N-Isocyanates: Versatile Intermediates in Heterocyclic Synthesis

By

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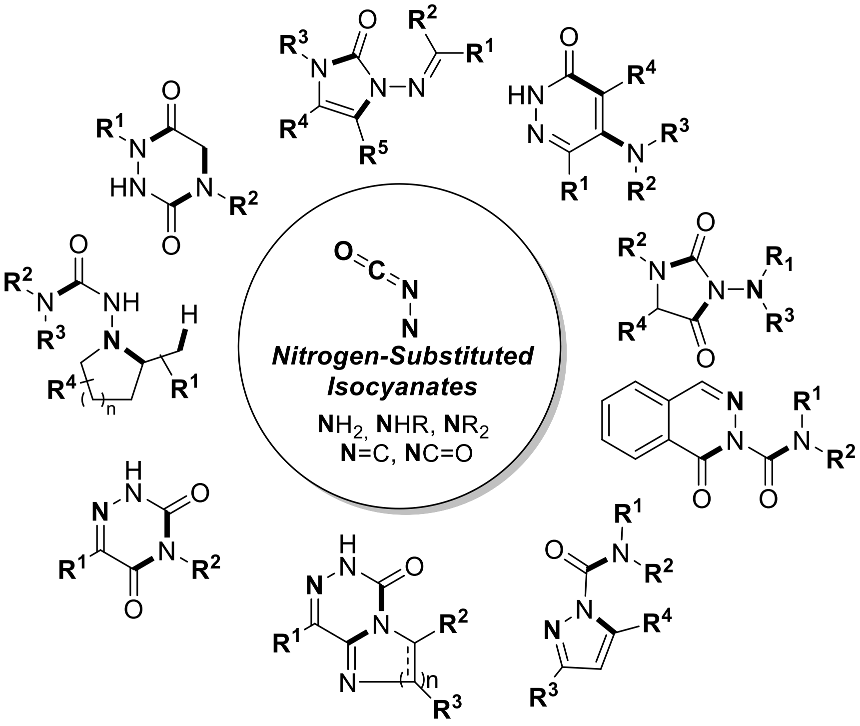
Abstract

Nitrogen heterocycles are present in nearly 60% of all small-molecule drugs approved by the US Food and Drug Administration. New innovative methods that streamline the synthesis of such heterocycles are therefore highly desirable. The use of new or underdeveloped reactive intermediates provides an excellent opportunity to develop novel heterocyclic syntheses. For example, nitrogen-substituted isocyanates (*N*-isocyanates) are a class of rare amphoteric isocyanates with high, but severely underdeveloped synthetic potential. The research efforts presented in this thesis have been directed towards the use of such intermediates for the rapid construction of heterocycles using cascade reactions. Using an *in situ* generation approach from masked (blocked) isocyanate precursors, we were able to control the homo dimerization of these species and design several cascade reactions forming more than 10 different classes of heterocycles using appropriate nitrogen nucleophiles. Given the importance of the N-N-C=O motif in pharmaceuticals and agrochemicals, *N*-isocyanates provide the opportunity to synthesize highly desirable cores for different industrial applications.

To illustrate the potential of this new tool in heterocyclic chemistry, more than 200 heterocycles were synthesized using this methodology. In Chapter 2, heterocycles incorporating only one atom from the *N*-isocyanate will be presented. More precisely, the first cascade reaction involving *N*-isocyanates for the rapid synthesis of saturated heterocycles will be presented. The incorporation of 2 atoms within the ring will then be discussed in Chapter 3 with the synthesis of hydantoins, imidazolones, thiazolines, pyrazoles and phthalazinones. Chapter 4 will focus on the incorporation of every atom in the heterocycle to form other bioactive cores such as azauracils, pyridazinones and azadiketopiperazines. Lastly, Chapter 5 will describe our efforts for the synthesis of acyclic molecules such as semicarbazides and aza-peptides.



Acknowledgements

In the last 5 years, so many people have impacted my life and helped to shape me as a scientist and a person. First of all, I would like to thank my supervisor André Beauchemin whose decision of taking me in 5 years ago changed my life. The motivation he provided by his wealth of knowledge and his love of research pushed me to work hard and achieve my goals. I will be forever grateful for the opportunity he provided me.

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Finally, these last 5 years would have been much more difficult without the love and the support of my friends and family. Especially, Alyssa Caissie and Cedric Jean Marie who always believed in me during my entire time in graduate school.

Thank you all.

“Yeah Mr. White, Yeah Science…”- Jesse Pinkman

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List of Abbreviations

Ac	acetyl
anti	against, opposite
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
Bu	butyl
cat.	catalytic
°C	degree Celsius
CDI	carbonyldimidazole
cis	on the same side
cm	centimetre
conc.	concentrated
Cy	cyclohexyl
δ	chemical shift in parts per million
d	deuterium (in NMR solvents)
DBU	1,8-diazabicycloundec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DIPEA	diisopropylethylamine
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(*N*,*N’*-dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
Et	ethyl
FLU	fluorenone

FT	Fourier transform
g	gram
h	hour
HBTU	*N*,*N*,*N′*,*N′*-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluorophosphate
HOMO	highest occupied molecular orbital
*h*ν	light
HRMS	high-resolution mass spectrometry
Hz	hertz
i	iso
IR	infrared
J	coupling constant
L	litre
LG	leaving group
LRMS	low-resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
m	meta
M	molar
Me	methyl
MCR	multicomponent reaction
mg	milligram
min	minute
mL	millilitre
mmol	millimole
Mom	methyl-*O*-methyl
MS	molecular sieves
NHC	*N*-heterocyclic carbene
Nuc	nucleophile
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
p	para

p-TSA	*p*-toluenesulfonic acid
Ph	phenyl
PMP	4-methoxyphenyl
ppm	parts per million
Pr	propyl
rt	room temperature
s	second
S*i*Pr	1,3-bis(2,6-diisopropylphenyl)-imidazolidene
S_n2	bimolecular nucleophilic substitution
syn	together, same side
t	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TDI	toluene diisocyanate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time of flight
Ts	*para*-toluenesulfonyl
UV	ultra-violet

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Chapter 1: Introduction

1.1: Isocyanates

Isocyanates, a class of heterocumulene compounds, have been used extensively since their discovery in 1848 by Wurtz.[1] Over 4,000 isocyanates are commercially available and more than 100,000 reactions have been reported using them in the literature.[2] As seen in Figure 1.1, they are amphoteric reagents that possess an electrophilic carbon and a nucleophilic heteroatom (e.g., nitrogen or oxygen).

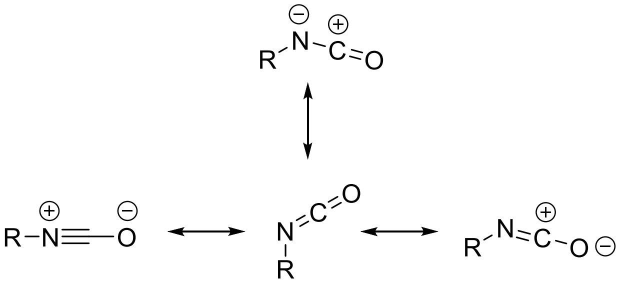
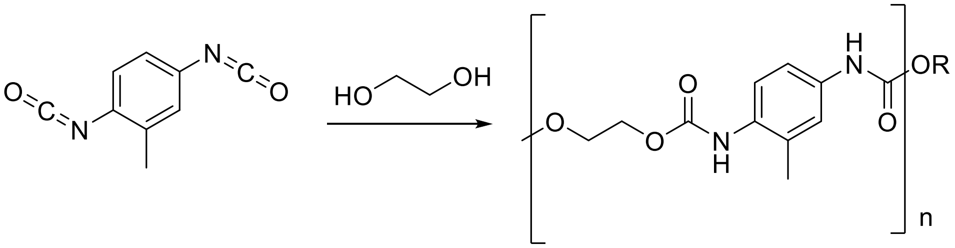


Figure 1.1: Resonance Structures of the Isocyanate Moiety

Given their high reactivity, isocyanates are commonly used as building blocks in chemical synthesis and have many different industrial applications. Most notably, diisocyanates are used in polymerization reactions to afford polyurethanes (Scheme 1.1). In 2011, 14 million tonnes of polyurethanes were produced, which corresponds to approximately 5% of global polymer production.[3]



Scheme 1.1: Polyurethane Formation Using Toluene Diisocyanate (TDI)

The potent electrophilicity of isocyanates is essential for these large scale processes, but can also lead to serious consequences. The major concern with isocyanates is their inherent toxicity. Workers that are regularly exposed to isocyanates can develop sensitivity issues and an increased risk of squamous cell respiratory carcinoma.[4]

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[1] Wang, Z. *Comprehensive Organic Name Reactions and Reagents*; Wiley: New York, **2009**, 1772-1774.

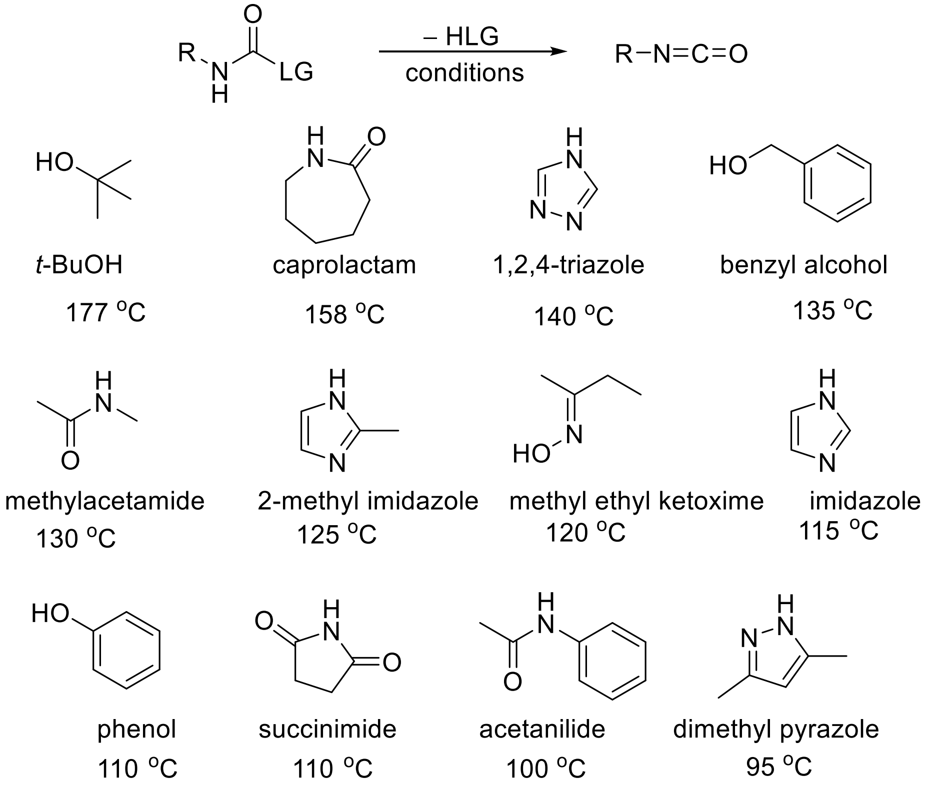
[2] Structure search performed on Reaxys.

[3] Engels, H.-W.; Pirkl, H.-G.; Albers, R.; Albach, R.W.; Krause, J.; Hoffman, A.; Casselmann, H.; Dormish, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 9422.

[4] Peters, J. M. *Proc. R. Soc. Med.* **1970**, *63*, 372.

1.2: Blocked Isocyanates

The high reactivity of isocyanates was tamed by the development of rearrangement reactions or by the used of blocked (masked) isocyanates that release the reactive isocyanate *in situ*. Blocked isocyanates are generally carbamates or ureas that will generate the desired isocyanates upon heating at different temperatures. They have been extensively studied and various blocking groups have been developed with a range of deblocking temperatures (Scheme 1.2).[5] The two major advantages of using blocked isocyanates are: 1) the controlled release of isocyanates at different temperatures controls their concentration over the course of the reaction, which ultimately leads to better reaction control; and 2) the reduced toxicity of the blocked form minimizes the risk of toxicity on industrial scale, making them attractive intermediates for the development of industrially relevant processes. Therefore, many different blocking groups have emerged with unique qualities or different modes of activation (base, acid, or metal catalysis and solvent-dependent rate), which are suited for their intended application.[5]



Scheme 1.2: Selected Blocking Groups and Their Deblocking Temperatures

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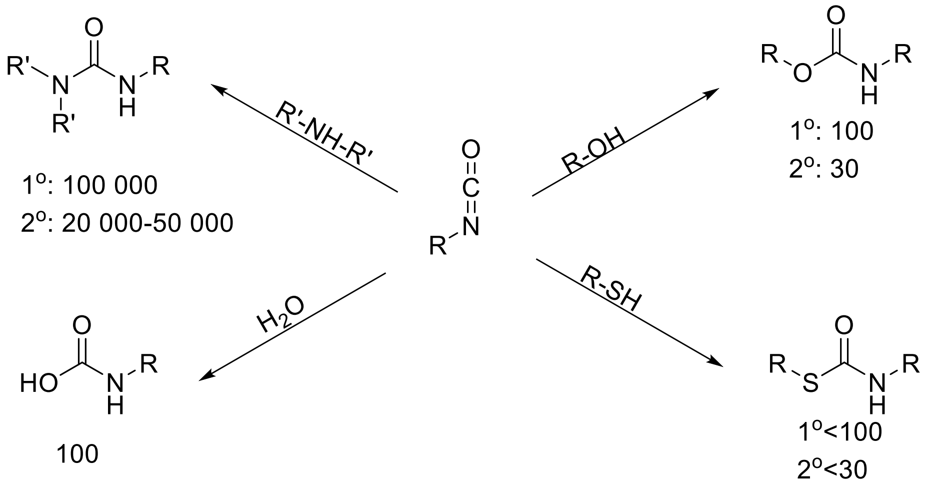
[5] (a) Wicks, D. A.; Wicks, Z. W. Jr. *Prog. Org. Coat.* **1999**, *36*, 148. (b) Wicks, D. A.; Wicks, Z. W. Jr. *Prog. Org. Coat.* **2001,** *41*, 1. c) Wicks, Z. W. Jr.; Jones, F. N.; Pappas, S. P.; Wicks, D. A. *Organic Coatings: Science and Technology*; Wiley-VCH: 2007, pp. 231-245. (c) Delebecq, E.; Pascault, J.-P.; Boutevin, B.; Ganachaud, F. *Chem. Rev.* **2013**, *113*, 80.

These blocking groups all function similarly; under thermolysis, the blocking group will leave to generate a free isocyanate that can react with a nucleophile present in the reaction medium. Since all these reactions are in equilibrium, the choice of a leaving group is crucial to the reaction. If the nucleophile is a better leaving group than the blocking group, a significant excess would be necessary to allow for sufficient conversion. The same would be true if the free blocking group is a better nucleophile than the one that was intended for use. However, if the blocking group is a poor nucleophile or if the nucleophile is a poor leaving group, only a stoichiometric amount of the nucleophile will be required to reach high conversion.

Since this equilibrium is critical for the success of the reaction, the rates of these reactions have been studied in great detail and classified according to the heteroatom nucleophile. As seen in Scheme 1.3, secondary alcohols and thiols are the slowest nucleophiles to add on to isocyanates.[6] Water, primary alcohols, and primary thiols react approximately three times faster. Generally, secondary amines react 200 to 500 times faster than primary alcohols and primary amines react up to 1,000 times faster.



Scheme 1.3: Relative Rates of Nucleophilic Attack on Isocyanates

1.3: Isocyanates in Heterocyclic Chemistry

Nucleophilic attack of isocyanates has its importance in industry, but as previously mentioned, isocyanates are amphoteric (having both a nucleophile and an electrophile). This amphotericity can be used for the development of reactions that create molecular complexity in a rapid fashion. Given the high heteroatom content of isocyanates, this functional group has been used extensively in heterocyclic chemistry. In the next section, a review of isocyanate reactivity in heterocyclic chemistry will be presented. Focus will be placed on transformations achieved in the last 20 years without the use of metals. Selected reports will be covered, along with four major

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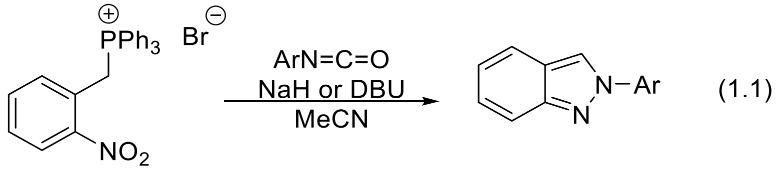
[6] Dyer, E.; Glenn, J.F.; Lendrat, E.G. *J. Org. Chem.* **1961**, *26*, 2919.

categories: heteroatoms as nucleophiles, carbon as a nucleophile, cycloadditions, and multicomponent reactions.

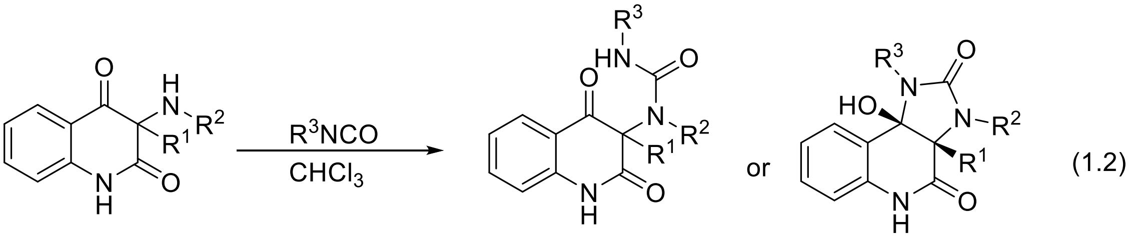
1.3.1: Isocyanates in Heterocyclic Chemistry - Heteroatom Nucleophiles

Given the affinity of isocyanates with heteroatoms, multiple cascade reactions were developed using heteroatom nucleophiles. In 2000, Weaver reported the synthesis of 2-aryl-2-*H*-indazoles using aryl-isocyanates and 2-nitrobenzyl phosphonium salt. Their scope is fairly limited (7 entries) with yields ranging from 40% to 62% (eq. 1.1).[7]



Two different mechanisms are proposed by the authors of the paper. The first involves Wittig-type reactivity followed by intramolecular trapping of the ketene imine. The second mechanism uses the oxygen of the nitro group to attack the isocyanate, and the resulting intermediate then cyclizing at the benzylic position. The latter reaction is only reported with aromatic isocyanates, but is nonetheless a good example of complexity generated from simple starting materials by either exploiting their high reactivity or their amphoteric potential.

In 2006, Klásek reported the use of 3-aminoquinoline-2,4-diones with isocyanates to form the urea-linked quinolone or the cyclic derivatives depending on the substitution pattern (eq. 1.2).[8]



It appears that when a primary amine (e.g. R^2 = H) is used, either a mixture of both cyclized and uncyclized products, or only uncyclized product is obtained. This is probably due to an unfavorable conformation of the resulting urea after the addition of the isocyanate. Nevertheless, when the R^2 group is large, the cyclization is favored and the cyclic derivative can be obtained in good yield (56-95%). This example showcases how conformation is important to consider in the design of reactions with isocyanates. Increasing the temperature would have favored rotation, but the authors commented that these substrates were prone to rearrangement at higher temperatures or when acid catalysis was employed.

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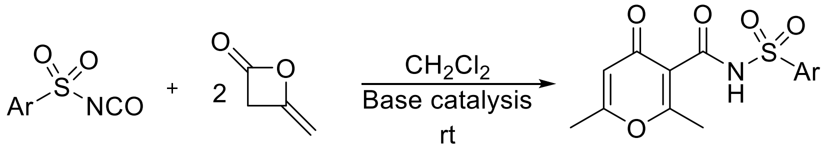
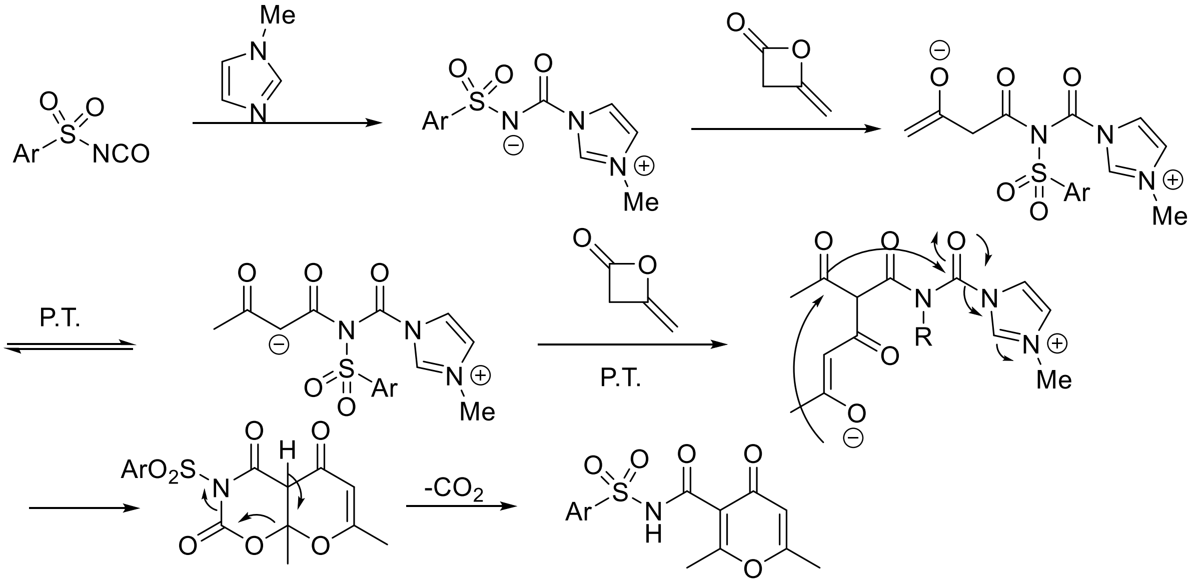
[7] Taher, A.; Ladwa, S.; Rajan, S. T.; Weaver, G. W. *Tetrahedron Lett.* **2000**, *41*, 9893.
[8] Klásek, A.; Lyčka, A.; Holčapek, M.; Hoza, I. *J. Heterocycl. Chem.* **2006**, *43*, 203.

In 2008, Alizadeh reported the synthesis of 1,3-oxazine-2,4-diones using arylsulfonyl isocyanates and diketene (eq. 1.3).[9]



(1.3)

An interesting aspect of this reaction was the use of a base as a nucleophilic catalyst. The authors suggest an attack of the base to form a nucleophilic urea that could open the activated lactone (Scheme 1.4).



Scheme 1.4: Base Activation of Isocyanates for the Synthesis of 1,3-Oxazine-2,4-diones

The amphotericity of the isocyanate is well controlled in this system. A catalyst is used to enhance both nucleophilic and electrophilic character of the isocyanate leading to increased reactivity. It is also important to note that different bases generate different products by different pathways, which demonstrates the potential of tuning the amphoteric character of isocyanates.

Similarly to the report by Klásek, two different cascade reactions using the nitrogen atom as a nucleophile followed by condensation were published in the *Journal of Heterocyclic Chemistry* in 2008 and 2011. The 2008 report by Hu used *β*-amino-phenylpropranone and aromatic isocyanates to produce dihydropyrimidin-2(1H)-one (eq. 1.3).[10]

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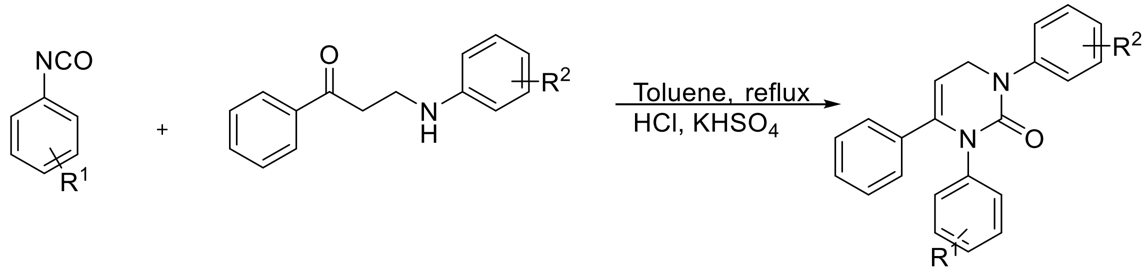
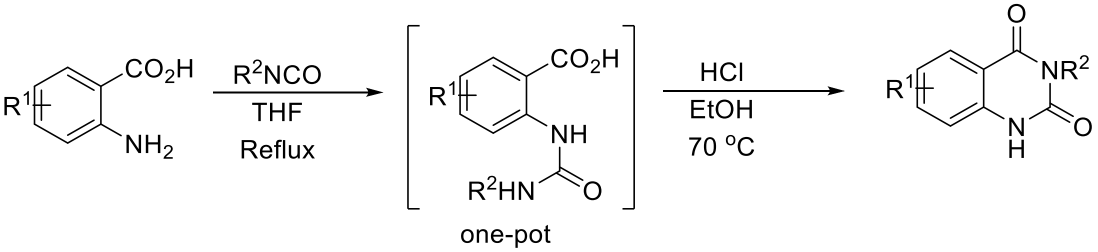
[9] Alizadeh, A.; Zohreh, N.; Zhu, L.-G. *Synthesis* **2008**, 2073.

[10] Xue, N.; Lu, X.; Hu, Y. *J. Heterocycl. Chem.* **2008**, *45*, 1095.



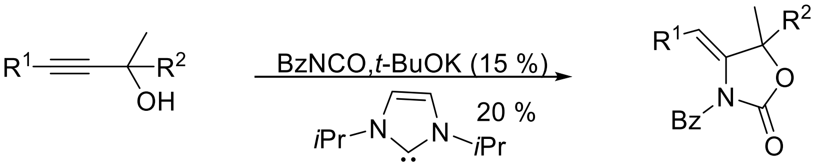
(1.3)

Similar reactivity was observed by Campeau when they reacted anthranilic acids with isocyanates in a one-pot fashion using high temperatures and acid catalysis (eq. 1.4).[11] Using this methodology, they were able to formally synthesize Zenarestat.



(1.4)

One year later, a report from Kang described the synthesis of oxazolidinones by the cascade reaction of propargylic alcohols and benzoyl isocyanate (eq. 1.5).[12]



(1.5)

The authors postulated base catalysis with their carbene catalyst, but strong bases alone cannot promote the reaction as efficiently. Another possible explanation would be that given the slow reaction rate of alcohols with isocyanates, the carbene is acting as a nucleophile to form an activated carbonyl that undergoes substitution with the propargyl alcohol. Nevertheless, this is a rare case of a cascade reaction that uses oxygen as a nucleophile on isocyanates.

The last example in this section does not involve heterocycles, but illustrates the versatility of isocyanates to form important molecules. In 2011, based on a literature precedent, Crich reported an elegant synthesis of amide bonds using carboxylic acids and isocyanates (eq. 1.6).[13]

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[11] Koay, N.; Campeau, L.-C. *J. Heterocycl. Chem.* **2011**, *48*, 473.

[12] Jo, K.; Maheswara, M.; Yoon, E.; Lee, Y. Y.; Yun, H.; Kang. E. J. *J. Org. Chem.* **2012**, *77*, 2924.

[13] Sasaki, K.; Crich, D. *Org. Lett.* **2011**, *13*, 2256.

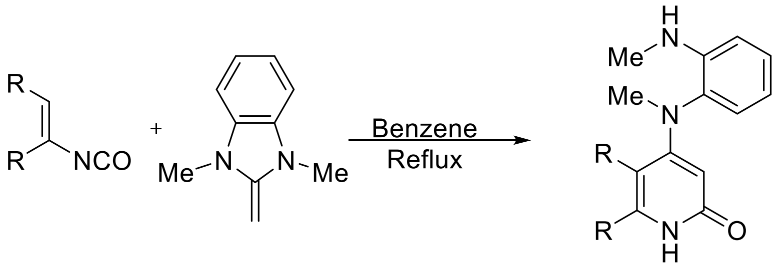
(1.6)

Under basic conditions, the carboxylate would attack the isocyanate to form an amide anion that could lose CO_2 through an acyl transfer-type mechanism to generate the desired amide bond. It is important to note that only aryl isocyanates were used, but Crich was able to report a diverse scope of anilides. Two years prior to this report, the same group had also demonstrated the use of thioacid derivatives with isocyanates to form amide bonds that are not limited to the anilide series.[14]

As seen in this section, the use of heteroatom nucleophiles is well documented in heterocyclic chemistry using isocyanates due to their high reactivity (Scheme 1.3). In particular, amines are well-suited reaction partners for the development of cascade reactions Their reactions with *N*-isocyanates will be discussed in the following chapters.

1.3.2: Isocyanates in Heterocyclic Chemistry - Carbon Nucleophiles

Carbon nucleophiles are less present in isocyanate chemistry, since they are inherently less nucleophilic than a heteroatom possessing a lone pair of electrons. Nevertheless, the synthetic community developed elegant solutions to overcome this lower reactivity and created synthetically-useful cascade reactions to form heterocycles using isocyanates and carbon nucleophiles. For example, enamines are alkenes with highly nucleophilic carbons due to conjugation with an electron-rich heteroatom. In 2003, Rigby reported the use of enamines in conjunction with vinyl isocyanates for the synthesis of substituted 4-aminopyridones (eq. 1.7).[15]



(1.7)

The scope of isocyanates is diverse, but the authors only used this specific enamine. The authors mentioned that typical enamines require reaction times of more than two days and harsher conditions to obtain reasonable yields. They attributed this reactivity to the enhancement of the nucleophilicity of the specific enamine they used. This study was the follow-up of their prior work that utilized carbene and vinyl isocyanates in a [4+1] cycloaddition.[16] Similar reactivity will be covered in the next section. Carbenes have also been used as nucleophiles with acyl

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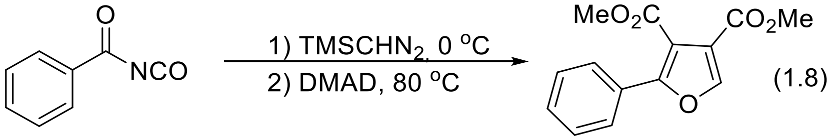
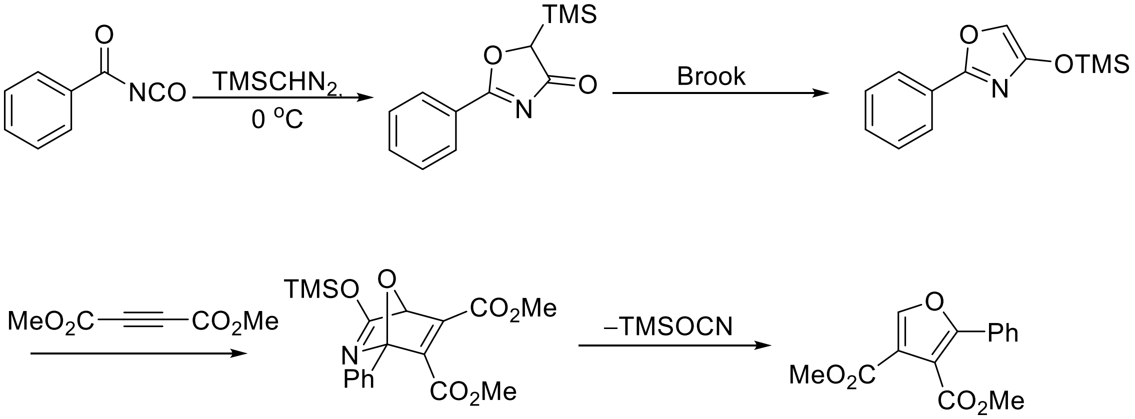
[14] Crich, D.; Sasaki, K. *Org. Lett.* **2009**, *11*, 3514.
[15] Rigby, J.; Lee, C.-S. *Org. Lett.* **2003**, *5*, 1151.
[16] Rigby, J. H.; Wang, Z. *Org. Lett.* **2002**, *4*, 4289.

isocyanates to generate substituted oxazoles, which can form substituted furans following a cycloaddition with an alkyne counterpart (eq. 1.8).[17]

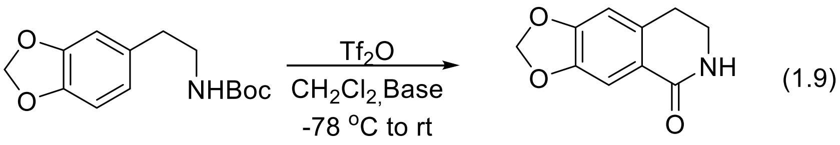


In this reaction, the amphoteric character of the isocyanate is extended to the oxygen atom of the amide. After the attack of the carbene, the intermediate can attack the resulting positive charge and form an oxazole following a Brook rearrangement. The resulting oxazole can then perform a cycloaddition and lose TMSOCN to form the desired furan ring (Scheme 1.5).



Scheme 1.5: Substituted Furan Synthesis Using Acyl Isocyanates

In addition to carbenes and enamines, conjugated π systems can also act as carbon nucleophiles in reactions with isocyanates. In 2013, Kim reported the use of Boc-protected amines as blocked isocyanates in a modified Bischler-Napieralski reaction (eq. 1.9).[18]



The use of Tf_2O is well known to activate amides, but when it is used with carbamates (Scheme 1.6), it could form an isocyanate which in this case is trapped by an electron-rich aromatic system. It is likely that the reaction proceeds through the formation of a stable triflate anion, followed by a *tert*-butyl cation. In this work, 13 different aromatic lactams were synthesized, 11 of which produced the corresponding bicyclic system in good yields. For the remaining two, the

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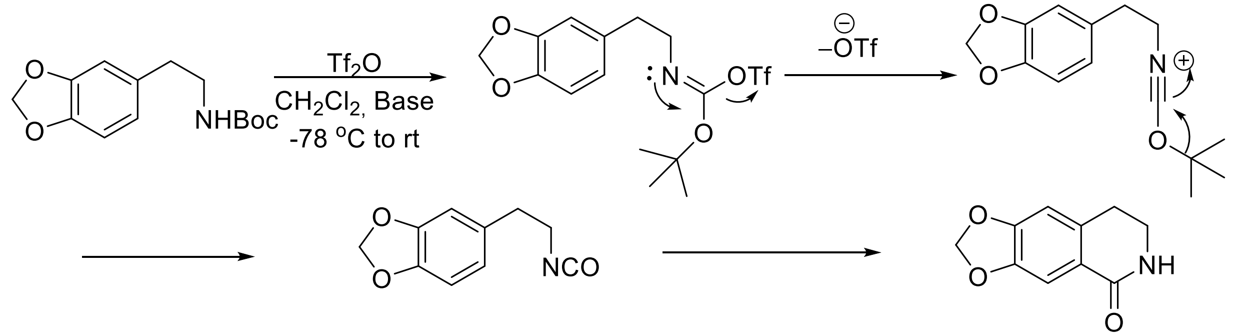
[17] Hari, Y.; Iguchi, T.; Aoyama, T. *Synthesis* **2004**, 1359.

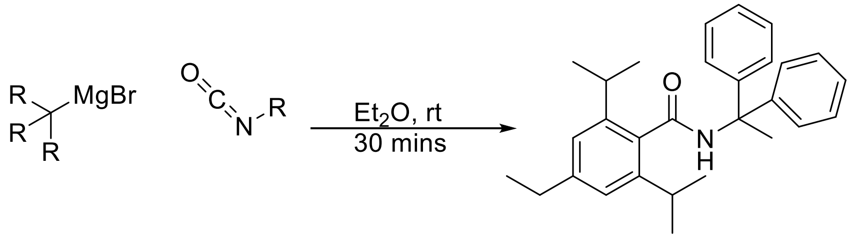
[18] In, J.; Hwang, S.; Kim, C.; Seo, J. H.; Kim, S. *Eur. J. Org. Chem.* **2013**, 965.

isocyanate was observed rather than the desired heterocycle. This occurred in the presence of electron-poor ring systems.



Scheme 1.6: Potential Mechanism for the Formation of Isocyanates from Boc-Protected Amines

The final example that will be covered does not form a heterocycle. When discussing carbon nucleophiles, Grignard reagents are one of the first things that come to mind. Bode used these reagents in 2012 to form sterically-hindered amides that could not be formed otherwise (eq. 1.10).[19]



(1.10)

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More than 25 hindered amides have been synthesized using this methodology to create a molecular scaffold that could not be made using classical coupling conditions. The high reactivity of isocyanates coupled with the nucleophilicity associated with the Grignard reagent makes this connectivity possible.

It is still suprising to see how underdevelop carbon nucleophile chemistry with isocyanate is given the hight reactivity of Grignard reagents for example.This limited reactivity is also represented in *N*-isocyanate reactivity which will be discussed in following chapters.

1.3.3: Isocyanates in Heterocyclic Chemistry: Cycloaddition Reactions

In 1996, Aoyama and Shioiri reported the use of acyl isocyanates to perform a [4+2] cycloaddition followed by a Brook rearrangement. According to the authors, the adduct is fairly

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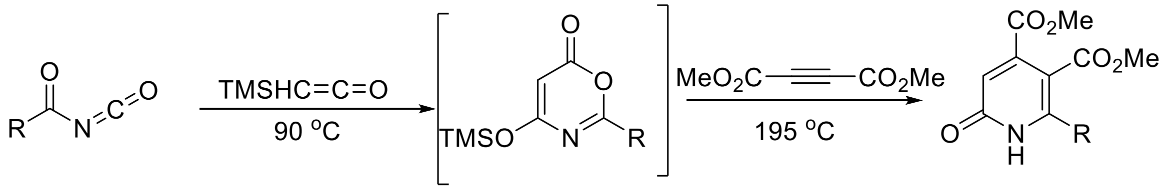
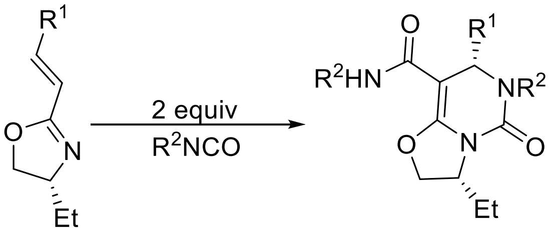
[19] Schäfer, G.; Matthey, C.; Bode, J. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 9173.

labile; therefore, they performed a subsequent [4+2] cycloaddition to synthesize a substituted 2-pyridone (eq. 1.11).[20]



(1.11)

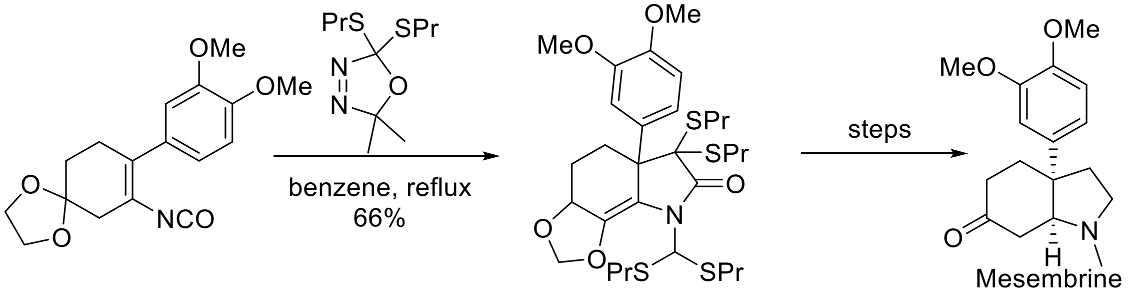
This is an elegant use of cycloadditions to synthesize heteroaromatic cores from readily available starting materials. Two years later, Elliott published an asymmetric hetero Diels-Alder reaction using oxazolines and isocyanates to yield pyrimidine derivatives (eq. 1.12).[21]



(1.12)

They only reported five examples with yields ranging from 20 to 32% and the authors suggested that the isolated isomer is the result of epimerization of the opposite diastereoisomer. They also comment on the possibility of a degradation pathway along the epimerization pathway, which may lead to the low yields that they obtained. Nevertheless, this is a good example of a hetero Diels-Alder reaction that yields molecular complexity in a single step.

In the previous section, Rigby reported the use of carbenes as a nucleophilic source of carbon (eq 1.7). Prior to that work, his group reported the use of carbenes for the development of a [4+1] cycloaddition with vinyl isocyanates for the synthesis of mesembrine (eq. 1.13).[22]



(1.13)

Their precursor generates a carbene upon thermolysis after releasing acetone and nitrogen gas. It can then perform a cycloaddition or a stepwise addition to process and trap the nitrogen with a second equivalent of carbene. Given the ease of access of the isocyanates (five steps from

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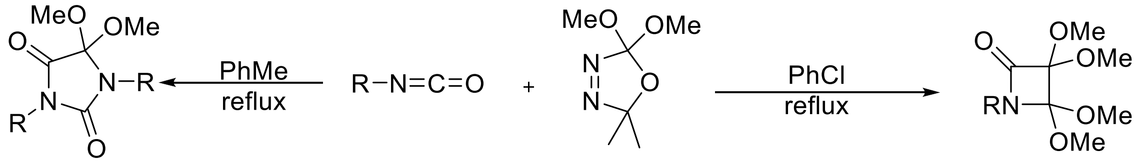
[20] Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1996**, *37*, 4973.

[21] Elliott, M.; Kruiswijk, E.; Willock, D. J. *Tetrahedron Lett.* **1998**, *39*, 8911.

[22] Rigby, J. H.; Dong, W. *Org. Lett.* **2000**, *2*, 1673.

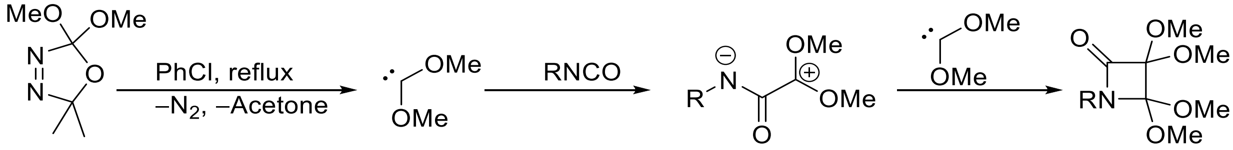
commercially available materials), this is a clever way to form the 5-membered ring and allows the synthesis of mesembrine in only 12 steps.

Six years later, the same group used a similar approach with a slightly different carbene precursor to perform a formal [2+1+1] cycloaddition using isocyanates and two equivalents of carbene (eq. 1.14).[23] The authors noted that solvent had an important effect on the reaction. When toluene was used as the solvent, two equivalents of the isocyanate combined to generate a 5-membered ring, but when the solvent was changed to chlorobenzene, the sole product was the β-lactam.



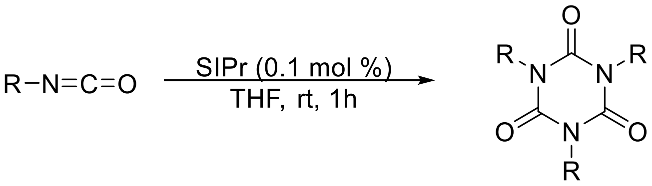
(1.14)

At first, the authors believed that they were forming tetramethoxyethylene under the reaction conditions and that this electron-rich alkene was used in a [2+2] cycloaddition as observed by Hoffman in 1964.[24] However, while using the alkene directly in the reaction conditions, they observed less than 10% product formation; therefore, the authors explained the reaction through a stepwise addition of two equivalents of carbene formed after the release of nitrogen gas and acetone. The first step would generate a dipole which would undergo a [3+1] cycloaddition (Scheme 1.7).



Scheme 1.7: Stepwise Process for the Formation of β-Lactams

Carbenes (NHC in this case) can also be used as catalysts to promote trimerization of isocyanates. In 2004, Louie reported a highly efficient system using only 0.1 mol% of SIPr, a known bulky *N*-heterocyclic carbene, for trimerization of isocyanates in excellent yield (eq. 1.15).[25]



(1.15)

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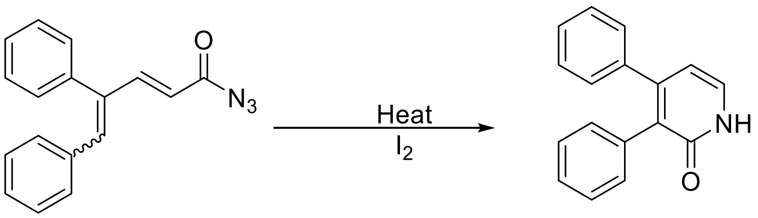
[23] Rigby, J. H.; Brouet, J.-C.; Burke, P. J.; Rohach, S.; Sidique, S.; Heeg, M. J. *Org. Lett.* **2006**, *8*, 3121.
[24] Hoffmann, R. W.; Hauser, H. *Tetrahedron Lett.* **1964**, 197.
[25] Duong, H. A.; Cross, M. J.; Louie, J. *Org. Lett.* **2004**, *6*, 4679.

Given the reactivity seen in this section, it is likely that the mechanism involves attack on the isocyanate by the carbene to generate a negative charge, which will then attack a second equivalent of the isocyanate to generate another negative charge. This negative charge will attack the activated carbonyl to form the 6-membered ring, a formal [2+2+2] product, and regenerate the catalyst. It is important to note that conditions for the dimerization are also reported in their optimization, but are not as effective as the trimerization, which is likely due to relative stability of the 6-membered ring (isocyanurate) versus the 4-membered ring (uretdione). Other reactions that use carbenes have been studied in similar fashions in the last 20 years, but will not be discussed further.[26,27,28]

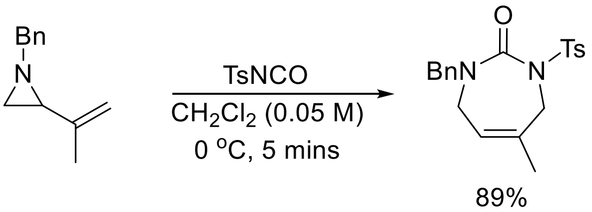
Pericyclic reactions can also be performed intramolecularly to synthesize heterocycles. In 2011, Chuang reported a cascade reaction using acyl azide as an isocyanate precursor in order to achieve an intramolecular cyclization to synthesize a substituted pyridone (eq. 1.16).[29]



(1.16)

The iodine was used in order to isomerize the π-system to provide the (*Z*)-alkene required for cyclization. Depending on the substitution pattern, other cycloadducts could also be obtained using the aromatic system for a cycloaddition reaction. Nevertheless, they were able to obtain the pyridone with 12 different substitution patterns with yields ranging from 12 to 88%. This represents a good example in which isocyanates can be used intramolecularly to generate valuable heterocycles *via* cycloaddition reactions.

In 2012, an example of a formal [5+2] cycloaddition was published by Saito using sulfonyl isocyanates with vinylaziridines to generate unsaturated cyclic ureas (eq. 1.17).[30]



(1.17)

Interestingly, depending on the solvent used, the 5- or 7-membered rings can be obtained. While dichloromethane seems to strictly favor the formation of the larger ring, DMF results in the

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[26] Rigby, J. H.; Cavezza, A.; Heeg, M. J. *Tetrahedron Lett.* **1999**, *40*, 2473.
[27] Cheng, Y.; Whang, Bo.; Cheng, L.-Q. *J. Org. Chem.* **2006**, *71*, 4418.
[28] Rigby, J. H.; Sidique, S. *Org. Lett.* **2007**, *9*, 1219.
[29] Chuang, T.-H.; Chang, W.-Y.; Li, C.-F.; Wen, Y.-C.; Tsai, C.-C. *J. Org. Chem.* **2011**, *76*, 9678.
[30] Kanno, E.; Yamanoi, K.; Koya, S.; Azumaya, I.; Masu, H.; Yamasaki, R.; Saito, S. *J. Org. Chem.* **2012**, *77*, 2142.

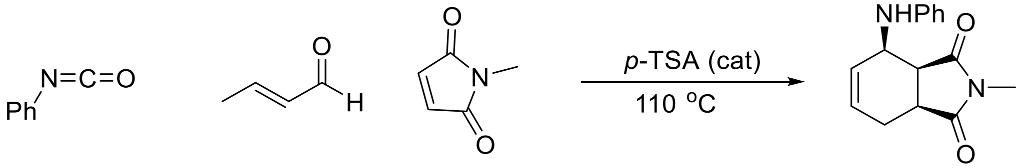
complete opposite selectivity with more than 19:1 ratio favoring the 5-membered ring. The authors mentioned that this reaction works only with sulfonyl isocyanates. When they performed the reaction using aromatic isocyanates, no reaction was observed at 0 °C, but they commented on the possibility to promote the reaction using higher temperatures (*i.e.*, 100 °C).

In this section, the ability to extend conjugated systems either on the isocyanates or their reaction partners to achieve intra- and intermolecular cycloadditions with carbon framework, heteroatoms, and carbenes has been demonstrated. All of these strategies were used to synthesize a variety of heterocycles by controlling different reaction pathways. In the next section, the development of multicomponent reactions using isocyanates to further control reaction pathways will be explored .

Pericyclic reactions represent one of the rare reactions known to date with nitrogen-substituted isocyanates other than solvolysis. As for any isocyanate reactivity, cycloaddition with *N*-isocyanates are also less developed. The Beauchemin group did significant work in this area, which will be discussed later in this chapter.

1.3.4: Isocyanates in Heterocyclic Chemistry: Multicomponent Reactions (MCR)

Given the highly reactive nature of isocyanates, selective reactions need to be developed in order to diminish the propensity of side reactions to occur. To achieve such selectivity, it is preferable that some of the components display no affinity for the isocyanates, but only for the intermediates generated during the reactions. This is precisely what Beller reported in 2005 while using aldehydes, dienophiles, and isocyanates to generate highly substituted cyclohexenes (eq. 1.18).[31] In this case, the aldehyde displays affinity only for the isocyanates and not the dienophile. As for the dienophile, it is only reactive toward the diene formed during the reaction.



(1.18)

The authors suggested two different pathways that lead to the same product (Scheme 1.8).

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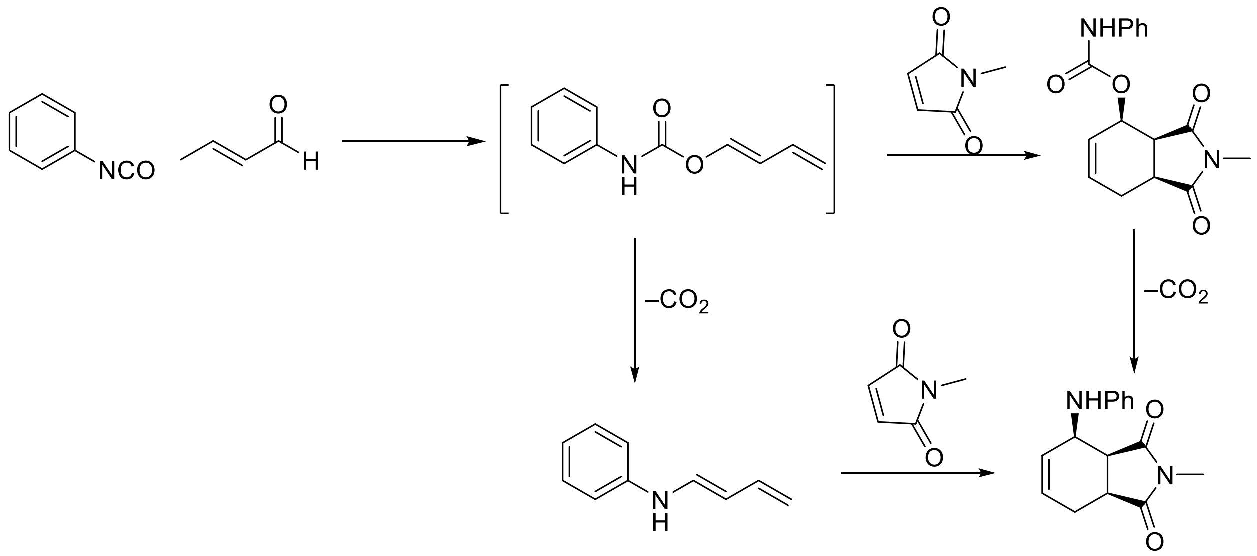
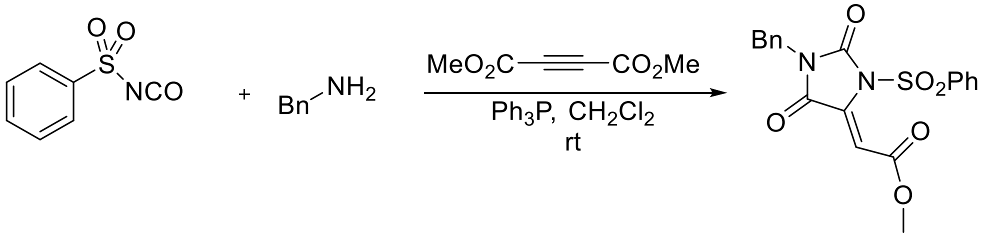
[31] Strübing, D.; Neumann, H.; Hübner, S.; Klaus, S.; Beller, M. *Org. Lett.* **2005**, *7*, 4321.



Scheme 1.8: Mechanism of the MCR Reaction using Aldehydes, Isocyanates, and Dienophiles

In both cases, the acid would help by catalyzing the addition-isomerization reaction of the aldehyde and isocyanate components. Following this, cycloaddition and decarboxylation in either order will afford the product. The authors did not commit to a preferred path, but they mentioned that the generated enamine would likely isomerize to the imine; however, they were never able to trap this intermediate using reverse electron demand Diels-Alder. Interestingly, three new stereocentres are formed, and the reaction only led to the formation of one diastereoisomer that is obtained through an *endo* addition of the dienophile during the Diels-Alder step of the reaction.

When complete selectivity cannot be achieved, a sequential one-pot procedure could be a good alternative for multicomponent reactions. In 2007, Alizadeh used this strategy to synthesize hydantoins using amines, isocyanates, and disubstituted-acetylene with a phosphine catalyst (eq. 1.19).[32]



(1.19)

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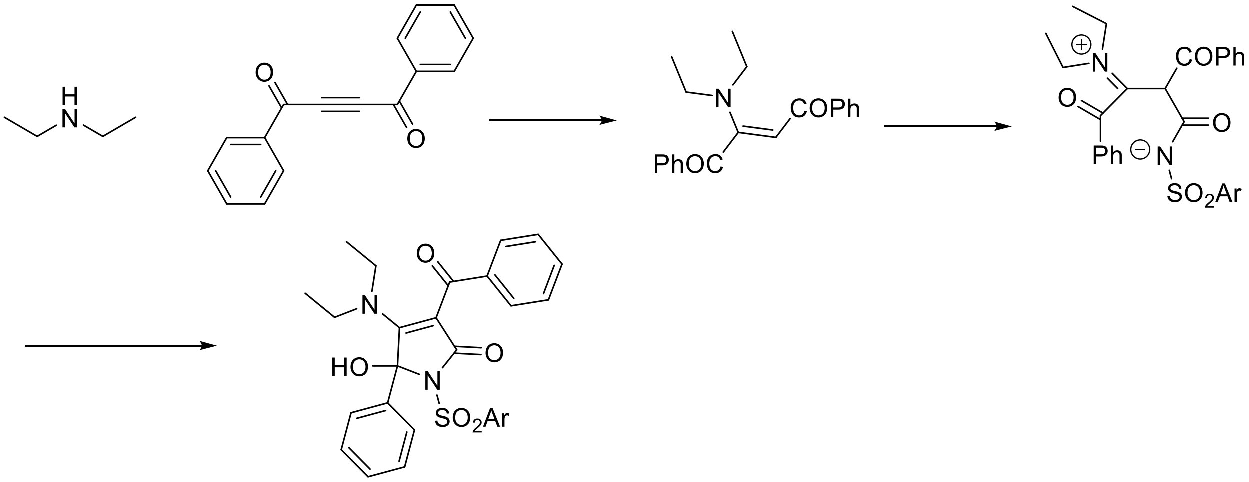
[32] Alizadeh, A.; Sheikhi, E. *Tetrahedron Lett.* **2007**, *48*, 4887.

While this is not a true MCR due to the premixing of the amine and isocyanate, it is still a remarkably selective reaction to form highly substituted products from simple and readily-available starting materials.

In the previous year, the same group published the same reaction with a different addition order. The amine adding on the benzoylacetylene generated an enamine which was used to add on isocyanates; this then cyclized back on the ketone (Scheme 1.9).[33] This group was also able to synthesize azetidine using similar conditions in 2008.[34]



Scheme 1.9: Reverse Addition Leads to Different Reactivity

It is evident from these two examples that this type of reactivity does not meet the requirements of an MCR, but it is impressive that modifying the order of addition can lead to two different heterocycles at room temperature.

In this section, we have seen that isocyanates can selectivity undergo MCRs to form valuable heterocycles. Given that every component has a specific affinity for one another, it is possible to perform one-pot cascades; alternatively, components can be added in a stepwise fashion to minimize side reactions. This controlled reactivity was the missing tool to truly exploit *N*-isocyanate chemistry developed prior to this thesis. This undeveloped chemistry will be discussed in the next section. In the following chapters, it will be shown how controlled reactivity was used to generate cascade reactions using *N*-isocyanates.

With the variety of reactions present in heterocyclic chemistry, it is evident that isocyanates are excellent reagents for the development of controlled reactivity and for the design of novel reaction sequences in order to build complexity in an elegant and rapid manner. In the next

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[33] Alizadeh, A.; Movahedi, F.; Masrouri, H.; Zhu, L.-G. *Synthesis* **2006**, 3431.
[34] Alizadeh, A.; Rezvanian, A. *Synthesis* **2008**, 1747.

section, underdeveloped nonconventional isocyanates will be compared to normal *C*-substituted isocyanates. More specifically, a closer look at the literature of *N*-isocyanates is necessary to demonstrate the untapped potential of such entities. Focus will be put on the early discovery of *N*-isocyanates: their generation (which represents most of the work done on them) and their reactivity.

1.4: Nitrogen-Substituted Isocyanates

In contrast to normal *C*-isocyanates, *N*-isocyanates are rare in the literature. In fact, a recent literature survey was performed and less than 70 publications were found on *N*-isocyanates and *N*-isothiocyanates, either forming, studying, postulating, or exploring the reactivity of these rare intermediates.[35]Arguably, *N*-isocyanates are heterocumulenes that have a similar synthetic potential compared to regular isocyanates. If the second nitrogen atom (βN) is sp^3 hybridized, one can argue that they have even more potential since this would add a 1,3 amphoteric character to the typical 1,2 character of regular isocyanates. Their scarcity is a consequence of their tendency to homo-dimerize at temperatures as low as -40°C and the inconvenience associated with their synthesis.[36] In this section, a literature review of *N*-isocyanate chemistry will be performed, followed with recent progress achieved in the Beauchemin group.

1.4.1: Generation of *N*-Isocyanates

1.4.1.1: Curtius Rearragement of Carbamoyl Azide

Given the popularity of isocyanates and the plethora of methods that are available to form them, it is normal that the first generation of unconventional isocyanates was achieved the same way. The acyl azide rearrangement to form isocyanates, also known as the Curtius rearrangement, was described in 1914.[37] It took thirteen years before that rearrangement was used to form aminoisocyanates from carbamoyl azides, which are considered rigid azides since the conditions required for their decomposition are quite harsh compared to typical acyl azides. Nevertheless, Stollé was able to study the decomposition of diphenylcarbamoyl azide under thermolysis conditions.[38] He found that, depending on the conditions, he could obtain different products. For example, when anhydrous solvent was used, cyclization to the indalone was observed (Scheme 1.10, top). When the reaction was performed in an alcohol solvent, the carbamate was obtained. Finally, when humidity was present, the decarbonylated product gave the hydrazine, which trapped another molecule of aminoisocyanate (Scheme 1.10).

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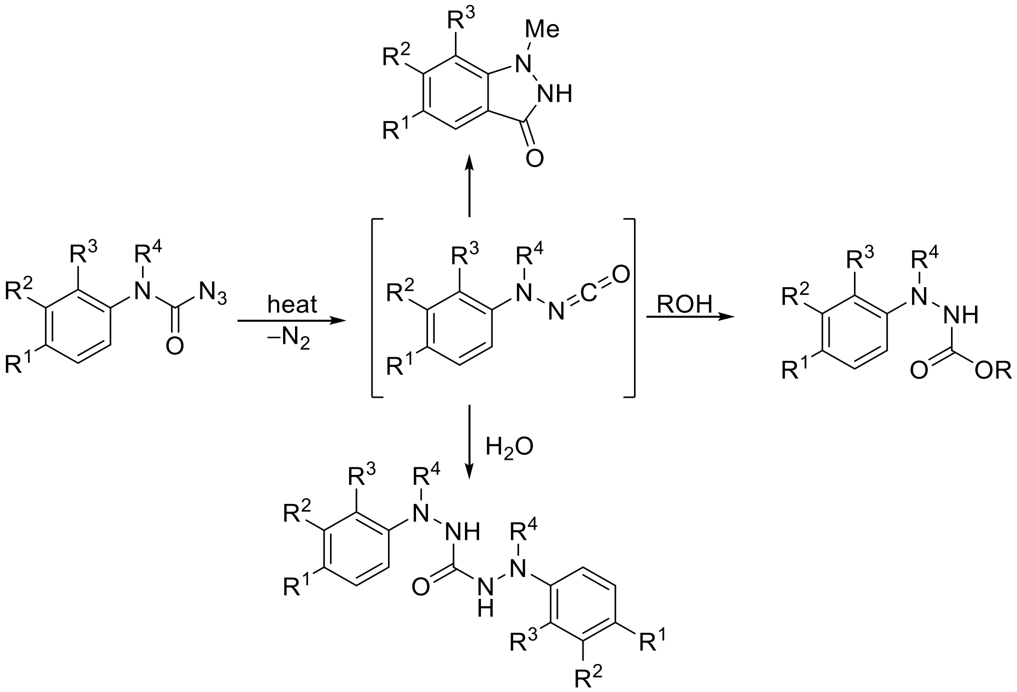
[35] For a complete list of publications, see: Vincent-Rocan, J.-F.; Ivanovich, R. A.; Clavette, C.; Leckett, K.; Bejjani, J.; Beauchemin, A. M. *Chem. Sci.* **2016**, *7*, 315.

[36] Wentrup, C.; Finnerty, J. J.; Koch, R. *Curr. Org. Chem*. **2011**, *15*, 1745.

[37] Curtius, Z. T. *Angew. Chem*. **1914**, *27*, 213.

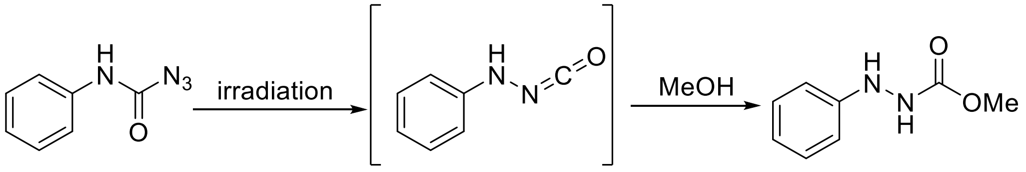
[38] Stollé, R. *J. Prakt. Chem*. **1927**, *116*, 192. (b) Stollé, R. *J. Prakt. Chem*. **1928**, *117*, 185.



Scheme 1.10: Stollé's Exploration of the Thermolysis of Diphenylcarbamoyl Azides

Later studies made by Baiocchi lead to the formation of benzimidazole from similar substrates.[39] This observation led to the conclusion that the mechanism of such rearrangements was not occurring through a nitrene intermediate, but rather *via* an S_N2-like displacement involving nitrogen gas as a leaving group. If the nitrogen was performing the displacement, the *N*-isocyanate would be obtained, similar to the case of Stollé. However, if the aromatic ring was participating at that stage, benzimidazole would be obtained as in Baiocchi's example.

Based on Stollé's pioneering work, Lwowski studied the rearrangement of a multitude of rigid azides in methanolic solvent. He found that while they did not rearrange in hydrocarbon solvents, every class of rigid azides gave products under photolytic conditions in methanol (eq 1.20).[40]



(1.20)

They also found that irradiation of monophenyl, monoethyl, and diethyl carbamoyl azides in hydrocarbon solvents led to the formation of higher molecular weight products without traces of any solvent group in their structures. In addition, when the reaction was performed in methanol,

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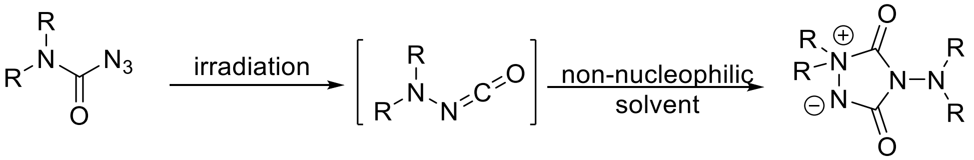
[39] Baiocchi, I.; Corsi, G.; Palazzo, G. *Ann. Chim. (Rome)* **1965**, *55*, 116.

[40] Lwowski, W.; De Mauriac, R.; Mattingly, T. W. Jr.; Scheiffele, E. *Tetrahedron Lett.* **1964**, 3285.

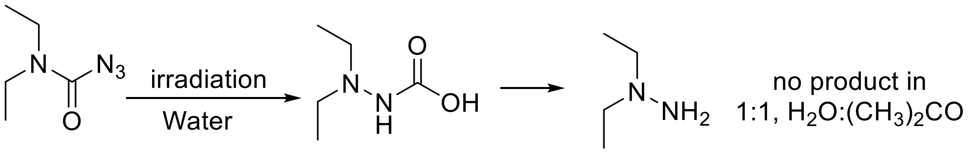
the carbazate was obtained. These higher molecular weight compounds were found to be aminimines, which can be obtained through dimerization of the corresponding *N*-isocyanate (eq. 1.21).[41]



(1.21)

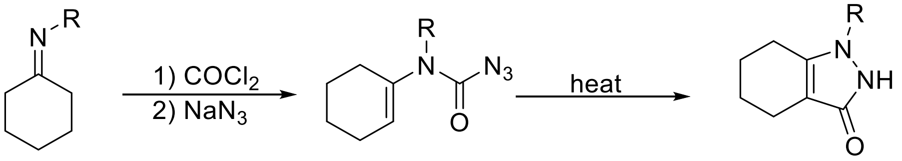
Interestingly, they found that the dimer was stable under refluxing conditions in methanol. However, if irradiation was performed in methanol, they were able to form the solvolysis product of the corresponding *N*-isocyanate indicating that these dimers can also act as masked aminoisocyanates. Moreover, if the irradiation was done in cyclohexane, no reaction was observed and the dimer was recovered.

Lwowski also reported that reactions carried out in water led to the isolation of the hydrazine after decarboxylation of the resulting acid. Interestingly, the rearrangement product was not obtained when the reaction was run in a 1:1 mixture of acetone and water, which illustrates the importance of the reaction medium for the formation of *N*-isocyanates (eq. 1.22).



(1.22)

Similarly, Chupp was able to form and trap a vinylaminoisocyanate using thermolysis of the corresponding azide (eq. 1.23).[42]



(1.23)

Chupp could not directly observe the formation of isocyanates under photolysis reaction conditions. The products that resulted were a good indication of the intermediate, but no distinct proof was recorded by these studies. In 2013, Wentrup was able to use an argon matrix to observe the generation of *N*-dimethylaminoisocyanate from the corresponding carbamoyl azide.[43] When dimethylcarbamoylazide was irradiated at a wavelength of 254 nm, an IR band was observed at 2200 cm^{-1} with a shoulder at 2226 cm^{-1}. According to calculations, this band can be assigned to the antisymmetric stretch of the NCO moiety in the dimethylaminoisocyanate.

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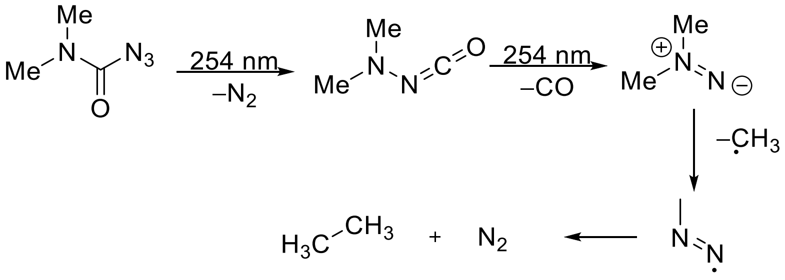
[41] Lwowski, W.; DeMauriac, R. A.; Murray, R. A.; Lunow, L. *Tetrahedron Lett.* **1971**, 425.

[42] Alt, G. H.; Chupp, J. P. *Tetrahedron Lett.* **1970**, 3155.

[43] Pasinszki, T.; Krebsz, M.; Tarczay, G.; Wentrup, C. *J. Org. Chem.* **2013**, *78*, 11985.

Interestingly, they found that after almost an hour of irradiation, an ethane peak appeared on the IR spectrum. It was concluded that the molecule was degrading into carbon monoxide, nitrogen gas, and ethane (Scheme 1.11). The same stretch (2230 cm^{-1}) was also observed by Lwowski in 1975, but the study was less precise due to the limited equipment available at the time.[44]

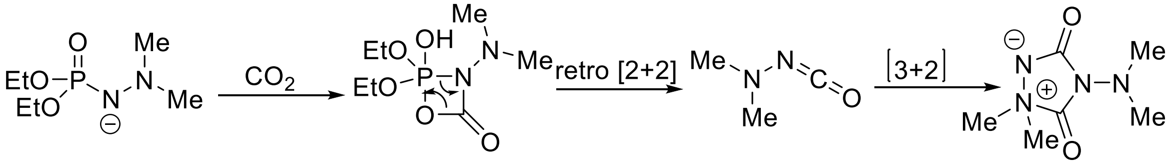


Scheme 1.11: Photodegradation of Dimethylcarbamoylazide in an Argon Matrix

Despite the need for UV light, these reports show good evidence for the existence of aminoisocyanates and provide evidence that they can be obtained from simple starting materials. However, given the conditions, only a small range of substrates were tolerated. In the next section, it will be shown that by using more elaborated starting materials and non-photolytic conditions, it is possible to access a more diverse range of *N*-isocyanates.

1.4.1.2: Ring Opening Formation of *N*-Isocyanates

It was mentioned earlier that Lwowski later proved that the high molecular weight compounds obtained were aminimines. This was strongly suggested by the work of Wadsworth and Emmons, which investigated the generation of aminoisocyanates by reacting phosphoroamidate anions with carbonyl compounds (eq. 1.24).[45] The resulting 4-membered ring could undergo a retro-cycloaddition to form the aminoisocyanates, which formed the aminimine dimer.

 (1.24)

Interestingly, they showed that in the presence of water and at room temperature, the dimer could be hydrolyzed followed by decarboxylation in order to produce the same carbazide resulting from trapping an *N*-isocyanate with the corresponding hydrazine. Given the low reactivity of H_2O towards isocyanates (see Scheme 1.3), it is likely that Stollé's intermediate (Scheme 1.10) was also generated from the dimer, instead of water attacking the aminoisocyanate. They also noticed that it was possible to perform a methyl shift while heating the dimers at 200 °C and then performing acid or base hydrolysis to give acyclic compounds. Additionally, they were able to

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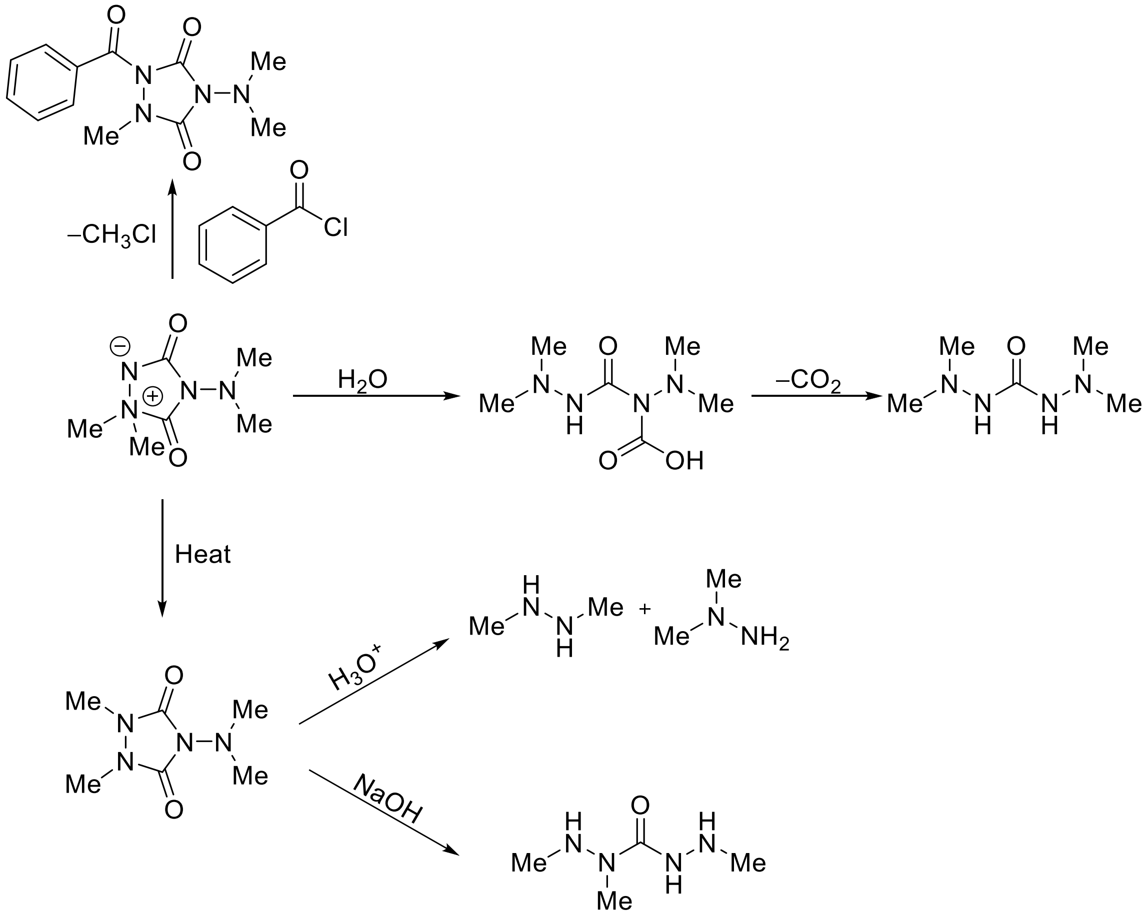
[44] Lwowski, W, de Mauriac, R. A.; Thompson, M. *J. Org. Chem.* **1975**, *40*, 2608.

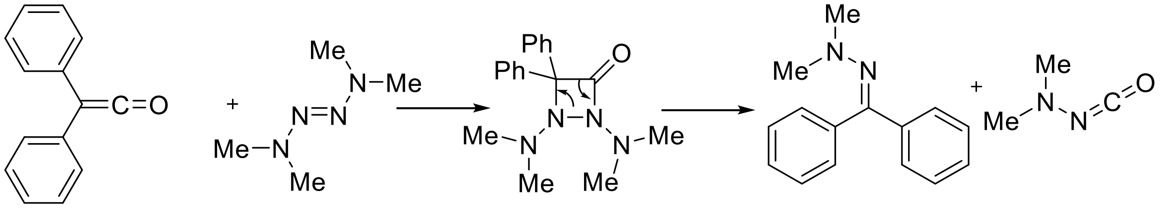
[45] Wadsworth, W. S.; Emmons, W. D. *J. Org. Chem.* **1967**, *32*, 1279.

acylate the dipolar compound followed by an S_N2 displacement of a methyl group to neutralize the heterocycle (Scheme 1.12).



Scheme 1.12: Exploration of the Reactivity of Aminoisocyanate Dimers

In 1971, Kerber was also able to generate a 4-membered ring that formed an aminoisocyanate intermediate. To do so, diphenylketene was reacted with tetramethyltetrazene (eq. 1.25).[46] The authors only reported a mixture of products obtained from the reaction and, although no concrete proof of formation of dimethylaminoisocyanate was ever recorded, the authors believed the product mixture arose from such a pathway.


(1.25)

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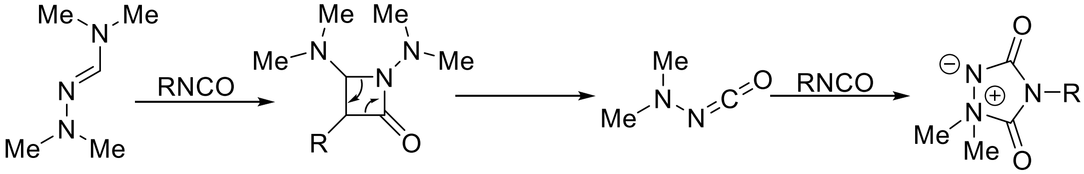
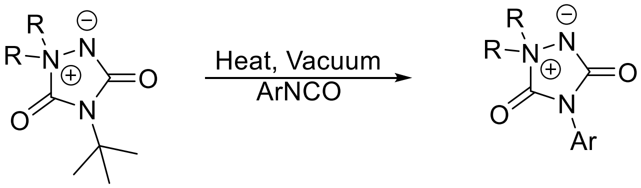
[46] Kerber, R. C.; Ryan, T. J. *J. Org. Chem.* **1971**, *36*, 1566.

Two years later, Seckinger performed a similar reaction. Using carbodiimide derivatives and an *N*-isocyanate as a cycloaddition partner, he was also able to form a 4-membered ring that released dimethylaminoisocyanate. He then isolated the cycloaddition product with another molecule of isocyanate (eq. 1.26).[47] They then used their new cyclic derivatives to survey the same type of reactivity that Wadsworth and Emmons have reported to synthesize a variety of different compounds.



(1.26)

5-Membered ring systems can also rearrange to form aminoisocyanates. Lwowski was able to demonstrate that trapping his azide with another molecule of isocyanate (*tert*-butyl isocyanate) generated another cyclic aminimide, which could form the aminoisocyanate at lower temperatures than the homo-dimer (eq. 1.27).[48] The system was performed under vacuum to remove any traces of *tert*-butyl isocyanate formed in the reaction.



(1.27)

In 1976, Warkentin reported the use of hydrazonooxadiazoline and heat in order to generate a variety of different molecular scaffolds that arose from an aminoisocyanate intermediate (Scheme 1.13).[49] If no trapping agent was introduced to the reaction medium, the thermolysis generated an iminoisocyanate which could react with a carbene in a [3+1] cycloaddition to yield the 4-membered cyclic azomethine imine in 35% yield. If methanol was present, they were able to observe the formation of benzophenone methyl carbazone. Finally, when phenylisocyanate was present, they observed the bicyclic compound shown in Scheme 1.13. This compound could only come from a [3+2] cycloaddition of another molecule of phenylisocyanate with the azomethine imine.

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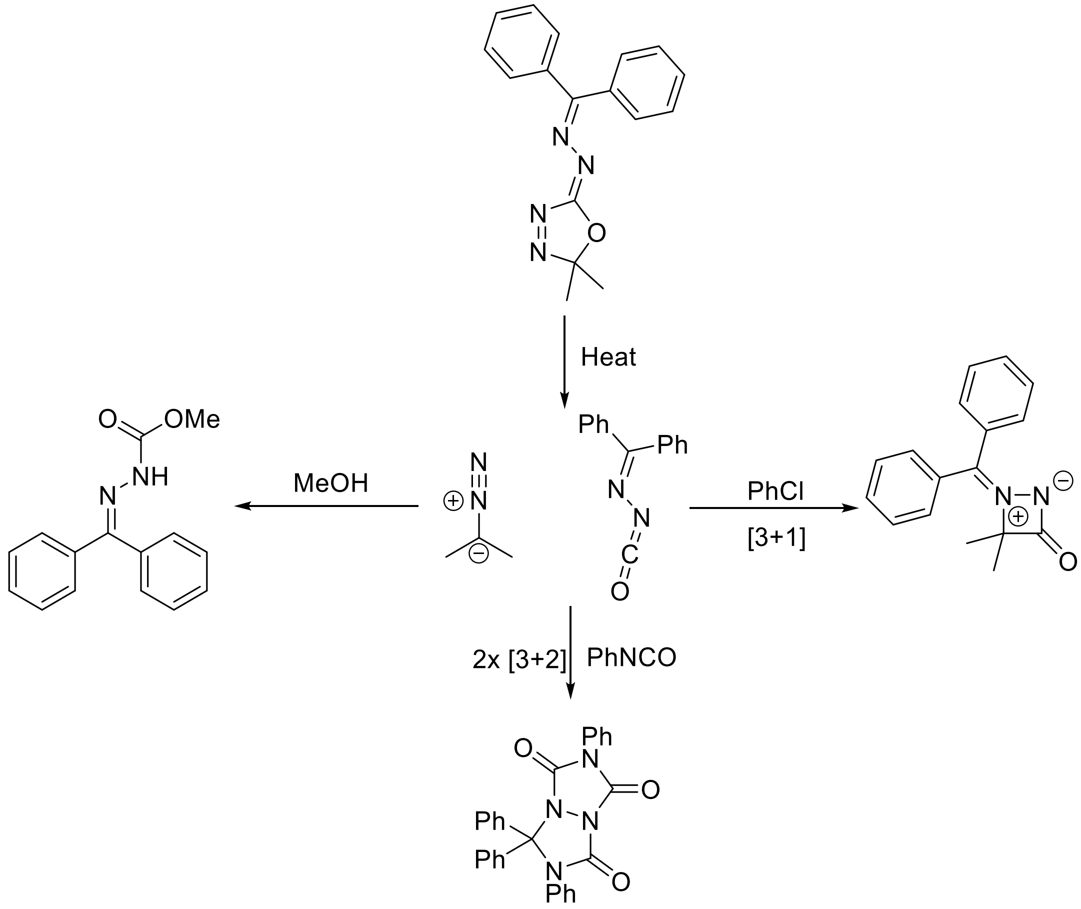
[47] Seckinger, K. *Helv. Chim. Acta* **1973**, *56*, 2061.
[48] Lockley, W. J. S.; Ramakrishnan, V. T.; Lwowski, W. *Tetrahedron Lett.* **1974**, 2621.
[49] Ramakrishnan, K.; Fulton, J. B.; Warkentin, J. *Tetrahedron Lett.* **1976**, 2685.



Scheme 1.13: Thermolysis of Hydrazonooxadiazoline and its Reactivity with Trapping Agents

It should be noted that the β-*N* of the *N*-isocyanate formed in Warkentin's experiment was sp^2-hybridized. These are even less present in the literature because most of the early work focused on the formation of the known dimethylaminoisocyanate. Another good example of sp^2 *N*-substituted isocyanate formation was published six years later by Jones. He began by reacting 1,3-dimesitylbenzo[c]furan and 4-phenyltriazoline-3,5-dione to form a hindered dipole. This dipole was able to generate the *imino*isocyanate at 110 ^{o}C which reacted with an olefinic or acetylenic trap to form a stable azomethine imine (eq. 1.28).[50]

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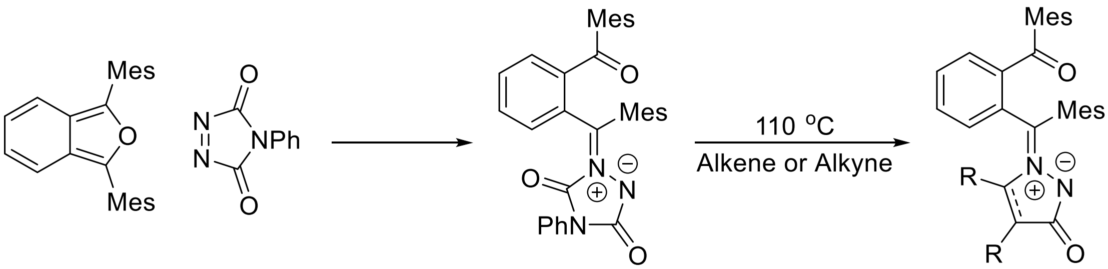
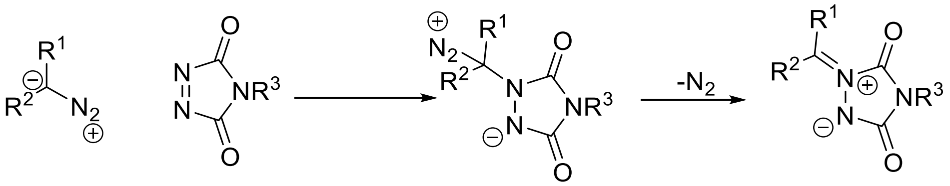
[50] Jones, D. W. *J. Chem. Soc. Chem. Commum.* **1982**, 766.



(1.28)

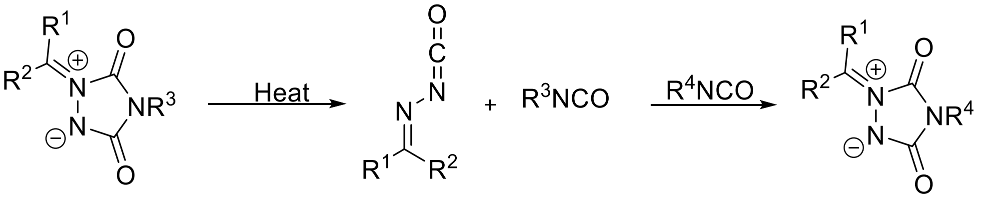
Again, by cycloreversion of a high heteroatom content cycle, Jones was able to form a transient *N*-isocyanate and perform an irreversible cycloaddition with an alkyne or an alkene to yield stable azomethine imines. The author also showed that without a trapping agent, dimers of the iminoisocyanate were obtained in small amounts. No more information was given, thus it is difficult to say if the remaining mass balance is the starting material. Nevertheless, this represents the first intermolecular aminocarbonylation reactions of alkenes and alkynes, performed using an iminoisocyanate. This reactivity was further improved by the Beauchemin group and will be discussed in section 1.4.5.

A similar cycloreversion approach to form iminoisocyanates was reported by Regitz in 1985. In his case, he reacted 4-phenyltriazoline-3,5-dione with a diazo compound at room temperature. Subsequent loss of nitrogen gas generated the azomethine imine (eq. 1.29).[51]



(1.29)

He was able to show the potential of these intermediates to form the aminoisocyanate by performing "criss-cross" reactions with other isocyanates to yield different azomethine imines (eq. 1.30).



(1.30)

Interestingly, the authors showed that by using a symmetrical bis(diazo) compound, bisazomethine imine could be formed. Unfortunately, no experiments were performed to demonstrate the potential of such molecules to form di-*N*-isocyanates.

In the last two cases that were discussed, isocyanates were used as blocking agents for iminoisocyanates. On a different note, Senet was able to generate dimethylaminoisocyanate by

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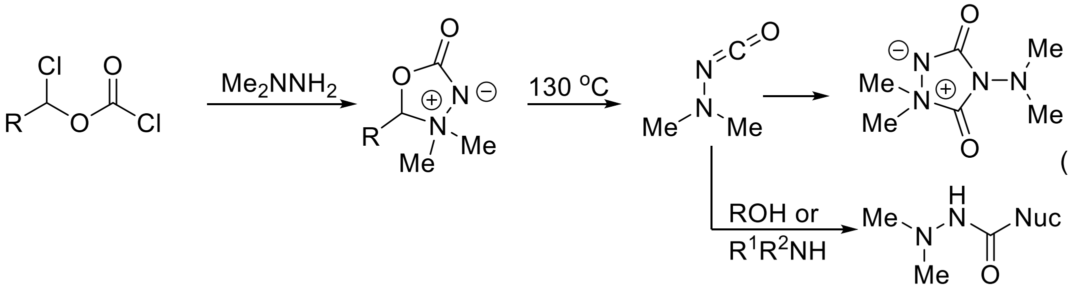
[51] Theis, W.; Bethäuser, W.; Regitz, M. *Chem. Ber.* **1985**, *118*, 28.

generating a carbonyl moiety. In fact, he used the thermolysis of carbalkoxy aminimides to generate dimethylaminoisocyanates. He proved this by observing the generation of the dimer discussed previously (eq. 1.31).[52] Interestingly, they were also able to observe a methyl shift to the neutral compound when the dimer was heated at 190 °C. They were also able to synthesize different carbazates and semicarbazides by adding the appropriate nucleophile (amines and alcohols) to the pot.



(1.31)

Eight years following this report, Squillacote and De Felippis published the possibility of generating *N*-isocyanates by generating carbonyl sulfide by ring opening. This discovery was achieved by serendipity, but explained the generation of an unexpected product (that was most likely formed *via* an *amido*isocyanate) (Scheme 1.14).[53] As shown, when attempting to achieve the double acylation of thiadiazolidinedione, they observed the rapid formation of the mono-acylated product and slow conversion to the major product of the reaction. They attributed the final product to a ring opening process, which lead to the formation of the amidoisocyanate that subsequently closed on itself prior to a second acylation event. The cycle used is similar (N-N instead of N=N) to Senet's intermediate (eq. 1.31) and will be discussed as an intermediate to synthesize aza-tripeptides in Chapter 5.

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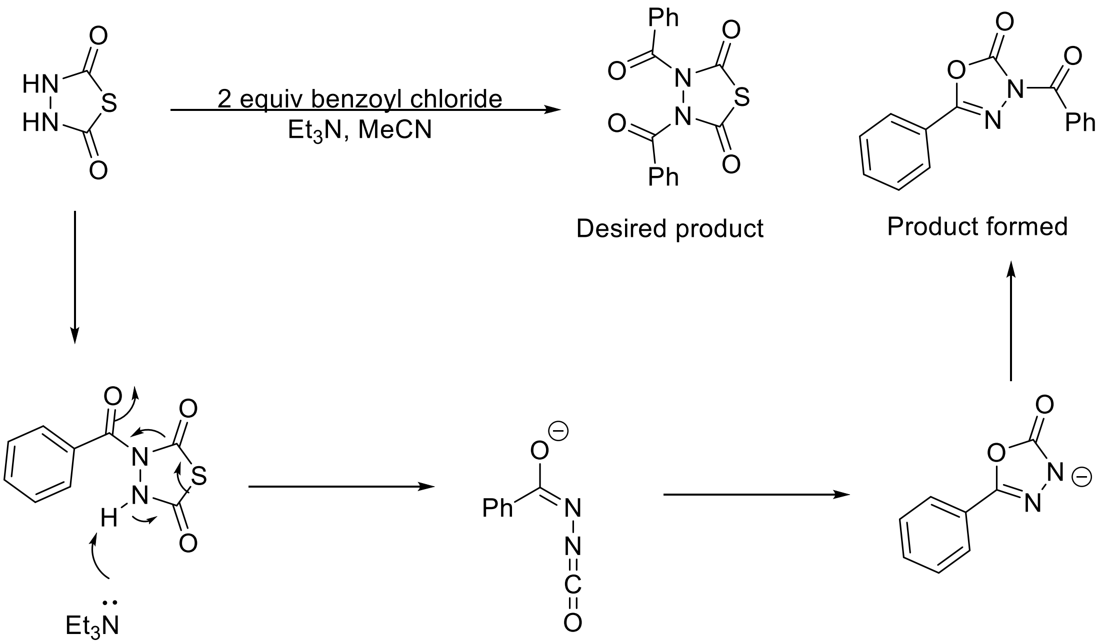
[52] Senet, J.-P.; Vergne, G.; Wooden, G. P. *Tetrahedron Lett.* **1986**, *27*, 6319.

[53] Squillacote, M.; De Felippis, J. *J. Org. Chem.* **1994**, *59*, 3564.



Scheme 1.14: Squillacote's Generation of Amidoisocyanate

As seen in this section, cycloreversion experiments appear to be a reliable source for generating *N*-isocyanates *in situ*. Multiple variations on the nitrogen atoms were tolerated. It was also demonstrated that different kinds of nitrogen-substituted isocyanates could be formed, such as aminoisocyanates, iminoisocyanates and amidoisocyanates. It seems that small heterocycles that have a high heteroatom content are particularly prone to the generation of *N*-isocyanates. This insight might lead to the generation of novel substituted *N*-isocyanates using this kind of strategy since different substitution could be incorporated on the second nitrogen atom. Preliminary results on that theme are discussed in chapter 5.

1.4.3: Thermolysis of Hydrazide Derivatives

A simple way of generating aminoisocyanates is by thermolysis of hydrazide derivatives. Synthesized with a suitable leaving group, it is easy to see the nitrogen forming the aminoisocyanate under basic conditions or thermolysis similar to the formation of ketenes. Perhaps not surprisingly, one of the first reports of aminoisocyanate was achieved akin to ketene generation. In fact, Acree was able to generate diphenylaminoisocyanate by reacting the corresponding hydrazine with phosgene (eq. 1.32).[54]

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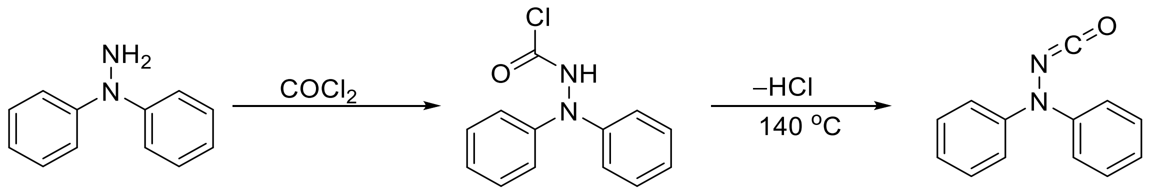
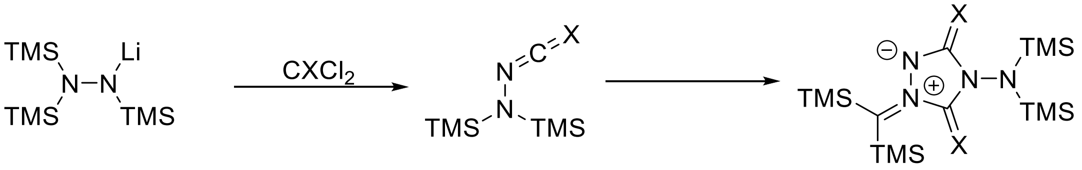
[54] Acree, S. F. *Ber. Deut. Chem. Ges.* **1903**, *36*, 3154.



(1.32)

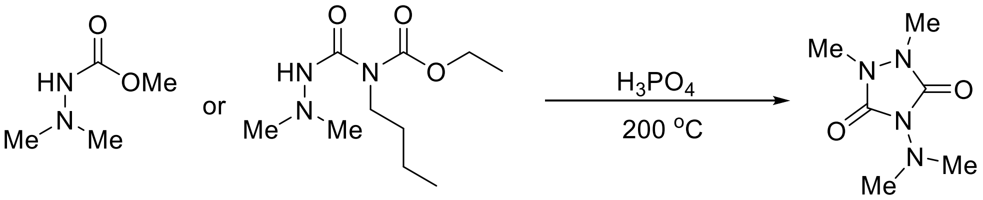
In 1978, Hübler synthesized TMS-protected aminoisocyanates using a related approach to that used by Acree 75 years earlier. Using lithium anions of the tri-TMS hydrazine and (thio)phosgene, Hübler was able to generate aminoisothiocyanates and observed the dimer (eq. 1.33). However, they did isolate the monomer of bis-TMS-aminoisothiocyanate and characterized it by IR and Raman spectroscopy.[55]



(1.33)

Similar studies were performed by Kirilin in 1999, in which he showed that different temperatures were necessary for the production of aminoisocyanates from different silicon precursors. They showed the difference in reactivity while treating those precursors with phosgene (Scheme 1.15).[56] Interestingly, the point of this study was to use the excess of *N*,*N*-dimethylhydrazine produced in Russia at the time by derivatizing it into something more useful and less toxic.

In their communication on phosphoramidate anions, Wadsworth and Emmons also reported the thermolysis of *N*,*N*-dimethyl ethylcarbazate and isolated the dimer after the methyl shift (the methyl shift was reported at 190 °C directly from the dimer by Senet). They were also able to synthesize the same product from an acylated semicarbazide (eq. 1.34).



(1.34)

In 1969, Larsen was able to show that gas chromatography could be used to study the thermal decomposition of aniline-based semicarbazide (eq. 1.35).[57] Interestingly both phenylisocyanate and the aminoisocyanate were formed, with the latter being the major product.

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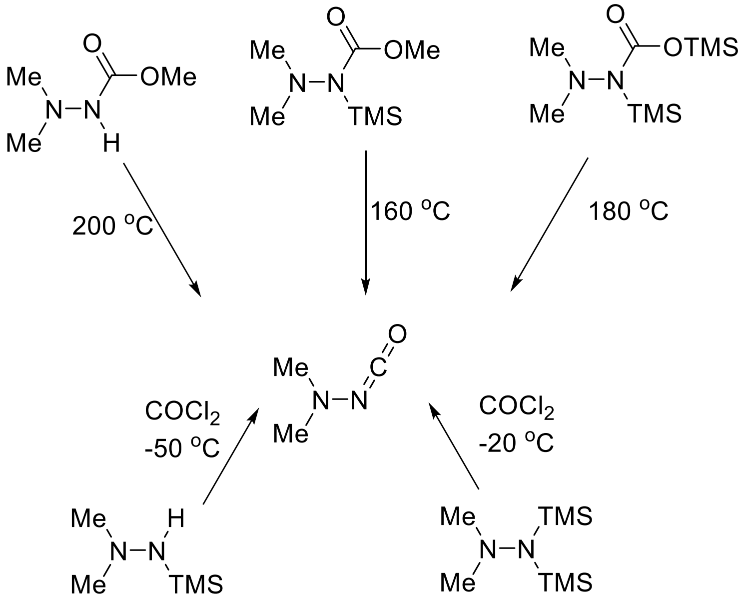
[55] Wibers, N.; Hübler, G. *Z. Naturforsch* **1978**, *33b*, 575.

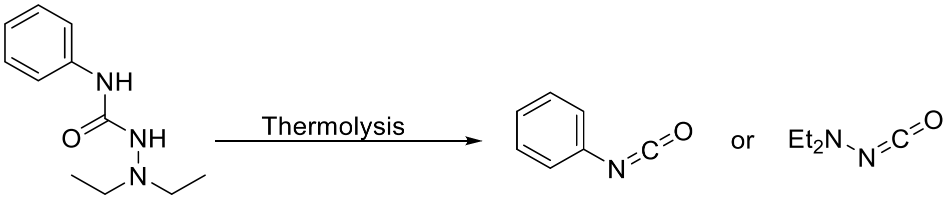
[56] Kirilin, A. D.; Dokuchayev, A. A.; Sokova, N. B.; Chernyshev, E. A. *Russ. Chem. Bull.* **1999**, *48*, 169.

[57] Larsen, C.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1969**, *23*, 322.



Scheme 1.15: Thermolysis of Silylated Hydrazides

Given the possibility of an anionic mechanism for the formation of an aminoisocyanate, the pK_as of the leaving groups could be compared in order to evaluate their potential to form the isocyanate. Since the pK_a of aniline is lower, it is suspected to be a better leaving group than the primary hydrazine.



(1.35)

In 1988, Maier and Teles reported the study of the formation of methoxy- and amino-substituted isocyanates. During the process, they discovered that the pyrolysis of methyl carbazate at 500°C produced an aminoisocyanate, which was observed in an argon matrix. They also produced the same intermediate from diaminofurazan. Finally, similar to Lwowski's work, they also synthesized the aminoisocyanate through the Curtius rearrangement of carbazates (Scheme 1.16).[58] In their studies, the authors noticed that a very rapid reaction occurred when they irradiated the aminoisocyanate at a wavelength of 254 nm, which produced carbon monoxide and aminonitrene. As previously discussed, this was also reported by Wentrup in 2013.

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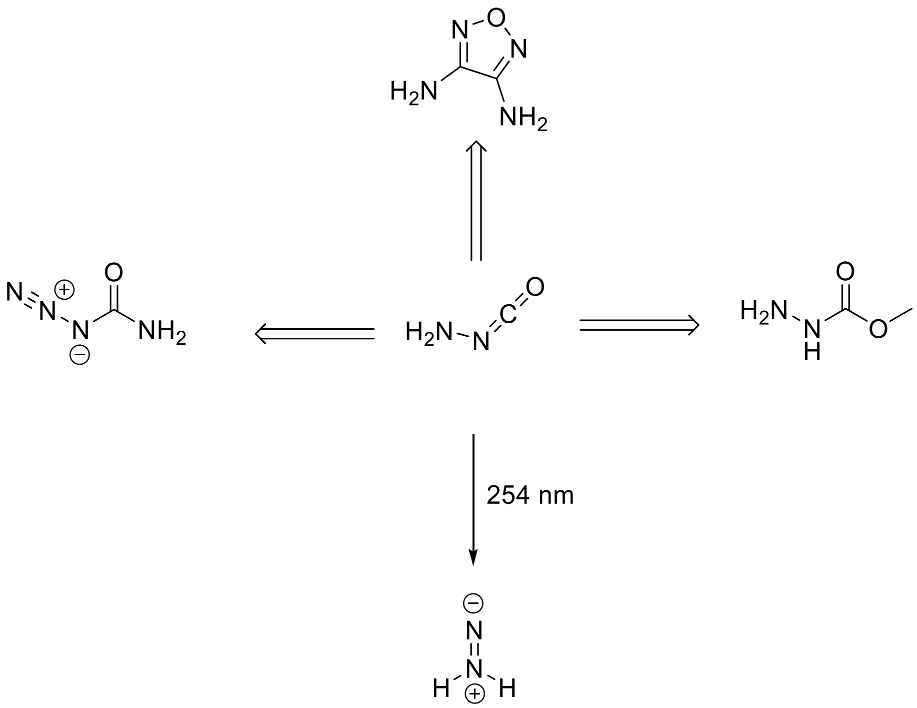
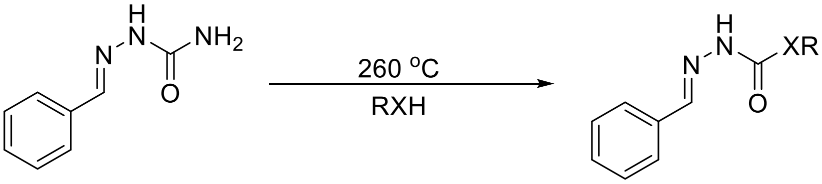
[58] Maier, G.; Teles, J. H. *Chem. Ber.* **1989**, *122*, 745.



Scheme 1.16: Maier's Syntheses of Aminoisocyanate

Semicarbazones can also be used as iminoisocyanate precursors. Shah and Chudgar used these precursors to synthesize azines and carbazones. The authors postulated a [2+2] cycloaddition followed by the extrusion of nitrogen and carbon monoxide to allow for the formation of azines. This is inconsistent with every dimerization reported. Another explanation would be the formation of hydrazones (decarboxylation of the adduct resulting from water adding onto the iminoisocyanate or the dimer) in the reaction conditions followed by dimerization. Nevertheless, the authors showed that when thermolysis was performed in the presence of an alcohol or an amine, it was possible to isolate the carbazone and the semicarbazone (eq. 1.36).[59]



(1.36)

In this section, one of the simplest methods of generating nitrogen-substituted isocyanates was investigated. The ease of synthesis, the possibility of using catalysis, and the diversity of structures influenced the Beauchemin group to choose this particular method for their own exploration, which will be discussed in the following chapters.

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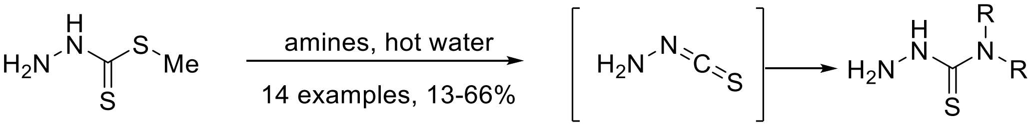
[59] Shah, S. N.; Chudgar, K. N. *Molecules* **2000**, *5*, 657.

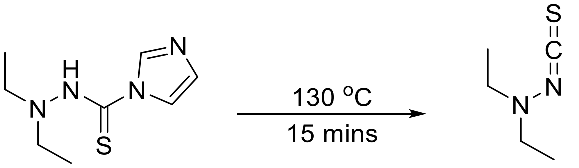
1.4.4. Aminoisothiocyanates

Despite a small interest of the synthetic community on aminoisocyanates, some studies were conducted on analogues of these reactive intermediates, such as their sulfur analogues: amino-isothiocyanates. The first two studies reporting the aminoisothiocyanates as intermediates were published in 1966. McElhinney was the first one to propose the intermediate while studying the formation of thiosemicarbazides from dithiocarbazates (eq. 1.37).[60]



(1.37)

McElhinney postulated the intermediate without having direct proof for the existence of the aminoisothiocyanates. However, in the same year, Anthoni, Larsen and Nielsen reported the observation of the aminothioisocyanate by IR spectroscopy at -78 °C starting from *N*,*N*-diethylthiocarbazoylimidazole (eq. 1.38).[61] They noticed an intense doublet near 2000 cm^{-1} that disappeared when the temperature of the reaction was increased to room temperature due to the formation of a dimer. This dimer showed a characteristic new peak at 1630 cm^{-1}, but no structure of the dimer was proposed.



(1.38)

Following this report, the same group published a series of papers that showed the reactivity profile of these highly reactive intermediates. They were able to synthesize seleno- and tellurothiocarbazic acid derivatives,[62] dithiocarbazic acids,[63] and thio(semi)carbazides.[64] More importantly, a complete study investigating the dimerization of these intermediates was reported in 1968 (Scheme 1.17).[65]

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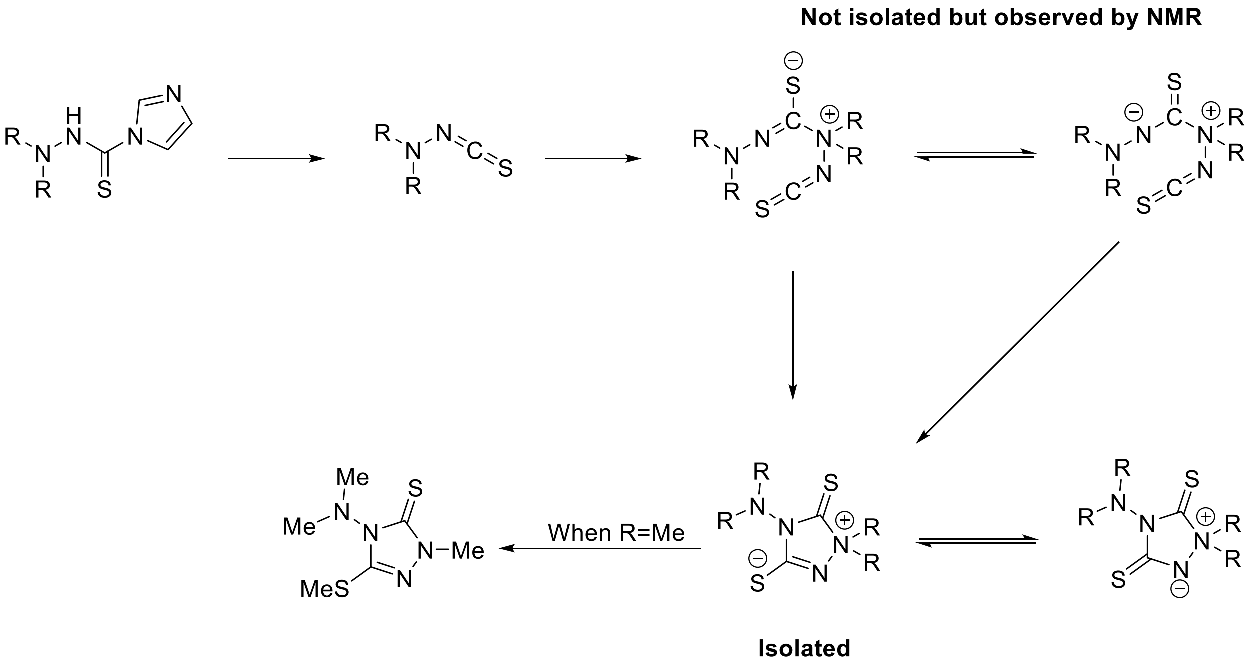
[60] McElhinney, R. S. *J. Chem. Soc.* **1966**, 950.
[61] Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta. Chem. Scand.* **1966**, *20*, 1714.
[62] Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta. Chem. Scand.* **1967**, *21*, 2571.
[63] Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta. Chem. Scand.* **1967**, *21*, 2580.
[64] Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta. Chem. Scand.* **1967**, *21*, 2061.
[65] Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta. Chem. Scand.* **1968**, *22*, 309.



Scheme 1.17: Dimerization Studies at Room Temperature

Interestingly, they showed that the dimerization was complete within one minute at room temperature when the R group was a methyl, ethyl, or propyl group, but took several hours when it was an isopropyl group. Moreover, a dilute solution of R = *i*-Pr only showed 10% dimerization after four days at room temperature, which highlights the steric effect of these large groups. This observation is in support of their proposed mechanism, since it has been proven that *N*,*N*-diisopropylethylamine cannot be quaternized by an alkyl halide.[66] The authors also published a different study with the synthesis of several deuterated versions of the dimer in order to study its degradation pathway by mass spectrometry.[67]

A different reactivity profile was found when *N*,*N*-diphenylaminoisothiocyanate was used. Indeed, a rearrangement occurred to form the thiocyanate at -80 °C (eq. 1.39).[68] Dimerization of the monomers with the smallest substituent (Me) is not operating under these conditions, demonstrating the ease of this rearrangement. They were also able to prove that the aminoisothiocyanate was an intermediate by trapping it with aniline.

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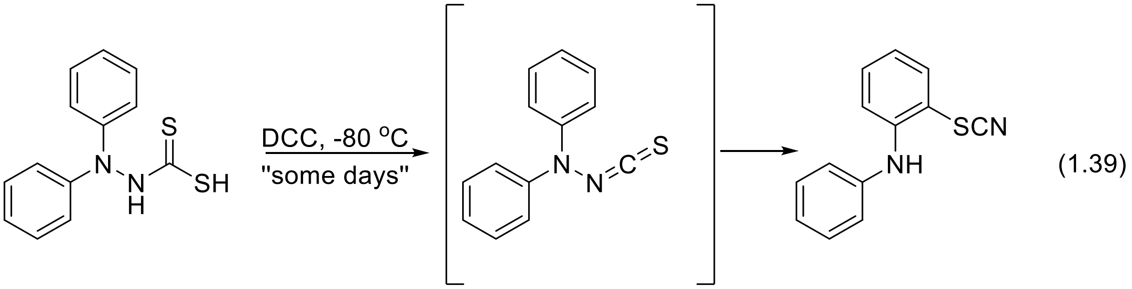
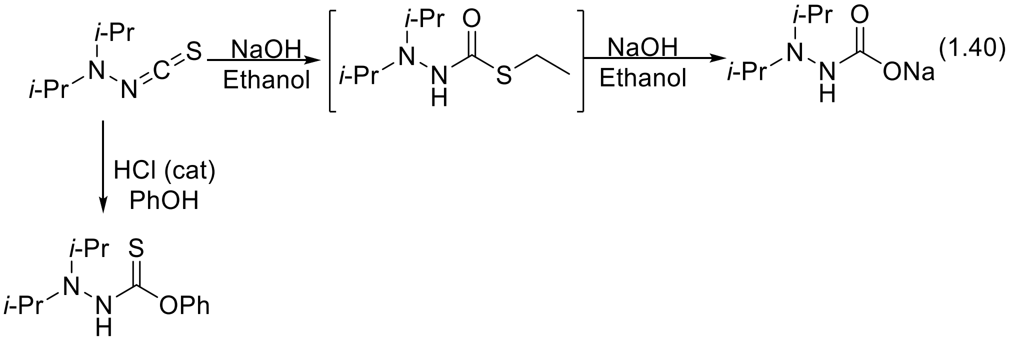
[66] Hünig, S.; Kiessel, M. *Chem. Ber.* **1958**, *91*, 380.
[67] Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta. Chem. Scand.* **1968**, *22*, 2493.
[68] Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta. Chem. Scand.* **1967**, *21*, 1201.



Following this study, they decided to exploit the stability of diisopropylaminoisothiocyanate and studied its reactivity toward nucleophiles.[69] Using nitrogen-based nucleophiles, the authors noted that the reactivity was not affected by having free hydroxyl, ester, carboxylic acid, or amide groups. Interestingly, the amine was always the nucleophile participating in the reaction except in the case of thioamines, where the sulfur atom was the nucleophilic species attacking the aminoisothiocyanate. Even anilines, aminophenol, and aminothiophenol were able to give the aromatic-substituted compounds.

Having established extensive knowledge for the formation of aminoisothiocyanates, the authors studied its formation by using different leaving groups other than their original imidazole. They first studied the decomposition of thiosemicarbazide using dimethylamine as a leaving group. Unsurprisingly, higher temperatures were required to synthesize the amino-isothiocyanate (*i.e.*, 230 °C), which was confirmed by GC since they already had the retention time from previous studies.[70] This was followed by the mass spectrometry analysis presented in the previous section.[55] When Anthoni and coworkers studied the outcome of using an oxygen nucleophile, strange behavior of the adduct was reported. In fact, under basic conditions, they postulated an alkyl shift between the oxygen and sulfur atoms; however, they observed that this pathway was not operating in acidic media (Scheme 1.18).[71]



Scheme 1.18: Alkyl Shift Under Basic Conditions

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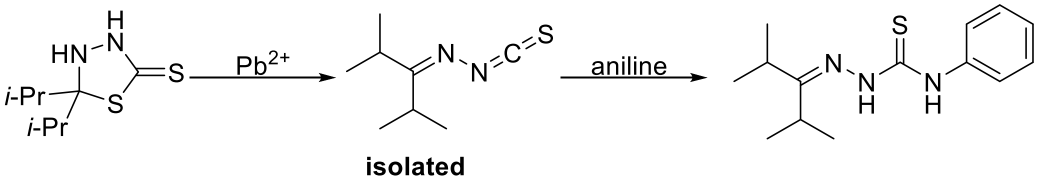
[69] Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta. Chem. Scand.* **1968**, *22*, 1898.
[70] Larsen, C.; Anthoni, U.; Nielsen, P. H. *Acta. Chem. Scand.* **1969**, *23*, 320.
[71] Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta. Chem. Scand.* **1969**, *23*, 1439.

Anthoni was also able to demonstrate that iminoisothiocyanates reacted similarly to their amino counterparts. They were able to isolate the stable monomer from the decomposition of the corresponding thiadiazolidine-2-thiones. In fact, they were able to demonstrate that the reaction toward aniline afforded the expected phenylthiosemicarbazone (eq. 1.40).[72]

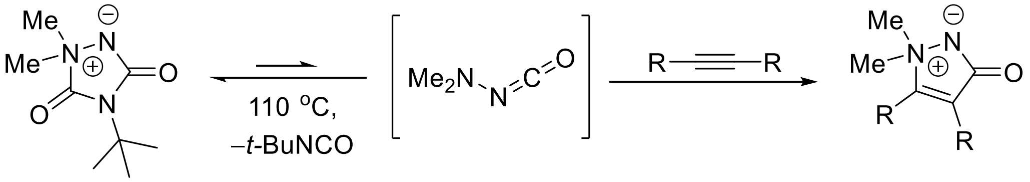


(1.40)

As for the aminoisocyanates, their sulfur derivatives are also scarce in the literature. As seen in this literature review, it seems that only one group was actively studying these intermediates and that little has been done after the involvement of these researchers until we became interested in these intermediates. Our contribution to this field will be discussed in Chapter 3. One exception is the work of Seckinger who also demonstrated the used of isothiocyanates to mimic his synthesis of aminoisocyanates (eq. 1.26).[47]

1.4.5: Reactivity of Aminoisocyanates

In section 1.4.1, several different strategies to form *N*-isocyanates were discussed, but the reported studies were not focused on the reactivity of these intermediates. Since the field was relatively unexplored, it is normal that studies focusing on *N*-isocyanate formation were conducted prior to the development of their reactivity. Nonetheless, these reactive intermediates can undergo solvolysis by alcoholic solvents, intramolecular nucleophilic attack, and some cycloadditions and heterocyclic syntheses were reported. No studies focused on exploiting the use of aminoisocyanates for organic transformations until Lwowski started to systematically study the cycloaddition profile of aminoisocyanates with different π-systems in the 1970s. He started by comparing the reactivity difference with different acetylenes (eq. 1.41).[73]



(1.41)

Interestingly, the authors noted that the more electron-poor the alkyne was, the better it was at reacting with the aminoisocyanate generated *in-situ*, suggesting a cycloaddition using the HOMO of the heterocumulene and the LUMO of the alkyne. The authors also noticed that only one regioisomer was obtained with using unsymmetrical partners such as phenylacetylene (eq. 1.42). When considering the regioselectivities, one might think that this also confirms the HOMO-

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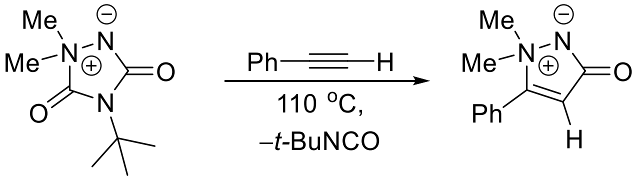
[72] Anthoni, U. Berg, C. *Acta. Chem. Scand.* **1969**, *23*, 3602.

[73] Lockley, W. J. S.; Lwowski, W. *Tetrahedron Lett.* **1974**, 4263.

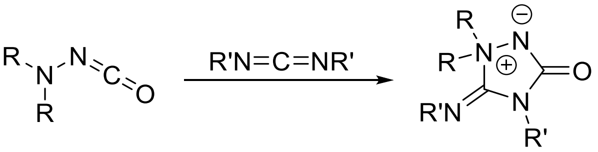
LUMO assignment, but any given combination in this case would have resulted in the same regioselectivity.



(1.42)

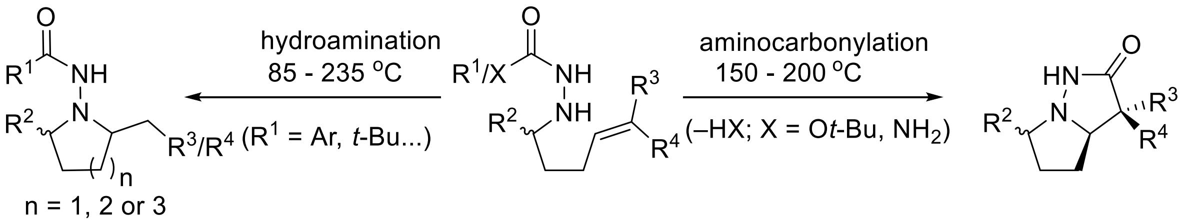
Additionally, they showed that most alkynes were reactive enough to participate in cycloaddition reactions except in the case of dialkyl acetylene, where the *N*-isocyanate dimer was isolated. In the other cases, the concentration of the free aminoisocyanate was controlled by a low solubility of the precursor in their reaction solvent (tetrachloroethylene); therefore it is difficult to assess the ability of the alkyne to compete with the dimerization reaction.

Lwowski was also able to demonstrate the outcome of the reaction while using carbodiimides as trapping agents (eq. 1.43).[74] As observed with other cyclic dipoles, they were able to use them as masked aminoisocyanates by releasing dimethylaminoisocyanate at 212°C in 2 minutes.



(1.43)

Other than Lwowski’s work, no report was published solely to explore the reactivity of aminoisocyanates. As seen in the previous pages, most of the reactivity was reported as a consequence of a new method to generate the reactive intermediate. In 2009, following a serendipitous finding, the Beauchemin group reported the use of hydrazides and carbazates for the synthesis of saturated heterocycles (eq. 1.44).[75]



(1.44)

While pursuing hydroamination reactions using hydrazide derivatives, the Beauchemin group discovered that another alkene amination product was obtained while using carbazates or semi-carbazides. The proposed reaction pathway involved the formation of an aminoisocyanate followed by a cycloaddition to give the cyclic β-aminocarbonyl motif. This report showed that

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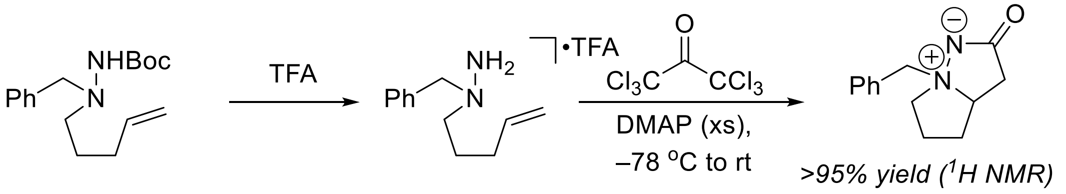
[74] Lwowski, W.; Kanemasa, S.; Murray, R. A.; Ramakrishnan, V. T.; Thiruvengadam, T. K.; Yoshida, K.; Subbaraj, A. *J. Org. Chem.* **1986**, *51*, 1719.

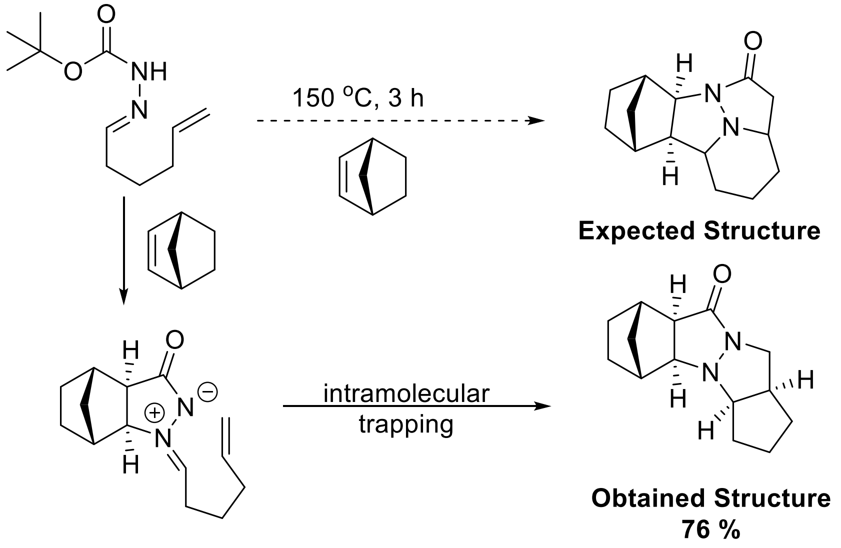
[75] Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Whipp, C. J.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.

carbazates and semicarbazides could be used as blocked (masked) aminoisocyanates, but were only effective for intramolecular cyclization reactions, which must be faster than the known dimerization pathway of these intermediates. DFT calculations performed suggested that the cyclization should proceed at room temperature ($\Delta G^{\ddagger} = 19.1$ kcal/mol).[76] Therefore, the high temperature requirement from that reaction must have arisen from the difficult formation of the isocyanates from the selected carbazate or semicarbazide. To prove this, Christian Clavette used a better leaving group and was able to demonstrate reactivity at room temperature (eq. 1.45).[77]



(1.45)

Following this work, the Beauchemin group focused their efforts on trying to build an intermolecular variant. As expected, most efforts toward using carbazates led to the dimerization adduct as the major product. However, a breakthrough was achieved when an intramolecular reaction using carbazone was attempted. Trying to build on their reported work on intramolecular cycloaddition, the group tried to form similar adducts while using carbazones to form azomethine imines that could be trapped by norbornene. Surprisingly, after X-ray analysis of the product, they found that the intermolecular reaction was occurring first, followed by intramolecular trapping of the azomethine imine (Scheme 1.19).[74]



Scheme 1.19: Initial Result with Iminoisocyanates

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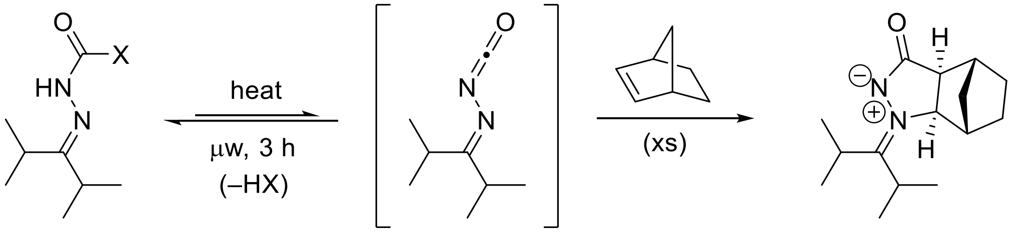
[76] At the B3LYP/TZVP level of theory, see reference 77 for details.

[77] Ivanovich, R. A.; Clavette, C.; Vincent-Rocan, J.-F.; Roveda, J.-G.; Gorelski, S. I.; Beauchemin, A. M. *Chem. Eur. J.* **2016**, *22*, 7906.

This result was the first experimental proof for the possibility of intermolecular reactivity using carbazones as a source of *N*-isocyanates. A full study was then made to find the best set of conditions to achieve intermolecular aminocarbonylation using carbazones. Screening of leaving groups showed similar trends to the blocked isocyanates series (Scheme 2) and the Beauchemin group selected phenol as the best option, given its ability to generate the *N*-isocyanate at lower temperatures and its ease of synthesis starting from phenyl carbonate (eq. 1.46).



(1.46)

X = O*t*-Bu: 150 °C, 98% yield

X = N(*i*-Pr)$_2$: 150 °C, 90% yield

X = OPh: 100 °C, 84% yield

X = SPh: 100 °C, 60% yield

As shown, the product of this reaction is a dipole. Therefore, bulky carbazones were needed to ensure product stability by shielding the azomethine imine. A thorough survey of carbazones revealed that a fluorenone-based reagent (LG = OPh) was optimal for this reaction.[78] A selected scope of this reactivity is shown in Scheme 1.20. It is worth mentioning that the fluorenone-derived iminoisocyanate was used in order to transform the obtained azomethine imine into a linear β-aminocarbonyl structure after reductive N-N bond cleavage.

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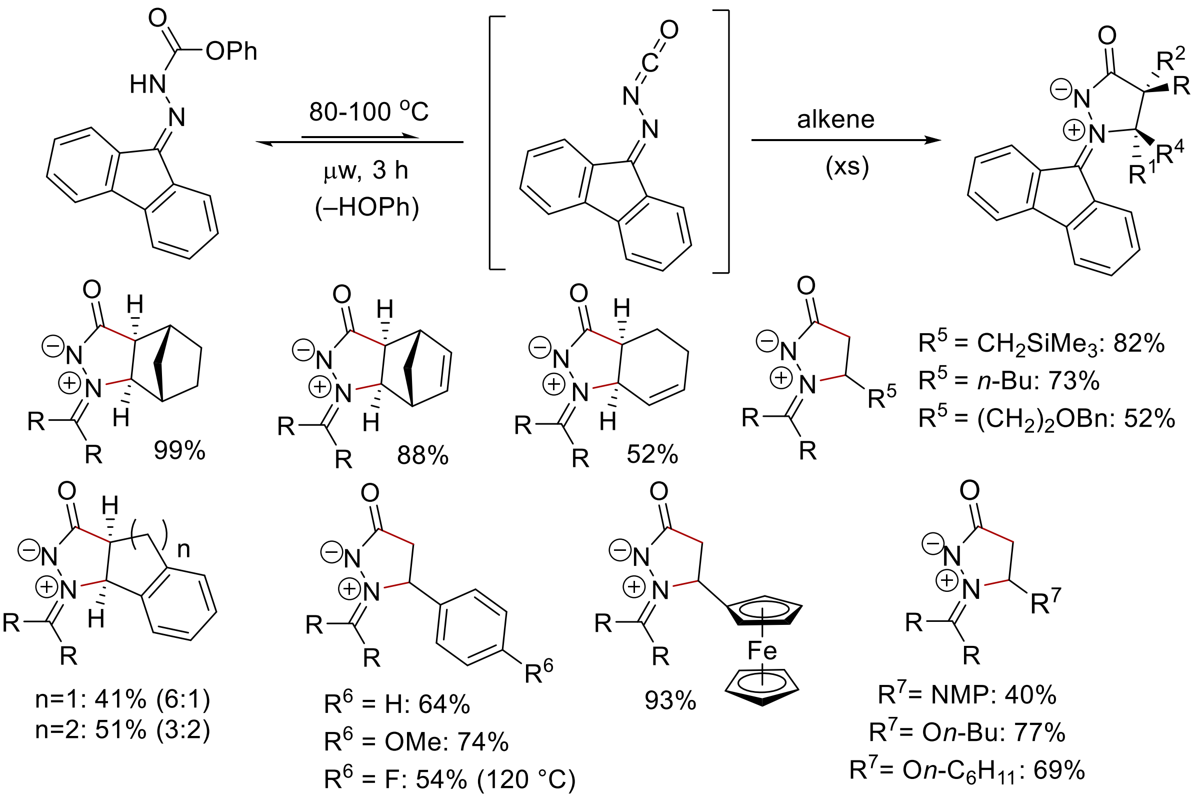
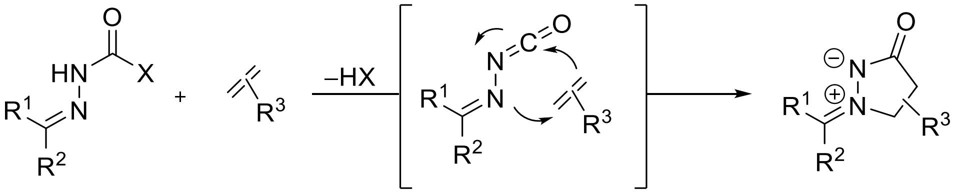
[78] Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc*. **2012**, *134,* 16111.



Scheme 1.20: Intermolecular Aminocarbonylation of Alkenes

After this study, the Beauchemin group remained active in this area and published a year later the synthesis of unsymmetrical azomethine imines using similar reactivity (eq. 1.47).[79] The reactivity was also expanded to aldehyde-derived blocked *N*-isocyanates affording the unsymmetrical azomethine imines.



(1.47)

Given the high reactivity of azomethine imines, the Beauchemin group also developed a rapid synthetic route to pyrazolones using a unique disconnection. By performing aminocarbonylation using vinyl ethers followed by aromatization induced upon reduction of the C=N double bond,

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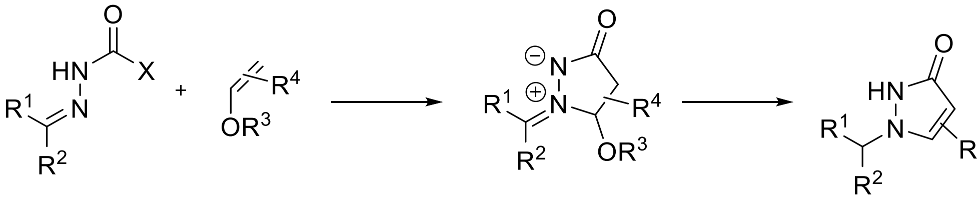
[79] Gan, W.; Moon, P. J.; Clavette, C.; Das Neves, N.; Markiewicz, T.; Toderian, A. B.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 1890.

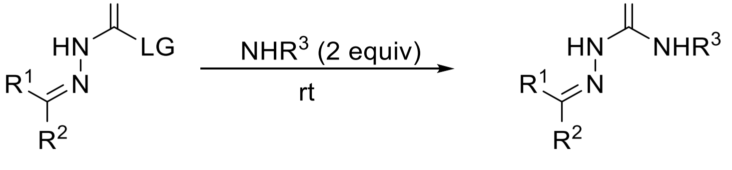
they were able to obtain 12 different pyrazolones, some of which that would be difficult to obtain using conventional routes to pyrazolones (eq. 1.48).[80]



(1.48)

It is important to note that this study also showed that base catalysis could be used to generate the iminoisocyanate at lower temperatures. Given the high reactivity of vinyl ethers, base catalysis helped with some substrates to prevent thermal decomposition of the reaction partners by reducing the temperature requirement for the formation of the *N*-isocyanate intermediate.

Intermolecular aminocarbonylation was an excellent proof of concept that showed that diverse reactivity profiles could be obtained while using *N*-isocyanates. Some limitations were still present, which included: 1) high temperatures were still required for intermolecular aminocarbonylation; 2) since high temperatures were needed, an excess of alkenes was often required in order to compete with dimerization. These only represent the first set of studies exploiting the synthetic potential of aminoisocyanates, building on Jones' seminal work on the reactivity of iminoisocyanates with alkenes. To fully exploit the synthetic potential of these reactive intermediates, reactivity needed to be tuned in order to obtain a pathway that would outcompete dimerization in a diverse range of conditions. This was first achieved by the Beauchemin group using carbazones while the work presented in this thesis was ongoing. In 2013, Keira Garland reported the simple synthesis of semi-carbazones based on a substitution reaction using amine nucleophiles. As seen in Scheme 1.3, amines are by far the most reactive nucleophiles toward isocyanates; therefore, it is fair to assume that this would also be the case with *N*-isocyanates in general. Using only two equivalents of amines, they were able to achieve reactivity at room temperature without any trace of dimerization (eq. 1.50).[81]



(1.50)

It is important to note that one equivalent of the amine could act as a mild base to promote formation of the isocyanates at room temperature while the other equivalent is used as a nucleophile. Catalysis with a stronger base in the presence of only one equivalent of a nucleophile will be discussed in the next chapters. While this study provided an example of reactions outcompeting *N*-isocyanate dimerization, its application was limited to the synthesis of

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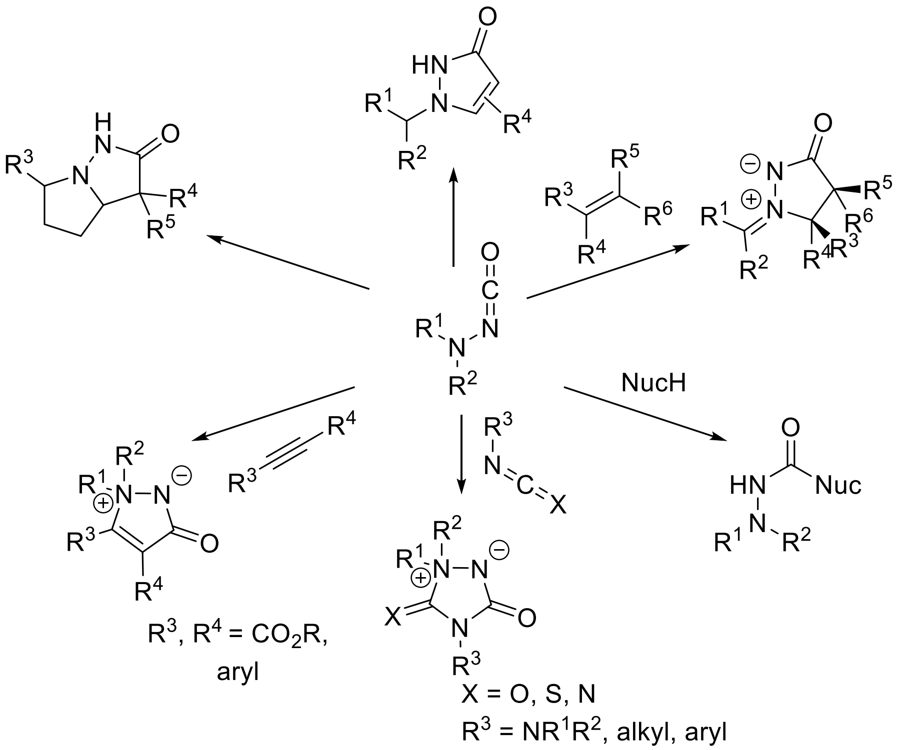
[80] Lavergne, K.; Bongers, A.; Betit, L.; Beauchemin, A. M. *Org. Lett.* **2015**, *17*, 3612.
[81] Garland, K.; Gan, W.; Depatie-Sicard, C.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 4074.

semicarbazones. In fact, this reactivity had been first developed to solve issues with the formation of some iminoisocyanate precursors that were required for the development of alkene aminocarbonylation.

As it was demonstrated, the diversity profile between aminoisocyanates and regular isocyanates is striking, mostly due to a lack of control over dimerization in most reactions of *N*-isocyanates chemistry (Section 1.3 vs Scheme 1.21). However, several publications suggested that controlled reactions could also be achieved, including difficult intermolecular reactions. The following section will describe how the work in this thesis took advantage of that fact to design different cascade reactions in order to significantly develop the synthetic potential of *N*-isocyanates.



Scheme 1.21: Known Reactivity of *N*-Isocyanates

1.5: Strategies for the Development of the Synthetic Potential of *N*-Isocyanates

As outlined in this chapter, isocyanates are well known organic synthons in heterocyclic chemistry; however, despite early discoveries, the nitrogen-substituted analogues remained a scientific curiosity for decades. To fully exploit their synthetic potential, the use of nitrogen nucleophiles was chosen in order to reduce their well-known propensity to dimerize and use them productively to synthesize a variety of different heterocyclic compounds that contain the N-N-C=O motif. This motif is present in many different pharmaceuticals and agrochemicals as shown in Figures 1.2 and 1.3.

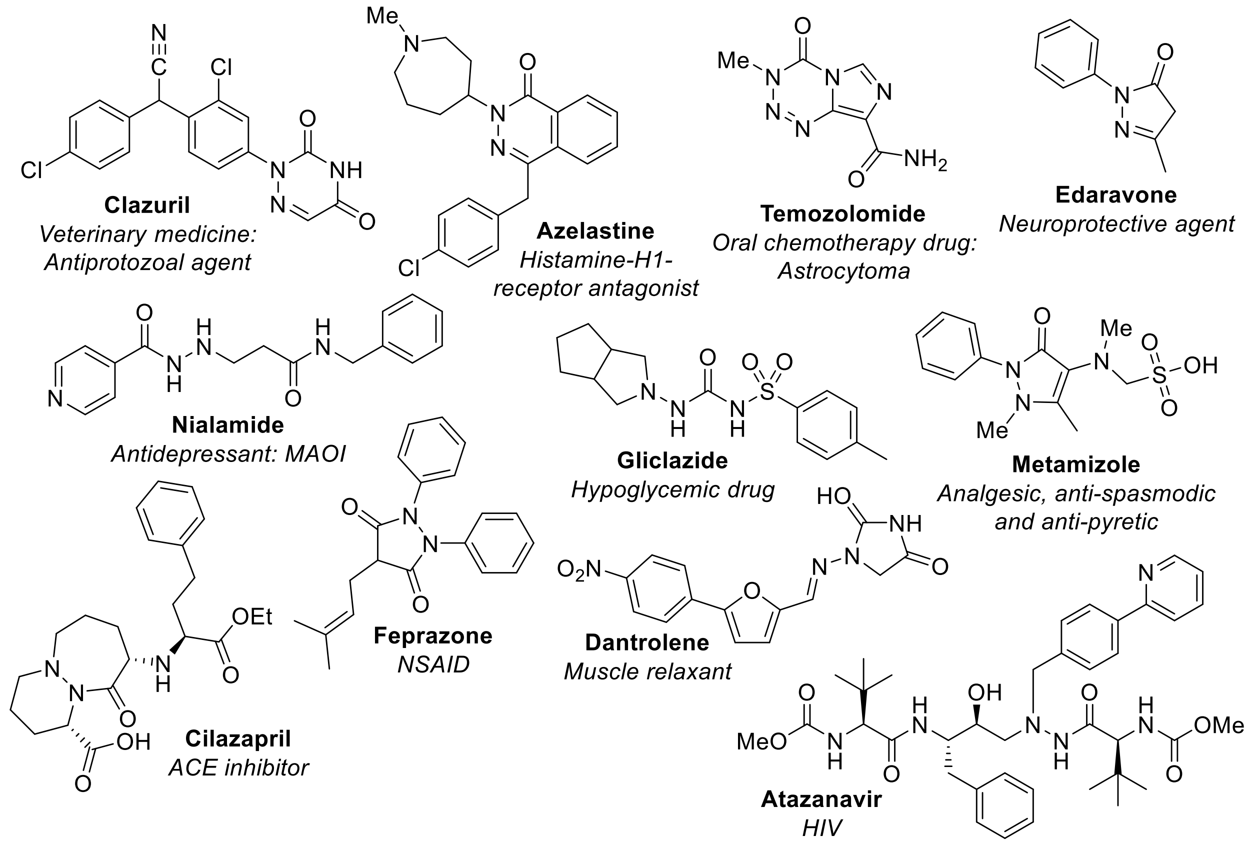


Figure 1.2: Selected Pharmaceuticals Containing the N-N-C=O Motif

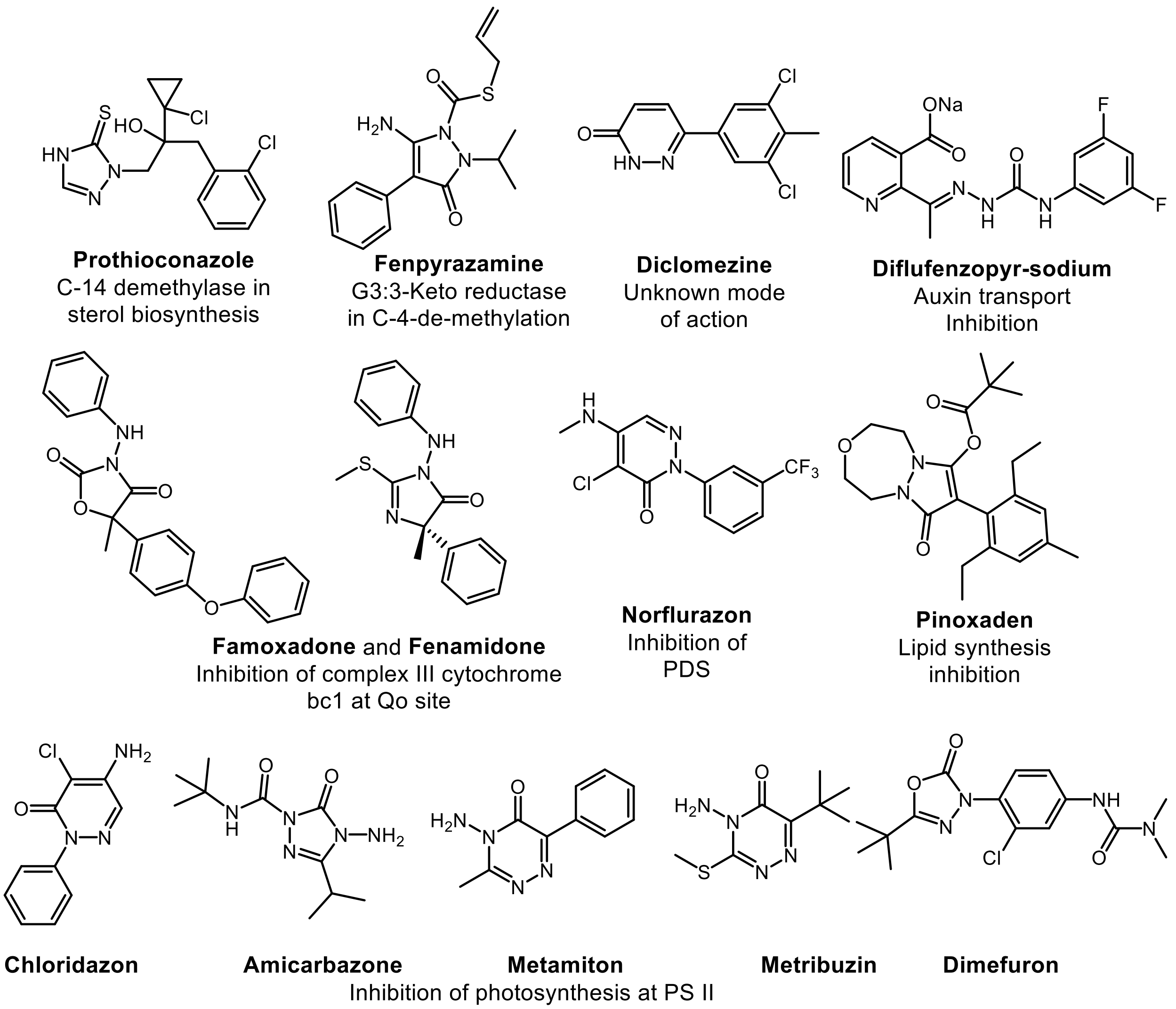
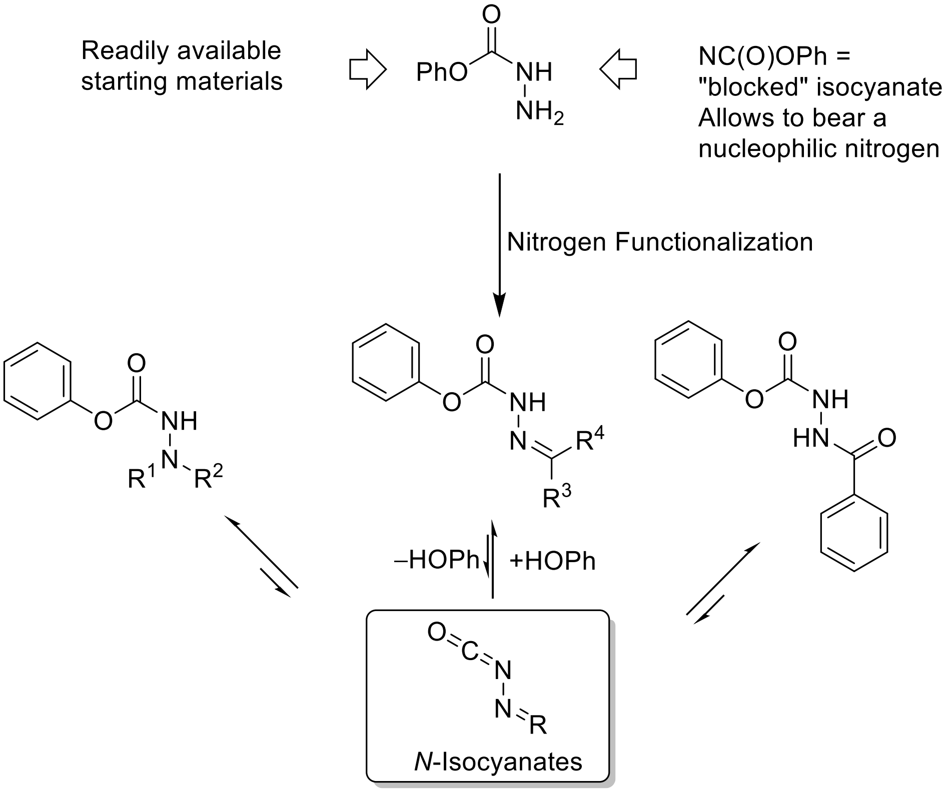


Figure 1.3: Selected Agrochemicals Containing the N-N-C=O Motif

Phenyl carbazate was chosen as a precursor in order to rapidly assemble multiple substrates that could undergo cascade reactions for the synthesis of a variety of heterocyclic compounds (Scheme 1.22). Using the simple reactivity of the β nitrogen (of phenyl carbazate) enabled the synthesis of a variety of masked *N*-isocyanates and the development of several types of cascade reactions. Given the different incorporation of the N-N-C=O motif in heterocyclic cores, the research in this thesis will be presented to show various strategies to access all of these incorporations of the motif in heterocycles. In Chapter 2, heterocycles containing only one atom within the ring will be discussed. The incorporation of two atoms in the heterocycle will be presented in Chapter 3, while Chapter 4 will focus on the incorporation of every atom into the heterocycle. Finally, the primary focus of Chapter 5 will be on acyclic molecules.

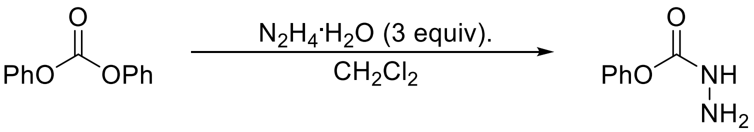


Scheme 1.22: Synthetic Scheme for the Rapid Synthesis of Masked *N*-Isocyanates

Chapter 2: *N*-Isocyanates in Heterocyclic Chemistry: Products with One Atom Within the Ring

2.1: Improvement of Phenyl Carbazate Synthesis

As mentioned in Section 1.5, the use of phenyl carbazate (eq. 2.1) is proposed as a pivotal building block for the development of reaction sequences using *N*-isocyanates. Therefore, multi-gram quantities will be needed in order to access a large quantity of several different building blocks. When the research in this thesis started, the synthesis of phenyl carbazate required an excess of reagent as well as flash column chromatography for purification (eq. 2.1).

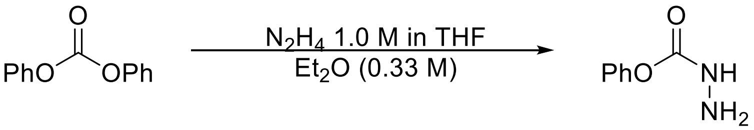


2.1

< 50%

(2.1)

Since chromatography was necessary, a full day of work was needed to obtain approximately 14 grams of carbazate **2.1**. In order to accelerate reaction discovery, an improved synthesis of this important starting material was necessary. Knowing that phenol was the only by-product in this reaction, different solvents where it would be soluble while phenyl carbazate **2.1** was not were examined. The absence of water was also crucial, and consequently the use of hydrazine hydrate was not possible; therefore a solution of hydrazine in THF was used. After screening solvent mixtures, 3:1 Et_2O:THF was found to be optimal and yielded approximately 75% of carbazate **2.1**, which was purified by filtration of the reaction mixture (eq. 2.2).



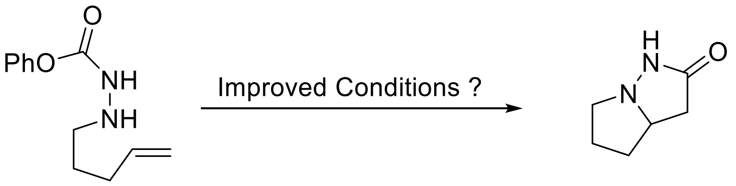
2.1

>70%

(2.2)

2.2: Discovery of the First Cascade Reaction Using Aminoisocyanate

With this improved synthesis, it was possible to get approximately 12 grams of product in only two hours of work by employing only a stoichiometric amount of each reagent. With a larger quantity of starting material available, an investigation to try to improve the intramolecular aminocarbonylation previously reported by our group was started in collaboration with Christian Clavette. Given the propensity of *N*-isocyanates to dimerize, conditions to diminish this side reaction were needed to afford a more general system.

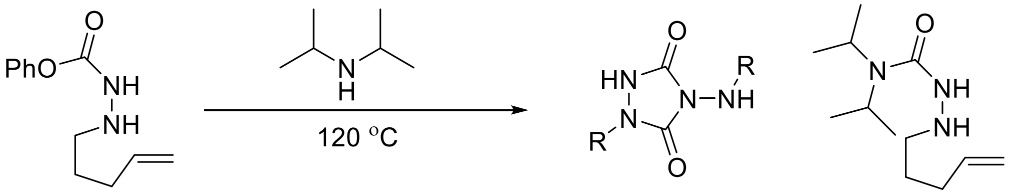


2.2 **2.3**

(2.3)

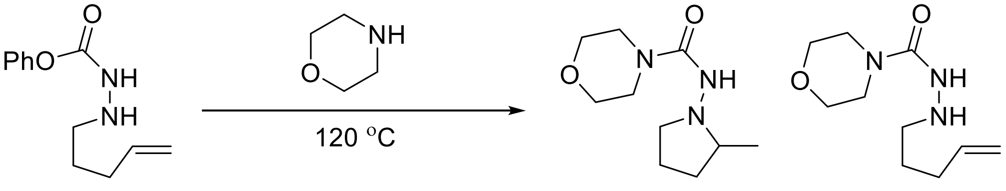
Previous studies of *N*-isocyanates in our laboratory revealed their high affinity with nitrogen nucleophiles. These nucleophiles were then tried to control the concentration of *N*-isocyanates, and consequently reduce the dimerization side-reaction. Diisopropylamine and morpholine were already identified as good leaving groups;[81] therefore, our investigation started using these as nucleophiles. A poor leaving group would only result in *N*-isocyanate trapping and would not result in any productive reactivity.

Diisopropylamine turned out to be too good of a leaving group: complete dimerization was observed when one equivalent was used (eq. 2.4). While running the reaction in diisopropylamine as a solvent, no desired aminocarbonylation was observed, nor was any dimerization. Instead, the substitution product **2.5** was obtained.



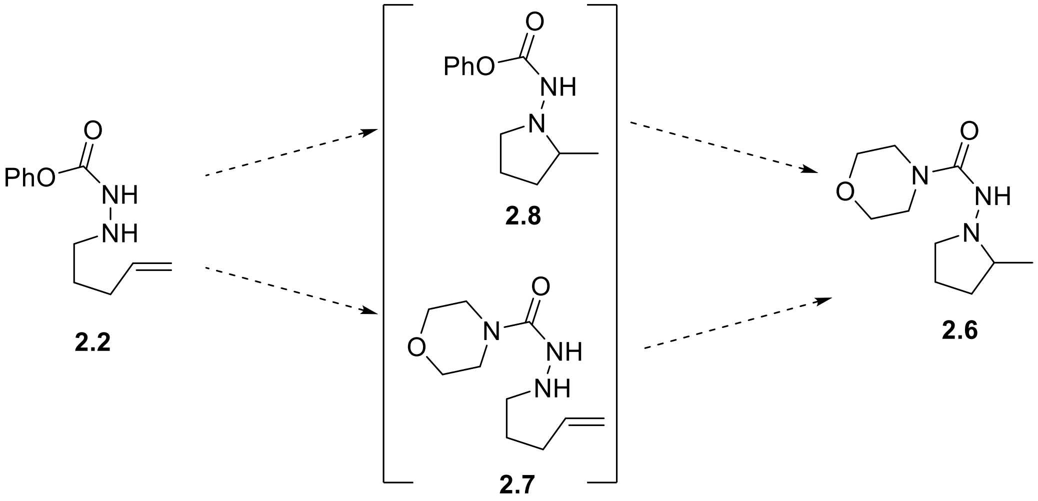
2.2 **2.4** **2.5** (2.4)

A reaction was attempted with morpholine in order to release the *N*-isocyanate slowly and achieve aminocarbonylation. Surprisingly, when carbazate **2.2** was subjected to the reaction conditions with morpholine, a mixture of two products was observed (eq. 2.5).



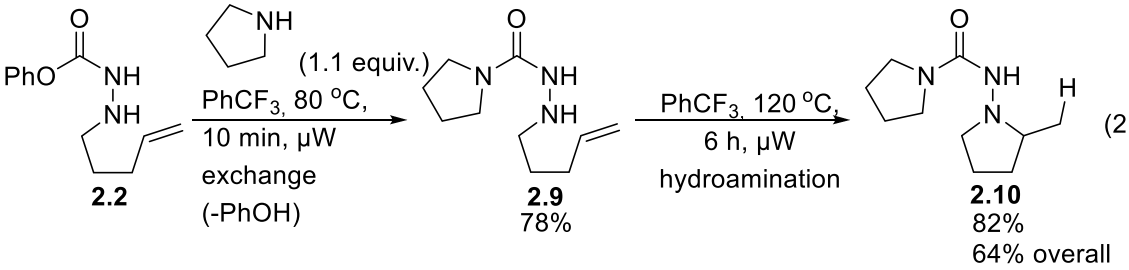
2.2 **2.6** **2.7** (2.5)

The expected substitution product **2.7** was observed, but the unexpected hydroamination product was observed as the major product after one hour at 120 °C. When the temperature was raised to 150 °C, product **2.6** was observed as the sole product of the reaction. This experiment opened the door for cascade reactions using *N*-isocyanates; however, at the time, it was unclear if the reaction proceeded *via* a substitution followed by the hydroamination of the resulting semi-carbazide or by hydroamination of the carbazate followed by substitution (Scheme 2.1).



Scheme 2.1: Potential Reaction Pathways for the Hydroamination Cascade

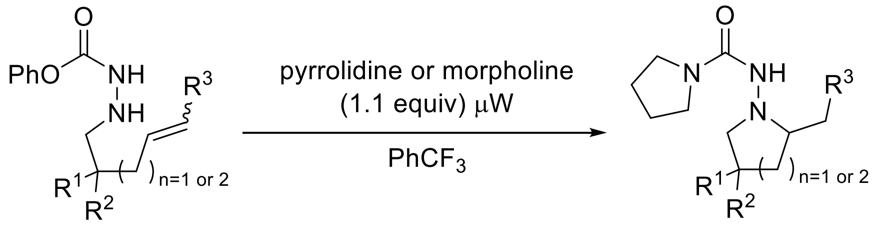
Since no hydroamination was observed when diisopropylamine was used, the pathway involving the formation of **2.8** followed by substitution seemed unlikely. For this reason, Christian Clavette started optimizing the reaction conditions in order to isolate the substitution product. The morpholine adduct **2.7** turned out to be reactive towards hydroamination and was isolated in high yield; however, the pyrrolidine adduct **2.9** was isolated in 78% yield after ten minutes at 80 °C. Heating this adduct at 120 °C for six hours provided the hydroamination product in 82% yield confirming the reaction pathway (eq. 2.6).

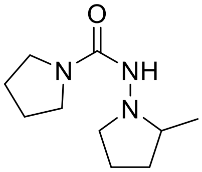


(2.6)

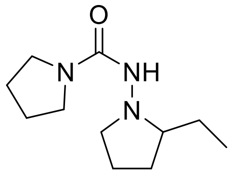
It became obvious that performing these two steps in a cascade reaction would be more efficient given the preliminary results obtained with morpholine. Therefore, the scope of this reaction was studied using different alkenyl chains. The results are summarized in Table 2.1. Using this methodology, 5- and 6-membered rings were constructed with a good tolerance of alkyl substituents on the ring.

Table 2.1: Substitution / Hydroamination Sequence Using Carbazates[a]

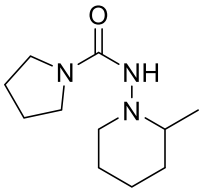




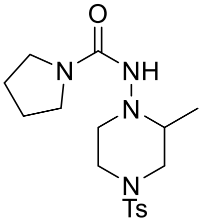
2.10 88%
120 °C, 6 h



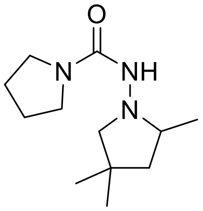
2.11 86%
175 °C, 6 h



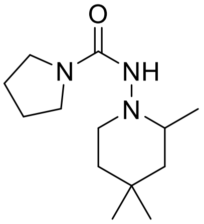
2.12 79%
175 °C,16 h



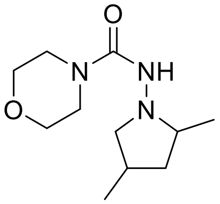
2.13 86%
175 °C, 6 h



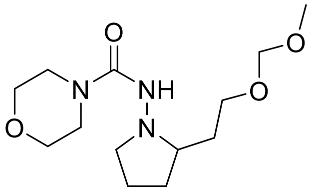
2.14 99%
80 °C, 6 h



2.15 82%
175 °C, 6 h



2.16 94%
120 °C, 6 h
d.r.: 1:1



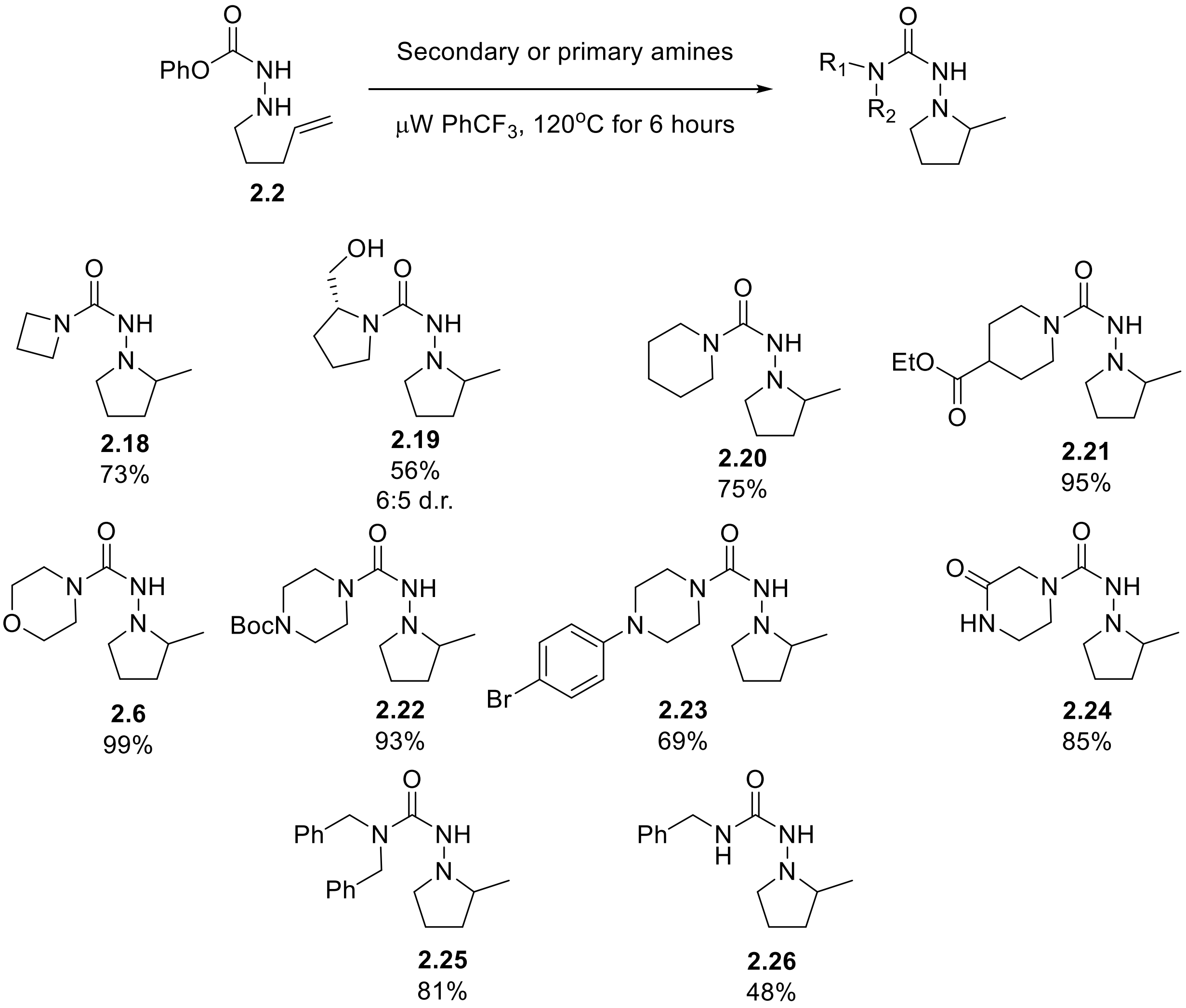
2.17 74%
175 °C, 6 h

[a]Conditions: Carbazate (1 equiv), amine (1.1 equiv) in $PhCF_3$ (0.3 M) heated in a sealed vial in a microwave reactor.

The one-pot procedure produced **2.10** in an excellent overall yield (88% versus 64% for the stepwise approach). Non-terminal alkenes (**2.11**, **2.17**) and 6-membered rings (**2.12**, **2.13**, **2.15**) required a higher temperature (175 °C), but furnished the pyrrolidine, piperidine, and piperazine cores in high yields. Additionally, the Thorpe-Ingold effect was beneficial in reducing the temperature (**2.14**) or the reaction time (**2.15**). Substitution on the alkenyl chain was tolerated, but did not result in any diastereoselectivity (**2.16**, d.r. = 1:1). Finally, the presence of a protected alcohol was tolerated, and highlighted the ability to further functionalize the heterocycle. In summary, these results show that modification of the alkenyl side-chain is well tolerated and that different saturated heterocycles could be obtained using this substitution-hydroamination sequence.

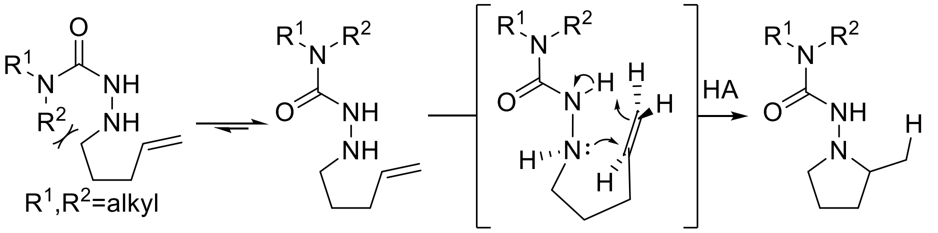
Before trying other cascade reactions, we decided to use this cascade to address a problem that we encountered many times in the development of intramolecular hydroamination reactions. The development of intramolecular methodologies is very lengthy since multiple steps are required to synthesize each starting material, including substrates that may not even yield the desired product. Using an intermolecular-intramolecular reaction cascade, it would be possible to generate multiple products from a common precursor. Using this concept, ten pyrrolidine-based semicarbazides were synthesized starting from carbazate **2.2**. These results are summarized in Table 2.2.

Table 2.2: Substitution / Hydroamination Cascade: Amine Scope[a]



[a]Conditions: Carbazate (1 equiv), amine (1.1 equiv) in PhCF$_3$ (0.3 M) heated in a sealed vial in a microwave reactor.

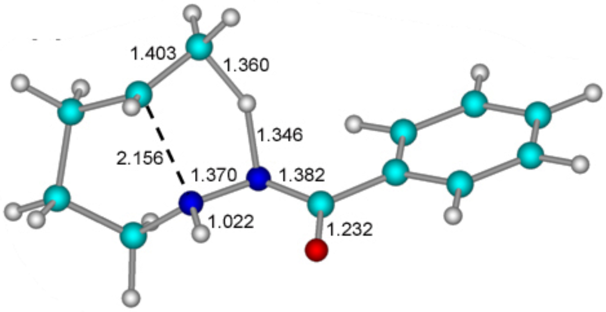
Cyclic and acyclic secondary amines were all well tolerated in this system. Azetidine- (**2.18**), piperidine- (**2.20**, **2.21**), morpholine- (**2.6**), and piperazine- (**2.22**, **2.23**) based nucleophiles all generated the desired semi-carbazides in good to excellent yields. The presence of an aryl bromide further illustrates the versatility of this metal-free approach as well as provided a functionalization handle. Functional groups were also tolerated. The chiral prolinol product (**2.19**) was isolated in moderate yield, but only showed modest diastereoselectivity. An ester (**2.21**), a protected amine (**2.22**), and the oxo-piperazine motifs all yielded the functionalized heterocycles in excellent yields. A secondary acyclic amine was also well tolerated, yielding the semicarbazide in 81%; however, primary benzylic amines only provided the desired product in modest yield. We attributed this lower yield to a difference in the conformational preferences of the resulting semicarbazide following the substitution (eq. 2.7).



(2.7)

E *Z*

The semicarbazides from primary amines have more flexibility and the *E*-conformation is thermodynamically favored as with other simple hydrazides.[82] In contrast, secondary amines form semicarbazides in which an A(1,3) allylic strain interaction is present between R^2 and the side chain on the β-nitrogen. This destabilizes the *E*-conformer and favors the *Z*-conformer of the semicarbazide, which is the reactive conformer in Cope-type hydrohydrazidation according to previous calculations (Scheme 2.2).[75]



Scheme 2.2: Previously Calculated Transition State for the Cope-Type Hydrohydrazidation

A previous study in our group led us to believe that the major factor contributing to mild conditions for Cope-type hydrohydrazidation was the acidity of the hydrazide.[83] In this communication, our group reported the use of 3,5-bis(trifluoromethyl)benzhydrazides as superior reagents for cyclization. The *para*-nitro derivative was even more effective, but was not used for solubility purposes. In Scheme 2.3, a selected scope is presented from that study.

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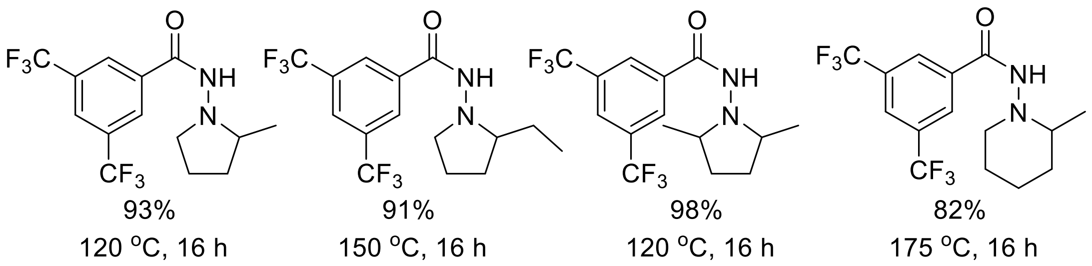
[82] Licandro, E.; Perdicchia, D. *Eur. J. Org. Chem.* **2004**, *4*, 665.

[83] Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J.-G.; Burrell, A.; Beauchemin, A. M. *Chem. Commun.* **2011**, *47*, 562.



Scheme 2.3: Selected Scope Using 3,5-Bis(trifluoromethyl)benzhydrazides[83]

While comparing these results with the ones in Table 2.1, no major differences were observed; however, the semicarbazides formed by the cascade reaction are more electron-rich. This goes against the acidity hypothesis since the pK_a of the α-nitrogen should be higher in these semicarbazides. For this reason, the data suggests that conformational preferences are also important in Cope-type hydrohydrazidations.

2.3: Conclusion and Perspectives

In this Chapter, the discovery of the first cascade reaction employing *N*-isocyanates was discussed.[84] Early studies in the Beauchemin group discarded carbazates as precursors for hydroamination given their ability to form aminoisocyanates under the reaction conditions. In this study, it was shown that trapping the reactive intermediate with a nucleophilic amine provided semicarbazides that were competent reagents in Cope-type hydrohydrazidations. This provided us with insight regarding important factors to consider with regard to reagent design for this particular reaction. More importantly, it provided us with a proof of concept that controlled cascade reactions were possible using nucleophilic amines and illustrated the amphoteric potential of the *N*-isocyanates (electrophilic carbon, nucleophilic β-nitrogen). The use of non-activated alkenes as electrophilic partners was encouraging given their inherent low reactivity. At that point, different projects were envisioned using different electrophiles in order to generate a variety of different heterocycles. Moreover, in this section, the electrophile was already attached to the *N*-isocyanate precursors, which ultimately reduced the diversity potential with lengthy syntheses. Using another amphoteric reagent as the participating reaction partner would ultimately provide a more convergent synthesis and will be discussed in the next chapter.

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[84] Clavette, C.; Vincent-Rocan, J.-F.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 12705.

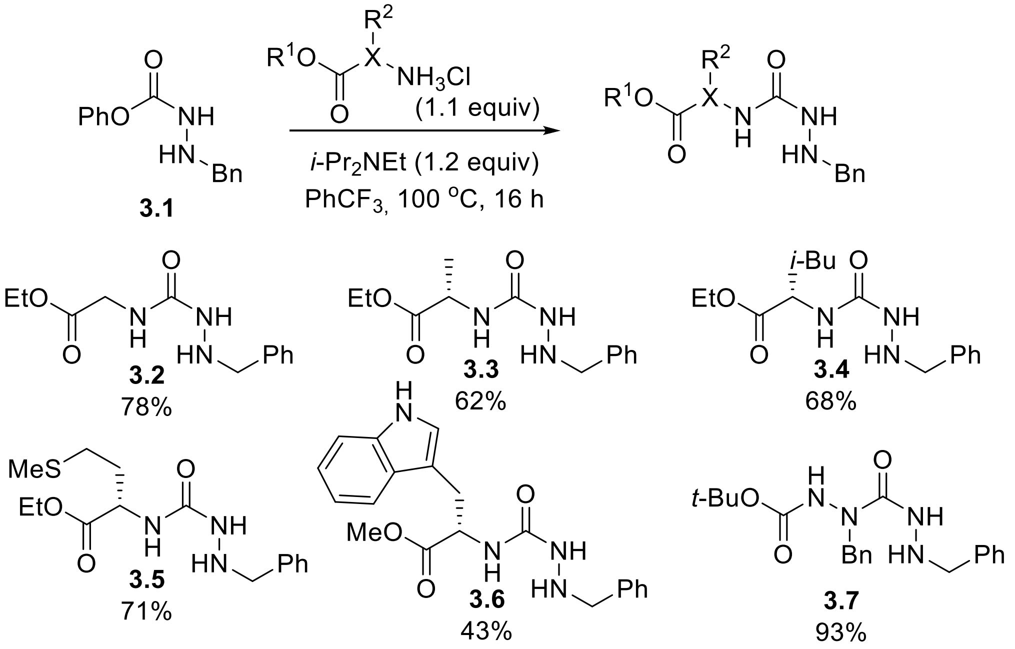
Chapter 3: *N*-Isocyanates in Heterocyclic Chemistry: Products With Two Atoms Within the Ring

3.1: Development of the First Cascade Reaction Using Iminoisocyanates

3.1.1: Synthesis of Aza-dipeptoids

In our first report discussed in the previous chapter, the use of simple carbazates for the synthesis of aza-dipeptides was reported. When the side chain did not have an alkene for hydroamination to occur, a substitution reaction on the blocked isocyanate using amino-esters derived from natural amino-acids was possible, yielding aza-dipeptoids. These motifs are important in peptidomimetics and will be discussed more in detail in Chapter 5. Using the simple carbazate **3.1**, we were able to synthesize six dipeptoid derivatives.[85] The results are displayed in Table 3.1.

Table 3.1: Dipeptoid Synthesis[a]



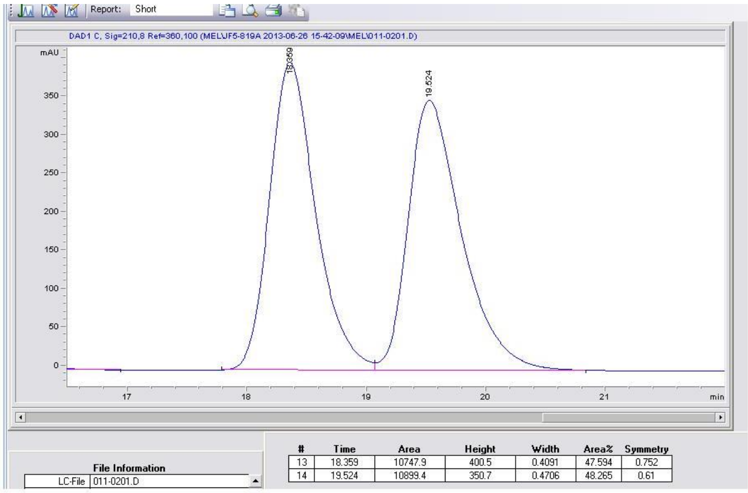
[a]Conditions: Carbazate (1 equiv), amino-ester (1.1 equiv), *i*-Pr$_2$NEt (1.2 equiv) in PhCF$_3$ (0.3 M) heated in a sealed vial in an oil bath for 16 hours.

Using commercially-available aminoesters, glycine- (**3.2**), alanine- (**3.3**), leucine- (**3.4**), methionine- (**3.5**), and tryptophan- (**3.6**) derived dipeptide subunits were produced in modest to good yields. Finally, using *tert*-butyl carbazate, the resulting azatide (**3.7**) was obtained in excellent yield; however, given the lower nucleophilicity of carbazates, ten equivalents were necessary to achieve a selective transformation. To ensure enantiopurity of the products, the reaction was also conducted with racemic alanine ethyl ester to afford the racemic form of product **3.3**. The chiral HPLC traces of both reactions are displayed in Scheme 3.1

---

[85] For recent synthesis of azapeptoids see: (a) Sarma, B. K.; Yousufuddin, M.; Kodadek, T. *Chem. Commun*. **2011**, 47, 1059. (b) Gibson, C.; Goodman, S. L.; Hahn, D.; Hölzemann, G.; Kessler, H. *J. Org. Chem*. **1999**, *64*, 7388. (c) Cheguillaume, A.; Lehardy, F.; Bouget, K.; Baudy-Floc'h, M.; Grel, P. L. *J. Org. Chem*. **1999**, *64*, 2924. (d) Aubin, S.; Martin, B.; Delcros, J.; Arlot-Bonnemains, Y.; BaudyFloc'h, M. *J. Med. Chem*. **2005**, *48*, 330.

HPLC analysis of racemic alanine derivative **(±)-3.3**

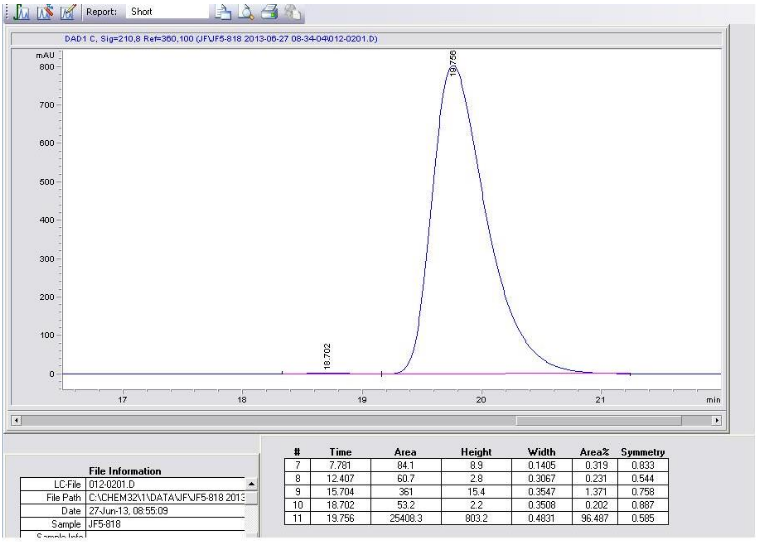


DAD1 C, Sig=210,8 Ref=360,100 (MEL\JF5-819A 2013-06-26 15-42-09\MEL\011-0201.D)

LC-File: 011-0201.D

#	Time	Area	Height	Width	Area%	Symmetry
13	18.359	10747.9	400.5	0.4091	47.594	0.752
14	19.524	10899.4	350.7	0.4706	48.265	0.61

HPLC analysis of enantioenriched alanine derivative **(*S*)-3.3**



DAD1 C, Sig=210,8 Ref=360,100 (JF\JF5-818 2013-06-27 08-34-04\012-0201.D)

LC-File: 012-0201.D
File Path: C:\CHEM32\1\DATA\JF\JF5-818 201
Date: 27-Jun-13, 08:55:09
Sample: JF5-818

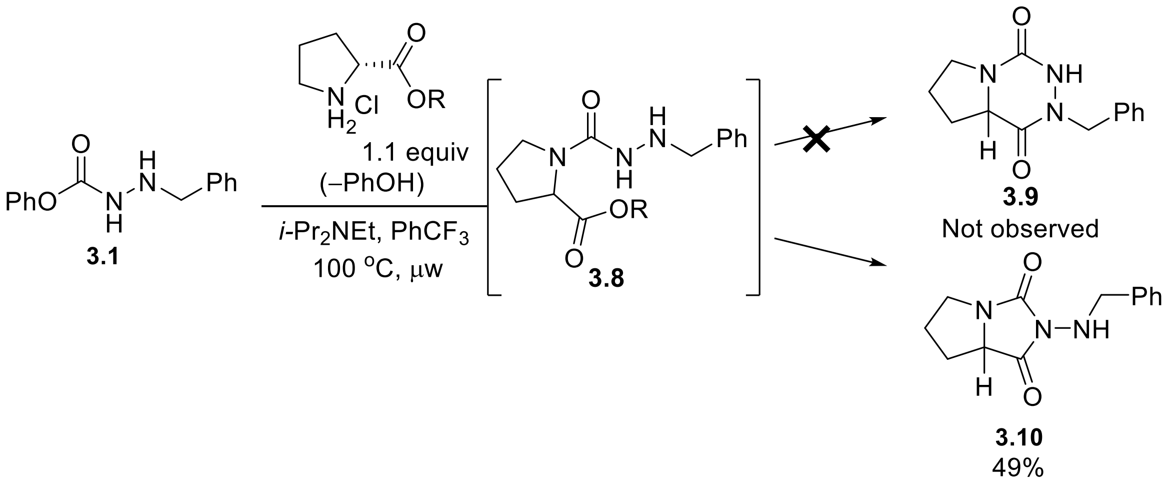
#	Time	Area	Height	Width	Area%	Symmetry
7	7.781	84.1	8.9	0.1405	0.319	0.833
8	12.407	60.7	2.8	0.3067	0.231	0.544
9	15.704	361	15.4	0.3547	1.371	0.758
10	18.702	53.2	2.2	0.3508	0.202	0.887
11	19.756	25408.3	803.2	0.4831	96.487	0.585

Scheme 3.1: Retention of Enantiopurity

When comparing the two samples, it is evident that the reaction yielded only one enantiomer in the bottom trace, as compared to the racemic one above. Therefore, we were confident that the dipeptide subunits were enantiopure. Having recently demonstrated the potential of *N*-isocyanates in heterocyclic synthesis, we began to question if it would be possible to induce cyclization on the ester moiety. This would be conceptually different from the hydroamination cascade, since the nucleophile and the electrophile would come from the same reagent.

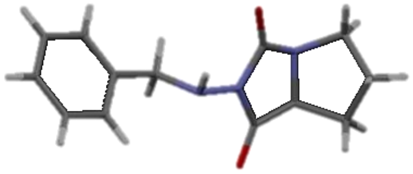
3.1.2: Aza-Hydantoins Synthesis Using Aminoisocyanates

With the help of Christian Clavette and an undergraduate student working under my supervision (Kyle Leckett), we started to investigate this idea and noticed that two different products could arise from this strategy. If the α-nitrogen was participating in the cyclization event, an aza-hydantoin would be obtained. As previously mentioned, if the β-nitrogen was cyclizing, the resulting 6-membered ring would be obtained, namely an aza-diketopiperazine. To test this hypothesis, we treated carbazate **3.1** with a proline ester and were pleased to observe complete selectivity for the cyclization forming a 5-membered ring (Scheme 3.2). However, we were also able to synthesize the 6-membered ring (aza-diketopiperazine) using a different synthetic strategy, which will be discussed in Chapter 4.



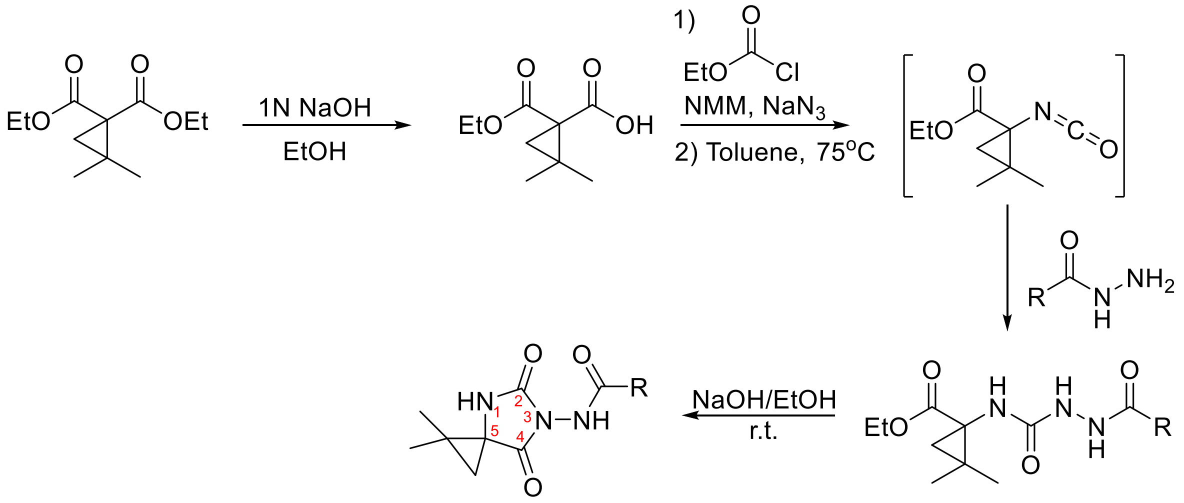
Scheme 3.2: Confirmation of Hydantoin Synthesis

Given the possibility for both products (**3.9** and **3.10**) to produce similar NMR spectra, X-ray diffraction of the crystalline product was performed to confirm the structure of **3.10**. This structure is shown in Scheme 3.3.



Scheme 3.3: X-Ray of Compound 3.10

Given the importance of hydantoins in the literature, this convergent approach is a powerful method for the rapid generation of aminohydantoins.[86] Most syntheses of aminohydantoins in the literature relied on multi-step syntheses (Scheme 3.4),[85b] transition metals, or multicomponent reactions that need further modifications. A similar approach to ours was reported in 2000 by a team at Procter & Gamble Pharmaceuticals (eq. 3.1).[85i] Interestingly, they never postulated an *N*-isocyanate intermediate and only reported a small scope based on Boc-protected hydrazine. Given the limitations of such approaches, our method has the advantage of using simple starting materials, relying on a 1 step procedure, and being broadly applicable.



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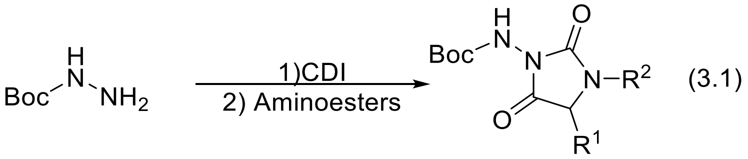
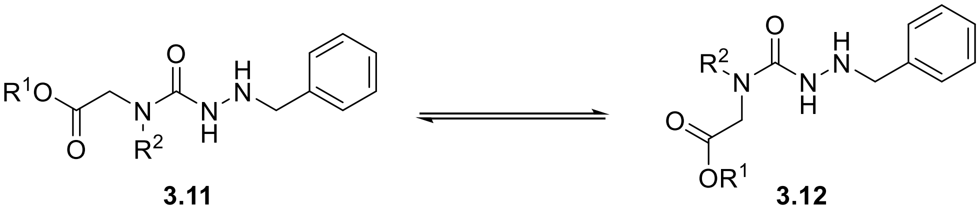
[86] For syntheses and bioactivities of *N*-substituted hydantoins see: (a) Novak, A.; Bezensek, J.; Groselj, U.; Golobic, A.; Stanovnik, B.; Svete, J. *ARKIVOC* **2011**, 18. (b) He, X.; Zhong, M.; Zhang, T.; Wu, W.; Wu, Z.; Yang, J.; Xiao, Y.; Pan, Y.; Qiu, G.; Hu, X. *Eur. J. Med. Chem.* **2010**, *45*, 5870. (c) Bourguet, C. B.; Proulx, C.; Klocek, S.; Sabatino, S.; Lubell, W. D. *J. Pept. Sci*. **2010**, *16*, 284. (d) Hashmi, I. A.; Aslam, A.; Ali, S. K.; Ahmed, V.-U.; Ali, F. I. *Synth. Commun*. **2010**, *40*, 2869. (e) Kurz, T.; Widyan K. *Tetrahedron Lett*. **2004**, *45*, 7049. (f) Hoffman, R. V.; Madan, S. *J. Org. Chem*. **2003**, *68*, 4876. (g) Sternberg, J. A.; Geffken, D.; Adams Jr., J. B.; Pçstages, R.; Stern-berg, C. G.; Campbell, C. L.; Moberg, W. K. *Pest Manage. Sci*. **2001**, *57*, 143. (h) Wu, S.; Janusz, J. M.; Sheffer, J. B. *Tetrahedron Lett*. **2000**, *41*, 1159. (i) Wu, S.; Janusz, J. M. *Tetrahedron Lett*. **2000**, *41*, 1165. (j) Hoffman, R. V.; Reddy, M. M.; Cervantes-Lee, F. *J. Org. Chem*. **2000**, *65*, 2591. (k) Yoon, J.; Cho, C.-W.; Han, H.; Janda, K. D. *J. Chem. Soc. Chem. Commun*. **1998**, 2703. (l) Florac, C.; Le Grel, P.; Baudy-Floc'h, M.; Robert, A. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1143. (m) Lalezari, I. *J. Heterocycl. Chem*. **1985**, *22*, 741. (n) Wright, G. C.; Michels, J. G.; Spencer, C. F. *J. Med. Chem*. **1969**, *12*, 379. (o) Milne, H. B.; Kilday, W. D. *J. Org. Chem*. **1965**, *30*, 67. (p) Milne, H. B.; Fish, D. W. *J. Org. Chem*. **1962**, *27*, 3177. (q) Jack, D. *J. Med. Pharm. Chem*. **1961**, *3*, 253. For a review on hydantoin synthesis and bioactivity, see: (r) Meusel, M.; Gütschow, M. *Org. Prep. Proc. Int.* **2004**, *36*, 391.

Scheme 3.4: Multi-Step Synthesis of Aminohydantoin



Our first result urged us to consider the conformational requirements for the reaction to occur. Under the same conditions, a primary α-aminoester only yielded substitution adducts (Table 3.1). As suggested by our hydroamination work, the conformation of these semicarbazide intermediates can greatly influence the reaction pathway. Presumably, in this case, the favored *s*-trans conformer resulting from the attack of a primary amine (R^2 = H, **3.11**) positions the ester too far from the nucleophilic nitrogen and the equilibrium disfavors cyclization to form the hydantoin (Scheme 3.5). In contrast, the equilibrium is more favorable when secondary amines were used (R^2 = alkyl) and this explained how cyclization is achieved using secondary amines such as a proline ester.



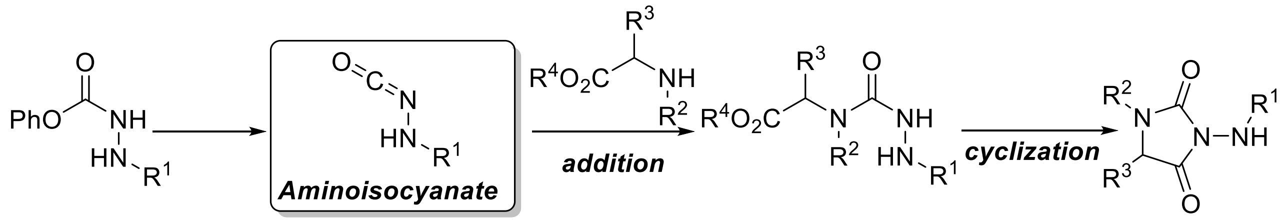
3.11
Not prone to cyclization

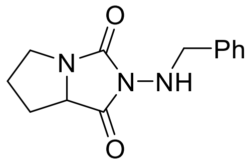
3.12
Prone to cyclization

Scheme 3.5: Equilibrium of Conformation for the Synthesis of Aminohydantoins

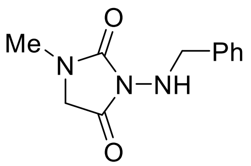
With this equilibrium in mind, we started to scope the reaction using natural amino ester derivatives and carbazate **3.1**; the results are summarized in Table 3.2.

Table 3.2: Scope using *N*-Benzyl Carbazates and Amino Esters[a]

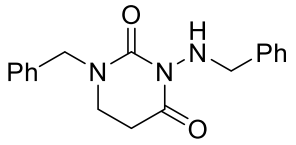




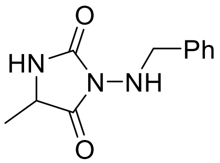
3.10
49%



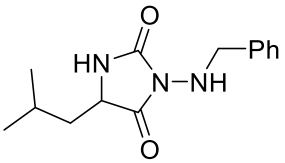
3.13
82%



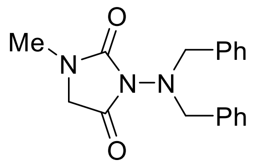
3.14
62%



3.15
70%



3.16
62%



3.17
81%

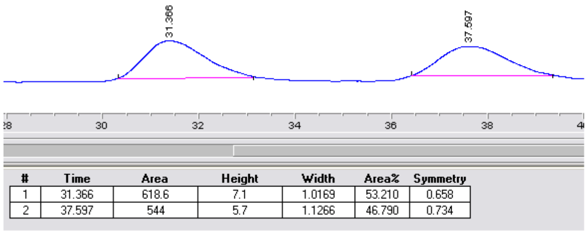
[a]Conditions: Carbazate (1 equiv), amino ester (1.1 equiv), DIPEA (1.2 equiv) in $PhCF_3$ (0.3 M) heated in a sealed vial in a microwave reactor for 6 hours.

In addition to proline (**3.10**), *N*-methyl glycine ester (**3.13**) was able to yield the substituted aminohydantoin in good yield. Primary amino esters also work, but require higher temperatures (150°C). Using these conditions, the hydantoins derived from alanine (**3.15**), and leucine (**3.16**) were synthesized in modest to good yield. It is important to note that most of these reactions were high yielding but the polarity of these compounds made their isolations by column chromatography difficult. The reaction was also tolerant of a doubly-substituted carbazate (**3.17**) to yield the substituted hydantoin in good yield. Finally, β-amino ester was also a competent reaction partner yielding dihydrouracil **3.14** in good yield.

As shown in Table 3.2, the products obtained in this reaction racemized. Indeed, while verifying the enantiopurity of our compounds using the racemic alanine adducts, we were disappointed to see an identical chiral HPLC trace for both compounds (Scheme 3.6). Given the pseudoaromatic character of the deprotonated hydantoin, it is likely that elevated temperatures could epimerize the α-carbon in mild, basic conditions. Nevertheless, this study represents a fast approach to hydantoins derived from natural α-amino acids.

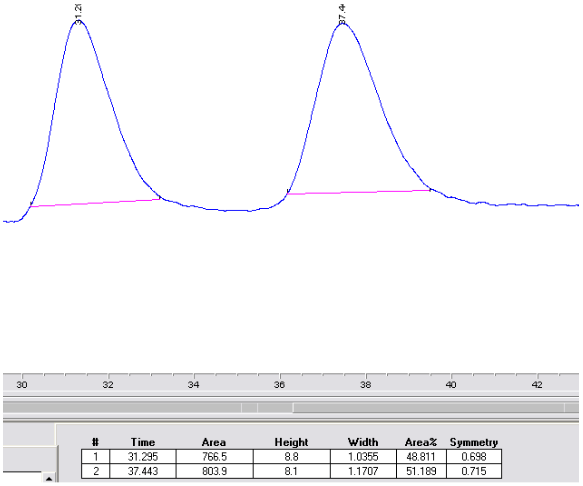
Since this reaction was completely selective for the cyclization using the α-nitrogen atom, we envisioned the use of carbazones as blocked *N*-isocyanates in a variant this reaction. This would be beneficial for two reasons: first, the synthesis of the precursors would avoid the use of column chromatography and a low yielding reduction reaction; second, as mentioned in the introduction, iminoisocyanates share the same reactivity trends as aromatic isocyanates (*i.e.*, more reactive than their sp^3 analogs); lastly, the hydantoins without any N-H bonds should be easier to purify which would possibly increase the yield of our reactions.

Chiral HPLC result of the cascade reaction with racemic alanine methyl ester*



#	Time	Area	Height	Width	Area%	Symmetry
1	31.366	618.6	7.1	1.0169	53.210	0.658
2	37.597	544	5.7	1.1266	46.790	0.734

Chiral HPLC result of the cascade reaction with L-alanine methyl ester

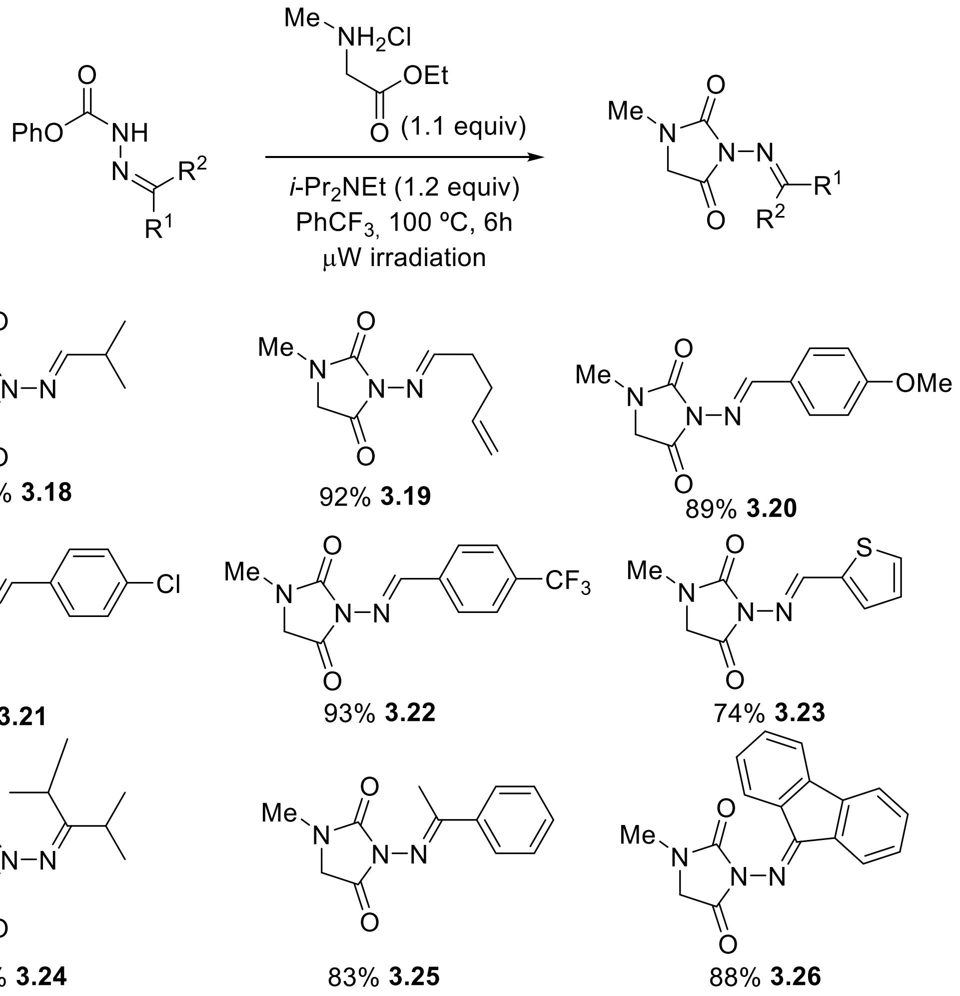


#	Time	Area	Height	Width	Area%	Symmetry
1	31.295	766.5	8.8	1.0355	48.811	0.698
2	37.443	803.9	8.1	1.1707	51.189	0.715

Scheme 3.6: Erosion of Enantiopurity

To establish the scope of this reaction, we selected *N*-methyl glycine ethyl ester given its higher yield with the carbazates and its availability. As predicted, a variety of carbazone-based blocked *N*-isocyanates were competent reaction partners. These results are shown in Table 3.3.

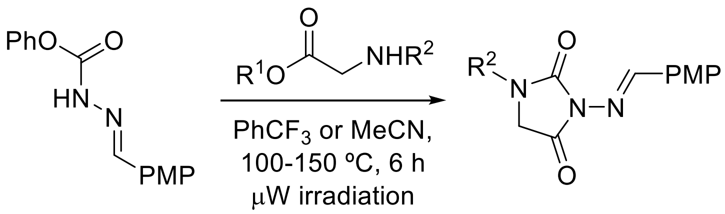
Table 3.3: Carbazone Scope Using *N*-Methyl Glycine Ester[a]

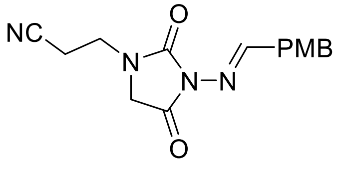


[a]Conditions: Carbazone (1 equiv), amino ester (1.1 equiv), *i*-Pr$_2$NEt (1.2 equiv) in PhCF$_3$ (0.3 M) heated in a sealed vial in a microwave reactor for 6 hours at 100 °C.

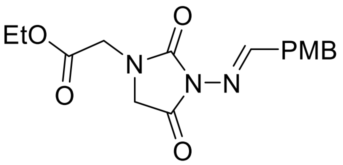
Aldehyde-derived aliphatic carbazones (**3.18**, **3.19**) yielded the desired product in good to excellent yields. Aromatic carbazones (**3.20**, **3.21**, **3.22**) were also tolerated with no obvious trend regarding electronic effects. Heteroaromatic carbazones (**3.23**) derived from aldehydes also furnished the bi-heterocycle in good yield. Ketone-derived carbazones were also tolerated including the bulky aliphatic diisopropyl group (**3.24**), as well as the aromatic derivatives of acetophenone (**3.25**) and fluorenone (**3.26**). Given the broad scope of carbazones, we then moved to explore different amino esters for the rapid generation of molecular diversity (Table 3.4).

Table 3.4: Amine Scope for the Synthesis of Hydantoins[a]

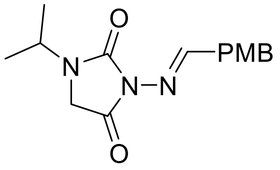




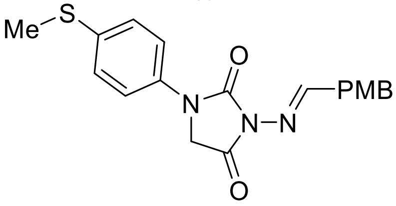
87% **3.27**



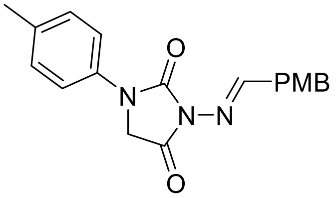
65% **3.28**



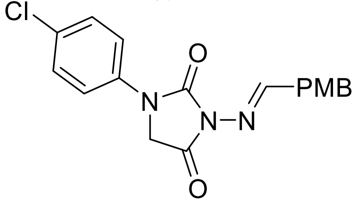
56% **3.29**



50% **3.30**



76% **3.31**



56% **3.32**

[a]Conditions: Carbazone (1 equiv), amino ester (1.1 equiv), *i*-Pr_2NEt(1.2 equiv) in $PhCF_3$ (0.3 M) heated in a sealed vial in a microwave reactor for 6 hours at 100-150 °C.

We were quite pleased to see that functional groups were not interfering with the reaction. For example, a nitrile group (Table 3.4, **3.27**) present on the amino ester did not affect the results of the reaction yielding the substituted hydantoin in 87% yield. An ester group (**3.28**) and a bulky amine (**3.29**) was also tolerated in the reaction, but afforded the product in lower yields. Finally, it was shown that anilines were competent reaction partners in the reaction. Given the lower nucleophilicity of anilines, the success of these reactions supported the involvement of highly electrophilic species such as *N*-isocyanates. Heteroatom-containing (**3.30**), electron-poor (**3.32**), and electron-neutral (**3.31**) anilines all afforded the parent hydantoins in modest to good yields. Given the bioactivity of hydantoins, we wanted to show the potential of our approach for the rapid synthesis of multiple drug analogs. To do so, we selected Azumolene as a drug candidate given its unique activity for the treatment of malignant hyperthermia (Scheme 3.7).[87] Since the hydantoin core is commercially available, most of the synthetic effort for the evaluation of analogs relied on condensation on different aldehydes.[88] In contrast, our method would give rise to analogs with modifications on the hydantoin ring system. An isomer of the hydantoin ring was synthesized since the second carbonyl is on the adjacent carbon. Second, multiple hydantoins were obtained with different substitutions on the free N-H of azumolene.

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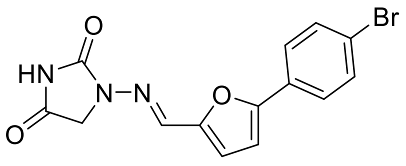
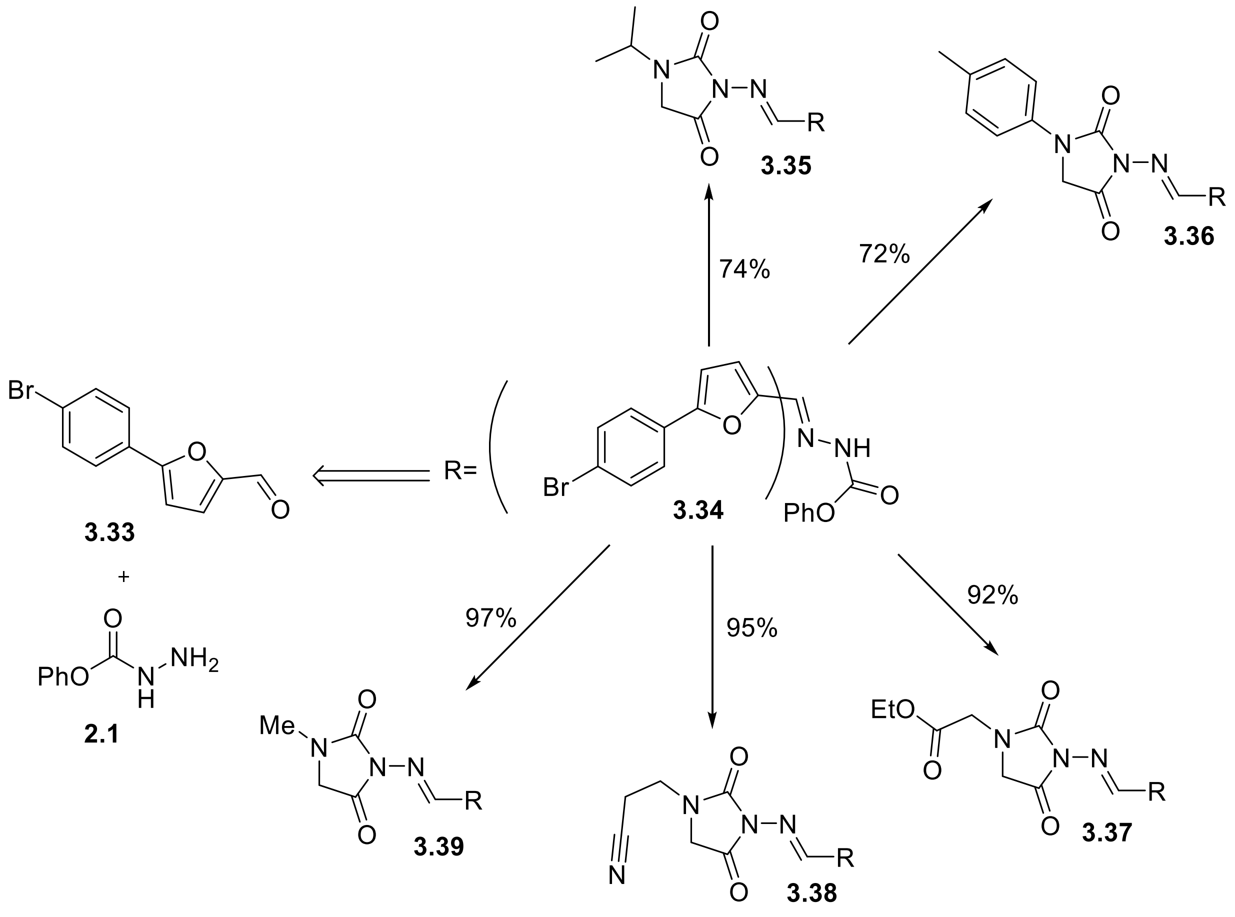
[87] For biological activity see: Do Carmo, P. L.; Zapata-Sudo, G.; Trachez, M. M.; Antunes, F.; Guimarães, S. E. F.; Debom, R.; Rizzi, M. D. R.; Sudo, R. T. *J. Vet. Intern. Med.* **2010**, *24*, 1224, and references cited therein.

[88] Snyder, H. R.; Davis, C. S.; Bickerton, R. K.; Halliday, R. P. *J. Med. Chem.* **1967**, *10*, 807.



Scheme 3.7: Structure of Azumolene

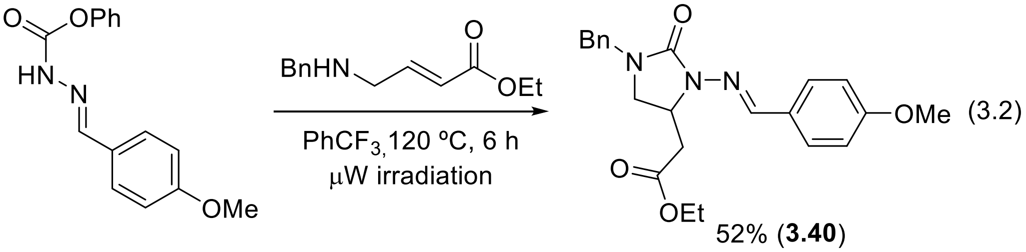
Using our improved method for the synthesis of phenyl carbazate and the commercially-available aldehyde (**3.33**), a large quantity of the semicarbazone precursor (**3.34**) was obtained without the use of column chromatography since the product precipitated out of the reaction. As displayed in Scheme 3.8, most isolated yields proved higher using this complex substrate (72-97%). Since every compound was purified by filtration, the variation in yields highlights the difficult purification process in the previous systems.



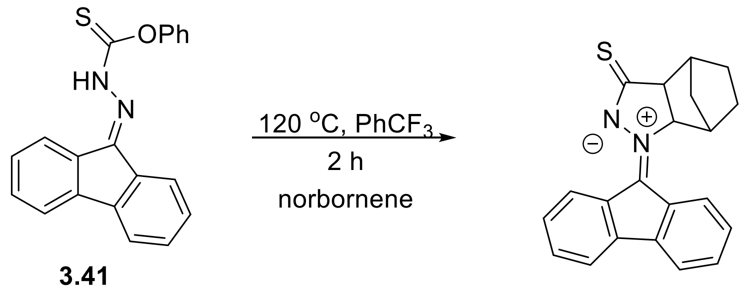
Scheme 3.8: Rapid Synthesis of Azumolene Derivatives

Pleasingly, a bulky amine (**3.35**), an aniline (**3.36**), an ester group (**3.37**), a nitrile group (**3.38**), and a simple *N*-methyl (**3.39**) were all tolerated in a more complex system to afford the functionalized azumolene analogues in good to excellent yields. In only six reactions, five drug analogs were synthesized without using column chromatography. We believe that this rapid synthesis illustrates the potential of *N*-isocyanates in medicinal chemistry.

Given the applicability of this method, the potential of similar cascade reactions was tested. For example, the same reaction using an unsaturated amino-ester was performed and we were pleased to see that a substitution/1,4-addition cascade could yield imidazolidinone **3.40** in modest yield (eq. 3.2).



This result reveals the potential of *N*-isocyanates towards other electrophiles and will be discussed later in this chapter. The potential of other *N*-isocyanates in this system was then tested. *N*-Isothiocyanates were already known in the group to be reactive toward alkenes,[89] but were never developed further since the synthesis of the chosen precursor was lengthy and not reproducible (Scheme 3.9).



3.41

Synthesis is long and low yielding

3.42

20 mg, 61%

Scheme 3.9: Previous *N*-Isothiocyanate Precursor

To streamline the synthesis of *N*-isothiocyanate precursors, the use of an aniline-derived leaving group was envisioned. The synthesis would be much simpler starting from commercial isothiocyanates and hydrazones or hydrazines. We finally opted for *para*-nitroaniline as a leaving group and attempted the synthesis of a derivative of **3.41**. Fortunately, the new precursor was easy to synthesize and aminothiocarbonylation was achieved in excellent yield on a 1 mmol scale (Scheme 3.10).

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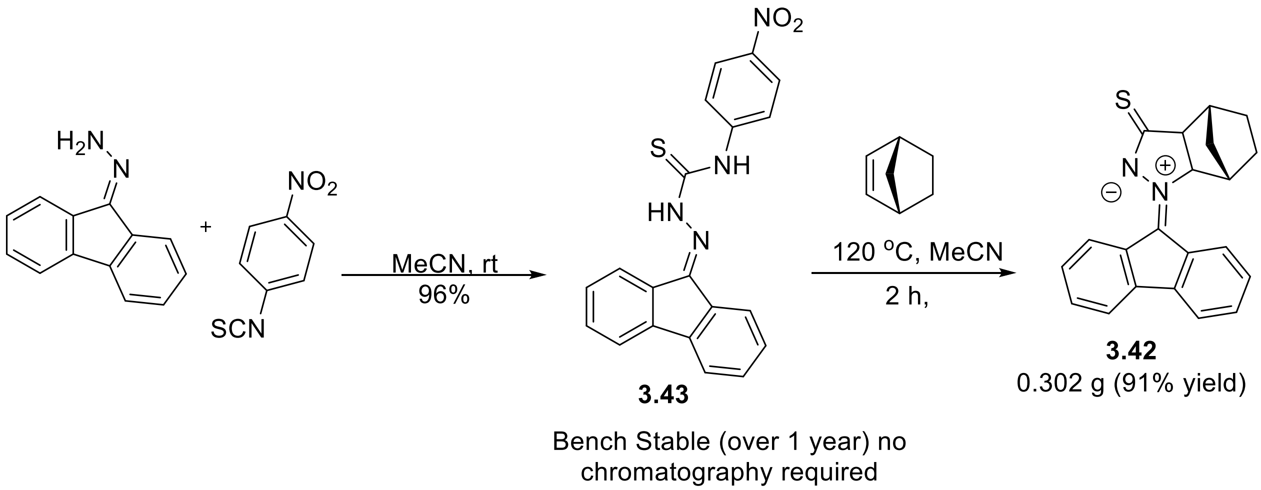
[89] Clavette, C.; Gan, W.; Markiewicz, T.; Toderian, A.; Beauchemin, A. M. **2013**, *Patent:* WO2013/67646 A1



3.43

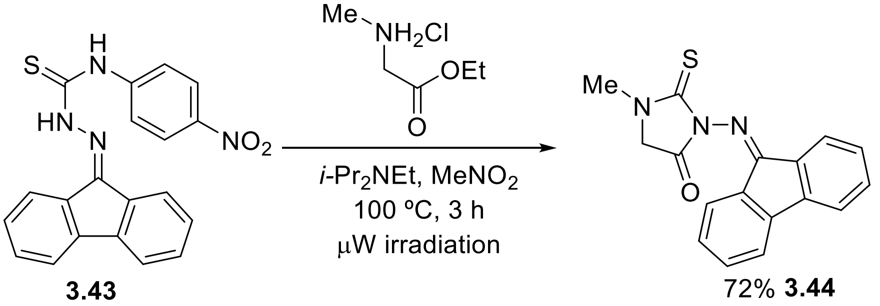
Bench Stable (over 1 year) no chromatography required

3.42

0.302 g (91% yield)

Scheme 3.10: Improved Synthesis of *N*-Isothiocyanates Precursors

This new strategy improved the synthesis of the precursor of this rare intermediate and allowed the synthesis of a large amount of *N*-isothiocyanate precursor. Moreover, it made it finally possible to use *N*-isothiocyanates to their full potential. Using **3.43** in our hydantoin synthesis, we were able to produce the thiohydantoin (**3.44**) in good yield (eq. 3.3).

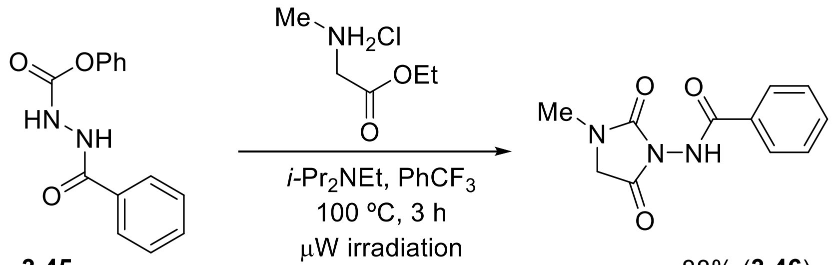


3.43

72% **3.44**

(3.3)

This discovery initiated different projects in the group which are currently still ongoing. One of them, which describes divergent reactions of *N*-isocyanates and *N*-isothiocyanates, will be discussed later in this Chapter. Finally, the outcome of the reaction using amidoisocyanates was tested. This reaction also proved effective with this different *N*-isocyanate to afford the amidohydantoin (**3.46**) in excellent yield (eq. 3.4).



3.45 88% (**3.46**) (3.4)

Overall, this system showed that it was possible to use multiple *N*-isocyanate precursors in a similar reaction.[90] We were able to show that amino-, imino-, and amidoisocyanates, as well as iminoisothiocyanates were all tolerated and reacted similarly with amino esters. We then began thinking about a system in which different *N*-isocyanate precursors would react differently, and lead to other useful products.

3.2. Diversity-Oriented Heterocyclic Synthesis Using Divergent Reactivity of *N*-Substituted Isothiocyanates

Having a streamlined synthesis for *N*-isocyanate and *N*-isothiocyanate precursors allowed us to focus our attention on a system that would result in divergent reactivity. In continuation of our work on the synthesis of bioactive compounds, we wanted to aim for two heterocycles that displayed interesting biological activities. Up to this point, we knew that the electrophile could be an ester or an alkene and that it could be present on the substrate itself (Chapter 2) or on the external partner (aminoesters). A literature search revealed that isothiocyanates could react with the alkyne by nucleophilic addition of the sulfur atom.[91] Combining this with the information provided by eq. 3.2, we envisioned the possibility of synthesizing different heterocycles by divergent reactivity towards propargylic amines (Scheme 3.11). This would represent a faster convergent synthesis of these bioactive heterocycles.[92,93]

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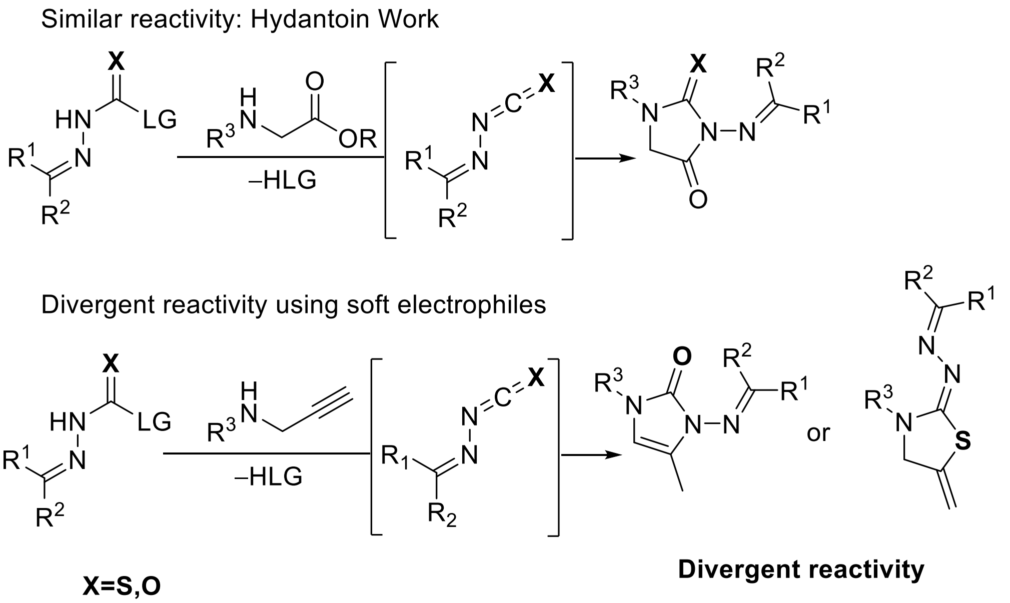
[90] Vincent-Rocan, J.-F.; Clavette, C.; Leckett, K.; Beauchemin, A. M. *Chem. Eur. J.* **2015**, *21*, 3886.

[91] For a review of isothiocyanates in heterocyclic chemistry see: Mukerjee A. K.; Ashare, R. *Chem. Rev.* **1991**, *91*, 1.

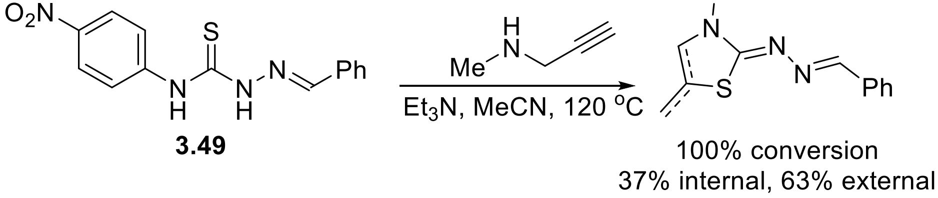
[92] For recent syntheses of imidazolones see: (a) Barluenga, J.; Gomez, N.; Palacios F.; Gotor, V. *Synthesis* **1981**, 561. (b) Gnichtel H.; Sinell, M. *Liebigs. Ann. Chem.* **1988**, 919. (c) Mehrotra, M. M.; Sternbach, D. D.; Rutkowske R. D.; Feldman, P. L. *J. Org. Chem.* **1995**, *60*, 7063. (d) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J.; Expeleta, J. M. *Tetrahedron* **1998**, *54*, 2291. (e) Lenarsic, R.; Kocevar, M.; Polanc, S. *J. Org. Chem.* **1999,** *64*, 2558. (f) Bombek, S.; Lenarsic, R.; Kocevar M.; Polanc, S. *Synthesis.* **2001**, *8*, 1237. (g) Zav'yalow, S. I.; Ezhova, G. I.; Kravchenko, N. E.; Kulikova, L. B.; Dorofeeva, O. V.; Rumyantseva E. E.; Zavozin, A. G. *Pharm. Chem. J.* **2004**, *38*, 256. (h) Bombek, S.; Pozgan, F.; Kocevar, M.; Polanc, S. *New J. Chem.* **2005**, *29*, 948. (i) Neochoritis, C.; Tsoleridis, C. A.; Stephanidou-Stephanatou, J. *Tetrahedron* **2008**, *64*, 3527. (j) Nezensek, J.; Groselj, U.; Stare, K.; Svete, J.; Stanovnik, B. *Tetrahedron* **2012**, *68*, 516. (k) Proulx, C.; Lubell, W. D. *Org. Lett.* **2012**, *14*, 4552. (l) Bezensek, J.; Groselj, U.; Stare, K.; Svete, J.; Stanovnik, B. *Arkivoc* **2014**, *2*, 294.

[93] For recent syntheses of thiazolidines see: (a) Thyagarajan, B. S.; Simon Nee Glowwienka, J. A. *Synth. Commun.* **1988**, *18*, 197. (b) Takahashi, H.; Yasui, S.; Tsunoi, S.; Shibata, I. *Eur. J. Org. Chem.* **2013**, *1*, 40. (c) Rashid, M.; Husain, A.; Shaharyat, M.; Mishra, R.; Hussain, A.; Afzal, O. *Eur. J. Med. Chem.* **2014**, *83*, 630.
(d) Viart, H. M.–F. T.; Larse, S.; Tassone, C.; Andresen, T. L.; Clausen, M. H. *Chem. Commun.* **2014**, *50*, 7800. (e) Fizer, M.; Slivka, M.; Rusanov, E.; Turov, A.; Lendel, V. J. *Heterocycl. Chem.* **2015**, *52*, 949. (f) Gomha, S. M.;



Scheme 3.11: Comparison of Amino Esters and Propargylic Amines Reactivity

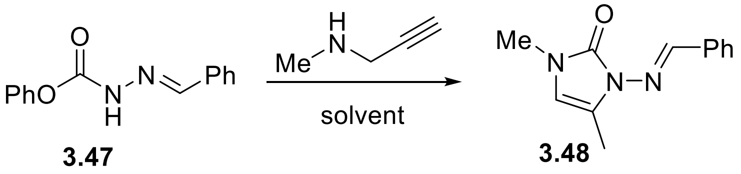
With the help of Joshua Derasp, we started by optimizing the reaction conditions using *N*-isocyanate precursor **3.47** since this reaction was the most complex cascade targeted to date. Indeed, to yield the desired product, a substitution, a cyclization, and an isomerization needed to occur. As seen in Table 3.5, a catalytic amount of base (Et_3N) was crucial for the reaction. Without this base, only five percent of product was observed with the substitution adduct being present as the major product. This was most likely due to a based-catalyzed hydroamination reaction. In addition, this base could also catalyze the isomerization step, resulting in the aromatic product forming more efficiently. The optimal reaction conditions were found to be 100 °C in MeCN for two hours under microwave irradiation. With optimal conditions in hand, the same reaction was performed on a similar *N*-isothiocyanate precursor **3.49** (eq. 3.5). Surprisingly, the reaction afforded the desired cyclization, but only 37% of this adduct isomerized to the internal alkene. This observation suggests that the isomerization is more difficult in this system. However, in addition to the diversity achieved by a different atom cyclizing, the product distribution differs, which is most likely due to their relative stabilities.



(3.5)

Riyadh, S. M.; Mahmmoud, E. A.; Elaasser, M. M. *Heterocycles* **2015**, *91*, 1227. (g) Mahdavi, M.; Bialam, M.; Saeedi, M.; Jafarpour, F.; Foroumadi, A.; Shafiee, A. *Synlett* **2015**, *26*, 173. (h) Ranjan, A.; Mandal, A.; Yerande, S. G.; Dethe, D. H. *Chem. Commun.* **2015**, *51*, 14215.

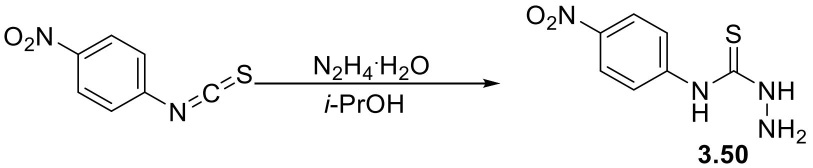
Table 3.5: Optimization of *N*-Isocyanate Cascade Involving *N*-Methylpropargylamine[a]



Entry	Source	Temp. (°C)	Base	Time (h)	Solvent	Yield[b] (%)
1	μW	100	none	3	MeCN	5
2	μW	100	Et_3N	1	MeCN	79
3	μW	100	Et_3N	2	MeCN	87(86)
4	μW	100	Et_3N	3	MeCN	90
5	μW	150	Et_3N	2	MeCN	86
6	Oil bath	100	Et_3N	14	$PhCF_3$	68

[a]Conditions: Carbazone (1.0 equiv), *N*-methylpropargylamine (1.1 equiv), Et_3N (20 mol %) and MeCN (0.3 M) were added to an oven-dried microwave vial heated in oil bath or microwave (μW) reactor. [b]NMR yield based on 1,3,5-trimethoxybenzene internal standard, isolated yield in parentheses.

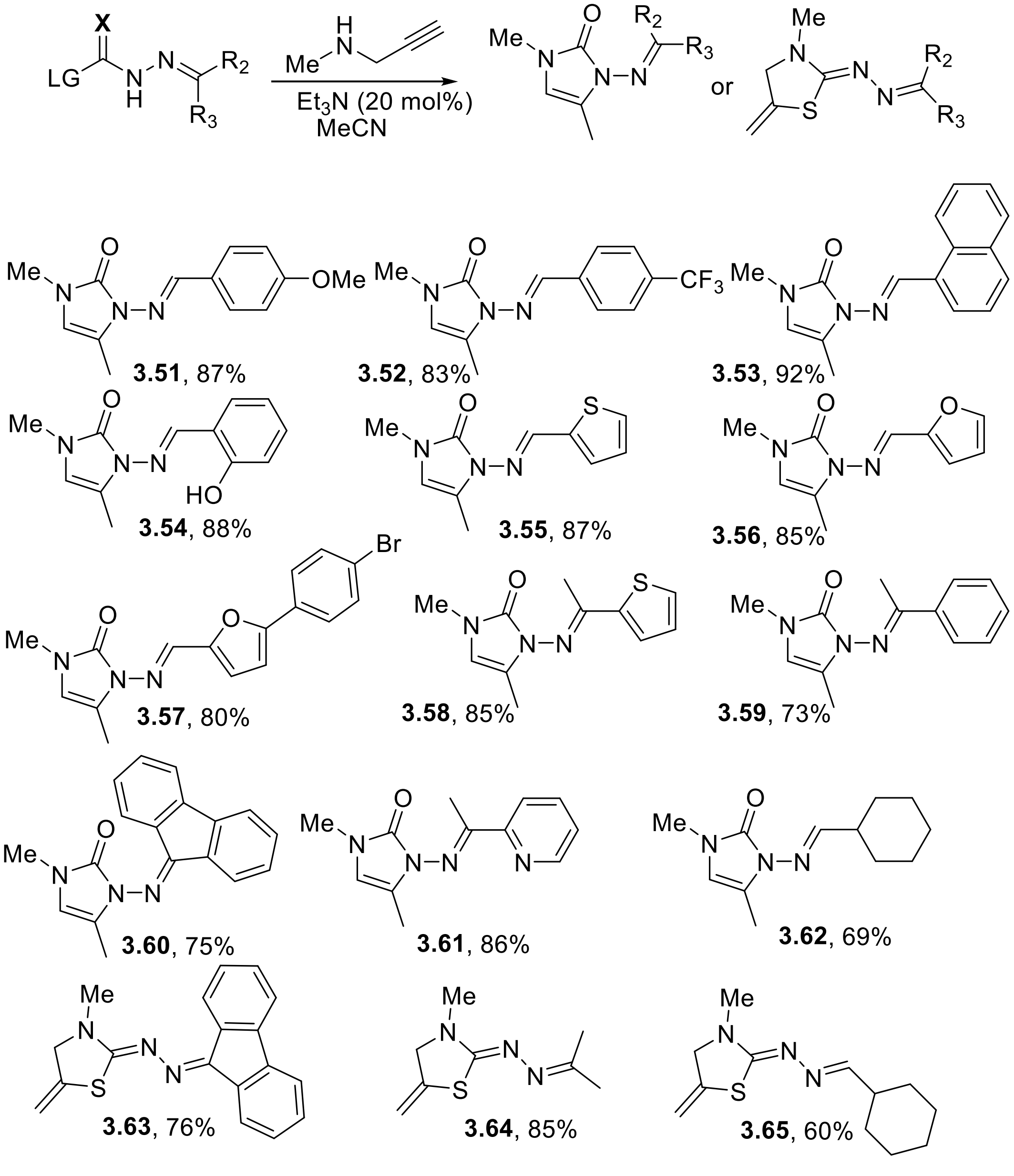
To synthesize precursor **3.49**, a different route needed to be develop since the hydrazone derived from benzaldehyde is known to be difficult to access. To do so, we were able to synthesize the thiosemicarbazide **3.50** (eq. 3.6) on large scale (up to 10 g). This building block was also stable on the bench for months and therefore gave access to different *N*-isothiocyanate precursors.



(3.6)

With the large-scale synthesis of precursor **3.50**, we were now able to access *N*-isothiocyanate precursors derived from simple ketones or aldehydes instead of hydrazones, which are not as readily available. With optimized conditions in hand and a way to access multiple precursors, we first explored the scope of this reaction using different precursors and *N*-methylpropargylamine. These results are displayed in Table 3.6.

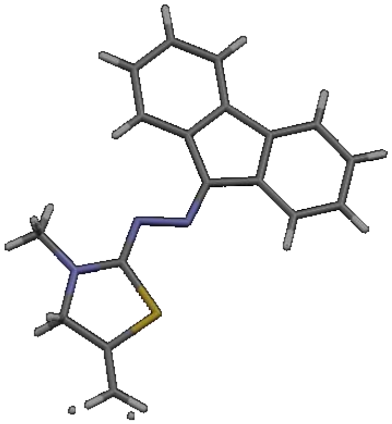
Table 3.6: Divergent Synthesis Using Different *N*-Iso(thio)cyanate Precursors[a]



[a]Conditions: Carbazones (1.0 equiv), *N*-methylpropargylamine (1.1 equiv), base (20 mol %) and MeCN (0.3 M) were added to an oven-dried microwave vial heated in oil bath or microwave (µW) reactor at 100°C (120 for thio).

First, the electronics of aromatic *N*-isocyanate precursors were studied. As shown in Table 3.6, the electronic parameters do not seem to have any effect on the reaction outcome. Comparing the outcome of reactions with iminoisocyanate precursors with electron-rich (**3.51**), electron-poor (**3.52**), electron-neutral (**3.53**), and even heteroatom-containing (**3.54**) aromatic compounds supports this statement. Heteroaromatic semi-carbazones derived from aldehydes were also tolerated with the synthesis of the imidazolones containing a thiophene (**3.55**) or a furan (**3.56**) in excellent yields. As for the hydantoin-forming cascade, more complex molecules can be accessed as illustrated by the synthesis of the azumolene derivative **3.57** in good yield. To study the effect of steric hindrance, different ketocarbazone precursors were tested and no drastic effect was found. The thiophene ketone-based carbazone **3.58** yielded the desired heterocycle in excellent yield, similar to the yield of its aldehyde-based analog (**3.55**). Acetophenone- (**3.59**) and fluorenone- (**3.60**) based ketocarbazones also yielded the corresponding imidazolones in good yields. Finally, an electron-poor ketocarbazone (**3.61**) also resulted in the desired compound in high yield. We were also pleased to see that aliphatic iminoisocyanates (**3.62**) were competent reaction partners, as illustrated by the formation of a cyclohexyl-substituted imidazolone.

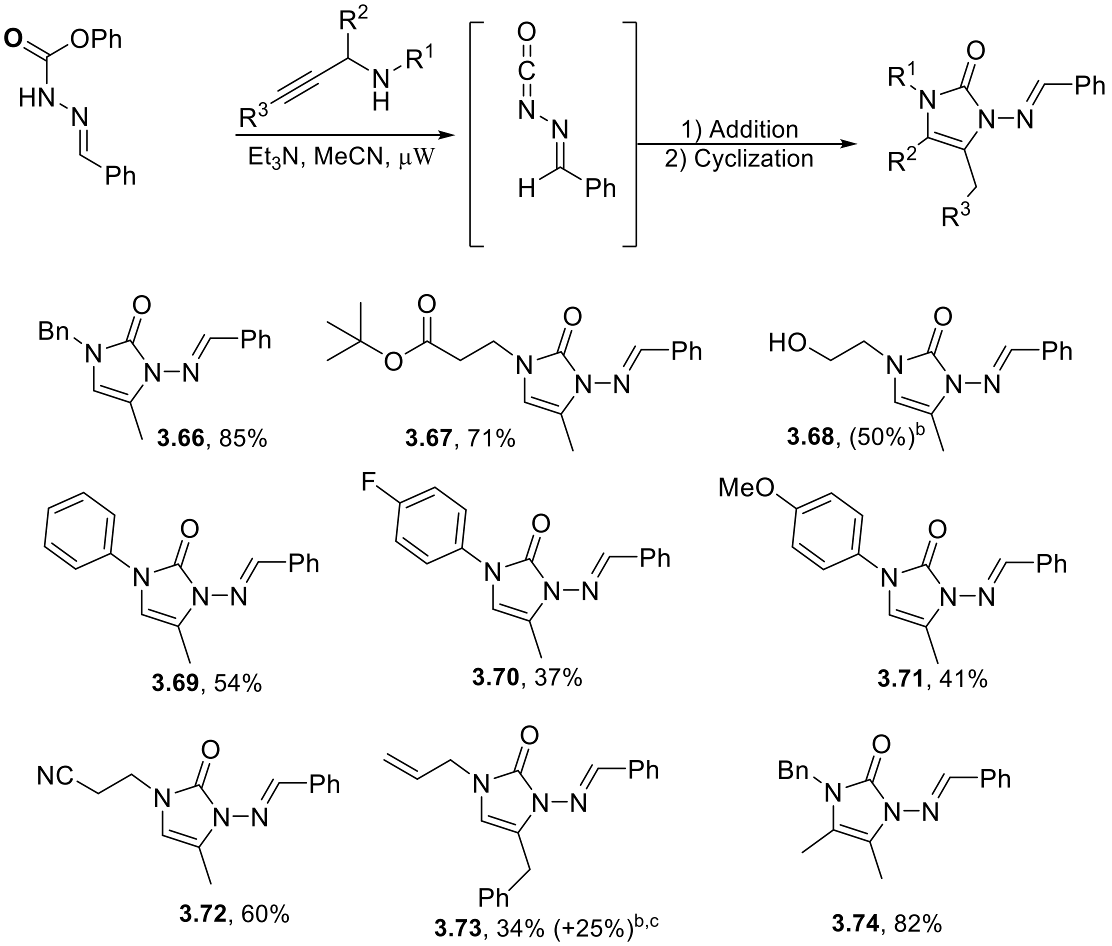
Different *N*-isothiocyanate precursors were then surveyed. While testing the fluorenone substrate that was used for the hydantoin synthesis, we were surprised to see no internal alkene (**3.63**) in contrast to 37% in eq. 3.5. Given the crystallinity of the corresponding heterocycle, X-ray analysis was performed to confirm the structure of our product. This structure clearly showed that the sulphur atom was participating in the cyclization and confirmed the presence of the exocyclic alkene.



Scheme 3.12: X-Ray of Compound 3.63

Similar reactivity was also observed with acetone-derived thiosemicarbazone (**3.64**), resulting in the exocyclic alkene in excellent yield. We then thought that the isomerization process was likely common to aldehyde-derived *N*-isothiocyanates, but compound **3.65** was obtained as the sole product from the same reaction conditions. It is still unclear what drives the isomerization in the case of *N*-isothiocyanates, but using conditions and substrates to suppress isomerization completely allowed for a selective transformation. The scope of different propargylic amines with the benzaldehyde-derived iminoisocyanate precursor and the fluorenone-derived iminoisothiocyanate precursor was then studied. The possibility of synthesizing these two compounds on a multi-gram scale without the use of column chromatography facilitated these studies. These results are displayed in Tables 3.7 and 3.8.

Table 3.7: Divergent Synthesis Using *N*-Isocyanate Precursor[a]

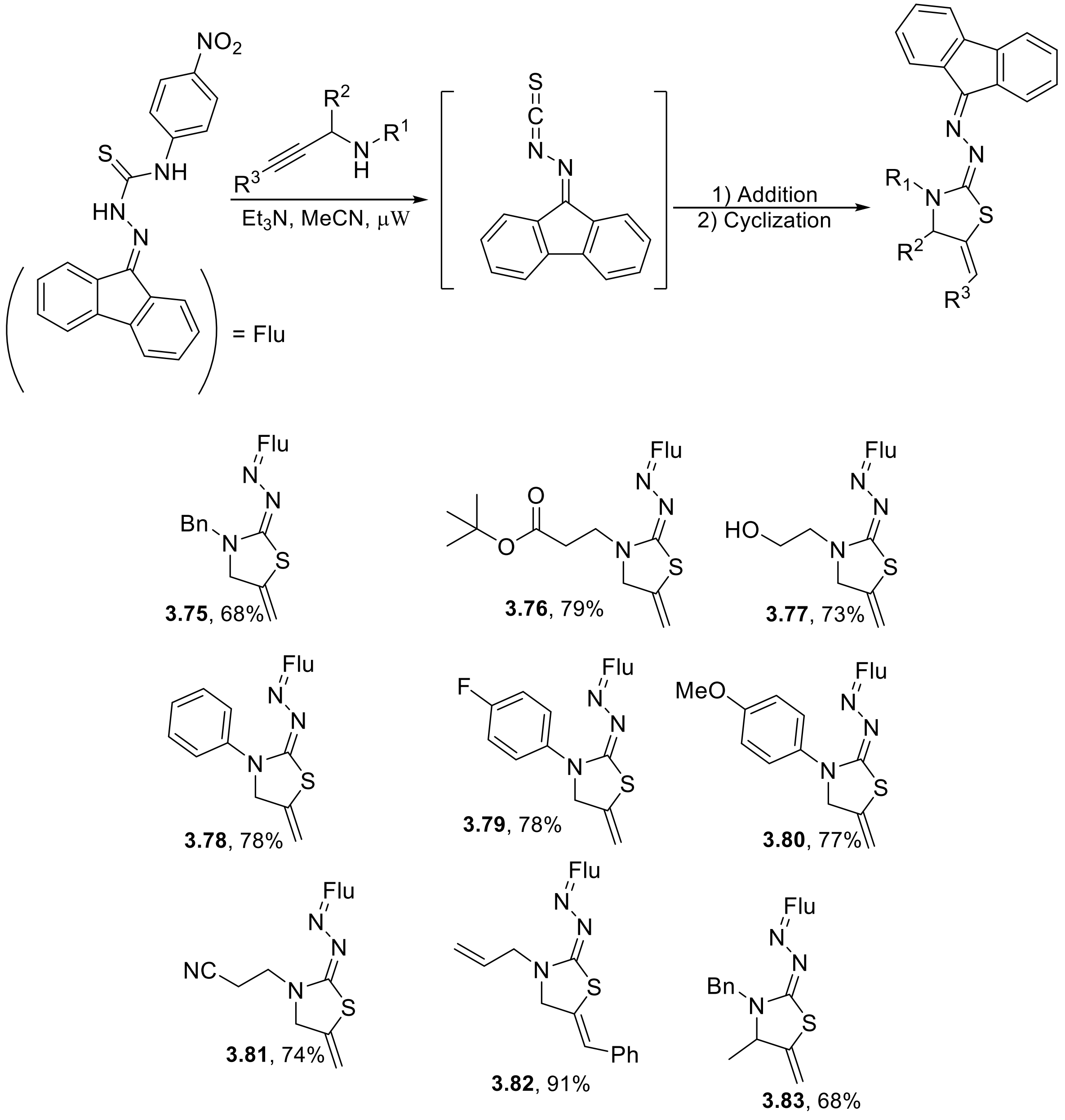


3.66, 85%
3.67, 71%
3.68, (50%)[b]
3.69, 54%
3.70, 37%
3.71, 41%
3.72, 60%
3.73, 34% (+25%)[b,c]
3.74, 82%

[a]Conditions: Carbazone (1.0 equiv), propargylic amines (1.1 equiv), Et$_3$N (20 mol %) and MeCN (0.3 M) were added to an oven-dried microwave vial heated in oil bath or microwave (μW) reactor at 100 °C. [b]Based on NMR yield [c]Yield for product with an exocyclic alkene.

As shown above, the reaction using *N*-isocyanates seems to be more variable (yields: 34-85%) than the reaction with *N*-isothiocyanates (yields: 68-91%). For the *N*-isocyanate precursor, *N*-benzyl propargyl amine was well tolerated yielding the desired heterocycle (**3.66**) in 85% yield. A *tert*-butyl ester (**3.67**) and a nitrile (**3.72**) were tolerated in the reaction conditions and yielded the imidazolones in good yields. A free hydroxyl group was partially tolerated yielding the sensitive heterocycle **3.68** in modest yield. Different propargylic anilines were then surveyed. No electronic trends were observed, but aniline- (**3.69**), 4-fluoroaniline- (**3.70**), and 4-methoxyaniline- (**3.71)** derived propargylic substrates all yielded the desired heterocycles in low to modest yields. Finally, a non-terminal (**3.73**) alkyne was also tolerated, but partially prevented the isomerization with 25% of exocyclic alkenes observed by NMR. A methyl group on the propargylic carbon (**3.74**) was a competent reaction partner yielding the desired imidazolone in good yield. The results for the reactions involving *N*-isothiocyanates proved completely different. Indeed, similar yields were obtained for most propargylic amines surveyed.

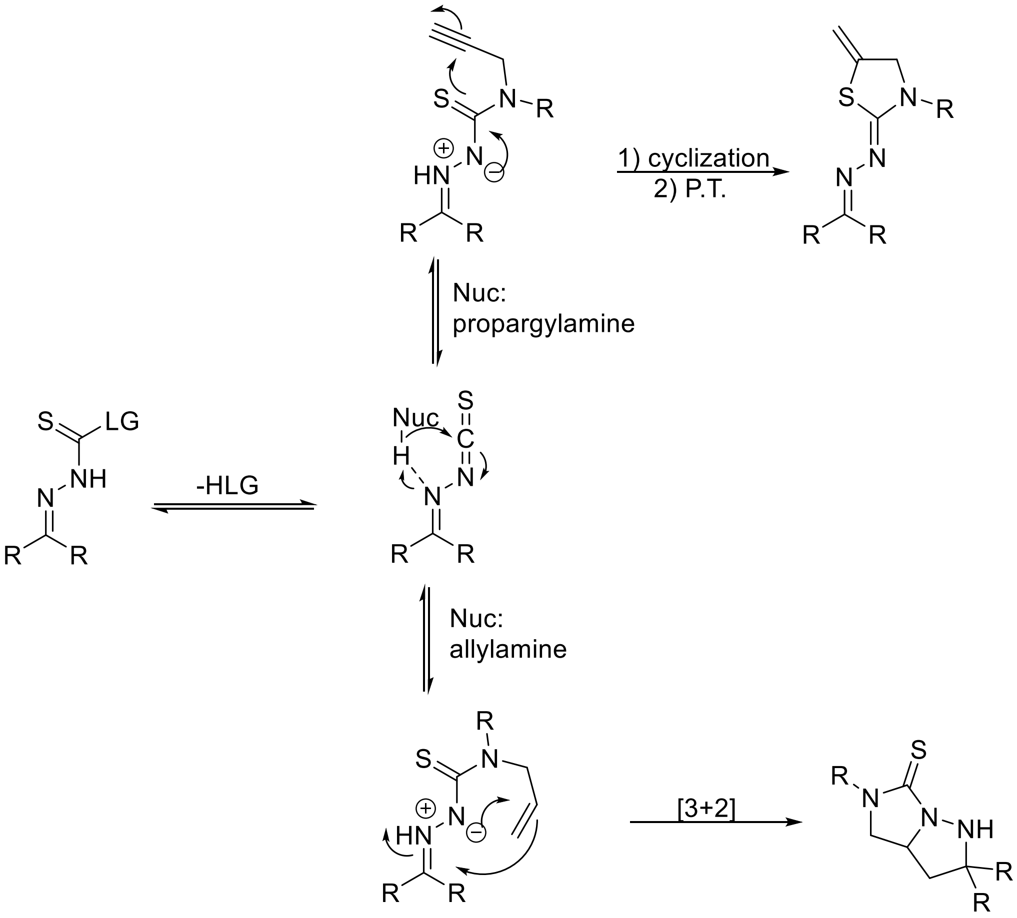
Table 3.8: Divergent Synthesis Using *N*-isothiocyanate Precursor[a]



3.75, 68%
3.76, 79%
3.77, 73%
3.78, 78%
3.79, 78%
3.80, 77%
3.81, 74%
3.82, 91%
3.83, 68%

[a]Conditions: Carbazone (1.0 equiv), propargylic amines (1.1 equiv), Et_{3N} (20 mol%) and MeCN (0.3 M) were added to an oven-dried microwave vial heated in oil bath or microwave (μW) reactor at 120°C.

The enhanced nucleophilicity and the non-reversibility of the reaction likely had an impact on the product formation compared to the *N*-isocyanates. Amines possessing an *N*-benzyl group (**3.75)**, an ester group (**3.76**), a nitrile (**3.81**), and a free hydroxyl group (**3.77**) all yielded the desired heterocycles in good yields. The aniline derivatives were also quite different in their reactions with *N*-isothiocyanates compared to *N*-isocyanates. The three electronically-different anilines (**3.78**, **3.79**, **3.80**) yielded the corresponding thiazolines in 77-78% yields. Overall, these observations suggest that the cyclization of the thiolate on the alkyne is more facile and accounts for the increased efficiency of the cascades involving *N*-isothiocyanates compared to *N*-isocyanates. Finally, a non-terminal alkyne (**3.82**) also yielded the desired heterocycle in excellent yield as only one isomer, which was verified by NOE analysis and previous, similar cyclization.[94] Finally, a methyl group on the propargylic carbon (**3.83)** is also tolerated. Overall, the data presented in Tables 3.7 and 3.8 shows a striking difference between the reactivity of *N*-isothiocyanates and *N*-isocyanates. Given the high nucleophilicity of *N*-isothiocyanates, we wondered if these derivatives would react with non-activated π-systems such as allyl amines. To test this hypothesis, the fluorenone-derived *N*-isothiocyanate was subjected to the same reaction conditions with diallylamine. We quickly discovered that a reaction was occurring and was optimal without the use of catalytic base and at 150 °C; however, hydrothiolation was not observed and the product of an intramolecular cycloaddition was obtained. A common azomethine imine was proposed for both pathways using *N*-isothiocyanates (Scheme 3.13).



Scheme 3.13: Different Reactivity of Propagylic and Allylic Amines

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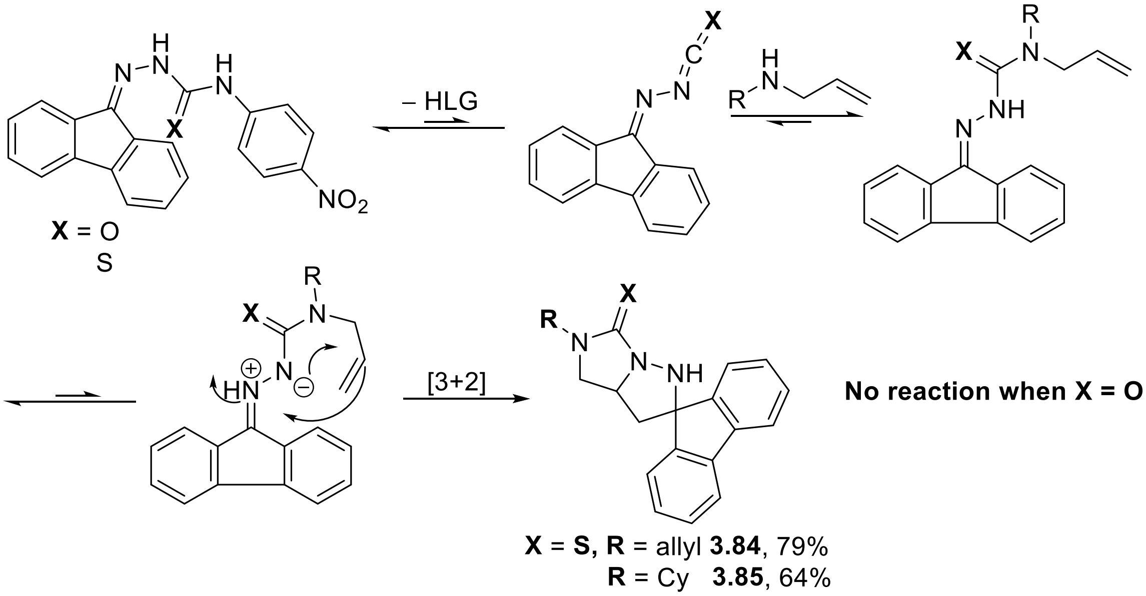
[94] Novikov, R. V.; Danilkina, N. A.; Balova, I. A. *Chem. Heterocycl. Compd*. **2011**, *47*, 758.

Since the alkene is not activated enough to act as an electrophile for a cyclization, the cycloaddition pathway is possible and yielded the new heterocyclic system. It was demonstrated that this reaction proceeds efficiently with both diallylamine and *N*-allyl-cyclohexylamine (Scheme 3.14). In the latter case however, four hours were necessary instead of two, most likely due to conformational preferences. The difference of reactivity was striking since the *N*-isocyanate precursor yielded no product most likely due to the increase stability of sulphur based azomethine imines. This new reactivity offers a good alternative to Overman's pioneering work on the *in situ* generation of similar (thiocarbonyl-substituted) azomethine imines.[95]



Scheme 3.14: Novel *In-Situ* Generation of Azomethine Imines

In summary, this study showed the requirement for studying differences in reactivity of reactive intermediates.[96] The expected differences in reactivity gave rise to the rapid synthesis of two different heterocyclic classes, but an unexpected pathway was discovered while using allylic amines with *N*-isothiocyanates. Moreover, it showed the potential of π-systems as reactive partners for the development of cascade reactions. Since the alkyne was part of an external molecule, we wondered if the alkyne could be on the substrate itself, thus allowing for different products to be formed.

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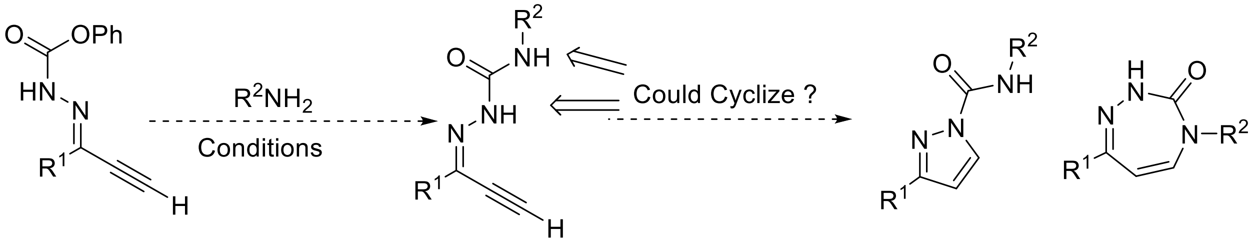
[95] For cycloaddition or related azomethine imines see: (a) Gergely, J.; Morgan, J. B.; Overman, L. E. *J. Org. Chem.* **2006**, *71*, 9144. (b) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159. (c) Katz, J. D.; Overman, L. E. *Tetrahedron* **2004**, *60*, 9559. (d) Bélanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Org. Chem.* **2002**, *67*, 7880.

[96] Vincent-Rocan, J.-F.; Derasp, J. S.; Beauchemin, A. M. *Chem. Commun.* **2015**, *51*, 16405.

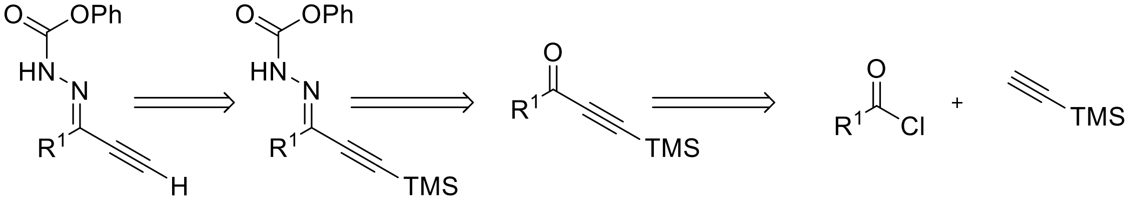
3.3: Diversity-Oriented Synthesis of Acyl Pyrazoles using *N*-Isocyanates

As mentioned in the previous section, the alkyne counterpart was identified as a good electrophilic partner for the development of cascade reactions using *N*-isocyanates. To enhance the chance of developing a successful system, in collaboration with Ryan Ivanovich (an undergraduate student under my supervision at the time), a substrate that could lead to two different and interesting heterocycles was designed (Scheme 3.15). Indeed, using the unsaturated alkynylcarbazone, two different cyclization pathways could operate to yield either the 5- or 7-membered rings. In the following section, Ryan's work will be described. However, it is important to mention that the entire project was based on my own design.



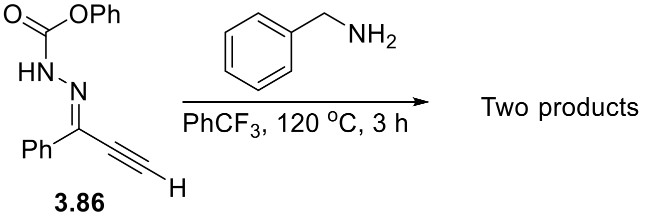
Scheme 3.15: Possible Products from Unsaturated Alkynes

To test this hypothesis, a rapid synthesis to generate the starting material was needed. Given the versatility of Sonogashira coupling reactions of acyl chlorides, we decided to proceed with a sequence of cross-coupling, condensation, and deprotection as shown in Scheme 3.16.



Scheme 3.16: Retrosynthetic Analysis for the Synthesis of Unsaturated Alkynes

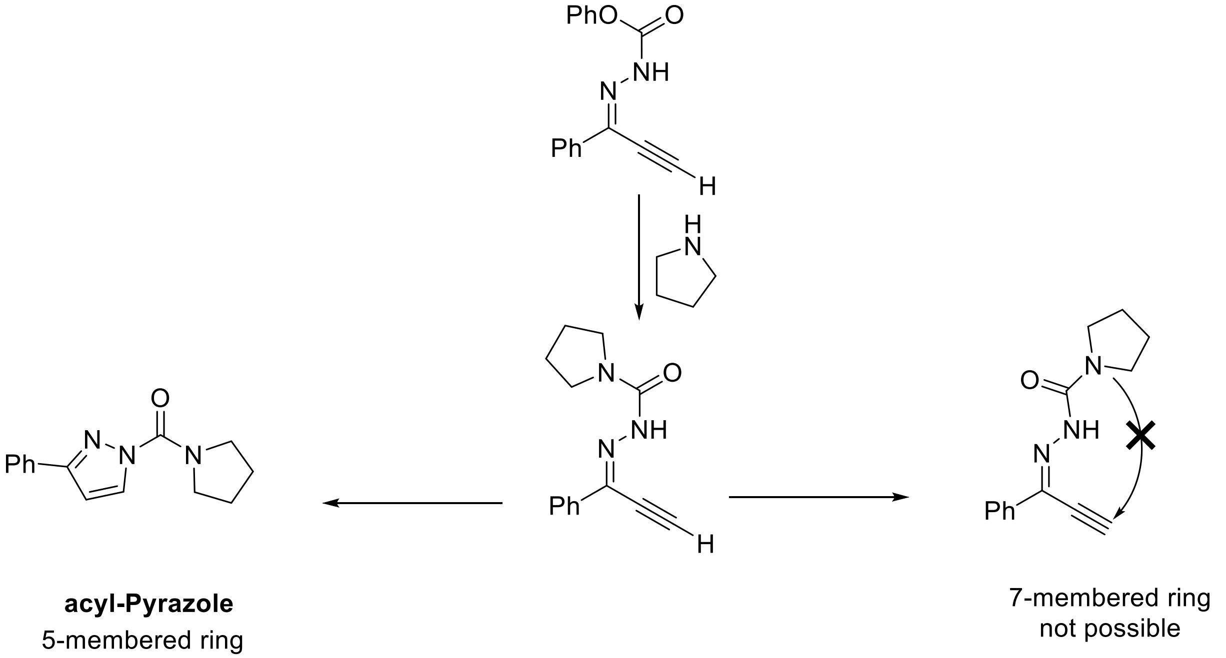
To validate this synthetic hypothesis, the reaction was tested with benzylamine and the starting material **3.86** (eq. 3.7).



3.86

(3.7)

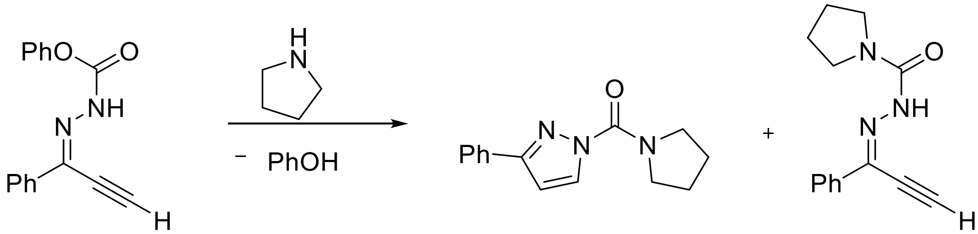
When the substrate **3.86** was subjected to the reaction conditions in $PhCF_3$ at 120 °C for 3 hours, two sets of different doublets were observed in the NMR spectrum. Each doublet could represent either the 5- or 7-membered rings. In order to get a better picture of this, the substitution product was isolated and the subsequent cyclization was optimized. To isolate the intermediate, **3.86** was subjected to benzylamine at 50 °C in the presence of DBU (10 mol %). Surprisingly, under these mild conditions, the substitution product did cyclize but only formed one of the products; however, both of these possible structures were unprecedented in the literature and it was impossible to distinguish between the two solely based on ^1H NMR. We thought that, by switching to a secondary amine, it would be possible to discriminate between the two pathways since the semi-carbazide adduct could not form the 7-membered ring (Scheme 3.17).



Scheme 3.17: Substrate Design for Pathway Discrimination

Under identical reaction conditions, a very similar set of doublets appeared which is consistent with the two pyrazole aromatic protons. At this point, we concluded that the pyrazole pathway was the only one operating. As will be discussed later, primary amines are slightly more sensitive and the second product seen in the previous reaction was a decomposition product of the pyrazole; therefore, the 7-membered ring was never obtained with this substrate. We then began a simple optimization of the conditions for the reactions of secondary amines, for which the results are presented in Table 3.9. Simply increasing the DBU loading to 20 mol % and changing the solvent to THF allowed us to achieve room temperature reactivity and isolate the acyl pyrazole **3.87** in 89% yield. Primary amines required slightly different conditions, but were also able to yield the acyl pyrazole in good yield after a short optimization of the reaction conditions (Table 3.10).

Table 3.9: Optimization of Pyrazole Synthesis Using a Secondary Amine[a]

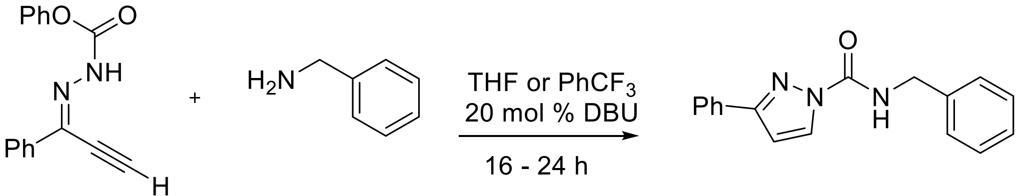


3.86 **3.87** **3.88**

Entry	Temp (°C)	Solvent	[**3.87**] %	Yield of **3.88** (%)	DBU
1	50	$PhCF_3$	59	41	10 mol%
2	50	$PhCF_3$	81	-	20 mol%
3	r.t.	$PhCF_3$	85	-	20 mol%
4	r.t.	THF	100 (89)[b]	-	20 mol%

[a]Conditions: Alkynyl carbazone (1.00 equiv), pyrrolidine (1.10 equiv) and DBU (0.1-0.2 equiv) in $PhCF_3$ or THF (0.3 M) at indicated temperature for 16 hours in a closed vial. All yields are NMR yields, taken using 1,3,5-trimethoxybenzene (TMB) as internal standard, unless otherwise indicated. [b]Isolated yield.

Table 3.10: Optimization of Pyrazole Synthesis Using a Primary Amine[a]

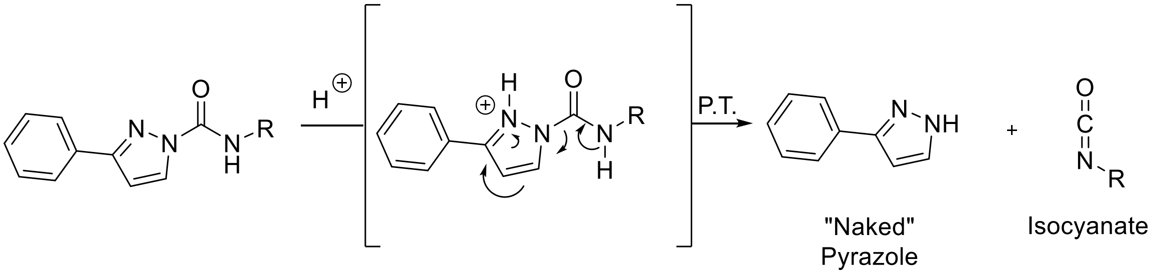


3.86 **3.89**

Entry	Temp (°C)	Time (h)	Solvent	[3.89] (%)
1	r.t.	24	THF	65
2	50	16	THF	39
3	r.t.	24	$PhCF_3$	78[b]

[a]Conditions: Alkynyl carbazone (1.00 equiv), amine (1.10 equiv) and DBU (0.20 equiv) in $PhCF_3$ or THF (0.3 M) at room temperature or 50 °C for 16 to 24 hours in a closed vial. Reactions were conducted at 0.1 mmol scale. All yields are NMR yields, taken using 1,3,5-trimethoxybenzene (TMB) as internal standard, unless otherwise indicated. [b]Isolated yield.

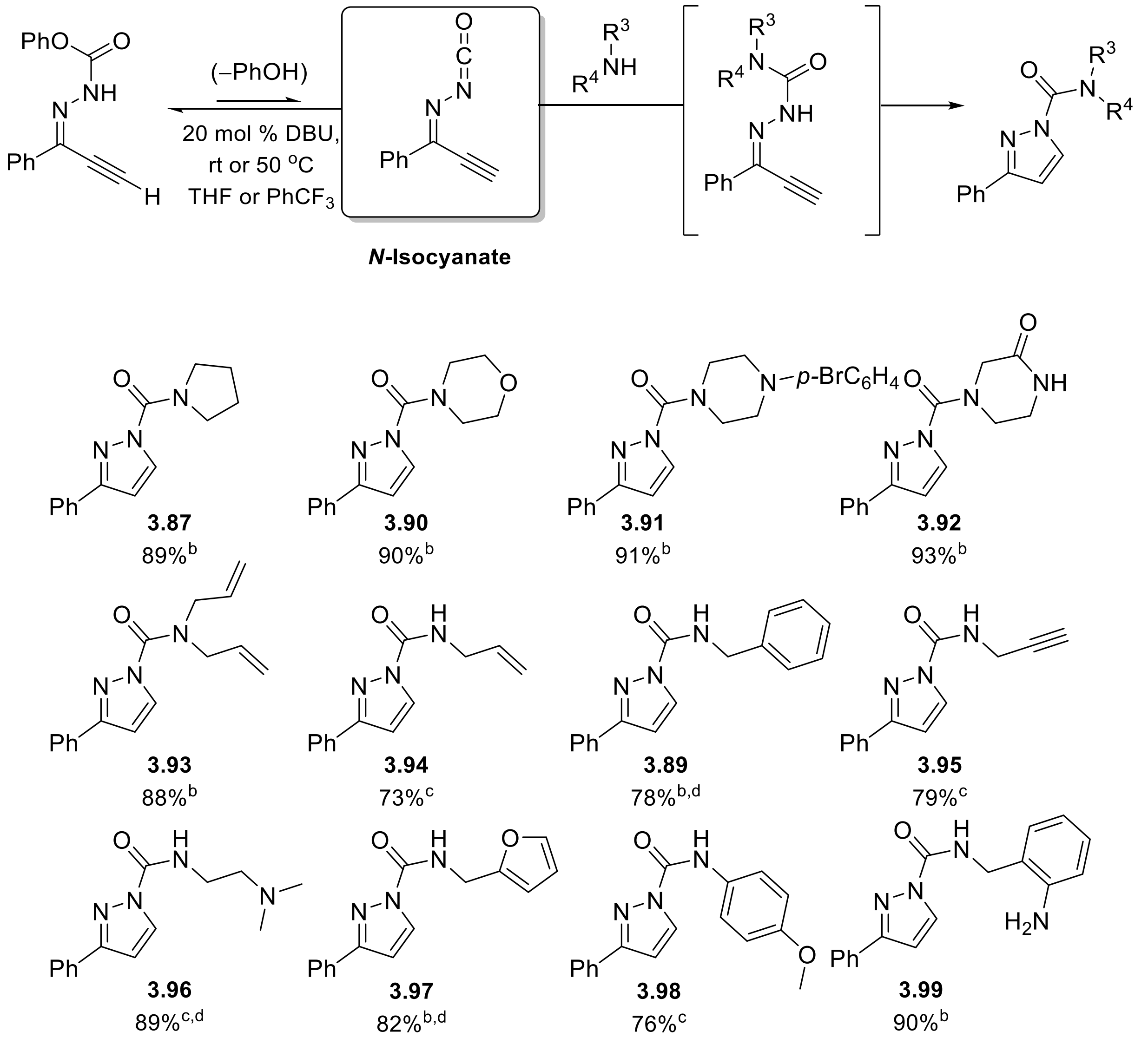
Interestingly, for the same reaction conditions as the pyrrolidine, the benzylamine product was only formed in 65% yield with a prolonged reaction time. Increasing the reaction temperature reduced the yield and the second product observed earlier became apparent. Changing the solvent to trifluorotoluene improved the yield of **3.89** to 78%, which was isolated using Et_3N-treated silica gel. The use of treated silica gel was necessary because, when purified with regular silica gel, the primary amine product **3.89** completely degraded to the other product. At this point, we knew that this second product was related to the decomposition of the acyl pyrazole, and thus the base-induced milder conditions were necessary for efficient reactions with primary amines. This observation highlights the strength of the base catalysis approach since harsher conditions would have made this project less applicable. The second product was then assigned to be the "naked" pyrazole formed by ejecting the pyrazole under thermolysis of mildly acidic conditions (Scheme 3.18). This observation is also in agreement with the use of pyrazoles as blocking groups for isocyanates as seen in Scheme 1.2.



Scheme 3.18: Decomposition Pathway Using Primary Amines

With this in mind, we started to scope the reaction using both primary and secondary amines. These results are presented in Table 3.11.

Table 3.11: Amine Scope for the Diversity-Oriented Acyl Pyrazole Synthesis[a]

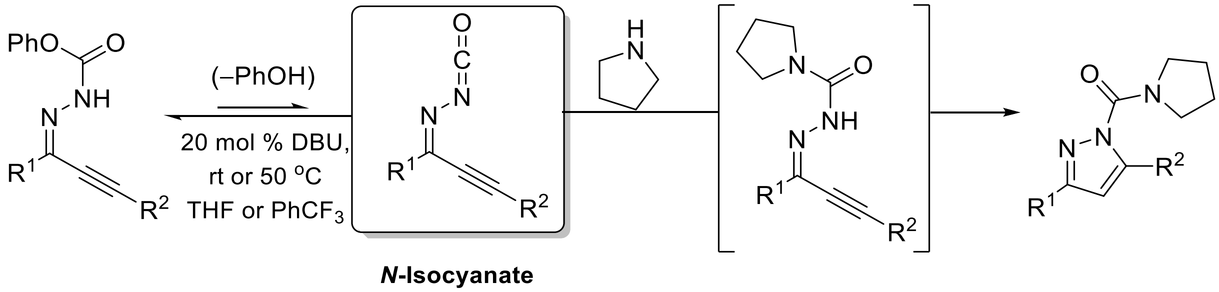


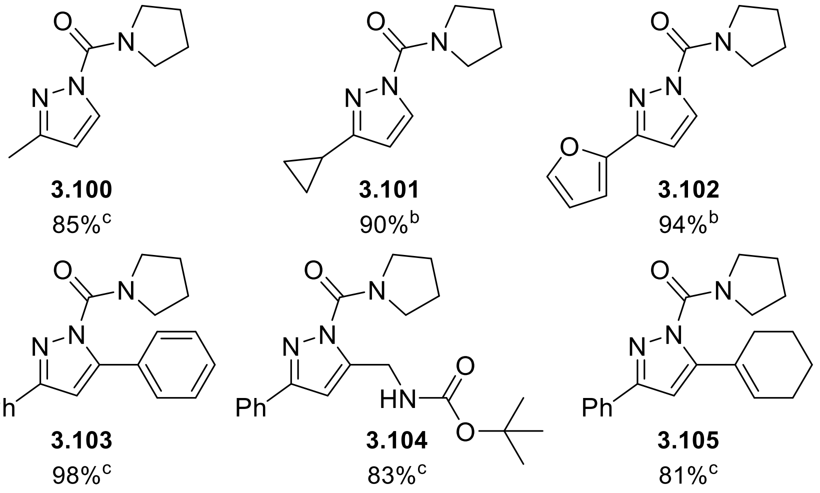
[a]Conditions: alkynyl carbazone (1 equiv), amine (1.1 equiv), DBU (20 mol %) in THF at room temperature or 50 °C for 16 h. [b]Reaction at room temperature. [c]Reaction at 50 °C. [d]Reaction conducted in $PhCF_3$.

Both primary and secondary amines with various functional groups were well tolerated in this system. Pyrrolidine (**3.87**), morpholine (**3.90**), a substituted piperazine (**3.91**), and oxo-piperazine (**3.92**) all provided the desired heterocycles in excellent yields. The presence of an aryl bromide (**3.91)** showcased the advantage of this method over a transition metal based system. The oxopiperazine (**3.92**) also showed that the system is chemoselective for the most nucleophilic nitrogen atom. A secondary acyclic amine (**3.93**) was also competent and yielded the acyl pyrazole in excellent yield. Benzylamine was optimized to react at room temperature, but it turned out to be more of an exception than the rule. Only benzylamine (**3.89**), furfuralamine (**3.97**), and *N*-benzylaniline (**3.99**) yielded the pyrazole at room temperature in good to excellent yield. Every other primary amine required a temperature of 50 °C to reach completion in 24 hours. Nevertheless, an allyl group (**3.94**), a propargyl group (**3.95**), an extra tertiary amine (**3.96**), and an aniline (**3.98**) were also tolerated in the reaction to provide the functionalized heterocycles in good to excellent yields. Overall, this mild system tolerates heterocycles, heteroatoms, allylic systems, propargylic systems, and aryl halides. The mild conditions offered by this base catalysis helped to broaden the scope of this reaction.

We then continued to explore the scope of this reaction by probing the effect of carbazone substitution with pyrrolidine as the amine source. The results are presented in Table 3.12.

Table 3.12: Carbazone Scope for the Diversity-Oriented Acyl Pyrazole Synthesis[a]



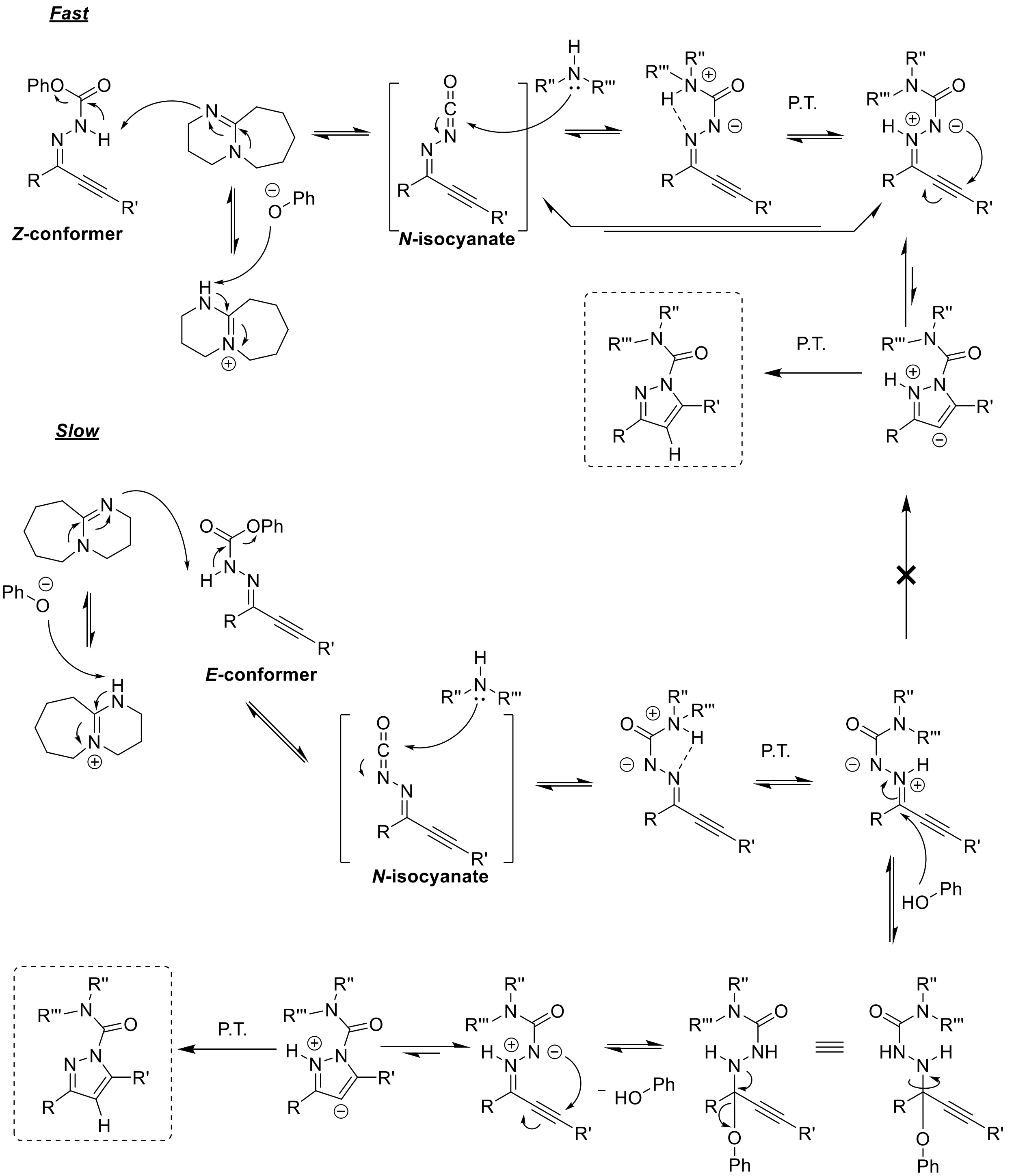


[a]Conditions: alkynyl carbazone (1 equiv), amine (1.1 equiv), DBU (20 mol %) in THF at room temperature or 50 °C for 16 h. [b]Reaction at room temperature. [c]Reaction at 50 °C.

Reducing the size of the phenyl substituent to a methyl group (**3.100**) shifted the conformational preference (see Scheme 3.19 for more details) which required an increase in the reaction temperature to 50 °C to compensate. A small increase in steric hindrance to cyclopropyl (**3.101**) or furyl (**3.102**) groups again led to room temperature reactivity and furnished the pyrazole in excellent yields. However, when the reaction was performed with internal alkynes, heating to 50 °C was again required to observe reaction completion. Encouragingly, a phenyl (**3.103**), a protected amine (**3.104**), and a 1-cyclohexenyl (**3.105**) substituent were all tolerated at this position and yielded the desired heterocycles in good to excellent yields.

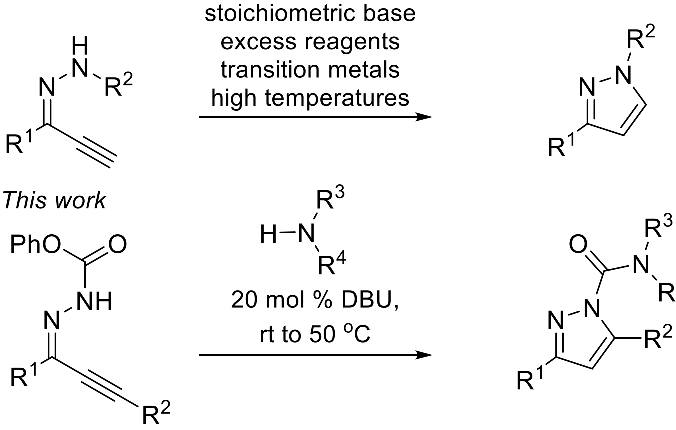
As previously mentioned, the methyl (R^1) carbazone (**3.100**) had a significant shift in configurational preference. NMR analysis of the starting material revealed a 9:1 preference for the *E*-isomer, which is not oriented to proceed with the cyclization. However a striking 85% yield was obtained, which was indicative of isomerization under the reaction conditions. It was known that this isomerization was possible at higher temperatures, but to see it at 50 °C was unexpected. We then wondered if the leaving group had any effect on the equilibrium. Since the substitution products were difficult to isolate, there was no evidence for this hypothesis. In Chapter 4 however, evidence will be presented that supports the help of the leaving group for reaction completion. Presented in Scheme 3.19 is a proposed mechanism that takes into account the phenol-induced isomerization of the hydrazone.

We believe the reaction is fast when starting with the *Z*-conformation (more present when R = phenyl) because the resulting azomethine imine is in the correct conformation to cyclize, which only requires a proton transfer to furnish the desired product. The same pathway can happen with the *E*-conformer; however, upon addition of the amine, the azomethine imine is not positioned properly to cyclize on the alkyne and thus the phenol (or a small excess of amine) can add on the azomethine imine to furnish a hemiaminal. This hemiaminal can now rotate freely. If the nitrogen expulses the phenol group while being in the pro *Z*-conformation, the resulting azomethine imine can proceed to the cyclization and form the final product.



Scheme 3.19: Mechanistic Hypothesis for the Formation of Acyl Pyrazoles

Interestingly, this process furnished acyl pyrazoles that are less common in the literature, but are present in bioactive compounds (e.g., in the core of the agrochemical Dimetilan) and are used in catalysis.[97,98]



Scheme 3.20: Comparison of Pyrazole Synthesis Using Hydrazone Derivatives[98]

This straightforward approach could therefore represent an interesting alternative for chemists to synthesize these rare pyrazoles. Moreover, this work represents a mild and broadly applicable pyrazole synthesis from hydrazones, since most methods use excess reagents, excess bases, or metal catalysis[99] (Scheme 3.20). Given the applicability of this synthesis, we decided to perform the reaction on a larger scale using a more industry-friendly solvent, 2-MeTHF (eq. 3.8). We were quite pleased to see that increasing the reaction scale to half of a gram and changing to this 'greener' solvent did not impact the yield of this reaction, making this acylpyrazole synthesis more practical.

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[97] For synthesis and biological activities, see: (a) Catarzi, D.; Colotta, V.; Varano, F.; Poli, D.; Squarcialupi, L.; Filacchioni, G.; Varani, K.; Vincenzi, F.; Andrea Borea, P.; Dal Ben, D.; Lambertucci, C.; Cristalli, G. *Bioorg. Med. Chem.* **2013**, *21*, 283. (b) Cheng, C. C.; Elslager, E. F.; Werbel, L. M.; Priebe, S. R.; Leopold, W. R. *J. Med. Chem.* **1986**, *29*, 1544. (c) Wright, J. B.; Dulin, W. E.; Markillie, J. H. *J. Med. Chem.* **1964**, *7*, 102. (d) Lunt, E.; Newton, C. G.; Smith, C.; Stevens, G. P.; Stevens, M. F. G.; Straw, C. G.; Walsh, R. J. A.; Warren, P. J.; Fizames, C.; Lavelle, F.; Langdon, S. P.; Vickers, L. M. *J. Med. Chem.* **1987**, *30*, 357. (e) Schepetkin, I. A.; Khlebnikov, A. I.; Quinn, M. T. *J. Med. Chem.* **2007**, *50*, 4928.

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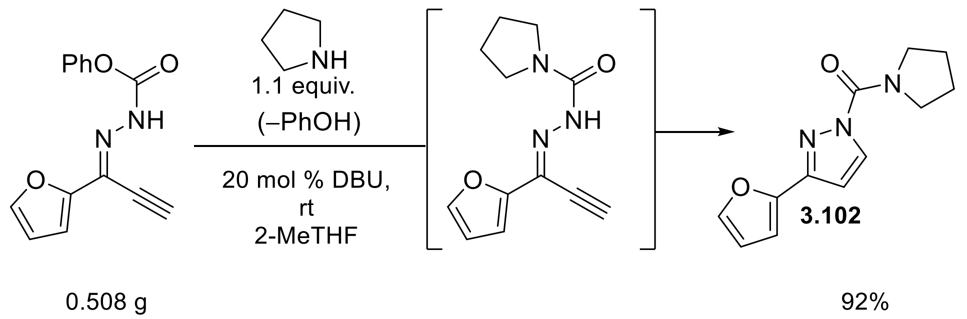

(3.8)

Overall, this study showed the potential and the need of base catalysis to develop milder syntheses based on *N*-isocyanate reactivity.[100] In this specific case, the use of a primary amine would have been impossible without the help of base catalysis that provided the *N*-isocyanate at room temperature. It also showed that configurational preference of the semicarbazone is irrelevant given that conditions are selected to allow the isomerization between the *E* and *Z* hydrazone isomers. Additionally, similarly to previous studies, it showed how we could take advantage of the α-nitrogen after a nucleophilic attack; however, only 5-membered rings have been formed thus far and the next section will show how we designed a system to access larger ring systems using the α-nitrogen as a nucleophile, as this is a strategy that has already allowed us to synthesize hydantoins, imidazolones, and pyrazoles.

3.4. Proof of Concept to Access 6-Membered Rings: Synthesis of Phthalazinones

As described previously in this thesis, the use of the α-nitrogen atom for cyclization proved to be a successful approach to access many heterocycles; however, only 5-membered rings have been obtained. To obtain a proof of concept for the formation of a 6-membered ring, we wanted to use a system that has already been proven to cyclize. To continue our work on bioactive targets, we performed a literature search to find a core that would meet these requirements. The phthalazinone core became an obvious choice given its bioactivity profile and the limited amount of synthetic pathways available.[101] In fact, synthesis of acyl phthalazinone often relied on the functionalization of the core using an isocyanate (Scheme 3.21).

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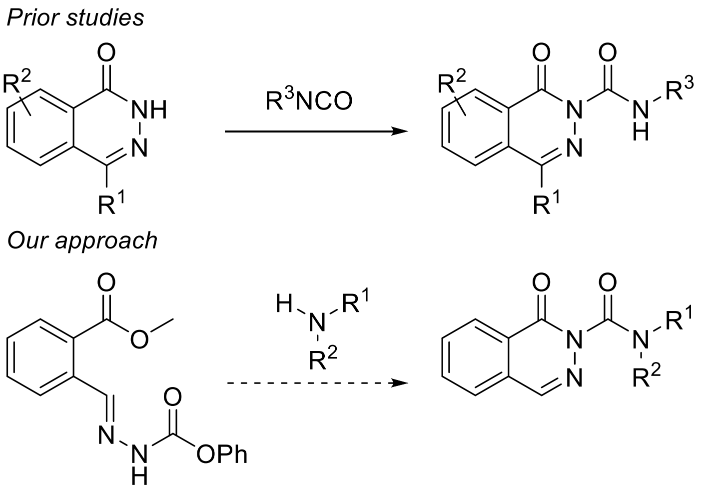
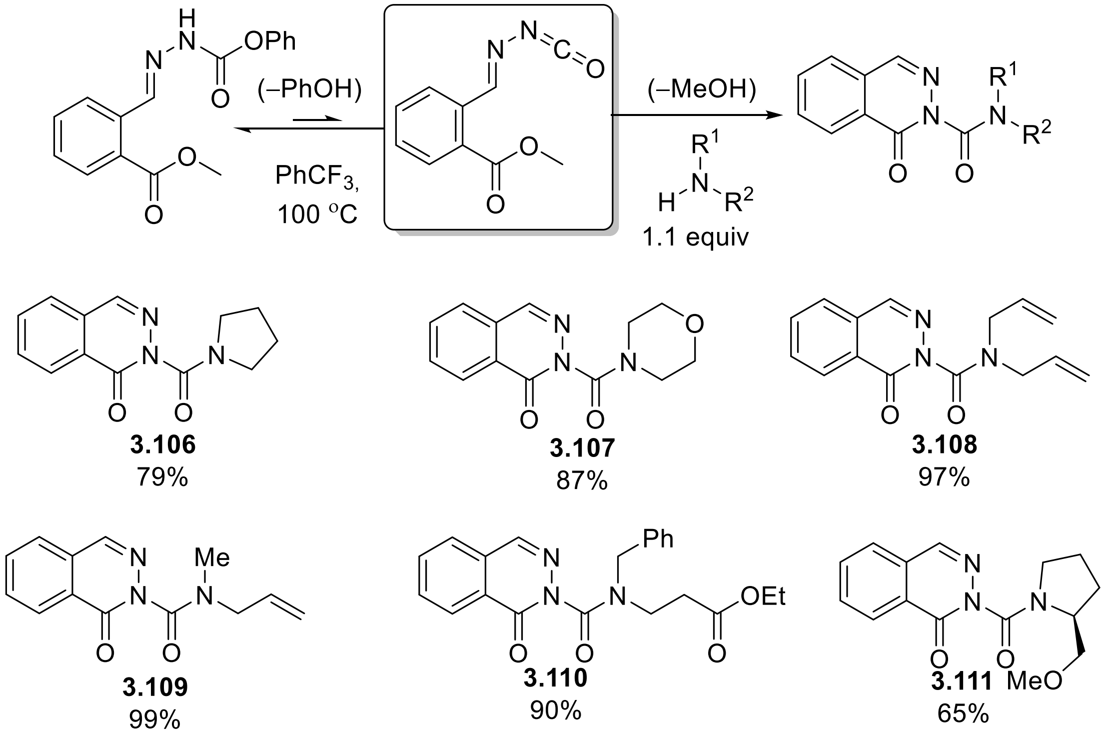


Scheme 3.21: Comparison of Existing Method vs. Aminoisocyanate Synthesis of Substituted Phthalazinones

Based on our hydantoin work, we were confident we could access the ring system by cyclization on the methyl ester. The aromaticity of the compound would be an additional driving force that was not present in the hydantoin system. This work would represent a safer alternative, given the toxicity of isocyanates, as compared to their blocked derivatives. A quick optimization of the reaction conditions showed that a temperature of 100 °C was required in $PhCF_3$ for 16 hours in order for the reaction to reach completion. The addition of a base (e.g., DBU or Et_3N) was not beneficial to the reaction, which indicated that the cyclization was more difficult than isocyanate formation in this system. Based on this, the scope of the reaction was investigated using several amines and the results are presented in Table 3.13. Secondary amines worked well in this system and typically afforded the desired heterocycle in excellent yields. Cyclic amines such as pyrrolidine (**3.106**) and morpholine (**3.107**) were tolerated and yielded the corresponding polycyclic compounds in good to excellent yields. Substituted pyrrolidine (**3.111**) was also tolerated in this system. Acyclic secondary amines required 48 hours to reach completion, but yielded the phtalazinones in almost quantitative yields. The unsymmetrical secondary amines (**3.109**, **3.110**) were obtained as a mixture of conformers, but were easily characterized by ^{1}H NMR.

Table 3.13: Phthalazinone Synthesis Using a Secondary Amine[a]

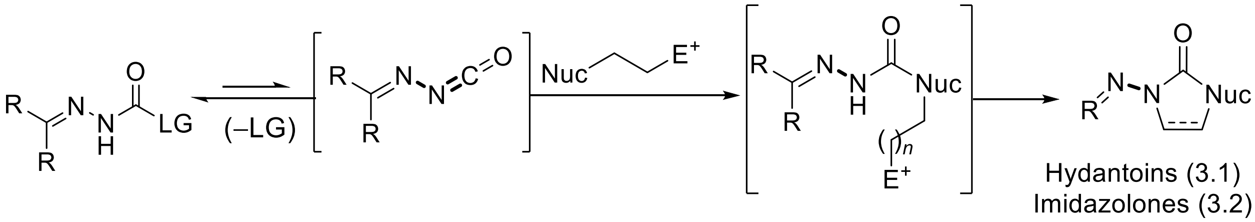


[a]Conditions: carbazone ester (1 equiv), amine (1.1 equiv) in $PhCF_3$ (0.3 M) heated in a sealed vial (oil bath, 100 °C, 18 h for cyclic amines or 48 h for acyclic amines).

Unfortunately, the use of primary amines, as for the pyrazole synthesis, yielded the "naked" phthalazinone under these conditions. The higher temperature requirement prevented us from expanding the scope of this reaction to include primary amines; however, this small scope showed the tolerance of allyl (**3.108**, **3.109)**, ester (**3.110**), and ether (**3.111**) functional groups. In addition, it gave us a proof of concept that 6-membered rings were obtainable, but that reaction optimization was needed to prevent any decomposition. The synthesis of 6-membered rings will be discussed in more detail in the next chapter.

3.5: Conclusion and Perspectives

In this Chapter, two complimentary methods using *N*-isocyanates for the rapid synthesis of a library of potentially bioactive compounds were presented. First, we observed that amphoteric *N*-isocyanates could react with other amphoteric molecules (Scheme 3.22). Using an amino ester, a library of hydantoins was synthesized using amino-, imino-, iminothio-, and amidoisocyanates. This provided the first study showing the similar reactivity of different types of *N*-isocyanates, yet allowing comparisons to be made. When using propargylic amines, we were able to synthesize imidazolones and thiazolines. In contrast to the previous work, this study was the first one comparing the *divergent* reactivity of *N*-isocyanates and *N*-isothiocyanates. Both precursors led to a rapid synthesis of these two heterocycles and highlighted the enhanced nucleophilicity of the iminothioisocyanates. This work also led to the discovery a new approach for the synthesis of complex azomethine imines.



Scheme 3.22: Reacting Two Amphoteric Reagents for the Synthesis of Heterocycles

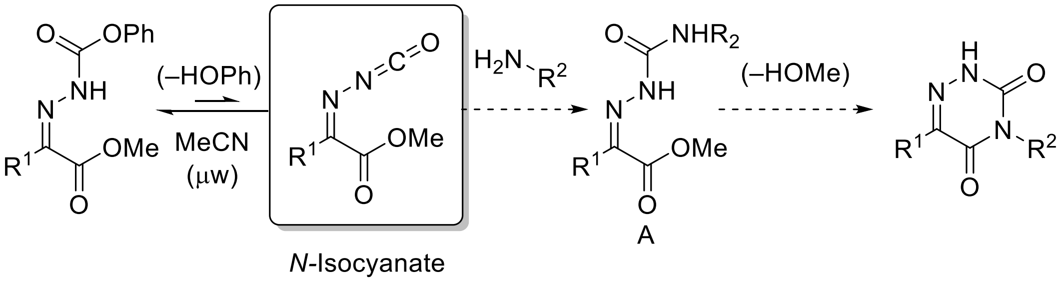
In addition, we saw that the elaboration of more complex systems could lead to the fast synthesis of heterocycles using an additional electrophile in the starting material. In Chapter 2, we used the β-nitrogen to perform the nucleophilic attack, whereas the α-nitrogen was used in this chapter.

So far, we have demonstrated the ability to increase the reactivity landscape of *N*-isocyanates to include more complex reactions other than substitution and cycloadditions. Multiple heterocycles were synthesized, but none of these examples have incorporated three atoms of the *N*-isocyanate inside a single ring system. With the information we learned about the nucleophilicity of the α- and β-nitrogen atoms and about conformational preferences, the inclusion of every atom in one heterocyclic core represented the most difficult transformation to date; our efforts targeting this will be discussed in the next Chapter.

Chapter 4: *N*-Isocyanates in Heterocyclic Chemistry: Three Atoms Within the Ring

4.1: Synthesis of Azauracils

As discussed in the previous chapter, the synthesis of heterocyclic compounds containing the 3 atoms of *N*-isocyanates represents the most difficult transformation targeted to date. However, the studies presented in previous chapters provided crucial information for the success of such approach. First, we learned that we needed to design a system where the α- and β-nitrogen atoms could not participate in a subsequent reaction. Second, we also learned aromatization was a good driving force for cyclization in the pyrazole and phthalazinone syntheses. Finally, we learned that esters are good electrophiles for a subsequent cyclization, as demonstrated by the hydantoin and phthalazinones-forming cascades. With this information in mind, the azauracils became an obvious choice, given their broad biological activities.[102] Our targeted cascade reaction is presented in eq. 4.1.



(4.1)

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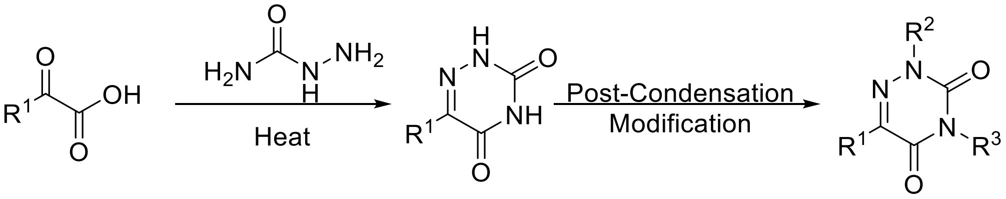
Surprisingly, despite the broad interest in unnatural DNA bases, almost no divergent syntheses were available. Most studies used alkylation of the commercially-available core to synthesize simple derivatives. This limits the diversity profile for the synthesis of azauracils since the modifications are installed on a fully synthesized core. In addition, the presence of two N-H bonds creates selectivity issues. We were confident we could achieve our synthesis since the core was synthesized using the semicarbazide-acid cyclization at a high temperature (Scheme 4.1).[103]



Scheme 4.1: Typical Azauracils Synthesis

Since simple α-ketoesters are commercially available, a simple condensation with our phenyl carbazate building block was necessary to achieve the synthesis of the desired starting material. Fortunately, cyclization started to operate at 150 °C but the optimal conditions were found to be irradiation at 175 °C for 6 hours. Given the aromatic stability of our product, these conditions did not induce any degradation and good yields were obtained. The initial scope using methyl pyruvate-derived semicarbazone is presented in Table 4.1. These reactions were tested with the help of an undergraduate student under my supervision, Julien Bejjani.

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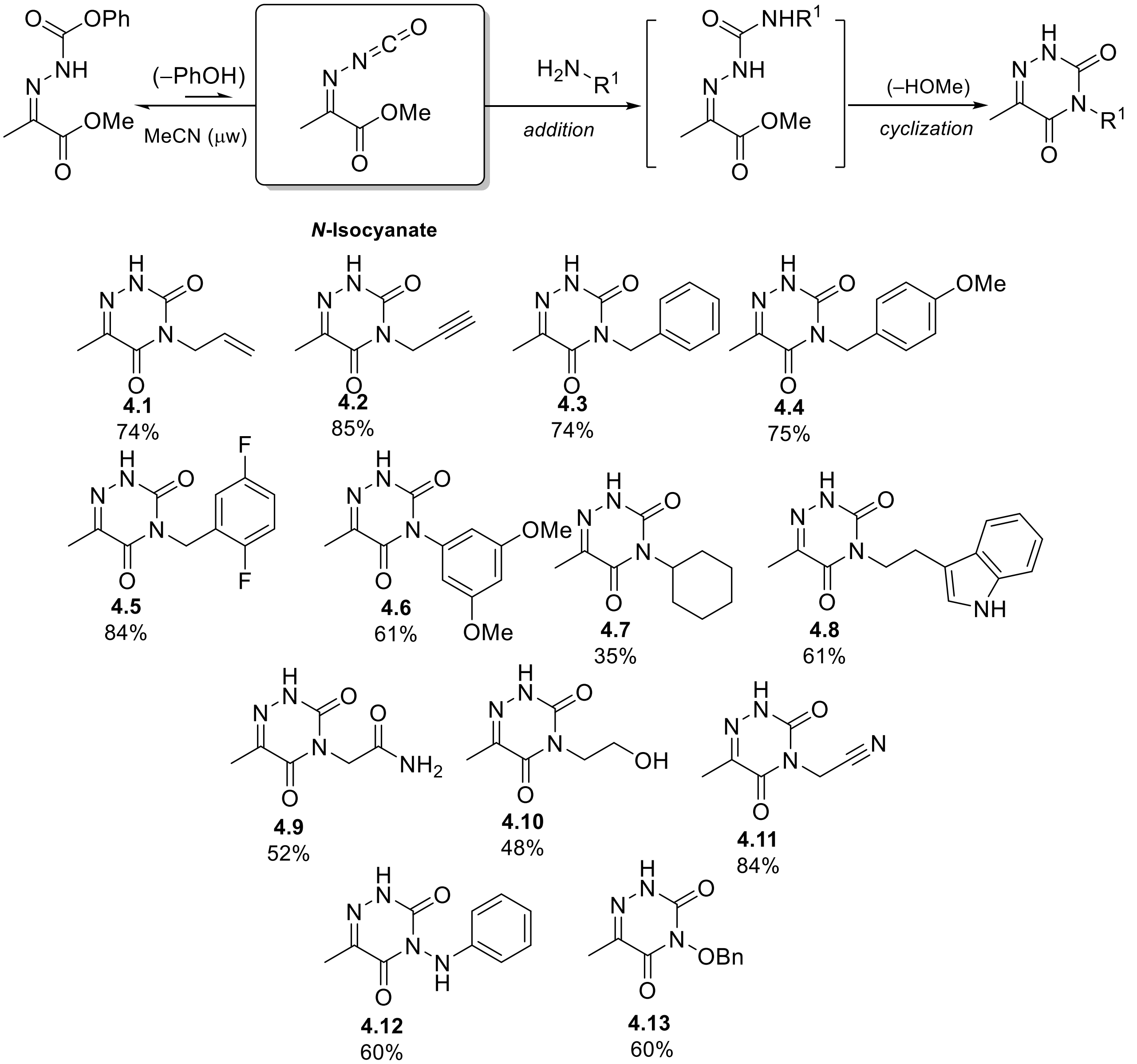
Table 4.1: Azauracil Synthesis: Amine Scope[a]



4.1 74%
4.2 85%
4.3 74%
4.4 75%
4.5 84%
4.6 61%
4.7 35%
4.8 61%
4.9 52%
4.10 48%
4.11 84%
4.12 60%
4.13 60%

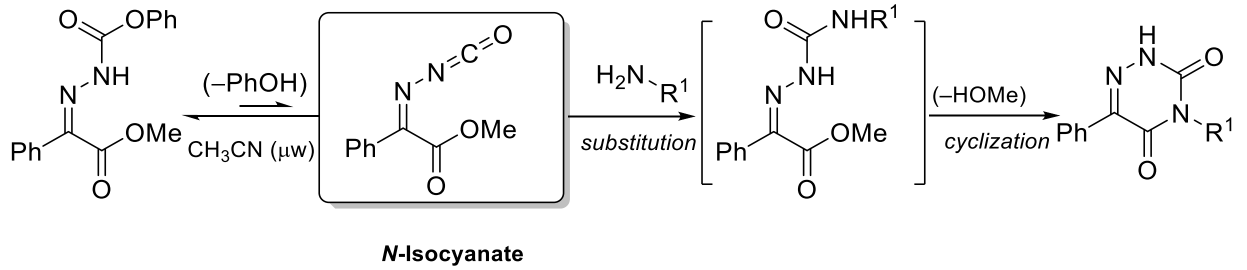
[a]Conditions: carbazone ester (1 equiv), amines (1.1 equiv) in MeCN (0.3 M) heated in a sealed vial microwave reactor, 175 °C, 6 h.

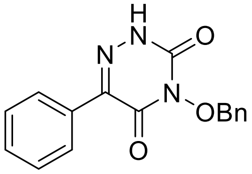
Despite the harsh conditions, this reaction proved to be broadly applicable to multiple primary amines. Simple allylic (**4.1**), propargylic (**4.2**) and benzylic (**4.3**) primary amines afforded the 6-membered heterocycle in good yields. Electron-rich (**4.4**) and poor (**4.5**) benzylic amines also reacted efficiently. An aniline (**4.6**) was also a competent reaction partner yielding the bicyclic compound in 61% yield. Bulkier amines such as cyclohexylamine (**4.7**) also reacted, but the cyclization was slower and only yielded 35% of the azauracil derivative after 6 hours. Heteroatoms are also well tolerated in this system as shown by the incorporation of an indole

(**4.8**), an amide (**4.9**), a free hydroxyl (**4.10**) and a nitrile group (**4.11**) in modest to good yields. Finally, we were also able to synthesize two azauracils with a heteroatom directly attached to the ring system. Indeed, using *O*-benzyl hydroxylamine (**4.13**) and phenyl hydrazine (**4.12**), the azauracils were obtained in 60% yield. It is important to note that 30% of uncyclized adduct was observed with the hydrazine derivative (**4.12**). The hydroxylamine adduct (**4.13**) is the first azauracil ever synthesized with an oxygen directly connected to the ring system.

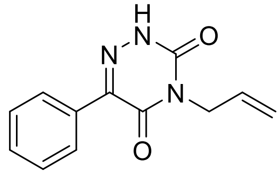
Given the absence of oxygen-substituted azauracils in the litterature, we decided to test its applicability with another carbazone ester. The comparable yield with the carbazone derived from methyl benzoylformate pushed us to explore the reaction scope of this readily available starting material. These results are presented in Table 4.2.

Table 4.2: Azauracils Scope Using Methyl Benzoylformate[a]

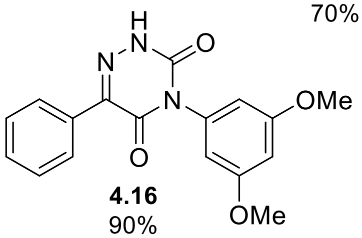




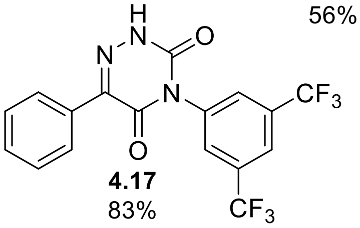
4.14
70%



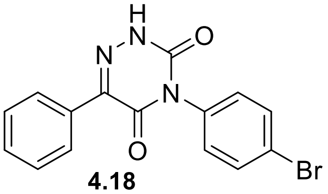
4.15
56%



4.16
90%



4.17
83%



4.18
77%

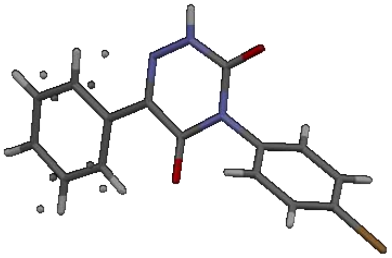
[a]Conditions: carbazone ester (1 equiv), amines (1.1 equiv) in MeCN (0.3 M) heated in a sealed vial microwave reactor, 175 °C, 6 h.

This modification was well tolerated with a range of different amines. The yield was higher using the hydroxylamine (**4.14**) but lower while using allylamine (**4.15**). While searching for difficult substrates to obtain with traditional methods, we considered that the arylation of the naked core could be quite difficult. In fact, only 9 biaryl azauracils are known in the literature.[104] Therefore, we probed the effect of aniline substitution on the reaction outcome. Electron-rich

---

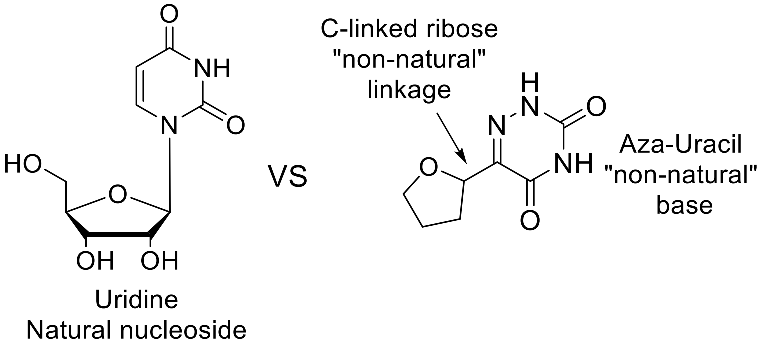
[104] To the best of our knowledge, no synthesis using arylation of the unfunctionalized core have been reported. For the synthesis of the biaryl azauracil compounds, see: (a) El-Bahaie, S. A.; Badawy, M. A.; Abdel-Hady, S. A.; Ibrahim, Y. A. *Heterocycles* **1983**, *20*, 51. (b) Ibrahim, Y. A.; Eid, M. M., Badawy, M. A.; Abdel-Hady, S. A. L. *J. Heterocycl. Chem.* **1981**, *18*, 953.

(**4.16**), electron-poor (**4.17**) and halogen-containing (**4.18**) anilines all yielded the biaryl azauracils in good to excellent yields. The crystallinity of **4.18** allowed us to obtain a crystal structure to secure the structure assignment. The X-ray structure obtained is presented in Scheme 4.2. This analysis confirmed the structure showing the extra aryl group to be perpendicular in order to accommodate the two carbonyl groups of the azauracil core.



Scheme 4.2: X-Ray Structure of 4.18

Other substituents were also considered providing an even broader scope for this cascade reaction. These results are presented in Table 4.3. We first looked at placing a THF ring at the R^1 position since it would mimic the furanose ring. The azauracils obtained would then be unnatural DNA bases linked through an unnatural nucleoside linkage (Scheme 4.3).

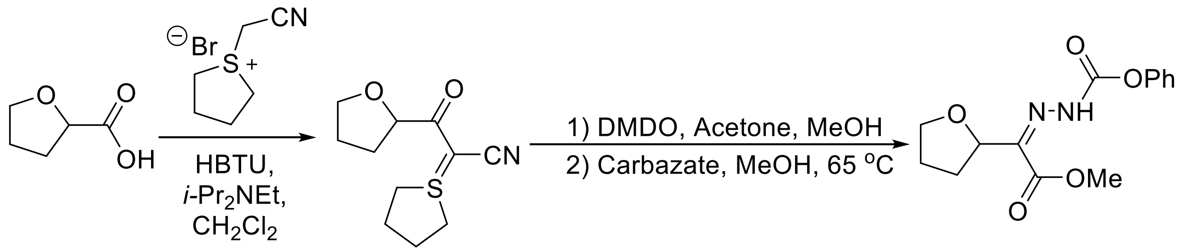


Scheme 4.3: Comparison of Natural Nucleoside with Our Synthetic Analogs

The synthesis of the starting material was not as trivial as for the other substrates. To do so, we looked at chemistry developed by the Bode group.[105] Starting from THF-2-COOH, we were able to synthesize the Bode's ylide which was then transformed into the ketoester. A condensation reaction with phenyl carbazate yielded the carbazone (Scheme 4.4).

---

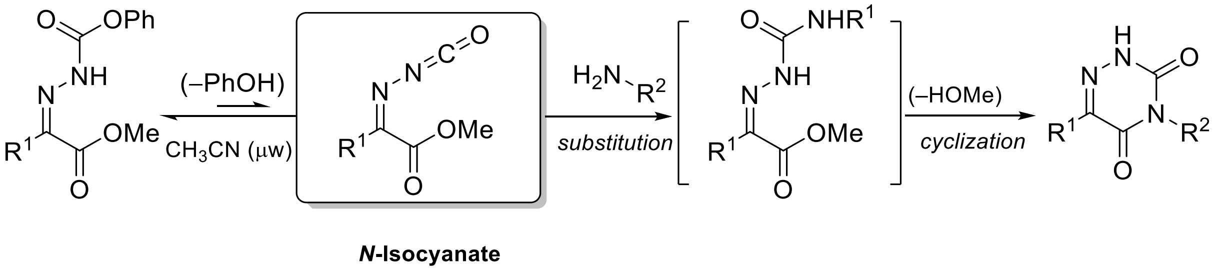
[105] Ju, L.; Lippert, A. R.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 4253.

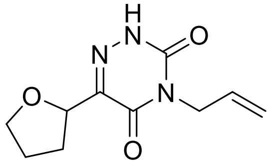


Scheme 4.4: Synthetic Sequence for the Synthesis of THF-Linked Semicarbazone

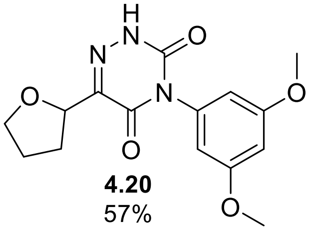
We were unable to access pure starting material but when crude material was subjected to the reaction conditions, the pure nucleoside analogues (**4.19**, **4.20**, and **4.21**) were obtained in modest but synthetically useful yields. We were also able to synthesize different azauracils bearing an ester (**4.22**), a simple hydrogen atom (**4.23**) and a thiophene (**4.24**) as side chains in good yields.

Table 4.3: Semicarbazone Scope in Azauracil Synthesis[a]

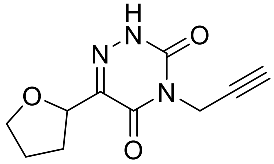




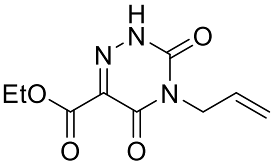
4.19
42%



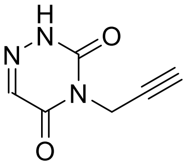
4.20
57%



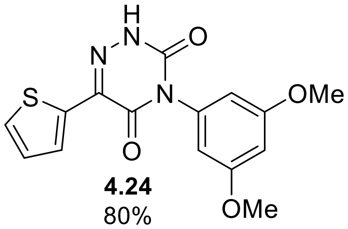
4.21
42%



4.22
64%



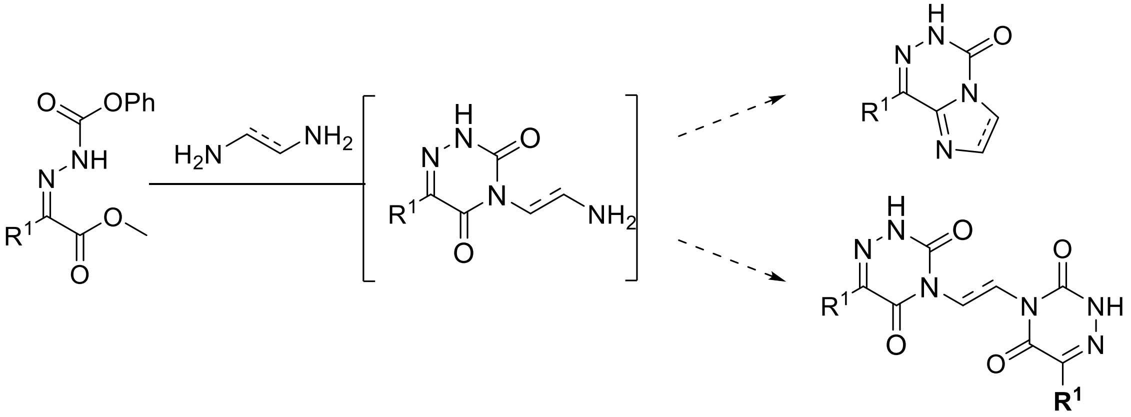
4.23
62%



4.24
80%

[a] Conditions: carbazone esters (1 equiv), amines (1.1 equiv) in MeCN (0.3 M) heated in a sealed vial microwave reactor, 175 °C, 6 h.

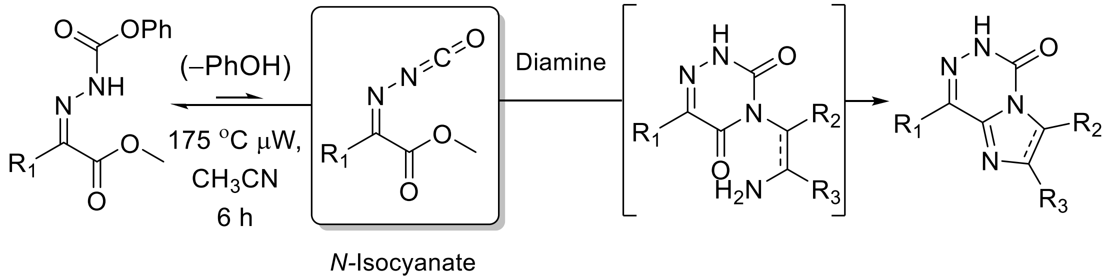
The scope of this transformation was already extensive with more than 24 entries including 6 different groups at the R^1 position and 15 different groups at R^2. Nevertheless, we were drawn to explore this reaction cascade using diamines in hopes of forming purine analogues. However, we were also aware of formation of a bis-azauracil could also occur (Scheme 4.5).

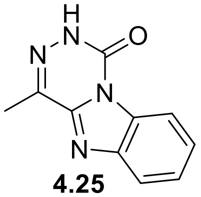


Scheme 4.5: Divergent Possibility Using Diamines

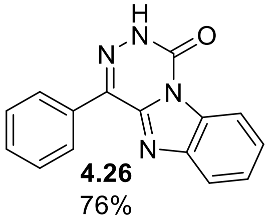
The hypothesis was tested with our first substrate and 2-aminoaniline and a product precipitated under our regular reaction conditions. We were pleased to confirm the structure of the bicyclic analog **4.25** by mass spectrometry and X-ray analysis (Scheme 4.6). We then decided to delineate the scope of this reaction, the results of which are presented in Table 4.4.

Table 4.4: Bicyclic Azauracils Using N-Isocyanates Cascade Reaction[a]

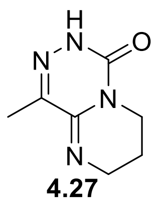




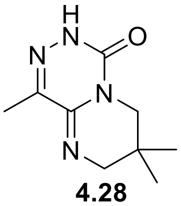
4.25
67%



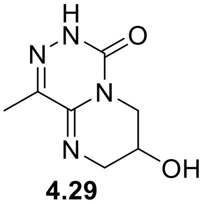
4.26
76%



4.27
64%



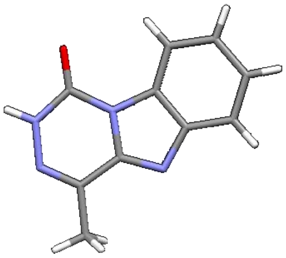
4.28
72%



4.29
55%

[a]Conditions: carbazone esters (1 equiv), amines (1.1 equiv) in MeCN (0.3 M) heated in a sealed vial microwave reactor, 175 °C, 6 h.

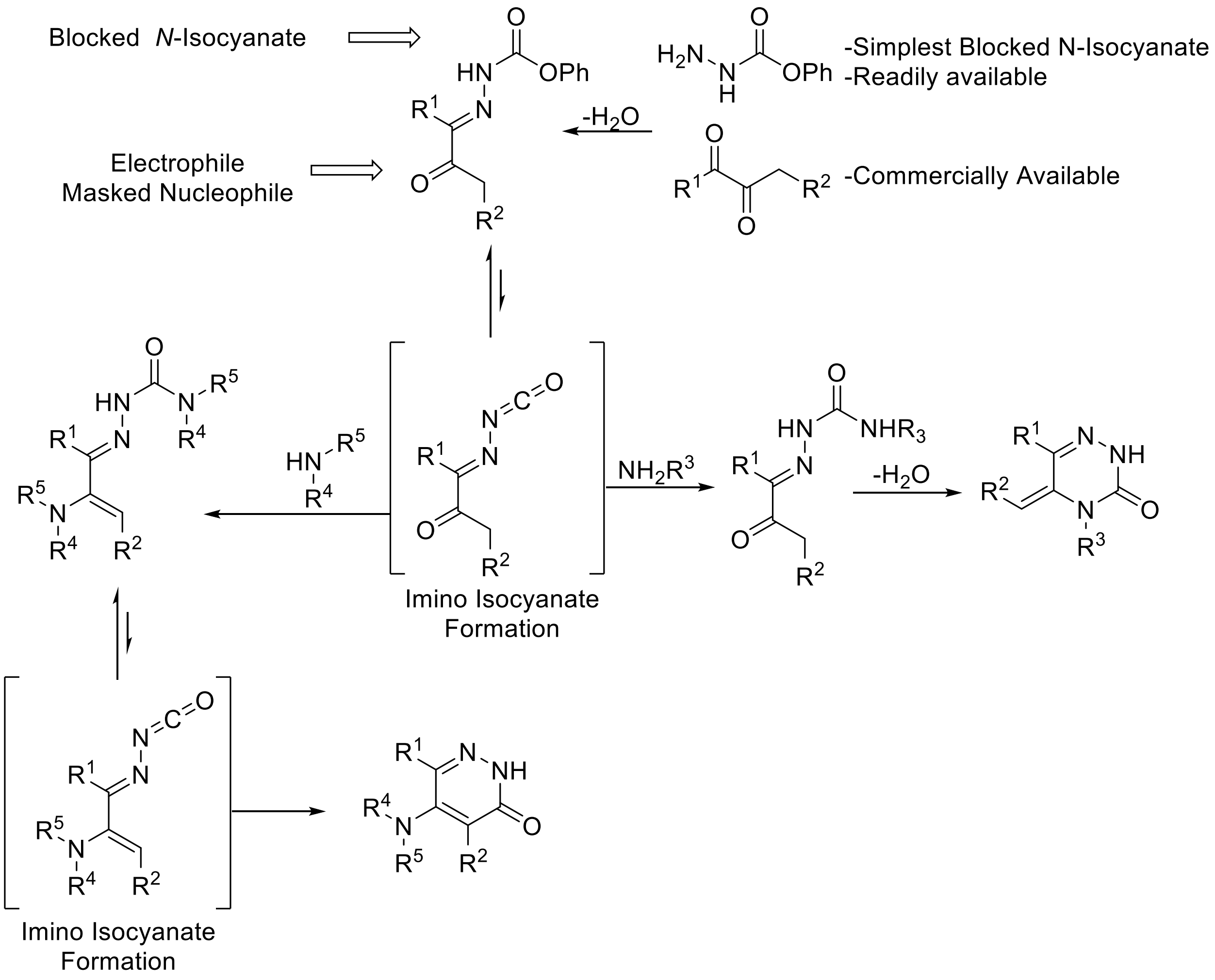
After isolation of a 67% yield of the bicycle **4.25**, the same reaction was performed with a phenyl-substituted *N*-isocyanate precursor. To our delight, the corresponding azauracil (**4.26**) was obtained in good yield. To push the methodology further, we tried the reaction with simple 1,3-diaminopropane. The reaction worked with this diamine (**4.27**), with a Thorpe-Ingold analog (**4.28**) and with a free hydroxyl group (**4.28**). To our surprise, this 6,6-bicyclic system was unknown in the literature, demonstrating the usefulness of developing simple cascade reactions using *N*-isocyanates.



Scheme 4.6: X-Ray Structure of 4.25

4.2: Divergent Synthesis Using Keto-Carbazones

With the success of this methodology, we naturally became interested in pursuing similar reactivity. We were especially interested in other systems which could lead to multiple heterocycles from a simple starting material. Given the reactivity of carbazone esters, we wondered if it would be possible to mimic their reactivity with keto-carbazones. By doing so, we thought it would be possible to generate two different heterocycles from a simple precursor. Indeed, the use of primary amines would lead to the incorporation of this nitrogen atom in the ring just like in the azauracil case (Scheme 4.7, right). However, we hoped that using secondary amines would lead to a reversible isocyanate formation and that an excess amine could help in forming an enamine, which would react with the isocyanates (Scheme 4.7, left). The reaction design is presented in Scheme 4.7.



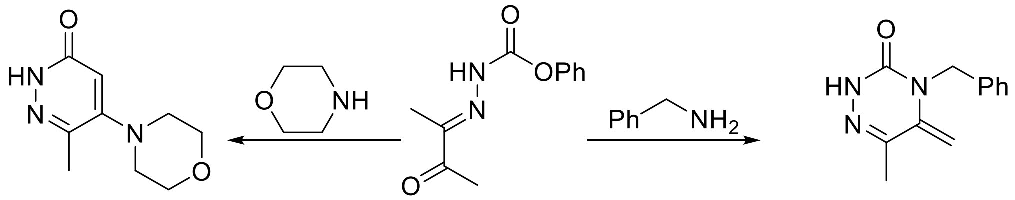
Scheme 4.7: Divergent Heterocyclic Synthesis Using Keto-Carbazones

This system is obviously different from the azauracils as the inherent instability of the exocyclic alkene could promote degradation of the product. This lability might explain the scarcity of triazinones with an exocyclic alkene in the literature.[106] Moreover, for the enamine part, we were expecting the energy requirement to have proper conformation of the enamine and the isocyanate to be quite high. However, given the low prevalence of enamine nucleophiles in *N*- and *C*-isocyanates[15,42] and the ease of access of the starting material, we were drawn into testing this system. With the help of Joshua Derasp, we started the investigation using the simple keto-carbazone derived from the symmetrical 2,3-butanedione (**4.30**, Table 4.5).

---

[106] (a) Pauldler, W. W.; Lee, J. *J. Org. Chem.* **1971**, 36, 3921. (b) Rasmussen, A.; Rise, F.; Undheim, K. *Acta Chim. Scand.* **1985**, 39b, 235. (c) Stanovnik, B.; Tisler, M.; Copar, A. *J. Heterocycl. Chem.* **1995**, *32*, 425. (d) Alekseyev, V. V.; Saminskaya, A. G.; Yakimovich, S. I. *Chem. Heterocycl. Compd. (N. Y., U. S.)* **2012**, *48*, 476.

