Novel postmodifications of the Ugi reaction

Dissertation

zur Erlangung des Doktorgrades der Naturwissenschaften
(Dr. rer. nat.)

der
Naturwissenschaftlichen Fakultät II
Chemie, Physik und Mathematik

der Martin-Luther-Universität
Halle-Wittenberg

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Verteidigung:	5. April 2016

So eine Arbeit wird eigentlich nie fertig,
man muß sie für fertig erklären,
wenn man nach Zeit und Umständen
das Mögliche daran getan hat.

GOETHE, Italienische Reise

Parts of this thesis have been published in:

Sebastian J. Welsch, Michael Umkehrer, Günther Ross, Jürgen Kolb, Christoph Burdack, Ludger A. Wessjohann; *$Pd^{II/IV}$ catalyzed oxidative cyclization of 1,6-enynes derived by Ugi-4-component reaction*;
Tetrahedron Letters **2011**, *52* (47), 6295-6297.

Sebastian J. Welsch, Cédric Kalinski, Michael Umkehrer, Günther Ross, Jürgen Kolb, Christoph Burdack, Ludger A. Wessjohann; *Palladium and copper catalyzed cyclizations of hydrazine derived Ugi products: facile synthesis of substituted indazolones and hydroxytriazafluorendiones*;
Tetrahedron Letters **2012**, *53* (18), 2298-2301.

Sebastian J. Welsch, Michael Umkehrer, Cedric Kalinski, Günther Ross, Christoph Burdack, Jürgen Kolb, Martina Wild, Anja Ehrlich, Ludger A. Wessjohann; *Synthesis of substituted imidazolines by an Ugi/Staudinger/aza-Wittig sequence;*
Tetrahedron Letters **2015**, *56* (8), 1025-1029.

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1. Acknowledment

Now with all the work done and euphoria setting in it is about time to look back. Although it will be my name only on the front cover many people have contributed in one way or another to this thesis and without their help it would still be *work in progress*.

First and foremost I want to thank PROF. LUDGER WESSJOHANN for his supervision and the great conceptual freedom he has granted me. He has been always open-minded for new ideas, and I enjoyed the fruitful discussions with him that granted me a glimpse on his vast knowledge. In addition his editing improved their overall readability of this thesis and the papers it is based upon by a great deal.

Second I want to thank PROF. RAINER BECKERT for his willing agreement to act as external reviewer.

Further my thanks go to DR. JÜRGEN KOLB and DR. CHRISTOPH BURDACK who have made this work possible in the first place. Without their constant efforts to keep Priaxon AG up and running there would have been no paycheck to live on and no lab to work in.

This very lab was the realm of DR. MICHAEL UMKEHRER. His experience in MCR chemistry and his tips and tricks proved to be invaluable. DR. CÉDRIC KALINSKI and DR. GÜNTHER ROß deserve a special notion for their ideas and constructive input – their suggestions laid the foundations for two chapters of this thesis. The specialist for stuck glass joints and all questions regarding purifications was DR. GARY REMENNIKOV. As a seasoned lab veteran he knew the tricks of his trade and shared them as happily as his jokes and entertaining stories.

Over the years several interns had come to my help, some for a few weeks and some for months: MARTINA WILD, BENEDIKT STIASNY, ANAIS OLIVA, LOUIS CORBEL-DEMAILLY, THIBAULT ANGLES D'ORTOLI and MARLENE AUBIN have run quite a few reactions, as did Priaxon's technician MARTIN FREDRICH. KATHARINA WOLF, technician at IPB Halle, has kindly taken care of all HRMS analyses and of ^{13}C NMR spectra while our lowband channel was out of order. Her colleague ANJA EHRLICH helped by conducting preparative column chromatography when Priaxon's instruments did not succeed.

Not chemistry related but no less important were the regular coffee breaks with NADINE KALINSKI. These daily chats kept me informed, cheered me up and diverted me from failed experiments and smashed glassware.

Finally to anyone I might have forgotten or whose support was so sublime that I failed to notice it: Thank you!

2. Abbreviations

3-CR	three component reaction
4-CR	four component reaction
°C	degree Celsius
δ	chemical shift
Ac	acetyl
AIBN	azobisisobutyronitrile
A_N	nucleophilic addition
APT	attached proton test
Ar	Aryl
ATRC	atom transfer radical cyclization
BINAP	2,2‘-bis(diphenylphosphino)-1,1‘-binaphthyl
bipy	2,2’-bipyridine
Bn	benzyl
BOC	*tert*-butyloxycarbonyl
BOC_2O	di-*tert*-butyl dicarbonate
cat	catalyst, catalytic
cm	centimeter
CV	column volume (dead volume of the filled column)
d	day(s) *or* dublett
dba	dibenzylideneacetone
DCM	dichloromethane
DeBOC	removal of a BOC protecting group
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
DVB	divinylbenzene
EA	ethyl acetate
eq.	equivalent(s)
ESI	electro spray ionisation
Et	ethyl
Et_2O	diethyl ether
EWG	electron withdrawing group
g	gramm
gHMBC	gradient heteronuclear multiple bond correlation spectrometry
grad	gradient
GRP	general reaction procedure
h	hour(s)
Hex	*n*-hexane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HV	high vacuum
Hz	Hertz
IMCR	isocyanide based multicomponent reaction
^{i}Pr	*iso*-propyl
iso	isocratic
J	coupling constant
KHDMS	potassium hexamethyldisilazide
$KO^{t}Bu$	potassium *tert*-butylate
m	*meta*

M	mol/L
MCR	multicomponent reaction
Me	methyl
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute(s)
mL	milliliter
mM	millimolar
mmol	millimol
Ms	mesyl
MS	mass spectrometry
µW	microwave
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectrometry
Nu	nucleophile
o	*ortho*
p	*para*
Ph	phenyl
ppm	parts per million
PS	polystyrene
py	pyridine
RCM	ring closing metathesis
R_f	retention factor
rt	room temperature
SAW	Staudinger/aza-Wittig
s. m.	starting material
S_N	nucleophilic substitution
S_NAr	nucleophilic aromatic substitution
^{t}Bu	*tert*-butyl
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilan *or* trimethylsilyl
tol	toluene
Ts	tosyl
U-4CR	Ugi four component reaction
UDC	Ugi reaction/deprotection/cyclization
USAW	Ugi/Staudinger/aza-Wittig
UV	ultraviolett
X	halogen *or* anion of a protic acid
Xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

3. Introduction

The need for new pharmaceutical agents with improved potency, fewer side effects, easier administration, or enabling completely new therapies is still unmatched. Despite all progress in life sciences finding a suitable pharmacophore remains a challenging task and often one has to rely on trial and error during the very first step of drug discovery. Starting around 1990 this *hit finding* process was supplemented increasingly by combinatorial chemistry which offers an elegant and efficient method for generating new potentially active structures. In the following *hit-to-lead* development and *lead optimization* phases computer aided drug design has been established as a valuable tool but those calculations and the hypotheses derived thereof have in the end to be verified in experiments.

During this whole search for compounds with (at least some of) the desired properties, the synthesis of often hundreds of different derivatives is required. Therefore short and efficient synthetic procedures are needed to minimize the expenses of time, material, personnel and – ultimately – money.

Multicomponent reactions (MCRs) meet these criteria in an excellent way: They offer a fast and efficient entry to a multitude of different scaffolds with easy-to-vary substituents. This makes them a proper choice for the generation of libraries for *hit finding* as well as the syntheses of compounds for the determination of structure-activity-relationships during later stages. This potential is multiplied further by postmodifications of the MCR scaffolds (see chapter 4.4) that significantly enlarge the accessible chemical space by increasing the complexity and diversity of the available molecules.

Therefore MCRs and their postmodifications are ideally suited for their use in drug discovery, be it for pharmaceutics or other active agents such as insecticides, herbicides and the like. Conversely there is a steady need for the development of new and improved postmodifications that enlarge the product portfolio and/or provide an easier and faster access to it.

4. Background

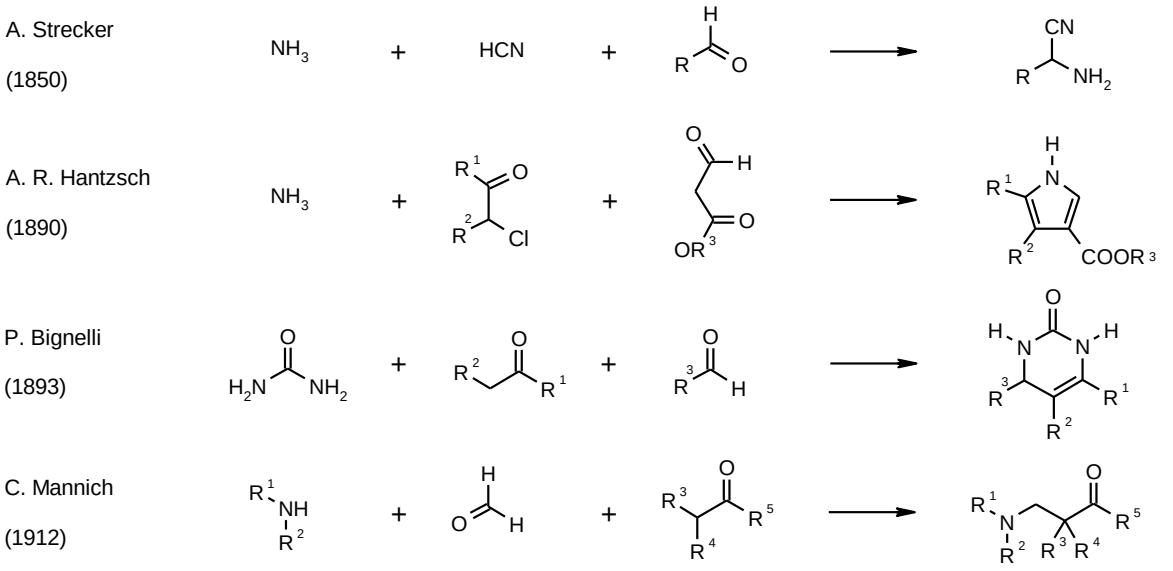
4.1. Definition and advantages of multicomponent reactions

A reaction is termed multicomponent reaction (MCR) when at least three different chemical entities enter into a reaction forming a product containing significant parts of the starting materials.[1]

MCRs can be seen as "concatenated sequences elementary organic reactions under similar conditions".[2] This leads to a number of advantages over usual (linear) organic syntheses:[3] In a normal reaction only two reagents or functional groups react with each other. The resulting product has to be purified before the next step requiring substantial amounts of time, work effort and material to be spent on this process, and giving – especially in long multi-step syntheses – vanishing small yields. On the contrary MCRs enable highly convergent synthetic routes. As several new bonds are formed in a single MCR, less synthetic steps are required. Therefore MCRs usually excel at the (little) effort required and the overall yield. In most cases they are highly atom efficient reactions producing less side products and waste which is especially relevant when they are used in large scale industrial context. Further their broad substrate scope offer a fast and facile access to a wide and easy to vary range of products. The chemical space covered by MCR chemistry is huge – it is growing exponentially with the multiplicity of the reaction and highly diverse, and contains numerous privileged scaffolds like dihydropyrimidines or diketopiperazines. [4–6]

4.2. Schematic overview over multicomponent reactions

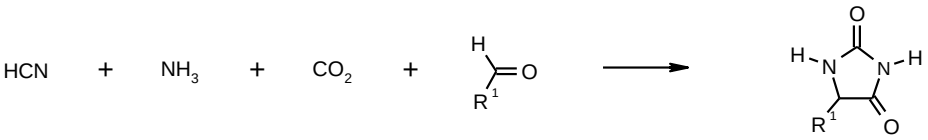
The reaction between bitter almond oil (hydrogen cyanide containing benzaldehyde) and ammonia to cyanobenzylamine described by LAURENT and GERHARDT in 1838 is considered the first MCR.[7] Twelve years later STRECKER published his well-known modification giving access to α-aminoacids.[8] Phosphorbioisosters of those aminoacids can be synthesized by the Kabachnik-Fields reaction.[9,10] The by far best studied MCR (by the number of publications) is the Mannich reaction. Similar products are obtained by the Petasis reaction in which the imine or iminium ion is arylated or vinylated by boronic acid or boronates.[11]



Scheme 1: Historic overview over important MCRs (adapted from [3])

M. Passerini
(1921)

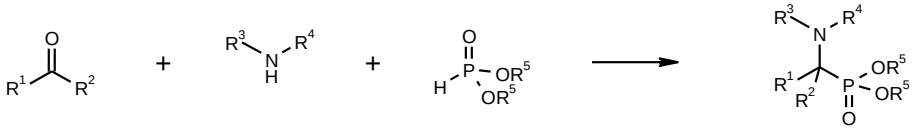
H. T. Bucherer
H. Bergs
(1934)



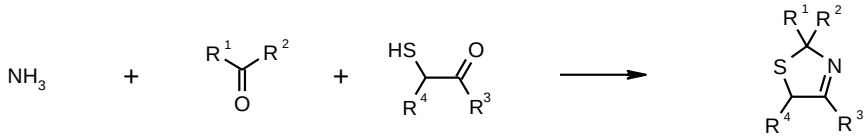
O. Roelen
(1938)

W. Reppe
(1939)

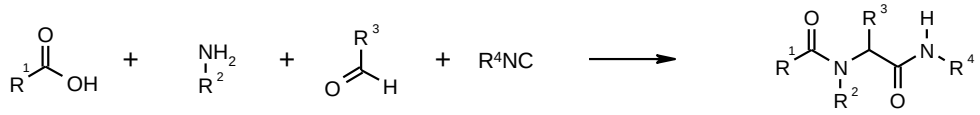
M. I. Kabachnik
E. K. Fields
(1952)



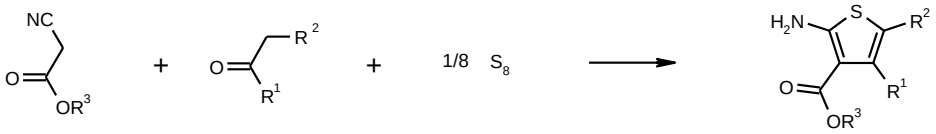
F. Asinger
(1958)



I. Ugi
(1959)

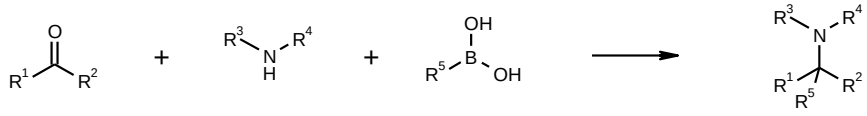


K. Gewald
(1966)



P. L. Pauson
I. U. Khand
(1971)

N. A. Petasis
(1993)



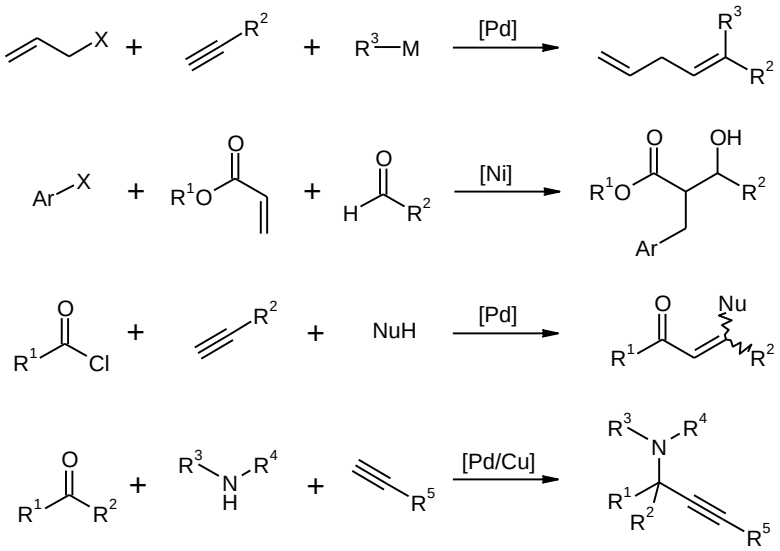
K. Bienaymé
C. Blackburn
K. Groebcke
(1998)

Scheme 1 (continued): Historic overview over important MCRs (adapted from [3])

Medically relevant heterocycles are produced by the Bignelli reaction (dihydropyrimidines),[12,13] the Bucherer-Bergs reaction (hydantoines)[14] and the Hantsch reaction (pyrroles and dihydropyridines).[15–17] 2-Aminothiophenes can be synthesized by the Gewald reaction.[18,19] The Asinger reaction which was originally published as a four component reaction (4-CR) gives also cyclic products. Today it is mostly used in its modified 3-CR variant with an increased substrate and product range.[20–22]

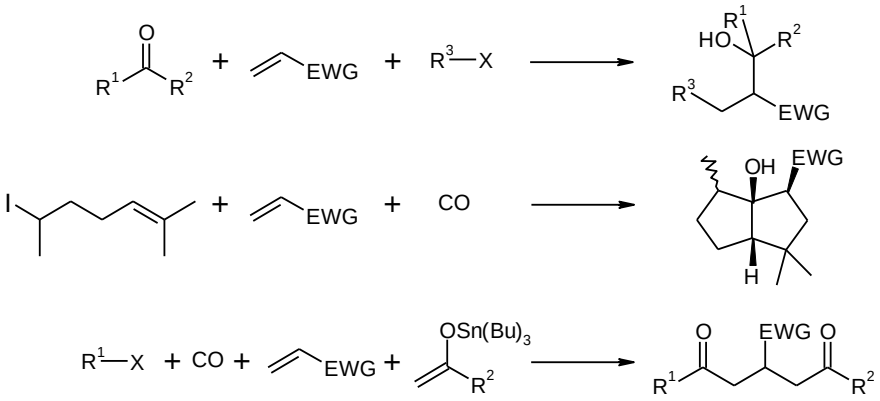
Of great industrial relevance are metal catalyzed MCRs like the hydroformylation of alkenes for the bulk synthesis of aldehydes,[23] the hydrocarboxylation of alkynes for the production of α,β-unsaturated carboxylic acids, esters, amides and anhydrides[24,25] or the Pauson-Khand reaction for the synthesis of substituted cyclopentenones.[26,27] There a plenty more examples but their complete enumeration is beyond the scope of this thesis, so only some examples are given with references for further reading (Scheme 2):[28,29]

- carbometallation and especially carbopalladation of alkenes, alkynes and allenes, and subsequent scavenging of the Pd intermediate, for example with activated alkenes or boronic acids,
- bisfunctionalisation of activated alkenes,
- reaction of in situ generated alkenones and alkynones in a Michael reaction/cyclocondensation
- addition of metal organyls to imines.



Scheme 2: Examples for metal catalyzed multicomponent reactions.[29]

Due to their intrinsic ability to chain reactions, radical reactions have also been employed in MCRs. Elegant MCR processes have been developed by proper choice of the reactants and thereby ensuring alternating reactions between nucleophilic and electrophilic radicals generated from suitably substituted unsaturated functionalities. Intramolecular reactions can be further controlled by appropriate placement of the participating functionalities with respect to the Baldwin rules. Scheme 3 shows three examples for radical three and four component reactions.[30–32]



Scheme 3: Examples for radical based multicomponent reactions.[29]

Among the most versatile and efficient MCRs are the isocyanide based multicomponent reactions (IMCR) like the Ugi reaction, the Passerini reaction or the Bienaymé–Blackburn–Groebcke reaction.[33–38] They exploit the unique chemistry of isocyanides which relies on the irreversible transition of the isocyanide carbon valency from II to IV. A great advantage of these IMCRs is their excellent tolerance for a wide variety of functional groups that can be used for further modifications of the MCR product. This opens an elegant entry to diversity and complexity orientated reactions. Especially the Ugi reaction excels in its high substrate diversity and robustness which makes it a prime choice and the most used IMCR. It will be explained in detail in the next section.

4.3. Ugi reaction

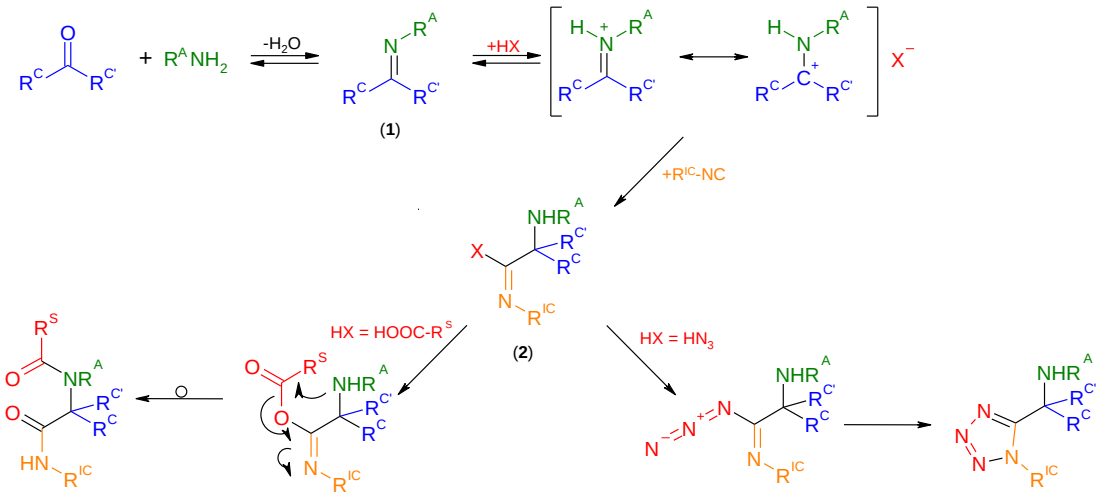
Among the known MCRs the Ugi reaction is one of the most versatile and variable,[39] offering a rapid and easy access to complex molecules. The exceptional range of potential starting materials – especially of the acid component – enables the construction of many structurally diverse products.

Closely related to the rise of the Ugi reaction is the chemistry of isocyanides. For a long time they have been shunned because of their lability, their difficult synthesis and – probably foremost – their obnoxious smell. Only after the discovery of the Ugi reaction and other isocyanide based reactions new and simpler syntheses have been developed.[a]

Table 1: Common starting materials for the U-4CR (adopted from [3]).

Amine component	Ammonia, primary/secondary amine, hydroxylamine, hydrazine and its derivatives
Carbonyl component	Aldehydes, ketones
Acid component	Carboxylic acids, carbonic acid, EWG-substituted phenols, cyanates, thiocyanates, selenocyanates, alkyl thiosulfate, dialkyl phosphate, hydrazoic acid, hydrogen selenide, hydrogen sulfide, water, carbon disulfide

Ivar UGI has proposed the following mechanism (Scheme 4[b]):[41] After condensation of the amine with the carbonyl component the resulting imine (**1**) is activated by protonation. The iminium ion and acid anion then add to the isocyanide carbon forming the so-called α-adduct (**2**). Depending on the exact nature of the amine and acid component the reaction can stop here or undergo further spontaneous reactions. The two reactions relevant for this thesis are depicted in Scheme 4:



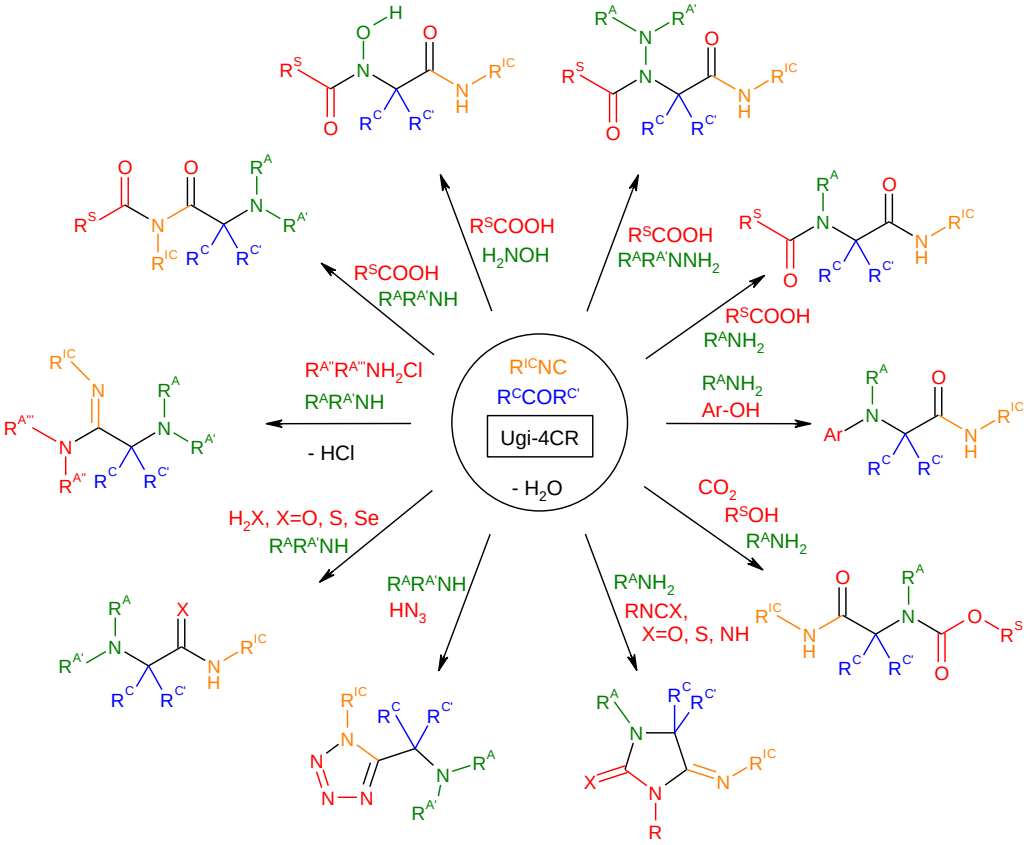
Scheme 4: Mechanism of the Ugi four component reaction.[1]

[a] More than 1000 different isocyanides are known today and for the most part are commercially available.[40]

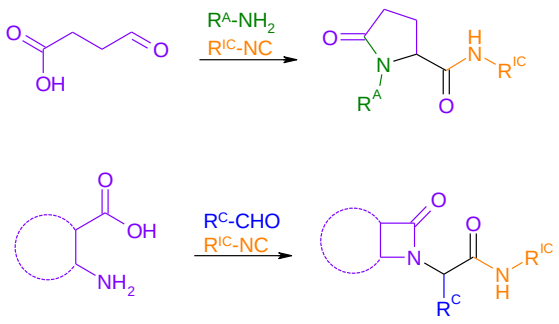
[b] The following color code will be used throughout this thesis: carbonyl component = blue, amine = green, acid component = red, isocyanide = orange, bifunctional component = purple.

When a primary amine and a carboxylic acid is employed, the NH of the α-adduct is acylated by an intramolecular Mumm type rearrangement (Scheme 4, left pathway). The impetus is the formation of two new stable amides. With HN_3 as acid component (generated *in situ* from TMS-N_3 and MeOH) ring closure of the azide moiety with the isocyanide nitrogen is effected and a tetrazole is formed (Scheme 4, right pathway).

Scheme 5 shows scaffolds which can be synthesized by a standard Ugi-4CR with monofunctional starting materials (adopted from [3]). By using bis- and trifunctional starting material a wide variety of heterocycles are accessible, i.e. lactames from β-amino acids or semicarbaldehydes (Scheme 6).[42,43]



Scheme 5: Products of the Ugi-4CR with monofunctional starting materials (adapted from [3]).



Scheme 6: Two examples for bifunctional starting materials in the U-4CR.[42,43]

4.4. Postmodifications of the Ugi reaction

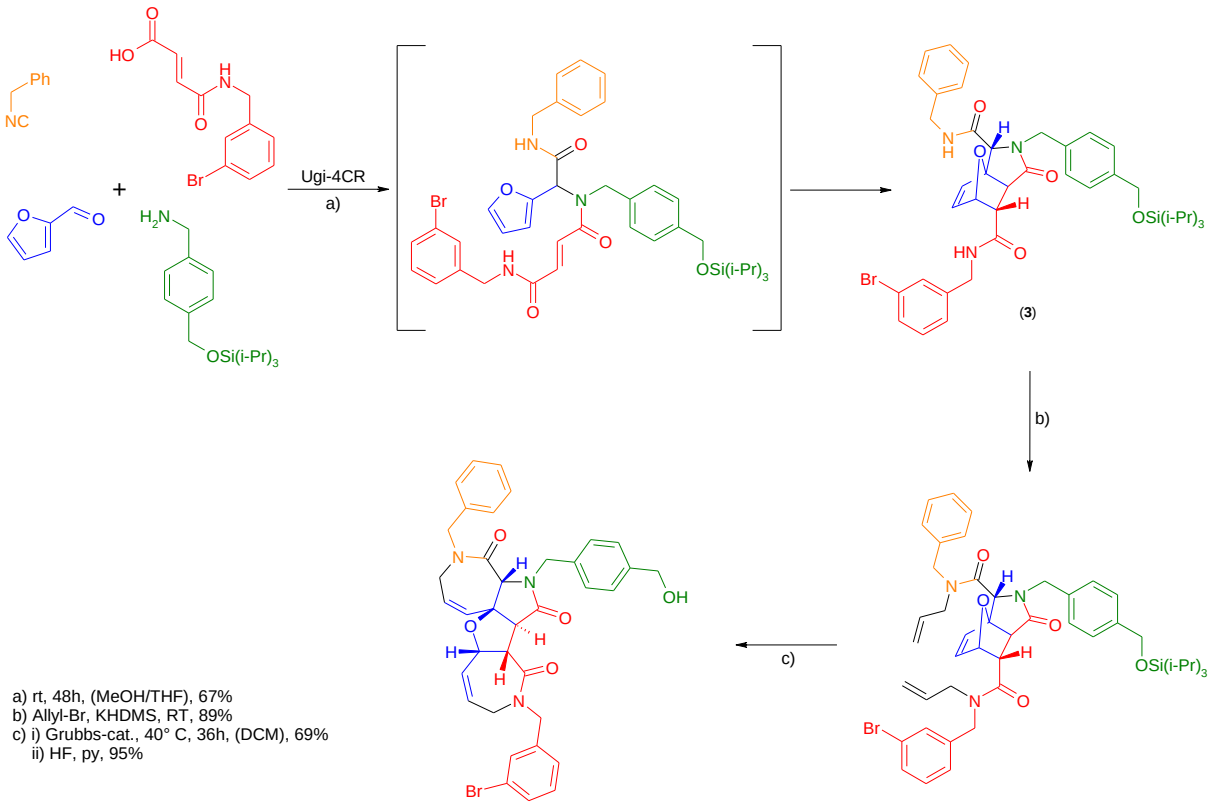
The products of the Ugi reaction are usually linear and peptide-like which limits their usability as drugs in several ways:[44] (i) Quick degradation under physiological conditions, (ii) a flexible core structure that is likely to bind to several targets and thereby causing undesired side effects, and (iii) poor bioavailability. Therefore several research groups have transformed the primary Ugi product in a second reaction – usually a cyclization – to overcome the aforementioned limitations. Those reactions (sequences) were termed *postmodifications* and allow a quick and easy access to a considerably larger and much more diverse chemical space than by MCR chemistry alone.[45–47]

The functional groups required for a postmodification reaction can either be introduced at the stage of the MCR by employing starting materials with appropriately placed (if necessary protected) functional groups, or are generated by the MCR. In another postmodification variant single residues on the Ugi scaffold can be selectively cleaved liberating existing functionalities within the core of the scaffold or generating new ones. Especially elegant synthesis can be realized by combinations of MCRs increasing the diversity of the products, in the best case exponentially.[1,48–53]

In the following selected examples of postmodifications of the Ugi reaction are given. Please refer to the following citations for a more comprehensive overview:[2,29,45,54–56]

4.4.1. Ugi/Diels-Alder/RCM

SCHREIBER *et al*. have published a Ugi-4CR/Diels-Alder cyclization/ring closure metathesis reaction sequence that demonstrates impressively how complex molecules can be generated in just a few steps based on the Ugi reaction. Starting with a simple Ugi-4CR reaction the primary product cyclizes

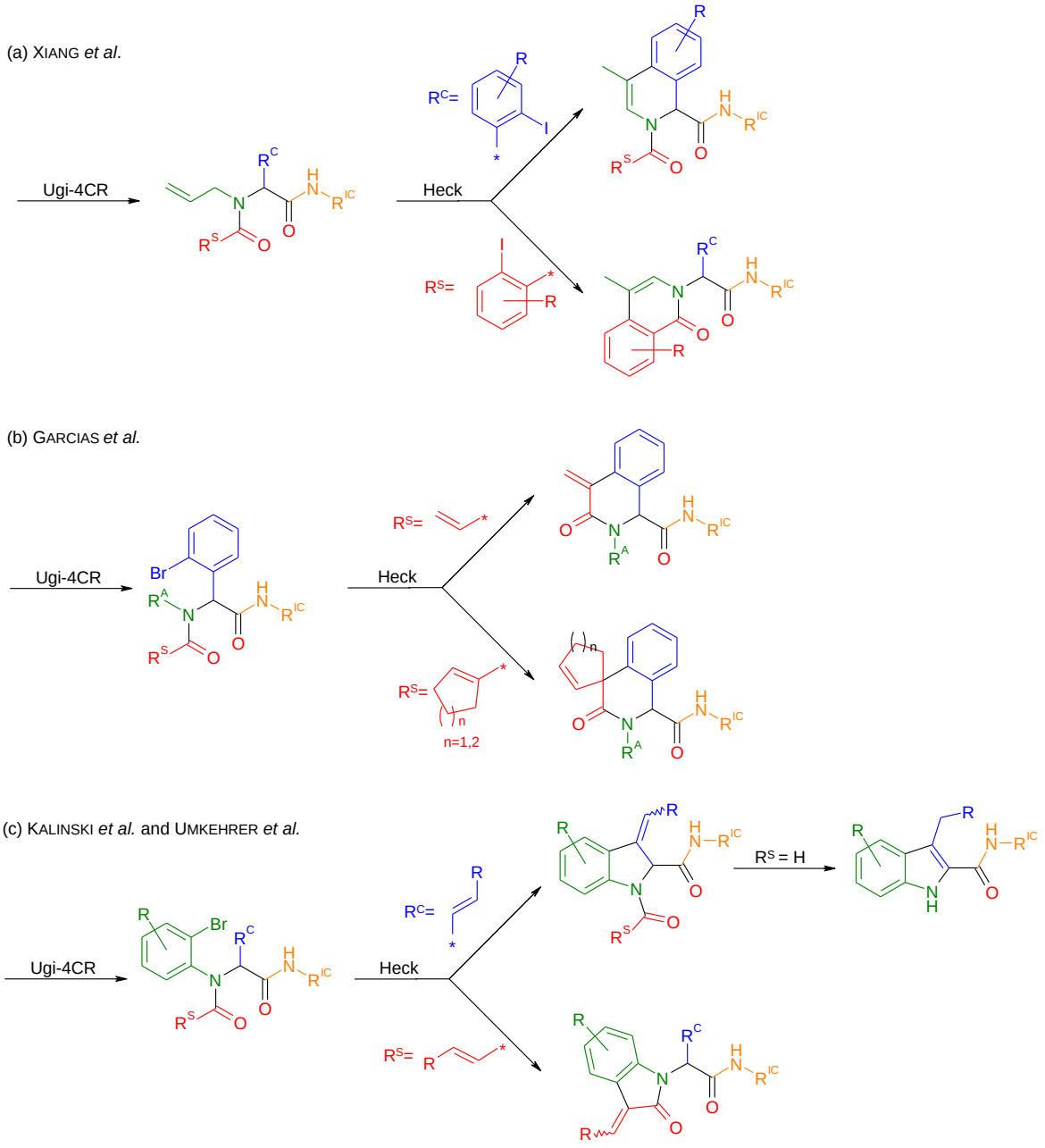


Scheme 7: Ugi/Diels-Alder/RCM reaction sequence.

in a Diels-Alder reaction *in situ* to the tricyclic system **3**. After double allylation it is converted to the final product by a RCM.

4.4.2. Metal catalyzed postmodifications

The first example of a combination of an Ugi reaction and a subsequent Heck reaction is XIANG's synthesis of 1,2-substituted 1,2-dihydroisoquinolines and 2H-isoquinolin-1-ones. The functionalities necessary for the Heck reaction were introduced with the amine component (allylamine) and the carbonyl or acid component (*o*-iodobenzaldehyde or *o*-iodobenzoic acid).[57] The exocyclic double bond of the primary Heck product isomerizes under the reaction conditions to the more stable endocyclic one (Scheme 8a).

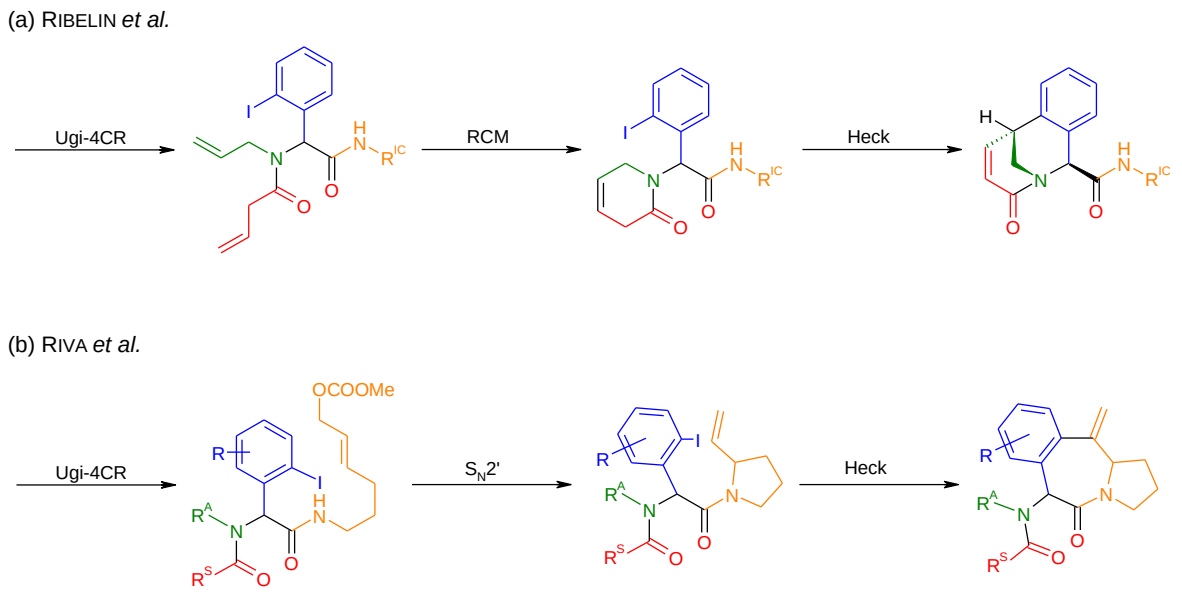


Scheme 8: Ugi/Heck reaction sequences.

By permutating the alkene and haloaryl functionalities around the Ugi scaffold 1,4-dihydroisoquinolin-3-ones can be obtained bearing an alkylidene substituent at position 4 or – with cycloalk-1-enyl carboxylic acids – a spiro substitution (Scheme 8b).[58] Further permutations have been published by UMKEHRER *et al.*[59] (*o*-bromaniline and α,β-unsaturated carboxylic acid to 3-alkylidene substituted indolones) and KALINSKI *et al.*[60] (o-bromaniline and α,β-unsaturated carbaldehydes to *N*-acylated dihydroindols and *N*-unsubstituted indoles; Scheme 8c).

RIBELIN *et al.*[61] developed a 3-step Ugi/RCM/Heck sequence which gives benzannulated bicyclic bridged lactames. The Michael acceptor generated during this reaction could be converted further with good diastereoselectivity (Scheme 9a).

Another 3-step sequence with two palladium catalyzed reactions was published by RIVA *et al.*[62] The two metal catalyzed reactions of this Ugi/S_N2'/Heck cascade can be even run in a one pot manner. The crucial building block of this sequence is the functionalized isocyanide: the allylcarbonate reacts with the secondary amide generated during the Ugi reaction to give a vinyl substituted pyrrolidine. This enters into the Heck reaction yielding the final product (Scheme 9b).

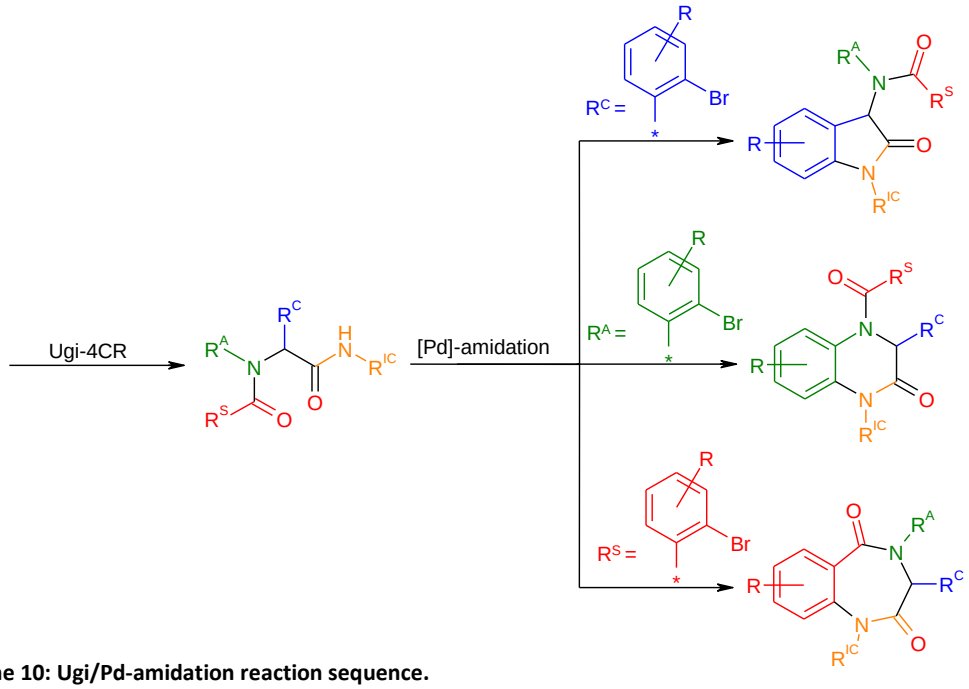


Scheme 9: Ugi/RCM/Heck (a) and Ugi/S_N2'/Heck (b) reaction sequences.

Another variant is the palladium catalyzed amidation.[63,64] As it involves the secondary amide generated by the Ugi reaction, only one additional functional group (an aryl halide) is necessary. This frees one residue and thereby adds a point of diversity. Depending on the position of the *o*-haloaryl residue indolones (from *o*-halobenzaldehydes), benzo-1,4-diazepin-2,5-diones (*o*-halobenzoic acids) or dihydroquinoxalines (*o*-haloanilines) can be synthesized (scheme 10). Copper catalyzes these reactions as well albeit with lower yields than palladium.[65]

When *o*-halosubstituted isocyanides are used, the resulting Ugi products can be cyclized under copper catalysis to 2-substituted benzoxazoles or – if a thiocarboxylic acid has been employed in the Ugi reaction – to benzthiazoles (scheme 11a).[66]

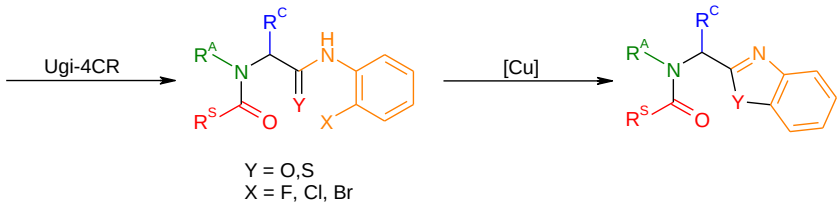
ZHU's group utilized this method for the synthesis of a series of 3-benzoxazolyl isoindolones (n = 0). The first (copper catalyzed) cyclization of the bifunctional Ugi product leads selectively to the benzoxazole, the second (palladium catalyzed) cyclization uses the newly created benzylic position



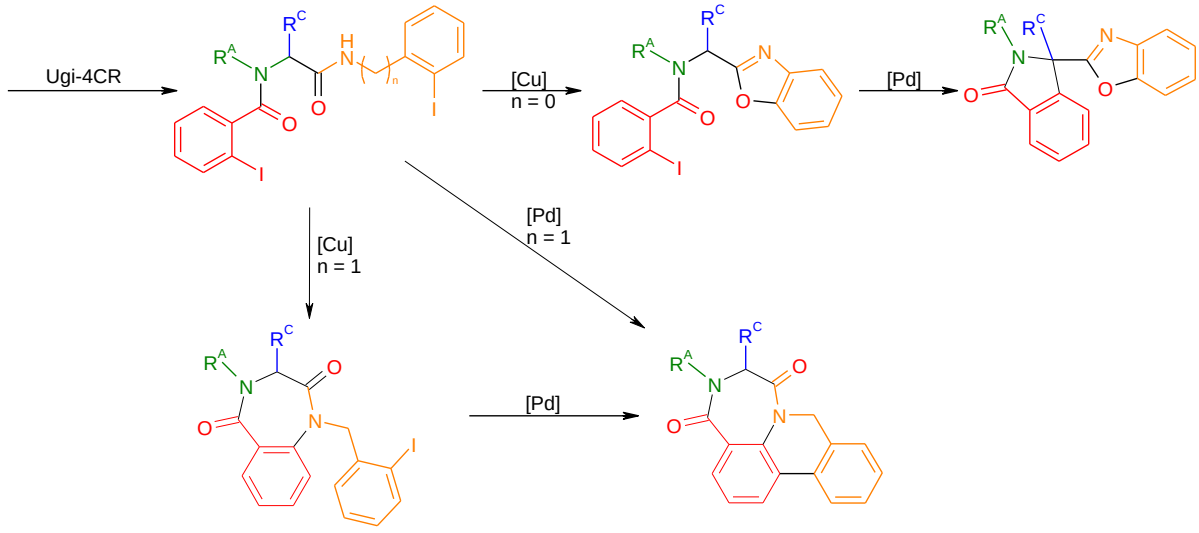
Scheme 10: Ugi/Pd-amidation reaction sequence.

for its ring closure to the final isoindolone. With benzylic isocyanides (n = 1) the copper catalyzed cyclization leads to the corresponding benzdiazepindiones which are afterwards transformed in a Heck reaction to the final tetracyclic products (scheme 11b).[67] The latter are also accessible directly from the Ugi products by a palladium catalyzed tandem reactions.[65]

(a) SPATZ *et al.*



(b) ZHU *et al.*

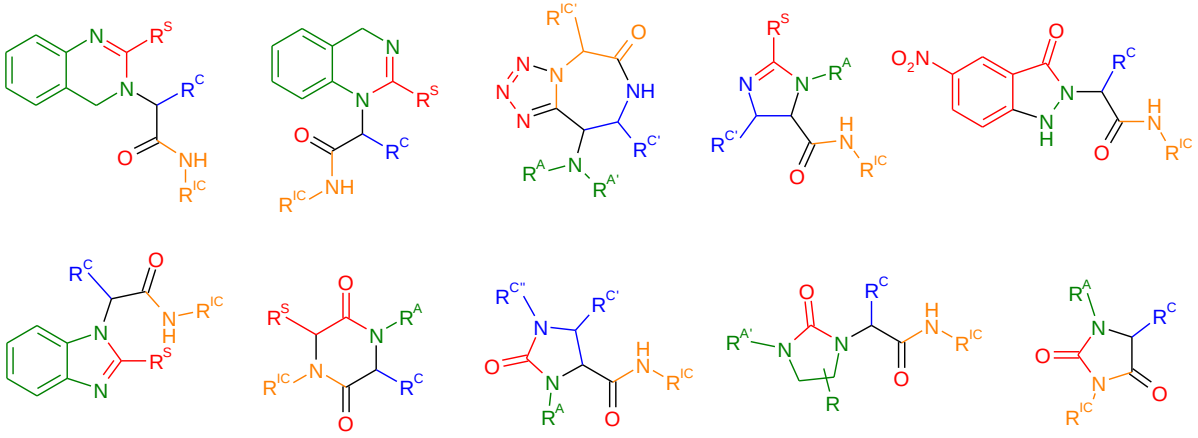


Scheme 11: Copper catalyzed cyclizations.

