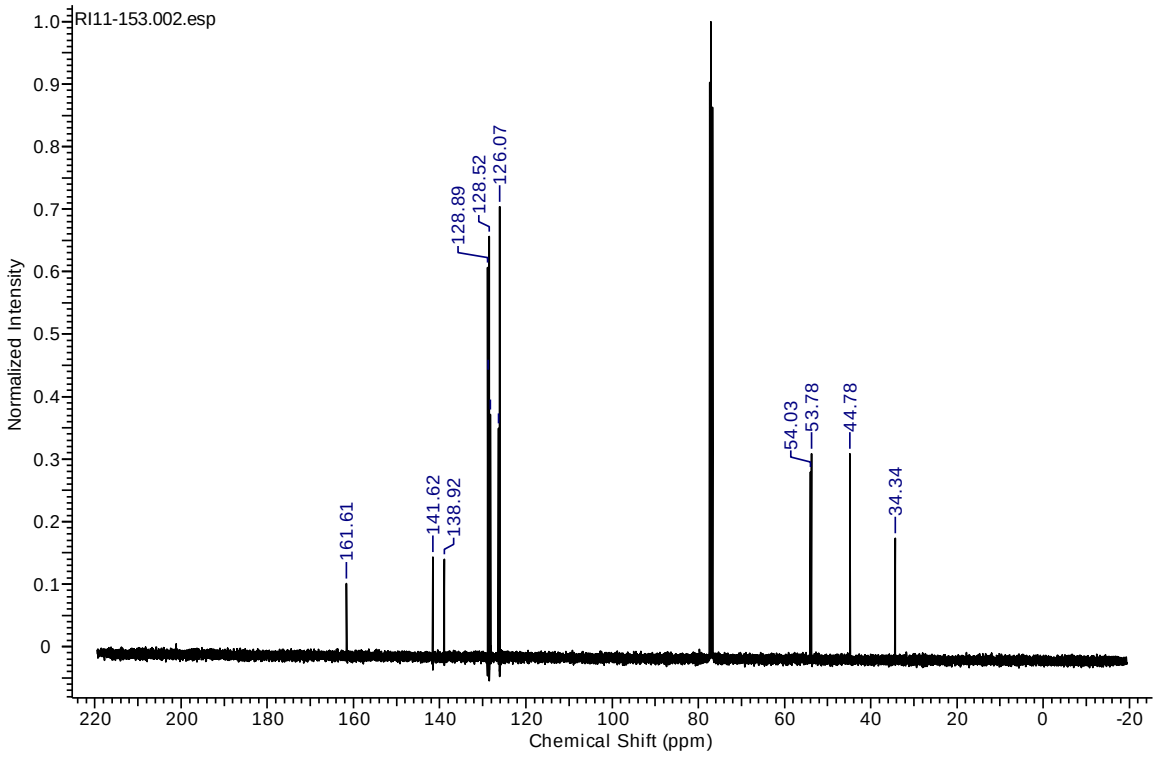

RI11-158.001.esp
Me
N
O
NH
Ph
Normalized Intensity
4.92
1.13
0.80
1.00
1.00
3.00
Chemical Shift (ppm)

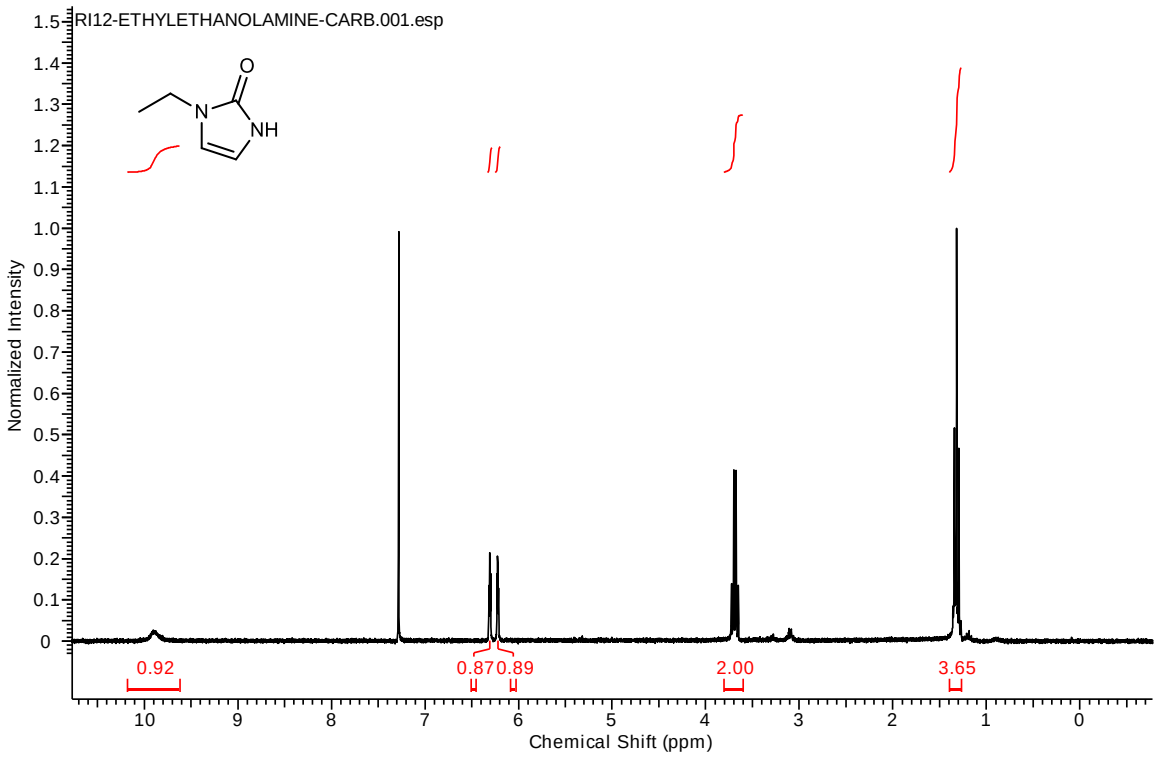

RI11-158.002.esp
128.93
128.22
126.07
162.14
141.54
56.09
53.69
30.57
Normalized Intensity
Chemical Shift (ppm)

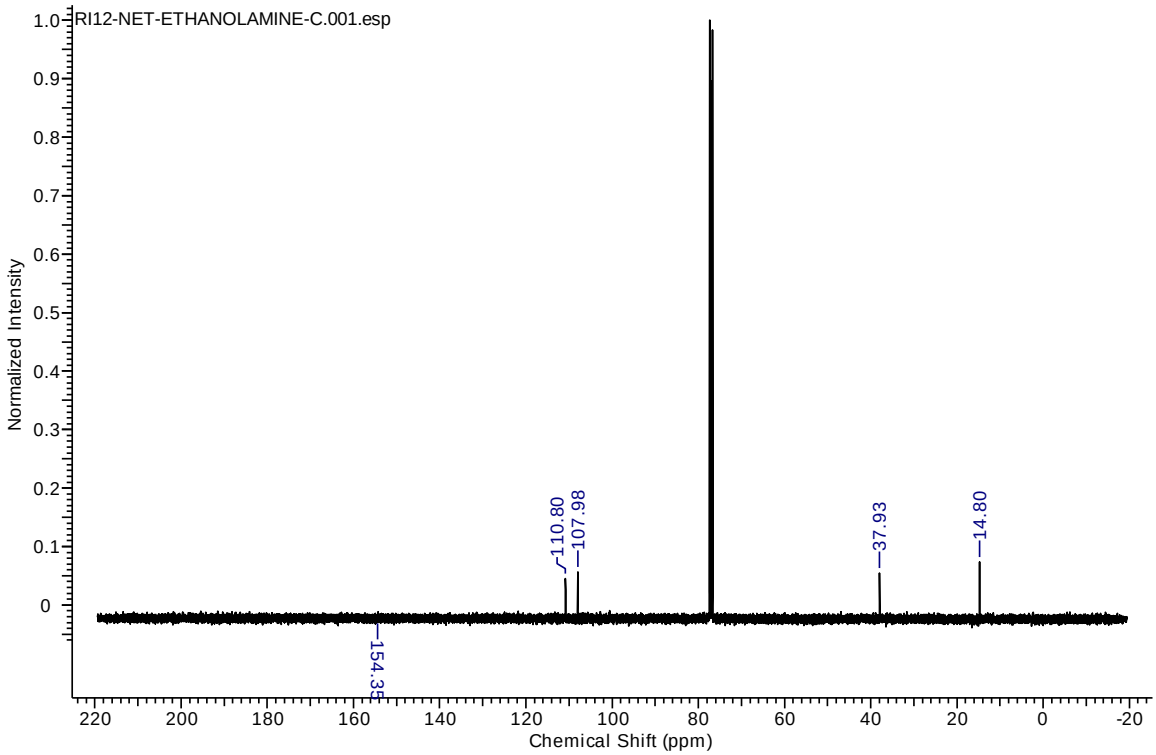

DP1277-2-F1.001.esp
Me
N
O
NH
Normalized Intensity
Chemical Shift (ppm)
0.82
2.00
1.02
3.02
2.25
3.29

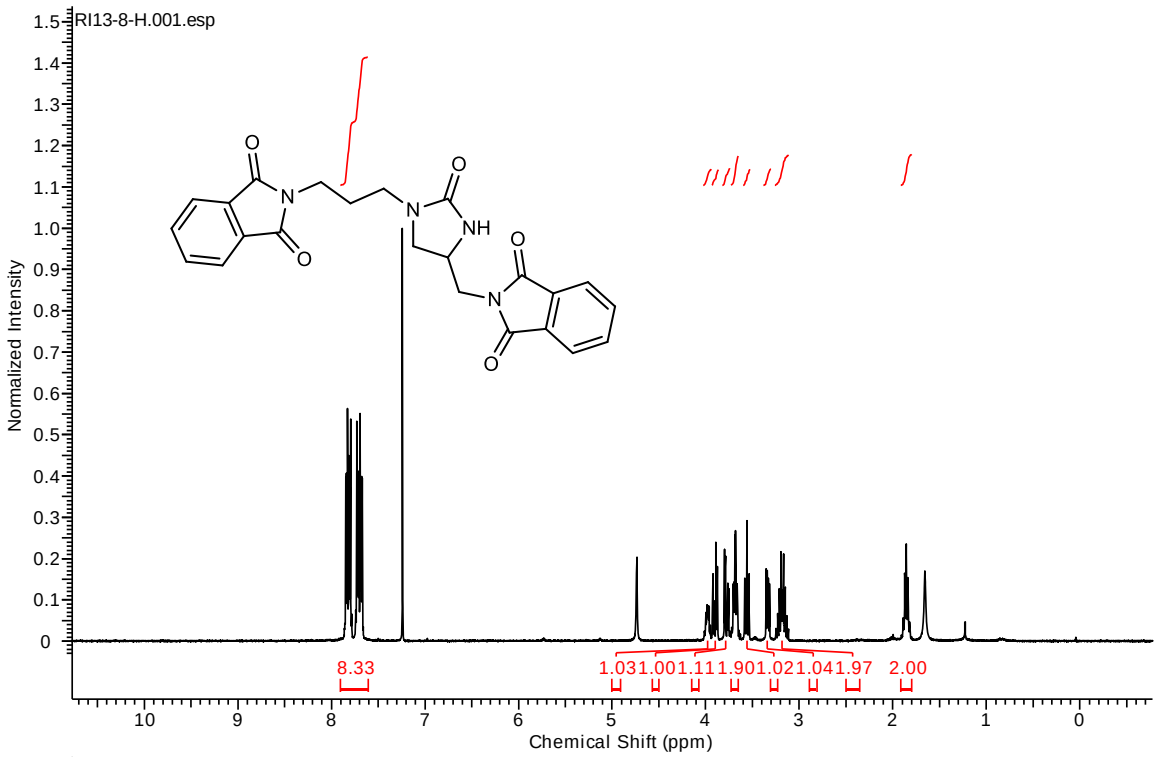

DP1157-F1.001.esp
Normalized Intensity
Chemical Shift (ppm)
162.19
52.88
51.10
30.49
28.64
9.59

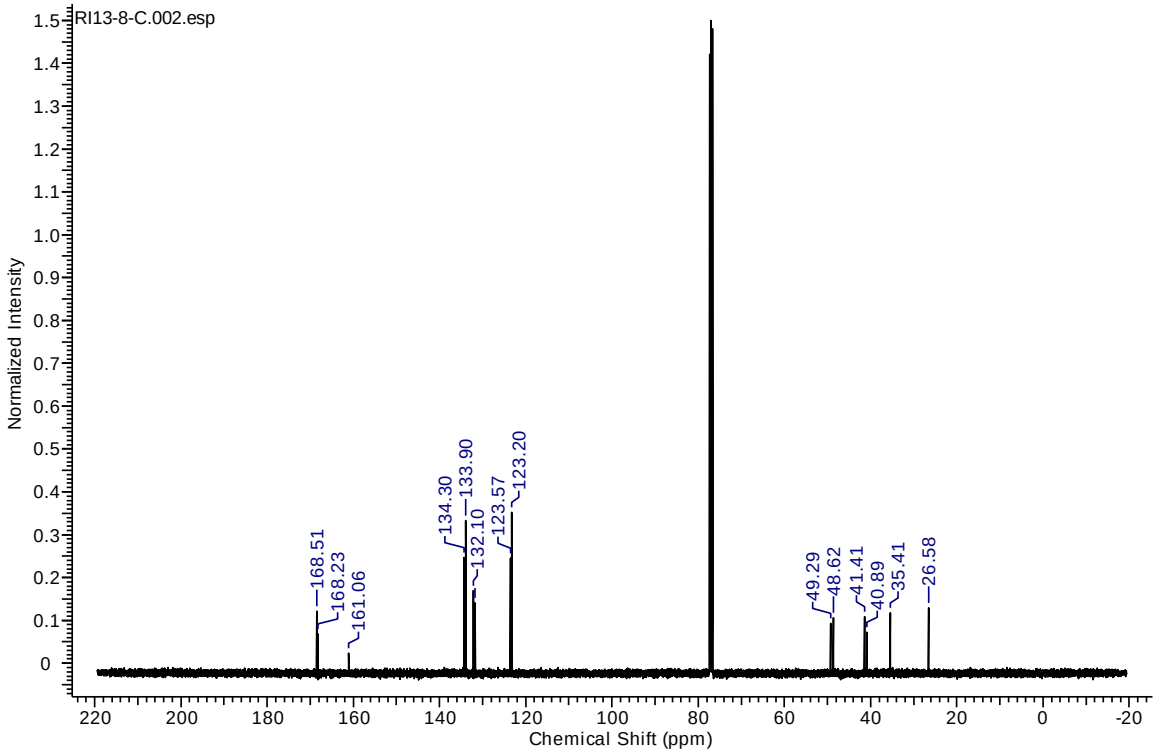

RI11-153-H_2.001.esp
Ph
O
N
NH
Ph
Normalized Intensity
10.00
0.90
0.98
1.00
1.98
0.96
0.01
Chemical Shift (ppm)

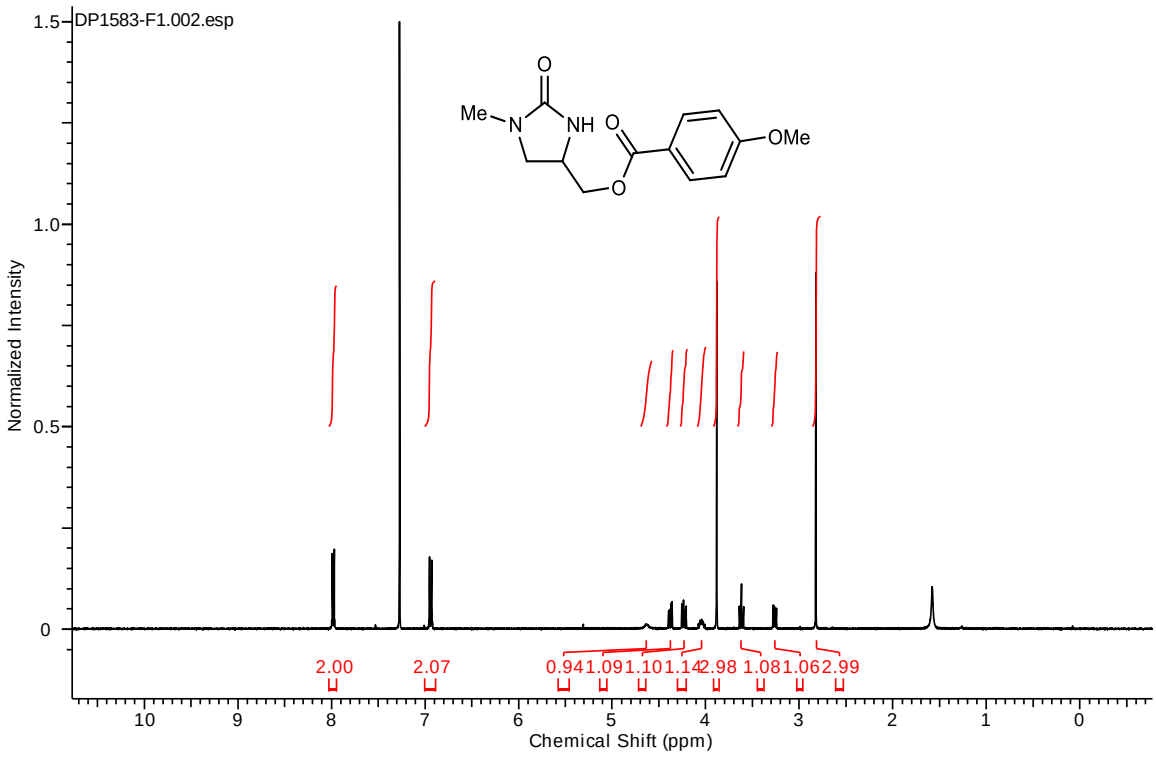

RI11-153.002.esp
161.61
141.62
138.92
128.89
128.52
126.07
54.03
53.78
44.78
34.34
Normalized Intensity
Chemical Shift (ppm)