Table 4.5: Optimization of Divergent Synthesis Using Keto-Carbazone 4.30[a]



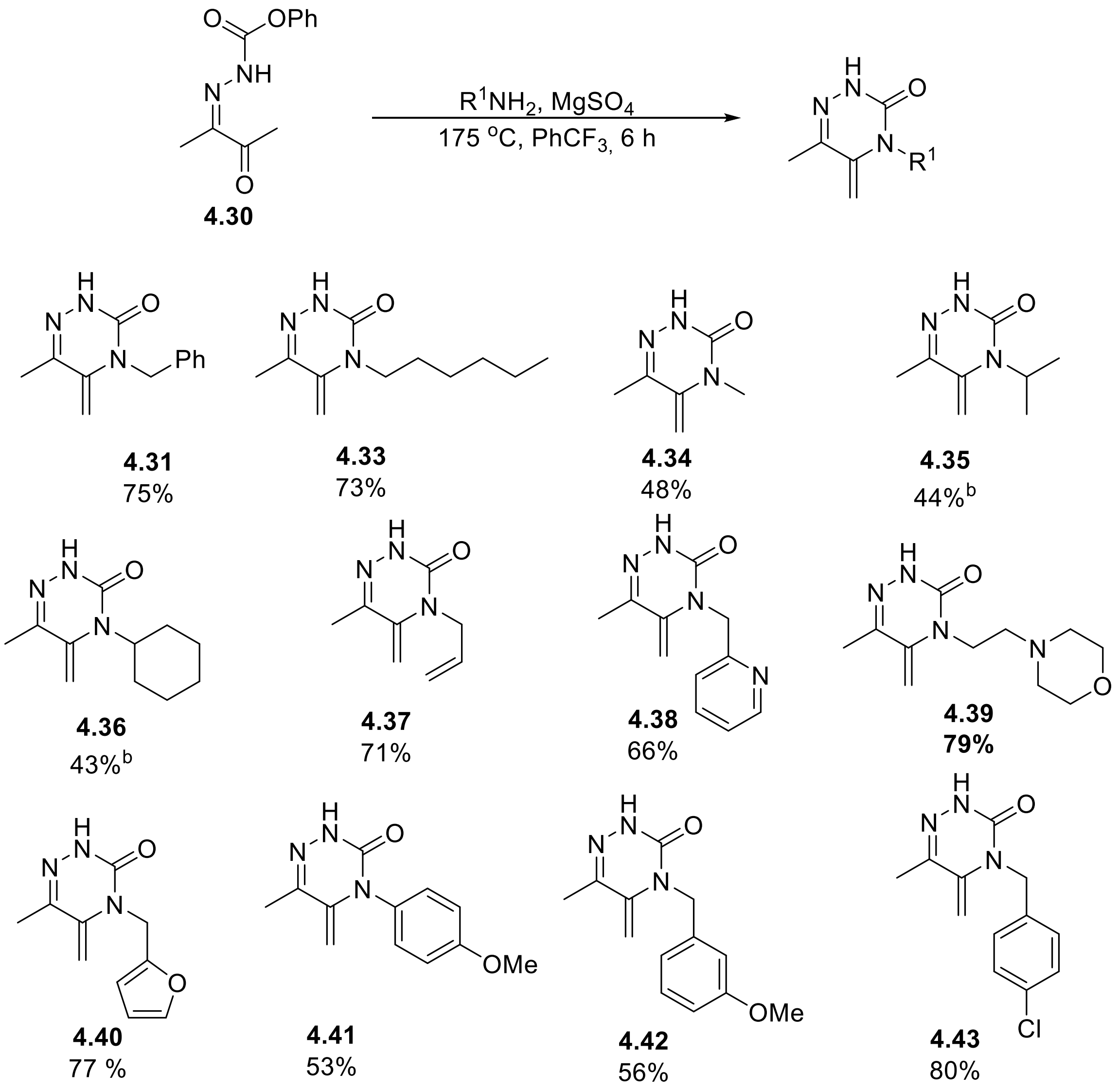
4.32 **4.30** **4.31**

Entry	Amine	Temp. (°C)	Time (h)	Additive	Yield[b] (%)
1	BnNH$_2$	150	2	None	34
2	BnNH$_2$	175	2	None	44
3	BnNH$_2$	200	2	None	37
4	BnNH$_2$	175	2	MgSO$_4$[c]	56
5	BnNH$_2$	175	2	Et$_3$N[d]	64
6	BnNH$_2$	175	2	AcOH[e]	94
7	BnNH$_2$	175	6	MgSO$_4$[c]	87
8	Morpholine	175	2	None	64
9	Morpholine	175	2	MgSO$_4$[c]	66
10	Morpholine	175	2	PivOH[f]	73
11	Morpholine	175	2	MgSO$_4$[c]+PivOH[f]	83

[a]Conditions: Carbazone (1.0 equiv), benzyl amine (1.1 equiv) in PhCF$_3$ (0.3 M) were heated in a microwave reactor. [b]Conditions: Carbazone (1.0 equiv), morpholine (3.0 equiv) in PhCF$_3$ (0.3 M) were heated in a microwave reactor. [c]Magnesium sulfate (1 equiv). [d]Triethylamine (0.2 equiv). [e]Acetic acid (0.2 equiv). [f]Pivalic acid (0.2 equiv). [g]NMR yield based on 1,3,5-trimethoxybenzene internal standard.

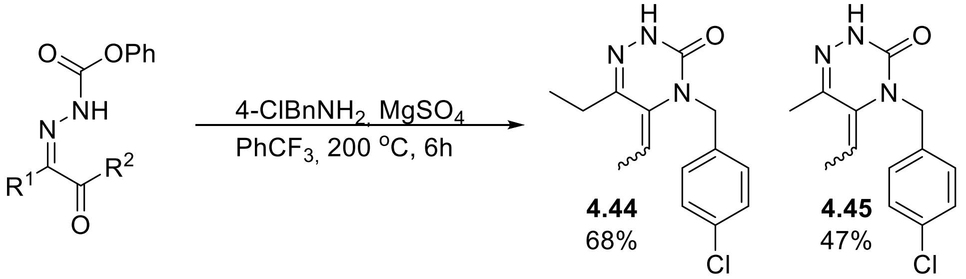
Given the higher electrophilicity of ketones (vs. esters), the optimization started (Table 4.5) at 150 °C with benzylamine which resulted in a modest 34% formation of the desired triazinone product **4.31**. The optimal temperature was found to be 175 °C and the use of additives helped this cascade reaction. Notably, acetic acid had a tremendous effect yielding the product in almost quantitative yield in only 2 hours. However, when performing the scope of the reaction, the use of acid was fairly limiting and therefore we opted for MgSO$_4$ for 6 hours as optimal conditions. Conversely, using 3 equivalents of morpholine at 175 °C for 2 hours yielded 64% of the desired compound (**4.32**). Again, the additives helped the reaction with an optimal mixture of pivalic acid and MgSO$_4$ yielding 83% of the pyridazinone **4.32**. With these optimized conditions in hand, we started to scope this reaction using keto-carbazone **4.30** and different primary amines. The results are summarized in Table 4.6. The isolated yield was lower than the NMR yield (75% of triazinone **4.31**). The difference between NMR and isolated yields most likely arose from the instability of the compound.

Table 4.6: Triazinones Synthesis : Primary Amine Scope[a]



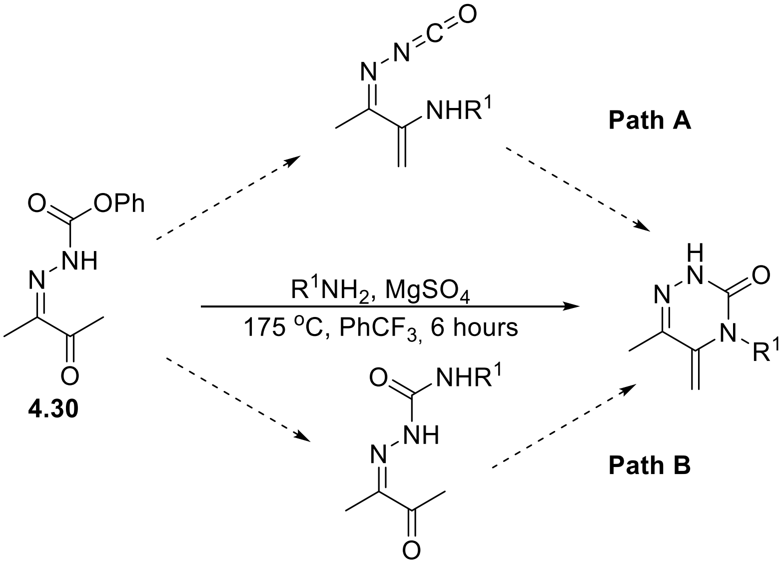
[a]Conditions: Keto-Carbazone (1 equiv), amines (1.1 equiv), $MgSO_4$ (1 equiv), in $PhCF_3$ (0.3 M) were heated in a microwave reactor for 6 hours at 175 °C. [b]Performed at 200 °C.

However, we were pleased with the isolated yield given the structure of the heterocycle bearing an exocyclic alkene. Different primary aliphatic amines also worked in this system (**4.33**, **4,34**). Bulky amines did not work as well. Under typical conditions, some isocyanate addition (uncyclized) product was still present and was inseparable from the desired heterocycle. Heating at 200°C was necessary to achieve complete cyclization. However, we found during the optimization that these conditions were detrimental to the sequence, explaining the modest yields using isopropylamine (**4.35**) and cyclohexylamine (**4.36**). Functional groups were well tolerated in the cascade reaction: allyl (**4.37**), pyridyl (**4.38**), morpholinoyl (**4.39)** and a furyl (**4.40**) groups all yielded the functionalized heterocycle in good yields. Electron-rich anilines (**4.41)** and benzylic amines (**4.42**) also worked in modest yields. Finally, an electron-poor benzylic amine yielded the pyridazinone **4.43** in 80% yield. With the applicability of primary amines, we felt that we only needed a small scope of keto-carbazones. To avoid selectivity problems during the condensation step, we decided to explore the use of diones that were known to undergo selective condensation reactions, and the results obtained from the parent *N*-isocyanate precursors are shown in Scheme 4.8. Given the extra steric hindrance, heating at 200 °C was necessary to reach reaction completion. Interestingly, only the symmetrical 3,4-hexanedione-based keto-carbazone (**4.44**) seems not to suffer from this increase in temperature with a 68% isolated yield of the desired heterocycle (1:2, *E*:*Z*). However, the other triazinone (**4.45**) seems to degrade under the reaction conditions only affording the corresponding heterocycle in modest yield.



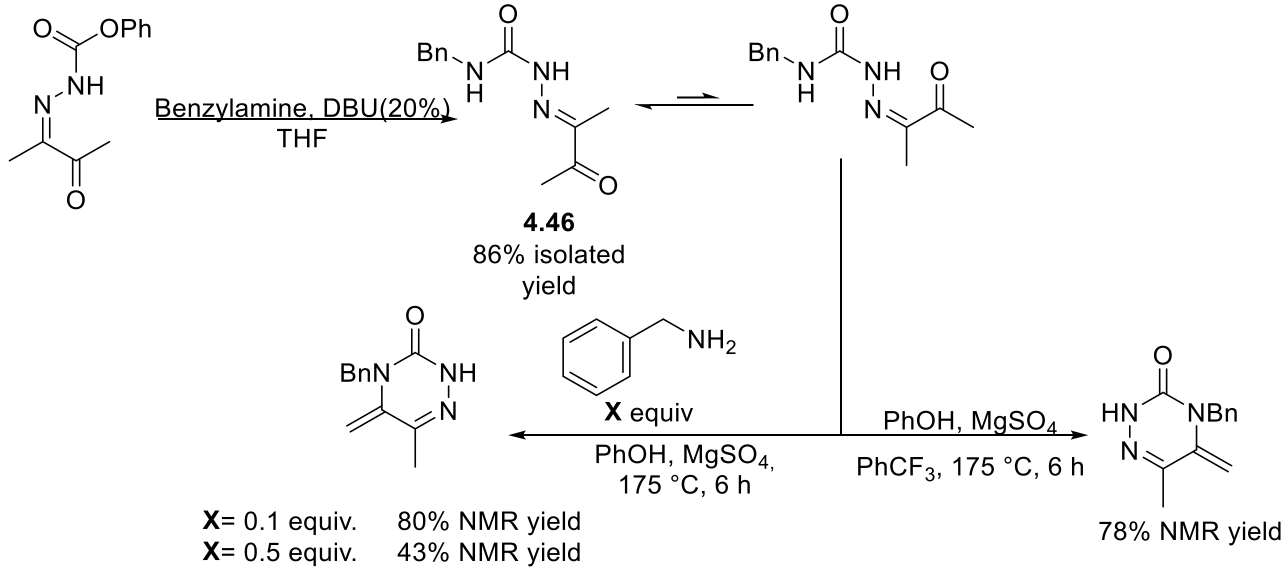
Scheme 4.8: Keto-Carbazones Scopes for Pyridazinones Synthesis

After the scope of that reaction was done, one question remained: given the ability of secondary amines to form the enamine, are primary amines forming the enamine and attacking the isocyanate with the nitrogen atom? Alternatively, the reaction mechanism could be the same one as proposed with the azauracils; an addition-cyclization cascade involving condensation onto the carbonyl group (Scheme 4.9).



Scheme 4.9: Possible Pathways for the Synthesis of Triazinones

To discriminate one pathway over the other, a semicarbazone adduct (**4.46**) was isolated and subjected to the reaction conditions. Under the same reaction conditions, **4.46** afforded the same yield suggesting the carbonyl condensation pathway is operating (Path B). However, it was still possible that the adduct reform the isocyanate followed by enamine formation. To probe this, a slight excess of amine was added to the reaction. This would replicate the optimal conditions of the enamine pathway (Path A) using secondary amines. When the exchange adduct (**4.46**) was subjected to the reaction conditions with 0.1 and 0.5 extra equivalents of benzylamine, a reduction in yield was observed as the amount of benzylamine increased (Scheme 4.10). An excess in amine should favor an enamine pathway (Path A), therefore this data suggest that the substitution / intramolecular addition (Path B) is the operating pathway. It is also important to note that **4.46** exists in the wrong conformer in solution, therefore isomerization needs to occur under these reaction conditions.



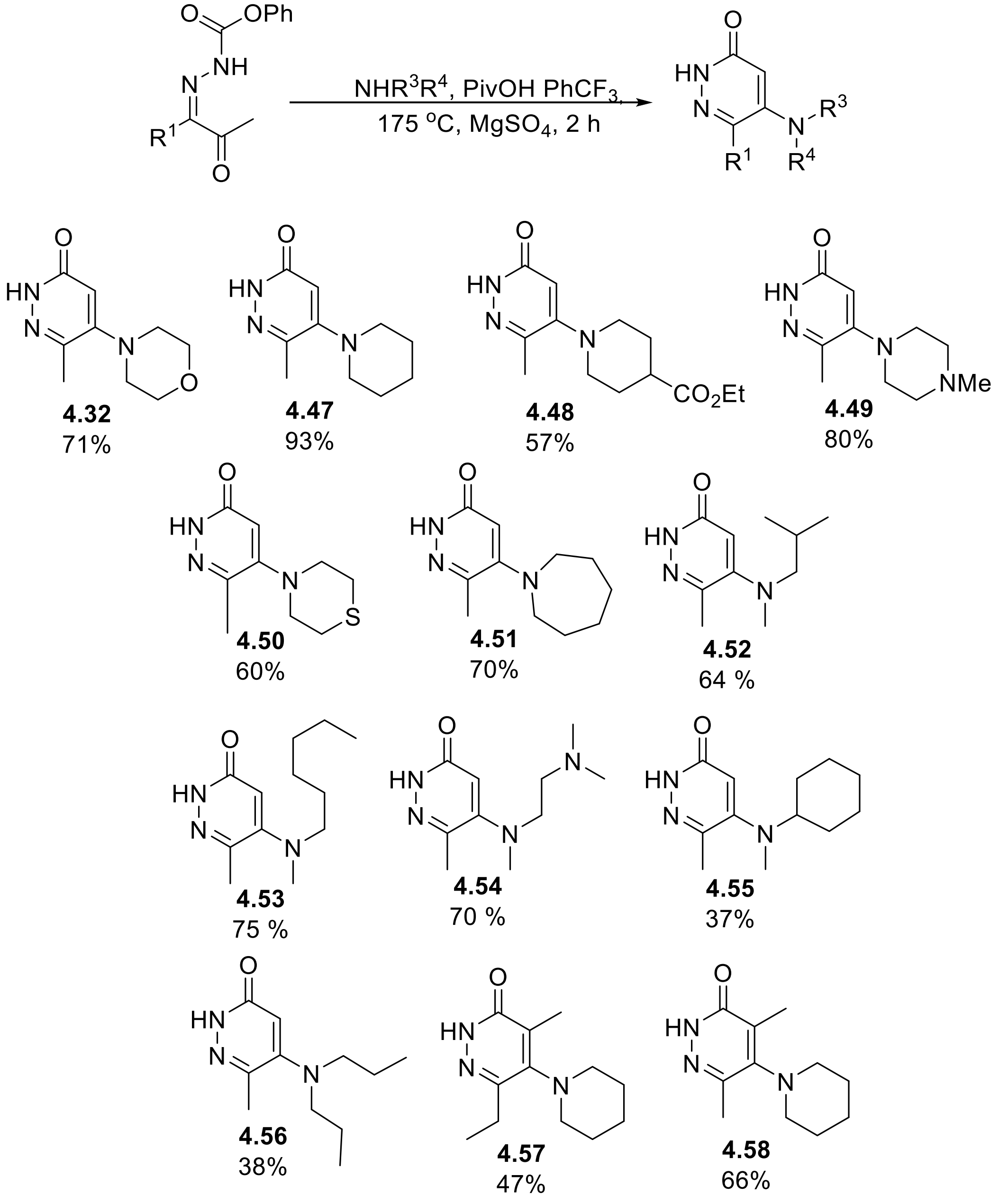
Scheme 4.10: Mechanistic Investigation

With a plausible mechanism identified for the reactions of primary amines, we started to evaluate the reaction scope of pyridazinone synthesis using secondary amines. This core has a broad spectrum of biological activities, with applications ranging from pharmaceuticals such as emorfazone to herbicides such as norfluazon. Therefore, a new diversity-oriented synthesis of this heterocycle would provide a useful addition to this literature.[107] These results are presented in Table 4.7.

---

[107] For selected publications on amino pyridazinone synthesis, see: (a) Cao, P.; Qu, J.; Burton, G.; Rivera, R. A.; *J. Org. Chem.* **2008**, 73, 7204. (b) Pattison, G.; Sandford, G.; Yufit, D. S.; Howard, J. A. K.; Christopher, J. A.; Miller, D. D. *J. Org. Chem.* **2009**, 74, 5533. (c) Schober, B. D.; Megyeri, G.; Kappe, T. *J. Heterocyclic chem.* **1990**, 27, 471. (d) Dury, K. *Angew. Chem.* **1960**, 72, 864. (e) Pollak, A.; Tisler, M. *Tetrahedron* **1965**, 21, 1323. (f) Landquist, J. K.; Thornber, C. W. *J. C. S. Perkin I* **1972**, 1114. (g) Fahmy, S. M.; Abed, N. M.; Mohareb, R. M.; Elnagdi, M. H. *Synthesis* **1982**, 490. (h) Homer, R. F.; Gregory, H.; Wiggins, L. F. *J. Chem. Soc.* **1948**, 2191.

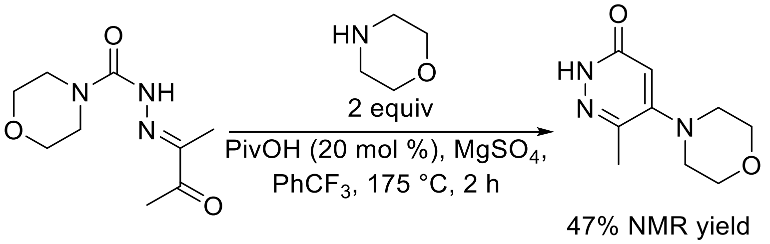
Table 4.7: Pyridazinones Synthesis : Secondary Amines Scope[a]



[a]Conditions: Keto-carbazone (1 equiv), amines (3 equiv), $MgSO_4$ (1 equiv), pivalic acid (20 mol %) in $PhCF_3$ (0.3 M) were heated in a microwave reactor for 2 hours at 175 °C.

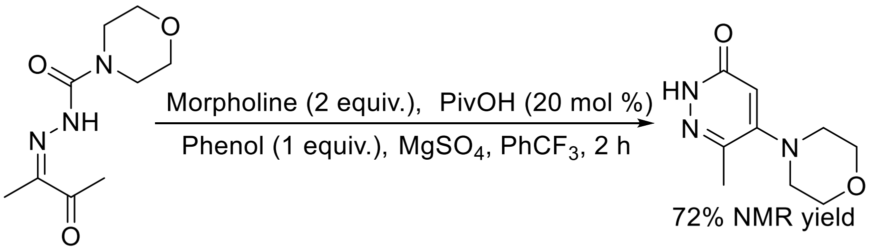
Piperidine (**4.47)** was a better reagent yielding the heterocycle in 93% yield. Substitution on the ring is less tolerated with a lower yield while an ester (**4.48**) is present. The piperazine ring is also tolerated while the second nitrogen atom is tertiary, and therefore unreactive (**4.49**). A sulfur atom is also tolerated as shown by the formation of the thiomorpholine adduct **4.50**. In addition, a larger ring such as azepane was also a competent reaction partner and yielded the desired heterocycle (**4.51**) in good yield. Due to difficulty with purification, the yield reported was obtained using an NMR internal standard. Finally, linear secondary amines also afforded the desired heterocycles in good yield when no steric hindrance was present on the α-carbons (**4.52**, **4.53** and **4.54**). The yield decreased with more hindered secondary amines (**4.55** and **4.56**). As for the previous system, this cascade was tested with different semi-carbazone starting materials using piperidine as a nucleophile. Surprisingly, the product derived from 3,4-hexanedione (**4.57**) only yielded the heterocycle in modest yield compared to 2,3-pentanedione (**4.58**).

Since excess amines seemed to inhibit reactivity in the previous case, we decided to conduct similar experiments. The exchange adduct was again isolated and submitted to the reaction conditions (eq. 4.2). Two equivalents of morpholine were added instead of three since one was consumed by the exchange reaction. Surprisingly, only a 47% yield was observed by NMR. We then thought that enamine formation may be faster than formation of the isocyanates but we were never able to isolate a stable enamine without forming the isocyanate.



(4.2)

Under these reaction conditions, nothing could help a dynamic equilibrium between the unreactive conformation and the reactive one. Having postulated the help of phenol in the pyrazole synthesis, we decided to resubmit the morpholine semicarbazone to the reaction conditions but with one equivalent of phenol (eq 4.4). With this extra equivalent the yield increased to be slightly lower than the cascade reaction (72% vs 83%). This might be indicative of a faster enamine formation with three equivalents of morpholine allowing some enamine to be formed before the isocyanate formation. This would allow a faster reaction since morpholine is a poorer leaving group than phenol. However, the yield increase while incorporating phenol in the reaction conditions is the first direct evidence of the participation of the leaving group in any of our systems. A phenol-induced dynamic equilibrium between multiple isomers is a possible explanation for the increased yield observed.



(4.3)

Overall, this study[108] showed the potential of a functional group within the *N*-isocyanate structure to act as electrophile and pronucleophile. We have shown that using keto-carbazones, the ketone can serve 2 purposes: (1) it can act as an electrophilic site for the newly-formed semi-

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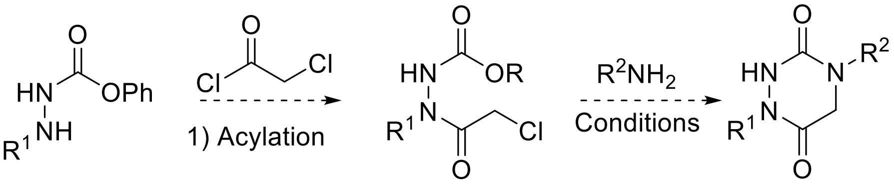
[108] Derasp, J. S., Vincent-Rocan, J.-F., Beauchemin, A. M. *Org. Lett.* **2016**, *18*, 658.

carbazone; and (2) it can act as a pronucleophile to give access to an enamine. Additions of enamines onto isocyanates are rare in both carbon-substituted and nitrogen-substituted isocyanates showing the potential of our approach. Finally, we also demonstrated evidence for the participation of the leaving group for the enamine pathway. This is the first evidence we collected that suggests the active participation of phenol in the reaction. With the azauracil synthesis, these two systems are displaying the potential of the carbonyl function to create unsaturated 6-membered rings using *N*-isocyanates as intermediates. However, the extra unsaturations lower the overall flexibility of the system making conformational and configurational preferences crucial for the reaction to occur efficiently. In order to access 6-membered rings at lower temperature, we wondered if carbazates could be used to access azadiketopiperazines. Our effort will be described in the next section.

4.3: Azadiketopiperazines from Carbazates as *N*-Isocyanate Precursors

So far, our journey in heterocyclic synthesis has been done systemically. One, two, or three atoms of the reactive intermediate were incorporated in aromatic and saturated (partially-saturated) heterocycles of 5- and 6-membered rings. Moreover, for the hydantoin case, we were not expecting that much selectivity for the α-nitrogen atom. With more experience in exploiting reaction cascades, we now know that this trend is well aligned with other systems. Therefore, to synthesize the azadiketopiperazine core,[109] a system where the β-nitrogen atom would react selectively needed to be designed. To do so, reacting the carbazate in its blocked formed with a doubly electrophilic specie, and then using a primary amine to form the subsequent bonds was imagined (Scheme 4.11).



Scheme 4.11: Azadiketopiperazine Synthesis Design

By reacting the blocked isocyanates, the carbazates are used as protecting groups to ensure the nucleophilicity of the β-nitrogen only. Depending on the conditions, the reaction could proceed by an S_N2 reaction followed by cyclization on the isocyanate (path A) or substitution via the isocyanate followed by cyclization by an S_N2 reaction (path B) (Scheme 4.12). However, knowing the reduced nucleophilicty of semicarbazides compared to secondary amines,

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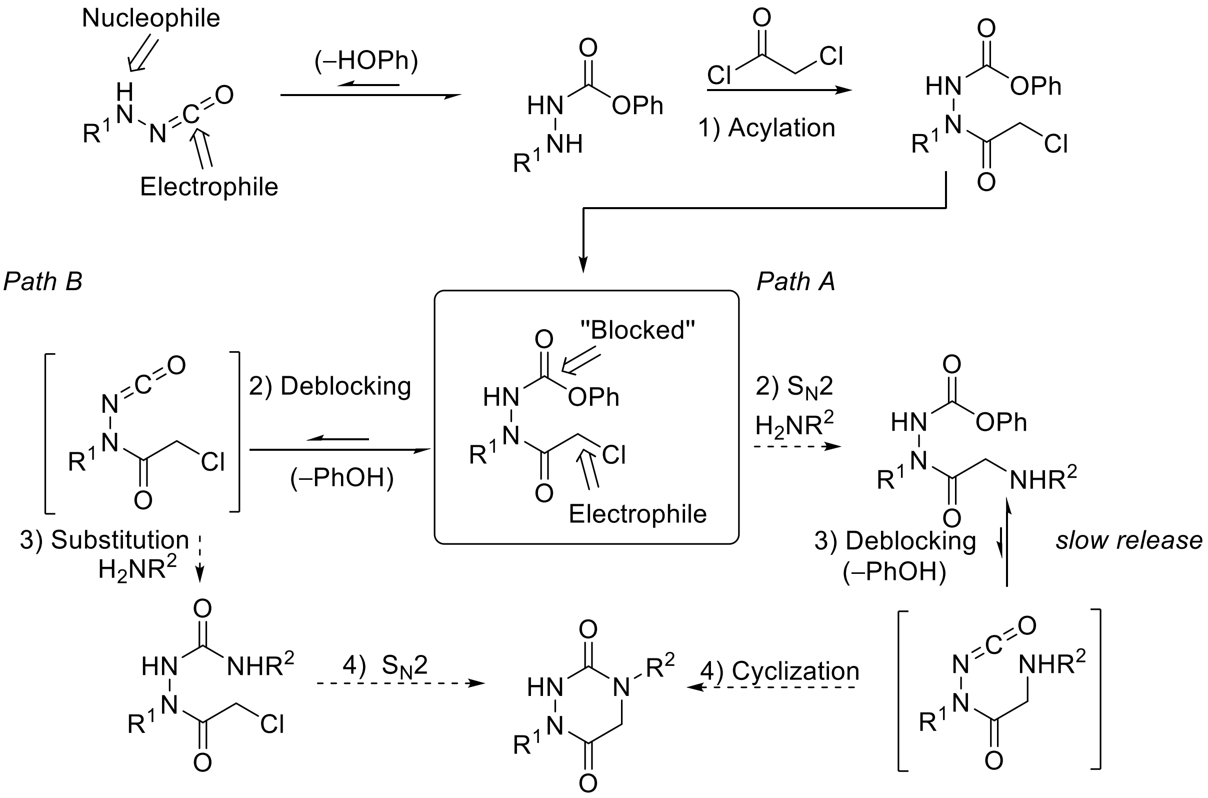
[109] For bioactivity and synthesis: (a) Schlogl, K.; Korger, G. *Monatsh. Chem.* **1951**, 814. (b) Maume, D; Lancelot, J.-C.; Robba, M. *J. Heterocycl. Chem.* **1979**, *16*, 1222. (c) Lancelot, J.-C.; Maume, D.; Robba, M. *J. Heterocycl. Chem.* **1981**, *18*, 746. (d) Lancelot, J.-C.; Maume, D.; Robba, M. *J. Heterocycl. Chem.* **1982**, *19*, 822. (e) Robba, M.; Lancelot, J.-C.; Maume, D. *J. Heterocyclic Chem.* **1983**, *20*, 430. (f) Schwan, T. *J. Heterocycl. Chem.* **1983**, *20*, 549. (g) Hoffman, R.; Nayyar, N. *J. Org. Chem.* **1995**, *60*, 5994. (h) Hoffman, R.; Reddy, M.; Klumas, C.; Cervantes-Lee, F. *J. Org. Chem.* **1998**, *63*, 9130. (i) Obreza, A.; Urleb, U. *Synth. Commun.* **2003**, *33*, 1018. (j) Bolognese, A.; Correale, G.; Manfra, M.; Esposito, A.; Novellino, E.; Lavecchia, A. *J. Med. Chem.* **2008,** *51*, 8157. (k) Bourguet, C.; Proulx, C.; Klocek, S.; Sabatino, D.; Lubell, W. *J. Pept. Sci.* **2010**, *16*, 296. (l) Bonnet, A.; Margathe, J.-F.; Radford, S.; Pflimlin, E.; Riche, S.; Doman, P.; Hibert, M.; Ganesan, A. *ACS Comb. Sci.* **2012**, *14*, 334. (m) Regenass, P.; Margathe, J.-F.; Mann, A.; Suffert J.; Hibert, M.; Girard, N.; Bonnet, D. *Chem. Commun.* **2014**, *50*, 9660.

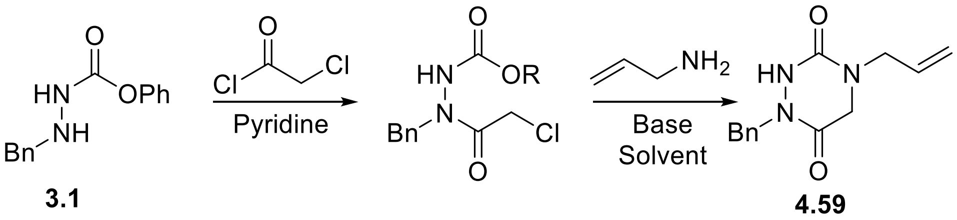
conditions to favor path A in order to use mild conditions were tried with the help of Ryan Ivanovich who was a graduate student in our group at the time.



Scheme 4.12: Possible Pathways for the Synthesis of Azadiketopiperazines

Knowing that only strong bases were inducing *N*-isocyanate formation from *O*-phenyl carbazate at low temperature, we began our optimization using mild bases in different solvents(Table 4.8). The first reaction was performed in THF using Et_3N as a base, and resulted in a modest 44 % yield of **4.59** (entry 1). However, this was a one-pot reaction starting from carbazate **3.1**. As shown above, this is the result of three steps (four if counting isocyanate formation). Therefore, we were quite optimistic about the possibility of optimizing further this one-pot sequence. A solvent scan revealed that acetonitrile was the optimal solvent (entries 2-5). Adding excess amine in solution, performed in order to increase the rate of the S_N2 reaction, also proved to be beneficial (entry 7). Indeed, using two equivalents of allylamine in THF and Et_3N as a base yielded 75% of azadiketopiperazine **4.59**.

Table 4.8: Optimization of Azadiketopiperazine Synthesis[a]



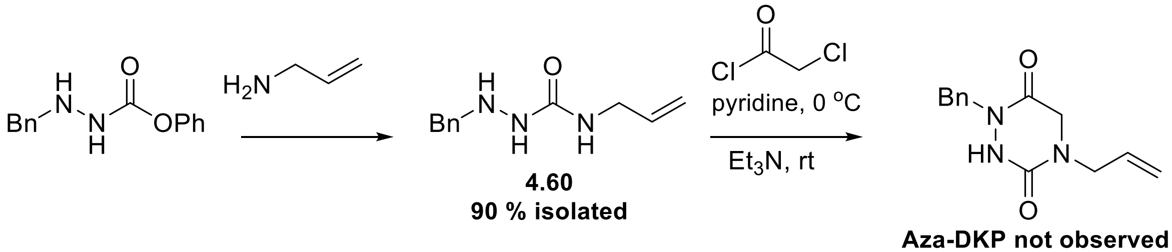
3.1

4.59

entry	solvent	amine equiv	base	yield (%)[b]
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[c]

[a] 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 room temp and stirred for 2 hours. A solution of amine (1.1-2.0 equiv) and base (2.5 equiv) in MeCN was added to the reaction (0.3 M) and stirred at room temp for 24 h. [b] NMR yield based on 1,3,5-trimethoxybenzene. [c] Isolated yield.

After the optimization, we were still unsure if path A (Scheme 4.12) was operating. To explore this further, the exchange reaction was performed first, followed by acylation and treatment with base (eq. 4.4). However, no product was observed when treating the acylated product with base in MeCN, indicating that it is not an intermediate in our reaction.



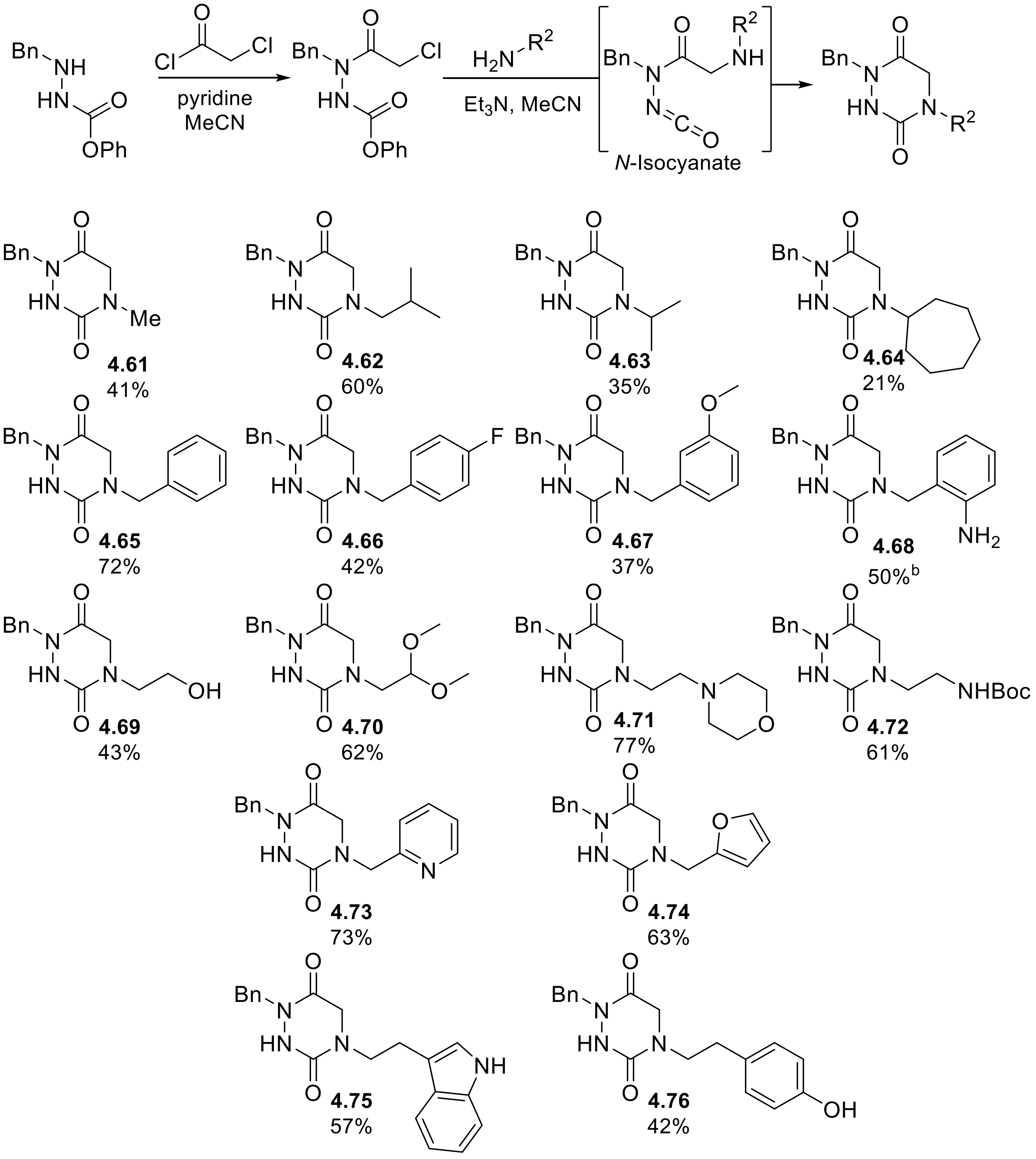
4.60
90 % isolated

Aza-DKP not observed

(4.4)

With the reaction conditions optimized and the reaction pathway secured, the scope of this reaction was explored by modifying the primary amine used (Table 4.9).

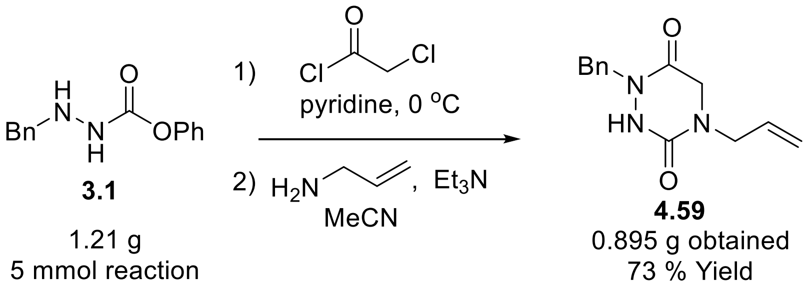
Table 4.9: Azadiketopiperazines Synthesis: Amine Scope[a]



[a]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 room temp and stirred for 2 h. A solution of amine (2 equiv) and Et_3N (2.5 equiv) in MeCN was added to the reaction (0.3 M) and stirred at room temp for 24 h. Isolated yields are shown. [b]^{1}H NMR yield based on 1,3,5-trimethoxybenzene as internal standard.

A wide variety of primary amines were compatible in our system. The use of methylamine afforded 41% of the desired heterocycle (**4.61**). Other aliphatic amines were also tolerated with non-bulky amines (**4.62**), but a reduction of the yield was observed when using α-branched amines (**4.63** and **4.64**). Different benzylic amines (**4.65-4.68**) were also tested and the yield seemed to be affected when the phenyl ring was substituted (**4.66-4.68**). In addition, a variety of functional groups were tolerated in this system. A free hydroxyl group (**4.69)**, a protected aldehyde (**4.70**), an amine (**4.72**) and a morpholino group (**4.71**) all yielded the desired 6-membered heterocycles in modest to good yields. Heterocycles could also be incorporated on the azadiketopiperazine core. A pyridine (**4.73**), a furan (**4.74**) and an indole (**4.75**) were introduced in good yields. Finally, a free phenol was also tolerated, yielding the azadiketopiperazine **4.76** in modest yield.

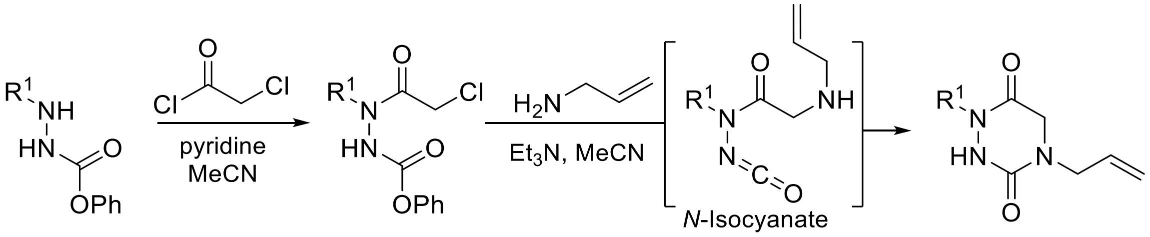
Given the applicability of this method, the scalability of this one-pot sequence needed to be demonstrated. To do so, the synthesis of **4.59** was attempted on a 5 mmol scale (more than 8 times bigger than the usual scale for this system). As seen in eq. 4.5, we were able to reproduce the yield obtained in our optimization on a gram-scale reaction. Given the availability of every reagent, the simplicity of this one-pot procedure and the mild conditions of the system, this synthesis provides a reliable alternative to synthesize a variety of azadiketopiperazines.

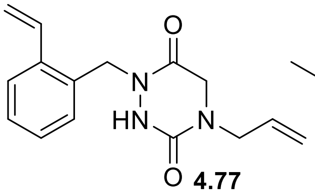


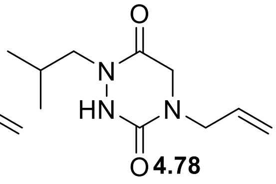
(4.5)

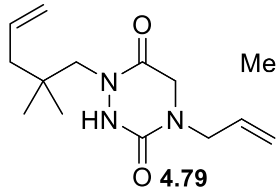
To further illustrate the versatility of this new azadiketopiperazine synthesis, different carbazates were tested. As mentioned in Chapter 2, an improved synthesis of phenyl carbazate that gave access to decagrams of material in less than 3 hours was crucial to improve the efficiency of this process. A simple condensation and reduction using $NaCNBH_3$ was used to synthesize the starting materials. The results of this substrate scope are presented in Table 4.10.

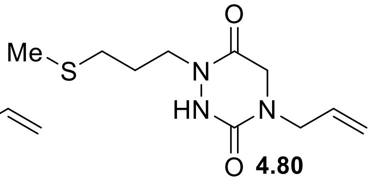
Table 4.10: Azadiketopiperazines Synthesis: Carbazate Scope[a]

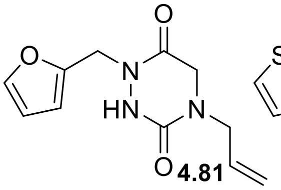


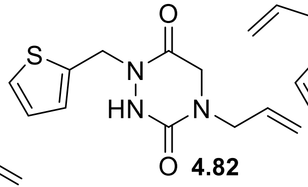

4.77
55%

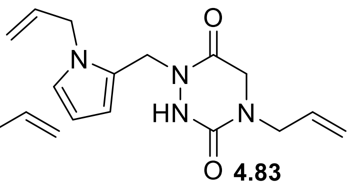

4.78
72%

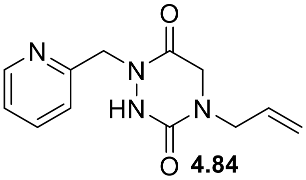

4.79
70%

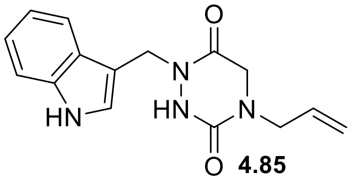

4.80
62%

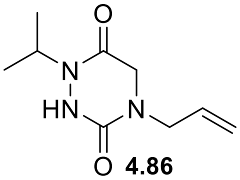

4.81
60%

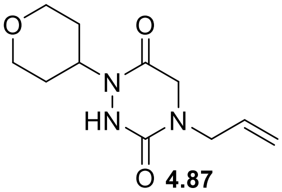

4.82
61%

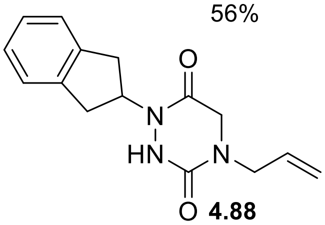

4.83
67%


4.84
56%


4.85
62%


4.86
66%


4.87
60%


4.88
50%

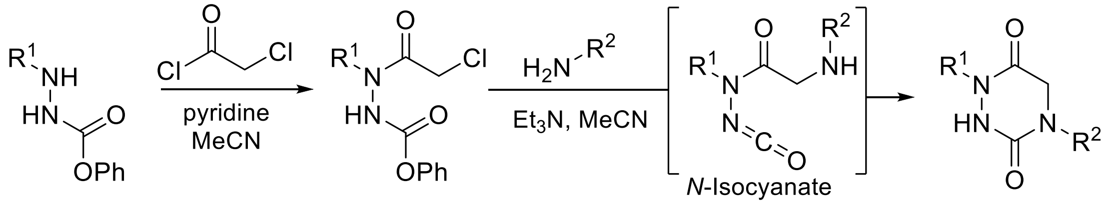
[a]Conditions: carbazate (1 equiv) stirring at 0 °C in MeCN (0.6 M); then pyridine (1.1 equiv), then chloroacetyl chloride (1.05 equiv). The solution was warmed to room temp and stirred for 2 h (or 16 h entries **4.87**, **4.88**). A solution of allylamine (2 equiv) and Et_3N (2.5 equiv) in MeCN was added to the reaction (0.3 M) and stirred at room temp for 24 h. Isolated yields are shown.

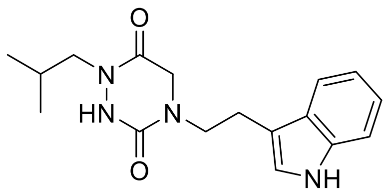
In comparison with trials involving various amines, almost no variation was observed while modifying the carbazate used in this one-pot sequence. This seems logical since these modifications are far from the reaction centre. Adding an extra alkenyl chain on the typical benzyl carbazate was tolerated and yielded the di-alkenyl azadiketopiperazine **4.77** in modest yield. Aliphatic carbazates with (**4.80**) or without (**4.78** and **4.79**) heteroatoms did not affect the yield of this reaction. Several heterocycles could also be present on the carbazate reagent. Indeed, a furan (**4.80**), a thiophene (**4.81**), a pyrrole (**4.82**), a pyridine (**4.83**) and an indole (**4.84**) were all tolerated to form the corresponding bi-heterocycles in good yields. Most notably, no significant difference in yield was observed while using α-branched carbazates as was observed with the amines scope. Therefore, the three ketone-derived carbazates (**4.86-4.88**) yielded the branched azadikeopiperazines with a small variation in yields.

With these findings, it became apparent that a lot of diversity could be incorporated around this often poorly-substituted core. The results obtained with amines and carbazates led us to believe that highly-functionalized heterocycles could be obtained using this method.

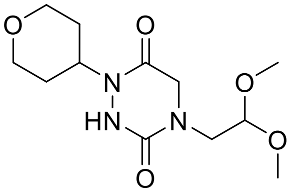
To obtain such a high degree of functionalization, we wondered if it was possible to react several complex amines and carbazates together. Given the commercial availability of amines and the improved availability of large amount of carbazates, we decided to pursue this idea and the results are shown in Table 4.11.

Table 4.11: Mixed Azadiketopiperazines Synthesis[a]

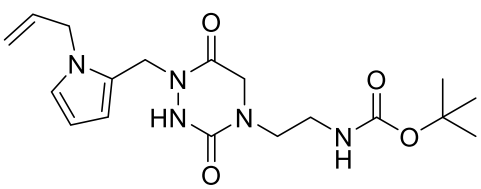




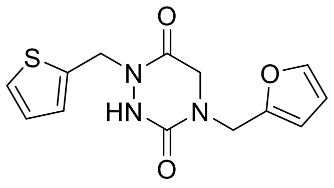
4.89
52%



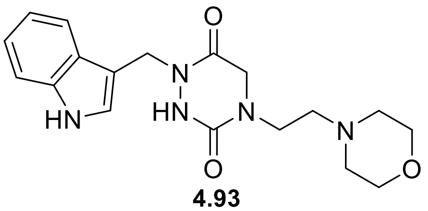
4.90
39%



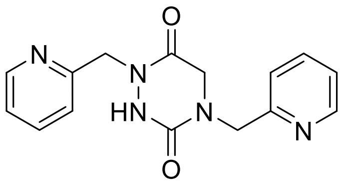
4.91
46%



4.92
69%



4.93
61%



4.94
33%

[a]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 room temp. and stirred for 2 h. A solution of amine (2 equiv) and Et_3N (2.5 equiv) in MeCN was added to the reaction (0.3 M) and stirred at room temp. for 24 h. Isolated yields are shown.

An aliphatic side chain and a heterocycle could be combined to yield the functionalized core **4.89** in modest yield. A branched heterocycle (easily incorporated on the carbazate part) and a protected aldehyde could also be incorporated (**4.90**) with a decrease in yield. However, for a one-pot sequence generating as much complexity, we feel that these ranges of yields are easily justifiable. Using the same design, a heterocycle and a protected amine could afford the small core with 5 nitrogen atoms and 4 oxygen atoms (**4.91**). The triheterocyclic core was also accessed by combining heterocyclic-containing carbazates and primary amines. Using this concept, the thiophene-furan (**4.92**), the indole-morpholine (**4.93**) and the pyridine-pyridine (**4.94**) combinations were synthesized in modest to good yields. Overall, these results showed that it is possible to obtain highly functionalized aza-diketopiperidines using simple and readily-available reagents. Most notably, the azadiketopiperazine **4.90** possess a heteroatom:carbon ratio of 2:3, a very high ratio for such molecules.

In summary, this study[110] showed that it is possible to obtain another 6-membered heterocycle under mild conditions using a weak base as catalyst. More than 30 examples were obtained in less than two months of work which illustrates the ease of synthesis that *N*-isocyanate precursors allow. Conceptually, it also demonstrated the ability of blocked isocyanates to act as hemi-labile protecting group since a nucleophilic attack was able to happen before releasing the electrophilic isocyanate. This concept is new in the chemistry of *N*-isocyanates, and could be used to develop more elaborate reaction sequences.

4.4: Conclusion and Perspectives

In the previous Chapters, we saw that we could use an electrophile as part of the substrate or as part of the incoming nucleophile to synthesize heterocycles containing either one or two atoms of the *N*-isocyanate motif *via* cascade reactions. In this chapter, the most challenging transformations were attempted: incorporating the three atoms inside the same heterocycle. Again, we showed that it was possible to achieve such a goal by designing substrates with built-in functionalities (aza-uracils, triazinones and pyridazinones) or by reacting a simple carbazate with a dielectrophilic reagent (azadiketopiperazine). Conceptually, we gained access to rare reactivity in this chapter. As previously mentioned, the synthesis of azauracils was poorly developed before our study that provided almost 30 pyrimidine derivatives. In addition, heterocyclic chemistry using enamines on isocyanates (*C*- and *N*-substituted) remains poorly developed. We were able to access this rare reactivity and used it in a cascade reaction for the synthesis of interesting bioactive cores. Finally, we also showed the possibility of blocked isocyanates to act as hemi-labile protecting groups by having a nucleophilic attack happen on a relatively poor electrophile (relative to the isocyanate) before releasing the highly reactive isocyanate. This chapter shows the knowledge acquired in the chemistry of *N*-isocyanates, along with carefully-designed systems that afford interesting motifs. Using base catalysis, we were finally able to obtain the desired azadiketopiperazine, a motif that interested us since the discovery of our hydantoin synthesis.

As seen in Chapter 1, the N-N-C=O motif is omnipresent in the agrochemical and the pharmaceutical industries. Given the variety of incorporation of this motif, we have shown in the last three chapters that *N*-isocyanate chemistry could be used as a modular approach for the incorporation of one, two, or three atoms within a heterocycle. To finish our systematic effort, the next chapter will present our efforts for the synthesis of linear molecules using blocked *N*-isocyanate precursors.

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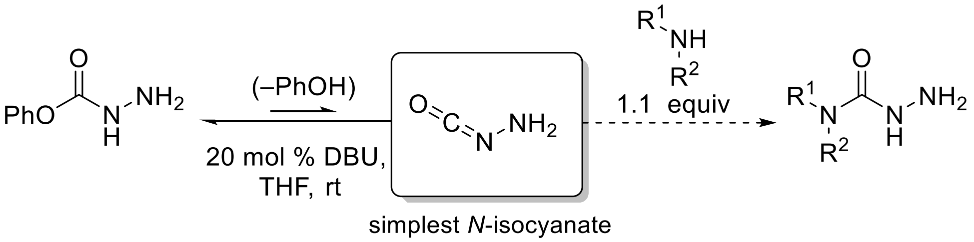
[110] Ivanovich, R. A.; Vincent-Rocan, J.-F.; Elkaeed, E.; Beauchemin A. M. *Org. Lett.* **2015**, *17*, 4898

Chapter 5: *N*-Isocyanates for the Synthesis of Acyclic Molecules

5.1: Simple Synthesis of Semicarbazides

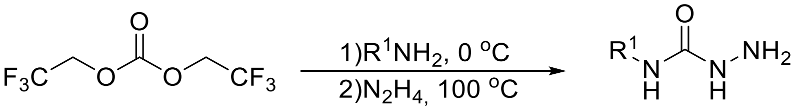
Most of the work shown in the first chapter for the development of *N*-isocyanates relied on addition reactions forming simple molecules. However, these additions were used mostly to prove the existence of the isocyanate intermediates and no systematic studies for the synthesis of useful synthons were known.

With our growing expertise in base catalysis, we envisioned using our improved access to phenyl carbazate in order to generate the simplest *N*-isocyanates and synthesize complex semicarbazides (eq. 5.1).



(5.1)

This would represent a milder and simpler alternative than the newest method for the synthesis of these simple semicarbazides (eq. 5.2).[111]



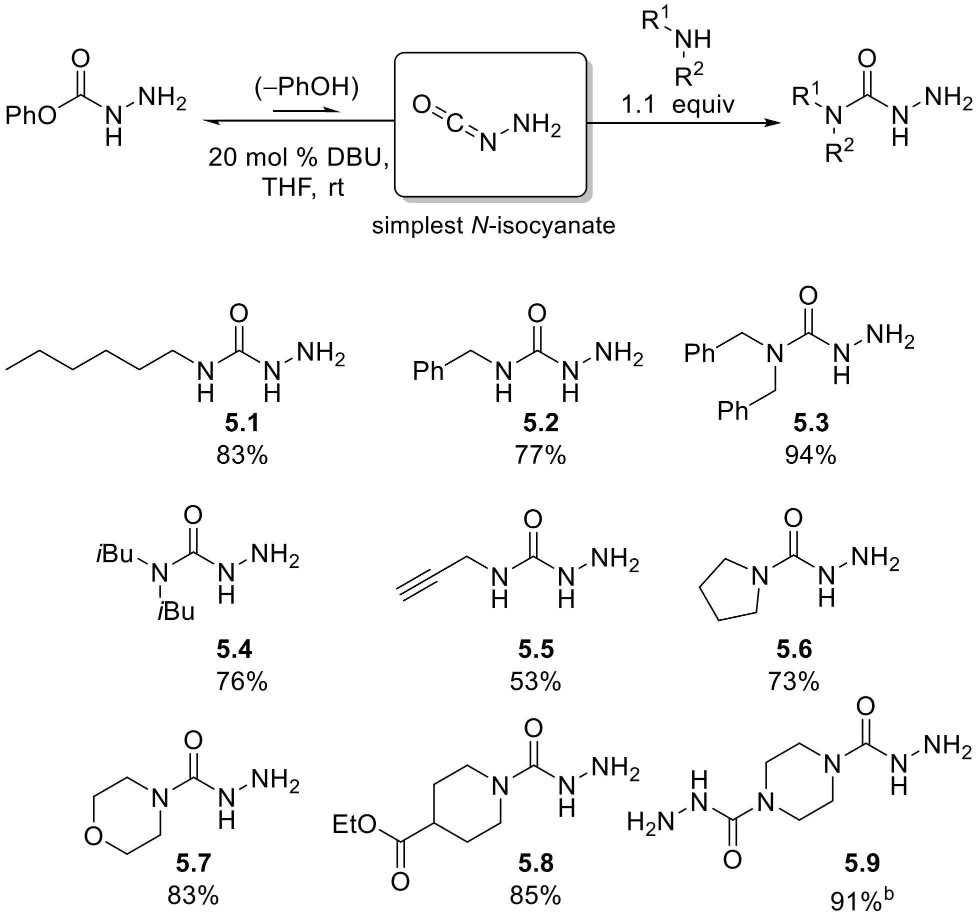
(5.2)

Given the reduced steric hindrance around this unsubstituted *N*-isocyanate, it was hypothesized that room temperature reactivity and a slow release of the reactive intermediate was essential to avoid dimerization. Fortunately, these simple conditions allowed access to several semi-carbazides and the results are presented in Table 5.1.

---

[111] Bogolubsky, A.; Moroz, Y. S.; Mykhailiuk, P. K.; Dmytriv, Y. V.; Pipko, S. E.; Babichenko, L. N.; Konovets, A. I.; Tolmachev, A. *RSC Adv.* **2015**, *5*, 1063. See also references cited therein.

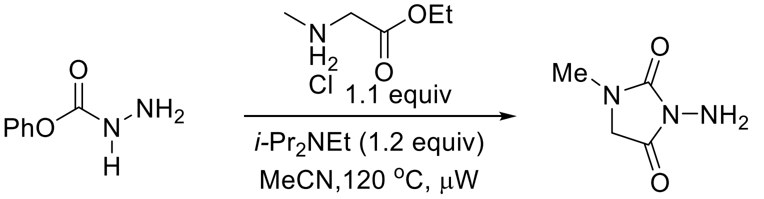
Table 5.1: Synthesis of Semicarbazides Using N-Isocyanate Precursors[a]



[a]Conditions: *O*-phenyl carbazate (1 equiv), amine (1.1 equiv), DBU (20 mol %) in THF (0.3 M) stirred at room temperature for 16 h. [b]Reaction with 0.5 equiv amine.

Overall, this system tolerated a variety of different amines. A simple aliphatic amine was tolerated and we were able to obtain the *n*-hexylamine-derived semicarbazide **5.1** in 83% yield. Primary (**5.2**) and secondary (**5.3)** benzylic amines were also competent reaction partners and yielded the desired compounds in good to excellent yields. Bulkier secondary amines were also used to generate the semi-carbazide of diisobutylamine amine (**5.4**) in good yield. Propargylamine also allowed access the functionalized semi-carbazide (**5.5**) in modest yield. Cyclic amines could also be used as nucleophiles to obtain pyrrolidine- (**5.6**), morpholine- (**5.7**) and piperidine- (**5.8**)substituted semi-carbazides in good yields. Finally, a double addition product (**5.9**) could also be formed while using 0.5 equivalents of piperazine. This opened the door to the use of *N*-isocyanate precursors in polymerization reactions. Overall, these results show that a precursor of the simplest *N*-isocyanate, NH_2NCO, could avoid dimerization if a nucleophilic amine is present in the reaction medium.

Based on this observation, it was decided to attempt some of the cascade reactions described previously using phenyl carbazate as the *N*-isocyanate precursor. This would give the possibility of further functionalization by providing a free NH_2 group after the cascade reaction. First, phenyl carbazate was subjected to the conditions of the hydantoin synthesis (eq. 5.3). Even on a gram scale, the reaction afforded the desired heterocycle in higher yield than with most carbazones.

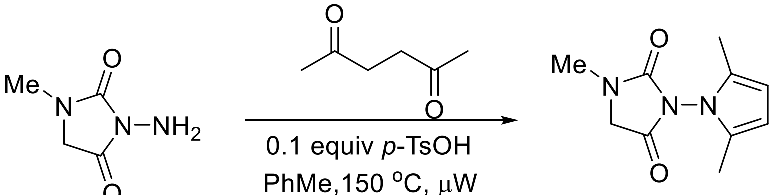


1.04 g

5.10
0.800 g, 91%

(5.3)

To show the potential of this strategy for further functionalization, this hydantoin was used in a Paal-Knorr pyrrole synthesis. This reaction allowed us to form the highly functionalized compound **5.11**, in which both nitrogens of the hydrazide moiety are present in 2 different heterocycles.

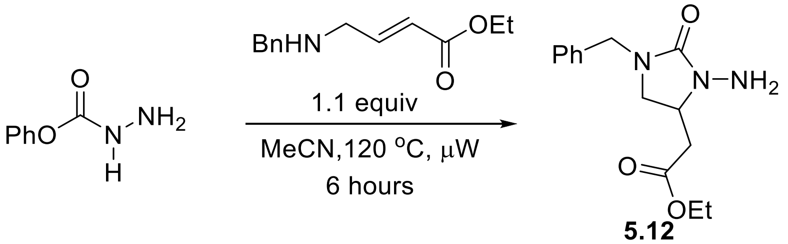


5.10

5.11
90%

(5.4)

The use of phenyl carbazate was also exploited in a reaction with a conjugated alkene in order to synthesize a highly functionalized imidazolinone (eq. 5.5). As for the hydantoin, the yield was significantly higher using phenyl carbazate. In addition, this provided a method to access a simple heterocycle possessing two functional groups for further functionalization (a free amine and an ester).



5.12
81%

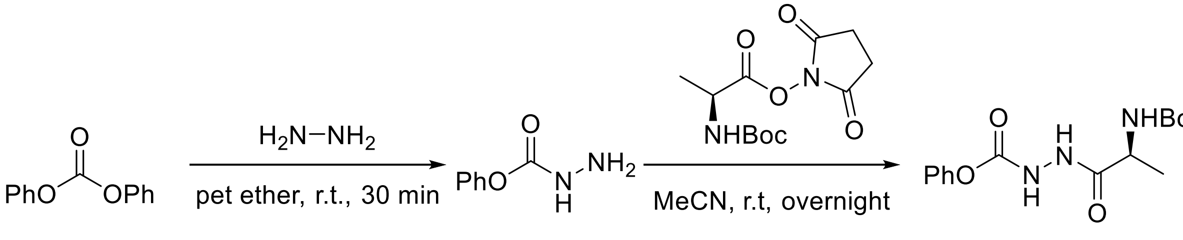
(5.5)

In order to show the potential of *N*-isocyanates for the synthesis of linear molecules, we started to wonder if phenyl carbazate could be used to build more complex molecules. The synthesis of aza-peptides was an obvious choice given their importance in peptidomimetic chemistry in recent years.[112]

5.2: Synthesis of Aza-Tripeptides

As discussed in this thesis, we know it is possible to use blocked *N*-isocyanates for addition of simple nitrogen nucleophiles. More specially, we already designed a system to synthesize aza-dipeptoids (side chain not on the *natural* nitrogen). In order to synthesize aza-tripeptides, a new substrate needed to be designed. With the help of several undergraduate students over the years, we aimed to create a mild and operationally-simple synthesis in order to compete with other syntheses.[113]

Having efficient access to phenyl carbazate provided a strong incentive to use this building block to build azapeptide motifs. Boc-protected amino acids were initially targeted to develop this reactivity. By mixing phenyl carbazate with Boc-Ala-OSu in acetonitrile, we were able to achieve a complete transformation in 16 hours (eq. 5.6). To purify these compounds, a repetitive basic wash with $NaHCO_3$ was accomplished to remove the *N*-hydroxysuccinimide byproduct. In combination with the optimized synthesis of phenyl carbazate, it is possible to synthesize a large quantity of aza-dipeptide without the need for column chromatography. However, compounds such as **5.13** are only stable for a limited number of days. Nevertheless, this stability was sufficient to pursue their development as azapeptide building blocks, given their ease of access.



5.13, 91%

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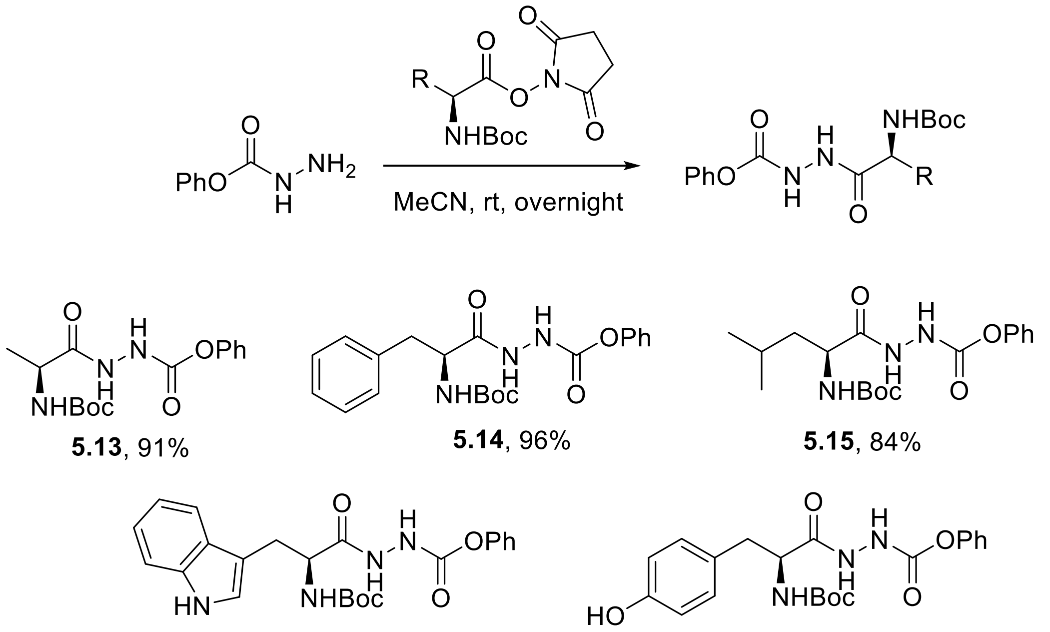
[112] Proulx, C.; Sabatino, D.; Hopewell, R.; Spiegel, J.; García Ramos, Y.; Lubell, W. D. *Future Med. Chem.* **2011**, *3*, 1139.

[113] For selected reports on aza-peptide synthesis, see: (a) Wieczerzak, E.; Drabik, P.; Łankiewicz, L.; Ołdziej, S.; Grzonka, Z.; Abrahamson, M.; Grubb, A.; Brömme, D. *J. Med. Chem.* **2002**, *45*, 4202. (b) Liley, M.; Johnson, T. *Tetrahedron Lett.* **2000**, *41*, 3983. (c) Verhelst, S. H.; Witte, M. D.; Arastu-Kapur, S.; Fonovic, M.; Bogyo, M. *Chembiochem*. **2006**, *7*, 943. (d) Boeglin, D.; Lubell, W. D. *J. Comb. Chem*. **2005**, *7*, 864. (e) Freeman, N. S.; Hurevich, M.; Gilon, C. *Tetrahedron* **2009**, *65*, 1737. (f) Boeglin, D.; Xiang, Z.; Sorenson, N. B.; Wood, M. S.; Haskell-Luevano, C.; Lubell, W. D. *Chem. Biol. Drug Des*. **2006**, *67*, 275. (g) Sabatino, D.; Proulx, C.; Klocek, S.; Bourguet, C. B.; Boeglin, D.; Ong, H.; Lubell, W. D. *Org. Lett*. **2009**, *11*, 3650. (h) Sabatino, D.; Proulx, C.; Pohankova, P.; Ong, H.; Lubell, W. D. *J. Am. Chem. Soc*. **2011**, *133*, 12493.

Before exploring this further, additional experiments were performed to ensure that this reactivity was general for a variety of *N*-protected activated amino acids. The reaction was thus tested on 5 different amino acid derivatives and the results are displayed in Table 5.2.

Table 5.2: Synthesis of a Masked N-Isocyanate on a Dipeptide Subunit[a]



5.13, 91%

5.14, 96%

5.15, 84%

5.16, 84%

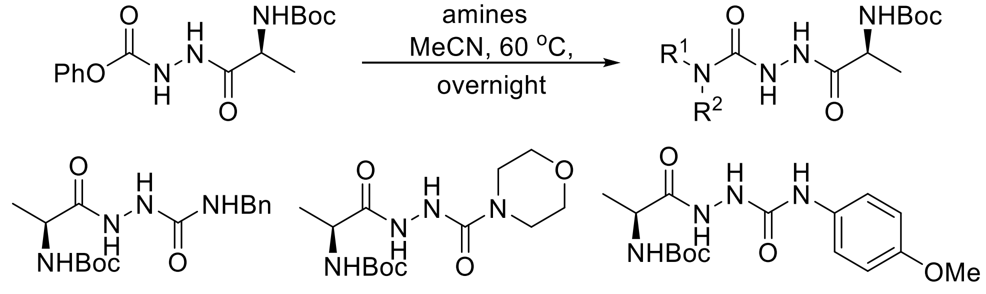
5.17, 84%

[a]Conditions: *O*-phenyl carbazate (1 equiv), activated esters (1.1 equiv), DBU (20 mol %) in THF (0.3 M) stirred at room temperature for 16 h.

Gratifyingly, multiple commercially available activated esters of natural amino acids were tolerated in this system. Phenylalanine- (**5.14**) and leucine- (**5.15**) derived aza-dipeptides were synthesized with no variation in yield. Tryptophan (**5.16**) and tyrosine (**5.17**) derivatives were also synthesized demonstrating the functional group tolerance of this approach.

With a general approach for the dipeptide core containing a masked *N*-isocyanate, it was necessary to establish the ability of such substrates to undergo nucleophilic addition with simple amines before trying the reaction with the more complex amino acid derivatives. A quick optimization revealed that acetonitrile at 60 °C with catalytic triethylamine was the ideal system to generate *N*-isocyanates that can be attacked by simple amines. The results obtained using this procedure are presented in Table 5.3.

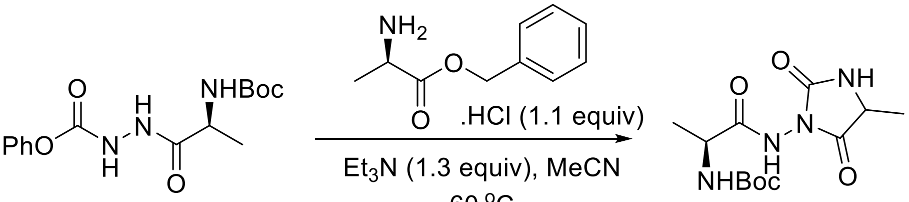
Table 5.3: Simple Amine Scan[a]



5.18, 87% **5.19**, 98% **5.20**, 76%[b]

[a]Conditions: Masked *N*-isocyanates (1 equiv), amine (1.1 equiv), Et_3N (20 mol%) in MeCN (0.3 M) stirred at 60 °C for 16 h. [b]Reaction with 3 equiv of amine.

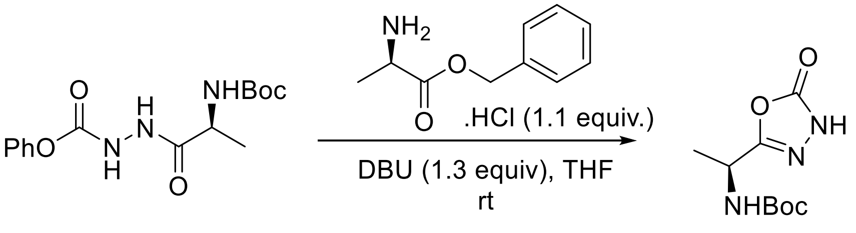
With confirmed reactivity in hand, the synthesis of aza-tripeptides could be investigated. Unfortunately, the use of benzyl esters of amino acids under optimized reaction conditions led to the formation of hydantoin **5.21** as the sole product (eq 5.6).



5.21

(5.6)

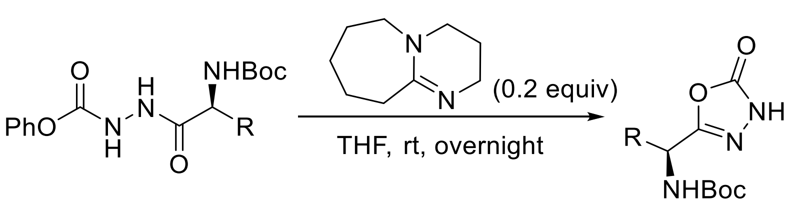
To form this hydantoin, the tripeptide was formed but further cyclized under these reactions conditions. However, given that other conditions allow for the mild generation of *N*-isocyanates, this substrate was subjected to optimized room temperature conditions using DBU as a catalyst. Under these conditions, the reaction seemed to be complete in 1 hour. However, a new ring system was isolated in this reaction (eq. 5.7).



5.22

(5.7)

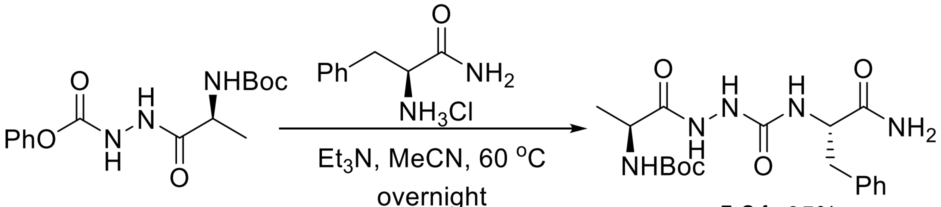
Knowing that this product was most likely coming from the intramolecular attack of the amide on the *N*-isocyanate, the reaction was optimized without any nucleophile being present. The results are shown in equation 5.8.



(5.8)

R = Me, **5.22**, 77%
Bn, **5.23**, 86%

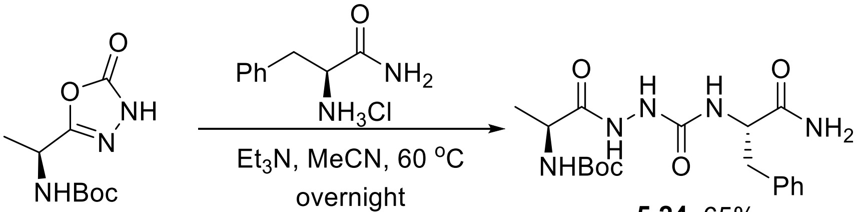
At this point, it became apparent that using amino esters would be problematic and the results shown above suggested that this reaction was most likely going through an oxadiazole intermediate. Therefore the use of other amino acids derivatives that would not cyclize to the hydantoin became attractive, and α-amino amides were selected as reaction partners. Trying the optimized conditions with phenylalanine amide yielded 65% of the aza-tripeptide which was purified by filtration. The amount of Et_3N needed to be adjusted given the use of the HCl salt of the starting amide, but no other modifications were made from the pre-optimized reaction conditions (eq. 5.9).



(5.9)

5.24, 65%

With a successful reaction in hand, it was possible to probe if the oxadiazolone intermediate previously isolated (eq. 5.8) in the room temperature reactivity was an intermediate in our reaction involving amido-isocyanates. In a study by Squillacote with related intermediates (Scheme 1.14), the formation of an intermediate was shown, but this work did not provide any data suggesting it could be reopened. Therefore, we subjected the isolated cycle to the exact same reaction conditions (eq. 5.10).

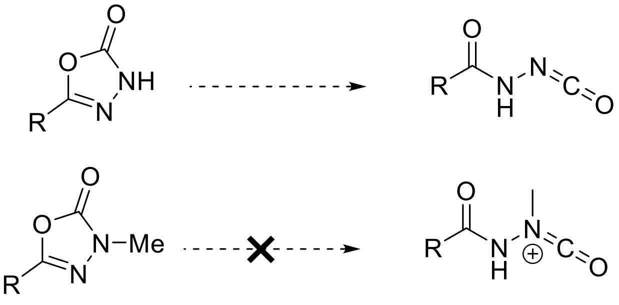


(5.10)

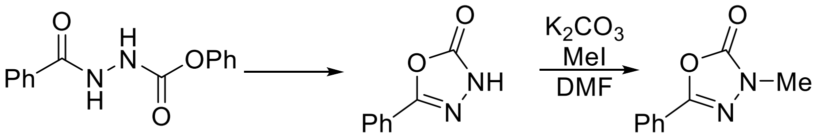
5.24, 65%

Interestingly, the same yield was obtained. This suggested that the oxadiazole ring was itself a source of masked *N*-isocyanate, or that it was electrophilic enough for a nucleophilic attack on the carbonyl. To probe this further it was decided to synthesize a simple oxadiazole and its *N*-methyl analogue. The underlying hypothesis was that the methylated version of the ring could not form the *N*-isocyanate intermediate, but would still be susceptible to nucleophilic attack.

Therefore, if the reaction was not operating with this substrate, it would strongly suggest the presence of an *N*-isocyanate (Scheme 5.1). To synthesize both starting materials, the precursor **3.45** was used under the conditions shown in equation 5.7, leading to the formation of 88% of the desired cycle. Finally, a simple methylation using MeI and K_2CO_3 in DMF was used in order to complete the synthesis of the methylated analogue (eq. 5.11).



Scheme 5.1: Pathway Discrimination Design



(5.11)

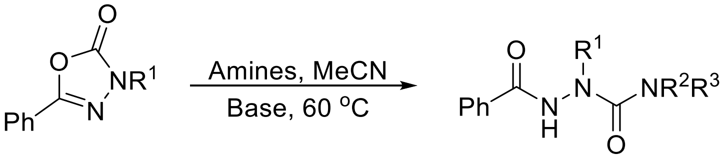
3.45

5.25
88%

5.26
94%

The investigation began by using both substrates under the same conditions used for the synthesis of aza-tripeptides. When the reaction was run in MeCN using a catalytic amount of base and allylamine as a nucleophile, substrate **5.25** allowed formation of the product in quantitative yield. However, less than 5% product was observed with **5.26**. To rule out the effect of steric hindrance the reaction involving **5.25** with *N*-methyl allylamine was performed and quantitative yield was also observed. Since these ring systems are commonly found in biologically-active molecules, we also tested the reaction with imidazole (based on the amino acid histidine) and *N*-methyl imidazole and the results were similar (Table 5.4).

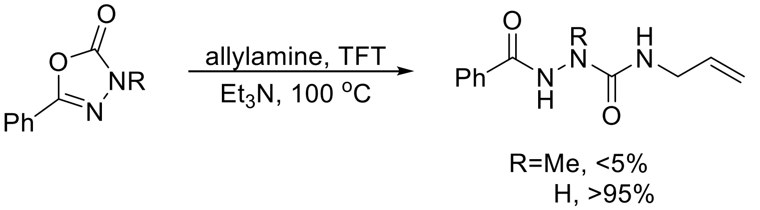
Table 5.4: Probing the N-isocyanate Pathway[a]



R^1	Amine	Base	Yield (%)
H	Allylamine	Et_3N	>95
Me	Allylamine	Et_3N	<5
H	*N*-Me allylamine	Et_3N	>95
H	Allylamine	Imidazole	>95
Me	Allylamine	Imidazole	<5
H	Allylamine	*N*-Me imidazole	>95
Me	Allylamine	*N*-Me imidazole	<5

[a]Conditions: Masked *N*-isocyanates (1.1 equiv), amine (1.0 equiv), base (20 mol%) in MeCN (0.3 M) stirred at 60 °C for 16 h.

The reaction was tried with harsher conditions using $PhCF_3$ at 100 °C for 16 hours but the same result was obtained: quantitative yield for the free N-H and less than 5% yield for the N-Me (eq. 5.12).



(5.12)

Overall this provides significant evidence for the involvement of an *N*-isocyanate for these types of reactions. Efforts are pursued in order to determine if this mechanism is common in other 5-membered ring systems. Other experiments will also be performed to have more definitive proof of an *N*-isocyanate involvement. Finally, we will also try to improve the yield for the tripeptide synthesis.

5.3: Conclusion and Perspectives

In this Chapter it was shown that phenyl carbazate itself could be a good reaction partner to furnish the simplest *N*-isocyanate in a controlled fashion. This allowed the synthesis of simple semi-carbazides that can be difficult to obtain by other means. This precursor was also used in cascade reactions for the synthesis of heterocycles with functional group handles. Phenyl carbazate was also used as nucleophile to generate a small library of dipeptide masked *N*-isocyanates, which allows the syntheses of aza-tripeptides without the use of flash chromatography or expensive coupling agents. During this study, a new potential source for masked *N*-isocyanates was discovered (oxadiazolones as masked heterocyclic derivatives) and more studies are undergoing to expand this discovery. This Chapter also concludes a journey on the exploration of reactivity using *N*-isocyanates by showing that acyclic molecules can also be obtained using this strategy, in addition to the heterocyclic chemistry presented in Chapters 2-4.

Overall, this thesis highlights that *N*-isocyanates hold considerable synthetic potential. The reactivity of such species was underdeveloped before this report. Presented herein are more than 200 heterocycles synthesized using related reactive intermediates, showing that a controlled release and functionalization of either the core or the incoming nucleophile can lead to diversity and complexity in an efficient manner. This exploration also included analogues of *N*-isocyanates such as their sulfur derivatives. Other isocyanate variants are pursued in our laboratory and will be reported in due course. I believe that this thesis is only the starting point and that multiple syntheses using *N*-isocyanates will be developed in the future[114] given the new tools in heterocyclic chemistry that this research provides.

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[114] For recent heterocyclic chemistry based on the research developed in this thesis see: Shao, J.; Liu, X.; Tang, P.; Luo, J.; Chen, W.; Yu, Y. *Org. Lett.* **2015**, *17*, 4502.

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 ($CDCl_3$ at 7.26 ppm, C_6D_6 at 7.15 ppm or DMSO-d_6 at 2.50 ppm for ^{1}H NMR and $CDCl_3$ 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-12.2 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.

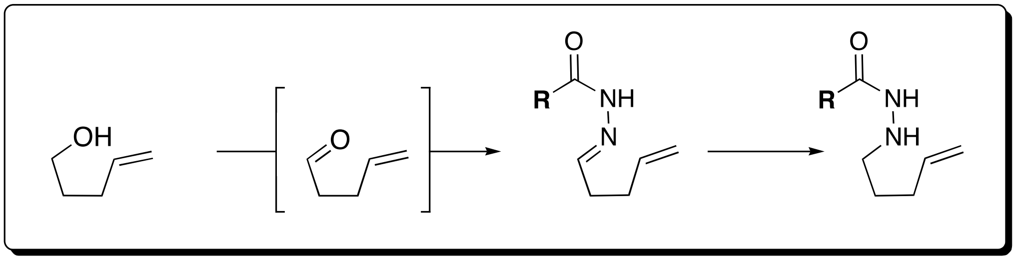
6.1: Supporting Information for Chapter 2

6.1.1: Improvement of Phenyl Carbazate (2.1) Synthesis

To a solution of diphenyl carbonate (21.4 g, 100 mmol) in 300 mL of petroleum ether in a 1 L round bottom-flask was added drop-wise 100 mL of hydrazine solution in THF (1 M, 100 mmol) 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. Petroleum ether (200 mL) 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 (for 30 minutes to afford 11.7 g of *O*-phenyl carbazate (76.7 mmol, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (t, *J* = 6.0 Hz, 2 H), 7.23 (t, J = 9.0 Hz, 1 H), 7.14 (d, J = 9.0 Hz, 2 H), 6.63-6.44 (br, 1 H), 4.02-3.79 (br, 2H). ^{13}C NMR (75 MHz, CDCl3): δ 156.9 (C), 150.7 (C), 129.4 (CH), 125.6 (CH), 121.4 (CH). 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 C7H8N2O2Na [M+Na]+ : 175.048. Found: 175.0862

6.1.2: Discovery of the First Cascade Reaction Using Amino-isocyanate (section 2.2)

Preparation of Substrates



General Procedure for the Synthesis of Carbazates.

General Procedure A: *Alcohol Oxidation:* Prepared according to the procedure by Mukai.[115] A flame-dried round bottom flask charged with a magnetic stir bar, alkenol, DMSO (3 equiv) and Et_3N (3 equiv) in dry CH_2Cl_2 was added SO_3•Pyr (3 equiv) at 0 °C. The reaction was monitored by TLC until completion. The reaction is quenched by addition of saturated aqueous ammonium chloride, and the mixture was extracted with CH_2Cl_2. The extract was washed with water and brine. The crude mixture was evaporated *in-vacuo*, and used without further purification. *Carbazate Condensation:* Prepared according to the procedure from the Leighton group.[116] To the crude mixture is added the corresponding carbazate and acetic acid in methanol. The mixture is refluxed until consumption of the aldehyde or hydrazide is judged complete by TLC. Corresponding crude hydrazone is directly reduced without further purification.

General Procedure B: *Hydrazone Reduction:* Prepared from a modified procedure by Lane.[117] The corresponding hydrazone was combined with $NaCNBH_3$ (3 equiv), a pinch of methyl orange and stirred in methanol. The solution was capped with a septum and purged for 5 minutes. Acetic acid was added dropwise until the solution becomes acidic. The reaction mixture is stirred for 3 hours. Excess acetic acid is then evaporated and pH is increased with saturated sodium bicarbonate solution and then with 10% NaOH (aq) to reach a pH of 8. Solution is extracted three times with dichloromethane and brine and dried over Na_2SO_4. Volatiles are removed from the organic phase in-vacuo and crude product is purified by column chromatography.

General Procedure C: An oven dried 5 mL µW tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkenyl hydrazide (1.0 equiv), amine (1.1 equiv), and α,α,α-trifluorotoluene (0.3 M) were added to the seal tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for three hours at 80 °C. The tube was cooled to ambient temperature, concentrated under reduced pressure and and purified by silica gel chromatography to give the corresponding products.

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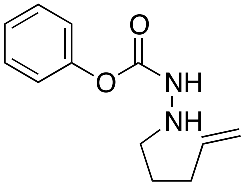
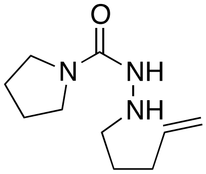
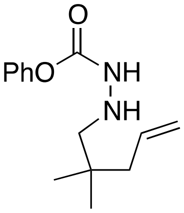
[115] Mukai, C. ; Nomura, I. ; Katagaki, S. *J. Org. Chem.* **2003**, 68, 1376.
[116] Leighton, J. L.; Berger, R.; Duff, K. *J. Am. Chem. Soc.* **2004**, 126, 5686.
[117] Lane, C. F. *Synthesis* **1975**, 135.



Phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate (2.2) : Synthesized according to general procedure **A** using 4-pentenol (1.31 g, 15.2 mmol). Condensation of aldehyde with carbazate was then performed using phenyl hydrazinecarboxylate (2.10 g, 13.8 mmol) in MeOH (46.0 mL). The product was directly reduced according to general procedure **B**. Crude mixture was purified by column chromatography using 5% EtOAc/CH_2Cl_2. The title compound was obtained as a white solid (0.712 g, 23%). TLC R_f = 0.24 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): *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.

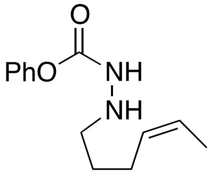


***N*'-(Pent-4-en-1-yl)pyrrolidine-1-carbohydrazide (Scheme 2.9) :** Synthesized according to general procedure **C** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate (0.617 g, 2.80 mmol), pyrrolidine (0.219 g, 3.08 mmol), and α,α,α-trifluorotoluene (9.3 mL). The crude mixture was purified by silica gel column chromatography using 100% EtOAc. The title compound was obtained as a white solid (0.336 g, 61%). TLC R_f = 0.13 in 40% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 5.89-5.75 (m, 1H), 5.89-5.75 (s, br, 1H), 5.06-4.93 (m, 2H), 3.62 (s, br, 1H), 3.32 (t, J = 6.7, 4H), 2.84 (t, *J* = 7.3, 2H), 2.15-2.07 (m, 2H), 1.94-1.86 (m, 4H), 1.59 (quintet, *J* = 7.4, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): *δ* 157.8 (C), 138.6 (CH), 114.8 (CH_2), 52.6 (CH_2), 45.5 (CH_2), 31.5 (CH_2), 27.3 (CH_2), 25.5 (CH_2). IR (film): 3500, 3238, 2980, 2872, 1653, 1546, 1402, 912, 759 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{19}N_3O$ [M]$^+$: 197.1528. Found: 197.1520.

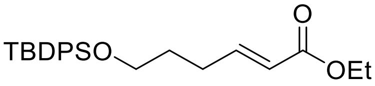


Phenyl 2-(2,2-dimethylpent-4-en-1-yl)hydrazinecarboxylate: Synthesized according to general procedure **A** using 2,2-dimethyl-4-pentenal (0.450 g, 4.00 mmol). Product was directly reduced according to general procedure **B**. The crude mixture was purified by column chromatography using 4% EtOAc/CH_2Cl_2. The title compound was obtained as a colorless oil (0.800 g, 81% over 2 steps). TLC R_f =

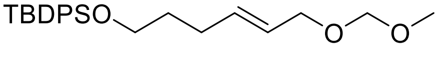
0.23 in 4% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.40-7.35 (m, 2H), 7.24-7.20 (m, 1H), 7.17-7.14 (m, 2H), 5.94-5-79 (m, 1H), 5.09 (s, 1H), 5.06-5.03 (m, 1H), 2.79 (s, 2H), 2.06 (d, *J* = 7.4 Hz, 2H), 0.96 (s, 6H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 155.7 (C), 150.7 (C), 135.0 (CH), 129.3 (CH), 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.



(*Z*)-Phenyl 2-(hex-4-en-1-yl)hydrazinecarboxylate : Synthesized according to general procedure **A** using (E)-4-hexen-1-ol (0.600 mL, 5.00 mmol). The product was directly reduced according to general procedure **B**. Crude mixture was purified by column chromatography using 2% MeOH/CH_2Cl_2. The title compound was obtained as a white amorphous solid (0.760 g, 65% over 3 steps). TLC R_f = 0.52 in 5% MeOH/ CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.40-7.35 (m, 2H), 7.24-7.19 (m, 1H), 7.17-7.14 (m, 2H), 6.79 (s, br, 1H), 5.54-5.36 (m, 2H), 3.91 (br s, 1H), 2.96 (t, *J* =7.2 Hz, 2H), 2.22-2.10 (m, 2H), 1.64-1.54 (m, 5H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 155.5 (C), 150.7 (C), 129.7 (CH), 129.3 (CH), 125.5 (CH), 124.5 (CH), 121.4 (CH), 51.4 (CH_2), 27.6 (CH_2), 24.3(CH_2), 12.8(CH_3). IR (film): 3016, 2931, 2919, 2851, 1724, 1655, 1555, 1474 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O_2$ $[M^+]$: 234.1368. Found: 234.1320.



The aldehyde[118] (4.00 g, 12.3 mmol) was dissolved in toluene (31.0 mL). Ethyl (triphenylphosphoranylidene) acetate (6.40 g, 18.4 mmol) was added and the solution was stirred at 115 °C for 16 hours. Hexane was added and the solution was filtered. The resulting solution was condensed under reduce pressure and purified by column chromatography to afford the *E*-isomer as a clear oil (3.70 g, 76%). TLC R_f = 0.50 in 20% EtOAc/Hex. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.71-7.68 (m, 4H), 7.48-7.38 (m, 6H), 7.00 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.71 (t, *J* = 6.1 Hz, 2H), 2.39-2.31 (m, 2H), 1.78-1.69 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.09 (s, 9H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 166.7 (C), 148.9 (CH), 135.6 (CH), 133.8 (C), 129.6 (CH), 127.7 (CH), 121.5 (CH), 62.9 (CH_2), 60.1 (CH_2), 30.9 (CH_2), 28.7 (CH_2), 26.9 (CH_3), 14.3 (CH_3). IR (film): 3071, 2931, 2858, 1717, 1653, 1589, 1472, 1428, 1390, 1367 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{24}H_{32}O_3Si[M]^+$: 396.2121. Found: 352.1555 (-EtO).



The unsaturated ester (2.90 g, 7.31 mmol) was dissolved in ether (35 mL). A 1.0 M solution of DIBAL-H in THF (16.1 mL) was added dropwise at 0 °C. The resulting solution was stirred at that temperature for one hour. HCl 1 M was added and the layers were separated. The aqueous layer was extracted 3 times

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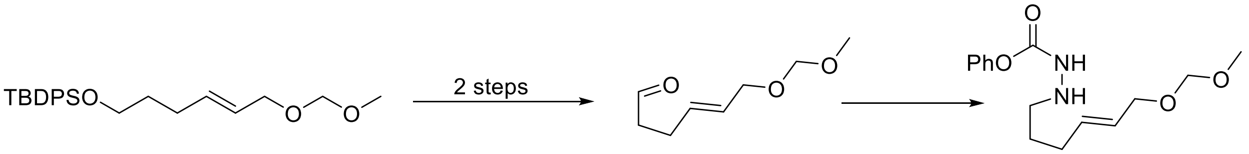
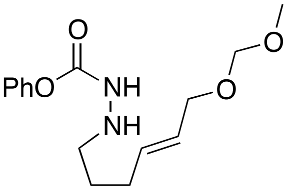
[118] Français, A., Leyva-Pérez, A., Etxebarria-Jardi, G., Peña, J., Ley, S. V. *Chem. Eur. J.* **2011**, *17*, 329.

with ether and the combined organic layers were dried over $MgSO_4$ and condensed under reduce pressure to afford the crude alcohol. The alcohol was dissolved in CH_2Cl_2 (35 mL) and DIPEA (1.92 mL, 11.0 mmol) was added followed by MomCl (0.830 mL, 11.0 mmol). The solution was stirred at room temperature until disappearance of the starting alcohol. Water was added and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, condensed under reduced pressure and purified by column chromatography to afford the pure product as a clear oil (2.20 g, 77% over 2 steps). TLC R_f = 0.25 in 7% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.71-7.66 (m, 4H), 7.47-7.36 (m, 6H), 5.78-5.69 (m, 1H), 5.63-5.53 (m, 1H), 4.65 (s, 2H), 4.01 (dd, *J* = 6.1, 1.0 Hz, 2H), 3.69 (t, *J* = 6.3 Hz, 2H), 3.39 (s, 3H), 2.19 (q, *J* = 7.5 Hz, 2H), 1.72-1.61 (m, 2H), 1.07 (s, 9H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 135.6 (CH), 134.6 (CH), 134.0 (CH), 129.5 (CH), 127.6 (CH), 126.0 (CH), 95.4 (CH_2), 67.9 (CH_2), 63.2 (CH_2), 55.2 (CH_3), 31.9 (CH_2), 28.6 (CH_2), 26.8(CH_3), 19.2 (C). IR (film): 3071, 2930, 2822, 1955, 1889, 1832, 1721, 1472, 1428 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{24}H_{34}O_3Si[M]^+$: 398.2277. Found: 340.1411 (-*t*-Bu).

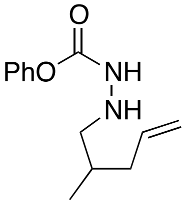


The protected alcohol (2.00 g, 5.00 mmol) was dissolved in THF (15.0 mL). The solution was cooled to 0 °C and a 1.0 M solution of TBAF in THF (6.00 mL) was added. The solution was warmed to room temperature and allowed to stir over night. NH_4Cl was added and the layers were separated. The aqueous layer was extracted 3 times with ether and the combined organic phase were dried over $MgSO_4$, condensed under reduced pressure and purified by a fast column chromatography to remove the siloxane. The resulting alcohol (0.600 g, 3.75 mmol) was dissolved in 20 mL of 9:1 pentane/CH_2Cl_2. Tempo (0.0580 g, 0.380 mmol) and $PhI(OAc)_2$ (1.33 g, 4.13 mmol) was added and the solution was allowed to stir for 5 hours. $NaHCO_3$ was added and the layers were separated. The aqueous layer was extracted 3 times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and condensed under reduce pressure to afford the crude material (aldehyde and iodobenzene).

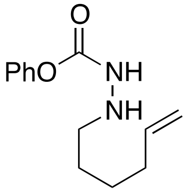


(*E*)-Phenyl 2-(6-(methoxymethoxy)hex-4-en-1-yl)hydrazinecarboxylate: Synthesized according to general procedure **A** using the crude aldehyde (3.75 mmol). The product was directly reduced according to general procedure **B**. The crude mixture was purified by column chromatography using 4% EtOAc/CH_2Cl_2. The title compound was obtained as a colorless oil (0.300 g, 20% over 5 steps). TLC R_f = 0.22 in 40% EtOAc/Hex. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.37-7.32 (m, 2H), 7.21-7.16 (m, 1H), 7.13-7.11 (m, 2H), 5.76-5.67 (m, 1H), 5.62-5.53 (m, 1H), 4.62 (s, 2H), 4.00 (d, *J* = 5.9 Hz, 2H), 3.35 (s, 3H), 2.92 (t, *J* = 7.1 Hz, 2H), 2.16-2.09 (m, 2H), 1.59 (q, *J* = 7.0 Hz). ^{13}C NMR (100 MHz; $CDCl_3$): δ 150.7 (C) , 133.9 (CH), 129.3

(CH), 126.4 (CH), 125.4 (CH), 121.4 (CH), 95.4 (CH_2), 67.8 (CH_2) 55.1 (CH_3), 51.1 (CH_2), 29.6 (CH_2), 27.0 (CH_2). IR (film): 2937, 1741, 1701, 1594, 1479, 1360, 1208 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{22}N_2O_4$ $[M]^+$: 294.1580. Found: 294.0618.



Phenyl 2-(2-methylpent-4-en-1-yl)hydrazinecarboxylate: (Synthesized according to general procedure **A** using crude alcohol[119] (0.501 g, 5.00 mmol). The product was directly reduced according to general procedure **B**. The crude mixture was purified by column chromatography using 4% EtOAc/CH_2Cl_2. The title compound was obtained as a colorless oil (0.300 g, 26% over 4 steps). TLC R_f = 0.38 in 30% EtOAc/hexanes. ^1H NMR (300 MHz; $CDCl_3$): δ 7.40-7.35 (m, 2H), 7.24-7.19 (m, 1H), 7.16-7.14 (m, 2H), 5.81 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.10-5.01 (m, 2H), 2.93-2.87 (m, 1H), 2.79-2.73 (m, 1H), 2.25-2.16 (m, 1H), 2.01-1.92 (m, 1H), 1.82-1.71 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 155.6 (C), 150.7 (C), 136.6 (CH), 129.3 (CH), 125.5 (CH), 121.4 (CH), 116.3 (CH_2), 57.6 (CH_2), 39.1 (CH_2), 31.5 (CH), 17.8 (CH_3). IR (film): 3076, 2961, 2928, 1701, 1606, 1595 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O_2$ $[M]^+$: 234.1368. Found: 234.1361.



Phenyl 2-(hex-5-en-1-yl)hydrazinecarboxylate. Synthesized according to general procedure **A** using 5-hexen-1-ol (0.600 mL, 5.00 mmol). The product was directly reduced according to general procedure **B**. The crude mixture was purified by column chromatography using 4% EtOAc/CH_2Cl_2. The title compound was obtained as a white amorphous solid (0.533 g, 43% over 3 steps). TLC R_f = 0.36 in 10% EtOAc/CH_2Cl_2. ^1H NMR (300 MHz; $CDCl_3$): δ 7.40-7.35 (m, 2H), 7.24-7.19 (m, 1H), 7.17-7.14 (m, 2H), 5.81 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.06-4.95 (m, 2H), 2.96 (t, *J* =6.9 Hz, 2H), 2.09 (q, *J* =6.9 Hz, 2H), 1.59-1.42 (m, 4H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 155.5(C), 150.7(C), 138.5 (CH), 129.3 (CH), 125.5 (CH), 121.4 (CH), 114.7 (CH_2), 51.6 (CH_2), 33.5 (CH_2), 27.1(CH_2), 26.2 (CH_2). IR (film): 2934, 2860, 1734, 1645, 1493, 1364, 1164 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O_2$ $[M]^+$: 234.1368. Found: 234.1371.

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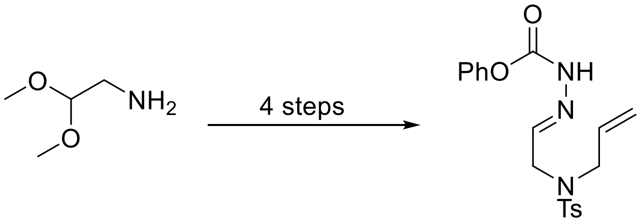
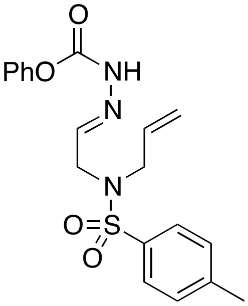
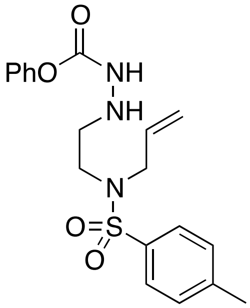
[119] Raghavan, S., Babu, V. S. *Chem. Eur. J.* **2011**, *17*, 8487.



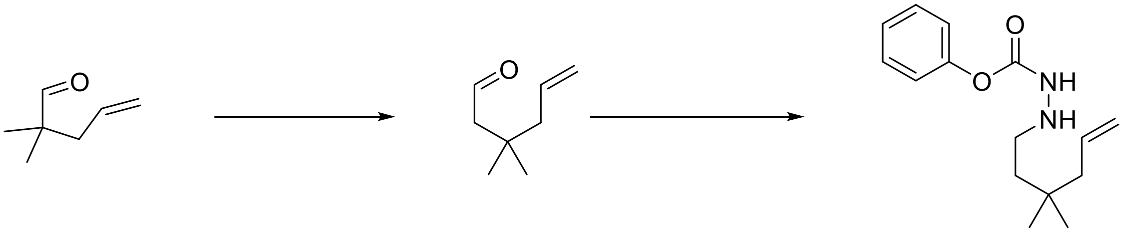
2-Aminoacetalaldehyde (3.15 g, 30.0 mmol) was dissolved in CH_2Cl_2 (150 mL). The solution was cooled to 0 °C and Et_3N (5.58 mL, 40.0 mmol) was added followed by TsCl (7.62 g, 40.0 mmol). The solution was warmed to room temperature and stirred for 2 hours. Water was added and the layers were separated. The aqueous phase was extracted 3 times with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and condensed under reduced pressure to afford the crude tosylated product. The tosylated amine was dissolved in dry DMSO (70 mL) and NaH 60 % (1.32 g, 33.0 mmol) was added slowly. The solution was stirred at room temperature for 30 minutes. Allyl bromide (4.35 g, 36.0 mmol) was added dropwise over 10 minutes and the solution was stirred for 1 hours. A 1:1 brine/water solution was added followed by EtOAc and the layers were separated. The aqueous layer was extracted several time and the combined organic layers were dried over $MgSO_4$ and condensed to afford the 4.70 g (52% over 2 steps) of the crude product.



Phenyl 2-(2-(*N*-allyl-4-methylphenylsulfonamido)ethylidene)hydrazinecarboxylate: The crude acetal (3.00 g, 10.0 mmol) was dissolved in acetone and 60.0 mL of HCl 2.0 M was added. The solution was stirred for one hour at 60 °C and 60.0 mL of HCl 2.00 M was added. The solution was stirred for another hour. CH_2Cl_2 was added and the layers were separated. The aqueous layer was extracted 3 times with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and condensed to afford the crude aldehyde. The aldehyde was dissolved in MeOH (50.0 mL) and phenyl carbazate (1.52 g, 10.0 mmol) was added. The solution was stirred at room temperature over-night. The solution was cooled to 0 °C and filtered to afford the clean product as a white amorphous solid (3.00 g, 77% over 2 steps.) TLC R_f = 0.87 in 5% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 11.49 (br s, 1H), 7.75-7.73 (m, 2H), 7.44-7.16 (m, 8H), 5.73-5.58 (m, 1H), 5.22-5.11 (m, 2H), 3.95-3.70 (m, 4H), 2.40 (s, 3H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 143.9 (C), 136.5 (C), 133.2 (CH), 130.4 (CH), 129.9 (CH), 127.6 (CH), 126.0 (CH), 122.3 (CH), 119.6 (CH_2), 51.0 (CH_2), 49.0 (CH_2), 21.5(CH_3). IR (film): 2337, 1636, 1226 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{19}H_{21}N_3O_4S$ [M^+]: 387.1253. Found: 387.1255



Phenyl 2-(2-(*N*-allyl-4-methylphenylsulfonamido)ethyl)hydrazinecarboxylate: Synthesized according to general procedure **B** using recrystallized hydrazone (1.00 g, 2.58 mmol). The crude mixture was purified by column chromatography using 2% MeOH/CH_2Cl_2. The title compound was obtained as a white amorphous solid (0.950 g, 95%). TLC R_f = 0.47 in 5% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.34 (dd, *J* = 11.0, 8.1 Hz, 4H), 7.24-7.18 (m, 1H), 7.17-7.12 (m, 2H), 5.64 (ddt, *J* = 17.0, 10.2, 6.5 Hz, 1H), 5.17-5.13 (m, 2H), 3.85 (d, *J* = 6.6 Hz, 2H), 3.34-330 (m, 2H), 3.09-3.05 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 155.4 (C), 150.7 (C), 143.6 (C), 132.9 (CH), 129.8 (CH), 129.3 (CH), 127.2 (CH), 125.5 (CH), 121.4 (CH), 119.5 (CH_2), 51.0 (CH_2), 48.9 (CH_2), 44.9 (CH_2), 21.5 (CH_3). IR (film): 2919, 2847, 1732, 1643, 1486, 1458 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{19}H_{23}N_3O_4S[M^+]$: 389.1909. Found: 235.1260 (-Ts).



Preparation followed procedure developed by Yu.[120] To a stirred suspension of (methoxymethyl)triphenylphosphonium bromide (5.00 g, 12.9 mmol) in 20.0 mL of anhydrous THF was slowly added a solution of potassium *tert*-butoxide (1.45 g, 12.9 mmol) in THF (20.0 mL) at 0 °C via cannula under argon. The resulting cherry-red solution was stirred at 0 °C for another 1 h. A solution of 2,2-dimethylpent-4-enal (1.07 g, 8.60 mmol) in THF (5.00 mL) was added dropwise and the resulting mixture was stirred at 20 °C for 2 h. The reaction was quenched by the addition of water (10.0 mL) and the reaction mixture turned from light cherry-red to yellow. The reaction mixture was evaporated under reduced pressure in a water bath (35 °C) to a volume of ca. 20 mL, then aqueous 30% H_2SO_4 (4.00 mL) was added at room temperature under stirring. The solution was stirred overnight and then a saturated $NaHCO_3$ solution (12 mL) was added. The reaction mixture was extracted with ether and the combined organic extract was washed with water, dried over $MgSO_4$, and concentrated to give light yellow oil. The crude material was used for the next steps.

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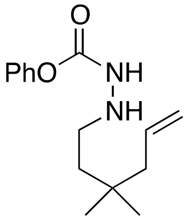
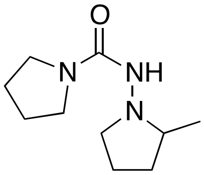
[120] Jiao, L., Yuan, C., Yu, Z.-X. *J. Am.Chem. Soc*. **2008**, *130*, 4421.



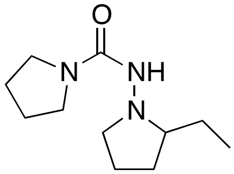
Phenyl 2-(3,3-dimethylhex-5-en-1-yl)hydrazinecarboxylate : Synthesized according to general procedure **A** using crude aldehyde (0.900 g, 7.13 mmol). The product was directly reduced according to general procedure **B**. The crude mixture was purified by column chromatography using 4% EtOAc/CH_2Cl_2. The title compound was obtained as a colorless oil (0.510 g, 23% over 4 steps). TLC R_f = 0.36 in 30% EtOAc/hexane. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.40-7.35 (m, 2H), 7.24-7.19 (m, 1H), 7.17-7.13 (m, 2H), 5.82 (ddt, *J* = 16.6, 10.4, 7.4 Hz, 1H), 5.08-4.99 (m, 2H), 3.00-2.94 (m, 2H), 1.98 (d, *J*= 7.4 Hz, 2H), 1.46-1.40 (m, 2H), 0.91 (s, 6H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 155.6 (C), 150.7 (C), 135.2 (CH), 129.3 (CH), 125.5 (CH), 121.4 (CH), 117.1 (CH_2), 47.7 (CH_2), 46.6 (CH_2), 39.1(CH_2), 32.5(C), 27.1 (CH_3). IR (film): 2956, 1703, 1590, 1166, 1097 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{22}N_2O_2$ $[M]^+$: 262.1681. Found: 262.1702

General Procedure for the substitution / Cope-type Hydroamination Sequence

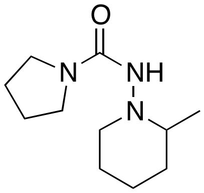
General Procedure D: An oven dried 5 mL microwave tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkenyl hydrazide (1.00 equiv.), amine (1.1 equiv.), and α,α,α-trifluorotoluene (0.3 M) were added to the seal tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for six hours at 120 °C under microwave irradiation. The tube was cooled to ambient temperature, volatiles were removed under reduced pressure and crude product purified by silica gel chromatography.



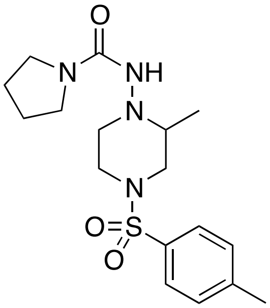
***N*-(2-Methylpyrrolidin-1-yl)pyrrolidine-1-carboxamide (2.10):** Synthesized according to general procedure **D** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate (0.197 g, 0.894 mmol), pyrrolidine (0.0699 g, 0.984 mmol), and α,α,α-trifluorotoluene (2.98 mL). The title compound was purified by column chromatography (4% MeOH/CH_2Cl_2) and obtained as a white solid (0.155 g, 88%). TLC R_f = 0.25 in 4% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.90 (s, br, 1H), 3.39-3.25 (m, 5H), 2.67 (dquintet, *J* = 9.2, 6.4 Hz, 1H), 2.55 (q, *J* = 8.8 Hz, 1H), 1.96-1.64 (m, 7H), 1.44 (dddd, *J* = 12.1, 10.2, 9.4, 6.5 Hz, 1H), 1.11 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 157.3 (C), 62.1 (CH), 56.3 (CH_2), 46.1 (CH_2), 30.5 (CH_2), 25.5 (CH_2), 20.2 (CH_2), 18.3 (CH_3). IR (film): 3230, 2968, 2869, 1645, 1542, 1394 cm^{-1}. HRMS (ES): Exact mass calcd for $C_{10}H_{19}N_3O$ $[M]^-$: 196.1488; found $[M]^-$: 196.0845. Alternatively, compound **2.10** could be obtained in a stepwise fashion under similar conditions as described above, but with the reaction time and temperature as indicated in equation 2.6. ^{1}H NMR analysis of the unpurified reaction mixture after the hydroamination step indicated a 82% NMR yield (determined using 1,3,5-trimethoxybenzene as internal standard).



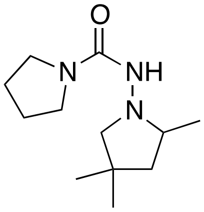
***N*-(2-Ethylpyrrolidin-1-yl)pyrrolidine-1-carboxamide (2.11) :** Synthesized according to general procedure **D** using (*Z*)-phenyl 2-(hex-4-en-1-yl)hydrazinecarboxylate (0.140 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol), and α,α,α-trifluorotoluene (2.00 mL). The title compound was purified by column chromatography (4% MeOH/CH_2Cl_2). The title compound was obtained as a white amorphous solid (0.127 g, 87%). TLC R_f = 0.19 in 4% MeOH/ CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 4.98 (br s, 1H), 3.44-3.31 (m, 4H), 3.15-3.11 (m, 1H), 2.93-2.85 (m, 1H), 2.54-2.40 (m, 2H), 1.89-1.81 (m, 4H), 1.68-160 (m, 4H), 1.43-130 (m, 1H), 1.28-1.18 (m, 1H), 1.10 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): *δ* 157.0 (C), 60.9 (CH), 58.1 (CH_2), 46.1 (CH_2), 33.9 (CH_2), 25.9 (CH_2), 25.4 (CH_2), 24.0 (CH_2), 19.7 (CH_3). IR (film): 2967, 2876, 1655, 1636, 1545, 1388 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{21}N_3O$ [M^+]: 211.1685. Found: 211.1625



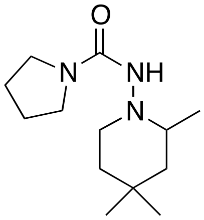
***N*-(2-Methylpiperidin-1-yl)pyrrolidine-1-carboxamide (2.12):** Synthesized according to general procedure **D** using phenyl 2-(hex-5-en-1-yl)hydrazinecarboxylate (0.140 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol), and α,α,α-trifluorotoluene (2.00 mL). The title compound was purified by column chromatography (4% MeOH/CH_2Cl_2). The title compound was obtained as a white amorphous solid (0.100 g, 79%). TLC R_f = 0.15 in 4% MeOH/ CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 4.98 (br s, 1H), 3.44-3.31 (m, 4H), 3.15-3.11 (m, 1H), 2.93-2.85 (m, 1H), 2.54-2.40 (m, 2H), 1.89-1.81 (m, 4H), 1.68-160 (m, 4H), 1.43-130 (m, 1H), 1.28-1.18 (m,1H), 1.10 (d, *J* = 6.2 Hz, 3H).^{13}C NMR (100 MHz; $CDCl_3$): *δ* 157.0 (C), 60.9 (CH), 58.1 (CH_2), 46.1 (CH_2), 33.9 (CH_2), 25.9 (CH_2), 25.4 (CH_2), 24.0 (CH_2), 19.7 (CH_3); IR (film) : 2939, 2859, 1635, 1547, 1402, 1374 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{21}N_3O$ [M^+]: 211.1685. Found: 211.1625.



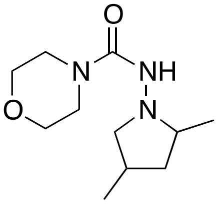
N-(2-Methyl-4-tosylpiperazin-1-yl)pyrrolidine-1-carboxamide (2.13): Synthesized according to general procedure **D** using phenyl 2-(2-(N-allyl-4-methylphenylsulfonamido)ethyl)hydrazinecarboxylate (0.233 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol) dissolved in α,α,α-trifluorotoluene (2.00 mL) and heated at 175 °C for six hours. The title compound was purified by column chromatography (4% MeOH/CH_2Cl_2) and obtained as a white amorphous solid (0.200 g, 86%). TLC R_f = 0.16 in 4% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.59 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.0, 2H), 5.31 (br s, 1H), 3.59-3.52 (m, 2H), 3.28 (t, J = 6.4 Hz 4H), 3.13-3.10 (m, 1H), 2.83-2.77 (m, 2H), 2.63 (td, J = 11.4, 2.7 Hz, 1H), 2.42 (s, 3H), 2.24 (t, J = 10.8 Hz, 1H), 1.82-178 (m, 4H), 1.05 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 156.0 (C), 144.0 (C), 131.8 (CH), 129.7 (CH), 127.7 (CH), 58.4 (CH), 55.3 (CH_2), 51.9 (CH_2), 46.1 (CH_2), 45.7 (CH_2), 25.3 (CH_2), 21.5 (CH_3), 16.2 (CH_3). IR (film): 2972, 2862, 1641, 1536, 1455, 1393, 1336 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{17}H_{26}N_4O_3S_1$ [M$^+$]: 366.1726. Found: 366.1721.



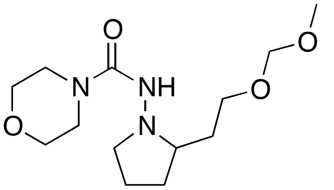
Phenyl 2-(2,2-dimethylpent-4-en-1-yl)hydrazinecarboxylate (2.14): Synthesized according to general procedure **D** using phenyl 2-(2,2-dimethylpent-4-en-1-yl)hydrazinecarboxylate (0.150 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol), and α,α,α-trifluorotoluene (2.00 mL). The title compound was purified by column chromatography (4% MeOH/CH_2Cl_2) and was obtained as a clear oil (0.136 g, 100%). TLC R_f = 0.18 in 4% MeOH/ CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.94 (br s, 1H), 3.43-3.32 (m, 4H), 2.99 (d, J = 8.7 Hz, 1H), 2.93-2.85 (m, 1H), 2.49 (d, J = 8.7 Hz, 1H), 1.87-1.78 (m, 4H), 1.69 (dd, J = 12.6, 7.2 Hz, 1H), 1.27 (dd, J = 12.5, 9.5 Hz, 1H), 1.09 (t, J = 3.0 Hz, 6H), 1.04 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 157.8 (C), 70.0 (CH), 62.0 (CH_2), 46.8 (CH_3), 46.4 (CH_3), 34.0 (C), 30.6 (CH_2), 29.5 (CH_2), 25.4 (CH_3), 18.5 (CH_2). IR (film): 2955, 2875, 1635, 1543, 1454, 1390 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{23}N_3O_1$ [M]$^+$: 225.1841. Found: 225.1811.



N-(2,4,4-Trimethylpiperidin-1-yl)pyrrolidine-1-carboxamide (2.15): Synthesized according to general procedure **D** using phenyl 2-(3,3-dimethylhex-5-en-1-yl)hydrazinecarboxylate (0.990 g, 0.380 mmol), pyrrolidine (0.0300 g, 0.420 mmol), and α,α,α-trifluorotoluene (2.00 mL. The title compound was purified by column chromatography (4% MeOH/CH_2Cl_2) and obtained as a white amorphous solid (0.0750 g, 82%). TLC R_f = 0.11 in 4% MeOH/ CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 5.04 (br s, 1H), 3.38-3.30 (m, 4H), 2.96-2.00 (m, 1H), 2.79-2.72 (m, 2H), 1.83 (dt, *J* = 6.6, 3.2 Hz, 4H), 1.61 (td, *J* = 13.2, 4.4 Hz, 1H), 1.30-1.24 (m, 3H), 1.03 (d, *J* = 6.1 Hz, 3H), 0.93 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): *δ* 157.0 (C), 55.7 (CH), 53.5 (CH_2), 47.1 (CH_2), 46.0 (CH_2), 38.4 (CH_2), 32.3 (CH_3), 29.1 (C), 25.4 (CH_2) 24.1 (CH_3), 20.1 (CH_3). IR (film): 2950, 2869, 1643, 1541, 1460, 1388, 1334 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{25}N_3O$ [M$^+$]: 239.1998. Found: 239.1948.

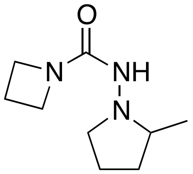


N-(2,4-Dimethylpyrrolidin-1-yl)morpholine-4-carboxamide (2.16): Synthesized according to general procedure **D** using phenyl 2-(2-methylpent-4-en-1-yl)hydrazinecarboxylate (0.110 g, 0.470 mmol), morpholine (0.0470 g, 0.520 mmol), and α,α,α-trifluorotoluene (2.00 mL). The title compound was purified by column chromatography (4% MeOH/CH_2Cl_2) and obtained as a white amorphous solid (1:1 mixture of diastereomers) (0.100 g, 94% yield). TLC R_f = 0.20 in 4% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 5.14 (br s, 1H), 3.75-3.61 (m, 4H), 3.56-3.34 (m, 5H), 2.91-2.68 (m, 2H), 2.28-2.04 (m, 2H), 1.71-1.47 (m, 1H), 1.11-0.98 (m, 6H). ^{13}C NMR (100 MHz; $CDCl_3$) *denotes isomer 159.2*(C) 158.7 (C), 66.6(2*) (CH_2), 64.4 (CH_2), 63.0* (CH_2), 62.0*(CH), 45.0 (CH_2), 44.8* (CH_2) 40.3 (CH_2), 38.9* (CH_2), 28.4* (CH) 28.0 (CH), 21.6*(CH_3) 20.1 (CH_3) 18.6 (CH_3), *18.3 (CH_3). IR (film): 2962, 2924, 2860, 1642, 1536, 1455, 1388, 1262 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{21}N_3O_2$ [M]$^+$: 227.1634. Found: 227.1607.

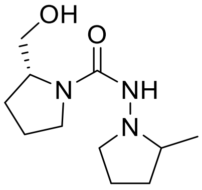


N-(2-(2-(Methoxymethoxy)ethyl)pyrrolidin-1-yl)morpholine-4-carboxamide (2.17): Synthesized according to general procedure **D** using (*E*)-phenyl 2-(6-(methoxymethoxy)hex-4-en-1-

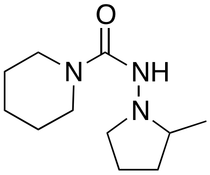
yl)hydrazinecarboxylate (0.132 g, 0.450 mmol), morpholine (0.440 g, 0.500 mmol), and α,α,α-trifluorotoluene. The title compound was purified by column chromatography (4% MeOH/CH_2Cl_2) and obtained as a colorless oil (0.0950 g, 74%). TLC R_f = 0.14 in 4% MeOH/ CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 5.29 (br s, 1H), 4.58 (s, 2H), 3.68-3.65 (m, 3H), 3.60-3.49 (m, 2H), 3.46-3.39 (m, 4H), 3.35-3.28 (m, 4H), 2.80-2.51 (m, 2H), 2.08-1.94 (m, 2H), 1.84-1.79 (m, 2H), 1.67-1.46 (m, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): *δ* 158.2 (C), 96.4 (CH_2), 66.5 (CH_2), 65.4 (CH_2), 64.3 (CH), 56.0 (CH_2), 55.2 (CH_3), 44.6 (CH_2), 33.2 (CH_2), 28.4 (CH_2), 20.4 (CH_2). IR (film): 3060, 2954, 2863, 2126, 2062, 1953, 1627 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{25}N_3O_4$ $[M]^+$: 287.1845. Found: 287.1839.



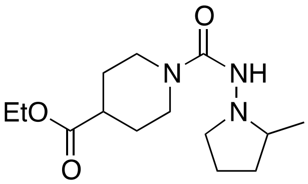
***N*-(2-Methylpyrrolidin-1-yl)azetidine-1-carboxamide (2.18):** Synthesized according to general procedure **D** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **2.2** (0.132 g, 0.600 mmol), azetidine (0.380 g, 0.660 mmol), and α,α,α-trifluorotoluene (2.00 mL). The title compound was purified by column chromatography (4% MeOH/CH_2Cl_2) and obtained as a white amorphous solid (0.0800 g, 73%). TLC R_f = 0.30 in 4% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 5.02 (br s, 1H), 4.16-3.94 (m, 4H), 3.18-3.12 (m, 1H), 2.49-2.34 (m, 2H), 2.22-2.12 (m, 2H), 1.94-1.83 (m, 1H), 1.72-1.63 (m, 2H), 1.42-1.29 (m, 1H), 1.09 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): *δ* 160.0 (C), 62.2 (CH), 56.7 (CH_2), 50.5 (CH_2), 30.2 (CH_2), 19.8 (CH_2), 17.9 (CH_3), 16.5 (CH_2). IR (film): 2955, 2883, 1627, 1563, 1494, 1414, 1293 cm^{-1}. HRMS (EI): Exact mass calcd for $C_9H_{17}N_3O_1$ $[M]^+$: 183.1372. Found: 183.1383.



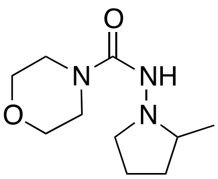
(2*S*)-2-(Hydroxymethyl)-*N*-(2-methylpyrrolidin-1-yl)pyrrolidine-1-carboxamide (2.19): Synthesized according to general procedure **D** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **2.2** (0.148 g, 0.669 mmol), (*S*)-(+)-prolinol (0.0745 g, 0.737 mmol) and α,α,α-trifluorotoluene (2.23 mL). The title compound was purified by column chromatography (4% MeOH/CH_2Cl_2) and obtained as a clear oil (0.0849 g, 56%; 6:5 mixture of diastereoisomers, 96% NMR yield). TLC R_f = 0.25 in 10% MeOH/CH_2Cl_2. ^{1}H NMR (400 MHz; $CDCl_3$): *denotes presence of diastereoisomer *δ* 5.57 (t, *J* = 11.0 Hz, 2H), 4.04-3.94 (m, 1H), 3.56-3.44 (m, 2H), 3.41-3.21 (m, 3H), 2.67-2.47 (m, 2H), 1.96-1.60 (m, 6H), 1.54-1.36 (m, 2H), 1.06 (dd, *J* = 6.1, 1.7 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): *δ* 159.2 (C), *159.0 (C), 67.5 (CH_2), 67.5 (CH_2), 62.2 (CH), *61.8 (CH), 60.8 (CH), *60.6 (CH), 56.2 (CH_2), *55.9 (CH_2), 47.0 (CH_2), *46.8 (CH_2), 30.3 (CH_2), *30.2 (CH_2), 28.5 (CH_2), *28.5 (CH_2), 24.3 (CH_2), *24.1 (CH_2), 20.1 (CH_2), *20.1 (CH_2), 18.2 (CH_3), *18.2 (CH_3). IR (film): 3416, 3260, 2109, 1646, 703 cm^{-1}. LRMS (EI): 84.1 (100%), 99.1 (48%), 55.1 (28%), 98.1 (19%), 70.1 (17%).



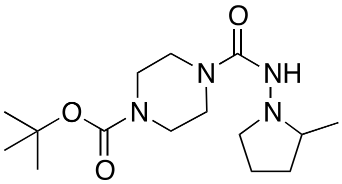
***N*-(2-Methylpyrrolidin-1-yl)piperidine-1-carboxamide (2.20):** Synthesized according to general procedure **D** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **2.2** (0.0985 g, 0.447 mmol), piperidine (0.0419 g, 0.492 mmol), and α,α,α-trifluorotoluene (1.49 mL). Product was purified by column chromatography using 2% MeOH/CH_2Cl_2. The title compound was obtained as a white solid (0.0704 g, 75%, 95% NMR yield). TLC R_f = 0.17 in 40% EtOAc/*n*-hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 5.05 (br s, 1H), 3.32 (t, *J* = 4.9 Hz, 4H), 3.24 (td, *J* = 8.4, 3.4 Hz, 1H), 2.65-2.57 (m, 1H), 2.48 (q, *J* = 8.9 Hz, 1H), 1.87 (dddd, *J* = 12.0, 9.6, 7.2, 4.7 Hz, 1H), 1.76-1.64 (m, 2H), 1.57-1.33 (m, 7H), 1.06 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): *δ* 158.7 (C), 62.3 (CH), 56.0 (CH_2), 45.5 (2 CH_2), 30.4 (CH_2), 25.7 (CH_2), 24.6 (CH_2), 20.1 (CH_2), 18.3 (CH_3). IR (film): 3246, 3066, 2934, 2852, 1634, 1548, 1404, 1092, 1089, 983 cm^{-1}. TOF HRMS (EI): Exact mass calcd for $C_{11}H_{21}N_3O$ [M^+]: 210.1687; found ES [M]$^-$: 210.1113.



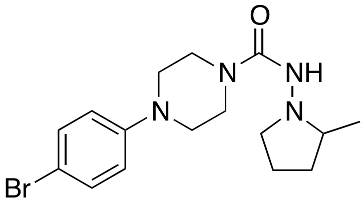
Ethyl 1-((2-methylpyrrolidin-1-yl)carbamoyl)piperidine-4-carboxylate (2.21): Synthesized according to general procedure **D** using 2-(pent-4-en-1-yl)hydrazinecarboxylate **2.2** (0.0800 g, 0.363 mmol), ethyl piperidine-4-carboxylate (0.0628 g, 0.400 mmol), and α,α,α-trifluorotoluene (1.21 mL). Product was purified by column chromatography using 1% MeOH/CH_2Cl_2. The title compound was obtained as a white solid (0.0663 g, 64%). TLC R_f = 0.38 in 5% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 4.99 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 4.01-3.94 (m, 2H), 3.23 (td, *J* = 8.5, 3.2 Hz, 1H), 2.87-2.79 (m, 2H), 2.61-2.52 (m, 1H), 2.48-2.37 (m, 2H), 1.91-1.80 (m, 3H), 1.75-1.54 (m, 4H), 1.44-1.34 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): *δ* 174.6 (C), 158.8 (C), 62.4 (CH), 60.6 (CH_2), 56.0 (CH_2), 44.1 (CH_2), 44.0 (CH_2), 41.2 (CH), 30.4 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 20.0 (CH_2), 18.3 (CH_3), 14.2 (CH_3). IR (film): 3386, 3315, 3074, 2967, 2853, 1730, 1699, 1535, 1364, 1173 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{25}N_3O_3$ [M]$^+$: 238.1896. Found: 238.1580 (-C_2H_5O).



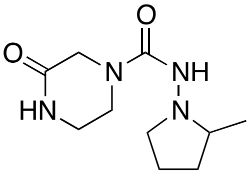
***N*-(2-Methylpyrrolidin-1-yl)morpholine-4-carboxamide (2.6).** Synthesized according to general procedure **D** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **2.2** (0.0542 g, 0.246 mmol), morpholine (0.0236 g, 0.271 mmol), and α,α,α-trifluorotoluene (0.820 mL). Product was purified by column chromatography using 30% EtOAc/*n*-hexanes. The title compound was obtained as a white solid (0.0518 g, 99% isolated). TLC R_f = 0.23 in 100% EtOAc. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 5.04 (s, 1H), 3.68-3.64 (m, 4H), 3.53-3.38 (m, 4H), 3.30-3.23 (m, 1H), 2.62 (qd, *J* = 6.4, 2.7 Hz, 1H), 2.50 (q, *J* = 8.9 Hz, 1H), 1.93 (dddd, *J* = 12.1, 9.5, 7.3, 4.9 Hz, 1H), 1.81-1.68 (m, 2H), 1.50-1.37 (m, 1H), 1.11 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): *δ* 158.8 (C), 66.6 (CH_2), 62.1 (CH), 55.7 (CH_2), 44.8 (CH_2), 30.3 (CH_2), 20.0 (CH_2), 18.2 (CH_3). IR (film): 3430, 2975, 2867, 1846, 1555, 1264, 1098 cm^{-1}. Exact mass calcd for $C_{10}H_{19}N_3O_2$ [M]$^+$: 213.1477. LRMS (EI): 84.1 (100%), 99.1 (68%), 70.0 (18%), 42.0 (14%), 162.0 (11%), 41.0 (11%), 56.1 (11%), 111.1 (11%).



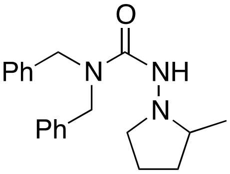
tert-Butyl-4-((2-methylpyrrolidin-1-yl)carbamoyl)piperazine-1-carboxylate (2.22): Synthesized according to general procedure **D** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **2.2** (0.897 g, 0.407 mmol), *N*-boc-piperazine (0.0834 g, 0.448 mmol), and α,α,α-trifluorotoluene (1.36 mL). The product was purified by column chromatography using 1% MeOH/CH_2Cl_2. The title compound was obtained as a white solid (0.117 g, 92%). TLC R_f = 0.3 in 4% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 5.19 (s, 1H), 3.43-3.34 (m, 8H), 3.22 (ddd, *J* = 8.8, 7.7, 3.6 Hz, 1H), 2.65-2.53 (m, 1H), 2.52-2.43 (m, 1H), 1.89 (dddd, *J* = 12.1, 9.4, 7.3, 4.9 Hz, 1H), 1.76-1.62 (m, 2H), 1.45-1.32 (m, 10H), 1.06 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): *δ* 158.8 (C), 154.6 (C), 80.0 (C), 62.3 (CH), 55.8 (CH_2), 44.3 (CH_2), 43.7 (CH_2), 30.2 (CH_2), 28.3 (CH_3), 19.9 (CH_2), 18.2 (CH_3). IR (film): 3474, 3245, 2374, 2860, 1690, 1636, 1364, 1240, 769 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{15}H_{28}N_4O_3$ [M]$^-$: 311.2183; found: 311.1182.



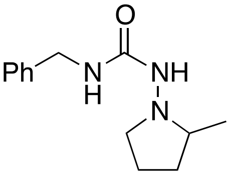
4-(4-Bromophenyl)-*N*-(2-methylpyrrolidin-1-yl)piperazine-1-carboxamide (2.23): Synthesized according to general procedure **D** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **2.2** (0.132 g, 0.600 mmol), 1-(4-bromophenyl)piperazine (0.160 g, 0.660 mmol), and α,α,α-trifluorotoluene (2.00 mL). The title compound was purified by column chromatography (3% MeOH/CH_2Cl_2).The title compound was obtained as a white amorphous solide (0.152 g, 69%). TLC R_f = 0.13 in 3% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 7.35 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 5.06 (br s, 1H), 3.72-3.52 (m, 4H), 3.31 (ddd, *J* = 8.8, 7.7, 3.36 Hz, 1H), 3.14 (t, *J* = 5.3 Hz, 4H), 2.70-2.58 (m, 1H), 2.52 (q, *J* = 8.9 Hz, 1H), 2.01-190 (m, 1H), 1.84-1.67 (m, 2H), 1.53-1.40 (m, 1H) 1.14 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz; CDCl3): *δ* 158.8 (C), 150.1 (C), 131.9 (CH), 117.9 (CH), 112.2 (C), 62.5 (CH), 56.0 (CH_2), 48.9 (CH_2), 44.3 (CH_2), 30.3 (CH_3), 19.9 (CH_2), 18.2 (CH_3). IR (film): 2983, 2834, 1627, 1486, 1269 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{23}N_4O_1Br_1$ [M]$^+$: 366.1055 Found: 366.1965.



_N_-(2-Methylpyrrolidin-1-yl)-3-oxopiperazine-1-carboxamide (2.24): Synthesized according to general procedure **D** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **2.2** (0.0799 g, 0.363 mmol), 2-oxopiperazine (0.0525 g, 0.499 mmol), and α,α,α-trifluorotoluene (1.21 mL). Product was purified by column chromatography using 10% MeOH/CH_2Cl_2. The title compound was obtained as a white solid (0.0698 g, 85%). TLC R_f = 0.35 in 10% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.98 (br s, 1H), 7.40 (br s, 1H), 3.90-3.76 (m, 2H), 3.51-3.39 (m, 2H), 3.15 (td, J = 5.3, 2.5 Hz, 2H), 3.05 (q, J = 6.2 Hz, 1H), 2.89 (dq, J = 13.9, 6.7 Hz, 1H), 2.70 (q, J = 8.7 Hz, 1H), 1.87 (dq, J = 12.5, 6.5 Hz, 1H), 1.70-1.60 (m, 2H), 1.34-1.22 (m, 1H), 0.97 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 166.7 (C), 156.7 (C), 59.2 (CH), 53.9 (CH_2), 47.6 (CH_2), 40.2 (CH_2), 40.0 (CH_2), 30.2 (CH_2), 19.9 (CH_2), 18.4 (CH_3). IR (film) 3386, 2256, 2129, 1662, 1052, 826 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{10}H_{18}N_4O_2$ [M$^+$]: 226.1430; found: 226.1422.



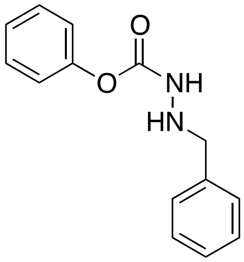
1,1-Dibenzyl-3-(2-methylpyrrolidin-1-yl)urea (2.25): Synthesized according to general procedure **D** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **2.2** (0.0488 g, 0.222 mmol), dibenzylamine (0.0482 g, 0.244 mmol), and α,α,α-trifluorotoluene (0.740 mL). The product was purified by column chromatography using 30% EtOAc/*n*-hexanes. The title compound was obtained as a white solid (0.0580 g, 81%). TLC R_f = 0.31 in 40% EtOAc/*n*-hexanes. ^{1}H NMR (300 MHz; CDCl3): δ 7.34-7.22 (m, 10H), 5.02 (s, 1H), 4.48 (s, 4H), 3.21 (td, J = 8.4, 3.3 Hz, 1H), 2.59-2.48 (m, 1H), 2.41 (q, J = 8.8 Hz, 1H), 1.89-1.59 (m, 3H), 1.44-1.31 (m, 1H), 1.01 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 158.6 (C), 137.8 (CH), 128.8 (CH), 127.6 (CH), 127.5 (CH), 61.8 (CH), 55.9 (CH_2), 50.5 (CH_2), 30.3 (CH_2), 20.1 (CH_2), 18.2 (CH_3). IR (film): 3422, 2097, 1645, 1087 cm^{-1}. LRMS (EI): 91.1 (100%), 84.1 (63%), 116.1 (0.4%), 99.1 (29%), 106.1 (29%).



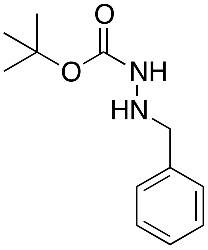
1-Benzyl-3-(2-methylpyrrolidin-1-yl)urea (2.26): Synthesized according to general procedure **D** using phenyl 2-(pent-4-en-1-yl)hydrazinecarboxylate **2.2** (0.0915 g, 0.415 mmol), benzylamine (0.222 g, 2.08 mmol), and α,α,α-trifluorotoluene (1.38 mL). The product was purified by column chromatography using 70% EtOAc/hexanes. The title compound was obtained as a white solid (0.0469 g, 48%). TLC R_f = 0.3 in 80% EtOAc/*n*-hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.35-7.22 (m, 5H), 6.35 (s, 1H), 5.23 (s, 1H), 4.52-4.37 (m, 2H), 3.23 (s, 1H), 2.50 (d, *J* = 20.3 Hz, 2H), 1.99-1.88 (m, 1H), 1.77-1.67 (m, 2H), 1.43-1.30 (m, 1H), 1.09 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): *δ* 158.6 (C), 137.8 (CH), 128.8 (CH), 127.6 (CH), 127.5 (CH), 61.8 (CH), 55.9 (CH_2), 50.5 (CH_2), 30.3 (CH_2), 20.1 (CH_2), 18.2 (CH_3). IR (film): 3430, 3191, 3023, 2970, 2023, 1672, 1537 cm^{-1}. LRMS (EI): 84.1 (100%), 85.08 (88%), 91.06 (66%), 41.04 (20%), 106.1 (19%).

6.2: Supporting Information for Chapter 3

6.2.1: Synthesis of Aza-dipeptoids (section 3.1.1)



Phenyl 2-benzylhydrazinecarboxylate (3.1). Synthesized according to general procedure **A** using phenyl hydrazine carboxylate (0.512 g, 3.37 mmol), benzaldehyde (0.393 g, 3.7 mmol) MeOH (11.2 mL). The crude hydrazone was directly reduced using sodium cyanoborohydride (0.696 g, 10.1 mmol) in MeOH (11.2 mL). The crude mixture was purified by column chromatography using 5% EtOAc/CH_2Cl_2. The title compound was obtained as a white solid (1.11 g, 33%). TLC R_f = 0.57 in 40% EtOAc/hexanes. ^{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; $CDCl_3$): *δ* 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). IR (film): 3294, 3032, 2853, 1938, 1736, 1496, 1456, 1204, 746, 695 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{14}N_2O_2$ [M]$^+$: 242.1055. Found: 242.1034.

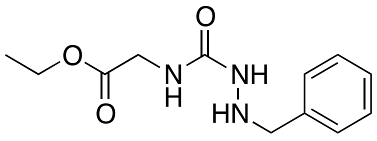


***tert*-Butyl 2-benzylhydrazinecarboxylate:** Synthesized according to general procedure **A** using *tert*-butyl carbazate (3.37 g, 25.5 mmol) and benzaldehyde (2.70 g, 25.4 mmol) in MeOH (77.0 mL). The crude hydrazone was directly reduced using sodium cyanoborohydride (5.27 g, 76.5 mmol) in MeOH (77.0 mL). The crude mixture was purified by column chromatography using 40% EtOAc/hexanes. The title compound was obtained as a clear oil (2.49 g, 43%). TLC R_f = 0.4 in 40% EtOAc/hexanes. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.32-7.24 (m, 5H), 6.24 (s, 1H), 3.96 (s, 2H), 3.88 (s, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz; $CDCl_3$): *δ* 156.8 (C), 137.7 (C), 129.1 (CH), 128.6 (CH), 127.6 (CH), 80.6 (C), 55.9 (CH_2), 28.5 (CH_3). IR (film):

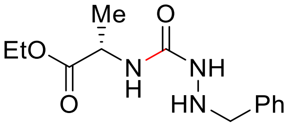
3409, 3340, 2979, 2937, 2861, 2439, 2284, 2151, 1953, 1700, 1520, 873 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{18}N_2O_2$ [M]$^+$: 222.1368. Found: 166.0748 (-*t*-Bu$^+$).

General Procedure for "aza-dipeptide" synthesis

General Procedure E: An oven dried 5 mL microwave tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The carbazate (1.00 equiv), aminoester hydrochloride salt (1.1 equiv), *N*,*N*-diisopropylethylamine (1.2 equiv) and α,α,α-trifluorotoluene (0.3 M) were added to the seal tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for 12 hours at 100 °C in an oil bath. The tube was cooled to ambient temperature, volatiles were removed under reduced pressure and crude product purified by silica gel chromatography.

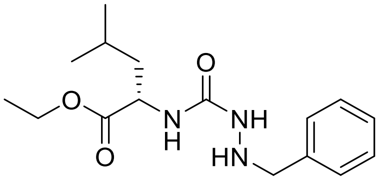


Ethyl 2-(2-benzylhydrazinecarboxamido)acetate (3.2): Synthesized according to general procedure E using phenyl 2-benzylhydrazinecarboxylate 3.1 (0.120 g, 0.494 mmol), glycine ethyl ester hydrochloride (0.0758 g, 0.543 mmol), *N*,*N*-diisopropylethylamine (0.766 g, 0.593 mmol), and α,α,α-trifluorotoluene (1.65 mL). The crude mixture was purified by column chromatography 1% MeOH/CH_2Cl_2. The title compound was obtained as a white solid (0.0972 g, 78%). TLC R_f = 0.46 in 100% EtOAc. ^{1}H NMR (300 MHz; $CDCl_3$): *denotes minor traces of isomer, δ 7.35-7.23 (m, 5H), 6.56-6.53 (m, 1H), 6.20 (s, br, 1H), 4.22-4.13 (m, 2H), 4.09-3.88 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.8 (C), 159.2 (C), 141.6 (C), 136.7 (CH), 129.6 (CH), 128.8 (CH), 128.7 (CH), 127.8 (CH), 126.8 (CH), 61.2 (CH_2), 56.5 (CH_2), *41.7 (CH_2), 41.5 (CH_2), 14.2 (CH_3). IR (film): 3344, 3283, 2983, 2941, 2857, 1748, 1653, 1542, 1212, 1181, 1037 cm^{-1}. HRMS (ESI-): Exact mass calcd for $C_{12}H_{17}N_3O_3$ [M]$^-$: 251.1217; found: 251.0730.

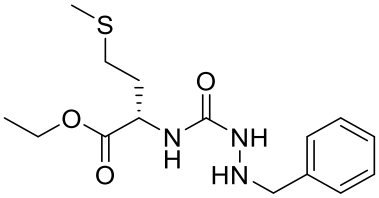


(*S*)-Ethyl 2-(2-benzylhydrazinecarboxamido)propanoate 3.3: Synthesized according to general procedure E using phenyl 2-benzylhydrazinecarboxylate 3.1 (0.0820 g, 0.340 mmol), L-alanine ethyl ester hydrochloride (0.0570 g, 0.370 mmol), *N,N*-diisopropylethylamine (0.0700 mL, 0.420 mmol), and α,α,α-trifluorotoluene (2.00 mL). The crude mixture was purified by column chromatography 5% MeOH/CH_2Cl_2. The title compound was obtained as a white solid (0.0056 g, 62%). $[\boldsymbol{\alpha}]_{\boldsymbol{d}}^{\mathbf{20}}$ (CH_2Cl_2) = -2.2, TLC R_f = 0.32 in 5% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.44-7.25 (m, 6H), 6.56 (br d, 1H), 6.23 (br s, 1H), 4.47-4.37 (m, 1H), 4.22-4.14. (m, 2H), 3.99-3.87 (m, 2H), 1.35-1.25 (m, 6H). ^{13}C NMR (100 MHz; $CDCl_3$): *denotes presence of minor isomer δ 173.6 (C), *172.5 (C), 158.6 (C), *158.6 (C), 136.6 (C), *135.7 (C), 129.3 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), *128.0 (CH), 127.8 (CH), 61.2 (CH_2), 56.5 (CH_2),

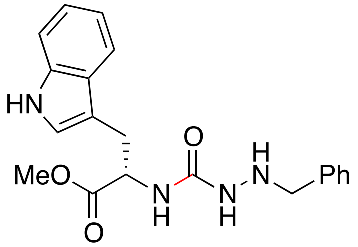
*54.4 (CH_2), *51.5 (CH), 48.1 (CH), 18.9 (CH_3), *17.4 (CH_3) 14.1 (CH_3). IR (film): 3259, 1720, 1652, 1543, 1456, 1421, 1265, 1207, 1180 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{13}H_{19}N_3O_3$: 265.1426; found: 265.1430.



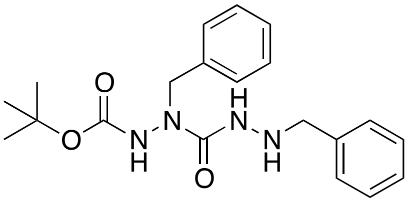
(*S*)-Ethyl 2-(2-benzylhydrazinecarboxamido)-4-methylpentanoate (3.4): Synthesized according to general procedure E using phenyl 2-benzylhydrazinecarboxylate 3.1 (0.164 g, 0.600 mmol), L-leucine ethyl ester hydrochloride (0.129 g, 0.660 mmol), *N,N*-diisopropylethylamine (0.140 mL, 0.720 mmol), and α,α,α-trifluorotoluene (1 mL). The crude mixture was purified by column chromatography 2% MeOH/CH_2Cl_2. The title compound was obtained as a white amorphous solid (0.125 g, 68 %). $[\alpha]_d^{20}$ (CH_2Cl_2) = -11.6, TLC R_f = 0.38 in 5 % MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.43-7.23 (m, 5H), 6.43 (br d, *J* = 9.1 Hz, 1H), 6.21 (br s, 1H), 4.45 (td, *J* = 9.0, 5.0 Hz, 1H), 4.23-4.11 (m, 2H), 4.04-3.85 (m, 2H), 1.70-1.46 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 5.7 Hz, 6H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 173.8 (C), 158.8 (C), 136.6 (C), 128.8 (CH), 128.6 (CH), 128.4 (CH), 127.8 (CH), 61.0 (CH_2), 56.6 (CH_2), 51.0 (CH), 41.8 (CH), 24.7 (CH), 22.9 (CH_3), 21.8 (CH_3), 14.1 (CH_3). IR (film): 3290, 2959, 1732, 1675, 1543, 1454 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{16}H_{25}N_3O_3$: 307.1896; Found: 307.1912.



(*S*)-Ethyl 2-(2-benzylhydrazinecarboxamido)-4-(methylthio)butanoate (3.5): Synthesized according to general procedure E using phenyl 2-benzylhydrazinecarboxylate 3.1 (0.164 g, 0.600 mmol), L-methionine ethyl ester hydrochloride (0.141 g, 0.660 mmol), *N,N*-diisopropylethylamine (0.140 mL , 0.720 mmol), and α,α,α-trifluorotoluene (1.00 mL). The crude mixture was purified by column chromatography 2% MeOH/CH_2Cl_2. The title compound was obtained as a white amorphous solid (0.139 g, 71%).$[\alpha]_d^{20}$ (CH_2Cl_2) = -7.8, TLC R_f = 0.3 in 5% CH_2Cl_2/MeOH. ^{1}H NMR (300 MHz; $CDCl_3$, 70°C): δ 7.41-7.18 (m, 5H), 6.62-6.39 (br d, 1H), 6.08-5.93 (br s, 1H), 4.71-4.39 (m, 1H), 4.23-4.08 (m, 2H), 4.04-3.83 (m, 2H), 2.63-2.37 (m, 2H), 2.15-1.75 (m, 5H), 1.33-1.17 (m, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): *denotes presence of minor isomer δ 172.6 (C), *171.6 (C), 158.9 (C), *153.4 (C), 136.7 (C), *135.8 (C), 129.3 (CH), 128.9 (CH), 128.7 (CH), 128.4 (CH), *128.0 (CH), 127.9 (CH), 61.4 (CH_2), 56.5 (CH_2), *54.8 (CH_2), *54.4 (CH), 51.8 (CH), 32.4 (CH_2), *30.5 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 15.4 (CH_3), *15.2 (CH_3), 14.2 (CH_3). IR (film): 3290, 2924, 1726, 1720, 1684, 1653, 1541 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{15}H_{23}N_3O_3S$: 325.1460; Found: 325.1413.



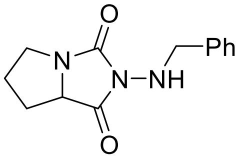
(*S*)-Methyl 2-(2-benzylhydrazinecarboxamido)-3-(1*H*-indol-3-yl)propanoate (3.6): Synthesized according to general procedure E using phenyl 2-benzylhydrazinecarboxylate 3.1 (0.0996 g, 0.411 mmol), (*S*)-methyl 2-amino-3-(1*H*-indol-3-yl)propanoate (0.1151 g, 0.452 mmol), *N,N*-diisopropylethylamine (0.0637 g, 0.493 mmol), and α,α,α-trifluorotoluene (1.37 mL). The crude mixture was purified by column chromatography 1% MeOH/CH_2Cl_2. The title compound was obtained as a brown oil (0.0642 g, 43%). $[\boldsymbol{\alpha}]_{\boldsymbol{d}}^{\boldsymbol{20}}$ (CH_2Cl_2) = +32.4, TLC R_f = 0.24 in 40% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.35-7.24 (m, 6H), 6.52-6.48 (m, 1H), 5.98 (br s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 2H), 3.44 (q, *J* = 6.2 Hz, 2H), 2.45 (t, *J* = 6.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): *denotes traces of conformers δ 172.3 (C), *171.2 (C), 157.5 (C), *155.2 (C), 137.0 (C), *136.7 (C), 135.9 (C), *135.8 (C), 128.3 (CH), *128.0 (CH), 127.7 (CH), *127.5 (CH), 127.1 (CH), *127.0 (CH), 126.7 (CH), *126.6 (CH), 123.7 (CH), *123.1 (CH), 120.5 (CH), *120.4 (CH), 118.0 (CH), *118.0 (CH), 117.9 (CH), *117.6 (CH), 110.9 (CH), *110.8 (CH), 108.9 (C), *107.5 (C), 55.1 (CH_3), *54.9 (CH_3), 52.8 (CH_2), *52.7 (CH), 51.1 (CH), 27.5 (CH_2), *26.6 (CH_2). IR (film): 3292, 1772, 1710, 1664, 1542, 1425, 1340 cm^{-1}. LRMS (EI): 130.1 (100%), 91.1 (12.4%), 131.1 (9%), 162.0 (4%), 334.1 (4%).



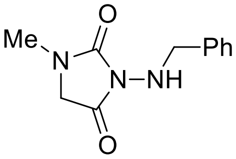
***tert*-Butyl 2-benzyl-2-(2-benzylhydrazinecarbonyl)hydrazinecarboxylate (3.7):** Synthesized according to general procedure E using phenyl 2-benzylhydrazinecarboxylate 3.1 (0.938 g, 0.387 mmol), *tert*-butyl 2-benzylhydrazinecarboxylate (0.861 g, 3.87 mmol), and α,α,α-trifluorotoluene (1.29 mL). The crude mixture was purified by column chromatography 40% EtOAc/hexanes. The title compound was obtained as a clear oil (0.132 g, 93%). TLC R_f = 0.46 in 40% EtOAc/hexanes. *denotes presence of minor isomer. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.32-7.23 (m, 11H), 6.24 (s, 1H), 4.80 (s, 3H), 3.97 (s, 2H), *1.41 (s, 9H), 1.38 (s, 9H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 158.5 (C), *154.5 (C), 154.2 (C), *45.3 (C), 137.3 (C), 135.9 (C), *134.2 (C), 129.4 (CH), 129.0 (CH), 128.9 (CH), *128.6 (CH), 128.6 (CH), 128.0 (CH), 127.6 (CH), *127.4 (CH), 82.4 (C), 56.2 (CH_2), 51.1 (CH_2), *28.4 (CH_3), 28.2 (CH_3). IR (film): 3264, 2979, 2930, 1957, 1713, 1645, 1447, 1364, 684 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{20}H_{26}N_4O_3$ [M$^+$]: 370.2005; Found [M$^+$]: 370.2003.

6.2.2: Synthesis of Hydantoins (section 3.1.2)

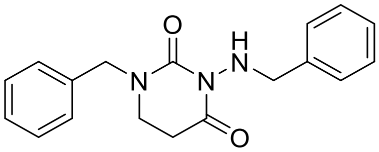
General Procedure F: An oven dried microwave tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The carbazate (1.0 equiv), amino-ester hydrochloride salt (1.1 equiv), *N,N*-diisopropylethylamine (1.2 equiv) and α,α,α-trifluorotoluene (MeCN and $MeNO_2$) (0.3 M) were added to the seal tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated between three and six hours at 80-150 °C. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.



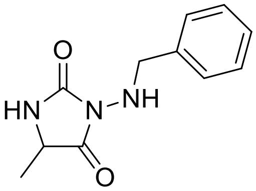
2-Benzylhexahydropyrrolo[1,2-*d*][1,2,4]triazine-1,4-dione (3.10): Synthesized according to general procedure **F** using phenyl 2-benzylhydrazinecarboxylate **3.1** (0.0990 g, 0.409 mmol), L-proline ethyl ester hydrochloride (0.0662 g, 0.400 mmol), *N,N*-diisopropylethylamine (0.0566 g, 0.437 mmol) and α,α,α-trifluorotoluene (1.21 mL) at 100 °C for 6 hours. Crude mixture was purified by column chromatography 10% EtOAc/CH_2Cl_2. The title compound was obtained as a white solid (0.0493 g, 49% yield). TLC R_f = 0.46 in 20% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 7.38-7.35 (m, 2H), 7.32-7.24 (m, 3H), 4.33 (s, 1H), 4.10 (s, 2H), 3.57 (dt, *J* = 11.2, 7.7 Hz, 1H), 3.19 (ddd, *J* = 11.2, 7.6, 5.2 Hz, 1H), 2.16 (dtd, *J* = 12.4, 7.1, 4.3 Hz, 1H), 2.01-1.91 (m, 2H), 1.49 (dq, *J* = 12.6, 9.0 Hz, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.7 (C), 159.2 (C), 135.7 (CH), 128.5 (CH), 128.1 (CH), 61.7 (CH), 54.5 (CH_2), 45.7 (CH_2), 27.5 (CH_2), 26.7 (CH_2). IR (film): 3276, 1774, 1713, 1493, 1456, 1404, 1219, 750, 698 cm^{-1}. Exact mass calcd for $C_{13}H_{15}N_3O_2$ $[M]^+$: 245.1164. LRMS(EI): 70.1 (100%), 91.1 (97%), 141.1 (71%), 106.1 (66%), 65.4 (19%), 39.0 (11%), 245.1 (0.2%). The X-Ray information is available from the Cambridge Crystallographic Data Centre: CCDC 1026461.



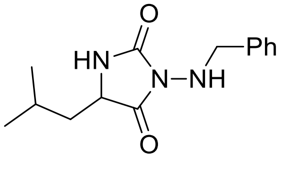
3-(Benzylamino)-1-methylimidazolidine-2,4-dione (3.13): Synthesized according to general procedure **F** using phenyl 2-benzylhydrazinecarboxylate **3.1** (0.0820 g, 0.340 mmol), sarcosine ethyl ester hydrochloride (0.0570 g, 0.370 mmol), *N,N*-diisopropylethylamine (0.0700 mL, 0.410 mmol) and α,α,α-trifluorotoluene (1.0 mL) at 100 °C for 6 hours. The title compound was purified by column chromatography (20% EtOAc/CH_2Cl_2) and was obtained as colorless amorphous solid (0.0610 g, 82%). TLC R_f = 0.19 in 20% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.42-7.39 (m, 2H), 7.34-7.27 (m, 3H), 4.11 (s, 2H), 3.76 (s, 2H), 2.95 (s, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 167.2 (C), 155.4 (C), 135.7 (C), 129.0 (CH), 128.3 (CH), 127.8 (CH), 54.5 (CH_2), 50.1 (CH_2), 29.8 (CH_2). IR (film): 2982, 1772, 1716, 1440, 1260, 1085. HRMS (EI): Exact mass calcd for $C_{11}H_{13}N_3O_2$ $[M]^+$: 219.1008. Found: 219.1003.



1,4-Dibenzyl-1,2,4-triazepane-3,7-dione (3.14): Synthesized according to general procedure F using phenyl 2-benzylhydrazinecarboxylate 3.1 (0.188 g, 0.777 mmol), ethyl 3-(benzylamino)propanoate (0.177 g, 0.855 mmol) and α,α,α-trifluorotoluene (2.59 mL) at 120 °C for 6 hours. The crude mixture was purified by column chromatography 40% EtOAc/CH_2Cl_2. The title compound was obtained as a clear oil (0.149 g, 62%). TLC R_f = 0.25 in 40% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): *δ* 7.41-7.26 (m, 8H), 7.16 (dd, *J* = 7.5, 1.9 Hz, 2H), 4.58 (s, 2H), 4.06 (s, 2H), 3.13 (t, *J* = 6.8 Hz, 2H), 2.63 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 166.8 (C), 153.1 (C), 136.2 (C), 135.8 (C), 129.4 (CH), 128.8 (CH), 128.2 (CH), 127.9 (CH), 127.9 (CH), 127.7 (CH), 54.8 (CH_2), 51.6 (CH_2), 40.0 (CH_2), 31.3 (CH_2). IR (film): 3293, 3063, 3032, 2922, 2865, 2238, 1717, 1675, 1493, 1436, 1375, 745, 701 cm^{-1}. HRMS(EI): Exact mass calcd for $C_{18}H_{19}N_3O_2$ $[M]^+$: 309.1477 Found: 310.1520.

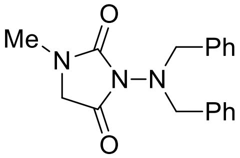


3-(Benzylamino)-5-methylimidazolidine-2,4-dione (3.15): Synthesized according to general procedure **F** using phenyl 2-benzylhydrazinecarboxylate **3.1** (0.0820 g, 0.340 mmol), L-alanine methyl ester (0.0520 g, 0.370 mmol), *N,N*-diisopropylethylamine (0.0700 mL, 0.410 mmol) and α,α,α-trifluorotoluene (1.00 mL) at 150 °C for 6 hours. The title compound was purified by column chromatography (6% MeOH/CH_2Cl_2) and was obtained as colorless amorphous solid (0.0550 g, 62%). TLC R_f = 0.35 in 6% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.42-7.38 (m, 2H), 7.36-7.29 (m, 3H), 6.6 (br s, 1H), 4.15 (s, 1H), 3.99 (q, *J* = 6.7 Hz, 1H), 1.35 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 172.4 (C), 156.2 (C). 135.6 (C), 129.3 (CH), 128.4 (CH), 128.0 (CH), 54.4 (CH_2), 51.5 (CH), 17.4 (CH_3). IR (film): 3236, 1761, 1709, 1684, 1420, 1317, 1215, 748, 706. HRMS (EI): Exact mass calcd for $C_{11}H_{13}N_3O_2$ $[M]^+$: 219.1008. Found: 219.0999.

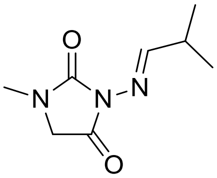


3-(Benzylamino)-5-isobutylimidazolidine-2,4-dione (3.16): Synthesized according to general procedure **F** using phenyl 2-benzylhydrazinecarboxylate **3.1** (0.0820 g, 0.340 mmol), L-leucine methyl ester (0.0670 g, 0.370 mmol), *N,N*-diisopropylethylamine (0.0700 mL, 0.410 mmol) and α,α,α-trifluorotoluene (1.00 mL) at 150 °C for 6 hours. The title compound was purified by column chromatography (3% MeOH/CH_2Cl_2) and was obtained as colorless amorphous solid (0.0550 g, 62%). TLC R_f = 0.29 in 3% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.42-7.38 (m, 2H), 7.36-7.29 (m, 3H), 6.68 (br s, 1H), 4.66 (t, *J*

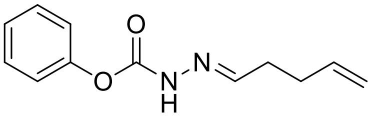
= 5.0 Hz, 1H), 4.14 (d, *J* = 4.7 Hz, 2H), 3.96 (ddd, *J* = 9.5, 4.1, 1.1 Hz, 1H), 1.83-1.63 (m, 2H), 1.4 (ddd, *J* = 13.5, 9.5, 5.1 Hz, 1H), 0.94 (dd, *J* = 6.4, 5.0 Hz, 6H). ^{13}C NMR (75 MHz; CDCl$_3$): δ 172.1 (C), 156.4 (C). 135.7 (C), 129.3 (CH), 128.4 (CH), 128.0 (CH), 54.4 (CH$_2$), 54.3 (CH), 40.7 (CH$_2$), 24.8 (CH), 23.0 (CH$_3$), 21.5 (CH$_3$). IR (film): 3273, 2959, 1772, 1763, 1718, 1204, 1161, 748, 698. HRMS (EI): Exact mass calcd for $C_{14}H_{19}N_3O_2$ [M]$^+$: 261.1477. Found: 261.1468.



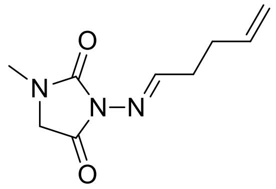
3-(Dibenzylamino)-1-methylimidazolidine-2,4-dione (3.17): Synthesized according to general procedure **F** using tert-butyl 2,2-dibenzylhydrazinecarboxylate (0.0890 g, 0.280 mmol), sarcosine ethyl ester hydrochloride (0.0500 g, 0.320 mmol), *N,N*-diisopropylethylamine (0.0600 mL, 0.44 mmol) and α,α,α-trifluorotoluene (1.00 mL) at 150 °C for 6 hours. The title compound was purified by column chromatography (4% EtOAc/CH$_2$Cl$_2$) and was obtained as colorless oil (0.0710 g, 81%). TLC R$_f$ = 0.36 in 5% EtOAc/CH$_2$Cl$_2$. ^{1}H NMR (300 MHz; CDCl$_3$): δ 7.48 (d, *J* = 6.8 Hz, 4H), 7.34-7.23 (m, 6H), 4.44-4.31 (m, 4H), 3.43 (s, 2H), 2.81 (s, 3H). ^{13}C NMR (75 MHz; CDCl$_3$): δ 167.8 (C), 155.7 (C), 136.5 (C), 129.1 (CH), 128.2 (CH), 127.6 (CH), 58.3 (CH$_2$), 49.8 (CH$_2$), 29.6 (CH$_3$). IR (film): 2984, 2866, 1769, 1718, 1554, 1497, 1452, 1410, 1244, 1099. HRMS (EI): Exact mass calcd for $C_{18}H_{19}N_3O_2$ [M]$^+$: 309.1477. Found: 309.1492.



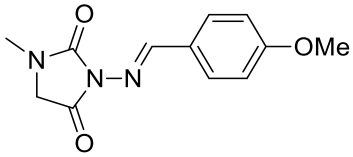
(*E*)-1-Methyl-3-((2-methylpropylidene)amino)imidazolidine-2,4-dione (3.18): Synthesized according to general procedure **F** using (E)-phenyl 2-(2-methylpropylidene)hydrazinecarboxylate (0.0700 g, 0.340 mmol), sarcosine ethyl ester hydrochloride (0.0570 g, 0.370 mmol), *N,N*-diisopropylethylamine (0.0700 mL, 0.410 mmol) and α,α,α-trifluorotoluene (1.00 mL) at 80 °C. The title compound was purified by column chromatography (6% EtOAc/CH$_2$Cl$_2$) and was obtained as a colorless oil (0.0520 g, 82%). TLC R$_f$ = 0.13 in 5% EtOAc/CH$_2$Cl$_2$. ^{1}H NMR (300 MHz; CDCl$_3$): δ 8.51 (d, *J* = 6.2 Hz, 1H), 3.88 (s, 2H), 3.02 (s, 3H), 2.69 (dq, *J* = 13.4, 6.8 Hz, 1H), 1.16 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz; CDCl$_3$): δ 169.4 (C), 165.9 (C), 50.0 (CH$_2$), 32.9 (CH), 29.8 (CH$_3$), 19.4 8 (CH$_3$). IR (film): 2941, 2928, 1724, 1653, 1452, 1410. HRMS (EI): Exact mass calcd for $C_8H_{13}N_3O_2$ [M]$^+$: 183.1008. Found: 183.0997.



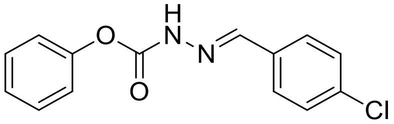
(*E*)-Phenyl 2-(pent-4-en-1-ylidene)hydrazinecarboxylate: Phenyl carbazate (1.00 g, 6.60 mmol) was dissolved in methanol (30.0 mL) in a round bottom flask charged with a stir bar. A 0.15 M stock solution of pentenal in CH$_2$Cl$_2$ was added (0.553 g, 6.6 mmol) and the reaction vessel was capped and allowed to stir over night at room temperature. The mixture was then concentrated under reduced pressure and purified by column chromatography (40% EtOAc/hexanes) and the title compound was obtained as a pale yellow oil. (1.15 g, 80%). TLC R_f = 0.38 in 40% EtOAa/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.13 (s, 1H), 7.38 (m, 2H), 7.21 (m, 3H), 5.84 (ddt, *J* = 10.3, 6.4, 6.4 Hz, 1H), 5.07 (m, 2H), 2.47 (m, 2H), 2.31 (m, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 136.7 (CH), 135.9 (C), 129.35 (CH), 125.9 (C), 125.7 (CH), 121.5 (CH), 115.8 (CH_2), 31.35 (CH_2), 30.63 (CH_2). IR (film): 3238, 3072, 2926, 2365, 1724, 1717, 1533, 1491, 1362, 1236, 1201 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{14}N_2O_2$ $[M]^+$: 218.1055. Found: 218.10492.



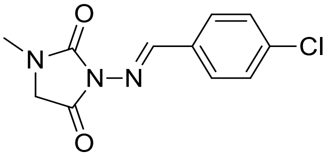
(*E*)-1-Methyl-3-(pent-4-en-1-ylideneamino)imidazolidine-2,4-dione (3.19): Synthesized according to general procedure **F** using (E)-phenyl 2-(pent-4-en-1-ylidene)hydrazinecarboxylate (0.100 g, 0.458 mmol), sarcosine ethyl ester hydrochloride (0.077 g, 0.504 mmol), *N,N*-diisopropylethylamine (0.096 mL, 0.550 mmol)and α,α,α-trifluorotoluene (2.00 mL) at 100 °C for 6 hours. The title compound was purified by column chromatography (60% EtOAc/hexanes) and was obtained as a pale yellow oil (0.0823 g, 92%). TLC R_f = 0.14 in 60% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ *denotes minor isomer 8.61 (t, *J* = 5.5 Hz, 1H), 6.35-6.31* (m, 1H), 6.24* (q, *J* = 5.6 Hz, 1H), 5.81 (ddt, *J* = 17.0, 10.3, 6.5 Hz, 1H), 5.09-4.97 (m, 2H), 3.87 (s, 2H), 2.99 (s, 3H), 2.55-2.48 (m, 2H), 2.36-2.29 (m, 2H), 2.08-2.0* (m, 2H), 1.38-1.20* (m, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 166.0 (C), 164.3 (CH), 154.3 (C), 136.6 (CH), 116.0 (CH_2), 50.1 (CH_2), 33.0 (CH_2), 30.1 (CH_2), 30.0 (CH_3). IR (film): 2852, 2366, 1772, 1706, 1485, 1446, 1404, 1332, 1242, 1166 cm^{-1}. HRMS (EI): Exact mass calcd for $C_9H_{13}N_3O_2$ $[M]^+$: 195.1008. Found: 195.10323.



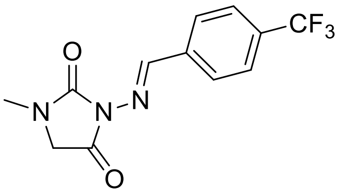
(*E*)-3-((4-Methoxybenzylidene)amino)-1-methylimidazolidine-2,4-dione (3.20): Synthesized according to general procedure **F** using phenyl 2-(4-methoxybenzylidene)hydrazinecarboxylate (0.100 g, 0.370 mmol), sarcosine ethyl ester hydrochloride (0.062 g, 0.407 mmol),), *N,N*-diisopropylethylamine (0.077 mL, 0.444 mmol) and α,α,α-trifluorotoluene (2.00 mL) at 100 °C for 6 hours. The title compound was purified by column chromatography (80% EtOAc/hexanes) and was obtained as a yellow amorphous solid (0.0430 g, 89%). TLC R_f = 0.16 in 80% EtOAc/hexanes ^{1}H NMR (300 MHz; $CDCl_3$): *denotes minor isomer δ 9.89* (s, 1H), 9.25 (s, 1H), 7.85* (d, *J* = 8.9 Hz, 2H), 7.79 (d, *J* = 8.7 Hz, 2H), 7.01* (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.95 (s, 2H), 3.90* (s, 3H), 3.87* (s, 2H), 3.86 (s, 3H), 3.07 (s, 3H), 3.02* (s, 3H) ^{13}C NMR (100 MHz; $CDCl_3$): δ 191.0* (CH), 166.1 (C), 162.7 (C), 158.6 (CH), 154.5 (C), 132.1* (CH), 130.4 (CH), 126.2 (C), 114.3 (CH_3), 55.5 (CH), 50.3 (CH_2), 30.1 (CH_3). IR (film): 1772, 1714, 1604, 1512, 1404, 1334, 1255, 1170 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O_3$ $[M]^+$: 247.0957. Found: 247.09490.



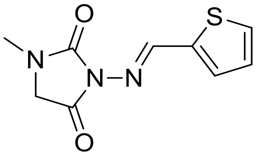
(*E*)-Phenyl 2-(4-chlorobenzylidene)hydrazinecarboxylate: Phenyl carbazate (0.608 g, 4.00 mmol) was dissolved in methanol (10.0 mL) completely in a round bottom flask charged with a stir bar. *p*-Chlorobenzaldehyde (0.562 g, 4.00 mmol) was then added to the mixture, followed by CH_3COOH (0.046 mL, 0.800 mmol) via syringe. Within seconds, a white precipitate formed inside the reaction vessel. The mixture was stirred at room temperature for 1 hour. This precipitate was then filtered and recrystallized in boiling EtOAc followed by a few drops of hexanes yielding the title compound as thin colorless needles (0.822 g, 75%). ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.32 (br s, 1H), 8.03 (br s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.40 (m, 4H), 7.25 (d, *J* = 12.2 Hz, 3H). ^{13}C NMR (100 MHz; DMSO-d_6) δ 152.1 (C), 150.7 (C), 144.8 (CH), 134.7 (C), 133.2 (C), 130.0 (CH), 129.2 (CH), 128.8 (CH), 125.9 (CH), 122.0 (CH). IR (film): 1731, 1562, 1549, 1493, 1263, 1263, 1207 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{11}N_2O_2Cl$ [M]$^+$: 274.0509. Found: 274.05436.



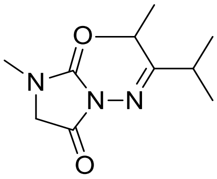
(*E*)-3-((4-Chlorobenzylidene)amino)-1-methylimidazolidine-2,4-dione (3.21): Synthesized according to general procedure **F** using (*E*)-phenyl 2-(4-chlorobenzylidene)hydrazinecarboxylate (0.100 g, 0.364 mmol), sarcosine ethyl ester hydrochloride (0.061 g, 0.400 mmol), *N,N*-diisopropylethylamine (0.075 mL, 0.437 mmol) and α,α,α-trifluorotoluene (2.00 mL) at 100 °C for 6 hours. The title compound was purified by column chromatography (20% EtOAc/CH_2Cl_2) and was obtained as a colorless amorphous solid (0.0430 g, 60%). TLC R_f = 0.33 in 20% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.40 (s, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.4 (d, *J* = 8.6 Hz, 2H), 3.96 (s, 2H), 3.07 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 166.1 (CH), 156.3 (C), 154.2 (C), 137.8 (C), 132.1 (C), 129.6 (CH), 129.2 (CH), 50.2 (CH_2), 30.1 (CH_3). IR (film): 1776, 1714, 1598, 1477, 1444, 1404, 1338, 1288, 1245, 1174, 1087 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{10}N_3O_2Cl$ [M]$^+$: 261.0462. Found: 251.04563.



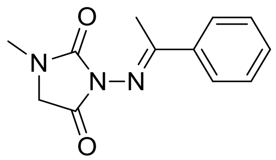
(E)-1-Methyl-3-((4-(trifluoromethyl)benzylidene)amino)imidazolidine-2,4-dione (3.22): Synthesized according to general procedure **F** using phenyl 2-(4-(trifluoromethyl)benzylidene)hydrazinecarboxylate (0.105 g, 0.340 mmol), sarcosine ethyl ester hydrochloride (0.0570 g, 0.370 mmol), *N,N*-diisopropylethylamine (0.0700 mL, 0.410 mmol) and α,α,α-trifluorotoluene (1.00 mL) at 120 °C for 6 hours. The title compound was purified by column chromatography (5 % EtOAc/CH_2Cl_2) and was obtained as a colorless amorphous solid (0.0900 g, 93%). TLC R_f = 0.20 in 5 % EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.52 (s, 1H), 7.93 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 3.97 (s, 2H), 3.07 (s, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 165.9 (C), 155.0 (C), 153.8 (C), 136.8 (C), 128.4 (CH), 125.6 (CH), 49.9 (CH_2), 30.0 (CH_3). IR (film): 2943, 2885, 1724, 1685, 1653, 1506, 1448, 1323, 1113. HRMS (EI): Exact mass calcd for $C_{12}H_{10}N_3O_2F_3$ $[M]^+$: 285.0725. Found: 285.0723.



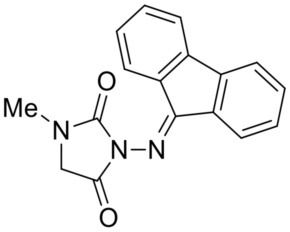
(*E*)-1-Methyl-3-((thiophen-2-ylmethylene)amino)imidazolidine-2,4-dione (3.23): Synthesized according to general procedure **F** using phenyl 2-(thiophen-2-ylmethylene)hydrazinecarboxylate (0.050 g, 0.203 mmol), sarcosine ethyl ester hydrochloride (0.034 g, 0.223 mmol), *N,N*-diisopropylethylamine (0.042 mL, 0.244 mmol) and MeCN (1.00 mL) at 100 °C for 6 hours. The title compound was purified by column chromatography (70% EtOAc/pet. ether) and was obtained as a yellow amorphous solid (0.0430 g, 74%). TLC R_f = 0.36 in 70% EtOAc/pet. ether. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.51 (s, 1H), 7.51 (d, *J* = 5.1 Hz, 1H), 7.45 (m, 1H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 3.95 (s, 2H), 3.06 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 165.9 (C), 154.2 (C), 152.3 (CH), 138.4 (C), 133.0 (CH), 130.7 (CH), 127.7 (CH), 50.2 (CH_2), 30.1 (CH_3). IR (film): 3085, 1780, 1714, 1589, 1454, 1400, 1338, 1321, 1296, 1242, 1226, 1155, 1089, 1045 cm^{-1}. HRMS (EI): Exact mass calcd for $C_9H_9N_3O_2S$ $[M]^+$: 223.0415. Found: 223.04255.



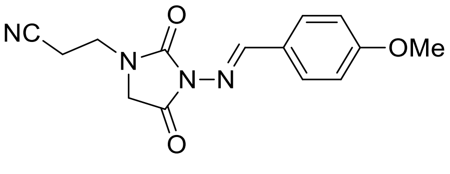
3-((2,4-Dimethylpentan-3-ylidene)amino)-1-methylimidazolidine-2,4-dione (3.24): Synthesized according to general procedure **F** using phenyl 2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate (0.149 g, 0.680 mmol), sarcosine ethyl ester hydrochloride (0.118 g, 0.740 mmol),), *N,N*-diisopropylethylamine (0.140 mL, 0.820 mmol) and α,α,α-trifluorotoluene (2.00 mL) at 100 °C for 6 hours. The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) and was obtained as colorless amorphous solid (0.0880 g, 65%). TLC R_f = 0.16 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.92 (s, 2H), 3.04 (s, 3H), 2.82 (dt, *J* = 13.7, 6.7 Hz, 2H), 1.29 (d, *J* = 6.8 Hz, 6H), 1.12 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 195.1 (C), 164.8 (C), 154.1 (C), 50.9 (CH_2), 31.7 (CH), 30.1 (CH_3), 22.6 (CH_3), 19.0 (CH_3). IR (film): 2968, 2935, 1772, 1712, 1622, 1474, 1456, 1362, 1169, 1013, 943. HRMS (EI): Exact mass calcd for $C_{11}H_{19}N_3O_2$ $[M]^+$: 225.1477 Found: 225.1464.



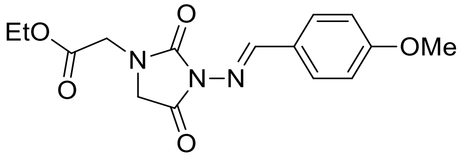
(*E*)-1-Methyl-3-((1-phenylethylidene)amino)imidazolidine-2,4-dione (3.25): Synthesized according to general procedure **F** using phenyl 2-(1-phenylethylidene)hydrazinecarboxylate (0.173 g, 0.680 mmol), sarcosine ethyl ester hydrochloride (0.118 g, 0.740 mmol), *N,N*-diisopropylethylamine (0.140 mL, 0.820 mmol) and α,α,α-trifluorotoluene (2.00 mL) at 100 °C for 6 hours. The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) and was obtained as colorless amorphous solid (0.130 g, 83%). TLC R_f = 0.19 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.96-7.93 (m, 2H), 7.53-7.40 (m, 3H), 4.01 (s, 2H), 3.10 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 174.9 (C), 164.4 (C), 154.0 (C), 136.1 (C), 131.4 (CH), 128.3 (CH), 127.6 (C), 50.8 (CH_2), 30.0 (CH_3), 17.7 (CH_3). IR (film): 2930, 1772, 1712, 1607, 1487, 1402, 1358, 1290, 1122, 932, 762, 692. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O_2$ $[M]^+$: 231.1008. Found: 231.1009.



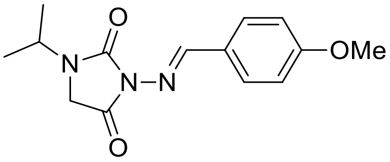
3-((9H-Fluoren-9-ylidene)amino)-1-methylimidazolidine-2,4-dione (3.26): Synthesized according to general procedure **F** using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.214 g, 0.680 mmol), sarcosine ethyl ester hydrochloride (0.118 g, 0.740 mmol), *N,N*-diisopropylethylamine (0.140 mL, 0.820 mmol) and α,α,α-trifluorotoluene (2.00 mL) at 100 °C for 6 hours. The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) and was obtained as yellow amorphous solid (0.175 g, 88%). TLC R_f = 0.36 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.94 (d, *J* = 7.5 Hz, 1H), 7.57-7.52 (m, 2H), 7.46-7.38 (m, 3H), 7.31-.7.26 (m, 1H), 7.22-7.16 (m, 1H), 4.09 (s, 2H), 3.11 (s, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 169.2 (C), 164.5 (C), 153.6 (C), 143.6 (C), 141.5 (C), 135.7 (C), 133.0 (CH), 132.6 (CH), 130.8 (C), 128.5 (CH), 128.4 (CH), 127.4 (CH), 124.2(CH), 120.4 (CH), 119.8 (CH), 50.9 (CH_2), 30.2 (CH_3). IR (film): 3072, 1780, 1716, 1609, 1593, 1400, 1350, 1163, 1144, 731. HRMS (EI): Exact mass calcd for $C_{17}H_{13}N_3O_2$ $[M]^+$: 291.1008. Found: 291.0987.



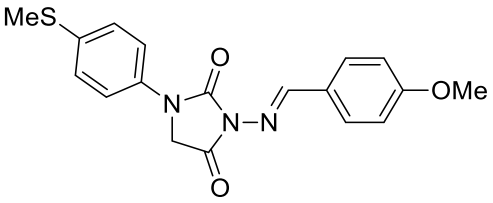
(*E*)-3-(3-((4-Methoxybenzylidene)amino)-2,4-dioxoimidazolidin-1-yl)propanenitrile (3.27): Synthesized according to general procedure **F** using phenyl 2-(4-methoxybenzylidene)hydrazinecarboxylate (0.050 g, 0.185 mmol), *N*-cyanoethyl glycine ethyl ester (0.032 g, 0.204 mmol), and MeCN (1.00 mL) at 100 °C for 6 hours. The title compound was purified by column chromatography (65% EtOAc/hexanes) and was obtained as a yellow oil (0.0463 g, 87%). TLC R_f = 0.28 in 65% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.22 (s, 1H), 7.78 (m, 2H), 6.94 (m, 2H), 4.15 (s, 2H), 3.85 (s, 3H), 3.75 (t, *J* = 6.4 Hz, 2H), 2.74 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 165.6 (C), 162.8 (C), 159.2 (CH), 154.3 (C) 130.4 (CH), 125.8 (C), 117.7 (C), 114.4 (CH), 55.5 (CH), 49.3 (CH_2), 39.8 (CH_2), 17.4 (CH_3). IR (film): 2250, 1772, 1712, 1598, 1512, 1456, 1413, 1334, 1247, 1170, 1026 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{14}N_4O_3$ $[M]^+$: 286.1066. Found: 286.10780.



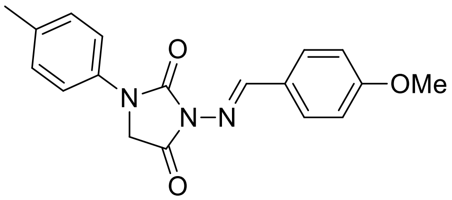
(*E*)-Ethyl 2-(3-((4-methoxybenzylidene)amino)-2,4-dioxoimidazolidin-1-yl)acetate (3.28): Synthesized according to general procedure **F** using phenyl 2-(4-methoxybenzylidene)hydrazinecarboxylate (0.050 g, 0.185 mmol), diethyl (methylimino)-diacetate (0.0386 g, 204 mmol) and MeCN (1.00 mL) at 120 °C for 6 hours. The title compound was purified by column chromatography (50% EtOAc/hexanes) and was obtained as a colorless amorphous solid (0.0382 g, 65%). TLC R_f = 0.23 in 50% EtOAc/hexanes ^{1}H NMR (300 MHz; $CDCl_3$): *denotes minor isomer δ 9.89* (s, 1H), 9.24 (s, 1H), 7.84* (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.01* (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.22 (s, 2H), 4.16* (s, 2H), 4.10 (s, 2H), 4.02* (s, 2H), 3.89* (s, 3H), 3.86 (s, 3H), 1.3 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 168.2 (C), 166.1 (C), 162.7 (C), 159.0 (CH), 154.8 (C), 130.4 (CH), 126.0 (C), 114.3 (CH), 62.0 (CH_2), 55.5 (CH_3), 48.9 (CH_2), 44.1 (CH_2), 14.3 (CH_3) IR (film): 2878, 2341, 1772, 1716, 1714, 1602, 1512, 1456, 1415, 1332, 1249, 1209, 1166, 1024 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{17}N_3O_5$ $[M]^+$: 319.1168. Found: 319.11570.



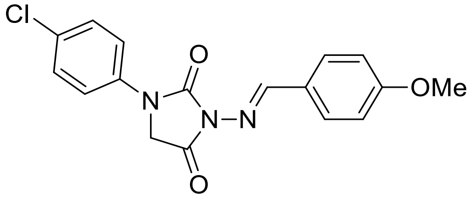
(*E*)-1-Isopropyl-3-((4-methoxybenzylidene)amino)imidazolidine-2,4-dione (3.29): Synthesized according to general procedure **F** using phenyl 2-(4-methoxybenzylidene)hydrazinecarboxylate (0.050 g, 0.185 mmol), ethyl 2-(propylamino)acetate hydrochloride (0.037 g, 0.204 mmol), *N,N*-diisopropylethylamine (0.039 mL, 0.222 mmol) and α,α,α-trifluorotoluene (1.00 mL) at 150 °C for 6 hours. The title compound was purified by column chromatography (40% EtOAc/hexanes) and was obtained as a yellow amorphous solid (0.0286 g, 56%). TLC R_f = 0.27 in 40% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.25 (s, 1H), 7.79 (m, 2H), 4.43 (spt, *J* = 6.8 Hz, 1H), 3.87 (s, 2H), 3.85 (s, 3H), 6.93 (m, 2H), 1.24 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 166.6 (C), 162.6 (C), 158.5 (CH), 153.6 (C), 130.3 (CH), 126.2 (C), 114.2 (CH), 55.5 (CH_3), 43.9 (CH), 43.7 (CH_2), 20.1 (CH_3). IR (film): 2884, 2356, 1772, 1706, 1598, 1515, 1456, 1407, 1328, 1242, 1168, 1145, 1027 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{17}N_3O_3$ $[M]^+$: 275.1270. Found: 275.12426.



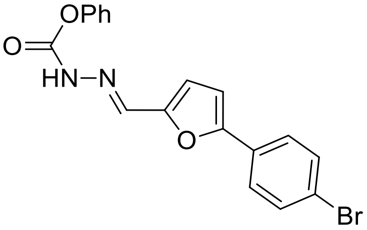
(*E*)-3-((4-Methoxybenzylidene)amino)-1-(4-(methylthio)phenyl)imidazolidine-2,4-dione (3.30): Synthesized according to general procedure **F** using phenyl 2-(4-methoxybenzylidene)hydrazinecarboxylate (0.050 g, 0.185 mmol), ethyl 2-(4-methylthiophenylamino)acetate (0.046 g, 0.204 mmol), and α,α,α-trifluorotoluene (1.00 mL) at 150 °C for 6 hours. The title compound was purified by filtration and was obtained as a yellow amorphous solid (0.0324 g, 50%). TLC R_f = 0.17 in 100% CH_2Cl_2. ^{1}H NMR (400 MHz; DMSO-d_6): δ 9.13 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 4.54 (s, 2H), 3.84 (s, 2H), 2.48 (s, 3H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 165.4 (C), 162.3 (C), 159.8 (CH), 151.5 (C), 135.2 (C), 133.2 (C), 130.0 (CH), 127.1 (CH), 125.7 (C), 119.3 (CH), 114.6 (CH), 55.5 (CH_3), 48.6 (CH_2), 15.3 (CH_3). IR (film): 2356, 1772, 1706, 1652, 1558, 1508, 1456, 1396, 1338, 1253, 1176, 1029 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{17}N_3O_3S$ $[M]^+$: 355.0991. Found: 355.09837.



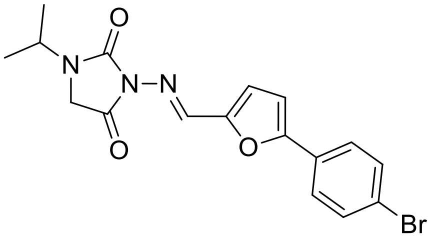
(*E*)-3-((4-Methoxybenzylidene)amino)-1-(p-tolyl)imidazolidine-2,4-dione (3.31): Synthesized according to general procedure **F** using phenyl 2-(4-methoxybenzylidene)hydrazinecarboxylate (0.100 g, 0.370 mmol), ethyl 2-(4-methylphenylamino)acetate (0.078 g, 0.407 mmol), and α,α,α-trifluorotoluene (2.00 mL) at 150 °C for 6 hours. The title compound was purified by filtration and was obtained as a colorless amorphous solid (0.0324 g, 50%). TLC R_f = 0.24 in 100% CH_2Cl_2. ^{1}H NMR (400 MHz; DMSO-d_6): δ 9.13 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.8, 2H), 4.53 (s, 2H), 3.84 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 165.5 (C), 162.2 (C), 159.7 (CH), 151.5 (C), 135.3 (C), 133.2 (C), 129.9 (CH), 129.5 (CH), 125.7 (CH), 118.6 (CH), 114.6 (CH), 55.5 (CH_3), 48.6 (CH_2), 20.4 (CH_3). IR (film): 2356, 1772, 1716, 1683, 1652, 1558, 1515, 1508, 1396, 1328, 1259, 1168 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{17}N_3O_3$ $[M]^+$: 323.1270. Found: 323.12458.



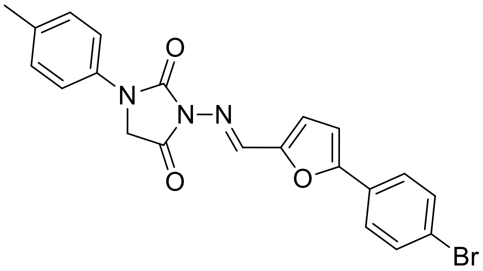
(*E*)-1-(4-Chlorophenyl)-3-((4-methoxybenzylidene)amino)imidazolidine-2,4-dione (3.12): Synthesized according to general procedure **F** using Phenyl 2-(4-methoxybenzylidene)hydrazinecarboxylate (0.050 g, 0.185 mmol), ethyl 2-(4-chlorophenylamino)acetate (0.044 g, 0.204 mmol) and α,α,α-trifluorotoluene (1.00 mL) at 150 °C for 6 hours. The title compound was purified by filtration and was obtained as a colorless amorphous solid (0.035 g, 56%). TLC R_f = 0.31 in 100% CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.25 (s, 1H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.57 (d, *J* = 9.2 Hz, 2H), 7.39 (d, *J* = 9.1 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.37 (s, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 164.5 (C), 163.0 (C), 159.9 (CH), 151.7 (C), 136.0 (C), 130.5 (CH), 130.3 (C), 129.6 (CH), 125.8 (C), 119.8 (CH), 114.4 (CH), 55.6 (CH_3), 48.4 (CH_2). IR (film): 1772, 1733, 1716, 1652, 1558, 1508, 1259, 1170 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{17}H_{14}N_3O_3Cl$ $[M]^+$: 343.0724. Found: 343.07001.



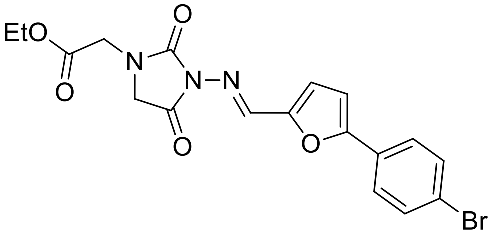
(*E*)-Phenyl 2-((5-(4-bromophenyl)furan-2-yl)methylene)hydrazinecarboxylate (3.34): To a solution of 5-(4-bromophenyl)furfural (1.25 g, 5.00 mmol) in methanol (25.0 mL) was added phenyl carbazate (0.761 g, 5.00 mmol) and the solution was stirred at room temperature overnight. The title compound was purified by filtration and obtained as a colorless amorphous solid (1.45g, 75 %). TLC R_f 0.73 in 20 % EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 11.76 (br s, 1H), 8.08 (s, 1H), 7.72-7.61 (m, 4H), 7.46-7.41 (m, 2H), 7.28-7.22 (m, 3H), 7.16 (d, *J* = 3.5 Hz, 1H), 7.01 (d, *J* = 3.6 Hz, 1H). ^{13}C NMR (75 MHz; DMSO-d_6,): δ 153.4 (C), 151.5 (C), 150.5 (C), 149.2 (C), 135.4 (CH), 131.9 (CH), 129.5 (CH), 128.7 (C), 125.8 (CH), 125.5 (CH), 121.7 (CH), 121.2 (C), 115.6 (CH), 109.0 (CH). IR (film): 2937, 2831,1734, 1684, 1653, 1558, 1506, 1447, 1202, 1109. HRMS (EI): Exact mass calcd for $C_{18}H_{13}BrN_2O_3[M]^+$: 384.0110 Found: 384.0090.



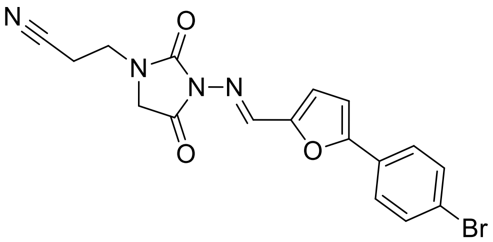
(*E*)-3-(((5-(4-Bromophenyl)furan-2-yl)methylene)amino)-1-isopropylimidazolidine-2,4-dione (3.35): Synthesized according to general procedure **F** using (*E*)-phenyl 2-((5-(4-bromophenyl)furan-2-yl)methylene)hydrazinecarboxylate **3.34** (0.231 g, 0.600 mmol), ethyl 2-(propylamino)acetate hydrochloride (0.120 g, 0.660 mmol), *N,N*-diisopropylethylamine (0.120 mL, 0.720 mmol) and α,α,α-trifluorotoluene (2.00 mL) at 150 °C for 6 hours. The title compound was purified by filtration and was obtained as a bright yellow amorphous solid (0.190 g, 74% yield). TLC R_f 0.53 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 9.16 (s, 1H), 7.82-7.60 (m, 4H), 7.27 (s, 2H), 4.25-4.11 (m, 1H) 4.03 (s, 2H), 1.25-1.11 (m, 6H). ^{13}C NMR (75 MHz; DMSO-d_6,): δ 166.8 (C), 154.9 (C), 152.6 (C), 148.3 (C), 145.8 (CH), 132.1 (CH), 129.3 (CH), 126.2 (CH), 121.8 (C), 119.9 (CH), 109.3 (CH), 43.7 (CH_2), 43.4 (CH) 19.6 (CH_3). IR (film): 2365, 1720, 1475, 1456, 1323, 1068. HRMS (EI): Exact mass calcd for $C_{17}H_{16}BrN_3O_3[M]^+$: 389.0375 Found: 389.0390.



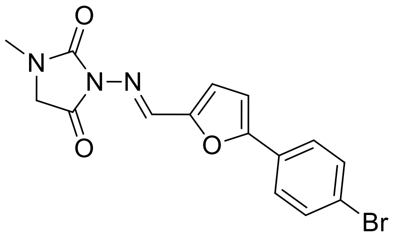
(*E*)-3-(((5-(4-Bromophenyl)furan-2-yl)methylene)amino)-1-(p-tolyl)imidazolidine-2,4-dione (3.36): Synthesized according to general procedure **F** using (*E*)-phenyl 2-((5-(4-bromophenyl)furan-2-yl)methylene)hydrazinecarboxylate **3.34** (0.231 g, 0.600 mmol), ethyl 2-(4-methylphenylamino)acetate (0.128 g, 0.660 mmol) and α,α,α-trifluorotoluene (2.00 mL) at 150 °C for 6 hours. The title compound was purified by filtration and was obtained as a pale yellow amorphous solid (0.190 g, 72%). TLC $R_f = 0.81$ in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.34 (s, 1H), 7.71-7.66 (m, 2H), 7.58-7.53 (m, 2H), 7.51-7.47 (m, 2H), 7.26-7.23 (m, 2H), 7.10 (d, *J* = 3.5 Hz, 1H), 6.82 (d, *J* = 3.7 Hz, 1H) 4.39 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$, 70°C): δ 164.8 (C), 158.4 (C), 148.0 (CH), 146.9 (CH), 140.2 (C), 136.5 (C), 134.8 (C), 133.2 (C), 131.6 (CH), 128.9 (CH), 128.0 (C), 125.9 (CH), 119.1 (CH), 118.8 (CH), 108.7 (CH), 48.3 (CH_2), 19.8 (CH_3). IR (film): 1722, 1522, 1506, 1441, 1391, 1263. HRMS (EI): Exact mass calcd for $C_{21}H_{16}BrN_3O_3[M]^+$: 437.0375. Found: 437.0358.



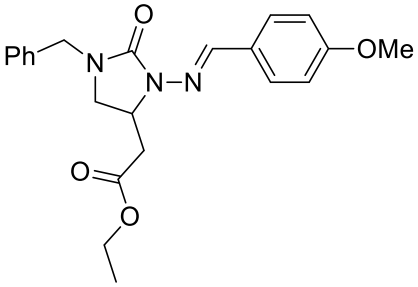
(*E*)-Ethyl 2-(3-(((5-(4-bromophenyl)furan-2-yl)methylene)amino)-2,4-dioxoimidazolidin-1-yl)acetate (3.37): Synthesized according to general procedure **F** using (*E*)-phenyl 2-((5-(4-bromophenyl)furan-2-yl)methylene)hydrazinecarboxylate **3.34** (0.231 g, 0.600 mmol), diethyl (methylimino)-diacetate (0.125 g, 0.660 mmol), and α,α,α-trifluorotoluene (2.00 mL) at 150 °C for 6 hours. The title compound was purified by filtration and was obtained as a bright yellow amorphous solid with residual phenol (yield corrected) (0.240 g, 92%). TLC R_f 0.3 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 9.14 (s, 1H), 7.78-7.75 (m, 2H), 7.69-7.66 (m, 2H), 7.32-7.26 (m, 2H), 4.22 (s, 2H), 4.17-4.12 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 168.4 (C), 166.4 (C), 155.2 (C), 154.0 (C), 148.0 (C), 146.7 (CH), 132.1 (CH), 129.3 (C), 126.3 (CH), 122.0 (C), 120.5 (CH), 109.4 (CH), 61.1 (CH_2), 48.9 (CH_2), 43.4 (CH_2), 14.0 (CH_3). IR (film): 2361, 1720, 1614, 1474, 1418, 1379, 1327. HRMS (EI): Exact mass calcd for $C_{18}H_{16}BrN_3O_5[M]^+$: 433.0273. Found: 433.0247.



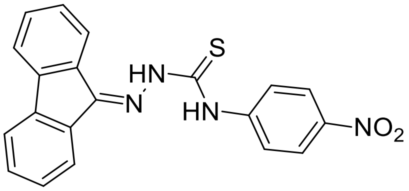
(*E*)-3-(3-(((5-(4-Bromophenyl)furan-2-yl)methylene)amino)-2,4-dioxoimidazolidin-1-yl)propanenitrile (3.38): Synthesized according to general procedure **F** using (*E*)-phenyl 2-((5-(4-bromophenyl)furan-2-yl)methylene)hydrazinecarboxylate **3.34** (0.135 g, 0.350 mmol), *N*-cyanoethyl glycine ethyl ester (0.0600 g, 0.380 mmol) and α,α,α-trifluorotoluene (1.00 mL) at 150 °C for 6 hours. The title compound was purified by filtration and was obtained as an orange amorphous solid with residual phenol (yield corrected) (0.134 g, 95%). TLC $R_f = 0.14$ in 5% EtOAc/CH_2Cl_2. ^1H NMR (300 MHz; DMSO-d_6): δ 9.15 (s, 1H), 7.78-7.66 (m, 4H), 7.32-7.26 (m, 2H), 4.15 (s, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.85 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 166.4 (C), 155.0 (C), 153.6 (CH), 148.1 (C), 146.2 (CH), 132.1 (CH), 128.3 (C), 126.2 (CH), 121.9 (C), 120.3 (CH), 118.9 (C), 109.3 (CH), 48.0 (CH_2), 38.6 (CH_2) 16.0 (CH_2). IR (film): 2535, 1720, 1521, 1475, 1410, 1324, 1072. HRMS (EI): Exact mass calcd for $C_{17}H_{13}BrN_4O_3[M]^+$: 400.0171. Found: 400.0183.



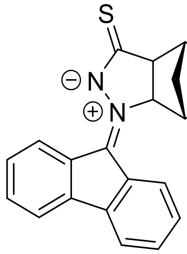
(*E*)-3-(((5-(4-Bromophenyl)furan-2-yl)methylene)amino)-1-methylimidazolidine-2,4-dione (3.39): Synthesized according to general procedure **F** using (*E*)-phenyl 2-((5-(4-bromophenyl)furan-2-yl)methylene)hydrazinecarboxylate **3.34** (0.231 g, 0.600 mmol), sarcosine ethyl ester hydrochloride (0.114 g, 0.660 mmol), *N,N*-diisopropylethylamine (0.140 mL, 0.72 mmol) and α,α,α-trifluorotoluene (2.00 mL) at 100 °C for 6 hours. The title compound was purified by filtration and was obtained as a colorless amorphous solid (0.211 g, 97%). TLC $R_f = 0.22$ in 5% EtOAc/CH_2Cl_2. ^1H NMR (300 MHz; DMSO-d_6): δ 9.17 (s, 1H), 7.80-7.75 (m, 2H), 7.71-7.66 (m, 2H), 7.30-7.27 (m, 2H), 4.05 (s, 2H), 2.91 (s, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 166.5 (C), 154.9 (C), 153.7 (C), 148.3 (C), 145.6 (CH), 132.0 (CH), 128.3 (C), 126.2 (CH), 121.8 (C), 119.8 (CH), 109.3 (CH), 49.8 (CH_2), 29.5 (CH_3), IR (film) 1726, 1474, 1410, 1325, 955. HRMS (EI): Exact mass calcd for $C_{15}H_{12}BrN_3O_3[M]^+$: 361.0062. Found: 361.0078.



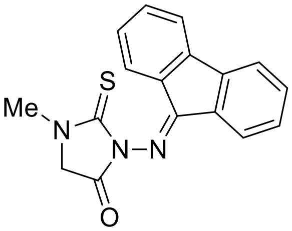
(*E*)-Ethyl 2-(1-benzyl-3-((4-methoxybenzylidene)amino)-2-oxoimidazolidin-4-yl)acetate (3.40): Synthesized according to general procedure **F** using phenyl 2-(4-methoxybenzylidene)hydrazinecarboxylate (0.0920 g, 0.340 mmol), ethyl *E*-4-(benzylamino)-2-butenoate (0.0810 g, 0.370 mmol) and α,α,α-trifluorotoluene (1.00 mL) at 120 °C for 6 hours. The title compound was purified by column chromatography (5% EtOAc/CH_2Cl_2) and was obtained as a yellow oil (0.0700 g, 52%). TLC R_f = 0.29 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.80 (s, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.39-7.28 (m, 5H), 6.91 (d, *J* = 8.4 Hz, 2H), 4.51-4.32 (m, 3H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 3.56 (t, *J* = 8.8 Hz, 1H), 3.09-3.00 (m, 2H), 2.48 (dd, *J* = 16.3, 9.5 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 170.7 (C), 160.9 (C), 157.0 (C), 149.3 (CH), 136.3 (C), 128.7 (CH), 128.6 (CH), 128.2 (CH), 127.8 (C), 127.6 (CH), 113.9 (CH), 60.7 (CH_2), 55.2 (CH_3), 53.0 (CH), 50.0 (CH_2), 46.8 (CH_2), 37.5 (CH_2), 14.0 (CH_3). IR (film): 2984, 2926, 1728, 1717, 1701, 1607, 1420, 1169, 1030, 749, 702. HRMS (EI): Exact mass calcd for $C_{22}H_{25}N_3O_4$ $[M]^+$: 395.1845. Found: 395.1842.



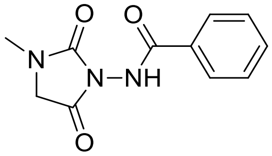
2-(9H-Fluoren-9-ylidene)-*N*-(4-nitrophenyl)hydrazinecarbothioamide (3.43): To a solution of 9-fluorenone hydrazone (1.94 g, 10 mmol) in MeCN (50.0 mL) is slowly added 4-nitrophenyl isothiocyanate (1.81 g, 10 mmol). The solution is stirred at room temperature overnight and the title compound was obtained by filtration as a yellow amorphous solid (3.60 g, 96%). TLC R_f = 0.65 in 20% EtOAC\CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 11.70 (br s, 1H), 10.79 (br s, 1H), 8.30-8.26 (m, 2H), 8.14-.8.09 (m, 4H), 7.96-7.83 (m, 2H), 7.58-7.36 (m, 4H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 205.8 (C), 177.6 (C), 148.6 (C), 145.3 (C), 143.7 (C), 141.7 (C), 139.8 (C), 136.3 (C), 131.9 (CH), 130.9 (CH), 129.2 (CH), 128.3 (CH), 128.2 (CH), 127.7(CH), 126.4 (CH), 124.5 (CH), 123.9 (CH), 123.0 (CH), 120.8 (CH), 120.4 (CH), 112.4 (CH). IR (film): 2943, 2891, 1652, 1558, 1506, 1339, 1175, 1078. HRMS (EI): Exact mass calcd for $C_{20}H_{14}N_4O_2S$ $[M]^+$: 374.0837. Found: 374.0860.



(4R,7S)-1-(9H-fluoren-9-ylidene)-3-thioxooctahydro-4,7-methanoindazol-1-ium-2-ide (3.42): To a solution of 2-(9H-fluoren-9-ylidene)-*N*-(4-nitrophenyl)hydrazinecarbothioamide (0.374 g, 1.00 mmol) in MeCN (20.0 mL) was added norbornene (0.942 g, 10.0 mmol). The solution was sealed in a microwave vial and irriated at 120°C for 2 hours. The title compound was purified by column chromatography (40% EtOAc/Hexanes) and was obtained as a red solid (0.302 g, 91%). TLC R_f 0.46 in 50% EtOAc in hexanes. ^{1}H NMR (300 MHz, $ClCD_3$): δ 8.96 (d, J = 7.80 Hz, 1H), 7.61 (d, J = 7.48 Hz, 1H), 7.56-7.49 (m, 2H), 7.47-7.38 (m, 2H), 7.34-7.26 (m, 2H), 4.85 (d, J = 6.77 Hz, 1H), 3.39 (d, J = 6.66 Hz, 1H), 2.99 (s, 1H), 2.84 (s, 1H), 1.77-1.71 (m, 2H), 1.54-1.43 (m, 3H), 1.24-1.19 (m, 1H). ^{13}C NMR (100 MHz, $ClCD_3$): δ 208.6 (C), 143.1 (C), 142.0 (C), 140.4 (C), 133.1 (CH), 132.3 (CH), 132.3 (CH), 131.2 (C), 129.9 (C), 129.6 (CH), 128.5 (CH), 126.1(CH), 121.4 (CH), 119.9 (CH), 74.6 (CH), 63.4 (CH), 43.1 (CH), 42.5 (CH), 32.2 (CH2), 26.9 (CH2), 25.6 (CH2). IR (film) 3230, 2927, 2851, 1744, 1721, 1533, 1491, 1246, 1210, 772 cm-1. LRMS(EI): Exact mass calcd for C21H18N2S [M]+:330.1185. Found: 180.1 (100%), 152.1 (24.4%), 86.0 (34.4%), 84.0 (50.3%), 76.0 (9.3%).



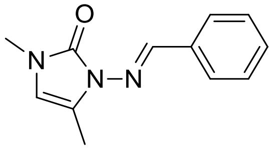
3-((9H-Fluoren-9-ylidene)amino)-1-methyl-2-thioxoimidazolidin-4-one (3.44): Synthesized according to general procedure **F** using 2-(9H-fluoren-9-ylidene)-*N*-(4-nitrophenyl)hydrazinecarbothioamide (0.128 g, 0.340 mmol), sarcosine ethyl ester hydrochloride (0.0590 g, 0.370 mmol), *N,N*-diisopropylethylamine (0.0700 mL, 0.420 mmol) and $MeNO_2$ (1.00 mL) at 100 °C for 3 hours. The title compound was purified by column chromatography (4% $EtOAc/CH_2Cl_2$) and was obtained as yellow amorphous solid (0.750 g, 72%). TLC R_f = 0.36 in 5% $EtOAc/CH_2Cl_2$. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.00 (dq, *J* = 7.5, 0.6 Hz, 1H), 7.5-7.53 (m, 2H), 7.44 (dtd, *J* = 11.9, 7.5, 1.1 Hz, 2H), 7.38-.7.34 (m, 1H), 7.34-7.28 (m, 1H), 7.21-7.15 (m, 1H) 4.27 (s,2H), 3.45 (s, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 180.0 (C), 170.7 (C), 164.6 (C), 143.8 (C), 141.8 (C), 135.5 (C), 133.4 (CH), 133.0 (CH), 130.8 (C), 128.7 (CH), 128.5 (CH), 127.3 (CH), 124.5(CH), 120.6 (CH), 119.9 (CH), 53.5 (CH_2), 34.3 (CH_3). IR (film): 2945, 2932, 2330, 1734, 1653, 1555, 1506, 1447. HRMS (EI): Exact mass calcd for $C_{17}H_{13}N_3OS$ $[M]^+$: 307.0779. Found: 307.0778.



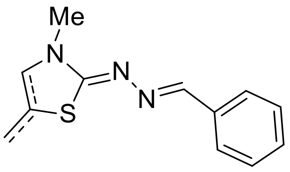
_N_-(3-Methyl-2,5-dioxoimidazolidin-1-yl)benzamide (3.46): Synthesized according to general procedure **F** using 1-benzoyl-2-phenoxycarbonylhydrazine (0.100 g, 0.390 mmol), sarcosine ethyl ester hydrochloride (0.066 g, 0.429 mmol), *N,N*-diisopropylethylamine (0.082 mL, 0.468 mmol) and α,α,α-trifluorotoluene (2.00 mL) at 100 °C for 3 hours. The title compound was purified by column chromatography (15% EtOAc/CH_2Cl_2 to elute phenol, then 2.5% MeOH/CH_2Cl_2) and was obtained as a yellow oil (0.0796 g, 88%). TLC R_f = 0.24 in 5% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.61 (s, 1H), 7.74 (m, 2H), 7.44 (m, 1H), 7.29 (m, 2H), 3.98 (s, 2H), 2.96 (s, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 167.5 (C), 165.7 (C), 154.9 (C), 132.8 (CH), 130.2 (C), 128.64 (CH), 127.9 (CH), 50.7 (CH_2), 30.4 (CH_3). IR (film): 3221, 2366, 1793, 1724, 1683, 1515, 1485, 1452, 1417, 1392, 1272, 1180, 1135 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{11}N_3O_3$ $[M]^+$: 233.0800. Found: 233.0819.

6.2.3: Diversity-Oriented Heterocyclic Synthesis using Divergent Reactivity of *N*-Substituted Iso(thio)cyanates (section 3.2)

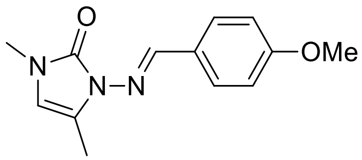
General procedure G: An oven-dried 5 mL microwave tube was charged with a stir bar, a carbarzone (1.0 equiv.), a propargylic amine (1.1 equiv.), Et_3N (20 mol %) and MeCN (0.3 M). The septum was removed and the tube was then quickly sealed with a microwave cap and heated for 2-6 hours at 100-150 °C in a microwave (μW) reactor. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.



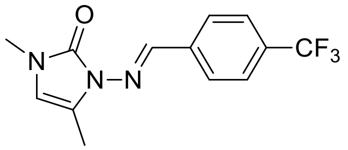
(_E_)-3-(Benzylideneamino)-1,4-dimethyl-1H-imidazol-2(3H)-one (3.48): Synthesized according to general procedure **G** using carbazone **3.47** (0.144 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 2 hours. The crude mixture was purified by column chromatography using 35 % EtOAc/Hexane and the pure compound was obtained as an off-white solid (0.126 g, 87%). TLC R_f = 0.21 in 35% EtOAc/Hexane. ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.89 (s, 1H), 7.74-7.71 (m, 3H), 7.38-7.34 (m, 3H), 5.87 (q, *J*= 1.37 Hz, 1H), 3.17 (s, 3H), 2.13 (d, *J* = 1.4 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 150.9 (CH), 150.1 (C), 135.2 (C), 130.2 (CH), 128.6 (CH), 127.4 (CH), 120.0 (C), 106.0 (CH), 30.0 (CH_3), 10.0 (CH_3). IR (film): 2955, 2853, 1653, 1522, 1506, 1394, 903 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O$ $[M]^+$: 215.1059. Found: 215.1056.



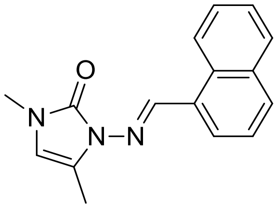
Equation 3.4: Synthesized according to general procedure **G** using thiosemicarbazone **3.49** (0.180 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. NMR analysis showed a ratio of 63 / 37 of products with exocyclic and endocyclic double bonds. A 6 hours reaction gave 67% (exo) and 27% and 2 hours at 150 °C gave 70% and 27% while comparing to phenol production.



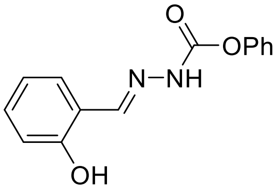
(*E*)-3-((4-Methoxybenzylidene)amino)-1,4-dimethyl-1H-imidazol-2(3H)-one (Table 3.51): Synthesized according to general procedure **G** using 4-methoxybenzaldehyde carbazone (0.162 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 2 hours. The crude mixture was purified by column chromatography using 10% EtOAc/CH_2Cl_2 and the pure compound was obtained as a off-white solid (0.126 g, 87%). TLC R_f = 0.18 in 10% EtOAc/CH_2Cl_2. ^1H NMR (300 MHz; $CDCl_3$): δ 9.84 (s, 1H), 7.74-7.69 (m, 2H), 6.96-6.91 (m, 2H), 5.91-5.90 (m, 1H), 3.85 (s, 3H), 3.23 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 161.3 (C), 151.1 (CH), 129.9 (CH), 127.9 (C), 120.0 (C), 114.0 (CH), 105.6 (CH), 55.3 (CH_3), 29.9 (CH_3), 9.9 (CH_3). IR (film): 1674, 1653, 1609, 1516, 1398, 1263, 1250, 1180, 1169, 1030 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{15}N_3O_2$ $[M]^+$: 245.1164. Found: 245.1123.



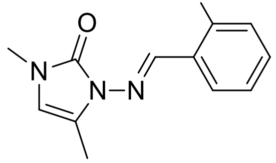
(*E*)-1,4-Dimethyl-3-((4-(trifluoromethyl)benzylidene)amino)-1H-imidazol-2(3H)-one (3.52): Synthesized according to general procedure **G** using 4-trifluoromethylbenzaldehyde carbazone (0.185 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 2 hours. The crude mixture was purified by column chromatography using 10% EtOAc/CH_2Cl_2 and the pure compound was obtained as a yellow solid (0.141 g, 83%). TLC R_f = 0.32 in 10% EtOAc/CH_2Cl_2. ^1H NMR (300 MHz; $CDCl_3$): δ 10.00 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 5.98-5.92 (m, 1H), 3.24 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 148.8 (CH), 127.3 (CH), 125.5 (CH), 119.9 (C), 106.4 (CH), 29.9 (CH_3), 9.9 (CH_3). IR (film): 1680, 1560, 1429, 1400, 1321, 1255, 1180, 1166 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{12}N_3OF_3$ $[M]^+$: 283.0932. Found: 283.0983.



(*E*)-1,4-Dimethyl-3-((naphthalen-1-ylmethylene)amino)-1H-imidazol-2(3H)-one (3.53): Synthesized according to general procedure **G** using naphthalene based carbazone (0.174 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 10% $EtOAc/CH_2Cl_2$ and the pure compound was obtained as a yellow solid (0.146 g, 92%). TLC R_f = 0.37 in 10% $EtOAc/CH_2Cl_2$. ^1H NMR (300 MHz; $CDCl_3$): δ 10.71 (s, 1H), 8.67 (dd, *J* = 8.3, 0.9 Hz, 1H), 8.06 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.93-7.88 (m, 2H), 7.61-7.50 (m, 3H), 5.96 (q, *J* = 1.2 Hz, 1H), 3.27 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 150.6 (CH), 130.7 (CH), 130.7 (C), 128.6 (CH), 127.0 (C), 126.9 (CH), 126.4 (CH), 126.0 (CH), 125.3 (CH), 124.1 (CH), 120.1 (C), 29.9 (CH_3), 10.1 (CH_3). IR (film): 1693, 1564, 1539, 1472, 1420, 1288, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{15}N_3O$ $[M]^+$: 265.1215. Found: 265.1224.

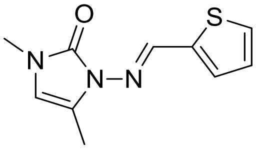


(*E*)-Phenyl 2-(2-hydroxybenzylidene)hydrazinecarboxylate: Phenyl carbazate (2.53 g, 16.6 mmol) was dissolved in methanol (50.0 mL) completely in a round bottom flask charged with a stir bar. Salicylaldehyde (1.77 mL, 16.7 mmol) was then added to the mixtue. The mixture was stirred at room temperature for 1 hour. The precipitate was then filtered and recrystallized in boiling EtOAc followed by a few drops of hexanes yielding the title compound as thin colorless needles (1.372 g, 32%). ^1H NMR (300 MHz; DMSO-d_6): δ 11.81 (br s, 1H), 10.71 (br s, 1H), 8.40 (br s, 1H), 7.56 (dd, *J* = 7.7, 1.6 Hz, 1H) 7.47-7.40 (m, 2H) 7.30-7.21 (m, 4H), 6.93-6.86 (m, 2H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 156.9 (C), 145.5 (C), 131.2 (CH), 139.5 (CH), 128.4 (CH) 125.6 (CH), 121.8 (CH), 119.4 (CH), 119.0 (C), 116.3 (CH). IR (film): 1684, 1675, 1663, 1649, 1514, 1456, 1393, 1307, 1248, 1166 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{12}N_2O_3$ $[M]^+$: 256.0845 Found: 256.0850

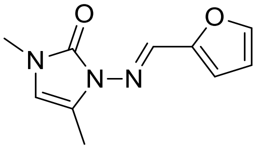


(*E*)-3-((2-Hydroxybenzylidene)amino)-1,4-dimethyl-1H-imidazol-2(3H)-one (3.54): Synthesized according to general procedure **G** using (*E*)-phenyl 2-(2-hydroxybenzylidene)hydrazinecarboxylate (0.154

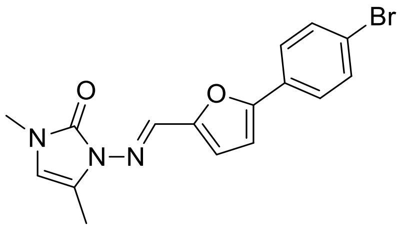
g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 2 hours. The crude mixture was purified by column chromatography using 10% $EtOAc/CH_2Cl_2$ and the pure compound was obtained as a white solid (0.122 g, 92%). TLC R_f = 0.4 in 10% $EtOAc/CH_2Cl_2$. ^1H NMR (300 MHz; $CDCl_3$): δ 10.87 (br s, 1H), 9.99 (s, 1H), 7.35-7.26 (m, 2H), 6.99-6.99 (m, 2H), 5.96 (s, 1H), 3.24 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 158.4 (C), 155.3 (CH), 132.1 (CH), 132.0 (CH), 119.7 (CH), 118.5 (C), 118.0 (C), 116.9 (CH), 106.5 (CH), 30.0 (CH_3), 9.9 (CH_3). IR (film): 1700, 1684, 1556, 1398, 1379, 1255 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O_2$ $[M]^+$: 231.1008. Found: 231.1007.



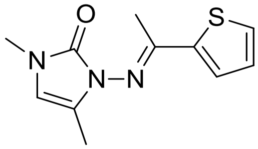
(*E*)-1,4-Dimethyl-3-((thiophen-2-ylmethylene)amino)-1H-imidazol-2(3H)-one (3.55): Synthesized according to general procedure **G** using thiopehene based carbazone (0.148 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 2 hours. The crude mixture was purified by column chromatography using 10% $EtOAc/CH_2Cl_2$ and the pure compound was obtained as a white solid (0.116 g, 87%). TLC R_f = 0.29 in 10% $EtOAc/CH_2Cl_2$. ^1H NMR (300 MHz; $CDCl_3$): δ 10.06 (s, 1H), 7.36 (dd, *J* = 9.4, 4.3 Hz, 2H), 7.08-7.05 (m, 1H), 5.93-5.89 (m, 1H) 3.22 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 145.7 (CH), 140.4 (C), 130.6 (CH), 128.1 (CH), 127.5 (CH), 119.8 (C), 118.5 (C), 105.9 (CH), 29.9 (CH_3), 9.8 (CH_3). IR (film): 1690, 1431, 1397, 1387, 1310, 1256 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{11}N_3OS$ $[M]^+$: 221.0623. Found: 221.0599.



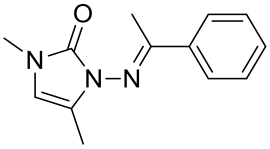
(*E*)-3-((Furan-2-ylmethylene)amino)-1,4-dimethyl-1H-imidazol-2(3H)-one (3.56): Synthesized according to general procedure **G** using furan based carbazone (0.138 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 2 hours. The crude mixture was purified by column chromatography using 10% $EtOAc/CH_2Cl_2$ and the pure compound was obtained as a white solid (0.105 g, 85%). TLC R_f = 0.32 in 10% $EtOAc/CH_2Cl_2$. ^1H NMR (300 MHz; $CDCl_3$): δ 9.83 (s, 1H), 7.54 (d, *J* = 1.4 Hz, 1H), 6.76 (dd, *J* = 3.4, 0.5 Hz, 1H), 6.49 (dd, *J* = 3.4, 1.7 Hz, 1H), 5.91 (q, *J* = 1.2 Hz, 1H), 3.21 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 150.1 (C), 145.6 (CH), 140.8 (CH), 119.9 (C), 114.3 (CH), 111.8 (CH), 106.0 (CH), 29.9 (CH_3), 9.9 (CH_3). IR (film): 1695, 1653, 1558, 1433, 1398, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{11}N_3O_2$ $[M]^+$: 205.0851. Found: 205.0866.



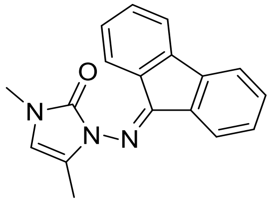
(*E*)-3-(((5-(4-Bromophenyl)furan-2-yl)methylene)amino)-1,4-dimethyl-1H-imidazol-2(3H)-one (3.57): Synthesized according to general procedure **G** using carbazone **3.34** (0.231 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by filtration and the pure compound was obtained as a light brown solid (0.175 g, 80%). TLC R_f = 0.41 in 10% $EtOAc/CH_2Cl_2$. ^1H NMR (300 MHz; DMSO-d_6): δ 9.73 (s, 1H), 7.73-7.62 (m, 4H), 7.20-7.10 (m, 2H), 6.34 (s, 1H), 3.12 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz; DMSO-*d*6): δ 153.8 (C), 149.3 (C), 139.4 (CH), 131.9 (CH), 128.6 (C), 125.8 (CH), 121.3 (C), 118.3 (CH), 117.0 (C), 109.1 (CH), 107.1 (CH), 29.6 (CH_3), 9.6 (CH_3). IR (film): 1657, 1556, 1436, 1251, 1067, 1028 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{14}N_3O_2Br$ $[M]^+$: 359.0269. Found: 359.0244.



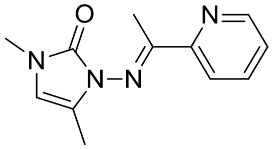
(*E*)-1,4-Dimethyl-3-((1-(thiophen-2-yl)ethylidene)amino)-1H-imidazol-2(3H)-one (3.58): Synthesized according to general procedure **G** using thiophene based carbazone (0.156 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 40% $EtOAc/CH_2Cl_2$ and the pure compound was obtained as a yellow oil (0.120 g, 85%). TLC R_f = 0.16 in 40% $EtOAc/CH_2Cl_2$. ^1H NMR (300 MHz; $CDCl_3$): δ 7.51 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.42 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.07 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.97 (q, *J* = 1.3 Hz, 1H), 3.24 (s, 3H), 2.42 (s, 3H), 2.03 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 165.6 (C), 142.2 (C), 129.9 (CH), 129.4 (CH), 127.3 (CH), 119.7 (C), 106.7 (CH), 30.4 (CH_3), 17.6 (CH_3), 10.0 (CH_3). IR (film): 1695, 1670, 1652, 1553, 1431, 1396, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{13}N_3OS$ $[M]^+$: 235.0779. Found: 235.0803.



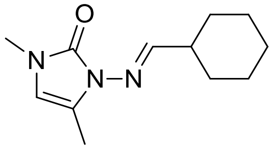
(*E*)-1,4-Dimethyl-3-((1-phenylethylidene)amino)-1H-imidazol-2(3H)-one (3.59): Synthesized according to general procedure **G** using acetophenone based carbazone (0.153 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 40% $EtOAc/CH_2Cl_2$ and the pure compound was obtained as a yellow oil (0.100 g, 73%). TLC R_f = 0.3 in 40% $EtOAc/CH_2Cl_2$. ^1H NMR (300 MHz; $CDCl_3$) δ 7.96-7.90 (m, 2H), 7.47-7.34 (m, 3H), 5.98 (q, *J* = 1.3 Hz, 1H), 3.23 (s, 3H), 2.39 (s, 3H), 2.03 (d, *J* = 1.4 Hz, 3H). ^{13}C NMR (100 MHz; CDCl$_3$): δ 170.9 (C), 148.3 (C), 137.1 (C), 130.5 (CH), 128.2 (CH), 127.2 (CH), 119.5 (C), 106.7 (CH), 30.3 (CH$_3$), 17.6 (CH$_3$), 10.0 (CH$_3$). IR (film): 1680, 1558, 1506, 1433, 1398, 1385, 1355, 1265, 1180 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{15}N_3O$ [M]$^+$: 229.1215. Found: 229.1220.



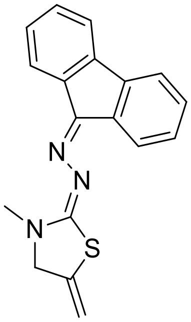
3-((9H-Fluoren-9-ylidene)amino)-1,4-dimethyl-1H-imidazol-2(3H)-one (3.60): Synthesized according to general procedure **G** using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.189 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et$_3$N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 20% EtOAc/CH$_2$Cl$_2$ and the pure compound was obtained as an orange solid (0.130 g, 75%). TLC R$_f$ = 0.10 in 20% EtOAc/CH$_2$Cl$_2$. ^{1}H NMR (300 MHz; CDCl$_3$): δ 7.51 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.92 (d, *J* = 7.5, 1H), 7.59 (dd, *J* = 7.4, 4.0 Hz, 2H), 7.42 (qd, *J* = 7.7, 1.1 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.32-7.27 (m, 1H), 7.24-7.19 (m, 1H) 6.10 (q, *J* = 1.4 Hz, 1H), 3.31 (s, 3H), 2.08 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (100 MHz; CDCl$_3$): δ 165.6 (C), 143.0 (C), 141.6 (C), 136.4 (C), 132.4 (CH), 131.9 (CH), 131.0 (C), 128.6 (CH), 128.2 (CH), 127.7 (CH), 123.6 (CH), 120.0 (CH), 119.8 (C), 119.7 (CH), 107.5 (CH), 30.6 (CH$_3$), 17.6 (CH$_3$), 10.2 (CH$_3$). IR (film): 1686, 1678, 1605, 1589, 1450, 1431, 1379, 1340, 1180 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{15}N_3O$ [M]$^+$: 289.1215. Found: 289.1252.



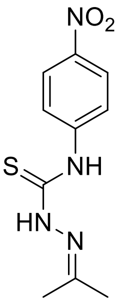
(*E*)-1,4-Dimethyl-3-((1-(pyridin-2-yl)ethylidene)amino)-1H-imidazol-2(3H)-one (3.61): Synthesized according to general procedure **G** using pyridine based carbazone (0.153 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et$_3$N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 20% EtOAc/CH$_2$Cl$_2$ and the pure compound was obtained as a yellow oil (0.119 g, 86%). TLC R$_f$ = 0.08 in 20% EtOAc/CH$_2$Cl$_2$. ^{1}H NMR (300 MHz; CDCl$_3$): δ 8.65 (d, *J* = 4.2 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.72 (td, *J* = 7.7, 1.6 Hz, 1H), 7.33 (dd, *J* = 6.4, 5.0 Hz, 1H) 6.00 (d, *J* = 1.2 Hz, 1H), 3.25 (s, 3H), 2.53 (s, 3H), 2.03 (d, *J* = 0.9 Hz, 3H). ^{13}C NMR (100 MHz; CDCl$_3$): δ 171.7 (C), 148.6 (CH), 136.2 (CH), 124.8 (CH), 122.0 (CH), 119.6 (C), 107.0 (CH), 30.4 (CH$_3$), 16.6 (CH$_3$), 10.0 (CH$_3$). IR (film): 1701, 1690, 1670, 1636, 1560, 1543, 1499, 1472, 1263, 1082 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{14}N_4O$ [M]$^+$: 230.1168. Found: 230.1158.



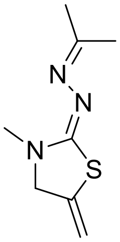
(*E*)-3-((Cyclohexylmethylene)amino)-1,4-dimethyl-1H-imidazol-2(3H)-one (3.62): Synthesized according to general procedure **G** using cyclohexyl based carbazone (0.148 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 10% $EtOAc/CH_2Cl_2$ and the pure compound was obtained as a white solid (0.0900 g, 68%). TLC $R_f = 0.31$ in 10% $EtOAc/CH_2Cl_2$. ^1H NMR (300 MHz; $CDCl_3$) δ 8.98 (d, *J* = 5.5 Hz, 1H), 5.82 (q, *J* = 1.2 Hz, 1H), 3.16 (s, 3H), 2.33-2.22 (m, 1H), 2.05 (d, *J* = 1.4 Hz, 1H), 1.87-1.62 (m, 5H), 1.38-1.17 (m, 5H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 161.3 (CH), 150.0 (C), 119.7 (C), 105.1 (CH), 41.8 (CH_3), 29.9 (CH_2), 29.7 (CH), 25.9 (CH_2), 25.4 (CH_2), 9.8 (CH_3). IR (film): 1684, 1664, 1345, 1265, 1248 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{19}N_3O$ $[M]^+$: 221.1528. Found: 221.1527.



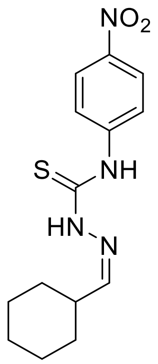
(*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-3-methyl-5-methylenethiazolidine (3.63): Synthesized according to general procedure **G** using thiosemicarbazone **3.43** (0.225 g, 0.600 mmol), *N*-methylpropargylamine (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography using 20% EtOAc/Hexanes and the pure compound was obtained as a yellow solid (0.139 g, 76%). TLC $R_f = 0.12$ in 20% EtOAc/hexanes. ^1H NMR (300 MHz; $CDCl_3$): δ 8.75-8.67 (m, 1H), 7.97-7.88 (m, 1H), 7.74-7.62 (m, 2H), 7.44-7.27 (m, 4H), 5.30-5.22 (m, 2H), 4.47-4.40 (m, 2H), 3.31-3.24 (m, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 141.3 (C), 140.1 (C), 137.7 (C), 132.0 (C), 129.7 (CH), 129.1 (CH), 129.0 (C), 127.6 (CH), 127.5 (CH), 121.7 (CH), 119.5 (CH), 119.5 (CH), 105.4 (CH_2), 59.2 (CH_2), 33.7 (CH_3). IR (film):1690, 1607, 1566, 1537, 1456, 1408, 1263 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{15}N_3S$ $[M]^+$: 305.0987. Found: 305.1005. The X-Ray information is available from the Cambridge Crystallographic Data Centre: CCDC 1420524.



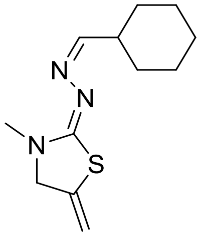
N-(4-Nitrophenyl)-2-(propan-2-ylidene)hydrazinecarbothioamide: To a solution of acetone (0.15 mL, 2.00 mmol) in MeOH (10.0 mL) was added *N*-(4-nitrophenyl)hydrazinecarbothioamide (0.425 g. 2.00 mmol) and the solution was stirred at reflux for 3 hours. Upon cooling, a solid precipitated and was collected by filtration to afford the desired product as a orange solid (0.250 g, 50%). TLC R_f = 0.29 in 10 % EtOAC/CH_2Cl_2. ^{1}H NMR (400 MHz; DMSO-*d*$_6$): δ 10.75 (br s, 1H), 10.25 (br s, 1H), 8.20 (d, *J* = 9.0 Hz, 2H), 8.07 (d, *J* = 9.2 Hz, 2H), 2.04 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (100 MHz; DMSO-*d*$_6$): δ 175.8 (C), 154.5 (C), 145.5 (C), 143.1 (C), 123.7 (CH), 123.5 (CH), 25.1 (CH_3), 18.1 (CH_3). IR (film):1637, 1596, 1558, 1523, 1330, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{12}N_4O_2S$ [M]$^+$: 252.0681. Found: 252.0694.



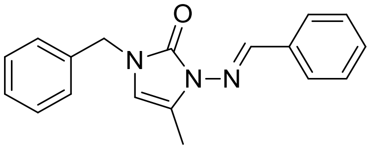
(*E*)-3-Methyl-5-methylene-2-(propan-2-ylidenehydrazono)thiazolidine (3.64): Synthesized according to general procedure **G** using *N*-(4-nitrophenyl)-2-(propan-2-ylidene)hydrazinecarbothioamide (0.0760 g, 0.300 mmol), *N*-methylpropargylamine (0.0230 g, 0.330 mmol), Et_3N (0.00600 g, 0.120 mmol) and MeCN (1.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography using 20% EtOAc/Hexanes and the pure compound was obtained as a yellow solid (0.0470 g, 85%). TLC R_f = 0.24 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 5.18-5.13 (m, 2H), 4.23 (t, *J* = 2.3 Hz, 2H), 3.02 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 164.4 (C), 159.8 (C), 138.7 (C), 104.6 (CH_2), 58.7 (CH_2), 33.3 (CH_3), 24.7 (CH_3), 18.1 (CH_3). IR (film):1679, 1638, 1593, 1466, 1389, 1263, 1068 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_{13}N_3S$ [M]$^+$: 183.0830. Found: 183.0835.



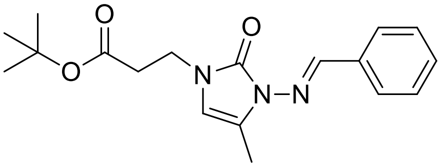
_N_-(4-Nitrophenyl)-2-(cyclohexylmethylene)hydrazinecarbothioamide: To a solution of cyclohexane carboxaldehyde (0.225 g, 2.00 mmol) in MeOH (10.0 mL) was added *N*-(4-nitrophenyl)hydrazinecarbothioamide (0.425 g. 2.00 mmol) and the solution was stirred at reflux for 3 hours. Upon cooling, a solid precipitated and was collected by filtration to afford the desired product as a yellow solid (0.375 g, 61%). TLC R_f = 0.36 in 10% EtOAC/CH_2Cl_2. ^{1}H NMR (400 MHz; DMSO-*d₆*): δ 8.25-8.14 (m, 3H), 8.05-8.02 (m, 2H), 7.45 (d, *J* = 5.7 Hz, 1H), 2.32-2.23 (m, 1H), 1.84-1.61 (m, 5H), 1.34-1.16 (m, 5H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 175.0 (C), 152.8 (CH), 145.4 (C), 143.2 (C), 123.7 (CH). 40.1 (CH), 29.5 (CH_2), 25.4 (CH_2), 25.0 (CH_2). IR (film): 2941, 1641, 1585, 1552, 1450, 1332, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{18}N_4O_2S$ [M]$^+$: 306.1150. Found: 306.1197.



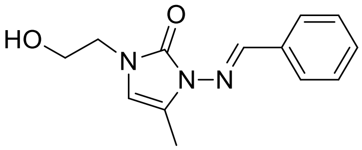
(*E*)-2-((*Z*)-(Cyclohexylmethylene)hydrazono)-3-methyl-5-methylenethiazolidine (3.65): Synthesized according to general procedure **G** using N-(4-nitrophenyl)-2-(cyclohexylmethylene)hydrazinecarbothioamide (0.0920 g, 0.300 mmol), *N*-methylpropargylamine (0.0230 g, 0.330 mmol), Et_3N (0.00600 g, 0.0600 mmol) and MeCN (1.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography using 20% EtOAc/Hexanes and the pure compound was obtained as a yellow oil (0.0430 g, 60%). TLC R_f = 0.30 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.59 (d, *J* = 5.8 Hz, 1H), 5.20-5.14 (m, 2H), 4.27 (t, *J* = 2.3 Hz, 2H), 3.02 (s, 3H), 2.33-2.22 (m, 1H), 1.89-1.63 (m, 5H), 1.38-1.17 (m, 5H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 166.5 (C), 160.7 (CH), 138.3 (C), 104.7 (CH_2), 58.9 (CH_2), 40.7 (CH), 33.3 (CH_3), 30.2 (CH_2), 26.0 (CH_2), 25.4 (CH_2). IR (film): 2910, 1639, 1585, 1423, 1392, 1265, 951 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{19}N_3S$ [M]$^+$: 237.1300. Found: 237.1329.



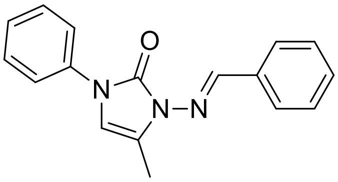
(*E*)-1-Benzyl-3-(benzylideneamino)-4-methyl-1H-imidazol-2(3H)-one (3.66): Synthesized according to general procedure **G** using carbazone **3.47** (0.146 g, 0.600 mmol), *n*-benzyl propargylamine (0.960 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 5% EtOAc/CH_2Cl_2 and the pure compound was obtained as an off white solide (0.148 g, 85%). TLC $R_f = 0.3$ in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.98 (s, 1H), 7.81-7.78 (m, 2H), 7.45-7.30 (m, 8H), 5.90 (d, *J* = 1.2 Hz, 1H), 4.79 (s, 2H), 2.18 (d, *J* = 1.0 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 151.2 (CH), 149.8 (C), 136.7 (C), 135.1 (C), 130.2 (CH), 128.7 (CH), 128.6 (CH), 127.8 (CH), 127.8 (CH), 120.4 (C), 104.6 (CH), 46.7 (CH_2), 10.0 (CH_3). IR (film): 2953, 2853, 1679, 1647, 1456, 1398, 1362, 1327, 1258 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{17}N_3O$ $[M]^+$: 291.1372. Found: 291.1387.



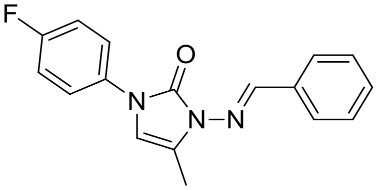
(*E*)-*tert*-Butyl 3-(3-(benzylideneamino)-4-methyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl)propanoate (3.67): Synthesized according to general procedure **G** using carbazone **3.47** (0.146 g, 0.600 mmol), the propargylic amine (0.121 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using a gradient of CH_2Cl_2 to 5% EtOAc/CH_2Cl_2 and the pure compound was obtained as a yellow oil (0.140 g, 71%). TLC $R_f = 0.47$ in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.91 (s, 1H), 7.79-7.73 (m, 2H), 7.42-7.37 (m, 3H), 6.02 (d, *J* = 1.2 Hz, 1H), 3.85 (t, *J* = 6.6 Hz, 2H), 2.62 (t, *J* = 6.6 Hz, 2H), 2.17 (d, *J* = 1.2 Hz, 3H), 1.45 (s, 9H) . ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.6 (C), 151.2 (CH), 135.1 (C), 130.2 (CH), 128.6 (CH), 127.3 (CH), 119.9 (C), 105.4 (CH), 81.1 (CH), 39.2 (CH_2), 35.2 (CH_2), 28.0 (CH_3), 9.9 (CH_3). IR (film): 1718, 1687, 1555, 1506, 1418, 1263 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{23}N_3O_3$ $[M]^+$: 329.1739. Found: 329.1710.



(*E*)-3-(Benzylideneamino)-1-(2-hydroxyethyl)-4-methyl-1H-imidazol-2(3H)-one (3.68): Synthesized according to general procedure **G** using carbazone **3.47** (0.146 g, 0.600 mmol), ethanolpropargylamine (0.0650 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 6 hours. After trying multiple purification methods and different reaction conditions that did not increase the yield or the purity of the obtained compound, a NMR yield was determined using ratio of phenol to the desired compound : 49-51%.



(*E*)-3-(Benzylideneamino)-4-methyl-1-phenyl-1H-imidazol-2(3H)-one (3.69): Synthesized according to general procedure **G** using carbazone **3.47** (0.146 g, 0.600 mmol), *n*-phenylpropargylamine (0.0870 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by Et_3N treated[121] column chromatography using 25% hexanes/CH_2Cl_2 and the pure compound was obtained as a yellow solid (0.0900 g, 54%). TLC R_f = 0.25 in 25% hexanes/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.98 (s, 1H), 7.84-7.77 (m, 2H), 7.63-7.58 (m, 2H), 7.48-7.40 (m, 5H), 7.29-7.23 (m, 1H), 6.37 (q, *J* = 1.3 Hz, 1H), 2.18 (d, *J* = 1.4 Hz, 3H) . ^{13}C NMR (100 MHz; $CDCl_3$): δ 151.8 (C), 135.0 (C), 130.4 (C), 129.2 (CH), 128.6 (CH), 127.5 (CH), 125.8 (CH), 121.7 (C), 121.6 (CH), 104.2 (CH), 10.1 (CH_3). IR (film): 1693, 1684, 1506, 1398, 1376, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{17}H_{15}N_3O$ $[M]^+$: 277.1215. Found: 227.1228.



(*E*)-3-(Benzylideneamino)-1-(4-fluorophenyl)-4-methyl-1H-imidazol-2(3H)-one (3.70): Synthesized according to general procedure **G** using carbazone **3.47** (0.146 g, 0.600 mmol), 4-fluoro-*n*-propargylaniline (0.0980 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified column chromatography using 6% EtOAc/Hexane and the pure compound was obtained as a yellow solid (0.0660 g, 37%). TLC R_f = 0.25 in 6% EtOAc/Hexane. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.95 (s, 1H), 7.81-7.78 (m, 2H), 7.57-7.53 (m, 2H), 7.44-7.41 (m, 3H), 7.15-7.09 (m, 2H), 6.29 (q, *J* = 1.2 Hz, 1H), 2.26 (d, *J* = 1.6 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 161.7 (C), 159.3 (C), 152.0 (CH), 148.6 (C), 135.0 (C), 133.0 (133.0 fluorine coupling) (C), 130.5 (CH), 128.7 (CH), 127.5 (CH), 123.6 (CH), 123.5 (CH), 121.8 (C), 116.1 (CH), 115.9 (CH), 10.1 (CH_3). IR (film): 2954, 2841, 1690, 1678, 1558, 1512, 1400, 1377, 1263 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{17}H_{14}N_3O$ $[M]^+$: 295.1121. Found: 295.1164.

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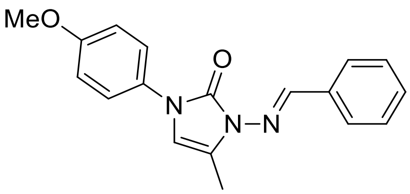
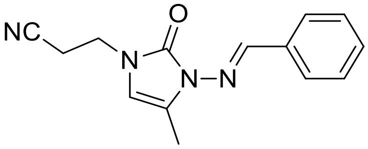
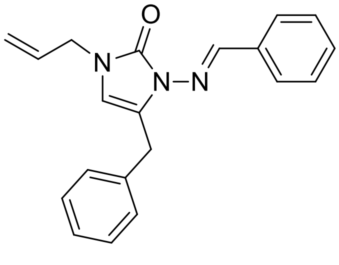
[121] Et_3N is crucial for separating product from phenol. Every solvent system without the use of Et_3N resulted in poor to no separation of the two compounds.



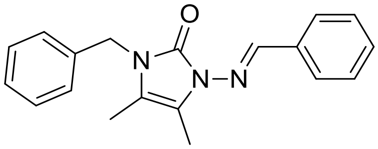
(*E*)-3-(Benzylideneamino)-1-(4-methoxyphenyl)-4-methyl-1H-imidazol-2(3H)-one (3.71): Synthesized according to general procedure **G** using carbazone **3.47** (0.146 g, 0.600 mmol), 4-methoxy-*n*-propargylaniline (0.106 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by filtration and the pure compound was obtained as an offwhite solid (0.0760 g, 41%). TLC R_f = 0.20 in 50% hexanes/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.98 (s, 1H), 7.81-7.78 (m, 2H), 7.50-7.46 (m, 1H), 7.44-7.41 (m, 3H), 6.98-6.94 (m, 2H), 6.28 (q, *J* = 1.4 Hz, 1H), 3.83 (s, 3H), 2.26 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 157.6 (C), 151.6 (CH), 148.7 (C), 135.0 (C), 130.3 (CH), 130.0 (C), 128.6 (CH), 127.4 (CH), 123.5 (CH), 121.1 (C), 114.3 (CH), 104.7 (CH), 55.5 (CH_3), 10.0 (CH_3). IR (film): 2960, 2849, 1684, 1653, 1555, 1520, 1506, 1397, 1255, 1251 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{17}N_3O_2$ $[M]^+$: 307.13208. Found: 307.13229.



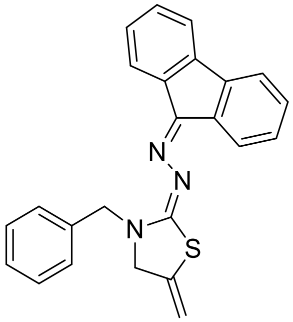
(*E*)-3-(3-(Benzylideneamino)-4-methyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl)propanenitrile (3.72): Synthesized according to general procedure **G** using carbazone **3.47** (0.146 g, 0.600 mmol), the propargylic amine (0.0710 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 6 hours. The crude mixture was purified by column chromatography using 6 % EtOAc/CH_2Cl_2 and the pure compound was obtained as a white solid (0.0920 g, 60%). TLC R_f = 0.40 in 6% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.84 (s, 1H), 7.79-7.73 (m, 2H), 7.44-7.39 (m, 3H), 6.07 (d, *J* = 1.4 Hz, 1H), 3.88 (t, *J* = 6.4 Hz, 2H), 2.74 (t, *J* = 6.5 Hz, 2H), 2.18 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 151.8 (CH), 149.3 (C), 134.7 (C), 130.4 (CH), 128.6 (CH), 127.4 (CH), 121.0 (C), 117.4 (C), 104.7 (CH), 39.4 (CH_2), 18.0 (CH_2), 9.9 (CH_3). IR (film): 2360, 1730, 1701, 1553, 1433, 1398, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{14}N_4O$ $[M]^+$: 254.1168. Found: 254.1155.



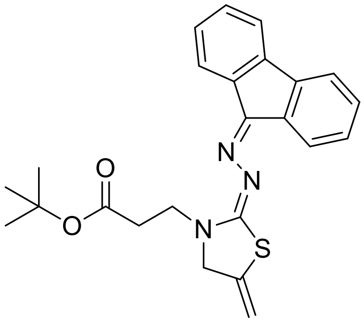
(*E*)-1-Allyl-4-benzyl-3-(benzylideneamino)-1H-imidazol-2(3H)-one (3.73): Synthesized according to general procedure **G** using carbazone **3.47** (0.146 g, 0.600 mmol), the propargylic amine (0.113 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. Purifications were unsuccessful (product seems to degrade and equilibrate threw isomerization), therefore another reaction was performed and 0.0114 g of 1,3,5-trimethoxybenzene was added as NMR internal standard. 35 % of desired product (endocyclic alkene) was observed with 14 % of the exocyclic present.



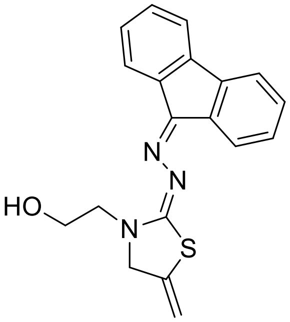
(*E*)-1-Benzyl-3-(benzylideneamino)-4,5-dimethyl-1H-imidazol-2(3H)-one (3.74): Synthesized according to general procedure **G** using carbazone **3.47** (0.146 g, 0.600 mmol), the propargylic amine (0.105 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by Et_3N treated silica gel column chromatography using 2% hexanes/CH_2Cl_2 and the pure compound was obtained as a white solid (0.150 g, 82%). TLC R_f = 0.12 in 2% hexanes/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.96 (s, 1H), 7.80-7.75 (m, 2H), 7.46-7.39 (m, 3H), 7.37-7.31 (m, 2H), 7.30-7.25 (m, 3H), 4.87 (s, 2H), 2.16 (d, *J* = 1.1 Hz, 3H), 1.94 (d, *J* = 1.1 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 150.7 (CH), 150.0 (C), 137.5 (C), 135.4 (C), 130.0 (CH), 128.7 (CH), 128.6 (CH), 127.4 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 115.2 (C), 112.0 (C), 44.1 (CH_2), 8.8 (CH_3), 8.3 (CH_3). IR (film): 1701, 1664, 1653, 1558, 1387, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{19}H_{19}N_3O$ $[M]^+$: 305.1528. Found: 305.1522.



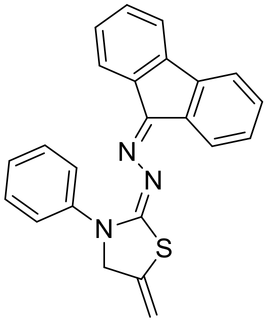
(*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-3-benzyl-5-methylenethiazolidine (3.75): Synthesized according to general procedure **G** using thiosemicarbazone **3.43** (0.225 g, 0.600 mmol), *n*-benzyl propargylamine (0.0960 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by filtration and the pure compound was obtained as a yellow solid (0.155g, 68%). TLC R_f = 0.27 in 40% CH_2Cl_2/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.64 (dt, *J* = 7.6, 0.6 Hz, 1H), 7.91-7.88 (m, 1H), 7.69-7.61 (m, 2H), 7.42-7.27 (m, 4H), 5.25-5.22 (m, 2H), 4.54 (t, *J* = 2.3 Hz, 2H), 3.93 (t, *J* = 6.6 Hz, 2H), 2.80 (t, *J* = 6.6 Hz, 2H), 1.48 (s, 9H) . ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.0 (C), 169.9 (C), 153.1 (C), 141.4 (C), 140.1 (C), 137.7 (C), 131.9 (C), 129.7 (CH), 129.2 (CH), 128.8 (CH), 127.6 (CH), 127.5 (CH), 121.7 (CH), 119.5 (CH), 119.4 (CH), 105.4 ($CH_{2)}$, 81.1 (C), 58.0 (CH_2), 43.0 (CH_2), 33.0 (CH_2), 28.0 (CH_3) . IR (film): 1684, 1647, 1554, 1506, 1107, 903 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{24}H_{19}N_3S$ $[M]^+$: 381.1300. Found: 381.1321.



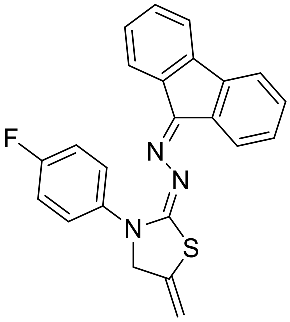
(*E*)- *tert*-Butyl 3-(2-((9H-fluoren-9-ylidene)hydrazono)-5-methylenethiazolidin-3-yl)propanoate (3.76): Synthesized according to general procedure **G** using thiosemicarbazone **3.43** (0.225 g, 0.600 mmol), the propargylic amine (0.121 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography using 20% EtOAc/Hexanes and the pure compound was obtained as a orange foam (0.200 g, 79%). TLC R_f = 0.27 in 20% EtOAc/hexanes. ^1H NMR (300 MHz; $CDCl_3$): δ 8.64 (dt, *J* = 7.6, 0.6 Hz, 1H), 7.91-7.88 (m, 1H), 7.69-7.61 (m, 2H), 7.42-7.27 (m, 4H), 5.25-5.22 (m, 2H), 4.54 (t, *J* = 2.3 Hz, 2H), 3.93 (t, *J* = 6.6 Hz, 2H), 2.80 (t, *J* = 6.6 Hz, 2H), 1.48 (s, 9H) . ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.0 (C), 169.9 (C), 153.1 (C), 141.4 (C), 140.1 (C), 137.7 (C), 131.9 (C), 129.7 (CH), 129.2 (CH), 128.8 (CH), 127.6 (CH), 127.5 (CH), 121.7 (CH), 119.5 (CH), 119.4 (CH), 105.4 ($CH_{2)},$ 81.1 (C), 58.0 (CH_2), 43.0 (CH_2), 33.0 (CH_2), 28.0 (CH_3) . IR (film): 1676, 1601, 1558, 1526, 1501, 1431, 1420, 1398, 1263 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{24}H_{25}N_3O_2S$ $[M]^+$: 419.1667. Found: 419.1666.



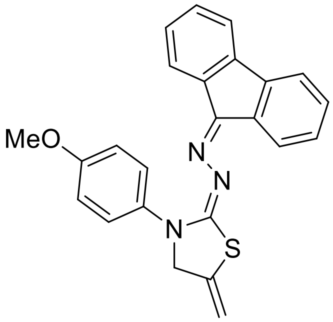
(*E*)-2-(2-((9H-fluoren-9-ylidene)hydrazono)-5-methylenethiazolidin-3-yl)ethanol (3.77): Synthesized according to general procedure **G** using thiosemicarbazone **3.43** (0.225 g, 0.600 mmol), ethanolpropargylamine (0.0650 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography using 100% EtOAc and the pure compound was obtained as a yellow solid (0.147 g, 73%). TLC R_f = 0.20 in 100% EtOAc. ^1H NMR (300 MHz; $CDCl_3$): δ 8.55 (d, *J* = 7.4 Hz, 1H), 7.87 (d, *J* = 7.4 Hz, 1H), 7.66 (d, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.40-7.29 (m, 4H), 5.25-5.20 (m, 2H), 4.55 (t, *J* = 2.2 Hz, 2H), 4.00 (t, *J* = 4.9 Hz, 2H), 3.84-3.82 (m, 2H) . ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.8 (C), 153.0 (C), 153.1 (C), 141.5 (C), 140.1 (C), 137.6 (C), 137.5 (C), 131.7 (C), 129.9 (CH), 129.3 (CH), 128.5 (CH), 127.8 (CH), 127.5 (CH), 121.7 (CH), 119.6 (CH), 119.5 (CH), 106.4 ($CH_{2)}$, 61.3 (CH_2), 58.8 (CH_2), 49.8 (CH_2). IR (film): 2960, 2853, 1535, 1495, 1416, 1265, 1141 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{24}H_{17}N_3OS$ $[M]^+$: 335.1092. Found: 335.1100.



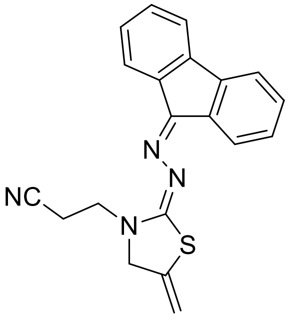
(*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-5-methylene-3-phenylthiazolidine (3.78): Synthesized according to general procedure **G** using thiosemicarbazone **3.43** (0.225 g, 0.600 mmol), *n*-phenylpropargylamine (0.0870 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified filtration and the pure compound was obtained as a orange solid (0.170 g, 78%). TLC R_f = 0.12 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-d_6): δ 8.34 (d, *J* = 7.6, 1H), 7.84-7.72 (m, 5H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.45-7.30 (m, 4H), 7.22-7.19 (m, 1H), 5.43 (d, *J* = 15.1 Hz, 2H), 5.11 (s, 2H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 169.0 (C), 152.8 (C), 140.6 (C), 139.7 (C), 136.5 (C), 135.8 (C), 130.6 (CH), 130.6 (C), 129.9 (CH), 128.9 (CH), 127.9 (CH), 125.7 (CH), 123.3 (CH), 121.2 (CH), 120.3 (CH), 120.3 (CH), 106.4 (CH_2), 58.8 (CH_2). IR (film): 1684, 1647, 1555, 1506, 1107 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{23}H_{17}N_3S$ $[M]^+$: 367.1143. Found: 367.1438.



(*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-3-(4-fluorophenyl)-5-methylenethiazolidine (3.79): Synthesized according to general procedure **G** using thiosemicarbazone **3.43** (0.225 g, 0.600 mmol), 4-fluoro-*n*-propargylaniline (0.0980 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified filtration and the pure compound was obtained as an orange solid (0.180 g, 78%). TLC R_f = 0.11 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-d_6): δ 8.26 (d, *J* = 7.6, 1H), 7.83-7.71 (m, 5H), 7.45-7.31 (m, 5H), 7.24-7.19 (m, 1H), 5.42 (d, *J* = 12.2 Hz, 2H), 5.08 (s, 2H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 168.6 (C), 152.8 (C), 140.3 (C), 139.4 (C), 136.3 (C), 135.7 (C), 130.4 (CH), 130.0 (CH), 129.4 (CH), 127.7 (CH), 127.4 (CH) 127.3 (CH), 125.5 (CH), 125.4 (CH), 120.8 (CH), 119.6 (CH), 119.6 (CH), 115.3 (CH), 115.0 (CH), 105.8 (CH_2), 58.6 (CH_2). IR (film): 1690, 1670, 1609, 1595, 1526, 1506, 1477, 1433, 1398 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{23}H_{16}N_3SF$ $[M]^+$: 385.1049. Found: 385.1015.



(*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-3-(4-methoxyphenyl)-5-methylenethiazolidine (3.80): Synthesized according to general procedure **G** using thiosemicarbazone **3.43** (0.225 g, 0.600 mmol), 4-methoxy-*n*-propargylaniline (0.106 g, 0.660 mmol), Et$_3$N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified filtration and the pure compound was obtained as a brown solid (0.170 g, 78%). TLC R$_f$ = 0.3 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; CDCl$_3$): δ 8.38 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.90 (dq, *J* = 7.4, 0.7 Hz, 1H), 7.63-7.57 (m, 4H), 7.38-7.27 (m, 3H), 7.15 (td, *J* = 7.6, 1.1 Hz, 1H), 7.03-6.99 (m, 2H), 5.31 (dq, *J* = 11.1, 2.1 Hz, 2H), 4.87 (t, *J* = 2.3 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz; CDCl$_3$): δ 168.9 (C), 157.3 (C), 154.2 (C), 144.3 (C), 140.4 (C), 137.5 (C), 136.8 (C), 133.2 (C), 131.7 (C), 130.0 (CH), 129.4 (CH), 128.7 (CH), 127.7 (CH), 127.5 (CH), 125.0 (CH), 121.9 (CH), 119.5 (CH), 119.5 (CH), 114.1 (C), 105.6 (CH$_2$), 59.4 (CH$_2$), 55.6 (CH$_3$). IR (film): 2968, 2854, 1734, 1555, 1497, 1246, 1022 cm^{-1}. HRMS (EI): Exact mass calcd for C$_{24}$H$_{19}$N$_3$OS [M]$^+$: 397.1249. Found: 397.1224.



(*E*)-3-(2-((9H-Fluoren-9-ylidene)hydrazono)-5-methylenethiazolidin-3-yl)propanenitrile (3.81): Synthesized according to general procedure **G** using a derivative of thiosemicarbazone **3.43**[122] (0.225 g, 0.600 mmol), the propargylic amine (0.0710 g, 0.660 mmol), Et$_3$N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography using 20% EtOAc/Hexanes and the pure compound was obtained as a orange solid (0.152 g, 74%). TLC R$_f$ = 0.27 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 8.59 (d, *J* = 7.2 Hz,1H), 7.84 (dd, *J* = 12.6, 7.3 Hz, 2H), 7.71 (d, *J* = 7.0 Hz, 1H), 7.49-7.30 (m, 4H), 5.39 (d, *J* = 12.3 Hz, 2H), 4.69-4.68 (m, 2H), 3.98 (t,

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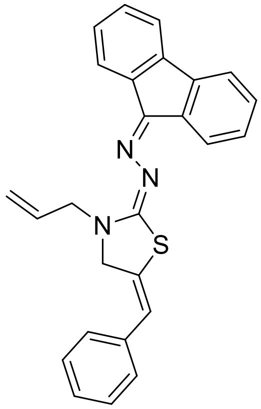
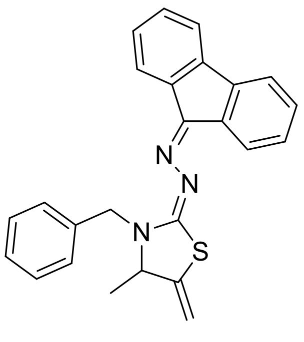
[122] *o*-Nitroaniline was used as leaving group to ensure good separation for the flash chromatography. For synthesis see: Lavergne, K.; MSc thesis, University of Ottawa, 2015

J = 6.6 Hz, 2H), 3.06 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (100 MHz; DMSO- *d*$_6$): δ 170.2 (C), 151.8 (C), 140.6 (C), 139.5 (C), 136.7 (C), 136.6 (C), 131.0 (CH), 130.4 (CH), 129.7 (C), 128.6 (CH), 128.1 (CH), 127.8 (CH), 121.0 (CH), 120.2 (CH), 120.2 (CH), 119.1 (C), 106.6 (CH$_2$), 60.0 (CH$_2$), 42.4 (CH$_2$), 33.0 (CH$_2$), 15.1 (CH$_2$). IR (film): 2314, 1684, 1601, 1458, 1420, 1398 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{20}H_{16}N_4S$ [M]$^+$: 344.1096. Found: 384.1126.

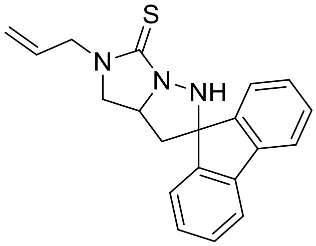


(2*E*,5*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-3-allyl-5-benzylidenethiazolidine (3.82): Synthesized according to general procedure **G** using thiosemicarbazone **3.43** (0.225 g, 0.600 mmol), the propargylic amine (0.113 g, 0.660 mmol), Et$_3$N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified filtration and the pure compound was obtained as an orange solid (0.223 g, 91%). TLC R$_f$ = 0.13 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; CDCl$_3$): δ 8.69 (d, *J* = 7.3, 1H), 7.99 (d, *J* = 7.0 Hz, 1H), 7.66 (dd, *J* = 11.8, 7.3 Hz, 2H), 7.46-7.27 (m, 9H), 7.22-7.19 (m, 1H), 6.55 (s, 1H), 6.00 (ddt, *J* = 16.9, 10.4, 6.2 Hz, 1H), 5.41-5.32 (m, 2H), 4.58 (d, *J* = 1.7 Hz, 2H), 4.35 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (100 MHz; CDCl$_3$): δ 169.3 (C), 141.4 (C), 140.2 (C), 137.6 (C), 135.9 (C), 131.9 (C), 131.5 (CH), 129.9 (CH), 129.3 (CH), 129.1 (C), 129.0 (CH), 128.6 (CH), 128.0 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH), 121.9 (CH$_2$), 120.2 (CH), 119.5 (CH), 119.5 (CH), 119.0 (CH$_2$), 58.4 (CH$_2$), 49.5 (CH$_2$). IR (film): 1602, 1533, 1522, 1460, 1263 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{26}H_{21}N_3S$ [M]$^+$: 407.1456. Found: 407.1665.

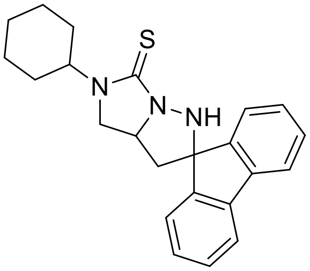


(*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-3-benzyl-4-methyl-5-methylenethiazolidine (3.83): Synthesized according to general procedure **G** using thiosemicarbazone **3,43** (0.225 g, 0.600 mmol), the propargylic amine (0.105 g, 0.660 mmol), Et$_3$N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography and the pure compound was obtained as an orange foam (0.161 g, 68%). TLC R$_f$ = 0.26 in 25% CH$_2$Cl$_2$/hexanes. ^{1}H NMR (300 MHz;

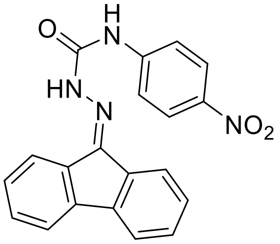
$CDCl_3$): δ 8.55-8.52 (m, 1H), 7.93-7.89 (m, 1H), 7.66-7.60 (m, 2H), 7.44-7.16 (m, 9H), 5.41 (d, *J* = 15.3, 1H), 5.23 (t, *J* = 1.97, 1H), 5.14 (t, *J* = 1.85, 1H), 4.53-4.43 (m, 2H), 1.45 (d, *J* = 6.40, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.2 (C), 153.2 (C), 143.7 (C), 141.4 (C), 140.2 (C), 137.8 (C), 136.3 (C), 131.9 (C), 129.8 (CH), 129.2 (CH), 128.9 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 121.7 (CH), 119.5 (CH), 119.5 (CH), 105.3 (CH_2), 62.5 (CH), 48.8 (CH_2), 20.3 (CH_3). IR (film): 2854, 1599, 1521, 1506, 1423, 1398, 1244 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{25}H_{21}N_3S$ $[M]^+$: 395.1456. Found: 395.1432.



5'-Allyl-3',3a',4',5'-tetrahydrospiro[fluorene-9,2'-imidazo[1,5-b]pyrazole]-6'(1'H)-thione (3.84): Synthesized according to general procedure **G** using thiosemicarbazone **3.43** (0.225 g, 0.600 mmol), diallylamine (0.0640 g, 0.660 mmol),) and MeCN (2.0 mL) and heated at 150 °C for 2 hours. The crude mixture was purified by column chromatography using 5% EtOAc/CH_2Cl_2 and the pure compound was obtained as yellow solid (0.158 g, 79%). TLC R_f = 0.4 in 5% EtOAc/CH_2Cl_2. ^1H NMR (300 MHz; DMSO-d_6): δ 7.73 (dd, *J* = 13.7, 7.2 Hz, 2H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.43-7.23 (m, 5H), 5.94-5.82 (m, 2H), 5.31-5.26 (m, 2H), 4.58-4.50 (m, 1H), 4.45-4.25 (m, 2H), 3.87 (dd, *J* = 10.7, 7.9 Hz, 1H), 3.68 (d, *J* = 10.6 Hz, 1H), 2.50-2.43 (m, 1H), 2.20-2.12 (m, 1H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 188.5 (C), 150.7 (C), 139.2 (C), 138.5 (C), 131.8 (CH), 128.7 (CH), 127.9 (CH), 127.8 (CH), 124.6 (CH), 123.8 (CH), 119.9 (CH), 119.6 (CH), 118.1 (CH_2), 74.7 (C), 60.6 (CH), 49.7 (CH_2), 49.6 (CH_2), 45.4 (CH_2). IR (film): 1680, 1610, 1553, 1379, 1360, 1310, 1255 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{20}H_{19}N_3S$ $[M]^+$: 333.1300. Found: 333.1292.



5'-Cyclohexyl-3',3a',4',5'-tetrahydrospiro[fluorene-9,2'-imidazo[1,5-b]pyrazole]-6'(1'H)-thione (3.85): Synthesized according to general procedure **G** using thiosemicarbazone **3.43** (0.225 g, 0.600 mmol), allylcyclohexylamine (0.0920 g, 0.660 mmol),) and MeCN (2.0 mL) and heated at 150 °C for 4 hours. The crude mixture was purified by column chromatography using 5% EtOAc/CH_2Cl_2 and the pure compound was obtained as a orange was obtained as a yellow solid (0.145 g, 64%). TLC R_f = 0.26 in 5% EtOAc/CH_2Cl_2. ^1H NMR (300 MHz; DMSO-d_6): δ 7.74 (dd, *J* = 14.4, 7.0 Hz, 2H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.42-7.22 (m, 5H), 5.85 (s, 1H), 4.51-4.41 (m, 2H), 3.85-3.79 (m, 1H), 3.70-3.67 (m, 1H), 2.42 (dd, *J* = 12.6, 6.7 Hz, 1H), 2.11-2.04 (m, 1H), 1.88-1.75 (m, 4H), 1.65 (d, *J* = 10.8 Hz, 1H), 1.55-1.28 (m, 4H), 1.19-1.08 (m, 1H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 187.6 (C), 150.7 (C), 148.4 (C), 139.2 (C), 128.7 (CH), 128.0 (CH), 127.8 (CH), 124.6 (CH), 123.8 (CH), 119.9 (CH), 119.6 (CH), 74.6 (C), 60.5 (CH), 55.3 (CH), 46.2 (CH$_2$), 45.4 (CH$_2$), 28.9 (CH$_2$), 28.8 (CH$_2$), 25.1 (CH$_2$), 25.0 (CH$_2$), 24.9 (CH$_2$). IR (film): 1680, 1653, 1556, 1456, 1263, 1226, 1032 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{23}H_{25}N_3S$ [M]$^+$: 375.1769. Found: 375.1797.

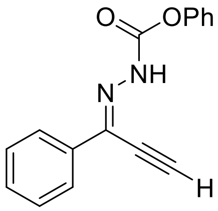


2-(9H-Fluoren-9-ylidene)-N-(4-nitrophenyl)hydrazinecarbamide: To a solution of 9-fluorenone hydrazone (1.94 g, 10 mmol) in MeCN (50.0 mL) was slowly added 4-nitrophenyl isocyanate (1.62 g, 10 mmol). The solution was stirred at room temperature for 3 hours and the title compound was obtained by filtration as a yellow amorphous solid (3.44 g, 96%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 10.64 (br s, 1H), 10.02 (br s, 1H), 8.06-8.03 (m, 1H), 8.01-7.96 (m, 2H), 7.93-7.90 (m, 1H), 7.85-7.83 (m, 1H), 7.57-7.52 (m, 1H), 7.48-7.36 (m, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 153.2 (C), 145.7 (C), 145.5 (C), 145.3 (C), 141.8 (C), 141.3 (C), 139.0 (C), 136.7 (C), 131.2 (CH), 130.0 (CH), 128.1 (CH), 127.0 (CH), 124.9 (CH), 122.2(CH), 120.7 (CH), 120.2 (CH), 118.9 (CH). IR (film): 1684, 1649, 1541, 1529, 1263 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{20}H_{14}N_4O_3$ [M]$^+$: 358.1060. Found: 358.1060.

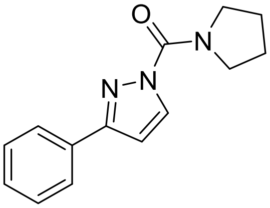
6.2.4: Diversity-Oriented Synthesis of Acyl-Pyrazole using *N*-Isocyanates (section 3.3)

General procedure H (substrate preparation): 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.

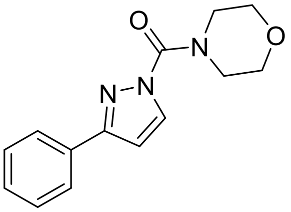
General procedure I: An oven-dried round bottom flask was charged with a stir bar, hydrazone (1.00 equiv), an amine (1.10 equiv), $PhCF_3$ or THF (0.3 M), and DBU (0.200 equiv). The reaction was conducted at room temperature or 50 °C. The reaction was concentrated under reduced pressure and purified by silica gel column chromatography to give the corresponding products.



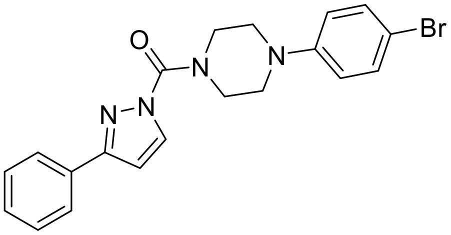
(*E*)-Phenyl-2-(1-phenylprop-2-yn-1-ylidene)hydrazinecarboxylate (3.86): Synthesized according to general procedure **H** using phenylcarbazate (1.90 g, 12.5 mmol), 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-one (2.78 g, 13.8 mmol), acetic acid (0.113 g, 0.150 mmol), and CH_3OH (42 mL, 0.3 M). TBAF (13.8 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.



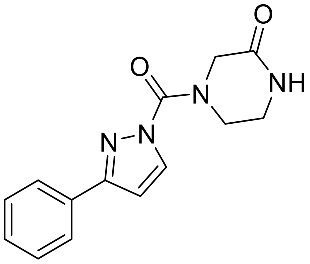
(3-Phenyl-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone (3.87): Synthesized according to general procedure **I** using hydrazone **3.86** (0.159 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 16 hours. The crude mixture was purified 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.



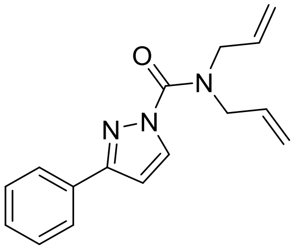
Morpholino(3-phenyl-1H-pyrazol-1-yl)methanone (3.90: Synthesized according to general procedure **I** using carbazone **3.86** (0.159 g, 0.600 mmol), morpholine (0.0871 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 16 hours. The crude mixture was purified by silica 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.



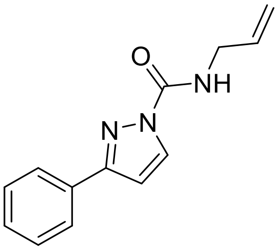
(4-(4-Bromophenyl)piperazin-1-yl)(3-phenyl-1H-pyrazol-1-yl)methanone (3.91): Synthesized according to general procedure **I** using carbazone **3.86** (0.0795 g, 0.300 mmol), 1-(4-bromophenyl)piperazine (0.0800 g, 0.330 mmol), DBU (0.0090 mL, 0.060 mmol), and THF (1.0 mL) at room temperature for 16 hours. 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.



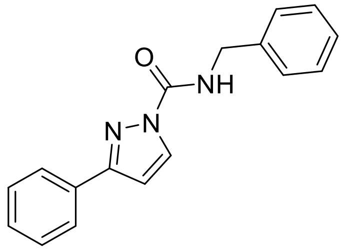
4-(3-Phenyl-1H-pyrazole-1-carbonyl)piperazin-2-one (3.92): Synthesized according to general procedure **I** using carbazone **3.86** (0.159 g, 0.600 mmol), 2-oxopiperazine (0.0661 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 16 hours. The crude mixture was purified 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. ^1H 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.



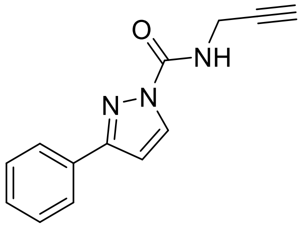
***N*,*N*-Diallyl-3-phenyl-1H-pyrazole-1-carboxamide (3.93):** Synthesized according to general procedure **I** using hydrazone **3.86** (0.159 g, 0.600 mmol), diallylamine (0.0800 mL, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 16 hours. The crude mixture was purified 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. ^1H 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.



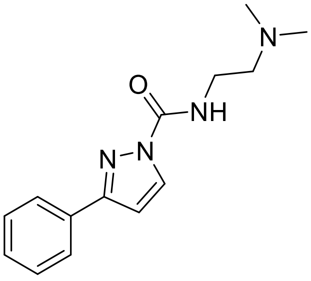
N-Allyl-3-phenyl-1H-pyrazole-1-carboxamide (3.94): Synthesized according to general procedure **I** using hydrazone **3.86** (0.159 g, 0.600 mmol), allylamine (0.050 mL, 0.66 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at 50 °C for 24 hours. The crude mixture was purified by Et_3N-treated silica 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.



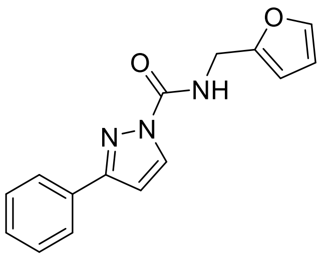
N-Benzyl-3-phenyl-1H-pyrazole-1-carboxamide (3.89): Synthesized according to general procedure **I** using carbazone **3.86** (0.159 g, 0.600 mmol), benzylamine (0.0701 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 24 hours. The crude mixture was purified by Et_3N-treated 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.



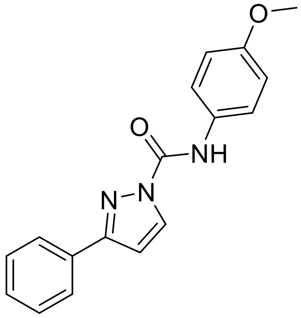
3-Phenyl-*N*-(prop-2-yn-1-yl)-1H-pyrazole-1-carboxamide (3.95): Synthesized according to general procedure **I** using carbazone **3.86** (0.159 g, 0.600 mmol), propargylamine (0.0363 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at 50 °C for 24 hours. The crude mixture was purified by 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.



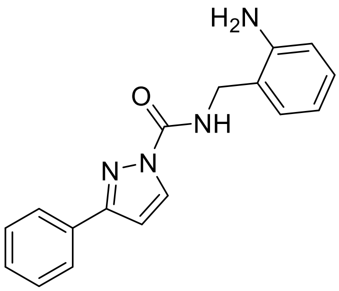
***N*-(2-(Dimethylamino)ethyl)-3-phenyl-1H-pyrazole-1-carboxamide (3.96):** Synthesized according to general procedure **I** using carbazone **3.86** (0.159 g, 0.600 mmol), *N,N*-dimethylethylenediamine (0.0582 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and $PhCF_3$ (2.0 mL) at 50 °C for 16 hours. The 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.



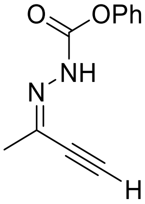
***N*-(Furan-2-ylmethyl)-3-phenyl-1H-pyrazole-1-carboxamide (3.97):** Synthesized according to general procedure **I** using carbazone **3.86** (0.159 g, 0.600 mmol), furfurylamine (0.0641 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 18 hours. The crude mixture 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. ^1H 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.



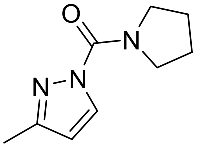
***N*-(4-Methoxyphenyl)-3-phenyl-1H-pyrazole-1-carboxamide (3.98):** Synthesized according to general procedure **I** using carbazone **3.86** (0.159 g, 0.600 mmol), *p*-methoxyaniline (0.0813 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 16 hours. The crude mixture 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. ^1H 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.



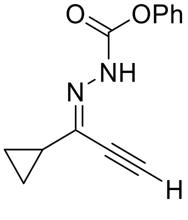
***N*-(2-Aminobenzyl)-3-phenyl-1H-pyrazole-1-carboxamide (3.99):** Synthesized according to general procedure **I** using carbazone **3.86** (0.159 g, 0.600 mmol), 2-aminobenzylamine (0.0701 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room temperature for 24 hours. The product precipitated 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. ^1H 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.



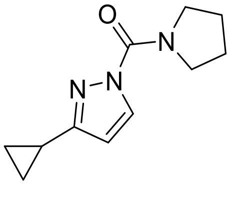
(*Z*)-Phenyl-2-(but-3-yn-2-ylidene)hydrazinecarboxylate: Synthesized according to general procedure **H** using phenylcarbazate (1.52 g, 10.0 mmol), the corresponding ketone (1.40 g, 10.0 mmol), and CH_3OH (50 mL, 0.2 M). TBAF (10.0 mL of a 1M solution in THF, 10.0 mmol) was added dropwise at -78 °C. 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. ^1H 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.



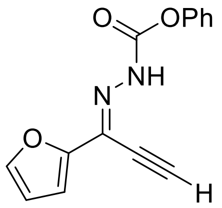
(3-Methyl-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone (3.100): Synthesized according to general procedure **I** using (*Z*)-phenyl-2-(but-3-yn-2-ylidene)hydrazinecarboxylate (0.122 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at 50 °C for 24 hours. The 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.



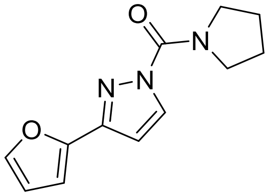
(*Z*)-Phenyl-2-(1-cyclopropylprop-2-yn-1-ylidene)hydrazinecarboxylate: Synthesized according to general procedure **H** using phenyl carbazate (1.32 g, 8.70 mmol), 1-cyclopropyl-3-(trimethylsilyl)prop-2-yn-1-one (1.59 g, 9.57 mmol), acetic acid (0.113 g, 0.131 mmol), and CH_3OH (30 mL, 0.3 M). TBAF (9.6 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.



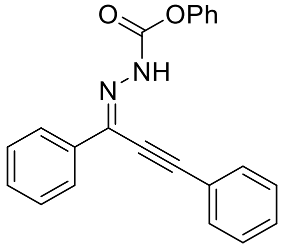
(3-Cyclopropyl-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone (3.101): Synthesized according to general procedure **I** using (*Z*)-phenyl-2-(1-cyclopropylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.137 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room 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.



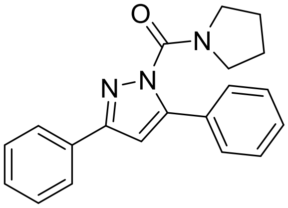
(*E*)-Phenyl-2-(1-(furan-2-yl)prop-2-yn-1-ylidene)hydrazinecarboxylate: Synthesized according to general procedure **H** using phenyl carbazate (0.959 g, 6.31 mmol), 1-furan-3-(trimethylsilyl)prop-2-yn-1-one (1.33 g, 6.94 mmol), acetic acid (0.0570 g, 0.150 mmol), and CH_3OH (21 mL, 0.3 M). TBAF (6.9 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 40% hexanes/CH_2Cl_2 to 60% 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.



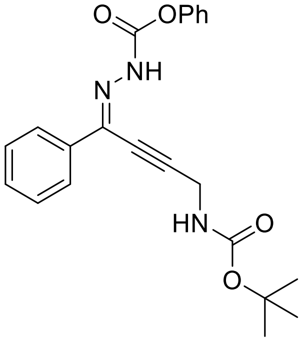
(3-(Furan-2-yl)-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone (3.102): Synthesized according to general procedure **I** using (*E*)-phenyl-2-(1-(furan-2-yl)prop-2-yn-1-ylidene)hydrazinecarboxylate (0.153 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol), DBU (0.020 mL, 0.12 mmol), and THF (2.0 mL) at room 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.



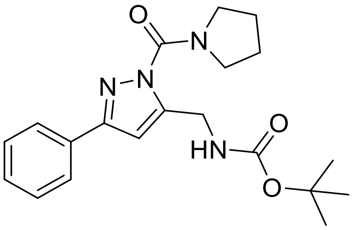
(*Z*)-Phenyl 2-(1,3-diphenylprop-2-yn-1-ylidene)hydrazinecarboxylate: Synthesized according to general procedure **H** using phenyl carbazate (1.23 g, 8.12 mmol), 1,3-diphenylprop-2-yn-1-one (1.84 g, 8.93 mmol), acetic acid (0.0730 g, 1.22 mmol), and CH_3OH (30 mL, 0.3 M). The crude mixture was purified 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.



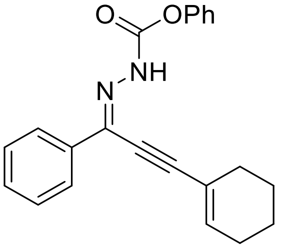
3,5-Diphenyl-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone (3.103): Synthesized according to general procedure **I** using (*Z*)-phenyl 2-(1,3-diphenylprop-2-yn-1-ylidene)hydrazinecarboxylate (0.102 g, 0.300 mmol), pyrrolidine (0.0237 g, 0.330 mmol), DBU (0.0090 mL, 0.060 mmol), and THF (1.0 mL) at 50 °C 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.



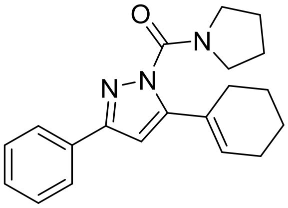
(*Z*)-Phenyl-2-(4-((tert-butoxycarbonyl)amino)-1-phenylbut-2-yn-1-ylidene) hydrazinecarboxylate: Synthesized according to general procedure **H** using phenyl carbazate (0.305 g, 2.00 mmol), *tert*-butyl-(4-oxo-4-phenylbut-2-yn-1-yl)carbamate (0.519 g, 2.00 mmol), and CH_3OH (10 mL, 0.3 M). The crude 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. ^1H 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.



***tert*-Butyl((3-phenyl-1-(pyrrolidine-1-carbonyl)-1H-pyrazol-5-yl)methyl) carbamate (3.104):** Synthesized according to general procedure **I** 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. ^1H 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.



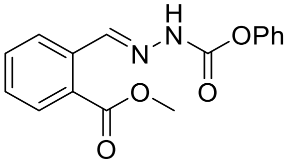
(*Z*)-Phenyl-2-(3-(cyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-ylidene) hydrazinecarboxylate: Synthesized according to general procedure **H** using phenyl carbazate (0.329 g, 2.16 mmol), 3-(cyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-one (0.500 g, 2.38 mmol), acetic acid (0.0200 g, 0.150 mmol), and CH_3OH (7.2 mL, 0.3 M) refluxed at 65 ^{o}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.



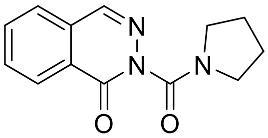
(5-(Cyclohex-1-en-1-yl)-3-phenyl-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone (3.105): Synthesized according to general procedure **I** using (*Z*)-phenyl-2-(3-(cyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-ylidene) hydrazinecarboxylate (0.103 g, 0.300 mmol), pyrrolidine (0.0237 g, 0.330 mmol), DBU (0.0090 mL, 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.

6.2.5: Synthesis of Phtalazinones (section 3.4)

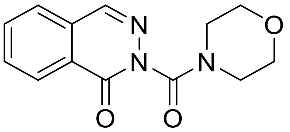
General procedure J: An oven-dried round bottom flask was charged with a stir bar, a carbazone ester (1.0 equiv), an amine (1.1 equiv), and $PhCF_3$ (0.3 M). The mixture was stirred at 100 °C for 18 or 48 hours. The reaction was cooled to ambient temperature, concentrated under reduced pressure, and purified by silica gel column chromatography to give the corresponding products.



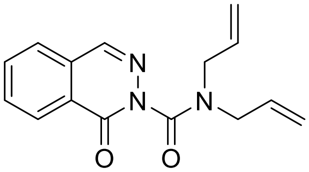
(*E*)-Phenyl-2-(2-(methoxycarbonyl)benzylidene)hydrazinecarboxylate: To a solution of phenyl carbazate (0.834 g, 5.48 mmol) in MeOH (30 mL) was added 2-methoxycarbonylbenzaldehyde (0.900 g, 5.48 mmol) and the solution was stirred at room temperature for 5 hours. The solution was condensed over reduced pressure to give a crude solid. Boiling ether was added to the solid and the pure product was collected by filtration as a white amorphous solid (1.45 g, 97%). TLC $R_f = 0.12$ in 10% $EtOAc/CH_2Cl_2$. ^1H NMR (300 MHz; DMSO-d_6): δ 11.90 (br s, 1H), 8.78 (br s, 1H), 7.97 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.87 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.65 (td, *J* = 7.6, 1.5 Hz, 1H), 7.56-7.51 (m, 1H), 7.46-7.41 (m, 2H), 7.29-7.21 (m, 3H), 3.88 (s, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 167.3 (C), 150.5 (C), 134.6 (C), 132.4 (CH), 130.5 (CH), 129.4 (CH), 129.3 (CH), 128.7 (CH), 127.7 (CH), 125.6 (CH), 125.0 (C), 121.4 (CH), 52.3 (CH_3). IR (film): 1715, 1684, 1564, 1489, 1477, 1435, 1266, 1202 cm^{-1}. HRMS (EI): Exact mass calcd for Calcd for $C_{10}H_9N_2O_3$ $[M]^+$: 205.0613 Found: 205.0523 (M – OPh).



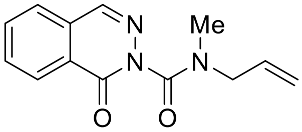
2-(Pyrrolidine-1-carbonyl)phthalazin-1(2H)-one (3.106): Synthesized according to general procedure **J** using (*E*)-phenyl-2-(2-(methoxycarbonyl)benzylidene)hydrazinecarboxylate (0.179 g, 0.600 mmol), pyrrolidine (0.0470 g, 0.660 mmol), and $PhCF_3$ (2.0 mL). The crude mixture was purified by silica gel column chromatography using 20% $EtOAc/CH_2Cl_2$ to afford the pure compound as an amorphous white solid (0.115 g, 79%). TLC $R_f = 0.24$ in 20% $EtOAc/CH_2Cl_2$. ^1H NMR (300 MHz; $CDCl_3$): δ 8.44 (dt, *J* = 7.7, 0.8 Hz, 1H), 8.23 (d, *J* = 0.5 Hz, 1H), 7.92-7.72 (m, 3H), 3.74-3.70 (m, 2H), 3.41 (t, *J* = 6.6 Hz, 2H), 2.05-1.88 (m, 4H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 157.5 (C), 151.7 (C), 139.1 (CH), 134.0 (CH), 132.2 (CH), 129.6 (CH), 128.0 (C), 126.9 (C), 126.4 (CH), 41.1 (CH_2), 41.1 (CH_2), 25.5 (CH_2), 24.7 (CH_2). IR (film): 2978, 2880, 1699, 1661, 1612, 1591, 1558, 1456, 1408, 1308, 1225 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{13}N_3O_2$ $[M]^+$: 243.1008. Found: 243.1013.



2-(Morpholine-4-carbonyl)phthalazin-1(2H)-one (3.107): Synthesized according to general procedure **J** using (*E*)-phenyl-2-(2-(methoxycarbonyl)benzylidene)hydrazinecarboxylate (0.179 g, 0.600 mmol), morpholine (0.0580 g, 0.660 mmol), and $PhCF_3$ (2.0 mL). The crude mixture was purified by silica gel column chromatography using 20% $EtOAc/CH_2Cl_2$ to afford the pure compound as an amorphous white solid (0.135 g, 87%). TLC R_f = 0.18 in 20% $EtOAc/CH_2Cl_2$. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.44-8.41 (m, 1H), 8.25 (d, *J* = 0.5 Hz, 1H), 7.91-7.71 (m, 3H), 3.84 (s, 4H), 3.73-3.70 (m, 2H), 3.37-3.34 (m, 2H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 158.1 (C), 152.5 (C), 139.5 (CH), 134.2 (CH), 132.4 (CH), 129.6 (C), 127.7 (C), 126.9 (CH), 126.6 (CH), 66.5 (CH_2), 66.3 (CH_2), 46.9 (CH_2), 44.4 (CH_2). IR (film): 2568, 1675, 1662, 1433, 1429, 1418, 1270, 1240, 1113 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{13}N_3O_3$ $[M]^+$: 259.0957. Found: 259.0963.

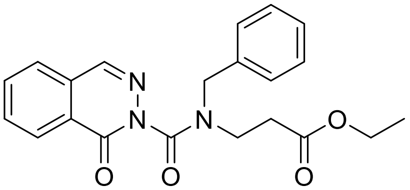


***N*,*N*-Diallyl-1-oxophthalazine-2(1H)-carboxamide (3.108):** Synthesized according to general procedure **J** using (*E*)-phenyl-2-(2-(methoxycarbonyl)benzylidene)hydrazinecarboxylate (0.179 g, 0.600 mmol), diallylamine (0.0640 g, 0.660 mmol), and $PhCF_3$ (2.0 mL). The crude mixture was purified by silica gel column chromatography using 5% $EtOAc/CH_2Cl_2$ to afford the pure compound as a colorless oil (0.161 g, 97%). TLC R_f = 0.43 in 5% $EtOAc/CH_2Cl_2$. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.41-8.38 (m,1H), 8.22 (s, 1H), 7.87-7.71 (m, 3H), 5.96-5.83 (m, 1H), 5.81-5.70 (m, 1H), 5.40 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.28 (dd, *J* = 10.1, 1.0 Hz, 1H), 5.13-5.06 (m, 2H), 4.17 (d, *J* = 5.5 Hz, 2H), 3.80 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 160.0 (C), 153.7 (C), 139.1 (CH), 134.0 (CH), 132.3 (CH), 131.2 (CH), 129.5 (C), 127.7 (C), 126.7 (CH), 126.5 (CH), 118.5 (CH_2), 118.1 (CH_2), 50.8 (CH_2), 50.0 (CH_2). IR (film): 1713, 1666, 1591, 1414, 1265, 1227, 1177 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{15}N_3O_2$ $[M]^+$: 269.1164. Found: 269.1153.

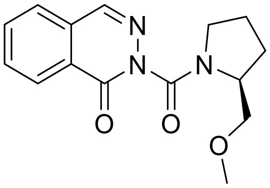


***N*-Allyl-*N*-methyl-1-oxophthalazine-2(1H)-carboxamide (3.109):** Synthesized according to general procedure **J** using (*E*)-phenyl-2-(2-(methoxycarbonyl)benzylidene)hydrazinecarboxylate (0.0900 g, 0.300 mmol), *N*-methylallylamine (0.0240 g, 0.330 mmol), and $PhCF_3$ (1.0 mL). The crude mixture was purified by silica gel column chromatography using 6% $EtOAc/CH_2Cl_2$ to afford the pure compound as a slightly yellow oil (0.0730 g, 100%). TLC R_f = 0.22 in 6% $EtOAc/CH_2Cl_2$. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.42-8.38 (m, 1H), 8.24-8.21 (m, 1H), 7.88-7.70 (m, 3H), 5.96-5.72 (m, 1H), 5.44-5.14 (m, 2H), 4.19-4.16 (m, 1.2H), 3.81-3.78 (m, 0.8H), 3.14 (s, 1.2H), 2.89 (s, 1.8H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 160.0 (C), 157.7 (C), 153.8 (C), 153.7 (C), 139.3 (CH), 139.1 (CH), 134.0 (CH), 132.3 (CH), 132.2 (CH), 132.2

(CH), 131.1 (CH), 129.6 (C), 129.5 (C), 127.7 (C), 126.8 (CH), 126.7 (CH), 126.5 (CH), 126.5 (CH), 118.8 (CH_2), 118.1 (CH_2), 53.4 (CH_2), 51.7 (CH_2), 35.2 (CH_3), 34.3 (CH_3). IR (film): 1717, 1668, 1558, 1477, 1266, 1236, 1202 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{13}N_3O_2$ $[M]^+$: 243.1008. Found: 234.1029.



Ethyl 3-(*N*-benzyl-1-oxo-1,2-dihydrophthalazine-2-carboxamido)propanoate (3.110): Synthesized according to general procedure **J** using (*E*)-phenyl-2-(2-(methoxycarbonyl)benzylidene)hydrazinecarboxylate (0.0900 g, 0.300 mmol), *N*-benzyl-3-aminopropionic acid ethyl ester (0.0670 g, 0.330 mmol), and $PhCF_3$ (1.0 mL). The crude mixture was purified by silica gel column chromatography using 6% EtOAc/CH_2Cl_2 to afford the pure compound as a slightly yellow oil (0.103 g, 90%). TLC R_f = 0.28 in 6% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.47-8.41 (m, 1H), 8.28-8.21 (m, 1H), 7.91-7.69 (m, 3H), 7.49-7.21 (m, 5H), 4.86 (s, 0.9H), 4.48 (s, 1.1H), 4.19-3.96 (m, 2H), 3.76-3.71 (m, 1H), 3.54-3.49 (m, 1H), 2.81-2.76 (m, 1H) 2.59-2.55 (m, 1H), 1.30-1.20 (m, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 171.6 (C), 170.8 (C), 158.2 (C), 154.6 (C), 153.9 (CH), 139.4 (CH), 139.3 (CH), 135.6 (C), 135.4 (C), 134.1 (CH), 134.1 (CH), 132.4 (CH), 132.3 (CH), 129.6 (C), 129.6 (C), 128.8 (CH), 128.7 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 126.8 (CH), 126.8 (CH), 126.6 (CH), 126.5 (CH), 60.7 (CH_2), 60.7 (CH_2), 53.2 (CH_2), 50.7 (CH_2), 43.7 (CH_2), 43.1 (CH_2), 33.3 (CH_2), 31.8 (CH_2), 14.1 (CH_4), 13.9 (CH_3). IR (film): 3335, 1771, 1723, 1654, 1632, 1616, 1601, 1265, 1171 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{21}H_{21}N_3O_4$ $[M]^+$: 379.1532. Found: 379.1556.

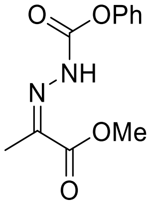


(*S*)-2-(2-(Methoxymethyl)pyrrolidine-1-carbonyl)phthalazin-1(2H)-one (3.111):
Synthesized according to general procedure **J** using (*E*)-phenyl-2-(2-(methoxycarbonyl)benzylidene)hydrazinecarboxylate (0.0900 g, 0.300 mmol), (*S*)-(+)-2-(methoxymethyl)pyrrolidine (0.0380 g, 0.330 mmol), and $PhCF_3$ (1.0 mL). The crude mixture was purified by silica gel column chromatography using 30% EtOAc/CH_2Cl_2 to afford the pure compound as a colorless oil (0.0560 g, 65%). TLC R_f = 0.28 in 30% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.40 (d, *J* = 7.6 Hz, 1H), 8.22 (s, 1H), 7.88-7.71 (m, 3H), 4.39-4.32 (m, 0.75H), 4.07-3.99 (m, 0.125H), 3.83-3.58 (m, 2H), 3.46-3.09 (m, 5H), 2.11-1.78 (m, 4H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 157.5 (C), 151.8 (C), 139.0 (CH), 138.8 (CH), 133.9 (CH), 132.2 (CH), 129.6 (C), 127.9 (C), 126.7 (CH), 126.4 (CH), 73.7 (CH_2), 71.4 (CH_2), 59.2 (CH), 58.9 (C), 58.0 (CH_3), 57.8 (CH_3), 47.7 (CH_2), 28.7 (CH_2), 27.8 (CH_2), 23.6 (CH_2), 22.5 (CH_3). IR (film): 1730, 1650, 1445, 1432, 1408, 1265, 1067 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{17}N_3O_3$ $[M]^+$: 287.1270. Found: 287.1274.

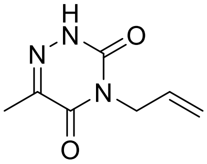
6.3: Supporting Information for Chapter 4

6.3.1: Synthesis of Azauracils (section 4.1)

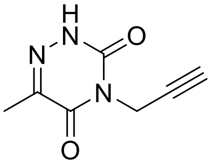
General procedure K: An oven-dried microwave tube was charged with a stir bar, a carbazone ester (1.0 equiv.), an amine (1.1 equiv.), and MeCN (0.3 M). The septum was removed and the tube was then quickly sealed with a microwave cap and heated for 6 hours at 175 °C. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel column chromatography to give the corresponding products.



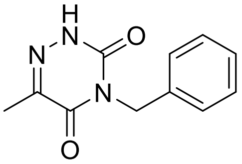
(*Z*)-Phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate: To a solution of methyl pyruvate (1.53 g, 15.0 mmol) in MeOH (75 mL) was added phenyl carbazate (2.29 g, 15.0 mmol) and the solution was stirred overnight. The crude mixture was purified by filtration to afford the pure product as an amorphous white solid (2.72 g, 77%). TLC R_f = 0.75 in 30% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 11.07 (br s, 1H), 7.48-7.41 (m, 2H), 7.31-7.21 (m, 3H), 3.74 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 164.8 (C), 150.3 (C), 129.6 (CH), 125.8 (CH), 121.8 (CH), 52.3 (CH_3), 13.1 (CH_3). IR (film): 3223, 1769, 1740, 1709, 1533, 1495, 1437, 1219, 1196, 1155, 1136 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{12}N_2O_4$ $[M]^+$: 236.0797. Found: 236.0797.



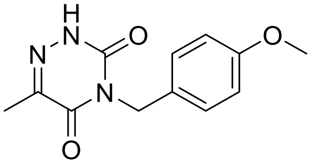
4-Allyl-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione (4.1): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.355 g, 1.50 mmol), allylamine (0.12 mL, 1.6 mmol), and MeCN (5 mL). The crude mixture was purified by silica gel column chromatography using 30% EtOAc/hexanes to afford the pure compound as an amorphous white solid (0.185 g, 74%). TLC R_f = 0.21 in 30% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.53 (br s, 1H), 5.88 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.36-5.24 (m, 2H), 4.54 (dt, *J* = 6.0, 1.3 Hz, 2H), 2.26 (s, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 156.1 (C), 150.2 (C), 143.7 (C), 130.1 (CH), 119.3 (CH_2), 42.2 (CH_2), 16.7 (CH_3). IR (film): 3205, 3086, 3070, 2928, 1717, 1647, 1728, 1616, 1448, 1379, 1348, 1277, 1209, 1173 cm^{-1}. HRMS (EI): Exact mass calcd for $C_7H_9N_3O_2$ $[M]^+$: 167.0695. Found: 167.0674.



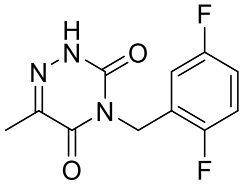
6-Methyl-4-(prop-2-yn-1-yl)-1,2,4-triazine-3,5(2H,4H)-dione (4.2): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), propargylamine (0.0460 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by silica gel column chromatography using 30% EtOAc/hexanes to afford the pure compound as an amorphous beige solid (0.105 g, 85%). TLC R_f = 0.12 in 30% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 12.38 (br s, 1H), 4.49 (d, *J* = 2.5 Hz, 2H). 3.17 (t, *J* = 2.4 Hz, 1H), 2.10 (s, 3H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 155.6 (C), 148.7 (C), 78.0 (C), 74.6 (CH), 28.6 (CH$_2$), 16.5 (CH$_3$). IR (film): 3246, 2955, 2924, 2116, 1720, 1655, 1647, 1612, 1448, 1410, 1379, 1348, 1275, 1209 cm^{-1}. HRMS (EI): Exact mass calcd for $C_7H_7N_3O_2$ [M]$^+$: 165.0538. Found: 165.0546.



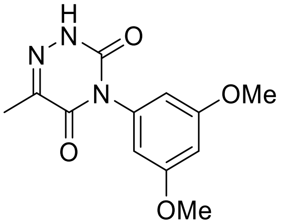
4-Benzyl-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione (4.3): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), benzylamine (0.0890 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by recrystallization using EtOAc/hexanes to afford the pure compound as an amorphous beige solid (0.105 g, 85%). TLC R_f = 0.28 in 30% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 12.34 (br s, 1H), 7.35-7.22 (m, 5H), 4.94 (s, 2H), 2.10 (s, 3H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 156.4 (C), 149.5 (C), 142.1 (C), 136.2 (C), 128.4 (CH), 127.8 (CH), 127.4 (CH), 42.5 (CH$_2$), 16.6 (CH$_3$). IR (film): 3227, 3096, 2922, 1717, 1647, 1612, 1448, 1352, 1280. 1201. HRMS (EI): Exact mass calcd for $C_{11}H_{11}N_3O_2$ [M]$^+$: 217.0851. Found: 217.0860.



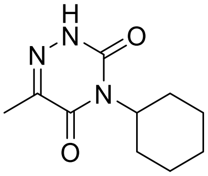
4-(4-Methoxybenzyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione (4.4): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), 4-methoxybenzylamine (0.114 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by silica gel column chromatography using 30% EtOAc/hexanes to afford the pure compound as an amorphous white solid (0.131 g, 75%). TLC R_f = 0.24 in 30% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 12.31 (br s, 1H), 7.29-7.24 (m, 2H), 6.88-6.83 (m, 2H) 4.86 (s, 2H), 3.71 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 158.6 (C), 156.4 (C), 149.5 (C), 129.7 (CH), 128.2 (C), 113.7 (CH), 55.1 (CH$_3$), 42.0 (CH$_2$), 16.6 (CH$_3$). IR (film): 3292, 2958, 2927, 1717, 1655, 1647, 1610, 1512, 1445, 1352, 1302, 1246, 1202, 1175 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O_3$ [M]$^+$: 247.0957. Found: 247.0958.



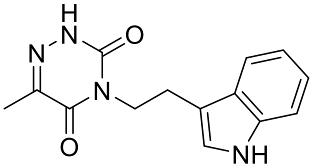
4-(2,5-Difluorobenzyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione (4.5): Synthesized according to general procedure **K** using (Z)-Phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), 2,5-difluorobenzylamine (0.119 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by recrystallization using CH_2Cl_2 to afford the pure compound as an amorphous off-white solid (0.160 g, 84%). TLC R_f = 0.17 in 30% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 12.34 (br s, 1H), 7.29-7.21 (m, 1H), 7.19-7.11 (m, 2H) 4.96 (s, 2H), 2.11 (s, 3H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 156.9 (C), 149.9 (C), 142.6 (C), 125.6 (125.5, 125.4, 125.3, coupling with fluorine) (C), 117.3 (117.2, 117.0, 116.9, coupling with fluorine) (CH), 116.2 (116.0, 116.0, 115.8, 115.7, 115.7, 115.6, coupling with fluorine) (CH), 37.1 (37.0, coupling with fluorine) (CH_2), 17.0 (CH_3). IR (film): 3267, 2924, 2851, 2368, 1717, 1645, 1632, 1489, 1437, 1369, 1348, 1273, 1182 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_9F_2N_3O_2$ $[M]^+$: 253.0663 Found: 253.0694.



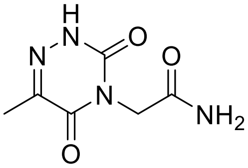
4-(3,5-Dimethoxyphenyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione (4.6): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), 3,5-dimethoxyaniline (0.127 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by filtration to afford the pure compound as an amorphous white solid (0.120 g, 61%). TLC R_f = 0.58 in 30% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 12.28 (br s, 1H), 6.58-6.56 (m, 1H), 6.51 (t, *J* = 2.2 Hz, 2H), 3.73 (s, 6H), 2.11 (s, 3H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 160.6 (C), 156.4 (C), 149.2 (C), 142.5 (C), 135.4 (C), 106.8 (CH), 100.5 (CH), 55.4 (CH_3), 16.6 (CH_3). IR (film): 3205, 3117, 2916, 1718, 1653, 1610, 1597, 1558, 1477, 1429, 1213, 1161 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O_4$ $[M]^+$: 263.0906. Found: 263.0897.



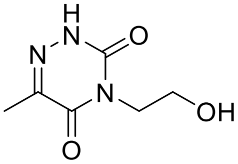
4-Cyclohexyl-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione (4.7): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), cyclohexylamine (0.0820g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by filtration to afford the pure compound as an amorphous white solid (0.0700 g, 51%). TLC R_f = 0.48 in 30% EtOac/hexanes. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 12.04 (br s, 1H), 4.52 (t, *J* = 11.6 Hz, 1H), 2.31-2.17 (m, 2H), 2.05 (s, 3H), 1.84-1.69 (m, 2H), 1.66-1.45 (m, 4H), 1.35-0.95 (m, 4H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 52.3 (CH), 33.3 (CH_2), 27.8 (CH_2), 25.7 (CH_2), 25.0 (CH_2), 24.5 (CH_2), 16.6 (CH_3). IR (film): 3259, 3248, 2930, 2858, 1728, 1639, 1616, 1558, 1435, 1217 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{15}N_3O_2$ $[M]^+$: 209.1164. Not found. LRMS m/z (relative intensity): 162.0 (3.8%), 143.1 (24.6%), 99.1 (24.6%), 56.1 (100%).



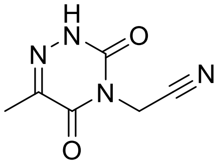
4-(2-(1H-Indol-3-yl)ethyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione (4.8): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), tryptamine (0.133 g, 0.830 mmol), and MeCN (2.5 mL). The product was purified by filtration to afford the pure compound as an amorphous white solid (0.125 g, 61%). TLC R_f = 0.85 in 30% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.26 (br s, 1H), 10.86 (br s, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.11-6.98 (m, 2H), 4.04-3.98 (m, 2H), 2.97-2.92 (m, 2H), 2.10 (s, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 156.4 (C), 149.4 (C), 141.9 (C), 136.4 (C), 127.1 (C), 122.9 (CH), 121.0 (CH), 118.4 (CH), 118.1 (CH), 111.4 (CH), 110.6 (CH), 39.9 (CH_2), 22.8 (CH_2), 16.6 (CH_3). IR (film): 3344, 1715, 1649, 1636, 1448, 1348, 1285, 1229, 1159 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{14}N_4O_2$ $[M]^+$: 270.1117. Found: 270.1100.



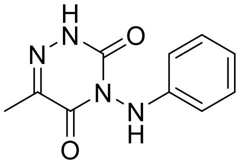
2-(6-Methyl-3,5-dioxo-2,3-dihydro-1,2,4-triazin-4(5H)-yl)acetamide (4.9): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), glycinamide hydrochloride (0.0920 g, 0.830 mmol), DIPEA (0.16 mL, 0.90 mmol), and MeCN (2.5 mL). The crude mixture was purified by silica gel column chromatography using EtOAc to afford the pure compound as an amorphous white solid (0.0550 g, 35%). TLC R_f = 0.14 in EtOAc. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.31 (br s, 1H), 7.60 (br s, 1H), 7.18 (br s, 1H) 4.30 (s, 2H), 2.10 (s, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 167.6 (C), 156.2 (C), 149.3 (C), 141.8 (C), 41.5 (CH_2), 16.5 (CH_3). IR (film): 3205, 3194, 3159, 2957, 1772, 1701, 1647, 1628, 1445, 1398, 1375, 1290, 1205, 1178, 1165 cm^{-1}. HRMS (EI): Exact mass calcd for $C_6H_8N_4O_3$ $[M]^+$: 184.0596. No mass found: 162.0, 142.1, 128.1, 100.0, 83.0, 72.0, 56.0.



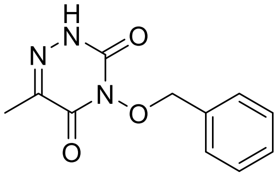
4-(2-Hydroxyethyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione (4.10): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), ethanolamine (0.0510 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by silica gel column chromatography using 85% EtOAc/hexanes to afford the pure compound as an amorphous white solid (0.610 g, 48%). TLC R_f = 0.30 in 85% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-d_6): δ 3.84 (t, *J* = 6.3 Hz, 2H), 3.52 (t, *J* = 6.3 Hz, 2H), 2.07 (s, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 156.6 (C), 149.6 (C), 141.8 (C), 57.1 (CH_2), 41.5 (CH_2) 16.6 (CH_3). IR (film): 3242, 2918, 2851, 2355, 1734, 1726, 1684, 1674, 1506, 1450, 1207 cm^{-1}. HRMS (EI): Exact mass calcd for $C_6H_9N_3O_3$ [M]$^+$: 171.0644. Found: 128.1 (– C_2H_5O).



2-(6-Methyl-3,5-dioxo-2,3-dihydro-1,2,4-triazin-4(5H)-yl)acetonitrile (4.11): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), aminoacetonitrile hydrochloride (0.0770g, 0.830 mmol), DIPEA (0.160 mL, 0.900 mmol), and MeCN (2.5 mL). The crude mixture was purified by silica gel column chromatography using 10% EtOAC/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.105 g, 84%). TLC R_f = 0.50 in 30% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 12.49 (br s, 1H), 4.79 (s, 2H), 2.11 (s, 3H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 155.6 (C), 148.5 (C), 142.0 (C), 115.0 (C), 27.1 (CH_2), 16.5 (CH_3). IR (film): 2922, 2853, 1734, 1647, 1635, 1607, 1445, 1379, 1331, 1277, 1213, 1175 cm^{-1}. HRMS (EI): Exact mass calcd for $C_6H_8N_4O_3$ [M]$^+$: 166.0491. Found: 166.0498.

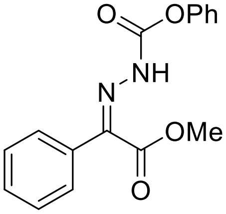


6-Methyl-4-(phenylamino)-1,2,4-triazine-3,5(2H,4H)-dione (4.12): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), phenylhydrazine (0.082 mL, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by silica gel column chromatography using 15% EtOAc/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.0980 g, 60%). TLC R_f = 0.45 in 30% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 12.42 (br s, 1H), 8.53 (s, 1H) 7.17-7.14 (m, 2H), 6.78-6.69 (m, 3H), 2.14 (s, 3H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 156.4 (C), 149.8 (C), 146.9 (C), 142.9 (C), 128.9 (CH), 119.9 (CH), 112.7 (CH), 16.9 (CH_3). IR (film): 3263, 2968, 2926, 1728, 1662, 1647, 1601, 1497, 1447, 1418, 1379, 1246, 1221, 1182 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{10}N_4O_2$ [M]$^+$: 218.0804 Found: 218.0816.

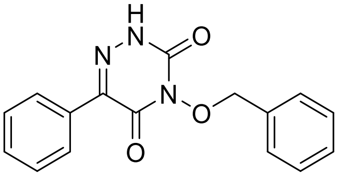


4-(Benzyloxy)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione (4.13): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), *O*-benzyl hydroxylamine (0.102 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was condensed *in vacuo* and the impurities were dissolved in CH_2Cl_2 before the product was purified by filtration to afford the pure compound as an amorphous white solid (0.105 g, 60%). TLC R_f = 0.71 in 30% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 12.42 (br s, 1H), 7.55-7.52 (m, 2H), 7.45-7.36 (m, 3H), 5.07 (s, 2H), 2.12 (s, 3H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 153.9 (C), 148.1 (C), 143.3 (C), 134.1 (C), 129.5 (CH), 129.0 (CH), 128.4 (CH), 77.6 (CH_2), 16.5 (CH_3). IR (film): 3182, 3126, 2937, 1715, 1682, 1641, 1454, 1420, 1379, 1286, 1236, 1211, 1171 cm^{-1}. HRMS (EI): Exact mass calcd for

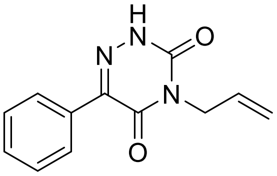
$C_{11}H_{11}N_3O_3$ $[M]^+$: 233.0800. Not found. Calcd for $C_4H_5N_3O_2$ $[M+H]^+$: 128.0460 Found: 128.0468 (M – OBn).



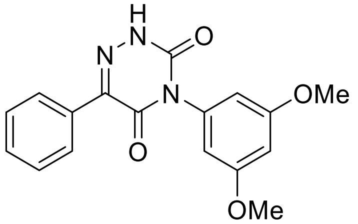
(*Z*)-Phenyl-2-(2-methoxy-2-oxo-1-phenylethylidene)hydrazinecarboxylate: To a solution of methyl benzolyformate (0.821g, 5.00 mmol) in MeOH (25 mL) was added phenyl carbazate (0.761 g, 5.00 mmol) and the solution was stirred overnight at 60 °C. The crude mixture was purified by recrystalisation with ether to afford the pure product as an amorphous white solid (1.25 g, 84%). TLC R_f =0.25 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-d_6): δ 11.67 (br s, 1H), 7.64-7.58 (m, 2H), 7.48-7.42 (m, 5H), 7.32-7.24 (m, 3H) 3.94 (s, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 163.1 (C), 151.9 (C), 150.3 (C), 130.1 (C), 130.0 (CH), 129.6 (CH), 128.7 (CH), 126.7 (CH), 125.8 (CH), 121.8 (CH), 53.0 (CH_3). IR (film): 1770, 1734, 1719, 1628, 1475, 1458, 1437, 1325, 1265, 1231, 1134 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{14}N_2O_4$ $[M]^+$: 298.0954. Found: 298.0927.



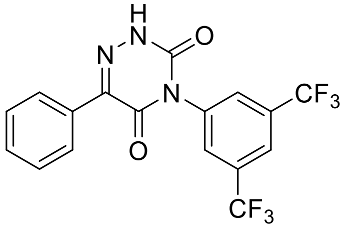
4-(Benzyloxy)-6-phenyl-1,2,4-triazine-3,5(2H,4H)-dione (4.14): Synthesized according to general procedure **K** using (*Z*)-phenyl-2-(2-methoxy-2-oxo-1-phenylethylidene)hydrazinecarboxylate (0.224 g, 0.750 mmol), *O*-benzyl hydroxylamine (0.102 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was condensed *in vacuo* and the impurities were dissolved in CH_2Cl_2 before the product was purified by filtration to afford the pure compound as an amorphous white solid (0.155 g, 70%). TLC R_f = 0.85 in 30% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.93 (br s, 1H), 7.90-7.84 (m, 2H), 7.61-7.53 (m, 2H), 7.49-7.38 (m, 6H), 5.14 (s, 2H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 153.4 (C), 147.8 (C), 134.1 (C), 132.3 (C), 129.6 (CH), 129.6 (CH), 129.0 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 77.6 (CH_2). IR (film): 3242, 3182, 2918, 1755, 1747, 1734, 1680, 1553, 1493, 1445, 1404, 1238, 1176 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{13}N_3O_3$ $[M]^+$: 295.0957. Found: 295.0962.



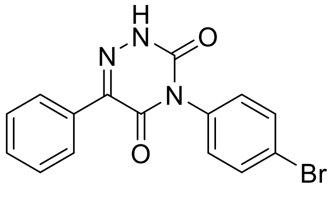
4-Allyl-6-phenyl-1,2,4-triazine-3,5(2H,4H)-dione (4.15): Synthesized according to general procedure **K** using (*Z*)-phenyl-2-(2-methoxy-2-oxo-1-phenylethylidene)hydrazinecarboxylate (0.224 g, 0.750 mmol), allylamine (0.060 mL, 0.83 mmol), and MeCN (2.5 mL). The crude mixture was purified by silica gel column chromatography using 20% EtOAc/hexanes to afford the pure compound as an amorphous yellow solid (0.100 g, 58%). TLC R_f = 0.22 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.42 (br s, 1H), 7.99-7.93 (m, 2H), 7.48-7.41 (m, 3H), 5.94 (ddt, *J* = 17.1, 10.2, 6.1 Hz, 1H), 5.42-5.27 (m, 2H), 4.62 (dt, *J* = 6.1, 1.4 Hz, 2H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 155.2 (C), 149.8 (C), 142.3 (C), 131.7 (C), 130.2 (CH), 130.1 (C), 128.3 (C), 128.3 (C), 119.6 (CH_2), 42.6 (CH_2). IR (film): 3242, 3207, 3105, 3091, 2988, 1713, 1651, 1643, 1558, 1495, 1441, 1297, 1223, 1178, 1124 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{11}N_3O_2$ $[M]^+$: 229.0851. Found: 229.0839.



4-(3,5-Dimethoxyphenyl)-6-phenyl-1,2,4-triazine-3,5(2H,4H)-dione (4.16): Synthesized according to general procedure **K** using (*Z*)-phenyl-2-(2-methoxy-2-oxo-1-phenylethylidene)hydrazinecarboxylate (0.224 g, 0.750 mmol), 3,5-dimethoxyaniline (0.127 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by filtration to afford the pure compound as an amorphous white solid (0.220 g, 90%). TLC $R_f = 0.85$ in 30% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.79 (br s, 1H), 7.88 (br s, 2H), 7.45 (br s, 3H), 6.60 (br s, 3H), 3.75 (br s, 6H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 160.6 (C), 155.7 (C), 148.9 (C), 141.3 (CH), 135.6 (C), 132.7 (C), 129.4 (CH), 128.1 (CH), 109.6 (CH), 100.5 (CH), 55.4 (CH_3). IR (film): 1715, 1564, 1444, 1370, 1290, 1265, 1118, 1065 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{17}H_{15}N_3O_4$ $[M]^+$: 325.1063. Found: 325.1075.

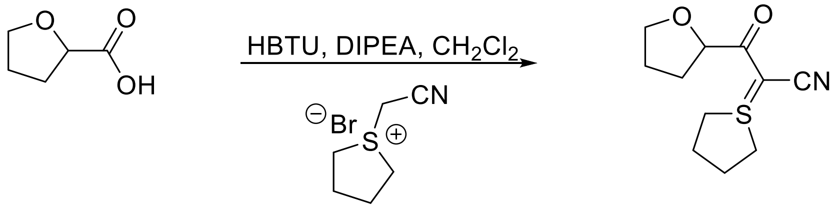


4-(3,5-Bis(trifluoromethyl)phenyl)-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione (4.17): Synthesized according to general procedure **K** using (*Z*)-phenyl-2-(2-methoxy-2-oxo-1-phenylethylidene)hydrazinecarboxylate (0.224 g, 0.750 mmol), 3,5-bistrifluoromethylaniline (0.190 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by filtration to afford the pure compound as an amorphous white solid (0.250 g, 83%). TLC $R_f = 0.9$ in 30 % EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 13.03 (br s, 1H), 8.31-8.27 (m, 3H), 7.93-7.87 (m, 2H), 7.50-7.45 (m, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 155.7 (C), 148.8 (C), 141.4 (C), 136.0 (C), 132.4 (C), 131.3 (C), 130.9 (C), 130.4 (CH), 130.3 (CH), 129.7 (CH), 128.2 (CH), 128.1 (CH). IR (film): 1770, 1718, 1684, 1558, 1472, 1437, 1373, 1265, 1225, 1177, 1136 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{17}H_{91}N_3O_2$ $[M]^+$: 401.0599. Found: 400.9956.

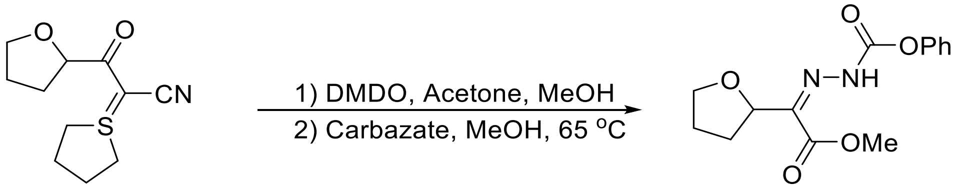


4-(4-Bromophenyl)-6-phenyl-1,2,4-triazine-3,5(2H,4H)-dione (4.18): Synthesized according to general procedure **K** using (*Z*)-phenyl-2-(2-methoxy-2-oxo-1-phenylethylidene)hydrazinecarboxylate (0.224 g, 0.750 mmol), 3-bromoaniline (0.143 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by filtration to afford the pure compound as an amorphous white solid (0.200 g, 77%). TLC R_f = 0.85 in EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.84 (br s, 1H), 7.90-7.84 (m, 2H), 7.75-7.70

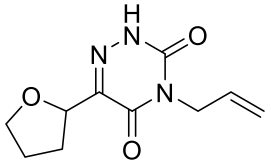
(m, 2H), 7.48-7.43 (m, 3H), 7.39-7.34 (m, 2H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 155.7 (C), 148.9 (C), 141.3 (C), 133.2 (C), 132.6 (C), 132.0 (CH), 130.9 (CH), 129.5 (CH), 128.1 (CH), 121.9 (C). IR (film): 2920, 2862, 1724, 1647, 1632, 1558, 1489, 1445, 1302, 1232, 1186, 1068 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{10}Br_1N_3O_2$ [M]$^+$: 342.9956. Found: 342.9956. The X-Ray information is available from the Cambridge Crystallographic Data Centre: CCDC 1420522.



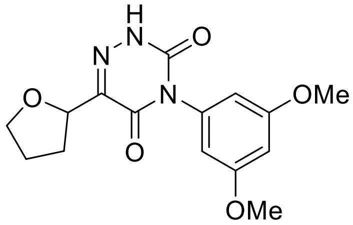
Tetrahydro-2-furoic acid (1.16 g, 10.0 mmol) was dissolved in CH_2Cl_2 (100 mL). HBTU (4.18 g, 11.0 mmol), DIPEA (5.29 mL, 30.0 mmol), and 1-(cyanomethyl)tetrahydro-1H-thiophenium bromide salt (2.29 g, 13.0 mmol) were added and the reaction was stirred at room temperature for 3 hours. The reaction was poured into saturated aqueous NH_4Cl (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified over silica gel by flash column chromatography using a gradient of 1:1 EtOAc:acetone to acetone to yield a white solid (2.10 g, 91%). TLC R_f = 0.32 in acetone. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 4.41-4.37 (m, 1H), 3.86-3.77 (m, 1H), 3.75-3.68 (m, 1H), 3.60-3.51 (m, 2H), 3.14-3.01 (m, 2H) 2.37-2.21 (m, 2H), 2.07-1.97 (m, 3H), 1.87-1.73 (m, 3H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 189.8 (C), 119.9 (C), 79.7 (CH), 68.3 (CH$_2$), 45.5 (CH$_2$), 45.2 (CH$_2$), 29.8 (CH$_2$), 28.0 (CH$_2$), 28.0 (CH$_2$), 25.4 (CH$_2$).



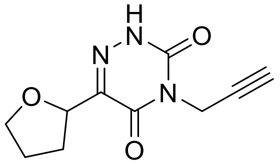
The ylide (0.225 g, 1.00 mmol) was dissolved in MeOH (10 mL). A solution of oxone in acetone (0.1 M, 20 mL, 2 mmol) was added slowly and the solution was stirred for 1 hour. An additional 5 mL were added and the solution was stirred for another hour. The solution was condensed under reduced pressure and the crude oil was dissolved in MeOH (5 mL) and phenyl carbazate (0.152 g, 1.00 mmol) was added. The solution was stirred at reflux overnight. The solution was concentrated and purified by silica gel flash column chromatography with 5% EtOAc:CH_2Cl_2 to afford the impure THF-semi-carbazone as a colorless oil (0.215 g, 74% , overestimated since material is not pure).



4-Allyl-6-(tetrahydrofuran-2-yl)-1,2,4-triazine-3,5(2H,4H)-dione (4.19): Synthesized according to general procedure **K** using impure carbazone ester (0.190 g, 0.650 mmol), allylamine (0.050 mL, 0.72 mmol), and MeCN (2.0 mL). The crude mixture was purified by silica gel column chromatography using 20% EtOAc/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.0600 g, 42%). TLC R_f = 0.18 in 20% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 12.46 (br s, 1H), 5.81 (ddt, *J* = 17.5, 10.1, 5.3 Hz, 1H), 5.15 (q, *J* = 1.4 Hz, 1H), 5.10 (dq, *J* = 4.8, 1.4 Hz, 1H), 4.87 (t, *J* = 6.8 Hz, 1H), 4.35 (dt, *J* = 5.3, 1.5 Hz, 2H), 3.86-3.72 (m, 2H), 2.11-1.82 (m, 4H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 149.0 (C), 143.6 (C), 131.5 (CH), 117.2 (CH_2), 75.0 (CH), 68.0 (CH_2), 41.2 (CH_2), 28.6 (CH_2), 25.4 (CH_2). IR (film): 3225, 2988, 2870, 1717, 1659, 1645, 1558, 1456, 1425, 1406, 1337, 1225, 1173, 1065 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{13}N_3O_3$ [M]$^+$: 223.0957. Found: 223.0960.