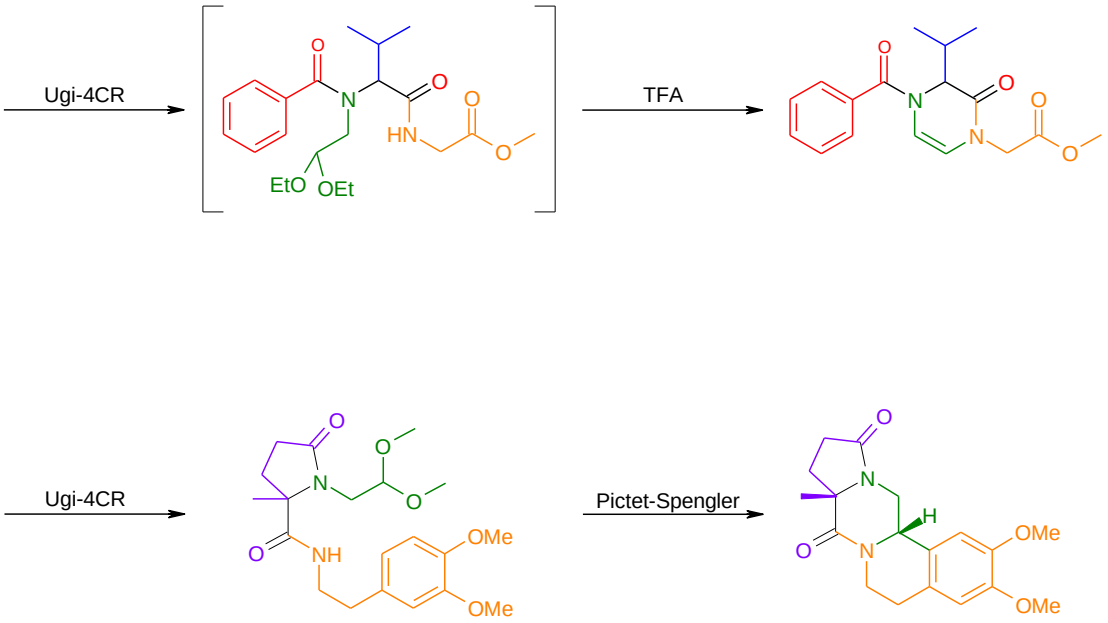
4.4.3. Ugi/Deprotection/Coupling (UDC) and related techniques

Postmodifications involving functional groups that are not orthogonal to those participating in the MCR necessitate the use of protecting groups. The prototype of those reaction sequences is the Ugi/DeBOC/Cyclization (UDC) technique developed by HULME *et al*. which relies on BOC protected amines. After cleavage of the BOC group the free amine is reacted in an ester aminolysis or a nucleophilic (aromatic) substitution.

This extremely flexible strategy is normally run as one pot procedure and has been successfully used for the synthesis of different substituted heterocycles such as cyclic ureas,[68] indazolones,[69] benzimidazoles,[70] imidazolines,[71] quinazolines,[72] diketopiperazines,[73] and tetrazolodiazepinones,[74] to name a few (scheme 12). Another suitable substrate class for this approach are acetals which have been used for i.e. the synthesis of dihydropyrazinones[75] and in an Ugi/Pictet-Spengler sequence[76,77] (Scheme 13).



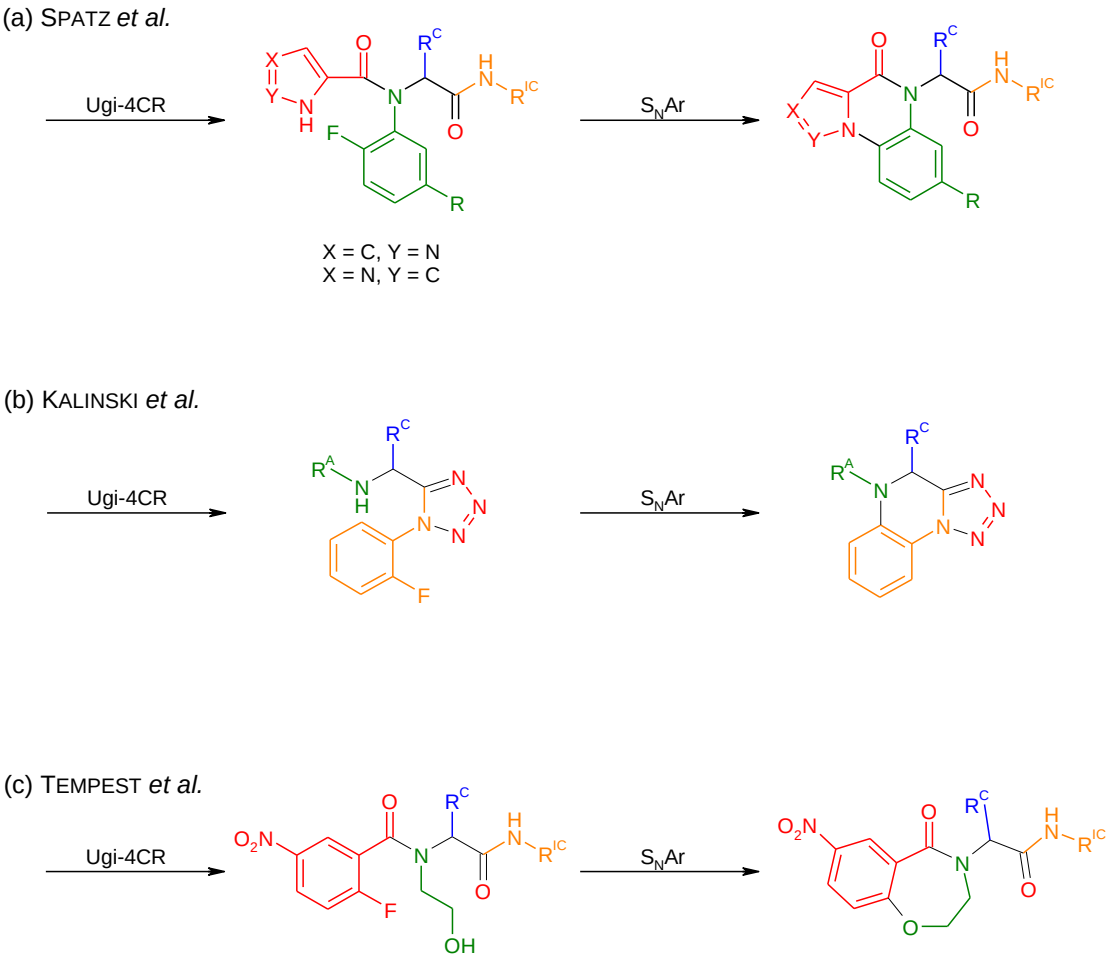
Scheme 12: Examples of scaffolds accessible by an UDC strategy.



Scheme 13: Dihydropyrazinone synthesis and Ugi/Pictet-Spengler reaction sequence.

4.4.4. Nucleophilic aromatic substitution (S_NAr)

S_NAr is an often chosen postmodification because the necessary electrophiles (usually fluoroaryls) are commercially readily available, orthogonal to the MCR functionalities and hence easily applicable. Besides the example mentioned above (indazolone synthesis; see chapter 6.3.2 for further details)[69] there are several more using either orthogonal nucleophiles (i.e. alcohols or nitrogen incorporated into aromatic systems) or nucleophilic positions generated during the MCR, thereby enabling efficient syntheses of diverse heterocycles (Scheme 14).[69,78,79]



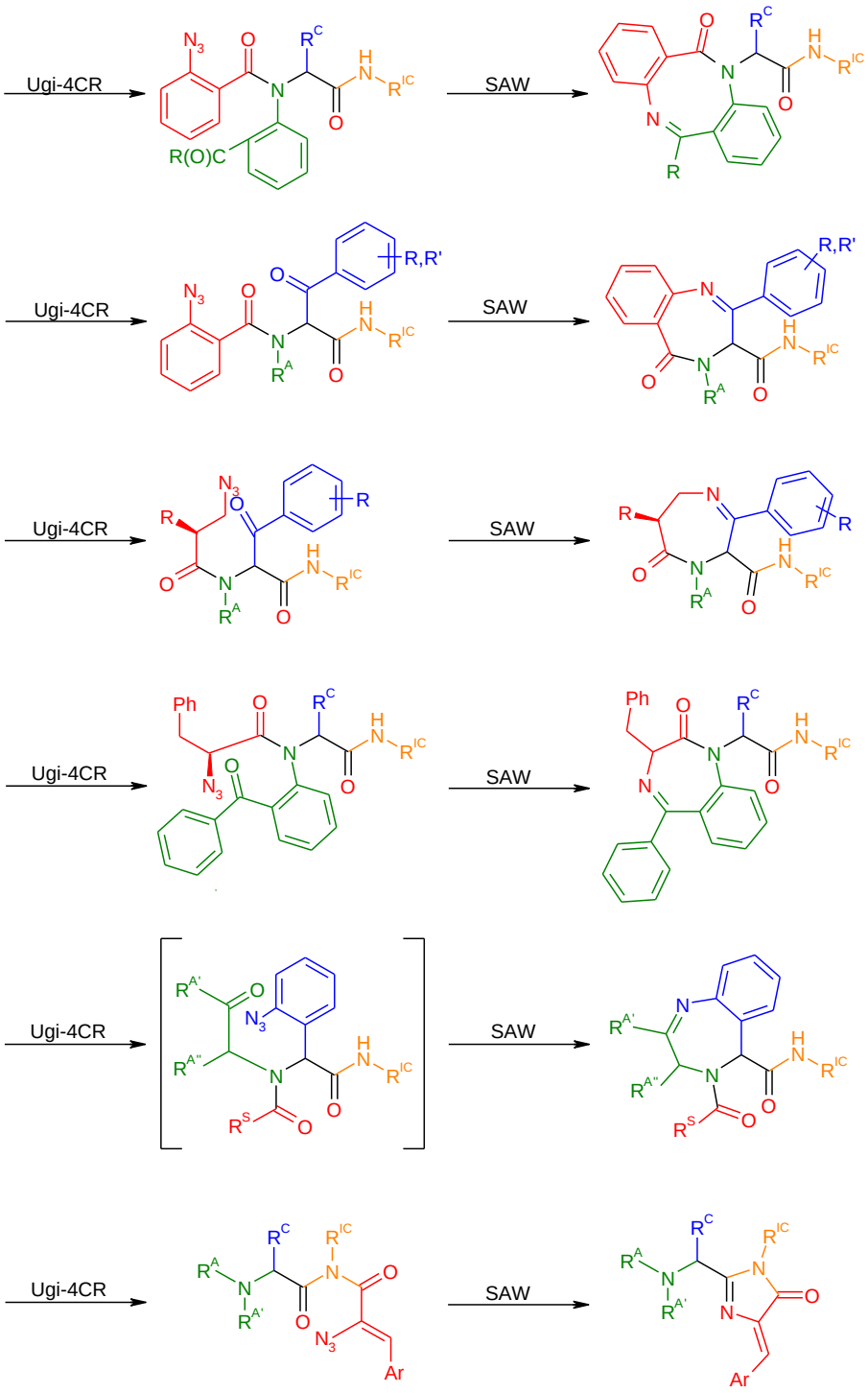
Scheme 14: Ugi/S_NAr reaction sequences.

4.4.5. Ugi/Staudinger/aza-Wittig

The intramolecular aza-Wittig reaction is a versatile and reliable organic transformation for the construction of small and medium sized nitrogen containing heterocycles.[47,80–87] It is usually conducted under mild conditions (neutral solvent, no acid, base or catalyst), high yielding and possesses good chemoselectivity, which altogether often marks it as the reaction of choice for natural product syntheses.[88–93] A wide variety of carbonyls can be used as substrates: aldehydes, ketones, carboxylic anhydrides,[84] acyl halides,[92] heterocumulenes (ketenes, (thio)isocyanates, CO_2, CS_2),[92,94–97] (thio)ester,[84,98–100] urethanes[101] and sulfoxides.[84] Amides have long been considered inert under these conditions[102–104] but were found to be reactive if properly activated by

electronwithdrawing substituents, i.e. as imides,[91,103–107] acylureas[108] or *N*-tosylated amides.[98] Reaction examples for unactivated amides are scarce and usually suffer from inferior yields.[102,109–111]

Several combinations of an Ugi reaction followed by (Staudinger)-aza-Wittig cyclization have been reported during the last six years, both as Staudinger/aza-Wittig/Ugi[112–118] and as Ugi/Staudinger/aza-Wittig[109,119–125] reaction sequence (USAW). While the former is a tool for generating imines which are otherwise hard to obtain the latter offers an elegant way for the cyclization of regular Ugi products.

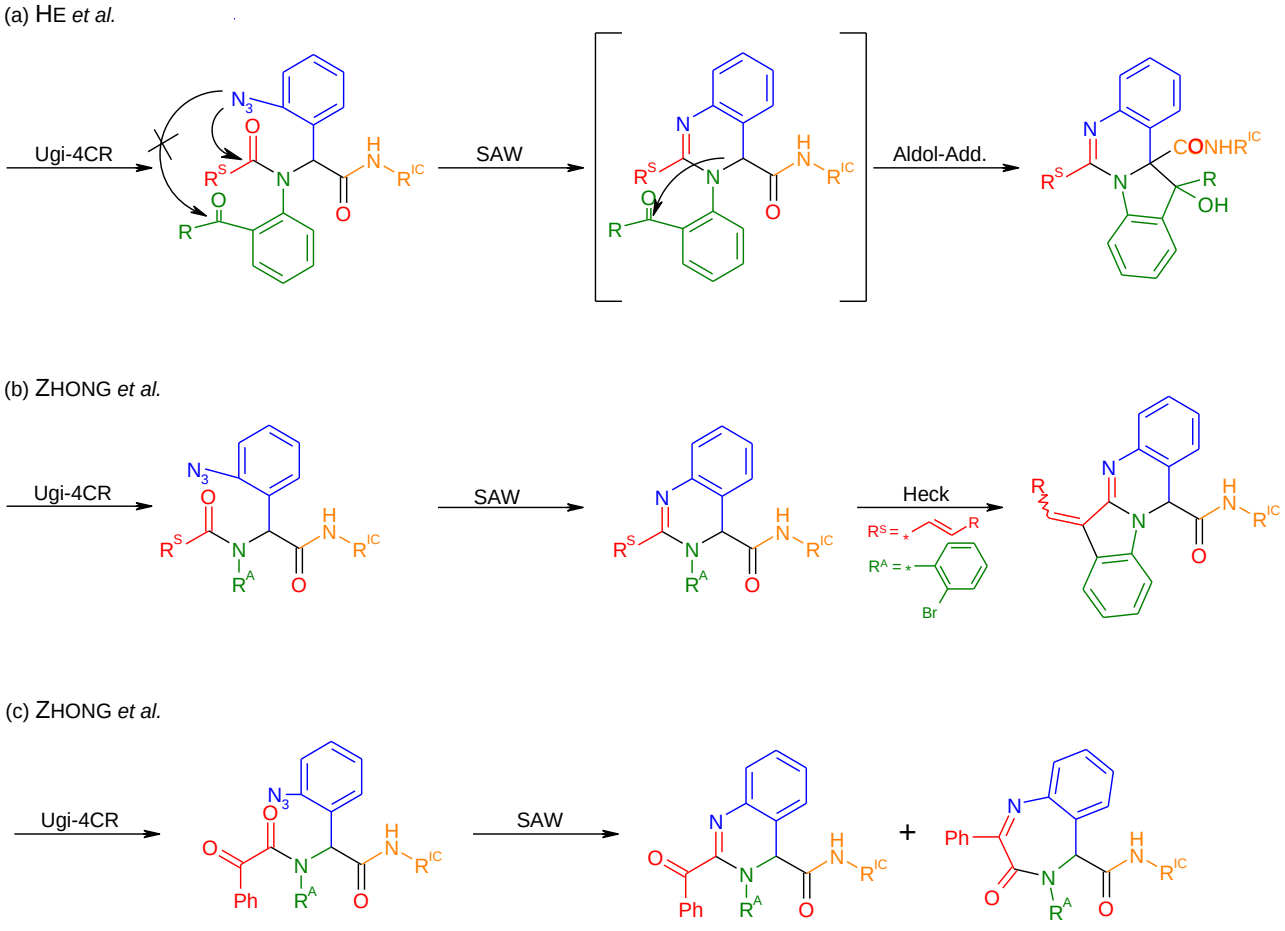


Scheme 15: Ugi/Staudinger/aza-Wittig reactions sequences.

The first example of an Ugi/Staudinger/aza-Wittig sequence was published by CORRES *et al*. who used *o*-azidobenzoic acid and *o*-aminophenone.[124] Further (intramolecular) variations employing *o*-azidobenzoic acid/phenylglyoxals,[123] azidoalkylcarboxylic acids/aminobenzophenones,[122] azidoalkylcarboxylic acids/phenylglyoxals[122] and azidobenzaldehyde/β-ketoamines[125] followed (Scheme 15). One of the most recent examples takes advantage of the imide structure that is generated by the use of a secondary amine in the Ugi reaction (scheme15, bottom).[126]

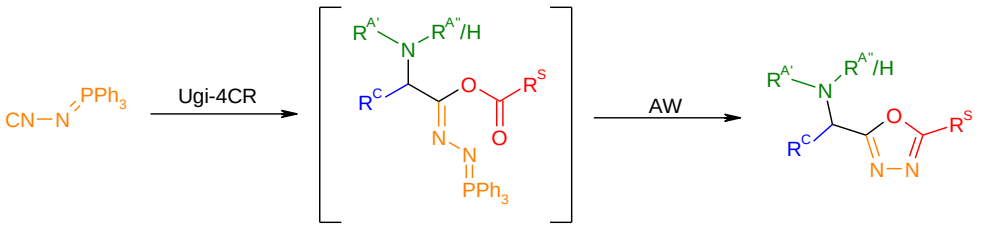
When HE *et al*. tried to extend that methodology to *o*-azidobenzaldehyde/aminobenzophenone systems they were surprised to learn that not the ketogroup but the tertiary amide of the Ugi scaffold engaged in the aza-Wittig reaction (Scheme 16a).[119] They reasoned that the EWG-substituted aryl activates the amide for the cyclization. Nearly at the same time another USAW sequence utilizing the tertiary amide generated in the course of the Ugi reaction as carbonyl component for the aza-Wittig cyclization was published by ZHONG *et al*. To overcome the low reactivity of the amide group they had to resort to the more reactive $PMePh_2$. PPh_3 led only in combination with certain acid residues (R^S = H, CF_3) to acceptable yields (Scheme 16b).[109]

The same group observed in a similar system with phenylglyoxylic acid that the product ratio bewtween the 6-membered dihydro-quinazoline and the 7-membered diazepinone is primarily dependant on the steric and electronic structure of the amine residue R^A and not on different reactivity of the two carbonyls (amide vs. ketone, Scheme 16c).[127]



Scheme 16: Ugi/Staudinger/aza-Wittig reaction sequences involving the tertiary amide of the Ugi scaffold.

With (*N*-isocyanimino)triphenylphosphorane as functionalized isocyanide RAMANZANI *et al.* were able to intercept the α-adduct of the Ugi reaction directly. The corresponding disubstituted oxadiazoles could be isolated in good yields (Scheme 17).[120,128,129]



Scheme 17: Ugi/aza-Wittig reaction sequence intercepting the α–adduct of the Ugi reaction.

4.4.6. Radical cyclizations

There are only few examples for radical based postmodifications, most of them by EL KAÏM's group.[c] For these intramolecular cyclizations xanthates have been employed, introduced either in form of the bifunctional starting material ethoxy thiocarbonyl-sulfanylacetic acid or via an S_N reaction after the MCR. Treatment with dilaurylperoxide as radical initiator yields the expected lactames as a racemic mixture in good yields (scheme 18a).[132] After switching the solvent to isopropanol this strategy could be expanded to alkyne-π-systems giving unsaturated lactames (Scheme 18b).[133]

Another atom transfer radical cyclization (ATRC) was published by YU *et al.* They used iodoacetic acid and allylamine and cyclized the Ugi-4CR products with triethylborane (Scheme 18c).[134]

In another system the same group used indole's quality as an efficient radical trapping agent in an intramolecular dearomatization-spirocyclization process.[135,136] Under the oxidative reaction conditions the initial peptidylanion is transformed into a radcial which adds to the reactive C-3 position yielding the spirocompound and the secondary radical at the C-2. This is then further oxidized to an iminium ion that reacts with the isocyanide derived amide to the final tetracyclic product (Scheme 19).[137]

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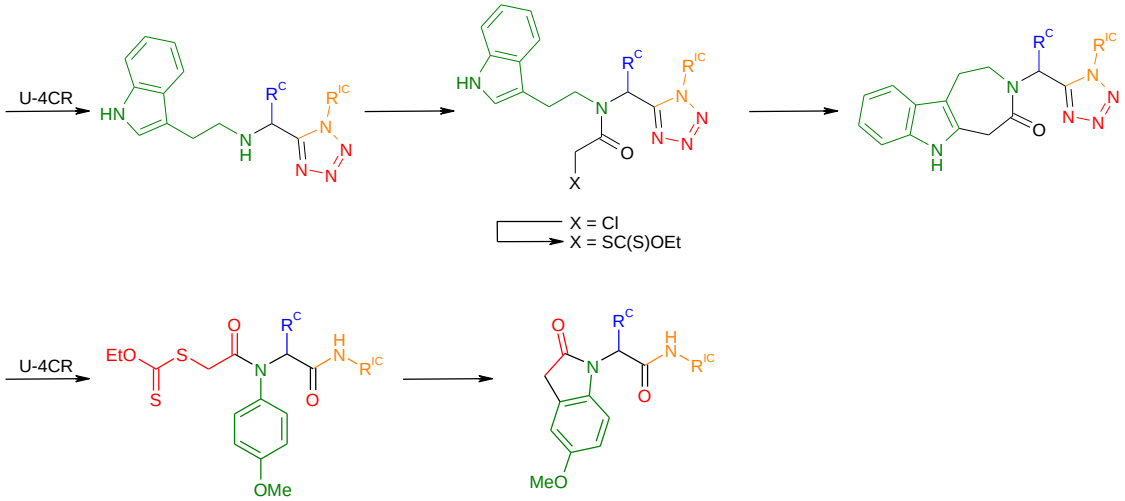
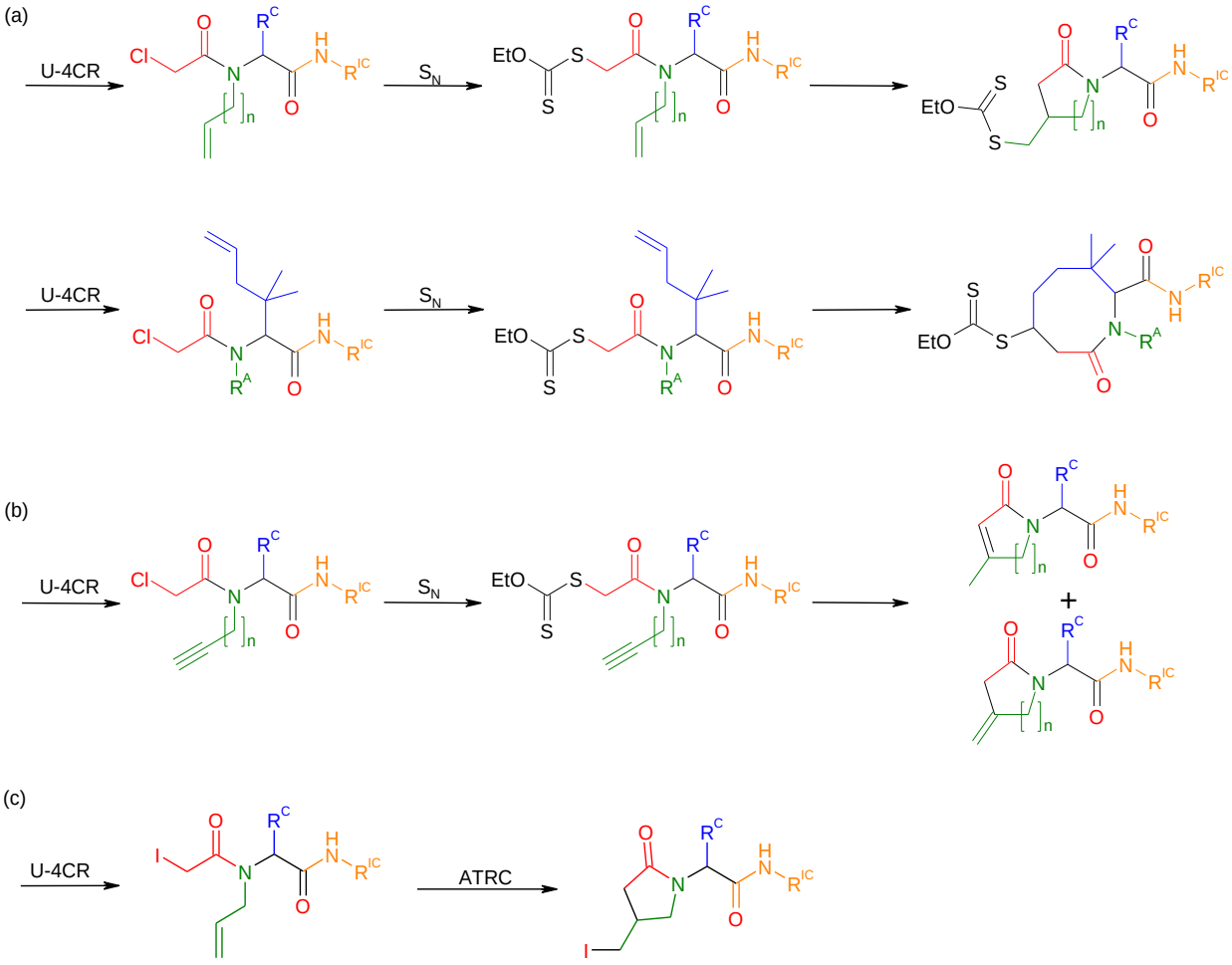
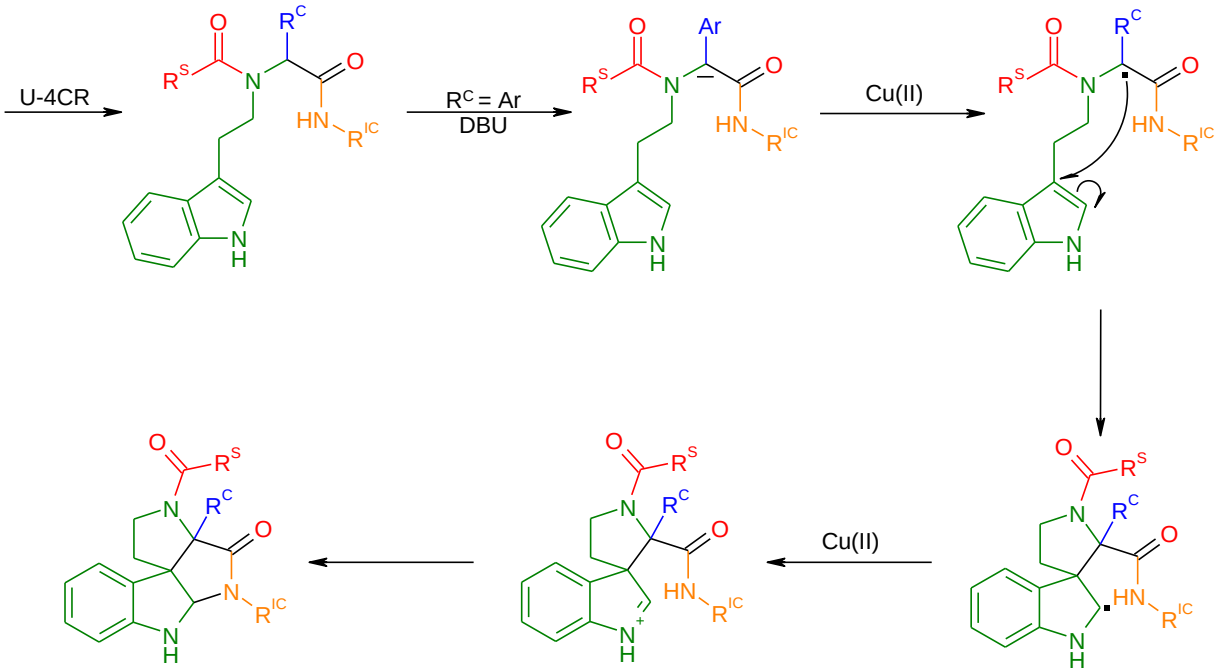
[c] NB: Two more papers on radical cyclizations of Ugi-4CR products have been published by GÁMEZ-MONTAÑO's group after the experiments shown in chapter 6.1 (pp. 29) had been conducted:[130,131]



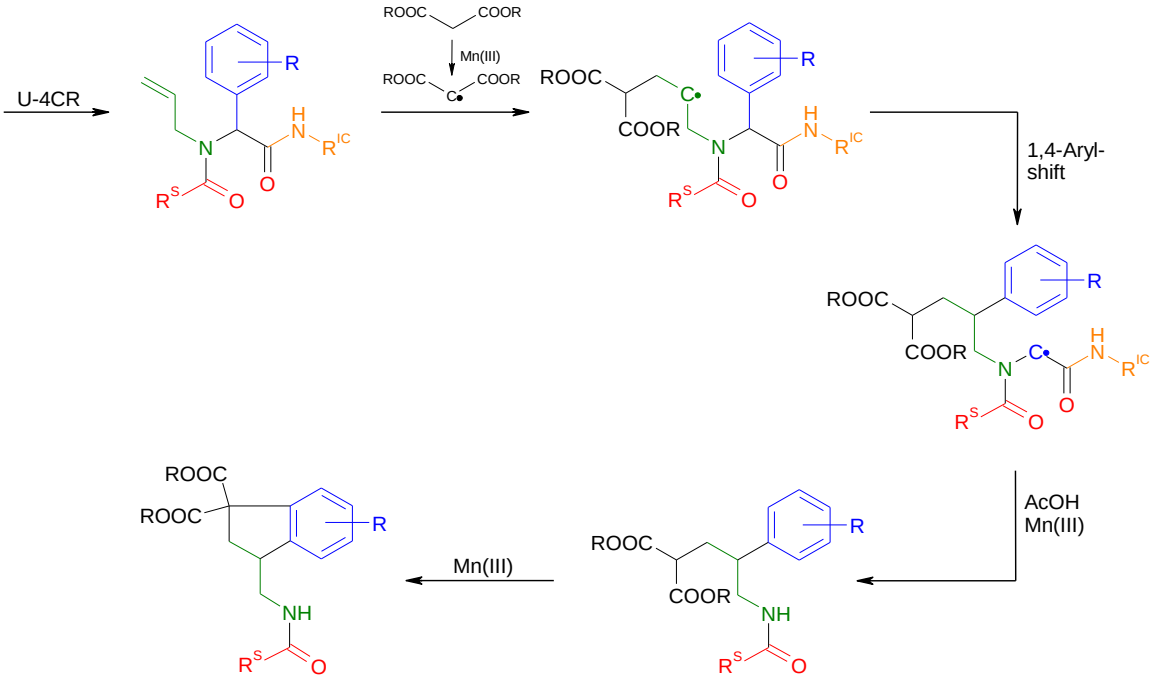


Scheme 18: Ugi/radical cyclizations (I).



Scheme 19: Ugi/radical cyclizations (II).

During the course of the only example of an intermolecular radical cyclization the bisamide structure characteristic for the Ugi reaction is broken up.[138] After initiation of the reaction by Mn(III) which reacts with the second component (the CH acidic malonic ester) the resulting radical adds to the double bond and triggers an 1,4-aryl shift. The resulting peptidyl radical is oxidized to its anion by excess Mn(III) which in turn is cleaved by the solvent acetic acid. The remaining fragment is further oxidized and cyclizes to the final indane (Scheme 20).



Scheme 20: Ugi/radical cyclizations (III).

5. General materials and methods

Isocyanides and 2-azido-1-phenyl-ethylamine were kindly provided by Priaxon AG, all other chemicals and solvents were bought from commercial vendors (Aaron Chemistry, ABCR, Acros, Apollo Scientific, TCI Europe, VWR) and used without further purification with the following exception: Chloroacetone (ABCR) was filtered through a short pad of basic aluminum oxide prior to use.

Column chromatography

Column diameter and height of the silica bed are provided in the experimental procedures.

silica	Macherey&Nagel or Merck , "Kieselgel 60", 0.063 – 0.200 mm
fine silica	Macherey&Nagel or Merck , "Kieselgel 60", 0.040 – 0.063 mm
aluminum oxide (basic)	Acros, 0.050 – 0.200 mm, 60A
aluminum oxide (neutral)	Acros, 0.050 – 0.200 mm, 60A

Thin layer chromatography

plates	Macherey&Nagel or Merck (aluminum sheets with Silica 60 F254).
detection	UV (254 and 366 nm), iodine vapor, staining with ninhydrine (1 % (m/v) in EtOH), staining with molybdate (5 % (m/v) ammonium moolybdate and 0.1 % (m/v) cer(IV)sulfate in 10 % sulfuric acid)

Flash chromatography

model	Varian IntelliFlash 971-FP
column	Varian (type "SF15-12g") or Macherey-Nagel (type "SF15-15g").

Column volumes (CV) refers to the filled column dead volume as stated by the manufacturer. Methods are reported in the following abbreviated form:

iso *#* for *x* CV	isocratic with *#* % of eluent B for *x* column volumes (CV)
grad *#-#'* in *x* CV	gradient from *#* % to *#'* % of eluent B in *x* column volumes (CV)

HPLC/MS:

Detector	Varian ProStar 325 (254/220 nm)
Column	Poroshell 120 SB-C18 column, 3×50 mm, particle size 2.7 µm
Eluent	H_2O + 0.1 % HCOOH and MeCN + 0.1 % HCOOH
Gradient	10/90 → 90/10 in 2 (reaction analysis) or 5 min (other)
Flow	1.25 ml/min
Mass spectrometer:	1200 L Quadrupol MS/MS
Ionization method:	ESI, positive Ionization
Detection range	80 – 1000 amu

High resolution mass spectrometry

Instrument Bruker Apex III Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer equipped with an Infinity cell, a 7.0 Tesla superconducting magnet (Bruker), an RF-only hexapole ion guide and an external electron spray ion source.

Max. error $< 2.00 \times 10^{-6}$

NMR-Spectroscopy

Instrument	Varian Oxford 400 (Mercury VX)
^{1}H-frequency	399.85 MHz
^{13}C-frequency	100.54 MHz
Temperature (unless noted otherwise)	25 °C

All spectra are referenced to tetramethylsilane as internal standard (δ = 0 ppm). For rotamer forming substances (i.e. most Ugi products) peaks are assigned to a certain rotamer if an unambigious assignment is possible. Splitting patterns are abbreviated with s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet), hept (heptet), m (multiplet), br (broad signal), and combinations thereof.

Microwave

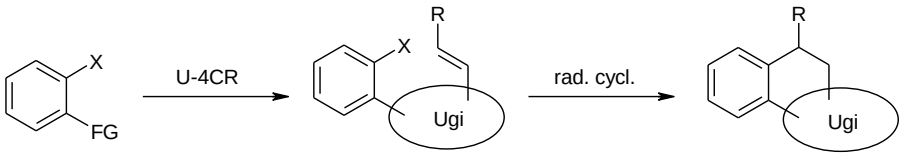
Instrument CEM Discover BenchMate

6. Results and discussion

6.1. Ugi/Radical cyclizations

Radical reactions are meanwhile a well-established tool in organic synthesis for elegant, mostly C—C bond forming processes, often surprisingly efficient.[139] Postmodification of an Ugi scaffold by radical cyclization has been published by EL-KAÏMS group[132,133,138,140,141] and YU *et al*.[134,142] (see 4.4.6 for details) using mostly atom transfer radical cyclizations.

Given the potential of radical reactions it was to be tested if simple *ortho*-halogenosubstituted aryls were suitable substrates for postmodification by radical means (Scheme 21). Those functional groups are well tolerated in MCRs and have been used extensively in the context of transition metal catalyzed postmodifications. After generation of the initial radical by homolytic dehalogenation the resulting σ-radical could add to a suitably placed unsaturated bond.



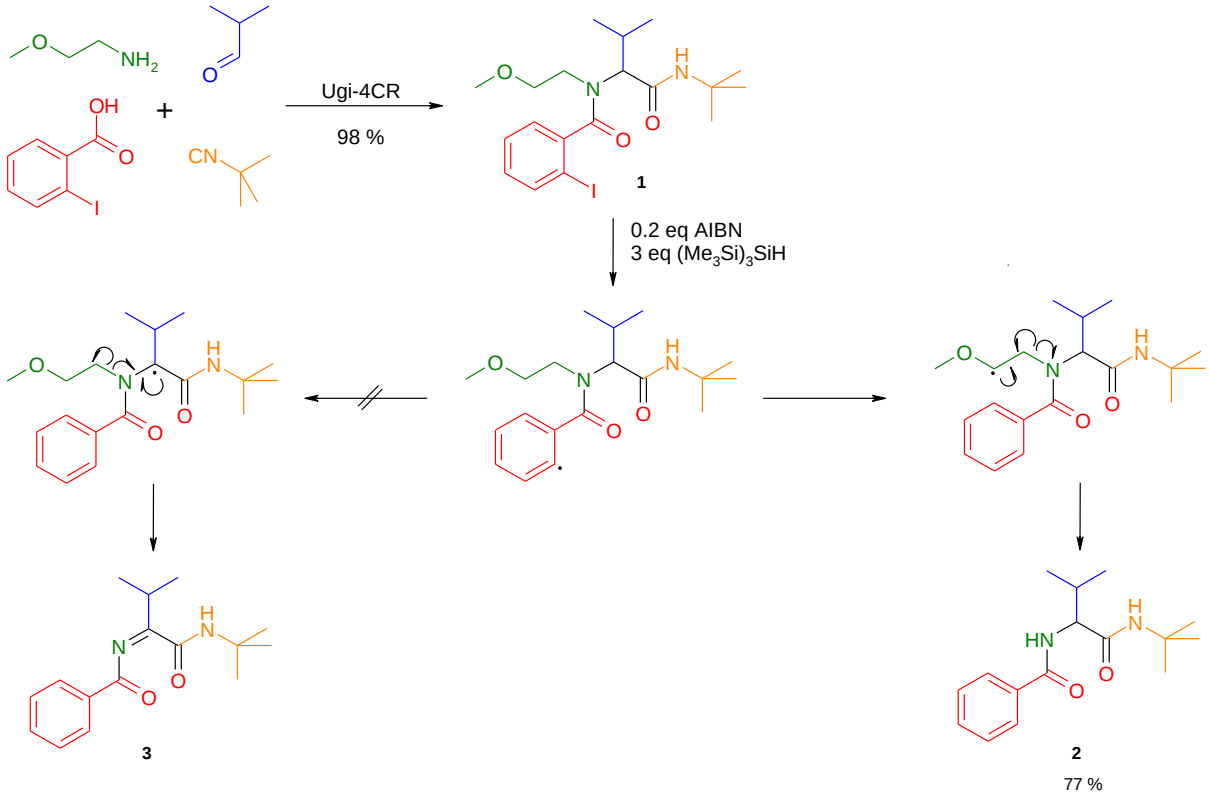
Scheme 21: Ugi-4CR/radical cyclization strategy.

6.1.1. Results and discussion

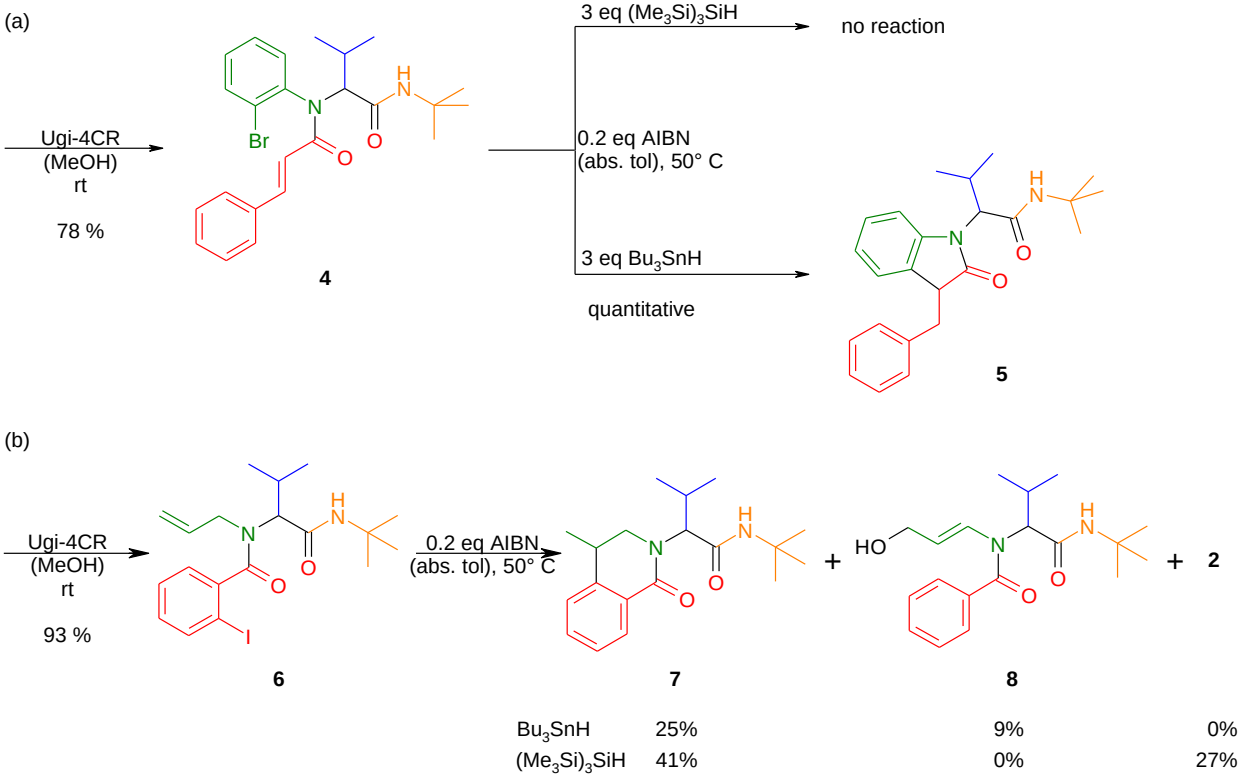
First Ugi products **1** and **3** were synthezised: **1** as negative control, that is to check whether the standard Ugi bisamide scaffold is stable under the reactions conditions of the radical reaction and compatible with all intermediates – after all the arylic σ-radicals involved are more energetic than the alkyl radicals usually used in this kind of transformations. Indeed systematic fragmentation of a similar Ugi products under radical conditions has been reported.[142]

1 was heated with 0.2 equiv. of AIBN as radical initiator in degassed toluene to 50 °C together with 3 equiv. of $(Me_3Si)_3SiH$ as hydride donor. $(Me_3Si)_3SiH$ is a nontoxic alternative of comparable reactivity to the usually employed Bu_3SnH.[139] Near to complete conversion was observed after 80 minutes with the main product being **2** generated by 1,6-hydrogen transfer and β-cleavage. Fortunately, no products (i.e. **3**) resulting from a formation of an (stabilized) peptidyl radical by 1,5-hydrogen transfer were found (Scheme 22).

With this result **4** was subjected into the cyclization with both $(Me_3Si)_3SiH$ and Bu_3SnH. The results were remarkably different: No reaction took place with the silane but quantitative conversion to the corresponding dihydroindolone **5** was achieved with the stannane (scheme 23a). With the inversely substituted Ugi product **6** (haloaryl substituent introduced with the acid component, double bond at the amine residue), $(Me_3Si)_3SiH$ accomplished better results but the cleavage of amine residue (leading to **2**) was still not neglible (This is a rare example for generating a vinylic radical via hydrogen abstraction (in this case 1,6-H)). The reason is the high reactivity of the aromatic σ-radical which is reflected in the respective bond dissociation energies:[143] Ar-H 112.9 (±0.6) kcal/mol, Vinyl-H: 110.7 (±0.7) kcal/mol). Therefore Bu_3SnH was chosen for future reactions.



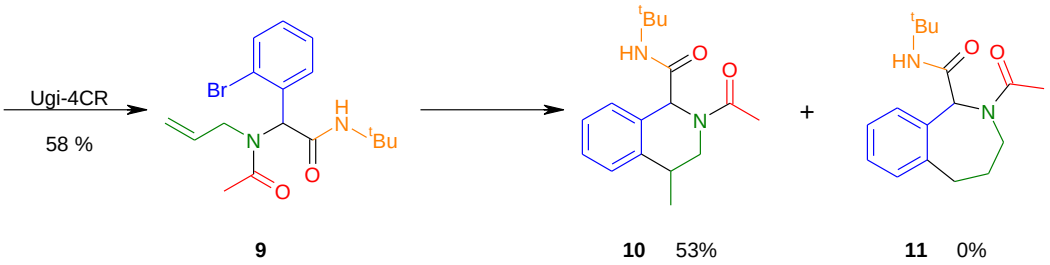
Scheme 22: Stability test for Ugi-4CR scaffold under radical conditions with TTMSS.



Scheme 23: Comparison of $(Me_3Si)_3SiH$ and Bu_3SnH as hydrogen donors.

