Investigation of 1,3,4–Oxadiazol–2(3H)–ones as Heterocyclic, Amidoisocyanate Precursors

By

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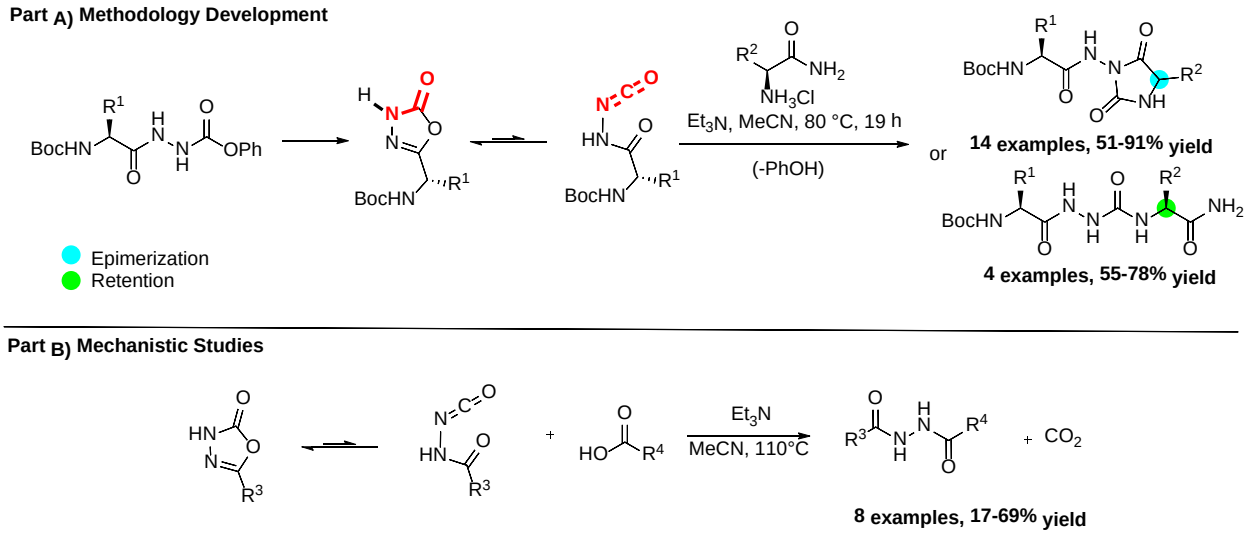
Abstract

Isocyanate chemistry is well-known and has been studied and exploited for years. *N*-Isocyanate derivatives, however, are scarce and far less understood. These are divided in three subclasses: the aminoisocyanates, the iminoisocyanates, and the rarest of them all, the amido-isocyanates. The latter are underdeveloped and understudied. Herein, studies that resulted in evidence for the existence of N_β–amido–isocyanates, and validated their use in a masked isocyanate strategy, will be described. Suitable precursors, N_β–acyl phenylcarbazide derivatives (activated aza-dipeptides), were synthesized in the context of aza–tripeptide synthesis. The 1,3,4–oxadiazol–2(3H)–one intermediate was formed quickly in the course of the reaction, and an equilibrium between the free N_β–amido–isocyanate and the 1,3,4–oxadiazol–2(3H)–ones was established. Longer reaction times, in presence of amino amide nucleophiles, led to the formation of hydantoins or aza–tripeptides with full consumption of both the starting material and the oxadiazolone intermediate, yielded 14 hydantoins and 4 aza-tripeptides in 51-79% isolated yields.

Experiments were performed to support the formation of an amido-isocyanate intermediate and discriminate between pathways possibly involving the formation of a tetrahedral oxyanionic intermediate versus the trapping of an *N*–isocyanate by a nucleophile. A control reaction in which the N_α in the starting material was methylated completely suppressed the formation of the isocyanate intermediate and shut down the reaction, lending supporting the isocyanate formation pathway. The hydrogen at this position is crucial for the formation of the isocyanate, which can be deprotonated and form a neutral isocyanate species. To further support the mechanistic hypothesis, established *C*–isocyanate chemistry, in which isocyanates react with carboxylates to form amides, was applied to a series of oxadiazolones. This transformation cannot occur in the absence of an isocyanate. This reaction yielded 8 different N_β–acyl hydrazides with moderate to good yields, again supporting the formation of the rare amido–isocyanates. Overall, this work supports the formation of amido–isocyanates in equilibrium with their corresponding 1,3,4–oxadiazol-2(3H)-ones

and validated that the latter are masked amido–isocyanates, species that have been rarely studied in the literature.



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I would like to thank Pr. André Beauchemin, for accepting me in his group of graduate students. It has been an amazing journey with a lot of encounters and knowledge sharing between all these other amazing chemists in the group over the years. André is an amazing human being, very understanding and helpful despite his high demand as a Graduate studies director job and more recently vice provost, graduate studies. I am infinitely grateful to have been able to achieve my graduate studies along his side. I couldn't have wished for a better PI. I definitely learned a lot from him. I would also like to thank the funding agencies such as FRQNT and QEII for scholarships and NSERC in the accomplishment of this project.

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Statement of Contributions

Note: All references to Figures, Schemes, Tables and Equations in this Statement of Contribution refer to Chapter 2, the published manuscript. ***WGM****: William Gagné-Monfette;* ***JFVR****: Jean-François Vincent-Rocan;* ***OCL****: Owen C. Lutes;* ***GFO****: Geneviève F. O'Keefe;* ***ADMJ****: Alexandria D.M. Jenneret;* ***CB****: Clare Blanger;* ***RAI****: Ryan A. Ivanovich;* ***AMB****: André M. Beauchemin*

JFVR initiated the project and developed the methodology for the synthesis of aza–tripeptides / hydantoins along with **CB**, an M1 intern, and **ADMJ**, an Honours student in the group. **JFVR** also completed an initial draft of the manuscript, which did not contain the carboxylate addition to oxadiazolones part of the project.

WGM determined the cause of the cyclization of the aza–tripeptides along with identifying the epimerization of the stereocenter on hydantoins. The previous misidentification of the hydantoin structures and missing characterization data necessitated repetition of all experiments and full characterization to support the newly suggested structures (Figure 9-Figure 10-Figure 11 and Equation 4-Equation 5 -Equation 6). During this time, **WGM** trained, mentored and supervised a 1st year undergraduate student **OCL**; **WGM** & **OCL** worked together on the optimization of the carboxylate addition to oxadiazolones and data for (Table 2-Table 5-Table 6-Table 7-Table 8) were acquired. Only results from Table 1 were not reacquired. **OCL** assisted in the acquisition of all the optimization data. All the fluorinated substrates were completed by **WGM** & **OCL**, with the exception of those obtained by **GFO,** an undergraduate student (summer internship after 2nd year of BSc program) that joined the group as an intern while **WGM** was on leave of absence. **GFO** worked under supervision of **RAI** and contributed to the synthesis, purification, and identification of products from Table 3 and Table 9.

WGM reviewed the original draft of the manuscript, then fully updated the draft to reflect all the new findings and data, including the carboxylate addition project. During the leave of absence, **WGM** completed the final edits to the manuscript requested by **AMB**, and it was published. Herein, the

manuscript is presented in Chapter 2, and unpublished results or results in the supporting information are in Chapter 3.

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List of Schemes

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List of Abbreviations

AcOH – acetic acid

BCU – *N*–benzoylated macrocyclic ureas

BOC – *tert*–butoxycarbonyl

br s – broad singlet

calcd – calculated

$CDCl_3$ – deuterated chloroform

CDI – 1,1'-carbonyldiimidazole

δ – chemical shift

d – doublet

DCM – Methylene chloride

DMSO-d_6 – deuterated dimethyl sulfoxide

DBU – 1,8-diazabicyclo[5.4.0]undec–7–ene

e.g. – exempli gratia

ESI+ – electrospray ionization in positive mode

Et_3N – triethylamine

EtOAc – ethyl acetate

eV – electronvolt

FTIR – Fourier–Transform Infrared Spectroscopy

g – gram

Hex – Hexanes

HRMS – high-resolution mass spectroscopy

i.e. – id est

iPrOH – 2-propanol

IR – infrared

J – coupling constant

L – levorotary

M – molar

m – multiplet

$MgSO_4$ – magnesium sulfate

MeCN – acetonitrile

MeOH – methanol

MHz – megaHertz

mL – millilitre

mmol – millimole

m/z – mass over charge ratio

$NaHCO_3$ – sodium bicarbonate

NCA – *N*–carboxyanhydrides

NH_4OH – ammonium hydroxide

NMI – *N*–methyl imidazole

NMR – nuclear magnetic resonance spectroscopy

$PhCF_3$ – α,α,α–trifluorotoluene

PhMe – toluene

PhNCO – phenyl isocyanate

PhOH – phenol

QTOF – quadrupole time of flight

Rf – retention factor

sat –saturated

SM – starting material

t – triplet

TGA – thermogravimetric analyses

THF – tetrahydrofuran

TLC – thin layer chromatography

ν – wave number

Chapter 1: Introduction

1.1 Isocyanates Background

First discovered in 1848 by Wurtz,[1] isocyanates are characterized by their amphoteric nature; they are both highly electrophilic and highly nucleophilic. Isocyanates are most known for their application in the polymer industry as monomers for polyurethanes. These polymers accounted for 5% of global production in 2011,[2] with about 14 million tons produced. An increase to 29 million metric tons is expected by 2029.[3] In addition to their importance to the polymer industry, isocyanates are also important in the agrochemical industry and in organic synthesis. Indeed, they are attractive small building blocks that allow the incorporation of the NCO motif with the highest possible atom economy.

1.2 Formation of *C*–Isocyanates

Carbon substituted isocyanates are generally synthesized from the reaction of an amine with phosgene or an equivalent reagent, such as triphosgene or CDI (Figure 1). Isocyanates can also be formed via the Curtius rearrangement in which an acyl azide undergoes a rearrangement to give an isocyanate and N_2. Other rearrangements produce isocyanates during the course of the reaction, but these are not isolated due to their reactivity under the reaction conditions (Figure 2). The Hoffman rearrangement occurs when an amide is treated with Br_2 and NaOH, generating an isocyanate, which in turn reacts with hydroxide, undergoes decarboxylation and yields an amine. The Lossen rearrangement generates an isocyanate from a hydroxamate ester. Typically, this intermediate will then react with an amine or with water to form ureas or amines, respectively.

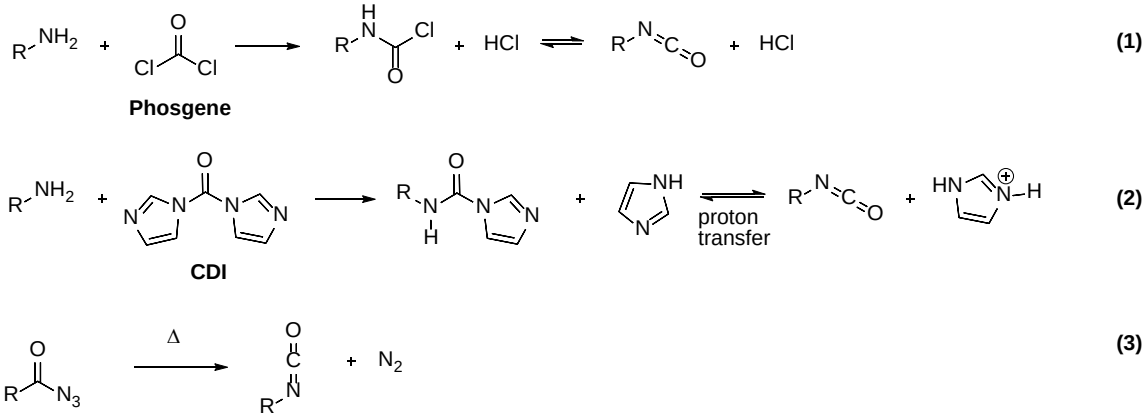


Figure 1: Examples of Syntheses of Free C-Isocyanates

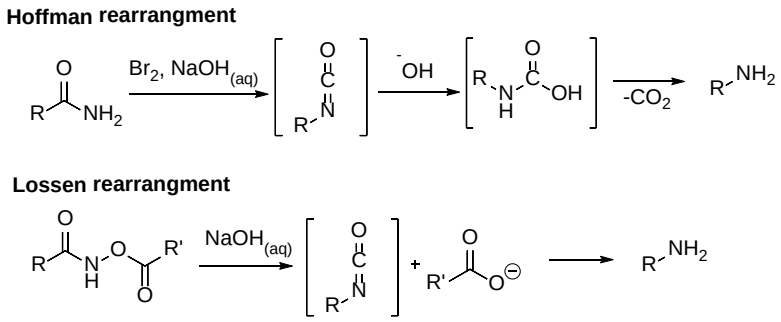
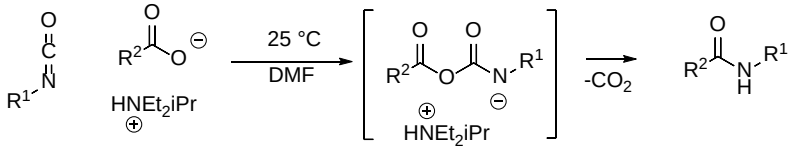


Figure 2: Examples of Trapping Reactive Intermediate C-Isocyanates

1.2.1 Reactivity of C-Isocyanates

Isocyanates are quite electrophilic reagents and will react with a variety of nucleophile such a amines to form ureas, alcohols to form carbamates, thiols to form thioureas.[4] More recently, Crich demonstrated the reactivity of C–substituted isocyanates with carboxylates as nucleophiles to form amides under mild basic conditions (Scheme 1).[5] This shows the high electrophilicity of isocyanates, since carboxylates are poor nucleophiles due to the delocalization of the negative charge over two oxygen atoms.

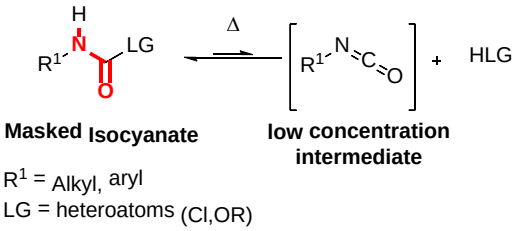


Scheme 1: Crich's Amide Bond Formation from Isocyanates & Carboxylic Acids

1.3 Masked Isocyanates

In their free form, isocyanates cause severe health and handling concerns. They are known to cause sensitization and exposure can be fatal. Their hygroscopicity makes storage difficult. To circumvent these issues, masked isocyanates were developed. A series of chemical motifs capable of releasing isocyanates at a controlled rate were investigated.[6] Masked isocyanates have shown to be less reactive than their free counterpart as they slowly release isocyanates *in situ*. They are bench stable and reduce the potential exposure to toxic free isocyanates, which makes them attractive for synthetic chemistry purposes. Masked isocyanates require heating, often above the boiling point of the solvents used to generate them, but catalytic reactions are common and can be performed at room temperature. Sealed tubes are usually used to achieve the desired temperature under pressure which also lowers the potential exposure. The susceptibility of masked isocyanate to oligomerize is significantly lower than free isocyanates, and this can allow for better control of the outcome of the reaction.

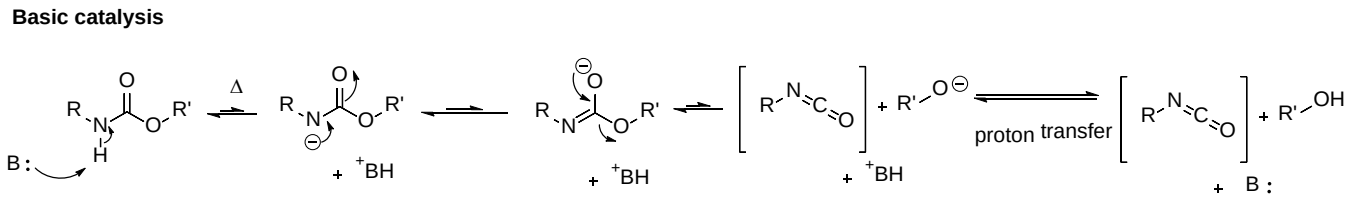
1.3.1 Acyclic Masked C-Isocyanates



Scheme 2: Generalized Equilibrium Between Masked & Free Isocyanates

Masked isocyanates are now a common type of reagents, behaving like isocyanates with a tamed reactivity compared to free isocyanates. Functional groups associated to masked isocyanates contain a motif such as (NHC(O)LG) (Scheme 2). Under proper conditions, usually base catalysis with heat, the isocyanate is released in situ and can react in the same way a free isocyanate would. An interesting feature of the masked isocyanates is that the isocyanate is released in an equilibrium which can be controlled with the reaction conditions (temperature, catalyst, solvent). Taking advantage of this

equilibrium allows control over the concentration of isocyanate generated (Scheme 3). This offers an alternative route to synthesize the various functional groups usually synthesized from free isocyanates with more control, and avoiding the formation of oligomerization products (Figure 3).



Scheme 3: Mechanism of Base-Catalyzed Deblocking of Carbamate to Yield C-Isocyanate

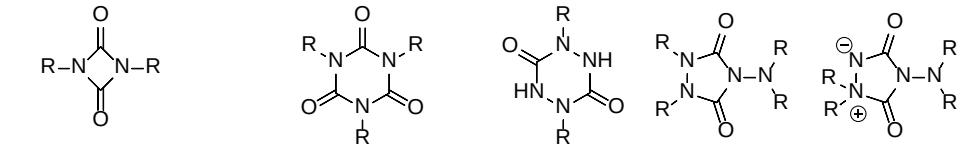


Figure 3: Selected Examples of Isocyanate Oligomers

Keeping the concentration low reduces the likelihood of encountering the problematic oligomerization, or polymerization of free isocyanates (Figure 3). The probability of intermolecular collision of two isocyanate molecules is consequently reduced. Due to dilute concentration of isocyanate molecules, there is less potential for exposure. Masked isocyanates, carbamates for example, are significantly less reactive and less toxic than isocyanates. Therefore, masked isocyanates can be reagents of choice to exploit the isocyanate reactivity. Moreover, they are bench stable and will not hydrolyze easily. Carbamates are typically used as protecting groups for amines, such as BOC. However, the *t*–butanoate is not a good leaving group, with a pKa (DMSO)= ~32 for the conjugate acid. TGA analyses have shown that very high temperatures (177 ºC) are required to release the isocyanate when *t*-BuO$^-$ is used as blocking group.[7] This makes t-butyl carbamates much more robust compared to the phenyl carbamate, phenol having a pKa (DMSO)= ~18 with a release temperature recorded at 110 ºC by TGA.[6,8,9] It is important to mention that any of these molecules must not be substituted at the nitrogen in

order to generate the isocyanate and would otherwise generate a higher energy, charged species, possessing a cationic nitrogen atom next to an electrophilic center (Figure 4).

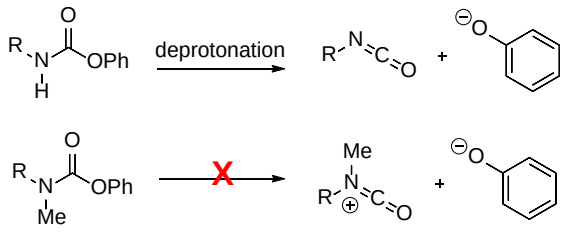
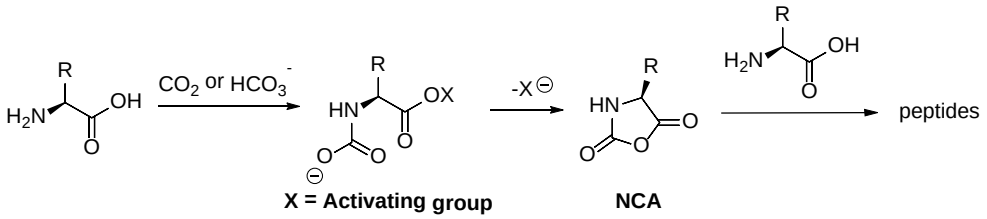


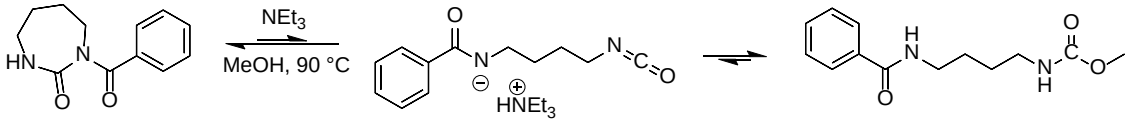
Figure 4: Requirement of N-H Presence in Masked Isocyanate

1.3.2 Cyclic Masked C-Isocyanates

As for cyclic precursors of carbon substituted isocyanates (masked C-isocyanates), the most notable examples are the *N*–carboxyanhydrides (NCA),[10–14] where the leaving group of the carbamate moiety is a tethered carboxylate on the same carbon chain which allows reversible ring opening or a ring closing (Scheme 4). Such heterocycles were reported for the first time in 1906 by Hermann Leuchs in the context of peptide formation.[15–17] The ability of the NCAs to polymerize under very mild conditions gave rise to high interest towards heterocyclic precursors in peptide synthesis. It was demonstrated that under prebiotic conditions (in presence of gases such as N_2 and CO_2, and a bicarbonate buffer), peptide formation could have been catalyzed through the formation of NCAs, which could generate a transient isocyanate in equilibrium, and allow amino acids oligomerization to form peptides.[10–14] The NCAs ability to be formed under prebiotic conditions, which has been demonstrated by a number of researchers, seems to be a reasonable explanation on how the first polypeptides were formed during this era. The equilibrium between the cyclic NCA and its opened form releasing a very reactive isocyanate is key to this oligomerization forming peptides (Scheme 4). Another example of cyclic carbon substituted masked isocyanates are N–benzoylated macrocyclic ureas (BCU) (Scheme 5).[18] However, they are restricted to the formation of carbamates due to the alcoholic solvent required for that reaction to occur.



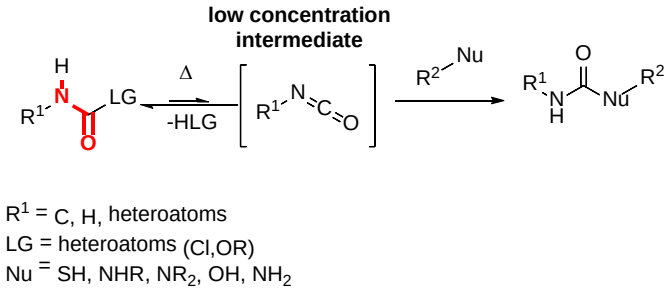
Scheme 4: Equilibrium of N-Carboxyanhydride (NCA) with Free Isocyanate



Scheme 5: BCU Isocyanate Formation Reaction

1.4 Reactivity of Masked C–Isocyanates

Masked isocyanates are significantly more stable at room temperature in terms of their ability to oligomerize or hydrolyze when compared to free *C*-isocyanates. However, at higher temperature or in presence of a catalyst (for example, a base such as a tertiary amine) (Scheme 3), masked isocyanates can react and release an isocyanate which can then react with nucleophiles and π–bonds. The ability to control the equilibrium allows the release of a minimal amount of the isocyanate circumventing the homo–oligomerization issue associated with those when used in a higher concentration or as their free form, which allows them to be trapped more selectively and form various new functional groups as such as ureas, thioureas, carbamates (Scheme 6).[19] Oligomerization is still possible but isn't as much of a problem as it is when free isocyanates are used.



Scheme 6: Generalized Reaction of Masked Isocyanates with Nucleophiles

The deblocking temperature of the masked isocyanates is dictated by the nature of the leaving group (LG) (Figure 5). When there is a better leaving group, the deblocking temperature is lower. Various leaving groups for masked *C*–isocyanates have been studied in the literature via TGA analyses. A trend can be observed where the deblocking temperature lowers according to the ability of the anionic leaving group to be stabilized. Aromatic ones have the lowest deblocking temperature and unstabilized anionic leaving group such as alkoxides (except phenol which is in resonance with the aromatic aryl) have very high deblocking temperature (Figure 5).[6,9,20,21]

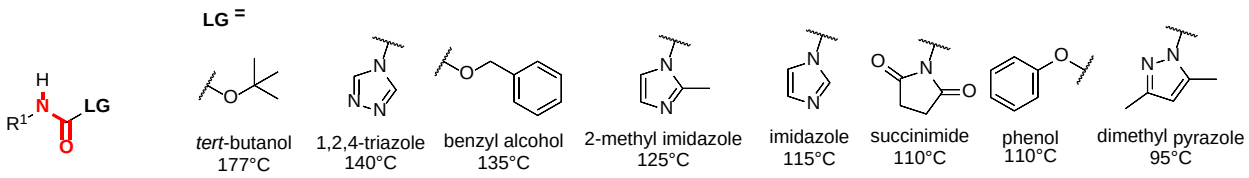
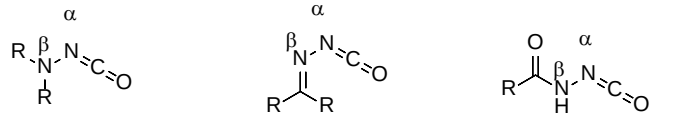


Figure 5: Selected Leaving Groups with Corresponding Deblocking Temperatures (via TGA)

Acquisition of the deblocking temperature by TGA analysis does not provide a representative temperature for the deblocking temperature and reactivity in solution. While these experiments are acquired in the solid state in absence of a catalyst, the chemistry presented in this thesis is done under basic conditions in solution. However, this TGA data provides a correlation between the nature of the leaving group and the rate of release of isocyanate. The deblocking of the isocyanate is related to the stability of the leaving group, weather its in solid phase or in solution. The trend is therefore still valid while the exact temperature is not. Depending on the application, the leaving group can be chosen accordingly. In previous studies from our group presented later in the introduction chapter, it was found

that phenol is a particularly good leaving group that allows control over the equilibrium with the released isocyanate and good reactivity for further derivatization. Indeed, masked isocyanates releasing phenol generally display a relatively low deblocking temperature (as indicated in Figure 5) as well as its good stability, either when isolated as a solid, or in solution.[22]

1.5 *N*–Isocyanates



amino–isocyanates **imino–isocyanates** **amido–isocyanates**

Figure 6: Three Types of N-Substituted Isocyanates

In comparison to carbon substituted isocyanates, heteroatom substituted isocyanates are far less studied because of their instability. Multiple studies have shown that their very reactive nature and amphotericity makes them hard or next to impossible to isolate. Nitrogen substituted isocyanates have been observed in the gas phase and in a frozen matrix,[23] but have never been isolated as free *N*-isocyanates due to their high tendency to oligomerize (some examples are shown in Figure 3). There is much interest in three classes of nitrogen substituted isocyanates: amino–isocyanates, imino–isocyanates and amido–isocyanates (Figure 6). The various hybridizations of the β–nitrogen confer different reactivities to each species. The importance of the NNCO motif is illustrated in Figure 7, through various examples of bioactive compounds containing the motif. Interest in this class of reagent motivated the Beauchemin group to explore ways to use heteroatom–substituted isocyanates, such as ONCO and NNCO, in a transient fashion to exploit their potential in heteroatom-rich molecule synthesis.

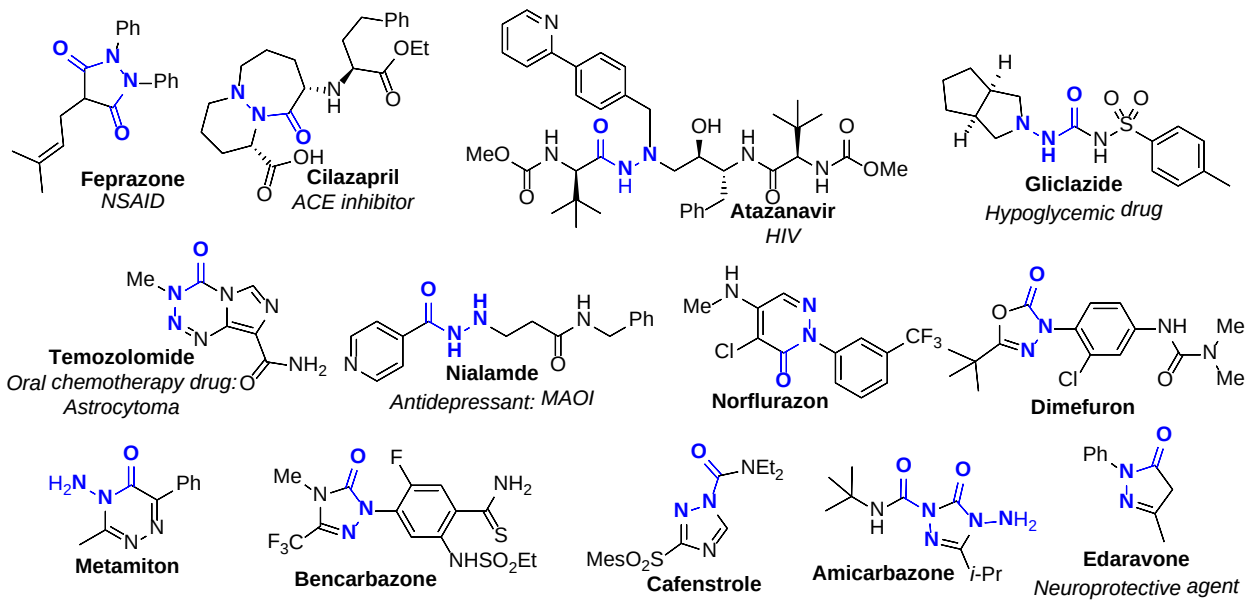


Figure 7: Various Bioactive Compounds Possessing NNCO Motifs

1.5.1 Aminoisocyanates

1.5.1.1 Observation and Identification

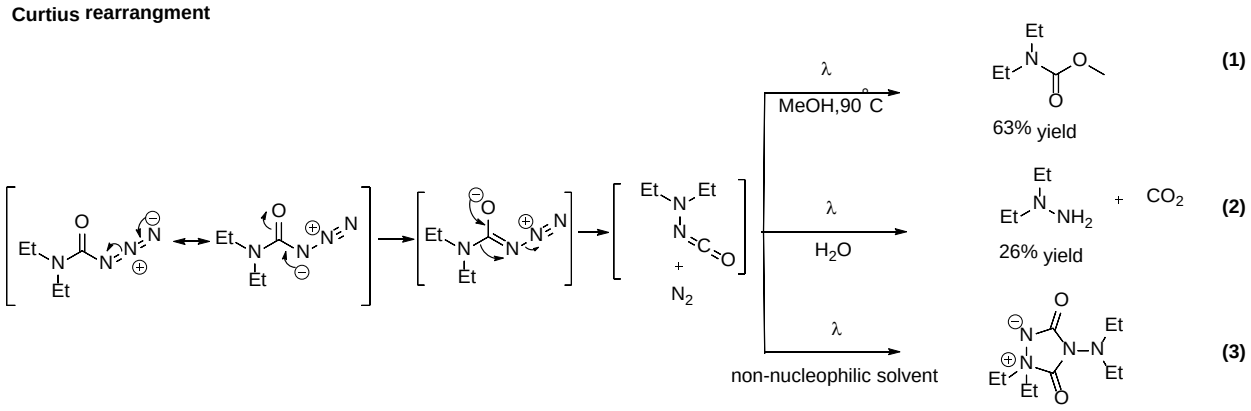
Amino–isocyanates were first characterized in 1975 by Lwowski via photolysis of dimethylcarbamoyl azide at 6 K in a Neon matrix.[24] He observed a very strong infrared band at 2230 cm^{-1} along with two other bands at 1025 cm^{-1} and 957 cm^{-1} which all eventually disappeared upon longer exposure to IR light. These three bands were attributed to the amino–isocyanate based on the IR spectrum analysis. The appearance followed by the disappearance of the associated bands suggested the generation and consumption of the amino–isocyanate in situ. Similarly, the simplest amino–isocyanate (unsubstituted at the N_β) was observed in a 10K Argon matrix 14 years later by Teles and Maier from the parent carbamoyl azide.[25] Photolysis and thermolysis experiments with the carbamoyl azide were performed to observe this amino–isocyanate, which was accomplished in an inert gas matrix.

Aminoisocyanates' amphotericity differs from carbon substituted isocyanates as the nucleophilic atom is the N_β instead of the N_α (Figure 6). The increased nucleophilicity of the sp^3 N_β allows dimerization even at temperatures as low as -40 °C.[26] These species are very rare, highly reactive, and unstable. Despite the difficulty to observe these intermediates, it is possible to exploit their reactivity by reacting *N*-

isocyanates as they form in solution. Based on previous research on their formation, the Beauchemin group investigated and developed the reactivity of amino–isocyanates.

1.5.1.2 Initial Formation Investigation of Aminoisocyanates

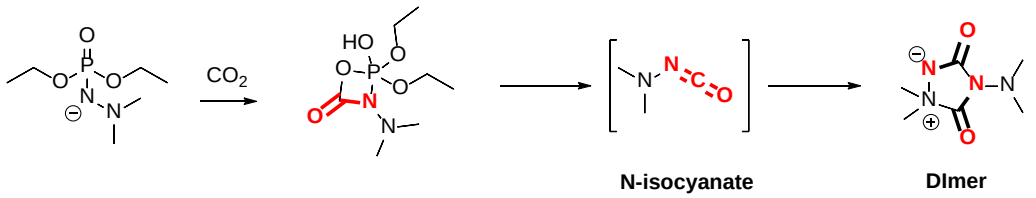
Formation of amino–isocyanates via the Curtius rearrangement from carbamoyl azides was studied in photolytic conditions by Stollé and Lwowski (Scheme 7).[24,27,28] These methods have major limitations. While their experiments support the formation of transient amino–isocyanates, solvolysis occurs in nucleophilic solvents, to yield either the carbamate in methanol, the hydrazine in presence of water or the dimer in non nucleophilic solvents, which supports an increase in concentration of the transient aminoisocyanate.



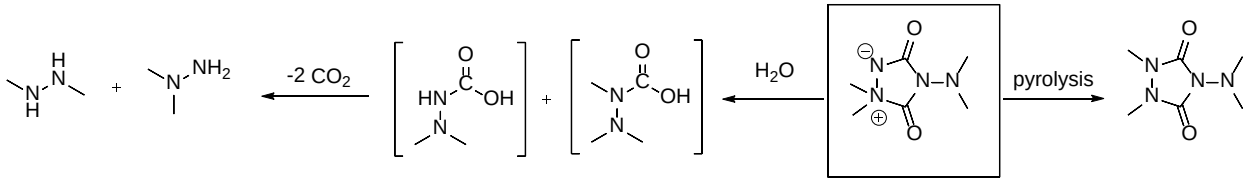
Scheme 7: Rigid Azide Experiments by Lwowski

Wadsworth and Emmons pioneered the investigation of the generation of the monomeric unit of an amino–isocyanate from ring opening of heterocyclic compounds. They initially investigated the possible retro [2+2] of the O-P-N heterocycle (Scheme 8) but only recovered a dimer. It was then thought the dimer could act as a masked aminoisocyanate, which led them to investigate the regeneration of the monomer by hydrolysis or pyrolysis of the dimer. These experiments only afforded a pair of hydrazines from the hydrolysis followed by decarboxylation of the intermediate carboxamic acid or a structural isomer obtained from pyrolysis, after the 1,2–methyl shift (Scheme 9). They tried to regenerate the

amino–isocyanate monomer from the dimer via hydrolysis or thermal decomposition, which only led to undesired products.[29]



Scheme 8: Wadsworth and Emmons Generation of Aminoisocyanates from a Heterocyclic Precursor



Scheme 9: Wadsworth and Emmons Dimer Fragmentation Experiments

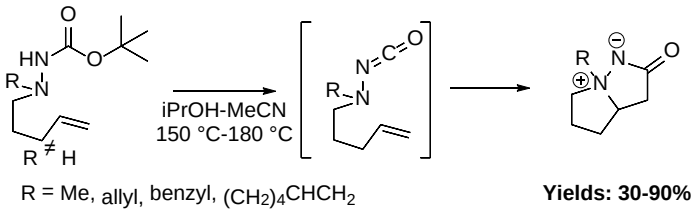
The multiple failed attempts at isolating the monomer led the Beauchemin group to believe that trapping the transient species could be a better approach to take advantage of these very reactive amino–isocyanates. Recent developments were made in our group that allowed in situ trapping of amino–isocyanates formed from carbamates.[30]

1.5.1.3 Recent Applications of Amino-Isocyanates

Different carbamates and their ability to release amino–isocyanates were investigated. It was discovered that different synthetic applications could be developed by changing the nature of the precursor: the masked amino–isocyanate. Over the years, multiple types of nitrogenated molecules have been synthesized taking advantage of transient amino–isocyanates to perform different reactions such as the aminocarbonylation, Friedel-Craft and Aza-Lossen reactions.

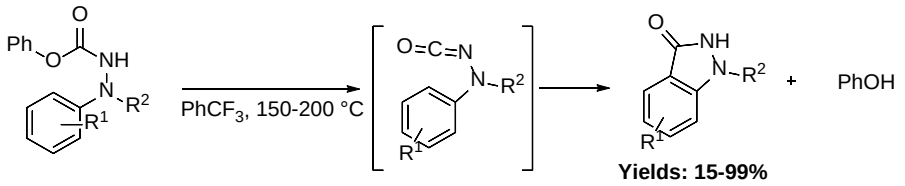
Amino isocyanates can behave as a dipole and undergo [3+2] cycloaddition with π–bonds, also known as the aminocarbonylation reaction, to generate aminimides (Scheme 10).[31–33] A number of fused,

bicyclic compounds were prepared via this intramolecular cyclization in modest to good yields. Interestingly, the reactivity of the substrate is dependent on the electronic character of the leaving group on the carbazate. The use of -O*t*Bu leaving group, as depicted in Scheme 10, results in aminocarbonylation via the *N*-isocyanate, whereas aryl groups, such as the 3,5-bis trifluoromethylbenzene group, increase the acidity of the NH of the carbazate and the product of Cope type hydroamination is obtained instead.



Scheme 10: Ivanovich et al Aminimide Synthesis via Aminocarbonylation

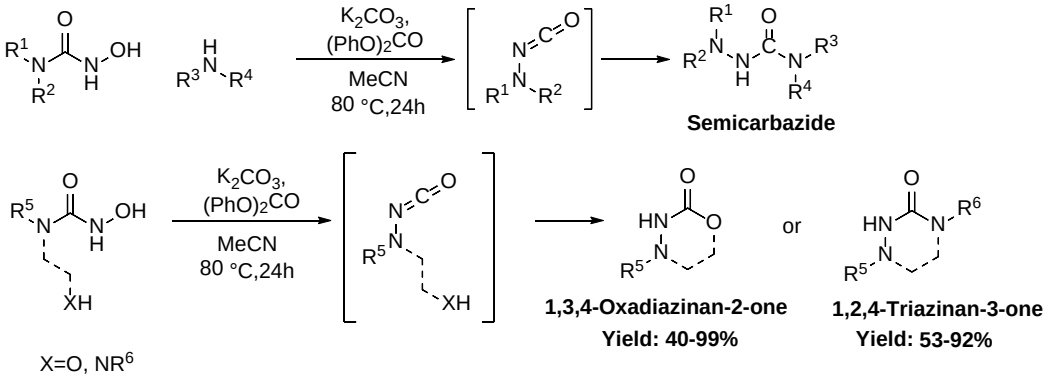
N–Aryl substituted amino–isocyanates can also engage in Friedel–Craft cyclization reactions to form indazolones.[22] The scope delineated by this study shows that N_β renders the aromatic group sufficiently nucleophilic despite that some substrates are bearing electron withdrawing groups such as halides. The ability to dearomatize and form the indazolone indicates a lower energy transition state which suggest the formation of a transient amino-isocyanate as the electrophile. This reaction is shown to be mostly heat dependant, as base or acid additives did not improve the yield. Quantitative yields were obtained at 180 ºC. Various leaving group were tested during development, and the phenol ability to enter a reversible equilibrium compared to the other leaving groups explained its best reactivity. Many alternative synthetic methods to these heterocycles can be found in the literature, while most of them involve transition metals, such as Buchwald-Hartwig-type cross coupling.



R^1= Cl, F, Me, iPr, 5,7-dimethyl
R^2=Me, Ph, Bn, iPr, 2-CH_2 furanyl, allyl, THP, indanyl, CH_2CO_2Et

Scheme 11: Elkaeed et al Indazolone Synthesis

An Aza–Lossen rearrangement was also developed from *N*–hydroxy–ureas (Figure 8). Upon activation in situ, these form a transient amino–isocyanate. These species can later be trapped by a nucleophile such as a secondary amine.[34] A variety of nitrogen containing species can be obtained, such as semicarbazides, 1,2,4–triazinan–3–one or 1,3,4–oxadiazinan–2–one. This work demonstrates the requirement of a secondary amine as nucleophile. Otherwise, a protecting group such as a tosyl was installed and later removed using conventional methods. Both intramolecular and intermolecular nucleophile proved efficient, to trap the transient aminoisocyanate and yield either one of the product aforementioned. In a case where the substituent on the N_β bears a chain with a terminal alkene that is long enough to allow a concerted hydro-hydrazidation reaction, the aminimide can also be obtained.[31]



X=O, NR^6

R^1,R^2 = Bn, iBu, allyl, Et, $(CH_2)_2OH$, morpholine,1-methyl piperazine

R^3,R^4 =Me, Et, Pr, Bn, iBu, t-Bu, sec-Bu, allyl, Cy, Ph, propargyl, morpholine, cyclopentyl, cylclopropyl,

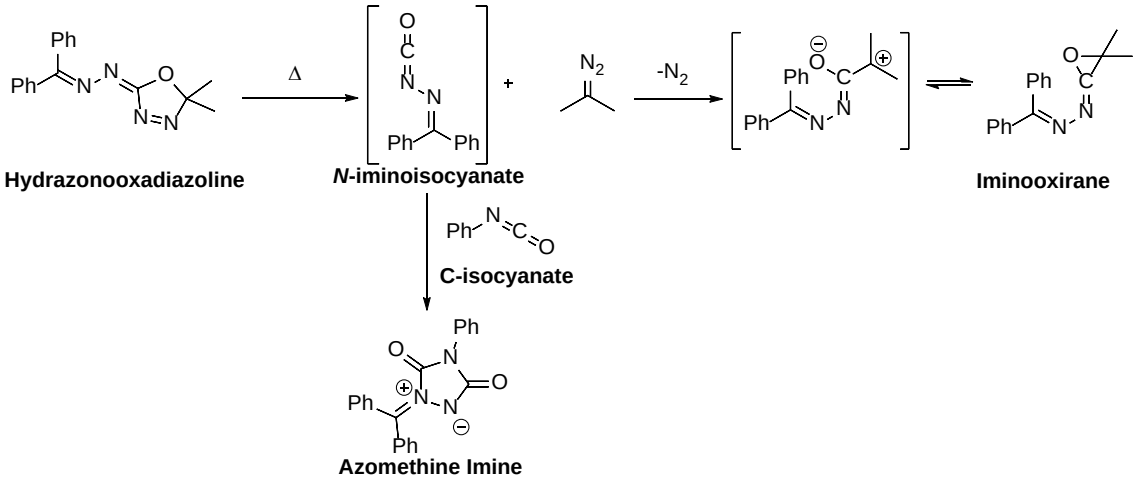
R^5 = Bn, CH_2-furanyl, Et, CH_2Cy, (*E*)-(2-methylbut-2-en-1-yl)

R^6 = Ph, Ts, $SO_2C_6H_4Br$

Figure 8: Polat et al Aza-Lossen Rearrangement

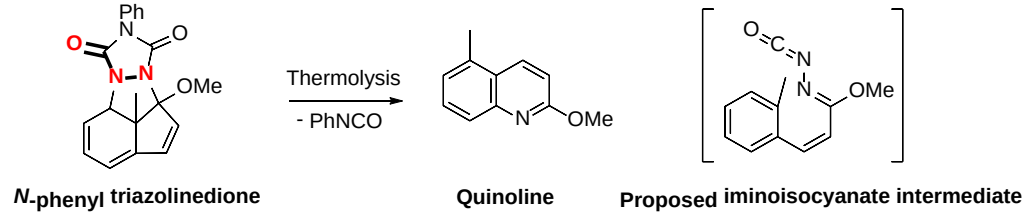
1.5.2 Iminoisocyanates

Iminoisocyanates were first reported by Warkentin in 1976 when hydrazonooxadiazolines were heated (Scheme 12).[35,36] Upon addition of a *C*–isocyanate, the azomethine imine and the iminooxirane were obtained. The formation of azomethine imines could be attributed to the formation of a transient imino–isocyanate and a subsequent [3+2] cycloaddition with the *C*–isocyanate. The formation of the iminooxirane could be explained by the reaction of the diazo side product, 2-diazopropropane, and the imino–isocyanate.



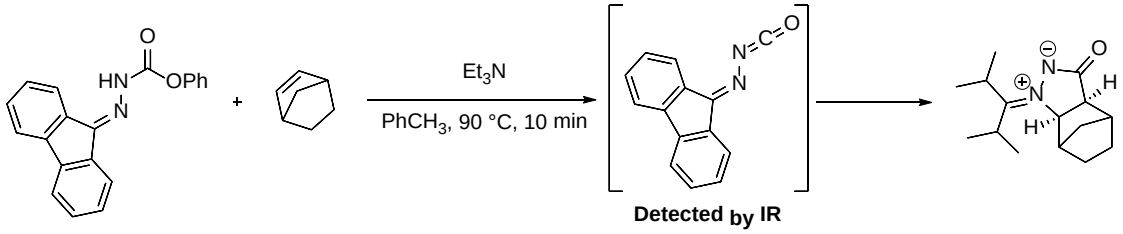
Scheme 12: Warkentin's Experiments with Hydrazonooxadiazoline

Five years later, Gilchrist *et al.* studied the thermolysis of *N*–phenyltriazolinedione (Scheme 13) and a nitrogenated product, a quinoline, was obtained which they hypothesized was obtained via the formation of an imino–isocyanate.[37] A few other authors reported reactions with transient imino–isocyanates.[38,39] The feasibility of using transient imino–isocyanate without prior isolation was supported by studies from Shah and Chudgar.[40] They have demonstrated that thermolytic cleavage of semicarbazones yields azine through the reaction of intermediate imino–isocyanates. However, such examples using an analogous methodology remain scarce to this day.



Scheme 13: Thermolysis of N–Phenyltriazolinedione by Gilchrist et al

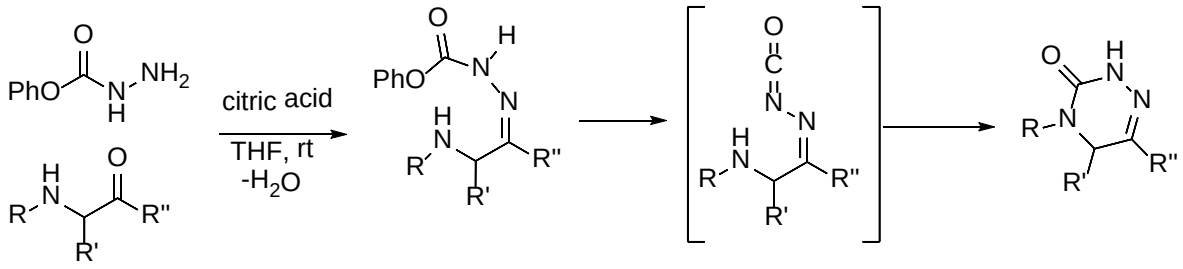
In 2017, Bongers et al. from the Beauchemin group studied the aminocarbonylation from hydrazones (Scheme 14).[41] The suggested pathway consisted of base–catalyzed imino–isocyanate formation and subsequent reaction with alkenes to form azomethine imines. The generation of an imino–isocyanate intermediate was supported by IR spectroscopy. A very specialized instrument was required to acquire these data in Flow-IR. Spectra analysis showed bands (2200–2300 cm^{-1}) that could not be attributed to starting material or products. Moreover, they were in good agreement with the reported values for *N*–isocyanates. Due to their low stability and high reactivity, such supporting data had never been obtained in previous literature involving imino–isocyanates.



Scheme 14: Bongers' Iminoisocyanate Trapping Experiment

In 2017, Dahab *et al*. reported a cascade reaction involving an imino–isocyanate (Scheme 15)[42] Following an initial hydrazone formation, a transient imino–isocyanate was formed under acid catalysis and subsequentially trapped by an intramolecular secondary amine to form a 1,2,4–triazin–3(2H)–one. Improvement in triazinone synthesis were published by Vuillermet *et al.* in our group.[43] A one pot synthesis was developed to access alpha amino iminoisocyanates using a sturdier blocking group, such a

t-butanolate allowed the obtention of a variety of triazinone in yield ranging from 45-82% under basic catalysis. Prior to this publication, the scope of the synthesis was restricted to anilines (R=Ar).

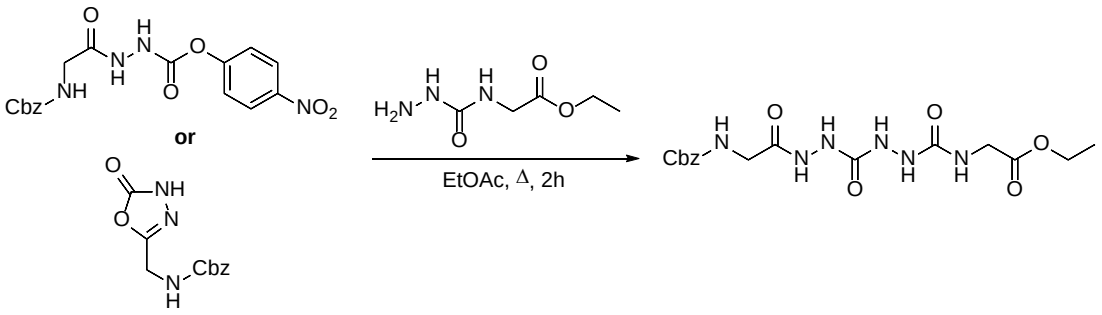


Scheme 15: Dahab et al. Iminoisocyanate Cascade

Overall, the success obtained in the study and applications of both amino and imino–isocyanates using a masked isocyanate approach led us to investigate an elusive third class: amido–isocyanates. The various hybridization of the N_β seems to have a significant impact on the reactivity and amido–isocyanates, with the partial sp^2 character of the nitrogen, was a natural extension to the exploration of the various categories of *N*–isocyanates.

1.5.3 Amidoisocyanates

In 1965, Gante reported on the synthesis of aza–tripeptides.[44] Gante wanted to develop a selective method for peptide elongation allowing the addition of a fragment on one side over the other (Scheme 16). It was achieved by using the 4-nitrophenylcarbamate as an activated blocking group on one side of the peptide while on the other side, a benzoyl was used, because of its lower reactivity. To validate the structure of the product he obtained, he synthesized the desired compound using another route, starting from the corresponding 1,3,4–oxadiazol–2(3H)–ones based on previous literature,[45] which led to the same product confirming the intended structure. Only in 1992 was the isocyanate formation hypothesis brought to light by Abeles.[46]



Scheme 16: Gante's Azapeptide Synthesis

Amido–isocyanates are rare in the literature. They have been studied unknowingly uniquely in a medicinal chemistry context. Abeles was looking at peptoïds containing aza–glycine residues. He sought after selective inhibition of cysteine peptidases, over serine peptidases. He used papain, a model enzyme for his inhibition experiments. Abeles first proposed in 1992 the covalent inhibition of papain by a tripeptide containing an aza–glycine residue via the formation of an intermediate amido–isocyanate acylating the enzyme.[46]

He initially envisioned a typical nucleophilic addition to the carbonyl forming a tetrahedral intermediate, but when he explored the reaction rates with various leaving group, he proposed a different mechanism, involving an amido–isocyanate. He noticed an 600x increase in the rate of inhibition from an alkoxide as a leaving group, with no stabilization of the anionic leaving group compared to a phenolate, where resonance contributes significantly to the stabilization of the resulting anion (Figure 9). Based on this observation, he proposed that the mechanism could involve the formation of an amido–isocyanate which would react significantly faster than a carbamate via a tetrahedral intermediate. He then postulated that the phenol substituted substrates were covalent inhibitor whereas alkoxy substituted carbamates were more likely to be reversible non–covalent inhibitors. A covalent binding will inhibit the enzyme irreversibly while a non covalent inhibitor can be displaced by a substrate with a reversible binding and compete for the substrate enzyme site. Abeles also noticed a side product is also formed; the 1,3,4–oxadiazol–2(3H)–ones and the release of the 4–nitrophenolate. He did not, however, investigate the possibility of an equilibrium between the heterocycle and the amido–isocyanate. In the context of this

thesis, it is important to note that there was also no suggestion of an equilibrium between the heterocycle and the amido-isocyanate.

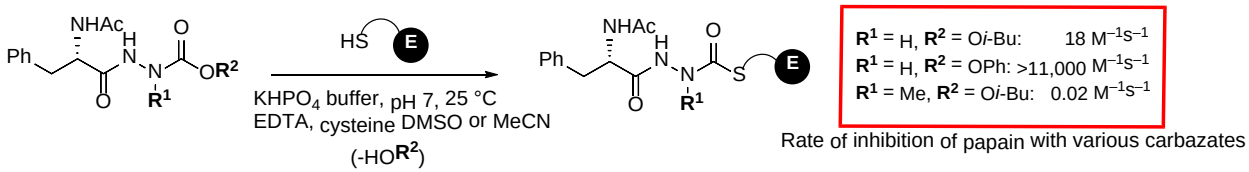
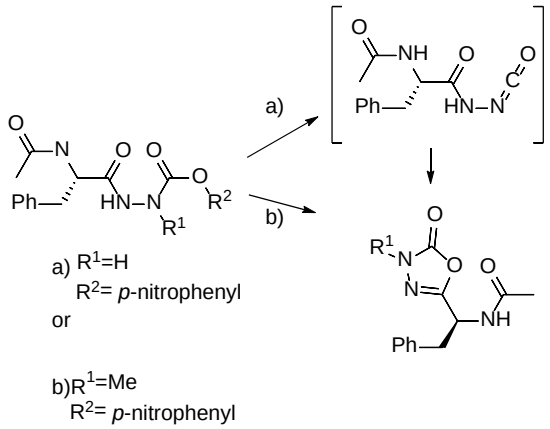


Figure 9: Abeles' Papain Inhibition Study

The potential for formation of transient amido-isocyanates from aza-peptides was again discussed in 1998 by Hanzlick.[47] He suggested that when R^1 is a proton, an amido–isocyanate can be released, while when R^1 is a methyl group, cyclization to the 1,3,4–oxadiazol–2(3H)–ones would proceed without the formation of an isocyanate (Scheme 17). In support of Abeles' study, Hanzlick also noticed a very high rate of inactivation of a cysteine protease and intended to use these azapeptides as enzyme titrant. Despite the very high rate of inactivation, he observed that the carbamate was also unstable in the buffer solution and would release *p*–nitrophenol. Since then, this hypothesis was never reinvestigated nor confirmed.



Scheme 17: Hanzlick's Proposed Mode of Decomposition of N_β–Acyl Carbazides

Amido–isocyanates can be formed from N_β–acyl carbazides (Scheme 17) with unsubstituted N_α (NH) with heat and this transformation can be catalyzed by base or less commonly, an acid. Abeles used

4-nitrophenylcarbamate as a reactive functional group as a tamed version of the corresponding carbamoyl chloride, which was too reactive and led to the formation of 1,3,4–oxadiazol–2(3H)–ones as an important side reaction. The 4-nitrophenylcarbamate provided enough stability to inhibit the targeted enzyme, papain, but not enough to completely prevent the formation of the 1,3,4–oxadiazol–2(3H)–ones. This prompted the investigation of the reactivity of oxadiazolones and its plausible mechanism of action.

1.5.3.1 1,3,4–Oxadiazol–2(3H)–ones

Kessler, in 1999, was also interested in the synthesis of aza-peptides in solid phase, using a FMOC protection strategy (Figure 10). When phosgene was used to obtain the carbamoyl chloride, the oxadiazolone was recovered instead, which is in agreement with the observation made by Gante and Abeles. Stempel also synthesized these heterocycles via a Hofmann reaction (Scheme 18).[48]

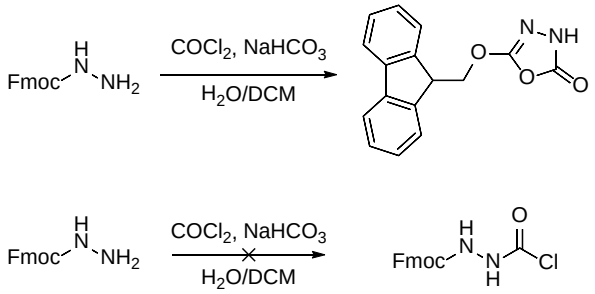
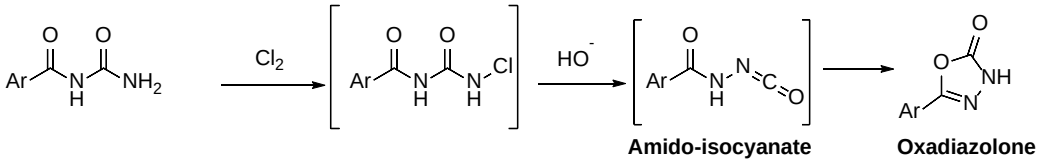


Figure 10: Kessler's Observation During Solid Phase Synthesis of Azapeptides

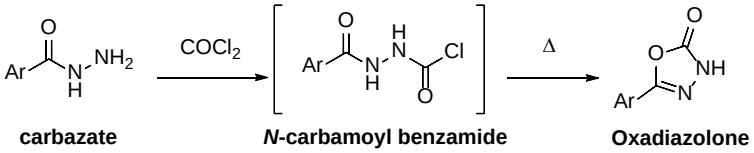
1.5.3.2 Reactivity of 1,3,4-oxadiazol-2(3H)-ones

1,3,4–Oxadiazol–2(3H)–ones are most commonly used as nucleophiles, both at the nitrogen or the oxygen, via the aromatic tautomer. It has been used to append oxadiazolones to target compounds rather than to use it as precursors for hydrazides. Stempel *et al*. presented a method to form hydrazides (more specifically, semi–carbazides) from these heterocycles without investigating the mechanism (Scheme 19).[45] Their interest in oxadiazolones came from a shortage of hydrazine, an important reagent needed to synthesize isonicotinic acid hydrazide. We can see from the report that oxadiazolones can be prepared from *N*-carbamoyl benzamide through a Hofmann rearrangement (Scheme 18), or from the

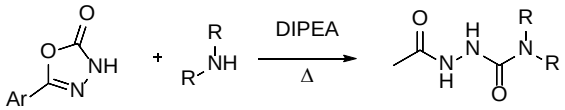
acylation of a carbazate with phosgene. The oxadiazolone that was obtained was reacted with amines under heat (70-184 ºC) to form semi-carbazides (Scheme 20). This work showed that oxadiazolones could also be used as electrophiles.