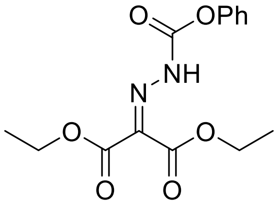


4-(3,5-Dimethoxyphenyl)-6-(tetrahydrofuran-2-yl)-1,2,4-triazine-3,5(2H,4H)-dione (4.20): Synthesized according to general procedure **K** using impure carbazone ester (0.175 g, 0.600 mmol), 3,5-dimethoxyaniline (0.102 g, 0.660 mmol), and MeCN (2.0 mL). The crude mixture was purified by silica gel column chromatography using 20% EtOAc/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.110 g, 57%). TLC R_f = 0.21 in 20% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 12.48 (br s, 1H), 6.56-6.57 (m, 1H), 6.54-6.43 (m, 2H), 4.90 (t, *J* = 6.7 Hz, 1H), 4.35 (dt, *J* = 5.3, 1.5 Hz, 2H), 3.88-3.74 (m, 8H), 2.13-1.80 (m, 4H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 160.6 (C), 155.4 (C), 149.0 (C), 144.2 (C), 135.2 (C), 106.8 (CH), 100.6 (CH), 75.0 (CH), 68.0 (CH_2), 55.4 (CH_3), 28.7 (CH_2), 25.4 (CH_2). IR (film): 3286, 3246, 2959, 1734, 1670, 1610, 1597, 1558, 1474, 1429, 1346, 1205, 1155 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{17}N_3O_5$ [M]$^+$: 319.1168. Found: 319.1159.

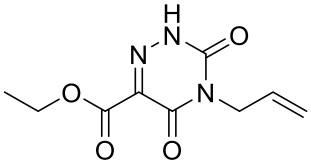


4-(Prop-2-yn-1-yl)-6-(tetrahydrofuran-2-yl)-1,2,4-triazine-3,5(2H,4H)-dione (4.21): Synthesized according to general procedure **K** using impure carbazone ester (0.175 g, 0.600 mmol), propargylamine (0.0360 g, 0.660 mmol), and MeCN (2.0 mL). The crude mixture was purified by silica gel column chromatography using 20% EtOAc/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.0700 g, 42%). TLC R_f = 0.20 in 20% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 12.59 (br s, 1H), 4.87 (t, *J* = 6.7 Hz, 1H), 4.48 (d, *J* = 2.2 Hz, 2H), 3.86-3.72 (m, 2H), 3.19 (s, 1H) 2.10-1.82 (m, 4H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 154.5 (C), 148.5 (C), 143.6 (C), 78.0 (C), 75.1 (CH), 73.7 (CH), 28.6

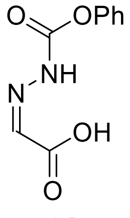
(CH$_2$), 28.5 (CH$_2$), 25.4 (CH$_2$). IR (film): 3244, 2924, 1713, 1655, 1620, 1531, 1452, 1425, 1346, 1242, 1223, 1167, 1055 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{11}N_3O_3$ [M]$^+$: 221.0800. Found: 221.0784.



Diethyl 2-(2-(phenoxycarbonyl)hydrazono)malonate: To a solution of diethylketomalonate (0.46 mL, 3.0 mmol) in MeOH (15 mL) was added phenyl carbazate (0.456 g, 3.00 mmol) and the solution was stirred overnight at 60 °C. The crude mixture was purified by silica gel column chromatography using 30% EtOAc/hexanes to afford the pure product as an amorphous white solid (0.404 g, 44%). TLC R$_f$ = 0.52 in 30% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.06 (br s, 1H), 7.47-7.41 (m, 2H), 7.32-7.22 (m, 3H), 4.36-4.22 (m, 4H) 1.29-1.21 (m, 6H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 161.4 (C), 160.7 (C), 151.6 (C), 150.2 (C), 134.0 (C), 130.0 (CH), 126.5 (CH), 121.9 (CH), 62.7 (CH$_2$), 62.3 (CH$_2$), 14.1 (CH$_3$), 13.9 (CH$_3$). IR (film): 3252, 2984, 2355, 1784, 1732, 1697, 1558, 1474, 1369, 1256, 1140, 1090 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{16}N_2O_6$ [M]$^+$: 308.1008. Found: 308.1039.

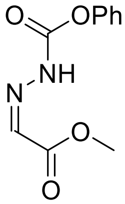


Ethyl 4-allyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylate (4.22): Synthesized according to general procedure **K** using Diethyl 2-(2-(phenoxycarbonyl)hydrazono)malonate (0.231 g, 0.750 mmol), allylamine (0.060 mL, 0.83 mmol), and MeCN (2.5 mL). The crude mixture was purified by silica gel column chromatography using 30% EtOAc/hexanes to afford the pure compound as an amorphous yellow solid (0.108 g, 64%). TLC R$_f$ = 0.17 in 30% EtOAC/hexanes. ^{1}H NMR (300 MHz; CDCl$_3$): δ 10.68 (br s, 1H), 5.86 (ddt, J = 16.9, 10.3, 6.2 Hz, 1H), 5.39-5.26 (m, 2H), 4.54 (d, J = 6.1 Hz, 2H), 4.44 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz; CDCl$_3$): δ 160.3 (C), 152.6 (C), 148.8 (C), 134.9 (C), 129.4 (CH), 120.2 (CH$_2$), 62.7 (CH$_2$), 42.7 (CH$_2$), 14.0 (CH$_3$). IR (film): 3267, 3001, 1717, 1670, 1647, 1578, 1431, 1408, 1317, 1242, 1136, 1014 cm^{-1}. HRMS (EI): Exact mass calcd for $C_9H_{11}N_3O_4$ [M]$^+$: 225.0750. Found: 225.0781.

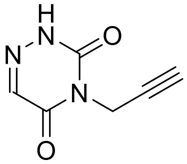


(*Z*)-2-(2-(Phenoxycarbonyl)hydrazono)acetic acid: To a solution of glycoxylic acid monohydrate (0.460 g, 5.00 mmol) in MeOH (25 mL) was added phenyl carbazate (0.761 g, 5.00 mmol) and the solution was stirred overnight. The crude mixture was purified by recrystalisation with ether to afford the pure product as an amorphous white solid (0.953 g, 92%). TLC R$_f$ = 0.64 in 30% EtOAc/CH$_2$Cl$_2$. ^{1}H NMR (300 MHz; DMSO-d_6): δ 13.12 (br s, 1H), 12.13 (br s, 1H), 7.46-7.40 (m, 3H), 7.30-7.20 (m, 3H).

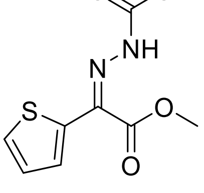
^{13}C NMR (75 MHz; DMSO-d_6): δ 164.3 (C), 129.6 (CH), 125.9 (CH), 121.8 (CH). IR (film): 3410, 3005, 2991, 1759, 1724, 1653, 1636, 1558, 1495, 1474, 1423 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{14}N_2O_4$ [M]$^+$: 208.0489. Not found. LRMS m/z (relative intensity) 181.0 (24.6%), 162.0 (2.3%), 112.0 (1.5%), 94.0 (69.2%), 69.0 (100%).



(*Z*)-Phenyl 2-(2-methoxy-2-oxoethylidene)hydrazinecarboxylate: To a solution of carbazone-acid (0.208 g, 1.00 mmol) in CH_2Cl_2 (2.5 mL) was added *N,N′* -dicyclohexylcarbodiimide (0.206 g, 1.00 mmol), 4-dimethylaminopyridine (0.0120 g, 0.100 mmol), and MeOH (0.080 mL, 2.0 mmol) and the solution was stirred overnight. The crude mixture was purified by silica gel column chromatography using 6% EtOAc/CH_2Cl_2 to afford the pure product as an amorphous white solid (0.185 g, 83%). TLC R_f = 0.20 in 6% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.23 (br s, 1H), 7.51-7.37 (m, 3H), 7.31-7.18 (m, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 163.0 (C), 129.6 (CH), 125.9 (CH), 121.7 (CH), 52.0 (CH_2). IR (film): 1713, 1597, 1555, 1537, 1493, 1437, 1350, 1196, 1132, 1047 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{10}N_2O_4$ [M]$^+$: 222.0641. Found: 222.0624.

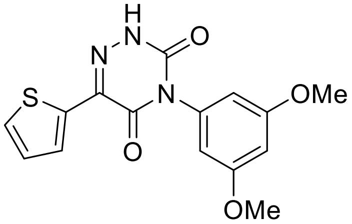


4-(Prop-2-yn-1-yl)-1,2,4-triazine-3,5(2H,4H)-dione (4.23): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(2-methoxy-2-oxoethylidene)hydrazinecarboxylate (0.167 g, 0.750 mmol), propargylamine (0.0460 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by silica gel column chromatography using 30% EtOAc/hexanes to afford the pure compound as an amorphous white solid (0.0700 g, 62%). TLC R_f = 0.14 in 30% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.71 (br s, 1H), 7.56 (s, 1H), 4.47 (d, *J* = 2.5 Hz, 2H). 3.19 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 154.8 (C), 148.8 (C), 135.2 (CH), 74.1 (CH), 28.9 (CH_2). IR (film): 3285, 3246, 2912, 1730, 1655, 1593, 1558, 1429, 1342, 1209, 1151, 1107 cm^{-1}. HRMS (EI): Exact mass calcd for $C_6H_5N_3O_2$ [M]$^+$: 151.0382. Found: 151.0391.

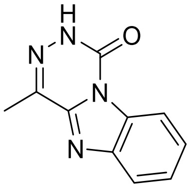


(*E*)-Phenyl-2-(2-methoxy-2-oxo-1-(thiophen-2-yl)ethylidene)hydrazine carboxylate: Synthesized according to the previous conditions using 2-oxo-2-(2-thienyl)acetic acid (0.500 g, 3.20 mmol). The crude product was directly reacted with phenyl carbazate (0.442 g, 2.91 mmol) in CH_3OH (15 mL) at 65 °C for 16 hours. The crude mixture was purified by silica gel flash column chromatography using 20%

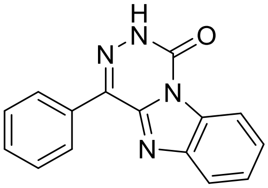
EtOAc/pet. ether. TLC R_f = 0.35 in 20% EtOAc/pet. ether. ^{1}H NMR (300 MHz; $CDCl_3$): δ 11.9 (br s, 1H), 7.61 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.41-7.33 (m, 3H), 7.24-7.21 (m, 3H), 7.02 (dd, *J* = 5.1, 3.8 Hz, 1H), 3.99 (s, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 161.9 (C), 150.7 (C), 130.1 (C), 129.6 (CH), 129.2 (CH), 128.5 (CH), 127.5 (CH), 126.0 (CH), 121.5 (CH), 53.1 (CH_3). IR (film): 3269, 1772, 1733, 1701, 1647, 1515, 1455, 1318, 1266, 1164, 1137, 1029 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{12}N_2O_4S$ $[M]^+$: 304.0518. Found: 304.0506.



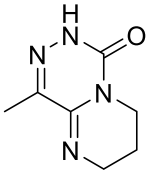
4-(3,5-Dimethoxyphenyl)-6-(thiophen-2-yl)-1,2,4-triazine-3,5(2H,4H)-dione (4.24): Synthesized according to general procedure **K** using (*E*)-phenyl-2-(2-methoxy-2-oxo-1-(thiophen-2-yl)ethylidene)hydrazine carboxylate (0.091 g, 0.300 mmol), 3,5-dimethoxyaniline (0.051 g, 0.330 mmol), and MeCN (1.0 mL). The crude mixture was purified by filtration to afford the pure compound as an amorphous white solid (0.220 g, 90%). TLC R_f = 0.30 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.70 (s, 1H), 7.89 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.65 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.12 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.56 (s, 3H), 3.71 (s, 6H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 160.6 (C), 154.9 (C), 148.7 (C), 137.1 (C), 135.4 (C), 135.2 (C), 128.9 (CH), 128.1 (CH), 127.7 (CH), 106.8 (CH), 100.6 (CH), 55.4 (CH_3). IR (film): 1772, 1733, 1716, 1668, 1647, 1558, 1455, 1265, 1188, 1141 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{13}N_3O_4S$ $[M]^+$: 331.0627. Found: 331.0647.



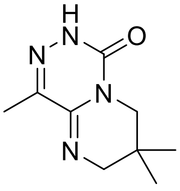
4-Methylbenzo[4,5]imidazo[1,2-d][1,2,4]triazin-1(2H)-one (4.25): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), 1,2-phenylenediamine (0.0900 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by filtration to afford the pure compound as an amorphous white solid (0.100 g, 67%). TLC R_f = 0.80 in 30% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 8.33-8.27 (m, 1H), 7.96-7.90 (m, 1H) 7.60-7.51 (m, 2H), 2.53 (s, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 146.1 (C), 143.0 (C), 139.4 (C), 129.3 (C), 126.2 (CH), 125.3 (CH), 120.5 (CH), 115.0 (CH), 108.7 (C), 16.8 (CH_3). IR (film): 2920, 2854, 2372, 1716, 1705, 1653, 1569, 1366, 1151 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_8N_4O$ $[M]^+$: 200.0698. Found: 200.0668. The X-Ray information is available from the Cambridge Crystallographic Data Centre: CCDC 1420523.



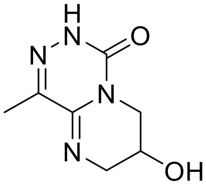
4-Phenylbenzo[4,5]imidazo[1,2-d][1,2,4]triazin-1(2H)-one (4.26): Synthesized according to general procedure **K** using (*Z*)-phenyl-2-(2-methoxy-2-oxo-1-phenylethylidene)hydrazinecarboxylate (0.224 g, 0.750 mmol), 1,2-phenylenediamine (0.0900 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by filtration to afford the pure compound as an amorphous white solid (0.150 g, 76%). TLC R_f = 0.80 in 30% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 13.17 (br s, 1H), 8.44-8.36 (m, 3H), 8.03-7.98 (m, 1H) 7.63-7.50 (m, 5H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 146.6 (C), 143.0 (C), 141.8 (C), 138.1 (C), 132.6 (C), 129.9 (CH), 128.9 (C), 128.4 (CH), 128.0 (C), 126.2 (CH), 125.3 (CH), 120.4 (CH), 115.0 (CH). IR (film): 2941, 1742, 1707, 1647, 1558, 1522, 1441, 1373, 1277, 1211. HRMS (EI): Exact mass calcd for $C_{15}H_{10}N_4O$ $[M]^+$: 262.0855. Found: 262.0840.



9-Methyl-3,4-dihydro-2H-pyrimido[1,2-d][1,2,4]triazin-6(7H)-one (4.27): Synthesized according to general procedure **K** using (Z)-Phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), diaminopropane (0.070 mL, 0.83 mmol), and MeCN (2.5 mL). The crude mixture was purified by silica gel column chromatography using 50% EtOAc/CH_2Cl_2 to pure EtOAc to afford the pure compound as an amorphous white solid (0.0800 g, 64%). TLC R_f = 0.08 in 50% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 11.27 (br s, 1H), 3.63 (t, *J* = 5.9 Hz, 2H) 3.42 (t, *J* = 5.3 Hz, 2H), 1.97 (s, 3H), 1.75 (quint., *J* = 5.7 Hz, 2 H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 148.4 (C), 142.8 (C), 142.0 (C), 43.4 (CH_2), 36.6 (CH_2), 19.0 (CH_2), 17.3 (CH_3). IR (film): 1684, 1626, 1551, 1433, 1373, 1315, 1265, 1194. HRMS (EI): Exact mass calcd for $C_7H_{10}N_4O$ $[M]^+$: 166.0855. Found: 166.0847.



3,3,9-Trimethyl-3,4-dihydro-2H-pyrimido[1,2-d][1,2,4]triazin-6(7H)-one (4.28): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), 2,2-dimethyl-1,3-diaminopropane (0.850 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by silica gel column chromatography using 50% EtOAc/CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.105 g, 72%). TLC R_f = 0.21 in 50% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-*d*$_6$): δ 11.32 (br s, 1H), 3.33 (s, 2H) 3.15 (s, 2H), 2.00 (s, 3H), 0.89 (s, 6H). ^{13}C NMR (75 MHz; DMSO-*d*$_6$): δ 148.6 (C), 142.6 (C), 141.0 (C), 55.6 (CH_2), 48.7 (CH_2), 25.8 (C), 24.1 (CH_3) 17.4 (CH_3). IR (film): 3225, 3082, 2964, 1684, 1676, 1622, 1558, 1475, 1437, 1375, 1300, 1265, 1155. HRMS (EI): Exact mass calcd for $C_9H_{14}N_4O$ $[M]^+$: 194.1168. Found: 194.1183.

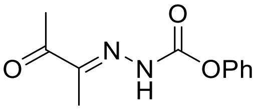


3-Hydroxy-9-methyl-3,4-dihydro-2H-pyrimido[1,2-d][1,2,4]triazin-6(7H)-one (4.29): Synthesized according to general procedure **K** using (*Z*)-phenyl 2-(1-methoxy-1-oxopropan-2-ylidene)hydrazinecarboxylate (0.177 g, 0.750 mmol), 1,3-diamino-2-propanol (0.750 g, 0.830 mmol), and MeCN (2.5 mL). The crude mixture was purified by removing soluble by-products in CH_2Cl_2 to afford the pure compound as an amorphous white solid (0.0750 g, 55%). TLC $R_f = 0.03$ in 50 % EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 11.27 (br s, 1H), 5.16-5.08 (m, 1H) 3.98 (br s, 1H), 3.71-3.62 (m, 1H), 3.54-3.43 (m, 2H), 3.38-3.27 (m, 2H), 1.99 (s, 3H).^{13}C NMR (75 MHz; DMSO-d_6): δ 148.8 (C), 142.6 (C), 141.5 (C), 58.7 (CH), 50.0 (CH_2), 44.2 (CH_2), 17.3 (CH_3). IR (film): 1716, 1662, 1617, 1558, 1434, 1427, 1418, 1265, 1236, 1225, 1177. HRMS (EI): Exact mass calcd for $C_7H_{10}N_4O_2$ $[M]^+$: 182.0804. Found: 182.0821.

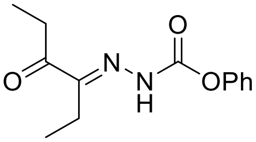
6.3.2: Divergent Synthesis Using Keto-Carbazones (section 4.2)

α-Ketocarbazones:

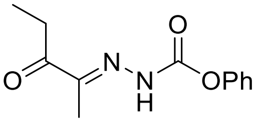
General Procedure L: *O*-Phenylcarbazate (1.0 equiv), 1,2 dione (1.1 equiv), and methanol (0.3 M) were added to a dry round bottom flask. The flask was capped with a septum and stirred overnight at room temperature. The reaction was then concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.



(*E*)-Phenyl 2-(3-oxobutan-2-ylidene)hydrazinecarboxylate (4.30): Synthesized according to general procedure **L** using *O*-phenylcarbazate (3.44 g, 20.0 mmol) and 2,3-butanedione (1.89 g, 22.0 mmol). The title compound was concentrated under reduced pressure to yield a pure white solid (4.01 g, 91%). TLC $R_f = 0.08$ in 30: 20: 50 CH_2Cl_2: Et_2O: Hexane. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.42-7.39 (m, 2H), 7.26-7.20 (m, 3H), 2.30 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.7 (C), 130.0 (CH), 126.3 (CH), 122.2 (CH), 24.7 (CH_3), 10.5 (CH_3). IR (film): 1266, 1145, 730, 717 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{13}N_2O_3$ $[M+H]^+$: 221.0882 Found: 221.0904.



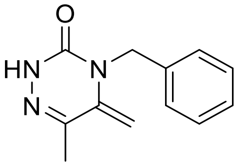
(*E*)-Phenyl 2-(4-oxohexan-3-ylidene)hydrazinecarboxylate: Synthesized according to general procedure **L** using *O*-phenylcarbazate (0.456 g, 3.00 mmol) and 3,4-hexanedione (0.376 g, 3.00mmol). The title compound was concentrated under reduced pressure, recrystallized in methanol, filtered and dried under reduced pressure to yield a pure white solid (0.574 g, 77%). TLC $R_f = 0.14$ in 30: 20: 50 CH_2Cl_2: Et_2O: Hexane. ^1H NMR (300 MHz, DMSO-d_6): δ 11.25-11.22 (m, 1H), 7.44-7.39 (m, 2H), 7.28-7.21 (m, 3H), 2.79 (q, J = 7.4 Hz, 2H), 2.54 (q, J = 7.5 Hz, 2H), 0.91 (dt, J = 20.7, 7.4 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 200.2 (C), 130.0 (CH), 126.2 (CH), 122.2 (CH), 29.7 (CH_2), 17.0 (CH_2), 10.6 (CH_3), 8.7 (CH_3). IR (film): 1741, 1685, 1487, 1265, 1190, 1130, 736 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{16}N_2O_3$ $[M+H]^+$: 249.1195 Found: 249.1226.



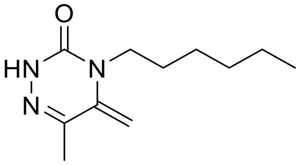
(*E*)-Phenyl 2-(3-oxopentan-2-ylidene)hydrazinecarboxylate: Synthesized according to general procedure **L** using *O*-phenylcarbazate (0.305 g, 2.00 mmol) and 2,3-pentanedione (0.220 g, 2.20 mmol) stirring at 0 °C for 6 hours. The title compound was concentrated under reduced pressure, dry loaded unto silica and purified by column chromatography (30% CH_2Cl_2/20% Ether/ 50% Hexane) to yield a pure white solid (0.291 g, 62%). TLC $R_f = 0.18$ in 30: 20: 50 CH_2Cl_2: Et_2O: Hexane. ^1H-NMR (300 MHz, DMSO-d_6): δ 7.48-7.42 (m, 2H), 7.31-7.23 (m, 3H), 2.83 (q, J = 7.3 Hz, 2H), 1.98 (s, 3H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 200.3 (C), 130.0 (CH), 126.3 (CH), 122.2 (CH), 29.5 (CH_2), 10.8 (CH_3), 8.7 (CH_3). IR (film): 1770, 1681, 1487, 1265, 1156, 1124, 736 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{15}N_2O_3$ $[M+H]^+$: 235.1038 Found: 235.1076.

Cascade Synthesis of Triazinones

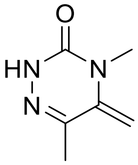
General Procedure M: An oven dried microwave tube was charged with the keto-carbazaone (1.0 equiv), $MgSO_4$ (1.0 equiv), primary amines (1.1 equiv) and α,α,α-trifluorotoluene (0.3 M). The tube was sealed with a microwave cap and heated for six hours 175 °C. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.



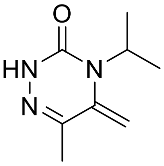
4-Benzyl-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.31): Synthesized according to general procedure **M** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), benzylamine (0.0710 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol).The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a white solid (0.0970 g, 75%). TLC $R_f = 0.29$ in 10% EtOAc/CH_2Cl_2. ^1H NMR (300 MHz, $CDCl_3$): δ 8.87 (br s, 1H), 7.37-7.24 (m, 5H), 4.94 (s, 2H), 4.32 (d, J = 2.8 Hz, 1H), 4.24 (d, J = 2.8 Hz, 1H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4 (C), 143.4 (C), 136.6 (C), 135.2 (C), 128.7 (CH), 127.4 (CH), 126.7 (CH), 90.6 (CH_2), 45.9 (CH_2), 19.0 (CH_3). IR (film): 1699, 1558, 1506, 1266, 736 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O$ $[M]^+$: 215.1059. Found: 215.1066.



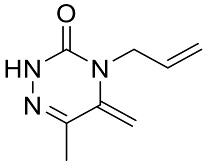
4-Hexyl-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.33): Synthesized according to general procedure **M** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), hexylamine (0.0670 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a beige solid (0.0920 g, 73%). TLC R_f = 0.31 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.70 (br s, 1H), 4.39-4.24 (m, 1H), 4.31-4.26 (m, 1H), 3.74-3.64 (m, 2H), 2.07 (s, 3H), 1.64-1.55 (m, 2H), 1.39-1.26 (m, 6H), 0.91-0.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.8 (C), 143.0 (C), 136.7 (C), 88.4 (CH_2), 42.1 (CH_2), 31.5 (CH_2), 26.5 (CH_2), 24.7 (CH_2), 22.5 (CH_2), 19.1 (CH_3), 14.0 (CH_3). IR (film): 1652, 1506, 1266, 732, 688 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{19}N_3O$ $[M]^+$: 209.1528. Found: 209.1524.



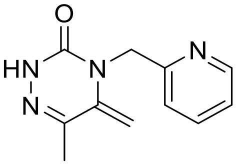
4,6-Dimethyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.34): Synthesized according to general procedure **M** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), 2.0 M methylamine in THF (0.033 mL, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a brown solid (0.0400 g, 48%). TLC R_f = 0.18 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.15 (br s, 1H), 4.35 (d, *J* = 2.3 Hz, 1H), 4.22 (d, *J* = 2.2 Hz, 1H), 3.11 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0 (C), 142.7 (C), 138.0 (C), 88.4 (CH_2), 28.8 (CH_3), 18.9 (CH_3). IR (film): 1652, 1265, 743, 705 cm^{-1}. HRMS (EI): Exact mass calcd for $C_6H_9N_3O$ $[M]^+$: 139.0746. Found: 139.0763.



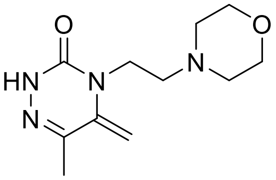
4-Isopropyl-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.35): Synthesized according to general procedure **M** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), isopropylamine (0.0390 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol) at 200 °C. The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a light brown solid (0.0440 g, 44%). TLC R_f = 0.19 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.81 (br s, 1H), 4.51-4.41 (m, 3H), 2.05 (s, 3H), 1.46 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3 (C), 143.6 (C), 136.8 (C), 90.3 (CH_2), 47.5 (CH), 19.1 (CH_3), 18.5 (CH_3). IR (film): 1683, 1265, 738, 706 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_{13}N_3O$ $[M]^+$: 167.1059. Found: 167.1015.



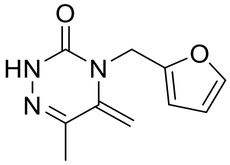
4-Allyl-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.37): Synthesized according to general procedure **M** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), allyl amine (0.0380 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a white solid (0.0700 g, 71%). TLC R_f = 0.26 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.98 (br s, 1H), 5.83-5.70 (m, 1H), 5.27-5.19 (s, 2H), 4.38-4.29 (m, 4H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9 (C), 143.1 (C), 136.7 (C), 130.4 (CH), 117.3 (CH_2), 89.7 (CH_2), 44.5 (CH_2), 19.0 (CH_3). IR (film): 1683, 1583, 1266, 732, 688 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{11}N_3O$ $[M]^+$: 165.0902. Found: 165.0908.



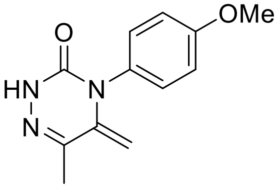
6-Methyl-5-methylene-4-(pyridin-2-ylmethyl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.38): Synthesized according to general procedure **M** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), 2-picolylamine (0.0710 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (40% EtOAc/CH_2Cl_2) to yield a beige solid (0.0860 g, 66%). TLC R_f = 0.14 in 40% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.03 (br s, 1H), 8.58-8.55 (m, 1H), 7.65 (td, *J* = 7.7, 1.7 Hz, 1H), 7.28-7.25 (m, 1H), 7.21-7.17 (m, 1H), 5.06 (s, 2H), 4.33 (q, *J* = 3.0 Hz, 2H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7 (C), 149.3 (CH), 149.3 (C), 143.4 (C), 136.9 (CH), 136.7 (C), 122.4 (CH), 121.0 (CH), 91.0 (CH_2), 48.0 (CH_2), 19.0 (CH_3). IR (film): 1683, 1265, 730, 700 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{12}N_4O$ $[M]^+$: 216.1011. Found: 216.0996.



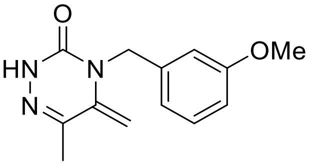
6-Methyl-5-methylene-4-(2-morpholinoethyl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.39): Synthesized according to general procedure **M** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), 4-(2-aminoethyl)morpholine (0.0860 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol) at 175 °C. The title compound was purified by column chromatography (10% MeOH/CH_2Cl_2) to yield a light brown solid (0.113 g, 79%). TLC R_f = 0.37 in 10% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.04 (br s, 1H), 4.36 (s, 2H), 3.88-3.83 (m, 2H) 3.72-3.69 (m, 4H), 2.59-2.52 (m, 6H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3 (C), 143.6 (C), 137.6 (C), 90.4 (CH_2), 57.1 (CH), 28.2 (CH_2), 26.3 (CH_2), 25.3 (CH_2), 19.2 (CH_3). IR (film): 1695, 1563, 1266, 730 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{17}N_3O$ $[M]^+$: 207.1372. Found: 207.1392.



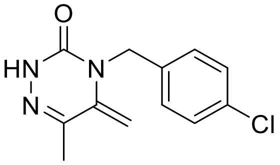
4-(Furan-2-ylmethyl)-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.40): Synthesized according to general procedure **M** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), 4-furfurylamine (0.0640 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a beige solid (0.0950 g, 77%). TLC R_f = 0.31 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.04 (br s, 1H), 7.35 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.34-6.30 (m, 2H), 4.89 (s, 2H), 4.54 (d, *J* = 2.8 Hz, 1H), 4.40 (d, *J* = 3.0 Hz, 1H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1 (C), 148.9 (C), 143.3 (C), 142.0 (CH), 136.6 (C), 110.4 (CH), 108.6 (CH), 89.9 (CH_2), 38.9 (CH_2), 19.0 (CH_3). IR (film): 1687, 1506, 1266, 730 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{11}N_3O_2$ [M]$^+$: 205.0851. Found: 205.0884.



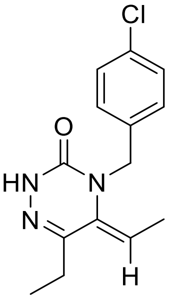
4-(4-Methoxyphenyl)-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.41): Synthesized according to general procedure **M** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), 4-methoxyaniline (0.0810 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (25% EtOAc/CH_2Cl_2) to yield a brown solid (0.0730 g, 53%). TLC R_f = 0.27 in 25% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (br s, 1H), 7.19-7.13 (m, 3H), 7.05-7.00 (m, 2H), 4.31 (d, *J* = 2.2 Hz, 1H), 3.87 (d, *J* = 2.2 Hz, 1H), 3.85 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6 (C), 148.5 (C), 143.3 (C), 139.8 (C), 129.5 (CH), 128.6 (C), 115.4 (CH), 91.5 (CH_2), 55.4 (CH_3), 19.0 (CH_3). IR (film): 1695, 1513, 1265, 750, 717 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O_2$ [M]$^+$: 231.1008. Found: 231.0997.



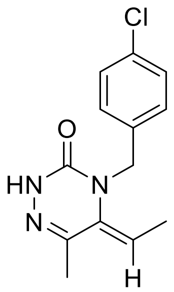
4-(3-Methoxybenzyl)-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.42): Synthesized according to general procedure **M** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), 3-methoxybenzylamine (0.0910 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a white solid (0.0820 g, 56%). TLC R_f = 0.24 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.90 (br s, 1H), 7.28-7.22 (m, 1H), 6.87-6.78 (m, 3H), 4.91 (s, 2H), 4.33 (d, *J* = 2.8 Hz, 1H), 4.24 (d, *J* = 2.7 Hz, 1H), 3.80 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9 (C), 149.3 (C), 143.3 (C), 136.9 (C), 136.6 (C), 129.7 (CH), 118.9 (CH), 112.5 (CH), 112.5 (CH), 90.6 (CH_2), 55.2 (CH_3), 45.8 (CH_2), 19.0 (CH_3). IR (film): 1683, 1506, 1271, 781 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{15}N_3O_2$ [M]$^+$: 245.1164. Found: 245.1136.



4-(4-Chlorobenzyl)-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.43): Synthesized according to general procedure **M** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), 4-chlorobenzylamine (0.0930 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a beige solid (0.120 g, 80%). TLC R_f = 0.30 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.16 (br s, 1H), 7.33-7.28 (m, 2H), 7.23-7.18 (m, 2H), 4.90 (s, 2H), 4.33 (d, *J* = 2.8 Hz, 1H), 4.18 (d, *J* = 2.7 Hz, 1H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4 (C), 143.3 (C), 136.7 (C), 133.2 (C), 128.9 (CH), 128.2 (CH), 90.5 (CH_2), 55.2, 45.3 (CH_2), 19.0 (CH_3). IR (film): 1652, 1510, 1259, 771 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{12}N_3OCl$ [M]$^+$: 249.0669. Found: 249.0677.

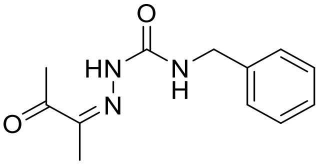


(*Z*)-4-Benzyl-6-ethyl-5-ethylidene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.44): Synthesized according to general procedure **M** using the corresponding keto-carbazone (0.149 g, 0.600 mmol), 4-chlorobenzylamine (0.0930 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol) at 200 °C. The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a white solid as a 2:1 mixture favoring the *Z* isomer (0.113 g, 68%). TLC R_f = 0.30 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (br s, 0.30H), 8.03 (br s, 0.60H) 7.31-7.26 (m, 2H), 7.17-7.10 (m, 2H), 5.18 (q, *J* = 7.5 Hz, 0.70H), 4.93-4.85 (m, 2.30H), 2.61 (q, *J* = 7.4 Hz, 0.6H), 2.39 (q, *J* = 7.4 Hz, 1.40H) 1.79 (d, *J* = 7.8 Hz, 1H), 1.75 (d, *J* = 7.6 Hz, 2H) 1.11 (t, *J* = 7,4 Hz, 1H), 1.02 (t, *J* = 7.4 Hz, 2H) . ^{13}C NMR (75 MHz, $CDCl_3$): * denotes minor isomer δ 152.9 (C), 149.9 (C), 135.8 (C), 133.1 (C), 131.3 (C), 128.8* (CH), 128.7 (CH), 128.1 (CH), 127.9* (CH), 109.1 (CH), 107.3* (CH), 48.3 (CH_2), 46.5* (CH_2), 28.3* (CH_2), 25.0 (CH_2), 13.6 (CH_3), 13.2* (CH_3), 11.3* (CH_3), 10.9 (CH_3). IR (film): 1695, 1265, 734, 705 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{16}N_3OCl$ [M]$^+$: 277.0982. Found: 277.0988.

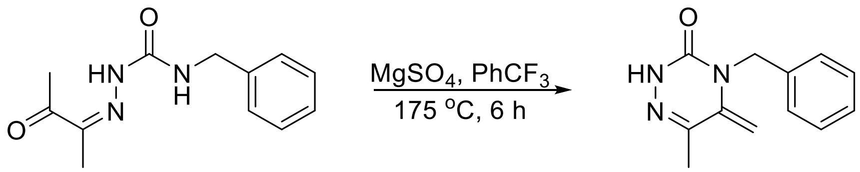


(*Z*)-4-Benzyl-5-ethylidene-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (4.45): Synthesized according to general procedure **M** using the corresponding keto-carbazone (0.141 g, 0.600 mmol), 4-chlorobenzylamine (0.0930 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol) at 200 °C. The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a white solid as a 2:1 mixture favoring the *Z* isomer (0.0750 g, 47%). TLC R_f = 0.18 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 10.59 (br s, 0.30H), 10.44 (br s, 0.60H) 7.41-7.35 (m, 2H), 7.27-7.15 (m, 2H), 5.05 (q, *J* = 7.5 Hz, 0.70H), 4.88-4.72 (m, 2.30H), 2.19 (s, 1.10H), 1.96 (s, 1.90H) 1.76 (d, *J* = 7.6 Hz, 1.10H), 1.62 (d, *J* = 7.6 Hz, 1.90H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): * denotes minor isomer δ 151.3 (C), 149.8 (C), 144.1* (C), 137.4 (C), 132.1 (C), 131.4* (CH), 131.3 (C), 130.6* (C), 128.5* (CH), 128.4 (CH), 128.2* (CH), 127.8 (CH), 105.7 (CH), 104.1* (CH), 47.3 (CH_2), 44.7* (CH_2), 22.7* (CH_3), 18.7 (CH_3), 13.0 (CH_3), 12.9* (CH_3). IR (film): 1651, 1558, 1263, 730, 703 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{14}N_3OCl$ $[M]^+$: 263.0825. Found: 263.0821.

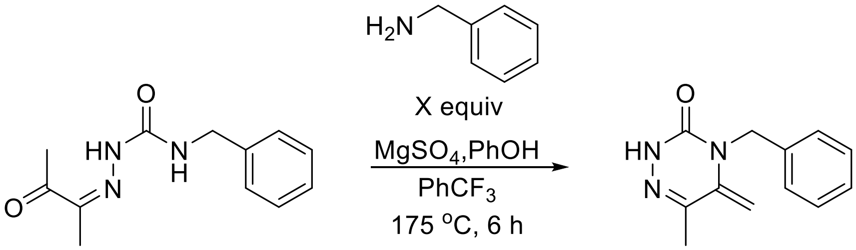
Scheme 4.9: Cyclization using Semi-Carbazone:



(*E*)-*N*-Benzyl-2-(3-oxobutan-2-ylidene)hydrazinecarboxamide (4.47): To a solution of keto-carbazone **1a** (0.220 g, 1.00 mmol) and benzylamine (0.118 g, 1.10 mmol) in THF (3.3 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0300 g, 0.200 mmol) and the solution was stirred at room temperature for 16 h. The solution was concentrated and purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a white solid (0.200 g, 86%). TLC R_f = 0.25 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 10.05 (br s, 1H), 7.70 (t, *J* = 6.2 Hz, 1H), 7.36-7.28 (m, 4H), 7.26-7.20 (m, 1H), 4.39 (d, *J* = 6.2 Hz, 2H), 2.39 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2 (C), 155.2 (C), 144.3 (C), 140.3 (C), 128.2 (CH), 126.9 (CH), 126.6 (CH), 42.7 (CH_2), 24.4 (CH_3), 9.4 (CH_3). IR (film): 1695, 1652, 1263, 732, 705 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{15}N_3O_2$ – (C_2H_3O) $[M]^+$: 190.0936. Found: 190.0979.



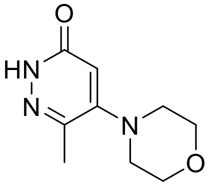
Performed according to general procedure **M** using keto semi-carbazone **4.47** (0.140 g, 0.600 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The solution was concentrated under reduced pressure. 1,3,5-trimethoxybenzene was added and ^{1}H NMR was used to determine a 85% NMR yield.



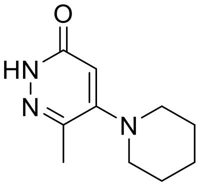
Performed according to general procedure **A** using keto semi-carbazone **4a** (0.140 g, 0.600 mmol), benzylamine (0.1 and 0.5 equiv), phenol (0.0540 g, 0.600 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The solution was concentrated under reduced pressure. 1,3,5-trimethoxybenzene was added and ^{1}H NMR was used to determine a 80% (with 0.1 equiv) and 43% (0.5 equiv) NMR yield.

Pyridazinone Scope

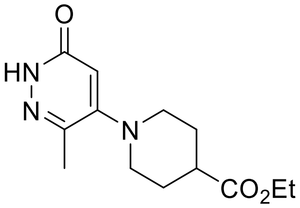
General Procedure N: An oven dried microwave tube was charged with the keto-carbazaone (1.0 equiv), $MgSO_4$ (1.0 equiv), pivalic acid (0.2 equiv), secondary amine (3.0 equiv) and α, α, α -trifluorotoluene (0.3 M). The tube was sealed with a microwave cap and heated for two hours 175 °C. The tube was cooled to ambient temperature, filtered, concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.



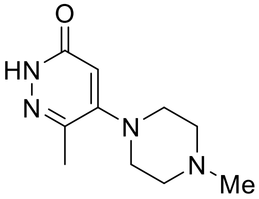
6-Methyl-5-morpholinopyridazin-3(2*H*)-one (4.32): Synthesized according to general procedure **N** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), morpholine (0.156 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.012o g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a light brown solid (0.0834 g, 71%). TLC $R_f = 0.28$ in 5% MeOH/EtOAc. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 12.40 (br s, 1H), 6.03 (s, 1H), 3.72-3.69 (m, 4H), 2.96-2.93 (m, 4H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 161.8 (C), 154.7 (C), 141.1 (C), 110.7 (CH), 65.8 (CH_2), 50.0 (CH_2), 18.7 (CH_3). IR (film): 1708, 1363, 1220, 910, 727 cm^{-1}. HRMS (EI): Exact mass calcd for $C_9H_{13}N_3O_2$ $[M]^+$: 195.1008. Found: 195.1034.



6-Methyl-5-(piperidin-1-yl)pyridazin-3(2*H*)-one (4.47): Synthesized according to general procedure **M** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), piperidine (0.1530 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a brown solid (0.107 g, 93%). TLC R_f = 0.34 in 5% MeOH/EtOAc. ^1H NMR (300 MHz, DMSO-d_6): δ 12.30 (br s, 1H), 5.96 (s, 1H), 2.90-2.87 (m, 4H), 2.20 (s, 3H) 1.65-1.50 (m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.9 (C), 155.7 (C), 141.4 (C), 110.1 (CH), 50.8 (CH_2), 25.3 (CH_2), 23.4 (CH_2) 18.4 (CH_3). IR (film): 1662, 1633, 904, 723 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{15}N_3O$ $[M]^+$: 193.1215. Found: 193.1211.

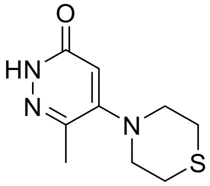


Ethyl-1-(3-methyl-6-oxo-1,6-dihydropyridazin-4-yl)piperidine-4-carboxylate (4.48): Synthesized according to general procedure **N** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), ethyl-4-piperidinecarboxylate (0.283 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a brown solid (0.0912 g, 57%). TLC R_f = 0.18 in 100% EtOAc. ^1H NMR (400 MHz, $CDCl_3$): δ 12.25 (s, 1H), 6.13 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.25 (d, *J* = 12.7 Hz, 2H), 2.68-2.61 (m, 2H), 2.42 (ddd, *J* = 14.2, 6.7, 3.3 Hz, 1H), 2.23 (s, 3H), 1.98 (dd, *J* = 13.5, 3.2 Hz, 2H), 1.81 (qd, *J* = 12.3, 3.4 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 4H). ^{13}C NMR (100 MHz, CDCl3): δ 174.3 (C), 163.8 (C), 156.1 (C), 142.9 (C), 111.1 (CH), 60.7 (CH_2), 49.8 (CH_2), 40.4 (CH), 27.9 (CH_2), 18.8 (CH_3), 14.2 (CH_3). IR (film): 2960, 1724, 1633, 1429, 1377, 1265, 1172, 1042, 730 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{19}N_3O_3$ $[M]^+$: 265.1426. Found: 265.1456

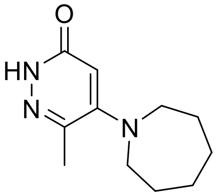


6-Methyl-5-(4-methylpiperazin-1-yl)pyridazin-3(2*H*)-one (4.49): Synthesized according to general procedure **N** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), *N*-methylpiperazine (0.0930 g, 1.80 mmol), pivalic acid (0.0120 g, 0.120 mmol) for 4 h without the addition of $MgSO_4$. The title compound was purified by column chromatography (50% MeOH/EtOAc) to yield a light brown solid (0.100 g, 80%). TLC R_f = 0.13 in 50% MeOH/EtOAc. ^1H NMR (400 MHz, $CDCl_3$): δ 12.33 (s, 1H), 6.13 (s, 1H), 2.98 (t, *J* = 4.7 Hz, 4H), 2.51 (t, *J* = 4.3 Hz, 4H), 2.29 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$):

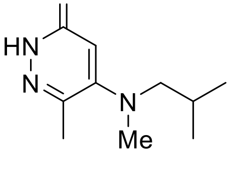
δ 163.7 (C), 155.6 (C), 142.5 (C), 111.0 (CH), 54.5 (CH_2), 49.9 (CH_2), 45.9 (CH_3), 19.1 (CH_3). IR (film): 2945, 1635, 1431, 1367, 1232, 1126, 852 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{16}N_4O$ $[M]^+$: 208.1324. Found: 208.1343.



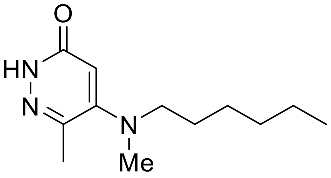
6-Methyl-5-thiomorpholinopyridazin-3(2*H*)-one (4.50): Synthesized according to general procedure **N** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), thiomorpholine (0.186 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a brown solid (0.0912 g, 57%). TLC R_f = 0.13 in 100% EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.89 (s, 1H), 6.18 (s, 1H), 3.24-3.20 (m, 4H), 2.77-2.74 (m, 4H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (C), 156.5 (C), 142.9 (C), 112.2 (CH), 52.5 (CH_2), 27.5 (CH_2), 18.7 (CH_3). IR (film): 1647, 1266, 730, 706 cm^{-1}. HRMS (EI): Exact mass calcd for $C_9H_{13}N_3OS$ $[M]^+$: 211.0779. Found: 211.0758.



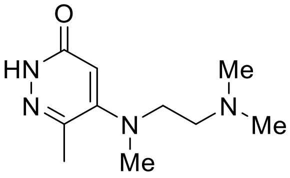
5-(Azepan-1-yl)-6-methylpyridazin-3(2*H*)-one (4.51): Synthesized according to general procedure **N** keto-carbazone **4.30** (0.132 g, 0.600 mmol), azepane (0.178 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol) at 200 °C. The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a yellow solid (0.0824 g, 47%). TLC R_f = 0.16 in 100% EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96 (s, 1H), 3.28 (t, *J* = 5.8 Hz, 4H), 2.33 (s, 3H), 1.74 (t, *J* = 1.6 Hz, 4H), 1.58 (dt, *J* = 6.0, 2.9 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7 (C), 154.8 (C), 140.2 (C), 105.2 (CH), 52.0 (CH_2), 28.2 (CH_2), 27.0 (CH_2), 22.3 (CH_3). IR (film): 2904, 1633, 1577, 1365, 1259, 1159, 727 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{17}N_3O$ $[M]^+$: 207.1371. Found: 207.1369.



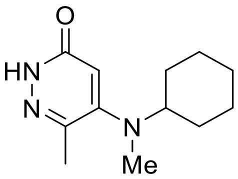
5-(Isobutyl(methyl)amino)-6-methylpyridazin-3(2*H*)-one (4.52): Synthesized according to general procedure **N** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), *N*-methylisobutylamine (0.157 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a brown solid (0.0750 g, 64%). TLC R_f = 0.12 in EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.79 (br s, 1H), 6.05 (s, 1H), 2.95-2.90 (m, 2H), 2.82 (s, 3H) 2.33 (s, 3H), 1.95 (dt, *J* = 13.5, 6.8 Hz, 1H), 0.87 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (C), 155.5 (C), 141.6 (C), 108.2 (CH), 61.1 (CH_2), 40.5 (CH_3), 31.5 (CH_2), 26.6 (CH), 20.9 (CH_3), 20.2 (CH_3). IR (film): 1635, 1265, 736, 699 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{17}N_3O$ $[M]^+$: 195.1372. Found: 195.1351.



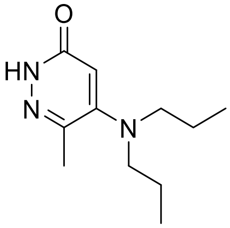
5-(Hexyl(methyl)amino)-6-methylpyridazin-3(2*H*)-one (4.53): Synthesized according to general procedure **N** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), *N*-methylhexylamine (0.208 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a light brown solid (0.100 g, 75%). TLC R_f = 0.15 in EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.59 (br s, 1H), 6.04 (s, 1H), 3.09-3.04 (m, 2H), 2.79 (s, 3H) 2.33 (s, 3H), 1.68-1.58 (m, 2H), 1.34-1.23 (m, 6H), 0.90-0.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4 (C), 155.5 (C), 141.6 (C), 108.0 (CH), 53.9 (CH_2), 39.3 (CH_3), 31.5 (CH_2), 27.1 (CH_2), 26.5 (CH_2), 22.5 (CH_2), 20.6 (CH_3), 13.9 (CH_3). IR (film): 1635, 1506, 1265, 734 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{21}N_3O$ $[M]^+$: 223.1685. Found: 223.1701.



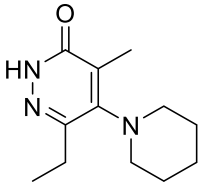
5-((2-(Dimethylamino)ethyl)(methyl)amino)-6-methylpyridazin-3(2*H*)-one (4.54): Synthesized according to general procedure **N** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), *N,N,N'*-trimethylethylenediamine (0.184 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 100% MeOH) to yield a light brown solid (0.0900 g, 71%). TLC R_f = 0.15 in MeOH. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.97 (br s, 1H), 6.08 (s, 1H), 3.24-3.20 (m, 2H), 2.82 (s, 3H) 2.51-2.46 (m, 2H), 2.33 (s, 3H), 2.23 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (C), 155.3 (C), 141.4 (C), 108.4 (CH), 58.6 (CH_2), 51.9 (CH_2), 45.7 (CH_3), 39.7 (CH_3), 20.5 (CH_3). IR (film): 1683, 1561, 1265, 742 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{18}N_4O$ ($-C_3H_8N$) $[M]^+$: 152.0824. Found: 152.0792.



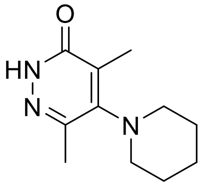
5-(Cyclohexyl(methyl)amino)-6-methylpyridazin-3(2*H*)-one (4.55): Synthesized according to general procedure **N** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), *N*-methylcyclohexylamine (0.202 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield an off white/brown solid (0.049 g, 37%). TLC R_f = 0.15 in 100% EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.69 (d, *J* = 0.2 Hz, 1H), 6.05 (s, 1H), 3.15 (tt, *J* = 11.5, 3.5 Hz, 1H), 2.64 (s, 3H), 2.30 (s, 3H), 1.84 (s, 2H), 1.73-1.63 (m, 3H), 1.50 (dd, *J* = 36.4, 3.1 Hz, 2H), 1.33-1.18 (m, 2H), 1.10 (tt, *J* = 12.5, 3.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (C), 155.7 (C), 142.2 (C), 108.9 (CH), 60.6 (CH), 32.5 (CH_3), 29.5 (CH_2), 25.9 (CH_2), 25.6 (CH_2), 20.2 (CH_3). IR (film): 2898, 1726, 1639, 1438, 727 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{19}N_3O$ $[M]^+$: 221.1528. Found: 221.1524.



5-(Dipropylamino)-6-methylpyridazin-3(2*H*)-one (4.56): Synthesized according to general procedure **N** using keto-carbazone **4.30** (0.132 g, 0.600 mmol), dipropylamine (0.182 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a brown solid (0.0630 g, 47%). TLC R_f = 0.14 in 60% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (s, 1H), 3.04-3.01 (m, 4H), 2.28 (s, 3H), 1.52 (sextet, *J* = 7.5 Hz, 4H), 0.84 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5 (C), 154.2 (C), 142.5 (C), 109.6 (CH), 53.1 (CH_2), 20.4 (CH_3), 20.1 (CH_2), 11.4 (CH_3). IR (film): 1647, 1108, 904, 717 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{19}N_3O$ $[M]^+$: 209.1528. Found: 209.1525.

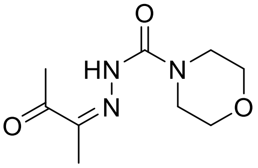


6-Ethyl-4-methyl-5-(piperidin-1-yl)pyridazin-3(2*H*)-one (4.57): Synthesized according to general procedure **N** using the corresponding keto-carbazone (0.148 g, 0.600 mmol), piperidine (0.153 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a yellow solid (0.0630 g, 47%). TLC R_f = 0.46 in 100% EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.27 (br s, 1H), 3.01 (m, 4H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.11 (s, 3H), 1.58 (m, 6H), 1.16 (q, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9 (C), 151.7 (C), 151.0 (C), 130.7 (C), 51.3 (CH_2), 26.6 (CH_2), 25.4 (CH_2), 24.2 (CH_2), 12.30 (CH_3), 12.27 (CH_3). IR (film): 2956, 1635, 1442, 1266, 725 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{19}N_3O$ $[M]^+$: 221.1528. Found: 221.1526.

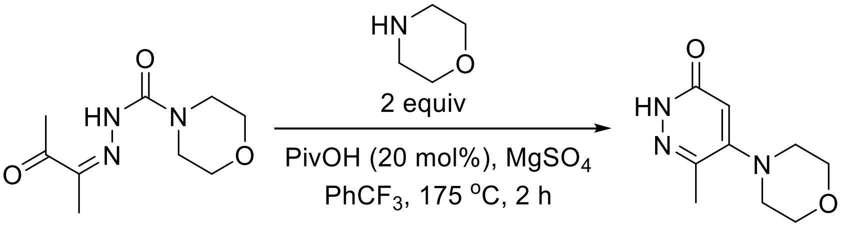


4,6-Dimethyl-5-(piperidin-1-yl)pyridazin-3(2*H*)-one (4.58): Synthesized according to general procedure **N** using keto-carbazone **4.30** (0.149 g, 0.600 mmol), piperidine (0.153 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield an off-white solid (0.0815 g, 66%). TLC R_f = 0.27 in 100% EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.46 (s, 1H), 3.00 (d, *J* = 5.3 Hz, 4H), 2.22 (s, 3H), 2.09 (s, 3H), 1.57 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1 (C), 152.0 (C), 146.6 (C), 129.3 (C), 51.2 (CH_2), 26.6 (CH_2), 24.2 (CH_2), 19.6 (CH_3), 12.2 (CH_3). IR (film): 1637, 1266, 730, 706 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{17}N_3O$ [M]$^+$: 207.1372. Found: 207.1379.

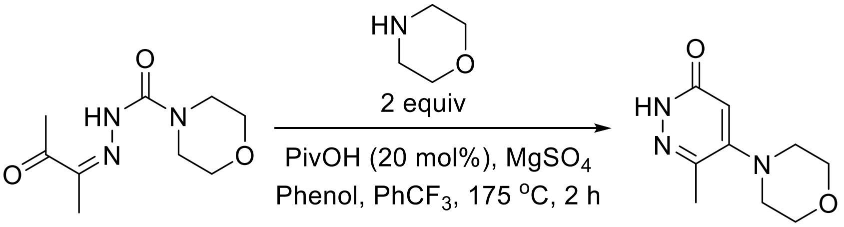
Equation 4.2 and 4.3: Enamine Cyclization on Semi-Carbazone



(*E*)-*N*'-(3-Oxobutan-2-ylidene)morpholine-4-carbohydrazide: To a solution of keto-carbazone **4.30** (0.220 g, 1.00 mmol) and morpholine (0.0960 g, 1.10 mmol) in THF (3.0 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0300 g, 0.200 mmol) and the solution was stirred at room temperature for 16 h. The solution was concentrated and purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield a white solid (0.169 g, 79%). TLC R_f = 0.13 in 50% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H), 3.70-3.59 (m, 8H), 2.29 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0 (C), 156.1 (C), 145.8 (C), 66.6 (CH_2), 46.1 (CH_2), 24.3 (CH_3), 8.4 (CH_3). IR (film): 1654, 1265, 1114, 981, 727, 698 cm^{-1}. HRMS (EI): Exact mass calcd for $C_9H_{16}N_3O_3$ [M+H]$^+$: 214.1147 Found: 214.1174.



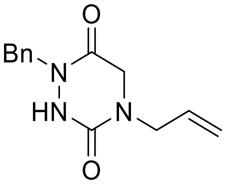
Performed according to general procedure **B** using keto semi-carbazone **4b** (0.128 g, 0.600 mmol), morpholine (0.103 g, 1.20 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The solution was concentrated under reduced pressure. 1,3,5-Trimethoxybenzene was added and ^{1}H NMR was used to determine a 47 % NMR yield



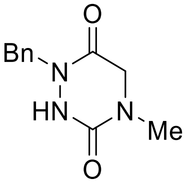
Performed according to general procedure **N** using the coresponding keto semi-carbazone (0.128 g, 0.600 mmol), morpholine (0.103 g, 1.20 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol) and phenol (0.0570 g, 0.600 mmol). The solution was concentrated under reduced pressure. 1,3,5-Trimethoxybenzene was added and ^{1}H NMR was used to determine a 72 % NMR yield

6.3.3: One-Pot Aza-DKP Sequence (section 4.3)

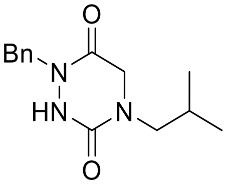
General procedure O: To an oven-dried 10 mL glass vial were added benzyl carbazate **3.1** (1.0 equiv, 0.0968 g, 0.0400 mmol,) and MeCN (1.4 mL, 0.60 M). The solution was allowed to stir in an ice bath until reaching 0 °C. To this solution was added pyridine (1.1 equiv, 0.0348 g, 0.0420 mmol), then chloroacetyl chloride (1.05 equiv, 0.0474 g, 0.0440 mmol). 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, 0.0800 mmol), and triethylamine (2.5 equiv, 0.102 g, 1.00 mmol) 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.



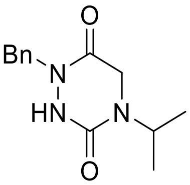
4-Allyl-1-benzyl-1,2,4-triazinane-3,6-dione (4.59): Synthesized according to general procedure **O** using allylamine (0.0460 g, 0.800 mmol). The title compound was purified by column chromatography (30% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0736 g, 75%). TLC R_f = 0.40 in 30% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (s, 1H), 7.39-7.26 (m, 5H), 5.73 (ddt, *J* = 16.8, 10.5, 6.1 Hz, 1H), 5.31-5.14 (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.



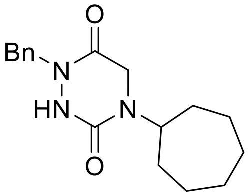
1-Benzyl-4-methyl-1,2,4-triazinane-3,6-dione (4.61): Synthesized according to general procedure **O** using methylamine (2.0 M in THF solution, 0.400 mL, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield a white crystalline solid (0.0361 g, 41%). TLC 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.



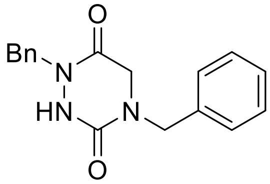
1-Benzyl-4-isobutyl-1,2,4-triazinane-3,6-dione (4.62): Synthesized according to general procedure **O** using isobutylamine (0.0585 g, 0.800 mmol). The title compound was purified by column chromatography (30% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0634 g, 60%). TLC R_f = 0.52 in 50% EtOAc/CH_2Cl_2. ^{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.



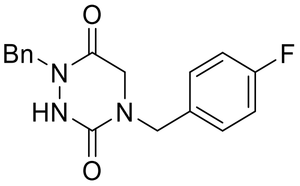
1-Benzyl-4-isopropyl-1,2,4-triazinane-3,6-dione (4.63): Synthesized according to general procedure **O** using isopropylamine (0.0473 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0346 g, 35%). TLC R_f = 0.48 in 50% 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.



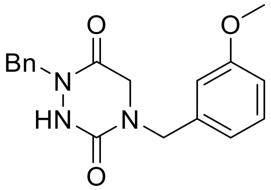
1-Benzyl-4-cycloheptyl-1,2,4-triazinane-3,6-dione (4.64): Synthesized according to general procedure **O** using cycloheptylamine (0.0906 g, 0.800 mmol). The title compound was purified by column chromatography (30% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0253 g, 21%). TLC R_f = 0.62 in 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.



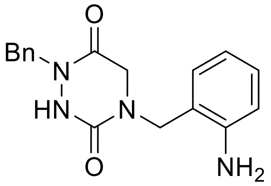
1,4-Dibenzyl-1,2,4-triazinane-3,6-dione (4.65): Synthesized according to general procedure **O** using benzylamine (0.0857 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0850 g, 72%). TLC R_f = 0.25 in 50% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (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.



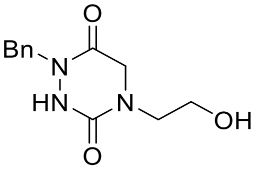
1-Benzyl-4-(4-fluorobenzyl)-1,2,4-triazinane-3,6-dione (4.66): Synthesized according to general procedure **O** using 4-fluorobenzylamine (0.100 g, 0.800 mmol). The title compound was purified by column chromatography (100% CH_2Cl_2 then 50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0526 g, 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.



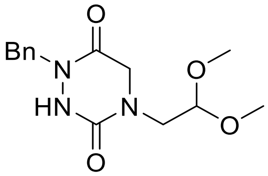
1-Benzyl-4-(3-methoxybenzyl)-1,2,4-triazinane-3,6-dione (4.67): Synthesized according to general procedure **O** using 3-methoxybenzylamine (0.102 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 then 2% MeOH/CH_2Cl_2) to yield an amorphous white solid (0.0482 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), 7.35-7.26 (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



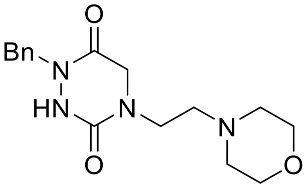
4-(2-Aminobenzyl)-1-benzyl-1,2,4-triazinane-3,6-dione (4.68): Synthesized according to general procedure **O** using 2-aminobenzylamine (0.0977 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 then 2% MeOH/CH_2Cl_2) to yield an amorphous white solid with minor impurities (presumably phenol). TLC R_f = 0.32 in 50% EtOAc/CH_2Cl_2. 50% yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.



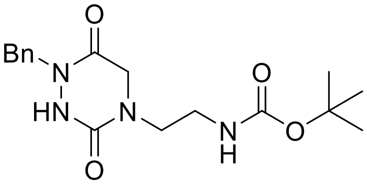
1-Benzyl-4-(2-hydroxyethyl)-1,2,4-triazinane-3,6-dione (4.69): Synthesized according to general procedure **O** using ethanolamine (0.0489 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2 then 10% MeOH/CH_2Cl_2) to yield an amorphous white solid (0.0430 g, 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.



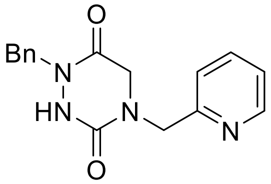
1-Benzyl-4-(2,2-dimethoxyethyl)-1,2,4-triazinane-3,6-dione (4.70): Synthesized according to general procedure **O** using aminoacetaldehyde dimethyl acetal (0.0841 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0730 g, 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.



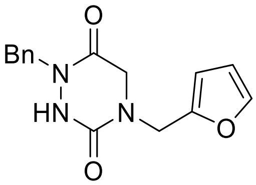
1-Benzyl-4-(2-morpholinoethyl)-1,2,4-triazinane-3,6-dione (4.71): Synthesized according to general procedure **O** using 4-(2-aminoethyl)morpholine (0.104 g, 0.800 mmol). The title compound was purified by column chromatography (100% EtOAc/CH_2Cl_2 then 2% CH_3OH/CH_2Cl_2) to yield an amorphous white 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.



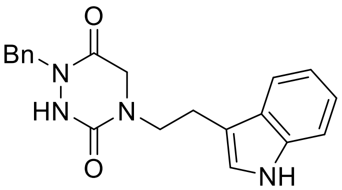
***tert*-Butyl (2-(1-benzyl-3,6-dioxo-1,2,4-triazinan-4-yl)ethyl)carbamate (4.72):** Synthesized according to general procedure **O** using *N*-Boc-ethylenediamine (0.128 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield an amorphous white solid (0.0850 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.



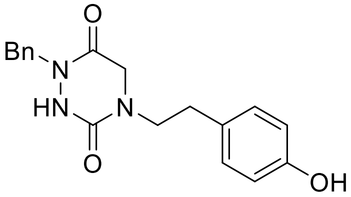
Benzyl-4-(pyridin-2-ylmethyl)-1,2,4-triazinane-3,6-dione (4.73): Synthesized according to general procedure **O** using 2-picolylamine (0.0865 g, 0.800 mmol). The title compound was purified by column chromatography (100% EtOAc then 5% CH_3OH/CH_2Cl_2) to yield an amorphous white solid (0.0870 g, 73%). 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 (4.74): Synthesized according to general procedure **O** 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.



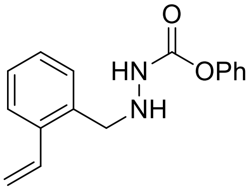
4-(2-(1H-Indol-3-yl)ethyl)-1-benzyl-1,2,4-triazinane-3,6-dione (4.75): Synthesized according to general procedure **O** using tryptamine (0.128 g, 0.800 mmol). The title compound was purified by column chromatography (50% $EtOAc/CH_2Cl_2$ then 2% CH_3OH/CH_2Cl_2) to yield an amorphous white solid (0.0795 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.



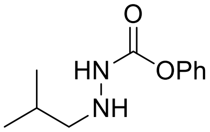
1-Benzyl-4-(4-hydroxyphenethyl)-1,2,4-triazinane-3,6-dione (4.76): Synthesized according to general procedure **O** using tyramine (0.109 g, 0.800 mmol). The title compound precipitated out of solution in 100% CH_2Cl_2 as a white solid to give pure product after aqueous extraction (0.0547 g, 42%). TLC R_f = 0.33 in 5% CH_3OH/CH_2Cl_2. ^1H 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.

Carbazate Synthesis (S.M. for Table 4.10)

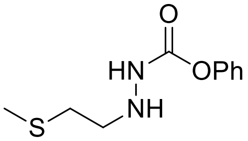
General Procedure P (Preparation of substrates): *Carbazate Condensation*: To a solution of the corresponding aldehyde or ketone in MeOH (0.3 M) was added *O*-phenyl carbazate (1.00 equiv). The reaction was carried out at room temperature (aldehyde) or refluxed in MeOH (ketone) until consumption of the 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.



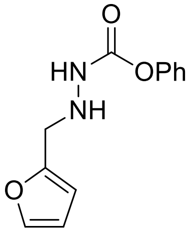
Phenyl 2-(2-vinylbenzyl)hydrazinecarboxylate: Synthesized according to general procedure **P** by stirring *O*-phenyl carbazate (1.33 g, 8.80 mmol) and 2-vinylbenzaldehyde (1.22 g, 9.23 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (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. ^1H NMR (300 MHz, $CDCl_3$): δ 7.62-7.55 (m, 1H), 7.45-7.13 (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-isobutylhydrazinecarboxylate: Synthesized according to general procedure **P** 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 7.42-7.32 (m, 2H), 7.25-7.18 (m, 1H), 7.18-7.11 (m, 2H), 2.77 (d, *J* = 6.9 Hz, 2H), 1.89-1.71 (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.

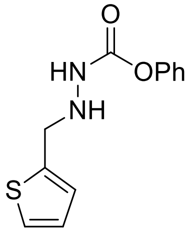


Phenyl 2-(3-(methylthio)propyl)hydrazine-1-carboxylate: Synthesized according to general procedure **P** by stirring *O*-phenyl carbazate (2.68 g, 17.6 mmol) and 3 (methylthio)propanal (1.83 g, 17.6 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 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 7.43-7.33 (m, 2H), 7.26-7.19 (m, 1H), 7.19-7.12 (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* = 7.0 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.

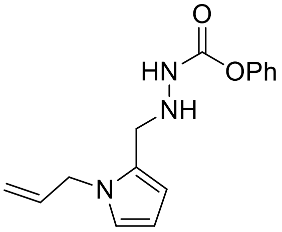


Phenyl 2-(furan-2-ylmethyl)hydrazine-1-carboxylate: Synthesized according to general procedure **P** by stirring *O*-phenyl carbazate (2.60 g, 17.1 mmol) and furfural (1.64 g, 17.1 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$

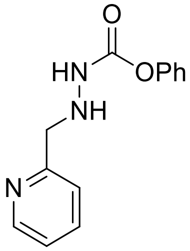
(3.22 g, 51.3 mmol) was added and allowed to stir for 16 h.The title compound was purified by column chromatography (100% CH_2Cl_2) to yield an amorphous white solid (3.48 g, 87%). TLC R_f = 0.20 in 100% CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 1.76, 0.8 Hz, 1H), 7.41-7.33 (m, 2H), 7.26-7.19 (m, 1H), 7.17-7.11 (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.



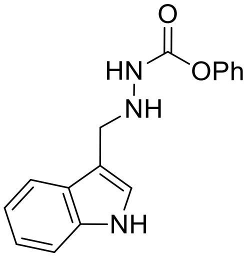
Phenyl 2-(thiophen-2-ylmethyl)hydrazine-1-carboxylate: Synthesized according to general procedure **P** by stirring *O*-phenyl carbazate (2.57 g, 16.9 mmol) and thiophene-2-carboxaldehyde (1.89 g, 16.9 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (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 7.42-7.35 (m, 2H), 7.30 (dd, *J* = 5.00, 1.3 Hz, 1H), 7.26-7.20 (m, 1H), 7.17-7.12 (m, 2H), 7.05-7.02 (m, 1H), 7.02-6.98 (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.



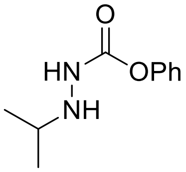
Phenyl 2-((1-allyl-1*H*-pyrrol-2-yl)methyl)hydrazinecarboxylate: Synthesized according to general procedure **P** by stirring *O*-phenyl carbazate (2.99 g, 19.6 mmol) and 1-allyl-1*H*-pyrrole-2-carboxaldehyde (2.65 g, 19.6 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted 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 7.45-7.36 (m, 2H), 7.29-7.21 (m, 1H), 7.21-7.12 (m, 2H), 6.70 (dd, *J* = 2.8, 1.9 Hz, 1H), 6.22-6.17 (m, 1H), 6.17-6.12 (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.



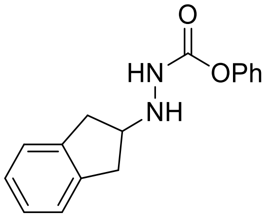
Phenyl 2-(pyridin-2-ylmethyl)hydrazinecarboxylate: Synthesized according to general procedure **P** by stirring *O*-phenyl carbazate (1.89 g, 17.6 mmol) and picolinaldehyde (2.64 g, 17.6 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (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), 7.38-7.25 (m, 3H), 7.23-7.17 (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.



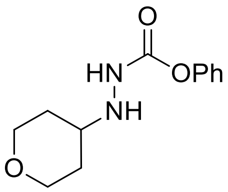
Phenyl 2-((1*H*-indol-3-yl)methyl)hydrazine-1-carboxylate: Synthesized according to general procedure **2** by stirring *O*-phenyl carbazate (2.27 g, 14.9 mmol) and indole-2-carboxaldehyde (2.17 g, 14.9 mmol) at room temperature in MeOH (0.3 M) overnight. The crude reaction was diluted in 2:1 MeOH:AcOH (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), 7.43-7.33 (m, 3H), 7.29 (d, *J* = 2.3 Hz, 1H), 7.25-7.17 (m, 1H), 7.25-7.03 (m, 3H), 7.03-6.94 (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.



P**henyl 2-isopropylhydrazine-1-carboxylate:** Synthesized according to general procedure **P** 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), 7.43-7.32 (m, 2H), 7.24-7.16 (m, 1H), 7.12-7.04 (m, 2H), 4.53 (br s, 1H), 3.14-3.01 (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.

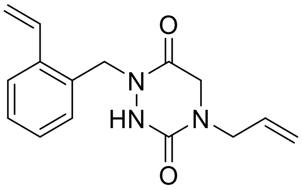


Phenyl 2-(2,3-dihydro-1*H*-inden-2-yl)hydrazine-1-carboxylate: Synthesized according to general procedure **P** by stirring *O*-phenyl carbazate (2.50 g, 16.4 mmol) and 1,3-dihydro-2*H*-inden-2-one (2.17 g, 16.4 mmol) at room temperature in MeOH (0.3 M) for 1 h. The crude reaction was diluted in 2:1 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), 7.41-7.37 (m, 2H), 7.24-7.18 (m, 3H), 7.13-7.09 (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.

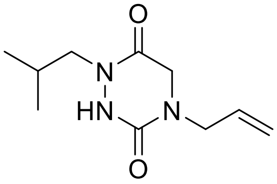


Phenyl 2-(tetrahydro-2*H*-pyran-4-yl)hydrazine-1-carboxylate: Synthesized according to general procedure **P** by refluxing *O*-phenyl carbazate (2.70 g, 17.7 mmol) and tetrahydro-4*H*-pyran-4-one (1.78 g, 17.7 mmol). The crude reaction was diluted in 2:1 MeOH:AcOH (0.2 M) and $NaBH_3CN$ (3.34 g, 53.1

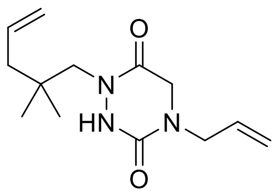
mmol) was added and allowed to stir for 16 h. The title compound was purified by column chromatography (50% Hexane/EtOAc) to yield an amorphous white solid (1.95 g, 47%). TLC R_f = 0.21 in 50% Hexane/EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.17-7.12 (m, 2H), 4.00 (dt, *J* = 11.6, 3.5 Hz, 2H), 3.42 (td, *J* = 11.4, 2.2 Hz, 2H), 3.28-3.14 (m, 1H), 1.84 (d, *J* = 12.4 Hz, 2H), 1.58-1.42 (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.



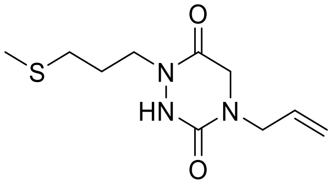
4-Allyl-1-(2-vinylbenzyl)-1,2,4-triazinane-3,6-dione (4.77): Synthesized according to general procedure **O** using the corresponding carbazate (0.107 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified 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), 7.34-7.26 (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), 5.24-5.16 (m, 2H), 4.76 (s, 2H), 3.86-3.78 (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.



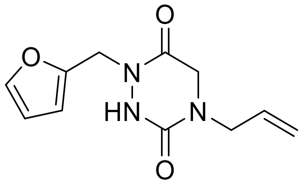
4-Allyl-1-isopropyl-1,2,4-triazinane-3,6-dione (4.78): Synthesized according to general procedure **O** using the corresponding carbazate (0.0830 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by 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 (m, 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.



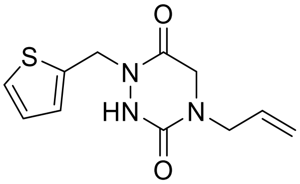
4-Allyl-1-(2,2-dimethylpent-4-en-1-yl)-1,2,4-triazinane-3,6-dione (4.79): Synthesized according to general procedure **O** using the corresponding carbazate (0.0993 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture 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), 5.90-5.69 (m, 2H), 5.27-5.14 (m, 2H), 5.10-4.97 (m, 2H), 3.82 (d, *J* = 5.7 Hz, 2H), 3.73 (s, 2H), 2.02-1.90 (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.



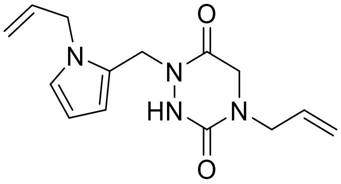
4-Allyl-1-(3-(methylthio)propyl)-1,2,4-triazinane-3,6-dione (4.80): Synthesized according to general procedure **O** using the corresponding carbazate (0.0960 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was 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.



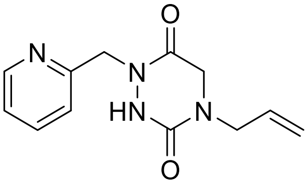
4-Allyl-1-(furan-2-ylmethyl)-1,2,4-triazinane-3,6-dione (4.81): Synthesized according to general procedure **O** using the corresponding carbazate (0.0930 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified 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.



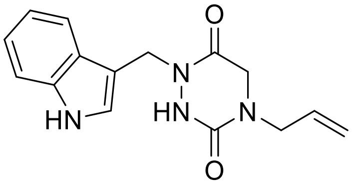
4-Allyl-1-(thiophen-2-ylmethyl)-1,2,4-triazinane-3,6-dione (4.82): Synthesized according to general procedure **O** using the corresponding carbazate (0.0990 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 50% EtOAc/CH$_2$Cl$_2$ to afford the pure compound as a white solid (0.0610 g, 61%). TLC R$_f$ = 0.33 in 50% EtOAc/CH$_2$Cl$_2$. ^{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.



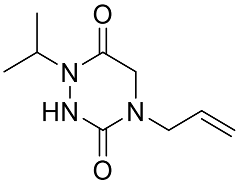
4-Allyl-1-((1-allyl-1*H*-pyrrol-2-yl)methyl)-1,2,4-triazinane-3,6-dione (4.83): Synthesized according to general procedure **O** using the correspoding carbazate (0.109 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified by silica gel column chromatography using 50% EtOAc/CH$_2$Cl$_2$ to afford the pure compound as a white solid (0.0735 g, 67%). TLC R$_f$ = 0.45 in 50% EtOAc/CH$_2$Cl$_2$. ^{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), 5.94-5.83 (m, 1H), 5.77-5.66 (m, 1H), 5.19 (d, J = 0.8 Hz, 1H), 5.17-5.13 (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.



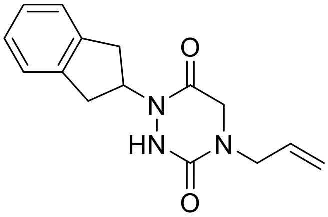
4-Allyl-1-(pyridin-2-ylmethyl)-1,2,4-triazinane-3,6-dione (4.84): Synthesized according to general procedure **O** using the corresponding carbazate (0.0970 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was purified 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.



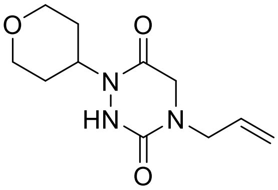
1-((1H-Indol-3-yl)methyl)-4-allyl-1,2,4-triazinane-3,6-dione (4.85): Synthesized according to general procedure **O** using the correspoding carbazate (0.113 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The title compound was purified by column chromatography (50% EtOAc/ CH_2Cl_2) to yield an amorphous white solid (0.0705 g, 62%). TLC R_f = 0.37 in 50% EtOAc/ CH_2Cl_2. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 10.99 (br s, 1H), 9.21 (br s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.39-7.27 (m, 2H), 7.11-7.01 (m, 1H), 6.99-6.89 (m, 1H), 5.69-5.55 (m, 1H), 5.13-4.98 (m, 2H), 4.75 (s, 2H), 3.75-3.56 (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 (4.86): Synthesized according to general procedure **O** using the corresponding carbazate (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.

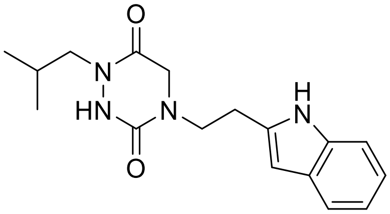


4-Allyl-1-(2,3-dihydro-1*H*-inden-2-yl)-1,2,4-triazinane-3,6-dione (4.87): Synthesized according to general procedure **O** using the corresponding carbazate (0.107 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 72 h and the amination for 24 h. The crude mixture 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.

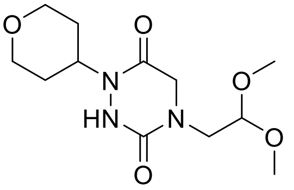


4-Allyl-1-(tetrahydro-2H-pyran-4-yl)-1,2,4-triazinane-3,6-dione (4.88): Synthesized according to general procedure **O** using the corresponding carbazate (0.0960 g, 0.400 mmol), allylamine (0.0460 g, 0.800 mmol). The acylation was allowed to stir for 16 h and the amination for 24 h. The crude mixture 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.

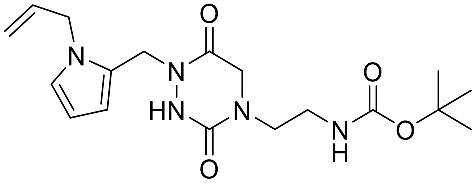
Mixed Aza-DKP Synthesis



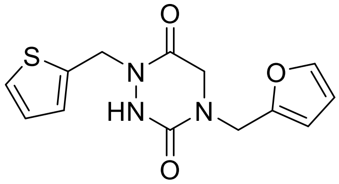
4-(2-(1H-Indol-2-yl)ethyl)-1-isobutyl-1,2,4-triazinane-3,6-dione (4.89) : Synthesized according to general procedure **O** using the corresponding carbazate (0.0830 g, 0.400 mmol), tryptamine (0.128 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture 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), 2.21-2.01 (m, 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.



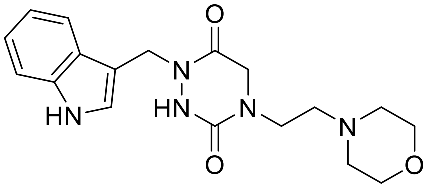
4-(2,2-Dimethoxyethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,2,4-triazinane-3,6-dione (4.90): Synthesized according to general procedure **O** using the corresponding carbazate (0.0960 g, 0.400 mmol), aminoacetaldehyde dimethyl acetal (0.0840 g, 0.800 mmol). The acylation was allowed to stir for 16 h and the 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.



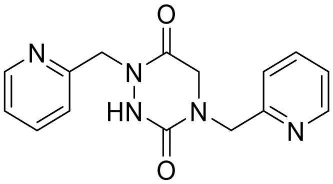
tert-Butyl (2-(1-((1-allyl-1H-pyrrol-2-yl)methyl)-3,6-dioxo-1,2,4-triazinan-4-yl)ethyl)carbamate (4.91): Synthesized according to general procedure **O** using the corresponding carbazate (0.109 g, 0.400 mmol), *N*-Boc ethylenediamine (0.128 g, 0.800 mmol). The acylation was allowed to stir for 2 h and 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 (4.92): Synthesized according to general procedure **O** using the corresponding carbazate (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.



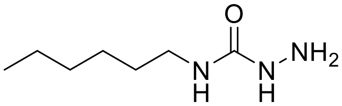
1-((1H-indol-3-yl)methyl)-4-(2-morpholinoethyl)-1,2,4-triazinane-3,6-dione (4.93): Synthesized according to general procedure **O** using the corresponding carbazate (0.113 g, 0.400 mmol), 4-(2-aminoethyl)morpholine (0.104 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 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), 7.23-7.09 (m, 4H), 4.94 (s, 2H), 3.99 (s, 2H), 3.74-3.56 (m, 4H), 3.37 (t, *J* = 6.2 Hz, 2H), 2.58-2.33 (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.



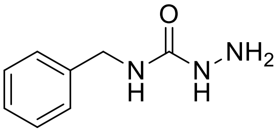
1,4-Bis(pyridin-2-ylmethyl)-1,2,4-triazinane-3,6-dione (4.94): Synthesized according to general procedure **O** using the corresponding carbazate (0.0970 g, 0.400 mmol), 2-picolylamine (0.0865 g, 0.800 mmol). The acylation was allowed to stir for 2 h and the amination for 24 h. The crude mixture was 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), 8.61-8.49 (m, 2H), 7.77-7.62 (m, 2H), 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.

6.4: Supporting Information for Chapter 5

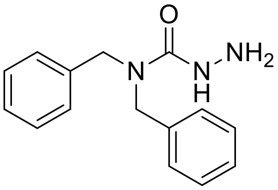
General procedure Q: An oven-dried round bottom flask was charged with a stir bar, phenyl carbazate (1.00 equiv), an amine (1.10 equiv), DBU (20 mol %), and THF (0.3 M). The mixture was stirred overnight, concentrated under reduced pressure, and purified by flash column chromatography.



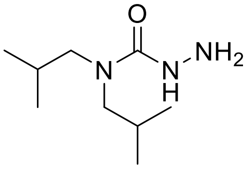
***N*-Hexylhydrazinecarboxamide (5.1):** Synthesized according to general procedure **Q** using phenyl carbazate (0.152 g, 1.00 mmol), hexylamine (0.15 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (5% CH_3OH/CH_2Cl_2) to yield a 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.



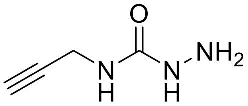
***N*-Benzylhydrazinecarboxamide (5.2):** Synthesized according to general procedure **Q** using phenyl carbazate (0.152 g, 1.00 mmol), benzylamine (0.12 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (8% CH_3OH/CH_2Cl_2) to yield 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.



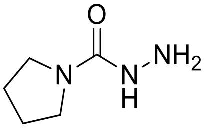
***N,N*-Dibenzylhydrazinecarboxamide (5.3):** Synthesized according to general procedure **Q** using phenyl carbazate (0.152 g, 1.00 mmol), *N,N*-dibenzylamine (0.21 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (3% CH_3OH/CH_2Cl_2) 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.



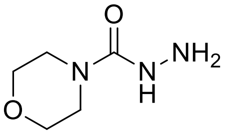
N,N-Diisobutylhydrazinecarboxamide (5.4): Synthesized according to general procedure **Q** using phenyl carbazate (0.152 g, 1.00 mmol), N,N-diisobutylamine (0.19 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (3% CH_3OH/CH_2Cl_2) to yield an amorphous yellow solid (0.142 g, 76%). TLC R_f = 0.15 in 5% CH_3OH/CH_2Cl_2. ^1H 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.



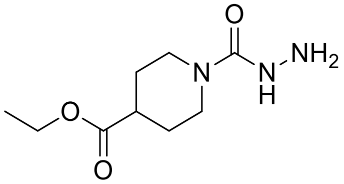
N-Propargylhydrazinecarboxamide (5.5): Synthesized according to general procedure **Q** using phenyl carbazate (0.152 g, 1.00 mmol), propargylamine (0.070 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (5% CH_3OH/CH_2Cl_2) to yield an amorphous white solid (0.0600 g, 54%). TLC R_f = 0.13 in 5% CH_3OH/CH_2Cl_2. ^1H 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%).



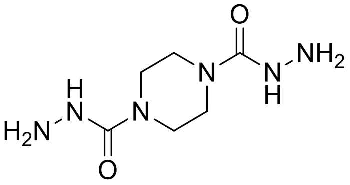
Pyrrolidine-1-carbohydrazide (5.6): Synthesized according to general procedure **Q** using phenyl carbazate (0.152 g, 1.00 mmol), pyrrolidine (0.090 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (8% CH_3OH/CH_2Cl_2) to yield a yellow oil (0.0940 g, 73%). TLC R_f = 0.37 in 8% CH_3OH/CH_2Cl_2. ^1H 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.



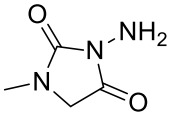
Morpholine-4-carbohydrazide (5.7): Synthesized according to general procedure **Q** using phenyl carbazate (0.152 g, 1.00 mmol), morpholine (0.095 mL, 1.1 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was obtained by filtration of the solution to yield a white amorphous solid (0.122 g, 84%). TLC $R_f = 0.27$ in 8% CH_3OH/CH_2Cl_2. ^1H 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.



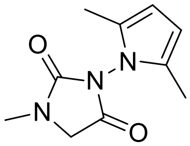
1-Hydrazinocarbonyl-piperidine-4-carboxylic acid ethyl ester (5.8): Synthesized according to general procedure **Q** using phenyl carbazate (0.152 g, 1.00 mmol), ethyl isonipecotate (0.173 g, 1.10 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound was purified by column chromatography (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. ^1H 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.



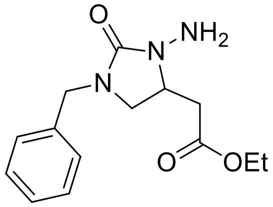
Piperazine-1,4-dicarbohydrazide (5.9): Synthesized according to general procedure **Q** using phenylcarbazate (0.152 g, 1.00 mmol), piperazine (0.0430 g, 0.500 mmol), DBU (0.0300 g, 0.200 mmol), and THF (3.3 mL). The title compound precipitated out of solution to afford the pure compound as an amorphous white solid (0.0930 g, 91%). ^1H 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.



Equation 5.2: 3-Amino-1-methylimidazolidine-2,4-dione (5.10): To a solution of phenyl carbazate (1.04 g, 6.80 mmol) in MeCN (20 mL) was added sarcosine ethyl ester hydrochloride (1.14 g, 7.40 mmol) and DIPEA (1.4 mL, 8.0 mmol) and the solution was stirred in a microwave reactor for 6 hours at 120 °C. The solution was concentrated under reduced pressure and purified by silica gel column chromatography using 8% MeOH/CH_2Cl_2 to afford the pure compound as a white amorphous solid (0.800 g, 91%). TLC R_f = 0.29 in 8% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.89 (s, 2H), 3.73 (br s, 2H), 3.03 (s, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 167.9 (C), 155.9 (C), 50.2 (CH_2), 29.9 (CH_3). IR (film): 1782, 1717, 1479, 1448, 1418, 1391, 1265, 1242 cm^{-1}. HRMS (EI): Exact mass calcd for $C_4H_7N_3O_2$ $[M]^+$: 129.0538. Found: 129.0536.

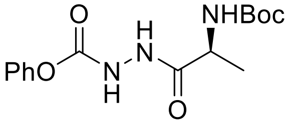


Equation 5.3: 3-(2,5-Dimethyl-1H-pyrrol-1-yl)-1-methylimidazolidine-2,4-dione (5.11): To a solution of amino hydantoin **5.10** (0.130 g, 1.00 mmol) in PhMe (4.0 mL) was added hexanedione (0.114 g, 1.00 mmol) and PTSA monohydrate (0.0200 g, 8.00 mmol) and the solution was stirred in a microwave reactor for 1 hour at 150 °C. The solution was concentrated under reduced pressure and purified by silica gel column chromatography using 10% EtOAc/CH_2Cl_2 to afford the pure compound as a white amorphous solid (0.187 g, 90%). TLC R_f = 0.54 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 5.88 (s, 2H), 4.07 (s, 2H), 3.07 (s, 3H), 2.06 (s, 6H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 166.4 (C), 153.2 (C), 127.6 (C), 105.4 (CH), 50.2 (CH_2), 30.3 (CH_3), 10.9 (CH_3). IR (film): 2984, 1760, 1712, 1450, 1438, 1291, 1265, 1242. HRMS (EI): Exact mass calcd for $C_{10}H_{13}N_3O_2$ $[M]^+$: 207.1008. Found: 207.1003.

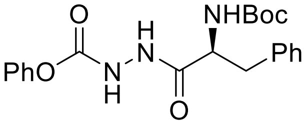


Equation 5.4: Ethyl 2-(3-amino-1-benzyl-2-oxoimidazolidin-4-yl)acetate (5.12): To a solution of phenyl carbazate (0.0910 g, 0.600 mmol) in MeCN (2.0 mL) was added ethyl (*E*)-4-(benzylamino)-2-butenoate (0.145 g, 0.660 mmol) and the solution was stirred in a microwave reactor for 6 hours at 120 °C. The solution was concentrated under reduced pressure and purified by silica gel column chromatography using EtOAc to afford the pure compound as a white amorphous solid (0.135 g, 81%). TLC R_f = 0.16 in EtOAc. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.36-7.24 (m, 5H), 6.31 (br s, 1H), 4.61-4.49 (m, 2H), 4.15-4.05 (m, 3H), 3.58-3.46 (m, 1H), 3.29 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.07 (dd, *J* = 11.7, 8.0 Hz, 1H), 2.53-2.36 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 170.4 (C), 155.6 (C), 137.1 (C), 128.46 (CH), 128.0 (CH), 127.4 (CH), 60.9 (CH_2), 50.5 (CH_2), 50.4 (CH_2), 49.7 (CH), 35.4

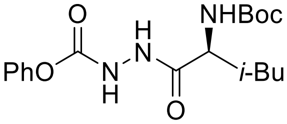
(CH_2), 14.0 (CH_3). IR (film): 3335, 1771, 1719, 1684, 1632, 1601, 1445, 1416, 1337 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{19}N_3O_3$ $[M]^+$: 277.1426. Found: 277.1427.



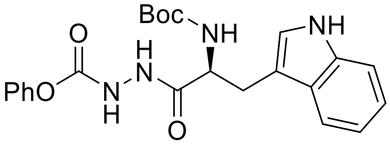
(*S*)-Phenyl 2-(2-((tert-butoxycarbonyl)amino)propanoyl)hydrazinecarboxylate (5.13): Boc-ala-OSu (2.87 g, 10.0 mmol) was dissolved in 50.0 mL MeCN in a round bottom flask charged with magnetic stir bar. Phenyl carbazate (1.53 g, 10.0 mmol) was added to the reaction mixture. The flask was capped and allowed to stir overnight at room temperature. The solution was diluted with EtOAc and washed several time with $NaHCO_3$. The organic layer was then dried and concentrated under reduced pressure and the title compound was obtained as white powder. (2.93 g, 91%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.33 (m,2H), 7.19 (m, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 5.29 (br s , 1H), 4.32 (br s, 1H), 1.41 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1 (C), 155.8 (C), 154.5 (C), 150.5(C), 129.3 (CH), 125.7 (CH), 121,4 (CH), 80.6 (C), 48.5 (CH), 28.3 (CH3), 18.1 (CH3). IR (film) 2962, 2887, 1716, 1645, 1593, 1588, 1477, 1456, 1434, 1382, 1336, 1263, 1234, 1195, 1163, 1128, 1070, 997, 962, 952, 902, 815, 649 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{15}H_{21}N_3O_5$ $[M]^+$: 323.1481, found $[M+Na]^+$: 346.1379.



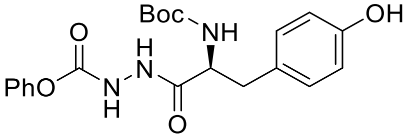
(*S*)-Phenyl 2-(2-((tert-butoxycarbonyl)amino)-3-phenylpropanoyl)hydrazinecarboxylate (5.14): Boc-phe-OSu (1.81 g, 5.00 mmol) was dissolved in 25 mL MeCN in a round bottom flask charged with magnetic stir bar. Phenyl carbazate (0.765 g, 5.00 mmol) was added to the reaction mixture. The flask was capped and allowed to stir overnight at room temperature. The solution was diluted with EtOAc and washed several time with $NaHCO_3$. The organic layer was then dried and concentrated under reduced pressure and the title compound was obtained as white powder. (1.92 g, 96%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.63 (br s,1H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.24 (m, 6H), 7.13 (br s, 2H), 5.29 (br s, 1H), 4.54 (br s, 1H), 3.09 (m, 2H), 1.36 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6 (C), 155.9 (C), 150.5 (C), 136.8 (C), 129.4 (CH), 129.3 (CH), 128.6 (CH), 127.0 (CH), 125.8 (CH), 121.4 (CH), 80.6 (C), 37.9 (CH), 28.2 (CH3), 25.3 (CH2). IR (film): 3296, 2985, 1733, 1685, 1670, 1627, 1593, 1521, 1475, 1455, 1438, 1365, 1355, 1338, 1292, 1263, 1259, 1153, 1130, 1110, 1043, 1024, 999, 891, 938, 730, 685, 673, 649 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{21}H_{25}N_3O_5$ $[M]^+$: 399.1794, found $[M+Na]^+$: 422.1692.



(*S*)-Phenyl 2-(2-((tert-butoxycarbonyl)amino)-4-methylpentanoyl)hydrazinecarboxylate (5.15): Boc-leu-OSu (1.64 g, 5.00 mmol) was dissolved in 25 mL MeCN in a round bottom flask charged with magnetic stir bar. Phenyl carbazate (0.765 g, 5.00 mmol) was added to the reaction mixture. The flask was capped and allowed to stir overnight at room temperature. The solution was diluted with EtOAc and washed several time with $NaHCO_3$. The organic layer was then dried and concentrated under reduced pressure and the title compound was obtained as white powder (1.54 g, 84 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (br s,1H), 7.32 (m, 2H), 7.19 (m, 1H), 7.12 (d, J = 7.6 Hz, 2H), 5.25 (br s, 1H), 4.34 (br s, 1H), 1.70 (m, 2H), 1.50 (m, 9H), 0.91 (d, J = 9.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9 (C), 156.2 (C), 154.4 (C), 150.6 (C), 129.3 (CH), 125.6 (CH), 121.3 (CH), 80.6 (C), 51.3 (CH), 41.4 (CH2), 24.5 (CH), 22.8 (CH3), 21.9 (CH3). IR (film): 3307, 2386, 3240, 3211, 2964, 1766, 1674, 1647, 1595, 1490, 1481, 1456, 1434, 1367, 1340, 1265, 1257, 1203, 1161, 1124, 1101, 1066, 1021, 1106, 989, 950, 794, 729, 688, 678 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{18}H_{27}N_3O_5$ [M]$^+$: 365.195, found [M+Na]$^+$: 388.1848.

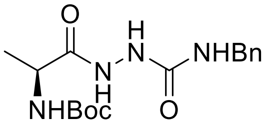


(S)-Phenyl 2-(2-((tert-butoxycarbonyl)amino)-3-(1H-indol-3-yl)propanoyl)hydrazinecarboxylate (5.16): Boc-trp-OSu (2.01 g, 5.00 mmol) was dissolved in 25 mL MeCN in a round bottom flask charged with magnetic stir bar. Phenyl carbazate (0.765 g, 5.00 mmol) was added to the reaction mixture. The flask was capped and allowed to stir overnight at room temperature. The flask was capped and allowed to stir overnight at room temperature. The solution was diluted with EtOAc and washed several time with $NaHCO_3$. The organic layer was then dried and concentrated under reduced pressure and the title compound was obtained as light brown powder. (1.85 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H) , 8.21 (s, 1H), 7.57 (m, 1H),7.33 (m, 3H), 7.18 (m, 2H) , 7.11(t, J = 7.4Hz, 2H), 7.04 (m, 2H), 5.28 (br s,1H), 4.57 (br s, 1H),1.32 (d, J = 5.7Hz, 2H), 1.32 (s, 9H). ^{13}C (100 MHz, $CDCl_3$): δ 171.9 (C), 155.8 (C), 154.9 (C), 150.4 (C), 136.1 (C), 129.4 (C), 125.8 (CH), 121.4 (CH), 119.6 (CH), 118,5 (CH), 111.4 (CH), 109.4 (C), 80.6 (C), 53.8 (CH), 33.3 (CH2), 28.2 (CH3). IR (film): 3307, 3286, 3240, 2964, 1766, 1674, 1647, 1596, 1490, 1481, 1456, 1434, 1392, 1367, 1340, 1265, 1257, 1203, 1167, 1124, 1101, 1066, 1024, 1006, 989, 950, 794, 729, 688, 678 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{23}H_{26}N_4O_5$ [M]$^+$: 438.1903, found [M+Na]$^+$ 461.1801.

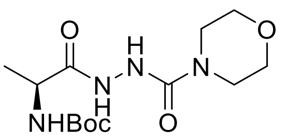


(*S*)-Phenyl 2-(2-((tert-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanoyl)hydrazinecarboxylate (5.17): Boc-tyr-OSu (1.89 g, 5.00 mmol) was dissolved in 25 mL MeCN in a round bottom flask charged with magnetic stir bar. Phenyl carbazate (0.765 g, 5.00 mmol) was added to the reaction mixture. The flask was capped and allowed to stir overnight at room temperature. The solution was diluted with EtOAc and washed several time with $NaHCO_3$. The organic layer was then dried and concentrated under reduced pressure and the title compound was obtained as white powder. (1.78 g, 85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.98 (s,1H) , 9.16 (s, 1H), 7.41 (m, 2H), 7.05 (m, 5H), 6.66 (d, J = 8.0 Hz, 2H), 4.14 (t, J = 7.7 Hz, 1H), 2.68 (m, 2H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.3 (C), 157.7 (C), 156.2 (C), 154.7 (C), 151.1(C), 130.5 (CH), 129.9 (CH), 128.4 (C), 125.8 (CH), 119.2 (CH), 115.6 (CH) 78.4 (C), 55.1(CH_2), 28.6 (CH_3). IR (film): 3307, 2962, 1762, 1741, 1695, 1645, 1506, 1488, 1474, 1434, 1388, 1367, 1338, 1265, 1193, 1163, 1132, 1070, 1047, 1004, 792, 686 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{21}H_{25}N_3O_6$ [M]$^+$: 415.1743, found [M+Na]$^+$ 438.1133.

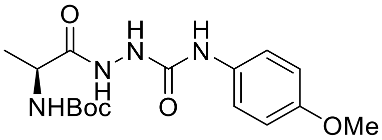
General procedure R: A round bottomed flask was charged with a stir bar, azadipeptides (1 equiv), amine (1.1 equiv), Et_3N (0.2 equiv) and MeCN (0.3 M). The flask was covered with a cap. The solution was stirred overnight at 60 °C. The crude mixture was concentrated under reduced pressure and purification by silica gel chromatography gave the corresponding aminosubstituted azadipeptide.



***tert*-Butyl 1-(2-(benzylcarbamoyl)hydrazinyl)-1-oxopropan-2-ylcarbamate (5.18):** Synthesized according to general procedure **R** using azadipeptide **5.13** (0.0970 g, 0.300 mmol), benzylamine (0.0350 g, 0.330 mmol), Et_3N (0.0060 g, 0.0060 mmol) and MeCN (1 mL). The crude mixture was purified by silica gel column chromatography using 100% EtOAc to afford the pure compound as a white solid (0.0880 g, 87%). TLC R_f = 0.23 in EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (br s, 1H), 7.30-7.21 (m, 5H), 6.35 (br s, 1H,), 5.23 (br s, 1H, NH), 4.35 (s, 2H), 4.13-4.04 (m, 1H), 1.35 (s, 9H), 1.34-1.31 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.9 (C), 158.6 (C), 157.0 (C), 138.7 (C), 128.5 (CH), 127.3 (CH), 127.1 (CH), 80.8 (C), 49.5 (CH), 43.9 (CH_2), 28.2 (CH_3); 17.3 (CH_3).



***tert*-Butyl 1-(2-(morpholine-4-carbonyl) hydrazinyl)-1-oxopropan-2-ylcarbamate (5.19):** Synthesized according to general procedure **R** using azadipeptide **5.13** (0.0970 g, 0.300 mmol), morpholine (0.0290 g, 0.66 mmol), Et_3N (0.00600 g, 0.00600 mmol) and MeCN (1 mL,). The crude mixture was purified by silica gel column chromatography using 100% EtOAc to afford the pure compound as a white solid (0.0930, 98%). TLC R_f = 0.20 in EtOAc. ^{1}H NMR H (300 MHz, $CDCl_3$) δ: 8.72 (br s, 1H), 7.42 (br s, 1H), 5.29 (br s, 1H,), 4.34-4.29 (m, 1H), 3.69 (t, *J* = 9.0 Hz, 4H), 3.44 (t, *J* = 9.0 Hz, 4H), 1.44 (s, 9H), 1.39 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.2 (C), 156.7 (C), 155.5 (C), 80.3 (C), 66.3 (CH_2), 48.8 (CH), 43.9 (CH_2), 28.3 (CH_3); 18.3 (CH_3). HRMS (EI): Exact mass calcd for $C_{13}H_{24}N_4O_5 - (t\text{-Bu})$ $[M]^+$: 260.1121. Found: 260.1148

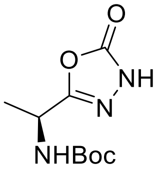


(*S*)-*tert*-Butyl (1-(2-((4-methoxyphenyl)carbamoyl)hydrazinyl)-1-oxopropan-2-yl)carbamate (5.20): Synthesized according to general procedure **R** using azadipeptide **5.13** (0.0970 g, 0.300 mmol), *p*-anisidine (0.111 g, 0.900 mmol), Et_3N (0.0060 g, 0.0060 mmol) and MeCN (1.0 mL). The crude mixture was purified by silica gel column chromatography using 100% EtOAc to afford the pure compound as a white solid (0.0800 g, 76%). TLC R_f = 0.23 in EtOAc. ^{1}H NMR H (300 MHz, DMSO-*d*$_6$): δ 9.84 (br s, 1H), 8.27 (br s, 1H), 8.07 (br s, 1H,), 7.39 (d, *J* = 9.0 Hz, 2H), 7.17 (br s, 1H), 6.83 (d, *J* = 9.0 Hz, 2H), 3.95 (quint, *J* = 6.7 Hz, 1H), 3.70 (s, 3H), 1.38 (s, 9H), 1.21 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ (ppm):

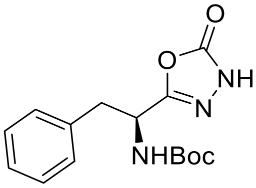
172.28 (C), 155.5 (C), 154.5 (C), 132.6 (C), 120.1 (CH), 113.76 (CH), 78.4 (C), 55.1 (CH_3), 48.7 (CH), 28.2 (CH_3); 17.5 (CH_3). HRMS (EI): Exact mass calcd for $C_{16}H_{24}N_4O_5$ $[M]^+$: 352.1747. Found: 352.1708.

Preparation of oxadiazolone cores (equation 5.8)

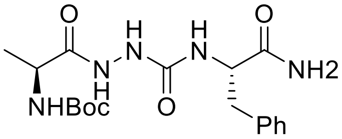
General procedure S: A round bottomed flask was charged with a stir bar, azadipeptide (1 equiv.), DBU (0.2 equiv.) and THF (0.3M). The flask was covered with a cap. The contents were stirred at room temperature overnight. The crude mixture was concentrated under reduced pressure and purification by silica gel chromatography gave the corresponding oxadiazoles cores.



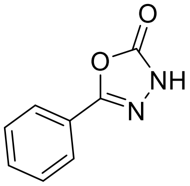
***tert*-Butyl 1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)ethylcarbamate (5.22):** Synthesized according to General procedure **S** using azadipeptide **5.13** (1.62 g, 5.00 mmol), DBU (0.150 mL, 1.00 mmol) and THF (15.0 mL, 0.30 M). The crude mixture was purified by silica gel column chromatography using 10% EtOAc/DCM to afford the pure compound as a white solid (0.886 g, 77%). TLC R_f = 0.23 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR H (300 MHz, DMSO-*d*$_6$): δ 12.18 (br s, 1H), 7.45 (d, *J* = 6.0 Hz, 1H), 4.50 (quint, *J* = 6.0 Hz, 1H), 1.38 (s, 9H), 1.30 (d, *J* = 6.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 157.5 (C), 154.9 (C), 154.8 (C), 78.5 (C), 42.8 (CH), 28.1 (CH_3), 17.2 (CH_3). HRMS (EI): Exact mass calcd for $C_9H_{15}N_3O_4$ – (*t*-Bu) $[M]^+$: 173.0437. Found: 173.0424.



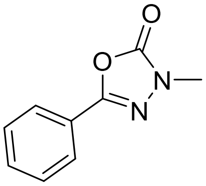
***tert*-Butyl 1-(5-oxo-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl)-2-phenylethylcarbamate (5.23)**: Synthesized according to general procedure **S** using azadipeptide **5.14** (0.120 g, 0.300 mmol), DBU (0.00900 mL, 0.0600 mmol) in THF (1 mL, 0.3M). The crude mixture was purified by silica gel column chromatography using 10% EtOAc/DCM to afford the pure compound as a white solid (0.0790 g, 86%). TLC R_f = 0.17 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR H (300 MHz, DMSO-*d*$_6$): δ 12.20 (br s, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.31-7.18 (m, 5H), 4.66 (quint, *J* = 9.0 Hz, 1H), 3.11-2.91 (m, 2H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 156.9 (C), 155.4 (C), 155.2 (C), 137.1 (C), 129.5 (CH), 128.6 (CH), 126.9 (CH), 79.1 (C), 49.1 (CH), 36.9 (CH_2) 28.1 (CH_3). HRMS (EI): Exact mass calcd for $C_{15}H_{19}N_3O_4$ – (*t*-Bu) $[M]^+$: 249.0750. Found: 249.0735



tert-Butyl 1-(2-(1-amino-1-oxo-3-phenylpropan-2-ylcarbamoyl)hydrazinyl-1- oxopropan-2-ylcarbamate (5.24): Synthesized according to general procedure **R** using azadipeptide **5.13** (0.213 g, 0.660 mmol), L-phenylalaninamide (0.121 g, 0.600 mmol), Et_3N (0.0790 g, 0.780 mmol) and MeCN (2 mL,). The crude mixture was purified by filtration to afford the pure compound as a white solid (0.153g, 65%). TLC R_f = 0.29 in 5% EtOAc/MeOH. ^{1}H NMR H (300 MHz, DMSO-d_6): δ 9.62 (br s, 1H), 7.98 (br s, 1H), 7.35 (br s, 1H), 7.27-7.15 (m, 5H), 7.08 (br s, 1H), 6.99 (d, *J* = 6.9 Hz, 1H), 6.25 (d, *J* = 8.3 Hz, 1H), 4.32-4.26 (m, 1H), 3.97-3.93 (m, 1H), 2.99 (dd, *J* = 13.7, 5.2 Hz, 1H), 2.84-2.77 (m, 1H), 1.37 (s, 9H), 1.17 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4 (C), 172.8 (C), 157.2 (C), 155.2 (C), 137.8 (C), 129.3 (CH), 128.1 (CH), 126.3 (CH), 78.2 (C), 54.1 (CH), 48.5 (CH) 38.1 (CH_2), 28.3 (CH_3), 18.0 (CH_3). HRMS (EI): Exact mass calcd for $C_{18}H_{27}N_5O_5 - (t\text{-Bu})$ $[M]^+$: 337.1386. Found: 337.1374.



5-Phenyl-1,3,4-oxadiazol-2(3H)-one (5.25): Synthesized according to general procedure **S** using carbazone **3.45** (1.28 g, 5.00 mmol), DBU (0.150 mL, 1.00 mmol) and THF (15.0 mL). The crude mixture was purified by silica gel column chromatography using 10% EtOAc/CH_2Cl_2 to afford the pure compound as a white solid (0.713 g, 88%). Spectroscopic data matched the data obtained from the commercially available material.



3-Methyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one (5.26): To a solution of **5.25** (0.973 g, 6.00 mmol) in DMF (24.0 mL) was added K_2CO_3 (2.07 g, 15.0 mmol) followed by iodomethane (0.450 mL, 7.20 mmol). The solution was stirred at room temperature overnight and was poured on cold water and extractred 6 times with chloroform (6 x 20 mL). 90 mL of EtOAc was added and the organic phase was washed 10 times with 24 mL of a 1:1 mixture of water:brine. The organic phase was dried and concentrated under reduced pressure to afford the pure product as a white solid (0.994 g, 94%). TLC R_f = 0.23 in 100% CH_2Cl_2. Spectroscopic data matched the published data.[123]

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[123] Bancerz, M.; Georges, M. K. *J. Org. Chem.* **2011**, *76*, 6377.

Appendix I

Claims to Original Research

1. Development of the first cascade reaction involving *N*-isocyanates for the synthesis of saturated heterocycles.
2. Development of the first cascade reaction involving iminoisocyanates for the synthesis of amino-hydantoins.
3. Exploration of the reactivity of amidoisocyanate and iminoisothiocyanates towards cascade reactions.
4. Design of a new precursor for the generation of aminoisothiocyanate.
5. Exploration of aminothiocarbonylation reactivity using *N*-isothiocyanates.
6. Development of base catalysed formation of isocyanates at room temperature.
7. Development of a mild synthesis of carbamoyl substituted pyrazoles.
8. Development of the synthesis of 6-membered aromatic rings containing the N-N-C=O motifs such as phtalazinones, azauracils, triazinones and pyridazinones.
9. Comparison of the reactivity of amino-isocyanates with their sulfur analogues amino-isothiocayantes for the divergent synthesis of imidazolones and thiazolines.
10. Discovery of a new *in situ* generation of azomethine imine and development of their reactivity
11. Exploration of azapeptides synthesis using amido-isocyanates.
12. Discovery of a novel masked *N*-isocyanates.

Publications from this Work.

1. *Diversity-Oriented Synthesis of Hydrazine-Derived Compounds from Amino Isocyanates Generated In Situ;* Clavette, C.;[†] Vincent-Rocan, J,-F.;[†] Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2013**, *52, 12705.*
2. *A Cascade Synthesis of Aminohydantoins Using In Situ-Generated N-Substituted Isocyanates;* Vincent-Rocan, J.-F.; Clavette, C.; Leckett, K.; Beauchemin, A. M. *Chem. Eur. J.* **2015**, *21*, 3886.
3. *One-Pot Synthesis of Aza-Diketopiperazines Enabled by Controlled Reactivity of N-Isocyanates Precursors;* Ivanovich, R. A.;[†] Vincent-Rocan, J.-F.;[†] Elkaeed, E. B.; Beauchemin, A. M. *Org. Lett.* **2015**, *17*, 4898.
4. *Diversity-Oriented Heterocyclic Synthesis using Divergent Reactivity of N-Substituted Iso(thio)cyanates;* Vincent-Rocan, J.-F.;[†] Derasp, J. S.;[†] Beauchemin, A. M. *Chem. Commun.* **2015**, *51*, 16405.
5. *Cascade Reactions of Nitrogen-Substituted Isocyanates: A New Tool in Heterocyclic Chemistry;* Vincent-Rocan, J.-F.; Ivanovich, R. A.; Clavette, C.; Leckett, K.; Bejjani, J.; Beauchemin, A. M. *Chem. Sci.* **2016**, *7*, 315.
6. *Divergent Reactivity of N-Isocyanates with 1° and 2° Amines: Acces to Pyridazinones and Triazinones;* Derasp, J. S.;[†] Vincent-Rocan, J.-F.;[†] Beauchemin, A. M. *Org. Lett.* **2016**, *18*, 658.

Publication from Graduates Studies (Outside of this Work)

7. *Studies on Difficult Intramolecular Hydroaminations in the Context of Four Syntheses of Alkaloids Natural Products;* Dion, I.; Vincent-Rocan, J.-F.; Zhang, L.; Cebrowski, P. H.; Lebrun, M.-E.; Pfeiffer, J. Y.; Bédard, A.-C.; Beauchemin, A. M. *J. Org. Chem.* **2013**, *78*, 12735.
8. *Intramolecular Alkene Aminocarbonylation Using Concerted Cycloadditions of Amino-Isocyanates;* Ivanovich, R. A.; Clavette, C.; Vincent-Rocan, J.-F.; Roveda, J.-G.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Eur. J.* **2016**, *22,* 7906.
9. *N-Isocyanates, N-isothiocyanates and their masked/blocked derivatives: Synthesis and Reactivity;* Vincent-Rocan, J.-F.; Beauchemin, A.M. *Synthesis* **2016**, *In press.*

Presentations from this Work

Oral Presentations:

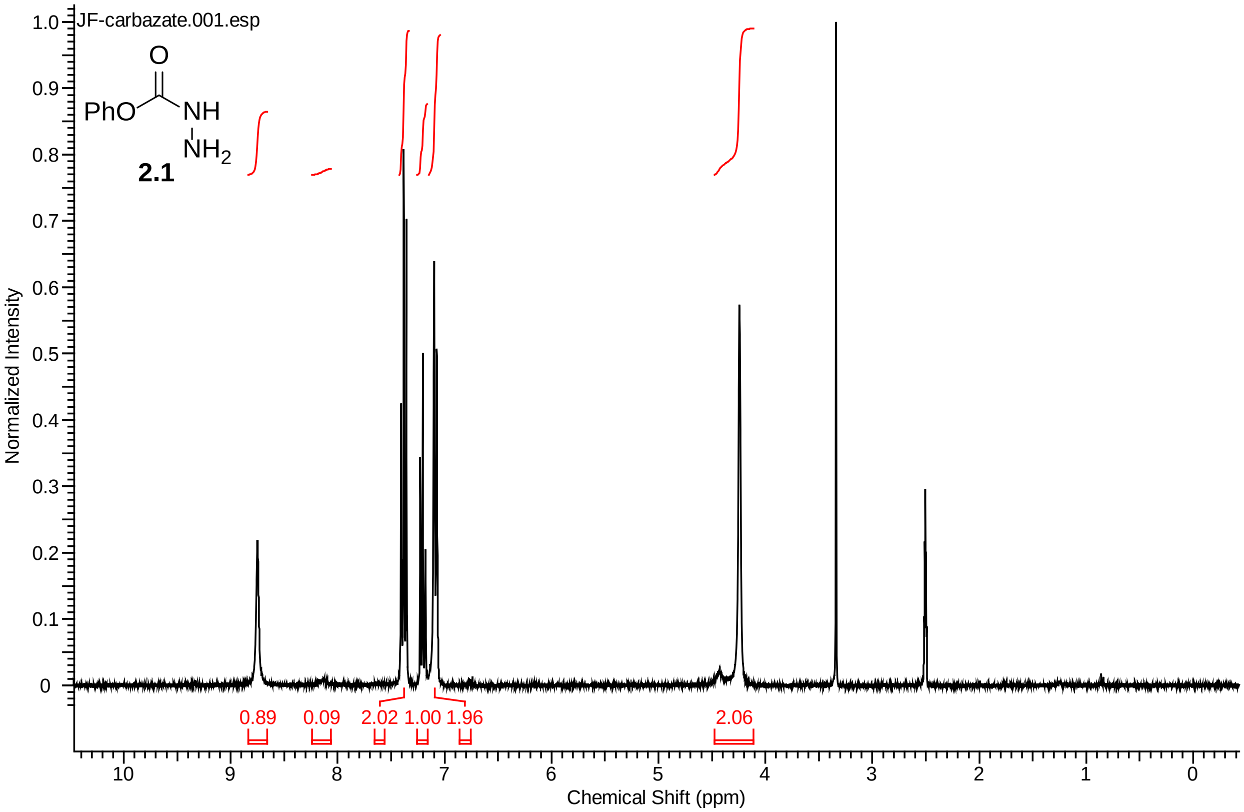
1. *Exploration of Amino-Isocyanates Reactivity*, QOMSBOC 2013, November **2013**, Sherbrooke.
2. *Masked Amino-Isocyanates: Powerful Building Block for Rapid Generation of Complexitiy*, 97th Canadian Chemistry Conference and Exhibition, June **2014**, Vancouver.
3. *Cascade Reactions of Nitrogen-Substituted Isocyanates: A New Tool in Heterocyclic Chemistry,* 251st ACS National Meeting and Exposition, March **2016**, San Diego

Poster Presentations:

4. *Development of Aminocarbonylation Using Simple Hydrazide Derivatives,* Uottawa Synthesis day 2012, June **2012**, Ottawa
5. *Aminoisocyanates: Useful Synthetic Tool,* 96th Canadian Chemistry Conference and Exhibition, May **2012**, Québec
6. *Cascade Reaction of Nitrogen-Substituted Isocyanates: A New Tool in Heterocyclic Chemistry,* QOMSBOC 2015, November **2015**, Montréal

Appendix II

Spectra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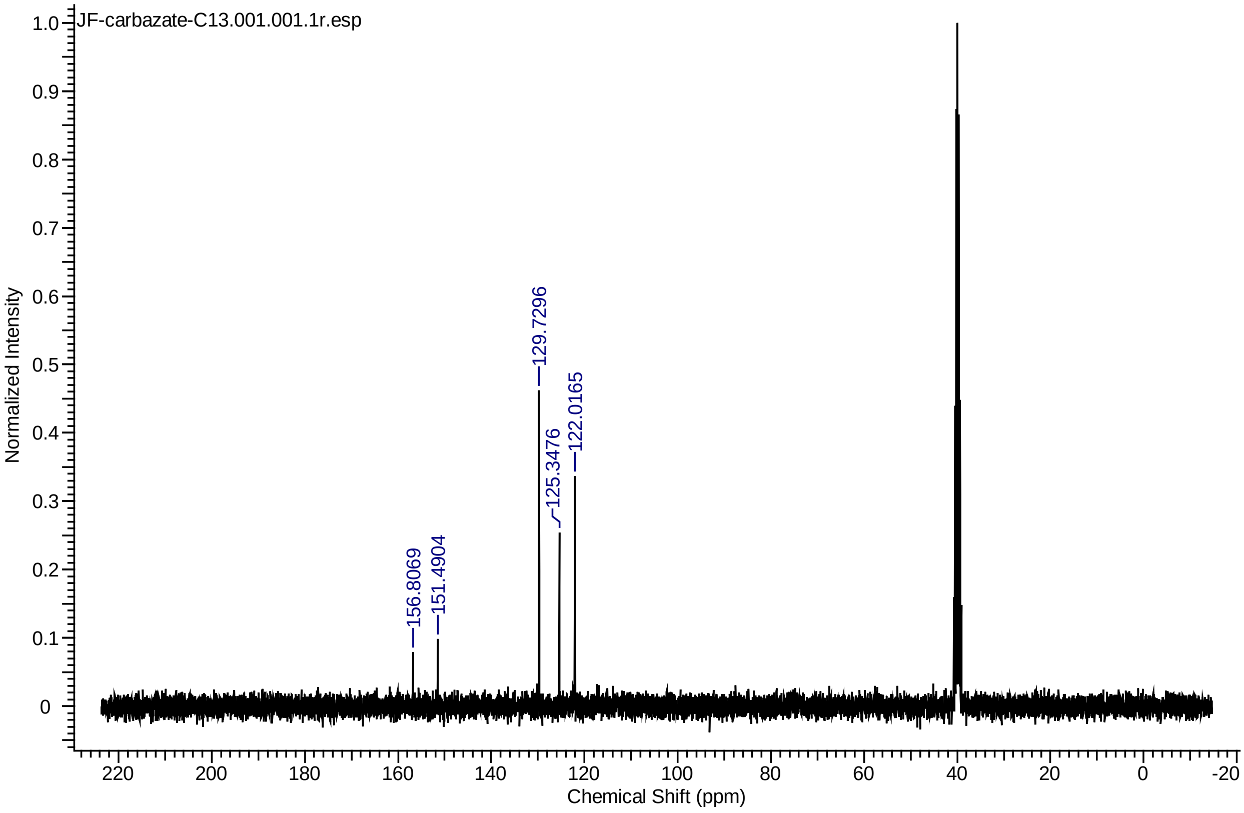
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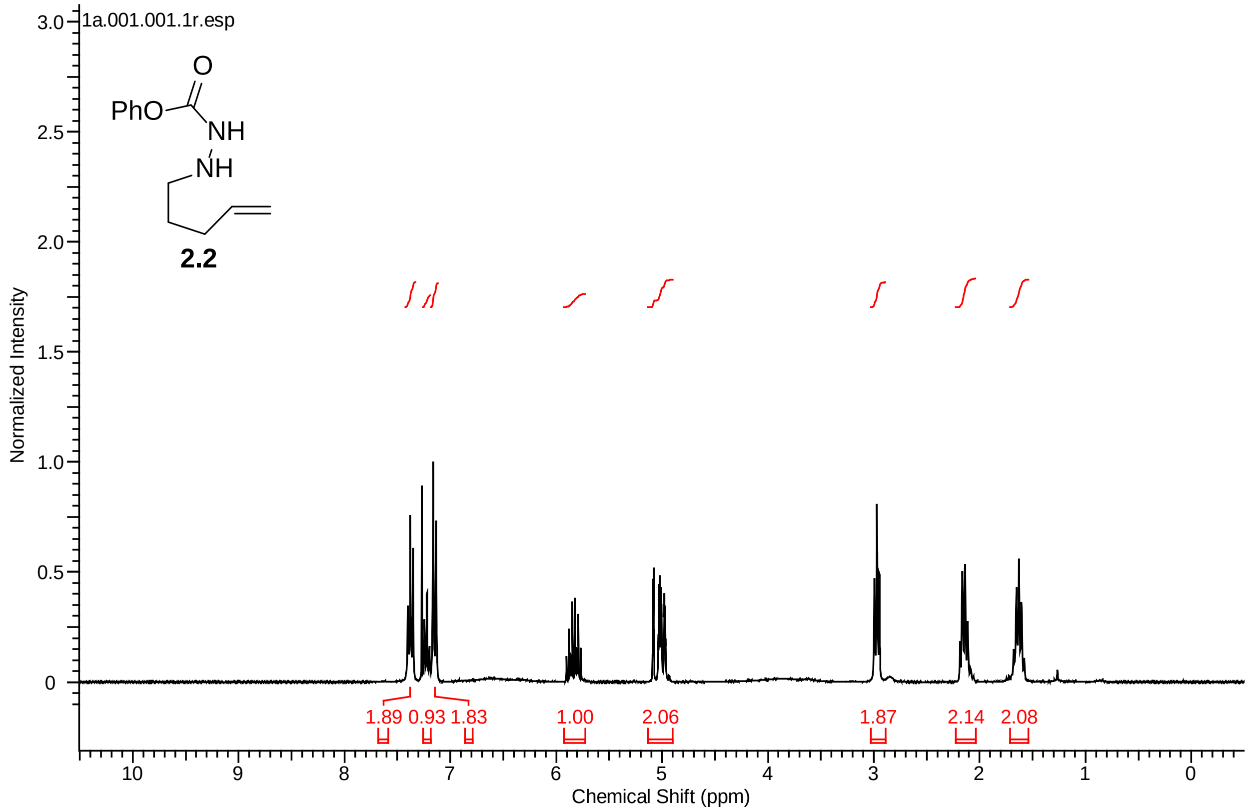
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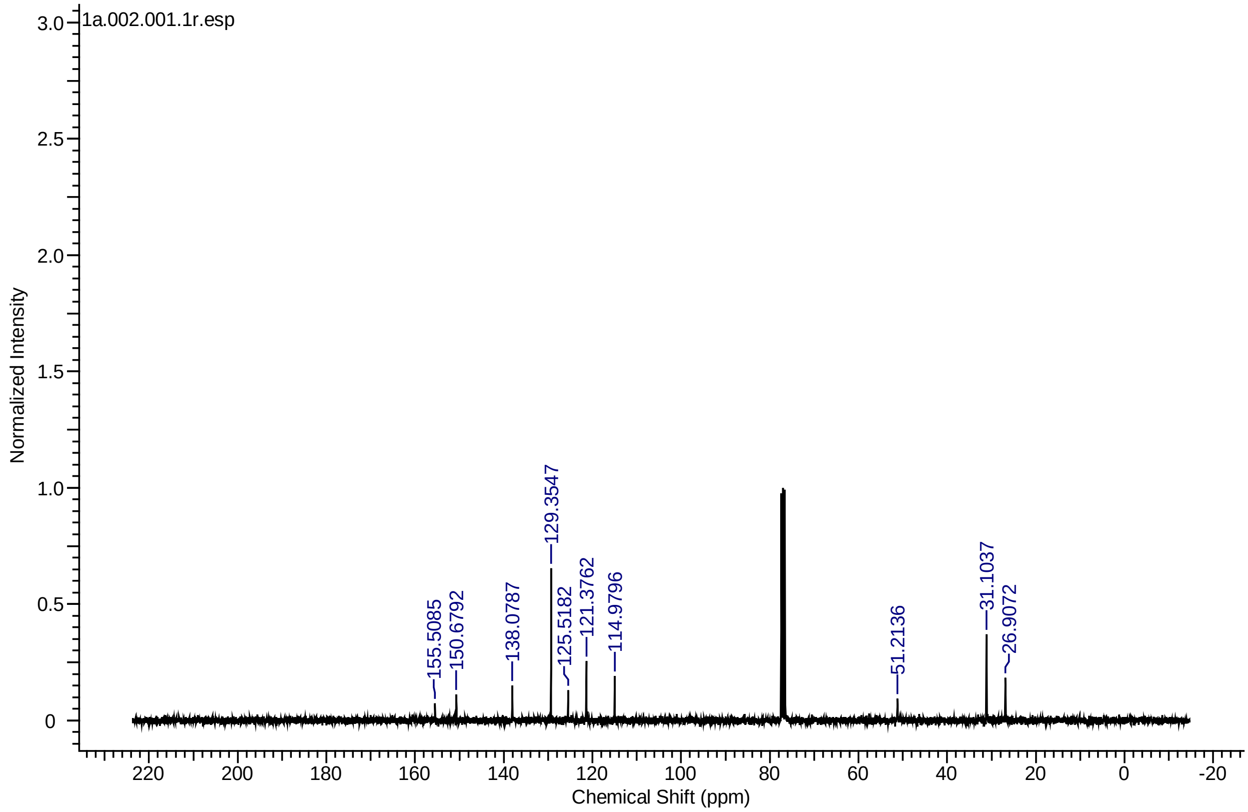
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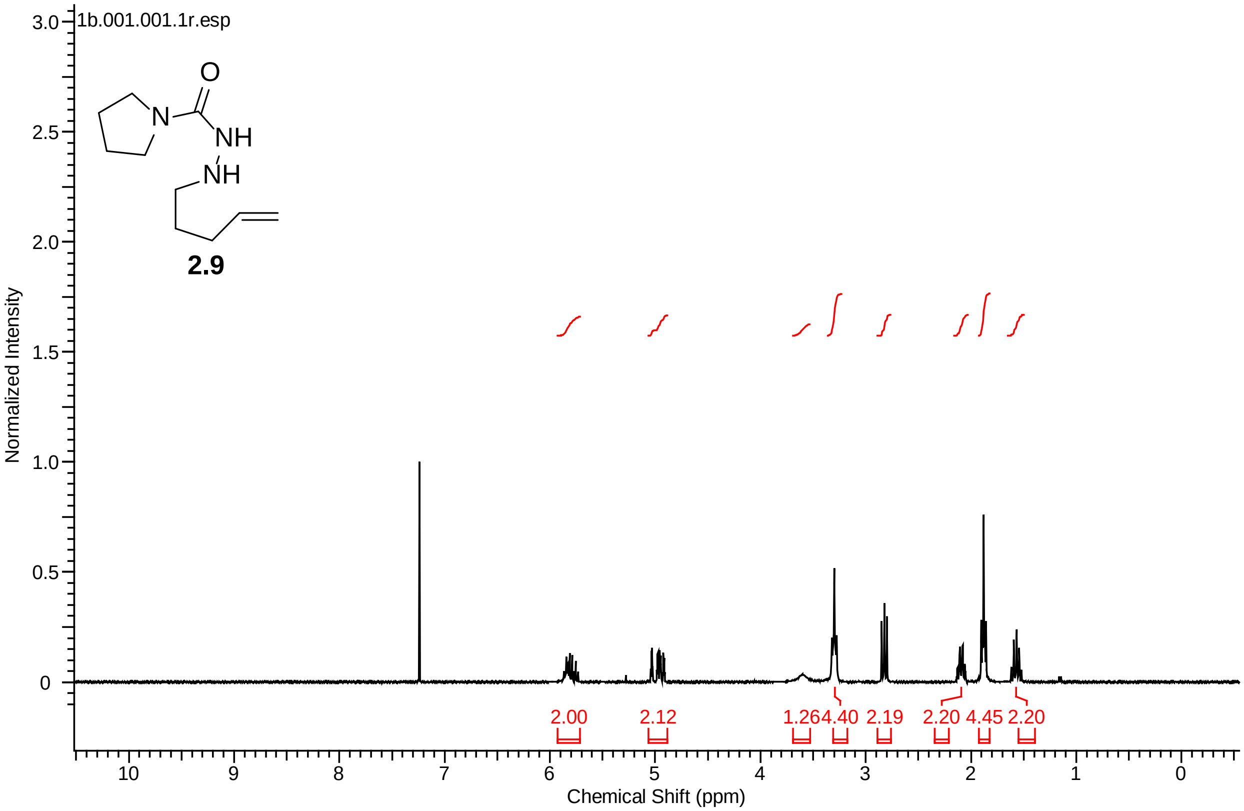
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0.5
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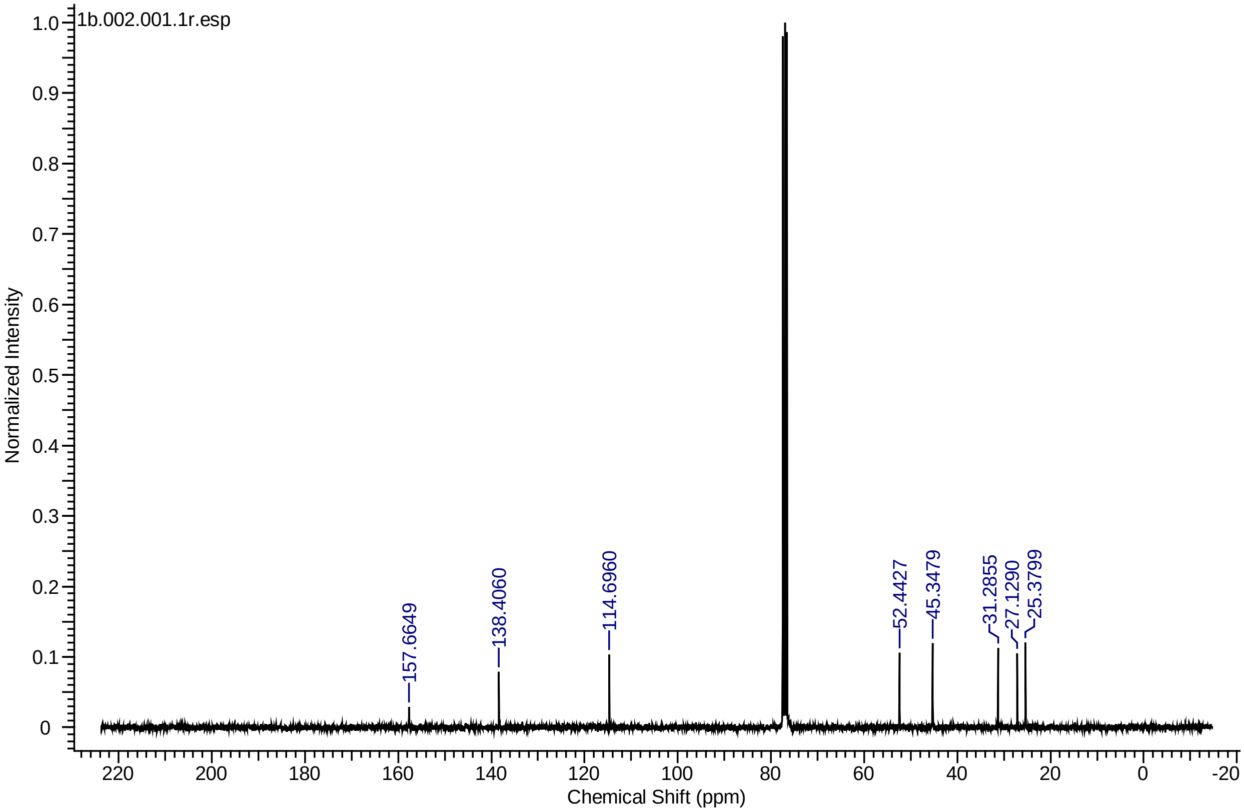
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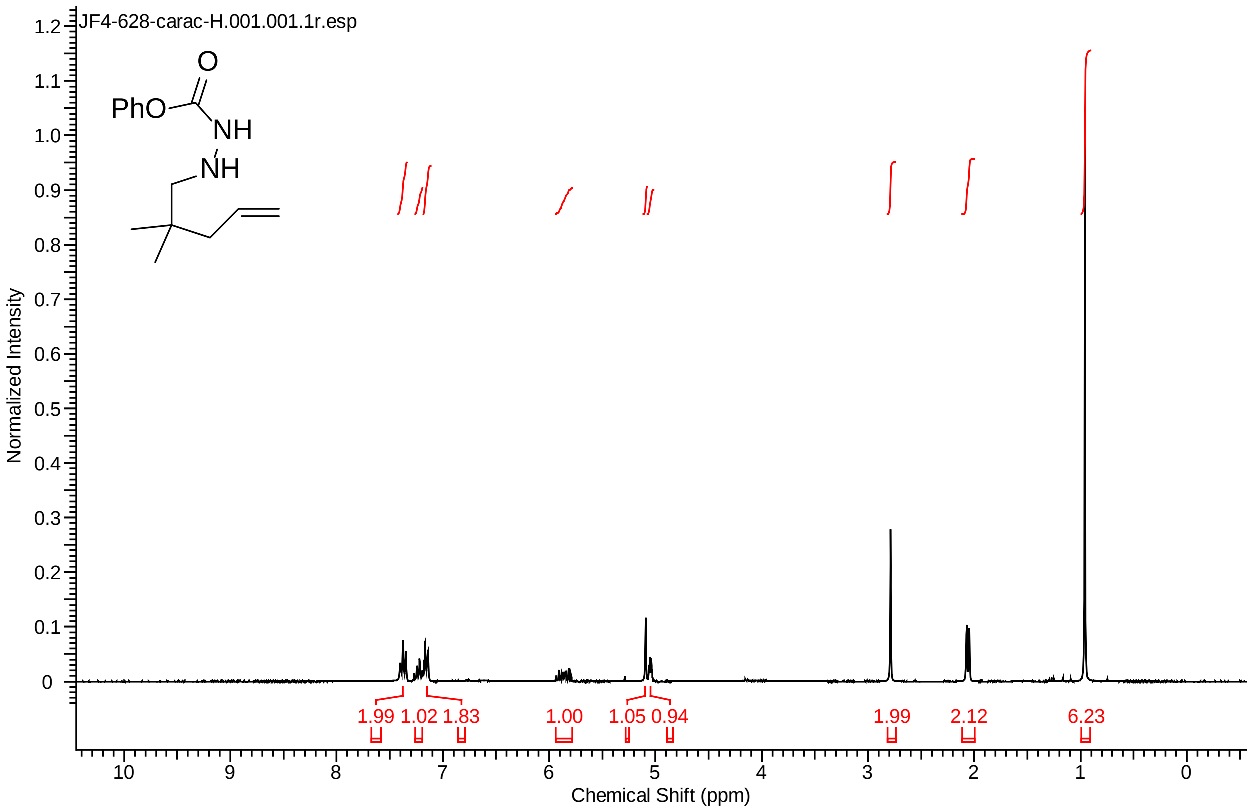
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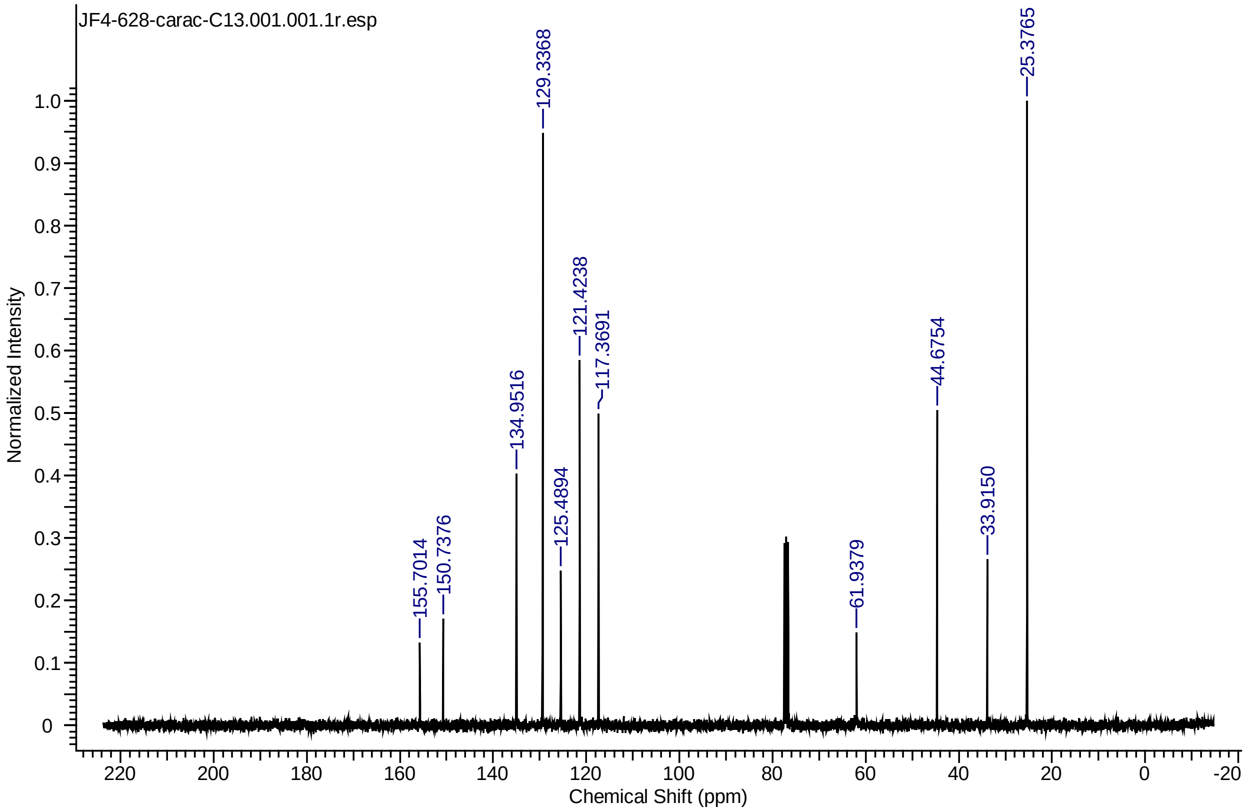
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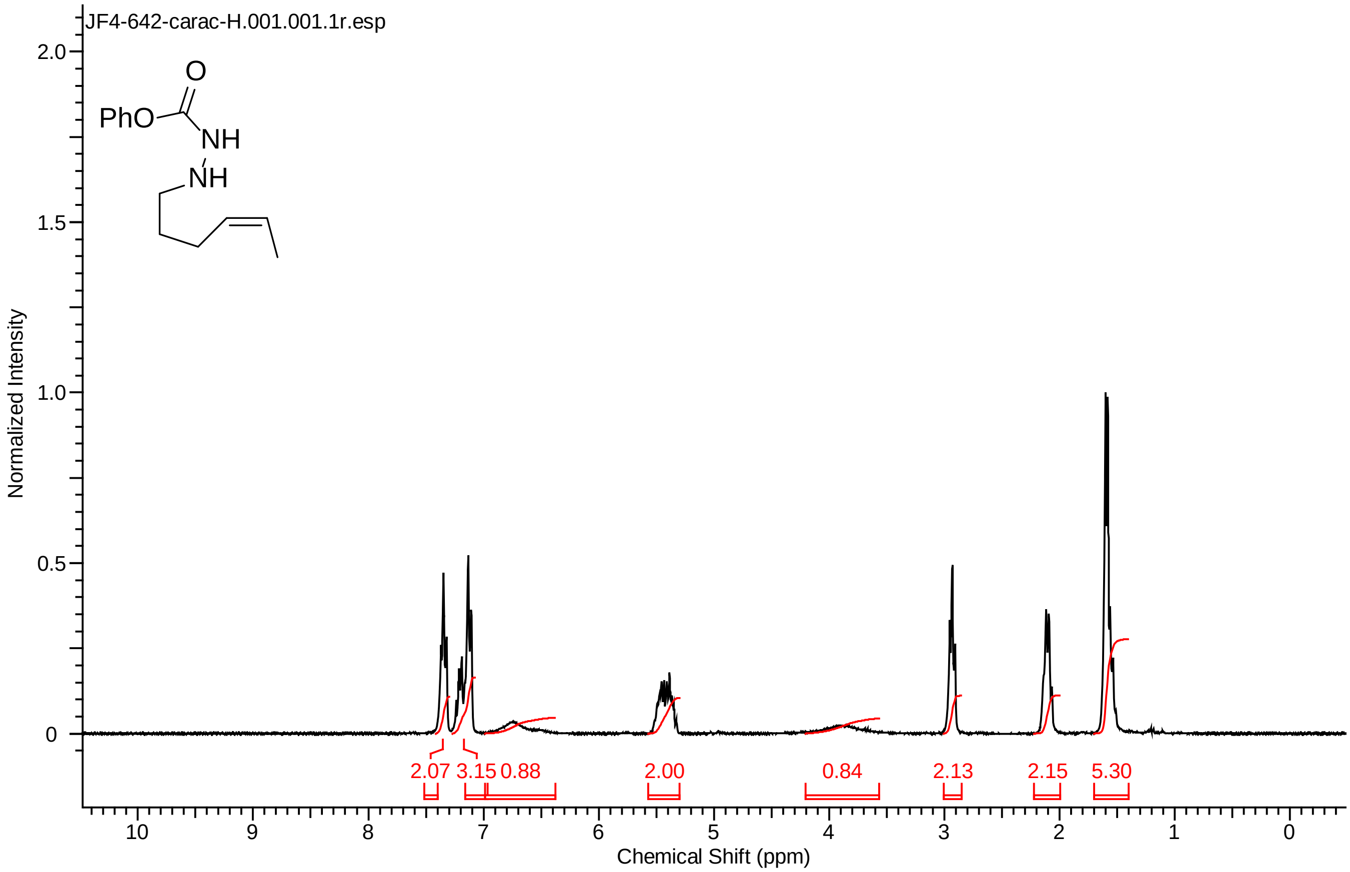
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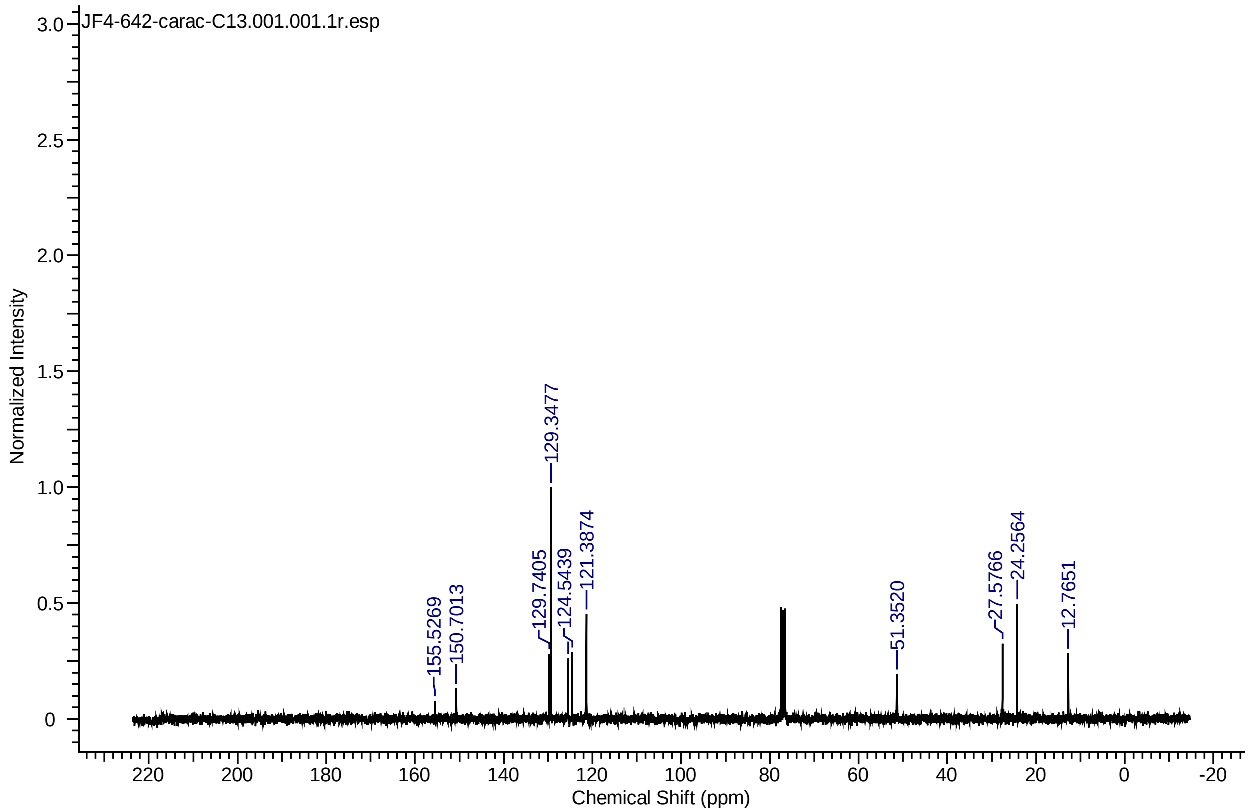
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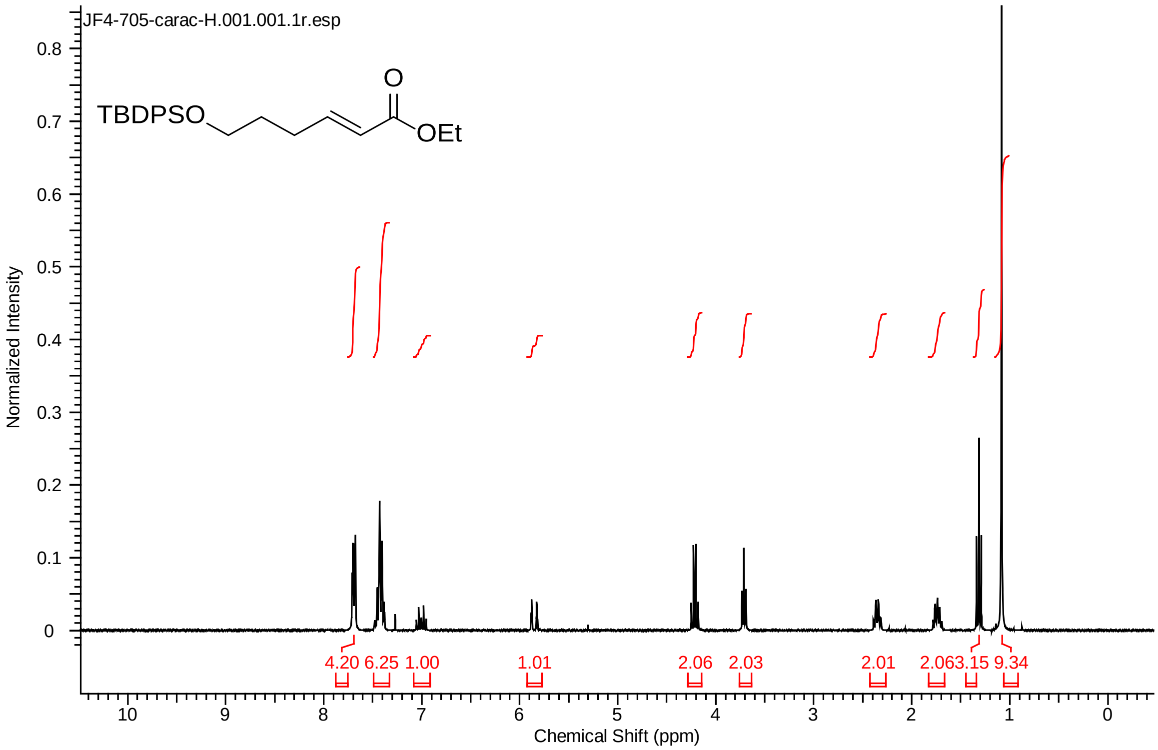
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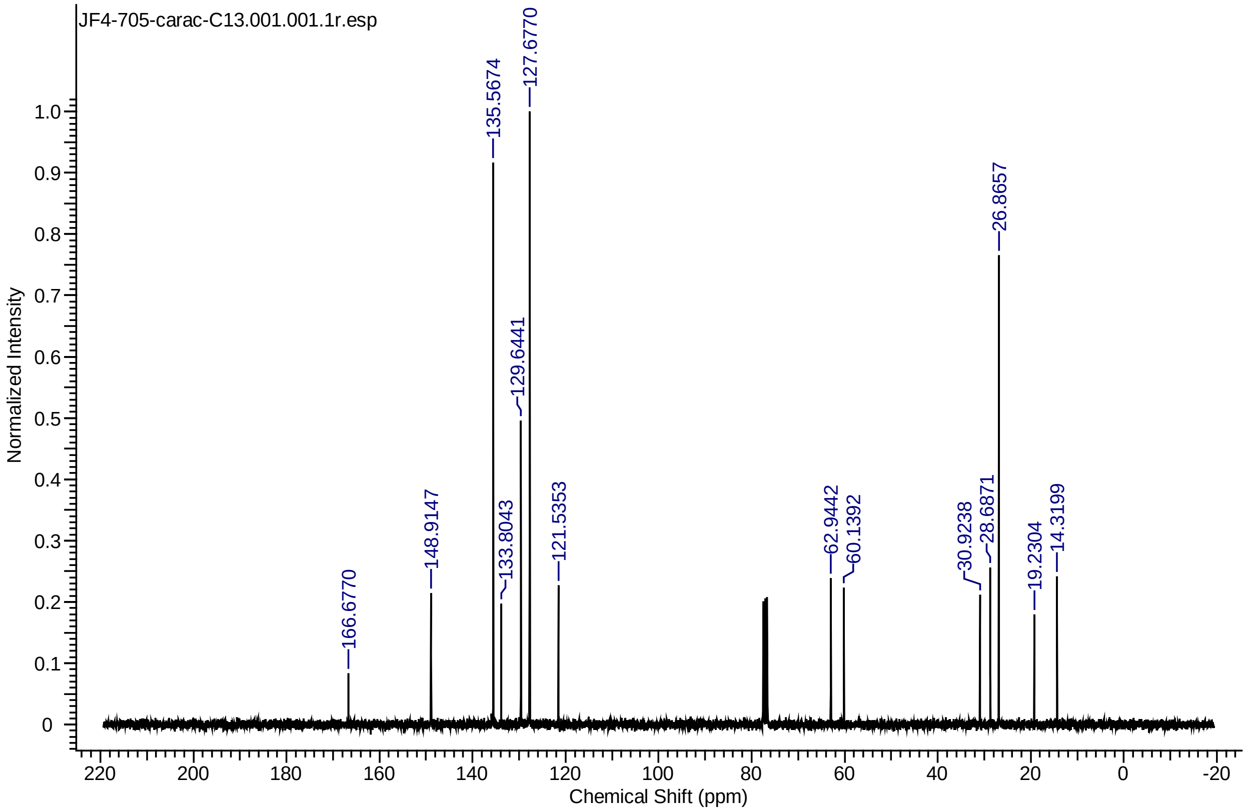
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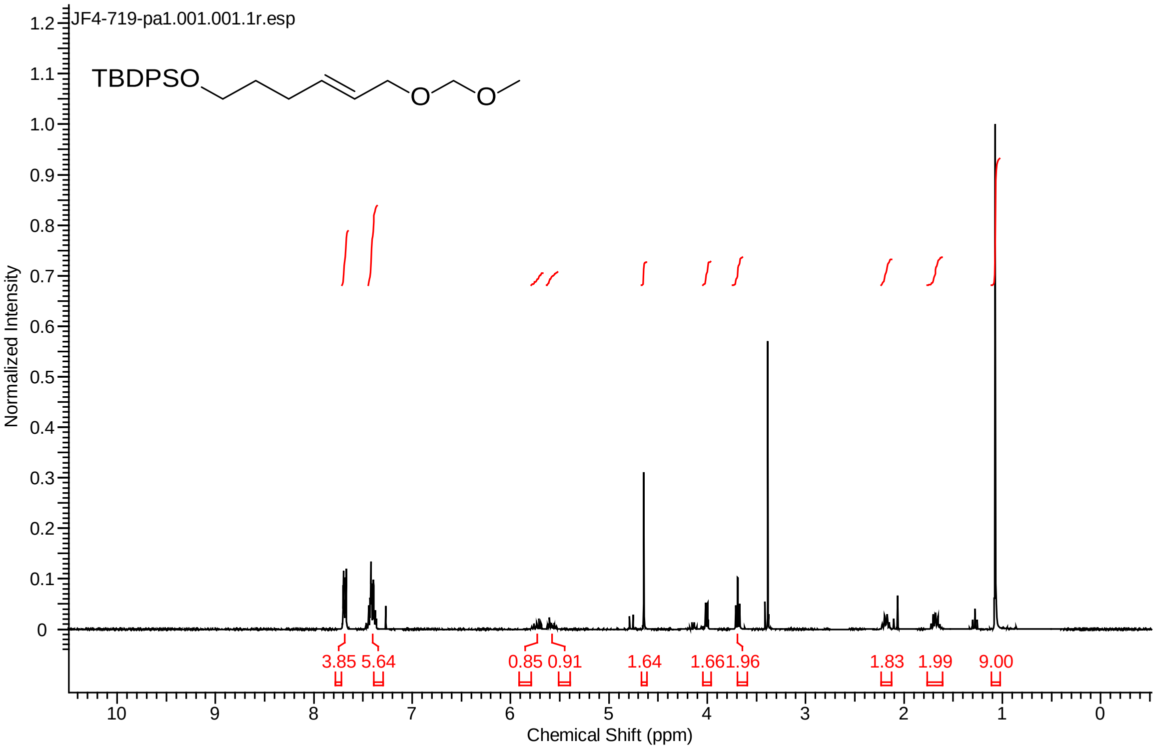
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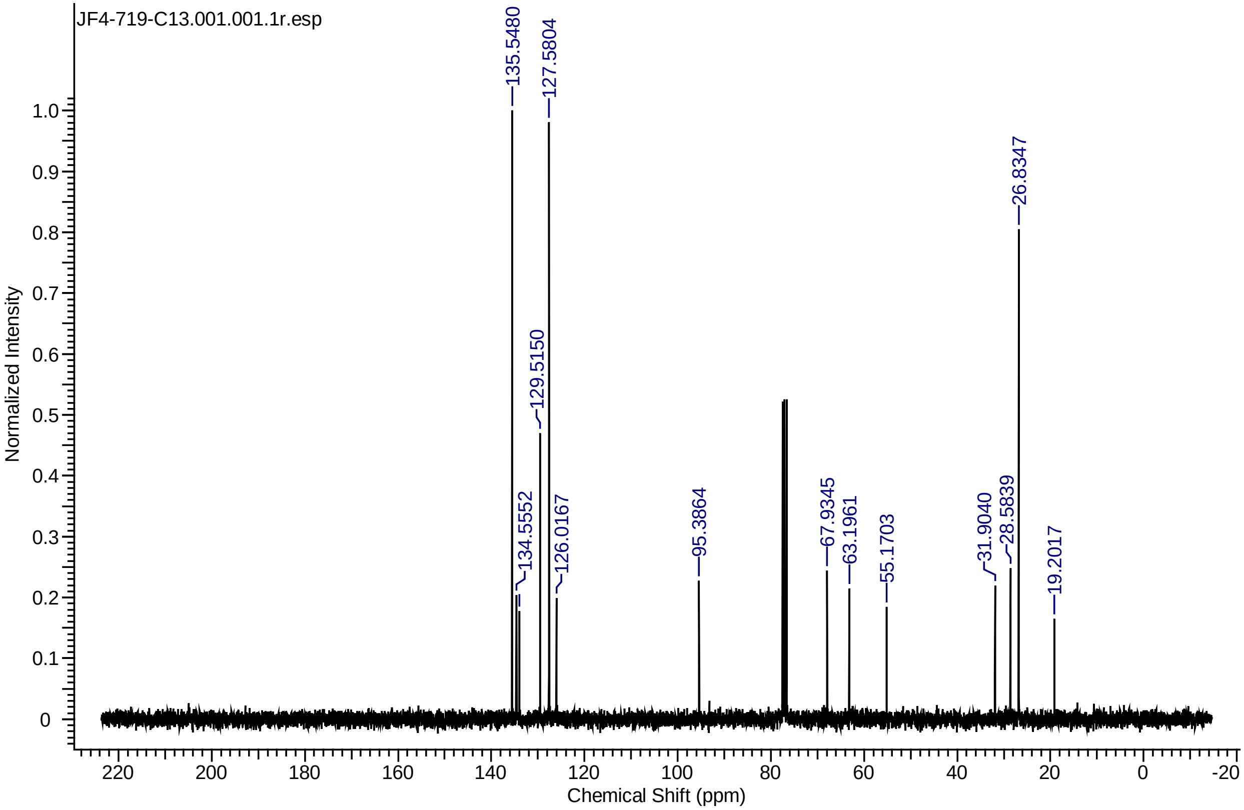
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0.6
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60
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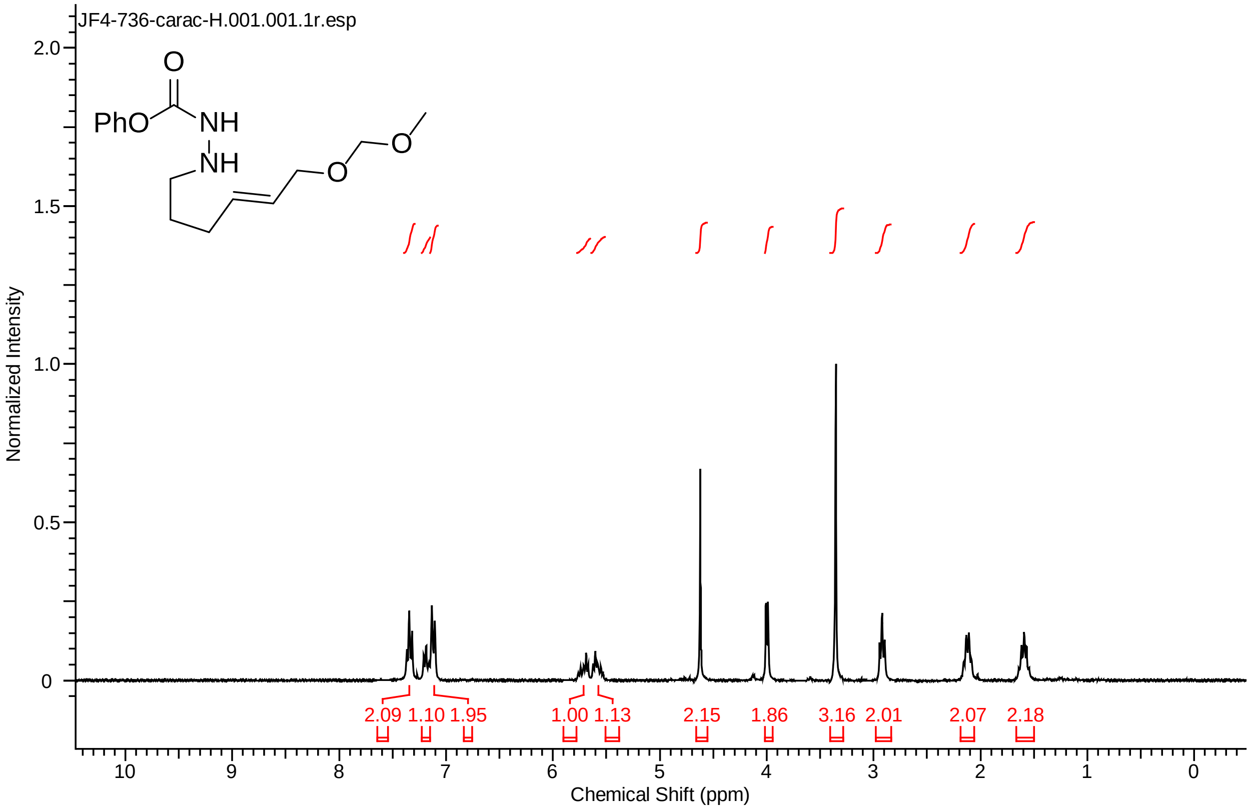
Chemical Shift (ppm)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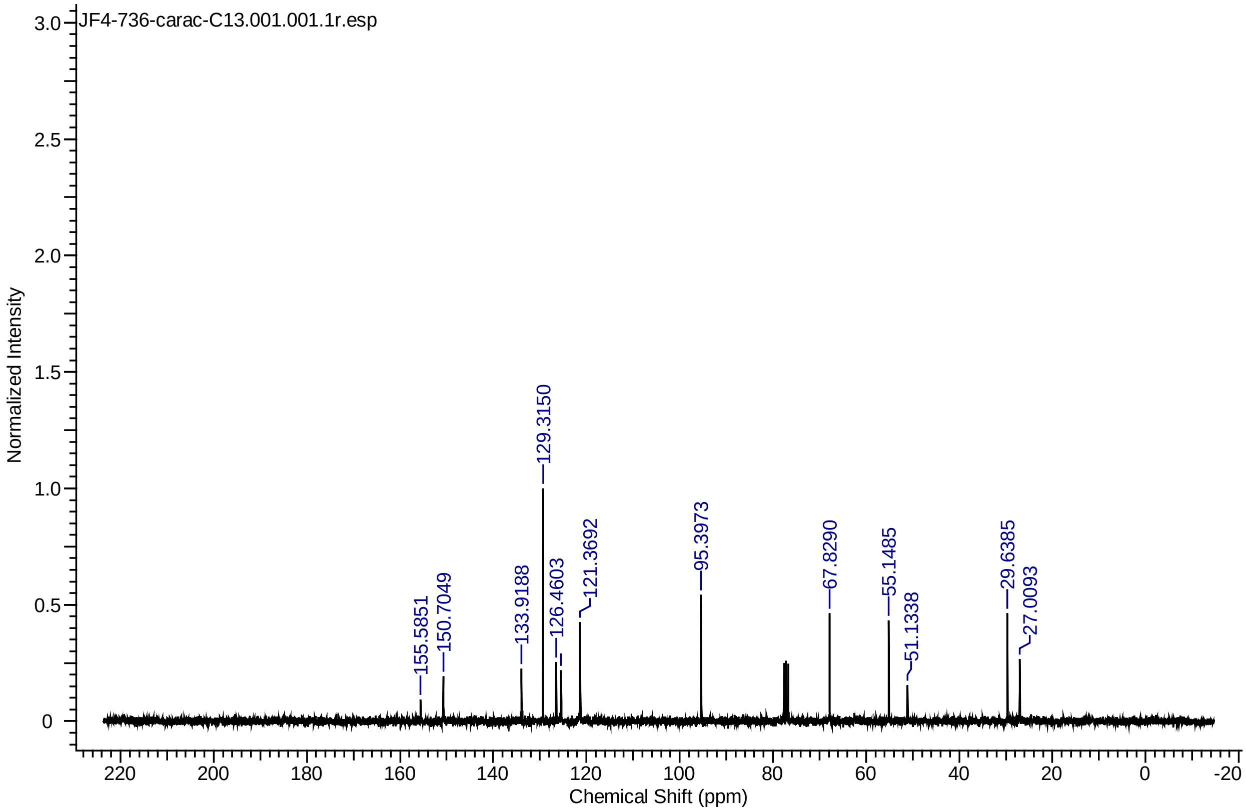
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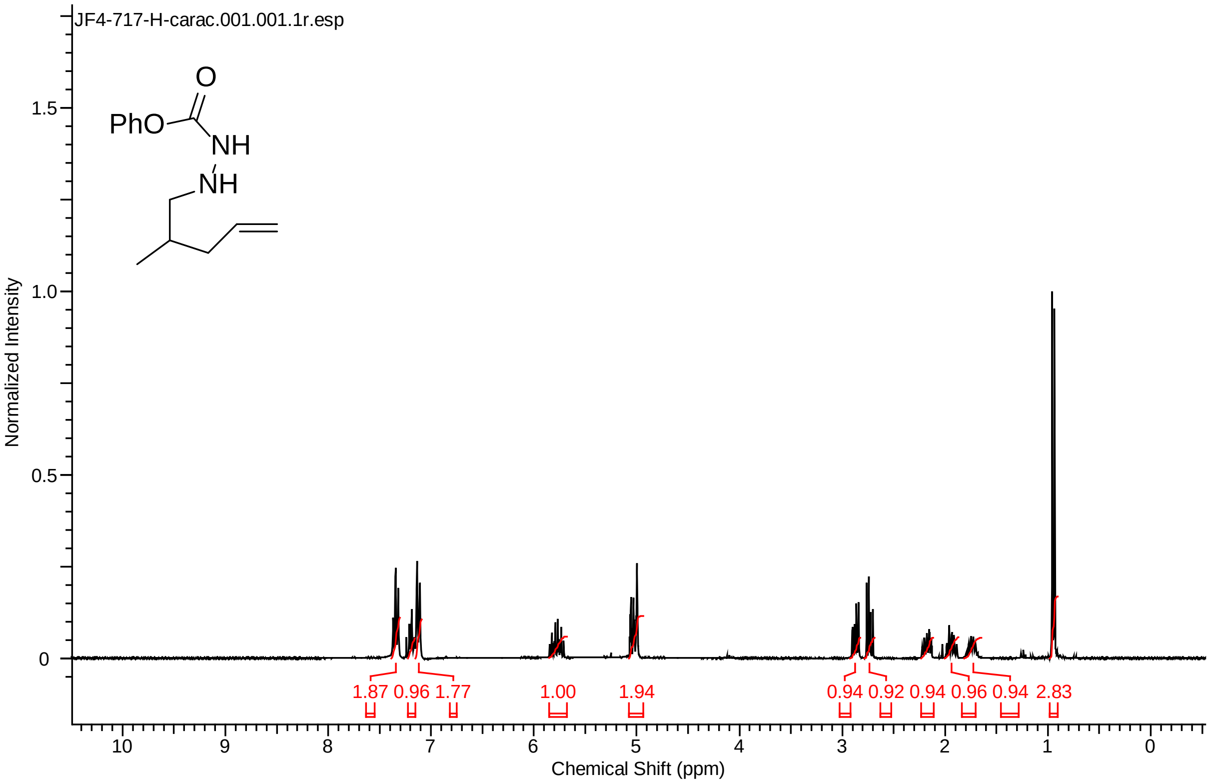
Chemical Shift (ppm)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0.94
0.96
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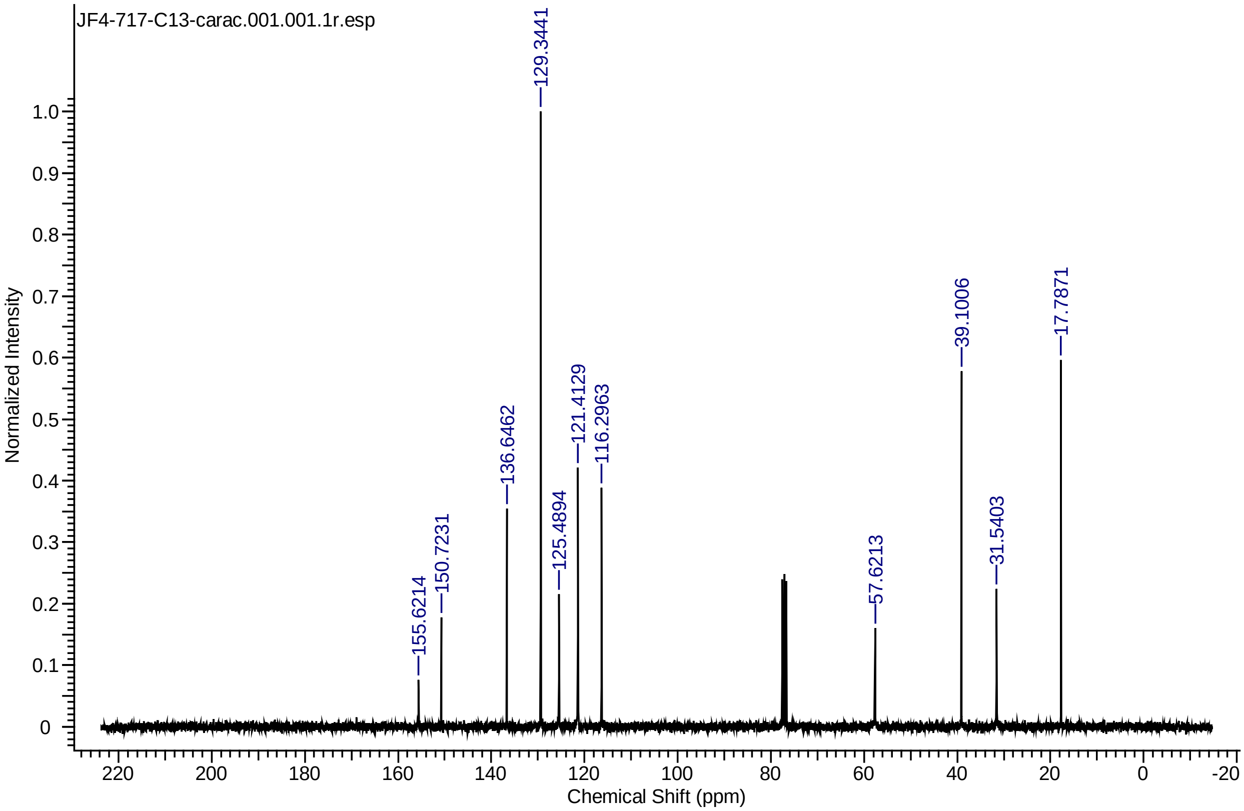
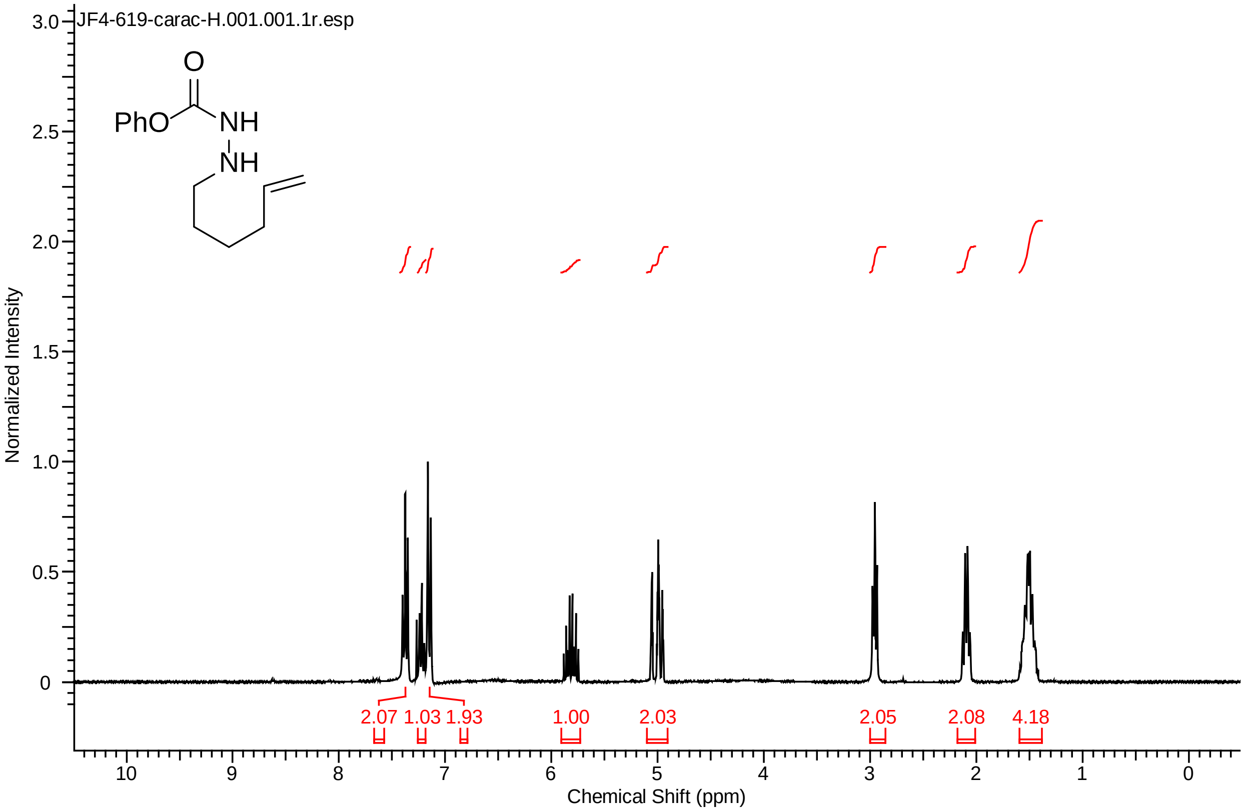
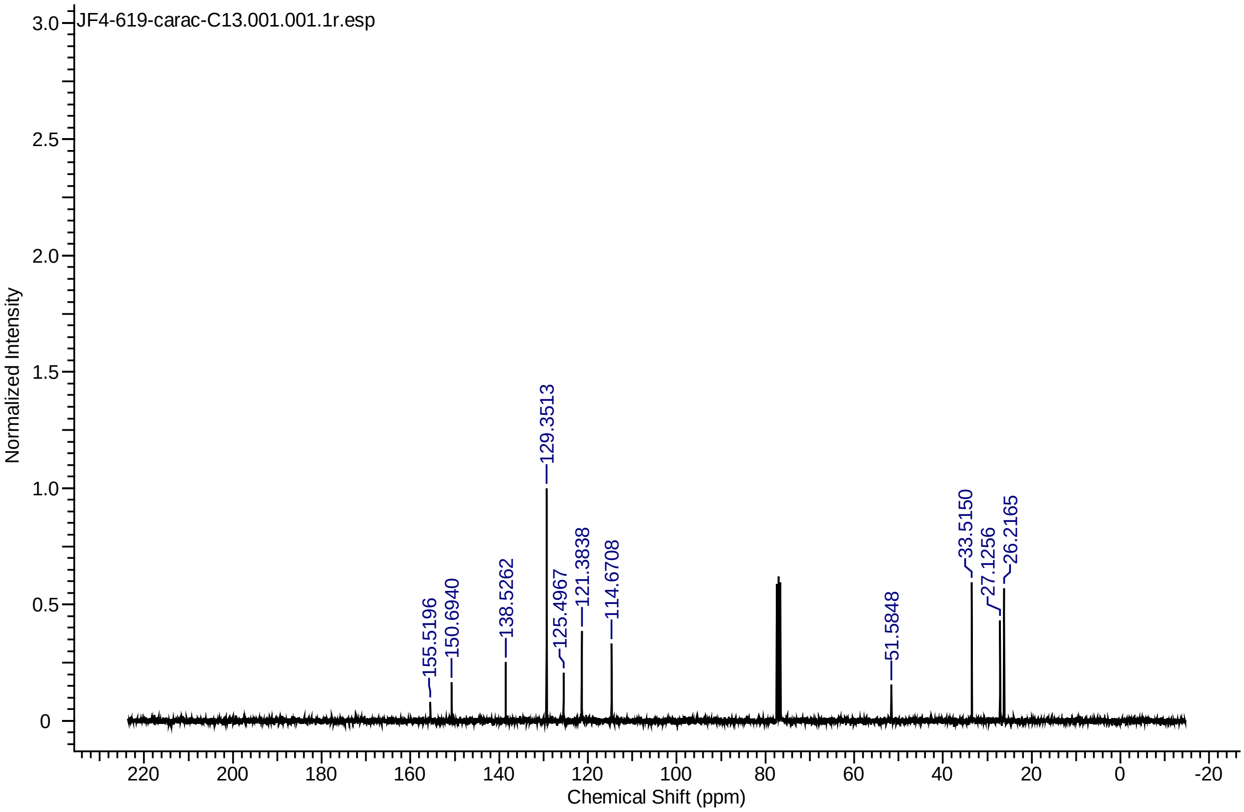
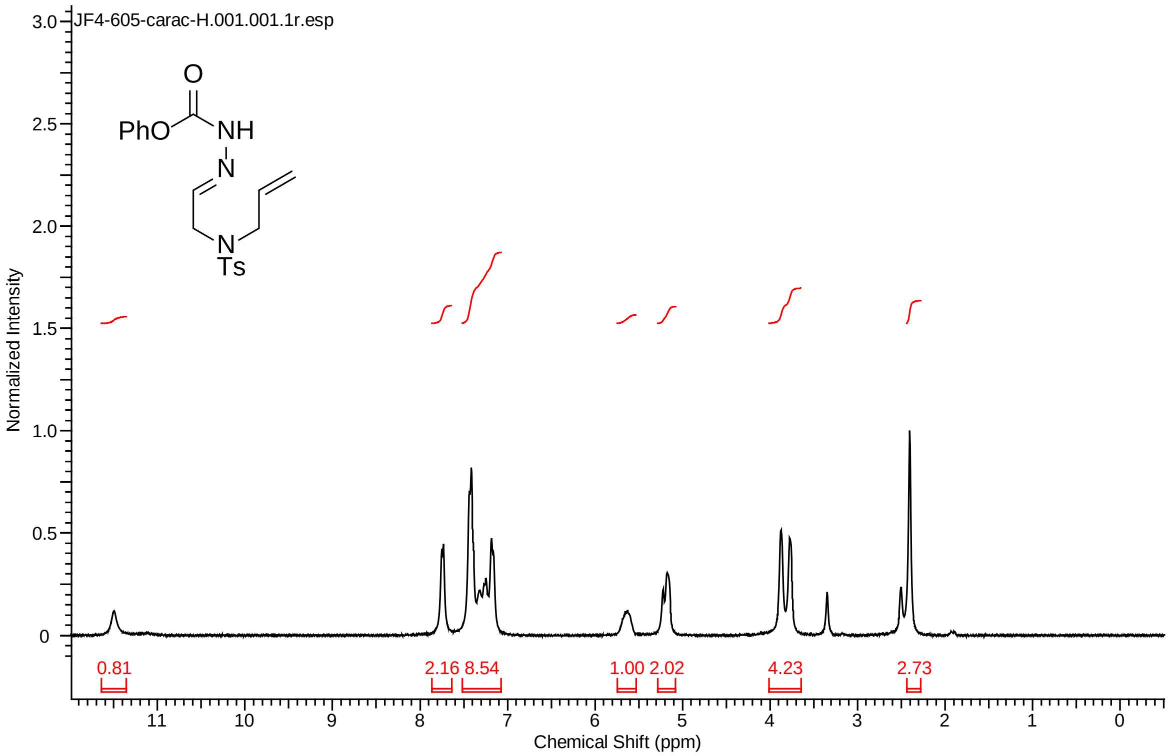
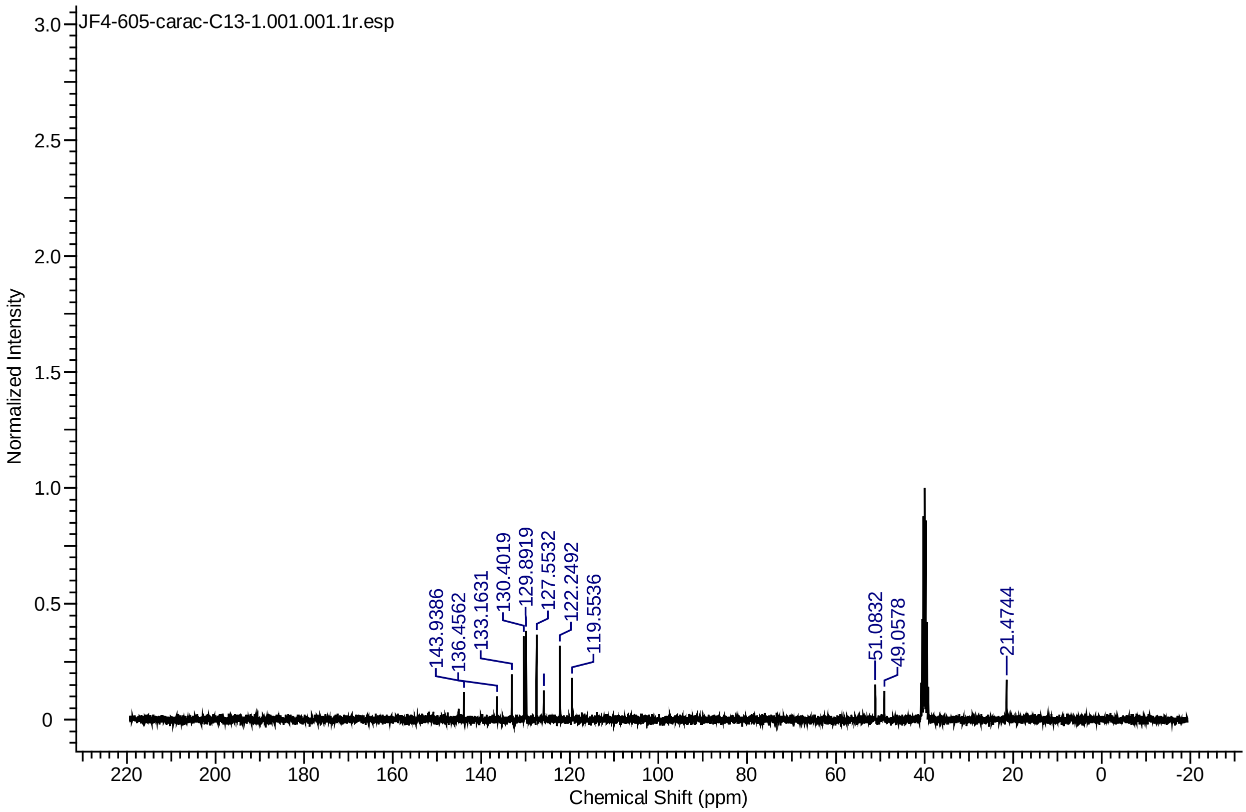
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

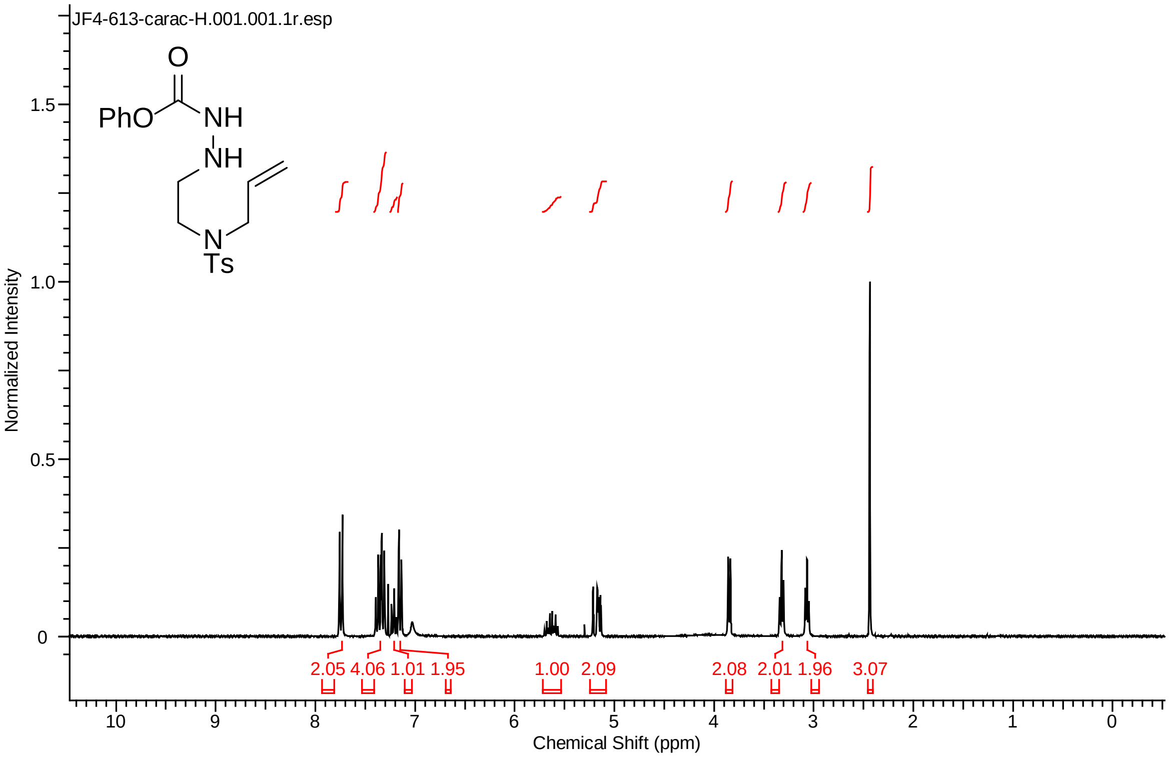

JF4-717-C13-carac.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
155.6214
150.7231
136.6462
129.3441
125.4894
121.4129
116.2963
57.6213
39.1006
31.5403
17.7871
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

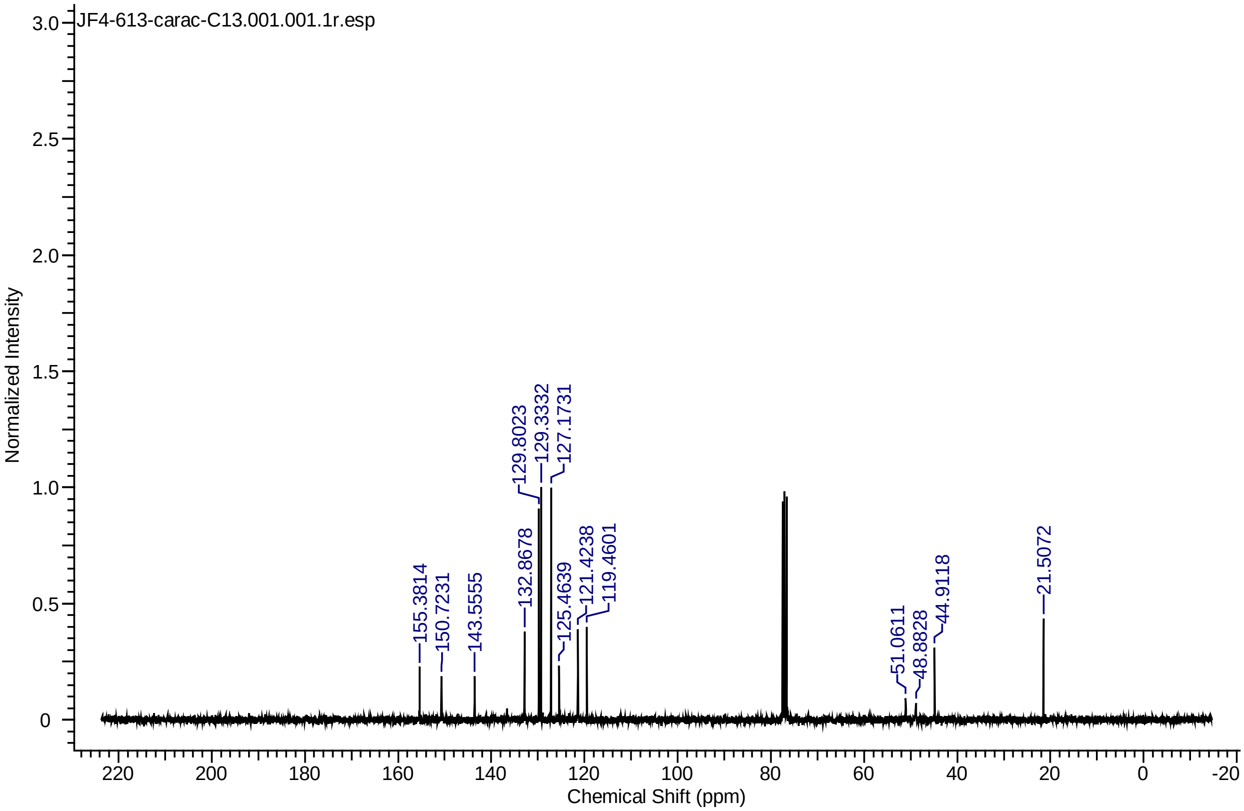

JF4-619-carac-H.001.001.1r.esp
PhO
O
NH
NH
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
2.07
1.03
1.93
1.00
2.03
2.05
2.08
4.18
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

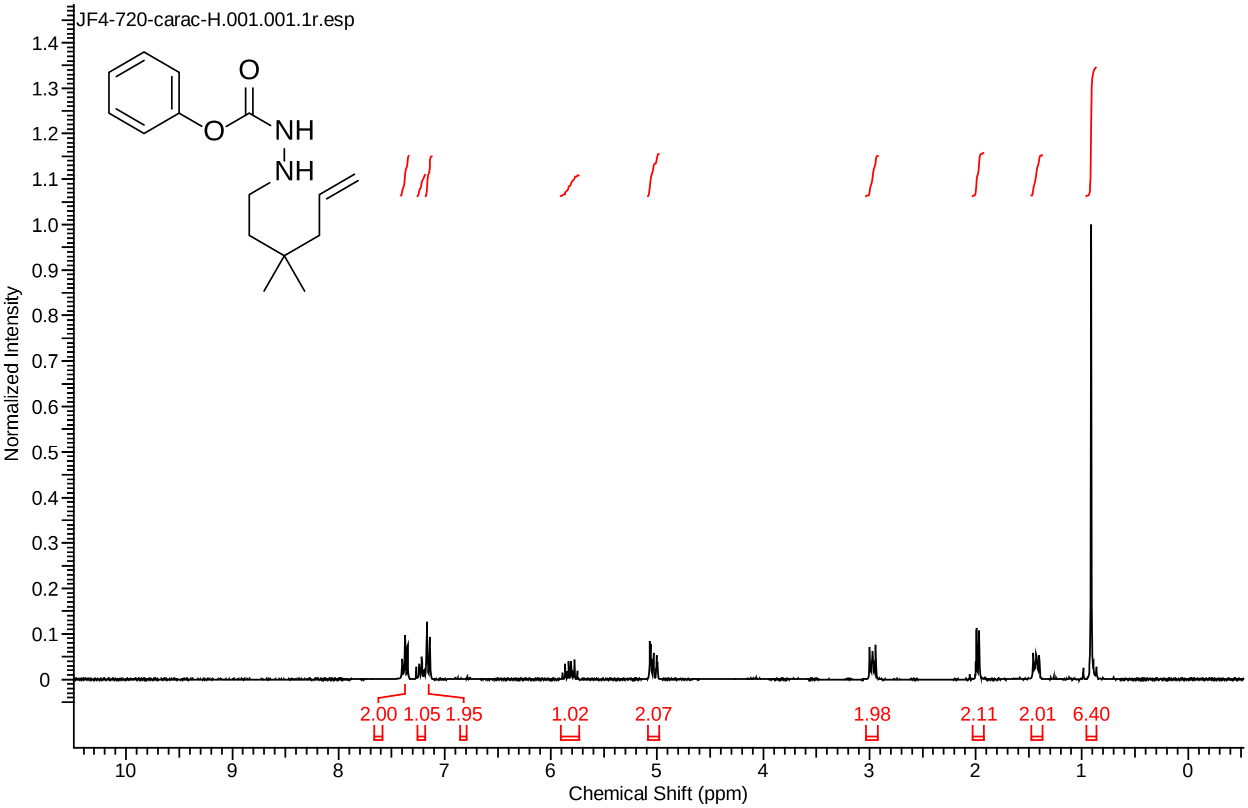

JF4-619-carac-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
155.5196
150.6940
138.5262
129.3513
125.4967
121.3838
114.6708
51.5848
33.5150
27.1256
26.2165
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

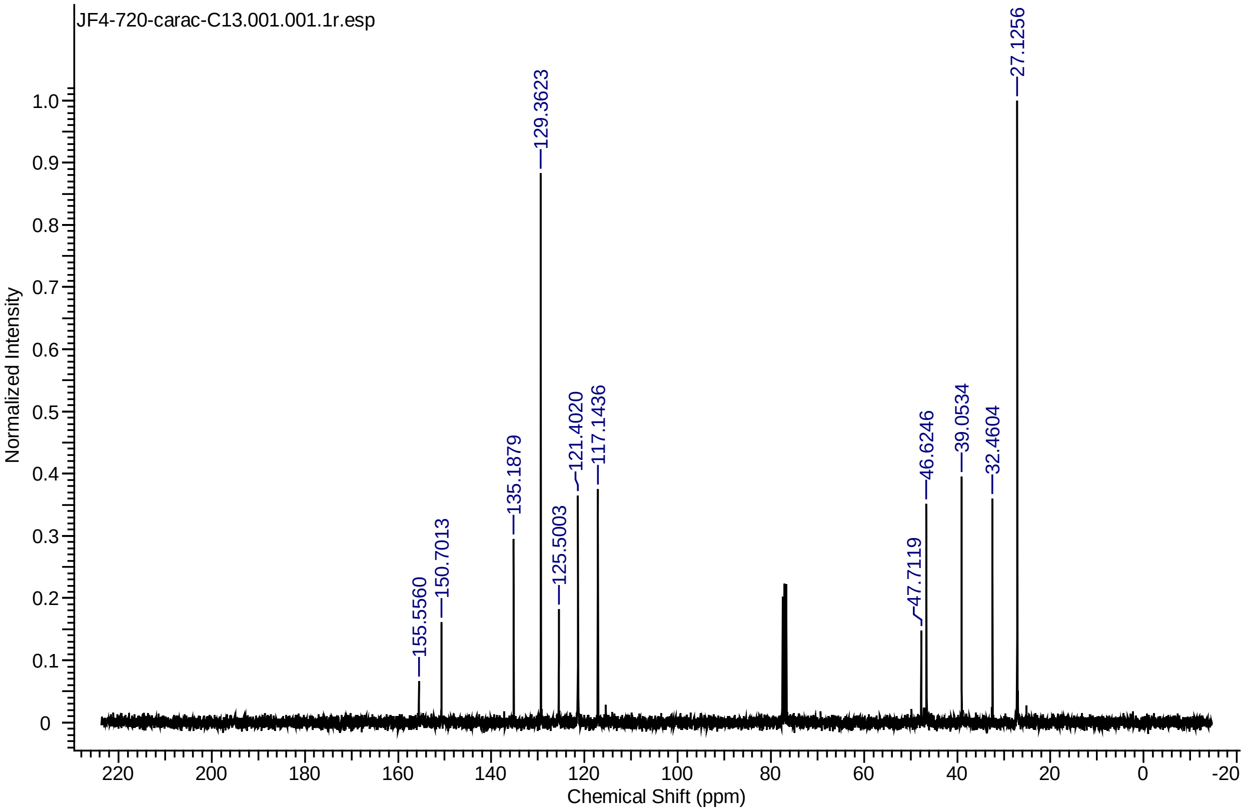

JF4-605-carac-H.001.001.1r.esp
O
PhO
NH
N
N
Ts
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
0.81
2.16
8.54
1.00
2.02
4.23
2.73
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

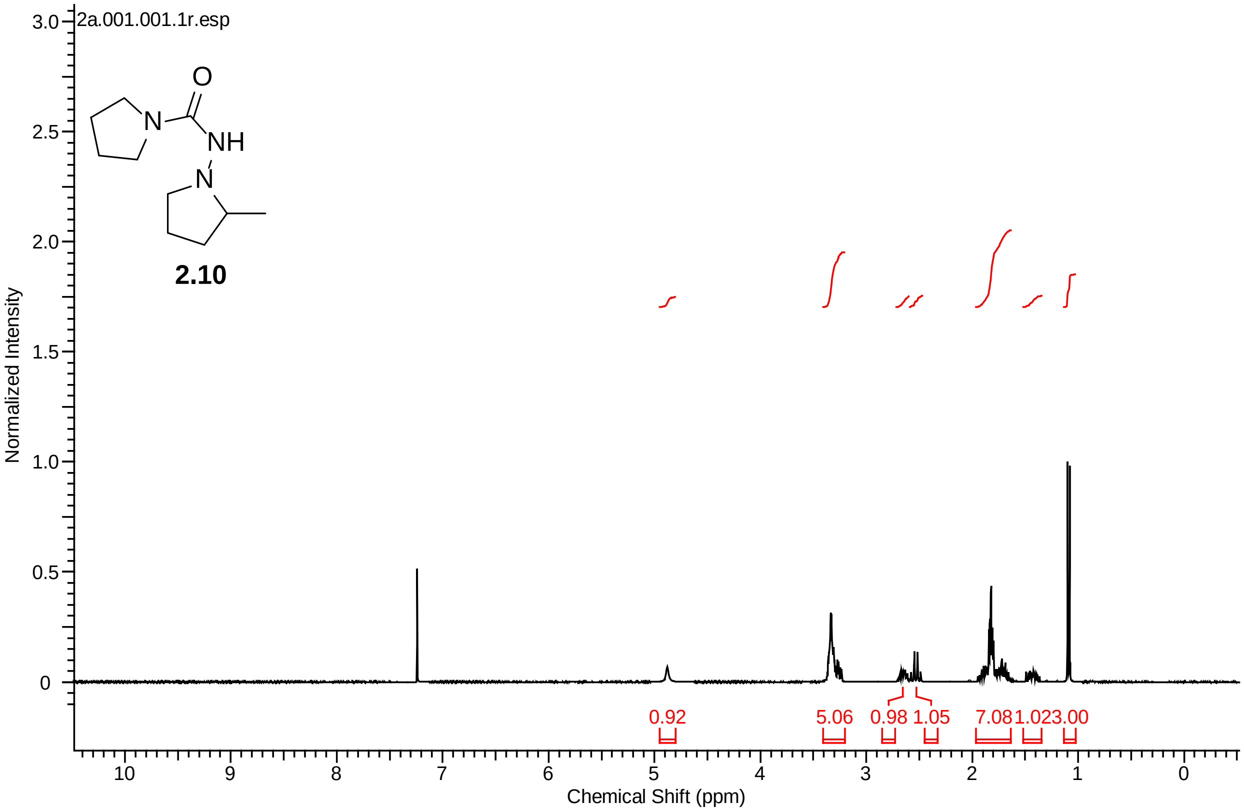

JF4-605-carac-C13-1.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
143.9386
136.4562
133.1631
130.4019
129.8919
127.5532
122.2492
119.5536
51.0832
49.0578
21.4744
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

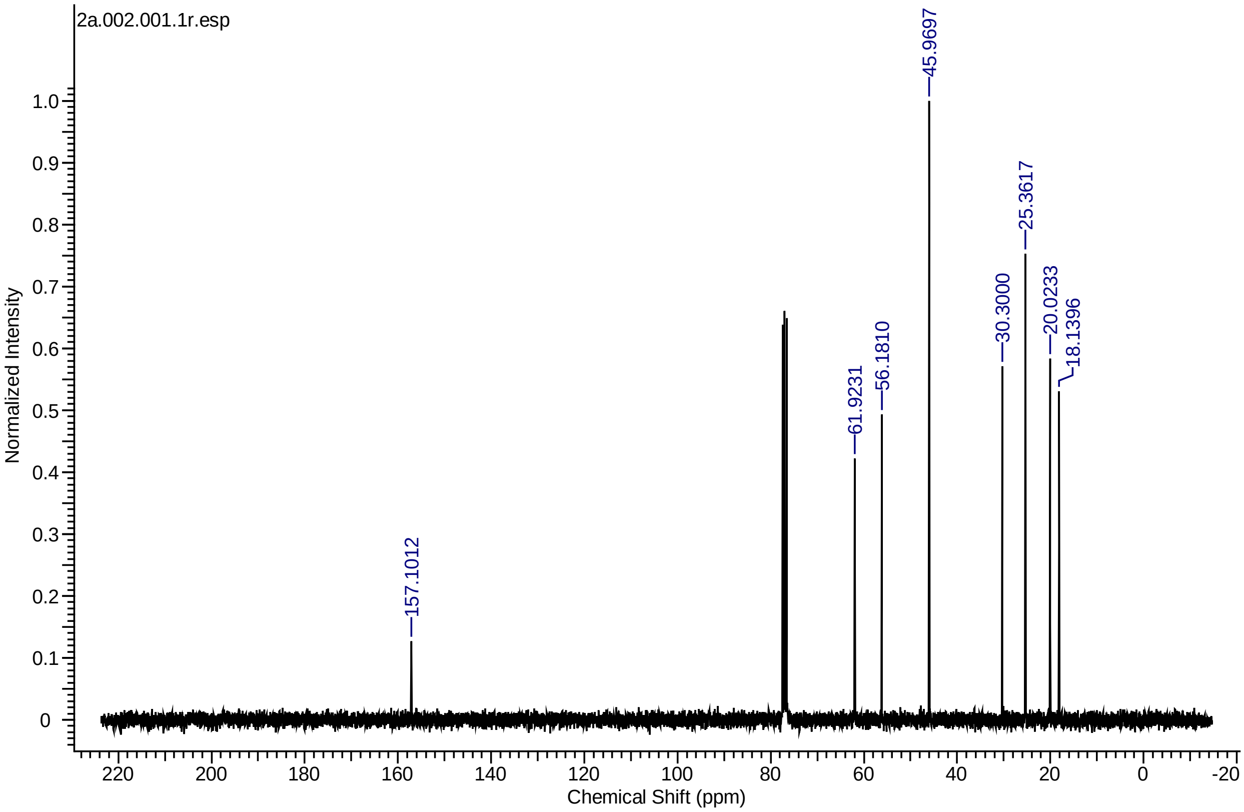

JF4-613-carac-H.001.001.1r.esp
O
PhO
NH
NH
N
Ts
Normalized Intensity
1.5
1.0
0.5
0
2.05
4.06
1.01
1.95
1.00
2.09
2.08
2.01
1.96
3.07
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

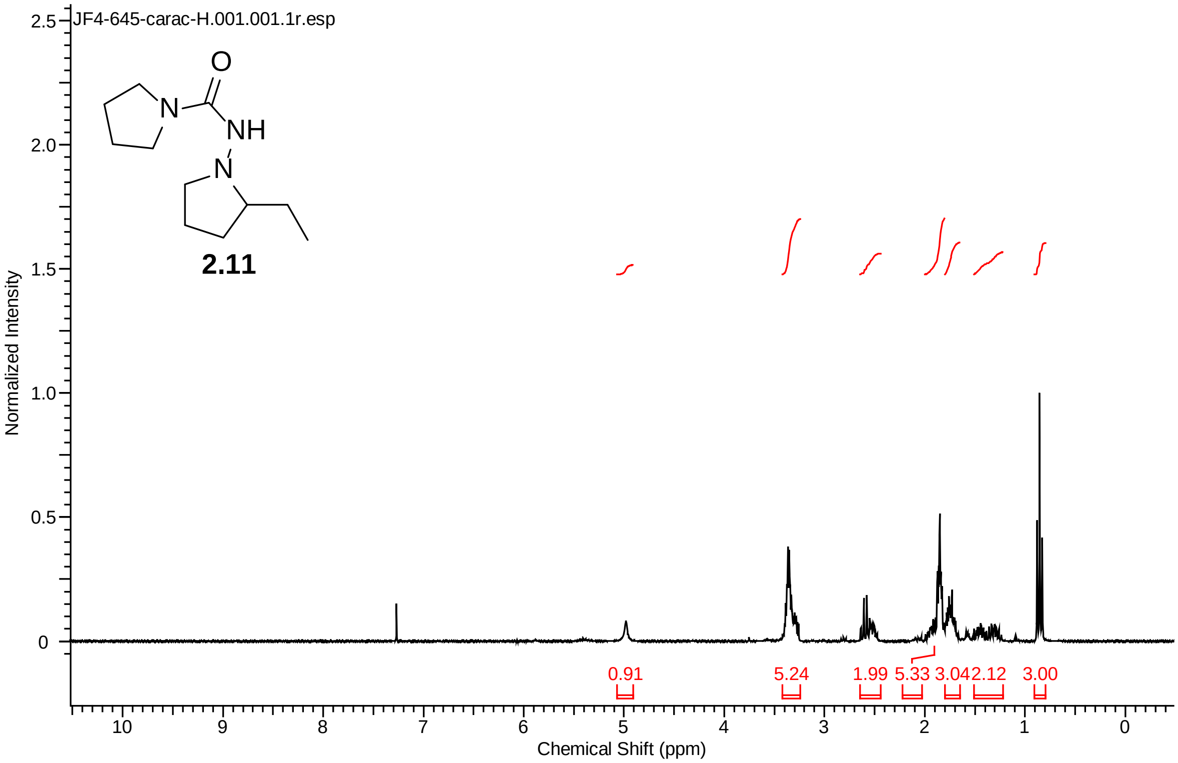

JF4-613-carac-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
155.3814
150.7231
143.5555
132.8678
129.8023
129.3332
127.1731
125.4639
121.4238
119.4601
51.0611
48.8828
44.9118
21.5072
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

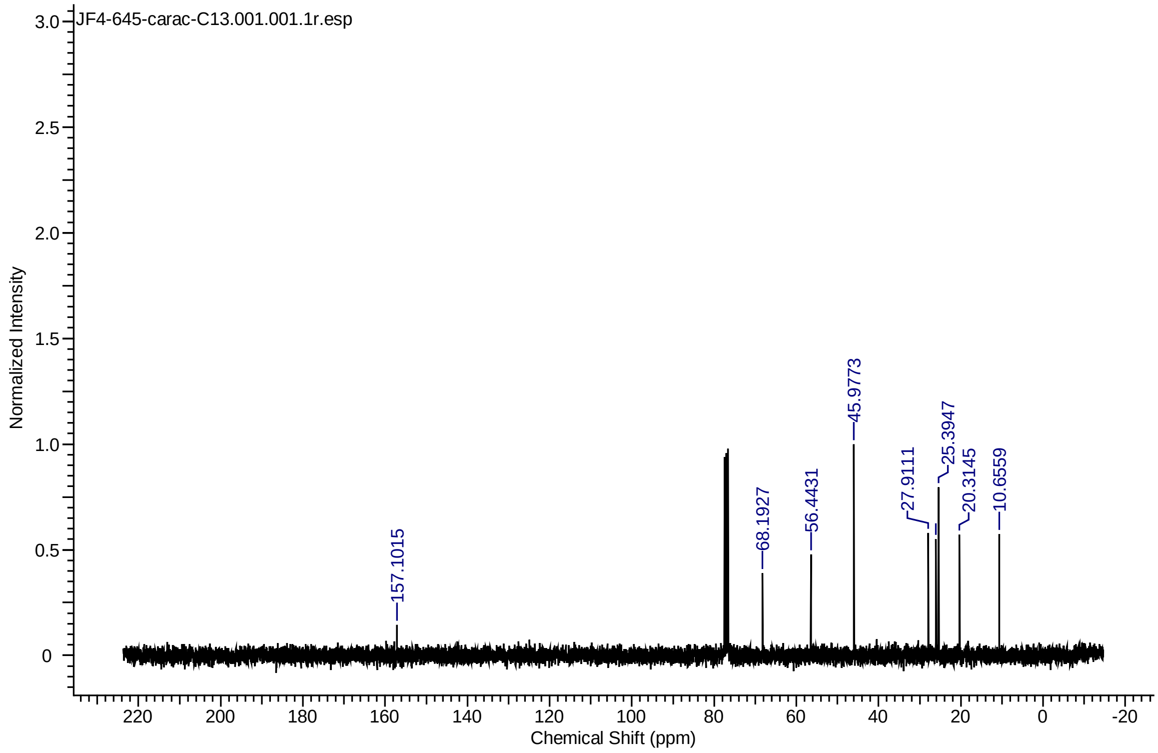

JF4-720-carac-H.001.001.1r.esp
O
O
NH
NH
Normalized Intensity
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2.00
1.05
1.95
1.02
2.07
1.98
2.11
2.01
6.40
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

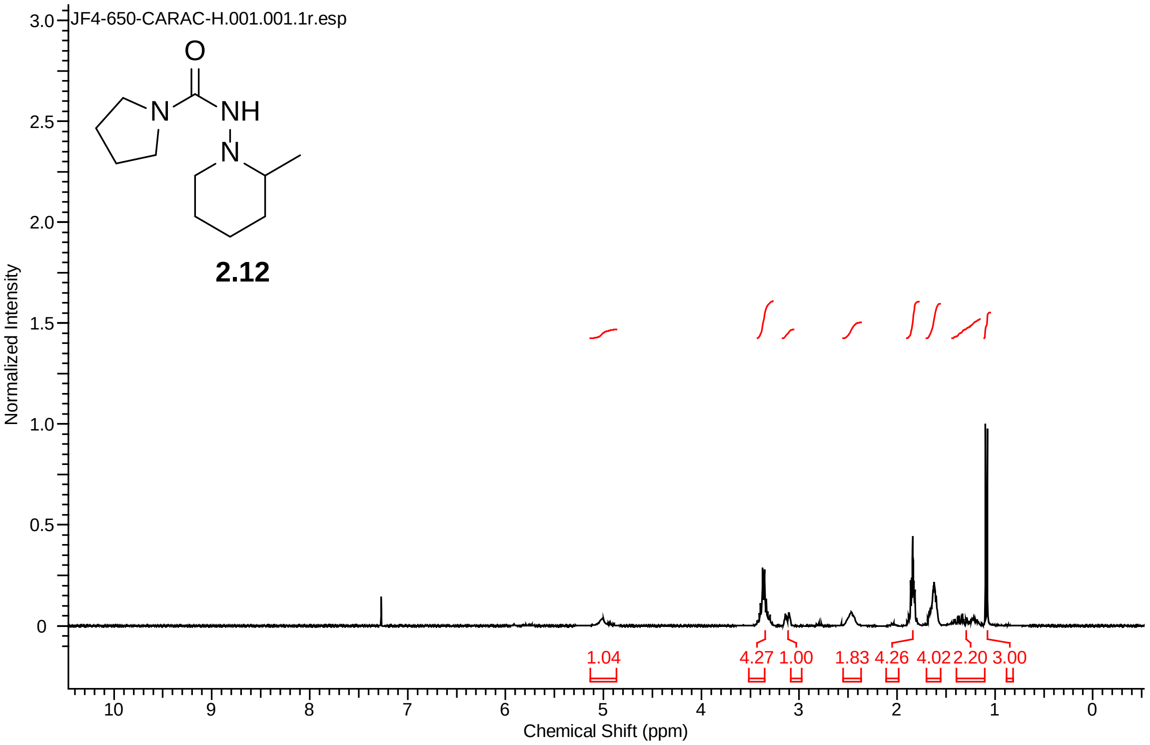

JF4-720-carac-C13.001.001.1r.esp
155.5560
150.7013
135.1879
129.3623
125.5003
121.4020
117.1436
47.7119
46.6246
39.0534
32.4604
27.1256
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

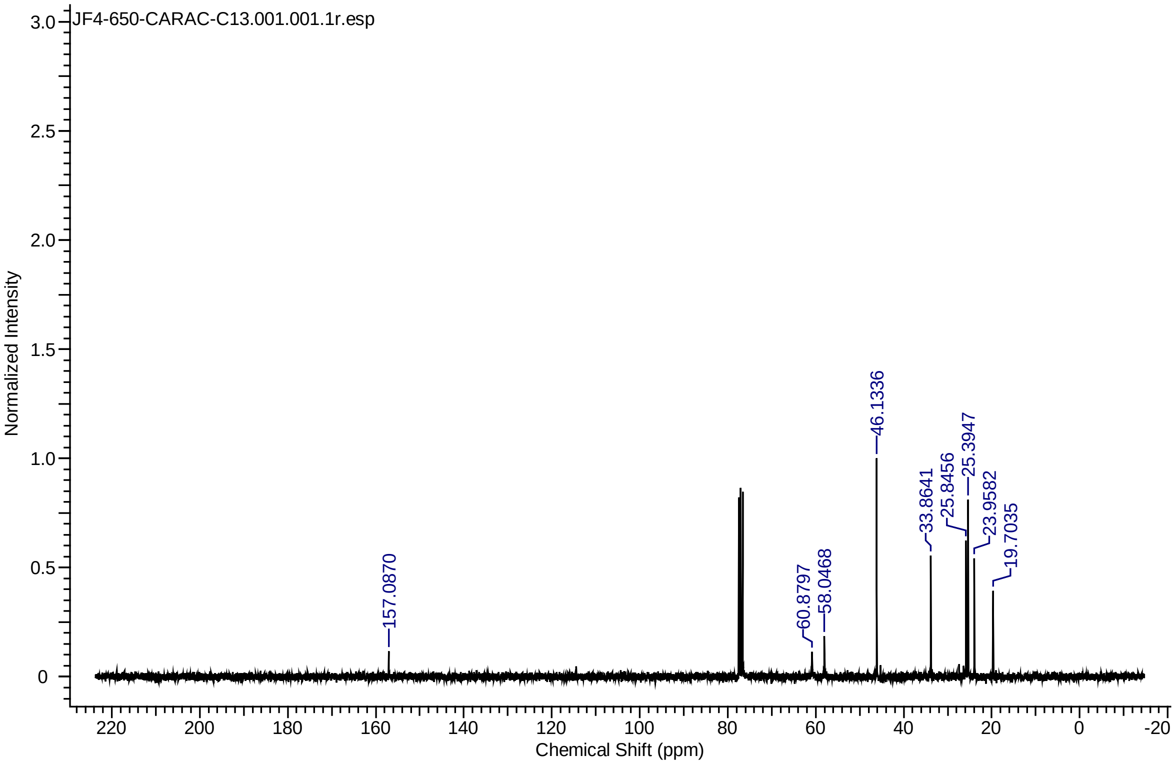

2.10
2a.001.001.1r.esp
O
N
NH
N
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
0.92
5.06
0.98
1.05
7.08
1.02
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

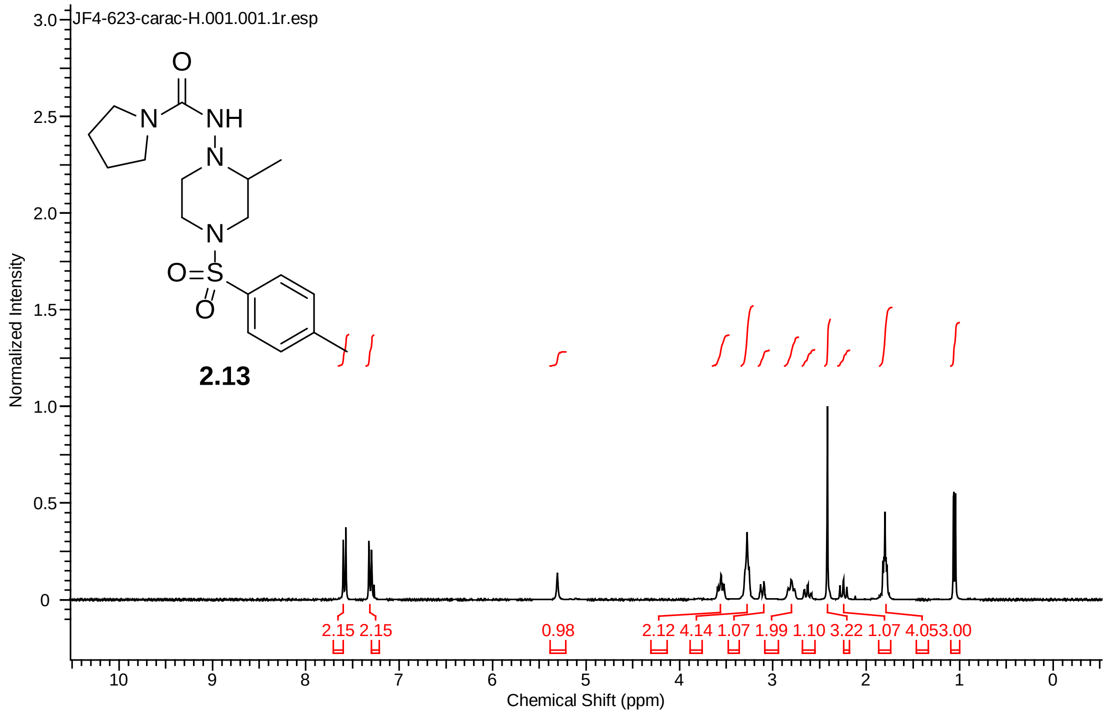

2a.002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
157.1012
61.9231
56.1810
45.9697
30.3000
25.3617
20.0233
18.1396
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

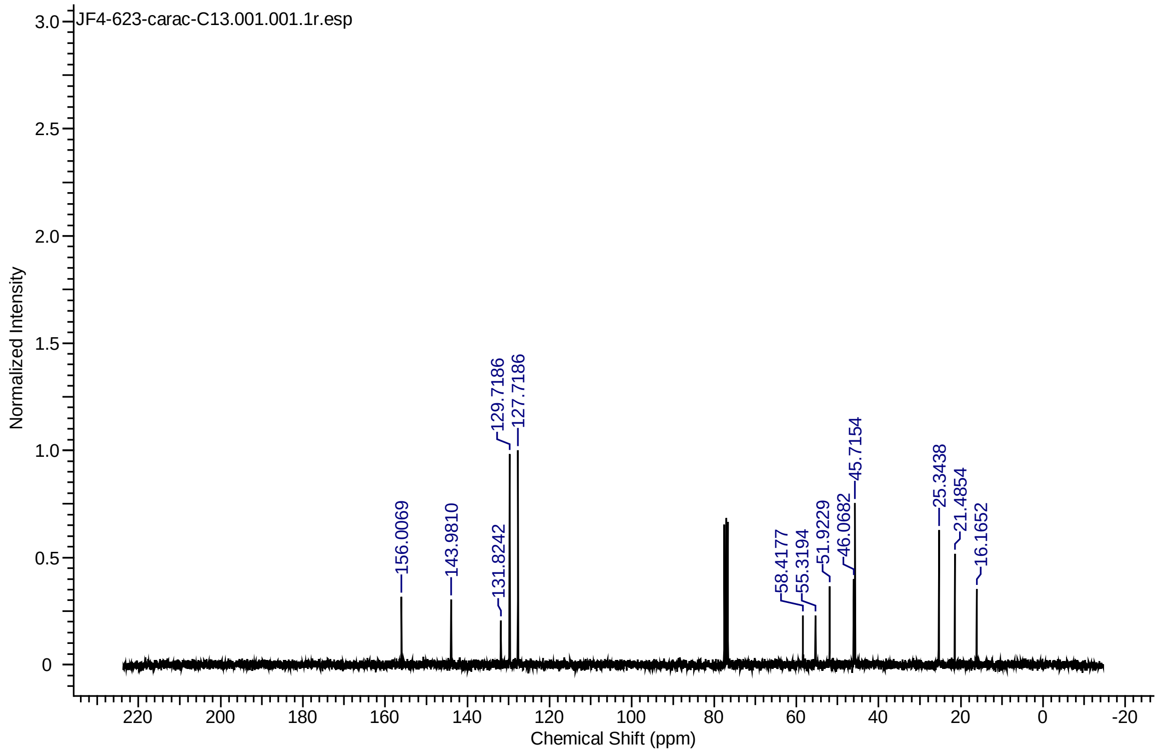

JF4-645-carac-H.001.001.1r.esp
O
N
NH
N
2.11
0.91
5.24
1.99
5.33
3.04
2.12
3.00
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

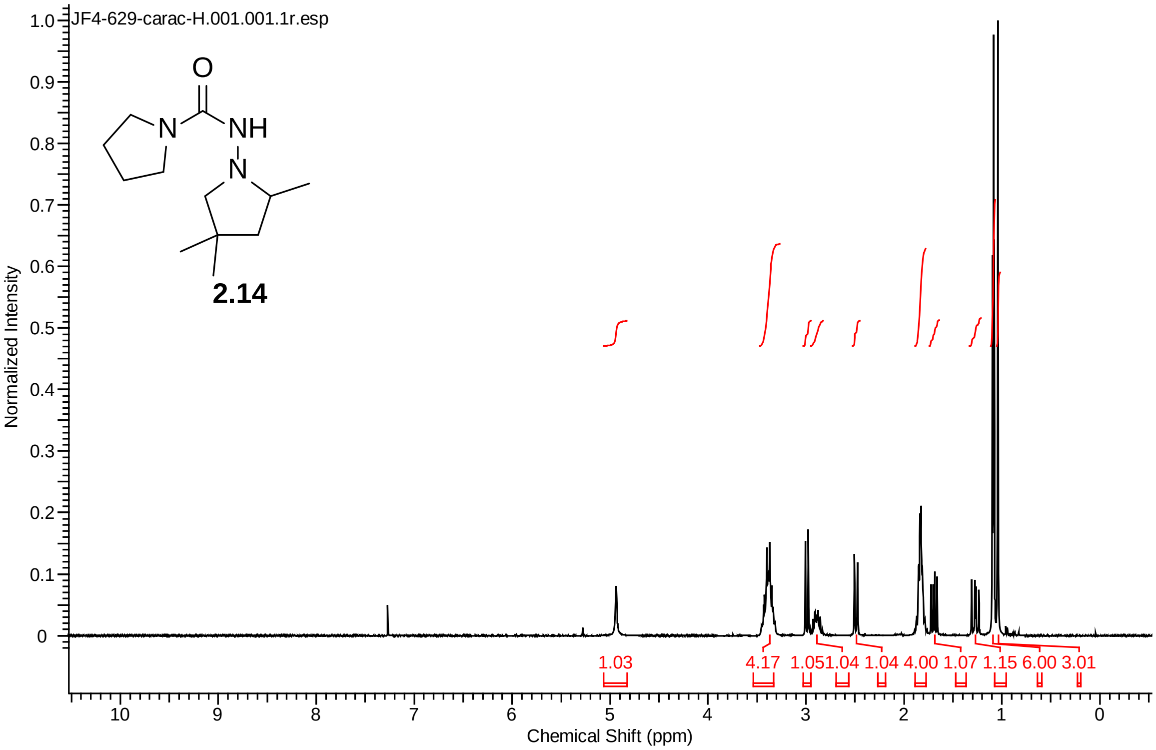

JF4-645-carac-C13.001.001.1r.esp
157.1015
68.1927
56.4431
45.9773
27.9111
25.3947
20.3145
10.6559
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

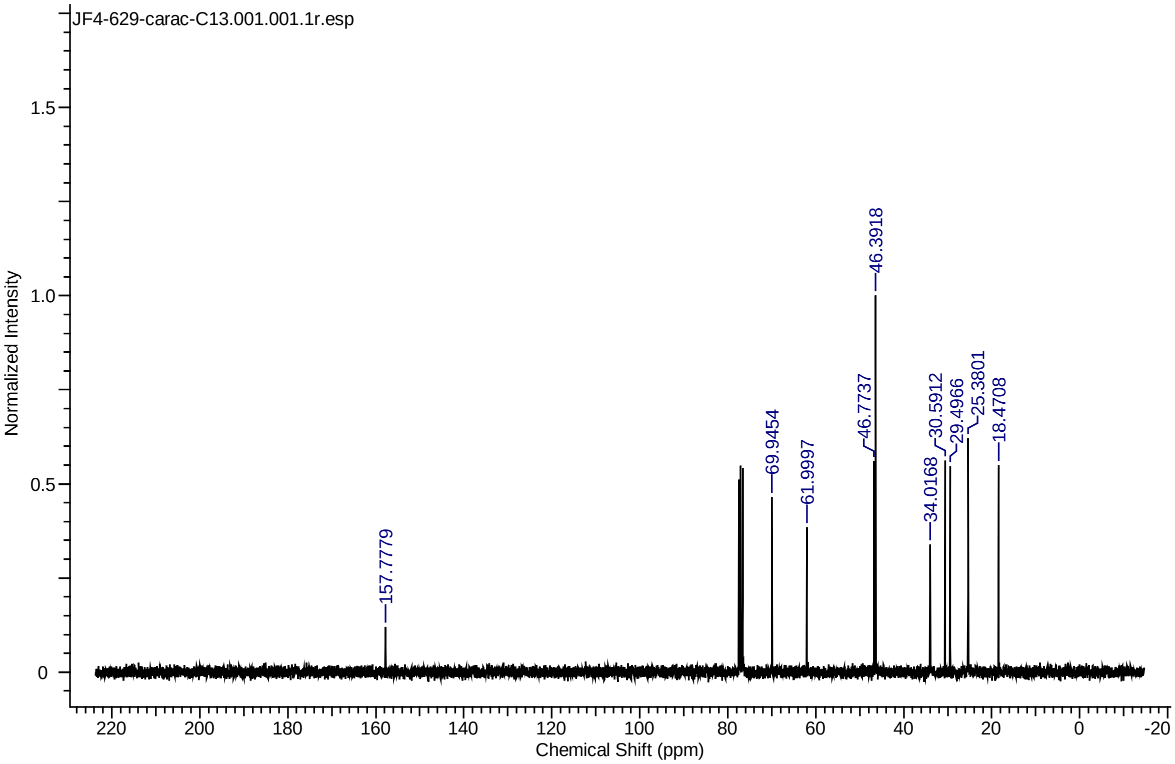

JF4-650-CARAC-H.001.001.1r.esp
O
N
NH
N
2.12
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
1.04
4.27
1.00
1.83
4.26
4.02
2.20
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

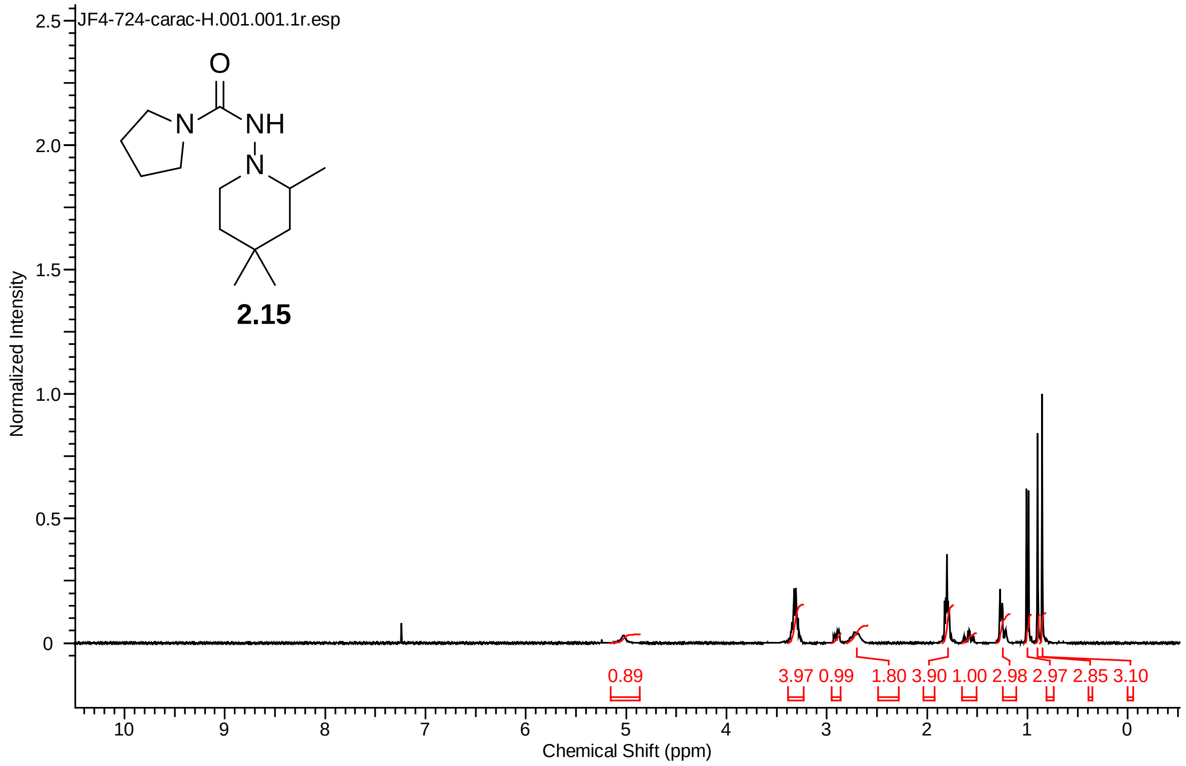

JF4-650-CARAC-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
157.0870
60.8797
58.0468
46.1336
33.8641
25.8456
25.3947
23.9582
19.7035
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

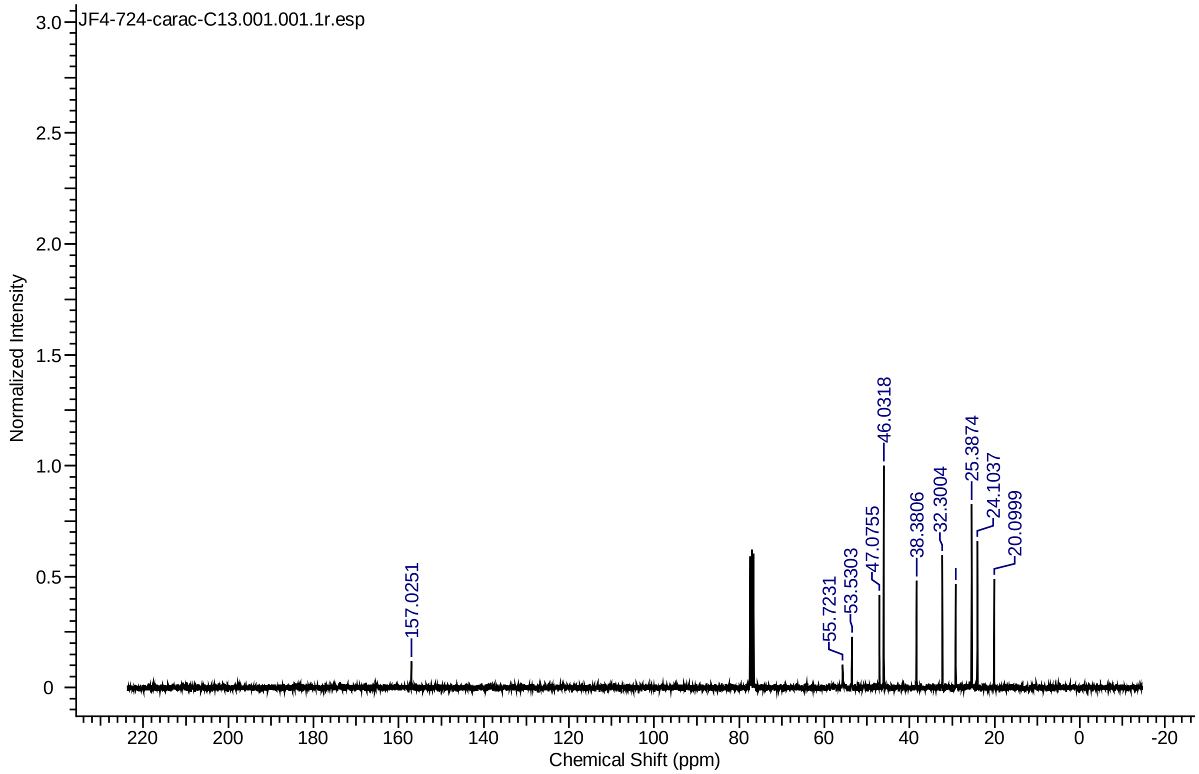

JF4-623-carac-H.001.001.1r.esp
O
N
NH
N
N
O=S
O
2.13
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
2.15 2.15 0.98 2.12 4.14 1.07 1.99 1.10 3.22 1.07 4.05 3.00
10 9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)

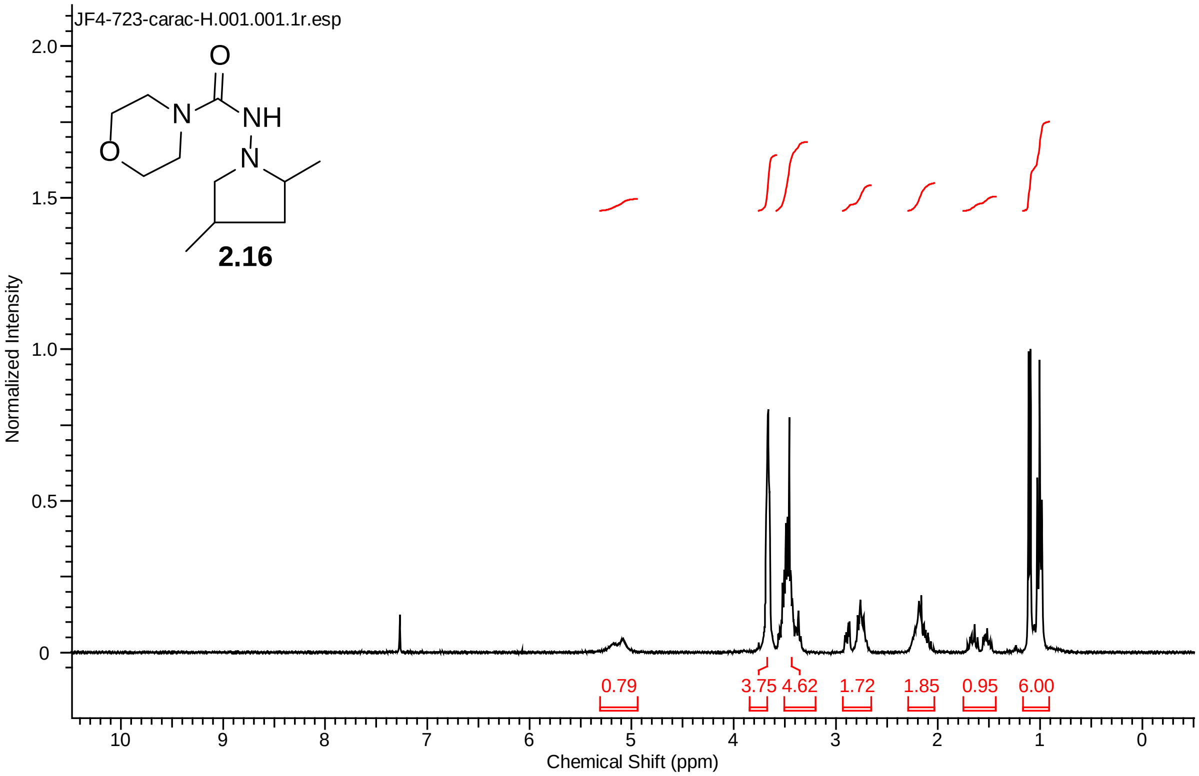

JF4-623-carac-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
156.0069
143.9810
131.8242
129.7186
127.7186
58.4177
55.3194
51.9229
46.0682
45.7154
25.3438
21.4854
16.1652
220 200 180 160 140 120 100 80 60 40 20 0 -20
Chemical Shift (ppm)

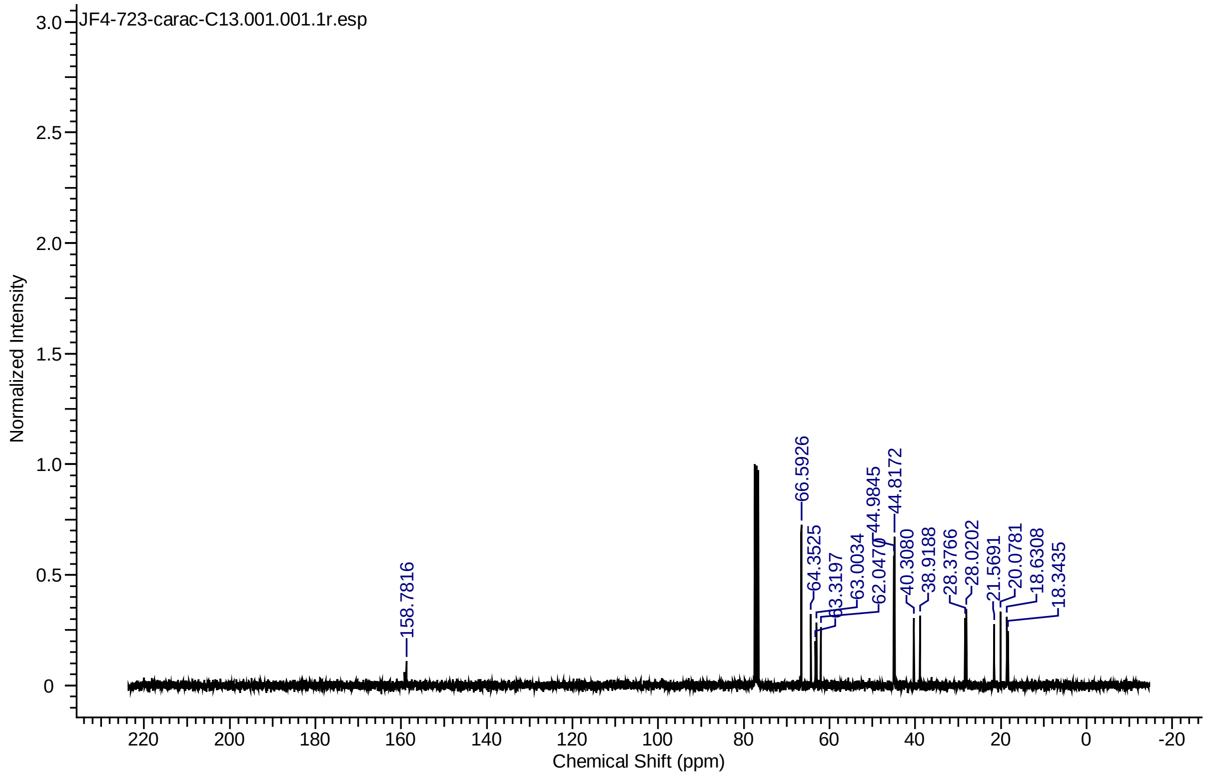

JF4-629-carac-H.001.001.1r.esp
O
N
NH
N
2.14
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.03
4.17
1.05
1.04
1.04
4.00
1.07
1.15
6.00
3.01
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

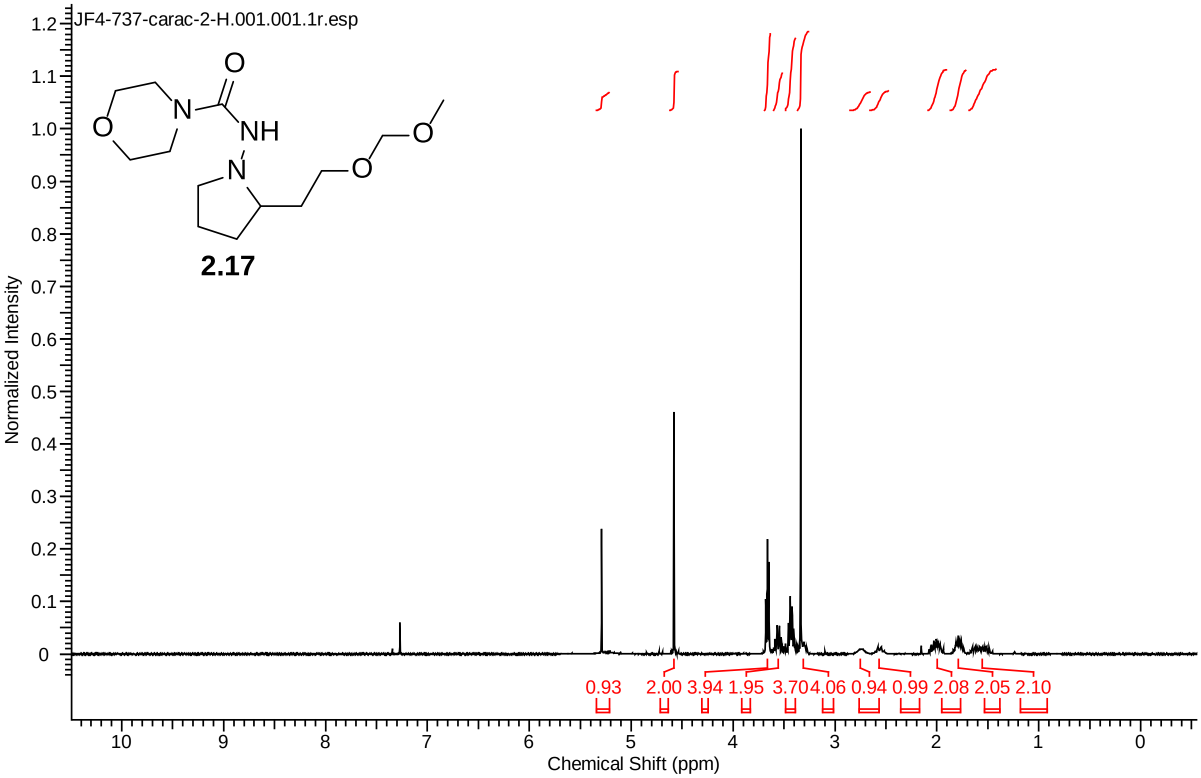

JF4-629-carac-C13.001.001.1r.esp
Normalized Intensity
1.5
1.0
0.5
0
157.7779
69.9454
61.9997
46.7737
46.3918
34.0168
30.5912
29.4966
25.3801
18.4708
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

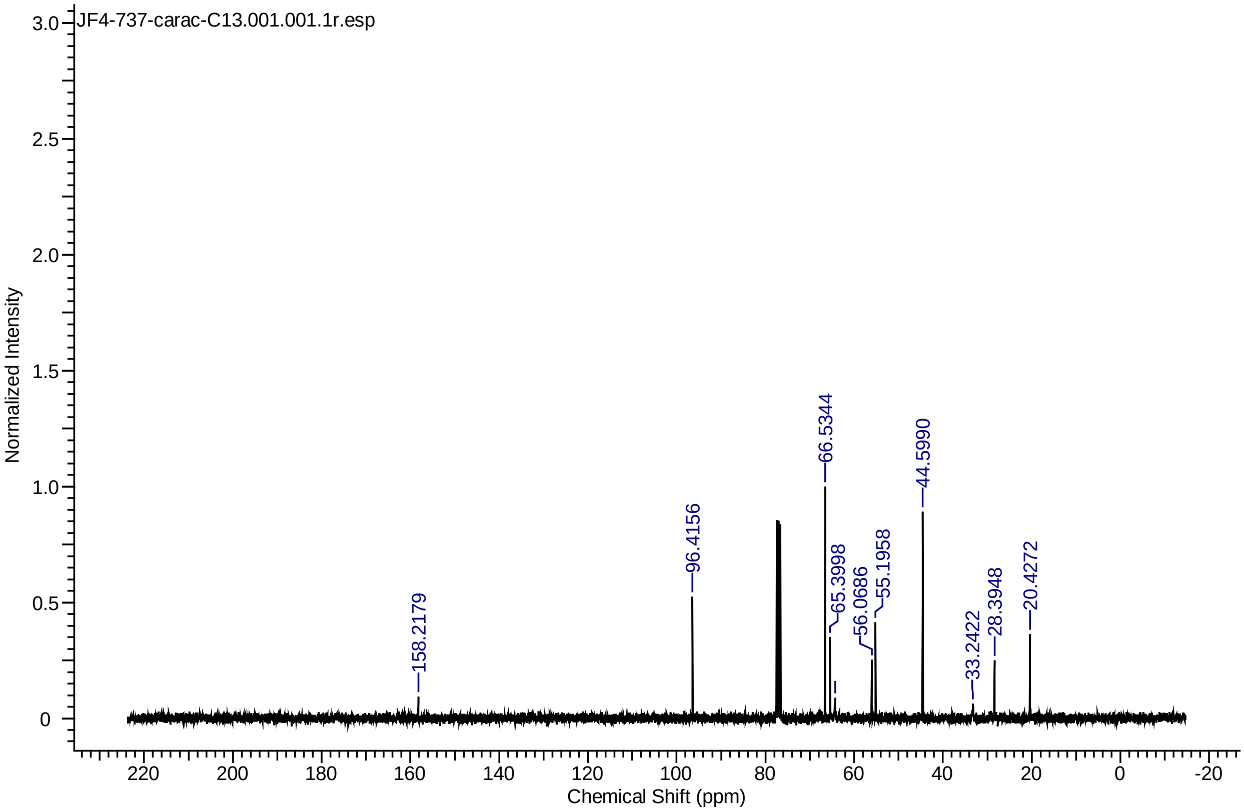

JF4-724-carac-H.001.001.1r.esp
O
N
NH
N
2.15
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0
0.89
3.97
0.99
1.80
3.90
1.00
2.98
2.97
2.85
3.10
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

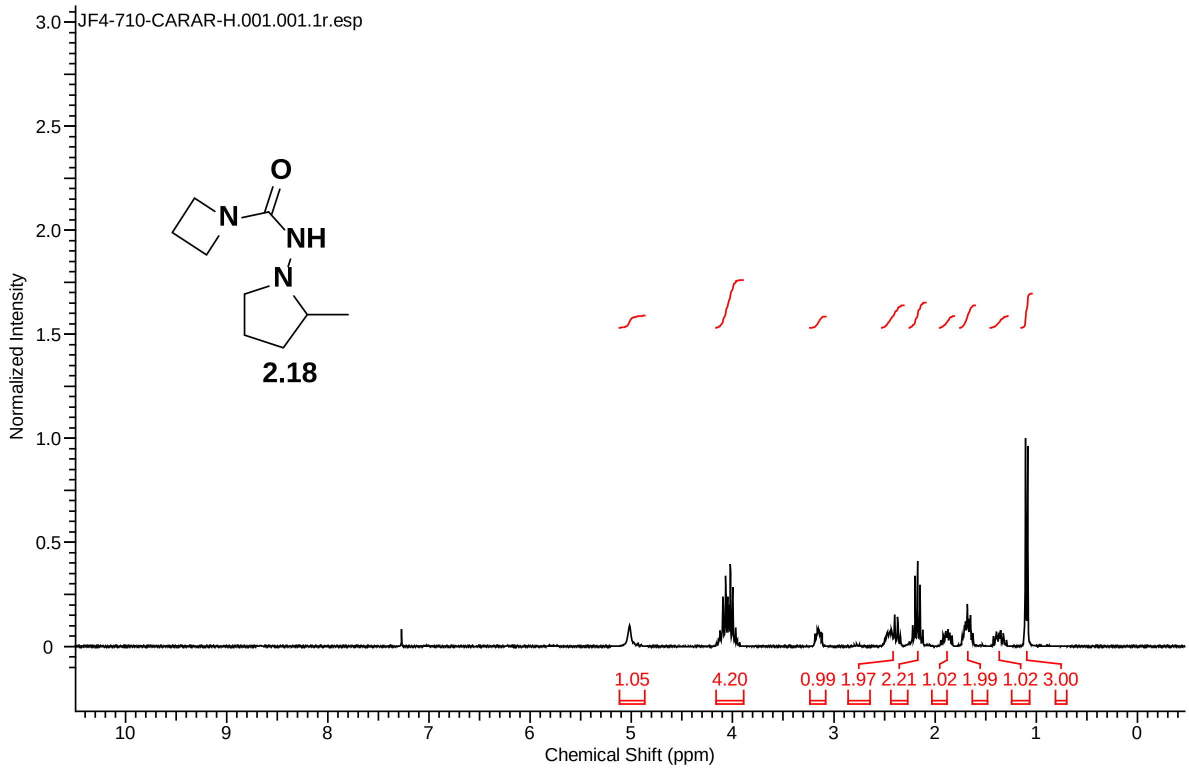

JF4-724-carac-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
157.0251
55.7231
53.5303
47.0755
46.0318
38.3806
32.3004
25.3874
24.1037
20.0999
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF4-723-carac-H.001.001.1r.esp
O
N
NH
N
O
2.16
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.79
3.75
4.62
1.72
1.85
0.95
6.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF4-723-carac-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
158.7816
66.5926
64.3525
63.3197
63.0034
62.0470
44.9845
44.8172
40.3080
38.9188
28.3766
28.0202
21.5691
20.0781
18.6308
18.3435
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

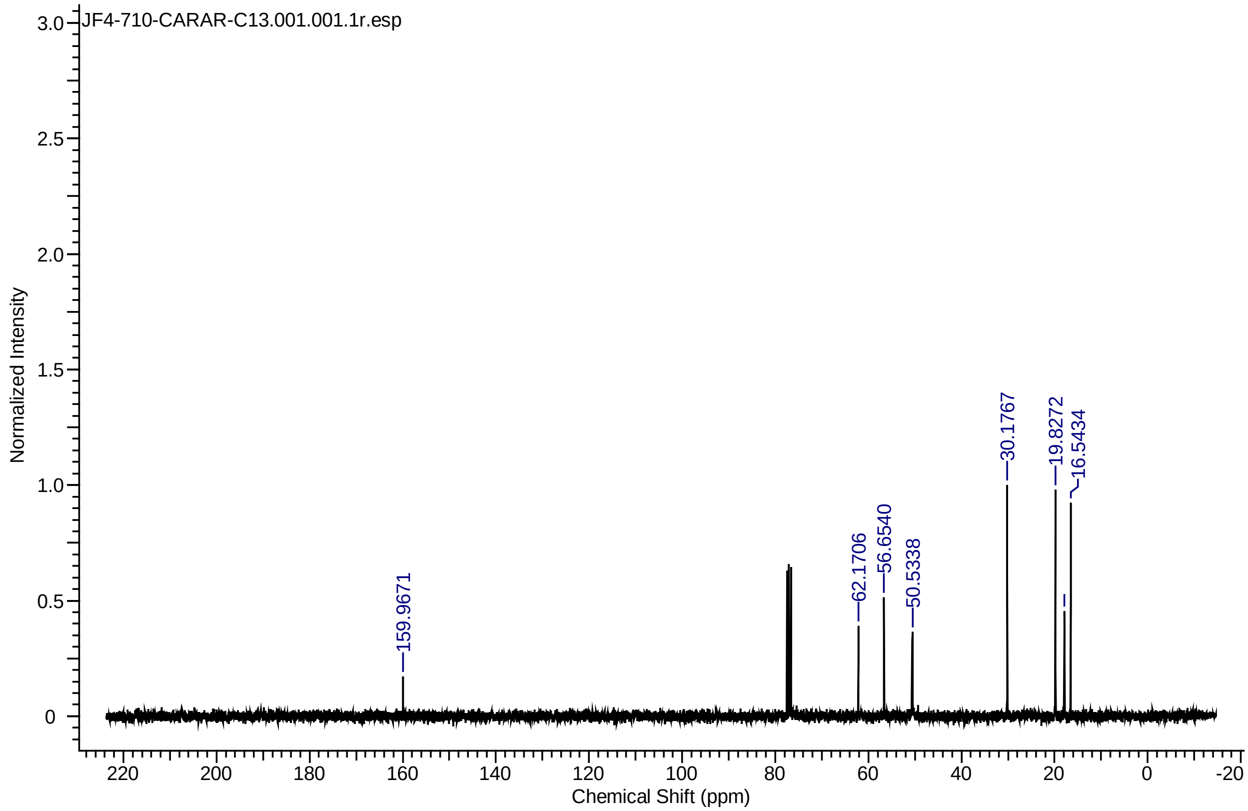

JF4-737-carac-2-H.001.001.1r.esp
O
N
NH
N
O
O
2.17
Normalized Intensity
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.93
2.00
3.94
1.95
3.70
4.06
0.94
0.99
2.08
2.05
2.10
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF4-737-carac-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
158.2179
96.4156
66.5344
65.3998
56.0686
55.1958
44.5990
33.2422
28.3948
20.4272
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

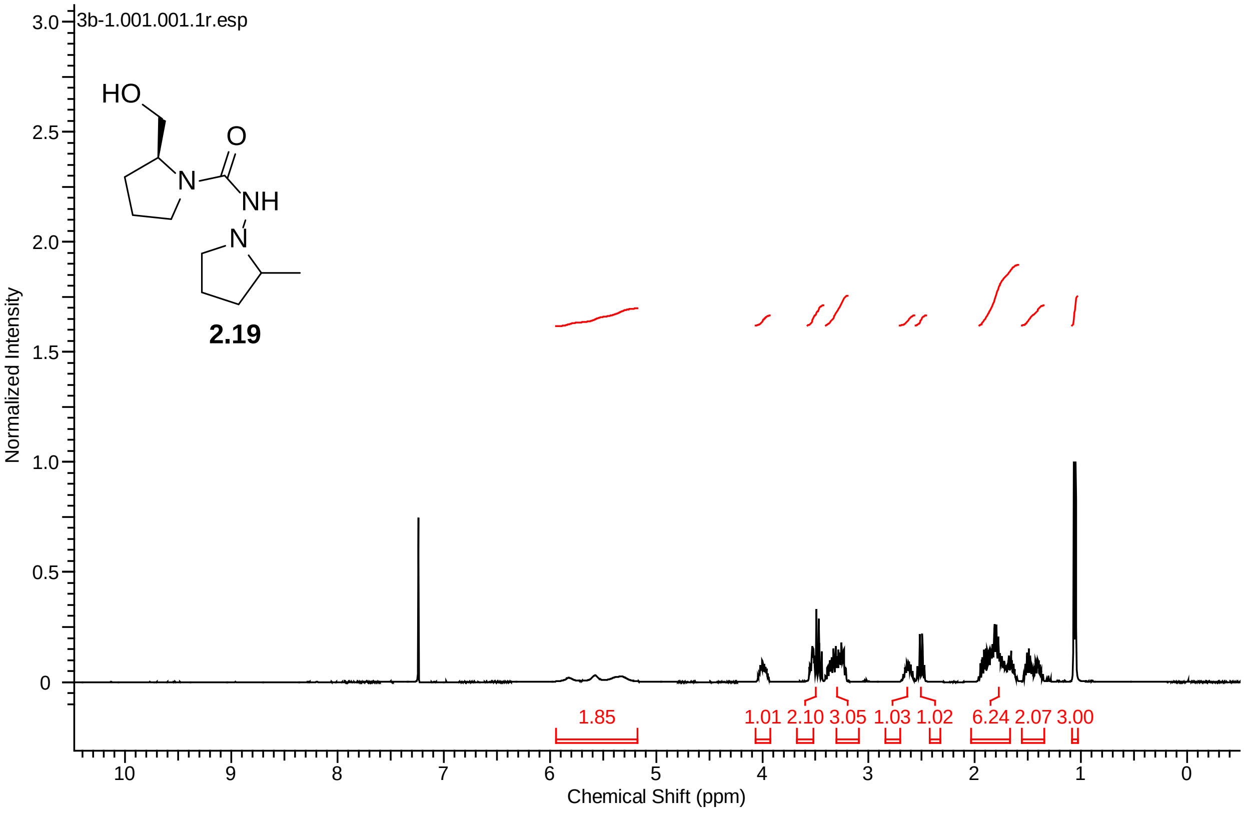


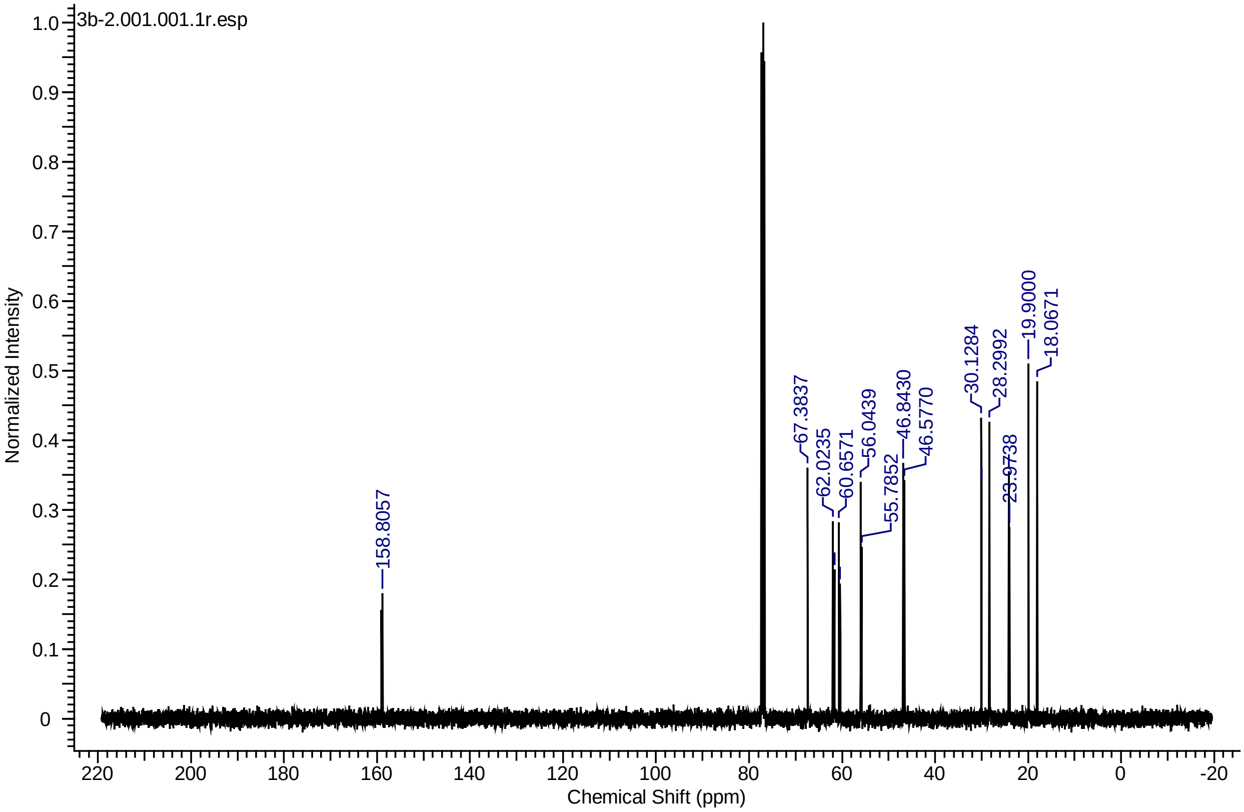
2.18

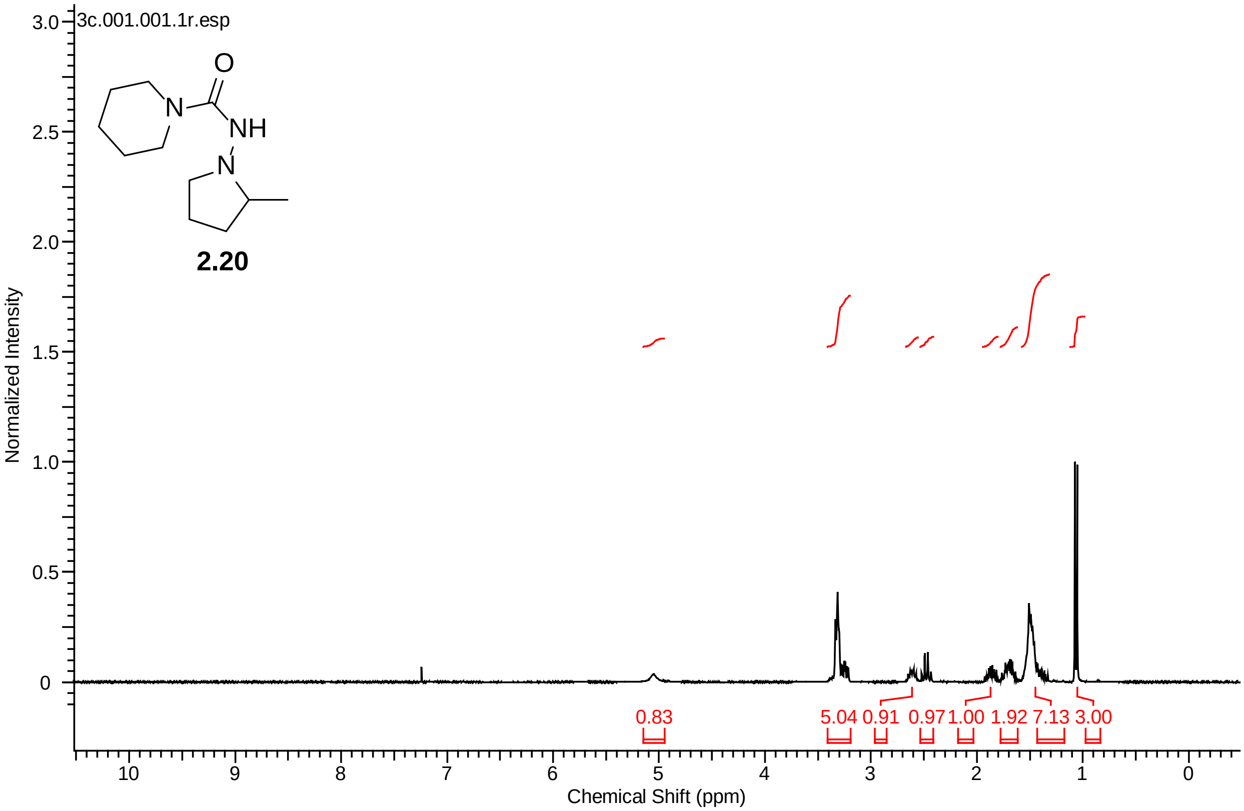
JF4-710-CARAR-H.001.001.1r.esp
O
N
NH
N
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
1.05
4.20
0.99
1.97
2.21
1.02
1.99
1.02
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)



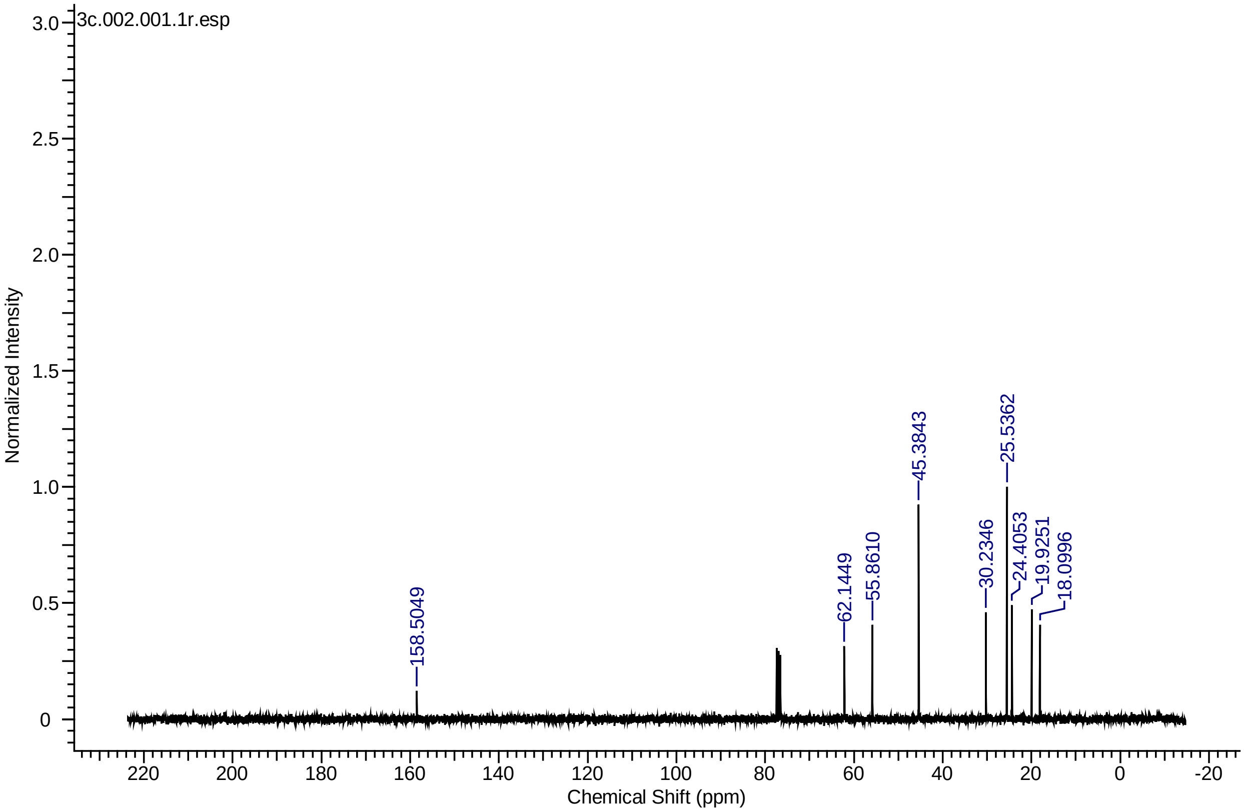
JF4-710-CARAR-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
159.9671
62.1706
56.6540
50.5338
30.1767
19.8272
16.5434
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

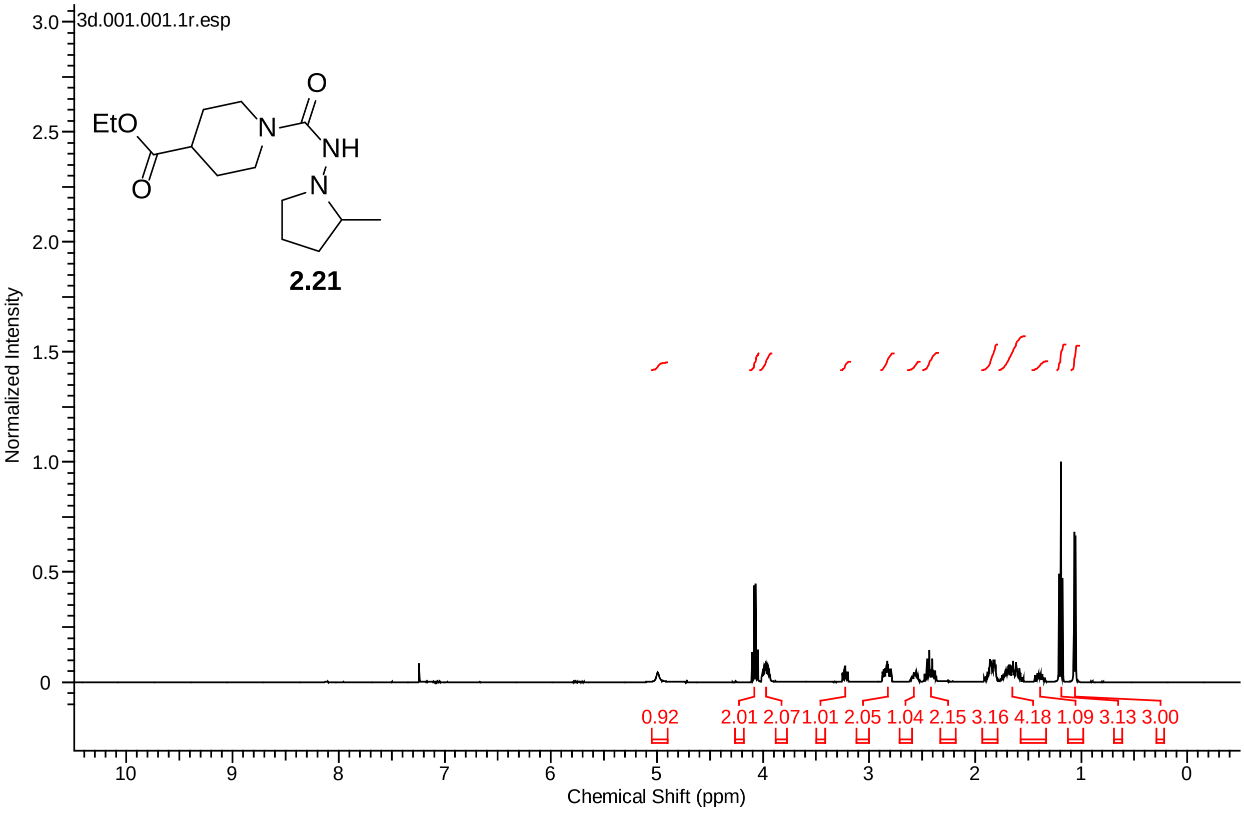

3b-1.001.001.1r.esp
HO
O
N
NH
N
2.19
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
1.85
1.01
2.10
3.05
1.03
1.02
6.24
2.07
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

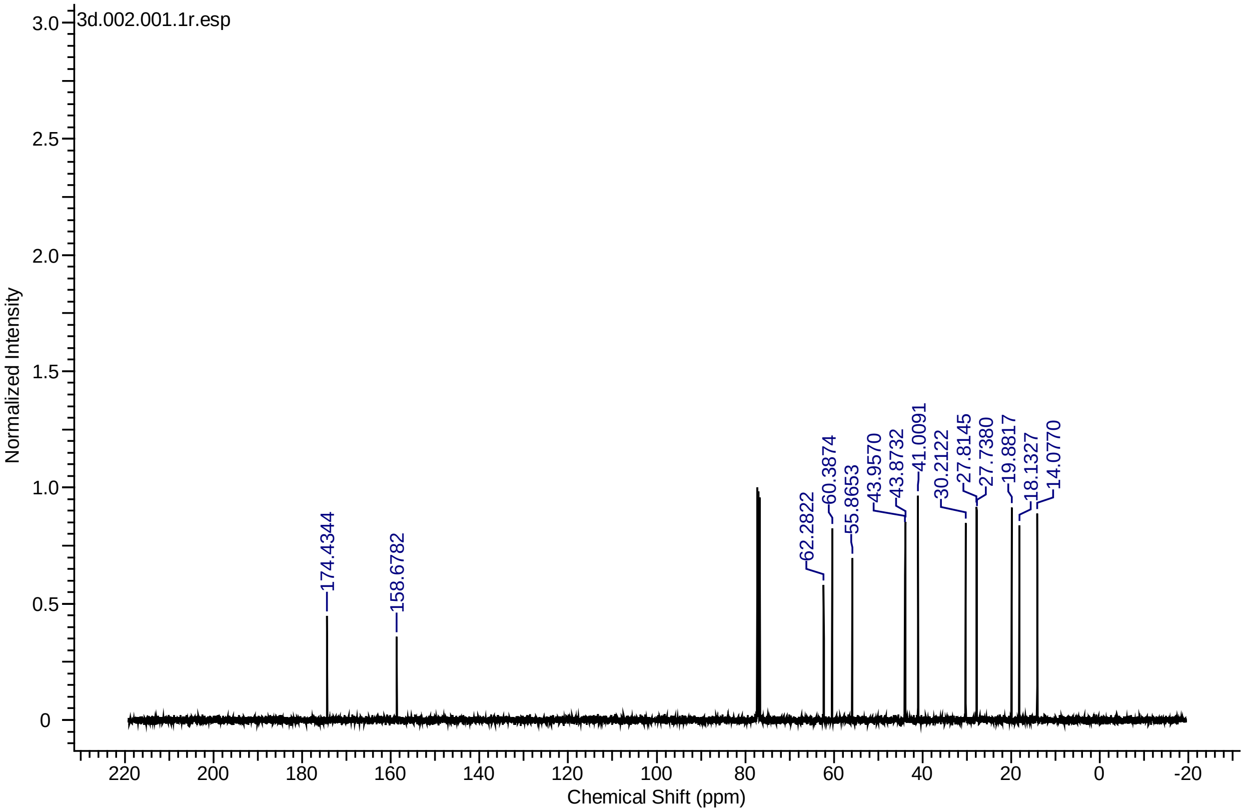

3b-2.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
158.8057
67.3837
62.0235
60.6571
56.0439
55.7852
46.8430
46.5770
30.1284
28.2992
23.9738
19.9000
18.0671
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

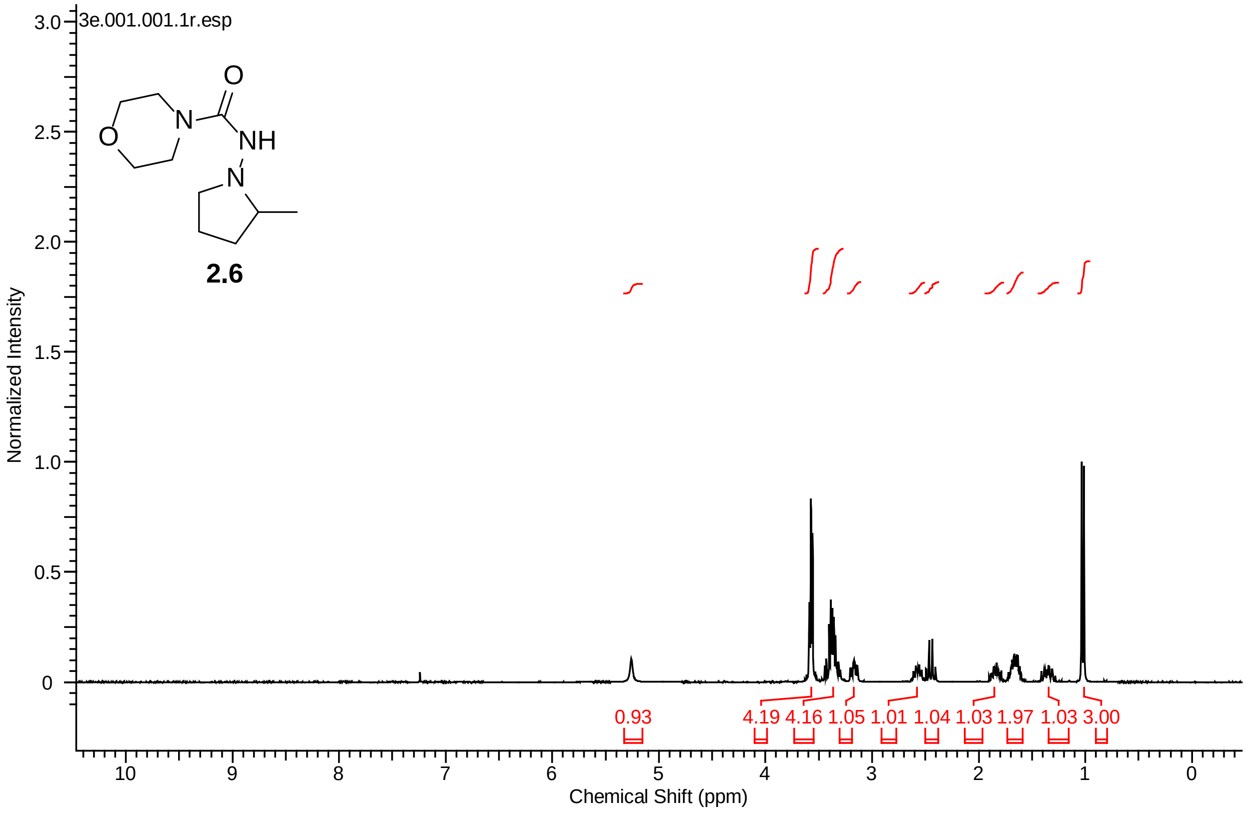

3c.001.001.1r.esp
O
N
NH
N
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
0.83
5.04
0.91
0.97
1.00
1.92
7.13
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

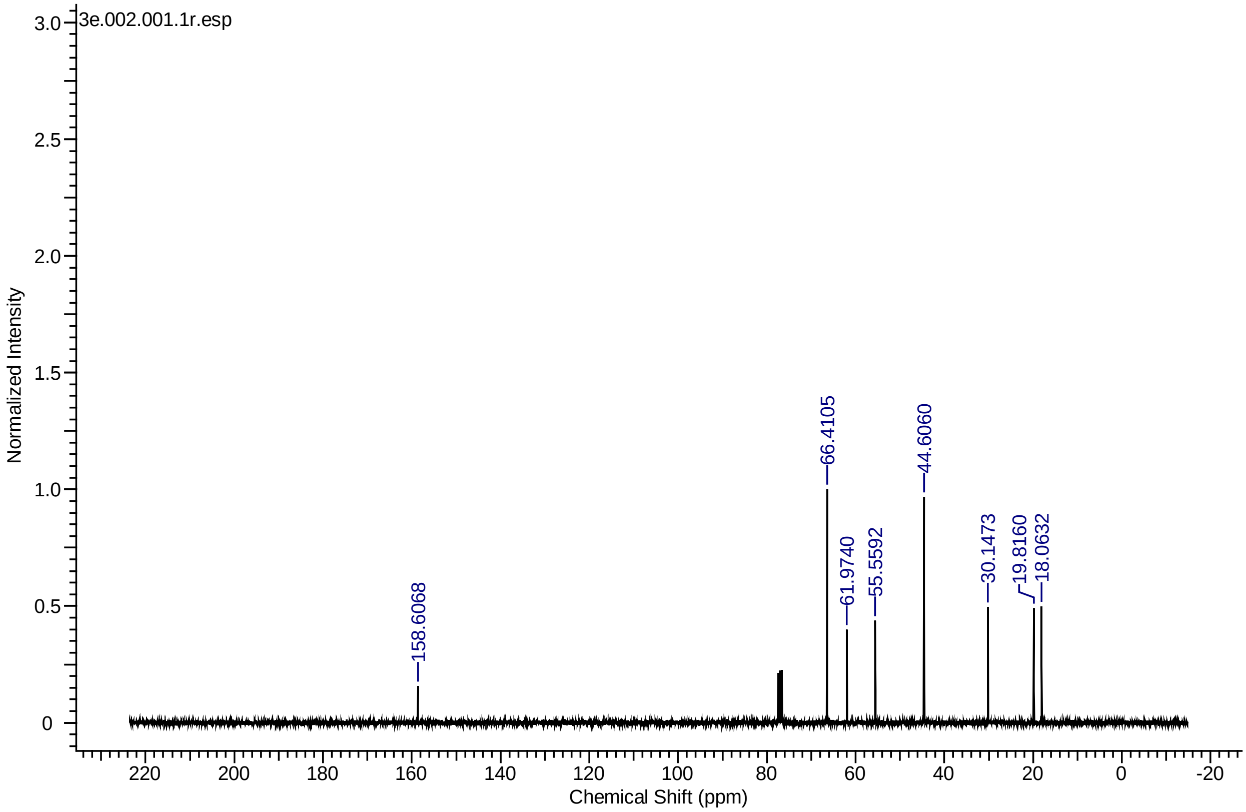
2.20

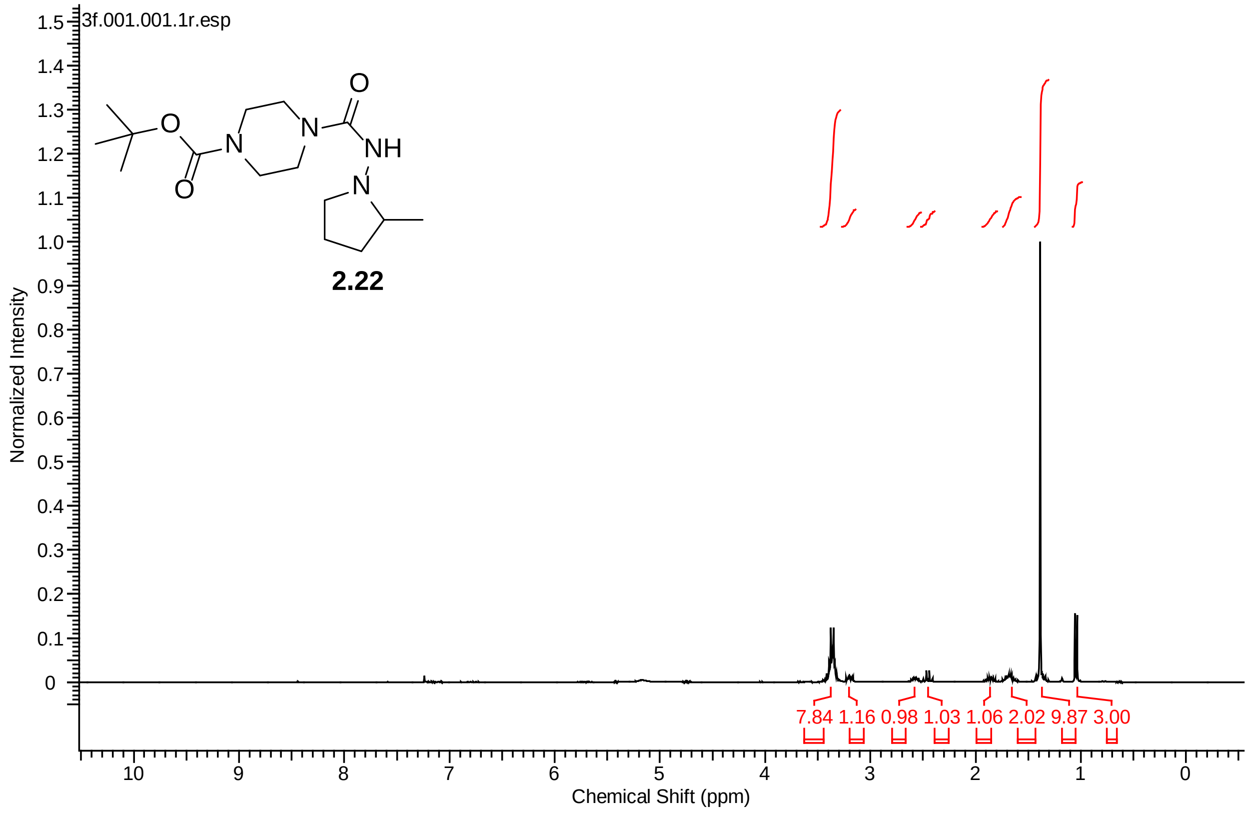

3c.002.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
158.5049
62.1449
55.8610
45.3843
30.2346
25.5362
24.4053
19.9251
18.0996
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


3d.001.001.1r.esp
EtO
O
N
O
NH
N
2.21
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
0.92
2.01
2.07
1.01
2.05
1.04
2.15
3.16
4.18
1.09
3.13
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


3d.002.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
174.4344
158.6782
62.2822
60.3874
55.8653
43.9570
43.8732
41.0091
30.2122
27.8145
27.7380
19.8817
18.1327
14.0770
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

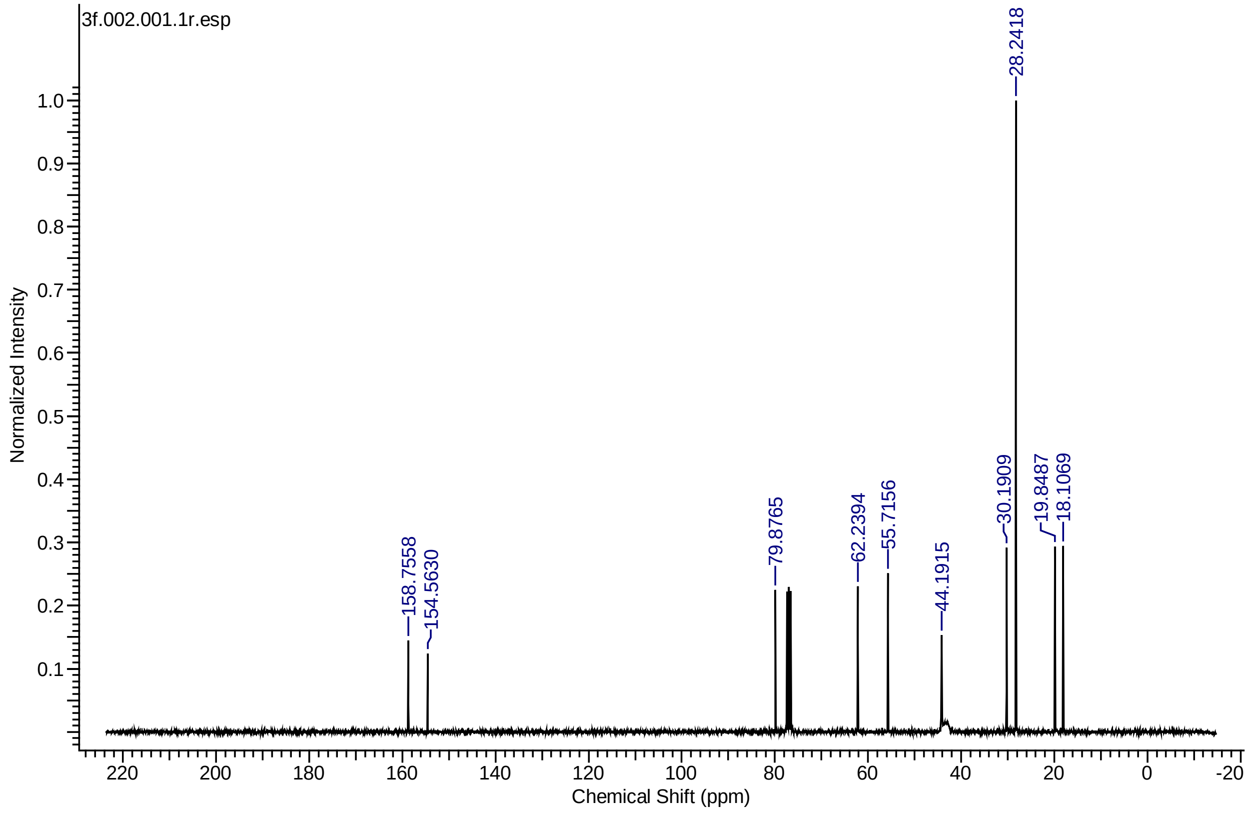

2.6
3e.001.001.1r.esp
O
N
NH
N
O
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
0.93
4.19
4.16
1.05
1.01
1.04
1.03
1.97
1.03
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


3e.002.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
158.6068
66.4105
61.9740
55.5592
44.6060
30.1473
19.8160
18.0632
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

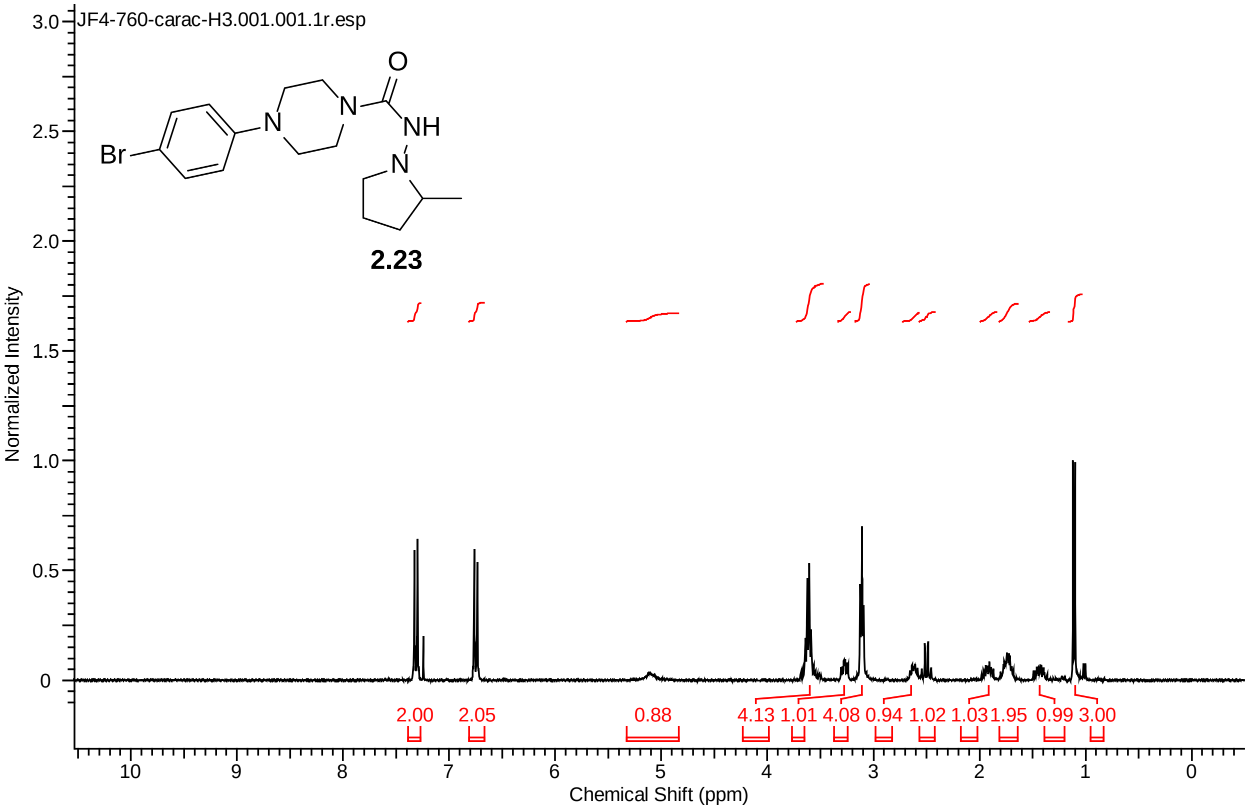


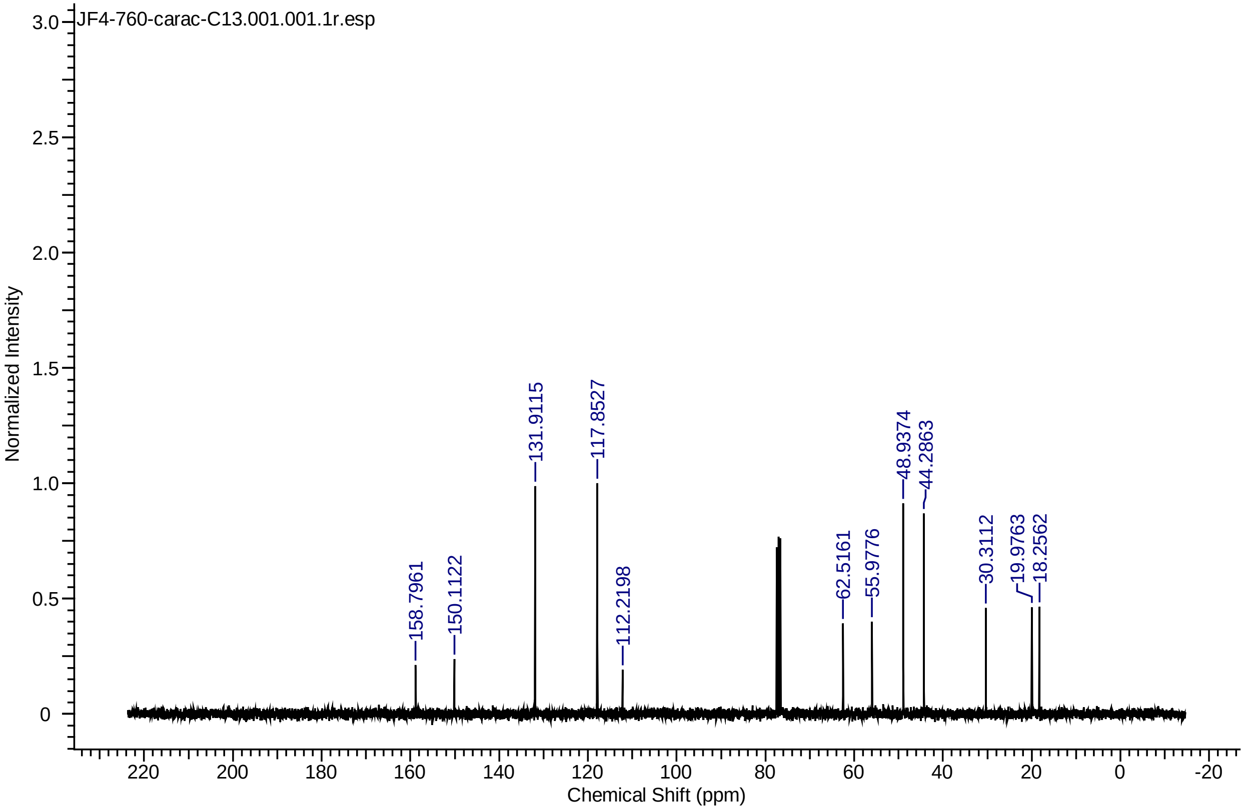
2.22

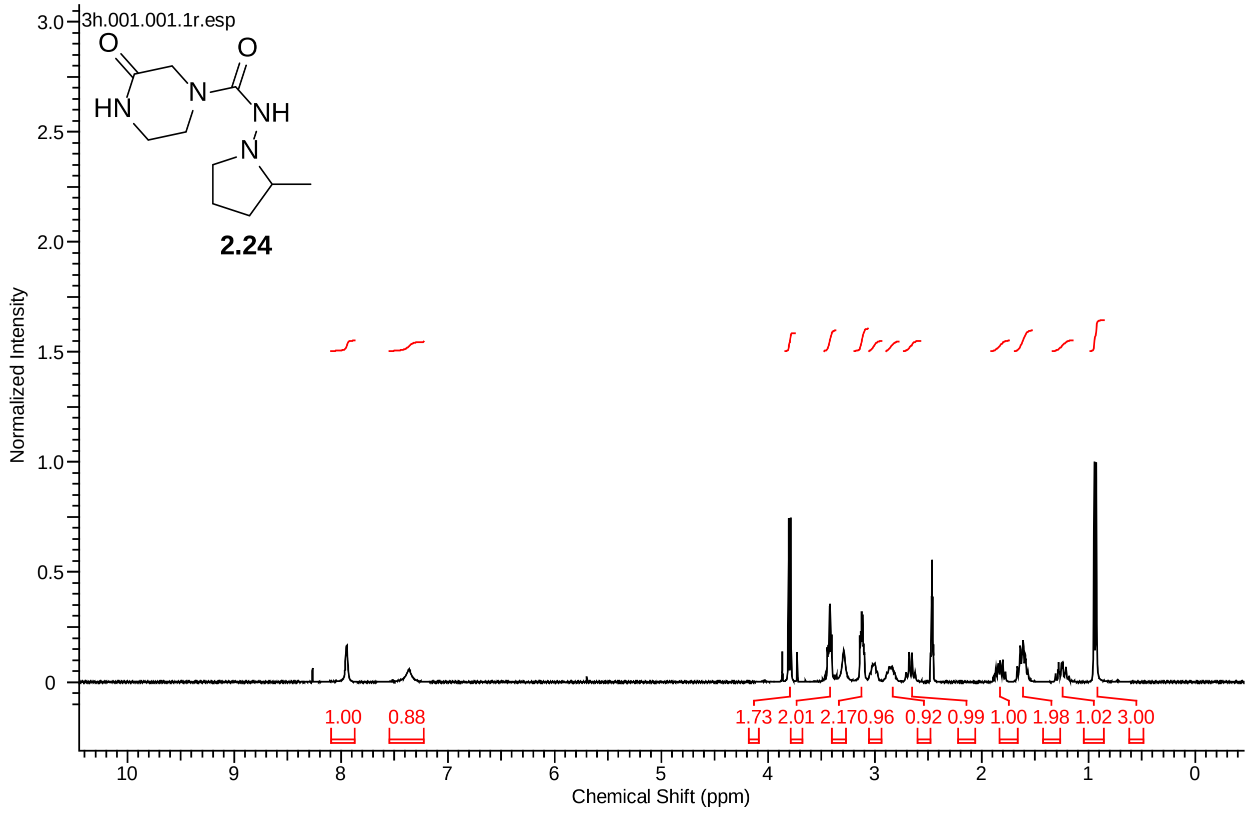
3f.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
7.84
1.16
0.98
1.03
1.06
2.02
9.87
3.00
O
N
NH
N
O
O
N

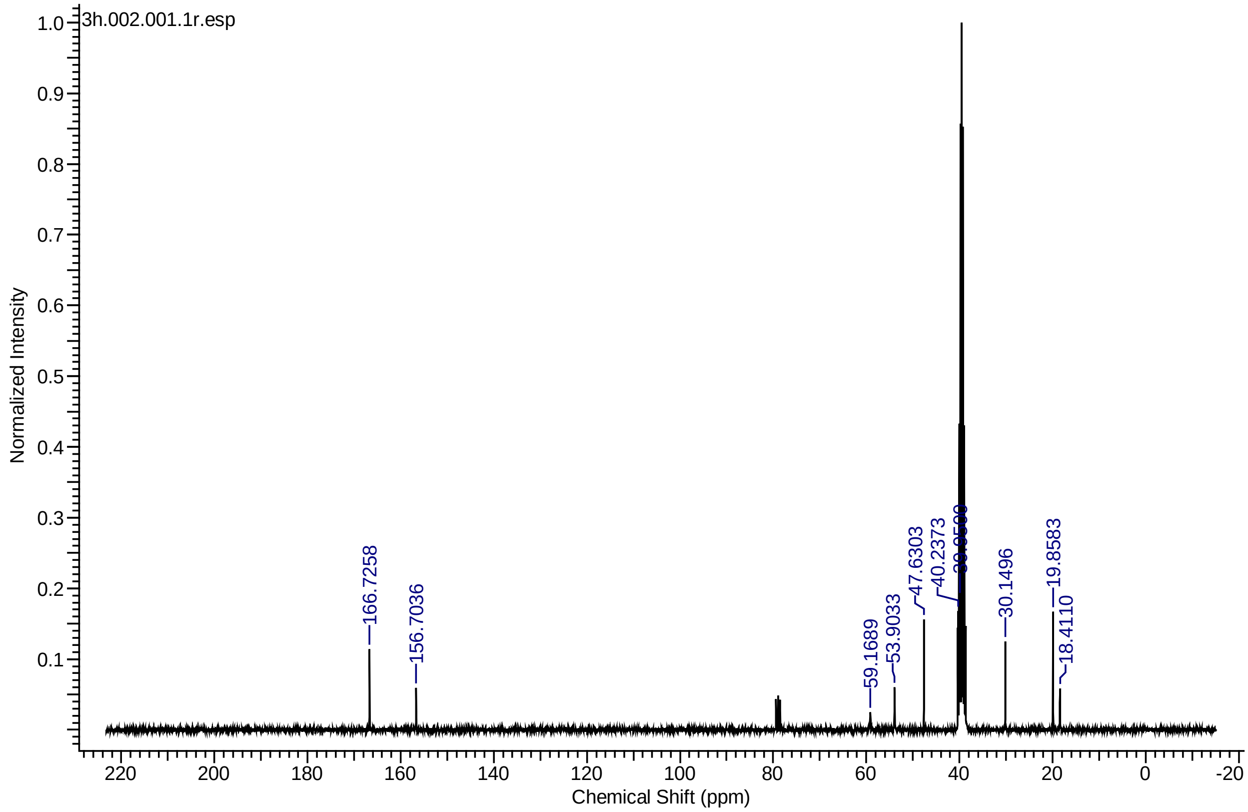


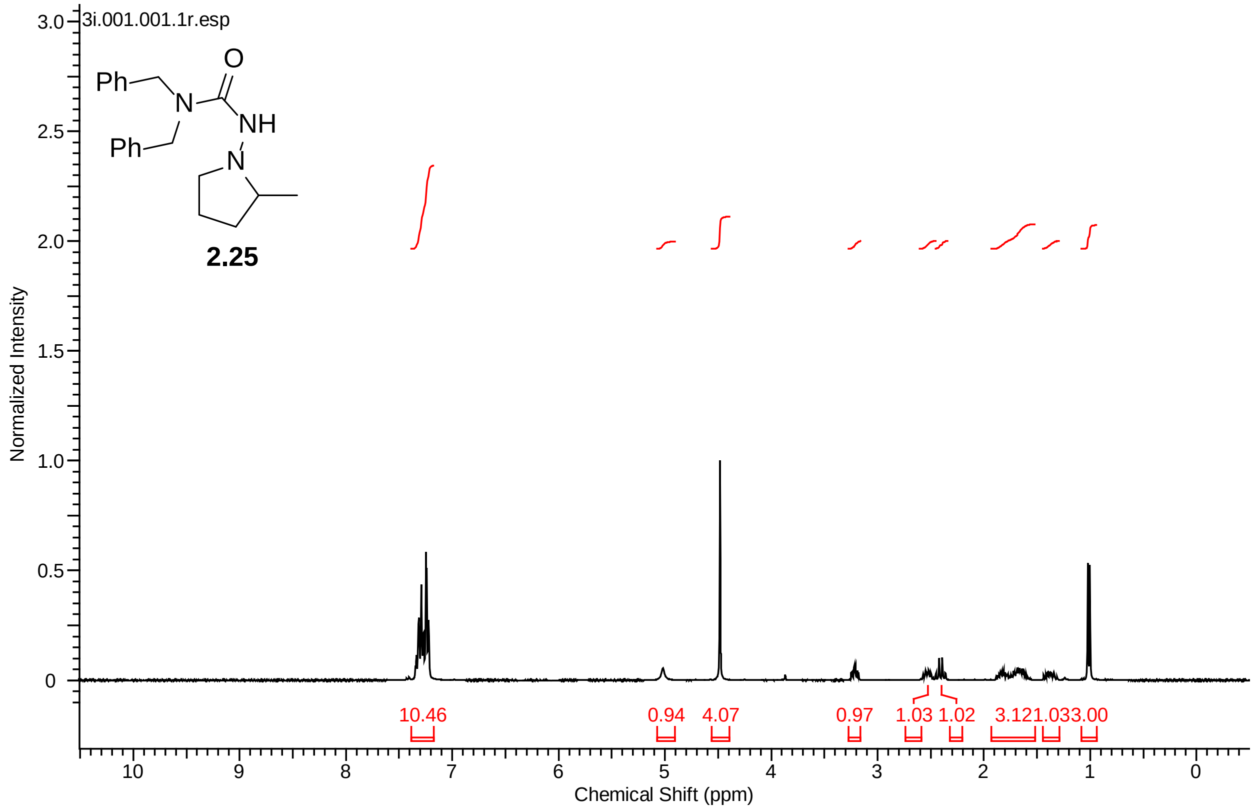
3f.002.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
158.7558
154.5630
79.8765
62.2394
55.7156
44.1915
30.1909
28.2418
19.8487
18.1069

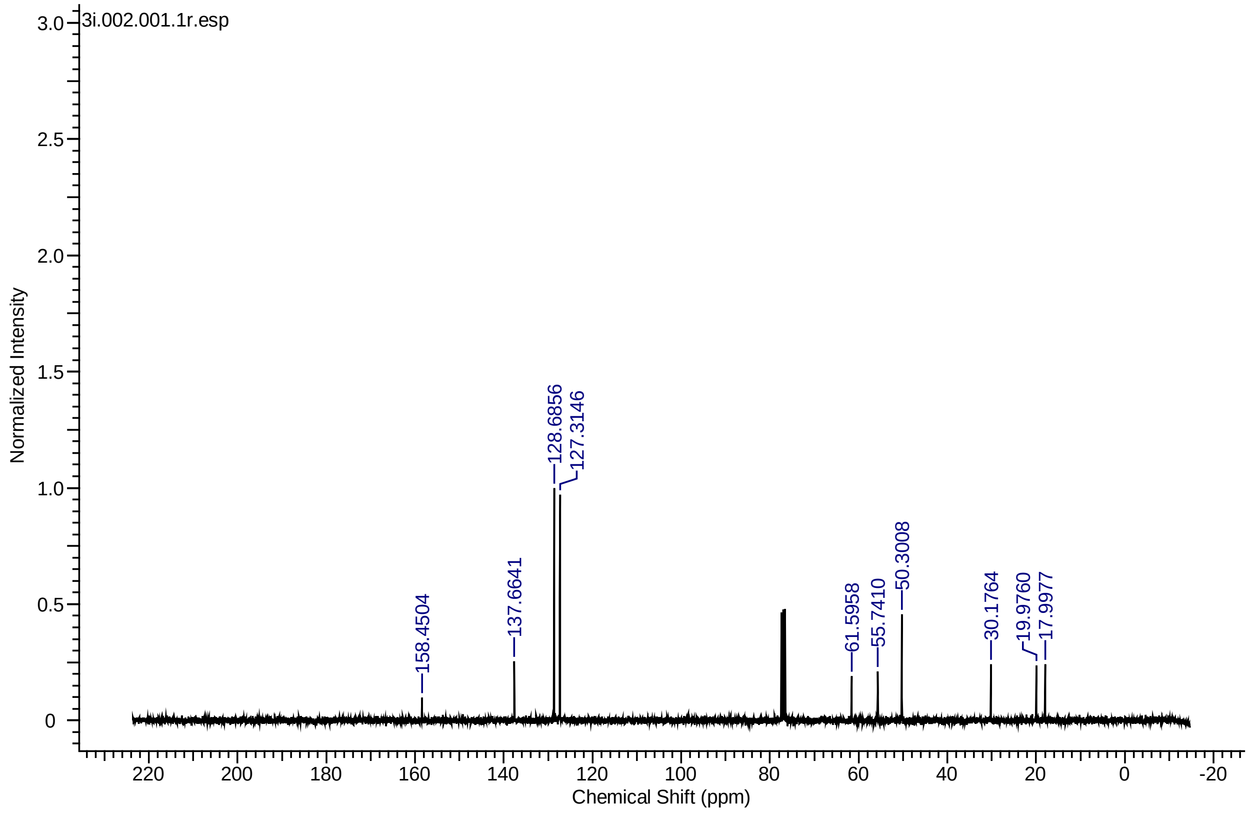

JF4-760-carac-H3.001.001.1r.esp
Br
N
N
O
NH
N
2.23
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
2.00
2.05
0.88
4.13
1.01
4.08
0.94
1.02
1.03
1.95
0.99
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

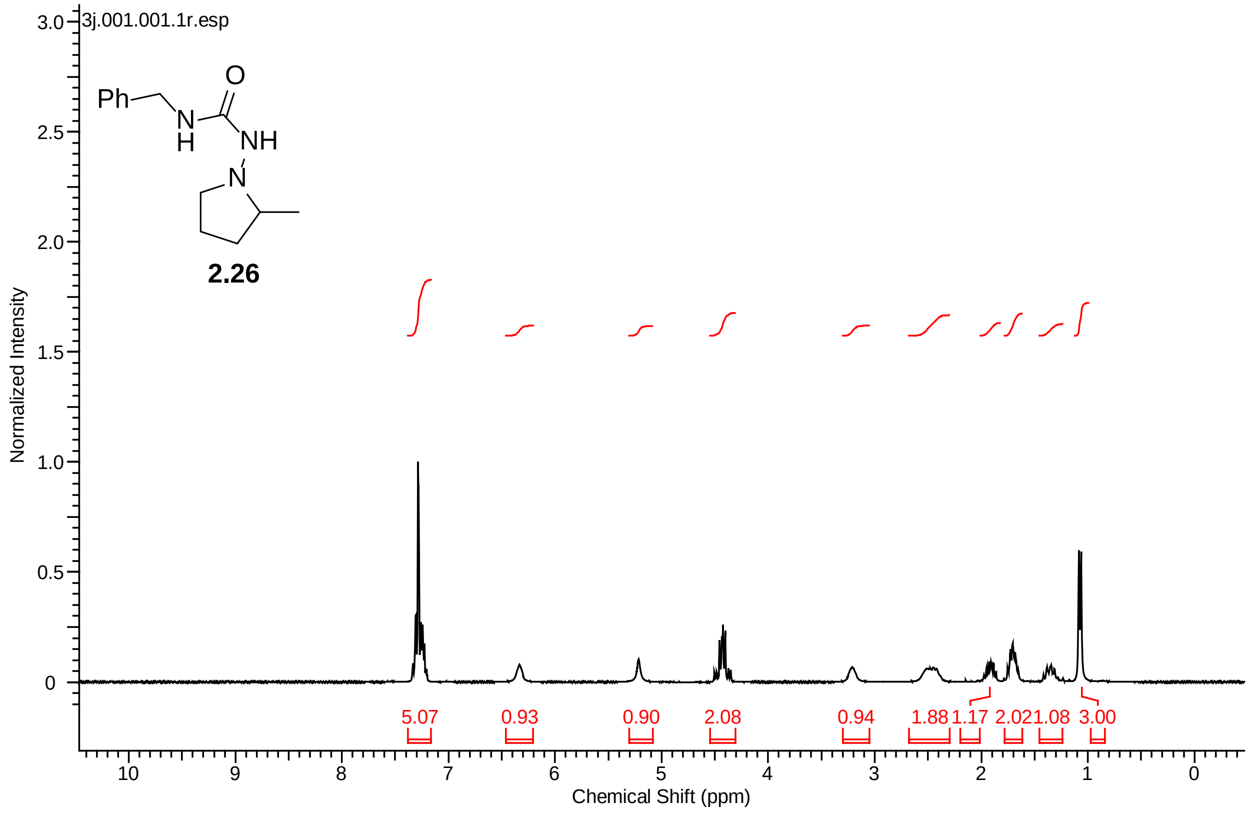

JF4-760-carac-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
158.7961
150.1122
131.9115
117.8527
112.2198
62.5161
55.9776
48.9374
44.2863
30.3112
19.9763
18.2562
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

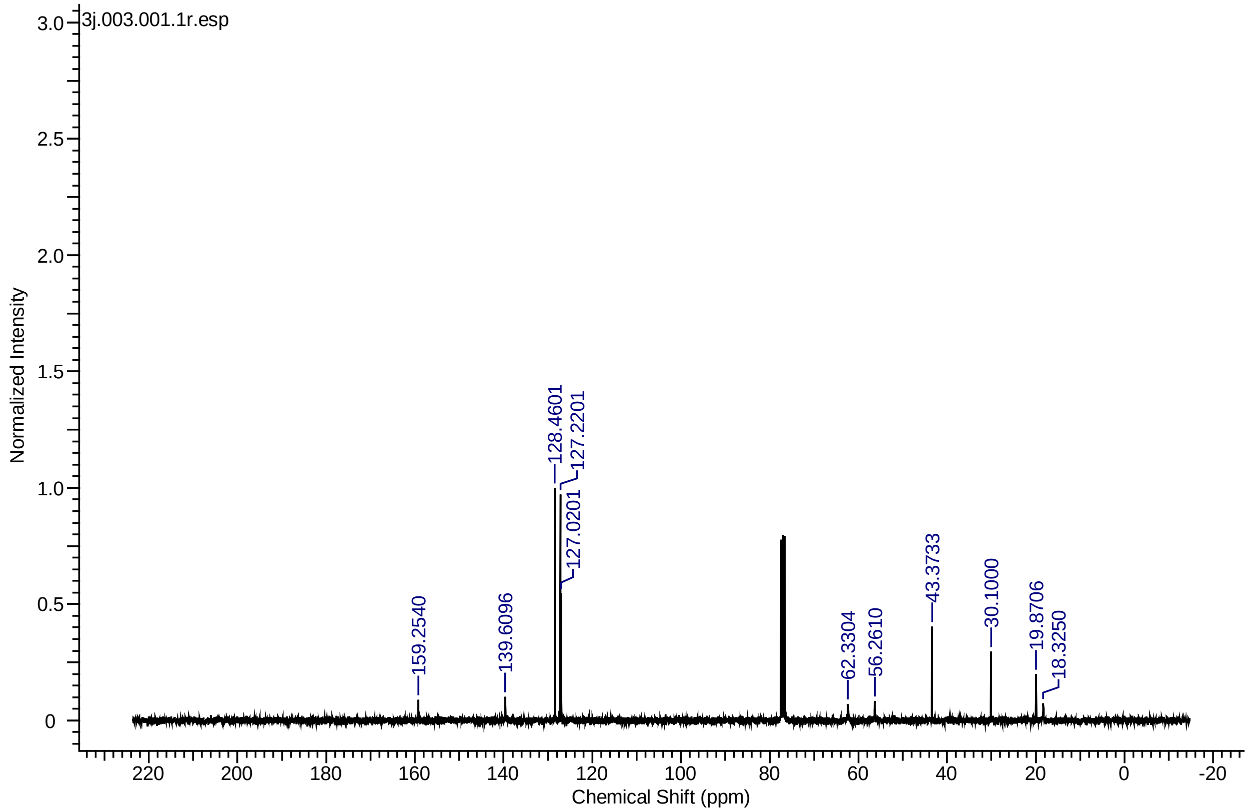

3h.001.001.1r.esp
O
O
HN
N
NH
N
2.24
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
1.00
0.88
1.73
2.01
2.17
0.96
0.92
0.99
1.00
1.98
1.02
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

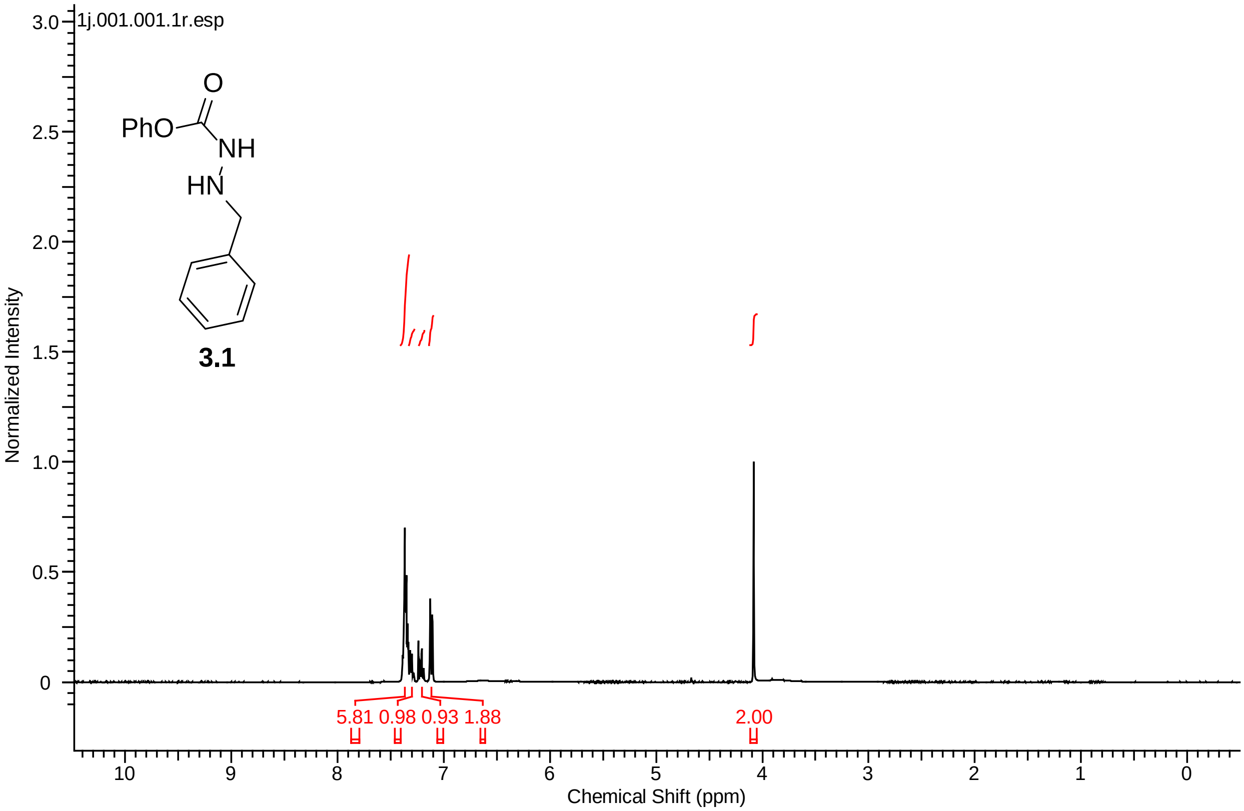

3h.002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
166.7258
156.7036
59.1689
53.9033
47.6303
40.2373
39.9500
30.1496
19.8583
18.4110
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

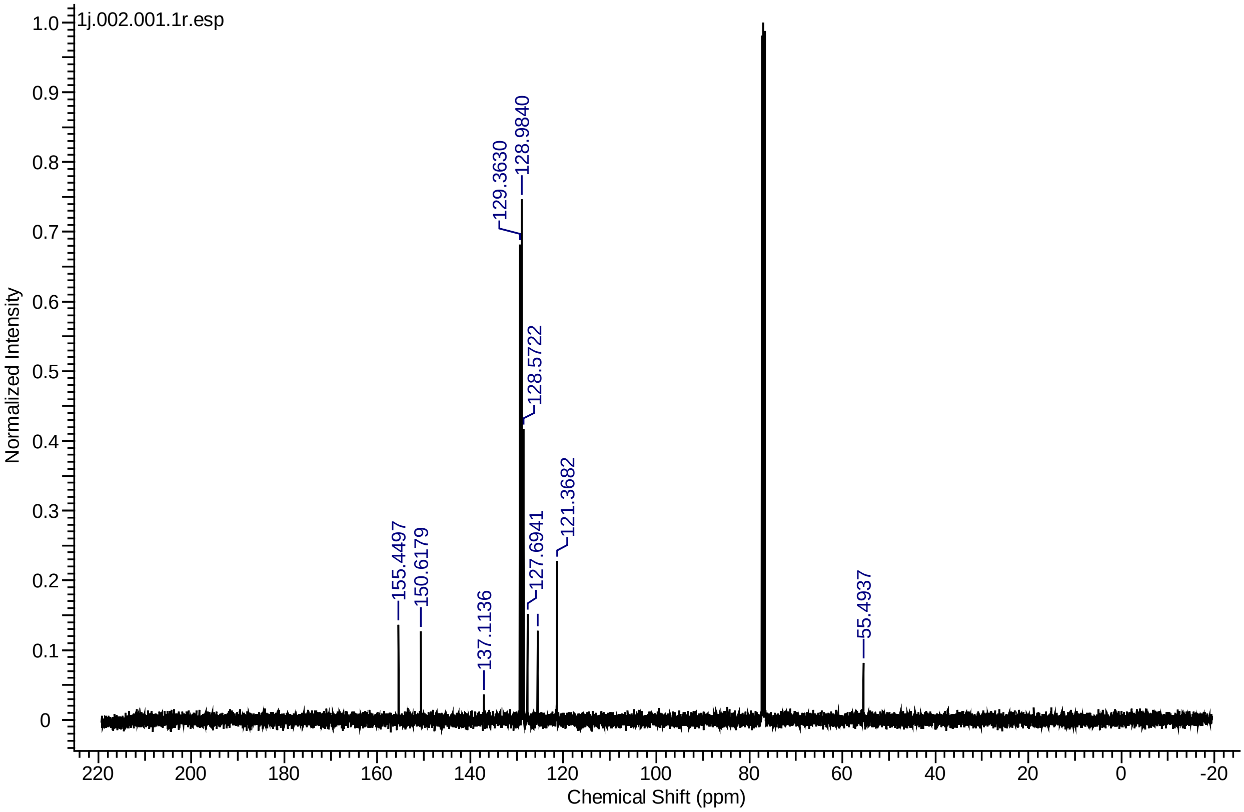

3i.001.001.1r.esp
Ph
N
O
NH
N
Ph
2.25
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
10.46
0.94
4.07
0.97
1.03
1.02
3.12
1.03
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

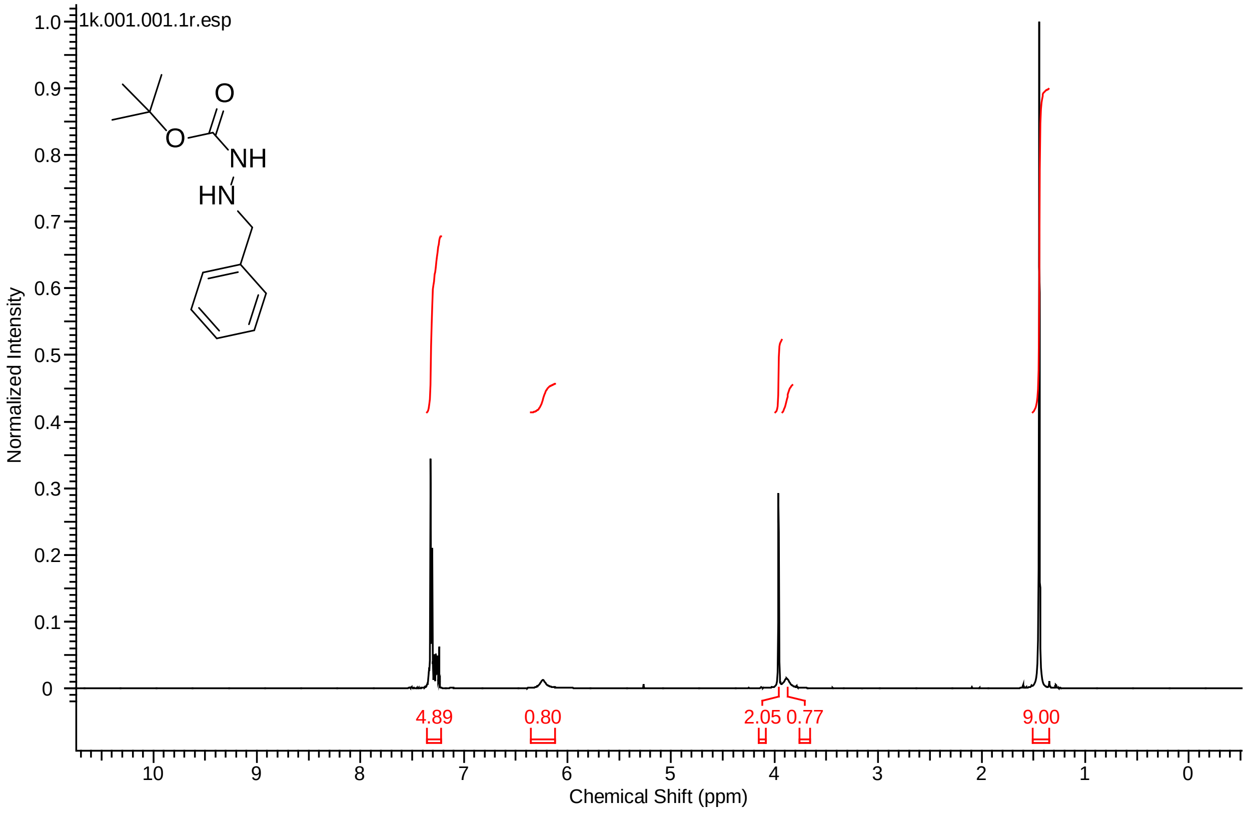

3i.002.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
158.4504
137.6641
128.6856
127.3146
61.5958
55.7410
50.3008
30.1764
19.9760
17.9977
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