Formation of **8** indicates that (1.) the degassing process of the solvent was incomplete and (2.) that hydride abstraction is competing with cyclization/addition to the unsaturated bond. The structure of **8** was confirmed by ^{1}H NMR (*cf*. appendix, p. 127) which clearly shows the formation of only one diastereomer and the signals for an allyl alcohol – as opposed to isomeric oxygenated (at the exocyclic methyl group) **7** which could have formed, too, but would exhibit two diastereomers.

So the remaining permutations of the two functionalities around the Ugi product were examined. Of the remaining six a single one gave positive results in the cyclization: Ugi product **9** could successfully be cyclized to yield **10** in good yield. No signs of the 7-membered ring species **11** were found here or in the cyclization of **6** (Scheme 24).



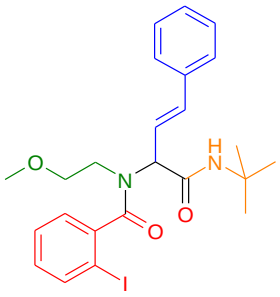
9 **10** 53% **11** 0%

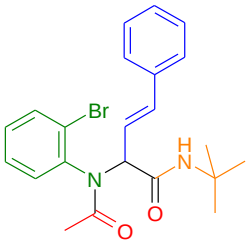
Scheme 24: Tested permutations (I).

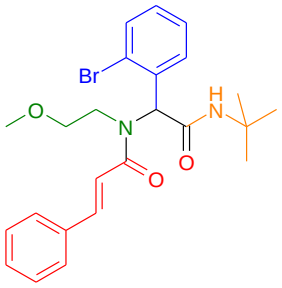
All other experiments did not yield any cyclized products in useful amounts (Scheme 25). While for **15** the Ugi reaction failed due to extensive addition of the solvent to the unsaturated bond which could not be circumvented by switching the solvent from methanol to isopropanol all other Ugi-4CRs performed as expected with good yields. Cyclization of **12** showed traces of product formation in HPLC/MS analysis, **13** and **14** were consumed completely and gave products that could be isolated and showed promising HPLC/MS spectra (purity > 90 %, correct molecular mass, sensible fragmentation pattern) but the ^{1}H NMR spectra did not match the proposed structures and showed significant amounts of Bu_3SnH or reactions products thereof. Attempts to remove the tin byproducts were unsuccessful (*vide infra*). Cyclization of **16** resulted only in the isolation of a small amount of dehalogenated product.

The reason for these results resides most likely in the rigidity of the Ugi scaffold itself. Isomerization of the double bond forming an enamide and an addition of the solvent to it have been ruled out by ^{1}H-NMR spectroscopy, and no cyclization should be disfavored according to Baldwin's rules.[144] **15** is disfavoured for cyclization in the s-*trans* amide form and thus failure is not surprising, but for all other combinations this is not an issue.

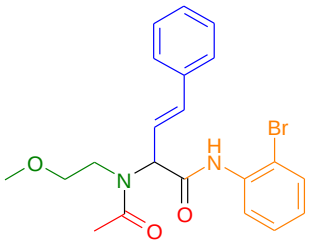
Experiments to enable the cyclizations by reducing the steric strain in the Ugi products were met with no success (Scheme 26). Synthesis of analogous Ugi products with smaller residues (ethylisocyanide replacing *tert*-butyl isocyanide (**17** – **19**), formaldehyde for isobutyraldehyde (**20**)) gave the appropriate compounds in acceptable yield. Crotonaldehyde did not give any of the Ugi products (**22** – **24**) regardless of the other three components. Upon subjecting **17** – **20** to the previous cyclization conditions none of the desired products could be isolated: besides the dehalogenated **22** only the notorious tin organyls were found.

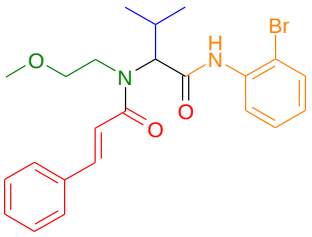






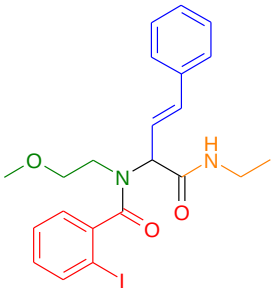
Ugi-4CR	**12** 78%	**13** 63%	**14** 79%
cyclization	traces	no product formation	no product formation

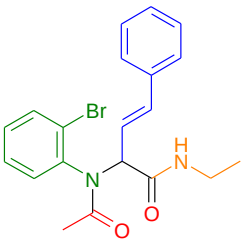


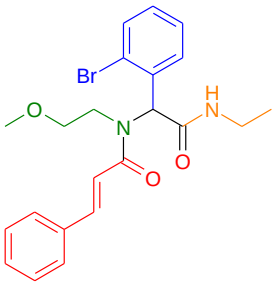


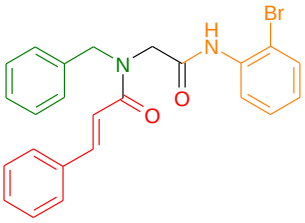
Ugi-4CR	**15** 0%	**16** 69%
cyclization	-	8% dehalogenated product

Scheme 25: Tested permutations (II).



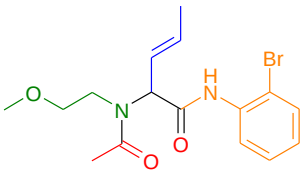




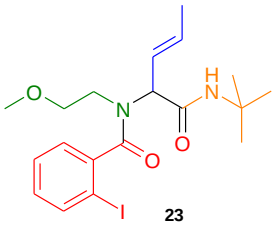


Ugi-4CR	**17** 54%	**18** 54%	**19** 48%	**20** 63%
cyclization	no product formation	no product formation	no product formation	24% dehalogenation (**21**)

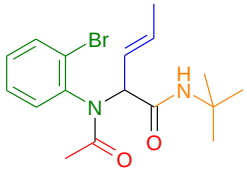
Scheme 26: Tested permutations (III).



22



23

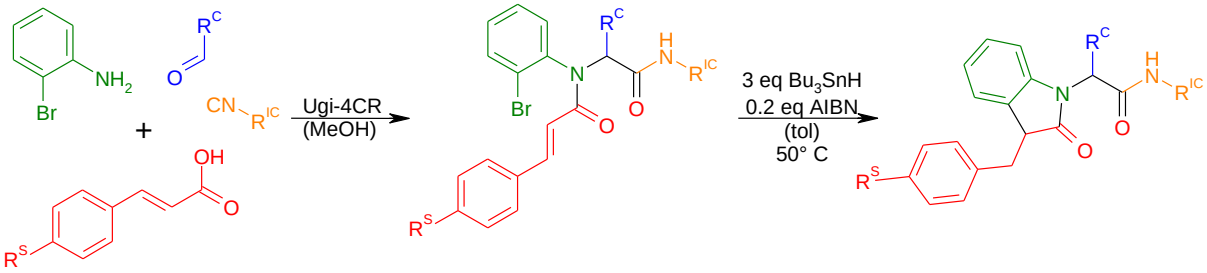


24

Scheme 27: Ugi-4CR attempts with crotonal.

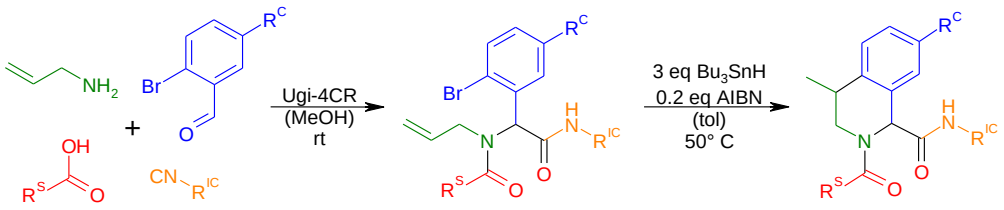
Next the scope of the successful cyclizations was to be examined with a small set of compounds (Table 2). All Ugi reactions performed well, leading to the appropriate products in up to 77 % for the dihydroindolone series and 91 % for the tetrahydroisoquinoline series. In contrast the behavior of the radical reactions was erratic, yielding the bicyclic products in only a few instances. No general pattern explaining this difference in reactivity is obvious as for example cyclization of chlorine substituted **31** leads to a **32** with very good yield and unsubstituted **4** produces **5** quantitatively whereas methoxy substituted **29** fails to give any product. In case of the tetrahydroisoquinoline series results are even worse as no cyclization except the initial test reaction came up positive.

Table 2: Synthesis of dihydroindolones.



R^C	R^S	R^{IC}	Ugi product	Isolated yield	Cyclization	Isolated yield
$CH(CH_3)_2$	H	$C(CH_3)_3$	**4**	77 %	**5**	99 %
$CH(CH_3)_2$	H	p-Cl-Ph	**25**	66 %	**26**	33 %
$CH(CH_3)_2$	H	p-MeO-Bn	**27**	57 %	**28**	0 %
$CH(CH_3)_2$	OMe	$C(CH_3)_3$	**29**	41 %	**30**	0 %
$CH(CH_3)_2$	Cl	$C(CH_3)_3$	**31**	50 %	**32**	80 %
Ph	H	$C(CH_3)_3$	**33**	59 %	**34**	0 %
H	H	$C(CH_3)_3$	**35**	59 %	**36**	0 %
Me, Me	H	$C(CH_3)_3$	**37**	37 %	**38**	0 %

Table 3: Synthesis of tetrahydroisoquinolones.



R^C	R^S	R^{IC}	Ugi product	Isolated yield	Cyclization	Isolated yield
H	CH_3	$C(CH_3)_3$	**9**	58 %	**10**	53 %
H	CH_3	CH_2CH_3	**39**	76 %	**40**	0 %
H	CH_3	1-Cyclohexenyl	**41**	80 %	**42**	0 %
H	CH_3	Ph	**43**	62 %	**44**	0 %
H	CH_3	Bn	**45**	76 %	**46**	0 %
H	Ph	$C(CH_3)_3$	**47**	68 %	**48**	0 %
4,5-OCH_2O-	CH_3	$C(CH_3)_3$	**49**	91 %	**50**	0 %
F	CH_3	$C(CH_3)_3$	**51**	74 %	**52**	0 %

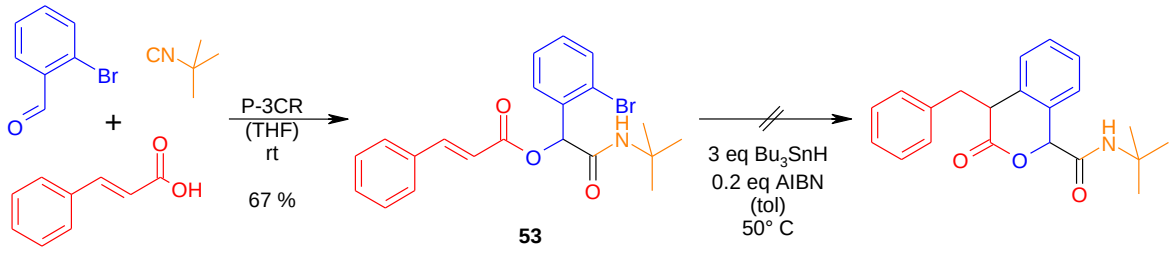
Although reaction monitoring by TLC showed usually complete conversion of the starting material and just one or two new product spots no product could be found after purification by column chromatography. Switching the stationary phase from silica to aluminum oxide (both neutral and basic) did not help. In most cases the only substances that could be isolated after column chromatography were reaction products of the stannane that aggravated all purifications attempts. Removal of these tin byproducts proved to be a major problem. Neither of the following methods[145–149] did accomplish its complete removal:

1. Washing the crude product with copious amounts of hexane.
2. Washing with aqueous 1M NH_4F.
3. Treatment with aqueous 1M NH_4F (formation of water insoluble Bu_3SnF), filtration or extraction with dichloromethane.
4. Oxidation with iodine (formation of Bu_3SnI, very easy to oberve due to decoloration of the added iodine), stirring with aqueous 1M NH_4F (fast formation of Bu_3SnF), then filtration or extraction.
5. Stirring with 1M NaOH (formation of Bu_3SnOH), washing of the organic phase.

The best results were obtained by method 3, but even after several iterations tin species were detectable with ^{1}H-NMR and MS. In few cases subsequent column chromatography effected the desired removal of the tin organyls, but failed for others.

Because of the short lifetimes of radicals molecule conformation plays a vital role. A molecule that is hindered in its internal rotation under reaction conditions may not be able to adopt the conformation necessary for a certain reaction. Indeed such a hampered system with axial chirality has been successfully used in a stereoselective synthesis via chirality transfer.[150] Increasing the flexibility can be achieved in two ways: higher reaction temperatures (facilitating the transition over rotational barriers) or reduction of the steric strain (lowering some rotational barriers). As the first method is not applicable with the internal thermolytic radical initiator used in these experiments the flexibility of the Ugi bisamide core structure was to be increased by using formaldehyde as carbonyl component (**35**) but met with no success. The same is true for blocking this position with an additional methyl group by employing acetone in the Ugi reaction (**37**) in order to prevent any attacks on this position as it had been observed by EL KAÏM *et al*. (see 4.4.6).[138]

Another way to increase the flexibility of the scaffold would be by replacing the tertiary amide by with an ester. Hence the Passerini product **53** was synthezised. It formed readily and was isolated in 67 % yield but – alas – the cyclization under the usual radical conditions (0.2 eq of AIBN, 3 eq. of Bu_3SnH in 10 ml dry degassed toluene at 50 °C for 48 h) failed to yield the desired product (Scheme 28).



Scheme 28: Attempted cyclization of P-3CR product 53.

Because of the overall poor reliability of the radical cyclization and the difficult removal of the tin byproducts which were fatal for any biological screening this reaction sequence was abandoned.

6.1.2. Conclusion

Radical cyclizations of Ugi-4CR products bearing *o*-halogenarylsubstituents and an alkene were examined. The Ugi-4CR scaffold was found to be stable under radical cylization conditions with Bu_3SnH as H-donor but not with $(Me_3Si)_3SiH$. Out of seven Ugi products with permutated functionalities three were successfully cyclized to the corresponding indolone, dihydroisoquinolinone or tetrahydroisoquinoline, respectively, but the cyclization proved to be unreliable and the separation of tin byproducts was tedious.

6.1.3. Contributions

M.W.[d] synthesized compounds **5**, **25**-**27**, **29**, **31**-**33**, **35**, **37**, **39**, **41**, **43**, **45**, **47**, **49** and **51**, T.A. **9**, **10**, **13**, **14**, **16**, **18**-**21** and **53**.

[d] Please refer to chapter 1 for full names.

6.1.4. Material and methods

General reaction procedure 1 **(GPR 1)**

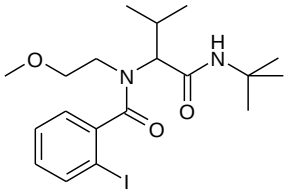
Equimolar amounts of amine and aldehyde were added to the solvent (1M) in a round bottom flask and stirred at room temperature for 2-4 hours. Then 1 equivalent of carboxylic acid is added and the reaction mixture is cooled to 0° C. After addition of 1 equivalent of isocyanide the mixture is stirred until analysis by HPLC or TLC indicates no further reaction progress. After evaporation of the solvent the residue was purified by washing with an appropriate solvent or column chromatography.

General reaction procedure 2 **(GPR 2)**

Equimolar amounts of amine and aldehyde were dissolved (1M) in a pressure tube and stirred at room temperature for 2-4 hours. Then 1 equivalent of carboxylic acid and 1 equivalent of isocyanide are added and the mixture is stirred until analysis by HPLC or TLC indicates no further reaction progress. After evaporation of the solvent the residue was purified by washing with an appropriate solvent or column chromatography.

Synthesis of *N*-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-2-iodo-*N*-(2-methoxy-ethyl)-benzamide (1)

The compound was prepared according to GRP 1 with 1.0 mL of methanol, 80.7 mg (1.12 mmol) of isobutyraldehyde, 81.3 mg (1.08 mmol) of 2-methoxyethylamine, 258 mg (1.04 mmol) of 2-iodobenzoic acid and 91.6 mg (1.10 mmol) of *tert*-butyl isocyanide. Purification by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/3, product-Rf = 0.30) yielded 451 mg (94 %) of the title compound.

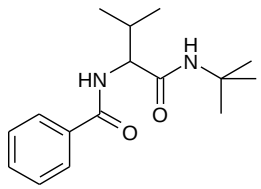


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (t, *J* = 8.5 Hz, 1H), 7.39 (tt, *J* = 7.5, 1.1 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 6.72 (s(br), 1H), 4.27 (s(br), 1H), 3.56 – 3.27 (m, 4H), 3.18 (s, 3H), 2.58 (s(br), 1H), 1.38 (s, 9H), 1.05 (d, *J* = 6.3 Hz, 6H).

MS (ESI): 483.1 (10, M+Na$^+$), 388.0 (8), 360.0 (24), 230.9 (100).

Synthesis of *N*-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-benzamide (2)

In a dry pressure tube with nitrogen atmosphere 52.2 mg (0.113 mmol, 1.0 eq.) of *N*-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-2-iodo-*N*-(2-methoxy-ethyl)-benzamide (2257, **1**), 4.5 mg (0.027 mmol, 0.2 eq.) of azoisobutyronitrile and 82.4 mg (0.331 mmol, 2.9 eq.) of tris(trimethylsilyl)silane are dissolved in 5.0 ml of toluene and heated in an oil bath to 50° C for 20 hours. After evaporation of the solvent *in vacuo* the crude product is purified by column chromatography (1 × 40 cm silica, ethyl acetate/hexane = 1/9 → 1/4, product-Rf = 0.18 [EA/Hex = 1/4]) to yield 6.6 mg (22 %) of the title compound.

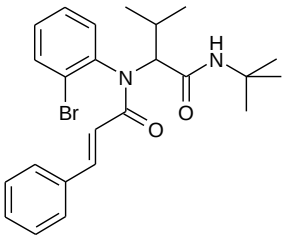


The title compound was also formed as a side product during the synthesis of **7** with tristrimethylsilylsilan as hydrogen donor (17.2 mg (27 %)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.54 – 7.48 (m, 1H), 7.47 – 7.40 (m, 2H), 6.92 (d, *J* = 8.6 Hz, 1H), 5.79 (s(br), 1H), 4.33 (dd, *J* = 8.6, 6.9 Hz, 1H), 2.15 (dsept, *J* = 6.7 Hz, 1H), 1.37 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H).

MS (ESI): 299.2 (26, M+Na$^+$), 277.1 (8, M+H$^+$), 204.1 (19), 176.1 (59), 105.0 (100).

Synthesis of 2-[(2-bromo-phenyl)-(3-phenyl-acryloyl)-amino]-*N*-*tert*-butyl-3-methyl-butyramide (4)

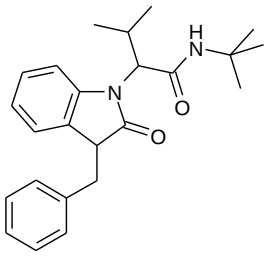


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 78.3 mg (1.09 mmol) of isobutyraldehyde, 195 mg (1.13 mmol) of 2-bromoaniline, 151 mg (1.02 mmol) of cinnamic acid and 87.3 mg (1.05 mmol) of *tert*-butyl isocyanide. Purification by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/4 → 1/1, product-Rf = 0.30 [EA/Hex = 1/4]) yielded 358 mg (77 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, two rotamers = 3/2; main rotamer only) δ 7.76 (s(br), 1H), 7.70 (d, *J* = 15.4 Hz, 1H), 7.67 – 7.60 (m, 1H), 7.46 – 7.41 (m, 1H), 7.34 – 7.22 (m, 7H), 6.08 (d, *J* = 15.5 Hz, 1H), 3.65 (d, *J* = 10.7 Hz, 1H), 2.81 – 2.69 (m, 1H), 1.39 (s, 9H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H).

MS (ESI): 479.3 (1, M+Na$^+$), 457.2 (1, M+H$^+$), 131.0 (100).

Synthesis of 2-(3-benzyl-2-oxo-2,3-dihydro-indol-1-yl)-*N*-*tert*-butyl-3-methyl-butyramide (5)

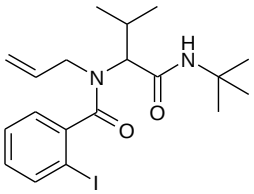


In a dry pressure tube with nitrogen atmosphere 103 mg (0.225 mmol, 1.0 eq.) of 2-[(2-bromo-phenyl)-(3-phenyl-acryloyl)-amino]-*N*-*tert*-butyl-3-methyl-butyramide (**3**), 8.7 mg (0.053 mmol, 0.2 eq.) of azoisobutyronitrile and 176 µl (190 mg, 0.654 mmol, 2.9 eq.) of tributyltin hydride are dissolved in 10.0 ml of dry degassed toluene and stirred at 50 °C for 6 hours. After evaporation of the solvent *in vacuo* the crude product is purified by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 0/1 → 1/1, product-Rf = 0.48 [EA/Hex = 1/3]) to yield 74.9 mg (99 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, main rotamer only) δ 7.27 – 7.18 (m, 5H), 7.12 (t, *J* = 7.3 Hz, 2H), 6.98 – 6.88 (m, 2H), 4.16 (d, *J* = 12.3 Hz, 1H), 3.82 – 3.77 (m, 1H), 3.47 (td, *J* = 13.7, 4.3 Hz, 1H), 3.04 – 2.98 (m, 1H), 2.83 – 2.72 (m, 1H), 1.27 (s, 9H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.43 (d, *J* = 6.0 Hz, 3H).

MS (ESI): 401.2 (58, M+Na$^+$), 379.2 (55, M+H$^+$), 306.1 (18), 278.1 (100), 91.1 (8).

Synthesis of *N*-allyl-*N*-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-2-iodo-benzamide (6)



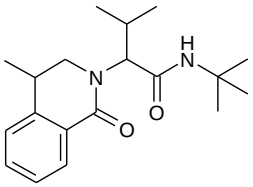
The compound was prepared according to GRP 1 with 1.0 mL of methanol, 75.3 mg (1.04 mmol) of isobutyraldehyde, 57.3 mg (1.00 mmol) of allylamine, 252 mg (1.02 mmol) of 2-iodobenzoic acid and 83.8 mg (1.01 mmol) of *tert*-butyl isocyanide. Purification by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/3, product-Rf = 0.55) yielded 411 mg (93 %) of the title compound.

^{1}H NMR (400 MHz, DMSO-*d*6, main rotamer only) δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.33 (s(br), 1H), 7.22 – 7.09 (m, 2H), 5.76 – 5.58 (m, 1H), 4.84 (d, *J* = 10.2 Hz, 1H), 4.64 (d, *J* = 17.1 Hz, 1H), 4.53 – 4.35 (m, 1H), 4.07 – 3.87 (m, 1H), 3.81 (s(br), 1H), 2.41 – 2.26 (m, 1H), 1.30 (s, 9H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).

MS (ESI): 465.1 (5, M+Na$^+$), 370.0 (18), 342.0 (18), 230.9 (100).

Synthesis of *N*-*tert*-butyl-3-methyl-2-(4-methyl-1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-butyramide (7)

With Bu_3SnH:



In a dry pressure tube with nitrogen atmosphere 105 mg (0.238 mmol, 1.0 eq.) of *N*-allyl-*N*-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-2-iodo-benzamide (**5**), 8.3 mg (0.050 mmol, 0.2 eq.) of azoisobutyronitrile and 207 µl (224 mg, 0.769 mmol, 3.2 eq.) of tributyltin hydride are dissolved in 7.0 ml of dry degassed toluene and stirred at 50 °C for 16 hours. After evaporation of the solvent *in vacuo* the crude product is purified by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 0/1 → 1/0, product-Rf = 0.86 [EA/Hex = 4/1]) to yield 39.5 mg (25 %) of the title compound.

With $(SiMe_3)_3SiH$:

In a dry pressure tube with nitrogen atmosphere 102 mg (0.231 mmol, 1.0 eq.) of *N*-allyl-*N*-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-2-iodo-benzamide (**5**), 10.1 mg (0.062 mmol, 0.2 eq.) of azoisobutyronitrile and 173 mg (0.696 mmol, 3.0 eq.) of tris(trimethylsilyl)silane are dissolved in 7.0 ml of dry degassed toluene and stirred at 50 °C for 16 hours. After evaporation of the solvent *in vacuo* the crude product is purified by column chromatography (1.0 × 40 cm silica, chloroform, product-Rf = 0.45) to yield 30.1 mg (41 %) of the title compound.

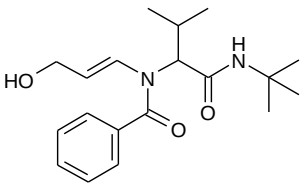
^{1}H NMR (400 MHz, $CDCl_3$)

diastereomer 1 (Me equatorial): δ 8.07 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.41 – 7.32 (m, 1H), 7.25 – 7.20 (m, 1H), 6.01 (s(br), 1H), 4.59 (d, *J* = 11.2 Hz, 1H), 3.81 (dd, *J* = 12.5, 4.9 Hz, 1H), 3.24 (dd, *J* = 12.4, 9.0 Hz, 1H), 3.13 – 3.00 (m, 2H), 2.41 – 2.24 (m, 1H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.30 (s, 9H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.0 Hz, 3H).

diastereomer 2 (Me axial): δ 8.07 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.41 – 7.32 (m, 1H), 7.25 – 7.20 (m, 1H), 5.97 (s(br), 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 3.66 (dd, *J* = 12.6, 5.5 Hz, 1H), 3.56 (dd, *J* = 12.6, 4.5 Hz, 1H), 3.13 – 3.00 (m, 2H), 2.41 – 2.24 (m, 1H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.31 (s, 9H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.89 (d, *J* = 6.2 Hz, 3H).

MS (ESI): 339.2 (92, M+Na^+), 244.1 (40), 216.2 (100).

Synthesis of *N*-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-*N*-(3-hydroxy-propenyl)-benzamide (8)

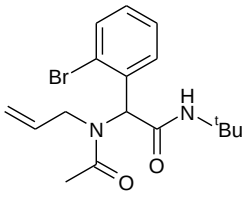


The title compound is formed as a side product during the synthesis of **6** with tributyltin hydride as hydrogen donor in the presence of oxygen. Product-Rf = 0.72 (EA/Hex = 9/1), 7.1 mg (9 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.35 (m, 5H), 6.54 (s(br), 1H), 6.44 (d, *J* = 14.1 Hz, 1H), 5.50 (dt, *J* = 13.8, 6.1 Hz, 1H), 4.46 (d, *J* = 11.3 Hz, 1H), 3.94 (d, *J* = 6.0 Hz, 2H), 2.68 – 2.54 (m, 1H), 1.92 (s(br), 1H), 1.34 (s, 9H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H).

MS (ESI): 355.2 (100, M+Na^+).

Synthesis of 2-(acetyl-allyl-amino)-2-(2-bromo-phenyl)-*N*-*tert*-butyl-acetamide (9)

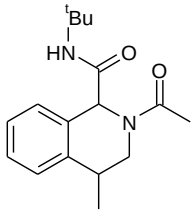


The compound was prepared according to GRP 2 with 1.0 mL of methanol, 189 mg (1.02 mmol) of 2-bromobenzaldehyde, 56.3 mg (0.99 mmol) of allylamine, 62.1 mg (1.03 mmol) of acetic acid and 82.6 mg (0.99 mmol) of *tert*-butyl isocyanide. Purification by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/3 → 1/2, product-Rf = 0.09 [EA/Hex = 1/3]) yielded 212 mg (58 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (t, *J* = 8.3 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 6.12 (s, 1H), 5.53 (s(br), 1H), 5.43 (ddt, *J* = 16.0, 10.5, 5.5 Hz, 1H), 4.97 – 4.83 (m, 2H), 3.93 (d, *J* = 5.5 Hz, 2H), 2.17 (s, 3H), 1.35 (s, 9H).

MS (ESI): 391.1 (12, M+Na$^+$), 389.1 (12, M+Na$^+$), 296.1 (9), 294.1 (9), 268.0 (7), 266.0 (7), 226.0 (100), 224.0 (100).

Synthesis of 2-acetyl-4-methyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid *tert*-butylamide (10)

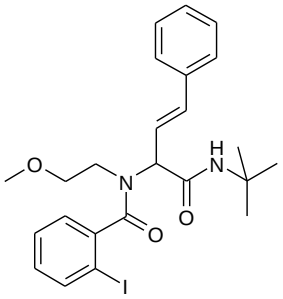


In a dry pressure tube with nitrogen atmosphere 150 mg (0.409 mmol, 1.0 eq.) of 2-(acetyl-allyl-amino)-2-(2-bromo-phenyl)-*N*-*tert*-butyl-acetamide (**9**), 13.4 mg (0.082 mmol, 0.2 eq.) of azoisobutyronitrile and 355 mg (1.22 mmol, 3.0 eq.) of tributyltin hydride are dissolved in 10 ml of dry degassed toluene and stirred at 50 °C for 18 hours. After evaporation of the solvent *in vacuo* the crude product is purified by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/3 → 1/2, product-Rf = 0.21 [EA/Hex = 1/1]) to yield 61.1 mg (53 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, 2 diastereomers = 9/1, main diastereomer only) δ 7.41 – 7.11 (m, 4H), 6.38 (s(br), 1H), 5.84 (s, 1H), 3.81 (dd, *J* = 13.4, 5.1 Hz, 1H), 3.40 (dd, *J* = 13.3, 11.4 Hz, 1H), 3.08 – 2.95 (m, 1H), 2.22 (s, 3H), 1.34 (s, 9H), 1.35 (d, *J* = 7.1 Hz, 3H).

MS (ESI): 311.1 (19, M+Na$^+$),146.0 (100).

Synthesis of *N*-((E)-1-*tert*-butylcarbamoyl-3-phenyl-allyl)-2-iodo-*N*-(2-methoxy-ethyl)-benzamide (12)

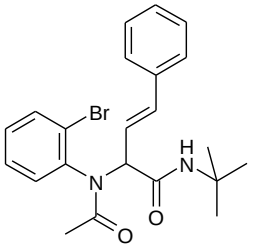


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 139 mg (1.05 mmol) of trans-cinnamaldehyde, 75.5 mg (1.01 mmol) of 2-methoxyethylamine, 284 mg (1.15 mmol) of 2-iodobenzoic acid and 85.1 mg (1.02 mmol) of *tert*-butyl isocyanide. Purification by column chromatography (1.5 × 40 cm silica, ethyl acetate/hexane = 1/3, product-Rf = 0.23) yielded 408 mg (78 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, extensive rotamer formation, main rotamer only) δ 7.83 (t, *J* = 8.6 Hz, 1H), 7.46 (s(br), 1H), 7.44 – 7.22 (m, 6H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.16 – 7.02 (m, 1H), 7.00 – 6.58 (m, 1H), 6.47 (s(br), 1H), 4.87 (d, *J* = 8.4 Hz, 1H), 3.62 – 3.31 (m, 4H), 3.24 (s, 3H), 1.40 (s, 9H).

MS (ESI): 553.2 (5, M+Na$^+$), 521.1 (16, M+H$^+$), 448.0 (20), 420.0 (14), 230.9 (100), 216.1 (35), 160.0 (54), 115.0 (75).

Synthesis of 2-[acetyl-(2-bromo-phenyl)-amino]-4-phenyl-but-3-enoic acid *tert*-butylamide (13)

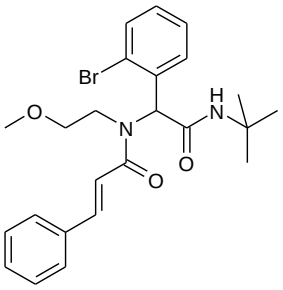


The compound was prepared according to GRP 2 with 1.0 mL of methanol, 134 mg (1.01 mmol) of trans-cinnamonaldehyde, 171 mg (1.00 mmol) of 2-bromoaniline, 63.4 mg (1.06 mmol) of acetic acid and 80.4 mg (0.97 mmol) of *tert*-butyl isocyanide. Purification by column chromatography (1.5 × 28 cm silica, ethyl acetate/hexane = 1/3 → 1/2, product-Rf = 0.14 [EA/Hex = 1/2]) yielded 270 mg (65 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, two rotamers = 3/1, main rotamer only) δ 7.76 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.43 – 7.19 (m, 5H), 7.12 (dd, *J* = 7.6, 2.0 Hz, 2H), 6.65 (d, *J* = 15.8 Hz, 1H), 6.15 (s(br), 1H), 5.79 (dd, *J* = 15.8, 9.4 Hz, 1H), 5.32 (d, *J* = 9.4 Hz, 1H), 1.86 (s, 3H), 1.39 (s, 9H).

MS (ESI): 453.2 (32, M+Na$^+$), 451.2 (32, M+Na$^+$), 431.2 (27, M+H$^+$), 429.2 (29, M+H$^+$), 358.0 (41), 356.0 (42), 330.1 (50), 328.1 (56), 288.0 (65), 286.0 (76), 216.1 (38), 160.1 (100), 130.0 (66), 115.1 (42).

Synthesis of *N*-[(2-bromo-phenyl)-*tert*-butylcarbamoyl-methyl]-*N*-(2-methoxy-ethyl)-3-phenyl-acrylamide (14)

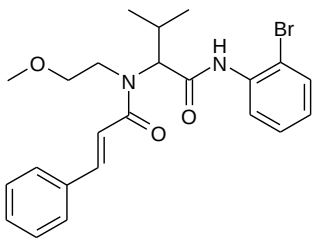


The compound was prepared according to GRP 2 with 1.0 mL of methanol, 183 mg (0.99 mmol) of 2-bromobenzaldehyde, 78.1 mg (1.04 mmol) of 2-methoxyethylamine, 147 mg (0.99 mmol) of cinnamic acid and 81.7 mg (0.98 mmol) of *tert*-butyl isocyanide. Purification by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/3 → 1/2, product-Rf = 0.18 [EA/Hex = 1/3]) yielded 373 mg (80 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, main rotamer only) δ 7.75 (d, *J* = 15.3 Hz, 1H), 7.69 – 7.59 (m, 2H), 7.51 (s(br), 2H), 7.34 (s(br), 5H), 7.29 – 7.19 (m, 1H), 6.90 (d, *J* = 15.2 Hz, 1H), 5.66 (s(br), 1H), 3.87 – 3.48 (m, 2H), 3.38 (s, 3H), 3.29 – 3.06 (m, 2H), 1.38 (s, 9H).

MS (ESI): 497.2 (5, M+Na$^+$), 495.2 (10, M+Na$^+$), 402.1 (20), 400.1 (21), 244.0 (27), 242.0 (27), 131.0 (100).

Synthesis of *N*-(2-bromo-phenyl)-2-[(2-methoxy-ethyl)-(3-phenyl-acryloyl)-amino]-3-methyl-butyramide (16)

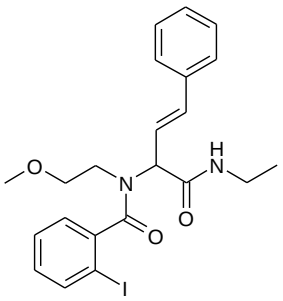


The compound was prepared according to GRP 2 with 1.0 mL of methanol, 75.8 mg (1.05 mmol) of isobutyraldehyde, 79.6 mg (1.06 mmol) of 2-methoxyethylamine, 150 mg (1.01 mmol) of cinnamic acid and 181 mg (0.99 mmol) of 2-bromophenyl isocyanide. Purification by column chromatography (1.5 × 31 cm silica, ethyl acetate/hexane = 1/3 → 1/2, product-Rf = 0.84 [EA/Hex = 1/1]) yielded 316 mg (71 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.21 (s(br), 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 15.4 Hz, 1H), 7.62 – 7.47 (m, 3H), 7.44 – 7.21 (m, 4H), 7.06 (d, *J* = 15.4 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 4.45 (s(br), 1H), 3.85 – 3.75 (m, 1H), 3.68 – 3.57 (m, 1H), 3.52 (t, *J* = 6.0 Hz, 2H), 3.27 (s, 3H), 2.71 (s(br), 1H), 1.11 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H).

MS (ESI): 481.2 (3, M+Na$^+$), 288.2 (10), 260.1 (7), 131.1 (100).

Synthesis of *N*-(1-ethylcarbamoyl-3-phenyl-allyl)-2-iodo-*N*-(2-methoxy-ethyl)-benzamide (17)

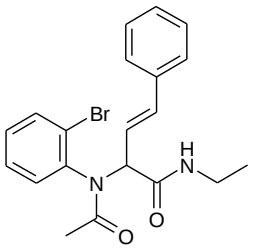


The compound was prepared according to GRP 2 with 1.0 mL of methanol, 141 mg (1.07 mmol) of trans-cinnamaldehyde, 80.1 mg (1.07 mmol) of 2-methoxyethylamine, 294 mg (1.19 mmol) of 2-iodobenzoic acid and 56.0 mg (1.02 mmol) of ethyl isocyanide. Purification by column chromatography (1.5 × 32 cm silica, ethyl acetate/hexane = 3/1 → 9/1, product-Rf = 0.49 [EA/Hex = 3/1]) yielded 266 mg (53 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, extensive rotamer formation, main rotamer only) δ 7.82 (dd, *J* = 13.4, 7.8 Hz, 1H), 7.46 (s(br), 1H), 7.43 – 7.16 (m, 7H), 7.16 – 6.95 (m, 2H), 6.93 – 6.56 (m, 1H), 4.95 (d, *J* = 8.0 Hz, 1H), 3.59 – 3.14 (m, 6H), 3.23 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H).

MS (ESI): 515.0 (13, M+Na$^+$), 492.0 (29, M+H$^+$), 447.9 (39), 419.9 (12), 230.8 (100), 188.0 (9), 114.9 (44).

Synthesis of 2-[acetyl-(2-bromo-phenyl)-amino]-4-phenyl-but-3-enoic acid ethylamide (18)

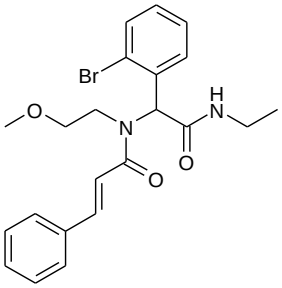


The compound was prepared according to GRP 2 with 1.0 mL of methanol, 134 mg (1.02 mmol) of trans-cinnamaldehyde, 173 mg (1.01 mmol) of 2-bromoaniline, 62.5 mg (1.04 mmol) of acetic acid and 50.3 mg (0.91 mmol) of ethyl isocyanide. Purification by column chromatography (1.5 × 27 cm silica, ethyl acetate/hexane = 1/3 → 1/1, product-Rf = 0.16 [EA/Hex = 1/1]) yielded 216 mg (59 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, main rotamer only) δ 7.82 – 7.09 (m, 9H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 15.8 Hz, 1H), 6.26 (s, 1H), 5.80 (dd, *J* = 15.8, 9.4 Hz, 1H), 5.42 (d, *J* = 9.4 Hz, 1H), 3.35 (p, *J* = 6.7 Hz, 3H), 1.86 (s, 3H), 1.18 (t, *J* = 7.3 Hz, 3H).

MS (ESI): 424.9 (23, M+Na$^+$), 422.9 (61, M+Na$^+$), 402.9 (53, M+H$^+$), 400.9 (51, M+H$^+$), 357.9 (62), 355.9 (66), 329.9 (85), 327.9 (100), 287.1 (75), 285.1 (86), 130.0 (100), 116.9 (46), 114.9 (45), 90.8 (22).

Synthesis of (E)-*N*-[(2-bromo-phenyl)-ethylcarbamoyl-methyl]-*N*-(2-methoxy-ethyl)-3-phenyl-acrylamide (19)

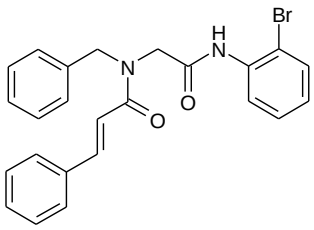


The compound was prepared according to GRP 2 with 1.0 mL of methanol, 186 mg (1.00 mmol) of 2-bromobenzaldehyde, 77.6 mg (1.03 mmol) of 2-methoxyethylamine, 150 mg (1.01 mmol) of cinnamic acid and 55.6 mg (1.01 mmol) of ethyl isocyanide. Purification by washing with 3× 2 ml of hexane yielded 213 mg (48 %) of the title compound.

^{1}H NMR (400 MHz, d4-TFA/d6-DMSO) δ 8.16 (s(br), 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.64 (s(br), 2H), 7.54 (d, *J* = 15.2 Hz, 1H), 7.50 – 7.29 (m, 6H), 7.17 (d, *J* = 14.7 Hz, 1H), 6.18 (s(br), 1H), 3.64 – 3.42 (m, 2H), 3.20 – 3.07 (m, 3H), 3.06 (s(br), 3H), 2.89 (s(br), 1H), 1.03 (t, *J* = 7.2 Hz, 3H).

MS (ESI): 469.0 (35, M+Na$^+$), 467.0 (26, M+Na$^+$), 401.9 (100), 399.9 (94), 243.9 (48), 241.9 (51), 130.9 (67).

Synthesis of *N*-benzyl-*N*-[(2-bromo-phenylcarbamoyl)-methyl]-3-phenyl-acrylamide (20)

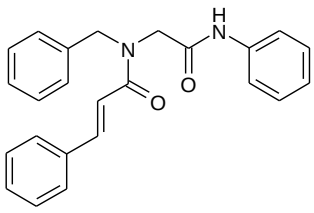


The compound was prepared according to GRP 2 with 1.0 mL of 2,2,2-trifluoroethanol, 75.0 mg (2.50 mmol) of para-formaldehyde, 106 mg (0.99 mmol) of benzylamine, 150 mg (1.01 mmol) of cinnamic acid and 181 mg (0.99 mmol) of 2-bromophenyl isocyanide. Purification by column chromatography (1.5 × 31 cm silica, ethyl acetate/hexane = 1/3 → 1/2, product-Rf = 0.25 [EA/Hex = 1/3]) yielded 282 mg (63 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.86 (s(br), 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 15.3 Hz, 1H), 7.59 – 7.42 (m, 4H), 7.41 – 7.20 (m, 8H), 7.02 – 6.86 (m, 2H), 4.84 (s, 2H), 4.27 (s, 2H).

MS (ESI): 472.9 (88, M+Na$^+$), 470.9 (92, M+Na$^+$), 450.9 (7, M+H$^+$), 448.9 (13, M+H$^+$), 278.1 (9), 131.0 (100), 102.9 (58), 90.9 (26).

Synthesis of *N*-benzyl-3-phenyl-*N*-phenylcarbamoylmethyl-acrylamide (21)



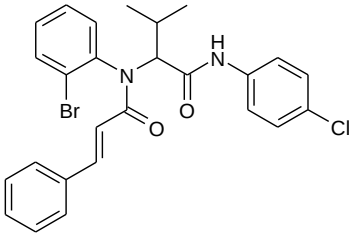
In a dry pressure tube with nitrogen atmosphere 173 mg (0.384 mmol, 1.0 eq.) of *N*-benzyl-*N*-[(2-bromo-phenylcarbamoyl)-methyl]-3-phenyl-acrylamide (**20**), 209 mg (1.27 mmol, 3.3 eq.) of azoisobutyronitrile and 351 mg (1.21 mmol, 3.1 eq.) of tributyltin hydride are dissolved in 15 ml of dry degassed toluene and stirred at 50 °C for 48 hours. After evaporation of the solvent *in vacuo* the crude product is dissolved in 25 mL of H_2O/MeOH (1/1), to which a solution of 218 mg of NH_4HF_2 in 20 mL of H_2O/MeOH (1/1) is added and stirred overnight. The resulting precipitate is removed by

filtration, the filter cake wached with 3× 20 mL ethyl acetate and the combined filtrates evaporated to dryness. Further purification by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/3 → 4/1, product-Rf = 0.21 [EA/Hex = 1/1]) yields 35.0 mg (24 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.97 (s(br), 1H), 7.86 (d, *J* = 15.3 Hz, 1H), 7.55 – 7.43 (m, 4H), 7.43 – 7.13 (m, 10H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 15.3 Hz, 1H), 4.85 (s, 2H), 4.20 (s, 2H).

MS (ESI): 393.0 (100, M+Na$^+$), 267.0 (48), 130.9 (69), 102.9 (39), 90.6 (55).

Synthesis of 2-[(2-bromo-phenyl)-(3-phenyl-acryloyl)-amino]-*N*-(4-chloro-phenyl)-3-methyl-butyramide (25)

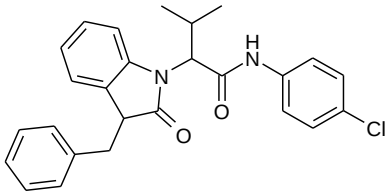


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 110 mg (1.53 mmol) of isobutyraldehyde, 177 mg (1.03 mmol) of 2-bromoaniline, 157 mg (1.06 mmol) of cinnamic acid and 144 mg (1.04 mmol) of 4-chlorophenyl isocyanide. Purification by column chromatography (2 × 40 cm silica, ethyl acetate/hexane = 1/4 → 1/1, product-Rf = 0.72 [EA/Hex = 1/2]) yielded 348 mg (66 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, several rotamers, main rotamer only) δ 10.53 (s, 1H), 7.78 (d, *J* = 15.4 Hz, 1H), 7.71 – 7.20 (m, 13H), 6.09 (d, *J* = 15.3 Hz, 1H), 3.67 (d, *J* = 11.8 Hz, 1H), 3.17 – 3.02 (m, 1H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 6.5 Hz, 3H).

MS (ESI): 535.0 (8, M+Na$^+$), 533.0 (6, M+Na$^+$), 385.9 (23), 227.9 (11), 225.9 (12), 130.9 (100).

Synthesis of 2-(3-benzyl-2-oxo-2,3-dihydro-indol-1-yl)-*N*-(4-chloro-phenyl)-3-methyl-butyramide (26)

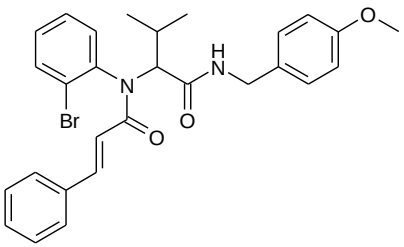


In a dry pressure tube with nitrogen atmosphere 250 mg (0.488 mmol, 1.0 eq.) of 2-[(2-bromo-phenyl)-(3-phenyl-acryloyl)-amino]-*N*-(4-chloro-phenyl)-3-methyl-butyramide (**25**), 17.0 mg (0.104 mmol, 0.2 eq.) of azoisobutyronitrile and 425 µl (460 mg, 1.58 mmol, 3.2 eq.) of tributyltin hydride are dissolved in 7.0 ml of dry degassed toluene and stirred at 50 °C for 18 hours. Then a solution of 70 mg of NH_4HF_2 in 20 mL of H_2O/MeOH (1/1) is added and stirred for 3h. The resulting precipitate is removed by filtration, the filter cake wached with 3× 10 mL of ethyl acetate and the combined filtrates evaporated to dryness. Further purification by column chromatography (2 × 40 cm silica, ethyl acetate/hexane = 1/7, product-Rf = 0.11) yields 70.1 mg (33 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, two diasteromers A/B = 5/4) δ 7.50 – 6.95 (m, 14H, AB), 4.26 (s(br), 1H, AB), 3.89 – 3.80 (m, 1HAB), 3.47 (dd, *J* = 13.3, 4.5 Hz, 1H, B), 3.44 (dd, *J* = 13.4, 4.6 Hz, 1H, A), 3.12 (dd, *J* = 13.9, 7.7 Hz, 1H, B), 3.10 (dd, *J* = 13.8, 7.7 Hz, 1H, A), 3.03 – 2.83 (m, 1H, AB), 1.10 (d, *J* = 6.1 Hz, 3H, B), 1.09 (d, *J* = 6.3 Hz, 3H, A), 0.62 (d, *J* = 6.6 Hz, 3H, B), 0.58 (s(br), 3H, A).