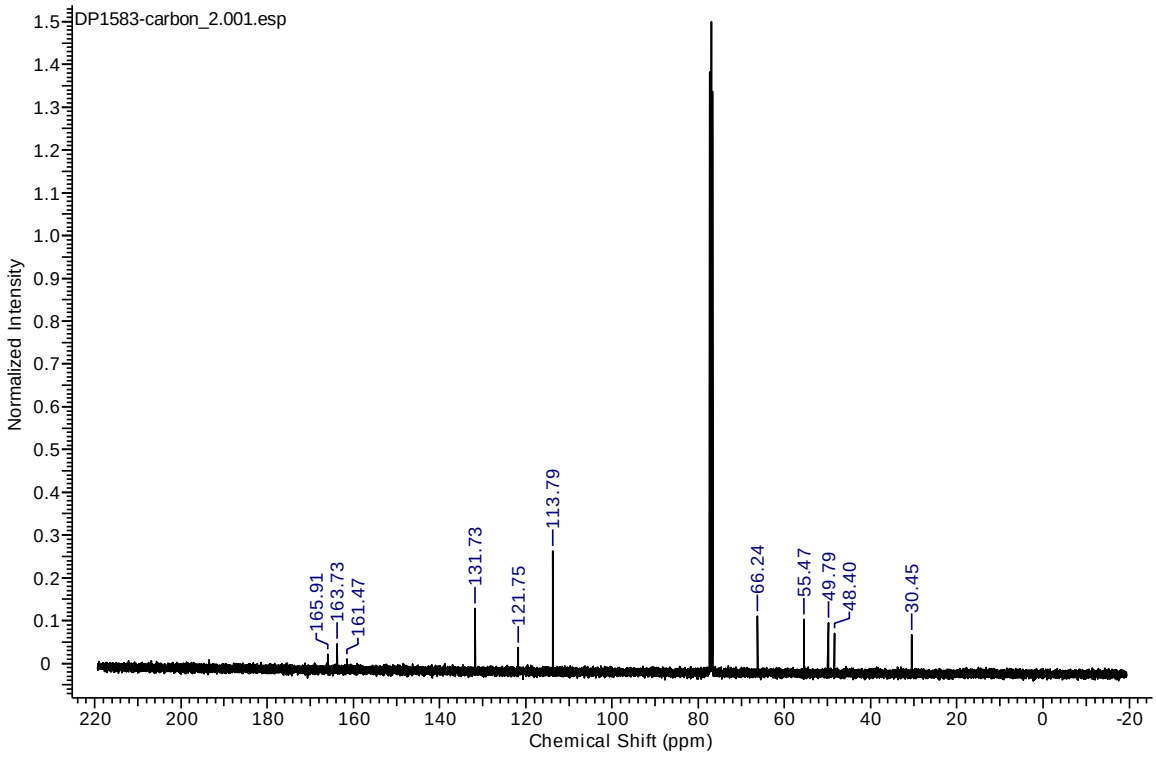

RI12-ETHYLETHANOLAMINE-CARB.001.esp
O
N
NH
Normalized Intensity
0.92
0.87
0.89
2.00
3.65
Chemical Shift (ppm)

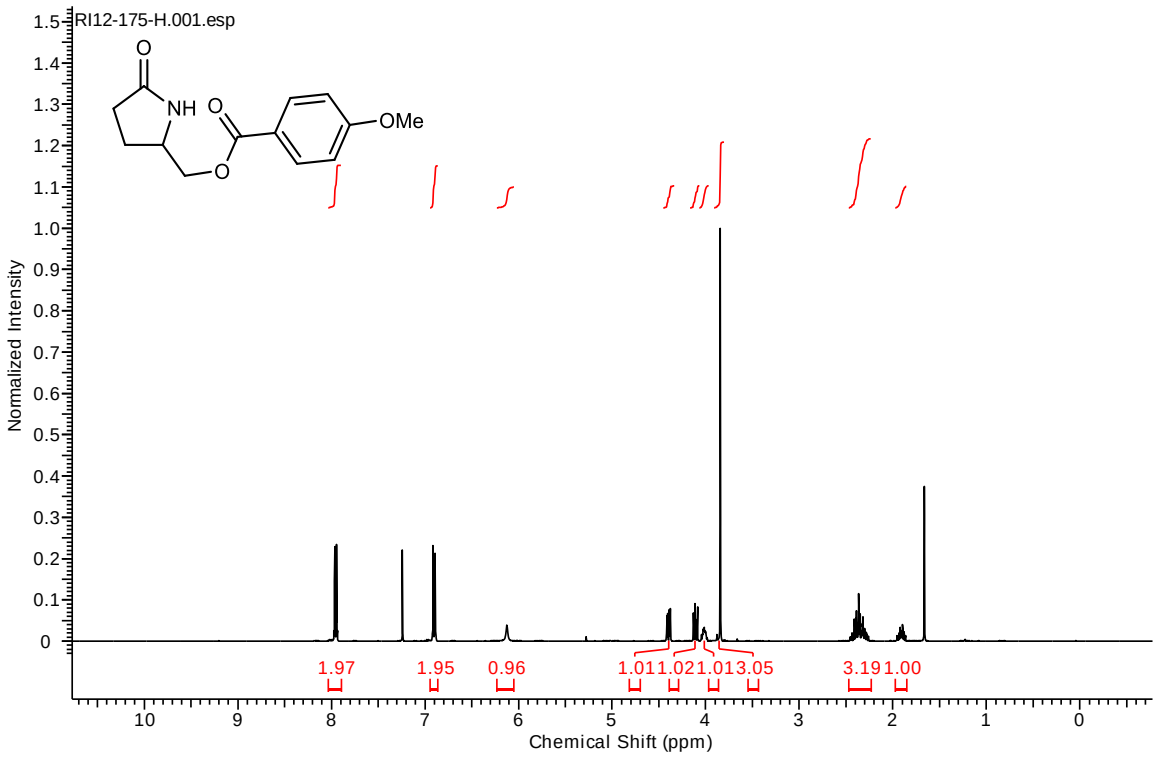

RI12-NET-ETHANOLAMINE-C.001.esp
Normalized Intensity
110.80
107.98
37.93
14.80
154.35
Chemical Shift (ppm)

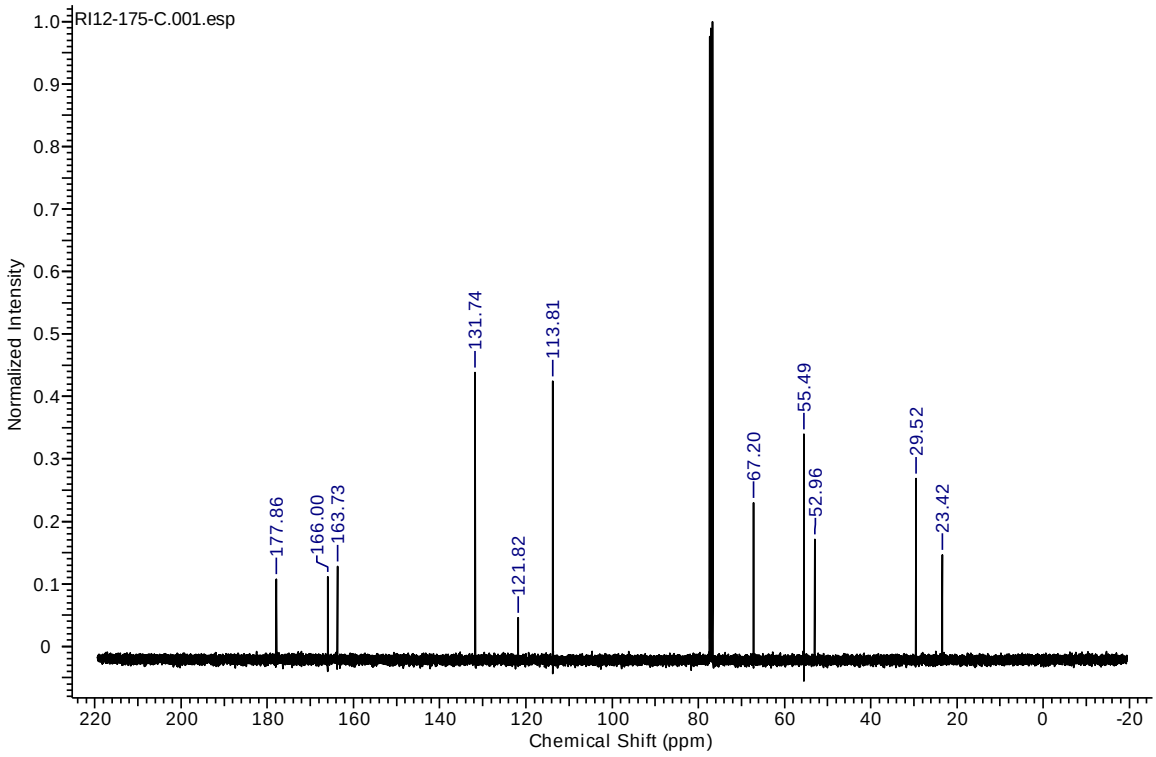

RI13-8-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
8.33
1.03
1.00
1.11
1.90
1.02
1.04
1.97
2.00

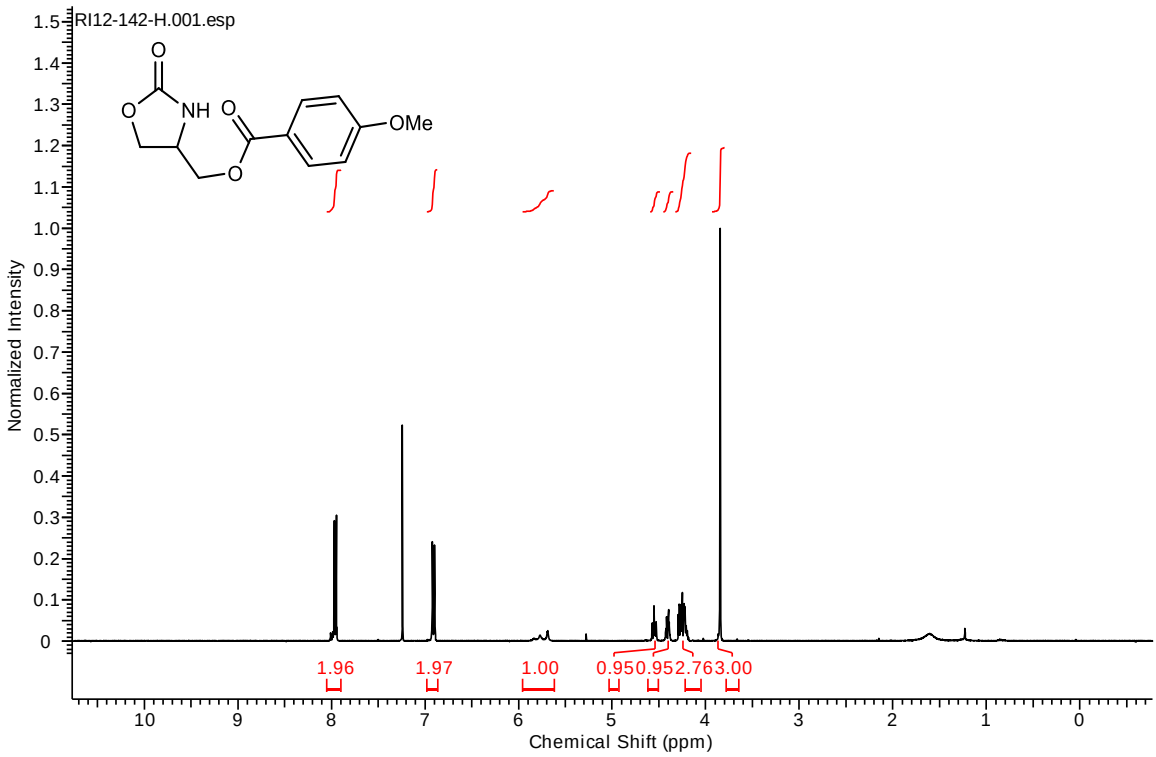

RI13-8-C.002.esp
Normalized Intensity
Chemical Shift (ppm)
168.51
168.23
161.06
134.30
133.90
132.10
123.57
123.20
49.29
48.62
41.41
40.89
35.41
26.58

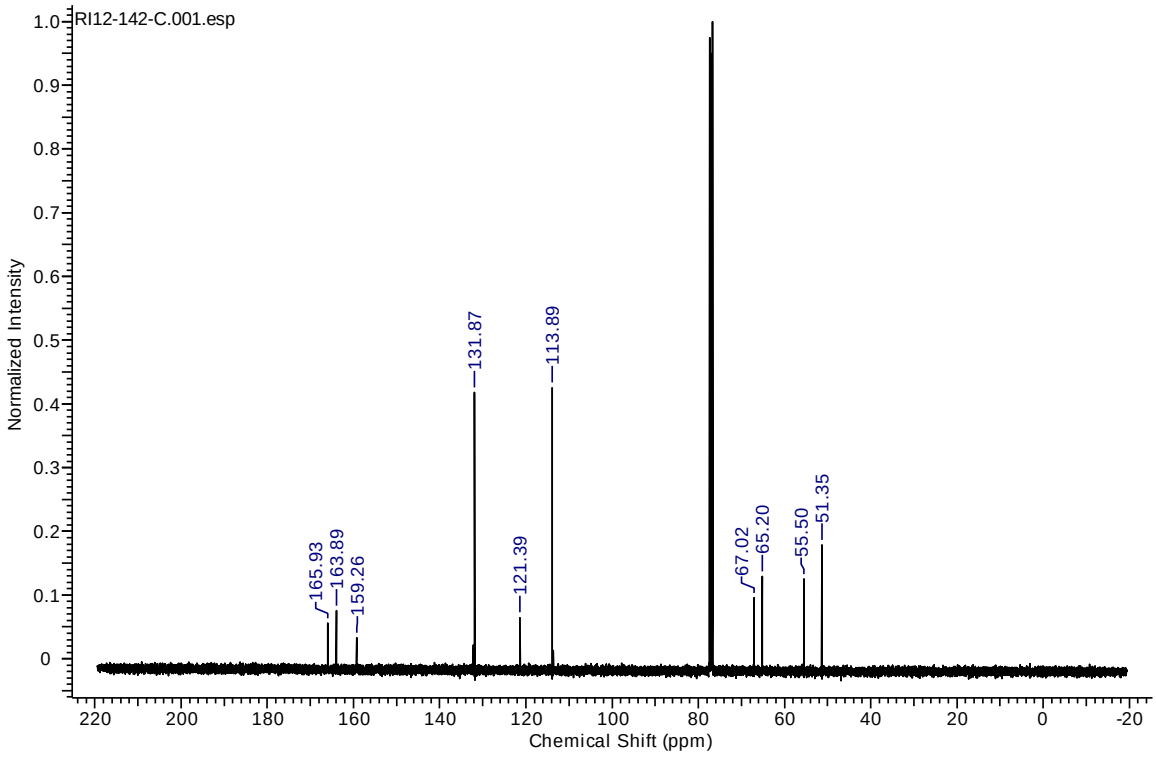

DP1583-F1.002.esp
Normalized Intensity
Chemical Shift (ppm)
2.00
2.07
0.94
1.09
1.10
1.14
2.98
1.08
1.06
2.99
Me
N
NH
O
OMe

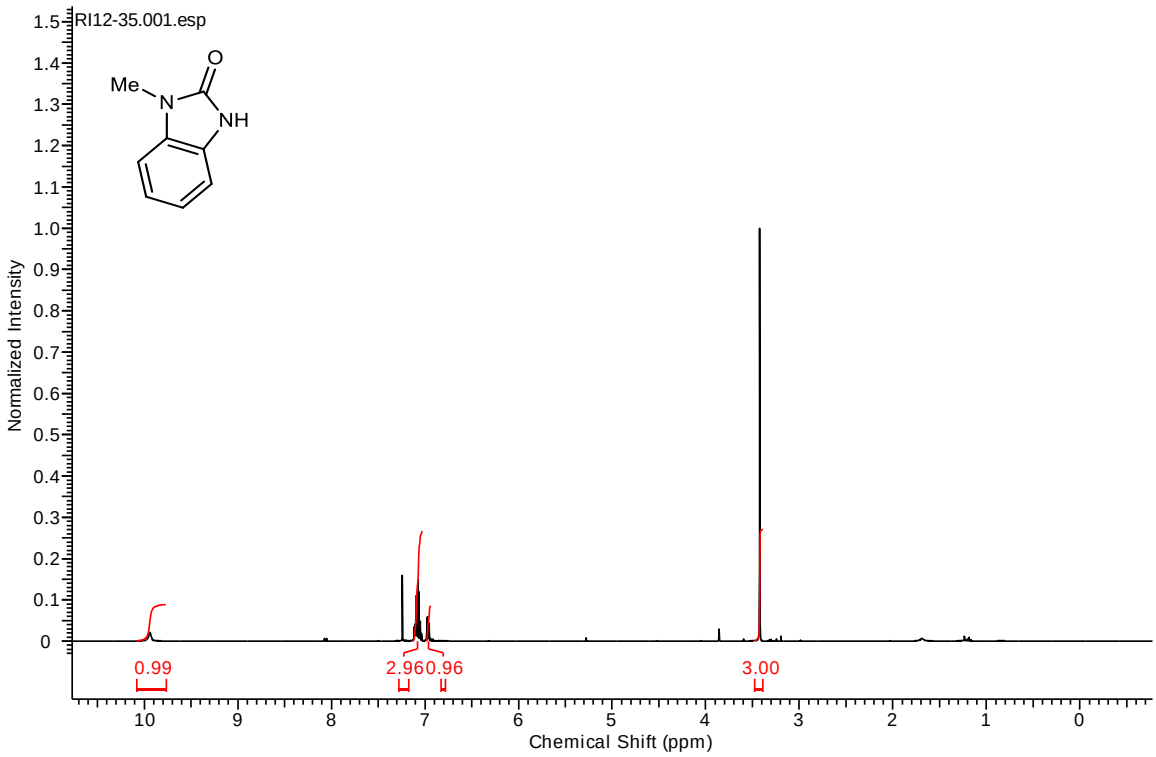

DP1583-carbon_2.001.esp
Normalized Intensity
Chemical Shift (ppm)
165.91
163.73
161.47
131.73
121.75
113.79
66.24
55.47
49.79
48.40
30.45

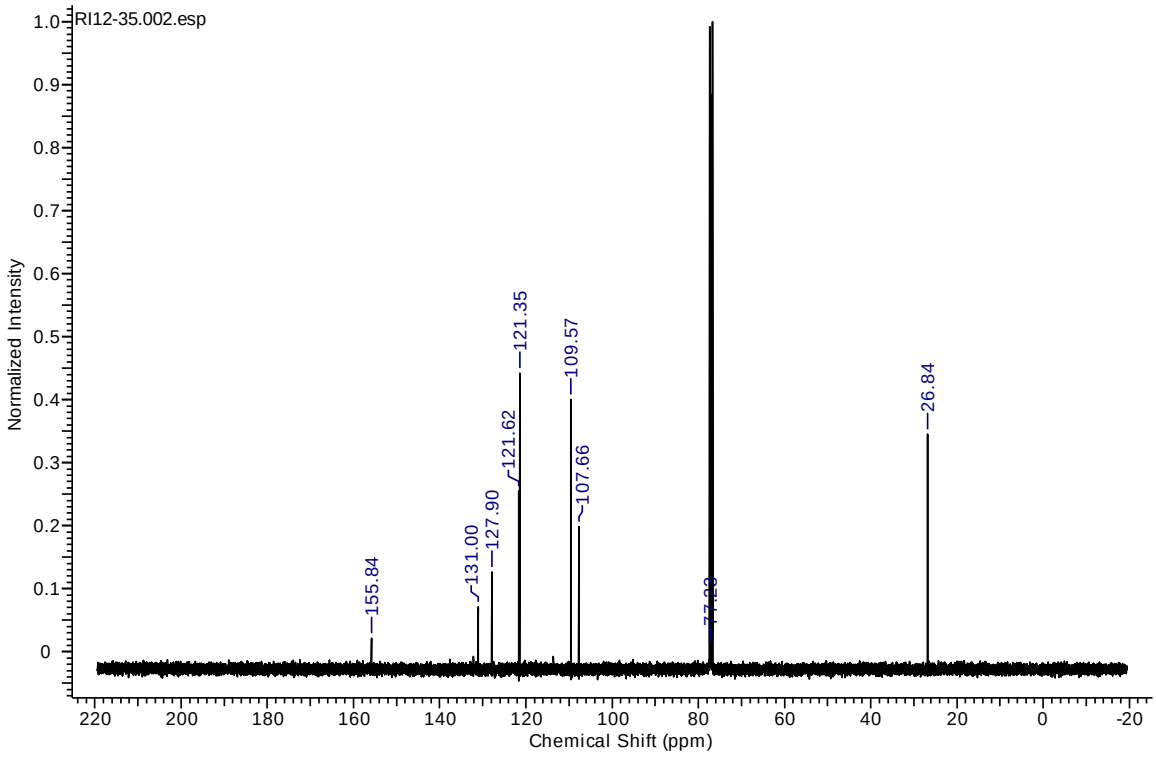

RI12-175-H.001.esp
O
NH
O
O
OMe
Normalized Intensity
1.97
1.95
0.96
1.01
1.02
1.01
3.05
3.19
1.00
Chemical Shift (ppm)