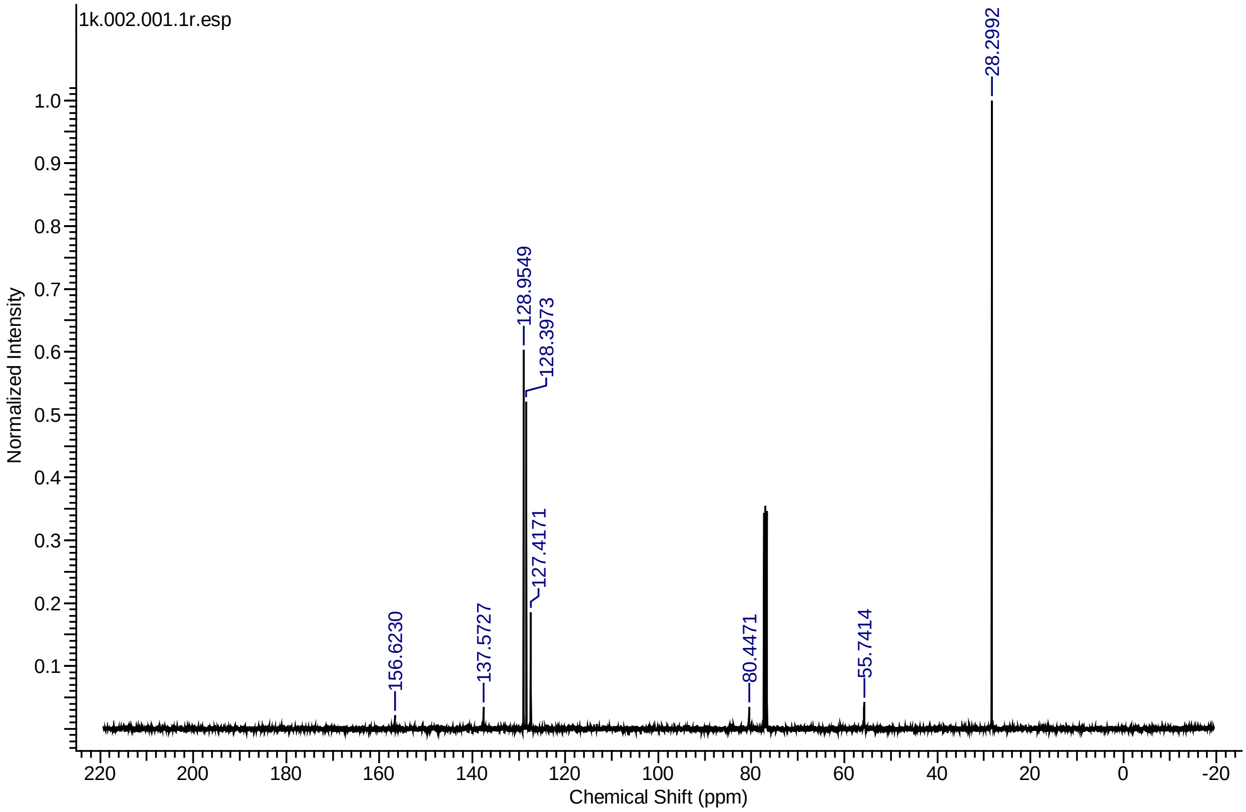

3j.001.001.1r.esp
Ph
N
H
O
NH
N
2.26
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
5.07
0.93
0.90
2.08
0.94
1.88
1.17
2.02
1.08
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

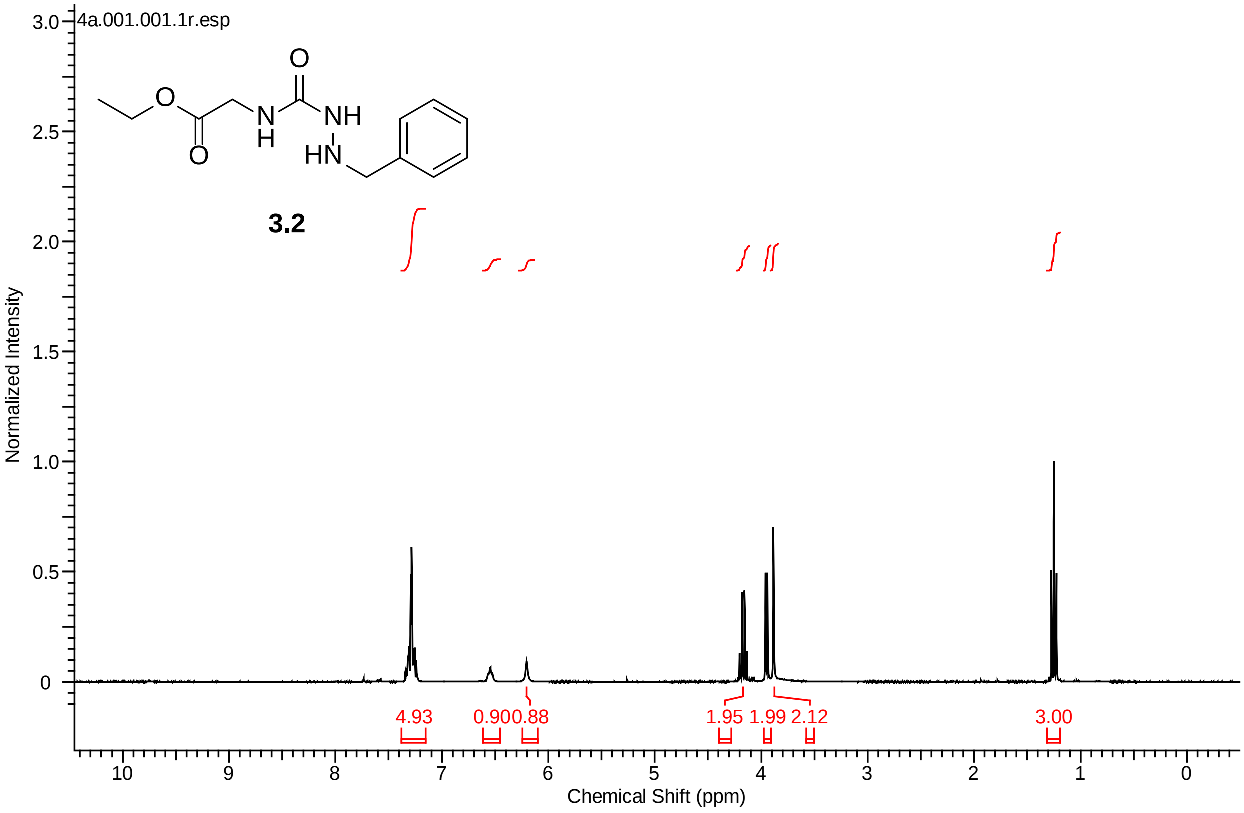

3j.003.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
159.2540
139.6096
128.4601
127.2201
127.0201
62.3304
56.2610
43.3733
30.1000
19.8706
18.3250
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

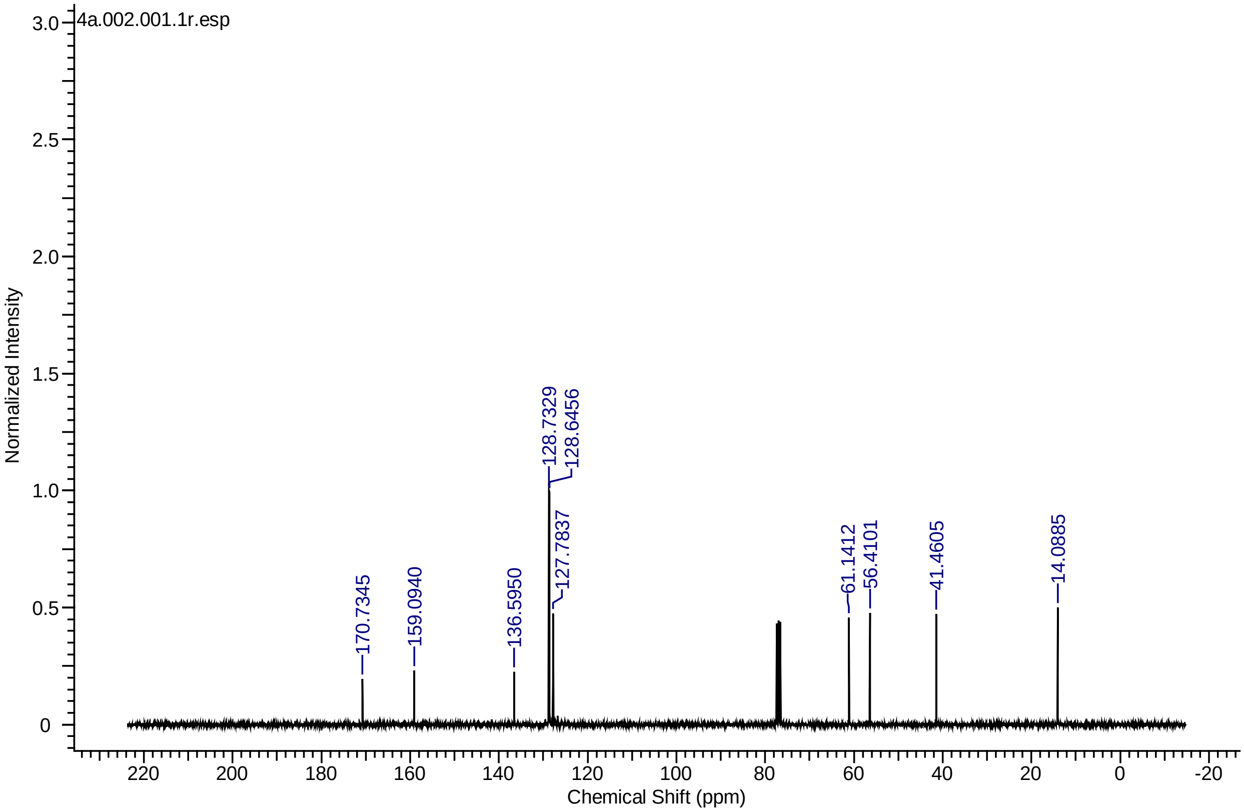

3.1
1j.001.001.1r.esp
PhO
O
NH
HN
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
5.81
0.98
0.93
1.88
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

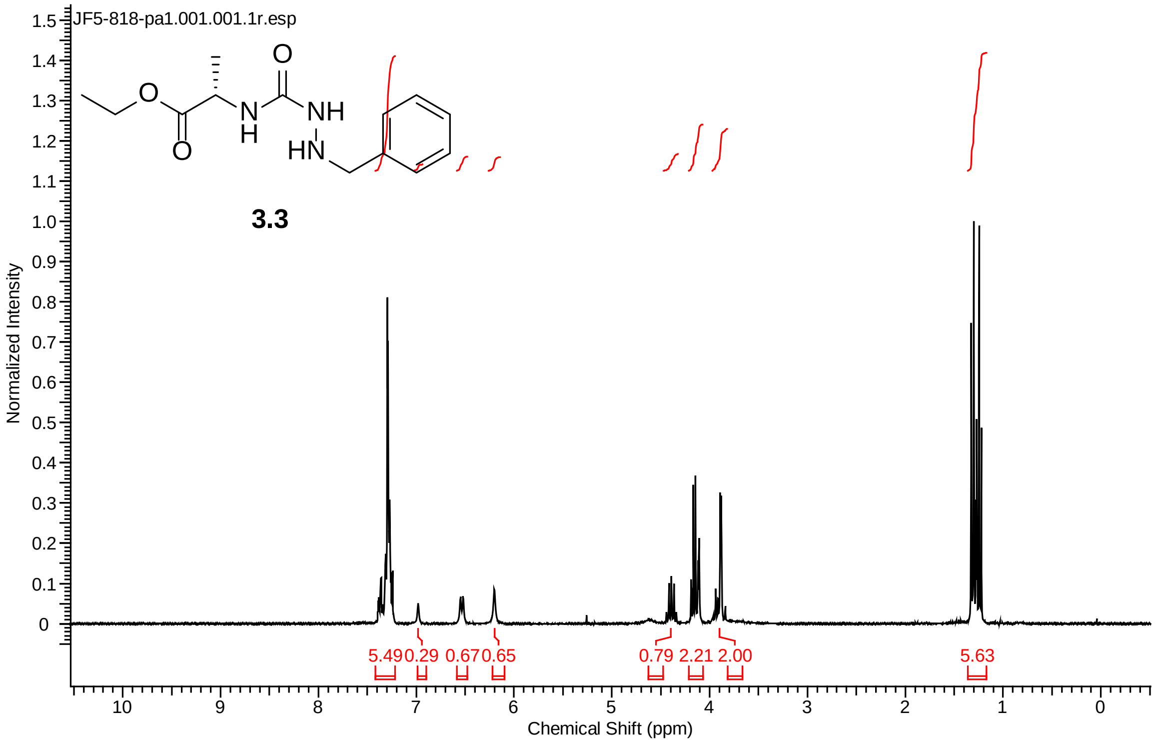

1j.002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
155.4497
150.6179
137.1136
129.3630
128.9840
128.5722
127.6941
121.3682
55.4937
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


1k.001.001.1r.esp
O
NH
HN
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
4.89
0.80
2.05
0.77
9.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


1k.002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
156.6230
137.5727
128.9549
128.3973
127.4171
80.4471
55.7414
28.2992
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

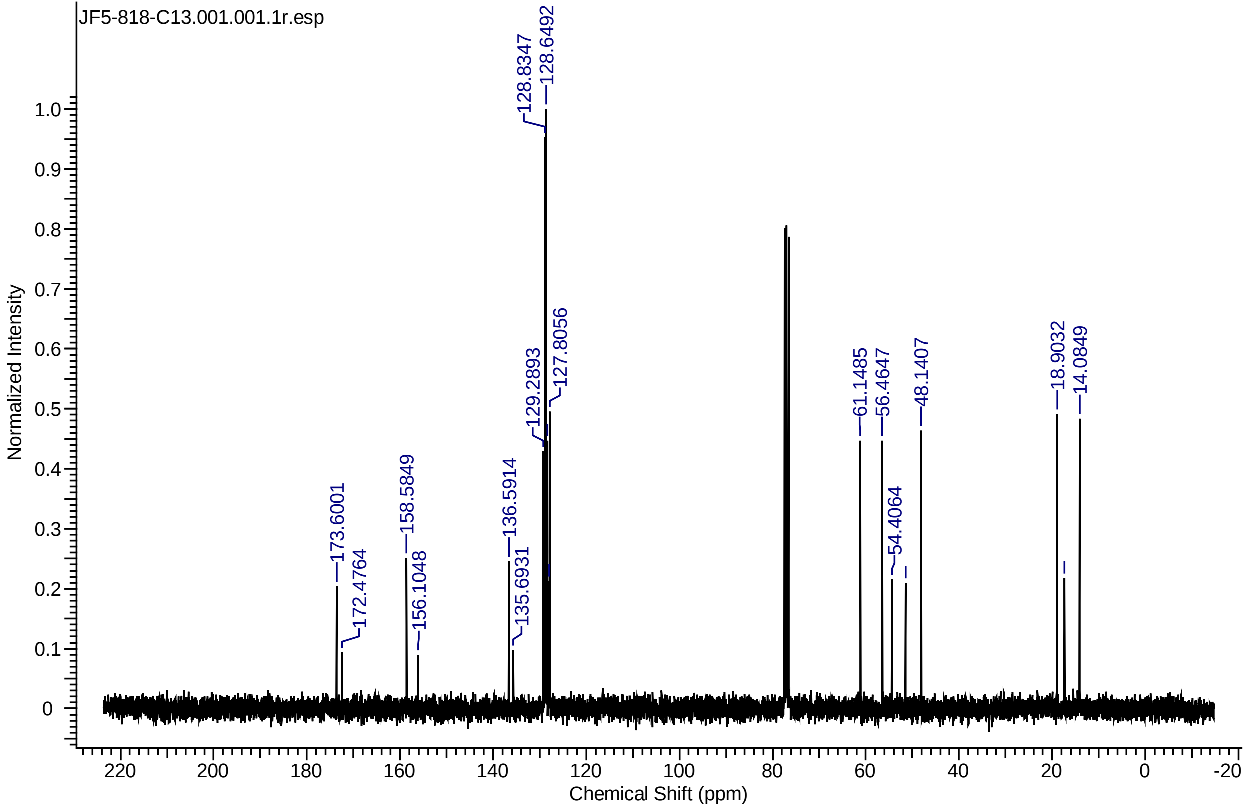

4a.001.001.1r.esp
3.2
O
O
N
H
NH
HN
O
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
4.93
0.90
0.88
1.95
1.99
2.12
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


4a.002.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
170.7345
159.0940
136.5950
128.7329
128.6456
127.7837
61.1412
56.4101
41.4605
14.0885
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

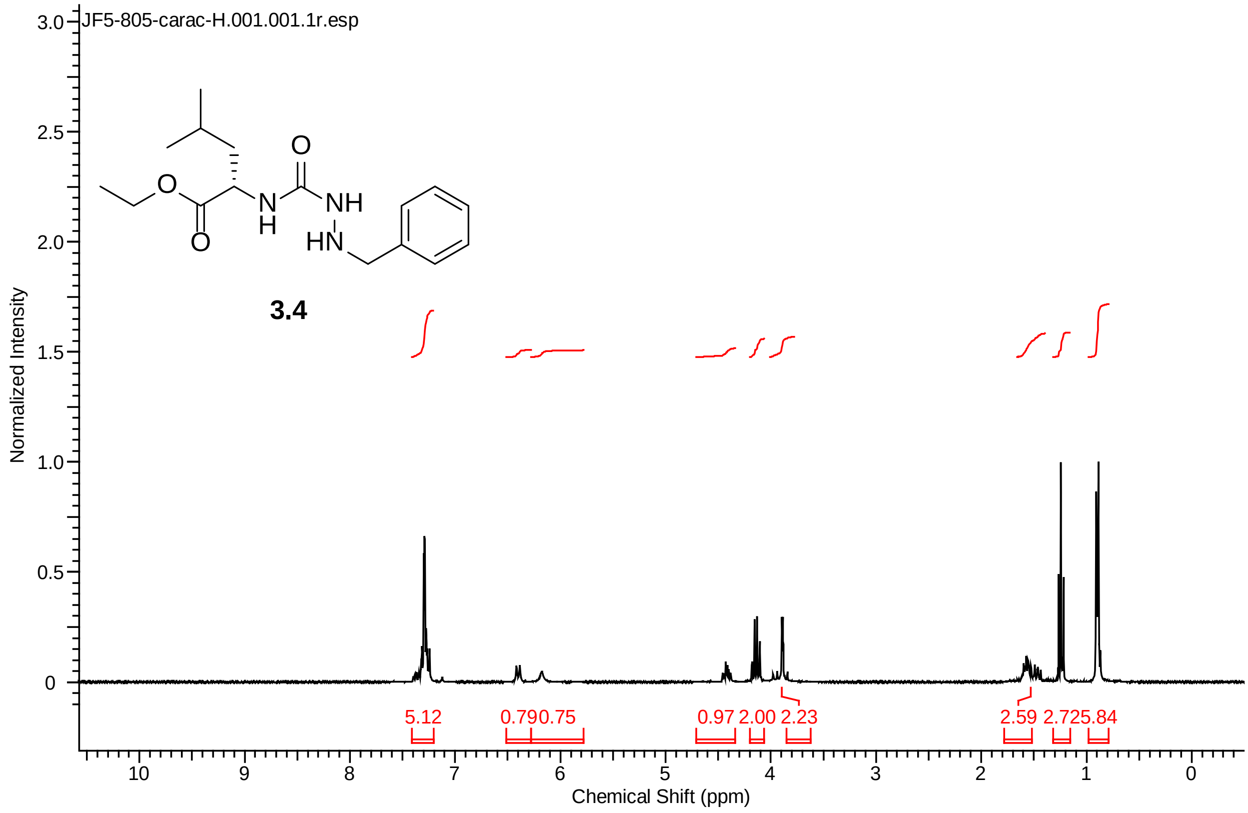


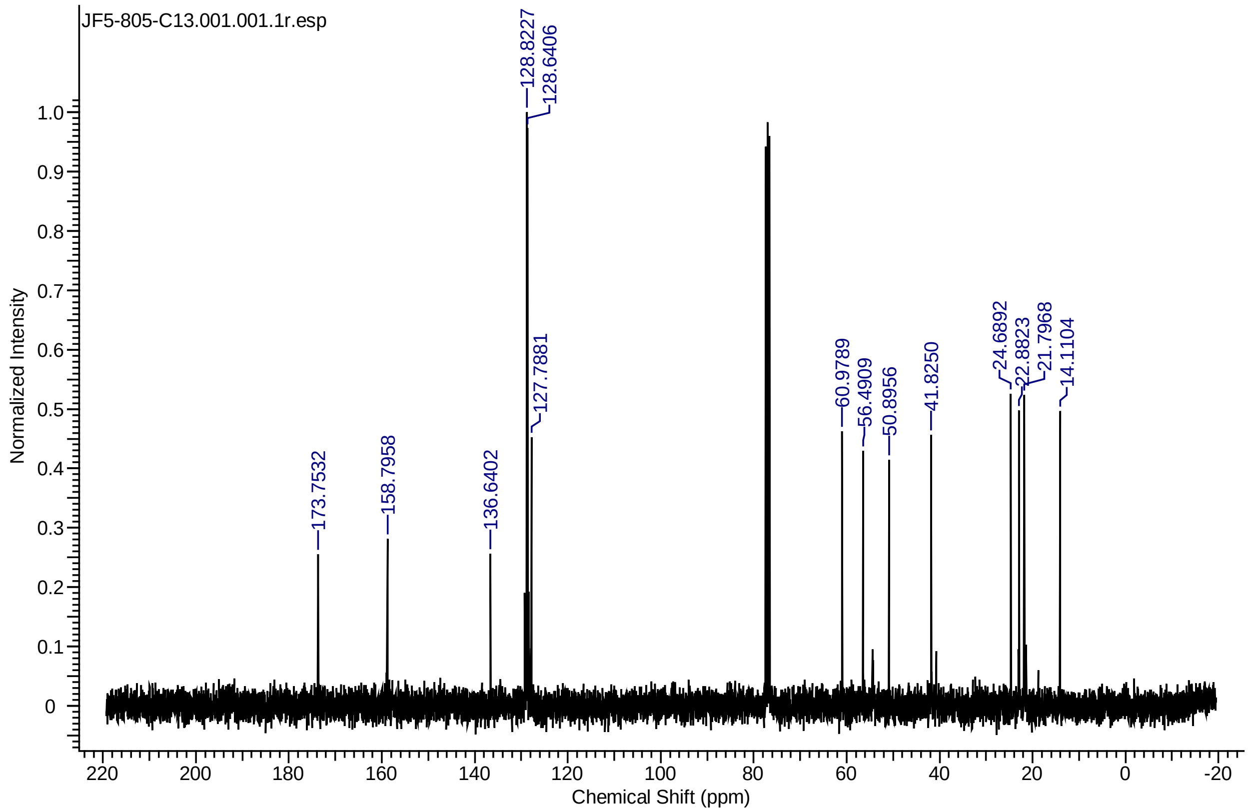
3.3

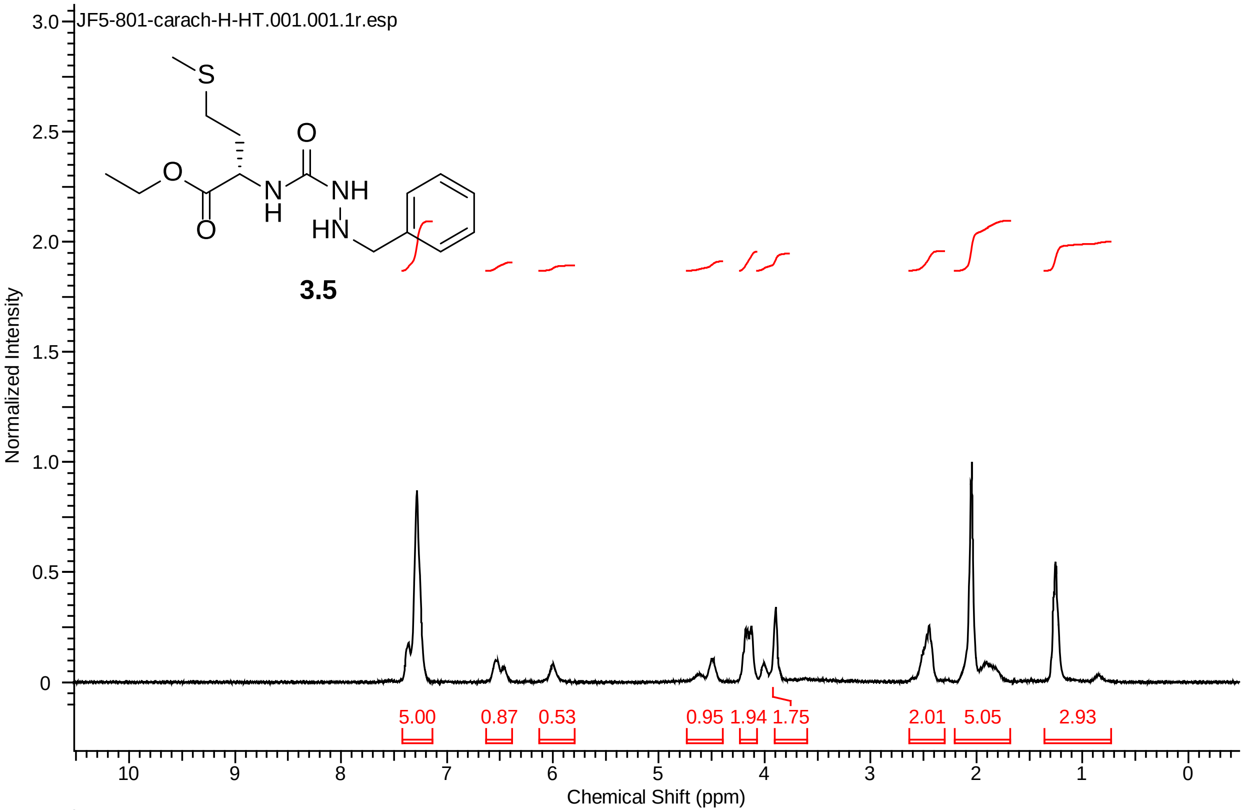
JF5-818-pa1.001.001.1r.esp
O
O
O
N
H
NH
HN
Normalized Intensity
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
5.49
0.29
0.67
0.65
0.79
2.21
2.00
5.63
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

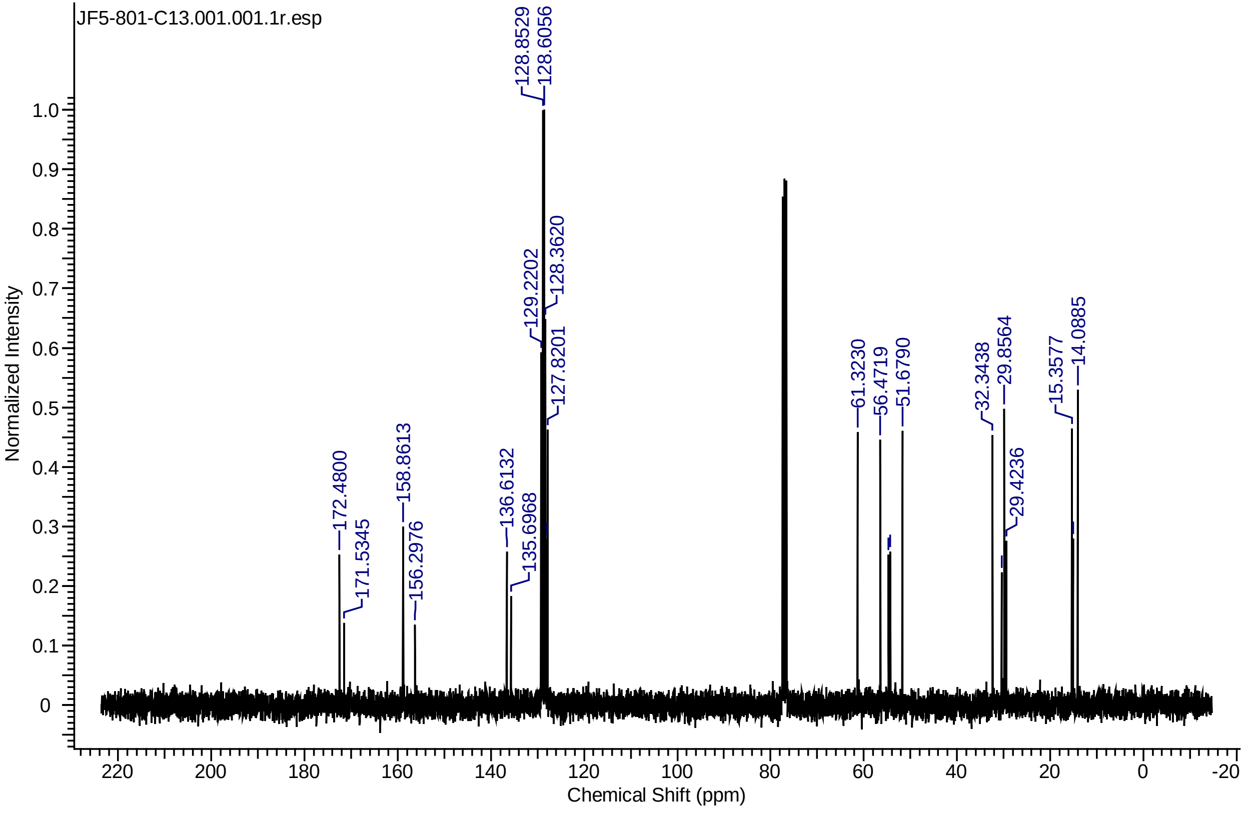


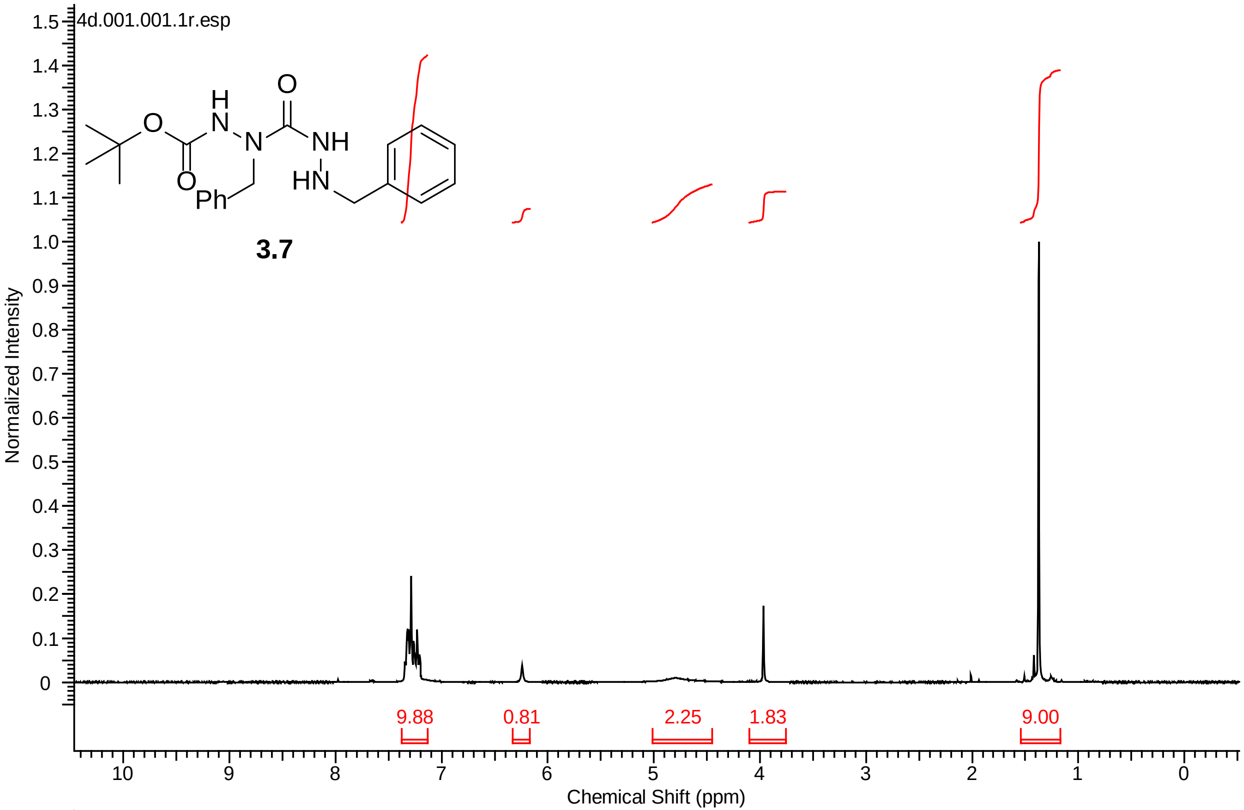
JF5-818-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
173.6001
172.4764
158.5849
156.1048
136.5914
135.6931
129.2893
128.8347
128.6492
127.8056
61.1485
56.4647
54.4064
48.1407
18.9032
14.0849
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

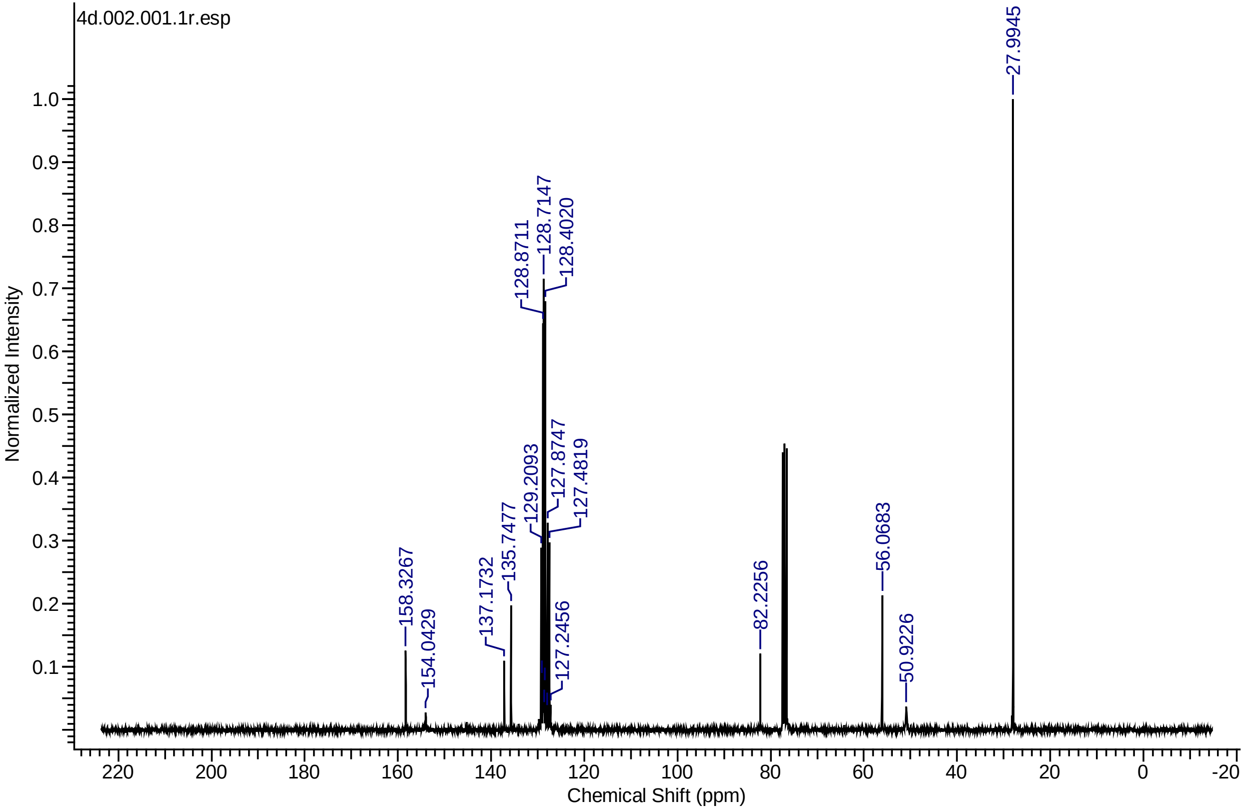

JF5-805-carac-H.001.001.1r.esp
3.4
O
O
O
N
H
NH
HN
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
5.12
0.79
0.75
0.97
2.00
2.23
2.59
2.72
5.84
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

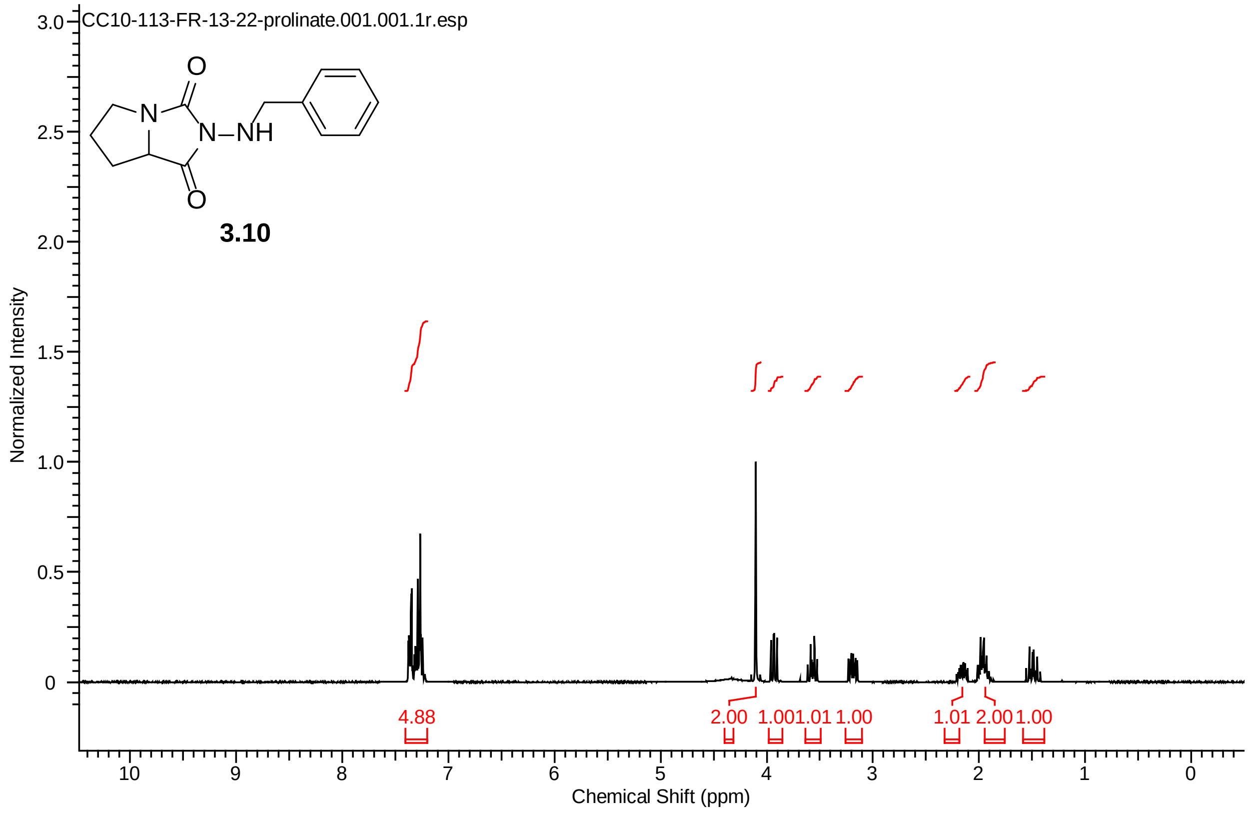

JF5-805-C13.001.001.1r.esp
173.7532
158.7958
136.6402
128.8227
128.6406
127.7881
60.9789
56.4909
50.8956
41.8250
24.6892
22.8823
21.7968
14.1104
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF5-801-carach-H-HT.001.001.1r.esp
S
O
O
N
H
O
NH
HN
3.5
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
5.00
0.87
0.53
0.95
1.94
1.75
2.01
5.05
2.93
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

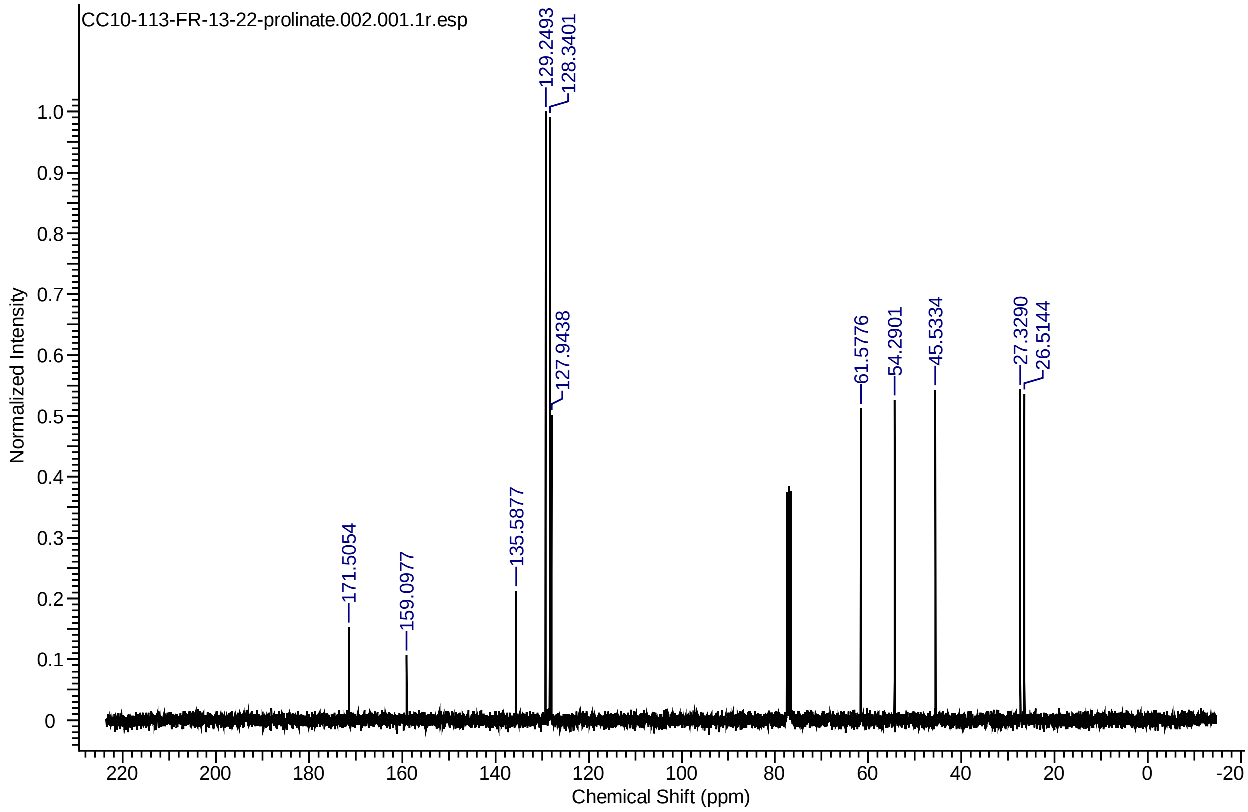

JF5-801-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
172.4800
171.5345
158.8613
156.2976
136.6132
135.6968
129.2202
128.8529
128.6056
128.3620
127.8201
61.3230
56.4719
51.6790
32.3438
29.8564
29.4236
15.3577
14.0885
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

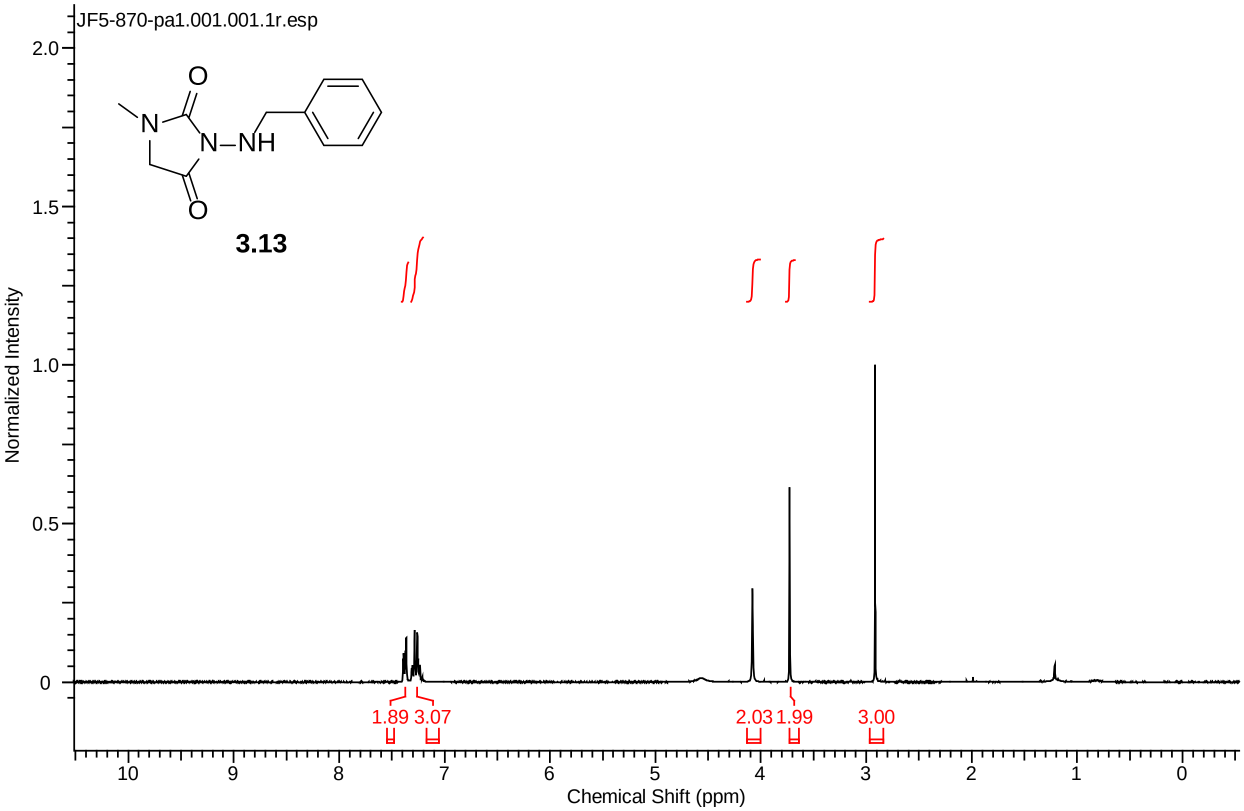

4d.001.001.1r.esp
O
H
N
N
O
NH
HN
O
Ph
3.7
Normalized Intensity
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
9.88
0.81
2.25
1.83
9.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

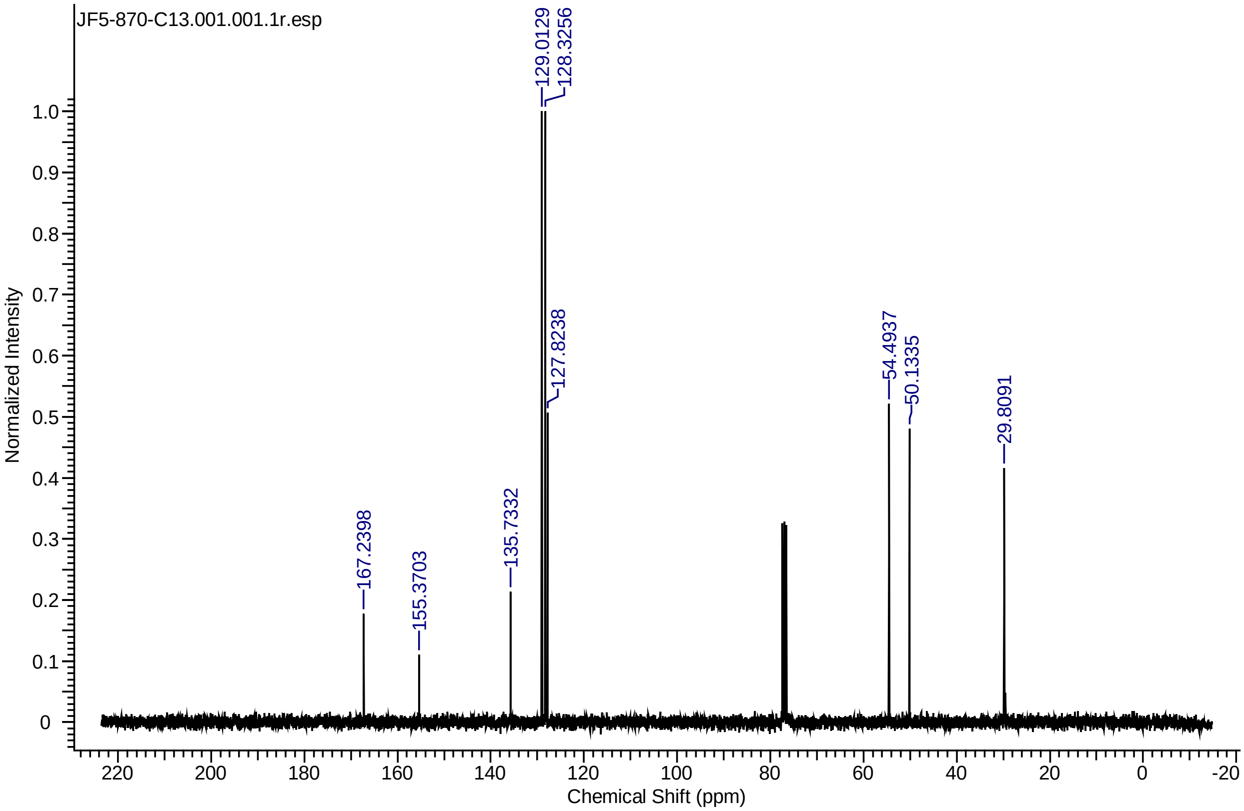

4d.002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
27.9945
128.8711
128.7147
128.4020
129.2093
127.8747
127.4819
135.7477
137.1732
158.3267
154.0429
127.2456
82.2256
56.0683
50.9226
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

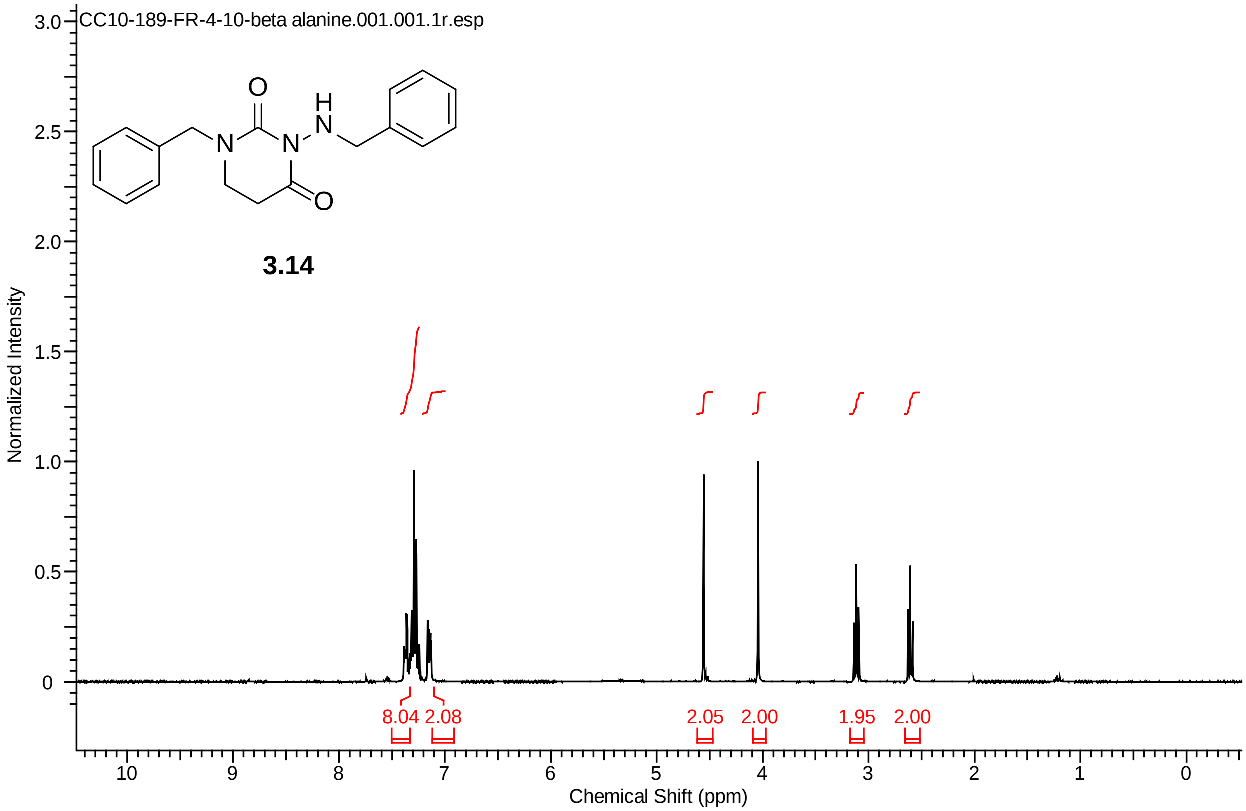

CC10-113-FR-13-22-prolinate.001.001.1r.esp
O
N
N–NH
O
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
4.88
2.00
1.00
1.01
1.00
1.01
2.00
1.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

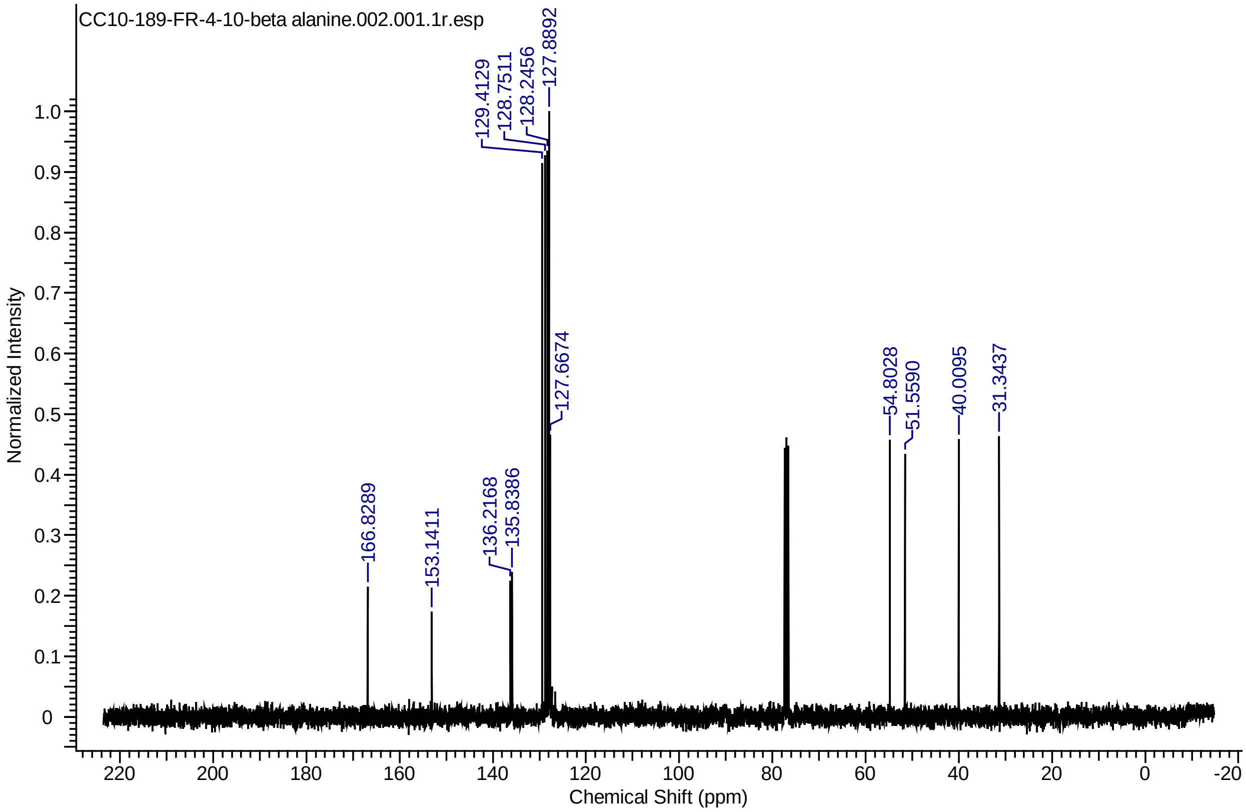
3.10

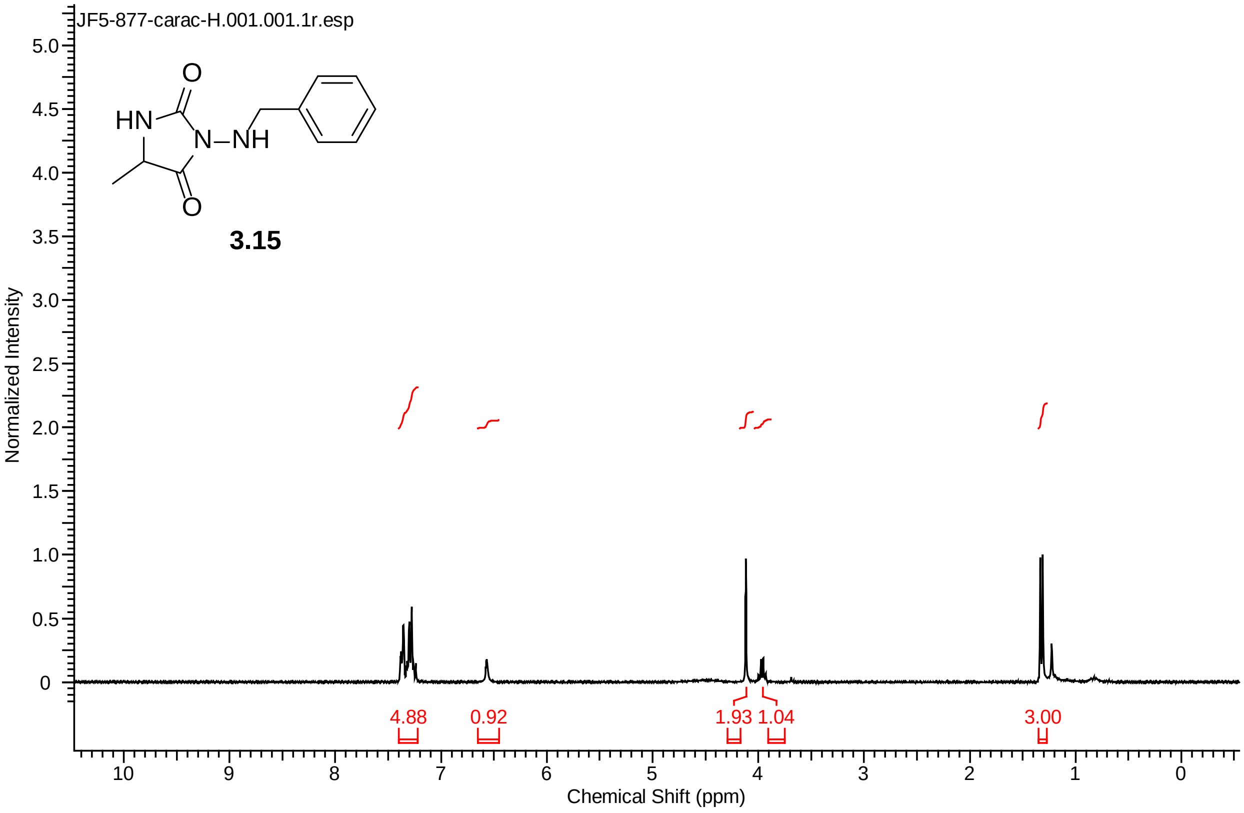

CC10-113-FR-13-22-prolinate.002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
171.5054
159.0977
135.5877
129.2493
128.3401
127.9438
61.5776
54.2901
45.5334
27.3290
26.5144
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

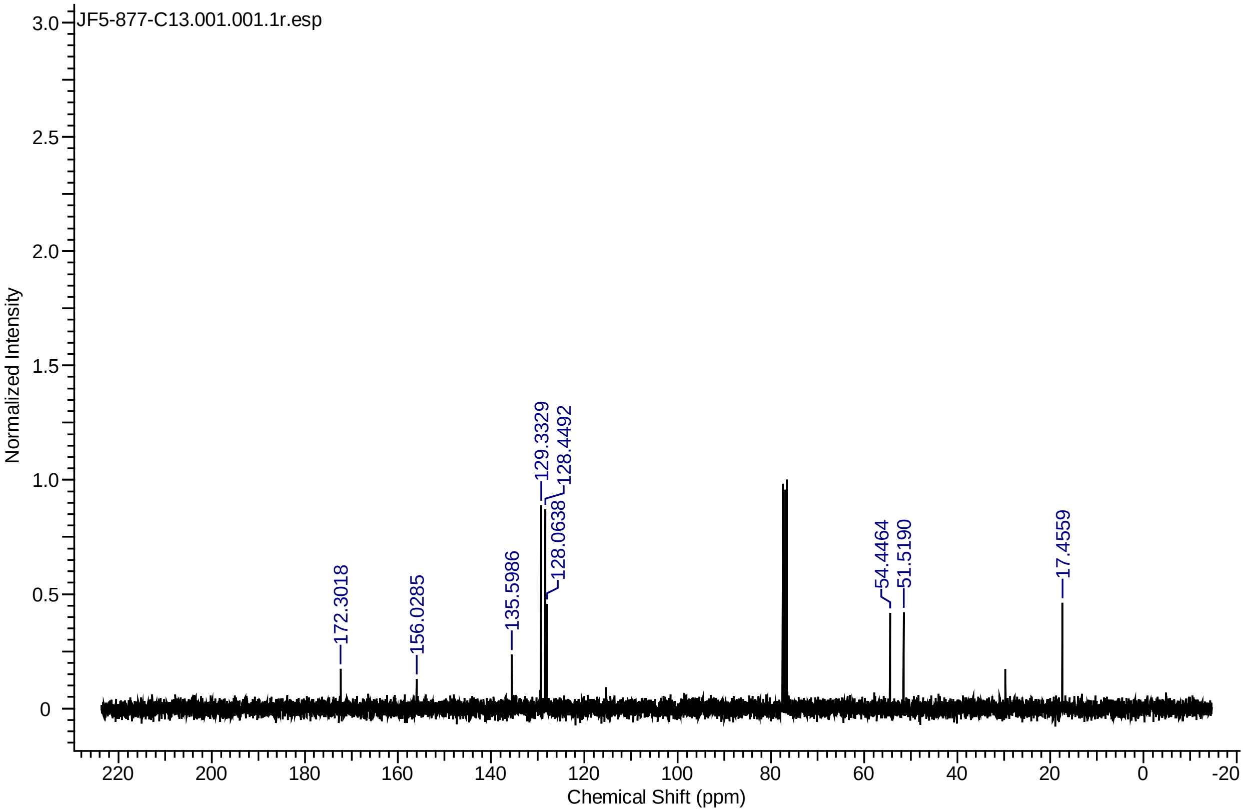

JF5-870-pa1.001.001.1r.esp
O
N
N–NH
O
3.13
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.89
3.07
2.03
1.99
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

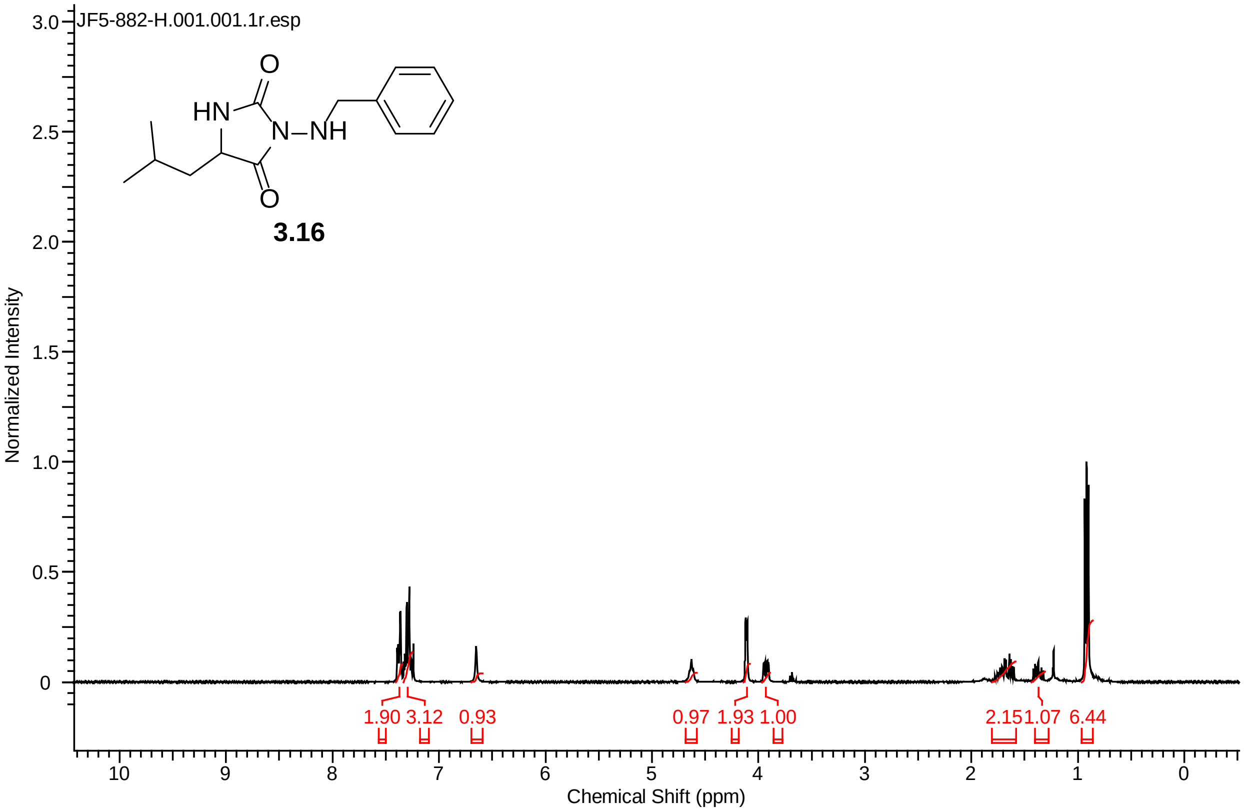

JF5-870-C13.001.001.1r.esp
129.0129
128.3256
127.8238
167.2398
155.3703
135.7332
54.4937
50.1335
29.8091
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

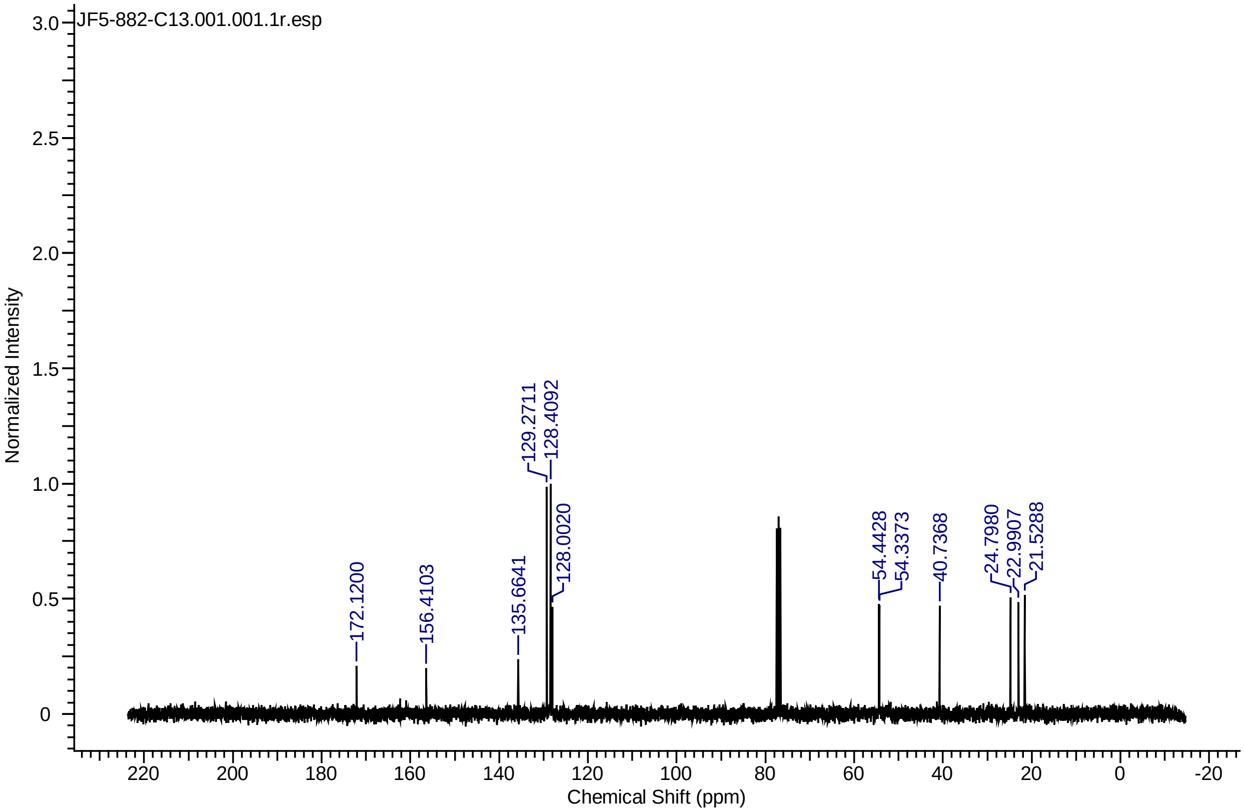

3.14
CC10-189-FR-4-10-beta alanine.001.001.1r.esp
O
H
N
N
N
O
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
8.04
2.08
2.05
2.00
1.95
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

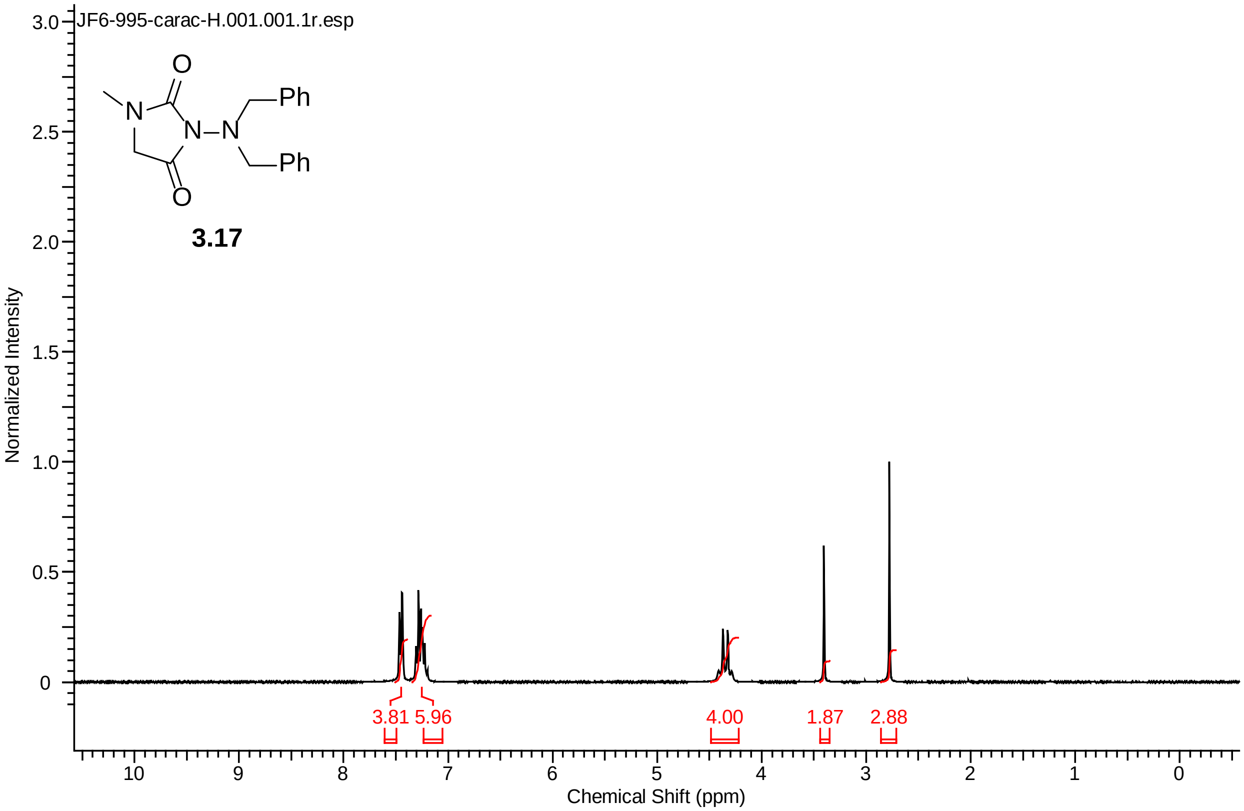

CC10-189-FR-4-10-beta alanine.002.001.1r.esp
129.4129
128.7511
128.2456
127.8892
127.6674
166.8289
153.1411
136.2168
135.8386
54.8028
51.5590
40.0095
31.3437
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

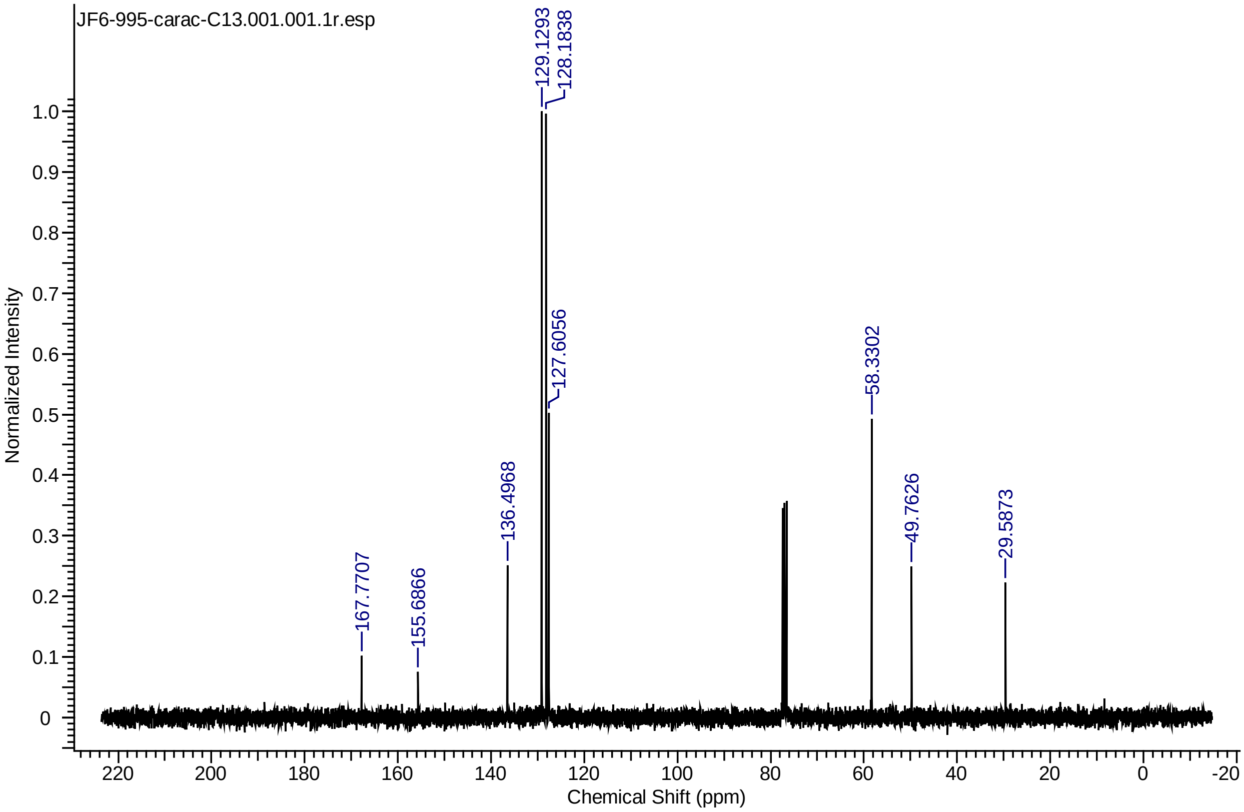

JF5-877-carac-H.001.001.1r.esp
HN
O
N–NH
O
3.15
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
4.88
0.92
1.93
1.04
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

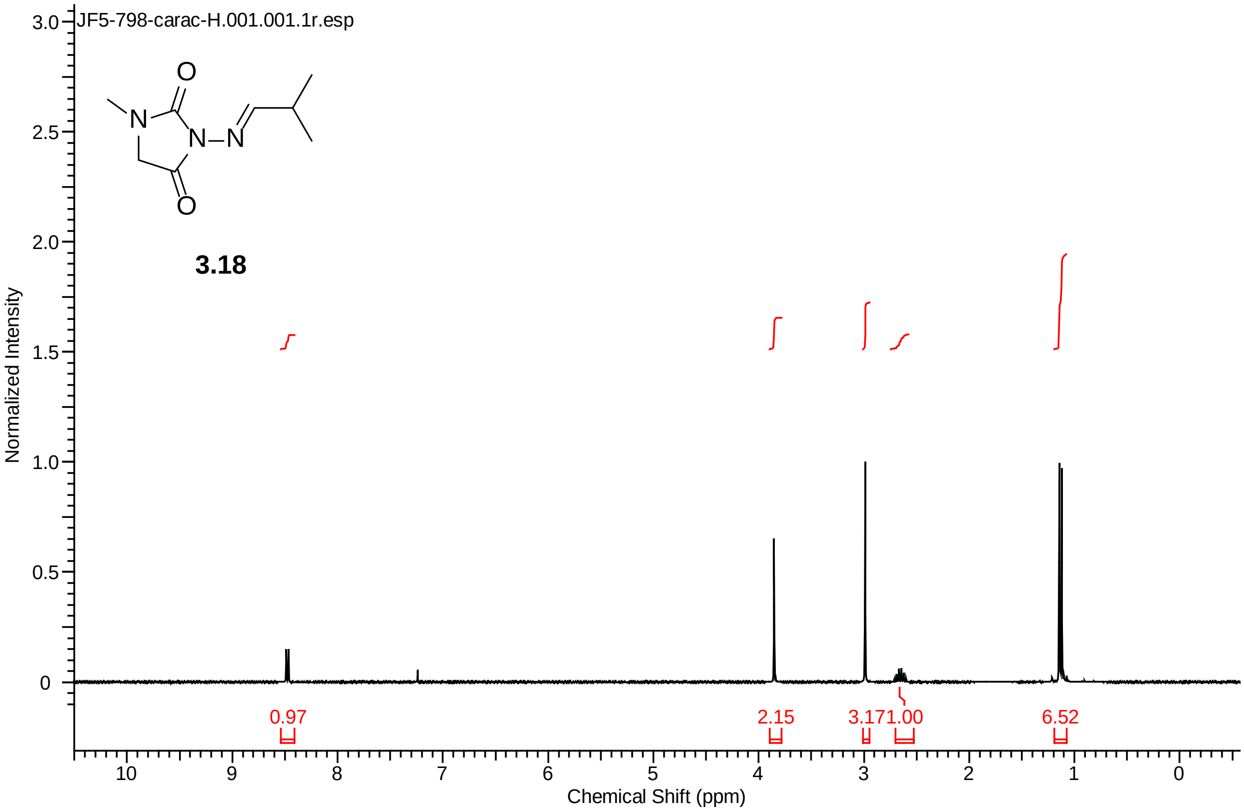

JF5-877-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
172.3018
156.0285
135.5986
129.3329
128.4492
128.0638
54.4464
51.5190
17.4559
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

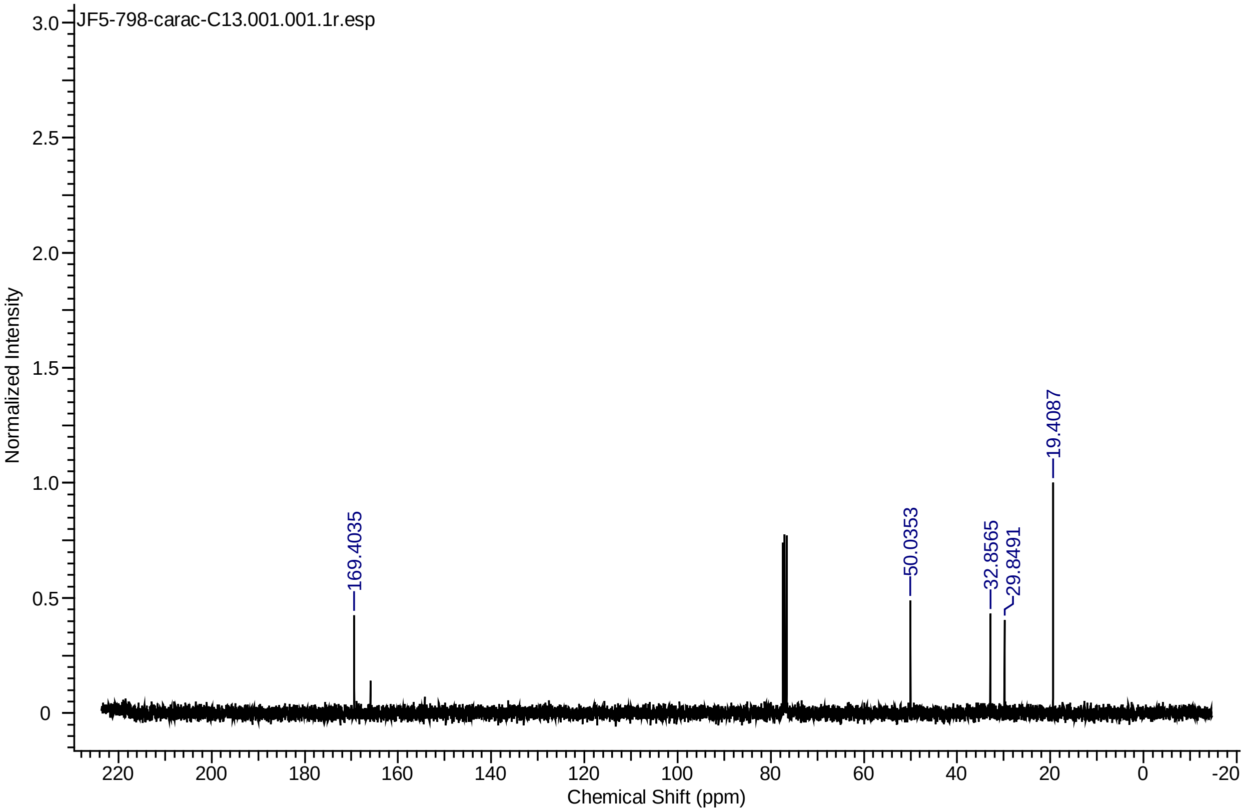

JF5-882-H.001.001.1r.esp
O
HN
N–NH
O
3.16
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
1.90
3.12
0.93
0.97
1.93
1.00
2.15
1.07
6.44
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

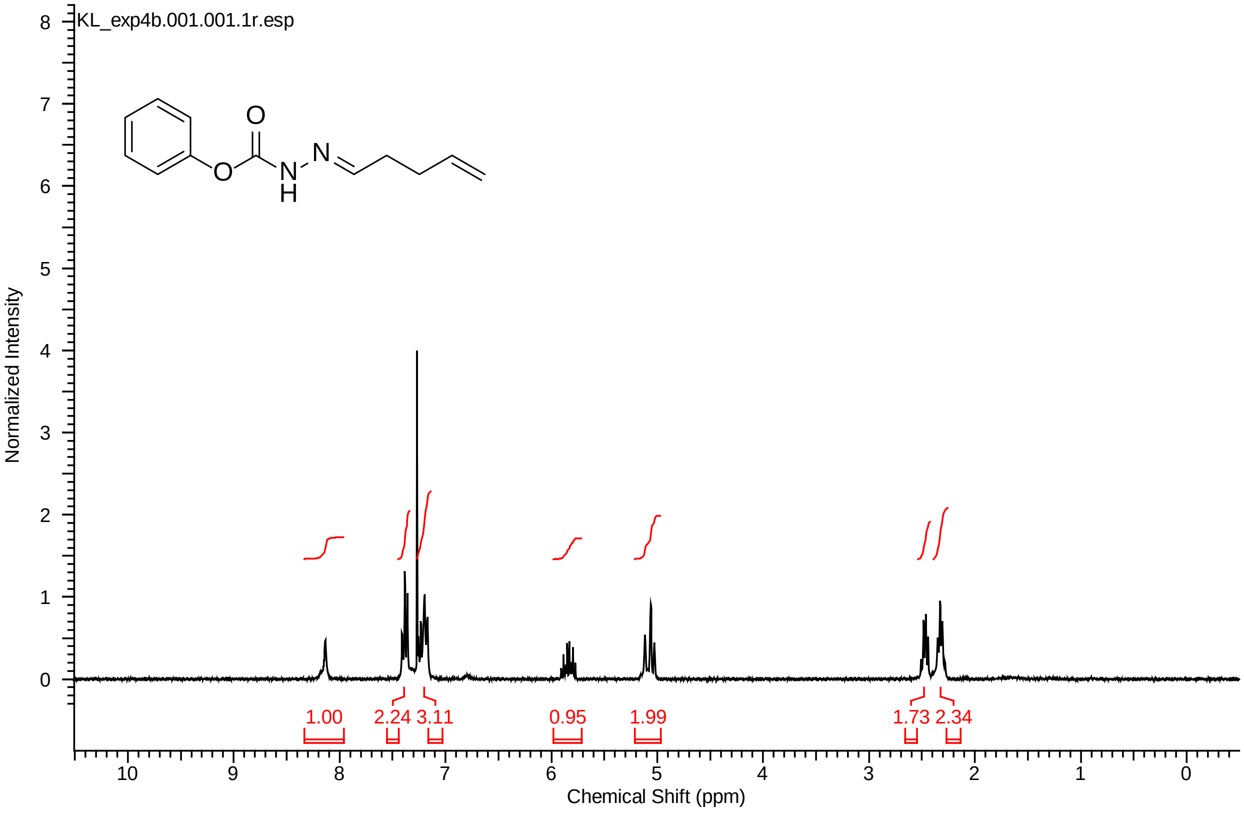

JF5-882-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
172.1200
156.4103
135.6641
129.2711
128.4092
128.0020
54.4428
54.3373
40.7368
24.7980
22.9907
21.5288
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

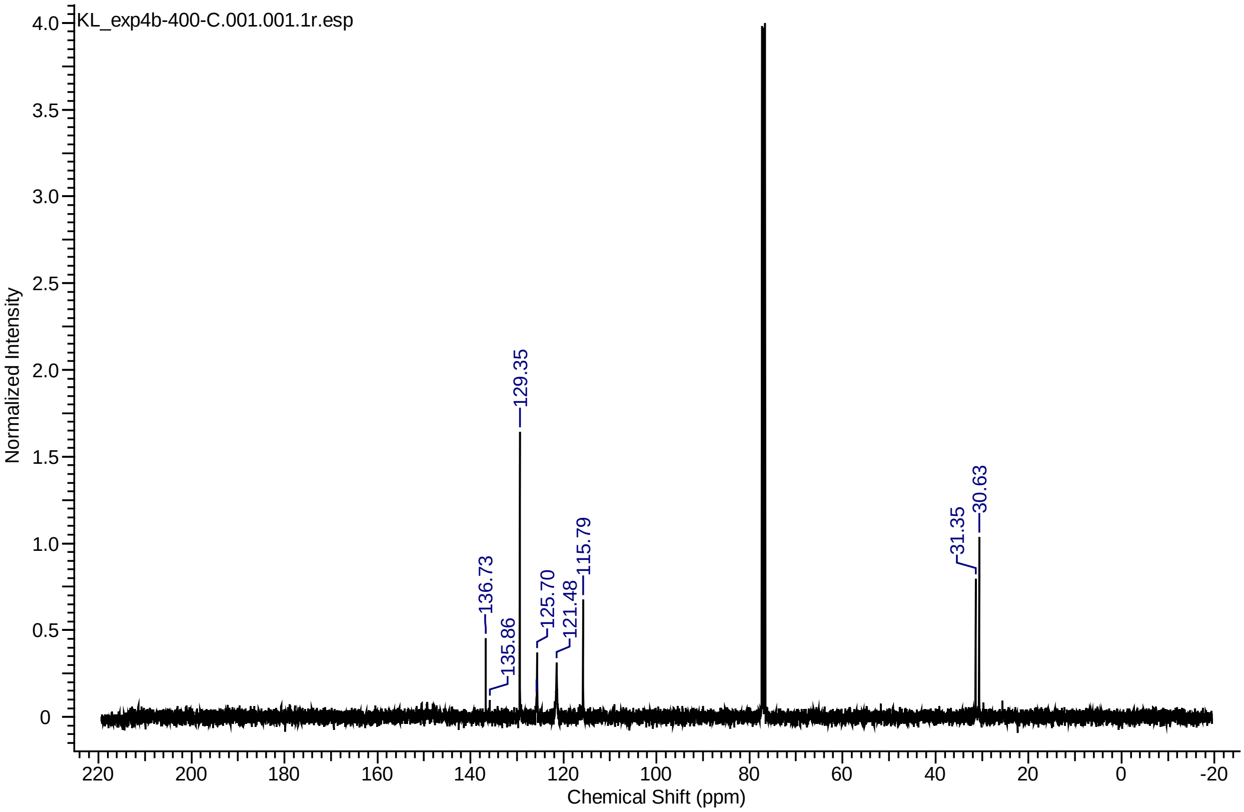

JF6-995-carac-H.001.001.1r.esp
O
N
N–N
Ph
Ph
O
3.17
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
3.81
5.96
4.00
1.87
2.88
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

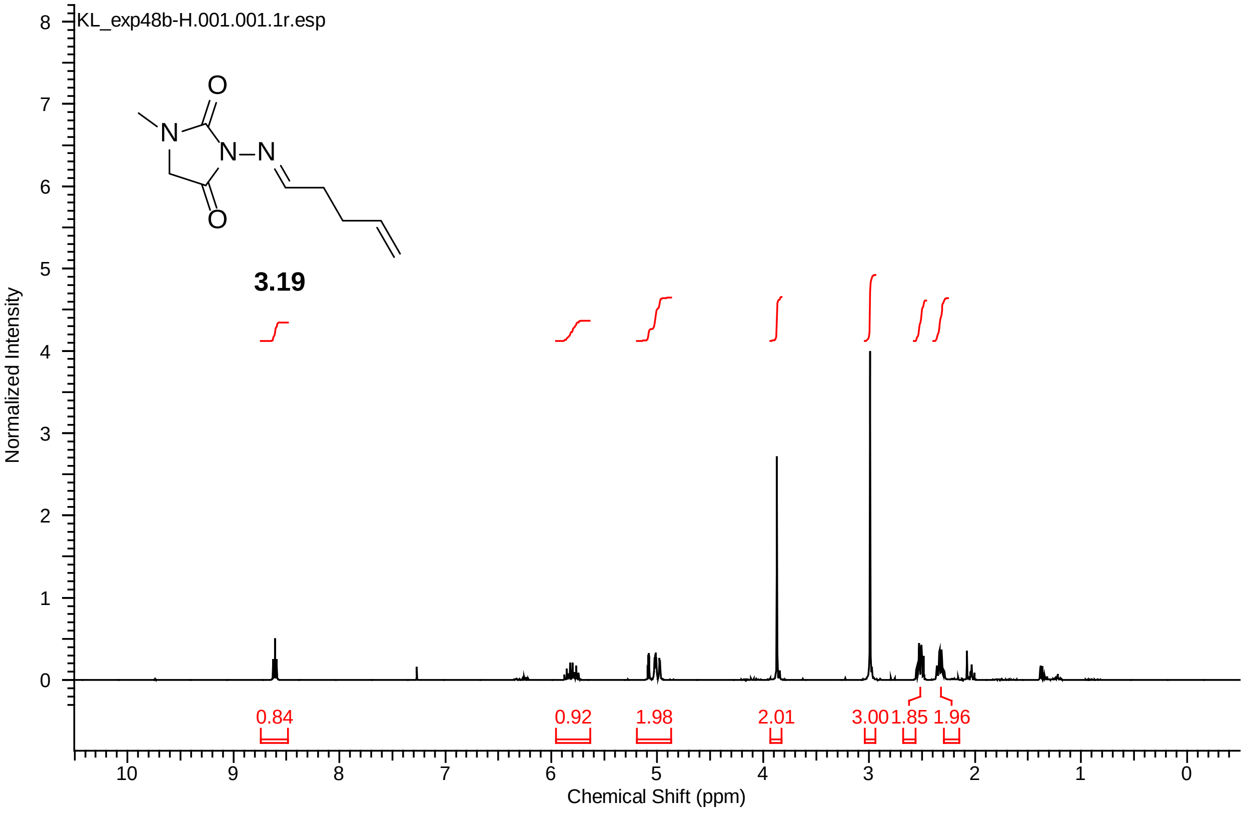

JF6-995-carac-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
167.7707
155.6866
136.4968
129.1293
128.1838
127.6056
58.3302
49.7626
29.5873
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF5-798-carac-H.001.001.1r.esp
3.18
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
0.97
2.15
3.17
1.00
6.52
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF5-798-carac-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
169.4035
50.0353
32.8565
29.8491
19.4087
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

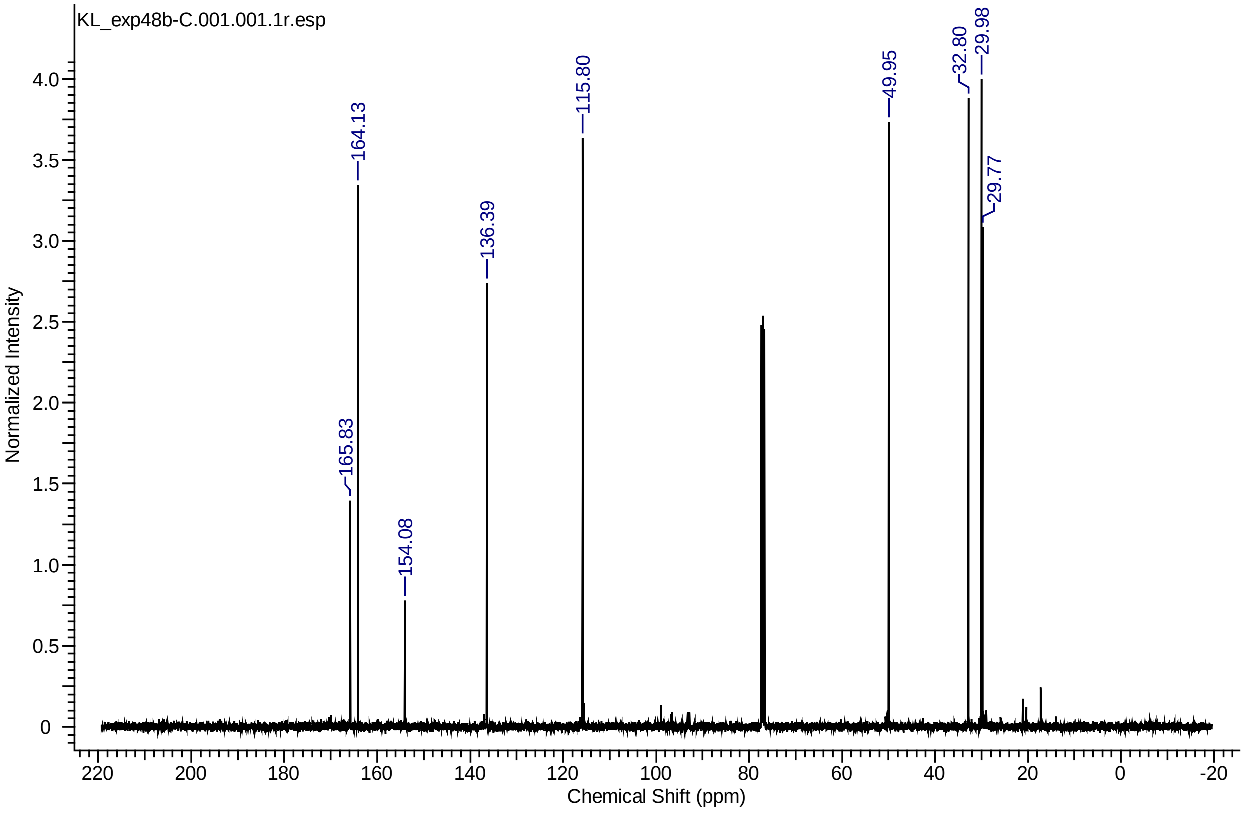

KL_exp4b.001.001.1r.esp
O
O
N
H
N
Normalized Intensity
8
7
6
5
4
3
2
1
0
1.00
2.24
3.11
0.95
1.99
1.73
2.34
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


KL_exp4b-400-C.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
136.73
135.86
129.35
125.70
121.48
115.79
31.35
30.63
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

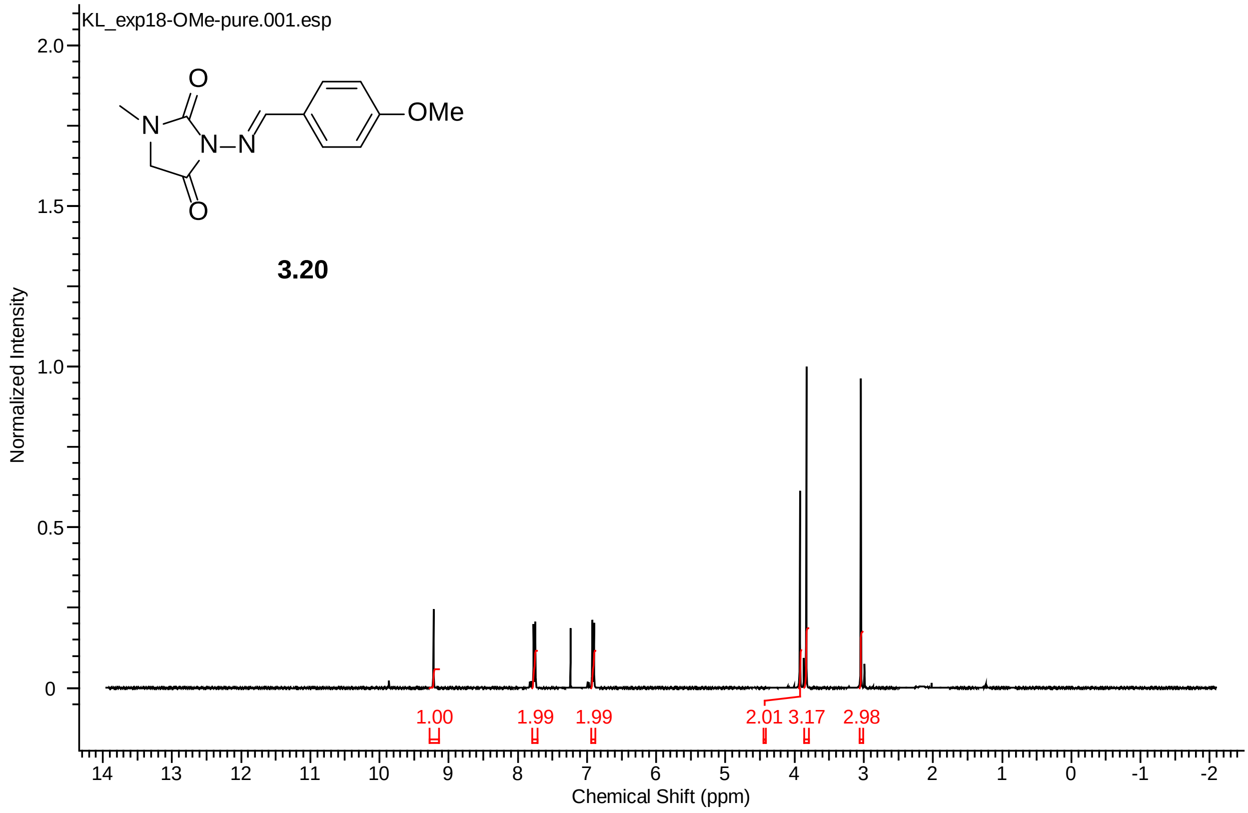


3.19

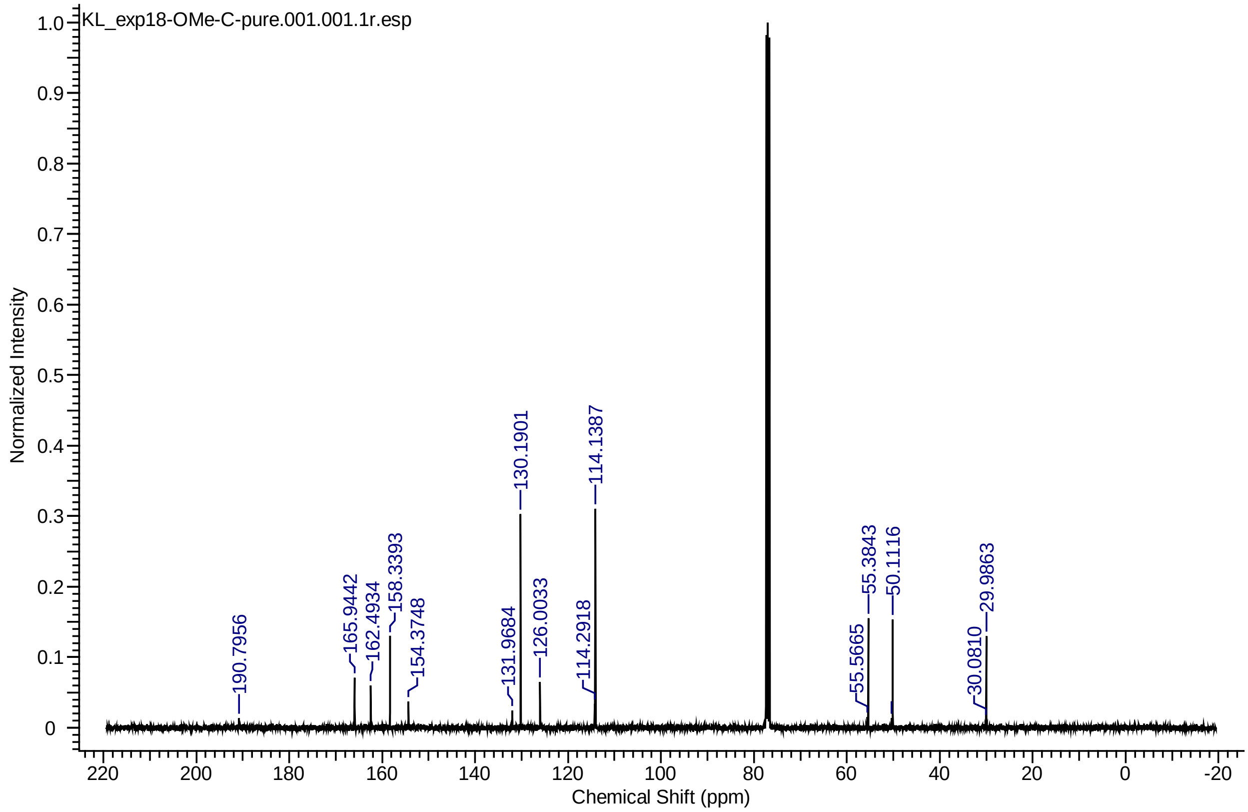
KL_exp48b-H.001.001.1r.esp
O
N
N–N
O
Normalized Intensity
8
7
6
5
4
3
2
1
0
0.84
0.92
1.98
2.01
3.00
1.85
1.96
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

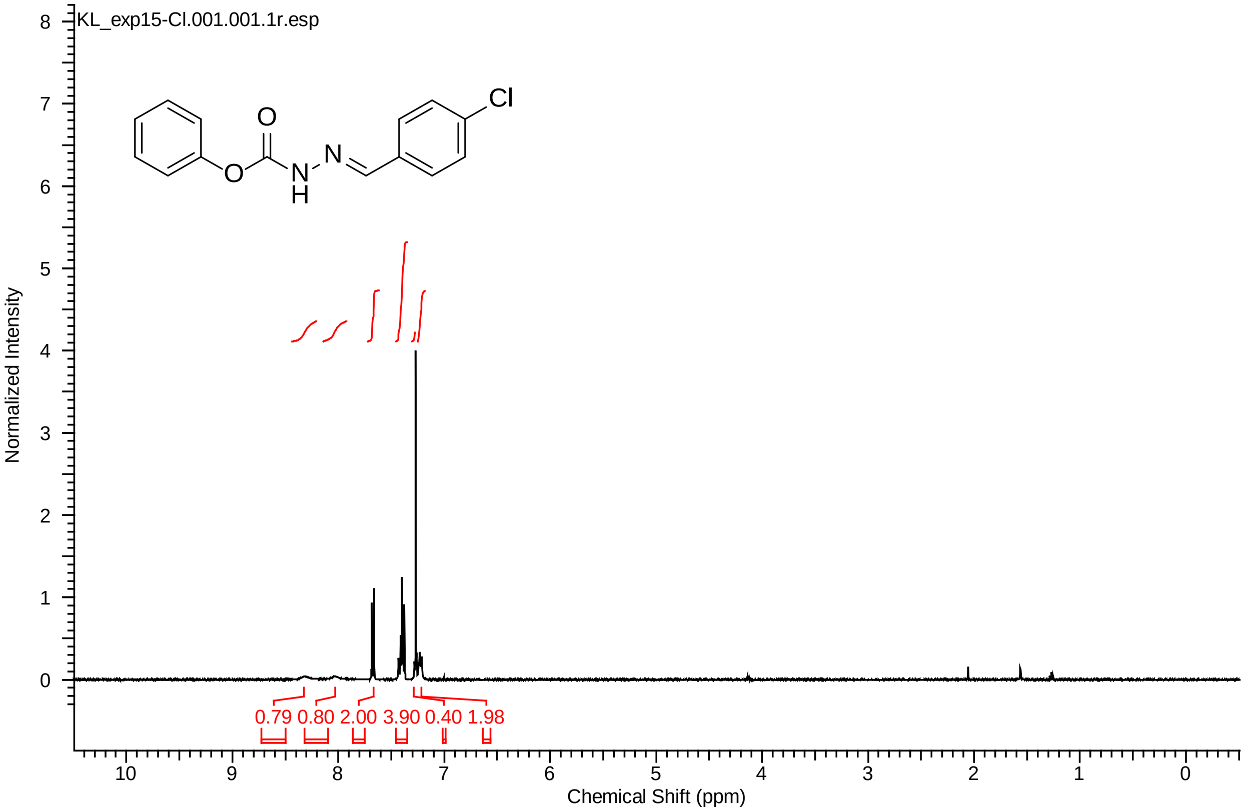


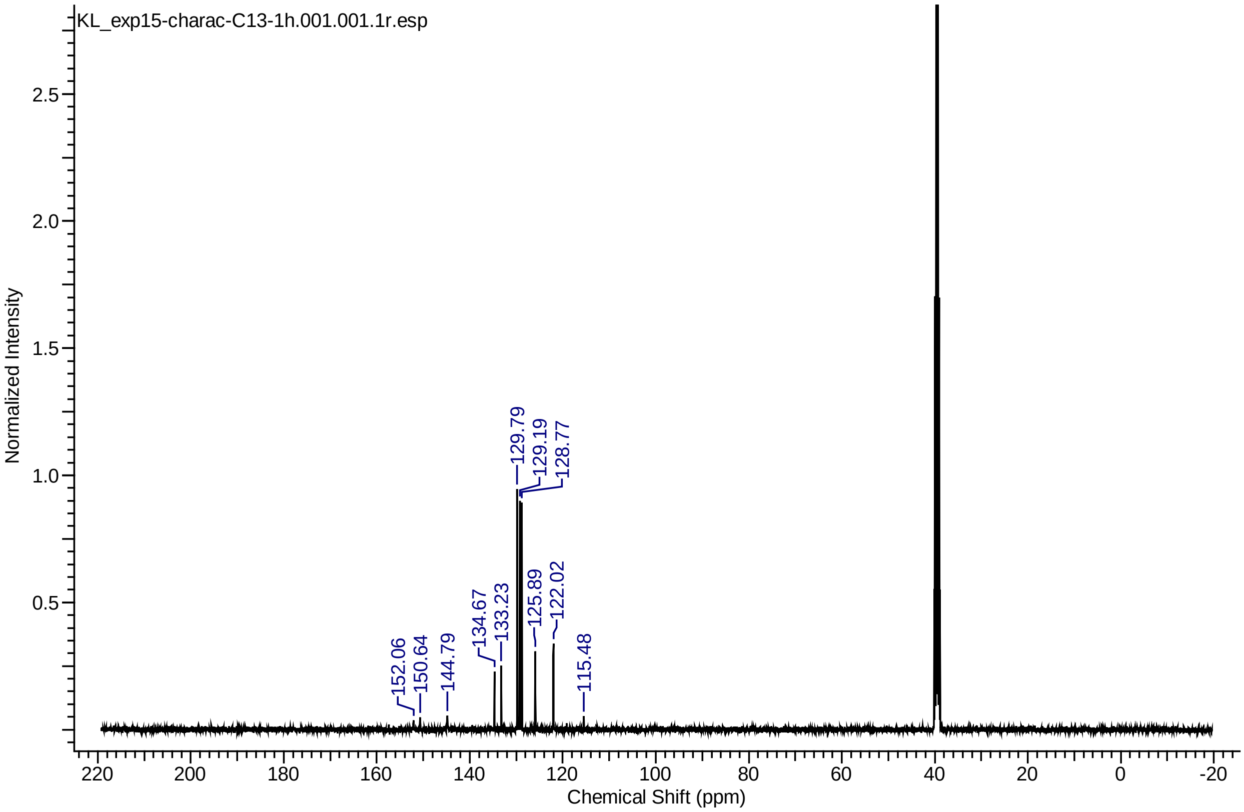
KL_exp48b-C.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
165.83
164.13
154.08
136.39
115.80
49.95
32.80
29.98
29.77
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

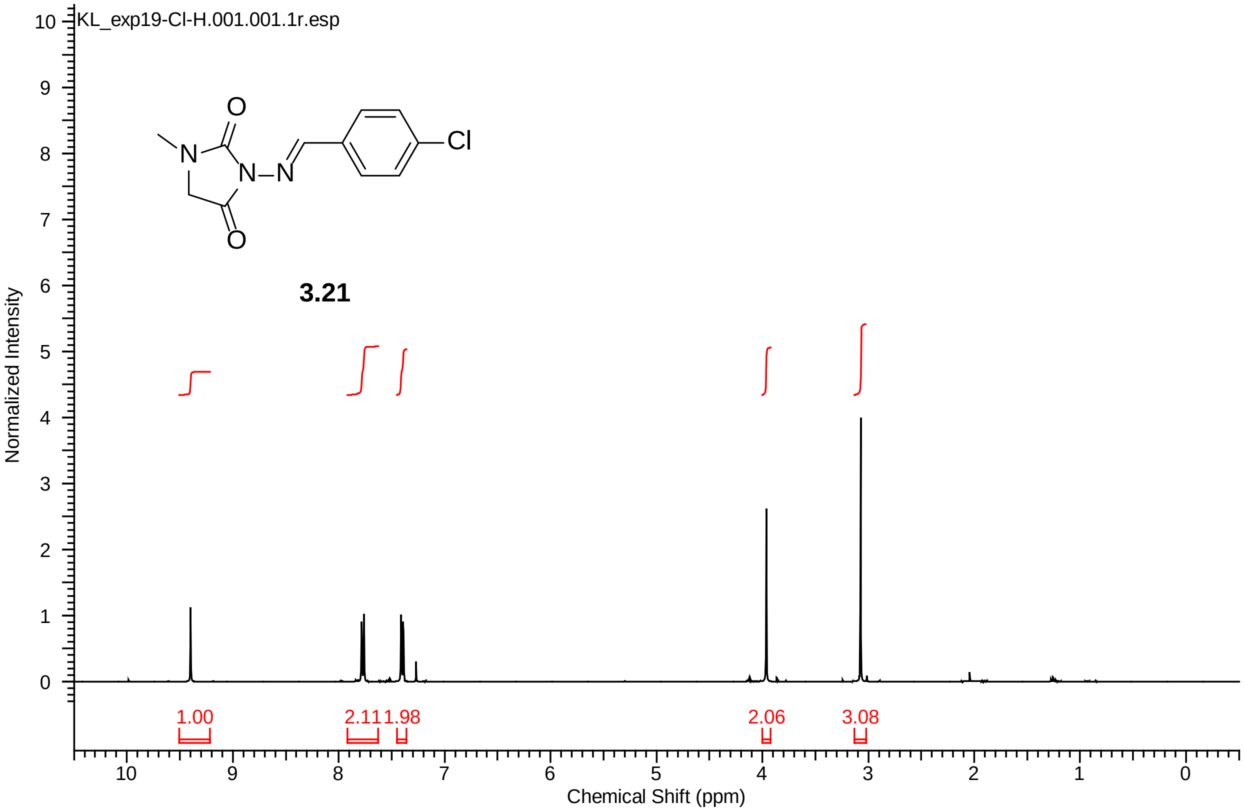

KL_exp18-OMe-pure.001.esp
O
N
N–N
OMe
O
2.0
1.5
1.0
0.5
0
Normalized Intensity
1.00
1.99
1.99
2.01
3.17
2.98
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

3.20

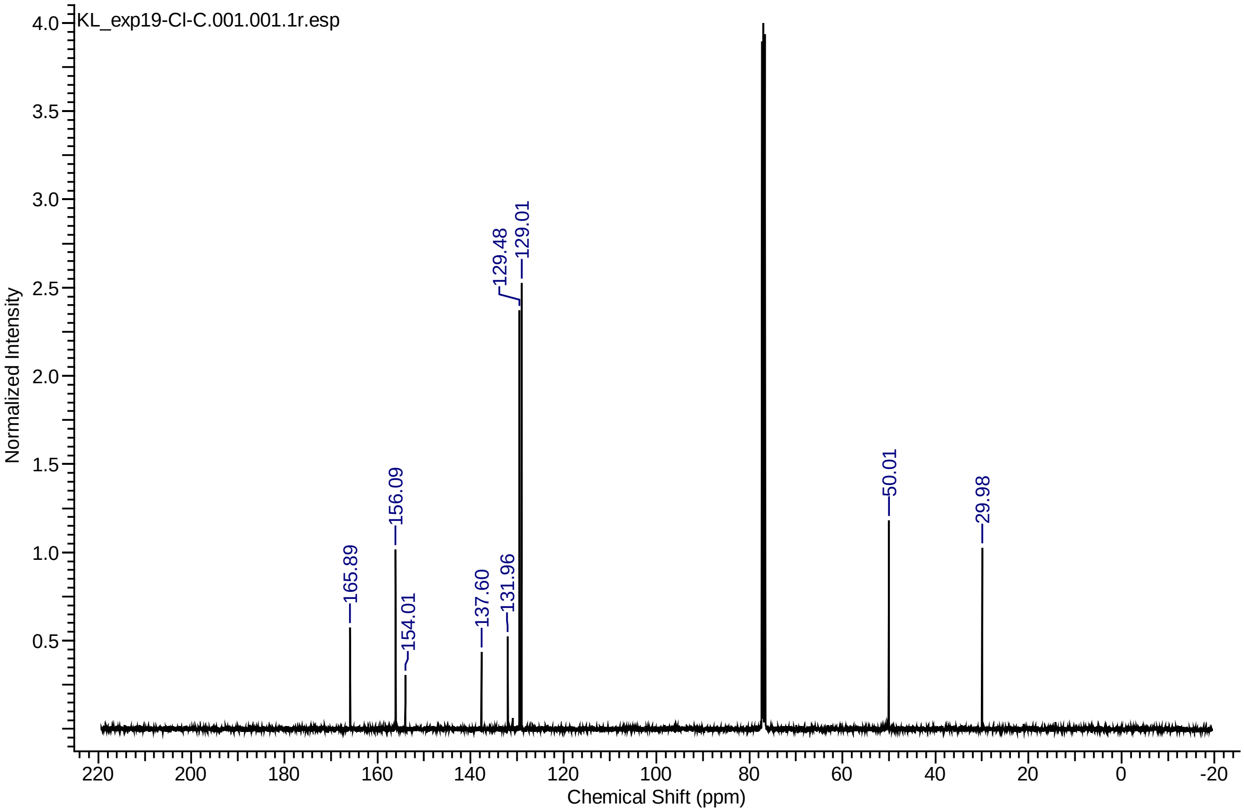

KL_exp18-OMe-C-pure.001.001.1r.esp
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Normalized Intensity
190.7956
165.9442
162.4934
158.3393
154.3748
131.9684
130.1901
126.0033
114.2918
114.1387
55.5665
55.3843
50.1116
30.0810
29.9863
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

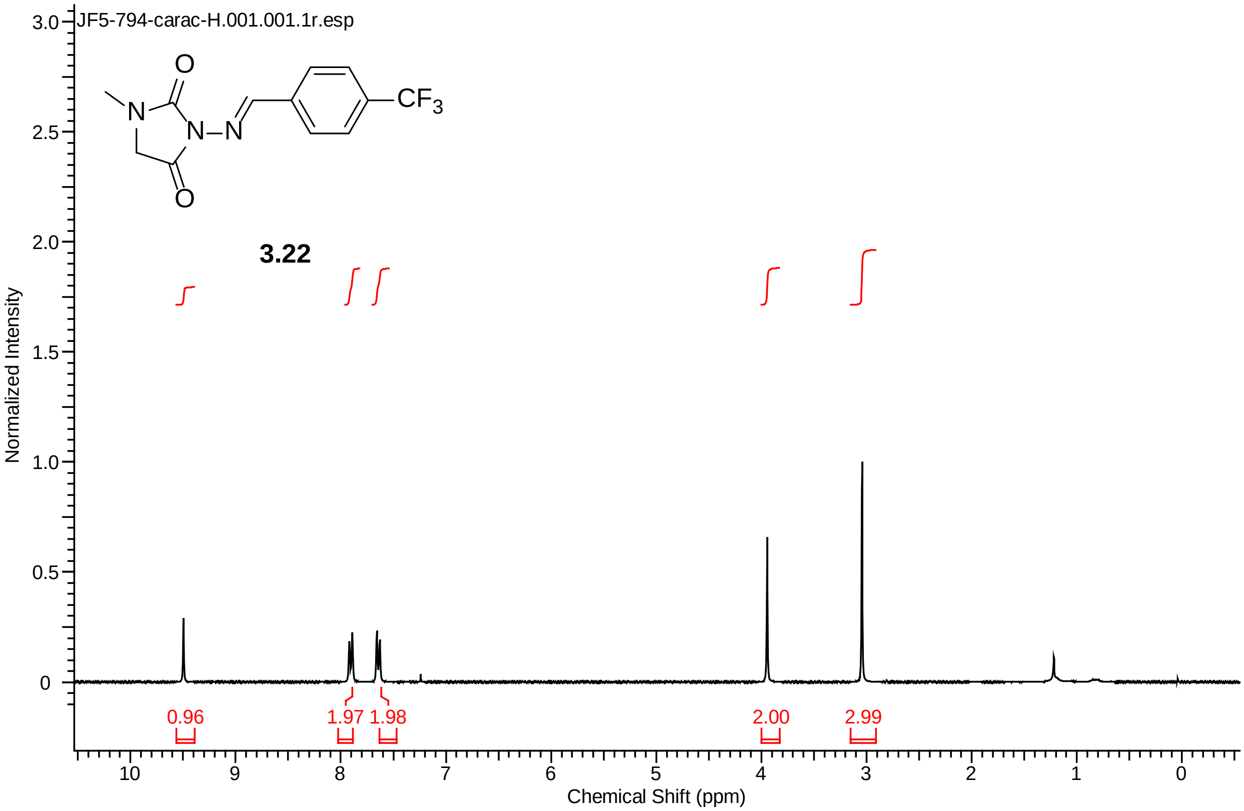

KL_exp15-Cl.001.001.1r.esp
Cl
O
O
N
H
N
Normalized Intensity
0.79
0.80
2.00
3.90
0.40
1.98
Chemical Shift (ppm)
10
9
8
7
6
5
4
3
2
1
0
8
7
6
5
4
3
2
1
0

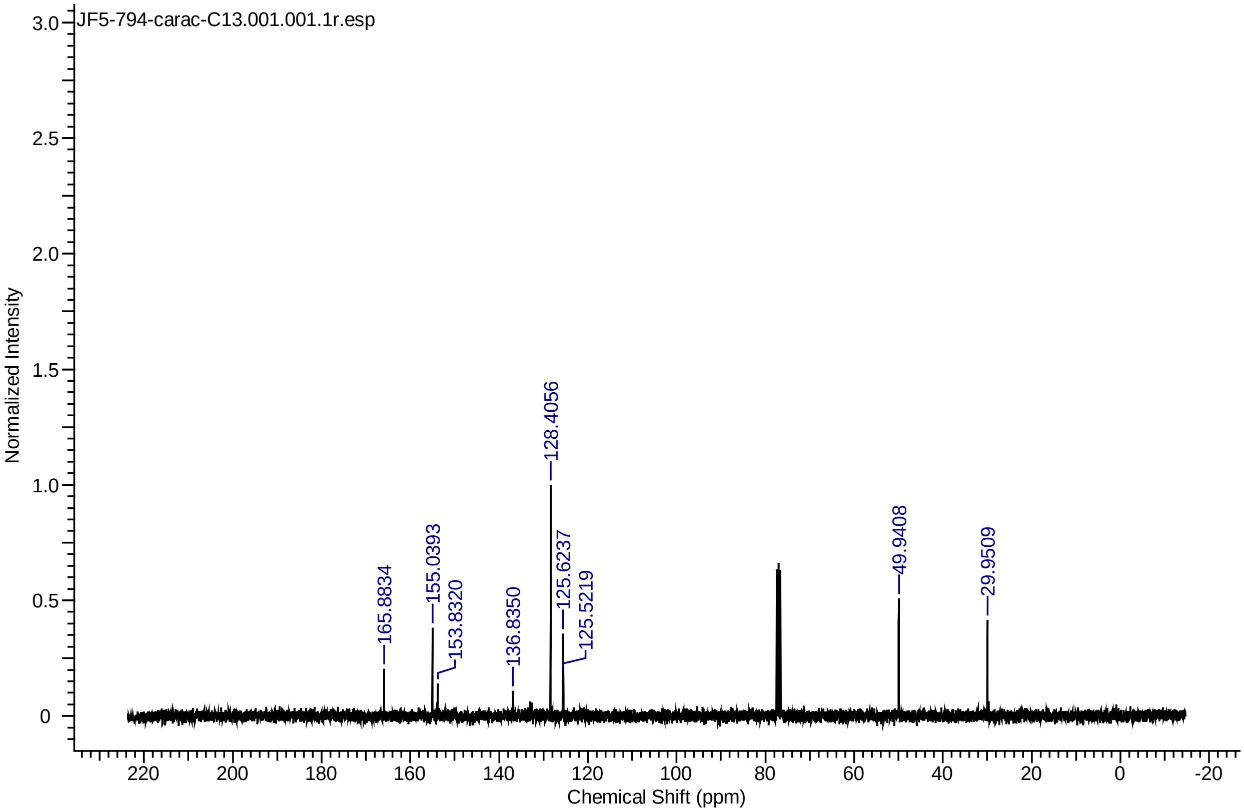

KL_exp15-charac-C13-1h.001.001.1r.esp
Normalized Intensity
152.06
150.64
144.79
134.67
133.23
129.79
129.19
128.77
125.89
122.02
115.48
Chemical Shift (ppm)
220
200
180
160
140
120
100
80
60
40
20
0
-20
2.5
2.0
1.5
1.0
0.5

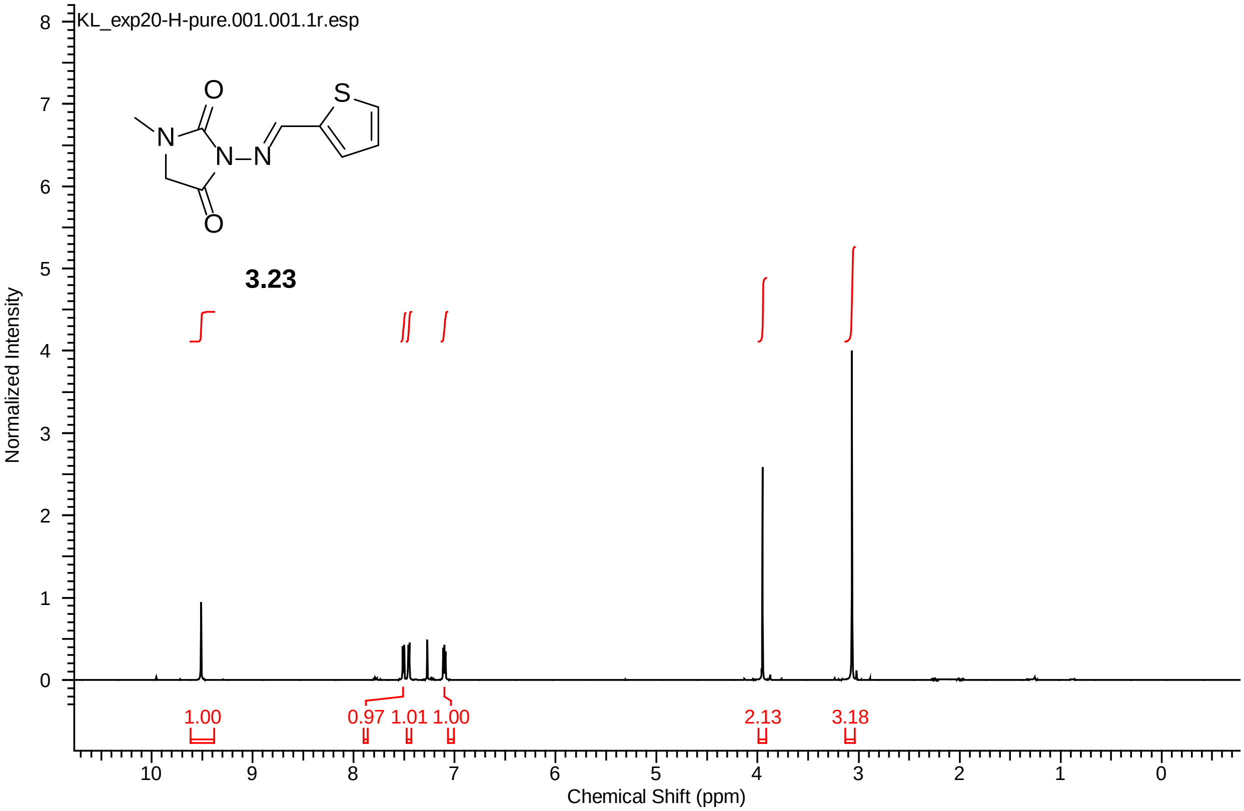

KL_exp19-Cl-H.001.001.1r.esp
Normalized Intensity
10
9
8
7
6
5
4
3
2
1
0
O
N
N
N
O
Cl
1.00
2.11
1.98
2.06
3.08
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

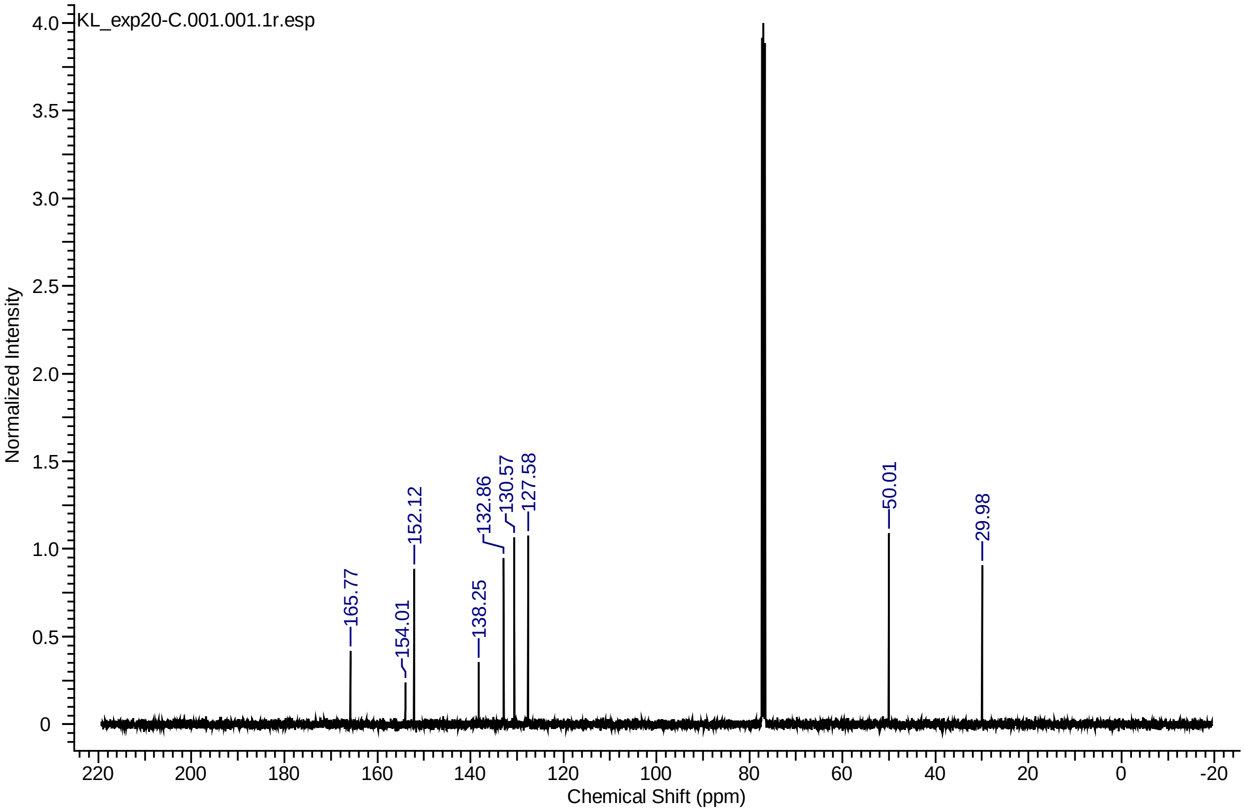
3.21

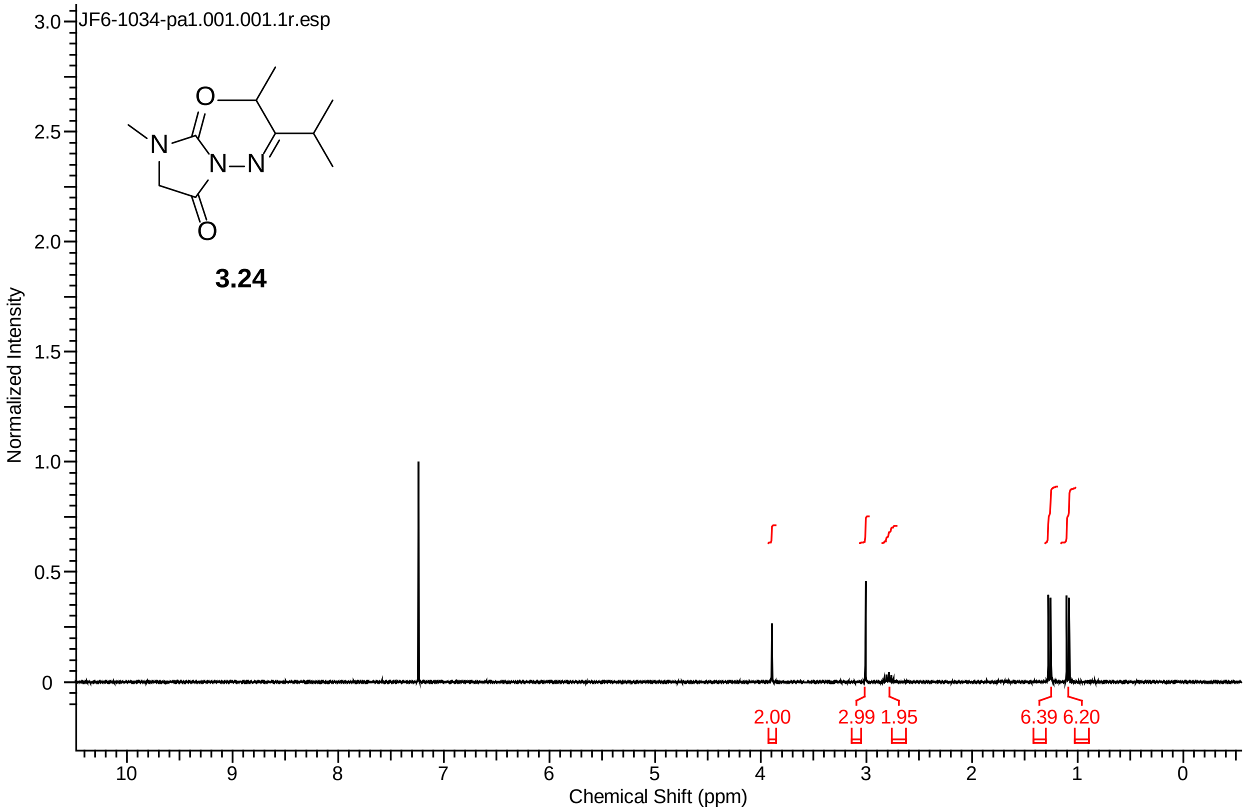

KL_exp19-Cl-C.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
165.89
156.09
154.01
137.60
131.96
129.48
129.01
50.01
29.98
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

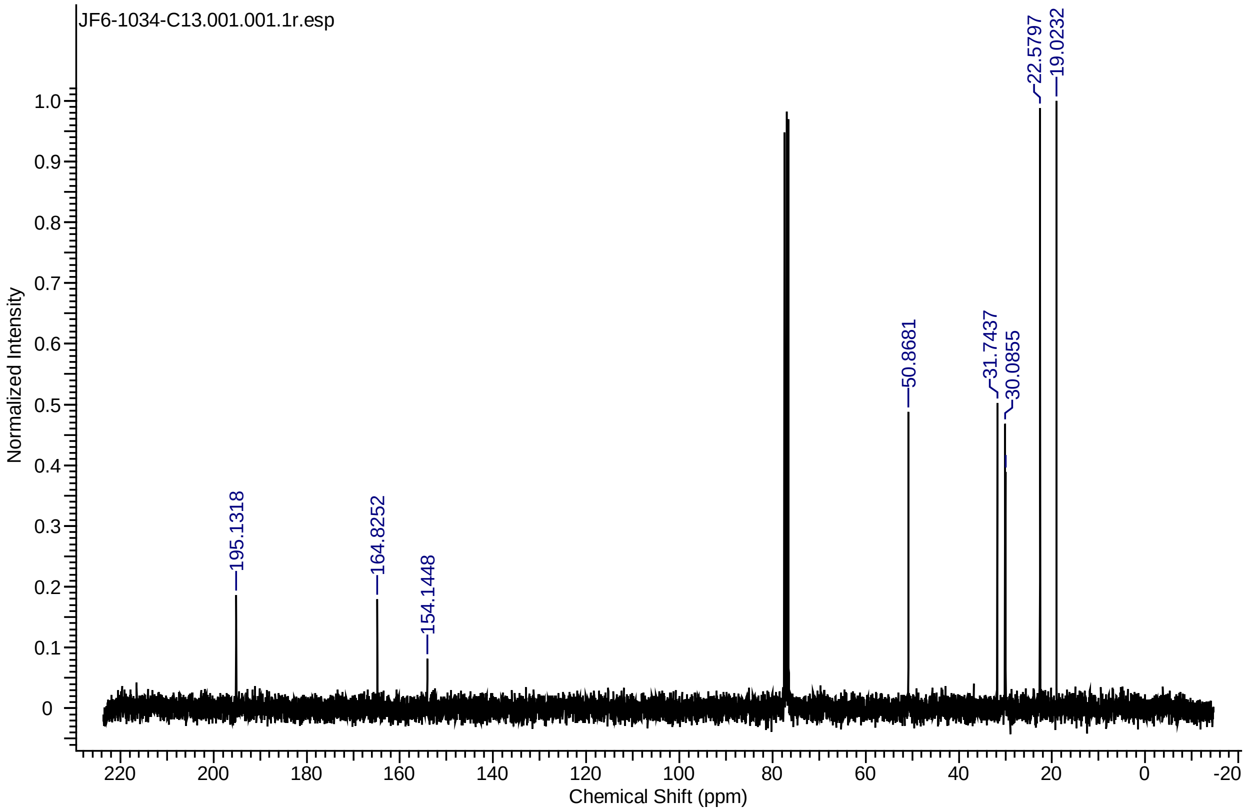

JF5-794-carac-H.001.001.1r.esp
O
N
N–N
O
CF3
3.22
0.96
1.97
1.98
2.00
2.99
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

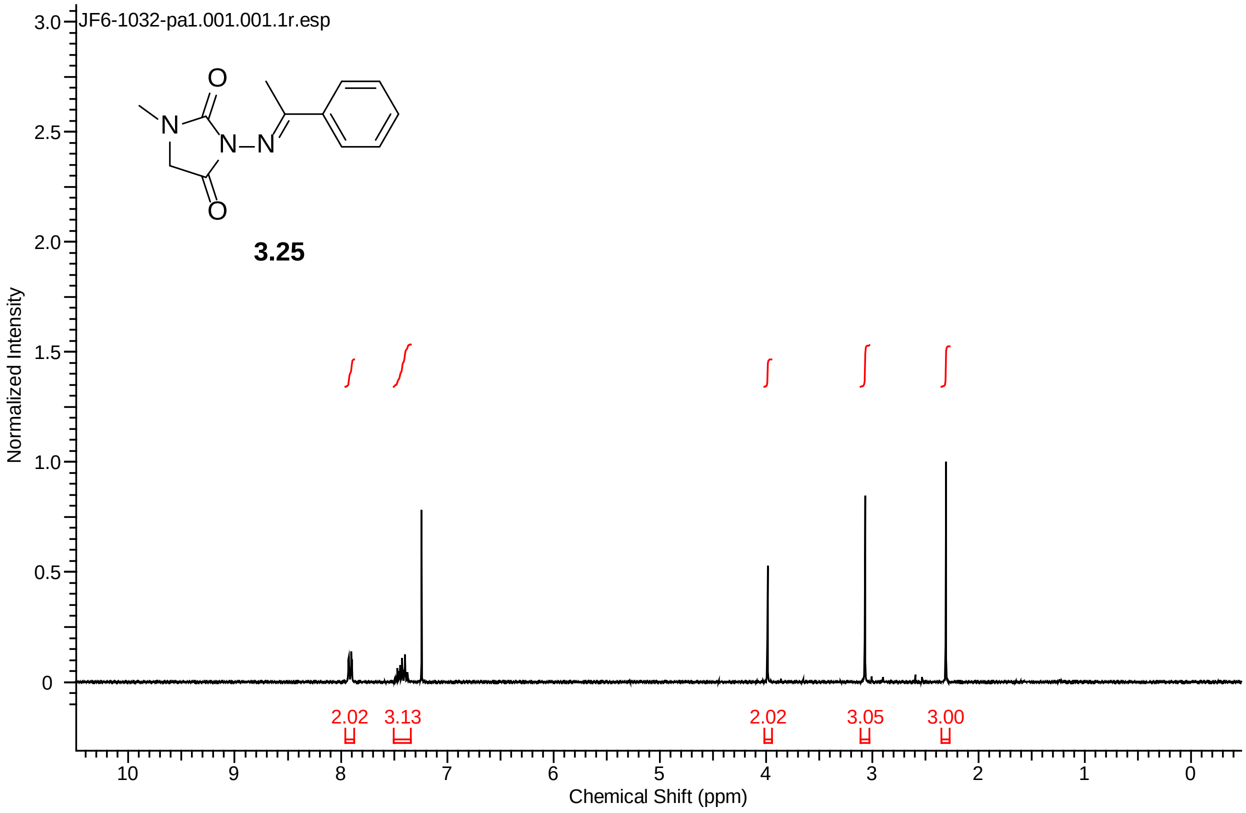

JF5-794-carac-C13.001.001.1r.esp
165.8834
155.0393
153.8320
136.8350
128.4056
125.6237
125.5219
49.9408
29.9509
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

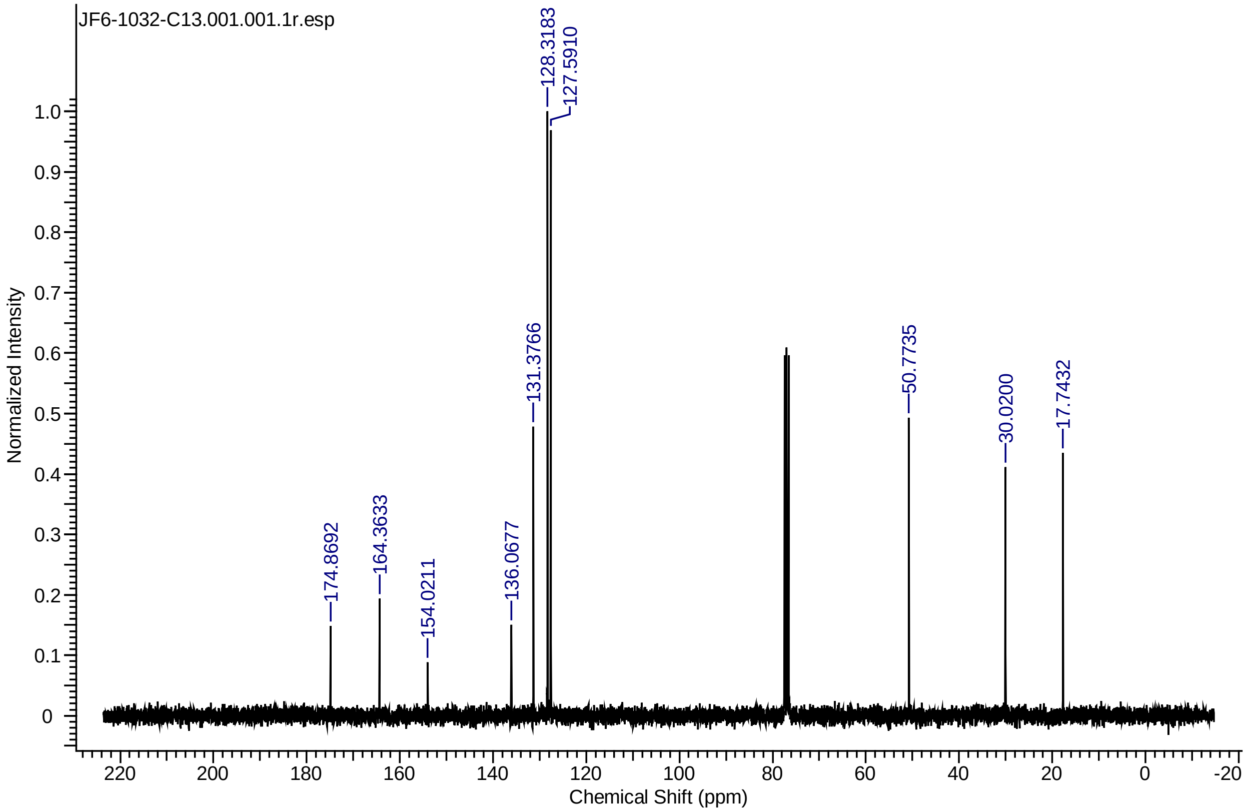

KL_exp20-H-pure.001.001.1r.esp
3.23
O
N
N–N
S
O
1.00
0.97
1.01
1.00
2.13
3.18
Normalized Intensity
8
7
6
5
4
3
2
1
0
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

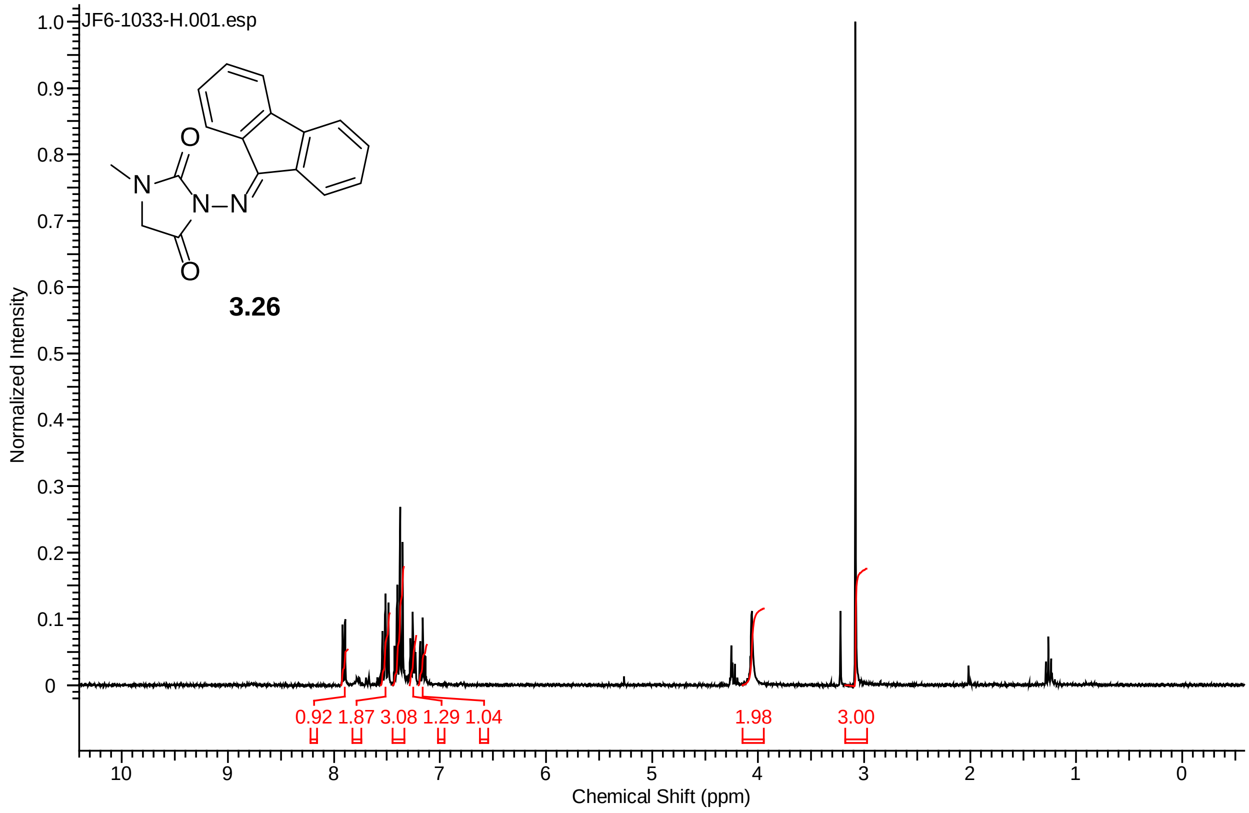

KL_exp20-C.001.001.1r.esp
165.77
154.01
152.12
138.25
132.86
130.57
127.58
50.01
29.98
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

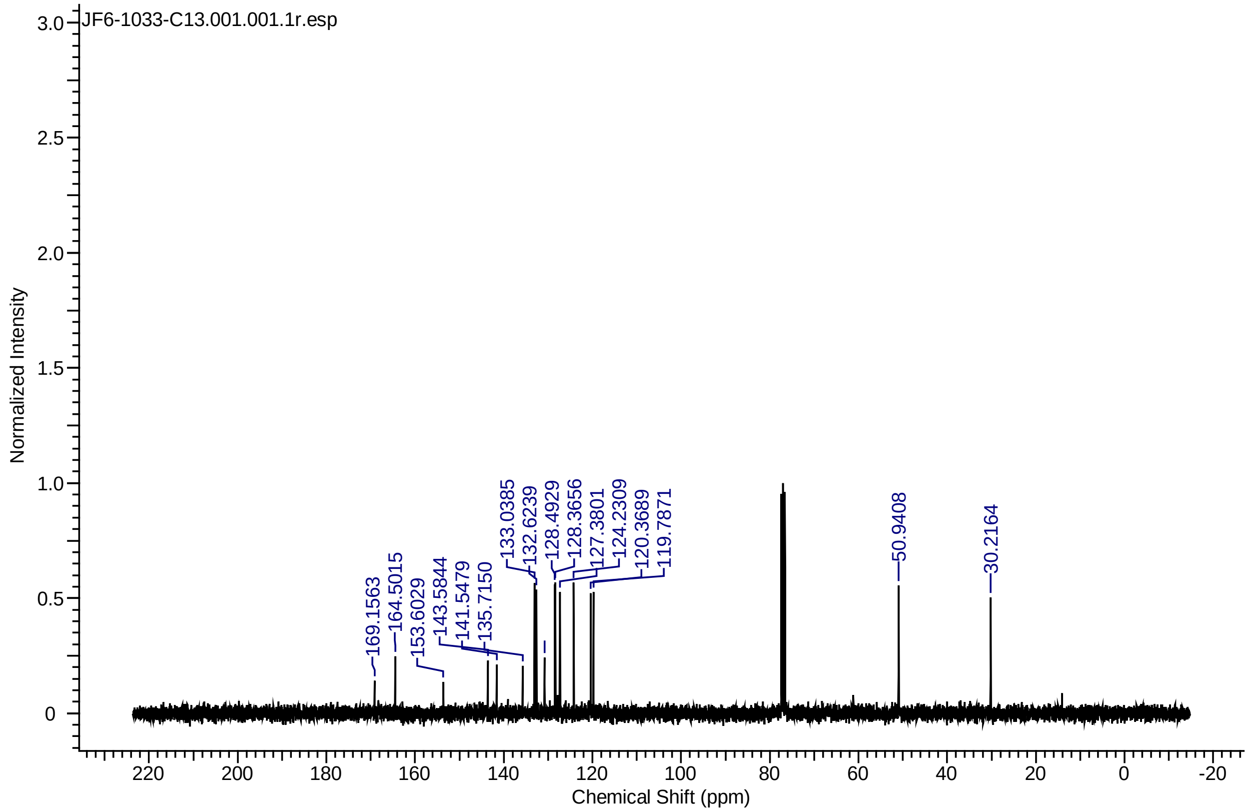

JF6-1034-pa1.001.001.1r.esp
3.24
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
2.00
2.99
1.95
6.39
6.20
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

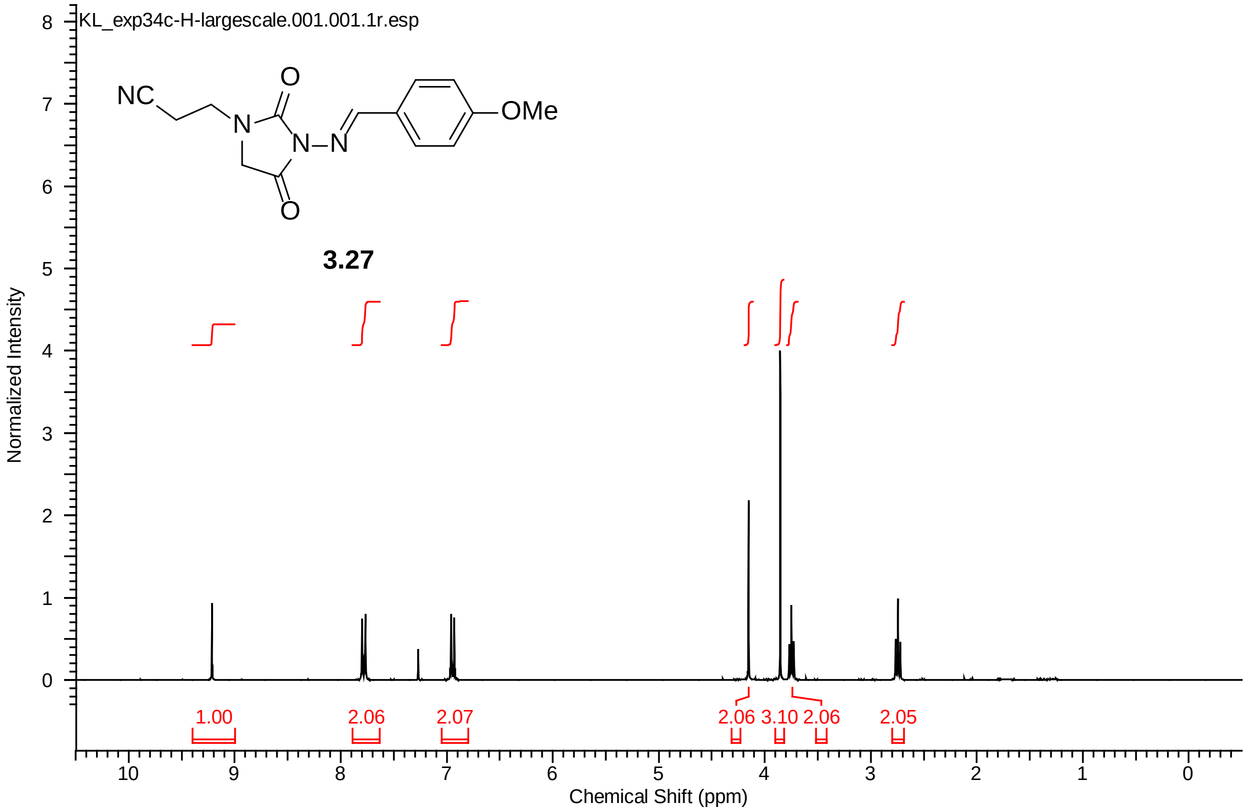

JF6-1034-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
195.1318
164.8252
154.1448
50.8681
31.7437
30.0855
22.5797
19.0232
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

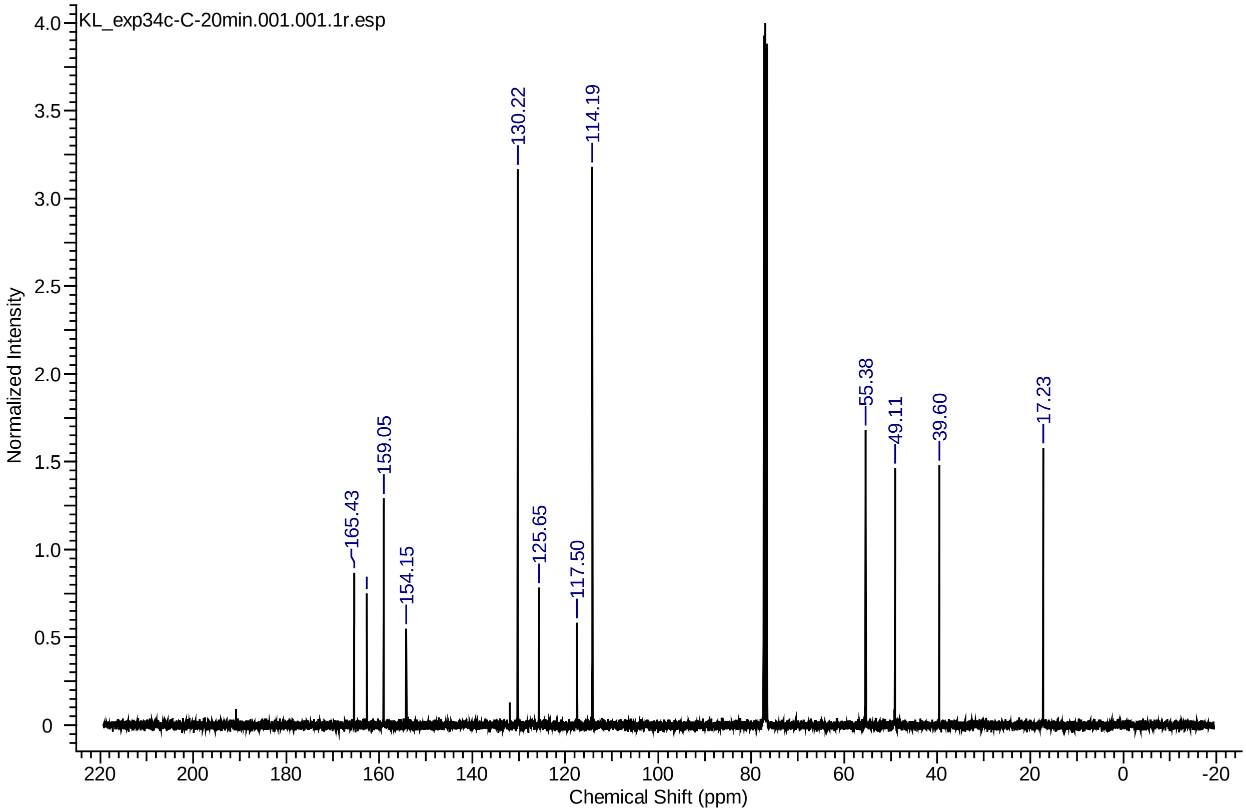

3.25
JF6-1032-pa1.001.001.1r.esp
O
N
N
N
O
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
2.02
3.13
2.02
3.05
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

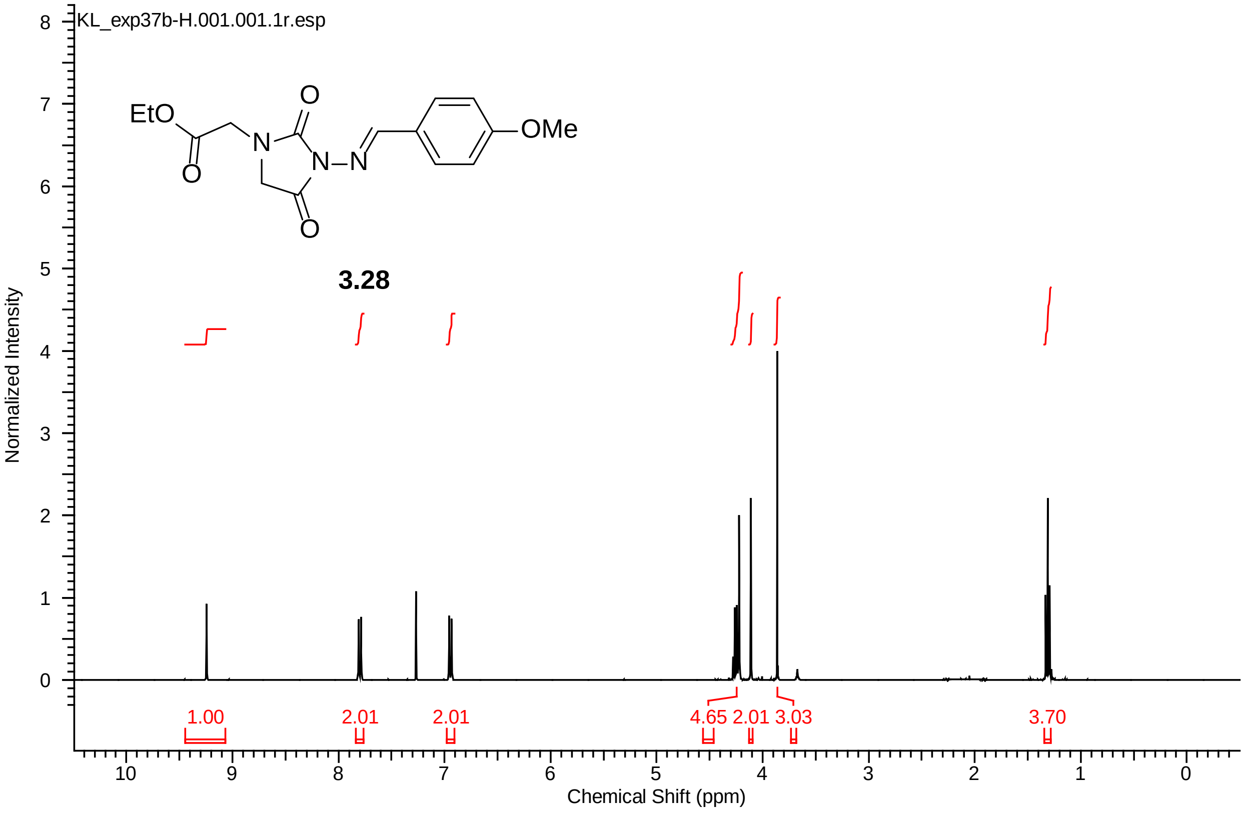

JF6-1032-C13.001.001.1r.esp
128.3183
127.5910
131.3766
174.8692
164.3633
154.0211
136.0677
50.7735
30.0200
17.7432
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

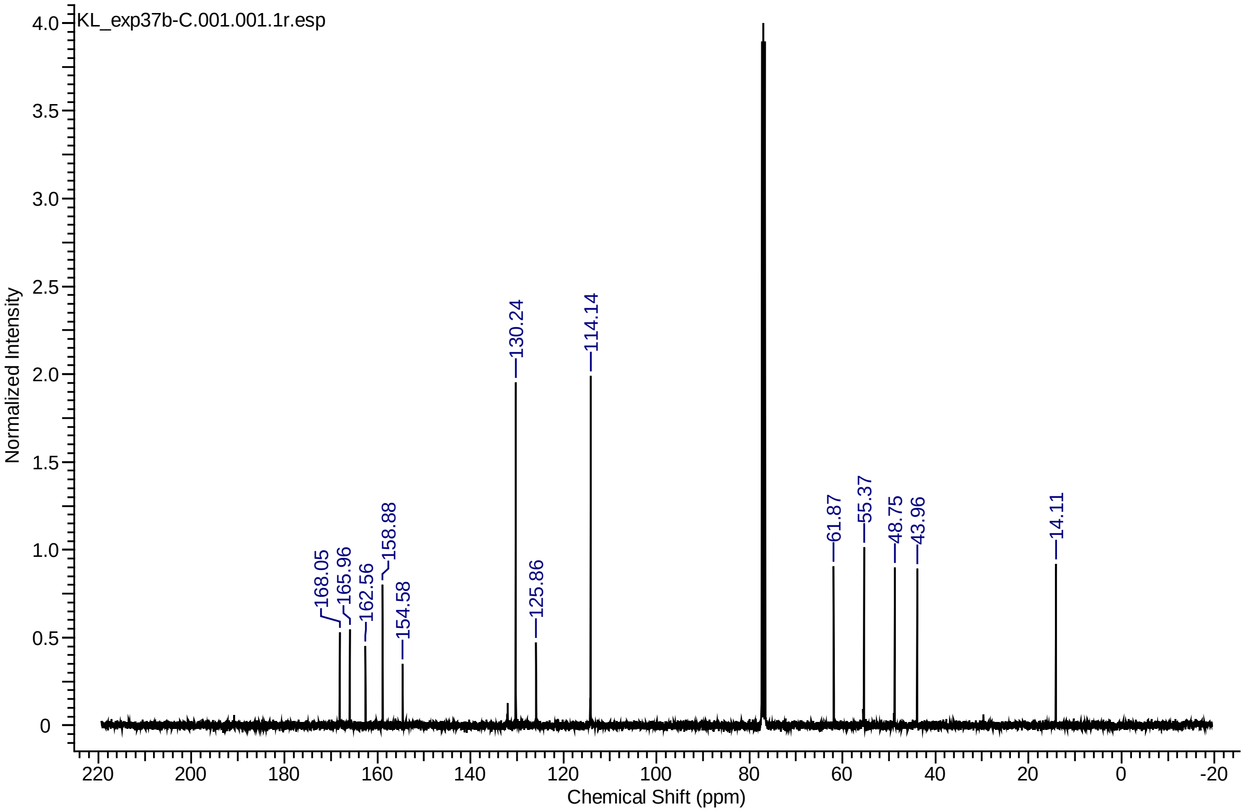

JF6-1033-H.001.esp
3.26
O
N
N–N
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.92
1.87
3.08
1.29
1.04
1.98
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

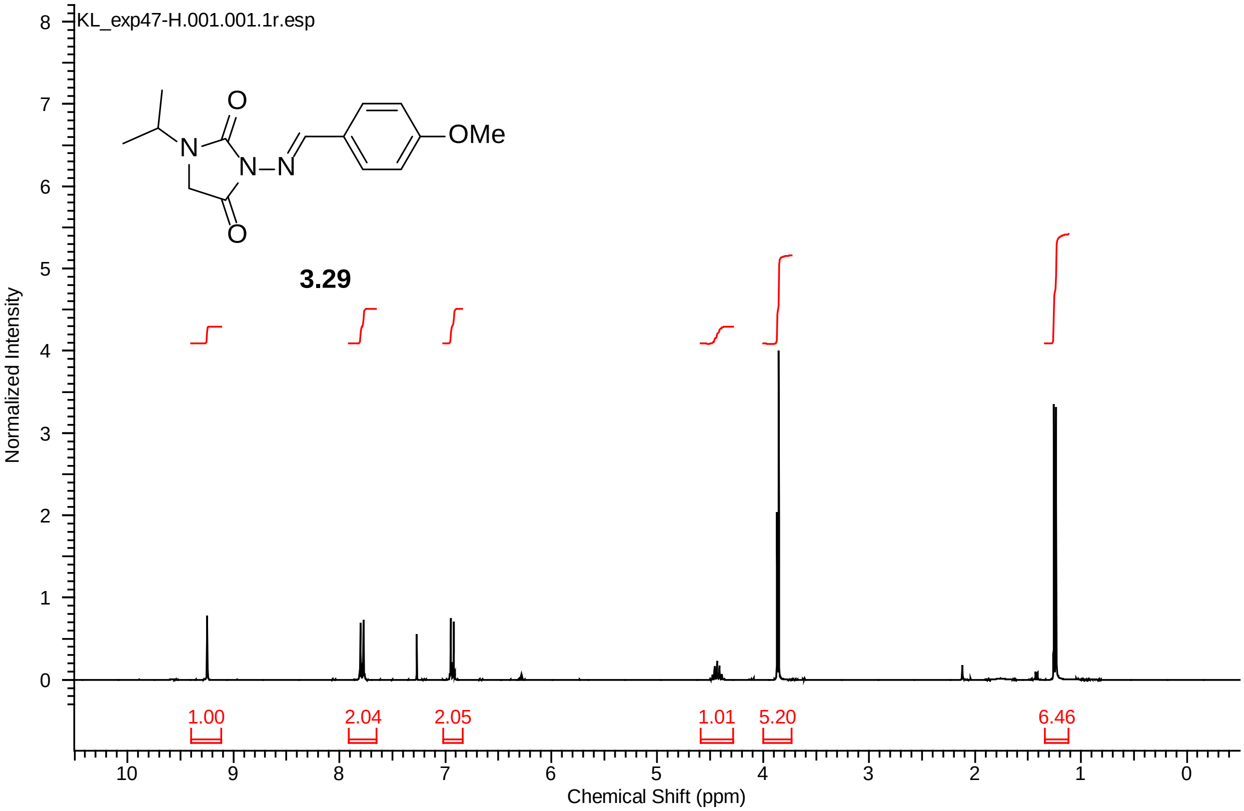

JF6-1033-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
169.1563
164.5015
153.6029
143.5844
141.5479
135.7150
133.0385
132.6239
128.4929
128.3656
127.3801
124.2309
120.3689
119.7871
50.9408
30.2164
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


KL_exp34c-H-largescale.001.001.1r.esp
NC
N
O
N–N
O
OMe
3.27
Normalized Intensity
8
7
6
5
4
3
2
1
0
1.00
2.06
2.07
2.06
3.10
2.06
2.05
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


KL_exp34c-C-20min.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
165.43
159.05
154.15
130.22
125.65
117.50
114.19
55.38
49.11
39.60
17.23
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

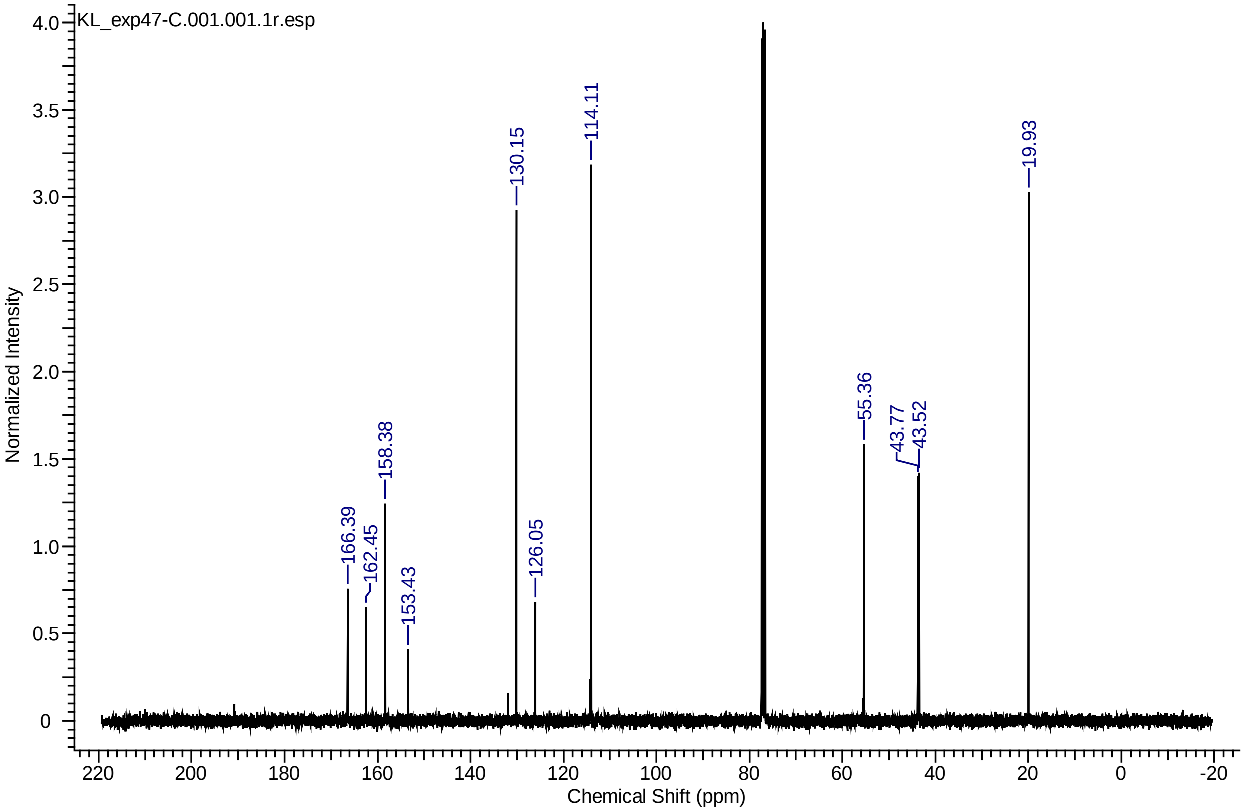

KL_exp37b-H.001.001.1r.esp
EtO
O
N
N–N
O
O
OMe
3.28
Normalized Intensity
8
7
6
5
4
3
2
1
0
1.00
2.01
2.01
4.65
2.01
3.03
3.70
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


KL_exp37b-C.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
168.05
165.96
162.56
158.88
154.58
130.24
125.86
114.14
61.87
55.37
48.75
43.96
14.11
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

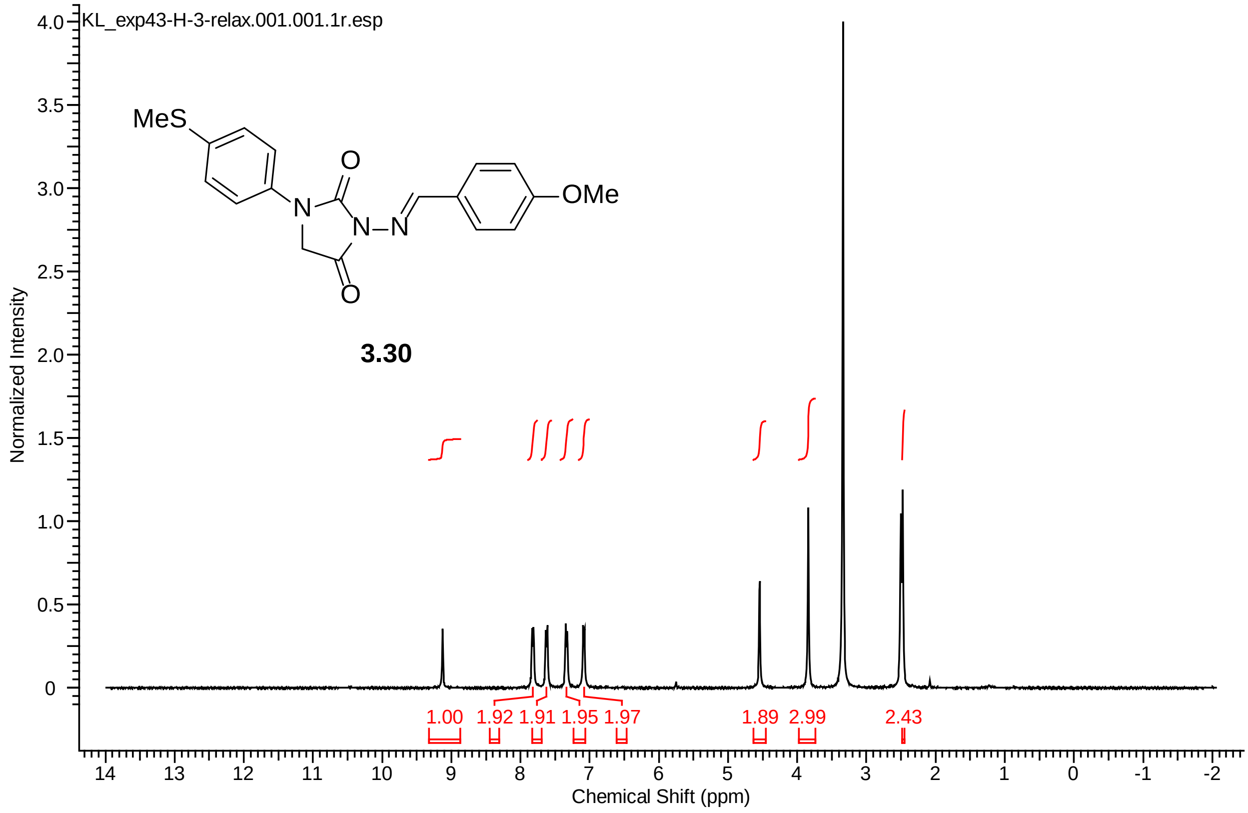


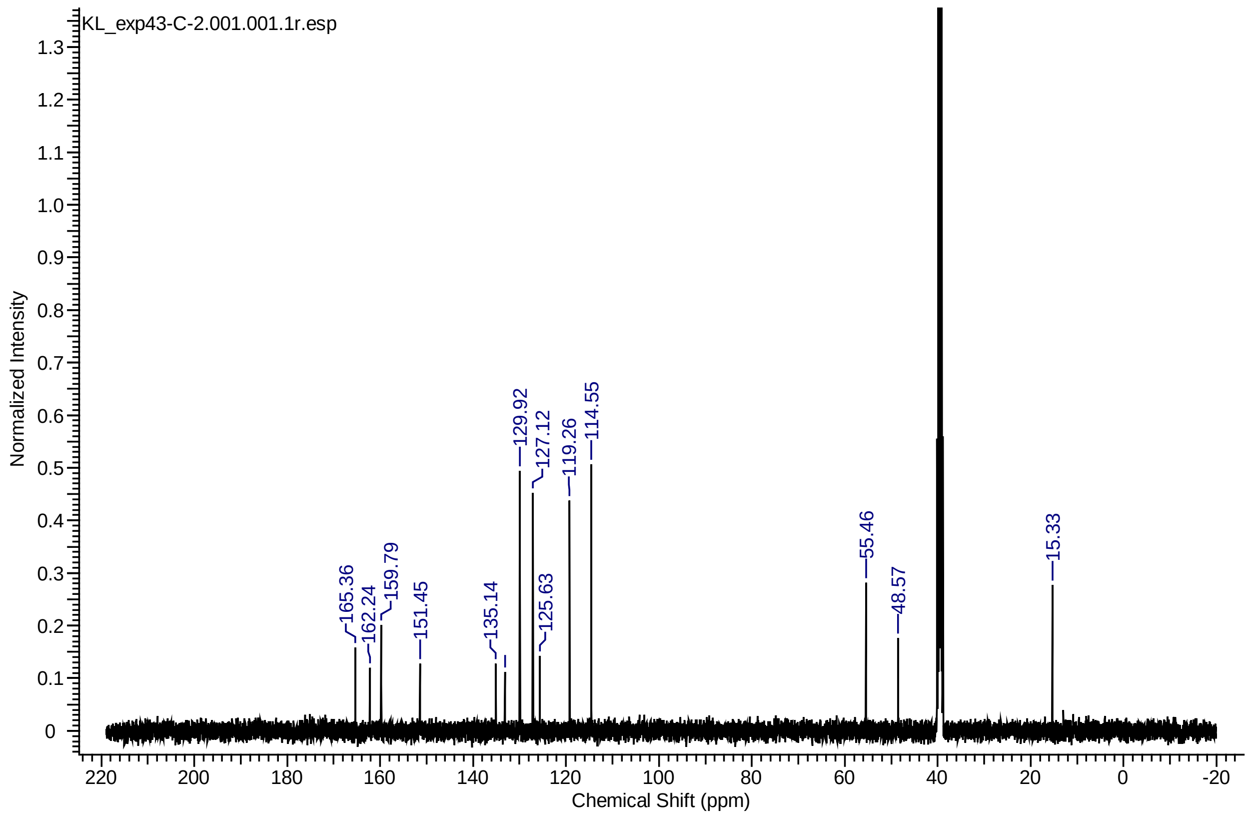
3.29

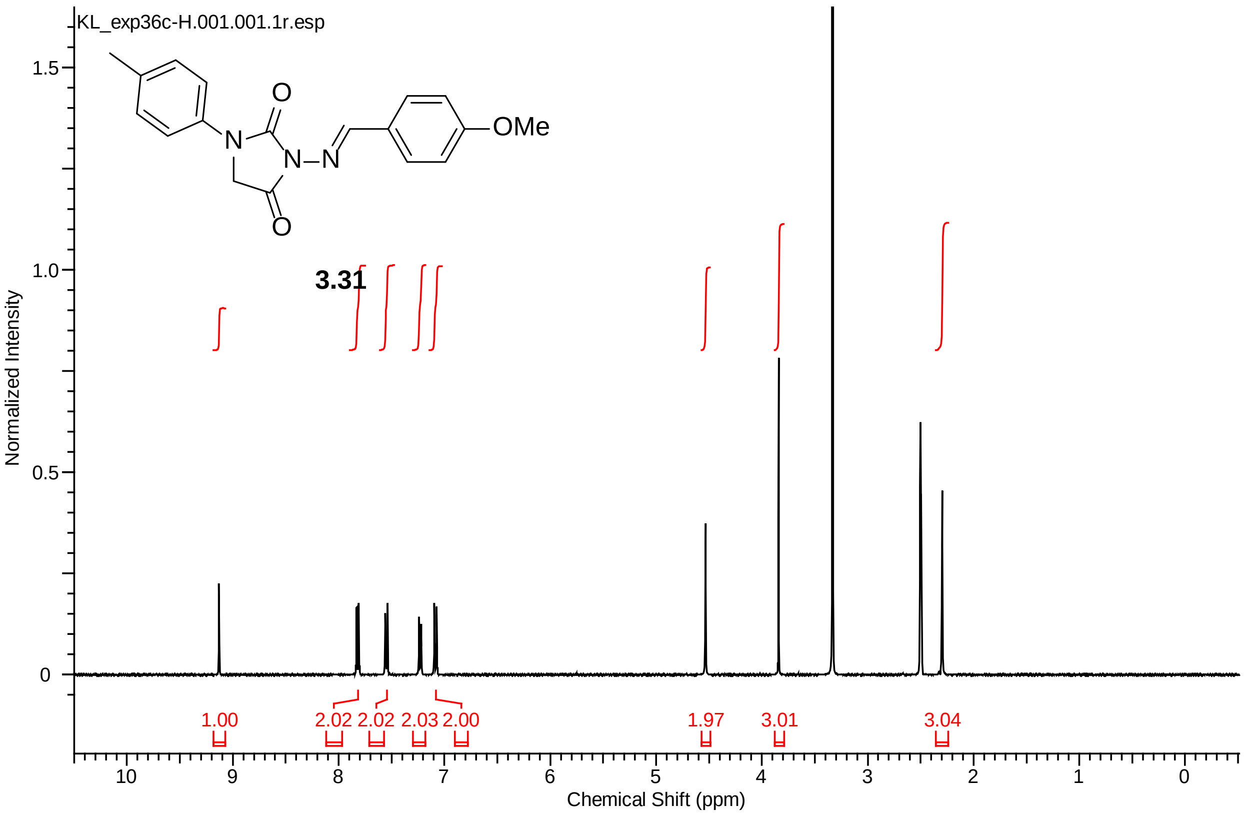
KL_exp47-H.001.001.1r.esp
O
N
N—N
OMe
O
Normalized Intensity
8
7
6
5
4
3
2
1
0
1.00
2.04
2.05
1.01
5.20
6.46
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

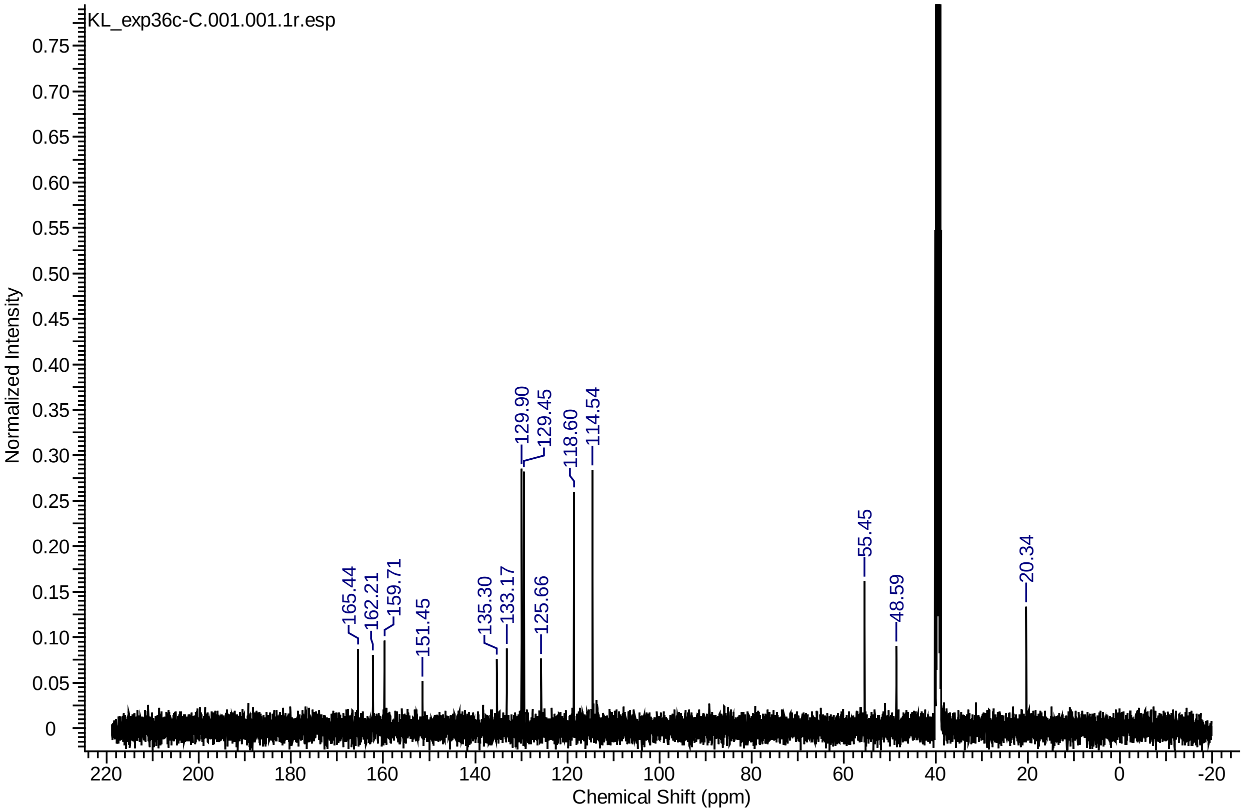


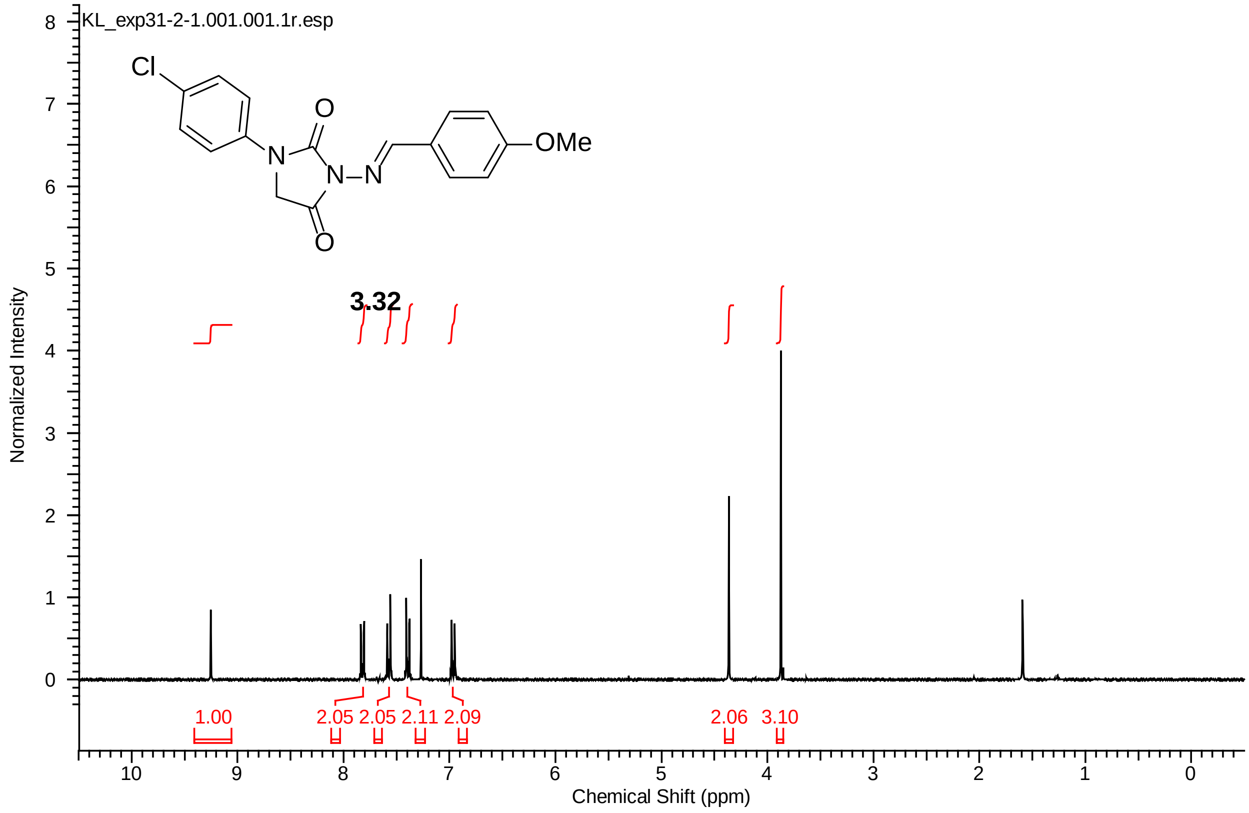
KL_exp47-C.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
166.39
162.45
158.38
153.43
130.15
126.05
114.11
55.36
43.77
43.52
19.93
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

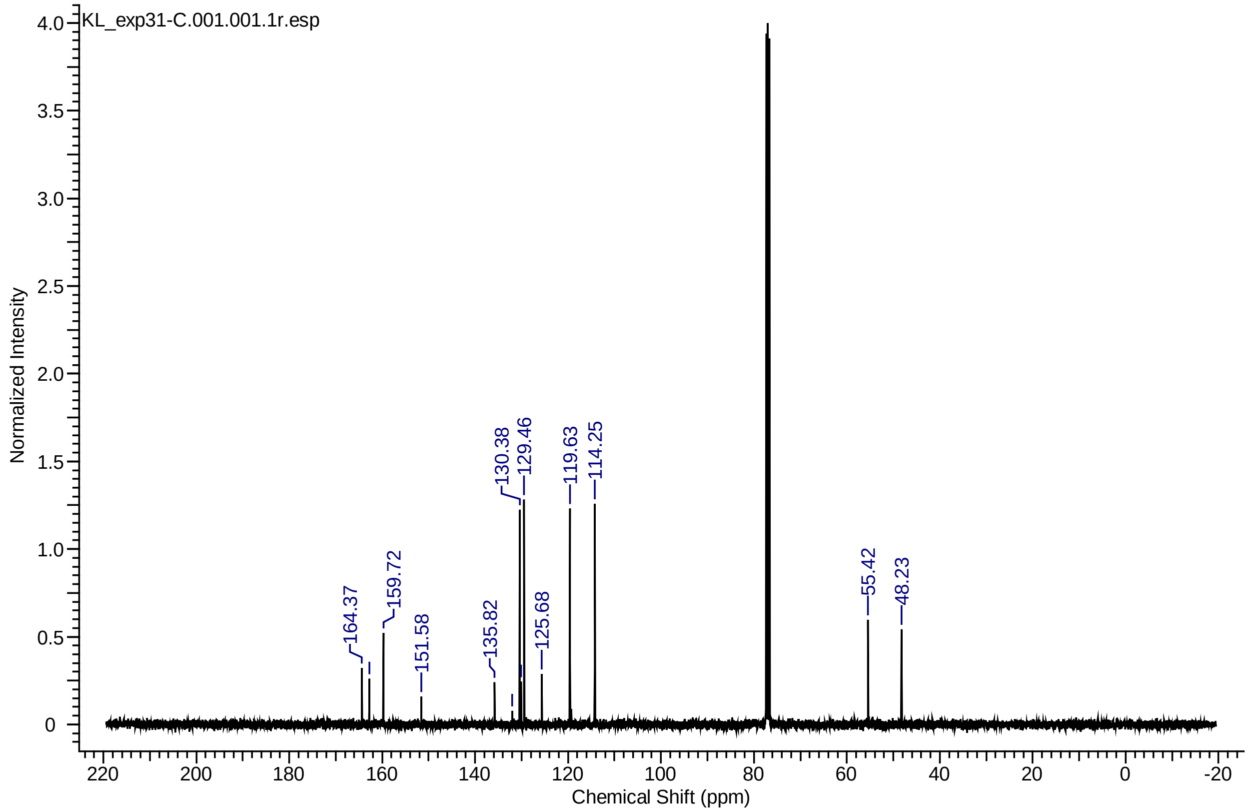

KL_exp43-H-3-relax.001.001.1r.esp
MeS
O
N
N–N
OMe
O
3.30
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
1.00
1.92
1.91
1.95
1.97
1.89
2.99
2.43
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

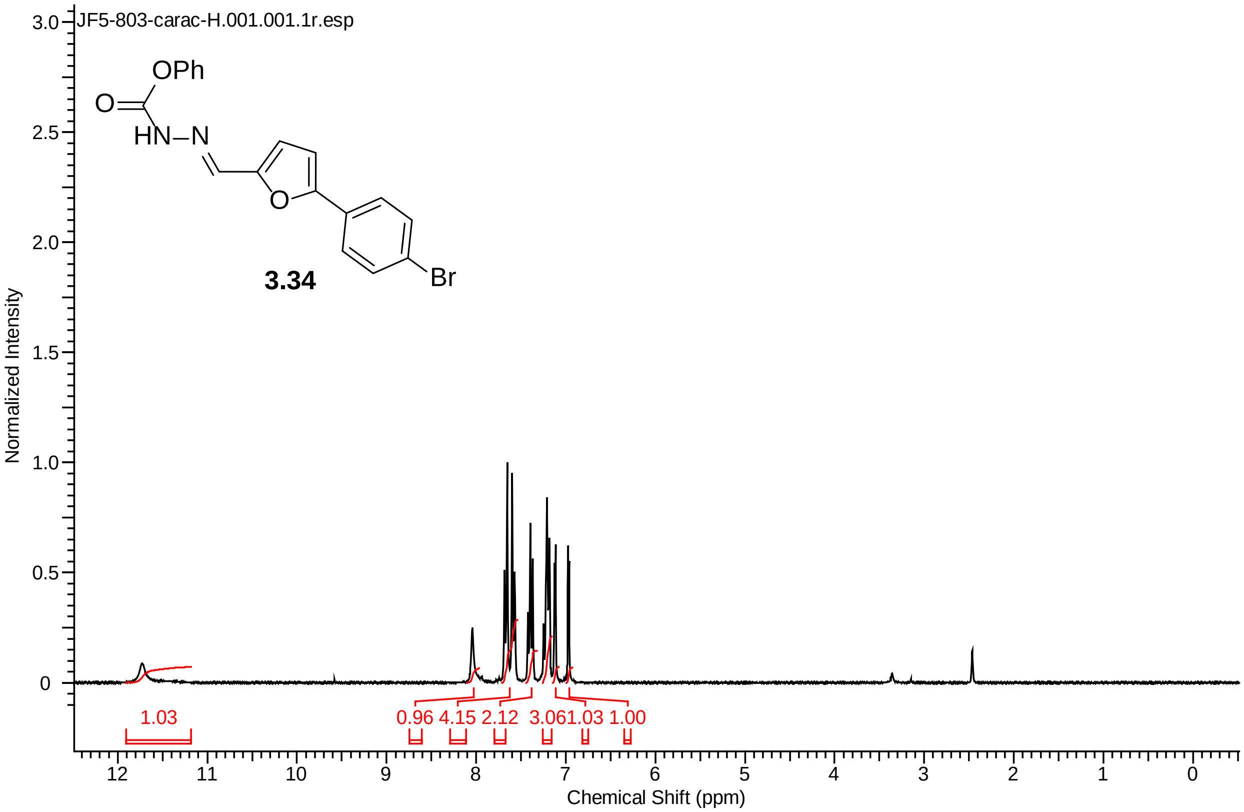

KL_exp43-C-2.001.001.1r.esp
Normalized Intensity
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
165.36
162.24
159.79
151.45
135.14
129.92
127.12
125.63
119.26
114.55
55.46
48.57
15.33
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

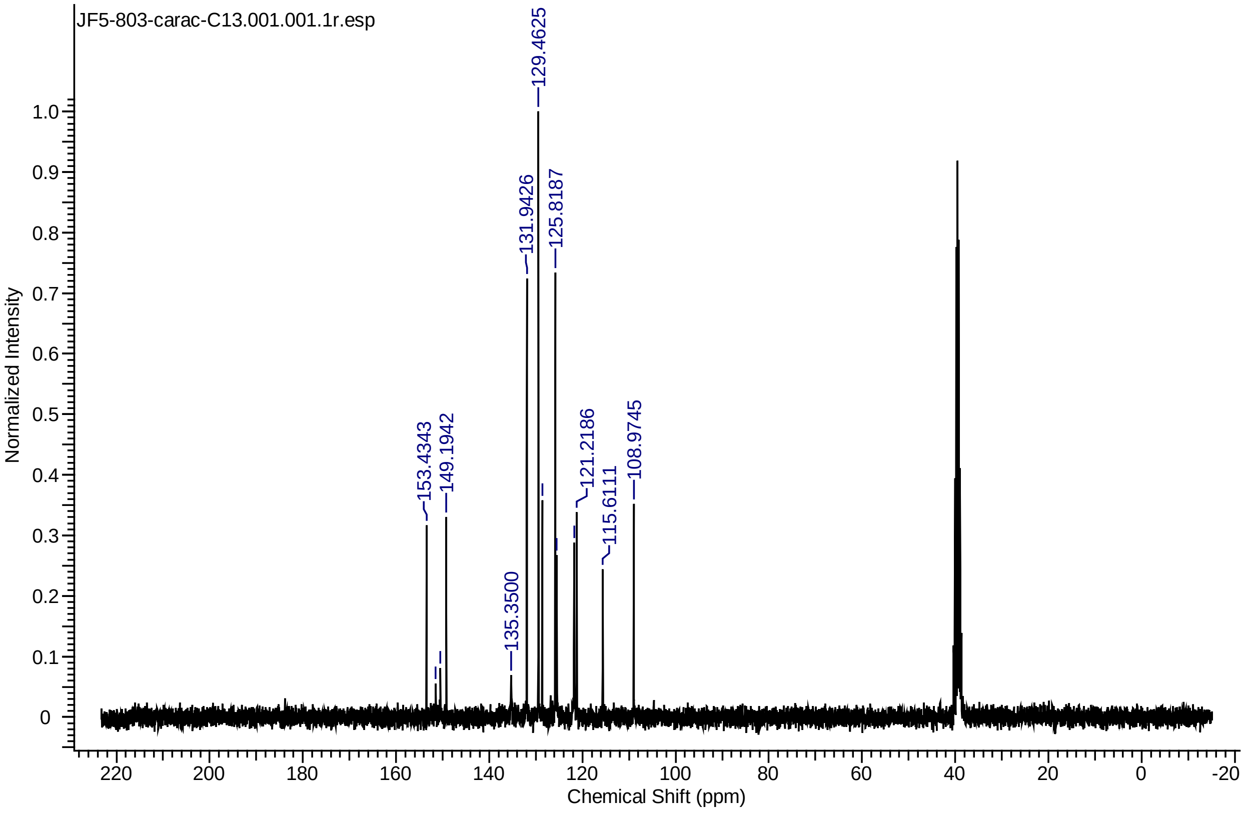

KL_exp36c-H.001.001.1r.esp
3.31
O
N
N–N
OMe
O
1.5
1.0
0.5
0
Normalized Intensity
1.00
2.02
2.02
2.03
2.00
1.97
3.01
3.04
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

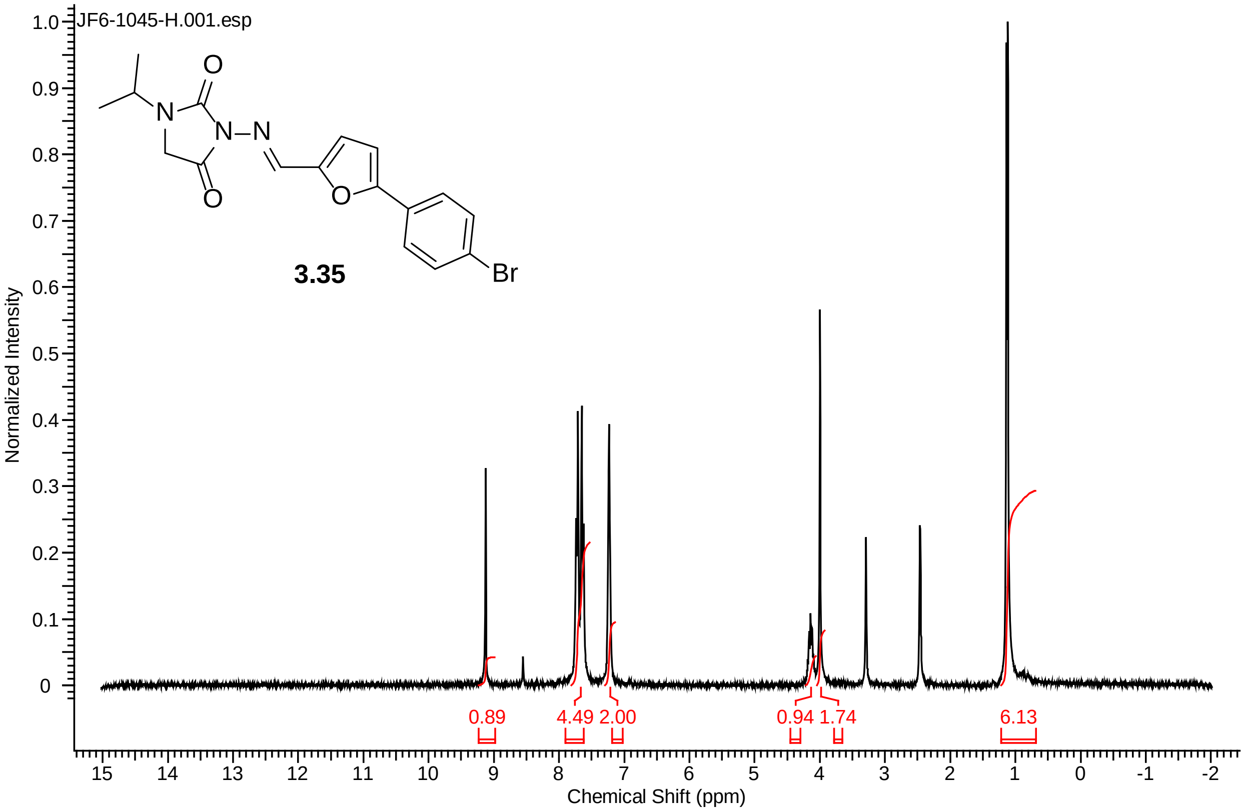

KL_exp36c-C.001.001.1r.esp
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
Normalized Intensity
165.44
162.21
159.71
151.45
135.30
133.17
129.90
129.45
125.66
118.60
114.54
55.45
48.59
20.34
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

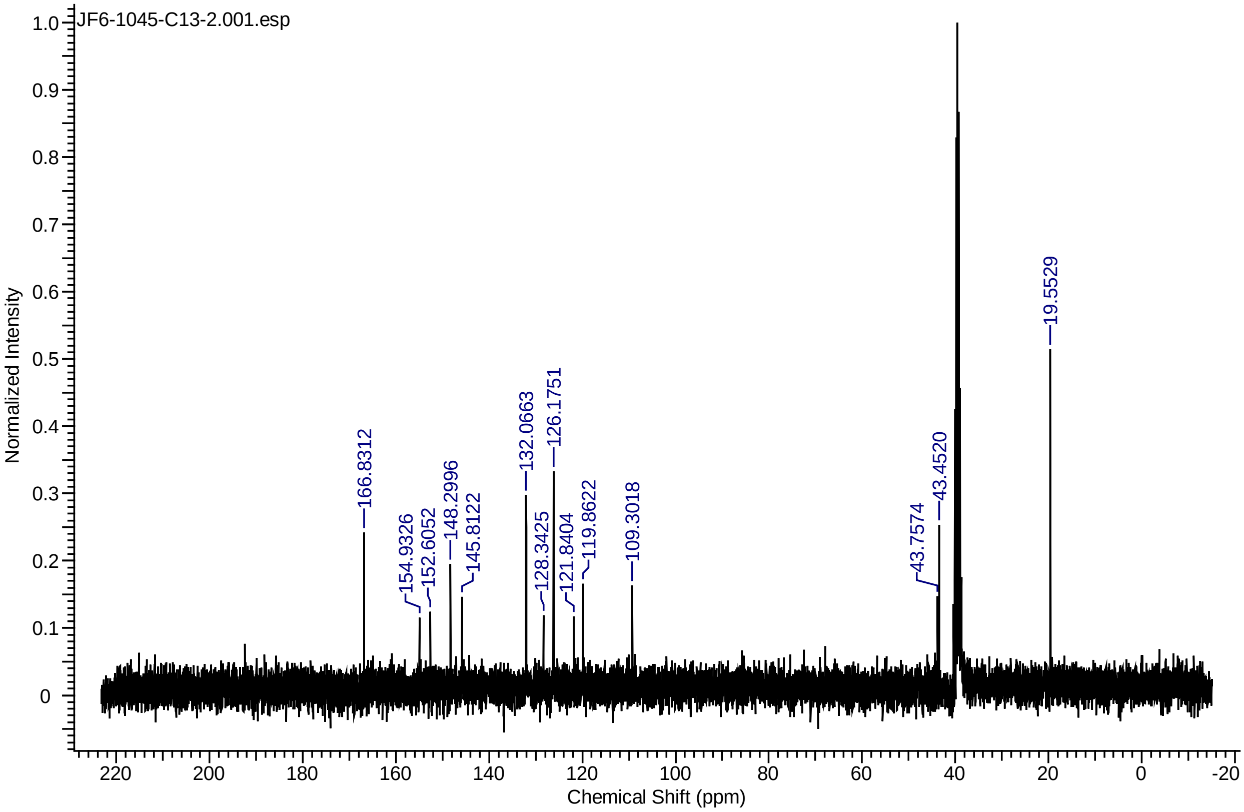

KL_exp31-2-1.001.001.1r.esp
Cl
O
N
N–N
OMe
O
3.32
1.00
2.05
2.05
2.11
2.09
2.06
3.10
Normalized Intensity
0
1
2
3
4
5
6
7
8
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

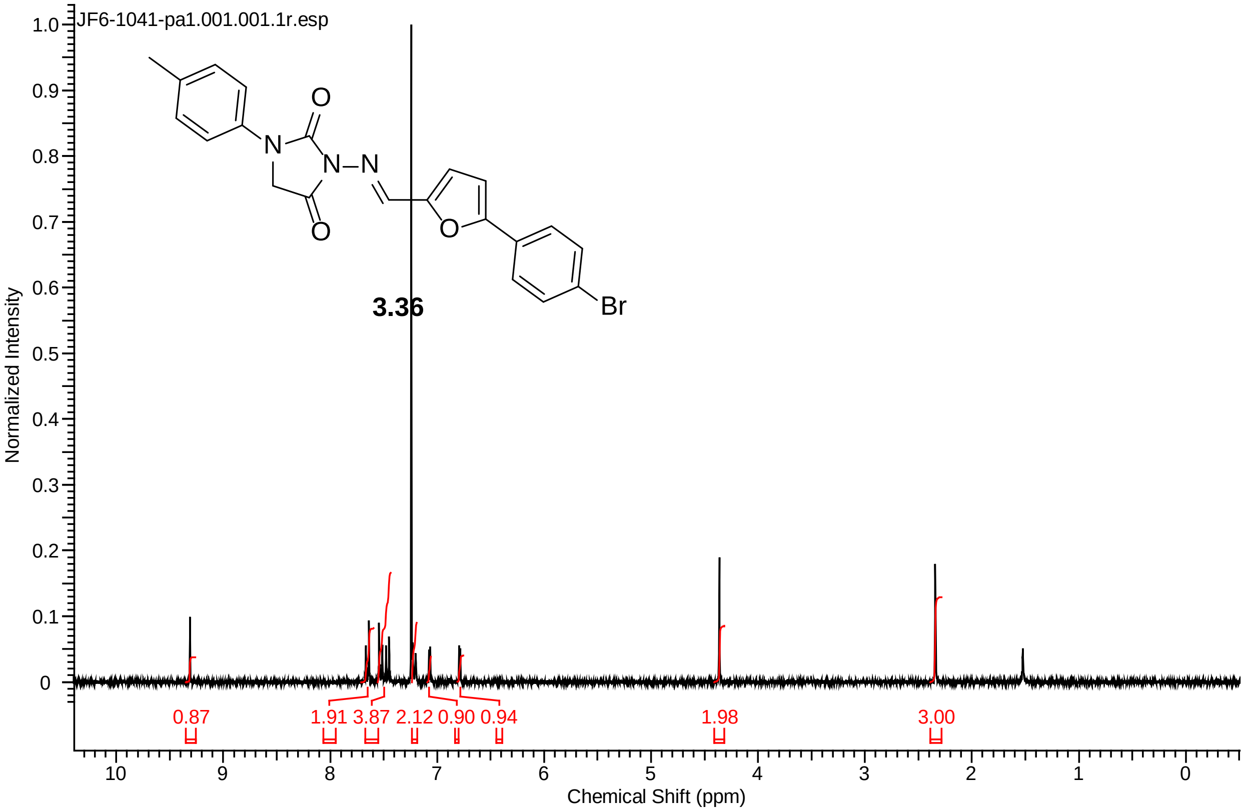

KL_exp31-C.001.001.1r.esp
164.37
159.72
151.58
135.82
130.38
129.46
125.68
119.63
114.25
55.42
48.23
Normalized Intensity
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

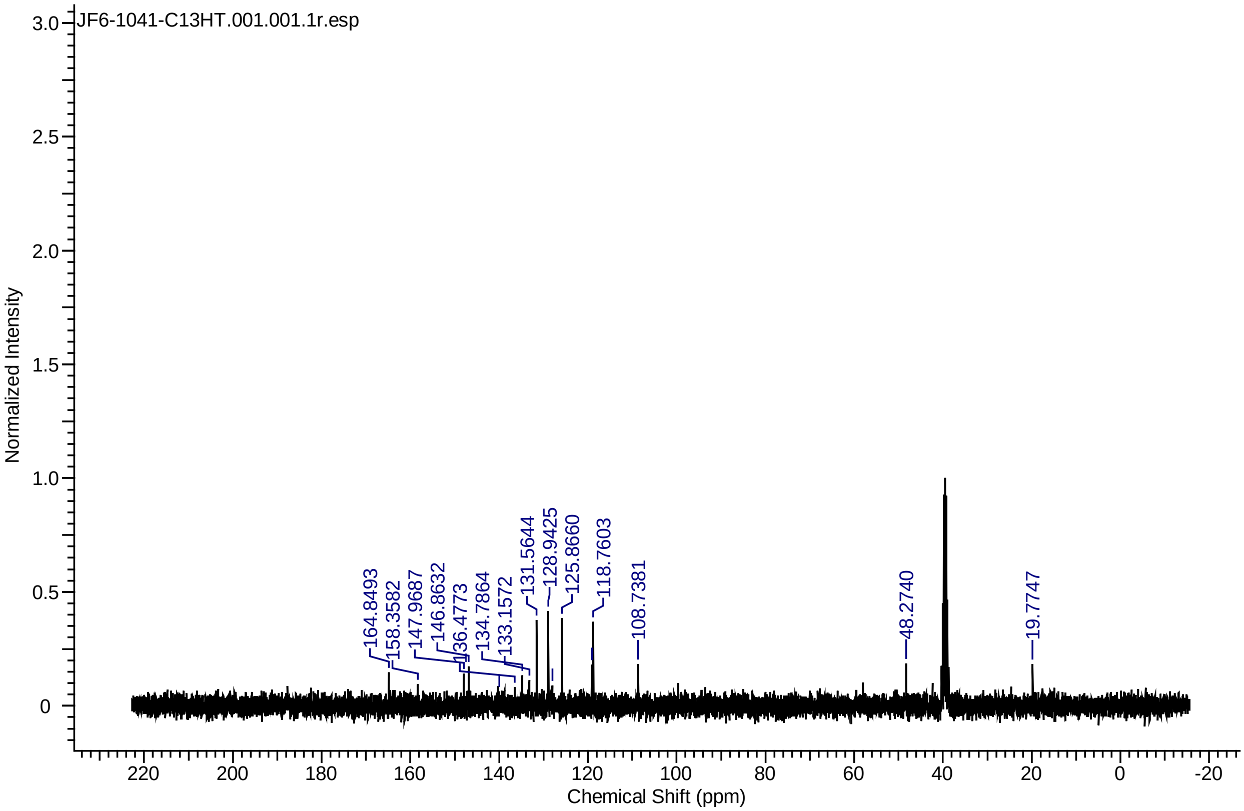

JF5-803-carac-H.001.001.1r.esp
OPh
O
HN–N
O
Br
3.34
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
1.03
0.96 4.15 2.12 3.06 1.03 1.00
12 11 10 9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)

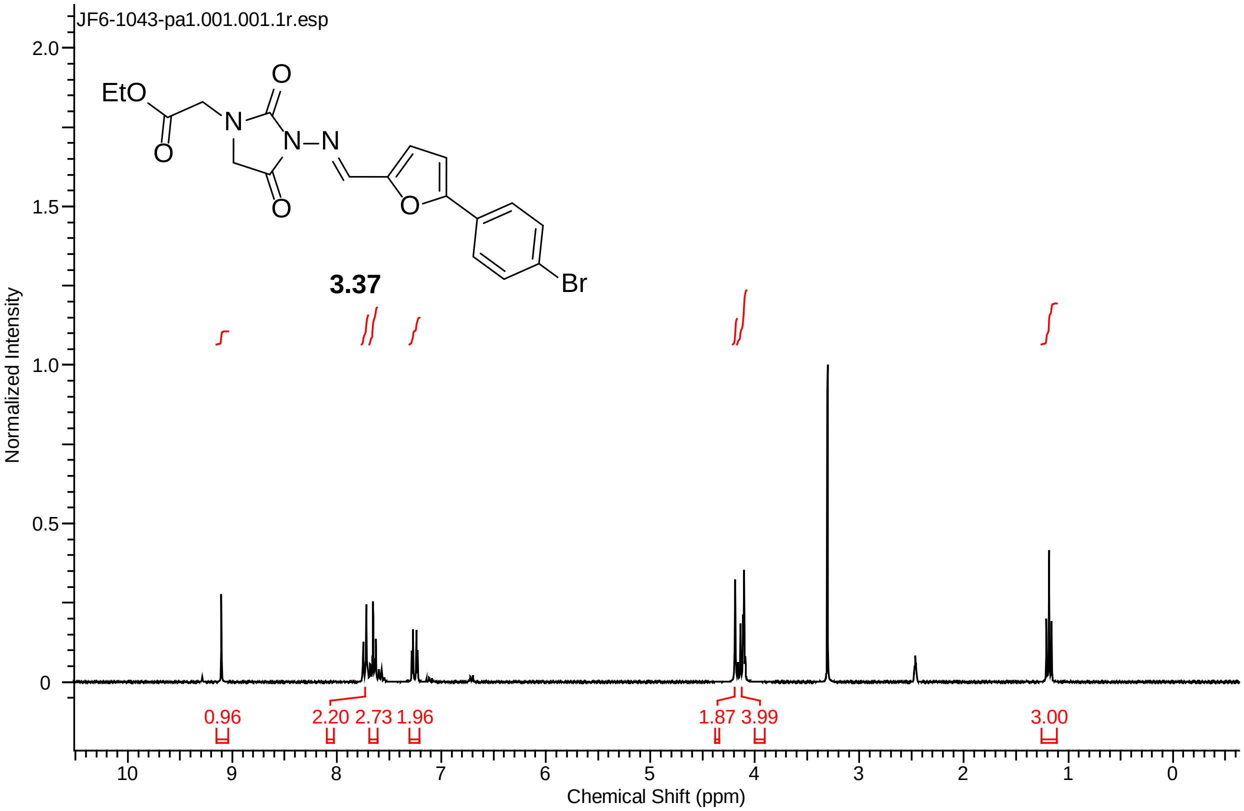

JF5-803-carac-C13.001.001.1r.esp
129.4625
131.9426
125.8187
153.4343
149.1942
121.2186
115.6111
108.9745
135.3500
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220 200 180 160 140 120 100 80 60 40 20 0 -20
Chemical Shift (ppm)

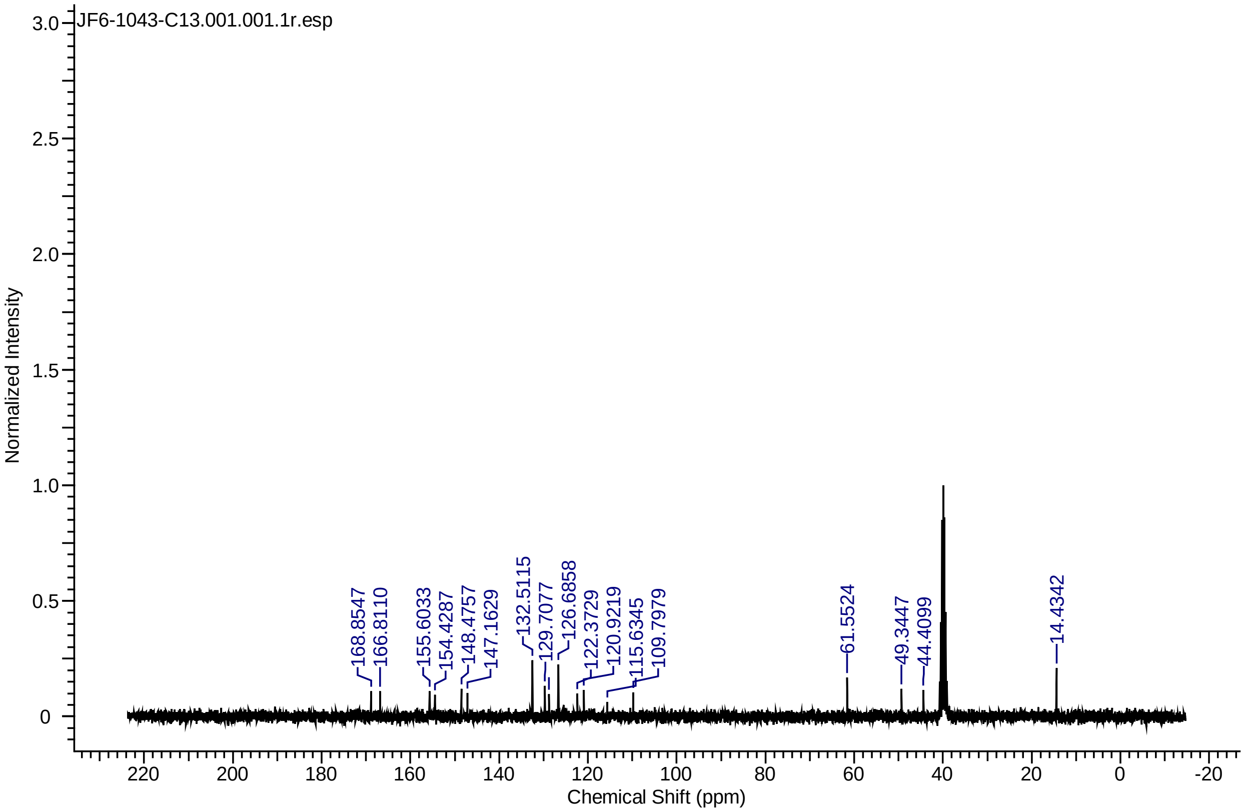

JF6-1045-H.001.esp
3.35
O
N
N–N
O
O
Br
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.89
4.49
2.00
0.94
1.74
6.13
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

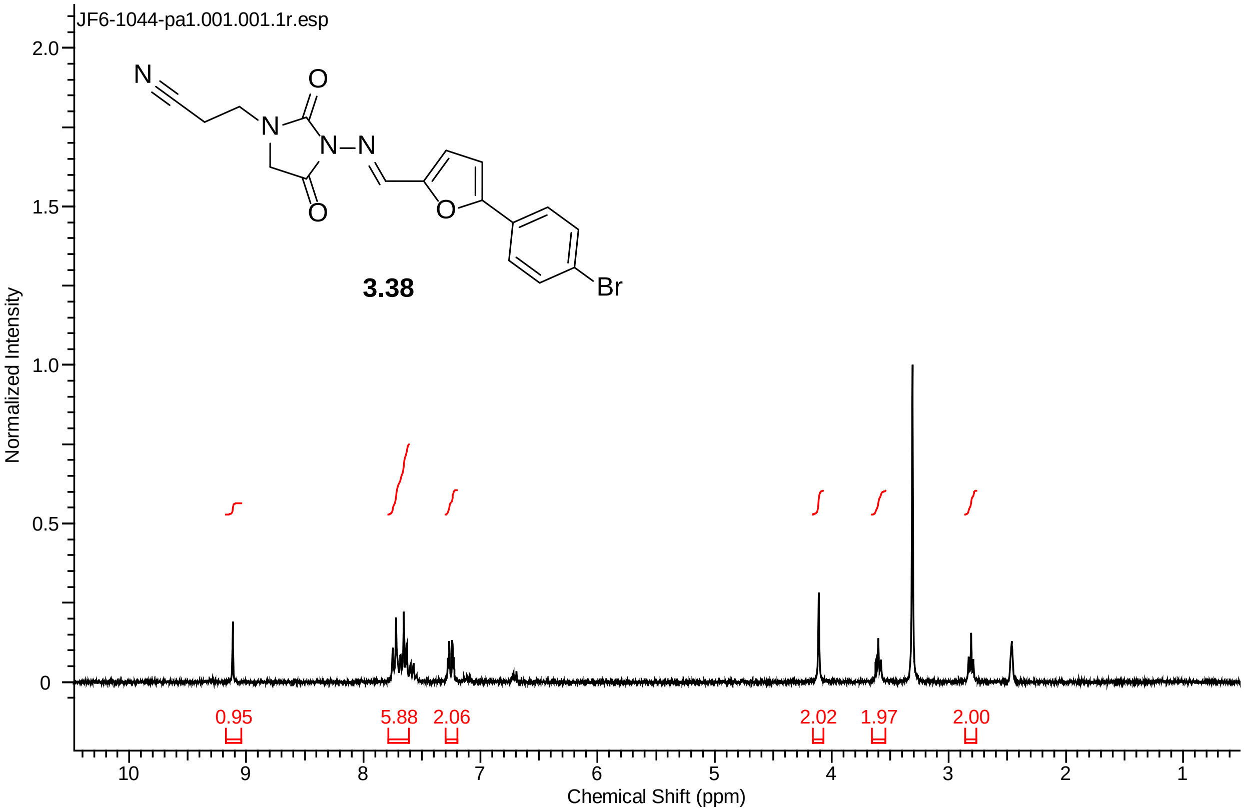

JF6-1045-C13-2.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
166.8312
154.9326
152.6052
148.2996
145.8122
132.0663
128.3425
126.1751
121.8404
119.8622
109.3018
43.7574
43.4520
19.5529
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

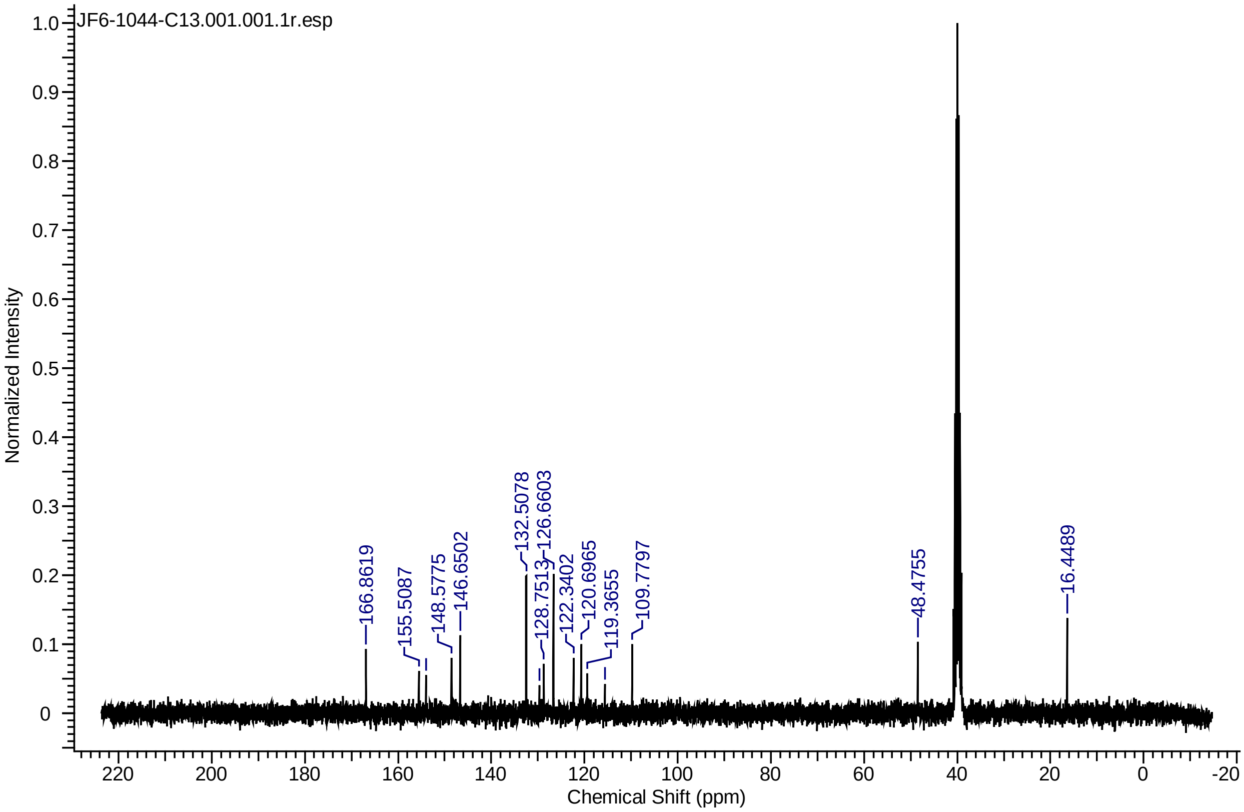

JF6-1041-pa1.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
O
N
N–N
O
O
Br
3.36
0.87
1.91
3.87
2.12
0.90
0.94
1.98
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

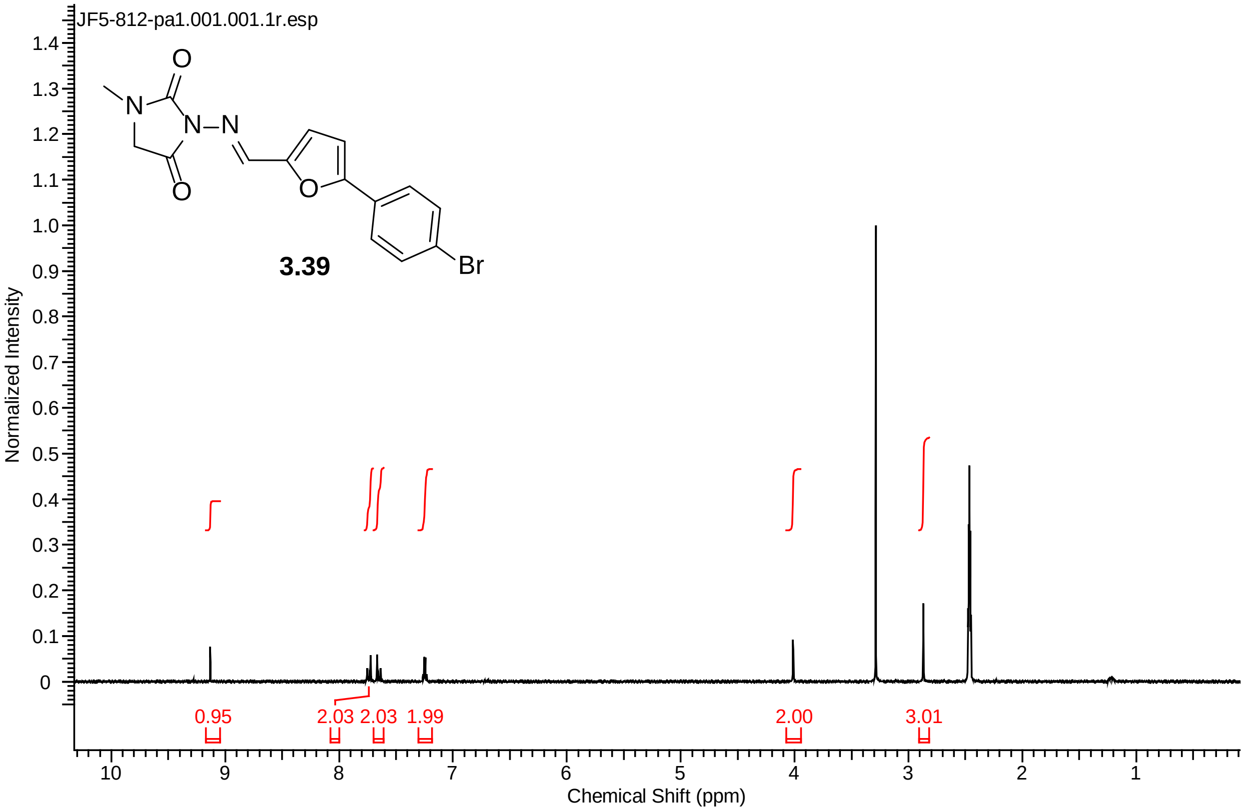

JF6-1041-C13HT.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
164.8493
158.3582
147.9687
146.8632
136.4773
134.7864
133.1572
131.5644
128.9425
125.8660
118.7603
108.7381
48.2740
19.7747
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

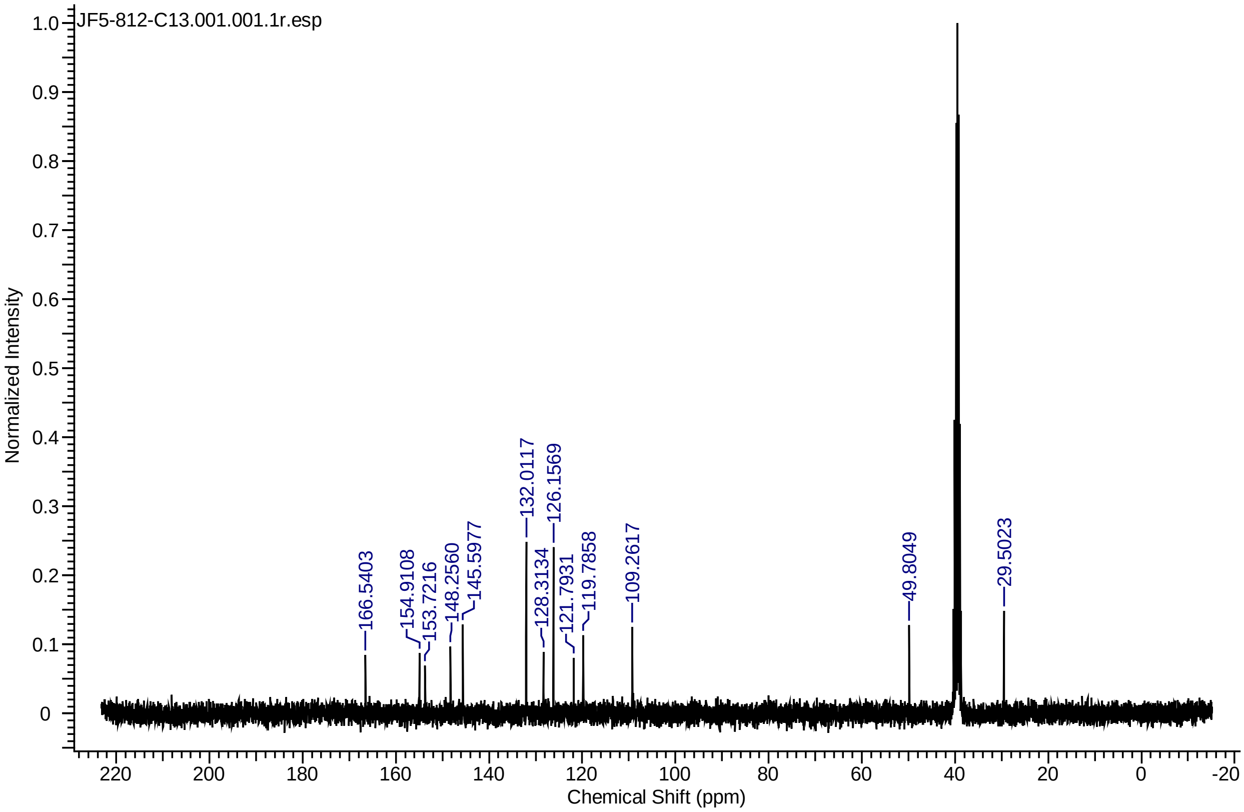

JF6-1043-pa1.001.001.1r.esp
EtO
O
N
O
N–N
O
O
Br
3.37
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.96
2.20
2.73
1.96
1.87
3.99
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

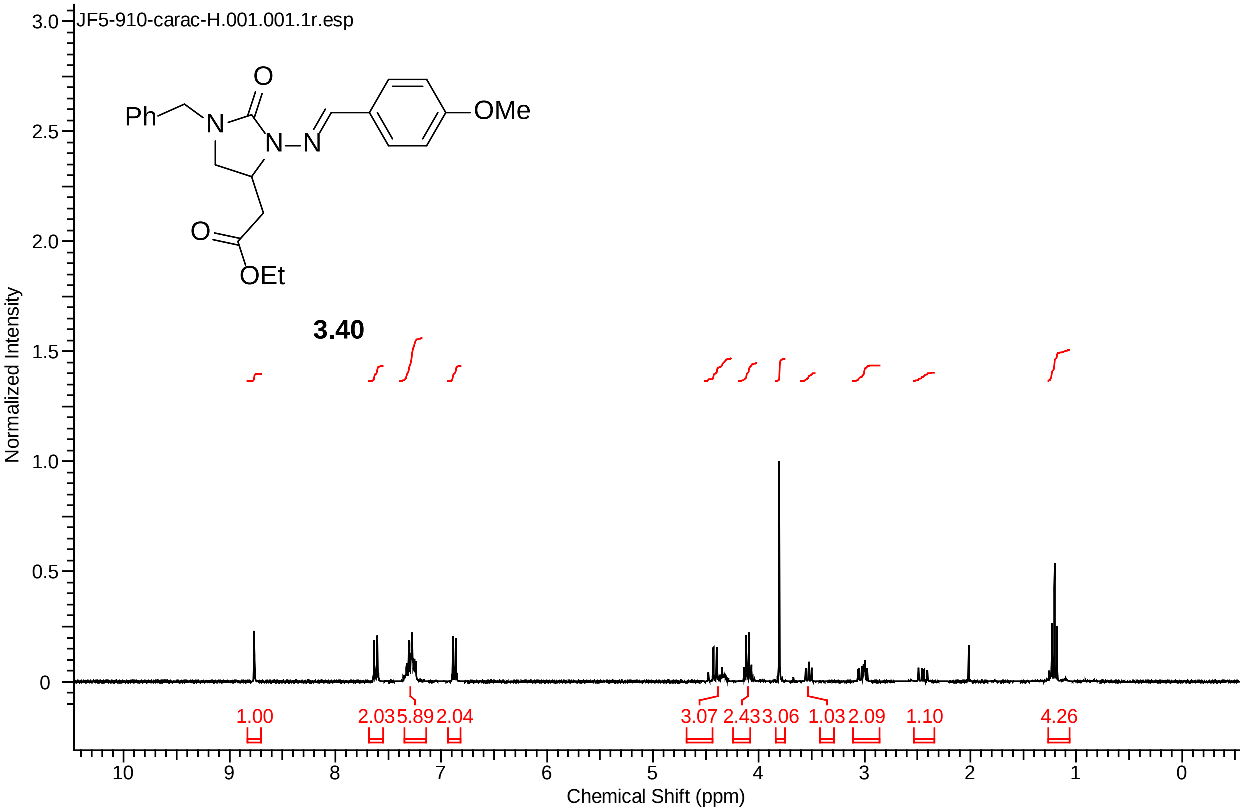

JF6-1043-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
168.8547
166.8110
155.6033
154.4287
148.4757
147.1629
132.5115
129.7077
126.6858
122.3729
120.9219
115.6345
109.7979
61.5524
49.3447
44.4099
14.4342
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

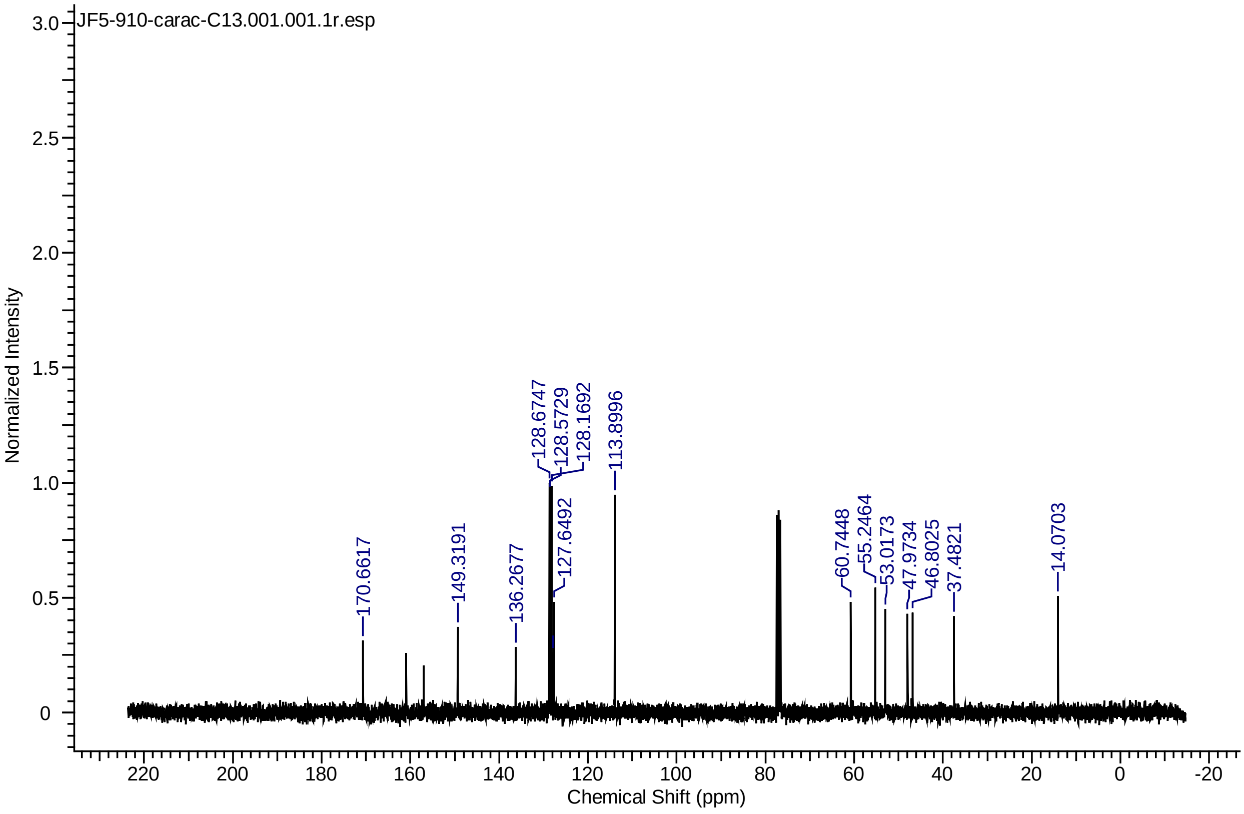

3.38
JF6-1044-pa1.001.001.1r.esp
N
O
N
N–N
O
O
Br
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.95
5.88
2.06
2.02
1.97
2.00
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

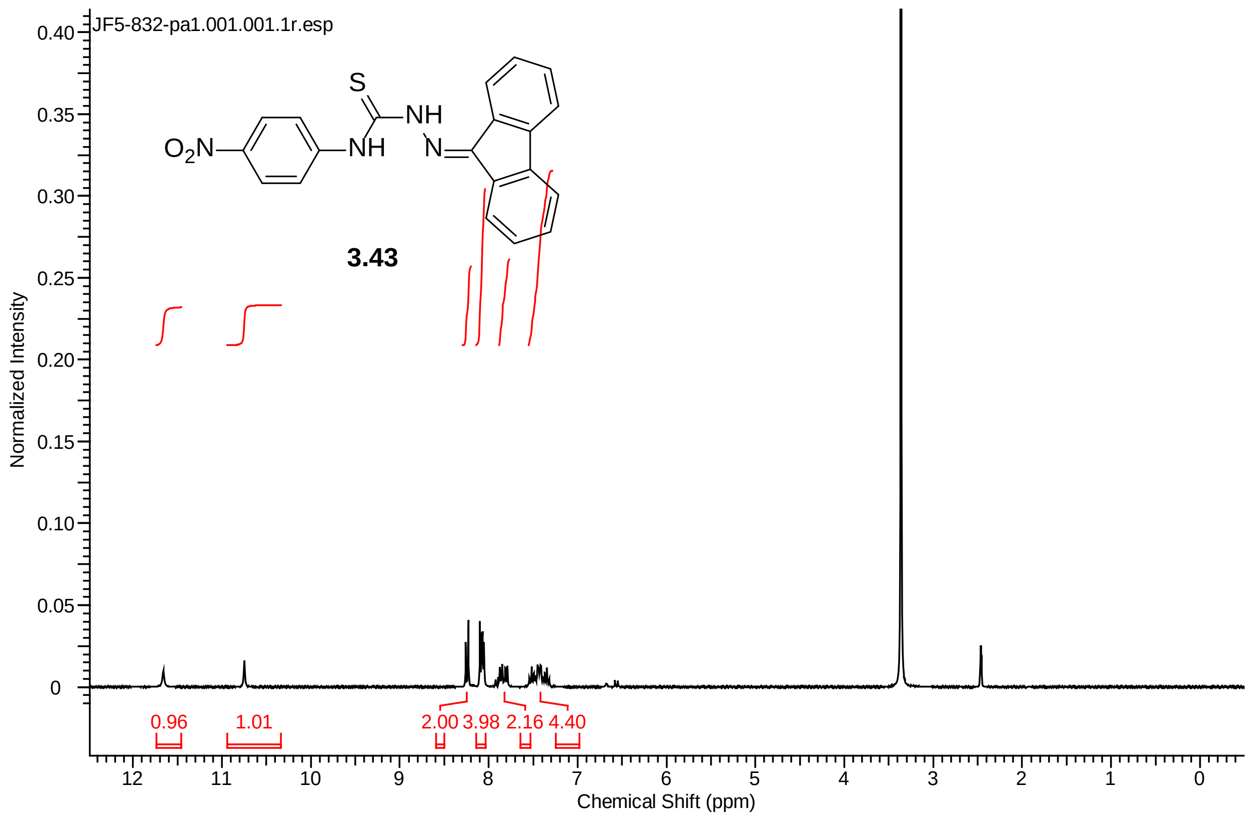

JF6-1044-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
166.8619
155.5087
148.5775
146.6502
132.5078
128.7513
126.6603
122.3402
120.6965
119.3655
109.7797
48.4755
16.4489
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

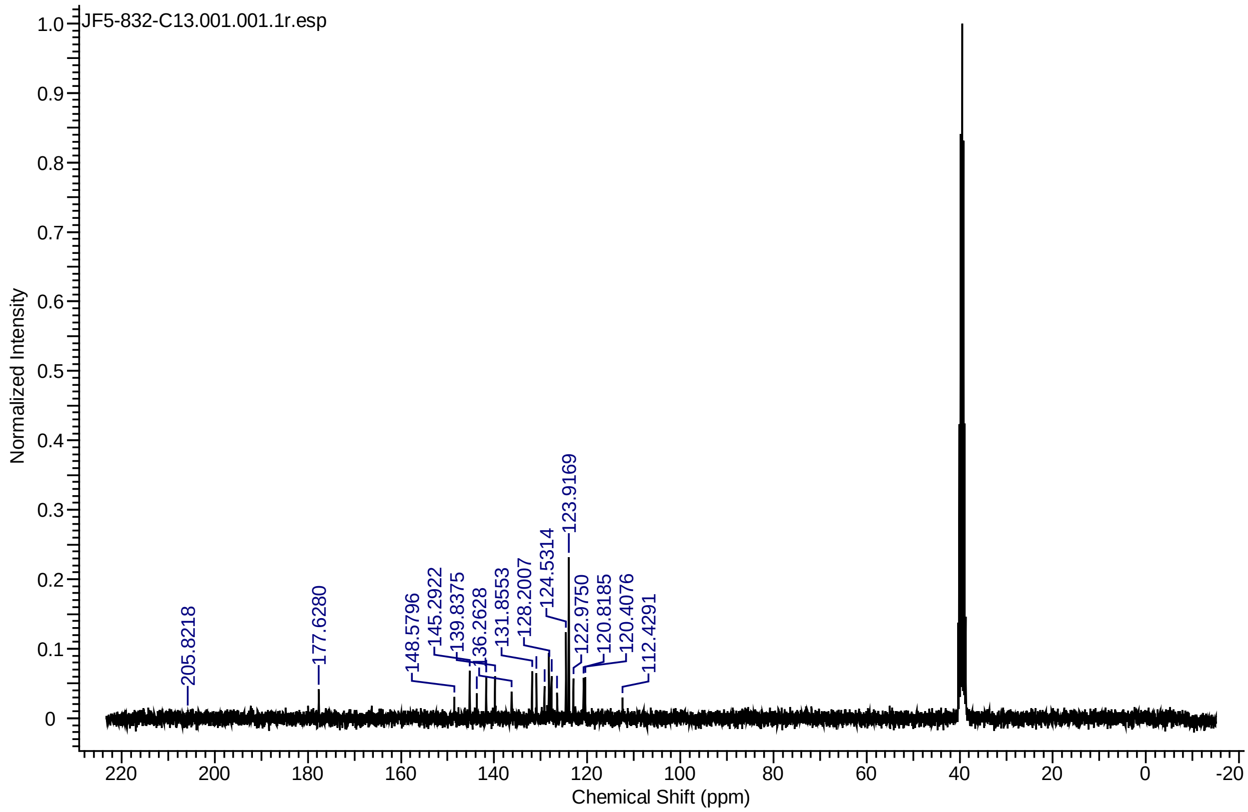

JF5-812-pa1.001.001.1r.esp
3.39
Br
O
N
N–N
Normalized Intensity
0.95
2.03
2.03
1.99
2.00
3.01
Chemical Shift (ppm)
10
9
8
7
6
5
4
3
2
1
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4

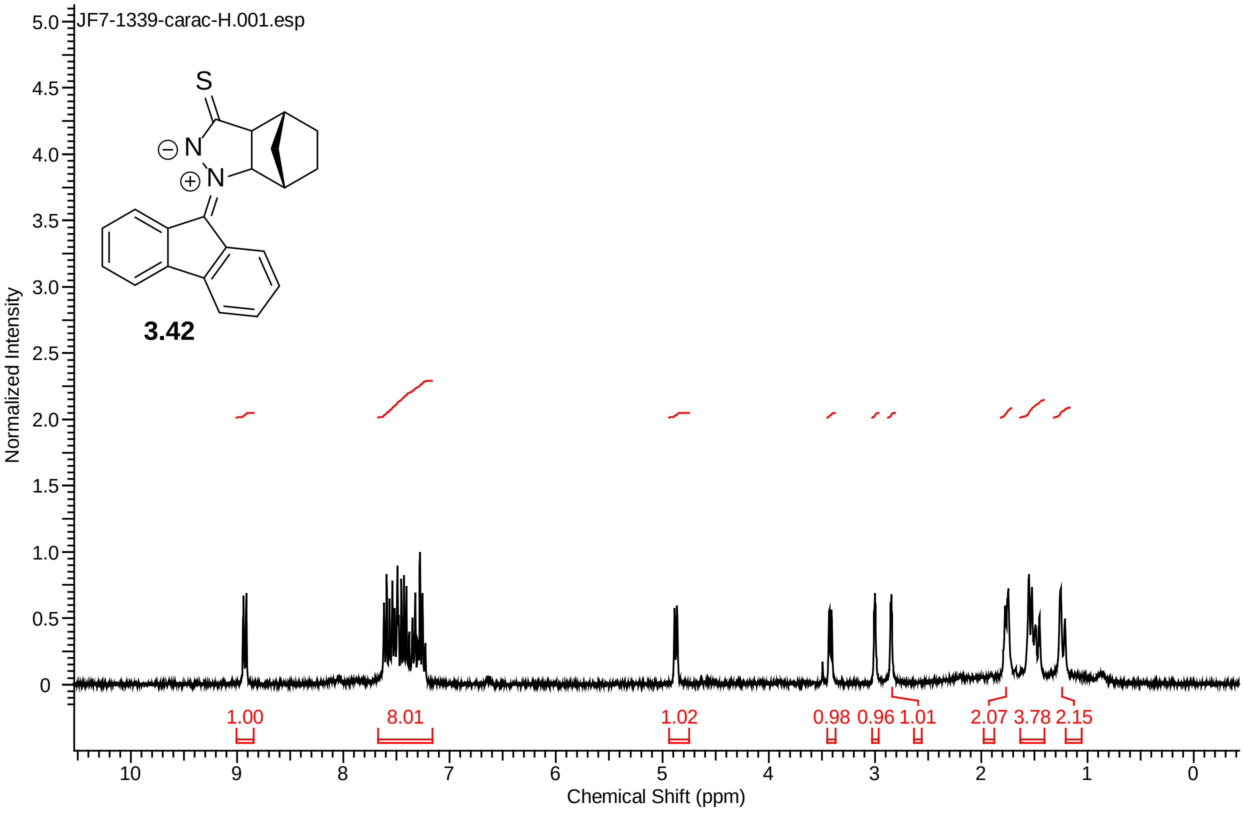

JF5-812-C13.001.001.1r.esp
Normalized Intensity
166.5403
154.9108
153.7216
148.2560
145.5977
132.0117
128.3134
126.1569
121.7931
119.7858
109.2617
49.8049
29.5023
Chemical Shift (ppm)
220
200
180
160
140
120
100
80
60
40
20
0
-20
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

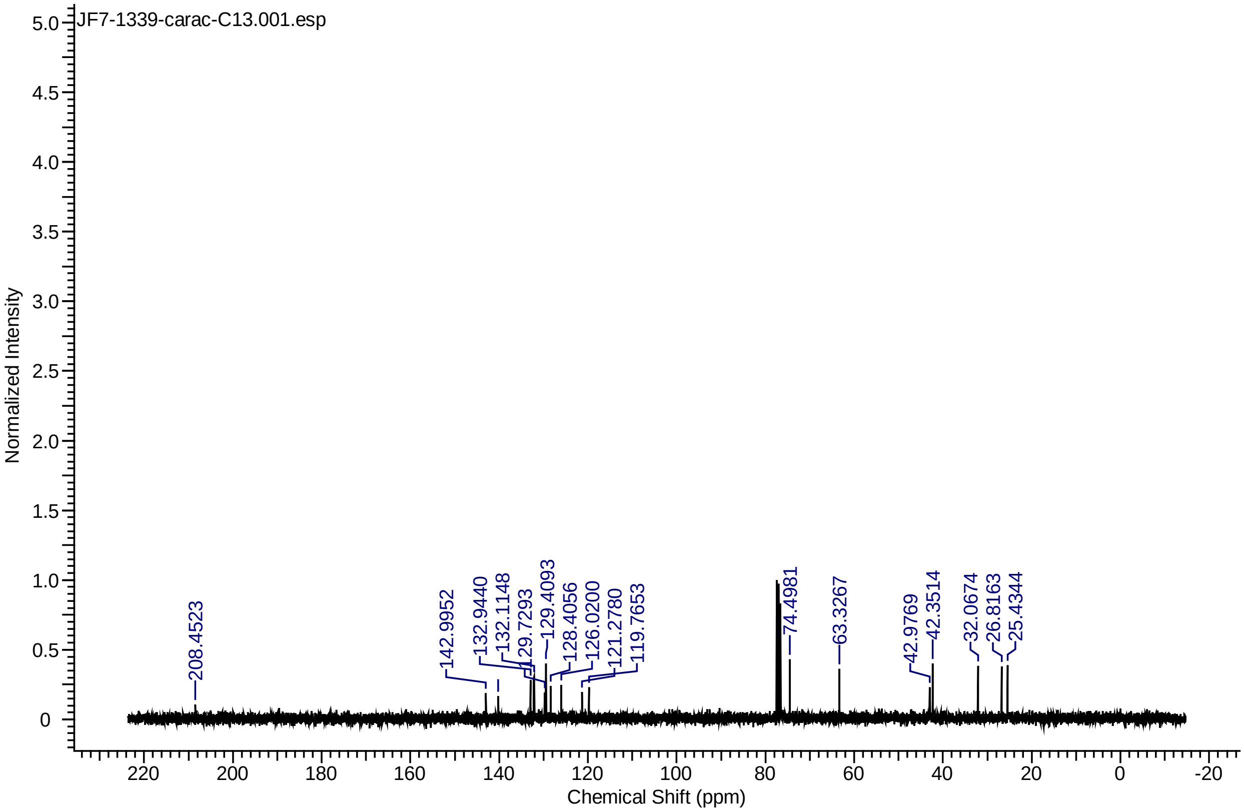

JF5-910-carac-H.001.001.1r.esp
Ph
N
O
N–N
OMe
O
OEt
3.40
1.00
2.03
5.89
2.04
3.07
2.43
3.06
1.03
2.09
1.10
4.26
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

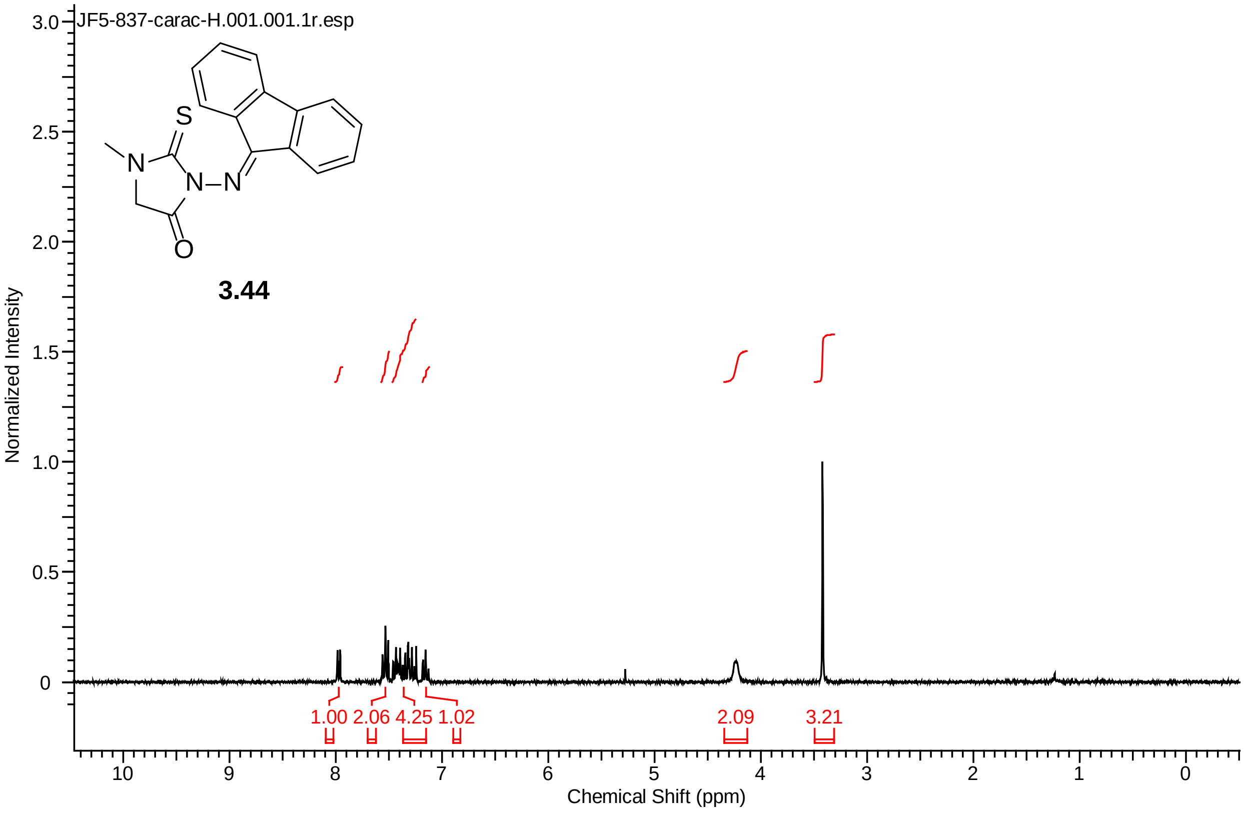

JF5-910-carac-C13.001.001.1r.esp
170.6617
149.3191
136.2677
128.6747
128.5729
128.1692
127.6492
113.8996
60.7448
55.2464
53.0173
47.9734
46.8025
37.4821
14.0703
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

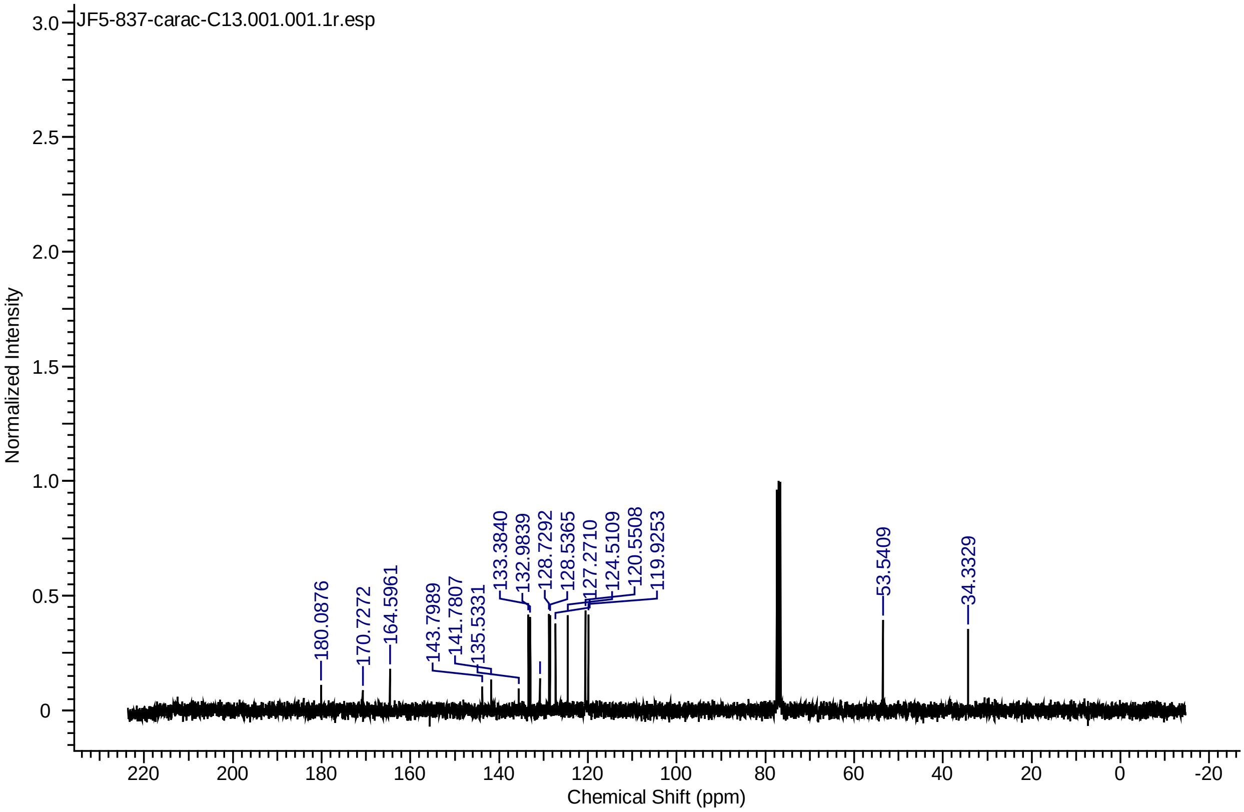

JF5-832-pa1.001.001.1r.esp
3.43
O_2N
NH
S
NH
N
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.96
1.01
2.00
3.98
2.16
4.40
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

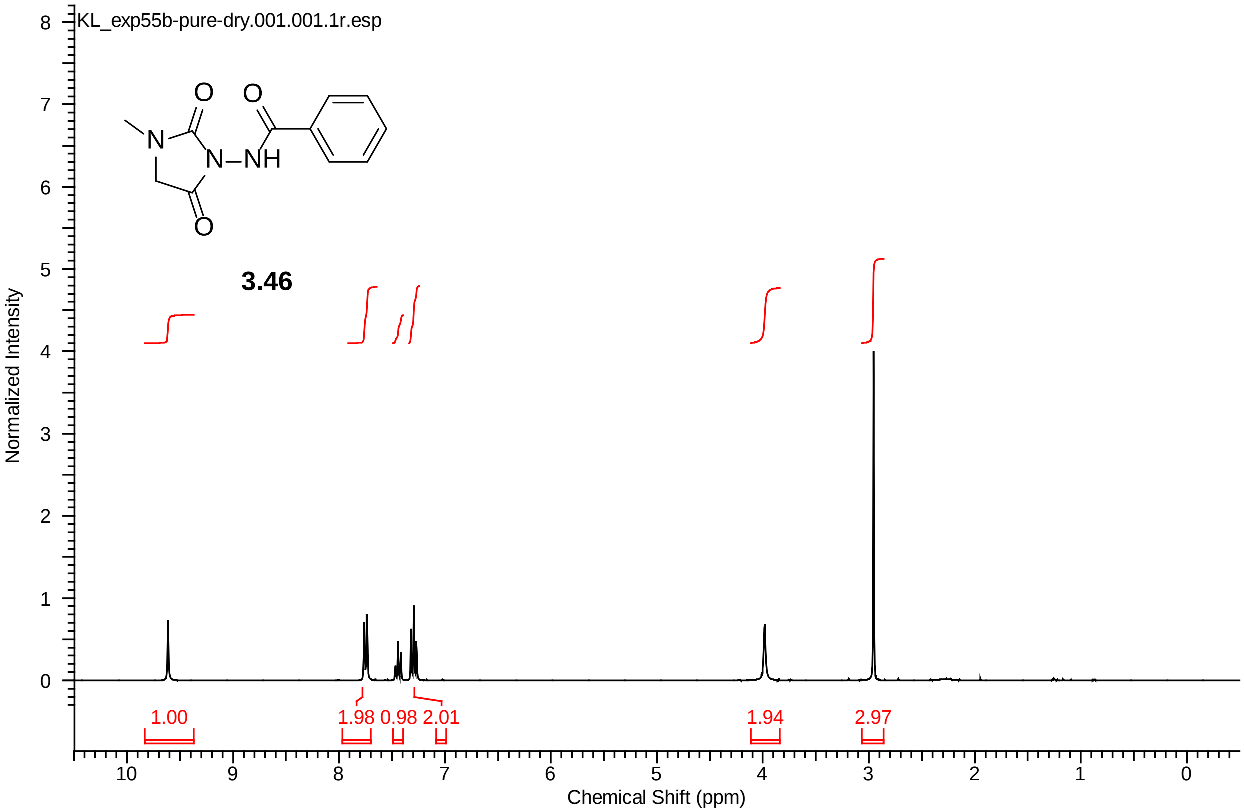

JF5-832-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
205.8218
177.6280
148.5796
145.2922
139.8375
136.2628
131.8553
128.2007
124.5314
123.9169
122.9750
120.8185
120.4076
112.4291
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF7-1339-carac-H.001.esp
3.42
S
N
N
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
1.00
8.01
1.02
0.98
0.96
1.01
2.07
3.78
2.15
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF7-1339-carac-C13.001.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
208.4523
142.9952
132.9440
132.1148
29.7293
129.4093
128.4056
126.0200
121.2780
119.7653
74.4981
63.3267
42.9769
42.3514
32.0674
26.8163
25.4344
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

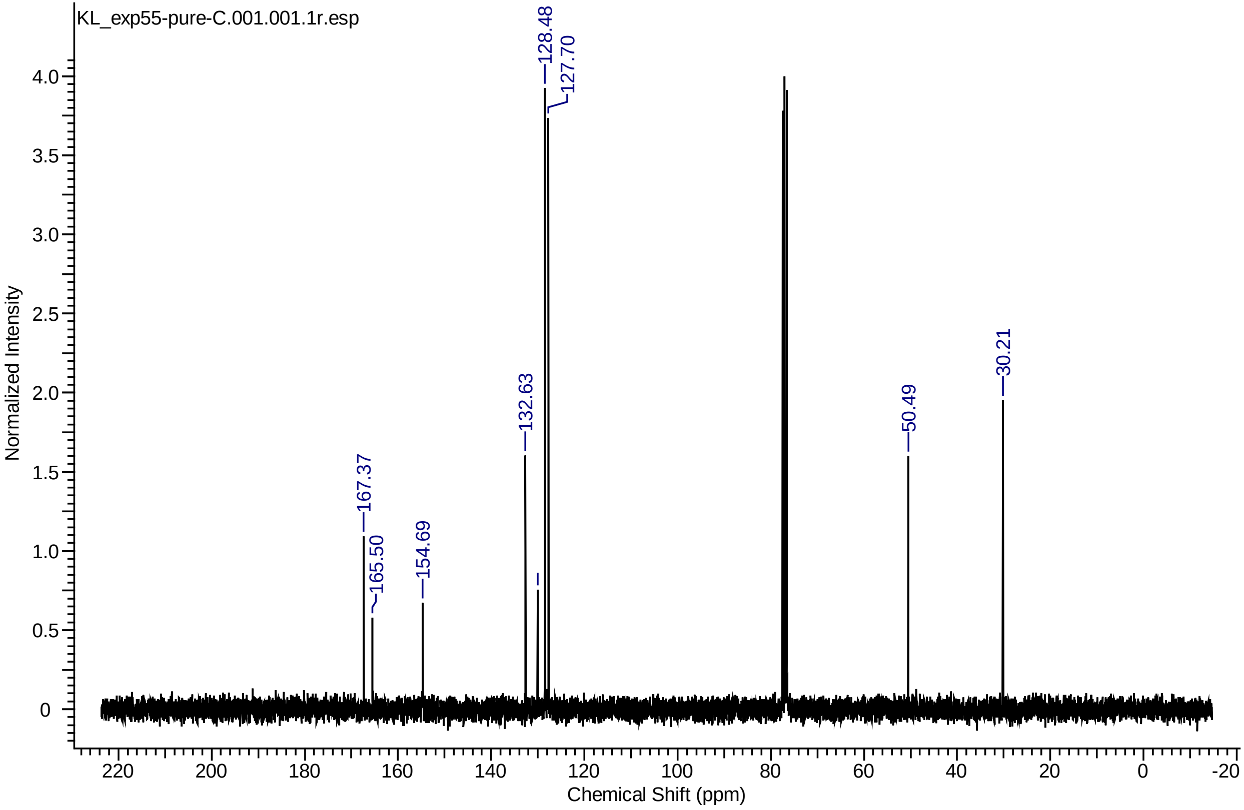

JF5-837-carac-H.001.001.1r.esp
S
N
N–N
O
3.44
1.00
2.06
4.25
1.02
2.09
3.21
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF5-837-carac-C13.001.001.1r.esp
180.0876
170.7272
164.5961
143.7989
141.7807
135.5331
133.3840
132.9839
128.7292
128.5365
127.2710
124.5109
120.5508
119.9253
53.5409
34.3329
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

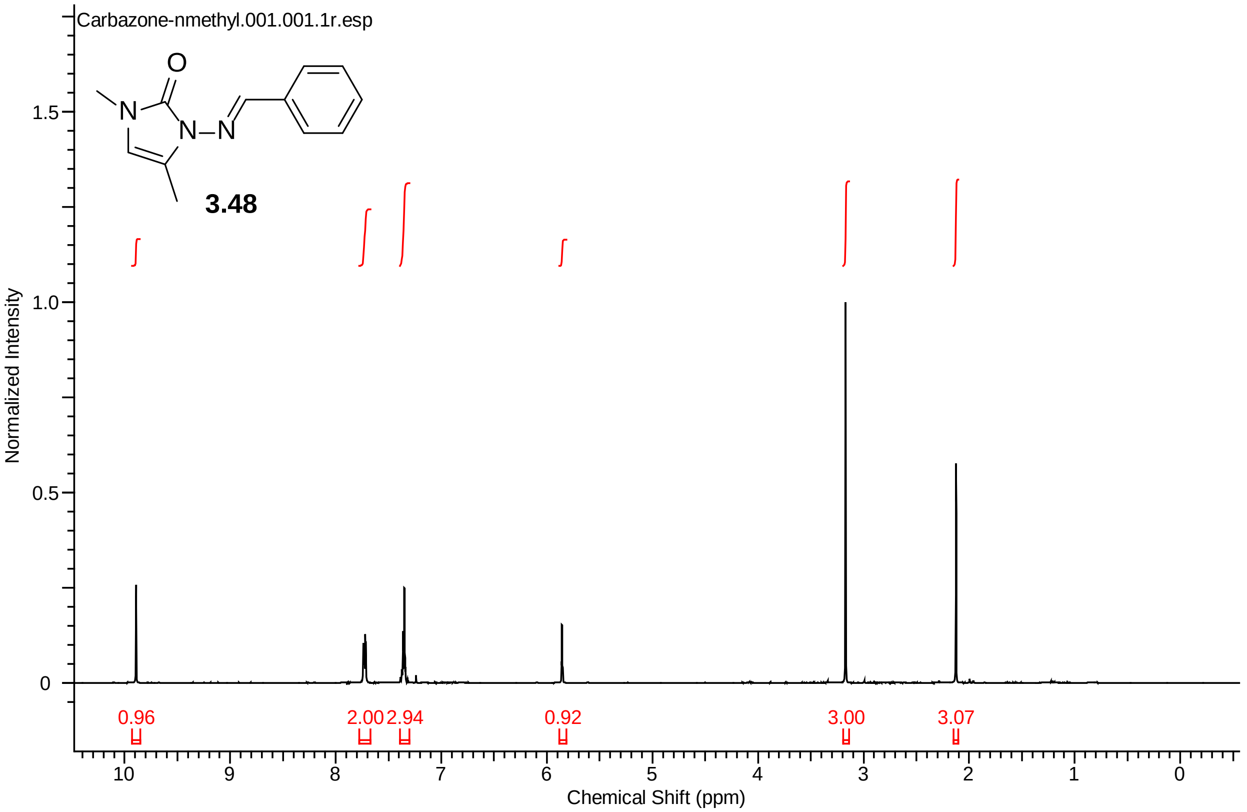


3.46

KL_exp55b-pure-dry.001.001.1r.esp
Normalized Intensity
0
1
2
3
4
5
6
7
8
1.00
1.98
0.98
2.01
1.94
2.97
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
O
O
N
N–NH
O

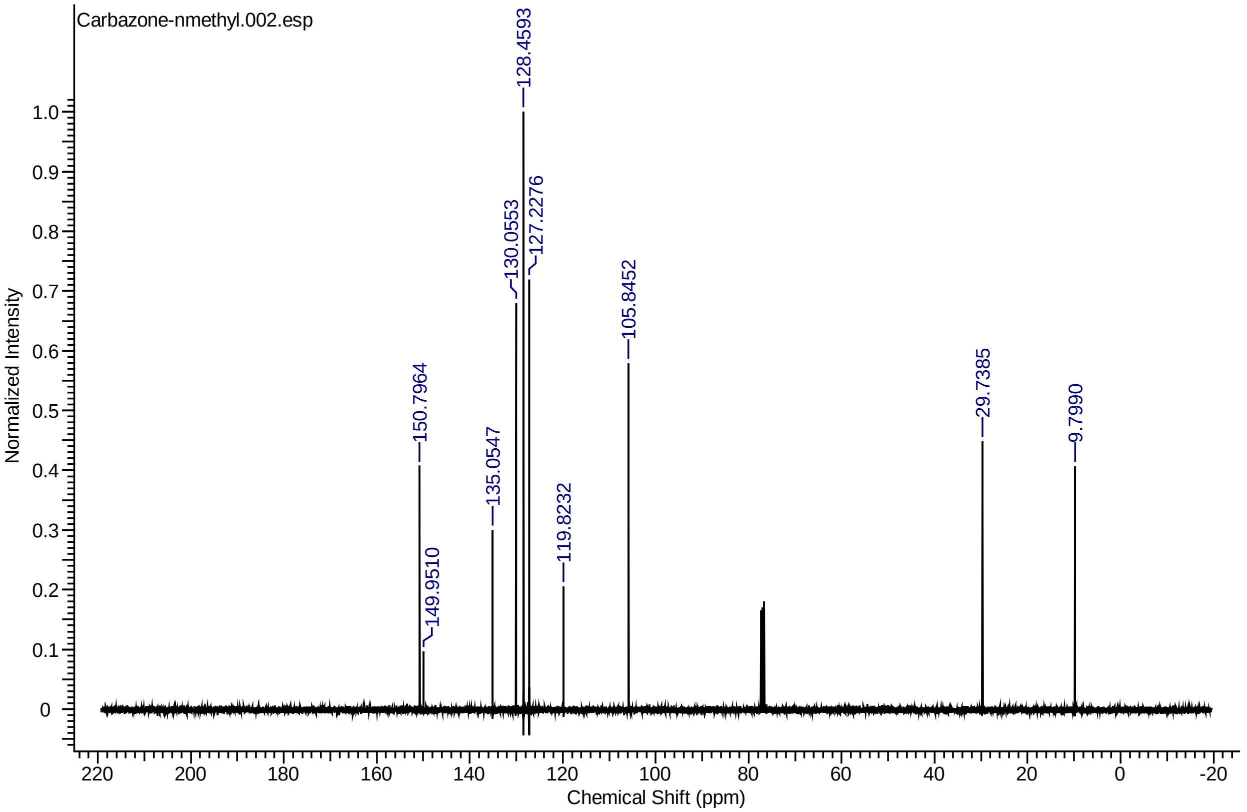


KL_exp55-pure-C.001.001.1r.esp
Normalized Intensity
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
167.37
165.50
154.69
132.63
128.48
127.70
50.49
30.21
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

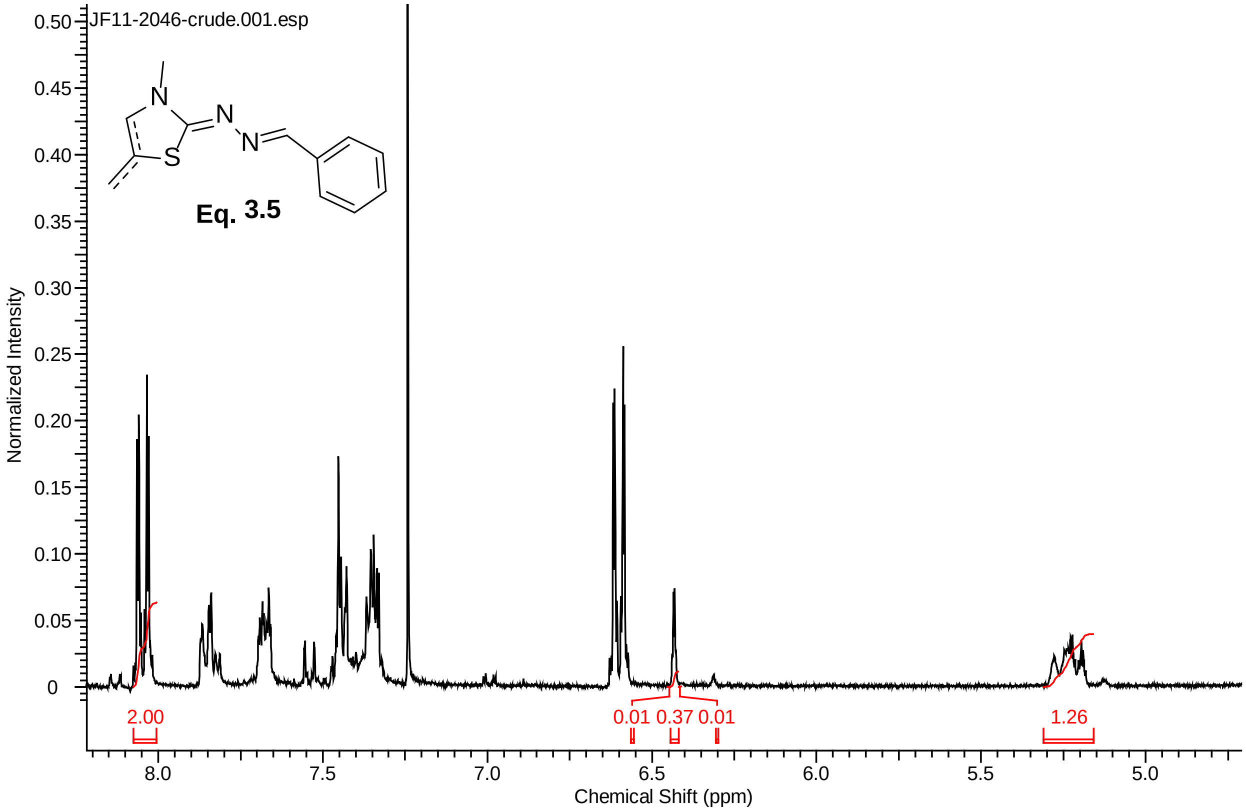


3.48

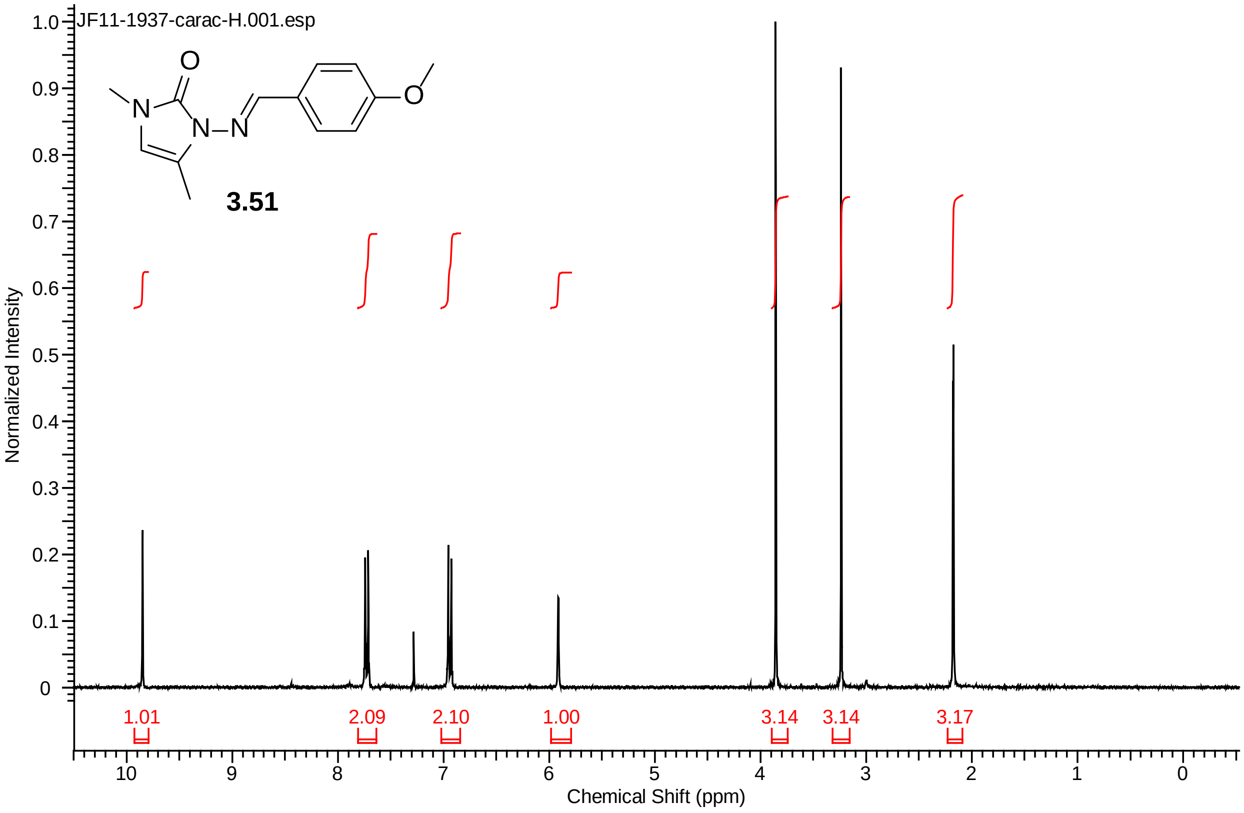
Carbazone-nmethyl.001.001.1r.esp
O
N
N–N
Normalized Intensity
1.5
1.0
0.5
0
0.96
2.00
2.94
0.92
3.00
3.07
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

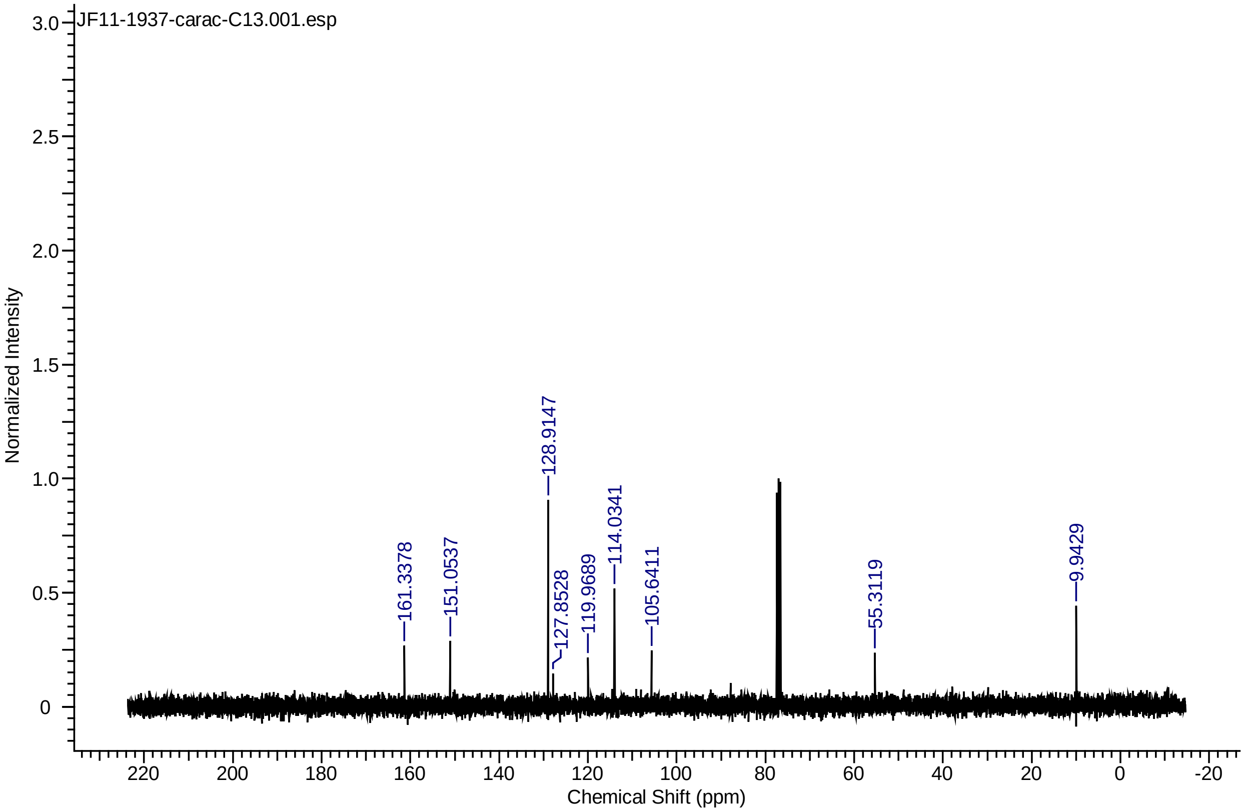


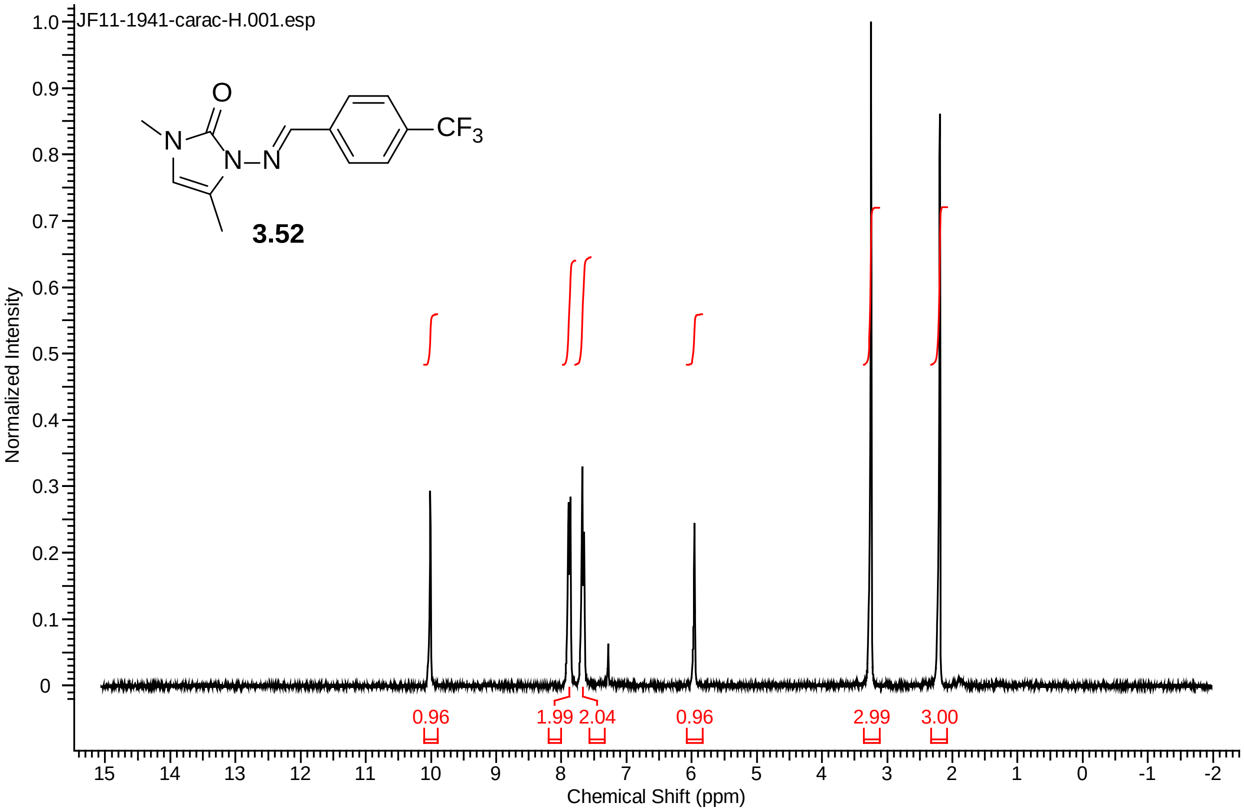
Carbazone-nmethyl.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
150.7964
149.9510
135.0547
130.0553
128.4593
127.2276
119.8232
105.8452
29.7385
9.7990
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

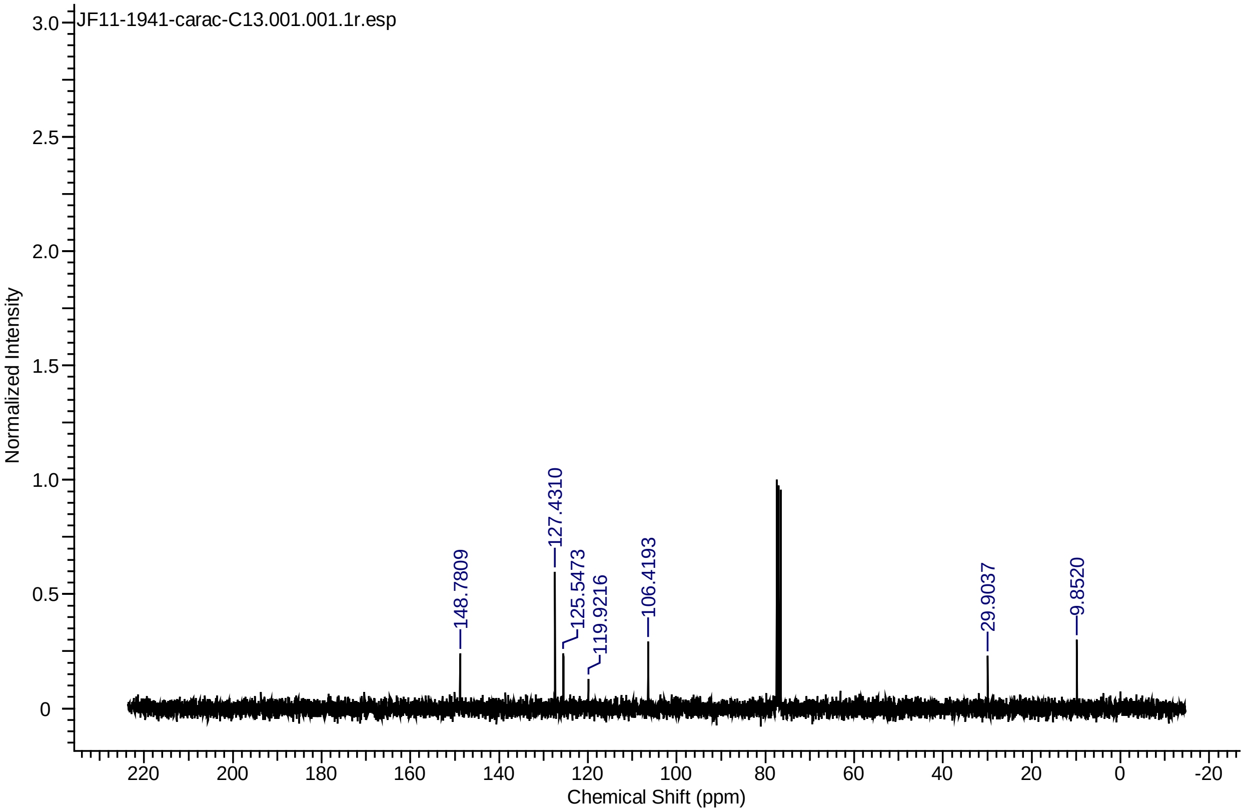


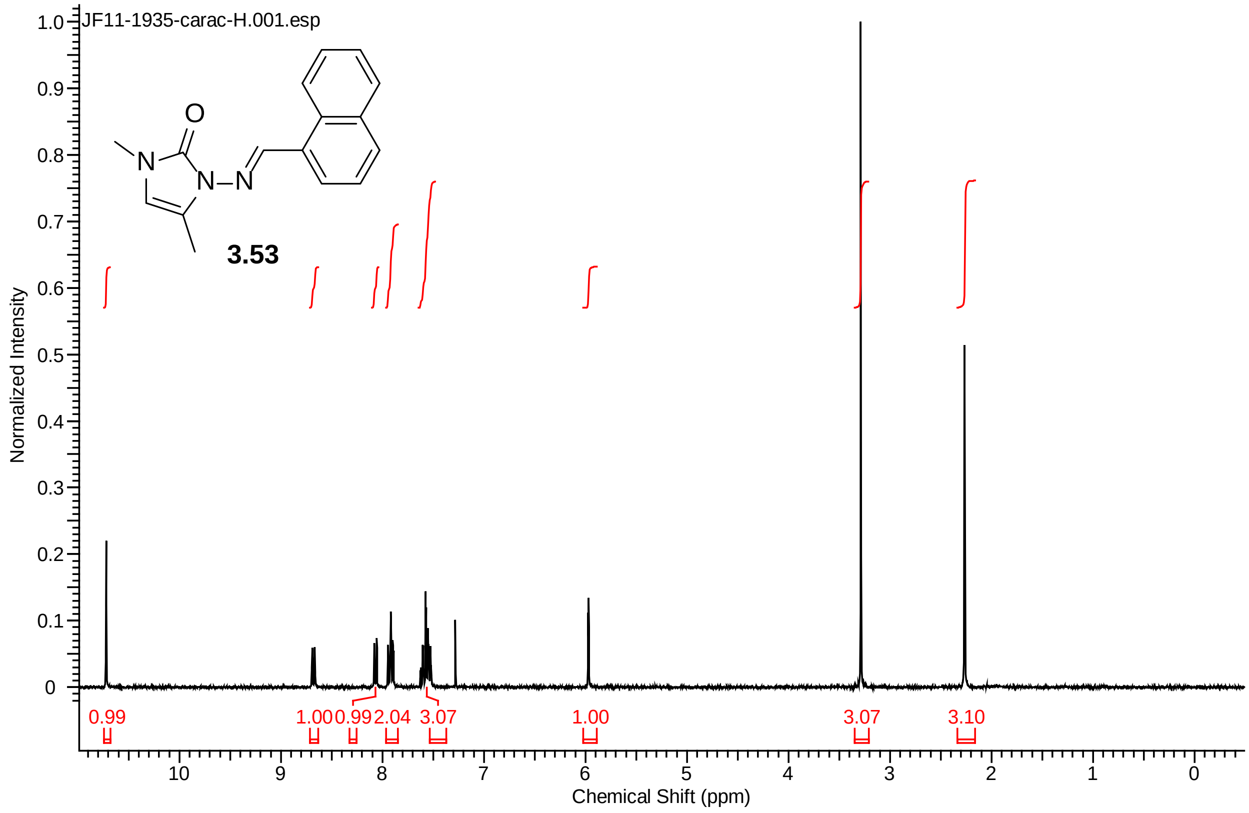
According to paranitroaniline production: 37 % isomerize and 63 % of desired product.