Scheme 18: Stempel's Oxadiazolone Synthesis via a Hofmann Rearrangement



Scheme 19: Stempel's Oxadiazolone Synthesis form Carbazates

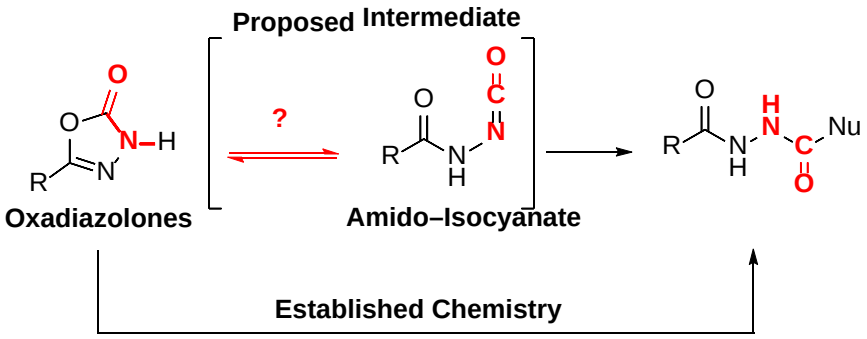


Scheme 20: Stempel et al Methodology for Addition of Amines to Oxadiazolones

The interesting results obtained by pioneers, such as Stempel, Gante's research were not driven by the mechanistic details of these reactions, but rather by the interest in their target compounds. In the effort to bring light to this field of chemistry, the Beauchemin group initiated research into a new methodology where oxadiazolones could be used as electrophiles and precursors for amido-isocyanate with a main focus on studying the formation of this elusive intermediate.

Project Objectives

Initial objectives were to synthesize aza–tripeptides using a methodology involving masked amido–isocyanates. However, initial work ended up demonstrating that these products were quite challenging to obtain and as such, we revisited the objectives. We provided evidence of the formation of a transient masked amido–isocyanate from aza–dipeptides (N_{β}–acyl phenylcarbazides). We aimed to evaluate and obtain experimental evidence to support the equilibrium of 1,3,4–oxadiazol–2(3H)–ones with the corresponding amido–isocyanate under various conditions, which we proposed below, exploiting the well–known reactivity of carbon substituted isocyanate, shown to react in a similar fashion to other types of nitrogen substituted isocyanates.



Herein, the reaction of β–amido–carbamates with nitrogenated nucleophiles under basic conditions along with heat to form hydantoins or aza–tripeptides will be presented. The reactivity of *C*–isocyanates was exploited to demonstrate and support the formation of a transient amidoisocyanate from aza–dipeptides (N_{β}–acyl phenylcarbazides) and provided evidence of an equilibrium between the latter and the corresponding 1,3,4–oxadiazol–2(3H)–ones. We present reactions with carboxylates and oxadiazolones under basic conditions to form hydrazides, following Crich's report of amide bonds formation from isocyanates and carboxylates to further support the formation of an isocyanate intermediate when reacting these heterocycles in basic conditions. Overall, we validated that N_{β}–acyl phenylcarbazide, as well as 1,3,4–oxadiazol–2(3H)–ones, act as masked amidoisocyanates via an equilibrium and can be reacted as such *in situ* to form amide bonds.

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Chapter 2: Published Manuscript

In Chapter 2, the manuscript published in *Chemistry: A European Journal*, in which William Gagné–Monfette is the first author, will be presented. The only difference is that the text of the manuscript was formatted to correspond to thesis guidelines. **All numbering remains unchanged from the published manuscript**. In addition to the results shown in the paper, unpublished supplementary results, along with a discussion on those can be found in Chapter 3.

Citation:

Gagné–Monfette, W.; Vincent–Rocan, J.–F.; Lutes, O. C.; O'Keefe, G. F.; Jeanneret, A. D. M.; Blanger, C.; Ivanovich, R. A.; Beauchemin, A. M. Investigation of Masked *N*–Acyl–*N*–Isocyanates: Support for Oxadiazolones as Blocked *N*–Isocyanate Precursors. *Chemistry – A European Journal*. **2021**, *27*, 14051–14056.

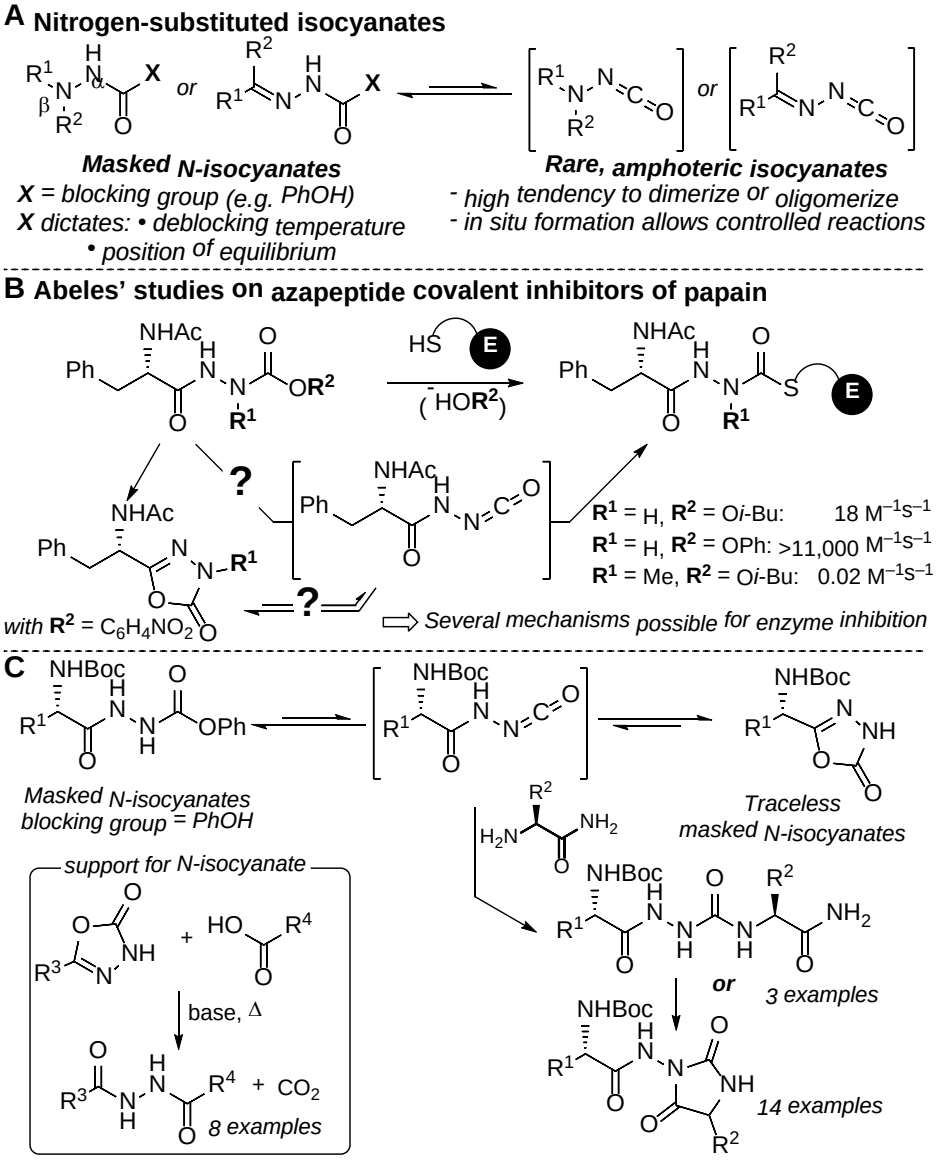
Abstract: In contrast to carbon-substituted isocyanates that are common building blocks, nitrogen-substituted isocyanates remain underdeveloped and reports on their *N*-acyl derivatives (i.e. amido-isocyanates) are exceedingly rare. Herein amido-isocyanates were investigated in the context of syntheses of aza-tripeptide and hydantoins subunits starting from simple bench-stable precursors. A key finding is that the amido-isocyanate formed *in situ* cyclized to yield an oxadiazolone, and that under suitable reaction conditions this heterocycle is a traceless blocked (masked) *N*-isocyanate. Using organic bases as catalysts and upon heating, oxadiazolone formation is observed, and various nucleophiles to provide the desired aza-dipeptides or hydantoins in moderate to high yields. Further support for an amido-isocyanate intermediate was obtained using carboxylic acids as nucleophiles, affording *N*-acylhydrazide products.

Keywords: nitrogen heterocycles • isocyanates • oxadiazolones • hydrazides • aza-peptides

Introduction

Carbon-substituted isocyanates are common organic synthons with diverse applications ranging from polymer synthesis to the development of pharmaceuticals and agrochemicals.[1] In contrast nitrogen-substituted isocyanates (*N*-isocyanates) are rare. Different types of *N*-isocyanates have been reported, with reactivity varying with the hybridization and substitution pattern on the β-nitrogen atom. Initial work has mostly focused on amino-isocyanates (sp^3-hybridized β-nitrogen atom), and imino-isocyanates (sp^2-β-N) were then investigated.[2] These reactive intermediates have also been observed directly, providing clear evidence for their formation despite a well-documented tendency to dimerize and yield other byproducts due to their high reactivity. Recently our group[2a] used *N*-isocyanates for the development of alkene cycloadditions yielding β-amino-carbonyl motifs, as well as nucleophilic additions [3] and cascade reactions forming NNCO containing products. The key approach enabling this was the use of masked (blocked) *N*-isocyanate precursors: bench-stable hydrazine derivatives that form the desired *N*-isocyanate upon heating or catalysis (Scheme 1A).[4] Synthetically, this work was motivated by the prevalence of the NNCO motif in over 50 pharmaceuticals and agrochemicals, and showed that controlled reactivity of *N*-isocyanates is possible. In contrast, amido-isocyanates (and other β-N acyl derivatives) remain exceedingly rare in the literature. Most notably, their likelihood as intermediates in the enzymatic inhibition by aza-peptides has been examined by Abeles (Scheme 1B) and Hanzlick,[5-6] highlighting the importance of the R^1 and R^2 groups on reactivity and selectivity, and that cyclization to form oxadiazolones was also a probable mode of decomposition for some precursors.[5] Both aza-peptides and oxadiazolones have been the focus of many studies in medicinal chemistry. Synthetically, oxadiazolones have been used in the synthesis of aza-peptide subunits.[7] From this literature survey, one can hypothesize that the high reactivity observed when R^1 = H is tied to the formation of amido-isocyanates. However, to our knowledge, the possible reversibility of the oxadiazolone cyclization as an approach to form *N*-acyl-*N*-isocyanates has not been proposed since the seminal work by Gante,[8] nor investigated in detail outside

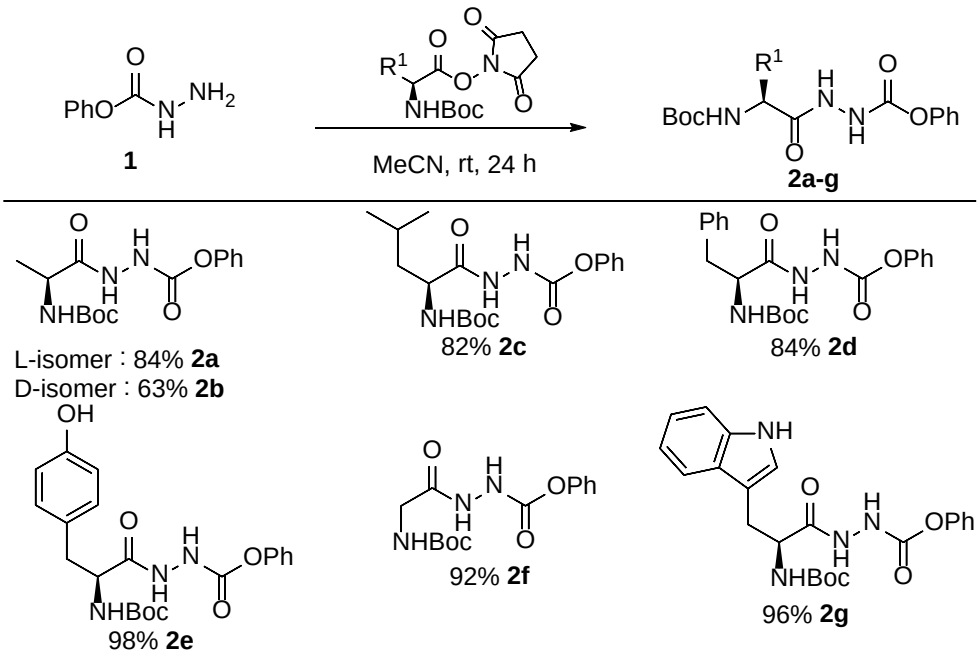
of medicinal chemistry efforts.[5-6] This is somewhat surprising given the high interest that cyclic isocyanate precursors have stimulated (e.g. *N*-carboxyanhydrides, NCA, and their ability to oligomerize under prebiotic conditions).[9] Herein, we provide evidence that oxadiazolones are intermediates in these reactions (formed from an amido-isocyanates, showing that they act as blocked *N*-isocyanates and present evidence that their high reactivity is likely associated with *in situ* isocyanate formation (Scheme 1C)).



Scheme 1 A) Examples of *N*-isocyanates and use of masked (blocked) *N*-isocyanate precursors. B) Abeles' work on aza-peptide inhibitors, indicating amido-*N*-isocyanates as possible intermediates and oxadiazolone formation as a decomposition pathway. C) This work, showing that acyclic masked *N*-isocyanates *and* oxadiazolones are suitable blocked (masked) *N*-isocyanates.

Results and Discussion

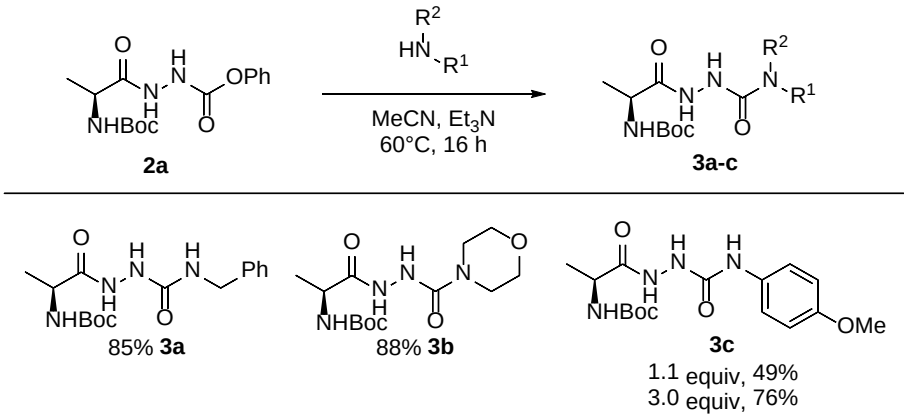
Recently, our group developed several reaction cascades using phenol as the blocking (masking) group for *N*-isocyanate precursors.[3e-h] Useful attributes of this group includes that most precursors are bench-stable crystalline solids, and that base or acid catalysis allows release of the desired *N*-isocyanate at or near room temperature. In the absence of catalysts, heating at temperatures around 80-110 °C leads to *in situ* formation of the *N*-isocyanate. Therefore, it was hypothesized that aza-dipeptide analogues possessing this leaving (blocking) group would allow aza-tripeptide formation under mild conditions. Substrates **2a-g** were synthesized in high yields via treatment of phenyl carbazate **1** with *O*-succinyl esters of natural amino acids (Scheme 2).



Scheme 2 Synthesis of masked *N*-isocyanate precursors. Conditions: Phenyl carbazate (1, 1.0 equiv), *N*-Boc-protected *O*-succinyl aminoester (1.0 equiv) in MeCN (0.2 M) at room temperature for 24 h (Isolated yields; 7.74 mmol scale).

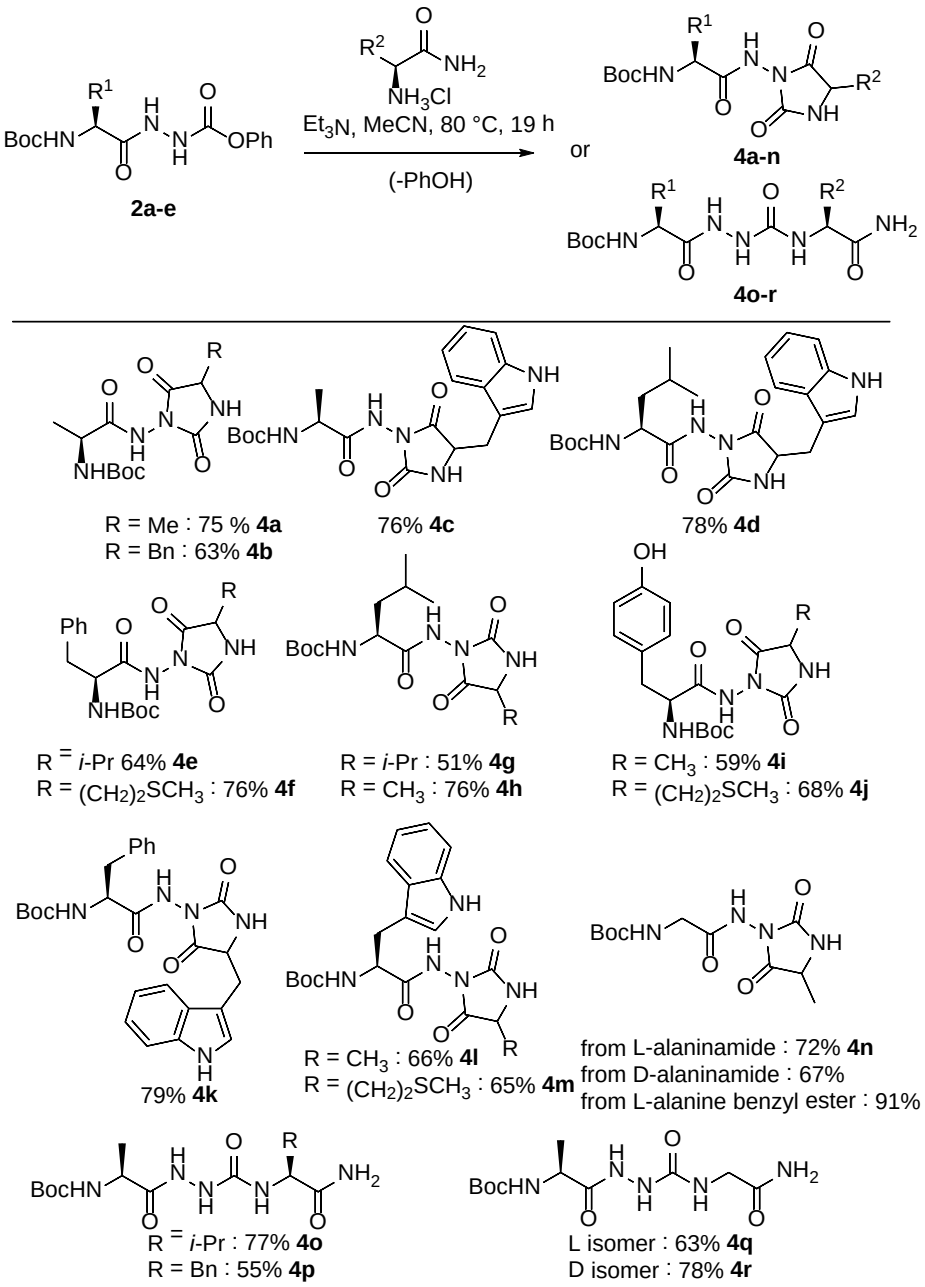
With a convenient synthesis of the *N*-isocyanate precursors, substitution reactions were attempted with simple amines. First, alanine derivative **2a** was reacted with benzylamine in THF at room temperature, using DBU as catalyst (20 mol%). While encouraging, only a modest 50% yield was obtained; usually substitution reactions with *N*-isocyanate precursors are higher yielding.[3f, 3h] Moreover, with the goal of

synthesizing aza-tripeptides, a solvent more polar than THF was deemed optimal. Therefore, new conditions were identified: the use of acetonitrile as solvent and triethylamine as base at 60-80 °C was tested with various simple amines (Scheme 3). Under these conditions, the reaction with benzylamine afforded semicarbazide **3a** in 85% yield. A secondary amine also proved capable, as shown by formation of the morpholine adduct **3b**. *p*-Anisidine, which displays reduced nucleophilicity, also proved to be a suitable nucleophile, but the reaction benefited from the use of a slight excess of the nucleophile (**3c**).



Scheme 3 Substitution with amines on blocked (masked) amido-isocyanate **2a**. Conditions: Reagent **2a** (1 equiv), amine (1.1 equiv), Et_3N (0.2 equiv) in MeCN (0.3 M), 80 °C, 16 h. Each product was also obtained in high yield at 60 °C.

Then the synthesis of aza-tripeptides was explored in Scheme 4 using the different masked amido-isocyanates formed in Scheme 2 and natural L-α-amino amides. It became quickly apparent that the nucleophilicity of amino amides was not optimal, similarly to the reaction with *p*-anisidine to form **3c**. Using an excess of nucleophile resulted in a heterogeneous mixture, however the desired reactivity using only 1.1 equivalent of the α-amino amides was possible at 80 °C (Scheme 4).

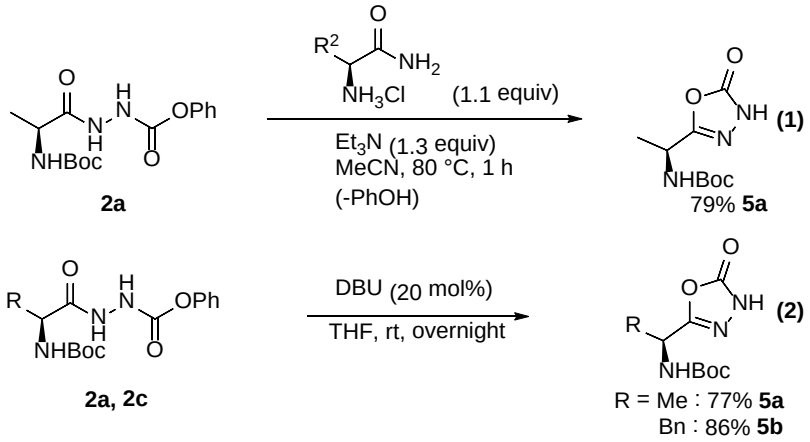


Scheme 4 Hydantoin and aza-tripeptide synthesis using masked amido-isocyanates. Conditions: Aza-dipeptide **2a-e** (1.1 equiv), L-amino amide hydrochloride (1.0 equiv), Et_3N (1.3 equiv) in MeCN (0.3 M), 80 °C, 19 h. All reactions were performed on a 1.98 mmol scale.

Gratifyingly, using masked amido-isocyanate precursors allowed rapid assembly of a small library of 18 compounds, which were either the hydantoins **4a-n** resulting from the intramolecular cyclization with extrusion of ammonia under mild conditions or the aza-tripeptides **4o-r** (Scheme 4). The alanine, leucine, phenylalanine, tyrosine, glycine and tryptophan derived aza-dipeptide precursors were reacted with

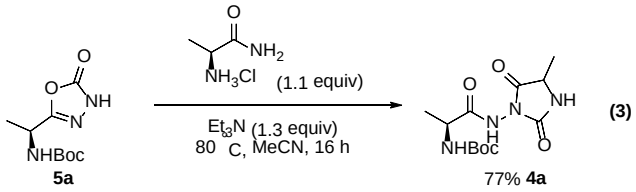
alanine, tryptophan, leucine, glycine and methionine amides. The amino-amides were used as their hydrochloride salts, and deprotonated *in situ* with triethylamine. Yields ranged from modest to good (51-91%) using only a small excess of nucleophile. Given the mild conditions and the ease of access from simple precursors, this provides a useful approach for the assembly of aza-tripeptide derived hydantoins. In rare cases where the solubility of the intermediate was low, the aza-tripeptide product precipitated (**4o-r**). Overall, this reactivity complements the work of Kessler using an oxadiazolone as a source of Fmoc-azaglycine.[7e-g]

All reactions in Scheme 4 were slower than typical *N*-isocyanate substitutions.[3f,3h] Therefore a reaction with substrate **2a** was closely monitored. Surprisingly, a fast consumption of the starting material was noted within the first hour. However, none of the desired product was formed at that time. Instead, an oxadiazolone was obtained from this reaction (Eq. 1). Reasoning that formation of this product did not require the presence of a nucleophile, the conditions were optimized using DBU as a base catalyst (Eq 2). While the scope of this cyclization was not delineated, this represents a mild synthesis of oxadiazolones.[8,10]



Having shown that oxadiazolones rapidly form under the reaction conditions, their reactivity as intermediates leading to aza-tripeptide products could then be investigated. As expected, subjecting 1,3,4-oxadiazol-2(3H)-ones **5a** to the reaction conditions led to formation of hydantoin **4a** in a 77% yield (Eq.

3), thus supporting its likelihood as an intermediate in the reaction using **2a** as the substrate (75% yield, Scheme 4)



Oxadiazolones as potential masked *N*-isocyanates

A thorough literature search revealed that oxadiazolones have been used for reactions with a variety of nucleophiles including amines,[11] hydrazines,[12] phenols,[7a] thiols,[7a] etc. However, to our knowledge the possibility that oxadiazolones could act as masked amido-isocyanates has not been addressed since the pioneering work of Gante,[8] and then of Abeles[5] and Hanzlick[6] specifically in the context of enzyme inhibition. Indeed, oxadiazolones are aromatic but possess reduced aromatic stabilization energy because of their high heteroatom content and could undergo a ring opening reaction to form a potent isocyanate electrophile. Such a pathway offers a mechanistic alternative to the formation of a tetrahedral intermediate by nucleophilic addition.[4] Moreover, due to the relatively acidic oxadiazolone N-H (pKa ≈ 6-8),[13] facile deprotonation under basic conditions disfavours the addition to the carbonyl. To test the hypothesis that oxadiazolone ring opening occurs to form a reactive amido-isocyanate electrophile, a simple substrate design was envisioned to discriminate between the possible reaction pathways. Indeed, the presence of a N-H on the oxadiazolone is required for the ring opening reaction and isocyanate formation to be facile (Figure 1, see also introduction). Thus, simple substrates containing N-H and N-Me substituents were synthesized (see SI), so that different reaction conditions could be tested for the addition of allylic amines (Table 1).

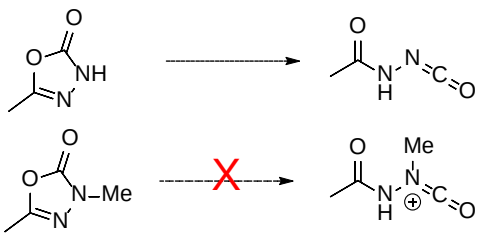
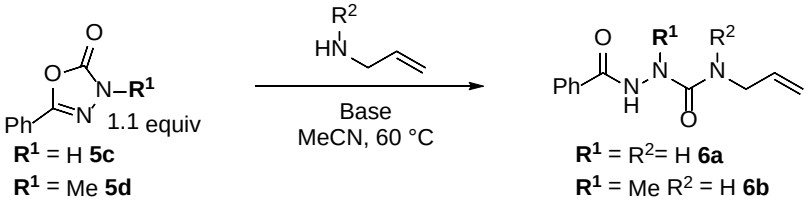


Figure 1 System design for possible discrimination between pathways involving a direct attack on the oxadiazolone, or attack on a transient amido-isocyanate intermediate

Table 1 Control Reactions to Probe the Possibility of an Amido-isocyanate Intermediate[a]



Entry	$\mathbf{R^1}$	Amine	Base	Yield (%)[b]/
1	H	allylamine	NMI	quantitative
2	H	allylamine	Et_3N	quantitative
3	H	allylamine	imidazole	quantitative
4	H	*N*-Me allylamine	Et_3N	quantitative
5	Me	allylamine	NMI	no reaction
6	Me	allylamine	Et_3N	no reaction
7	Me	allylamine	imidazole	no reaction

[a]Conditions: **5c** or **5d** (1.1 equiv), amine (1.0 equiv), base (0.2 equiv) in MeCN (0.3 M), 60 °C, 16 h. [b]Yield was determined by analysis using ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. See SI for an unoptimized isolation procedure. NMI: *N*-methylimidazole.

At first, reactions were performed under the conditions used in Table 1, and indicated that N-Me derivative **5d** was unreactive while quantitative conversion was observed for the free N-H substrate **5c** (Table 4, entries 1-4). Various conditions were then tested. To ensure that the reaction was not limited to primary amines, *N*-methylallylamine was used and also showed a quantitative formation of the product **6b** (entry 4). To explore this reactivity in the presence of a weaker base, the reactions with imidazole and *N*-methyl imidazole were performed and similar results were obtained (entries 4-7). To rule out the possibility that the reaction of *N*-methyl substrate **5d** could occur at a higher temperature, the reaction was

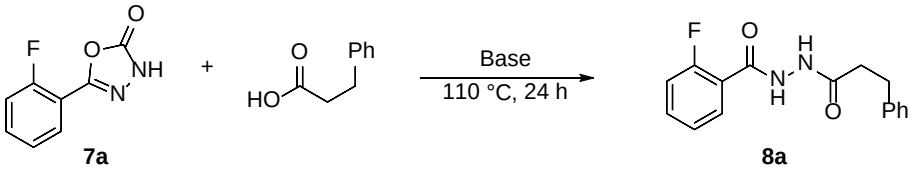
also performed at 100 °C and again similar results were obtained: quantitative conversion for the free N-H oxadiazolone **5c**, and no reaction with the N-Me substrate **5d**. The same experiments were performed using the L-alanine derived substrate **2a** and allylamine or *N*-methylallylamine and afforded similar results (see SI for details). These results are consistent with the aforementioned hypothesis and are well aligned with the reactivity trends documented by Abeles (Scheme 1).[5-6]

To further support our hypothesis, we chose a reaction that is only likely to occur if the reaction undergoes the formation of an isocyanate. It is well established that carboxylic acids[14],[15] react with isocyanates to form amides.[16] Recently, Crich showed that using Hunig's base (i-Pr_2NEt) as a base results in room temperature reactivity.[17] The generally accepted mechanism involves a nucleophilic attack of the carboxylate onto the isocyanate followed by a cyclization of the resulting anion and decarboxylation via retro [2+2] to yield the corresponding amide. It is also established that masked isocyanates undergo this transformation, but typically under somewhat more forcing conditions due to the need to form the isocyanate *in situ* via a reversible equilibrium.[16] Investigating the reaction of carboxylates with oxadiazolones could thus provide further support for the formation of *N*-isocyanates under the reaction conditions and provide a new synthetic approach to synthesize *N*-acyl hydrazides. Toward this goal, hydrocinnamic acid and oxadiazolone **7a** were selected as model substrates to explore this reactivity. Selected optimization results are shown in Table 2, and results of the exploration of the generality of this reactivity is shown in Table 3.

A variety of N_β-acyl hydrazides were successfully synthesized, using both aliphatic and aromatic carboxylic acids along with three different oxadiazolones (Table 3). This was achieved under optimized conditions relying on heating at 110 °C in the presence of a base. Eight different N_β-acyl hydrazides were obtained in yields ranging from 17 to 72%. NMR yields, determined by ^{19}F NMR spectroscopy, were generally higher (62-86%), but isolation proved very challenging for some products (**8g** and **8h**). In fact, only hindered product **8e** could be easily isolated by column chromatography. For some reactions, homodimeric *N*-acyl hydrazide byproducts were also obtained in low yields (10-20%), inherently

resulting in lower yields for the formation of the desired products.[18a] Overall, despite limitations as a synthetic route to form N_β-acyl hydrazides, this reactivity is consistent with the mechanistic hypothesis involving formation of a *N*-isocyanate from the oxadiazolone, and established reactions between carboxylic acids or carboxylate ions with isocyanates.

Table 2. Optimization of the addition of hydrocinnamic acid to oxadiazolones **7a**.[a]

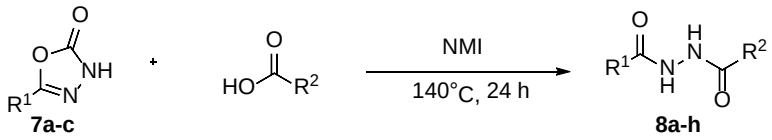


7a **8a**

Entry	Base	Solvent	Yield[b]	Leftover SM[b]
1	none	MeCN	0%	85%
2	Et_3N	MeCN	70%	2%
3	4-methylmorpholine	MeCN	49%	6%
4	*i*-Pr_2NEt	MeCN	43%	0%
5	1-methylimidazole	MeCN	68%	5%
6	Et_3N	$MeNO_2$	64%	0%

[a]Conditions: Oxadiazolone **7a** (1.0 equiv.), MeCN (0.3 M), carboxylic acid (1.1 equiv.), base (2 equiv.), 110 °C, 24 h. [b]Yield determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard. All reactions were carried in a sealed microwave vial.

Table 3. Exploration of various carboxylic acids to form hydrazides[a]



7a-c **8a-h**

Entry	R^1	R^2	yield (%), product
1	2-FC_6H_4	hydrocinnamic	72, **8a**
2	2-FC_6H_4	acetic	65, **8b**
3	2-FC_6H_4	propionic	69, **8c**
4	2-FC_6H_4	isobutyric	63, **8d**
5	2-FC_6H_4	pivalic	58, **8e**
6	2-FC_6H_4	4-anisic	50, **8f**
7	4-MeC_6H_4	hydrocinnamic	17, **8g**
8	CH_3	hydrocinnamic	35, **8h**

[a]Conditions: Oxadiazolone (1.0 equiv.), MeCN (0.3 M), carboxylic acid (1.1 equiv.) followed by *N*-methyl imidazole (NMI, 2 equiv.); 140 °C, 24 h. All reactions were carried in a sealed microwave vial.

In summary, the work in this section shows that substitution reactions involving *N*-acyl-*N*-isocyanate precursors **2a-e** involve the formation of an oxadiazolone intermediate and supports that *N*-isocyanates can be formed by a ring opening reaction possible with N-H oxadiazolones. In contrast, as shown in Table 1, *N*-Me oxadiazolones are unreactive even in the presence of good nucleophiles such as allylic amines. These results, combined with results in Table 3 showing that carboxylate ions yield N_β-acyl hydrazides suggest that amido-isocyanates are possible intermediates. Finally, this suggestion is aligned with the isocyanate literature where a few reactions to form such reactive intermediates from heterocycles have been reported.[1b,1d,2k-m,4,9]

Conclusion

In summary, aza-dipeptides derived from phenyl carbazate were synthesized and used as masked amido-isocyanates in the synthesis of aza-tripeptide-derived hydantoins or aza-tripeptides (X-azaGly-Y). Reactions proved slower than related reactions of *N*-isocyanate precursors, and further investigation indicated that the amido-isocyanate intermediates cyclized to form 1,3,4-oxadiazol-2(3H)-ones. However,

under suitable conditions, this cyclization appeared reversible, and oxadiazolones acted as traceless masked amido-isocyanates and allowed formation of the desired products. Further experiments were performed to support the possibility that oxadiazolones undergo ring opening to form *N*-isocyanates in situ, including addition of carboxylic acids under basic conditions yielding N_{β}-acyl hydrazide products. To our knowledge, this is the first time such a pathway is proposed and supported experimentally. Overall, this work provides calibration on the reactivity of rare amido-isocyanates, including their ability to minimize dimerization side-reactions that are often problematic with other *N*-isocyanates and to form metastable cyclic products. This unique property might allow the development of new reactivity and efforts along these lines are currently ongoing in our laboratory. More broadly, this suggests that 1,3,4-oxadiazol-2(3H)-ones should be added to the list of cyclic isocyanate precursors, which include *N*-carboxyanhydrides and cyclic ureas.

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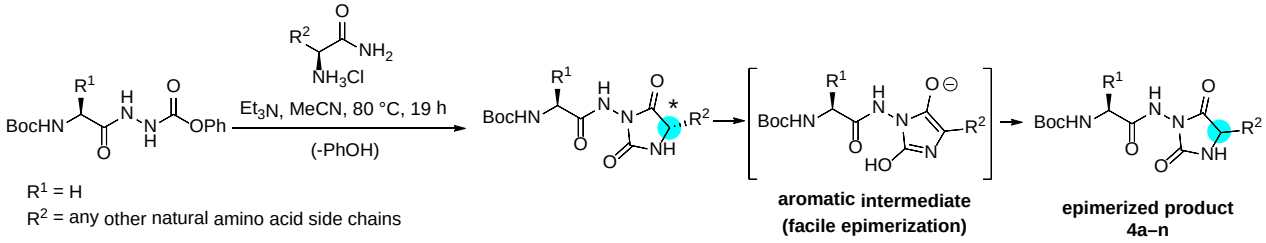
Chapter 3: Additional Experiments

This chapter will present the results of additional experiments related to those reported in Chapter 2, but did not appear in the published manuscript. Section 3.1 will present evidence and discussion with regards to the epimerization of the stereocenter of isolated hydantoins and justify the rationale for not defining the stereochemistry at that position in the manuscript. Section 3.2 will present selected experimental data describing the extensive optimization performed for the carboxylate addition to oxadiazolones. *The numbering of Schemes, Figures and Tables will pick up again from the end of Chapter 1.*

3.1 Epimerization of Hydantoin Stereocenter

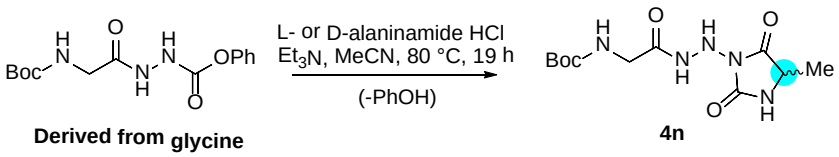


Scheme 21: Proposed Route for Epimerization of Hydantoins

In theory, the use an enantiopure masked *N*-isocyanate and an enantiopure amido amine would result in a product that was diastereomerically pure. However, it was recognized that the hydantoin products would likely easily epimerize under the reaction conditions.[1, 2] Deprotonation at the chiral center (and tautomerization at the other carbonyl) results in a highly stabilized, aromatic enolate (Scheme 21). Unfortunately, there are no examples of compounds similar to **4a–n** in Scheme 21 (see Scheme 4 for more details) reported in the literature, i.e. hydantoins formed from the cyclization of such aza–tripeptide precursors with which to compare optical rotation, and it was impossible to discern if the stereocenter on the hydantoin ring had epimerized.

To further study the potential epimerization of the hydantoins, control substrates were prepared in which the masked *N*-isocyanate was derived from the achiral glycine. Two products were prepared, one from L-alanimide and one from D-alanimide. If no epimerization were occurring under the reaction conditions, one would expect that pure enantiomers would be formed, with optical rotations that were equal in magnitude and opposite in sign. The products isolated, however, were found to have optical rotations very close to zero. Based on early experiments in this project, it was known the addition of amino esters to aza-dipeptides resulted in the formation of hydantoins. This cyclization was believed to be faster than the corresponding cyclization with amino amides due to the increased electrophilicity of the ester. It was hypothesized that products prepared via the ester route might not be as susceptible to epimerization. When **4n** was prepared via this alternate route (using the benzyl ester amino acid) and the measured optical rotation was significantly higher than the amino amide route.

Table 1: Evaluation of Hydantoin Epimerization



Derived from glycine **4n**

Entry	Starting Material	Optical Rotation
1	From L–alaninamide•HCl:	$[\alpha]_D^{25}$ = 0.5° (c.: 1.00, MeOH).
2	From D–alaninamide•HCl:	$[\alpha]_D^{25}$ = -0.8° (c.: 1.00, MeOH).
3	From L–alanine benzyl ester•HCl:	$[\alpha]_D^{25}$ = -8.3° (c.: 1.00, MeOH).

Many more efforts to separate the enantiomers of **4n** on chiral HPLC columns failed. Attempts with other compounds where diastereoisomers could be present (e.g., **4b**, **4c**) also failed. In parallel, NMR analyses proved challenging, likely due to the presence of rotamers in solution. Multiple temperatures were tested (rt, 50 °C, 80 °C, 100 °C) and the spectra obtained at 100 °C allowed coalescence of the rotamers in all cases by ^{1}H NMR spectroscopy. Unfortunately, the stereocenters are relatively far to each other, and this is likely what makes analysis by NMR spectroscopy (i.e., distinguishing diastereoisomers)

and chiral column chromatography (separating stereoisomers) difficult. Thus, based on the evidence obtained from the formation of compound **4n**, significant epimerization (R^2) is likely for all hydantoins shown in Scheme 21, and accounts for the notation employed to describe the hydantoin stereochemistry.

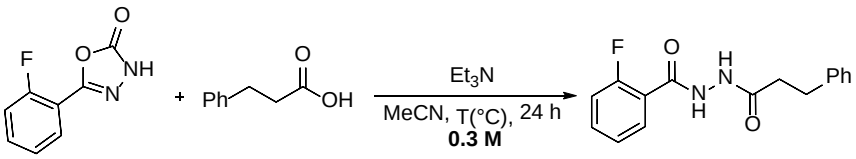
3.2 Optimization of Carboxylate Addition to Oxadiazolones

Note: The experiments in this section were performed in conjunction with undergraduate Owen C. Lutes and Genevieve F. O'Keefe.

A fluorinated substrate was chosen strategically to facilitate determination of NMR yields by ^{19}F NMR, using an internal standard of α,α,α–trifluorotoluene. The very wide spectral window allowed for the sole identification of fluorinated compounds with very well separated signals. Experiments to determine the relaxation time of the ^{19}F-containing substrate were performed, and in subsequent experiments, the relaxation time was set above this value, to ensure quantitative results. As for the carboxylic acid, we chose hydrocinnamic acid to avoid any electronic effects that could hinder the reaction or steric effects.

During the optimization and the screening of various bases, it was found that using NMI was beneficial for purification purposes and yielded less fluorinated side products. We therefore used this base instead of the original triethylamine that was used. It was found that there was not a significant difference in yield between 100 and 120 ºC (Table 2). We chose to pursue the optimization and scope at 110 ºC. When Geneviève O'Keefe investigated different carboxylates, it was noted that an increase in temperature to 140 ºC was beneficial in some cases, such as for the sterically hindered carboxylic acids.

Table 2: Optimization of Temperature for Carboxylic Acid Addition to Oxadiazolones

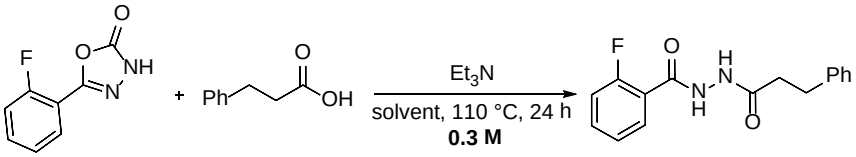


Entry	Temp (°C)	NMR Yield (%)[a]	SM Leftover (%)[a]
1	90	58	11
2	100	75	0
3	110	70	2
4	120	77	0

[a]Yields determined by ^{19}F NMR spectroscopy with $PhCF_3$ as internal standard

In terms of solvent, it was found that non-nucleophilic, polar aprotic solvents were ideal, and acetonitrile and nitromethane stood out with similar results, giving 58 and 64% yield respectively (Table 3). Acetonitrile was selected for further optimization, although some reactions that gave odd results in acetonitrile were better controlled in nitromethane. Under the reaction conditions, each solvent permitted proper dissolution of all the reagents. With the use of acetonitrile or nitromethane, we observed complete consumption of the starting material, whereas in every other solvent tested, there was remaining oxadiazolone starting material (up to about 30%).

Table 3: Optimization of Solvent for Carboxylic Acid Addition to Oxadiazolones

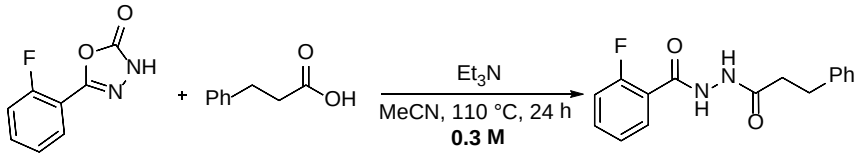


Entry	Solvent	NMR Yield (%)[a]	SM Leftover (%)[a]
1	DMSO	23	8
2	THF	19	32
3	Dioxane	11	27
4	$MeNO_2$	64	0
5	PhMe	45	28
6	MeCN	58	0

[a]Yields determined by ^{19}F NMR spectroscopy with $PhCF_3$ as internal standard

The initial conditions used the oxadiazolone as the limiting reagent. It was found that a slight excess of the carboxylic acid compared to the oxadiazolone (1.1 eq) along with a 2-fold excess of base yielded the optimal results (Table 4). A larger excess of the carboxylic acid and base, which was used for optimization, was not optimal, nor was using the carboxylic acid as the limiting reagent. We evaluated this aspect especially because of the challenging purification, in which the excess carboxylic acid was found as a contaminant in many cases.

Table 4: Optimization of Equivalents for Carboxylic Acid Addition to Oxadiazolones

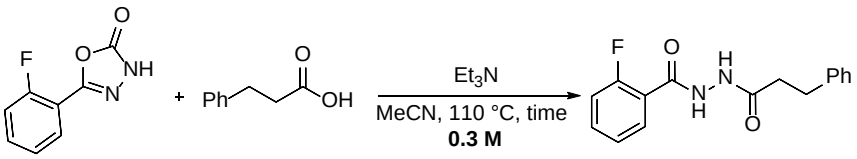


Entry	Oxadiazolone Eq.	Carboxylic Acid Eq.	Et_3N Eq.	NMR Yield[a] (%)	Comments
1	1	3	4	58	Original Conditions
2	1	1.1	2	70 (3% unconsumed oxadiazolone)	Best Conditions
3	1.5	1	3	70 (33% unconsumed oxadiazolone)	Carboxylic acid as lim. reagent

[a]Yields determined by ^{19}F NMR spectroscopy with $PhCF_3$ as internal standard

Pursuing with the initial set of conditions, we looked at the optimal reaction time. We found that 24 hours yielded the best results with only 2% of remaining SM and a 70% yield for the desired product (Table 5).

Table 5: Optimization of Reaction Time for Carboxylic Acid Addition to Oxadiazolones

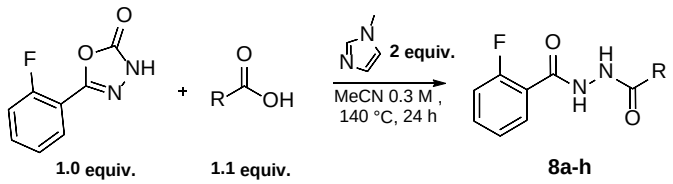


Entry	Time (h)	NMR Yield (%)[a]	SM Leftover (%)[a]
1	2	17	50
2	4	34	17
3	8	35	7
4	16	40	5
5	24	70	2

[a]Yields determined by ^{19}F NMR spectroscopy with $PhCF_3$ as internal standard

There was a major discrepancy observed between the NMR yields and the isolated yields. This was attributed to the high number of H-bonding atoms found in the molecule, which can interact with the silanol groups of the silica used for purification. Pure products could be isolated, but the yield was significantly reduced in comparison to the NMR yields (Table 6). We hypothesized that the product adhered strongly to the silica, however multiple column flushes with various polar solvents, the yield was not improved. Recrystallization attempts failed and purification on C-18 silica was impossible due to the insolubility of the product in water. Pre-treatment of silica with bases or acids such as AcOH, NH_4OH or Et_3N did not improve the recovered yield. Optimization of a liquid-liquid extraction was also carried out and did not have a beneficial effect. However, despite these purification challenges, the formation and isolation of the product of a carboxylate addition supports the formation of a transient amido–isocyanate.

Table 6: Substate Scope of Carboxylic Acids Adding to Oxadiazolones



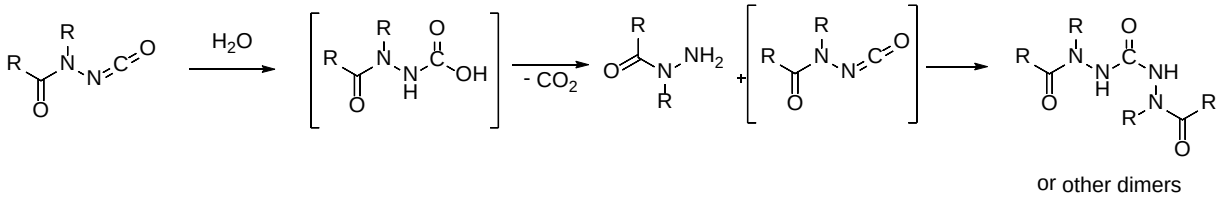
Entry	Carboxylic Acid	NMR Yield (%)[a]	Isolated Yield (%)
1	Hydrocinnamic	64	70
2	Acetic	69	65
3	Propionic	86	67
4	Cyclohexanecarboxylic	50	N/A
5	Isobutyric	75	N/A
6	Pivalic	67	50
7	*p*-Anisic	70	50
8	2,6-dichlorophenylacetic	0	0
9	4-trifluoromethylbenzoic	25	N/A

[a]Yields determined by ^{19}F NMR spectroscopy with $PhCF_3$ as internal standard

An interesting observation was made during the scope study of this reaction. In some cases, the isocyanate dimer was observed (up to 30% dimer), especially when using sterically hindered carboxylic acids such as pivalic acid or cyclohexyl carboxylic acid; these required a longer time (48 h) to drive the reaction to completion. The equilibrium between masked *N*-isocyanate and free *N*-isocyanate maintains a low concentration of the reactive species. It was hypothesized that long reaction times, however, promote dimerization in the absence of any other nucleophilic species.

Several control reactions were performed to understand the factors that promote dimerization. An experiment was performed under standard conditions, with the addition of water. It was envisioned that hydrolysis of the isocyanate into the hydrazine could lead to dimerization. This experiment did not lead to more than expected dimer formation (Scheme 22). The oxadiazolone and the hydrazide were then subjected to stability tests. The compounds were heated in the presence and absence of base but didn't

result in any dimer formation. It was concluded that this dimer formation occurs only in the presence of the carboxylic acid (carboxylate). The reasons for the observations remain unclear.



Scheme 22: Potential Hydrolysis of Amido-Isocyanates to Yield Dimers

References for Chapter 3

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Chapter 4: Conclusions and Future Work

4.1 Conclusions

In conclusion, we found that the phenyl carbazate derived aza–dipeptides were undergoing a first cyclization to yield 1,3,4–oxadiazol–2(3H)–ones in equilibrium with a free N_{β}–acyl isocyanate. The synthesis of aza–tripeptide using a masked *N*–isocyanate strategy proved difficult due to a possible intramolecular cyclization yielding hydantoins in most cases. The aza–tripeptides could only be recovered when insoluble in the reaction medium and recovered as a precipitate. This is an inherent property of the molecules. Extensive optimization of the conditions for every tripeptide could be done to find the proper medium that will lead them to precipitate. We however decided that this was not the goal of this project rather than proving the existence of a transient N_{β}–acyl isocyanate, which was a better contribution to the literature on these species because of their scarcity. However, the formation of a transient amidoisocyanate rather than the formation of a tetrahedral oxyanionic intermediate is strongly supported by the N_{β}–acyl hydrazide resulting from carboxylates addition to 1,3,4–oxadiazol–2(3H)–ones and the α–NH methylation completely prevented the reaction from happening. This is the first time experimental evidence of on the formation of the rare N_{β}–acyl isocyanates are supporting such a pathway. It had been proposed, but never supported experimentally. This work fills the gap in the literature about the reactivity and the formation of the rare amido–isocyanates. Their ability to limit dimerization, often encountered with such species, makes them synthetically attractive. The formation of a metastable intermediate could allow further development along those lines. In the end, 1,3,4–oxadiazol–2(3H)–ones should be added to the list of cyclic isocyanates precursors such as those mentioned in the introduction.

4.2 Future Work

Prior to this work, the Beauchemin group has relied on acyclic masked *N*-isocyanates to generate all reactive intermediates, that would often react to form cyclic products. However, this study

demonstrated conclusively that *hetereocycles* may effectively act as masked *N*-isocyanates as well. A variety of heterocycles could be envisioned that have potential to behave in a manner similar to oxadiazolones, wherein under proper conditions, a *N*–isocyanate is released and could then be trapped in–situ. Such reactivity is a direct analogy to the reactivity of *N*-carboxyanhydride presented in the introduction of this thesis. An early version of this concept was briefly investigated by Daniel Wallace, an undergraduate student in the group, with molecules such as 4–benzyl–1,3,4–oxadiazinan–2–one (Figure 11 (1)). In this case, it was concluded that the equilibrium favored the starting material too heavily, thus impeding the release of the corresponding *N*–isocyanate with a nucleophile. There are a variety of other potential heterocycles that have yet to be studied in that context; this work will continue as the group continues to explore masked *N*-isocyanates and the reactivity of the wide range of possible *N*-isocyanate intermediates.

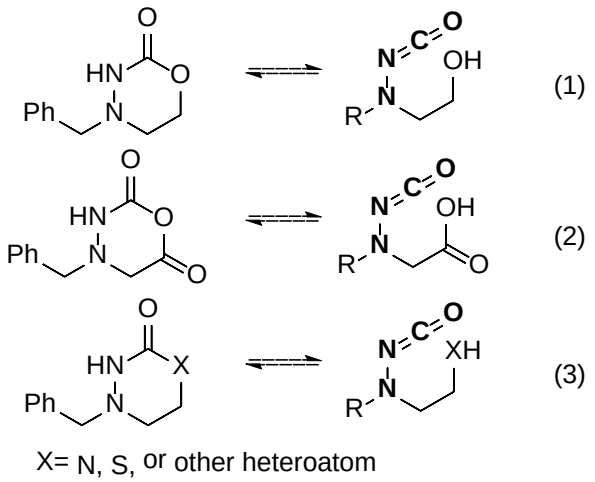


Figure 11: Potential Heterocycles as Masked N-Isocyanates

Publications and Presentations from this Work

Publications

Gagné–Monfette, W.; Vincent–Rocan, J.–F.; Lutes, O. C.; O'Keefe, G. F.; Jeanneret, A. D. M.; Blanger, C.; Ivanovich, R. A.; Beauchemin, A. M. Investigation of Masked *N*–Acyl–*N*–isocyanates: Support for Oxadiazolones as Blocked *N*–Isocyanate Precursors. *Chemistry – A European Journal* **2021**, *27*, 14051–14056.

Presentations

Poster Presentation QOMSBOC 2022 (McMaster U) "Investigation of Masked *N*–Acyl–*N*–Isocyanates: Support for Oxadiazolones as Blocked *N*–Isocyanate Precursors".

Poster Presentation 1st Annual Symposium OmegaChem (Quebec City) 2022 "Investigation of Masked *N*–Acyl–*N*–Isocyanates: Support for Oxadiazolones as Blocked *N*–Isocyanate Precursors".

Poster Presentation IUPAC/CCCE 2021 (online). "Investigation of Masked *N*–Acyl–*N*–Isocyanates: Support for Oxadiazolones as Blocked *N*–Isocyanate Precursors".

Claims to Original Research

1. The formation of amido-isocyanates from oxadiazolones was studied and it was established that oxadiazolones can act as masked amido-isocyanates.

2. The addition of carboxylates to oxadiazolones to form hydrazides was discovered, optimized and the substrate scope of the reaction was determined.

3. The stereochemical outcome of the reaction forming the hydantoins via masked *N*-acyl isocyanates was carefully studied; it was concluded that epimerization is likely occurring for these products.

Chapter 5: Supporting Information

Note: The data presented in this chapter are from the supporting information of the manuscript presented in Chapter 2.

General Information

All heated reactions were done in a temperature–controlled oil bath. Purification of reaction products was completed by flash chromatography using SiliCycle 40–63 μm silica gel. Analytical thin layer chromatography (TLC) was done on aluminum plates precoated with 60 Å F_{254} silica gel and visualization of the TLC plates was completed using either UV light (254 nm) or ninhydrin followed by heating for all the peptides related molecules. For hydrazides, multiple stains have been used depending on the substrate (most of the time, Cerium–ammonium molybdate was the stain of choice).

^{1}H NMR and ^{13}C NMR were recorded on Bruker AVANCE 300 MHz, 400 MHz and 500 MHz spectrometers Spectral data was reported in ppm using solvent as the reference ($CDCl_3$ at 7.26 ppm, DMSO–d_6 at 2.50 ppm or methanol–d_4 at 3.31 ppm for ^{1}H NMR. For ^{13}C, the references were as follow: $CDCl_3$ at 77.16 ppm or DMSO–d_6 at 39.52 ppm or methanol–d_4 at 49.2 ppm. ^{1}H NMR data was reported: multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet), coupling constant(s) in Hz and integration. Trifluorotoluene ($PhCF_3$) was used as an internal standard for the acquisition of ^{19}F NMR of fluorinated compounds and the chemical shift set at (–63.67 ppm). Infrared (IR) spectra were obtained with neat thin films on a sodium chloride disk and were recorded on a Bomen Michelson 100 Fourier transform infrared spectrometer (FTIR) or were acquired neat on a crystal. High resolution mass spectroscopy (HRMS) was either performed on a Kratos Concept–11A mass spectrometer with an electron beam of 70 eV for electron ionization, and Electrospray ionization spectra were acquired on a Waters Global QTOF model GAA039 at the Ottawa–Carleton Mass Spectrometry Centre. Optical

rotation was measured on an Anton Paar MCP 500 modular circular polarimeter using a 10 mm cell at 25 °C at 589 nm and the $[a]_D^{25}$ is given in °.

Note: NMR spectra of compounds of series **2a–g** were obtained at room temperature, to avoid formation of oxadiazolones occurring at high temperatures. NMR spectra of compounds **3a–c** as well as **6b** and **4a–r** were acquired in DMSO–*d*$_6$ at 100 °C to achieve coalescence of the rotamers signals and facilitate the analyses. Otherwise, in many cases, hydrazides will show a minor rotamer, especially by ^{13}C NMR.

Materials

Unless noted otherwise, all reagents were obtained commercially and used without further purification.