MS (ESI): 455.0 (15, M+Na$^+$), 433.0 (30, M+H$^+$), 306.0 (28), 278.0 (100), 250.0 (29), 90.9 (12).

Synthesis of 2-[(2-bromo-phenyl)-(3-phenyl-acryloyl)-amino]-N-(4-methoxy-phenyl)-3-methyl-butyramide (27)

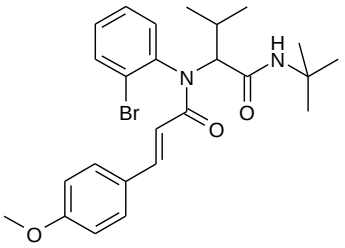


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 77.2 mg (1.07 mmol) of isobutyraldehyde, 186 mg (1.08 mmol) of 2-bromoaniline, 166 mg (1.12 mmol) of cinnamic acid and 150 mg (1.02 mmol) of 4-methoxybenzyl isocyanide. Purification by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/4 → 1/1, product-Rf = 0.06 [EA/Hex = 1/4]) yielded 302 mg (57 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, two rotamers = 2/1, main rotamer only) δ 8.25 (s, 1H), 7.69 (d, *J* = 15.4 Hz, 1H), 7.70 – 7.55 (m, 2H), 7.44 (td, *J* = 7.6, 1.5 Hz, 1H), 7.32 – 7.18 (m, 8H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.06 (d, *J* = 15.4 Hz, 1H), 4.51 (dd, *J* = 14.6, 6.1 Hz, 1H), 4.36 (tt, *J* = 14.8, 5.1 Hz, 1H), 3.81 – 3.74 (m, 4H), 2.93 – 2.77 (m, 1H), 1.08 (d, *J* = 6.5 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H).

MS (ESI): 545.8 (2, M+Na$^+$), 543.8 (5, M+Na$^+$), 227.9 (10), 225.9 (11), 120.9 (100).

Synthesis of 2-{(2-bromo-phenyl)-[3-(4-methoxy-phenyl)-acryloyl]-amino}-*N*-*tert*-butyl-3-methyl-butyramide (29)



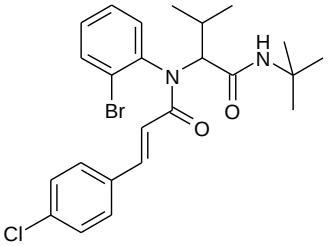
The compound was prepared according to GRP 1 with 1.0 mL of methanol, 79.6 mg (1.10 mmol) of isobutyraldehyde, 175 mg (1.02 mmol) of 2-bromoaniline, 189 mg (1.06 mmol) of 4-methoxycinnamic acid and 87.8 mg (1.06 mmol) of *tert*-butyl isocyanide. Purification by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/6, product-Rf = 0.16) yielded 203 mg (41 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, two rotamers = 2/1, main rotamer) δ 7.86 (s(br), 1H), 7.72 – 7.57 (m, 2H), 7.46 – 7.20 (m, 5H), 6.80 (d, *J* = 8.6 Hz, 2H), 5.94 (d, *J* = 15.3 Hz, 1H), 3.79 (s, 3H), 3.61 (d, *J* = 10.8 Hz, 1H), 2.86 – 2.71 (m, 1H), 1.39 (s, 9H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H).

1H NMR (400 MHz, Chloroform-*d*) δ 7.72 – 7.57 (m, 2H), 7.46 – 7.20 (m, 5H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.41 (s, 1H), 5.98 (d, *J* = 15.4 Hz, 1H), 4.42 (d, *J* = 10.8 Hz, 1H), 3.79 (s, 3H), 2.64 – 2.49 (m, 1H), 1.31 (s, 9H), 1.17 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H).

MS (ESI): 511.0 (6, M+Na$^+$), 509.0 (8, M+Na$^+$), 415.9 (21), 413.9 (25), 161.0 (100).

Synthesis of 2-{(2-bromo-phenyl)-[3-(4-chloro-phenyl)-acryloyl]-amino}-*N*-*tert*-butyl-3-methyl-butyramide (31)



The compound was prepared according to GRP 1 with 1.0 mL of methanol, 80.3 mg (1.11 mmol) of isobutyraldehyde, 176 mg (1.02 mmol) of 2-bromoaniline, 190 mg (1.04 mmol) of 4-chlorocinnamic acid and 91.1 mg (1.10 mmol) of *tert*-butyl isocyanide. The crude reaction mixture is diluted with 5.0 ml of dichloromethan and washed with each 5.0 ml of 10 % aqueous NaOH, water and 10 % HCl. The organic phase is then dried over $MgSO_4$, filtrated and evaporated to dryness. The remaining solid is washed with small amounts of diethylether to yield 250 mg (50 %) of the title compound.

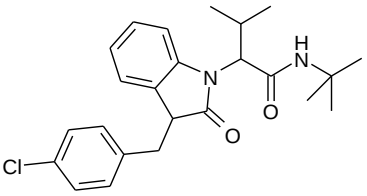
^{1}H NMR (400 MHz, Chloroform-*d*, two rotamers 3/2)

major rotamer: δ 7.71 – 7.60 (m, 3H), 7.48 – 7.36 (m, 1H), 7.36 – 7.25 (m, 1H), 7.29 – 7.16 (m, 5H), 6.04 (d, *J* = 15.4 Hz, 1H), 3.67 (d, *J* = 10.5 Hz, 1H), 2.84 – 2.64 (m, 1H), 1.39 (s, 9H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H).

minor rotamer: δ 7.71 – 7.60 (m, 3H), 7.48 – 7.36 (m, 1H), 7.36 – 7.25 (m, 1H), 7.29 – 7.16 (m, 4H), 6.30 (s, 1H), 6.08 (d, *J* = 15.5 Hz, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 2.61 – 2.48 (m, 1H), 1.31 (s, 9H), 1.16 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H).

MS (ESI): 515.0 (2, M+Na$^+$), 513.0 (2, M+Na$^+$), 493.0 (2, M+H$^+$), 491.0 (3, M+H$^+$), 419.9 (12), 417.9 (14), 167.0 (30), 164.9 (100).

Synthesis of *N*-*tert*-Butyl-2-[3-(4-chloro-benzyl)-2-oxo-2,3-dihydro-indol-1-yl]-3-methyl-butyramide (32)

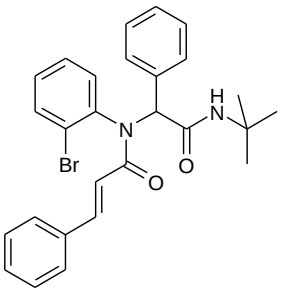


In a dry pressure tube with nitrogen atmosphere 195 mg (0.396 mmol, 1.0 eq.) of 2-{(2-bromo-phenyl)-[3-(4-chloro-phenyl)-acryloyl]-amino}-*N*-*tert*-butyl-3-methyl-butyramide (**31**), 15.8 mg (0.096 mmol, 0.2 eq.) of azoisobutyronitrile and 345 µl (373 mg, 1.28 mmol, 3.2 eq.) of tributyltin hydride are dissolved in 7.0 ml of dry degassed toluene and stirred at 50 °C for 18 hours. Then a solution of 70 mg of NH_4HF_2 in 15 mL of H_2O/MeOH (1/1) is added and stirred overnight. The resulting precipitate is removed by filtration, the filter cake washed with 3× 10 mL of ethyl acetate and the combined filtrates evaporated to dryness. Further purification by column chromatography (2 × 40 cm silica, ethyl acetate/hexane = 1/4, product-Rf = 0.43) yields 130 mg (80 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, two diastereomers A/B = 9/7) δ 7.33 – 7.11 (m, 2×4H, AB), 7.08 – 6.94 (m, 2×4H, AB), 6.18 (s(br), 1H, B), 6.05 (s(br), 1H, A), 4.18 – 4.06 (m, 2×1H, AB), 3.79 (dd, *J* = 7.7, 4.3 Hz, 1H, A), 3.76 (dd, *J* = 7.7, 4.7 Hz, 1H, B), 3.42 (dd, *J* = 11.9, 4.4 Hz, 1H, B), 3.38 (dd, *J* = 11.7, 4.7 Hz, 1H, A), 3.09 (dd, *J* = 7.7, 4.4 Hz, 1H, A), 3.06 (dd, *J* = 7.7, 4.3 Hz, 1H, B), 2.82 – 2.69 (m, 2×1H, AB), 1.26 (s, 9H, B), 1.23 (s, 9H, A), 1.05 (d, *J* = 6.5 Hz, 3H, A), 1.02 (d, *J* = 6.5 Hz, 3H, B), 0.58 (d, *J* = 6.6 Hz, 3H, A), 0.38 (d, *J* = 6.7 Hz, 3H, B).

MS (ESI): 437.0 (15, M+Na$^+$), 435.0 (35, M+Na$^+$), 415.0 (21, M+H$^+$), 413.0 (100, M+H$^+$), 340.0 (14), 338.0 (35), 314.1 (11), 312.0 (64), 126.9 (3), 124.8 (14).

Synthesis of *N*-(2-bromo-phenyl)-*N*-(*tert*-butylcarbamoyl-phenyl-methyl)-3-phenyl-acrylamide (33)

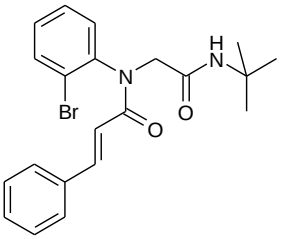


In a 10 mL flask 148 mg (1.39 mmol) of benzaldehyde and 175 mg (1.02 mmol) of 2-bromoanilineare dissolved in 1.0 mL of 2,2,2-trofluoroethanol and stirred at rt overnight. Then 151 mg (1.02 mmol) of cinnamic acid and 89.8 mg (1.08) of *tert*-butyl isocyanide are added. The reaction mixture is stirred at rt for another 48 hours, diluted with 10 mL of DCM, washed with 10 mL of saturated NaHCO3 solution and 10 mL of 1N HCl, dried over magnesium sulfate and filtrated. After evaporation of the solvent *in vacuo* 296 mg of the title compound are obtained (59 %).

^{1}H NMR (400 MHz, Chloroform-*d*, three rotamers = 8/2/1, main rotamer only) δ 7.99 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.74 (d, *J* = 15.5 Hz, 1H), 7.39 – 7.21 (m, 9H), 7.19 – 7.04 (m, 4H), 6.10 (d, *J* = 15.6 Hz, 1H), 6.04 (s, 1H), 5.74 (s(br), 1H), 1.37 (s, 9H).

MS (ESI): 515.0 (2, M+Na$^+$), 513.0 (2, M+Na$^+$), 493.0 (2, M+H$^+$), 491.0 (2, M+H$^+$), 419.9 (16), 417.9 (16), 261.9 (8), 259.9 (8), 130.9 (100), 105.9 (11).

Synthesis of *N*-(2-bromo-phenyl)-*N*-(*tert*-butylcarbamoyl-methyl)-3-phenyl-acrylamide (35)

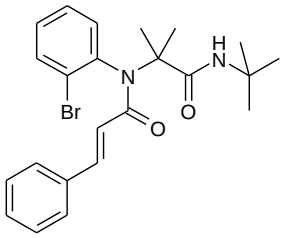


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 32.0 mg (1.07 mmol) of para-formaldehyde, 183 mg (1.06 mmol) of 2-bromoaniline, 156 mg (1.05 mmol) of cinnamic acid and 85.7 mg (1.03 mmol) of *tert*-butyl isocyanide. Purification by column chromatography (1.5 × 33 cm silica, ethyl acetate/hexane = 1/4 → 1/1, product-Rf = 0.19 [EA/Hex = 1/4]) yielded 251 mg (59 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (d, *J* = 15.7 Hz, 1H), 7.73 – 7.70 (m, 1H), 7.47 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.41 (td, *J* = 7.6, 1.4 Hz, 1H), 7.34 – 7.27 (m, 6H), 6.45 (s, 1H), 6.13 (d, *J* = 15.5 Hz, 1H), 4.70 (d, *J* = 14.9 Hz, 1H), 3.76 (d, *J* = 14.9 Hz, 1H), 1.38 (s, 9H).

MS (ESI): 438.9 (4, M+Na$^+$), 436.9 (4, M+Na$^+$), 416.9 (12, M+H$^+$), 414.9 (14, M+H$^+$), 343.9 (15), 341.9 (20), 130.9 (100), 102.9 (9).

Synthesis of *N*-(2-bromo-phenyl)-*N*-(1-*tert*-butylcarbamoyl-1-methyl-ethyl)-3-phenyl-acrylamide (37)

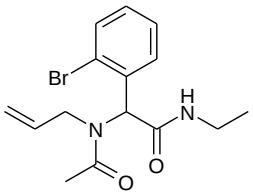


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 70.2 mg (1.21 mmol) of acetone, 180 mg (1.05 mmol) of 2-bromoaniline, 162 mg (1.09 mmol) of cinnamic acid and 91.8 mg (1.10 mmol) of *tert*-butyl isocyanide. Purification by column chromatography (1.5 × 33 cm silica, ethyl acetate/hexane = 1/4 → 1/2, product-Rf = 0.15 [EA/Hex = 1/4]) yielded 173 mg (37 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.65 (d, *J* = 15.4 Hz, 1H), 7.57 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.49 – 7.37 (m, 1H), 7.39 – 7.28 (m, 1H), 7.30 – 7.19 (m, 5H), 6.54 (s(br), 1H), 5.94 (d, *J* = 15.4 Hz, 1H), 1.49 (s, 3H), 1.40 (s, 9H), 1.39 (s, 3H).

MS (ESI): 467.0 (4, M+Na$^+$), 465.0 (5, M+Na$^+$), 371.9 (13), 369.9 (15), 343.9 (2), 341.9 (6), 130.9 (100).

Synthesis of 2-(acetyl-allyl-amino)-2-(2-bromo-phenyl)-*N*-ethyl-acetamide (39)

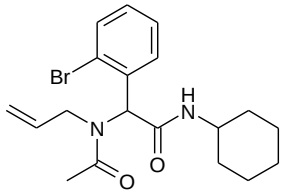


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 208 mg (1.12 mmol) of 2-bromobenzaldehyde, 57.1 mg (1.00 mmol) of allylamine, 60.9 mg (1.01 mmol) of acetic acid and 59.2 mg (1.07 mmol) of ethyl isocyanide. Purification by washing with 2× 3.0 mL diethyl ether yielded 258 mg (76 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, main rotamer only) δ 7.65 – 7.53 (m, 2H), 7.32 (td, *J* = 7.7, 1.2 Hz, 1H), 7.21 (td, *J* = 7.6, 1.6 Hz, 1H), 6.19 (s, 1H), 5.84 (s(br), 1H), 5.45 (ddt, *J* = 17.3, 10.9, 5.7 Hz, 1H), 5.02 – 4.84 (m, 2H), 3.94 (d, *J* = 5.6 Hz, 2H), 3.38 – 3.21 (m, 2H), 2.17 (s, 3H), 1.12 (t, *J* = 7.3 Hz, 3H).

MS (ESI): 352.9 (31, M+Na$^+$), 350.9 (28, M+Na$^+$), 216.0 (100), 160.0 (81).

Synthesis of 2-(acetyl-allyl-amino)-2-(2-bromo-phenyl)-*N*-cyclohex-1-enyl-acetamide (41)

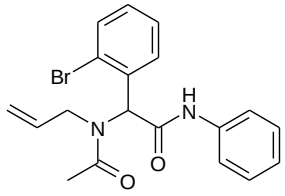


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 186 mg (1.01 mmol) of 2-bromobenzaldehyde, 57.8 mg (1.01 mmol) of allylamine, 66.0 mg (1.10 mmol) of acetic acid and 110 mg (1.03 mmol) of 1-cyclohexenyl isocyanide. Purification by washing with 3× 3.0 mL diethyl ether yielded 316 mg (80 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.53 (m, 2H), 7.33 (t, *J* = 7.1 Hz, 1H), 7.23 (d, *J* = 6.3 Hz, 1H), 6.75 (s(br), 1H), 6.22 (s, 1H), 6.08 (s(br), 1H), 5.46 (ddt, *J* = 16.3, 10.7, 5.4 Hz, 1H), 5.00 – 4.85 (m, 2H), 3.93 (d, *J* = 5.5 Hz, 2H), 2.17 (s, 3H), 2.14 – 2.02 (m, 4H), 1.77 – 1.49 (m, 4H).

MS (ESI): 414.8 (70, M+Na$^+$), 412.9 (100, M+Na$^+$), 225.9 (71), 223.9 (70), 170.8 (11), 168.8 (9).

Synthesis of 2-(acetyl-allyl-amino)-2-(2-bromo-phenyl)-*N*-phenyl-acetamide (43)

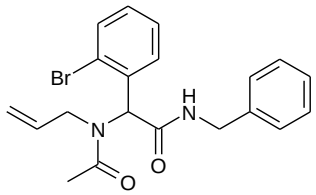


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 191 mg (1.03 mmol) of 2-bromobenzaldehyde, 57.2 mg (1.00 mmol) of allylamine, 61.8 mg (1.03 mmol) of acetic acid and 106 mg (1.03 mmol) of phenyl isocyanide. Purification by washing with 4× 3.0 mL diethyl ether yielded 239 mg (62 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (s(br), 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.30 – 7.18 (m, 3H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.48 (s, 1H), 5.50 (ddt, *J* = 16.1, 10.6, 5.6 Hz, 1H), 5.05 – 4.86 (m, 2H), 3.99 (d, *J* = 5.6 Hz, 2H), 2.19 (s, 3H).

MS (ESI): 410.9 (46, M+Na$^+$), 408.9 (44, M+Na$^+$), 225.9 (85), 223.9 (100).

Synthesis of 2-(acetyl-allyl-amino)-2-(2-bromo-phenyl)-*N*-benzyl-acetamide (45)

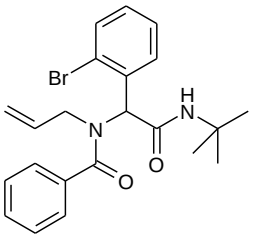


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 192 mg (1.03 mmol) of 2-bromobenzaldehyde, 66.7 mg (1.17 mmol) of allylamine, 66.4 mg (1.11 mmol) of acetic acid and 120 mg (1.02 mmol) of benzyl isocyanide. Purification by washing with 5× 2.0 mL diethyl ether yielded 313 mg (76 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, main rotamer only) δ 7.62 – 7.54 (m, 2H), 7.36 – 7.27 (m, 3H), 7.27 – 7.17 (m, 4H), 6.24 (s, 1H), 6.16 (s(br), 1H), 5.45 (ddt, *J* = 15.9, 10.6, 5.6 Hz, 1H), 5.00 – 4.87 (m, 2H), 4.51 (dd, *J* = 15.2, 5.9 Hz, 1H), 4.43 (dd, *J* = 14.7, 5.7 Hz, 1H), 3.94 (d, *J* = 5.7 Hz, 2H), 2.18 (s, 3H).

MS (ESI): 424.9 (50, M+Na$^+$), 422.9 (75, M+Na$^+$), 225.9 (90), 223.9 (100), 170.9 (13), 168.9 (11).

Synthesis of *N*-allyl-*N*-[(2-bromo-phenyl)-*tert*-butylcarbamoyl-methyl]-benzamide (47)

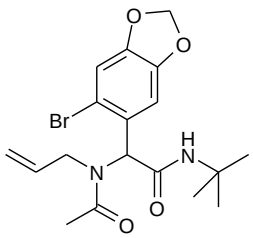


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 204 mg (1.10 mmol) of 2-bromobenzaldehyde, 61.0 mg (1.07 mmol) of allylamine, 124 mg (1.02 mmol) of benzoic acid and 86.1 mg (1.04 mmol) of *tert*-butyl isocyanide. Purification by washing with 2× 3.0 mL diethyl ether yielded 298 mg (68 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 – 7.30 (m, 8H), 7.22 (td, *J* = 7.7, 1.8 Hz, 1H), 5.95 (s(br), 1H), 5.70 (s(br), 1H), 5.50 (s(br), 1H), 4.77 (d, *J* = 10.4 Hz, 1H), 4.67 (d, *J* = 16.6 Hz, 1H), 3.89 (s(br), 2H), 1.39 (s, 9H).

MS (ESI): 452.9 (8, M+Na$^+$), 450.9 (8, M+Na$^+$), 430.9 (2, M+H$^+$), 428.9 (2, M+H$^+$), 357.9 (10), 355.9 (10), 329.9 (5), 327.9 (7), 104.9 (100).

Synthesis of 2-(acetyl-allyl-amino)-2-(6-bromo-benzo[1,3]dioxol-5-yl)-*N*-*tert*-butyl-acetamide (49)

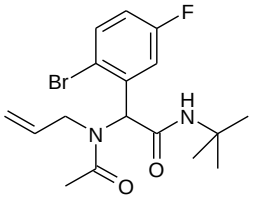


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 232 mg (1.01 mmol) of 6-bromopiperonal, 59.9 mg (1.05 mmol) of allylamine, 61.4 mg (1.02 mmol) of acetic acid and 90.2 mg (1.09 mmol) of *tert*-butyl isocyanide. Purification by washing with 3× 3.0 mL diethyl ether yielded 376 mg (91 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.12 (s, 1H), 7.03 (s, 1H), 6.01 (s, 2H), 5.98 (s, 1H), 5.55 (s(br), 1H), 5.57 – 5.42 (m, 1H), 5.00 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 3.93 (d, *J* = 5.5 Hz, 2H), 2.16 (s, 3H), 1.35 (s, 9H).

MS (ESI): 434.9 (22, M+Na$^+$), 432.9 (28, M+Na$^+$), 412.9 (3, M+H$^+$), 410.9 (2, M+H$^+$), 339.8 (25), 337.9 (25), 311.8 (16), 309.8 (21), 269.8 (100), 267.8 (98), 161.9 (28).

Synthesis of 2-(acetyl-allyl-amino)-2-(2-bromo-5-fluoro-phenyl)-*N*-*tert*-butyl-acetamide (51)

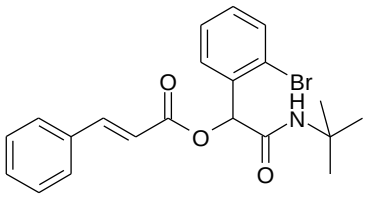


The compound was prepared according to GRP 1 with 1.0 mL of methanol, 248 mg (1.22 mmol) of 2-bromo-5-fluoronenzaldehyde, 57.6 mg (1.01 mmol) of allylamine, 68.4 mg (1.14 mmol) of acetic acid and 90.8 mg (1.09 mmol) of *tert*-butyl isocyanide. Purification by column chromatography (1.5 × 35 cm silica, ethyl acetate/hexane = 1/4 → 1/1, product-Rf = 0.09 [EA/Hex = 1/4]) yielded 289 mg (74 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*, two rotamers = 10/1, main rotamer only) δ 7.54 (dd, *J* = 8.8, 5.4 Hz, 1H), 7.41 (dd, *J* = 9.7, 3.1 Hz, 1H), 7.04 – 6.90 (m, 1H), 6.04 (s, 1H), 5.62 (s(br), 1H), 5.48 (ddt, *J* = 16.3, 10.8, 5.5 Hz, 1H), 5.00 – 4.89 (m, 2H), 3.96 (d, *J* = 5.7 Hz, 2H), 2.18 (s, 3H), 1.35 (s, 9H).

MS (ESI): 408.9 (24, M+Na$^+$), 406.9 (31, M+Na$^+$), 387.0 (5, M+H$^+$), 385.0 (2, M+H$^+$), 313.8 (22), 311.8 (15), 285.8 (9), 283.8 (7), 243.8 (86), 241.8 (100).

Synthesis of 2-iodo-benzoic acid 1-*tert*-butylcarbamoyl-3-phenyl-allyl ester (53)



188 mg (1.02 mmol) of 2-bromobenzaldehyde, 149 mg (1.01 mmol) of cinnamic acid and 81.2 mg (0.98 mmol) of *tert*-butyl isocyanide were dissolved in 1.0 ml of tetrahydrofuran and stirred at room temperature for 20 hours. After evaporation of the solvent in vacuo the crude product was purified by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/4 → 4/1, product-Rf = 0.31 [EA/Hex = 4/1]) to yield 274 mg (67 %) of the title compound.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 16.0 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.57 – 7.51 (m, 2H), 7.43 – 7.33 (m, 4H), 7.25 – 7.19 (m, 1H), 6.55 (d, *J* = 16.0 Hz, 1H), 6.40 (s, 1H), 5.98 (s(br), 1H), 1.37 (s, 9H).

MS (ESI): 440.2 (29, M+Na$^+$), 438.0 (36, M+Na$^+$), 418.2 (41, M+H$^+$), 416.0 (58, M+H$^+$), 241.8 (10), 239.8 (11), 185.8 (15), 183.9 (15), 130.9 (100), 102.9 (37).

6.2. $Pd^{II/IV}$ catalyzed cycloaddition of 1,6-enynes

Parts of this chapter have been published in:

Sebastian J. Welsch, Michael Umkehrer, Günther Ross, Jürgen Kolb, Christoph Burdack, Ludger A. Wessjohann; *$Pd^{II/IV}$ catalyzed oxidative cyclization of 1,6-enynes derived by Ugi-4-component reaction*;
Tetrahedron Letters **2011**, *52* (47), 6295-6297.

6.2.1. Introduction

Palladium catalyzed transformations are among the most powerful and versatile methods in organic synthesis to construct C–C and C-heteroatom bonds and often offer a unique access to structures which are otherwise difficult to obtain.[151] While most of these reactions proceed through Pd^0/Pd^{II} catalytic cycles an increasing number of reactions involving Pd^{IV} complexes as key intermediates have been reported during the last years.[152]

Compared to the Pd^0/Pd^{II} catalysis Pd^{II}/Pd^{IV} has several advantages: (i) It requires the use of only weak bases, (ii) a strict exclusion of air and moisture is not necessary making them operationally simpler, (iii) the newly formed bonds (e.g., sp^2 and sp^3 C–OAc, C–OCH_2CF_3, C–I, C–F) are often highly complementary to those achievable by classical $Pd^{0/II}$ catalysis and so is (iv) the tolerance for functional groups (e.g., Ar-Br and Ar-I are completely stable under oxidative catalytic reaction conditions).[151]

The $Pd^{II/IV}$ catalyzed oxidative cyclization of 1,6-enynes developed by the SANFORD[153] and TSE[154] groups offers a facile entry to the bicyclo[3.1.0]hexane skeleton. This structural motif is found in several natural products with potent antibiotic activity.[155] Furthermore it has been utilized as a key intermediate in the synthesis of the natural products[156] like ambruticin S[157] and for the stereoselective synthesis of drugs (*i.e.* pregablin[158], protein kinase inhibitor JTT-010[159]) and highly functionalized organic molecules via nucleophilic ring opening of the bicyclic core structure.[160–163]

While several $Pd^{0/II}$ mediated postmodifications have been published,[57–63,67,164,165] there are no examples involving $Pd^{II/IV}$-chemistry. Therefore it should be examined if this promising cyclization could be used with enynes generated by an Ugi reaction.

6.2.2. 1,6-enynes generated by an Ugi reaction

As initial test system, phenylpropiolic acid was chosen because of its high stability and good reactivity in Ugi reactions. Allylamine served as small and flexible unsubstituted alkene (the rates of olefin insertion of substituted alkenes are known to be slow compared to undesired side reactions)[158]. With bulky *tert*-butylisocyanide that will minimize potential side reactions with the secondary amide formed,[63] and with benzaldehyde as the carbonyl compound the expected Ugi product **1a** was obtained in 64 % yield. Subsequent heating at 80 °C with 1.1 equiv. of iodosobenzenediacetate, 5 mol% $Pd(OAc)_2$ and 6 mol% 2,2'-bipyridyl in dry acetic acid[e] under a N_2 atmosphere[154] lead to the

[e] Besides being an excellent polar solvent, acetic acid serves as hydride donor reducing β-hydride elimination.[166]

cyclic product **1b**.[f] Although HPLC-analysis showed no formation of any specific byproducts the conversion did not proceed cleanly, probably due to the Pd-mediated intermolecular reactions between the unsaturated functionalities and/or further reactions of the double acceptor-substituted cyclopropane ring moiety.[167] ^{1}H-NMR analysis showed a mixture of two diastereomers in a ratio of 3:2 (Table 4, entry 1). In order to simplify the spectra, achiral compounds **2a** and **3a** were synthesized in good to excellent yields. Subsequent cyclization was slower for both of them compared to **1a** and accordingly the cyclopropanes **2b** and **3b** were isolated in lower yield (entries 2 and 6). Compound **3b** demonstrates that a bulky tertiary substitution at the lactam nitrogen is tolerated.

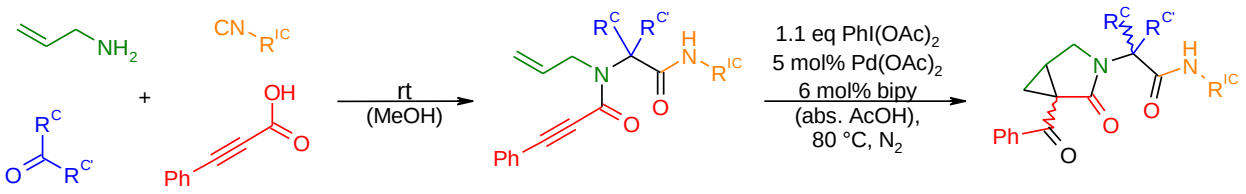


Table 4: Synthesized Ugi and cyclization products.

Entry	R^C, $R^{C'}$	R^{IC}	Ugi-4CR[1]		Cyclization product		d.r.
1	Ph, H	^{t}Bu	**1a**	64 %	**1b**	51 %	3:2
2	H, H	^{t}Bu	**2a**	96 %	**2b**	47 %	-
3	H, H	^{t}Bu	**2a**	96 %	**2b**[2]	45 %	-
4	H, H	^{t}Bu	**2a**	96 %	**2b**[3]	0 %	-
5	H, H	^{t}Bu	**2a**	96 %	**2b**[4]	52 %	-
6	Me, Me	^{t}Bu	**3a**	70 %	**3b**	49 %	-
7	^{i}Pr, H	^{t}Bu	**4a**	99 %	**4b**	17 %[5]	5:4
8	p-Cl-C_6H_4, H	^{t}Bu	**5a**	92 %	**5b**	9 %	1.1:1
9	p-MeO-C_6H_4, H	^{t}Bu	**6a**	93 %	**6b**	0 %	-
10	H, H	Et	**7a**	80 %	**7b**	38 %	-
11	H, H	Ph	**8a**	33 %	**8b**	20 %	-
12	H, H	Bn	**9a**	89 %	**9b**	43 %	-
13	H, H	CH_2COOMe	**10a**	88 %	**10b**	29 %	-
14	H, H	C_2H_4OMe	**11a**	91 %	**11b**	0 %	-
15	H, H	C_2H_4OMe	**11a**	91 %	**11b**[4]	40 %	-
16	^{i}Pr, H	Et	**12a**	85 %	**12b**[6]	0 %	-
17	Ph, H	Bn	**13a**	84 %	**13b**	32 %	1.1:1

[1] isolated yield [2] microwave [3] without bipy [4] no aqueous workup [5] purity 85 % [6] 105 °C

Reaction monitoring for **2b** showed increased side product formation and therefore the reaction was repeated using microwave heating. It was expected that a shorter reaction time would produce less side products and polymer. Indeed, complete conversion was achieved after 9 h at 80 °C with a substantial decrease of byproducts. Disappointingly the isolated yield was lower than with conventional heating. Closer investigation revealed that the product partially degrades during the purification on silica. Switching to neutral aluminum oxide alleviated this problem. When

[f] For a detailed mechanism please refer to [153].

iodosobenzenediacetate was substituted with hydrogen peroxide as a milder oxidant[152] the reaction proceeded with more side products and a worse conversion.

Entry 4 shows an experiment without using 2,2'-bipyridyl as ligand which leads only to degradation of the starting material and demonstrates the necessity of this additive to avoid side reactions[168,169] such as β-hydride elimination or protonolysis of the carbon–palladium bond (which is in agreement with the results published by LYONS and SANFORD[155]).

After this proof of concept the influence of both the aldehyde and the isocyanide moieties on the cyclization was examined. Though they may seem remote to the alkene and alkyne they have been found to influence the cyclization by altering the electronic properties of the lactam nitrogen.[170,171] Additionally, the secondary amide stemming from the isocyanide can act as ligand for the palladium and it may alter the catalytic properties of the intermediate palladium complexes. Finally, the tolerance for functional groups can be easily tested by placing them at the distant (isocyanide derived) end. The results are summarized in Table 4.

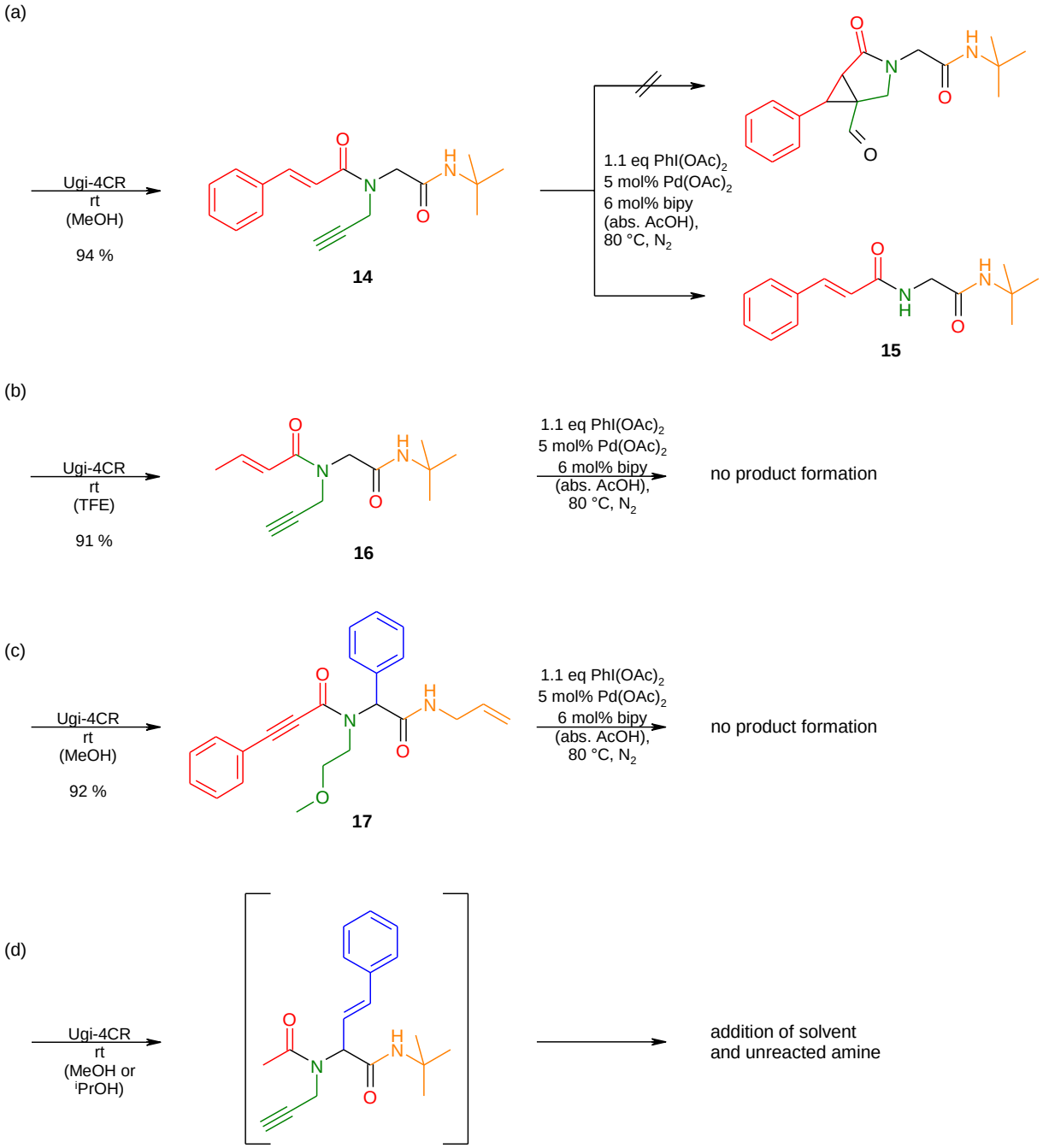
First the steric influence of the aldehyde derived residue was tested with isobutyraldehyde as the carbonyl component. While the MCR went smoothly, subsequent cyclization led to a complex mixture with only minor amounts of the product (entry 7). Replacement of the bulky *tert*-butyl isocyanide with ethylisocyanide and therefore reduction in the steric strain in the Ugi product did not improve the reaction. An increase of the reaction temperature to 105 °C caused complete degradation of the starting material (entry 16).

Substituted benzaldehydes were examined next. Again, the Ugi reaction afforded the enynes **5a** and **6a** in very good yields but in contrast to the unsubstituted benzaldehyde the cyclization went poorly, yielding only small amounts of the desired cyclopropanes **5b** (9 %) and traces of **6b** which degraded during the aqueous workup (entries 8 and 9).

Finally the influence of the exocyclic amide substituent was tested by using an array of different isocyanides (small and bulky aliphatic, phenylic, benzylic, functionalized aliphatic). Most MCR products were easily obtained with good to excellent yields and the following cyclization produced the corresponding bicycles. Among the tested isocyanides, benzylisocyanide performed best (entry 12) whereas phenylisocyanide gave the lowest yield in this series indicating that the cyclization is susceptible to subtle changes in the substrate structure. Cyclization of **10a** and **11a** showed so far the cleanest conversion (estimated by HPLC). This may be attributed to the oxygen atom(s) acting as an intramolecular ligand for the catalyst, stabilizing the intermediates. Both reactions suffered from severe degradation during aqueous workup (entries 13 and 14). Indeed, **11b** could only be obtained after skipping the extraction step entirely (entry 15). Transferring this procedure to substrate **2a** improved the yield slightly (entry 5). Compound **7a** performed similar but showed an increased tendency for degradation upon prolonged heating.

Permutations

Shifting the ene and yne functionalities to different residues in the Ugi product would allow the construction of similar bicyclic scaffolds with different substitution patterns. Using for example propargylamine and a 3-substituted acrylic acid such as crotonic or cinnamic acid would allow the construction of a disubstituted cyclopropane with an aldehyde for further functionalization. Therefore the feasibility of these reactions was examined.



Scheme 29: Permutations of the ene and yne functionalities.

Propargylamine in combination with an unsaturated acid, paraformaldehyde and *tert*-butyliso-cyanide gave the desired Ugi product in excellent yield (trans cinnamic acid (**14**): 94 %, crotonic acid (**16**) 91 %). Subjecting **14** to the cyclization conditions affected cleavage of the propargyl group instead of cyclization. Removal of propargyl and allyl protecting groups by transition metals is well

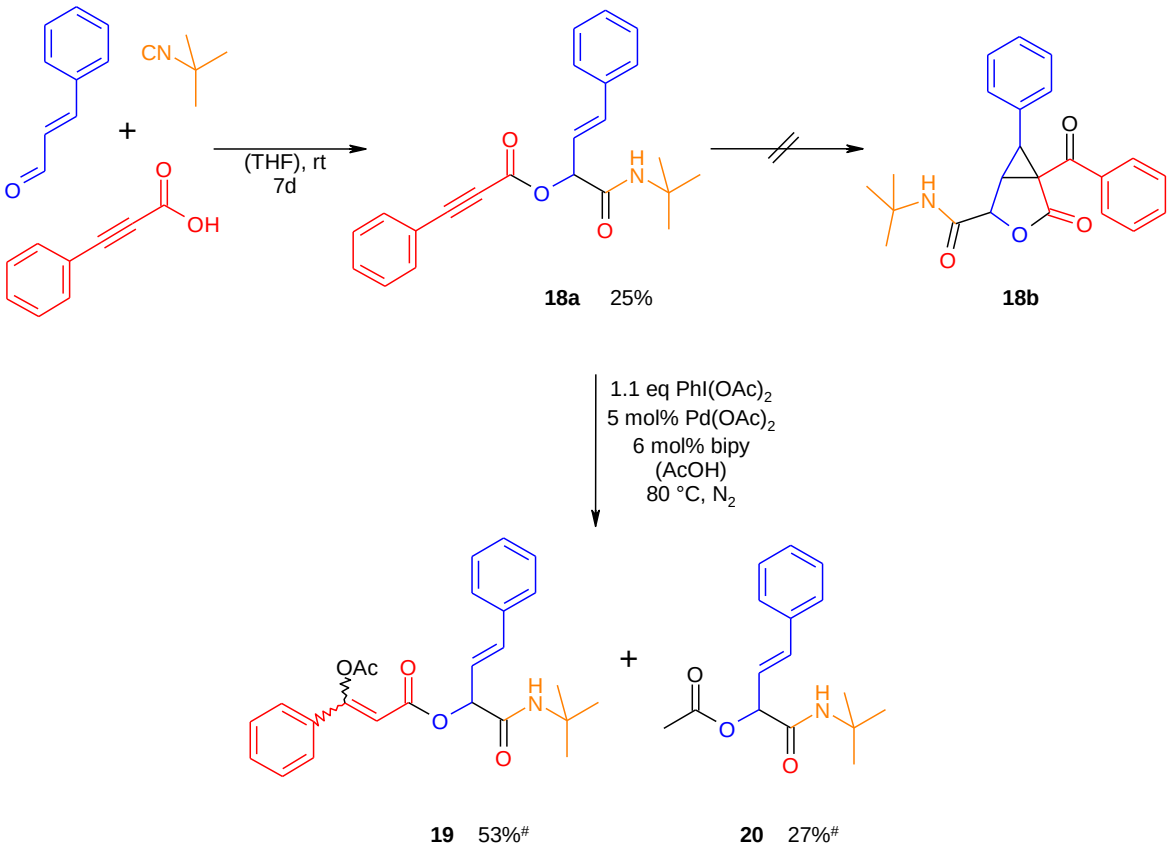
known but usually done under basic conditions.[172–175] The more reactive crotonic acid derivative **16** gave rise to wild mixture of unspecified products with no sign of the desired structure (scheme 29a,b).

Ugi reaction of phenylpropiolic acid and allylisocyanide with benzaldehyde and 2-methoxyethylamine yielded **17** in 92 %. Submitting it into the oxidative cyclization did not lead to the desired 8-membered ring but to an unknown product which degraded during aqueous workup (scheme 29c).

In contrast to the other – well behaving – Ugi reactions the reaction with trans-cinnamonaldehyde and acetic acid resulted in an inseparable reaction mixture of several products arising from nucleophilic attack by unreacted amine and solvent and only minor amounts of the usual Ugi product. Switching the solvent from methanol to isopropylalcohol reduced the amount of the respective byproducts but amine addition was still predominant (scheme 29d).

6.2.3. 1,6-enynes generated by an Passerini reaction

Transferring this synthetic strategy to a Passerini-3CR based sequence would offer access to bicyclic lactones[153] and after saponification to highly substituted cyclopropylcarboxylic acids. Thus the Passerini reaction between phenylpropiolic acid, cinnamon aldehyde and *tert*-butylisocyanide was tested and yielded **18a** after 7d with 25 %. Exposing it to the cyclization conditions lead to the addition of acetic acid (**19**) and the transesterification (**20**) instead of the desired bicyclus **18b**.



Scheme 30: Examination of an analogue Passerini-cycloaddition sequence (#HPLC yield (254 nm)).

6.2.4. Conclusion

Four different types of enynes were synthesized by Ugi-4CRs. One class (ene = allylamine, yne = phenylpropargylic acid) could be further reacted by $Pd^{II/IV}$ catalyzed oxidative cyclization leading to a number of substituted 3-aza-bicycle[3.1.0]hexan-2-ones. This represents the first example of a postmodification of an Ugi reaction by $Pd^{II/IV}$ catalysis. Subjecting a Passerini-3CR product to the same conditions led to transesterification and addition of the solvent.

6.2.5. Contributions

G.R.[g] came up with general idea of this sequence, M.W. synthezised compounds **11b**, **12a**/**b**, **13a**. L.A.W. and M.U. edited the manuscript prior to submission.

[g] Please refer to chapter 1 for full names.

6.2.6. Materials and methods

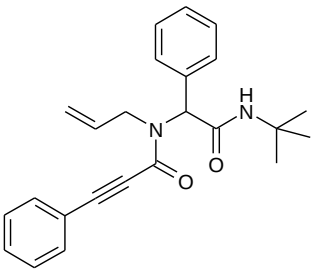
General reaction procedure 1 **(GRP1; Ugi reaction)**
In a round bottom flask 1 mmol of amine and 1 mmol of aldehyde/ketone are added to the solvent and stirred for 2 hours. After cooling the reaction mixture to 0 °C, 1 mmol of carboxylic acid and 1 mmol of isocyanide are added and the mixture is stirred in the melting ice bath for 1d. After evaporation of the solvent, the crude product is further purified by washing or column chromatography.

General reaction procedure 2 **(GRP2; Ugi reaction)**
In a pressure tube 1 mmol of each amine, para-formaldehyde, isocyanide and carboxylic acid were dissolved in 2,2,2-trifluoroethanol and stirred at 50 °C for 36 h. After evaporation of the solvent the product was purified by column chromatography.

General reaction procedure 3 **(GRP3; [$Pd^{II/IV}$]-cyclization)**
In a dry pressure tube with an inert atmosphere (argon or nitrogen) 1 eq. of enyne, 5 mol% $Pd(OAc)_2$, 6 mol% 2,2'-bipyridyl and 1.1 equivalents of iodosobenzenediacetate are dissolved in dry acetic acid. The reaction mixture is heated at 80 °C (oil bath temperature) until TLC or HPLC shows complete conversion of the starting material. Then water is added to form a milky suspension which is extracted twice with ethyl acetate. The combined organic phases are washed with water and brine, dried over Na_2SO_4 and filtrated. After evaporation of the solvent *in vacuo* the crude product is further purified by column chromatography.