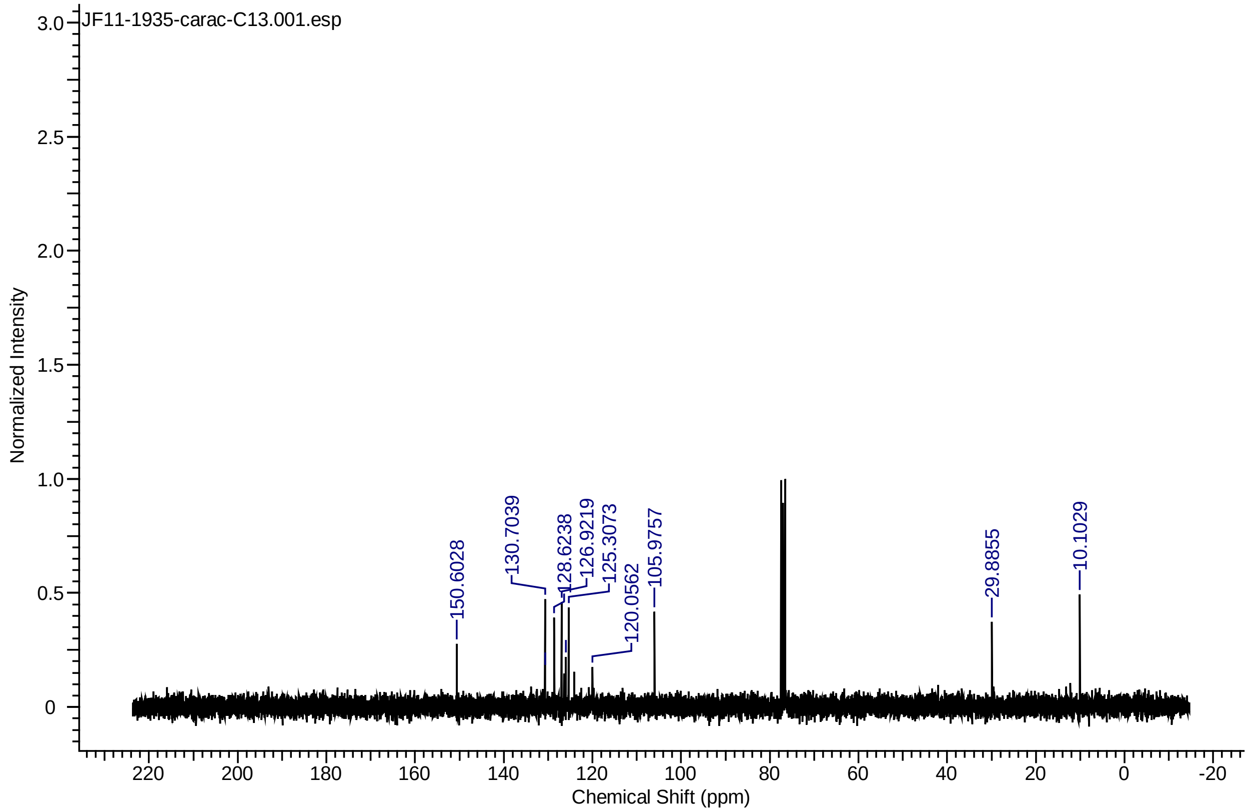

JF11-1937-carac-H.001.esp
O
N
N–N
O
3.51
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.01
2.09
2.10
1.00
3.14
3.14
3.17
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

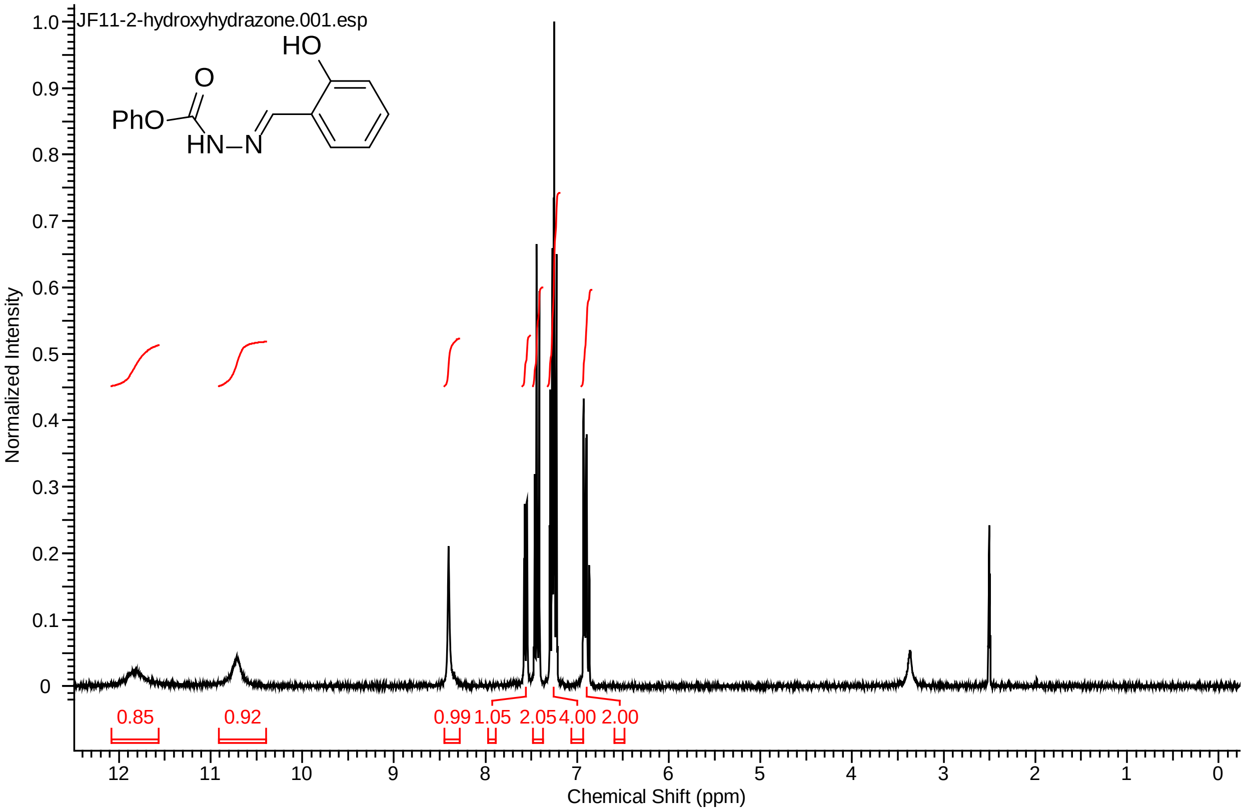

JF11-1937-carac-C13.001.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
161.3378
151.0537
128.9147
127.8528
119.9689
114.0341
105.6411
55.3119
9.9429
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

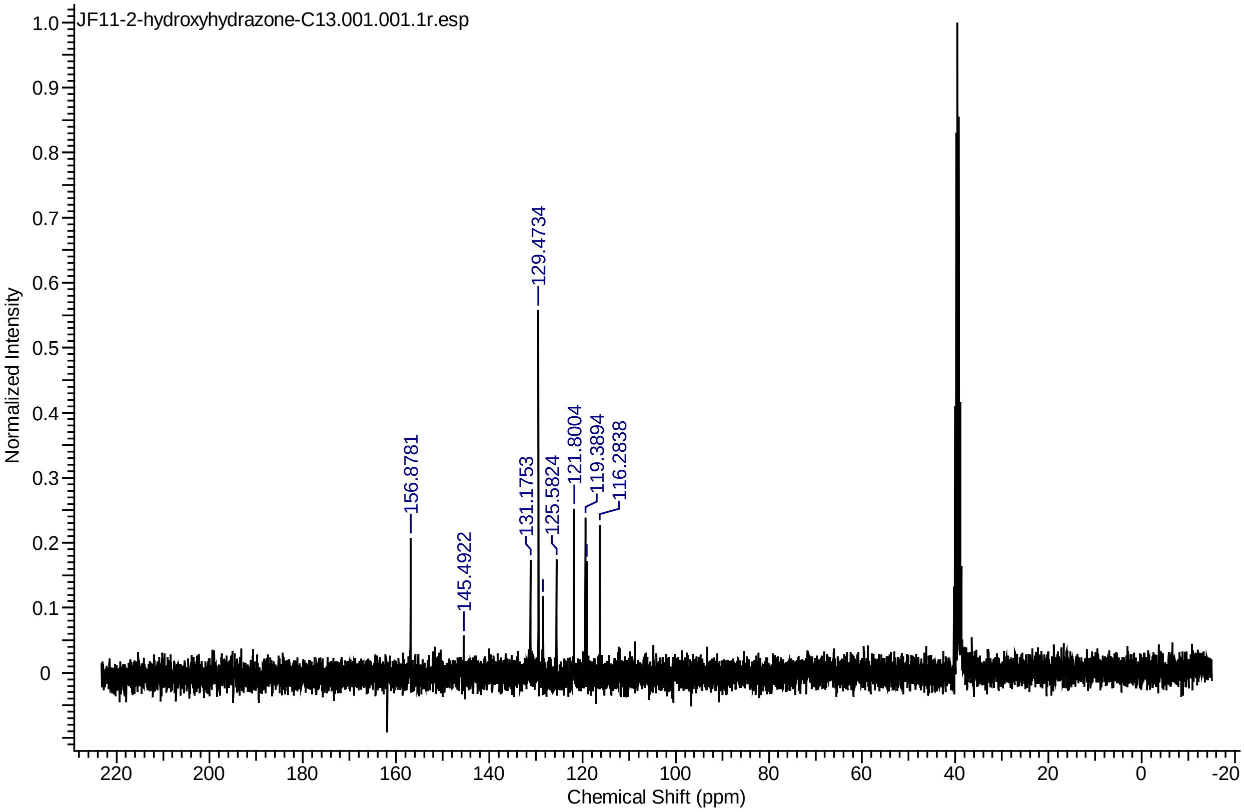

JF11-1941-carac-H.001.esp
O
N
N–N
CF$_3$
3.52
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.96
1.99
2.04
0.96
2.99
3.00
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

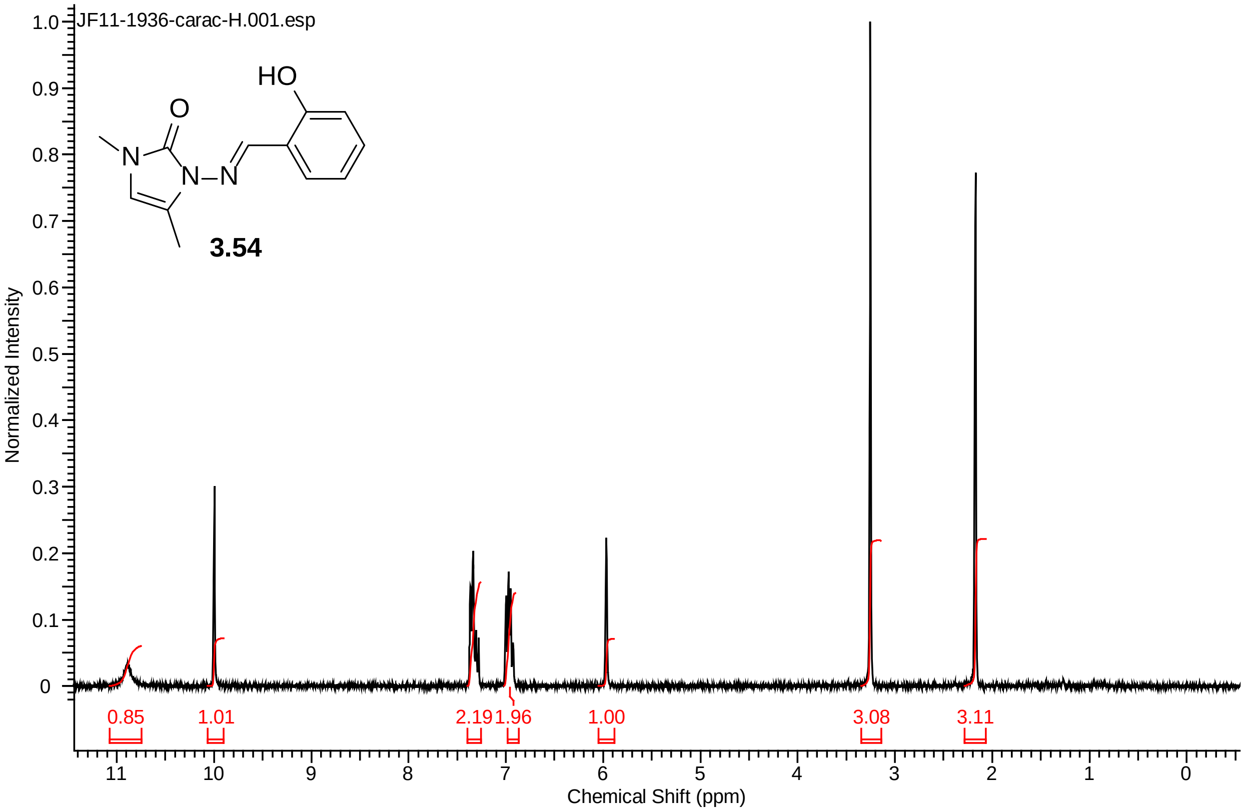

JF11-1941-carac-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
148.7809
127.4310
125.5473
119.9216
106.4193
29.9037
9.8520
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF11-1935-carac-H.001.esp
3.53
O
N
N–N
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.99
1.00
0.99
2.04
3.07
1.00
3.07
3.10
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF11-1935-carac-C13.001.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
150.6028
130.7039
128.6238
126.9219
125.3073
120.0562
105.9757
29.8855
10.1029
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

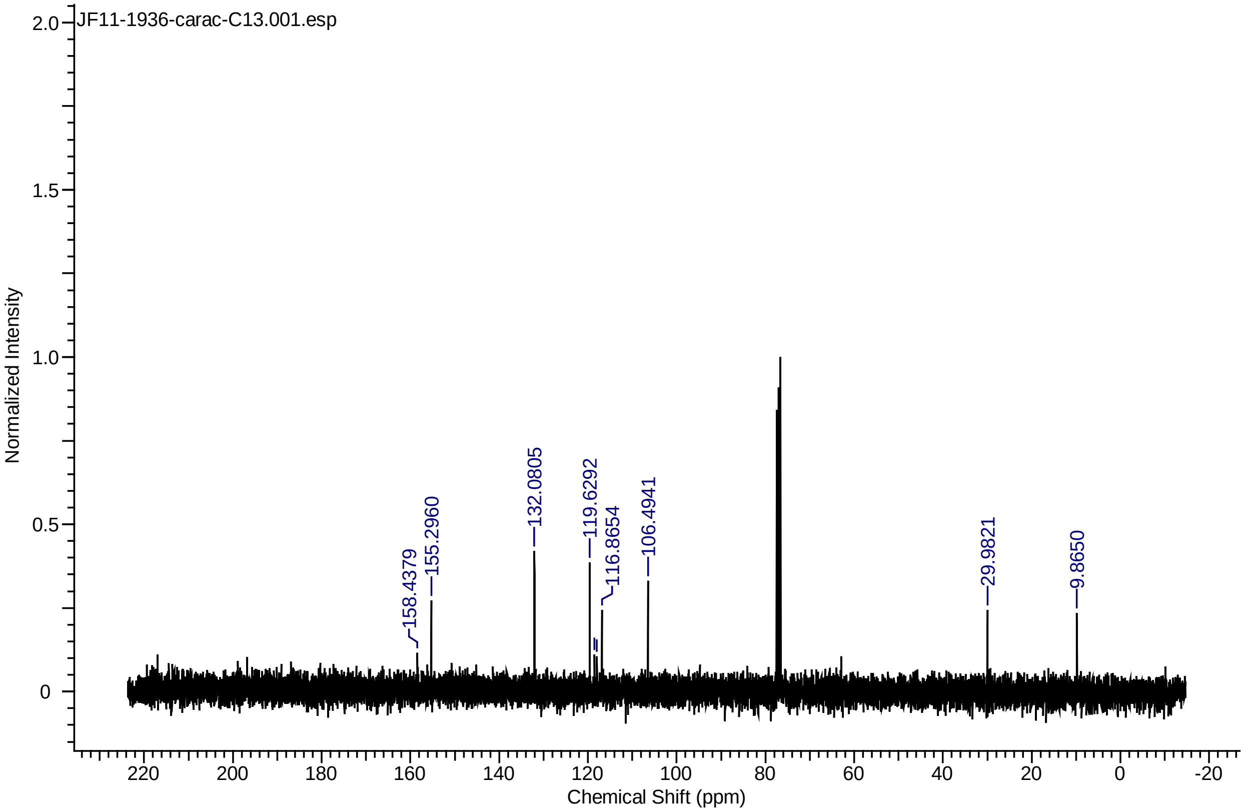

JF11-2-hydroxyhydrazone.001.esp
HO
O
PhO
HN–N
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.85
0.92
0.99
1.05
2.05
4.00
2.00
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF11-2-hydroxyhydrazone-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
156.8781
145.4922
131.1753
129.4734
125.5824
121.8004
119.3894
116.2838
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

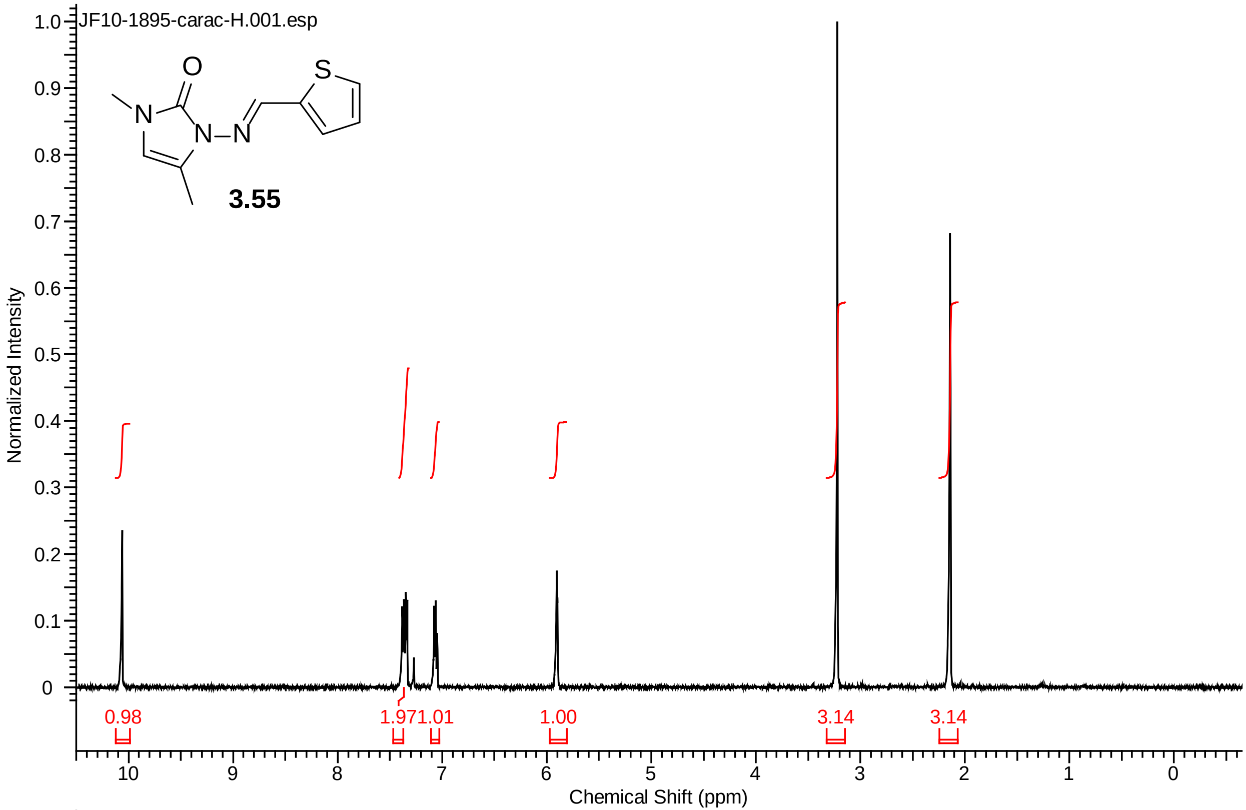


3.54

JF11-1936-carac-H.001.esp
HO
O
N
N–N
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.85
1.01
2.19
1.96
1.00
3.08
3.11
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

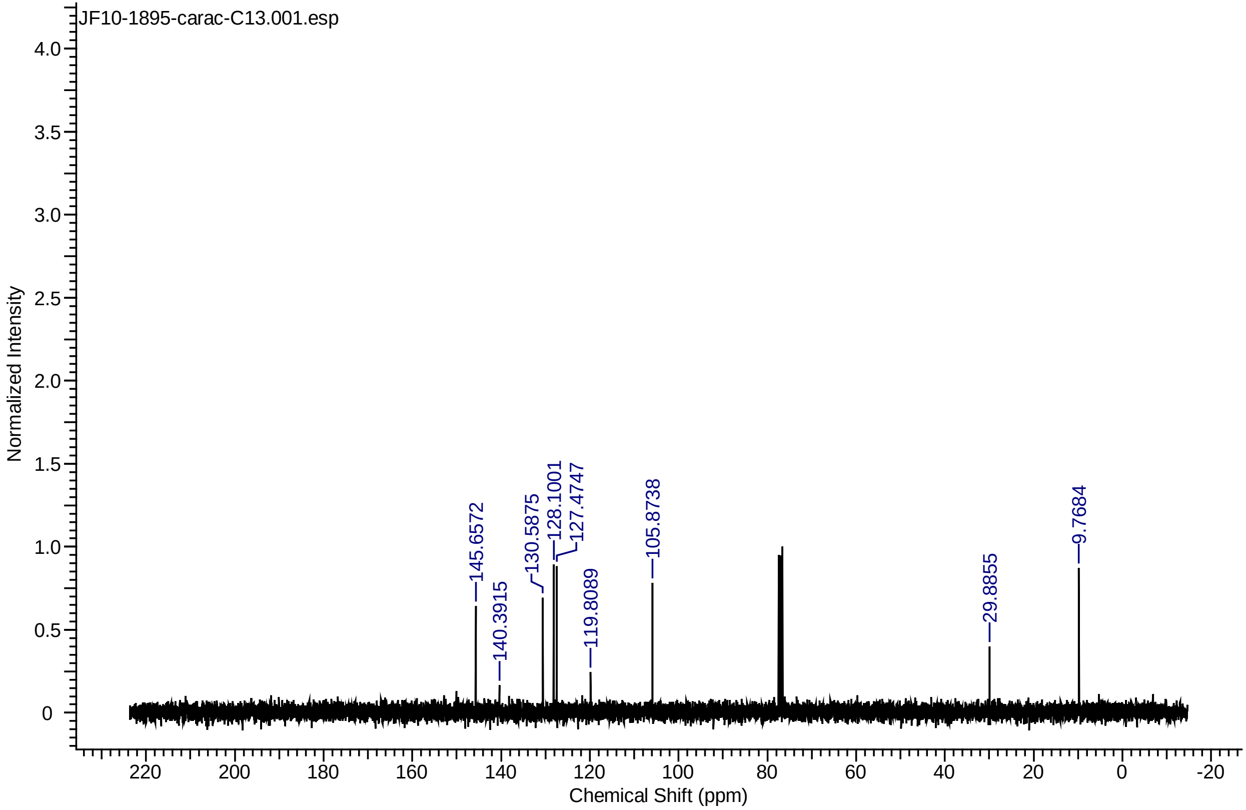


JF11-1936-carac-C13.001.esp
Normalized Intensity
2.0
1.5
1.0
0.5
0
158.4379
155.2960
132.0805
119.6292
116.8654
106.4941
29.9821
9.8650
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

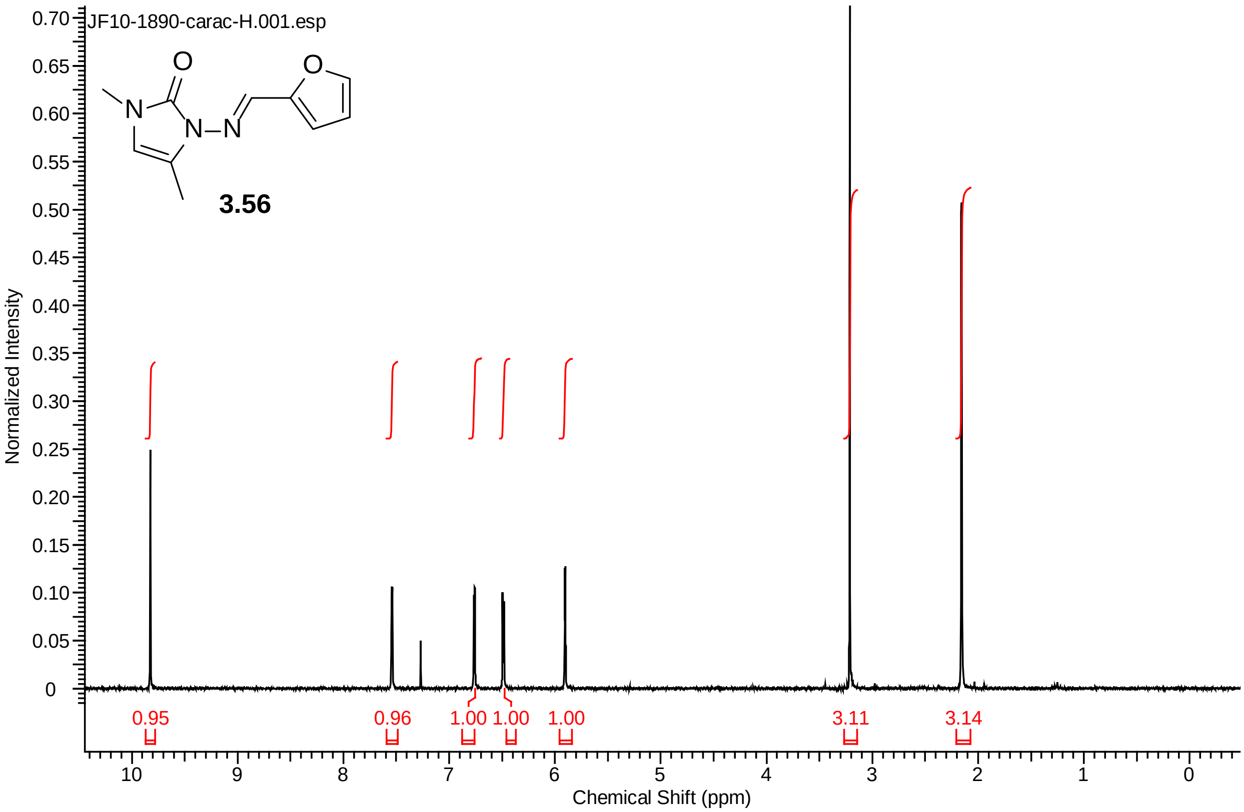


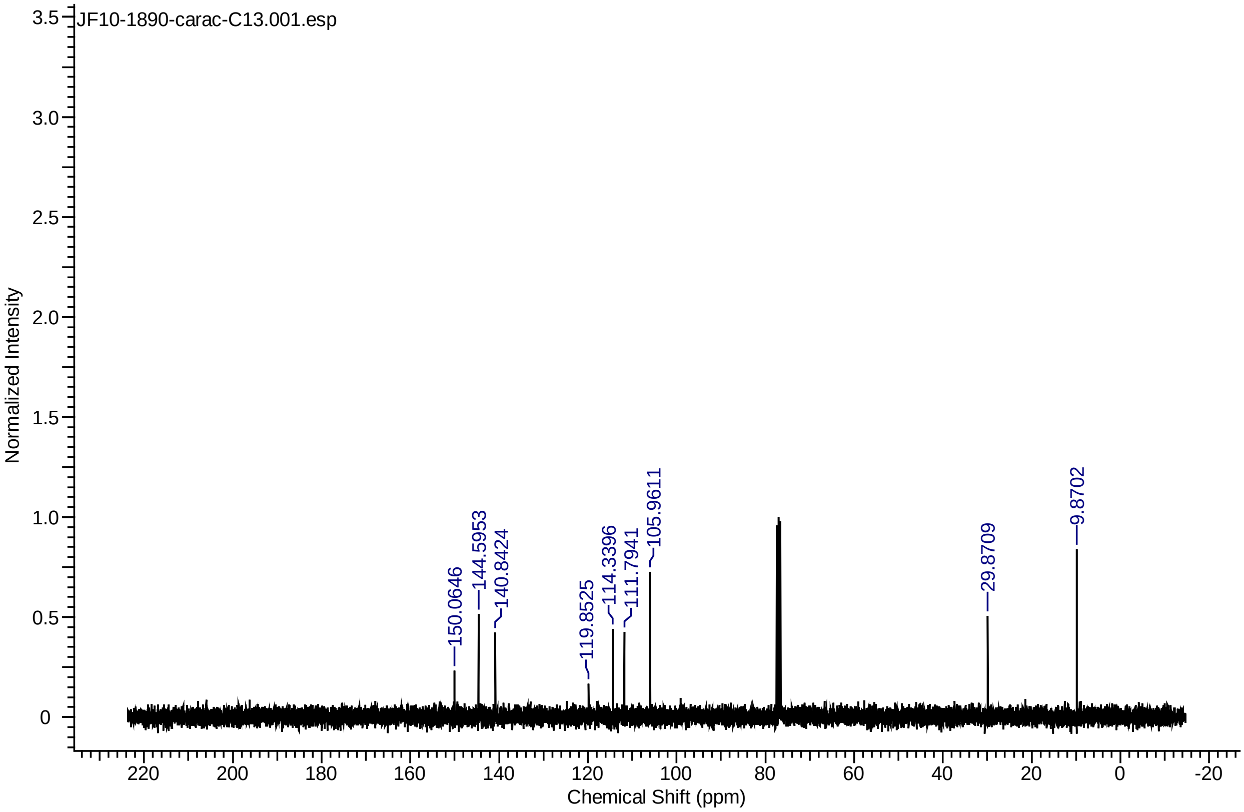
3.55

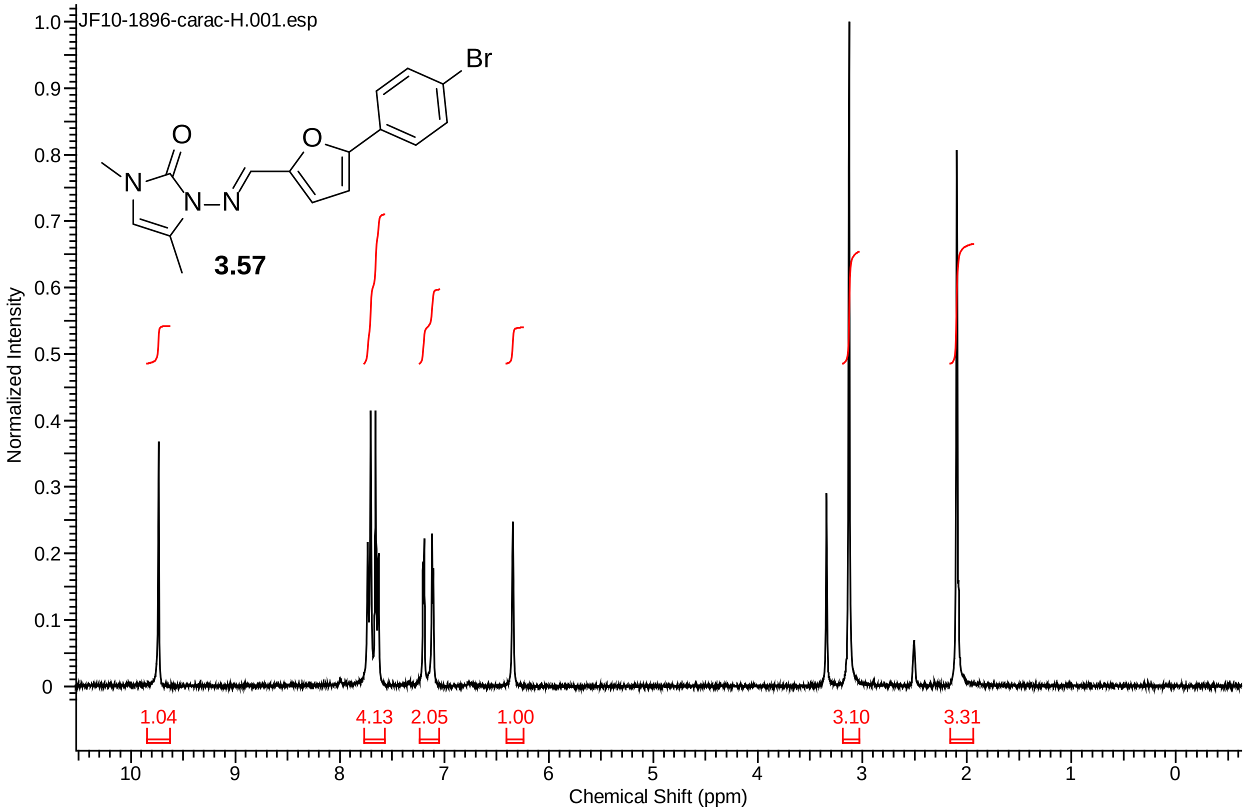
JF10-1895-carac-H.001.esp
O
N
N–N
S
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.98
1.97
1.01
1.00
3.14
3.14
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

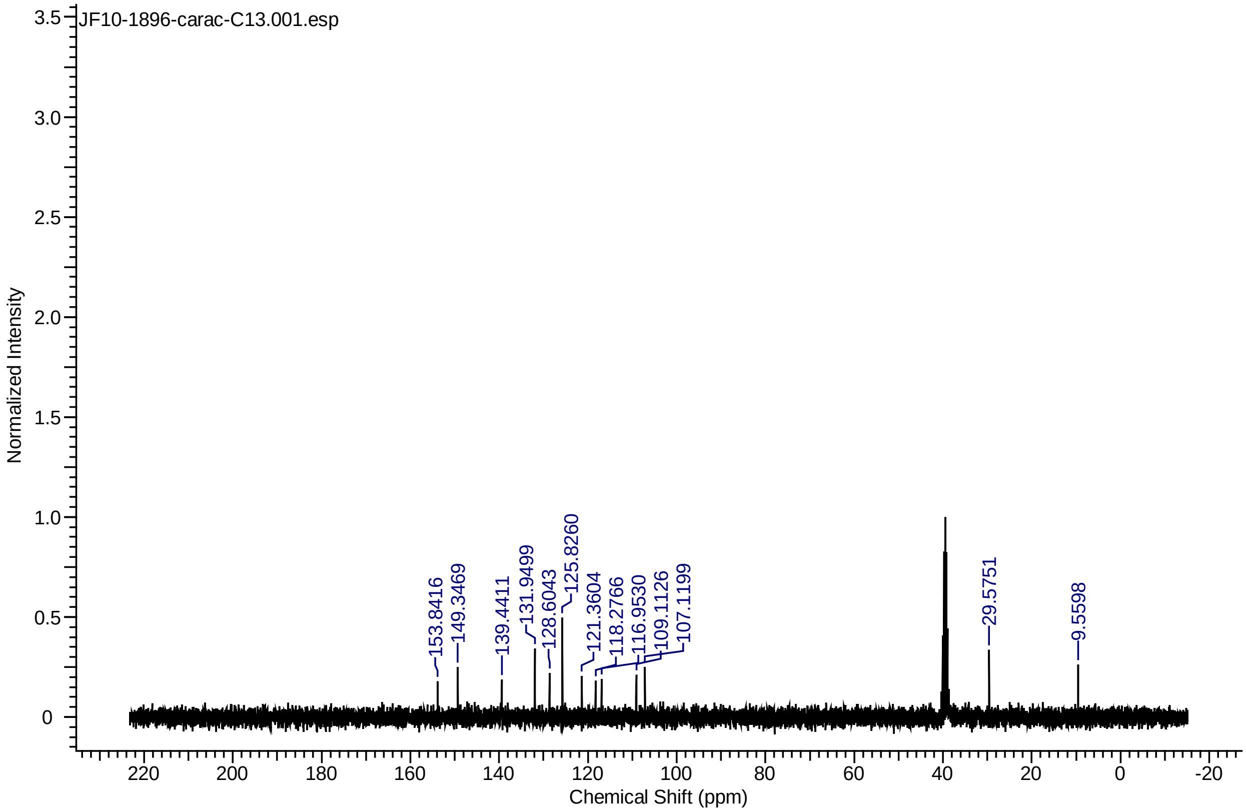


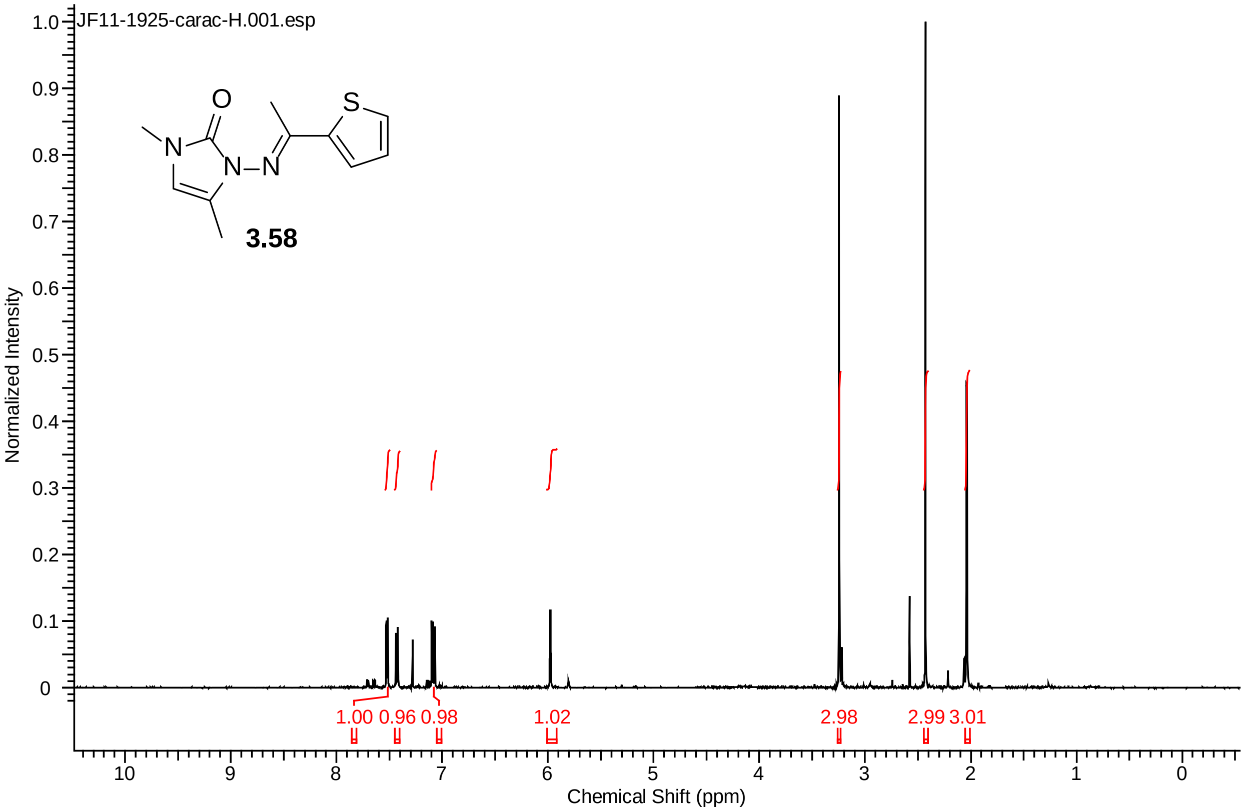
JF10-1895-carac-C13.001.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
145.6572
140.3915
130.5875
128.1001
127.4747
119.8089
105.8738
29.8855
9.7684
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF10-1890-carac-H.001.esp
3.56
O
N
N–N
O
Normalized Intensity
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.95
0.96
1.00
1.00
1.00
3.11
3.14
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF10-1890-carac-C13.001.esp
Normalized Intensity
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
150.0646
144.5953
140.8424
119.8525
114.3396
111.7941
105.9611
29.8709
9.8702
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

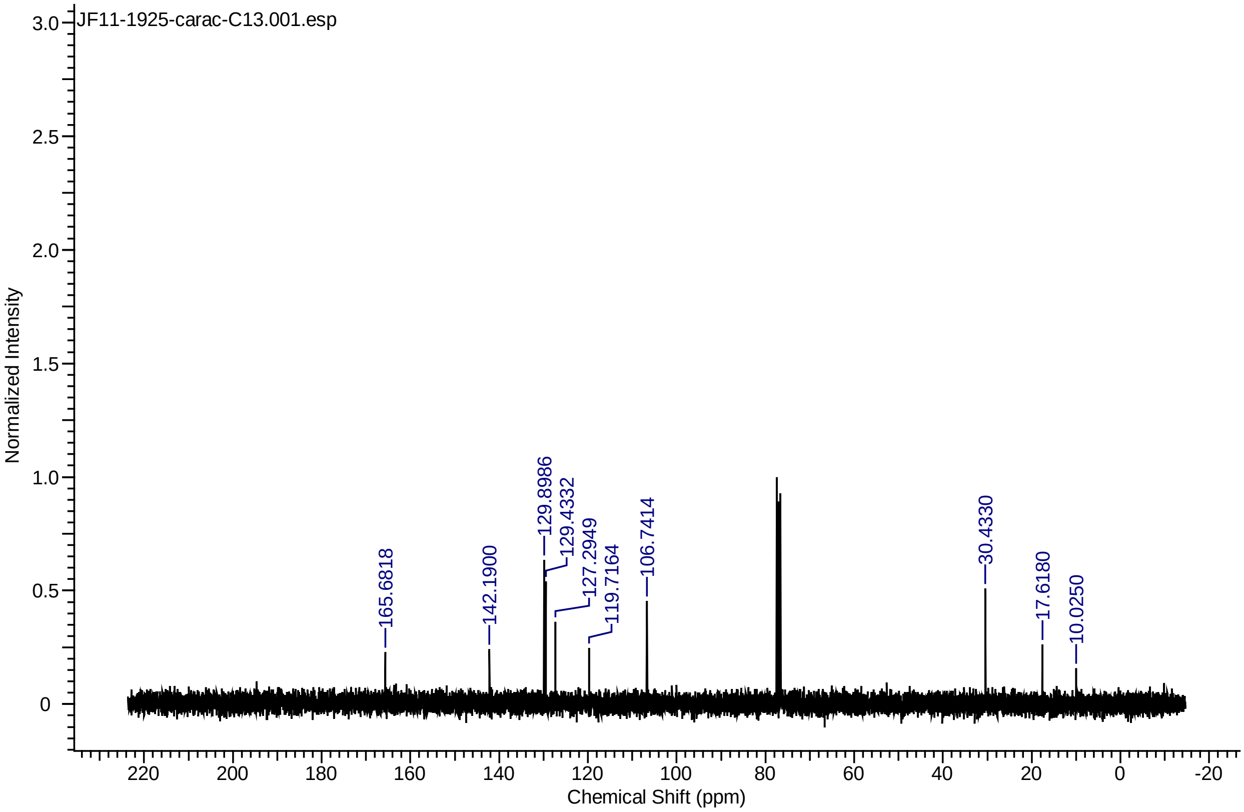

JF10-1896-carac-H.001.esp
Br
O
O
N
N–N
3.57
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.04
4.13
2.05
1.00
3.10
3.31
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF10-1896-carac-C13.001.esp
Normalized Intensity
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
153.8416
149.3469
139.4411
131.9499
128.6043
125.8260
121.3604
118.2766
116.9530
109.1126
107.1199
29.5751
9.5598
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

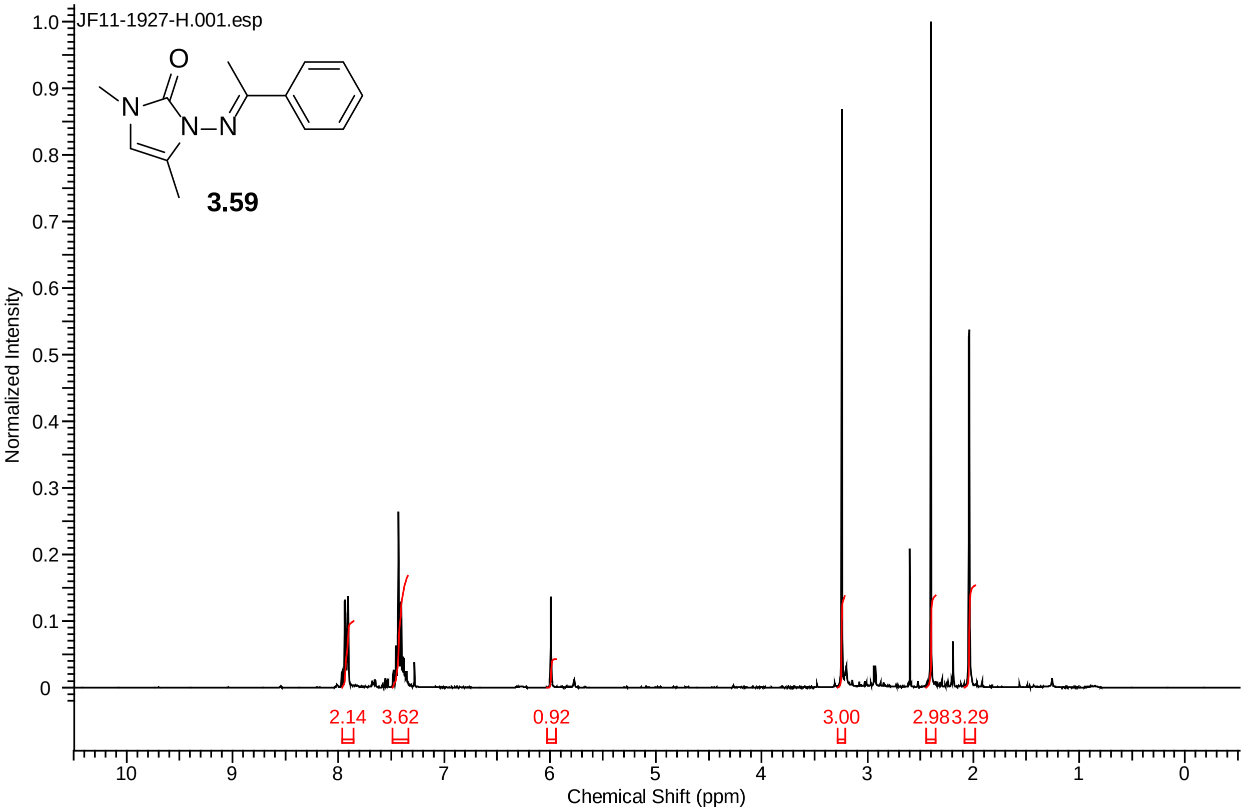


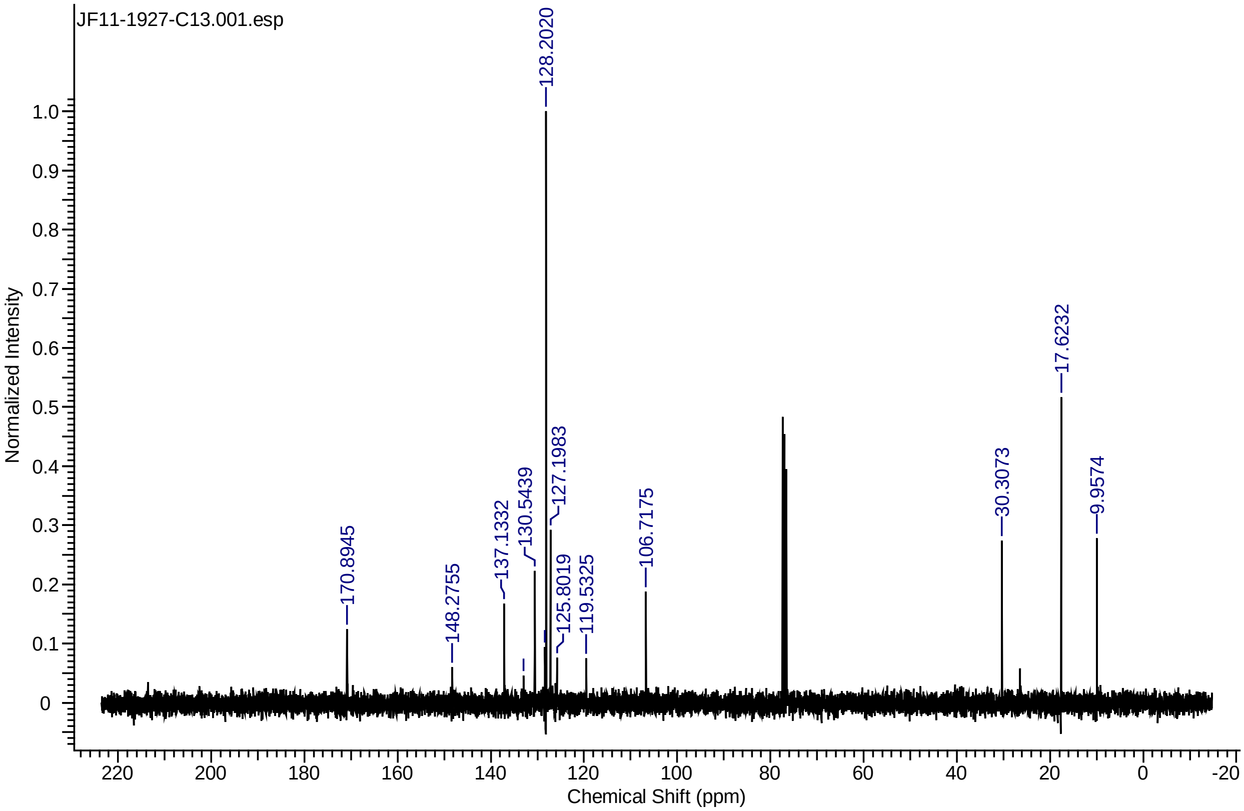
3.58

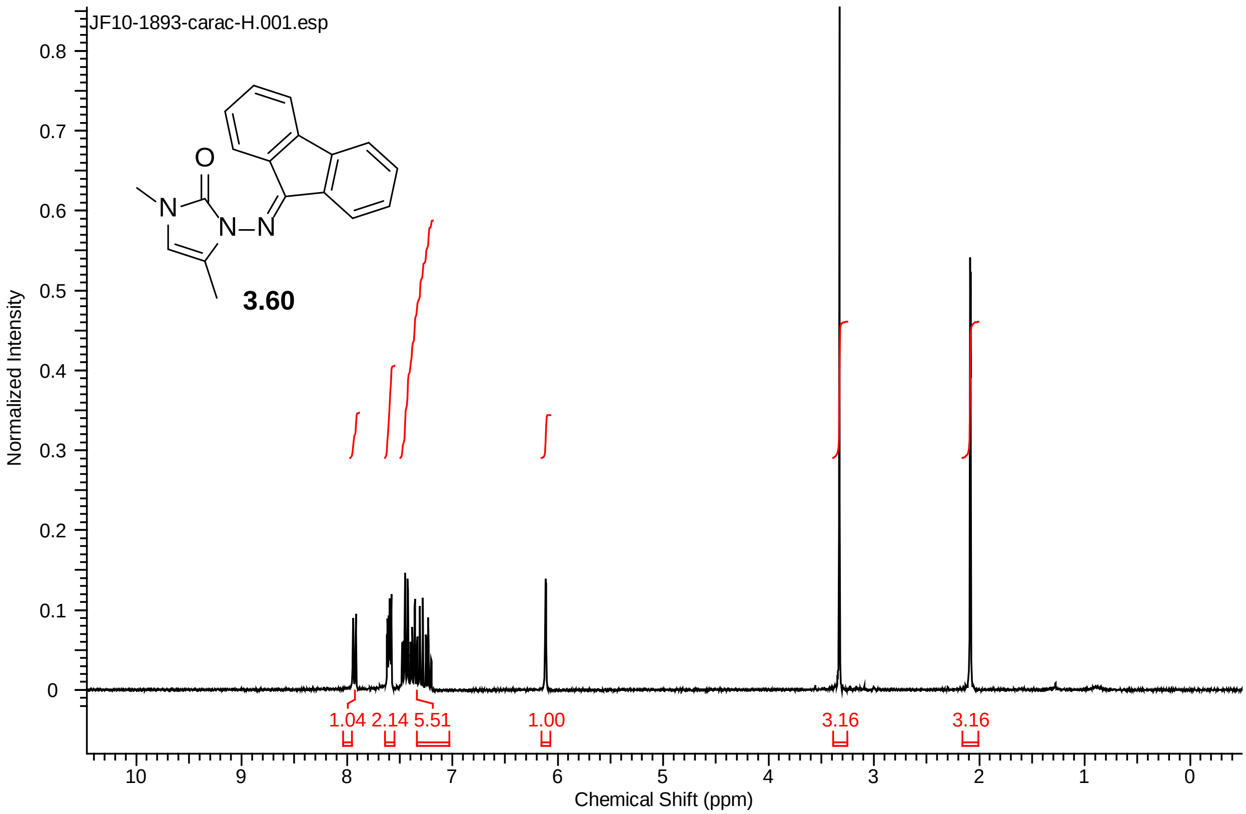
JF11-1925-carac-H.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
0.96
0.98
1.02
2.98
2.99
3.01
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
O
N
N
N
S

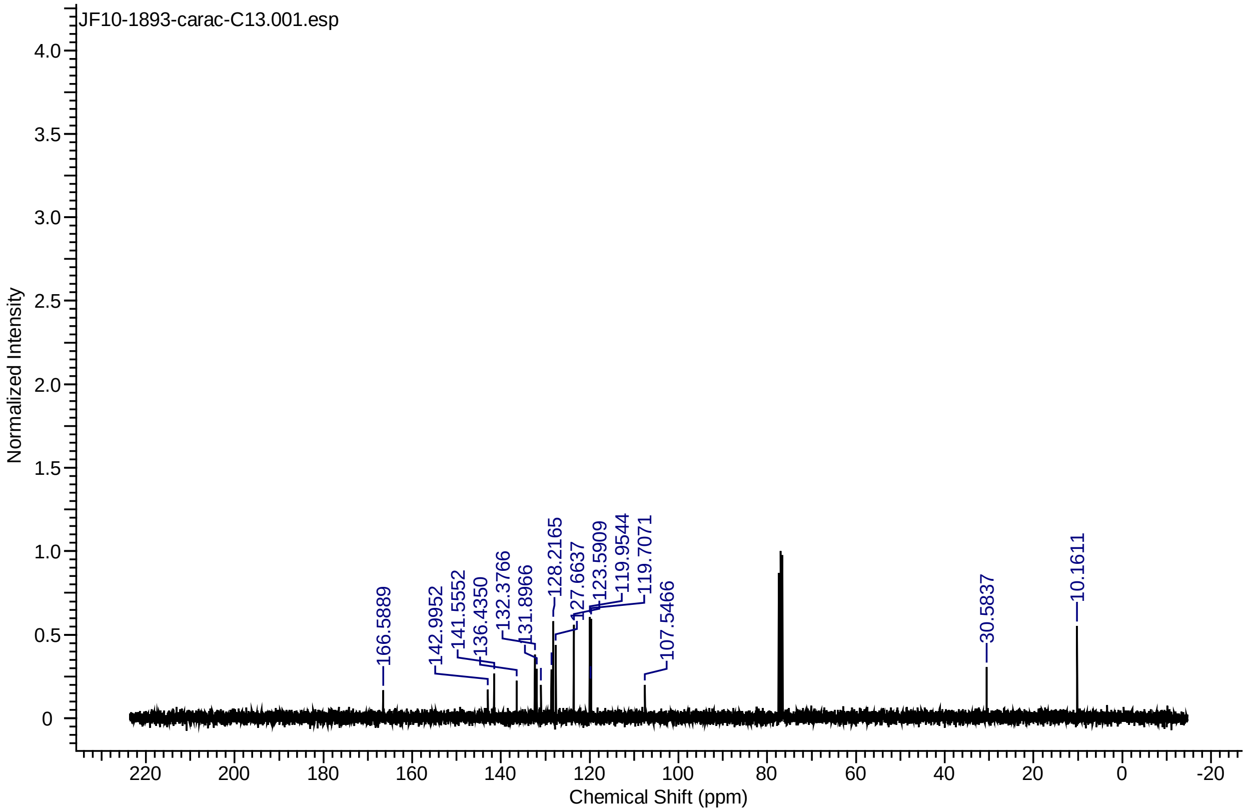


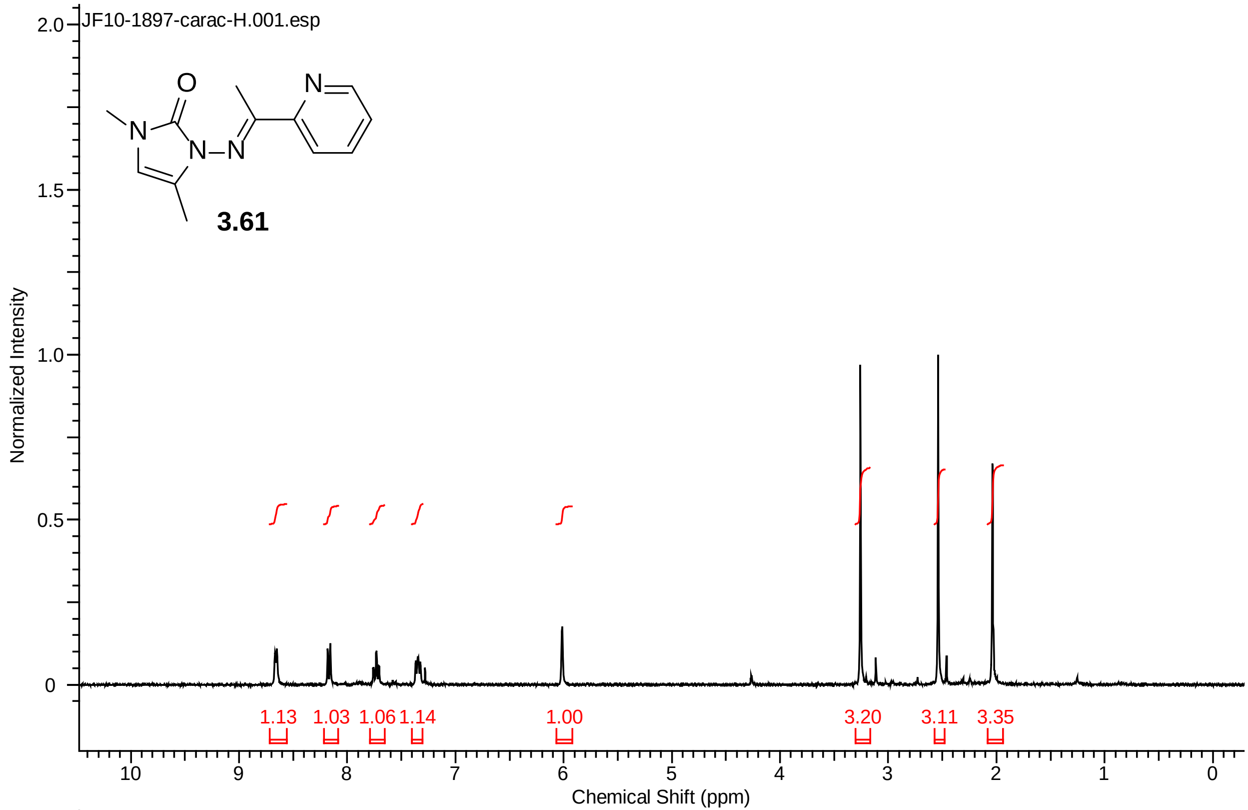
JF11-1925-carac-C13.001.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
165.6818
142.1900
129.8986
129.4332
127.2949
119.7164
106.7414
30.4330
17.6180
10.0250
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

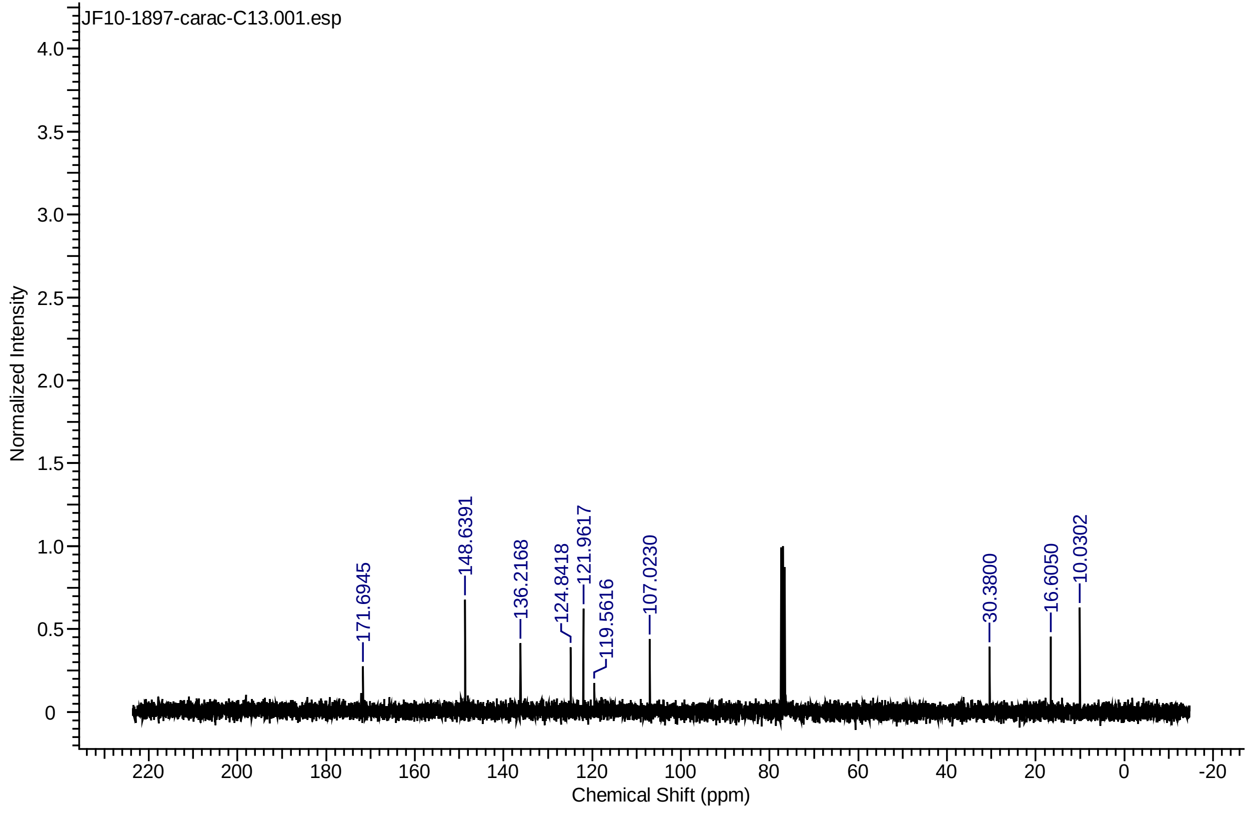

JF11-1927-H.001.esp
O
N
N–N
3.59
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2.14
3.62
0.92
3.00
2.98
3.29
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

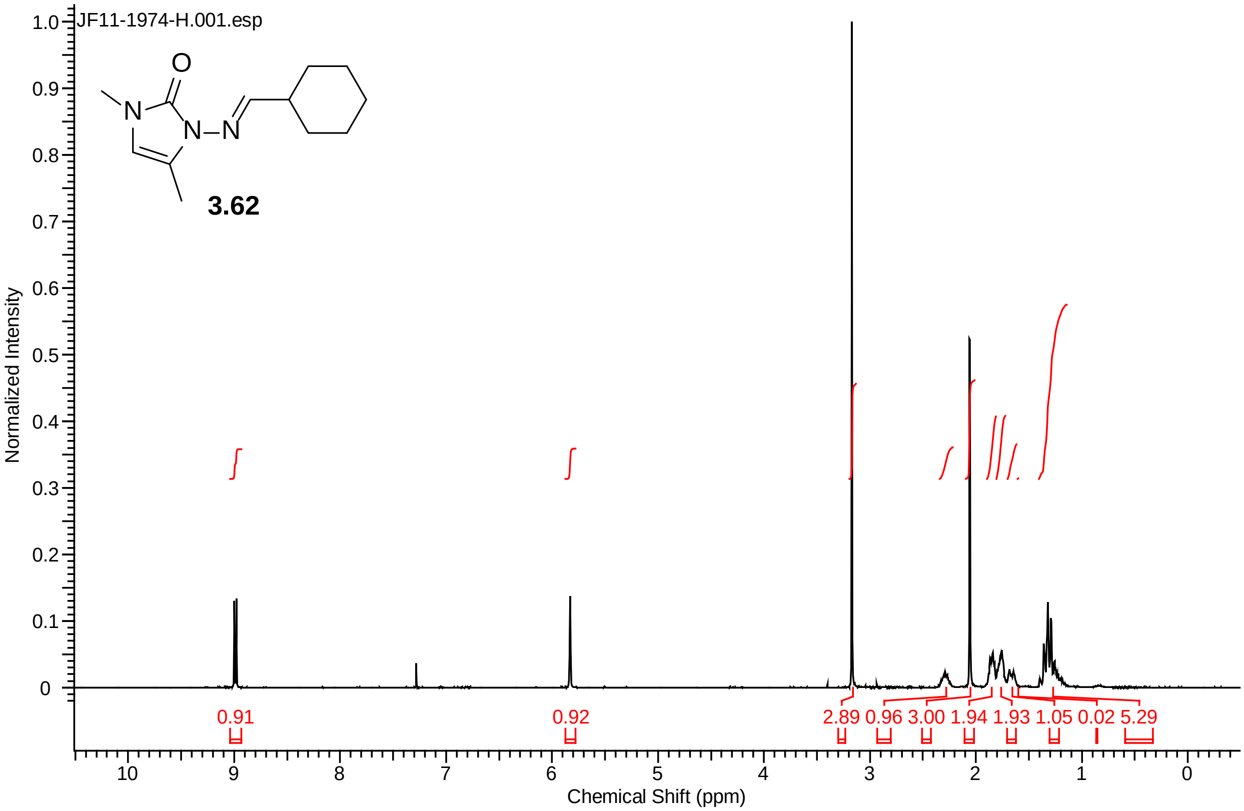

JF11-1927-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
170.8945
148.2755
137.1332
130.5439
128.2020
127.1983
125.8019
119.5325
106.7175
30.3073
17.6232
9.9574
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

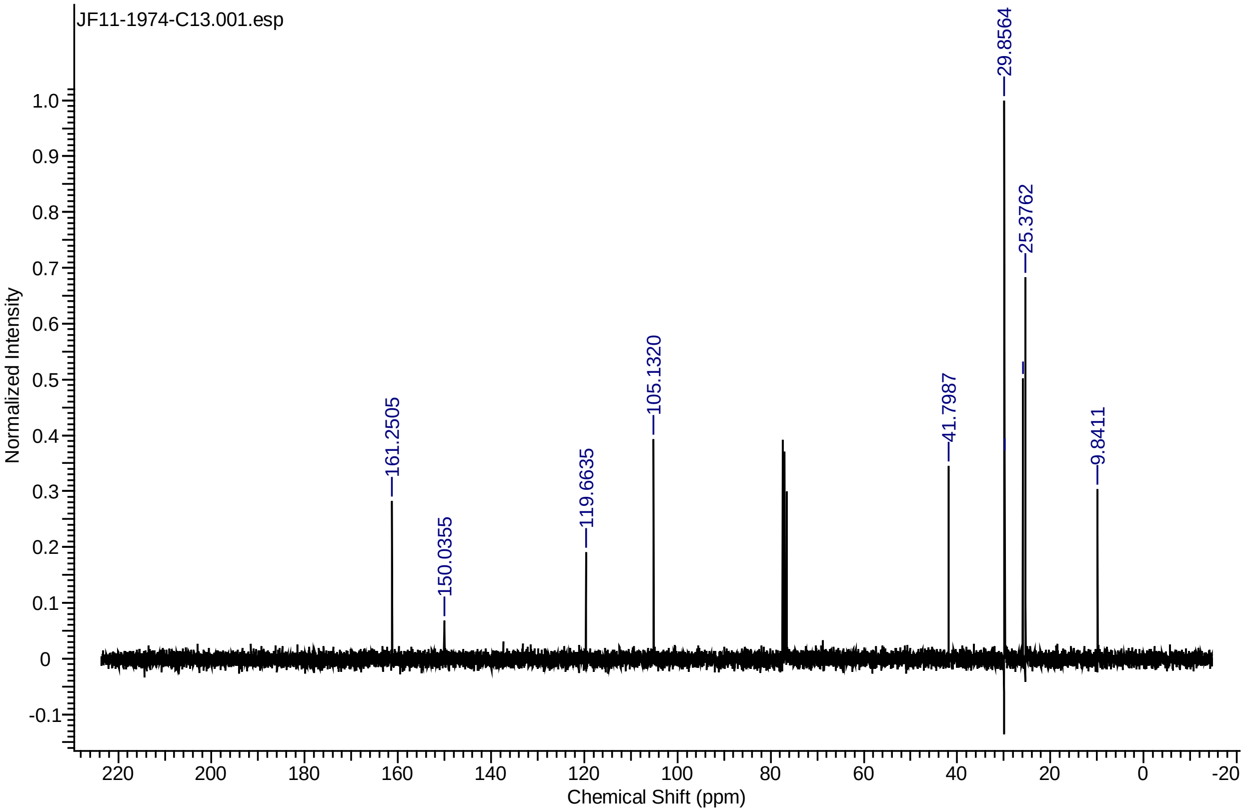

JF10-1893-carac-H.001.esp
O
N
N–N
3.60
Normalized Intensity
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.04
2.14
5.51
1.00
3.16
3.16
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

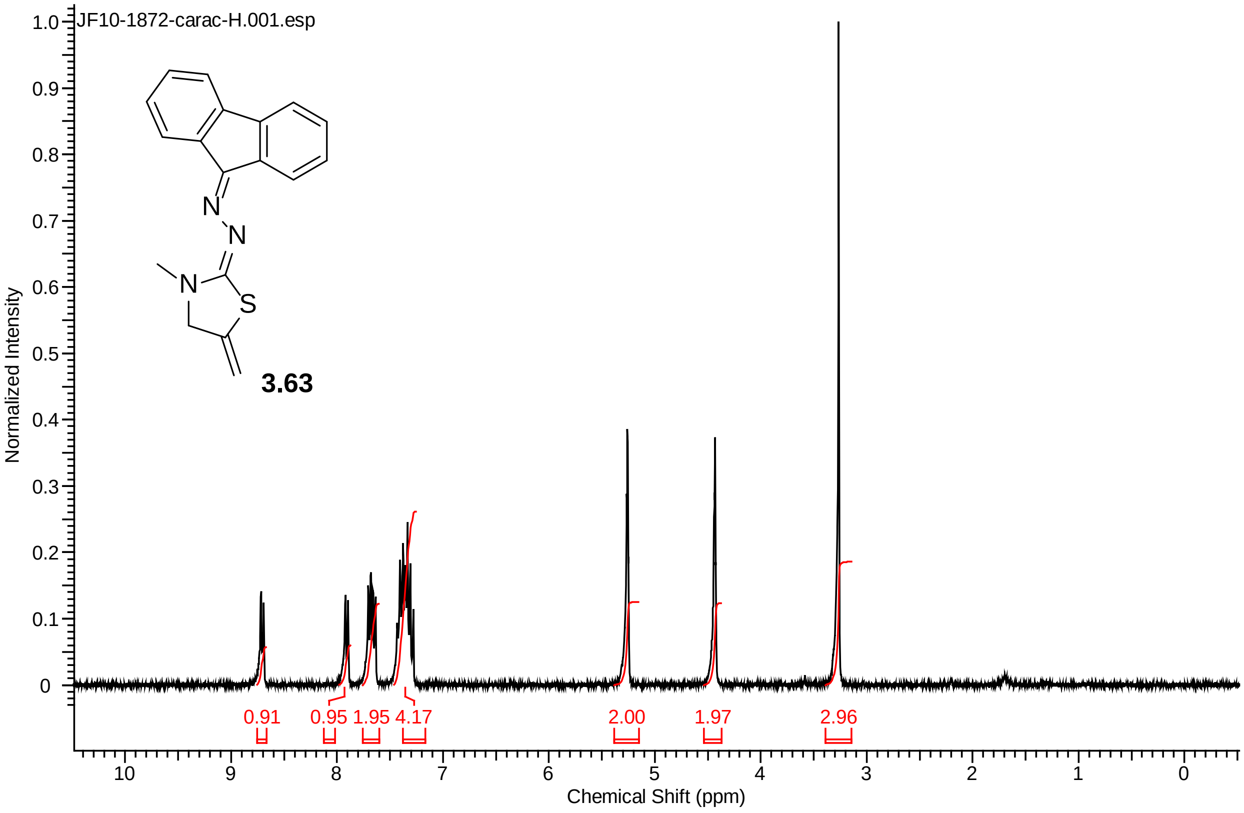

JF10-1893-carac-C13.001.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
166.5889
142.9952
141.5552
136.4350
132.3766
131.8966
128.2165
127.6637
123.5909
119.9544
119.7071
107.5466
30.5837
10.1611
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

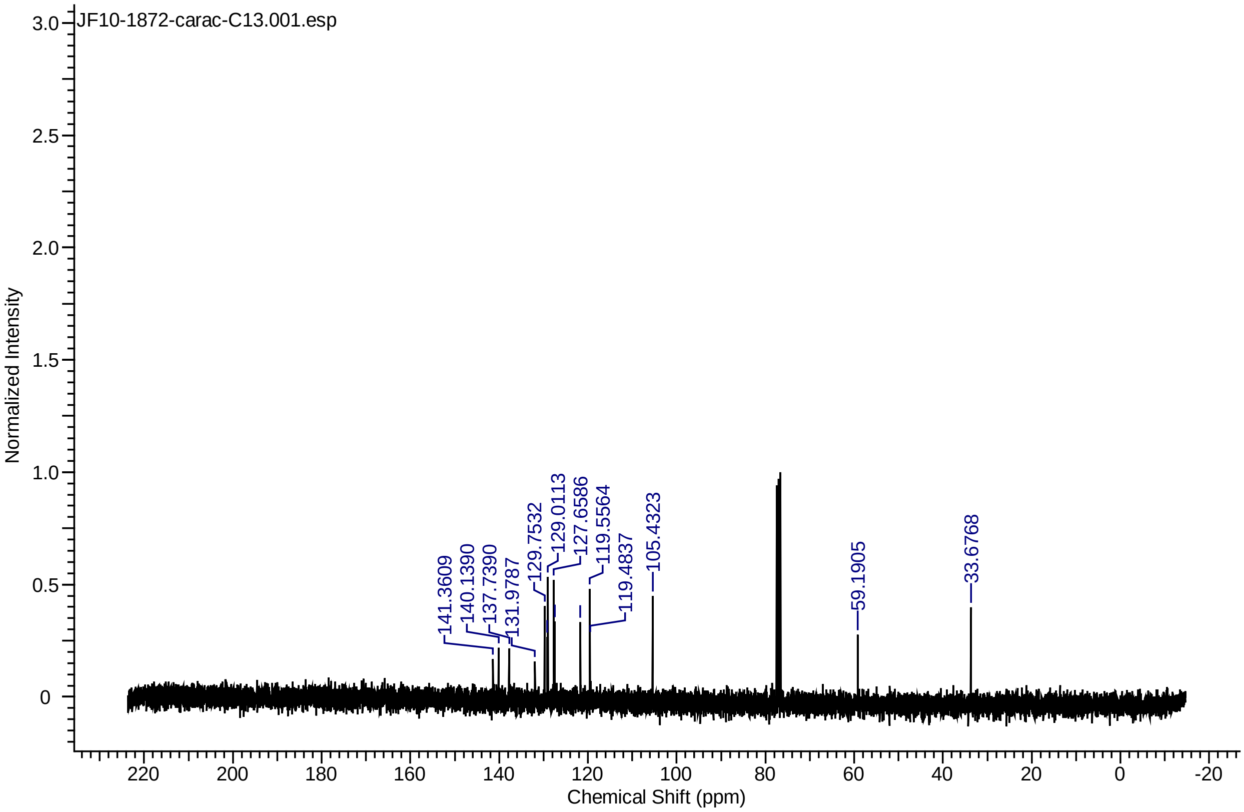

JF10-1897-carac-H.001.esp
3.61
O
N
N–N
N
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.13
1.03
1.06
1.14
1.00
3.20
3.11
3.35
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

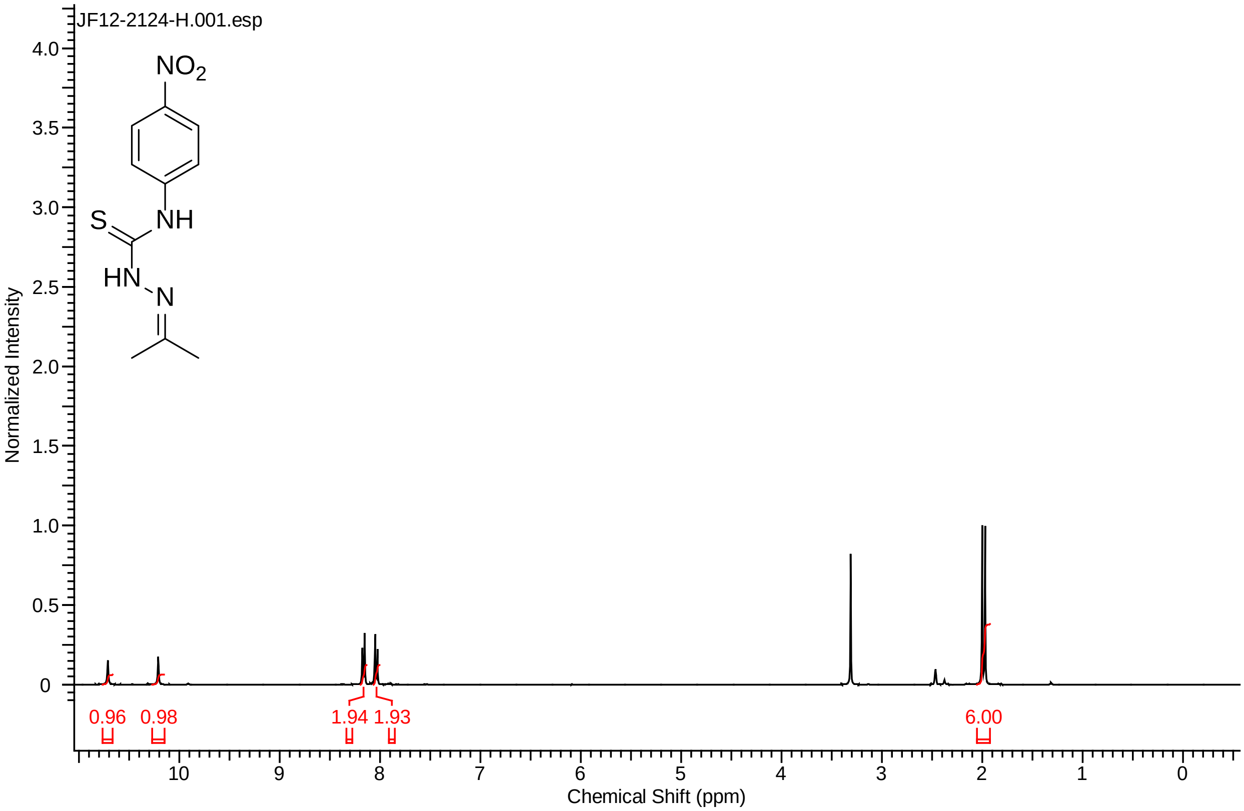

JF10-1897-carac-C13.001.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
171.6945
148.6391
136.2168
124.8418
121.9617
119.5616
107.0230
30.3800
16.6050
10.0302
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

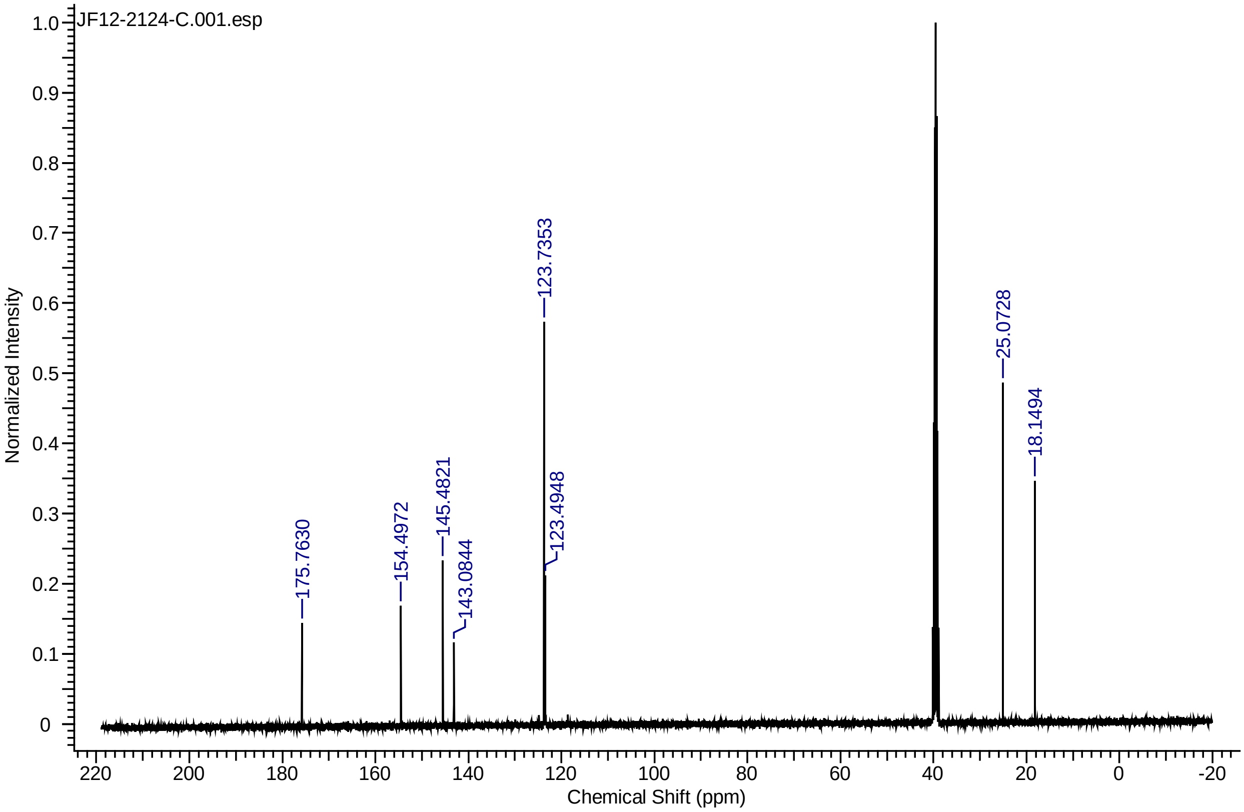

3.62
JF11-1974-H.001.esp
O
N
N–N
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.91
0.92
2.89
0.96
3.00
1.94
1.93
1.05
0.02
5.29
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

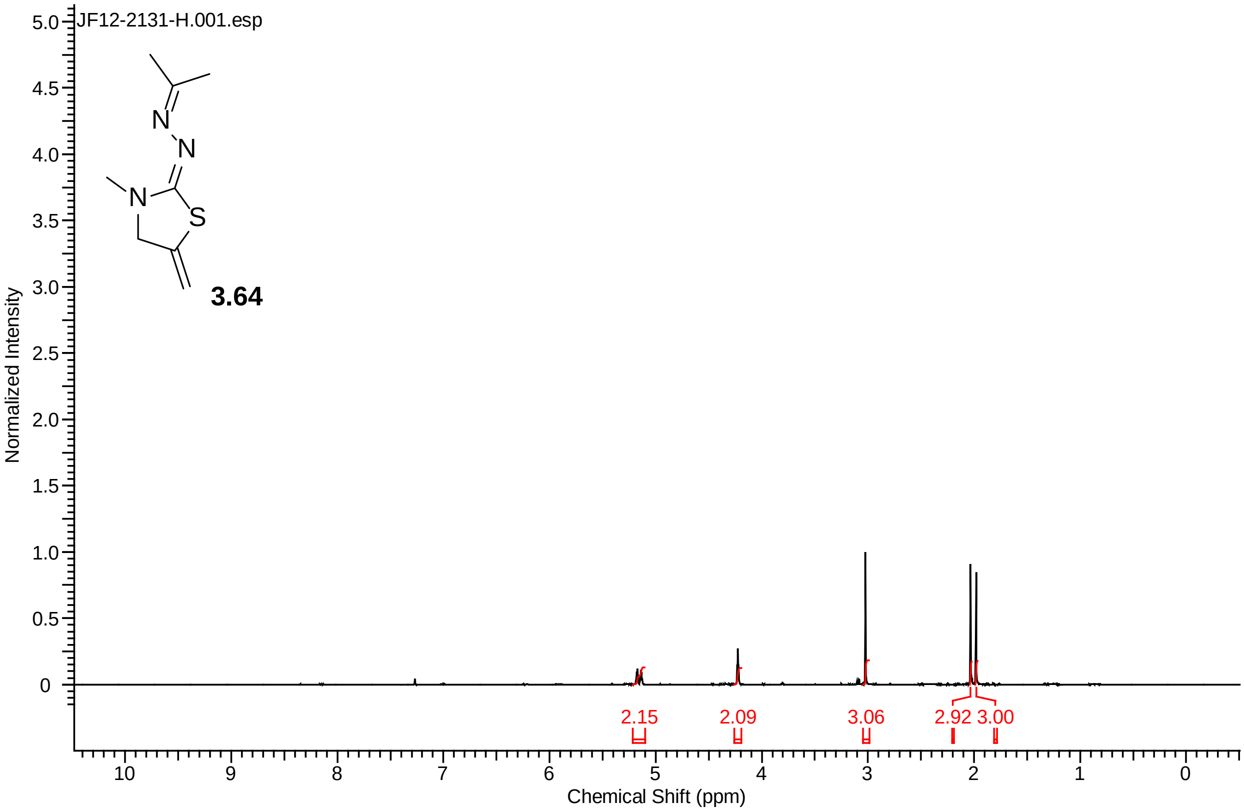

JF11-1974-C13.001.esp
161.2505
150.0355
119.6635
105.1320
41.7987
29.8564
25.3762
9.8411
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

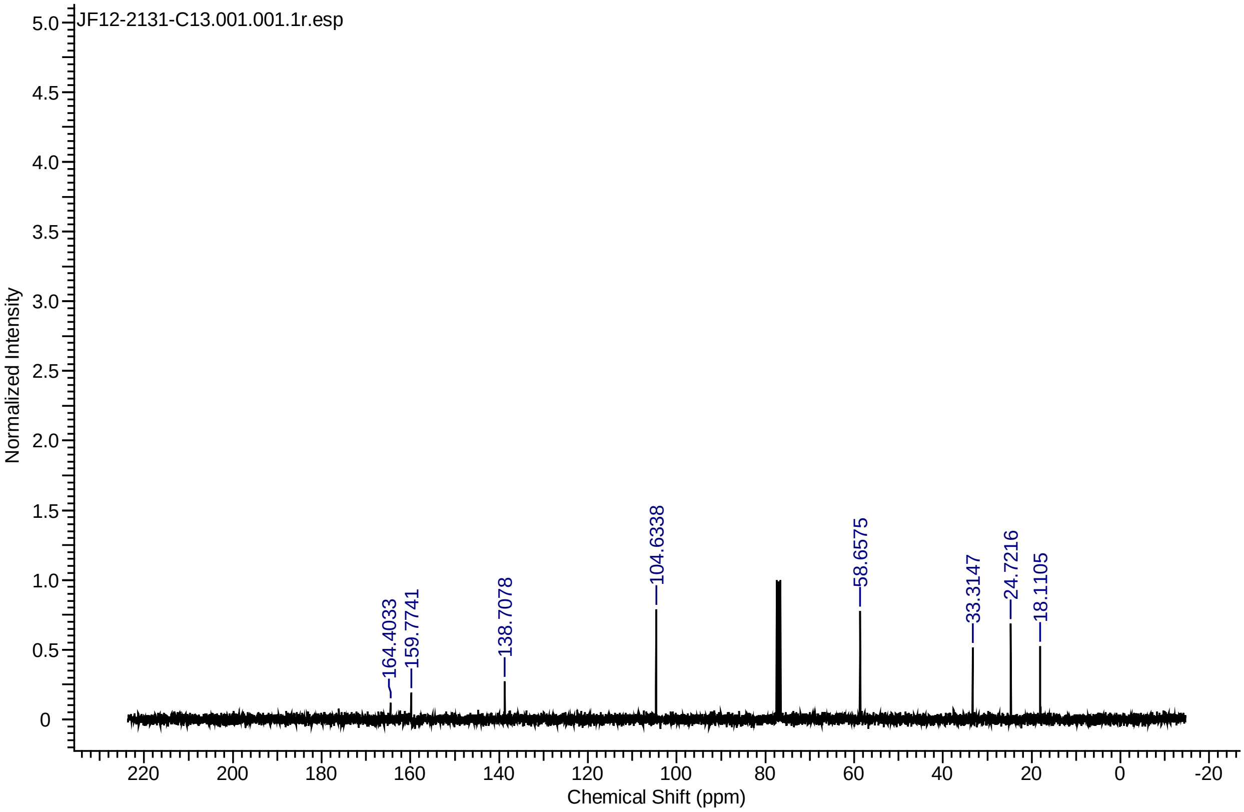

JF10-1872-carac-H.001.esp
N
N
N
S
3.63
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.91
0.95
1.95
4.17
2.00
1.97
2.96
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

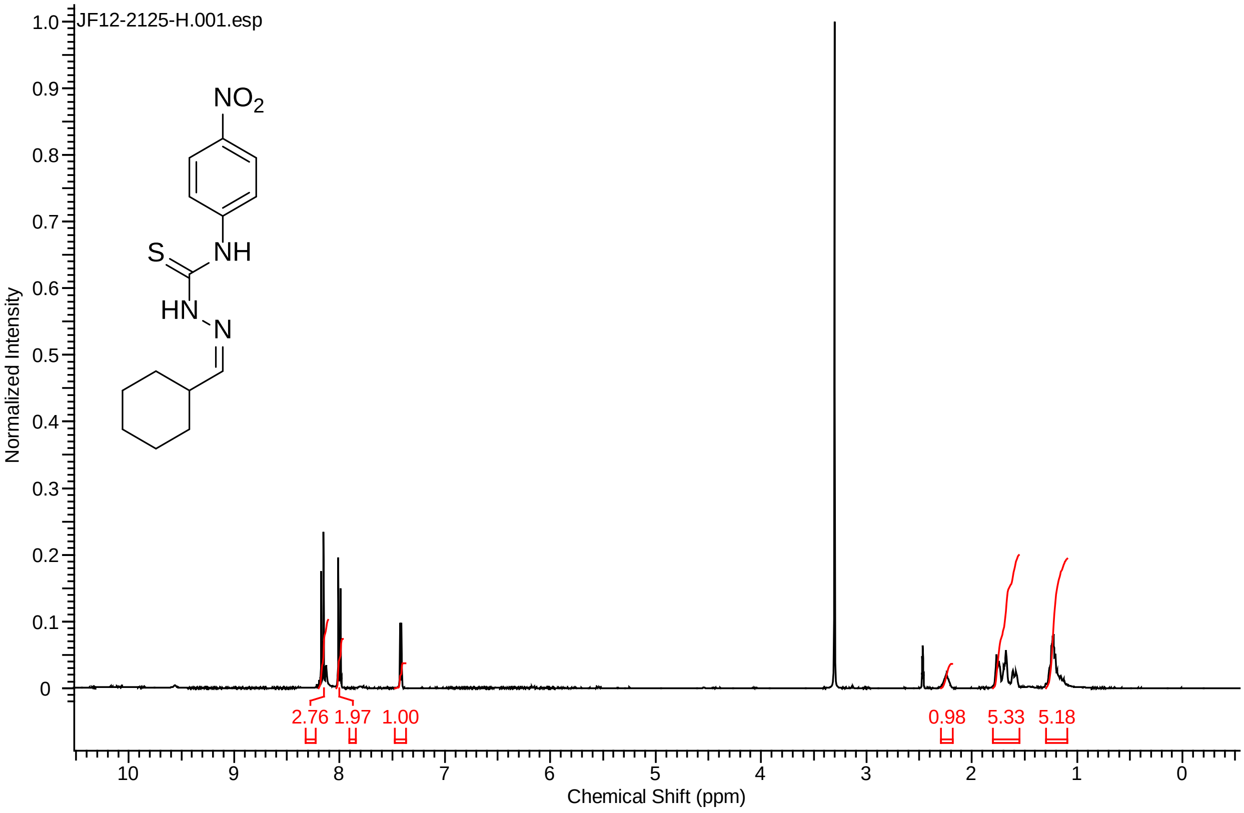

JF10-1872-carac-C13.001.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
141.3609
140.1390
137.7390
131.9787
129.7532
129.0113
127.6586
119.5564
119.4837
105.4323
59.1905
33.6768
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

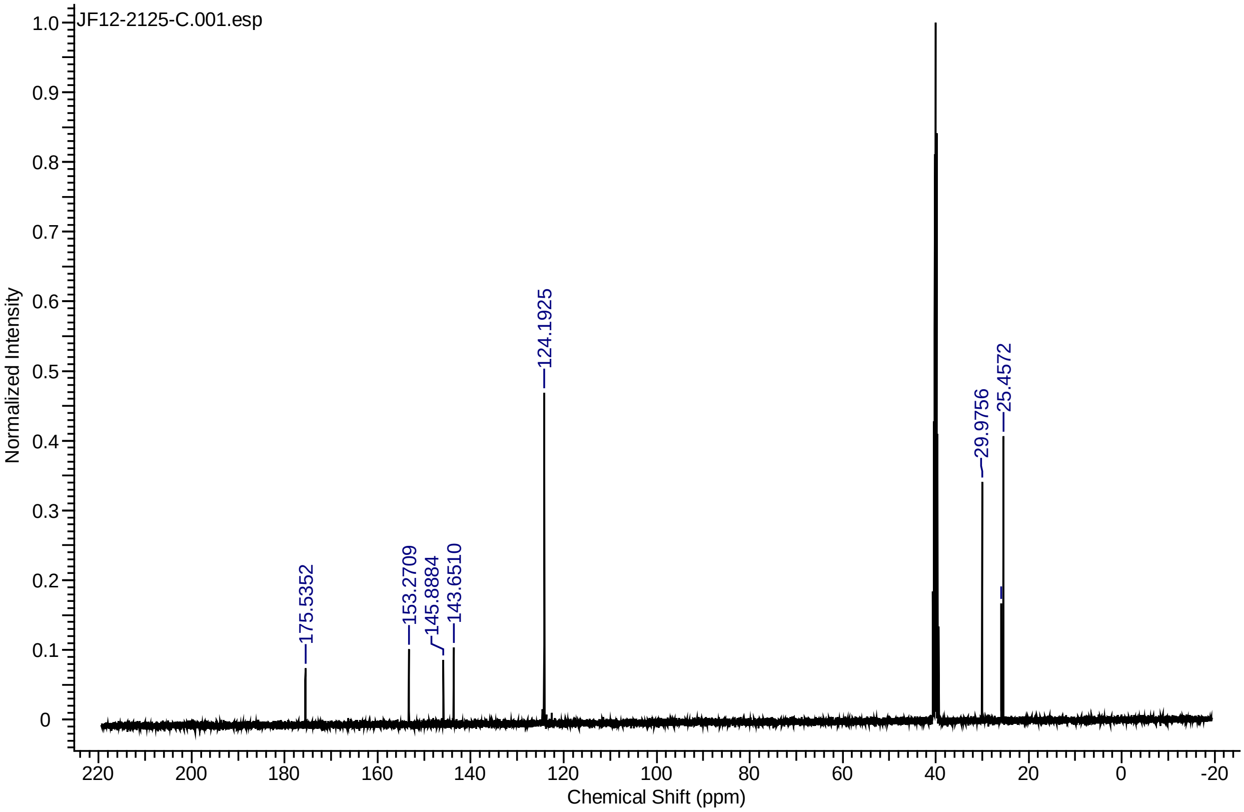

JF12-2124-H.001.esp
NO2
S
NH
HN
N
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
0.96
0.98
1.94
1.93
6.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

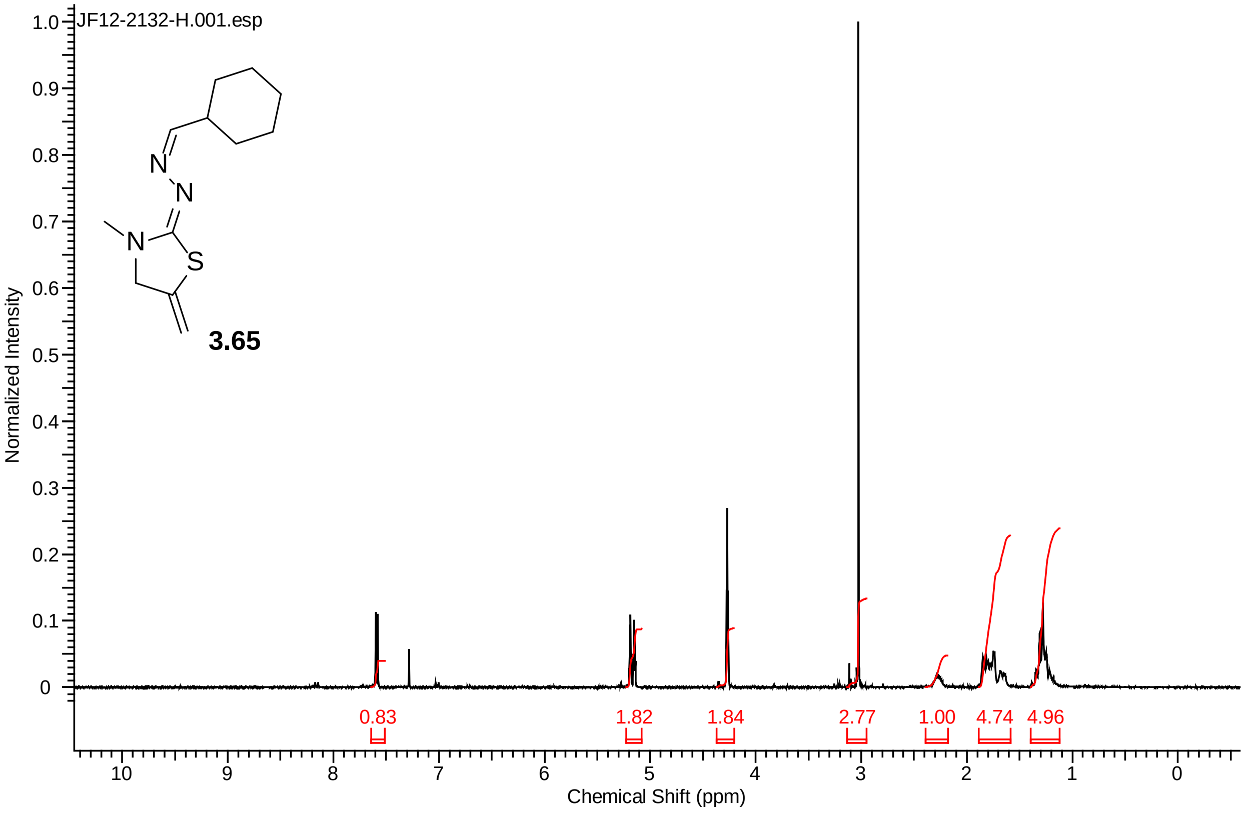

JF12-2124-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
175.7630
154.4972
145.4821
143.0844
123.7353
123.4948
25.0728
18.1494
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF12-2131-H.001.esp
N
N
N
S
3.64
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
2.15
2.09
3.06
2.92
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

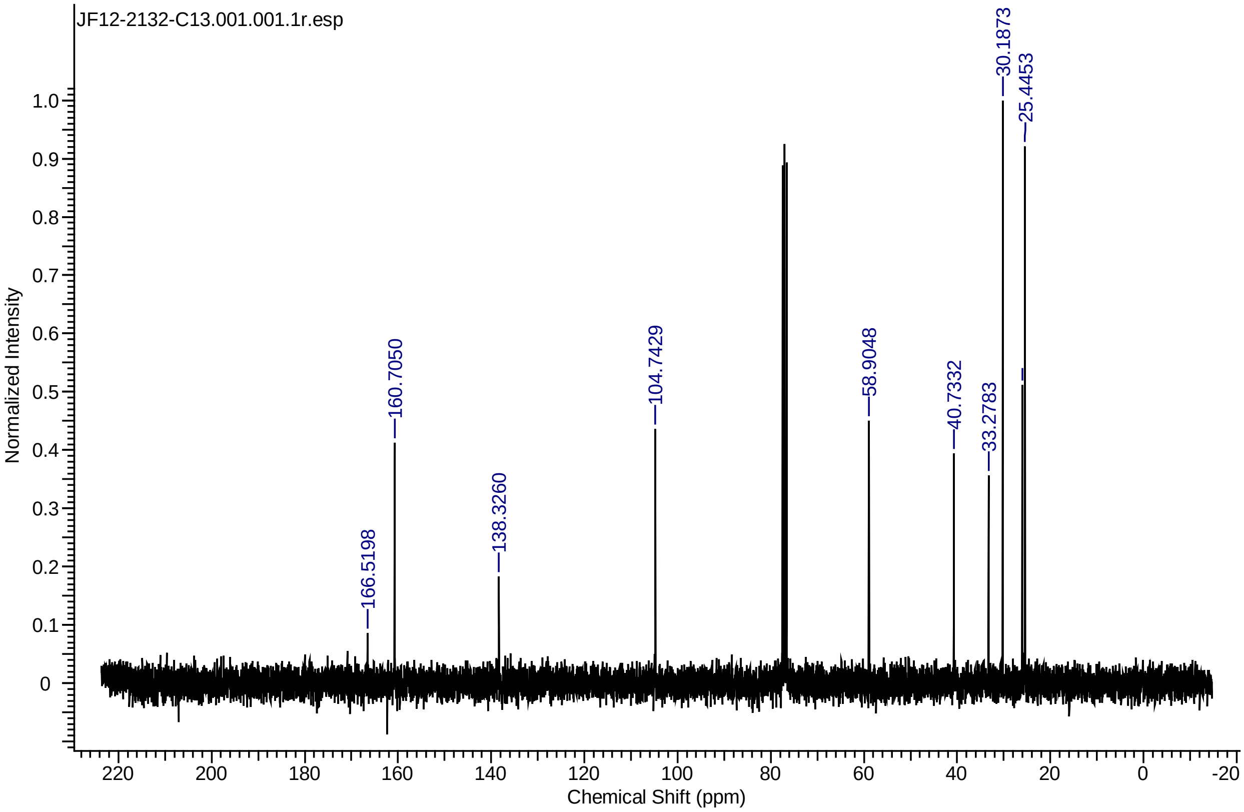

JF12-2131-C13.001.001.1r.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
164.4033
159.7741
138.7078
104.6338
58.6575
33.3147
24.7216
18.1105
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

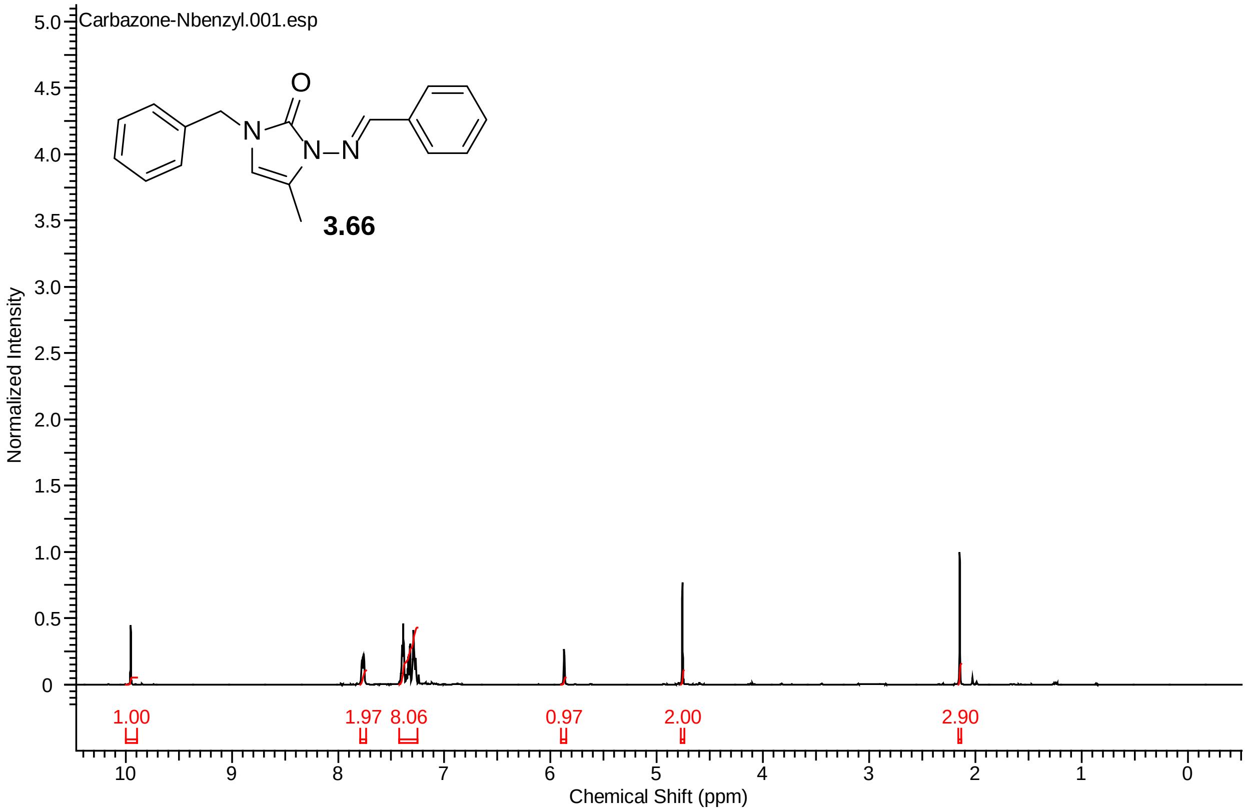

JF12-2125-H.001.esp
NO2
NH
S
HN
N
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2.76
1.97
1.00
0.98
5.33
5.18
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

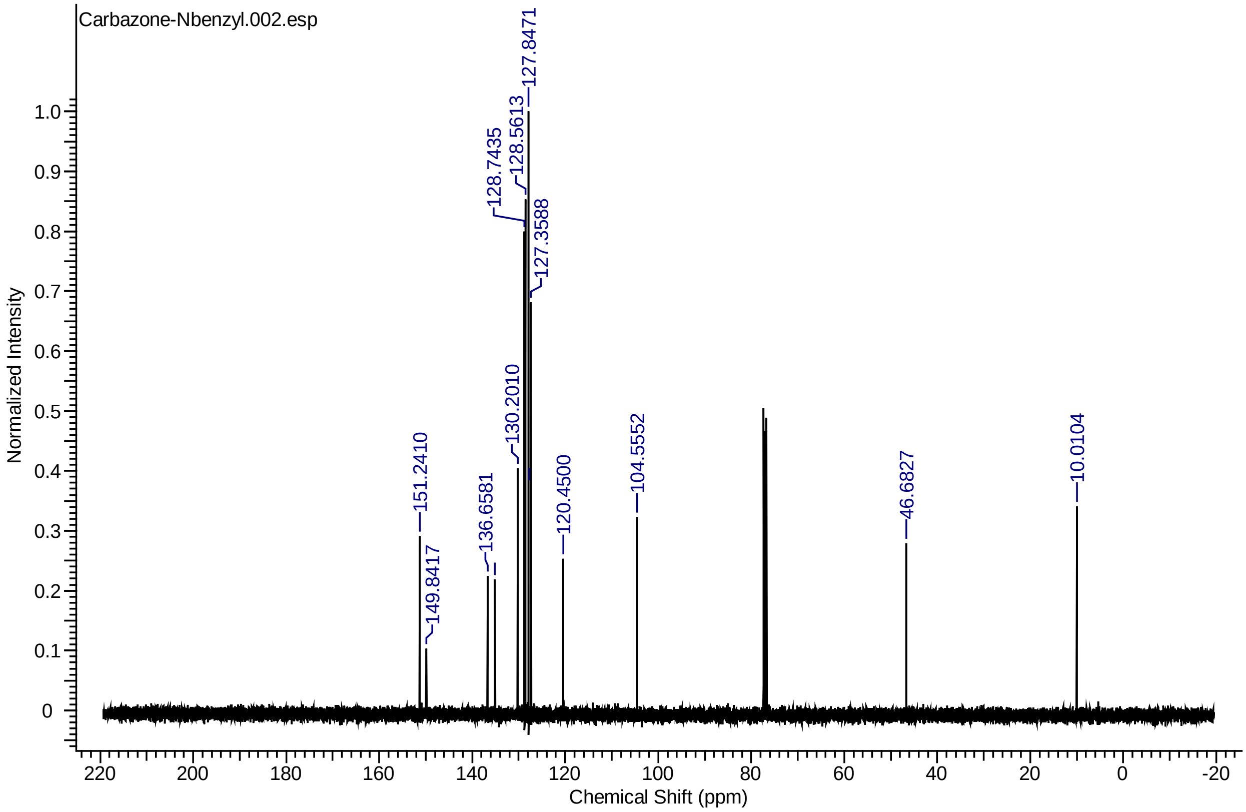

JF12-2125-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
175.5352
153.2709
145.8884
143.6510
124.1925
29.9756
25.4572
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

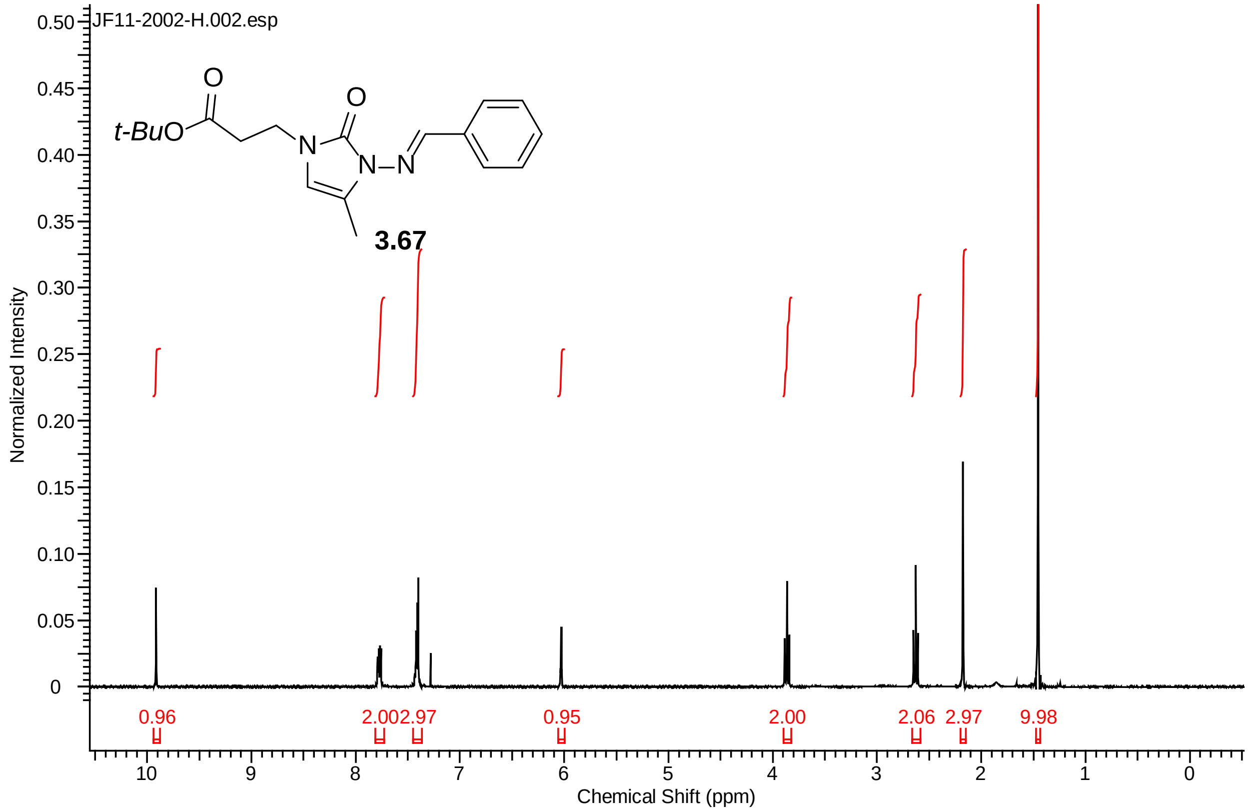

3.65

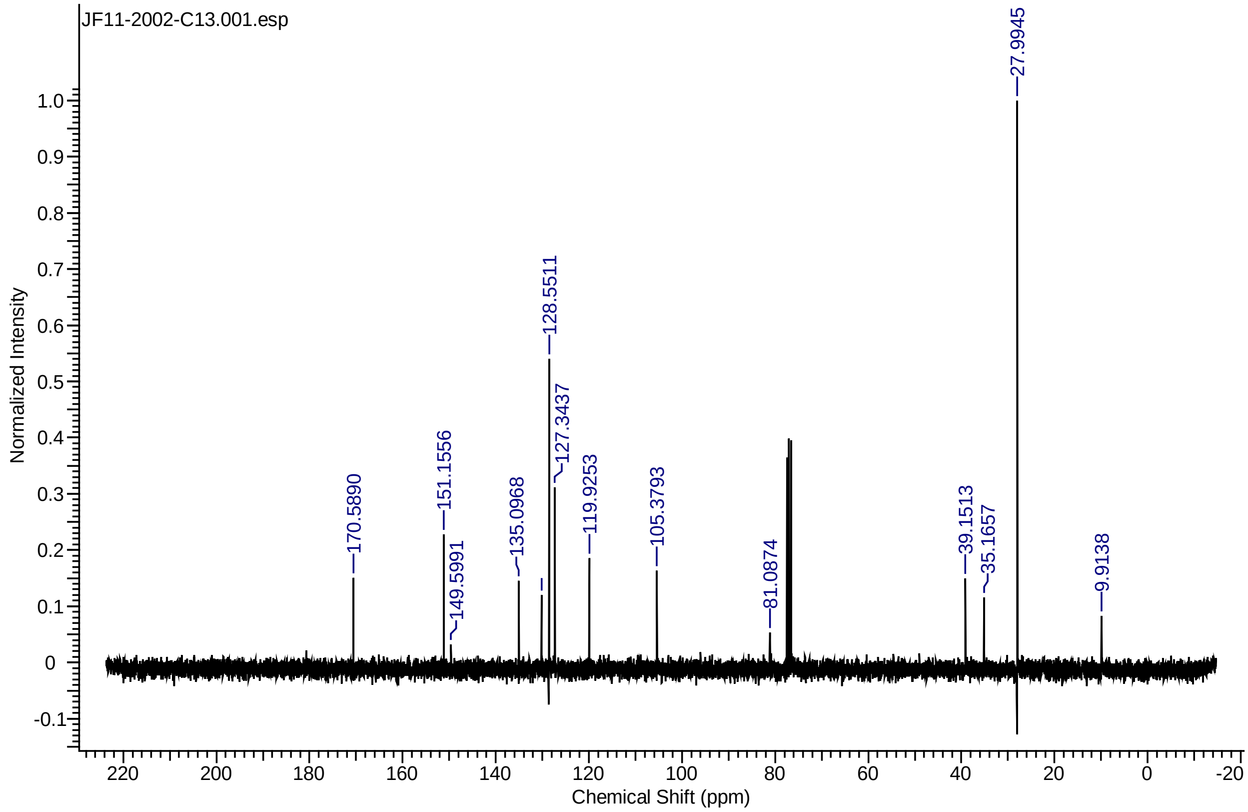
JF12-2132-H.001.esp
N
N
N
S
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.83
1.82
1.84
2.77
1.00
4.74
4.96
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

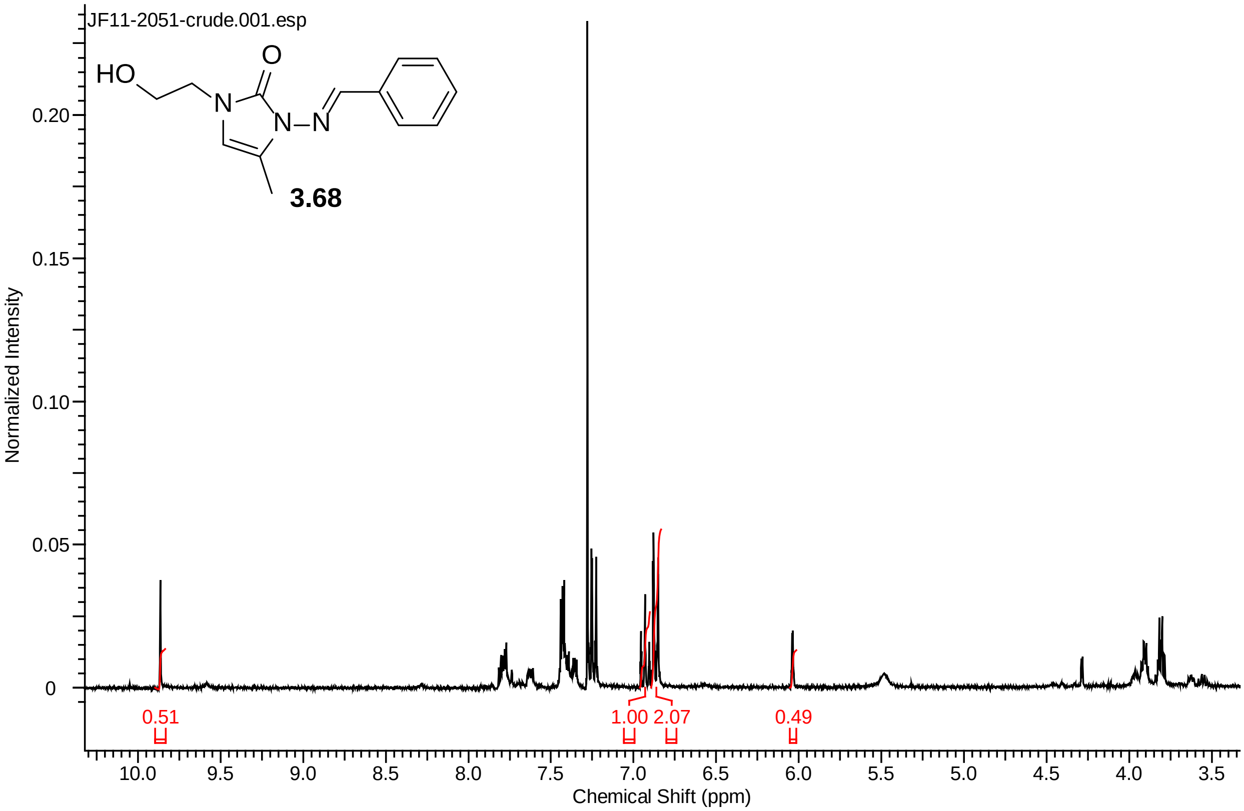

JF12-2132-C13.001.001.1r.esp
166.5198
160.7050
138.3260
104.7429
58.9048
40.7332
33.2783
30.1873
25.4453
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

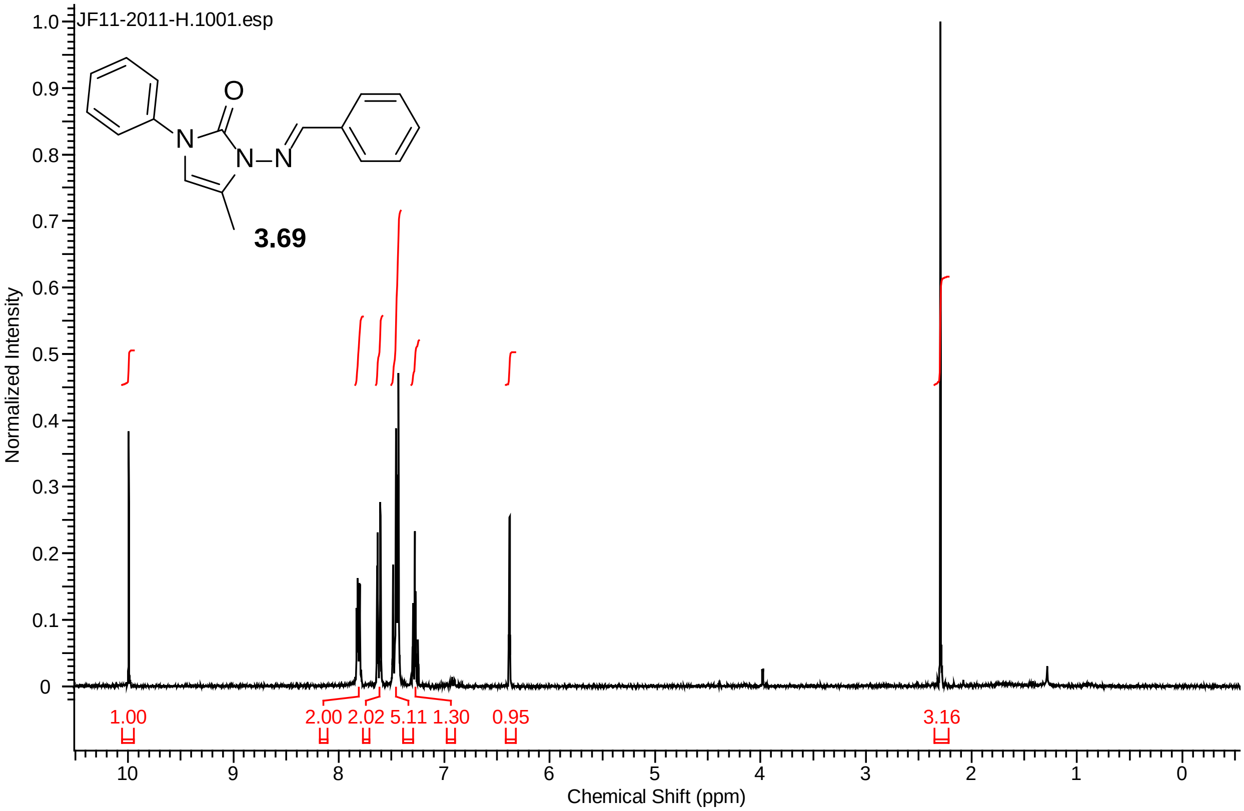

Carbazone-Nbenzyl.001.esp
O
N
N–N
3.66
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
1.00
1.97
8.06
0.97
2.00
2.90
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

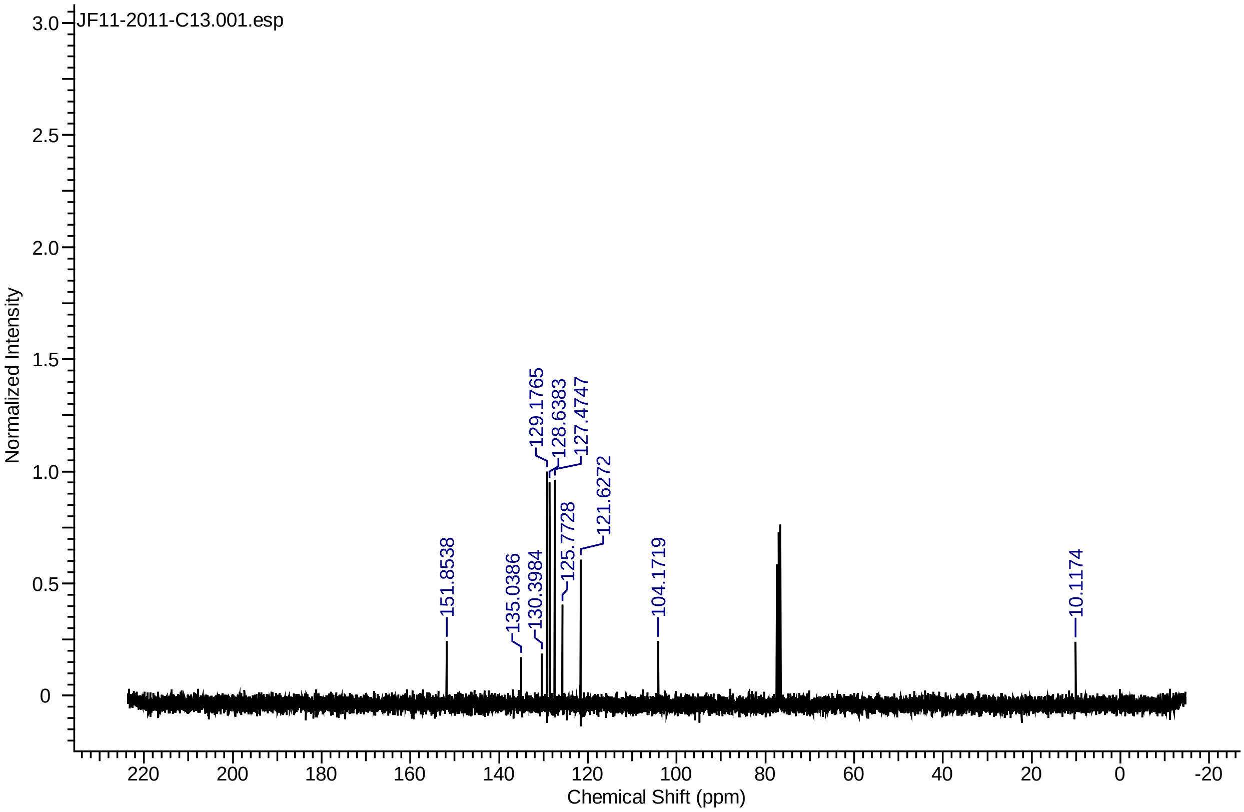

Carbazone-Nbenzyl.002.esp
127.8471
128.5613
128.7435
127.3588
130.2010
151.2410
136.6581
149.8417
120.4500
104.5552
46.6827
10.0104
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

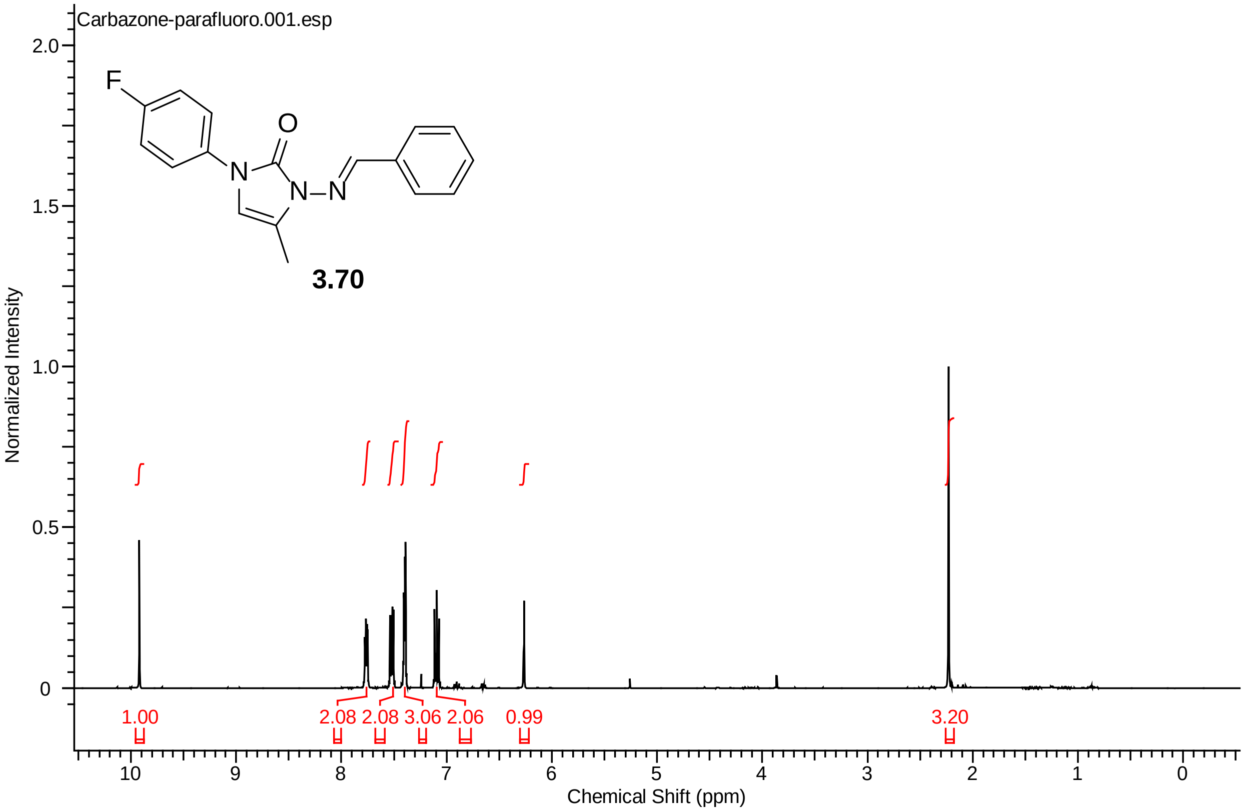

JF11-2002-H.002.esp
t-BuO
O
O
N
N–N
3.67
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.96
2.00
2.97
0.95
2.00
2.06
2.97
9.98
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

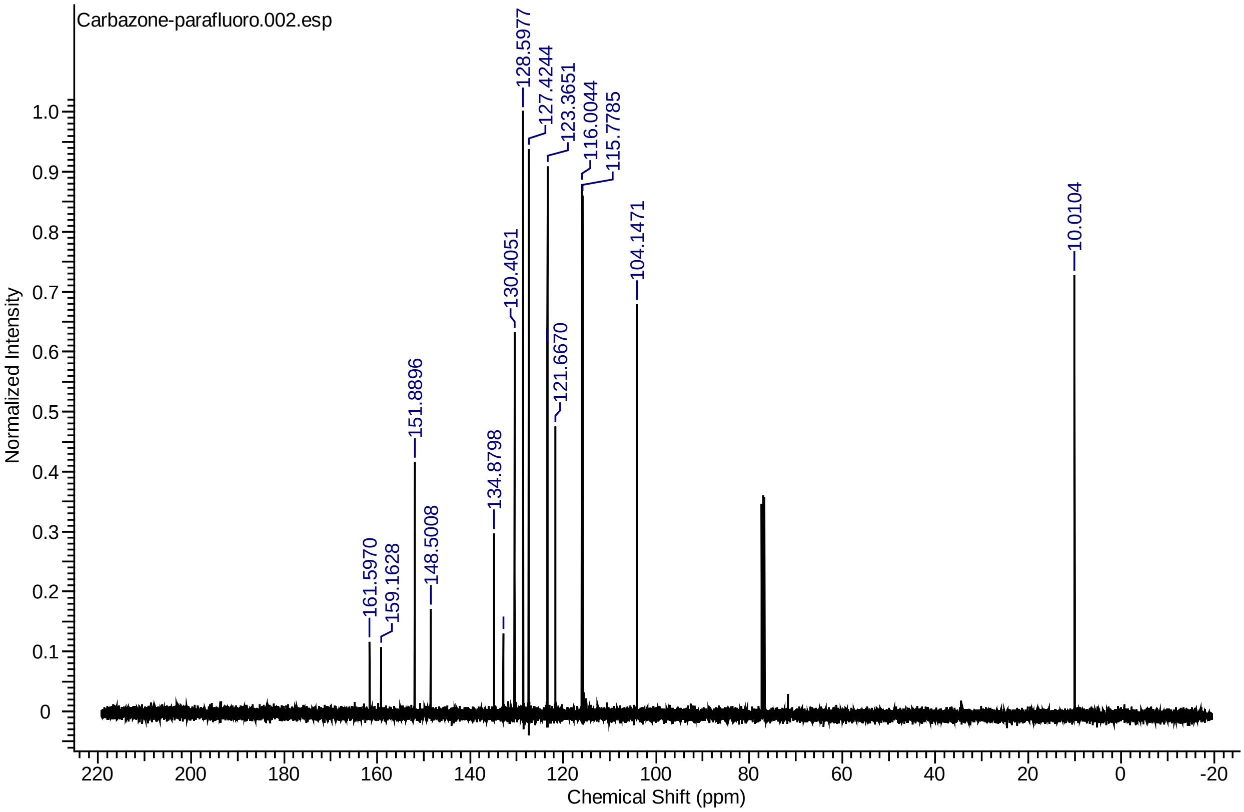

JF11-2002-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
170.5890
151.1556
149.5991
135.0968
128.5511
127.3437
119.9253
105.3793
81.0874
39.1513
35.1657
27.9945
9.9138
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

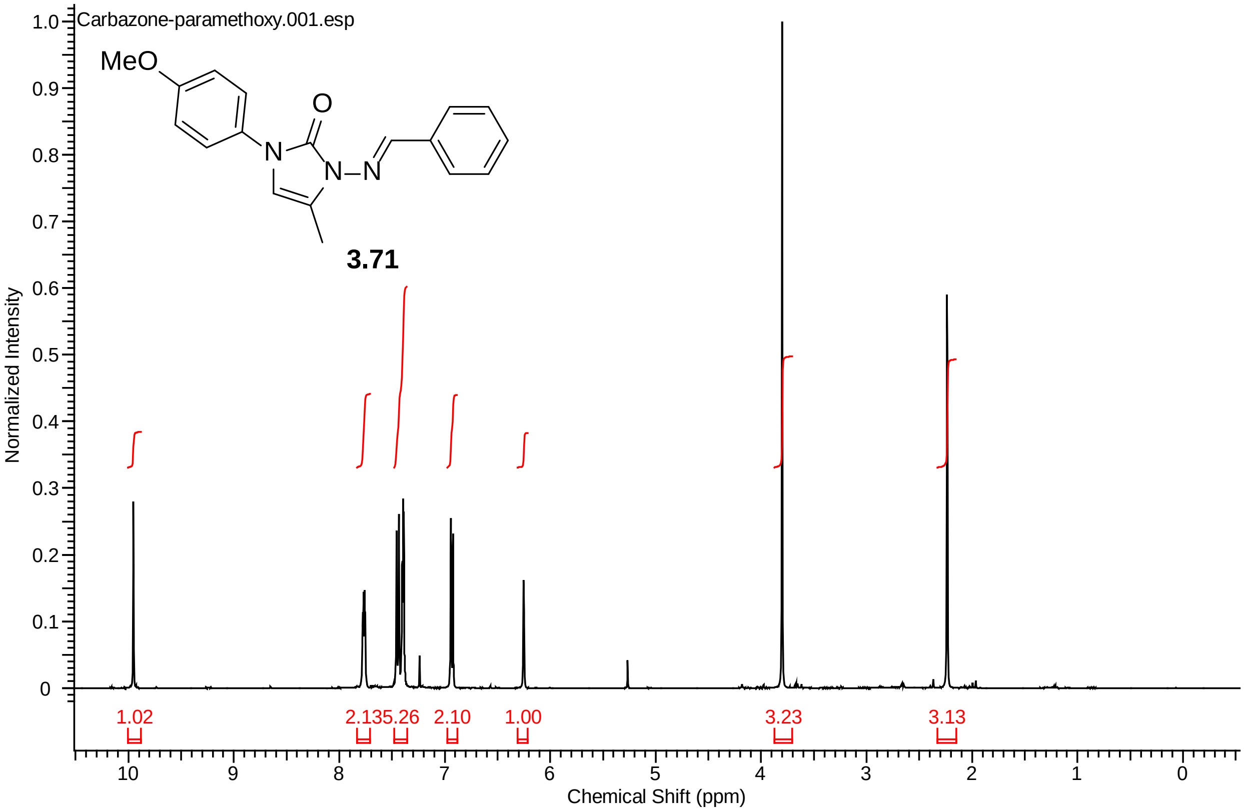

JF11-2051-crude.001.esp
HO
O
N
N–N
3.68
Normalized Intensity
0.20
0.15
0.10
0.05
0
0.51
1.00
2.07
0.49
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
Chemical Shift (ppm)


JF11-2011-H.1001.esp
O
N
N–N
3.69
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
2.00
2.02
5.11
1.30
0.95
3.16
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

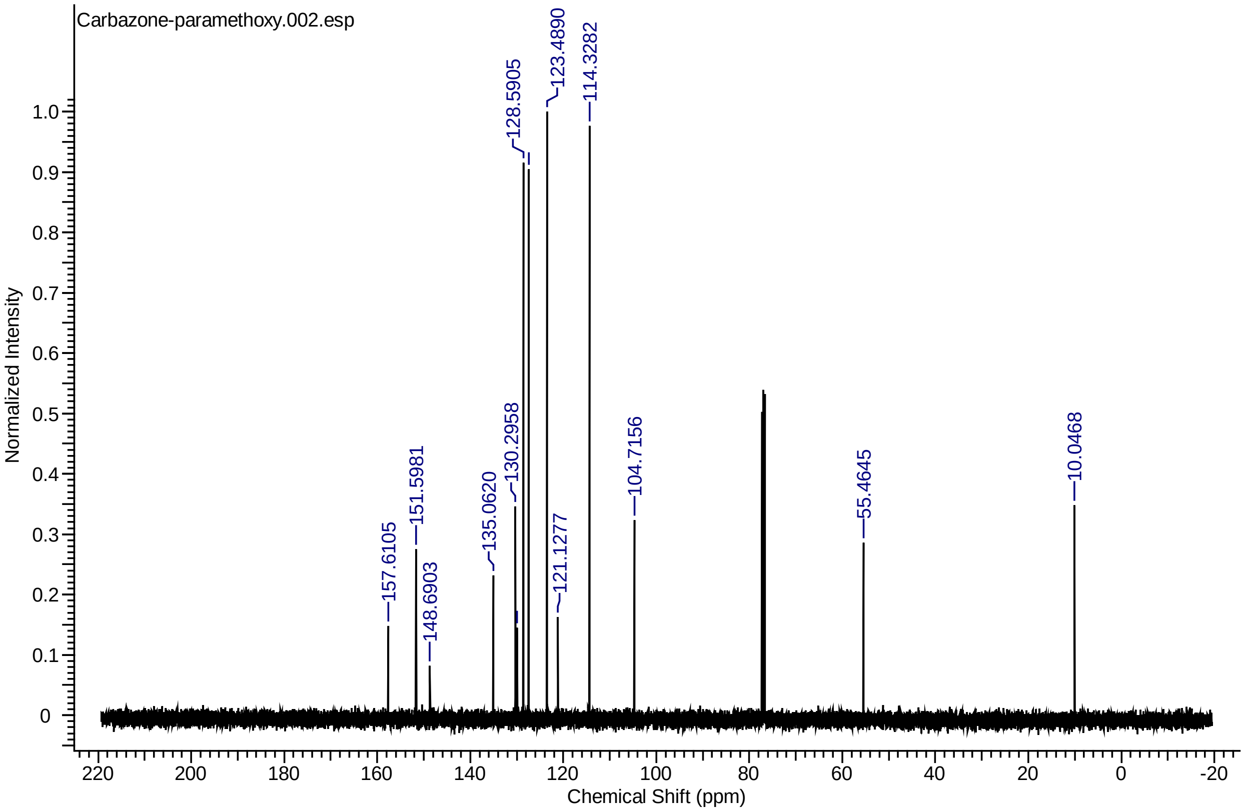

JF11-2011-C13.001.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
151.8538
135.0386
130.3984
129.1765
128.6383
127.4747
125.7728
121.6272
104.1719
10.1174
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

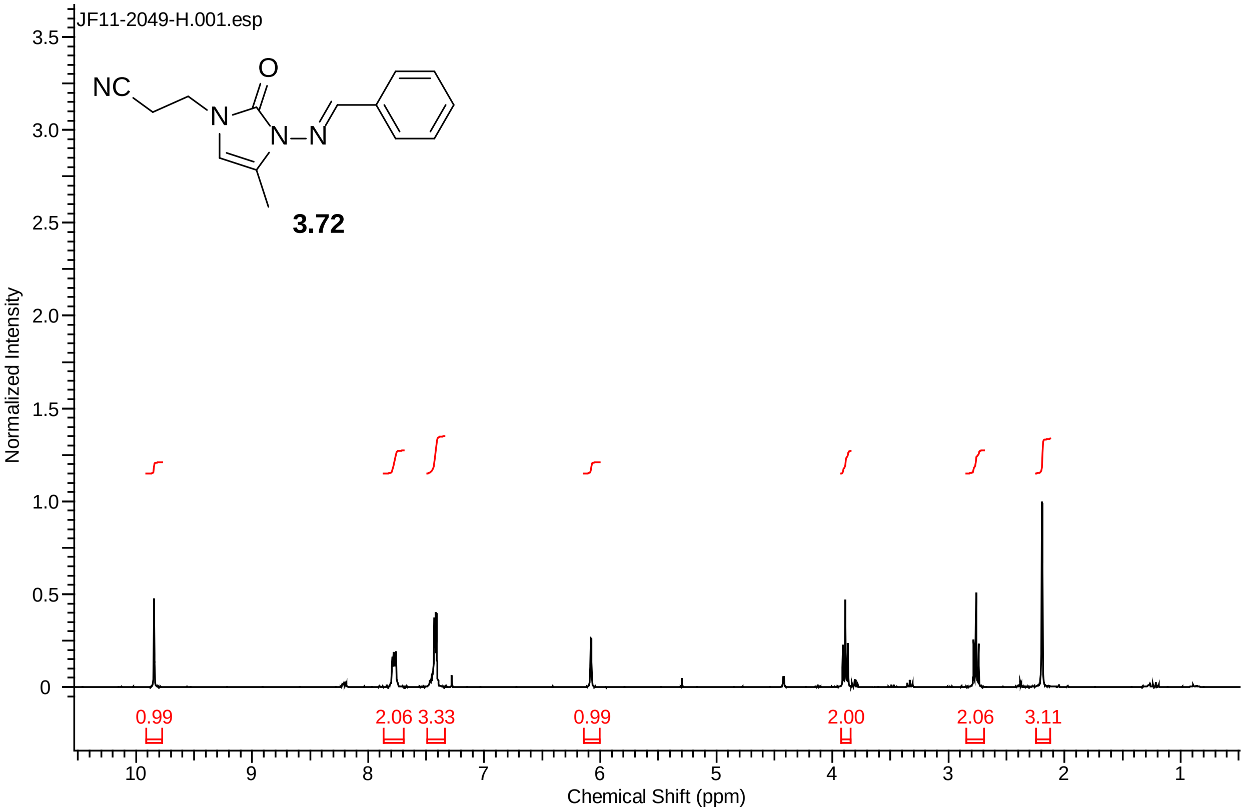

Carbazone-parafluoro.001.esp
F
O
N
N–N
3.70
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.00
2.08
2.08
3.06
2.06
0.99
3.20
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

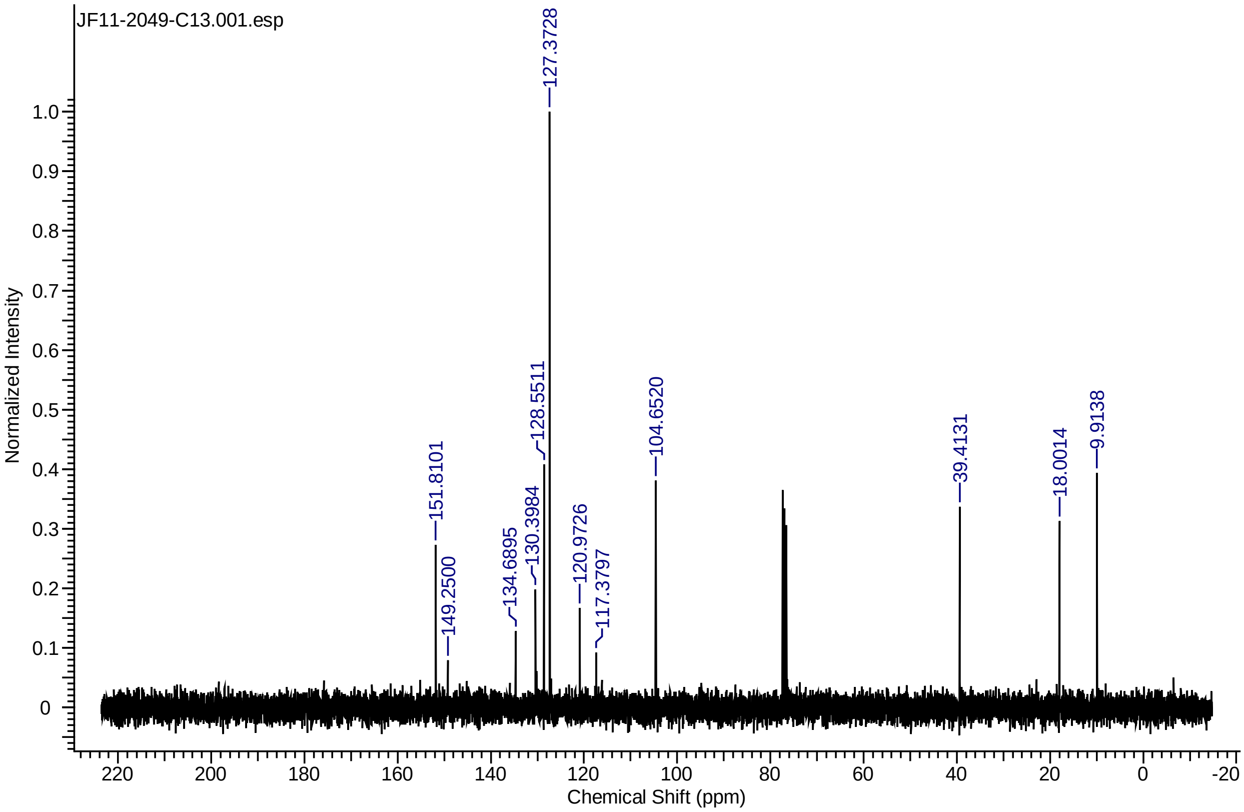

Carbazone-parafluoro.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
161.5970
159.1628
151.8896
148.5008
134.8798
130.4051
128.5977
127.4244
123.3651
121.6670
116.0044
115.7785
104.1471
10.0104
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

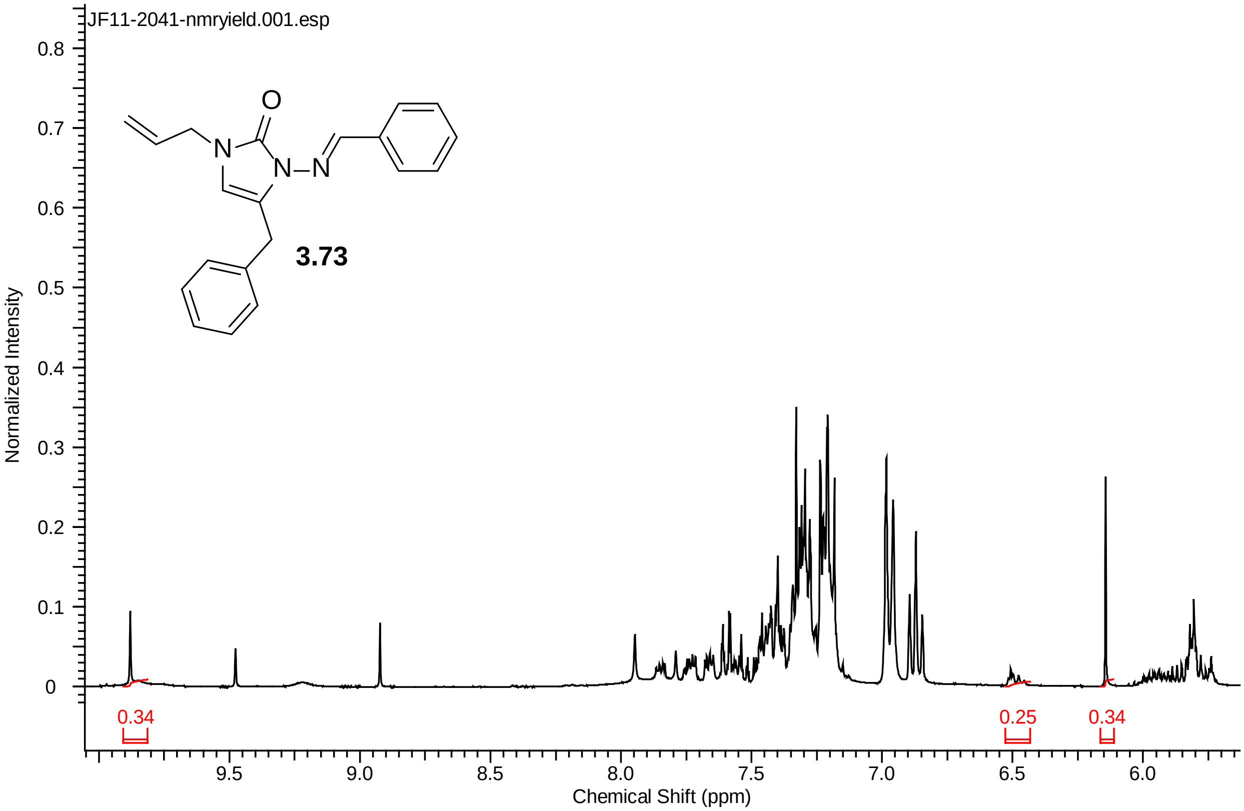

Carbazone-paramethoxy.001.esp
MeO
O
N
N–N
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.02
2.13
5.26
2.10
1.00
3.23
3.13
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

3.71


Carbazone-paramethoxy.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
157.6105
151.5981
148.6903
135.0620
130.2958
128.5905
123.4890
121.1277
114.3282
104.7156
55.4645
10.0468
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF11-2049-H.001.esp
NC
O
N
N–N
3.72
Normalized Intensity
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
0.99
2.06
3.33
0.99
2.00
2.06
3.11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

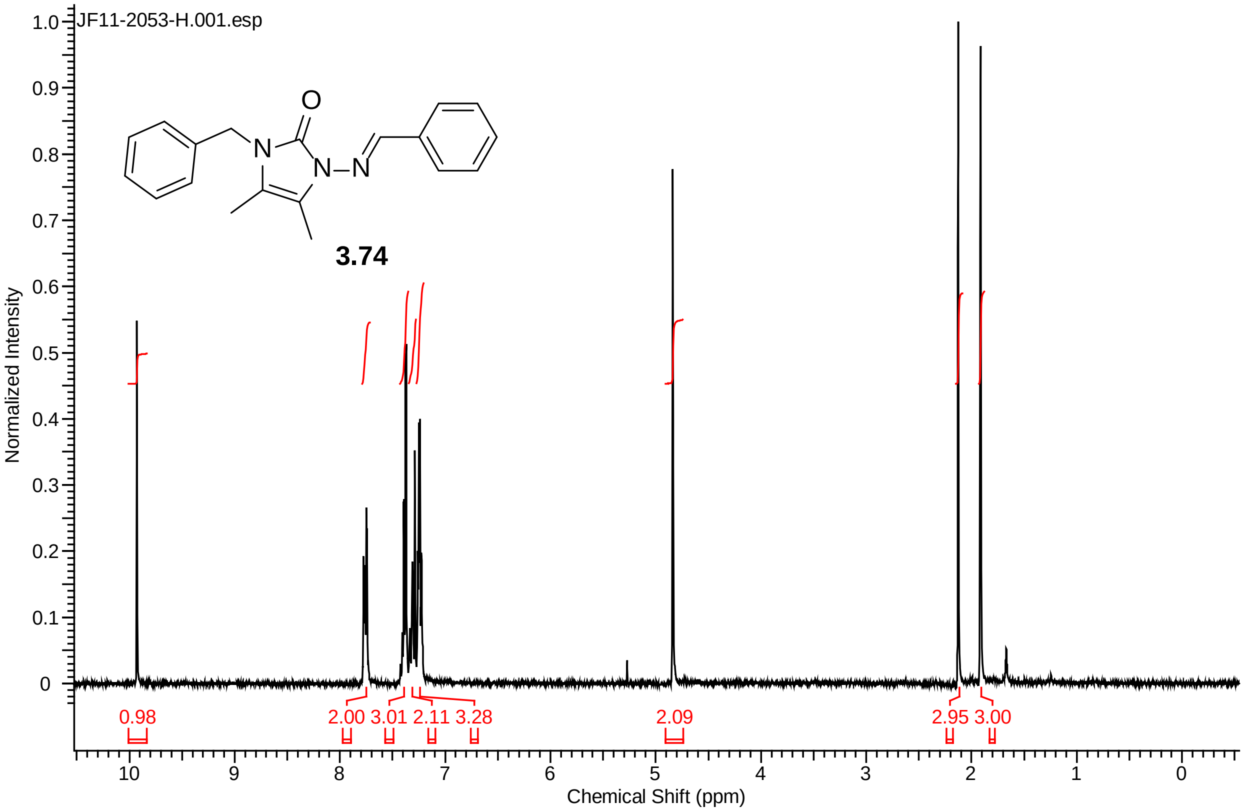

JF11-2049-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
151.8101
149.2500
134.6895
130.3984
128.5511
127.3728
120.9726
117.3797
104.6520
39.4131
18.0014
9.9138
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)



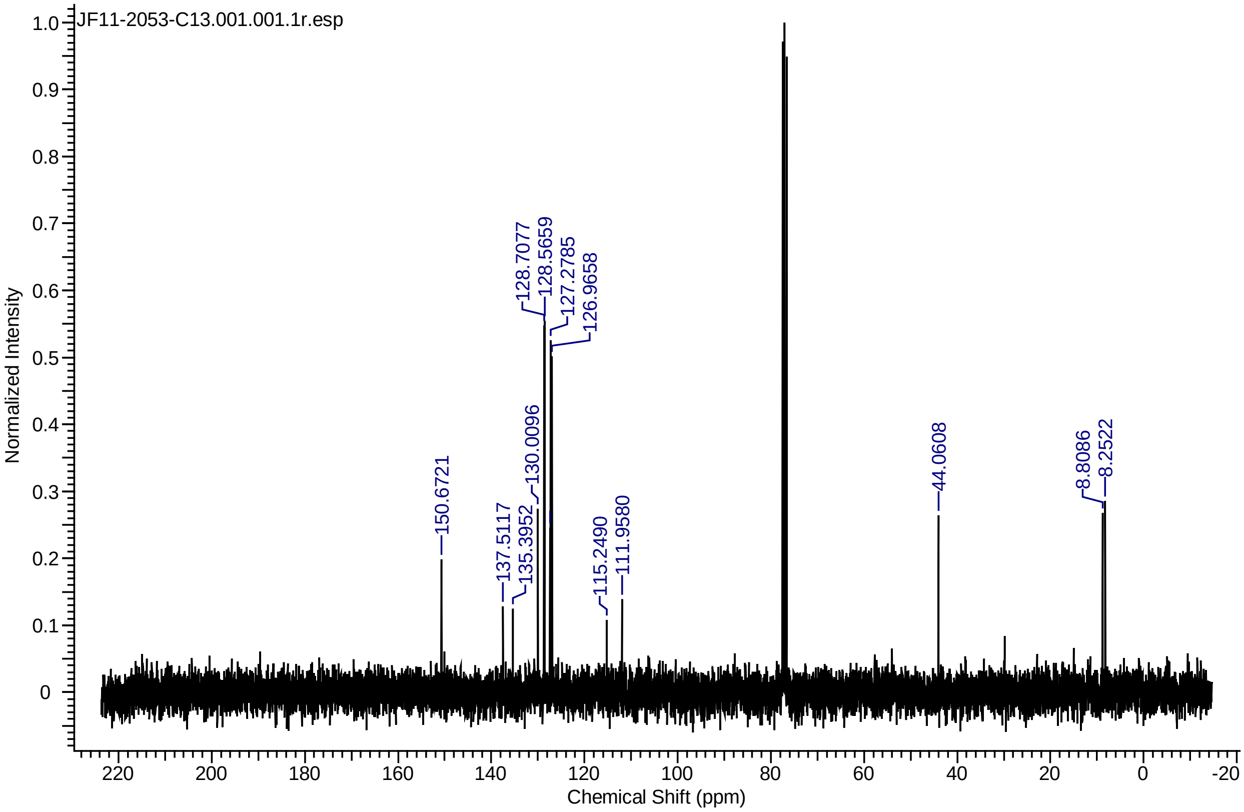
11.4 mg of TMB = 0.0678 mmol

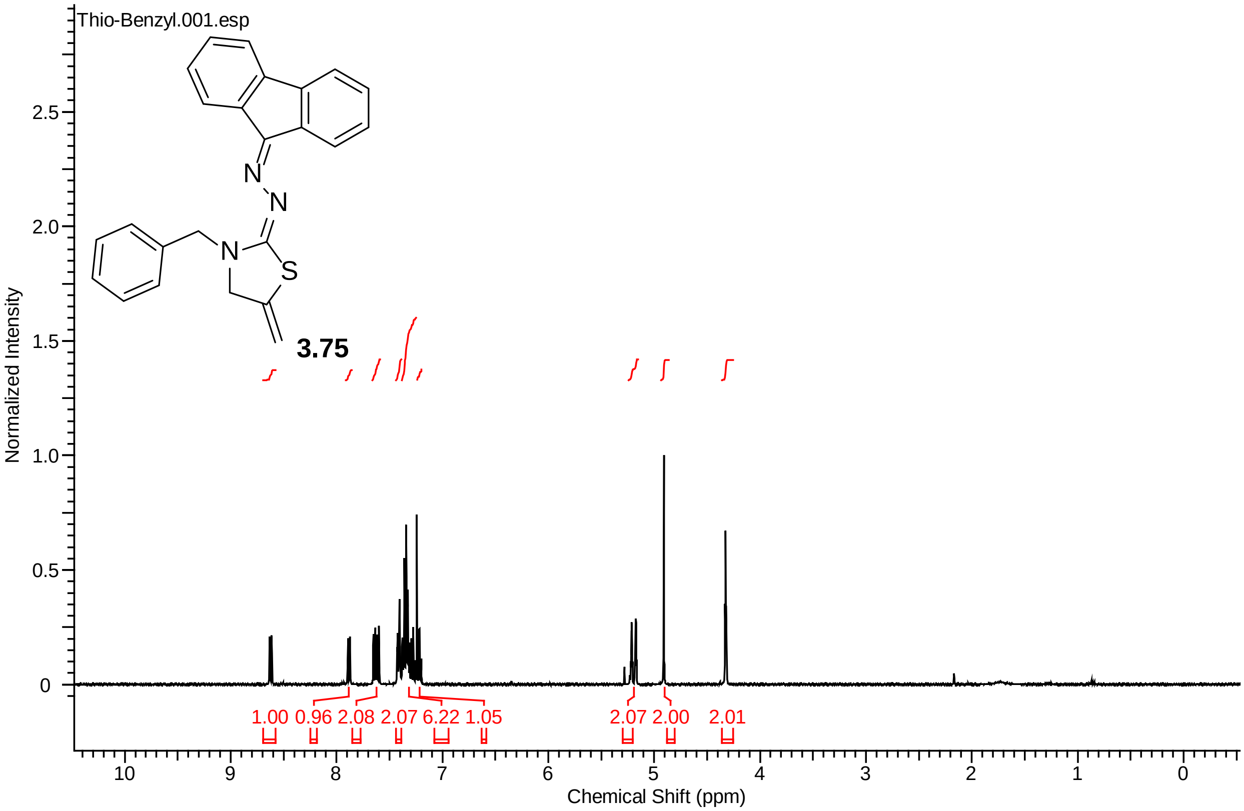
0.600 mmol/ 0.0678 mmol = 8.34

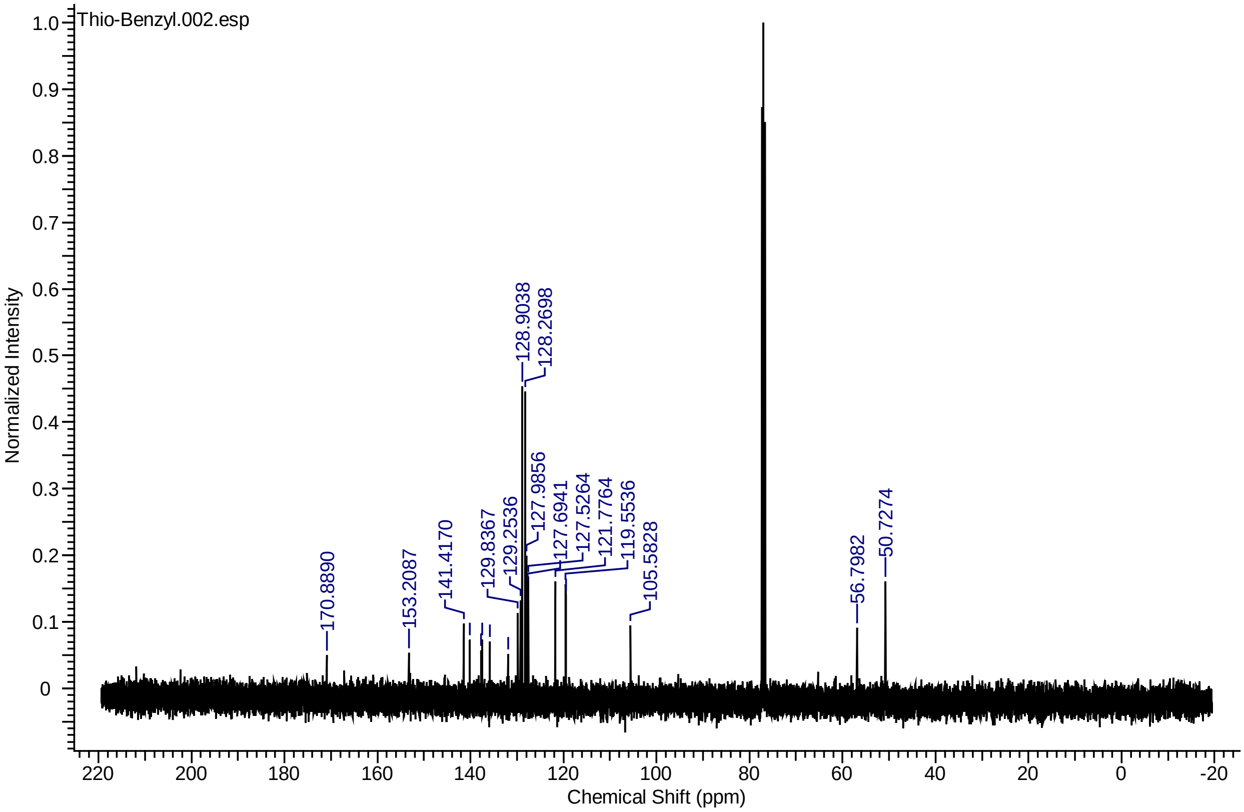
3 proton (tmd signal)/8.34 = 0.34 proton

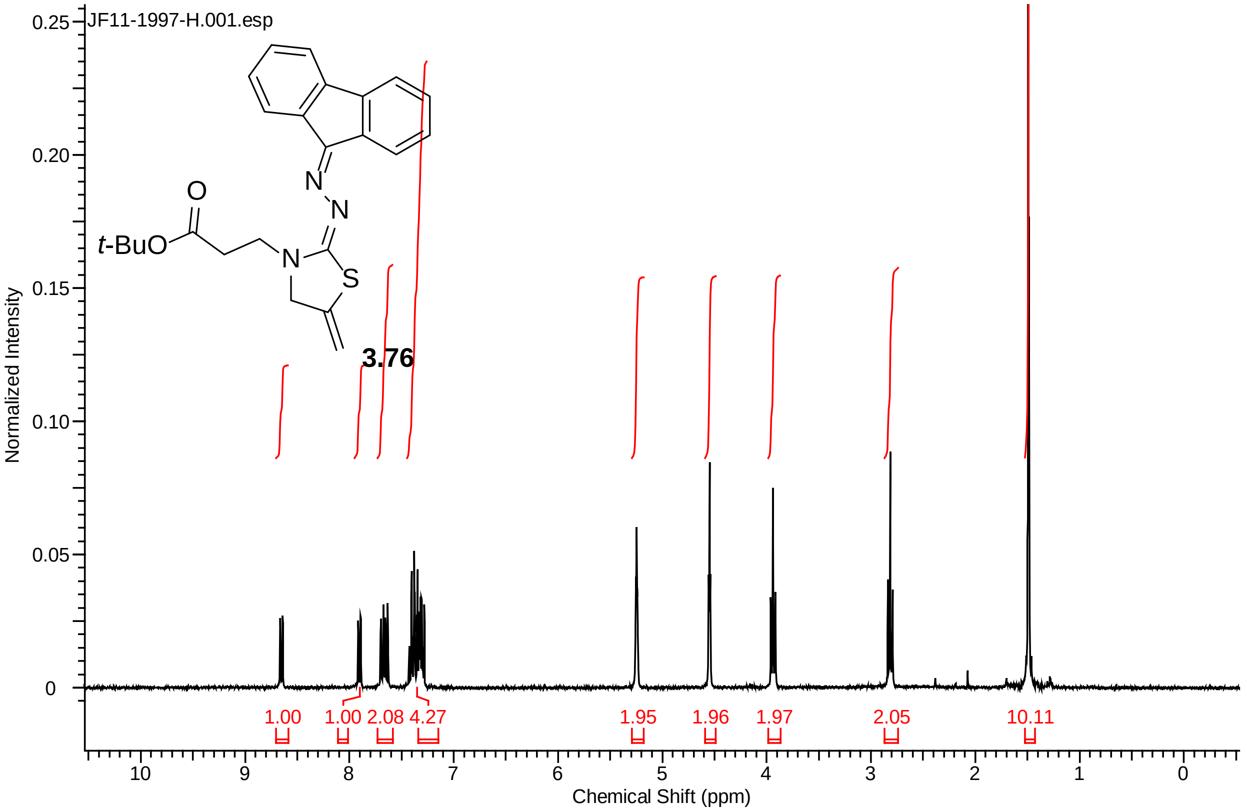

JF11-2053-H.001.esp
O
N
N–N
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.98
2.00
3.01
2.11
3.28
2.09
2.95
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

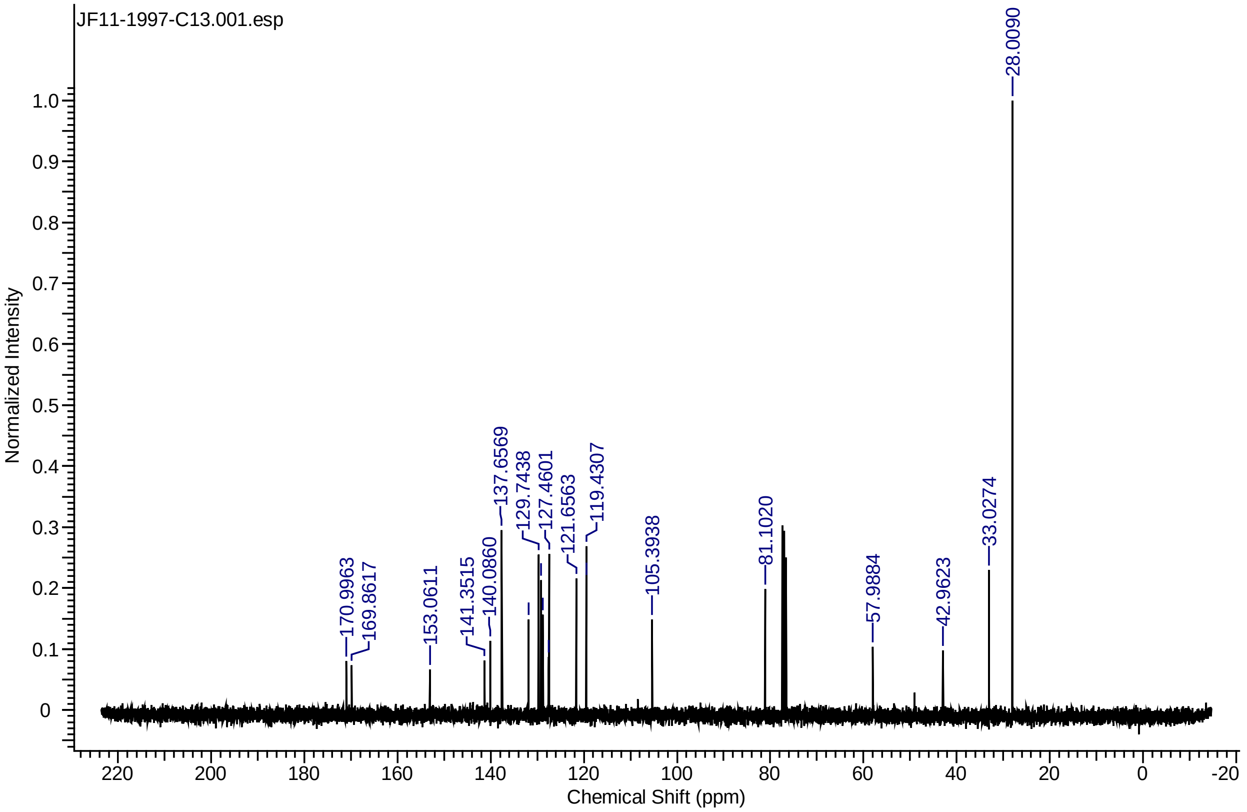
3.74

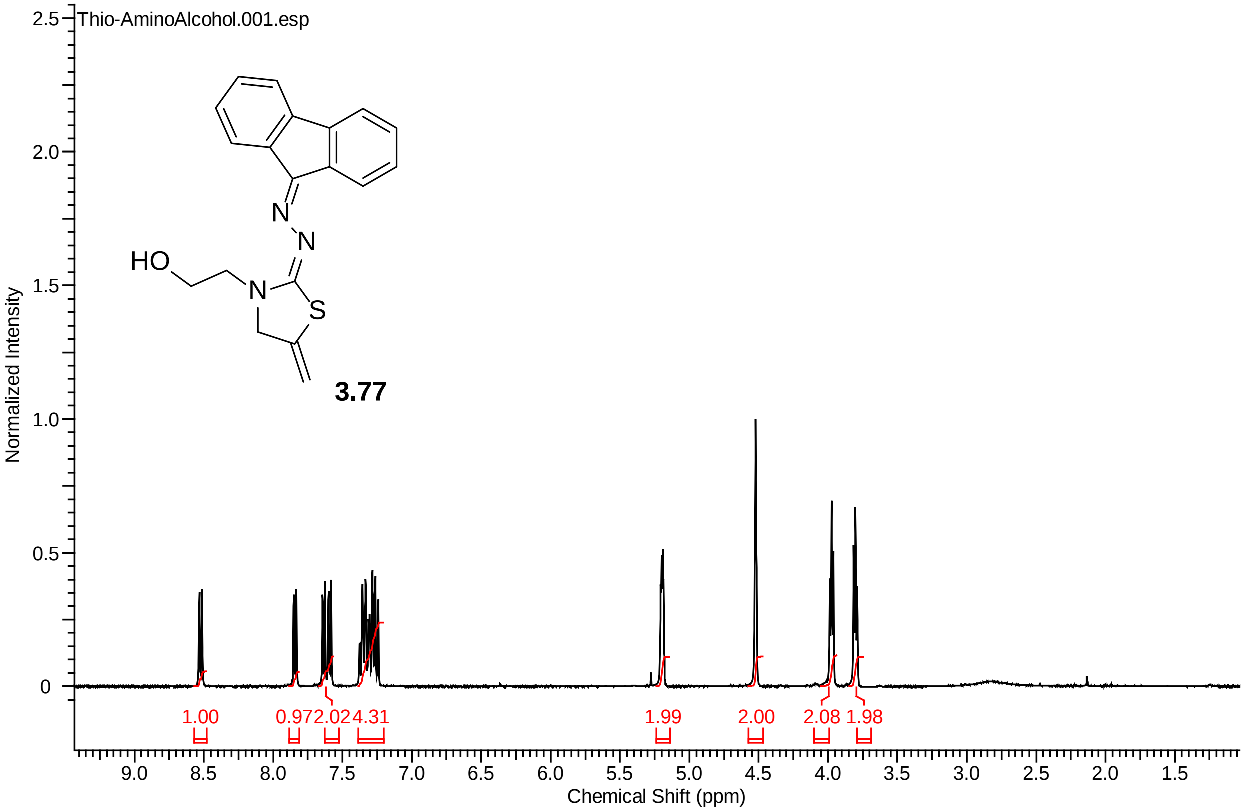

JF11-2053-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
150.6721
137.5117
135.3952
130.0096
128.7077
128.5659
127.2785
126.9658
115.2490
111.9580
44.0608
8.8086
8.2522
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

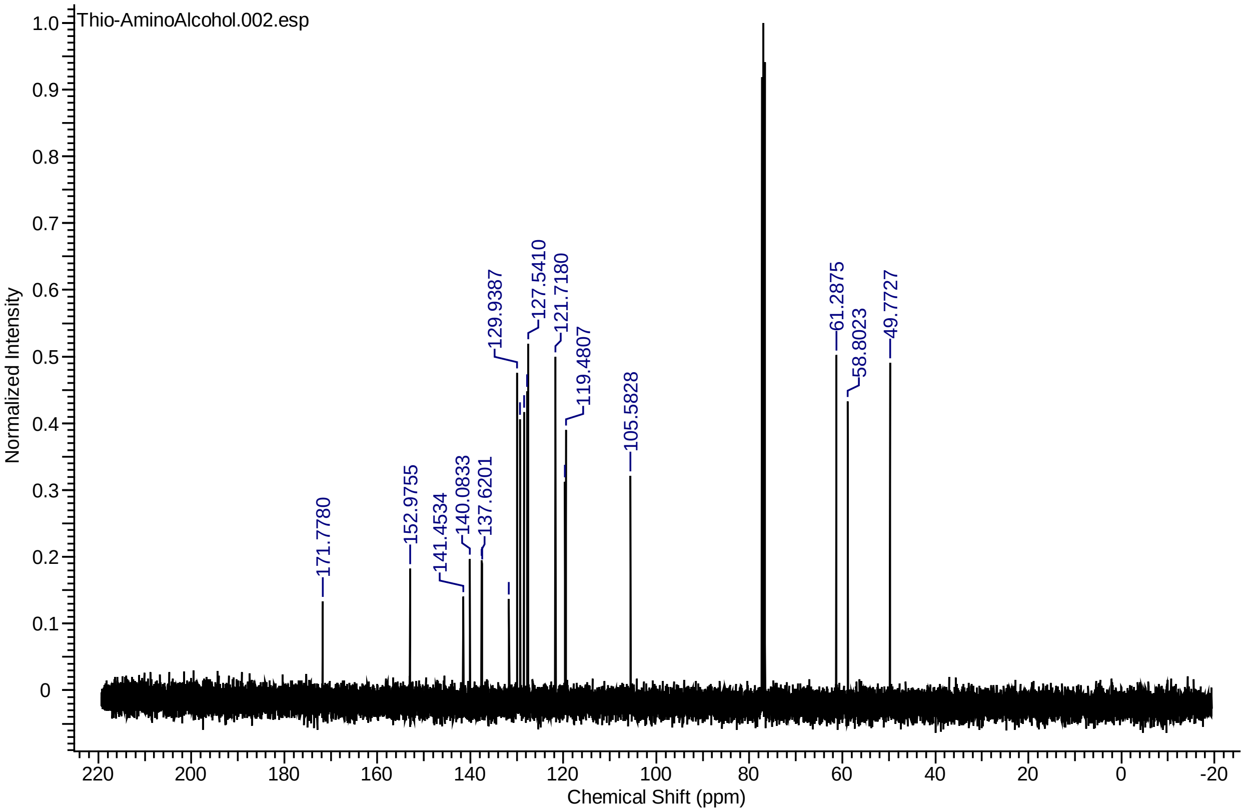

Thio-Benzyl.001.esp
N
N
N
S
3.75
Normalized Intensity
0
0.5
1.0
1.5
2.0
2.5
1.00
0.96
2.08
2.07
6.22
1.05
2.07
2.00
2.01
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

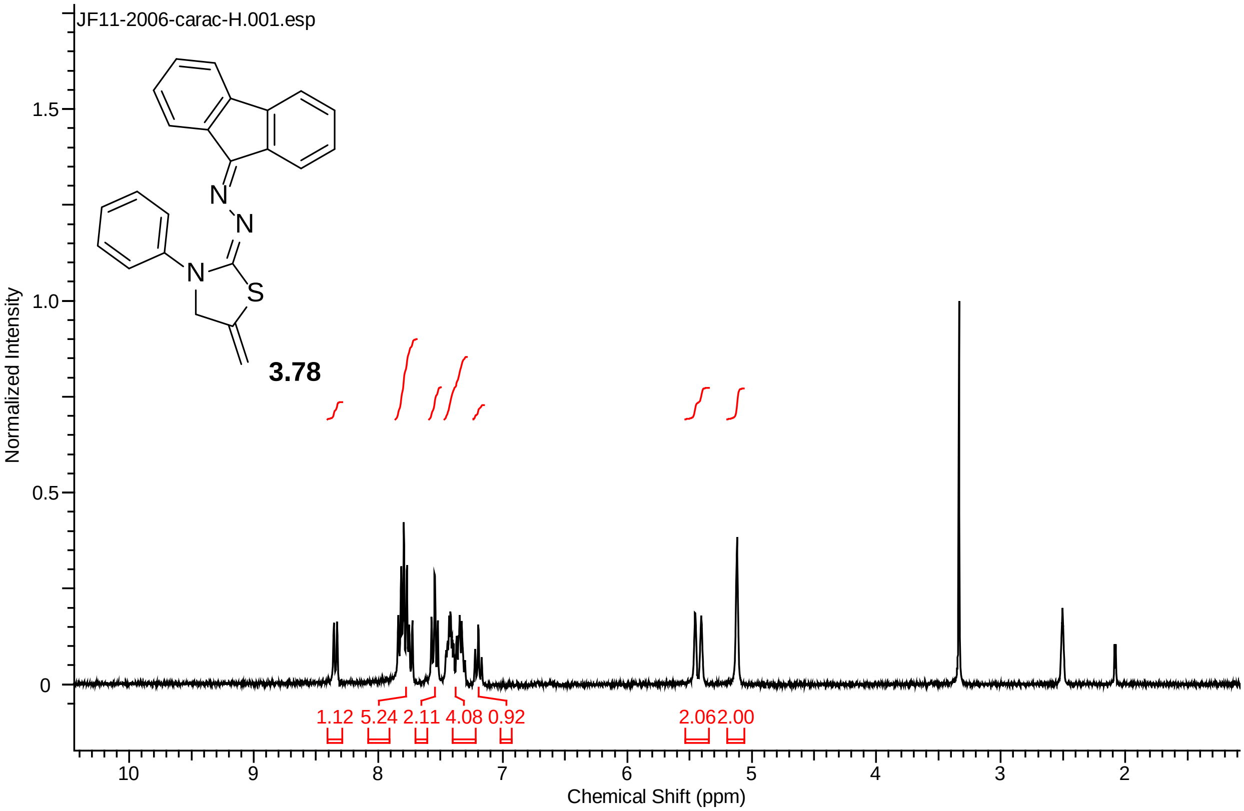

Thio-Benzyl.002.esp
170.8890
153.2087
141.4170
129.8367
129.2536
128.9038
128.2698
127.9856
127.6941
127.5264
121.7764
119.5536
105.5828
56.7982
50.7274
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

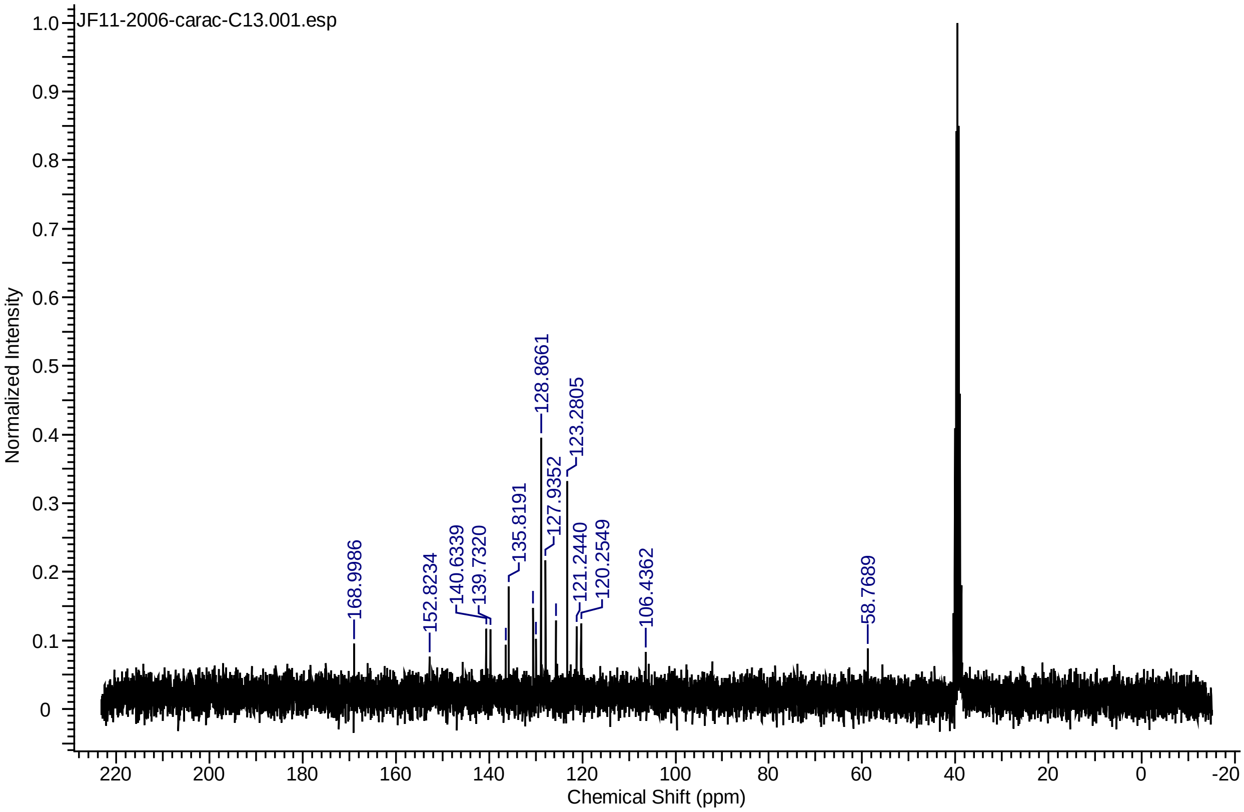

3.76
JF11-1997-H.001.esp
t-BuO
O
N
N
N
S
Normalized Intensity
0.25
0.20
0.15
0.10
0.05
0
1.00
1.00
2.08
4.27
1.95
1.96
1.97
2.05
10.11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

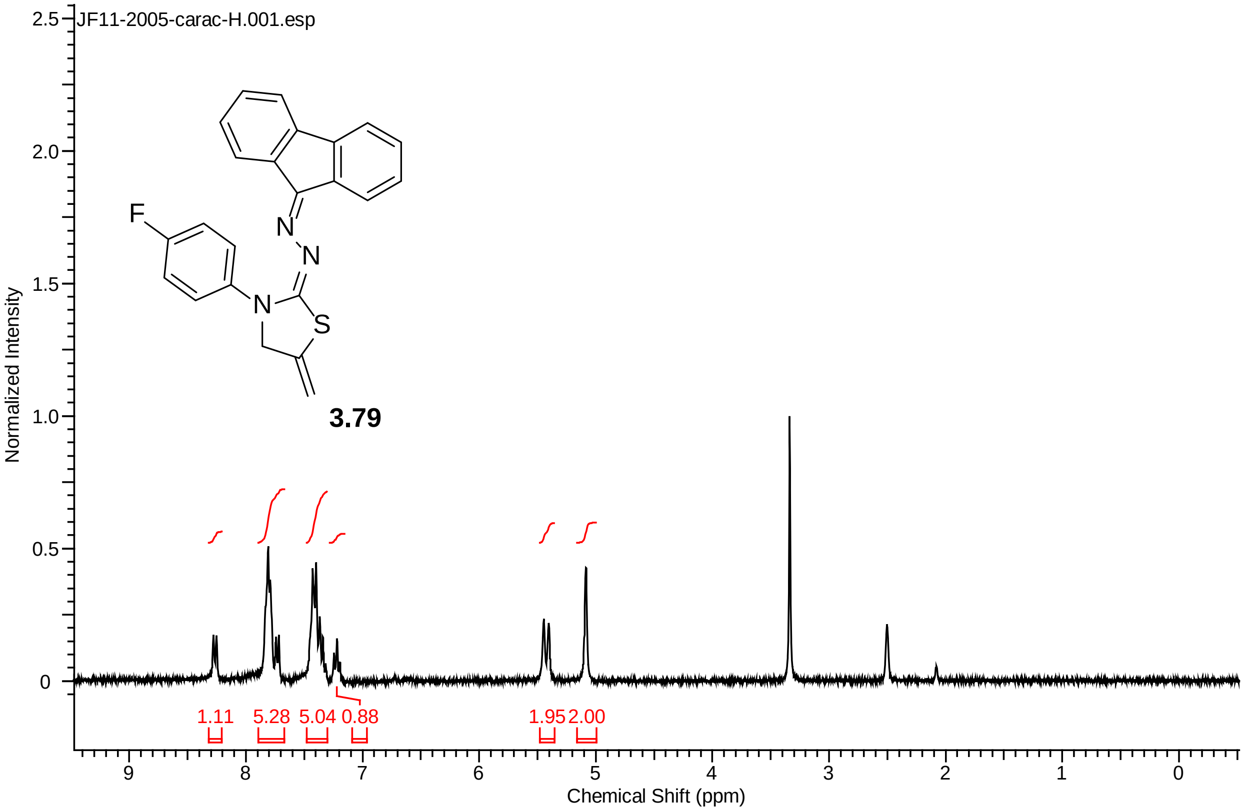

JF11-1997-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
170.9963
169.8617
153.0611
141.3515
140.0860
137.6569
129.7438
127.4601
121.6563
119.4307
105.3938
81.1020
57.9884
42.9623
33.0274
28.0090
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


3.77
Thio-AminoAlcohol.001.esp
HO
N
N
N
S
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0
1.00
0.97
2.02
4.31
1.99
2.00
2.08
1.98
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
Chemical Shift (ppm)

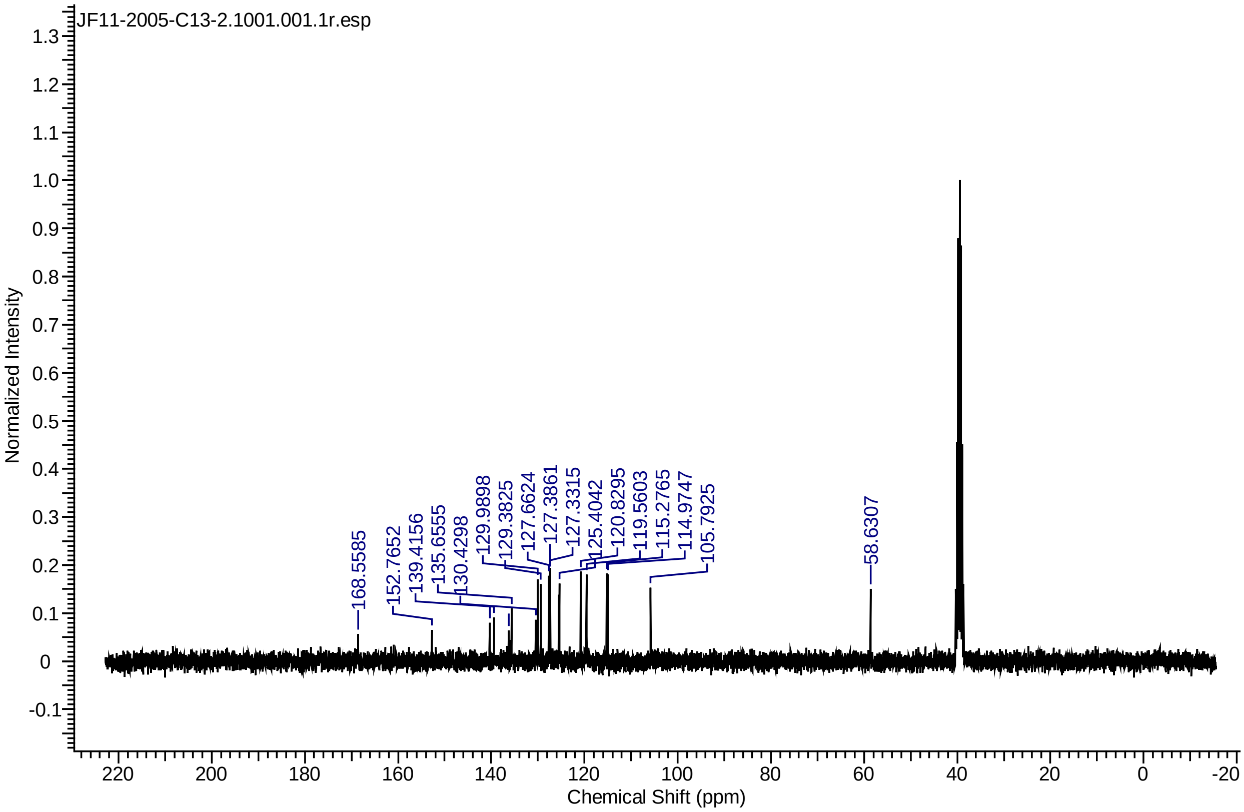

Thio-AminoAlcohol.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
171.7780
152.9755
141.4534
140.0833
137.6201
129.9387
127.5410
121.7180
119.4807
105.5828
61.2875
58.8023
49.7727
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

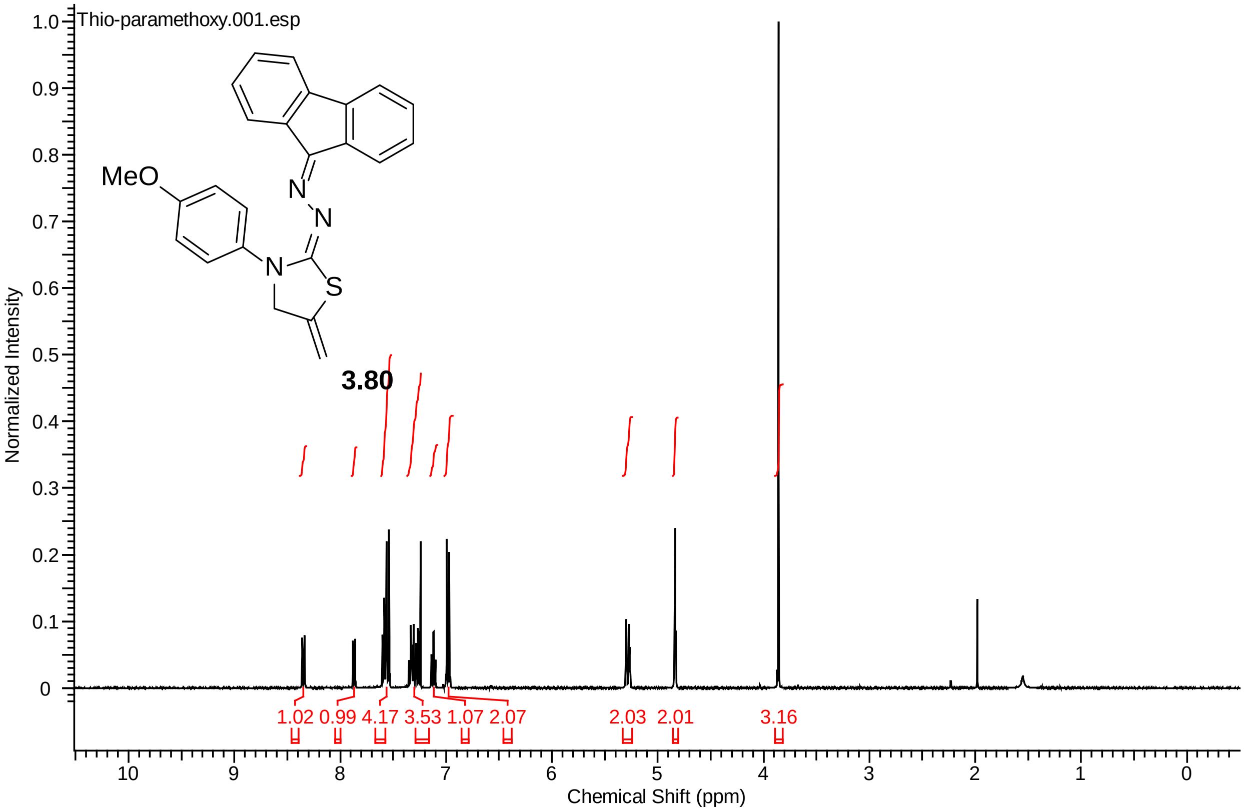

JF11-2006-carac-H.001.esp
N
N
N
S
3.78
1.12
5.24
2.11
4.08
0.92
2.06
2.00
Normalized Intensity
1.5
1.0
0.5
0
10
9
8
7
6
5
4
3
2
Chemical Shift (ppm)


JF11-2006-carac-C13.001.esp
168.9986
152.8234
140.6339
139.7320
135.8191
128.8661
127.9352
123.2805
121.2440
120.2549
106.4362
58.7689
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)


JF11-2005-carac-H.001.esp
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0
F
N
N
N
S
1.11
5.28
5.04
0.88
1.95
2.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

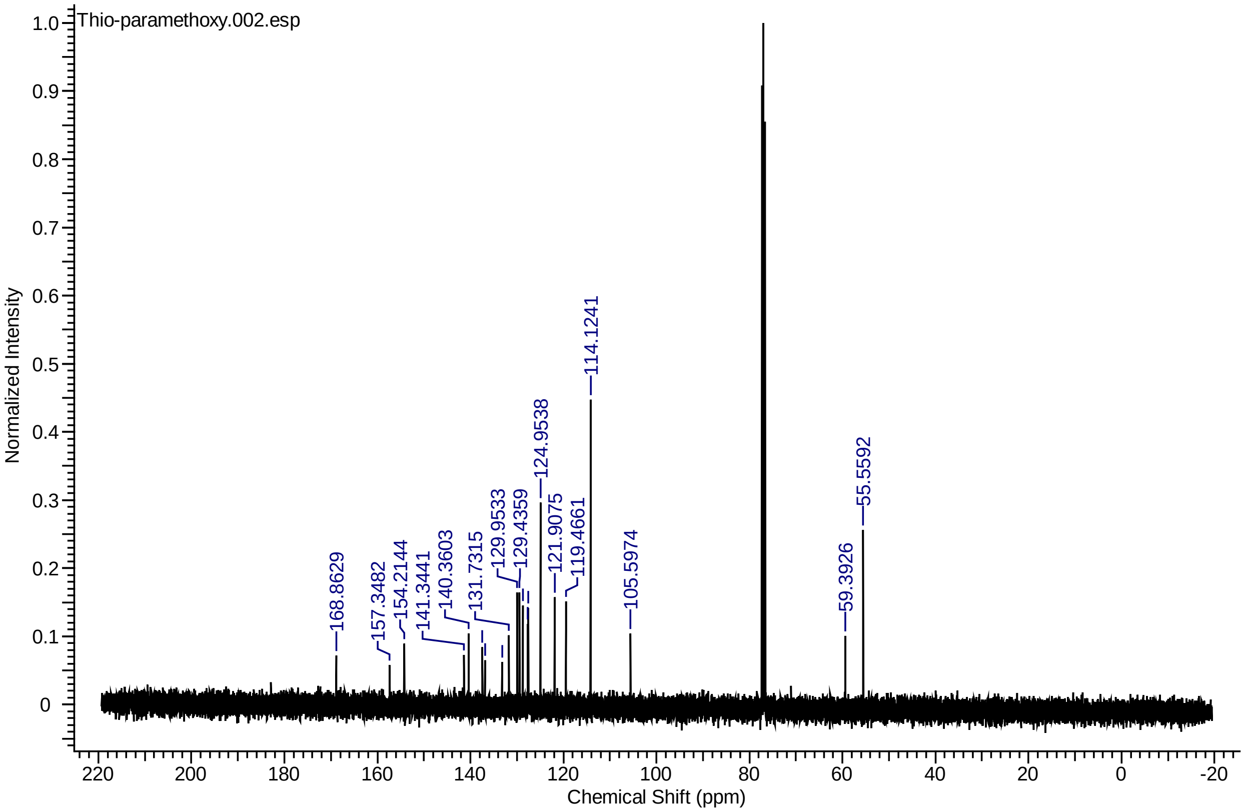
3.79


JF11-2005-C13-2.1001.001.1r.esp
Normalized Intensity
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
-0.1
168.5585
152.7652
139.4156
135.6555
130.4298
129.9898
129.3825
127.6624
127.3861
127.3315
125.4042
120.8295
119.5603
115.2765
114.9747
105.7925
58.6307
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

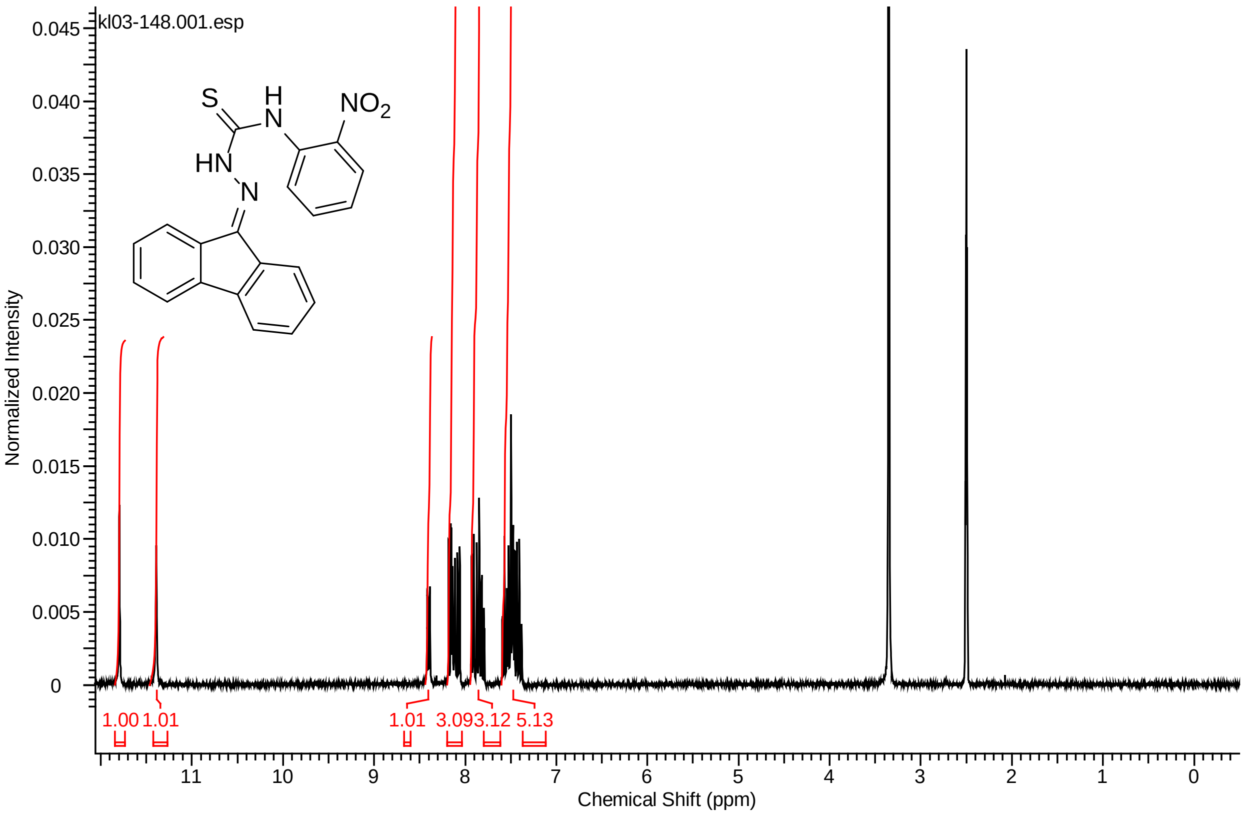


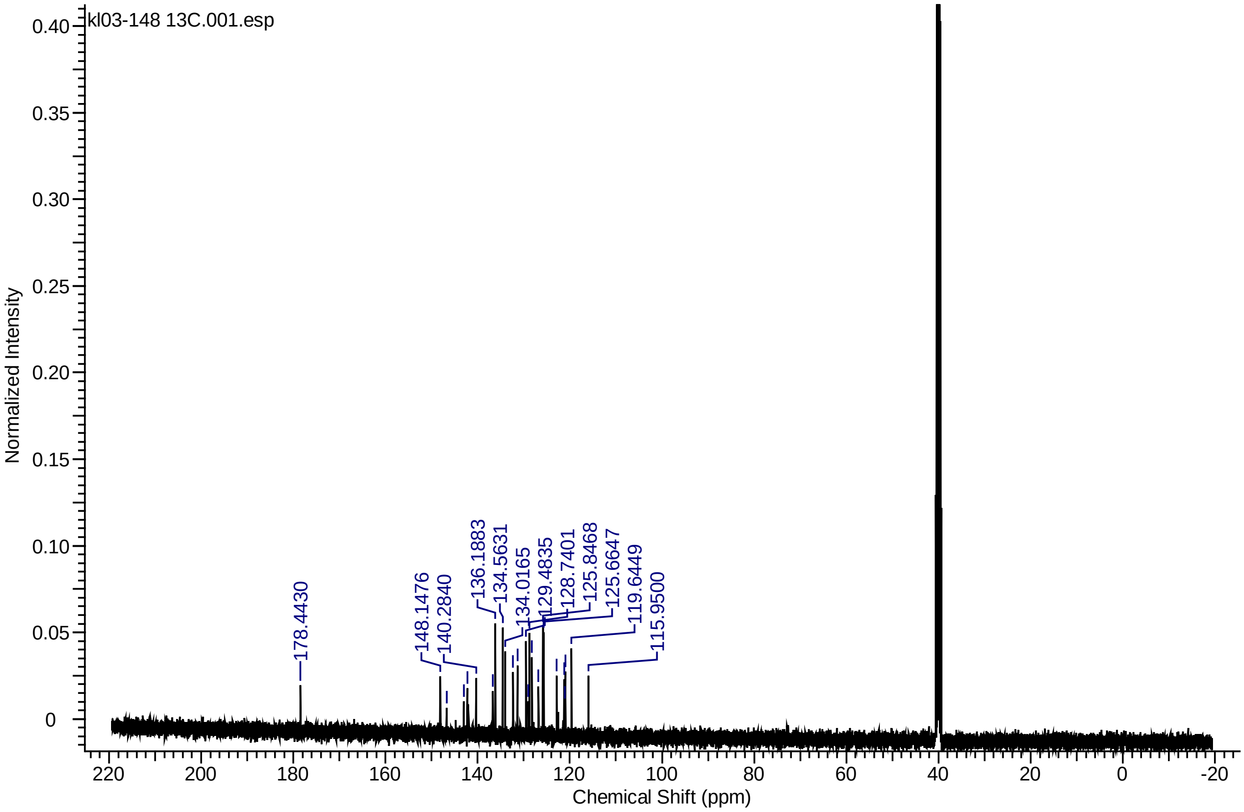
3.80

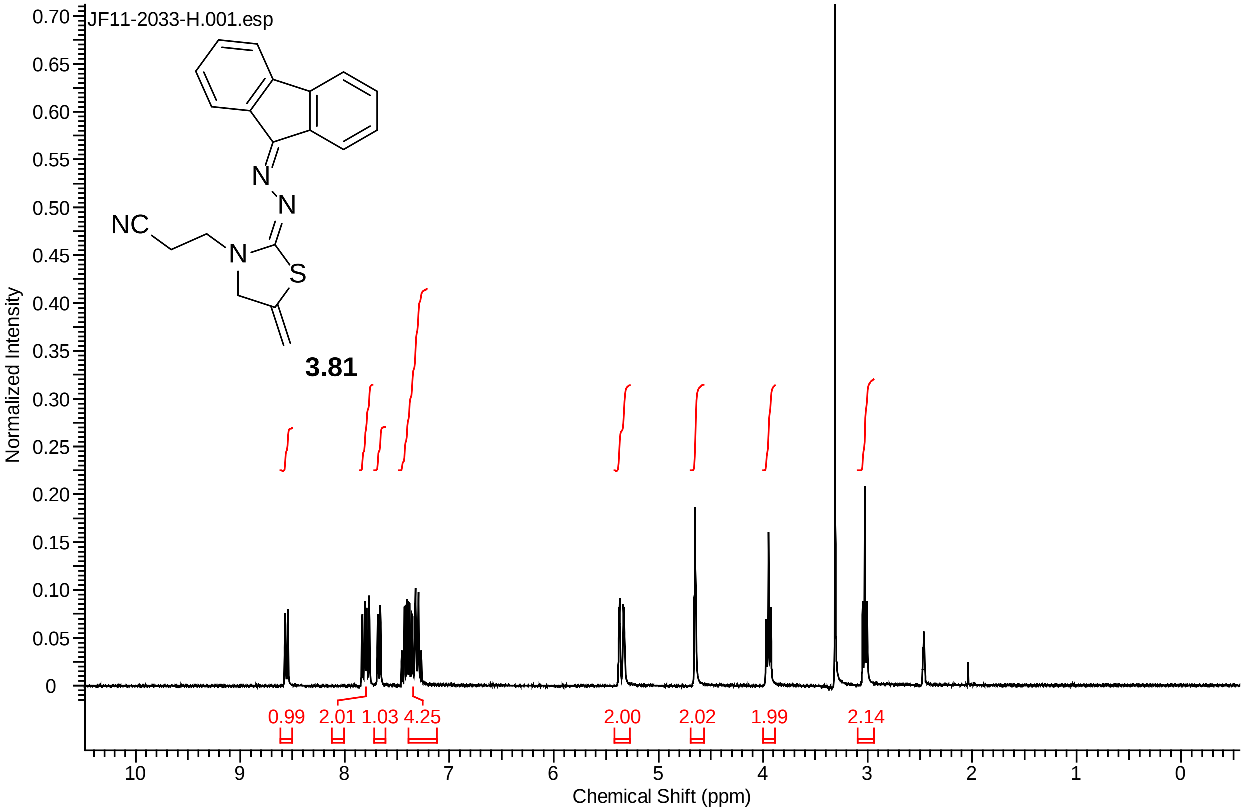
Thio-paramethoxy.001.esp
MeO
N
N
N
S
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.02
0.99
4.17
3.53
1.07
2.07
2.03
2.01
3.16
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

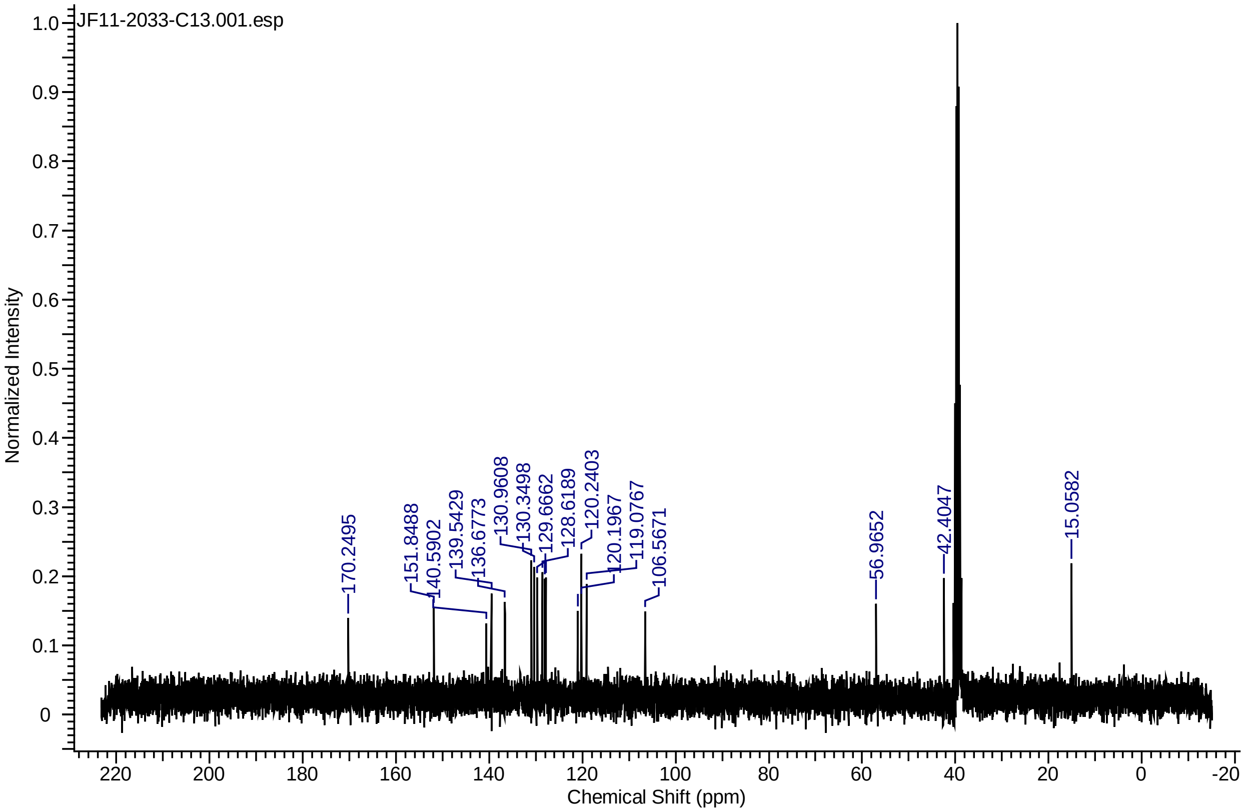


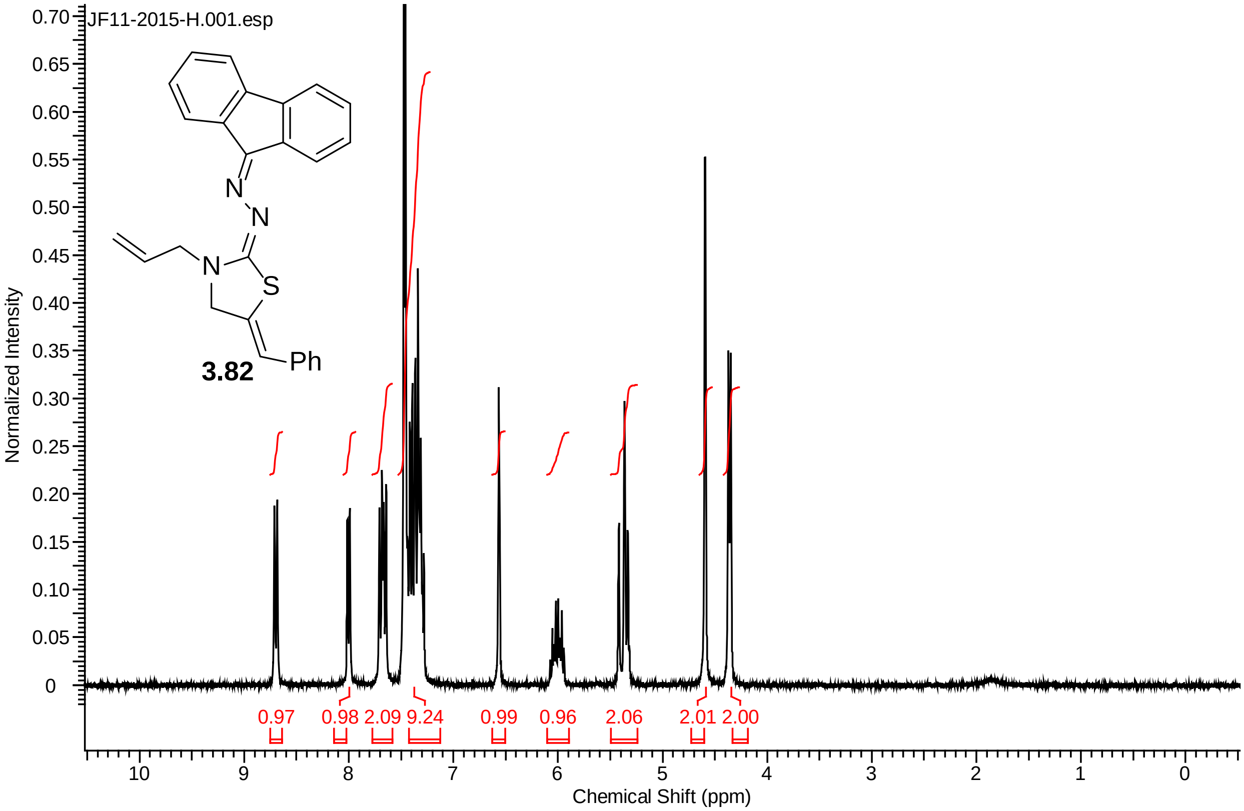
Thio-paramethoxy.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
168.8629
157.3482
154.2144
141.3441
140.3603
131.7315
129.9533
129.4359
124.9538
121.9075
119.4661
114.1241
105.5974
59.3926
55.5592
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

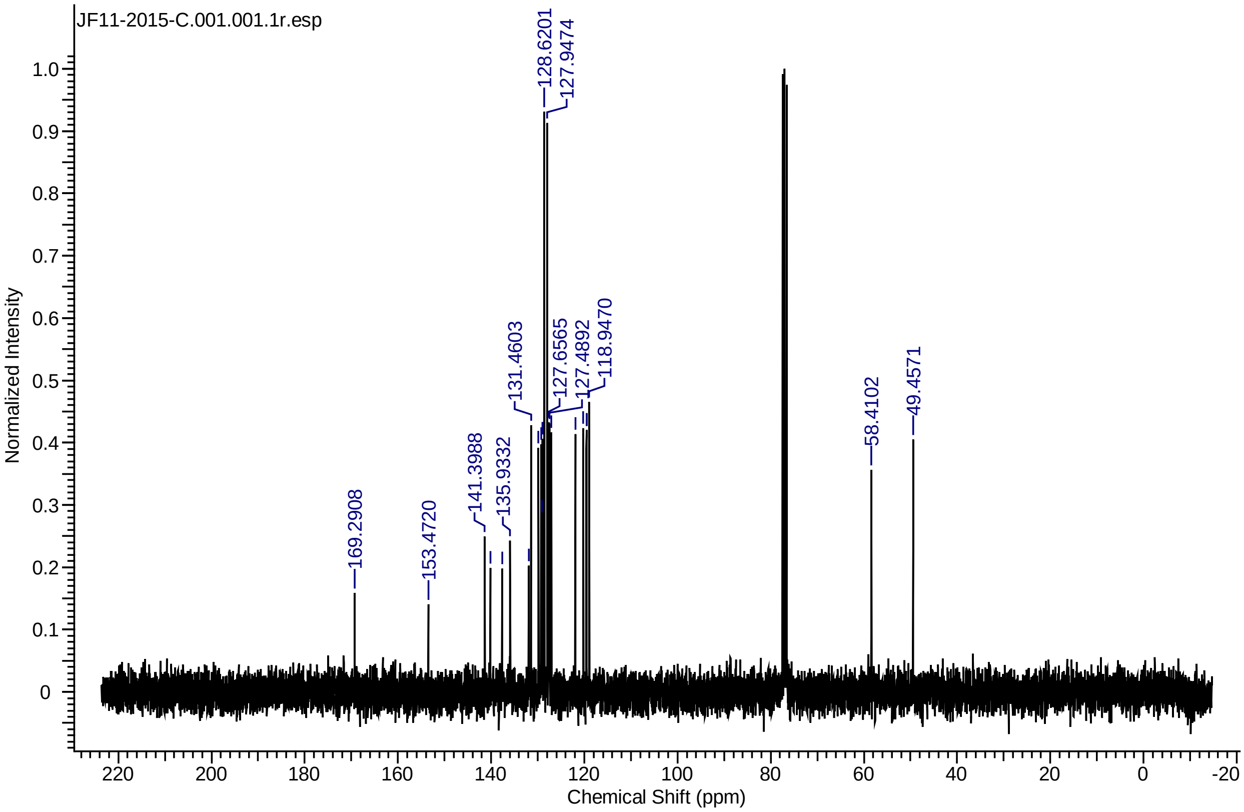

kl03-148.001.esp
S
H
N
NO2
HN
N
Normalized Intensity
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0
1.00
1.01
1.01
3.09
3.12
5.13
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

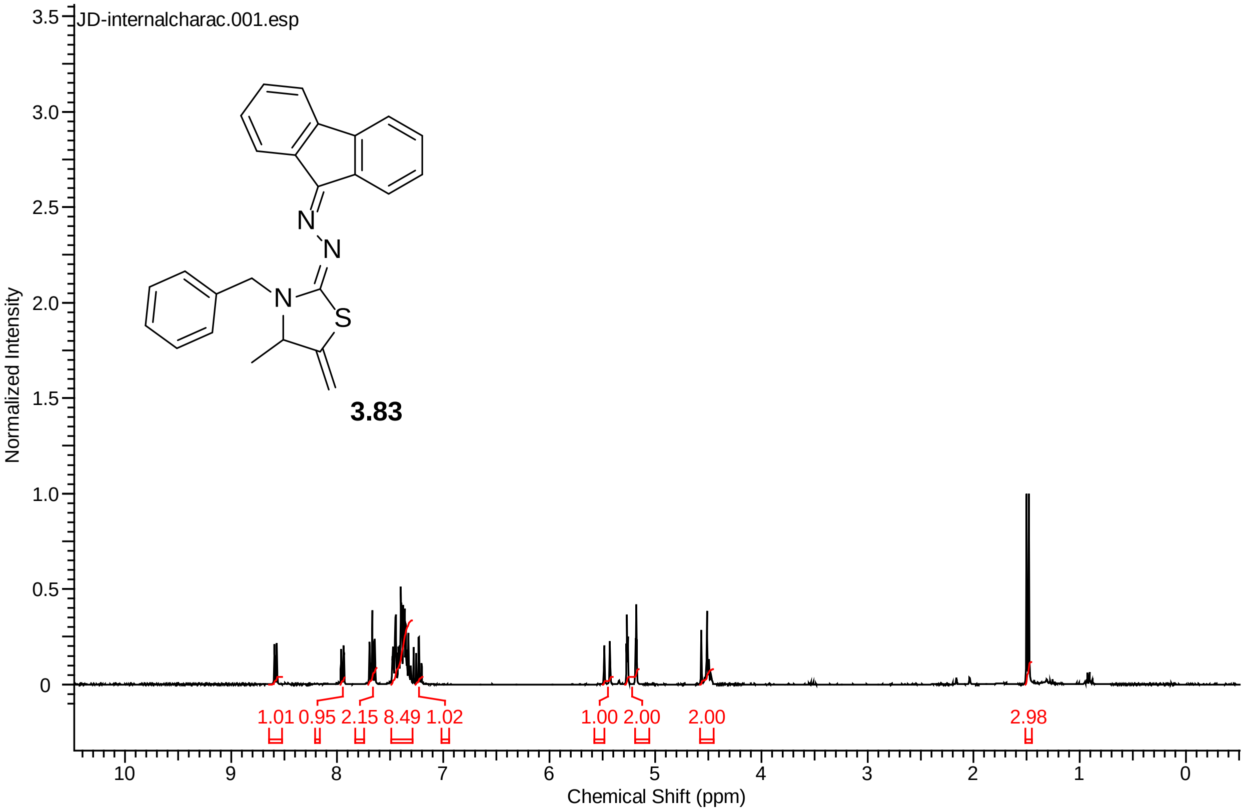

kl03-148 13C.001.esp
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
178.4430
148.1476
140.2840
136.1883
134.5631
134.0165
129.4835
128.7401
125.8468
125.6647
119.6449
115.9500
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

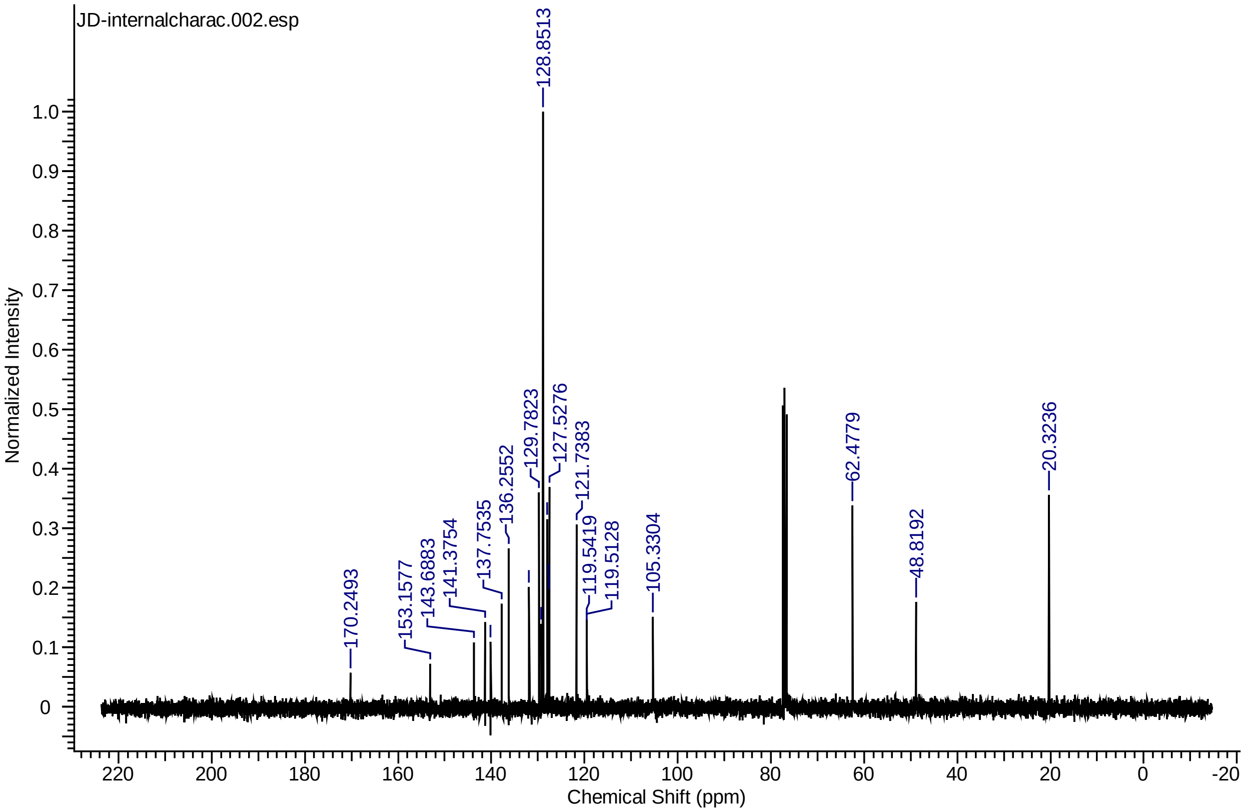

JF11-2033-H.001.esp
NC
N
N
N
S
3.81
Normalized Intensity
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.99
2.01
1.03
4.25
2.00
2.02
1.99
2.14
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

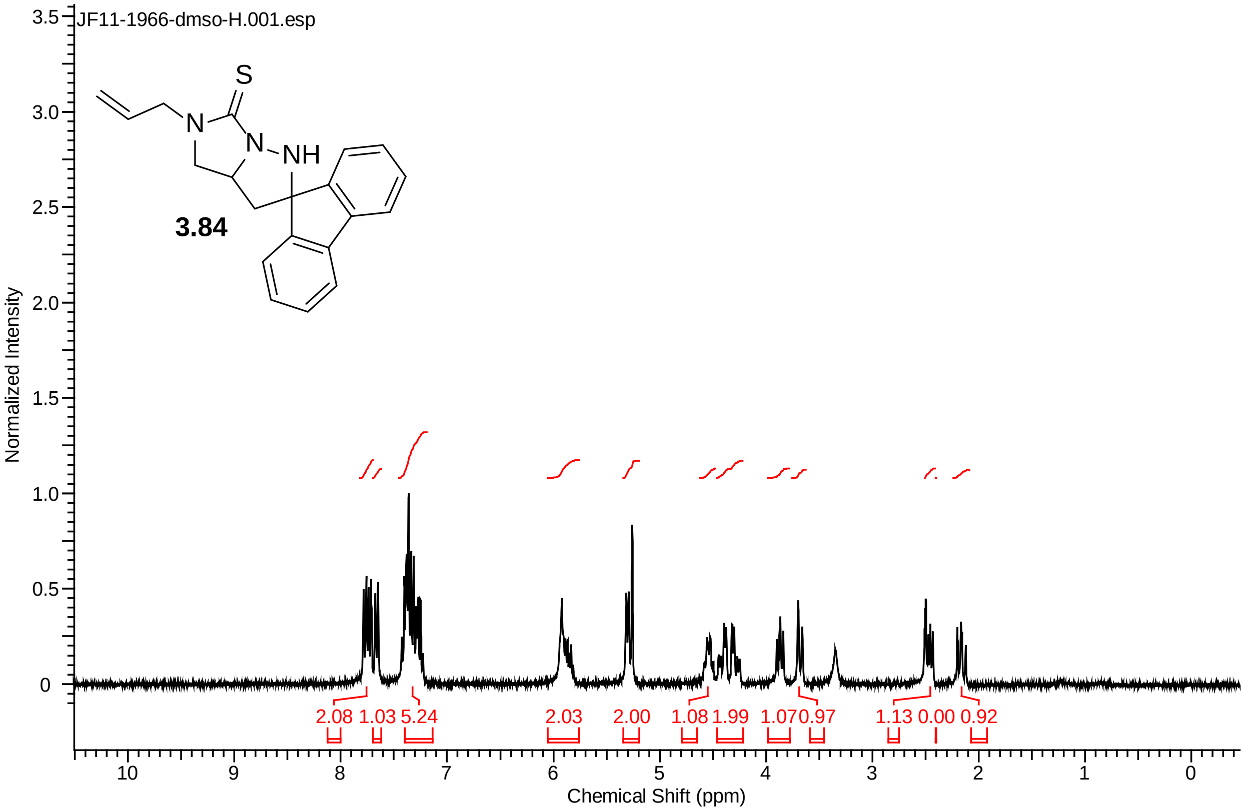

JF11-2033-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
170.2495
151.8488
140.5902
139.5429
136.6773
130.9608
130.3498
129.6662
128.6189
120.2403
120.1967
119.0767
106.5671
56.9652
42.4047
15.0582
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

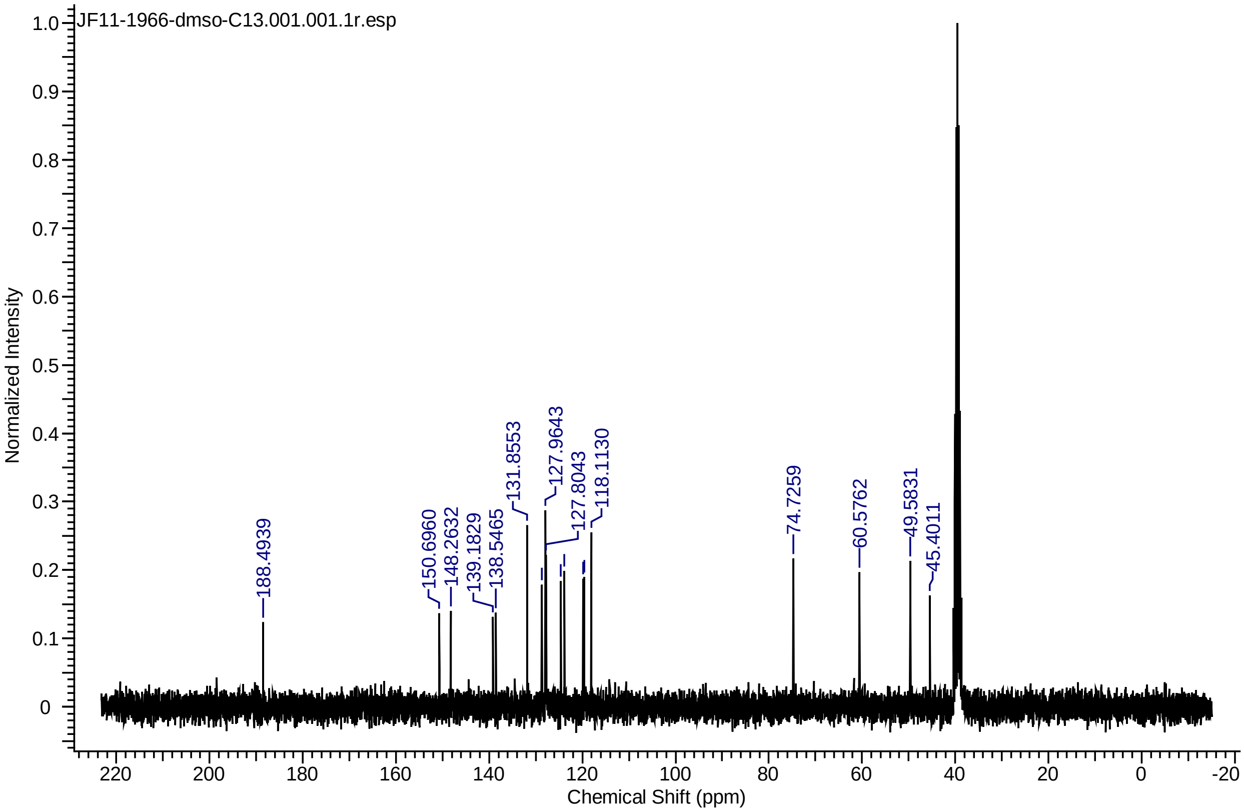

JF11-2015-H.001.esp
3.82
N
N
N
S
Ph
Normalized Intensity
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.97
0.98
2.09
9.24
0.99
0.96
2.06
2.01
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

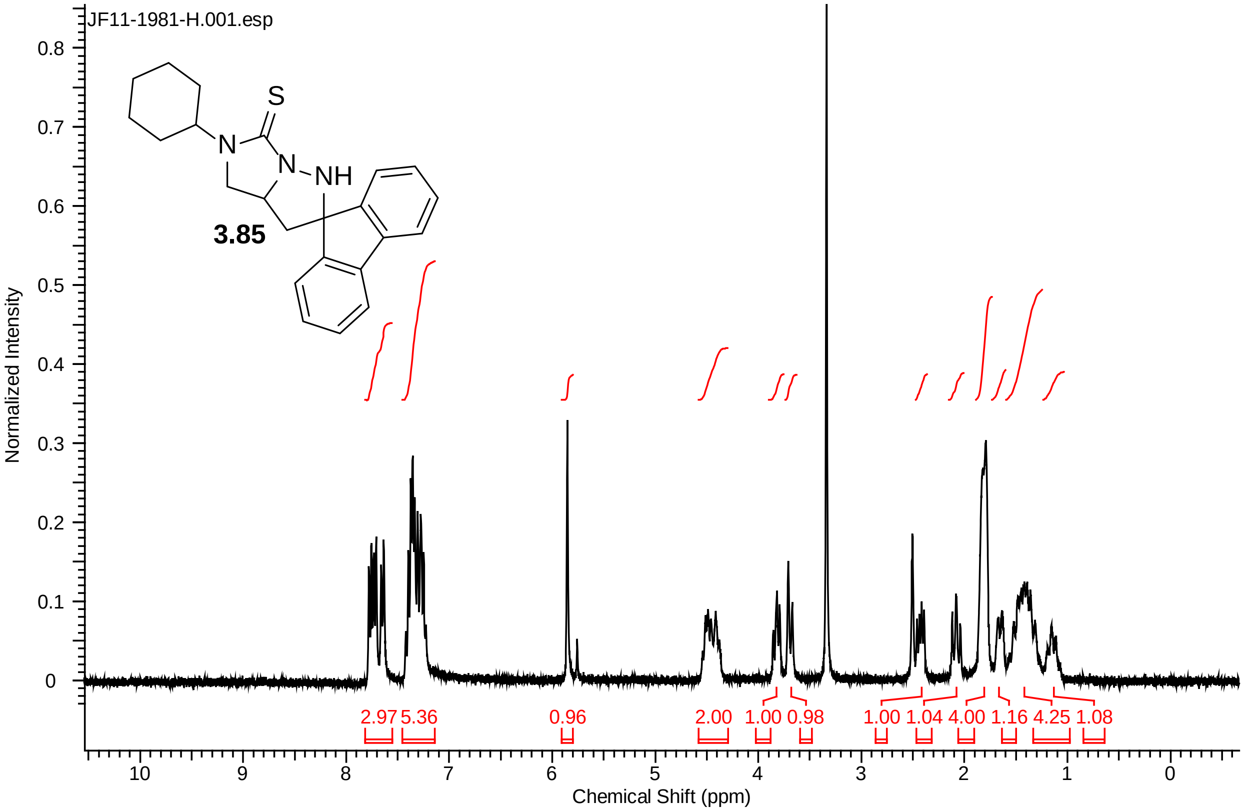

JF11-2015-C.001.001.1r.esp
169.2908
153.4720
141.3988
135.9332
131.4603
128.6201
127.9474
127.6565
127.4892
118.9470
58.4102
49.4571
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

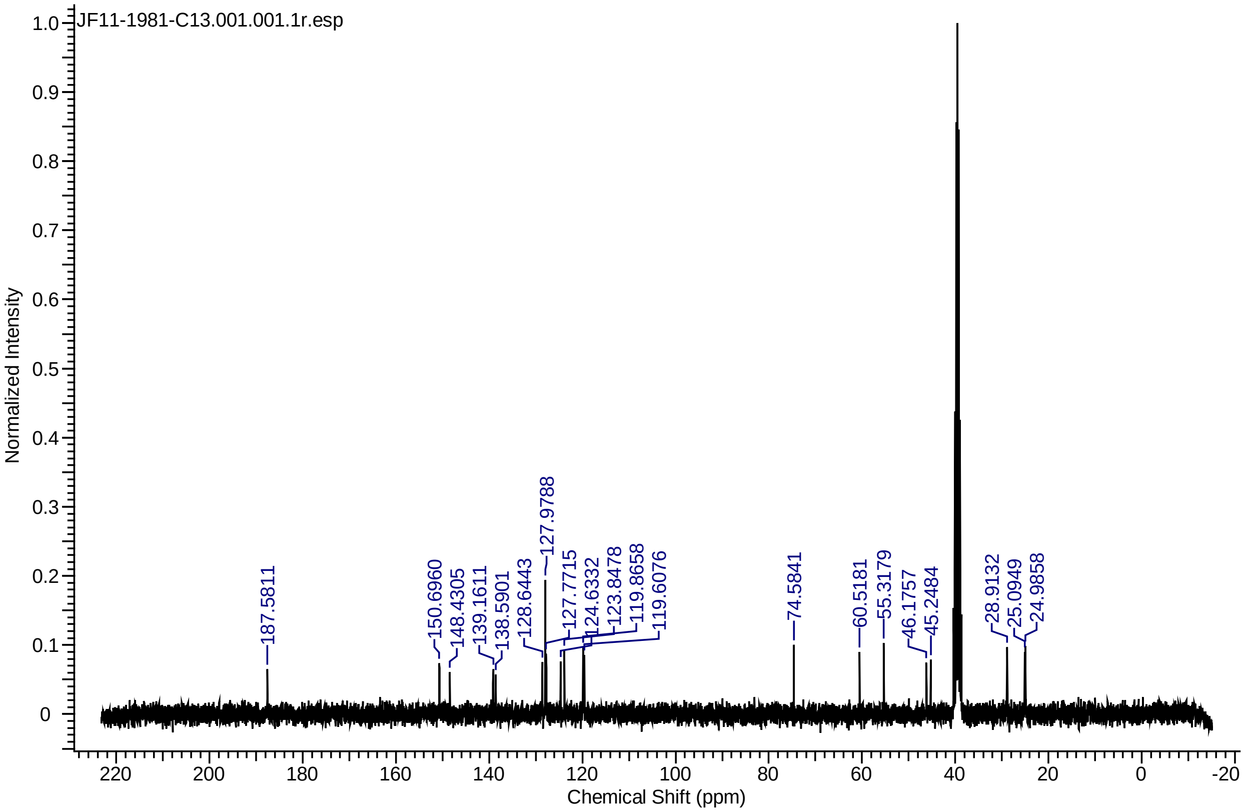

JD-internalcharac.001.esp
Normalized Intensity
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
N
N
N
S
3.83
1.01
0.95
2.15
8.49
1.02
1.00
2.00
2.00
2.98
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

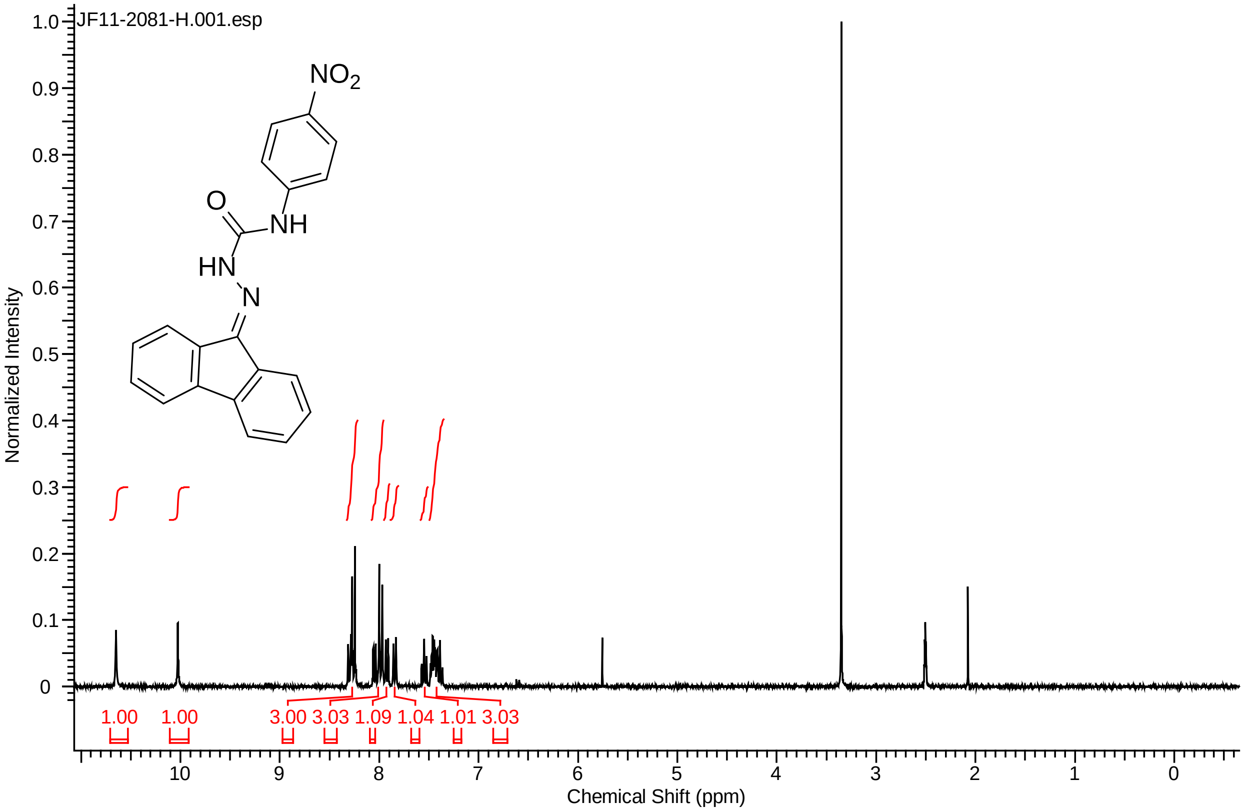

JD-internalcharac.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
170.2493
153.1577
143.6883
141.3754
137.7535
136.2552
129.7823
128.8513
127.5276
121.7383
119.5419
119.5128
105.3304
62.4779
48.8192
20.3236
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

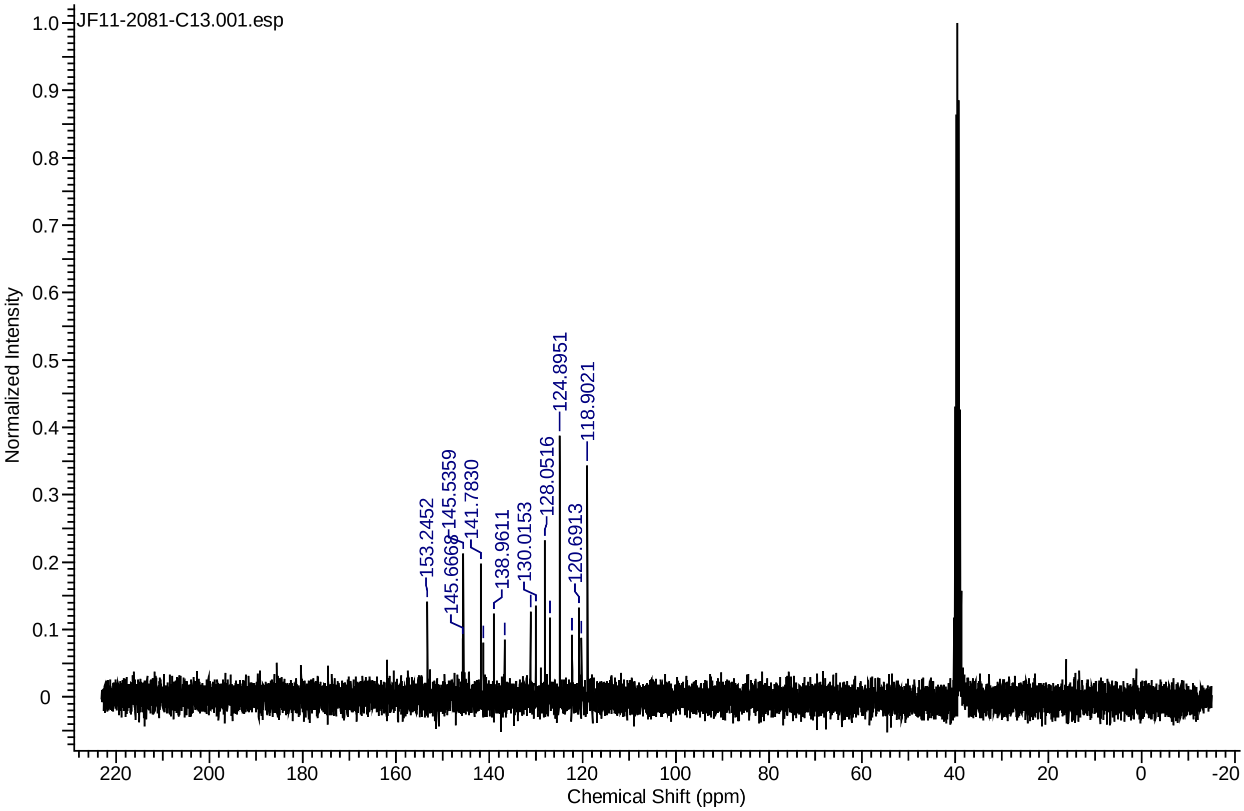

JF11-1966-dmso-H.001.esp
S
N
N
NH
3.84
Normalized Intensity
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
2.08 1.03 5.24
2.03
2.00
1.08 1.99
1.07 0.97
1.13 0.00 0.92
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

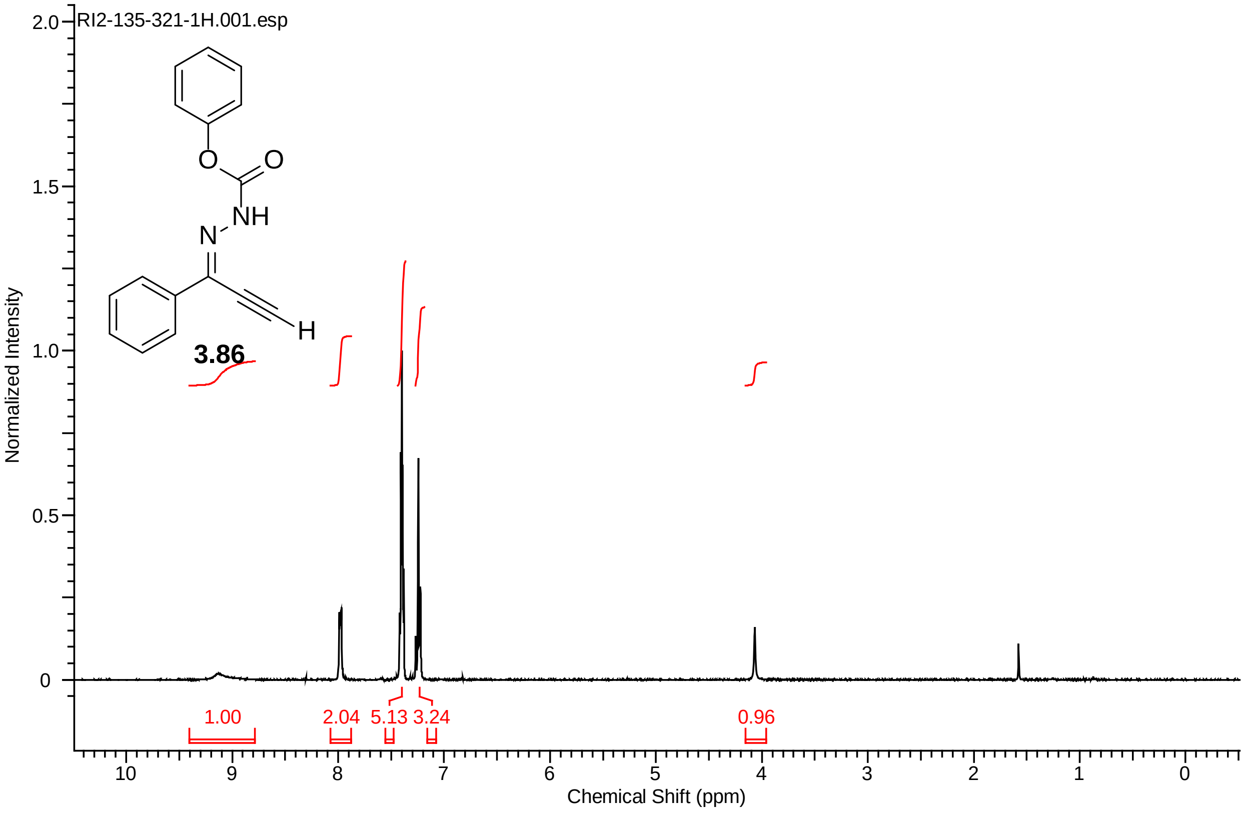

JF11-1966-dmso-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
188.4939
150.6960
148.2632
139.1829
138.5465
131.8553
127.9643
127.8043
118.1130
74.7259
60.5762
49.5831
45.4011
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

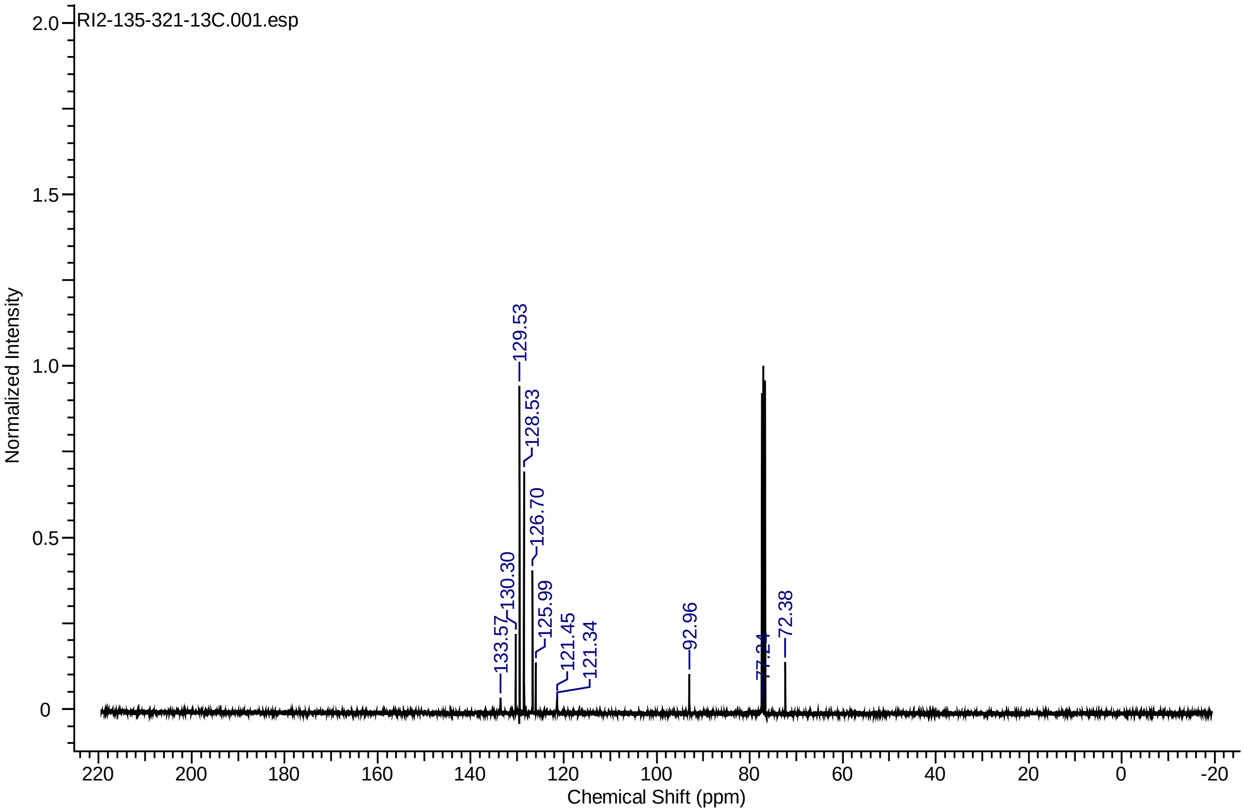

JF11-1981-H.001.esp
S
N
N
NH
3.85
Normalized Intensity
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2.97
5.36
0.96
2.00
1.00
0.98
1.00
1.04
4.00
1.16
4.25
1.08
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

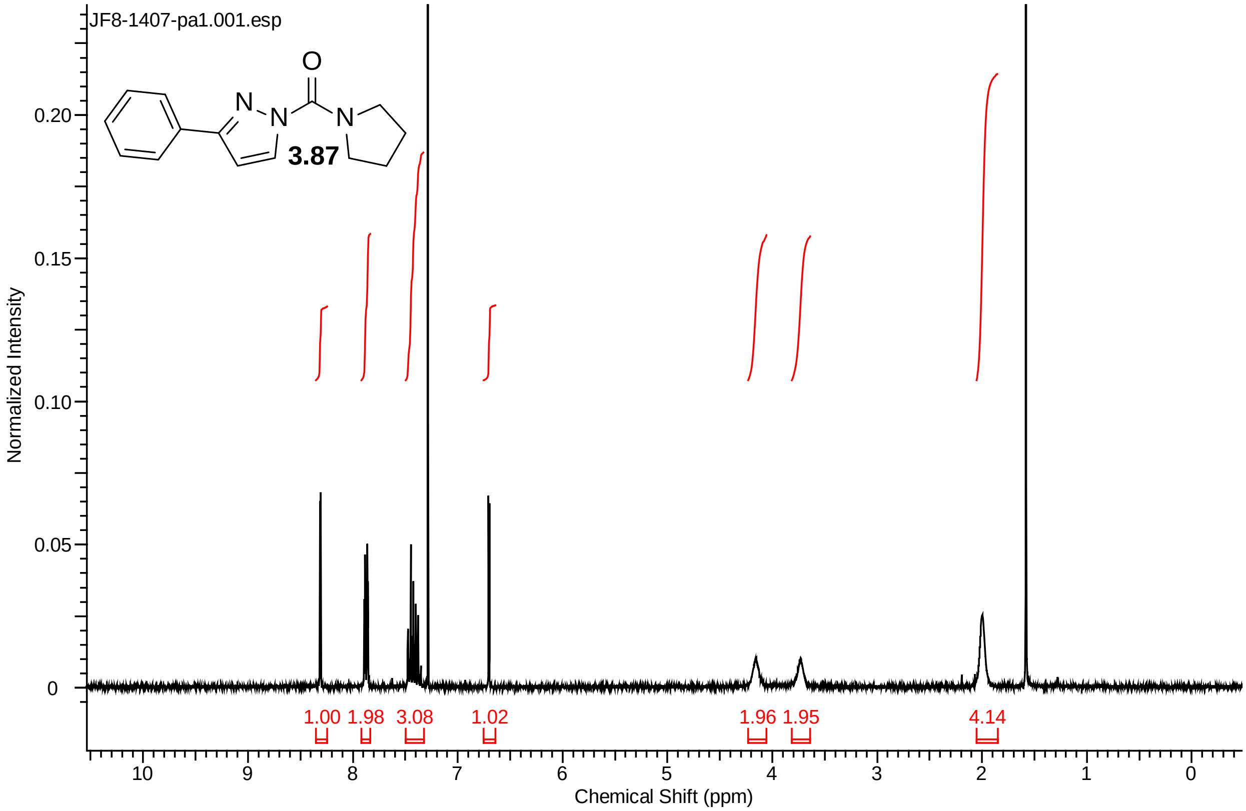

JF11-1981-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
187.5811
150.6960
148.4305
139.1611
138.5901
128.6443
127.9788
127.7715
124.6332
123.8478
119.8658
119.6076
74.5841
60.5181
55.3179
46.1757
45.2484
28.9132
25.0949
24.9858
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

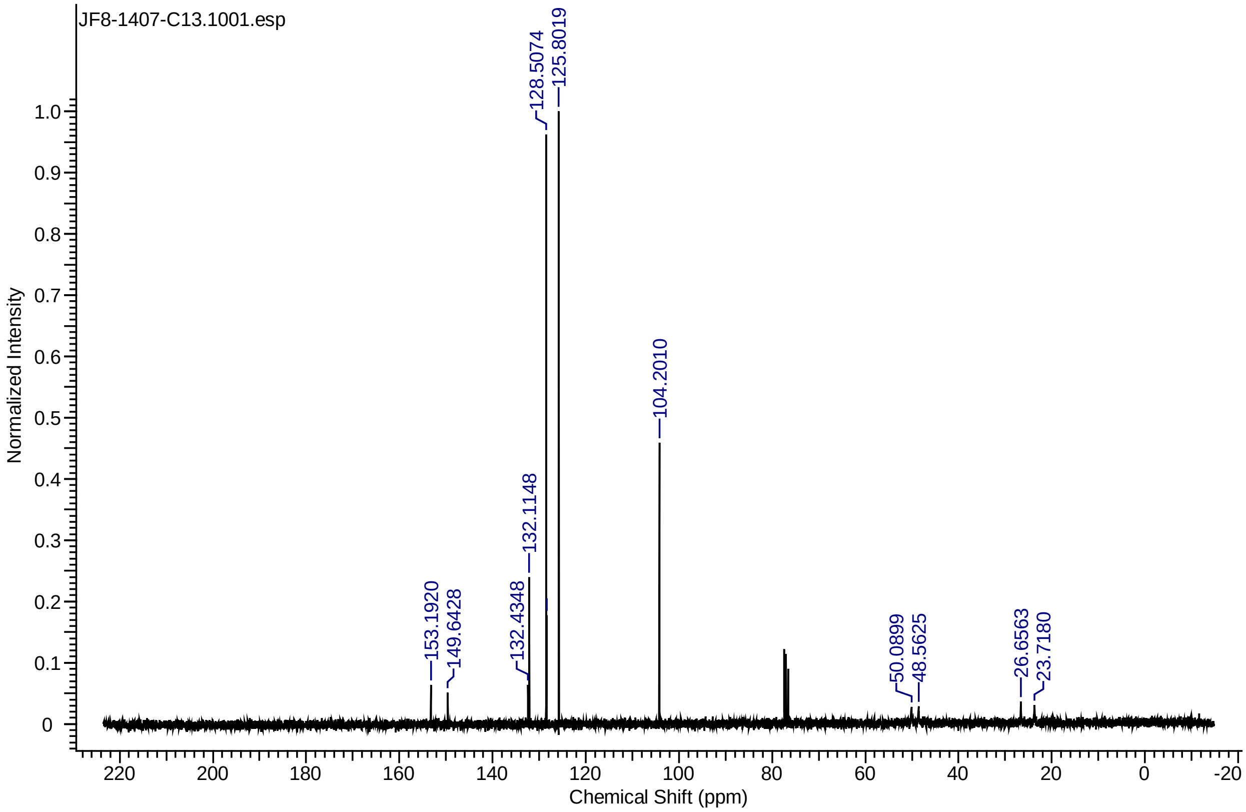

JF11-2081-H.001.esp
NO2
O
NH
HN
N
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
1.00
3.00
3.03
1.09
1.04
1.01
3.03
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

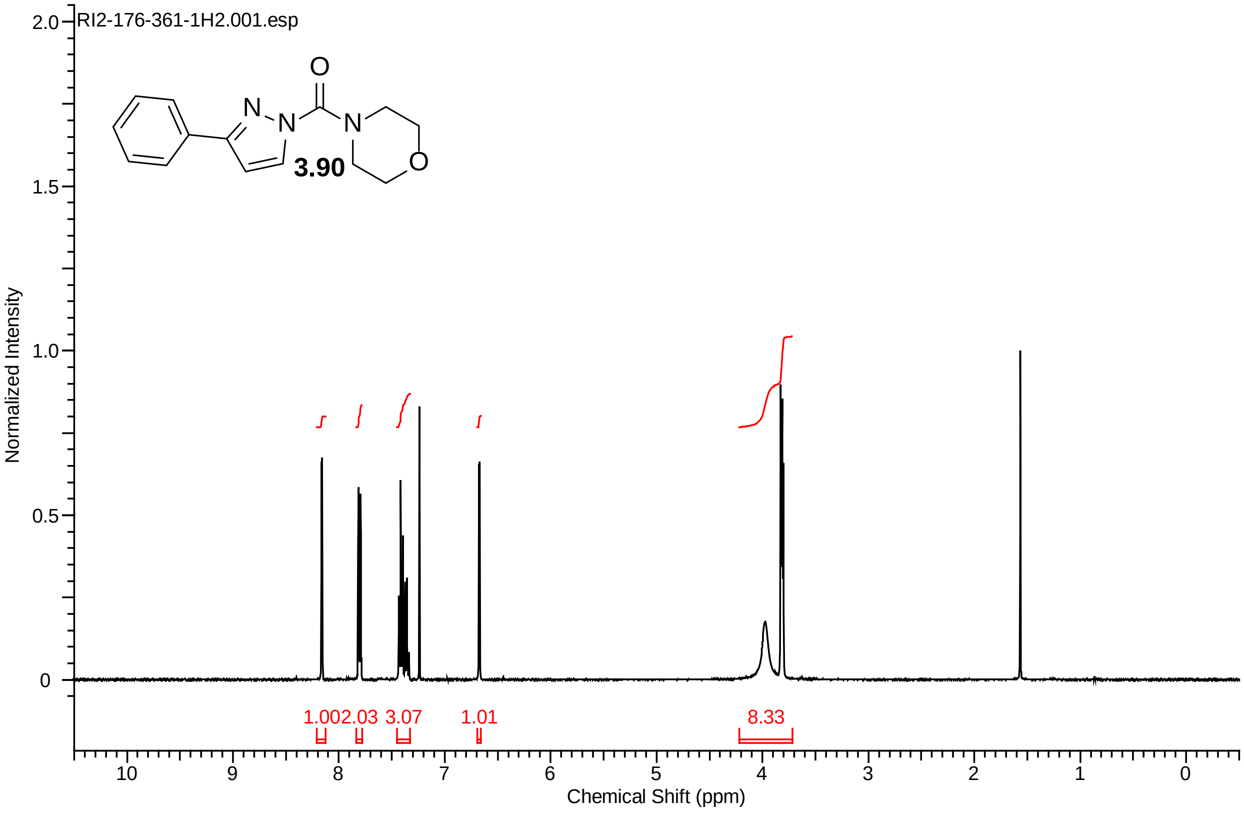

JF11-2081-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
153.2452
145.6669
145.5359
141.7830
138.9611
130.0153
128.0516
124.8951
120.6913
118.9021
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

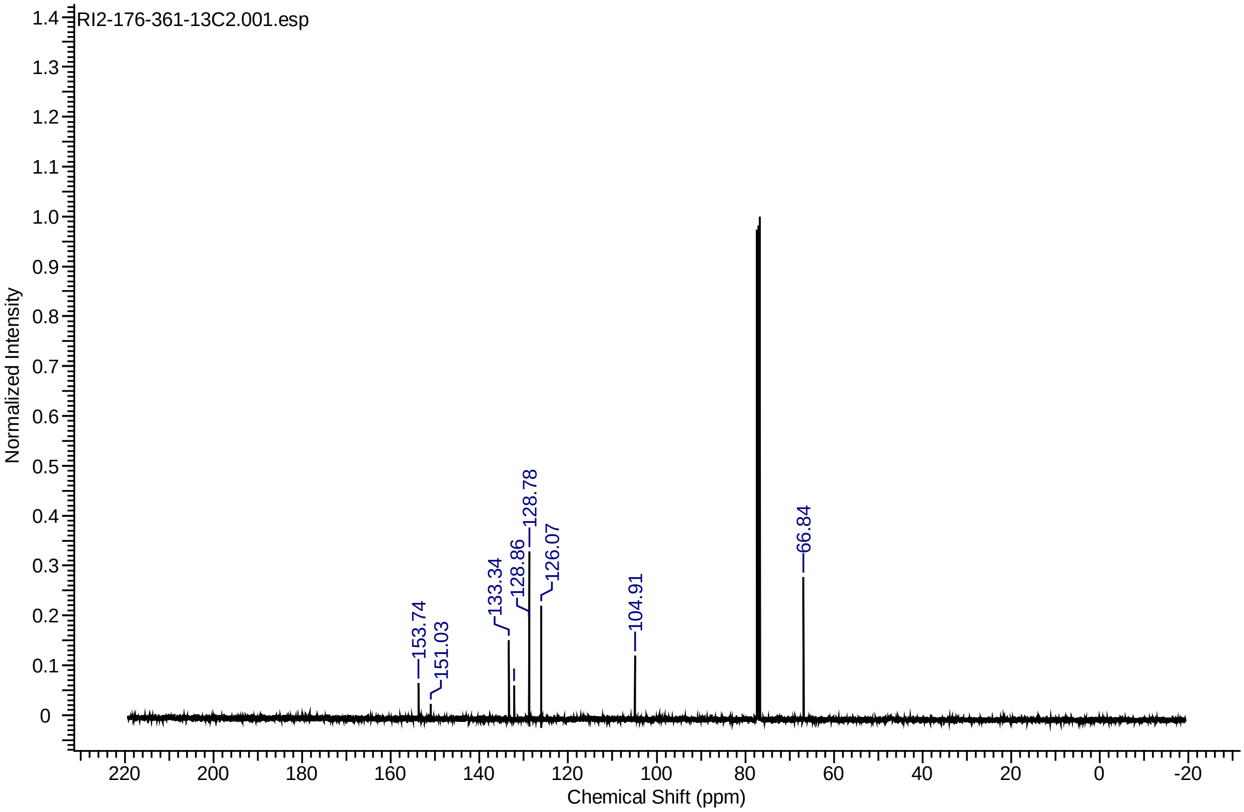

RI2-135-321-1H.001.esp
O
O
NH
N
H
3.86
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.00
2.04
5.13
3.24
0.96
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

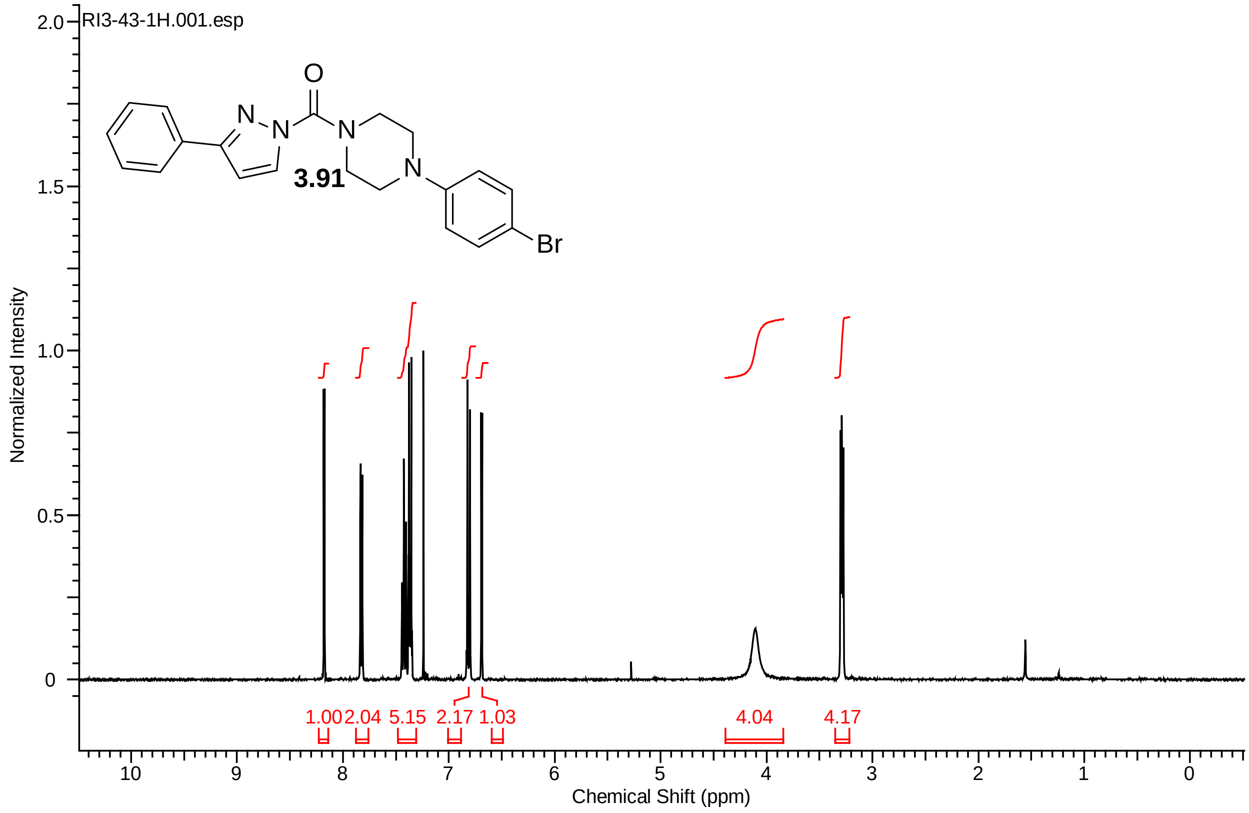

RI2-135-321-13C.001.esp
Normalized Intensity
2.0
1.5
1.0
0.5
0
133.57
130.30
129.53
128.53
126.70
125.99
121.45
121.34
92.96
77.24
72.38
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

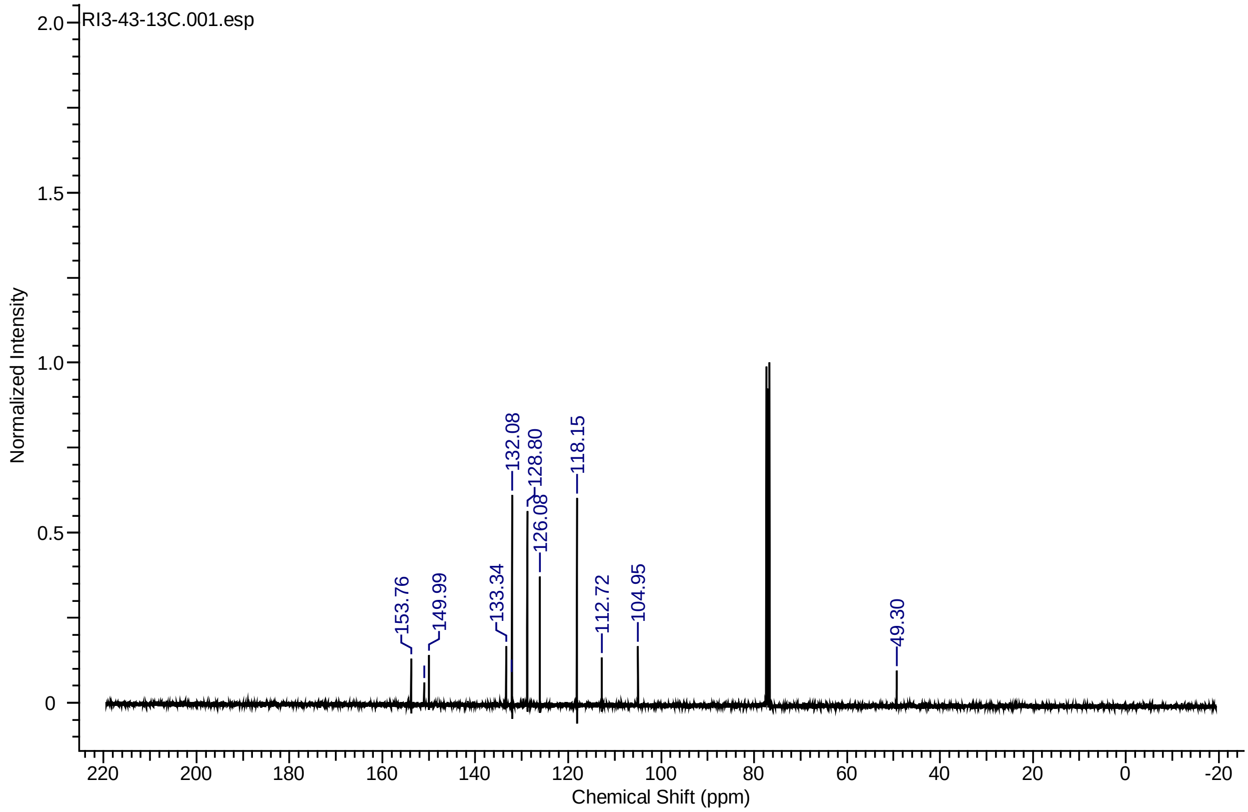

JF8-1407-pa1.001.esp
O
N
N
N
3.87
Normalized Intensity
0.20
0.15
0.10
0.05
0
1.00
1.98
3.08
1.02
1.96
1.95
4.14
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

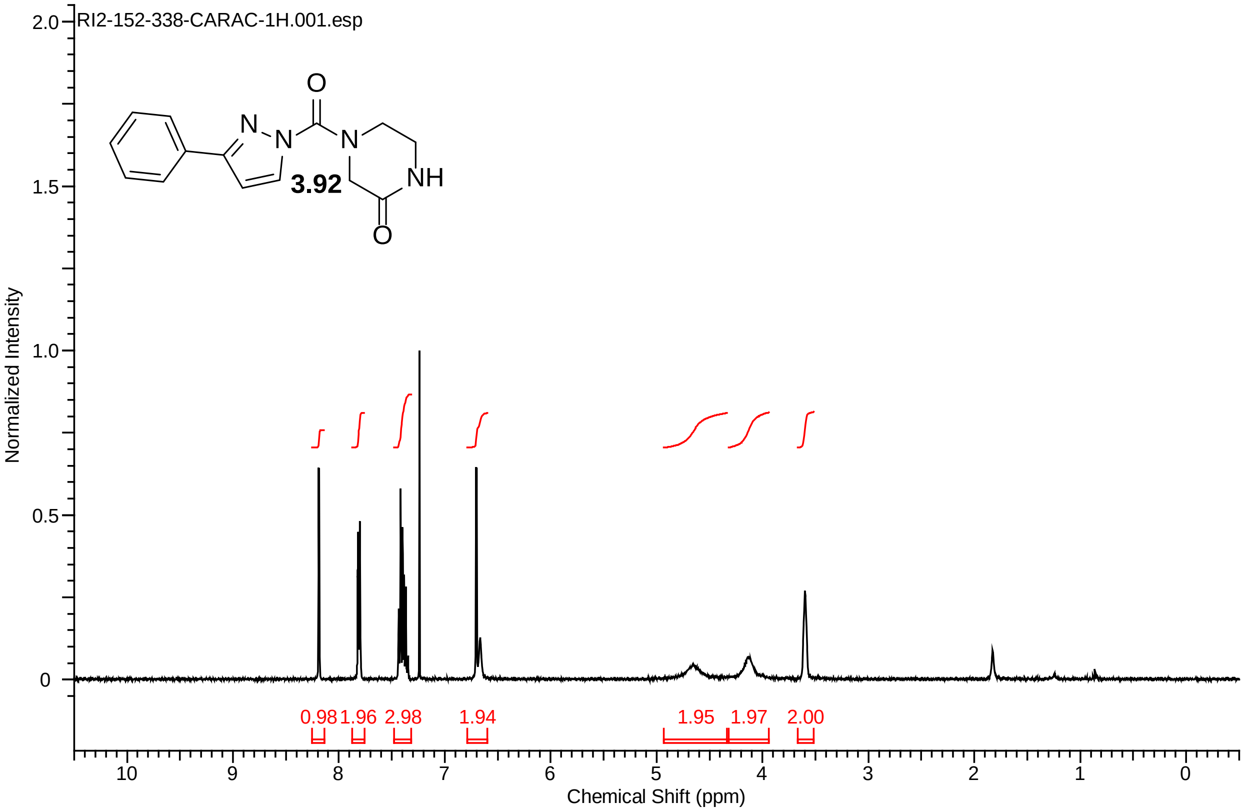

JF8-1407-C13.1001.esp
128.5074
125.8019
104.2010
132.1148
153.1920
149.6428
132.4348
50.0899
48.5625
26.6563
23.7180
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

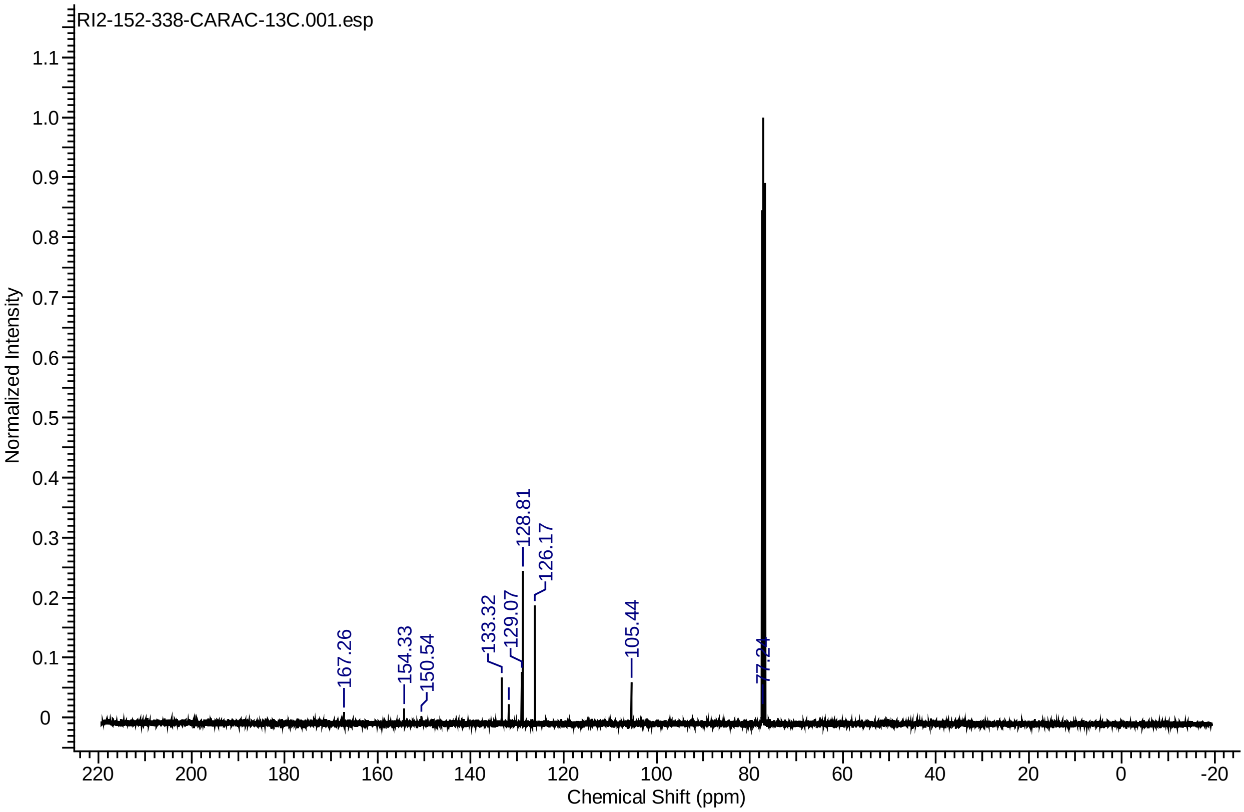

RI2-176-361-1H2.001.esp
3.90
O
N
N
N
O
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.00
2.03
3.07
1.01
8.33
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

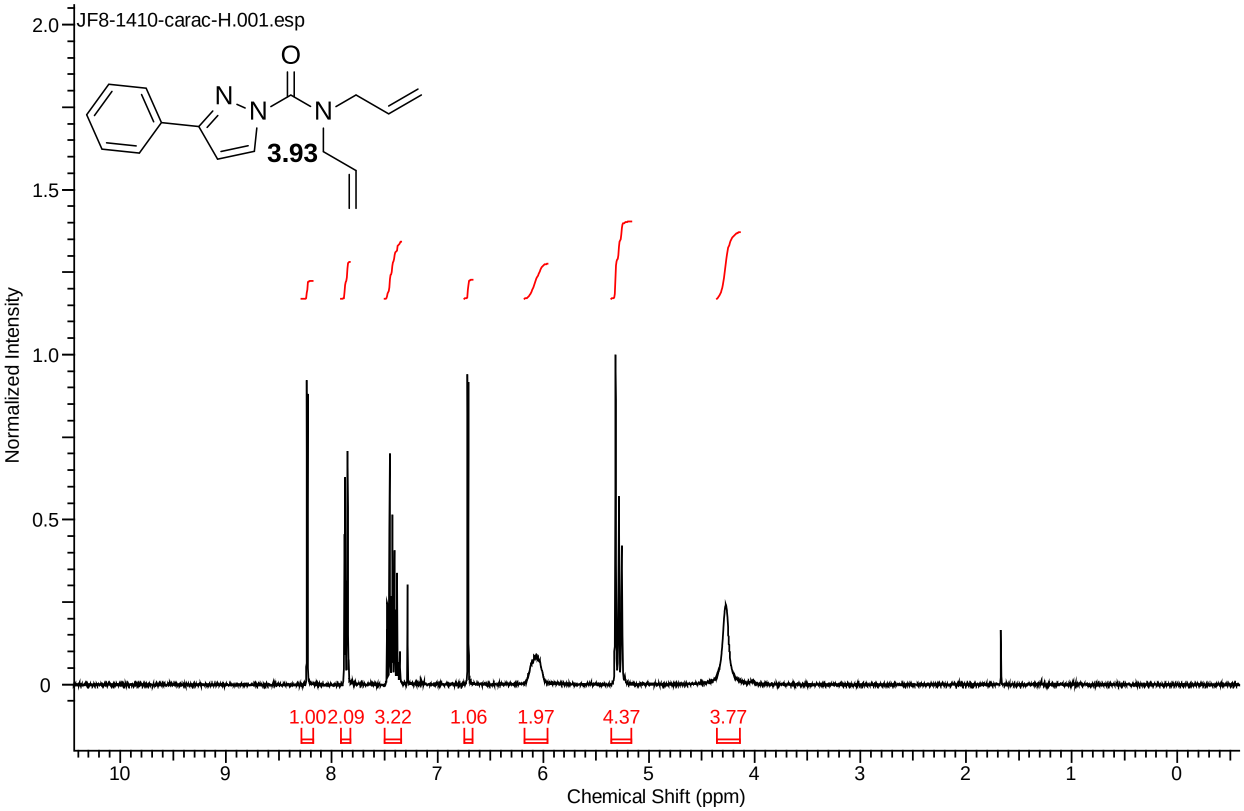

RI2-176-361-13C2.001.esp
Normalized Intensity
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
153.74
151.03
133.34
128.86
128.78
126.07
104.91
66.84
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

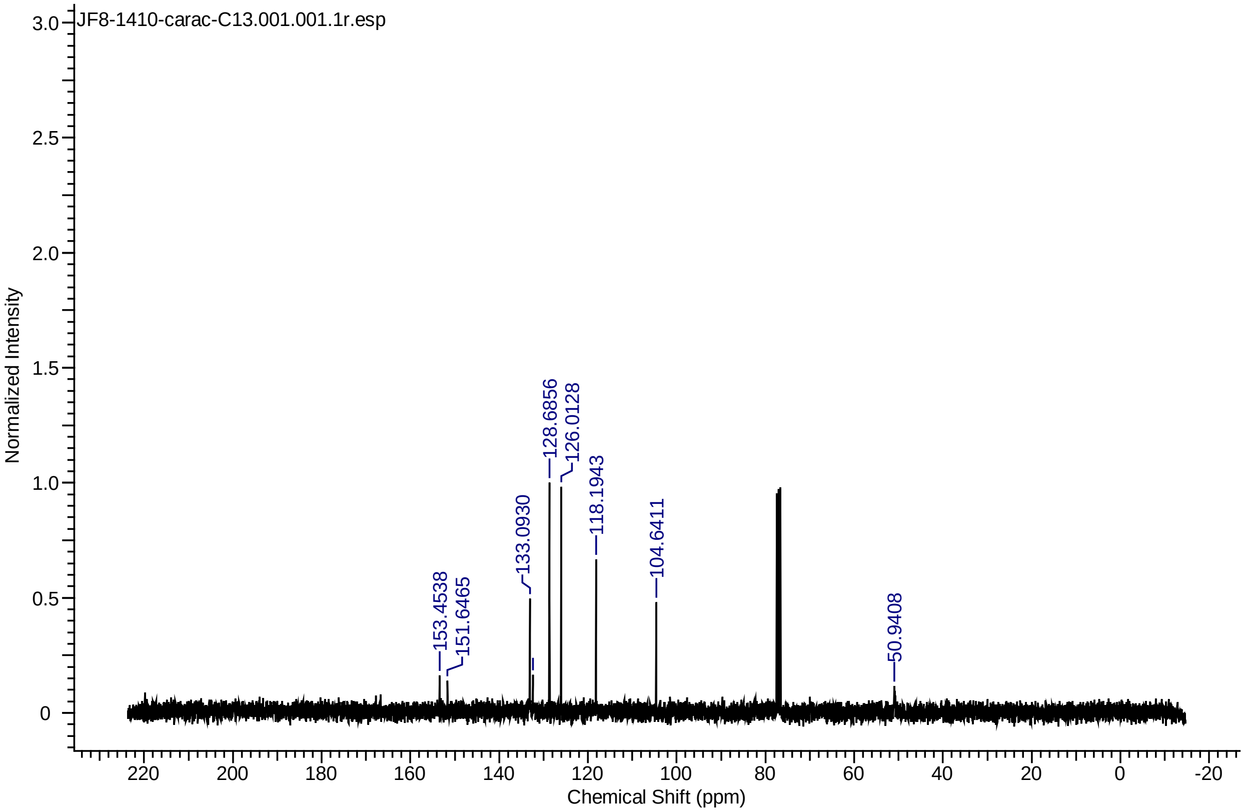

RI3-43-1H.001.esp
O
N
N
N
N
3.91
Br
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.00
2.04
5.15
2.17
1.03
4.04
4.17
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

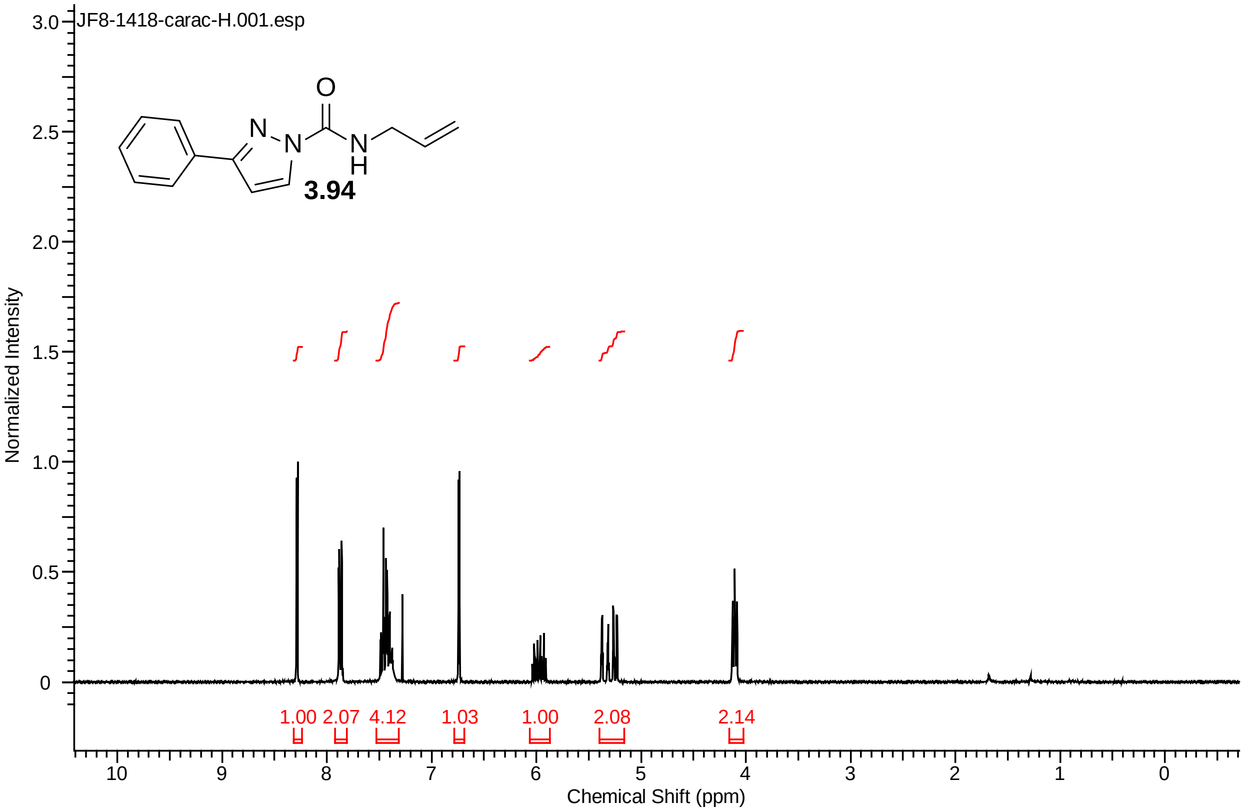

RI3-43-13C.001.esp
Normalized Intensity
2.0
1.5
1.0
0.5
0
153.76
149.99
133.34
132.08
128.80
126.08
118.15
112.72
104.95
49.30
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

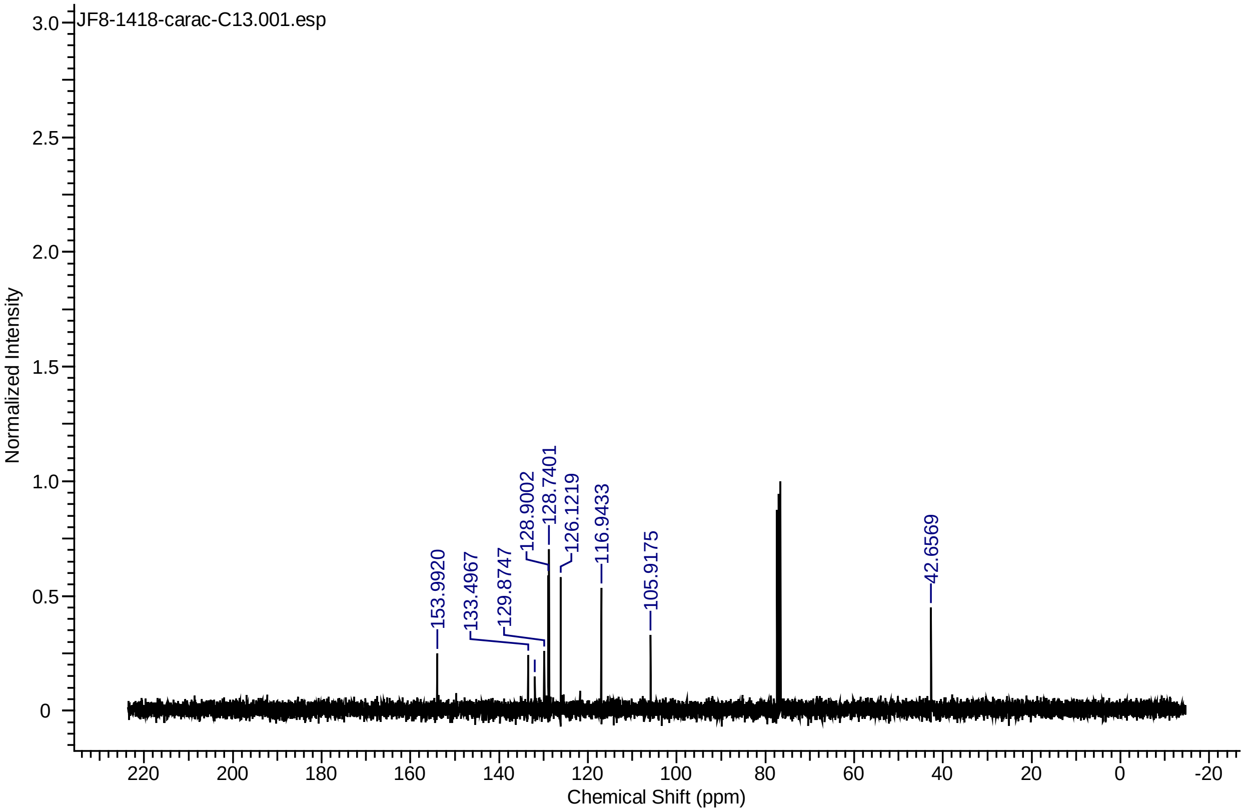

RI2-152-338-CARAC-1H.001.esp
O
N
N
N
NH
O
3.92
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.98
1.96
2.98
1.94
1.95
1.97
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

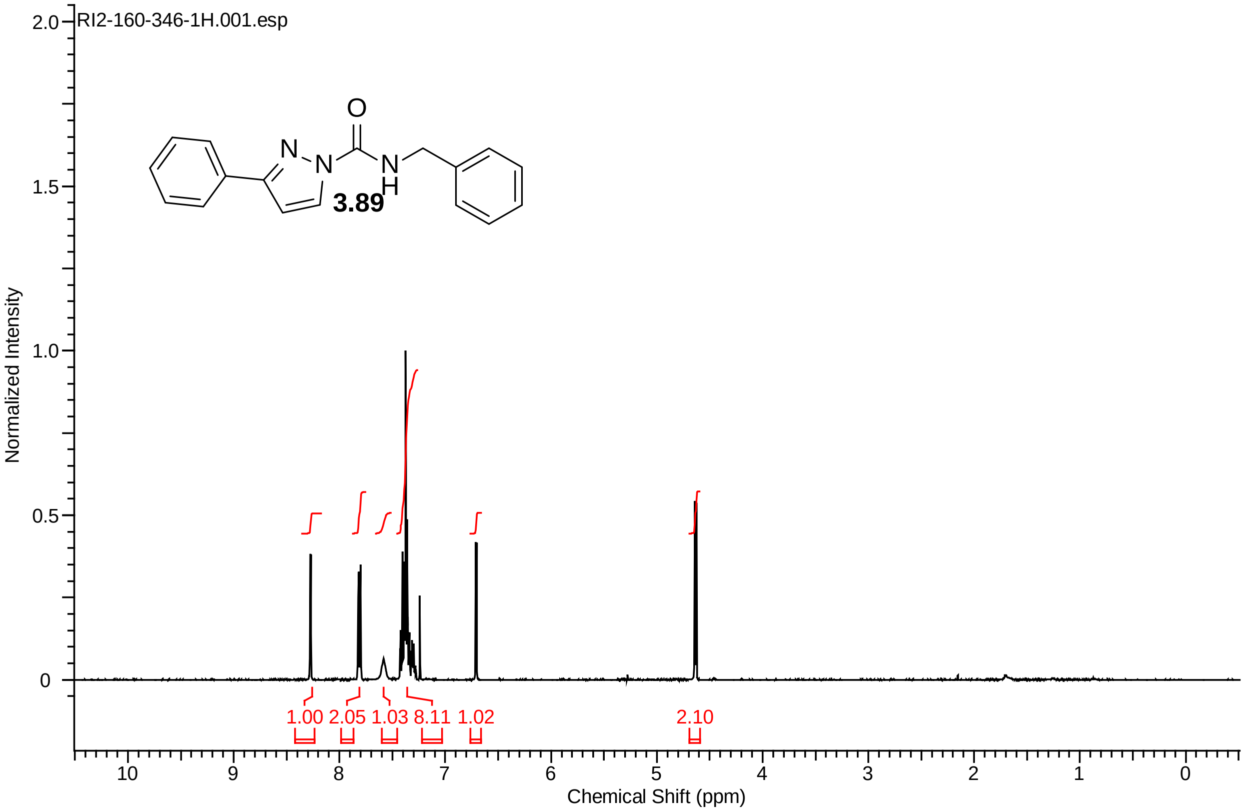

RI2-152-338-CARAC-13C.001.esp
Normalized Intensity
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
167.26
154.33
150.54
133.32
129.07
128.81
126.17
105.44
77.24
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

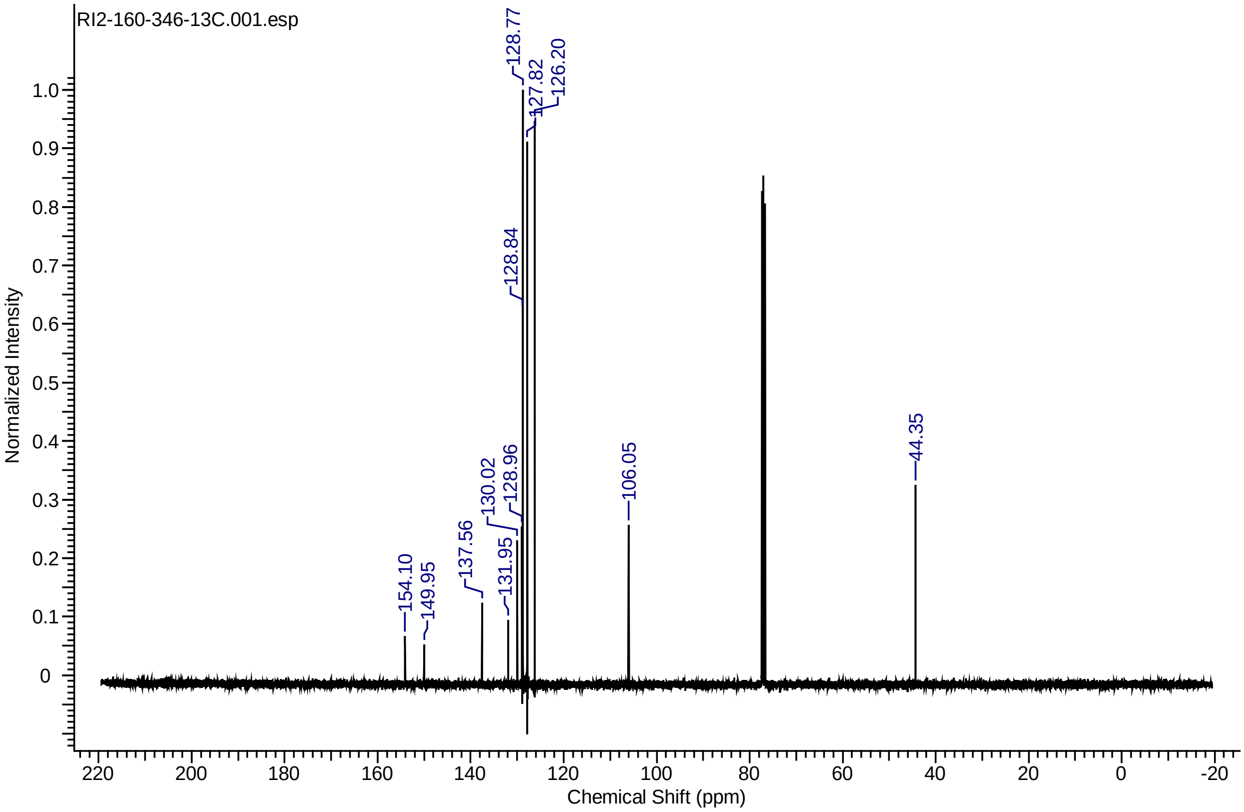

JF8-1410-carac-H.001.esp
O
N
N
N
3.93
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.00
2.09
3.22
1.06
1.97
4.37
3.77
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

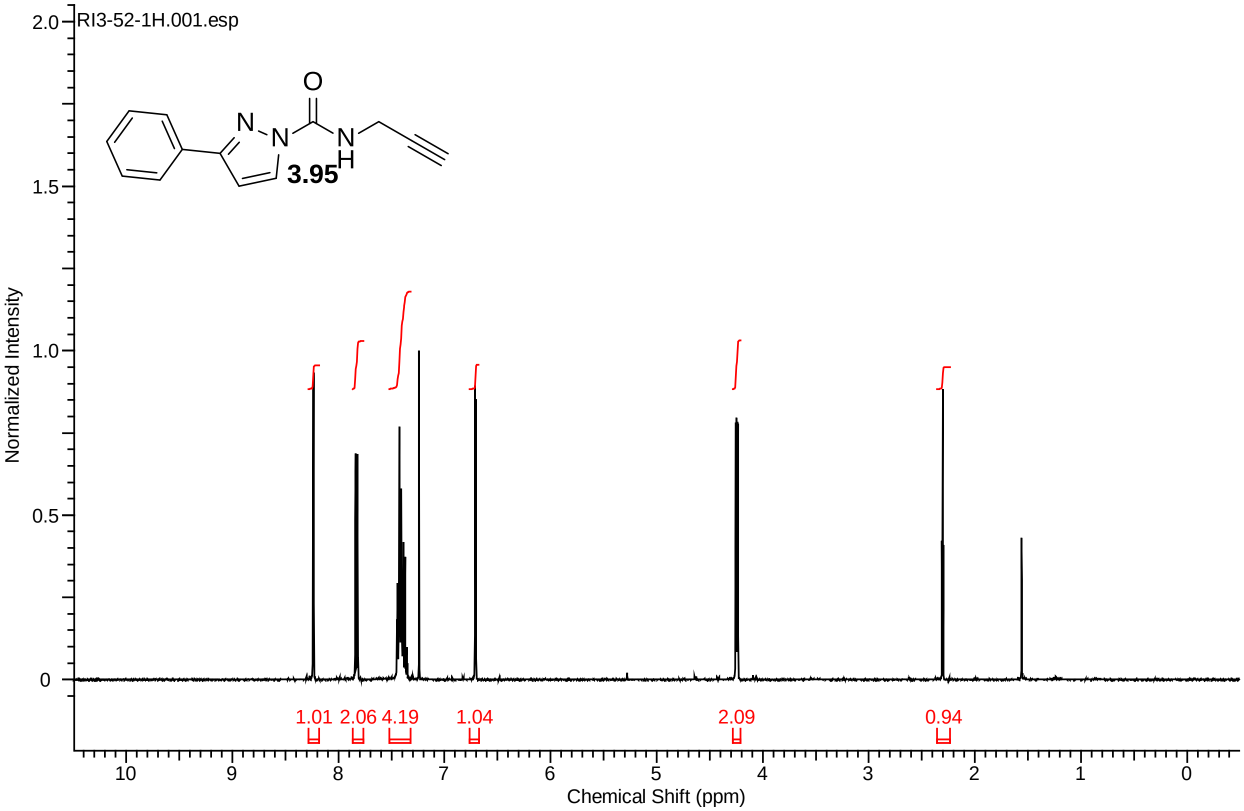

JF8-1410-carac-C13.001.001.1r.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
153.4538
151.6465
133.0930
128.6856
126.0128
118.1943
104.6411
50.9408
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF8-1418-carac-H.001.esp
O
N
N
N
H
3.94
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)

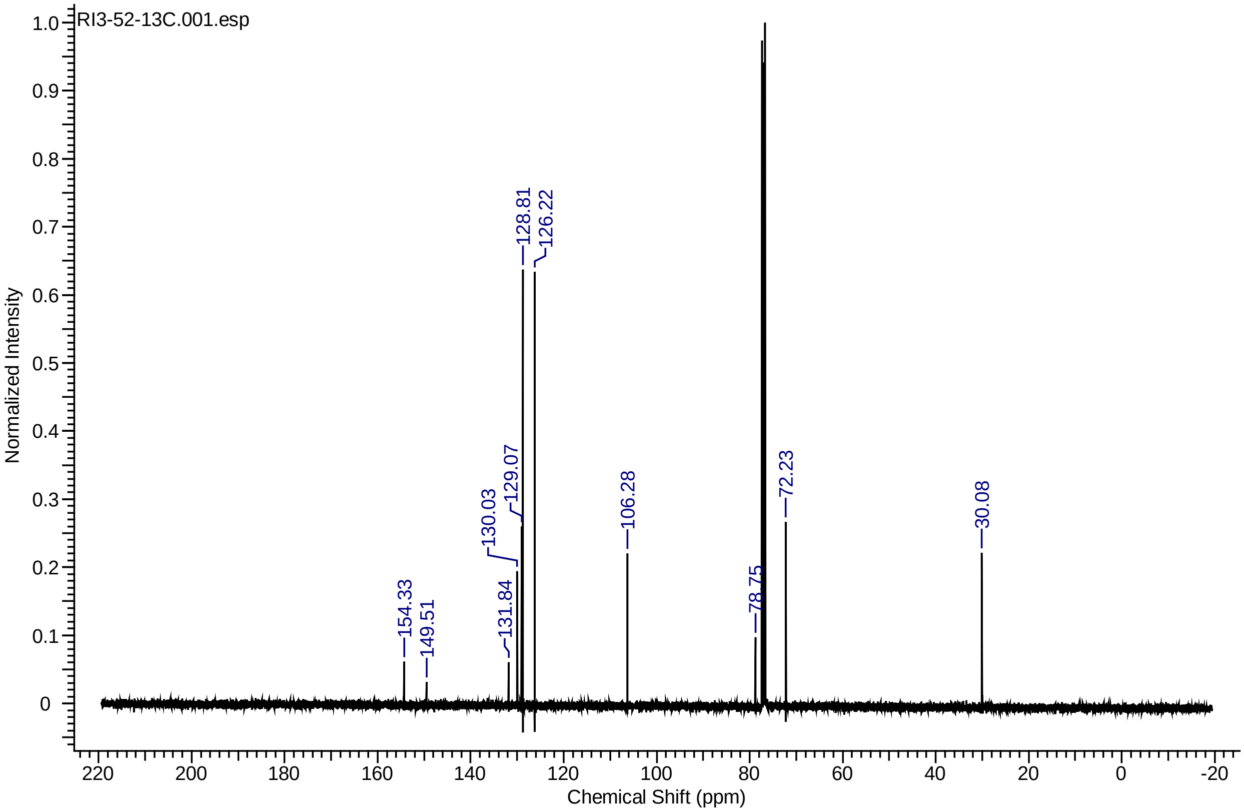

JF8-1418-carac-C13.001.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
153.9920
133.4967
129.8747
128.9002
128.7401
126.1219
116.9433
105.9175
42.6569
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

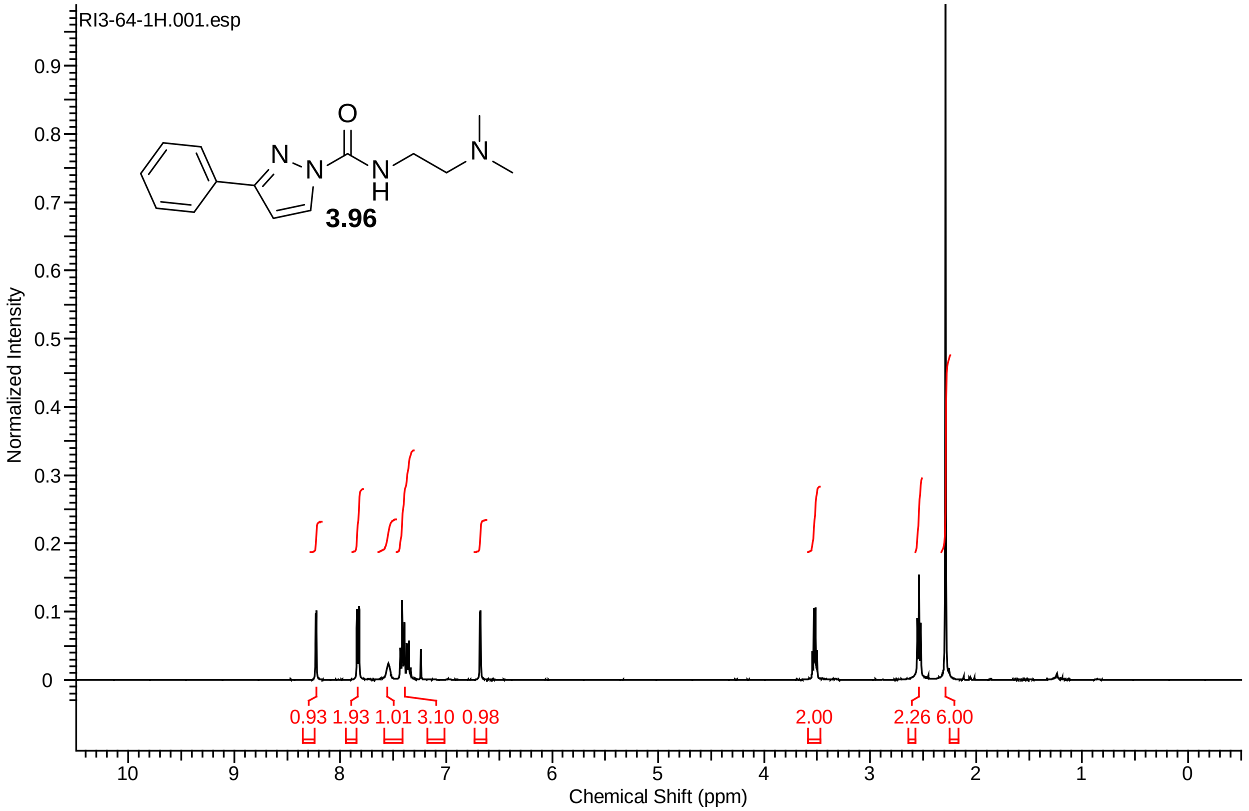

RI2-160-346-1H.001.esp
3.89
O
N
N
N
H
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.00
2.05
1.03
8.11
1.02
2.10
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

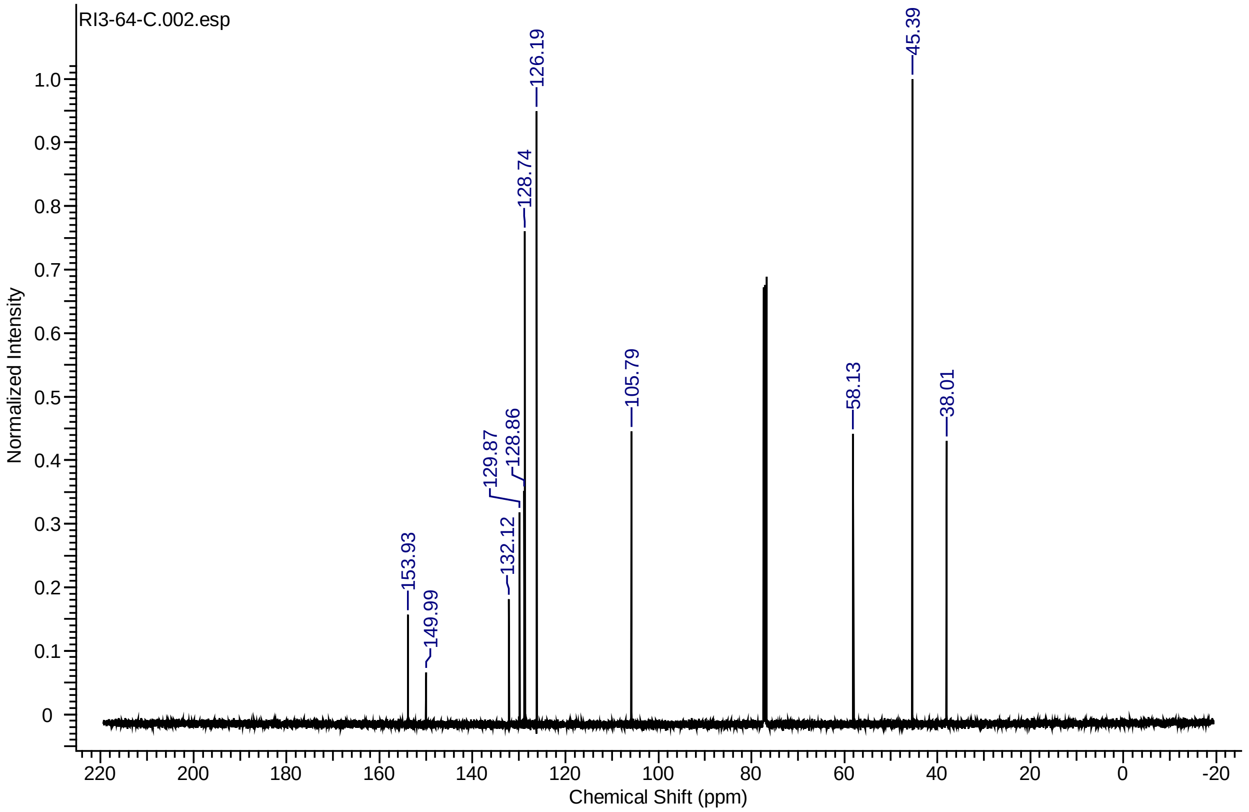

RI2-160-346-13C.001.esp
128.77
127.82
126.20
128.84
154.10
149.95
137.56
131.95
130.02
128.96
106.05
44.35
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

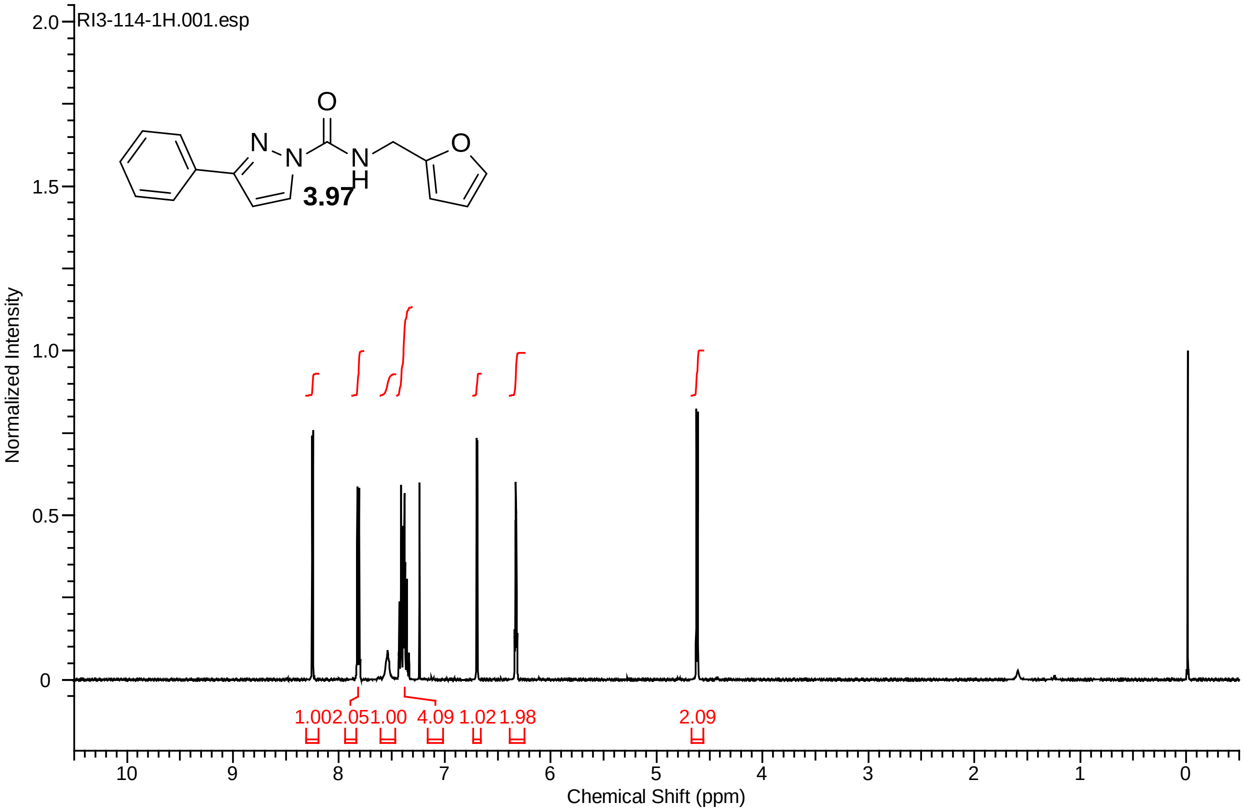

RI3-52-1H.001.esp
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.01
2.06
4.19
1.04
2.09
0.94
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
O
N
N
N
H

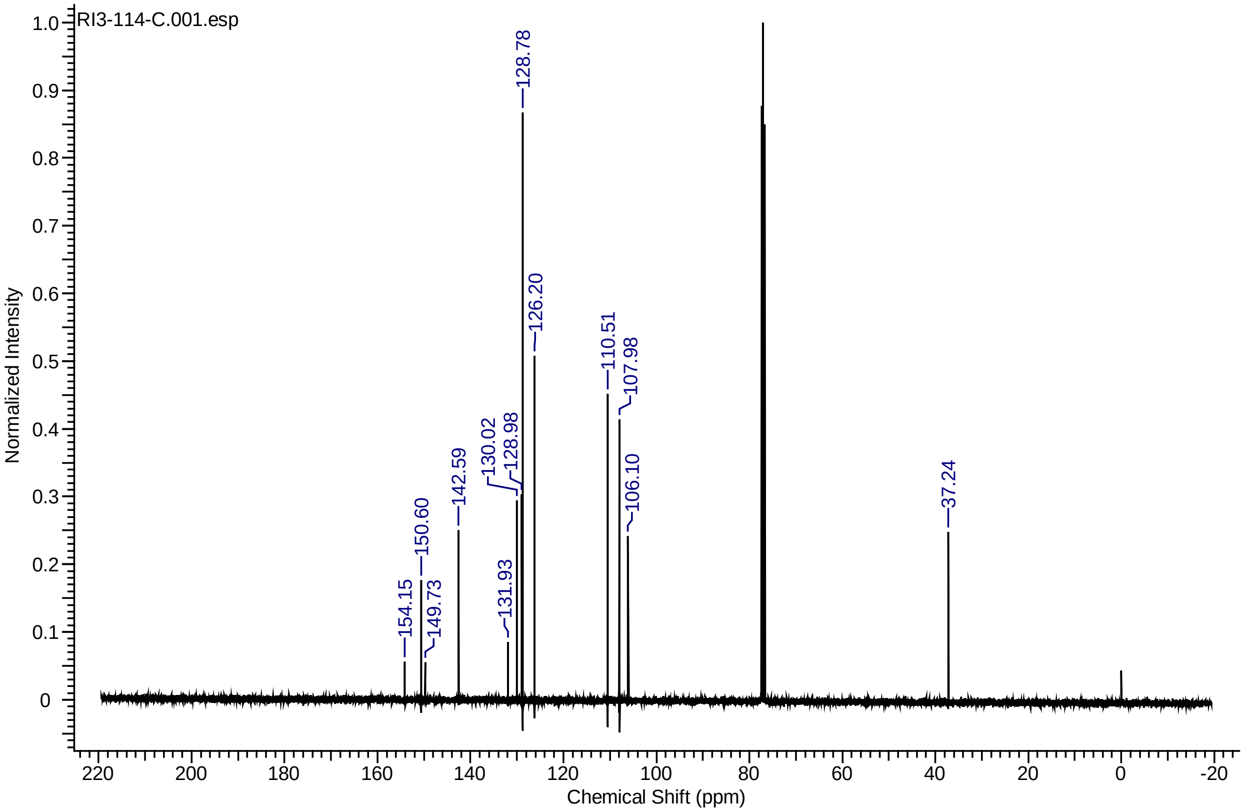
3.95

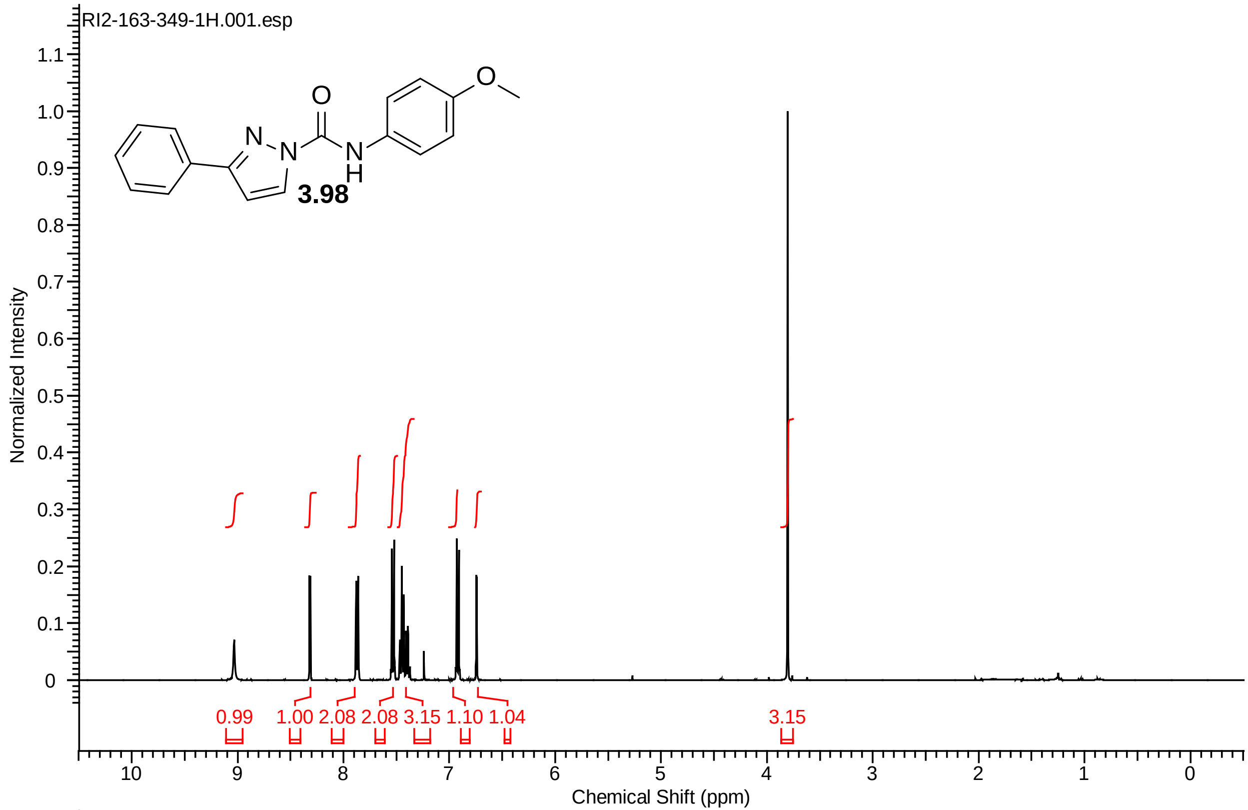

RI3-52-13C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
154.33
149.51
131.84
130.03
129.07
128.81
126.22
106.28
78.75
72.23
30.08
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

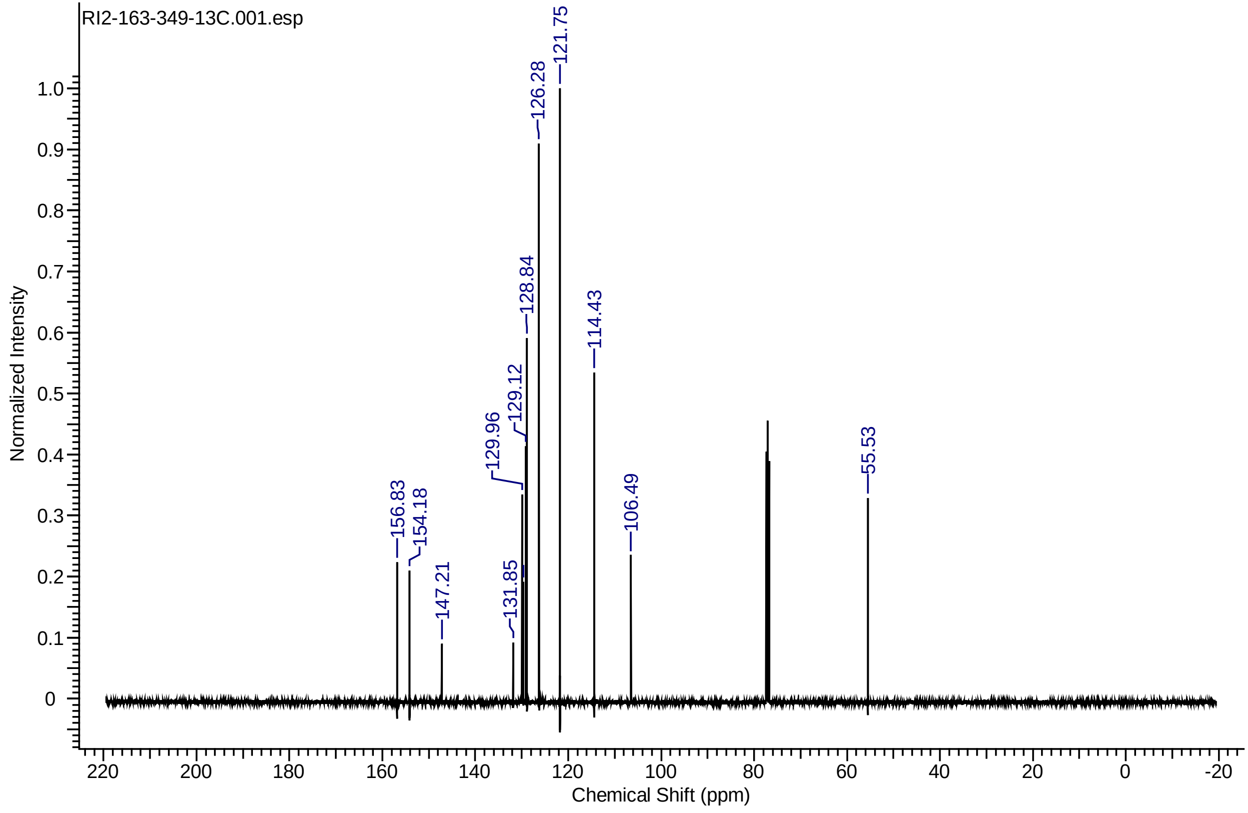

RI3-64-1H.001.esp
3.96
O
N
N
N
H
N
Normalized Intensity
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.93
1.93
1.01
3.10
0.98
2.00
2.26
6.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

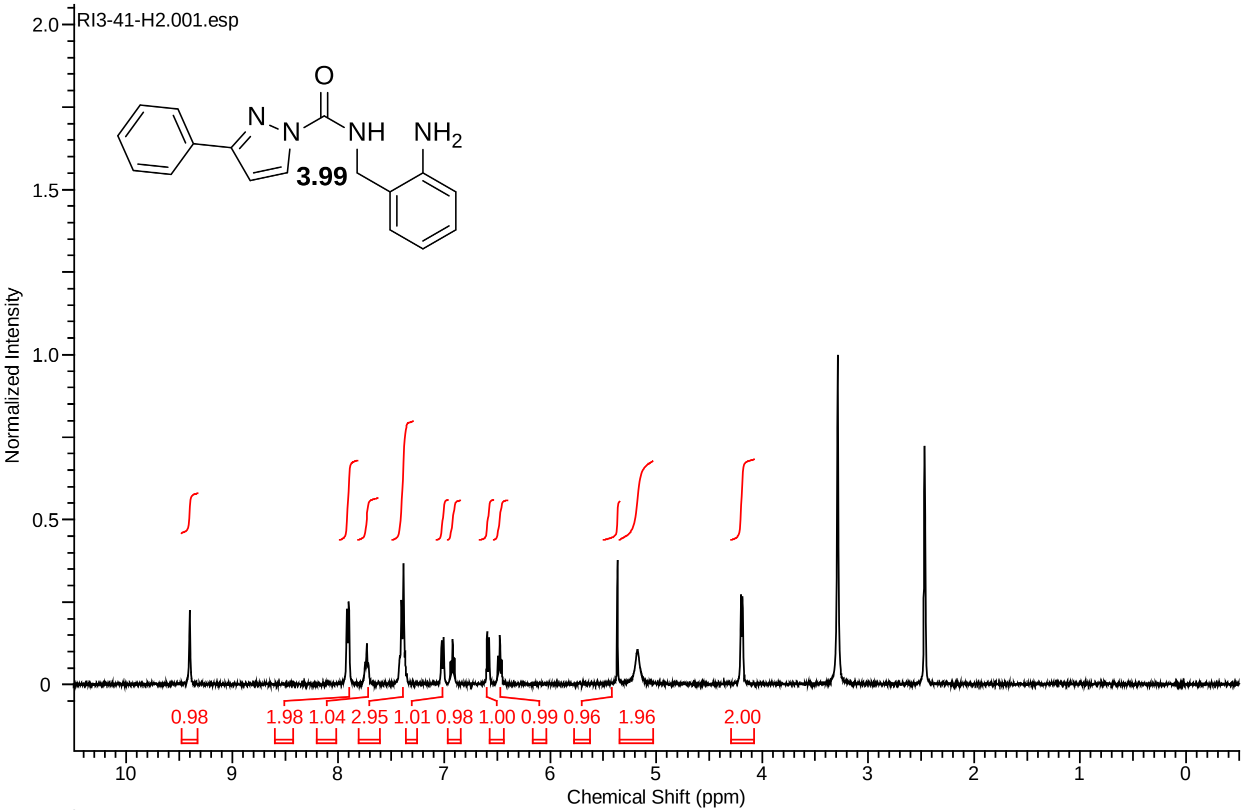

RI3-64-C.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
153.93
149.99
132.12
129.87
128.86
128.74
126.19
105.79
58.13
45.39
38.01
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

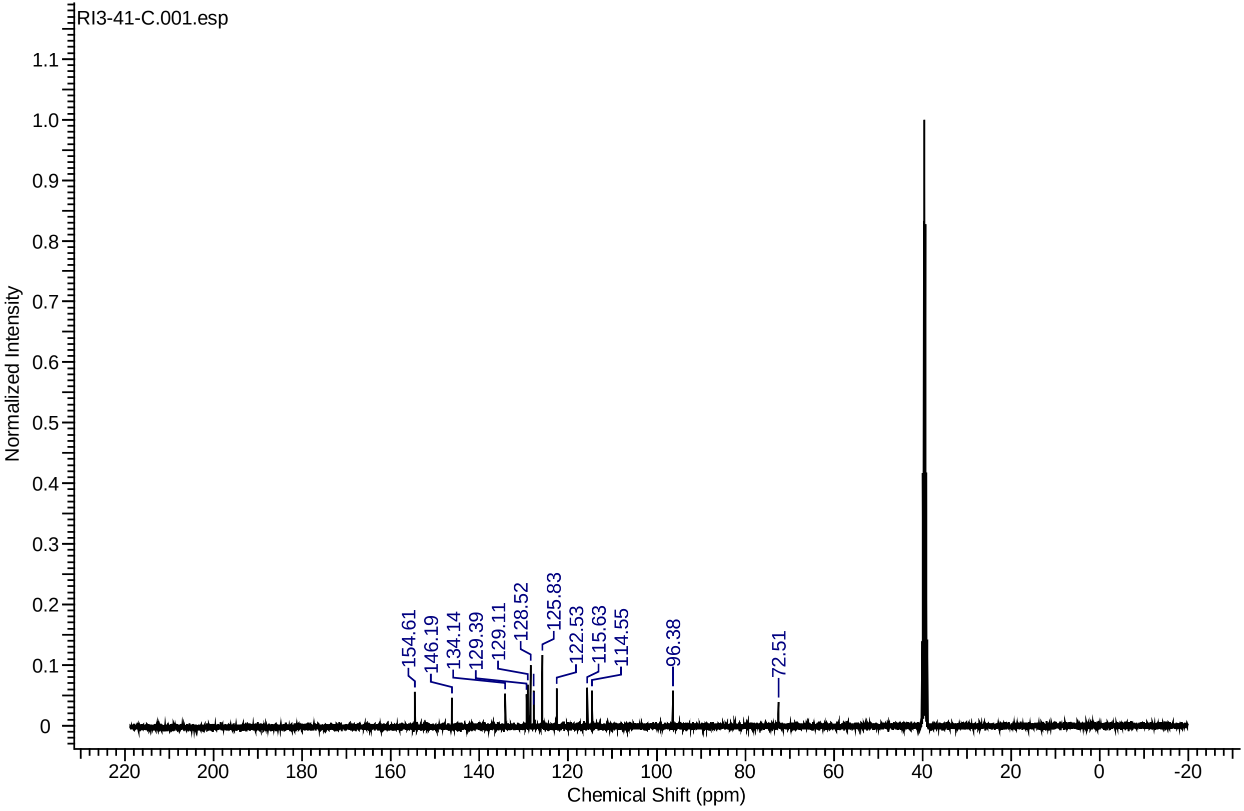

RI3-114-1H.001.esp
3.97
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.00
2.05
1.00
4.09
1.02
1.98
2.09
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

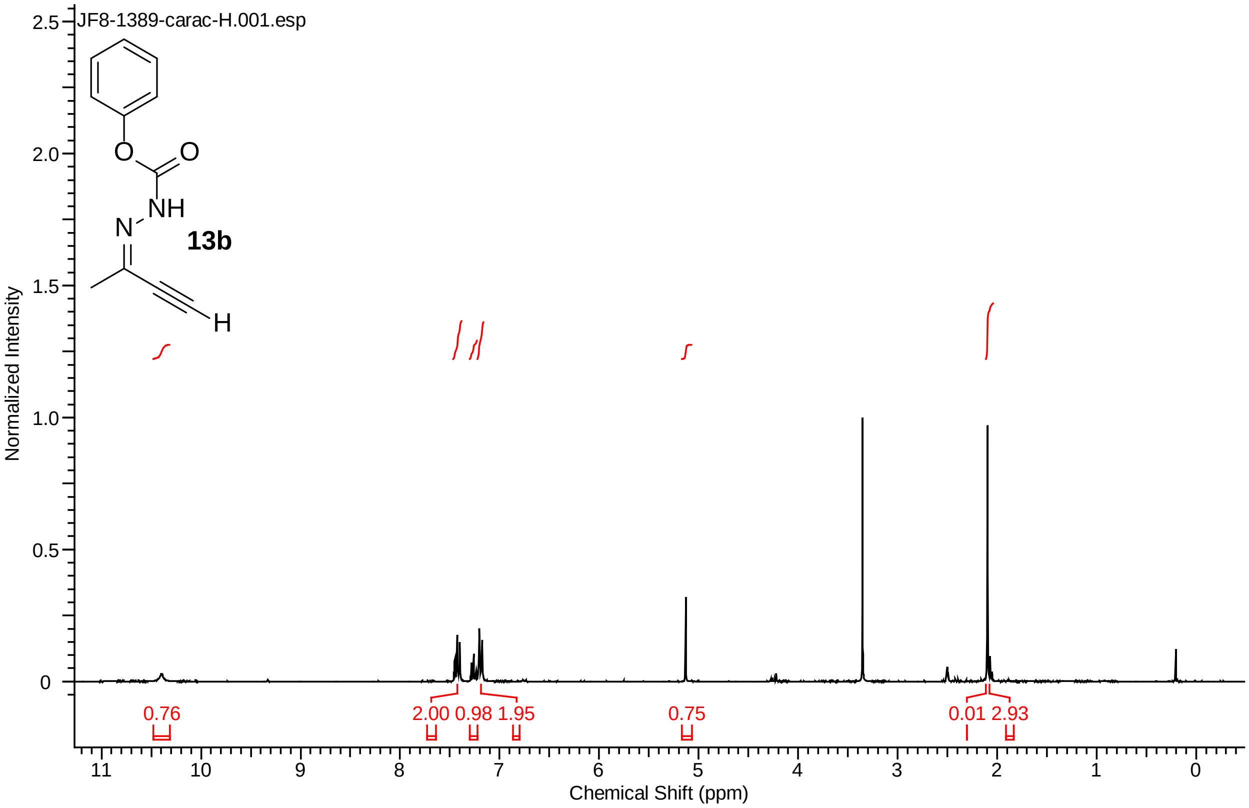

RI3-114-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
154.15
150.60
149.73
142.59
131.93
130.02
128.98
128.78
126.20
110.51
107.98
106.10
37.24
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

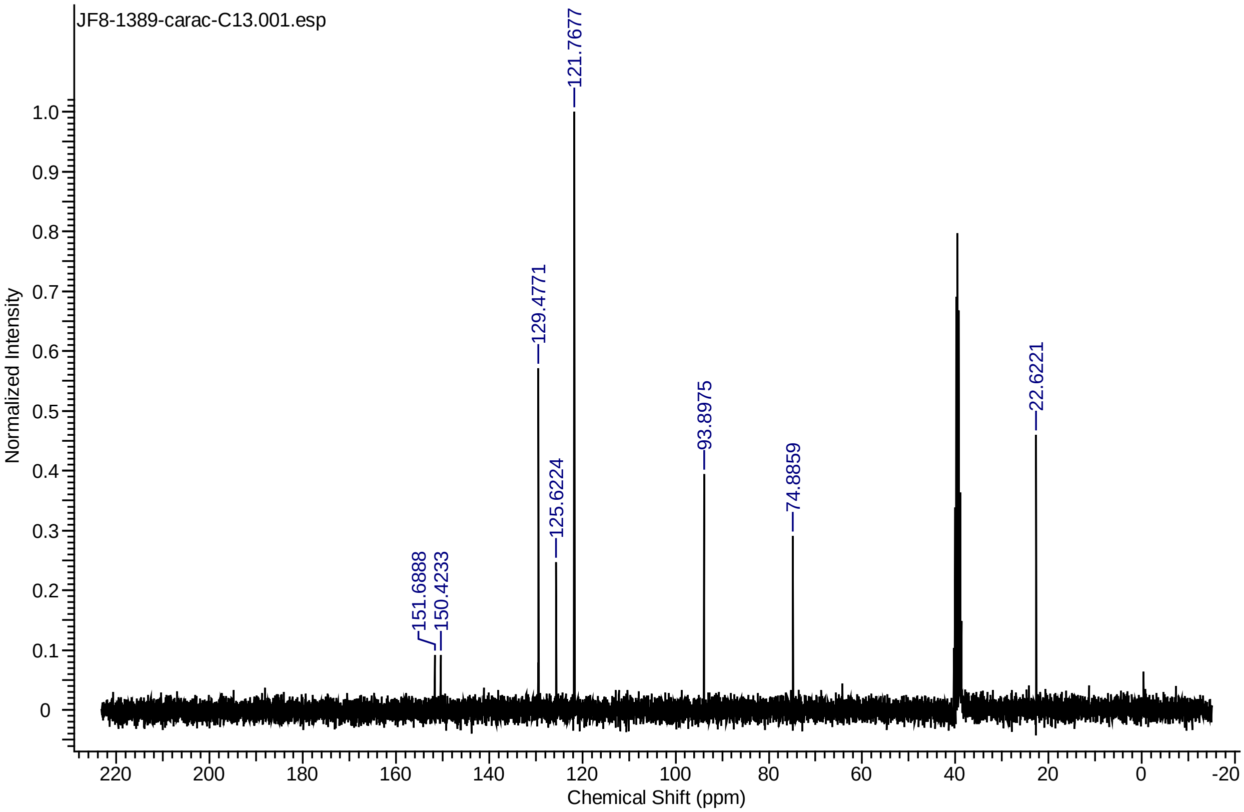

3.98
RI2-163-349-1H.001.esp
O
N
N
N
H
O
Normalized Intensity
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.99
1.00
2.08
2.08
3.15
1.10
1.04
3.15
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

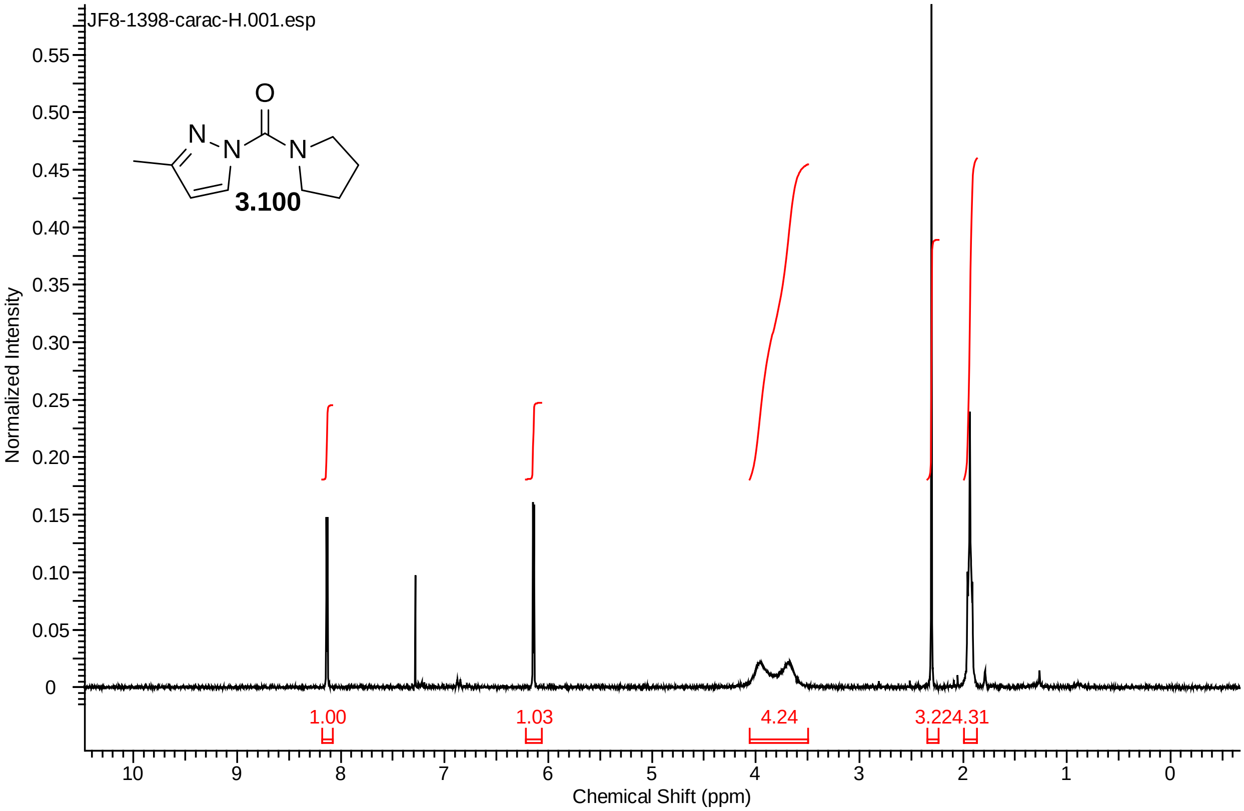

RI2-163-349-13C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
156.83
154.18
147.21
131.85
129.96
129.12
128.84
126.28
121.75
114.43
106.49
55.53
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

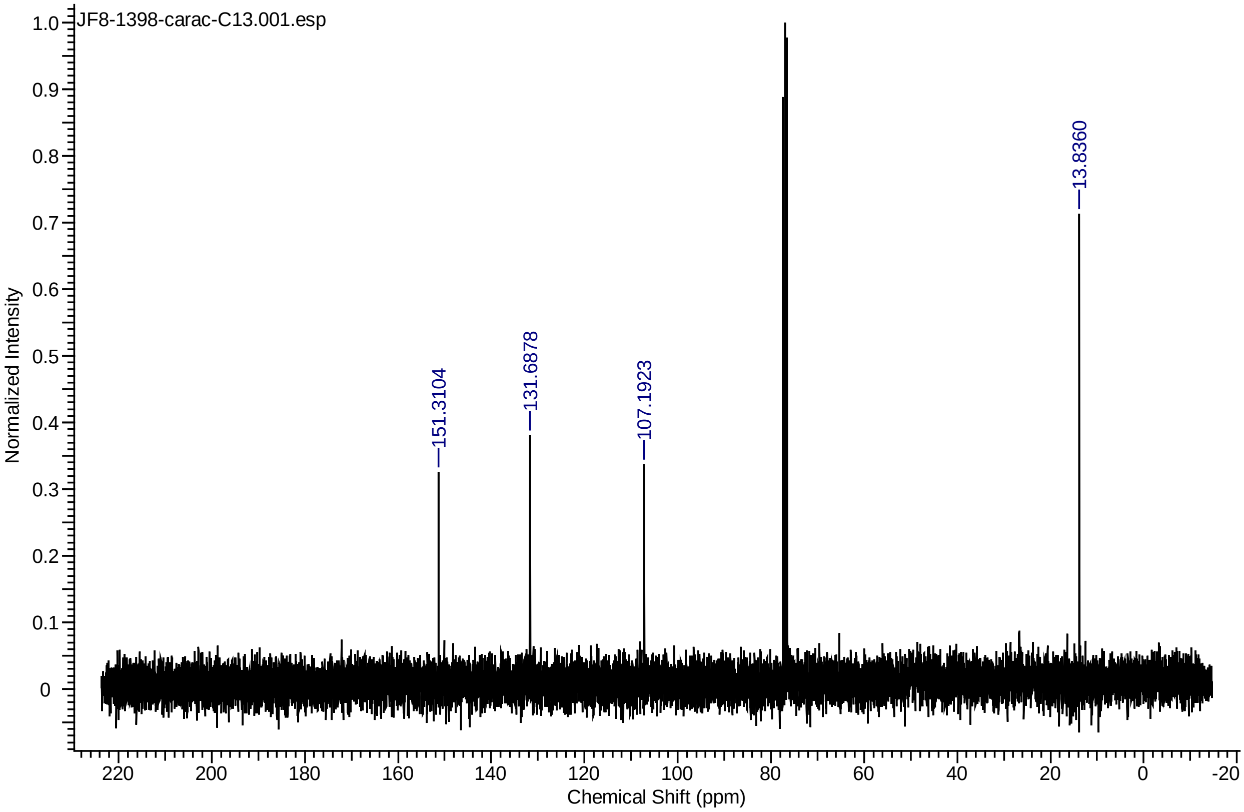

RI3-41-H2.001.esp
3.99
O
N
N
NH
NH2
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.98
1.98
1.04
2.95
1.01
0.98
1.00
0.99
0.96
1.96
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

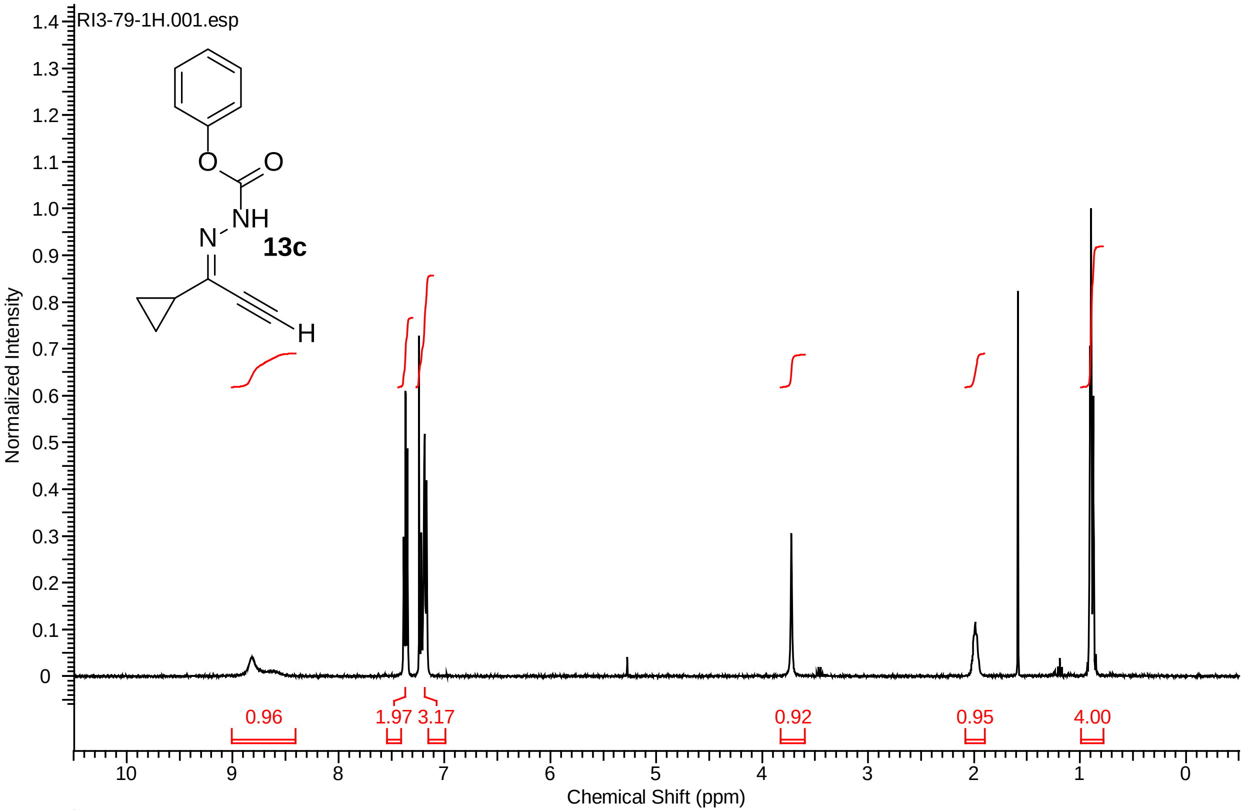

RI3-41-C.001.esp
Normalized Intensity
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
154.61
146.19
134.14
129.39
129.11
128.52
125.83
122.53
115.63
114.55
96.38
72.51
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

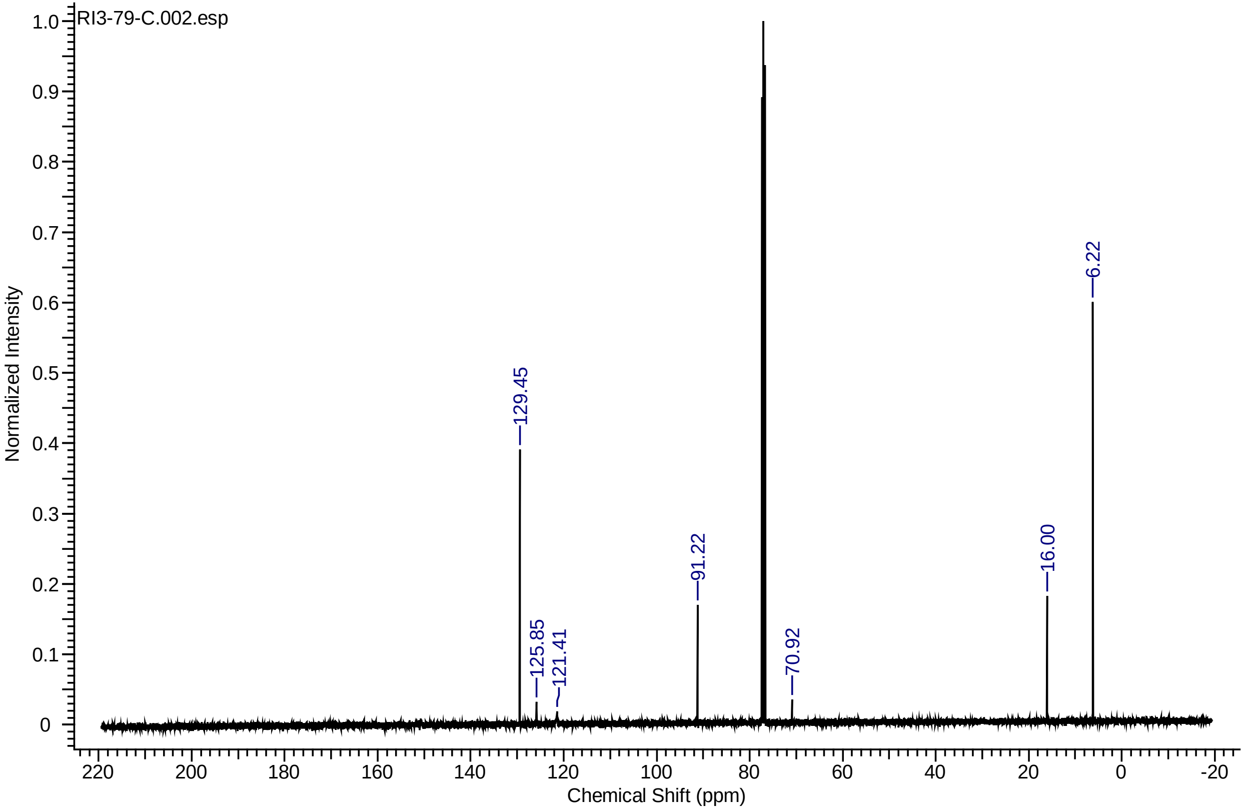

JF8-1389-carac-H.001.esp
O
O
NH
N
13b
H
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0
0.76
2.00
0.98
1.95
0.75
0.01
2.93
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

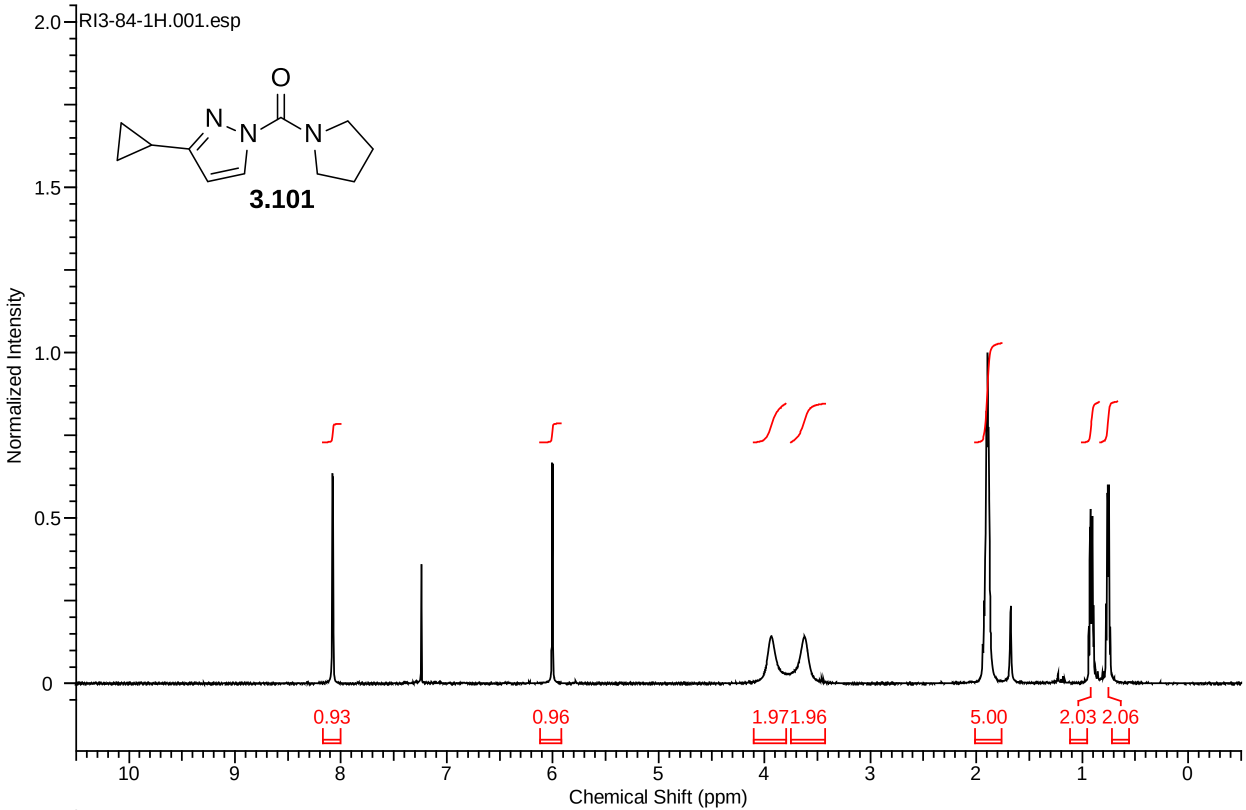

JF8-1389-carac-C13.001.esp
151.6888
150.4233
129.4771
125.6224
121.7677
93.8975
74.8859
22.6221
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF8-1398-carac-H.001.esp
O
N
N
N
3.100
Normalized Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
1.00
1.03
4.24
3.22
4.31
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

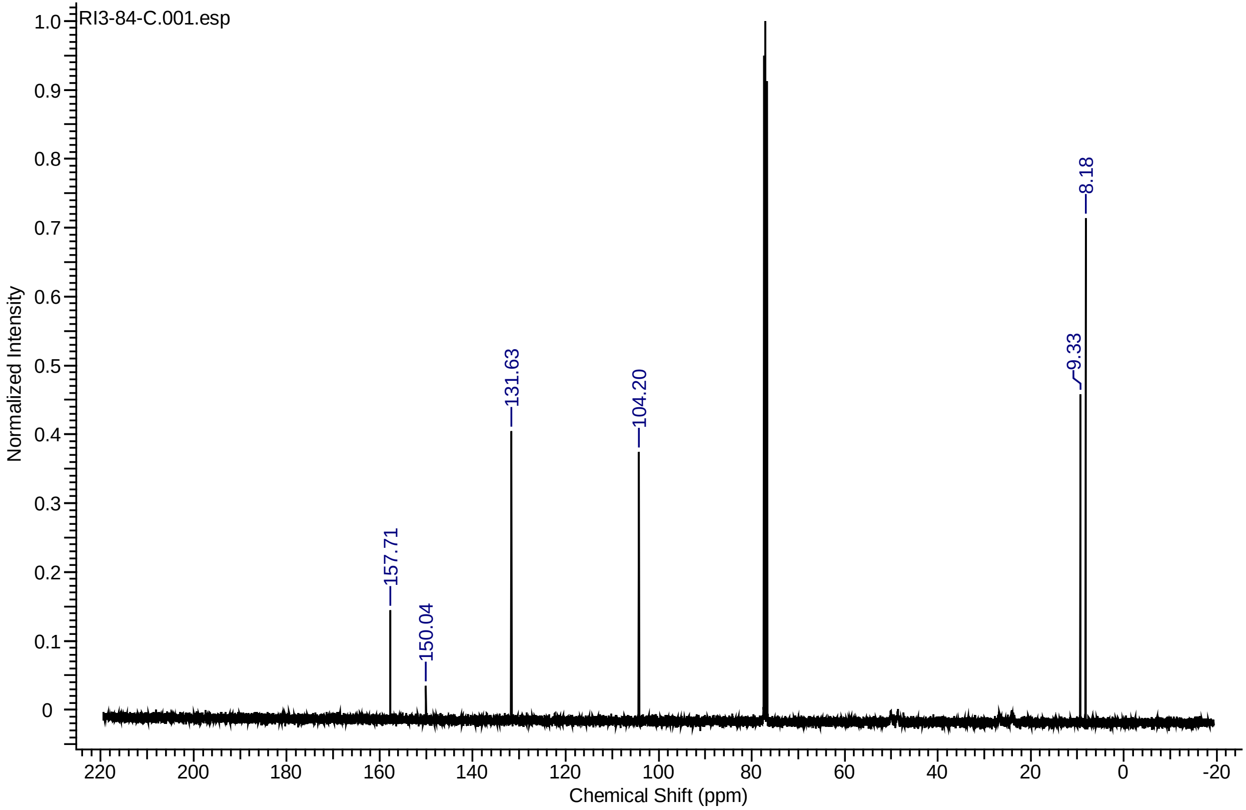

JF8-1398-carac-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
151.3104
131.6878
107.1923
13.8360
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

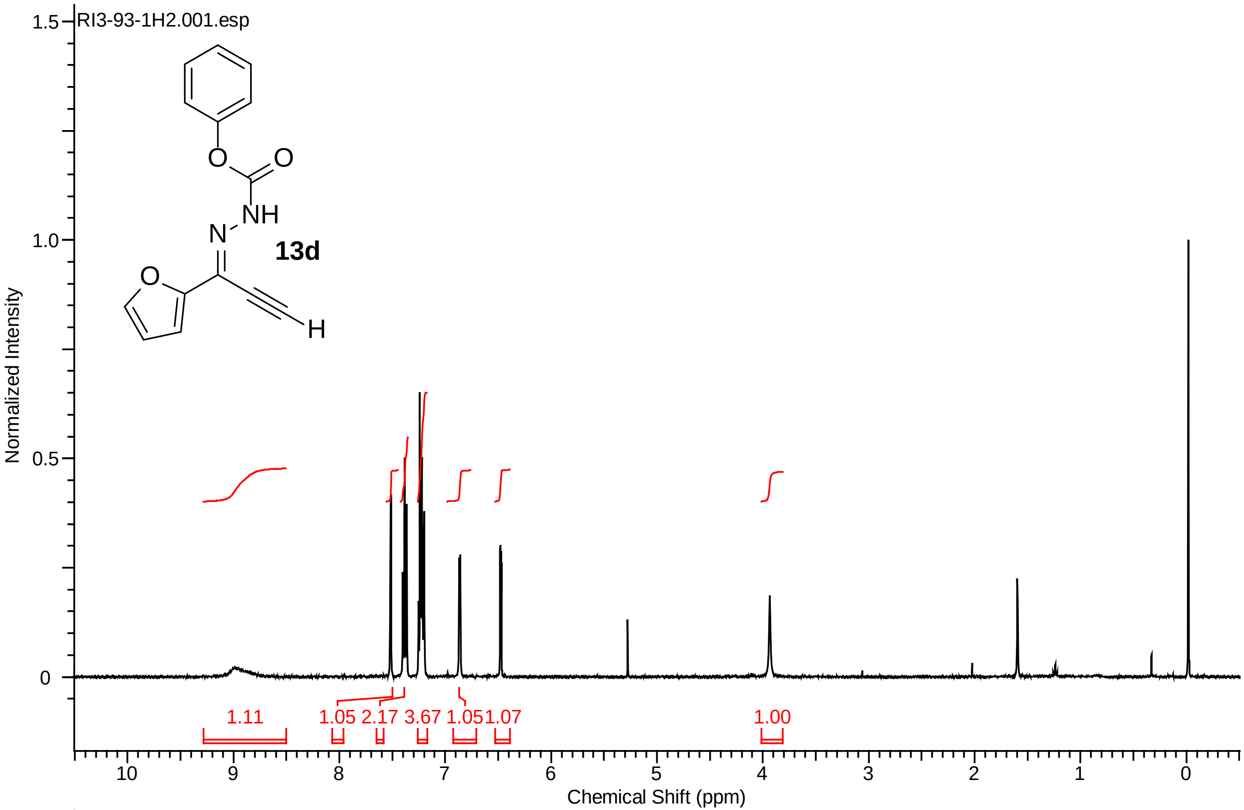

RI3-79-1H.001.esp
O
O
NH
N
H
13c
0.96
1.97
3.17
0.92
0.95
4.00
Normalized Intensity
Chemical Shift (ppm)
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10
9
8
7
6
5
4
3
2
1
0