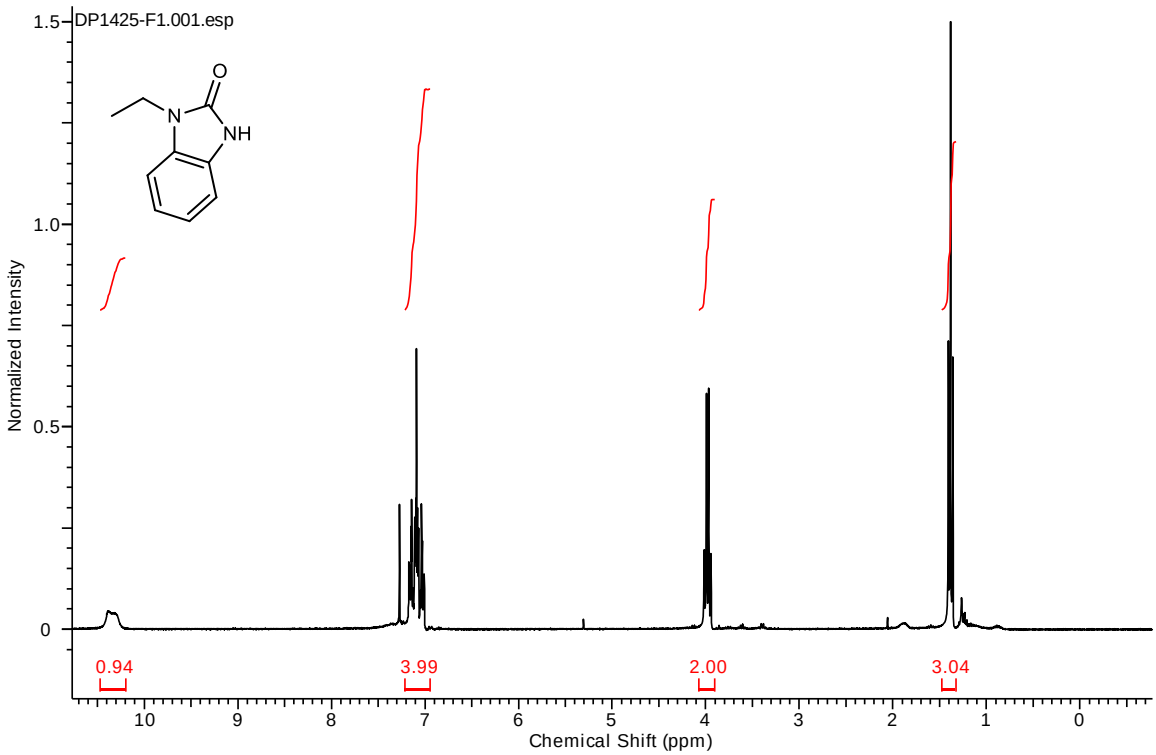

RI12-175-C.001.esp
Normalized Intensity
177.86
166.00
163.73
131.74
121.82
113.81
67.20
55.49
52.96
29.52
23.42
Chemical Shift (ppm)

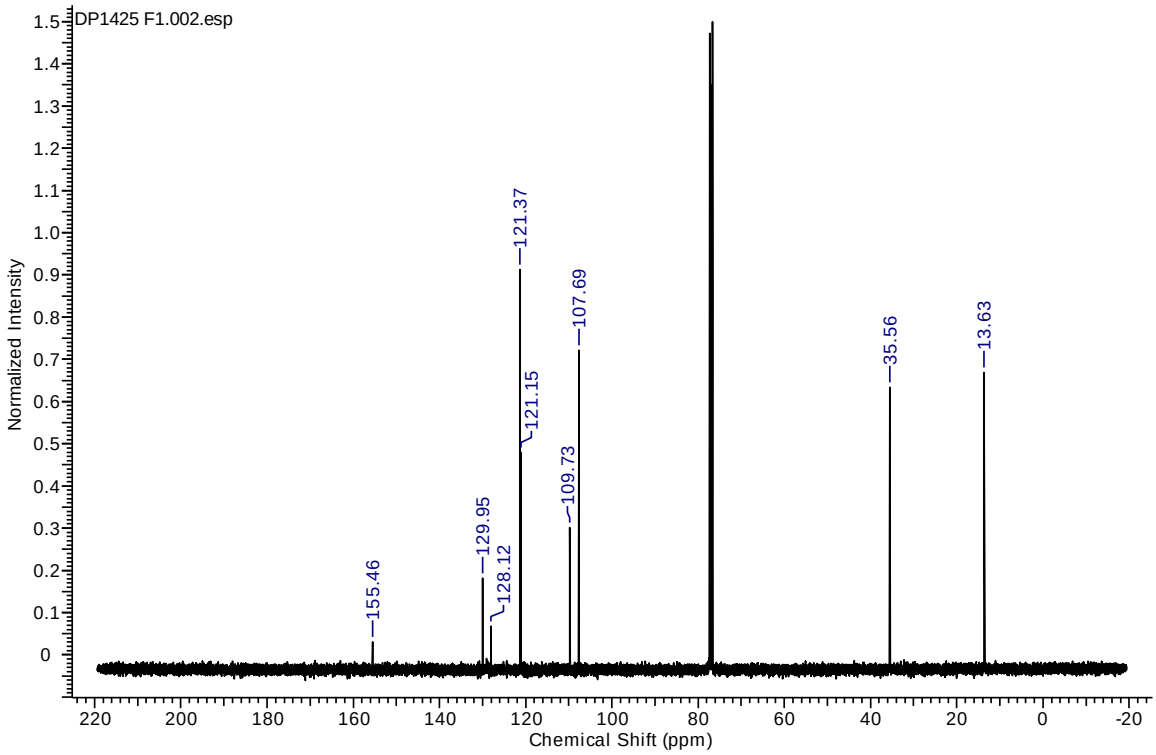

RI12-142-H.001.esp
O
O
NH
O
O
OMe
Normalized Intensity
1.96
1.97
1.00
0.95
0.95
2.76
3.00
Chemical Shift (ppm)

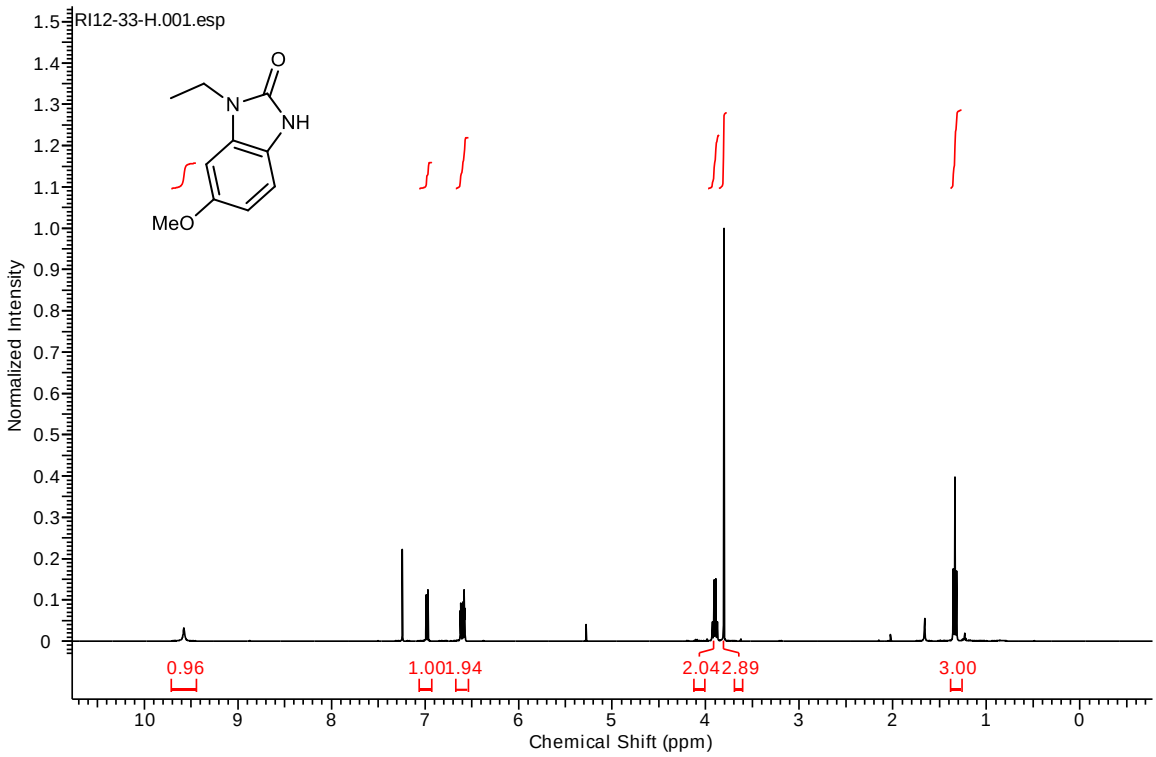

RI12-142-C.001.esp
Normalized Intensity
165.93
163.89
159.26
131.87
121.39
113.89
67.02
65.20
55.50
51.35
Chemical Shift (ppm)

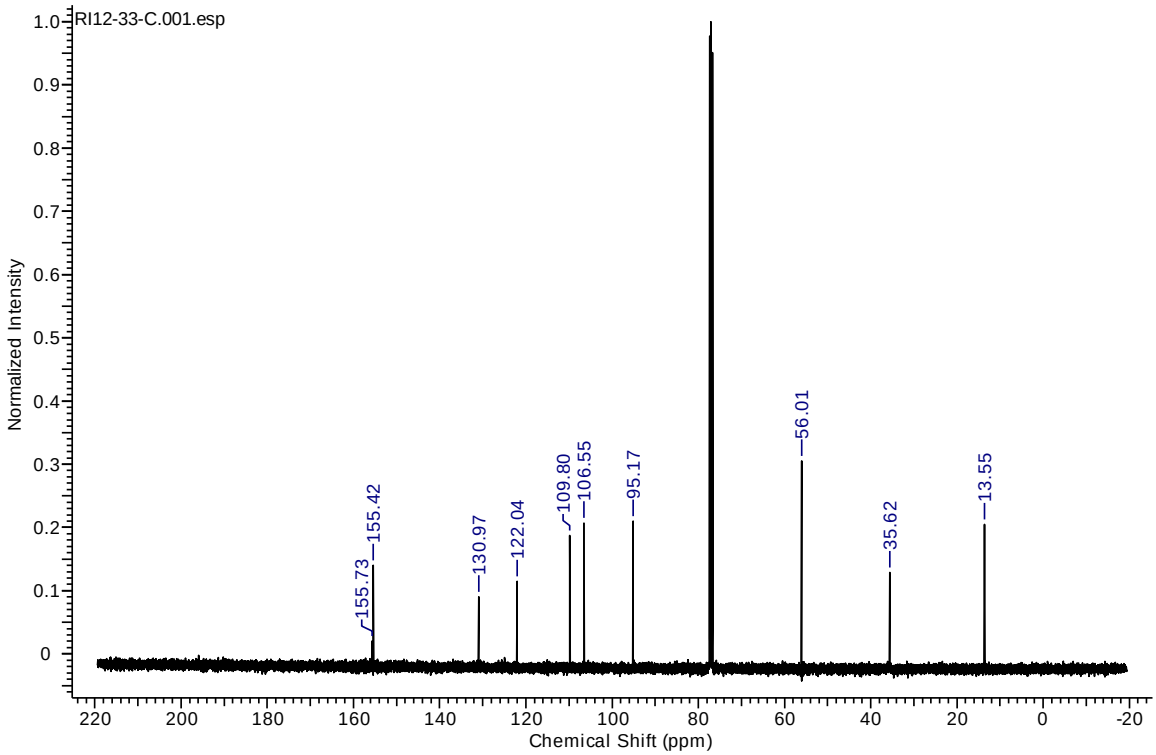

RI12-35.001.esp
Me
N
O
NH
Normalized Intensity
0.99
2.96
0.96
3.00
Chemical Shift (ppm)

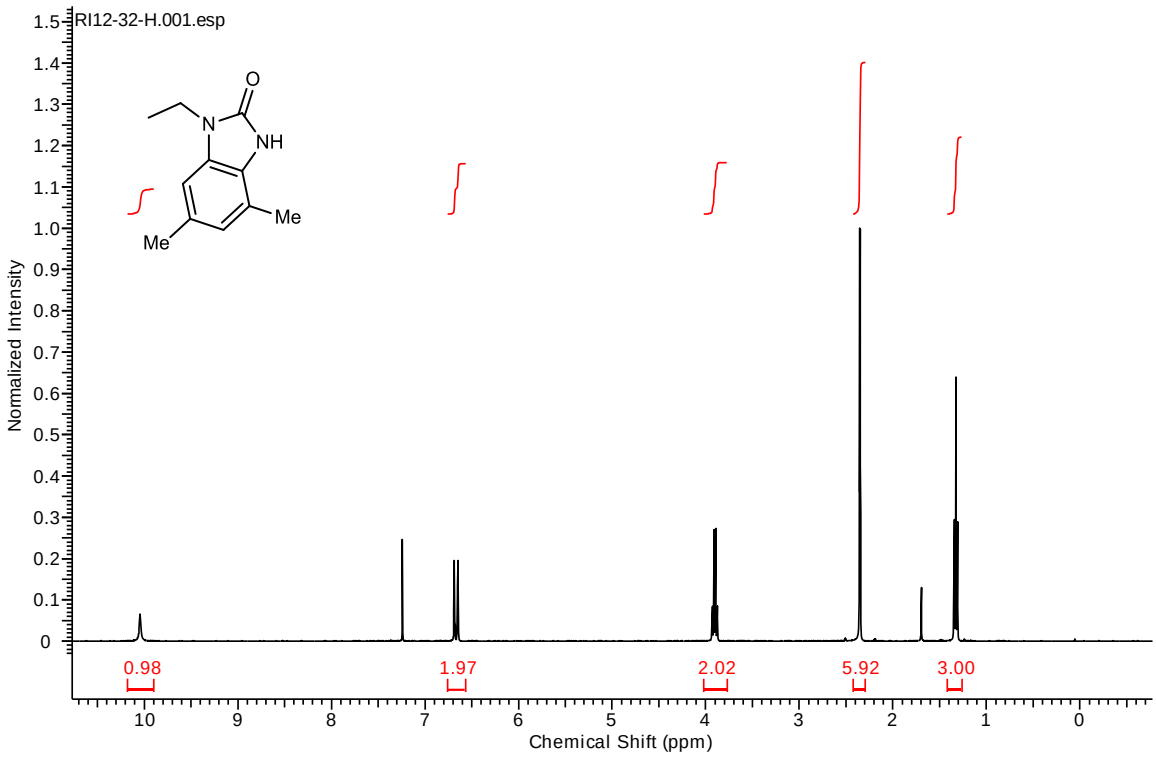

RI12-35.002.esp
Normalized Intensity
155.84
131.00
127.90
121.62
121.35
109.57
107.66
77.00
26.84
Chemical Shift (ppm)

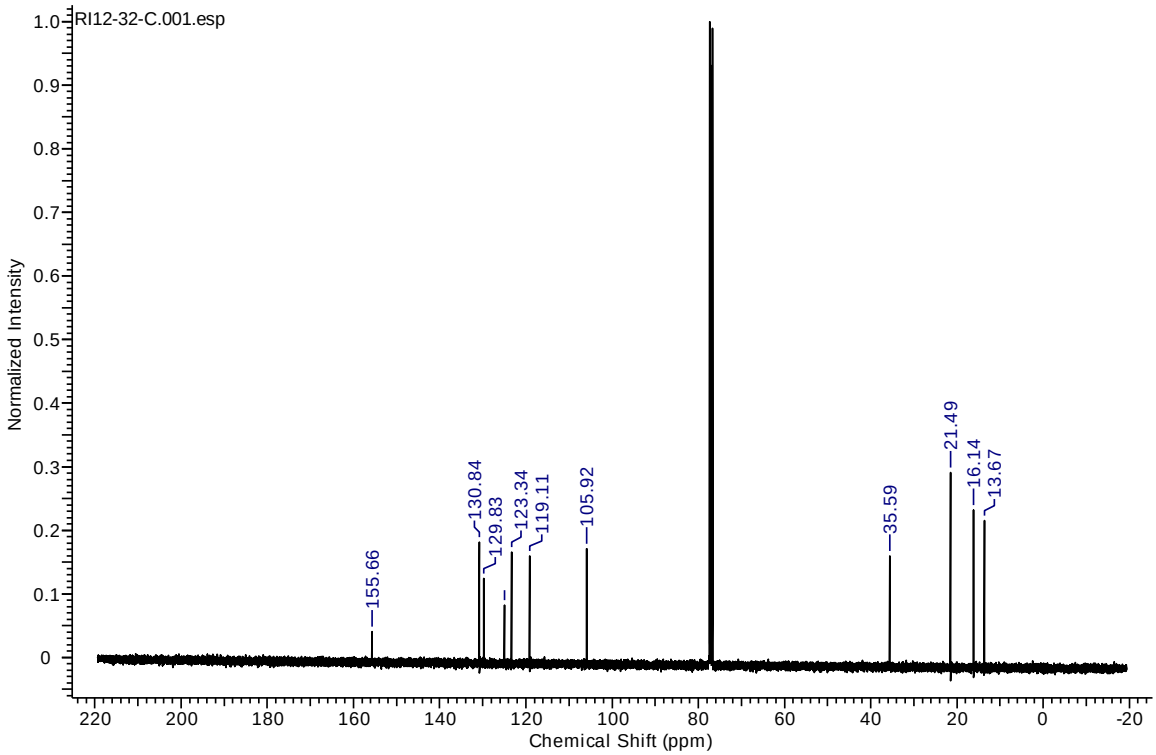

DP1425-F1.001.esp
O
N
NH
Normalized Intensity
0.94
3.99
2.00
3.04
Chemical Shift (ppm)