General reaction procedure 4 **(GRP4; [$Pd^{II/IV}$]-cyclization)**
In a dry pressure tube with an inert atmosphere (argon or nitrogen) 1 eq. of enyne, 5 mol% $Pd(OAc)_2$, 6 mol% 2,2'-bipyridyl and 1.1 equivalents of iodosobenzenediacetate are dissolved in dry acetic acid. The reaction mixture is heated at 80 °C (oil bath temperature) until TLC or HPLC shows complete conversion of the starting material. After evaporation of the solvent *in vacuo* the crude product is further purified by column chromatography.

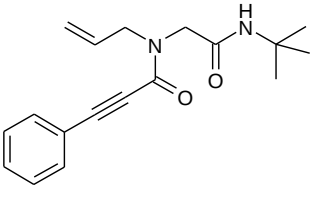
Synthesis of 3-phenyl-propynoic acid allyl-(*tert*-butylcarbamoyl-phenyl-methyl)-amide (1a)
The compound was prepared according to *GRP1* with 1 ml of methanol, 64.7 mg (1.13 mmol) of allylamine, 110 mg (1.04 mmol) of benzaldehyde, 163 mg (1.11 mmol) of phenylpropiolic acid and 83.6 mg (1.01 mmol) of *tert*-butylisocyanide. The newly formed precipitate was washed with methanol and acetone to yield 241 mg (64 %) of the title compound as white solid.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.50 (m, 2H), 7.44 – 7.34 (m, 8H), 5.92 (s, 1H), 5.66 (s (br), 1H), 5.54 (m, 1H), 5.01 – 4.86 (m, 2H), 4.44 – 4.34 (m, 1H), 4.25 – 4.16 (m, 1H), 1.36 (s, 9H).

MS (ESI): 397.2 (35, M+Na^+), 375.3 (9, M+H^+), 302.2 (94), 274.2 (28), 191.1 (7),144.1 (7), 129.0 (100).

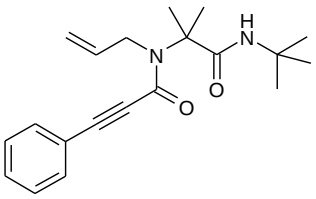
Synthesis of 3-phenyl-propynoic acid allyl-(*tert*-butylcarbamoyl-methyl)-amide (2a)
The compound was prepared according to *GRP2* with 3 ml of 2,2,2-trifluorethanol, 121 mg (2.12 mmol) of allylamine, 59.9 mg (1.99 mmol) of *para*-formaldehyde, 301 mg (2.06 mmol) of phenylpropiolic acid and 171 mg (2.06 mmol) of *tert*-butylisocyanide. After purification by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/2 → 1/1, product-R_f = 0.55 [ethyl acetate/hexane = 1/1]) 576 mg (96 %) of the title compound were obtained as a white solid.



^{1}H NMR (400 MHz, DMSO, 2 rotamers A/B=1.1/1) δ 7.74 (s, 1H, A), 7.64 – 7.58 (m, 2H+3H, AB), 7.56 – 7.44 (m, 2×3H, AB), 5.99 – 5.84 (m, 1H, B), 5.76 (m, 1H, A), 5.25 – 5.13 (m, 2×2H, AB), 4.25 (d, *J* = 5.6 Hz, 2H, B), 4.10 (s, 2H, A), 3.99 (d, *J* = 5.8 Hz, 2H, A), 3.89 (s, 2H, B), 1.25 (s, 9H, B), 1.22 (s, 9H, A).

MS (ESI): 321.2 (31, M+Na$^+$), 299.2 (50, M+H$^+$), 226.1 (100), 198.1 (19), 129.0 (87).

Synthesis of 3-phenyl-propynoic acid allyl-(1-*tert*-butylcarbamoyl-1-methyl-ethyl)-amide (3a)

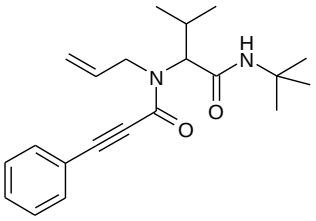


The compound was prepared according to *GRP1* with 1 ml of methanol, 63.8 mg (1.12 mmol) of allylamine, 66.6 mg (0.90 mmol) of acetone, 149 mg (1.02 mmol) of phenylpropiolic acid and 86.7 mg (1.04 mmol) of *tert*-butylisocyanide. After purification by column chromatography (1.5 × 40 cm silica, ethyl acetate/hexane = 1/2 → 1/1, product-R_f = 0.36 [ethyl acetate/hexane = 1/2]) 229 mg (70 %) of the title compound were obtained.

^{1}H NMR (400 MHz, DMSO, main rotamer only) δ 7.59 (d, *J* = 6.9 Hz, z2H), 7.54 – 7.42 (m, 3H), 6.46 (s, 1H), 5.99 (dd, *J* = 17.0, 10.5, Hz, 1H), 5.39 (d, *J* = 17.0 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.39 (d, *J* = 5.5 Hz, 2H), 1.37 (s, 6H), 1.23 (s, 9H).

MS (ESI): 349.2 (17, M+Na$^+$), 254.1 (98), 226.1 (29), 129.0 (100).

Synthesis of 2-[allyl-(3-phenyl-propynoyl)-amino]-*N*-*tert*-butyl-3-methyl-butyramide (4a)



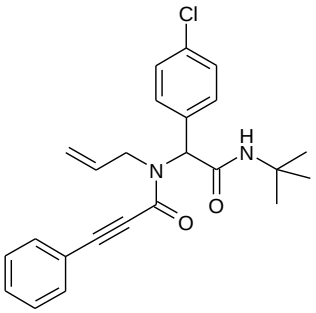
The compound was prepared according to *GRP1* with 1 ml of methanol, 59.8 mg (1.05 mmol) of allylamine, 79.2 mg (1.10 mmol) of isobutyraldehyde, 164 mg (1.12 mmol) of phenylpropiolic acid and 93.2 mg (1.12 mmol) of *tert*-butylisocyanide. After purification by column chromatography (1.5 × 40 cm silica, ethyl acetate/hexane = 1/9 → 1/2, product-R_f = 0.68 [ethyl acetate/hexane = 1/2]) 337 mg (99 %) of the title compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$, main rotamer only) δ 7.58 – 7.52 (m, 2H), 7.47 – 7.34 (m, 3H), 6.17 (s (br), 1H), 5.93 (dd, *J* = 16.8, 10.2 Hz, 1H), 5.29 (d, *J* = 16.2 Hz, 1H), 5.19 (d, *J* = 10.1 Hz, 1H), 4.40 (dd, *J* = 16.2, 6.7 Hz, 1H), 4.29 – 4.12 (m, 2H), 2.50 – 2.34 (m, 1H), 1.33 (s, 9H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H).

HRMS: 363.2043 (M+Na$^+$, calc.), 363.2041 (found).

MS (ESI): 363.2 (28, M+Na$^+$), 268.1 (36), 240.1 (52), 129.0 (100).

Synthesis of 3-phenyl-propynoic acid allyl-[*tert*-butylcarbamoyl-(4-chloro-phenyl)-methyl]-amide (5a)

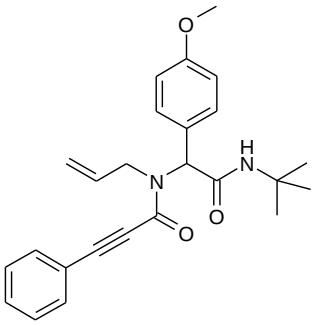


The compound was prepared according to *GRP1* with 1 ml of methanol, 62.9 mg (1.10 mmol) of allylamine, 146 mg (1.04 mmol) of 4-chlorobenzaldehyde, 150 mg (1.02 mmol) of phenylpropiolic acid and 86.0 mg (1.03 mmol) of *tert*-butylisocyanide. After purification by column chromatography (1.5 × 20 cm silica, ethyl acetate/hexane = 1/4, product-R_f = 0.44) 378 mg (92 %) of the title compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B=4/1) δ 7.56 (d, *J* = 7.2 Hz, 2H, B), 7.52 (d, *J* = 7.1 Hz, 2H, A), 7.46 – 7.29 (m, 2×7H, AB), 6.05 (s, 1H, B), 5.87 (s, 1H, A), 5.79 (s (br), 1H, A), 5.76 (s (br), 1H, B), 5.63 – 5.54 (m, 2×1H, AB), 5.07 – 4.88 (m, 2×2H, AB), 4.37 (dd, *J* = 16.8, 5.6 Hz, 1H, A), 4.23 (dd, *J* = 16.8, 6.0 Hz, 1H, B), 3.93 (d, *J* = 6.0 Hz, 2H, AB), 1.38 (s, 9H, B), 1.36 (s, 9H, A).

MS (ESI): 431.1 (35, M+Na$^+$), 336.0 (20), 308.1 (13), 129.0 (100).

Synthesis of 3-phenyl-propynoic acid allyl-[*tert*-butylcarbamoyl-(4-methoxy-phenyl)-methyl]-amide (6a)

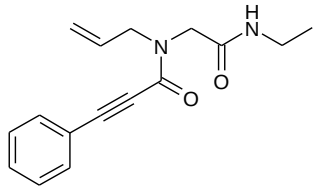


The compound was prepared according to *GRP1* with 1 ml of methanol, 60.1 mg (1.05 mmol) of allylamine, 141 mg (1.04 mmol) of *p*-anisaldehyde, 157 mg (1.07 mmol) of phenylpropiolic acid and 92.0 mg (1.11 mmol) of *tert*-butylisocyanide. After purification by column chromatography (1.5 ×30 cm silica, ethyl acetate/hexane = 1/4 → 1/2, product-R_f = 0.42 [ethyl acetate/hexane = 1/4]) 338 mg (93 %) of the title compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B=4/1) δ 7.57 (d, *J* = 7.0 Hz, 2H, B), 7.51 (d, *J* = 6.9 Hz, 2H, A), 7.46 – 7.27 (m, 2×5H, AB), 6.98 – 6.84 (m, 2×2H, AB), 6.03 (s, 1H, B), 5.86 (s, 1H, A), 5.72 – 5.42 (m, 2×2H, AB), 5.03 – 4.85 (m, 2×2H, AB), 4.37 (dd, *J* = 16.8, 5.8 Hz, 1H, A), 4.18 (dd, *J* = 16.8, 5.9 Hz, 1H, A), 3.93 (d, *J* = 6.1 Hz, 2H, B), 3.82 (s, 3H, AB).

MS (ESI): 427.2 (5, M+Na$^+$), 405.3 (1, M+H$^+$), 332.2 (7), 304.2 (6), 221.1 (24), 192.2 (7), 168.1 (8), 144.0 (7), 129.0 (100), 109.0 (2).

Synthesis of 3-phenyl-propynoic acid allyl-ethylcarbamoylmethyl-amide (7a)

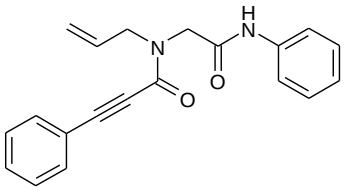


The compound was prepared according to *GRP2* with 3 ml of 2,2,2-trifluorethanol, 68.3 mg (1.20 mmol) of allylamine, 34.4 mg (1.15 mmol) of *para*-formaldehyde, 147 mg (1.00 mmol) of phenylpropiolic acid and 52.4 mg (0.95 mmol) of ethylisocyanide. After purification by column chromatography (1.5 × 20 cm silica, ethyl acetate/hexane = 2/1, product-R_f = 0.40 [ethyl acetate/hexane = 1/1]) 215 mg (80 %) of the title compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B=2/1) δ 7.58 – 7.31 (m, 2×5H, AB), 6.32 (s (br), 2×1H, AB), 5.95 – 5.67 (m, 2×1H, AB), 5.38 – 5.16 (m, 2×2H, AB), 4.37 (d, *J* = 5.8 Hz, 2H, A), 4.27 (s, 2H, B), 4.13 (d, *J* = 6.1 Hz, 2H, B), 4.04 (s, 2H, A), 3.45 – 3.17 (m, 2×2H, AB), 1.15 (t, *J* = 7.3 Hz, 2×4H, AB).

MS (ESI): 292.6 (15, M+Na$^+$), 197.7 (8), 128.9 (100).

Synthesis of 3-phenyl-propynoic acid allyl-phenylcarbamoylmethyl-amide (8a)

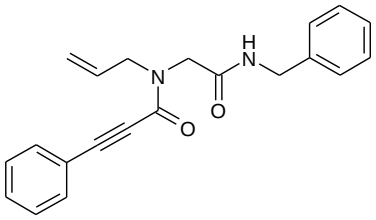


The compound was prepared according to *GRP2* with 3 ml of 2,2,2-trifluorethanol, 65.0 mg (1.14 mmol) of allylamine, 44.0 mg (1.47 mmol) of *para*-formaldehyde, 153 mg (1.04 mmol) of phenylpropiolic acid and 110 mg (1.07 mmol) of phenylisocyanide. After purification by column chromatography (1.5 × 30 cm silica, chloroform/methanol = 99/1, product-R_f = 0.28 [ethyl acetate/hexane = 1/2]) 105 mg (33 %) of the title compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B=5/1) δ 8.51 (s (br), 1H, A), 8.05 (s (br), 1H, B), 7.62 – 7.25 (m, 2×9H, AB), 7.11 (m, 2×1H, AB), 6.00 – 5.74 (m, 2×1H, AB), 5.40 – 5.24 (m, 2×2H, AB), 4.49 – 4.36 (m, 2×2H, AB), 4.22 (d, *J* = 6.3 Hz, 2H, B), 4.19 (s, 2H, A).

MS (ESI): 341.2 (15, M+Na$^+$), 226.1 (5), 198.1 (5), 129.0 (100).

Synthesis of 3-phenyl-propynoic acid allyl-(benzylcarbamoyl-methyl)-amide (9a)

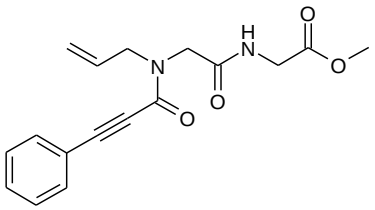


The compound was prepared according to *GRP2* with 3 ml of 2,2,2-trifluorethanol, 59.0 mg (1.03 mmol) of allylamine, 30.6 mg (1.02 mmol) of *para*-formaldehyde, 147 mg (1.00 mmol) of phenylpropiolic acid and 129 mg (1.10 mmol) of benzylisocyanide. After purification by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/2 → 1/1, product-R_f = 0.19 [ethyl acetate/hexane = 1/2]) 295 mg (89 %) of the title compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B=3/1) δ 7.60 – 7.10 (m, 2×10H, AB), 6.59 (s (br), 1H, A), 6.39 (s (br), 1H, B), 5.96 – 5.66 (m, 2×1H, AB), 5.36 – 5.17 (m, 2×2H, AB), 4.50 (d, *J* = 5.9 Hz, 2H, B), 4.45 (d, *J* = 5.9 Hz, 2H, A), 4.37 (d, *J* = 5.9 Hz, 2H, A), 4.32 (s, 2H, B), 4.12 (d, *J* = 6.4 Hz, 2H, B), 4.09 (s, 2H, A).

MS (ESI): 355.2 (8, M+Na^+), 333.2 (2, M+H^+), 226.1 (25), 198.1 (19), 129.0 (100), 91.0 (3).

Synthesis of {2-[allyl-(3-phenyl-propynoyl)-amino]-acetylamino}-acetic acid methyl ester (10a)

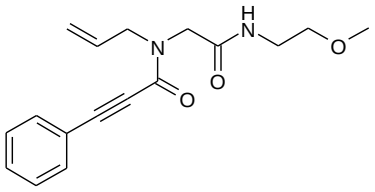


The compound was prepared according to *GRP2* with 3 ml of 2,2,2-trifluorethanol, 64.4 mg (1.13 mmol) of allylamine, 29.7 mg (0.99 mmol) of *para*-formaldehyde, 151 mg (1.03 mmol) of phenylpropiolic acid and 109 mg (1.10 mmol) of methyl isocyanoacetate. After purification by column chromatography (1.5 × 20 cm silica, ethyl acetate/hexane = 2/1, product-R_f = 0.40) 277 mg (88 %) of the title compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B=5/2) δ 7.61 – 7.50 (m, 2×2H, AB), 7.49 – 7.31 (m, 2×3H, AB), 6.76 (s (br), 1H, A), 6.70 (s (br), 1H, B), 5.92 – 5.76 (m, 2×1H, AB), 5.37 – 5.19 (m, 2×2H, AB), 4.38 (d, *J* = 5.8 Hz, 2H, A), 4.35 (s, 2H, B), 4.18 (d, *J* = 6.2 Hz, 2H, B), 4.12 (s, 2H, A), 4.10 (d, *J* = 5.8 Hz, 2H, B), 4.05 (d, *J* = 5.5 Hz, 2H, A), 3.76 (s, 3H, A), 3.72 (s, 3H, B).

MS (ESI): 337.1 (39, M+Na^+), 128.9 (100).

Synthesis of 3-phenyl-propynoic acid allyl-[(2-methoxy-ethylcarbamoyl)-methyl]-amide (11a)

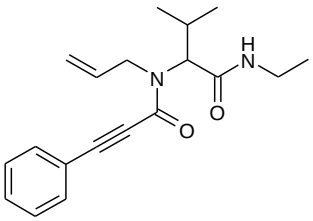


The compound was prepared according to *GRP2* with 3 ml of 2,2,2-trifluorethanol, 67.1 mg (1.18 mmol) of allylamine, 30.1 mg (1.00 mmol) of *para*-formaldehyde, 156 mg (1.07 mmol) of phenylpropiolic acid and 91.7 mg (1.08 mmol) of 2-methoxyethylisocyanide. After purification by column chromatography (1.5 × 20 cm silica, ethyl acetate/hexane = 2/1 → 9/1, product-R_f = 0.21 [ethyl acetate/hexane = 2/1]) 274 mg (91 %) of the title compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B=2/1) δ 7.59 – 7.49 (m, 2×2H, AB), 7.48 – 7.32 (m, 2×3H, AB), 6.48 (s (br), 1H, A), 6.41 (s (br), 1H, B), 5.93 – 5.68 (m, 2×1H, AB), 5.34 – 5.19 (m, 2×2H, AB), 4.37 (d, *J* = 5.9 Hz, 2H, A), 4.28 (s, 2H, B), 4.14 (d, *J* = 6.2 Hz, 2H, B), 4.06 (s, 2H, A), 3.56 – 3.40 (m, 2×4H, AB), 3.36 (s, 3H, A), 3.28 (s, 3H, B).

MS (ESI): 323.2 (29, M+Na^+), 226.1 (22), 198.1 (17), 129.0 (100).

Synthesis of 2-[allyl-(3-phenyl-propynoyl)-amino]-*N*-ethyl-3-methyl-butyramide (12a)

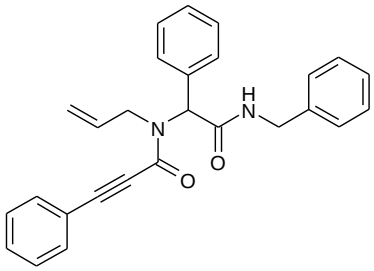


The compound was prepared according to *GRP1* with 1 ml of methanol, 64.4 mg (1.13 mmol) of allylamine, 85.7 mg (1.19 mmol) of isobutyraldehyde, 145 mg (0.99 mmol) of phenylpropiolic acid and 56.9 mg (1.03 mmol) of ethylisocyanide. After purification by column chromatography (1.5 ×20 cm silica, ethyl acetate/hexane = 1/2, product-R_f = 0.30) 265 mg (85 %) of the title compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B≈6/1) δ 7.61 – 7.51 (m, 2×2H, AB), 7.49 – 7.31 (m, 2×3H, AB), 6.39 (s (br), 1H, A), 5.97 – 5.87 (m, 2×1H, AB), 5.61 (s (br), 1H, B), 5.36 – 5.06 (m, 2×2H, AB), 4.48 – 4.08 (m, 3H+2H, AB), 4.00 – 3.87 (m, 1H, B), 3.32 – 3.19 (m, 2×2H, AB), 2.58 – 2.39 (m, 2×1H, AB), 1.14 (t, *J* = 7.1 Hz, 3H, B), 1.12 (t, *J* = 7.3 Hz, 3H, A), 1.02 (d, *J* = 6.4 Hz, 3H, B), 0.98 (d, *J* = 6.5 Hz, 3H, A), 0.96 (d, *J* = 7.0 Hz, 3H, B), 0.89 (d, *J* = 6.6 Hz, 3H, A).

MS (ESI): 335.3 (36, M+Na^+), 268.2 (6), 240.2 (15), 129.0 (100).

Synthesis of 3-phenyl-propynoic acid allyl-(benzylcarbamoyl-phenyl-methyl)-amide (13a)

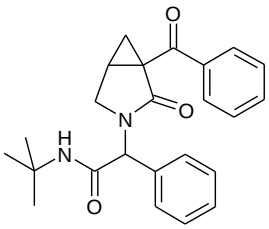


The compound was prepared according to *GRP1* with 1 ml of methanol, 63.1 mg (1.11 mmol) of allylamine, 152 mg (1.43 mmol) of benzaldehyde, 148 mg (1.01 mmol) of phenylpropiolic acid and 115 mg (0.98 mmol) of benzylisocyanide. After purification by column chromatography (1.5 ×25 cm silica, ethyl acetate/hexane = 1/3, product-R_f = 0.19) 344 mg (84 %) of the title compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B=4/1) δ 7.55 – 7.47 (m, 2×2H, AB), 7.46 – 7.21 (m, 2×13H, AB), 6.28 (s, 1H, B), 6.25 (s (br), 1H, B), 6.18 (s (br), 1H, A), 5.95 (s, 1H, A), 5.65 – 5.47 (m, 2×1H, AB), 5.06 – 4.93 (m, 2H, A), 4.89 – 4.78 (m, 2H, B), 4.64 – 4.56 (m, 1H, B), 4.56 – 4.44 (m, 2H+1H, AB), 4.40 (dd, *J* = 16.8, 5.7 Hz, 1H, A), 4.22 (dd, *J* = 16.7, 6.0 Hz, 1H, A), 4.09 – 4.00 (m, 1H, B), 3.96 – 3.88 (m, 1H, B).

MS (ESI): 431.3 (34, M+Na^+), 302.2 (5), 274.2 (4), 191.1 (3), 129.0 (100).

Synthesis of 2-(1-benzoyl-2-oxo-3-aza-bicyclo[3.1.0]hex-3-yl)-*N*-*tert*-butyl-2-phenyl-acetamide (1b)



The compound was prepared according to *GRP3* with 55.7 mg (0.15 mmol) of **1a**, 72.2 mg (0.22 mmol) iodosobenzenediacetate, 1.9 mg (0.012 mmol) bipyridyl, 4.1 mg (0.018 mmol) palladium acetate and 2.0 mL of dry acetic acid. After completion of the reaction the mixture was diluted with 5.0 mL of water and extracted with 2× 5.0 mL of ethyl acetate. The combined organic phases are washed with 2× 10 ml of water and 1× 10 ml of brine, dried and filtrated. Purification by column chromatography (1.5 × 30 cm neutral aluminum oxide, ethyl acetate/hexane = 1/5 → 4/1, product-R_f = 0.09 [ethyl acetate/hexane = 1/5]) yielded 29.7 mg (51 %) of the title compound as a off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$, 2 diastereomers A/B = 3/2) δ 7.97 – 7.93 (m, 2H, A), 7.82 – 7.77 (m, 2H, B), 7.56 – 7.51 (m, 2×1H, AB), 7.46 – 7.28 (m, 2×7H, AB), 5.70 (s, 1H, B), 5.68 (s (br), 1H, A), 5.56 (s, 1H, A), 5.45 (s (br), 1H, B), 4.27 (dd, *J* = 10.8, 5.8 Hz, 1H, A), 3.90 (d, *J* = 10.5 Hz, 1H, B), 3.23 (dd, *J* = 10.5, 5.9 Hz, 1H, B), 3.04 (d, *J* = 10.9 Hz, 1H, A), 2.36 – 2.28 (m, 2×1H, AB), 2.05 (dd, *J* = 8.2, 4.2 Hz, 1H, A), 1.99 (dd, *J* = 7.8, 4.9 Hz, 1H, B), 1.50 – 1.45 (m, 1H, B), 1.35 (s, 9H, A), 1.31 (s, 9H, B), 0.93 (t, *J* = 4.8 Hz, 1H, A).

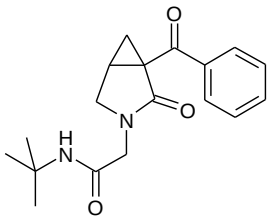
^{13}C NMR (101 MHz, $CDCl_3$, 2 diastereomers A/B = 3/2) δ 194.8 (B), 194.6 (A), 172.4 (A), 171.9(B), 168.5(A), 168.0 (B), 136.6 (B), 136.4 (A), 134.9 (A), 134.7 (B), 133.4, 133.0, 130.1, 129.2, 129.1, 129.1,

128.8, 128.8, 128.7, 128.4, 128.3, 128.2, 59.0 (A), 58.4 (B), 51.9 (A), 51.9 (B), 46.1 (A), 45.4 (B), 38.7 (A), 38.4 (B), 28.6 (B), 28.6 (A), 23.9 (A), 23.0 (B), 18.9 (B), 17.7 (A).

HRMS: 413.1836 ($M+Na^+$, calc.), 413.1834 (found)

MS (ESI): 414.4 (12, $M+Na^+$), 391.3 (100, $M+H^+$), 318.1 (15), 290.2 (34).

Synthesis of 2-(1-benzoyl-2-oxo-3-aza-bicyclo[3.1.0]hex-3-yl)-*N*-*tert*-butyl-acetamide (2b)



The compound was prepared according to *GRP4* with 258 mg (0.87 mmol) of **2a**, 320 mg (0.99 mmol) iodosobenzenediacetate, 23.5 mg (0.15 mmol) bipyridyl, 9.8 mg (0.044 mmol) palladium acetate and 5.0 mL of dry acetic acid. Purification by column chromatography (1.5 × 30 cm neutral aluminum oxide, ethyl acetate/hexane/formic acid = 50/50/1 → 90/10/1, product-R_f = 0.50 [ethyl acetate/hexane/formic acid = 90/10/1]) yielded 137 mg (52 %) of the title compound.

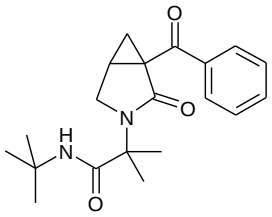
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 2H), 7.59 – 7.50 (m, 1H), 7.49 – 7.40 (m, 2H), 5.96 (s (br), 1H), 3.98 (dd, *J* = 10.5, 5.8 Hz, 1H), 3.79 (d, *J* = 15.7 Hz, 1H), 3.66 (d, *J* = 15.7 Hz, 1H), 3.53 (d, *J* = 10.5 Hz, 1H), 2.43 (dt, *J* = 7.9, 5.2 Hz, 1H), 2.08 (dd, *J* = 7.9, 4.6 Hz, 1H), 1.29 (s, 9H), 1.24 (t, *J* = 4.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.4, 172.4, 166.9, 136.5, 133.1, 129.1, 128.4, 51.4, 49.1, 46.9, 38.2, 28.7, 23.2, 18.5.

HRMS: 337.1523 ($M+Na^+$, calc.), 337.1520 (found)

MS (ESI): 337.0 (64, $M+Na^+$), 314.9 (39, $M+H^+$), 258.9 (13), 241.9 (19), 214.0 (100).

Synthesis of 2-(1-benzoyl-2-oxo-3-aza-bicyclo[3.1.0]hex-3-yl)-*N*-*tert*-butyl-acetamide (3b)



The compound was prepared according to *GRP3* with 185 mg (0.57 mmol) of **3a**, 207 mg (0.64 mmol) iodosobenzenediacetate, 6.7 mg (0.043 mmol) bipyridyl, 6.3 mg (0.028 mmol) palladium acetate and 4.0 mL of dry acetic acid. After completion of the reaction the mixture was diluted with 30 mL of water and extracted with 2× 50 mL of ethyl acetate. The combined organic phases are washed with 2× 50 ml of water and 1× 50 ml of brine, dried and filtrated. Purification by column chromatography (1.5 × 40 cm neutral aluminum oxide, ethyl acetate/hexane = 1/1 → 9/1, product-R_f = 0.50 [ethyl acetate/hexane = 4/1]) yielded 95.1 mg (49 %) of the title compound as a brown resin.

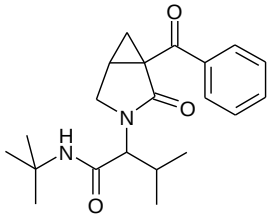
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 2H), 7.58 – 7.49 (m, 1H), 7.47 – 7.40 (m, 2H), 5.96 (s (br), 1H), 3.95 (dd, *J* = 10.4, 5.7 Hz, 1H), 3.62 (d, *J* = 10.4 Hz, 1H), 2.37 (dt, *J* = 7.8, 5.2 Hz, 1H), 2.07 (dd, *J* = 8.0, 4.7 Hz, 1H), 1.53 (s, 3H), 1.49 (s, 3H), 1.30 (s, 9H), 1.12 (t, *J* = 4.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.4, 172.8, 172.5, 136.4, 133.1, 129.2, 128. 3, 59.7, 51.2, 46.7, 39.2, 28.6, 24.2, 24.1, 23.0, 17.7.

HRMS: 365.1836 ($M+Na^+$, calc.), 365.1834 (found)

MS (ESI): 365.2 (29, $M+Na^+$), 343.2 (100, $M+H^+$), 270.1 (66), 242.1 (74).

Synthesis of 2-(1-benzoyl-2-oxo-3-aza-bicyclo[3.1.0]hex-3-yl)-*N*-*tert*-butyl-3-methyl-butyramide (4b)

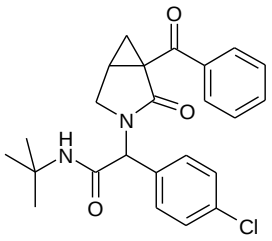


The compound was prepared according to *GRP3* with 96.3 mg (0.28 mmol) of **4a**, 106 mg (0.33 mmol) iodosobenzenediacetate, 4.3 mg (0.028 mmol) bipyridyl, 3.8 mg (0.017 mmol) palladium acetate and 3.0 mL of dry acetic acid. After completion of the reaction the mixture was diluted with 5.0 mL of water and extracted with 2× 15 mL of ethyl acetate. The combined organic phases are washed with 35 ml of water and 1× 35 ml of brine, dried and filtrated. Purification by column chromatography (1.5 × 30 cm neutral aluminum oxide, ethyl acetate/hexane = 1/4 → 1/1, product-R_f = 0.45 [ethyl acetate/hexane = 1/2]) yielded 17.1 mg (17 %) of the title compound as a brown resin.

HRMS: 379.1992 ($M+Na^+$, calc.), 379.1991 (found)

MS (ESI): 379.3 (37, $M+Na^+$), 357.3 (27, $M+H^+$), 284.2 (32), 256.2 (100), 178.1 (16), 110.0 (9), 105.0 (9).

Synthesis of 2-(1-benzoyl-2-oxo-3-aza-bicyclo[3.1.0]hex-3-yl)-*N*-*tert*-butyl-2-(4-chloro-phenyl)-acetamide (5b)



The compound was prepared according to *GRP3* with 99.4 mg (0.24 mmol) of **5a**, 93.3 mg (0.29 mmol) iodosobenzenediacetate, 5.4 mg (0.035 mmol) bipyridyl, 7.5 mg (0.033 mmol) palladium acetate and 4.0 mL of dry acetic acid. After completion of the reaction the mixture was diluted with 25 mL of water and extracted with 2× 30 mL of ethyl acetate. The combined organic phases are washed with 3× 35 ml of water and 1× 35 ml of brine, dried and filtrated. Purification by column chromatography (1.5 × 30 cm neutral aluminum oxide, ethyl acetate/hexane = 1/4, product-R_f = 0.10) yielded 9.3 mg (9 %) of the title compound as a brown resin.

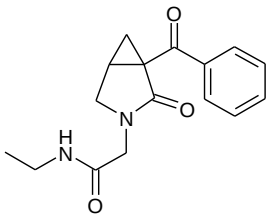
^{1}H NMR (400 MHz, $CDCl_3$, racemic mixture) δ 7.94 (d, *J* = 7.3 Hz, 2H, A), 7.79 (d, *J* = 7.1 Hz, 2H, B), 7.59 – 7.27 (m, 2×7H, AB), 5.62 (s, 1H, B), 5.56 (s (br), 1H, A), 5.49 (s, 1H, A), 5.40 (s (br), 1H, B), 4.25 (dd, *J* = 10.7, 5.9 Hz, 1H, A), 3.88 (d, *J* = 10.5 Hz, 1H, B), 3.25 (dd, *J* = 10.5, 5.9 Hz, 1H, B), 3.06 (d, *J* = 10.7 Hz, 1H, A), 2.42 – 2.30 (m, 2×1H, AB), 2.07 (dd, *J* = 7.8, 4.6 Hz, 1H, A), 2.00 (dd, *J* = 7.9, 4.5 Hz, 1H, B), 1.47 – 1.42 (m, 1H, B), 1.37 (s, 9H, A), 1.32 (s, 9H, B), 0.93 (t, *J* = 4.9 Hz, 1H, A).

^{13}C NMR (101 MHz, $CDCl_3$, racemic mixture) δ 194.4 (A), 193.6 (B), 172.4 (A), 171.9 (B), 168.0 (A), 167.6 (B), 136.6 (B), 136.4 (A), 135.0 (B), 134.9 (A), 133.5, 133.3, 133.1, 133.1, 130.5, 130.2, 129.3, 129.2, 129.1, 128.5, 128.4, 128.3, 58.3 (A), 57.7 (B), 52.0 (A), 52.0 (B), 45.9 (A), 45.3 (B), 38.5 (A), 38.3 (B), 28.6 (B), 28.6 (A), 22.8 (A), 22.7 (B), 19.0 (B), 17.8 (A).

HRMS: 447.1446 ($M+Na^+$, calc.), 447.1443 (found)

MS (ESI): 447.2 (53, $M+Na^+$), 427.3 (36, $M+H^+$), 425.3 (100, $M+H^+$), 352.1 (44), 324.1 (91), 178.1 (35), 140.0 (32), 105.0 (60).

Synthesis of 2-(1-benzoyl-2-oxo-3-aza-bicyclo[3.1.0]hex-3-yl)-*N*-ethyl-acetamide (7b)



The compound was prepared according to *GRP3* with 82.4 mg (0.30 mmol) of **7a**, 113 mg (0.35 mmol) iodosobenzenediacetate, 5.1 mg (0.033 mmol) bipyridyl, 5.0 mg (0.022 mmol) palladium acetate and 4.0 mL of dry acetic acid. After completion of the reaction the mixture was diluted with 20 mL of water and extracted with 2× 25 mL of ethyl acetate. The combined organic phases are washed with 3× 40 ml of water and 1× 40 ml of brine, dried and filtrated. Purification by column chromatography (1.5 × 30 cm

neutral aluminum oxide, ethyl acetate/hexane = 4/1 → pure ethyl acetate, product-R_f = 0.18 [ethyl acetate/hexane = 4/1]) yielded 33.2 mg (38 %) of the title compound.

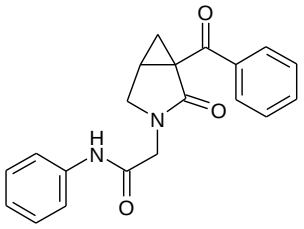
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.5 Hz, 2H), 7.60 – 7.51 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 6.12 (s (br)z, 1H), 3.97 (dd, *J* = 10.5, 5.8 Hz, 1H), 3.92 (d, *J* = 15.6 Hz, 1H), 3.72 (d, *J* = 15.6 Hz, 1H), 3.55 (d, *J* = 10.5 Hz, 1H), 3.35 – 3.12 (m, 2H), 2.47 (dt, *J* = 7.2, 5.4 Hz, 1H), 2.07 (dd, *J* = 7.7, 4.6 Hz, 1H), 1.27 (dd, *J* = 7.3, 4.6 Hz, 1H), 1.09 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 172.6, 167.6, 136.5, 133.2, 129.1, 128.4, 49.2, 46.6, 38.2, 34.5, 22.9, 18.8, 14.7.

HRMS: 309.1210 ($M+Na^+$, calc.), 309.1209 (found)

MS (ESI): 309.0 (52, $M+Na^+$), 287.0 (5, $M+H^+$), 214.1 (87), 104.9 (100).

Synthesis of 2-(1-benzoyl-2-oxo-3-aza-bicyclo[3.1.0]hex-3-yl)-*N*-phenyl-acetamide (8b)



The compound was prepared according to *GRP3* with 94.5 mg (0.30 mmol) of **8a**, 104 mg (0.32 mmol) iodosobenzenediacetate, 2.8 mg (0.018 mmol) bipyridyl, 5.7 mg (0.025 mmol) palladium acetate and 1.0 mL of dry acetic acid. After completion of the reaction the mixture was diluted with 6.0 mL of water and extracted with 2× 10 mL of ethyl acetate. The combined organic phases are washed with 3× 15 ml of water and 1× 20 ml of brine, dried and filtrated. Purification by column chromatography (1.5 × 30 cm neutral aluminum oxide, ethyl acetate/hexane = 1/1, product-R_f = 0.23) yielded 20.0 mg (20 %) of the title compound.

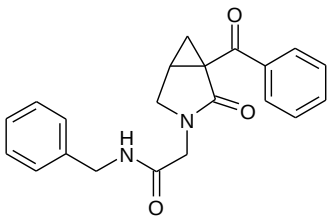
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s (br)zj, 1H), 7.88 (d, *J* = 7.3 Hz, 2H), 7.56 – 7.47 (m, 2H), 7.41 – 7.32 (m, 3H), 7.29 – 7.22 (m, 3H), 7.08 (t, *J* = 7.3 Hz, 1H), 4.12 (d, *J* = 15.6 Hz, 1H), 4.12 (dd, *J* = 6.9, 6.8 Hz, 1H), 4.03 (dd, *J* = 10.5, 5.8 Hz, 1H), 3.80 (d, *J* = 15.6 Hz, 1H), 3.58 (d, *J* = 10.5 Hz, 1H), 2.47 (dt, *J* = 7.8, 5.3 Hz, 1H), 2.12 (dd, *J* = 7.8, 4.8 Hz, 1H), 1.28 (t, *J* = 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 166.0, 137.4, 136.4, 133.2, 129.3, 129.0, 128.9, 128.5, 124.6, 120.1, 119.9, 49.4, 48.3, 38.2, 23.3, 18.7.

HRMS: 357.1210 ($M+Na^+$, calc.), 357.1208 (found)

MS (ESI): 356.7 (100, $M+Na^+$), 213.9 (76), 104.9 (40).

Synthesis of 2-(1-benzoyl-2-oxo-3-aza-bicyclo[3.1.0]hex-3-yl)-*N*-benzyl-acetamide (9b)



The compound was prepared according to *GRP3* with 113 mg (0.34 mmol) of **9a**, 125 mg (0.39 mmol) iodosobenzenediacetate, 6.4 mg (0.041 mmol) bipyridyl, 5.2 mg (0.023 mmol) palladium acetate and 5.0 mL of dry acetic acid. After completion of the reaction the mixture was diluted with 5.0 mL of water and extracted with 2× 10 mL of ethyl acetate. The combined organic phases are washed with 3× 15 ml of water and 1× 20 ml of brine, dried and filtrated. Purification by column chromatography (1.5 × 30 cm neutral aluminum oxide, ethyl acetate/hexane = 1/1 → 2/1, product-R_f = 0.30 [ethyl acetate/hexane = 1/1]) yielded 51.1 mg (43 %) of the title compound.

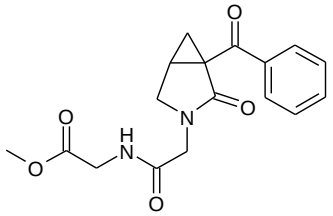
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 2H), 7.36 – 7.24 (m, 3H), 7.22 (d, *J* = 6.9 Hz, 2H), 6.46 (t (br), *J* = 5.0 Hz, 1H), 4.52 – 4.27 (m, 3H), 3.97 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.96 (d, *J* = 15.9 Hz, 1H), 3.80 (d, *J* = 15.7 Hz, 1H), 3.55 (d, *J* = 10.5 Hz, 1H), 2.47 (dt, *J* = 7.9, 5.3 Hz, 1H), 2.04 (dd, *J* = 7.8, 4.5 Hz, 1H), 1.22 (t, *J* = 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 172.7, 167.8, 137.9, 136.4, 133.2, 129.1, 128.6, 128.4, 127.6, 127.4, 49.1, 45.9, 43.4, 38.3, 23.0, 18.6.

HRMS: 371.1366 ($M+Na^+$, calc.), 371.1363 (found)

MS (ESI): 371.1 (99, $M+Na^+$), 348.9 (93, $M+H^+$), 241.9 (68), 213.9 (100), 104.9 (16), 90.9 (25).

Synthesis of [2-(1-benzoyl-2-oxo-3-aza-bicyclo[3.1.0]hex-3-yl)-acetylamino]-acetic acid methyl ester (10b)



The compound was prepared according to *GRP3* with 103 mg (0.33 mmol) of **10a**, 128 mg (0.40 mmol) iodosobenzenediacetate, 5.4 mg (0.035 mmol) bipyridyl, 8.4 mg (0.037 mmol) palladium acetate and 4.0 mL of dry acetic acid. After completion of the reaction the mixture was diluted with 25 mL of water and extracted with 2× 20 mL of ethyl acetate. The combined organic phases are washed with 3× 35 ml of water and 1× 25 ml of brine, dried and filtrated. Purification by column chromatography (1.5 × 30 cm neutral aluminum oxide, ethyl acetate/hexane = 9/1 → 15/1, product-R_f = 0.23 [ethyl acetate/hexane = 9/1]) yielded 31.4 mg (29 %) of the title compound.

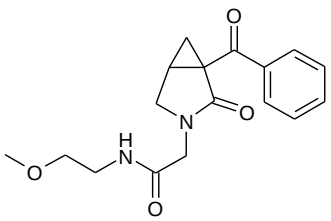
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.77 (m, 2H), 7.59 – 7.49 (m, 1H), 7.49 – 7.37 (m, 2H), 6.61 (t (br), *J* = 4.9 Hz, 1H), 4.04 – 3.91 (m, 4H), 3.87 (d, *J* = 15.9 Hz, 1H), 3.54 (d, *J* = 10.4 Hz, 1H), 2.49 (dt, *J* = 8.0, 5.2 Hz, 1H), 2.08 (dd, *J* = 8.1, 4.5 Hz, 1H), 1.34 (t, *J* = 4.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 172.6, 170.0, 168.2, 136.5, 133.2, 129.1, 128.4, 52.4, 48.9, 46.1, 41.0, 38.2, 23.0, 18.9.

HRMS: 353.1108 ($M+Na^+$, calc.), 353.1106 (found)

MS (ESI): 353.2 (37, $M+Na^+$), 331.2 (19, $M+H^+$), 242.1 (16), 214.1 (100), 105.0 (75).

Synthesis of 2-(1-benzoyl-2-oxo-3-aza-bicyclo[3.1.0]hex-3-yl)-*N*-(2-methoxy-ethyl)-acetamide (11b)



The compound was prepared according to *GRP4* with 114 mg (0.38 mmol) of **11a**, 156 mg (0.48 mmol) iodosobenzenediacetate, 9.8 mg (0.063 mmol) bipyridyl, 10.5 mg (0.047 mmol) palladium acetate and 5.0 mL of dry acetic acid. Purification by column chromatography (1.5 × 30 cm neutral aluminum oxide, ethyl acetate/hexane = 1/1 → ethyl acetate/methanol = 1/1, product-R_f = 0.70 [ethyl acetate/methanol = 4/1]) yielded 63.3 mg (40 %) of the title compound.

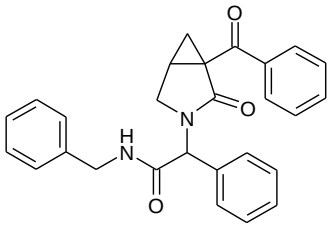
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.77 (m, 2H), 7.59 – 7.50 (m, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 6.32 (s (br), 1H), 3.94 (dd, *J* = 10.2, 5.6 Hz, 1H), 3.90 (d, *J* = 15.8 Hz, 1H), 3.83 (d, *J* = 15.8 Hz, 1H), 3.53 (d, *J* = 10.4 Hz, 1H), 3.46 – 3.41 (m, 4H), 3.33 (s, 3H), 2.47 (dt, *J* = 7.7, 5.3 Hz, 1H), 2.06 (dd, *J* = 7.9, 4.5 Hz, 1H), 1.30 (t, *J* = 4.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.4, 172.5, 167.7, 136.5, 133.2, 129.1, 128.4, 70.8, 58.7, 48.9, 45.9, 39.2, 38.2, 22.9, 18.8.

HRMS: 339.1315 ($M+Na^+$, calc.), 339.1312 (found)

MS (ESI): 339.2 (62, $M+Na^+$), 317.2 (30, $M+H^+$), 242.1 (29), 214.1 (100), 105.0 (30).

Synthesis of 2-(1-benzoyl-2-oxo-3-aza-bicyclo[3.1.0]hex-3-yl)-*N*-benzyl-2-phenyl-acetamide (13b)



The compound was prepared according to *GRP3* with 132 mg (0.32 mmol) of **13a**, 119 mg (0.37 mmol) iodosobenzenediacetate, 6.8 mg (0.044 mmol) bipyridyl, 5.7 mg (0.025 mmol) palladium acetate and 7.0 mL of dry acetic acid. After completion of the reaction the mixture was diluted with 40 mL of water and extracted with 2× 50 mL of ethyl acetate. The combined organic phases are washed with 3× 100 ml of water and 1× 100 ml of brine, dried and filtrated. Purification by column chromatography (1.5 × 30 cm neutral aluminum oxide, ethyl acetate/hexane = 1/9 → 4/1, product-R_f = 0.74 [ethyl acetate/hexane = 1/1]) yielded 43.9 mg (32 %) of the title compound.