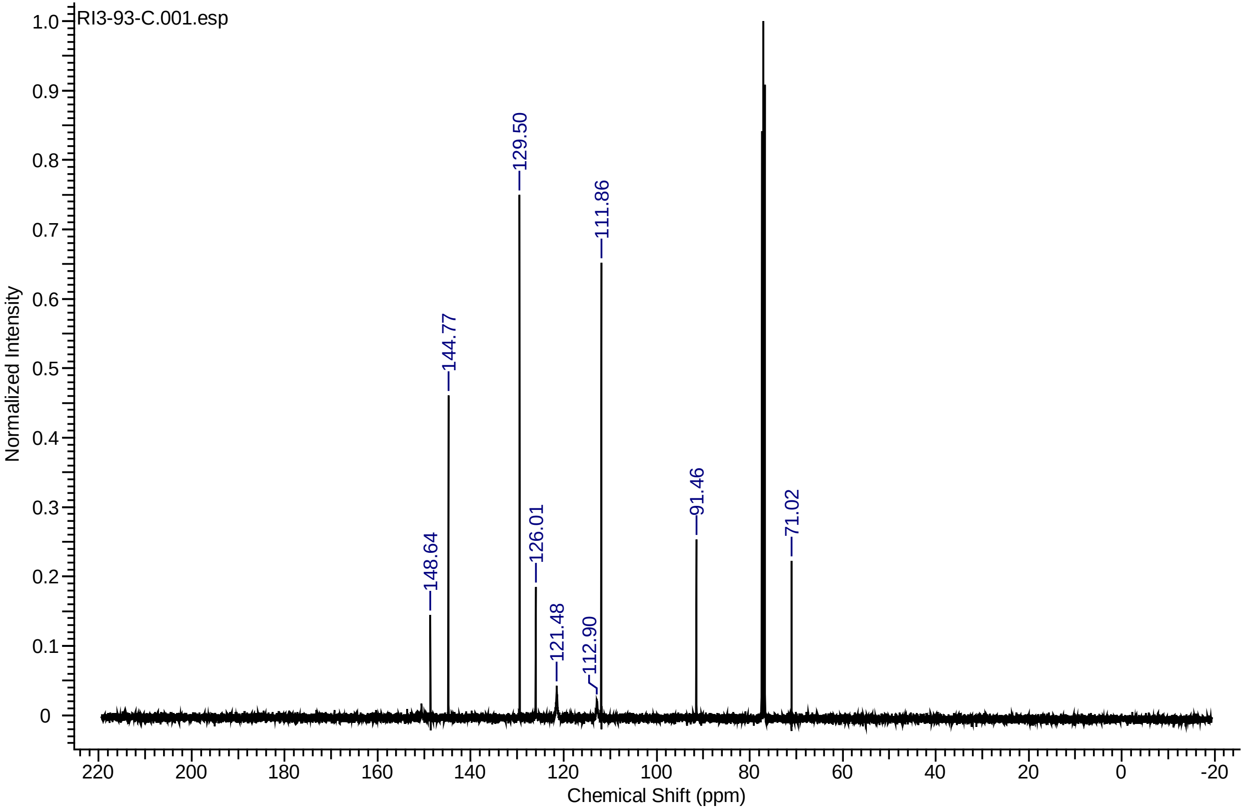

RI3-79-C.002.esp
129.45
125.85
121.41
91.22
70.92
16.00
6.22
Normalized Intensity
Chemical Shift (ppm)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20

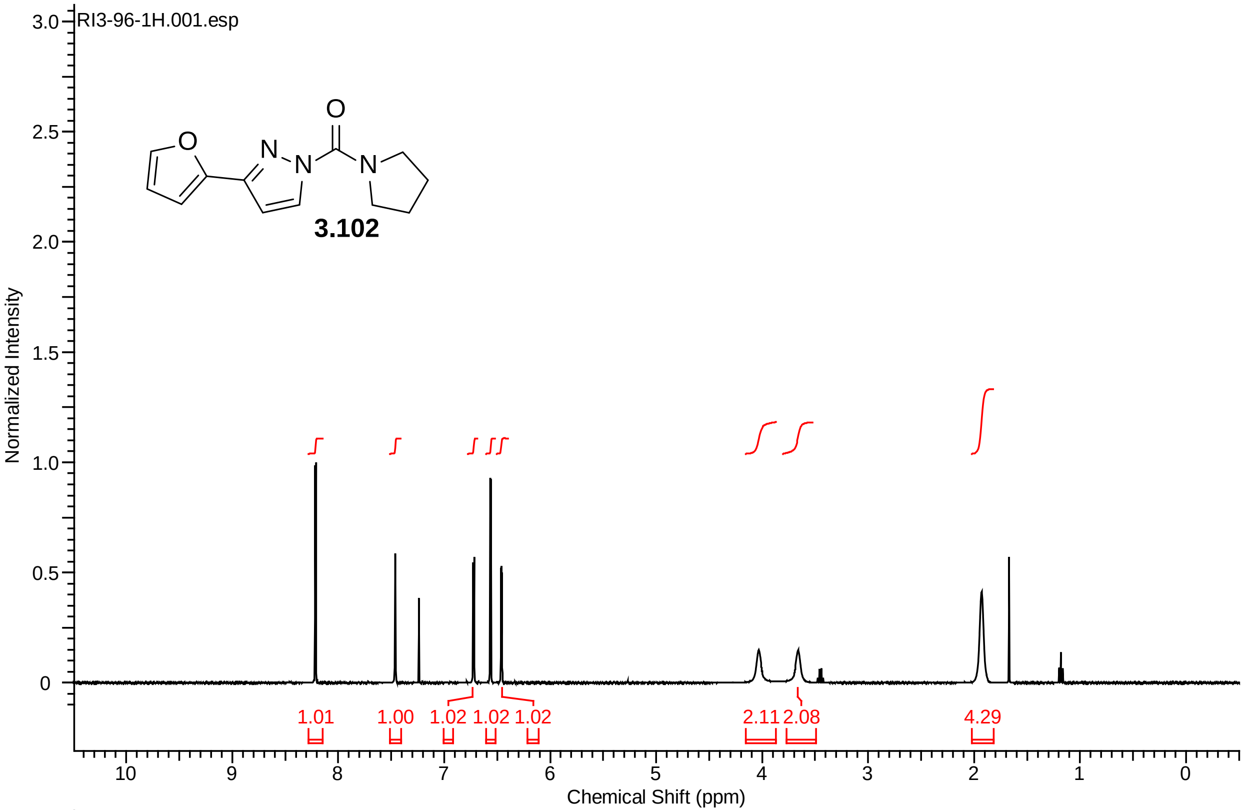

RI3-84-1H.001.esp
O
N
N
N
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.93
0.96
1.97
1.96
5.00
2.03
2.06
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

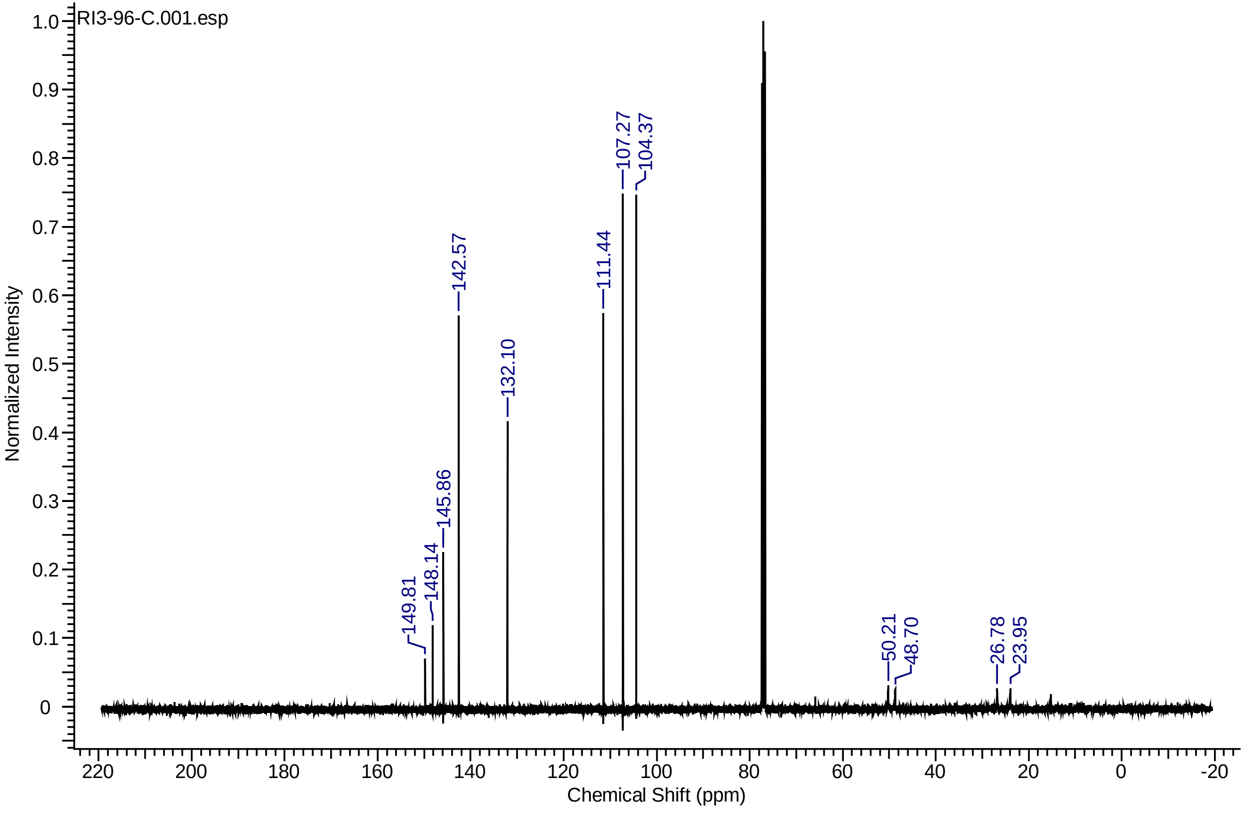
3.101

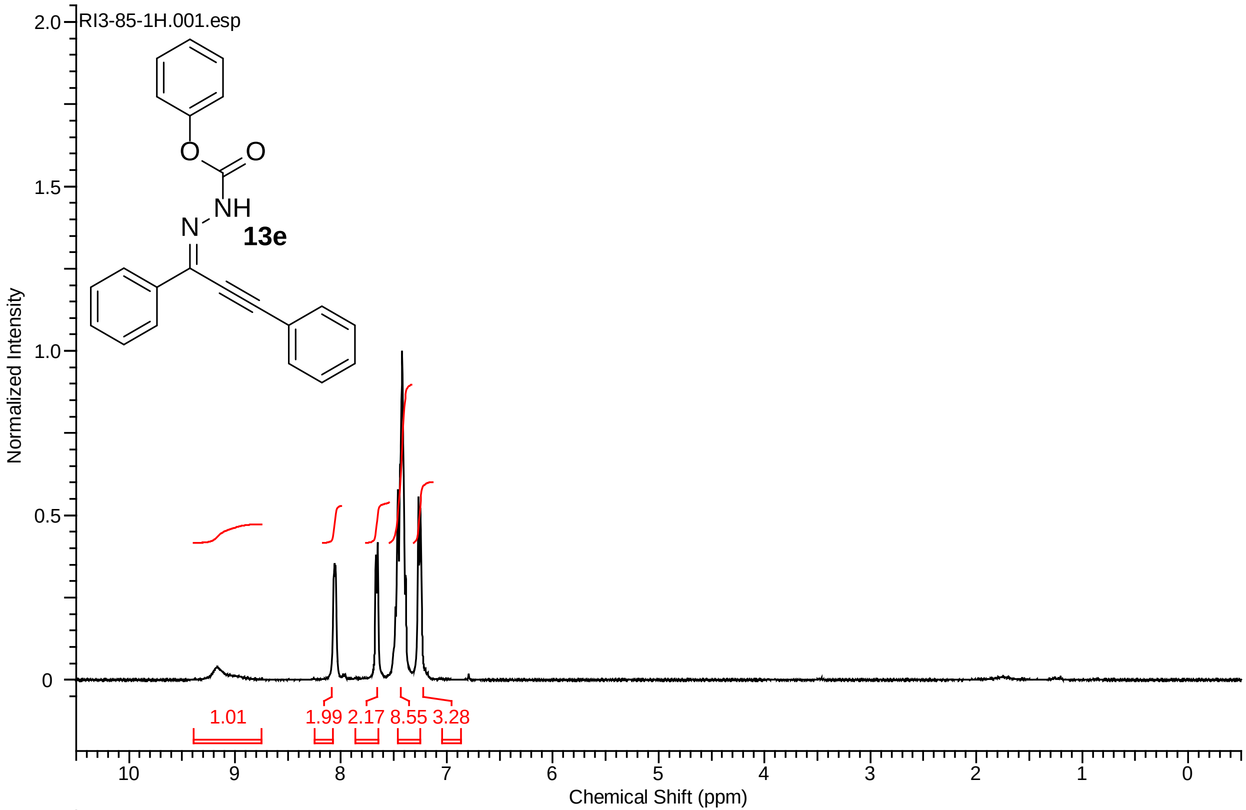

RI3-84-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
157.71
150.04
131.63
104.20
9.33
8.18
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

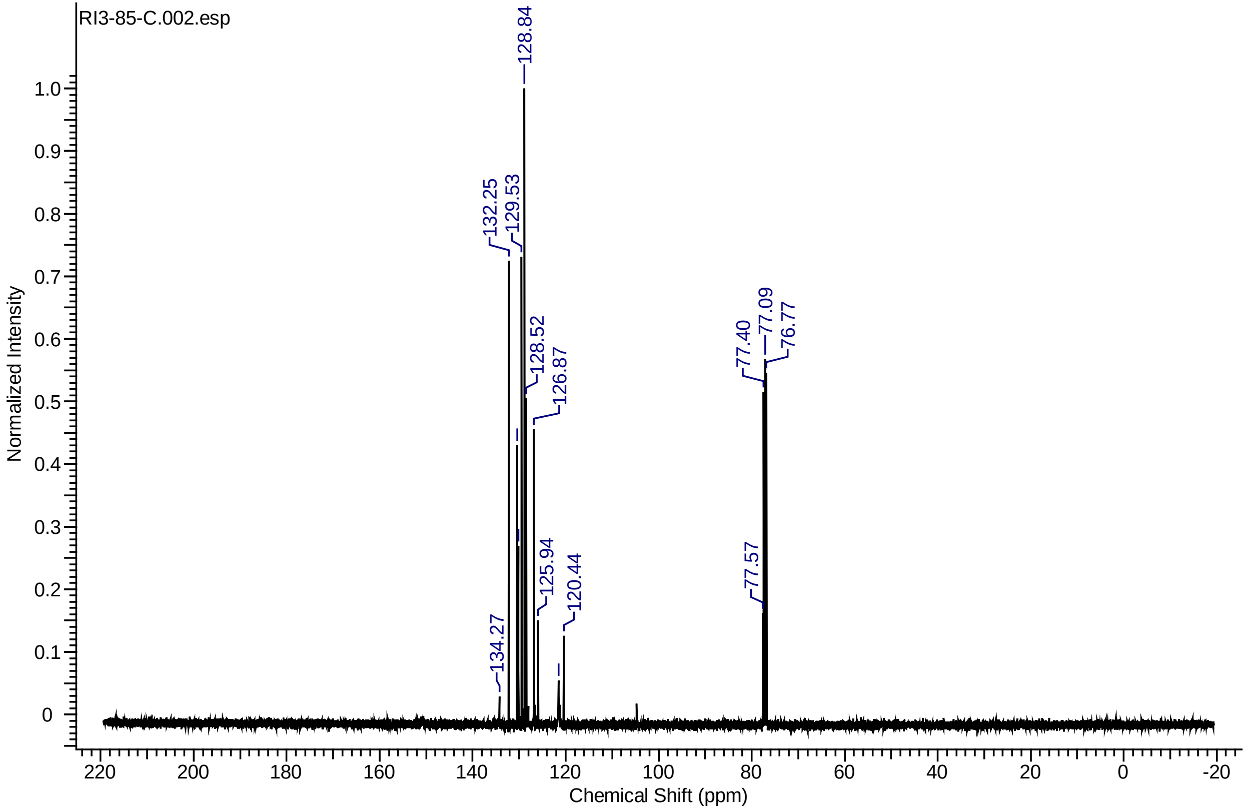

RI3-93-1H2.001.esp
O
O
NH
N
13d
O
H
Normalized Intensity
1.5
1.0
0.5
0
1.11
1.05
2.17
3.67
1.05
1.07
1.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

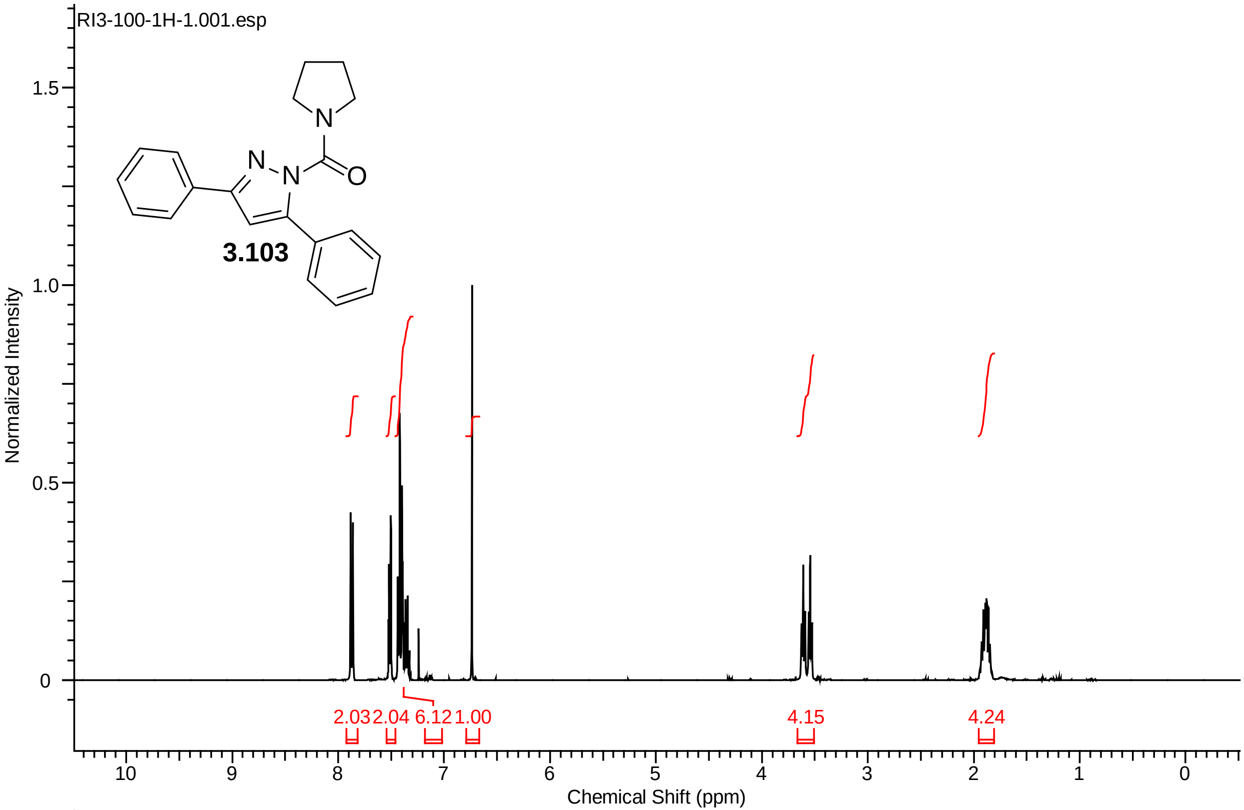

RI3-93-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
148.64
144.77
129.50
126.01
121.48
112.90
111.86
91.46
71.02
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

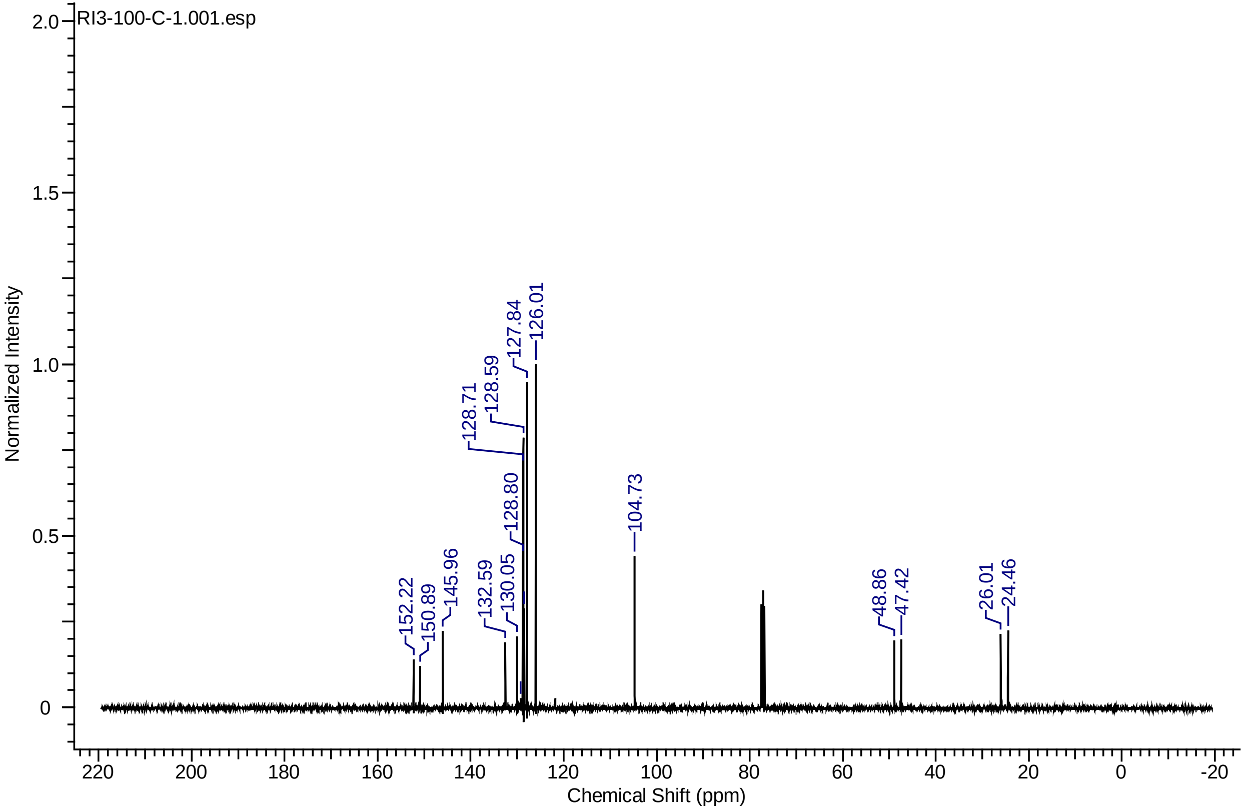

RI3-96-1H.001.esp
3.102
O
N
N
O
N
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
1.01
1.00
1.02
1.02
1.02
2.11
2.08
4.29
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

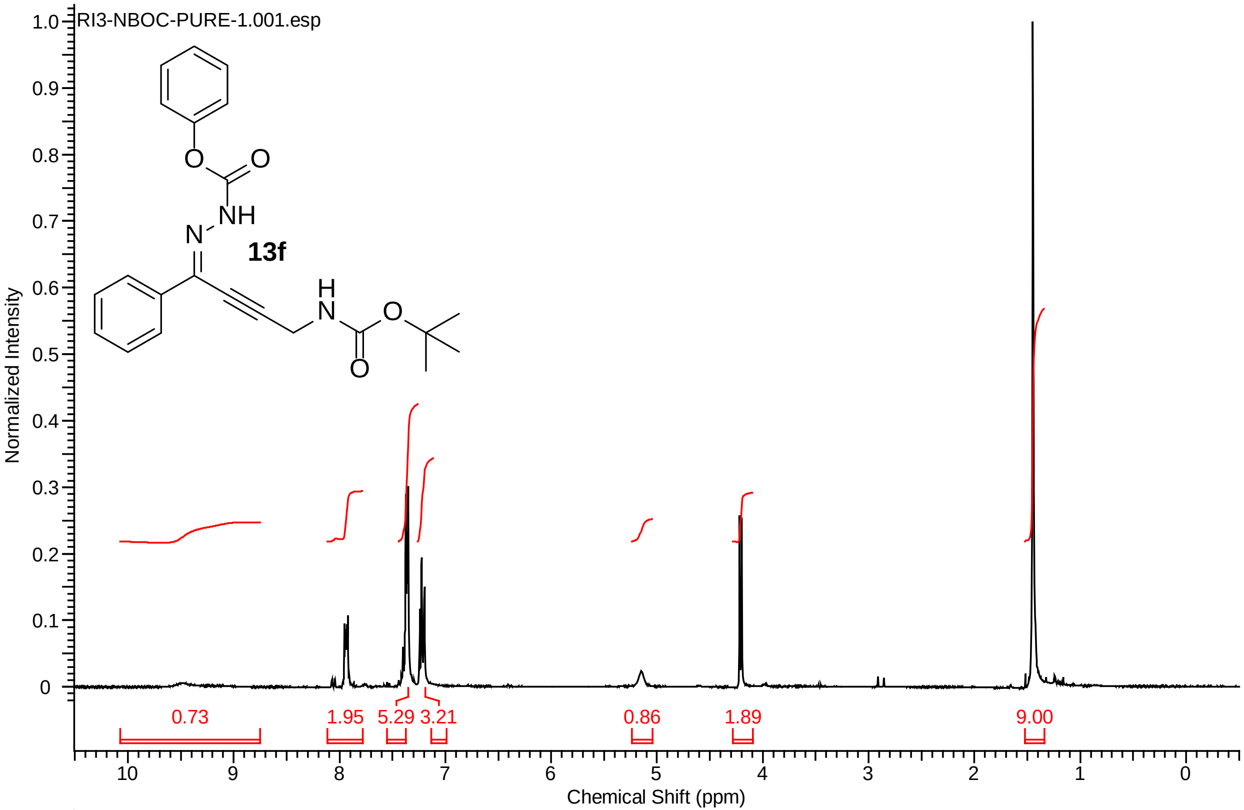

RI3-96-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
149.81
148.14
145.86
142.57
132.10
111.44
107.27
104.37
50.21
48.70
26.78
23.95
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

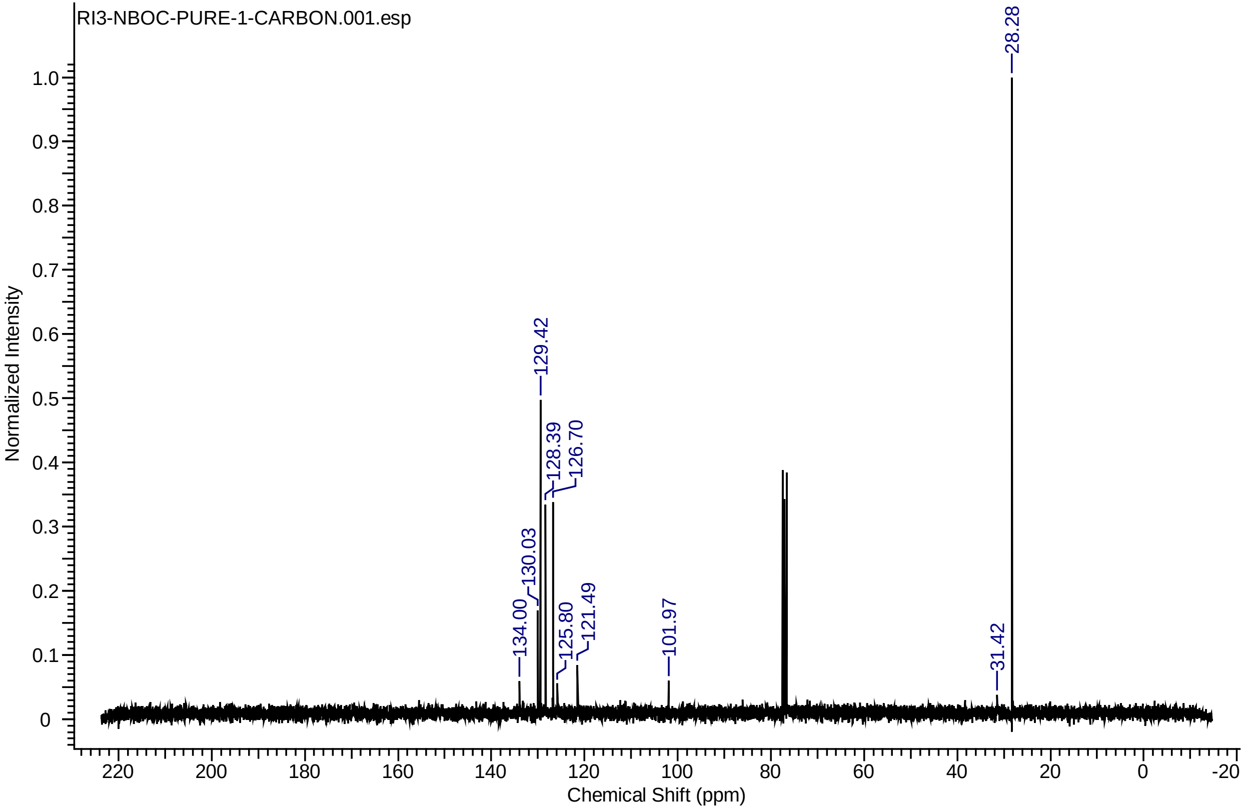

RI3-85-1H.001.esp
O
O
NH
N
13e
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.01
1.99
2.17
8.55
3.28
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

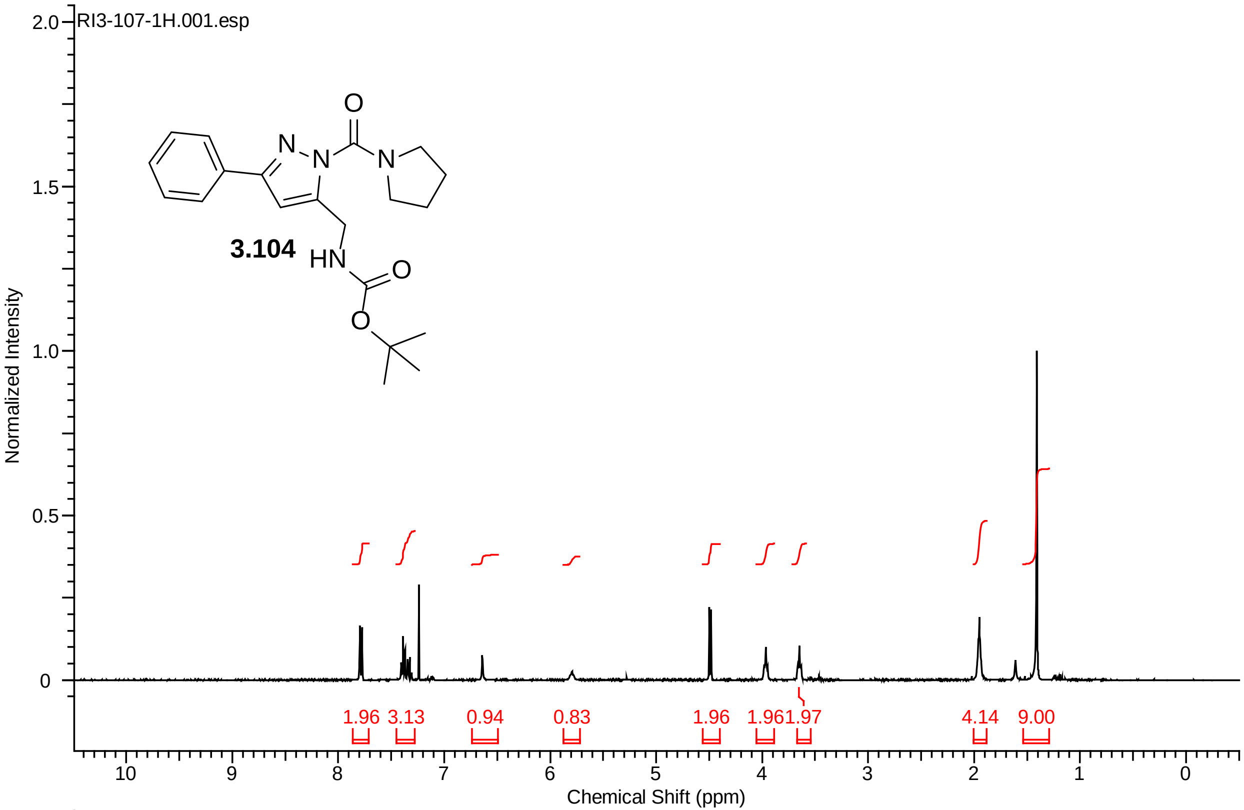

RI3-85-C.002.esp
128.84
132.25
129.53
128.52
126.87
77.40
77.09
76.77
125.94
120.44
77.57
134.27
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


RI3-100-1H-1.001.esp
3.103
N
N
N
O
Normalized Intensity
1.5
1.0
0.5
0
2.03
2.04
6.12
1.00
4.15
4.24
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

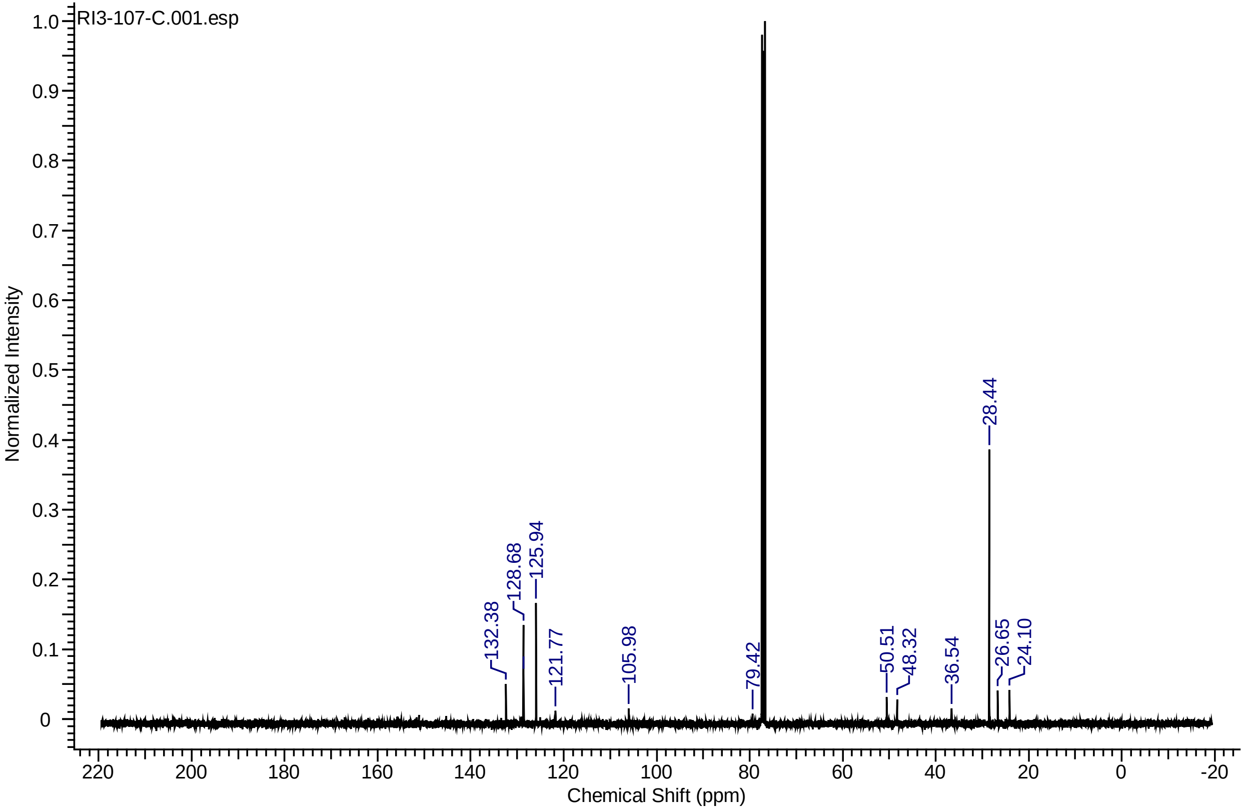

RI3-100-C-1.001.esp
Normalized Intensity
2.0
1.5
1.0
0.5
0
152.22
150.89
145.96
132.59
130.05
128.80
128.71
128.59
127.84
126.01
104.73
48.86
47.42
26.01
24.46
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

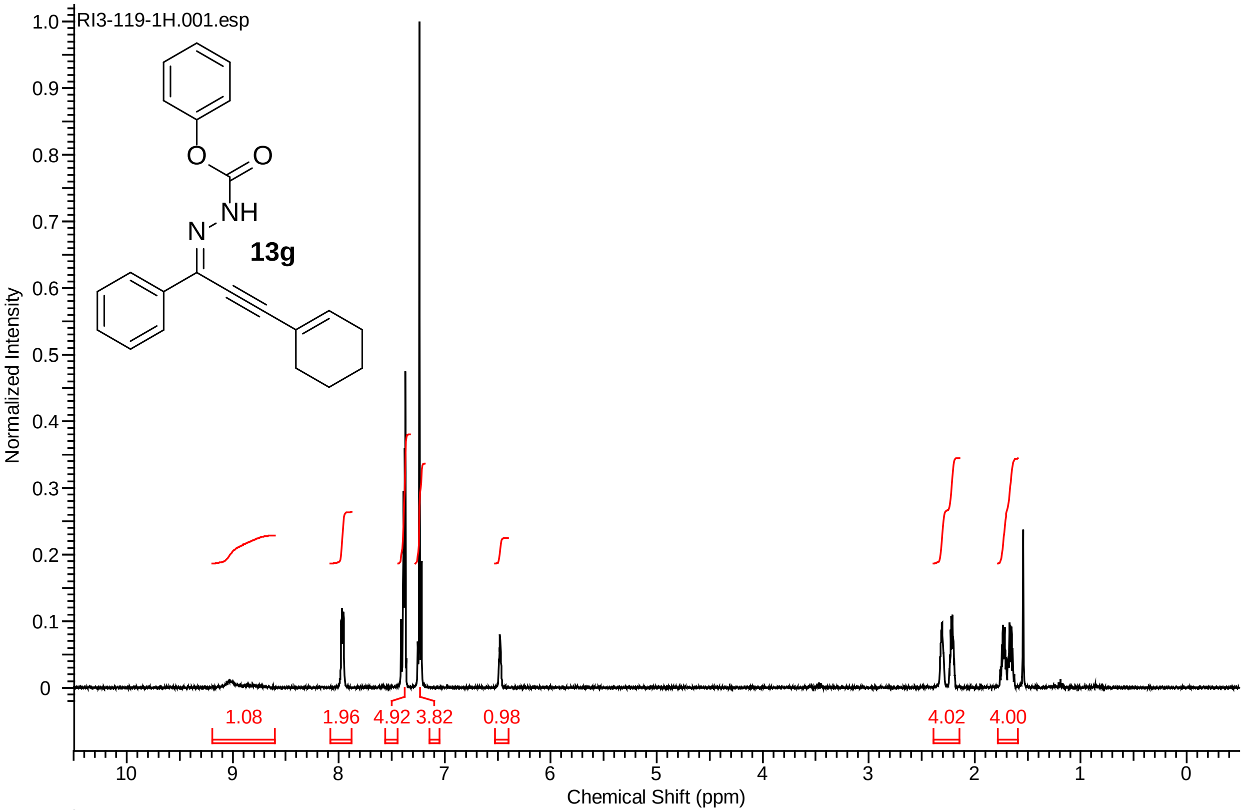

RI3-NBOC-PURE-1.001.esp
O
O
NH
N
13f
H
N
O
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.73
1.95
5.29
3.21
0.86
1.89
9.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

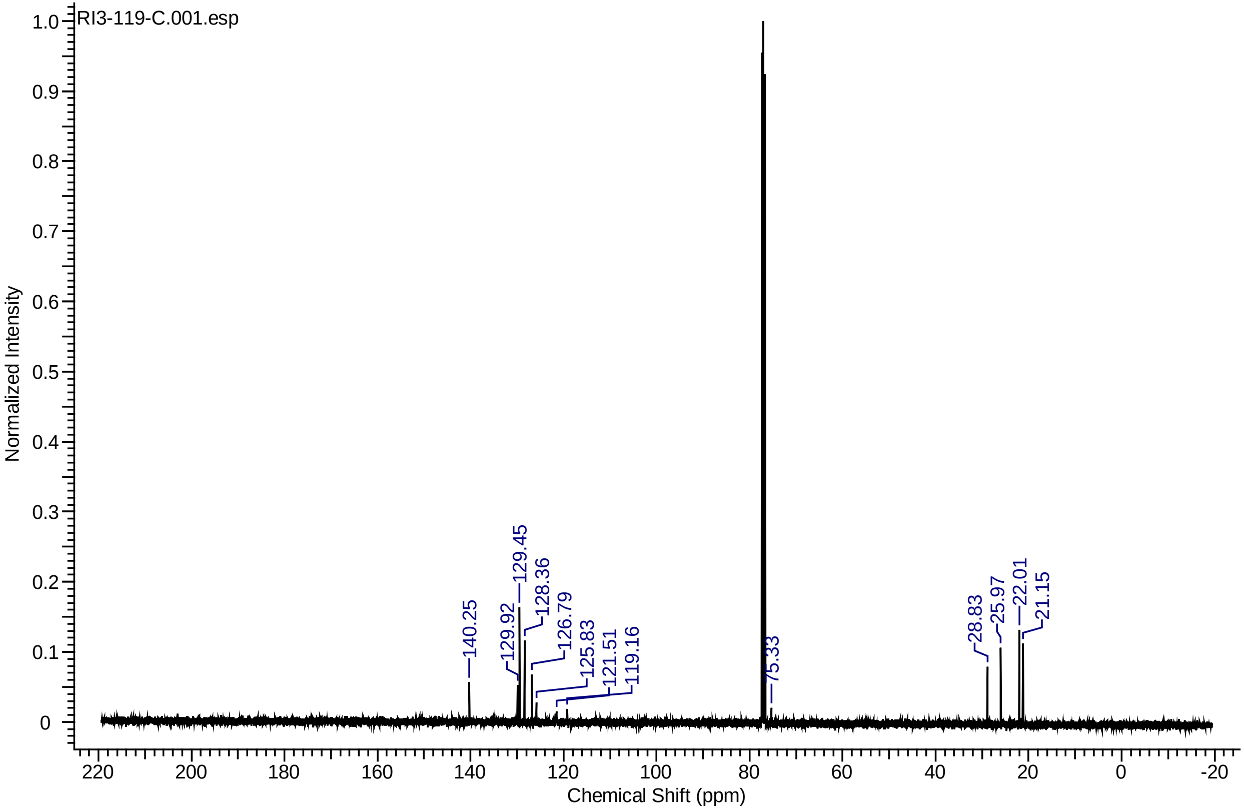

RI3-NBOC-PURE-1-CARBON.001.esp
28.28
129.42
128.39
126.70
130.03
134.00
125.80
121.49
101.97
31.42
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

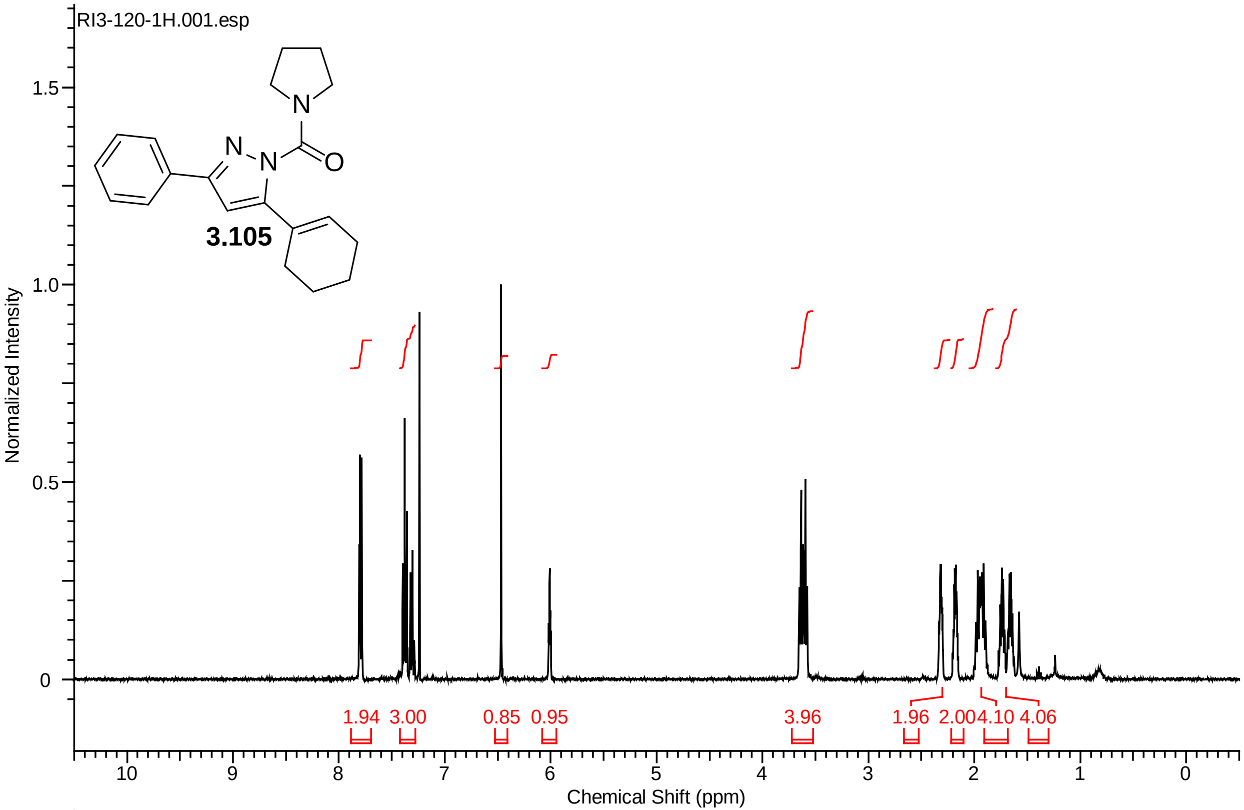

3.104

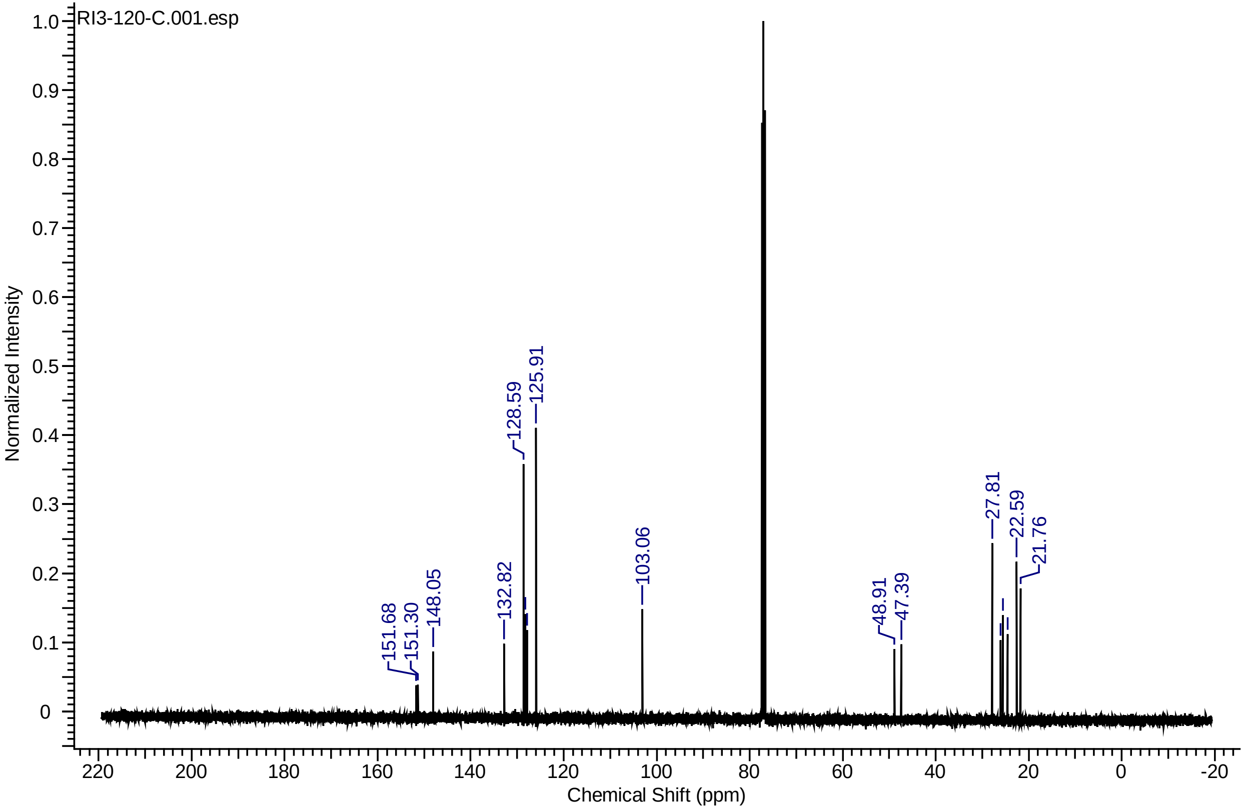
RI3-107-1H.001.esp
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.96
3.13
0.94
0.83
1.96
1.96
1.97
4.14
9.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
N
N
N
O
HN
O
O

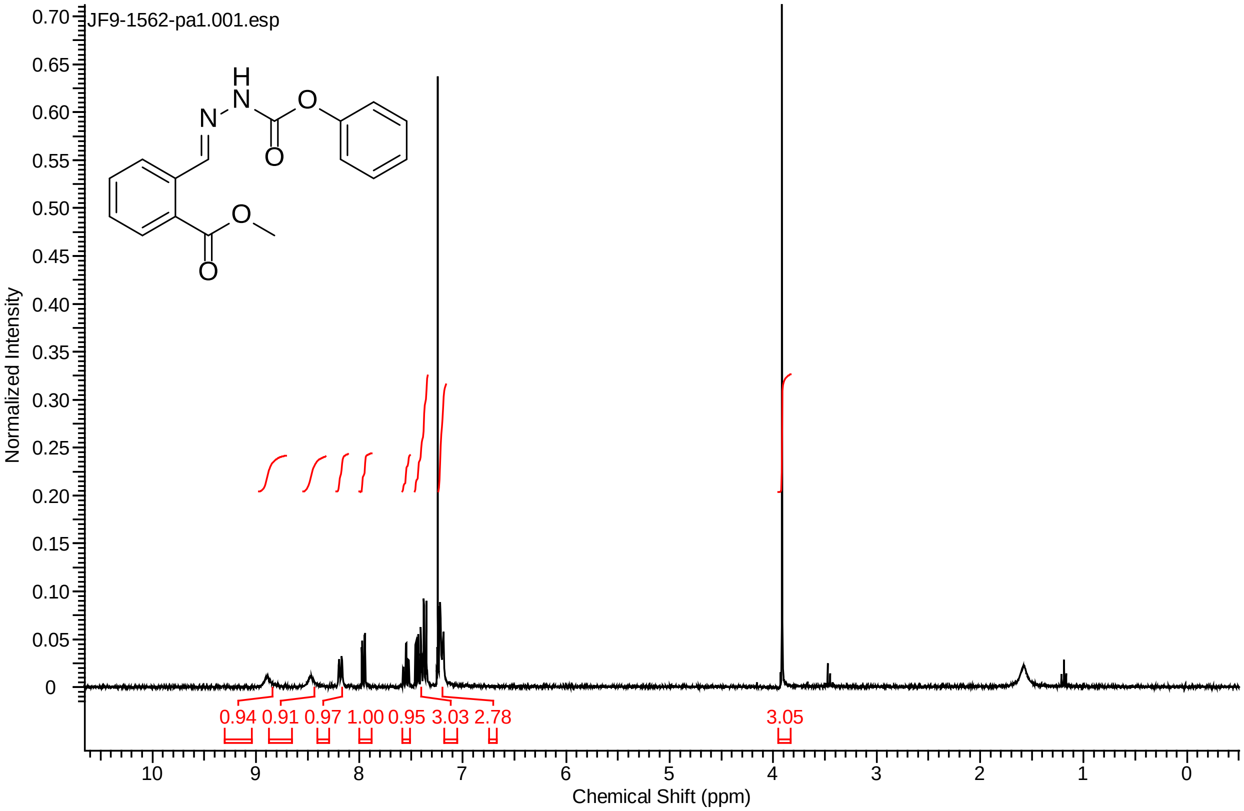

RI3-107-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
132.38
128.68
125.94
121.77
105.98
79.42
50.51
48.32
36.54
28.44
26.65
24.10
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

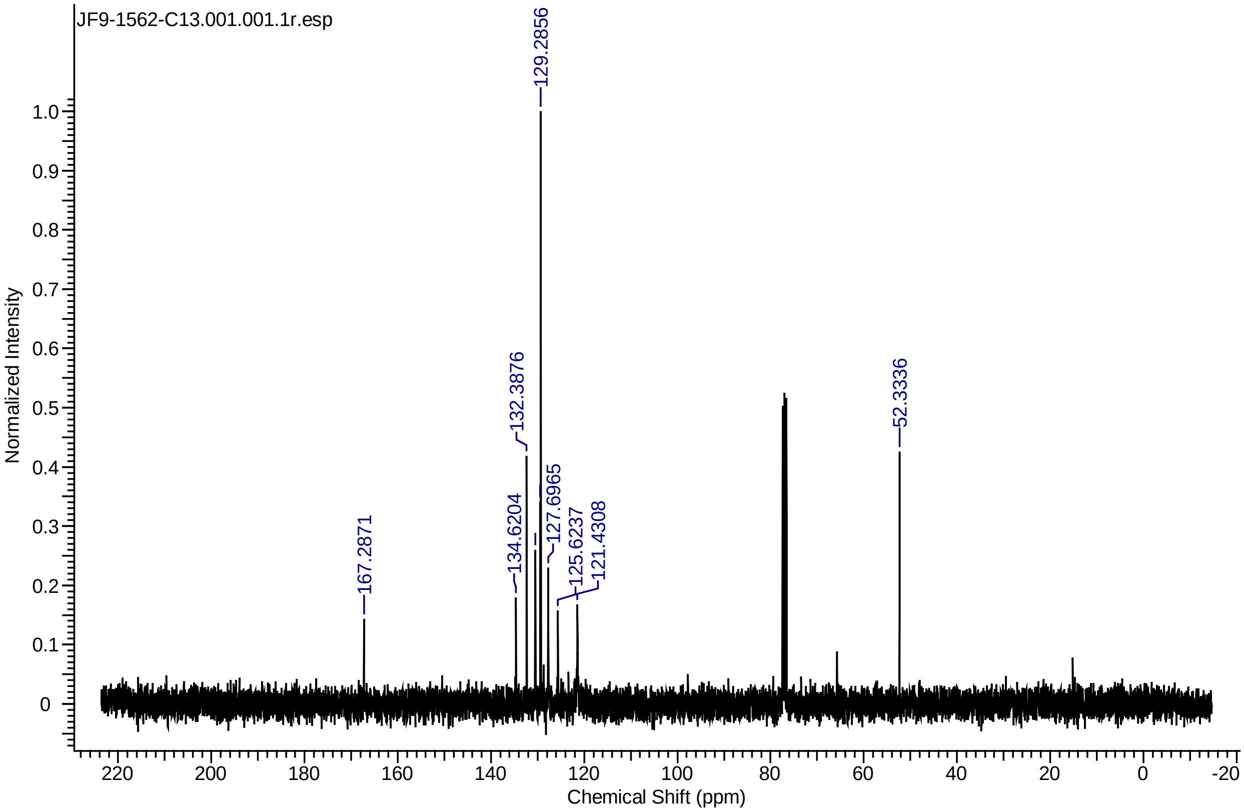

RI3-119-1H.001.esp
13g
O
O
NH
N
Normalized Intensity
1.08
1.96
4.92
3.82
0.98
4.02
4.00
Chemical Shift (ppm)
10
9
8
7
6
5
4
3
2
1
0

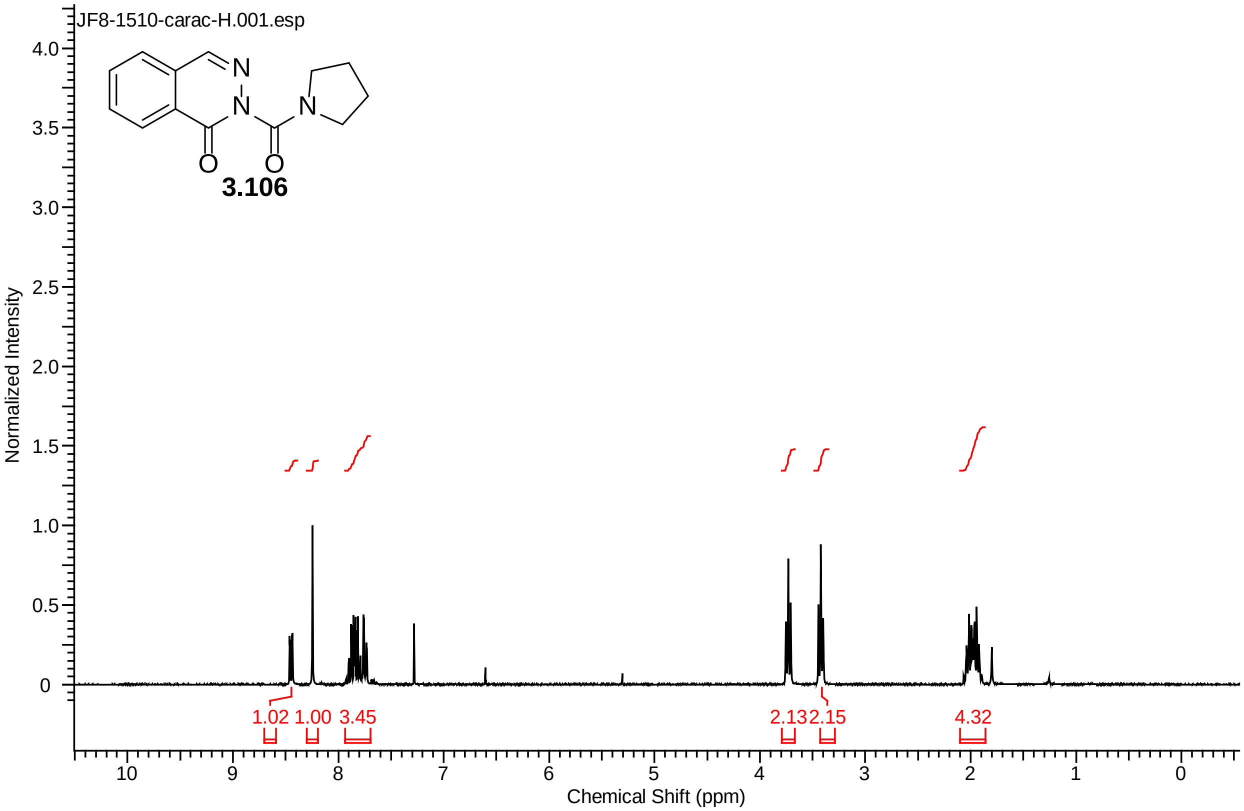

RI3-119-C.001.esp
Normalized Intensity
140.25
129.92
129.45
128.36
126.79
125.83
121.51
119.16
75.33
28.83
25.97
22.01
21.15
Chemical Shift (ppm)
220
200
180
160
140
120
100
80
60
40
20
0
-20

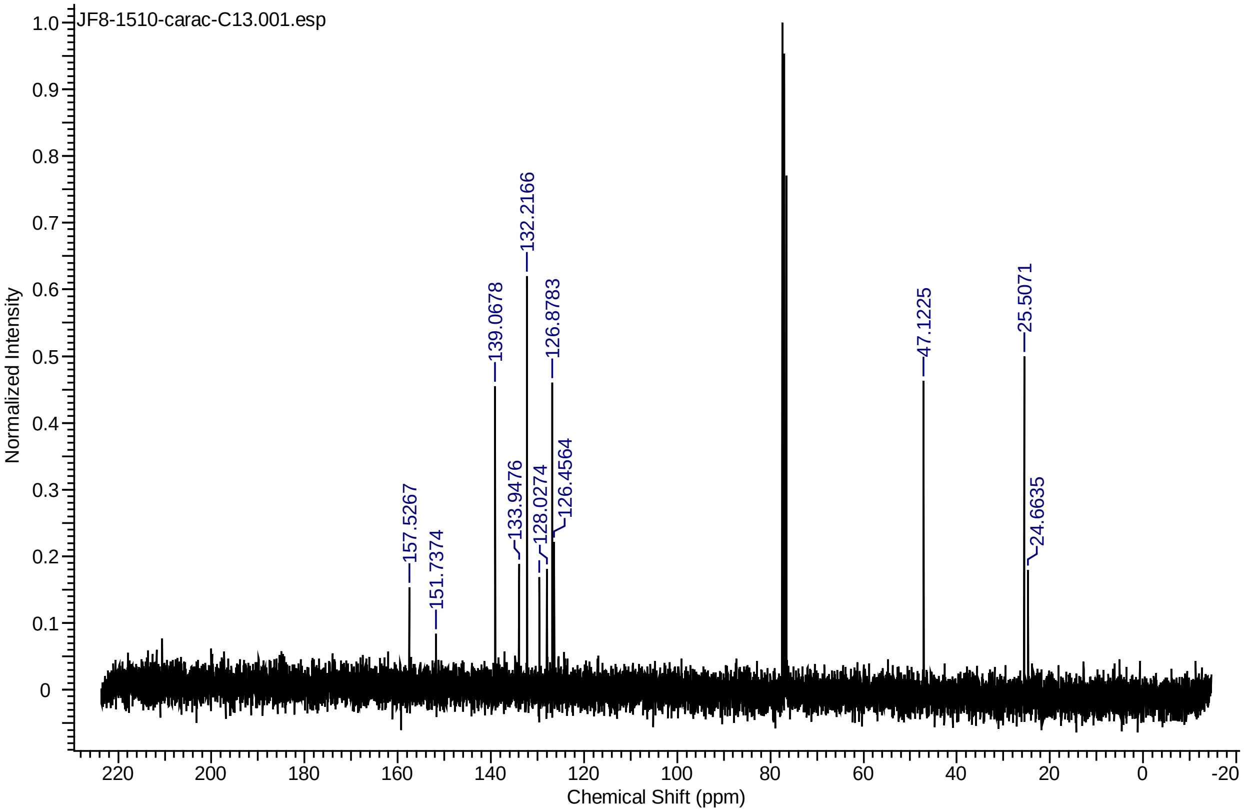

RI3-120-1H.001.esp
N
N
N
O
3.105
Normalized Intensity
1.5
1.0
0.5
0
1.94
3.00
0.85
0.95
3.96
1.96
2.00
4.10
4.06
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

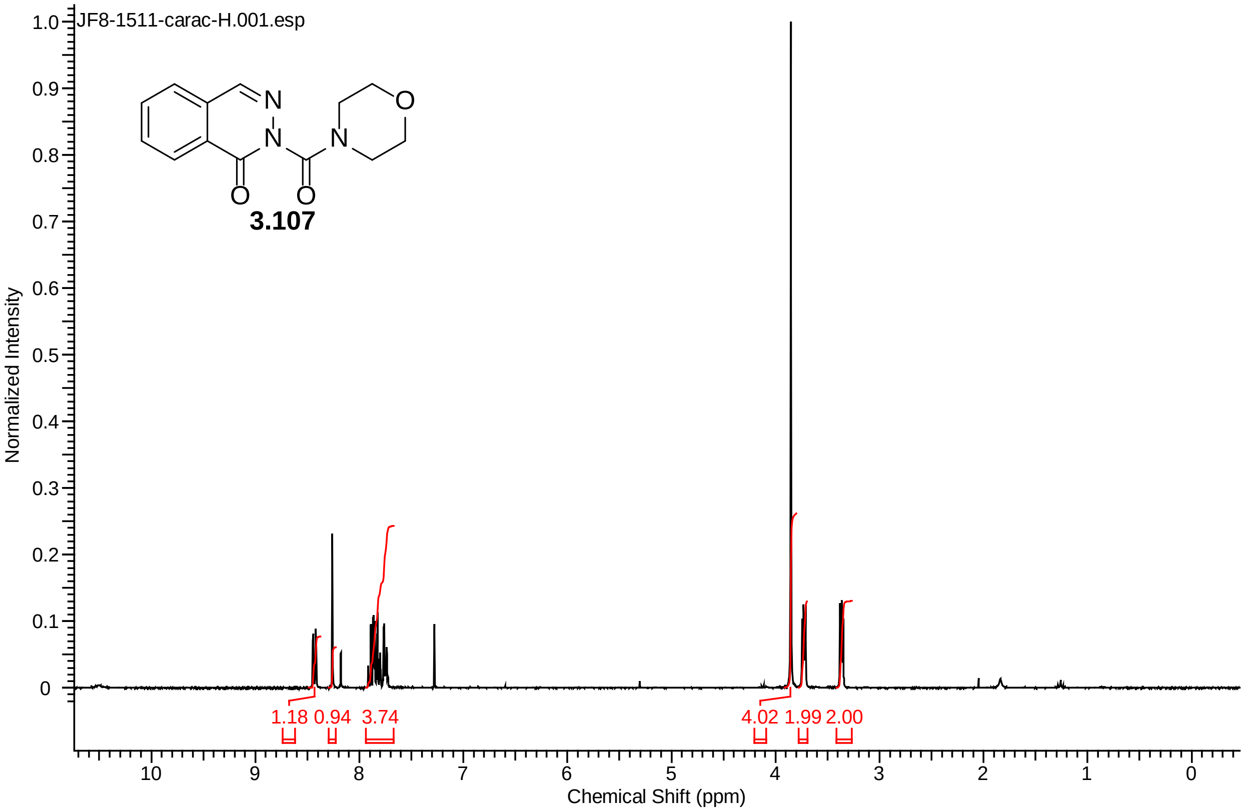

RI3-120-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
151.68
151.30
148.05
132.82
128.59
125.91
103.06
48.91
47.39
27.81
22.59
21.76
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF9-1562-pa1.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.94
0.91
0.97
1.00
0.95
3.03
2.78
3.05


JF9-1562-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
167.2871
134.6204
132.3876
129.2856
127.6965
125.6237
121.4308
52.3336

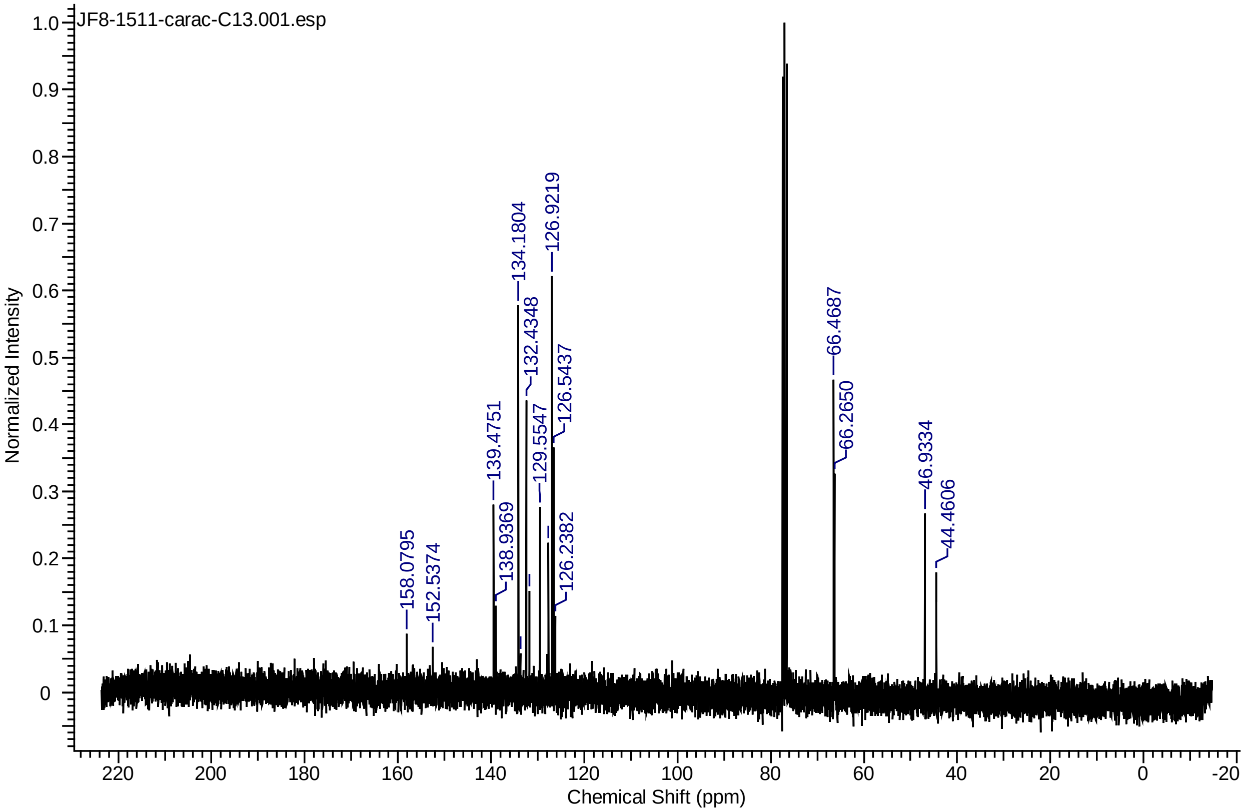

JF8-1510-carac-H.001.esp
N
N
N
O
O
3.106
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
1.02
1.00
3.45
2.13
2.15
4.32
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF8-1510-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
157.5267
151.7374
139.0678
133.9476
132.2166
128.0274
126.8783
126.4564
47.1225
25.5071
24.6635
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

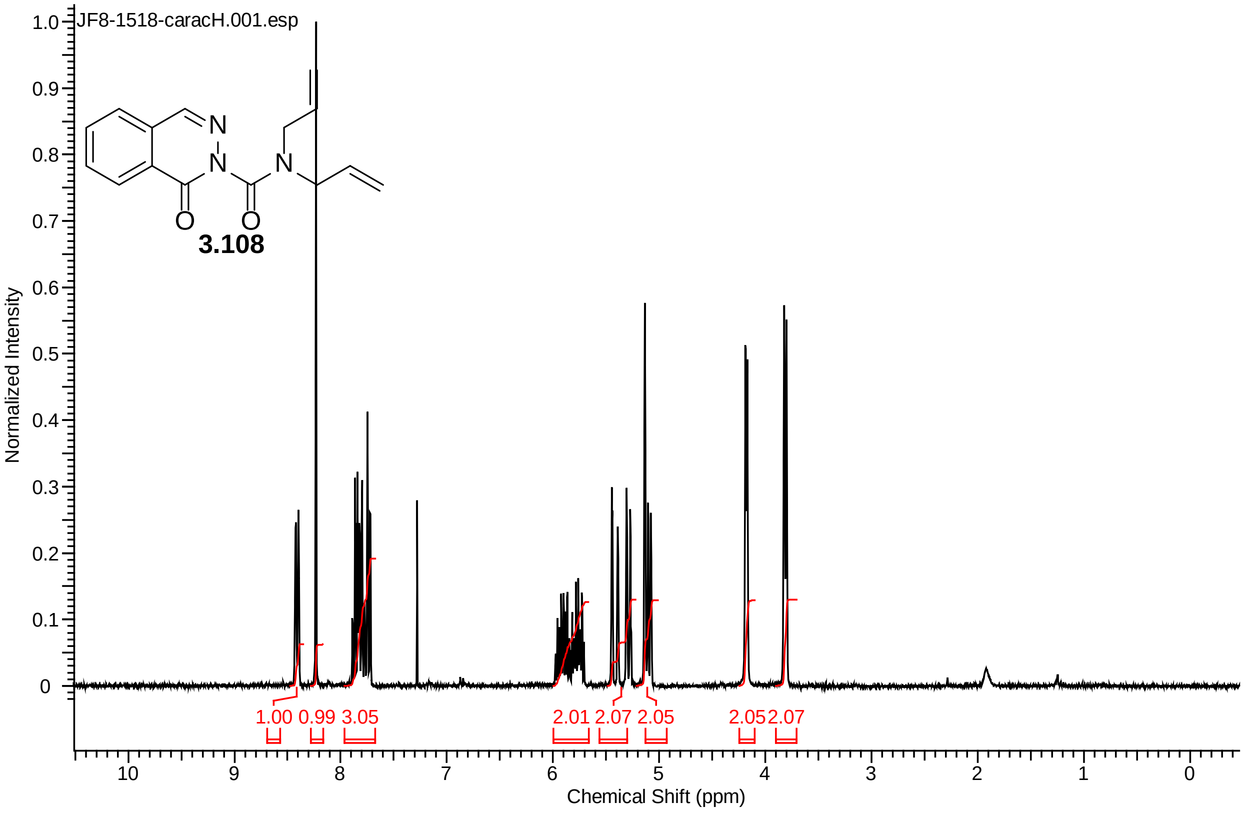


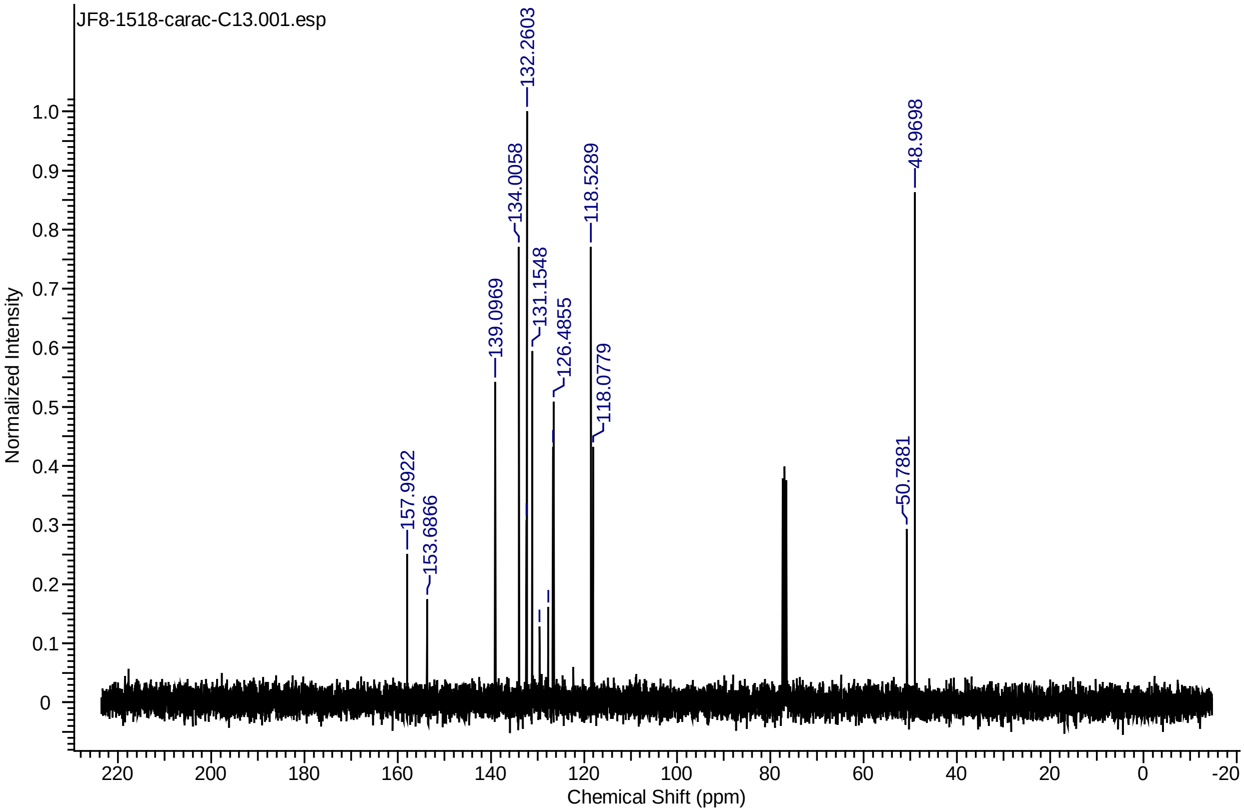
3.107

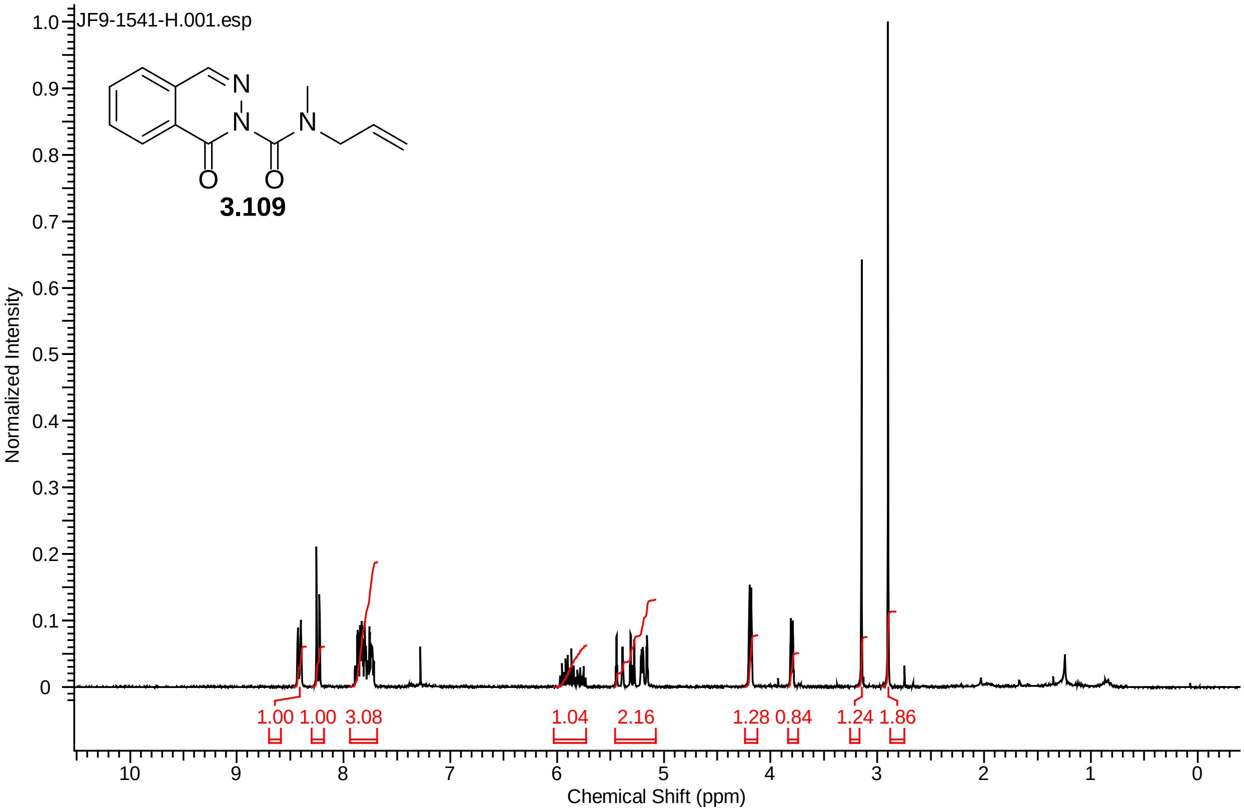
JF8-1511-carac-H.001.esp
N
N
N
O
O
O
1.18
0.94
3.74
4.02
1.99
2.00
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

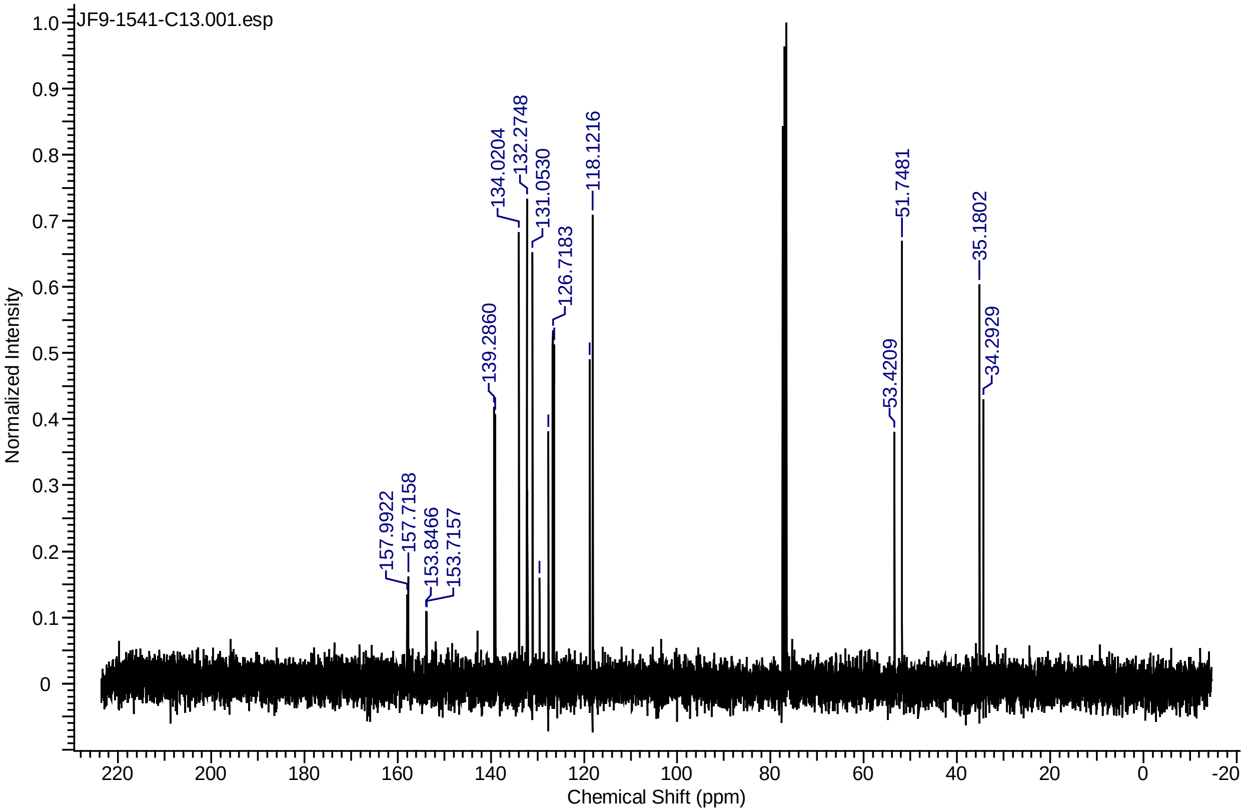


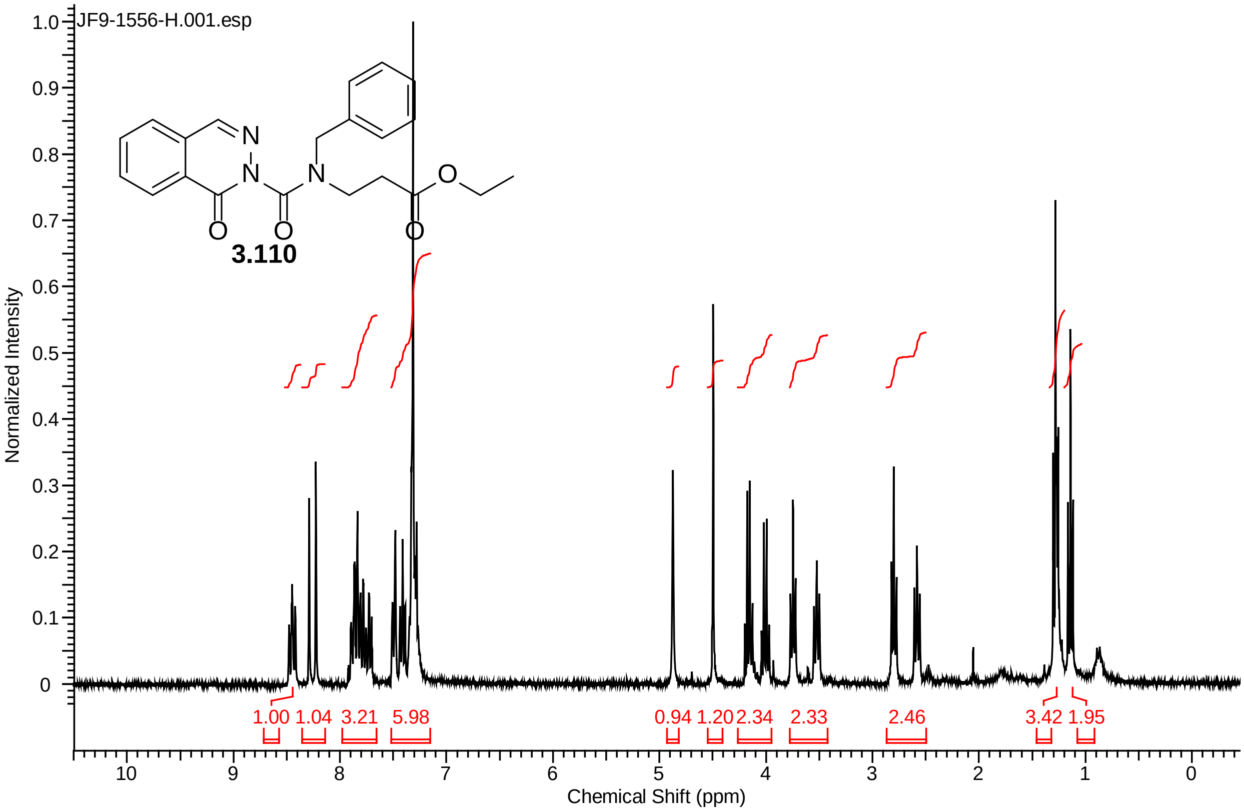
JF8-1511-carac-C13.001.esp
158.0795
152.5374
139.4751
138.9369
134.1804
132.4348
129.5547
126.9219
126.5437
126.2382
66.4687
66.2650
46.9334
44.4606
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF8-1518-caracH.001.esp
3.108
N
N
N
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
1.00
0.99
3.05
2.01
2.07
2.05
2.05
2.07
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

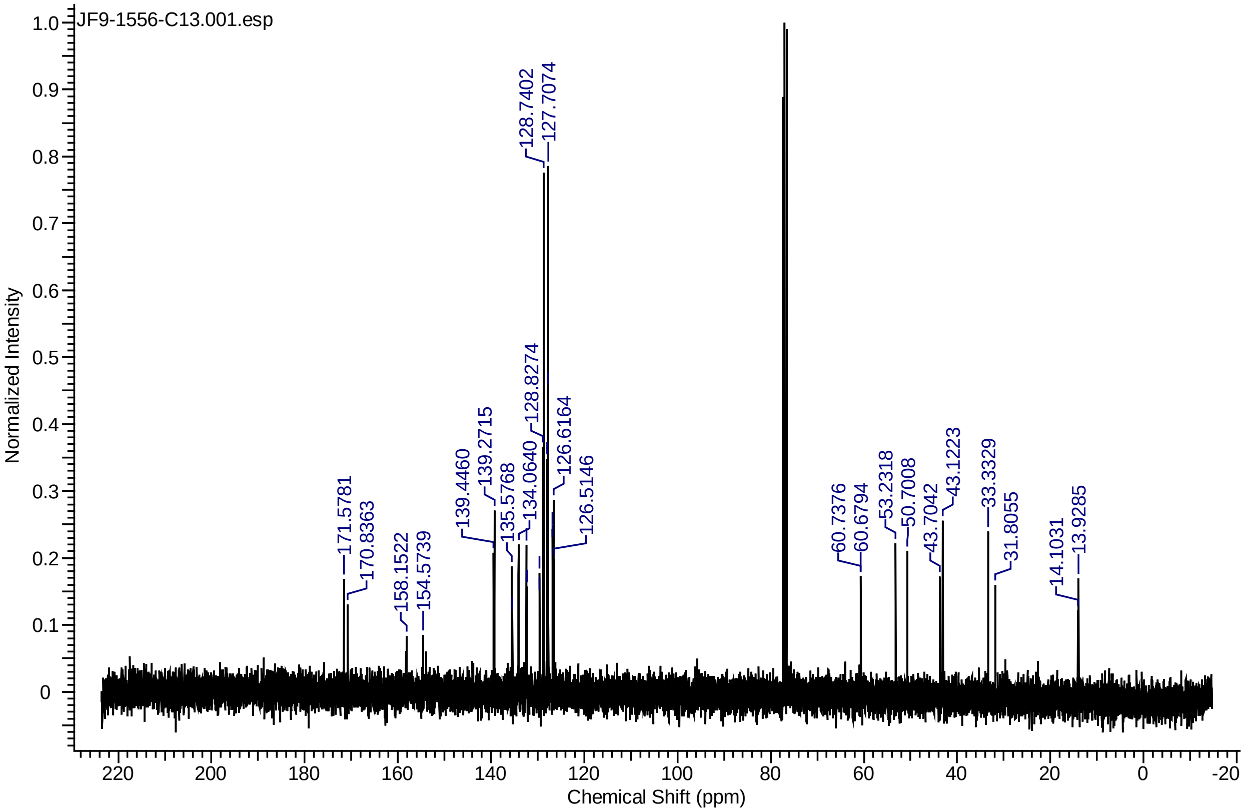

JF8-1518-carac-C13.001.esp
157.9922
153.6866
139.0969
134.0058
132.2603
131.1548
126.4855
118.5289
118.0779
50.7881
48.9698
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

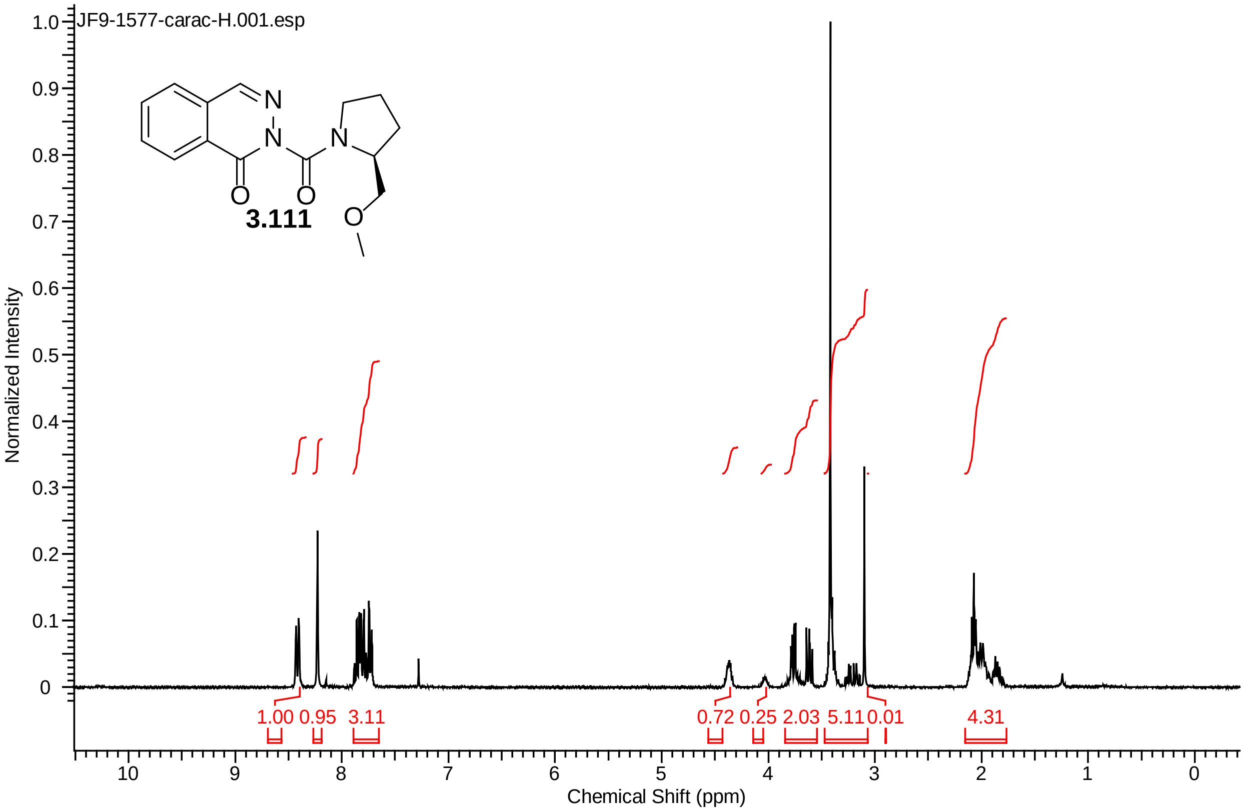

JF9-1541-H.001.esp
3.109
N
N
N
O
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
1.00
3.08
1.04
2.16
1.28
0.84
1.24
1.86
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

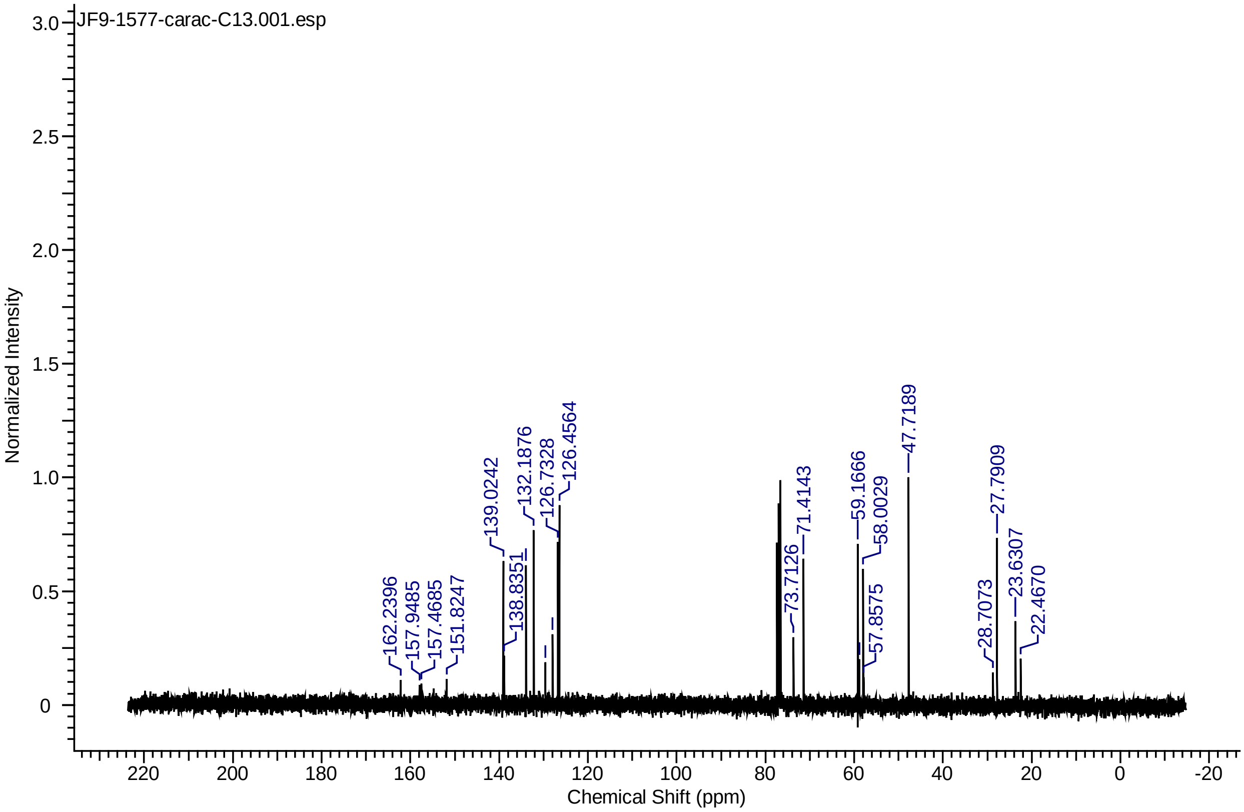

JF9-1541-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
157.9922
157.7158
153.8466
153.7157
139.2860
134.0204
132.2748
131.0530
126.7183
118.1216
53.4209
51.7481
35.1802
34.2929
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

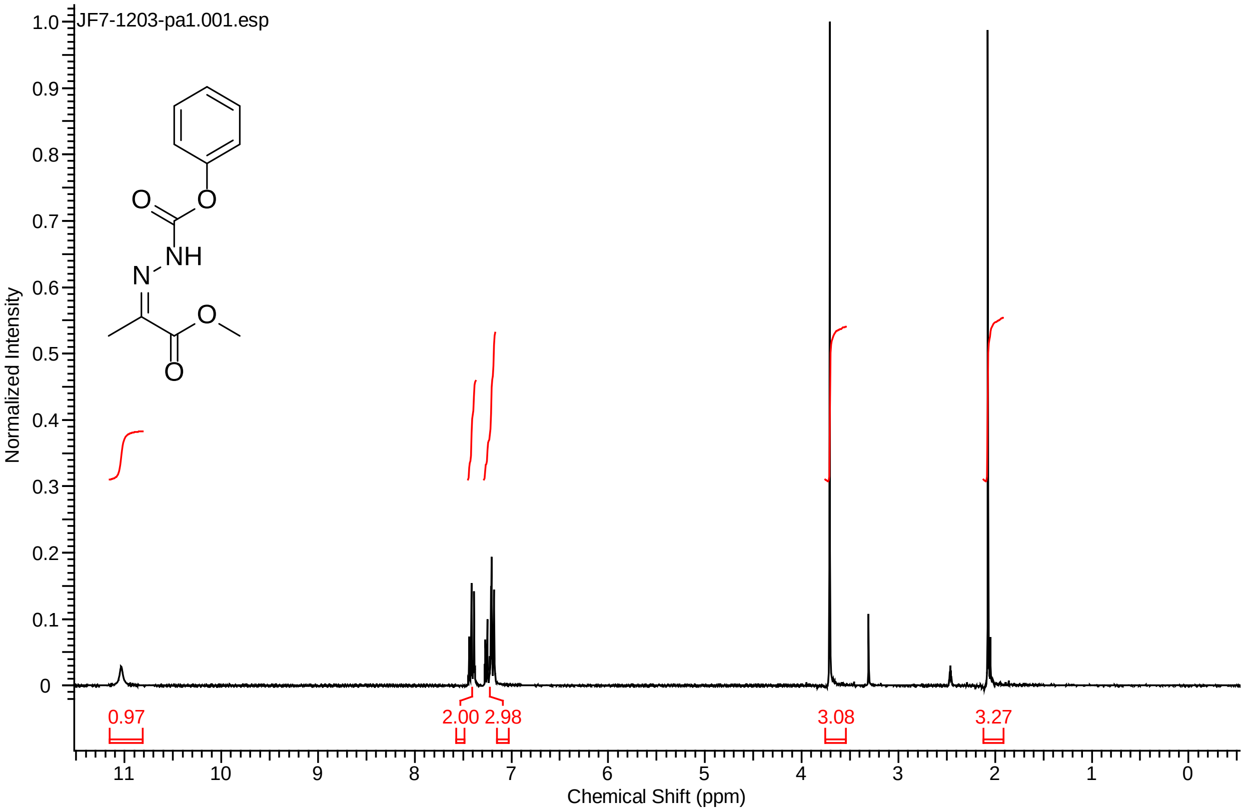

3.110

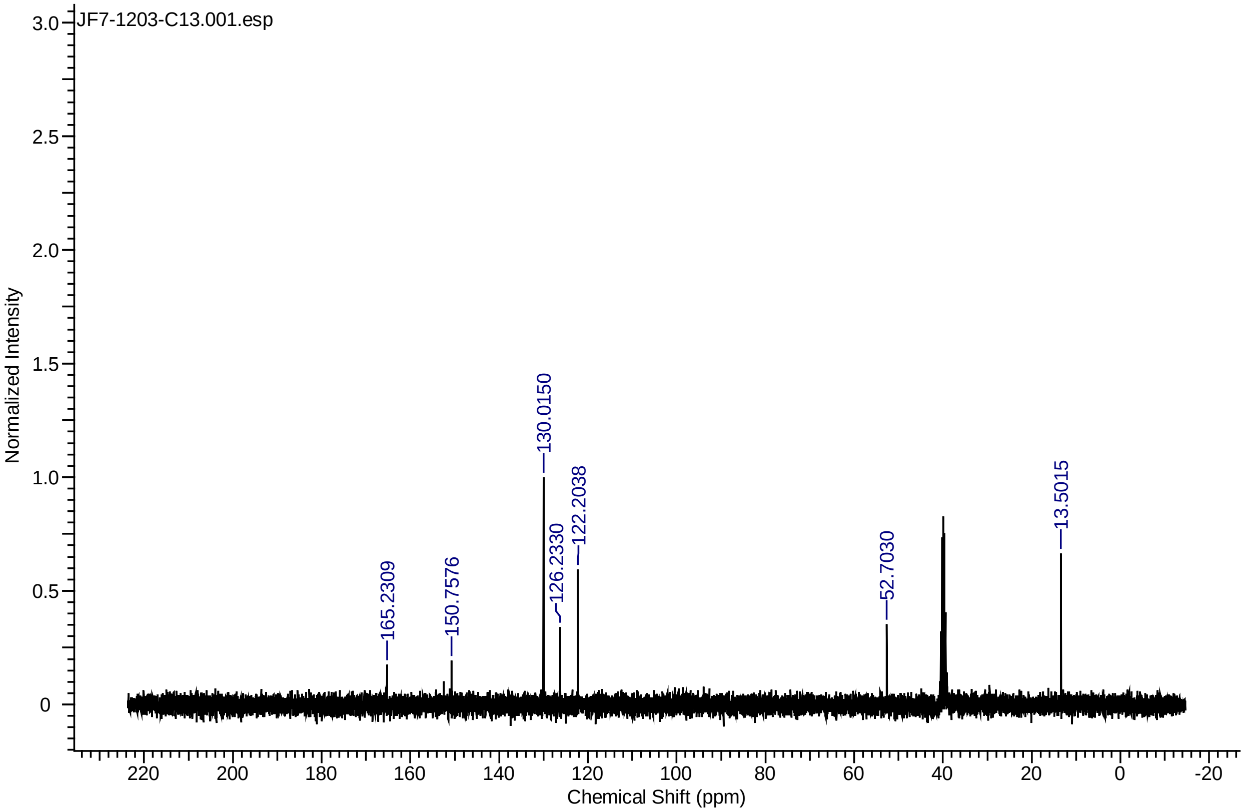
JF9-1556-H.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
N
N
N
O
O
O
O
1.00
1.04
3.21
5.98
0.94
1.20
2.34
2.33
2.46
3.42
1.95
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

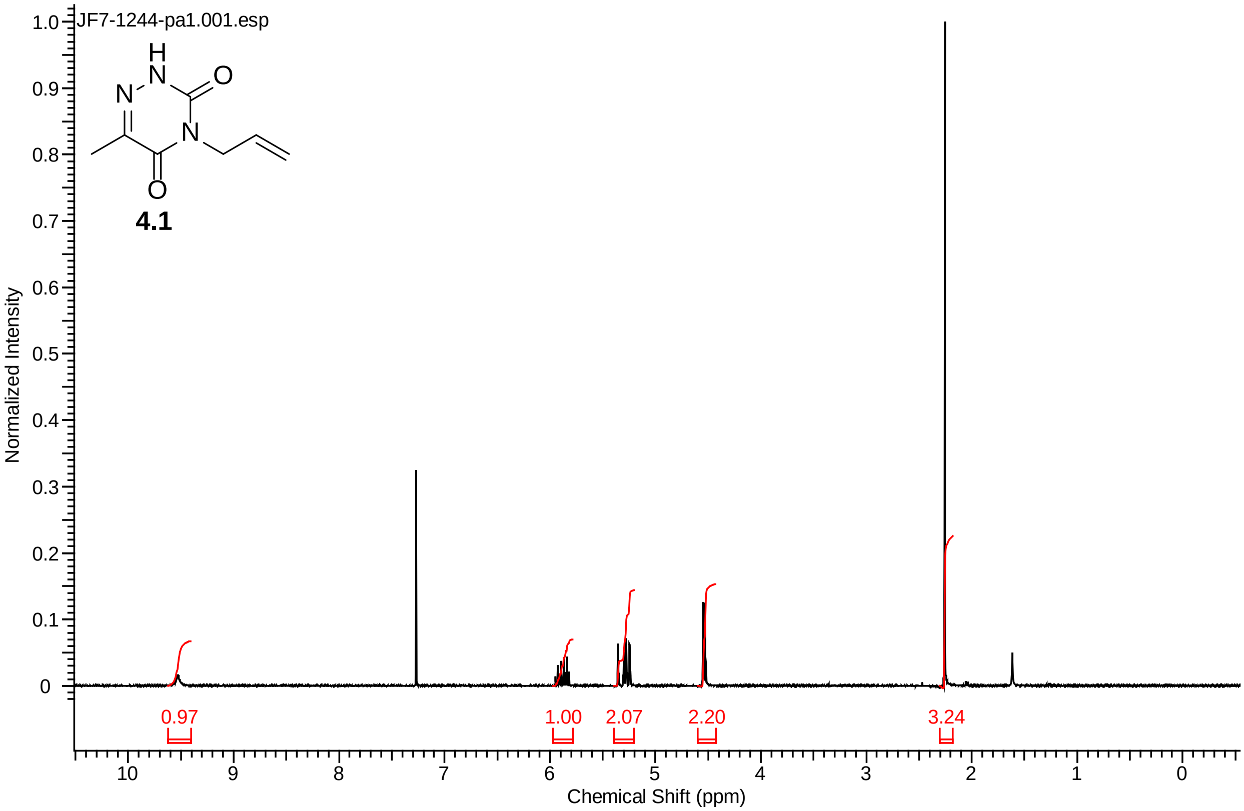

JF9-1556-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
171.5781
170.8363
158.1522
154.5739
139.4460
139.2715
135.5768
134.0640
128.8274
128.7402
127.7074
126.6164
126.5146
60.7376
60.6794
53.2318
50.7008
43.7042
43.1223
33.3329
31.8055
14.1031
13.9285
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

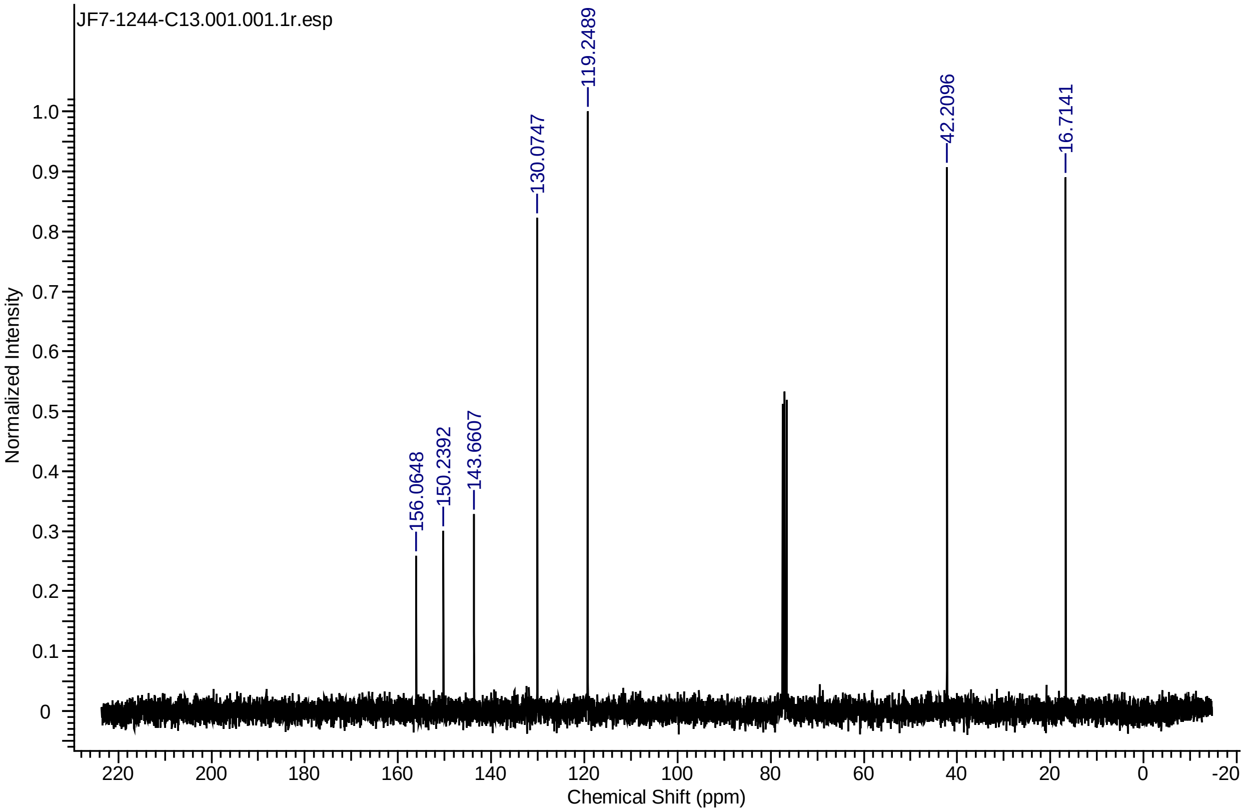

JF9-1577-carac-H.001.esp
3.111
N
N
N
O
O
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
0.95
3.11
0.72
0.25
2.03
5.11
0.01
4.31
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

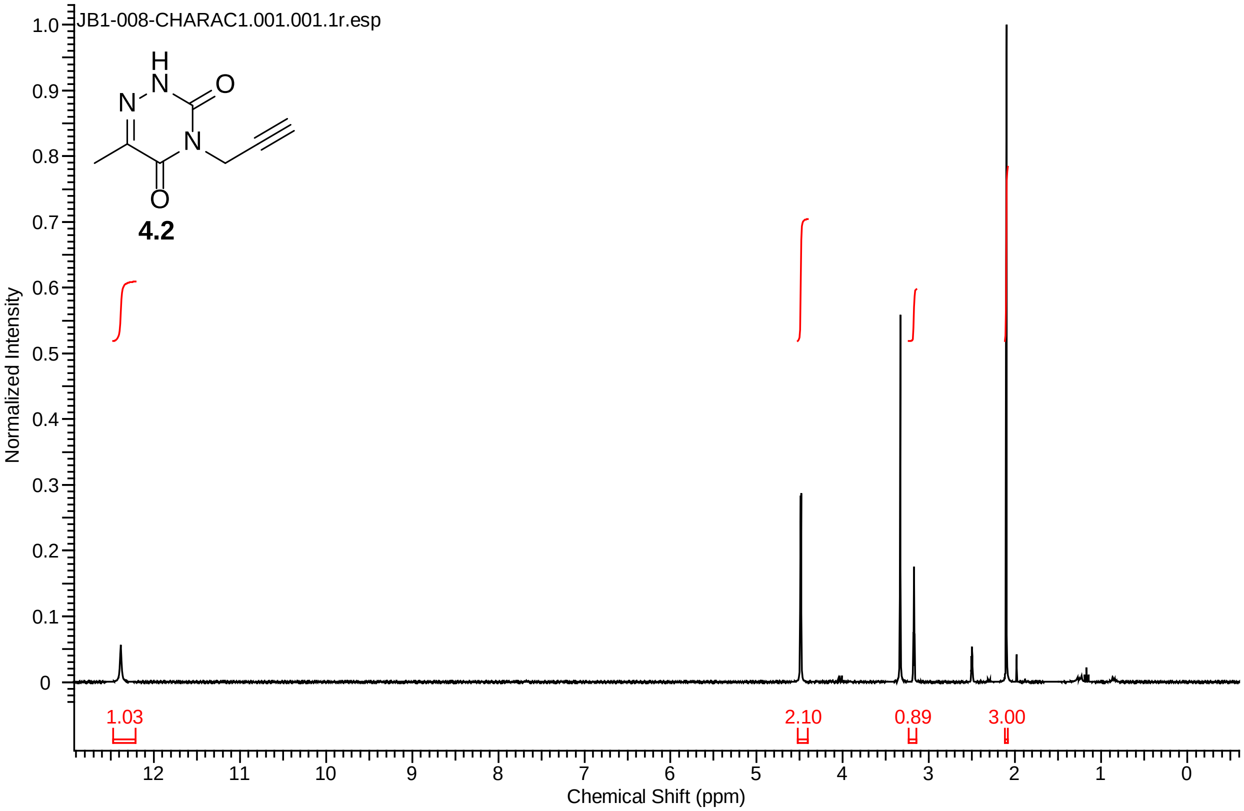

JF9-1577-carac-C13.001.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
162.2396
157.9485
157.4685
151.8247
139.0242
138.8351
132.1876
126.7328
126.4564
73.7126
71.4143
59.1666
58.0029
57.8575
47.7189
28.7073
27.7909
23.6307
22.4670
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF7-1203-pa1.001.esp
O
O
NH
N
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
0.97
2.00
2.98
3.08
3.27
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

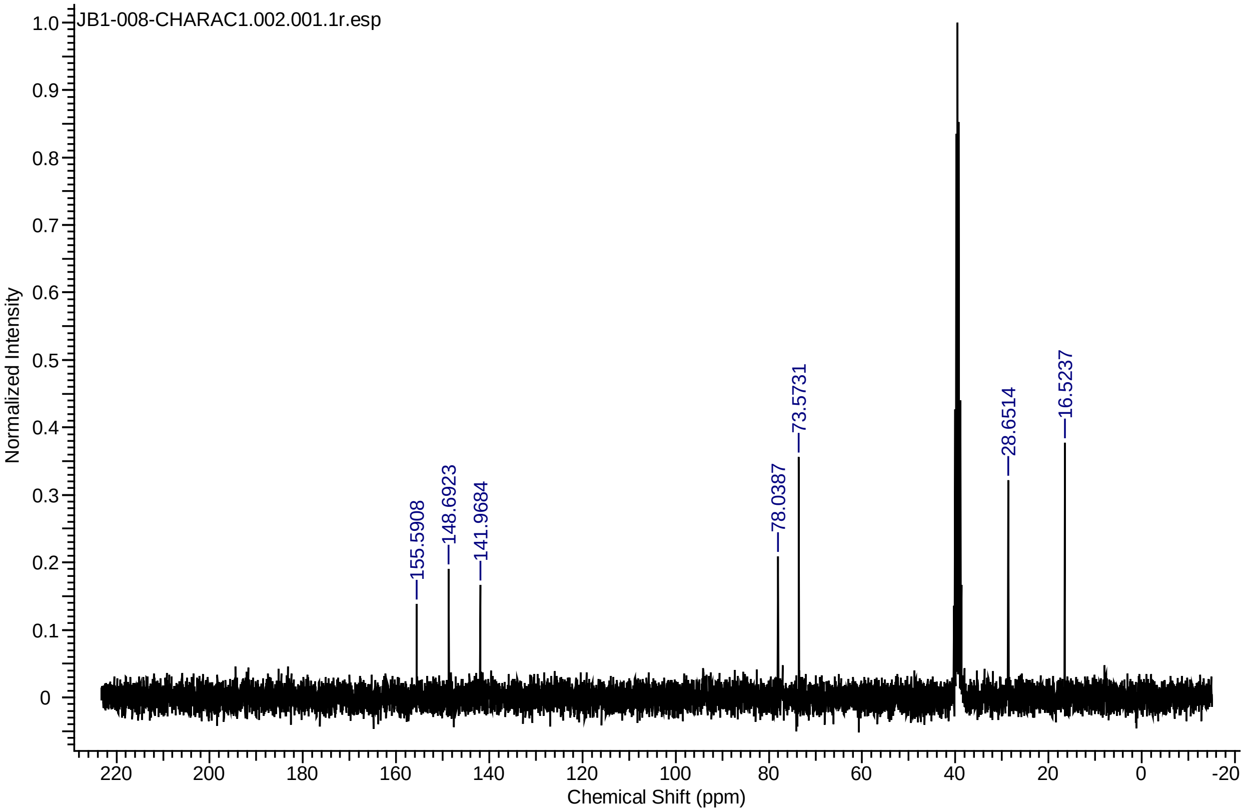

JF7-1203-C13.001.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
165.2309
150.7576
130.0150
126.2330
122.2038
52.7030
13.5015
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

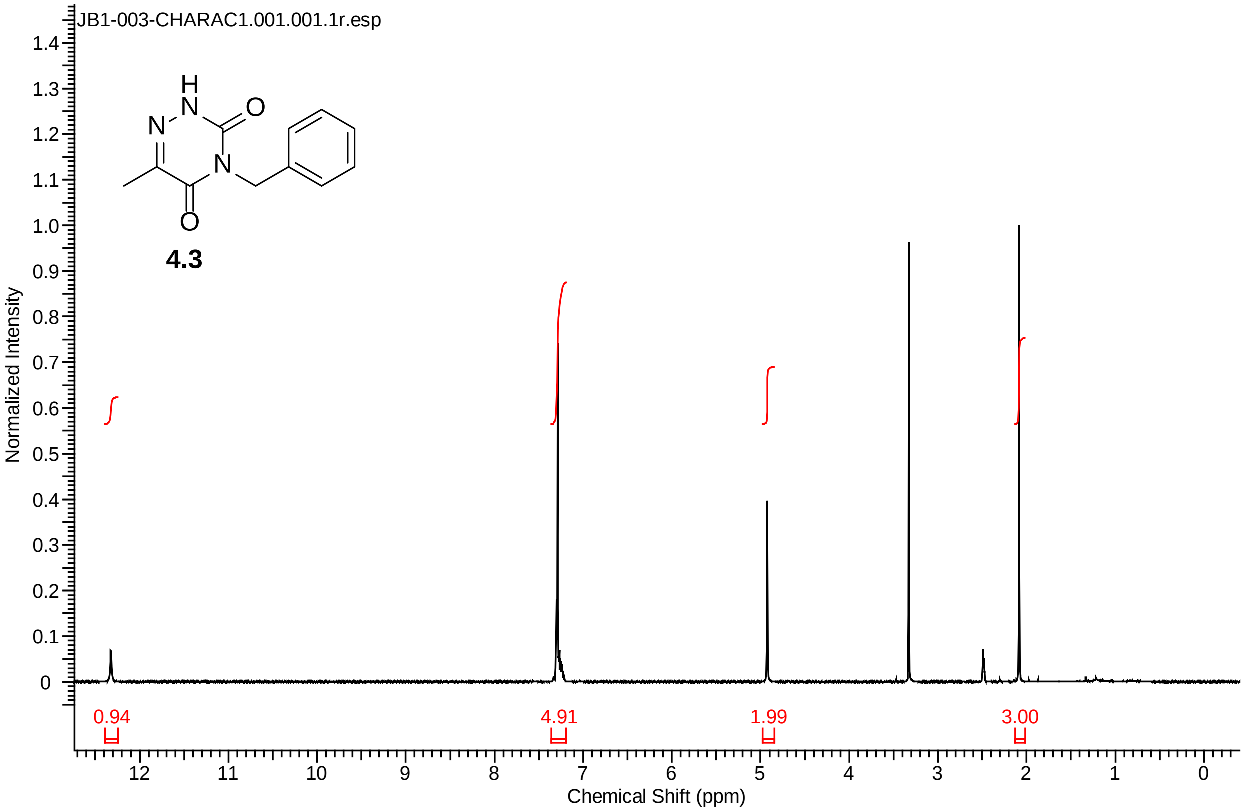

JF7-1244-pa1.001.esp
H
N
N
O
N
O
4.1
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.97
1.00
2.07
2.20
3.24
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

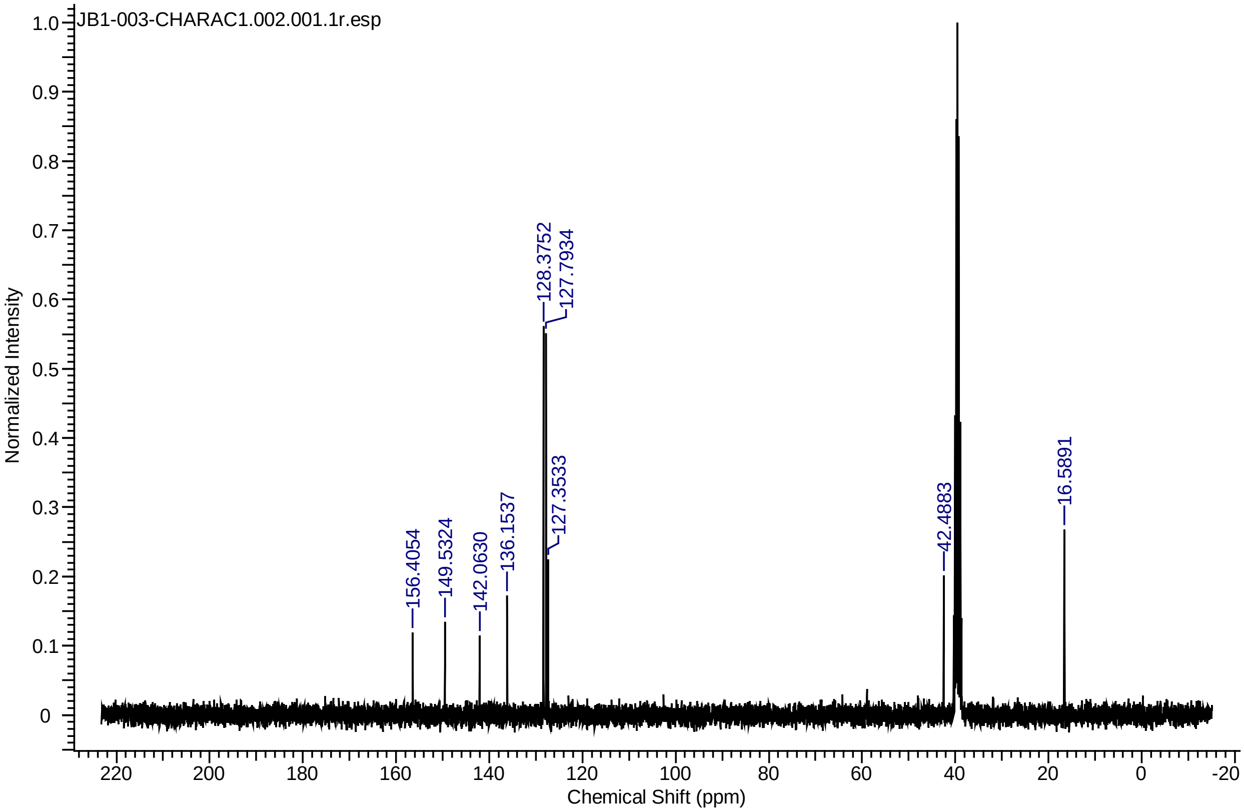

JF7-1244-C13.001.001.1r.esp
156.0648
150.2392
143.6607
130.0747
119.2489
42.2096
16.7141
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

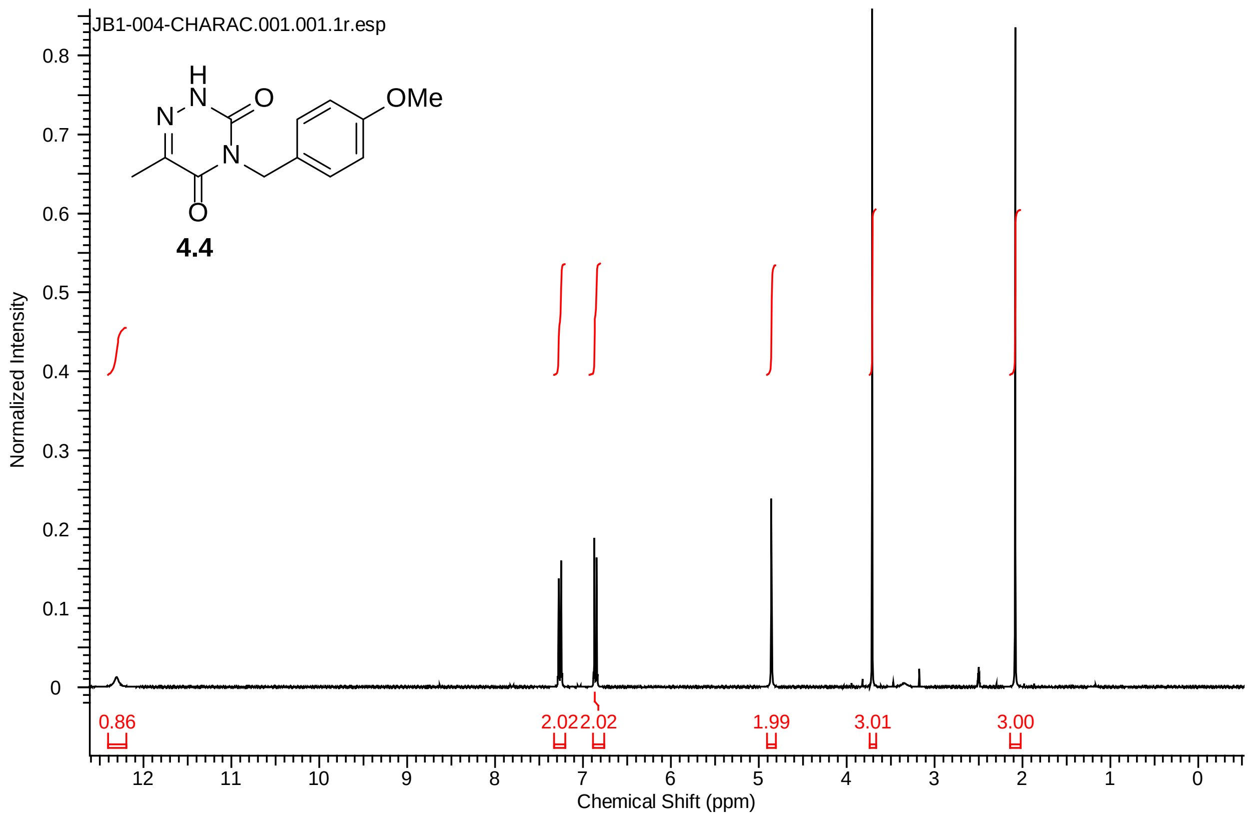

JB1-008-CHARAC1.001.001.1r.esp
H
N
N
O
N
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.03
2.10
0.89
3.00
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

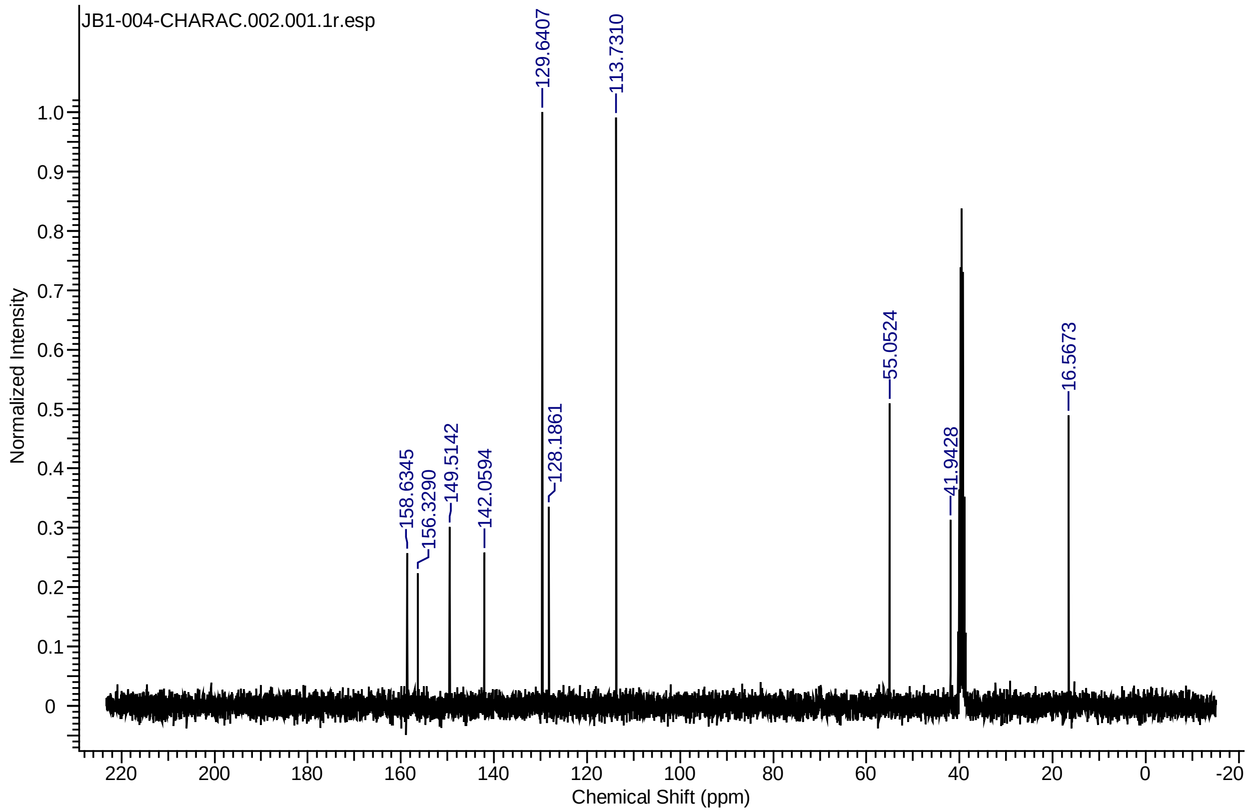
4.2

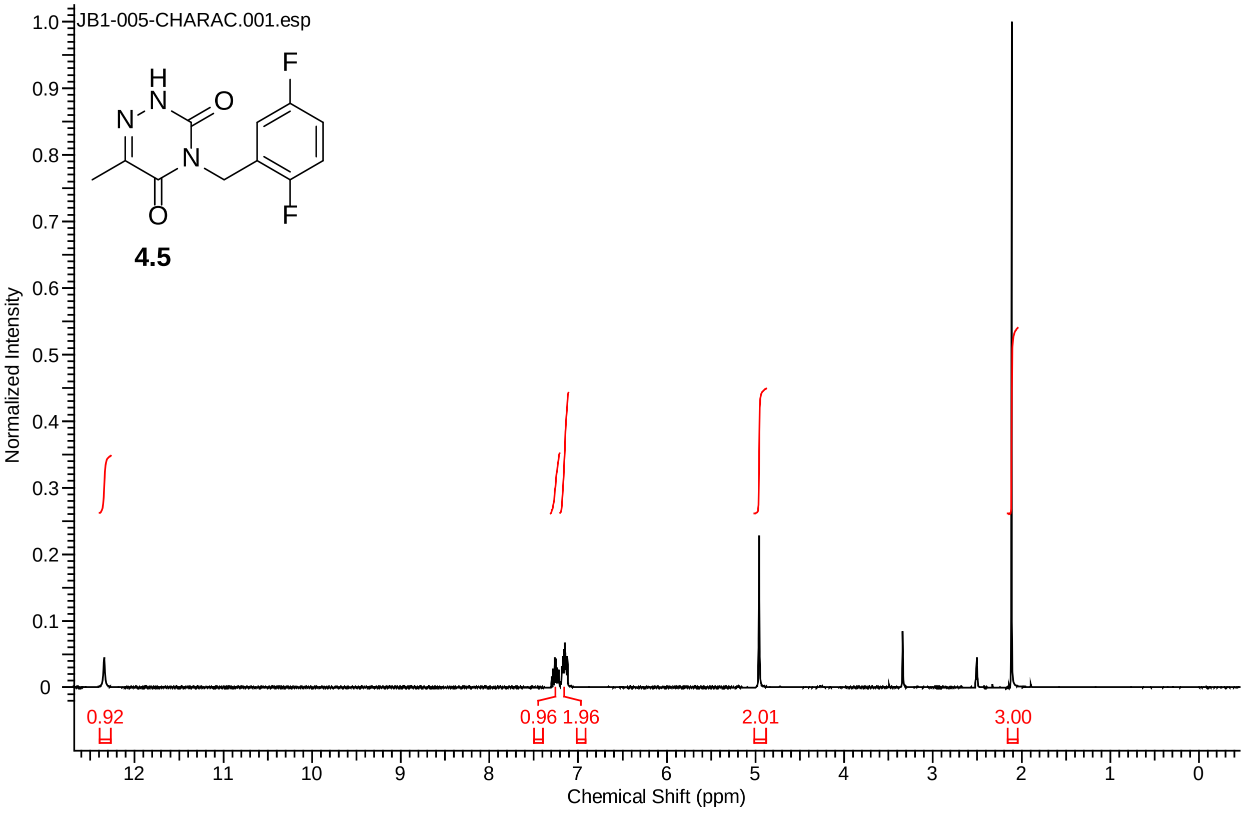

JB1-008-CHARAC1.002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
155.5908
148.6923
141.9684
78.0387
73.5731
28.6514
16.5237
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

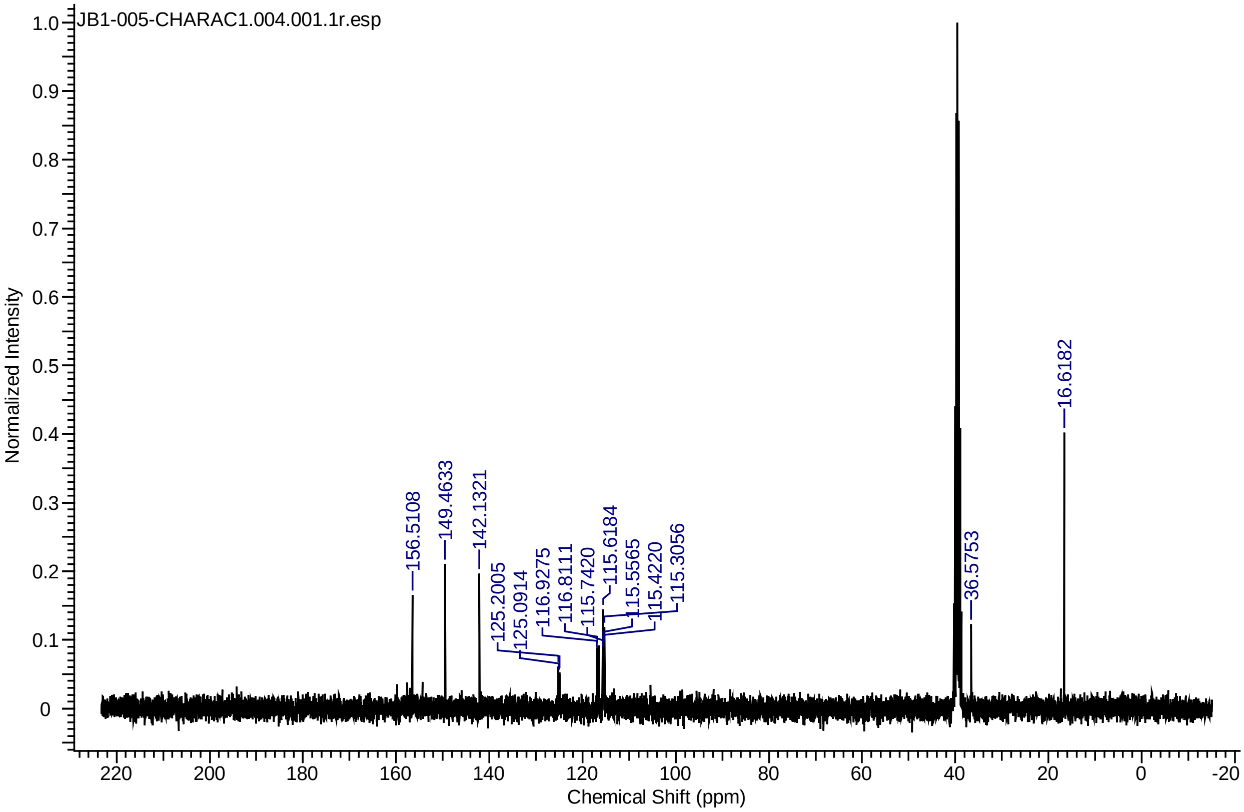

JB1-003-CHARAC1.001.001.1r.esp
H
N
N
O
N
O
4.3
Normalized Intensity
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.94
4.91
1.99
3.00
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

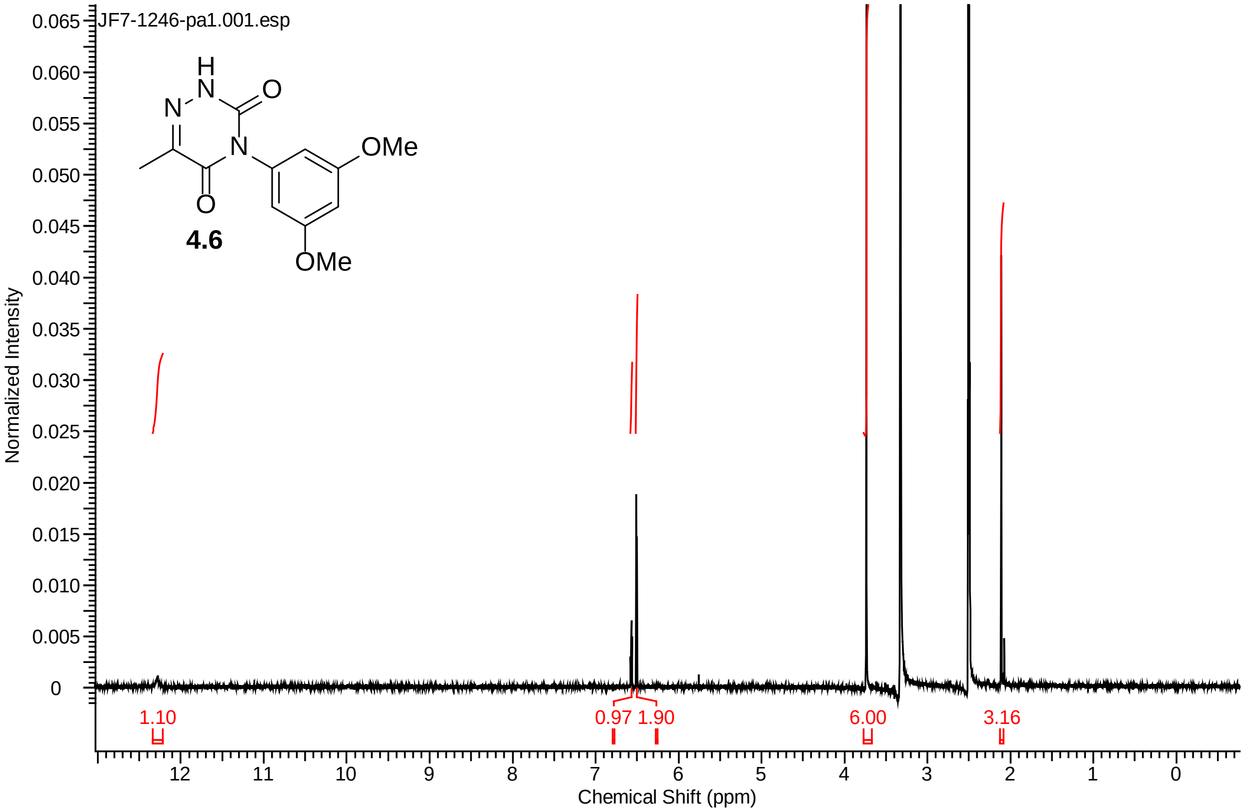

JB1-003-CHARAC1.002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
156.4054
149.5324
142.0630
136.1537
128.3752
127.7934
127.3533
42.4883
16.5891
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

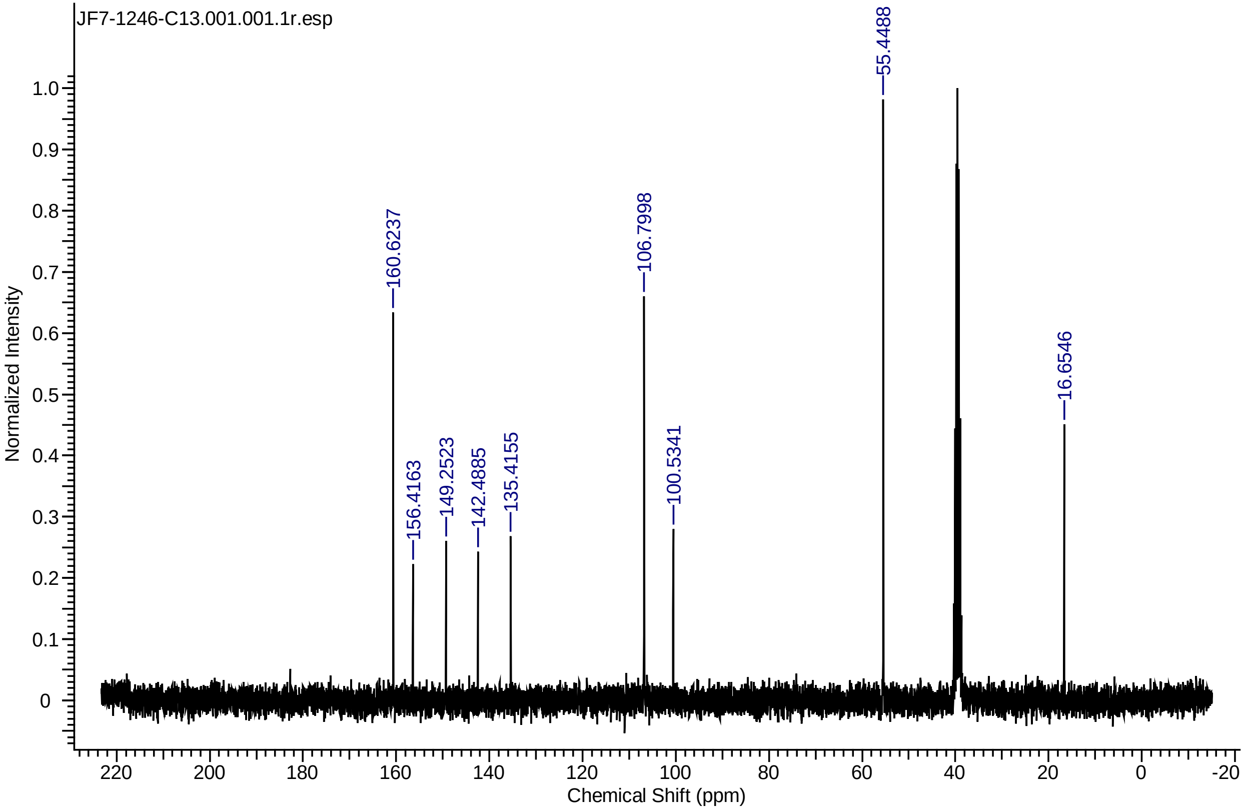

JB1-004-CHARAC.001.001.1r.esp
H
N
N
O
N
O
OMe
4.4
Normalized Intensity
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.86
2.02
2.02
1.99
3.01
3.00
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

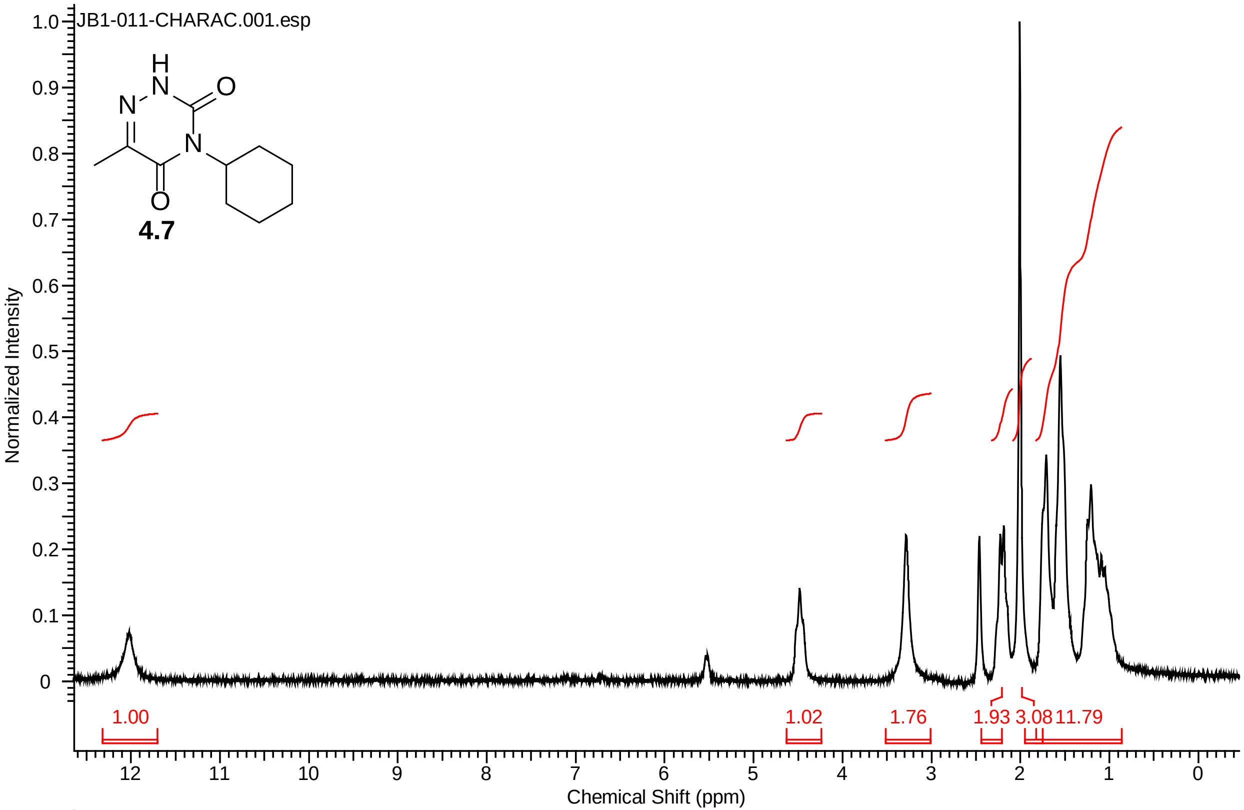

JB1-004-CHARAC.002.001.1r.esp
129.6407
113.7310
55.0524
16.5673
158.6345
156.3290
149.5142
142.0594
128.1861
41.9428
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

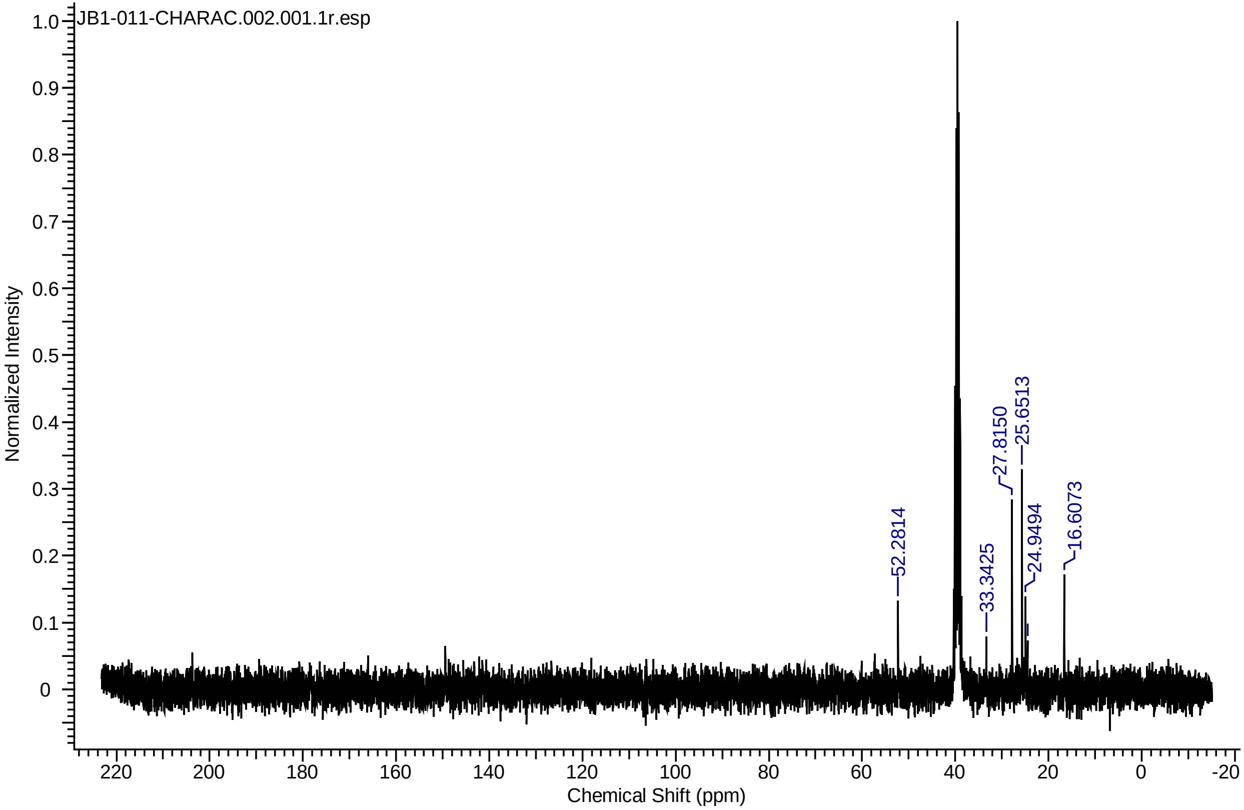

JB1-005-CHARAC.001.esp
4.5
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.92
0.96
1.96
2.01
3.00
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

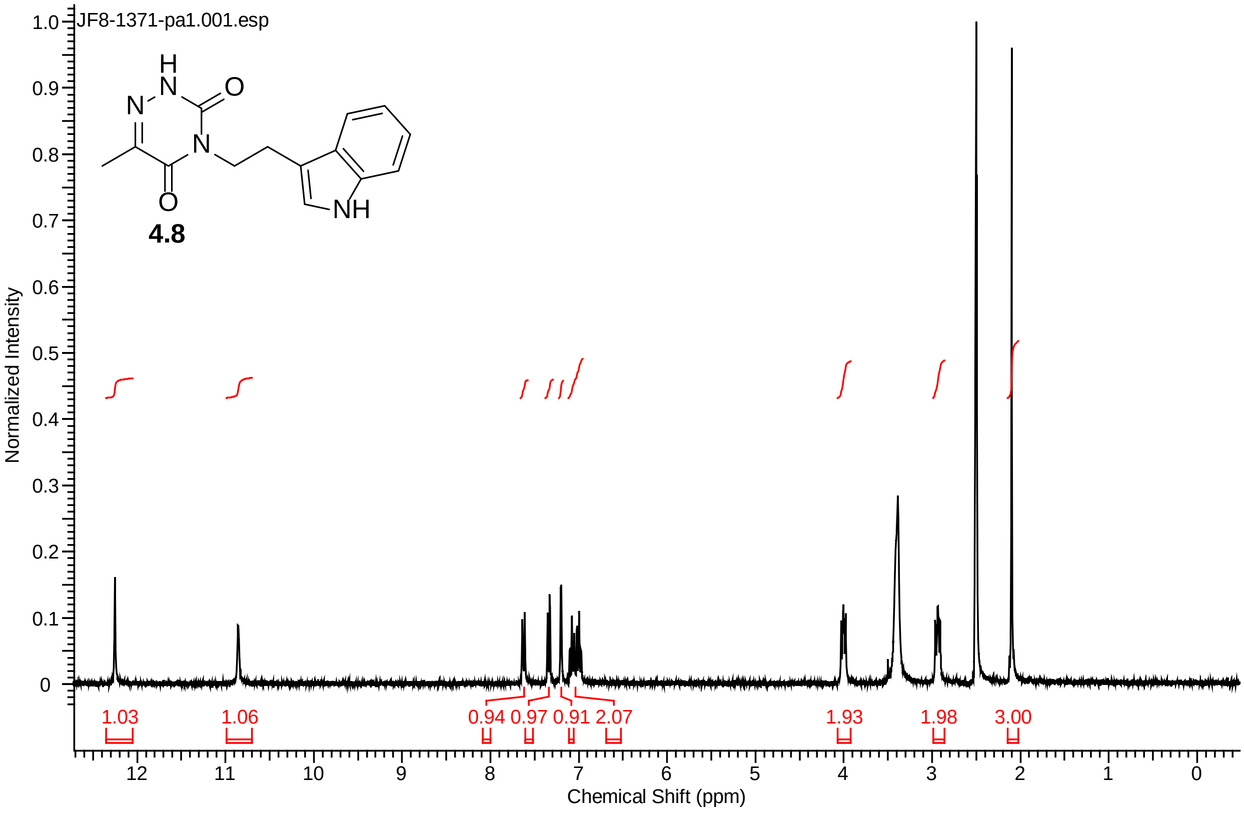

JB1-005-CHARAC1.004.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
156.5108
149.4633
142.1321
125.2005
125.0914
116.9275
116.8111
115.7420
115.6184
115.5565
115.4220
115.3056
36.5753
16.6182
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

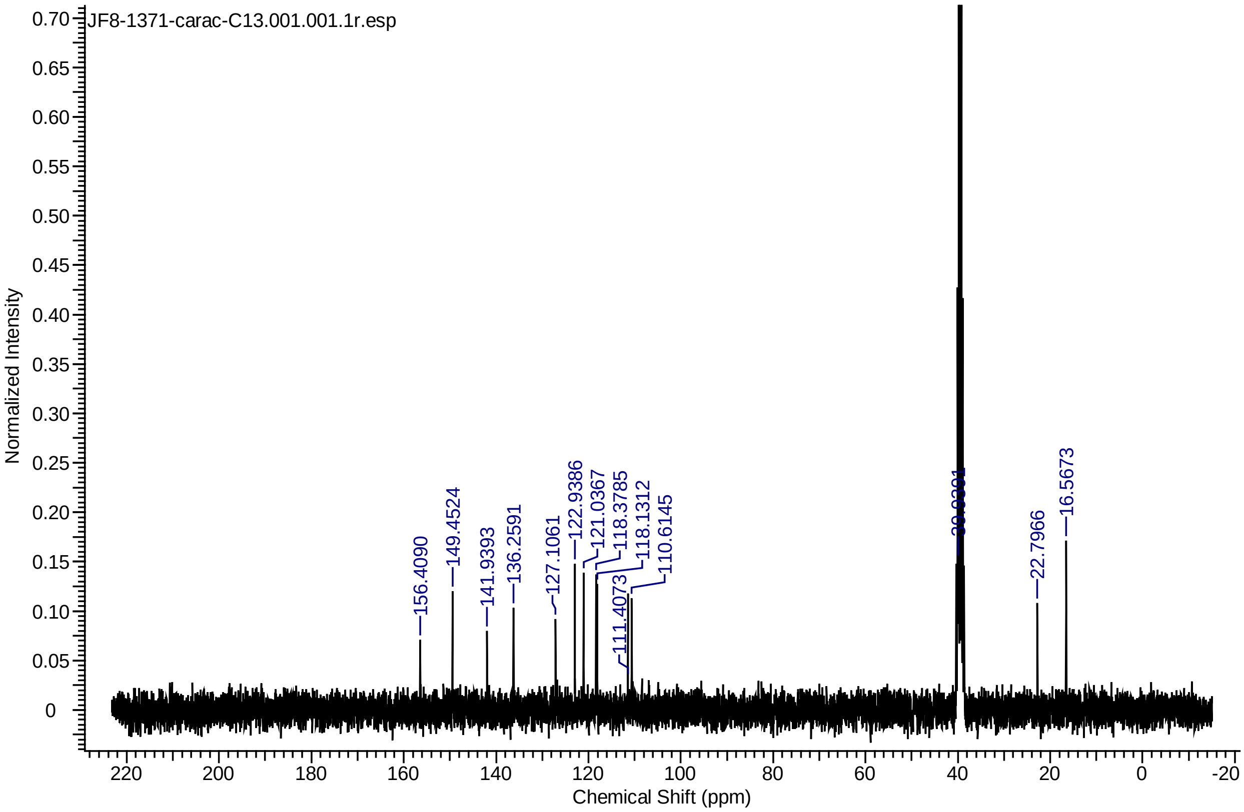

JF7-1246-pa1.001.esp
H
N
N
O
N
OMe
O
OMe
4.6
Normalized Intensity
0.065
0.060
0.055
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0
1.10
0.97
1.90
6.00
3.16
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

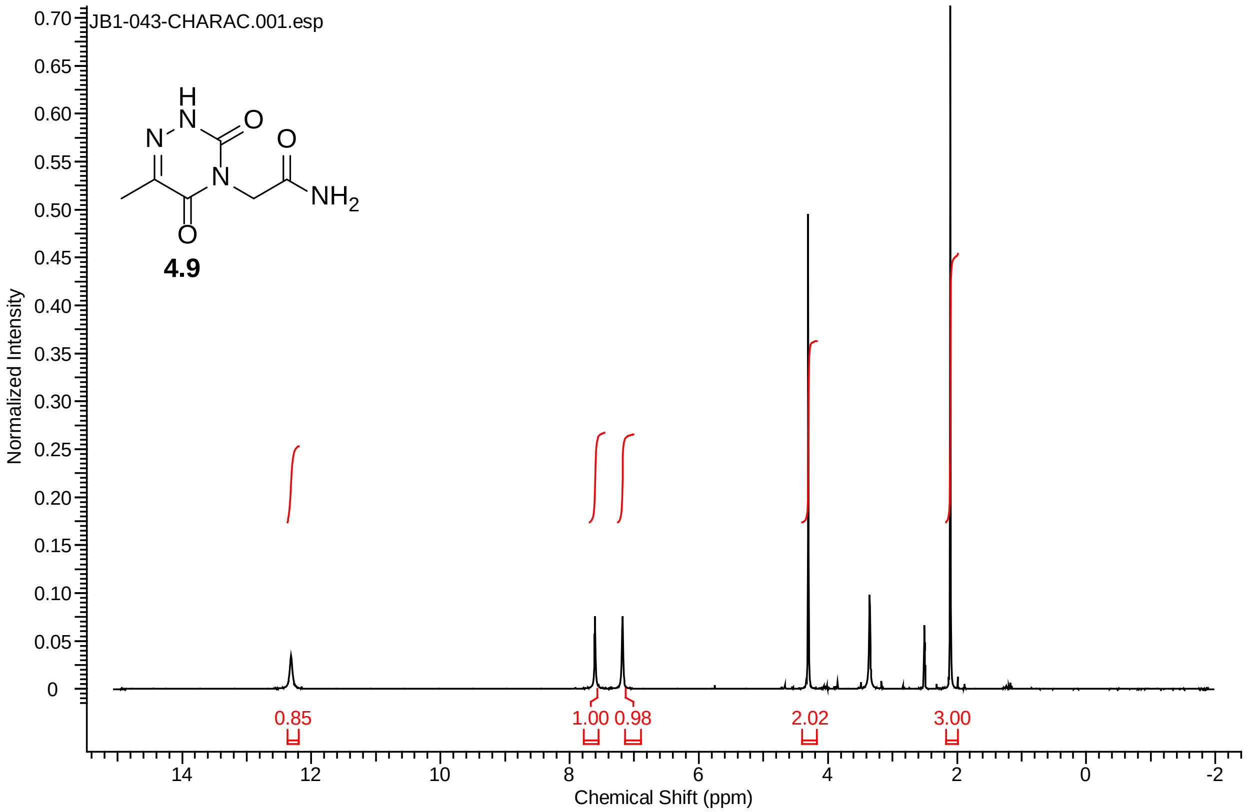

JF7-1246-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.6237
156.4163
149.2523
142.4885
135.4155
106.7998
100.5341
55.4488
16.6546
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

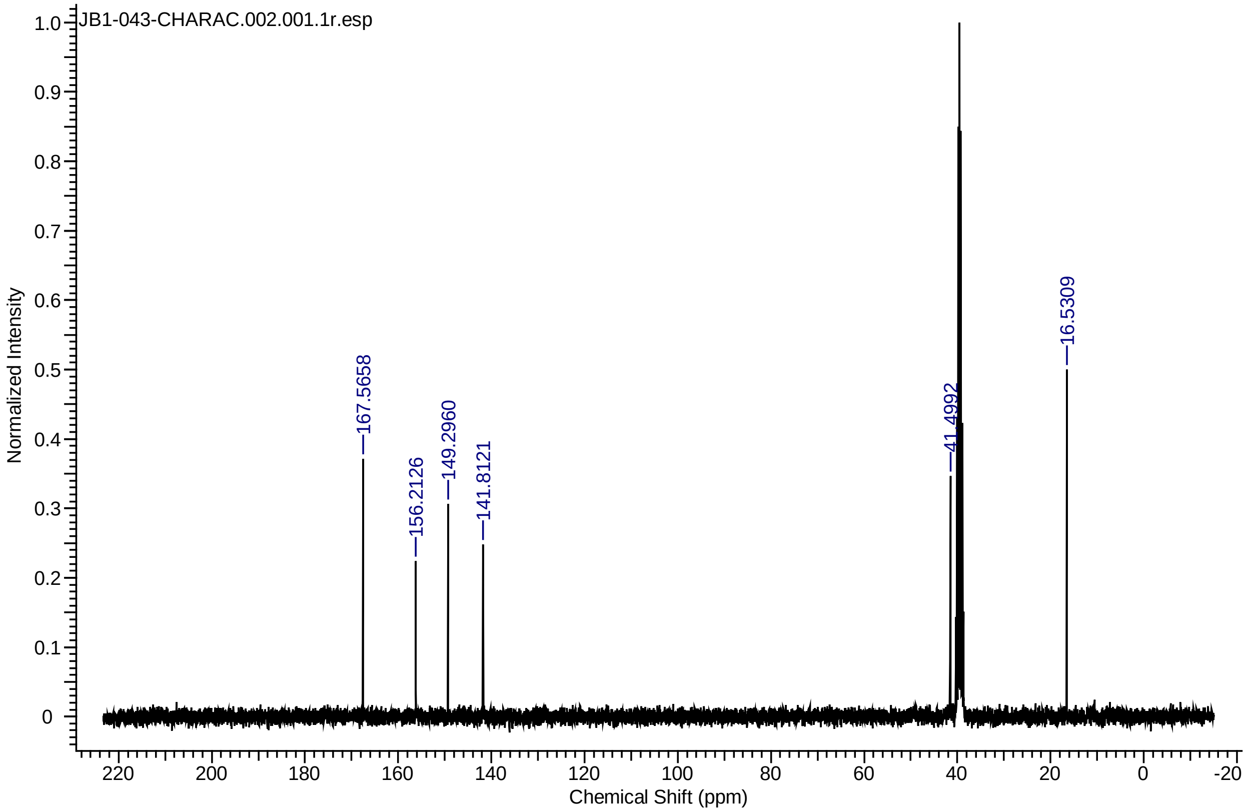

JB1-011-CHARAC.001.esp
H
N
N
O
N
O
4.7
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
1.02
1.76
1.93
3.08
11.79
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

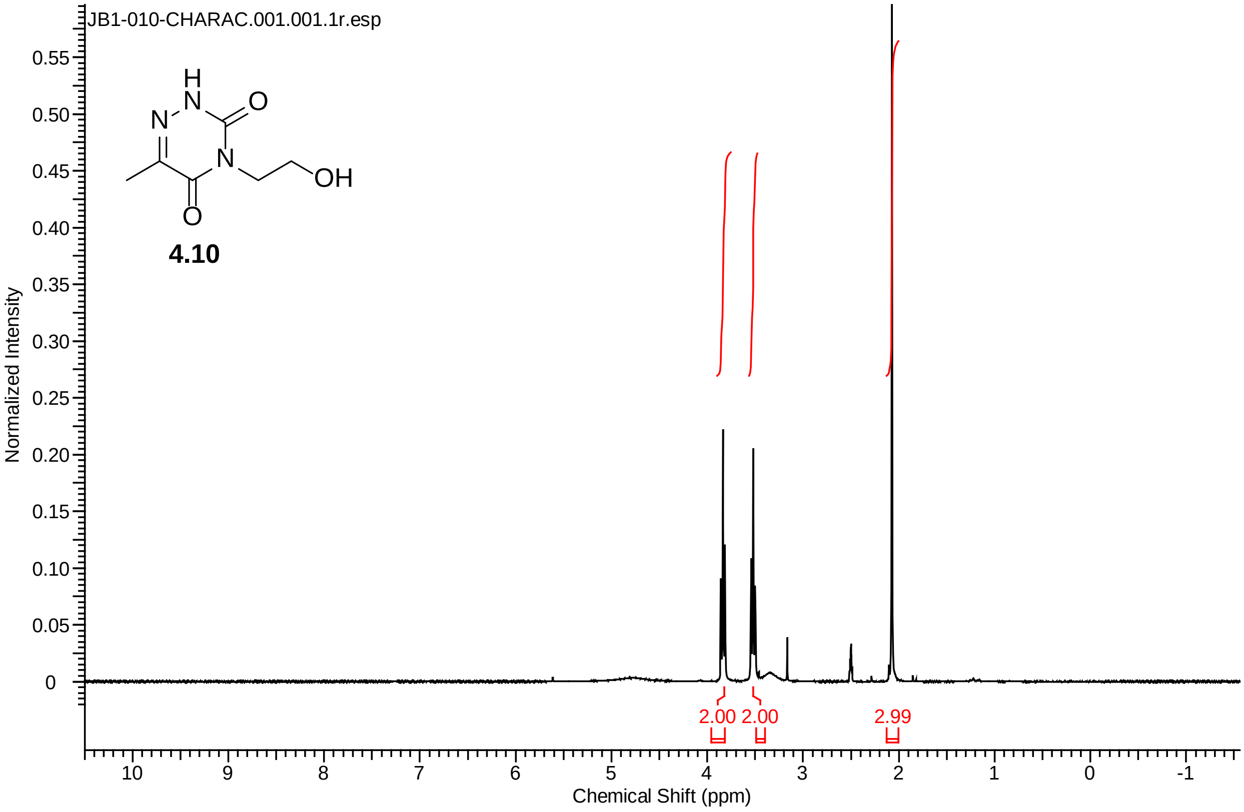

JB1-011-CHARAC.002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
52.2814
33.3425
27.8150
25.6513
24.9494
16.6073
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

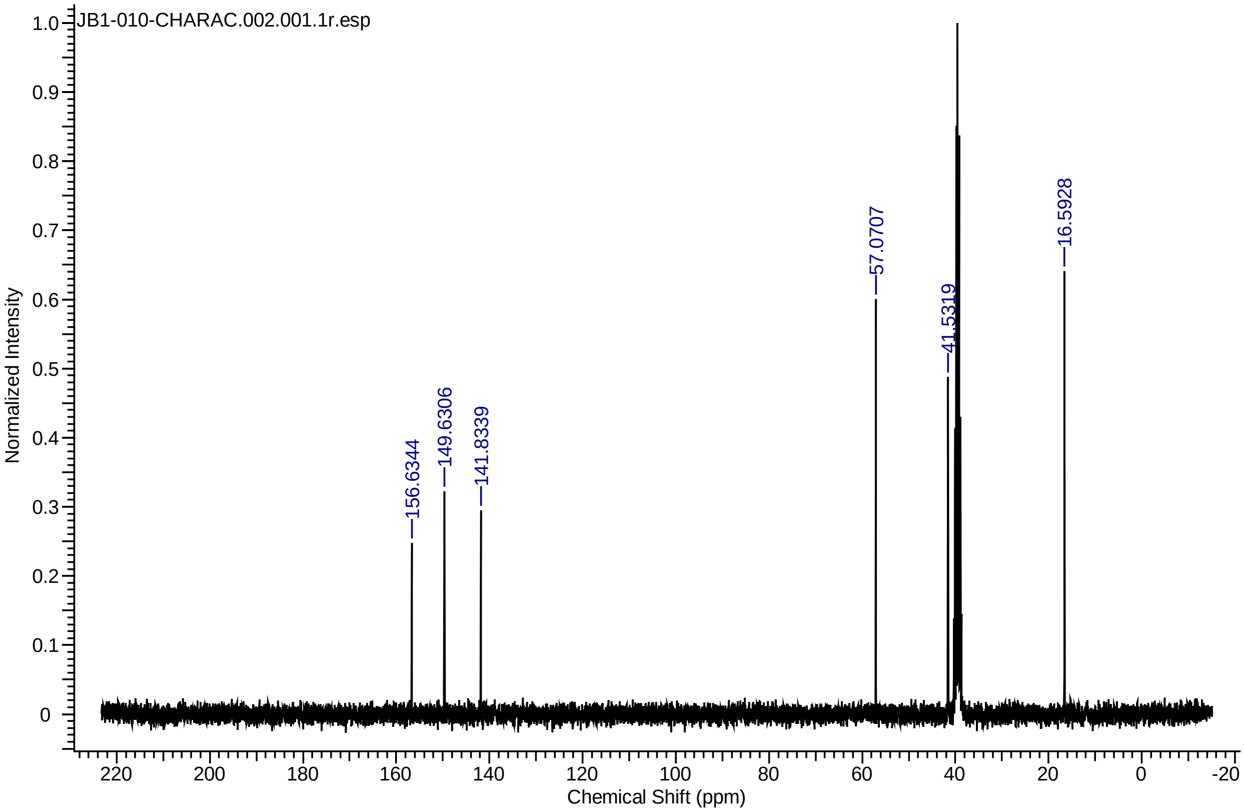

JF8-1371-pa1.001.esp
H
N
N
O
N
O
4.8
NH
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.03
1.06
0.94
0.97
0.91
2.07
1.93
1.98
3.00
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

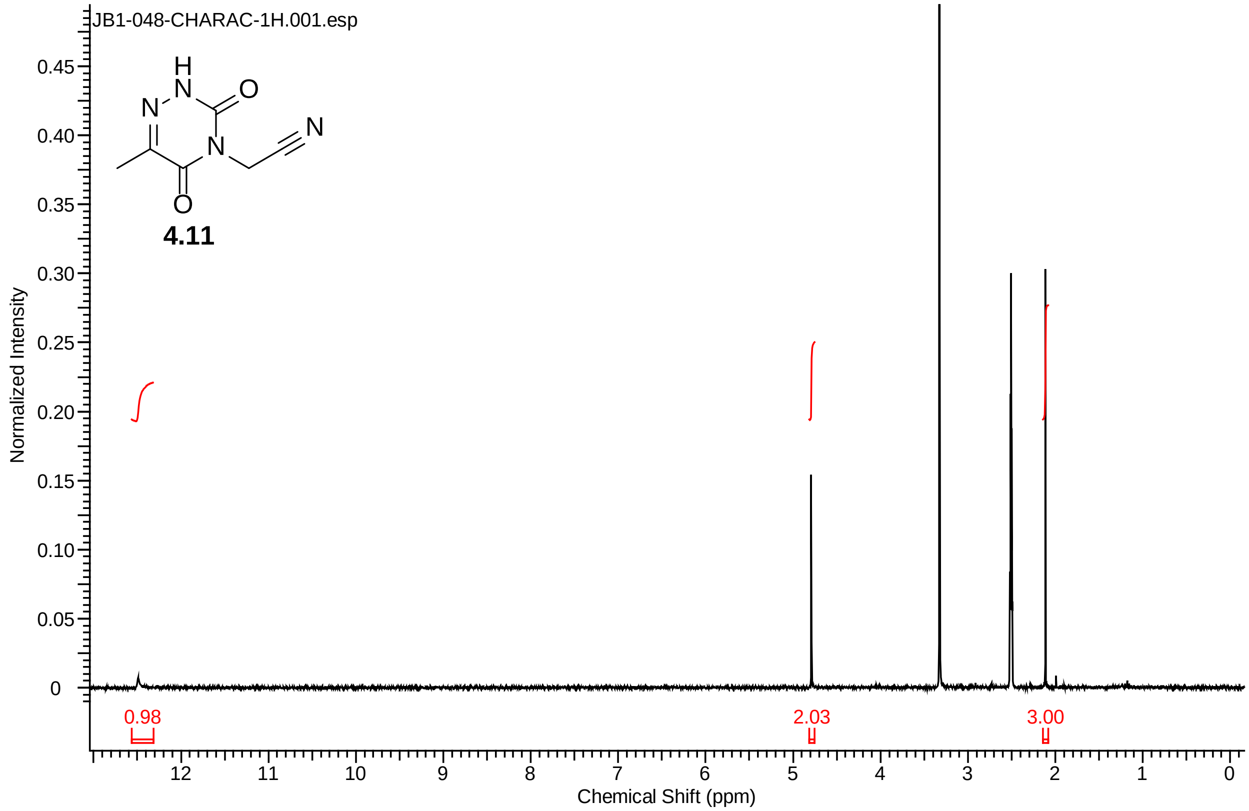

JF8-1371-carac-C13.001.001.1r.esp
Normalized Intensity
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
156.4090
149.4524
141.9393
136.2591
127.1061
122.9386
121.0367
118.3785
118.1312
111.4073
110.6145
39.9391
22.7966
16.5673
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

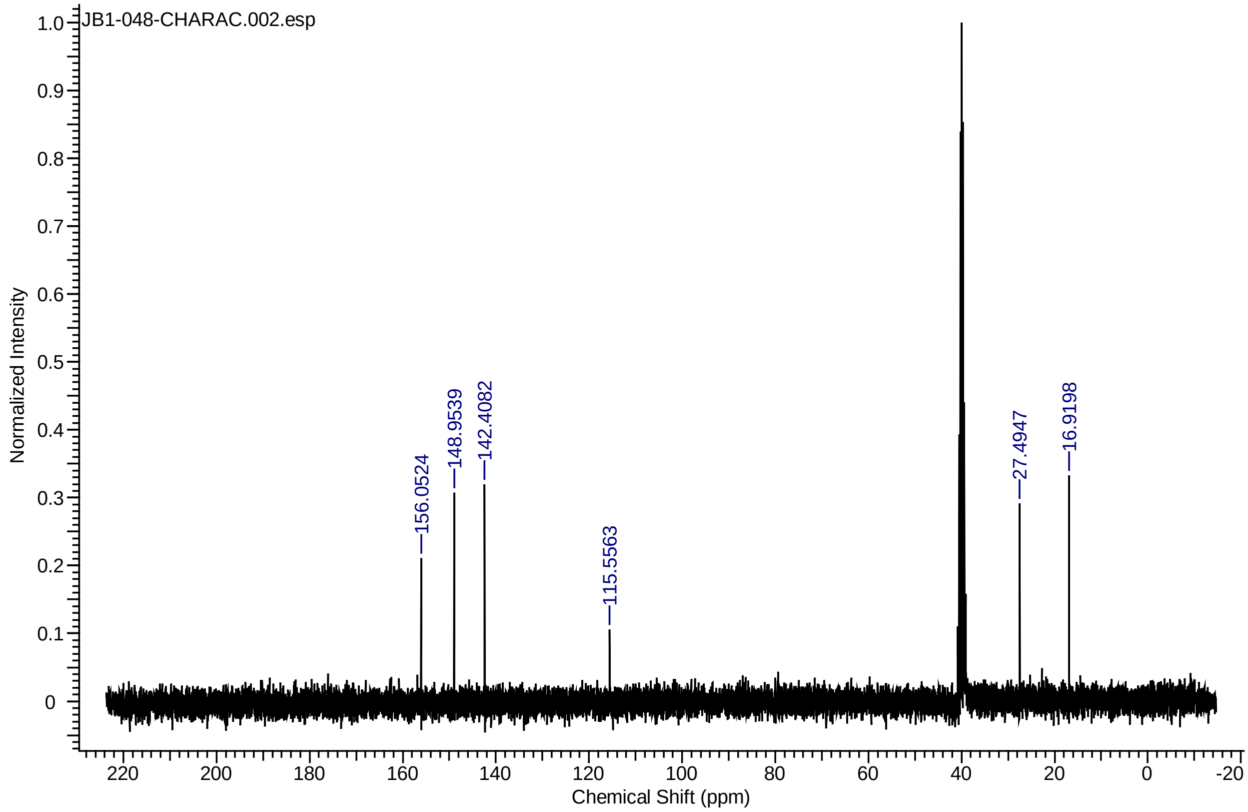

JB1-043-CHARAC.001.esp
4.9
H
N
N
O
O
N
NH2
O
Normalized Intensity
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.85
1.00
0.98
2.02
3.00
14
12
10
8
6
4
2
0
-2
Chemical Shift (ppm)

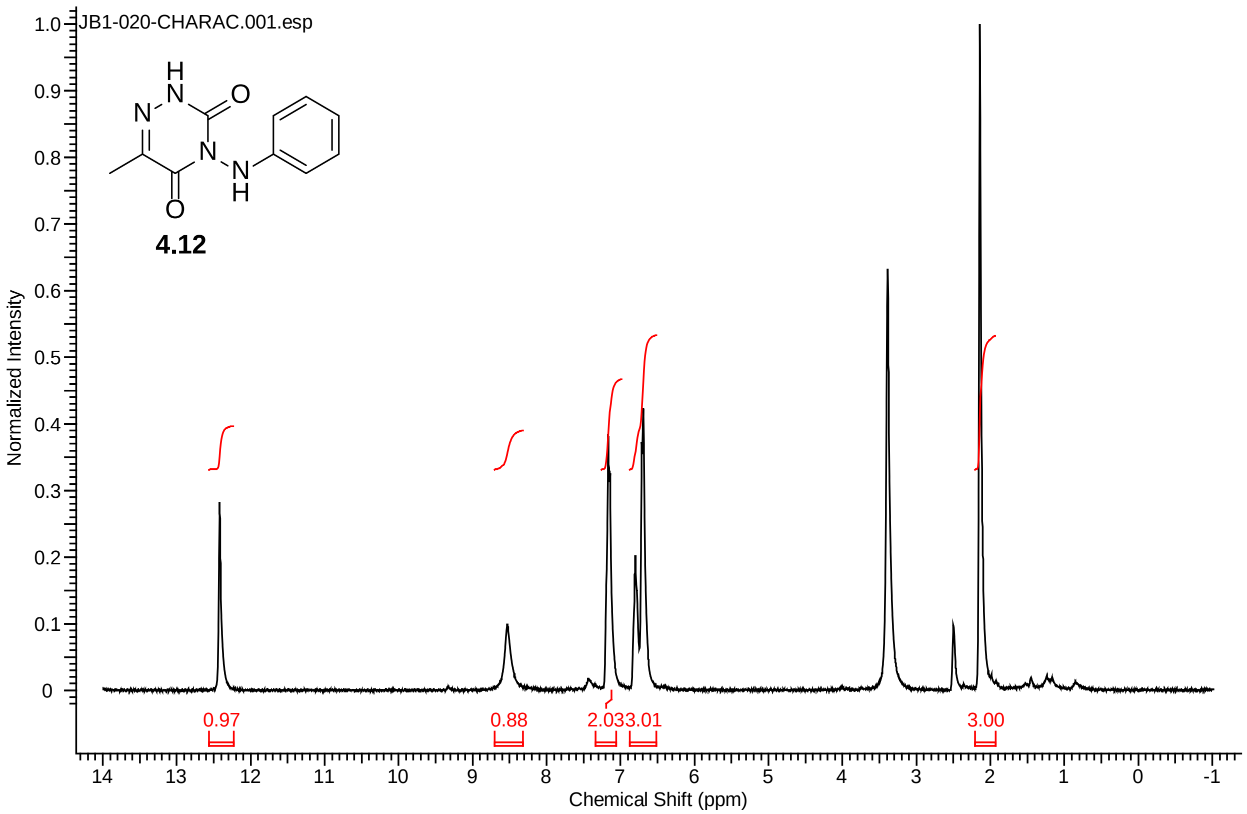

JB1-043-CHARAC.002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
167.5658
156.2126
149.2960
141.8121
41.4992
16.5309
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

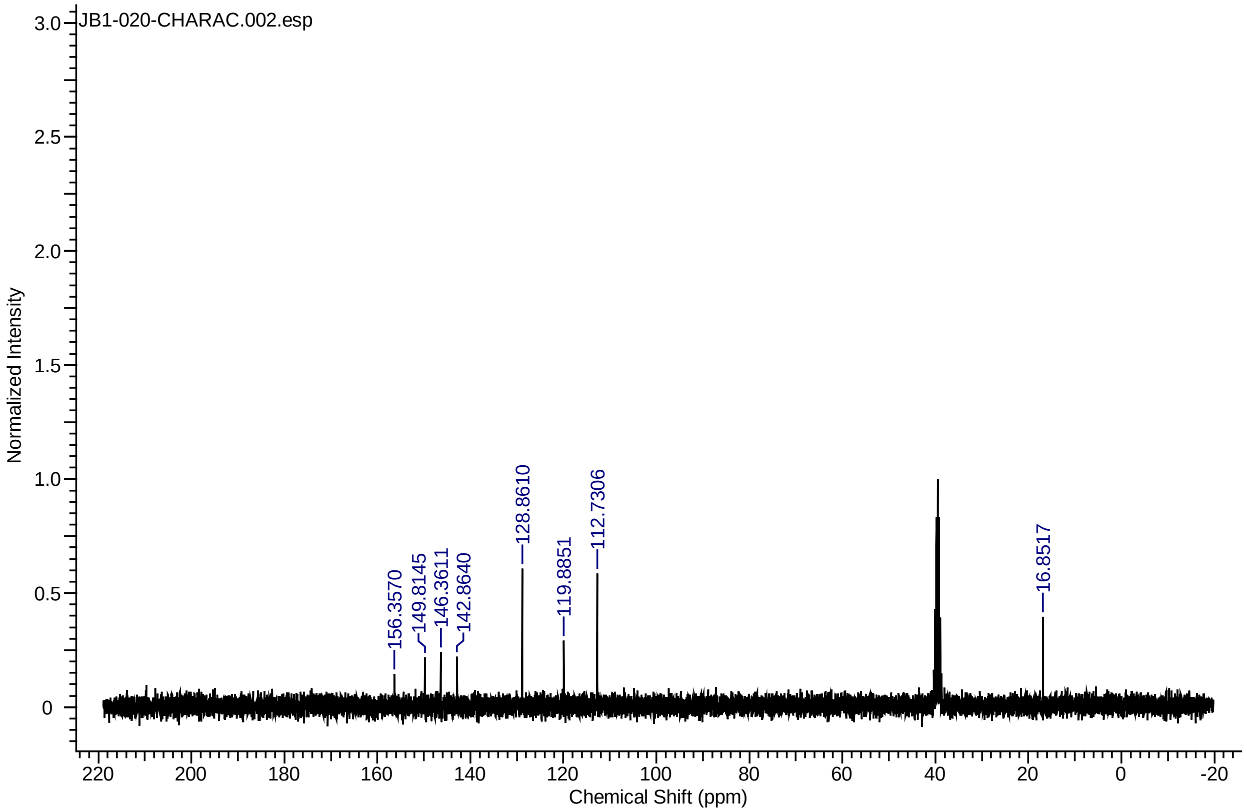

JB1-010-CHARAC.001.001.1r.esp
H
N
N
O
N
OH
O
4.10
Normalized Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
2.00
2.00
2.99
10
9
8
7
6
5
4
3
2
1
0
-1
Chemical Shift (ppm)

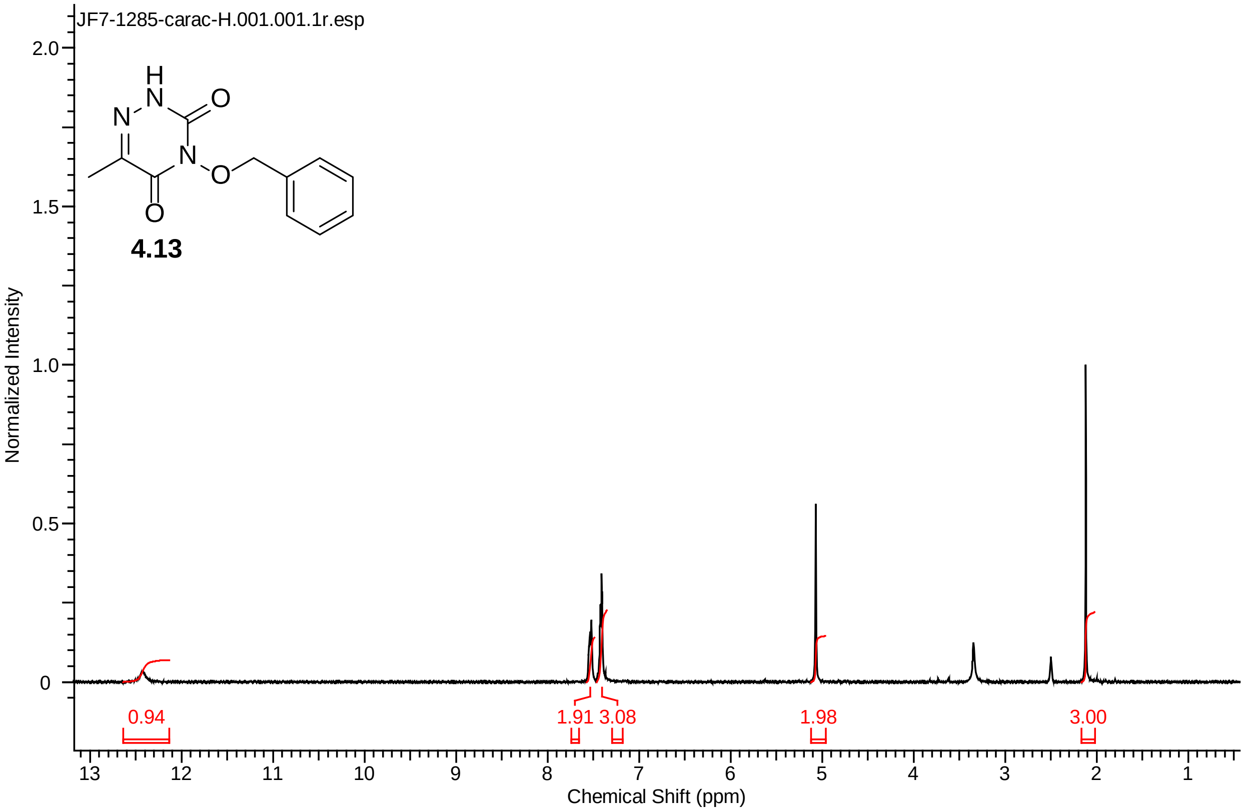

JB1-010-CHARAC.002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
156.6344
149.6306
141.8339
57.0707
41.5319
16.5928
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

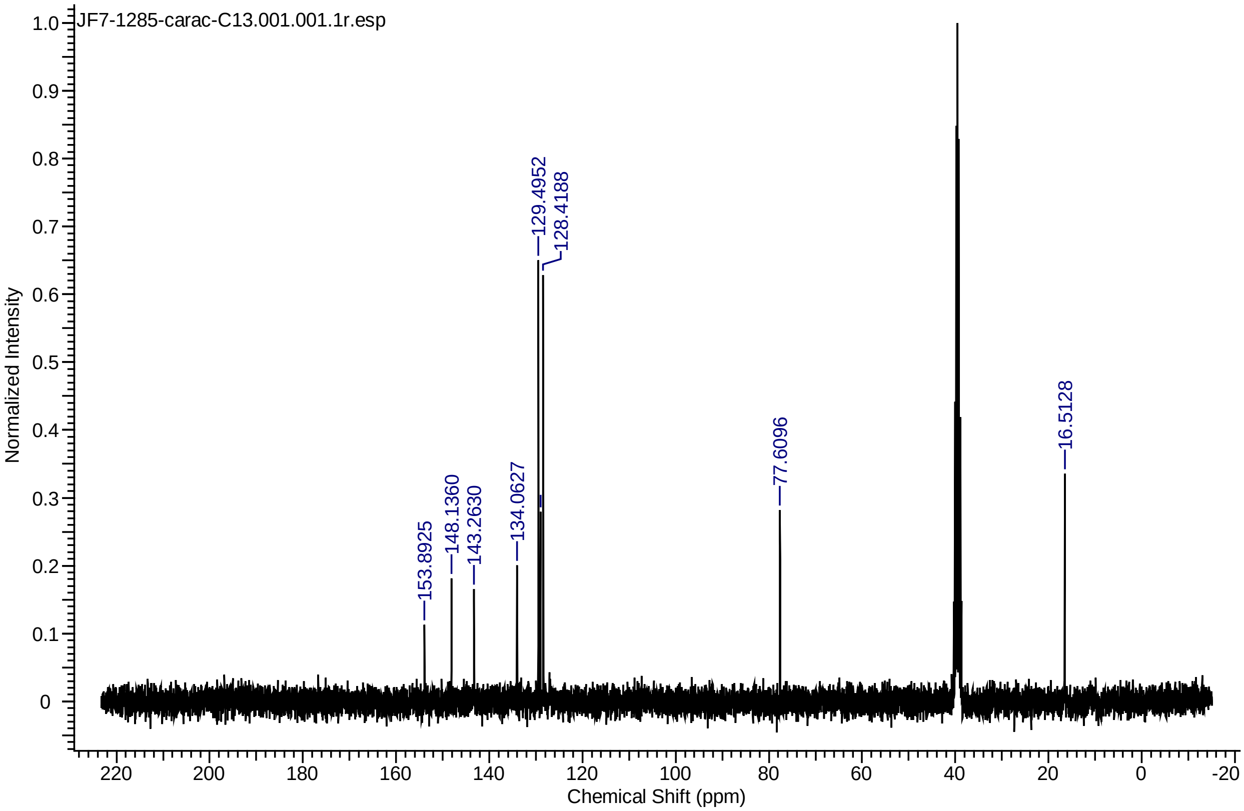

JB1-048-CHARAC-1H.001.esp
H
N
N
O
N
N
O
4.11
Normalized Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.98
2.03
3.00
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

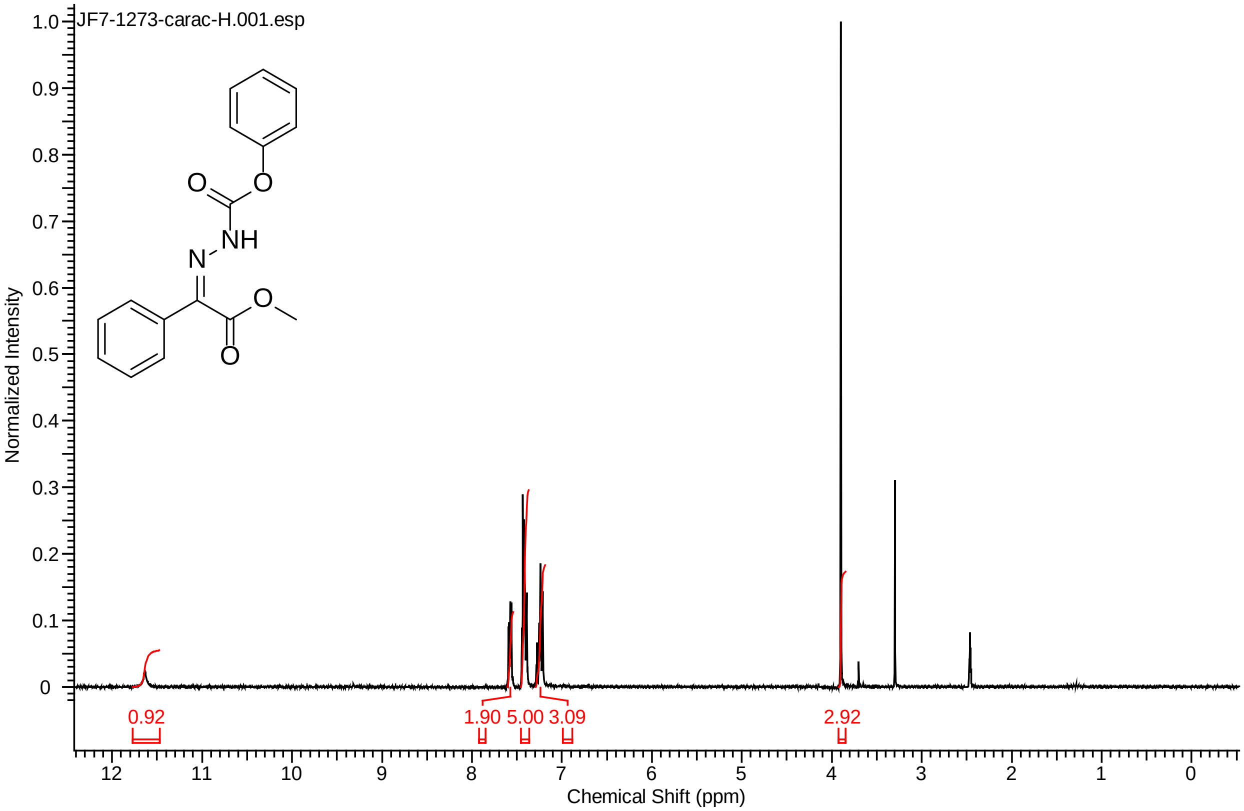

JB1-048-CHARAC.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
156.0524
148.9539
142.4082
115.5563
27.4947
16.9198
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

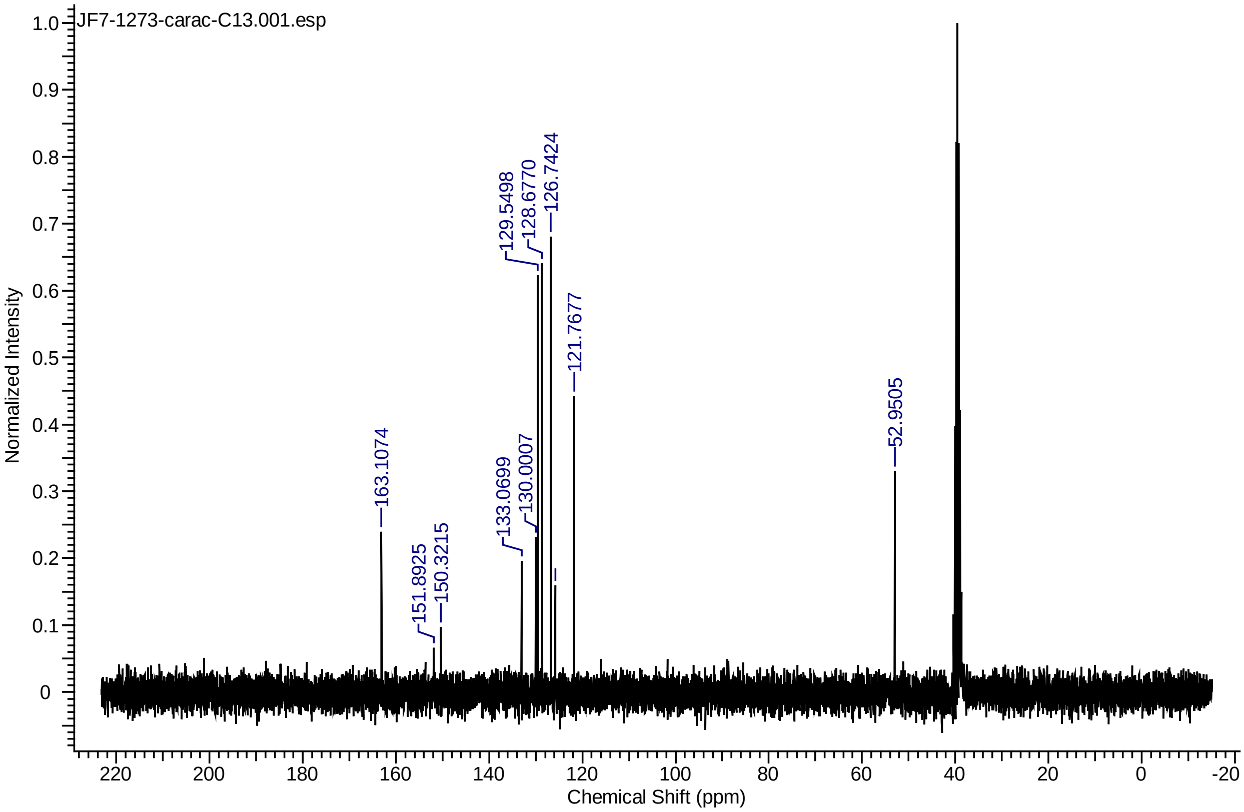

JB1-020-CHARAC.001.esp
4.12
Normalized Intensity
Chemical Shift (ppm)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.97
0.88
2.03
3.01
3.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1

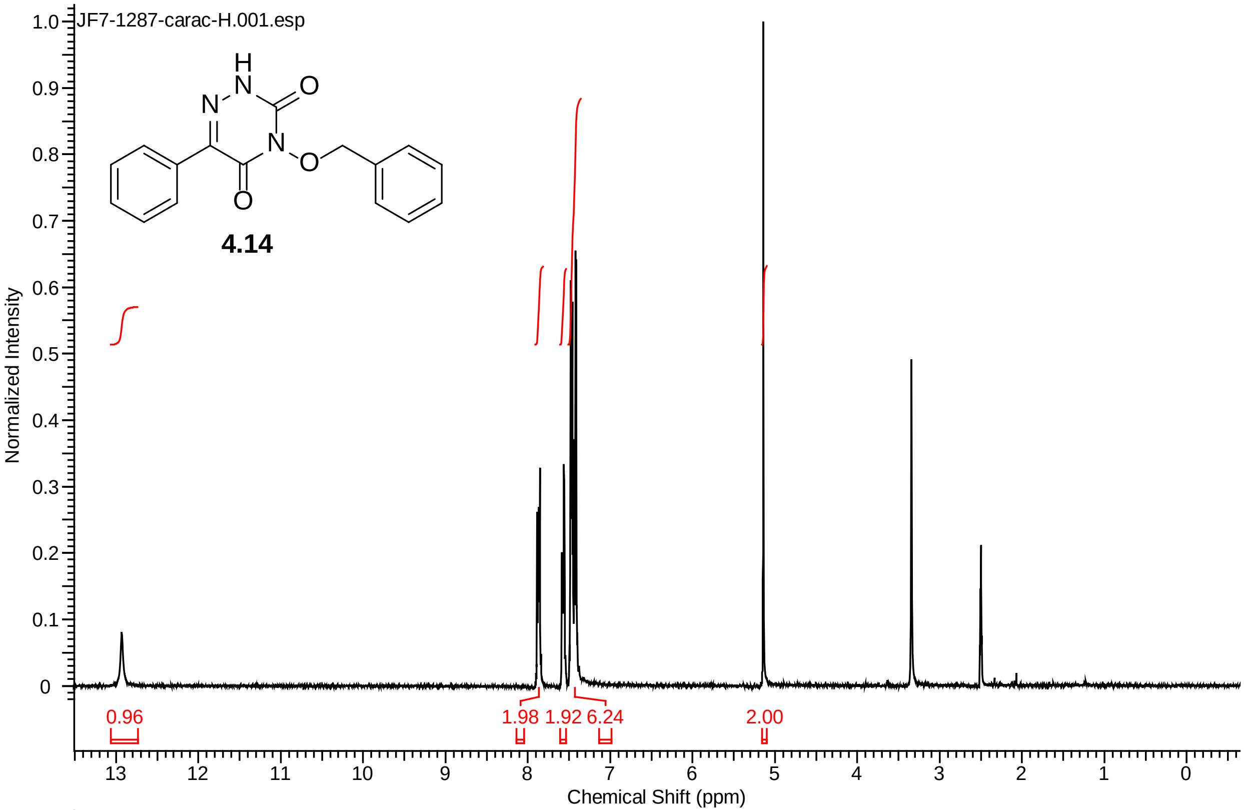

JB1-020-CHARAC.002.esp
Normalized Intensity
Chemical Shift (ppm)
3.0
2.5
2.0
1.5
1.0
0.5
0
156.3570
149.8145
146.3611
142.8640
128.8610
119.8851
112.7306
16.8517
220
200
180
160
140
120
100
80
60
40
20
0
-20

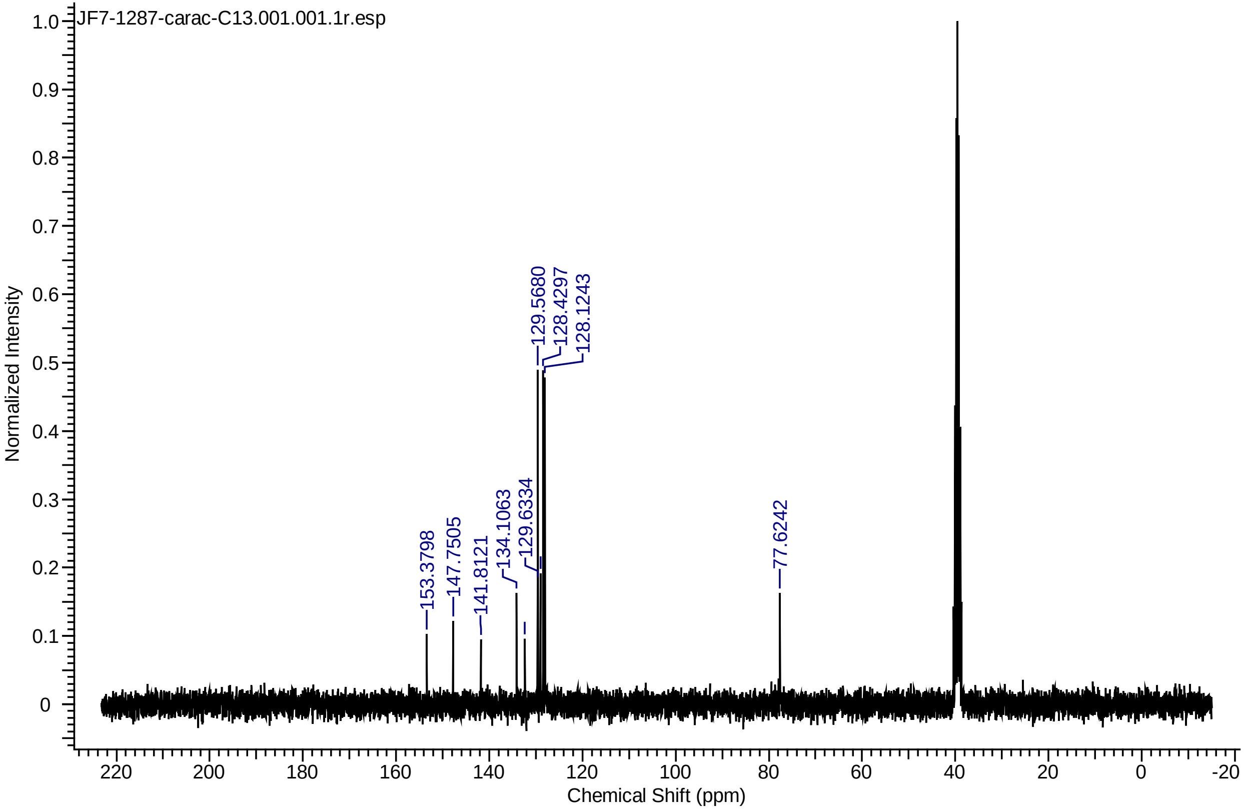

4.13
JF7-1285-carac-H.001.001.1r.esp
H
N
N
O
N
O
O
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.94
1.91
3.08
1.98
3.00
13
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

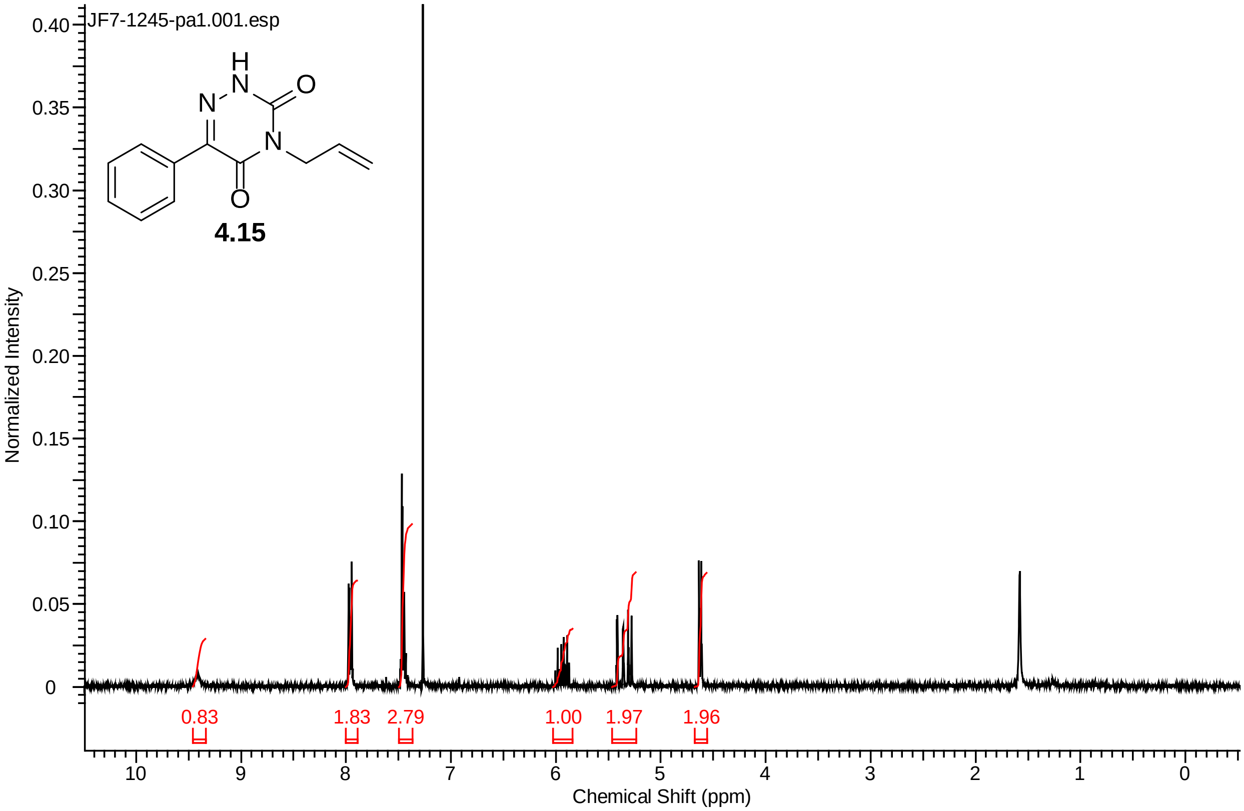

JF7-1285-carac-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
153.8925
148.1360
143.2630
134.0627
129.4952
128.4188
77.6096
16.5128
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

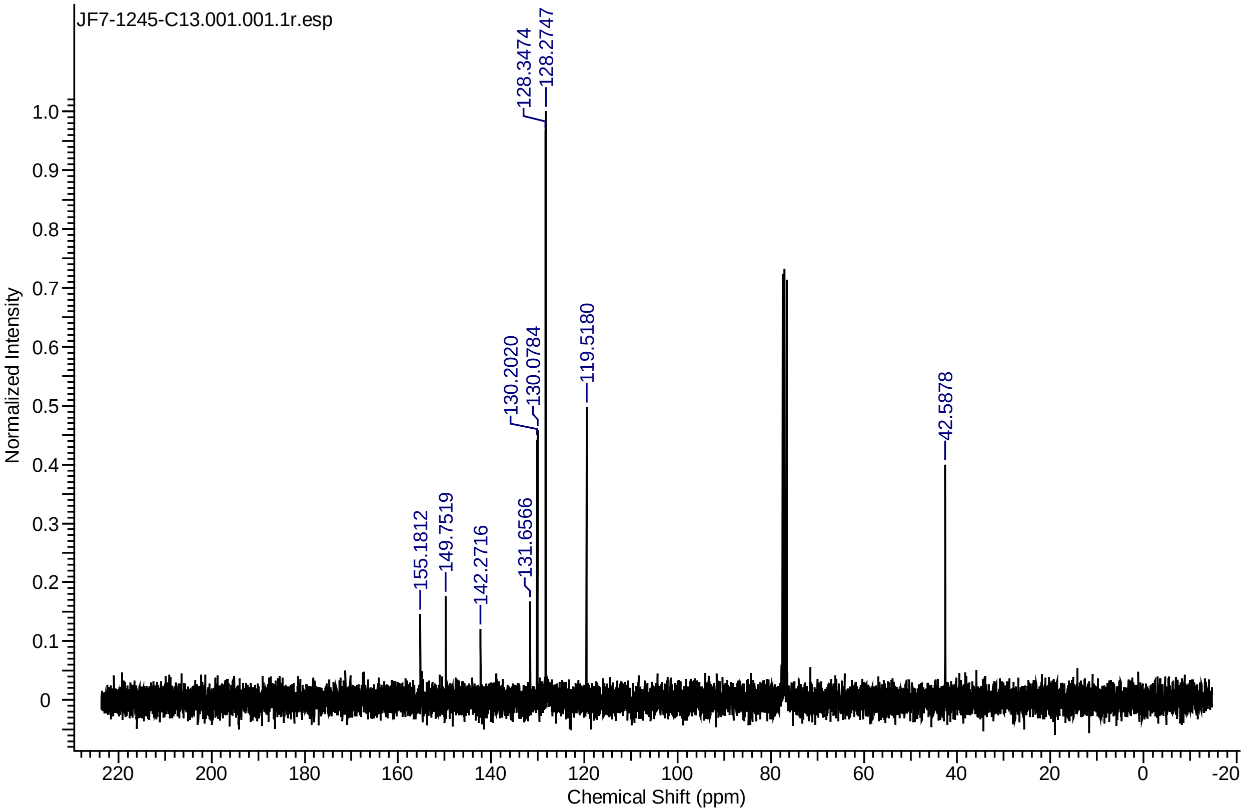

JF7-1273-carac-H.001.esp
O
O
NH
N
O
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.92
1.90
5.00
3.09
2.92
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

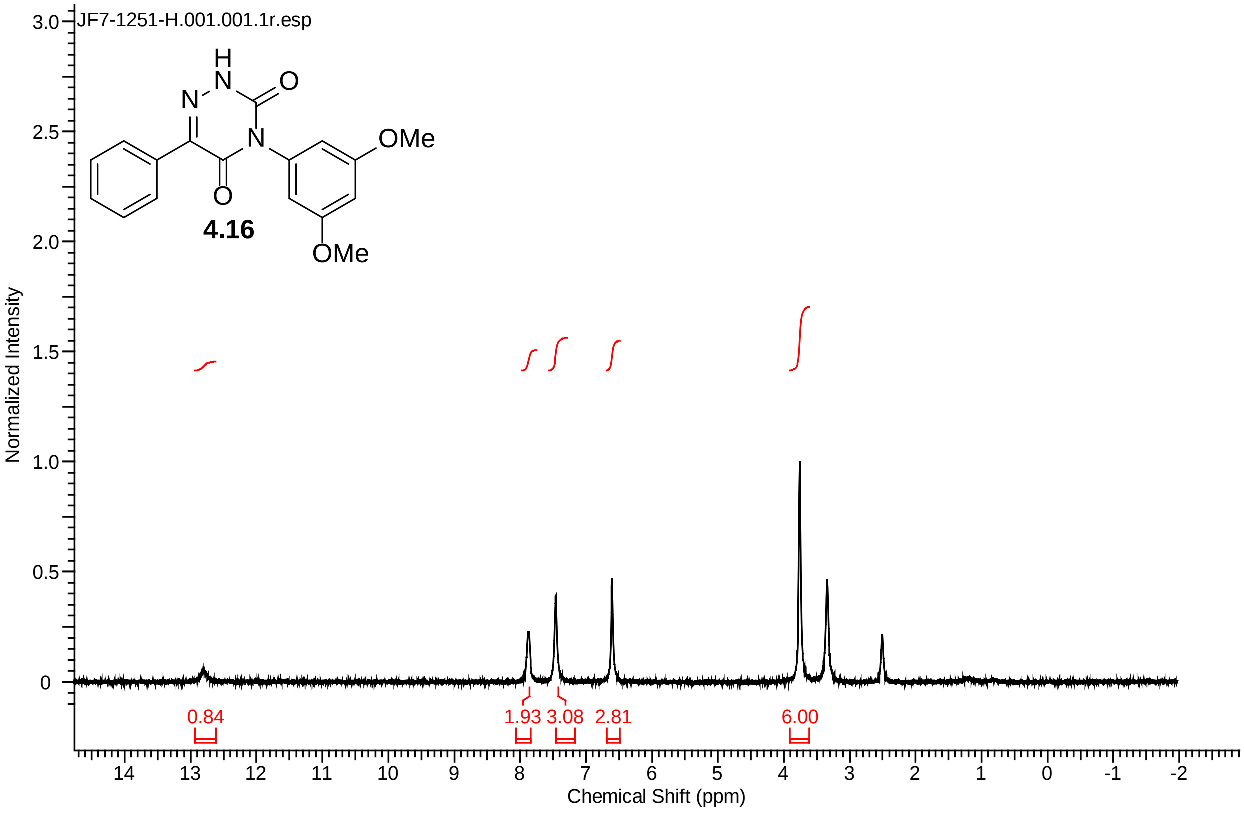

JF7-1273-carac-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
163.1074
151.8925
150.3215
133.0699
130.0007
129.5498
128.6770
126.7424
121.7677
52.9505
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

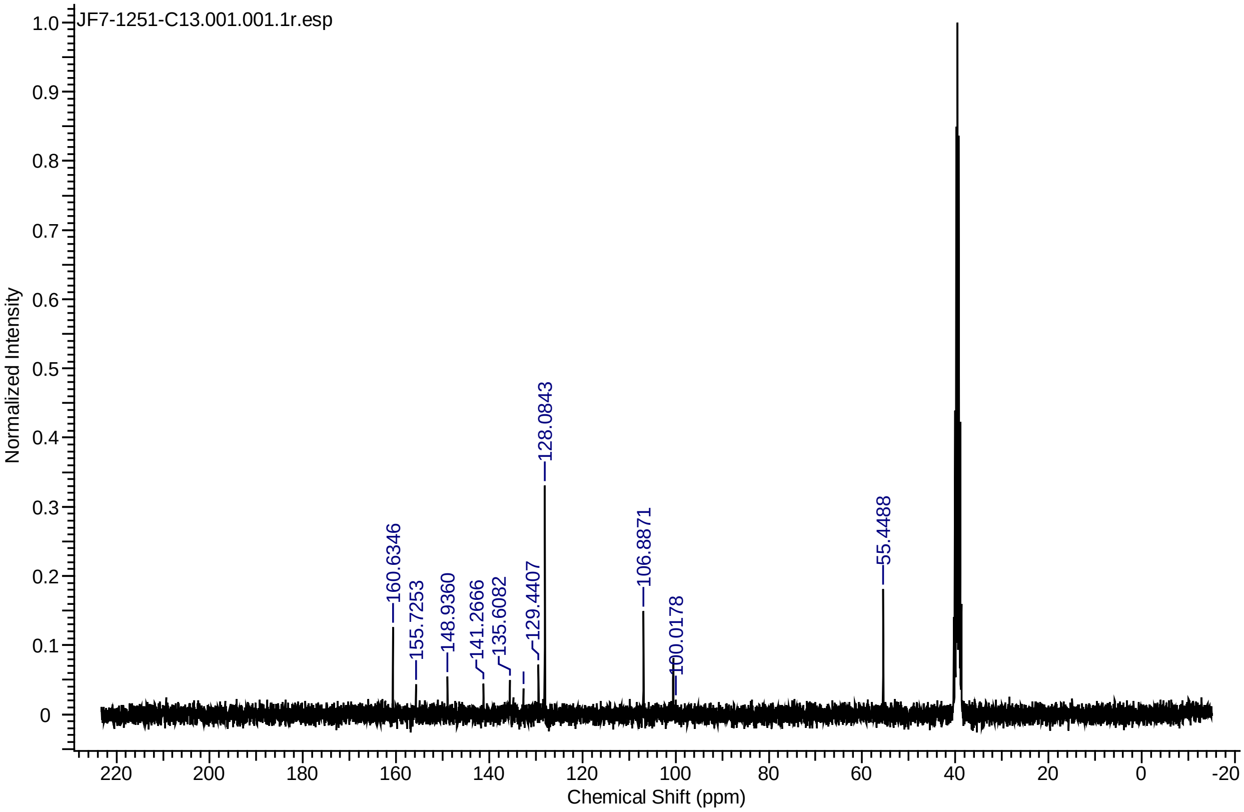

JF7-1287-carac-H.001.esp
4.14
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.96
1.98
1.92
6.24
2.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

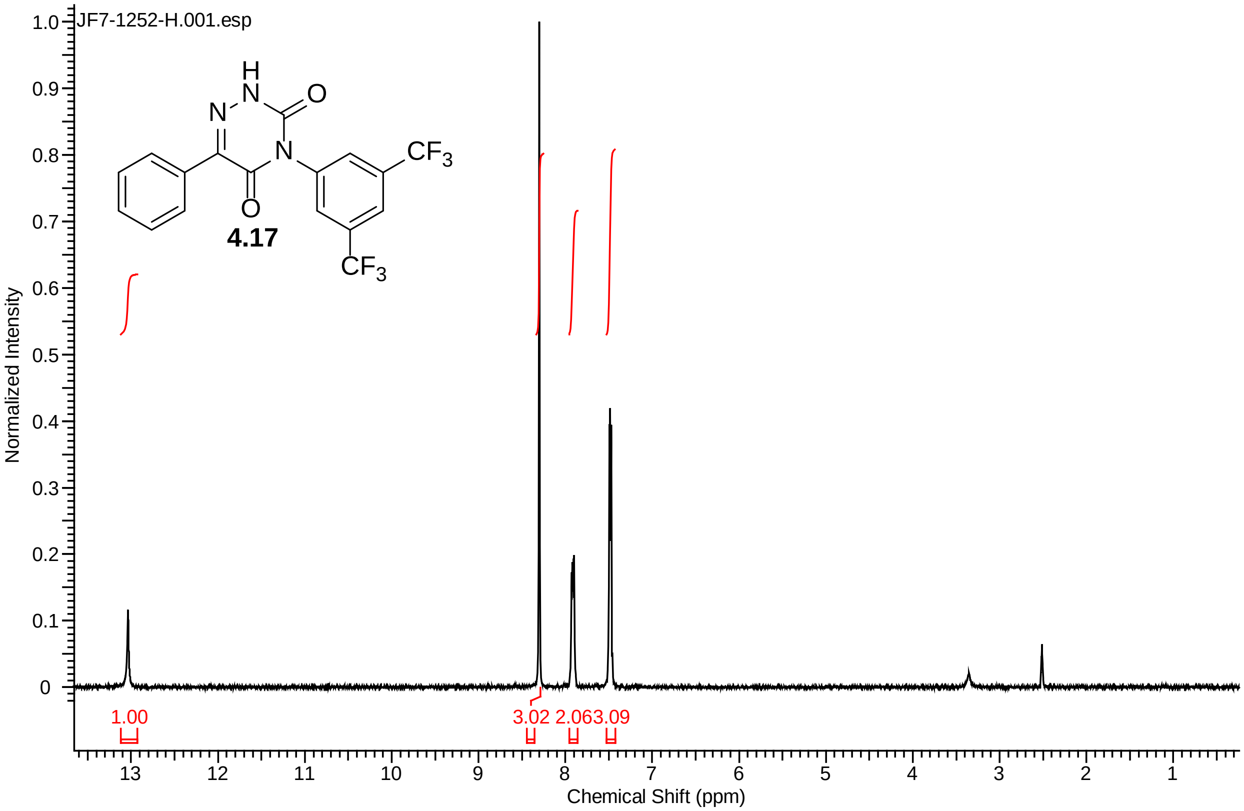

JF7-1287-carac-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
153.3798
147.7505
141.8121
134.1063
129.6334
129.5680
128.4297
128.1243
77.6242
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

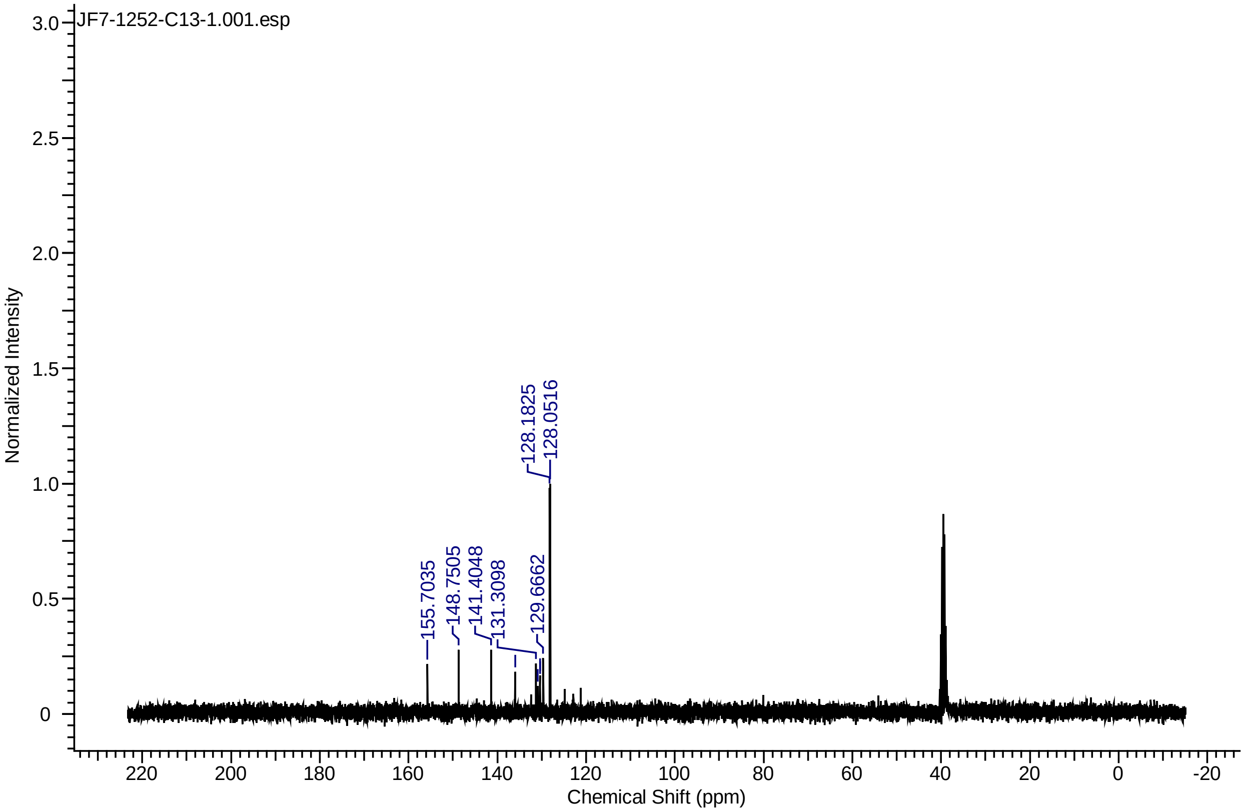

JF7-1245-pa1.001.esp
4.15
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.83
1.83
2.79
1.00
1.97
1.96
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

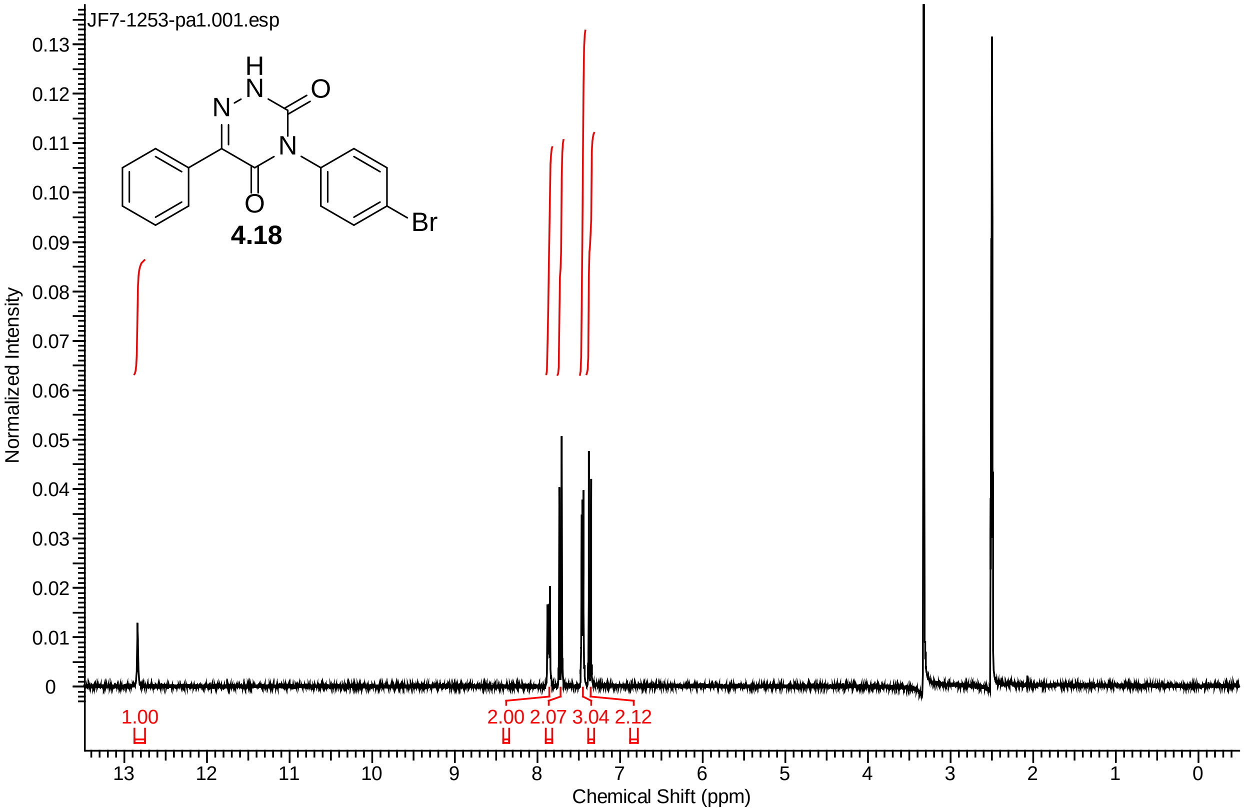

JF7-1245-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
155.1812
149.7519
142.2716
131.6566
130.2020
130.0784
128.3474
128.2747
119.5180
42.5878
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

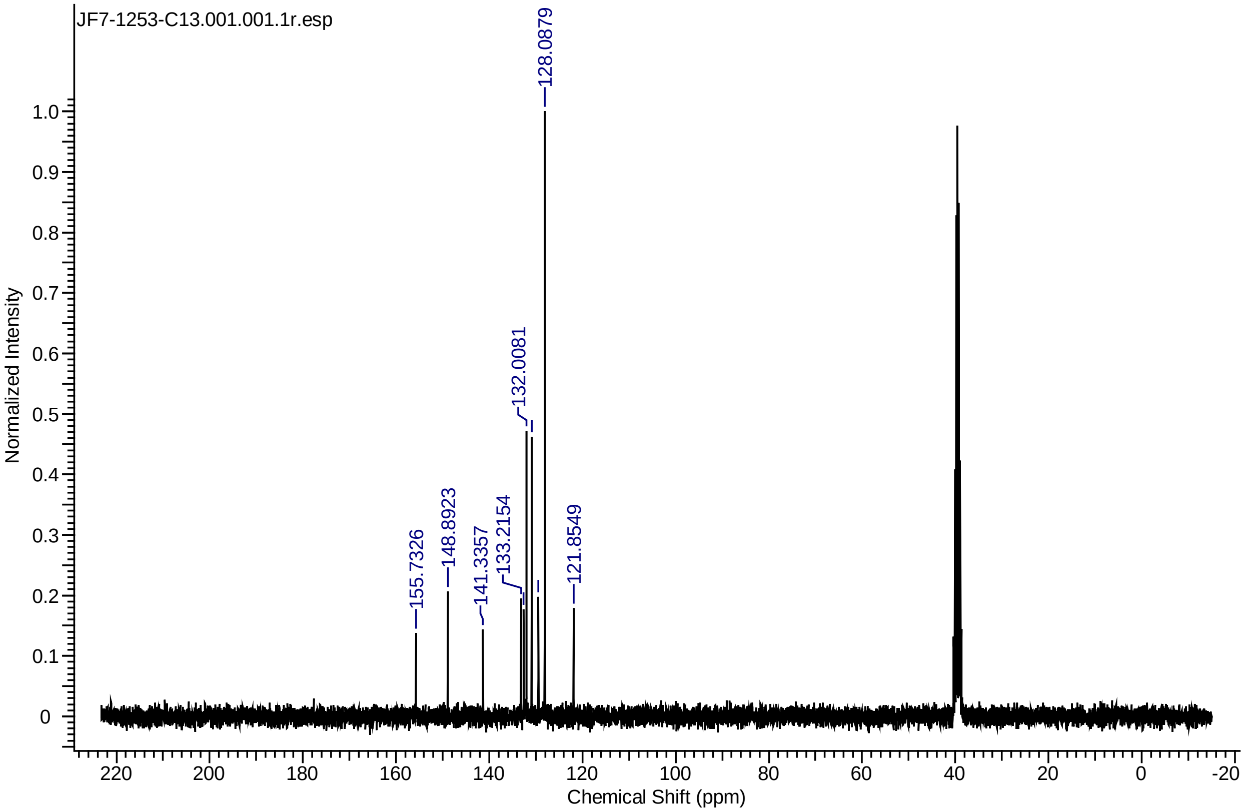

JF7-1251-H.001.001.1r.esp
4.16
H
N
N
O
N
O
OMe
OMe
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
0.84
1.93
3.08
2.81
6.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

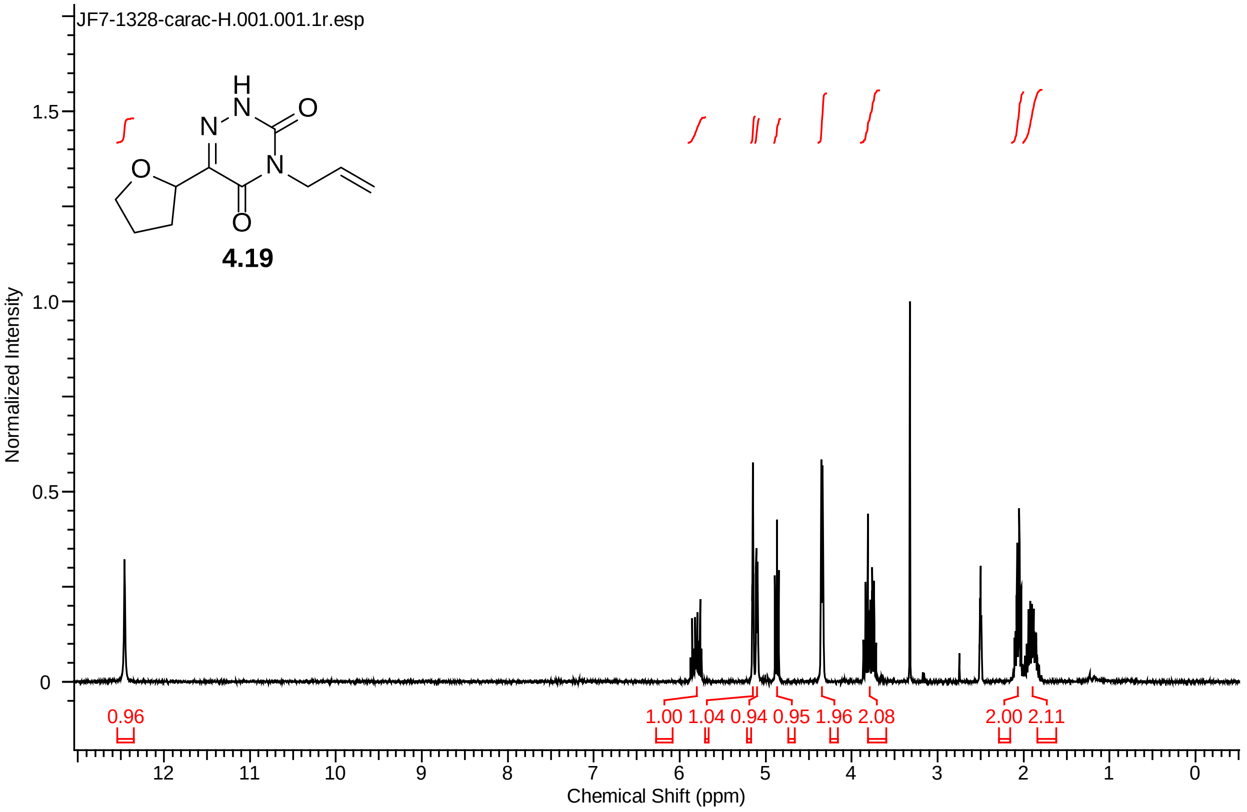

JF7-1251-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.6346
155.7253
148.9360
141.2666
135.6082
129.4407
128.0843
106.8871
100.0178
55.4488
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

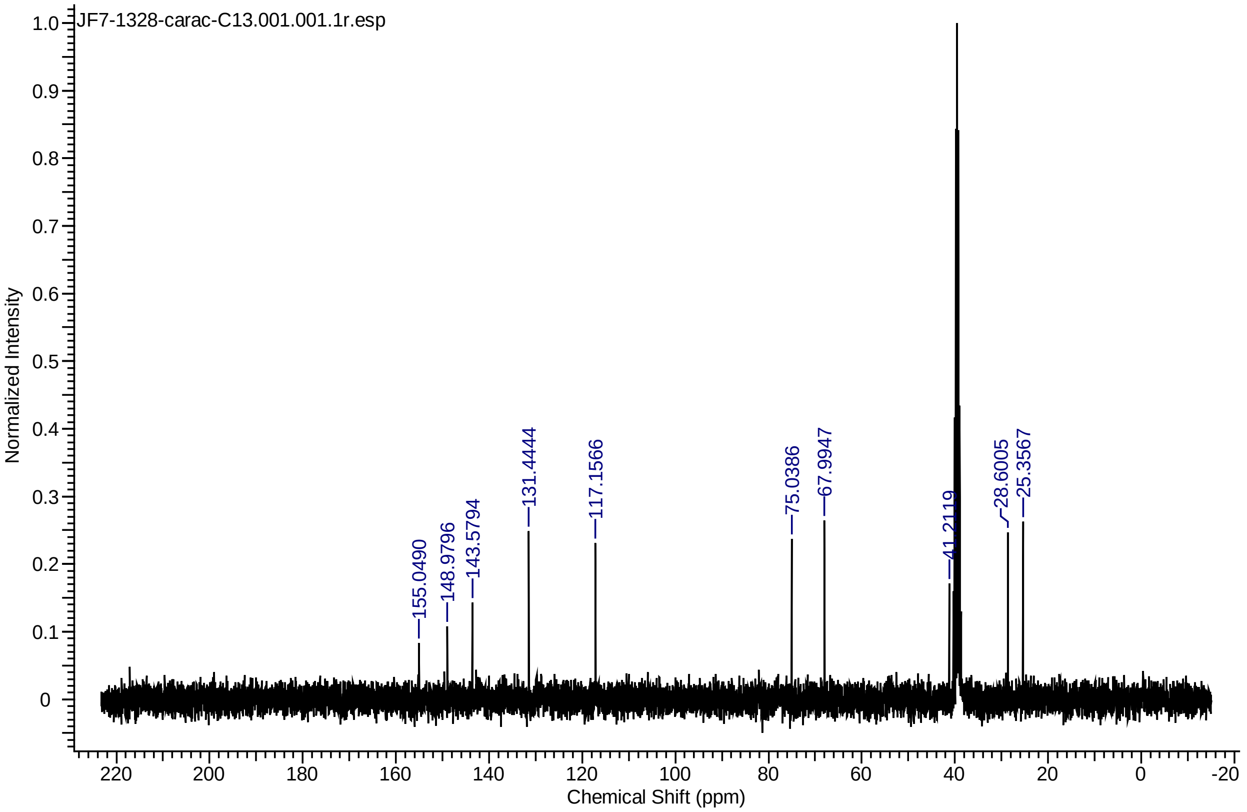

JF7-1252-H.001.esp
4.17
H
N
N
N
O
O
CF3
CF3
1.00
3.02
2.06
3.09
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
13
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

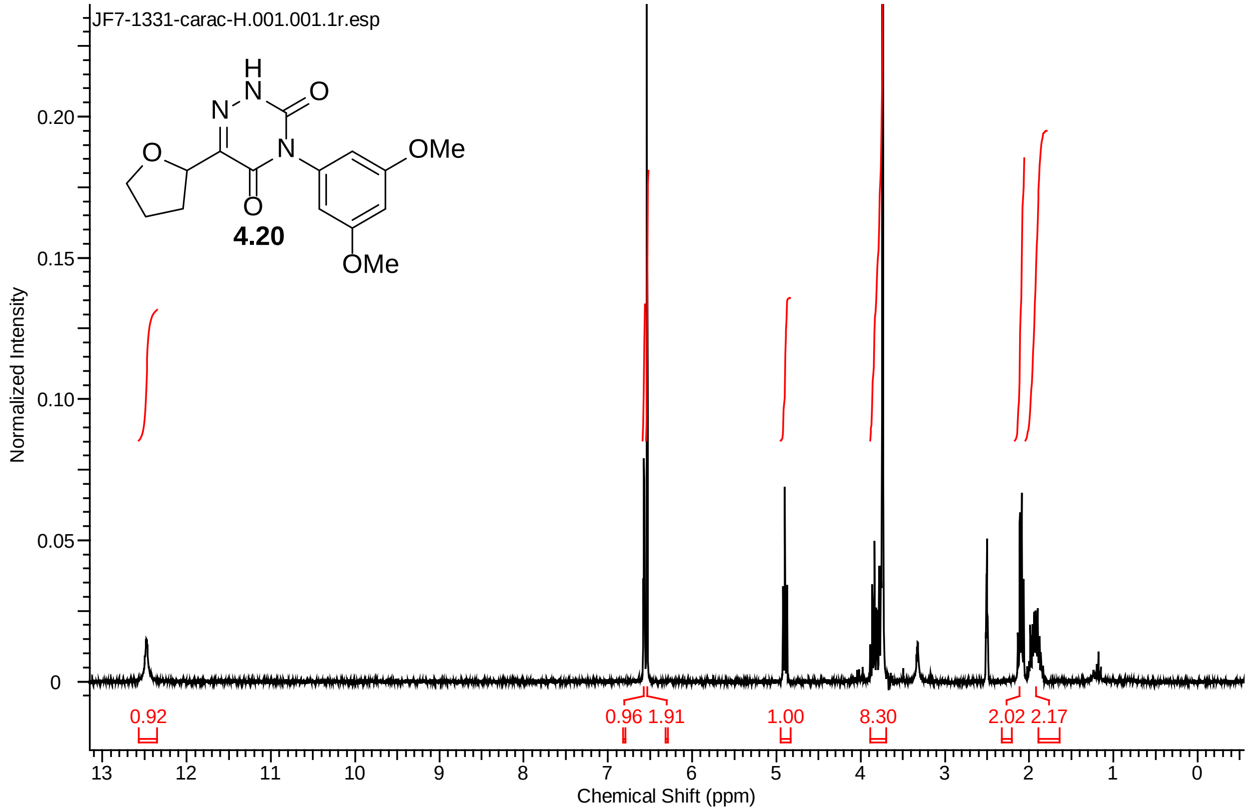

JF7-1252-C13-1.001.esp
155.7035
148.7505
141.4048
131.3098
129.6662
128.1825
128.0516
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

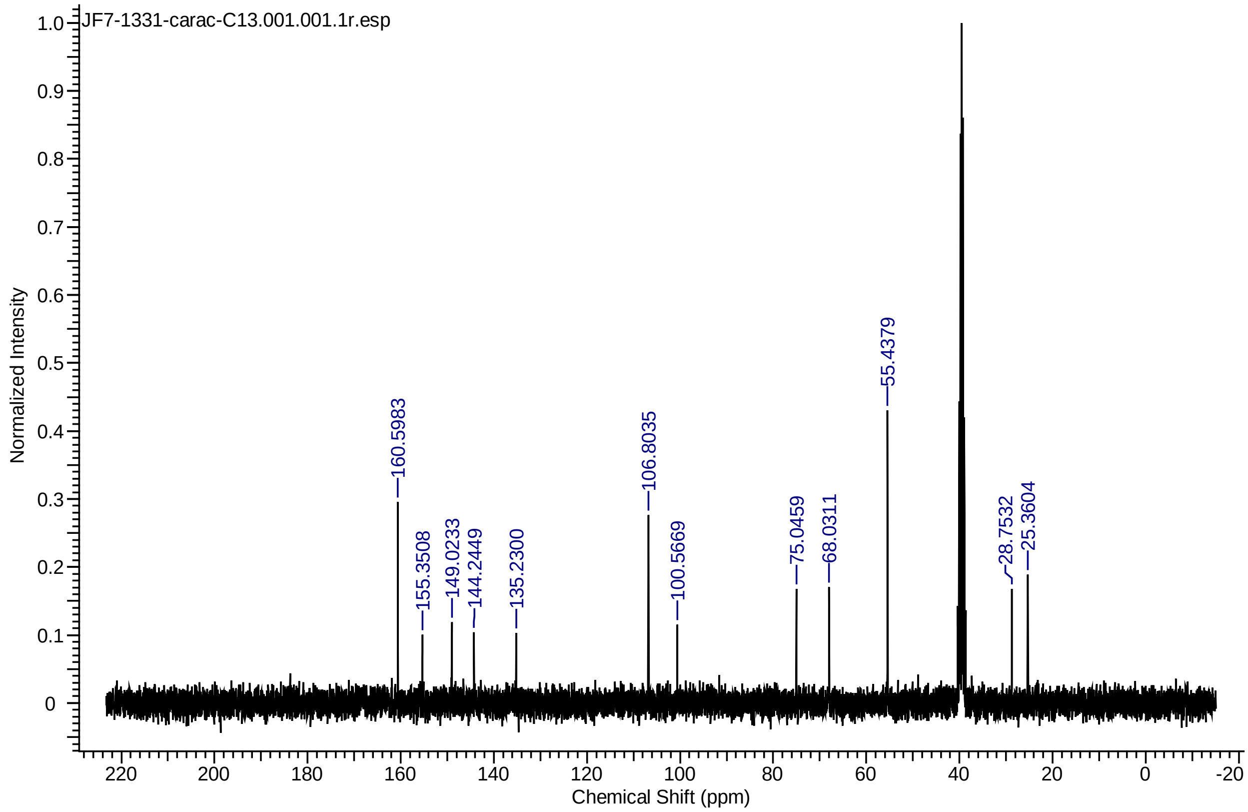

JF7-1253-pa1.001.esp
4.18
Br
Normalized Intensity
Chemical Shift (ppm)
1.00
2.00
2.07
3.04
2.12

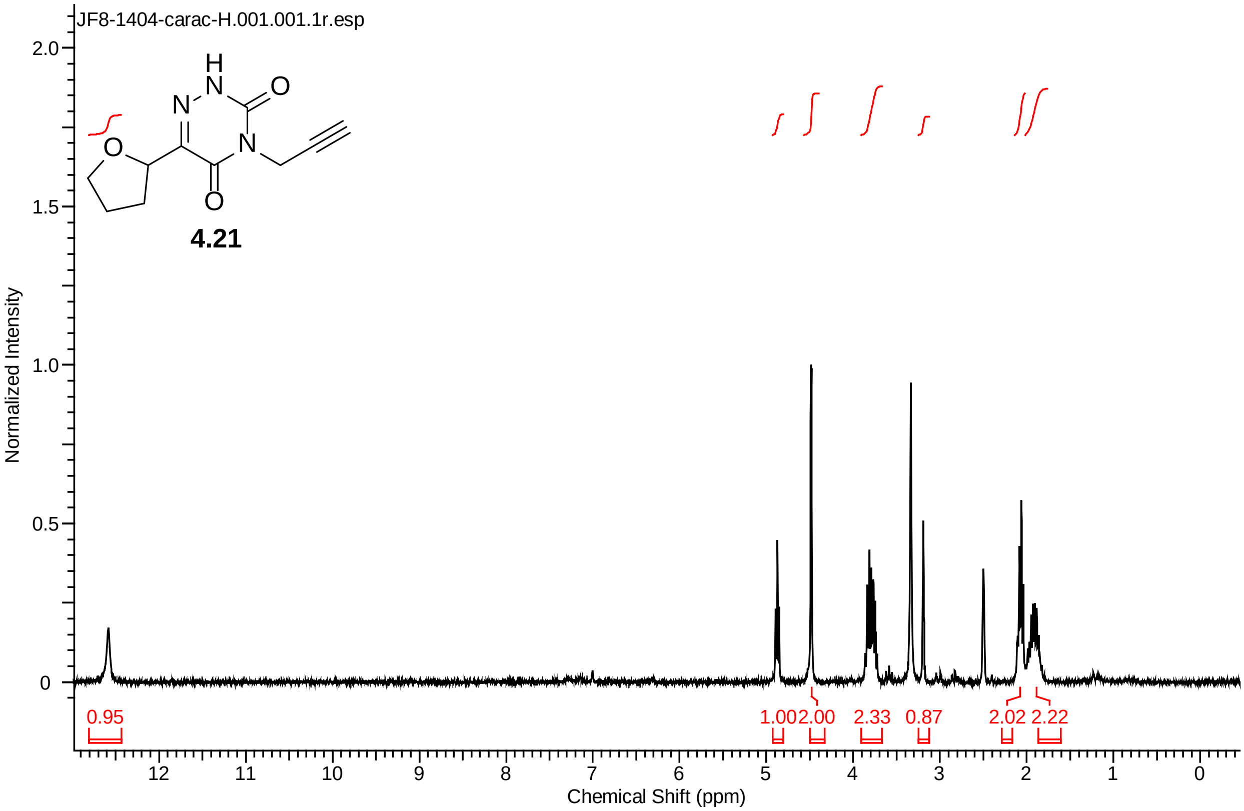

JF7-1253-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
155.7326
148.8923
141.3357
133.2154
132.0081
128.0879
121.8549

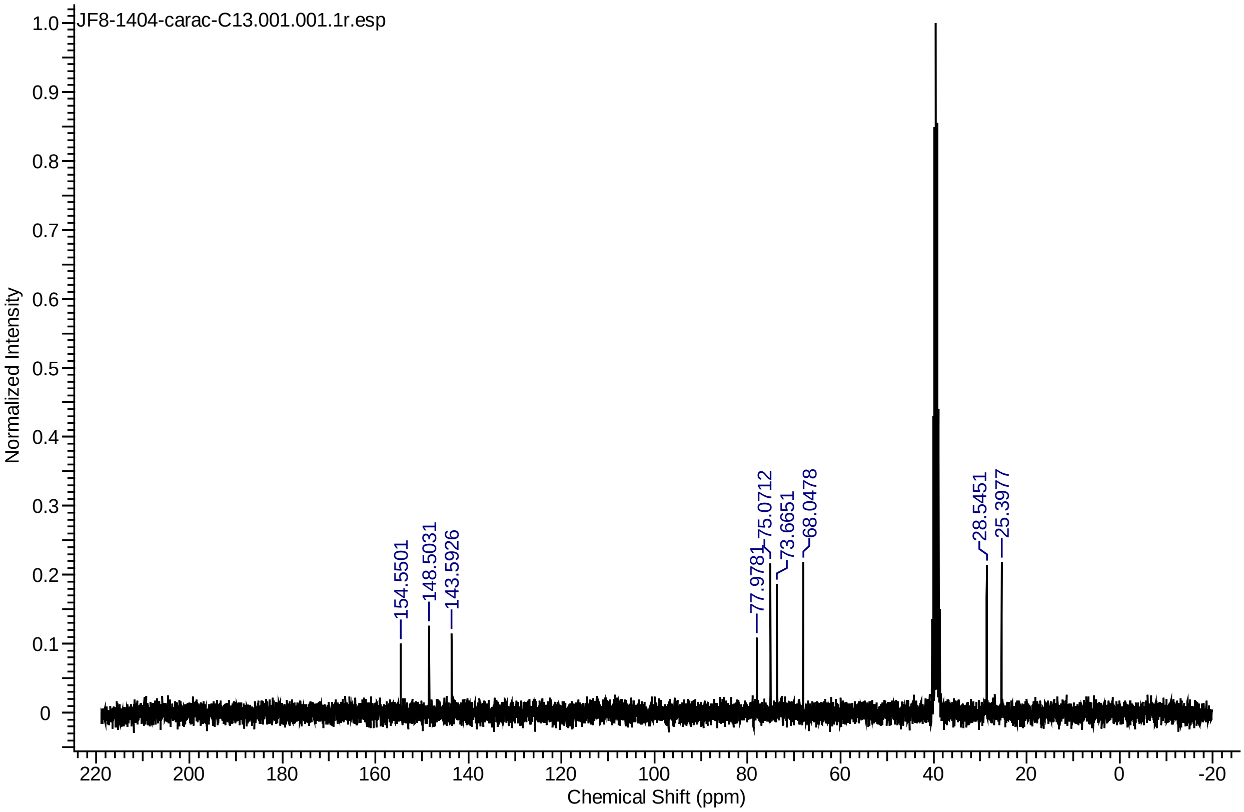

JF7-1328-carac-H.001.001.1r.esp
H
N
N
O
N
O
O
4.19
Normalized Intensity
1.5
1.0
0.5
0
0.96
1.00
1.04
0.94
0.95
1.96
2.08
2.00
2.11
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

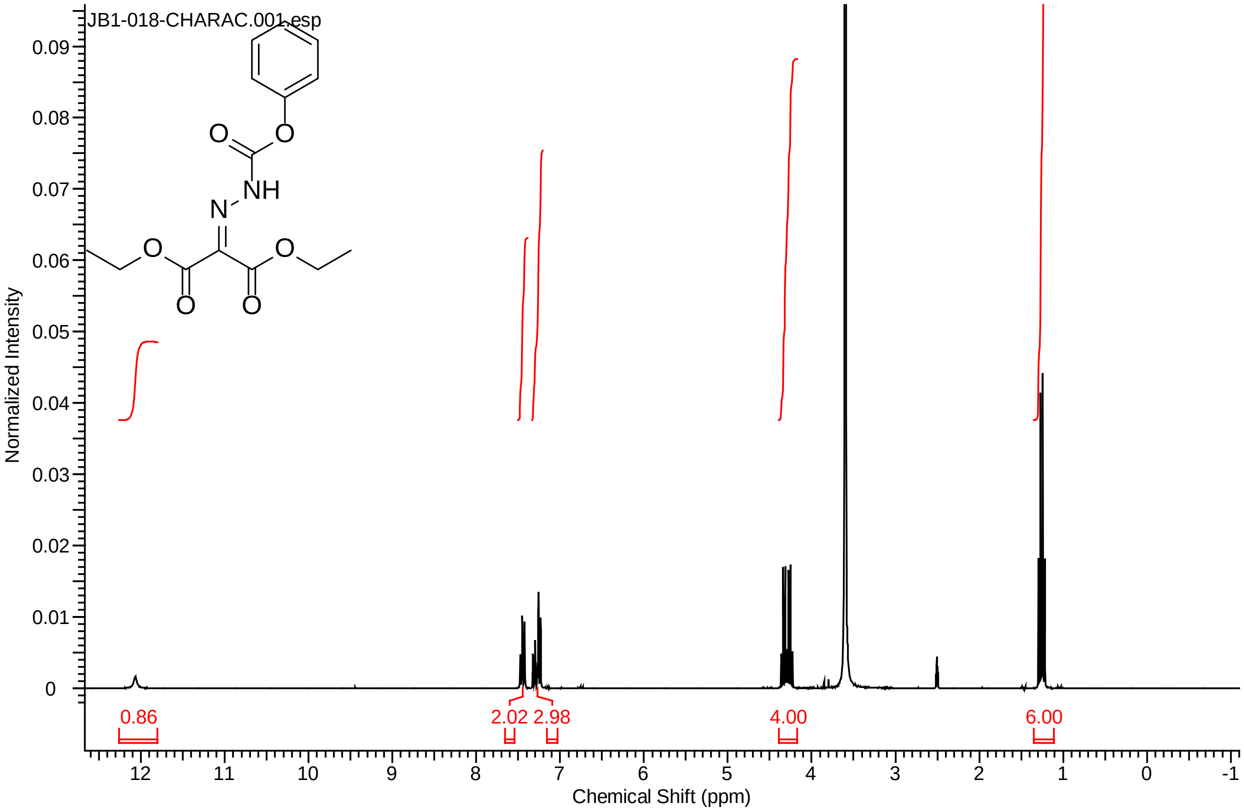

JF7-1328-carac-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
155.0490
148.9796
143.5794
131.4444
117.1566
75.0386
67.9947
41.2119
28.6005
25.3567
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

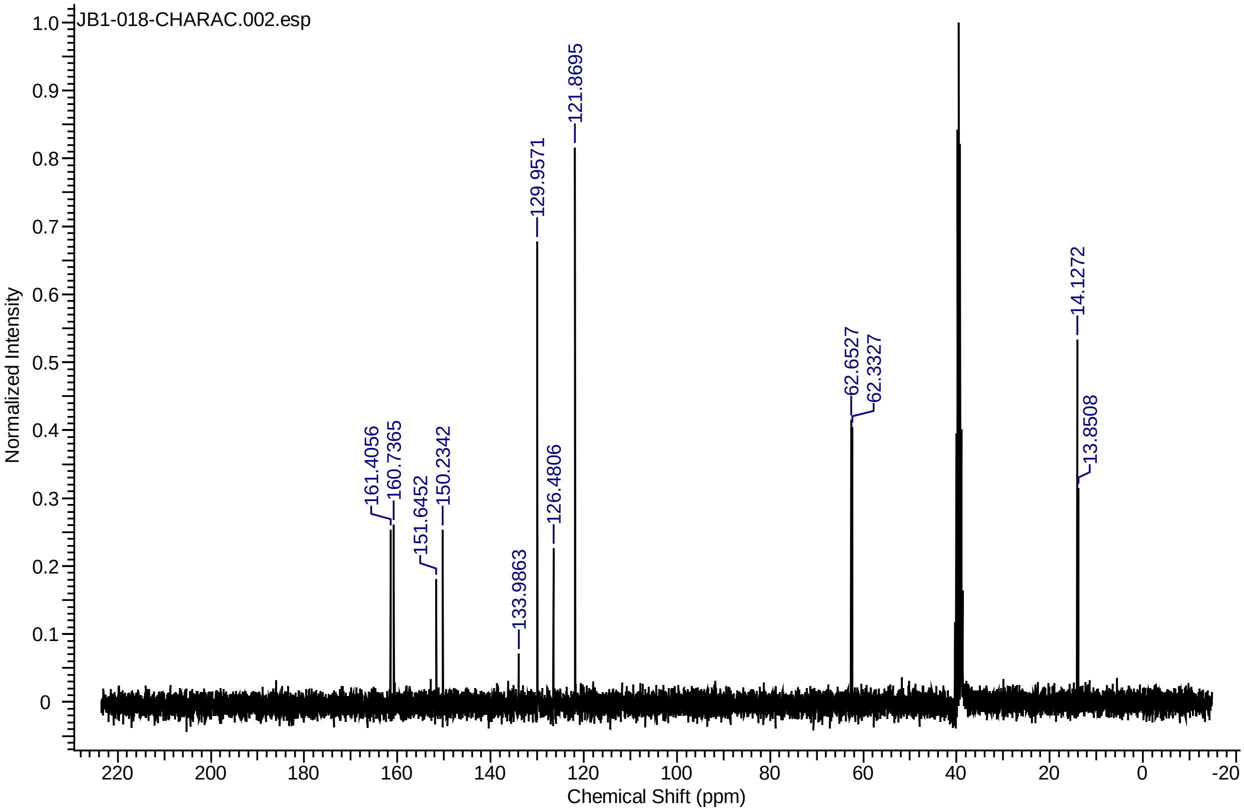

JF7-1331-carac-H.001.001.1r.esp
4.20
H
N
N
O
N
O
O
OMe
OMe
Normalized Intensity
0.20
0.15
0.10
0.05
0
0.92
0.96
1.91
1.00
8.30
2.02
2.17
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

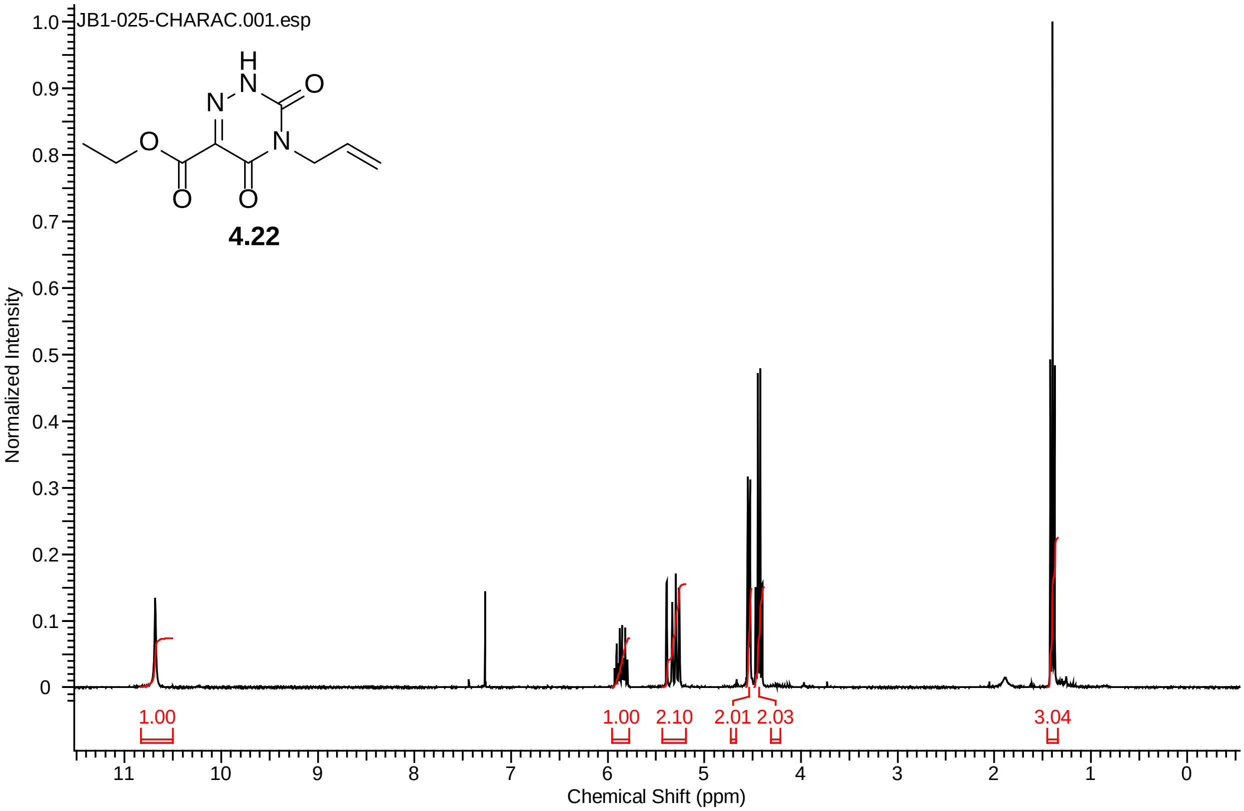

JF7-1331-carac-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.5983
155.3508
149.0233
144.2449
135.2300
106.8035
100.5669
75.0459
68.0311
55.4379
28.7532
25.3604
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF8-1404-carac-H.001.001.1r.esp
4.21
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.95
1.00
2.00
2.33
0.87
2.02
2.22
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

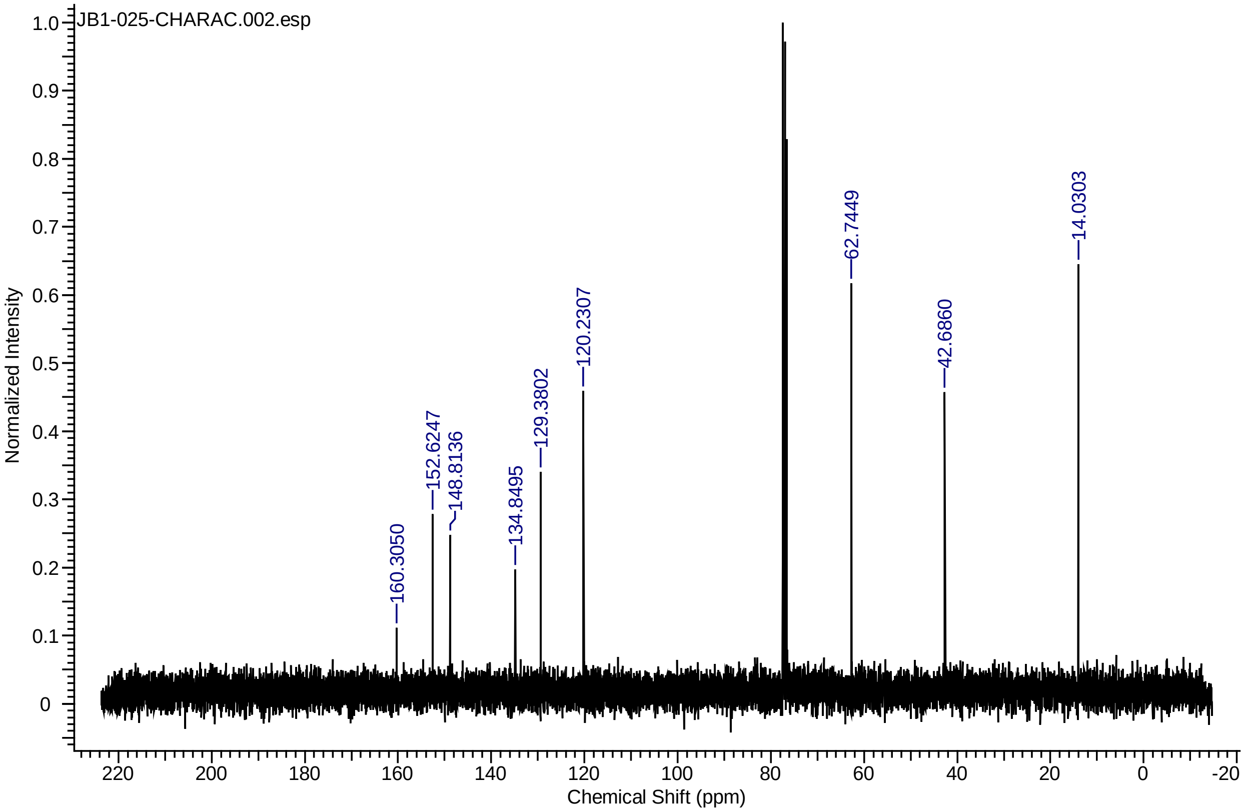

JF8-1404-carac-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
154.5501
148.5031
143.5926
77.9781
75.0712
73.6651
68.0478
28.5451
25.3977
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

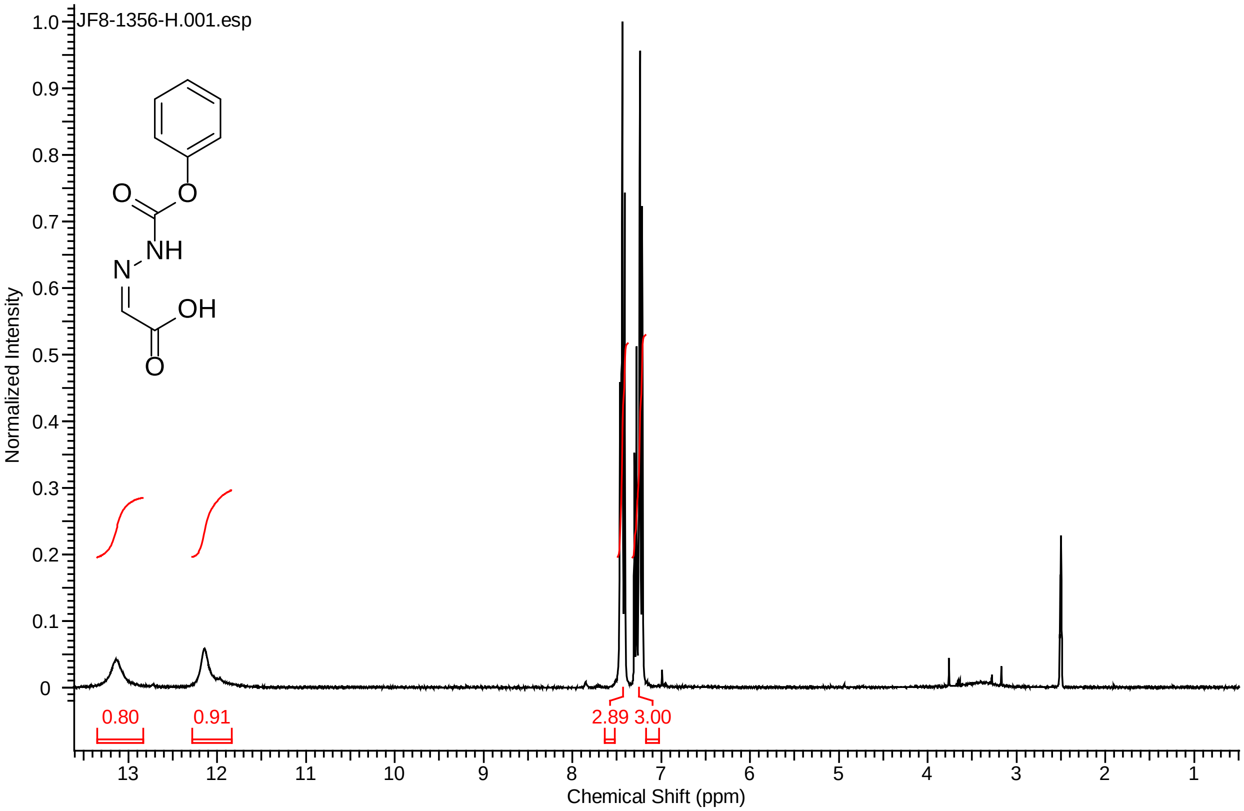

JB1-018-CHARAC.001.esp
O
O
NH
N
O
O
O
O
Normalized Intensity
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0.86
2.02
2.98
4.00
6.00
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
Chemical Shift (ppm)

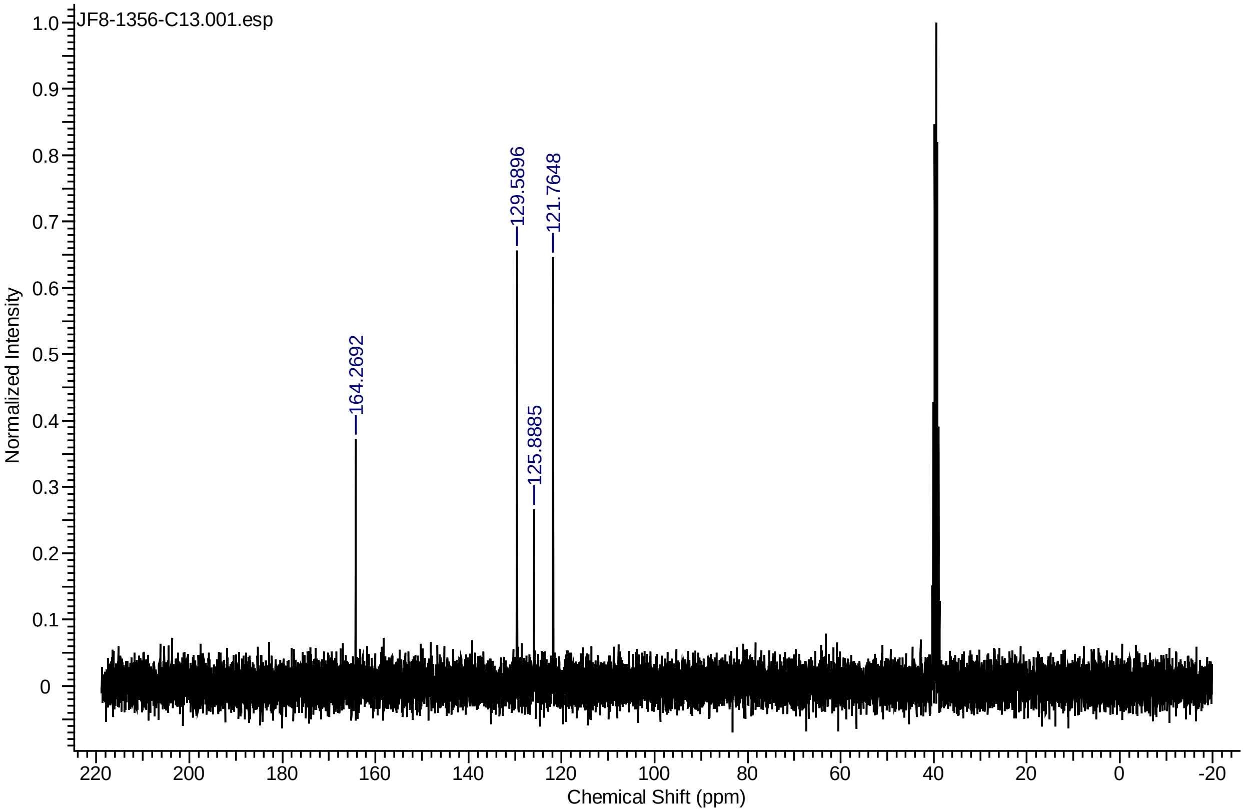

JB1-018-CHARAC.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
161.4056
160.7365
151.6452
150.2342
133.9863
129.9571
126.4806
121.8695
62.6527
62.3327
14.1272
13.8508
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

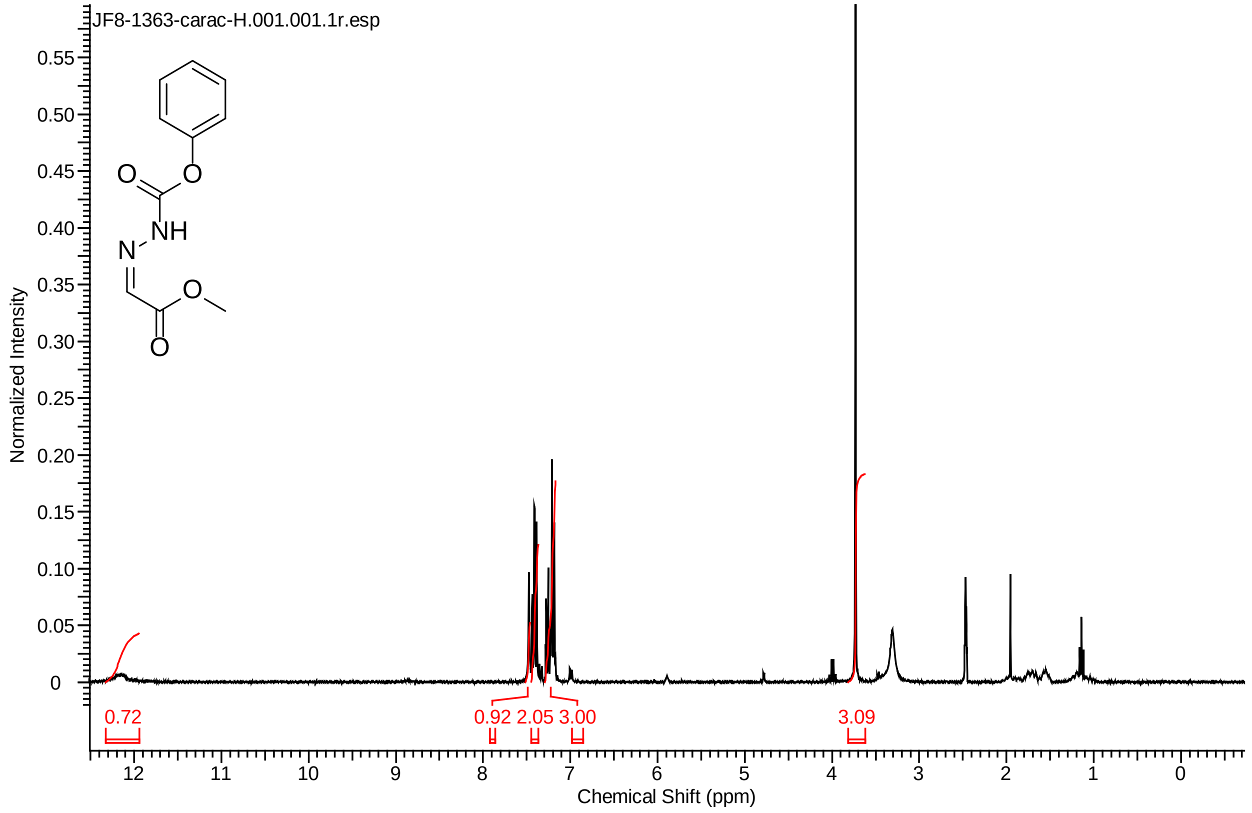

JB1-025-CHARAC.001.esp
H
N
N
O
O
N
O
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
1.00
2.10
2.01
2.03
3.04
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

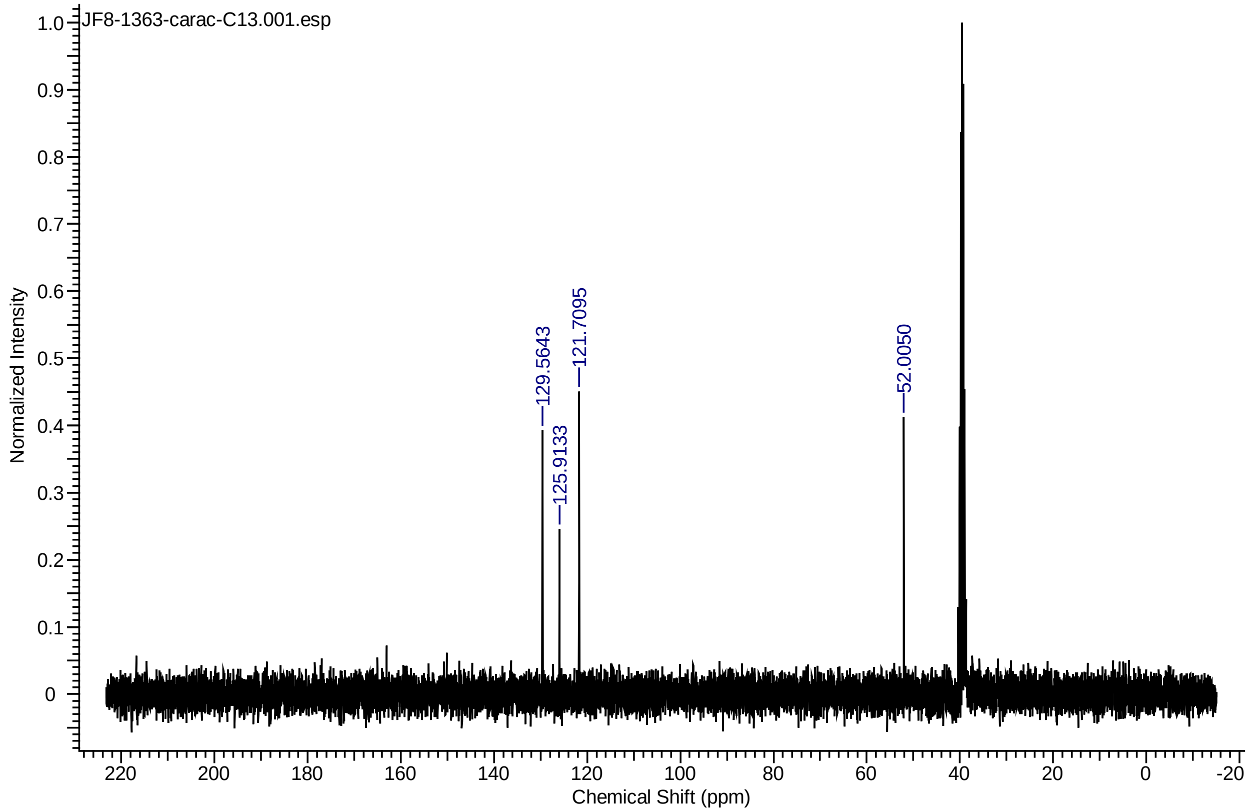
4.22

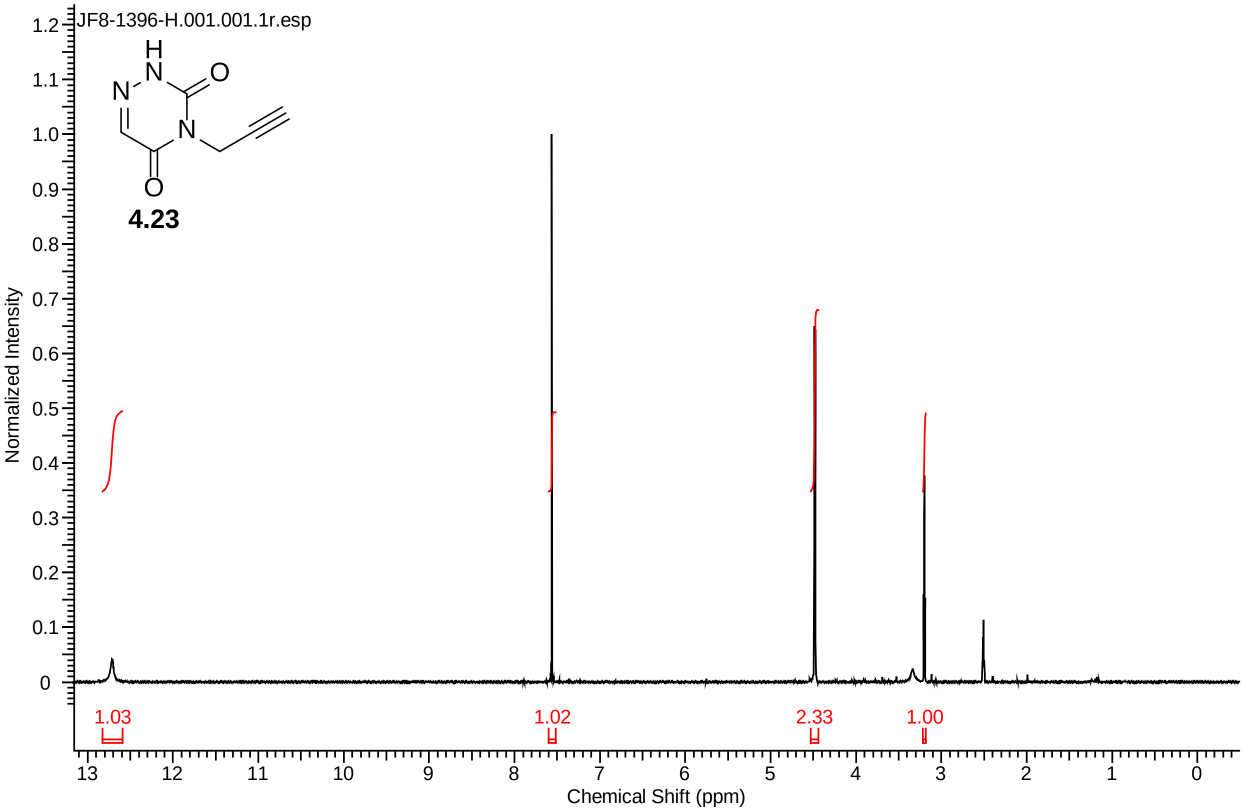

JB1-025-CHARAC.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.3050
152.6247
148.8136
134.8495
129.3802
120.2307
62.7449
42.6860
14.0303
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

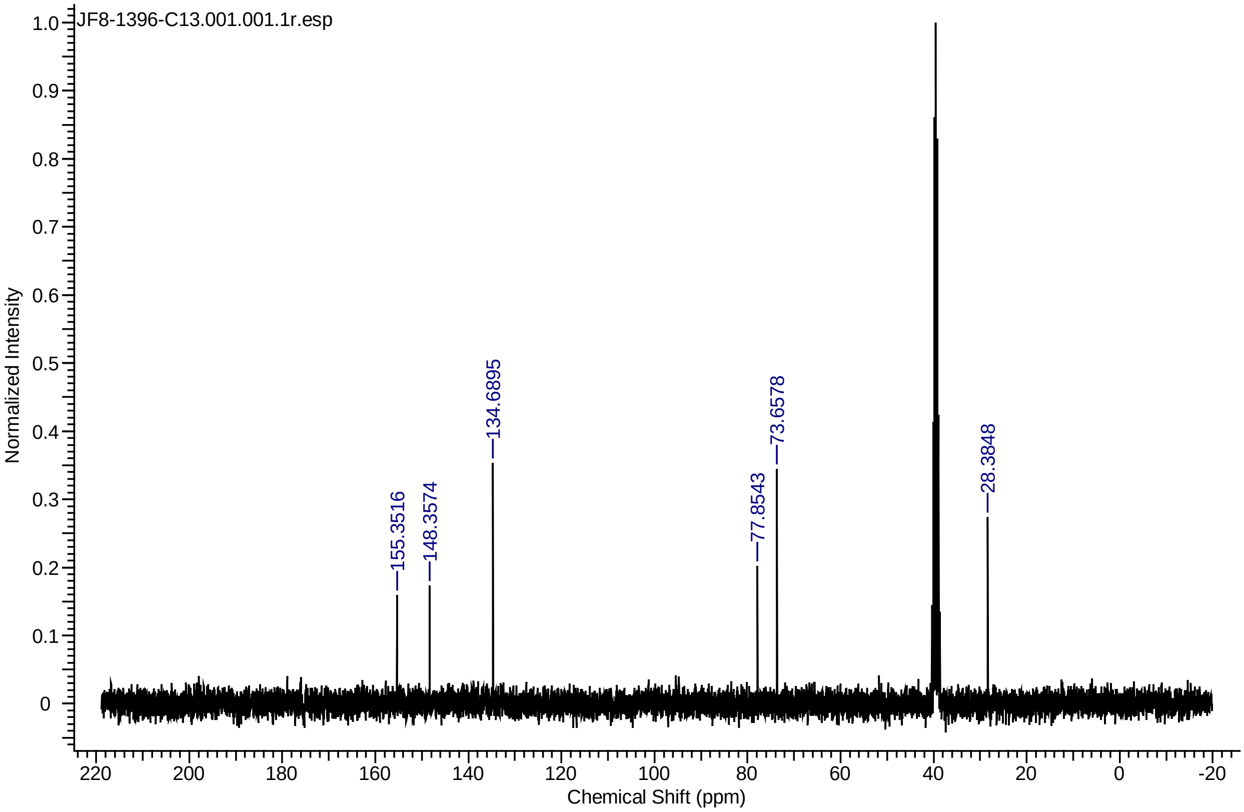

JF8-1356-H.001.esp
O
O
NH
N
OH
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.80
0.91
2.89
3.00
13
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

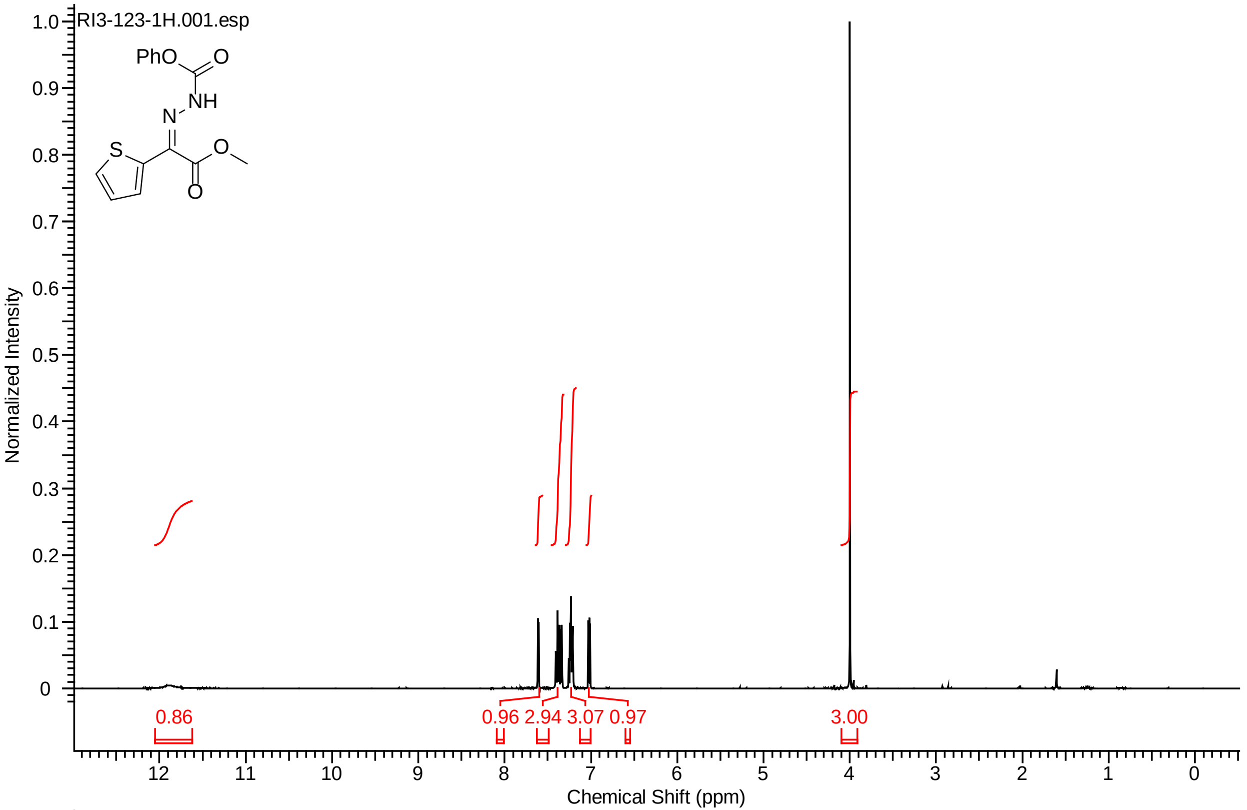

JF8-1356-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
164.2692
129.5896
125.8885
121.7648
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

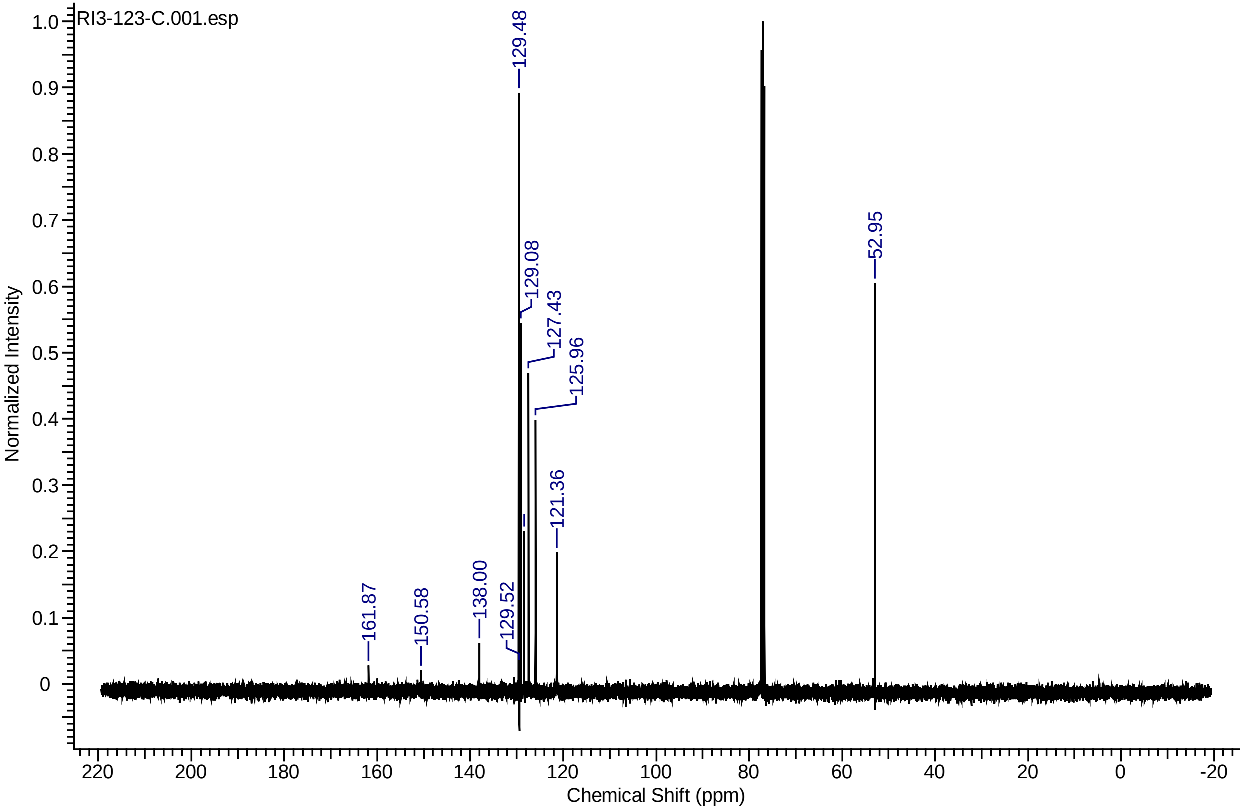

JF8-1363-carac-H.001.001.1r.esp
Normalized Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
O
O
NH
N
O
O
0.72
0.92
2.05
3.00
3.09
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

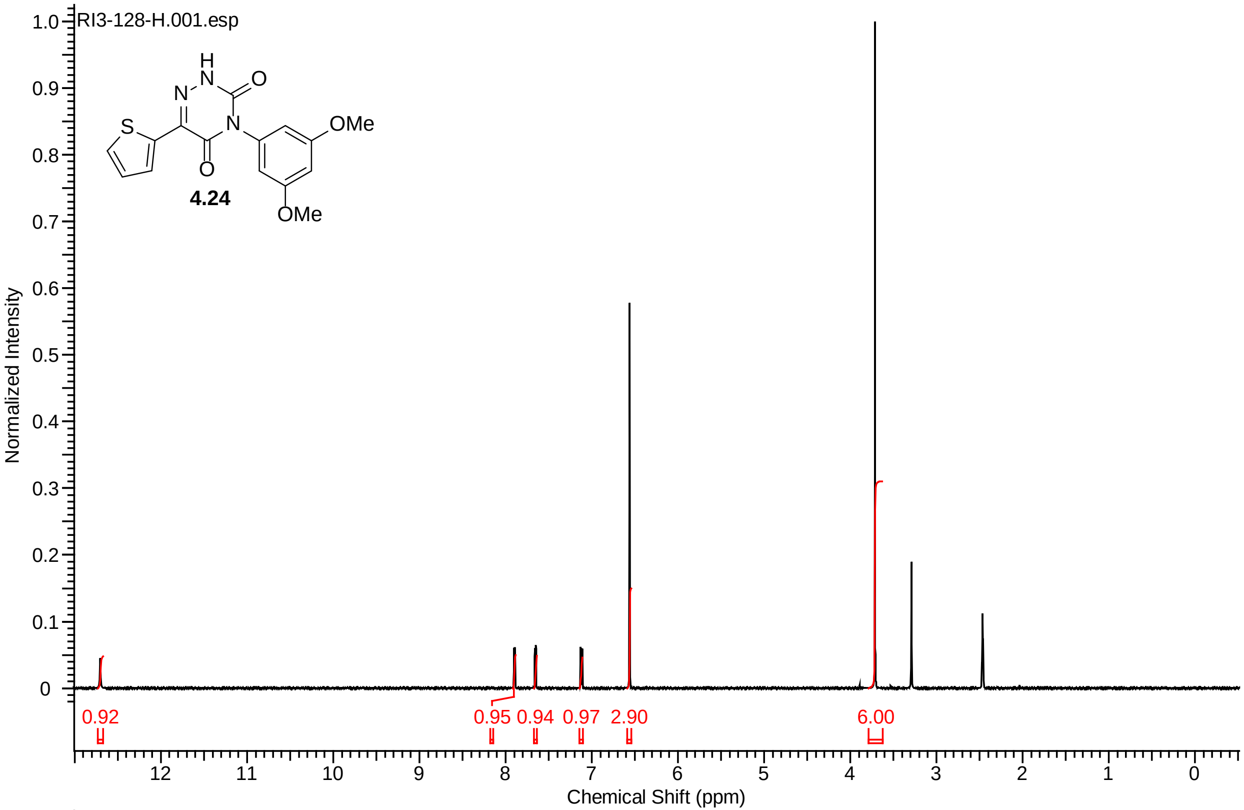

JF8-1363-carac-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
129.5643
125.9133
121.7095
52.0050
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

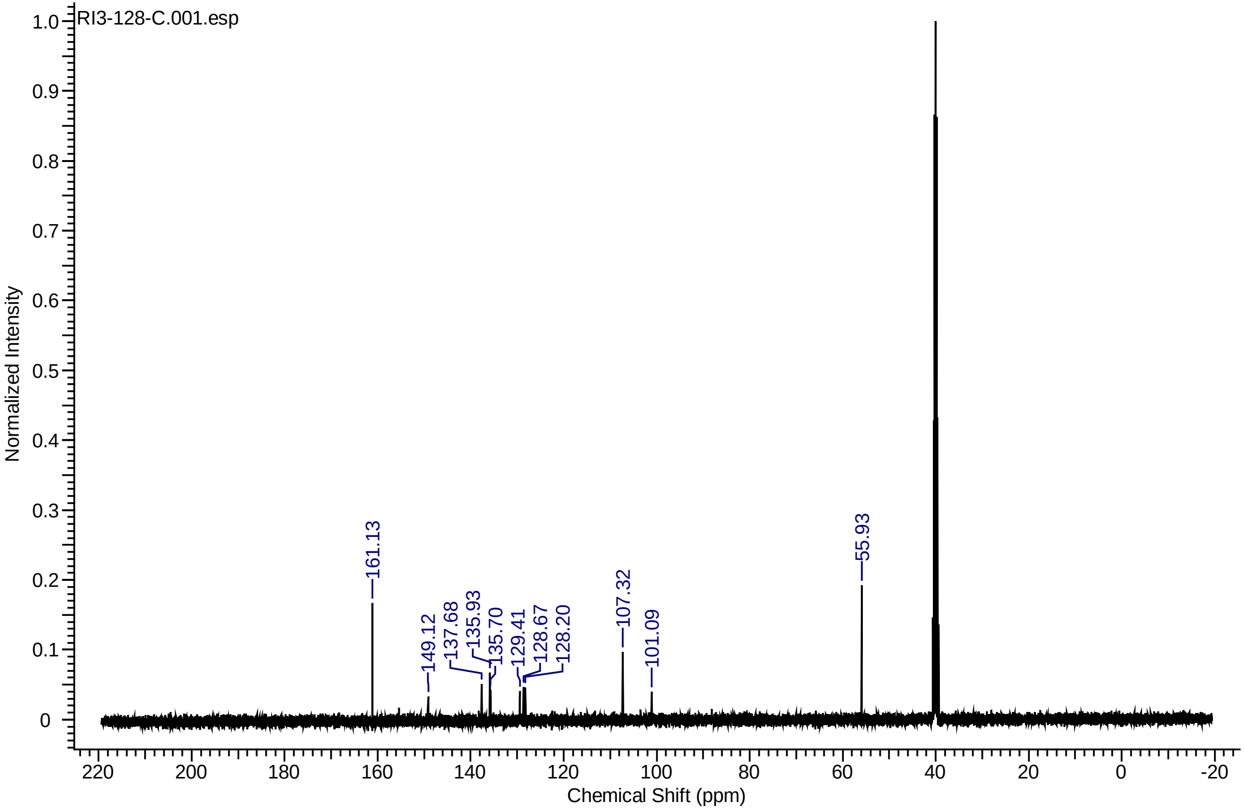

JF8-1396-H.001.001.1r.esp
H
N
N
O
N
O
4.23
Normalized Intensity
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.03
1.02
2.33
1.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

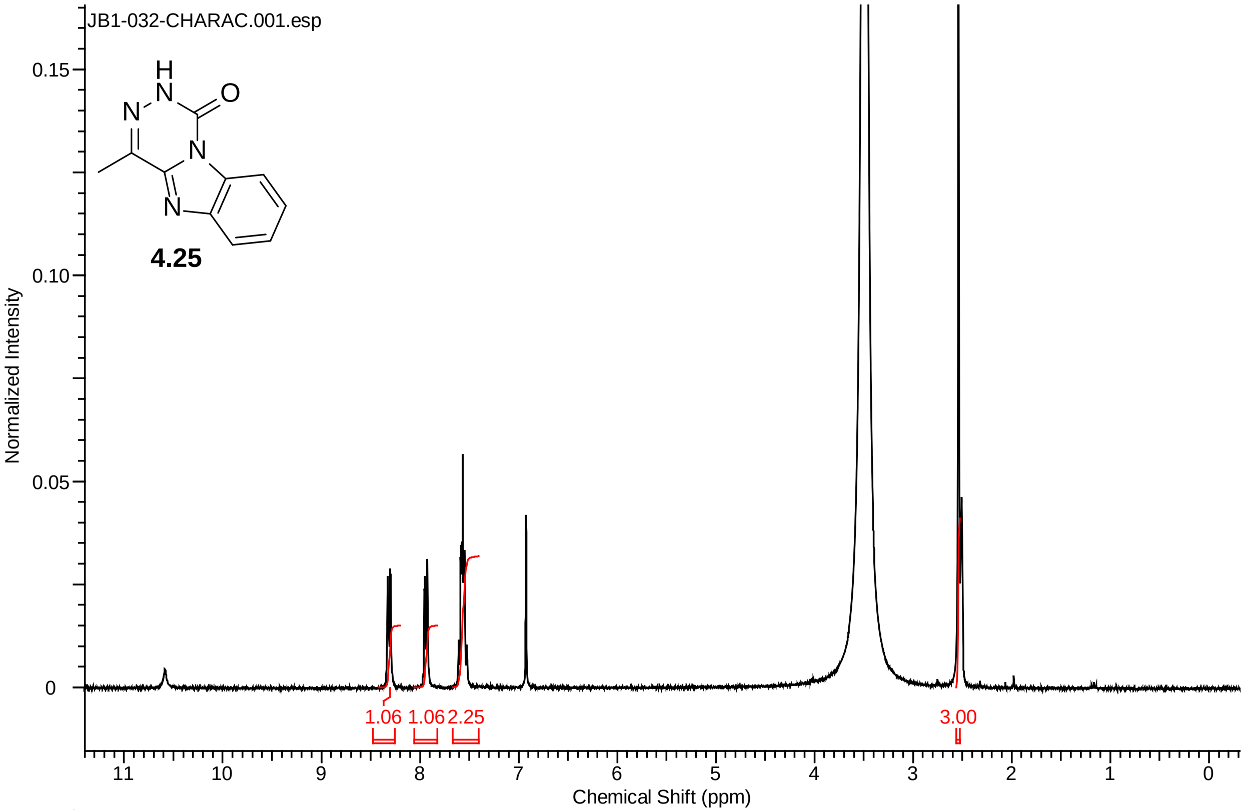

JF8-1396-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
155.3516
148.3574
134.6895
77.8543
73.6578
28.3848
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

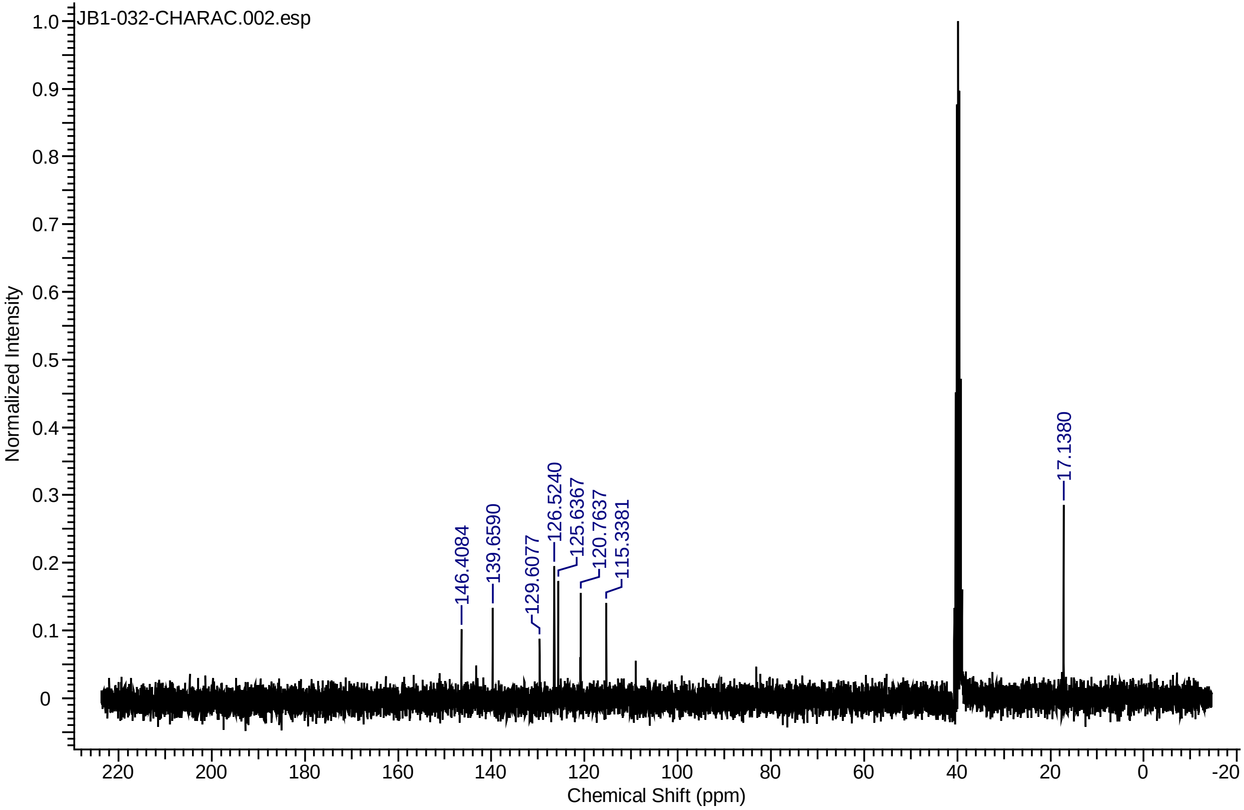

RI3-123-1H.001.esp
PhO
O
NH
N
S
O
O
Normalized Intensity
0.86
0.96
2.94
3.07
0.97
3.00
Chemical Shift (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0

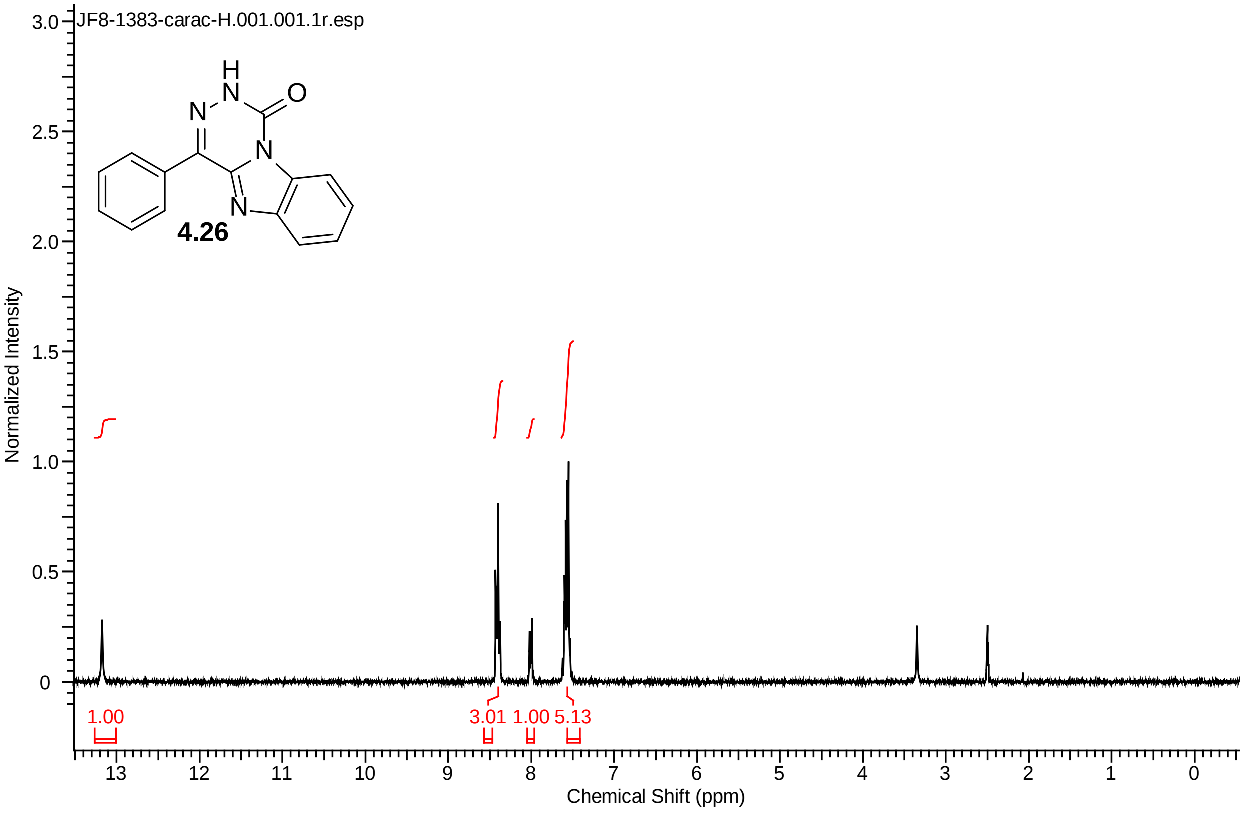

RI3-123-C.001.esp
Normalized Intensity
161.87
150.58
138.00
129.52
129.48
129.08
127.43
125.96
121.36
52.95
Chemical Shift (ppm)
220
200
180
160
140
120
100
80
60
40
20
0
-20

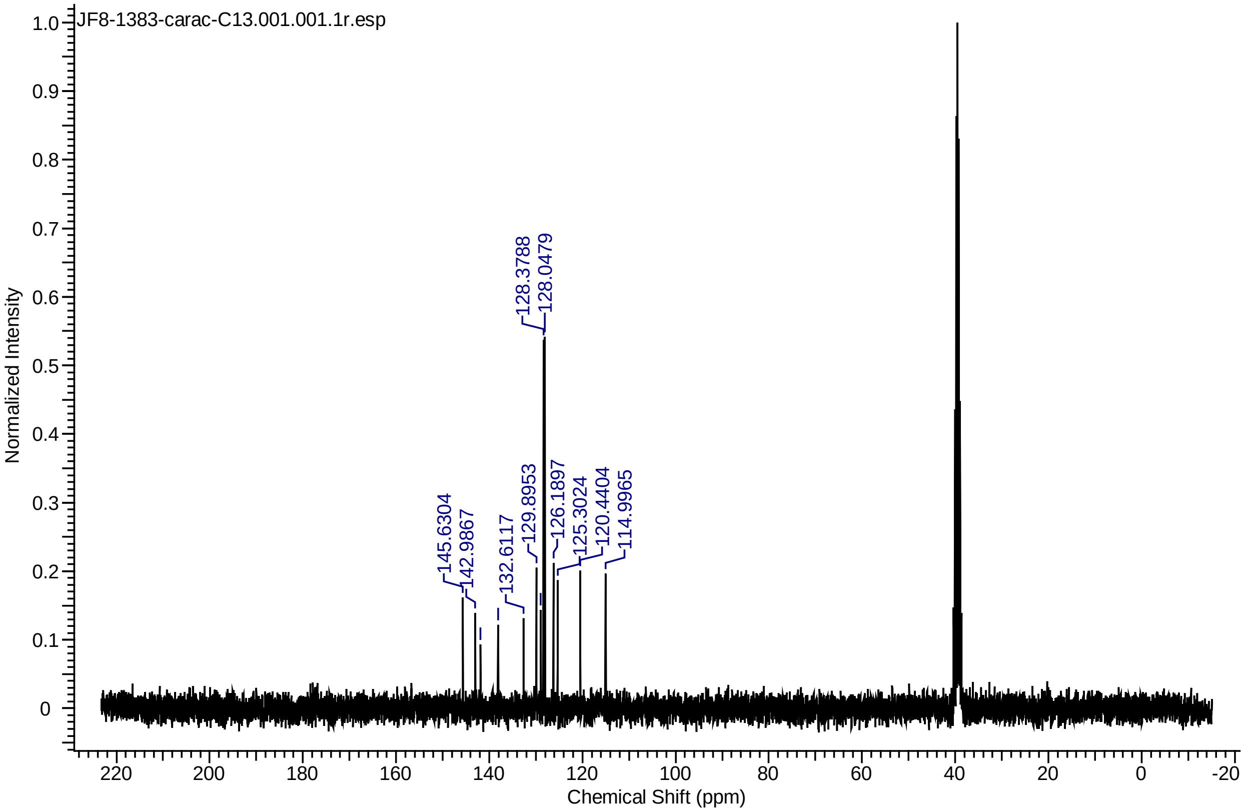

RI3-128-H.001.esp
H
N
N
O
S
N
OMe
O
4.24
OMe
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.92
0.95
0.94
0.97
2.90
6.00
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

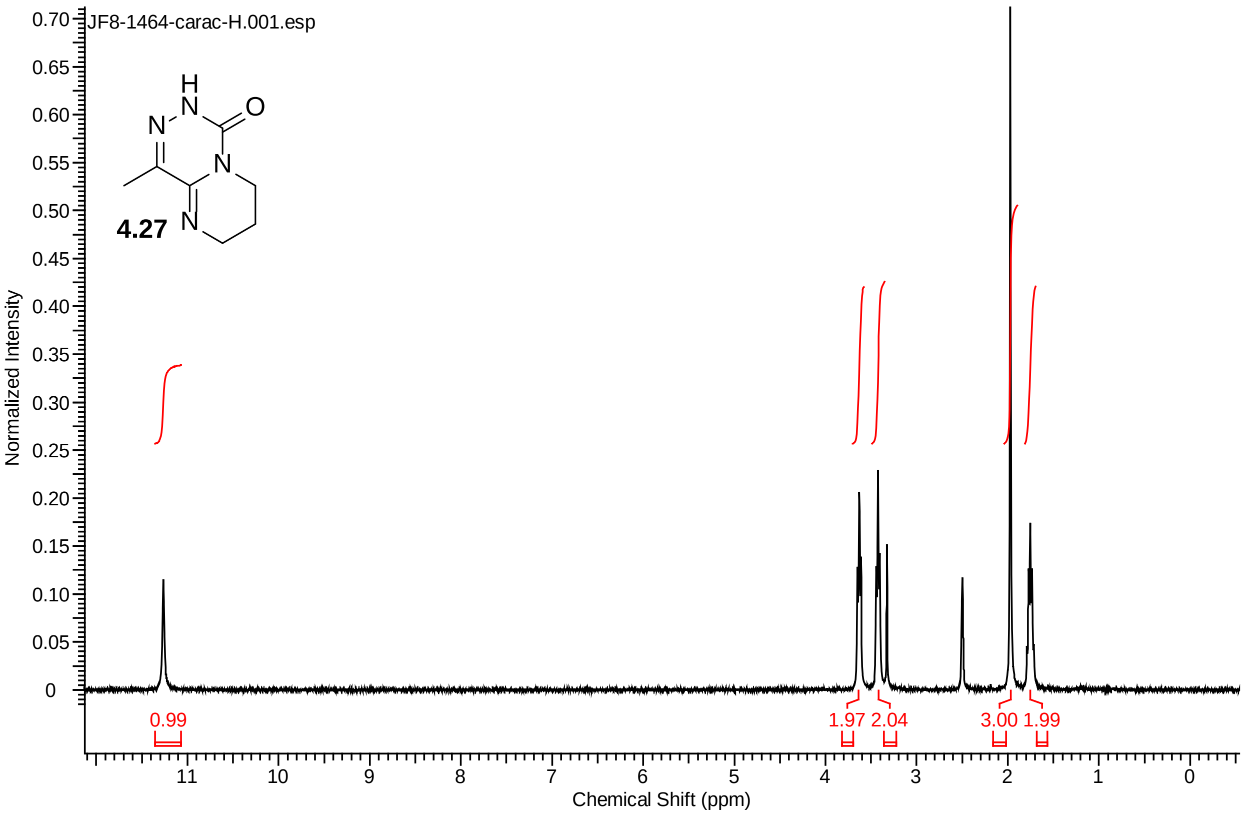

RI3-128-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
161.13
149.12
137.68
135.93
135.70
129.41
128.67
128.20
107.32
101.09
55.93
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

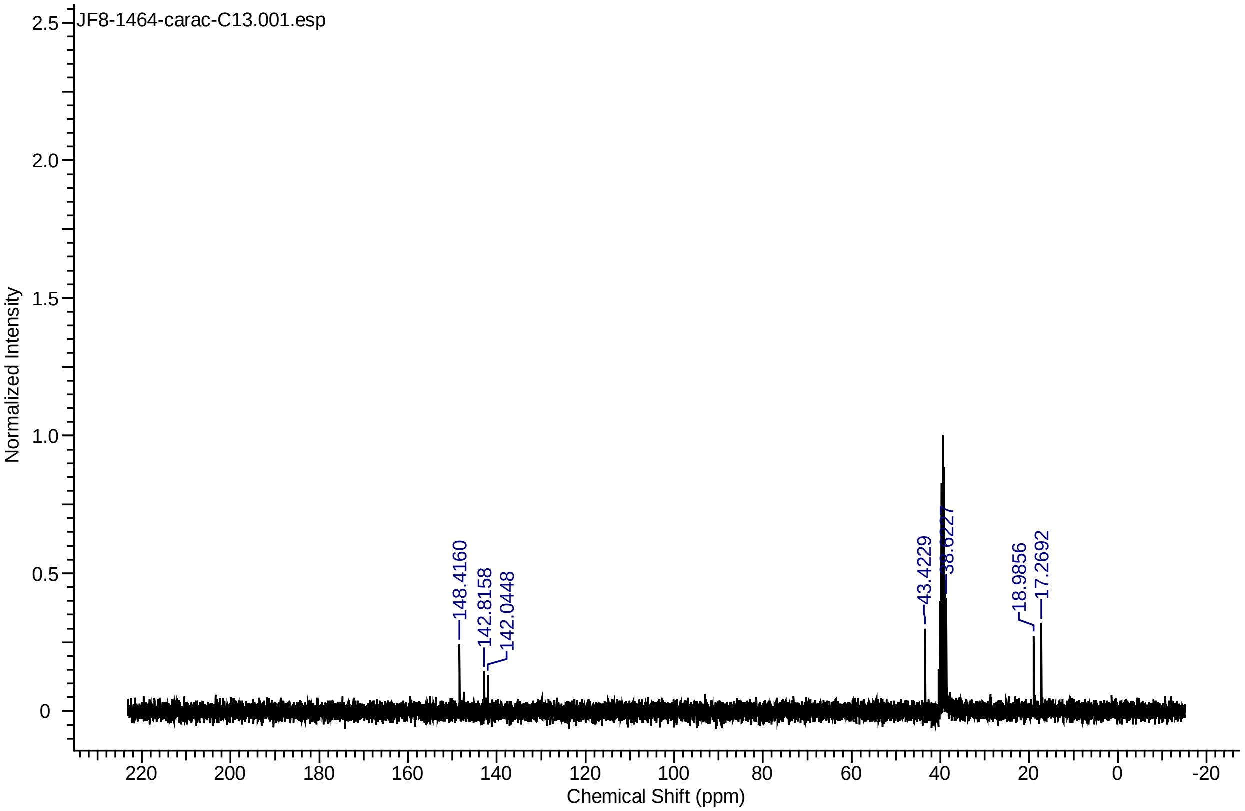

JB1-032-CHARAC.001.esp
H
N
N
O
N
N
4.25
Normalized Intensity
0.15
0.10
0.05
0
1.06
1.06
2.25
3.00
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

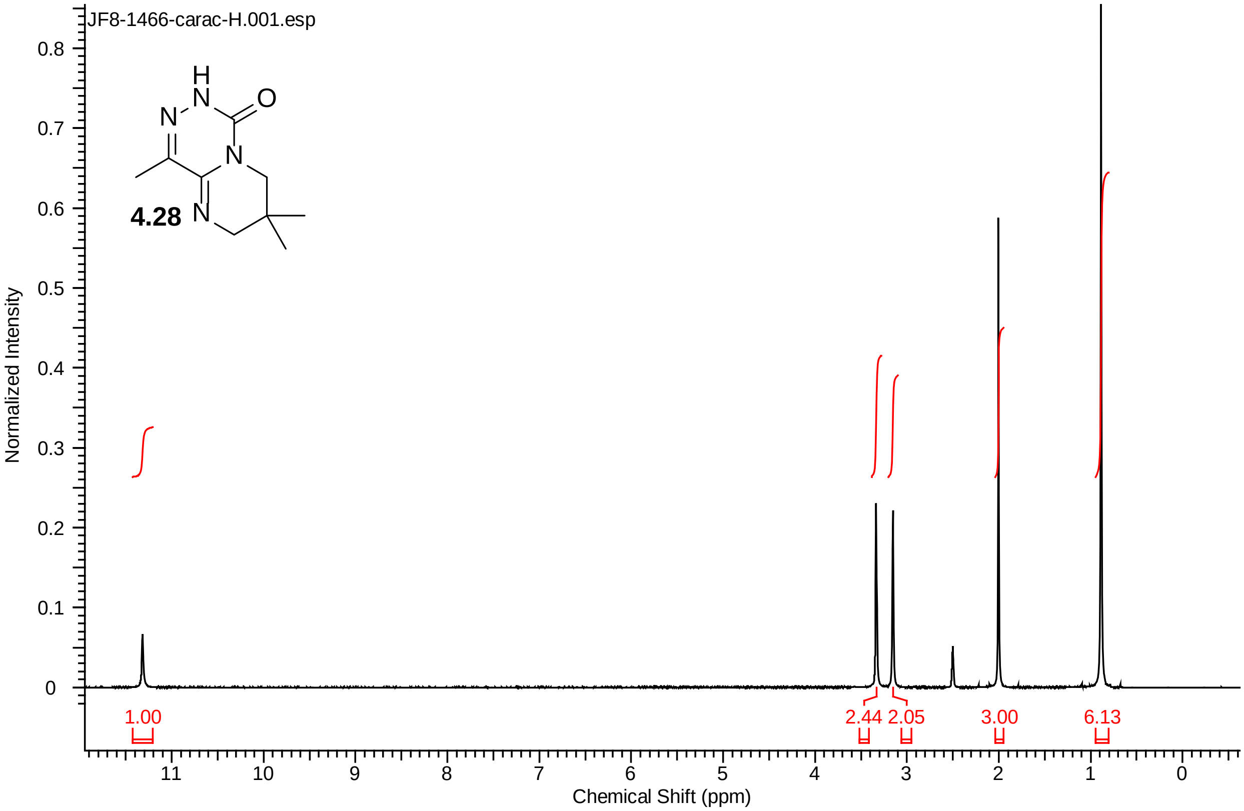

JB1-032-CHARAC.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
146.4084
139.6590
129.6077
126.5240
125.6367
120.7637
115.3381
17.1380
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

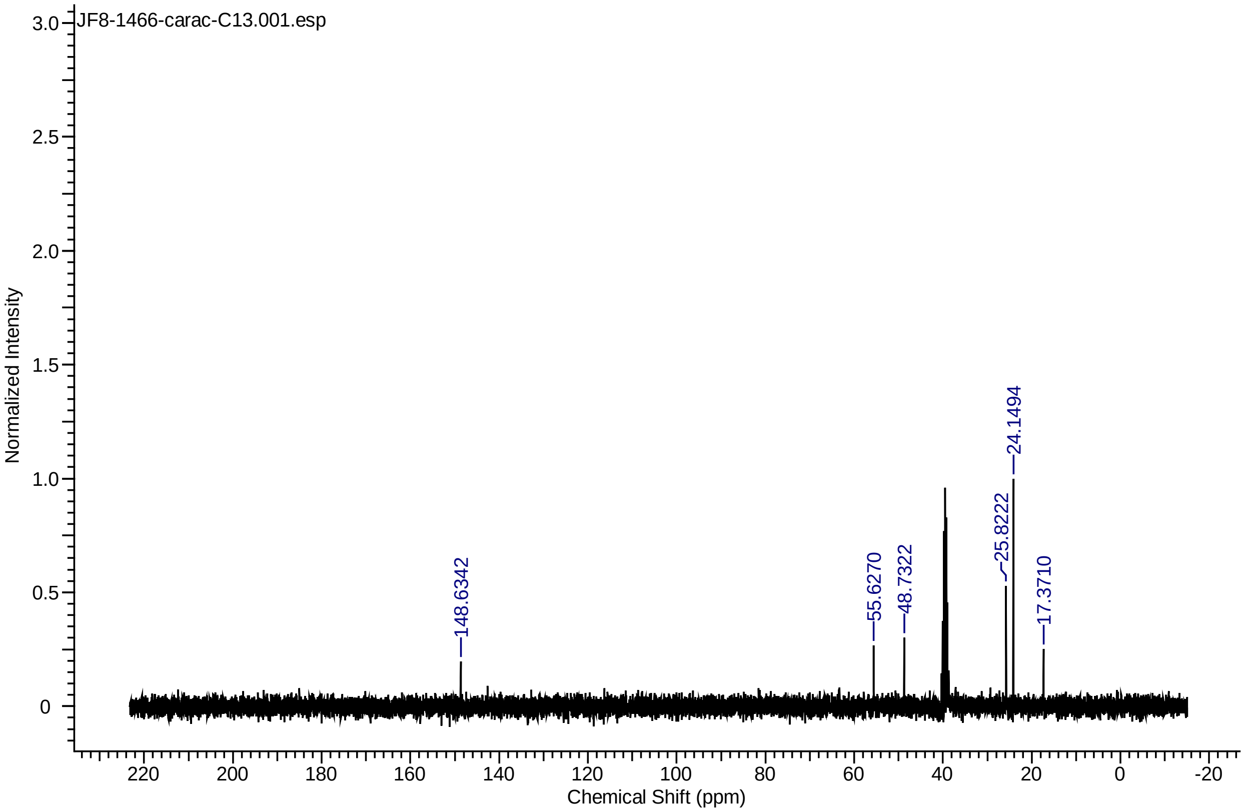

JF8-1383-carac-H.001.001.1r.esp
4.26
Normalized Intensity
Chemical Shift (ppm)
1.00
3.01
1.00
5.13
3.0
2.5
2.0
1.5
1.0
0.5
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0