General Procedures

General procedure 1 for synthesis of aza–dipeptides: Compounds 2a–g

To a 250 mL round–bottom flask, phenyl carbazate (1.0 equiv.), *N*–Boc protected amino acid *O*–succinimide (1.0 equiv.) and MeCN (0.2 M) were added and the flask was covered with a septum. The content was stirred at room temperature for 24 hours under inert atmosphere. The reaction mixture was evaporated under reduced pressure, and then taken in EtOAc and extracted with a saturated aqueous solution of $NaHCO_3$ (1:1). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding to the *aza*–dipeptides in high purity. If needed, purification on silica gel was performed afterwards to afford the pure *aza*–dipeptide.

General procedure 2 for synthesis of semicarbazides: Compounds 3a–c

A large microwave vial was charged with a stir bar, *aza*–dipeptides **2a–g** (1.0 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 for 19 hours at 80 °C. The crude mixture was concentrated under reduced pressure and dry loaded on silica gel by dissolving in MeOH and purified by silica gel chromatography to give the corresponding aminosubstituted *aza*–dipeptide.

General procedure 3 for synthesis of *aza*–tripeptides derived hydantoins and *aza*–tripeptides

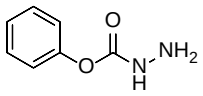
A large microwave vial was charged with a stir bar, *aza*–dipeptide **2a–g** (1.1 equiv.), amino amide hydrochloride (1.0 eq.), triethylamine (1.3 eq.) and MeCN (0.3 M) and was sealed. The content was stirred in an oil bath at 80 °C for 19 hours. The reaction mixture was either filtered or was concentrated under reduced pressure and dry loaded on Silica gel by dissolving in MeOH and purified by silica gel chromatography to give the corresponding hydantoin or *aza*–tripeptides.

General procedure 4 for synthesis of *N*–acyl hydrazides

To a clean dry microwave vial charged with a stir bar was added the corresponding 1,3,4–oxadiazol–2(3H)–one **5a–5c** or **7a to 7c** (1.0 equiv.), the carboxylic acid (1.1 eq) and MeCN (0.3M) followed by the addition of *N*–methylimidazole (2 eq). The vial was sealed, and the reaction was stirred in an oil bath at 140 °C for 24 h. Upon completion, the reaction was concentrated via rotary evaporation and dry loaded on silica gel by dissolving in MeOH to be purified by silica gel chromatography.

Note : As per the nature of the compounds, it is possible to see appearance of characteristic rotamer peaks by both ^{1}H and ^{13}C NMR since they were acquired at room temperature.

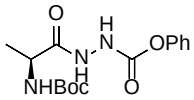
Characterization Data



1 Phenyl carbazate

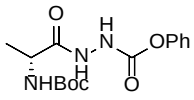
To a 1,000 mL round–bottom flask, diphenyl carbonate (21.4 g, 100 mmol) was dissolved in petroleum ether (300 mL). Then, hydrazine (1M in THF) (100 mL, 100 mmol) was added dropwise over 3.5 hour and the reaction mixture was left to stir at room temperature for an additional 30 minutes. The precipitate was washed and triturated with petroleum ether (3x), filtered and dried. The filtrate was concentrated to

dryness, dissolved in a minimal amount of THF, a large amount of petroleum ether was added and the mixture was cooled down to 0 °C for 30 minutes to induce recrystallization. The solid was again filtered and washed with petroleum ether to give a white powder (13.9 g, yield = 91%). TLC R_f = 0.20 and 0.32 in 50% EtOAc/Hex. [1] Characterization of this compound matched the literature.[2]



2a Phenyl 2–((*tert*–butoxycarbonyl)–L–alanyl)hydrazine–1–carboxylate

Synthesized according to the general procedure 1 using phenyl carbazate **1** (1.18 g, 7.74 mmol), Boc–L–Ala–OSu (2.22 g, 7.74 mmol) and MeCN (40.0 mL, 0.2 M). (2.08 g, yield = 83%). TLC R_f = 0.46 (EtOAc/Hex 1:1), $[\alpha]_D^{25}$ = –66.8° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.68 (s, 1H), 7.46 – 7.02 (m, 5H), 5.40 (s, 1H), 4.34 (s, 1H), 1.57 – 1.27 (m, 12H).^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 156.0, 150.7, 129.5, 125.9, 121.5, 80.7, 48.6, 28.4, 18.2. IR (ν, film, cm^{-1}): 1735, 1688, 1654, 1563. HRMS (ESI+): Exact mass calcd for $C_{15}H_{21}N_3O_5Na$ $[M+Na]^+$: 346.1379 m/z. Found: 346.1394 m/z.

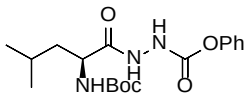


2b Phenyl 2–((*tert*–butoxycarbonyl)–D–alanyl)hydrazine–1–carboxylate

Synthesized according to the general procedure 1 using phenyl carbazate **1** (1.18 g, 7.74 mmol), Boc–D–Ala–OSu (2.22 g, 7.74 mmol) and MeCN (40.0 mL, 0.2 M). (1.59 g, yield = 63%). TLC R_f = 0.46 (EtOAc/Hex 1:1), $[\alpha]_D^{25}$ = 61.6° (c.: 1.00, MeOH). ^{1}H NMR (400 MHz, Methanol–d_4) δ 7.37 (t, *J* = 7.9 Hz, 2H), 7.27 – 7.19 (m, 1H), 7.19 – 7.06 (m, 2H), 4.25 – 4.00 (m, 1H), 1.45 (s, 9H), 1.36 (d, *J* = 7.2 Hz,

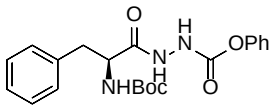
[1] This compound shows as two spots by TLC. Previous attempts to isolate only one spot led to a poor yield.
[2] A. Jayaraman, E. Cho, F. M. Irudayanathan, J. Kim, S. Lee, *Adv. Synth. Catal.* **2018**, *360*, 130.

3H). ^{13}C NMR (101 MHz, Methanol–d_4) δ 175.5, 157.6, 156.6, 152.3, 130.4, 126.7, 122.6, 80.6, 50.2, 28.7, 18.4. IR (ν, film, cm^{-1}): 3267, 2981, 1675, 1490, 1366, 1203, 1161. HRMS (ESI+): Exact mass calcd for $C_{15}H_{21}N_3O_5Na$ [M+Na]$^+$: 346.1377 m/z. Found: 346.1379 m/z.



2c Phenyl 2–((*tert*–butoxycarbonyl)–L–leucyl)hydrazine–1–carboxylate[3]

Synthesized according to the general procedure 1 using phenyl carbazate **1** (1.18 g, 7.74 mmol), Boc–L–Leu–OSu (2.51 g, 7.74 mmol) and MeCN (40.0 mL, 0.2 M), at room temperature for 22 hours. The crude was taken in MeOH, dry loaded on silica gel and purified 30% EtOAc/Hex to afford the desired compound as a white powder (2.32 g, yield = 82%). TLC R_f = 0.33 (EtOAc/Hex 1:3) $[\alpha]_D^{25}$ = –15.8° (c.: 1.00, MeOH). ^{1}H NMR (400 MHz, Methanol–d_4) δ 7.37 (t, J = 7.9 Hz, 2H), 7.22 (t, J = 7.4 Hz, 1H), 7.19 – 7.07 (m, 2H), 4.25 – 4.03 (m, 1H), 1.82 – 1.64 (m, 1H), 1.64 – 1.51 (m, 2H), 1.50 – 1.34 (m, 9H), 0.95 (t, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, Methanol–d_4) δ 175.4, 157.8, 156.6, 152.3, 130.4, 126.7, 122.6, 120.5, 116.2, 80.6, 53.00, 42.3, 41.5, 28.7, 25.8, 23.3, 23.0, 22.0. IR (ν, film, cm^{-1}): 1736, 1688, 1560, 1506. HRMS (ESI+): Exact mass calcd for $C_{18}H_{27}N_3O_5Na$ [M+Na]$^+$: 388.1848 m/z. Found: 388.1844 m/z.

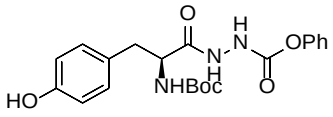


2d Phenyl 2–((*tert*–butoxycarbonyl)–L–phenylalanyl)hydrazine–1–carboxylate[3]

Synthesized according to the general procedure 1 using phenyl carbazate **1** (1.18 g, 7.74 mmol), Boc–L–Phe–OSu (2.81 g, 7.74 mmol) and MeCN (40.0 mL, 0.2 M). At the end of the reaction, the precipitate formed was filtered and washed with Et_2O (3x) to afford the desired compound pure. The filtrate was

[3] The ^{13}C NMR spectrum shows a minor rotamer.

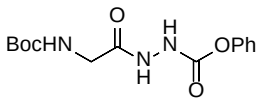
evaporated to dryness, taken in EtOAc and extracted with $NaHCO_{3\,(sat)}$ (4x), dried over $MgSO_4$, filtered and evaporated to dryness. The crude was then dissolved in ether and chilled to –20 °C overnight to recrystallize and afford the rest of the desired compound as a white powder (2.61 g, 84%). TLC R_f = 0.68 (EtOAc/Hex 1:1)[4] $[\alpha]_D^{20}$ = –16.2° (c.: 1.00, MeOH). ^{1}H NMR (400 MHz, Methanol–d_4) δ 7.59 – 6.91 (m, 10H), 4.41 (dd, *J* = 8.4, 4.4 Hz, 0.75H), 4.38 – 4.28 (m, 0.20H), 3.19 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.87 (dd, *J* = 13.6, 9.6 Hz, 1H), 1.73 – 1.00 (m, *J* = 15.8 Hz, 9H).^{13}C NMR (101 MHz, Methanol–d_4) δ 174.1, 157.5, 156.6, 152.3, 138.4, 130.5, 130.4, 129.5, 129.4, 127.9, 127.7, 126.7, 122.6, 120.5, 116.2, 80.6, 55.9, 39.3, 28.6. IR (ν, film, cm^{-1}): 1735, 1682, 1558, 1511. HRMS (ESI+): Exact mass calcd for $C_{21}H_{25}N_3O_5Na$ $[M+Na]^+$: 422.1692 m/z. Found: 422.1701 m/z.



2e Phenyl 2–((*tert*–butoxycarbonyl)–L–tyrosyl)hydrazine–1–carboxylate[3]

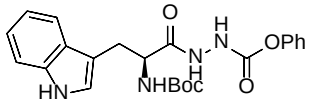
Synthesized according to the general procedure 1 using phenyl carbazate **1** (1.18 g, 7.74 mmol), Boc–L–Tyr–OSu (2.93 g, 7.74 mmol) and MeCN (40.0 mL, 0.2 M). The compound was obtained in high purity, as a white powder (3.14 g, yield = 98%). TLC R_f = 0.32 (EtOAc/Hex 1:1) $[\alpha]_D^{25}$ = 11.8° (c.: 1.00, DMSO–d_6). ^{1}H NMR (400 MHz, Methanol–d_4) δ 7.38 (t, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 2H), 6.78 – 6.57 (m, 2H), 4.46 – 4.19 (m, 1H), 3.14 – 2.99 (m, 1H), 2.87 – 2.67 (m, 1H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, Methanol–d_4) δ 174.3, 157.5, 157.2, 156.6, 152.3, 131.5, 130.4, 129.0, 126.7, 122.6, 116.2, 80.6, 57.6, 56.1, 38.6, 34.7, 28.6, 26.7, 26.0. IR (ν, film, cm^{-1}): 1737, 1685, 1654, 1506. HRMS (ESI+): Exact mass calcd for $C_{21}H_{25}N_3O_6Na$ $[M+Na]^+$: 438.1641 m/z. Found: 438.1641 m/z.

[4] The R_f of this compound changed to 0.58 in that eluent system once purified.



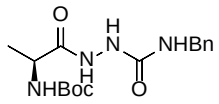
2f Phenyl 2–((*tert*–butoxycarbonyl)glycyl)hydrazine–1–carboxylate

Synthesized according to the general procedure 1 using phenyl carbazate **1** (1.18 g, 7.74 mmol), Boc–Gly–OSu (2.11 g, 7.74 mmol) and MeCN (40.0 mL, 0.2 M), at room temperature for 29.5 hours. The compound was obtained as a white powder (2.20 g, yield = 92%). Please note that traces of EtOAc are present in the product isolated and used for characterization. TLC R_f = 0.36 (EtOAc/Hex 3:5) ^{1}H NMR (400 MHz, Methanol–d_4) δ 7.37 (t, *J* = 7.9 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.18 – 7.06 (m, 2H), 3.86 – 3.70 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, Methanol–d_4) δ 172.2, 158.3, 156.8, 152.3, 130.4, 126.7, 122.6, 80.7, 43.2, 28.7. IR (ν, film, cm^{-1}): 3263, 2989, 1682, 1487, 1367, 1203, 1159. HRMS (ESI+): Exact mass calcd for $C_{14}H_{19}N_3O_5Na$ $[M+Na]^+$: 332.1222 m/z. Found: 332.1215 m/z.



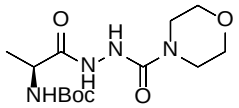
2g Phenyl 2–((*tert*–butoxycarbonyl)–L–tryptophyl)hydrazine–1–carboxylate[3]

Synthesized according to the General procedure 1 using phenyl carbazate **1** (1.18 g, 7.74 mmol), Boc–L–Trp–OSu (3.11 g, 7.74 mmol) and MeCN (40.0 mL, 0.2 M), at room temperature for 29.5 hours. After extraction, the compound was obtained in high purity as a pink powder (3.27 g, yield = 96%). $[\alpha]_D^{25}$ = –17.6° (c.: 1.01, MeOH). TLC R_f = 0.56 (EtOAc/Hex 1:1). ^{1}H NMR (400 MHz, Methanol–d_4) δ 7.38 (t, *J* = 7.9 Hz, 2H), 7.34 – 7.05 (m, 8H), 4.47 – 4.25 (m, 1H), 3.24 – 3.00 (m, 1H), 2.94 – 2.72 (m, 1H), 1.45 – 1.24 (m, 9H).^{13}C NMR (101 MHz, Methanol–d_4) δ 174.1, 157.5, 156.7, 152.3, 138.4, 130.5, 130.4, 129.5, 129.4, 127.9, 127.7, 126.7, 122.6, 120.5, 116.2, 80.7, 55.9, 39.3, 28.6, 28.4. IR (ν, film, cm^{-1}): 1706, 1680, 1654, 1558. HRMS (ESI+): Exact mass calcd for $C_{23}H_{26}N_4O_5Na$ $[M+Na]^+$: 461.1801 m/z. Found: 461.1807 m/z.



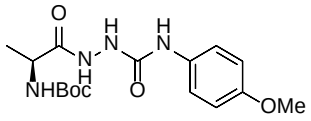
3a *tert*–Butyl 1–(2–(benzylcarbamoyl)hydrazinyl)–1–oxopropan–2–ylcarbamate

Synthesized according to general procedure 2 using *aza*–dipeptide **2a** (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 (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 (101 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).



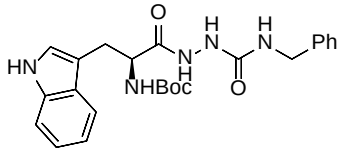
3b *tert*–Butyl (*S*)–(1–(2–(morpholine–4–carbonyl)hydrazinyl)–1–oxopropan–2–yl)carbamate

Synthesized according to general procedure 2 using *aza*–dipeptide **2a** (0.320 g, 0.990 mmol), morpholine (0.095 mL, 1.1 mmol), Et_3N (0.028 mL, 0.20 mmol) and MeCN (3 mL). The crude mixture was purified by flash chromatography using a gradient from 2% MeOH/EtOAc to 10% MeOH/EtOAc to afford the compound in good purity as a white solid (0.276 g, 88%). TLC R_f = 0.31 (EtOAc/Hex 1:50) $[\alpha]_D^{25}$ c=1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 8.62 (s, 2H), 6.22 (s, 1H), 4.22 – 3.97 (m, 1H), 3.66 – 3.47 (m, 4H), 3.47 – 3.29 (m, 4H), 1.41 (s, 9H), 1.26 (d, J = 7.1 Hz, 3H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 171.5, 156.4, 154.2, 77.7, 65.4, 48.1, 43.6, 27.7, 17.9. IR (ν, film, cm^{-1}): 3300, 2979, 1674, 1643, 1516, 1165. HRMS (ESI+): Exact mass calcd for $C_{13}H_{24}N_4O_5Na$ $[M+Na]^+$: 339.1644 m/z. Found: 339.1652 m/z.



3c *tert*–Butyl (*S*)–(1–(2–((4–methoxyphenyl)carbamoyl)hydrazinyl)–1–oxopropan–2–yl)carbamate

Synthesized according to general procedure 1 using *aza*–dipeptide **2a** (0.320 g, 0.990 mmol), *p*–anisidine (0.134 g, 1.09 mmol), Et_3N (0.028 mL, 0.20 mmol) and MeCN (3.0 mL). The crude mixture was purified by silica gel column chromatography using 90% EtOAc to afford the pure compound as a purple solid (0.171 g, 49 %). TLC R_f = 0.34 (EtOAc/Hex 1:10) $[\alpha]_D^{25}$ = 13.8° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 9.39 (s, 1H), 8.14 (s, 1H), 7.76 (s, 1H), 7.34 (dd, *J* = 9.0, 1.2 Hz, 2H), 6.84 (dd, *J* = 9.1, 1.2 Hz, 2H), 6.48 (s, 1H), 4.08 (s, 1H), 3.73 (d, *J* = 1.3 Hz, 3H), 1.42 (d, *J* = 1.2 Hz, 9H), 1.27 (dd, *J* = 7.0, 1.1 Hz, 3H).^{13}C NMR (76 MHz, DMSO–d_6) δ 171.8, 154.8, 154.6, 154.5, 132.1, 120.1, 120.0, 113.7, 78.0, 54.9, 27.7, 17.2. IR (ν, film, cm^{-1}): 3299, 2977, 1683, 1514, 1459, 1242, 1164, 1030. HRMS (ESI+): Exact mass calcd for $C_{16}H_{24}N_4O_5Na$ [M+Na]$^+$: 375.1644 m/z. Found: 375.1639 m/z.

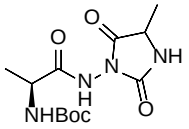


S3.1 *tert*–Butyl (*S*)–(1–(2–(benzylcarbamoyl)hydrazinyl)–3–(1H–indol–3–yl)–1–oxopropan–2–yl)carbamate

Synthesized according to general procedure 2 using *aza*–dipeptide **2g** (0.320 g, 0.990 mmol), benzylamine (0.012 mL, 1.1 mmol), Et_3N (0.028 mL, 0.20 mmol) and MeCN (3 mL). The crude mixture was dry loaded on silica gel and then purified by silica gel column chromatography using an eluent made of 100% EtOAc to afford the compound with high purity as a white solid (0.282 g, 85%). TLC R_f = 0.38 (EtOAc) $[\alpha]_D^{25}$ = –19.6° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 9.30 (s, 1H), 7.60 (s, 1H),

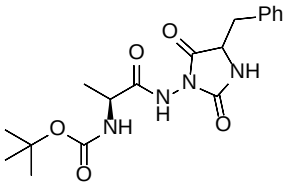
7.40 – 7.15 (m, 5H), 6.46 (d, *J* = 25.2 Hz, 2H), 4.36 – 4.19 (m, 2H), 4.05 (s, 1H), 1.38 (s, 9H), 1.24 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 171.6, 157.4, 154.6, 139.7, 127.5, 126.5, 126.0, 77.9, 48.2, 42.5, 27.7, 17.3. IR (ν, film, cm^{-1}): 3267, 2984, 1663, 1533, 1247, 1162, 696. HRMS (ESI+): Exact mass calcd for $C_{23}H_{26}N_4O_5Na$ [M+Na]$^+$: 359.1695 m/z. Found: 359.1713 m/z.

Hydantoins and *aza*–tripeptides (Scheme 4)



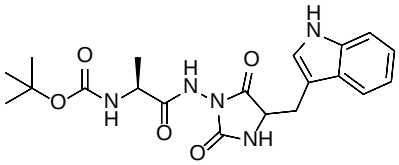
4a *tert*–Butyl ((2*S*)–1–((4–methyl–2,5–dioxoimidazolidin–1–yl)amino)–1–oxopropan–2–yl)carbamate

Synthesized according to the general procedure 3 using alanine *aza*–dipeptide **2a** (0.640 g, 1.98 mmol), L–alaninamide hydrochloride (0.224 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (6.0 mL, 0.3 M) The crude mixture was purified by silica gel column chromatography using gradient elution from 50% to 90% EtOAc/Hex to afford the compound in good purity as a white powder (0.404 g, 75%). TLC R_f = 0.43 (MeOH/EtOAc 1:100) $[\alpha]_D^{20}$ = –35.2° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 9.98 (s, 1H), 8.01 (s, 1H), 6.40 (d, *J* = 6.0 Hz, 1H), 4.33 – 4.04 (m, 2H), 1.42 (s, 9H), 1.31 (t, *J* = 6.9 Hz, 6H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 172.6, 172.2, 155.2, 154.2, 79.0, 51.4, 49.1, 28.7, 18.8, 17.8. IR (ν, film, cm^{-1}): 1737, 1708, 1653, 1558, 1521. HRMS (ESI+): Exact mass calcd for $C_{12}H_{20}N_4O_5Na$ [M+Na]$^+$: 323.1324 m/z. Found: 323.1331 m/z. This compound was also synthesized using 5a as starting material in the exact conditions listed above. 74% yield of the desired compound was isolated.



4b *tert*–Butyl ((2*S*)–1–((4–benzyl–2,5–dioxoimidazolidin–1–yl)amino)–1–oxopropan–2–yl)carbamate[5]

Synthesized using L–alanine *aza*–dipeptide **2a** (0.213 g, 0.659 mmol), L–phenylalaninamide hydrochloride (0.120 g, 0.600 mmol), triethylamine (0.109 mL, 0.782 mmol) and MeCN (2.0 mL, 0.3 M) The crude mixture was purified via flash chromatography using gradient elution from 50% EtOAc/Hex to 80% (0.142 g, 63%). TLC R_f = 0.20 (EtOAc/Hex 3:5) $[\alpha]_D^{25}$ = –25.0° (c.: 0.98, MeOH).[6] ^{1}H NMR (300 MHz, DMSO–d_6) δ 9.92 (s, 1H), 8.00 (s, 1H), 7.43 – 7.00 (m, 5H), 6.33 (s, 1H), 4.49 – 4.31 (m, 1H), 4.23 – 4.05 (m, 1H), 3.14 – 3.00 (m, 1H), 3.00 – 2.81 (m, 1H), 1.38 (s, 9H), 1.25 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 172.2, 171.1, 155.2, 154.2, 136.2, 129.9, 128.6, 127.1, 79.0, 56.5, 49.1, 37.6, 28.7, 18.8. IR (ν, film, cm^{-1}): 3269, 2980, 1732, 1688, 1162. HRMS (ESI+): Exact mass calcd for $C_{18}H_{24}N_4O_5Na$ [M+Na]$^+$: 399.1644 m/z. Found: 399.1665 m/z.

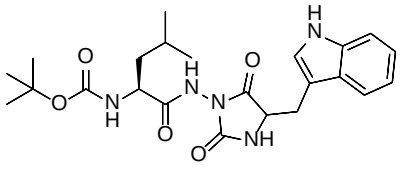


4c *tert*–Butyl ((2*S*)–1–((4–((1H–indol–3–yl)methyl)–2,5–dioxoimidazolidin–1–yl)amino)–1–oxopropan–2–yl)carbamate

[5] **Also synthesized with D-Phe-NH_2 HCl with Hunig's base at 60°C with a 40% yield and with L-Phe-NH_2, triethylamine, at 80 °C, with a yield of 59%.

[6] Average of two samples.

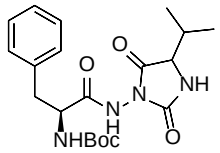
Synthesized according to the general procedure 3 using alanine *aza*–dipeptide **2a** (0.640 g, 1.98 mmol), L–tryptophanamide hydrochloride (0.432 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (6.0 mL, 0.3 M) at 80 °C for 19 hours. The crude mixture was purified by silica gel column chromatography using gradient elution from 60% to 90% EtOAc/Hex to afford the pure compound as an orange powder (0.570 g, 76%). TLC R_f = 0.19 (EtOAc/Hex 3:5) $[\alpha]_D^{25}$ = –26.4° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.62 (s, 1H), 9.96 (s, 1H), 8.02 (s, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.20 (s, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.36 (s, 1H), 4.44 (t, *J* = 5.6 Hz, 1H), 4.26 – 4.06 (m, 1H), 3.27 (d, *J* = 4.3 Hz, 1H), 3.22 (s, 1H), 3.09 (dd, *J* = 15.2, 6.0 Hz, 1H), 2.96 (s, 1H), 1.41 (s, 9H), 1.26 (t, *J* = 14.2 Hz, 3H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 171.3, 170.5, 154.2, 153.4, 135.8, 127.1, 123.4, 120.4, 117.9, 117.7, 110.8, 107.7, 78.0, 55.5, 48.1, 27.7, 26.7, 17.8. IR (ν, film, cm^{-1}): 1705, 1682, 1654, 1560, 1534, 1451. HRMS (ESI+): Exact mass calcd for $C_{20}H_{25}N_5O_5Na$ $[M+Na]^+$: 438.1744 m/z. Found: 438.1753 m/z.



4d *tert*–Butyl ((2*S*)–1–((4–((1H–indol–3–yl)methyl)–2,5–dioxoimidazolidin–1–yl)amino)–4–methyl–1–oxopentan–2–yl)carbamate

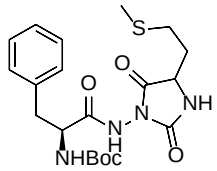
Synthesized according to the general procedure 3 using L–leucine *aza*–dipeptide **2c** (0.705 g, 1.93 mmol), L–tryptophanamide hydrochloride (0.419 g, 1.80 mmol), triethylamine (0.32 mL, 2.3 mmol) and MeCN (6.0 mL, 0.3 M). The crude mixture was purified by silica gel column chromatography using gradient elution starting from 60% to 75% EtOAc/Hex to afford the desired compound in good purity as an orange powder (0.621 g, 78%). TLC R_f = 0.54 (EtOAc/Hex 7:10). $[\alpha]_D^{25}$ = –25.2° (c.: 0.99, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.62 (s, 1H), 10.00 (s, 1H), 8.01 (s, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.20 (s, 1H), 7.13 – 7.04 (m, 1H), 7.04 – 6.94 (m, 1H), 6.30 (d, *J* = 7.2 Hz, 1H), 4.44 (t, *J* =

5.7 Hz, 1H), 4.17 (dd, *J* = 14.7, 6.9 Hz, 1H), 3.24 (dd, *J* = 15.1, 4.5 Hz, 1H), 3.09 (ddd, *J* = 15.1, 6.3, 3.3 Hz, 1H), 1.82 – 1.65 (m, 1H), 1.61 – 1.49 (m, 3H), 1.42 (s, 10H), 0.99 – 0.87 (m, *J* = 6.6, 4.9, 1.8 Hz, 7H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 171.5, 155.4, 154.4, 136.8, 128.1, 124.5, 121.4, 118.9, 118.7, 111.8, 108.8, 79.0, 56.5, 52.3, 28.7, 27.8, 27.7 , 24.7, 23.2, 22.1. IR (ν, film, cm^{-1}):1737, 1685, 1654, 1558, 1506. HRMS (ESI+): Exact mass calcd for $C_{23}H_{31}N_5O_5Na$ [M+Na]$^+$: 480.2234 m/z. Found: 480.2223 m/z.



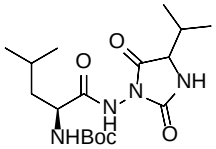
4e *tert*–Butyl ((*S*)–1–(((*S*)–4–isopropyl–2,5–dioxoimidazolidin–1–yl)amino)–1–oxo–3–phenylpropan–2–yl)carbamate

Synthesized according to the general procedure 3 using L–phenylalanine *aza*–dipeptide **2d** (0.791g, 1.98 mmol), L–valinamide hydrochloride (0.275 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (2.0 mL, 0.3 M). The crude mixture was purified by silica gel column chromatography using 100% EtOAc as an eluent to afford the pure compound as an orange powder (0.621 g, 78%). TLC R_f = 0.54 (EtOAc/Hex 7:10) $[\alpha]_D^{25}$ = –25.2° (c.: 0.99, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.62 (s, 1H), 10.00 (s, 1H), 8.01 (s, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.20 (s, 1H), 7.13 – 7.04 (m, 1H), 7.04 – 6.94 (m, 1H), 6.30 (d, *J* = 7.2 Hz, 1H), 4.44 (t, *J* = 5.7 Hz, 1H), 4.17 (dd, *J* = 14.7, 6.9 Hz, 1H), 3.24 (dd, *J* = 15.1, 4.5 Hz, 1H), 3.09 (ddd, *J* = 15.1, 6.3, 3.3 Hz, 1H), 1.82 – 1.65 (m, 1H), 1.61 – 1.49 (m, 3H), 1.42 (s, 10H), 0.99 – 0.87 (m, *J* = 6.6, 4.9, 1.8 Hz, 7H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 171.5, 155.4, 154.4, 136.8, 128.1, 124.5, 121.4, 118.9, 118.7 , 111.8 , 108.8 , 79.00 , 56.5 , 52.3 , 28.7 , 27.8 , 27.7 , 24.7, 23.2, 22.1. IR (ν, film, cm^{-1}): 1737, 1685, 1654, 1558, 1506. HRMS (ESI+): Exact mass calcd for $C_{23}H_{31}N_5O_5Na$ [M+Na]$^+$: 480.2234 m/z. Found: 480.2223 m/z.



4f *tert*–butyl ((2*S*)–1–((4–(2–(methylthio)ethyl)–2,5–dioxoimidazolidin–1–yl)amino)–1–oxo–3–phenylpropan–2–yl)carbamate

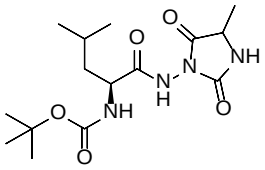
Synthesized according to the general procedure 3 using L–phenylalanine *aza*–dipeptide **2d** (0.791g, 1.98 mmol), L–methionine amide hydrochloride (0.333 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (2.0 mL, 0.3 M) at 80 °C for 17 hours. The crude mixture was dry loaded on silica gel using MeOH and was purified by silica gel column chromatography using a gradient from 60% to 80% EtOAc in Hexanes as an eluent to afford the pure compound as an (0.599 g, 76%). TLC R_f = 0.35 (EtOAc/Hex 7:10). $[\alpha]_D^{25}$ = –16.1° (c.: 0.98, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.21 (s, 1H), 8.14 (s, 1H), 7.43 – 7.05 (m, 5H), 6.36 (s, 1H), 4.41 (td, *J* = 9.2, 4.6 Hz, 1H), 4.26 (dd, *J* = 6.7, 5.2 Hz, 1H), 3.20 – 2.80 (m, 3H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.15 – 1.82 (m, 5H), 1.33 (s, 9H).^{13}C NMR (76 MHz, DMSO–d_6) δ 170.5, 170.2, 153.4, 137.0, 128.7, 127.4, 125.7, 78.0, 53.8, 37.4, 31.0, 28.0, 27.6, 14.1. IR (ν, film, cm^{-1}): 1737, 1685, 1654, 1558, 1506. HRMS (ESI+): Exact mass calcd for $C_{23}H_{31}N_5O_5Na$ $[M+Na]^+$: 475.1627 m/z. Found: 475.1627 m/z.



4g *tert*–Butyl ((*S*)–1–(((*S*)–4–isopropyl–2,5–dioxoimidazolidin–1–yl)amino)–4–methyl–1–oxopentan–2–yl)carbamate

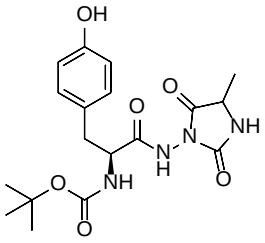
Synthesized according to the general procedure 3 using L–leucine *aza*–dipeptide **2c** (0.723 g, 1.98 mmol), L–valine amide hydrochloride (0.275 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (2.0

mL, 0.3 M) at 80 °C for 21 hours. The crude mixture was dry loaded on silica gel using MeOH and was purified by silica gel column chromatography using a gradient from 50% to 70% EtOAc in Hexanes as an eluent to afford the pure compound as an (0.343 g, 51%). TLC R_f = 0.43 (EtOAc/Hex 2:5) $[\alpha]_D^{25}$ = –56.3° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.0 (s, 1H), 8.0 (s, 1H), 6.3 (s, 1H), 4.3 – 4.1 (m, 1H), 4.0 (d, *J* = 3.9 Hz, 1H), 2.2 – 2.0 (m, 1H), 1.9 – 1.6 (m, 1H), 1.6 – 1.5 (m, 2H), 1.4 (s, 9H), 1.1 – 0.9 (m, 12H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 170.8, 170.0, 154.4, 153.8, 77.9, 59.9, 51.2, 40.9, 29.4, 27.7, 23.7, 22.2, 21.1, 17.6, 15.7. IR (ν, film, cm^{-1}): 1737, 1685, 1654, 1558, 1506. HRMS (ESI+): Exact mass calcd for $C_{23}H_{31}N_5O_5Na$ [M+Na]$^+$: 393.2114 m/z. Found: 393.2114 m/z.



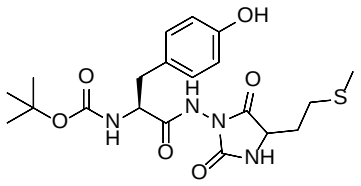
4h *tert*–Butyl ((2S)–4–methyl–1–((4–methyl–2,5–dioxoimidazolidin–1–yl)amino)–1–oxopentan–2–yl)carbamate

Synthesized according to the general procedure 3 using L–leucine *aza*–dipeptide **2c** (0.723 g, 1.98 mmol), L–alaninamide hydrochloride (0.236 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (6.0 mL, 0.3 M) at 80 °C for 19 hours. The crude mixture was dry loaded on silica gel using MeOH and was purified by silica gel column chromatography using gradient elution from 50% to 80% EtOAc/Hex to afford the pure compound as a white powder (0.466 g, 76%). TLC R_f = 0.18 (EtOAc/Hex 1:1) $[\alpha]_D^{25}$ = –34.0° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.13 (s, 1H), 8.11 (s, 1H), 6.51 (s, 1H), 3.05 (s, 2H), 1.82 – 1.62 (m, 1H), 1.53 (t, *J* = 7.1 Hz, 2H), 1.41 (s, 9H), 1.31 (d, *J* = 6.9 Hz, 3H), 0.91 (dd, *J* = 6.5, 4.9 Hz, 6H). ^{13}C NMR (75 MHz, DMSO–d_6) δ 172.5, 171.9, 155.4, 154.2, 78.9, 52.2, 51.3, 28.6, 24.7, 23.1, 22.1, 17.8. IR (ν, film, cm^{-1}): 1703, 1688, 1651, 1560. HRMS (ESI+): Exact mass calcd for $C_{15}H_{26}N_4O_5Na$ [M+Na]$^+$: 365.1803. Found: 365.1801.



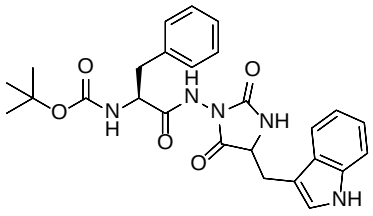
4i *tert*–Butyl ((2*S*)–3–(4–hydroxyphenyl)–1–((4–methyl–2,5–dioxoimidazolidin–1–yl)amino)–1–oxopropan–2–yl)carbamate

Synthesized according to the general procedure 3 using L–tyrosine *aza*–dipeptide **2f** (0.823 g, 1.98 mmol), L–alaninamide hydrochloride (0.224 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (6.0 mL, 0.3 M) at 80 °C for 19 hours. The crude mixture was dry loaded on silica gel using MeOH and was purified by silica gel column chromatography using gradient elution starting from 80% EtOAc/Hex to 100% EtOAc to afford the compound in acceptable purity as a white powder (0.415 g, 59%). Please note that traces of EtOAc are present in the product isolated and used for characterization. TLC R_f = 0.45 (EtOAc). TLC Rf = 0.38 (EtOAc/Hex 4:5) $[\alpha]_D^{25}$ = –14.2° (c.: 1.00, MeOH).. ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.14 (s, 1H), 8.72 (s, 1H), 8.03 (s, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 6.22 (s, 1H), 4.40 – 4.23 (m, 1H), 4.17 (q, *J* = 6.9 Hz, 1H), 3.09 – 2.83 (m, 2H), 2.76 (dd, *J* = 14.0, 9.2 Hz, 1H), 1.43 – 1.30 (m, 12H).^{13}C NMR (76 MHz, DMSO–d_6) δ 171.6, 170.3, 155.4, 154.24, 153.2, 129.5, 127.1, 114.6, 78.0, 54.1, 50.4, 36.7, 27.6, 16.8. IR (ν, film, cm^{-1}): 1740, 1682, 1655, 1560, 1511, 1453. HRMS (ESI+): Exact mass calcd for $C_{18}H_{24}N_4O_6$ $[M+Na]^+$: 415.1613 m/z. Found: 415.1594 m/z.



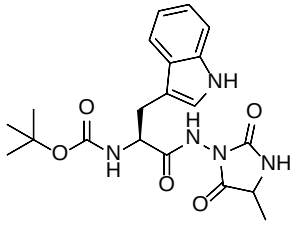
4j *tert*–Butyl ((2*S*)–3–(4–hydroxyphenyl)–1–((4–(2–(methylthio)ethyl)–2,5–dioxoimidazolidin–1–yl)amino)–1–oxopropan–2–yl)carbamate

Synthesized according to the general procedure 3 using L–tyrosine *aza*–dipeptide **2f** (0.823 g, 1.98 mmol), L–methioninamide hydrochloride (0.333 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (3.00 mL, 0.3 M). The crude mixture was purified by silica gel column chromatography using gradient elution starting from 70% to 80% EtOAc/Hex to afford the compound in good purity as a white powder (0.558 g, 68%). TLC R_f = 0.54 (EtOAc/Hex 85:100) $[\alpha]_D^{25}$ = –13.0° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.16 (s, 1H), 8.74 (s, 1H), 8.13 (s, 1H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 6.21 (d, *J* = 6.5 Hz, 1H), 4.43 – 4.13 (m, 2H), 3.06 – 2.84 (m, 2H), 2.76 (dd, *J* = 14.2, 9.1 Hz, 1H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.16 – 1.98 (m, 4H), 1.92 (dt, *J* = 14.0, 6.9 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, DMSO–d_6) δ 170.5, 170.3, 155.5, 154.3, 153.4, 129.5, 127.0, 114.6, 78.0, 54.1, 53.8, 36.7, 31.0, 28.0, 27.6, 14.1. IR (*ν*, film, cm^{-1}): 1737, 1685, 1656, 1636, 1508, 1453. HRMS (ESI+): Exact mass calcd for $C_{20}H_{28}N_4O_6SNa$ $[M+Na]^+$: 475.1629 m/z. Found: 475.1627 m/z.



4k *tert*–Butyl ((2*S*)–1–((4–((1H–indol–3–yl)methyl)–2,5–dioxoimidazolidin–1–yl)amino)–1–oxo–3–phenylpropan–2–yl)carbamate

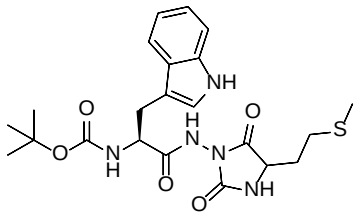
Synthesized according to the general procedure 3 using L–phenylalanine *aza*–dipeptide **2d** (0.791 g, 1.98 mmol), L–tryptophanamide hydrochloride (0.432 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (6.0 mL, 0.3 M). The crude mixture was purified by silica gel column chromatography using gradient elution starting from 60% to 70% EtOAc/hex to afford the pure compound as an orange powder (0.700 g, 79%). Please note that traces of EtOAc are present in the product isolated and used for characterization. TLC R_f = 0.60 (EtOAc/Hex 7:10) $[\alpha]_D^{25}$ = –13.3° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.63 (s, 1H), 10.17 (s, 1H), 8.05 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.12 (m, 7H), 7.14 – 6.94 (m, 2H), 6.29 (d, *J* = 5.9 Hz, 1H), 4.51 – 4.31 (m, 2H), 3.33 – 3.19 (m, 1H), 3.19 – 3.03 (m, 2H), 2.93 – 2.77 (m, 2H), 1.43 – 1.25 (m, 9H).^{13}C NMR (76 MHz, DMSO–d_6) δ 170.5, 154.2, 153.4, 137.0, 135.8, 128.7, 127.1, 125.7, 123.5, 120.4, 117.9, 117.7, 110.8, 107.7, 107.7, 78.0, 55.5, 53.9, 37.5, 27.6, 26.8, 26.7. IR (ν, film, cm^{-1}): 1735, 1685, 1656, 1558, 1506, 1453. HRMS (ESI+): Exact mass calcd for $C_{26}H_{29}N_5O_5Na$ [M+Na]$^+$: 514.2047 m/z. Found: 514.2066 m/z.



4l *tert*–Butyl ((2*S*)–3–(1H–indol–3–yl)–1–((4–methyl–2,5–dioxoimidazolidin–1–yl)amino)–1–oxopropan–2–yl)carbamate

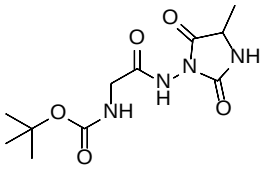
Synthesized according to the general procedure 3 using L–tryptophan *aza*–dipeptide **2g** (0.289 g, 0.659 mmol), L–alaninamide hydrochloride (0.075 g, 0.60 mmol), triethylamine (0.11 mL, 0.79 mmol) and MeCN (2.0 mL, 0.3 M. The crude mixture was purified by silica gel chromatography using a gradient elution form 85% EtOAc/Hex to 100 EtOAc to afford the compound as a white powder (0.491 g, 66%). TLC R_f = 0.49 (EtOAc). $[\alpha]_D^{20}$ = –34.1° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.55 (s,1H), 10.20 (s, 1H), 8.05 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.22 (s, 1H), 7.14 –

6.91 (m, 2H), 6.18 (s, 1H), 4.45 (td, *J* = 8.2, 4.5 Hz, 1H), 4.19 (q, *J* = 6.9 Hz, 1H), 3.34 – 3.15 (m, 2H), 3.12 – 2.84 (m, 3H), 1.40 – 1.29 (m, 12H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 171.6, 170.4, 154.3, 153.3, 135.8, 127.2, 123.4, 120.3, 117.8, 117.7, 110.7, 109.2, 78.0, 53.5, 50.4, 27.7, 27.6, 16.8. IR (ν, film, cm^{-1}): 1685, 1651, 1562, 1511, 1453. HRMS (ESI+): Exact mass calcd for $C_{20}H_{25}N_5O_5$ [M+Na]$^+$: 438.1742 m/z. Found: 438.1753 m/z.



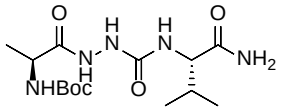
4m *tert*–Butyl ((2*S*)–3–(1H–indol–3–yl)–1–((4–(2–(methylthio)ethyl)–2,5–dioxoimidazolidin–1–yl)amino)–1–oxopropan–2–yl)carbamate

Synthesized according to the general procedure 3 using L–tryptophan *aza*–dipeptide **2g** (0.851 g, 1.98 mmol), L–methioninamide hydrochloride (0.333 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (6.0 mL, 0.3 M). The crude mixture was purified by silica gel column chromatography using gradient elution starting from 75% to 80% EtOAc/Hex to afford the compound as a white powder (0.559 g, 65%). TLC R_f = 0.70 (EtOAc). $[\alpha]_D^{25}$ = –30.8° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.54 (s, 1H), 10.22 (s, 1H), 8.15 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 1.7 Hz, 1H), 7.03 (dt, *J* = 14.9, 7.0 Hz, 2H), 6.17 (s, 1H), 4.45 (td, *J* = 8.5, 4.6 Hz, 1H), 4.32 – 4.20 (m, 1H), 3.24 (dd, *J* = 15.3, 4.2 Hz, 1H), 3.11 – 2.87 (m, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.15 – 1.81 (m, 5H), 1.32 (s, 9H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 170.6, 170.5, 154.3, 153.5, 135.8, 127.2, 123.4, 120.3, 117.8, 117.7, 110.7, 109.2, 78.0, 53.8, 53.5, 31.0, 28.0, 27.7, 27.6, 14.1. IR (ν, film, cm^{-1}): 1654, 1638, 1563, 1508, 1456. HRMS (ESI+): Exact mass calcd for $C_{22}H_{29}N_5O_5S$ [M+Na]$^+$: 498.1779 m/z. Found: 498.1787 m/z.



4n *tert*–Butyl (2–((4–methyl–2,5–dioxoimidazolidin–1–yl)amino)–2–oxoethyl)carbamate[7]

Synthesized according to the general procedure 3 using glycine *aza*–dipeptide **2e** (0.600 g, 1.98 mmol), L–alaninamide hydrochloride (0.224 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (6.0 mL, 0.3 M). The crude mixture was then purified by silica gel column with an eluant made of 95% EtOAc/Hex to afford the pure compound as a white powder (0.373 g, 72%). TLC R_f = 0.38 (EtOAc). $[\alpha]_D^{25}$ = 0.5° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 9.98 (s, 1H), 8.02 (s, 1H), 6.53 (s, 1H), 4.16 (q, *J* = 6.8 Hz, 1H), 3.74 (d, *J* = 6.2 Hz, 2H), 2.94 (s, 1H), 1.42 (s, 9H), 1.33 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 171.6, 168.1, 155.0, 153.2, 77.9, 50.4, 41.6, 27.7, 16.8. IR (ν, film, cm^{-1}): 3272, 2982, 1728, 1683, 1507, 1450, 1236, 1159. HRMS (ESI+): Exact mass calcd for $C_{11}H_{18}N_4O_5Na$ $[M+Na]^+$: 309.1171 m/z. Found: 309.1175 m/z.

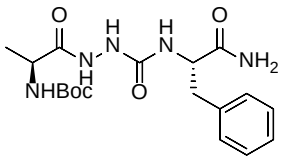


4o *tert*–Butyl ((*S*)–1–(2–(((*S*)–1–amino–3–methyl–1–oxobutan–2–yl)carbamoyl)hydrazinyl)–1–oxopropan–2–yl)carbamate

Synthesized according to the general procedure 3 using alanine *aza*–dipeptide **2a** (0.640 g, 1.98 mmol), L–valinamide hydrochloride (0.275 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (6.0 mL, 0.3 M). It was filtered and washed with ether. The solid was then dissolved in MeOH and dry loaded

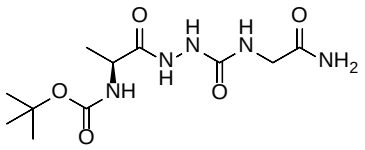
[7] The compound was also synthesized using D-alaninamide•HCl (enantiomer) under identical conditions, providing 0.346 g of product **4n** (67% yield). Then the compound was also synthesized using L-Ala-OBn•HCl under identical conditions, providing 0.468 g of product **4n** (91% yield). NMR spectra were in good agreement and optical rotation values support that epimerization occurred. $[\alpha]_D^{25}$ = 0.5° from L-alaninamide vs. $[\alpha]_D^{25}$ = –0.8° from D-alaninamide vs. $[\alpha]_D^{25}$ = –8.3° from L-Ala-OBn•HCl (c.: 1.00, MeOH for all samples).

on silica gel, then eluted on silica gel with a gradient starting 5% to 15% MeOH/EtOAc to afford the pure compound as a white powder (0.483 g, 77%). TLC R_f = 0.41 (MeOH/EtOAc 5:100). $[\alpha]_D^{25}$ = –13.95° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 9.28 (s, 1H), 7.76 (s, 1H), 6.80 (s, 2H), 6.35 (s, 1H), 6.04 (d, *J* = 8.7 Hz, 1H), 4.26 – 3.86 (m, 2H), 2.00 (dq, *J* = 13.3, 6.8 Hz, 1H), 1.41 (s, 9H), 1.25 (d, *J* = 7.1 Hz, 3H), 0.88 (dd, *J* = 13.1, 6.8 Hz, 6H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 172.8, 171.8, 157.0, 154.4, 77.8, 57.6, 30.1, 27.7, 18.6, 17.6, 17.0. IR (ν, film, cm^{-1}): 1732, 1656, 1508, 1487. HRMS (ESI+): Exact mass calcd for $C_{14}H_{27}N_5O_5Na$ [M+Na]$^+$: 368.1901 m/z. Found: 368.1910 m/z.



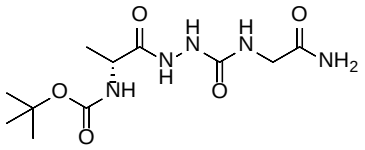
4p *tert*–Butyl (*S*)–(1–(2–(benzylcarbamoyl)hydrazinyl)–1–oxopropan–2–yl)carbamate

Synthesized using L–alanine *aza*–dipeptide **2a** (0.627 g, 1.98 mmol), L–phenylalaninamide hydrochloride (0.361 g, 1.80 mmol), *N*,*N*–diisopropylethylamine (0.41 mL, 2.3 mmol) and MeCN (6.0 mL, 0.3 M).The crude mixture was filtered to collect the precipitate and washed with Et_2O (3x). The resulting solid was dissolved in MeOH, dry loaded on silica gel and purified via flash chromatography using gradient elution from 16% *i*–PrOH/PhMe to 20% *i*–PrOH/PhMe (0.392 g, 55%). TLC R_f = 0.47 (*i*–PrOH/PhMe 2:5). $[\alpha]_D^{25}$ = –23.2° (c.: 0.98, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 9.21 (s, 1H), 7.76 (s, 1H), 7.36 – 7.08 (m, 5H), 6.82 (s, 2H), 6.33 (s, 1H), 6.16 (d, *J* = 7.9 Hz, 1H), 4.47 – 4.28 (m, 1H), 4.17 – 3.94 (m, 1H), 3.13 – 2.81 (m, 2H), 1.41 (s, 9H), 1.23 (d, *J* = 7.0 Hz, 3H).^{13}C NMR (76 MHz, DMSO–d_6) δ 172.7, 156.6, 154.4, 137.4, 128.6, 127.4, 125.5, 77.9, 53.8, 48.2, 37.6, 27.7, 17.6. IR (ν, film, cm^{-1}): 3279, 2980, 1662, 1522, 1247, 1162. HRMS (ESI+): Exact mass calcd for $C_{18}H_{27}N_5O_5Na$ [M+Na]$^+$: 416.191 m/z. Found: 416.1899 m/z.



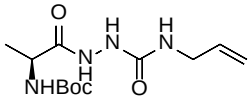
4q *tert*–Butyl (*S*)–(1–(2–((2–amino–2–oxoethyl)carbamoyl)hydrazinyl)–1–oxopropan–2–yl)carbamate

Synthesized according to the general procedure 3 using L–alanine *aza*–dipeptide **2a** (0.627 g, 1.98 mmol), glycinamide hydrochloride (0.199 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (6.0 mL, 0.3 M). The compound precipitated in the reaction mixture. The precipitate was filtered and washed with MeCN (3x). The filtrate was evaporated to dryness, taken into a minimal amount of MeCN, Et_2O was added and the mixture was cooled down to 0 °C for 30 minutes to induce precipitation. The impure solid recovered was dry loaded on silica gel using MeOH and purified via flash chromatography using 15% MeOH/EtOAc to afford the desired compound as a white powder (0.342 g, 63%). TLC R_f = 0.38 (MeOH/EtOAc 3:20). $[\alpha]_D^{25}$ = –35.2° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 9.19 (s, 1H), 7.81 (s, 1H), 6.75 (s, 2H), 6.53 – 6.01 (m, 2H), 4.06 (s, 1H), 3.62 (d, *J* = 5.6 Hz, 2H), 1.41 (s, 9H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.19 (s, 3H). ^{13}C NMR (75 MHz, DMSO–d_6) δ 172.1, 170.9, 157.2, 154.5, 78.0, 48.2, 42.3, 27.7, 17.3. IR (ν, film, cm^{-1}): 3354, 3311, 2978, 1683, 1652, 1511, 1292, 1248, 1166, 1071. HRMS (ESI+): Exact mass calcd for $C_{11}H_{21}N_5O_5Na$ $[M+Na]^+$: 326.1429 m/z. Found: 326.1440 m/z.



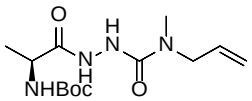
4r *tert*–Butyl (*R*)–(1–(2–((2–amino–2–oxoethyl)carbamoyl)hydrazinyl)–1–oxopropan–2–yl)carbamate

Synthesized according to the general procedure 3 using D–alanine *aza*–dipeptide **2b** (0.627 g, 1.98 mmol), glycinamide hydrochloride (0.199 g, 1.80 mmol), triethylamine (0.33 mL, 2.3 mmol) and MeCN (6.0 mL, 0.3 M). The compound precipitated in the reaction mixture. The precipitate was filtered and washed with MeCN (3x). The filtrate was evaporated to dryness, taken into MeOH, dry loaded and purified via silica gel chromatography using 15% MeOH/EtOAc to afford the desired compound as a white powder (0.426 g, 78%). TLC R_f = 0.38 (MeOH/EtOAc 3:20). $[\alpha]_D^{25}$ = 31.7° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 9.19 (s, 1H), 7.81 (s, 1H), 6.75 (s, 2H), 6.53 – 6.01 (m, 2H), 4.06 (s, 1H), 3.62 (d, *J* = 5.6 Hz, 2H), 1.41 (s, 9H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.19 (s, 3H). ^{13}C NMR (75 MHz, DMSO–d_6) δ 172.1, 170.9, 157.2, 154.5, 78.0, 48.2, 42.3, 27.7, 17.3. IR (ν, film, cm^{-1}): 3354, 3311, 2978, 1683, 1652, 1594, 1511. HRMS (ESI+): Exact mass calcd for $C_{11}H_{21}N_5O_5Na$ [M+Na]$^+$: 326.1435 m/z. Found: 326.1440 m/z.



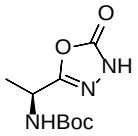
***S4.1 tert*–Butyl (*S*)–(1–(2–(allyl(methyl)carbamoyl)hydrazinyl)–1–oxopropan–2–yl)carbamate**

Synthesized using *tert*–butyl (*S*)–(1–(5–oxo–4,5–dihydro–1,3,4–oxadiazol–2–yl)ethyl)carbamate (L–alanine *aza*–dipeptide) **2a** (0.245 g, 1.07 mmol), *N*–allylmethylamine (0.112 mL, 1.17 mmol), triethylamine (0.045 mL, 0.32 mmol) and MeCN (3.6 mL) at 60 °C for 18 h. The crude mixture was evaporated, taken in MeOH and dry loaded on Silica gel and purified via flash chromatography using gradient elution starting at 2% MeOH/DCM up to 4% MeOH/DCM (0.271 g, 84%). TLC R_f = 0.67 (MeOH/DCM 1:100) $[\alpha]_D^{25}$ = –11.1° (c.: 1.01, MeOH).^{13}C NMR (76 MHz, DMSO–d_6) δ 158.2, 155.6, 136.6, 115.1, 78.9, 49.1, 42.2, 28.7, 18.3. IR (ν, film, cm^{-1}): 3327, 2984, 2936, 1782, 1683, 1511, 1249, 1155, 1050. HRMS (ESI+): Exact mass calcd for $C_{12}H_{22}N_4O_4Na$ [M+Na]$^+$: 309.1539 m/z. Found: 309.1559 m/z.



***S4.2 tert*–Butyl (*S*)–(1–(2–(allylcarbamoyl)hydrazinyl)–1–oxopropan–2–yl)carbamate**

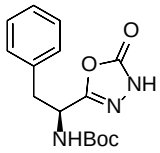
Synthesized using *tert*–butyl (S)–(1–(5–oxo–4,5–dihydro–1,3,4–oxadiazol–2–yl)ethyl)carbamate (0.275 g, 1.2 mmol), allylamine (0.099 mL, 1.3 mmol), triethylamine (0.050 mL, 0.36 mmol) and MeCN (4 mL) at 60 °C for 18 h. The crude mixture was evaporated, taken in MeOH and dry loaded on silica gel and purified via flash chromatography using 6% MeOH/DCM (0.296 g, 86%). TLC R_f = 0.62 (MeOH/DCM 1:100). $[\alpha]_D^{25}$ = –51.2° (c.: 1.00, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.0 (s, 1H), 8.4 (s, 1H), 7.9 (d, *J* = 7.0 Hz, 2H), 7.7 – 7.2 (m, 3H), 5.8 (ddt, *J* = 15.9, 10.4, 5.4 Hz, 1H), 5.3 – 5.0 (m, 2H), 3.9 (d, *J* = 5.5 Hz, 2H), 2.8 (s, 3H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 167.0, 134.5, 134.0, 131.6, 128.6, 127.8, 116.8, 51.1, 34.1. IR (ν, film, cm^{-1}): 3273, 2980, 1651, 1496, 1365, 1247, 1162. HRMS (ESI+): Exact mass calcd for $C_{13}H_{24}N_4O_4Na$ $[M+Na]^+$: 323.1695 m/z. Found: 323.1669 m/z.



5a *tert*–Butyl (*S*)–(1–(5–oxo–4,5–dihydro–1,3,4–oxadiazol–2–yl)ethyl)carbamate

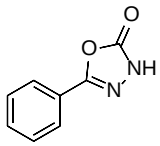
Synthesized using L–Ala dipeptide **2a** (0.500 g, 1.55 mmol), 1,8–diazabicyclo[5.4.0]undec–7–ene (0.046 mL, 0.31 mmol) and THF(5 mL) at room temperature for 19 h. The reaction mixture was evaporated to dryness and dry loaded on silica gel using MeOH for column chromatography using gradient elution from 25% EtOAc/Hex to 50% EtOAc/Hex to afford the desired compound (0.303 g, 85%). TLC R_f = 0.51 (EtOAc/Hex 1:1). $[\alpha]_D^{25}$ = –69.6° (c.: 1.02, MeOH). ^{1}H NMR (300 MHz, DMSO–d_6) δ 6.9 (s, 1H), 4.7 – 4.4 (m, 1H), 1.4 (s, 7H), 1.4 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 158.1, 155.4, 155.2,

79.1, 43.8, 28.6, 17.7. IR (ν, film, cm^{-1}): 3278, 3057, 1639, 1532, 1341, 1242, 912, 684, 623. HRMS (ESI+): Exact mass calcd for $C_9H_{15}N_3O_4Na$ $[M+Na]^+$: 252.0960 m/z. Found: 252.0949 m/z.