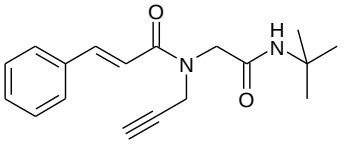
^{1}H NMR (400 MHz, $CDCl_3$, 2 diastereomers A/B=3/2) δ 8.14 – 8.03 (m, 2H, A), 8.01 – 7.89 (m, 2H, B), 7.87 – 7.76 (m, 2H, B), 7.64 – 7.07 (m, 13H + 11H, AB), 6.26 (t (br), *J* = 5.6 Hz, 1H, A), 6.14 (t (br), *J* = 5.3 Hz, 1H, B), 5.85 (s, 1H, B), 5.73 (s, 1H, A), 4.51 – 4.42 (m, 2H, A), 4.44 – 4.34 (m, 2H, B), 4.25 (dd, *J* = 9.6, 4.7 Hz, 1H, A), 3.89 (d, *J* = 10.5 Hz, 1H, B), 3.28 (dd, *J* = 10.5, 5.9 Hz, 1H, B), 3.11 (d, *J* = 10.7 Hz, 1H, A), 2.35 (dt, *J* = 12.9, 5.0 Hz, 1H, AB), 2.04 (dd, *J* = 7.9, 4.6 Hz, 1H, A), 1.97 (dd, *J* = 7.9, 4.4 Hz, 1H, B), 1.48 (t, *J* = 4.7 Hz, 1H, B), 0.94 (t, *J* = 4.8 Hz, 1H, A).

^{13}C NMR (101 MHz, $CDCl_3$, 2 diastereomers A/B=3/2) δ 194.7 (B), 194.5 (A), 172.5 (A), 172.0 (B), 169.1 (A), 168.8 (B), 137.7, 137.6, 136.6 (B), 136.4 (A), 134.3, 134.0, 133.5, 133.1, 130.1, 129.2, 129.2, 129.1, 129.1, 129.0, 129.0, 128.9, 128.7, 128.4, 128.2, 127.7, 127.6, 127.6, 127.5, 58.9 (A), 58.3 (B), 46.0 (A), 45.5 (B), 43.7, 43.7, 38.6 (B), 38.4 (A), 23.6 (A), 22.8 (B), 19.0 (B), 17.8 (A).

HRMS: 447.1679 ($M+Na^+$, calc.), 447.1676 (found)

MS (ESI): 447.2 (77, $M+Na^+$), 425.2 (68, $M+H^+$), 318.1 (49), 290.1 (100), 143.9 (26), 105.0 (18), 91.0 (32).

Synthesis of *N*-(*tert*-butylcarbamoyl-methyl)-3-phenyl-*N*-prop-2-ynyl-acrylamide (14)



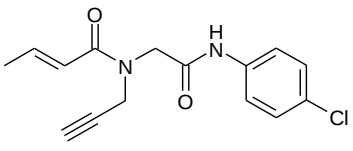
In a pressure tube with 3 ml of 2,2,2-trifluorethanol 67.7 mg (1.23 mmol) of propargylamine, 33.6 mg (1.12 mmol) of *para*-formaldehyde, 154 mg (1.04 mmol) of *trans*-cinnamic acid and 97.1 mg (1.17 mmol) of *tert*-butylisocyanide were mixed at 0 °C and stirred for 2 days. After evaporation of the solvent *in vacuo* the crude product was purified by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/2 → 1/1, product-R_f = 0.19 [ethyl acetate/hexane = 1/2]) 291 mg (94 %) of the title compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B= 1/1) δ 7.77 (d, *J* = 14.8 Hz, 2×1H, AB), 7.55-7.51 (m, 2×2H, AB), 7.39 (s, 2×3H, AB), 6.94 (d, *J* = 15.2 Hz, 1H, A or B), 6.66 (d, *J* = 15.2 Hz, 1H, A or B), 6.12 (s (br), 1H, A or B), 6.04 (s (br), 1H, A or B), 4.39 (s, 2H, A or B), 4.32 (s, 2H, A or B), 4.09 (d, *J* = 10.4 Hz, 2×2H, AB), 2.38 (s, 1H, A or B), 2.34 (s, 1H, A or B), 1.34 (s, 2×9H, AB).

HRMS: 321.1573 ($M+Na^+$, calc.), 321.1569 (found).

MS (ESI): 321.2 (5, $M+Na^+$), 299.2 (2, $M+H^+$), 226.1 (23), 131.0 (100), 103.0 (19).

Synthesis of but-2-enoic acid (*tert*-butylcarbamoyl-methyl)-prop-2-ynyl-amide (16)



In a pressure tube with 1 ml of 2,2,2-trifluorethanol 59.3 mg (1.08 mmol) of propargylamine, 38.0 mg (1.27 mmol) of *para*-formaldehyde, 84.5 mg (0.98 mmol) of crotonic acid and 139 mg (1.01 mmol) of 4-chlorophenyl isocyanide were mixed at 0 °C and stirred at room temperature over night. After evaporation of the solvent *in*

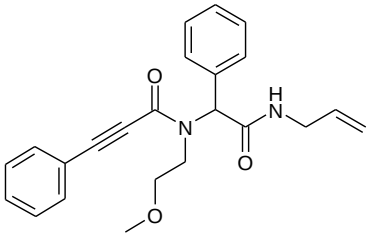
vacuo the crude product was purified by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/1, product-R_f = 0.43 [ethyl acetate/hexane = 1/1]) 261 mg (91 %) of the title compound were obtained.

^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B = 1.1/1) δ 9.86 (s(br), 1H, B), 9.71 (s(br), 1H, A), 7.78 – 7.46 (m, 2H), 7.29 – 7.17 (m, 2H), 6.99 – 6.83 (m, 1H), 6.40 (d, *J* = 15.6 Hz, 1H, A), 6.20 (d, *J* = 14.7 Hz, 1H, B), 4.39 – 4.23 (m, 4H), 2.97 (s, 1H), 1.93 (d, *J* = 6.8 Hz, 3H, A), 1.87 (d, *J* = 6.8 Hz, 3H, B).

MS (ESI): ($M+Na^+$), 312.9 (100, $M+Na^+$), 309.9 (82, $M+Na^+$), 150.0 (9).

Synthesis of 3-phenyl-propynoic acid (allylcarbamoyl-phenyl-methyl)-(2-methoxy-ethyl)-amide (17)

The compound was prepared according to GRP1 with 80.0 mg (1.07 mmol) of 2-methoxyethylamine, 114 mg (1.07 mmol) of benzaldehyde, 146 mg (1.00 mmol) of phenylpropiolic acid, 80.0 mg (1.19 mmol) of allylisocyanide and 1.0 ml of methanol. Purification by preparative chromatography (Polaris C-18, 20 × 250 mm, acetonitrile/water/formic acid) yielded 345 mg (92 %) of the title compound.



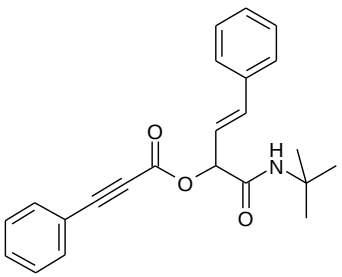
^{1}H NMR (400 MHz, DMSO, 2 Rotamers A/B = 3/2) δ 8.62 (t, *J* = 5.6 Hz, 1H, B), 8.39 (t, *J* = 5.7 Hz, 1H, A), 7.70 – 7.64 (m, 2H, B), 7.64 – 7.57 (m, 2H, A), 7.56 – 7.23 (m, 2×8H, AB), 6.20 (s, 1H, B), 5.98 (s, 1H, A), 5.87 – 5.69 (m, 2×1H, AB), 5.17 – 4.94 (m, 2×2H, AB), 3.80 (t (br), *J* = 4.6 Hz, 2H, B), 3.75 (t (br), *J* = 4.4 Hz, 2H, A), 3.69 (t, *J* = 7.1 Hz, 2H, A), 3.51 (ddd, *J* = 14.2, 9.3, 5.5 Hz, 1H, B), 3.40 – 3.33 (m, 1H, B), 3.28 – 3.17 (m, 2×1H, AB), 3.04 (s, 3H, A), 2.99 (s, 3H, B), 2.87 (dt, *J* = 9.9, 6.9 Hz, 1H, A), 2.73 – 2.63 (m, 1H, B).

HRMS: 399.1679 ($M+Na^+$, calc.), 399.1676 (found).

MS (ESI): 399.3 (27, $M+Na^+$), 377.3 (4, $M+H^+$), 320.2 (96), 292.2 (25), 191.1 (10), 162.1 (7), 129.0 (100).

Synthesis of phenyl-propynoic acid 1-*tert*-butylcarbamoyl-3-phenyl-allyl ester (18)

138 mg (1.04 mmol) of *trans*-cinnamonaldehyde, 188 mg (1.28 mmol) of phenylpropiolic acid and 85.0 mg (1.02 mmol) of *tert*-butylisocyanide were mixed at 0 °C in 1.0 ml of tetrahydrofuran and the resulting mixture stirred for 7 days at room temperature. Purification by column chromatography (1.5 × 40 cm silica, ethyl acetate/hexane = 1/9, product-R_f = 0.11) yielded 91.2 mg (25 %) of the title compound.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.60 (m, 2H), 7.52 – 7.27 (m, 8H), 6.80 (d, *J* = 15.9 Hz, 1H), 6.31 (dd, *J* = 15.9, 6.9 Hz, 1H), 5.95 (s, 1H), 5.76 (dd, *J* = 6.9, 1.1 Hz, 1H), 1.41 (s, 9H).

MS (ESI): 384.2 (29, $M+Na^+$), 238.1 (5), 216.1 (100), 160.1 (38), 132.0 (7), 117.0 (14).

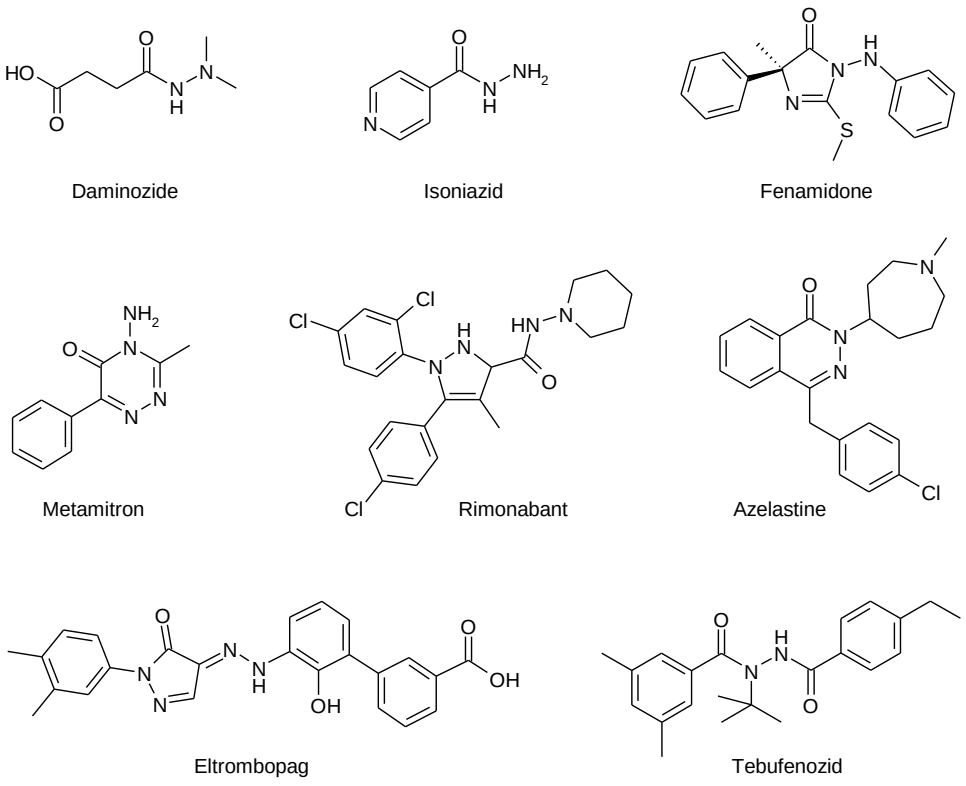
6.3. Cyclizations of hydrazine derived Ugi-4CR products

Parts of chapter 6.3.2. have been published in:

Sebastian J. Welsch, Cédric Kalinski, Michael Umkehrer, Günther Ross, Jürgen Kolb, Christoph Burdack, Ludger A. Wessjohann; *Palladium and copper catalyzed cyclizations of hydrazine derived Ugi products: facile synthesis of substituted indazolones and hydroxytriazafluorendiones*; *Tetrahedron Letters* **2012**, *53* (18), 2298-2301.

6.3.1. Introduction

The acyl hydrazine (hydrazide) motif is an important pharmacophore. Drugs containing this structural motif have been on the market for more than a hundred years. Today it is found in numerous marketed drugs[176] (i.e. isoniazid (antibiotic), azelastin (histamine antagonist), rimonabant (anorectic antiobesity), eltrombopag (thrombopoietin receptor agonist)) and in crop protecting agents (i.e. tebufenozide, metamitron, fenamidone, daminozide). In addition to these, bioactive compounds with this motif are studied for their antitumor properties[177] and as novel antibiotics.[178–181]

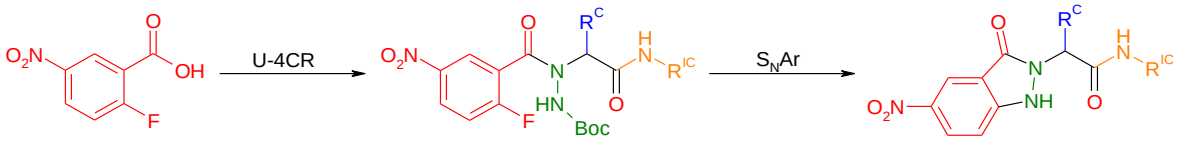


Scheme 31: Active agents containing an acyl hydrazide motif (daminozide: plant growth regulator, [182] isoniazid: antitubercolosis,[183] fenamidone: fungicide,[184] metamitron: herbicide,[185] rimonabant: antiobesity,[186] azelastine: histamine antagonist,[187] eltrombopag: thrombopoietin receptor agonist, [188] tebufenozid: insecticide.[189])

6.3.2. Ugi-4CR cyclization by palladium and copper catalysis

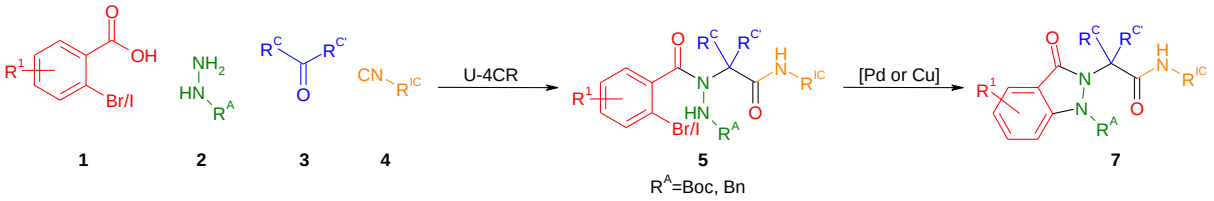
Indazolone derivatives have attracted increasing attention due to their promising pharmacological properties,[190,191] including anti-inflammatory,[192,193] antiallergic,[194] antipsychotic,[195] hypolipidemic[196] and cytostatic[197] activities. A variety of synthetic routes have been reported,[191,198] but all of these require multiple steps and in some cases the use of dangerous intermediates. The only multicomponent reaction based synthesis following the UDC (Ugi reaction/deprotection/cyclization) strategy has been published by TEMPEST *et al.*[69] It consists of an Ugi-4CR with BOC-protected hydrazine as amine component and 2-fluoro-5-nitrobenzoic acid as acid component, followed by BOC removal of the Ugi product and subsequent nucleophilic aromatic substitution (Scheme 32).

The major drawback of this sequence is the necessity of a strong acceptor in the cyclization step which restricts the diversity of the product space accessible with readily available starting materials considerably. Furthermore the nitro group is among those functionalities medicinal chemists try to avoid.[199] Further, the versatility of this reaction sequence has been explored with only four examples, and despite the use of solid phase bound reagents and the thereby easy purification the overall yield did not exceed 50 %.



Scheme 32: Indazolone synthesis via Ugi-S_NAr-strategy.[69]

To remedy these problems the synthesis was to be optimized with the goal to develop an improved MCR based synthesis. Employing a transition metal catalysed cyclization should broaden the substrate scope and thereby increase the versatility of this pathway and – hopefully – the yield, too. Especially palladium mediated cyclizations have been successfully employed for MCR postmodifications on numerous occasions.[57–63,67,164,165,200] Thus the following sequence was envisioned comprising an Ugi reaction of a protected hydrazine (**2**, R^A = BOC or Bn) and an *o*-bromo- or *o*-iodobenzoic acid (**1**), an oxo compound (**3**, ketone or aldehyde) and an isocyanide (**4**, R^{IC}) followed by palladium catalyzed cyclization (Scheme 33).



Scheme 33: Indazolone synthesis via Ugi reaction and palladium or copper catalysed amidation/amination.

In a preliminary experiment, equimolar amounts of BOC-protected hydrazine, isobutyraldehyde, *o*-bromobenzoic acid and *tert*-butylisocyanide were stirred in methanol (1 M) at room temperature. The reaction went smoothly and the Ugi product **5a** was isolated with 94 % yield (Table 6, entry 1). Subsequent deprotection with 20 % trifluoroacetic acid in dichloromethane yielded the free hydrazide **6a** which was subjected to varied cyclization conditions selected from procedures reported in literature.[201–203] Entries 1-3 in table 1 show results of a starting catalyst (ligand) variation. Only the $Pd_2dba_3/P(^tBu)_3$ system gave complete conversion and yielded the desired indazolone **8a** without side products (isolated yield 71 %).

Table 5: Screening of catalysts and conditionsfor the Pd-catalyzed cyclization of 5a/6a to indazolone 8a. All reactions were performed in anhydrous toluene under nitrogen at 110 °C.

Entry	Catalyst	Base	s.m.	HPLC Yield[1]
1	5 mol% $Pd(PPh_3)_4$	1.4 eq Na^tOBu, 1.6 eq K_2CO_3	**6a**	59 %
2	3.5 mol% $Pd(OAc)_2$, 5 mol% dppf	1.4 eq Na^tOBu	**6a**	40 %
3	10 mol% Pd_2dba_3, 5 mol% $P(^tBu)_3$	2 eq Na^tOBu, 2 eq K_2CO_3	**6a**	82 %[2]
4	5 mol% Pd_2dba_3, 6 mol% BINAP	2 eq NaOPh, 2 eq Cs_2CO_3	**5a**	64 %
5	2 mol% Pd_2dba_3, 10 % Xantphos	2 eq Cs_2CO_3	**5a**	> 99 %
6	2 mol% Pd_2dba_3, 10 mol% dppf	2 eq Na^tOBu	**5a**	> 99 %

[1] 254 nm [2] isolated yield after chromatography: 71 % (see Table 6)

This catalytic system (entry 3) was used to synthesize compounds **7g** and **8a-f** (*v.i.*), but it turned out that other conditions would allow the direct, one step conversion of the Ugi products to the desired cyclization products **8** without a dedicated deprotection step. Those alternative cyclization conditions leave the BOC protecting group in place and thereby retain the possibility to further elaborate the products without having to re-protect the nitrogen again.

As the catalytic system employed above requires a free amino group and does not work with electron deficient nitrogen, different ligands and conditions were tested for this cyclization.[203] (Table 5, entries 4-6). Both xantphos/Cs_2CO_3 (entry 5) and dppf/NaO^tBu (entry 6) led to a clean and complete conversion of **5a** to **8a** with the latter being considerably faster (36 and 14 h, respectively) As all three test reactions proceeded surprisingly with complete intrinsic deprotection the previous conditions (entry 3) were re-examined to test if they could effect the same. Subjecting **5a** directly to the above cyclization conditions (cf. Table 5, entry 3) gave only traces of **8a** with the majority of the starting material unchanged. In another control experiment without palladium slow deprotection of **5a** producing **6a** was observed indicating that only after thermal cleavage of the BOC group cyclization of the free amine occurs.

With this catalytic system (Table 5, entry 3) the scope and versatility of this sequence was examined (Table 6). The Ugi products were obtained in moderate to good yields. The cyclization works for both electron deficient and electron rich benzoic acids but the yield of the latter suffers from increased side product formation (Table 6, entries 1, 5, 6). Besides aliphatic aldehydes ketones can be easily employed in the Ugi reaction but the deprotected bisamide **6d** degraded during final purification on silica (Table 6, entry 4, cf. Table 7, entry 4). The use of different isocyanides was somewhat hindered by incomplete conversions during the cyclization (Table 6, entry 2, 3). *N'*-alkyl substituted hydrazides are also suitable substrates, but the liberation of the free base from the benzylhydrazine dihydrochloride salt proved to be difficult. Among the bases tested (triethylamine, sodium hydroxide, potassium carbonate) only sodium hydroxide used *in situ* gave some amounts of **5g** (entry 7). Liberation prior the Ugi reaction failed as well as the use of potassium carbonate and triethylamine *in situ* (compare chapter 6.4.2). These detrimental basic reaction conditions are reflected in the low yield of the Ugi reaction which performs best under acidic conditions.

Finally it was to be tested if palladium could be substituted by copper which is also a well-known catalyst of amide arylations. Besides being much cheaper than palladium, copper complexes exhibit a rich chemistry that enables easy tuning of the reactivity.[204,205] Stirring **5a'** (the apostrophe denotes

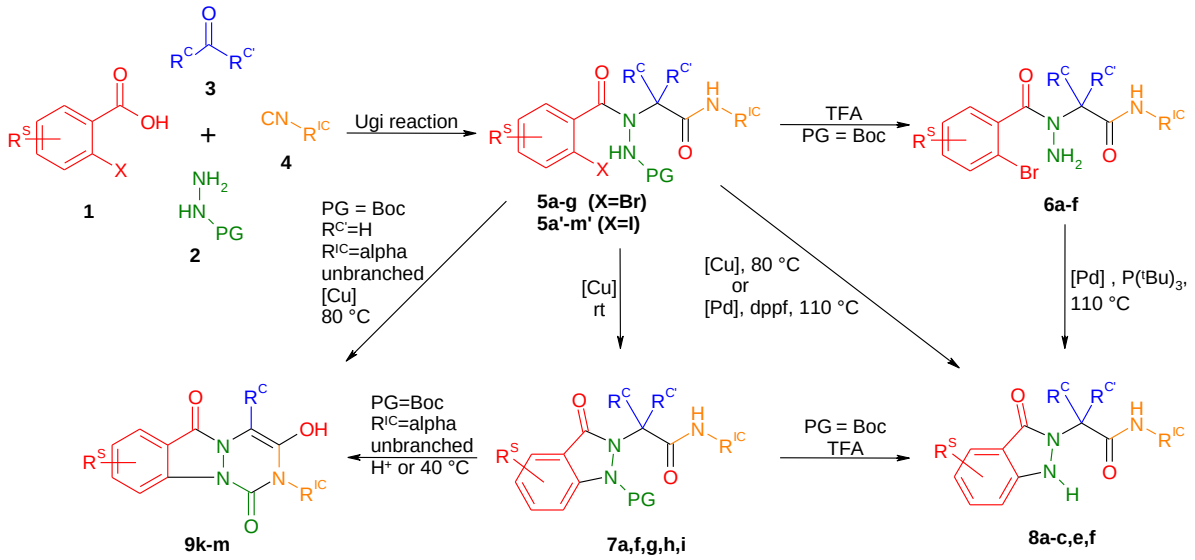


Table 6: [Pd]-cyclizations: X=Br, 10 mol% Pd_2dba_3, 5 mol% P^tBu_3, 2 eq NaO^tBu, 2 eq Cs_2CO_3, dry toluene, 110 °C, overnight.

Entry	R^S	PG	R^C, $R^{C'}$	R^{IC}	Ugi-4CR		DeBOC-Ugi		Product[1]	
1	H	BOC	^{i}Pr, H	^{t}Bu	**5a**	94 %	**6a**	51 %	**8a**	71 %
2	H	BOC	^{i}Pr, H	4-Cl-Ph	**5b**	64 %	**6b**	61 %	**8b**	20 %
3	H	BOC	^{i}Pr, H	4-MeO-Bn	**5c**	86 %	**6c**	34 %	**8c**	16 %
4	H	BOC	-$(CH_2)_5$-	^{t}Bu	**5d**	36 %	**6d**	degr.		—
5	5-NO_2	BOC	^{i}Pr, H	^{t}Bu	**5e**	70 %	**6e**	83 %	**8e**	52 %
6	5-MeO	BOC	^{i}Pr, H	^{t}Bu	**5f**	79 %	**6f**	69 %	**8f**	25 %
7	H	Bn	^{i}Pr, H	^{t}Bu	**5g**	11 %	n.a.		**7g**	77 %

[1] isolated yield

Table 7: [Cu]-cyclizations: X=I, PG=BOC; 5 mol% CuI, 2 eq Cs_2CO_3, dry DMF. Conditions: A: rt; B: rt, 10 mol% 1,10-phenanthrolin; C: 80 °C; D: 80 °C, 10 mol% 1,10-phenanthrolin.

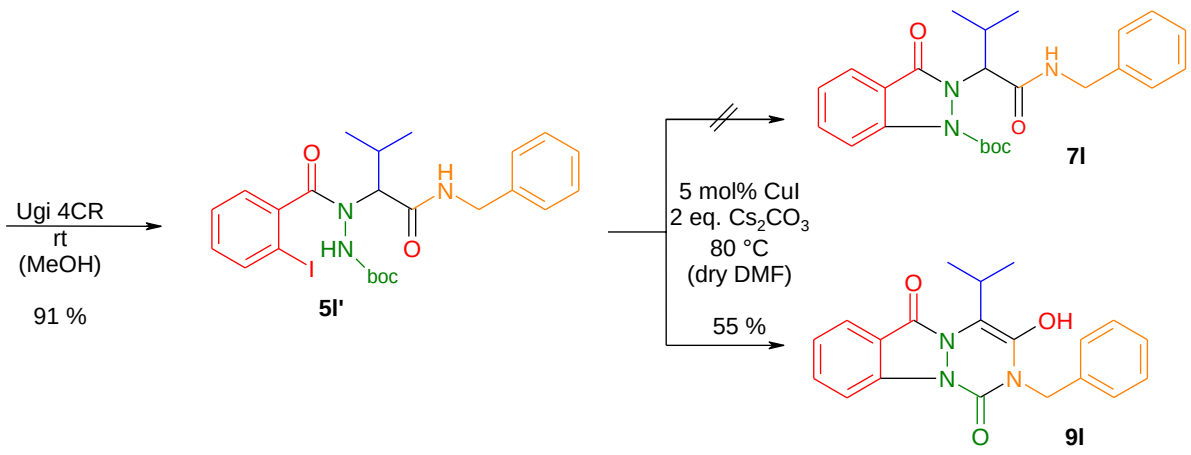
Entry	R^S	R^C, $R^{C'}$	R^{IC}	Ugi-4CR		Cyclization conditions	Product[1]	
1	H	^{i}Pr, H	^{t}Bu	**5a'**	73 %	A	**7a**	93 %
2	H	^{i}Pr, H	^{t}Bu	**5a'**	73 %	B	**7a**	95 %[2]
3	5-MeO	^{i}Pr, H	^{t}Bu	**5f**	95 %	A	**7f**	12 %
4	H	Me, Me	^{t}Bu	**5h'**	73 %	A	**7h**	77 %
5	H	^{i}Pr, H	Ph	**5i'**	90 %	A	**7i**	67 %
6	H	^{i}Pr, H	CH_2CH_2OMe	**5k'**	82 %	A	**7k'**	degr.
7	H	^{i}Pr, H	Bn	**5l'**	91 %	A	**9l**	57 %
8	H	^{i}Pr, H	^{t}Bu	**5a'**	73 %	C	**8a**	55 %
9	H	^{i}Pr, H	^{t}Bu	**5a'**	73 %	D	**8a**	59 %
10	5-NO_2	^{i}Pr, H	^{t}Bu	**5e**	77 %	C	**8e**	99 %
11	5-MeO	^{i}Pr, H	^{t}Bu	**5f**	95 %	C	**8f**	38 %
12	H	^{i}Pr, H	Ph	**5i'**	90 %	C	**8j**	degr.
13	H	^{i}Pr, H	CH_2CH_2OMe	**5k'**	82 %	C	**9k**	75 %
14	H	^{i}Pr, H	Bn	**5l'**	91 %	C	**9l**	55 %
15	H	^{i}Pr, H	4-MeO-Bn	**5c'**	77 %	C	**9c**	82 %
16	H	^{i}Pr, H	4-F_3C-Bn	**5m'**	48 %	C	**9m**	61 %

[1] isolated yield [2] HPLC yield (254 nm)

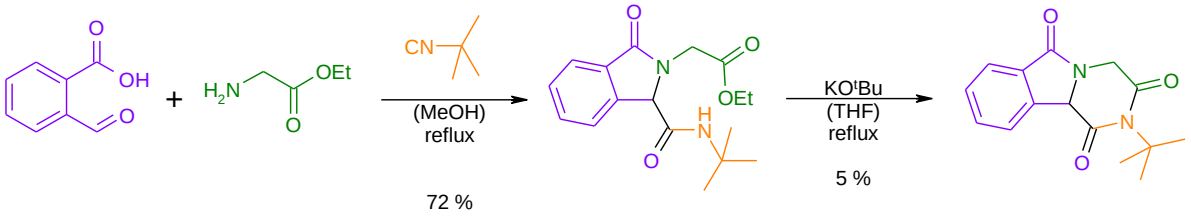
the use of aryliodides instead of bromides) in anhydrous DMF under a nitrogen atmosphere with 5 mol% copper iodide, 10 mol% 1,10-phenanthroline and 2 equivalents of cesium carbonate[206] for half an hour resulted in a complete and clean conversion of the starting material. Surprisingly no ligand seems to be required for this cyclization: a control reaction without 1,10-phenanthroline performed similar and gave 93 % of the still BOC-protected product **7a** along with 4 % deprotected **8a** within 30 minutes. This finding is in contrast to previous reports in literature.[205] The reaction tolerates both aldehydes and ketones but Ugi products of the latter have a tendency to degrade (hydrolyze?) on silica and therefore have to be purified with care, e.g. on basic aluminum oxide. Treatment of **7a** and **7h** with 20 % TFA in dichloromethane gave the free indazolone in 46 % and 62 % yield, respectively.

Phenylic isocyanides worked fine (Table 7, entry 5) but alkyl isocyanides lead to different results: reaction monitoring via HPLC/MS showed a clear conversion also for benzylic isocyanides and 2-methoxyethyl isocyanide to the desired BOC-protected indazolones but these proved to be instable at elevated temperatures. While **7k** degraded already upon heating to 40 °C (water bath temperature of the rotary evaporator) to several different products (including deprotected indazolone and hydroxytriazafluorendione, *vide infra*), **7l** was converted to a new product which was identified by HPLC/MS and NMR as hydroxytriazafluorendione **9l** (scheme 34): HPLC/MS analysis showed a clean conversion to a single product. m/z$^+$ value was 26 higher than the expexted one of the deprotected indazolone **8l** (+28 (for CO) -2 (ring closure)). In the ^{1}H-NMR (*cf.* p. 177) several changes are observed compared to the usual indazolone spectra: The benzylic protons show a singulett instead of a dd which means that the amide has been transformed from a secondary into a tertiary. Accordingly the NH signal is vanished and instead a new singulett of an acidic proton has appeared (addition of a drop of D_2O supresses it). Further the C*H*$(CH_3)_2$ signal is simplified from a dhept/m to hept, and naturally the ^{t}Bu signal of the BOC group is no longer present. The same reaction took place when BOC cleavage was attempted *in situ* with 20 % TFA.

Interestingly enough Ugi *et al.* have published a very similar structure obtained by using two bifunctional starting materials an Ugi reaction – 2-acyl benzoic acid and amino acid esters – albeit in poor yield (Scheme 35).[207]



Scheme 34: Unexpected formation of hydroxytriazafluorendione 9l.

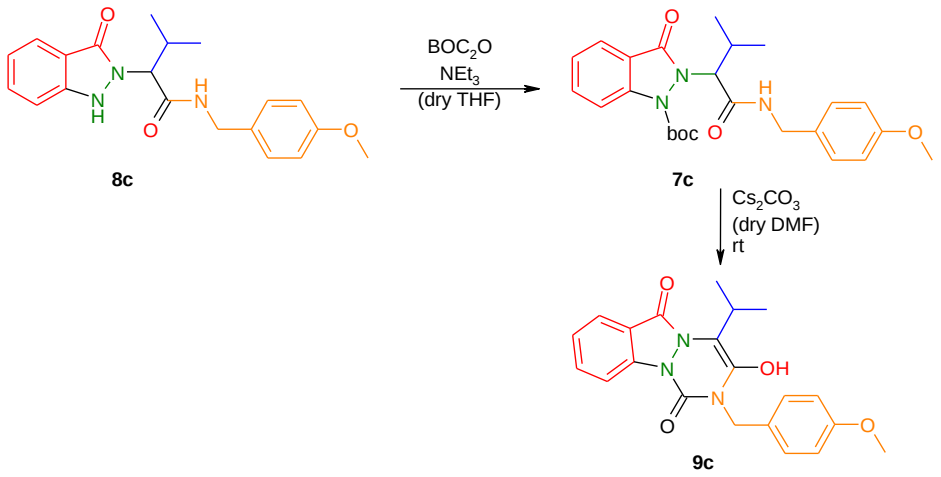


Scheme 35: Diazafluorentrione synthesis by Ugi *et al*.

Intrigued by this unusal behaviour of the BOC-group, cyclizations at higher temperature were investigated. Subjecting **1a'** to previous cyclization conditions at 80 °C led directly to the free indazolone **8a** irrespective of the presence of 1,10-phenanthroline (Table 7, entries 8 and 9). Reaction monitoring showed that thermal BOC cleavage occurs at a much lower rate than cyclization and that the rate of the latter is strongly dependent on the substituents at the benzoic acid residue: while the cyclization reaction of the nitro substituted substrate is finished within a few minutes even at rt, reactions of electronrich aryliodide moieties require several hours at elevated temperatures to achieve complete conversions. In the same order increasing amounts of different, inseparable dimers of the free indazolone were formed which were in the case of **8f** the main product (entries 10 and 11).

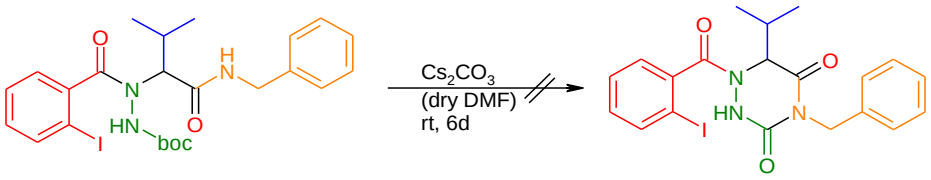
When more nucleophilic and sterically less hindered (unsubstituted α-carbon) isocyanides were employed, the aforementioned hydroxytriazafluorendiones were formed in a clean reaction and isolated as the sole products (entries 13 – 15). Apparently BOC acts as intramolecular acylation source annealing a third cycle by an attack of the secondary amide nitrogen originating from the isocyanide building block initially.

To enlighten this reaction, **8c** (prepared by palladium catalysis) was converted into its *N*-BOC protected analogue **7c** (scheme 36). To simulate the conditions used for the copper catalyzed reaction workup *N,N*-dimethylformamide was added to the crude product of **7c** and the mixture evaporated at 60 °C to dryness. HPLC analysis of the residue showed only **7c** and no signs of any degradation or conversion to **9c**. The cyclization did not happen until the addition of cesium carbonate to a DMF solution of **7c** at room temperature and stirring overnight. This shows that this second cyclization is not induced by copper but by the basic conditions in combination with a polar solvent (otherwise it would have been occurred under the basic conditions of Pd-catalyzed cyclization in toluene; scheme 28).



Scheme 36: Cyclization of BOC-indazolone 7c in the absence of copper.

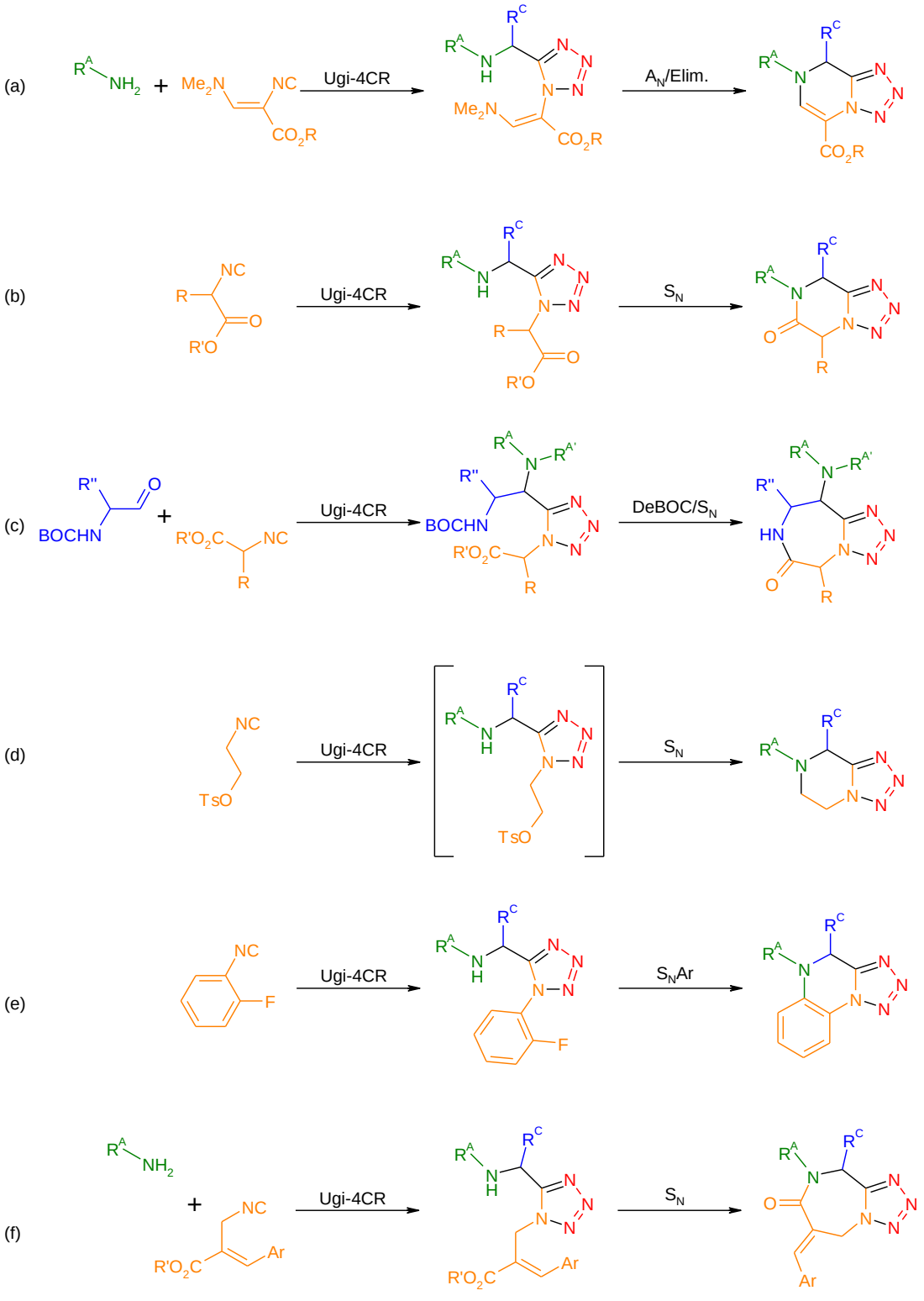
In contrast, **5l'** when subjected to the above conditions that affect the cyclization of **7c** to **9c,** no reaction takes place even after 6 days. Obviously the indazolone plays a vital role in 1.) stabilizing an intermediate transition state and thereby activating the BOC group, and/or 2.) swaying the molecule conformation towards a state favoring the cyclization (Scheme 37).



Scheme 37: No cyclization occurs without prior indazolone formation.

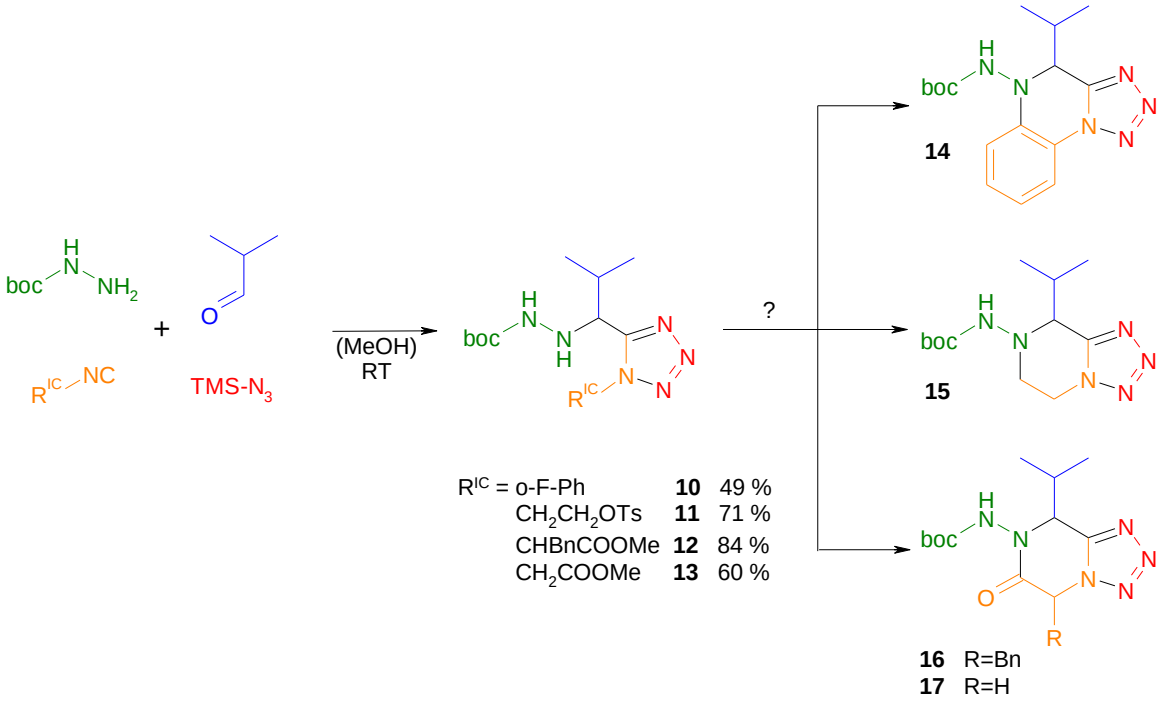
6.3.3. Cyclizations of hydrazine derived tetrazol-Ugi-4CR products

The Ugi reaction with hydrazoic acid generating disubstituted tetrazoles was first published by Ugi in 1961.[208] Since then several postmodifications have been published (Scheme 38).[74,79,209–211] Of those the three most straightforward cyclizations, depicted in Scheme 38b, d and e, should be examined with hydrazine as the amine component.



Scheme 38: Tetrazol-Ugi reactions and subsequent cyclization.

The Ugi reaction with BOC-protected hydrazine, isobutyraldehyde, azidotrimethylsilan and (i) 2-fluorophenylisocyanide, (ii) 2-isocyanoethyltosylate and (iii) 2-isocyano-3-phenyl-propionic acid methyl ester at rt in methanol produced the desired MCR products with acceptable to good yields (Scheme 39; **10**: 49 %, **11**: 71 %, **12**: 84 %).



Scheme 39: Potential scaffolds from hydrazine derived Ugi-4CR products.

The usual conditions for the nucleophilic aromatic substitution (potassium or cesium carbonate, DMF, 150 °C, microwave, 60 min)[79] lead to no reaction. Even under more forcing conditions (10 equiv. NEt_3, microwave, 200 °C, 60 min) the Ugi product proved to be astonishingly stable – not even thermal cleavage of the BOC group was observed. Therefore the order of the two reaction steps cyclization/deprotection was reversed hoping that the more nucleophilic and sterically less demanding free hydrazine would enter into the cyclization. Treatment of **10** with 20 % TFA in DCM led to degradation of the starting material. This happened also in the presence of 1 equiv. of anisol as a cation scavenger and with a reduced acid concentration (10 % TFA in DCM). Running the reaction at 0 °C prevented not only the deterioration of **10** but any reaction. Slow warming of the reaction in the melting/molten ice bath resulted again in decomposition.

Using the alkylating isocyanide 2-isocyanoethyltosylate no *in situ* cylization occurred occurred, unlike reactions with normal amines.[212] Experiments to affect the cyclization by increasing the temperature lead to the gradual decay of the monocyclic tetrazole **11** (most likely via elimination of the tosylate and further reactions of the unsaturated products) and gave only traces of the desired bicyclic tetrazolo-*N*-amino-piperazine. Addition of bases (potassium carbonate, triethylamine, sodium methoxide, potassium *tert*-butylate) was not productive – either no reaction took place, or intermediate **11** degraded. Traces of product were found using triethylamine at 50 °C but this may be solely related to the increased temperature. Surprisingly the MCR product could be isolated by column chromatography in good yield (71 %). Further experiments for the cyclization of the purified compound proved to be fruitless. As before, the reaction either did not proceed at all (potassium carbonate, triethylamine, sodium methoxide; rt to 40 °C) or resulted in degradation of the starting material (potassium *tert*-butylate).

Thus the reversed strategy (deprotection first, then cyclization) was tested, too, but to no avail: treating **11** with TFA in DCM (10 % and 20 %; with and without anisol) resulted in degradation.

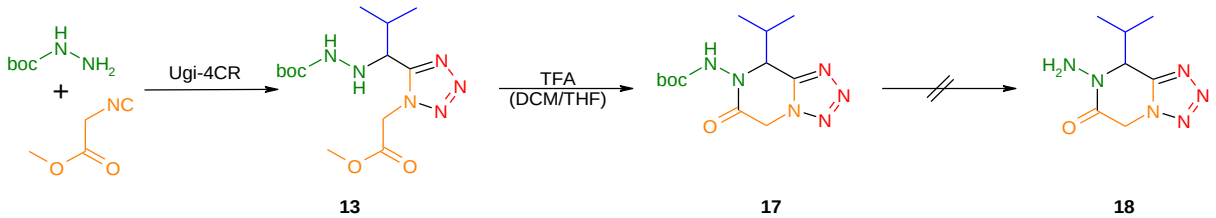
Cyclization of **12** to the carboxylic hydrazide by the usual means (refluxing in methanol)[74] failed to give any positive results. Addition of potassium carbonate or triethylamine at room temperature affected (slow) saponification. Heating to 90 °C (K_2CO_3) and 50 °C (NEt_3), respectively, lead to slow degradation of the starting material. Usage of potassium *tert*-butylate at 0 °C to room temperature yielded only traces of desired product.

As with the other two tetrazoles the order of cyclization and BOC-cleavage was to be reversed. With 10 % TFA in DCM no reaction took place. Increasing the acid concentration to 20 % did lead to conversion but no product formation regardless of the presence or absence of anisol.