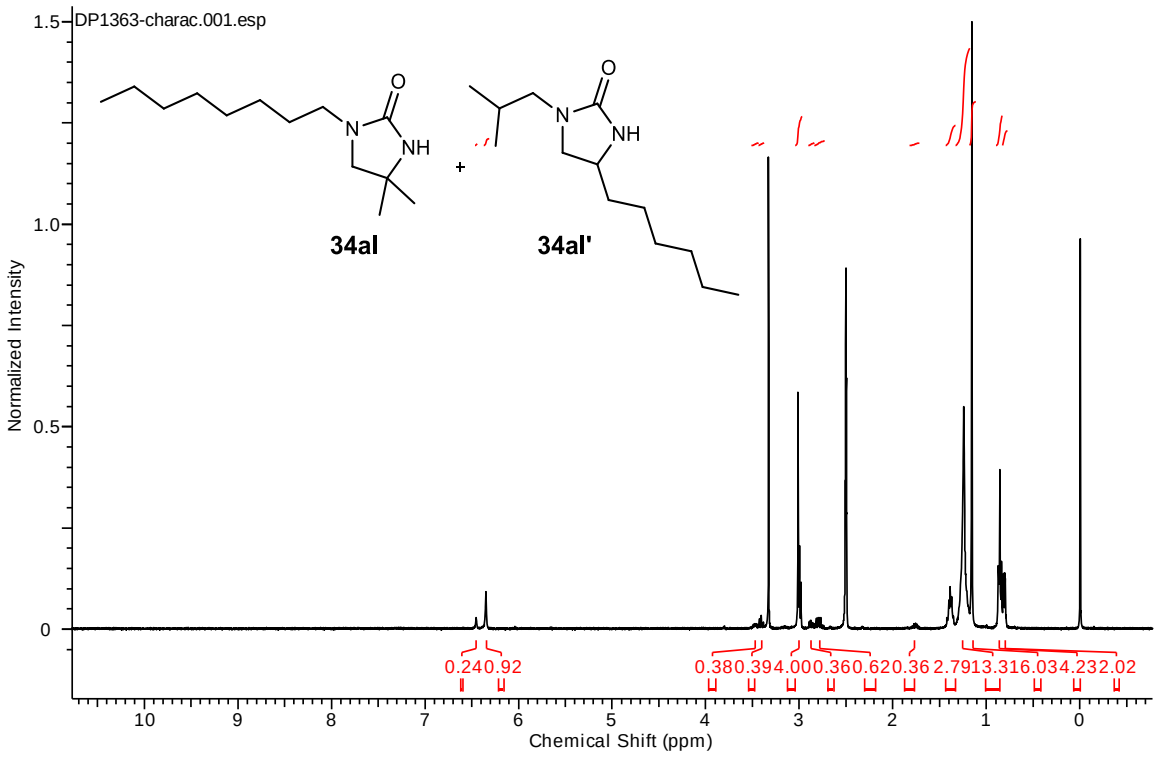

DP1425 F1.002.esp
Normalized Intensity
155.46
129.95
128.12
121.37
121.15
109.73
107.69
35.56
13.63
Chemical Shift (ppm)

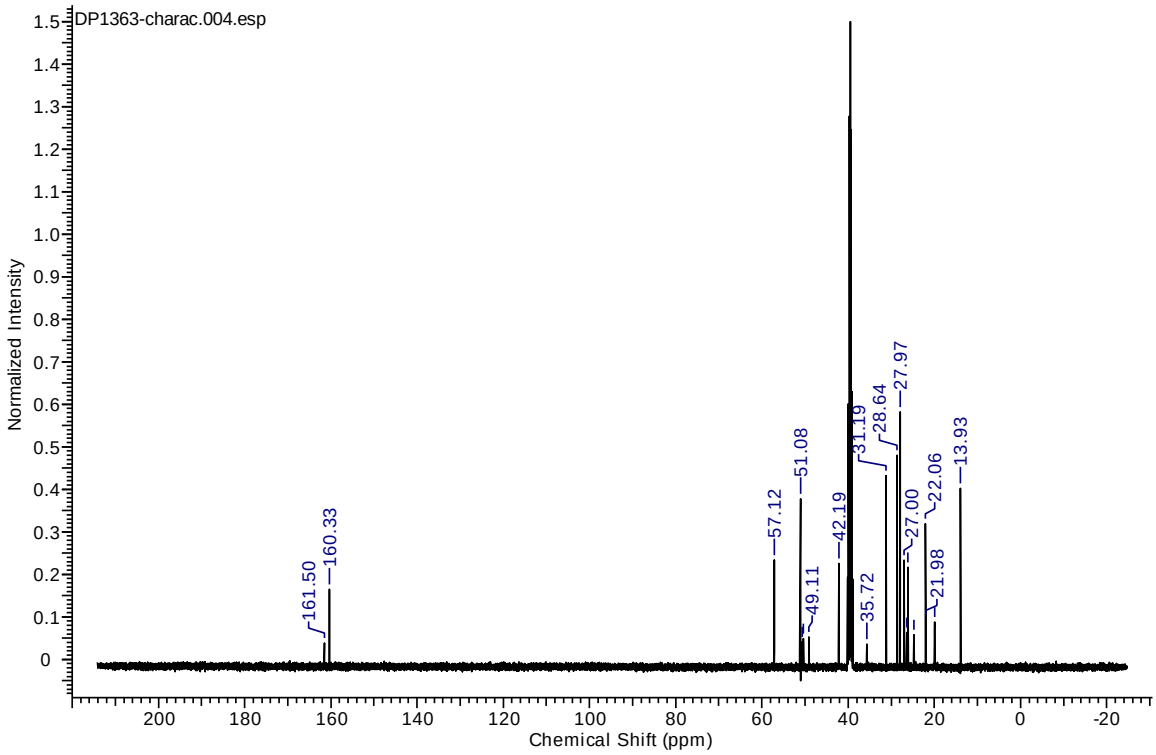

RI12-33-H.001.esp
O
N
NH
MeO
Normalized Intensity
0.96
1.00
1.94
2.04
2.89
3.00
Chemical Shift (ppm)

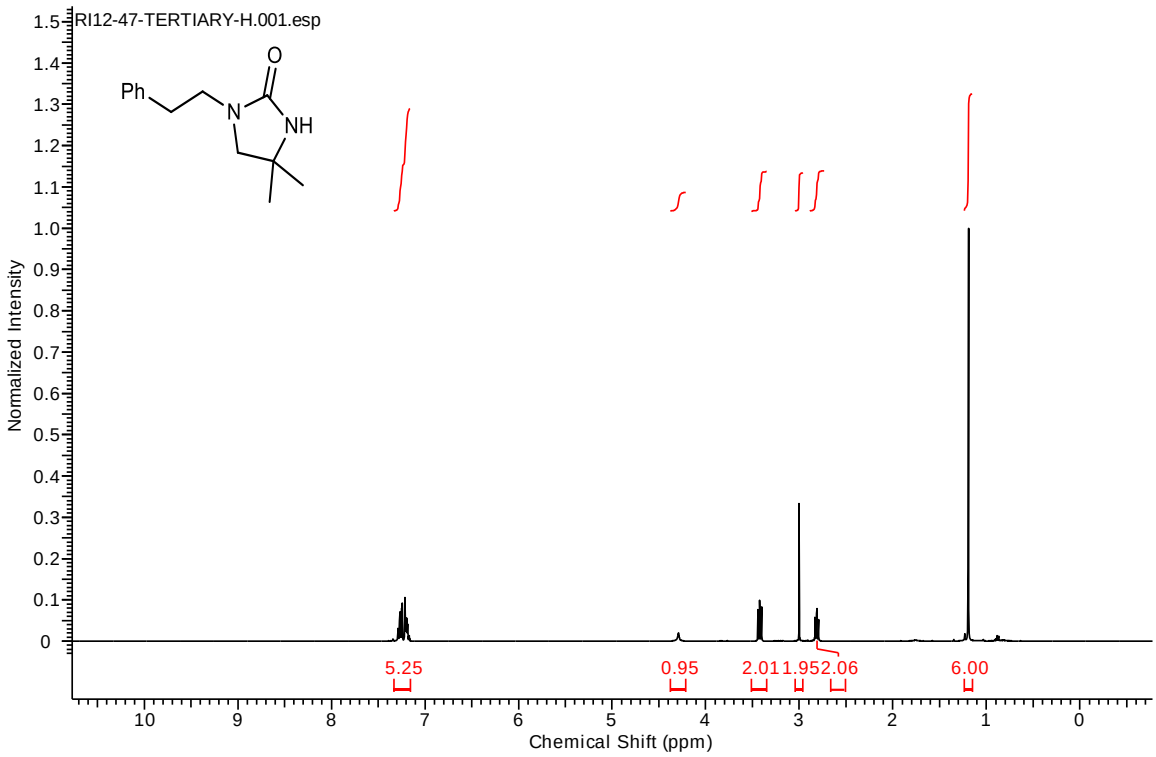

RI12-33-C.001.esp
Normalized Intensity
155.73
155.42
130.97
122.04
109.80
106.55
95.17
56.01
35.62
13.55
Chemical Shift (ppm)

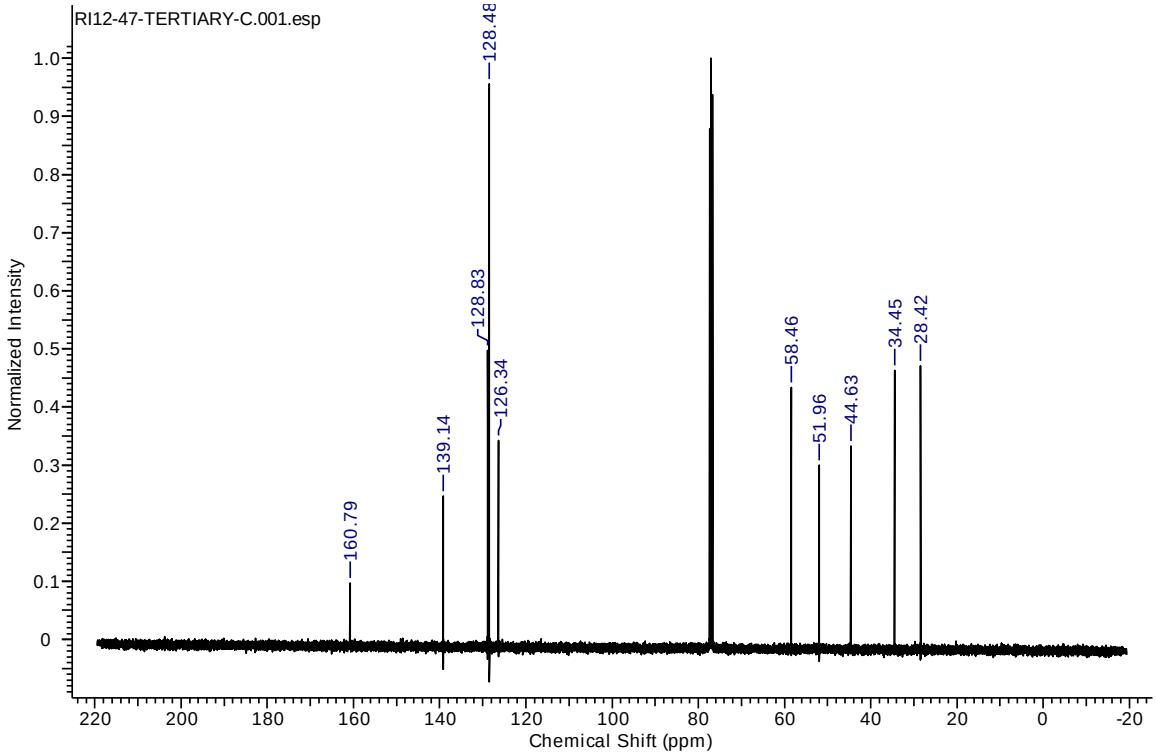

RI12-32-H.001.esp
O
N
NH
Me
Me
Normalized Intensity
0.98
1.97
2.02
5.92
3.00
Chemical Shift (ppm)

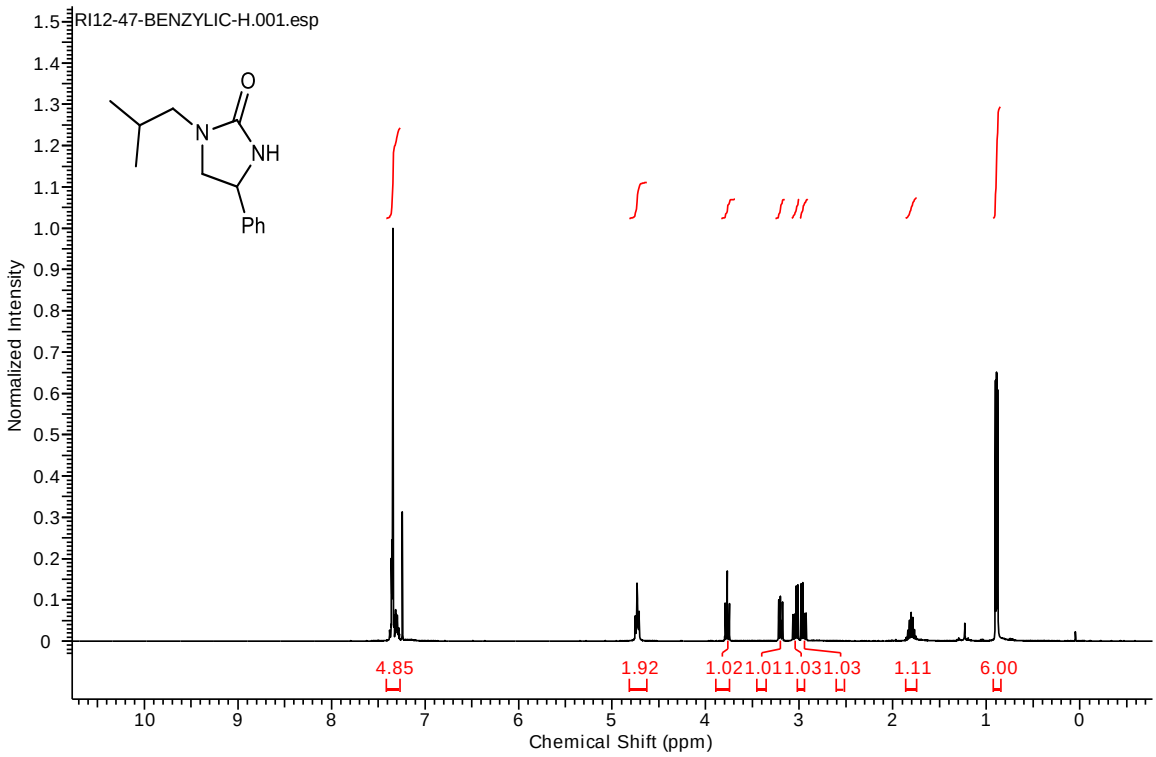

RI12-32-C.001.esp
Normalized Intensity
155.66
130.84
129.83
123.34
119.11
105.92
35.59
21.49
16.14
13.67
Chemical Shift (ppm)

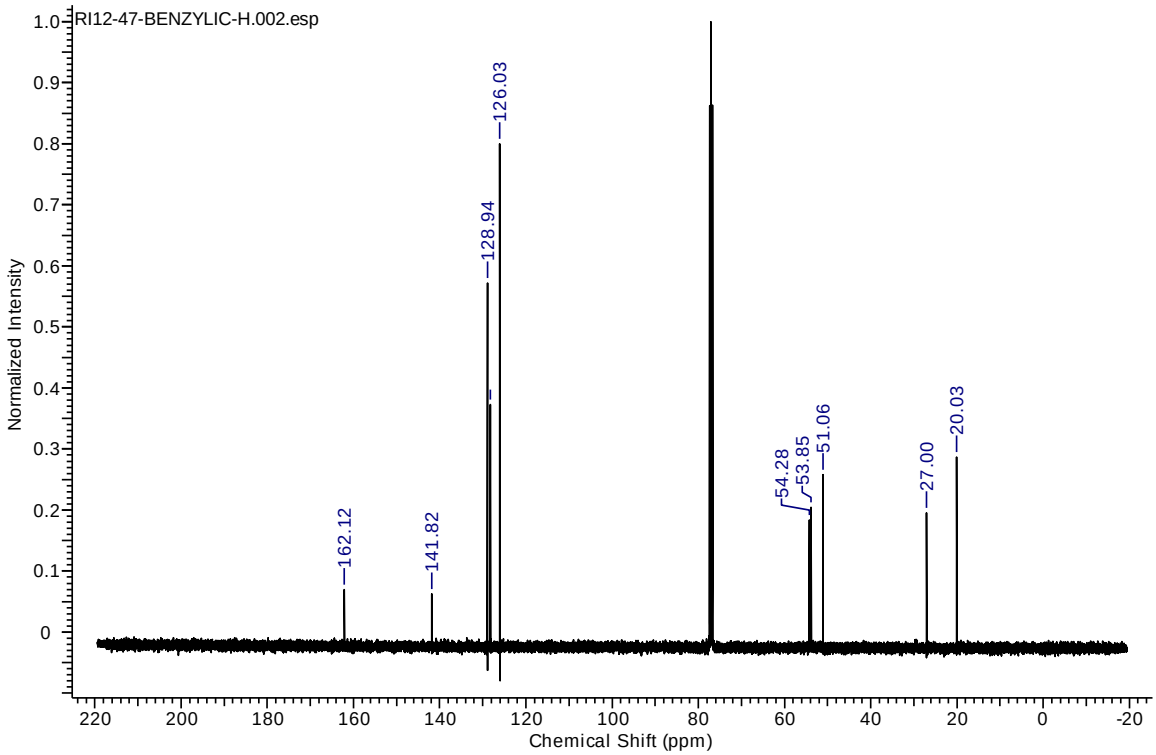

DP1363-charac.001.esp
34al
34al'
Normalized Intensity
Chemical Shift (ppm)
0.24 0.92 0.38 0.39 4.00 0.36 0.62 0.36 2.79 13.31 6.03 4.23 2.02

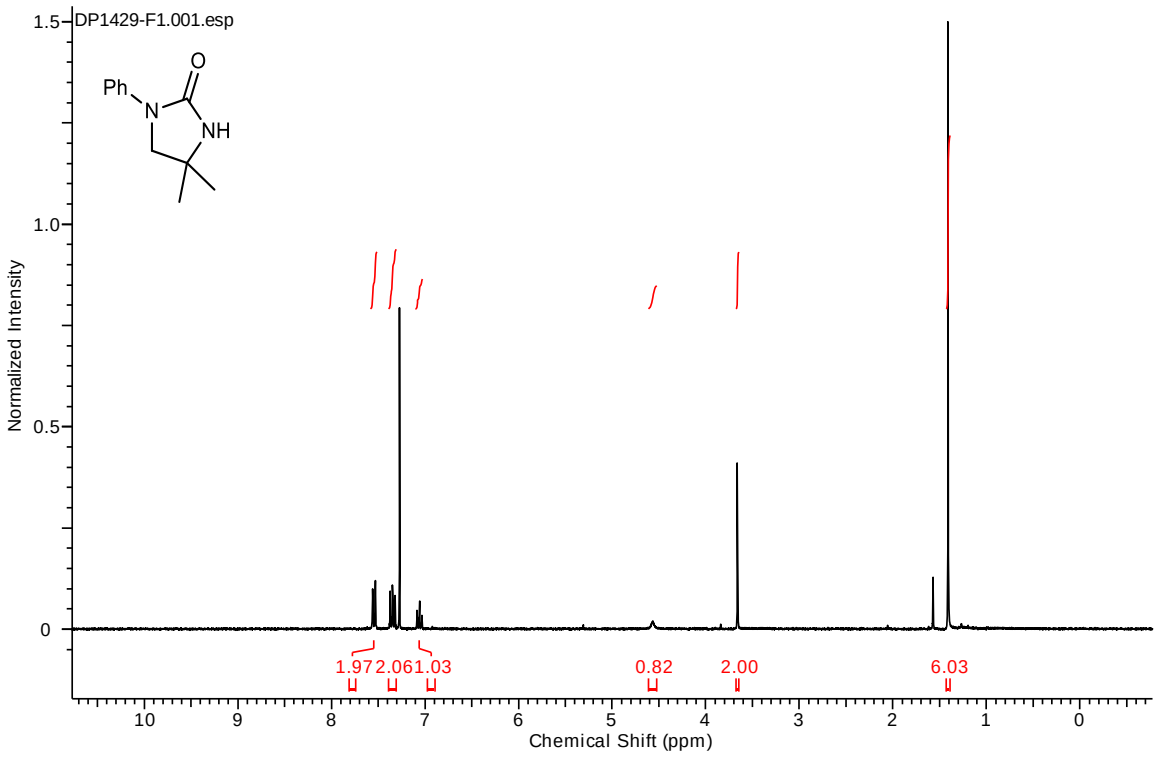

DP1363-charac.004.esp
Normalized Intensity
Chemical Shift (ppm)
161.50
160.33
57.12
51.08
49.11
42.19
35.72
31.19
28.64
27.97
27.00
22.06
21.98
13.93