5b *tert*–Butyl (*S*)–(1–(5–oxo–4,5–dihydro–1,3,4–oxadiazol–2–yl)–2–phenylethyl)carbamate

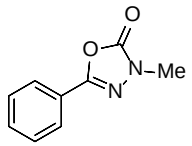
Synthesized using *aza*–dipeptide **2d** (0.12 g, 0.30 mmol), DBU (0.009 mL,0.06 mmol) in THF (1 mL, 0.3M). The crude mixture was purified by silica gel column chromatography using 10% EtOAc/DCM to afford the pure compound as a white solid (0.079 g, 86%). TLC R_f = 0.17 (EtOAc/CH_2Cl_2 1:10). ^{1}H NMR (300 MHz, DMSO–d_6): δ 12.20 (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): δ156.9, 155.4, 155.2, 137.1, 129.5, 128.6, 126.9, 79.1, 49.1, 36.9, 28.1. HRMS (EI): Exact mass calcd for $C_{15}H_{19}N_3O_4$ – t–Bu[M–(*t*–Bu)]+: 249.0750. Found: 249.0735



5c 5–Phenyl–1,3,4–oxadiazol–2(3H)–one

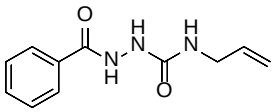
Phenyl carbazate **1** (1.20 g, 7.89 mmol) was dissolved in chloroform (150 mL) and triethylamine (1.1 mL, 8.0 mmol) was added. The reaction mixture was cooled down to 0 °C for 20 minutes and benzoyl chloride (0.93 mL, 7.9 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes until full consumption of the starting material and was then evaporated to dryness and taken in THF. DBU (0.24 mL, 2.0 mmol) was then added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was evaporated to dryness and dry loaded on Silica gel using MeOH for column chromatography using 25% EtOAc/Hex to afford the desired compound as an off–white powder (1.13 g,

88%) TLC R_f = 0.28 (EtOAc/Hex 1:4). ^{1}H NMR (300 MHz, DMSO–d_6) δ 12.57 (s, 1H), 7.78 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.64 – 7.42 (m, 3H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 154.5, 153.8, 131.4, 129.2, 125.3, 124.0. IR (ν, film, cm^{-1}): 1685, 1558, 1508, 1462. HRMS (EI): Exact mass calcd for $C_8H_6N_2O_2$ $[M]^+$: 162.0429 m/z. Found: 162.0434 m/z.



5d 3–Methyl–5–phenyl–1,3,4–oxadiazol–2(3H)–one

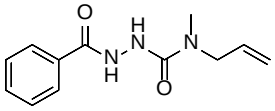
In a 100 mL round–bottom flask, 5–(phenyl)–1,3,4–oxadizole–2(3H)–one (0.162 g, 0.999 mmol), iodomethane (0.075 mL, 1.2 mmol), potassium carbonate (0.346 g, 2.50 mmol) and dimethylformamide (4.0 mL, 0.25 M) were stirred at 27 °C for 16 hours. The crude mixture was poured onto ice water and extracted with chloroform (4x15 mL). The organic layer was washed with water. EtOAc (15 mL) was added to the organic phase and further extracted with 1:1 water:brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a white solid (0.152 g, 86%). TLC R_f = 0.18 (EtOAc/Hex 1:20). ^{1}H NMR (300 MHz, DMSO–d_6) δ 7.77 (d, *J* = 6.2 Hz, 2H), 7.55 (d, *J* = 7.0 Hz, 3H), 3.39 (s, 3H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 153.1, 152.0, 131.6, 129.3, 125.2, 123.5, 32.5. IR (ν, film, cm^{-1}): 1680, 1659, 1511, 1453. HRMS (EI): Exact mass calcd for $C_9H_8N_2O_2$ $[M]^+$: 176.0586 m/z. Found: 176.6142 m/z.



6a *N*–Allyl–2–benzoylhydrazine–1–carboxamide

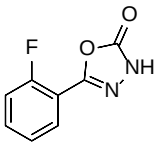
Synthesized using 5–phenyl–1,3,4–oxadiazol–2(3H)–one **5c** (0.195 g, 1.20 mmol), allylamine (0.099 mL, 1.3 mmol), triethylamine (0.050 mL, 0.36 mmol) and MeCN (3.4 mL, 0.3M) at 60°C for 18 hours. The crude mixture was cooled down to 0 °C for 30 minutes, then filtered and washed with cold Et_2O. The

filtrate was cooled to –40 °C for 1 hour and filtered again to recover the desired compound (0.148 g, 56%). TLC R_f = 0.53 (EtOAc). ^{1}H NMR (300 MHz, DMSO–d_6) δ 9.8 (s, 1H), 7.9 (d, J = 8.2 Hz, 1H), 7.6 (s, 1H), 7.6 – 7.4 (m, 3H), 6.3 (s, 1H), 5.9 – 5.8 (m, 1H), 5.2 – 5.1 (m, 1H), 5.1 – 5.0 (m, 1H), 3.8 – 3.7 (m, 2H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 167.0, 158.5, 136.7, 133.7, 131.8, 128.6, 127.9, 115.1, 42.2. IR (ν, film, cm^{-1}): 3278, 3057, 1639, 1532, 1341, 1242, 997, 912, 684, 623. HRMS (ESI+): Exact mass calcd for $C_{11}H_{13}N_3O_2Na$ $[M+Na]^+$: 242.0905. Found: 242.0909.



6b *N*–Allyl–2–benzoyl–*N*–methylhydrazine–1–carboxamide

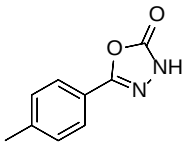
Synthesized using 5–phenyl–1,3,4–oxadiazol–2(3H)–one **5c** (0.174 g, 1.10 mmol), *N*–allylmethylamine (0.112 mL, 1.17 mmol), triethylamine (0.050 mL, 0.36 mmol) and MeCN (3.4 mL, 0.3 M) at 60 °C for 18 hours. The crude mixture was cooled down to 0 °C for 30 minutes, then filtered and washed with cold Et_2O. The filtrate was cooled to –40 °C for 1 hour and filtered again to recover the desired compound (0.133 g, 53%). TLC R_f = 0.44 (EtOAc). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.0 (s, 1H), 8.4 (s, 1H), 7.9 (d, J = 7.0 Hz, 2H), 7.7 – 7.2 (m, 3H), 5.8 (ddt, J = 15.9, 10.4, 5.4 Hz, 1H), 5.3 – 5.0 (m, 2H), 3.9 (d, J = 5.5 Hz, 2H), 2.8 (s, 3H). ^{13}C NMR (76 MHz, DMSO–d_6) δ 167.0, 134.5, 134.0, 131.6, 128.6, 127.8, 116.8, 51.1, 34.1. IR (ν, film, cm^{-1}): 3234, 1638, 1574, 1491, 1241. HRMS (ESI+): Exact mass calcd for $C_{12}H_{15}N_3O_2Na$ $[M+Na]^+$: 256.1062 m/z. Found: 256.1053 m/z.



7a 5–(2–Fluorophenyl)–1,3,4–oxadiazol–2(3H)–one

To a clean and dry round bottom flask charged with a stir bar, was added the phenyl carbazate **1** (1.2 g, 7.9 mmol, 1.0 equiv.) and Et_3N (1.1 mL, 7.89 mmol, 1.0 equiv.) in $CHCl_3$ (100 mL). The reaction mixture

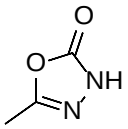
was cooled to 0 °C for 20 minutes in an ice bath. 2–Fluorobenzoyl chloride (0.97 mL, 7.97 mmol, 1.01 equiv.) was dissolved in $CHCl_3$ (30 mL) and added dropwise to the reaction mixture, and it was stirred for 30 minutes. The total volume of $CHCl_3$ amounted to 130 mL (0.06 M). The solvent was evaporated thoroughly, the crude mixture then dissolved in THF (25 mL, 0.3 M) and DBU was added (0.24 mL, 2.01 mmol, 0.2 eq); the mixture stirred at room temperature overnight. Upon completion, the reaction was concentrated via rotary evaporation and the product was purified by gradient silica gel chromatography (from 25% to 30% EtOAc/Hexanes) to yield the compound as a white solid (1.02 g, 71 %).TLC R_f: 0.30 (EtOAc/Hex 1:4).^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.82 (td, *J* = 7.6, 1.8 Hz, 1H), 7.52 (dddd, *J* = 8.3, 7.4, 5.0, 1.8 Hz, 1H), 7.80 (td, *J* = 7.7, 1.1 Hz, 1H), 7.23 (ddd, *J* = 10.8, 8.6, 1.3 Hz, 1H).^{13}C NMR (101 MHz, DMSO–d_6) δ 159.0 (d, *J* = 256.2 Hz), 154.2, 150.5 (d, *J* = 5.0 Hz), 133.4 (d, *J* = 8.5 Hz), 128.4 (d, *J* = 1.5 Hz), 125.1 (d, *J* = 3.6 Hz), 116.9 (d, *J* = 20.3 Hz), 112.2 (d, *J* = 11.1 Hz). ^{19}F NMR (377 MHz, DMSO–d_6) δ –113.9. IR (FTIR): IR (ν, neat, cm^{-1}): 3218, 1595, 1475. HRMS (EI): Exact mass calcd for $C_8H_5FN_2O_2$ $[M]^+$ 180.0335 m/z. Found: 180.0317 m/z.



7b 5–(p–Tolyl)–1,3,4–oxadiazol–2(3H)–one

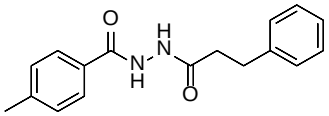
To a clean and dry round bottom flask charged with a stir bar was added the phenyl carbazate **1** (1.28 g, 8.41 mmol, 1.0 equiv.) and Et_3N (1.2 mL, 8.4 mmol, 1.0 equiv.) in $CHCl_3$ (100 mL). The reaction mixture was cooled to 0 °C for 20 minutes in an ice bath. Then, p–toluoyl chloride (1.31 g, 8.47 mmol, 1.01 equiv.) was dissolved in $CHCl_3$ (30 mL) and added dropwise to the reaction mixture, and it was stirred for 30 minutes. The total volume of $CHCl_3$ amounted to 130 mL (0.06 M). The solvent was evaporated, the mixture was then dissolved in THF (25 mL, 0.3 M) and DBU was added (0.25 mL, 1.68 mmol, 0.2 eq); the mixture stirred at room temperature overnight. Upon completion, the reaction was concentrated via rotary evaporation and the product was purified by silica gel flash chromatography (20%

EtOAc:Hexanes) to yield the compound as a white solid (1.2 g, 81%). TLC Rf: 0.26 (EtOAc/Hex 1:5)^{1}H NMR (400 MHz, Chloroform–*d*) δ 9.07 (s, 1H), 7.86 – 7.58 (m, 2H), 7.31 – 7.26 (m, 2H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, Chloroform–*d*) δ 155.7, 154.8, 142.5, 129.9, 125.9, 121.1, 21.8. IR (ν, neat, cm^{-1}): 750, 1592, 3195. Exact mass calcd for $C_9H_8N_2O_2$ $[M]^+$ 176.0586 m/z. Found: 176.0604 m/z.



7c 5–Methyl–1,3,4–oxadiazol–2(3H)–one

Acetic acid hydrazide[8] (2.22 g, 30.0 mmol, 1.0 equiv.) was dissolved in THF (50 mL) and cooled down to 0 °C. A solution of diphenyl carbonate (6.43 g, 30.0 mmol, 1.0 equiv.) in THF (50 mL) was added dropwise and was stirred for approximately 2 hours. It was then warmed to room temperature. Once warmed, DBU (0.913 g, 0.9 mL, 6.00 mmol, 0.2 equiv.) and the reaction mixture was reflux overnight. The crude mixture was then purified via flash chromatography (50% EtOAc/Hex) TLC R_f : 0.54 The product was recovered as a white powder (2.94 g, 98%). TLC R_f: 0.54 (EtOAc/Hex 1:1) ^{1}H NMR (400 MHz, DMSO–d_6) δ 12.00 (s, 1H), 2.18 (s, 3H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 155.2, 154.4, 11.7. IR (ν, neat, cm^{-1}): 1643, 1762, 3306.



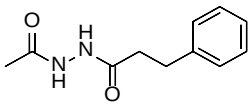
8g 4–Methyl–*N′*–(3–phenylpropanoyl)benzohydrazide[9]

Synthesized according to the general procedure 4 using **7b** (0.176 g, 1 mmol), hydrocinnamic acid (0.017 g, 1.1 mmol), *N*–methyl imidazole (0.16 mL, 2 mmol) and MeCN (3.0 mL, 0.3 M). The crude mixture was purified by silica gel column chromatography using isocratic elution at 40% EtOAc/Hexanes to

[8] Wang, B.; Ke, S.; Kishore, B.; Xu, X.; Zou, Z.; Li, Z., *Synth. Commun.* **2012,** *42*, 2327-2336.

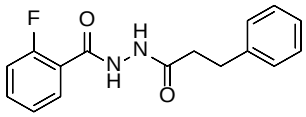
[9] A HSQC NMR spectrum was obtained to confirm the presence of the proton underneath the DMSO peak.

afford the pure compound as a white powder (0.047 g, 17%). TLC R_f = 0.33 (EtOAc/Hexanes 2:5) ^{1}H NMR (400 MHz, DMSO–d_6) δ 10.2 (s, 1H), 9.9 (s, 1H), 7.8 – 7.7 (m, 2H), 7.4 – 7.1 (m, 7H), 2.9 – 2.8 (m, 2H), 2.5 – 2.5 (m, 2H), 2.4 (s, 3H). ^{13}C NMR (126 MHz, DMSO–d_6) δ 170.8, 165.3, 141.7, 141.0, 129.7, 128.9, 128.3, 128.2, 127.5, 126.0, 34.9, 30.7, 21.0. IR (ν, neat, cm^{-1}): 3193 (br), 1594, 1449, 695. HRMS (ESI+): Exact mass calcd for $C_{17}H_{18}N_2O_2Na$ $[M+Na]^+$: 305.1266 m/z. Found: 305.1289 m/z.



8h *N′*–Acetyl–3–phenylpropanehydrazide

Synthesized according to the general procedure 4 using **7c** (0.100g, 1 mmol), hydrocinammic acid (0.165 g, 1.1 mmol), *N*–methyl imidazole (0.16 mL, 2 mmol) and MeCN (3.0 mL, 0.3 M. The crude mixture was dry loaded on silica gel using MeOH and was purified by silica gel column chromatography with 99% EtOAc/1% AcOH to afford the desired compound as a white powder (0.073 g, 35%). TLC R_f: 0.16 (EtOAc). ^{1}H NMR (400 MHz, DMSO–d_6) δ 9.7 (s, 2H), 7.3 – 7.1 (m, 5H), 2.8 (t, J = 7.7 Hz, 2H), 2.4 (t, J = 7.4 Hz, 2H), 1.8 (s, 3H). ^{13}C NMR (126 MHz, DMSO–d_6) δ 170.6, 168.4, 141.5, 128.8, 128.7, 126.4, 35.2, 31.2, 20.9. IR (ν, neat, cm^{-1}): 3188, 1596, 1476. HRMS (ESI+): Exact mass calcd for $C_{11}H_{14}N_2O_2Na$ $[M+Na]^+$: 229.0953 m/z. Found: 229.0962 m/z.

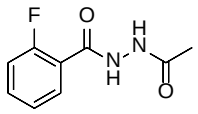


8a 2–Fluoro–*N′*–(3–phenylpropanoyl)benzohydrazide[9]

Synthesized according to the general procedure 4 using **7a** (0.180g, 1 mmol), hydrocinammic acid (0.165 g, 1.1 mmol), *N*–methyl imidazole (0.16 mL, 2 mmol) and MeCN (3.0 mL, 0.3 M). The crude mixture was dry loaded on Silica gel using MeOH and was purified by silica gel column chromatography with 40% EtOAc/Hexanes to afford the desired compound in good purity as a white powder (0.205 g, 72%).

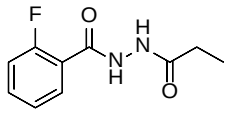
TLC R_f = 0.31 (EtOAc/Hexanes 2:5). ^{1}H NMR (400 MHz, DMSO–d_6) δ 10.1 (s, 2H), 7.6 – 7.5 (m, 2H), 7.3 – 7.2 (m, 6H), 7.2 – 7.1 (m, 1H), 2.8 (dd, *J* = 8.8, 6.8 Hz, 2H), 2.5 – 2.4 (m, 2H). IR (ν, neat, cm^{-1}): 3234 (br), 1771. HRMS (ESI+): Exact mass calcd for $C_{16}H_{15}N_2O_2FNa$ $[M+Na]^+$: 309.1015 m/z. Found: 309.1020 m/z.^{1}H NMR (300 MHz, Chloroform–*d*) δ 9.6 (d, *J* = 8.7 Hz, 2H), 8.0 (td, *J* = 7.7, 1.9 Hz, 1H), 7.6 – 7.4 (m, 1H), 7.3 – 7.1 (m, 8H), 3.1 – 3.0 (m, 2H), 2.7 – 2.6 (m, 2H).^{13}C NMR (101 MHz, Chloroform–*d*) δ 168.4, 161.8, 159.3, 159.2 (d, *J* = 3.2 Hz), 140.3, 134.2 (d, *J* = 9.4 Hz), 131.7 (d, *J* = 1.9 Hz), 128.4 (d, *J* = 29.1 Hz), 126.4, 124.9 (d, *J* = 3.2 Hz), 118.4 (d, *J* = 11.8 Hz), 116.3 (d, *J* = 24.2 Hz), 35.7, 31.3.^{19}F NMR (377 MHz, DMSO–d_6) δ –115.8. IR (ν, neat, cm^{-1}) 3125, 1601, 1472, 751. HRMS (ESI+): Exact mass calcd for $C_{16}H_{15}FN_2O_2Na$ $[M+Na]^+$: 309.1015 m/z. Found: 309.1013 m/z.

*^{13}C experiments indicate the presence of rotamers.



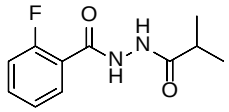
8b *N′*–Acetyl–2–fluorobenzohydrazide

Synthesized according to the general procedure 4 using **7a** (0.180 g, 1 mmol), glacial acetic acid (0.063 mL, 1.1 mmol), *N*–methyl imidazole (0.16 mL, 2 mmol) and MeCN (3.0 mL, 0.3 M) at 140 °C for 24 hours. The crude mixture was purified by silica gel column chromatography using gradient elution from 60% to 100% EtOAc/DCM to afford the desired compound as a white powder (0.127 g, 65%). TLC R_f = 0.18 (EtOAc). ^{1}H NMR (500 MHz, DMSO–d_6) δ 10.1 (s, 1H), 10.0 (s, 1H), 7.7 – 7.5 (m, 2H), 7.4 – 7.2 (m, 2H), 1.9 (s, 3H). ^{13}C NMR (126 MHz, DMSO–d_6) δ 168.2, 163.0 (d, *J* = 1.8 Hz), 160.2, 158.2, 132.9 (d, *J* = 8.5 Hz), 130.1 (d, *J* = 2.9 Hz), 124.5 (d, *J* = 3.6 Hz), 122.3 (d, *J* = 14.9 Hz), 116.2 (d, *J* = 22.0 Hz), 20.6. ^{19}F NMR (377 MHz, DMSO–d_6) δ –115.8. IR (ν, neat, cm^{-1}) 3184 (br), 3005 (br), 1635, 768. HRMS (EI): Exact mass calcd for $C_9H9N_2O_2F$ $[M]^+$: 196.0648 m/z. Found: 196.00698 m/z.



8c 2–Fluoro–*N′*–propionylbenzohydrazide

Synthesized according to the general procedure 4 using **7a** (0.180 g, 1 mmol), propionic acid (0.08 mL, 1.1 mmol), *N*–methyl imidazole (0.16 mL, 2 mmol) and MeCN (3.0 mL, 0.3 M). The crude mixture was purified by silica gel column chromatography 30% EtOAc/DCM with 1% NH_4OH to afford the pure compound as a white powder (0.163 g, 76%). TLC R_f = 0.29 (EtOAc/DCM 3:10) with 1% NH_4OH ^{1}H NMR (500 MHz, DMSO–d_6) δ 10.1 (s, 1H), 10.0 – 9.8 (m, 1H), 7.7 – 7.5 (m, 2H), 7.4 – 7.2 (m, 2H), 2.2 (q, *J* = 7.6 Hz, 2H), 1.1 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO–d_6) δ 172.4, 163.5 (d, *J* = 1.5 Hz), 160.7, 158.7, 133.4 (d, *J* = 8.4 Hz), 130.5 (d, *J* = 2.8 Hz), 125.0 (d, *J* = 3.4 Hz), 122.8 (d, *J* = 14.8 Hz), 116.7 (d, *J* = 21.9 Hz), 26.9, 10.1. ^{19}F NMR (377 MHz, DMSO–d_6) δ –115.8. IR (ν, neat, cm^{-1}) 3092 (br), 1734 (br), 823. HRMS (EI): Exact mass calcd for $C_{10}H_{11}N_2O_2F$ $[M]^+$: 210.2084 m/z Found: 210.07881 m/z.

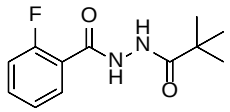


8d 2–Fluoro–*N′*–isobutyrylbenzohydrazide[9]

Synthesized according to the general procedure 4 using **7a** (0.180g, 1 mmol), isobutyric acid (0.1 mL, 1.1 mmol), *N*–methyl imidazole (0.16 mL, 2 mmol) and MeCN (3.0 mL, 0.3 M). The crude mixture was purified by silica gel column chromatography 30% EtOAc/DCM with 1% NH_4OH to afford the pure compound as a white powder (0.141 g, 63%). TLC Rf = 0.33 (EtOAc/Hexanes 3:10+ 1% NH_4OH). ^{1}H NMR (400 MHz, DMSO–d_6) δ 10.15 – 9.79 (m, 2H), 7.60 – 7.49 (m, 2H), 7.33 – 7.21 (m, 2H), 2.51 – 2.40 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 6H).^{13}C NMR (126 MHz, DMSO–d_6) δ 175.7, 163.5, 160.7, 158.7,

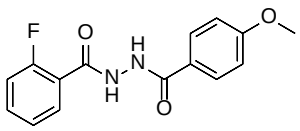
133.3 (d, *J* = 8.3 Hz), 130.5 (d, *J* = 2.9 Hz), 125.0 (d, *J* = 3.6 Hz), 122.9 (d, *J* = 14.8 Hz), 116.7 (d, *J* = 21.9 Hz), 32.6, 19.8. ^{19}F NMR (377 MHz, DMSO–d_6) δ –115.8. IR (ν, neat, cm^{-1}): 3185 (br), 1596, 1477. HRMS (EI): Exact mass calcd for $C_{11}H_{13}N_2O_2F$ $[M]^+$: 224.2354 m/z. Found: 224.09703 m/z.

*^{13}C experiments indicates the presence of rotamers.



8e 2–Fluoro–*N′*–pivaloylbenzohydrazide

Synthesized according to the general procedure 4 using **7a** (0.180 g, 1 mmol), pivalic acid (0.112 g, 1.1 mmol), *N*–methyl imidazole (0.16 mL, 2 mmol) and MeCN (3.0 mL, 0.3 M) at 140 °C for 48 hours. The crude mixture was purified by silica gel column chromatography with 40% EtOAc/Hexanes to afford the pure compound as a white powder (0.139 g, 58%). TLC R_f = 0.37 (EtOAc/DCM 1:10 + 1% NH_4OH). ^{1}H NMR (400 MHz, DMSO–d_6) δ 10.1 – 9.9 (m, 1H), 9.6 (s, 1H), 7.7 – 7.5 (m, 2H), 7.4 – 7.3 (m, 2H), 1.2 (s, 9H).^{13}C NMR (126 MHz, DMSO–d_6) δ 177.1, 163.8 (d, *J* = 1.6 Hz), 160.7, 158.7, 133.3 (d, *J* = 8.3 Hz), 130.5 (d, *J* = 3.0 Hz), 125.0 (d, *J* = 3.5 Hz), 123.1 (d, *J* = 14.9 Hz), 116.7 (d, *J* = 21.8 Hz), 38.1, 27.7. IR (ν, neat, cm^{-1}) 3223 (br), 1615, 1484, 748. HRMS (ESI+): Exact mass calcd for $C_{12}H_{15}N_2O_2FNa$ $[M+Na]^+$: 261.1015 m/z. Found: 261.1013 m/z.



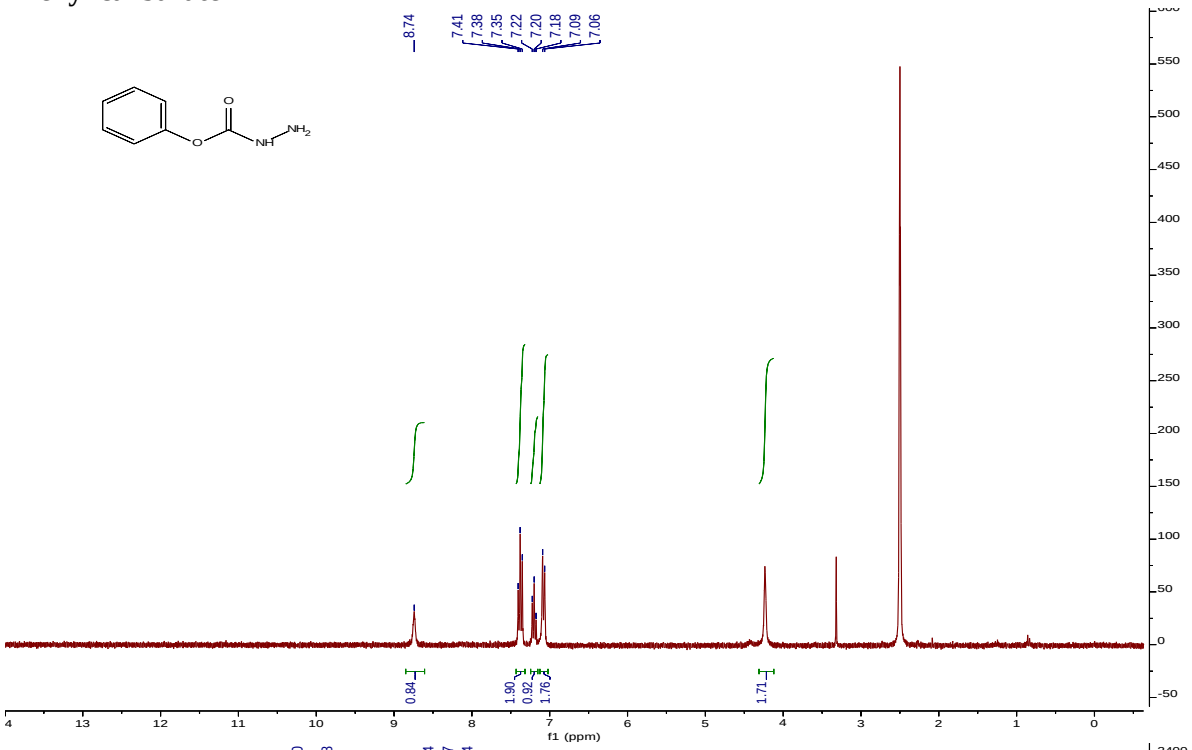
8f 2–Fluoro–*N′*–(4–methoxybenzoyl)benzohydrazide

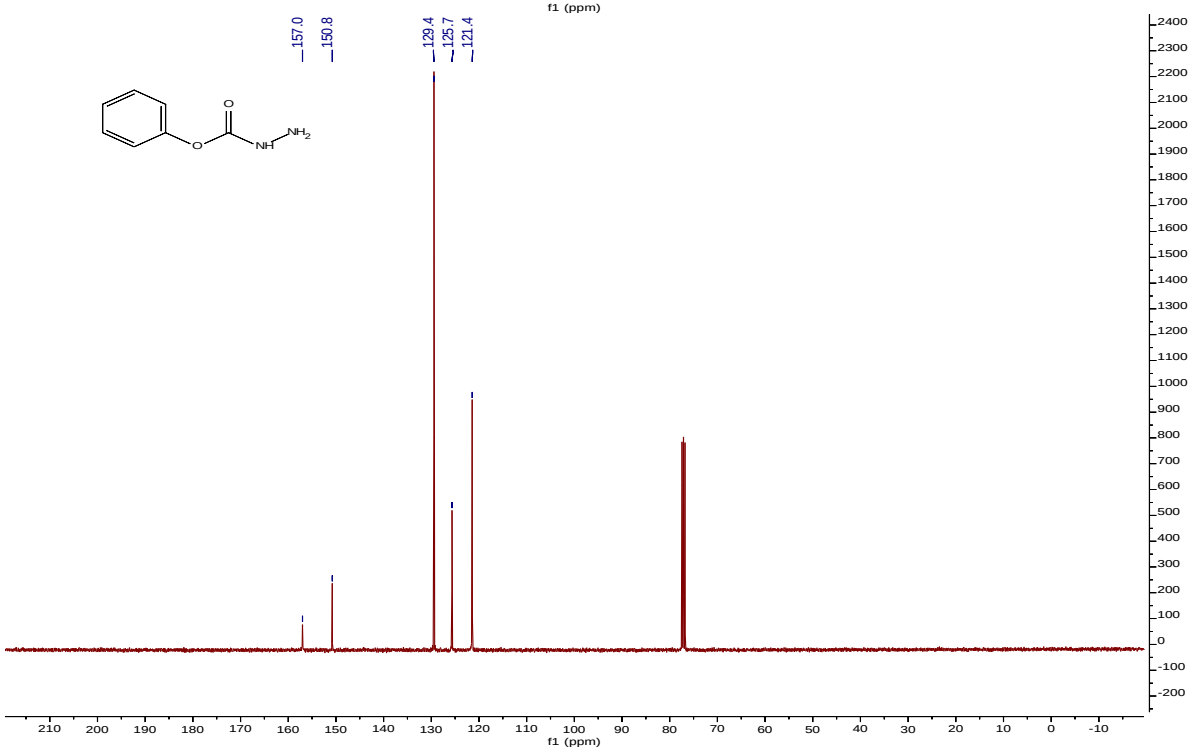
Synthesized according to the general procedure 4 using **7a** (0.180 g, 1 mmol), 4–anisic acid[10] (0.167 g, 1.1 mmol), *N*–methyl imidazole (0.16 mL, 2 mmol) and MeCN (3.0 mL, 0.3 M) at 140 °C for 24 hours. The crude mixture was purified by silica gel column chromatography with 45% EtOAc/Hexanes to afford the pure compound as a white powder (0.133 g, 46%). TLC R_f = 0.34 (EtOAc/Hexanes 45:100). ^{1}H NMR (300 MHz, DMSO–d_6) δ 10.4 (s, 2H), 8.0 – 7.8 (m, 2H), 7.8 – 7.5 (m, 2H), 7.4 – 7.3 (m, 2H), 7.2 – 7.0 (m, 2H), 3.8 (s, 3H).^{13}C NMR (76 MHz, DMSO–d_6) δ 165.0, 163.6 (d, *J* = 1.5 Hz), 162.1, 157.6, 133.0 (d, *J* = 8.5 Hz), 130.1 (d, *J* = 3.0 Hz), 129.4, 124.6, 124.6, 122.5 (d, *J* = 14.8 Hz), 116.3 (d, *J* = 21.9 Hz), 113.7, 55.4. IR (ν, neat, cm^{-1}) 3223 (br), 1615, 1484, 748.^{19}F NMR (377 MHz, DMSO–d_6) δ –115.6. HRMS (ESI+): Exact mass calcd for $C_{15}H_{13}N_2O_3F$ $[M+H]^+$: 288.0910 m/z. Found: 288.0929 m/z

[10] Anisic acid was recrystallized from EtOH to afford brownish needles prior to the reaction.

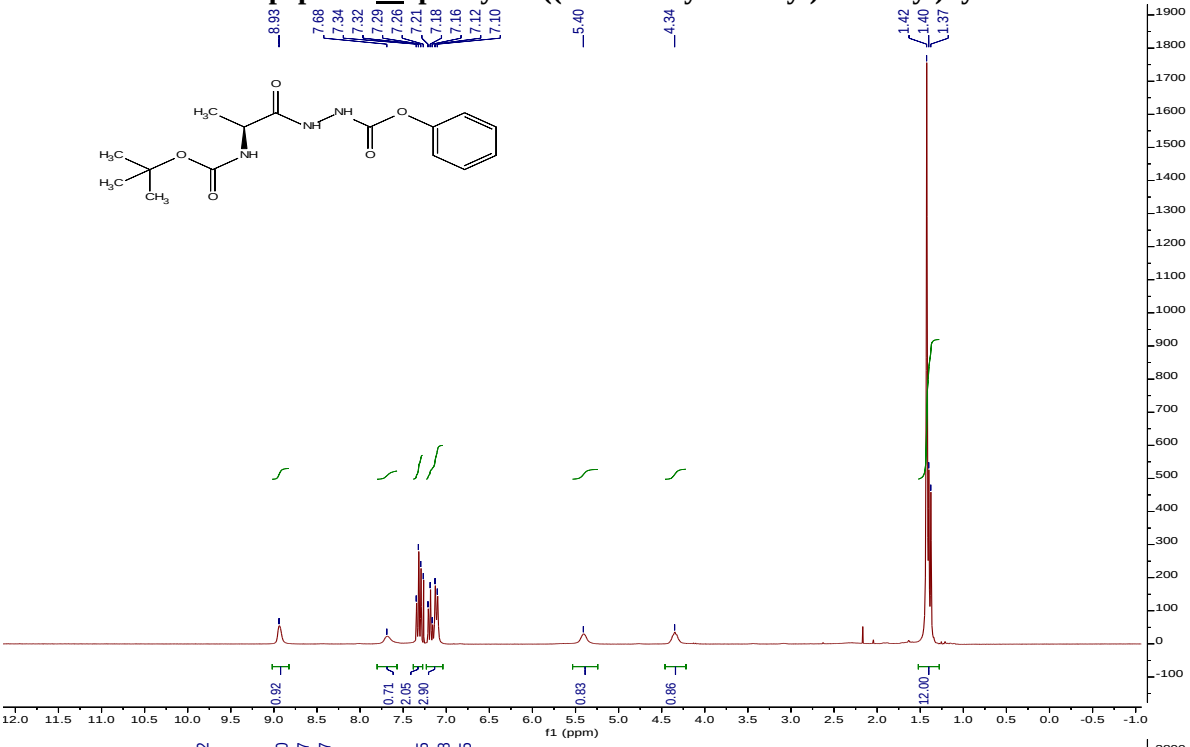
Chapter 6: Spectra

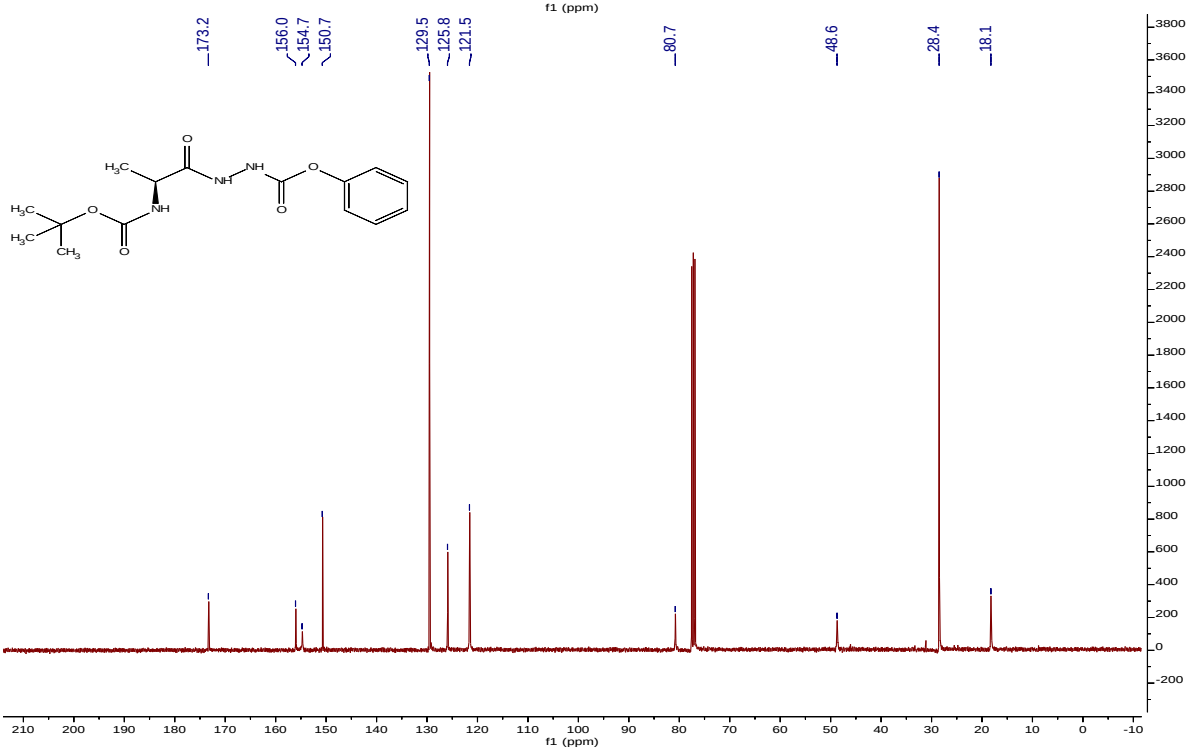
1 Phenyl carbazate



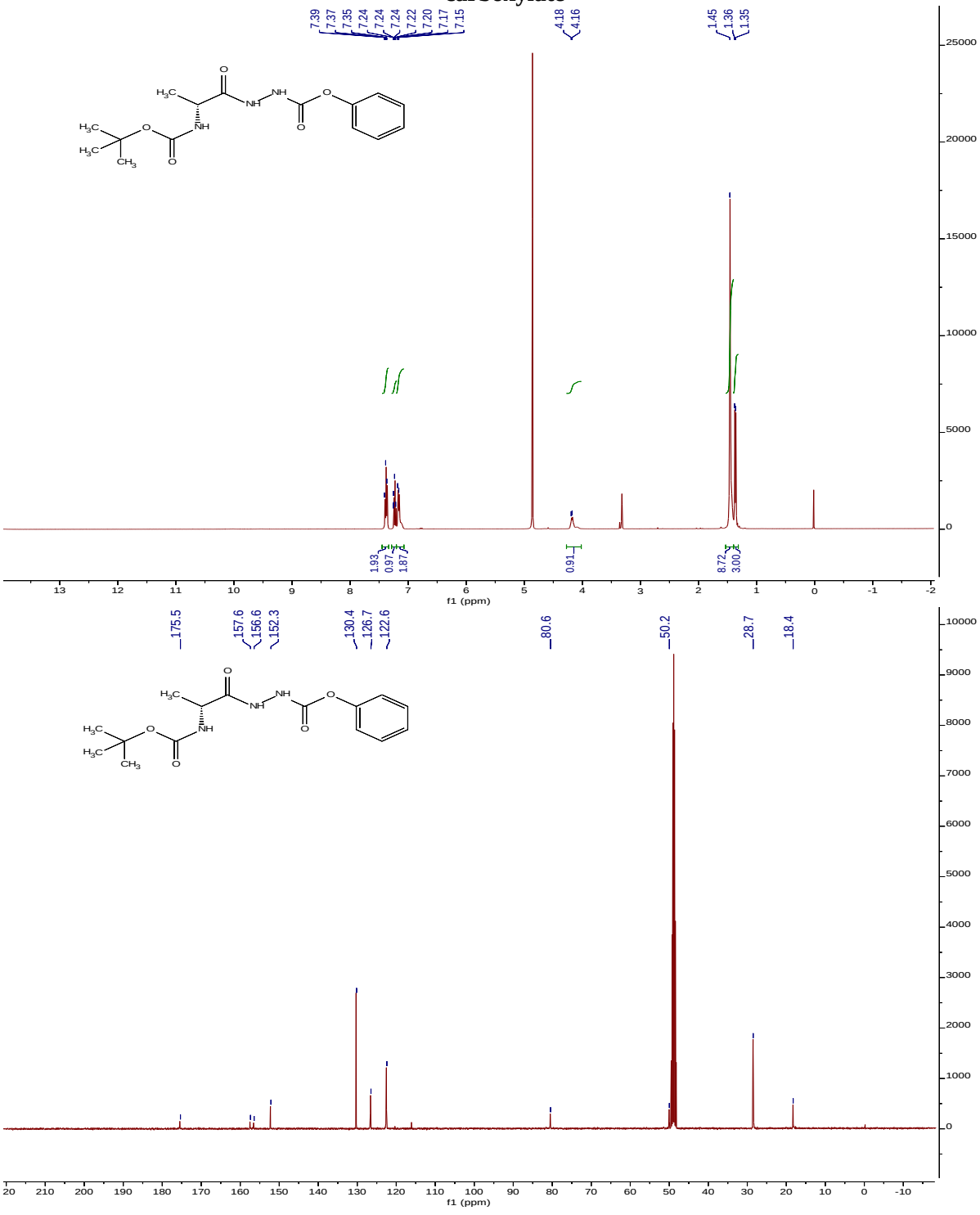


2a L-Alanine *aza*–dipeptide or phenyl 2-((*tert*-butoxycarbonyl)-L-alanyl)hydrazine-1-carboxylate

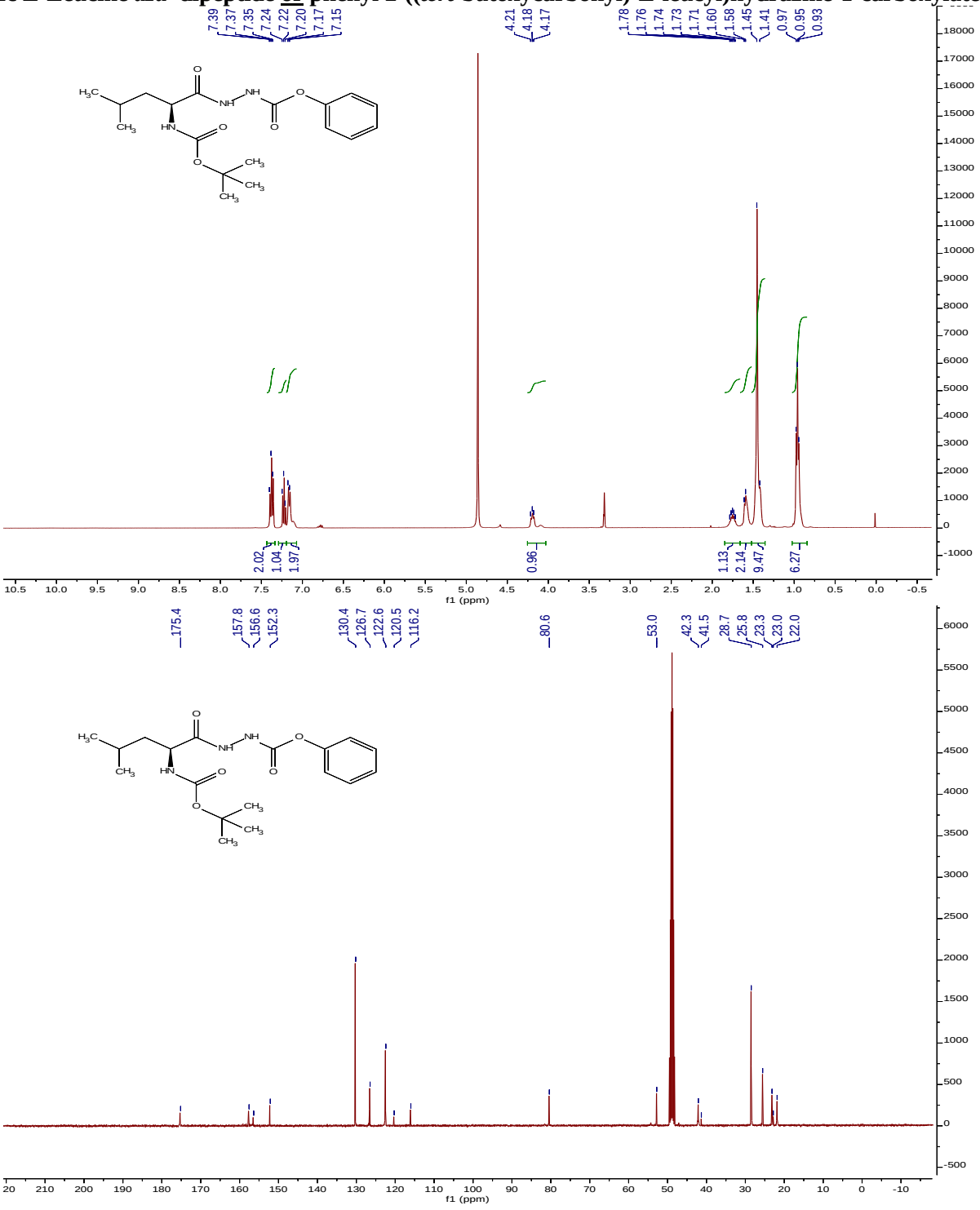




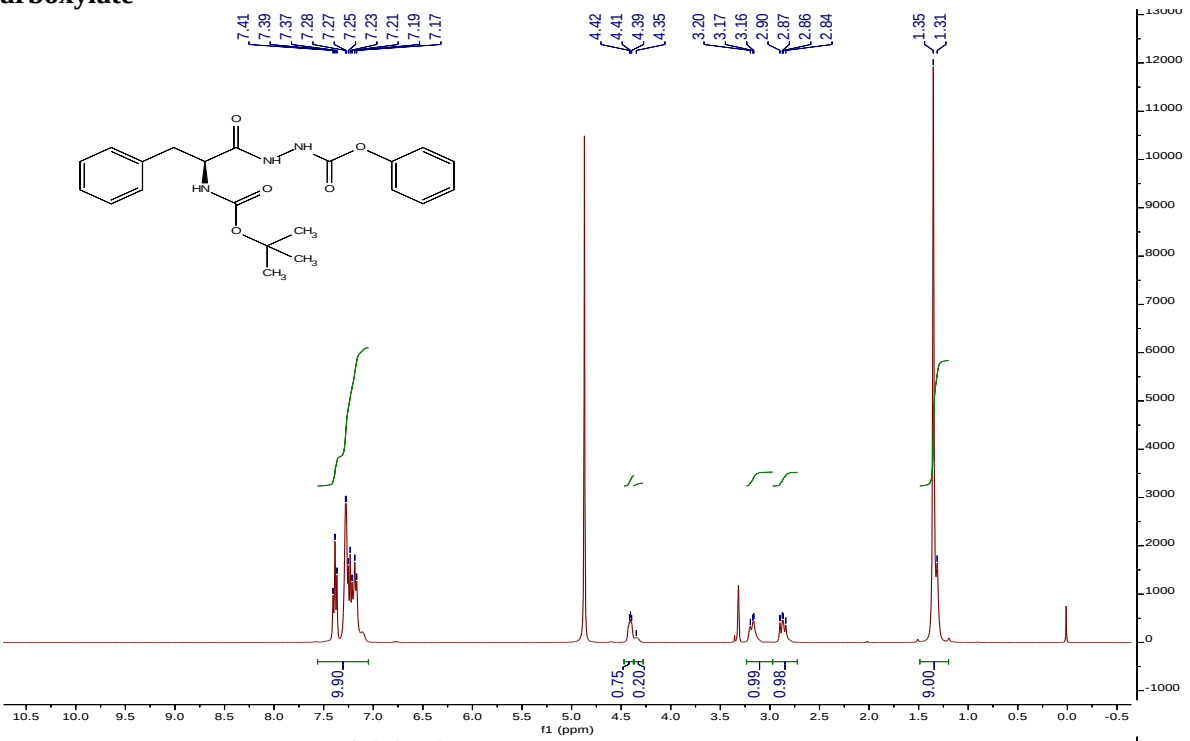
2b D-Alanine dipeptide <u>or</u> phenyl 2-((*tert*-butoxycarbonyl)-D-alanyl)hydrazine-1-carboxylate

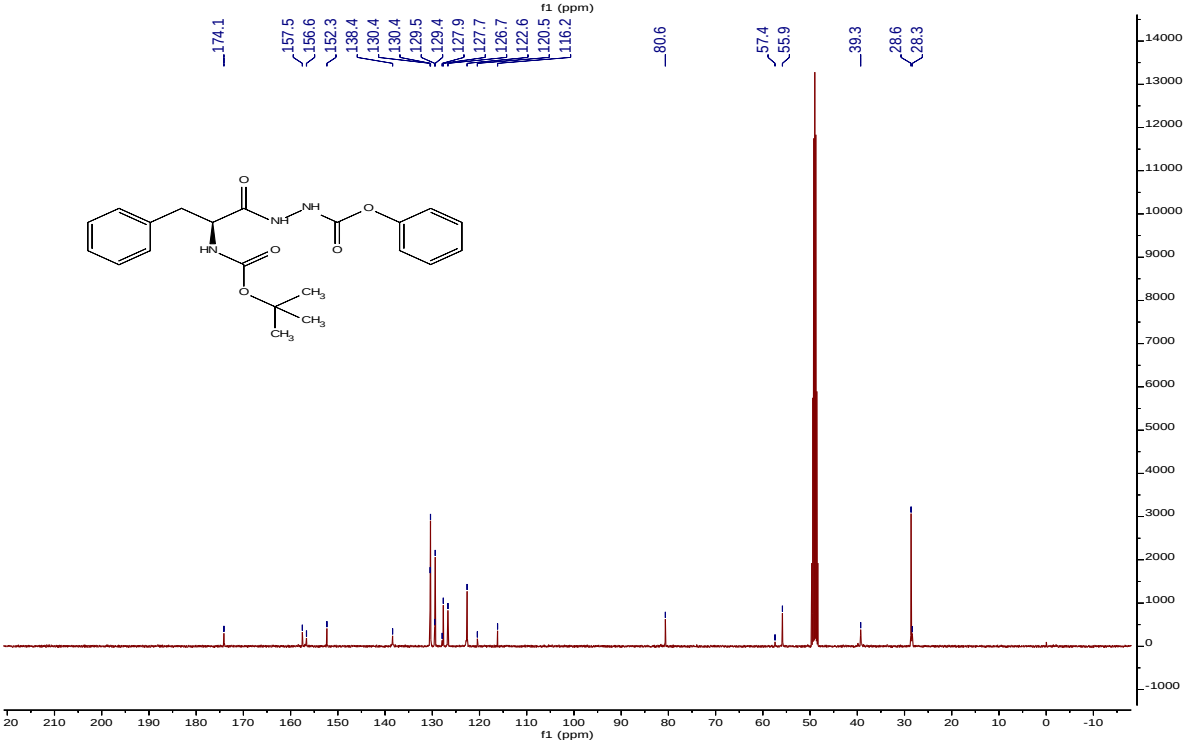


2c L-Leucine *aza*–dipeptide or phenyl 2-((*tert*-butoxycarbonyl)-L-leucyl)hydrazine-1-carboxylate

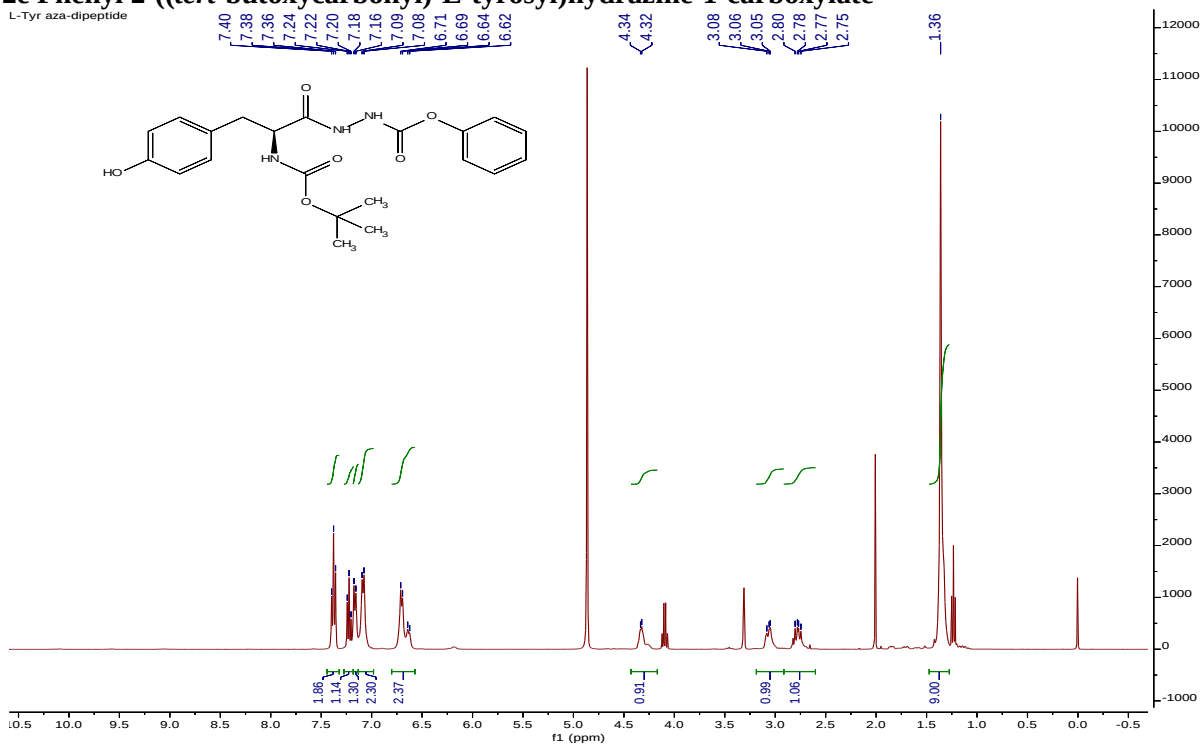


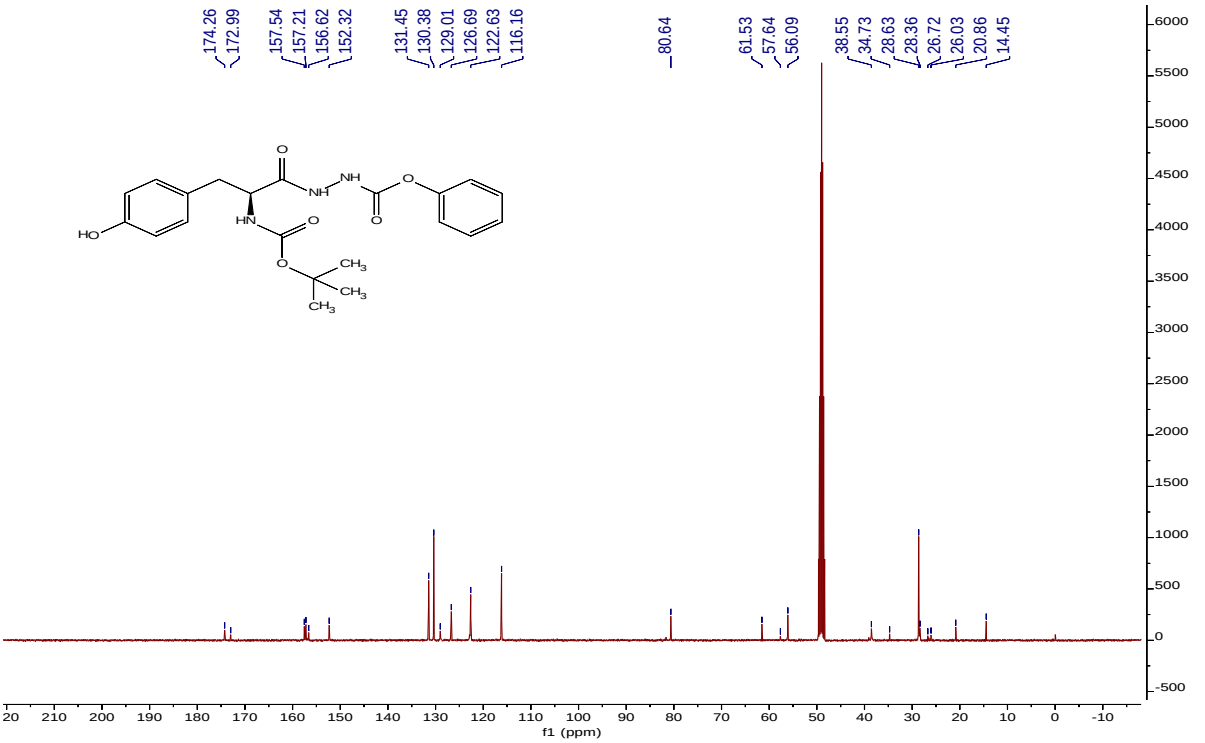
2d L-Phenylalanine *aza*–dipeptide <u>or</u> phenyl 2-((*tert*-butoxycarbonyl)-L-phenylalanyl)hydrazine-1-carboxylate