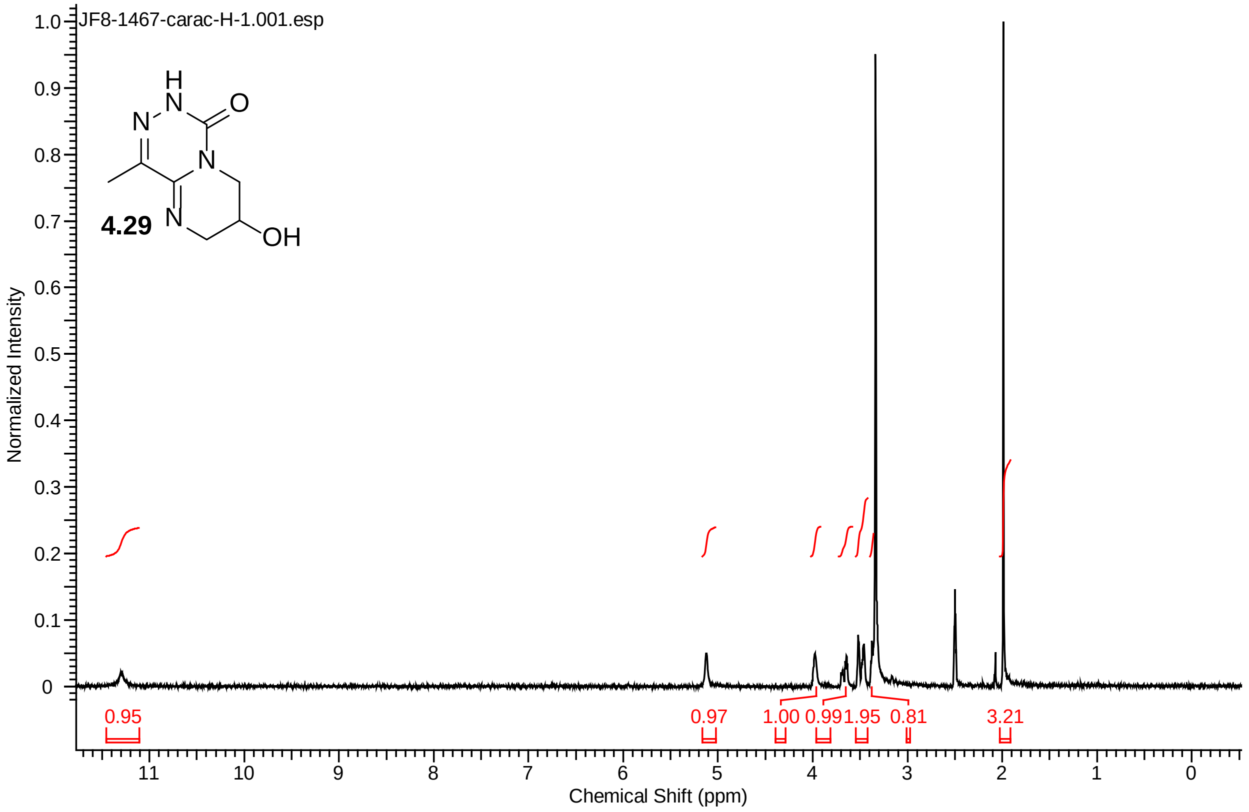

JF8-1383-carac-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
145.6304
142.9867
132.6117
129.8953
128.3788
128.0479
126.1897
125.3024
120.4404
114.9965
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20

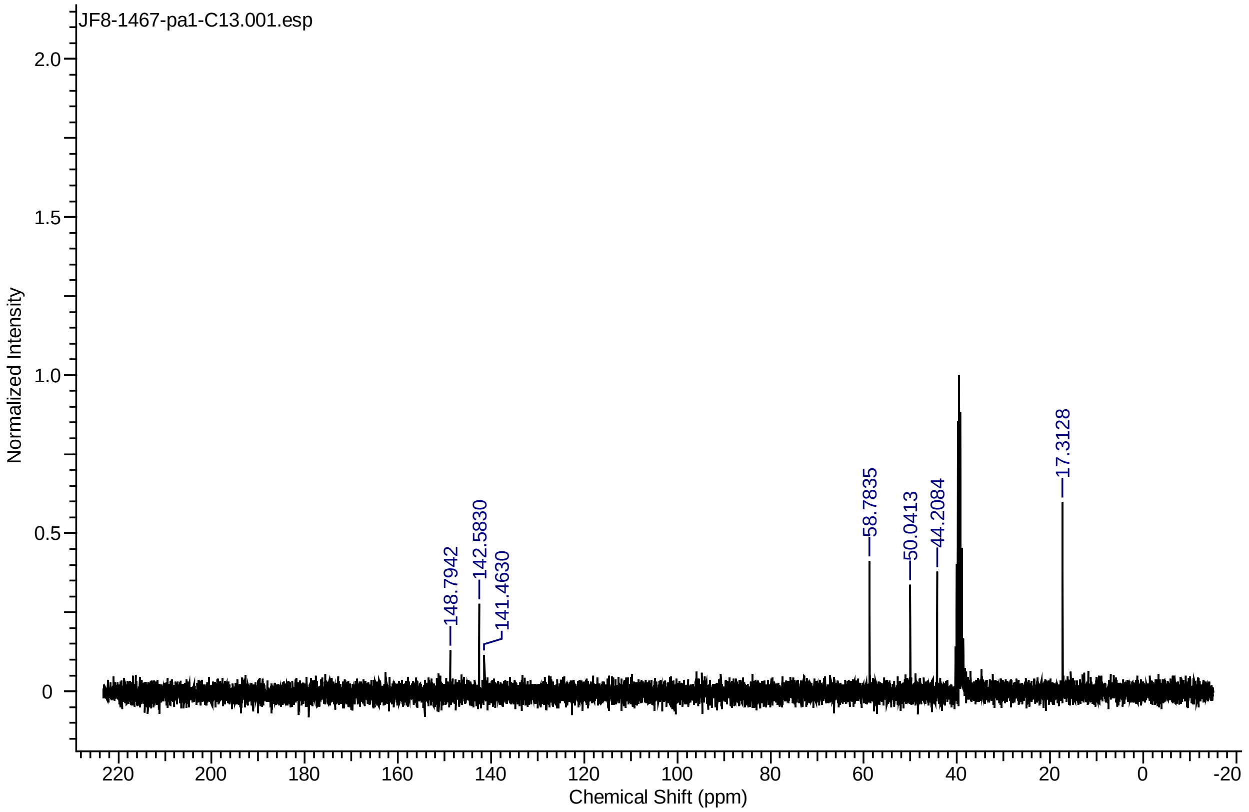

JF8-1464-carac-H.001.esp
H
N
N
O
N
N
4.27
Normalized Intensity
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.99
1.97
2.04
3.00
1.99
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

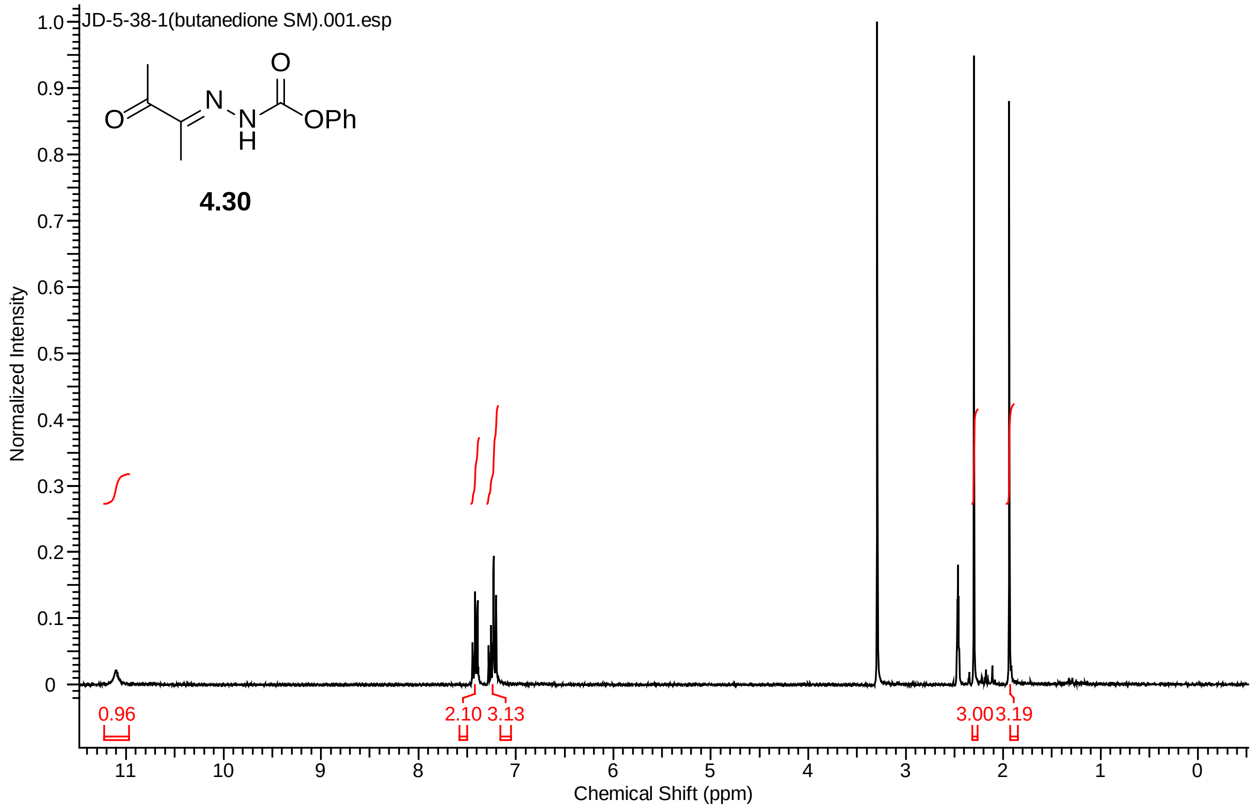

JF8-1464-carac-C13.001.esp
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0
148.4160
142.8158
142.0448
43.4229
38.6227
18.9856
17.2692
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

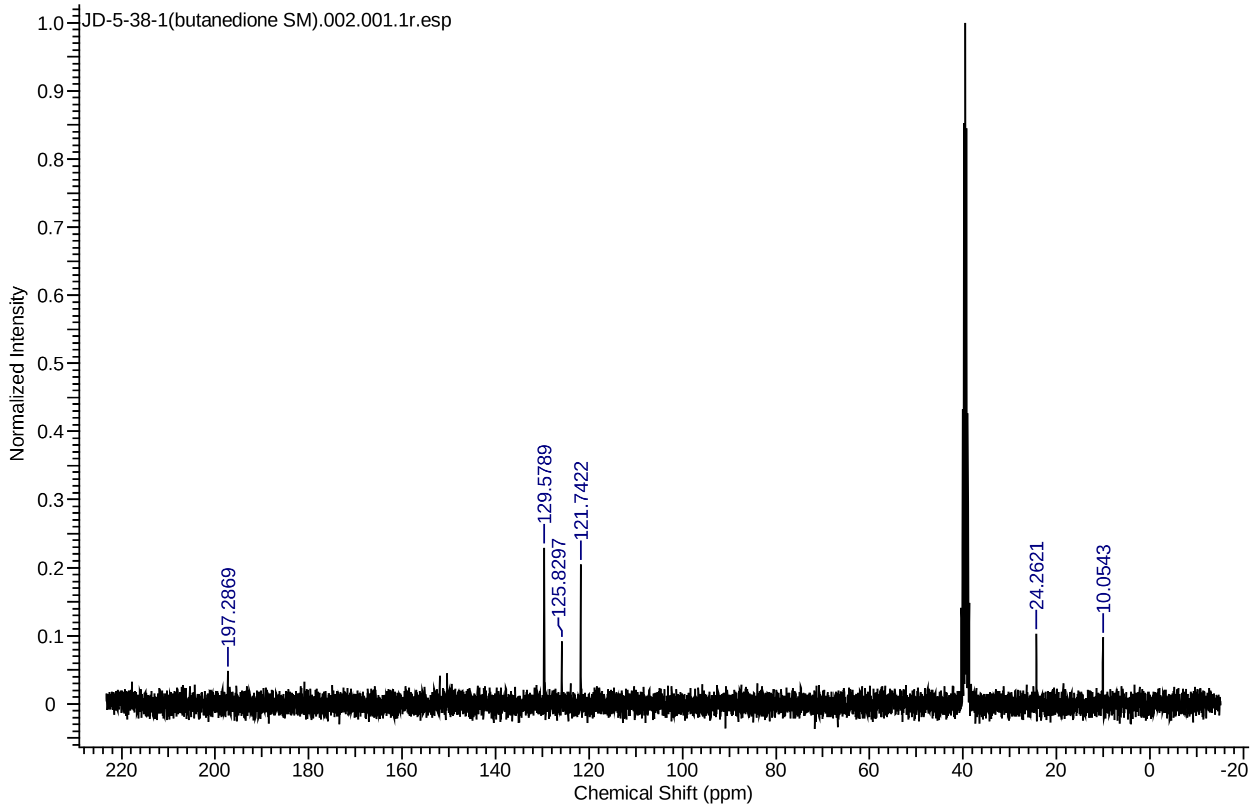

JF8-1466-carac-H.001.esp
4.28
H
N
N
O
N
N
Normalized Intensity
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
2.44
2.05
3.00
6.13
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

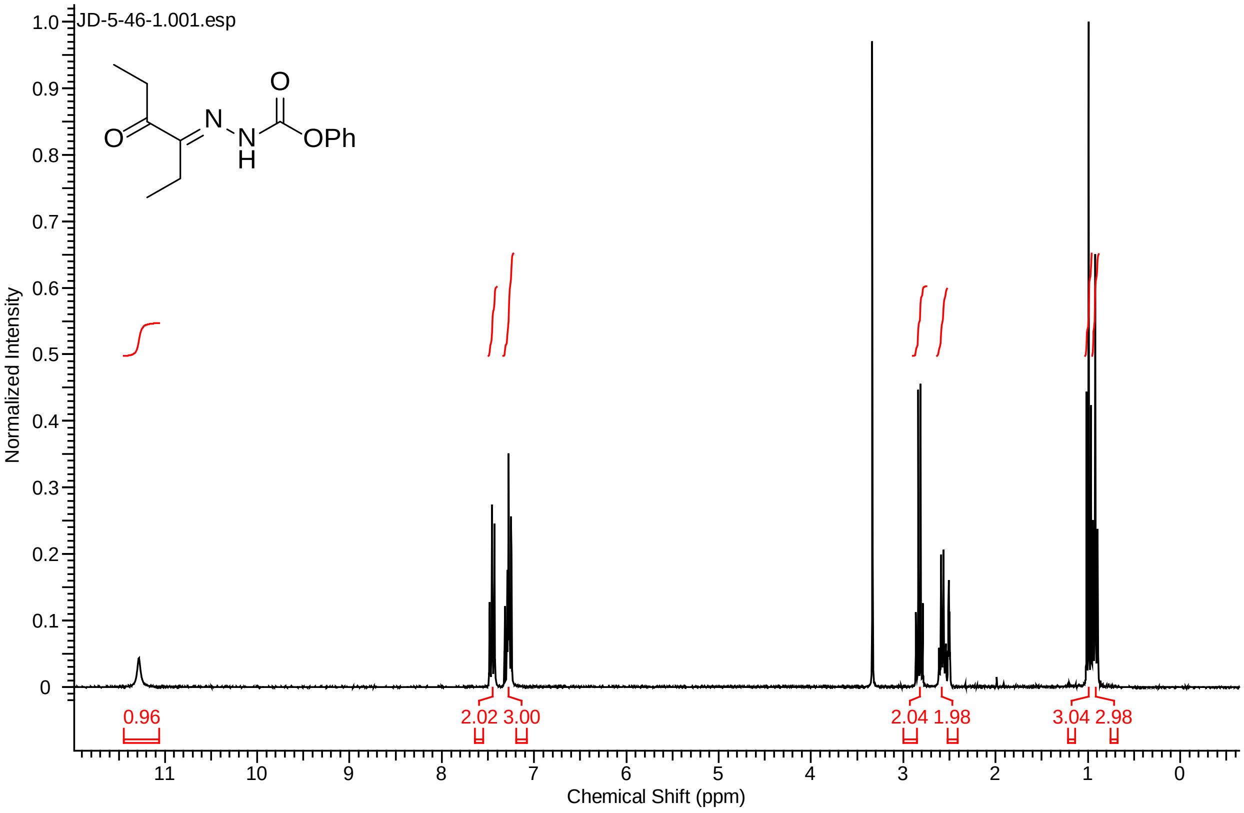

JF8-1466-carac-C13.001.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
148.6342
55.6270
48.7322
25.8222
24.1494
17.3710
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

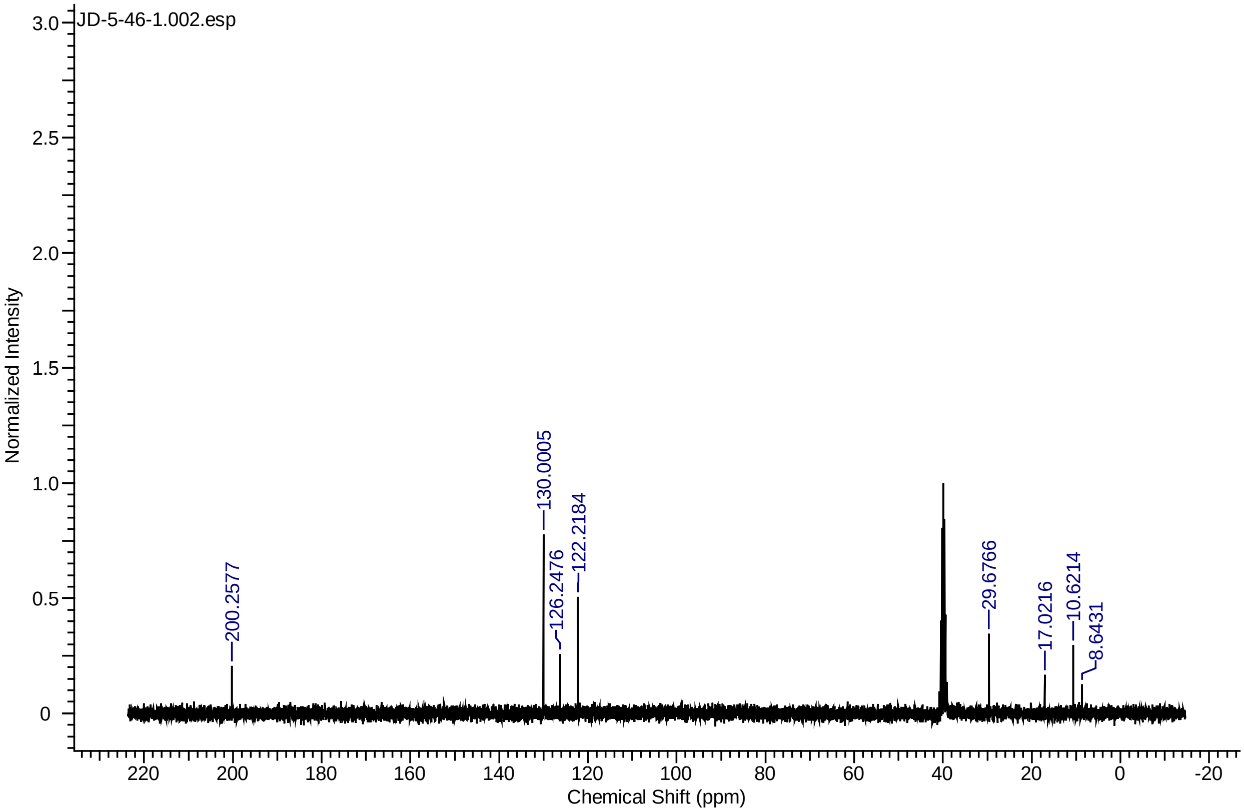

JF8-1467-carac-H-1.001.esp
4.29
H
N
N
O
N
N
OH
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.95
0.97
1.00
0.99
1.95
0.81
3.21
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

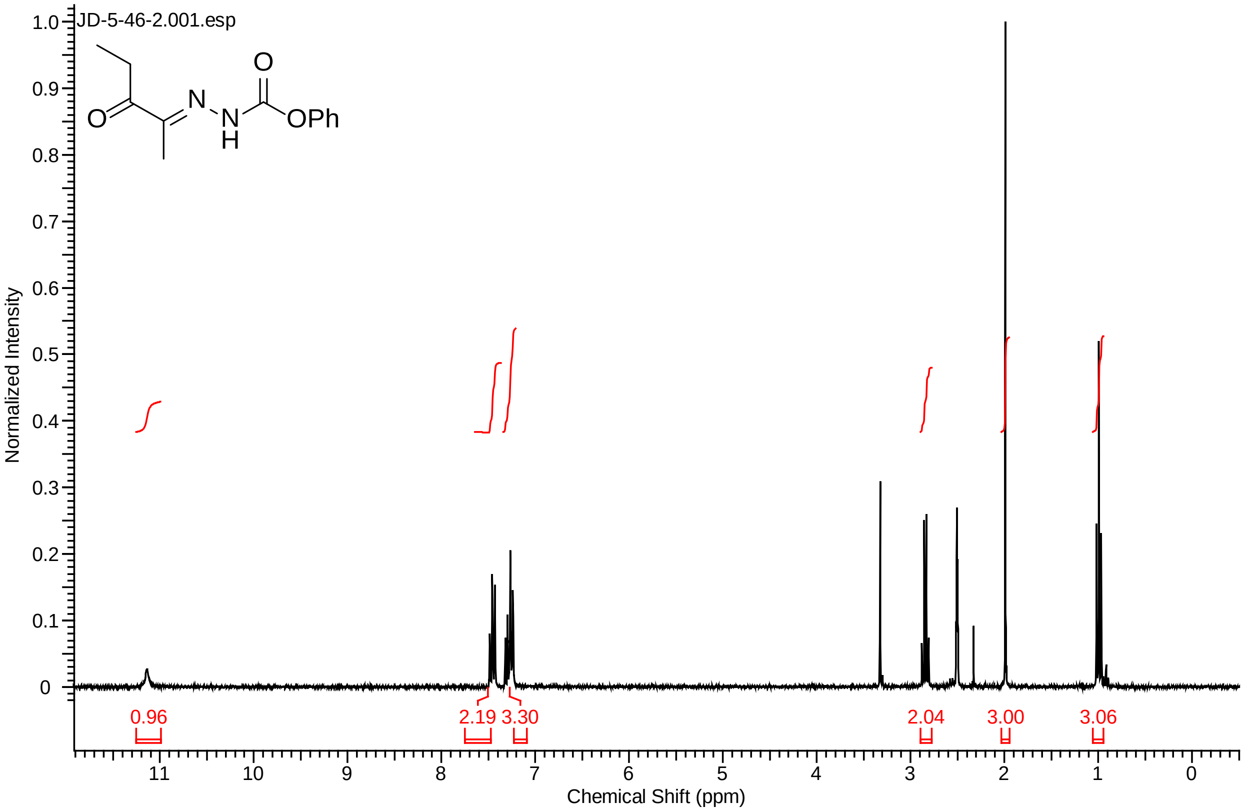

JF8-1467-pa1-C13.001.esp
Normalized Intensity
2.0
1.5
1.0
0.5
0
148.7942
142.5830
141.4630
58.7835
50.0413
44.2084
17.3128
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

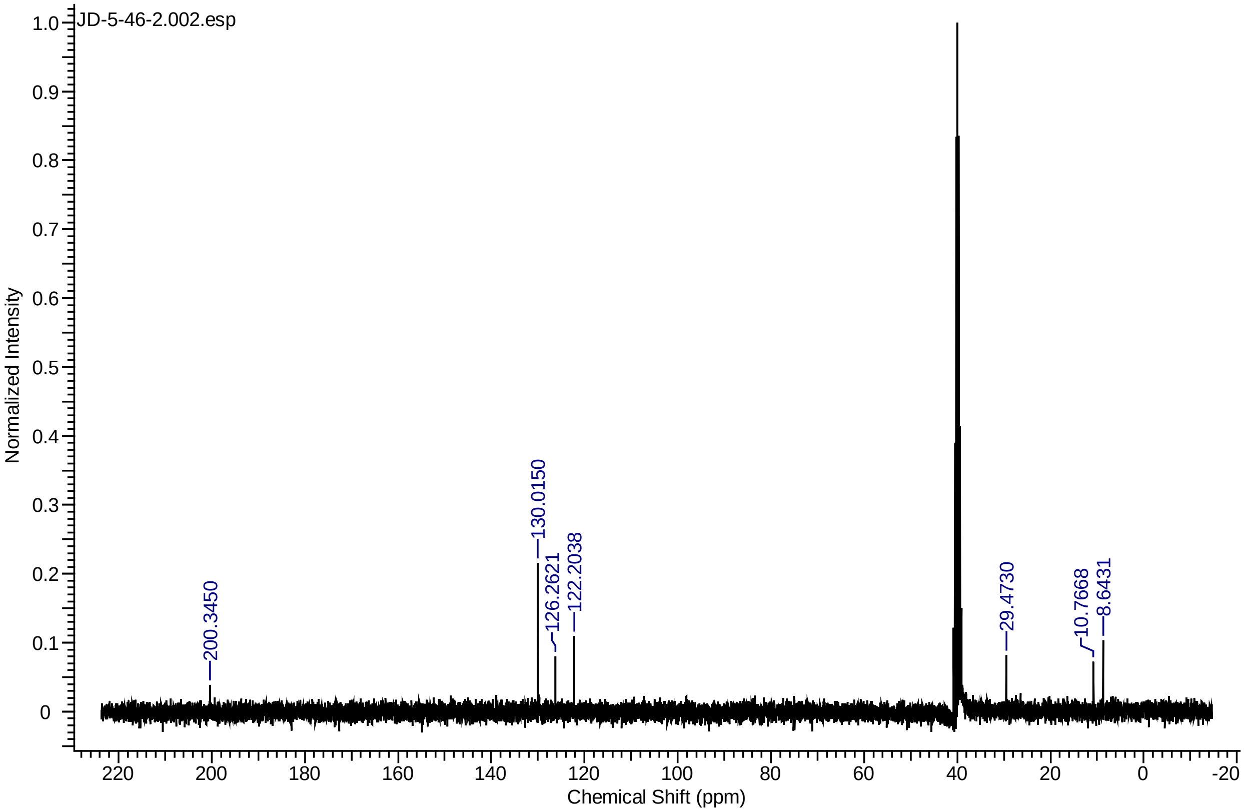

JD-5-38-1(butanedione SM).001.esp
O
N
N
H
O
OPh
4.30
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.96
2.10
3.13
3.00
3.19
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

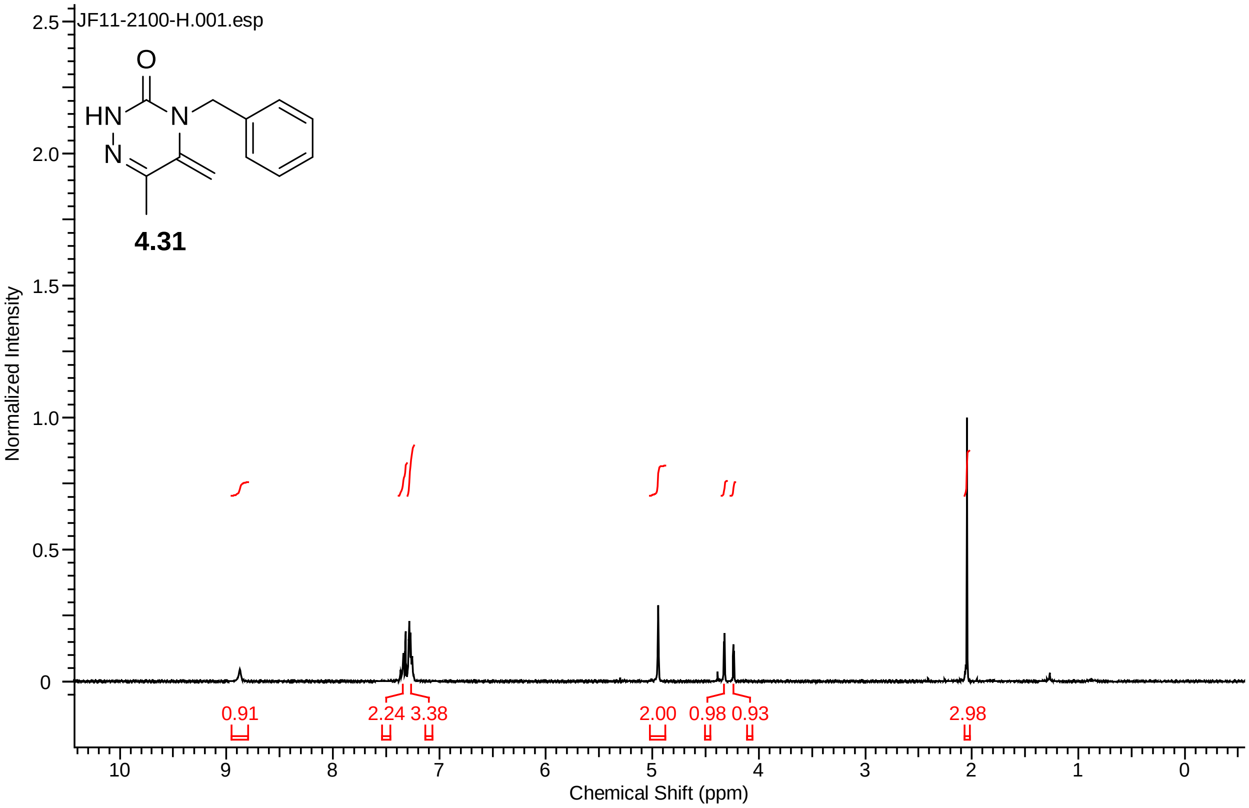

JD-5-38-1(butanedione SM).002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
197.2869
129.5789
125.8297
121.7422
24.2621
10.0543
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

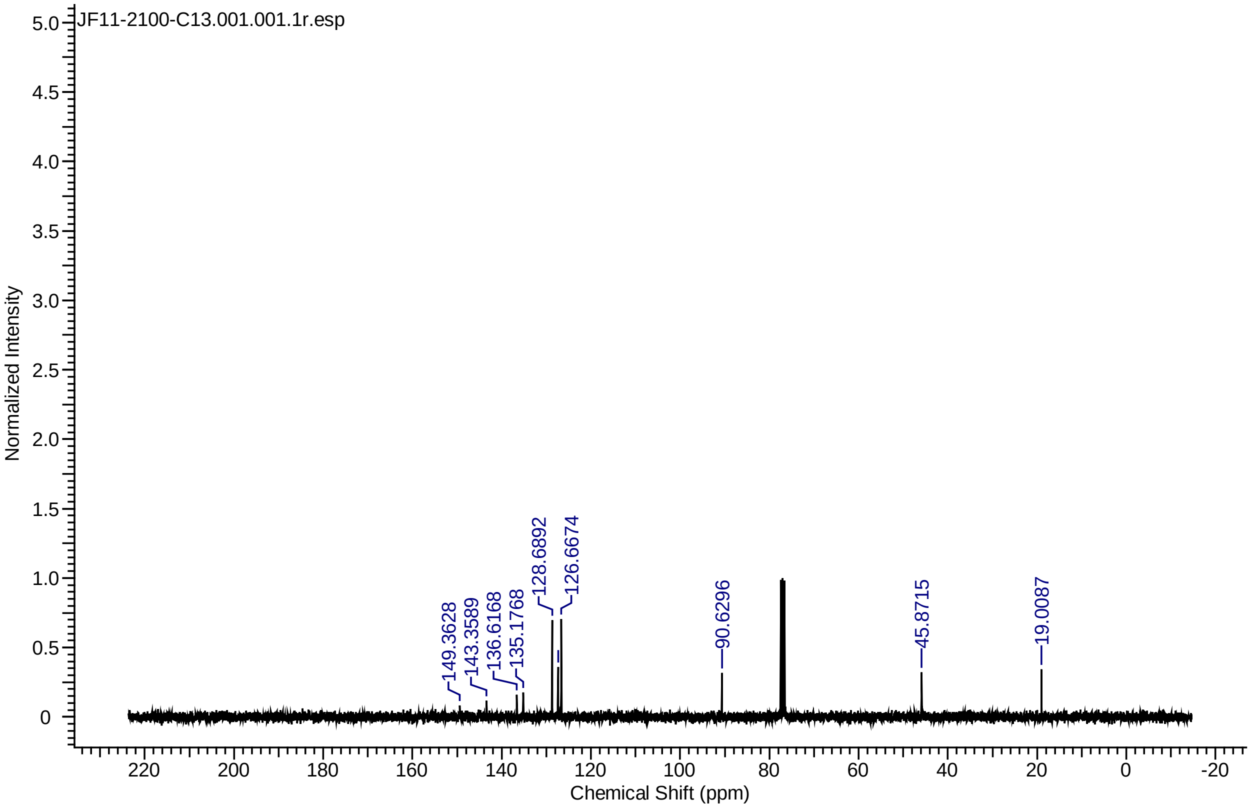

JD-5-46-1.001.esp
O
N
N
H
O
OPh
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.96
2.02
3.00
2.04
1.98
3.04
2.98
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

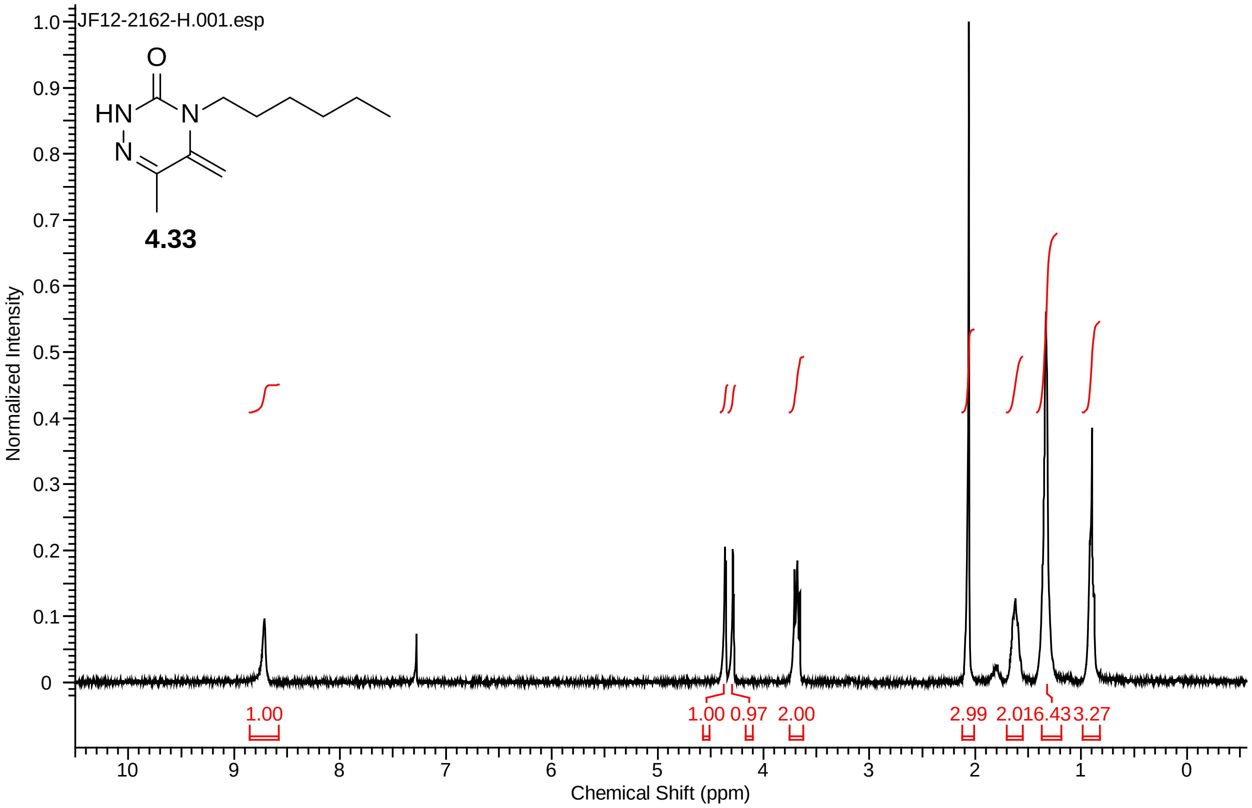

JD-5-46-1.002.esp
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
200.2577
130.0005
126.2476
122.2184
29.6766
17.0216
10.6214
8.6431
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

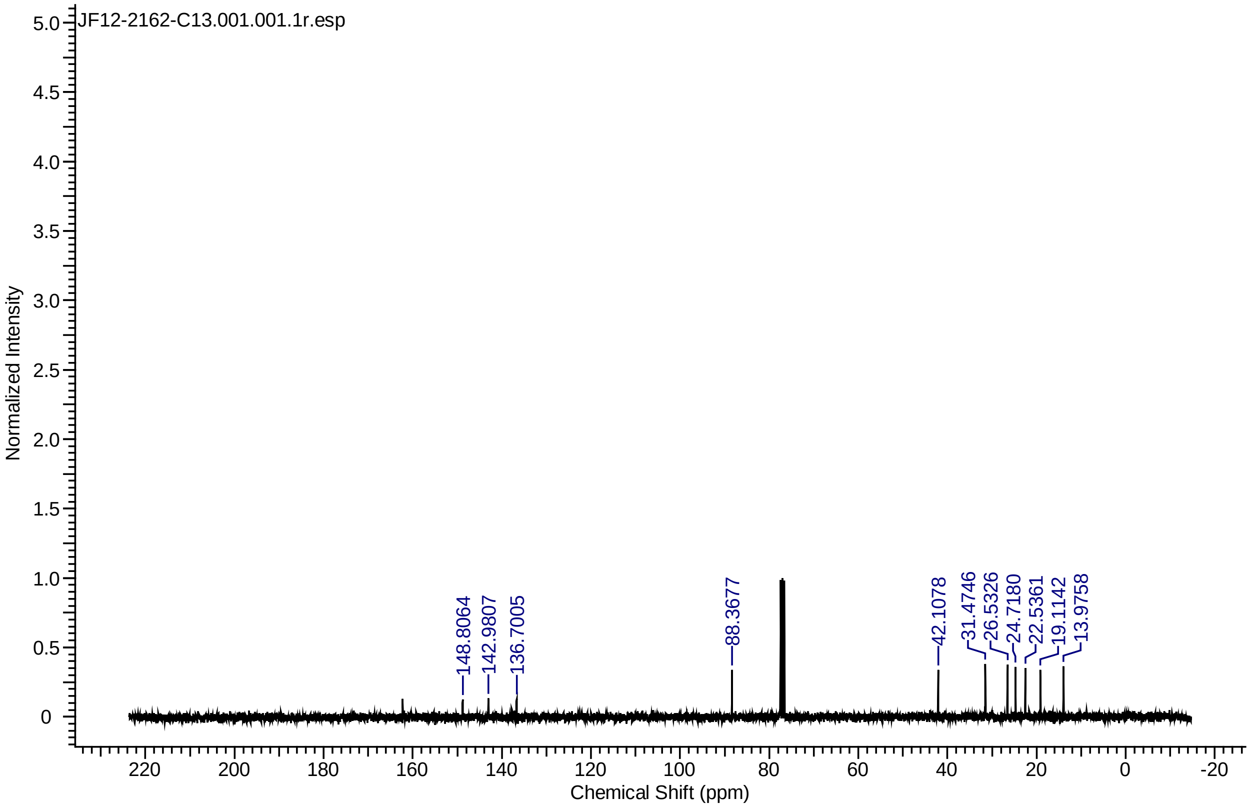

JD-5-46-2.001.esp
O
N
N
H
O
OPh
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.96
2.19
3.30
2.04
3.00
3.06
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

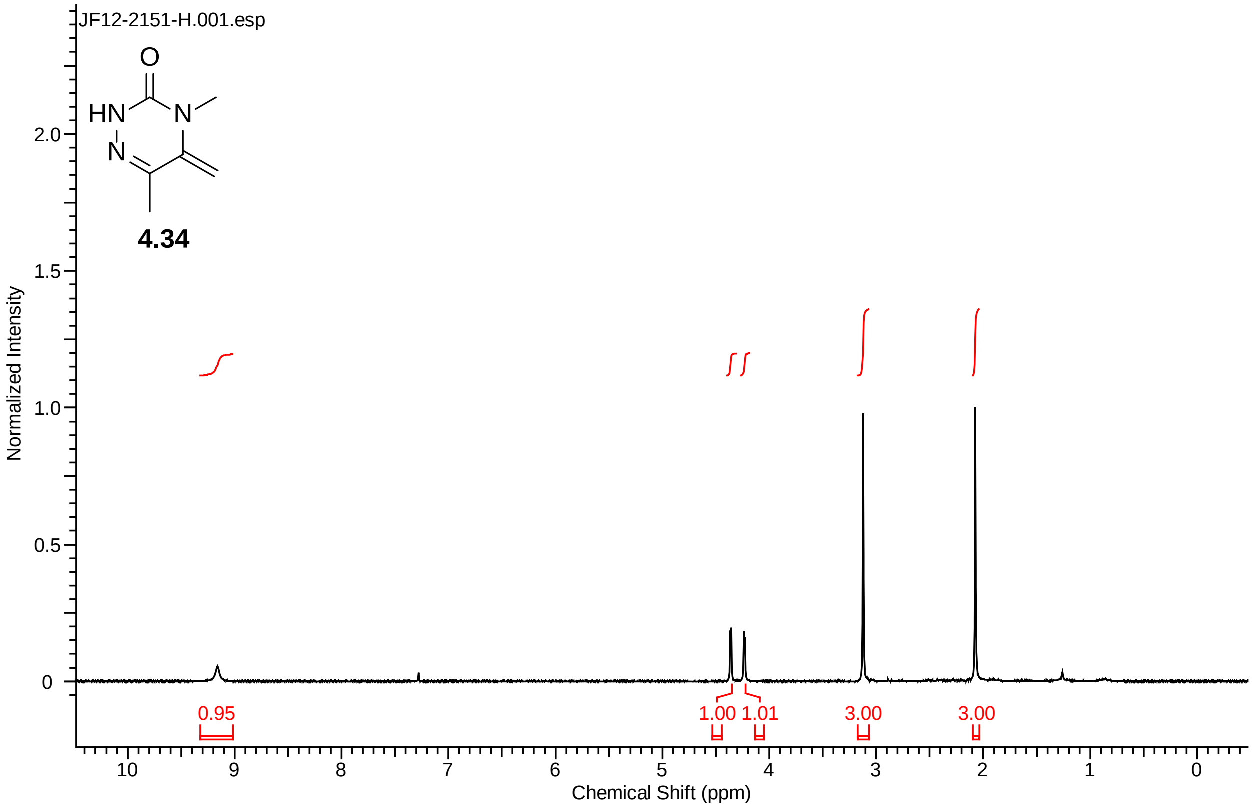

JD-5-46-2.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
200.3450
130.0150
126.2621
122.2038
29.4730
10.7668
8.6431
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

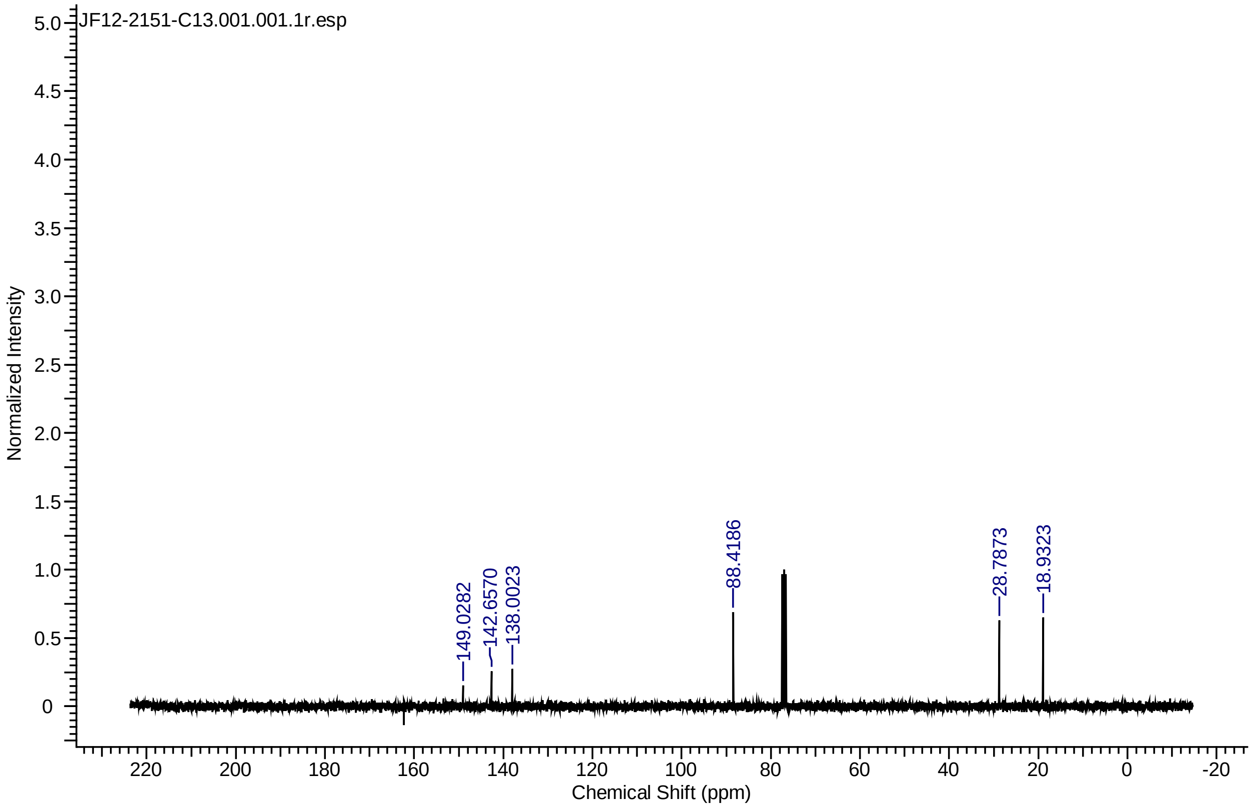

JF11-2100-H.001.esp
O
HN
N
N
4.31
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0
0.91
2.24
3.38
2.00
0.98
0.93
2.98
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

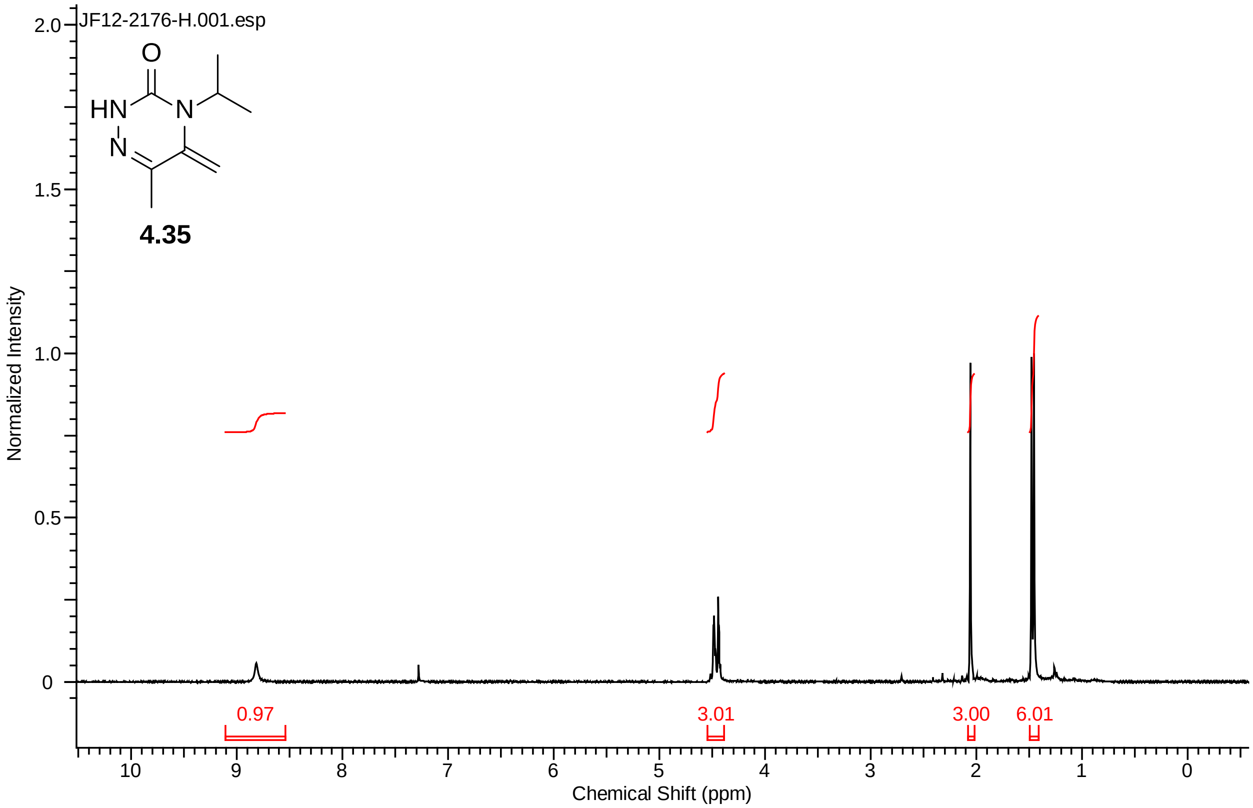

JF11-2100-C13.001.001.1r.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
149.3628
143.3589
136.6168
135.1768
128.6892
126.6674
90.6296
45.8715
19.0087
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

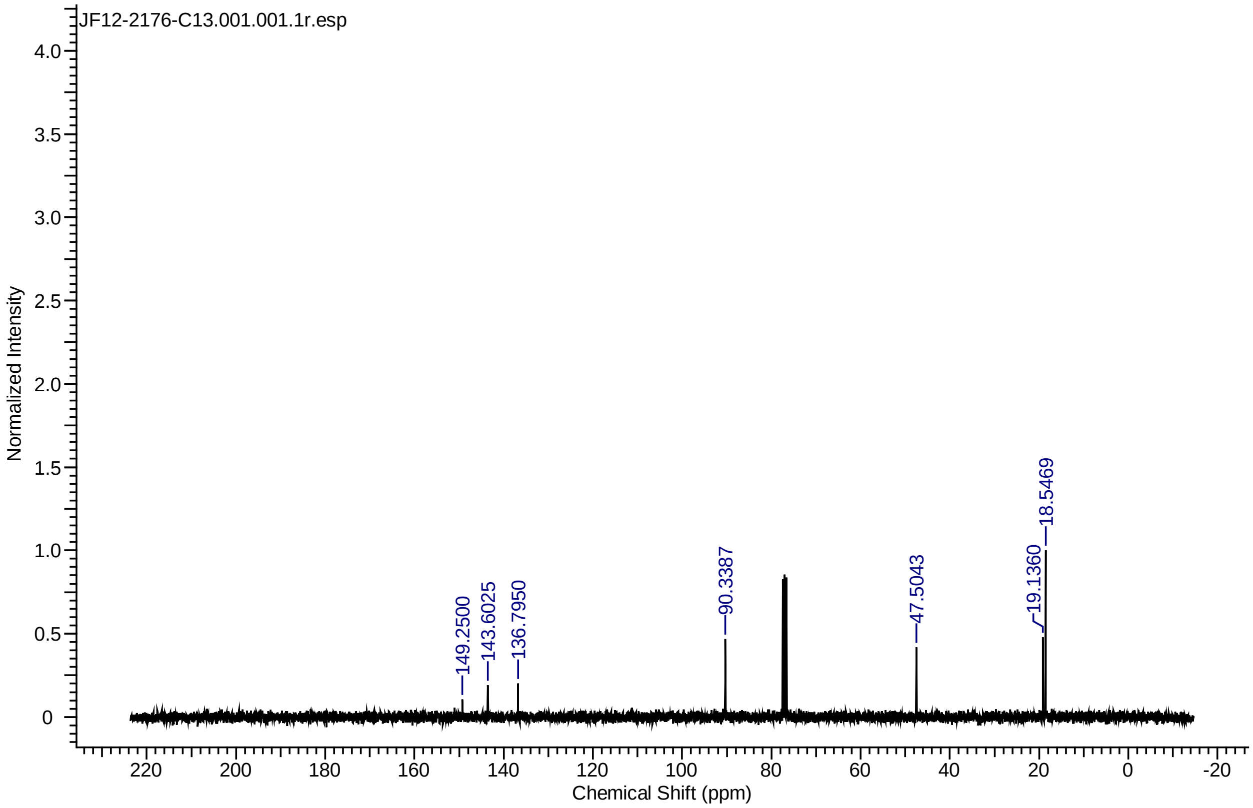

JF12-2162-H.001.esp
O
HN
N
N
4.33
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
1.00
0.97
2.00
2.99
2.01
6.43
3.27
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

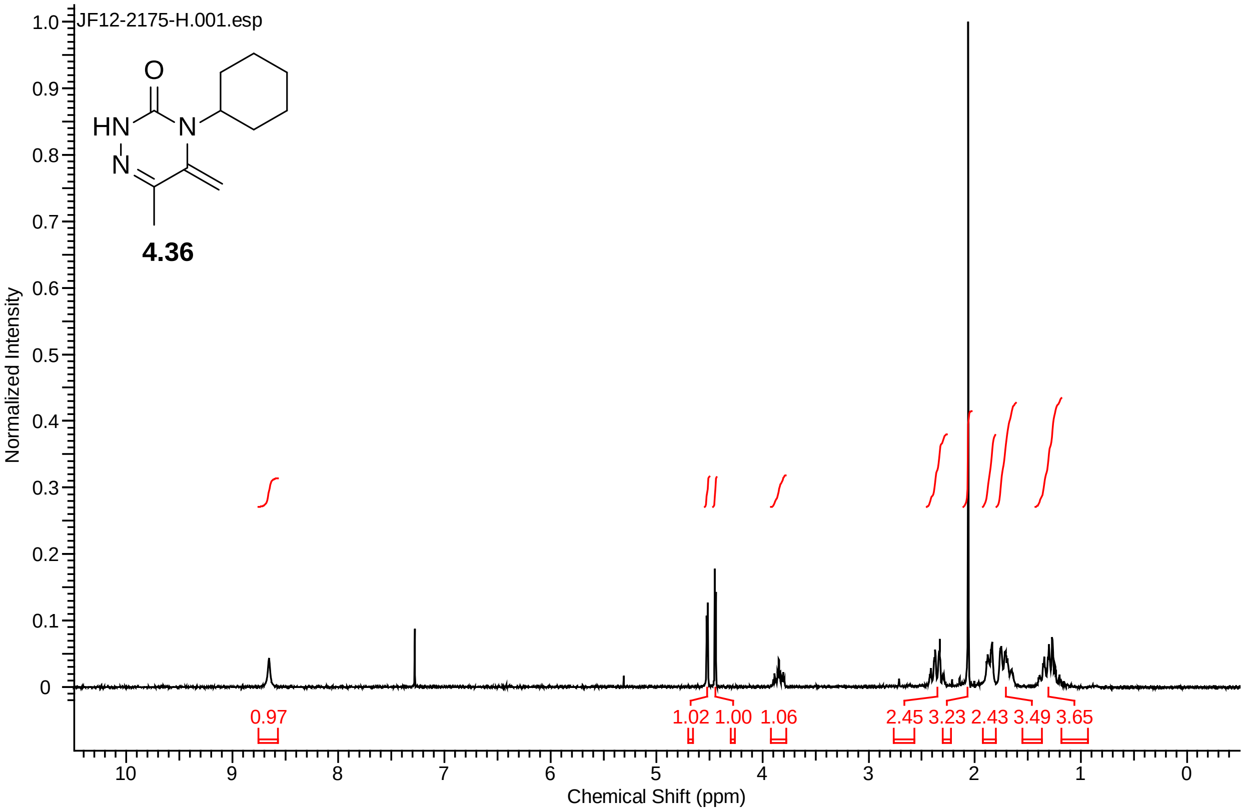

JF12-2162-C13.001.001.1r.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
148.8064
142.9807
136.7005
88.3677
42.1078
31.4746
26.5326
24.7180
22.5361
19.1142
13.9758
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

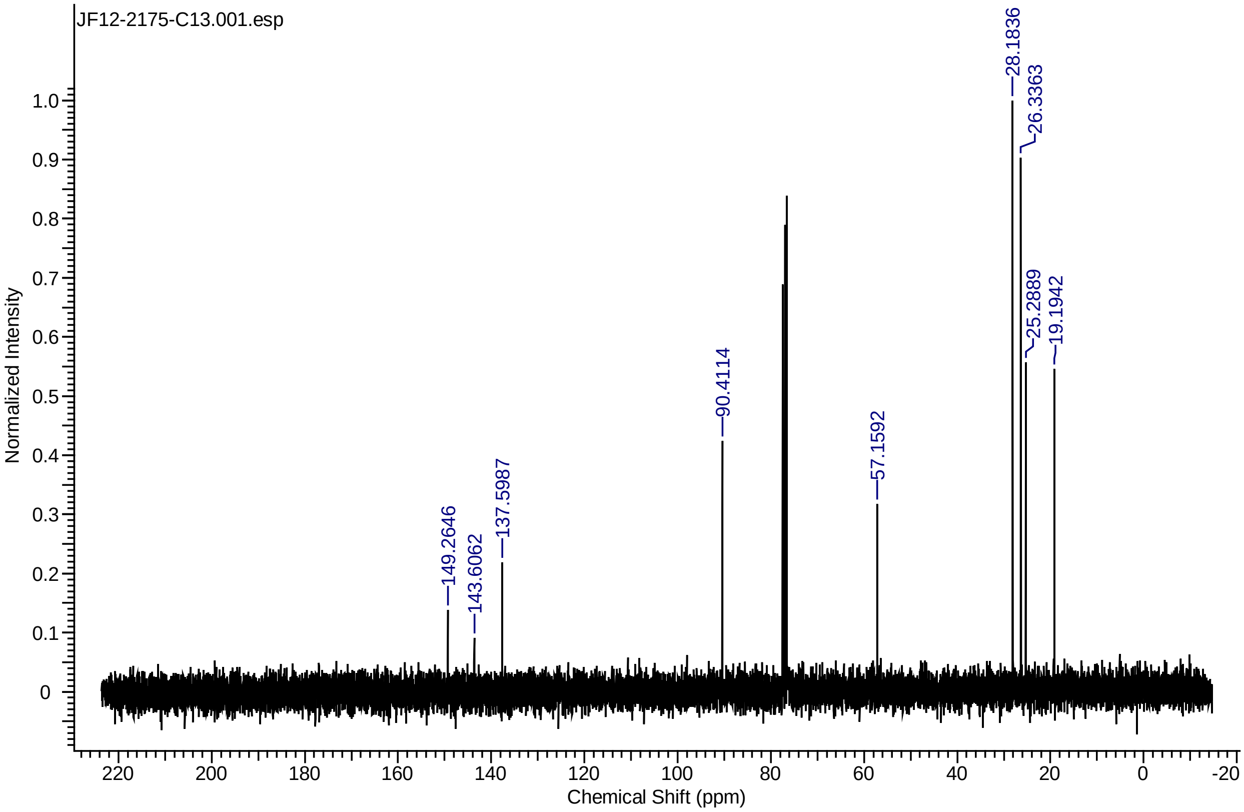

JF12-2151-H.001.esp
O
HN
N
N
4.34
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.95
1.00
1.01
3.00
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

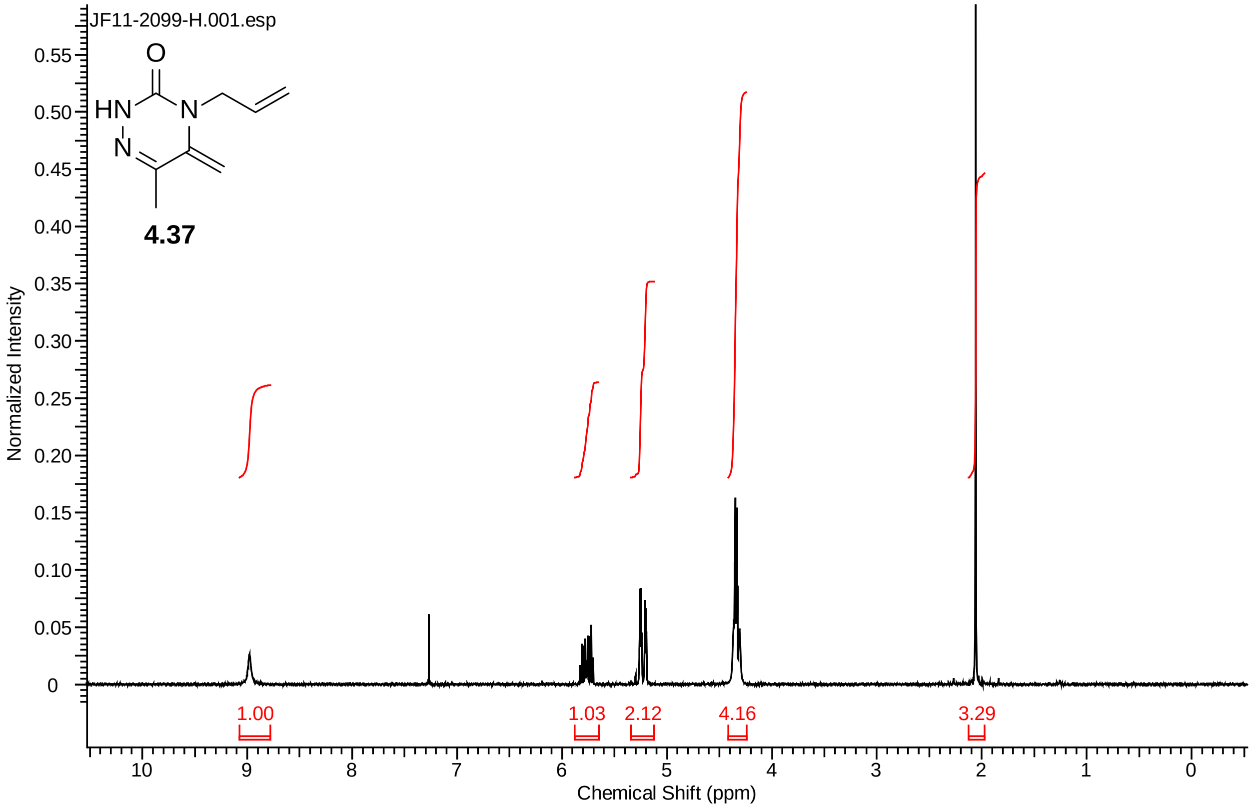

JF12-2151-C13.001.001.1r.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
149.0282
142.6570
138.0023
88.4186
28.7873
18.9323
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

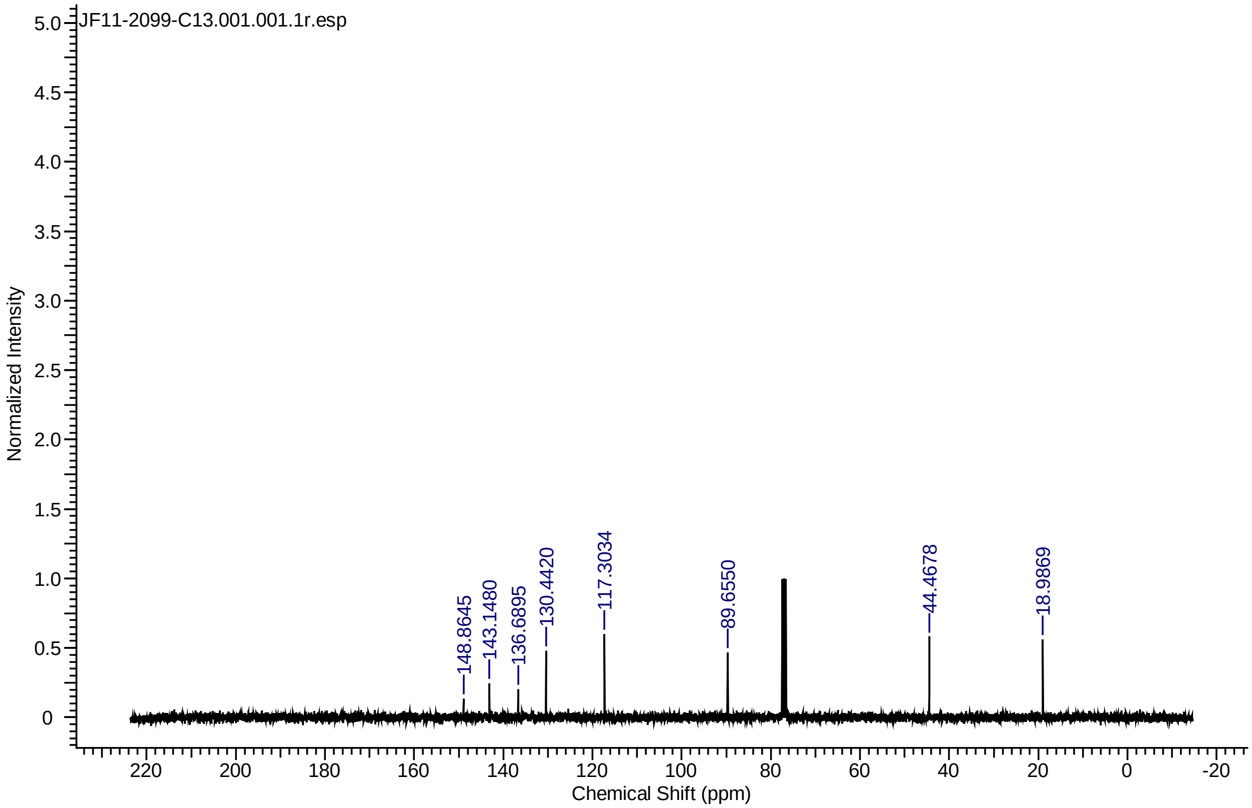

JF12-2176-H.001.esp
O
HN
N
N
4.35
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.97
3.01
3.00
6.01
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

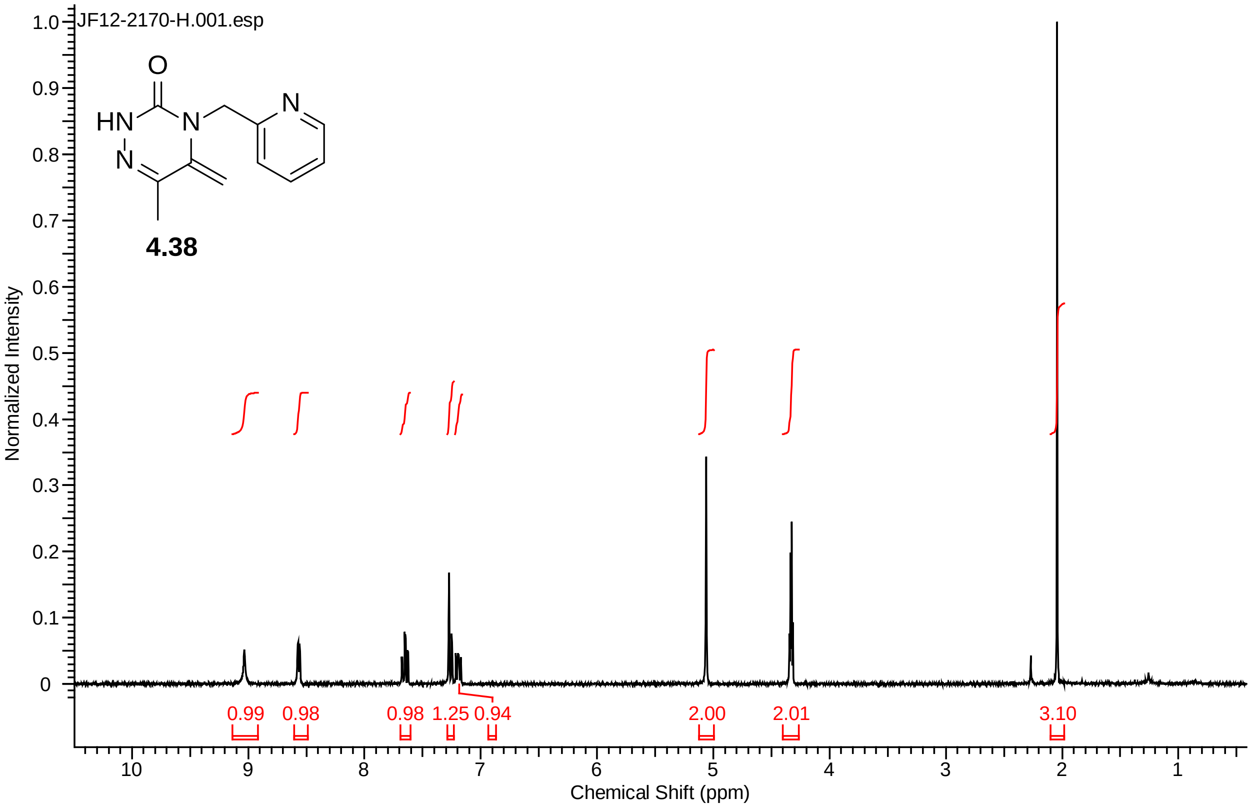

JF12-2176-C13.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
149.2500
143.6025
136.7950
90.3387
47.5043
19.1360
18.5469
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

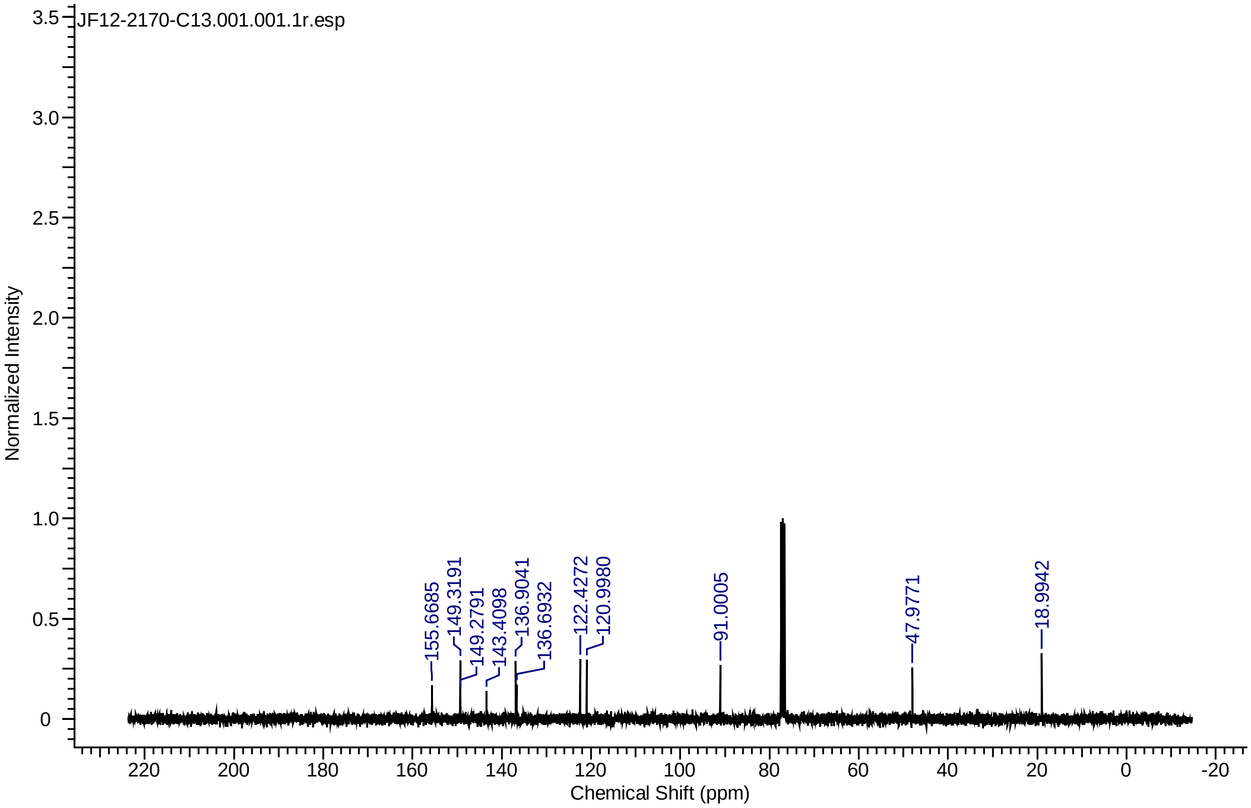

JF12-2175-H.001.esp
O
HN
N
N
4.36
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.97
1.02
1.00
1.06
2.45
3.23
2.43
3.49
3.65
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

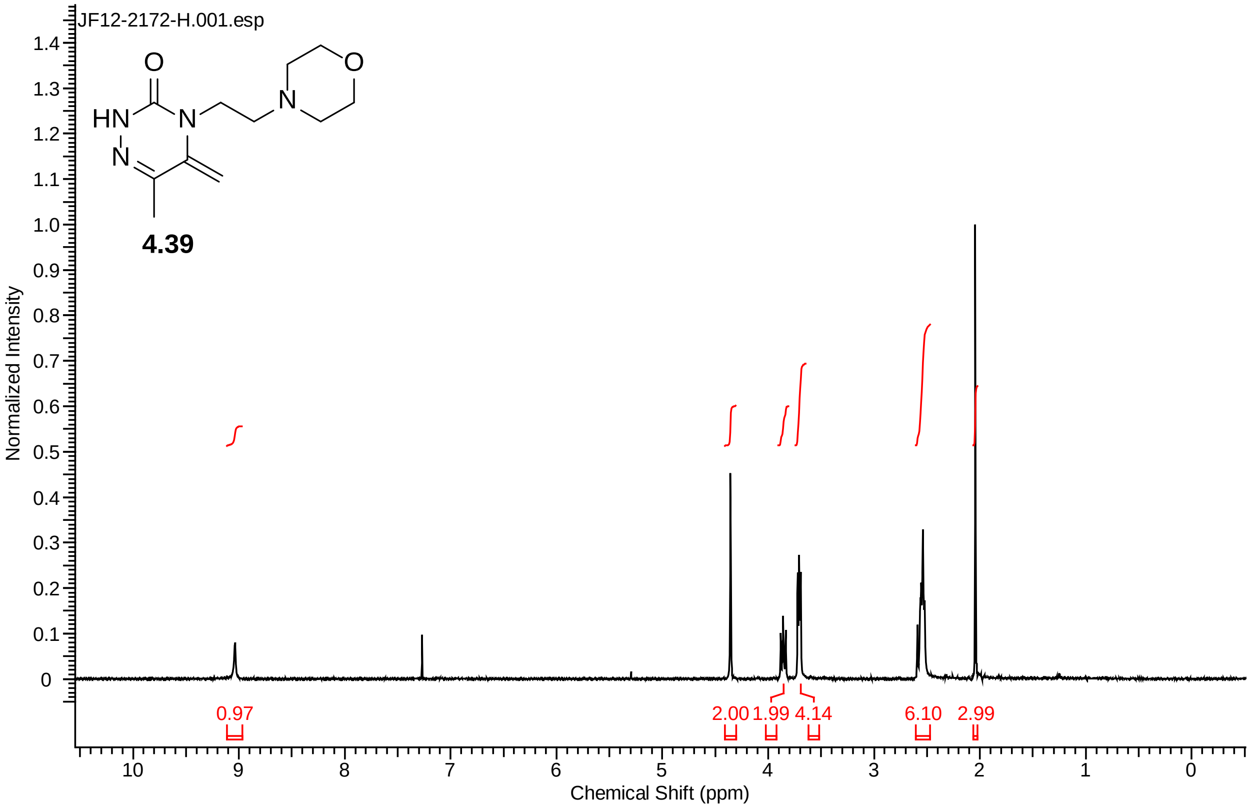

JF12-2175-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
149.2646
143.6062
137.5987
90.4114
57.1592
28.1836
26.3363
25.2889
19.1942
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

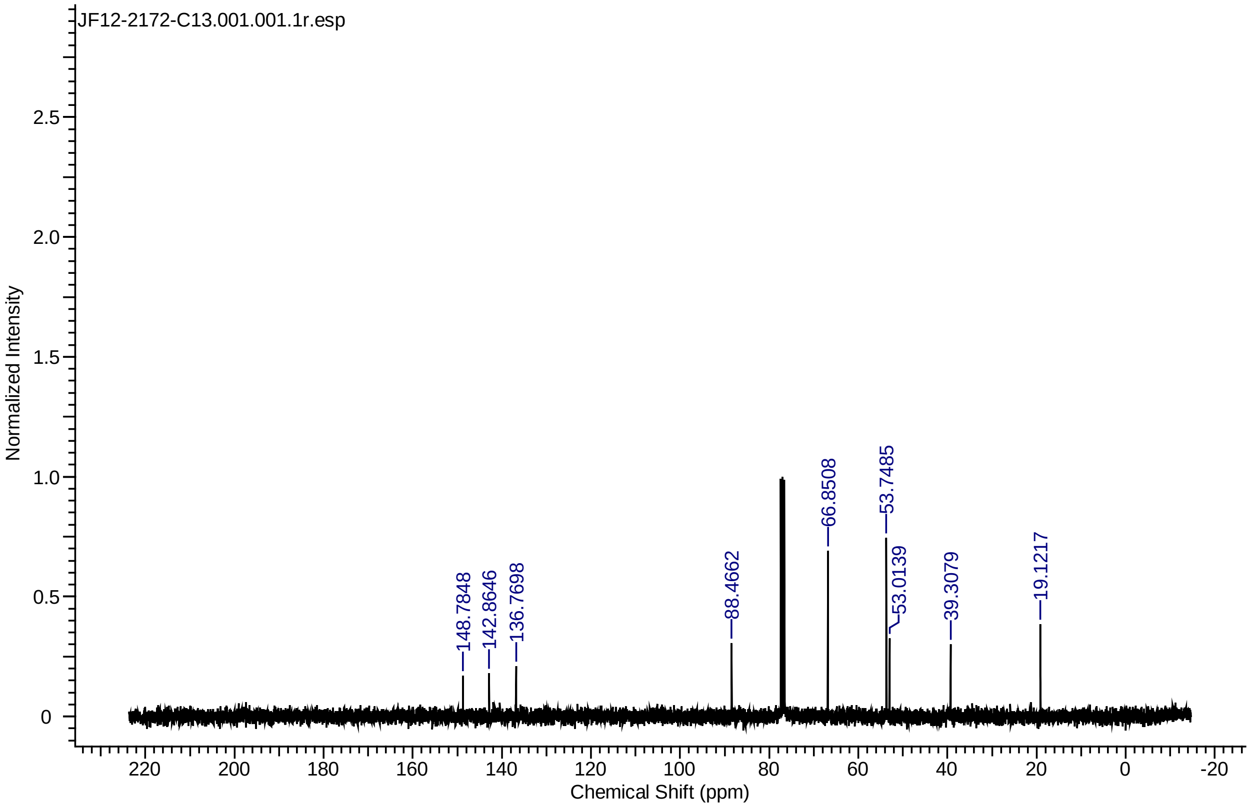

JF11-2099-H.001.esp
O
HN
N
N
4.37
Normalized Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
1.00
1.03
2.12
4.16
3.29
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

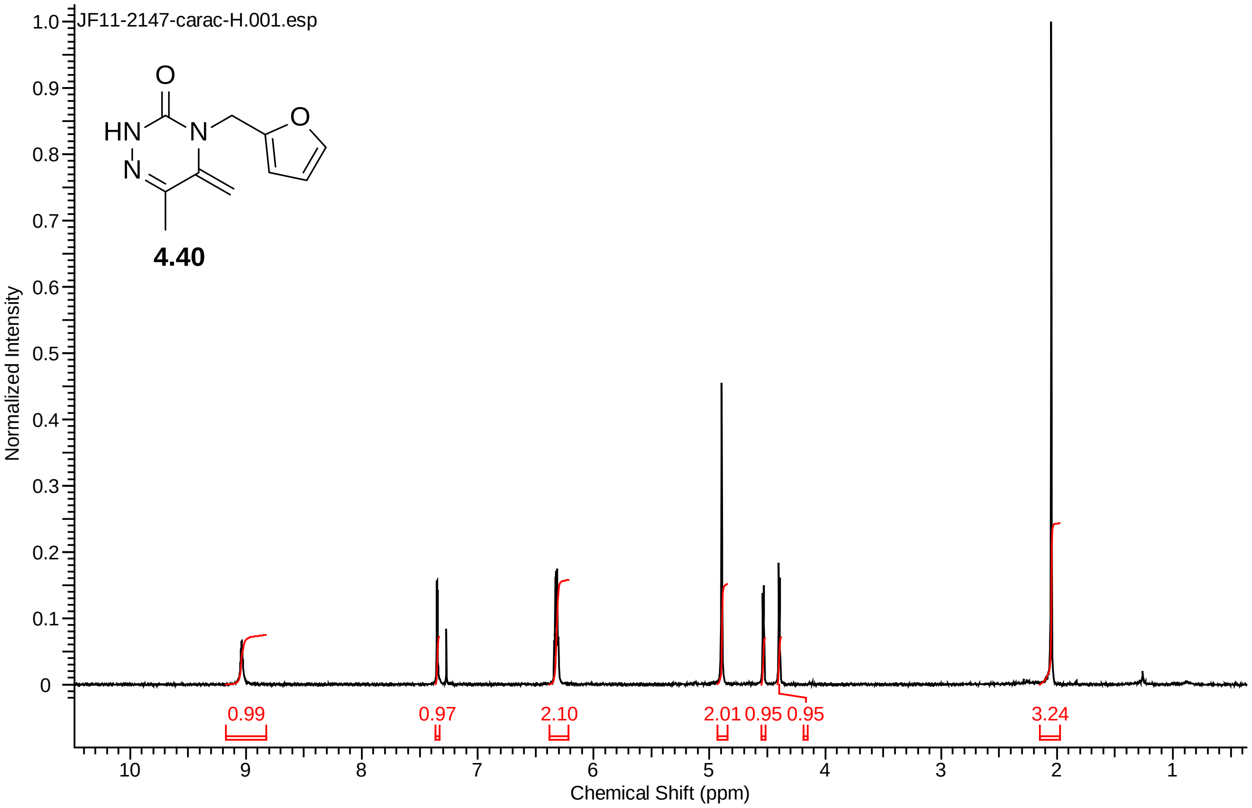

JF11-2099-C13.001.001.1r.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
148.8645
143.1480
136.6895
130.4420
117.3034
89.6550
44.4678
18.9869
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF12-2170-H.001.esp
4.38
O
HN
N
N
N
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.99
0.98
0.98
1.25
0.94
2.00
2.01
3.10
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


JF12-2170-C13.001.001.1r.esp
Normalized Intensity
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
155.6685
149.3191
149.2791
143.4098
136.9041
136.6932
122.4272
120.9980
91.0005
47.9771
18.9942
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

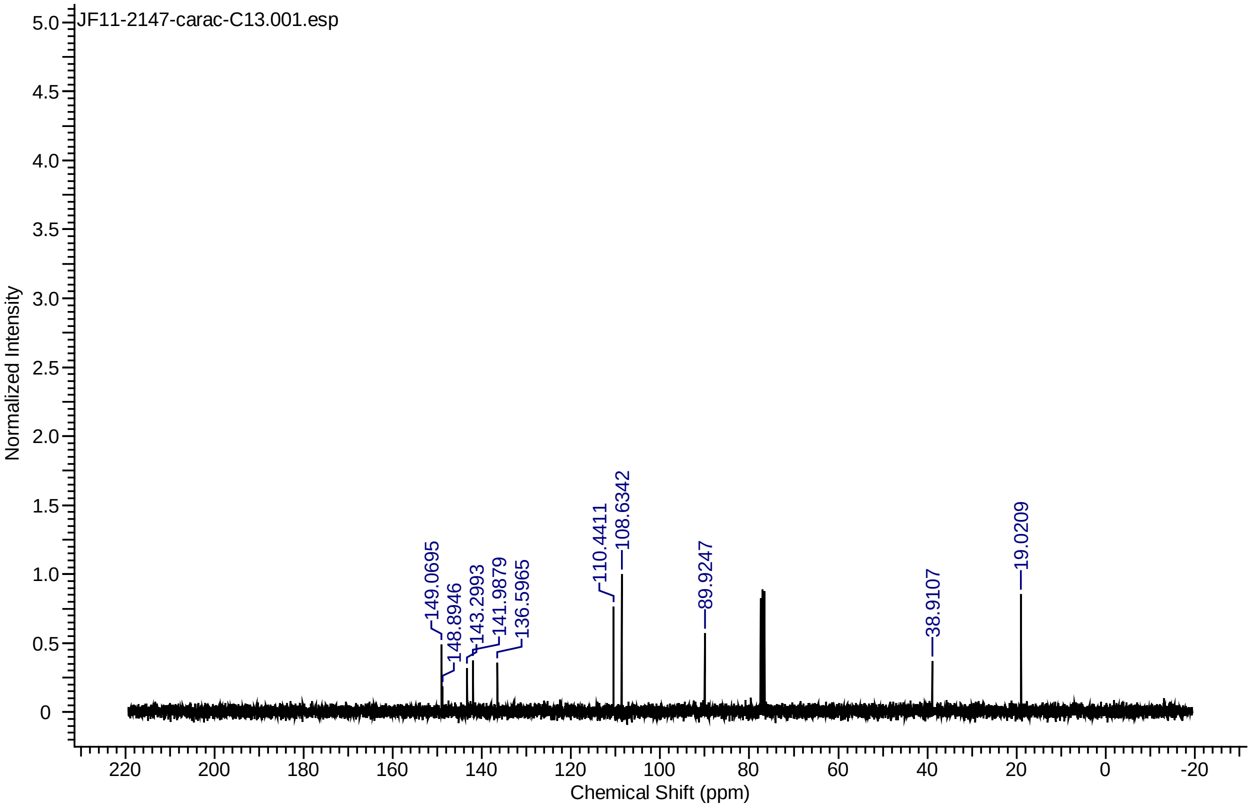

JF12-2172-H.001.esp
Normalized Intensity
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
O
HN
N
N
N
O
4.39
0.97
2.00
1.99
4.14
6.10
2.99
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF12-2172-C13.001.001.1r.esp
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0
148.7848
142.8646
136.7698
88.4662
66.8508
53.7485
53.0139
39.3079
19.1217
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

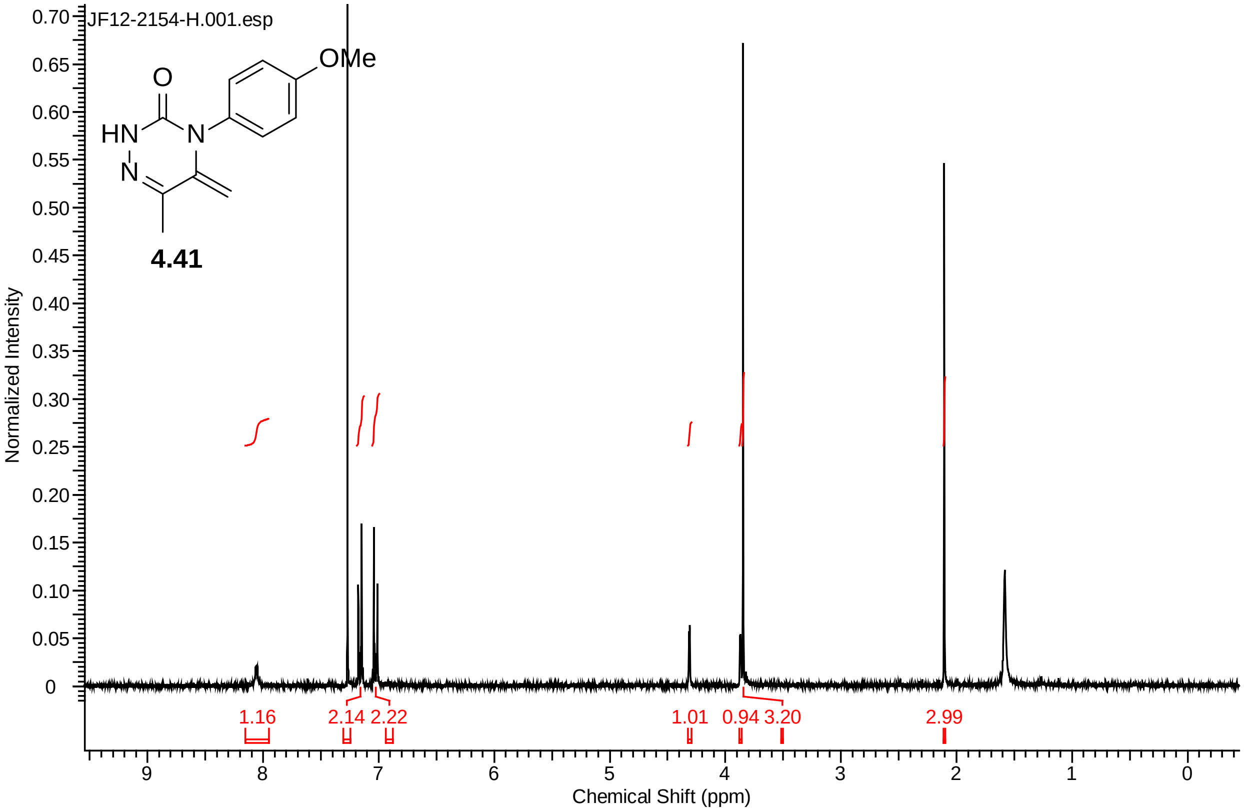


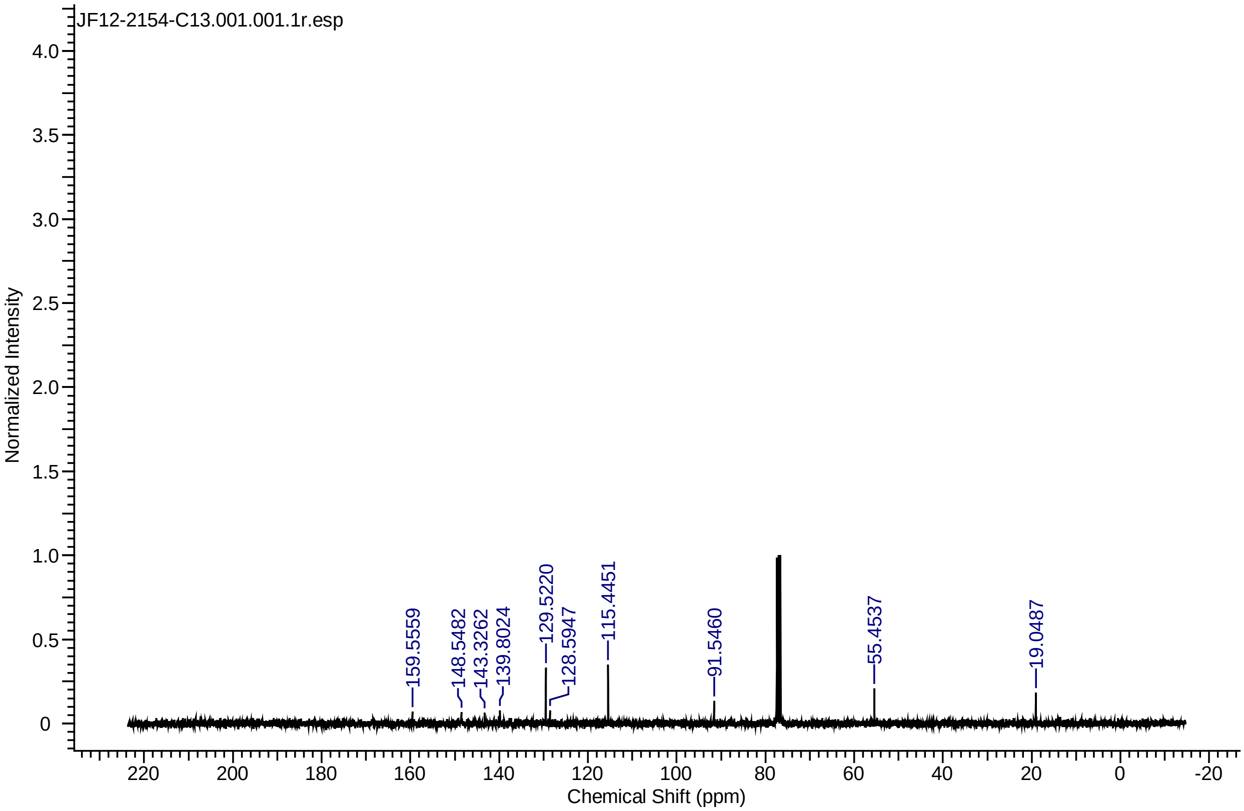
4.40

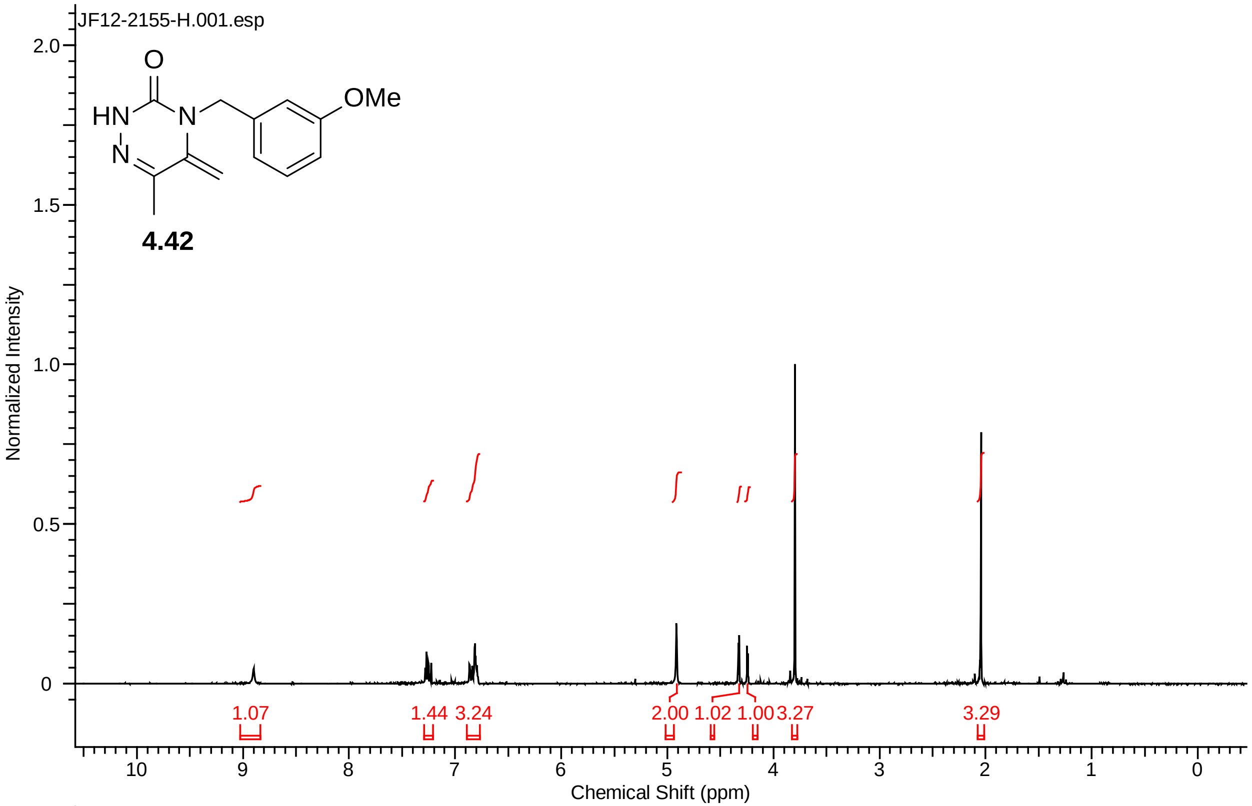
JF11-2147-carac-H.001.esp
O
HN
N
N
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.99
0.97
2.10
2.01
0.95
0.95
3.24
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

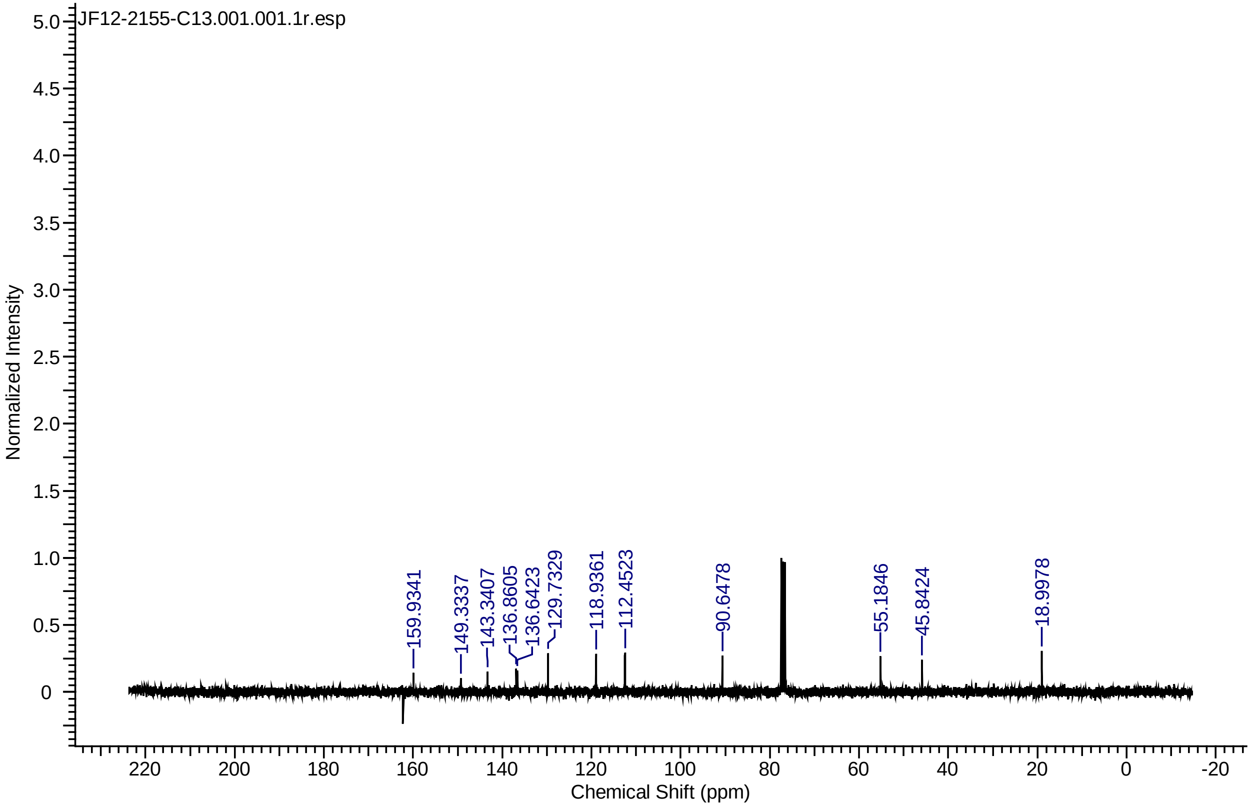


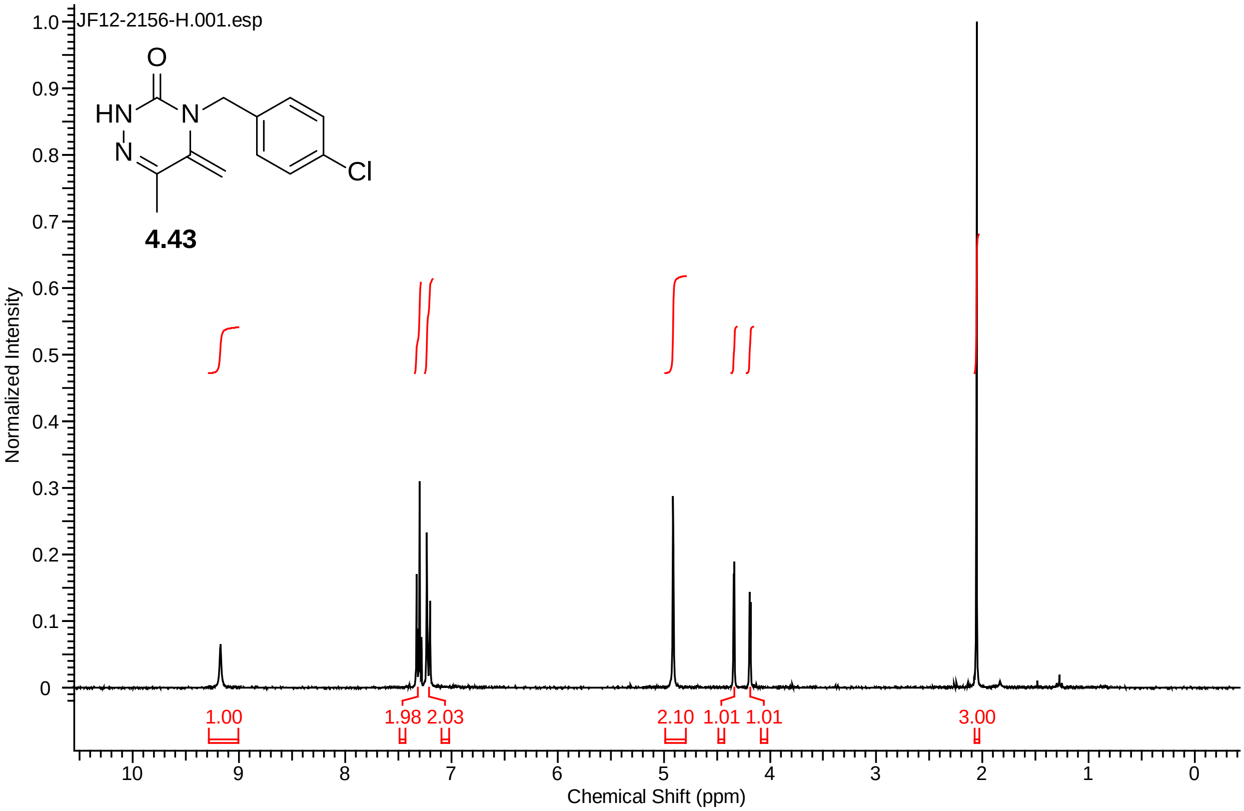
JF11-2147-carac-C13.001.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
149.0695
148.8946
143.2993
141.9879
136.5965
110.4411
108.6342
89.9247
38.9107
19.0209
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

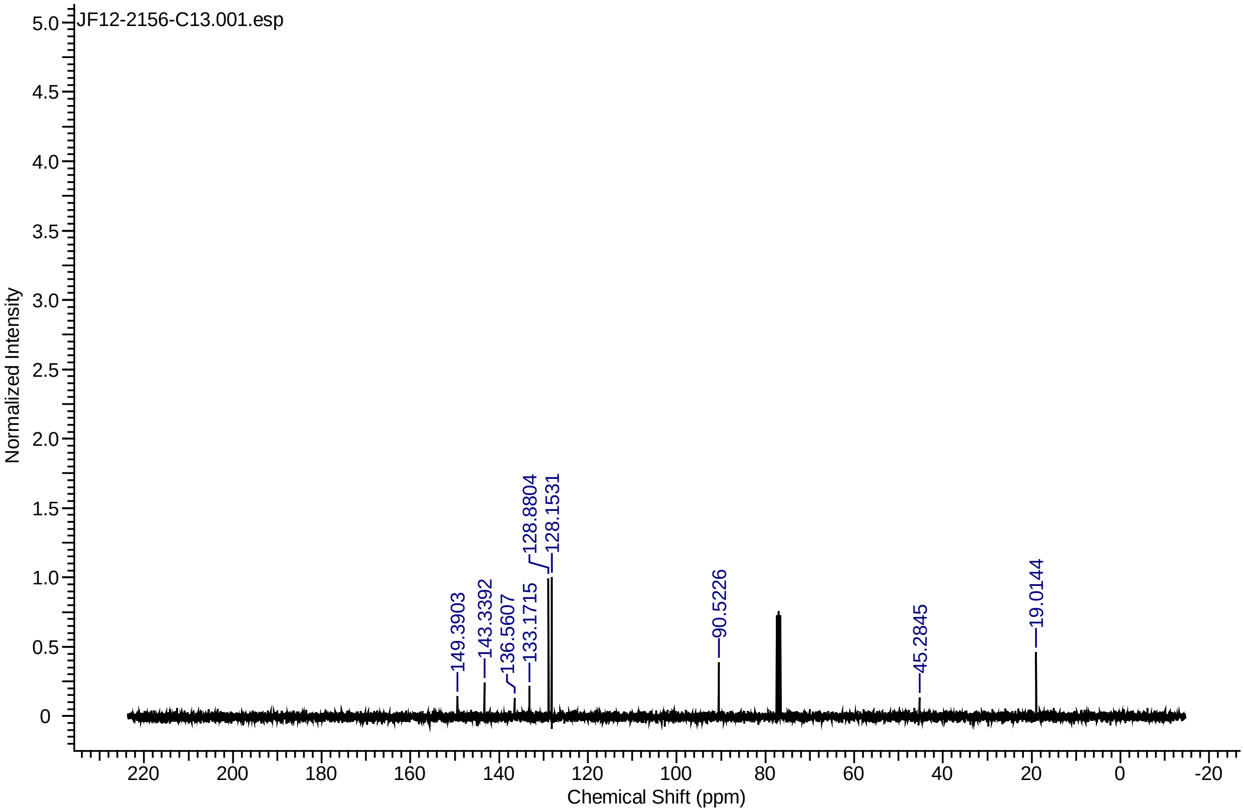

JF12-2154-H.001.esp
OMe
O
HN
N
N
4.41
Normalized Intensity
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
1.16
2.14
2.22
1.01
0.94
3.20
2.99
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

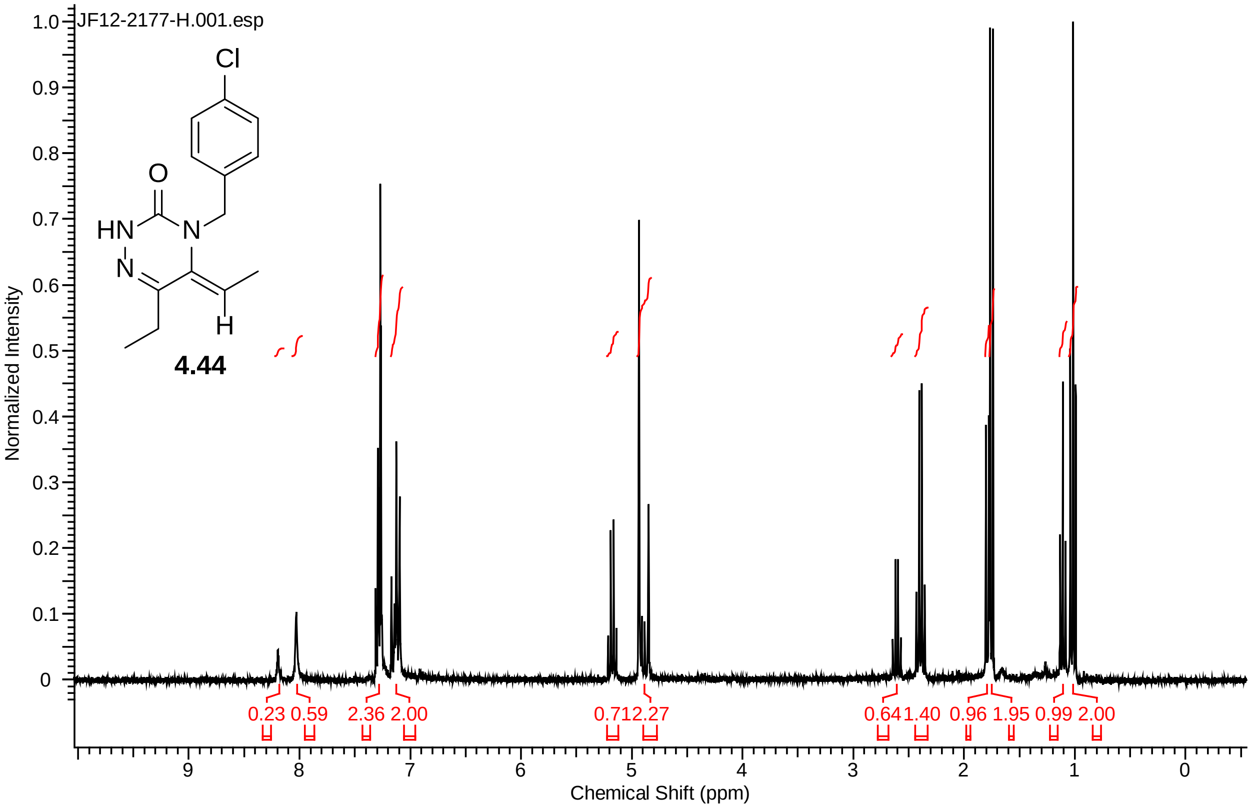

JF12-2154-C13.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
159.5559
148.5482
143.3262
139.8024
129.5220
128.5947
115.4451
91.5460
55.4537
19.0487
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF12-2155-H.001.esp
O
HN
N
N
OMe
4.42
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.07
1.44
3.24
2.00
1.02
1.00
3.27
3.29
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

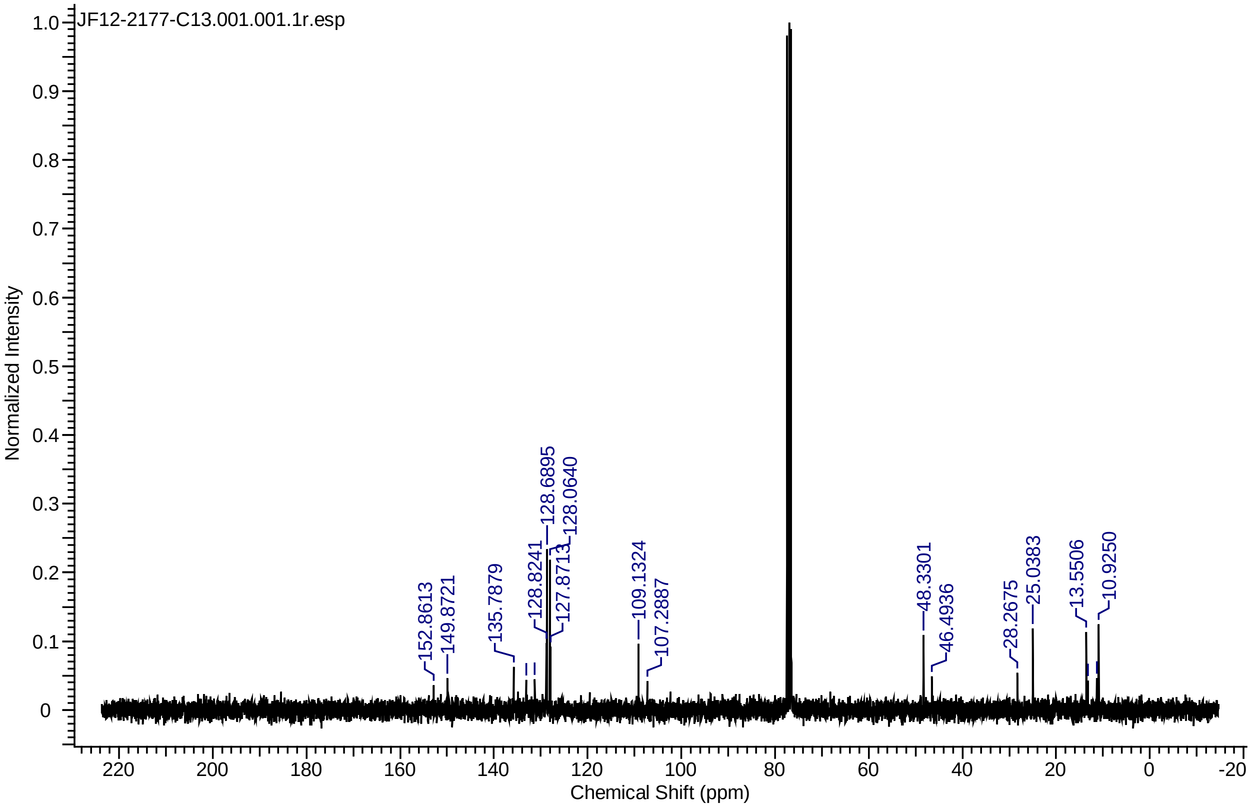

JF12-2155-C13.001.001.1r.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
159.9341
149.3337
143.3407
136.8605
136.6423
129.7329
118.9361
112.4523
90.6478
55.1846
45.8424
18.9978
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

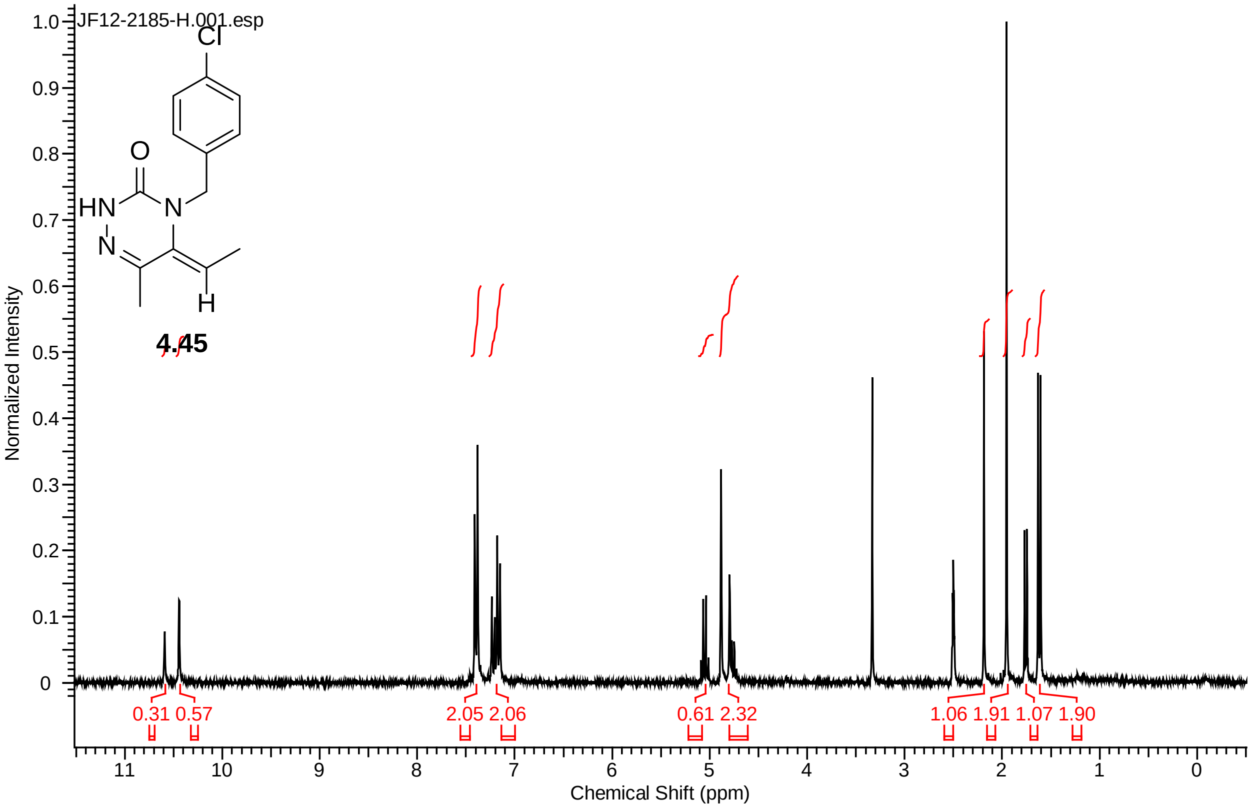

JF12-2156-H.001.esp
O
HN
N
N
Cl
4.43
1.00
1.98
2.03
2.10
1.01
1.01
3.00
Normalized Intensity
Chemical Shift (ppm)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10
9
8
7
6
5
4
3
2
1
0

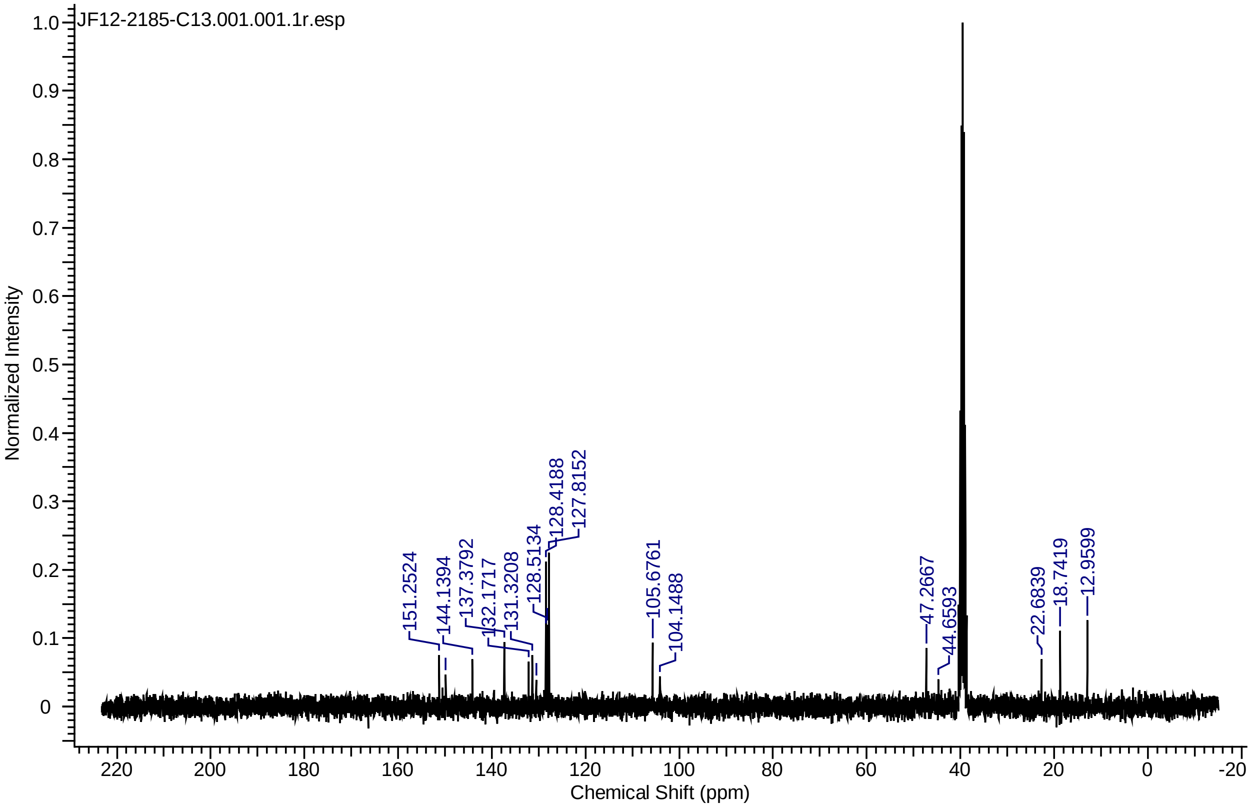

JF12-2156-C13.001.esp
149.3903
143.3392
136.5607
133.1715
128.8804
128.1531
90.5226
45.2845
19.0144
Normalized Intensity
Chemical Shift (ppm)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
220
200
180
160
140
120
100
80
60
40
20
0
-20

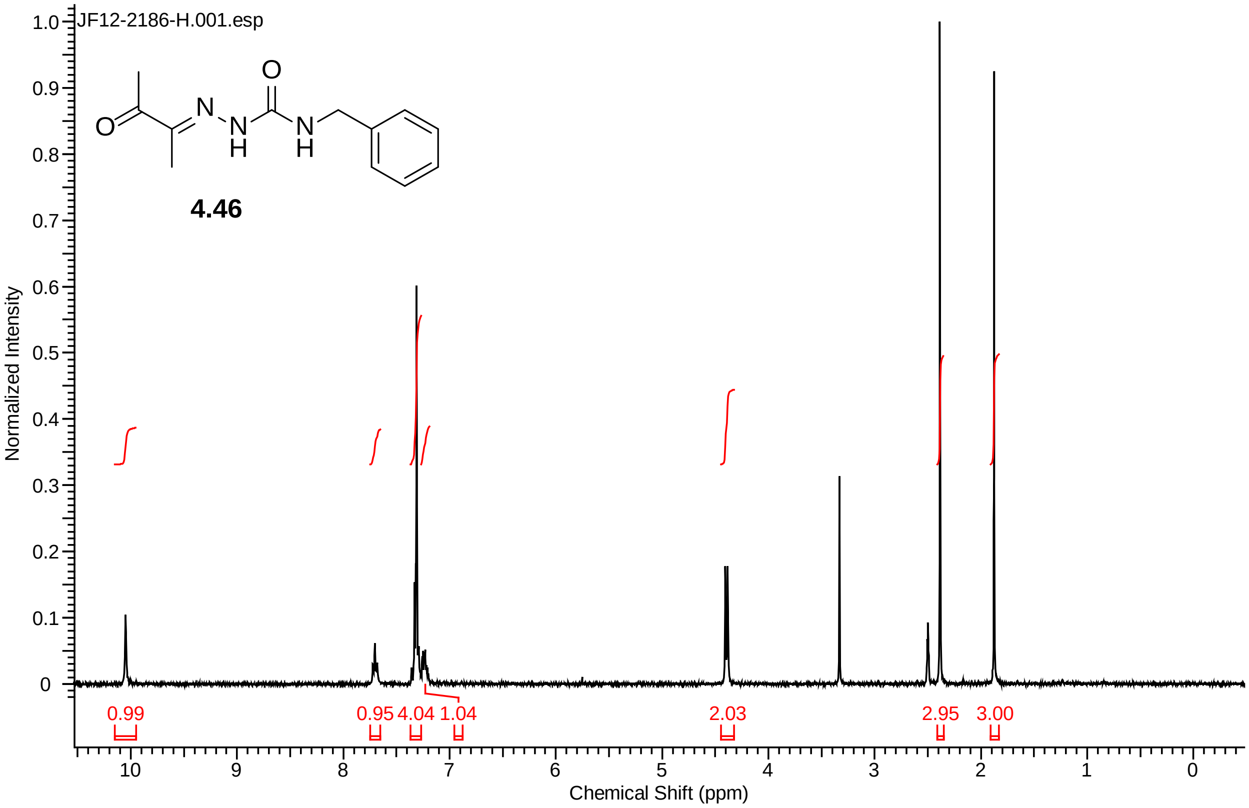

JF12-2177-H.001.esp
Cl
O
HN
N
N
H
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.23
0.59
2.36
2.00
0.71
2.27
0.64
1.40
0.96
1.95
0.99
2.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

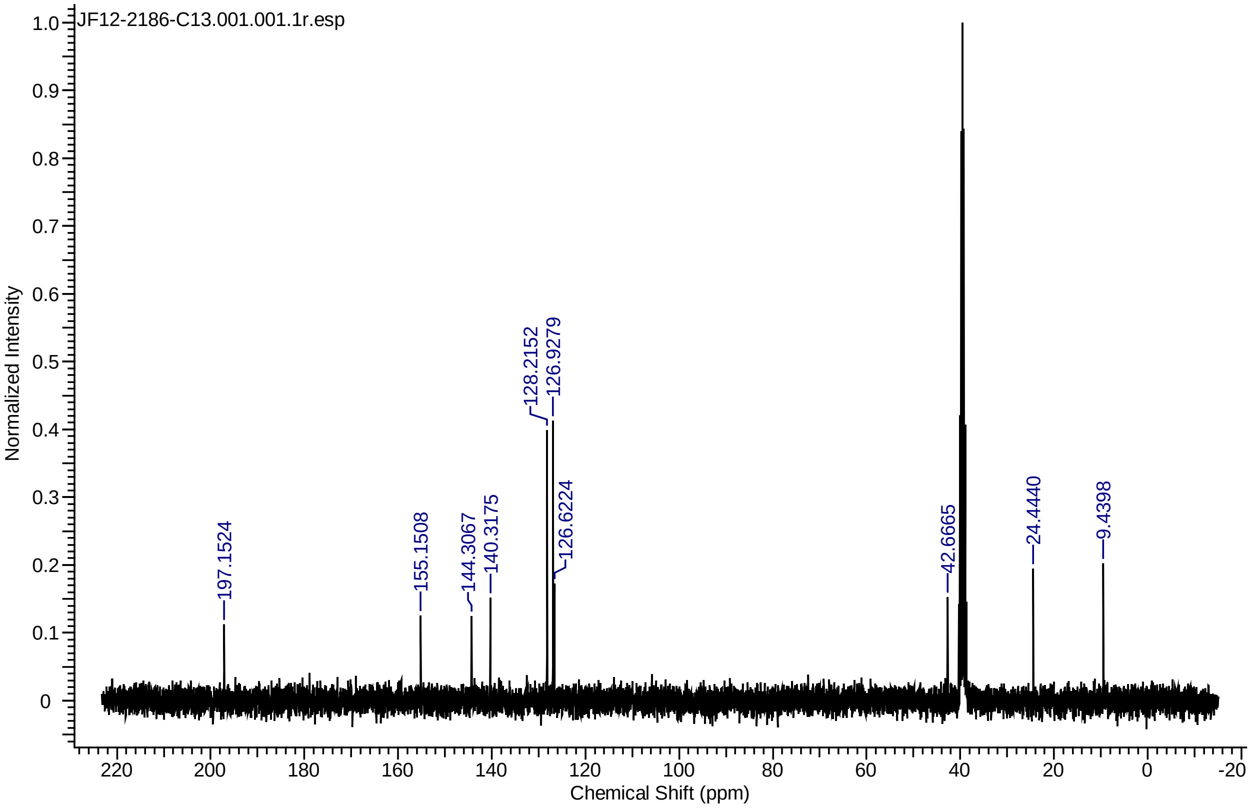
4.44

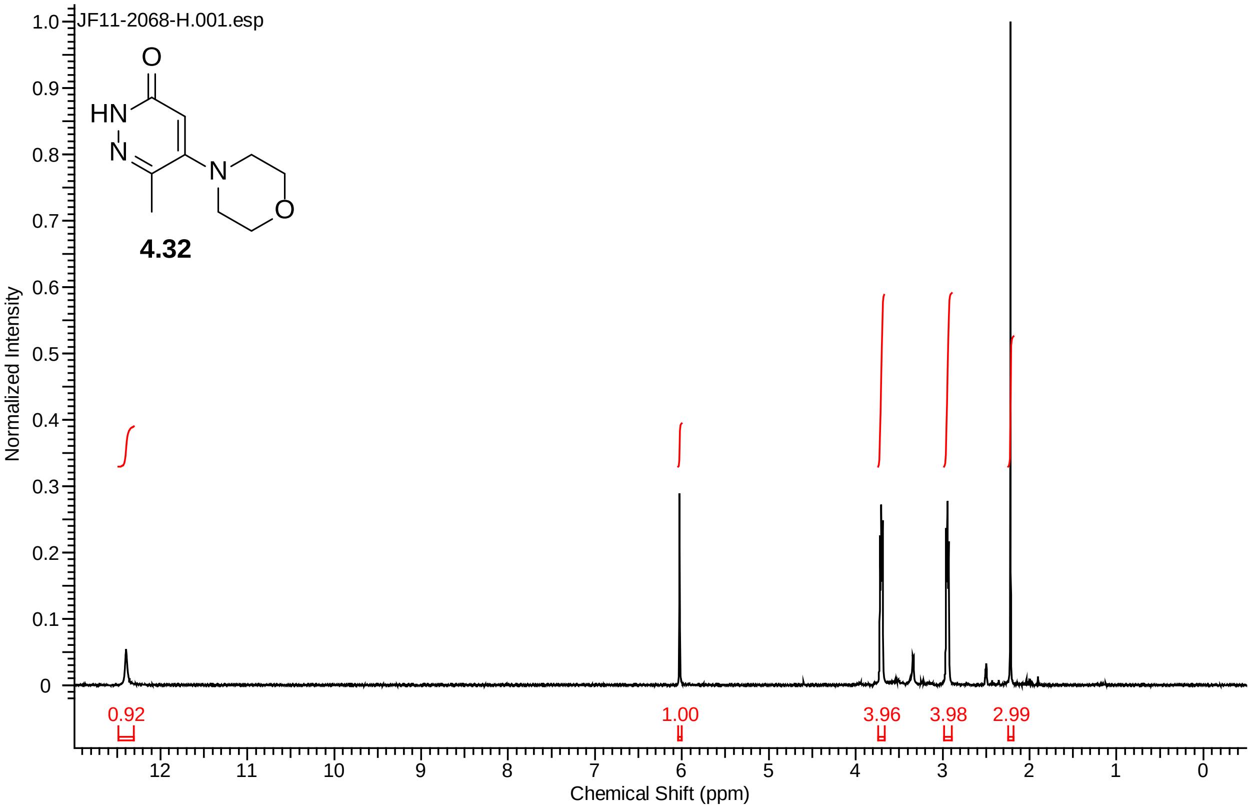

JF12-2177-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
152.8613
149.8721
135.7879
128.8241
128.6895
128.0640
127.8713
109.1324
107.2887
48.3301
46.4936
28.2675
25.0383
13.5506
10.9250
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

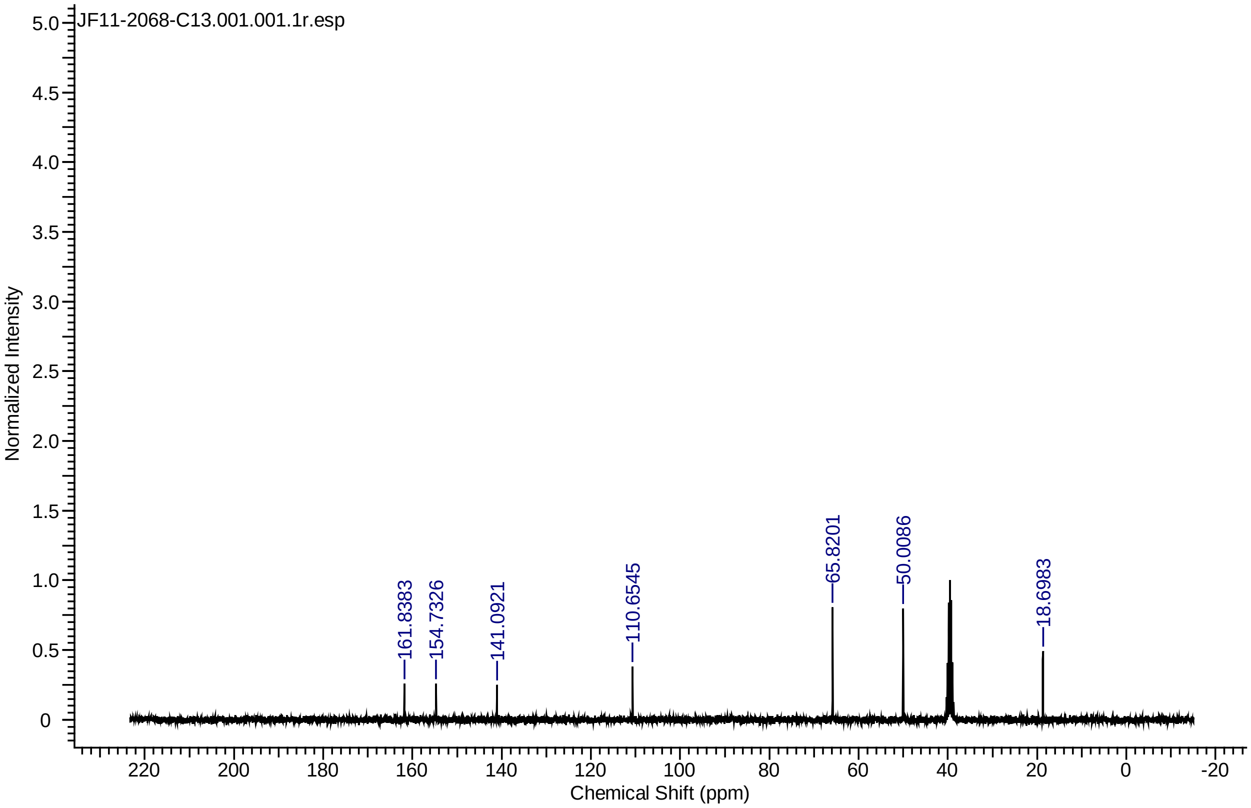

JF12-2185-H.001.esp
Cl
O
HN
N
N
H
4.45
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.31
0.57
2.05
2.06
0.61
2.32
1.06
1.91
1.07
1.90
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

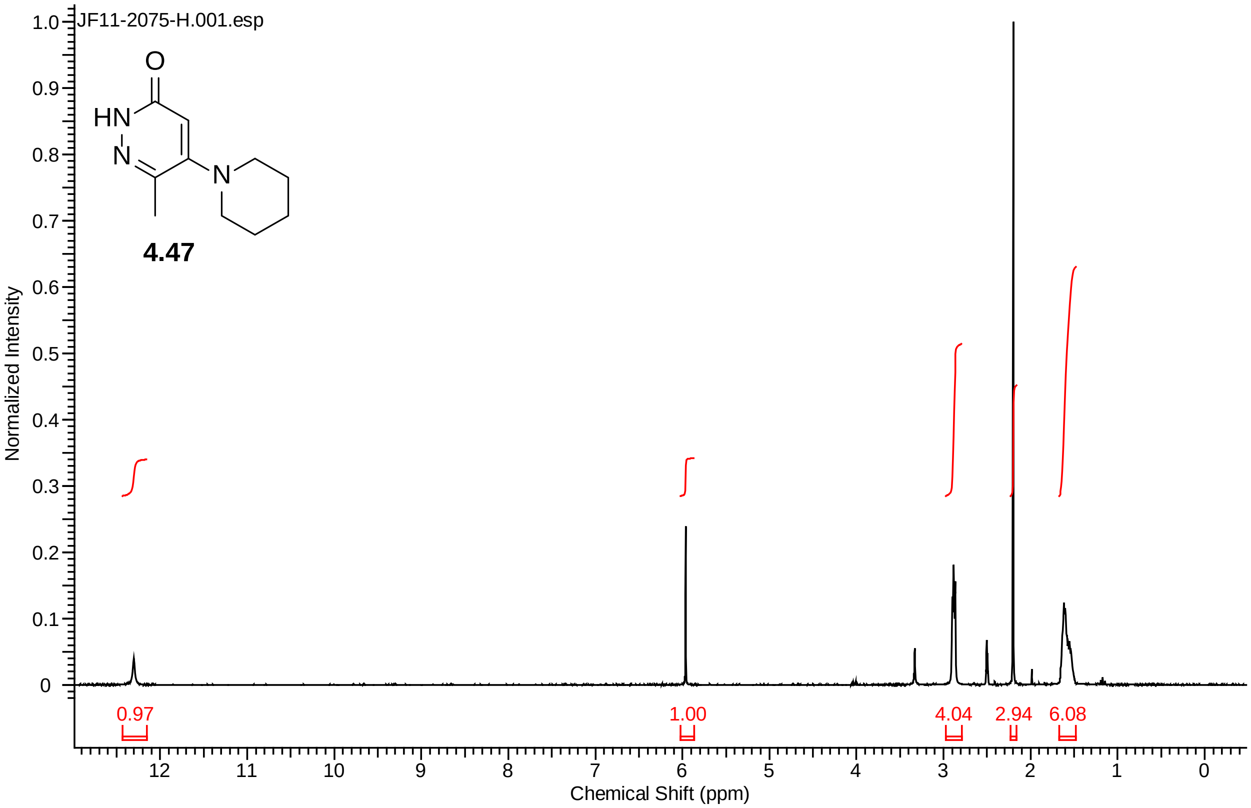

JF12-2185-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
151.2524
144.1394
137.3792
132.1717
131.3208
128.5134
128.4188
127.8152
105.6761
104.1488
47.2667
44.6593
22.6839
18.7419
12.9599
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

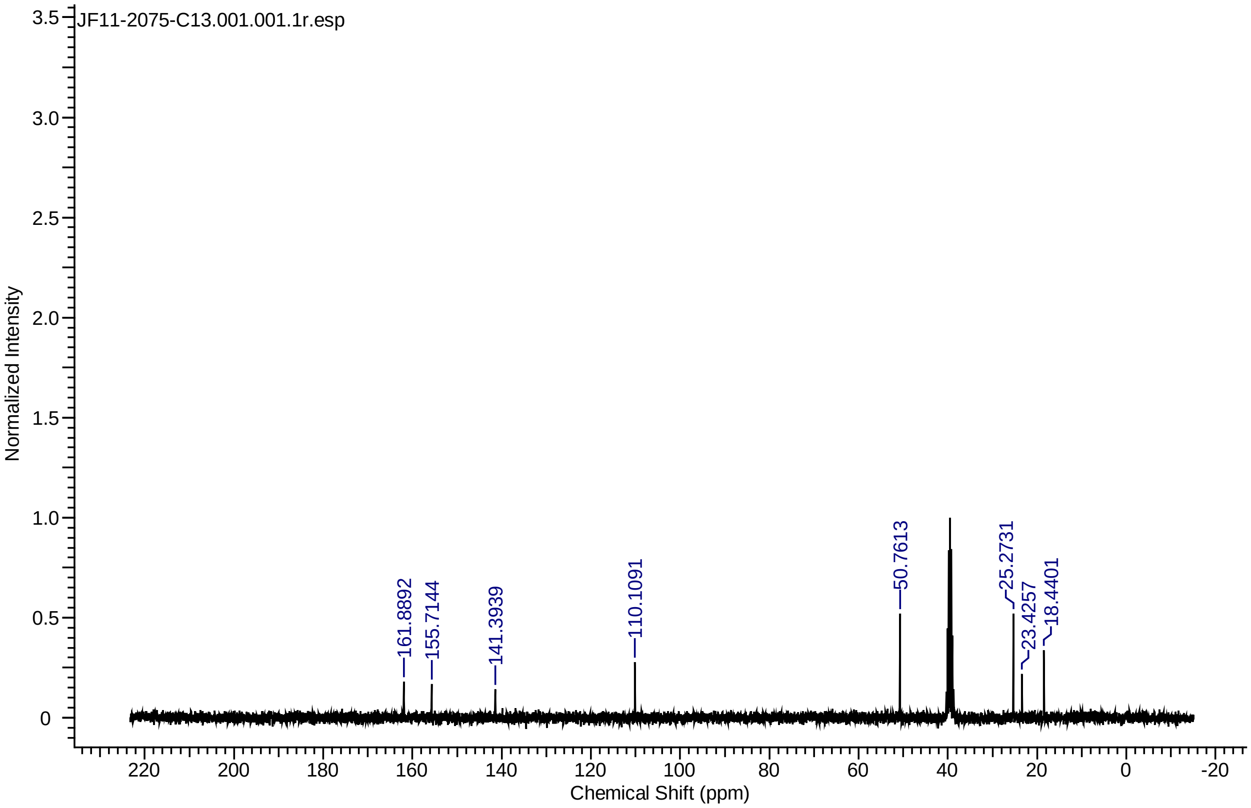

JF12-2186-H.001.esp
4.46
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.99
0.95
4.04
1.04
2.03
2.95
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

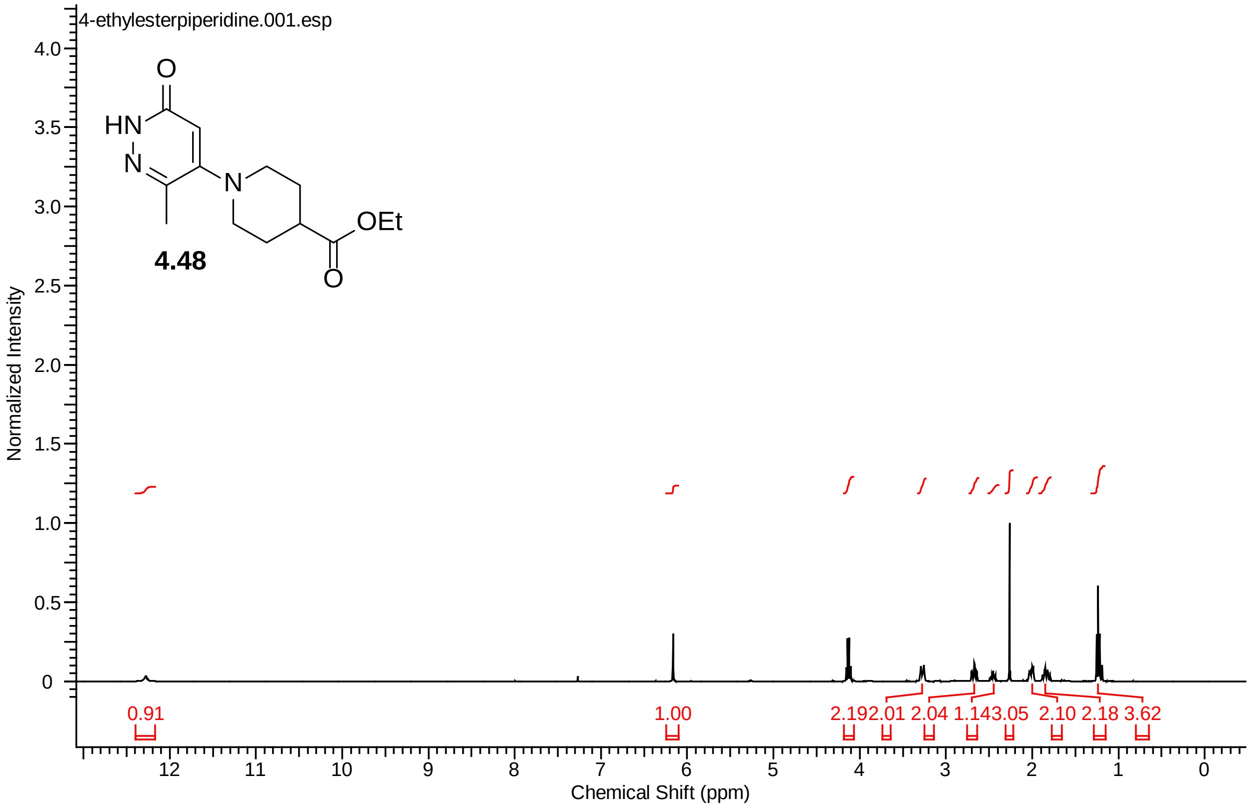

JF12-2186-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
197.1524
155.1508
144.3067
140.3175
128.2152
126.9279
126.6224
42.6665
24.4440
9.4398
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

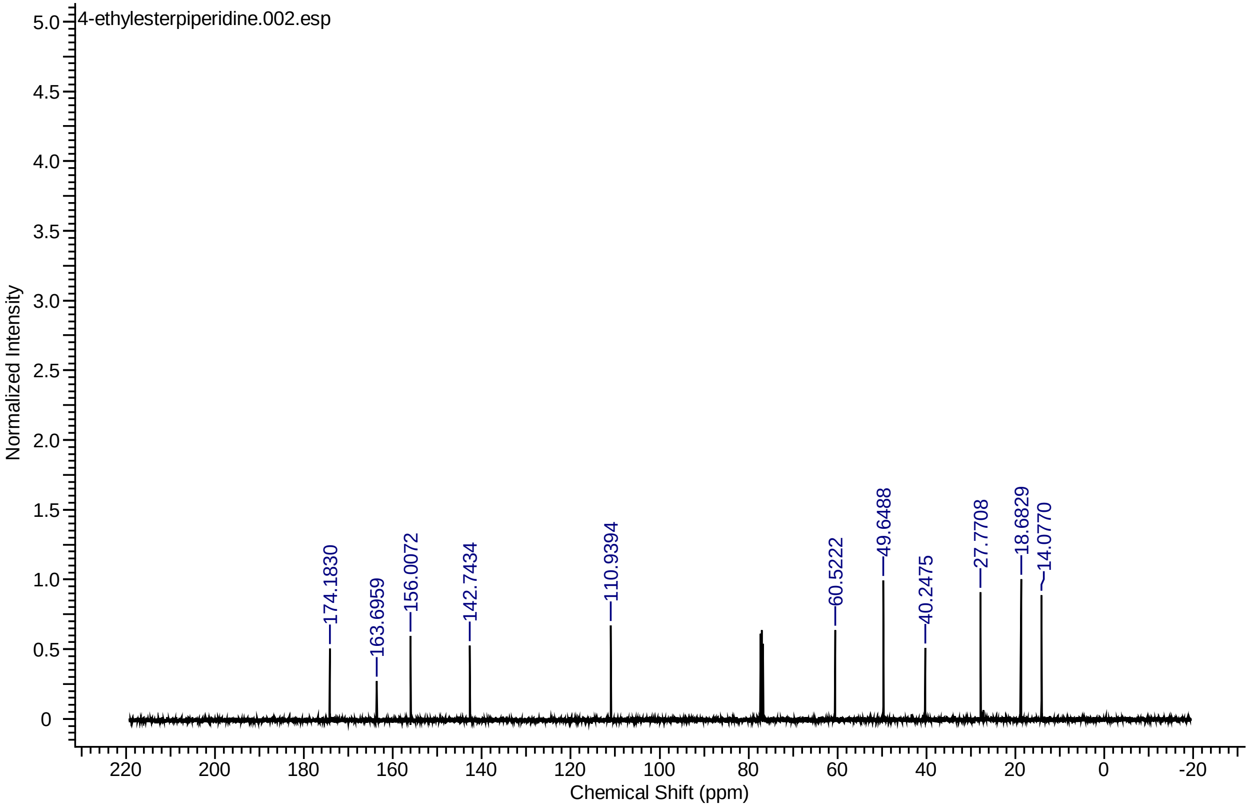

JF11-2068-H.001.esp
HN
N
O
N
O
4.32
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.92
1.00
3.96
3.98
2.99
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

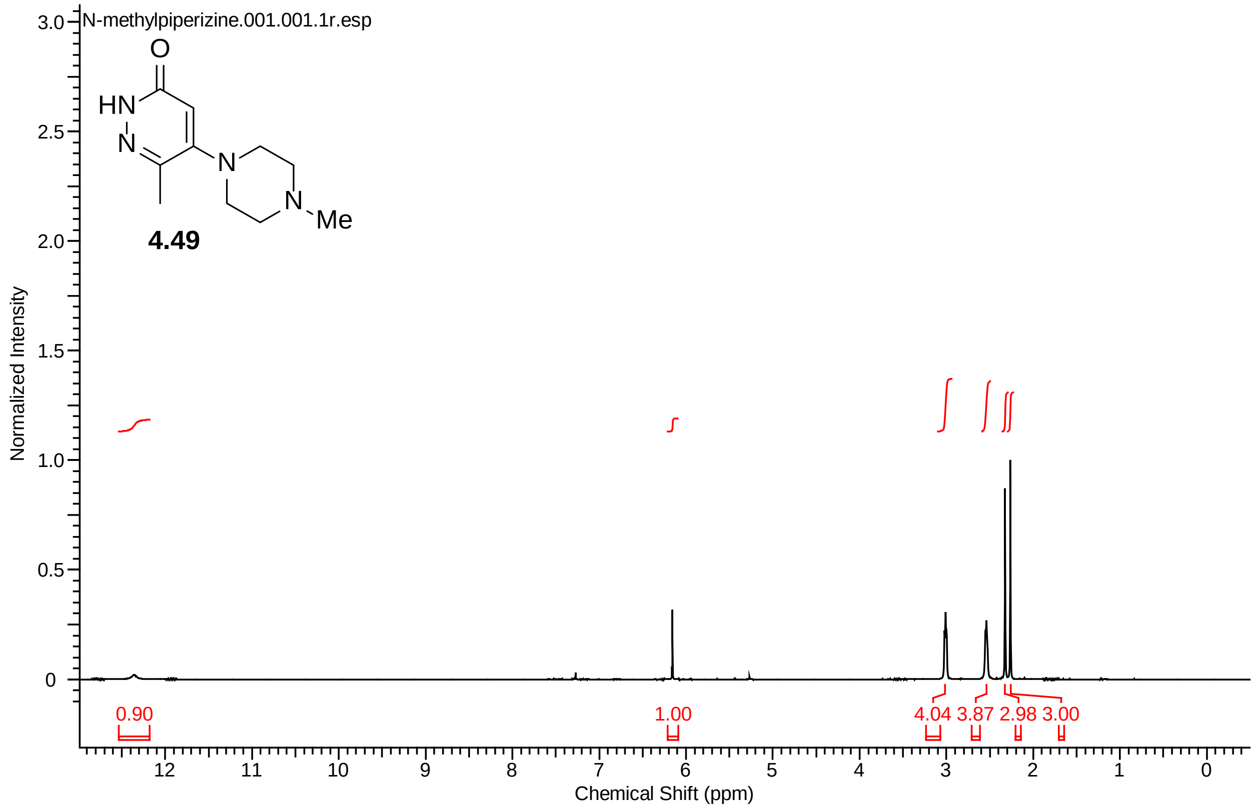

JF11-2068-C13.001.001.1r.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
161.8383
154.7326
141.0921
110.6545
65.8201
50.0086
18.6983
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

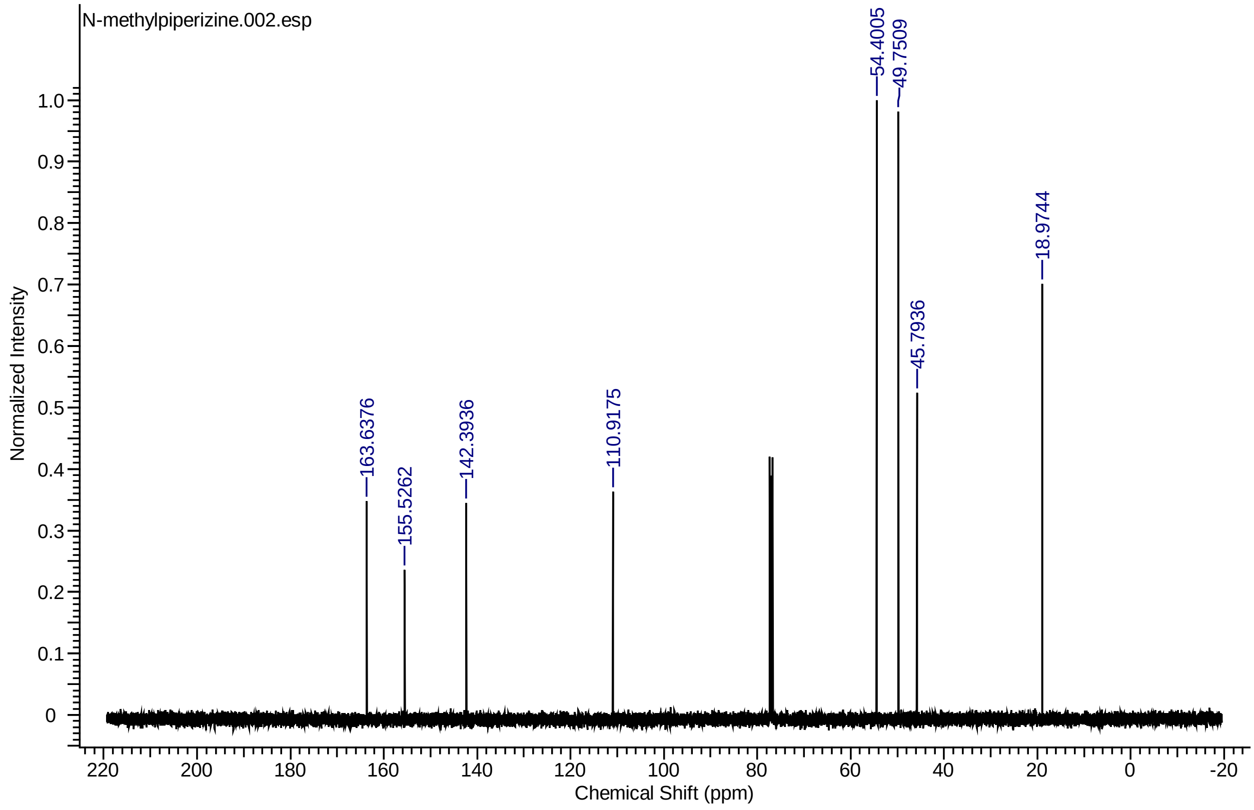

JF11-2075-H.001.esp
O
HN
N
N
4.47
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.97
1.00
4.04
2.94
6.08
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

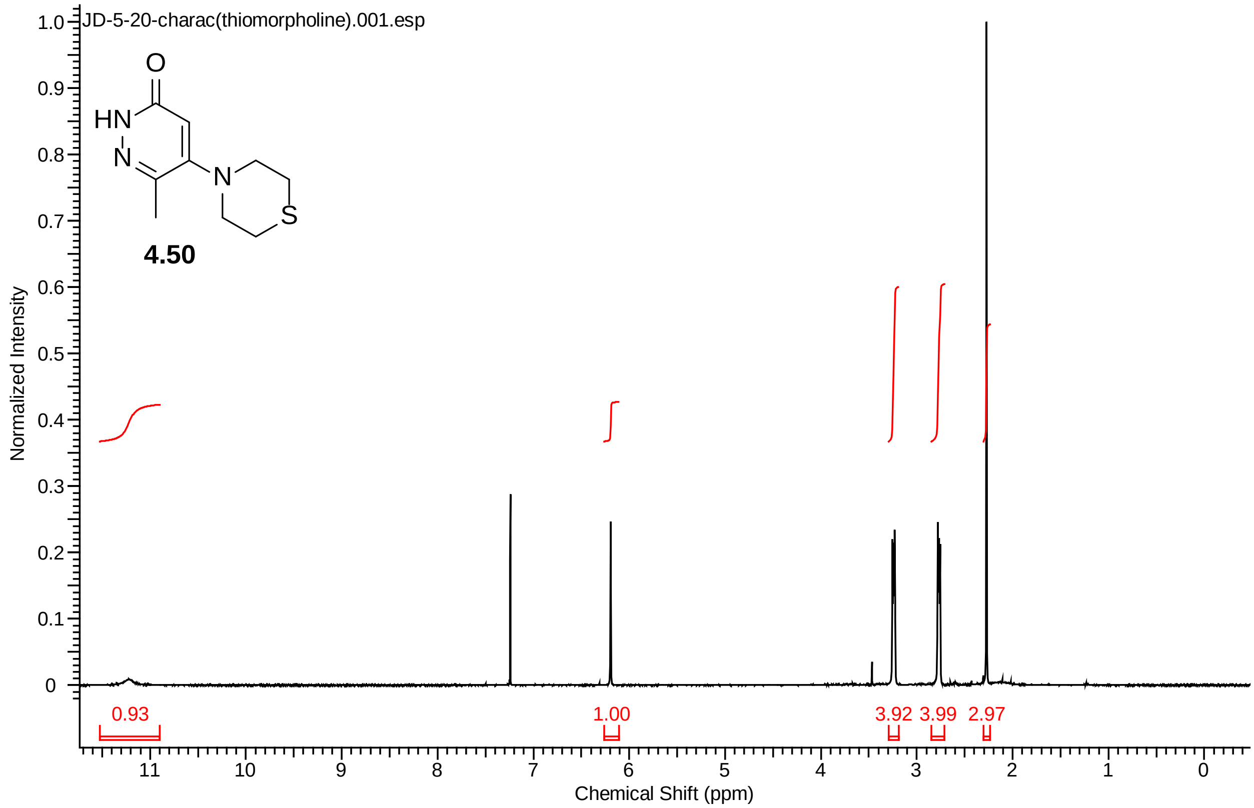

JF11-2075-C13.001.001.1r.esp
Normalized Intensity
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
161.8892
155.7144
141.3939
110.1091
50.7613
25.2731
23.4257
18.4401
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

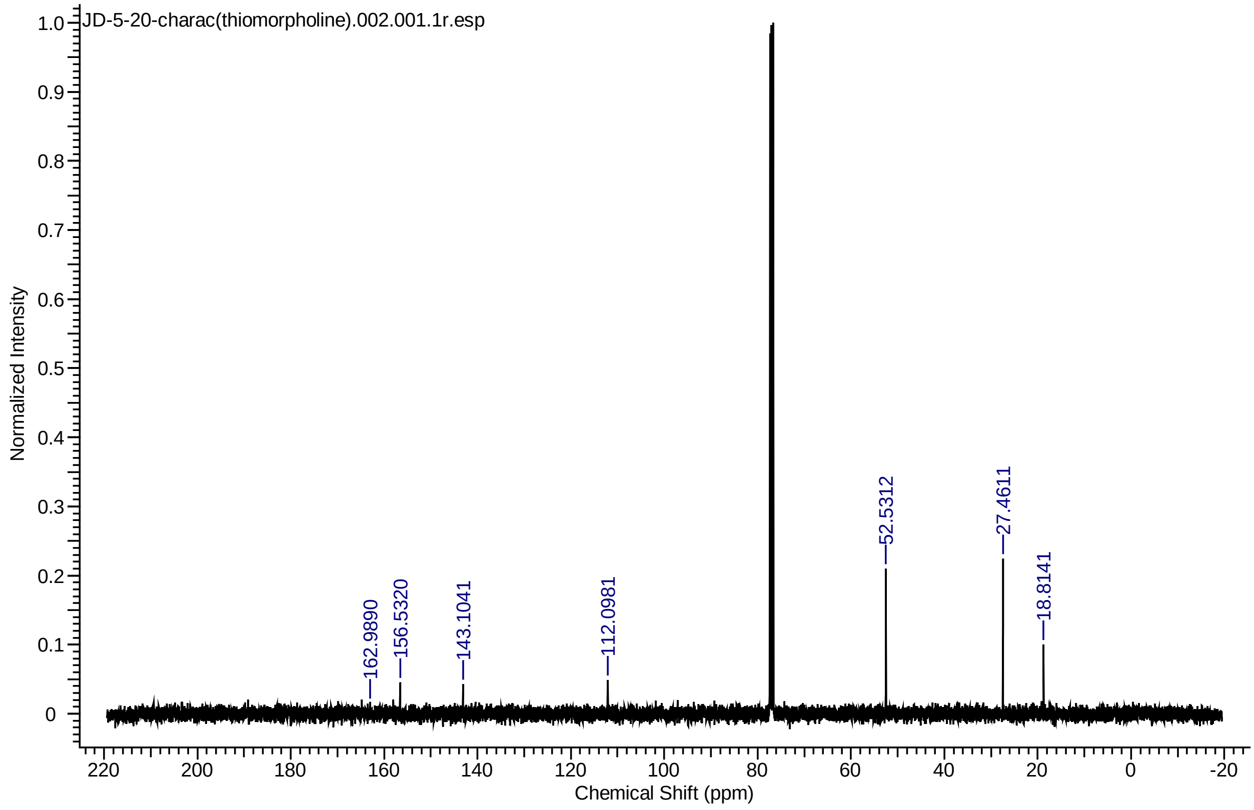

4-ethylesterpiperidine.001.esp
O
HN
N
N
OEt
O
4.48
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
0.91
1.00
2.19
2.01
2.04
1.14
3.05
2.10
2.18
3.62
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

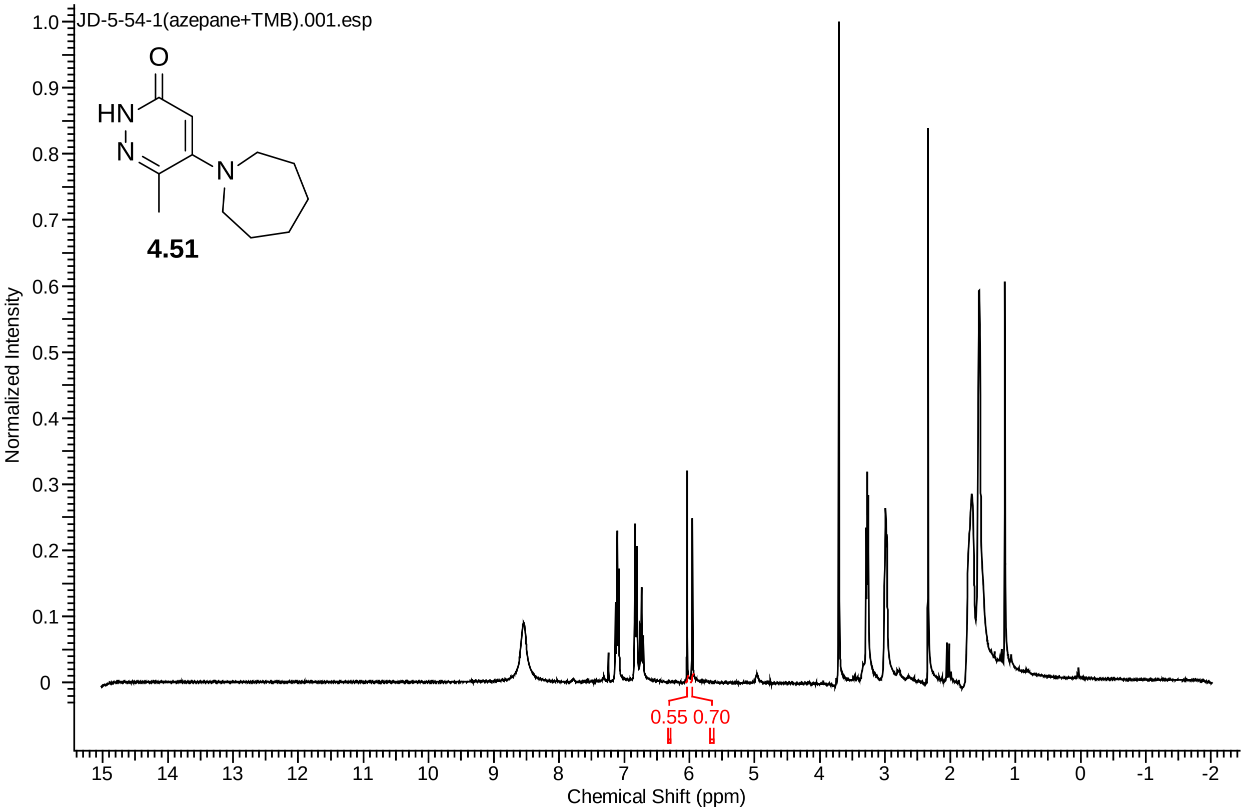

4-ethylesterpiperidine.002.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
174.1830
163.6959
156.0072
142.7434
110.9394
60.5222
49.6488
40.2475
27.7708
18.6829
14.0770
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


N-methylpiperizine.001.001.1r.esp
O
HN
N
N
N
Me
4.49
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
0.90
1.00
4.04
3.87
2.98
3.00
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

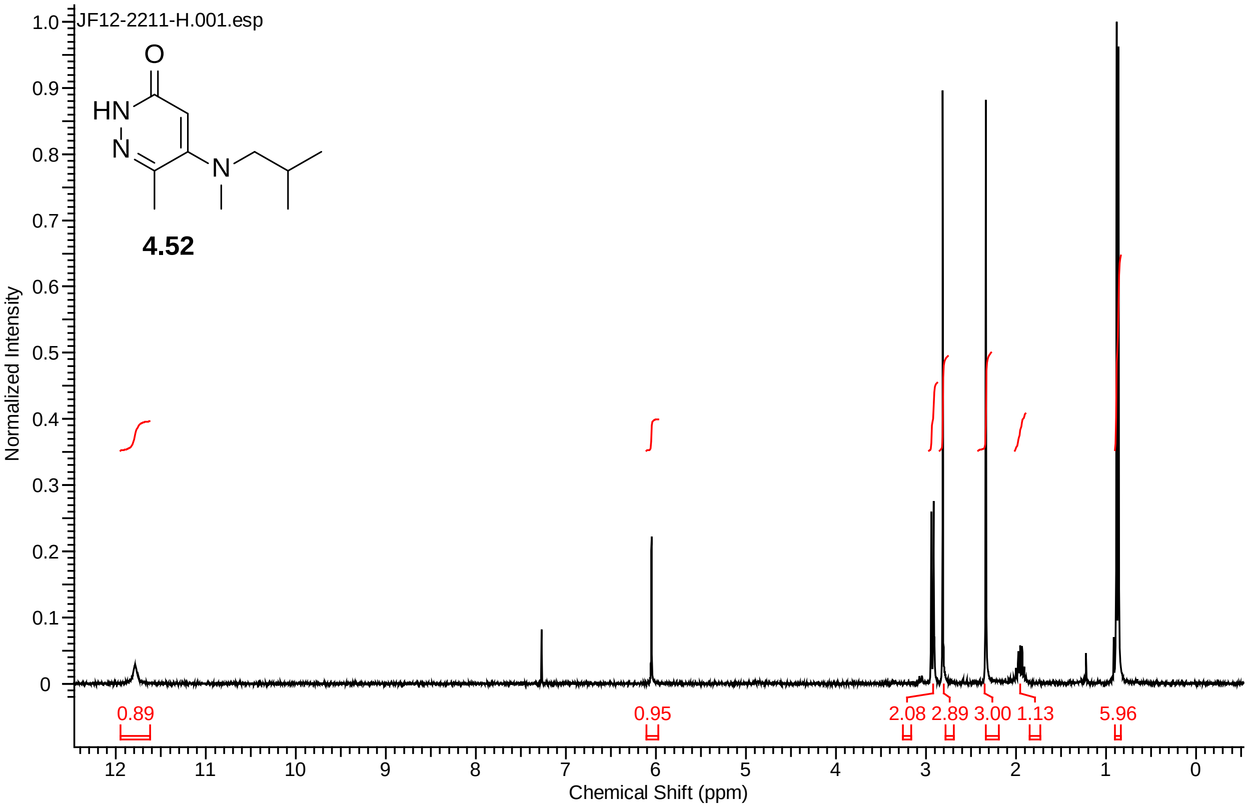

N-methylpiperizine.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
163.6376
155.5262
142.3936
110.9175
54.4005
49.7509
45.7936
18.9744
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

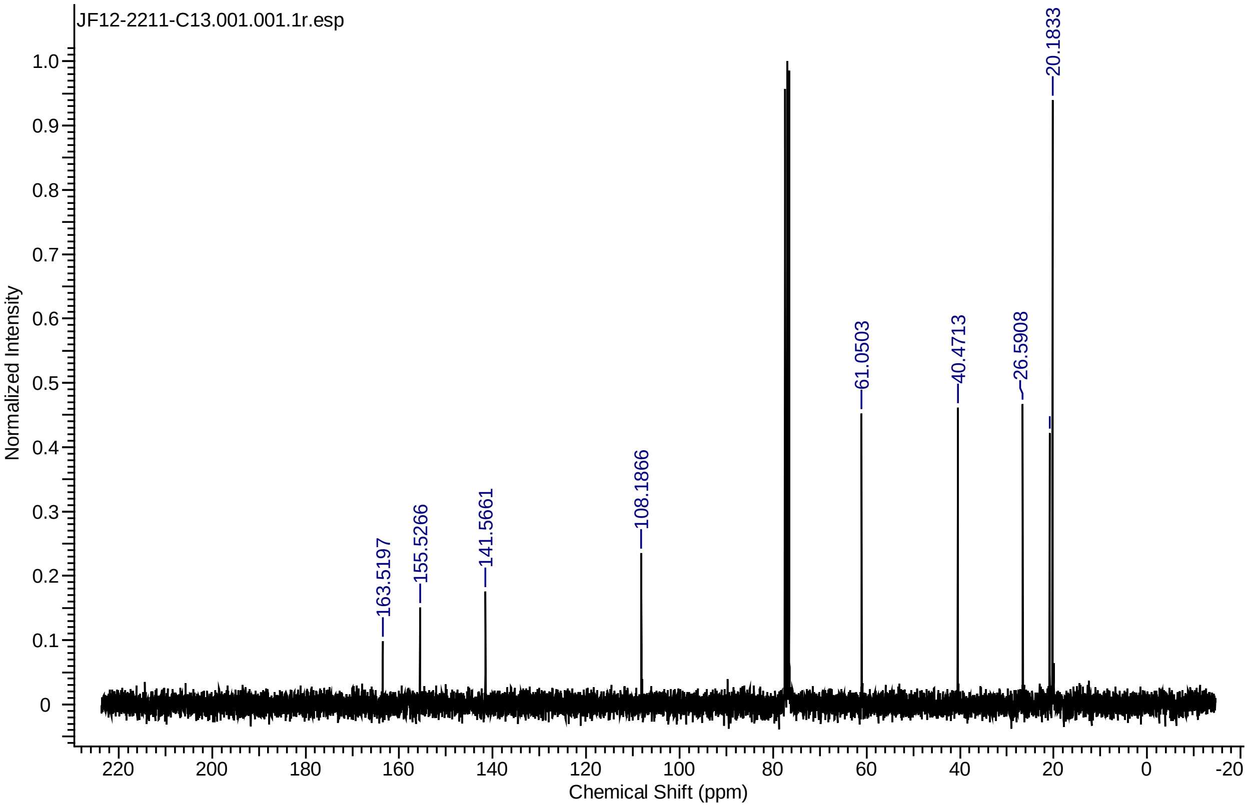

JD-5-20-charac(thiomorpholine).001.esp
O
HN
N
N
S
4.50
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.93
1.00
3.92
3.99
2.97
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

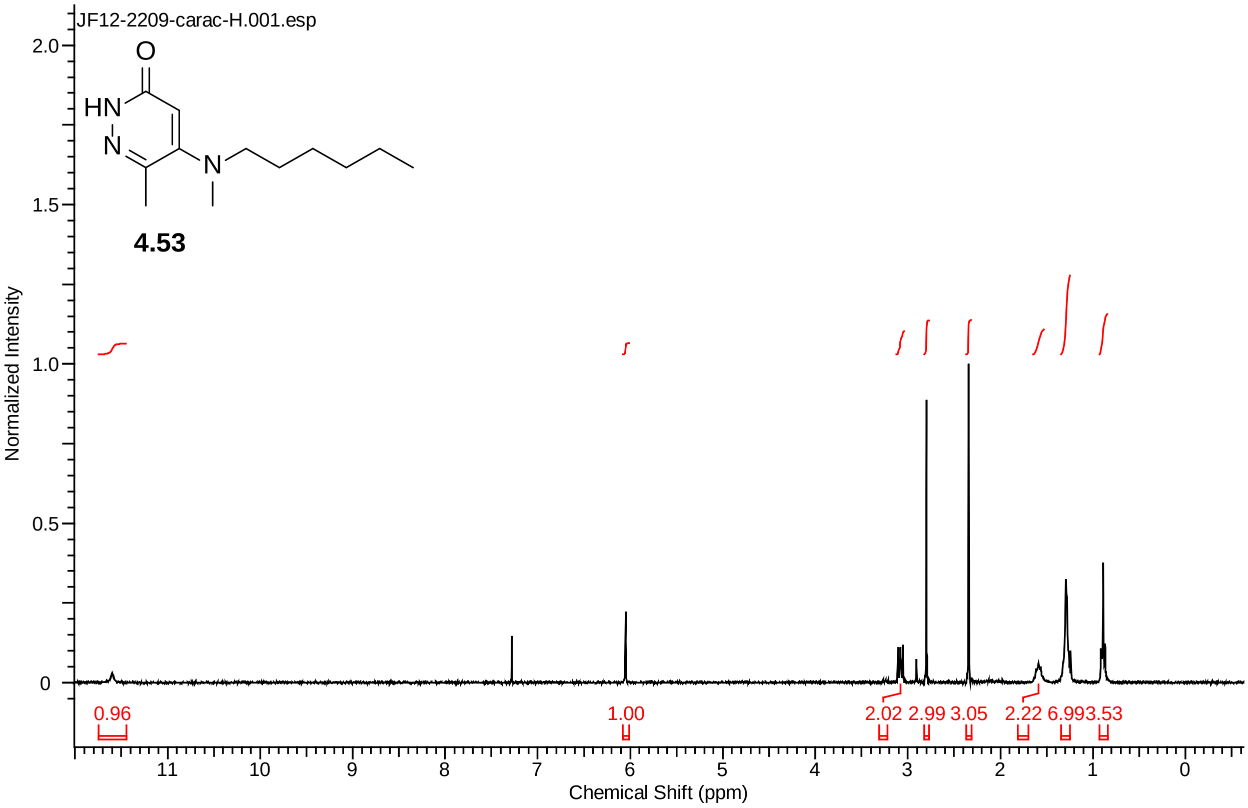

JD-5-20-charac(thiomorpholine).002.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
162.9890
156.5320
143.1041
112.0981
52.5312
27.4611
18.8141
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

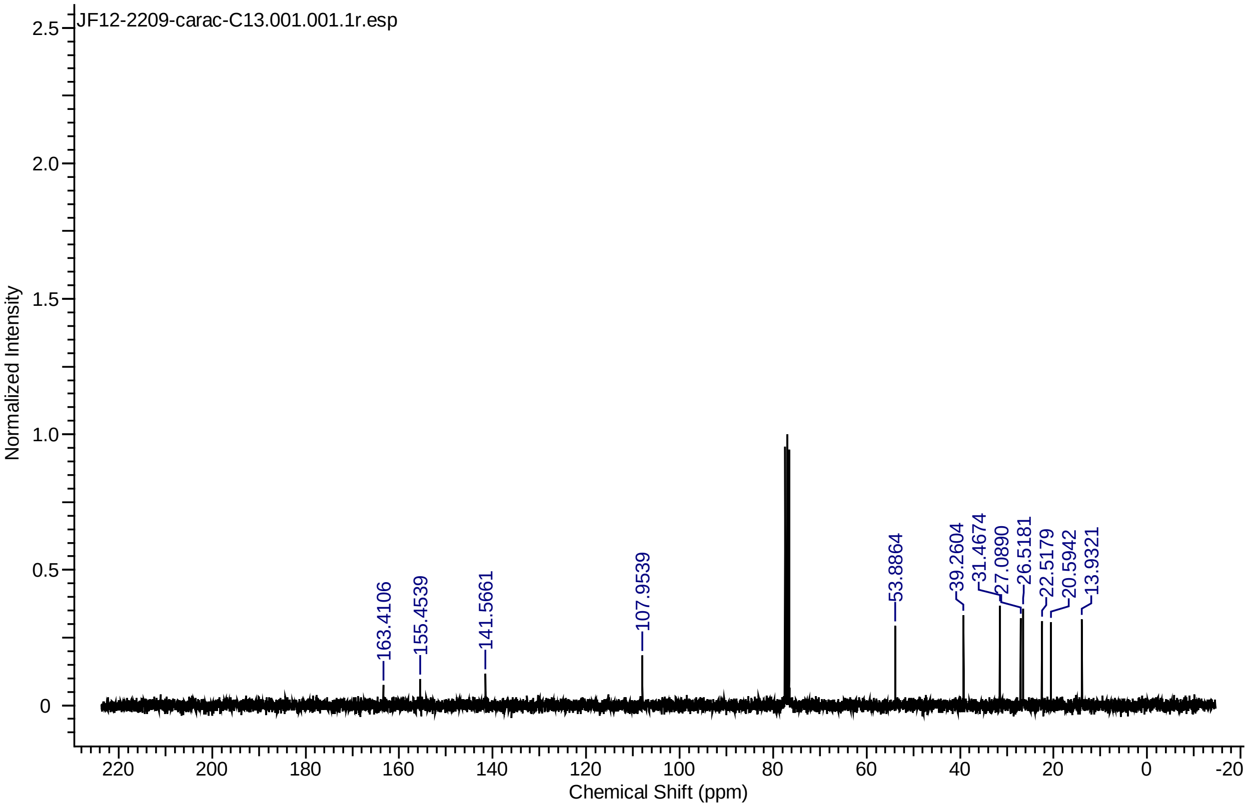


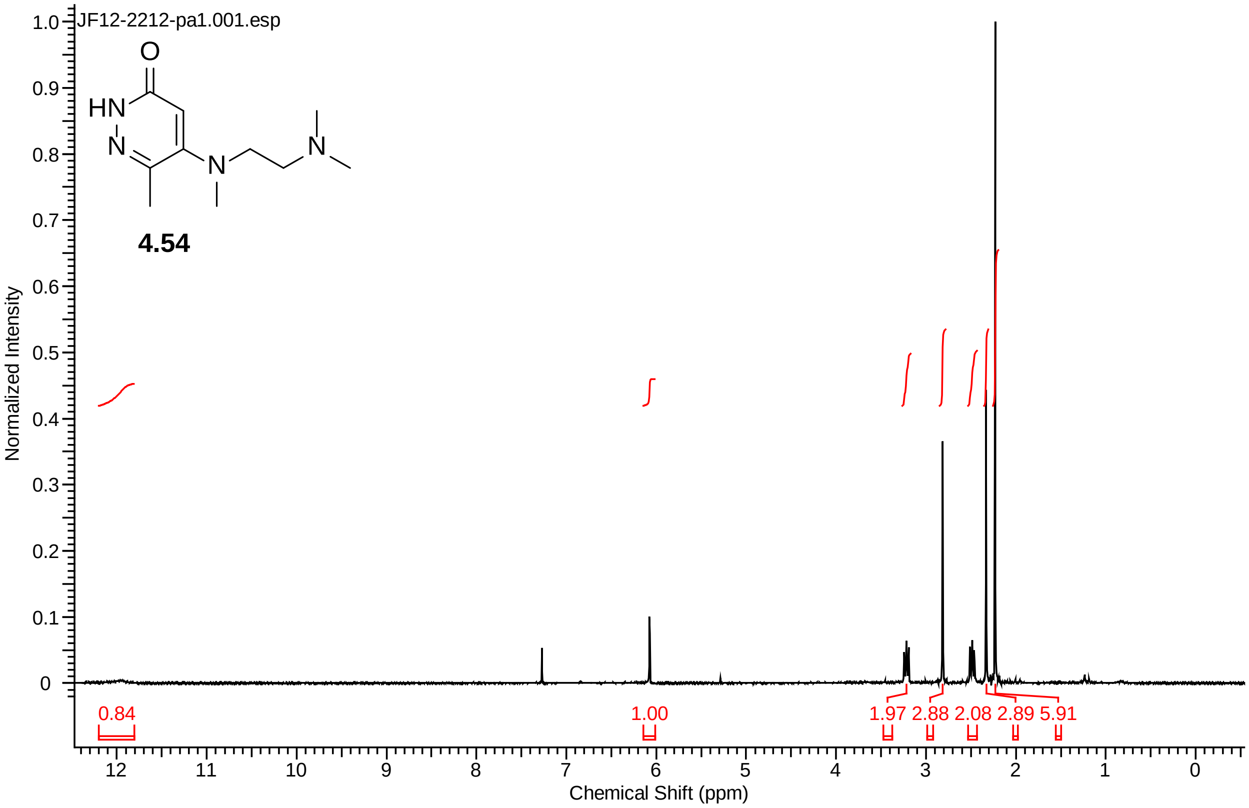
18.0 mg of Trimethoxybenzene (TMB) = 0.11 mmol. We performed a 0.600 mmol scale reaction; therefore we integrated the TMB peak at 0.55 (5.45 times lower than 3 since we added 5.45 times less internal standard.). The alkene peak (equivalent to 1 proton) showed a 70% NMR yield.

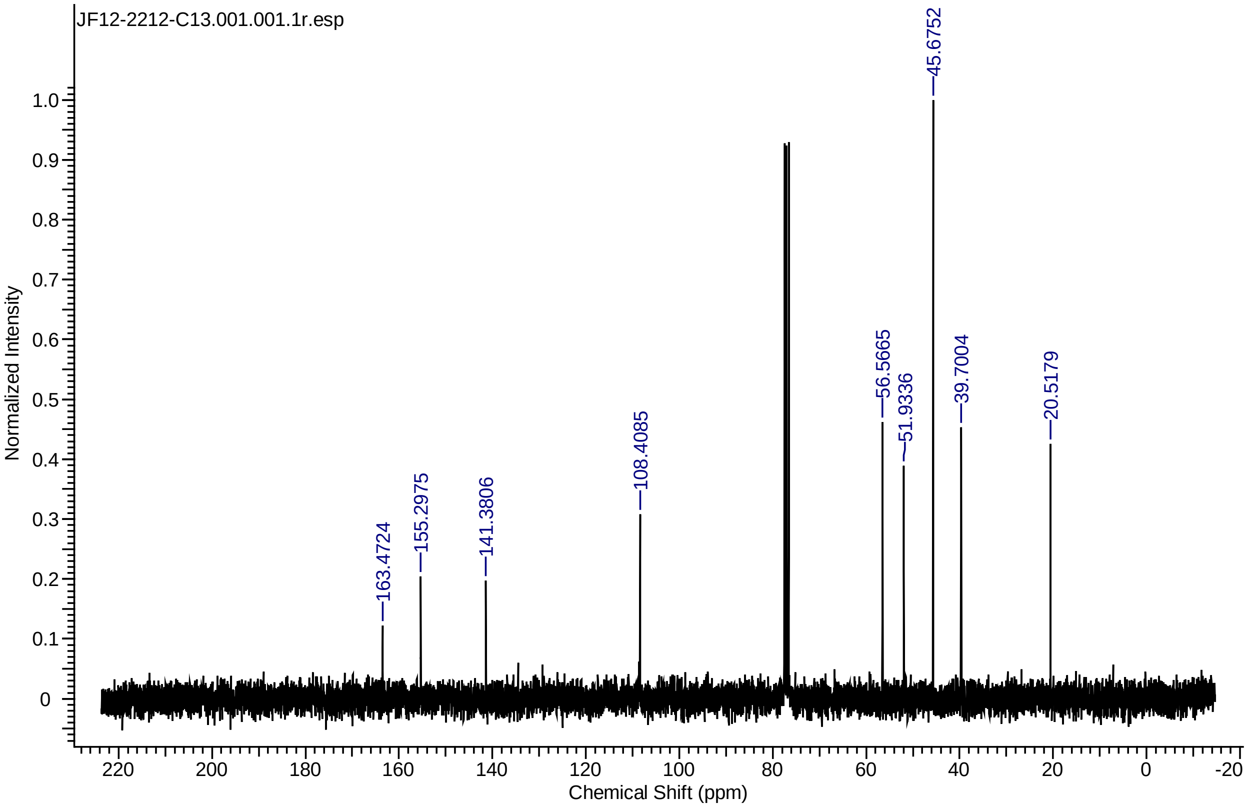

JF12-2211-H.001.esp
4.52
O
HN
N
N
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.89
0.95
2.08
2.89
3.00
1.13
5.96
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

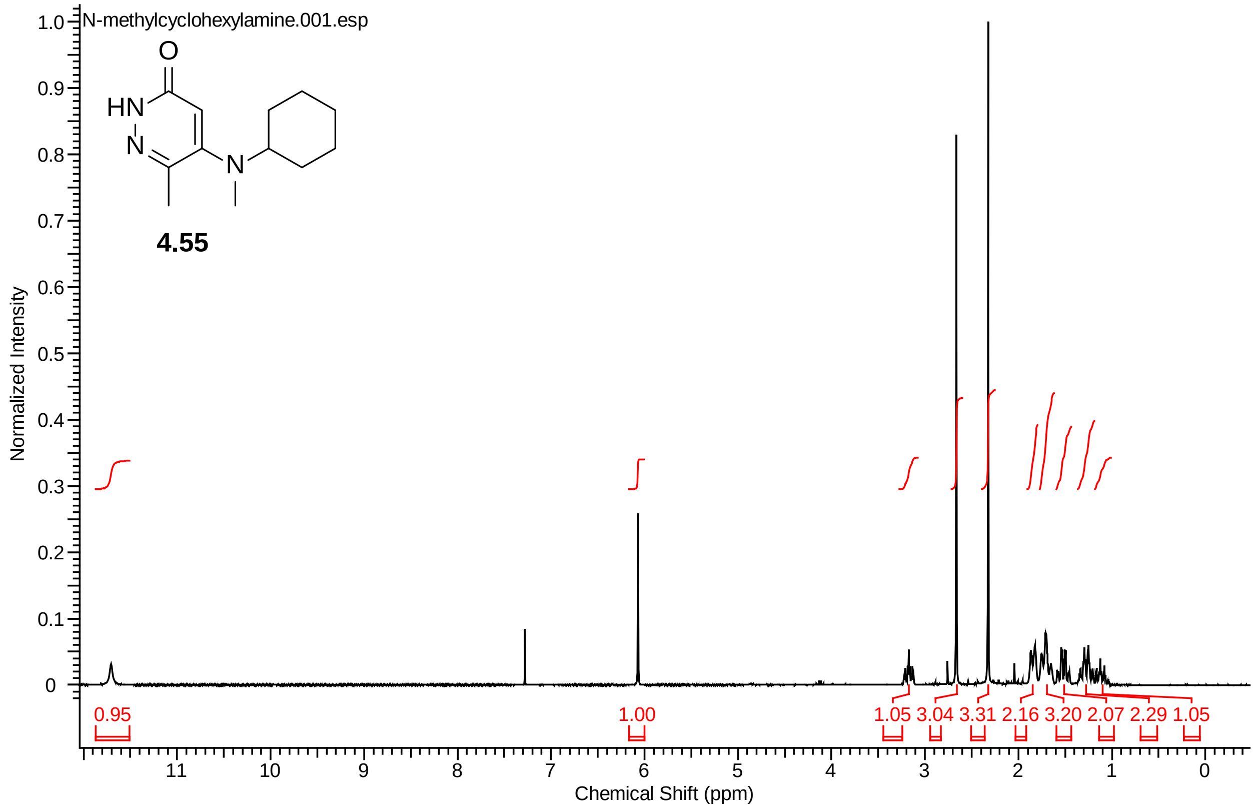

JF12-2211-C13.001.001.1r.esp
163.5197
155.5266
141.5661
108.1866
61.0503
40.4713
26.5908
20.1833
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

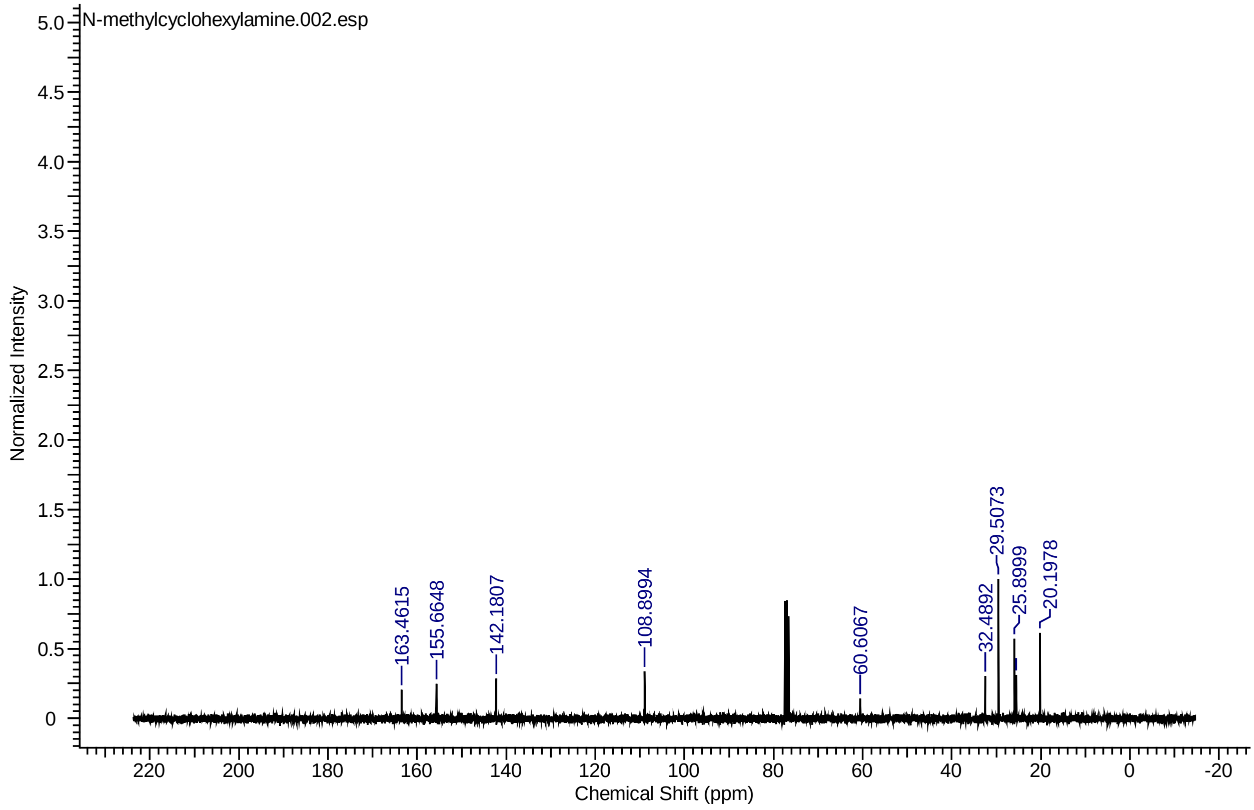

4.53
JF12-2209-carac-H.001.esp
O
HN
N
N
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.96
1.00
2.02
2.99
3.05
2.22
6.99
3.53
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

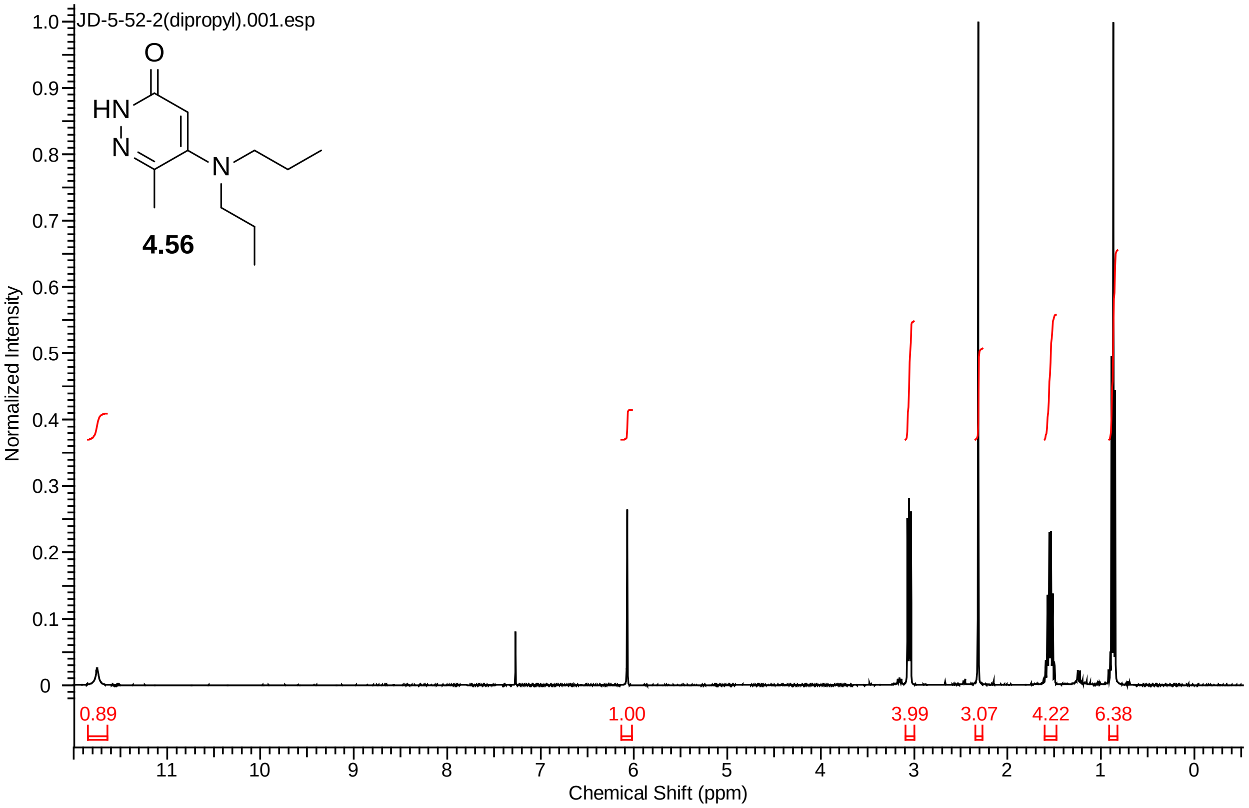

JF12-2209-carac-C13.001.001.1r.esp
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0
163.4106
155.4539
141.5661
107.9539
53.8864
39.2604
31.4674
27.0890
26.5181
22.5179
20.5942
13.9321
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

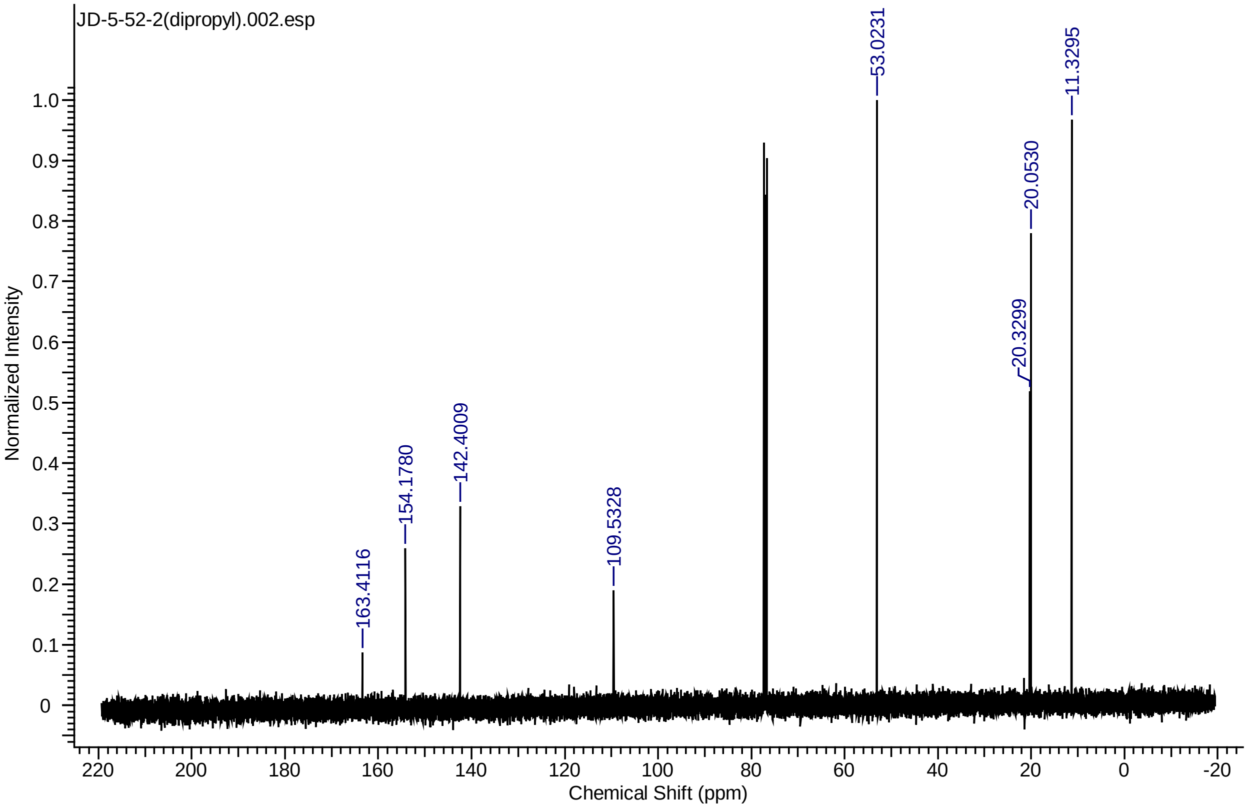

JF12-2212-pa1.001.esp
O
HN
N
N
N
4.54
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.84
1.00
1.97
2.88
2.08
2.89
5.91
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

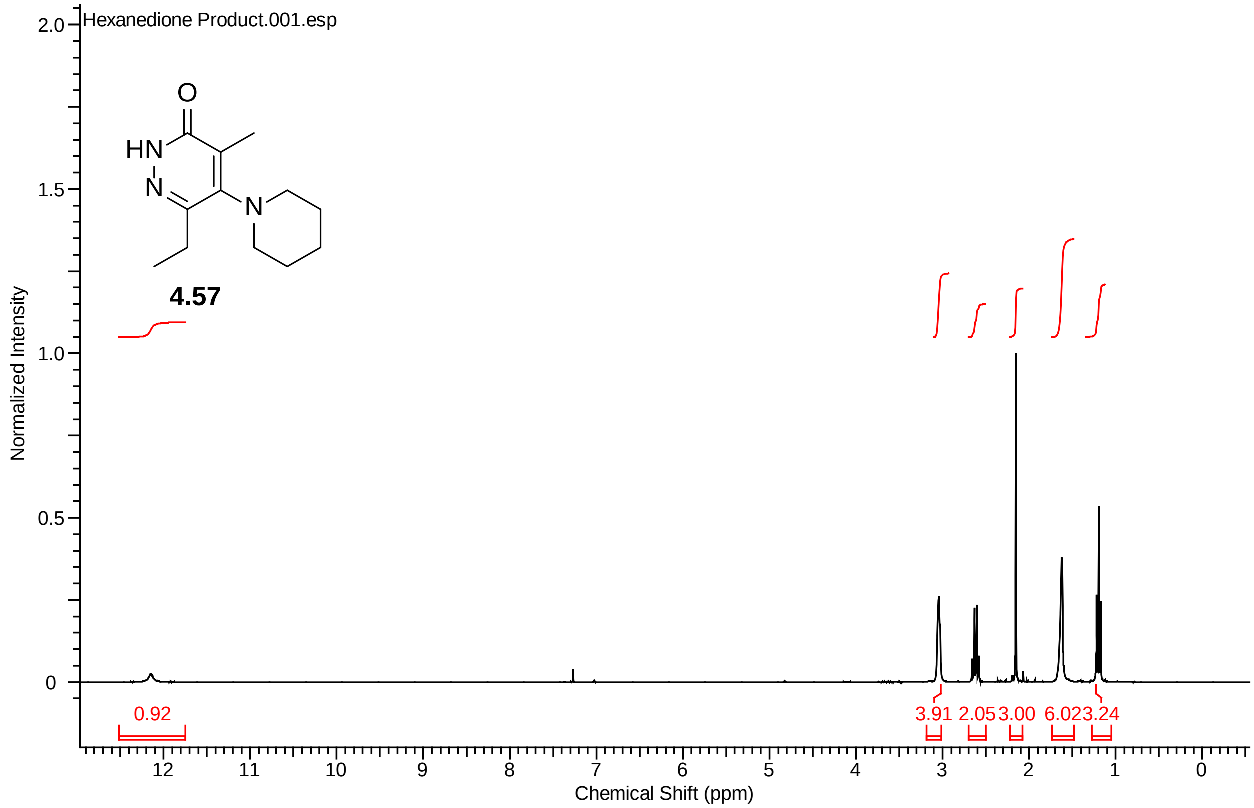

JF12-2212-C13.001.001.1r.esp
163.4724
155.2975
141.3806
108.4085
56.5665
51.9336
45.6752
39.7004
20.5179
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

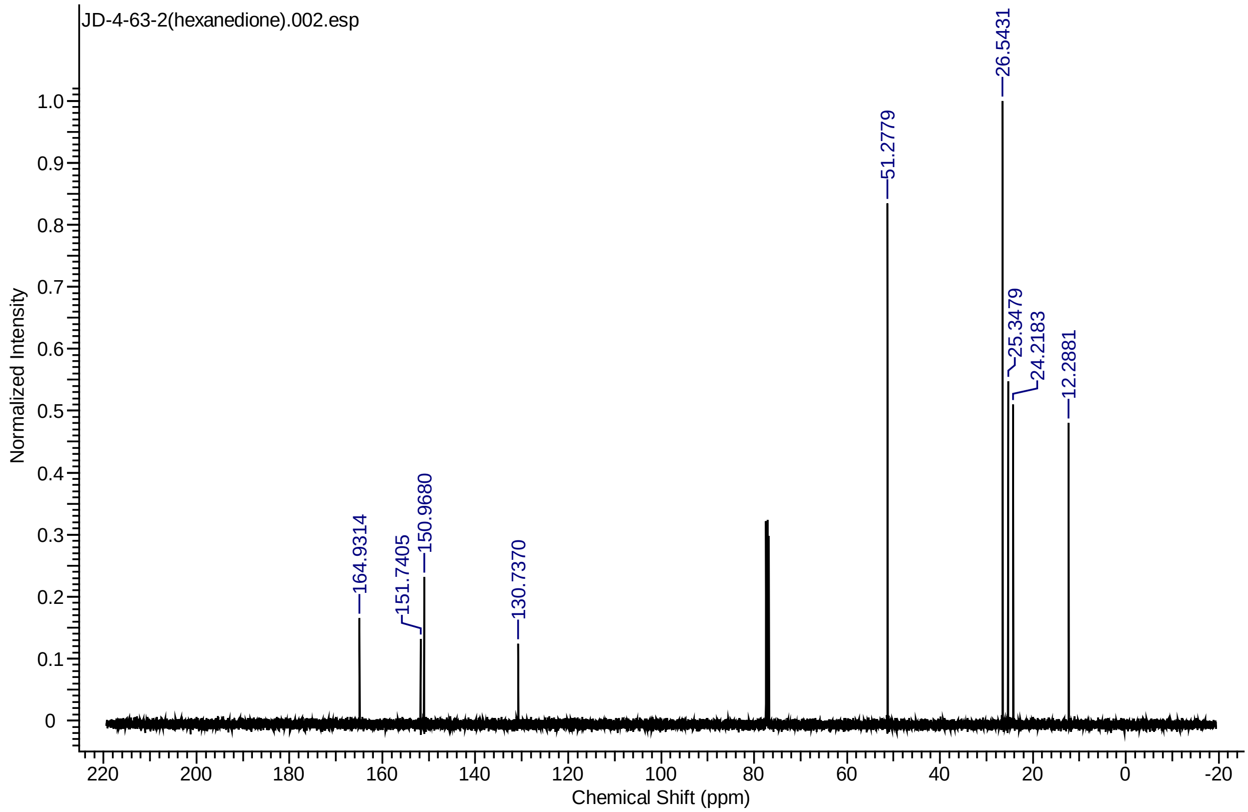

N-methylcyclohexylamine.001.esp
O
HN
N
N
4.55
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.95
1.00
1.05
3.04
3.31
2.16
3.20
2.07
2.29
1.05
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

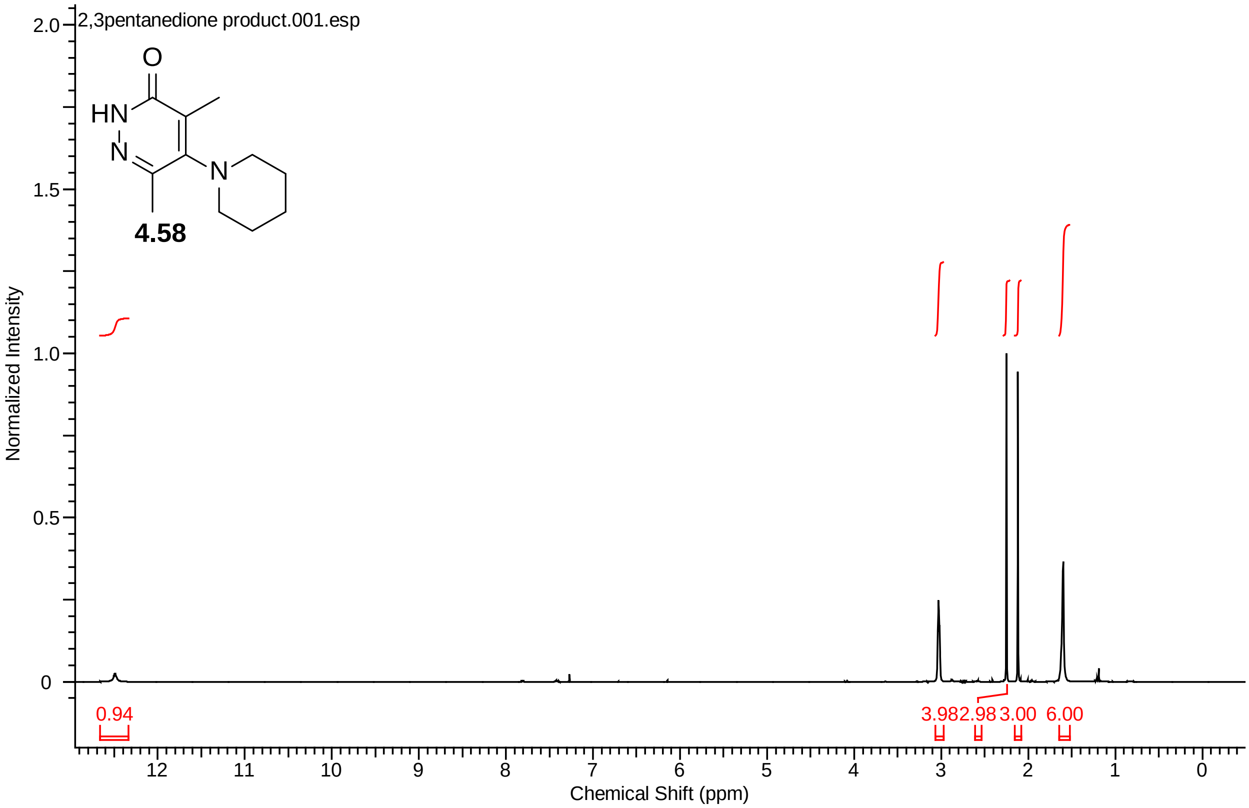

N-methylcyclohexylamine.002.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
163.4615
155.6648
142.1807
108.8994
60.6067
32.4892
29.5073
25.8999
20.1978
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

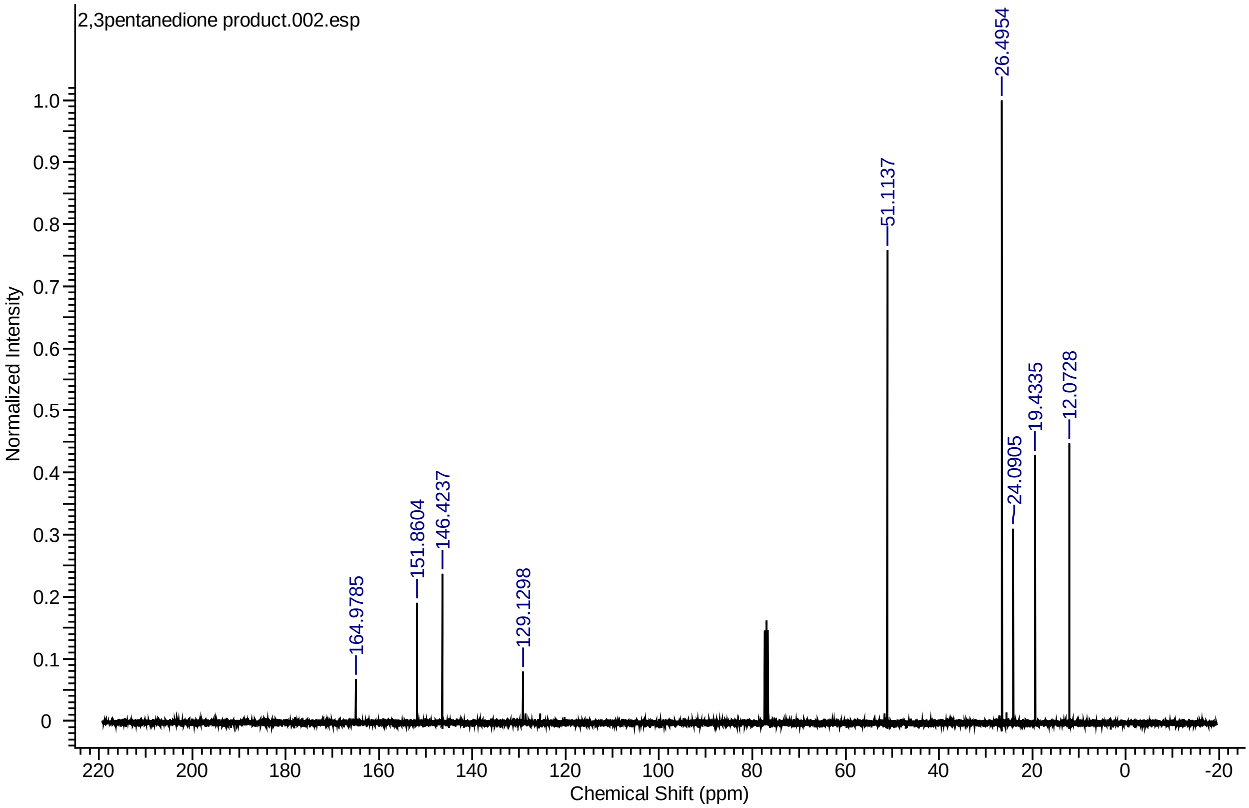

JD-5-52-2(dipropyl).001.esp
O
HN
N
N
4.56
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.89
1.00
3.99
3.07
4.22
6.38
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

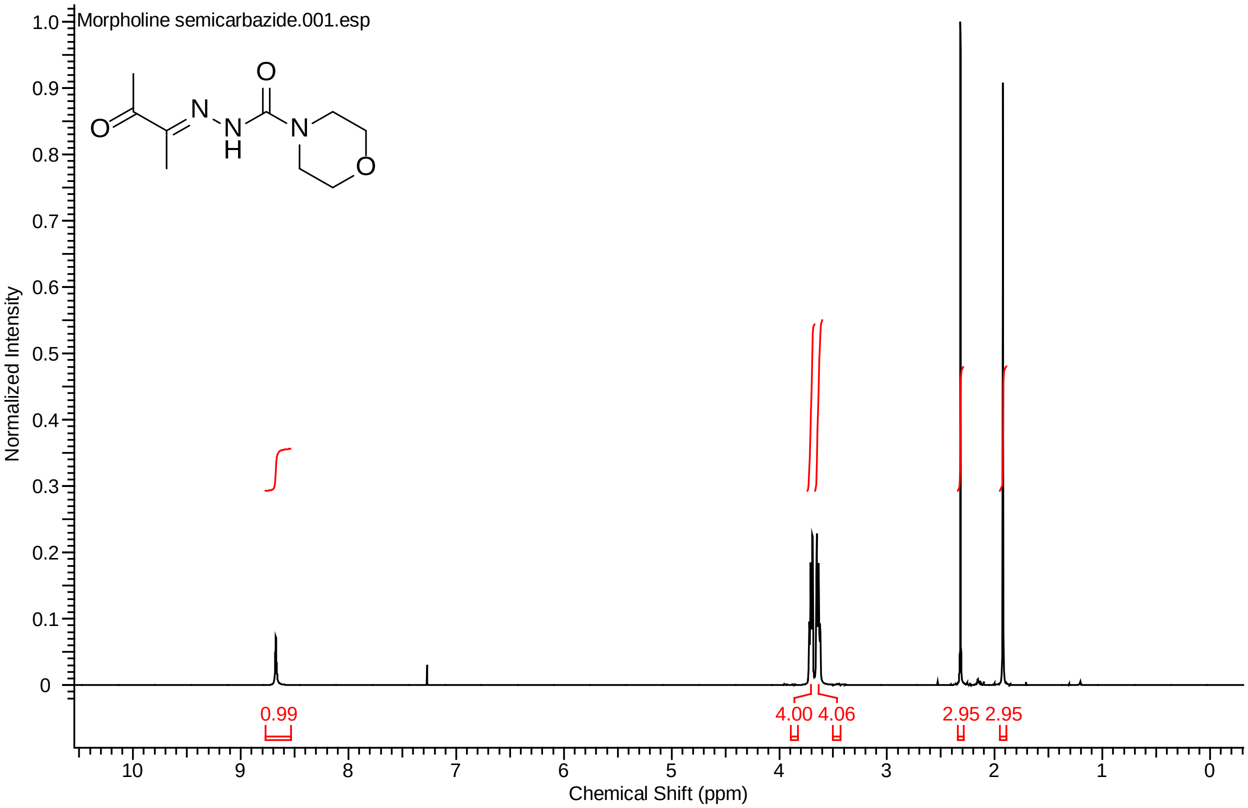

JD-5-52-2(dipropyl).002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
163.4116
154.1780
142.4009
109.5328
53.0231
20.3299
20.0530
11.3295
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

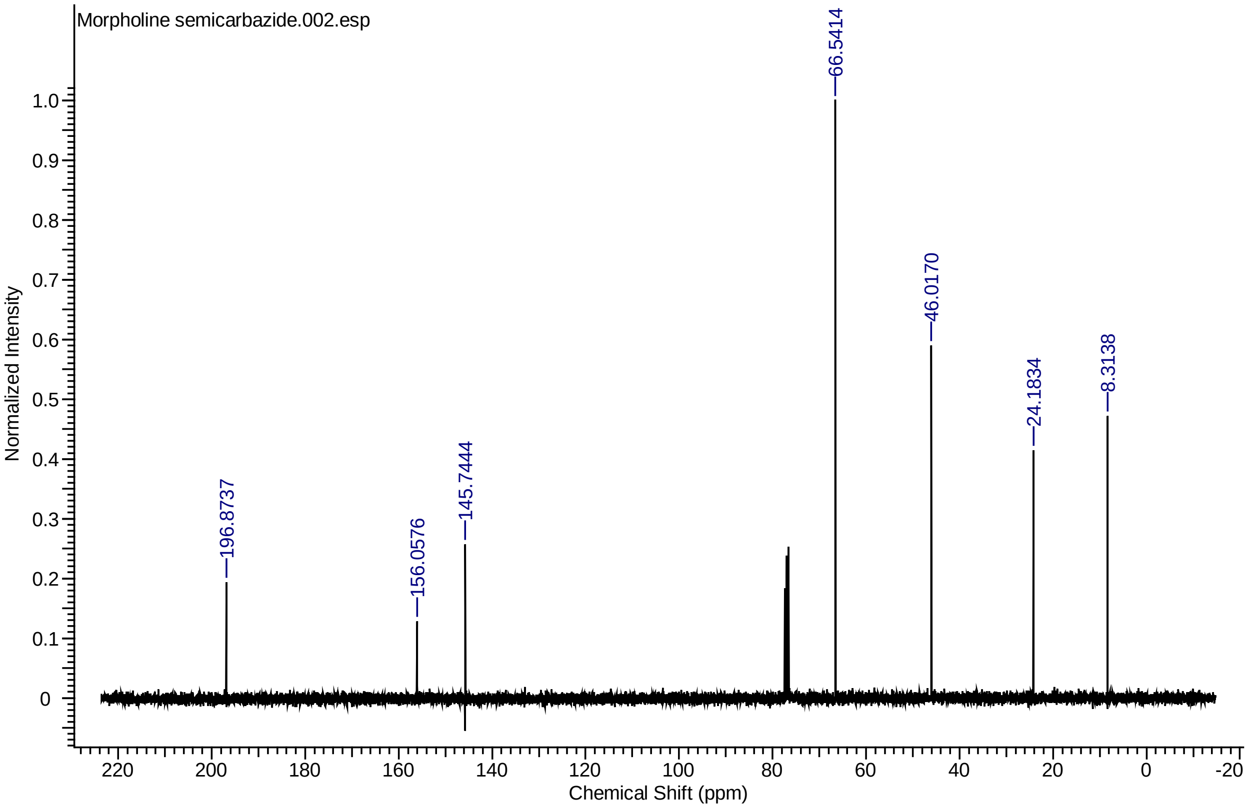

Hexanedione Product.001.esp
O
HN
N
N
4.57
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.92
3.91
2.05
3.00
6.02
3.24
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

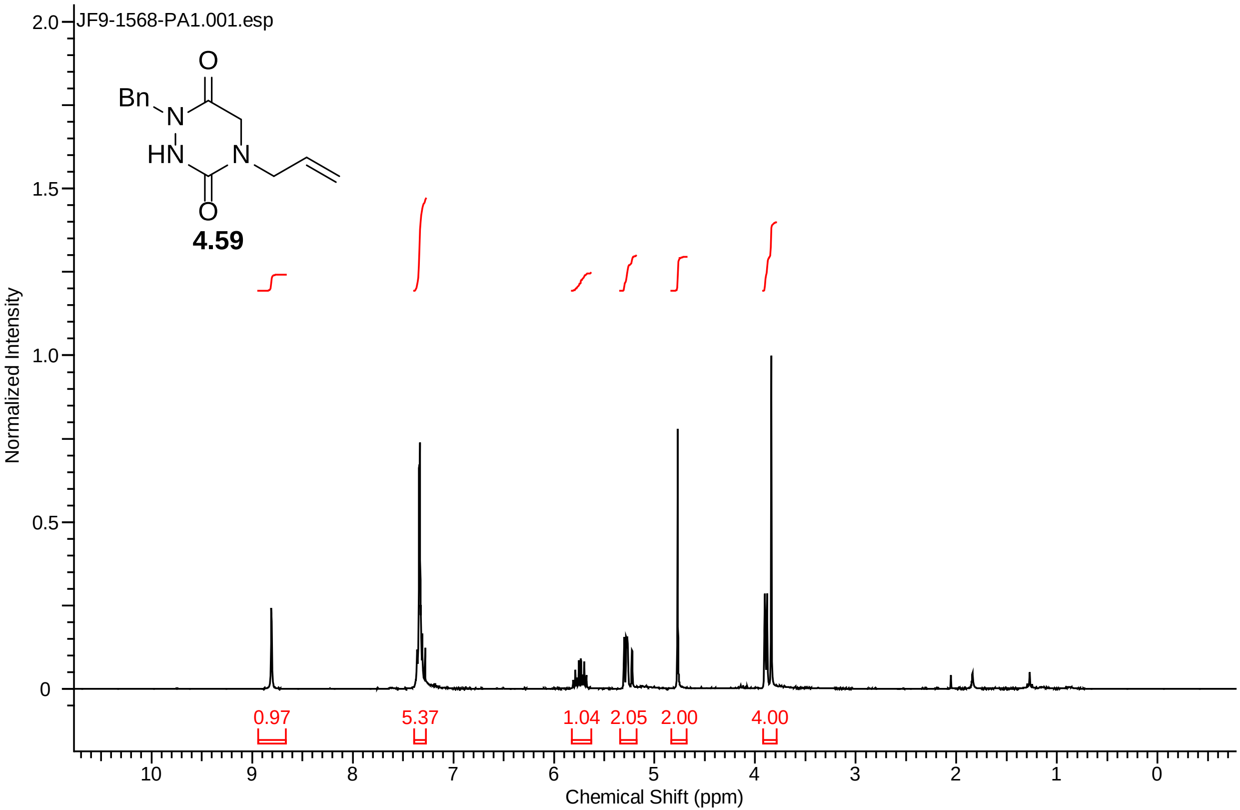

JD-4-63-2(hexanedione).002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
164.9314
151.7405
150.9680
130.7370
51.2779
26.5431
25.3479
24.2183
12.2881
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


2,3pentanedione product.001.esp
O
HN
N
N
4.58
0.94
3.98
2.98
3.00
6.00
Normalized Intensity
2.0
1.5
1.0
0.5
0
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

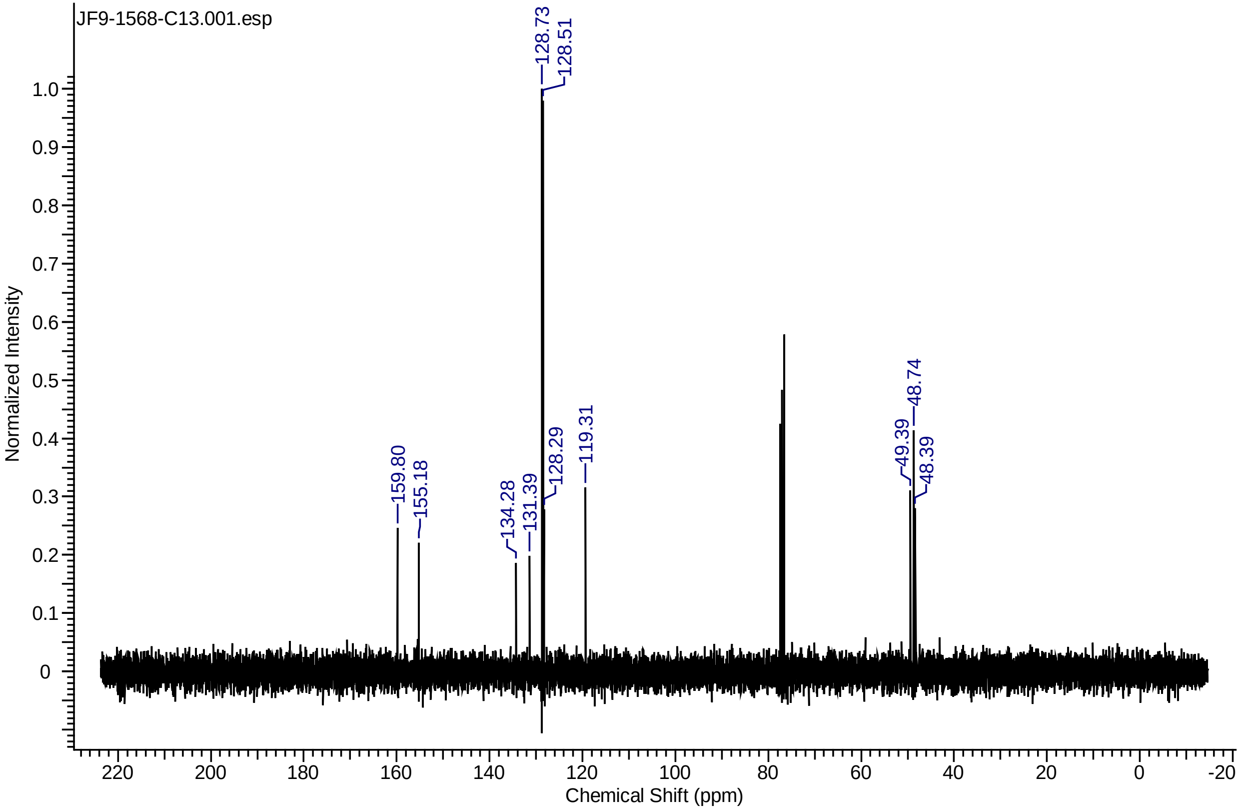

2,3pentanedione product.002.esp
164.9785
151.8604
146.4237
129.1298
51.1137
26.4954
24.0905
19.4335
12.0728
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

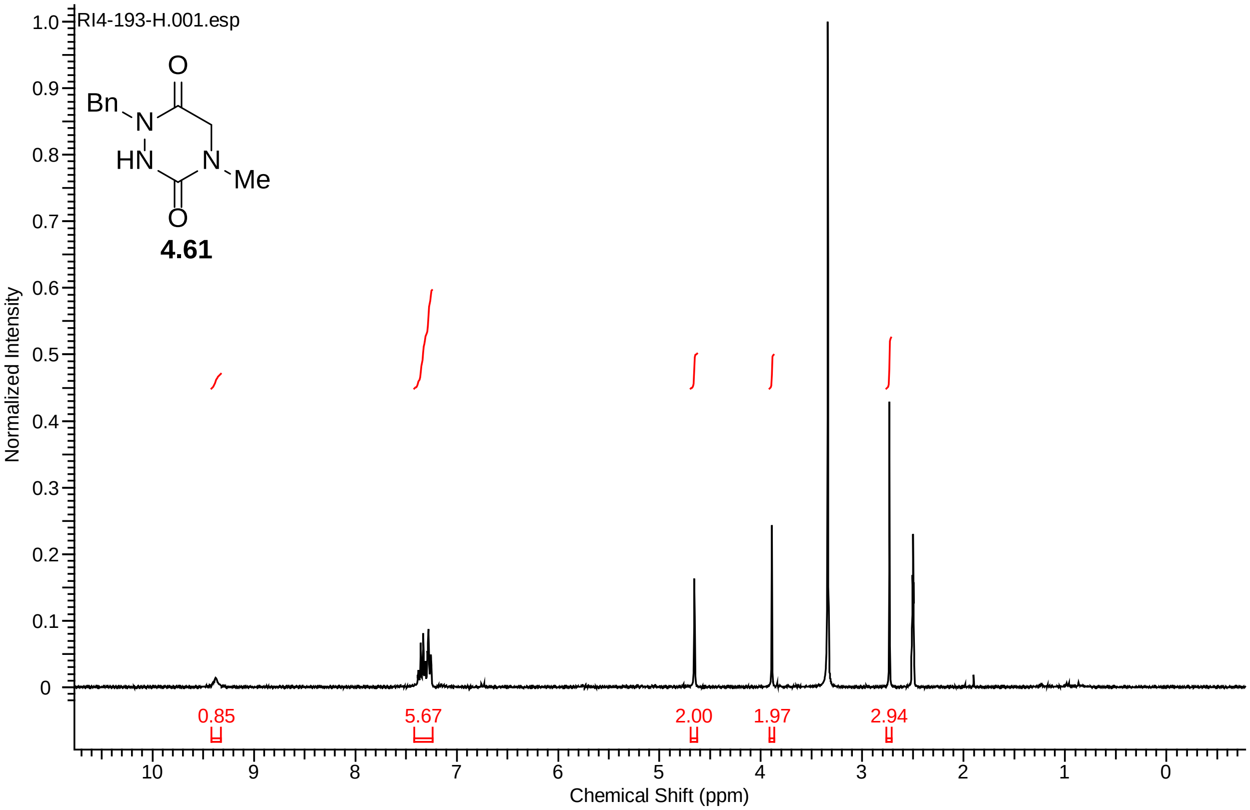

Morpholine semicarbazide.001.esp
O
N
N
H
N
O
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.99
4.00
4.06
2.95
2.95
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

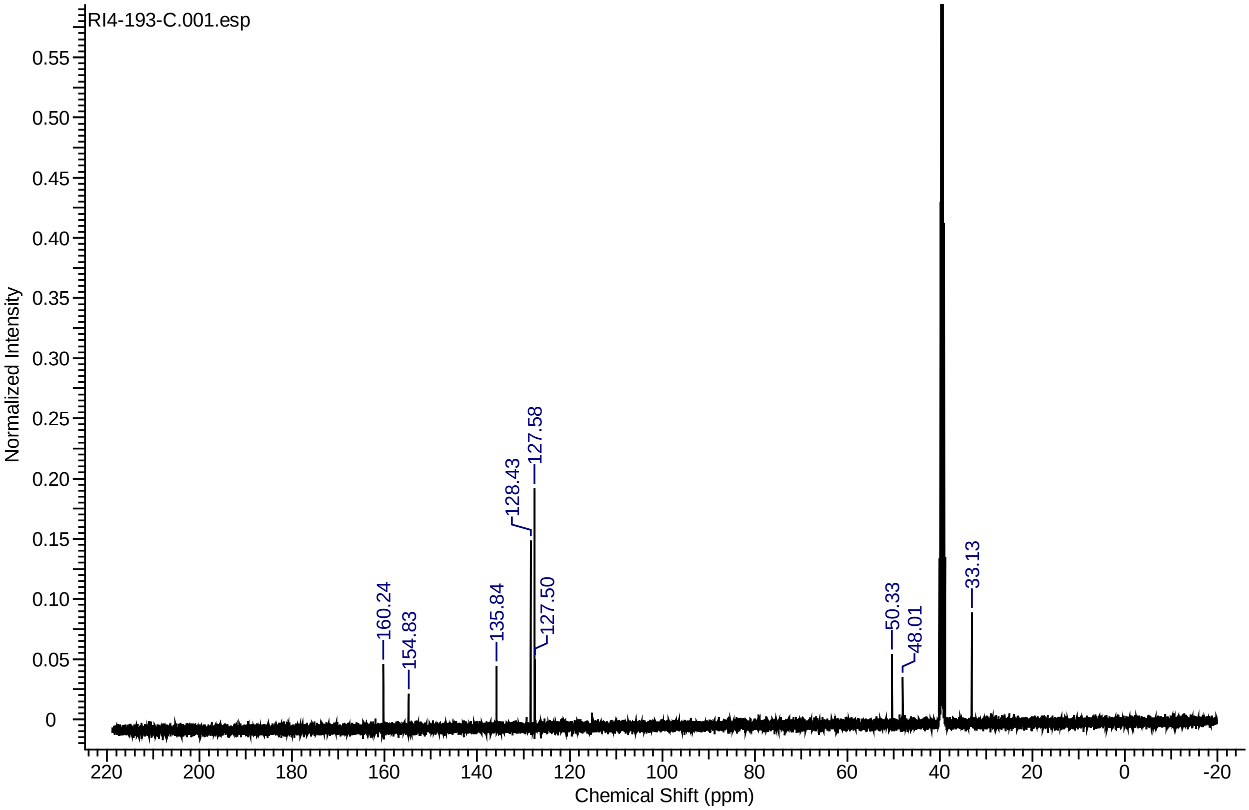

Morpholine semicarbazide.002.esp
196.8737
156.0576
145.7444
66.5414
46.0170
24.1834
8.3138
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

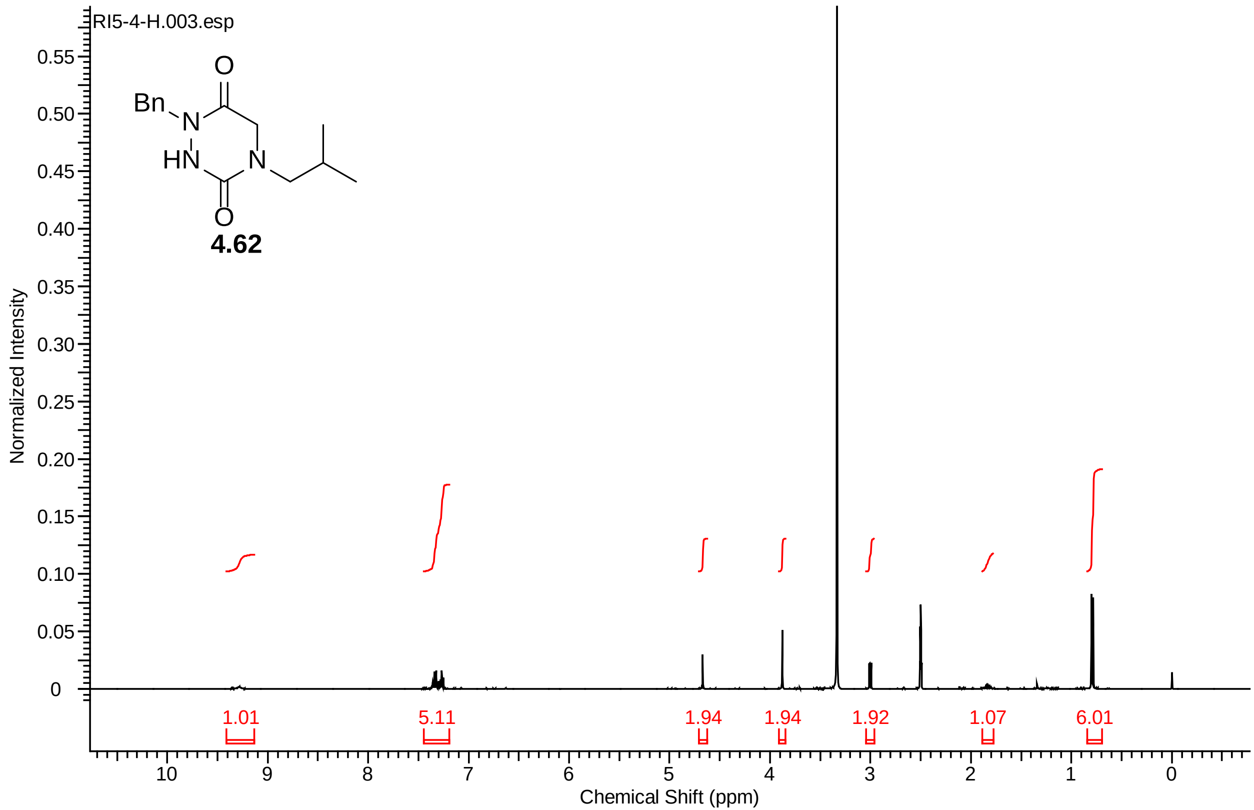

JF9-1568-PA1.001.esp
Bn
N
HN
N
O
O
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.97
5.37
1.04
2.05
2.00
4.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

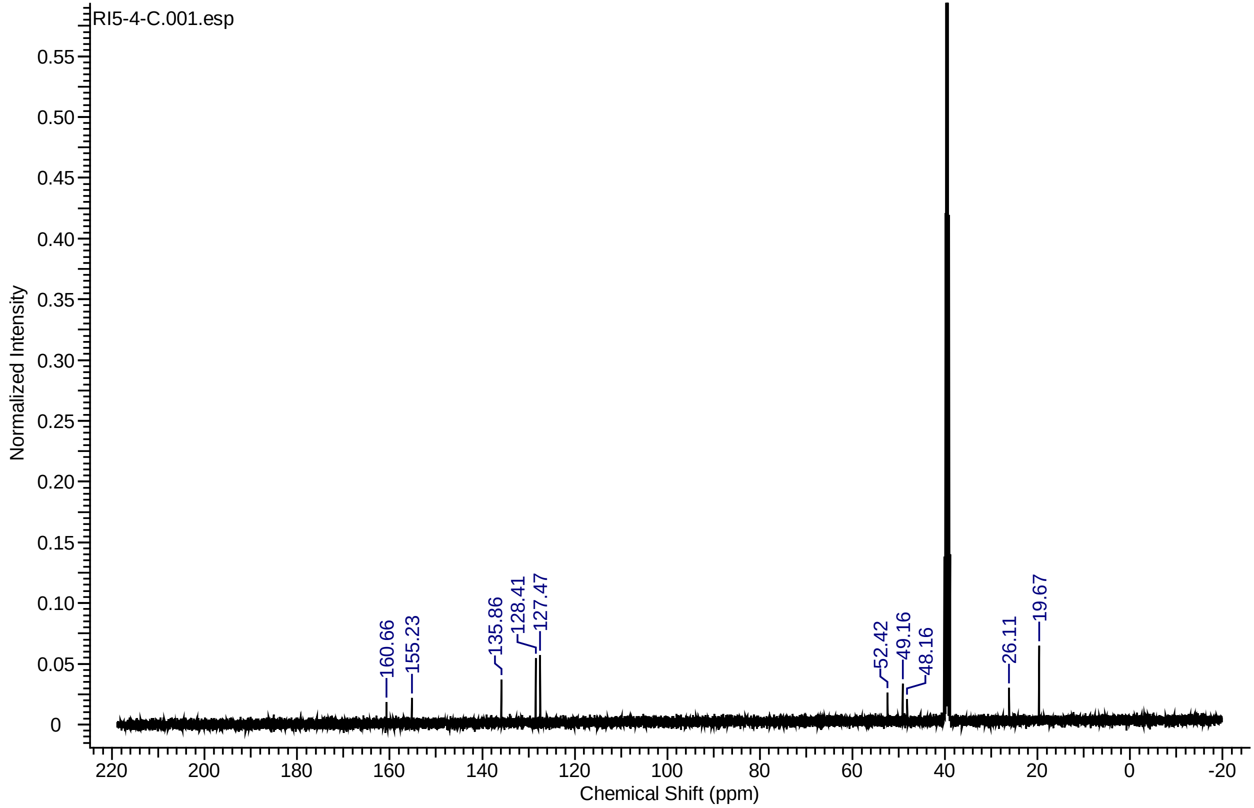
4.59

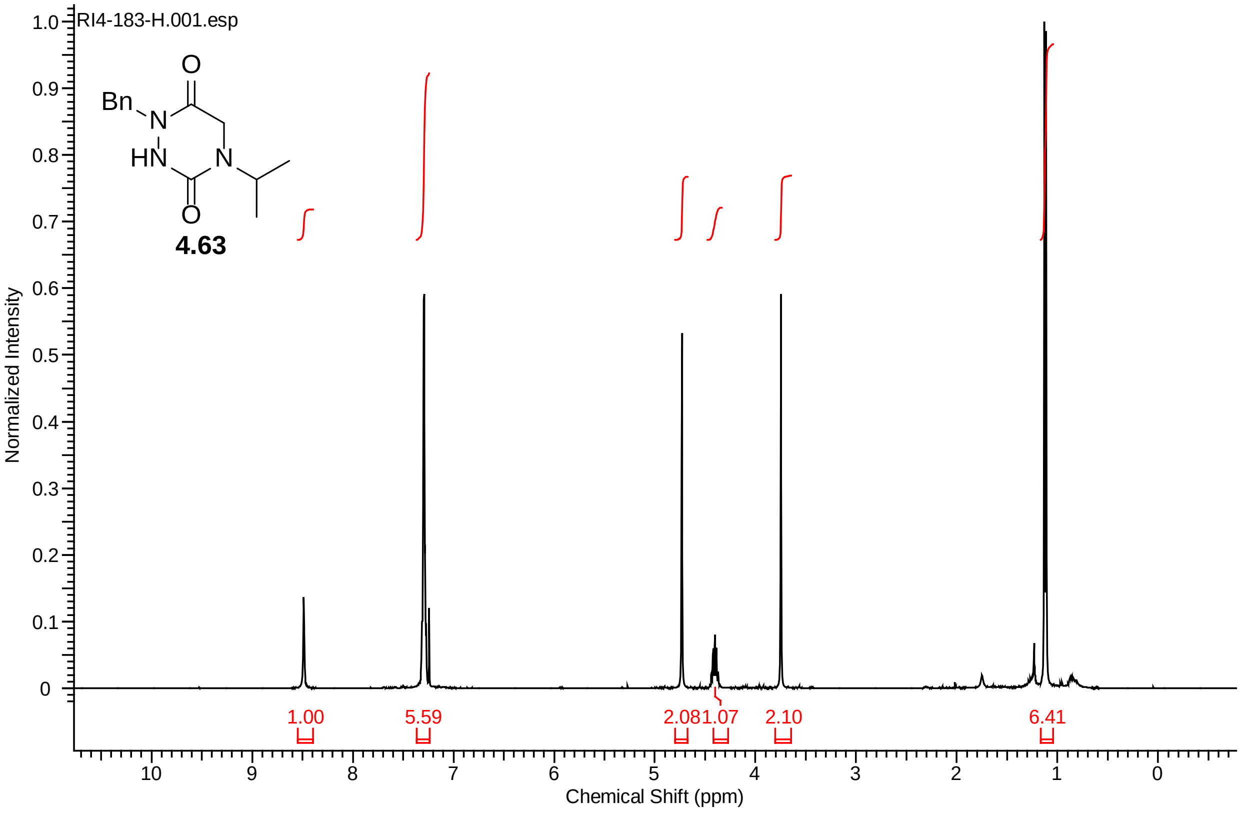

JF9-1568-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
159.80
155.18
134.28
131.39
128.73
128.51
128.29
119.31
49.39
48.74
48.39
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

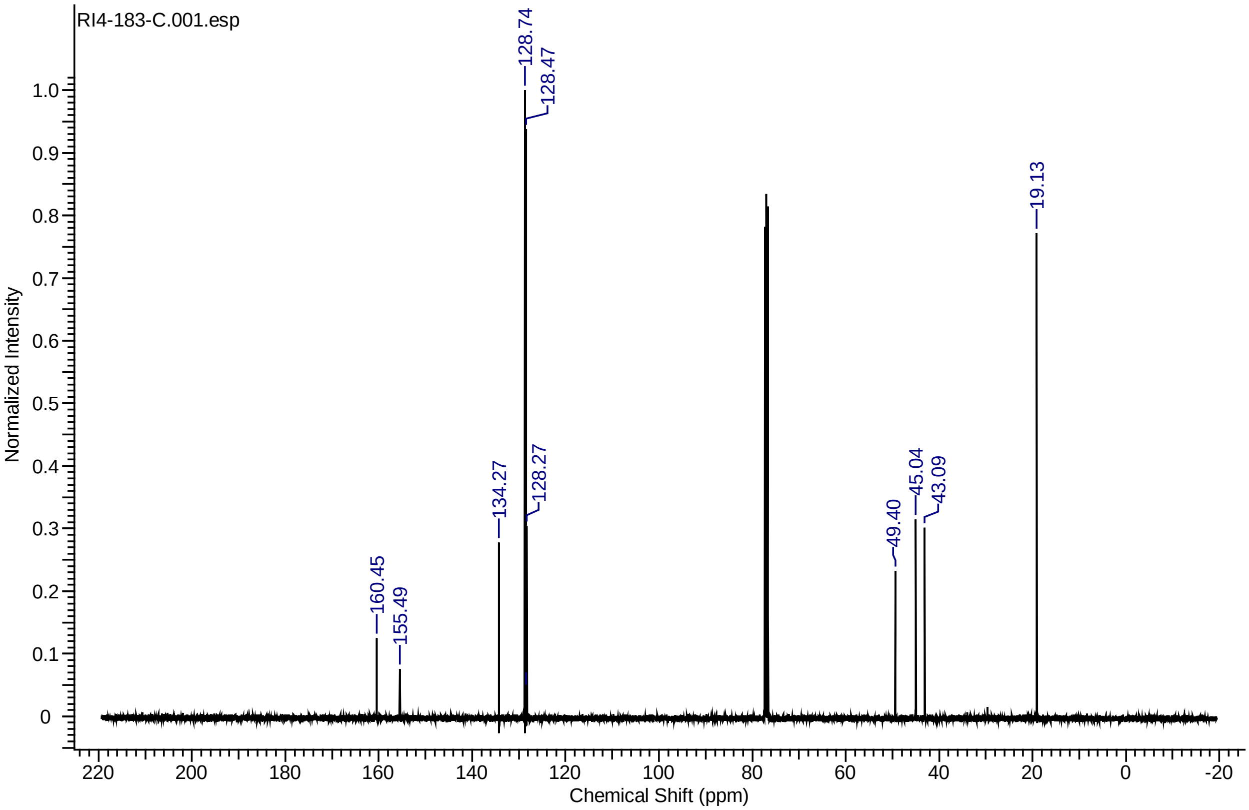

RI4-193-H.001.esp
Bn
N
HN
N
Me
O
O
4.61
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.85
5.67
2.00
1.97
2.94
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

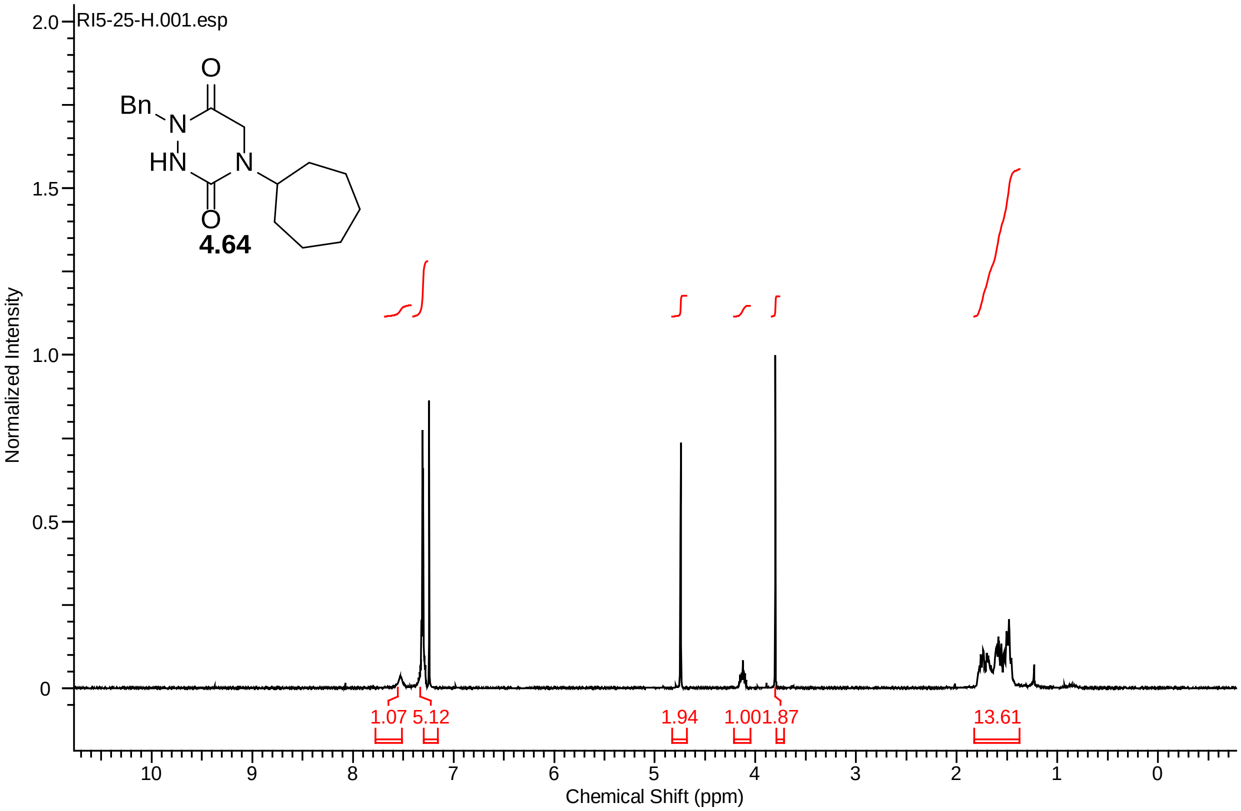

RI4-193-C.001.esp
Normalized Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
160.24
154.83
135.84
128.43
127.58
127.50
50.33
48.01
33.13
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


RI5-4-H.003.esp
Bn
N
HN
N
O
O
4.62
Normalized Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
1.01
5.11
1.94
1.94
1.92
1.07
6.01
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

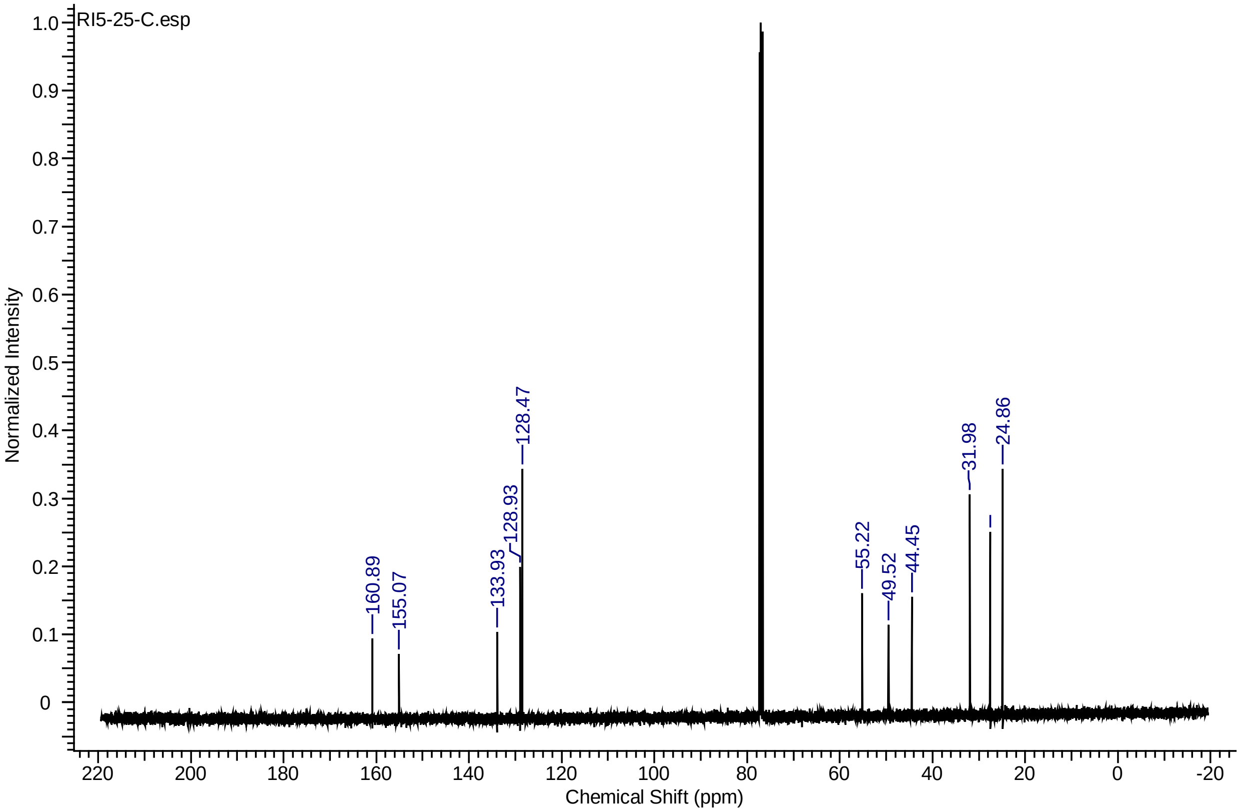

RI5-4-C.001.esp
Normalized Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
160.66
155.23
135.86
128.41
127.47
52.42
49.16
48.16
26.11
19.67
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


RI4-183-H.001.esp
Bn
N
HN
N
O
O
4.63
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
5.59
2.08
1.07
2.10
6.41
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

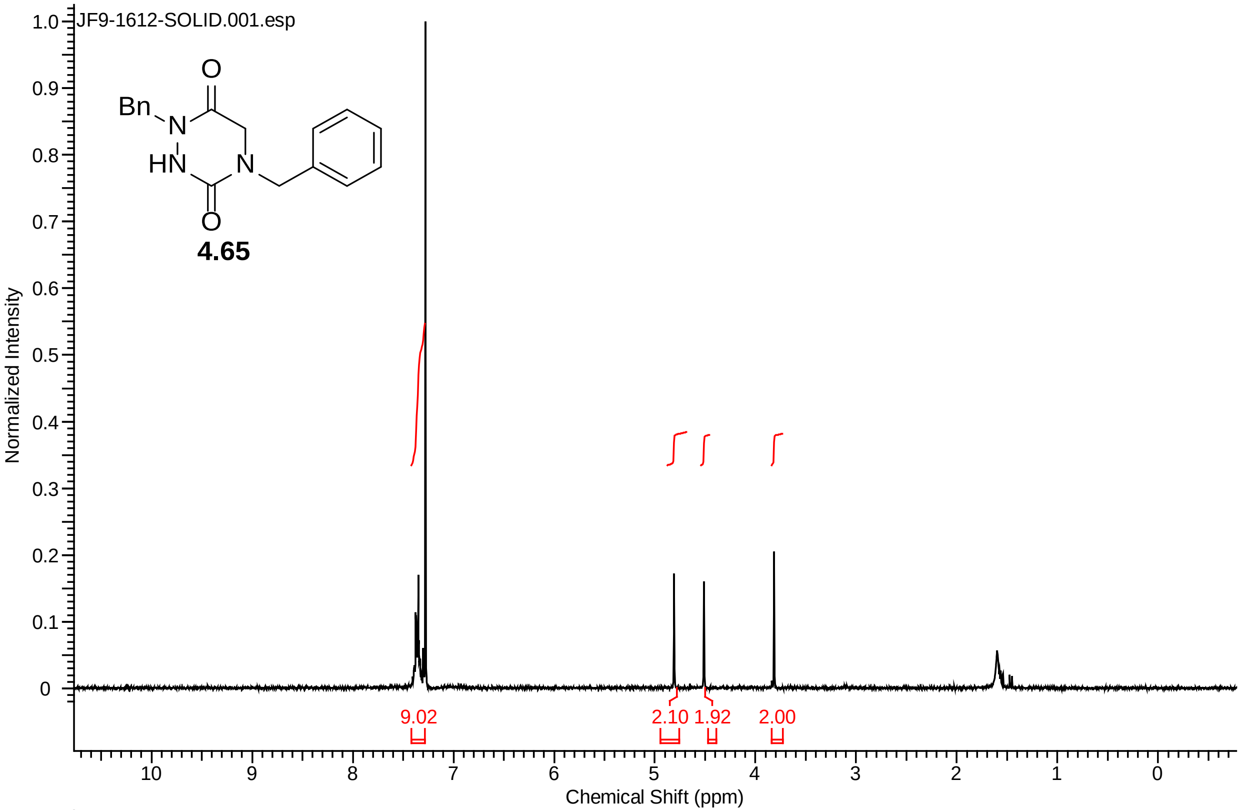

RI4-183-C.001.esp
128.74
128.47
19.13
134.27
128.27
160.45
155.49
49.40
45.04
43.09
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

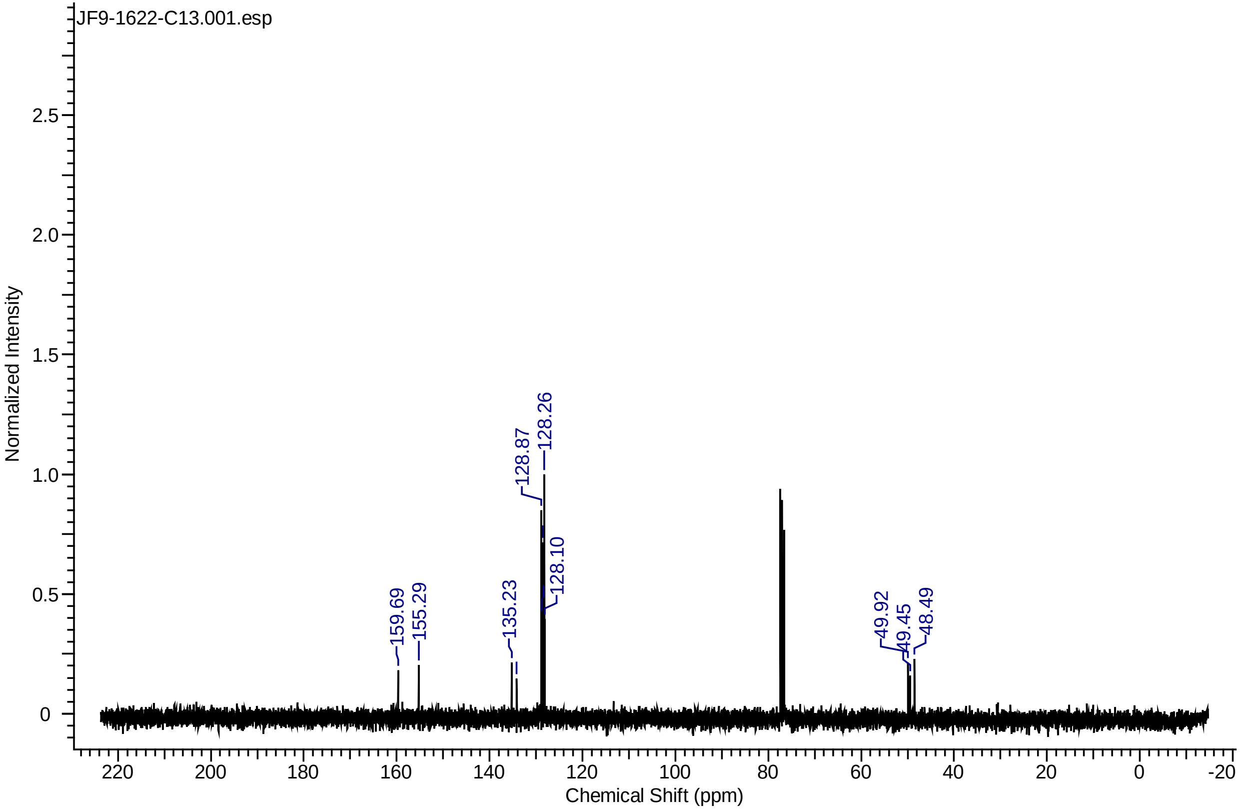

4.64

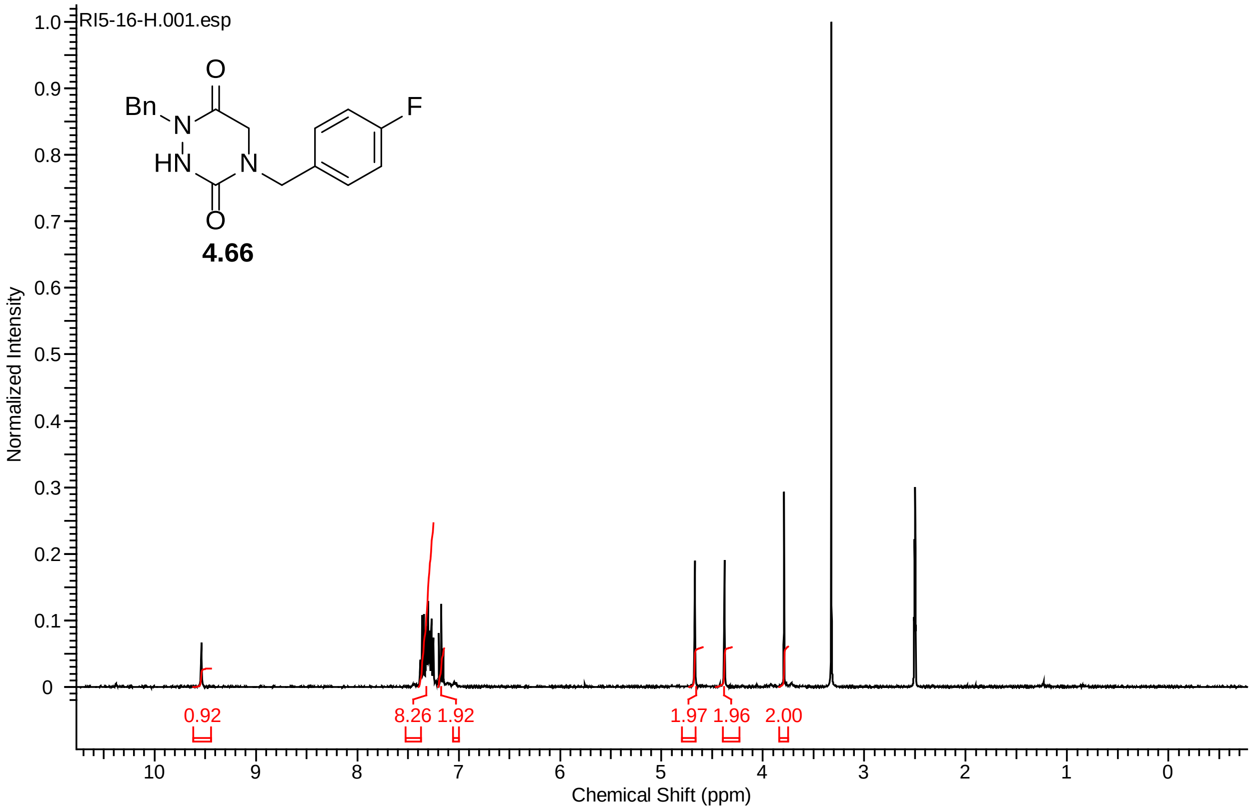
RI5-25-H.001.esp
Bn
N
HN
N
O
O
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.07
5.12
1.94
1.00
1.87
13.61
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

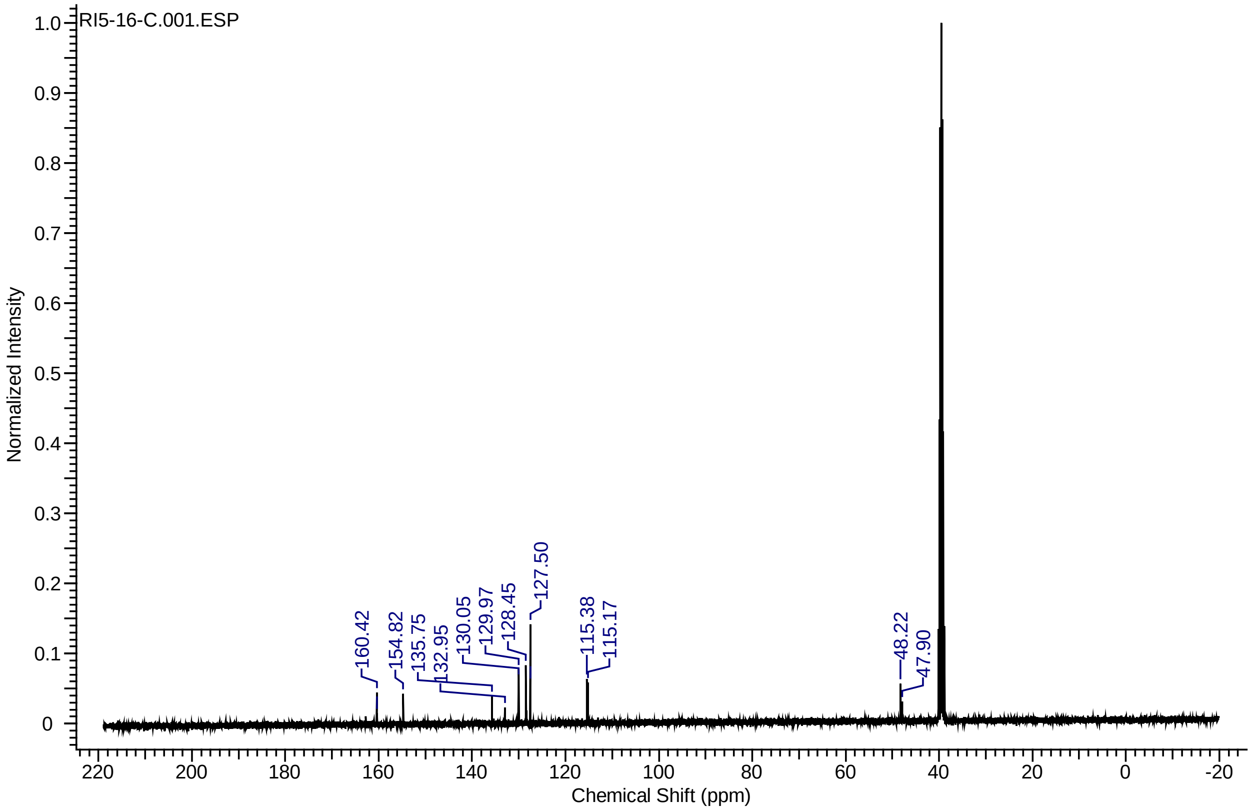


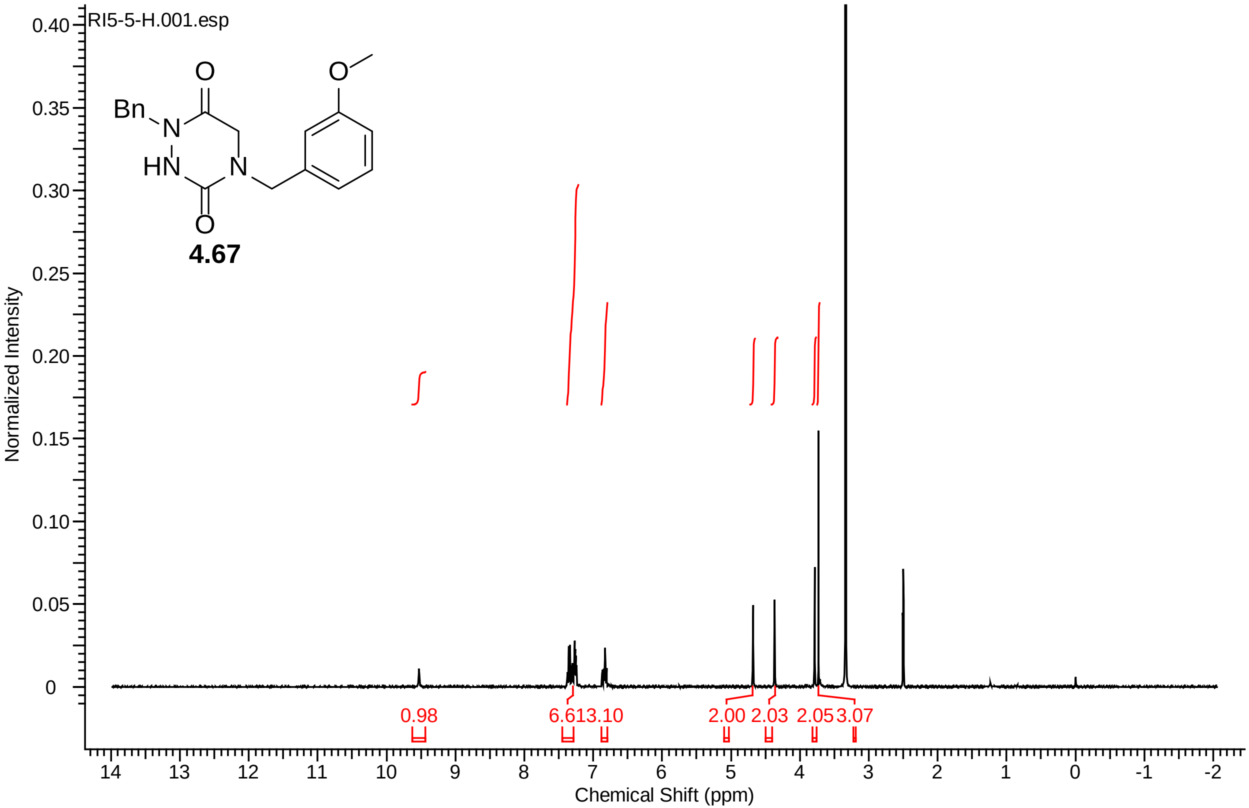
RI5-25-C.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.89
155.07
133.93
128.93
128.47
55.22
49.52
44.45
31.98
24.86
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

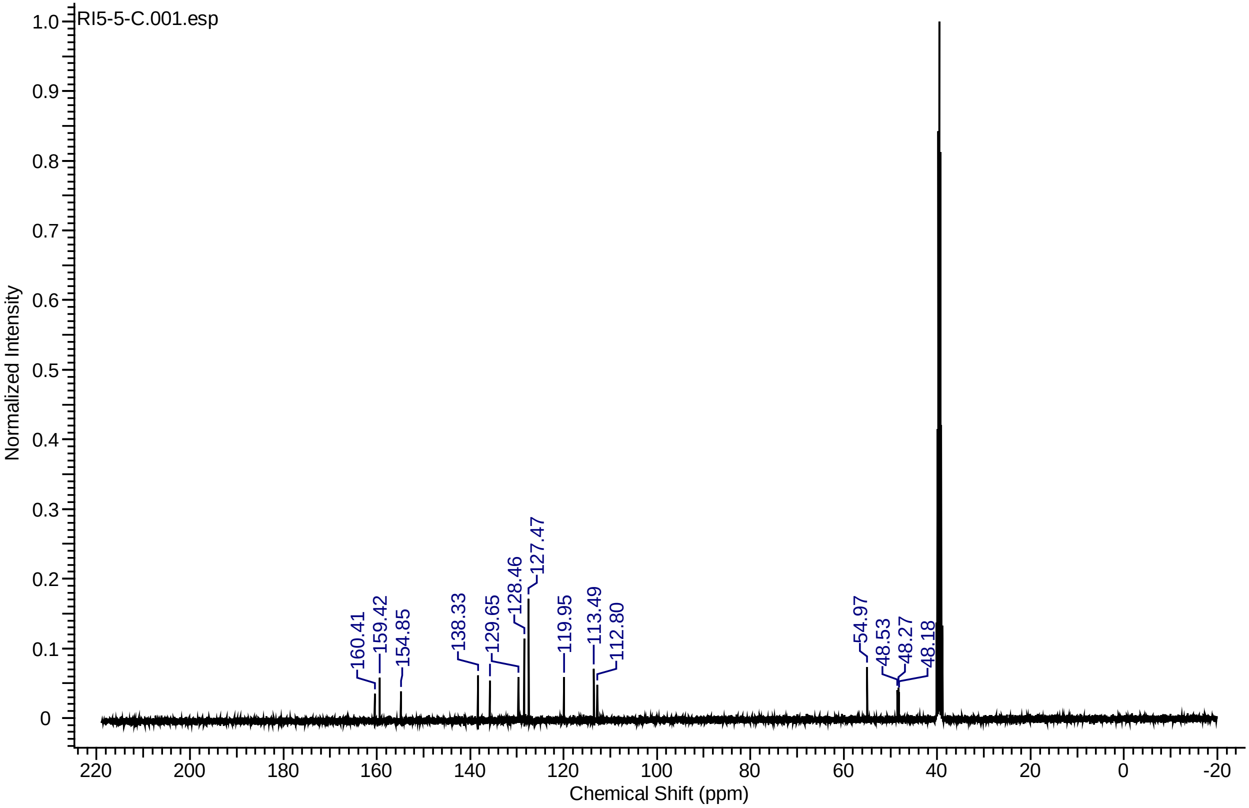

JF9-1612-SOLID.001.esp
Bn
N
HN
N
O
O
4.65
9.02
2.10
1.92
2.00
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

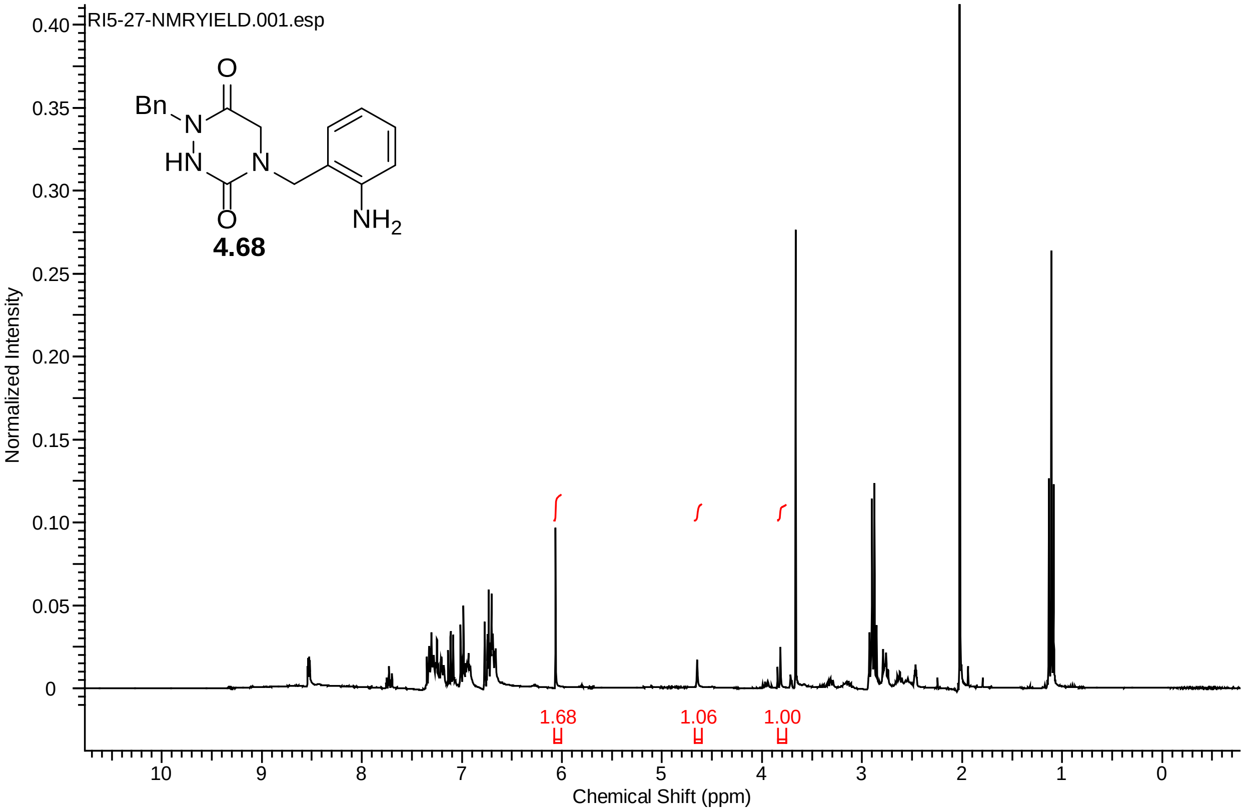

JF9-1622-C13.001.esp
159.69
155.29
135.23
128.87
128.26
128.10
49.92
49.45
48.49
Normalized Intensity
0
0.5
1.0
1.5
2.0
2.5
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


RI5-16-H.001.esp
Bn
N
HN
N
O
O
F
4.66
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.92
8.26
1.92
1.97
1.96
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

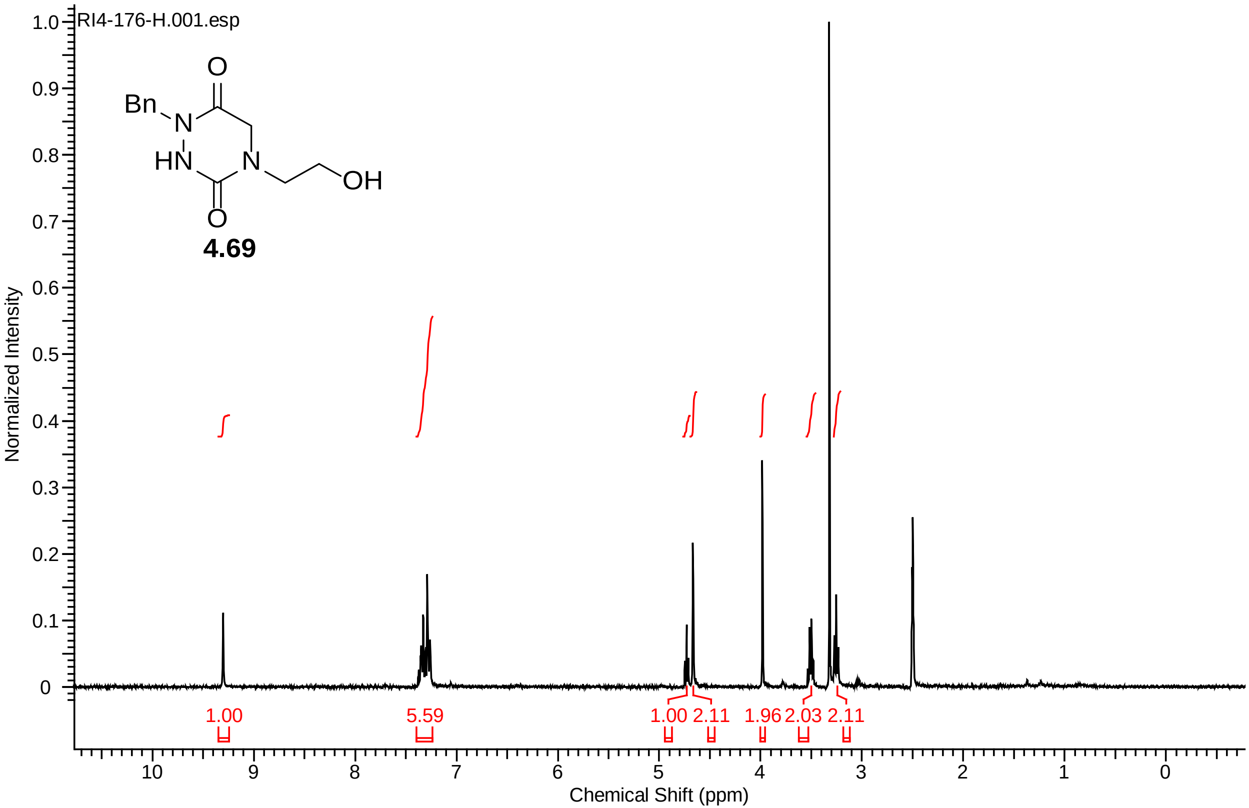

RI5-16-C.001.ESP
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.42
154.82
135.75
132.95
130.05
129.97
128.45
127.50
115.38
115.17
48.22
47.90
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

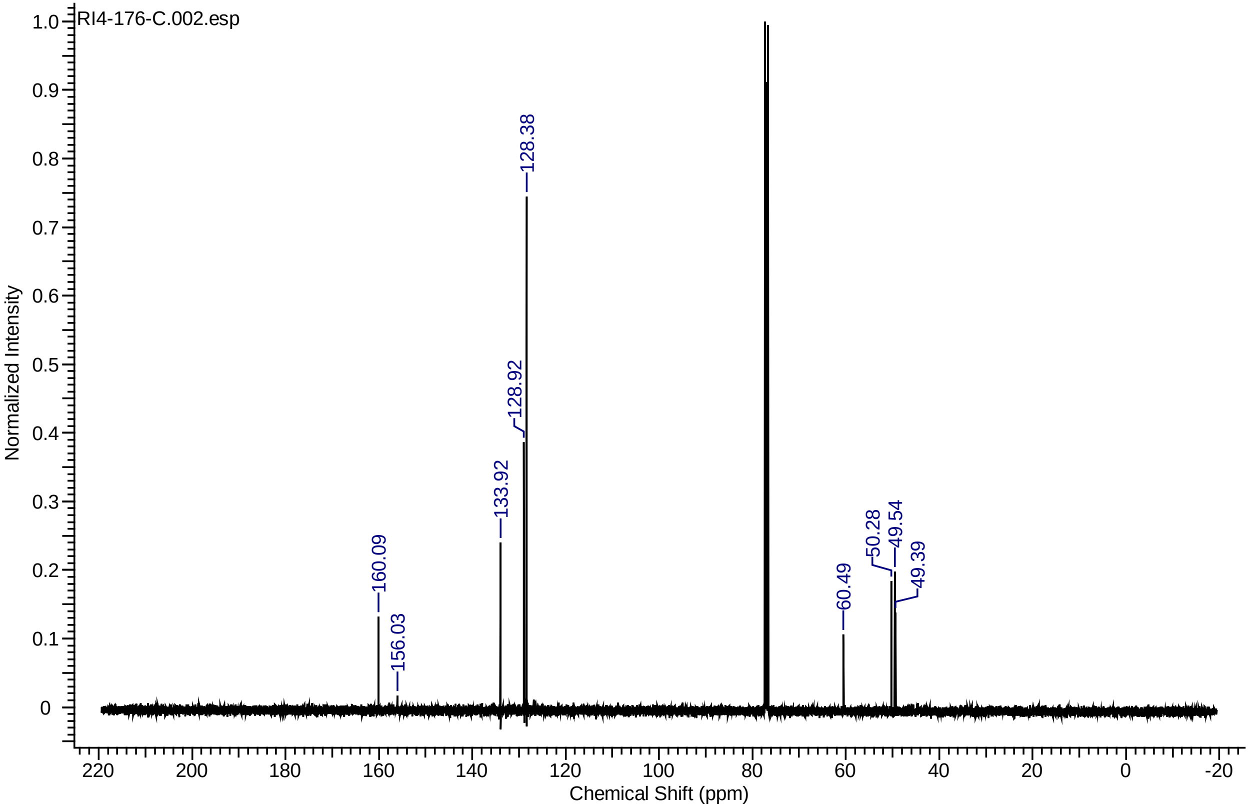

4.67
RI5-5-H.001.esp
Bn
N
HN
N
O
O
O
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.98
6.61
3.10
2.00
2.03
2.05
3.07
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

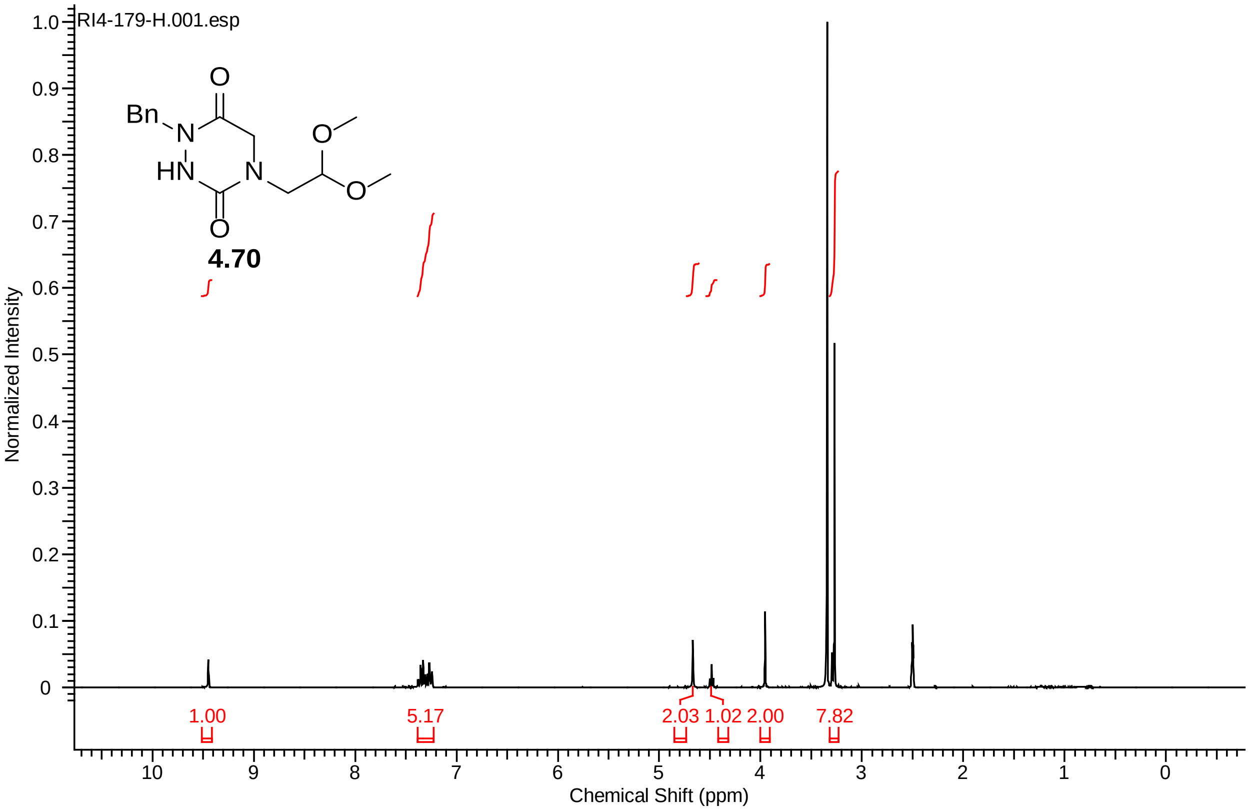

RI5-5-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.41
159.42
154.85
138.33
129.65
128.46
127.47
119.95
113.49
112.80
54.97
48.53
48.27
48.18
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)



37.8 mg TMB used standard.