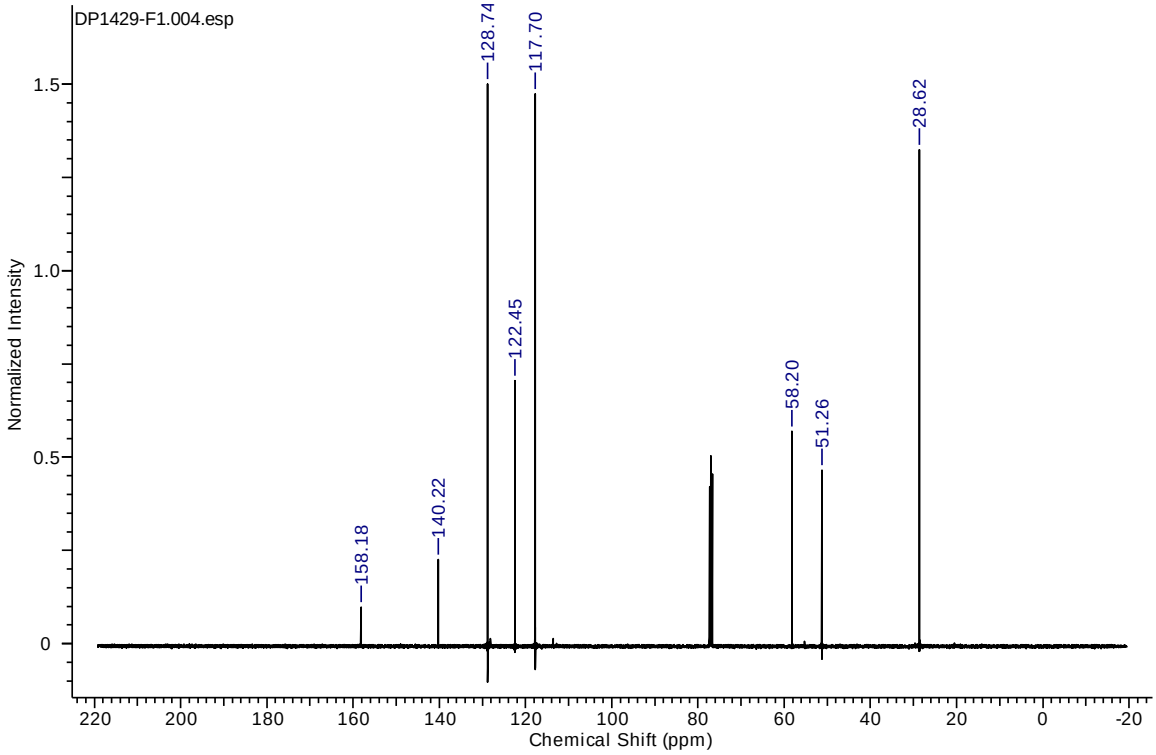

RI12-47-TERTIARY-H.001.esp
Ph
N
O
NH
Normalized Intensity
5.25
0.95
2.01
1.95
2.06
6.00
Chemical Shift (ppm)

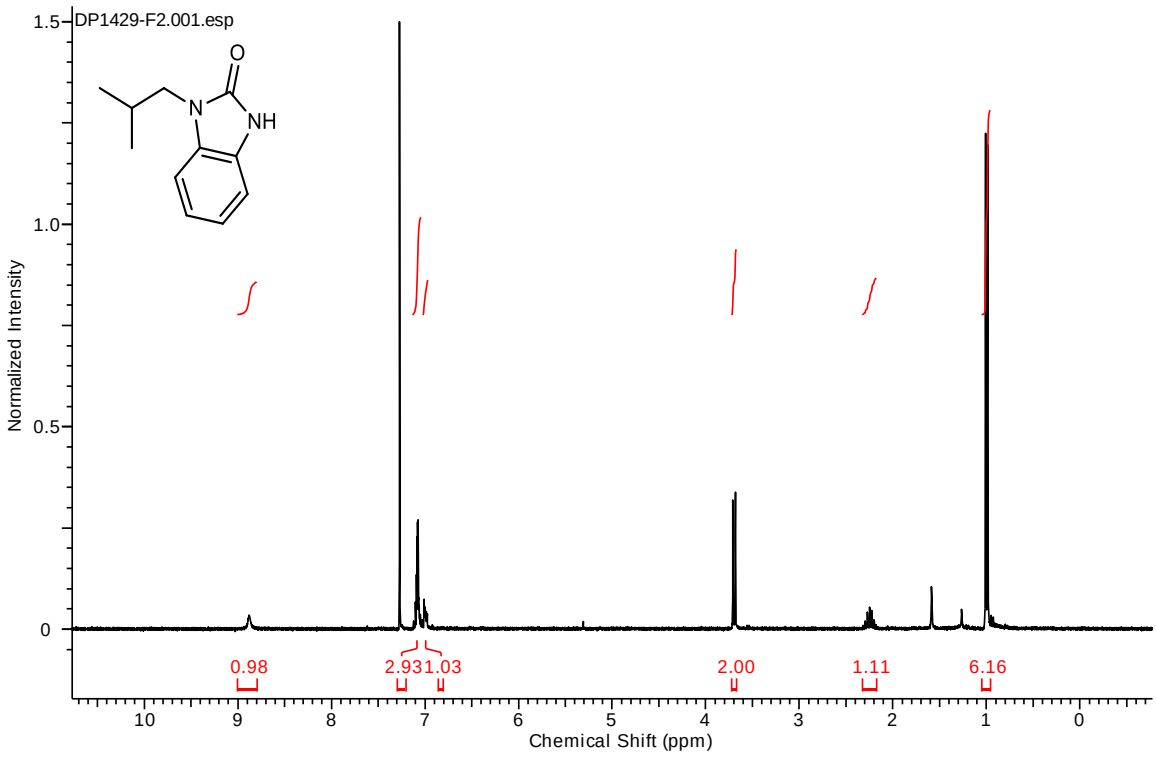

RI12-47-TERTIARY-C.001.esp
128.48
128.83
126.34
139.14
160.79
58.46
51.96
44.63
34.45
28.42
Normalized Intensity
Chemical Shift (ppm)

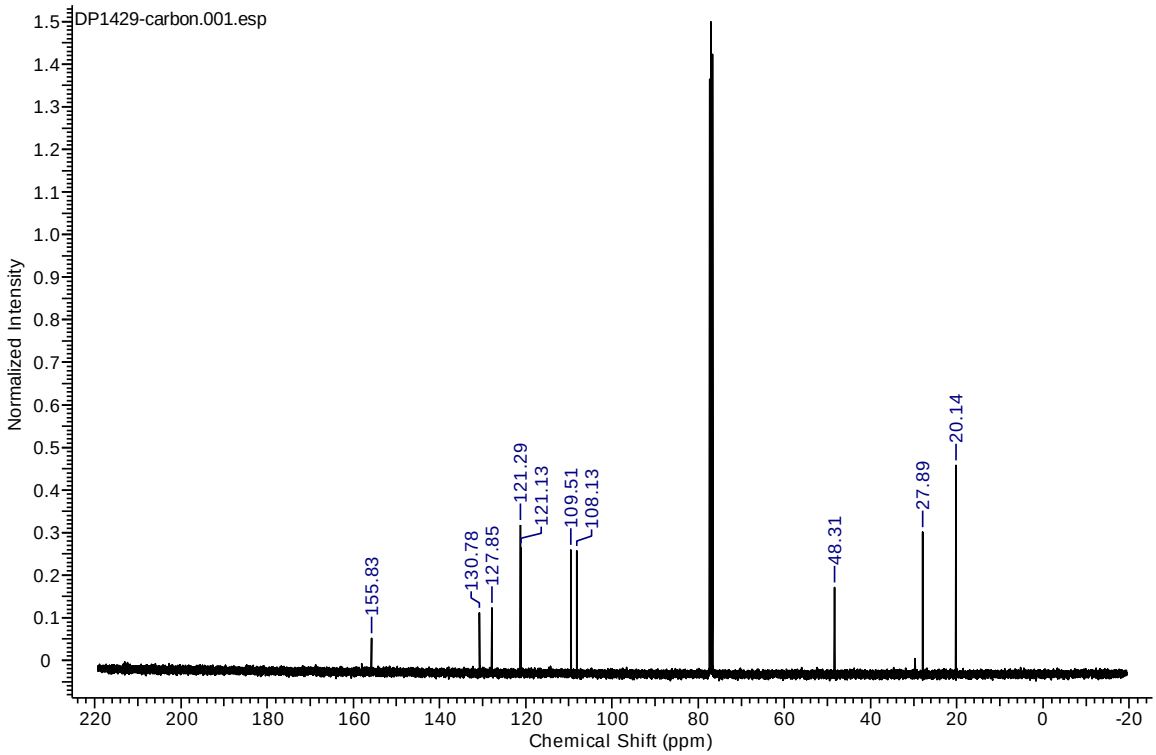

RI12-47-BENZYLIC-H.001.esp
O
N
NH
Ph
Normalized Intensity
4.85
1.92
1.02
1.01
1.03
1.03
1.11
6.00
Chemical Shift (ppm)

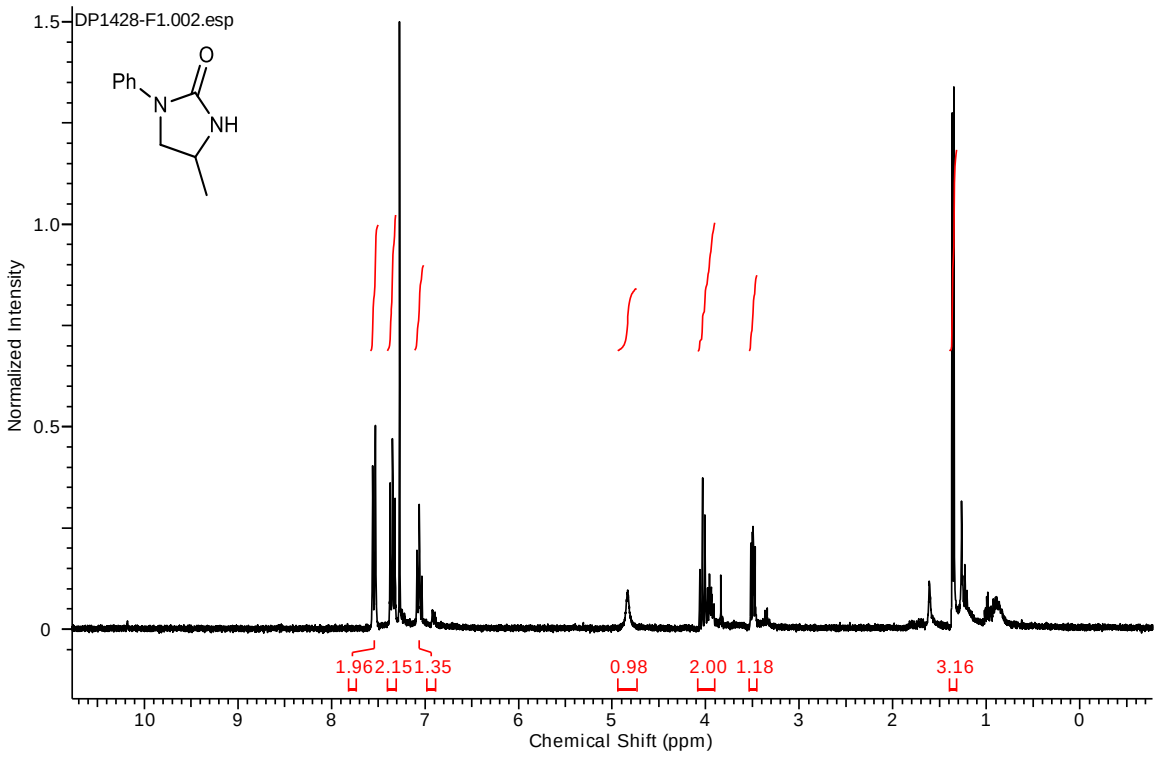

RI12-47-BENZYLIC-H.002.esp
Normalized Intensity
162.12
141.82
128.94
126.03
54.28
53.85
51.06
27.00
20.03
Chemical Shift (ppm)

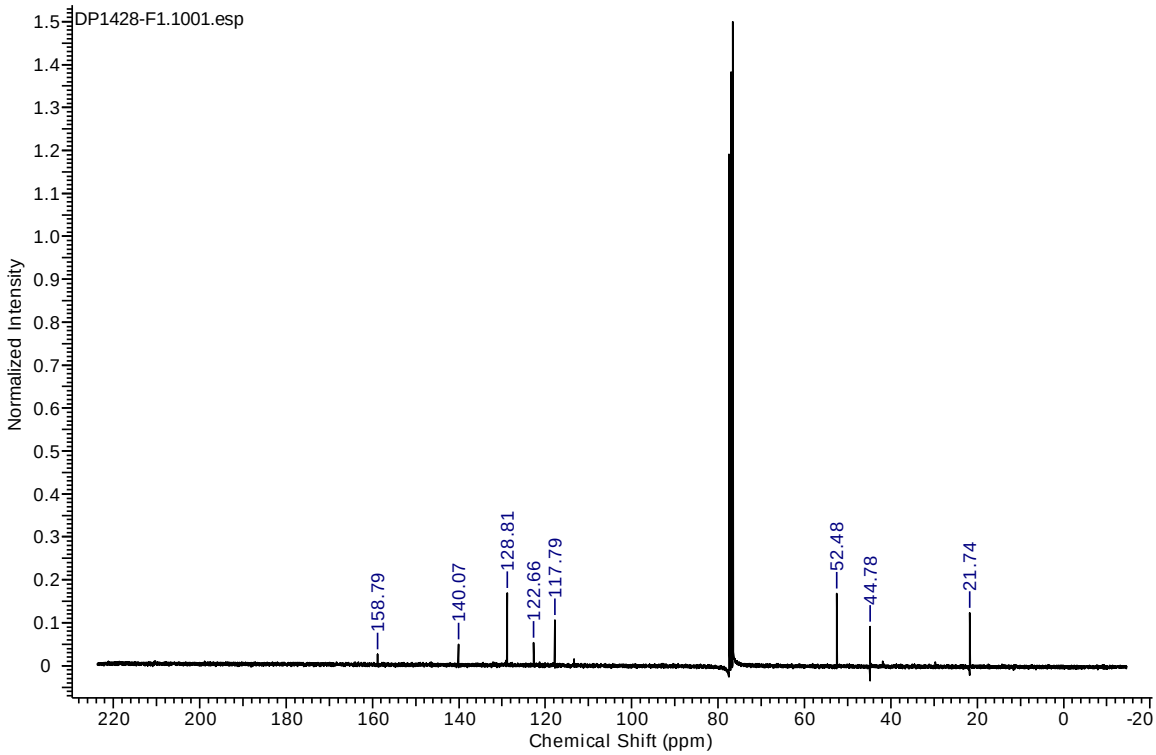

DP1429-F1.001.esp
Ph
N
O
NH
Normalized Intensity
1.5
1.0
0.5
0
1.97
2.06
1.03
0.82
2.00
6.03
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

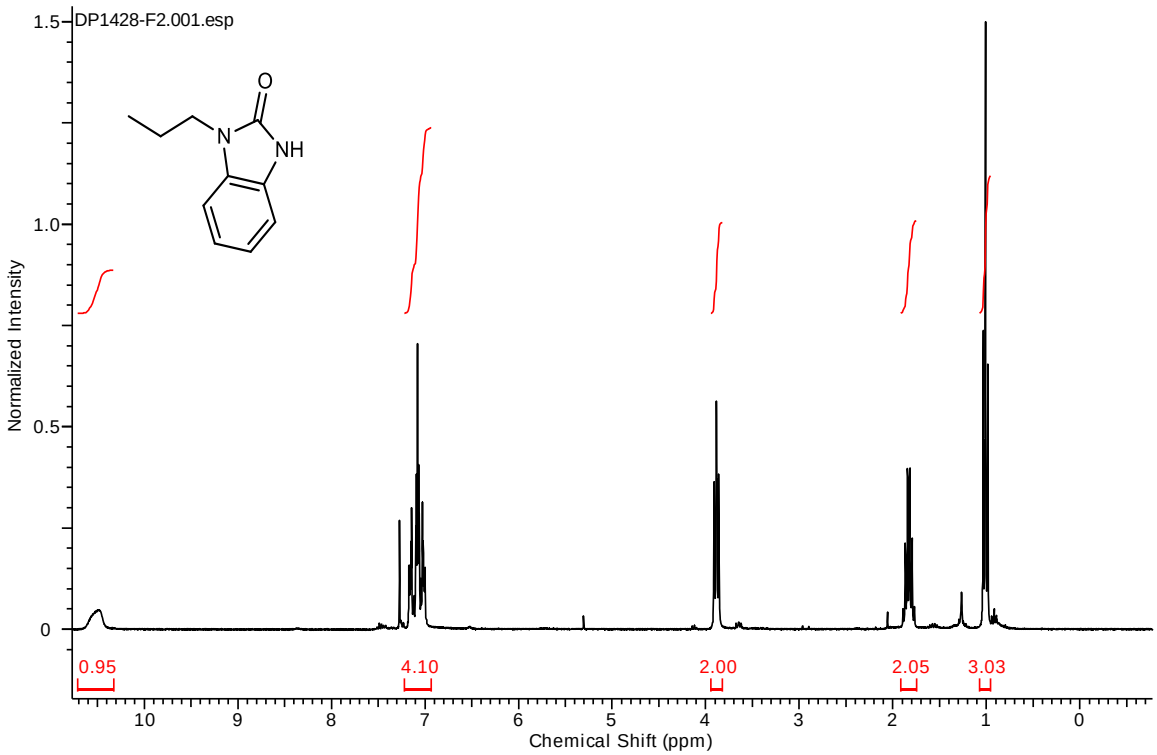

DP1429-F1.004.esp
Normalized Intensity
1.5
1.0
0.5
0
128.74
117.70
28.62
122.45
58.20
51.26
158.18
140.22
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