One possible reason for the failure of all these cyclization experiments may be the steric demand of system: BOC group, isopropyl residue and α-substitution at the isocyanoester in the last case. Hence Ugi product **13** was synthesized from methyl isocyanoacetate in good yield (60 %; Scheme 40). Interestingly traces of the cyclized product **17** were found during the purification by column chromatography on silica. This indicates that under suitable acidic conditions a cyclization could be effected. Encouraged by this observation a solution of a few milligrams of **13** in THF was treated with what was thought to be 20 % TFA in DCM (THF/DCM/TFA = 5/4/1). Delightfully **18** precipitated after 1.5 d as a white powder. But when this experiment was repeated with a bigger amount of **13** no product at all was obtained: THF/DCM/TFA = 5/4/1 (10 % TFA) to 5/4/3.15 (24 %) affected no reaction at all, higher concentrations (5/4/6.15, 41 %) consumed the starting material without producing any of **17** or **18**.

As it turned out the TFA solution prepared in narrow-necked volumetric flask had been shaken only three times which was verly likely insufficient to create a homogenous solution.[h] For this reason a series of different mixtures with an overall acid concentration ranging from 10 % to 50 % in steps of 10 % was examined (THF/DCM/TFA = 5/4/1 to 5/0/5).[i] The reactions with 30 – 50 % acid showed little to no product formation. 20 % gave – along with several unknown side products – some of**,** and 10 % mainly **17**, but the latter reaction was very slow and not complete until after 46 days (*sic*!). Treatment of **17** with 20 % TFA in DCM in the presence of 10 vol% of thiophenol as cation scavenger[213] lead to the formation of several unidentified products without any trace of **18**.

Given the difficulties encountered during these syntheses and the long reaction time for the only successful reaction no further experiments were conducted.



13 **17** **18**

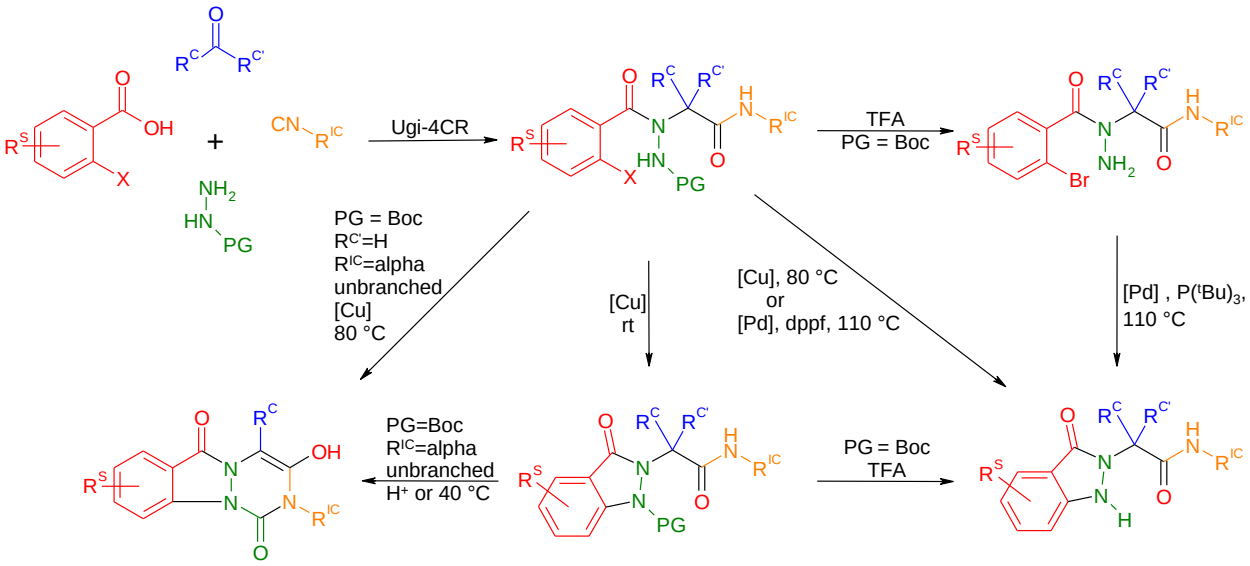
Scheme 40: Synthesis of 7-(BOC-amino)-8-isopropyl-tetrazolo[1,5-a]piperidin-6-one.

[h] From the author's own experience with AAS.

[i] Besides those an array of other conditions was tested in parallel but these conditions provided none of the two products: DCM/TFA/anisole = 6/3/1, DCM/TFA/anisole = 0/3/7, DCM/THF/TFA/anisole = 1/1/1/1, MeOH/TFA/anisole = 5/3/2, DCM/TFA/thiophenol = 6/3/1, TFA/thiophenol = 5/2, 0.5 M HCl in MeOH, 1M HCl in ethyl acetate, 2M HCl in Et_2O, 5-6M HCl in ^{i}PrOH, conc. HCl.

6.3.4. Conclusion

An improved synthesis of highly substituted indazolones has been developed. It requires less synthetic steps, offers superior yields and adds a fourth point of diversity. The cyclization can be effected either by palladium and copper catalysis and can be applied to both BOC protected, alkyl substituted and free hydrazides. The copper protocol is operationally simple and robust, requires only copper(I)iodide and no extra ligand and can be run at room temperature. Cleavage of the BOC protecting group (necessary during the Ugi-4CR) can be accomplished concomitantly by running the cyclization at elevated temperatures. Ugi products of α-unsubstituted isocyanides engage under the reaction conditions of the copper catalysis in a second cyclization to form hitherto undescribed hydroxytriazafluorendiones. In this second cyclization the BOC group acts as CO source. It was found that this unusual behaviour is bound to the presence of the indazolone (simple BOC hydrazides do not enter into this reaction) and is independent of Cu but requires a polar solvent and a base.



Scheme 41: Reaction network for Indazolone and hydroxytriazafluorendione synthesis.

Three known cyclizations strategies for tetrazol-Ugi-4CR products (S_NAr, intramolecular alkylation, intramolecular ester aminolysis) were tried to be transferred to their hydrazine analogues. While the Ugi reactions were unproblematic, both cyclization and deprotection of the Ugi products proved to be difficult and led only in one instance to the desired product.

6.3.5. Contributions

C.K.[j] came up with the initial idea, L.A.W., G.R. and M.U edited the paper prior to submission. B.S. synthesized compound **5m'**, **7h**, **8h**, **9m',** C.K. **5b**, **6b/c**; L.C. **5d**, **6a**, **8b/c**; M.A. **18**, M.W. **11**, **12**; T.A. **5g**, **6e/f**, **7g**. K.W. recorded same of the NMR spectra.

[j] Please refer to chapter 1 for full names.

6.3.6. Materials and methods

General reaction procedure 1 **(GRP1, Ugi reaction)**
1 equiv. of amine and 1 equiv. of the carbonyl component (aldehyde or ketone) are dissolved in methanol and stirred for 1 h (aldehydes) or overnight (ketones). Then 1 equiv. of carboxylic acid and 1 equiv. of isocyanide are added. The resulting mixture is stirred for 1 d (aldehydes) or 3-7 d (ketones). After evaporation of the solvent the crude product is purified by washing the precipitated product with an appropriate solvent or column chromatography or flash chromatography.

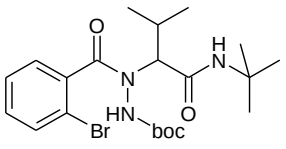
General reaction procedure 2 **(GRP2, BOC cleavage)**
The BOC-protected Ugi product is dissolved in dichloromethane, TFA is added and the mixture is stirred until analysis by TLC or HPLC shows complete conversion. The reaction mixture is then diluted with dichloromethane and poured into saturated aqueous sodium hydrogen carbonate solution. The aqueous layer is extracted with dichloromethane and the combined organic layers are dried over magnesium sulfate, filtrated and the solvent evaporated. The crude product is further purified by column chromatography.

General reaction procedure 3 **(GRP3, Cu-cyclization at RT)**
In a dry Schlenk tube filled with nitrogen 1 equiv. of Ugi product is dissolved in dry DMF together with 10 mol% of Copper(I)iodide and 1.1 equiv. of cesium carbonate and stirred at rt until reaction is completed (HPLC). Then the reaction mixture is filtered through celite, stripped of its solvent and purified by column chromatography.

General reaction procedure 4 **(GRP4, Pd-cyclization)**
In a dry pressure tube filled with nitrogen 1 equiv. Ugi product is dissolved in dry toluene together with 10 mol% of Pd2dba3, 5 mol% of PtBu3, 2 equiv. of NaOtBu and 2 equiv. of K2CO3 and stirred for 18h at 110 °C. Then the reaction mixture is filtered through celite, stripped of its solvent and purified by column chromatography.

General reaction procedure 5 **(GRP5, Cu-cyclization at 80 °C)**
In a dry Schlenk tube filled with nitrogen 1 equiv. of Ugi product is dissolved in dry DMF together with 10 mol% of Copper(I)iodide and 1.1 equiv. of cesium carbonate and stirred at 80 °C for 18 h. Then the reaction mixture is filtered through celite, stripped of its solvent and purified by column chromatography.

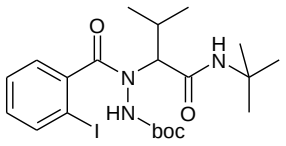
Synthesis of *N'*-(2-bromo-benzoyl)-*N'*-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-hydrazinecarboxylic acid *tert*-butyl ester (5a)



The compound was prepared according to *GRP1* with 1.5 mL of methanol, 197 mg (1.49 mmol) of *tert*-butylcarbazate, 121 mg (1.68 mmol) of isobutyraldehyde, 327 mg (1.63 mmol) 2-bromobenzoic acid and 123 mg (1.48 mmol) of *tert*-butylisocyanide. Purification by column chromatography (silica, ethyl acetate/hexane = 1/4) yielded 665 mg (94 %) of the title compound.

MS (ESI): 492.0 (8, $M+Na^+$), 413.9 (73), 296.9 (27), 182.9 (73). 113.0 (100).

Snythesis of *N'*-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-*N'*-(2-iodo-benzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (5a')



The compound was prepared according to *GRP1* with 4.0 mL of methanol, 530 mg (4.01 mmol) of *tert*-butylcarbazate, 292 mg (4.05 mmol) of isobutyraldehyde, 1011 mg (4.08 mmol) 2-iodobenzoic acid and 339 mg (4.08 mmol) of *tert*-butylisocyanide. Purification by column

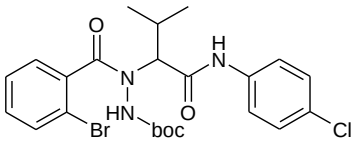
chromatography (2 × 20 cm silica, chloroform/methanol = 99.5/0.5 → 90/10, product R_f = 0.20 [chloroform/methanol 99.5/0.5]) yielded 1518 mg (73 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, main rotamer only) δ 7.88 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.47 (s, 1H), 4.75 (d, *J* = 10.3 Hz, 1H), 2.16 – 2.03 (m, 1H), 1.32 (s, 9H), 1.24 – 1.14 (m, 12H), 1.02 (d, *J* = 6.6 Hz, 3H).

HRMS: 540.1330 ($M+Na^+$, calc.), 540.1319 (found).

MS (ESI): 540.0 (11, $M+Na^+$), 461.9 (81), 388.8 (6), 344.8 (37), 316.8 (7), 230.8 (100), 112.9 (12).

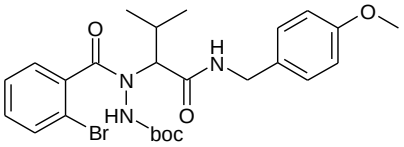
Synthesis of *N'*-(2-bromo-benzoyl)-*N'*-[1-(4-chloro-phenylcarbamoyl)-2-methyl-propyl]-hydrazine-carboxylic acid *tert*-butyl ester (5b)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 134 mg (1.01 mmol) of *tert*-butylcarbazate, 81.0 mg (1.12 mmol) of isobutyraldehyde, 206 mg (1.02 mmol) 2-bromobenzoic acid and 136 mg (0.99 mmol) of 4-chlorophenylisocyanide. Purification by column chromatography (silica, ethyl acetate/hexane = 1/2, R_f = 0.34) yielded 336 mg (64 %) of the title compound as an off-white solid.

MS (ESI): 546.0 (74, $M+Na^+$), 467.9 (21), 341.0 (25), 182.9 (100), 154.8 (19).

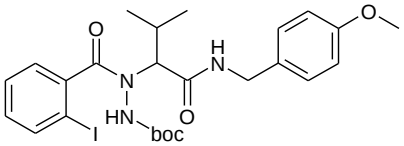
Synthesis of *N'*-(2-bromo-benzoyl)-*N'*-[1-(4-methoxy-benzylcarbamoyl)-2-methyl-propyl]-hydrazinecarboxylic acid *tert*-butyl ester (5c)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 142 mg (1.07 mmol) of *tert*-butylcarbazate, 84.2 mg (1.17 mmol) of isobutyraldehyde, 208 mg (1.03 mmol) 2-bromobenzoic acid and 149 mg (1.01 mmol) of 4-methoxybenzylisocyanide. Purification by column chromatography (silica, ethyl acetate/hexane = 1/2, product R_f = 0.38) yielded 458 mg (86 %) of the title compound as a white solid.

MS (ESI): 556.0 (35, $M+Na^+$), 478.0 (87), 340.8 (21), 296.8 (35), 182.8 (58), 120.9 (100), 112.9 (29).

Synthesis of N'-(2-Iodo-benzoyl)-*N'*-[1-(4-methoxy-benzylcarbamoyl)-2-methyl-propyl]-hydrazine-carboxylic acid *tert*-butyl ester (5c')

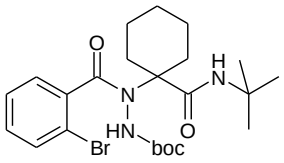


The compound was prepared according to *GRP1* with 1.0 mL of methanol, 134 mg (1.01 mmol) of *tert*-butylcarbazate, 81.8 mg (1.13 mmol) of isobutyraldehyde, 269 mg (1.08 mmol) 2-iodobenzoic acid and 147mg (1.00 mmol) of 4-methoxybenzylisocyanide. Purification by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/4, product R_f = 0.48 [ethyl acetate/hexane = 1/2]) yielded 448 mg (77 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s (br), 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.47 (s, 1H), 7.28 (m, 3H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.88 – 6.81 (m, 2H), 6.70 (s (br), 1H), 4.70 (d, *J* = 10.0 Hz, 1H), 4.35 (s, 2H), 3.79 (s, 3H), 2.29 – 2.14 (m, 1H), 1.20 (s, 9H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H).

MS (ESI): 604.0 (9, $M+Na^+$), 525.9 (40), 344.9 (17), 230.8 (30), 120.9 (100), 112.9 (16).

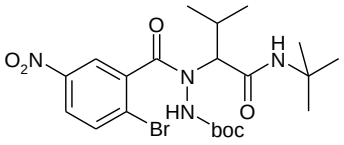
Synthesis of *N'*-(2-bromo-benzoyl)-*N'*-(1-*tert*-butylcarbamoyl-cyclohexyl)-hydrazinecarboxylic acid *tert*-butyl ester (5d)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 134 mg (1.01 mmol) of *tert*-butylcarbazate, 96.7 mg (0.99 mmol) of cyclohexanone, 206 mg (1.02 mmol) 2-bromobenzoic acid and 83.7 mg (1.01 mmol) of *tert*-butylisocyanide. Purification by column chromatography (3.0 × 45 cm silica, ethyl acetate/hexane = 1/2, product R_f = 0.36) yielded 177 mg (36 %) of the title compound.

MS (ESI): 496.0 (14, M+Na^+), 439.9 (40), 366.8 (24), 182.9 (29), 139.0 (100).

Synthesis of *N'*-(2-bromo-5-nitro-benzoyl)-*N'*-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-hydrazine-carboxylic acid *tert*-butyl ester (5e)

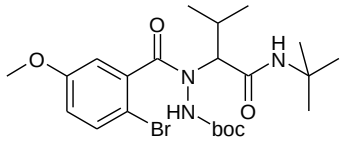


The compound was prepared according to *GRP1* with 2.0 mL of methanol, 266 mg (2.01 mmol) of *tert*-butylcarbazate, 146 mg (2.02 mmol) of isobutyraldehyde, 496 mg (2.02 mmol) 2-bromo-5-nitrobenzoic acid and 172 mg (2.07 mmol) of *tert*-butylisocyanide. Purification by washing the precipitate three times with diethyl ether yielded 792 mg (70 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, main rotamer only) δ 8.35 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.94 (s, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 6.02 (s, 1H), 4.60 (d, *J* = 10.2 Hz, 1H), 2.24 – 2.00 (m, 1H), 1.36 (s, 9H), 1.18 (d, *J* = 10.3 Hz, 12H), 1.03 (d, *J* = 6.4 Hz, 3H).

MS (ESI): 537.9 (3, M+Na^+), 458.9 (28), 341.8 (6), 112.9 (100).

Synthesis of *N'*-(2-bromo-5-methoxy-benzoyl)-*N'*-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-hydra-zinecarboxylic acid *tert*-butyl ester (5f)

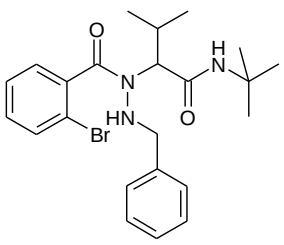


The compound was prepared according to *GRP1* with 1.0 mL of methanol, 135 mg (1.02 mmol) of *tert*-butylcarbazate, 76.9 mg (1.07 mmol) of isobutyraldehyde, 236 mg (1.02 mmol) 2-bromo-5-methoxybenzoic acid and 90.7 mg (1.09 mmol) of *tert*-butylisocyanide. Purification by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/4, product R_f = 0.66 [ethyl actetate/hexane = 1/2]) yielded 473 mg (95 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.34 (d, *J* = 8.9 Hz, 1H), 7.01 (s, 1H), 6.76 (dd, *J* = 8.8, 2.7 Hz, 1H), 5.94 (s, 1H), 4.52 (d, *J* = 10.3 Hz, 1H), 3.77 (s, 3H), 2.24 – 2.05 (m, 1H), 1.36 (s, 9H), 1.22 (s, 9H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H).

MS (ESI): 522.0 (12, M+Na^+), 444.0 (100), 370.9 (13), 326.9 (40), 298.9 (15), 214.8 (98), 112.9 (52).

Synthesis of 2-[*N'*-benzyl-*N*-(2-bromo-benzoyl)-hydrazino]-*N*-*tert*-butyl-3-methyl-butyramide (5g)



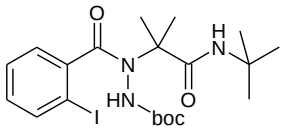
196 mg (1.01 mmol) of benzylhydrazine dihydrochloride were stirred at room temperature in 1.0 mL of methanol with 79.7 mg (1.99 mmol) sodium hydroxide for 15 min. Then 75.5 mg (1.05 mmol) of isobutyraldehyde were added and the mixture was stirred for 45 min. Then 200 mg (0.99 mmol) of 2-bromobenzoic acid and 79.8 mg (0.96 mmol) of *tert*-butylisocyanide were added. The resulting mixture was stirred overnight, washed with 10 mL of water and extracted with 10 mL of dichloromethane. After evaporation the crude product was purified by

column chromatography (silica, ethyl acetate/hexane = 1/2 → 2/1, product R_f = 0.78 [ethyl acetate/hexane = 1/2]) yielding 50.0 mg (11 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (t, *J* = 7.1 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.45 – 7.08 (m, 7H), 6.71 (d, *J* = 6.9 Hz, 1H), 4.46 – 3.81 (m, 3H), 2.72 – 2.57 (m, 1H), 1.39 (s, 9H), 1.32 (d, *J* = 8.5 Hz, 3H), 1.11 (d, *J* = 5.7 Hz, 3H).

MS (ESI): 460.0 (63, M+H$^+$), 386.9 (28), 358.9 (12), 182.8 (61), 177.1 (47), 160.0 (73), 90.9 (100).

Synthesis of *N'*-(1-*tert*-butylcarbamoyl-1-methyl-ethyl)-*N'*-(2-iodo-benzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (5h')

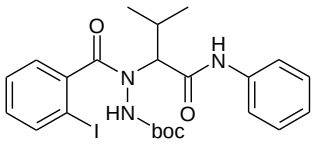


The compound was prepared according to *GRP1* with 1.0 mL of methanol, 142 mg (1.07 mmol) of *tert*-butylcarbazate, 66.0 mg (1.14 mmol) of acetone, 262 mg (1.06 mmol) 2-iodobenzoic acid and 86.7 mg (1.04 mmol) of *tert*-butylisocyanide. Purification by column chromatography (1.5 × 25 cm silica chloroform/methanol 99.5/0.5, product R_f = 0.23 [chloroform/methanol = 99/1]) yielded 369 mg (70 %) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.19 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.06 (td, *J* = 7.8, 1.5 Hz, 1H), 6.80 (s, 1H), 1.66 (s, 3H), 1.41 (s, 9H), 1.39 (s, 3H), 1.25 (s, 9H).

MS (ESI): 526.0 (7, M+Na$^+$), 504.0 (10, M+H$^+$), 447.9 (81), 374.8 (14), 230.8 (43), 116.9 (9), 98.9 (100).

Synthesis of *N'*-(2-iodo-benzoyl)-*N'*-(2-methyl-1-phenylcarbamoyl-propyl)-hydrazinecarboxylic acid *tert*-butyl ester (5i')

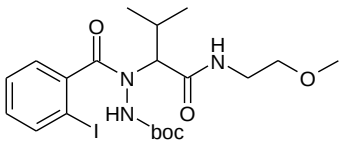


The compound was prepared according to *GRP1* with 1.0 mL of methanol, 146 mg (1.10 mmol) of *tert*-butylcarbazate, 75.7 mg (1.04 mmol) of isobutyraldehyde, 273 mg (1.10 mmol) 2-iodobenzoic acid and 114 mg (1.11 mmol) of phenylisocyanide. Purification by flash chromatography yielded 484 mg (90 %) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, several rotamers) δ 7.90 – 7.00 (m, 11H), 4.80 (d, *J* = 10.0 Hz, 1H), 2.53 – 2.30 (m, 1H), 1.29 – 1.20 (m, 10H), 1.16 – 1.07 (m, 5H).

MS (ESI): 559.9 (84, M+Na$^+$), 481.8 (63), 405.8 (34), 388.8 (100), 344.8 (29), 248.8 (9), 230.8 (89), 154.0 (8), 113.0 (63).

Synthesis of *N'*-(2-iodo-benzoyl)-*N'*-[1-(2-methoxy-ethylcarbamoyl)-2-methyl-propyl]-hydrazine-carboxylic acid *tert*-butyl ester (5k')

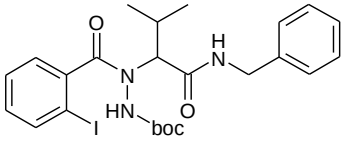


The compound was prepared according to *GRP1* with 1.0 mL of methanol, 142 mg (1.07 mmol) of *tert*-butylcarbazate, 72.2 mg (1.00 mmol) of isobutyraldehyde, 267 mg (1.08 mmol) 2-iodobenzoic acid and 97.4 mg (1.14 mmol) of 2-methoxyethylisocyanide. Purification by flash chromatography yielded 426 mg (82 %) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, main rotamer only) δ 7.82 – 7.69 (m, 1H), 7.51 – 7.28 (m, 3H), 7.13 – 6.96 (m, 1H), 6.47 (s, 1H), 4.66 (d, *J* = 10.1 Hz, 1H), 3.48 (s, 4H), 3.35 (s, 3H), 2.29 – 2.15 (s (br), 1H), 1.21 (s, 12H), 1.03 (d, *J* = 6.5 Hz, 3H).

MS (ESI): 541.9 (16, M+Na$^+$), 463.8 (100), 419.9 (6).

Synthesis of *N'*-(1-benzylcarbamoyl-2-methyl-propyl)-*N'*-(2-iodo-benzoyl)-hydrazinecarboxylic acid *tert*-butyl ester (5l')

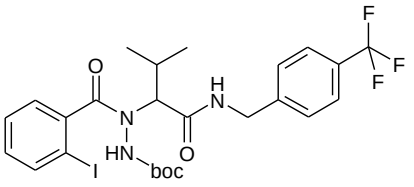


The compound was prepared according to *GRP1* with 1.0 mL of methanol, 144 mg (1.09 mmol) of *tert*-butylcarbazate, 76.3 mg (1.06 mmol) of isobutyraldehyde, 273 mg (1.10 mmol) 2-iodobenzoic acid and 132 mg (1.13 mmol) of benzylisocyanide. The newly formed precipitate is washed with 3× 2 ml hexane to yield 351 mg (91 %) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.7 Hz, 1H), 7.50 – 7.29 (m, 7H), 7.12 – 6.94 (m, 2H), 6.62 (s, 1H), 4.69 (d, *J* = 10.1 Hz, 1H), 4.51 – 4.35 (m, 2H), 2.23 (s, 1H), 1.20 (s, 12H), 1.02 (d, *J* = 6.5 Hz, 3H).

MS (ESI): 573.9 (17, M+Na$^+$), 551.9 (1, M+H$^+$), 495.8 (100), 419.9 (12), 344.8 (7).

Synthesis of *N'*-(2-iodo-benzoyl)-*N'*-[2-methyl-1-(4-trifluoromethyl-benzylcarbamoyl)-propyl]-hydrazinecarboxylic acid *tert*-butyl ester (5m')

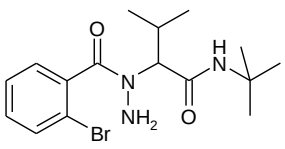


The compound was prepared according to *GRP1* with 1.0 mL of methanol, 134 mg (1.01 mmol) of *tert*-butylcarbazate, 72.2 mg (1.00 mmol) of isobutyraldehyde, 250 mg (1.01 mmol) 2-iodobenzoic acid and 185 mg (1.00 mmol) of 4-trifluoromethylbenzylisocyanide. Purification by column chromatography (silica, ethyl acetate/hexane = 1/4) yielded 297 mg (48 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.64 (m, 1H), 7.63 – 6.96 (m, 9H), 4.80 – 4.29 (m, 3H), 2.33 – 2.16 (m, 1H), 1.20 (s, 9H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H).

MS (ESI): 642.0 (34, M+Na$^+$), 620.0 (1, M+H$^+$), 564.1 (100), 520.0 (17), 388.9 (8), 249.2 (7).

Synthesis of 2-[*N*-(2-bromo-benzoyl)-hydrazino]-*N*-*tert*-butyl-3-methyl-butyramide (6a)

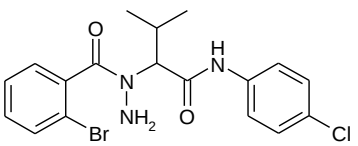


The compound was prepared according to *GRP2* with 654 mg (1.39 mmol) of **5a** in 0.8 mL of dichloromethane and 0.6 mL of TFA. Purification by column chromatography (silica, ethyl acetate/hexane = 1/4 → 1/1, product R_f = 0.16 [ethyl acetate/hexane = 1/3]) yielded 263 mg (51 %) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.25 – 7.15 (m, 2H), 6.05 (s (br), 1H), 4.54 (d, *J* = 11.1 Hz, 1H), 4.09 (s (br), 2H), 2.44 – 2.33 (m, 1H), 1.37 (s, 9H), 1.05 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H).

MS (ESI): 263.0 (23, M+Na$^+$), 370.0 (29, M+H$^+$), 296.9 (40), 182.9 (100), 154.9 (9).

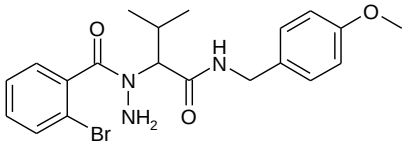
Synthesis of 2-[*N*-(2-bromo-benzoyl)-hydrazino]-*N*-(4-chloro-phenyl)-3-methyl-butyramide (6b)



The compound was prepared according to *GRP2* with 336 mg (0.64 mmol) of **5b** in 10 % of TFA in dichloromethane and 70.2 mg (0.65 mmol) of anisole. After washing the crude product was purified by column chromatography (silica, ethyl acetate/hexane = 1/2, product R_f = 0.42) yielded 167 mg (61 %) of the title compound as a yellowish solid.

MS (ESI): 445.7 (19, M+Na$^+$), 268.9 (12), 182.8 (100), 154.7 (20).

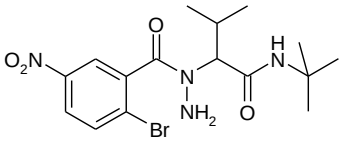
Synthesis of 2-[*N*-(2-bromo-benzoyl)-hydrazino]-*N*-(4-methoxy-benzyl)-3-methyl-butyramide (6c)



The compound was prepared according to *GRP2* with 358 mg (0.67 mmol) of **5c** in 10 % of TFA in dichloromethane. After washing the crude product was purified by column chromatography (silica, ethyl acetate/hexane = 1/1, product R_f = 0.22) yielded 98.3 mg (34 %) of the title compound as a white solid.

MS (ESI): 455.9 (76, M+Na$^+$), 434.3 (42, M+H$^+$), 296.7 (21), 268.8 (44), 182.6 (52), 121.0 (100).

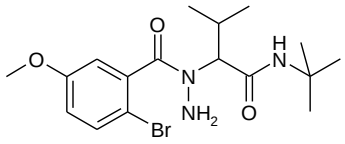
Synthesis of 2-[*N*-(2-bromo-5-nitro-benzoyl)-hydrazino]-*N*-*tert*-butyl-3-methyl-butyramide (6e)



The compound was prepared according to *GRP2* with 425 mg (0.82 mmol) of **5e** in 15 % of TFA in dichloromethane. After washing the crude product was purified by column chromatography (silica, ethyl acetate/hexane = 1/2, product R_f = 0.49) yielded 283 mg (83 %) of the title compound as a white solid.

MS (ESI): 414.9 (92, M+H$^+$), 341.9 (72), 313.8 (43), 244.8 (28), 227.8 (100), 86.9 (35).

Synthesis of 2-[*N*-(2-bromo-5-methoxy-benzoyl)-hydrazino]-*N*-*tert*-butyl-3-methyl-butyramide (6f)

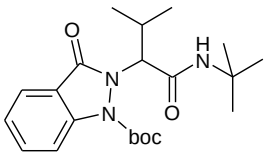


The compound was prepared according to *GRP2* with 390 mg (0.78 mmol) of **5f** in 20 % of TFA in dichloromethane. After washing the crude product was purified by column chromatography (silica, ethyl acetate/hexane = 1/2 → 2/1, product R_f = 0.49) yielded 200 mg (69 %) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7 Hz, 1H), 6.83 – 6.71 (m, 2H), 5.93 (s (br), 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.09 (s, 2H), 3.79 (s, 3H), 2.48 – 2.30 (m, 1H), 1.37 (s, 9H), 1.05 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H).

MS (ESI): 422.0 (8, M+Na$^+$), 400.0 (42, M+H$^+$), 326.9 (48), 298.9 (27), 212.8 (100).

Synthesis of 2-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-3-oxo-2,3-dihydro-indazole-1-carboxylic acid *tert*-butyl ester (7a)



The compound was prepared according to *GRP5* with 41.9 mg (0.081 mmol) of **5a'**, 5.0 mL of dry *N,N*-dimethylformamide, 1.4 mg (0.0074 mmol) of copper(I)iodide and 28.3 mg (0.087 mmol) of cesium carbonate and stirred at 80 °C for 1 h. The crude product was purified by column chromatography (1 × 20 cm silica, ethyl acetate/hexane = 1/4, product R_f = 0.45) yielding 29.3 mg (93 %) of the title compound as a white solid.

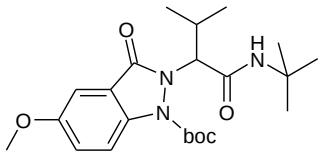
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.89 – 7.85 (m, 2H), 7.65 (ddd, *J* = 8.4, 7.3, 1.2 Hz, 1H), 7.45 – 7.32 (m, 1H), 4.00 (d, *J* = 11.3 Hz, 1H), 2.89 (dhept, *J* = 11.3, 6.6 Hz, 1H), 1.64 (s, 9H), 1.37 (s, 9H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.64 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 166.2, 150.4, 144.3, 133.8, 124.8, 123.4, 118.8, 115.6, 87.0, 76.3, 50.8, 28.6, 28.1, 27.3, 19.7, 19.5.

HRMS: 390:2393 (M+H$^+$, calc.), 390.2386 (found).

MS (ESI): 412.1 (17, M+Na$^+$), 390.1 (51, M+H$^+$), 312.0 (22), 290.0 (71), 217.0 (27), 189.0 (100), 119.8 (7).

Synthesis of 2-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-5-methoxy-3-oxo-2,3-dihydro-indazole-1-carboxylic acid *tert*-butyl ester (7f)

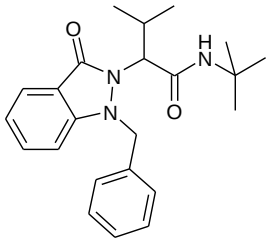


The compound was prepared according to *GRP3* with 205 mg (0.41 mmol) of **5f'**, 4.0 mL of dry *N,N*-dimethylformamide, 9.6 mg (0.050 mmol) of copper(I)iodide and 165 mg (0.51 mmol) of cesium carbonate and for 15 h. The crude product was purified by column chromatography (1 × 30 cm silica, ethyl acetate/hexane = 1/4, product R_f = 0.53 [dichloromethane/methanol = 95/5]) yielding 20.6 mg (12 %) of the title compound as a green oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s (br), 1H), 7.76 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.25 (s, 2H), 4.01 (d, *J* = 11.3 Hz, 1H), 3.86 (s, 3H), 2.97 – 2.80 (m, 1H), 1.62 (s, 9H), 1.37 (s, 9H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.65 (d, *J* = 6.5 Hz, 3H).

MS (ESI): 420.1 (72, M+H$^+$), 320.0 (100), 219.0 (60), 150.1 (8).

Synthesis of 2-(1-benzyl-3-oxo-1,3-dihydro-indazol-2-yl)-*N*-*tert*-butyl-3-methyl-butyramide (7g)



The compound was prepared according to *GRP4* with 50.3 mg (0.11 mmol) of **5g**, 3.0 mL of dry toluene, 9.8 mg (0.011 mmol) of Pd_2dba_3, 1.1 mg (0.0054 mmol) of P^tBu_3, 20.4 mg (0.21 mmol) of NaO^tBu and 29.7 mg (0.21 mmol) of K_2CO_3 and stirred at 110 °C for 18h. The crude product was purified by column chromatography (silica, ethyl acetate/hexane = 1/2, product R_f = 0.63) yielding 31.7 mg (77 %) of the title compound.

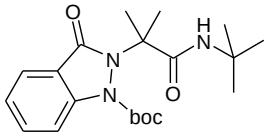
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.88 (m, 1H), 7.33 – 7.15 (m, 5H), 6.83 (td, *J* = 7.4, 0.9 Hz, 1H), 6.48 (s (br), 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 6.37 (s (br), 1H), 4.80 (d, *J* = 17.6 Hz, 1H), 4.68 (d, *J* = 17.7 Hz, 1H), 2.90 (hept, *J* = 6.7 Hz, 1H), 1.14 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 168.1, 137.6, 134.4, 128.6, 127.9, 126.8, 126.2, 119.1, 115.2, 55.1, 51.9, 49.1, 32.4, 28.2, 16.8, 16.4.

HRMS: 380.2333 (M+H$^+$, calc.),380.2331 (found).

MS (ESI): 402.1 (100, M+Na$^+$), 380.1 (89, M+H$^+$), 279.0 (32), 263.9 (17), 209.9 (35), 188.9 (10), 90.9 (40).

Synthesis of 2-(1-*tert*-butylcarbamoyl-1-methyl-ethyl)-3-oxo-2,3-dihydro-indazole-1-carboxylic acid *tert*-butyl ester (7h)

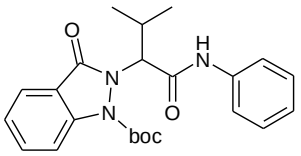


The compound was prepared according to *GRP3* with 205 mg (0.41 mmol) of **5h'**, 2.0 mL of dry *N,N*-dimethylformamide, 7.5 mg (0.039 mmol) of copper(I)iodide and 144 mg (0.44 mmol) of cesium carbonate and stirred for 3 h. The crude product was purified by column chromatography (basic aluminum oxide, dichloromethane/methanol = 97/3) yielding 115 mg (77 %) of the title compound as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.07 (s (br), 1H), 1.61 (s, 9H), 1.56 (s,6H), 1.39 (s, 9H).

MS (ESI): 397.9 (8, M+Na$^+$), 376.1 (46, M+H$^+$), 267.2 (56), 175.1 (100).

Synthesis of 2-(2-methyl-1-phenylcarbamoyl-propyl)-3-oxo-2,3-dihydro-indazole-1-carboxylic acid *tert*-butyl ester (7i)

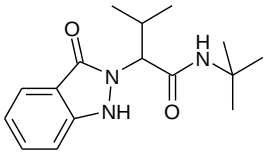


The compound was prepared according to *GRP3* with 104 mg (0.19 mmol) of **5i'**, 2.0 mL of dry *N,N*-dimethylformamide, 2.6 mg (0.014 mmol) of copper(I)iodide and 124 mg (0.38 mmol) of cesium carbonate and stirred for 3 h. The crude product was purified by column chromatography (1.5 × 28 cm silica, 100 % chloroform, product R_f = 0.20) yielding 53 mg (67 %) of the title compound with a puritiy of 88 % (254 nm).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.72 – 7.60 (m, 3H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 4.30 (d, *J* = 11.4 Hz, 1H), 3.05 (dhept, *J* = 11.8, 6.6 Hz, 2H), 1.64 (s, 9H), 1.11 (d, *J* = 6.7 Hz, 3H), 0.70 (d, *J* = 6.5 Hz, 3H).

MS (ESI): 432.0 (45, M+Na$^+$), 410.0 (37, M+H$^+$), 310.0 (100), 189.0 (29).

Synthesis of *N-tert*-butyl-3-methyl-2-(3-oxo-1,3-dihydro-indazol-2-yl)-butyramide (8a)



Method A: The compound was prepared according to *GRP4* with 158 mg (0.43 mmol) of **6a**, 3.0 mL of dry toluene, 39.9 mg (0.044 mmol) of Pd_2dba_3, 9.0 mg (0.044 mmol) of P^tBu_3, 84.3 mg (0.88 mmol) of NaO^tBu and 118 mg (0.85 mmol) of K_2CO_3 and stirred at 110 °C for 18h. The crude product was purified by column chromatography (silica, ethyl acetate/hexane = 1/1 → 9/1, product R_f = 0.26 [ethyl acetate/hexane = 1/1]) yielding 87.3 mg (71 %) of the title compound as a brown solid.

Method B: The compound was prepared according to *GRP5* with 211 mg (0.51 mmol) of **5a'**, 4.0 mL of dry *N,N*-dimethylformamide, 5.6 mg (0.029 mmol) of copper(I)iodide and 145 mg (0.45 mmol) of cesium carbonate and stirred at 80 °C for 21 h. The crude product was purified by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/1, product R_f = 0.30) yielding 70.3 mg (59 %) of the title compound.

Method C: The compound was prepared according to *GRP2* with 32.1 mg (0.082 mmol) of **7a** in 20 % of TFA in dichloromethane. After washing the crude product was purified by column chromatography (1 × 25 cm silica, ethyl acetate/hexane = 1/2 → 1/1, product R_f = 0.16 [ethyl acetate/hexane = 1/1]) yielding 13.7 mg (46 %) of the title compound.

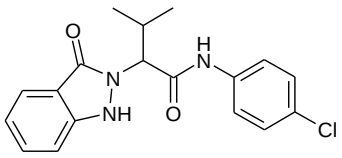
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.84 (s, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.50 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 5.15 (d, *J* = 10.1 Hz, 1H), 2.54 (dhept, *J* = 10.1, 6.7 Hz, 1H), 1.38 (s, 9H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 161.0, 146.4, 131.5, 123.6, 121.7, 117.9, 112.4, 62.1, 51.6, 31.1, 28.6, 19.6, 19.2.

HRMS: 312.1688 (M+Na$^+$, calc.), 312.1682 (found).

MS (ESI): 290.0 (100, M+H$^+$), 216.9 (14), 188.9 (32).

Synthesis of *N*-(4-chloro-phenyl)-3-methyl-2-(3-oxo-1,3-dihydro-indazol-2-yl)-butyramide (8b)



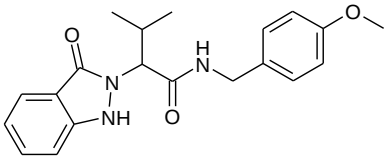
The compound was prepared according to *GRP5* with 204 mg (0.36 mmol) of **5b'**, 3.0 mL of dry *N,N*-dimethylformamide, 3.5 mg (0.018 mmol) of copper(I)iodide and 127 mg (0.39 mmol) of cesium carbonate and stirred at 80 °C for 4 h. The crude product was purified by column chromatography (1.5 × 20 cm silica, ethyl acetate/hexane = 2/1, product R_f = 0.35) yielding 12.0 mg (10 %) of the title compound.

^{1}H NMR (400 MHz, DMSO) δ 10.80 (s, 1H), 10.04 (s, 1H), 7.78 – 7.62 (m, 3H), 7.59 – 7.47 (m, 1H), 7.46 – 7.37 (m, 2H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 4.96 (d, *J* = 10.5 Hz, 1H), 2.60 – 2.39 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.69 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, DMSO) δ 169.1, 161.8, 147.3, 137.8, 132.2, 129.5, 129.5, 128.3, 123.7, 121.9, 121.6, 116.6, 113.6, 63.1, 30.4, 21.8, 19.6.

MS (ESI): 366.0 (19, M+Na^+), 344.0 (22, M+H^+) 189.0 (100), 119.9 (10).

Synthesis of *N*-(4-methoxy-benzyl)-3-methyl-2-(3-oxo-1,3-dihydro-indazol-2-yl)-butyramide (8c)



The compound was prepared according to *GRP4* with 98.3 mg (0.23 mmol) of **6c**, 2.0 mL of dry toluene, 20.7 mg (0.023 mmol) of Pd_2dba_3, 3.8 mg (0.019 mmol) of P^tBu_3, 44.0 mg (0.46 mmol) of NaO^tBu and 62.5 mg (0.45 mmol) of K_2CO_3 and stirred at 110 °C for 18h. The crude product was purified by column chromatography (silica, ethyl acetate/hexane = 1/1 → 2/1, product R_f = 0.60 [ethyl acetate/hexane = 2/1]) yielding 12.6 mg (16 %) of the title compound as a yellow solid.

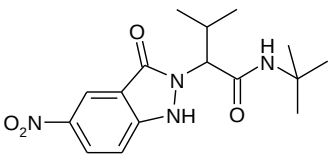
^{1}H NMR (400 MHz, CDC_3) δ 8.67 (s, 1H), 7.71 (t (br), *J* = 5.2 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.21 – 7.17 (m, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.86 – 6.73 (m, 2H), 4.99 (d, *J* = 10.4 Hz, 1H), 4.49 (dd, *J* = 14.5 , 6.0 Hz, 1H), 4.25 (dd, *J* = 14.5, 4.9 Hz, 1H), 3.77 (s, 3H), 2.57 (dhept, *J* = 10.3, 6.7 Hz, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 159.0, 132.0, 131.7, 129.5, 129.3, 128.6, 127.3, 123.7, 121.9, 114.0, 112.3, 62.1, 55.2, 43.1, 30.6, 19.4, 19.0.

HRMS: 353.1739 (M+H^+, calc.), 353.1734 (found).

MS (ESI): 354.1 (64, M+H^+), 189.1 (19), 121.0 (100).

Synthesis of *N-tert*-butyl-3-methyl-2-(5-nitro-3-oxo-1,3-dihydro-indazol-2-yl)-butyramide (8e)



The compound was prepared according to *GRP5* with 101 mg (0.39 mmol) of **5e**, 3.0 mL of dry *N,N*-dimethylformamide, 3.8 mg (0.020 mmol) of copper(I)iodide and 142 mg (0.44 mmol) of cesium carbonate and stirred at 80 °C for 3 h. The crude product was purified by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/9 → 1/1, then 100 % methanol, product R_f = 0.18 [ethyl acetate/hexane = 1/1]) yielding 130 mg (99 %) of the title compound as a black solid.

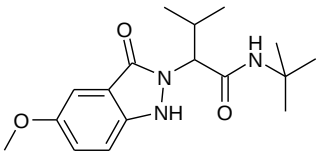
^{1}H NMR (400 MHz, CD_3OD) δ 8.70 (d, *J* = 1.9 Hz, 1H), 8.36 (dd, *J* = 9.2, 2.2 Hz, 1H), 7.44 (d, *J* = 9.2 Hz, 1H), 4.76 (d, *J* = 10.4 Hz, 1H), 2.49 (dhept, *J* = 10.4, 6.7 Hz, 1H), 1.35 (s, 9H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, CD_3OD) δ 170.0, 161.6, 147.8, 143.0, 127.6, 121.8, 115.3, 113.4, 64.5, 52.5, 31.7, 28.7, 19.5, 19.2.

HRMS: 357.1539 ($M+Na^+$, calc.), 357.1533 (found).

MS (ESI): 335.0 (100, $M+H^+$), 262.1 (9), 233.9 (31).

Synthesis of *N-tert*-butyl-2-(5-methoxy-3-oxo-1,3-dihydro-indazol-2-yl)-3-methyl-butyramide (8f)



The compound was prepared according to *GRP4* with 101 mg (0.25 mmol) of **5f**, 3.5 mL of dry toluene, 22.6 mg (0,025 mmol) of Pd_2dba_3, 3.2 mg (0.016 mmol) of P^tBu_3, 48.7 mg (0.51 mmol) of NaO^tBu and 70.7 mg (0.51 mmol) of K_2CO_3 and stirred at 110 °C for 18h. The crude product was purified by column chromatography (silica, ethyl acetate/hexane = 4/1, product R_f = 0.16 [ethyl acetate/hexane = 2/1]) yielding 40 mg (25 %) of the title compound.

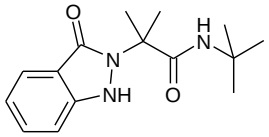
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s (br), 1H), 7.23 (t, *J* = 1.5 Hz, 1H), 7.16 – 7.13 (m, 2H), 6.56 (s (br), 1H), 4.74 (d, *J* = 10.3 Hz, 1H), 3.84 (s, 3H), 2.53 (dhept, *J* = 10.3, 6.7, Hz, 1H), 1.37 (s, 9H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 161.6, 155.6, 141.6, 122.5, 118.5, 113.8, 104.0, 62.9, 55.8, 52.0, 30.7, 28.6, 19.4, 19.0.