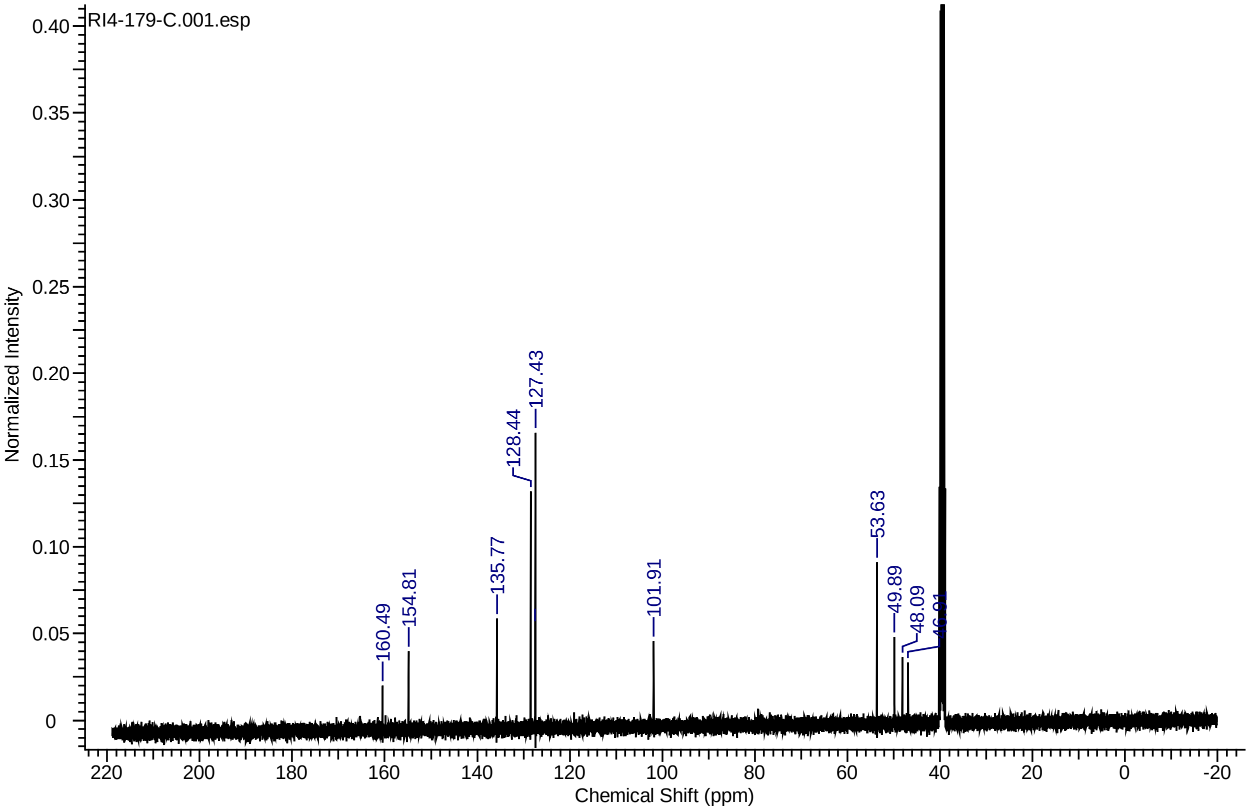

RI4-176-H.001.esp
O
Bn
N
HN
N
OH
O
4.69
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
5.59
1.00
2.11
1.96
2.03
2.11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


RI4-176-C.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.09
156.03
133.92
128.92
128.38
60.49
50.28
49.54
49.39
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

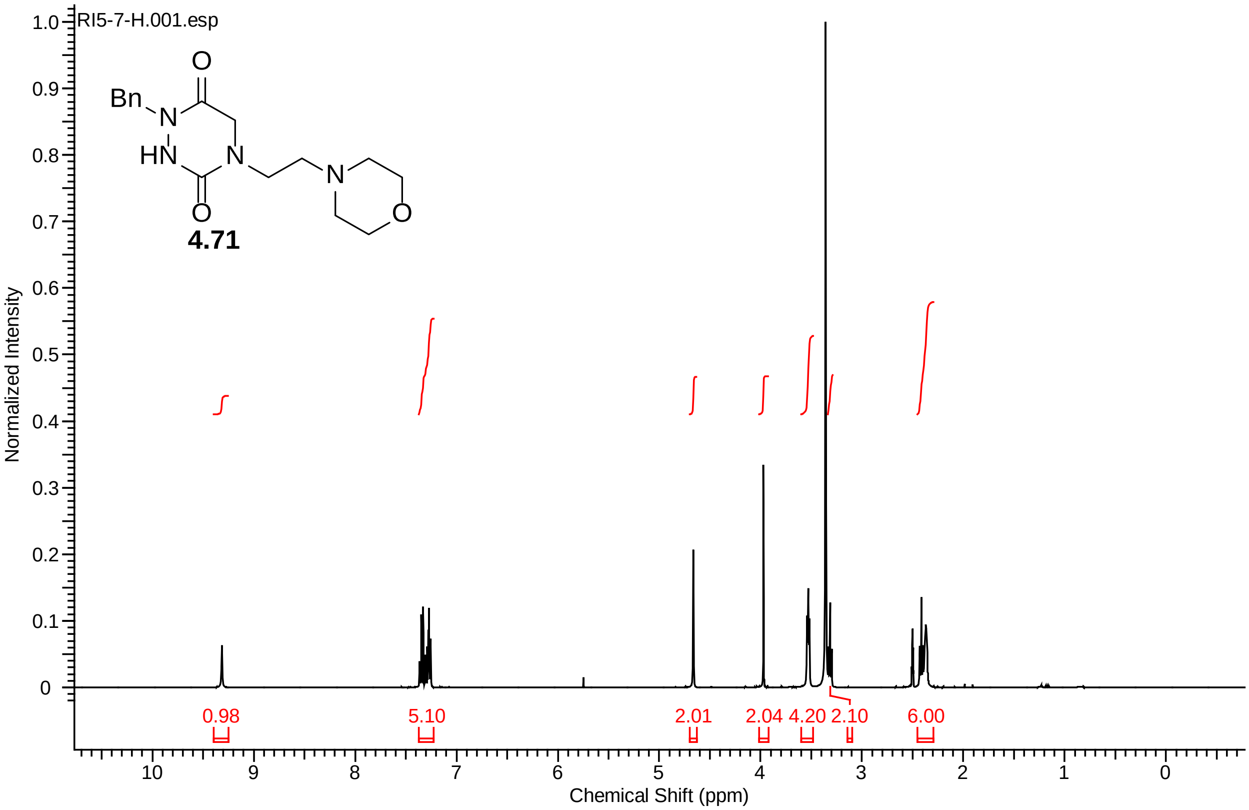


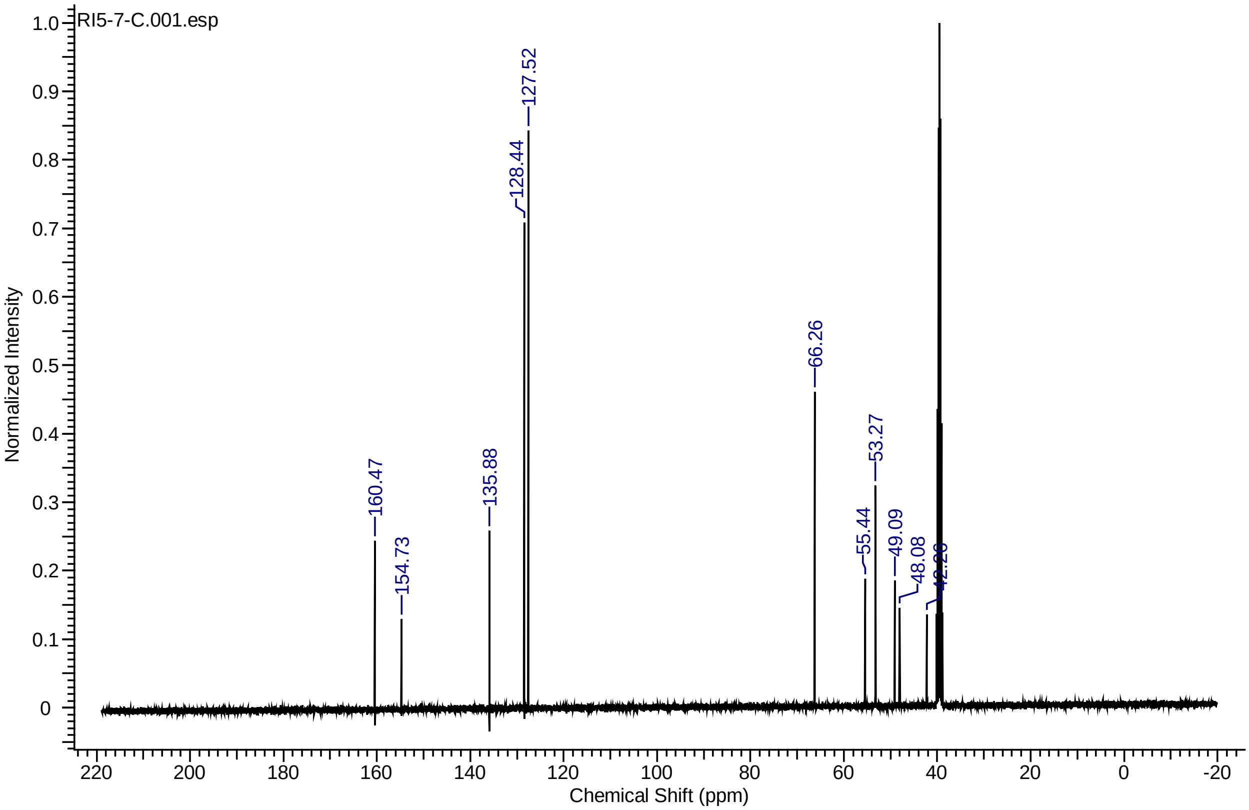
4.70

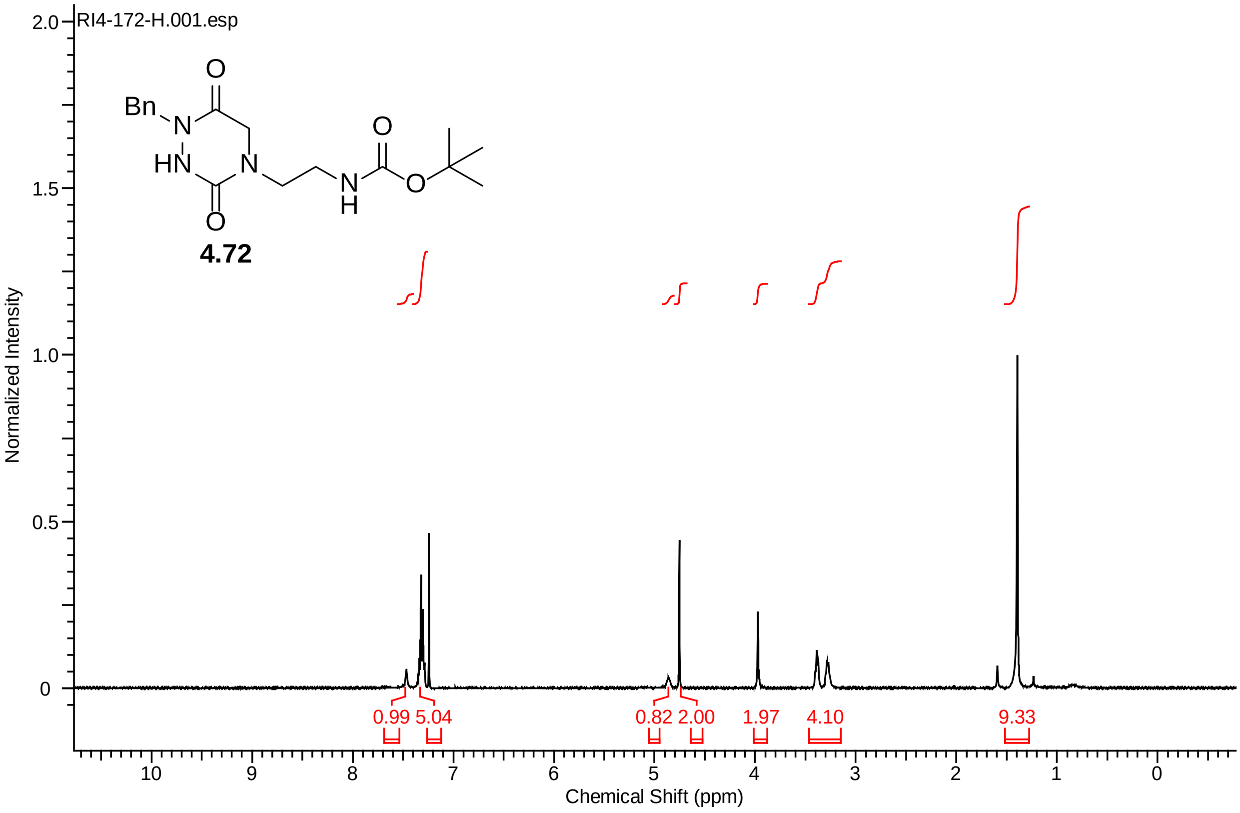
RI4-179-H.001.esp
Bn
N
HN
N
O
O
O
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
5.17
2.03
1.02
2.00
7.82
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)



RI4-179-C.001.esp
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
160.49
154.81
135.77
128.44
127.43
101.91
53.63
49.89
48.09
46.91
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

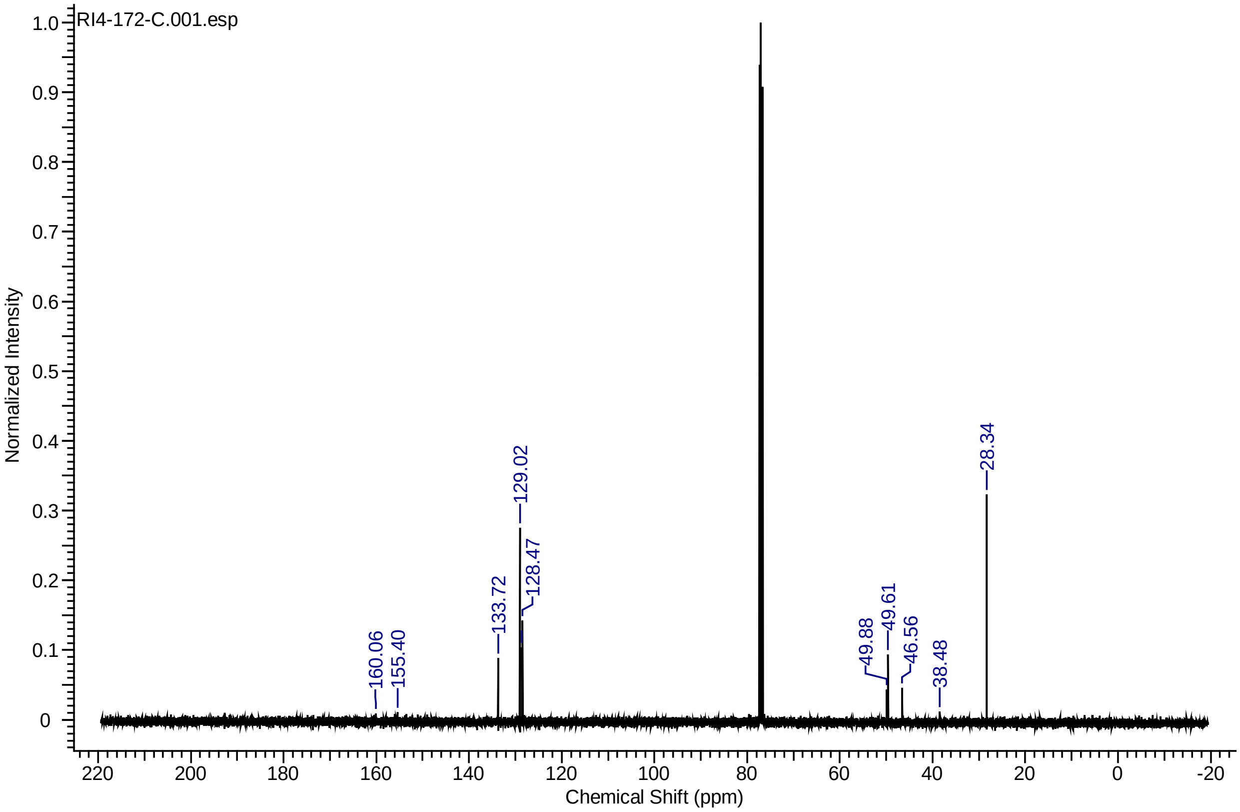

RI5-7-H.001.esp
Bn
N
HN
N
N
O
O
O
4.71
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.98
5.10
2.01
2.04
4.20
2.10
6.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


RI5-7-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
160.47
154.73
135.88
128.44
127.52
66.26
55.44
53.27
49.09
48.08
42.26
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

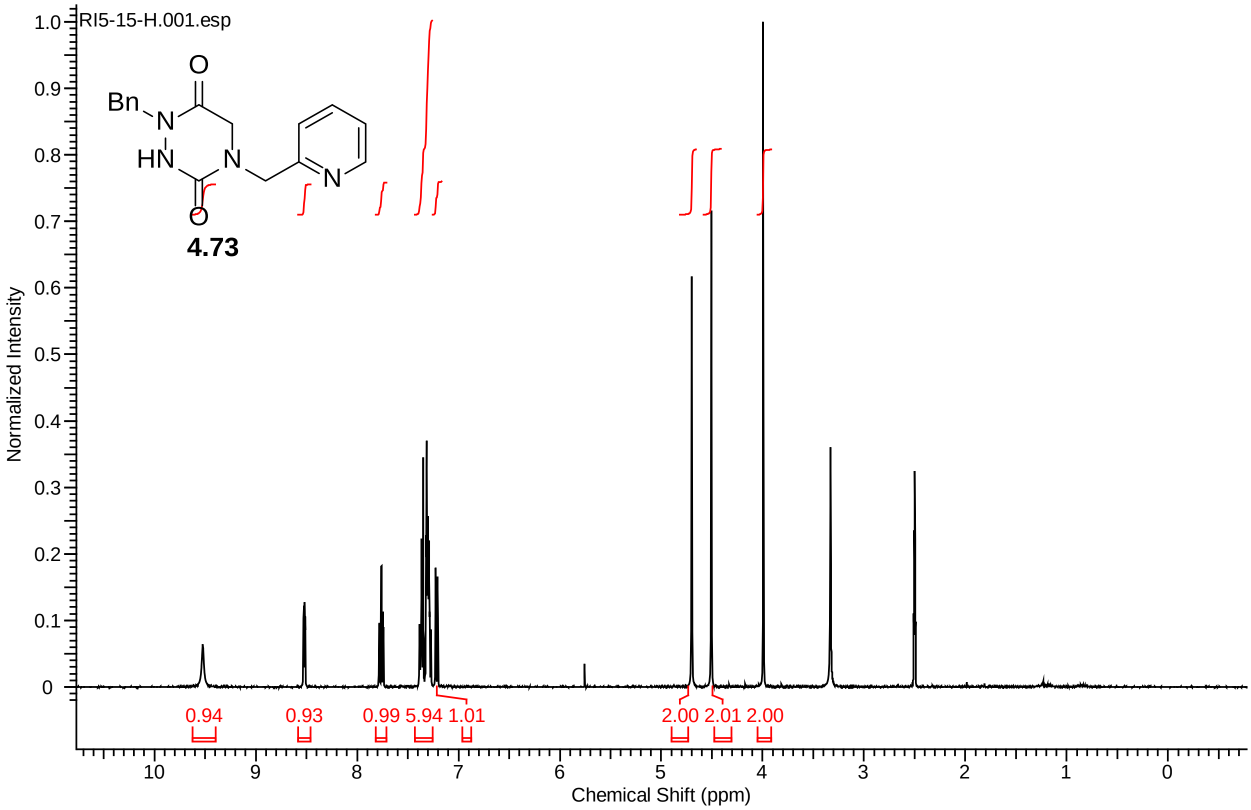


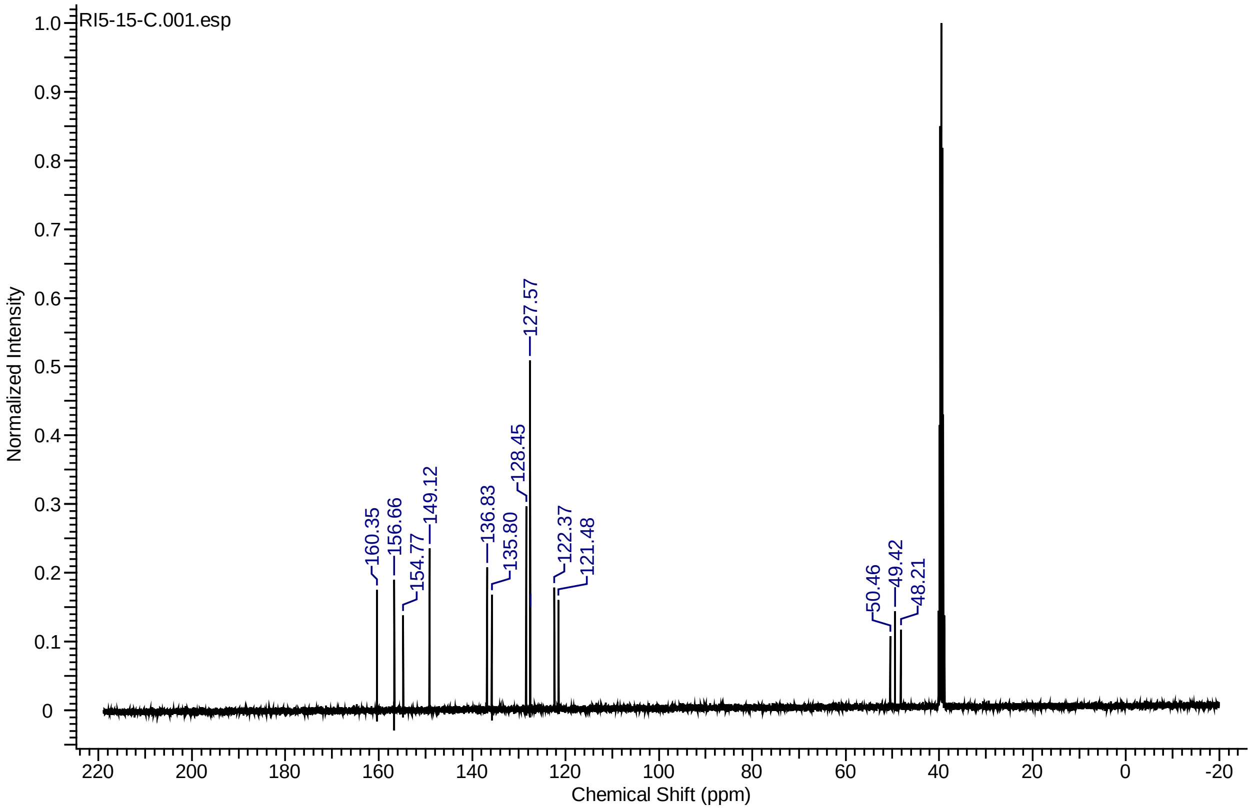
4.72

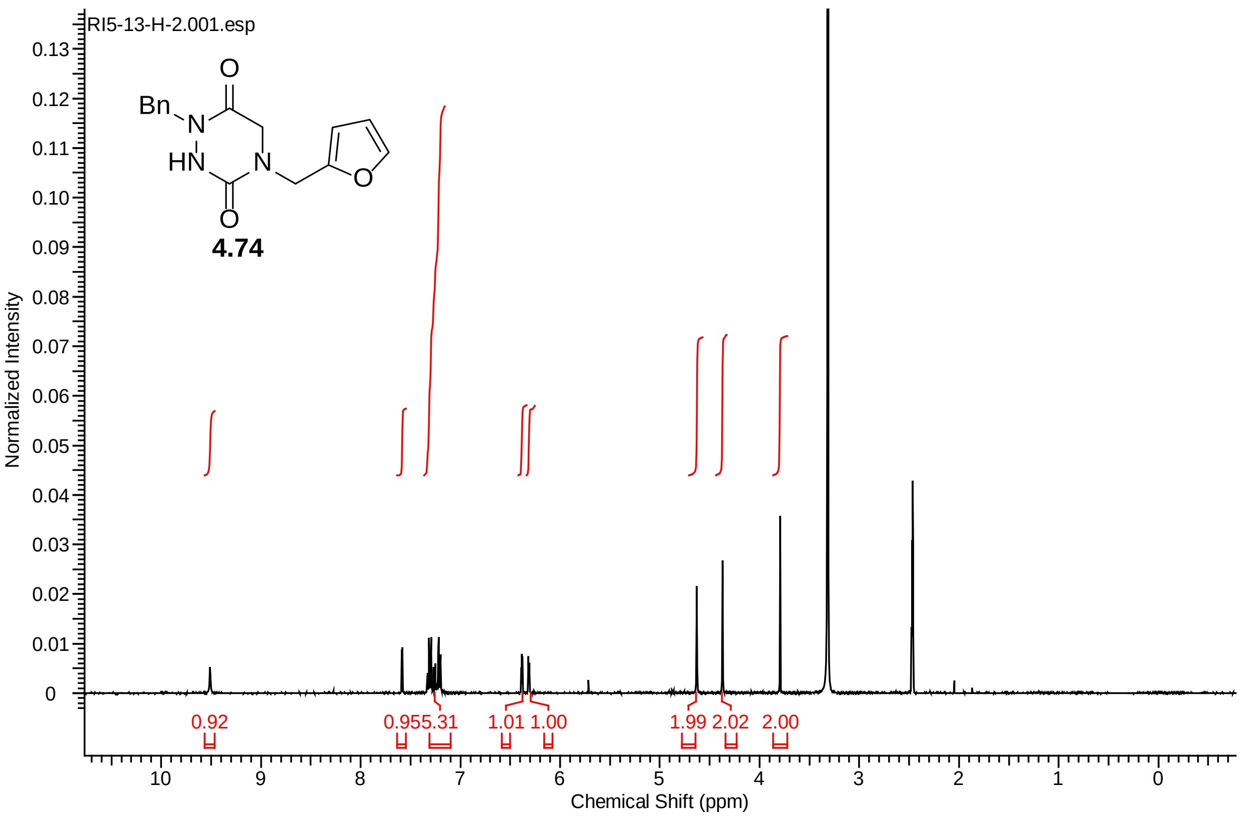
RI4-172-H.001.esp
Bn
N
HN
N
O
O
O
N
H
O
0.99
5.04
0.82
2.00
1.97
4.10
9.33
Normalized Intensity
2.0
1.5
1.0
0.5
0
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

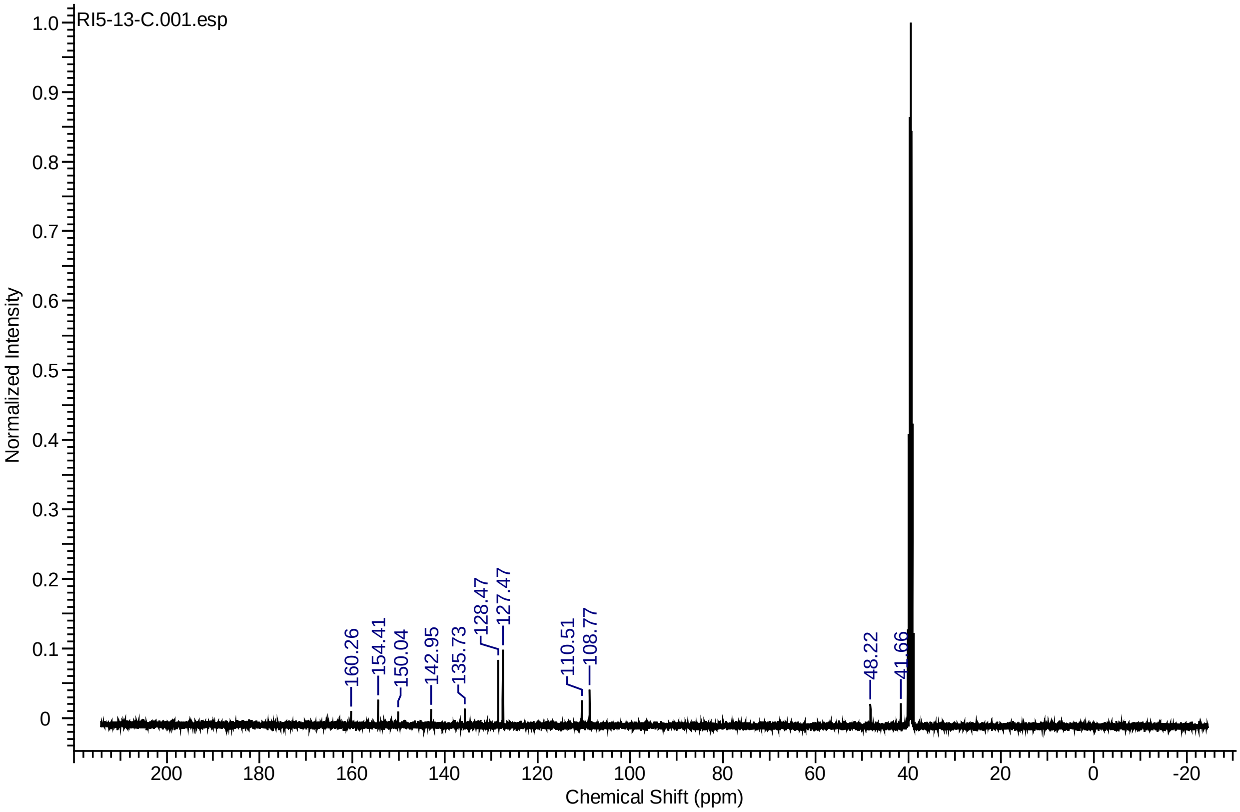


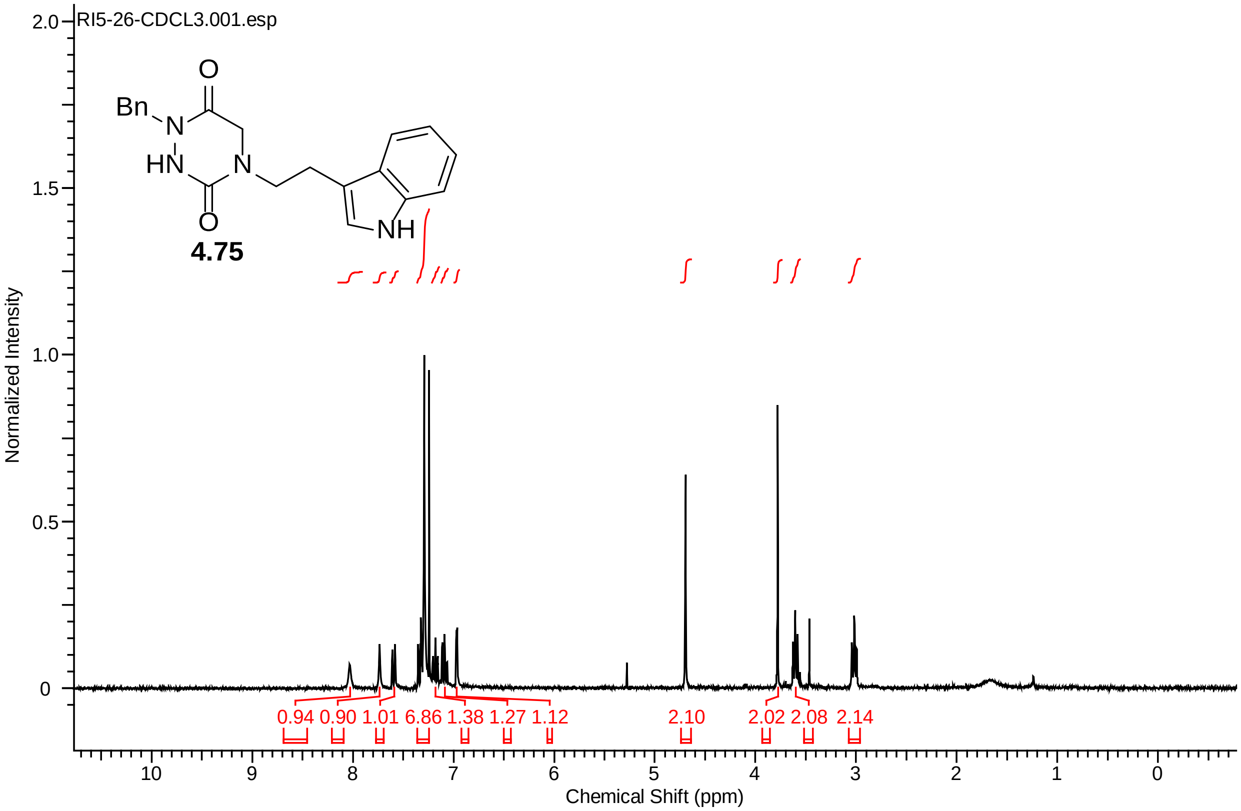
RI4-172-C.001.esp
160.06
155.40
133.72
129.02
128.47
49.88
49.61
46.56
38.48
28.34
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

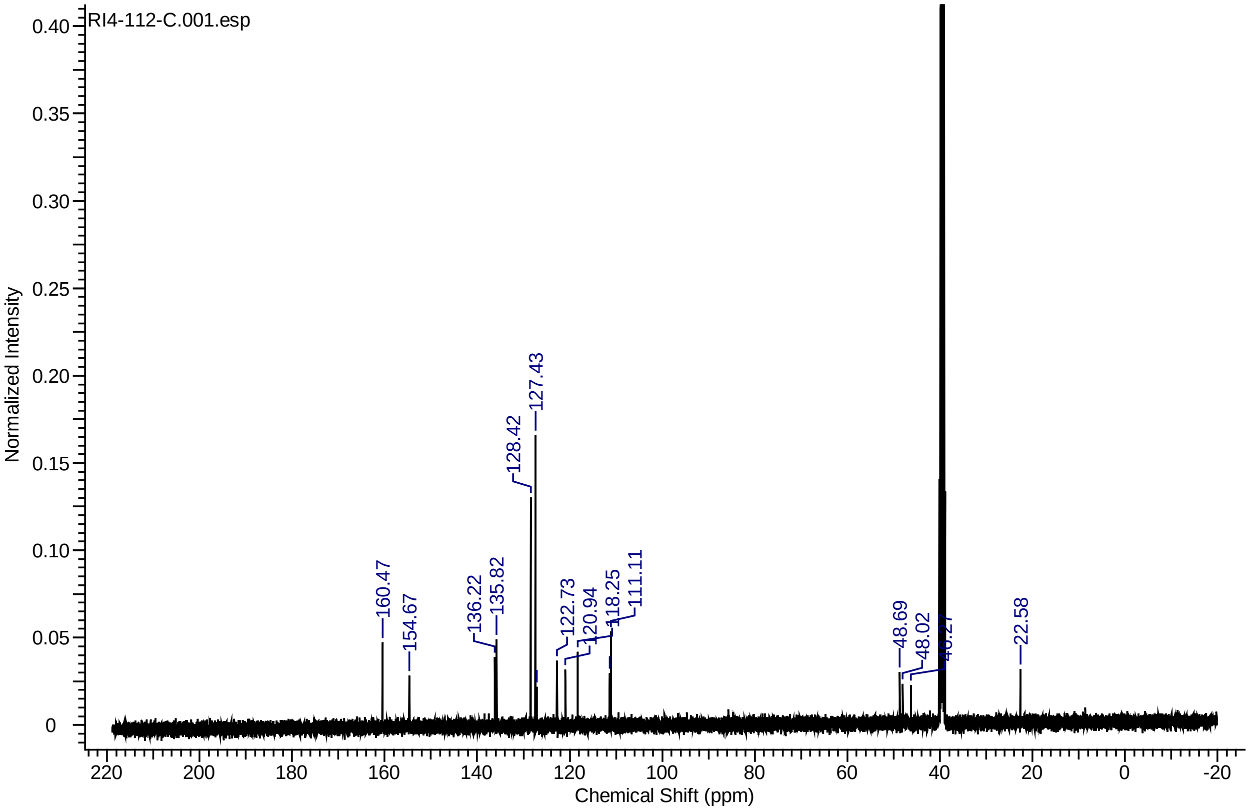

RI5-15-H.001.esp
Bn
N
HN
N
N
O
O
4.73
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.94
0.93
0.99
5.94
1.01
2.00
2.01
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

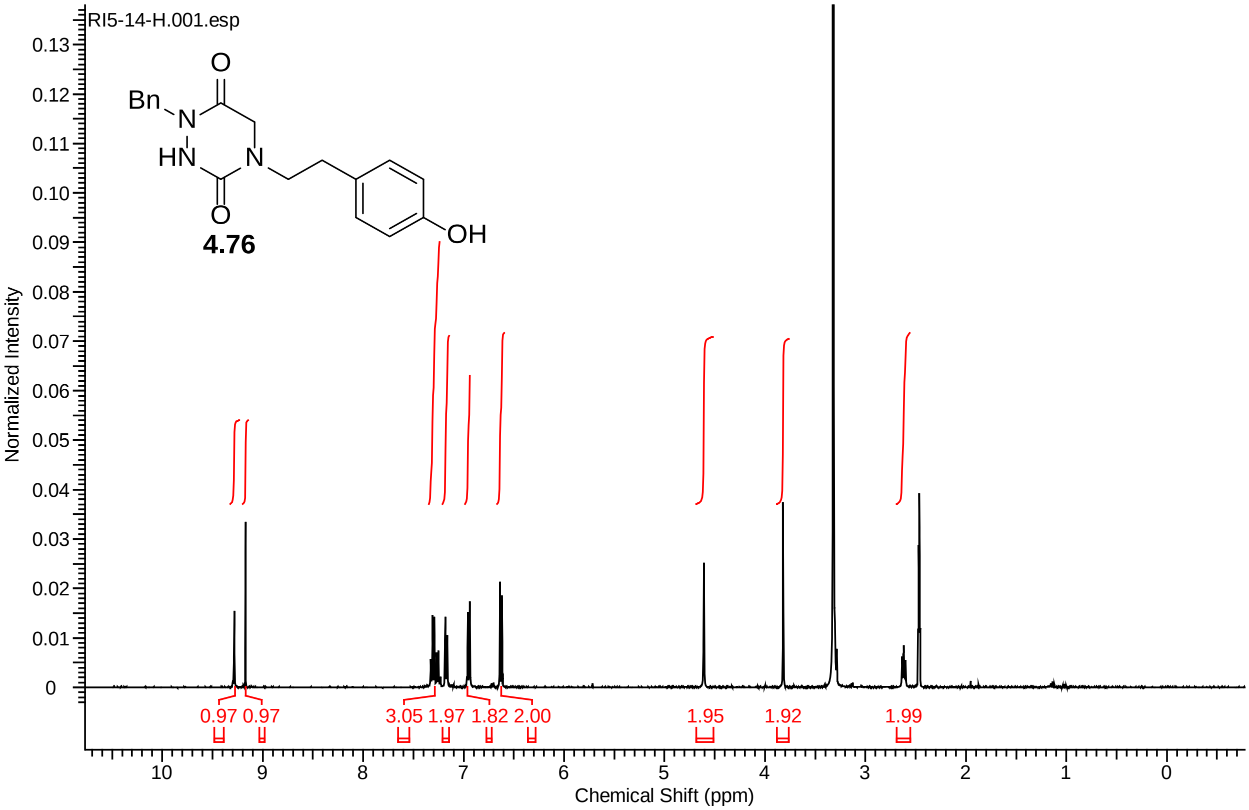

RI5-15-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.35
156.66
154.77
149.12
136.83
135.80
128.45
127.57
122.37
121.48
50.46
49.42
48.21
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

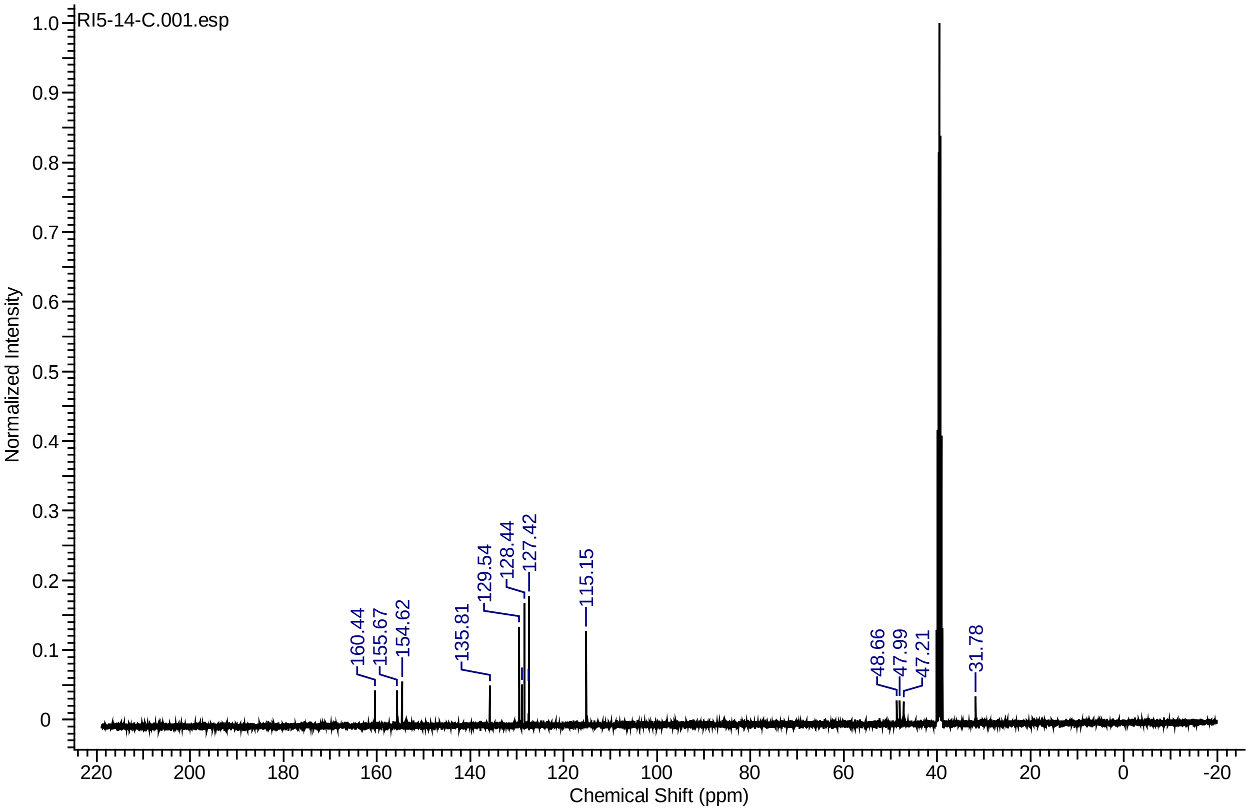

RI5-13-H-2.001.esp
Bn
N
HN
N
O
O
O
4.74
0.92
0.95
5.31
1.01
1.00
1.99
2.02
2.00
Normalized Intensity
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

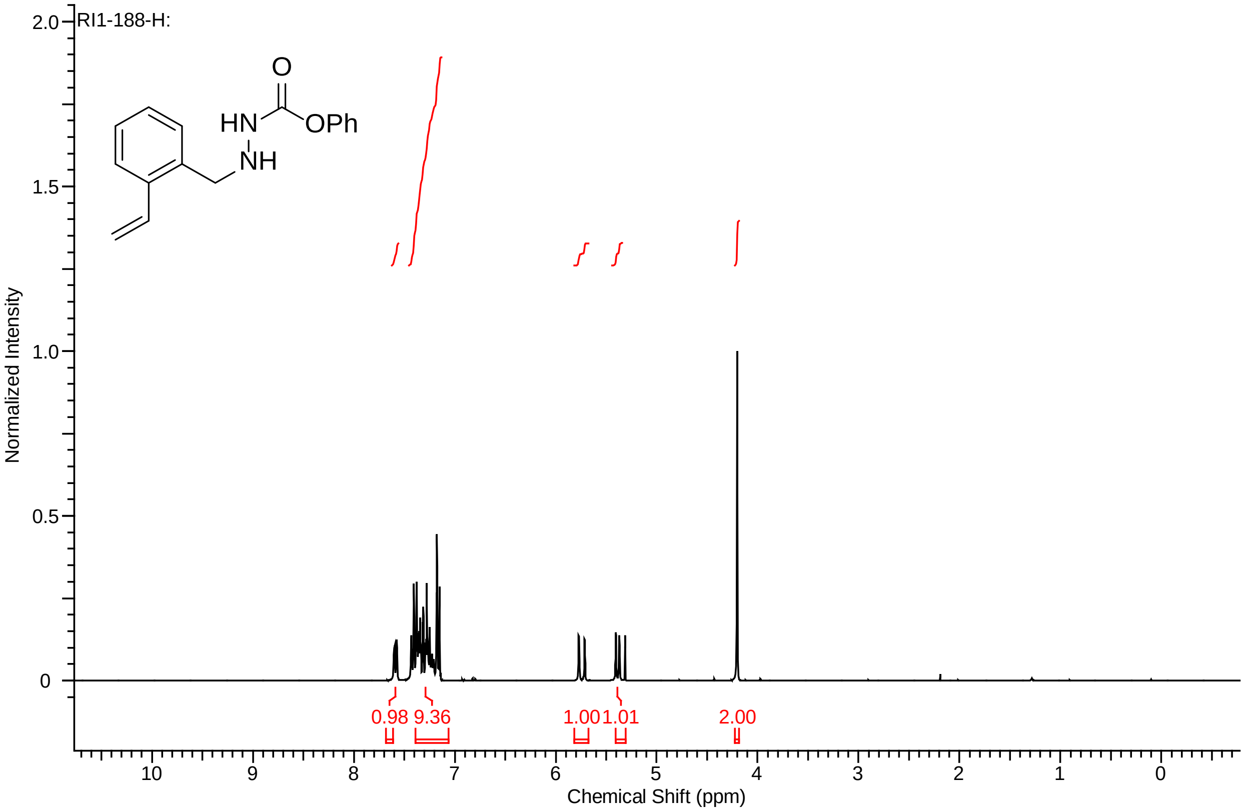

RI5-13-C.001.esp
160.26
154.41
150.04
142.95
135.73
128.47
127.47
110.51
108.77
48.22
41.66
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

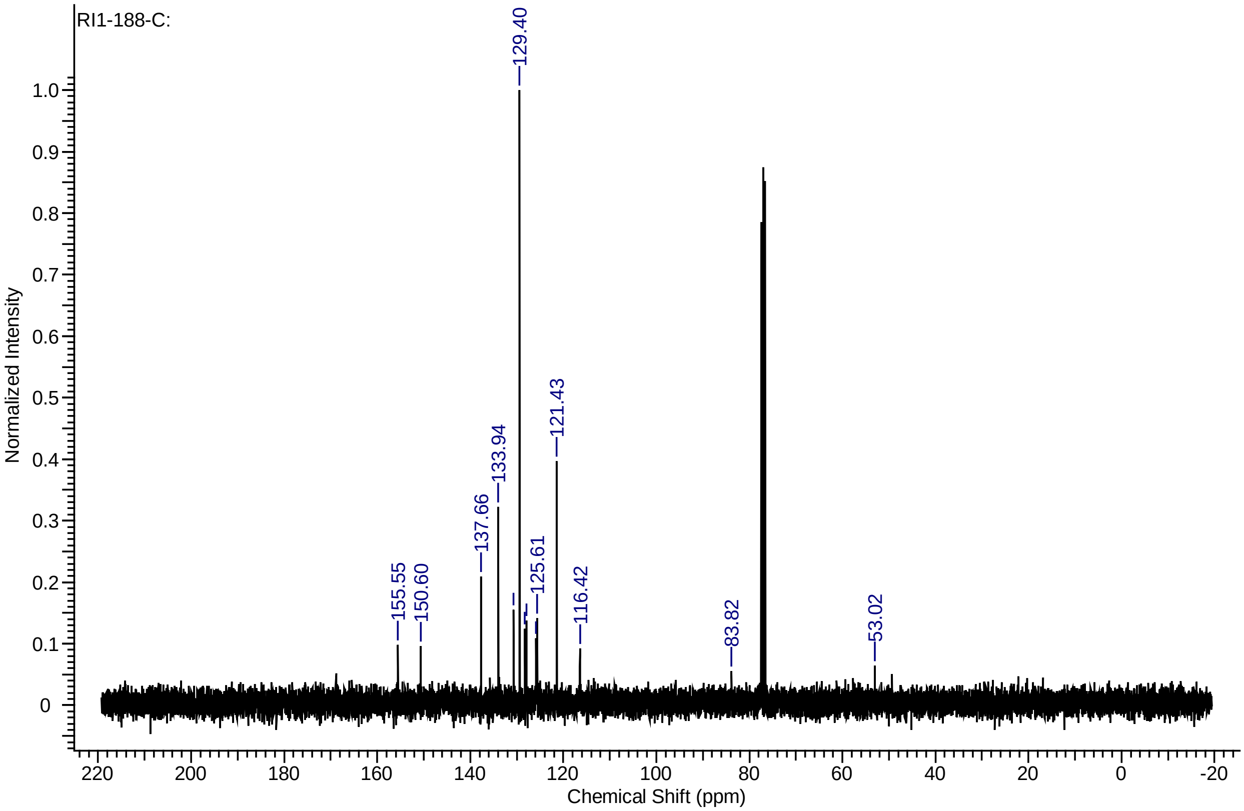

RI5-26-CDCL3.001.esp
Bn
N
HN
N
O
O
NH
4.75
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.94
0.90
1.01
6.86
1.38
1.27
1.12
2.10
2.02
2.08
2.14
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

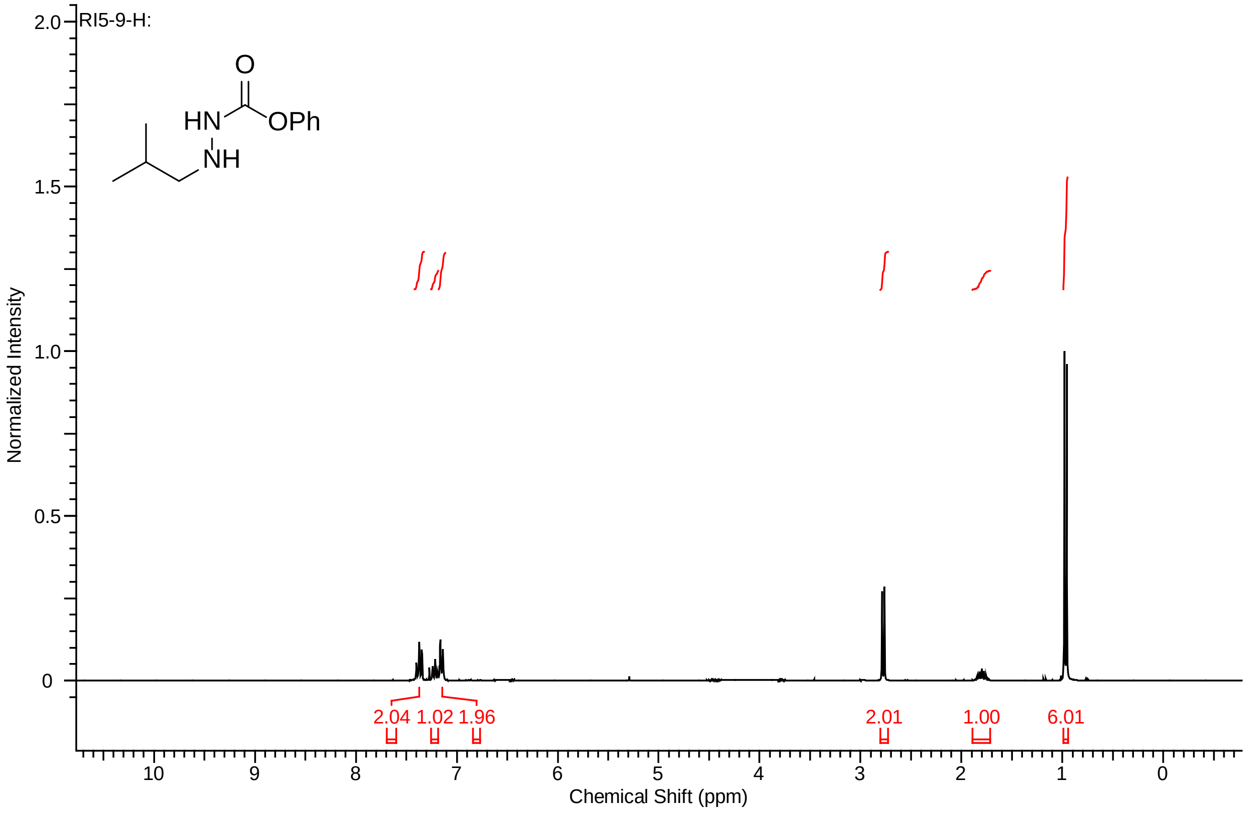

RI4-112-C.001.esp
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
160.47
154.67
136.22
135.82
128.42
127.43
122.73
120.94
118.25
111.11
48.69
48.02
46.27
22.58
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

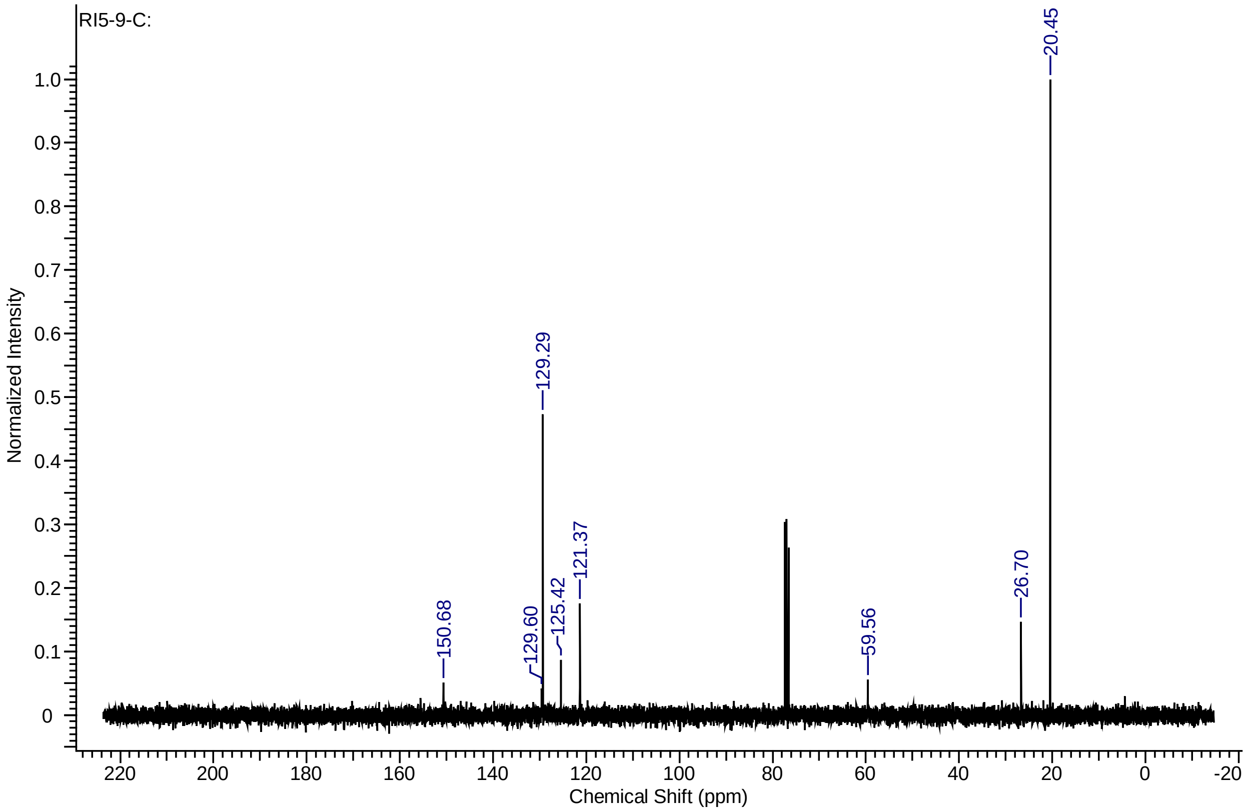

RI5-14-H.001.esp
4.76
Bn
N
HN
N
O
O
OH
Normalized Intensity
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0.97 0.97
3.05 1.97 1.82 2.00
1.95
1.92
1.99
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

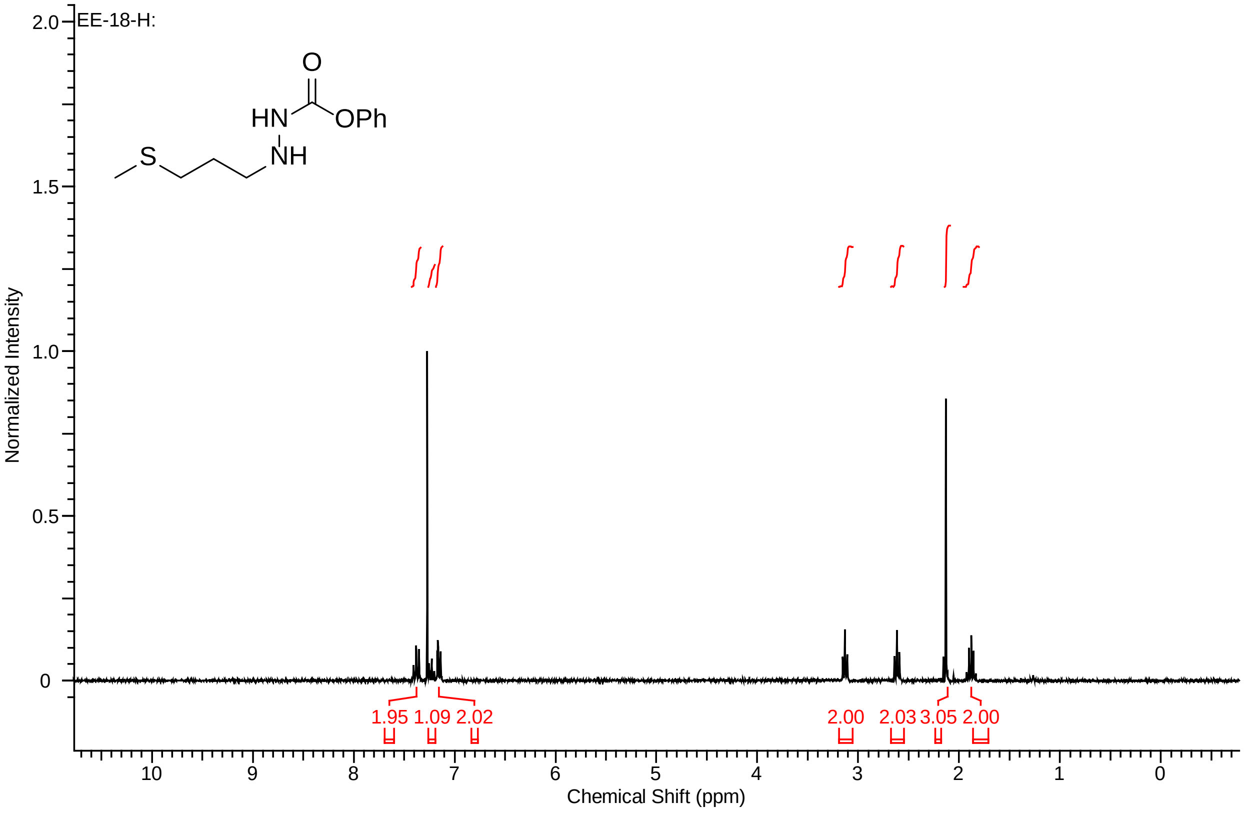

RI5-14-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.44
155.67
154.62
135.81
129.54
128.44
127.42
115.15
48.66
47.99
47.21
31.78
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

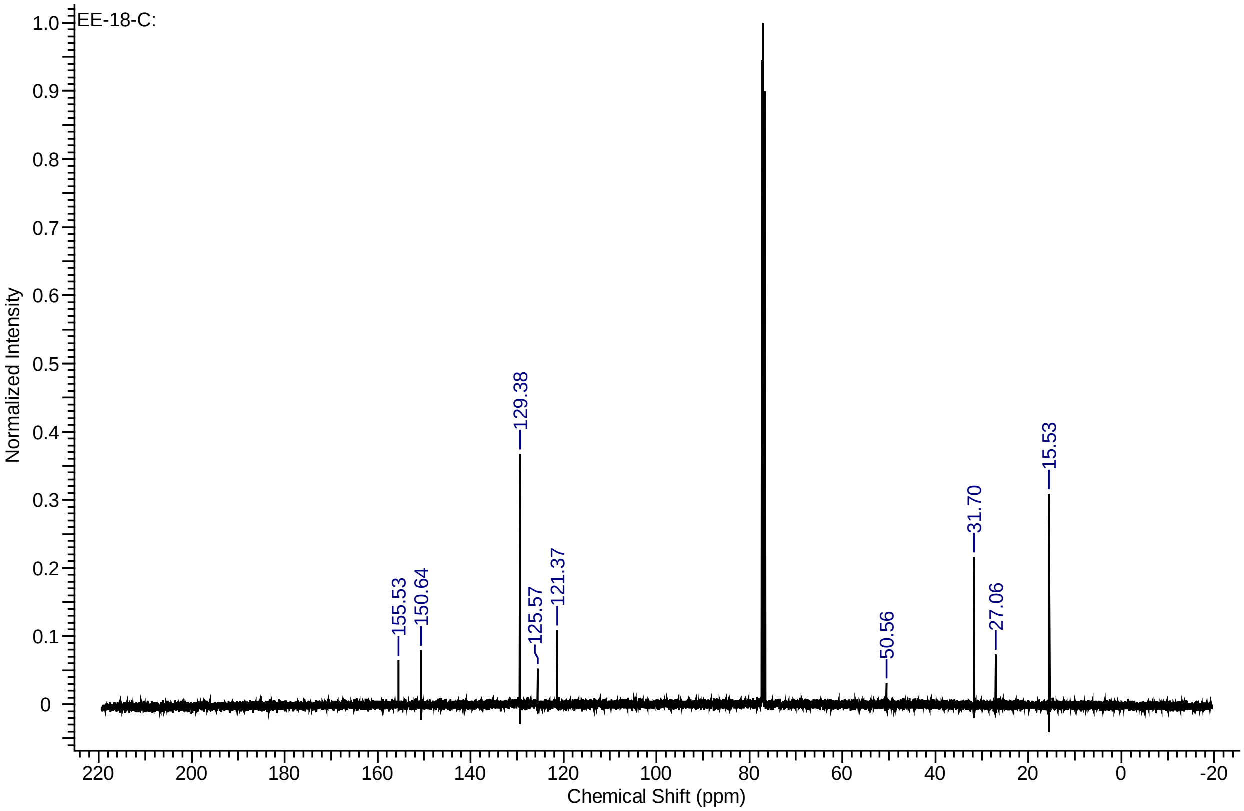

RI1-188-H:
O
HN
OPh
NH
2.0
1.5
1.0
0.5
0
Normalized Intensity
0.98
9.36
1.00
1.01
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

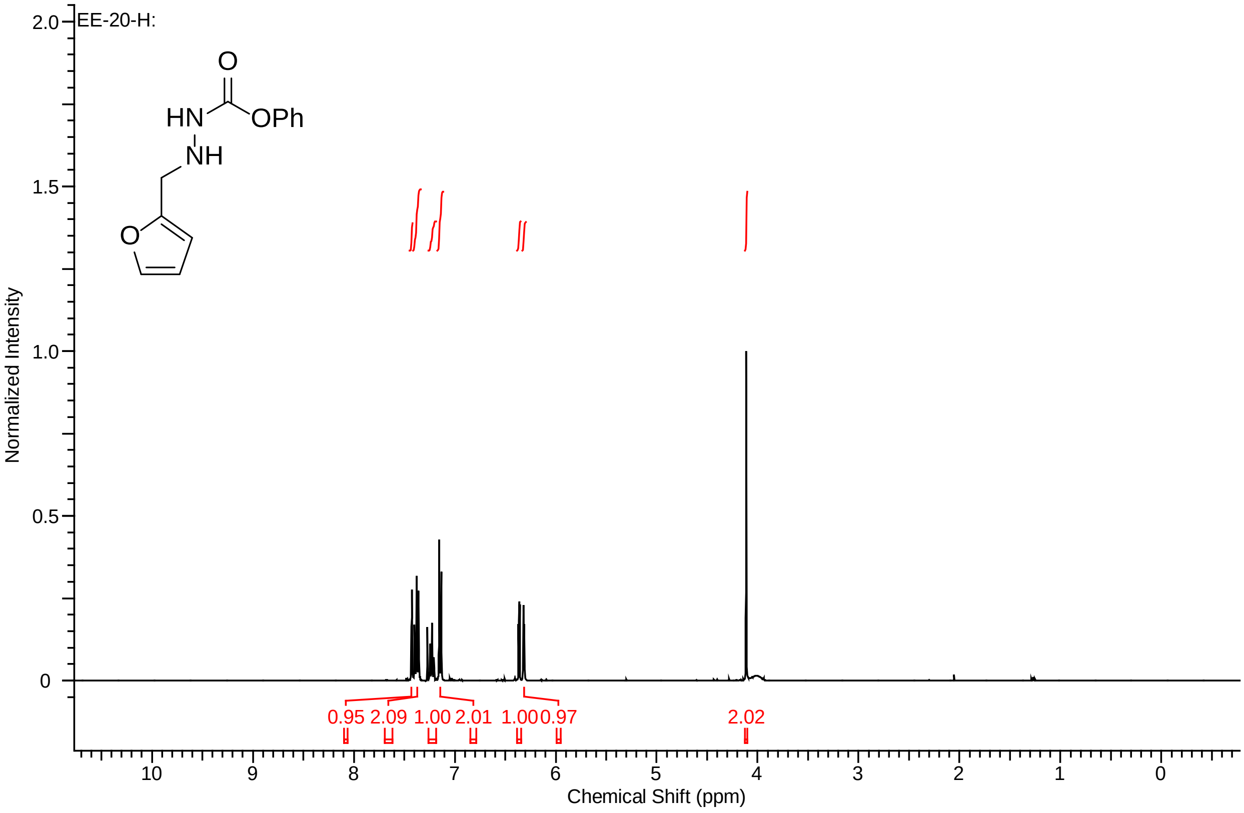

RI1-188-C:
129.40
121.43
133.94
137.66
125.61
155.55
150.60
116.42
83.82
53.02
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Normalized Intensity
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

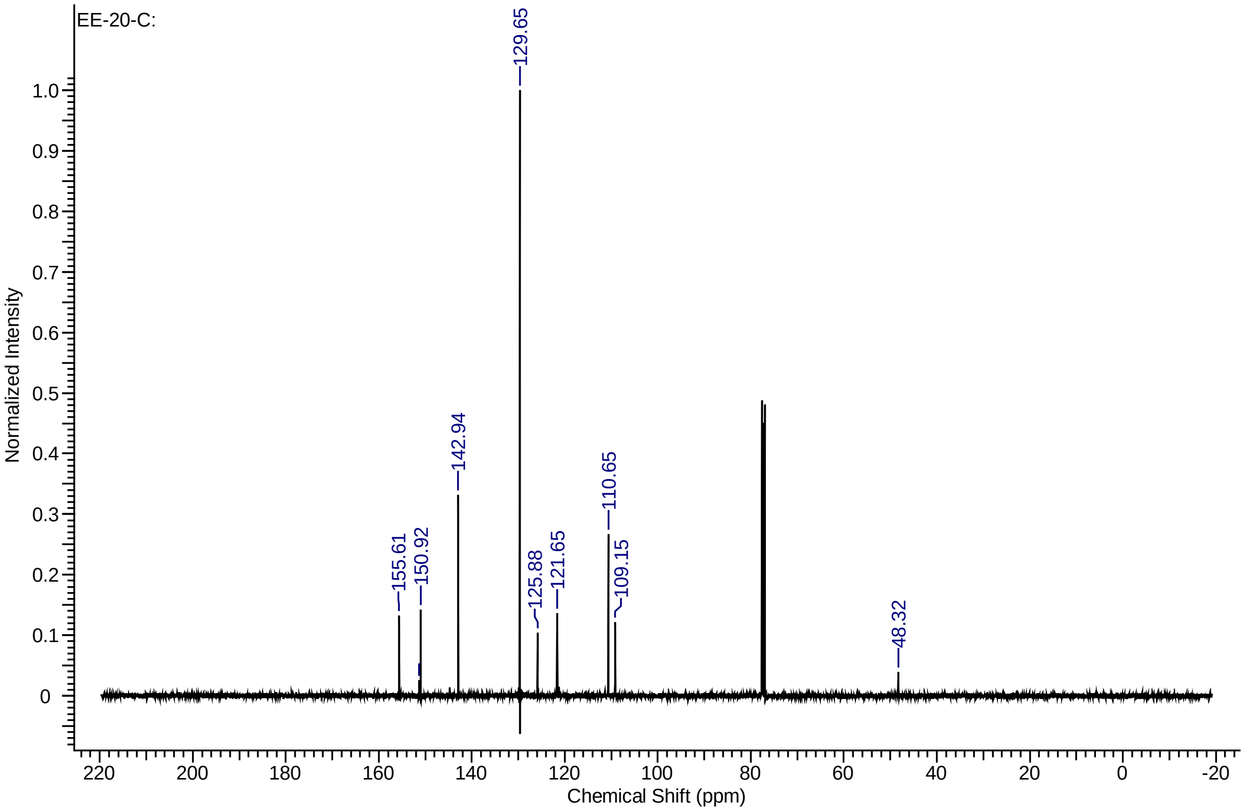

RI5-9-H:
O
HN
OPh
NH
2.0
1.5
1.0
0.5
0
Normalized Intensity
2.04
1.02
1.96
2.01
1.00
6.01
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

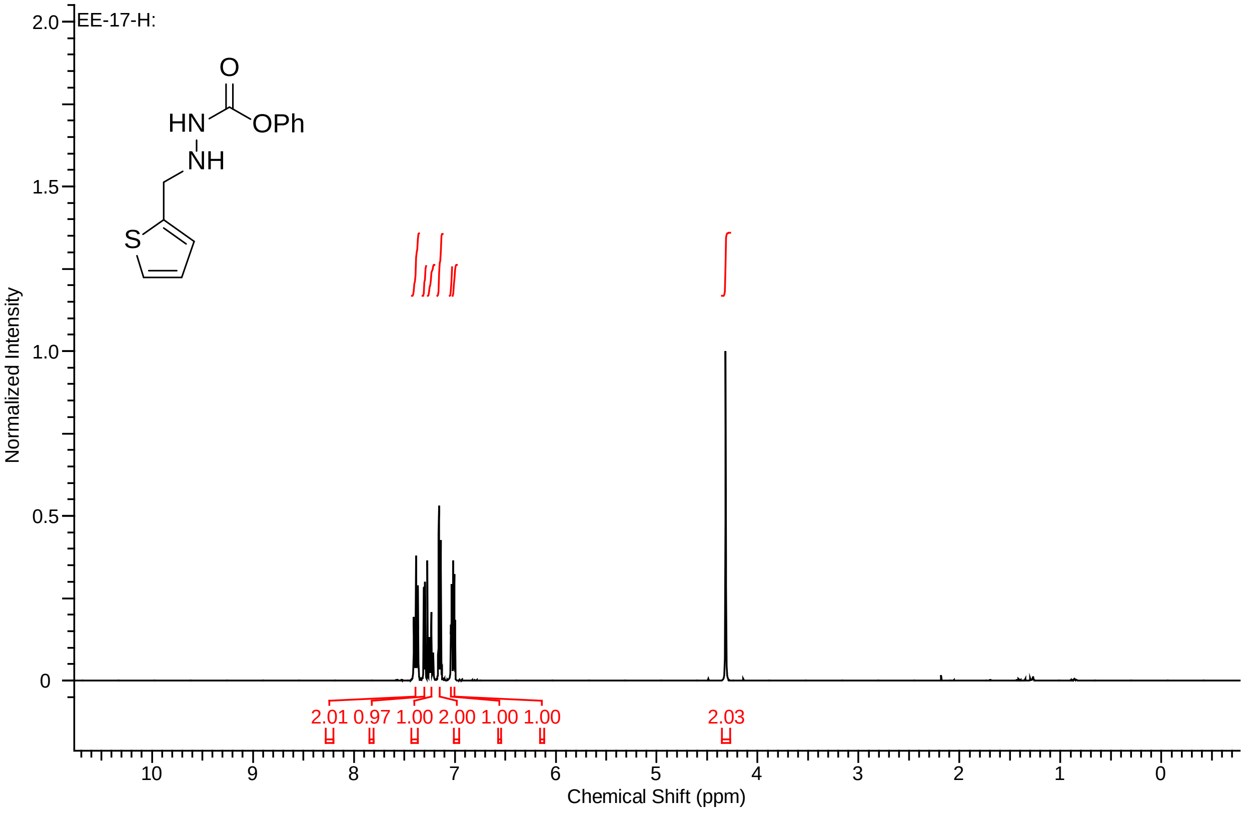

RI5-9-C:
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Normalized Intensity
150.68
129.60
129.29
125.42
121.37
59.56
26.70
20.45
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

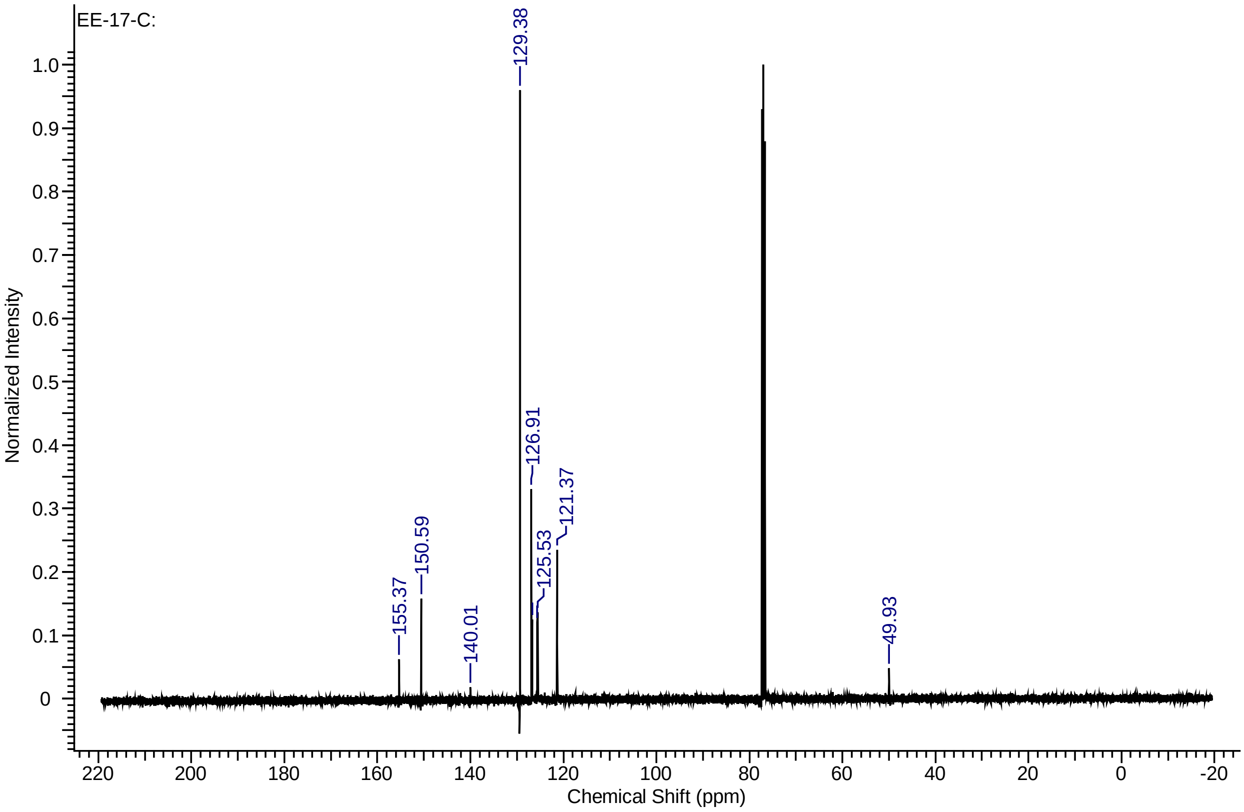

EE-18-H:
O
HN
OPh
S
NH
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.95
1.09
2.02
2.00
2.03
3.05
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

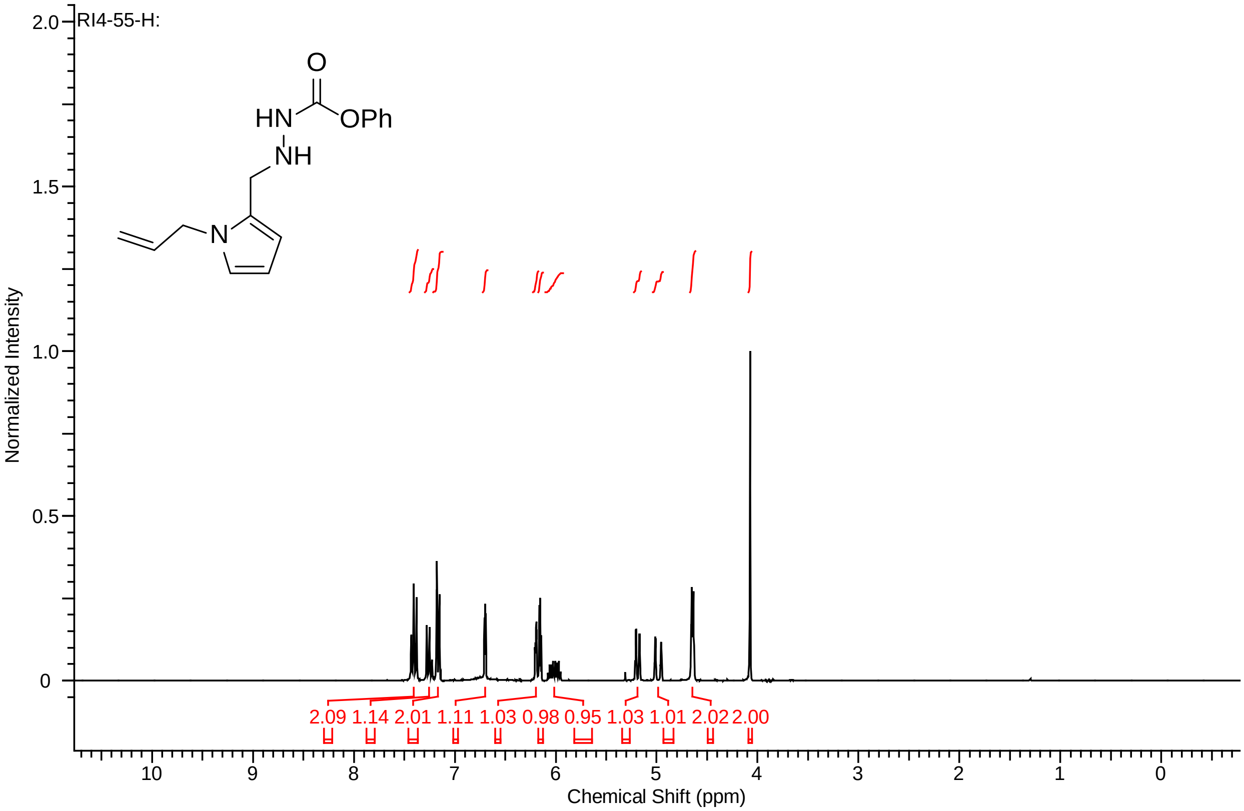

EE-18-C:
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
155.53
150.64
129.38
125.57
121.37
50.56
31.70
27.06
15.53
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

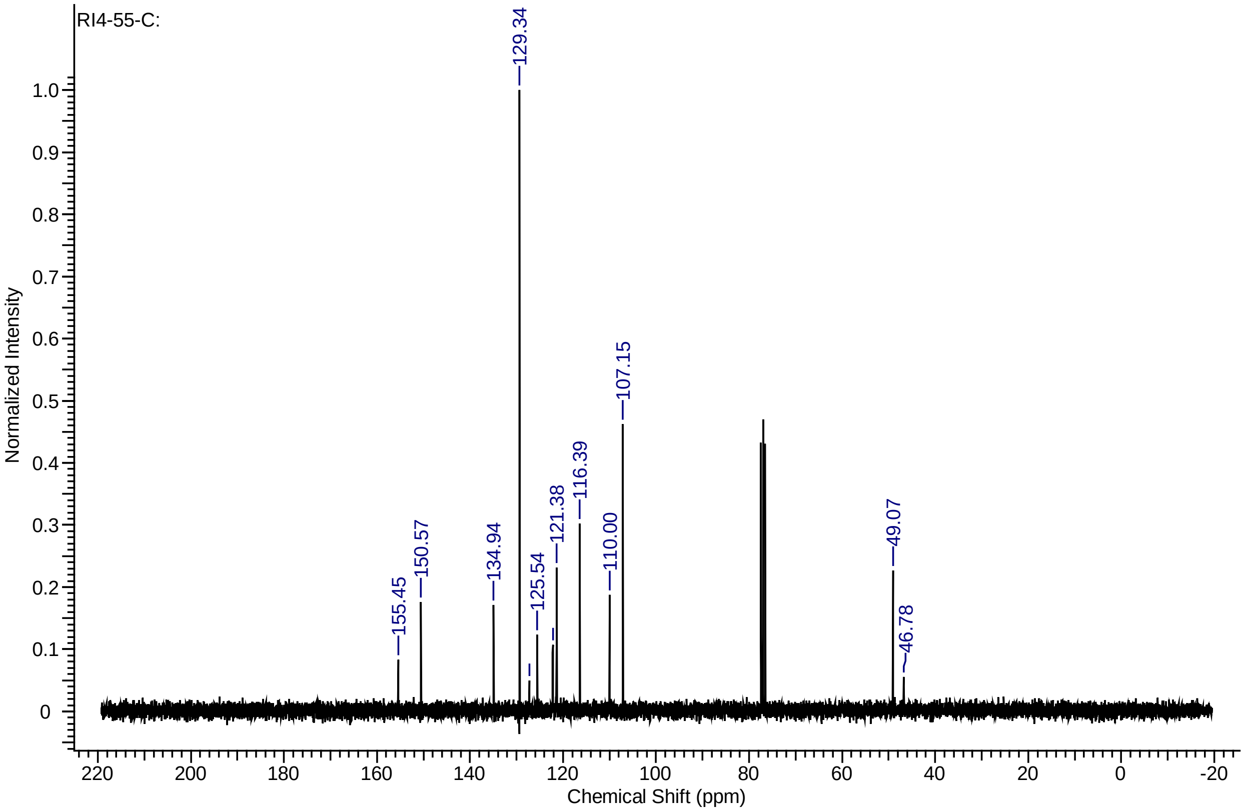

EE-20-H:
O
HN
OPh
NH
O
2.0
1.5
1.0
0.5
0
Normalized Intensity
0.95
2.09
1.00
2.01
1.00
0.97
2.02
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

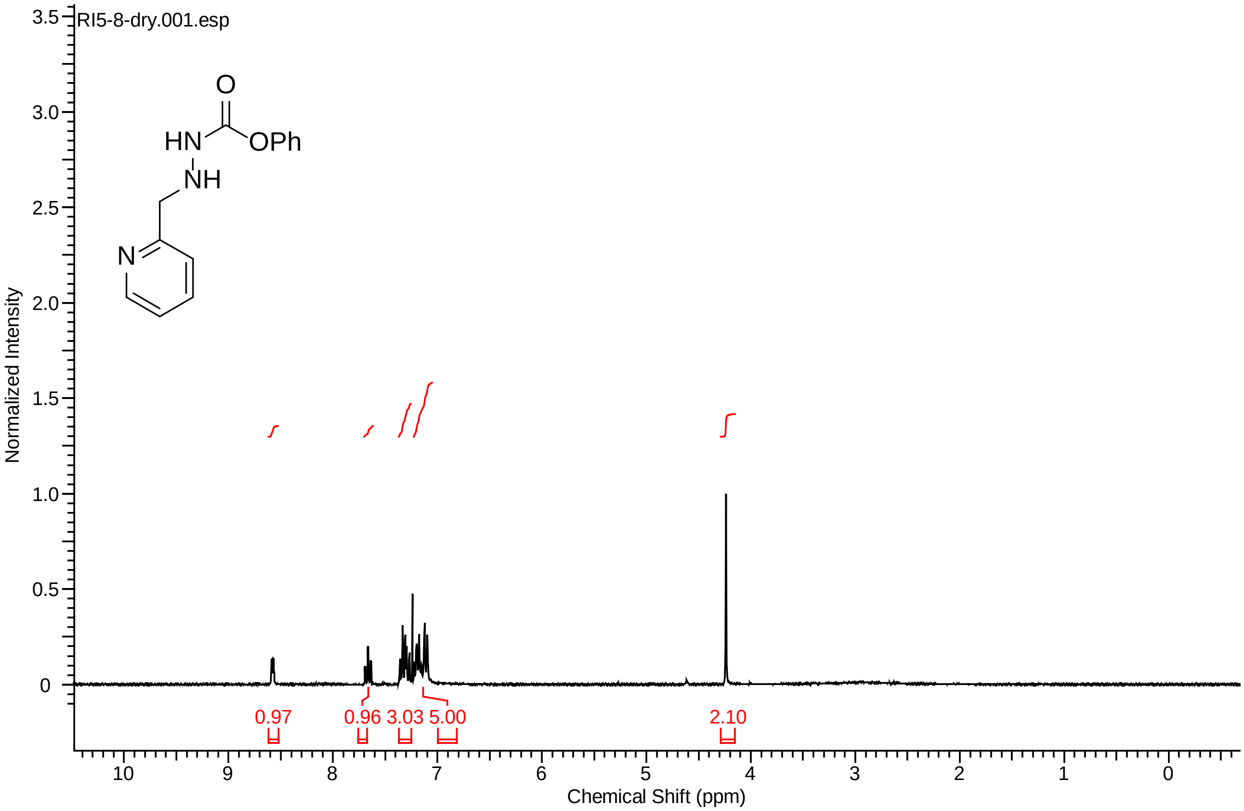

EE-20-C:
129.65
142.94
110.65
155.61
150.92
125.88
121.65
109.15
48.32
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Normalized Intensity
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

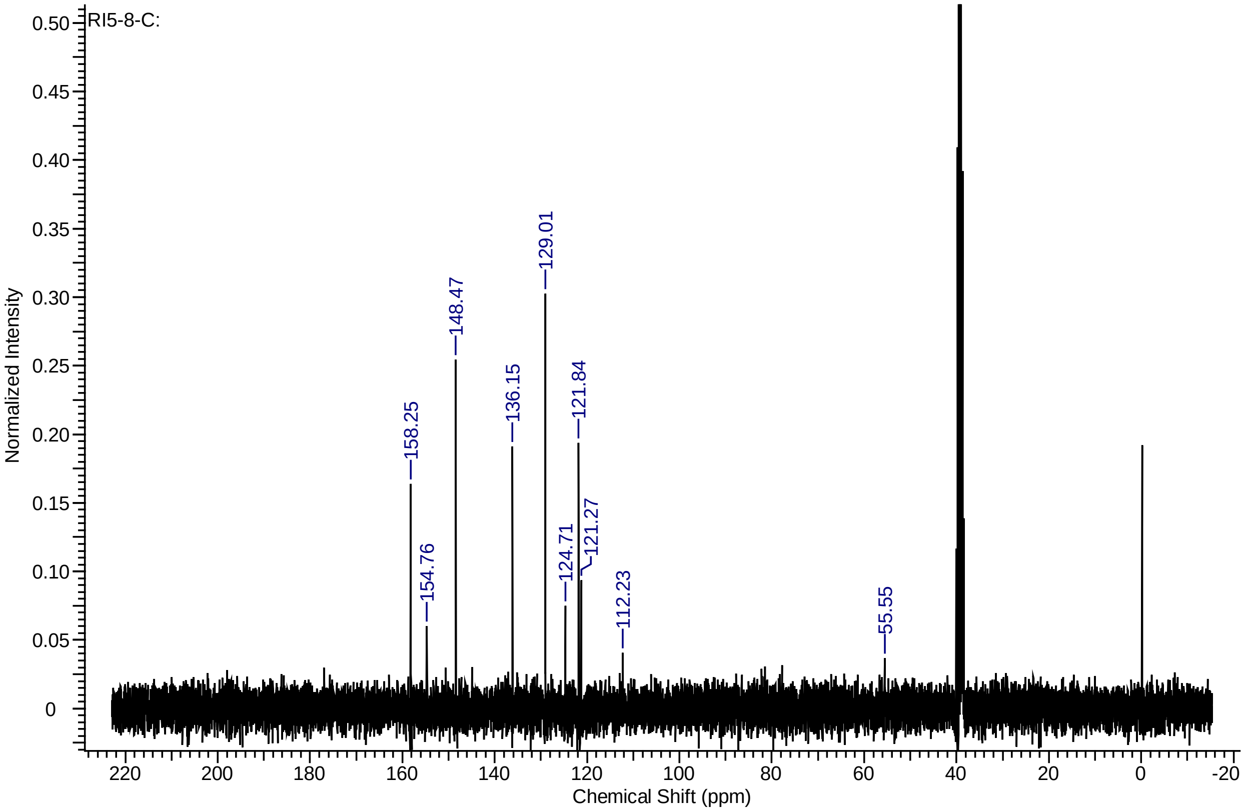

EE-17-H:
O
HN
OPh
NH
S
Normalized Intensity
2.0
1.5
1.0
0.5
0
2.01 0.97 1.00 2.00 1.00 1.00
2.03
10 9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)

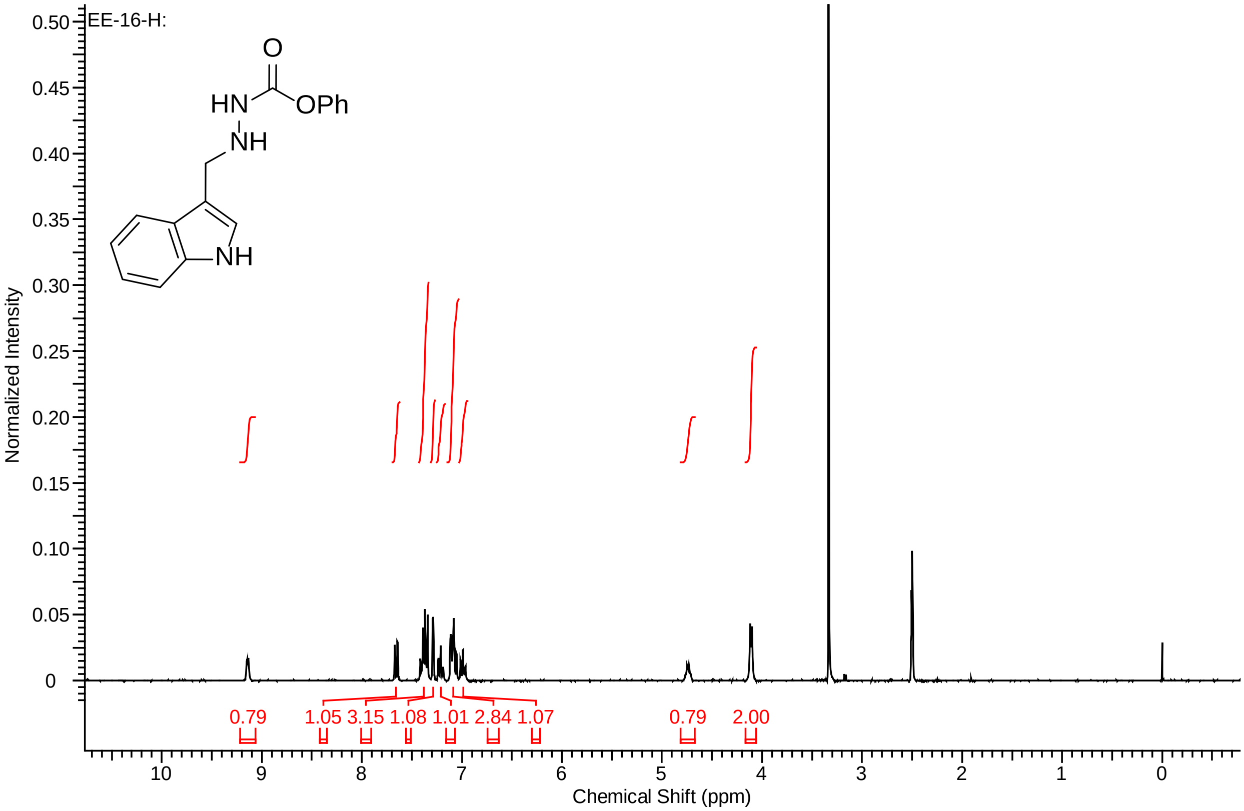

EE-17-C:
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
155.37
150.59
140.01
129.38
126.91
125.53
121.37
49.93
220 200 180 160 140 120 100 80 60 40 20 0 -20
Chemical Shift (ppm)

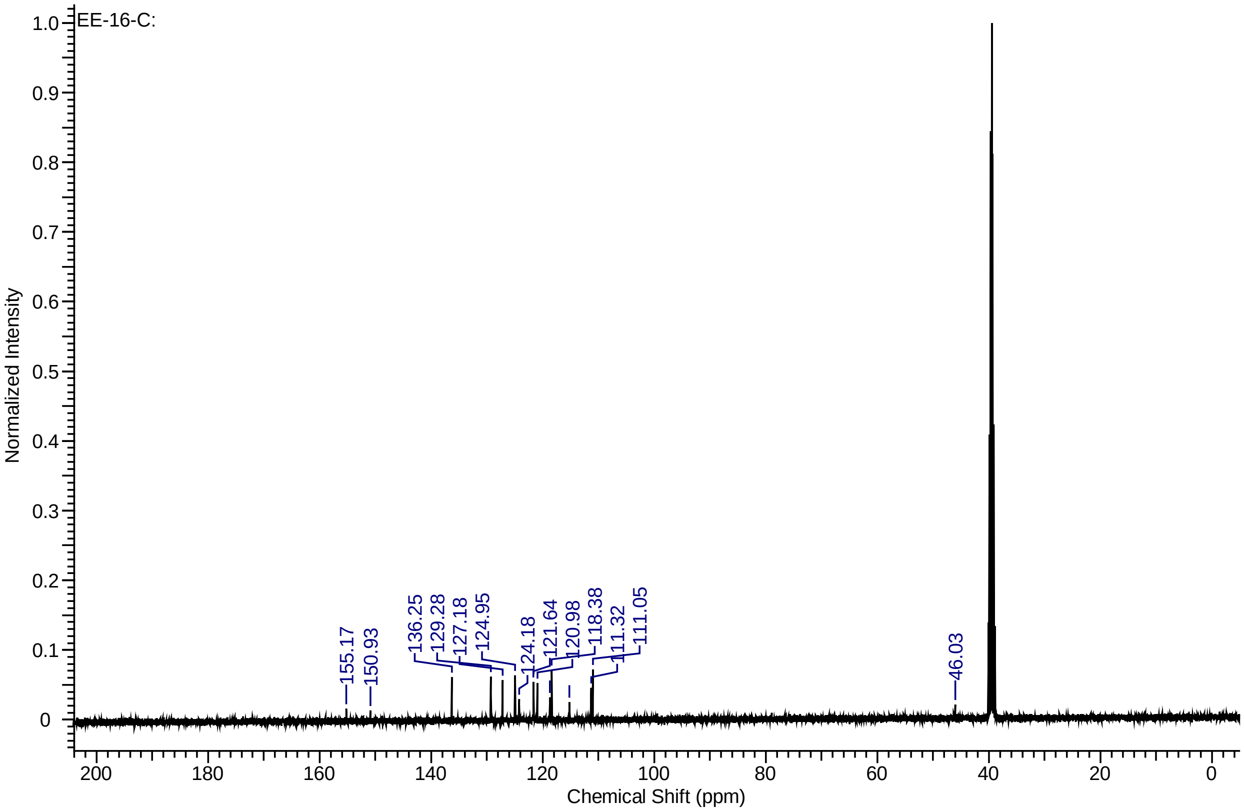

RI4-55-H:
HN
O
OPh
NH
N
2.09
1.14
2.01
1.11
1.03
0.98
0.95
1.03
1.01
2.02
2.00
Normalized Intensity
Chemical Shift (ppm)

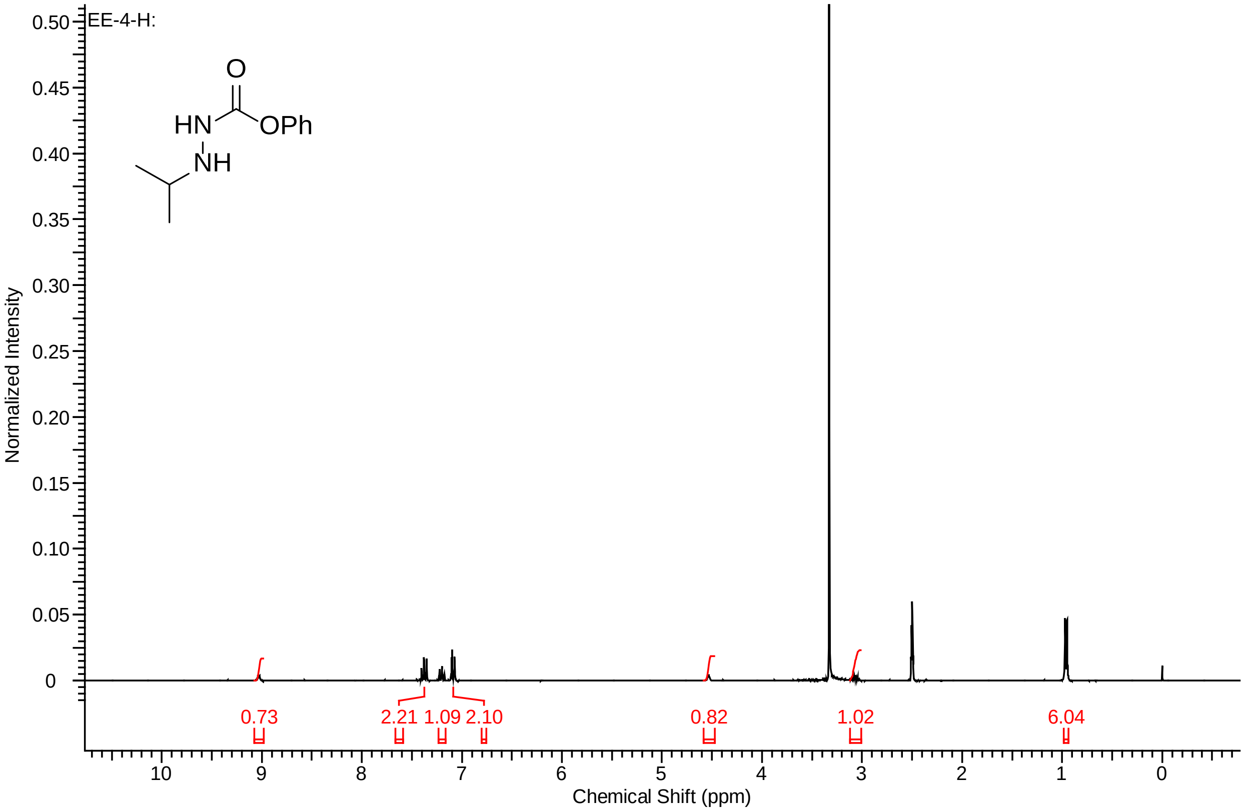

RI4-55-C:
155.45
150.57
134.94
129.34
125.54
121.38
116.39
110.00
107.15
49.07
46.78
Normalized Intensity
Chemical Shift (ppm)

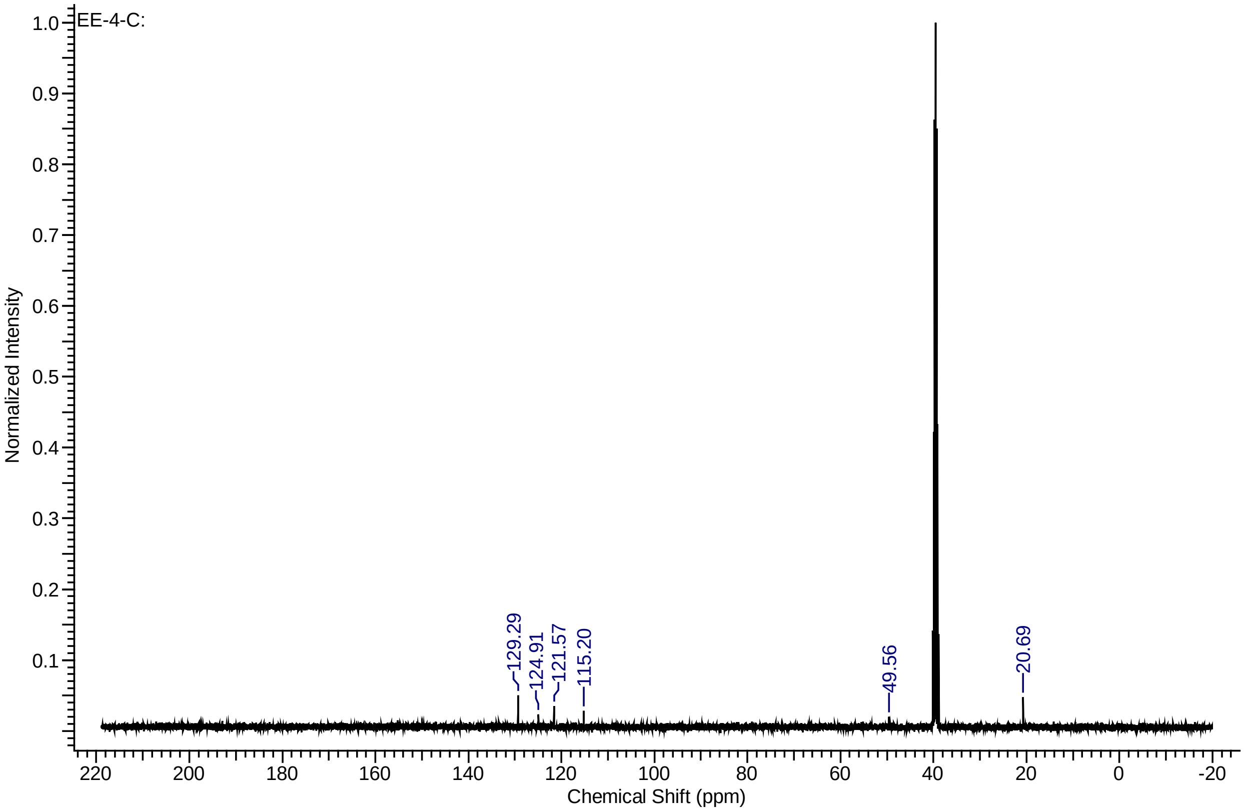

RI5-8-dry.001.esp
HN
NH
O
OPh
N
Normalized Intensity
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
0.97
0.96
3.03
5.00
2.10
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

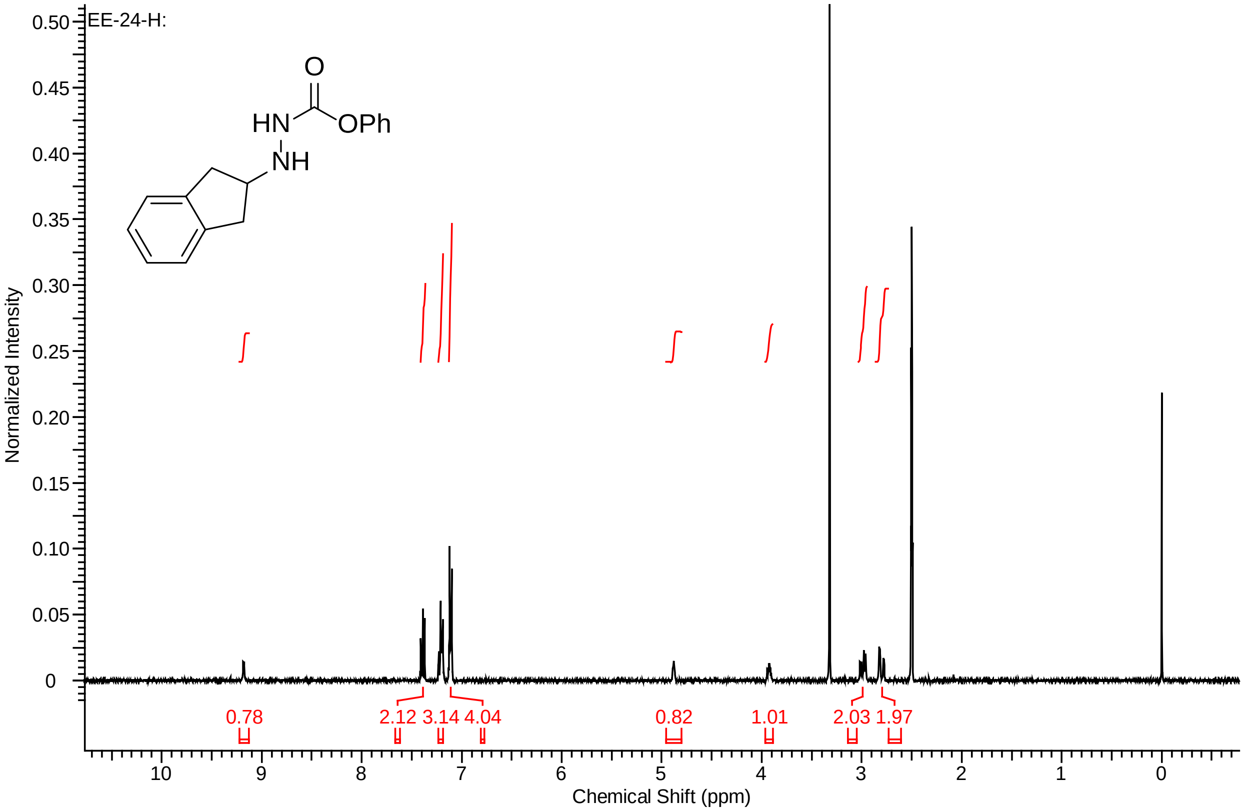

RI5-8-C:
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
158.25
154.76
148.47
136.15
129.01
124.71
121.84
121.27
112.23
55.55
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

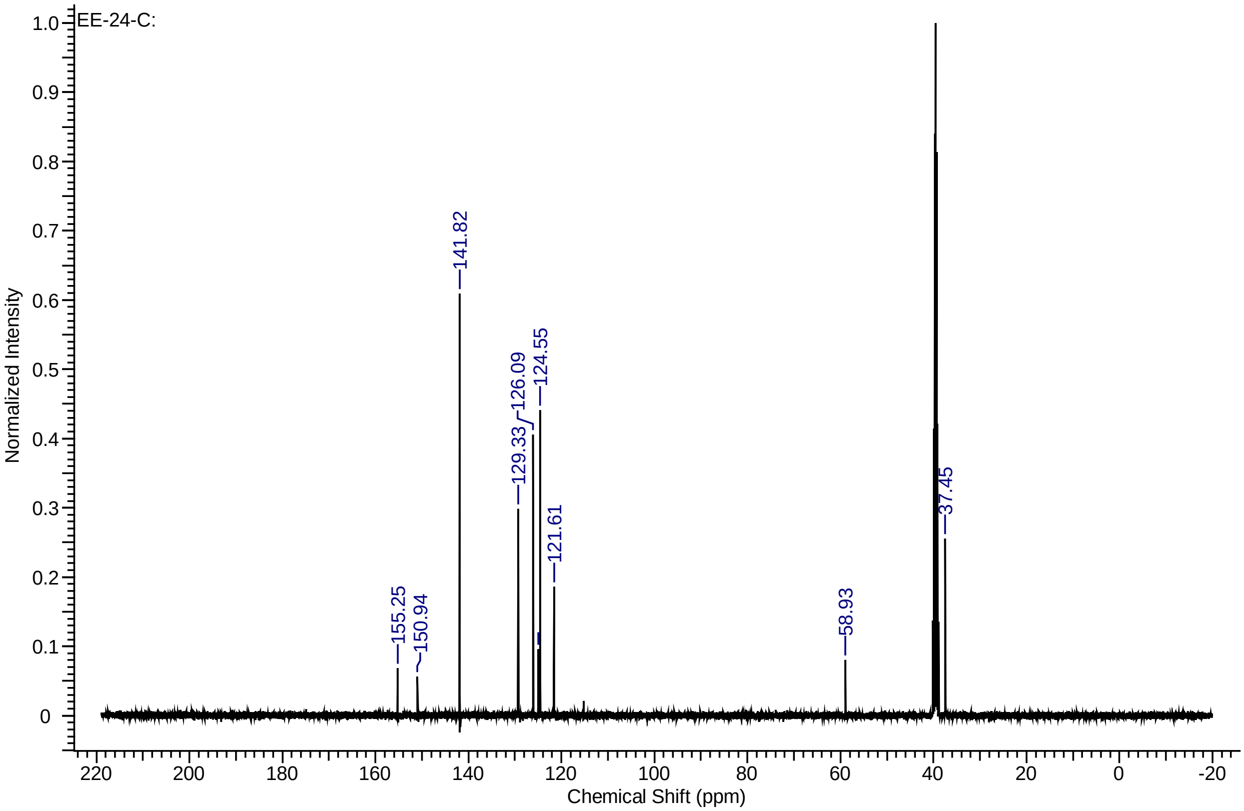

EE-16-H:
O
HN
OPh
NH
NH
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.79
1.05
3.15
1.08
1.01
2.84
1.07
0.79
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

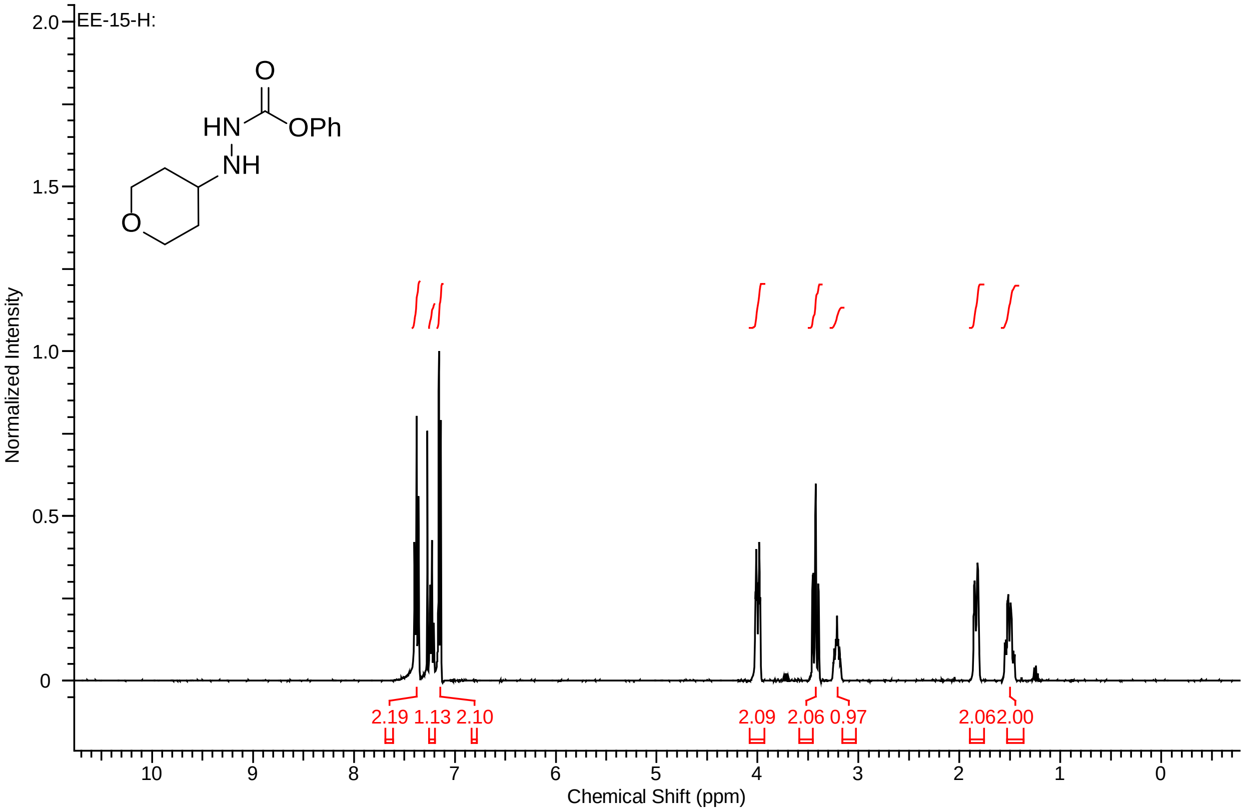

EE-16-C:
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
155.17
150.93
136.25
129.28
127.18
124.95
124.18
121.64
120.98
118.38
111.32
111.05
46.03
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

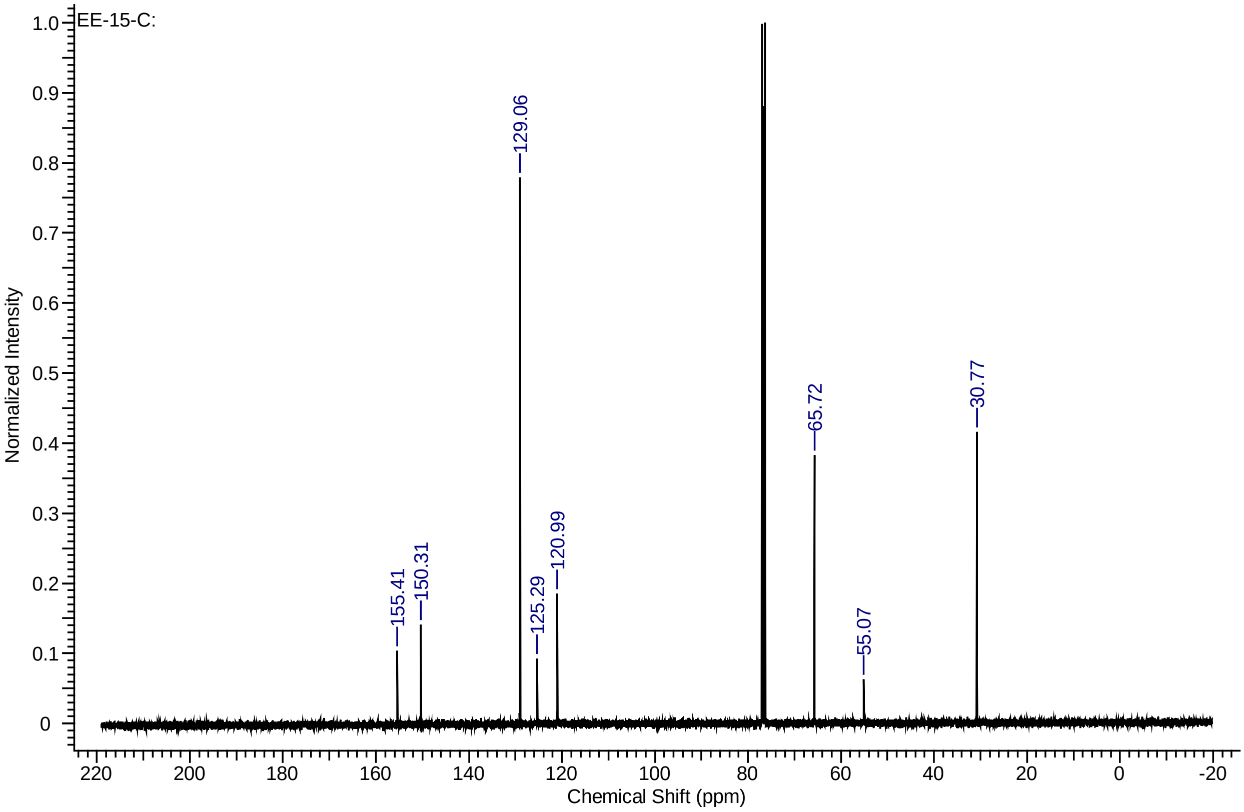

EE-4-H:
O
HN
OPh
NH
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.73
2.21
1.09
2.10
0.82
1.02
6.04
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

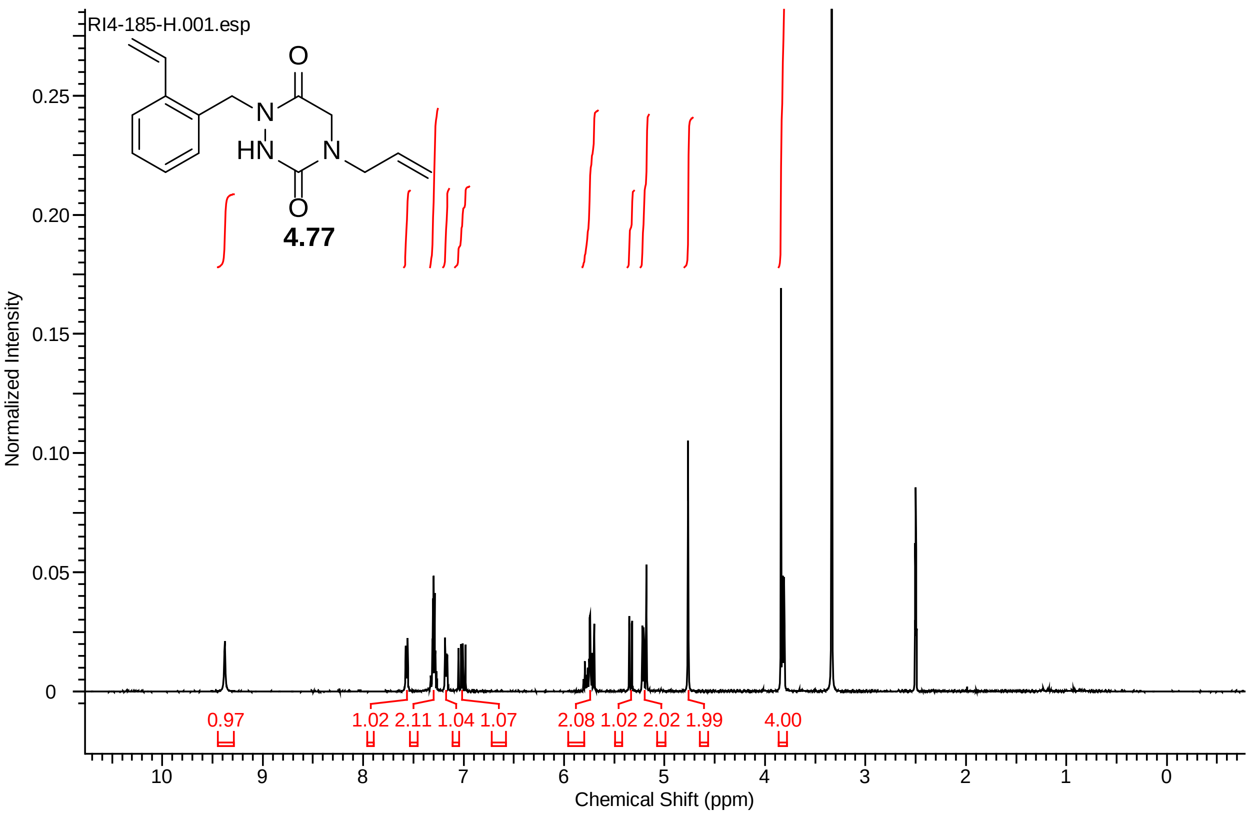

EE-4-C:
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
129.29
124.91
121.57
115.20
49.56
20.69
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

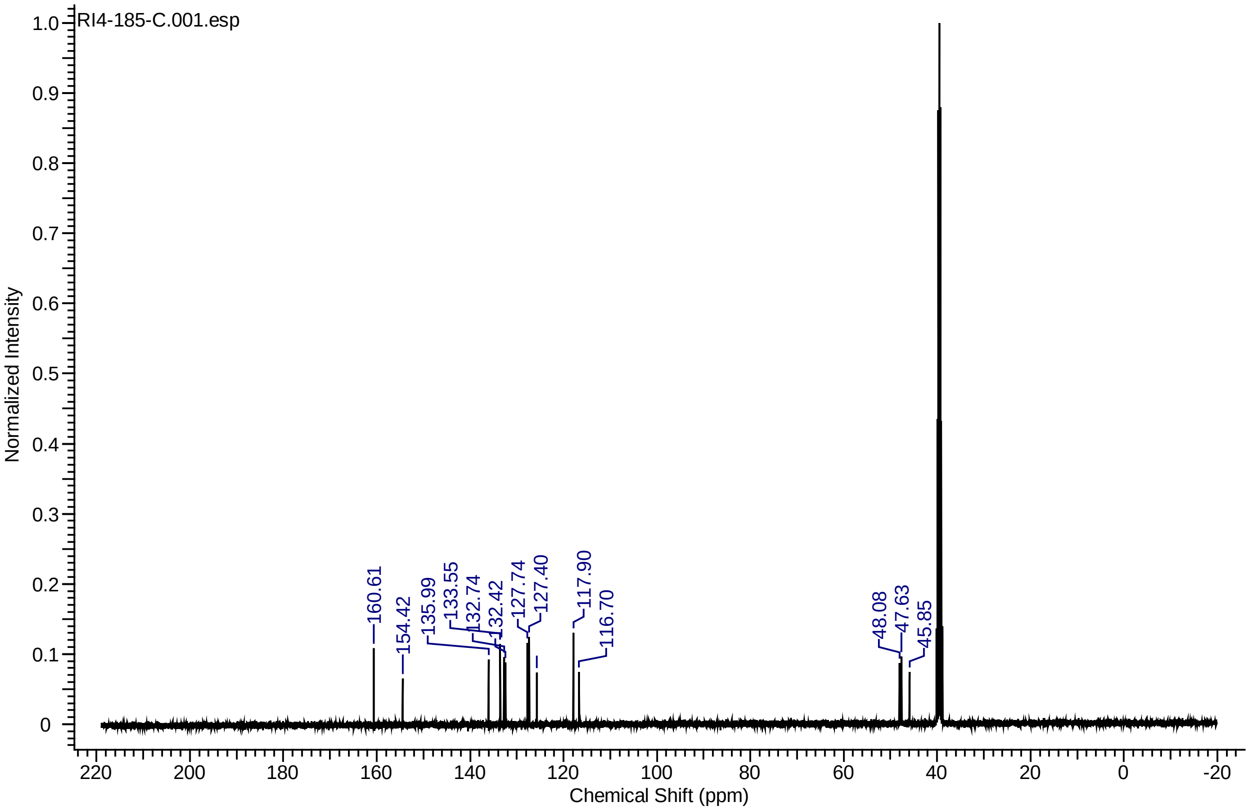

EE-24-H:
O
HN
OPh
NH
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.78
2.12
3.14
4.04
0.82
1.01
2.03
1.97
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

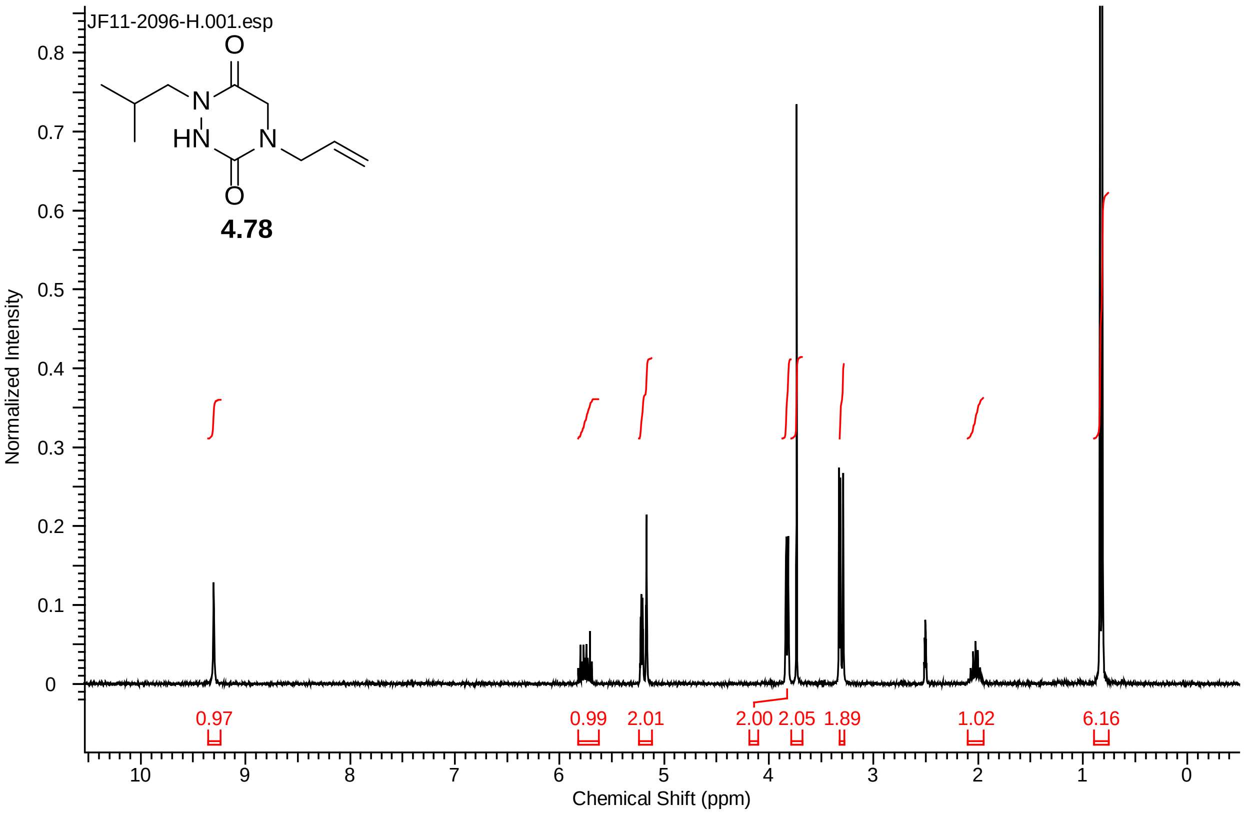

EE-24-C:
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
155.25
150.94
141.82
129.33
126.09
124.55
121.61
58.93
37.45
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

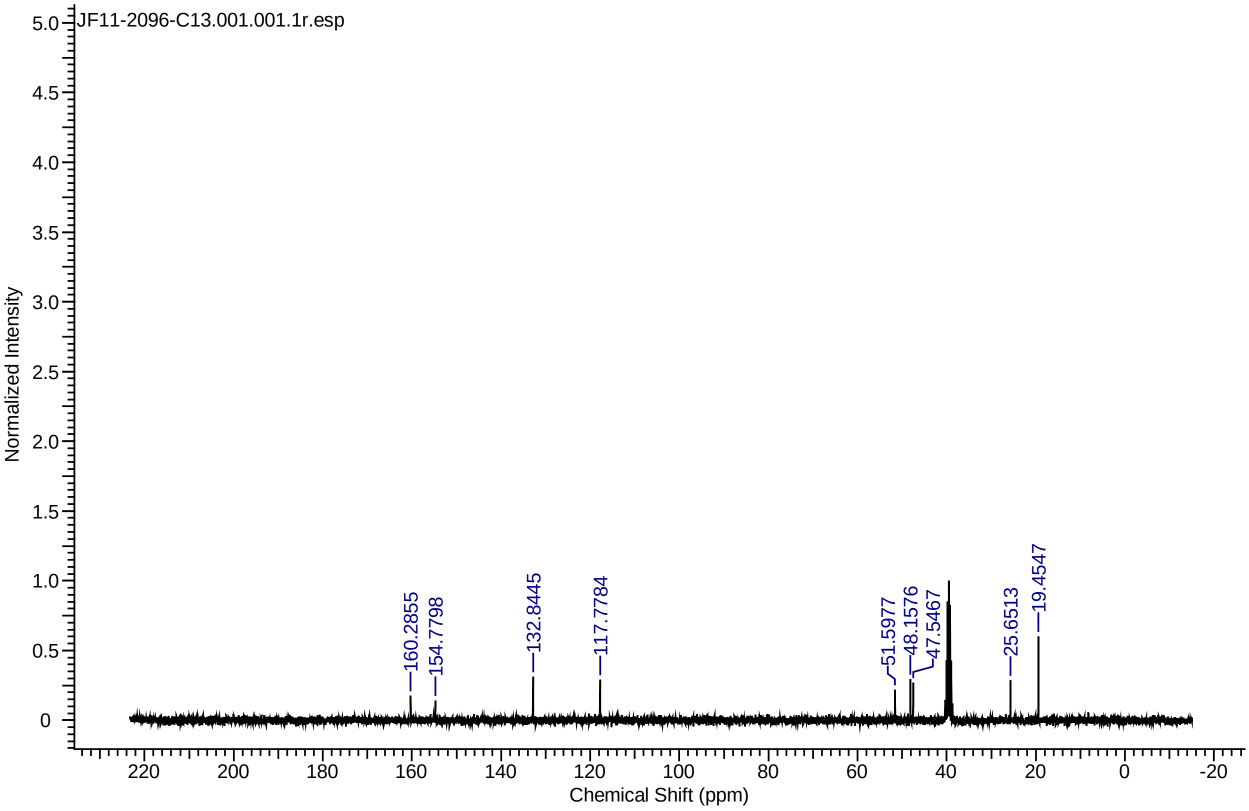

EE-15-H:
O
HN
OPh
NH
O
2.19 1.13 2.10
2.09 2.06 0.97
2.06 2.00
Normalized Intensity
2.0
1.5
1.0
0.5
0
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

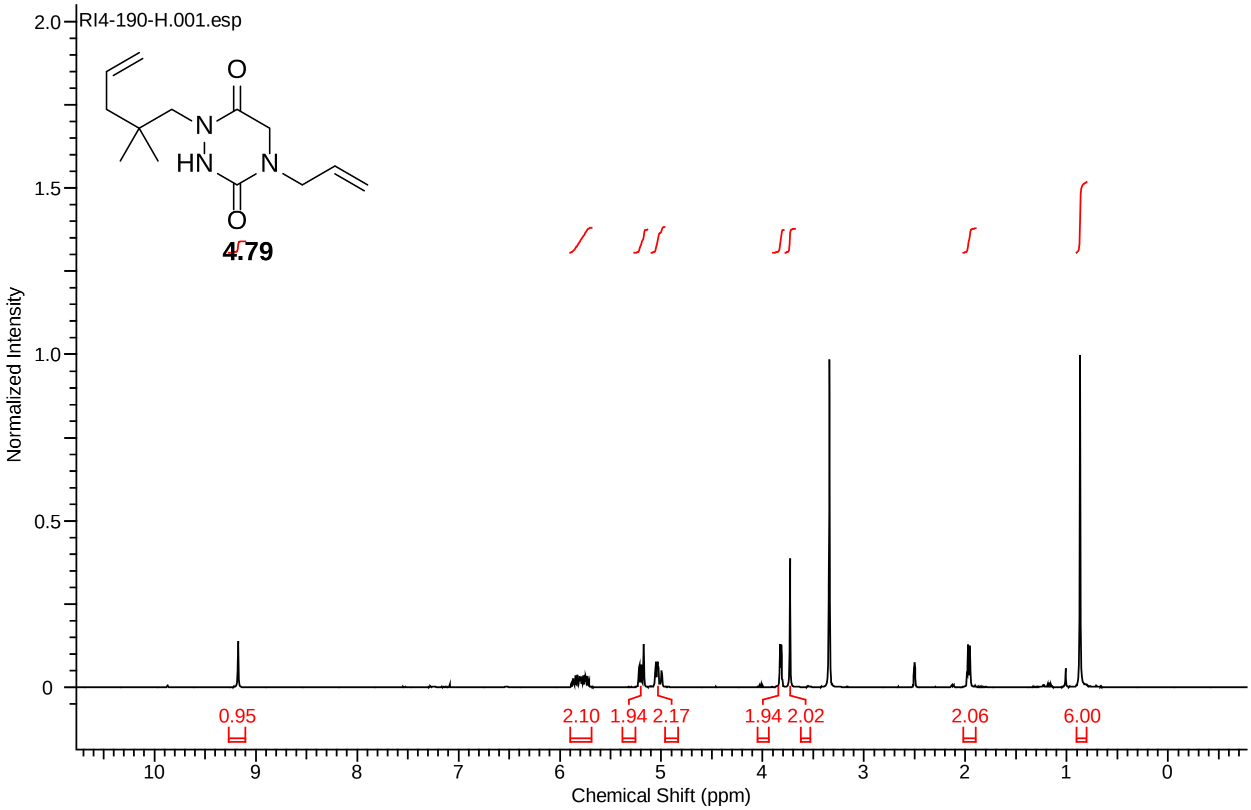

EE-15-C:
155.41
150.31
129.06
125.29
120.99
65.72
55.07
30.77
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

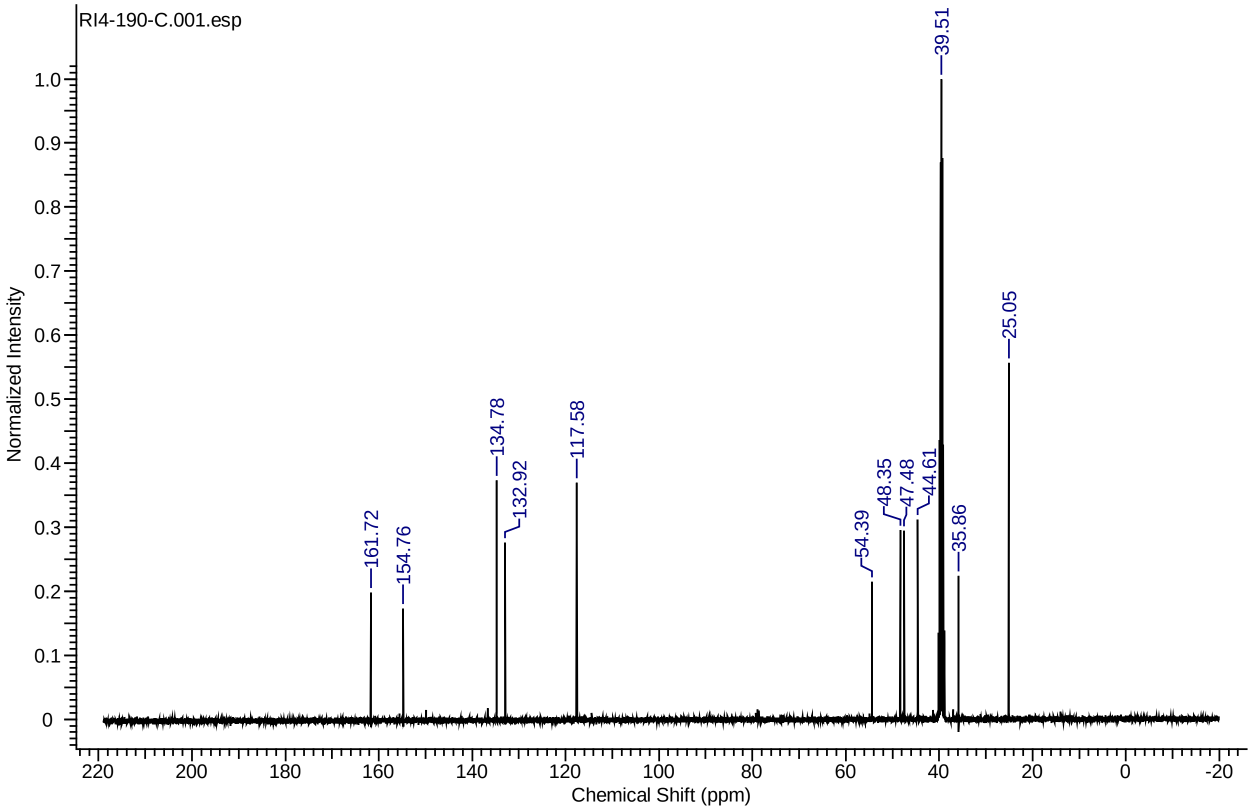

RI4-185-H.001.esp
O
N
HN
N
O
4.77
Normalized Intensity
0.25
0.20
0.15
0.10
0.05
0
0.97
1.02
2.11
1.04
1.07
2.08
1.02
2.02
1.99
4.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

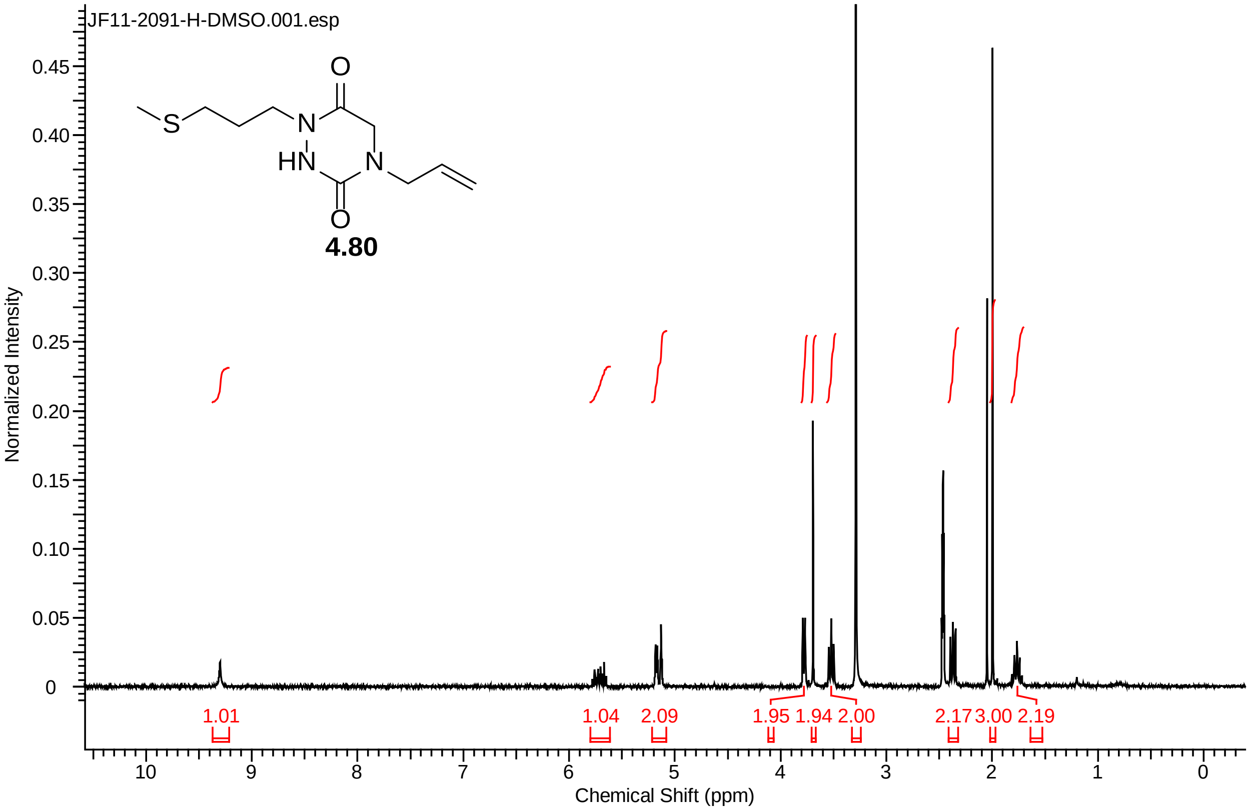

RI4-185-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.61
154.42
135.99
133.55
132.74
132.42
127.74
127.40
117.90
116.70
48.08
47.63
45.85
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

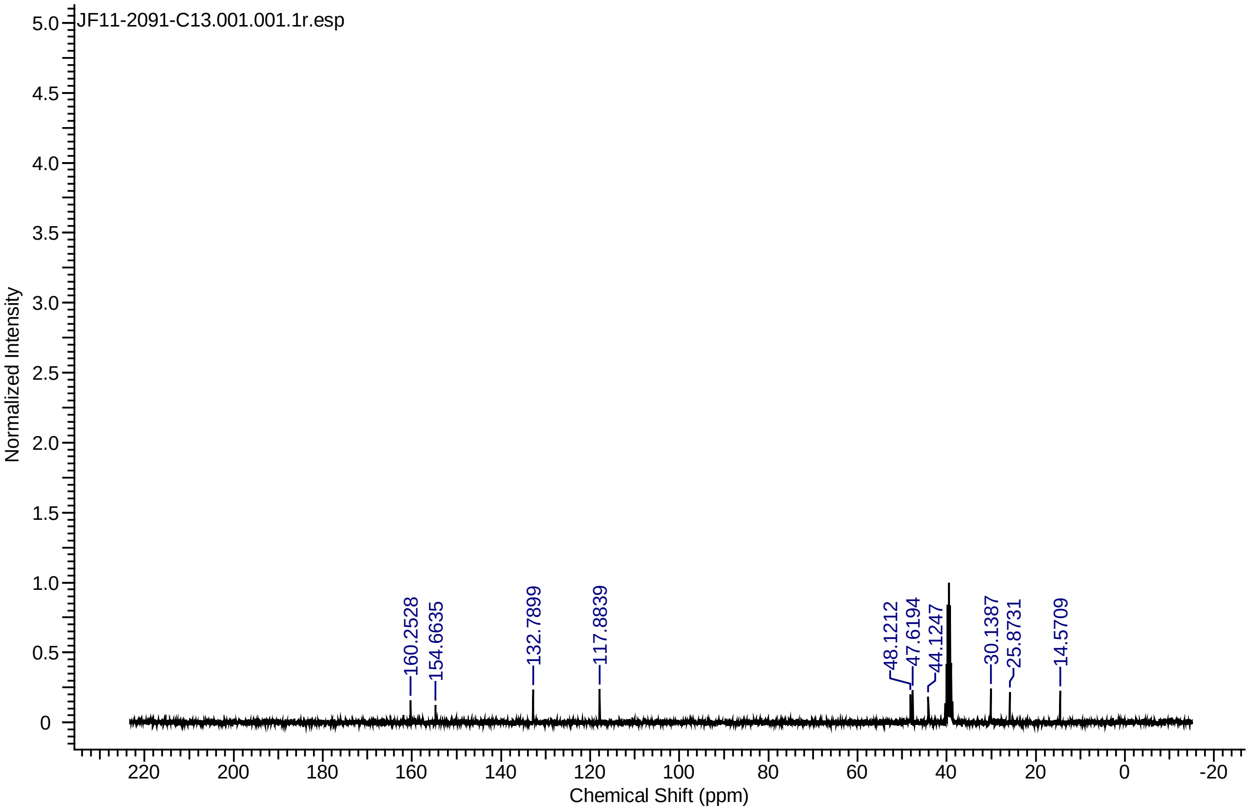

JF11-2096-H.001.esp
O
N
HN
N
O
4.78
Normalized Intensity
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.97
0.99
2.01
2.00
2.05
1.89
1.02
6.16
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

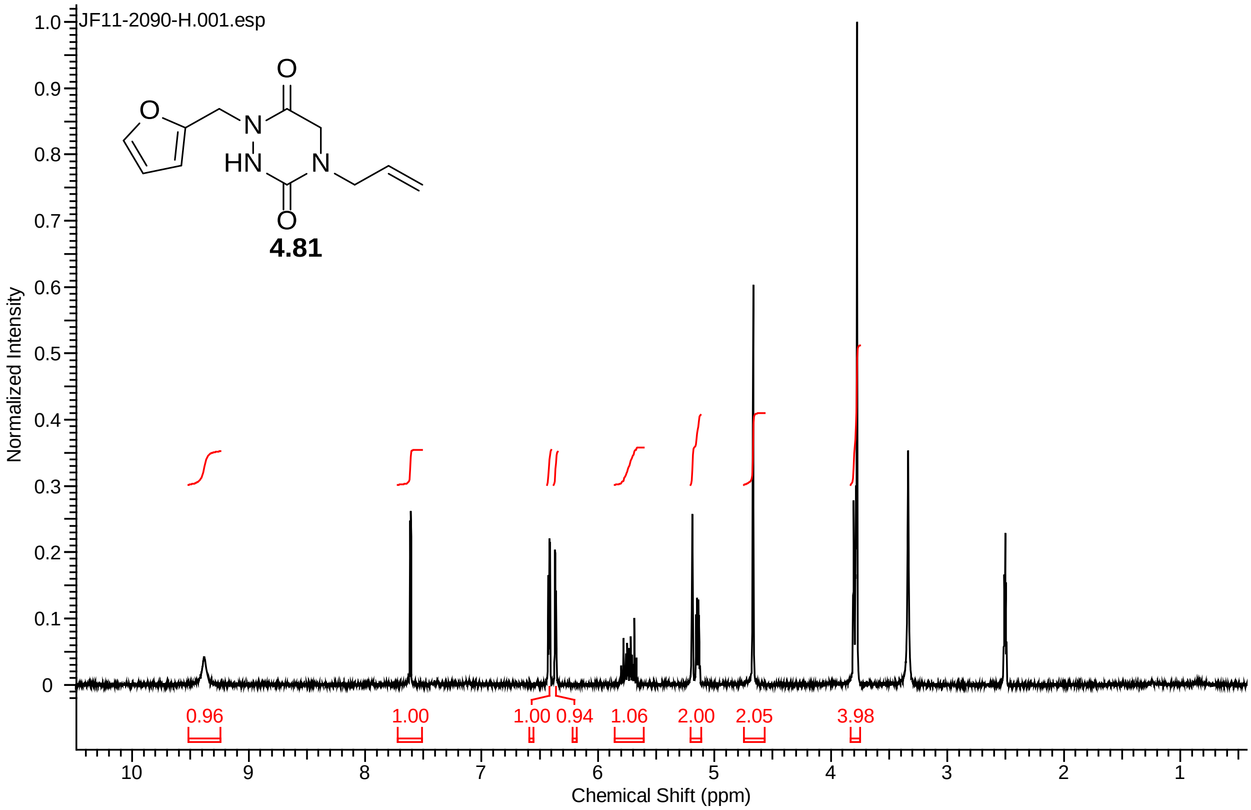

JF11-2096-C13.001.001.1r.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
160.2855
154.7798
132.8445
117.7784
51.5977
48.1576
47.5467
25.6513
19.4547
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

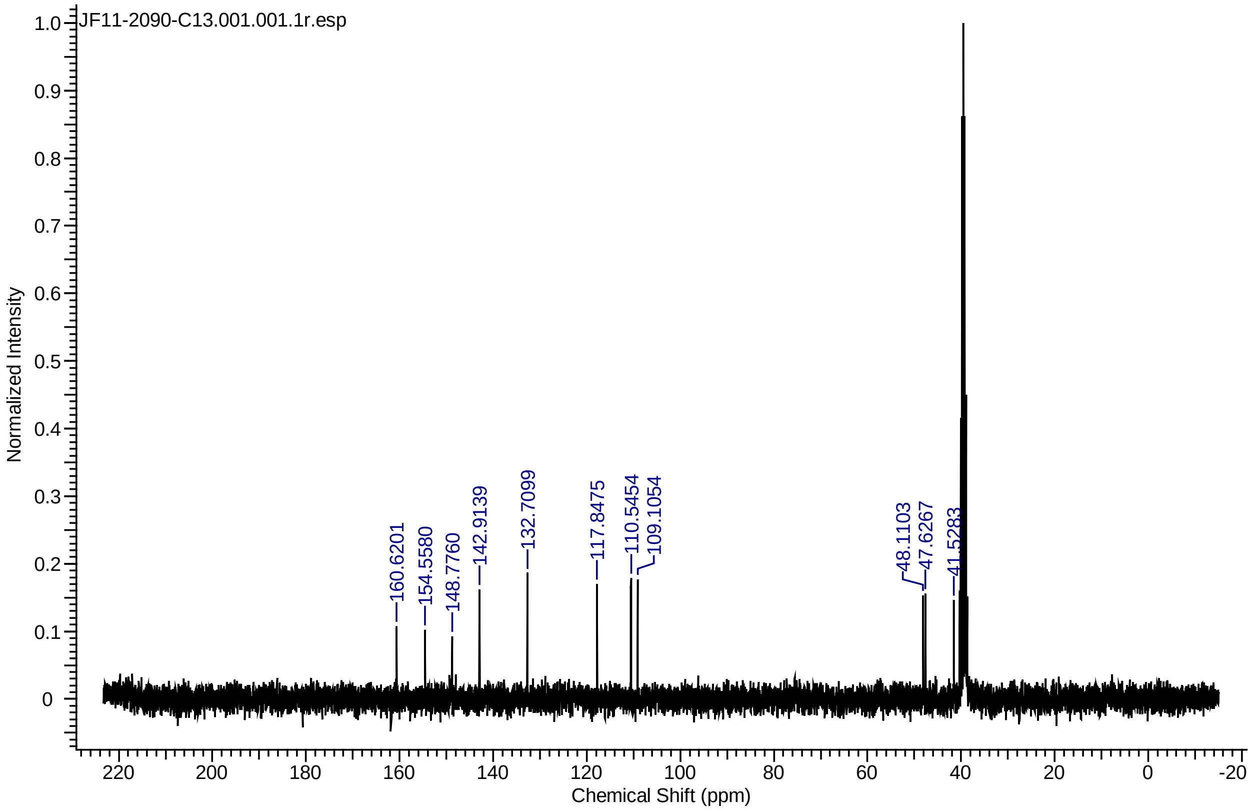

RI4-190-H.001.esp
O
N
HN
N
O
4.79
0.95
2.10
1.94
2.17
1.94
2.02
2.06
6.00
Normalized Intensity
2.0
1.5
1.0
0.5
0
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

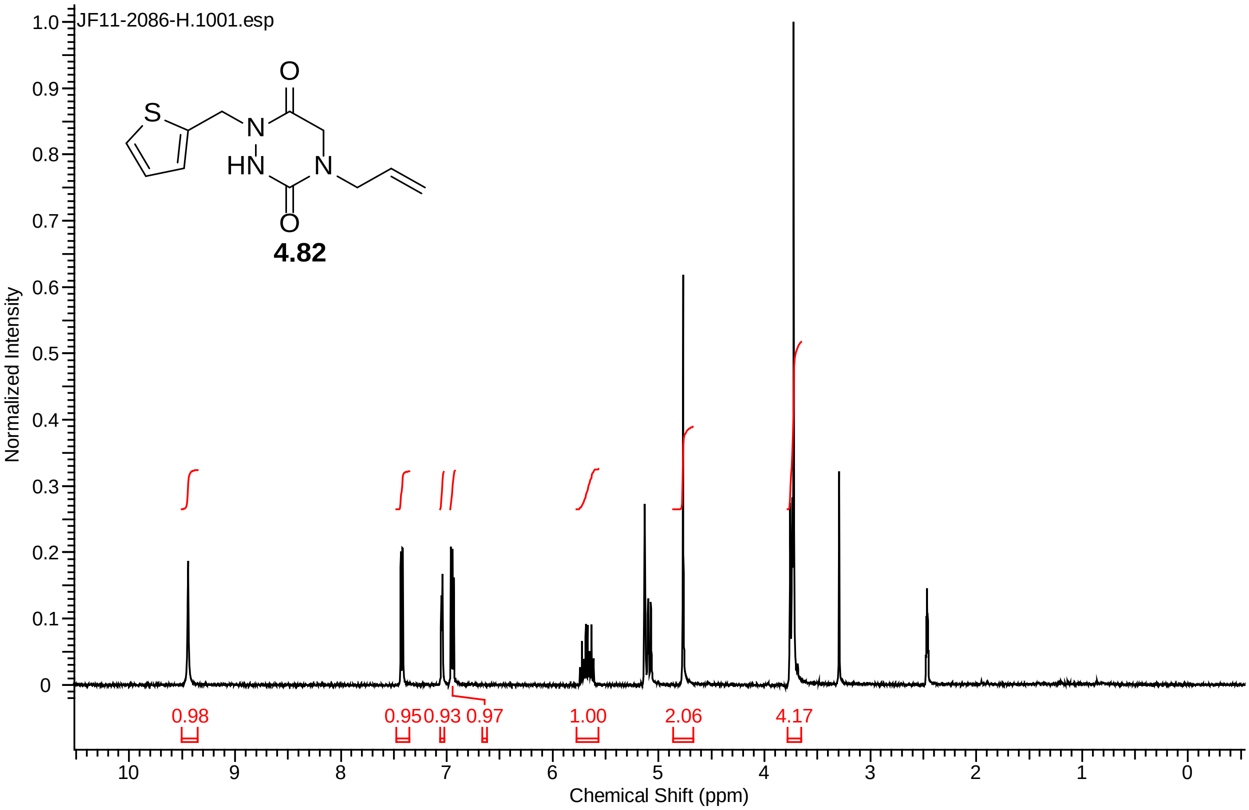

RI4-190-C.001.esp
161.72
154.76
134.78
132.92
117.58
54.39
48.35
47.48
44.61
39.51
35.86
25.05
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

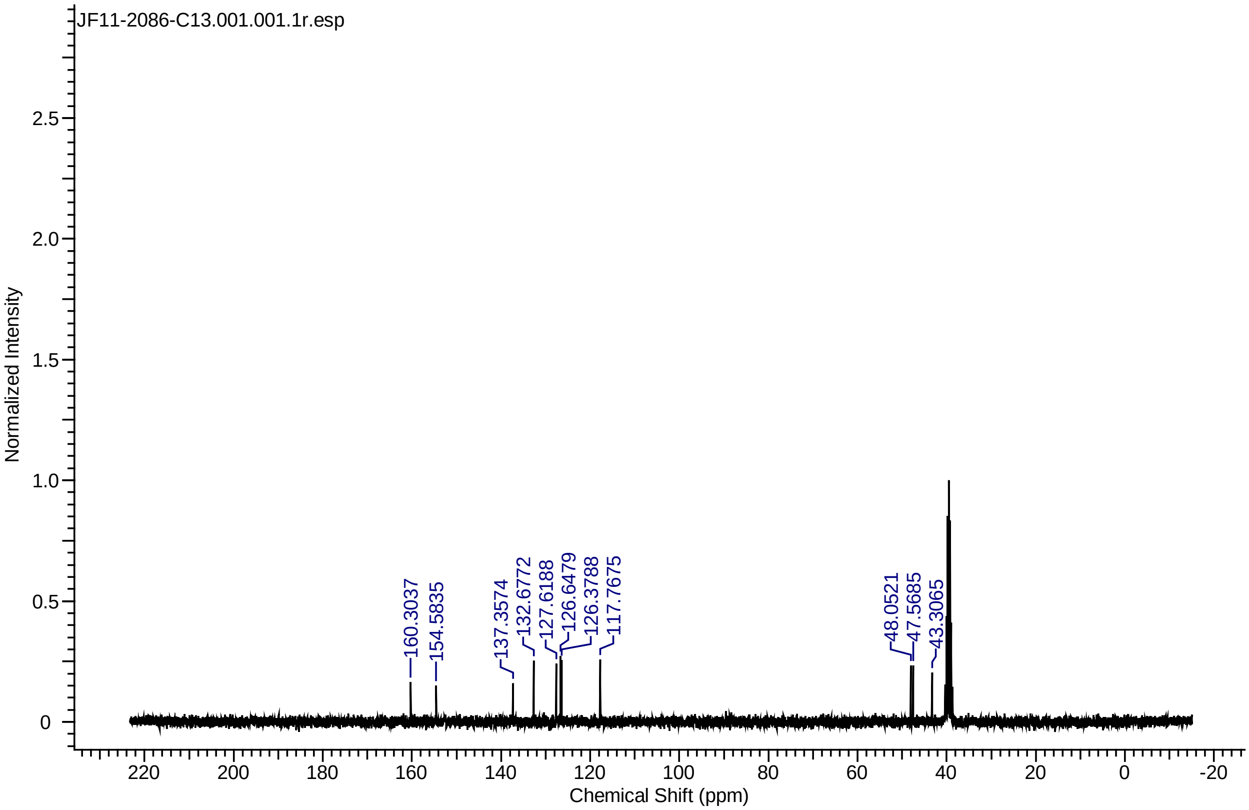

JF11-2091-H-DMSO.001.esp
O
S
N
HN
N
O
4.80
Normalized Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
1.01
1.04
2.09
1.95
1.94
2.00
2.17
3.00
2.19
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

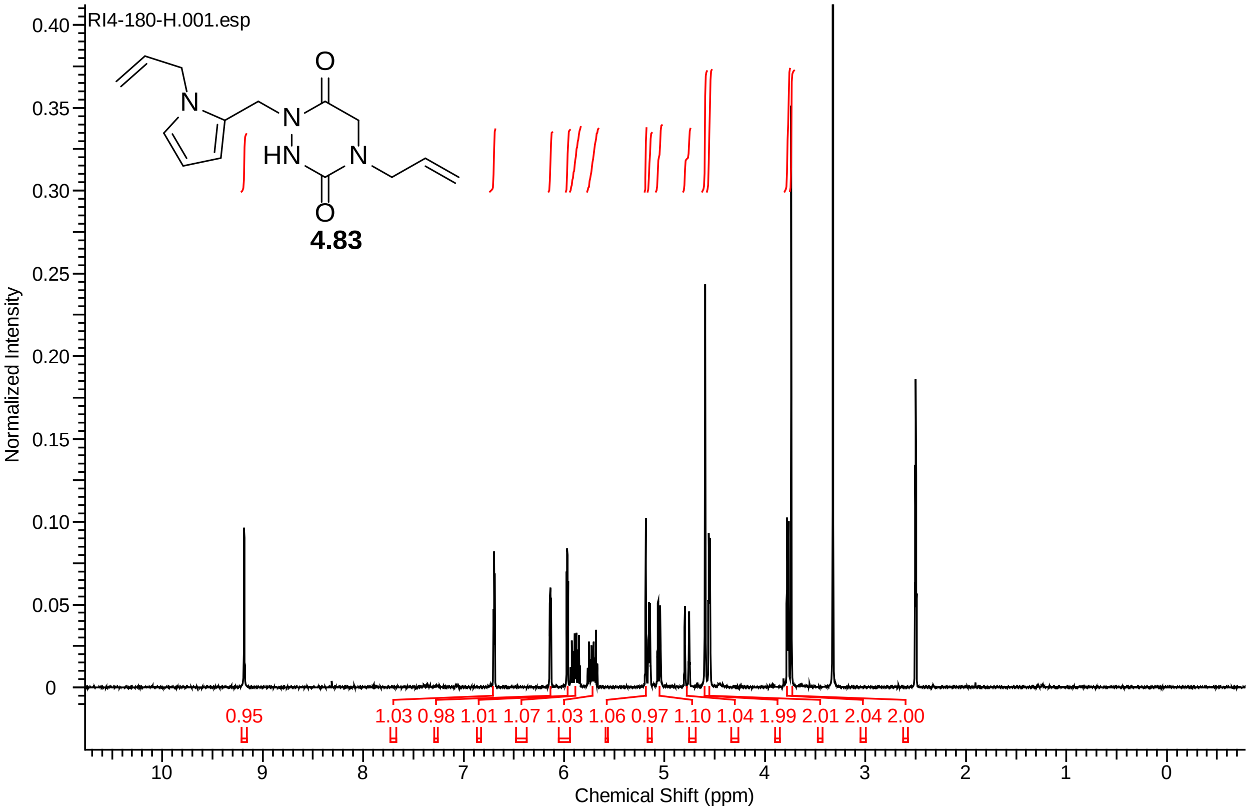

JF11-2091-C13.001.001.1r.esp
Normalized Intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
160.2528
154.6635
132.7899
117.8839
48.1212
47.6194
44.1247
30.1387
25.8731
14.5709
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

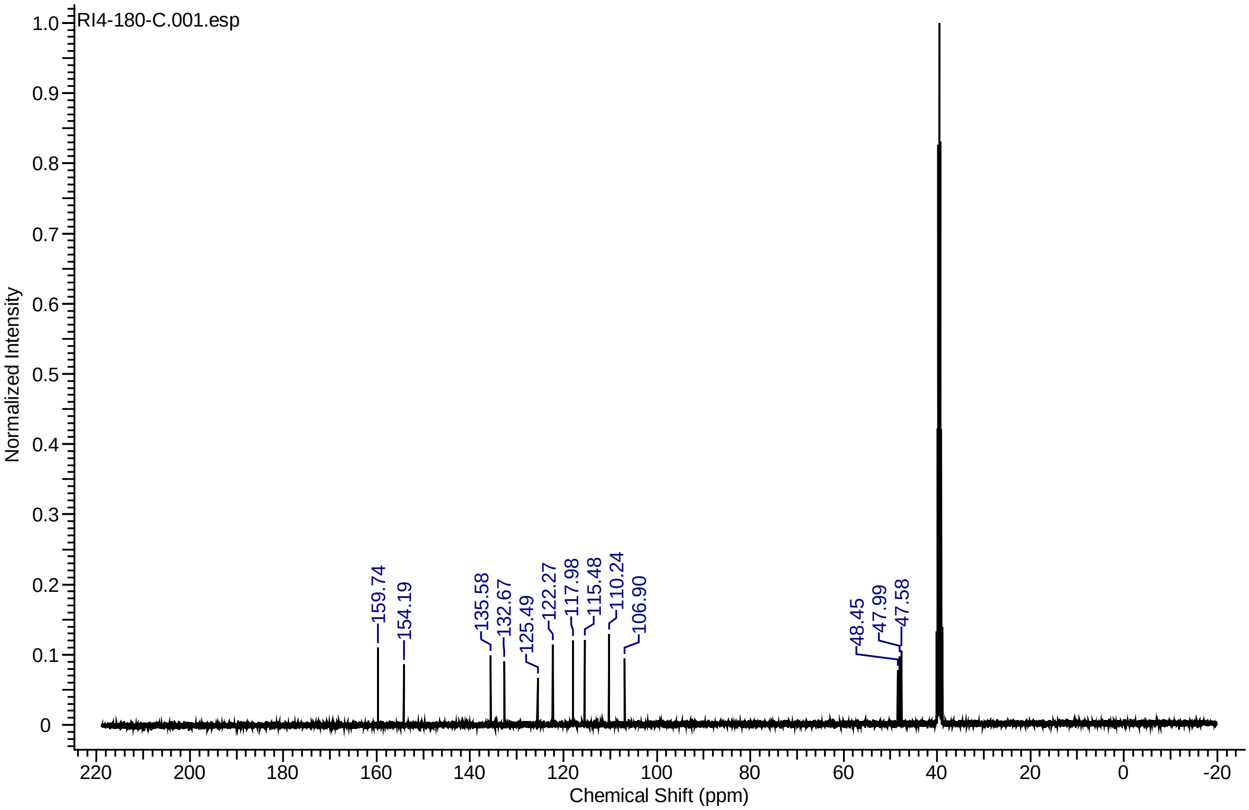

JF11-2090-H.001.esp
O
N
O
HN
N
O
4.81
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.96
1.00
1.00
0.94
1.06
2.00
2.05
3.98
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

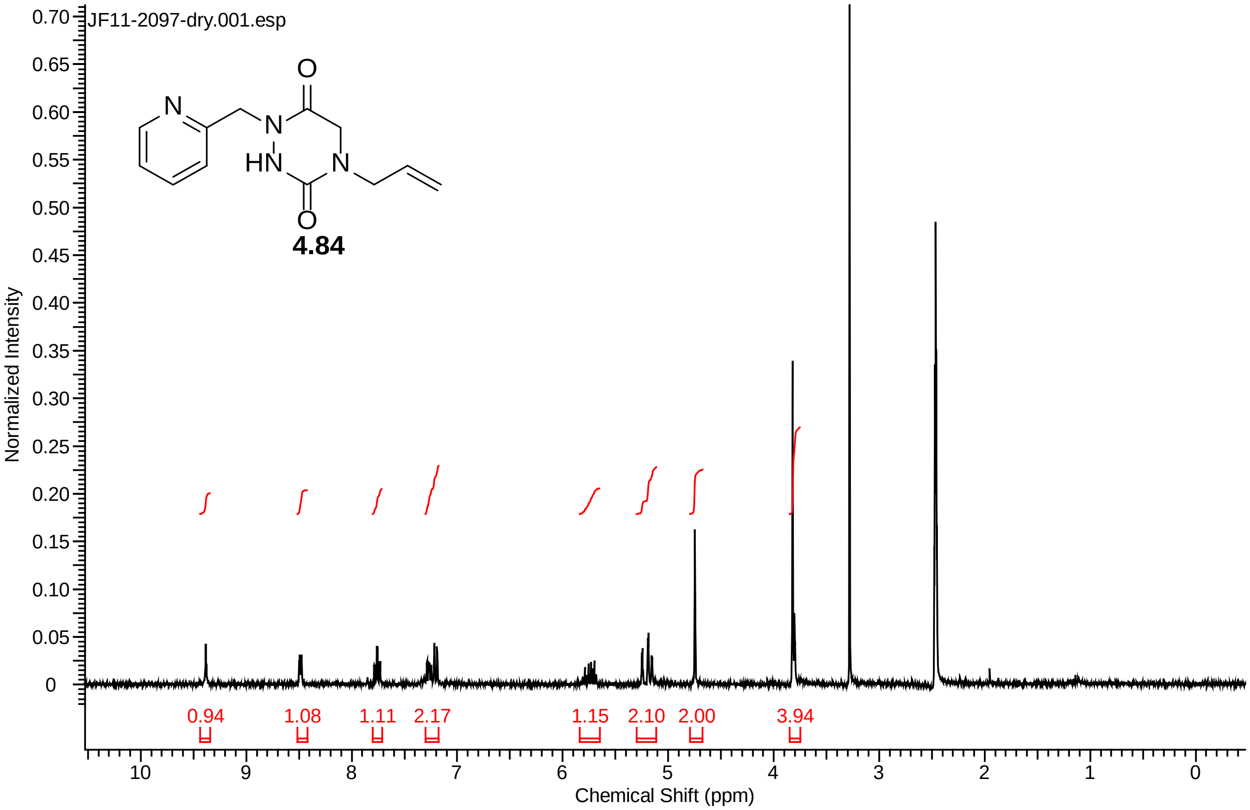

JF11-2090-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.6201
154.5580
148.7760
142.9139
132.7099
117.8475
110.5454
109.1054
48.1103
47.6267
41.5283
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF11-2086-H.1001.esp
S
N
HN
N
O
O
4.82
Normalized Intensity
0.98
0.95
0.93
0.97
1.00
2.06
4.17
Chemical Shift (ppm)

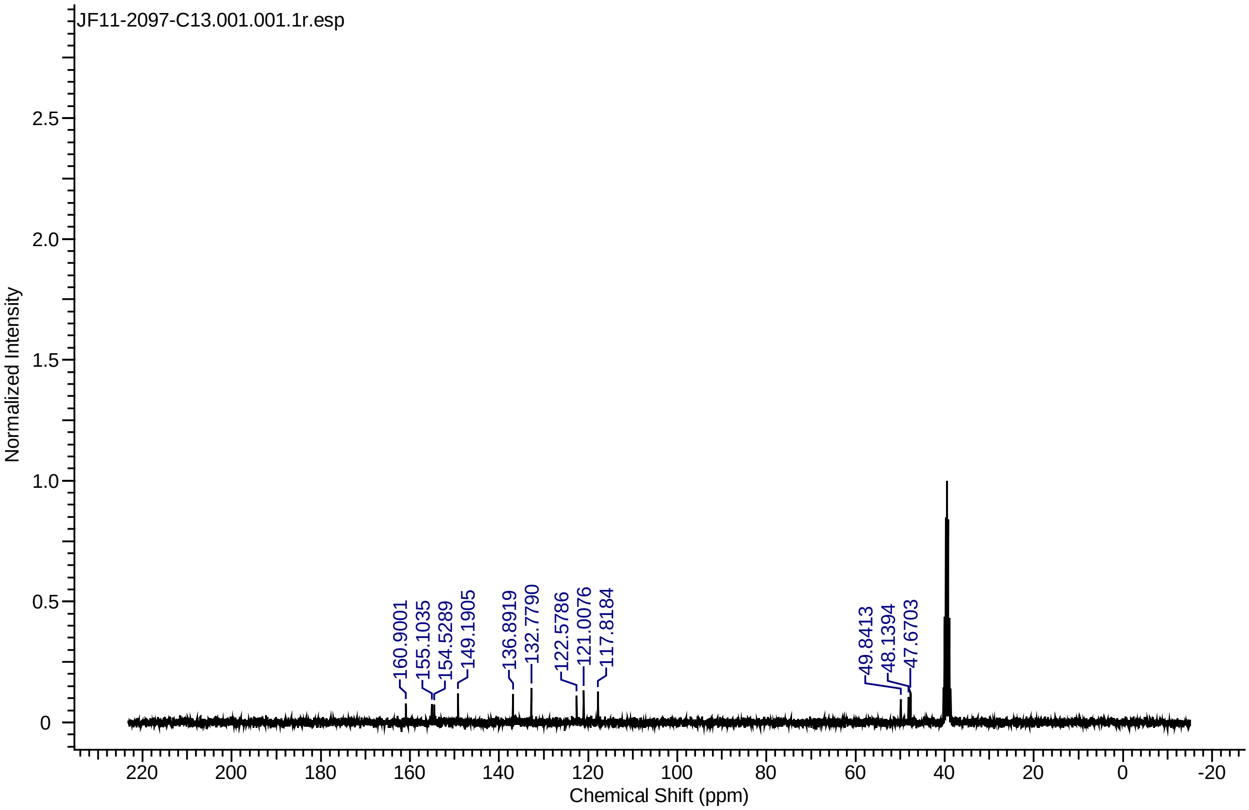

JF11-2086-C13.001.001.1r.esp
Normalized Intensity
160.3037
154.5835
137.3574
132.6772
127.6188
126.6479
126.3788
117.7675
48.0521
47.5685
43.3065
Chemical Shift (ppm)

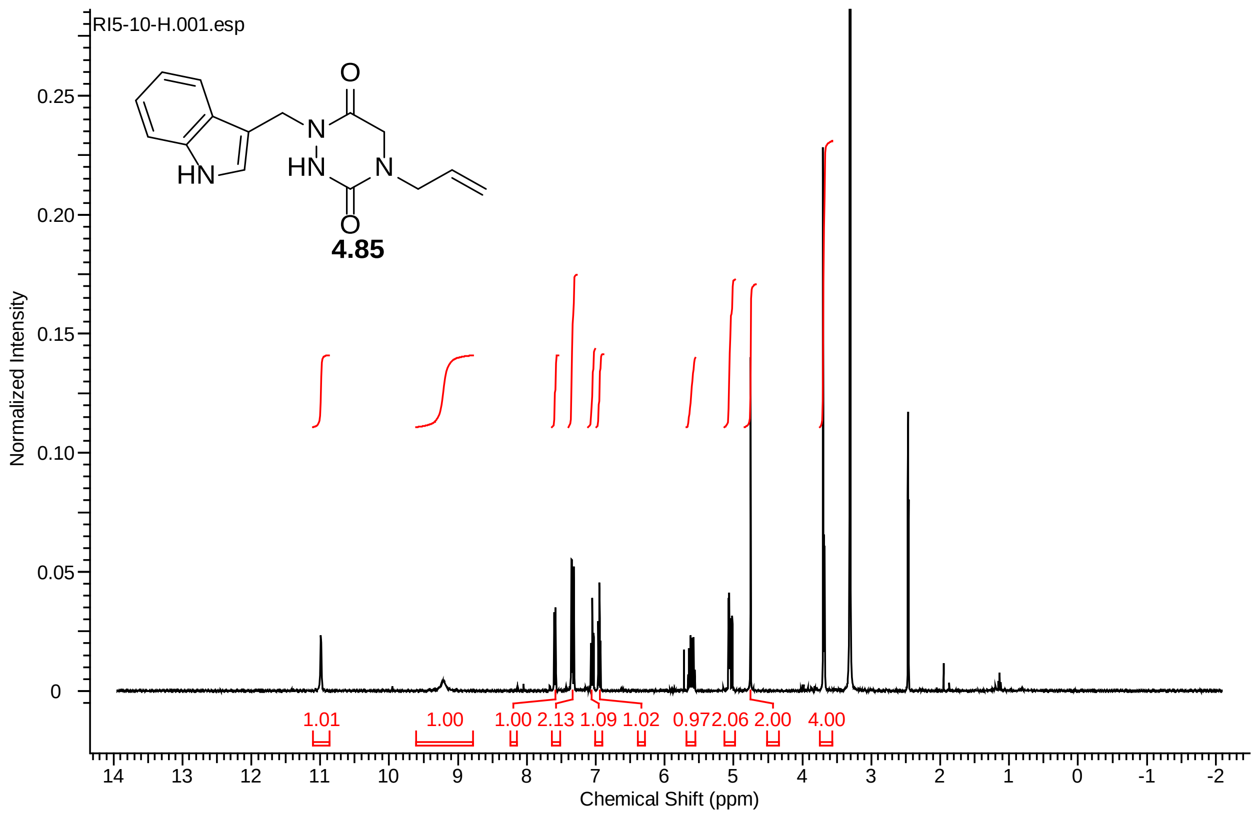

RI4-180-H.001.esp
4.83
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.95
1.03
0.98
1.01
1.07
1.03
1.06
0.97
1.10
1.04
1.99
2.01
2.04
2.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

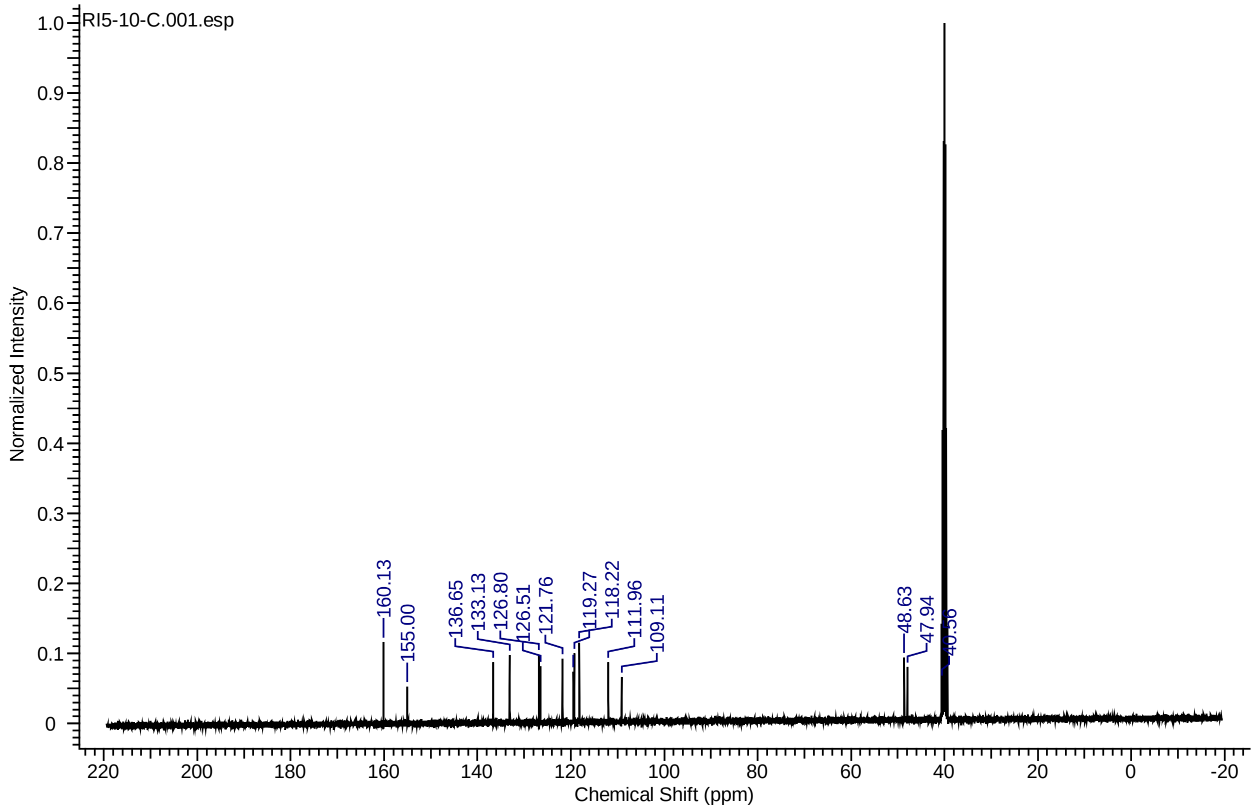

RI4-180-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
159.74
154.19
135.58
132.67
125.49
122.27
117.98
115.48
110.24
106.90
48.45
47.99
47.58
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

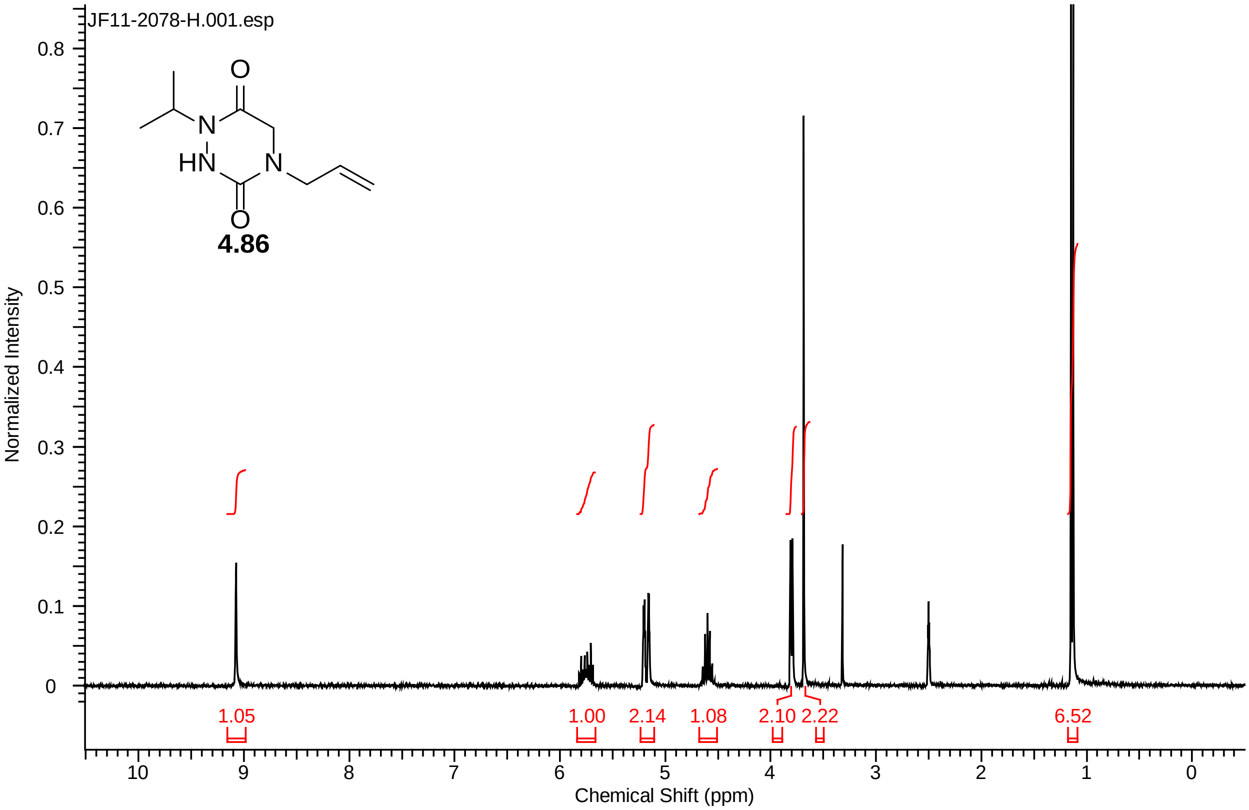

JF11-2097-dry.001.esp
N
N
HN
N
O
O
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
Normalized Intensity
0.94
1.08
1.11
2.17
1.15
2.10
2.00
3.94
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

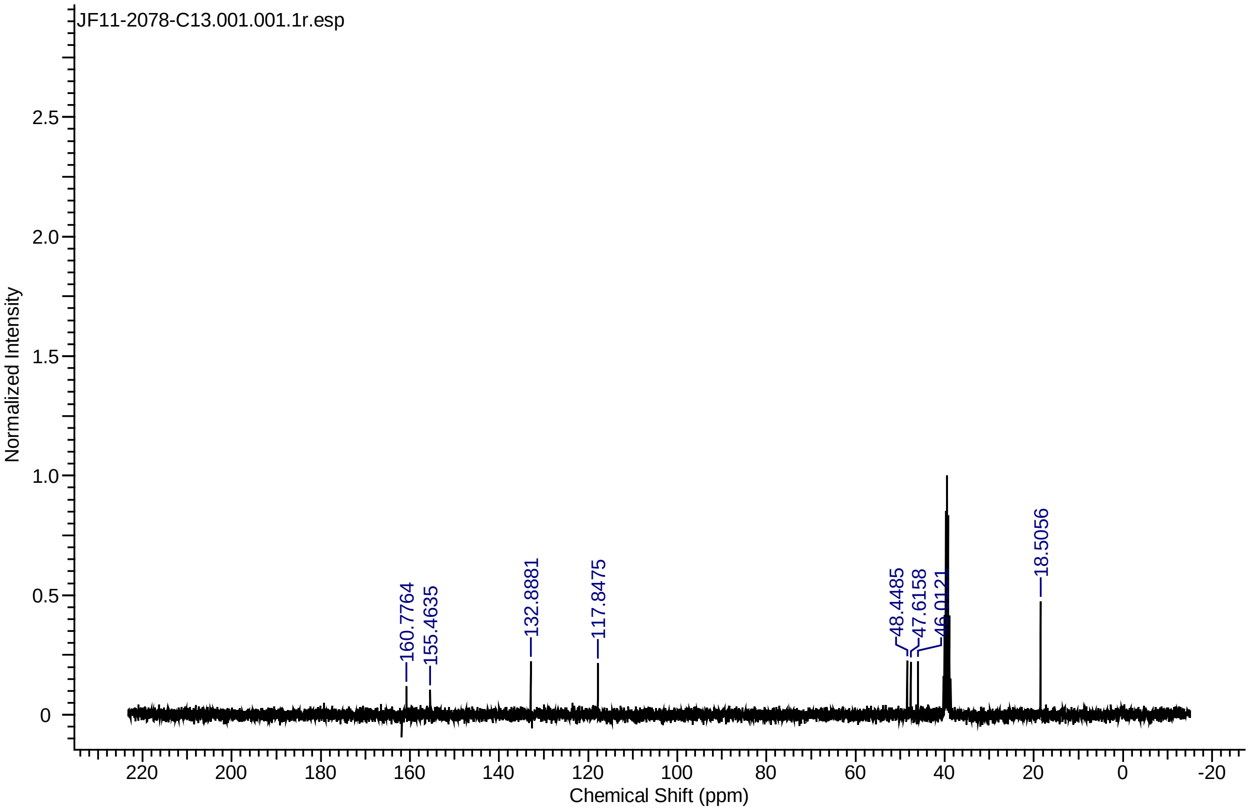
4.84

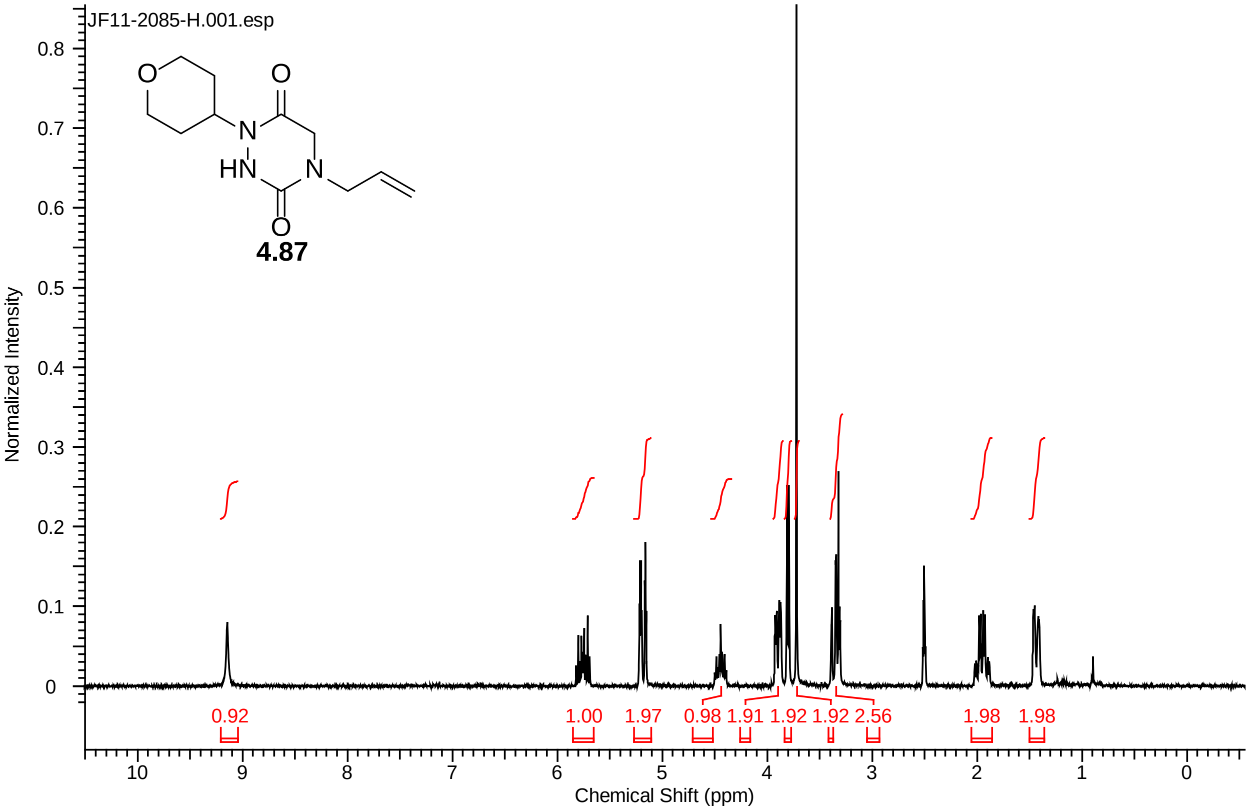

JF11-2097-C13.001.001.1r.esp
2.5
2.0
1.5
1.0
0.5
0
Normalized Intensity
160.9001
155.1035
154.5289
149.1905
136.8919
132.7790
122.5786
121.0076
117.8184
49.8413
48.1394
47.6703
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

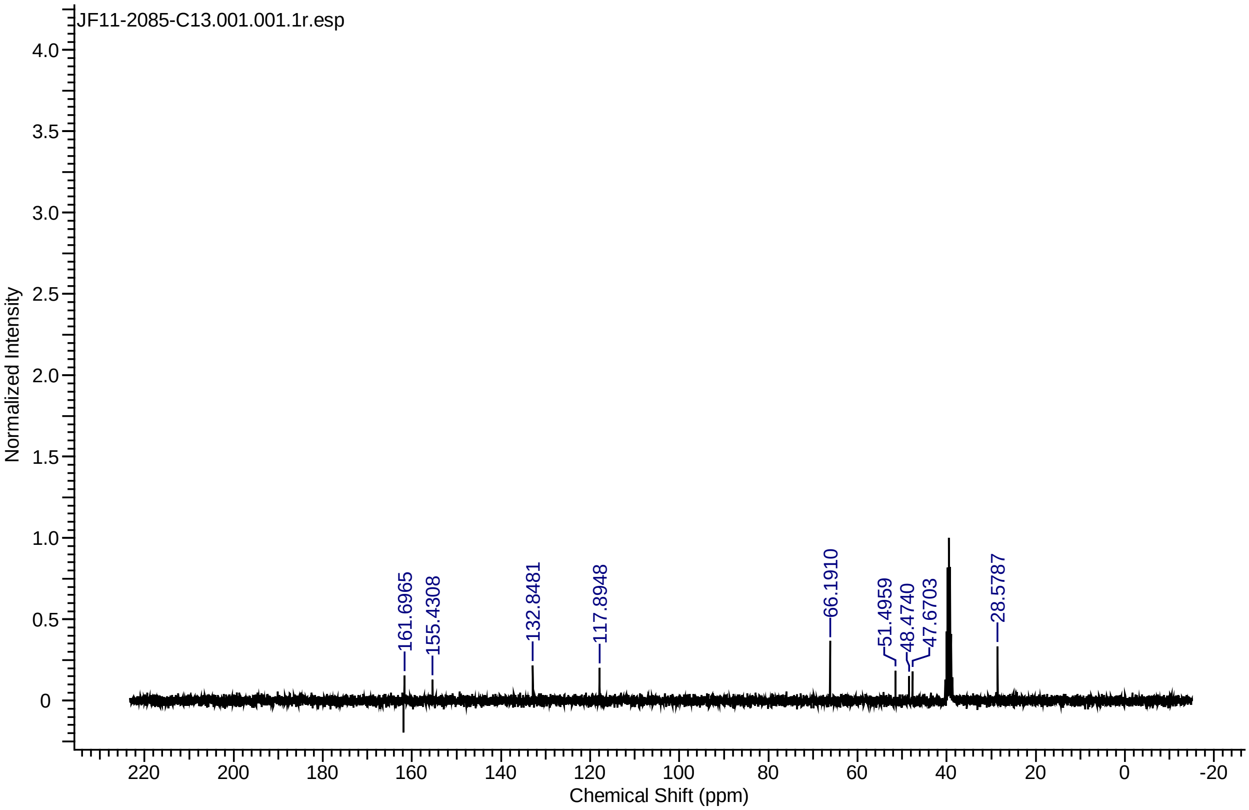

RI5-10-H.001.esp
O
N
HN
N
HN
O
4.85
Normalized Intensity
0.25
0.20
0.15
0.10
0.05
0
1.01
1.00
1.00
2.13
1.09
1.02
0.97
2.06
2.00
4.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

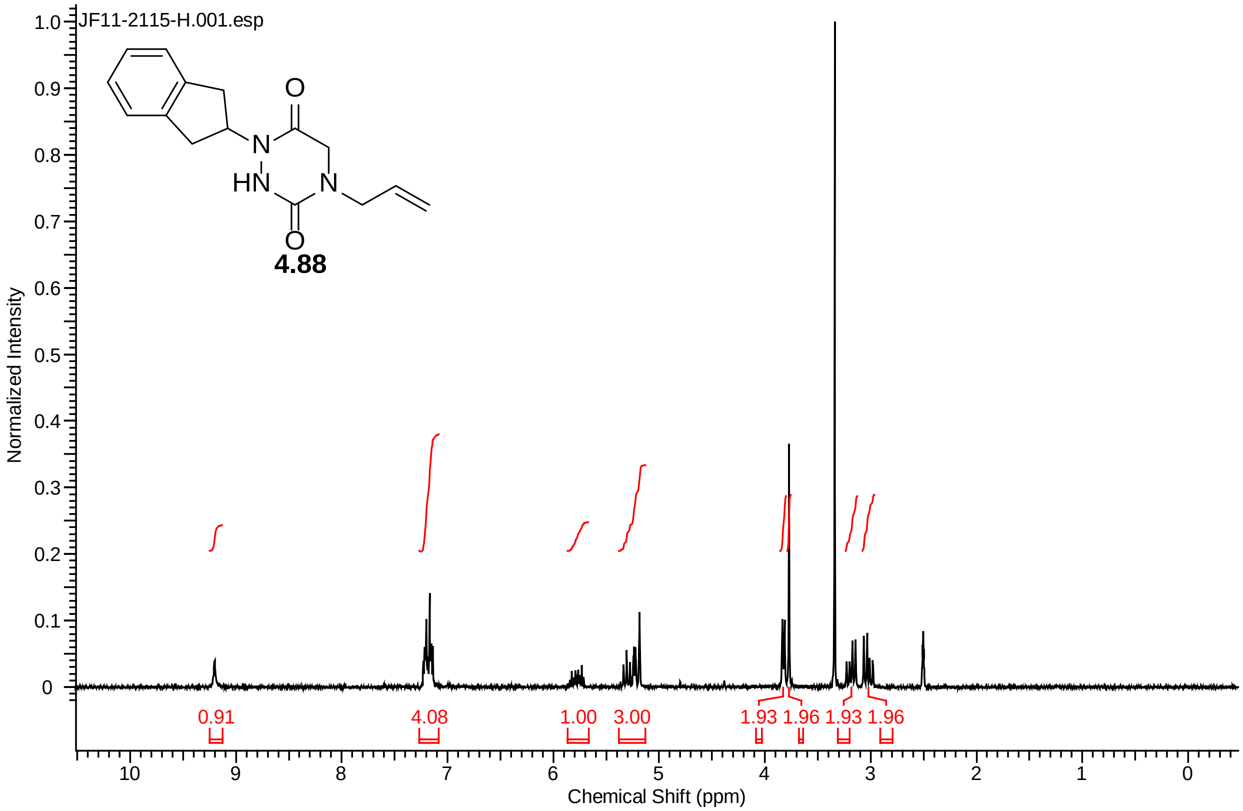

RI5-10-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.13
155.00
136.65
133.13
126.80
126.51
121.76
119.27
118.22
111.96
109.11
48.63
47.94
40.56
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

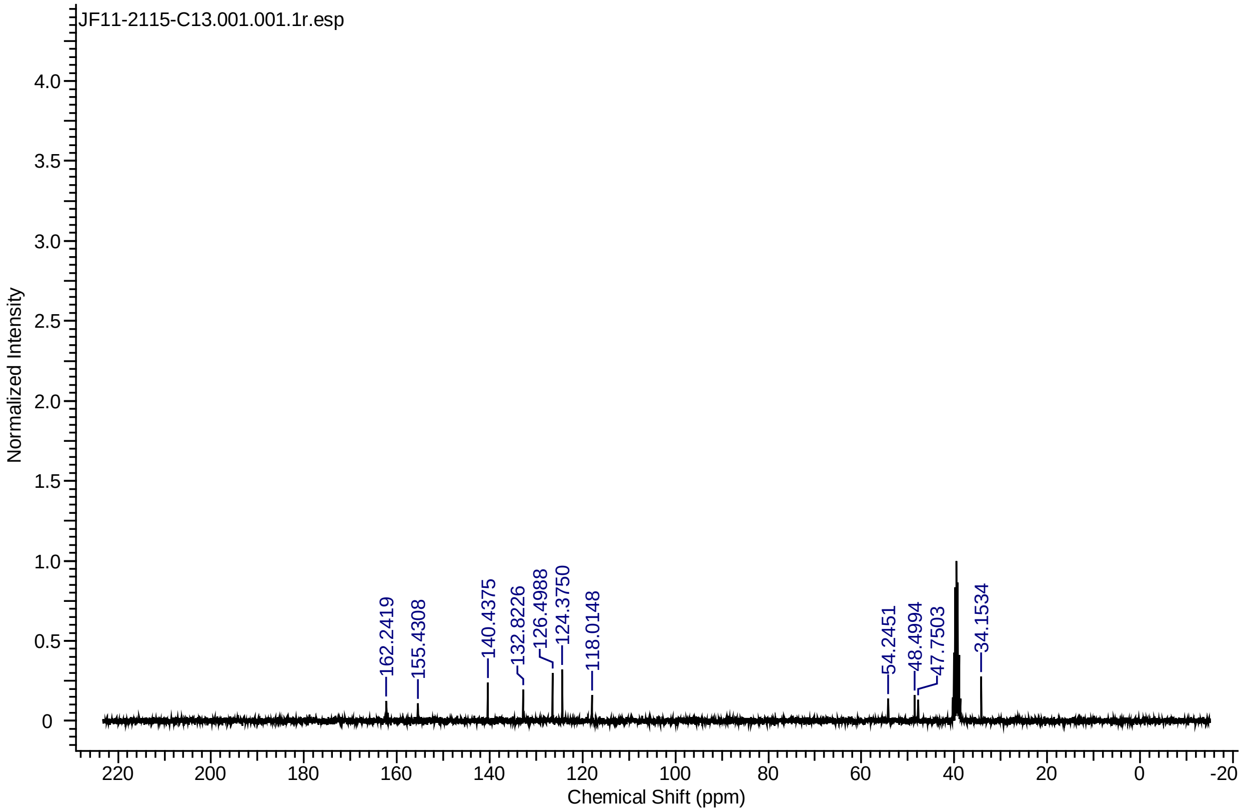

JF11-2078-H.001.esp
4.86
O
N
HN
N
O
Normalized Intensity
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.05
1.00
2.14
1.08
2.10
2.22
6.52
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

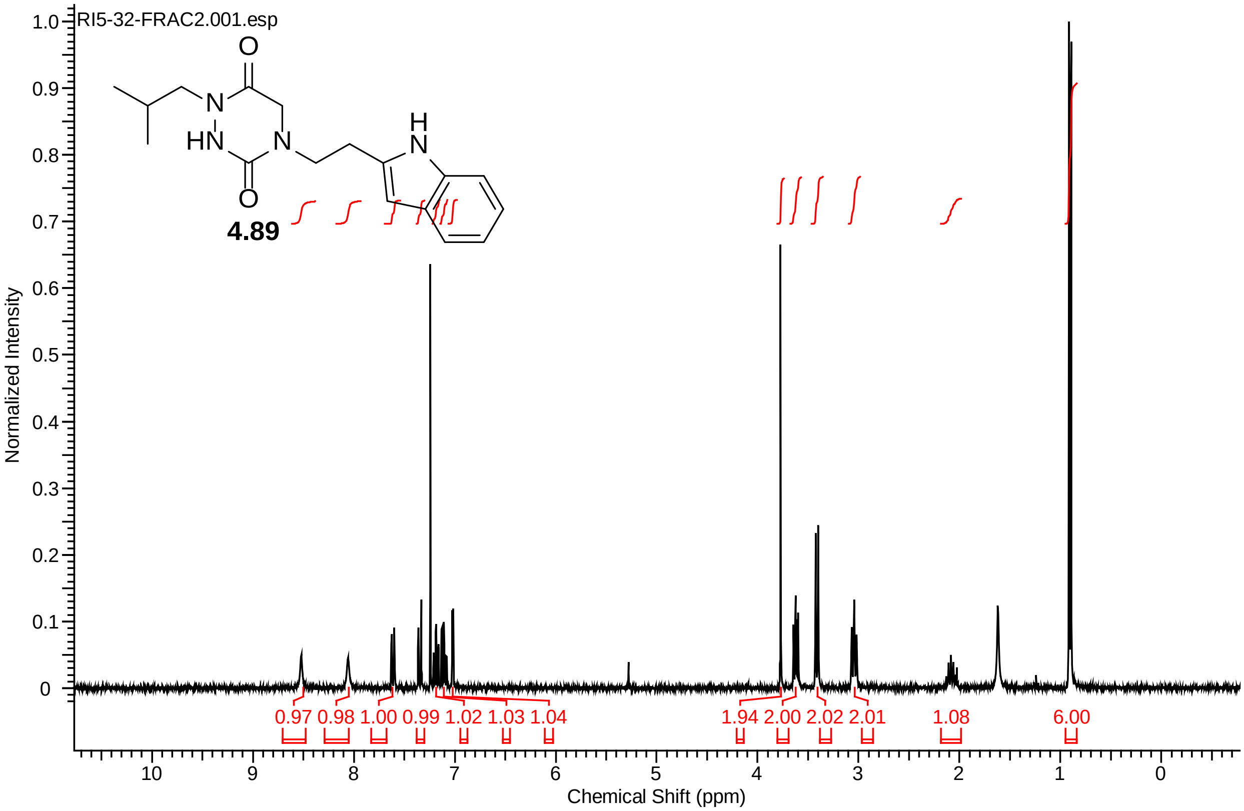

JF11-2078-C13.001.001.1r.esp
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0
160.7764
155.4635
132.8881
117.8475
48.4485
47.6158
46.0121
18.5056
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF11-2085-H.001.esp
4.87
O
N
HN
N
O
O
Normalized Intensity
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.92
1.00
1.97
0.98
1.91
1.92
1.92
2.56
1.98
1.98
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF11-2085-C13.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
161.6965
155.4308
132.8481
117.8948
66.1910
51.4959
48.4740
47.6703
28.5787
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

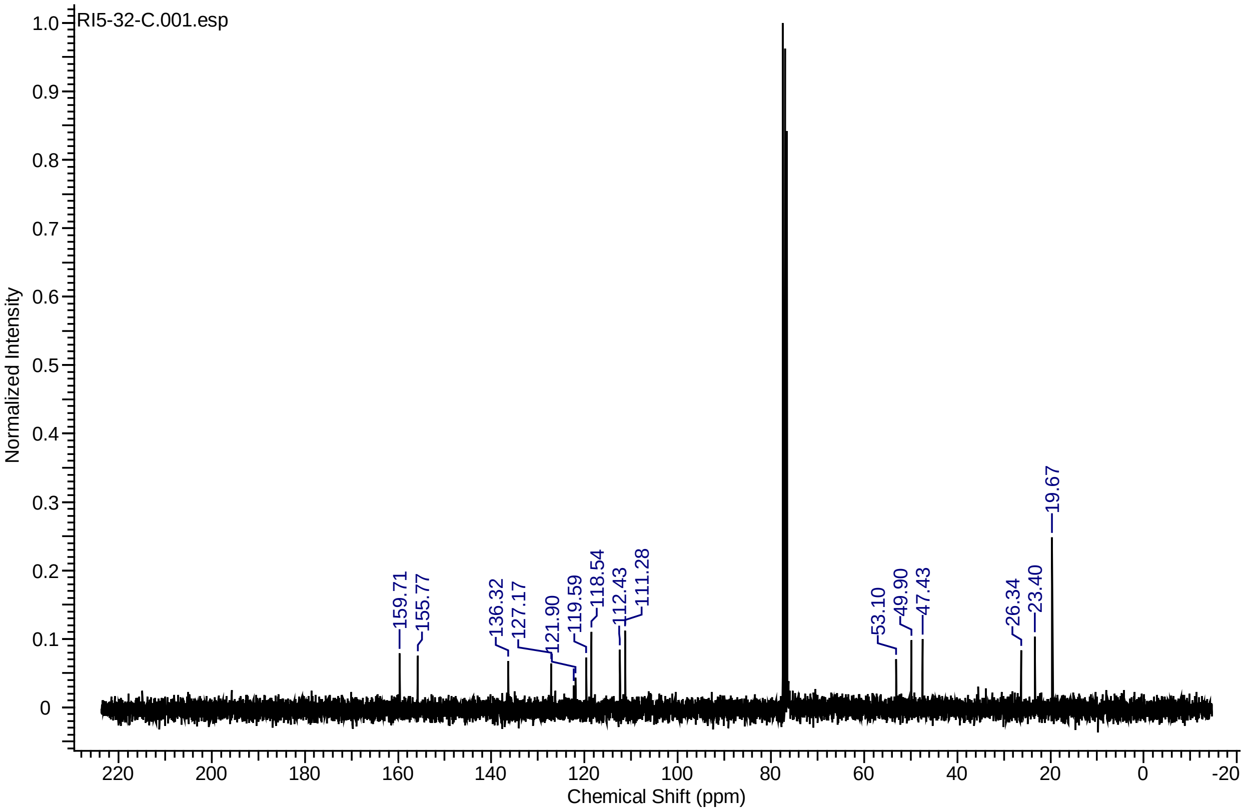

4.88
JF11-2115-H.001.esp
O
N
HN
N
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.91
4.08
1.00
3.00
1.93
1.96
1.93
1.96
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF11-2115-C13.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
162.2419
155.4308
140.4375
132.8226
126.4988
124.3750
118.0148
54.2451
48.4994
47.7503
34.1534
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

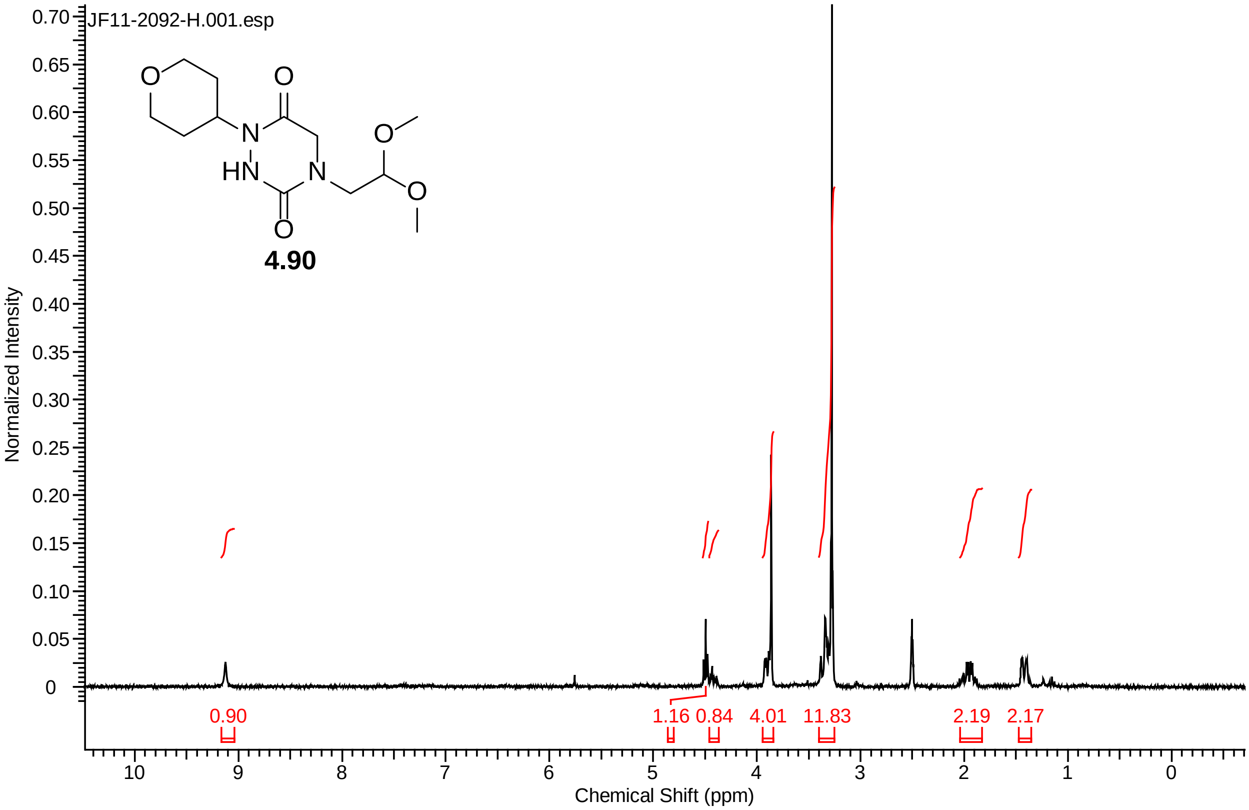


4.89

RI5-32-FRAC2.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
O
N
HN
N
O
H
N
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
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

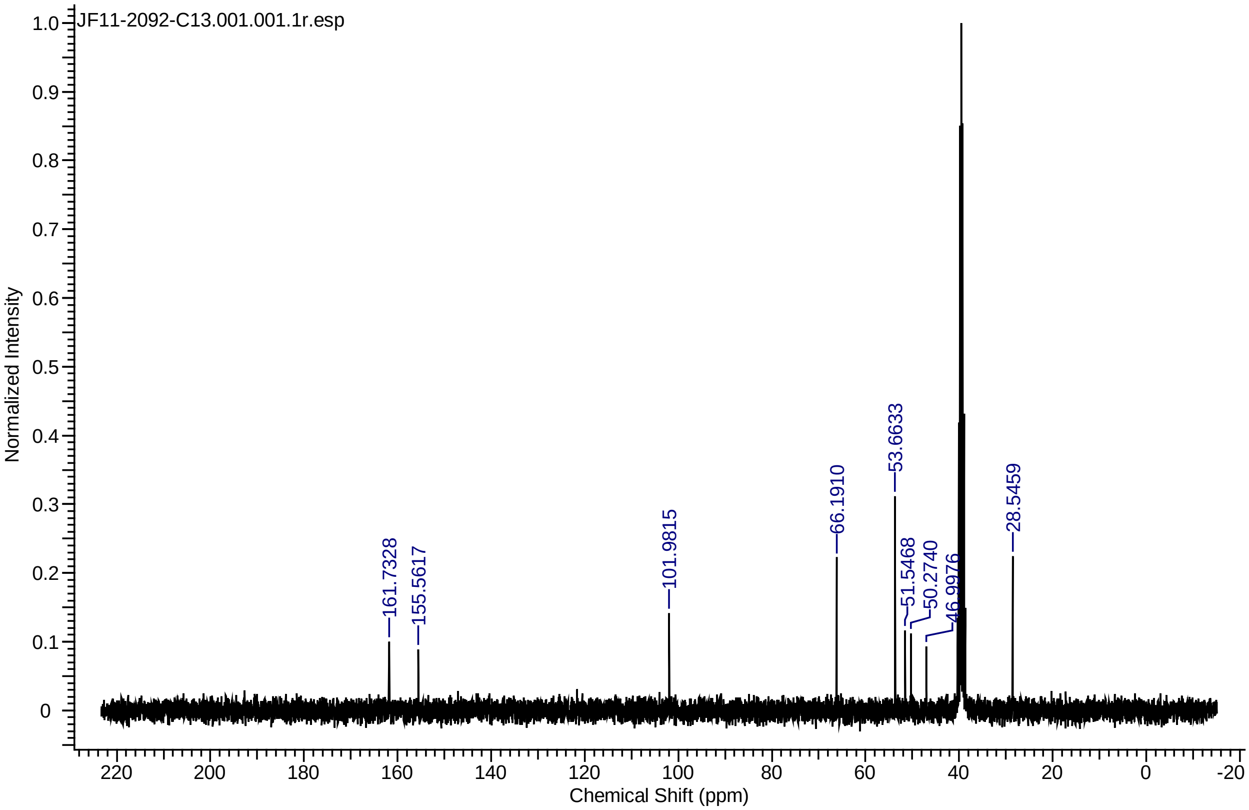


RI5-32-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
159.71
155.77
136.32
127.17
121.90
119.59
118.54
112.43
111.28
53.10
49.90
47.43
26.34
23.40
19.67
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

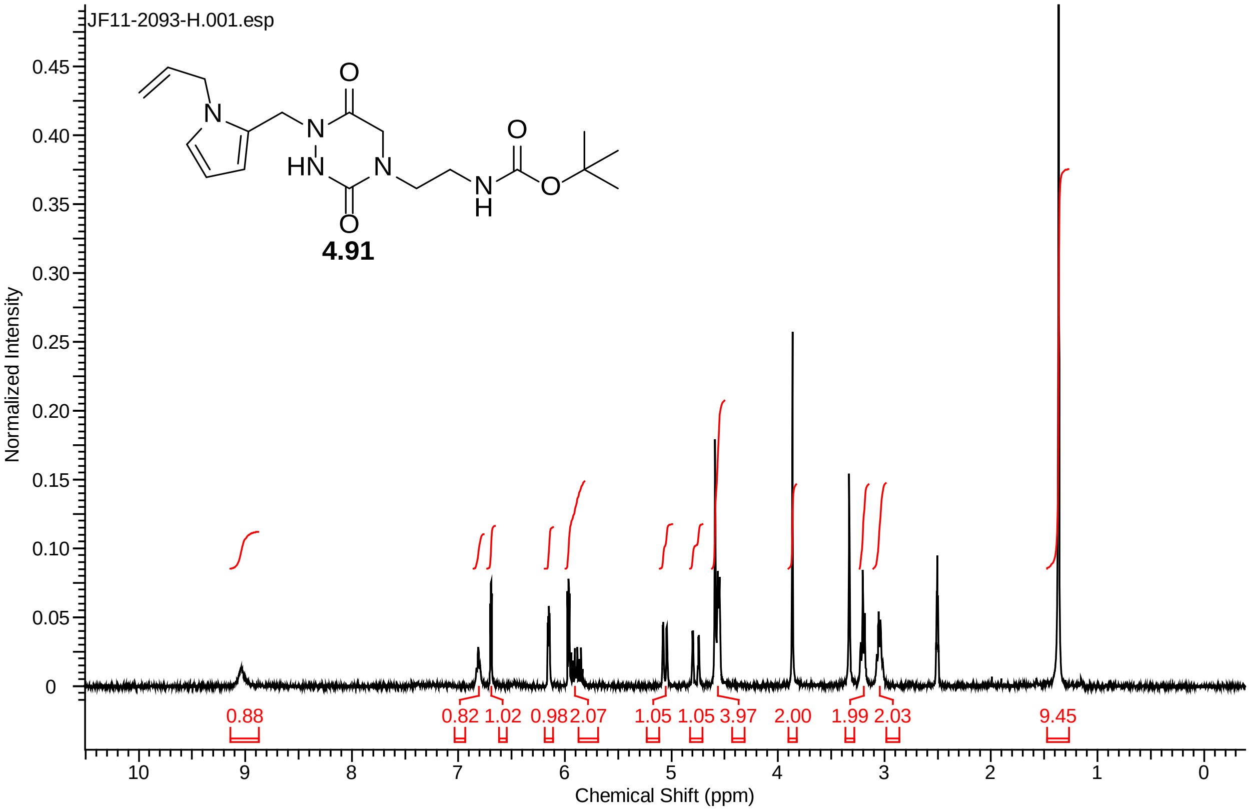


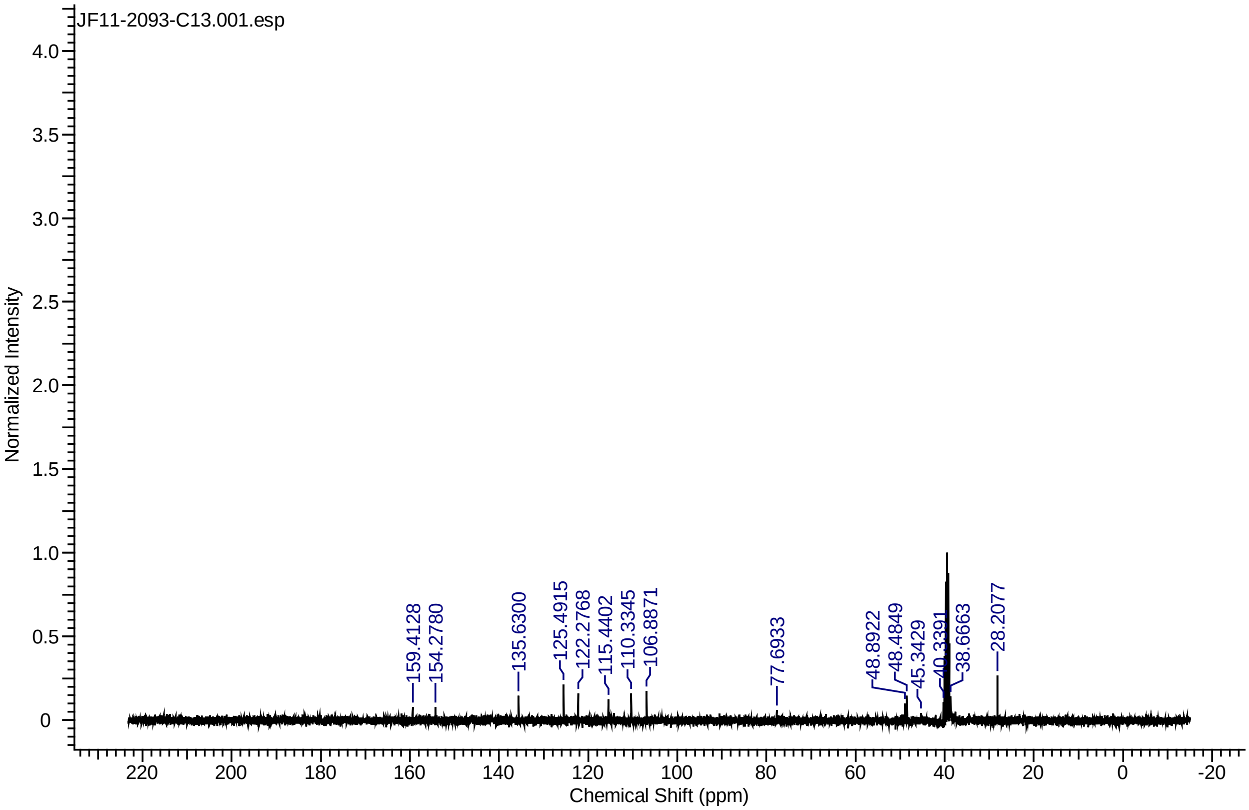
4.90

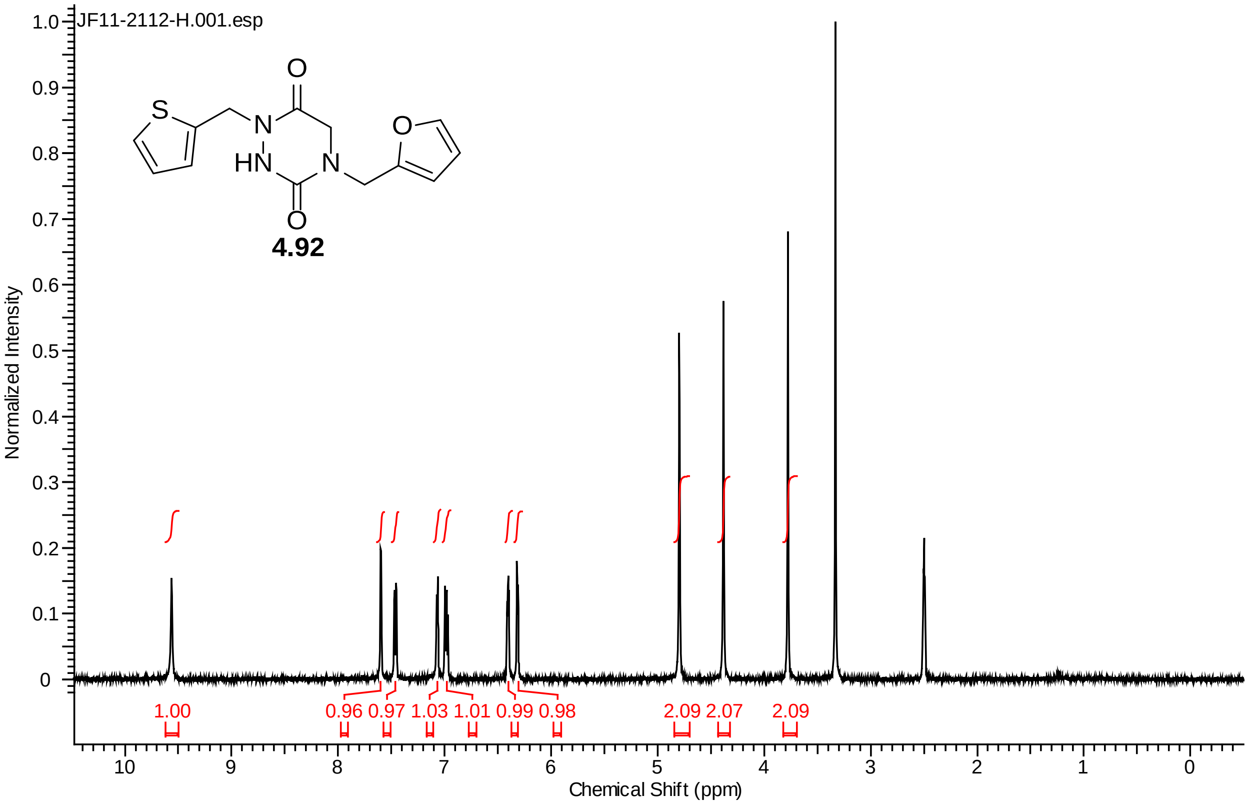
JF11-2092-H.001.esp
O
N
HN
O
N
O
O
Normalized Intensity
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.90
1.16
0.84
4.01
11.83
2.19
2.17
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)



JF11-2092-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
161.7328
155.5617
101.9815
66.1910
53.6633
51.5468
50.2740
46.9976
28.5459
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

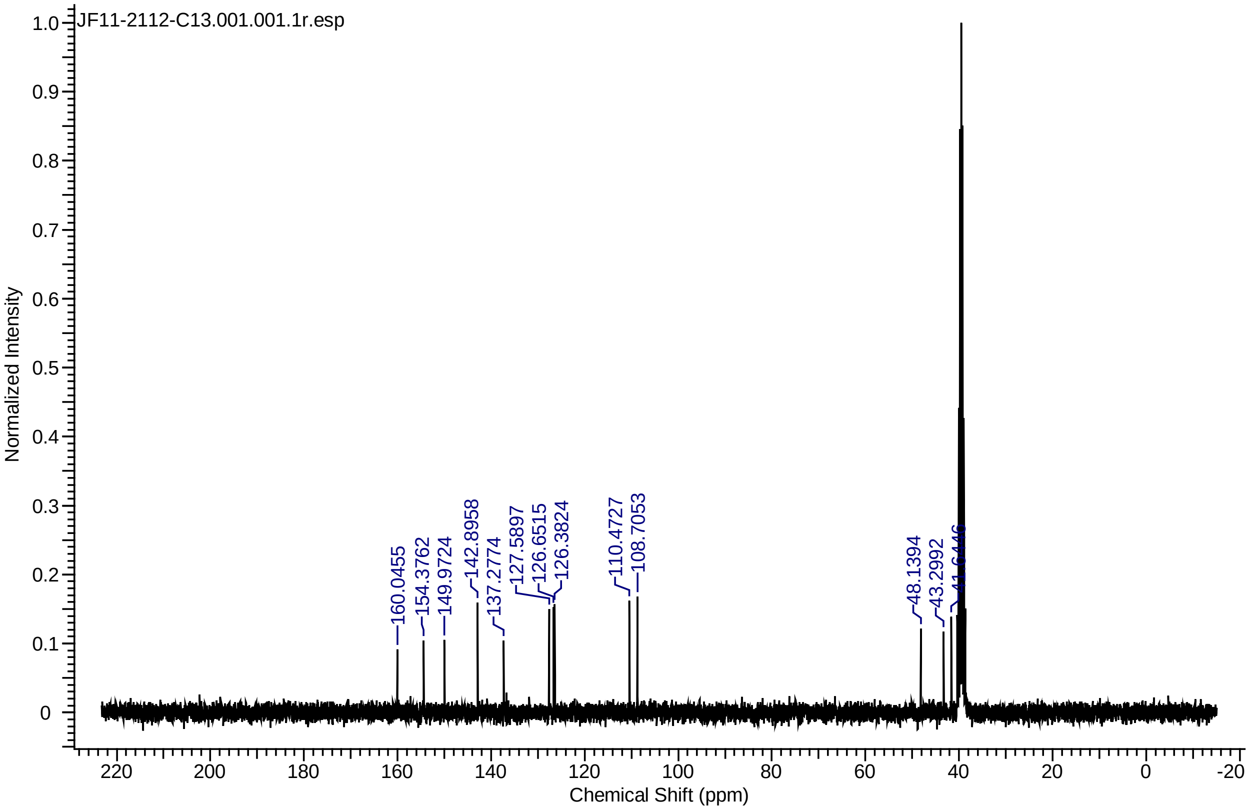

JF11-2093-H.001.esp
4.91
Normalized Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.88
0.82
1.02
0.98
2.07
1.05
1.05
3.97
2.00
1.99
2.03
9.45
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


JF11-2093-C13.001.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
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
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

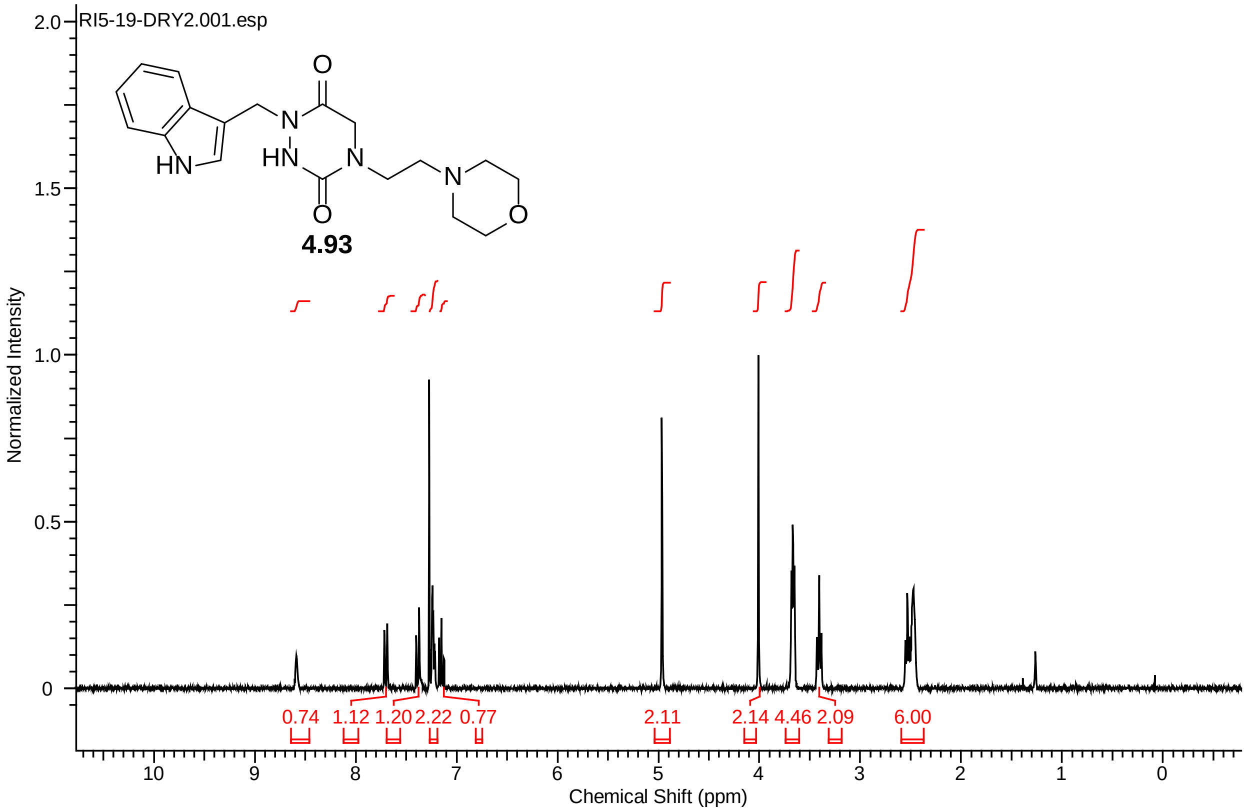


4.92

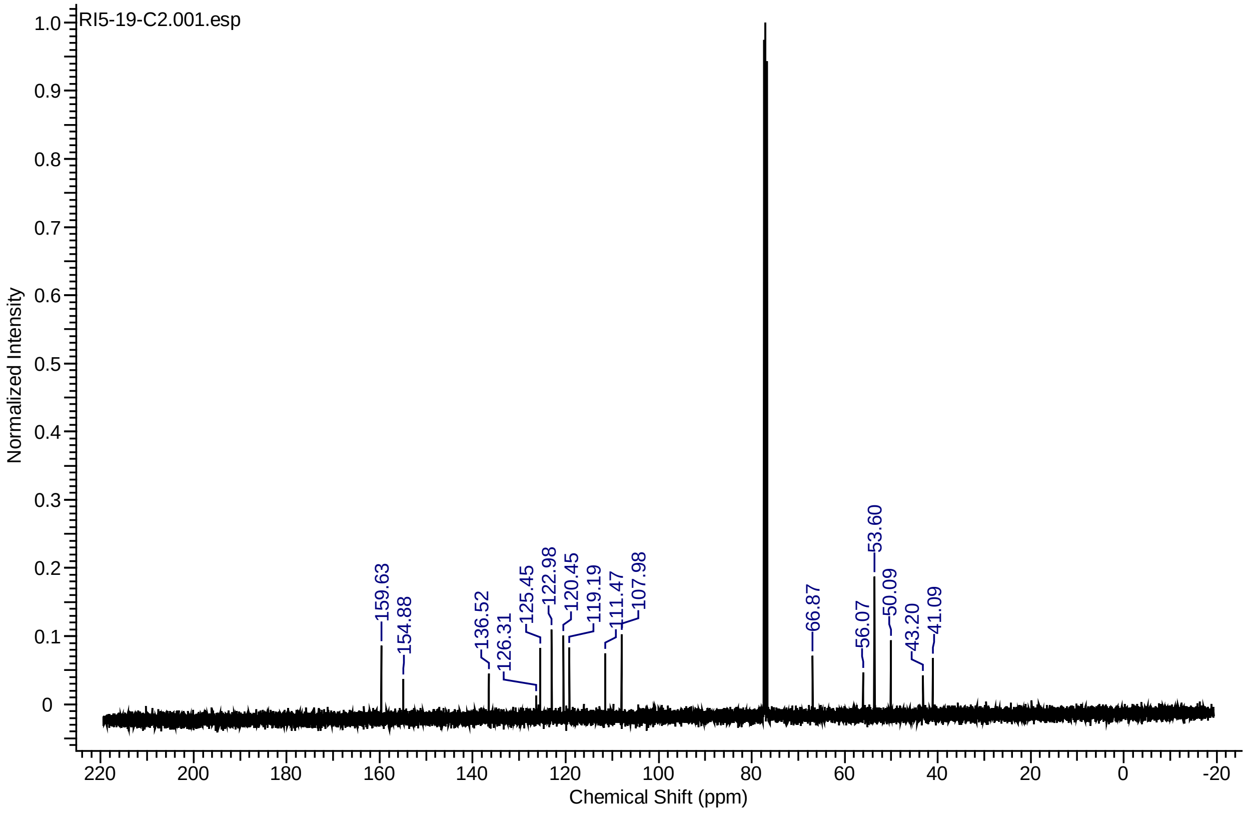
JF11-2112-H.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
S
N
HN
N
O
O
O
1.00
0.96
0.97
1.03
1.01
0.99
0.98
2.09
2.07
2.09
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

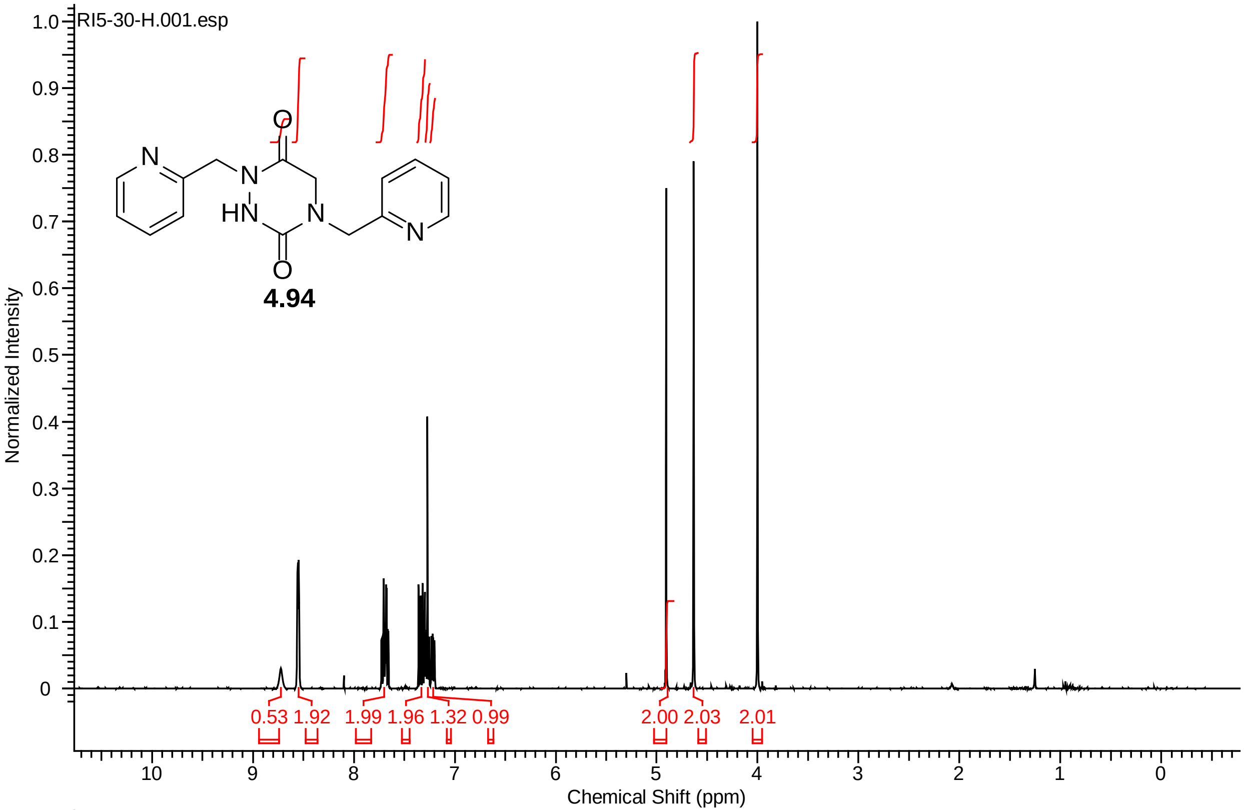


JF11-2112-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.0455
154.3762
149.9724
142.8958
137.2774
127.5897
126.6515
126.3824
110.4727
108.7053
48.1394
43.2992
41.6446
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

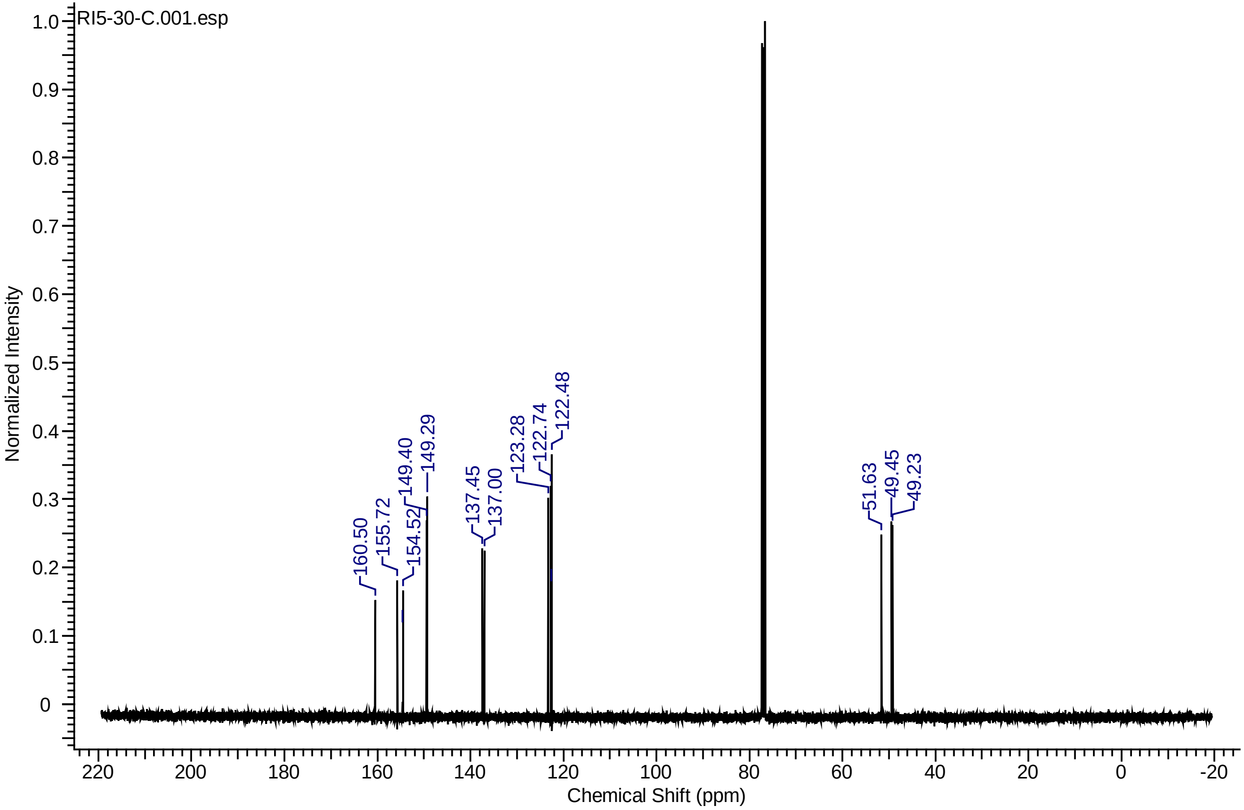

RI5-19-DRY2.001.esp
O
N
HN
N
N
O
O
HN
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.74
1.12
1.20
2.22
0.77
2.11
2.14
4.46
2.09
6.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

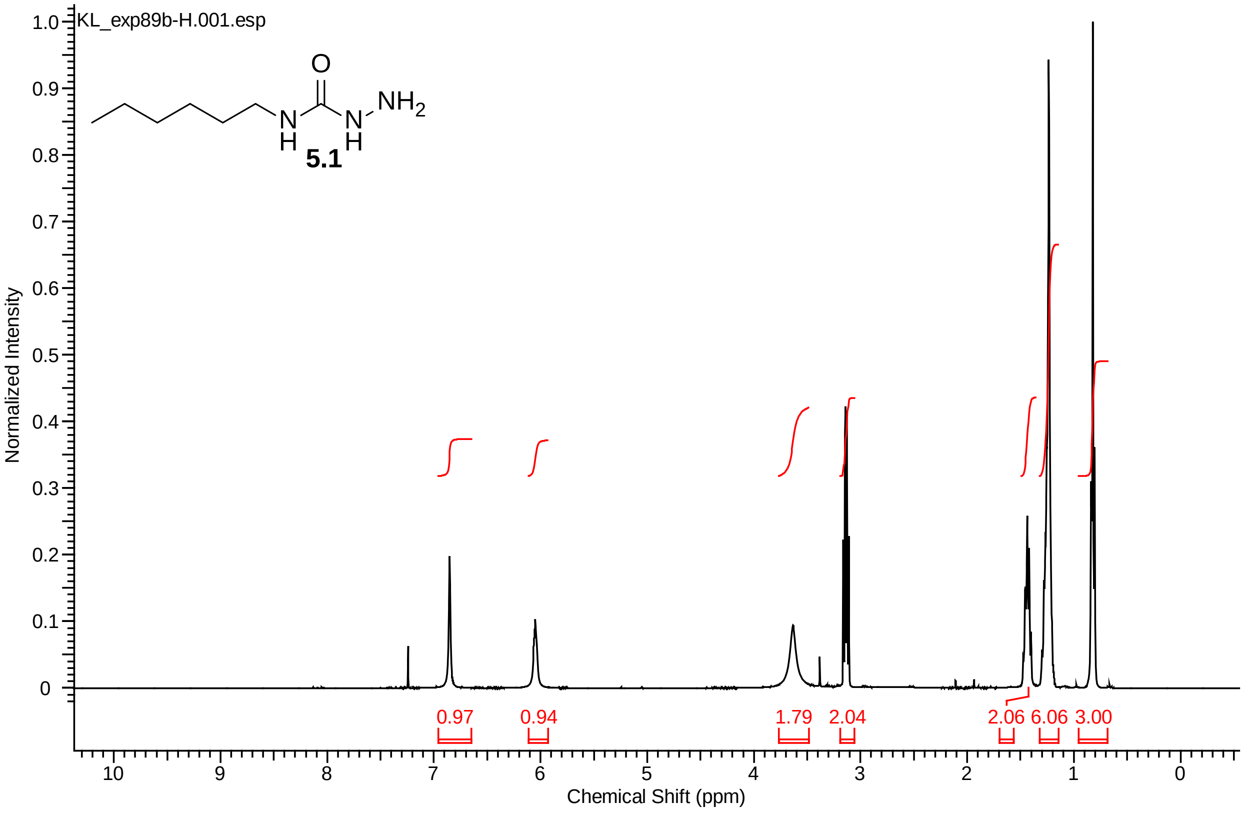
4.93

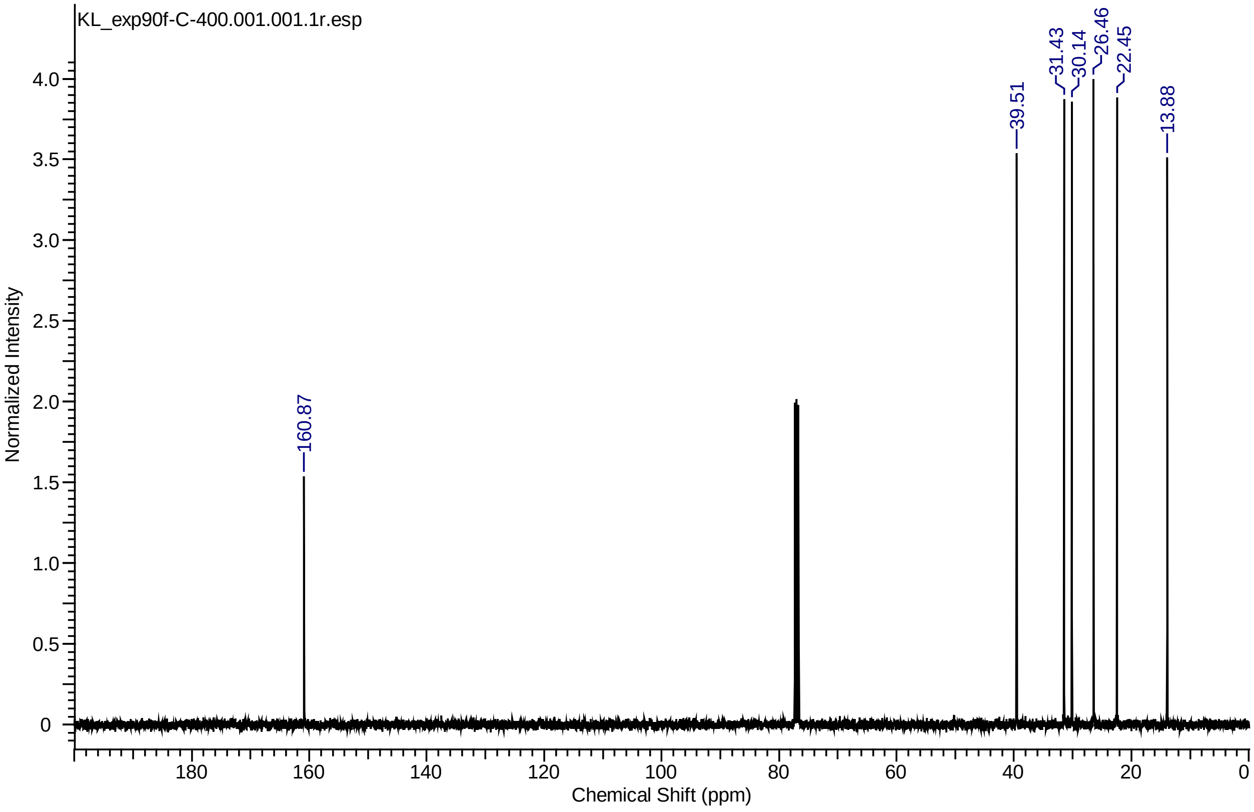

RI5-19-C2.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
159.63
154.88
136.52
126.31
125.45
122.98
120.45
119.19
111.47
107.98
66.87
56.07
53.60
50.09
43.20
41.09
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

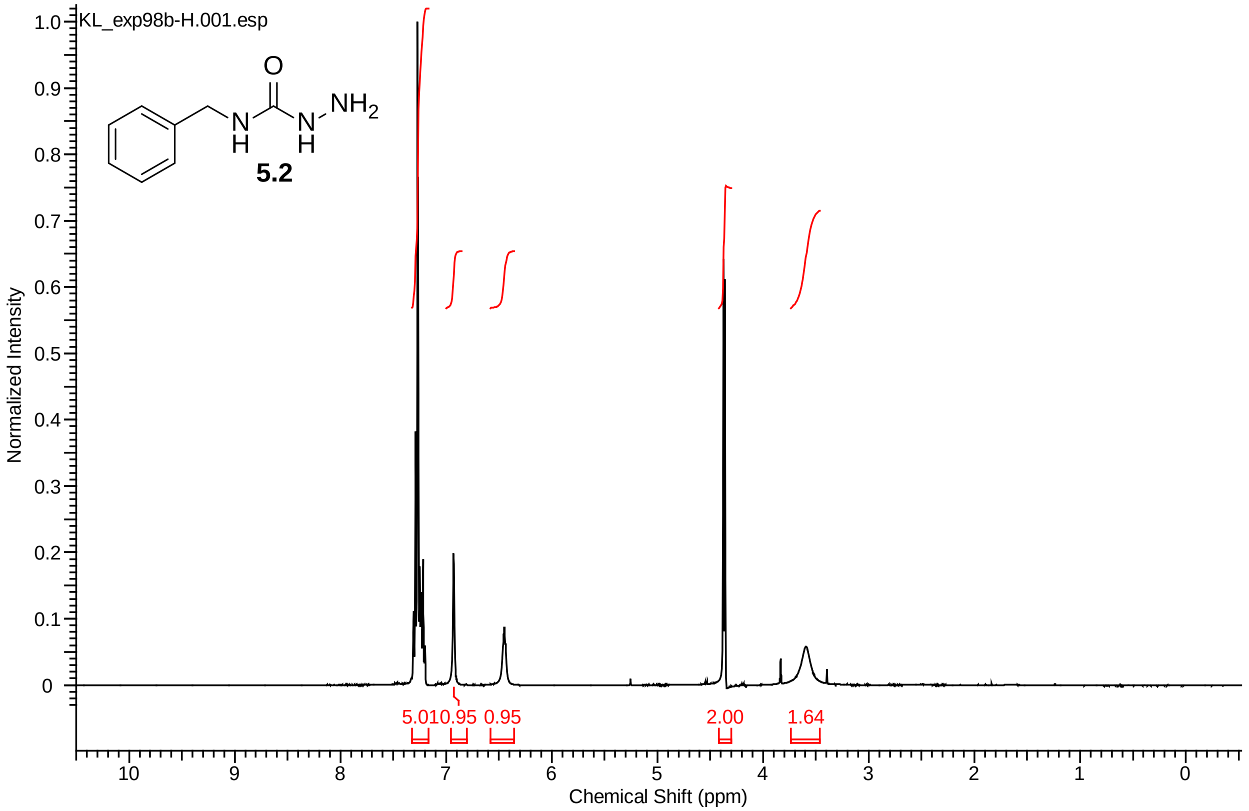

RI5-30-H.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
O
N
N
HN
N
N
O
0.53
1.92
1.99
1.96
1.32
0.99
2.00
2.03
2.01
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

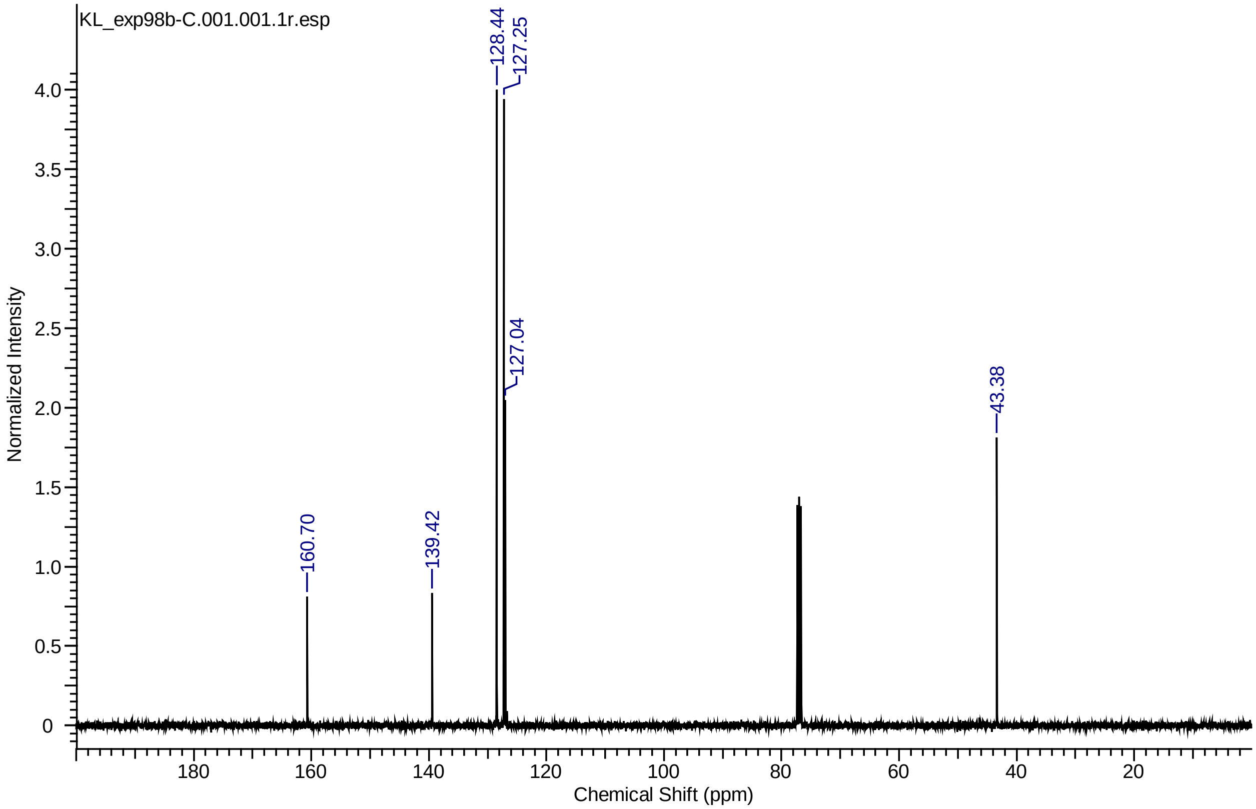
4.94

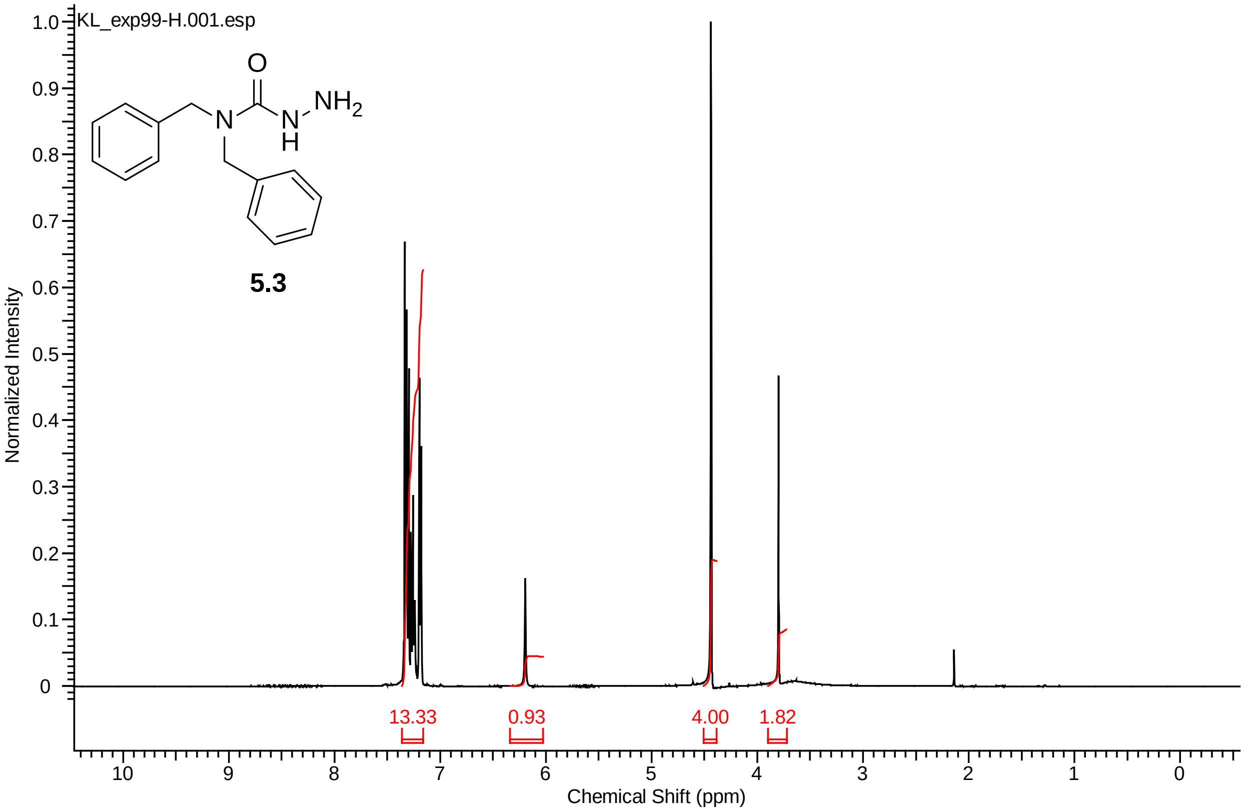

RI5-30-C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.50
155.72
154.52
149.40
149.29
137.45
137.00
123.28
122.74
122.48
51.63
49.45
49.23
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

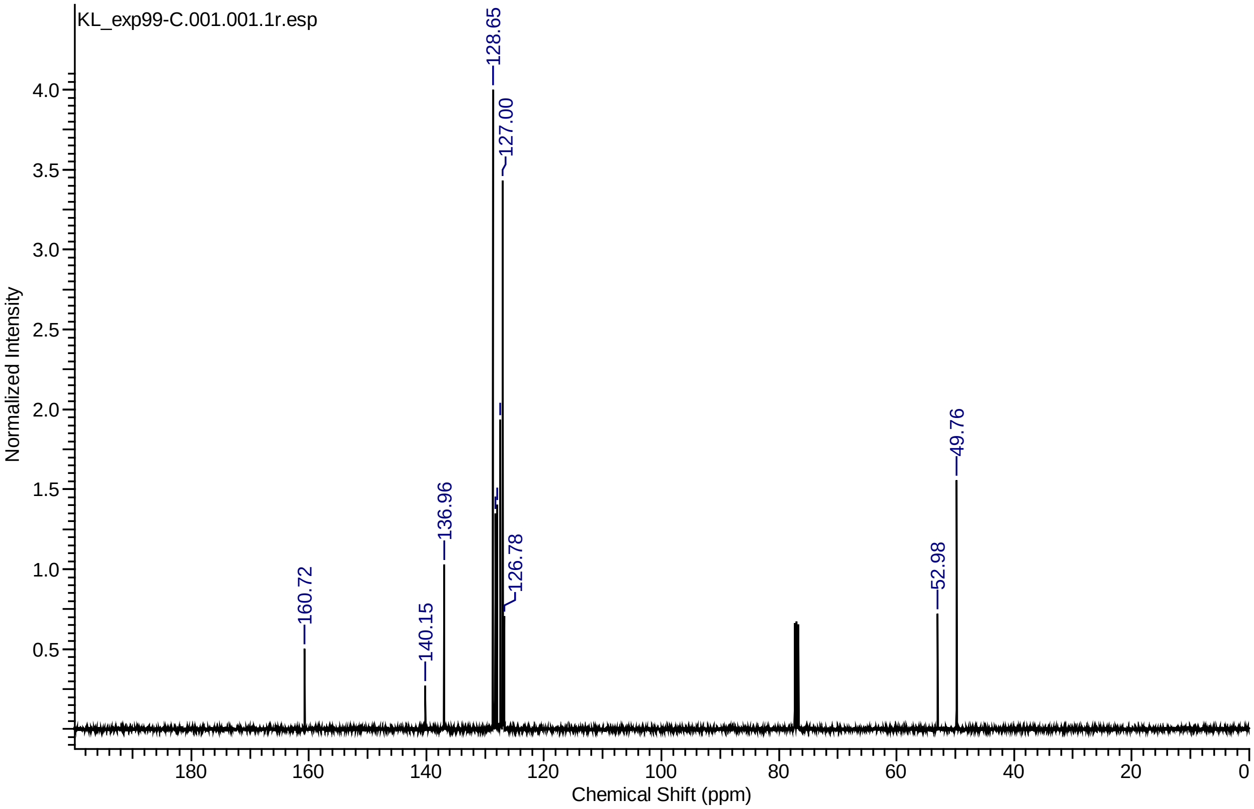

KL_exp89b-H.001.esp
O
NH2
N
H
N
H
5.1
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.97
0.94
1.79
2.04
2.06
6.06
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

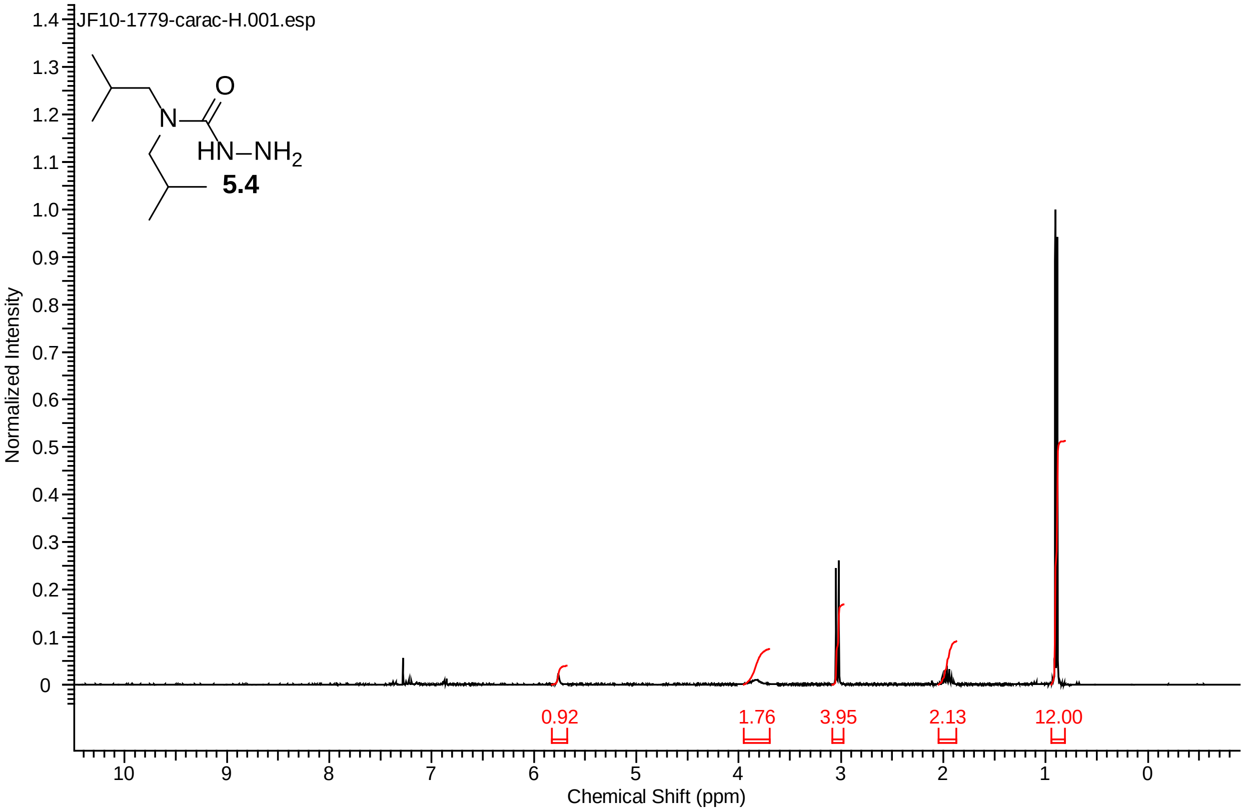

KL_exp90f-C-400.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
160.87
39.51
31.43
30.14
26.46
22.45
13.88
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

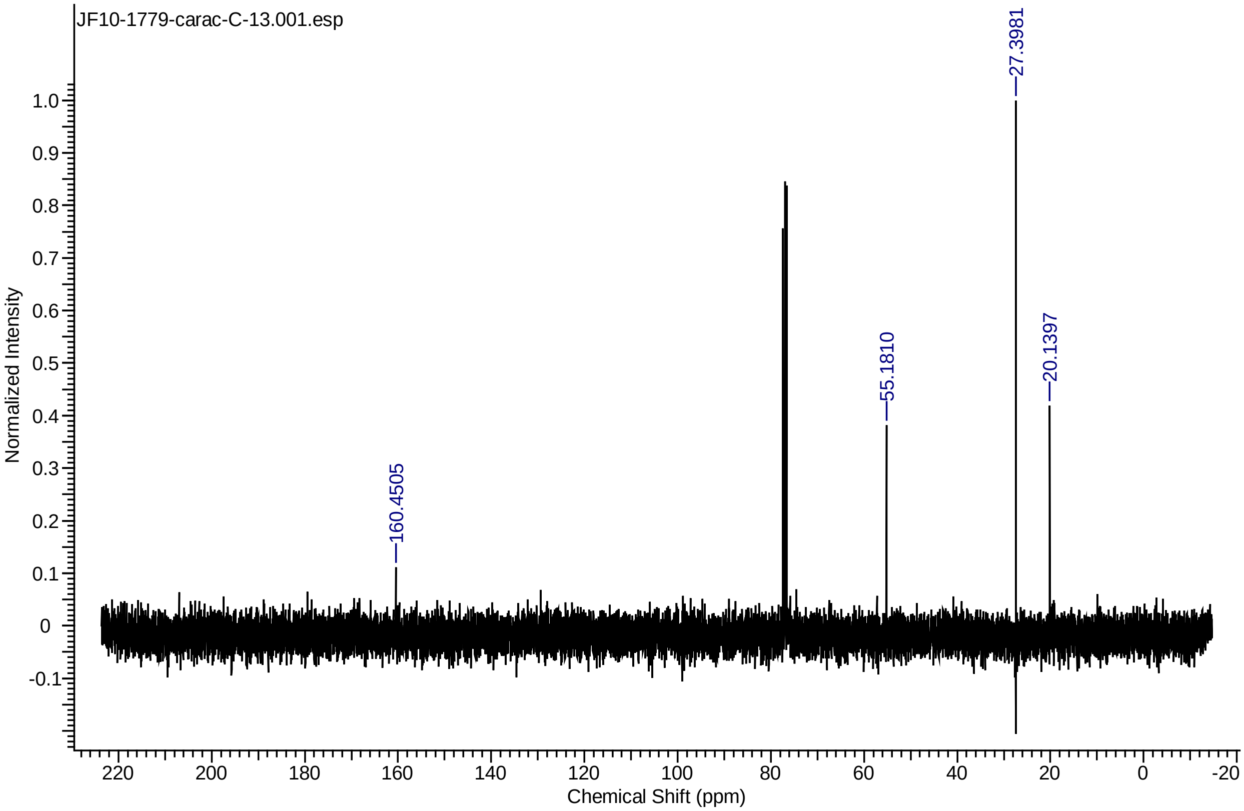

KL_exp98b-H.001.esp
O
NH2
N
H
N
H
5.2
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
5.01
0.95
0.95
2.00
1.64
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

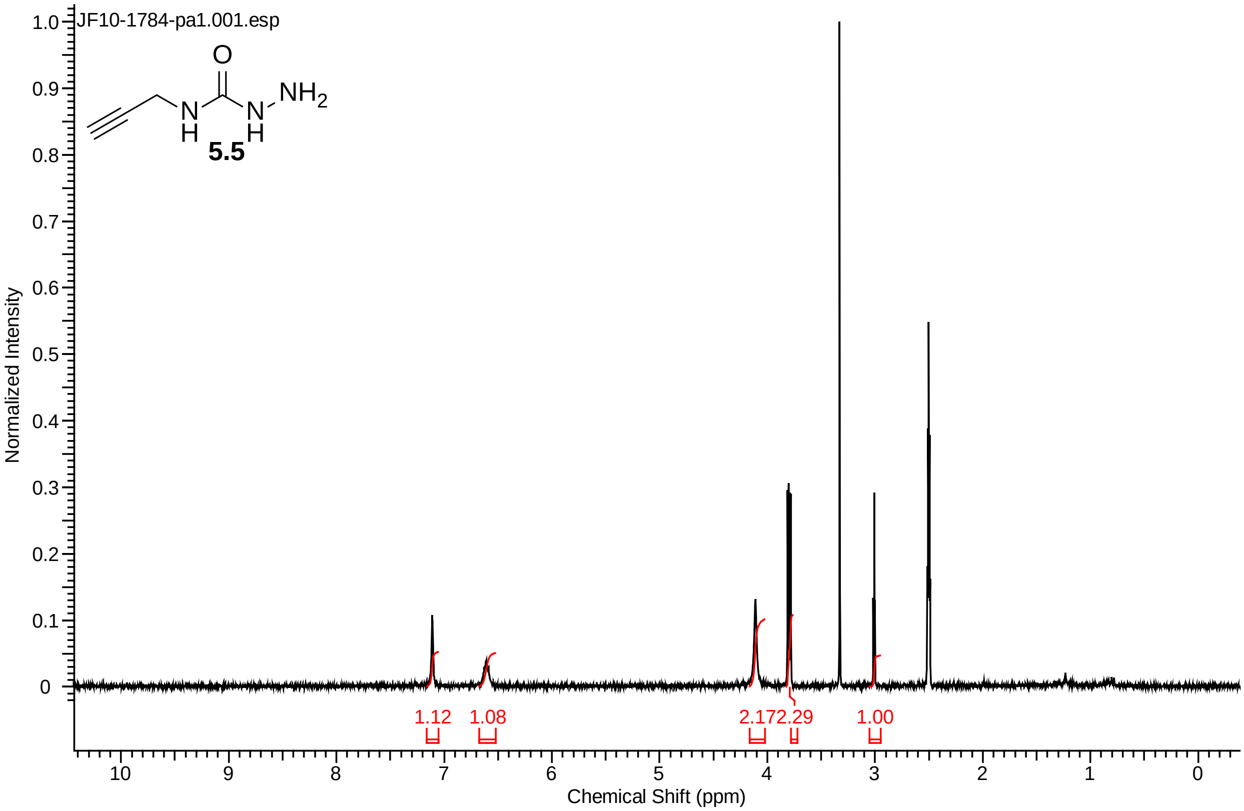

KL_exp98b-C.001.001.1r.esp
128.44
127.25
127.04
160.70
139.42
43.38
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)

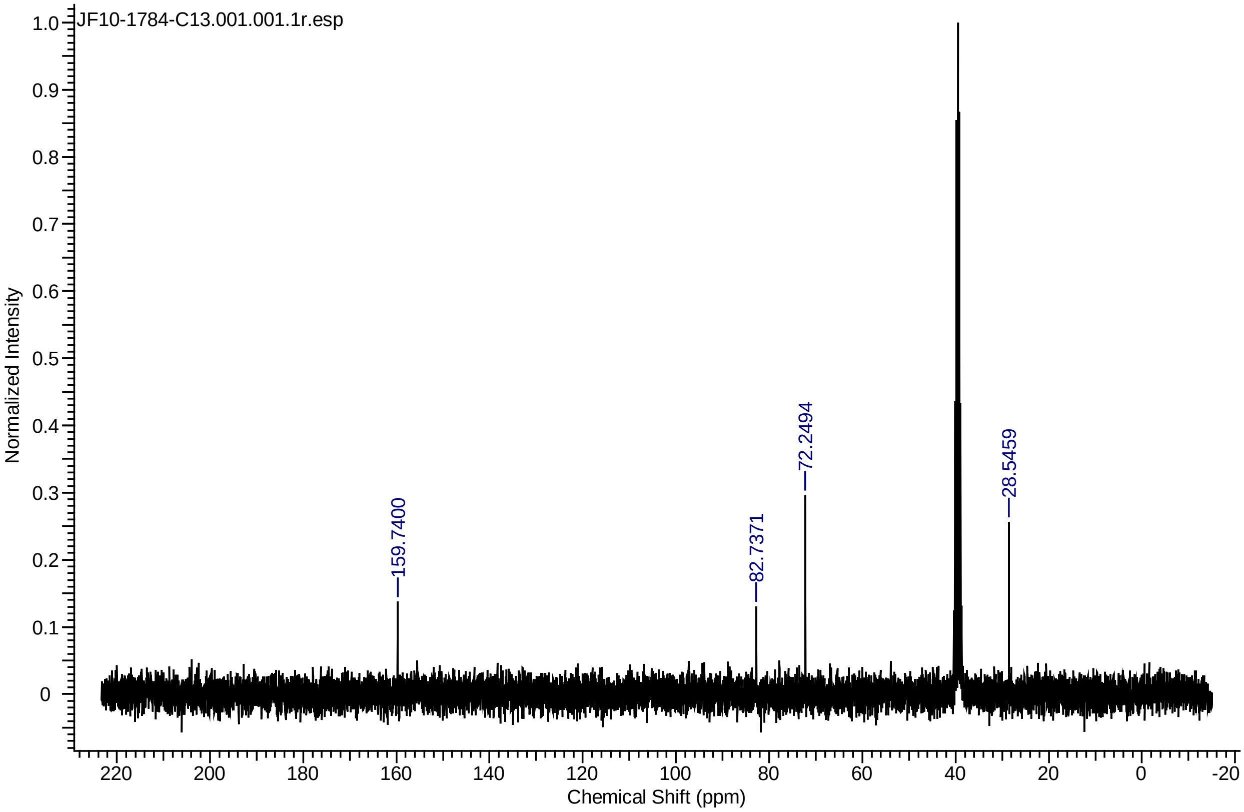

KL_exp99-H.001.esp
O
N
N
H
NH2
5.3
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
13.33
0.93
4.00
1.82
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

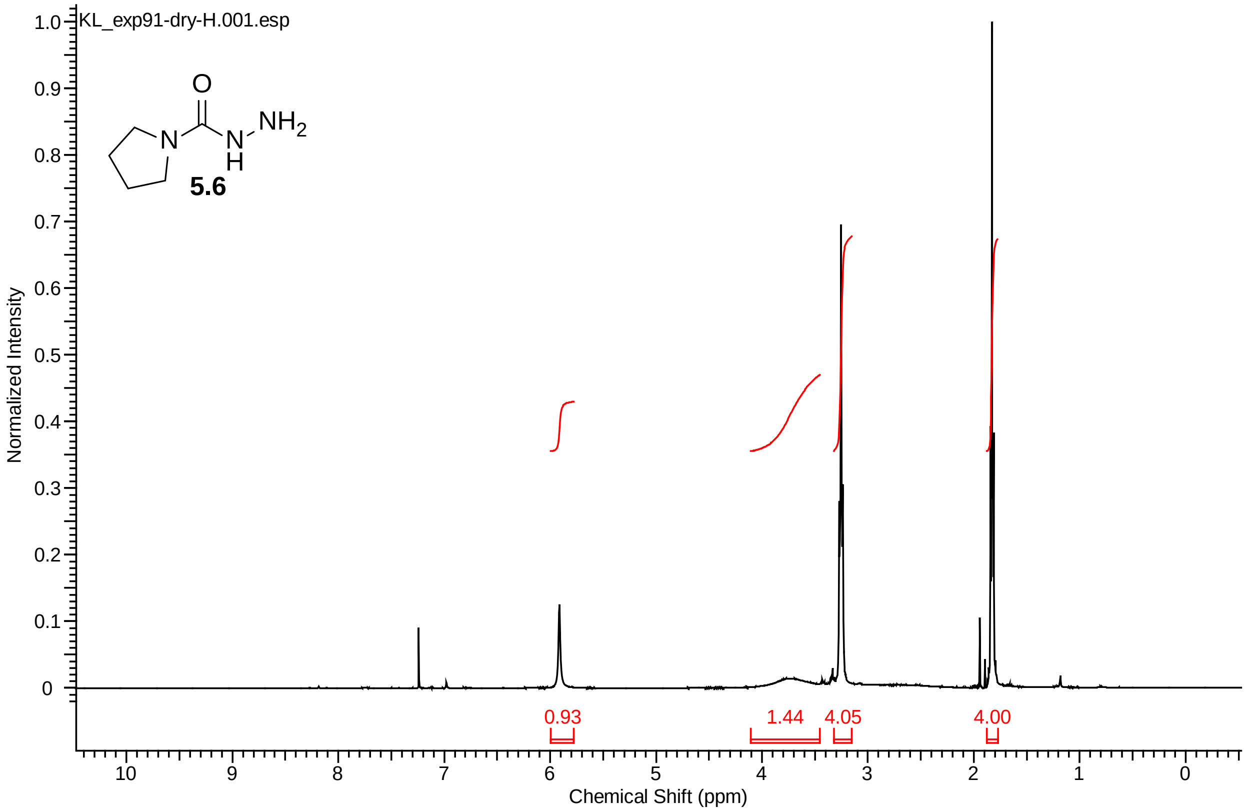

KL_exp99-C.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
160.72
140.15
136.96
128.65
127.00
126.78
52.98
49.76
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

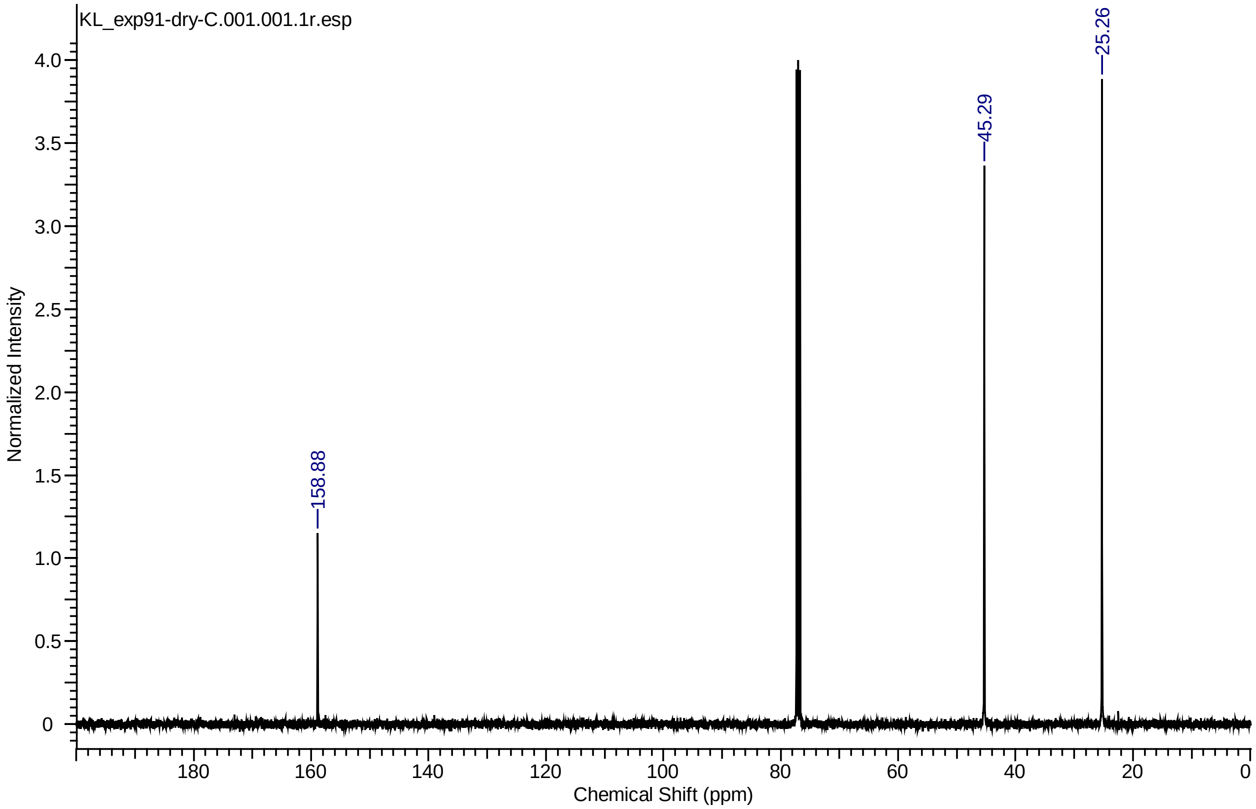

JF10-1779-carac-H.001.esp
O
N
HN–NH2
5.4
Normalized Intensity
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.92
1.76
3.95
2.13
12.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

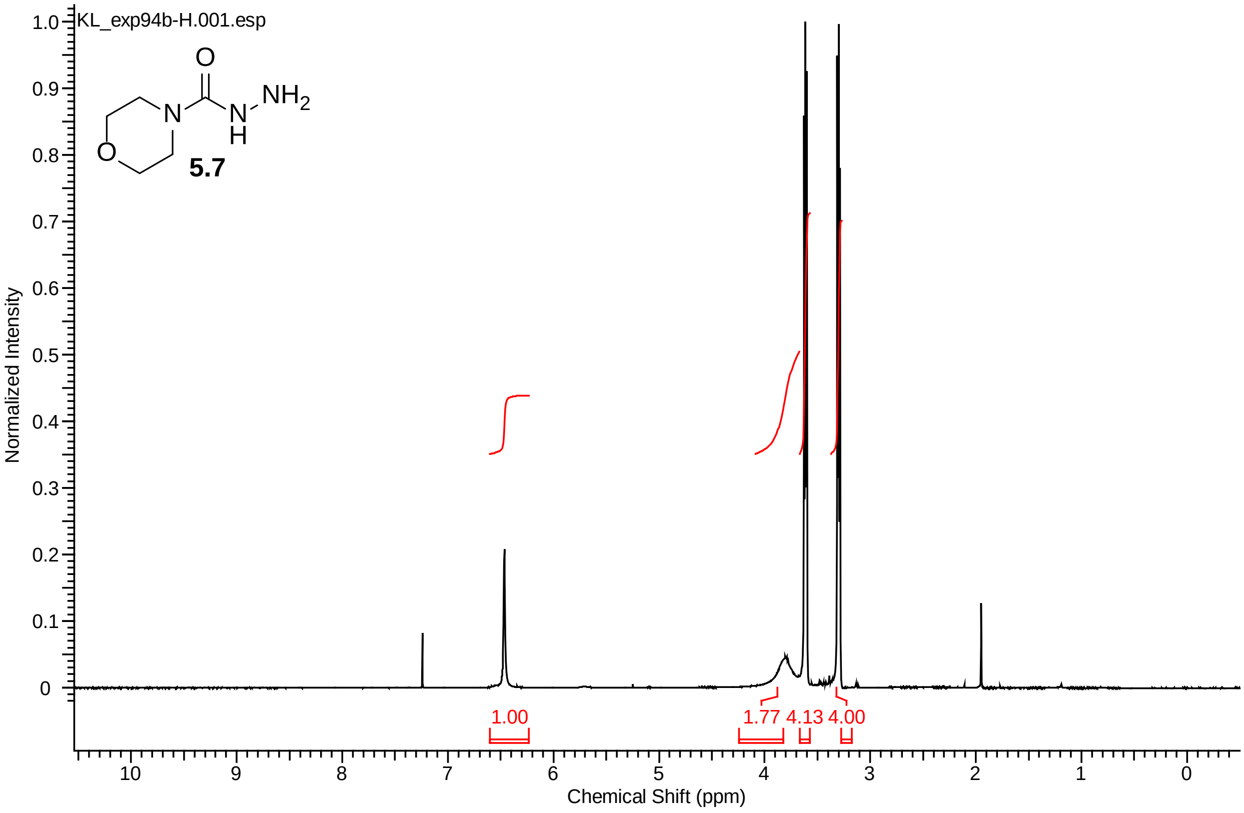

JF10-1779-carac-C-13.001.esp
160.4505
55.1810
27.3981
20.1397
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

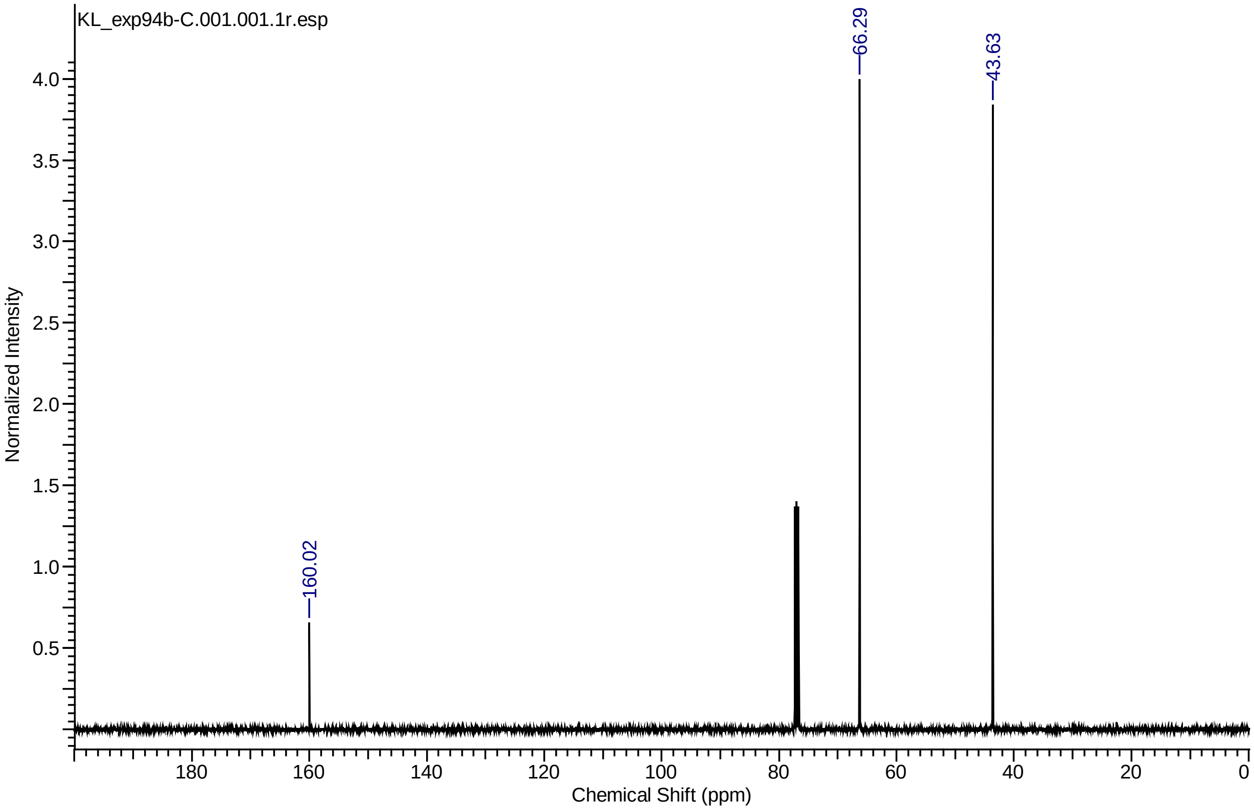

JF10-1784-pa1.001.esp
O
N
H
N
H
NH2
5.5
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.12
1.08
2.17
2.29
1.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

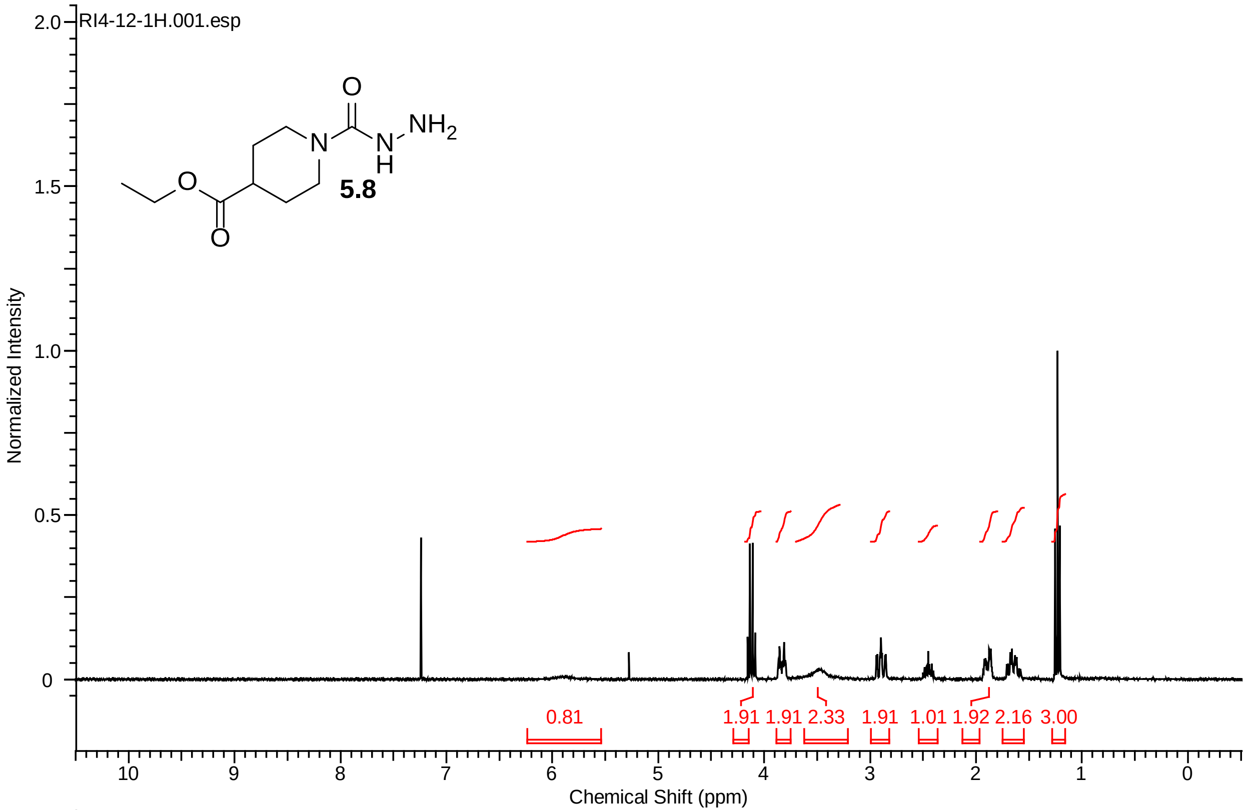

JF10-1784-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
159.7400
82.7371
72.2494
28.5459
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

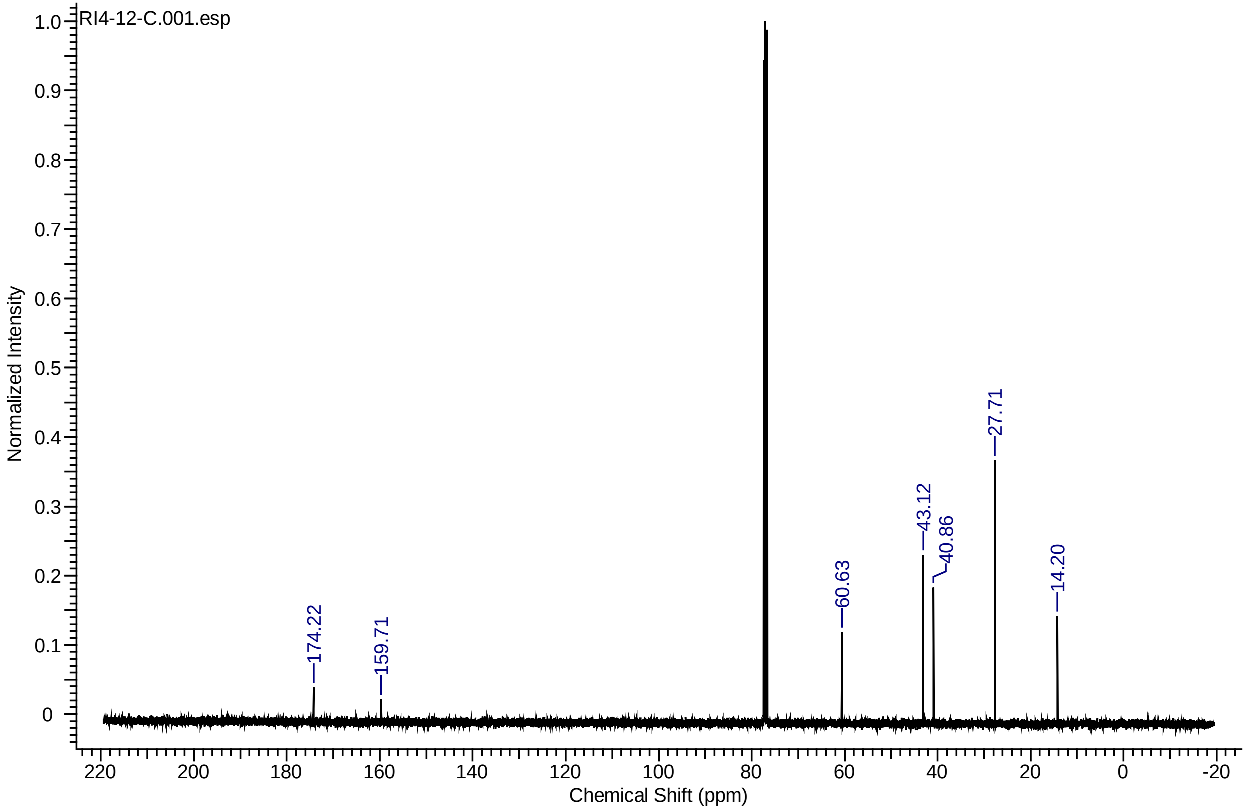

KL_exp91-dry-H.001.esp
O
N
N
H
NH2
5.6
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.93
1.44
4.05
4.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

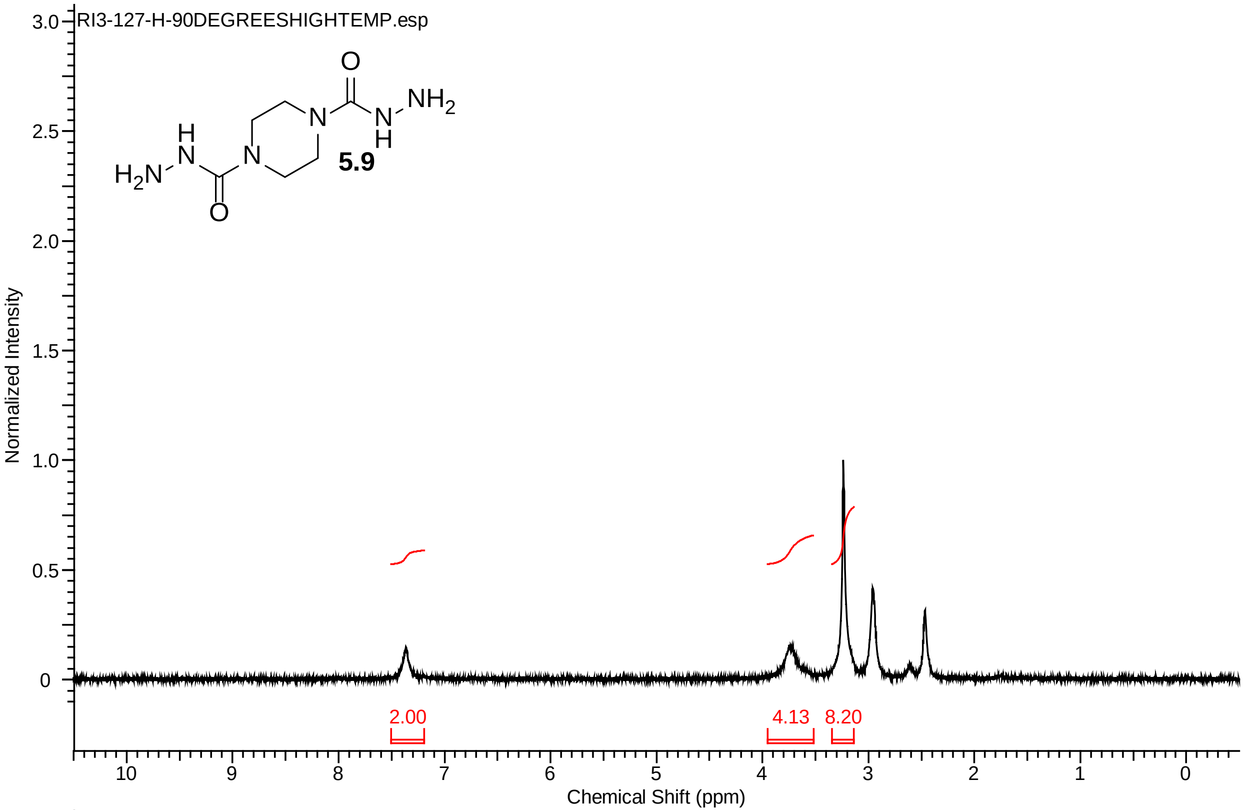

KL_exp91-dry-C.001.001.1r.esp
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
158.88
45.29
25.26
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


KL_exp94b-H.001.esp
5.7
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
1.00
1.77
4.13
4.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


KL_exp94b-C.001.001.1r.esp
160.02
66.29
43.63
Normalized Intensity
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

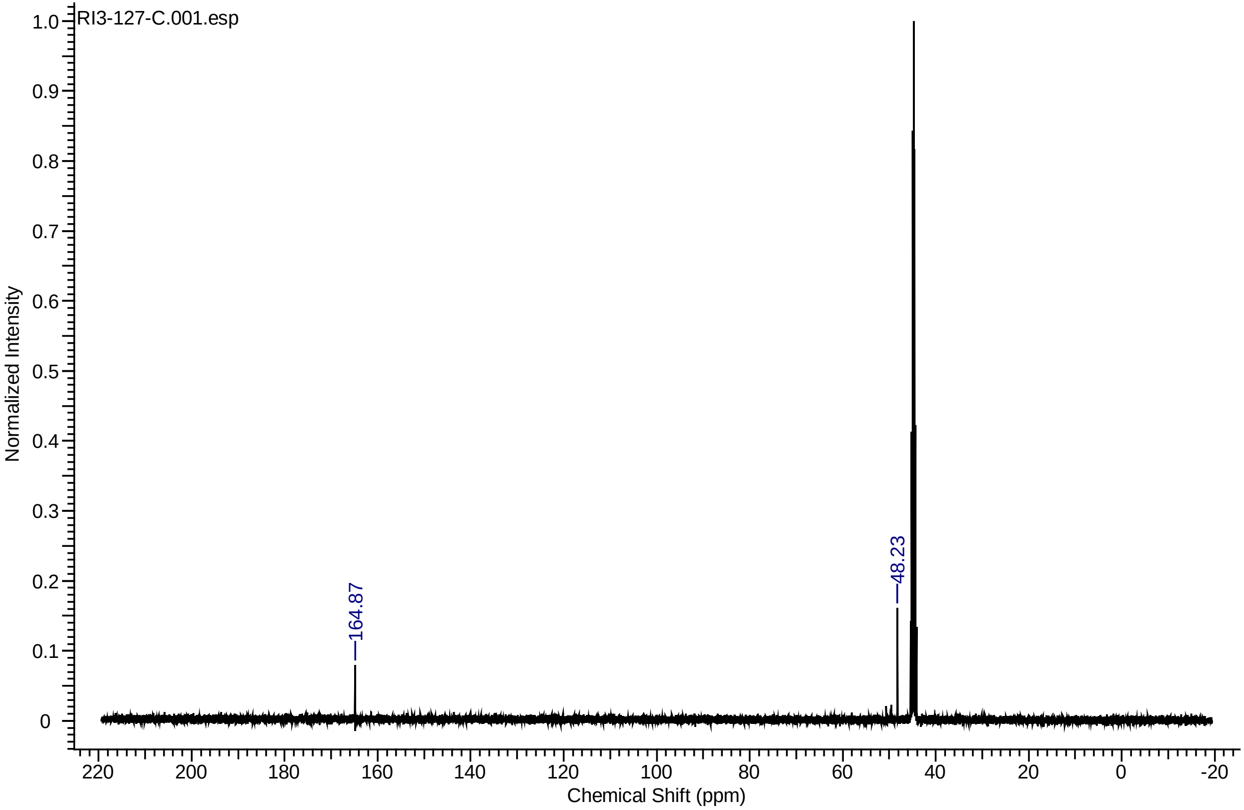

RI4-12-1H.001.esp
5.8
O
NH2
N
H
N
O
O
Normalized Intensity
2.0
1.5
1.0
0.5
0
0.81
1.91
1.91
2.33
1.91
1.01
1.92
2.16
3.00
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


RI4-12-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
174.22
159.71
60.63
43.12
40.86
27.71
14.20
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

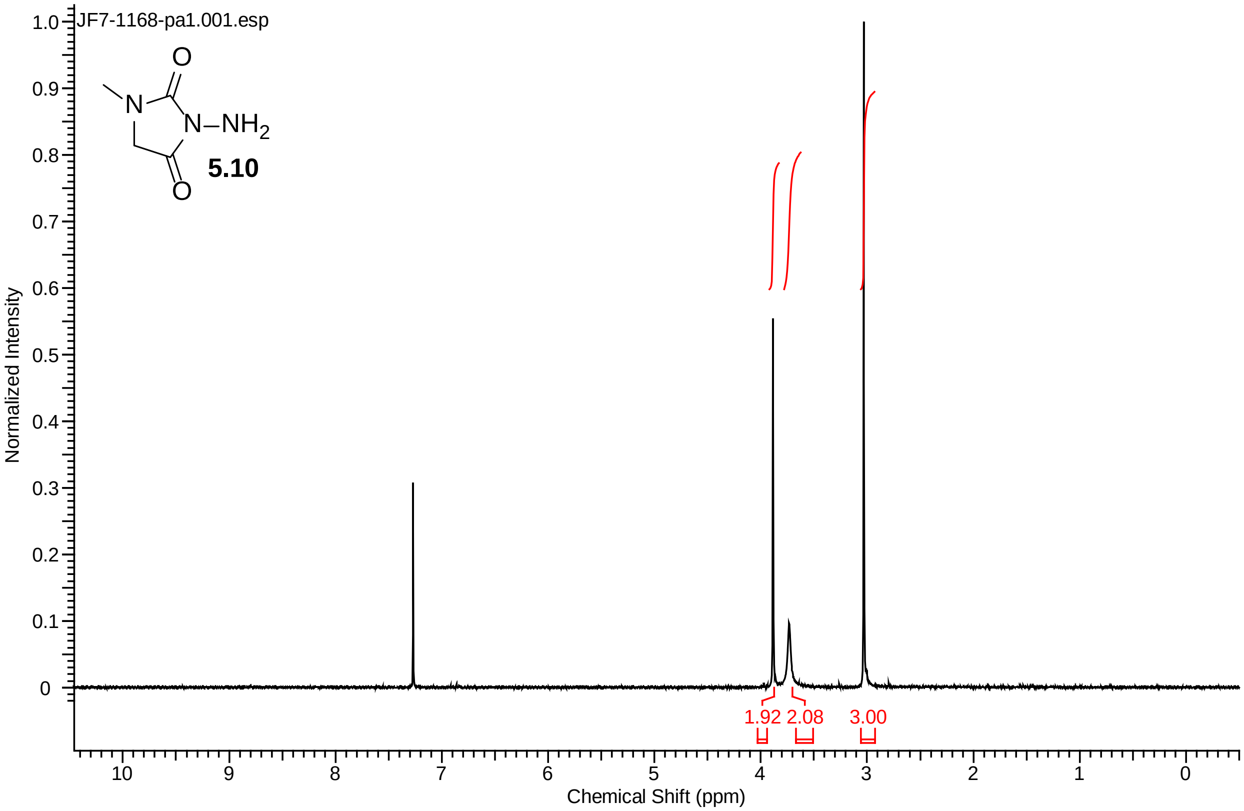


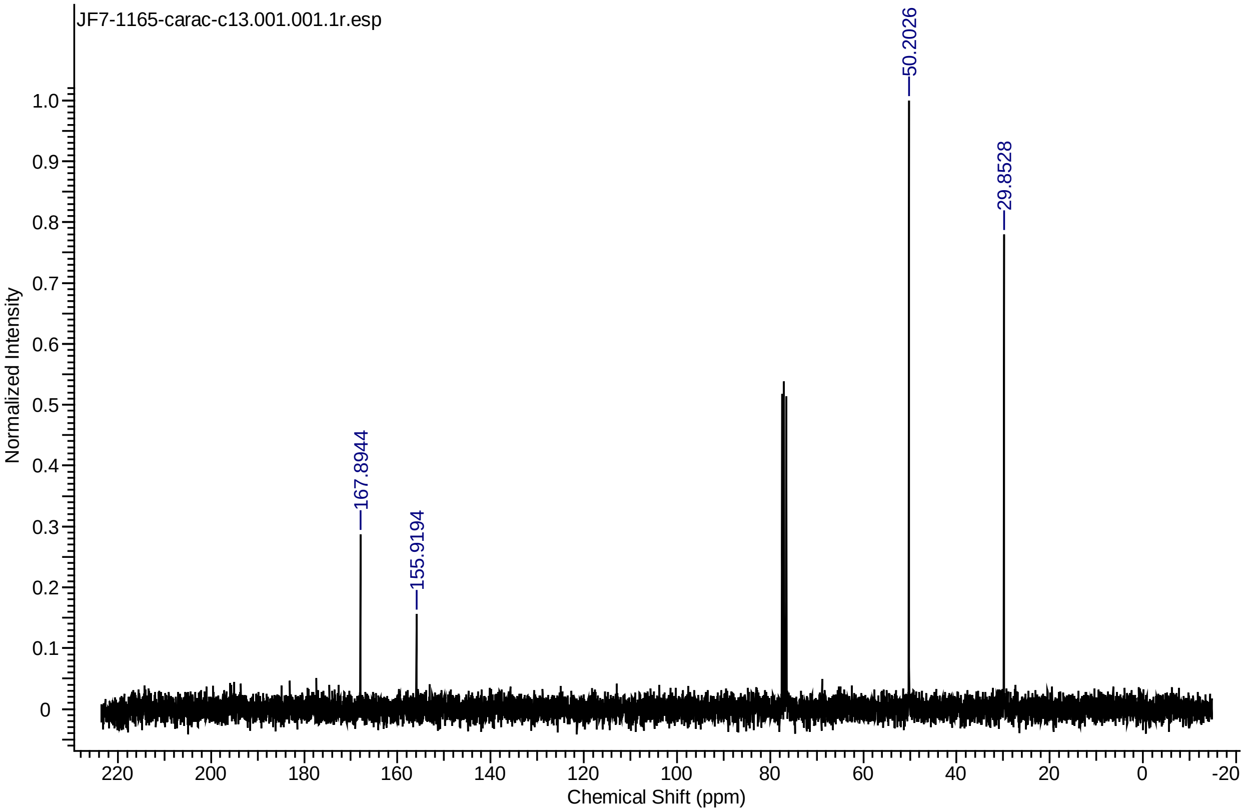
5.9

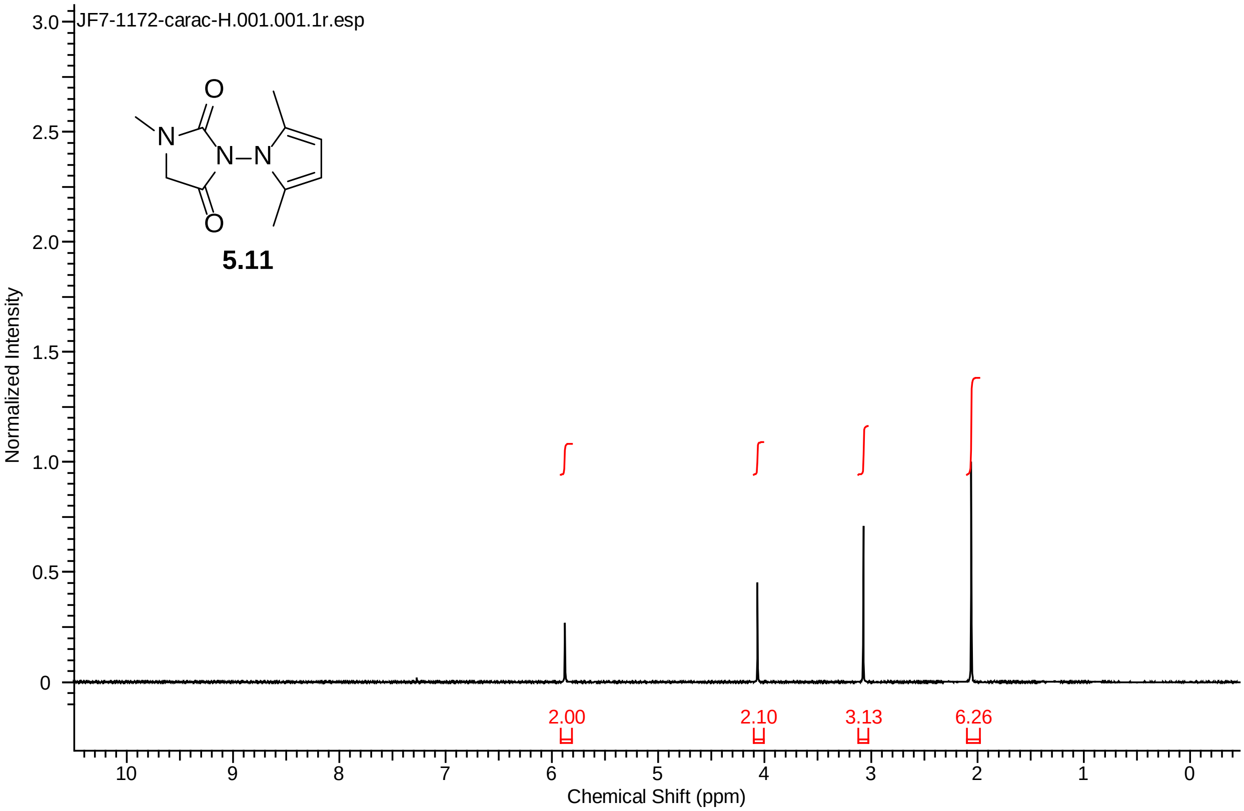
RI3-127-H-90DEGREESHIGHTEMP.esp
O
NH2
N
N
H
H
N
H2N
N
O
3.0
2.5
2.0
1.5
1.0
0.5
0
Normalized Intensity
2.00
4.13
8.20
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

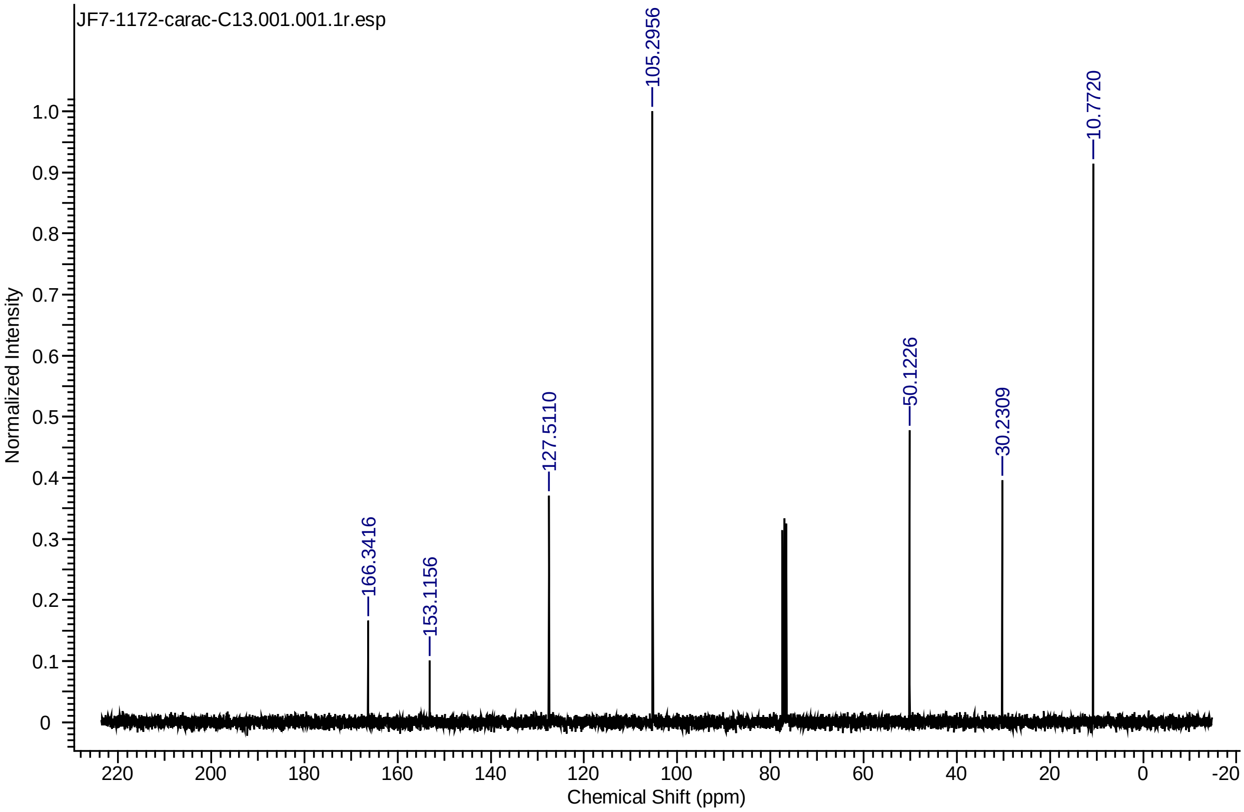


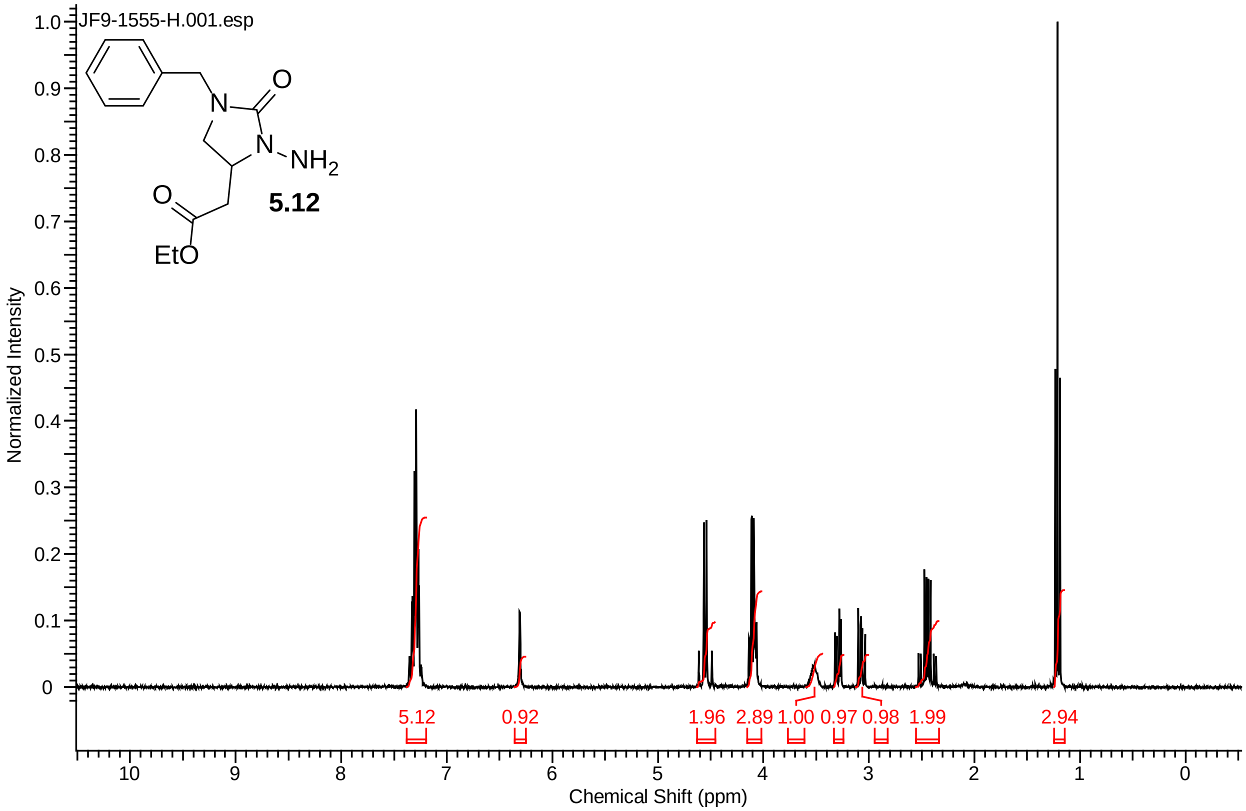
RI3-127-C.001.esp
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Normalized Intensity
164.87
48.23
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

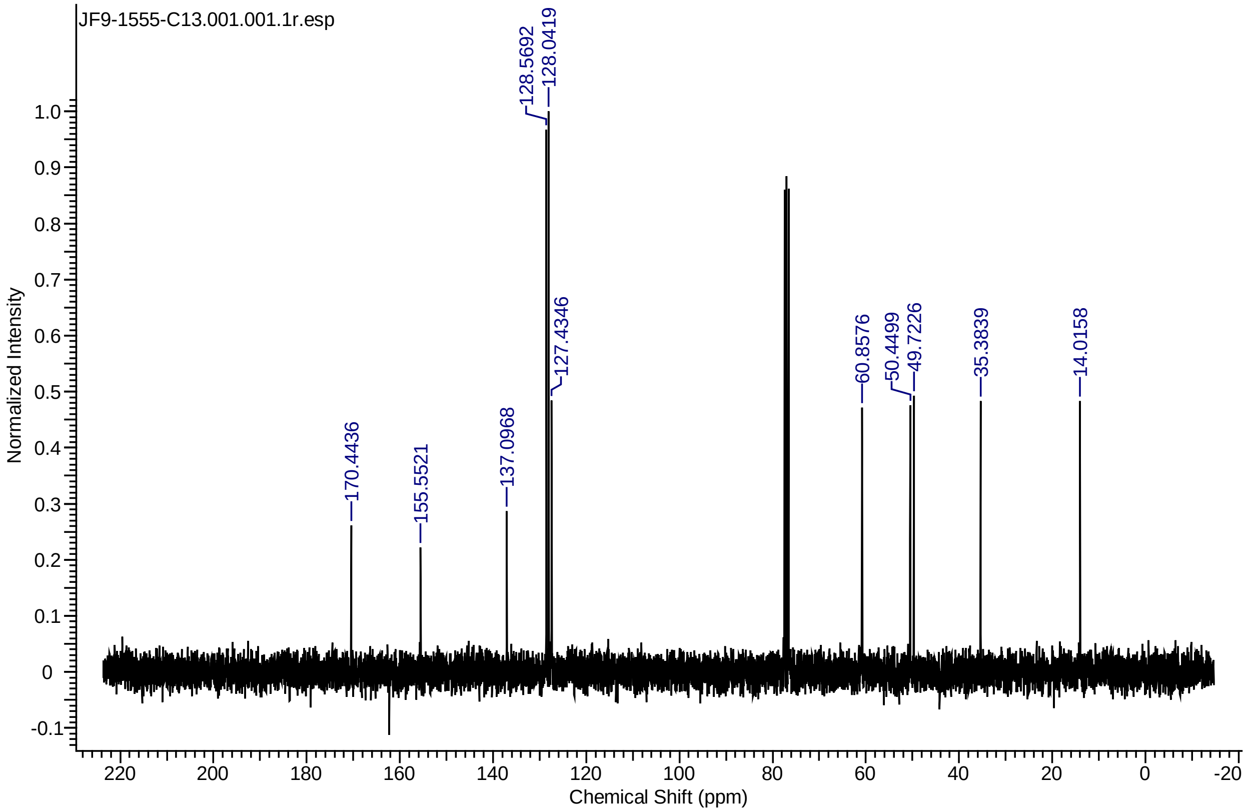

JF7-1168-pa1.001.esp
5.10
1.92
2.08
3.00
Normalized Intensity
Chemical Shift (ppm)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10
9
8
7
6
5
4
3
2
1
0

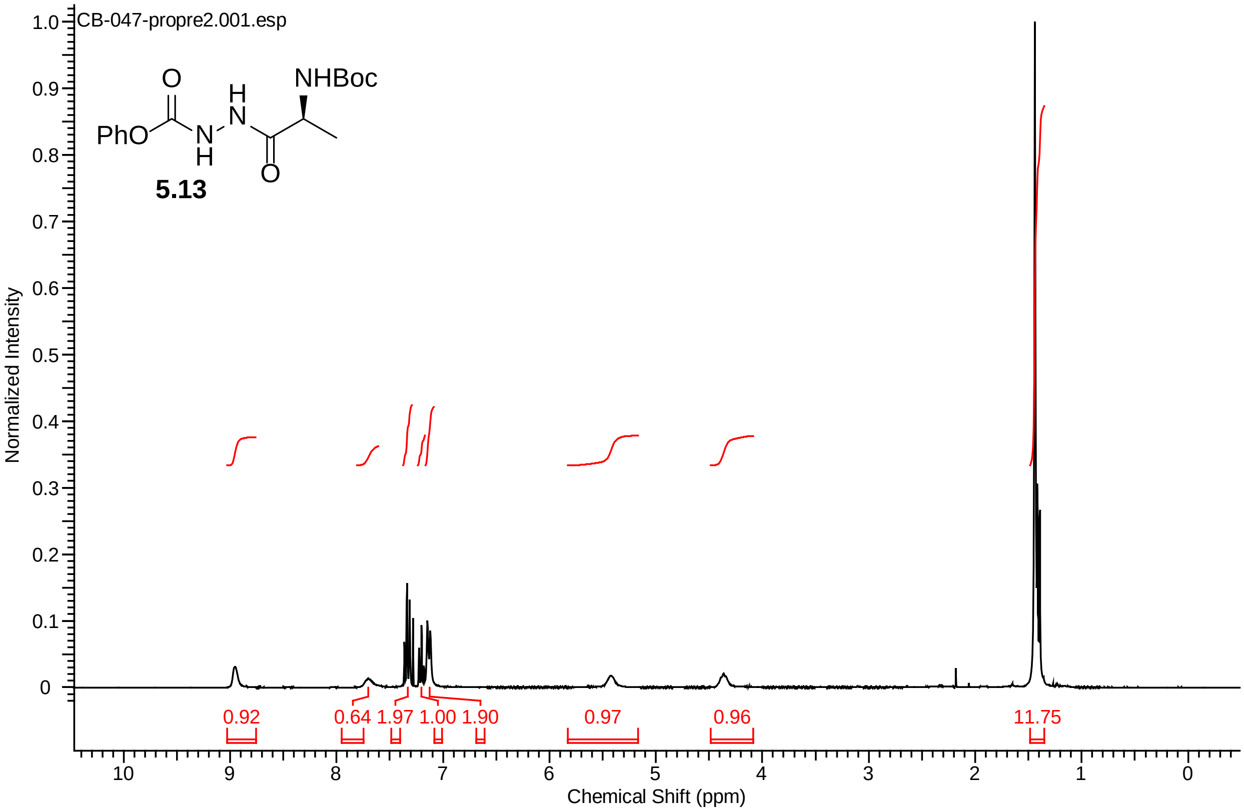

JF7-1165-carac-c13.001.001.1r.esp
167.8944
155.9194
50.2026
29.8528
Normalized Intensity
Chemical Shift (ppm)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20

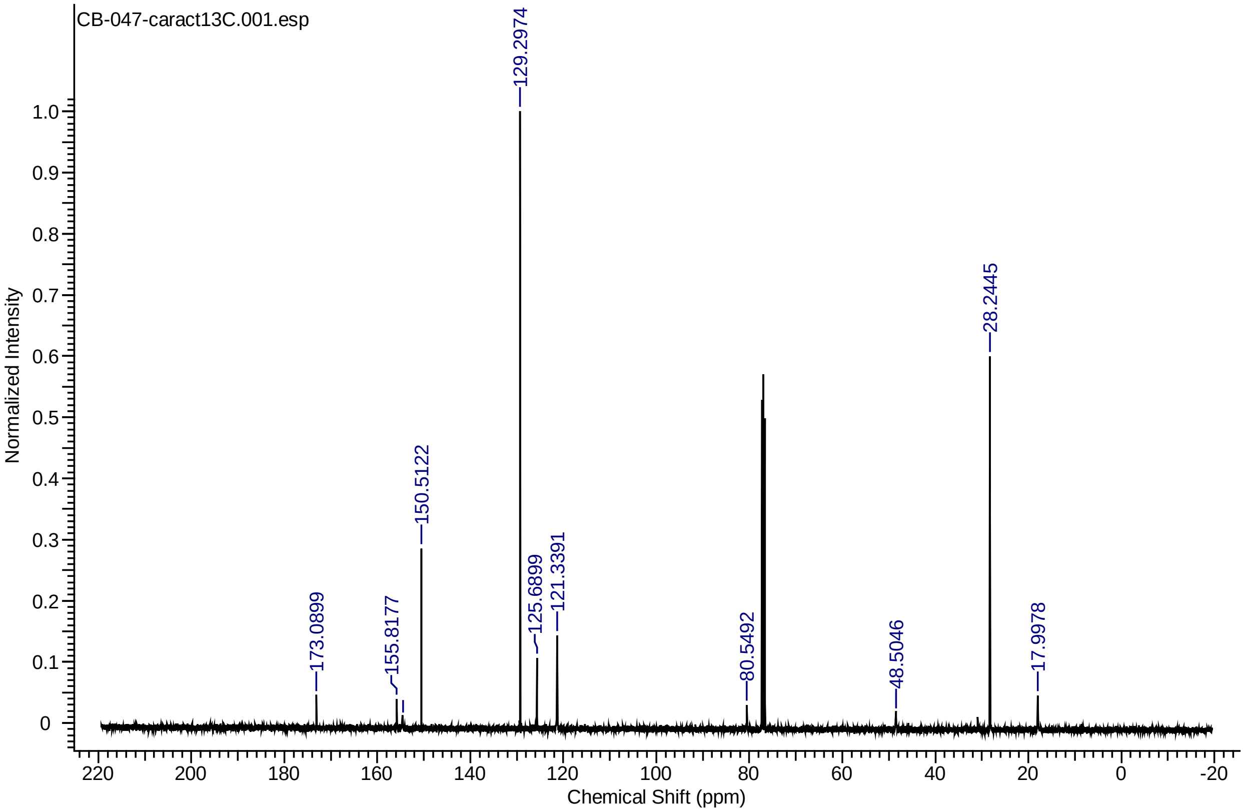

JF7-1172-carac-H.001.001.1r.esp
5.11
Normalized Intensity
3.0
2.5
2.0
1.5
1.0
0.5
0
2.00
2.10
3.13
6.26
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

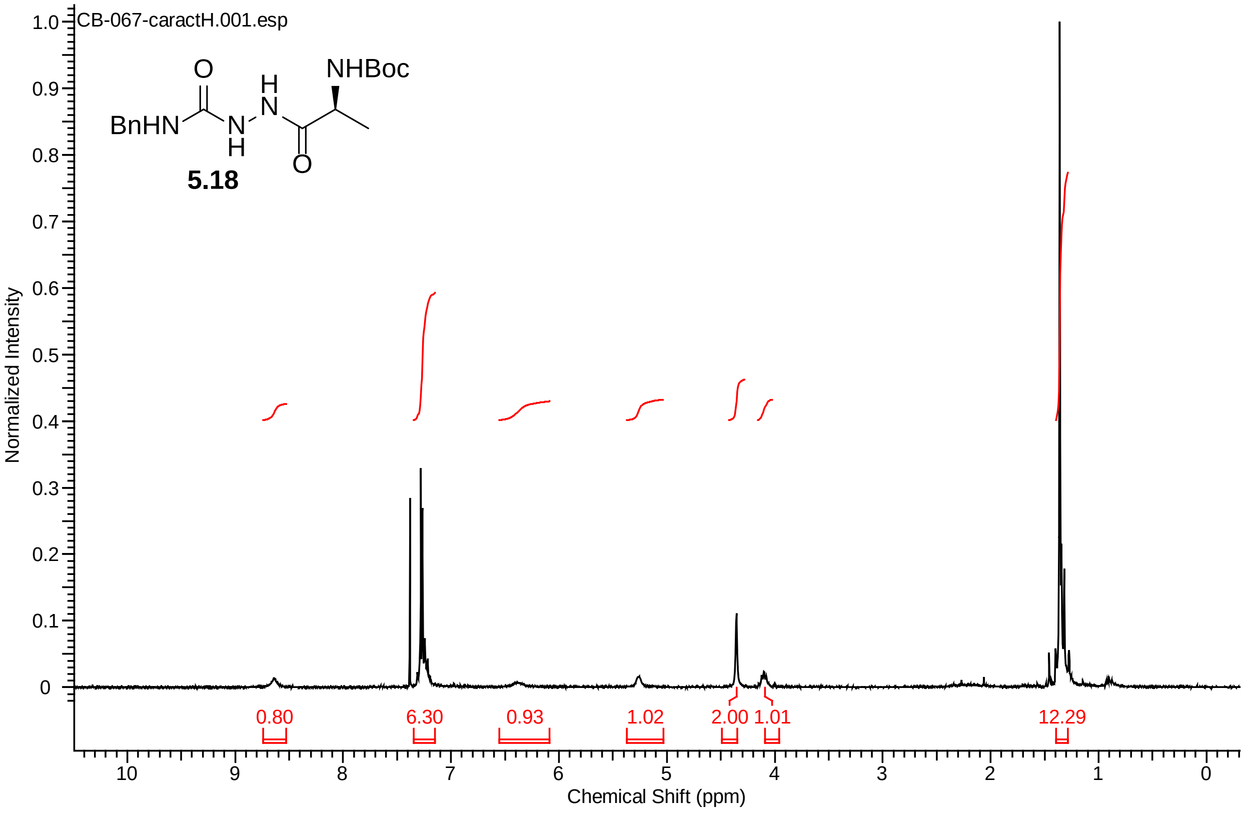

JF7-1172-carac-C13.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
166.3416
153.1156
127.5110
105.2956
50.1226
30.2309
10.7720
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

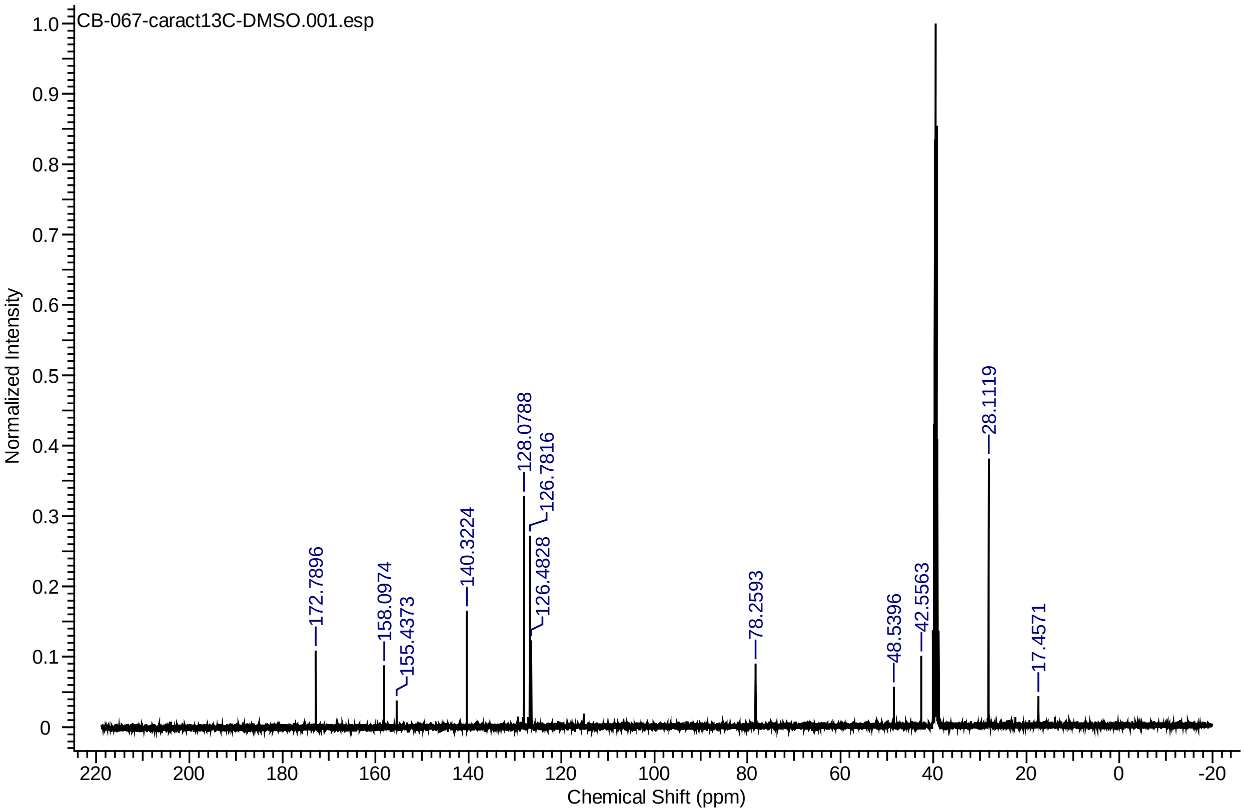

JF9-1555-H.001.esp
O
N
N
NH2
5.12
O
EtO
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
5.12
0.92
1.96
2.89
1.00
0.97
0.98
1.99
2.94
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

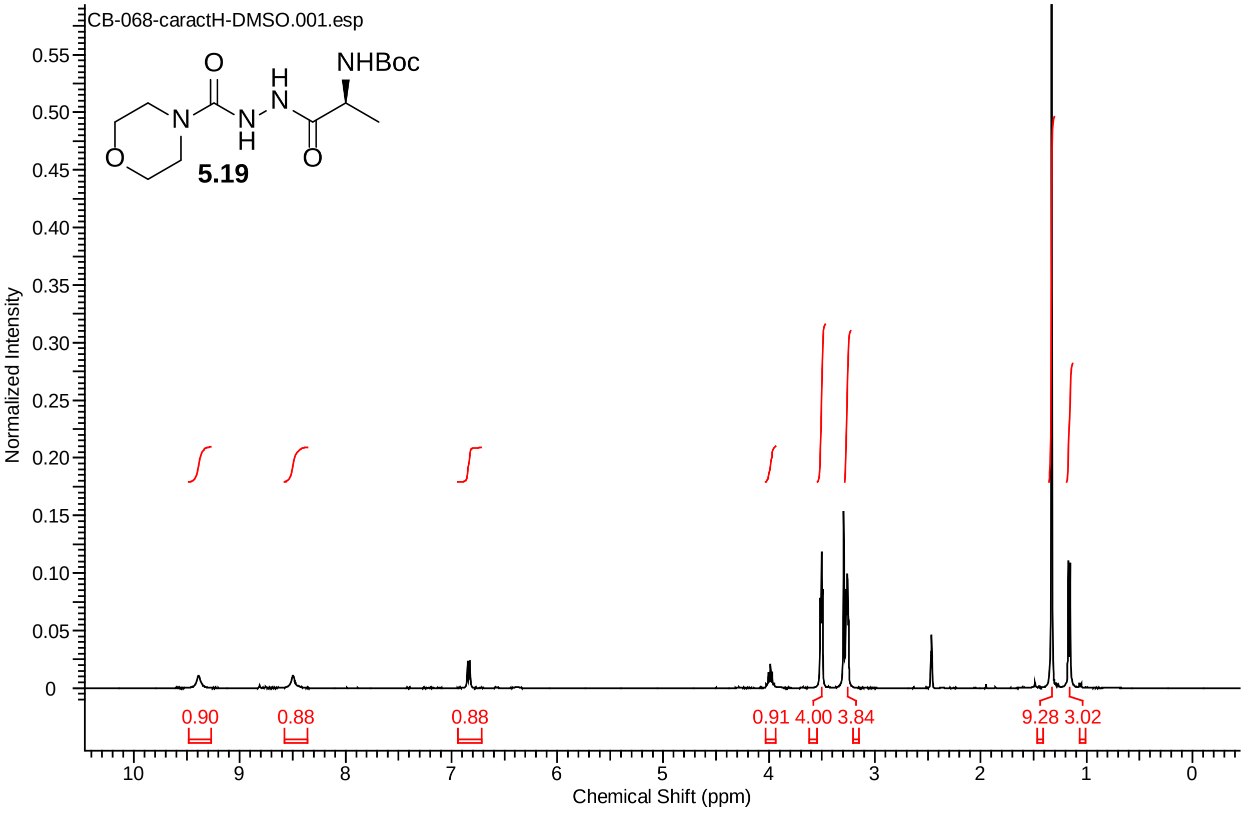

JF9-1555-C13.001.001.1r.esp
128.5692
128.0419
127.4346
137.0968
155.5521
170.4436
60.8576
50.4499
49.7226
35.3839
14.0158
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

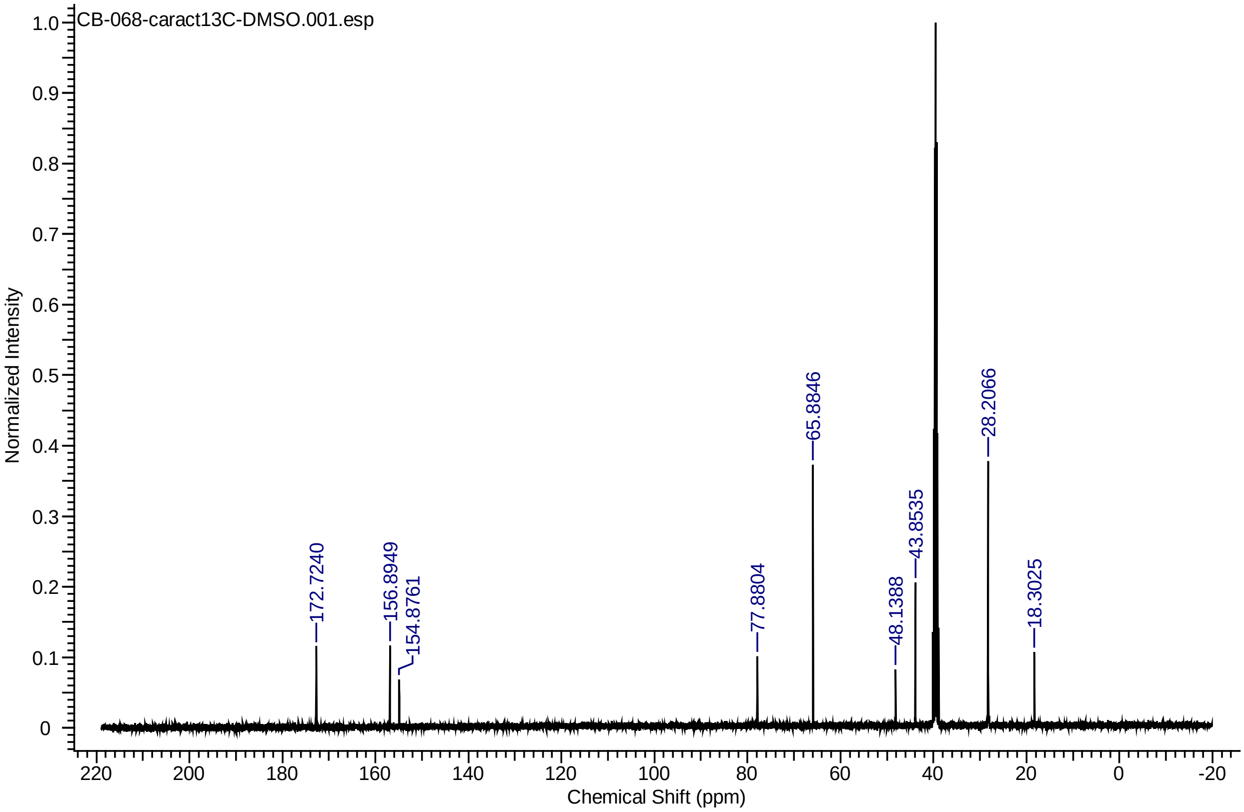

CB-047-propre2.001.esp
PhO
O
N
H
H
N
O
NHBoc
5.13
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.92
0.64
1.97
1.00
1.90
0.97
0.96
11.75
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

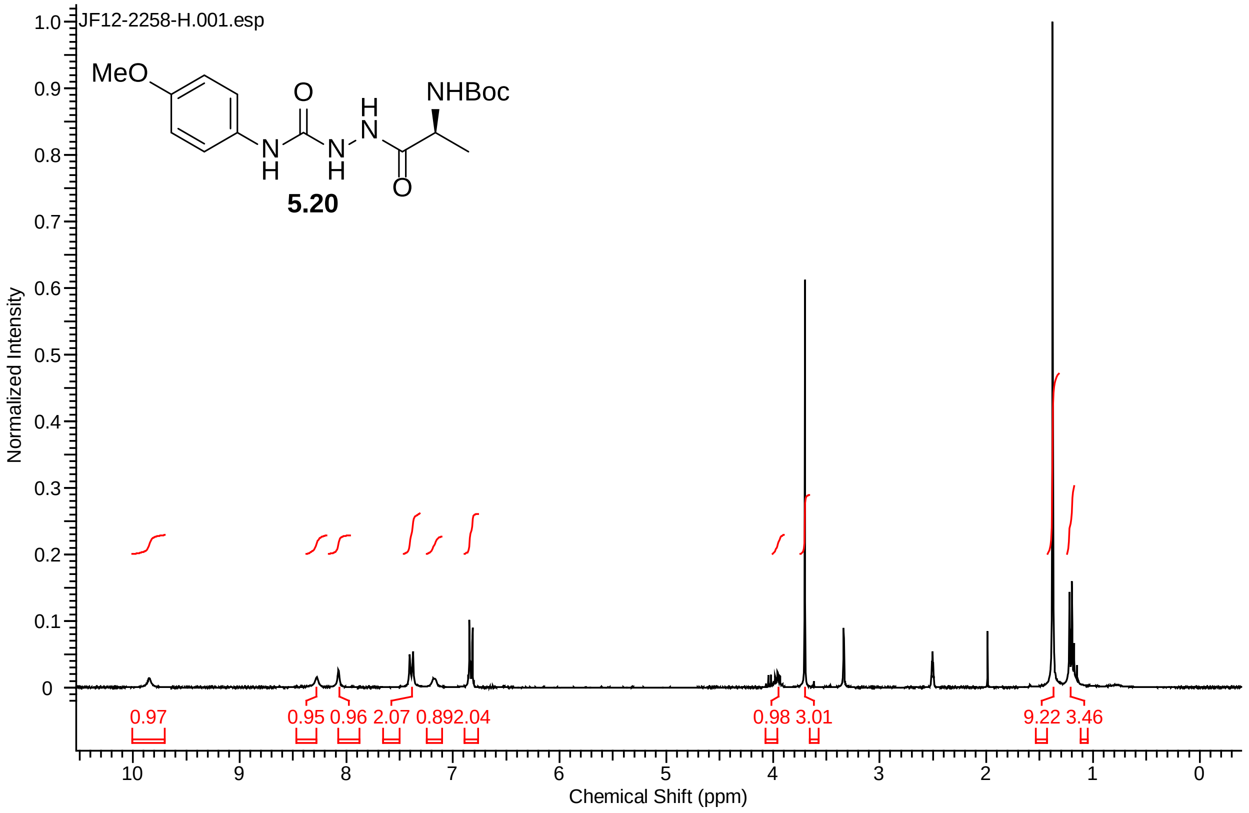

CB-047-caract13C.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
173.0899
155.8177
150.5122
129.2974
125.6899
121.3391
80.5492
48.5046
28.2445
17.9978
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


CB-067-caractH.001.esp
BnHN
O
H
N
N
H
NHBoc
O
5.18
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.80
6.30
0.93
1.02
2.00
1.01
12.29
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


CB-067-caract13C-DMSO.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
172.7896
158.0974
155.4373
140.3224
128.0788
126.7816
126.4828
78.2593
48.5396
42.5563
28.1119
17.4571
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

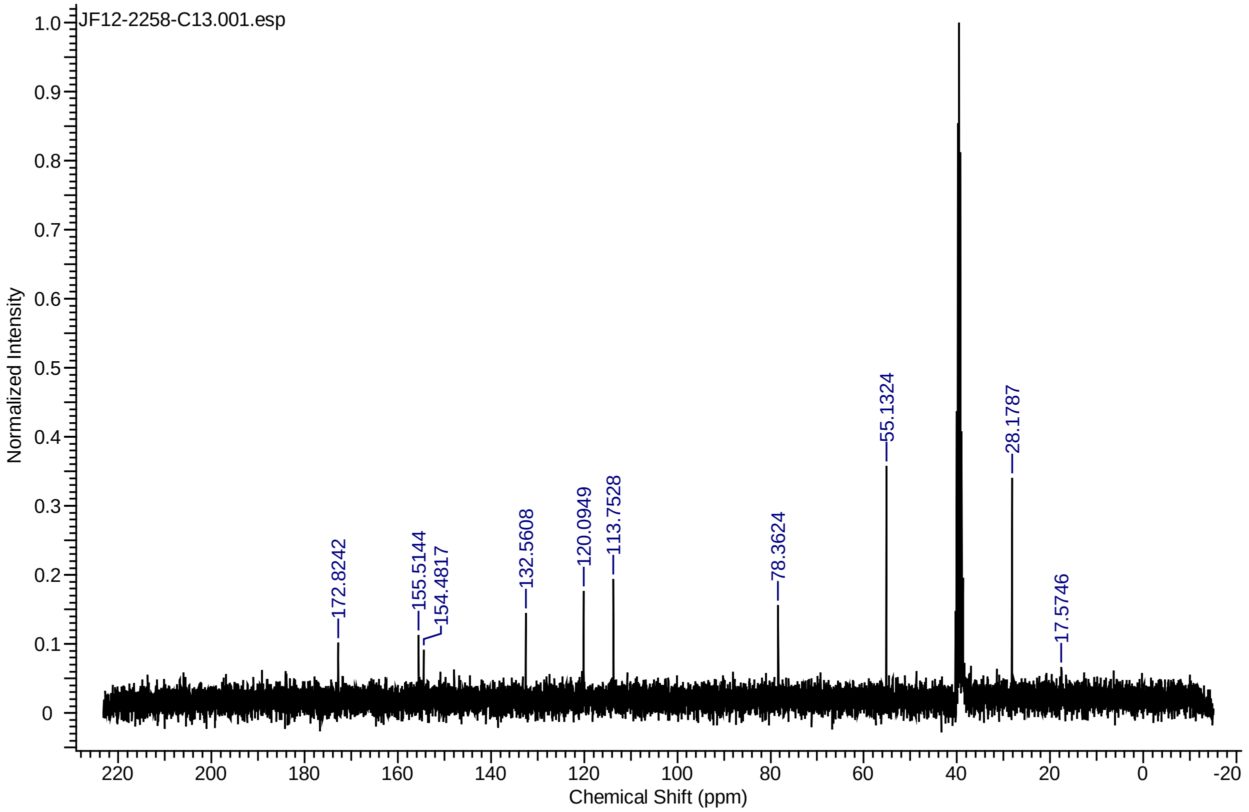

CB-068-caractH-DMSO.001.esp
NHBoc
O
H
N
N
N
H
O
O
5.19
Normalized Intensity
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.90
0.88
0.88
0.91
4.00
3.84
9.28
3.02
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


CB-068-caract13C-DMSO.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
172.7240
156.8949
154.8761
77.8804
65.8846
48.1388
43.8535
28.2066
18.3025
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

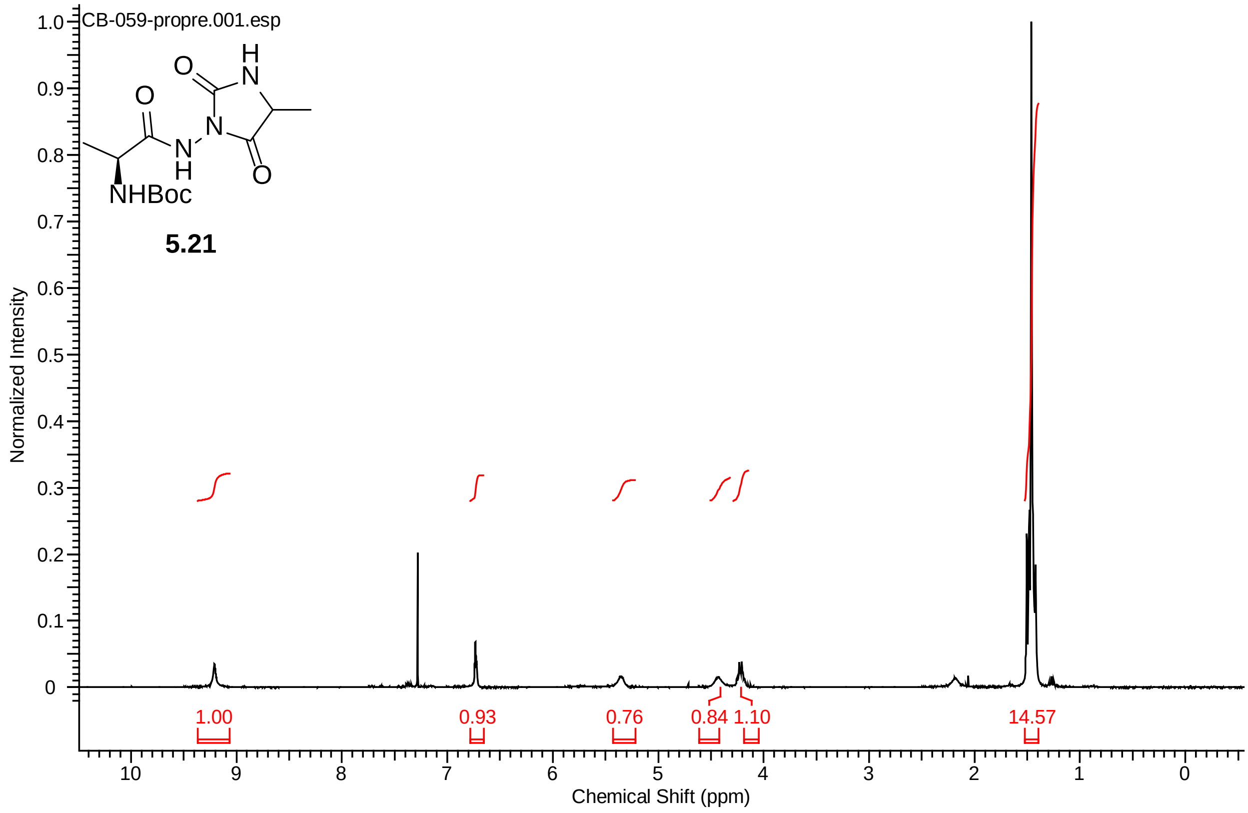


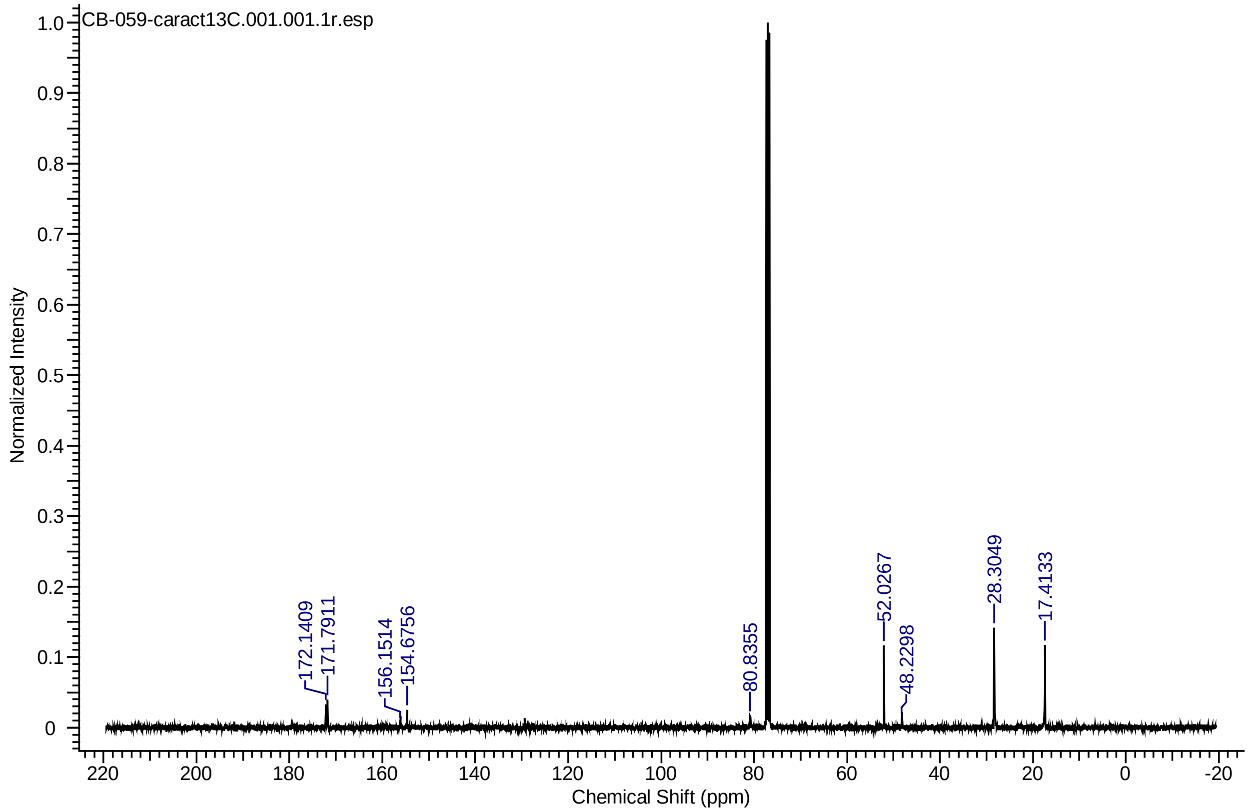
5.20

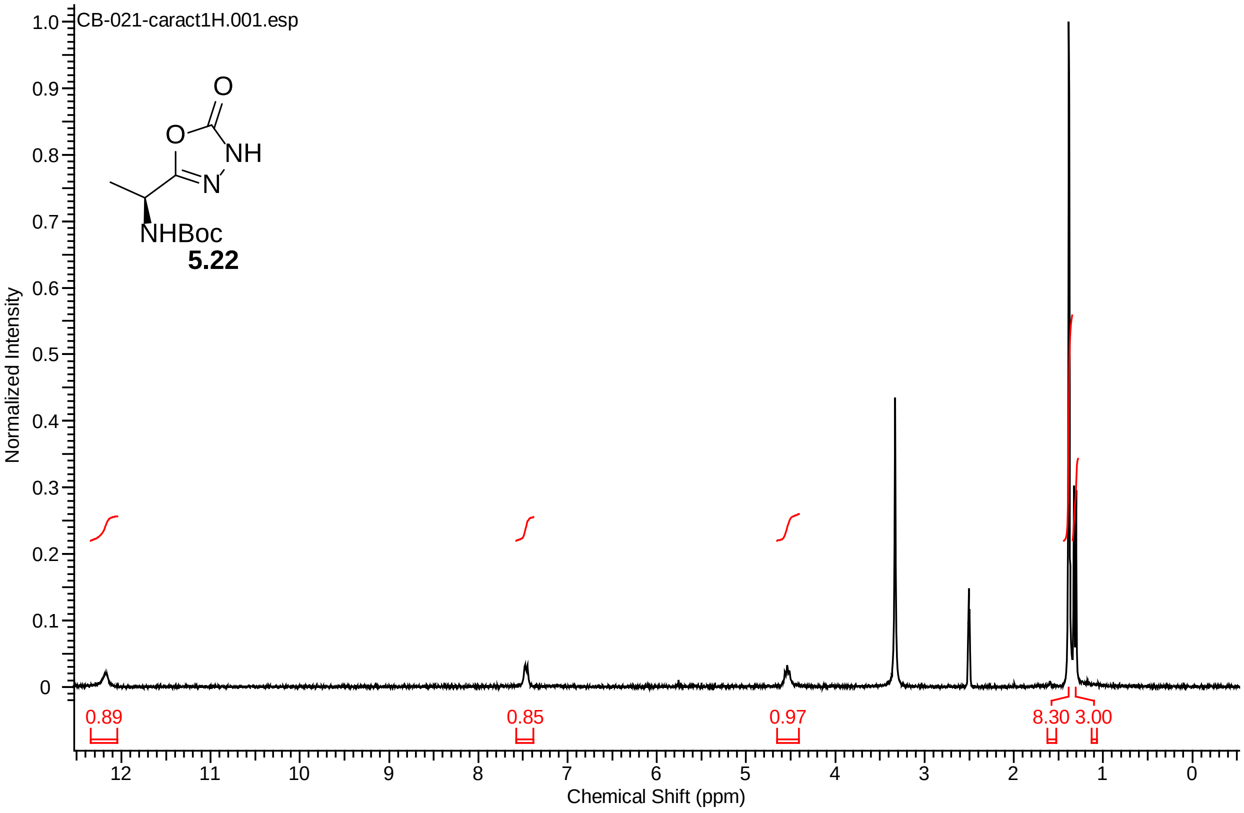
JF12-2258-H.001.esp
MeO
O
H
N
NHBoc
N
H
N
H
O
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.97
0.95
0.96
2.07
0.89
2.04
0.98
3.01
9.22
3.46
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

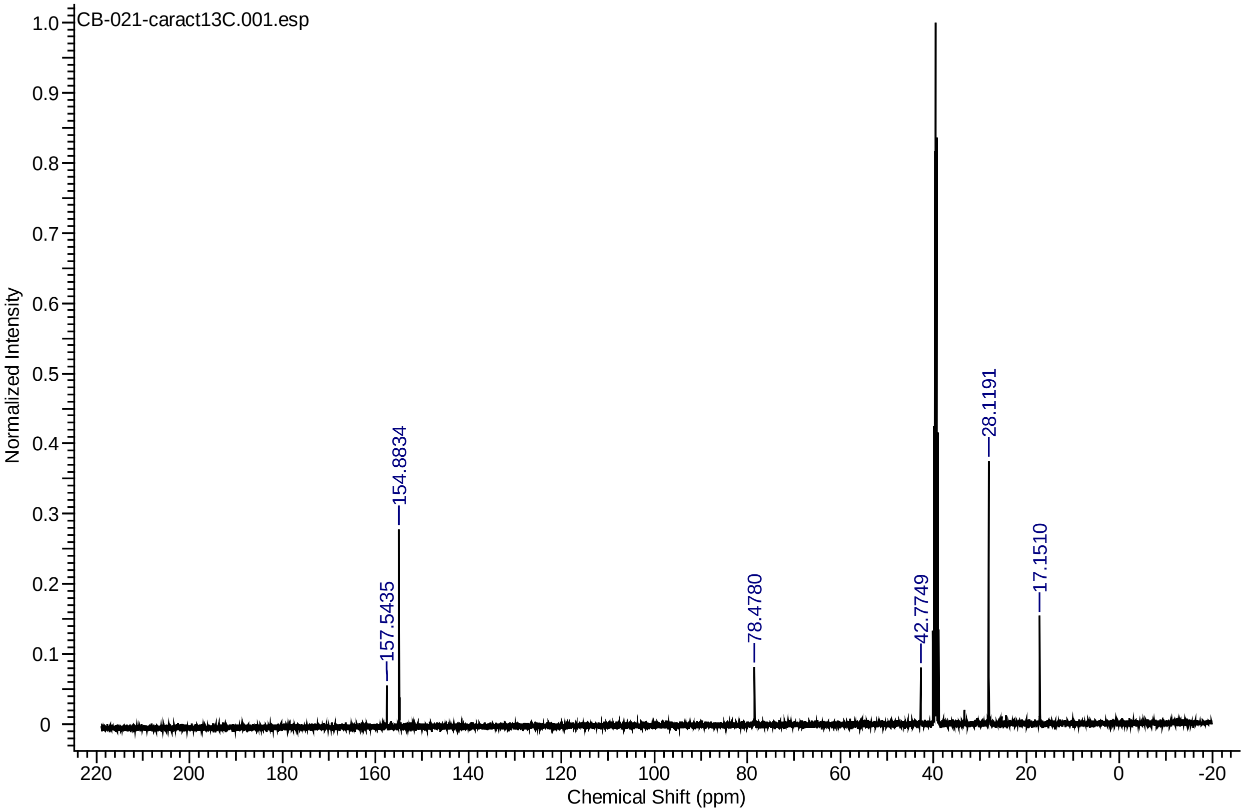


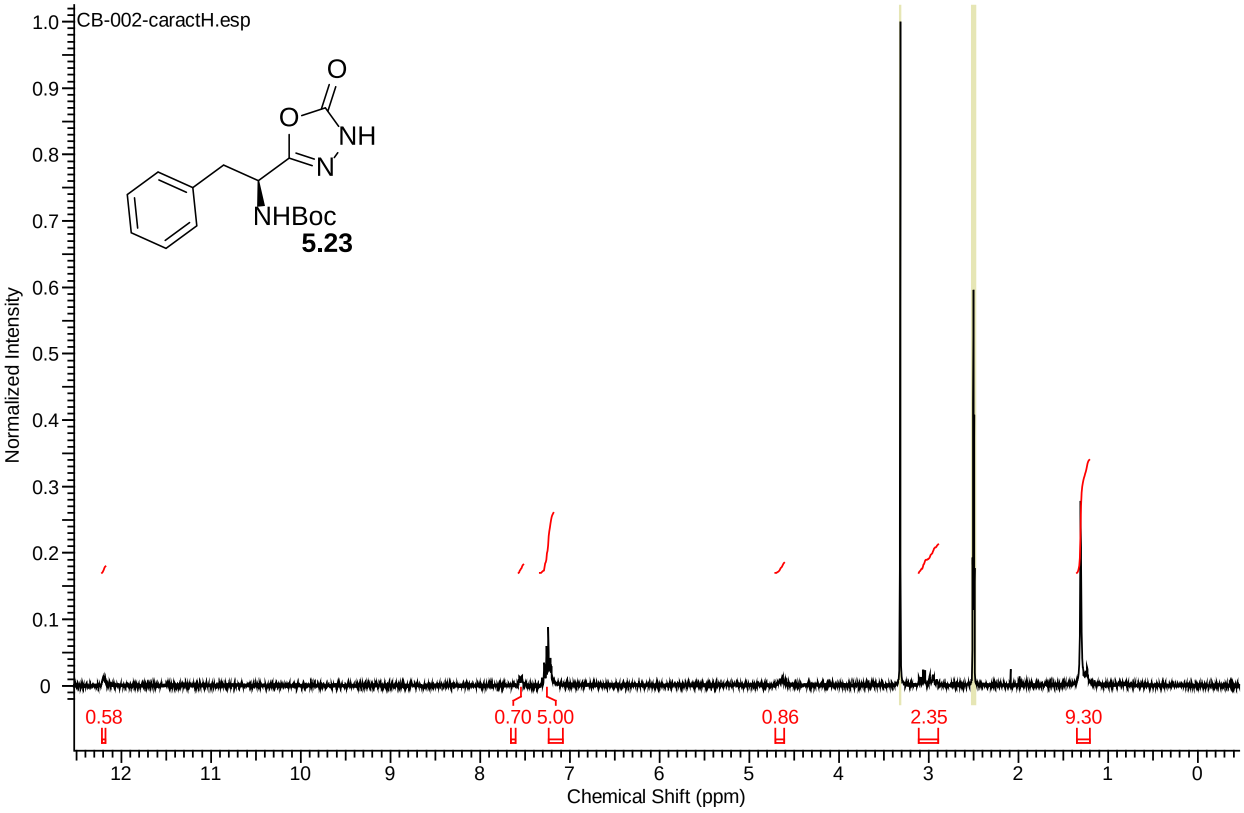
JF12-2258-C13.001.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
172.8242
155.5144
154.4817
132.5608
120.0949
113.7528
78.3624
55.1324
28.1787
17.5746
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

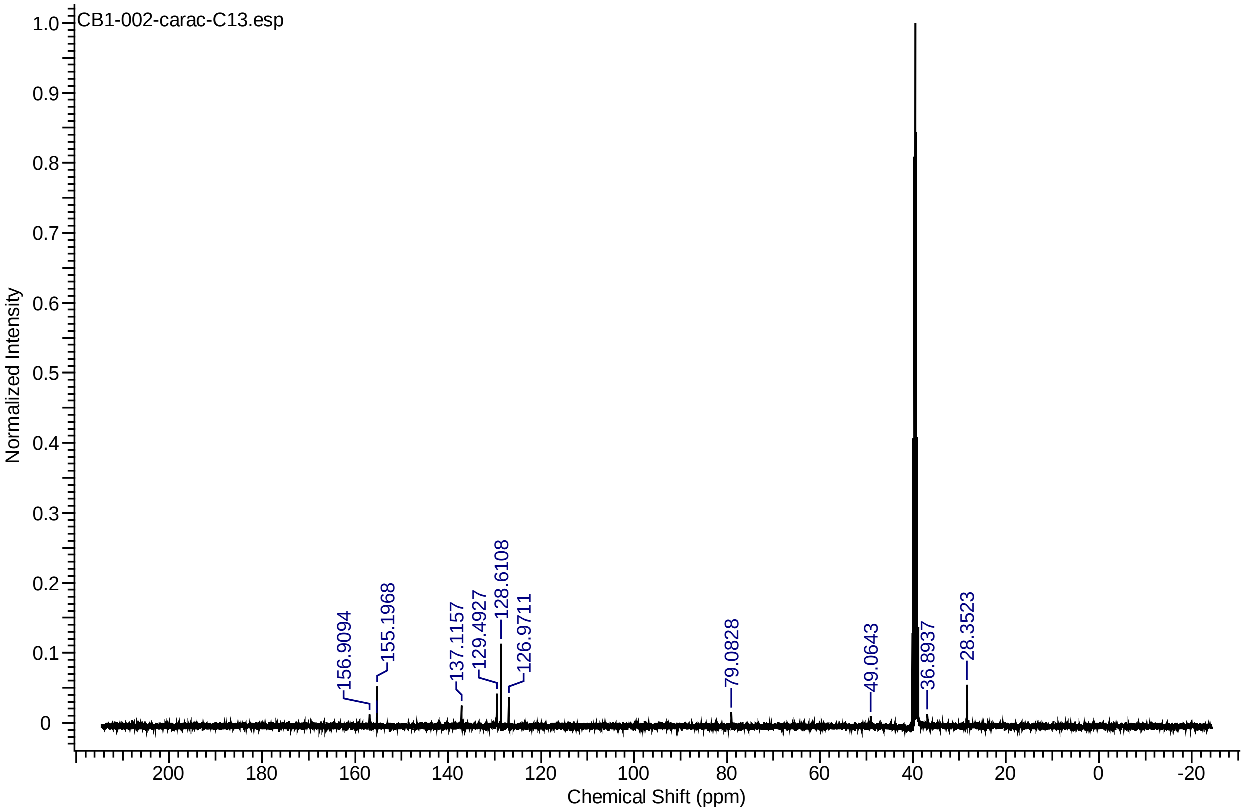

CB-059-propre.001.esp
O
H
N
O
N
N
H
O
NHBoc
5.21
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
0.93
0.76
0.84
1.10
14.57
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

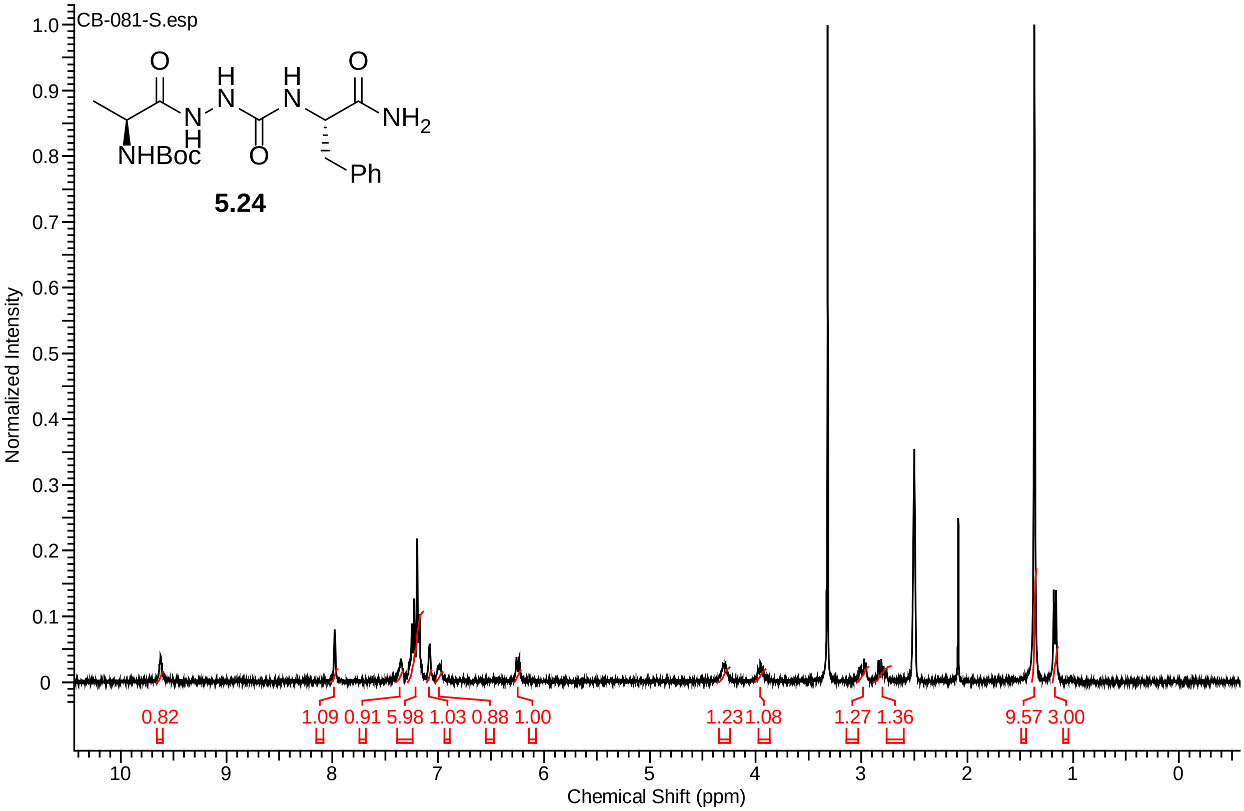

CB-059-caract13C.001.001.1r.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
172.1409
171.7911
156.1514
154.6756
80.8355
52.0267
48.2298
28.3049
17.4133
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

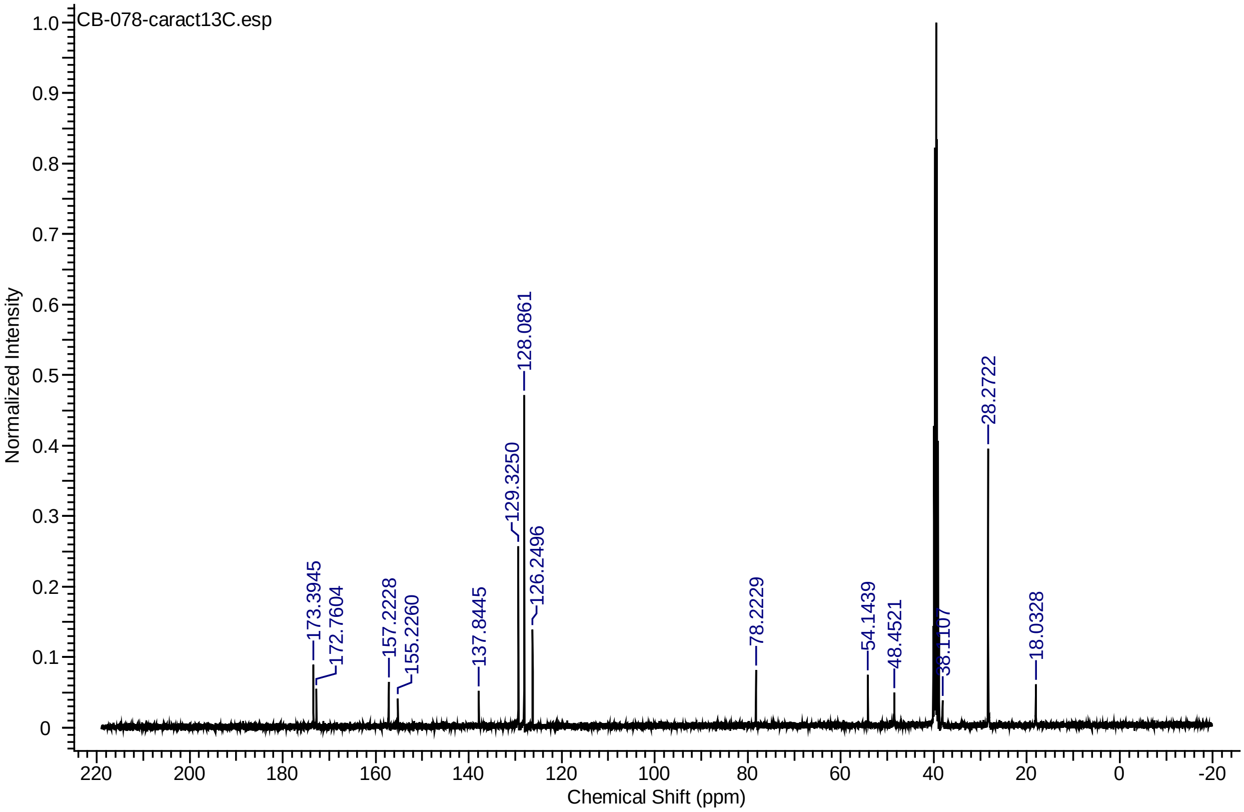

CB-021-caract1H.001.esp
O
O
NH
N
NHBoc
5.22
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.89
0.85
0.97
8.30
3.00
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


CB-021-caract13C.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
157.5435
154.8834
78.4780
42.7749
28.1191
17.1510
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


CB-002-caractH.esp
O
O
NH
N
NHBoc
5.23
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.58
0.70
5.00
0.86
2.35
9.30
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


CB1-002-carac-C13.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
156.9094
155.1968
137.1157
129.4927
128.6108
126.9711
79.0828
49.0643
36.8937
28.3523
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


CB-081-S.esp
NHBoc
NH2
Ph
O
H
N
5.24
Normalized Intensity
0.82
1.09
0.91
5.98
1.03
0.88
1.00
1.23
1.08
1.27
1.36
9.57
3.00
Chemical Shift (ppm)
10 9 8 7 6 5 4 3 2 1 0


CB-078-caract13C.esp
Normalized Intensity
173.3945
172.7604
157.2228
155.2260
137.8445
129.3250
128.0861
126.2496
78.2229
54.1439
48.4521
38.1107
28.2722
18.0328
Chemical Shift (ppm)
220 200 180 160 140 120 100 80 60 40 20 0 -20