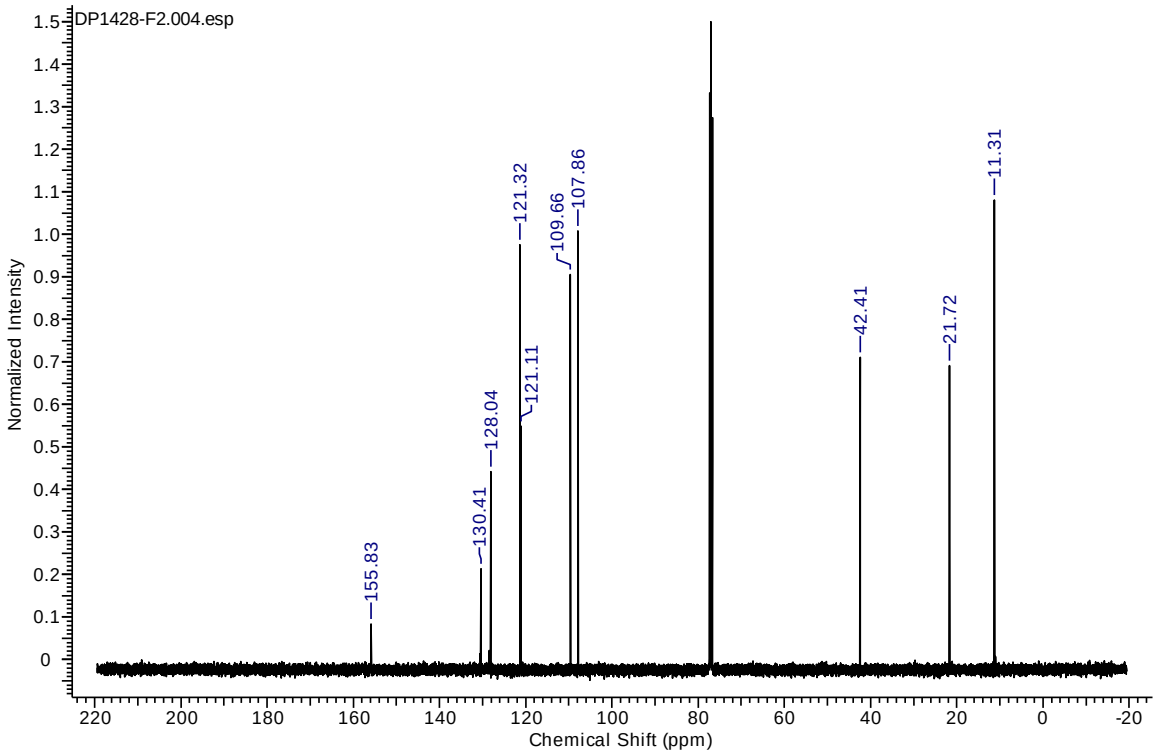

DP1429-F2.001.esp
O
N
NH
Normalized Intensity
1.5
1.0
0.5
0
0.98
2.93
1.03
2.00
1.11
6.16
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

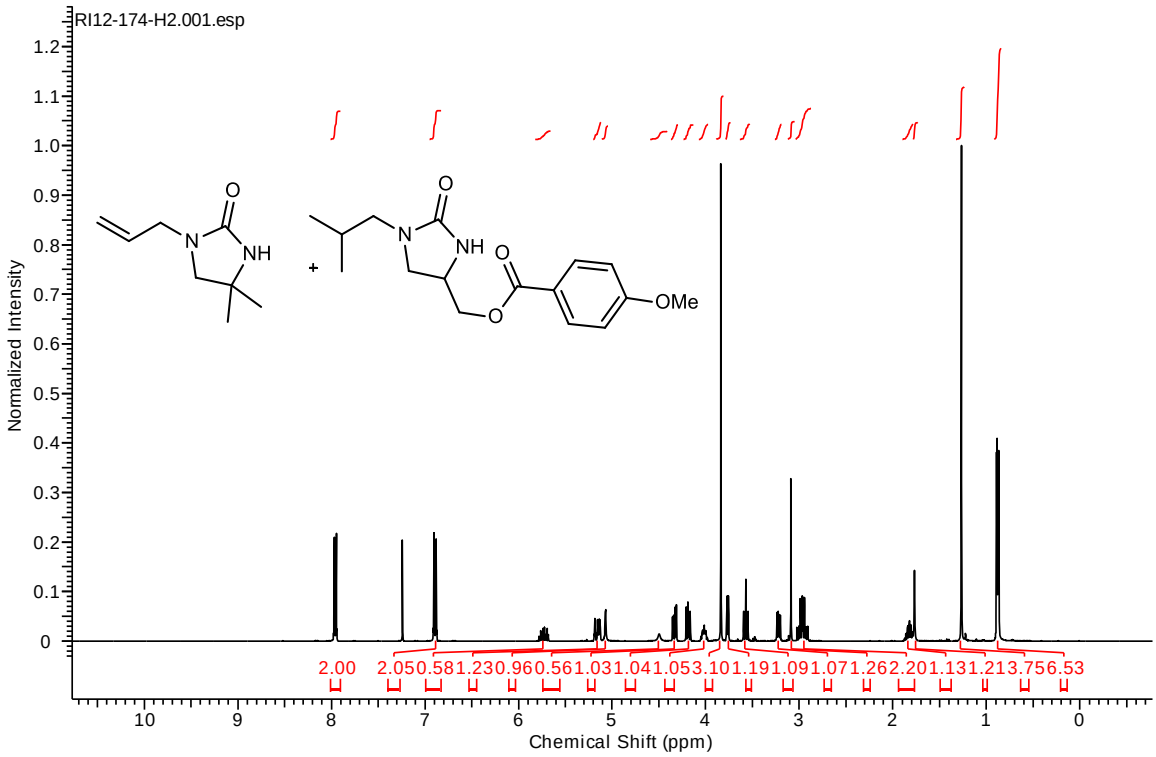

DP1429-carbon.001.esp
Normalized Intensity
155.83
130.78
127.85
121.29
121.13
109.51
108.13
48.31
27.89
20.14
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

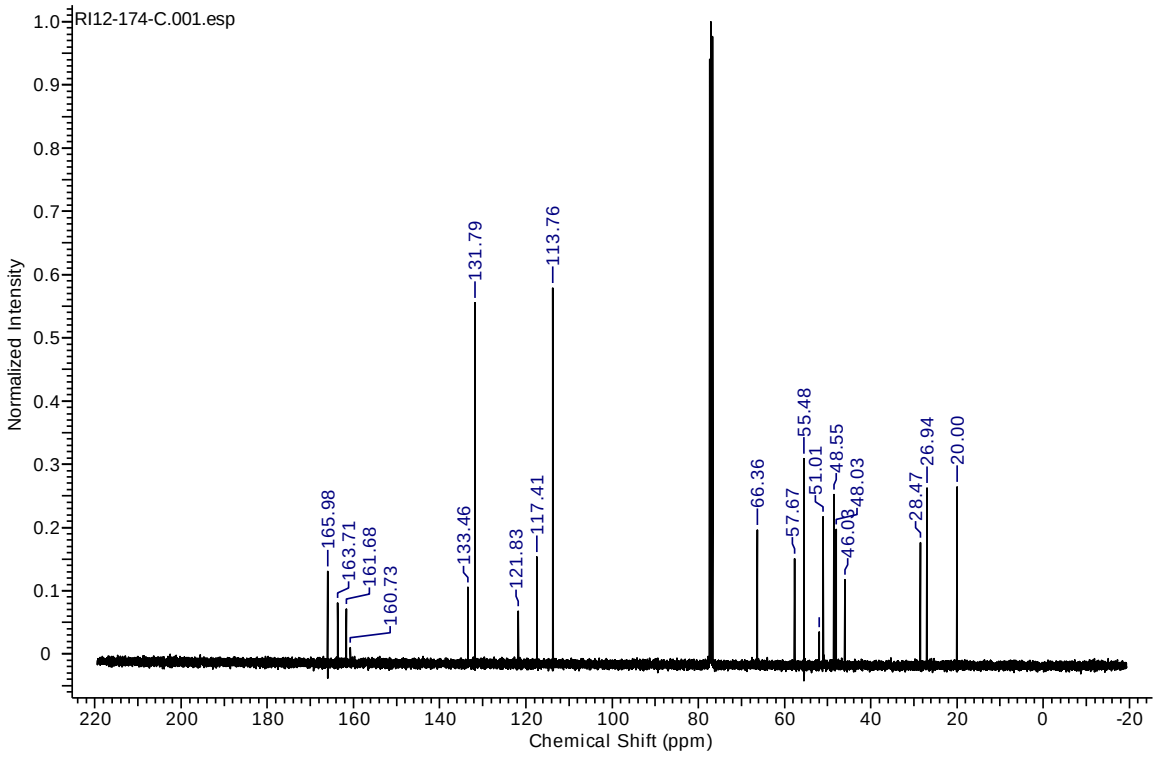

DP1428-F1.002.esp
Ph
N
O
NH
Normalized Intensity
1.96
2.15
1.35
0.98
2.00
1.18
3.16
Chemical Shift (ppm)

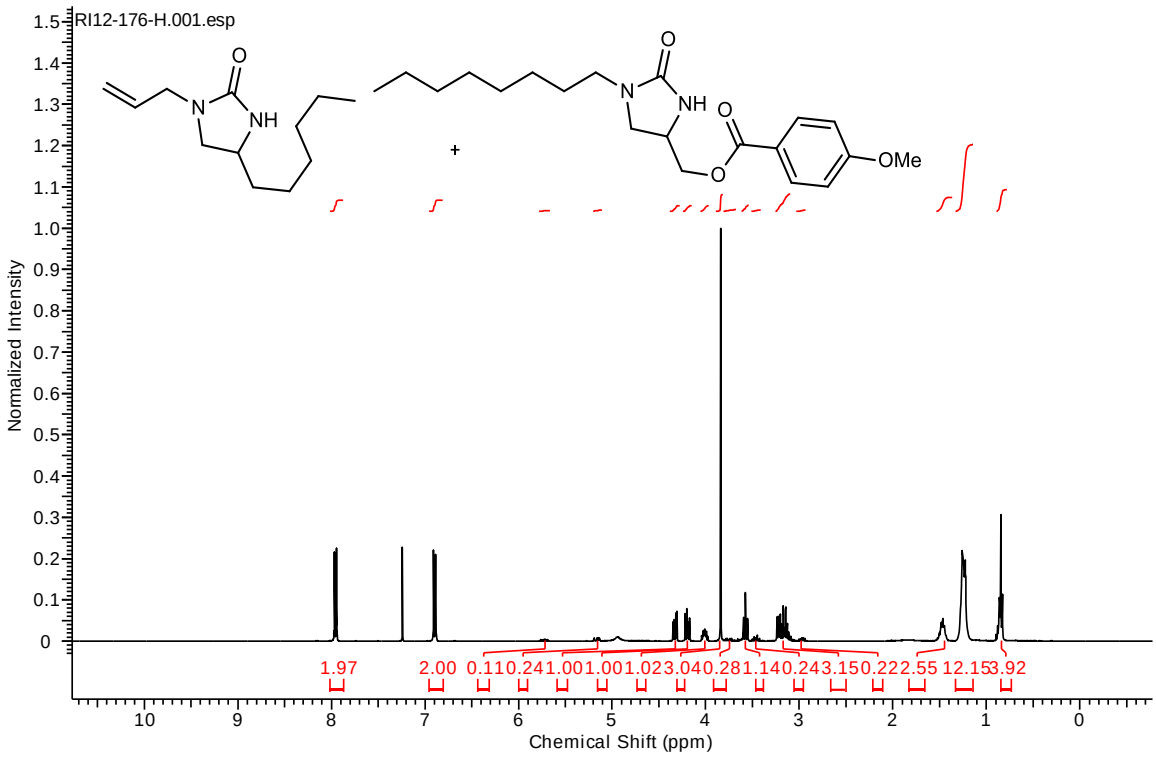

DP1428-F1.1001.esp
Normalized Intensity
158.79
140.07
128.81
122.66
117.79
52.48
44.78
21.74
Chemical Shift (ppm)

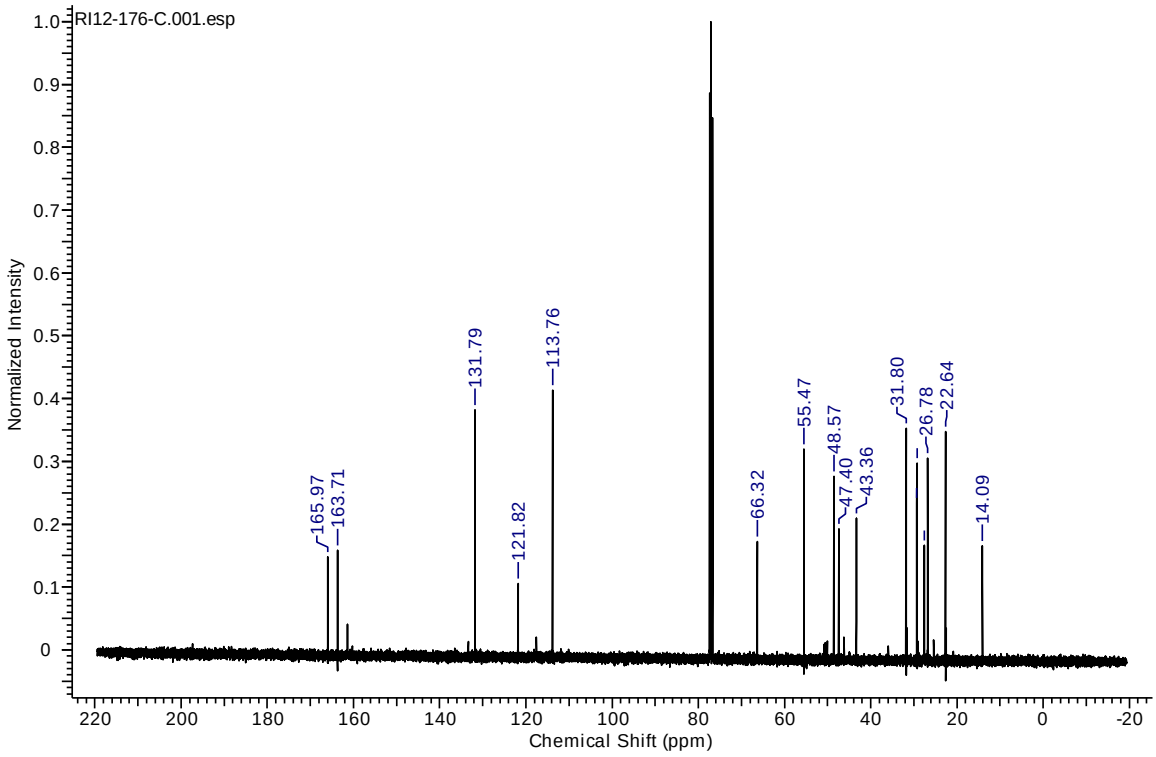

DP1428-F2.001.esp
O
N
NH
Normalized Intensity
0.95
4.10
2.00
2.05
3.03
Chemical Shift (ppm)

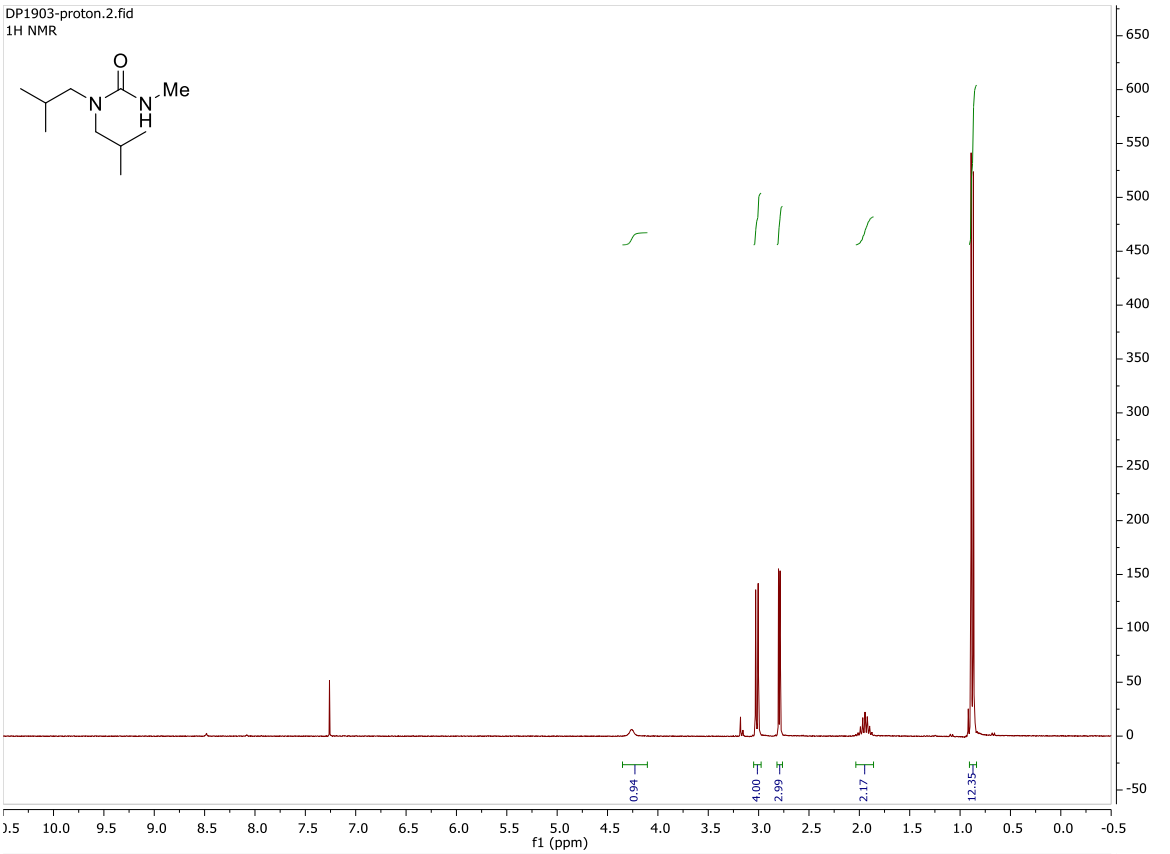

DP1428-F2.004.esp
155.83
130.41
128.04
121.11
121.32
109.66
107.86
42.41
21.72
11.31
Normalized Intensity
Chemical Shift (ppm)

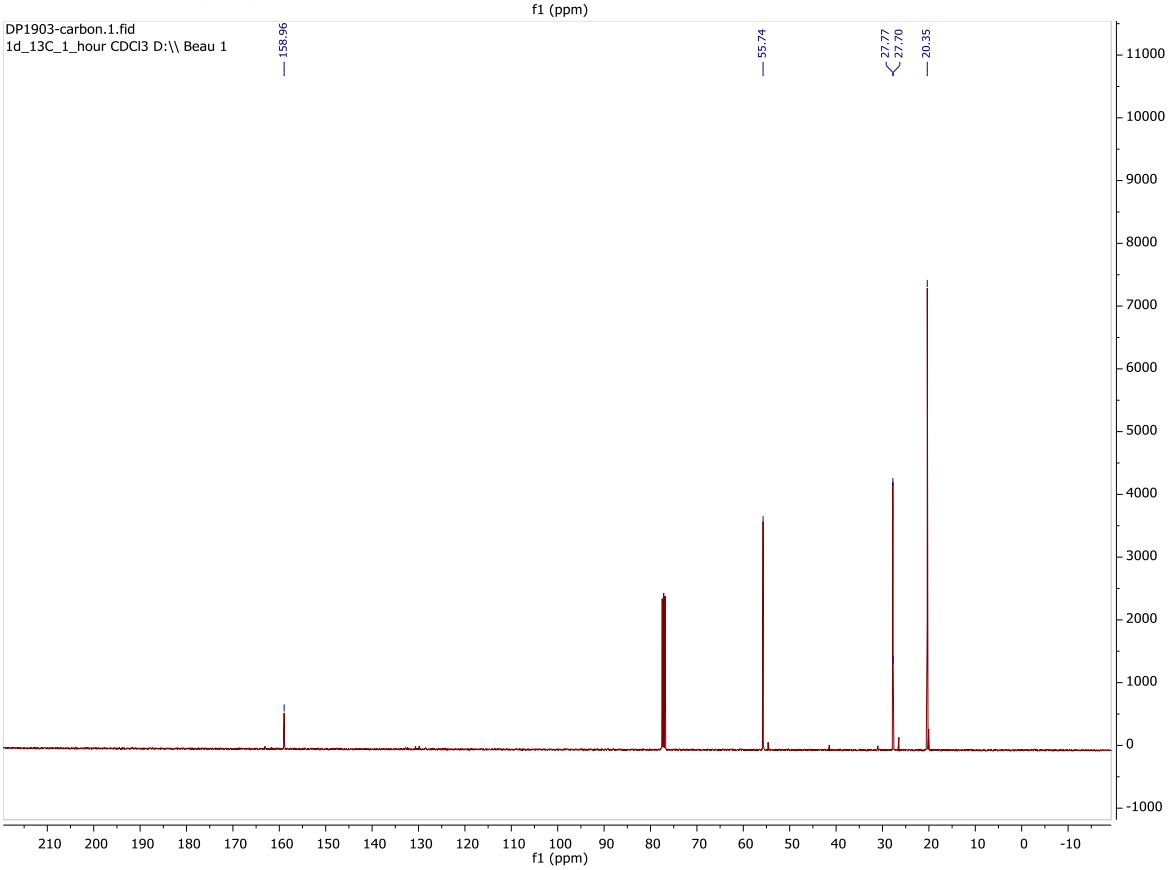

RI12-174-H2.001.esp
Normalized Intensity
Chemical Shift (ppm)
2.00 2.05 0.58 1.23 0.96 0.56 1.03 1.04 1.05 3.10 1.19 1.09 1.07 1.26 2.20 1.13 1.21 3.75 6.53
NH
O
N
NH
O
O
O
OMe