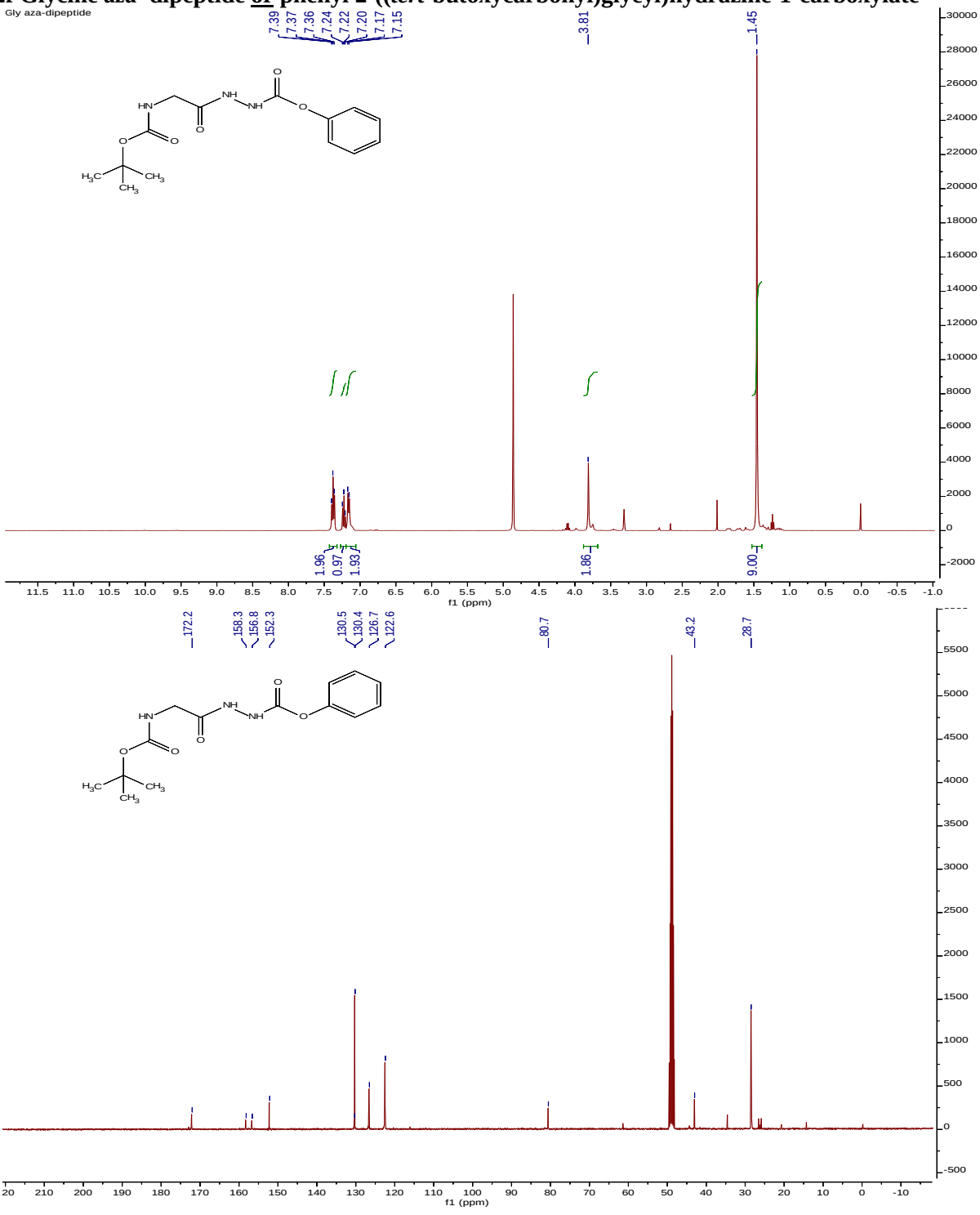


2e Phenyl 2-((*tert*-butoxycarbonyl)-L-tyrosyl)hydrazine-1-carboxylate

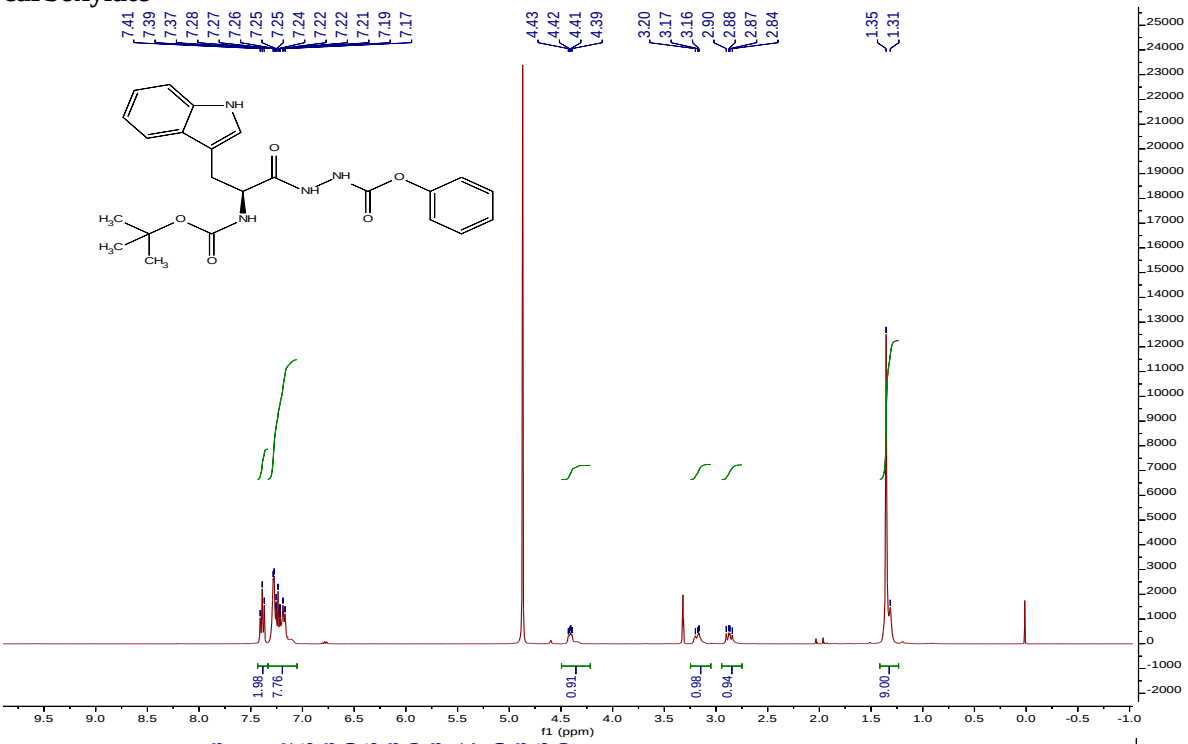


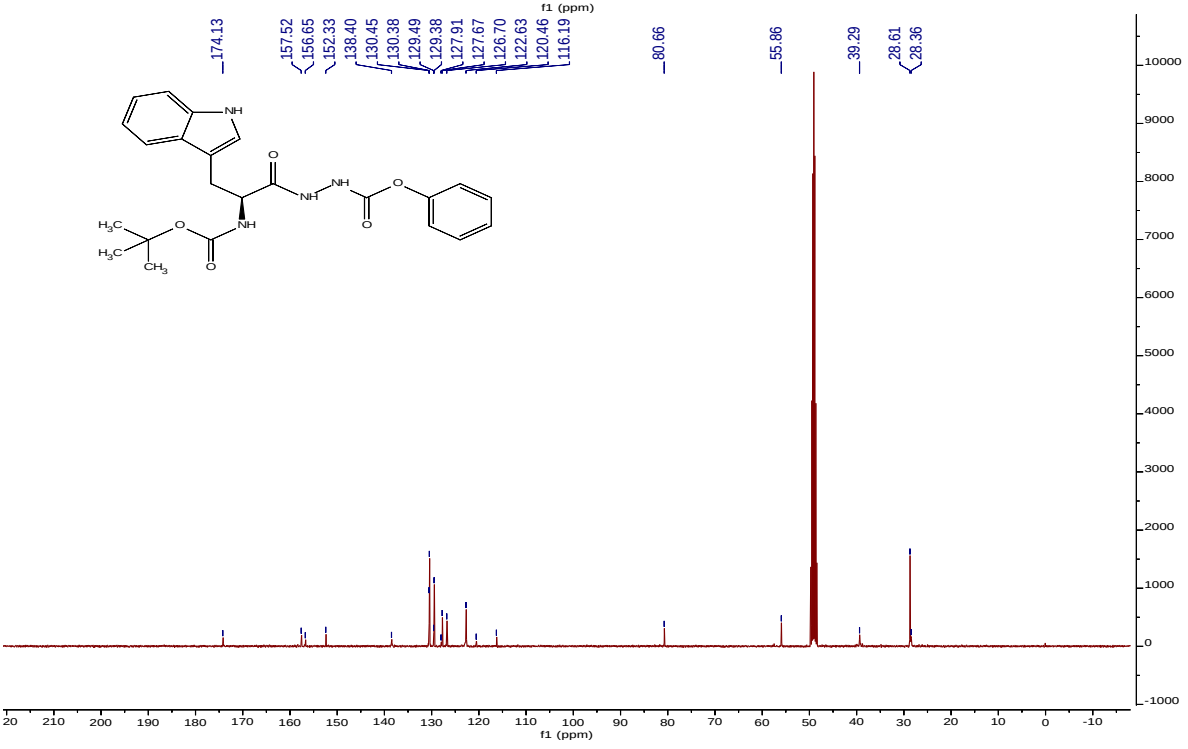


2f Glycine *aza*–dipeptide <u>or</u> phenyl 2-((*tert*-butoxycarbonyl)glycyl)hydrazine-1-carboxylate

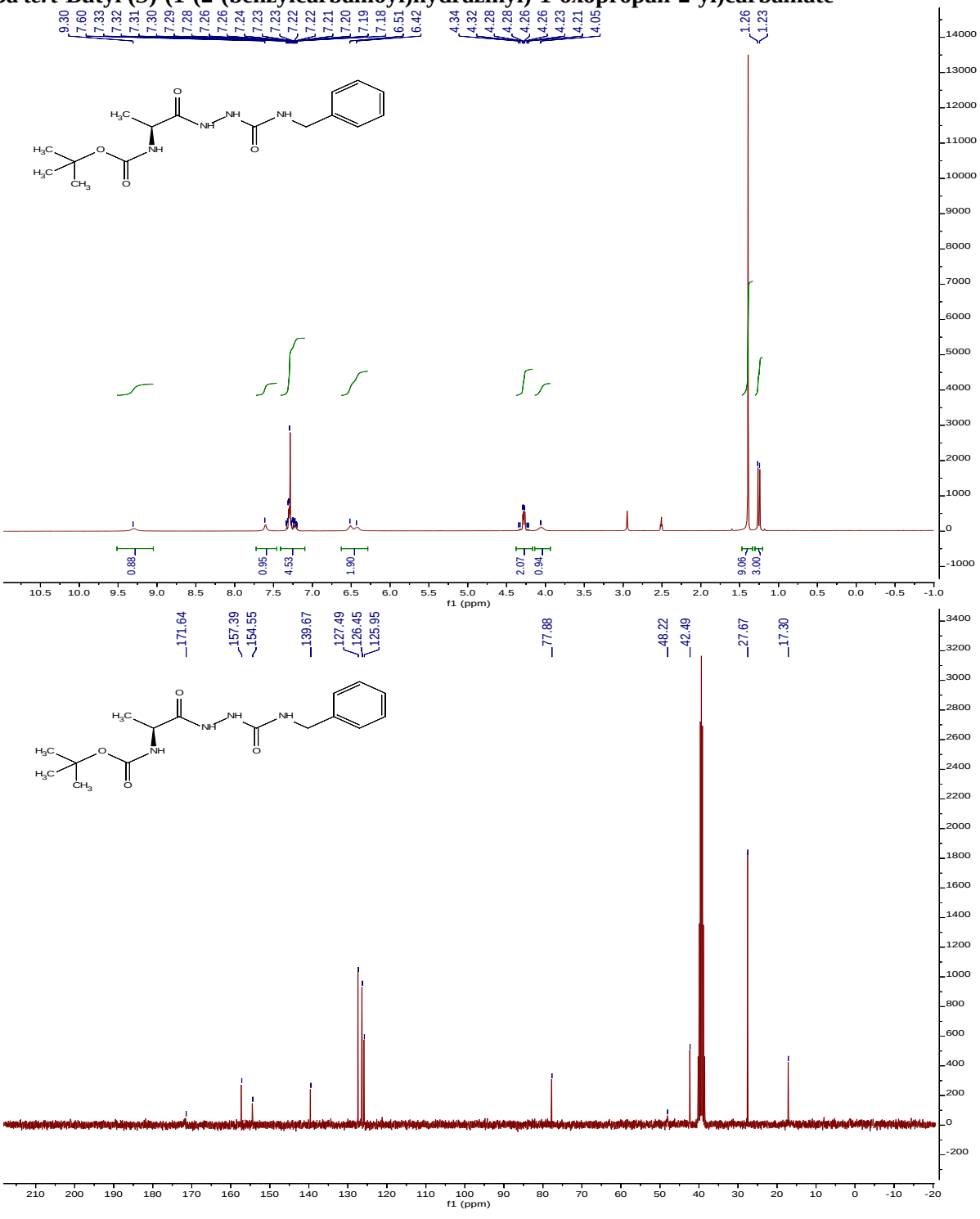


2g Tryptophan *aza*–dipeptide <u>or</u> phenyl 2-((*tert*-butoxycarbonyl)-L-tryptophyl)hydrazine-1-carboxylate

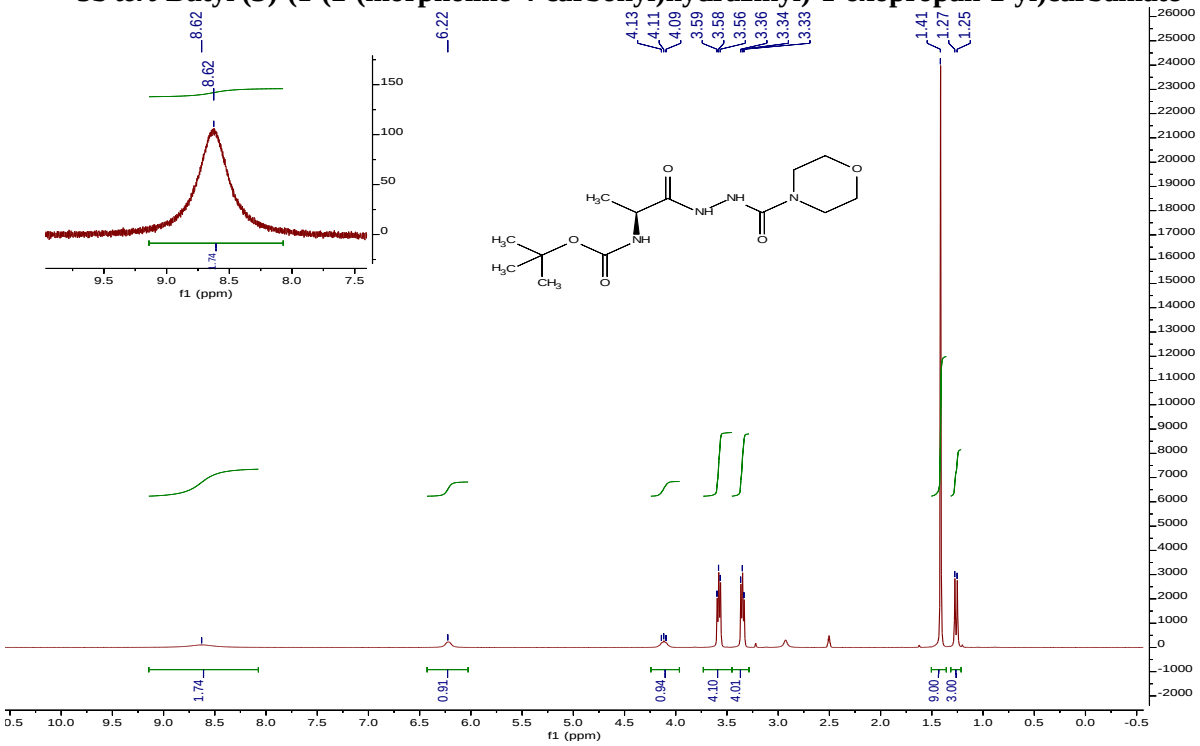


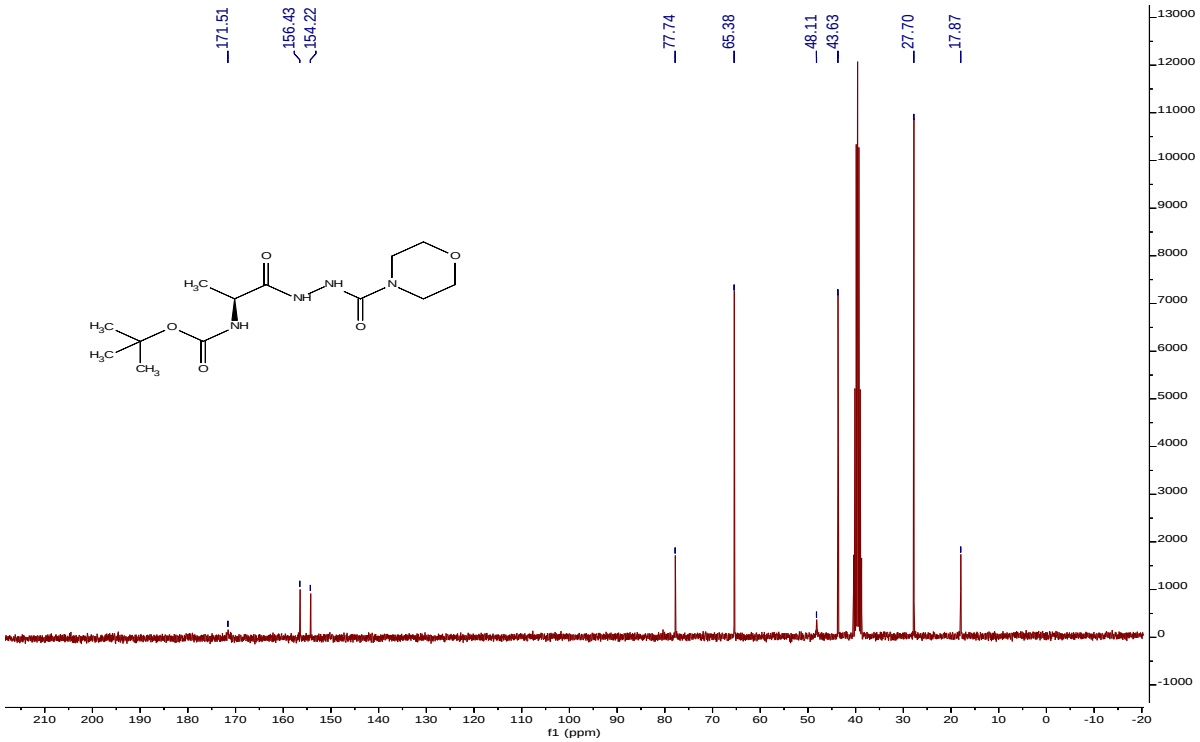


3a *tert*-Butyl (*S*)-(1-(2-(benzylcarbamoyl)hydrazinyl)-1-oxopropan-2-yl)carbamate

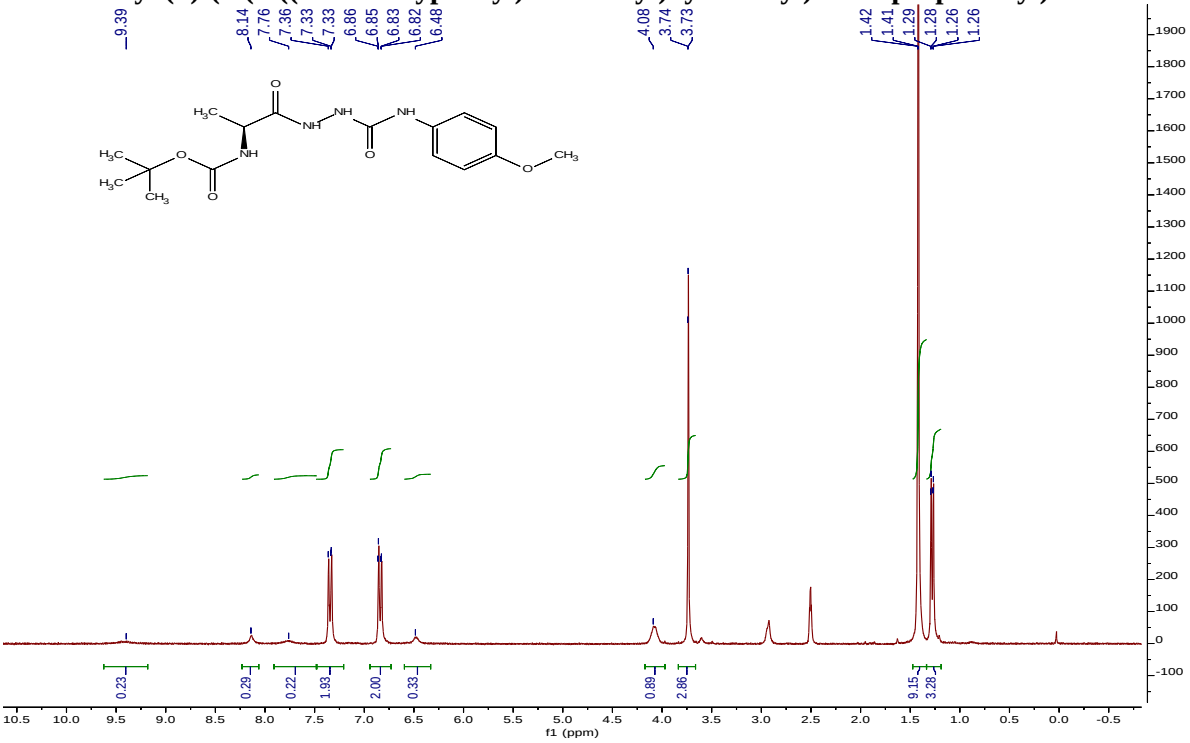


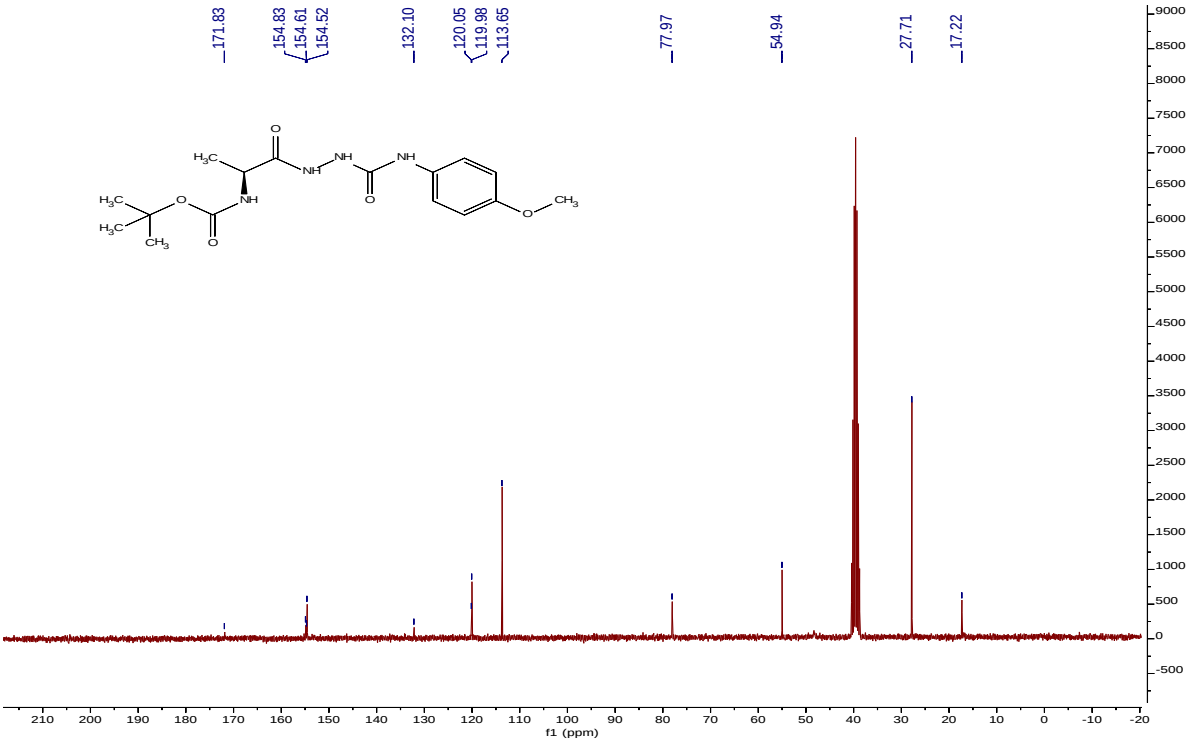
3b *tert*-Butyl (*S*)-(1-(2-(morpholine-4-carbonyl)hydrazinyl)-1-oxopropan-2-yl)carbamate



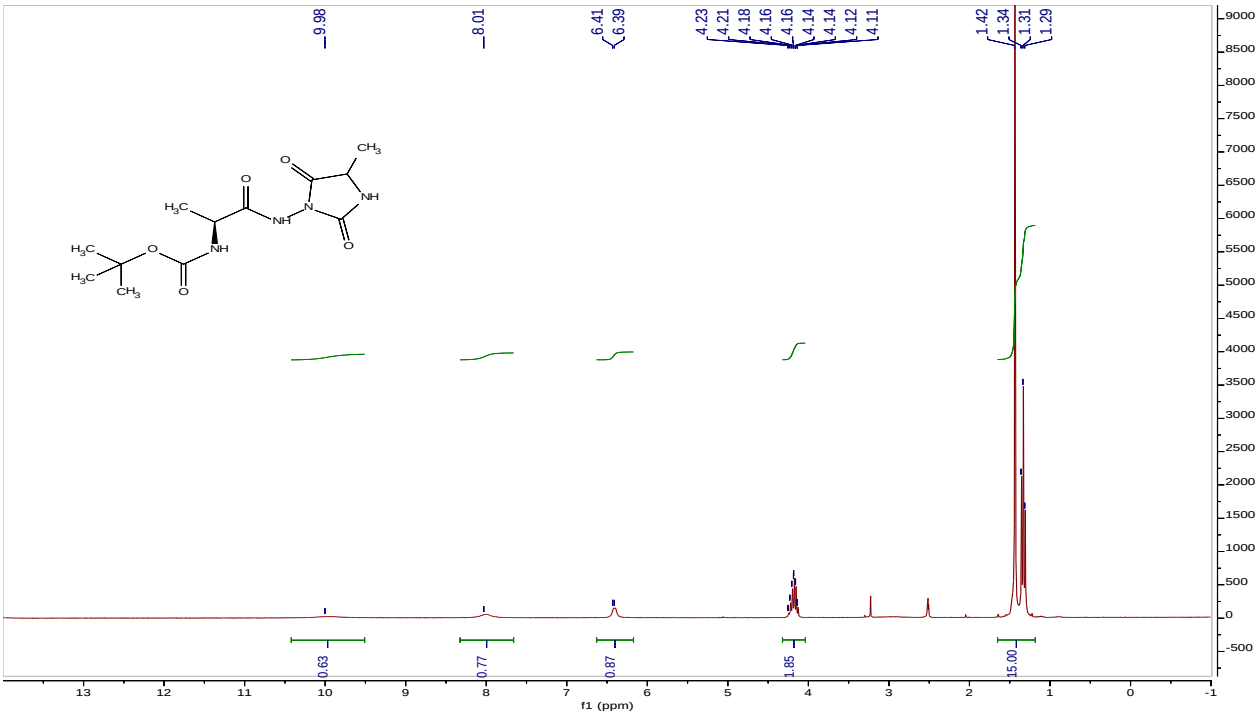


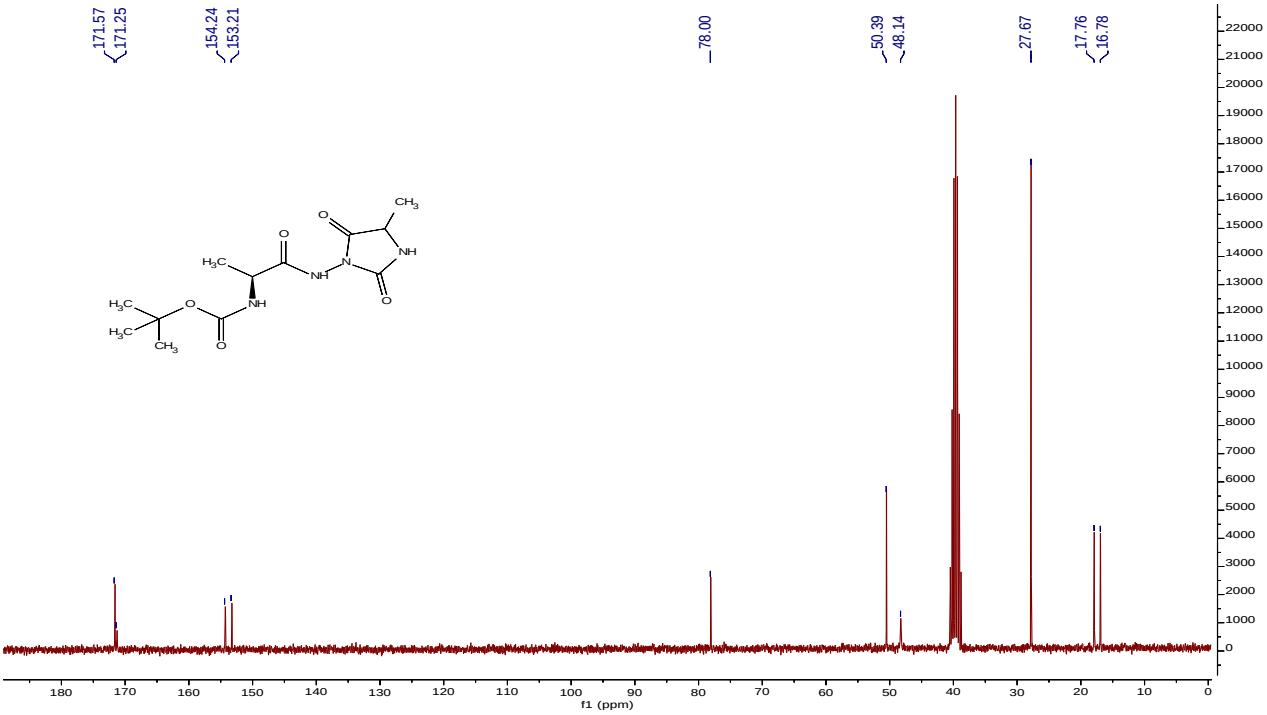
3c *tert*-Butyl (*S*)-(1-(2-((4-methoxyphenyl)carbamoyl)hydrazinyl)-1-oxopropan-2-yl)carbamate



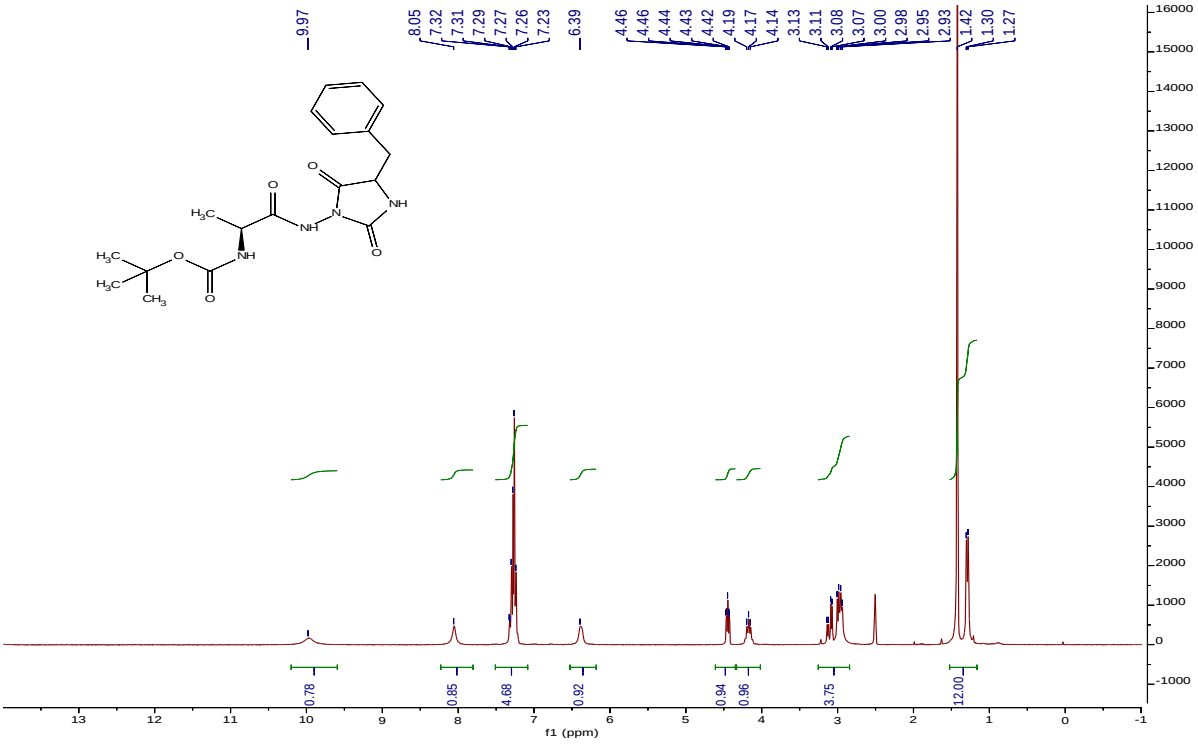


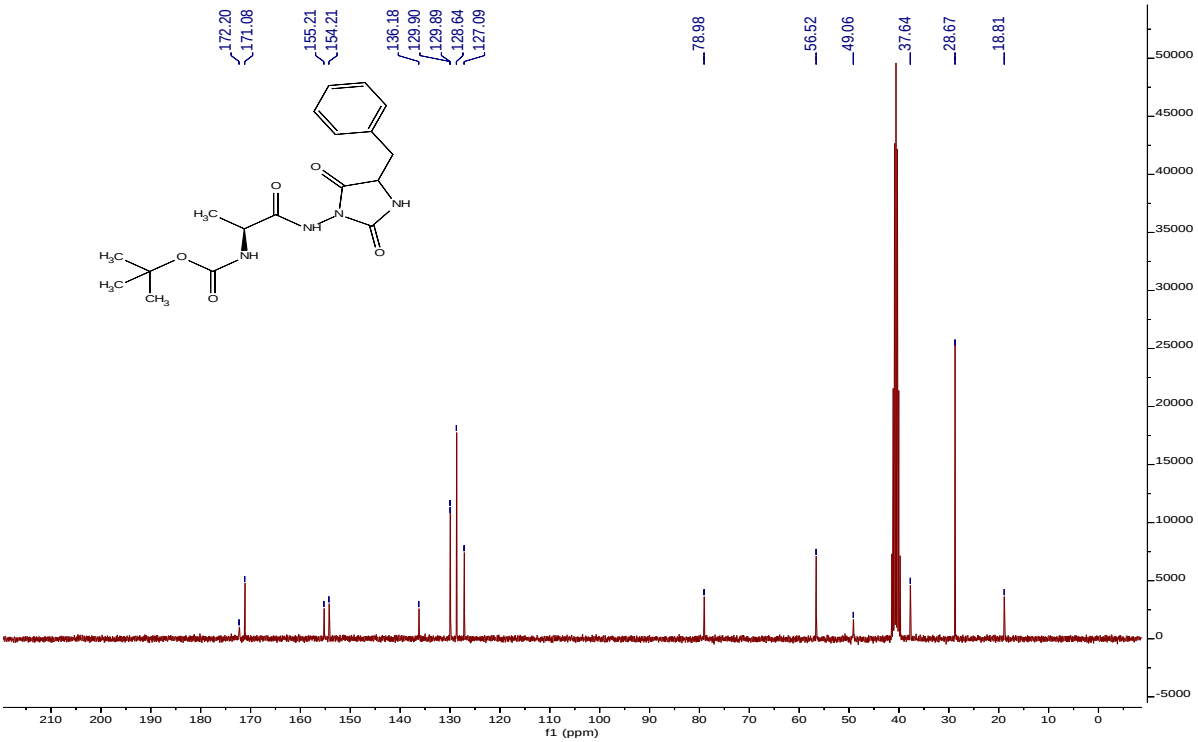
4a *tert*-Butyl ((2*S*)-1-((4-methyl-2,5-dioxoimidazolidin-1-yl)amino)-1-oxopropan-2-yl)carbamate



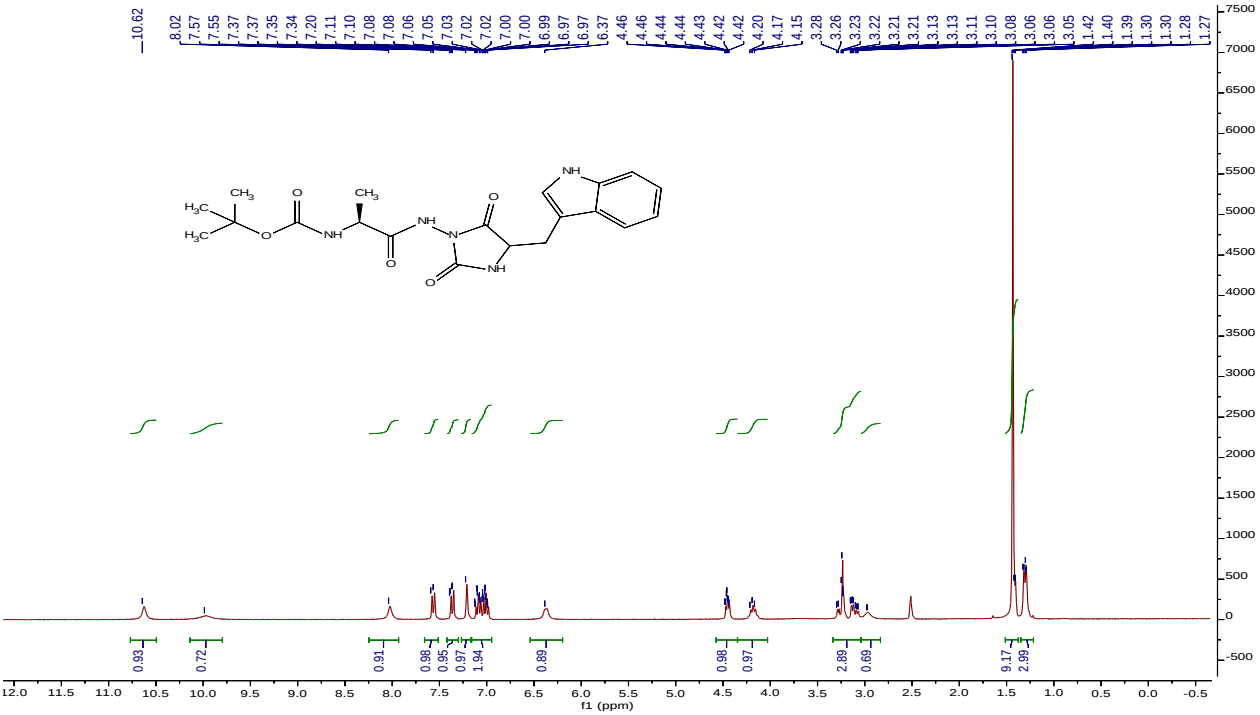


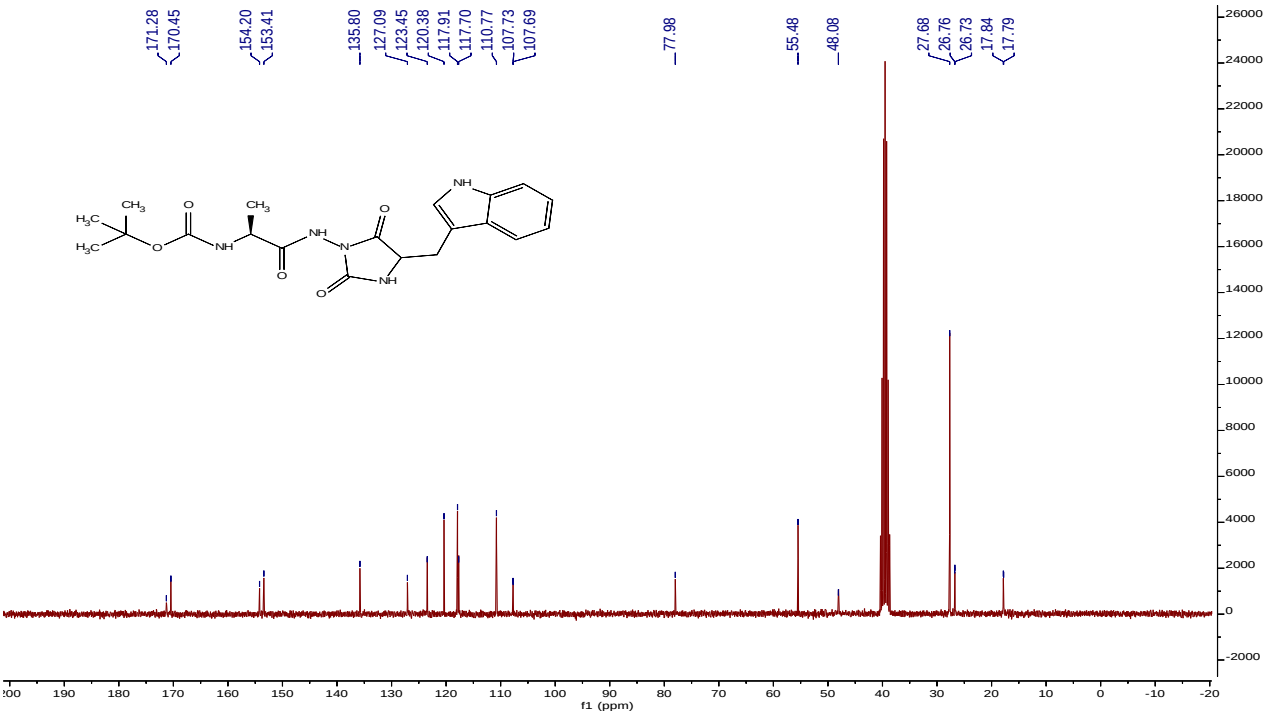
4b *tert*-Butyl ((2*S*)-1-((4-benzyl-2,5-dioxoimidazolidin-1-yl)amino)-1-oxopropan-2-yl)carbamate



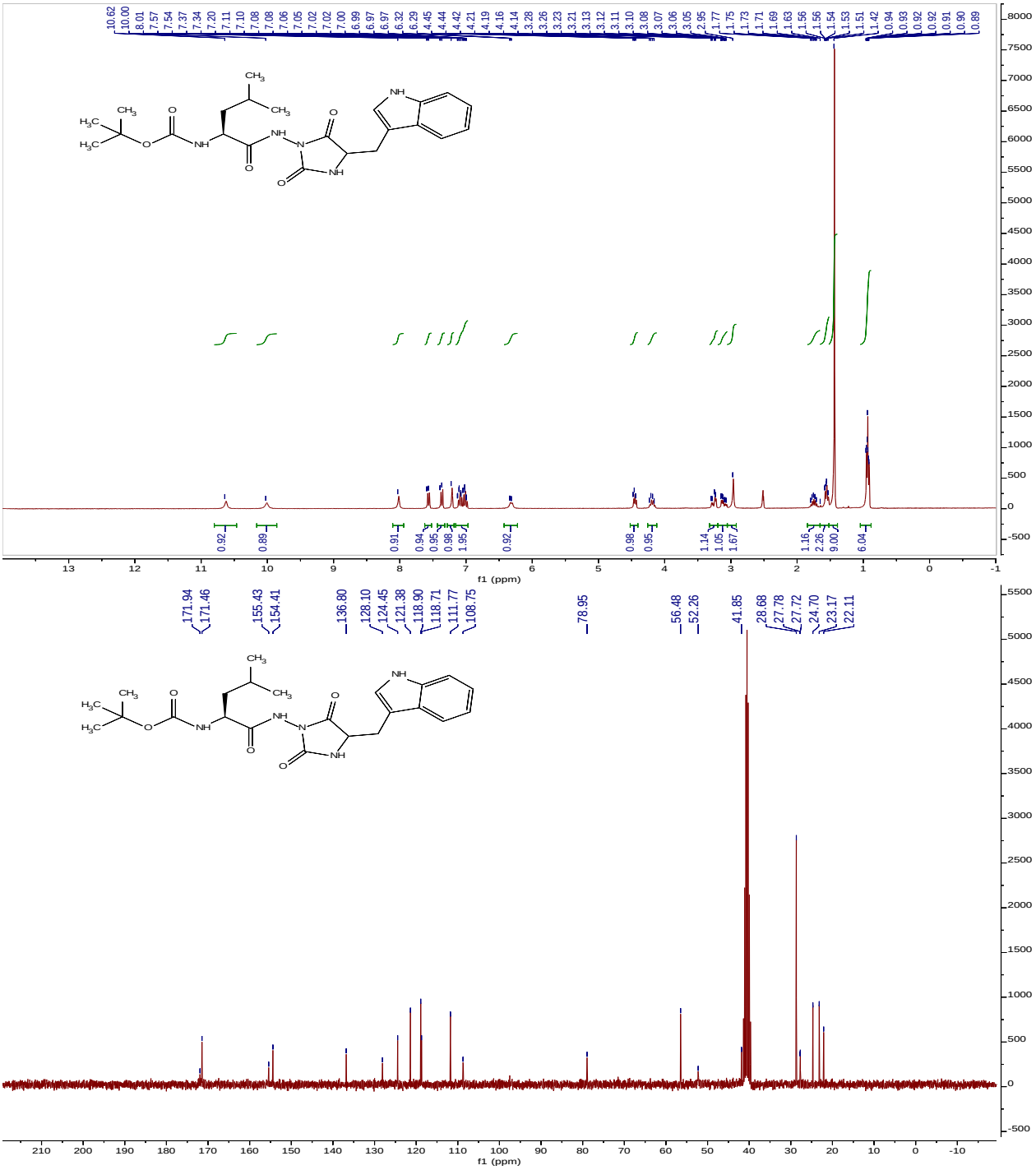


4c *tert*-Butyl ((2*S*)-1-((4-isopropyl-2,5-dioxoimidazolidin-1-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate

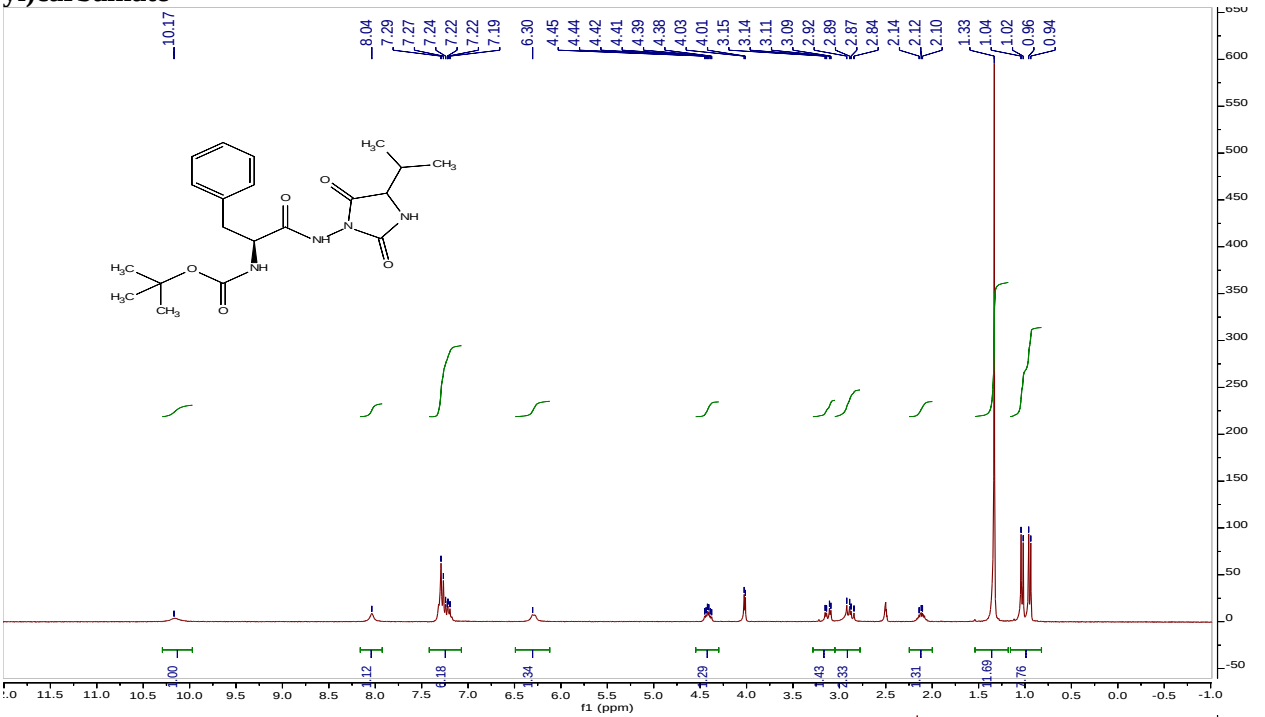


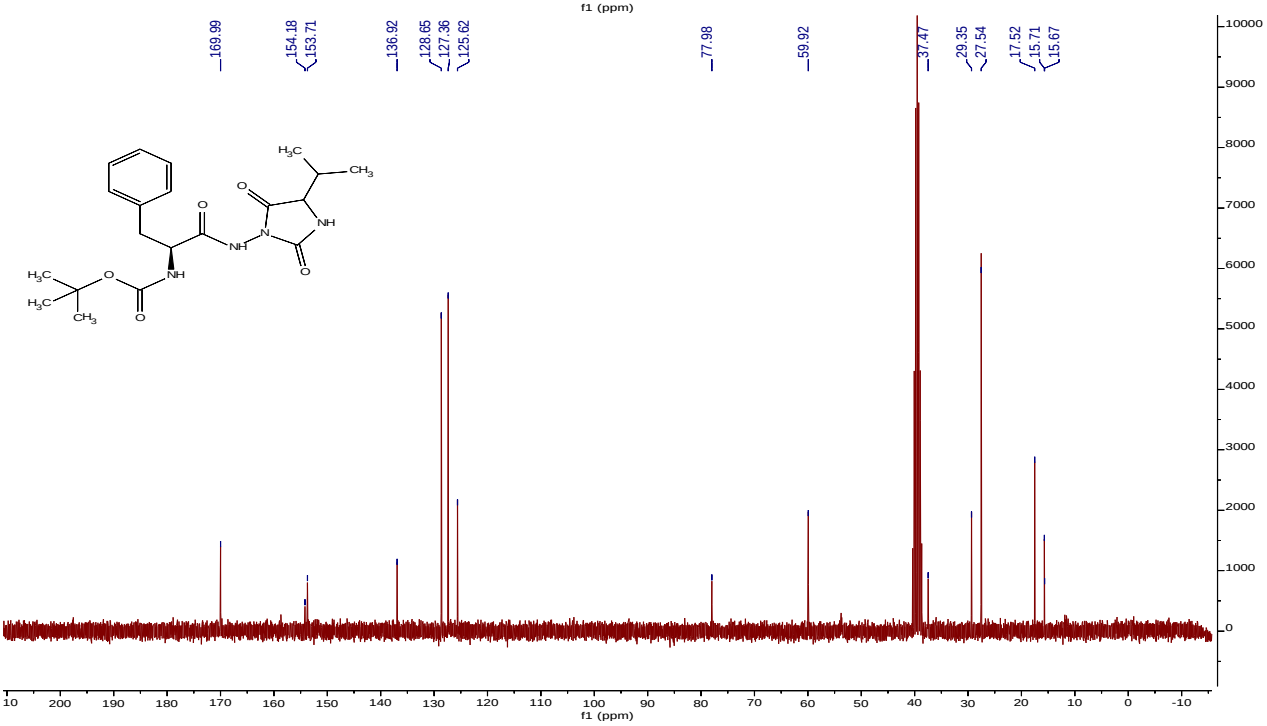


4d *tert*-Butyl ((*S*)-1-(((*S*)-4-((1H-indol-3-yl)methyl)-2,5-dioxoimidazolidin-1-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate

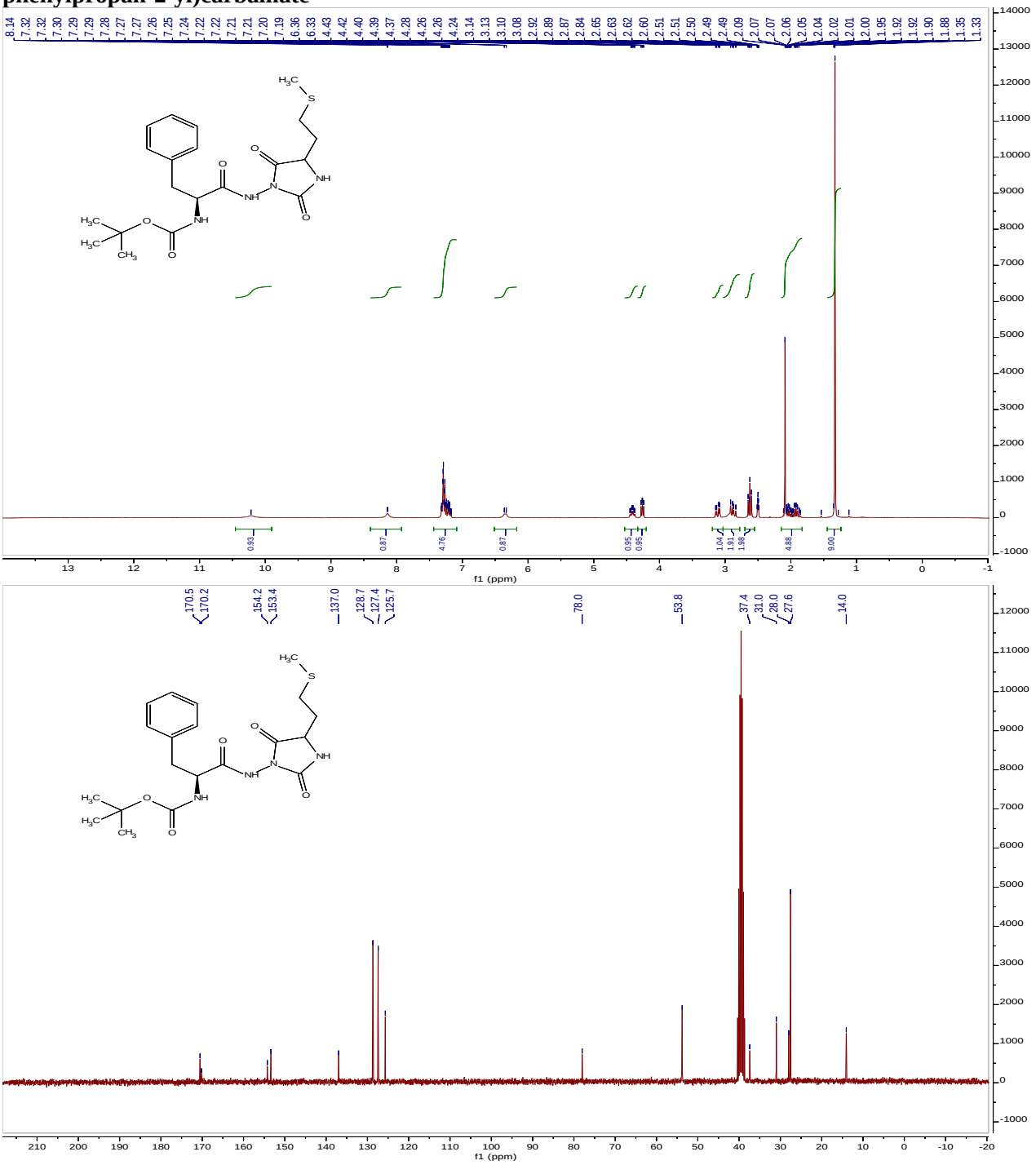


4e *tert*-Butyl ((2*S*)-1-((4-isopropyl-2,5-dioxoimidazolidin-1-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate

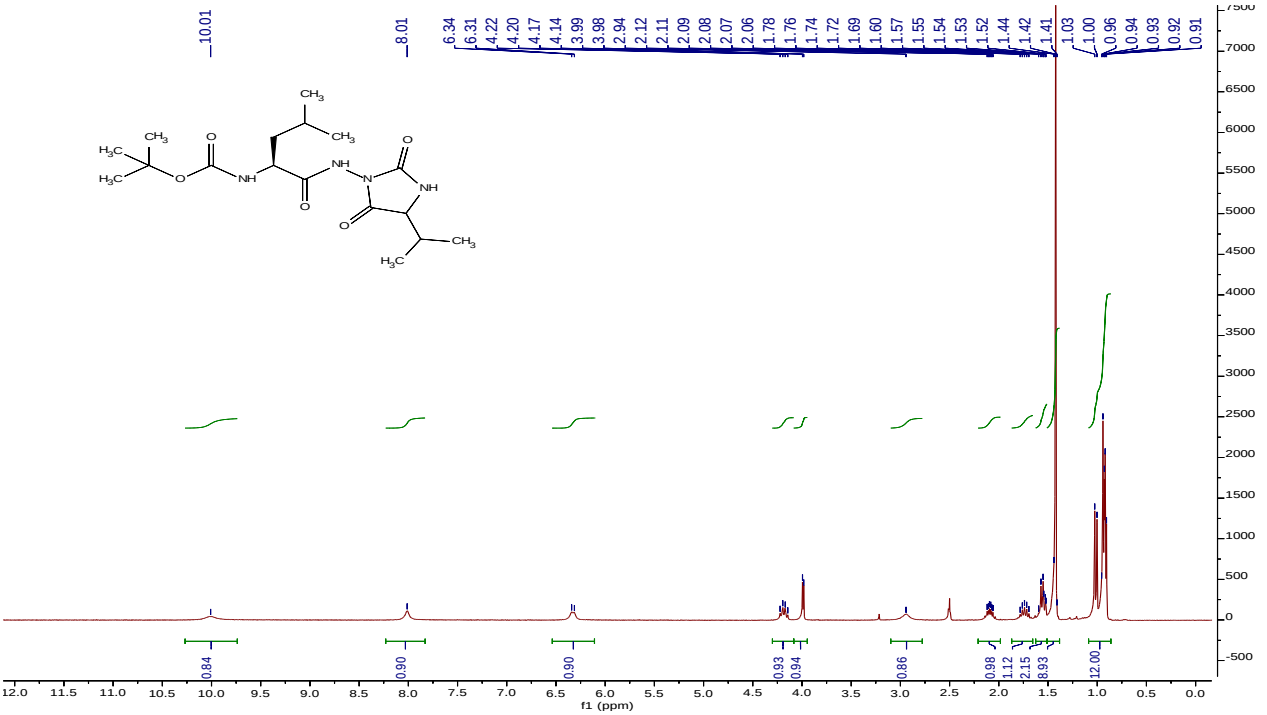


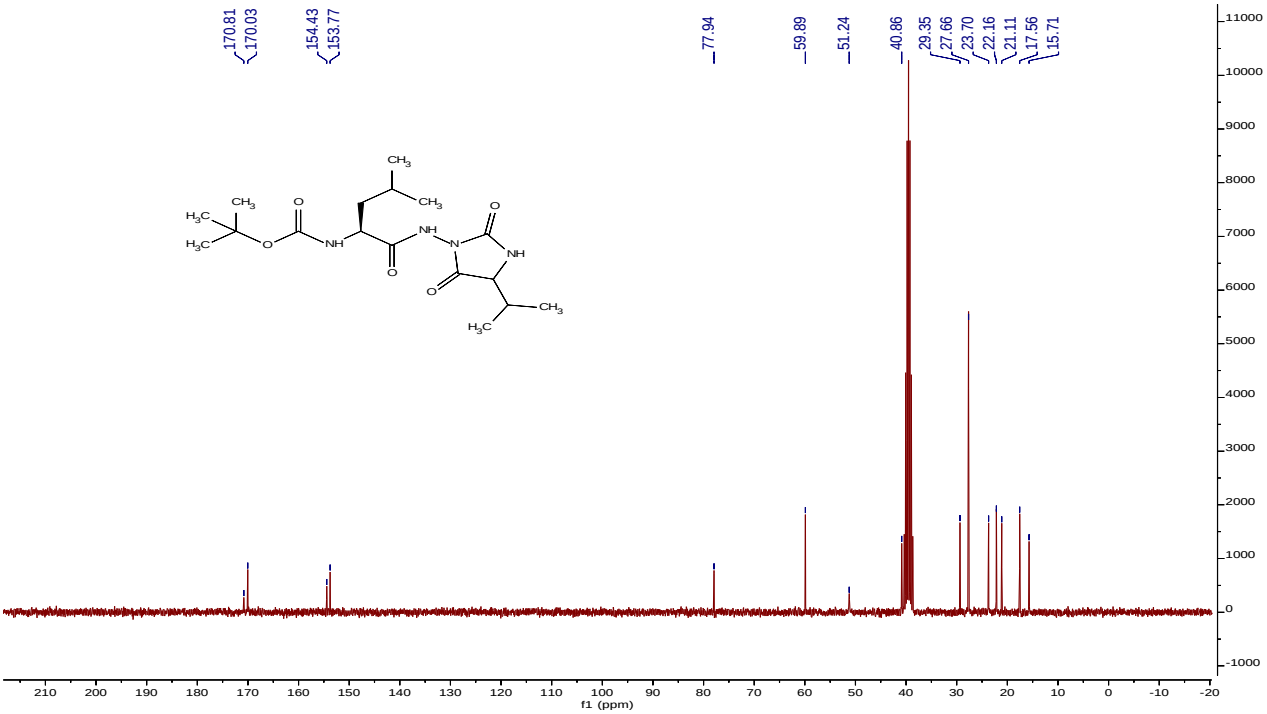


4f *tert*-Butyl ((2*S*)-1-((4-(2-(methylthio)ethyl)-2,5-dioxoimidazolidin-1-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate

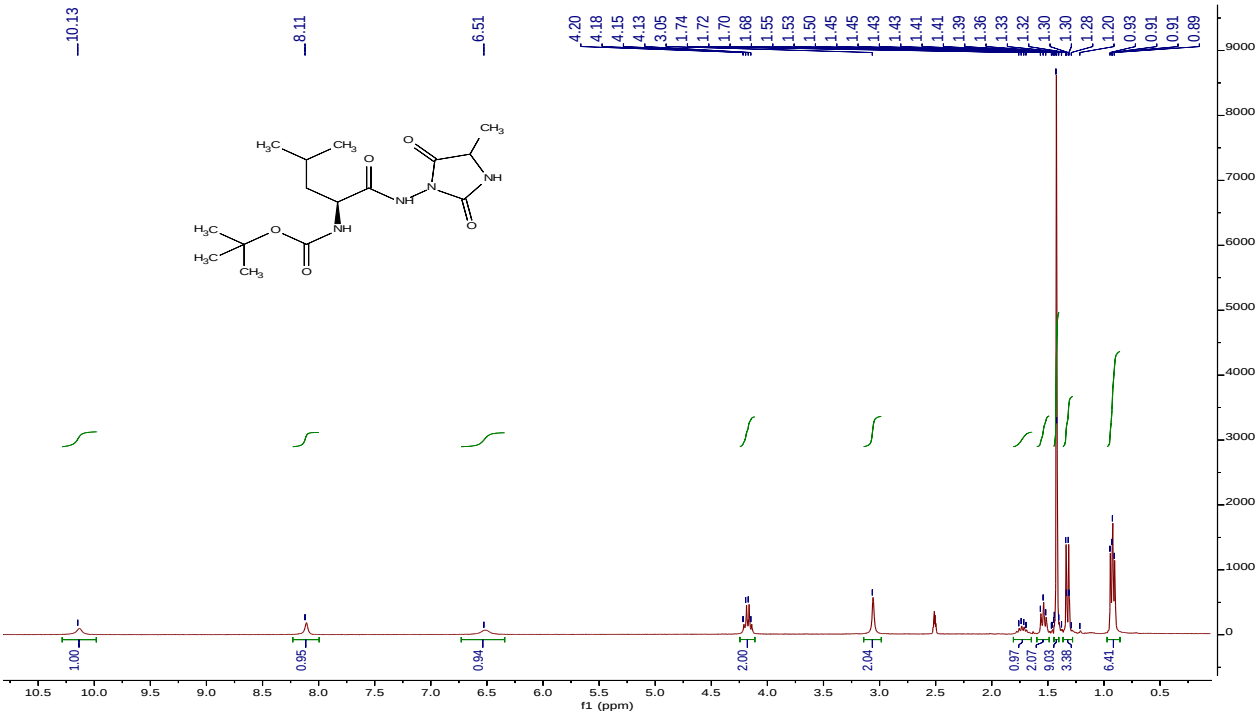


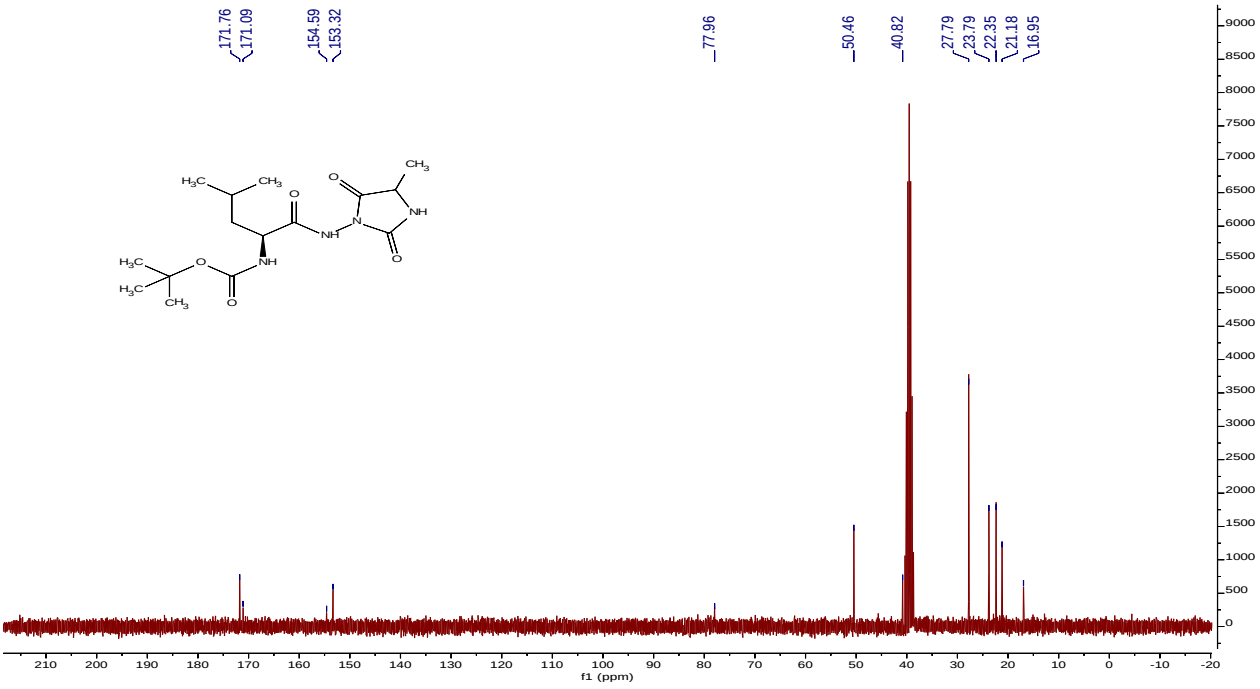
4g (*S*)-2-Amino-*N*-((*S*)-4-isopropyl-2,5-dioxoimidazolidin-1-yl)-4-methylpentanamide



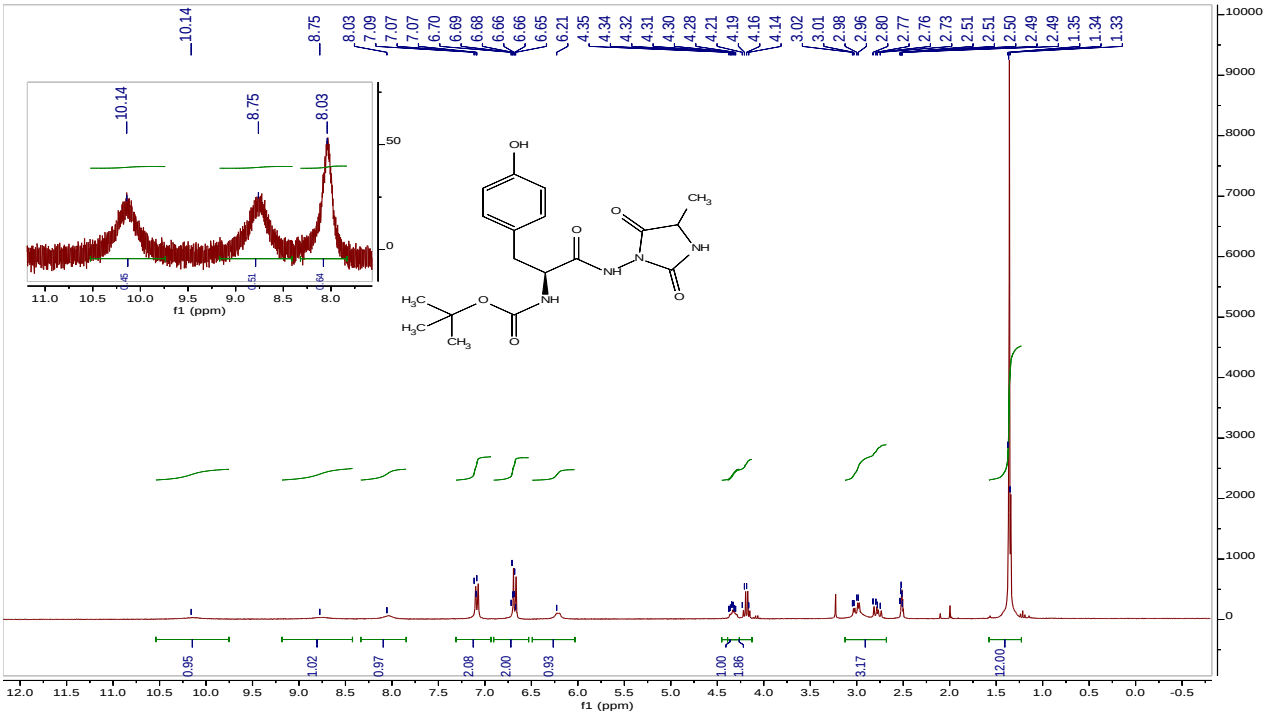


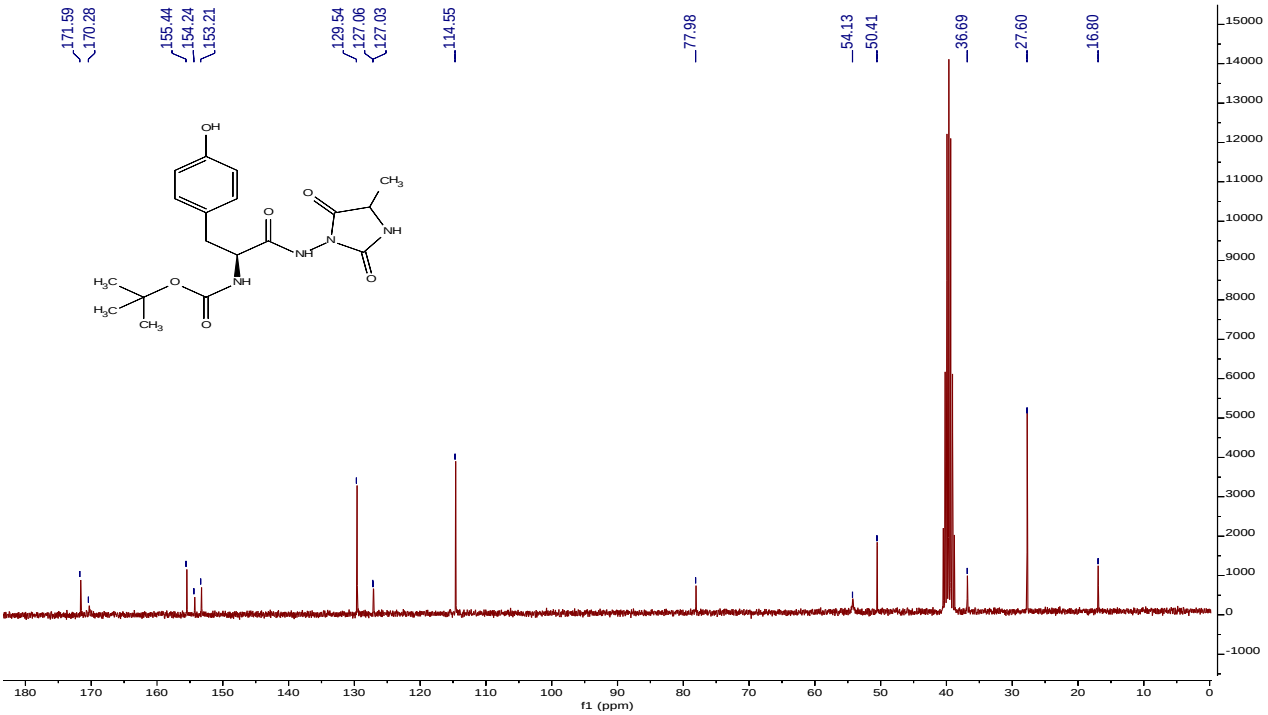
4h *tert*-Butyl ((2*S*)-4-methyl-1-((4-methyl-2,5-dioxoimidazolidin-1-yl)amino)-1-oxopentan-2-yl)carbamate



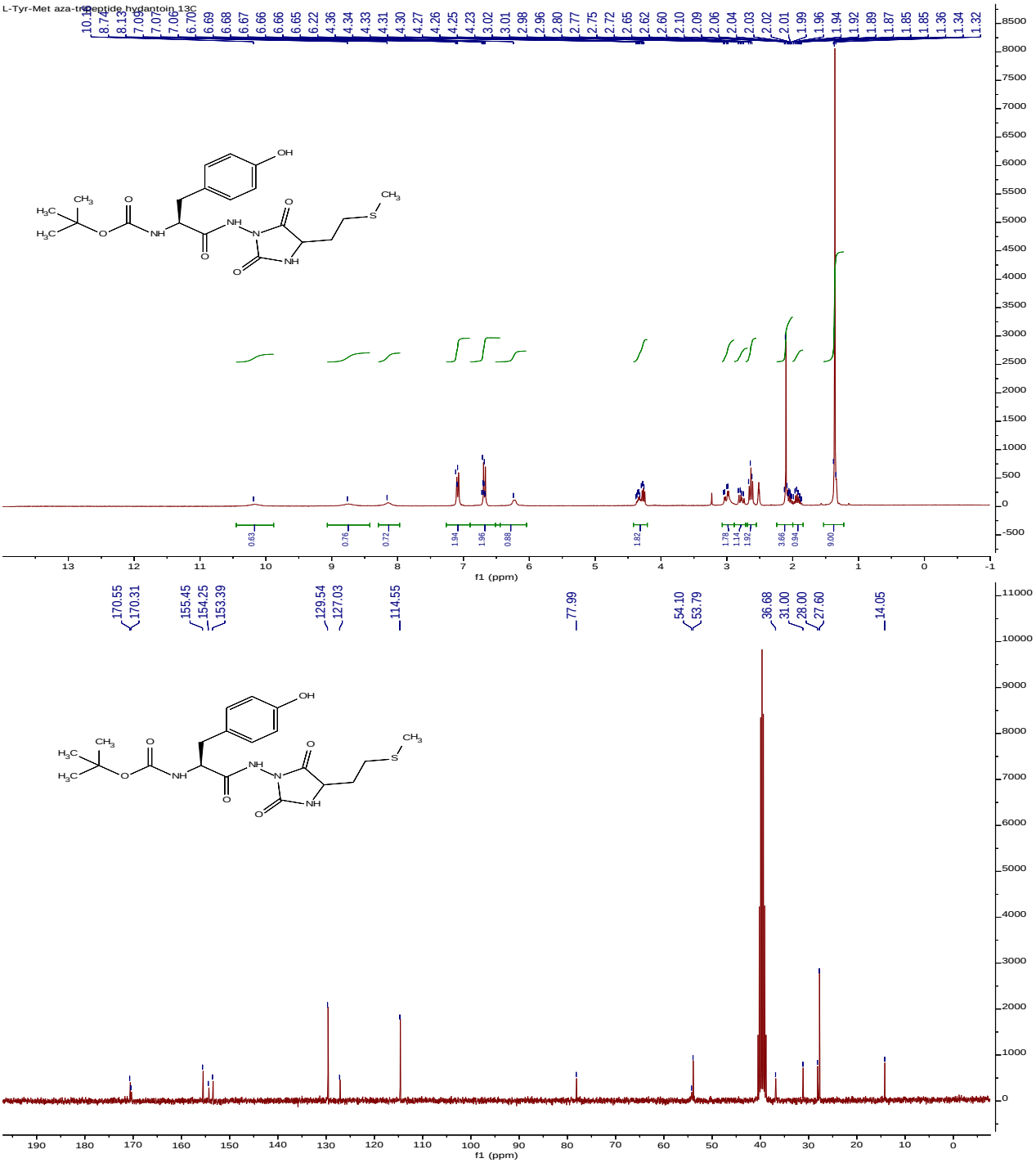


4i *tert*-Butyl ((2*S*)-3-(4-hydroxyphenyl)-1-((4-methyl-2,5-dioxoimidazolidin-1-yl)amino)-1-oxopropan-2-yl)carbamate

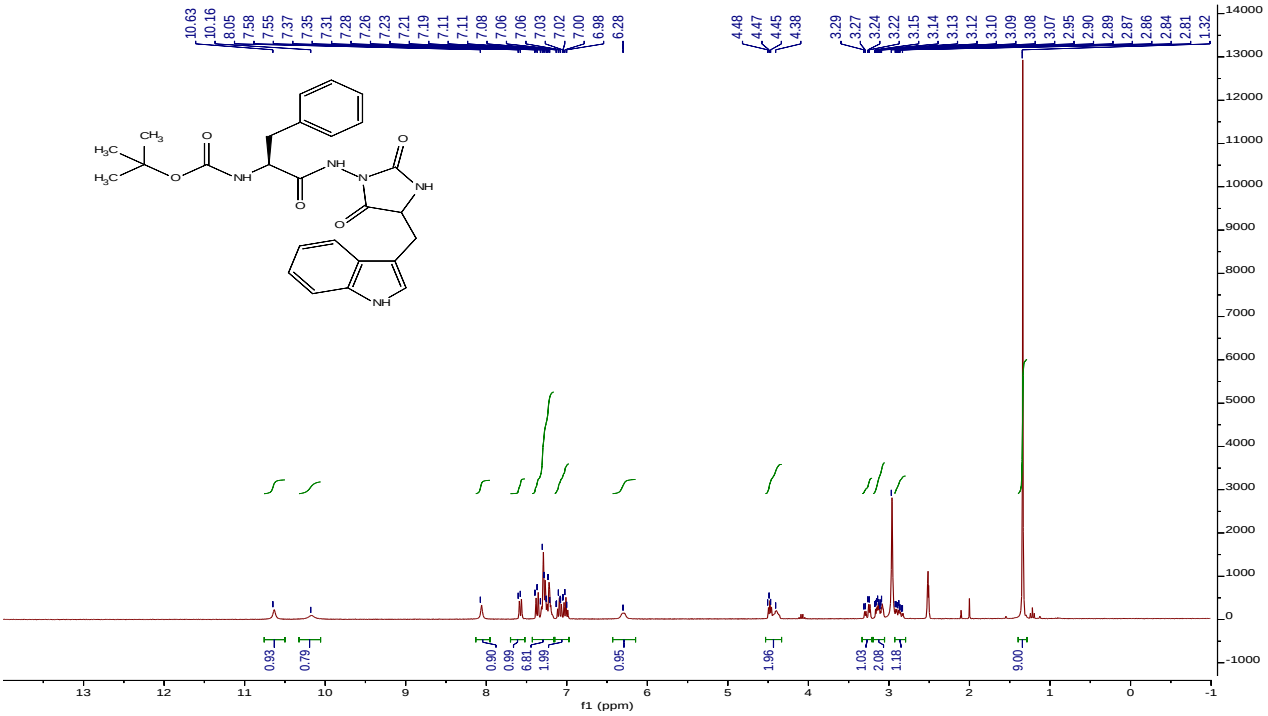


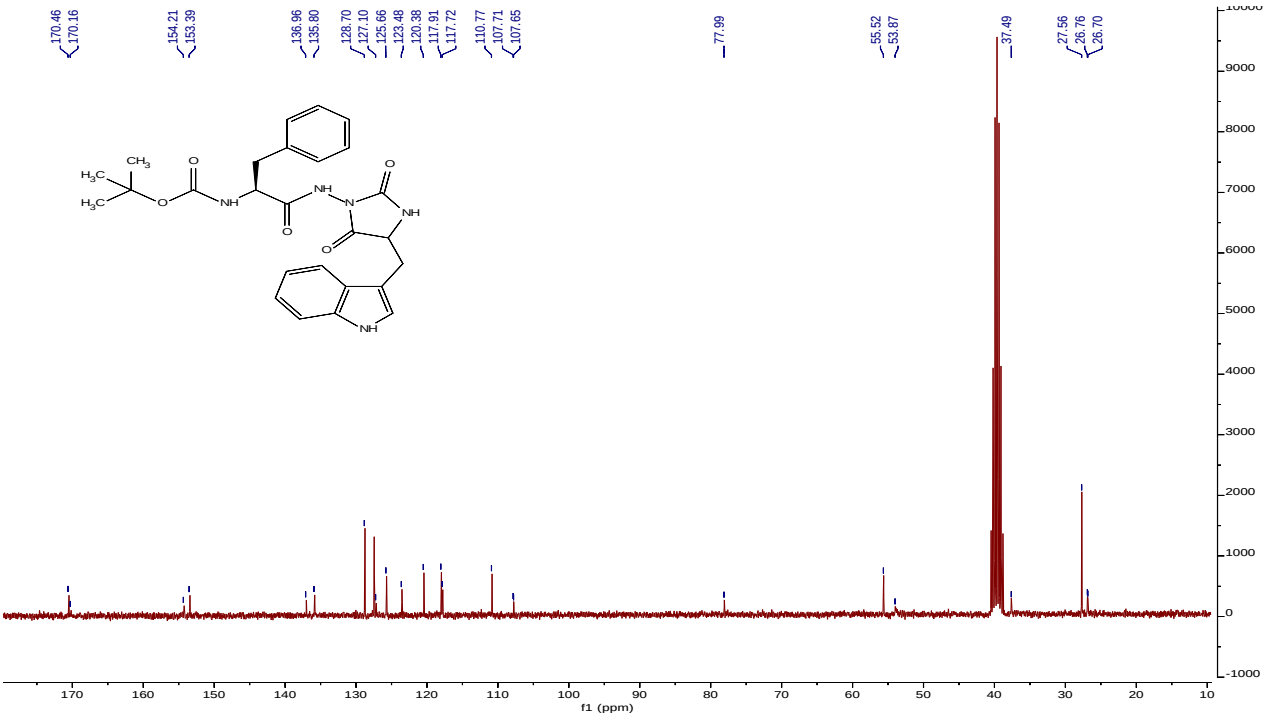


4j *tert*-Butyl ((2*S*)-3-(4-hydroxyphenyl)-1-((4-(2-(methylthio)ethyl)-2,5-dioxoimidazolidin-1-yl)amino)-1-oxopropan-2-yl)carbamate

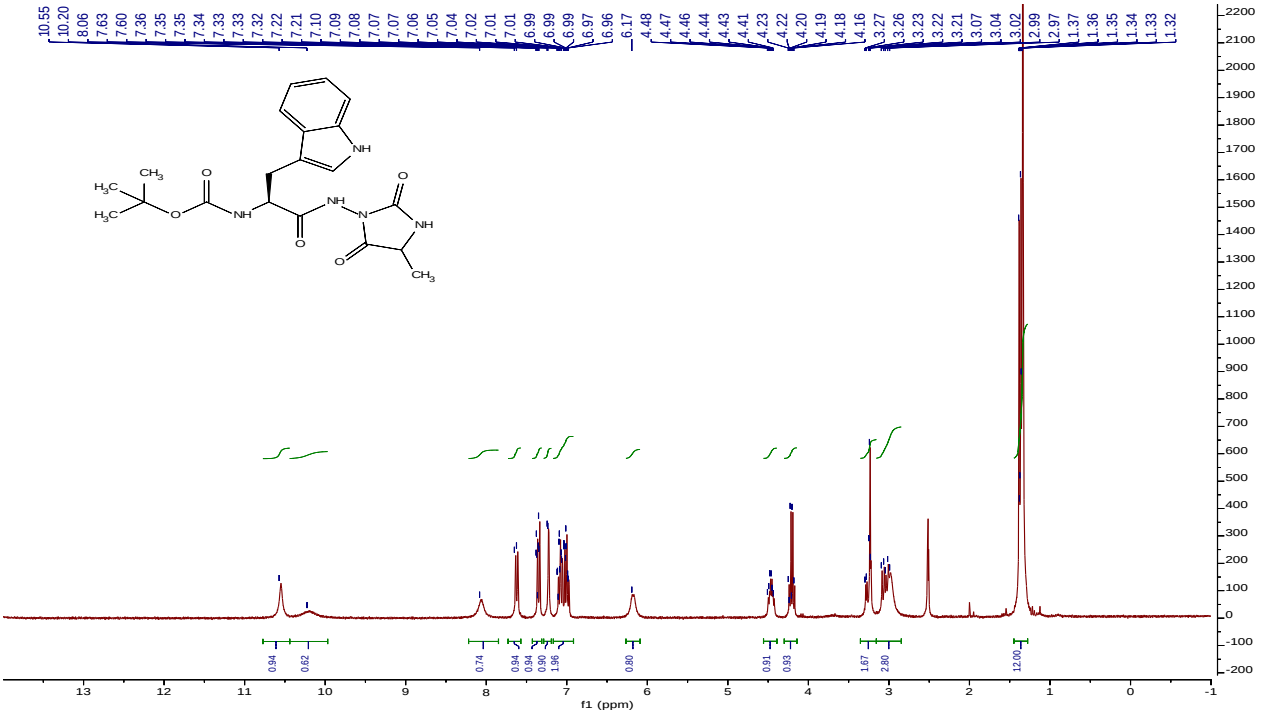


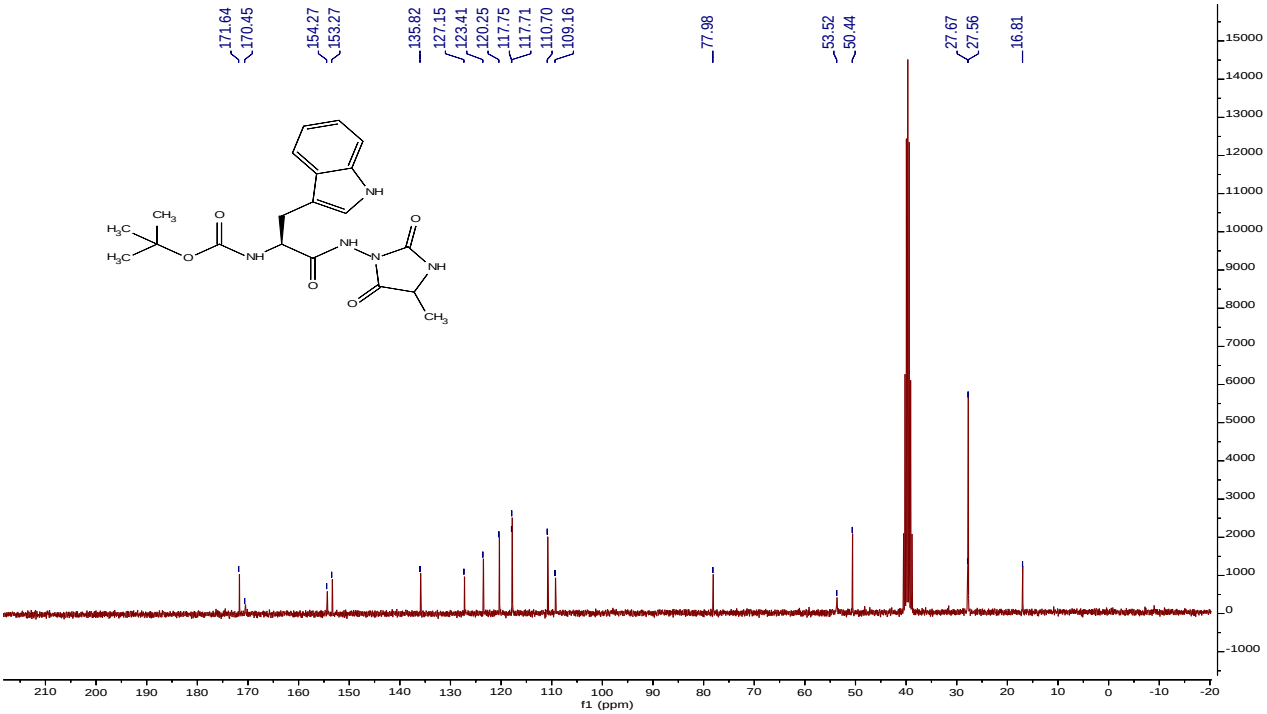
4k *tert*-Butyl ((2*S*)-1-((4-((1H-indol-3-yl)methyl)-2,5-dioxoimidazolidin-1-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate



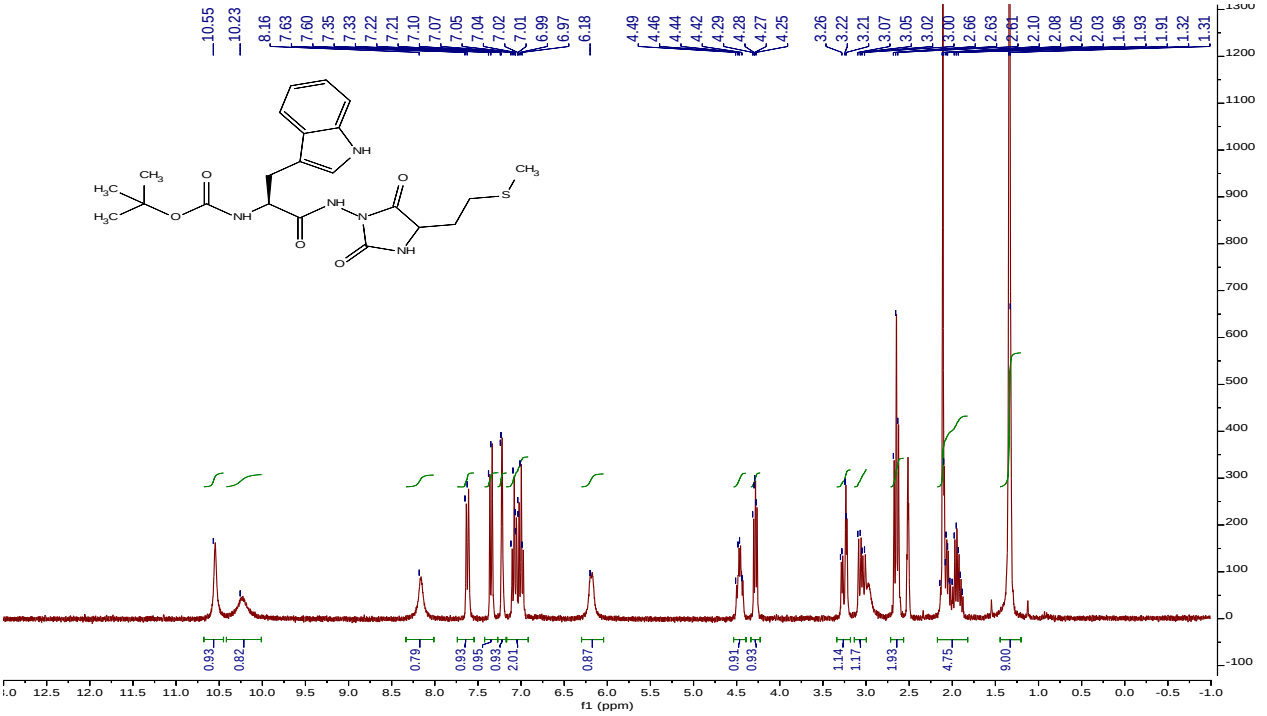


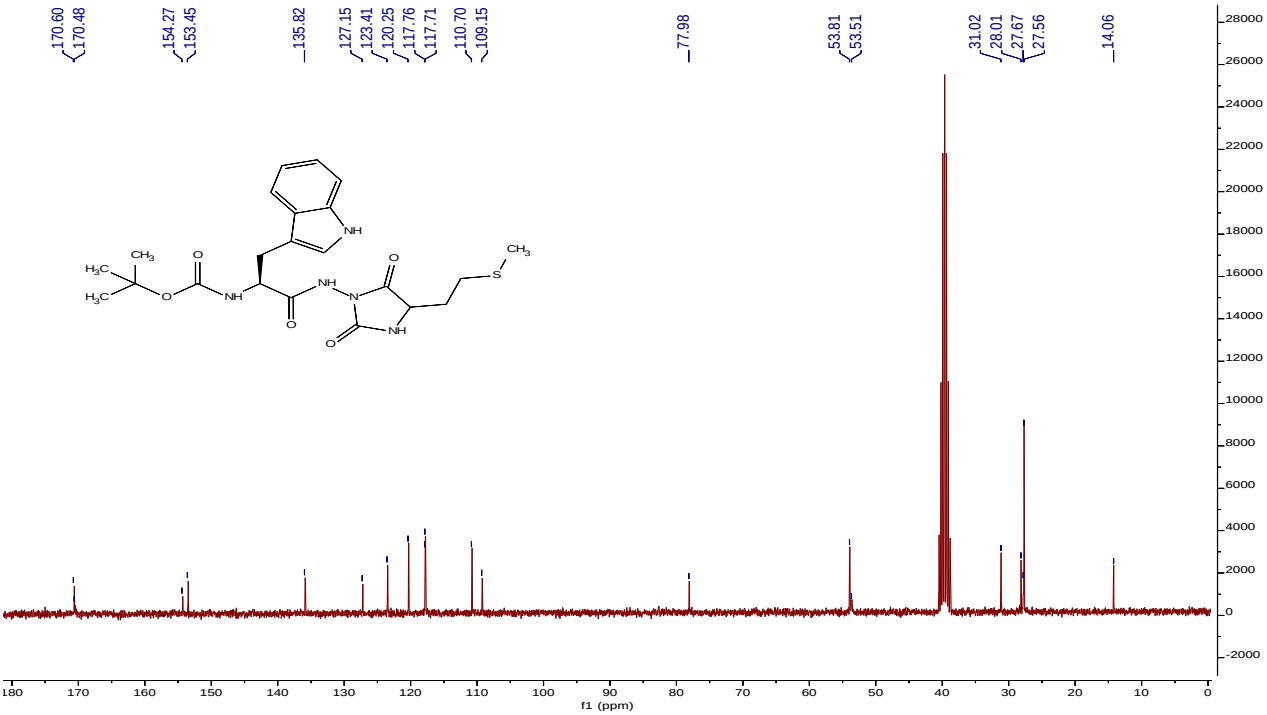
4l *tert*-Butyl ((2*S*)-3-(1H-indol-3-yl)-1-((4-methyl-2,5-dioxoimidazolidin-1-yl)amino)-1-oxopropan-2-yl)carbamate



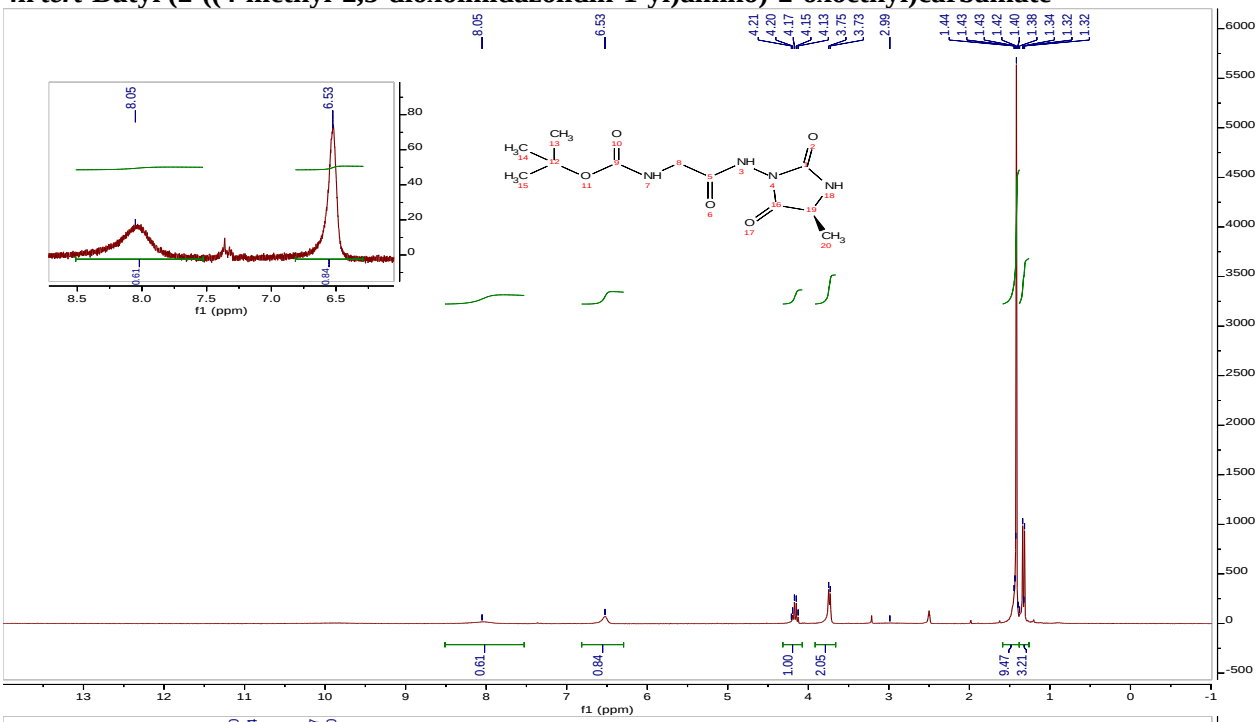


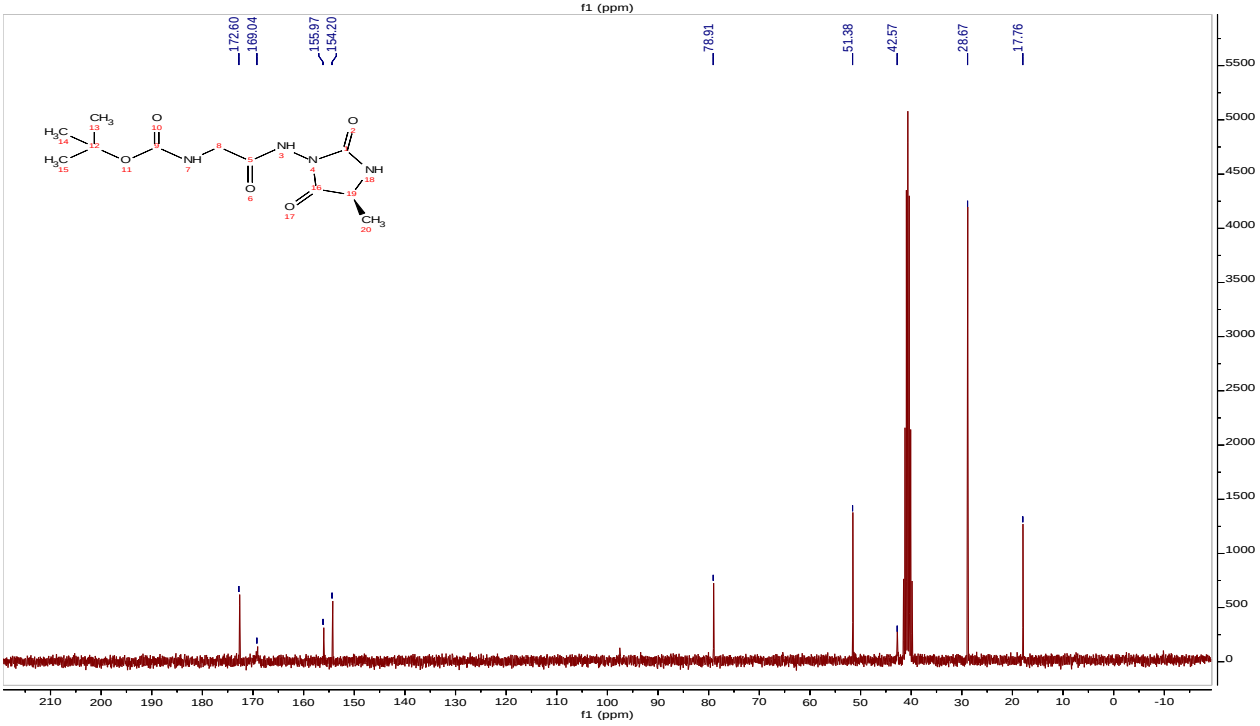
4m *tert*-Butyl ((2*S*)-3-(1H-indol-3-yl)-1-((4-(2-(methylthio)ethyl)-2,5-dioxoimidazolidin-1-yl)amino)-1-oxopropan-2-yl)carbamate



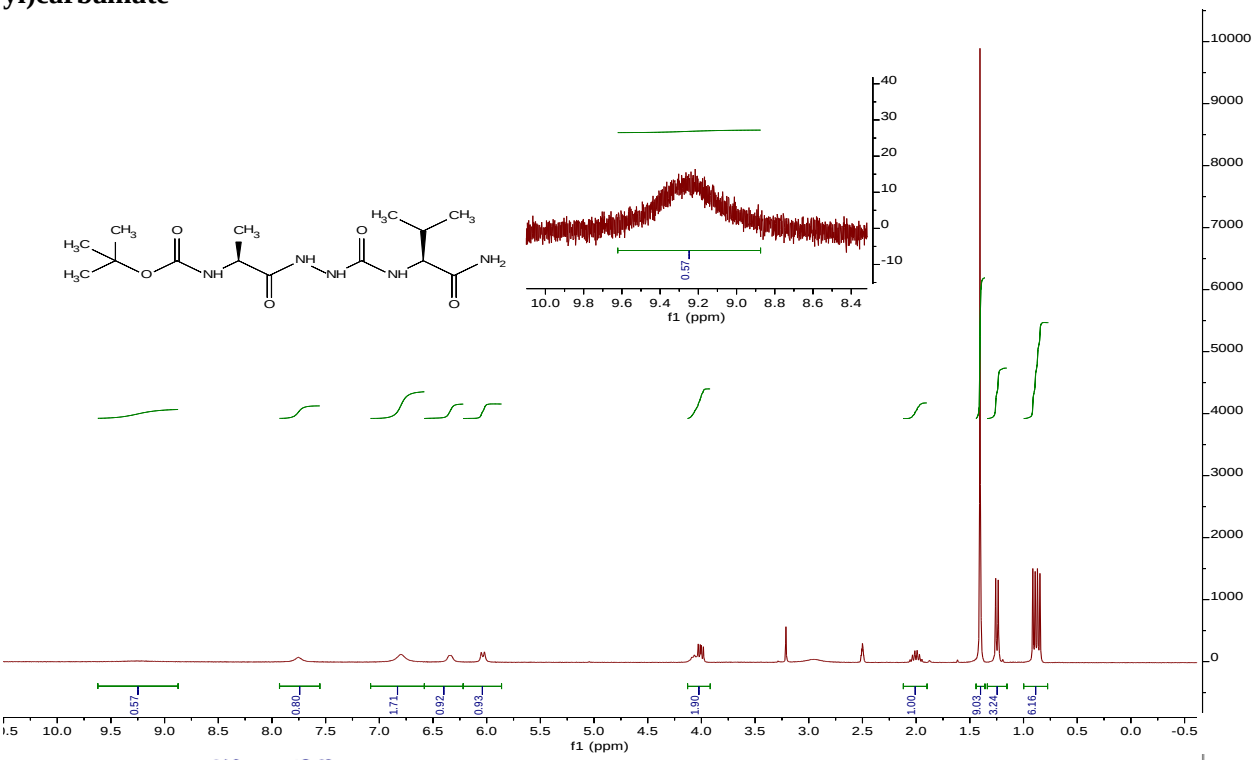


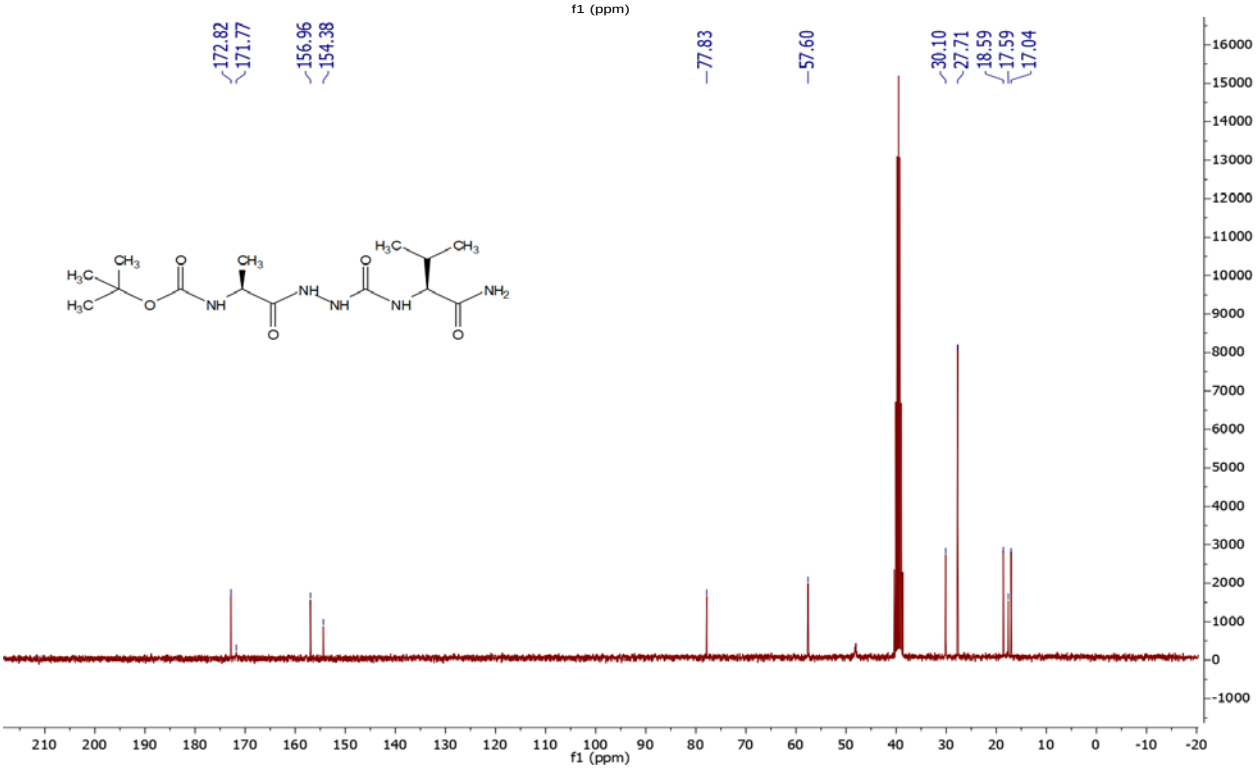
4n *tert*-Butyl (2-((4-methyl-2,5-dioxoimidazolidin-1-yl)amino)-2-oxoethyl)carbamate



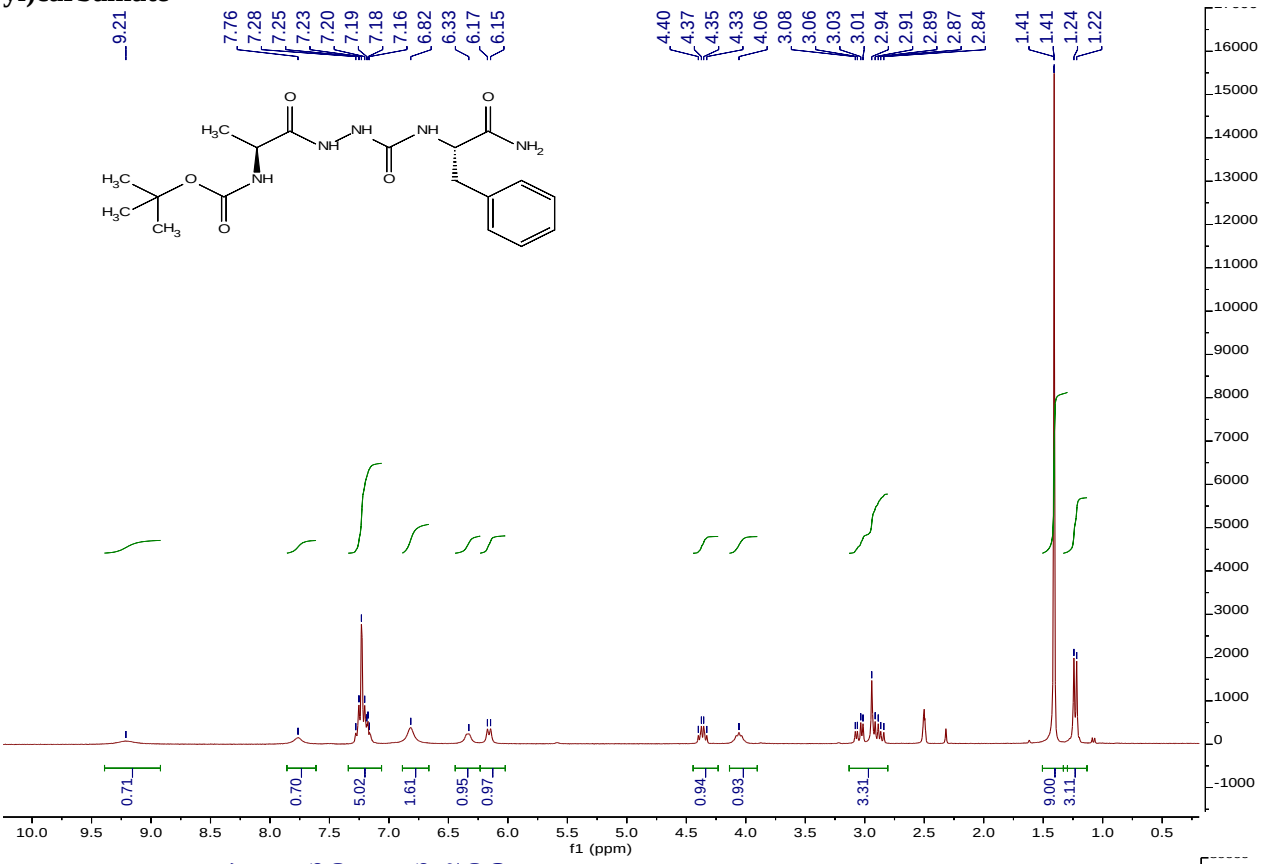


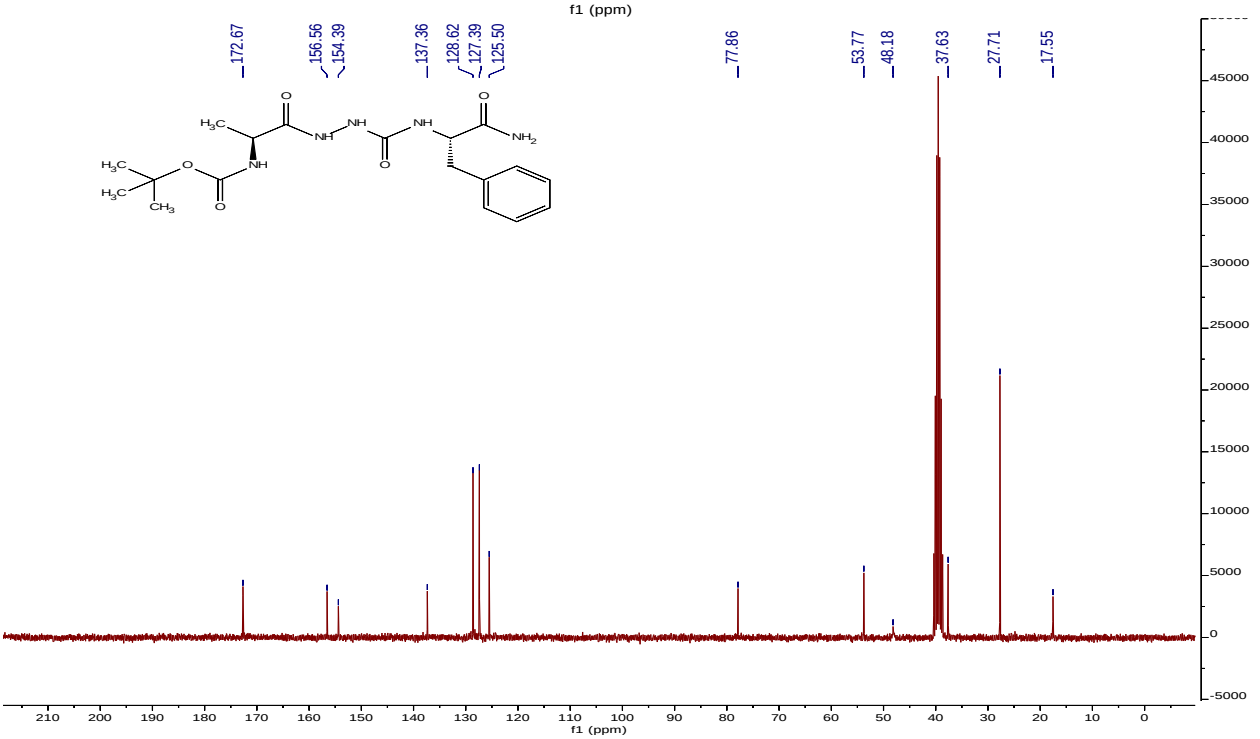
4o *tert*-Butyl (*S*,*S*)-(1-(2-((2-amino-2-oxo-1-(2-propyl)ethyl)carbamoyl)hydrazinyl)-1-oxopropan-2-yl)carbamate



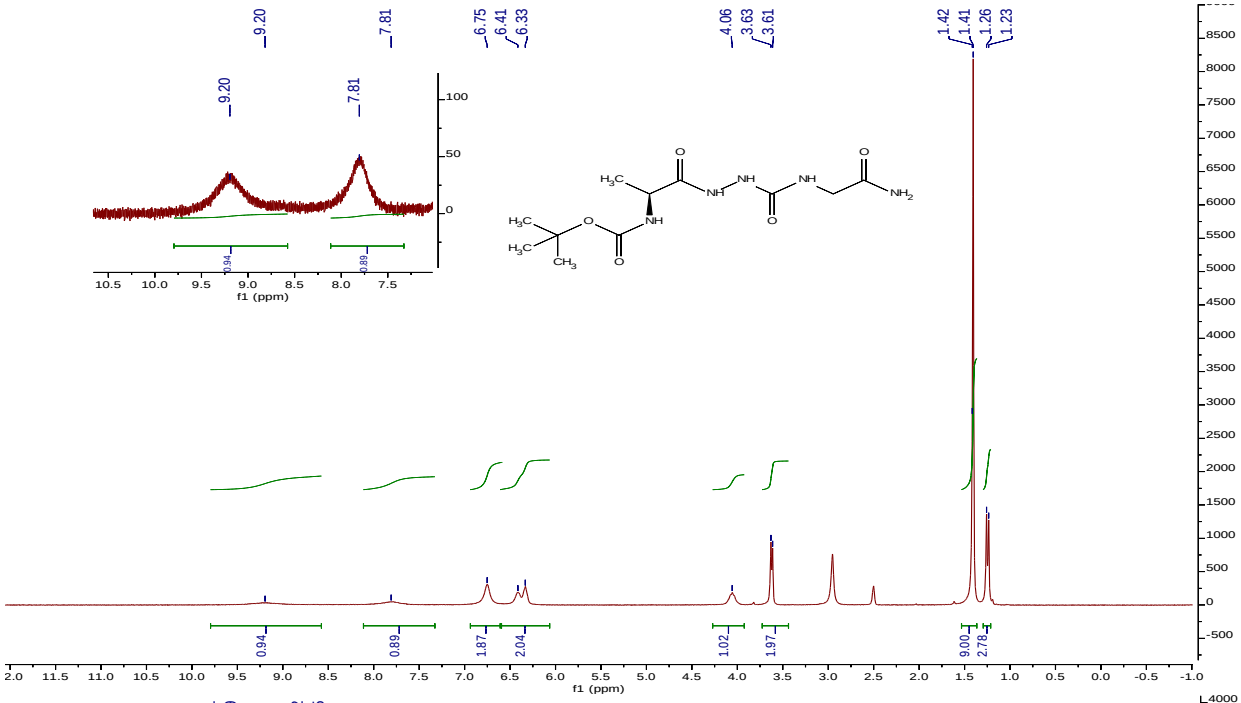


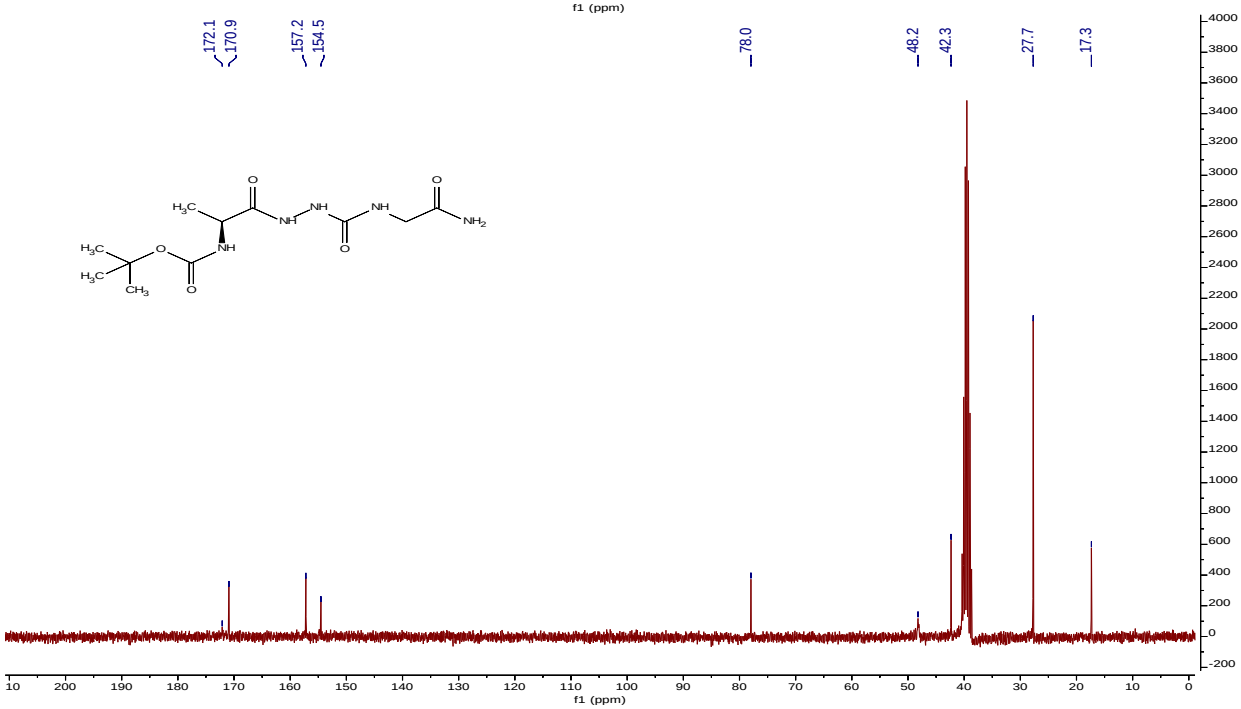
4p *tert*-Butyl (*S,S*)-(1-(2-(2-amino-1-benzyl-2-oxoethyl-carbamoyl)hydrazinyl)-1-oxopropan-2-yl)carbamate