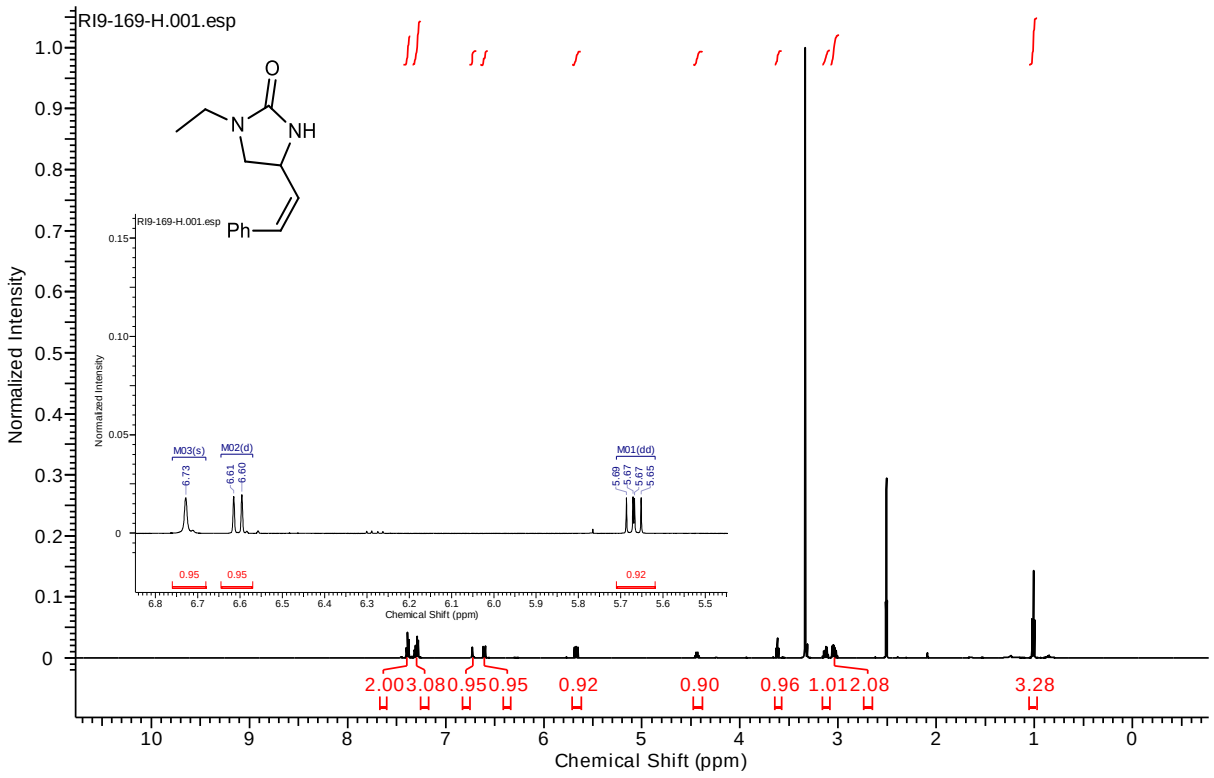

RI12-174-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
165.98
163.71
161.68
160.73
133.46
131.79
121.83
117.41
113.76
66.36
57.67
55.48
51.01
48.55
48.03
46.08
28.47
26.94
20.00

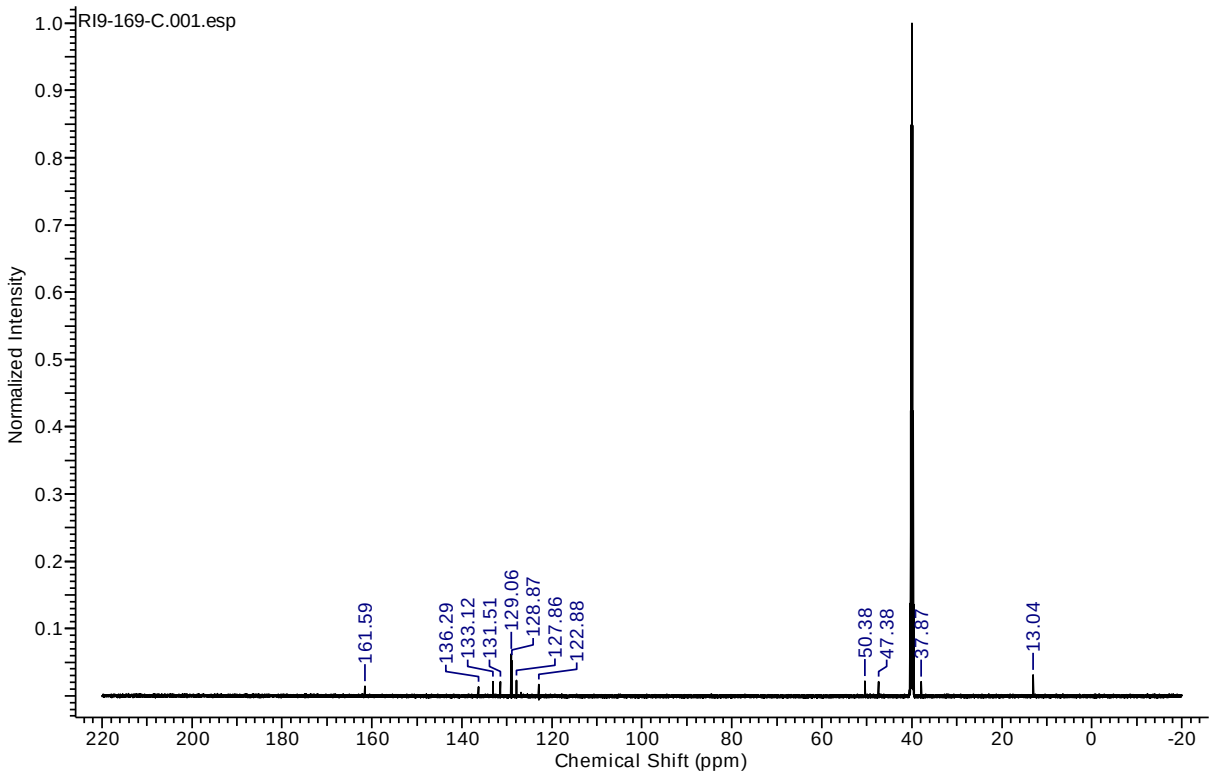

RI12-176-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.97
2.00
0.11
0.24
1.00
1.00
1.02
3.04
0.28
1.14
0.24
3.15
0.22
2.55
12.15
3.92
OMe

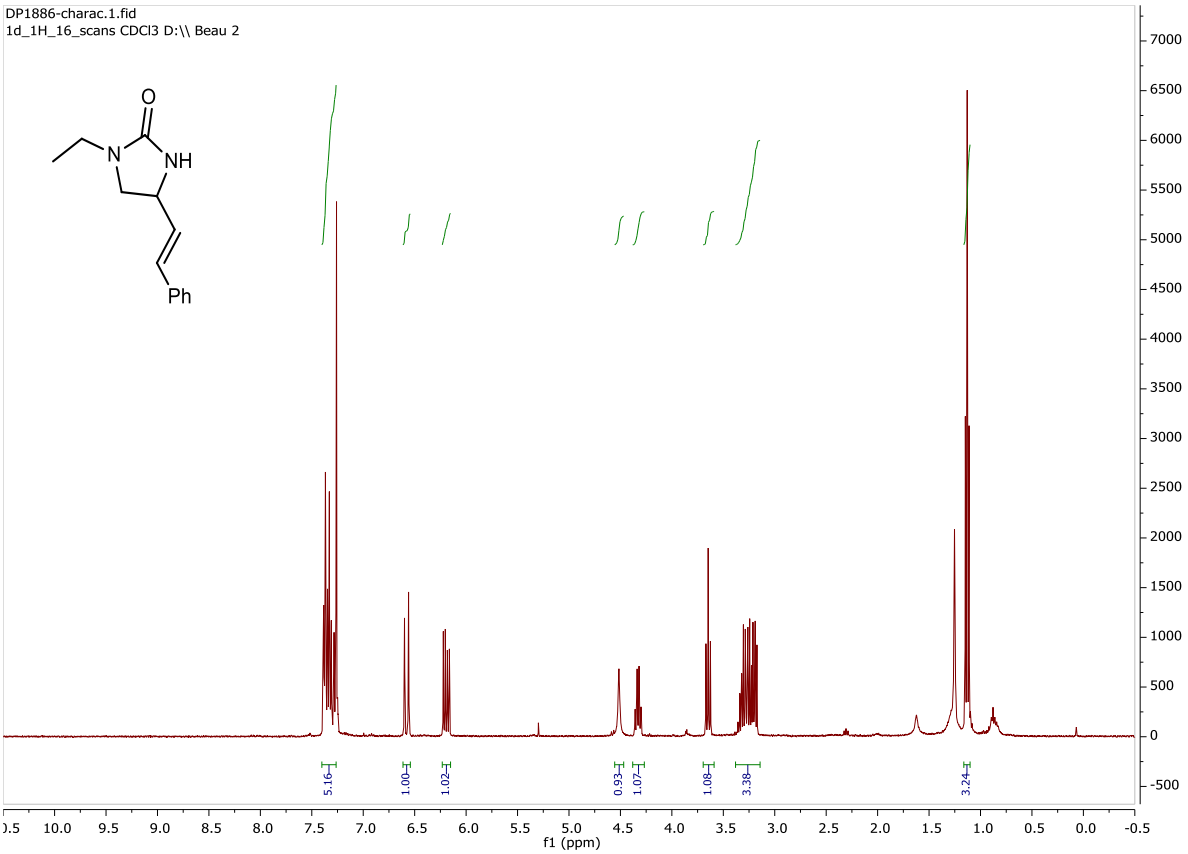

RI12-176-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
165.97
163.71
131.79
121.82
113.76
66.32
55.47
48.57
47.40
43.36
31.80
26.78
22.64
14.09

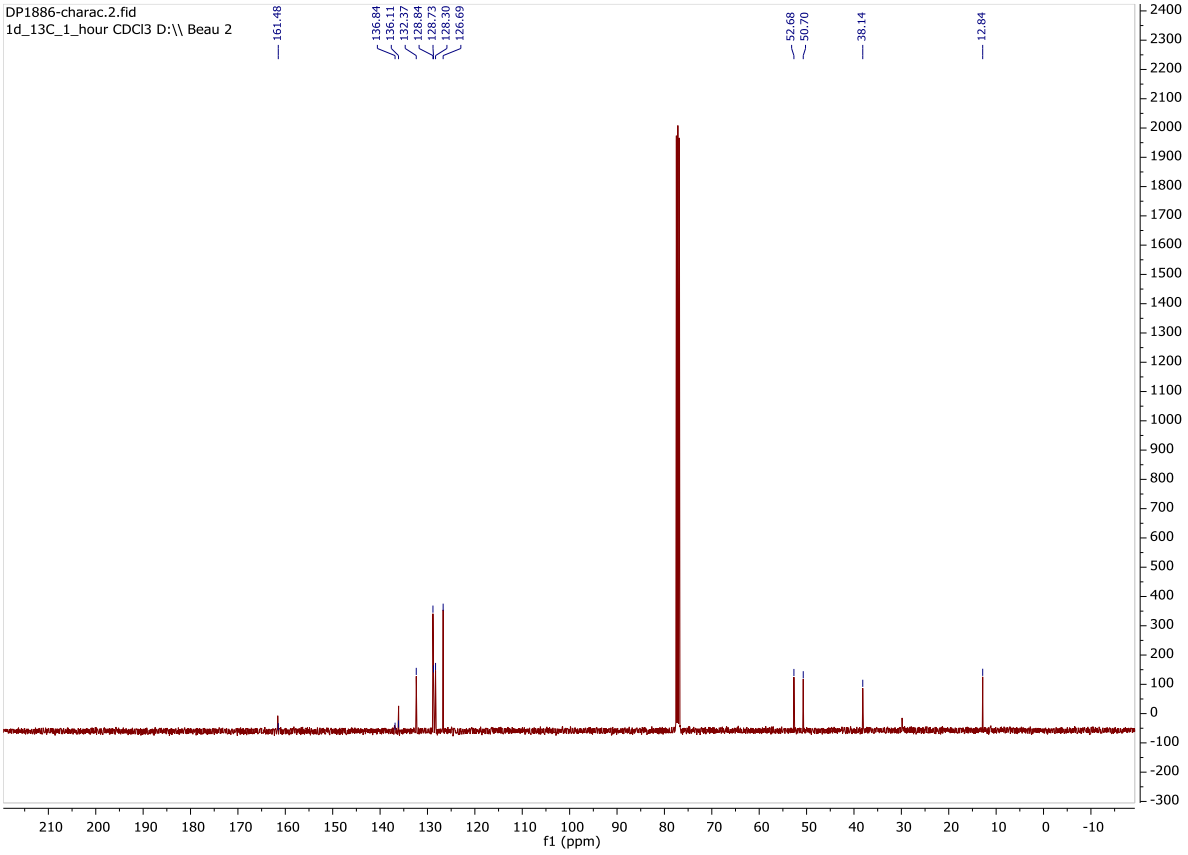

DP1903-proton.2.fid
1H NMR
O
N
N
H
Me
0.94
4.00
2.99
2.17
12.35
f1 (ppm)

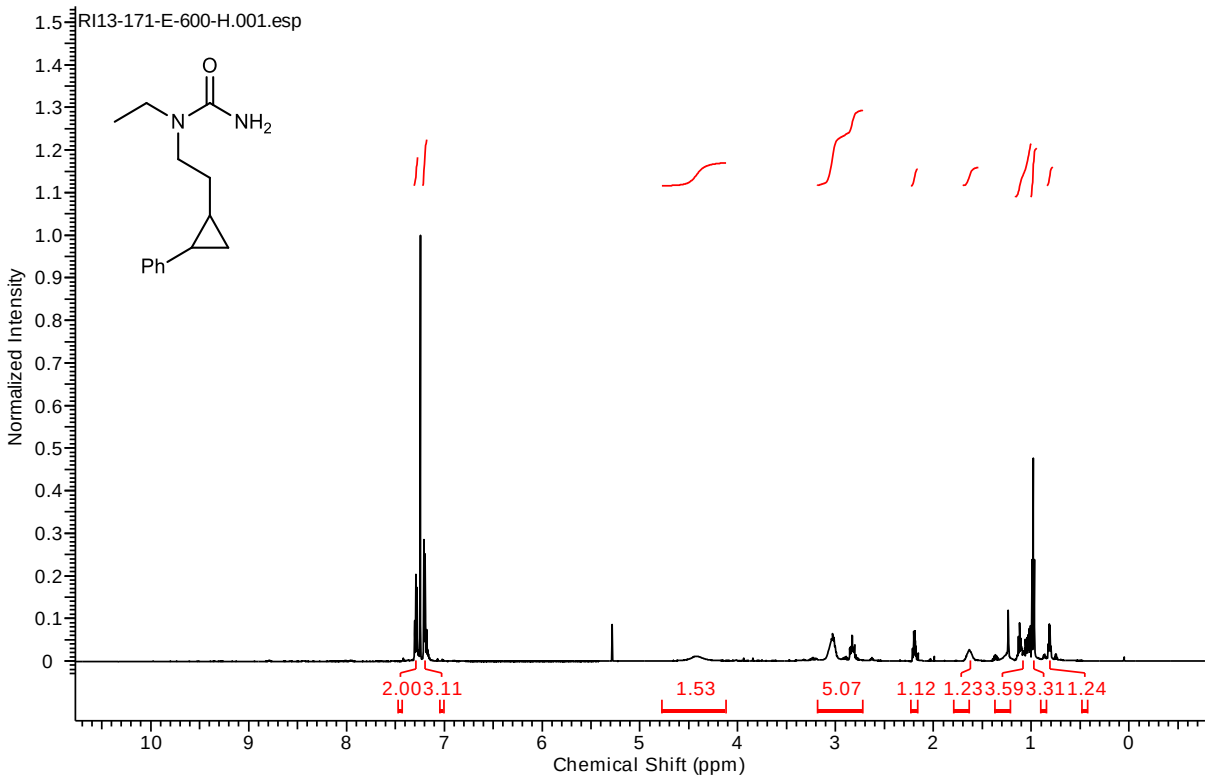

DP1903-carbon.1.fid
1d_13C_1_hour CDCl3 D:\\ Beau 1
158.96
55.74
27.77
27.70
20.35
f1 (ppm)

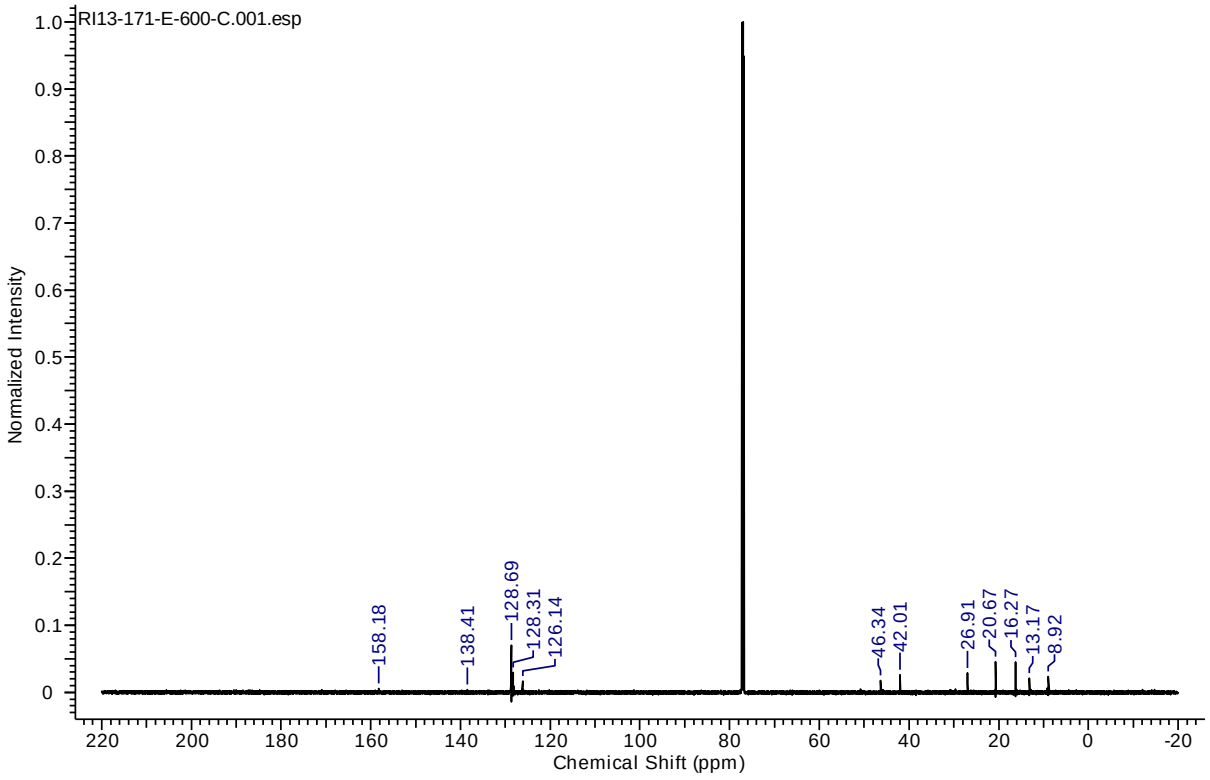

RI9-169-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
2.00 3.08 0.95 0.95 0.92 0.90 0.96 1.01 2.08 3.28
M03(s)
M02(d)
M01(dd)
6.73
6.61
6.60
5.69
5.67
5.67
5.65
0.95
0.95
0.92
O
N
NH
Ph

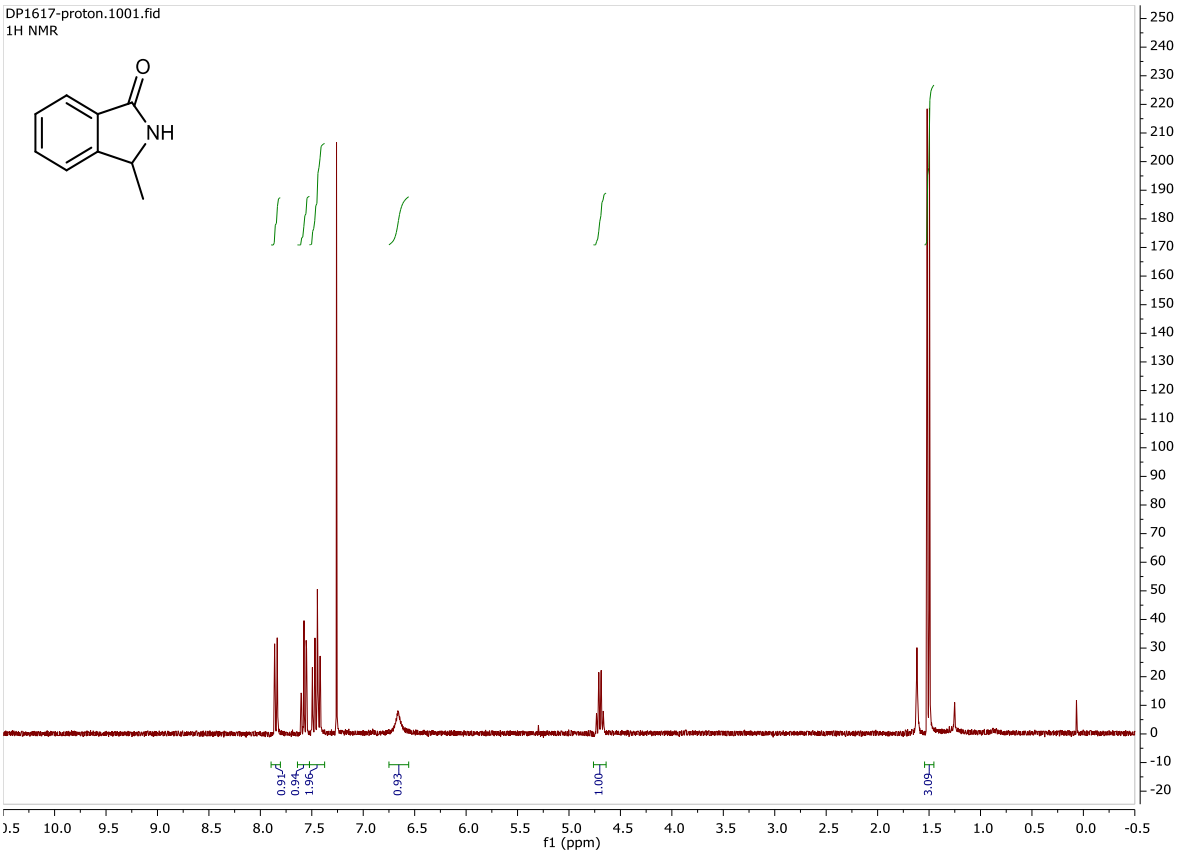

RI9-169-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
161.59
136.29
133.12
131.51
129.06
128.87
127.86
122.88
50.38
47.38
37.87
13.04

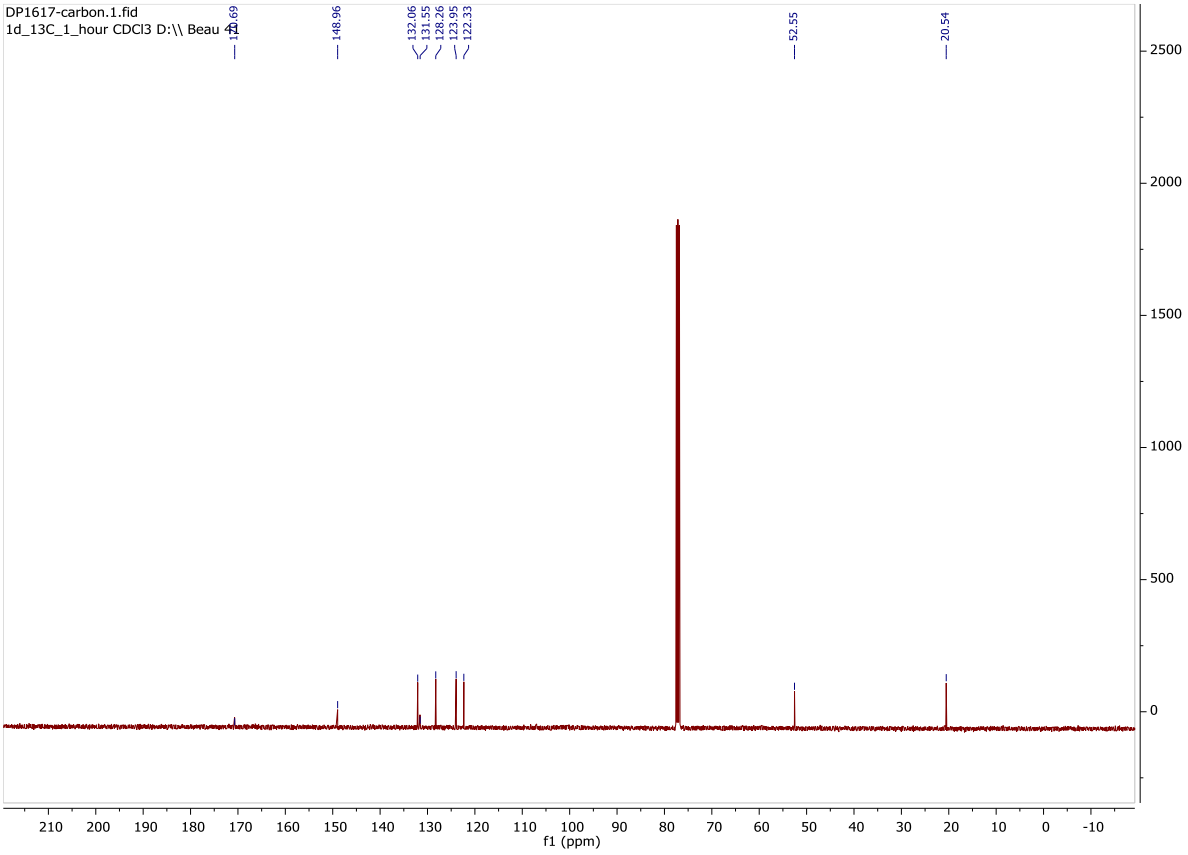

DP1886-charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 2
O
N
NH
Ph
5.16
1.00
1.02
0.93
1.07
1.08
3.38
3.24
f1 (ppm)

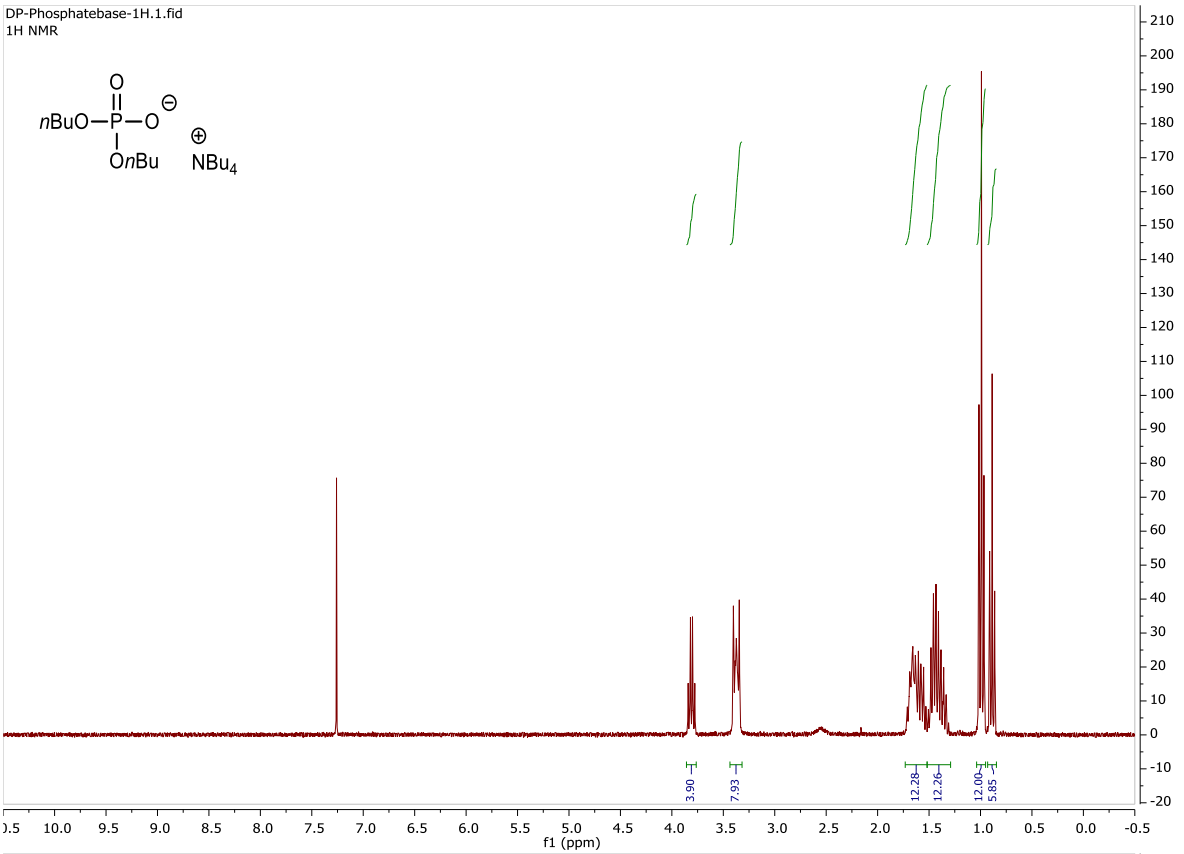

DP1886-charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 2
161.48
136.84
136.11
132.37
128.84
128.73
128.30
126.69
52.68
50.70
38.14
12.84
f1 (ppm)

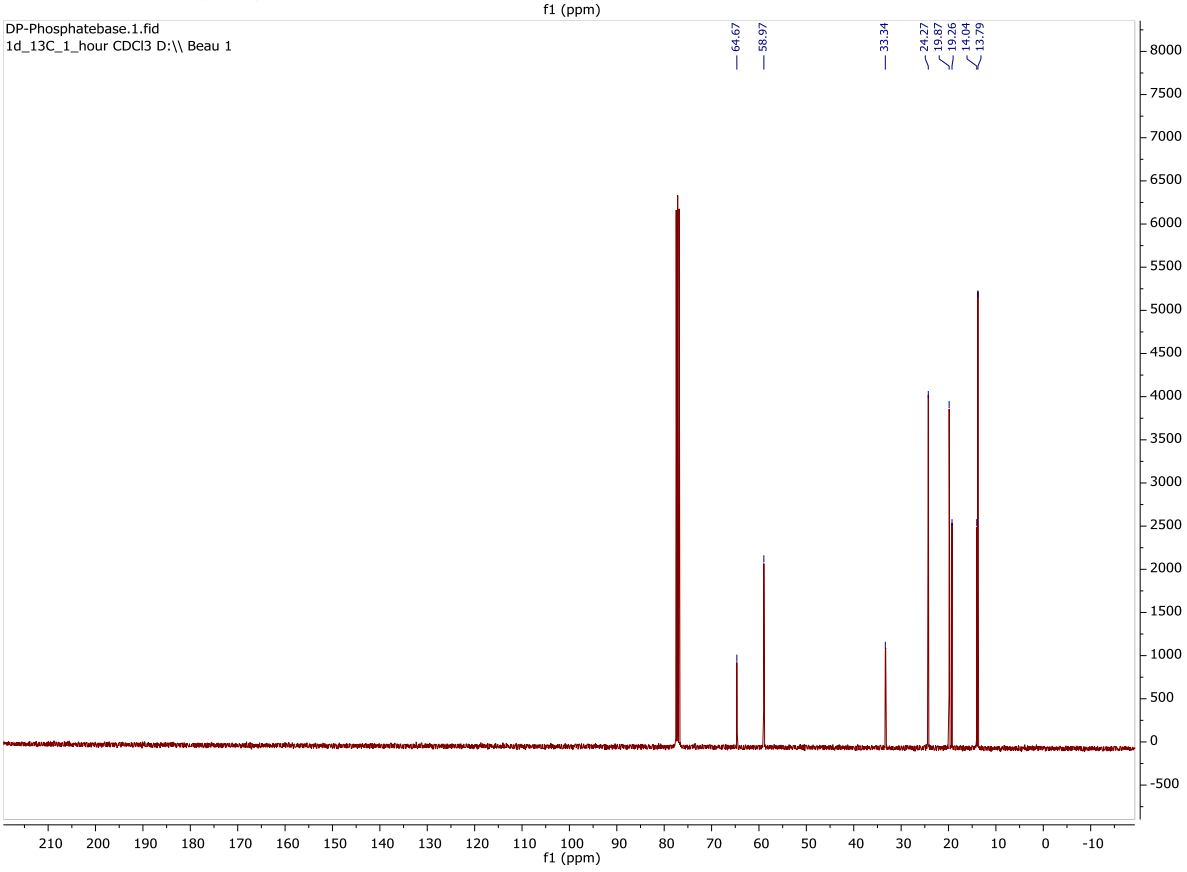

RI13-171-E-600-H.001.esp
O
N
NH2
Ph
Normalized Intensity
2.00
3.11
1.53
5.07
1.12
1.23
3.59
3.31
1.24
Chemical Shift (ppm)

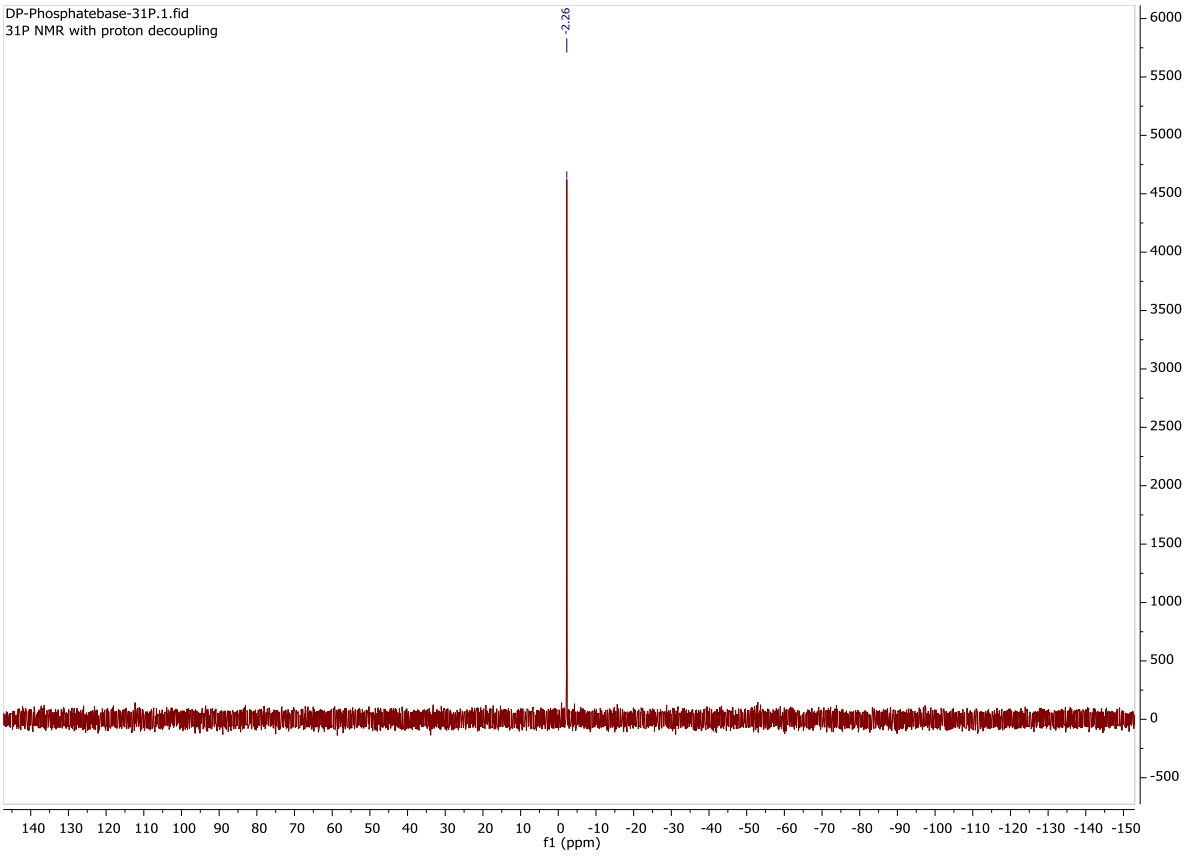

RI13-171-E-600-C.001.esp
Normalized Intensity
158.18
138.41
128.69
128.31
126.14
46.34
42.01
26.91
20.67
16.27
13.17
8.92
Chemical Shift (ppm)


DP1617-proton.1001.fid
1H NMR
O
NH
0.91
0.94
1.96
0.93
1.00
3.09
f1 (ppm)


DP1617-carbon.1.fid
1d_13C_1_hour CDCl3 D:\\ Beau 4
169.69
148.96
132.06
131.55
128.26
123.95
122.33
52.55
20.54
f1 (ppm)


DP-Phosphatebase-1H.1.fid
1H NMR
nBuO—P—O
OnBu
NBu4
3.90
7.93
12.28
12.26
12.06
5.85
f1 (ppm)


DP-Phosphatebase.1.fid
1d_13C_1_hour CDCl3 D:\\ Beau 1
64.67
58.97
33.34
24.27
19.87
19.26
14.04
13.79
f1 (ppm)


DP-Phosphatebase-31P.1.fid
31P NMR with proton decoupling
-2.26
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150
f1 (ppm)