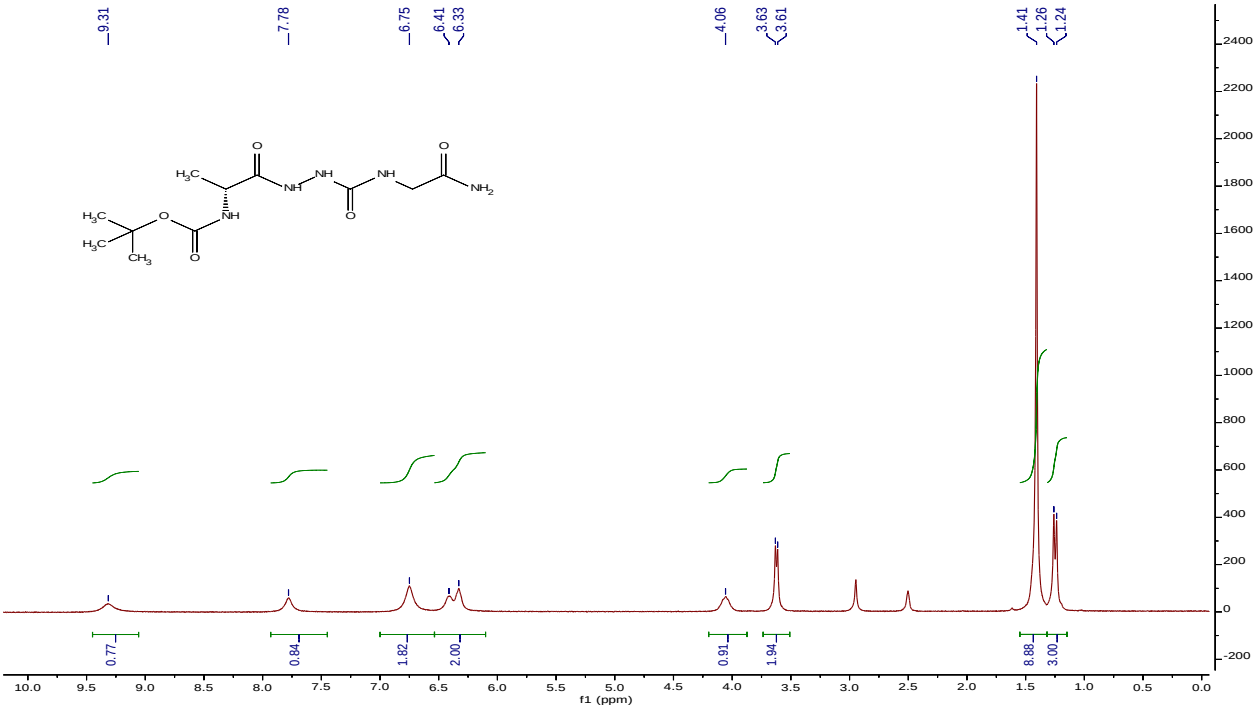


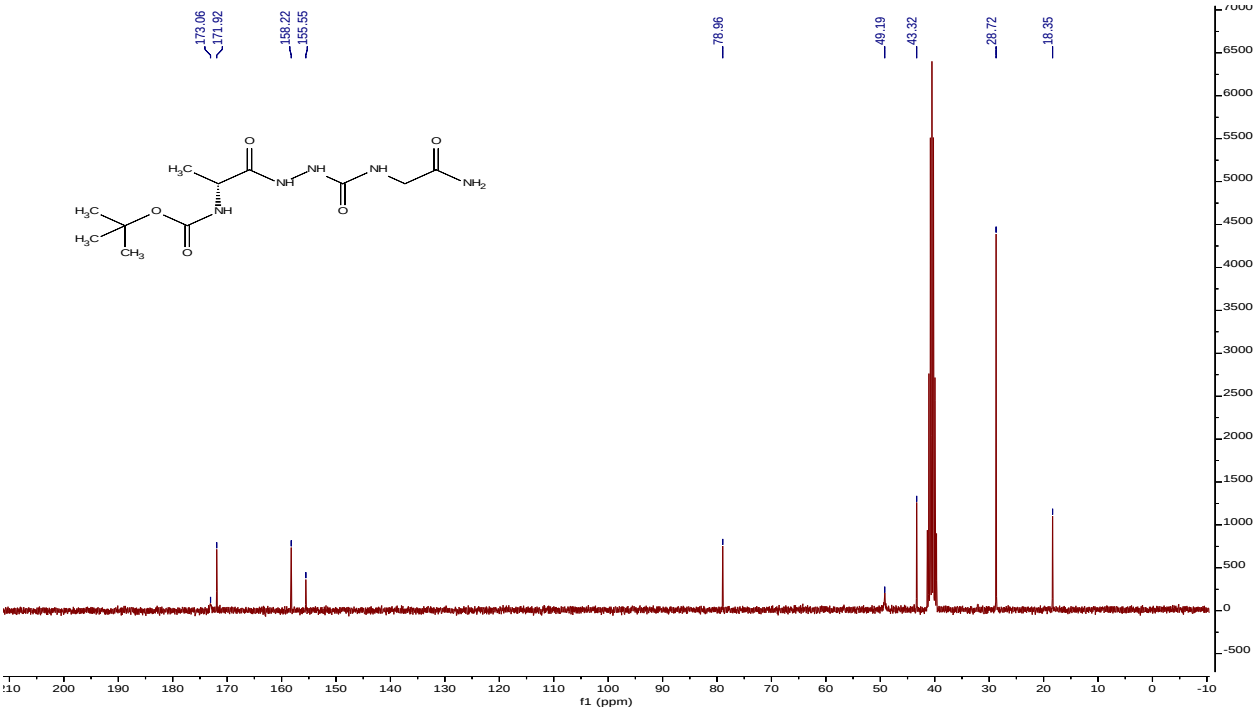
4q *tert*-Butyl (*S*)-(1-(2-((2-amino-2-oxoethyl)carbamoyl)hydrazinyl)-1-oxopropan-2-yl)carbamate



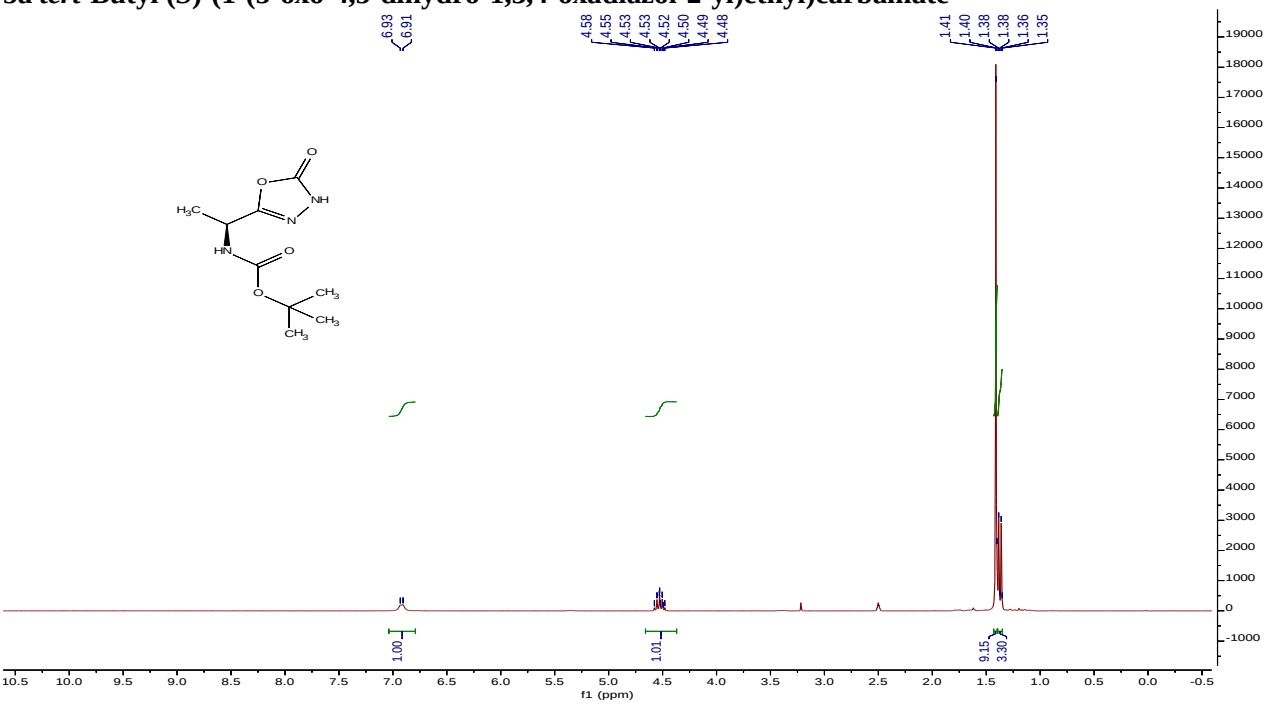


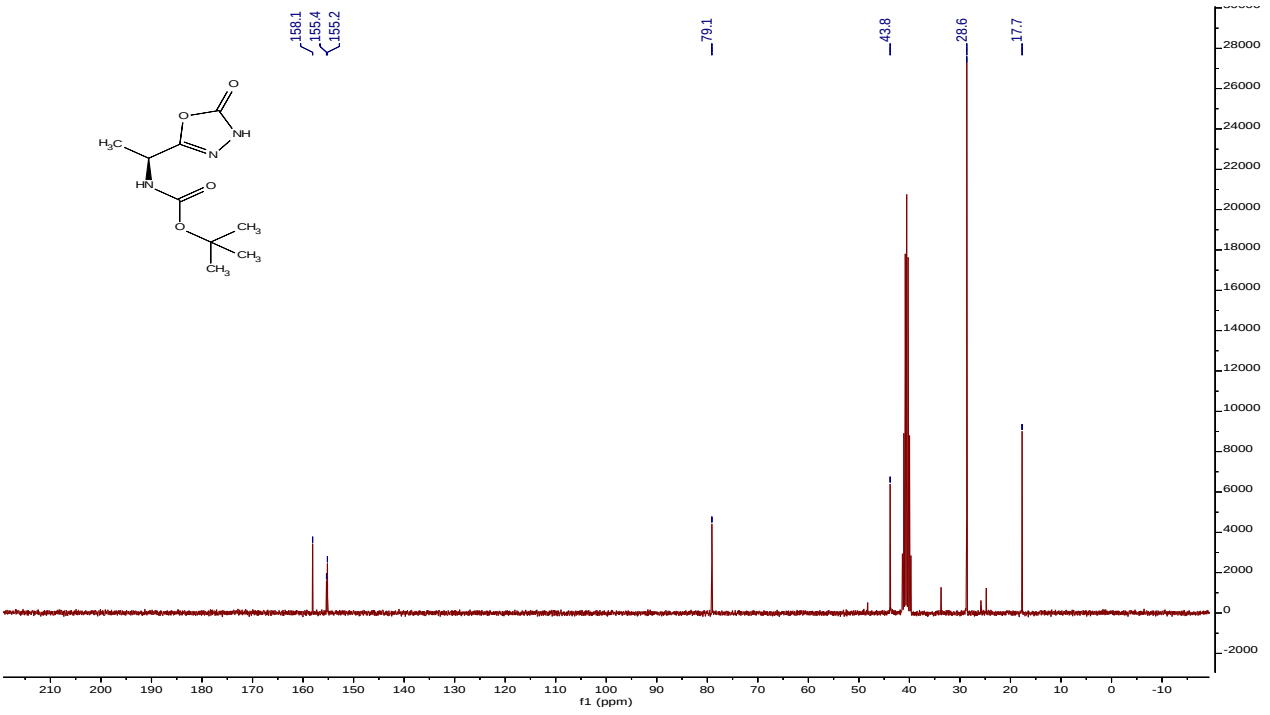
4r *tert*-Butyl (*R*)-(1-(2-((2-amino-2-oxoethyl)carbamoyl)hydrazinyl)-1-oxopropan-2-yl)carbamate



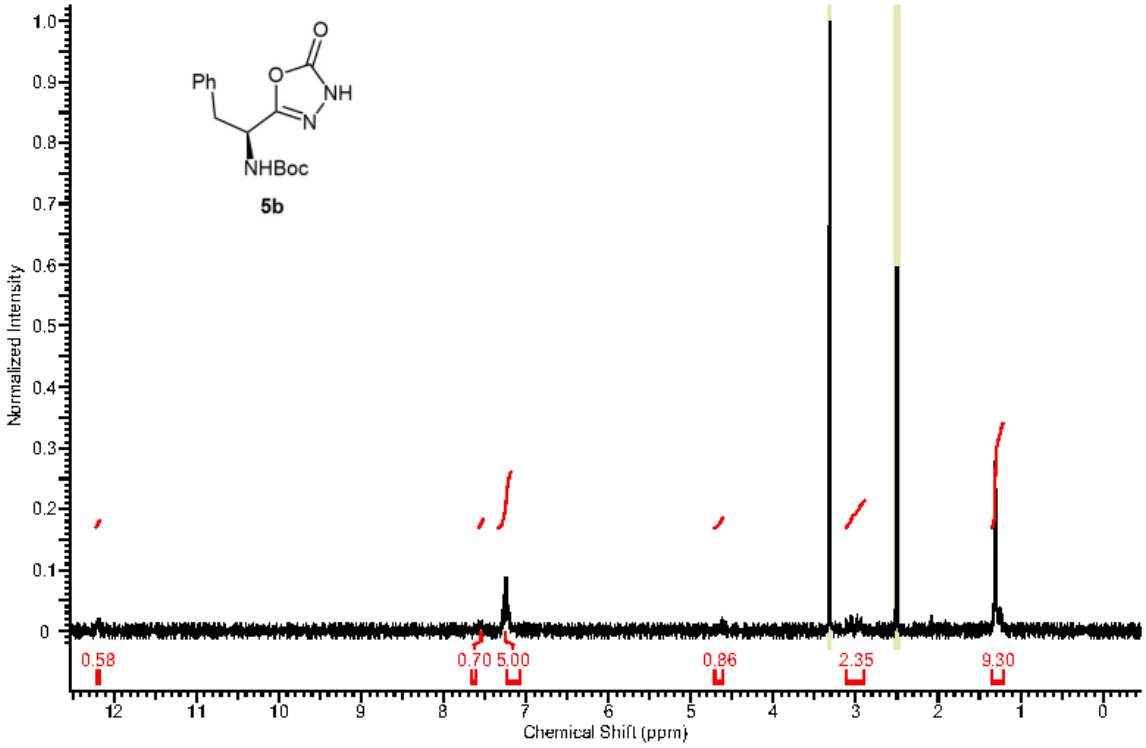


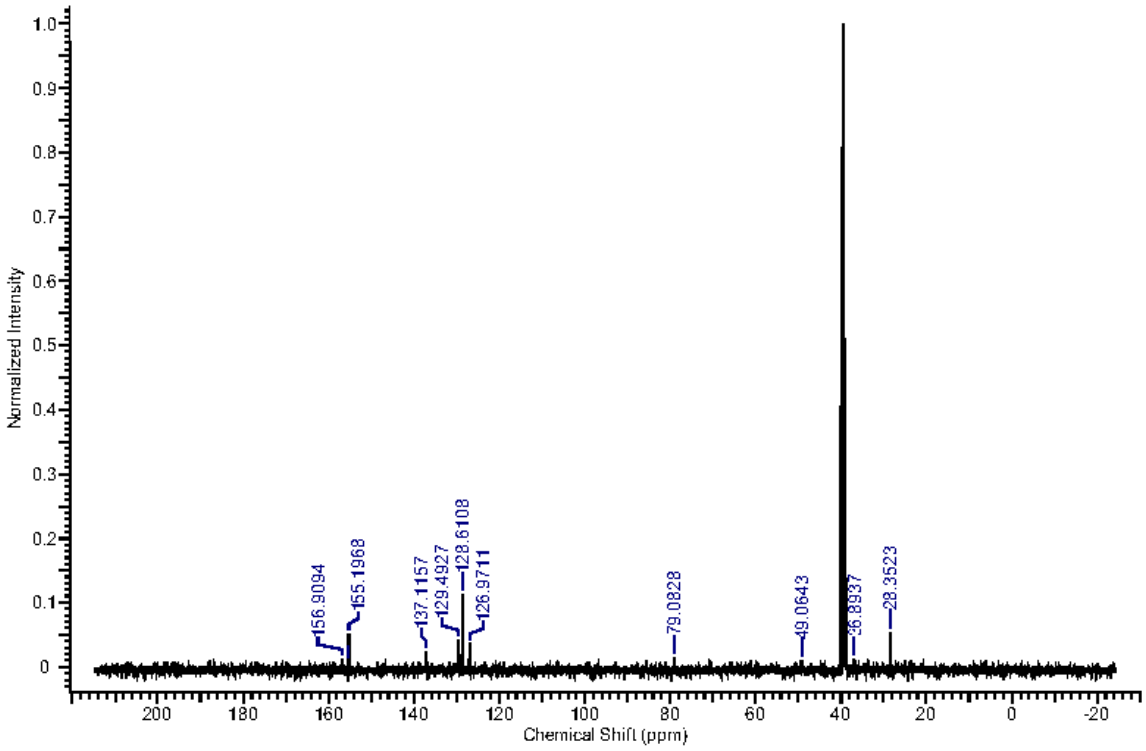
5a *tert*-Butyl (*S*)-(1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)ethyl)carbamate



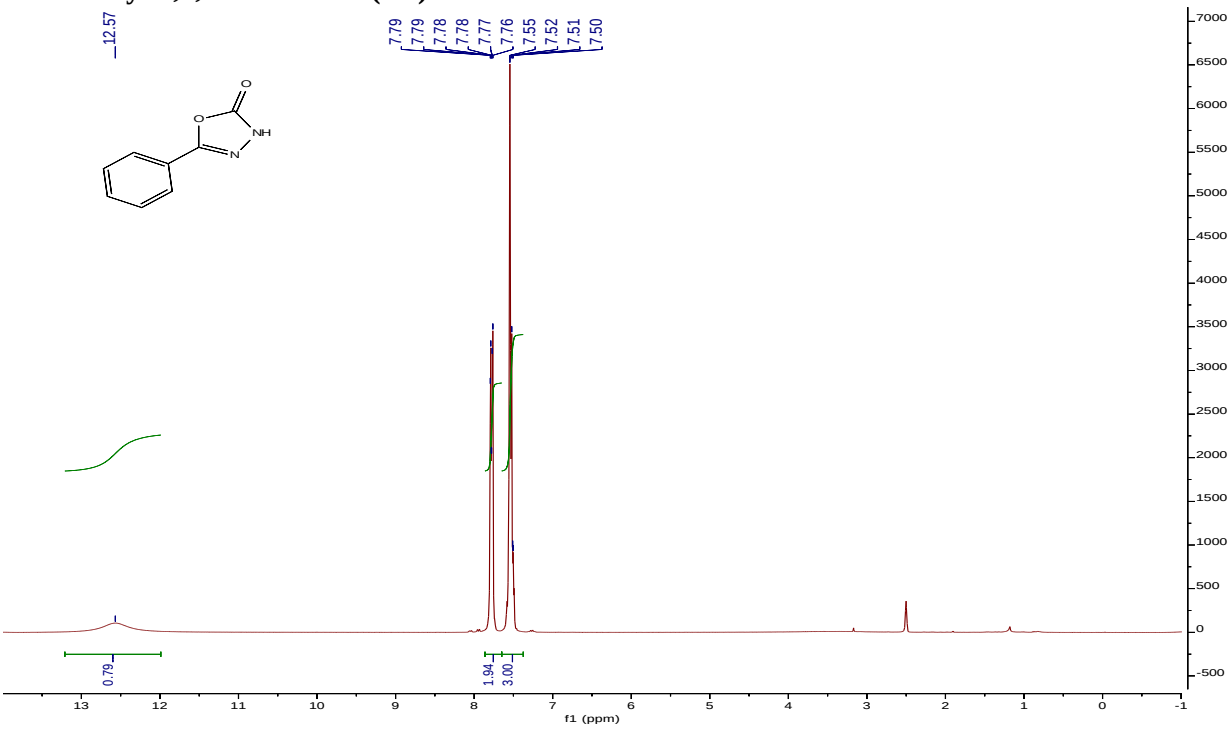


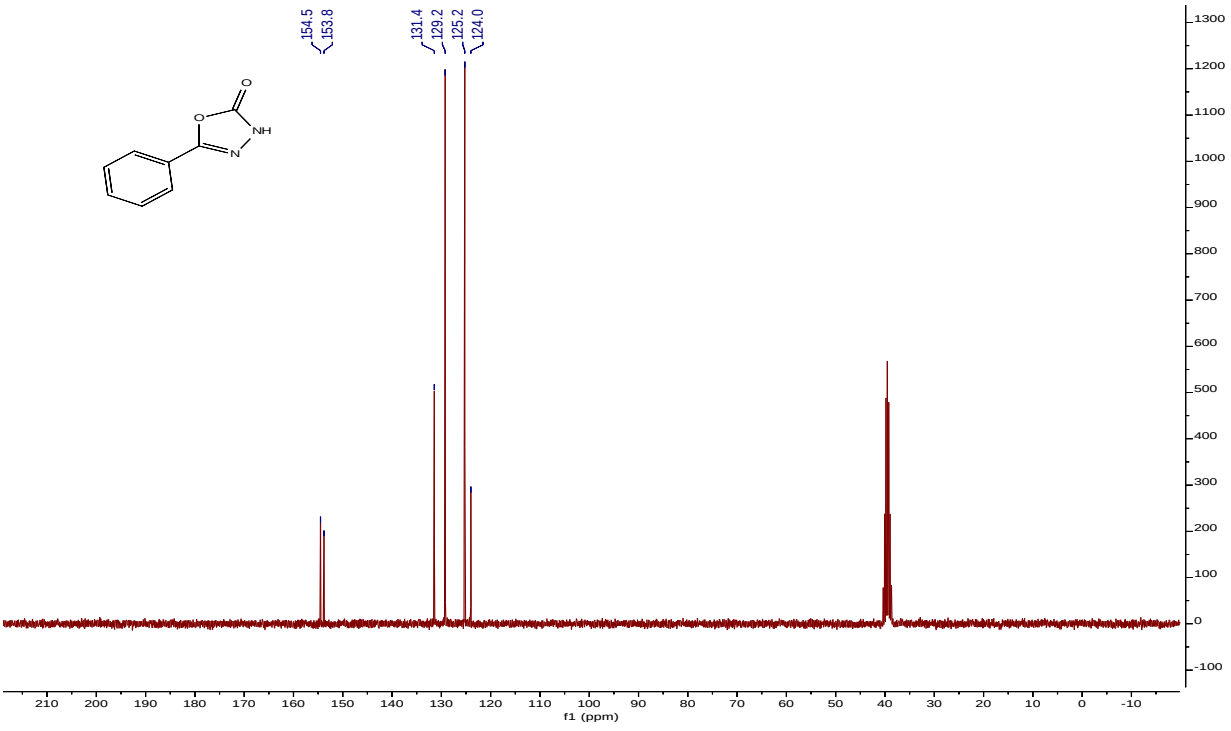
5b *tert*-Butyl (*S*)-(1-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenylethyl)carbamate



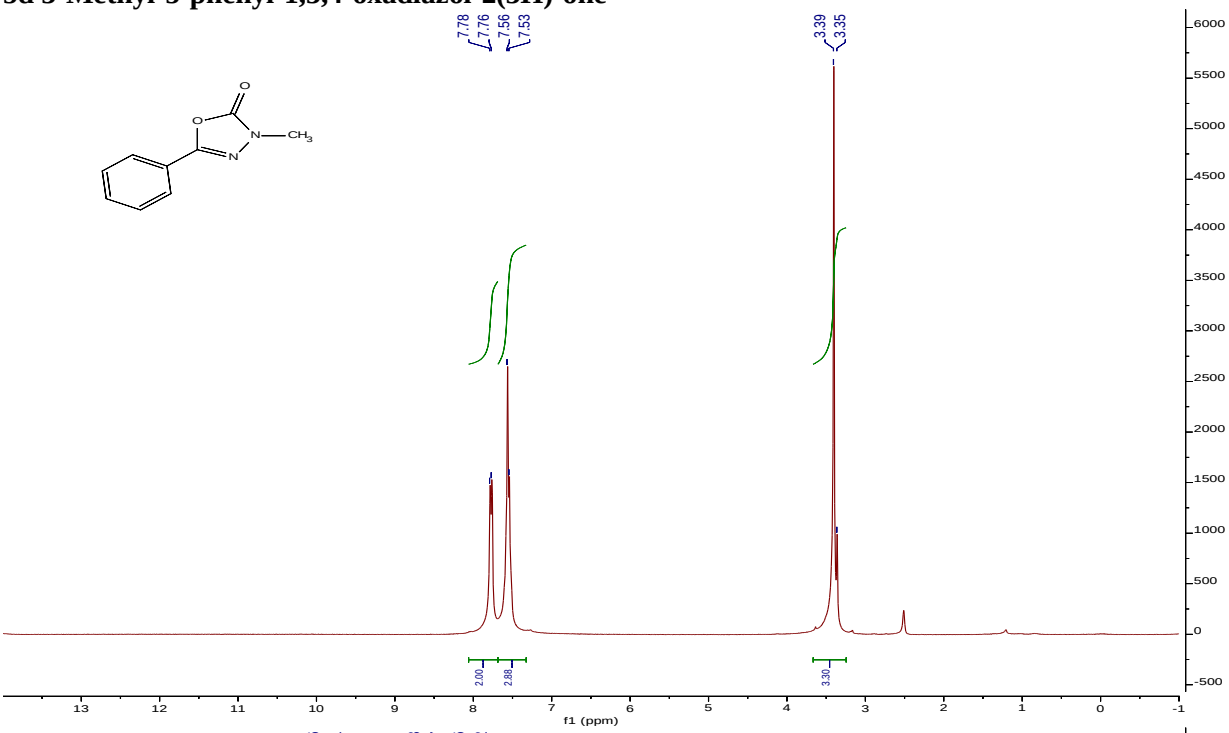


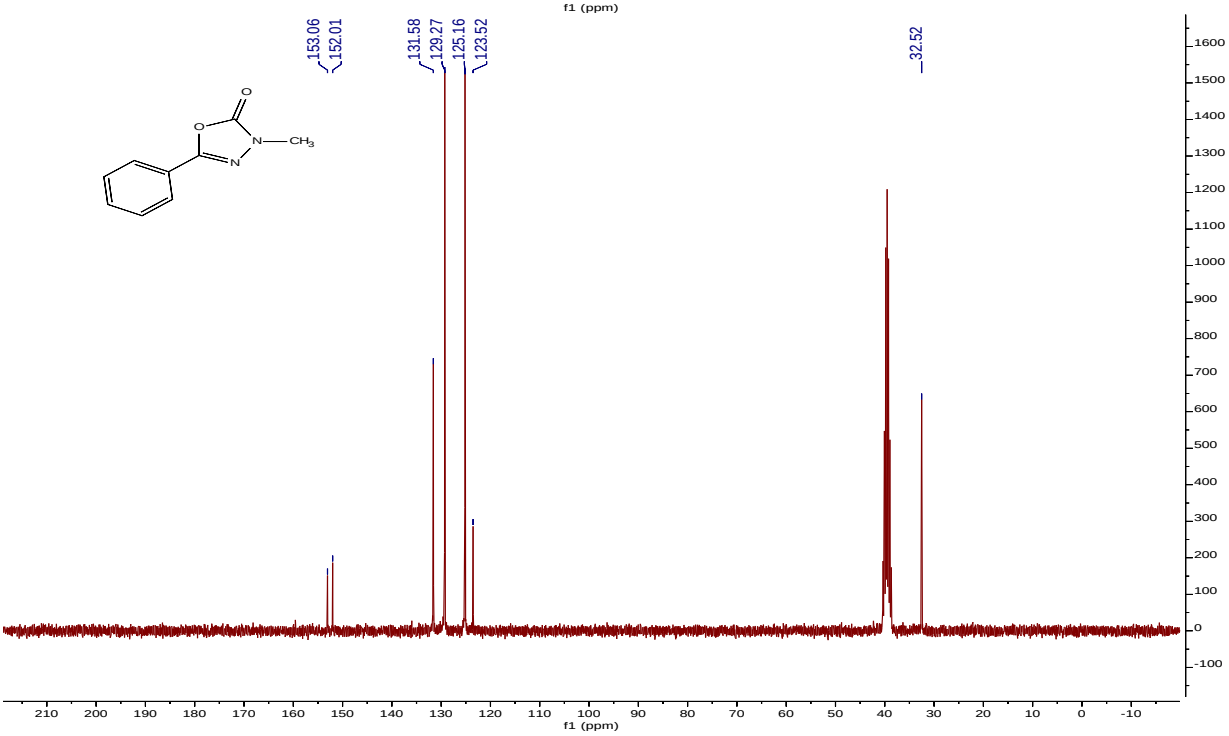
5c 5-Phenyl-1,3,4-oxadiazol-2(3H)-one



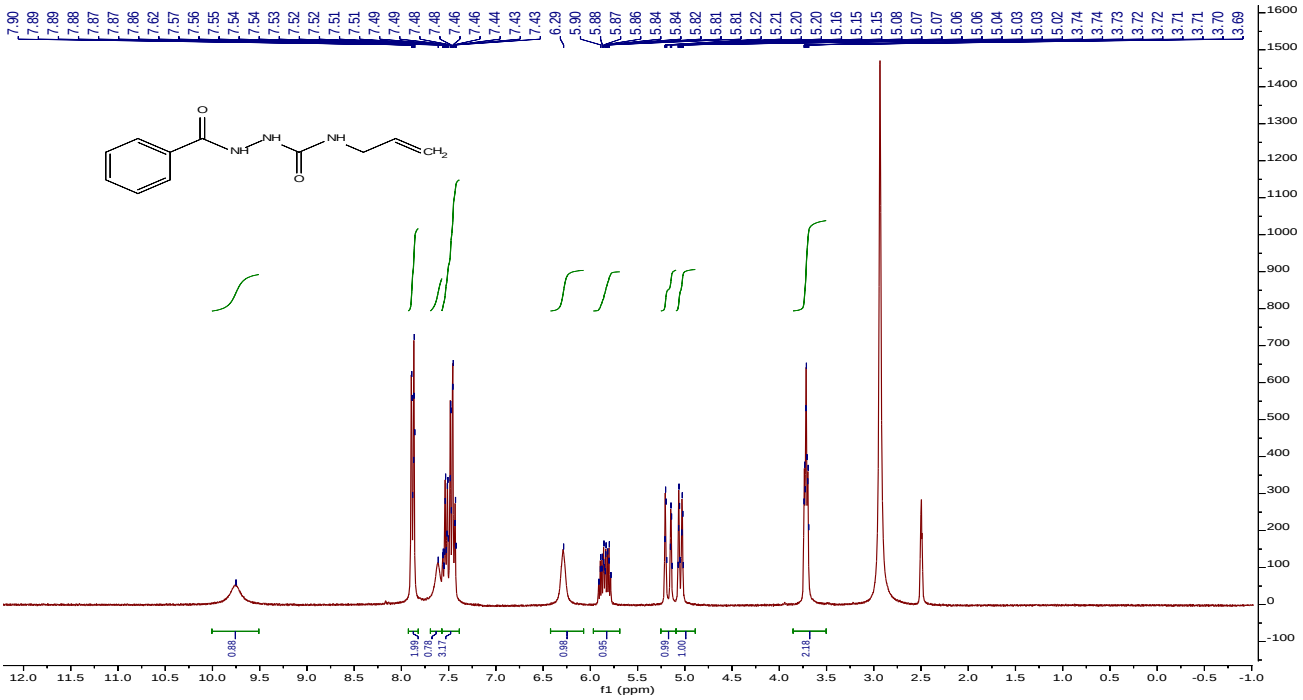


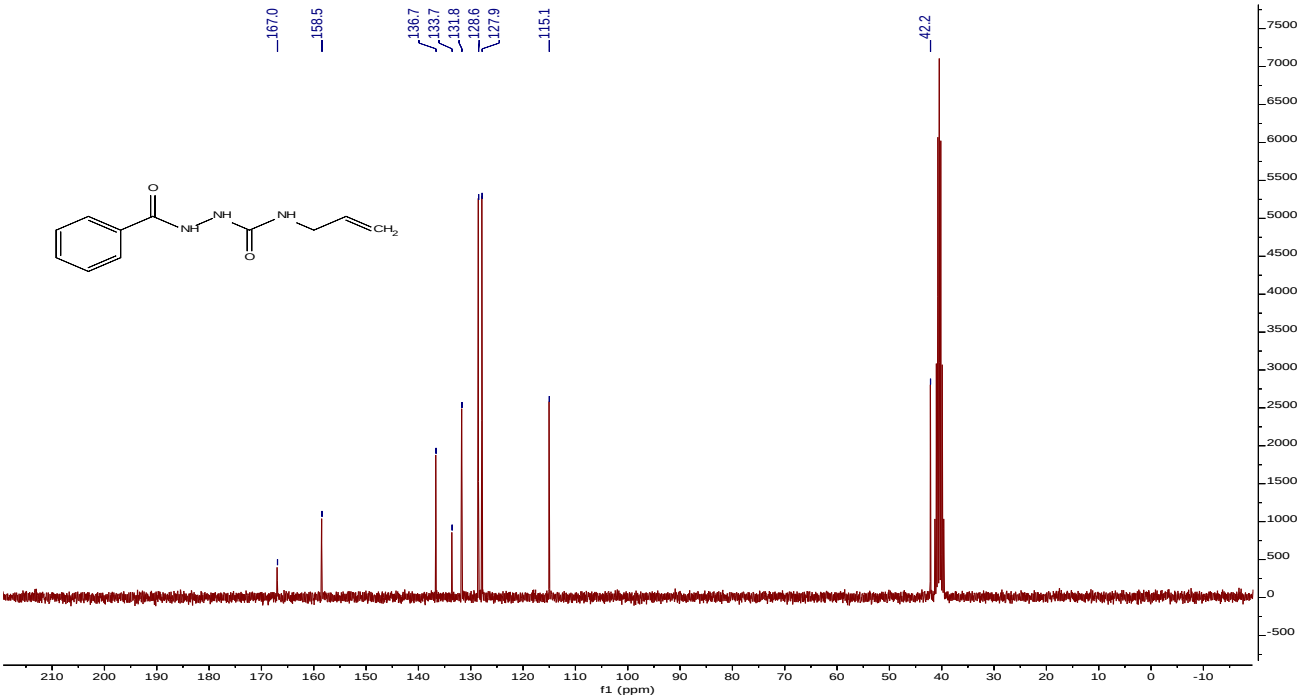
5d 3-Methyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one



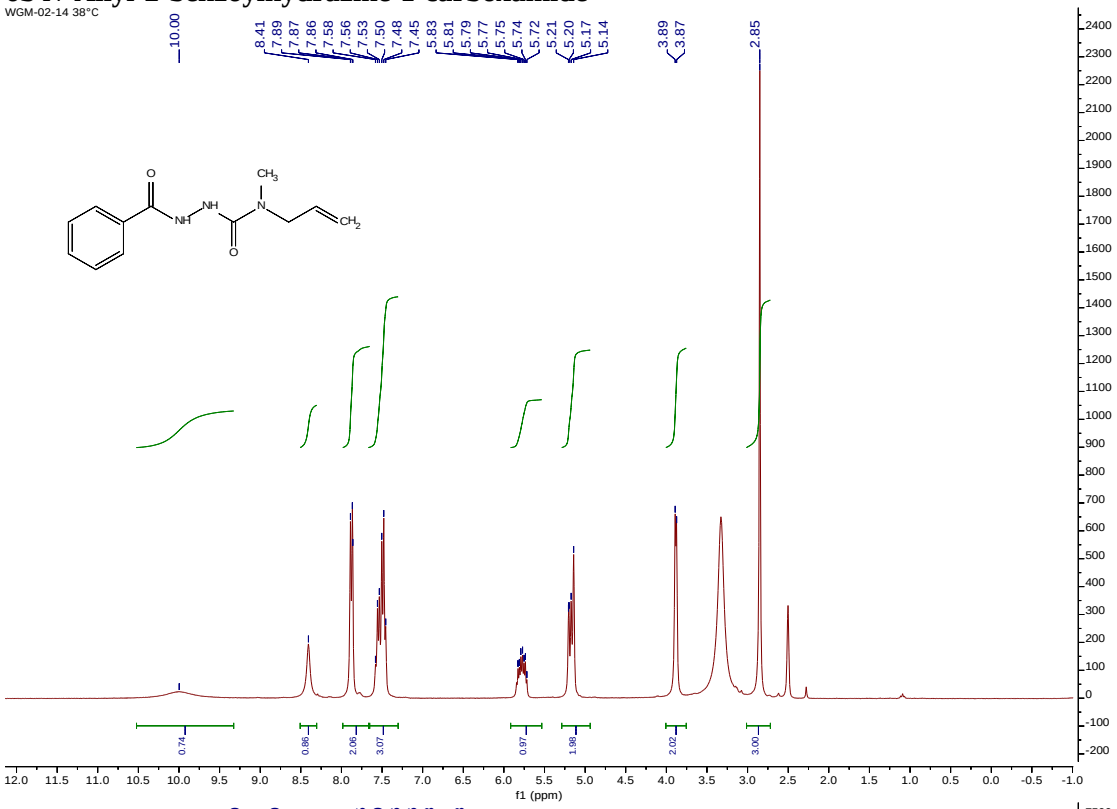


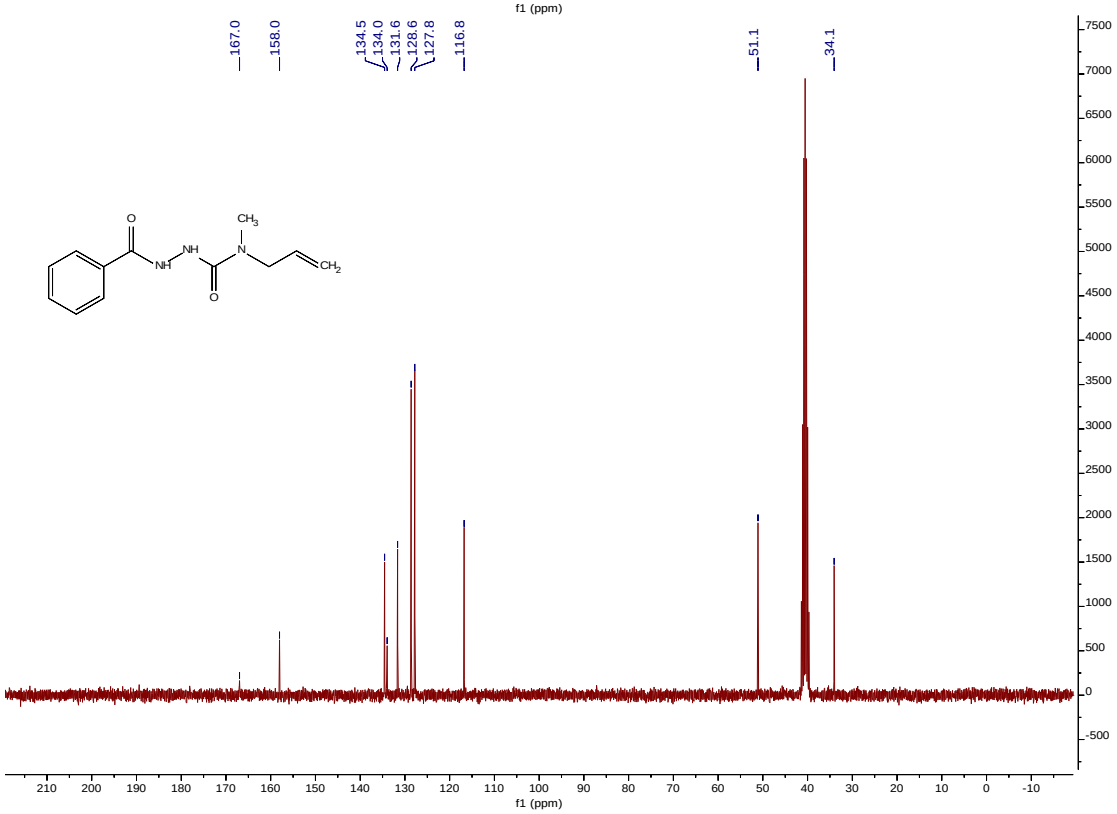
6a *N*-Allyl-2-benzoylhydrazine-1-carboxamide



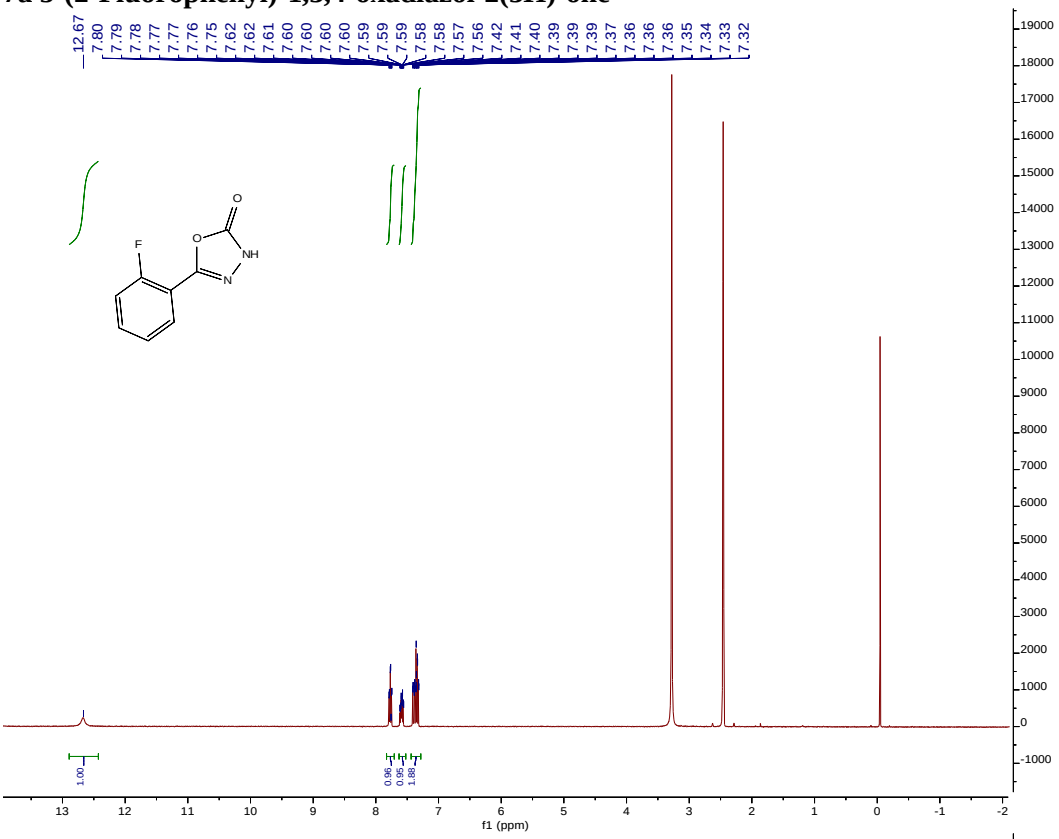


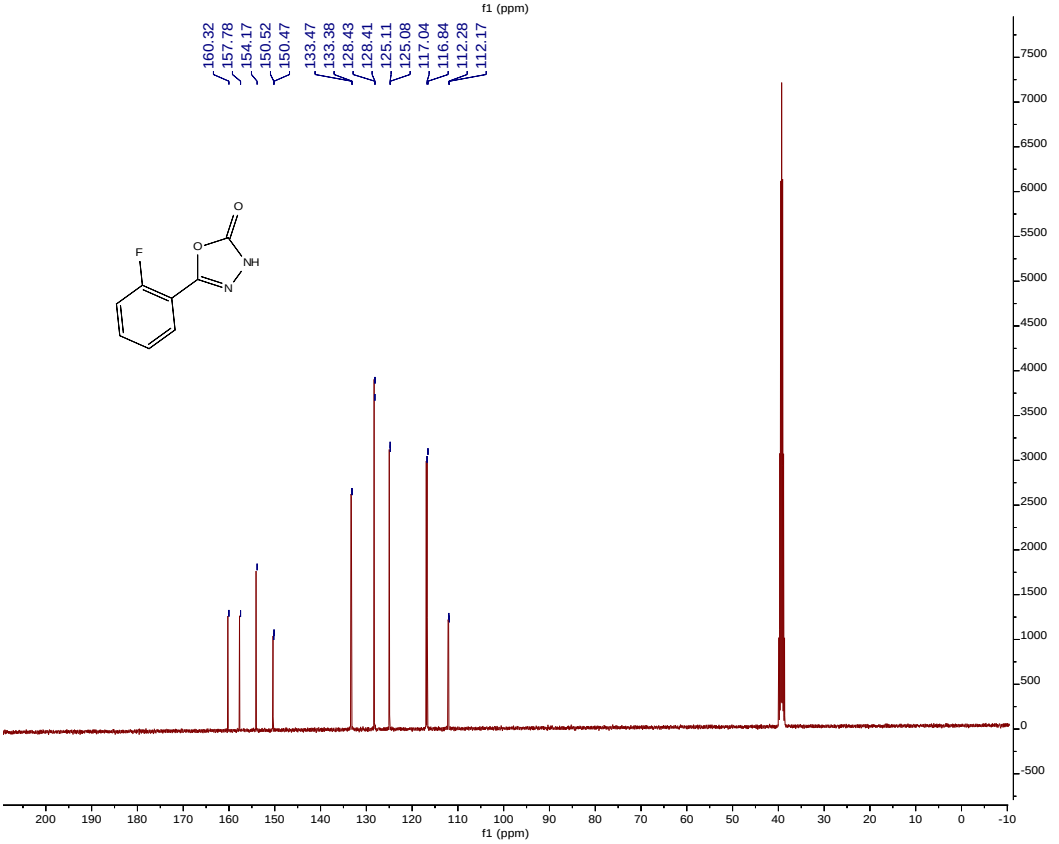
6b *N*-Allyl-2-benzoylhydrazine-1-carboxamide

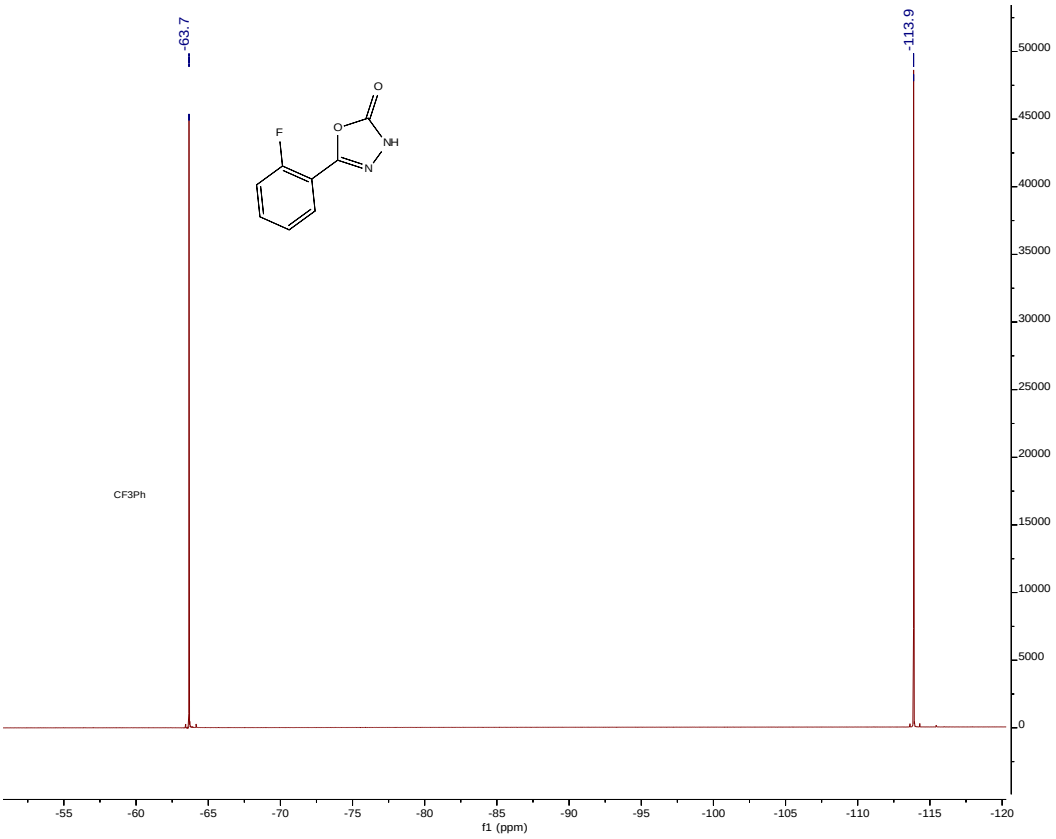




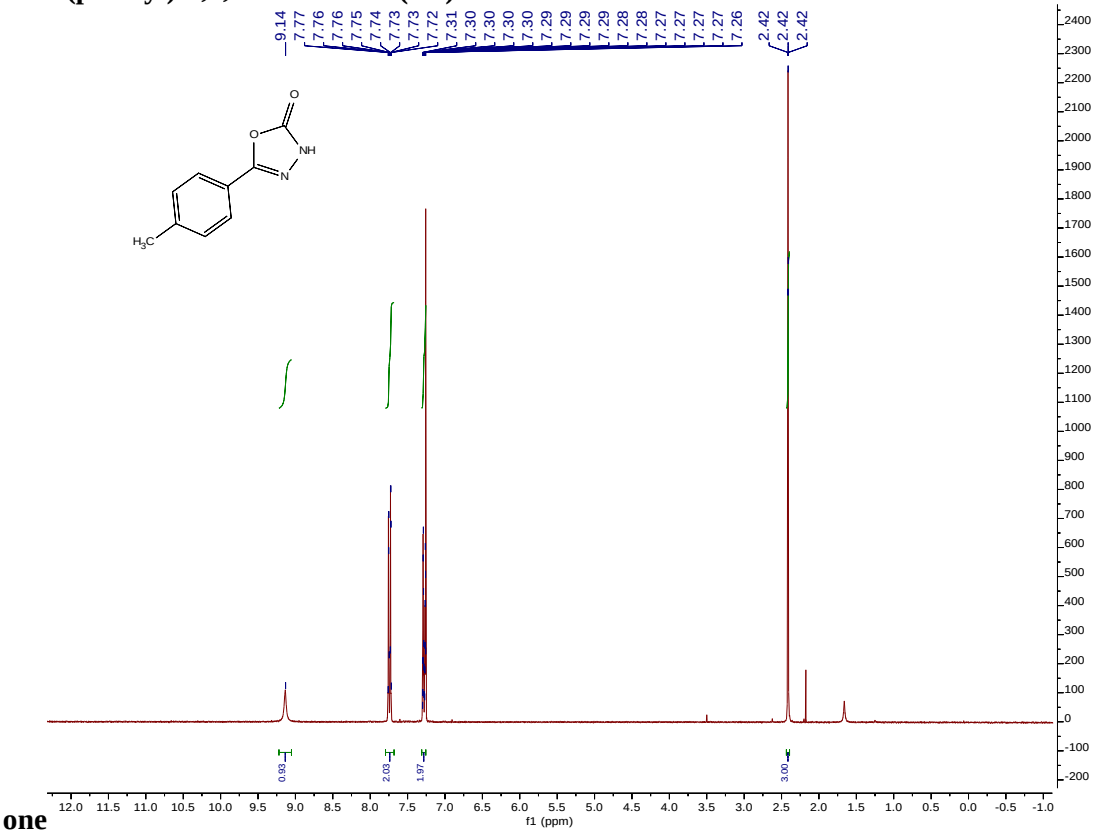
7a 5-(2-Fluorophenyl)-1,3,4-oxadiazol-2(3H)-one

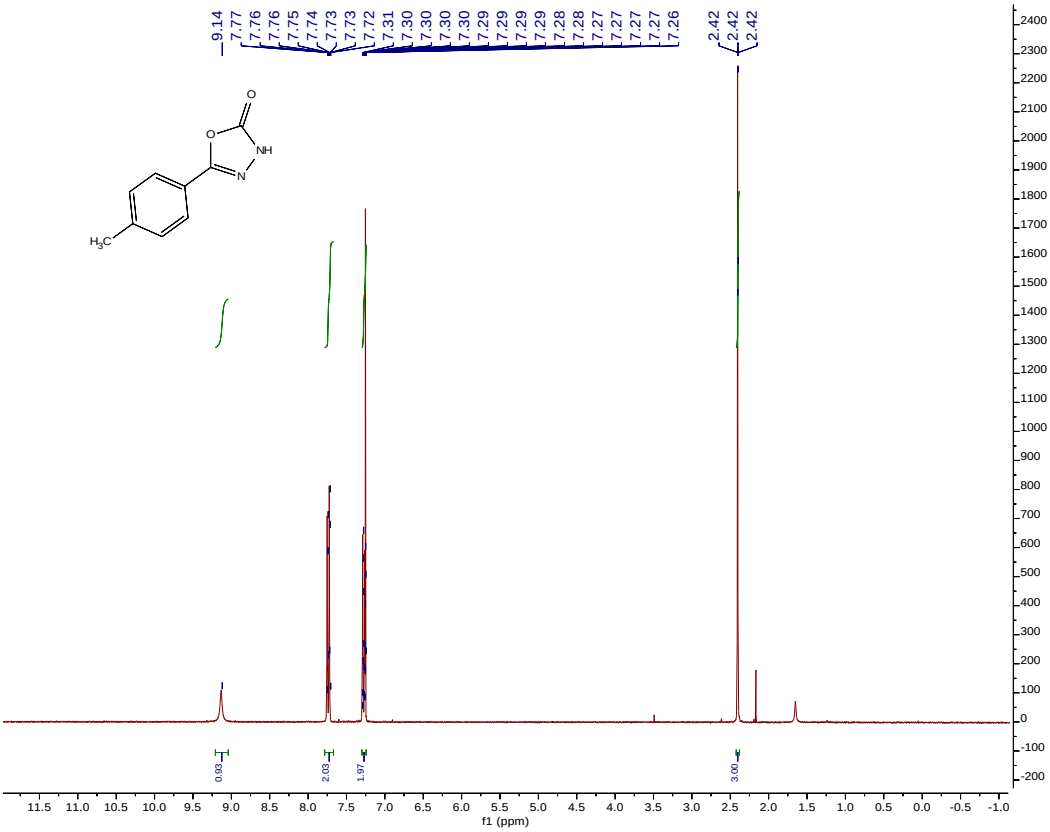




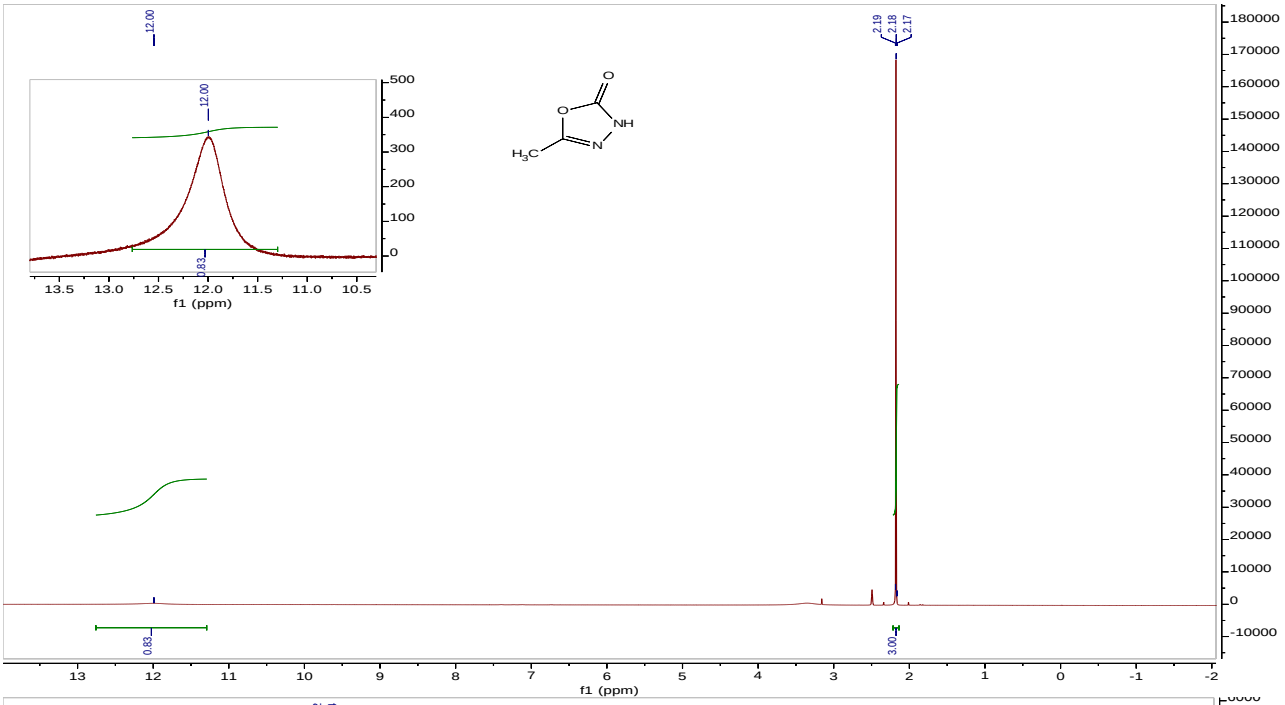

-63.7
-113.9
O
O
NH
N
F
CF3Ph
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
f1 (ppm)

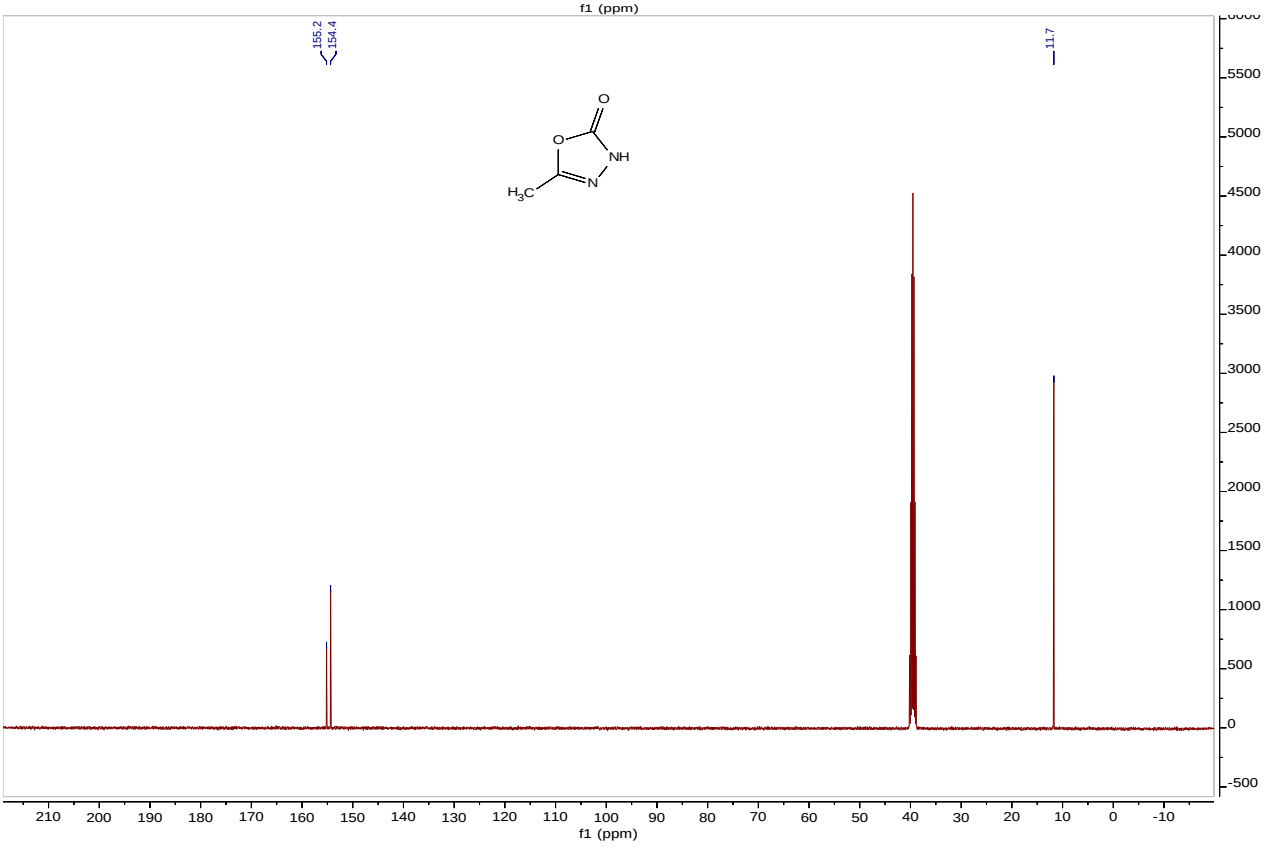
7b 5-(p-Tolyl)-1,3,4-oxadiazol-2(3H)-one



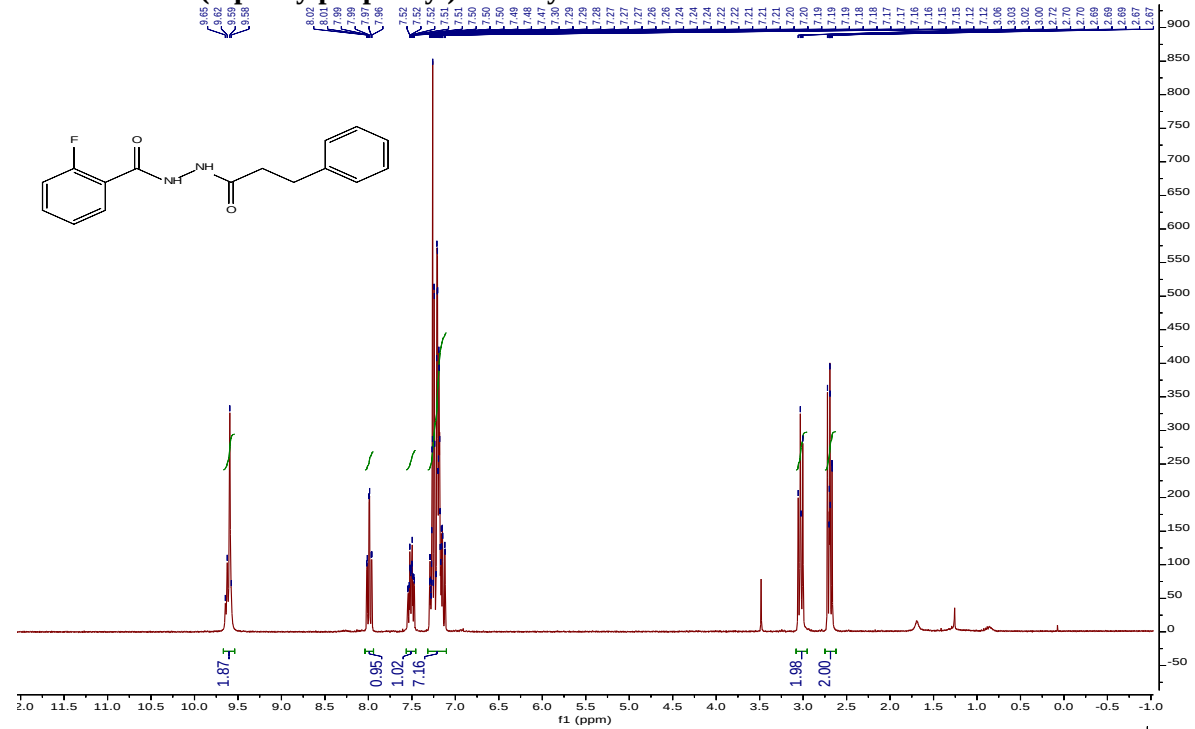


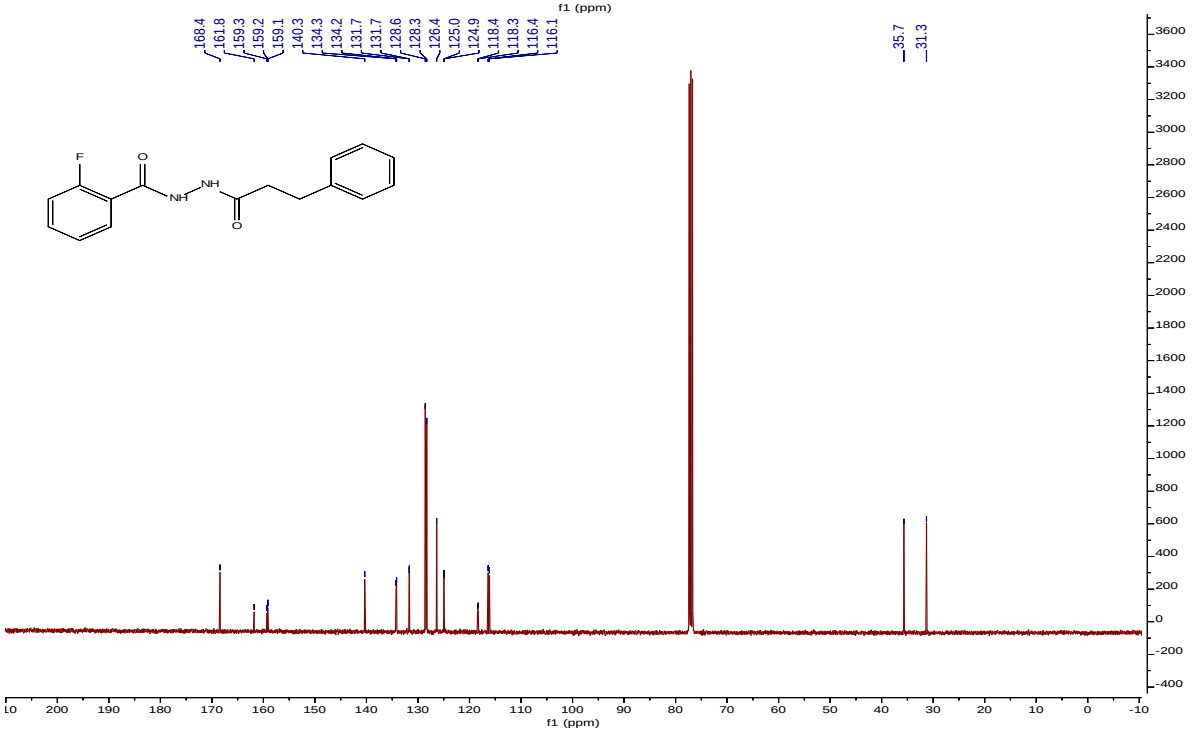
7c 5-Methyl-1,3,4-oxadiazol-2(3H)-one

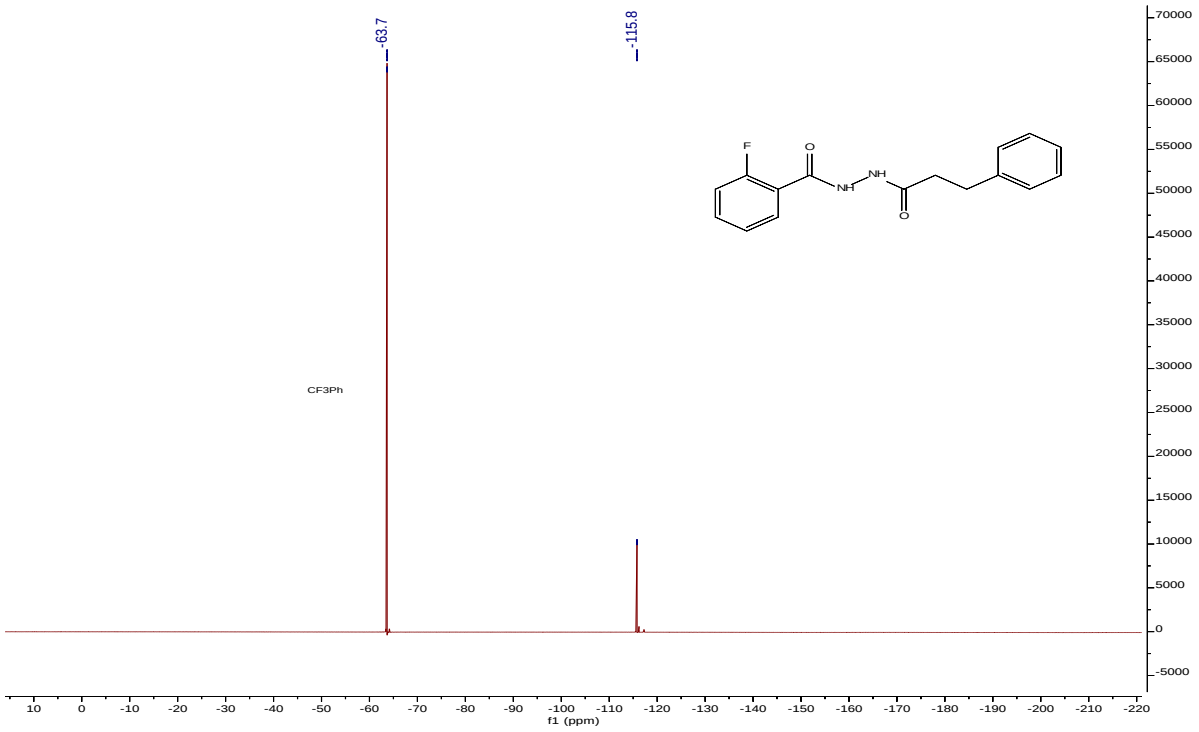




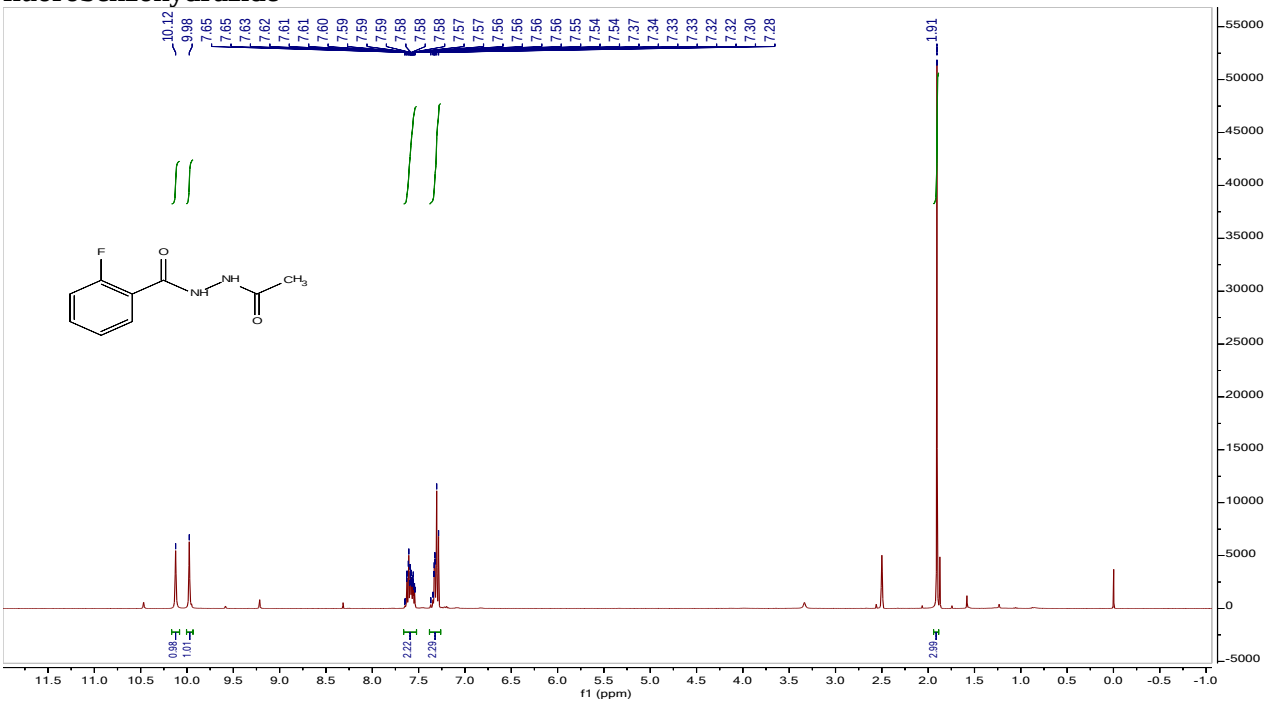
8a 2-Fluoro-*N*'-(3-phenylpropanoyl)benzohydrazide

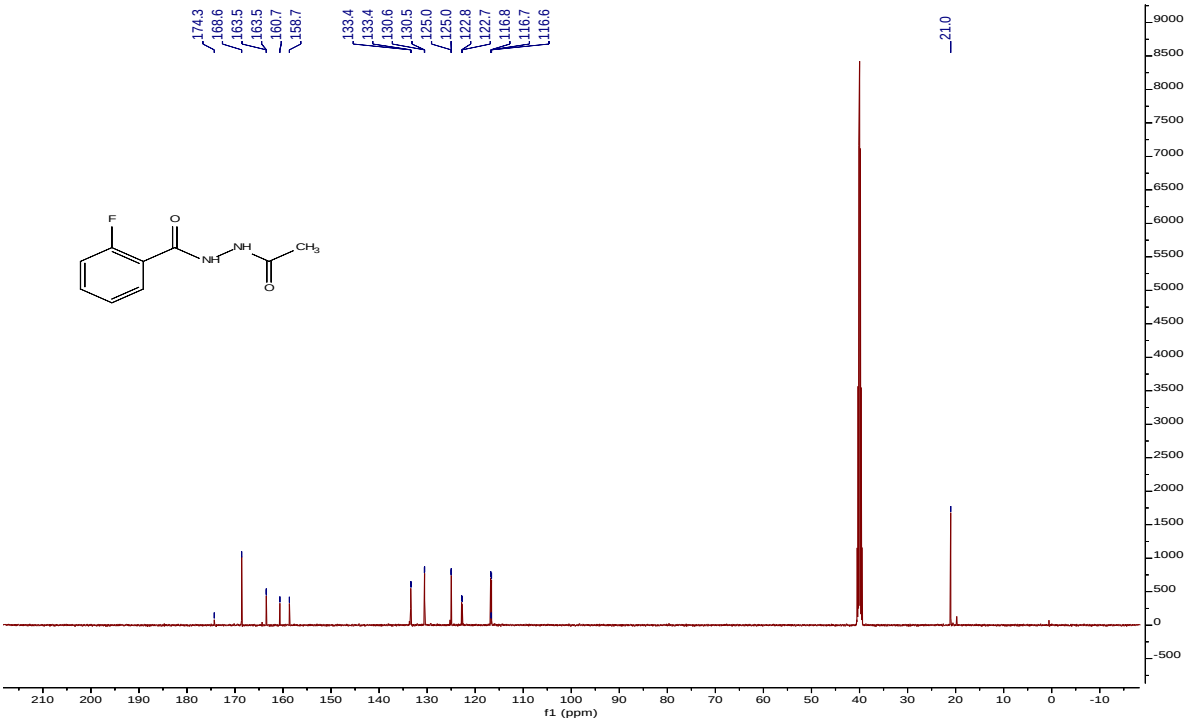


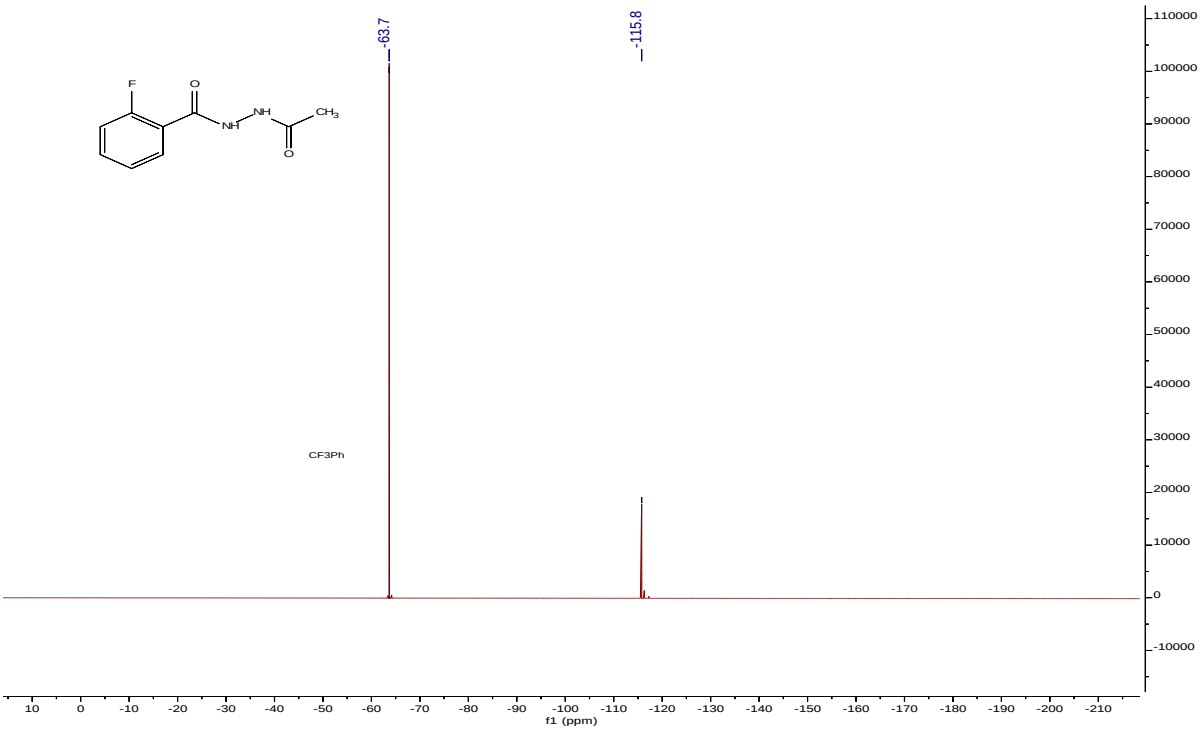



-63.7
-115.8
CF3Ph
F
O
NH
NH
O
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)

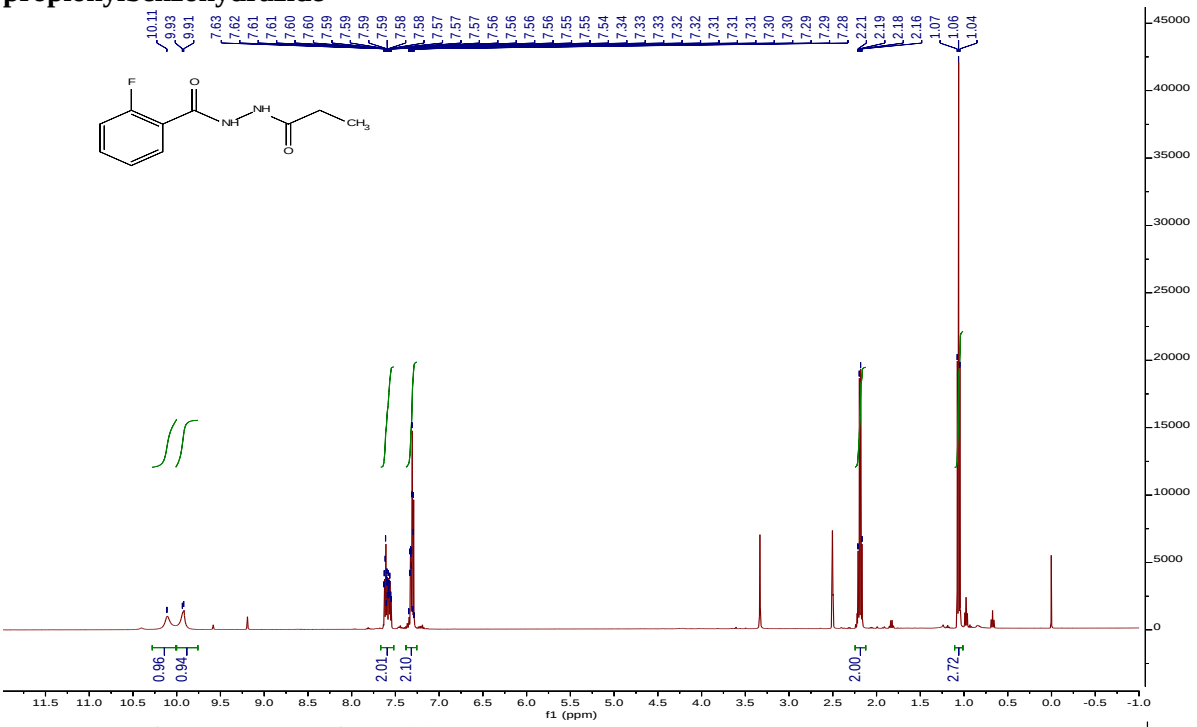
8b *N*'-Acetyl-2-fluorobenzohydrazide

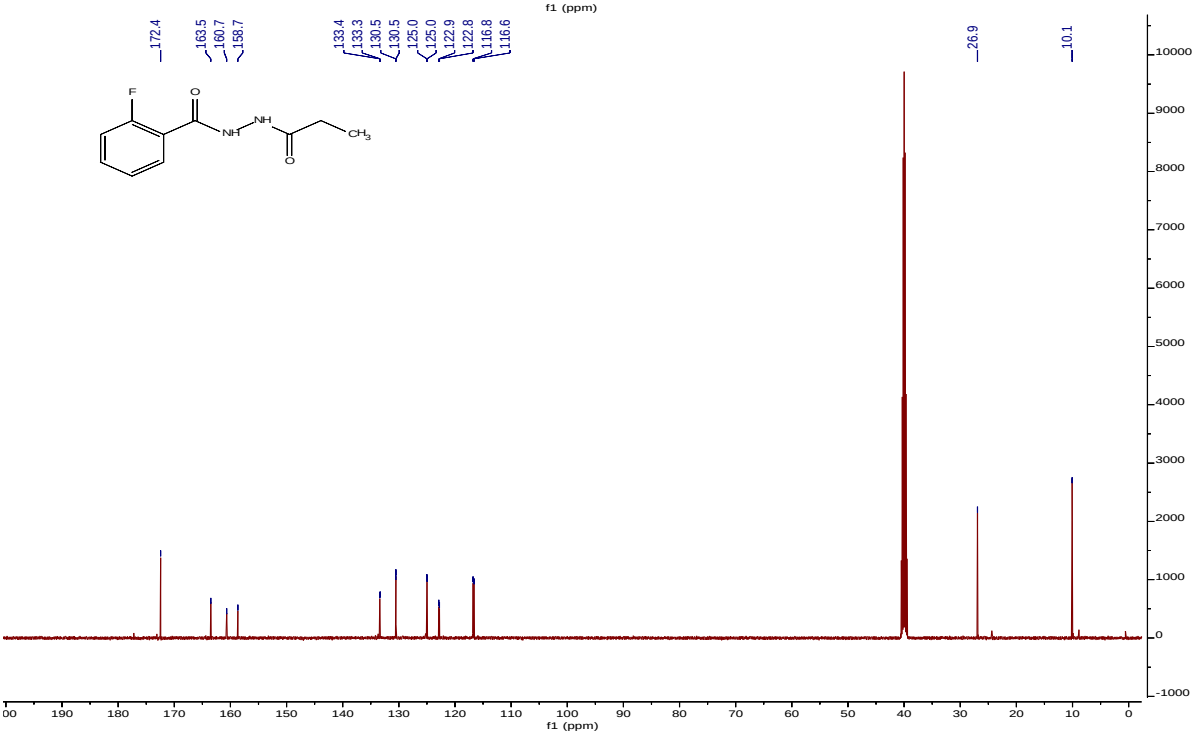


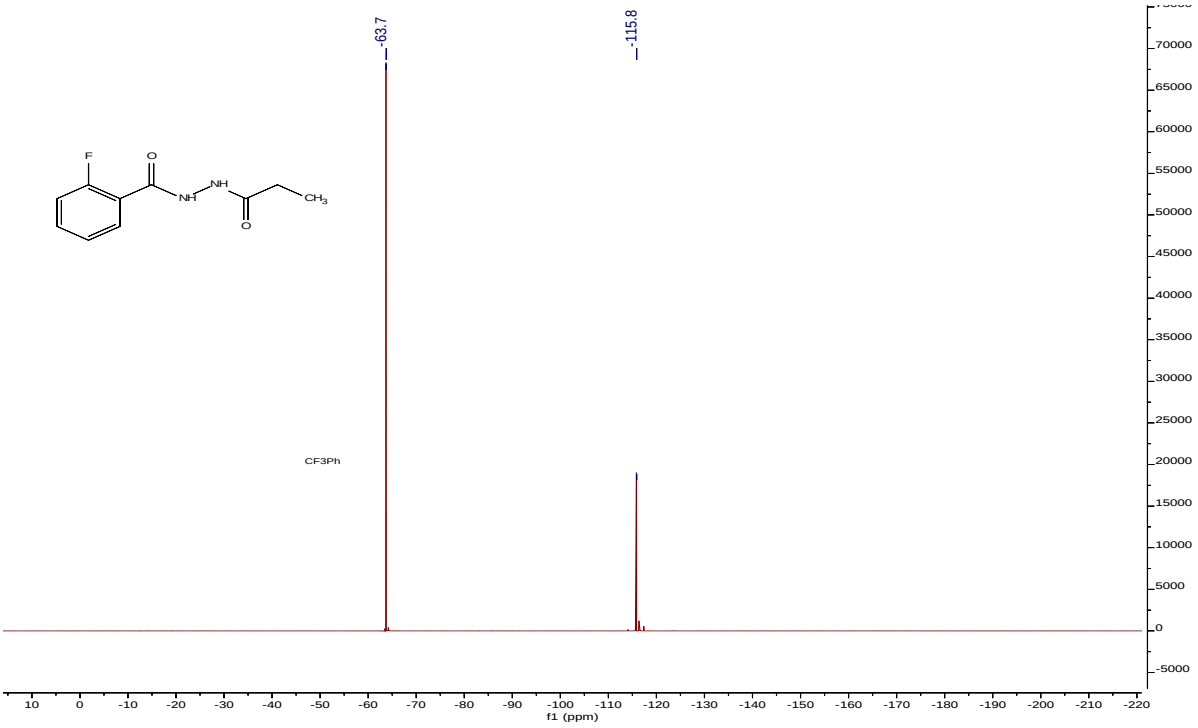



-63.7
-115.8
F
O
NH
NH
CH3
O
CF3Ph
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

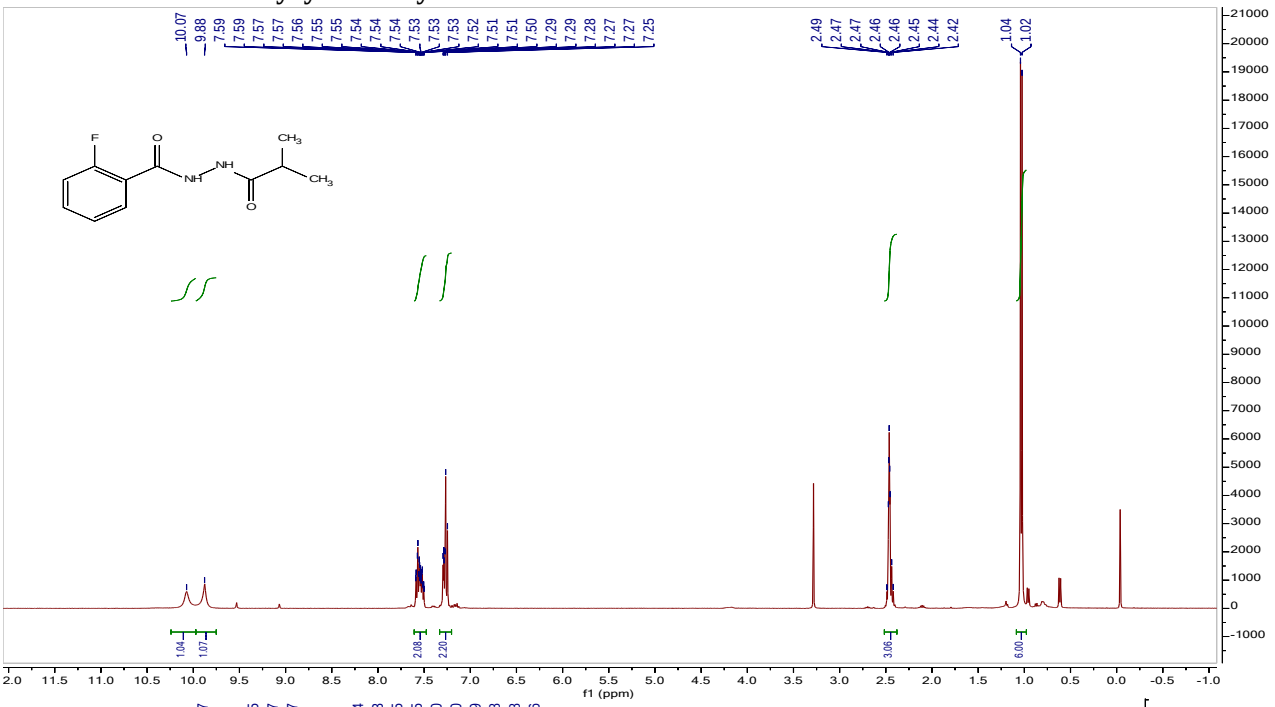
8c 2-Fluoro-*N*'-propionylbenzohydrazide

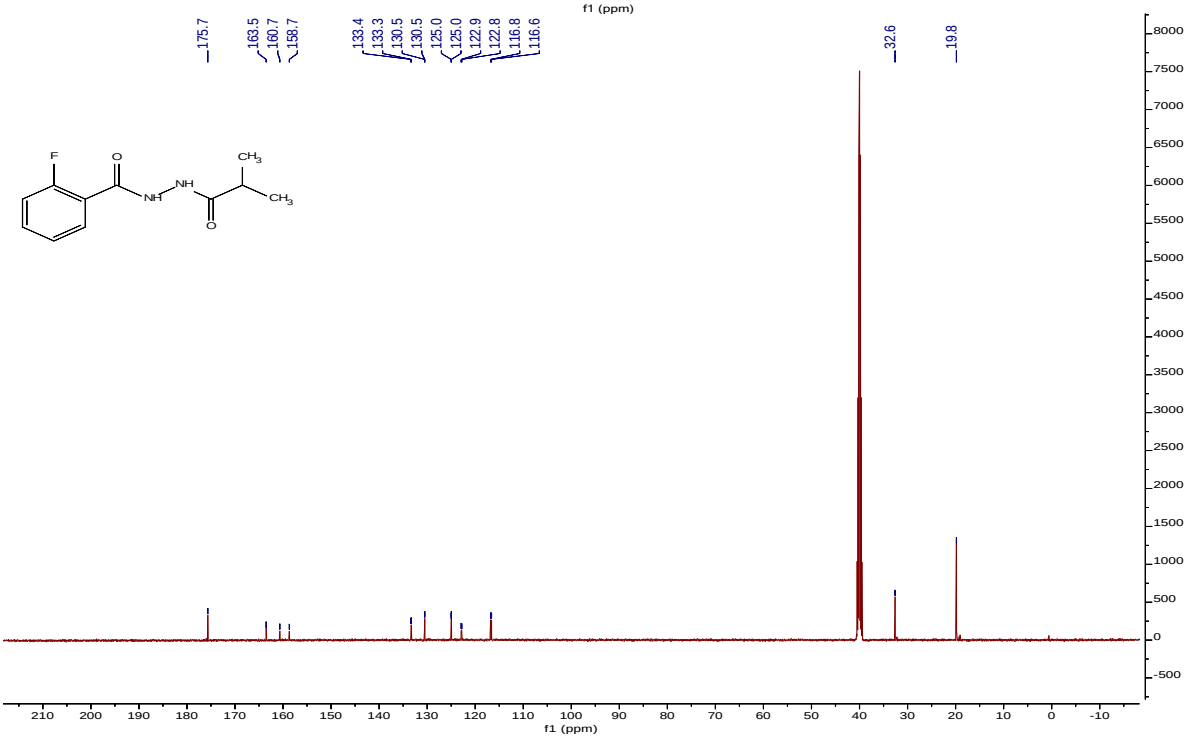


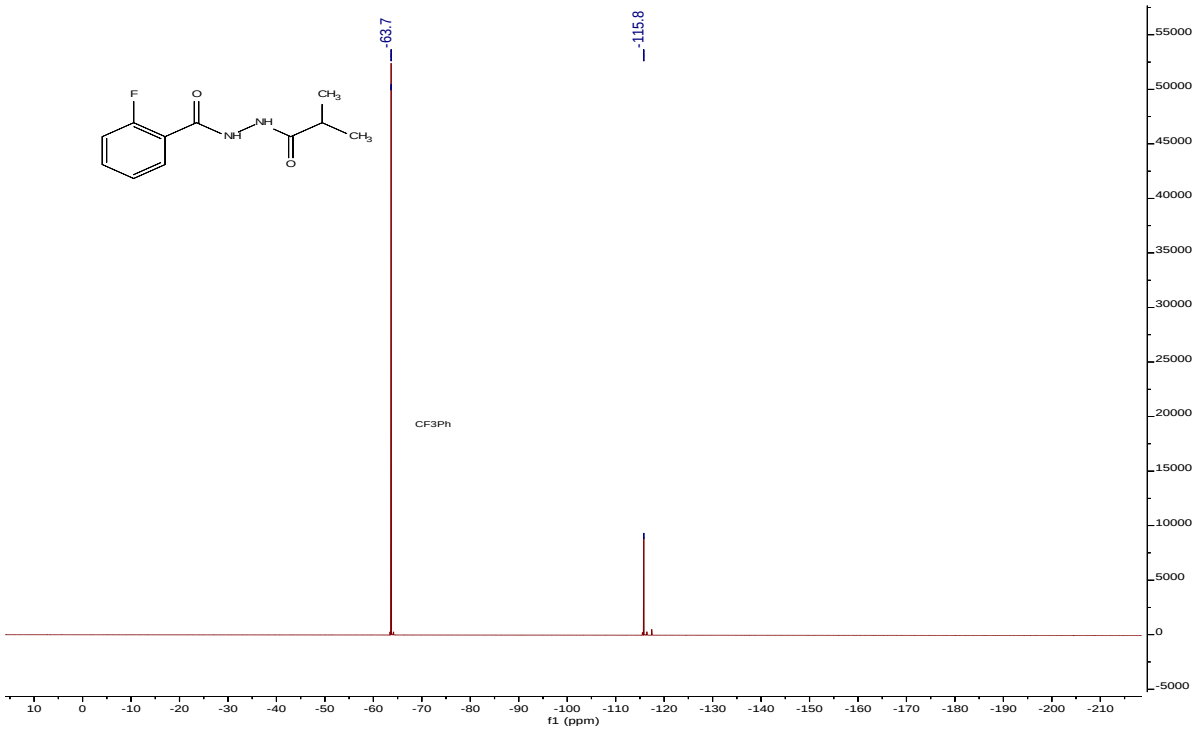



-63.7
-115.8
F
O
NH
NH
O
CH3
CF3Ph
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)

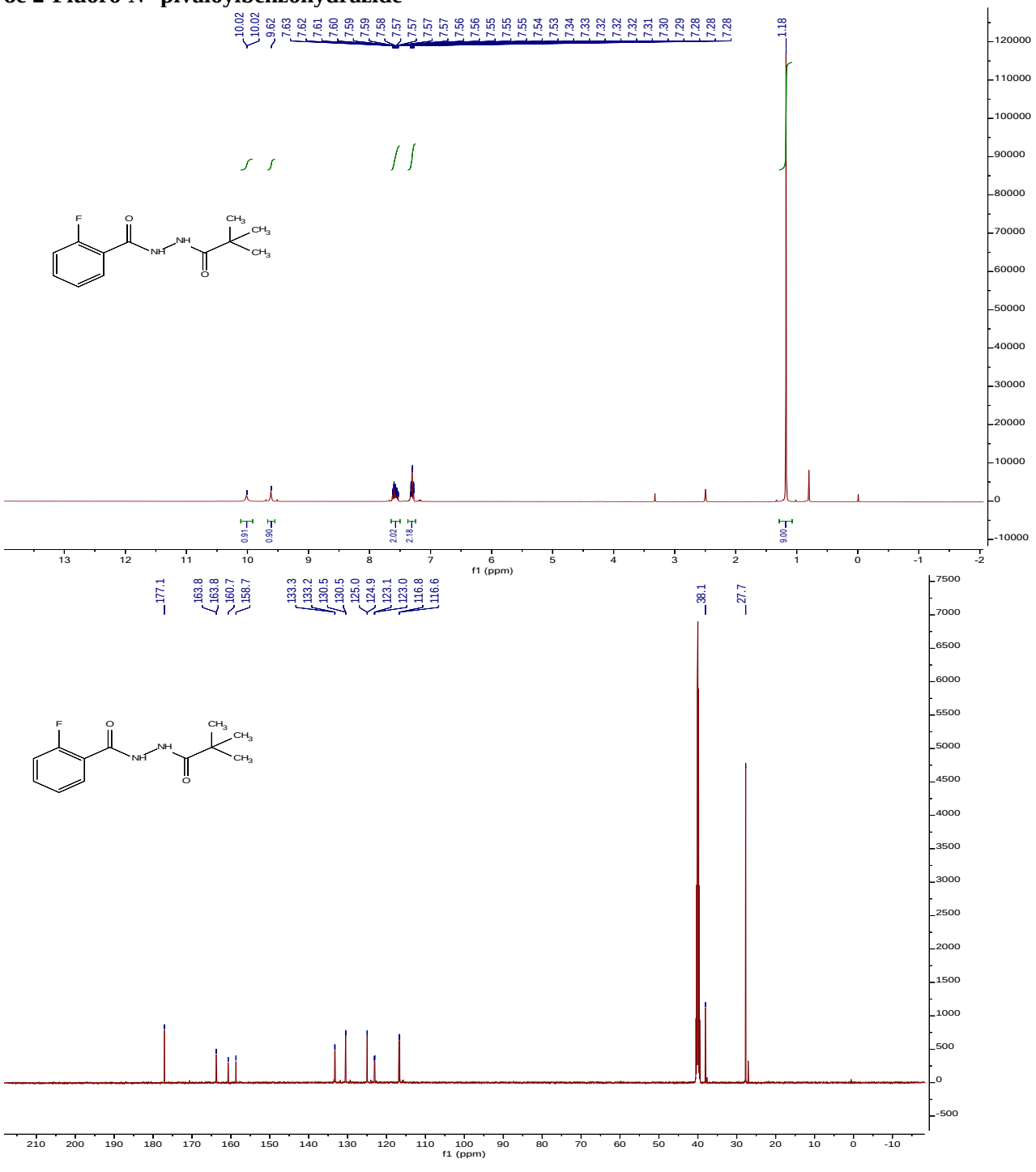
8d 2-Fluoro-*N*'-isobutyrylbenzohydrazide

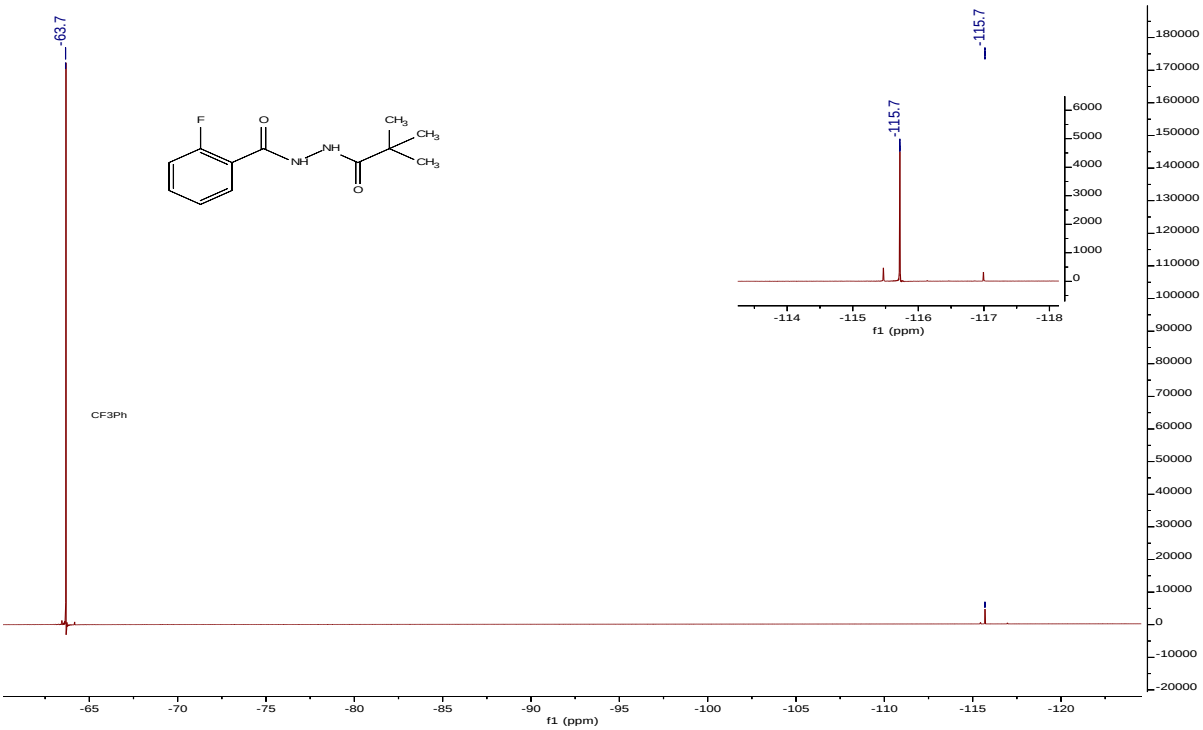




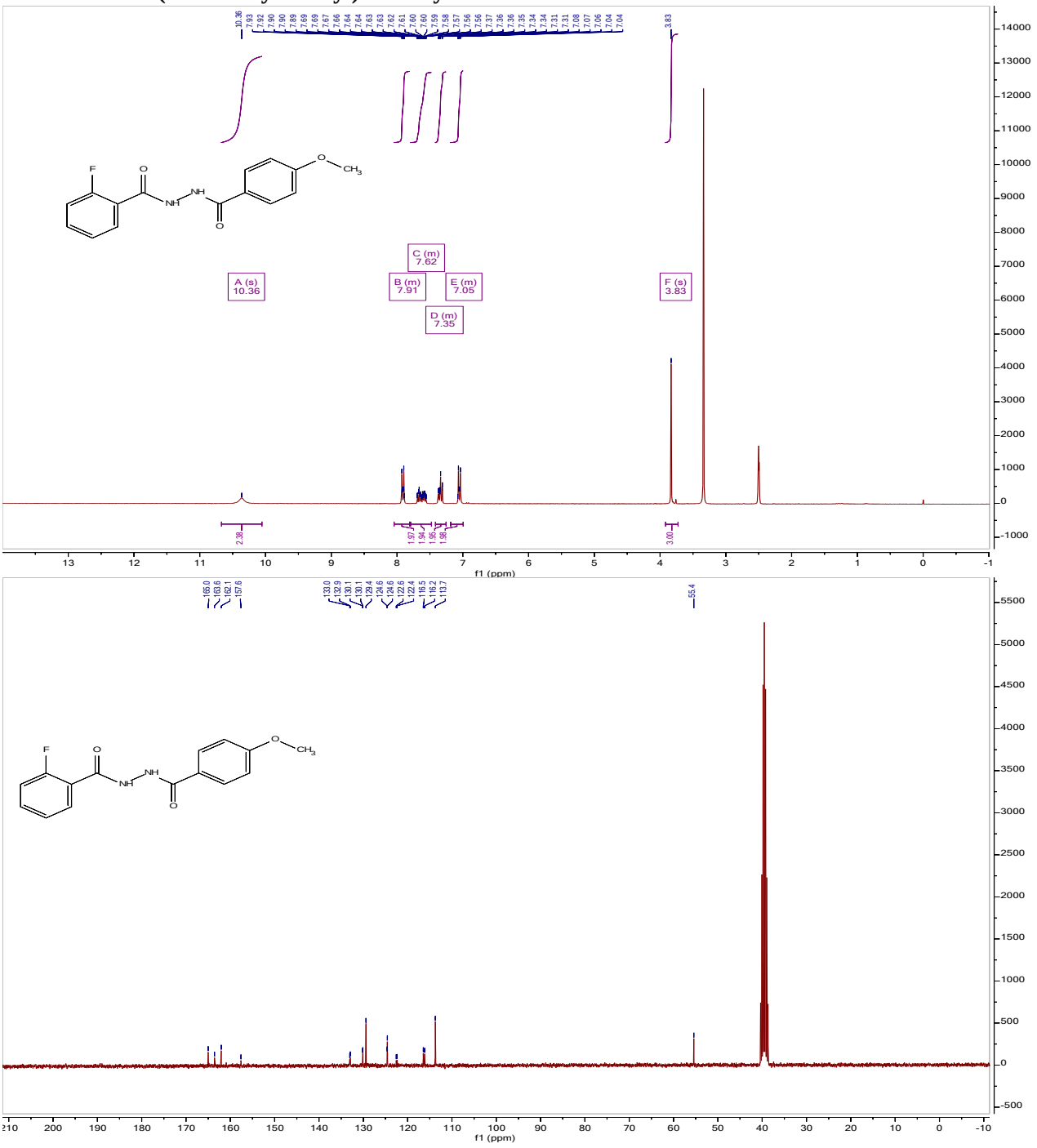

-63.7
-115.8
F
O
NH
NH
CH3
CH3
O
CF3Ph
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

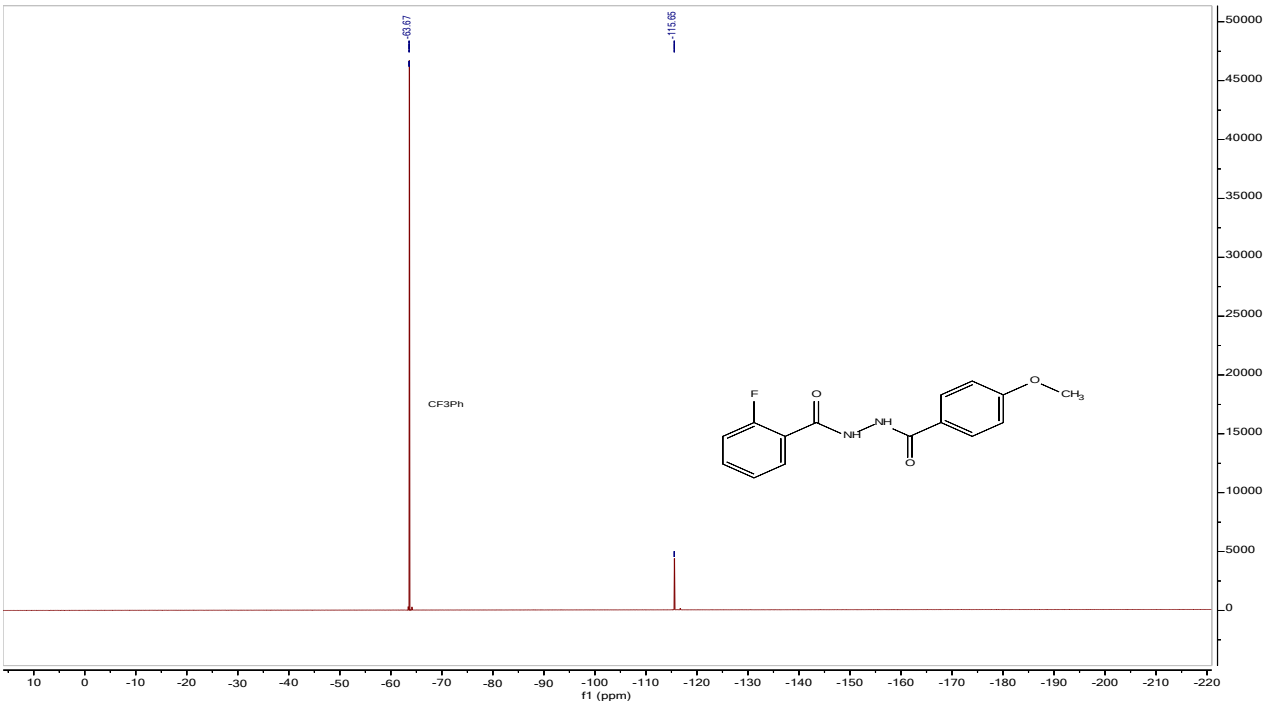
8e 2-Fluoro-*N*'-pivaloylbenzohydrazide



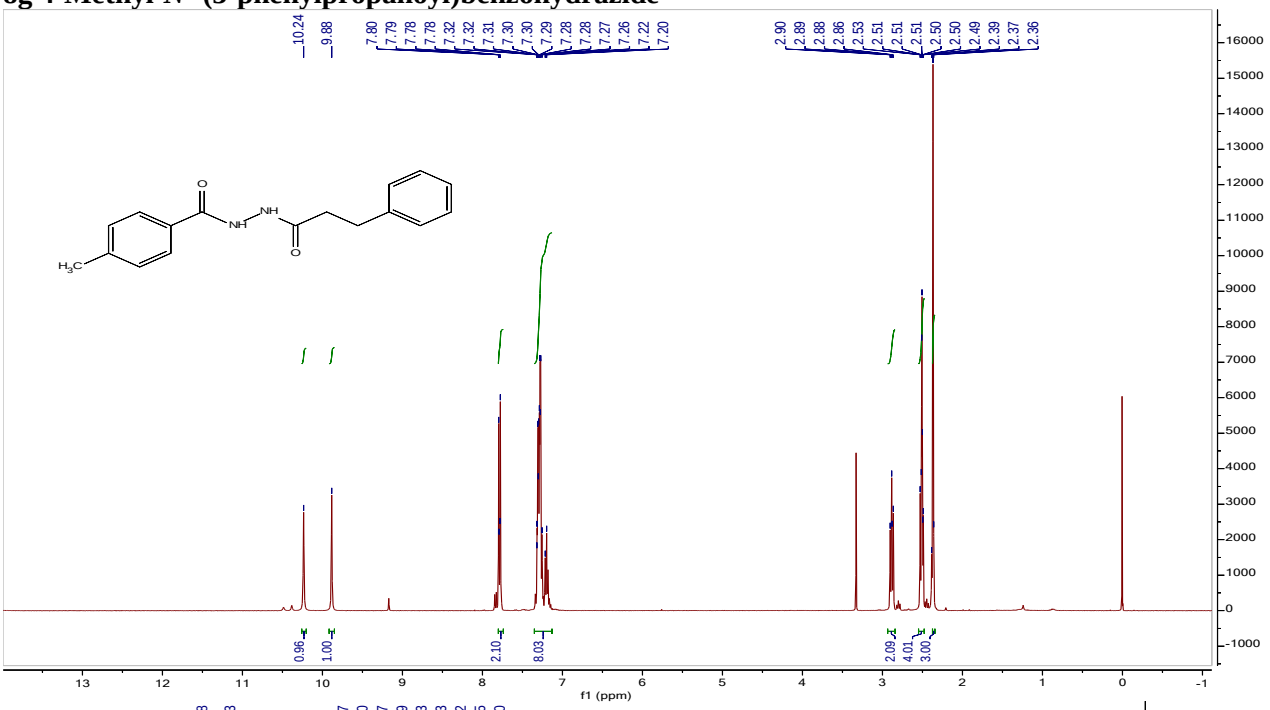

-63.7
-115.7
F
O
NH
NH
O
CH3
CH3
CH3
CF3Ph
f1 (ppm)
f1 (ppm)

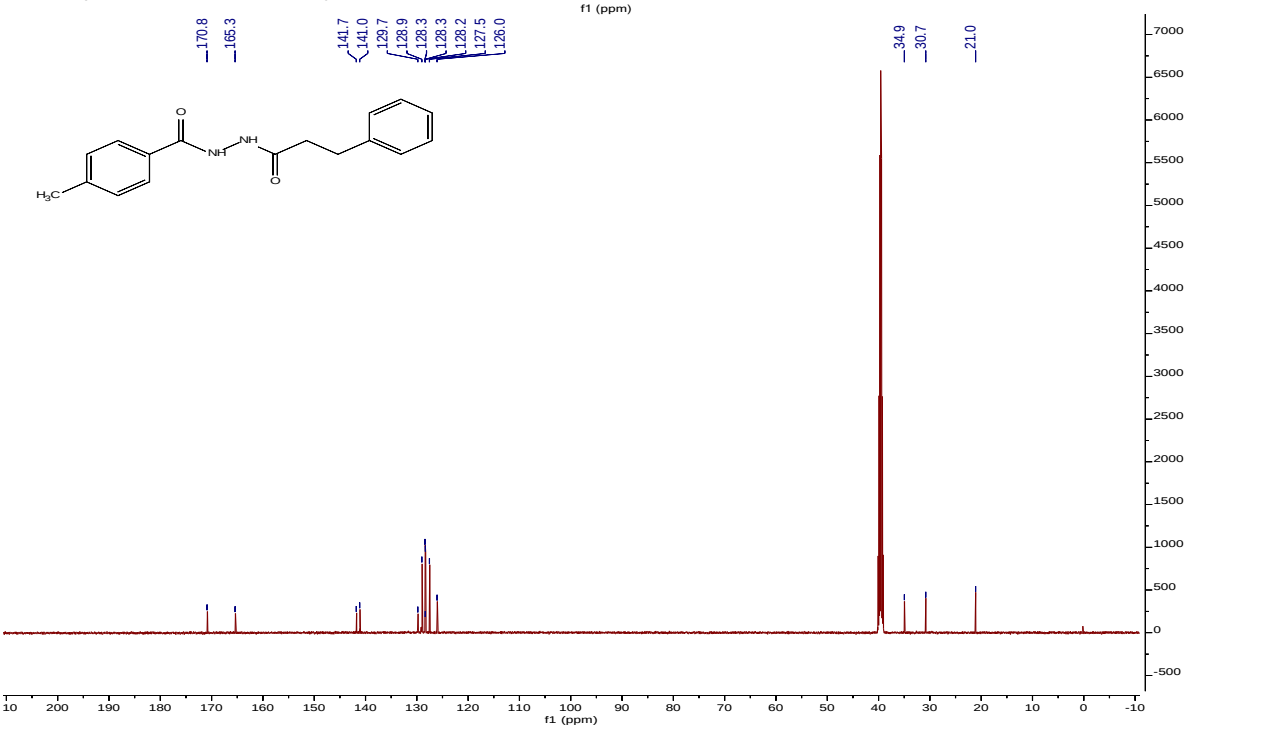
8f 2-Fluoro-*N'*-(4-methoxybenzoyl)benzohydrazide




63.67
115.65
CF3Ph
F
O
NH
NH
O
O
CH3
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)

8g 4-Methyl-*N*'-(3-phenylpropanoyl)benzohydrazide





8h *N'*-Acetyl-3-phenylpropanehydrazide