HRMS: 320.1974 ($M+H^+$, calc.),320.1969 (found).

MS (ESI): 342.0 (30, $M+Na^+$), 320.0 (43, $M+H^+$), 246.9 (26), 219.0 (100), 148.8 (21).

Synthesis of *N-tert*-butyl-2-(3-oxo-1,3-dihydro-indazol-2-yl)-isobutyramide (8h)



The compound was prepared according to *GRP2* with 22.4 mg (0.062 mmol) of **7h** in 20 % of TFA in dichloromethane yielding 11.2 mg (62 %) of the title compound.

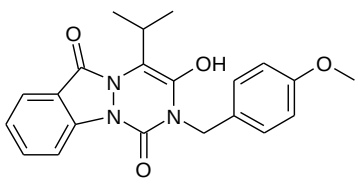
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.8 Hz, 1H), 7.61 – 7.48 (m, 1H), 7.40 (s (br), 1H), 7.24 – 7.15 (m, 2H), 6.51 (s (br), 1H), 1.78 (s, 6H), 1.35 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 164.6, 147.5, 132.3, 123.8, 122.7, 120.1, 112.6, 64.4, 51.4, 28.6, 28.5, 23.8, 23.7.

HRMS: 298.1531 ($M+Na^+$, calc.), 298.1526 (found).

MS (ESI): 276.3 (100, $M+H^+$), 175.0 (76).

Synthesis of 2-hydroxy-1-isopropyl-3-(4-methoxy-benzyl)-3H-3,4a,9a-triaza-fluorene-4,9-dione (9c)



The compound was prepared according to *GRP5* with 202 mg (0.35 mmol) of **5c'**, 3.0 mL of dry *N,N*-dimethylformamide, 3.7 mg (0.019 mmol) of copper(I)iodide and 128 mg (0.39 mmol) of cesium carbonate and stirred at 80 °C for 15 h. The crude product was purified by column chromatography (2.0 × 22 cm silica, ethyl acetate/hexane = 1/1) yielding 107 mg (82 %) of the title compound.

1H NMR ($CDCl_3$):δ 8.07 (dd, J = 7.8, 1.4 Hz, 1H), 7.80 (dd, J = 8.1, 0.6 Hz, 1H), 7.62 (ddd, J = 7.5, 1.6, 0.7 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.31 (td, J = 7.7, 1.1 Hz, 1H), 6.90 – 6.82 (m, 2H), 6.68 (s, 1H), 4.70 (s, 2H), 3.79 (s, 3H), 2.26 (hept, J = 6.9 Hz, 1H), 1.00 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.9 Hz, 3H).

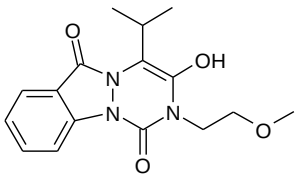
13C NMR (101 MHz, CDCl3) δ 169.5, 161.5, 159.5, 153.5, 135.0, 134.1, 130.3, 128.6, 127.1, 125.6, 121.50, 120.4, 114.1, 75.8, 55.2, 42.4, 36.5, 16.2, 15.2.

HRMS: 380.1610 ($M+H^+$, calc.), 380.1605 (found).

MS (ESI): 402.0 (10, $M+Na^+$), 380.0 (51, $M+H^+$), 120.9 (100).

Synthesis of 2-hydroxy-1-isopropyl-3-(2-methoxy-ethyl)-3H-3,4a,9a-triaza-fluorene-4,9-dione (9k)

The compound was prepared according to *GRP5* with 99.8 mg (0.19 mmol) of **5k'**, 2.0 mL of dry *N,N*-dimethylformamide, 3.3 mg (0.017 mmol) of copper(I)iodide and 134 mg (0.41 mmol) of cesium carbonate and stirred at 80 °C for 1 h. The crude product was purified by column chromatography (1.5 × 24 cm fine silica, 100 % chloroform, product R_f = 0.33 [chloroform/methanol = 98/2]) yielding 45.9 mg (75 %) of the title compound.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.83 – 7.80 (m, 1H), 7.63 (td, *J* = 7.8, 1.6 Hz, 1H), 7.33 (td, *J* = 7.7, 1.0 Hz, 1H), 6.56 (s, 1H), 3.96 – 3.74 (m, 2H), 3.69 – 3.58 (m, 2H), 3.35 (s, 1H), 2.30 (hept, *J* = 6.9 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H).

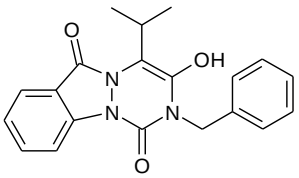
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 161.4, 153.5, 135.0, 134.2, 128.6, 125.6, 121.5, 120.4, 75.8, 68.5, 58.6, 38.7, 36.4, 16.1, 15.2.

HRMS: 340.1273 ($M+Na^+$, calc.), 340.1268 (found).

MS (ESI): 359.0 (32, $M+H^+$+MeCN), 318.0 (100, $M+H^+$), 172.0 (38).

Synthesis of 3-benzyl-2-hydroxy-1-isopropyl-3H-3,4a,9a-triaza-fluorene-4,9-dione (9l)

The compound was prepared according to *GRP5* with 194 mg (0.35 mmol) of **5l'**, 4.0 mL of dry *N,N*-dimethylformamide, 4.8 mg (0.025 mmol) of copper(I)iodide and 176 mg (0.54 mmol) of cesium carbonate and stirred at 80 °C for 4.5 h. The crude product was purified by column chromatography (silica, ethyl acetate/hexane = 1/3 → 1/2) yielding 84.0 mg (55 %) of the title compound as a white solid.



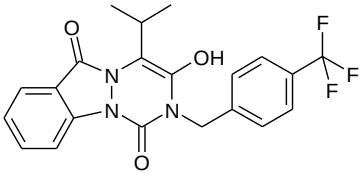
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.86 – 7.76 (m, 1H), 7.62 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.38 – 7.28 (m, 4H), 6.83 (s, 1H), 4.76 (s, 2H), 2.27 (hept, *J* = 6.9 Hz, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 161.5, 153.4, 134.9, 134.8, 134.2, 128.8, 128.8, 128.6, 128.4, 125.7, 121.5, 120.4, 75.8, 42.9, 36.5, 16.2, 15.2.

HRMS: 372.1324 ($M+Na^+$, calc.), 372.1319 (found).

MS (ESI): 350.0 (100, $M+H^+$), 333.2 (15), 91.0 (22).

Synthesis of 2-hydroxy-1-isopropyl-3-(4-trifluoromethyl-benzyl)-3H-3,4a,9a-triaza-fluorene-4,9-dione (9m)



The compound was prepared according to *GRP5* with 152 mg (0.25 mmol) of **5m'**, 2.5 mL of dry *N,N*-dimethylformamide, 21.0 mg (0.11 mmol) of copper(I)iodide and 90.5 mg (0.28 mmol) of cesium carbonate and stirred at 80 °C for 14 h. The crude product was purified by column chromatography (basic aluminum oxide with chloroform/methanol = 99.5/0.5) yielding 61.7 mg (61 %) of the title compound.

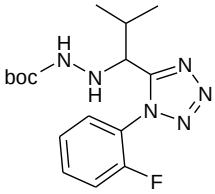
1H NMR (400 MHz, CDCl3) δ 8.09 (dd, J = 7.8, 1.4 Hz, 1H), 7.83 – 7.70 (m, 1H), 7.68 – 7.59 (m, 3H), 7.58 – 7.51 (m, 2H), 7.33 (td, J = 7.7, 1.0 Hz, 1H), 6.88 (s, 1H), 4.81 (s, 2H), 2.29 (hept, J = 6.9 Hz, 1H), 1.03 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.9 Hz, 3H).

13C NMR (101 MHz, CDCl3) δ 169.4, 161.5, 153.2, 138.6, 134.7, 134.2, 129.1, 128.7, 125.9, 125.9, 125.9, 125.9, 125.8, 121.5, 120.5, 76.0, 42.4, 36.5, 16.2, 15.2.

HRMS: 440.1198 ($M+Na^+$, calc.), 440.1192 (found).

MS (ESI): 459.1 (23, $N+H^+$+MeCN), 418.1 (100, $M+H^+$), 172.1 (36).

Synthesis of *N'*-{1-[1-(2-fluoro-phenyl)-1H-tetrazol-5-yl]-2-methyl-propyl}-hydrazinecarboxylic acid *tert*-butyl ester (10)

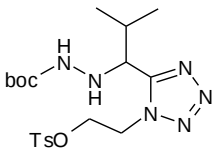


144 mg (1.09 mmol) of *tert*-butylcarbazate and 78.1 mg (1.08 mmol) of isobutyraldehyde are stirred in 2.0 mL of methanol for 1 h at room temperature. Then 126 mg (1.09 mmol) of azidotrimethylsilane and 127 mg (1.05 mmol) of 2-fluorophenylisocyanide are added and the resulting mixture is stirred at room temperature for 18h. After evaporation of the solvent the crude product is purified by column chromatography (1 × 30 cm silica, dichloromethane, product R_f = 0.46) yielding 179 mg (49 %) of the title compound.

^{1}H NMR ($CDCl_3$) δ 7.62 (d, *J* = 5.2 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.41 – 7.27 (m, 2H), 6.25 (s (br), 1H), 4.39 (s (br), 1H), 3.99 (s (br), 1H), 2.16 (m, 1H), 1.40 (s, 9H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).

MS (ESI): 373.1 (100, $M+Na^+$), 351.0 (11, $M+H^+$), 295.0 (23), 273.0 (92), 131.0 (55), 87.0 (13).

Synthesis of toluene-4-sulfonic acid 2-{5-[1-(*N'*-*tert*-butoxycarbonyl-hydrazino)-2-methyl-propyl]-tetrazol-1-yl}-ethyl ester (11)

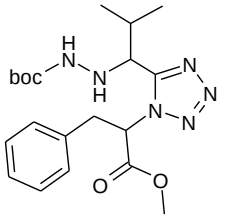


136 mg (1.03 mmol) of *tert*-butylcarbazate and 81.5 mg (1.13 mmol) of isobutyraldehyde are stirred at room temperature in 1.5 mL of methanol for 1 h. Then 124 mg (1.08 mmol) of azidotrimethylsilane and 244 mg (1.08 mmol) of 2-isocyanoethyltosylate are added and the resulting mixture is stirred for 19 h. After evaporation of the solvent the crude product is purified by column chromatography (2 × 40 cm silica, ethyl acetate/hexane = 1/2 → 1/1, product R_f = 0.57 [ethyl acetate/hexane = 1/1]) yielding 325 mg (69 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, main rotamer only) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.38 (s(br), 1H), 5.05 – 4.97 (m, 1H), 4.67 (dt, *J* = 14.8 Hz, *J* = 4.2 Hz, 1H), 4.55 – 4.50 (m, 2H), 4.48 – 4.38 (m, 1H), 4.36 (d(br), *J* = 8.0 Hz, 1H), 2.46 (s, 3H), 2.21 – 2.12 (m, 1H), 1.41 (s, 9H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H).

MS (ESI): 477.1 (26, $M+Na^+$), 455.1 (10, $M+H^+$), 399.0 (94), 268.9 (100), 205.0 (27), 131.0 (97).

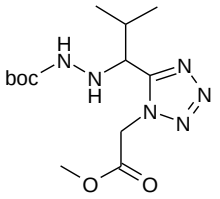
Synthesis of 2-{5-[1-(*N'*-*tert*-butoxycarbonyl-hydrazino)-2-methyl-propyl]-tetrazol-1-yl}-3-phenyl-propionic acid methyl ester (12)



142 mg (1.07 mmol) of *tert*-butylcarbazate and 76.5 mg (1.06 mmol) of isobutyraldehyde are stirred at room temperature in 1.5 mL of methanol for 1 h. Then 120 mg (1.04 mmol) of azidotrimethylsilane and 194.5 mg (1.03 mmol) of methyl 2-isocyano-3-phenylpropionate are added and the resulting mixture is stirred for 3 d. After evaporation of the solvent the crude product is purified by column chromatography (2 × 40 cm silica, chloroform/methanol = 99.5/0.5, product R_f = 0.34) yielding 351 mg (81 %) of the title compound.

MS (ESI): 441.1 (53, M+Na^+), 419.1 (20, M+H^+), 363.0 (96), 233.0 (61), 163.0 (37), 131.0 (100), 120.9 (100), 87.0 (13).

Synthesis of {5-[1-(*N'*-*tert*-butoxycarbonyl-hydrazino)-2-methyl-propyl]-tetrazol-1-yl}-acetic acid methyl ester (13)

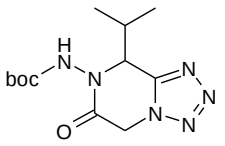


132 mg (1.00 mmol) of *tert*-butylcarbazate and 72.6 mg (1.01 mmol) of isobutyraldehyde are stirred at room temperature in 1.0 mL of methanol for 1 h. Then 115 mg (1.00 mmol) of azidotrimethylsilane and 108 mg (1.09 mmol) of methyl isocyanoacetate are added and the resulting mixture is stirred for 7 d. After evaporation of the solvent the crude product is purified by column chromatography (1.5 × 30 cm silica, ethyl acetate/hexane = 1/2, product R_f = 0.20) yielding 199 mg (60 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (s (br), 1H), 5.38 (d, *J* = 17.3 Hz, 1H), 5.32 (d, *J* = 17.5 Hz, 1H), 4.42 (s (br), 1H), 4.36 (d, *J* = 8.8 Hz, 1H), 3.84 (s, 3H), 2.13 – 1.93 (m, 1H), 1.43 (s, 9H), 1.21 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

MS (ESI): 351.0 (8, M+Na^+), 329.0 (12, M+H^+), 273.0 (100), 131.0 (17).

Synthesis of (8-isopropyl-6-oxo-5,6-dihydro-8H-tetrazolo[1,5-a]pyrazin-7-yl)-carbamic acid *tert*-butyl ester (17)



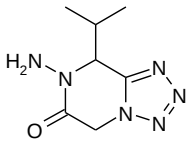
108 mg (0.33 mmol) of **16** are dissolved in 1.0 ml of dry tetrahydrofuran, 0.8 ml of dry dichloromethane and 0.2 ml of trifluoroacetic acid are added and the resulting mixture is stirred until HPLC analysis shows complete conversion of the starting material (46 d). Purification by column chromatography (1.5 × 33 cm silica, ethyl acetate/hexane = 1/3 → 9/1, product R_f = 0.20 (ethyl acetate/hexane = 1/2) yields 73.1 mg (75 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$) δ 6.71 (s (br), 1H), 5.31 (d, *J* = 18.0 Hz, 1H), 5.11 (d, *J* = 16.9 Hz, 1H), 5.10 (s (br), 1H), 2.63 (dheptett, *J* = 7.2, 3.7 Hz, 1H), 1.50 (s, 9H), 1.25 (d, *J* = 7.1 Hz, 3H), 0.70 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR ($CDCl_3$) δ 160.8, 154.7, 148.6, 83.4, 63.1, 47.9, 31.5, 28.1, 18.4, 15.7.

MS (ESI): 297.2 (100, M+H^+), 241.1 (84).

Synthesis of 7-amino-8-isopropyl-7,8-dihydro-tetrazolo[1,5-a]pyrazin-6-one (18)



N.B. The title compound could be synthesized successfully only in a single test reaction. Attempts to reproduce this reaction failed (see chapter 6.3.3).

10 mg of **13** are dissolved in 0.4 ml of dry tetrahydrofuran. To this 0.5 ml of a solution of TFA in dry dichloromethane (the exact concentration remains unclear, the possible range is 0 – 50 %) is added and stirred at room temperature for 1.5 d. The newly formed white precipitate is filtered off and yields 6 mg (99 %) of the title compound.

^{1}H NMR (DMSO-d_6) δ 5.44 (d, *J* = 17.5 Hz, 1H), 5.32 (d, *J* = 17.5 Hz, 1H), 4.95 (s (br), 1H), 4.76 (s (br), 2H), 2.67 (dhept, *J* = 7.0, 3.2 Hz, 1H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.50 (d, *J* = 6.8 Hz, 3H).

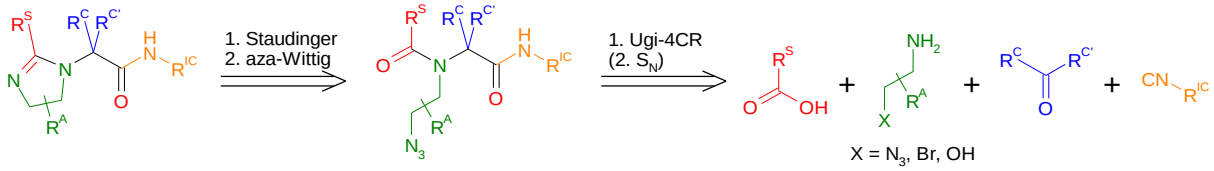
^{13}C NMR (DMSO) δ 160.1, 148.6, 61.4, 47.3, 29.8, 18.2, 15.2.

MS (ESI): 238.0 (34, M+MeCN+H$^+$), 197.0 (100, M+H$^+$), 87.0 (6).

6.4. Ugi/Staudinger/aza-Wittig

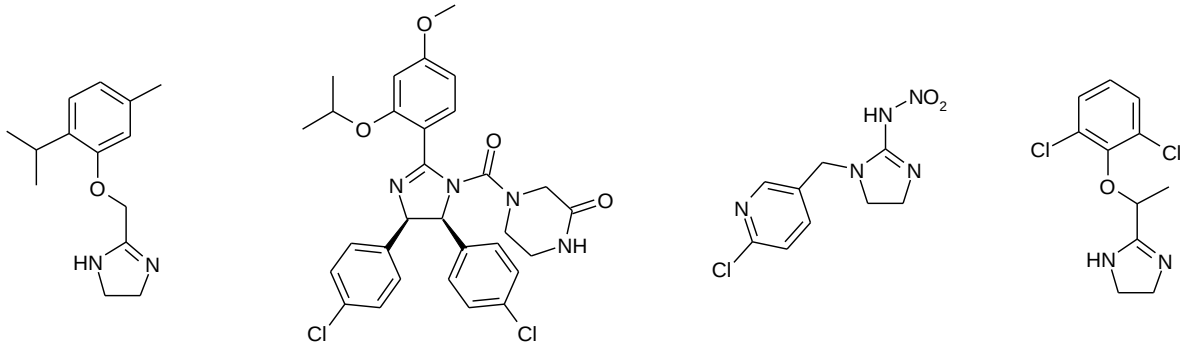
6.4.1. Introduction

As shown in 4.4.5 there is only one report for each the use of an alkyl azide (as opposed to aryl azides yielding benzene annulated products)[122] and the involvement of one of the amide functions generated during the Ugi reaction in the aza-Wittig cyclization.[109] Therefore the following synthesis of 2-(acetamid-2-yl)-imidazolines with up to five points of diversity by means of an Ugi/Staudinger/aza-Wittig sequence was envisioned (Scheme 42).



Scheme 42: Imidazoline synthesis by an Ugi/Staudinger/aza-Wittig reaction sequence.

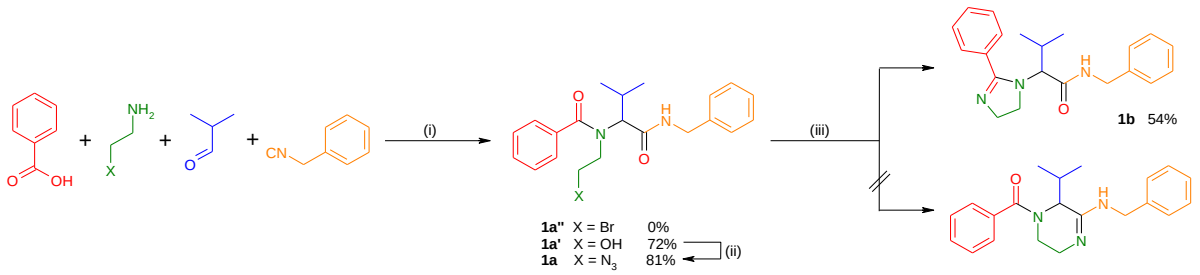
Not only would this transformation reduce the peptide character of the primary Ugi product but also enable the rapid synthesis of (dihydro-)imidazolines. This interesting scaffold has found numerous uses, e.g. in natural product chemistry,[88] pharmaceutical chemistry,[214] organic synthesis,[98] coordination chemistry and heterogenous catalysis,[215] and is an essential structural element in several bioactive agents (scheme 43).[176]



Scheme 43: Bioactive agents containing an imidazoline: tymazoline (nasal decongestant),[216] Nutlin-3 (anti-cancer, phase I completed),[217] lofexidine (anti-hypertensive, treatment of physical opioide withdrawal symptoms)[218] and imidacloprid (insecticide).[219]

6.4.2. Results and discussion

First, the Ugi reaction of a suitably substituted amine, isobutyraldehyde, benzoic acid and benzyl isocyanide in methanol (1M) at room temperature was run (scheme 44). While 2-bromoethylamine (used as its hydrobromide salt and liberated in situ with 1 eq of NEt_3) gave no product formation at all, 2-aminoethanol reacted smoothly to the desired product and was isolated after column chromatography in 72 % yield. Transformation into the azide was effected with known methods:[220] After activation with MsCl in dry THF and subsequent treatment with an excess of sodium azide at room temperature, **1a** was obtained in 81 % yield. Reacting **1a** with 1 eq. of triphenylphosphine in dry toluene led to visible gas evolution and the intermediate iminophosphane, this was then heated in a microwave reactor to 150 °C for 20 minutes.



Scheme 44: (i) (MeOH), rt, 22h, 72 %, (ii) a) MsCl, NEt3, (dry THF), rt, overnight, b) NaN3, (dry DMF), rt, 6h, 81 %, (iii) a) PPh3, (dry toluene), rt, 2h, b) microwave, 150 °C, 20 min, 54 %.

HPLC/MS analysis indicated (1.) that iminophosphane formation was complete after 1h, and (2.) that the aza-Wittig cyclization yielded only a single product without any side products. Analysis by NMR spectroscopy (gHMBC, NOESY) confirmed the imidazoline structure: Crosspeaks were found in the gHMBC spectrum between all of the -CH_2CH_2- protons and only one C(=X)N carbon, and in the NOESY spectrum between one methyl group, the isopropyl-H and two protons of the ethylene bridge (*cf.* pp. 188-190). Especially the latter rules out the aminopiperazine structure as the respective groups are placed at opposite sides of the core cycle. Furthermore these findings are consistent with the observation of ZHONG *et al*. who found that only the tertiary amide of an Ugi product reacted in an intramolecular aza-Wittig cyclization.[109]

With these promising results the reaction conditions were examined next (Table 8). First several runs at different temperatures for 10 minutes were performed: Unsurprisingly, no reaction took place at lower temperatures. At 110 °C the conversion started, at 130 °C the reaction was nearly complete, and at 150 °C no more starting material could be detected. Given the fact that 10 min. at 130 °C led to near complete conversion the reaction is probably finished within a minute at 150 °C. Nonetheless the reaction time was not reduced further for two reasons: First to keep a safety margin for substituents that do not perform as well as those in this single example, and second because no side product formation or other adverse effects was observed at this temperature.

The reaction can be run with conventional heating, too (Table 8, entry 6). Exclusion of air and moisture is not strictly necessary but advantageous as far as side product formation is concerned (entries 7, 8).

Table 8: Evaluation of reaction conditions. Reaction conditions unless noted otherwise: 1 eq PPh_3, dry toluene, nitrogen atmosphere, microwave, 150 °C, 10 minutes unless stated otherwise.

Entry	Conditions	Result*
1	50 °C	no reaction
2	80 °C	no reaction
3	110 °C	conversion < 10 %
4	130 °C	conversion > 95 %
5	150 °C	clean, complete conversion
6	reflux, 1h	clean, complete conversion
7	ambient atmosphere	slight side product formation
8	non-dry toluene	slight side product formation
9	resin bound PPh_3 (1 eq)	longer reaction time for iminophosphane formation, clean and complete conversion

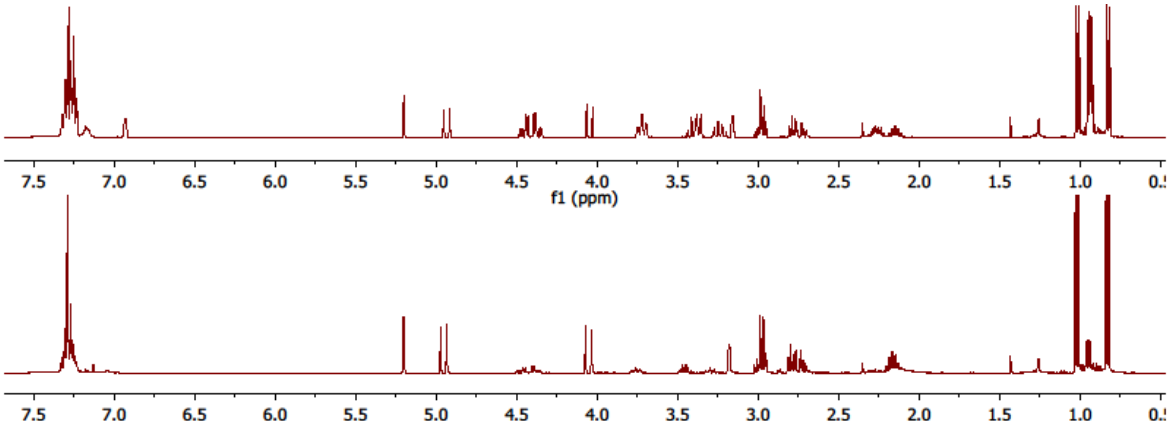
*estimated by HPLC/MS

When triphenylphosphine is replaced with its polymer bound equivalent (1.2 – 1.5 mmol/g, crosslinked with 1 % divinylbenzene, 200-400 mesh) the reaction time of the Staudinger reaction is significantly increased but in return the pure product can be obtained by simple filtration and washing with dichloromethane in near quantitative yield.

With this optimized protocol at hand a small library was synthesized to evaluate the influence of the different substituents. In order to further simplify the synthesis 2-aminoethanol was replaced by 2-azidoethylamine which can be easily prepared in multigram quantities in one step from cheap 2-bromoethylamine.[221] Substituted azidoethylamines were synthesized from the corresponding amino alcohols according to WANNAPORN *et al.*[220] The Ugi reactions with these azidoalkylamines were noticeably exothermic and surprisingly fast – in most cases the reaction was finished within less than 5 minutes, yet clean and high yielding. The yield primarily depends on the isocyanide (benzyl isocyanide gave the best results in this set). The relatively low yield for entry 16 can be attributed to the fact that this amine had to be used as its hydrochloride salt and was liberated in situ with 1 eq. of triethylamine. Since Ugi reactions perform best in acidic and not well in basic medium,[2] this is not ideal, but generation of the free base prior to the Ugi reaction leads to no product formation at all (compare to p. 67). In two of three instances where The Ugi reaction yields diastereomers they could be separated during column chromatography (entries 15, 16).

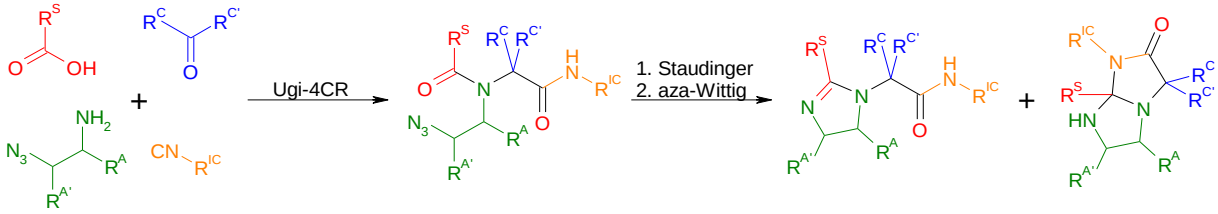
The cyclization proved to be very reliable, producing the desired imidazolines in often quantitative amount. In some cases an additional purification by column chromatography was required which is reflected in reduced yields (entries 7, 12, 13). Both electron rich and poor aromatic substituents are tolerated for R^S (entries 2-5). For the cyclization of **6a** and **7a** two scouting experiments were performed with normal triphenylphosphine to ensure that the reaction time is sufficient. While **6a** was completely converted within the given 10 minutes, **7a** required 30 minutes. Both reactions show in their HPLC chromatograms some side product formation. In the course of the subsequent purification by column chromatography **6b** hydrolyzed completely. When the experiment was repeated, it was found that (1.) the product obtained was actually a 1/1 mixture of amidine **6b** and *ortho*-amidine **6c** (*vide infra*), and (2.) that **6b** was converted for the most part upon standing in $CDCl_3$ at room temperature to **6c** within one day (Figure 1). Further attempts to isolate **6c** were unfruitful due to rapid hydrolysis of the product.

Figure 1: ^{1}H NMR spectra of the cyclization products of 6a. Top: Directly after the cyclization: 6b/6c = 3/2. Bottom: Same sample after standing 24h at room temperature: 6b/6c = 1/5.



The carbonyl residues R^C, $R^{C'}$ have no adverse influence either as long as at least one of them is a H (entries 8, 9). For geminal substitutions (entry 10) exerting a strong Thorpe-Ingold effect for the second cyclization, the formation to the *ortho*-amidine **10c** occurred in varying amounts (50 % and 17 % NMR yield in two separate runs); i.e. obviously the rate of equilibration depends on subtle influences like pH. Substitution at the azide side chain is tolerated in both α- and β-position. Unlike the β -carbon which is configurationally unstable (both diastereomers of **16a** racemized partially giving mixtures with a de of 1/3.) the α-carbon retains its stereochemical configuration during the aza-Wittig cyclization even with R^A = Ph (entry 15). One remarkable difference in the cyclization of the two diastereomers of **15a** is that *d1* reacted quantitatively without any side products or *o*-amidine formation whereas *d2* produced not only less **15b** but also a significant amount of **15c**. In general the amount of *o*-amidine formed seems to be dependent on the size of R^S (steric shielding of the amidine), $R^C/R^{C'}$ (Thorpe-Ingold effect) and the steric repulsion of $R^{A/A'}$ and $R^{C/C'}$.

Table 9: Compounds synthesized by Ugi-Staudinger-aza-Wittig-sequence.



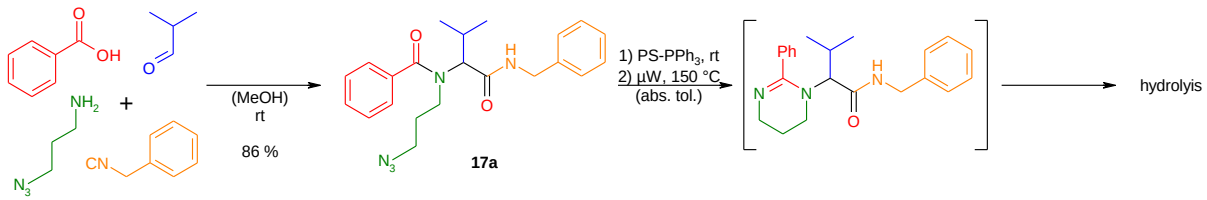
Entry	R^S	R^C, $R^{C'}$	R^{IC}	R^A, $R^{A'}$	Ugi product	Yield[a]	Imidaz-oline	Yield[a]	*o*-amidine	Yield[b]
1	Ph	^{i}Pr, H	Bn	H, H	**1a**	90 %	**1b**	99 %	**1c**	0 %
2	4-Cl-Ph	^{i}Pr, H	Bn	H, H	**2a**	85 %	**2b**	97 %	**2c**	< 2 %
3	4-MeO-Ph	^{i}Pr, H	Bn	H, H	**3a**	92 %	**3b**	99 %	**3c**	0 %
4	2-Thiophenyl	^{i}Pr, H	Bn	H, H	**4a**	84 %	**4b**	69 %	**4c**	0 %
5	4-Pyridyl	^{i}Pr, H	Bn	H, H	**5a**	90 %	**5b**	92 %	**5c**	7 %
6	H	^{i}Pr, H	Bn	H, H	**6a**	79 %	**6b**	0 %	**6c**	80 %.
7	Me	^{i}Pr, H	Bn	H, H	**7a**	87 %	**7b**[c]	60 %	**7c**[c]	4 %
8	Ph	H, H	Bn	H, H	**8a**	89 %	**8b**	99 %	**8c**	0 %
9	Ph	Ph, H	Bn	H, H	**9a**	85 %	**9b**	99 %	**9c**	0 %
10	Ph	Me, Me	Bn	H, H	**10a**	87 %	**10b**	0 % (50-85%)[b]	**10c**	15-50 %
11	Ph	^{i}Pr, H	Ph	H, H	**11a**	64 %	**11b**	99 %	**11c**	0 %
12	Ph	^{i}Pr, H	^{t}Bu	H, H	**12a**	60 %	**12b**	79 %	**12c**	7 %
13	Ph	^{i}Pr, H	$(CH_2)_2OMe$	H, H	**13a**	59 %	**13b**	72 %	**13c**	10 %
14	Ph	^{i}Pr, H	Bn	Bn, H	**14a**	93 %	**14b**	93 %	**14c**	5 %
15	Ph	^{i}Pr, H	Bn	Ph, H	**15a**	*d1*: 54 % *d2*: 36 %	**15b**	*d1*: 99 % *d2*: 36 %[d]	**15c**	*d1*: 0 % *d2*: 25 %
16	Ph	^{i}Pr, H	Bn	H, Me	**16a**	*d1*: 21 % *d2*: 22 %	**16b**	*d1*: 74 % *d2*: 97 %	**16c**	*d1*: 0 % *d2*: 0 %

[a] isolated yield [b] determined by ^{1}H-NMR analysis of the reaction mixture [c] reaction time: 30 min [d] TFA salt

The *o*-amidines were identified and characterized by NMR-spectroscopy (Figure 1 and pp. 201-205). In the ^{1}H spectrum of **6c,** the signals of the benzylic protons (2 d at 4.95 and 4.05 ppm) exhibit only a geminal coupling of ^2J=14.7 Hz and are more separated than the dd correlating to the NHCH_2Ph group of the aza-Wittig product (two dd at 4.45 and 4.37 ppm). This indicates a reaction of the

amide-NH of **6a** with concomitant conformational fixation. Additionally, there is a new singlet at 5.20 ppm which is linked to a carbon-signal at 91.0 ppm; both values are similar to what is expected for a C*H*NN'N'' moiety and described in the only publication for this type of structure.[222] Further another new, broad singlet for the CHN*H*N'N'' shows up at 2.1 ppm (overlaid with the multiplet of the isopropyl C*H*$(CH_3)_2$). This signal shows coupling in a NOESY experiment to the imidazoline -CH_2- through spin diffusion (cross peak with the same phase as the diagonal peaks implying a polarization transfer through bonds). Isolation of the *o*-amidines was attempted but failed due to hydrolysis of the product (**6c**), re-equilibration (**10b**/**c**) or insufficient yield (**15c**).

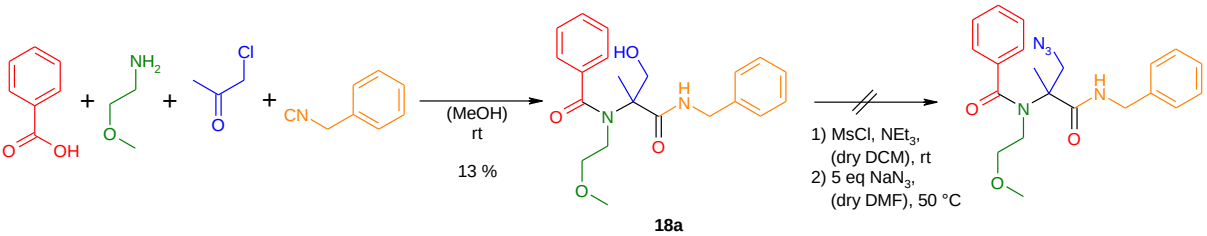
Attempts to expand this methodology to the synthesis of larger ring cyclic amidines were unsuccessful (Scheme 45). 3-Azidopropylamine was prepared in analogy to 2-azidoethylamine[221] and reacted as smoothly in the Ugi reaction. Iminophosphorane formation was unproblematic but the cyclization yielded only a mixture of (eventually) hydrolyzed or otherwise deteriorated products.



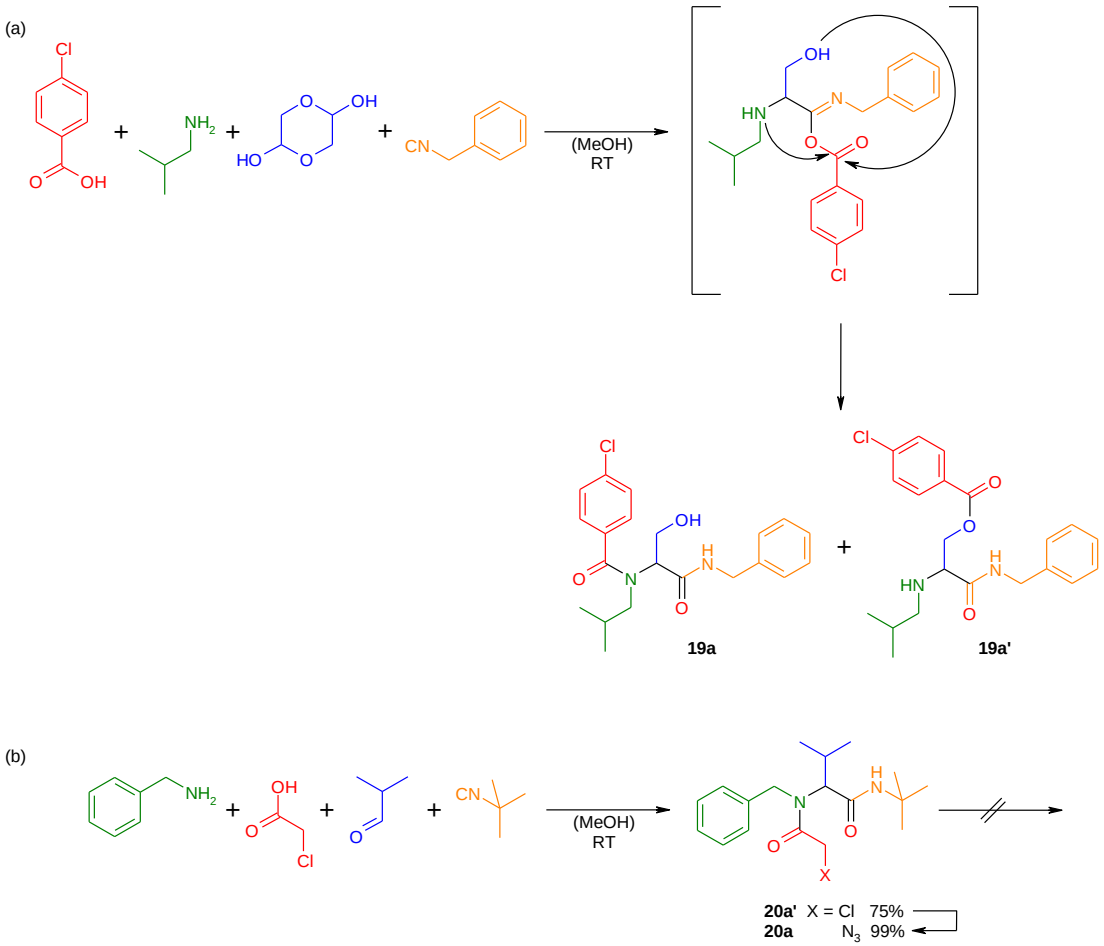
Scheme 45: Attempted tetrahydropyrimidine synthesis.

Finally the synthesis of amidines with different substitution patterns was examined by placing the azido group at other residues of the Ugi product. Chloroacetone (scheme 46) could be reacted with 2-methoxyethylamine, benzoic acid and benzyl isocyanide in an Ugi reaction but hydrolyzed *in situ* to give i.a. **18a** in a low yield. Activation with mesyl chloride and subsequent treatment with sodium azide in dry DMF at 50 °C led to complete degradation of the starting material within 5h. This might be attributed to the quaternary carbon next to the leaving group. Therefore chloroacetone was substituted with glycolaldehyde (scheme 47a). The Ugi reaction with its dimer yielded a mixture of the regular Ugi-4CR product **19a** and an isomer **19a'**, resulting from an alternative Mumm-type rearrangement with the alcohol as the internal nucleophile.[223,224] The mixture proved to be inseparable by standard column chromatography and was therefore abandoned.

In the last permutation the azide was placed at the acid derived side chain (scheme 47b). Ugi reaction with chloroacetic acid gave **20a'** which was easily converted into azide **20a**. Treatment with triphenylphosphine led to the corresponding iminophosphane which refused to cyclize. Even at 180 °C for 1h neither traces of the desired product nor any degradation products were formed. Presumably the steric hindrance with an isopropyl and a *tert*-butyl is too demanding.



Scheme 46: Tested permutations (I).



Scheme 47: Tested permutations (II).

6.4.3. Conclusion

Ugi-4CR products derived from 2-azidoethylamine were formed surprisingly quickly (within a few minutes) and in high yield. They were further cyclized to substituted 2-(acetamid-2-yl)-imidazolines with up to five points of diversity by means of a Staudinger/aza-Wittig reaction sequence utilizing the tertiary amide (formed during the Ugi-4CR) as carbonyl component. By employing polymerbound phosphane and microwave heating the cyclization was operationally very easy: In most cases only filtration and washing was required to give the pure imidazolines in often near quantitative yields. In some cases the formation of the corresponding *ortho*-amidines was observed.

6.4.4. Contributions

L.A.W.[k] edited the manuscript prior to submission. A.E. purified **10c** and **15c** by preparative chromatography. L.S. synthesized compounds **3b**, **5b**, **6b**, **7b**, **8b**, **9b**, **11b**, **14a**, **15b** and building block **III** and **V**, M.W.synthesized building block **VI**.

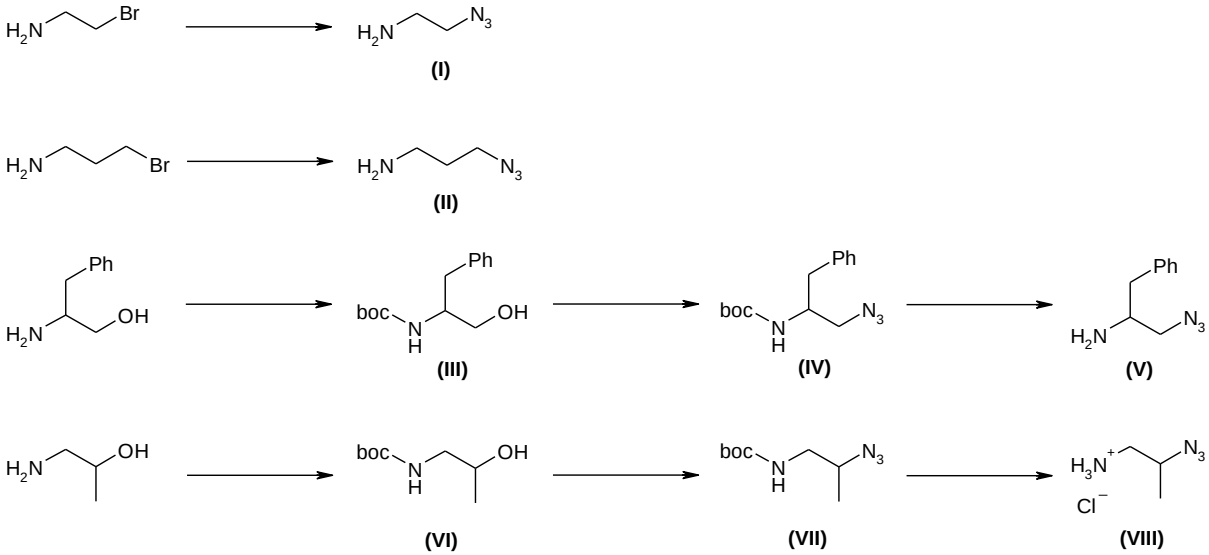
[k] Please refer to chapter 1 for full names.

6.4.5. Material and methods

General reaction procedure 1 **(GRP 1; Ugi reaction)**
Equimolar amounts of amine and aldehyde were added to the solvent (1M) in a round bottom flask and stirred at room temperature for 2-4 hours. Then 1 equivalent carboxylic acid and 1 equivalent isocyanide are added and the mixture stirred until analysis by HPLC or TLC indicates no further reaction progress. After evaporation of the solvent the residue was purified by column chromatography or flash chromatography.

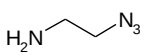
General reaction procedure 2 **(GRP2; Staudinger-aza-Wittig reaction)**
In a 15 mL microwave vial with nitrogen atmosphere 1 equivalent of an azido-Ugi product is dissolved in 5-10 mL of dry toluene.1 Equivalent of triphenylphosphine or resin bound triphenylphosphine (1.2-1.5 mmol/g, crosslinked with 1 % DVB, mesh 200-400)) is added and stirred for 2 hours (PPh_3) or overnight (PS-PPh_3). In case of the resin bound phosphane it might be necessary to add more solvent to ensure sufficient stirring and mixing of the solid and the liquid phase. The reaction mixture is then placed into the microwave reactor and heated to 150 °C for 10 minutes unless noted otherwise. The polymer is filtered off, washed with 5 ml of dichloromethane and the combined filtrates are evaporated to dryness. If necessary the substances are further purified by column chromatography on silica with ethyl acetate buffered with 5 % of triethylamine.

Syntheses of building blocks



Synthesis of 2-azido-ethylamine (I)

[NOTE OF CAUTION: Low molecular weight azides can be explosive and must be handled accordingly!]

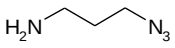


In a 100 mL round bottom flask 10.0 g (48.8 mmol) of 2-bromoethylamine hydrobromide and 9.59 g (148 mmol) of sodium azide are dissolved in 50 mL of water and stirred at 80 °C for 19 h. After the reaction mixture has cooled to rt, 16.5 g of potassium hydroxide are added in small portions. After the reaction mixture has cooled to rt it is extracted with 5× 40 mL of diethylether. The combined organic phases are dried over magnesium sulfate, filtered and most of the solvent removed *in vacuo* (the potential explosion hazard and low boiling point of the product bars the complete removal of solvent in a rotary evaporator without losing significant amounts of product) to yield a yellow liquid (3.82 g of a ethereous solution containing 3.09 g of the title compound, 74 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (t, *J* = 5.7 Hz, 2H), 2.89 (t, *J* = 5.7 Hz, 2H), 1.36 (s (br), 2H).

Synthesis of 3-azido-propylamine (II)

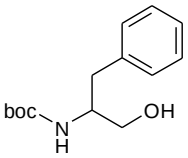
[NOTE OF CAUTION: Low molecular weight azides can be explosive and must be handled accordingly!]



In a 25 mL round bottom flask 1.02 g (4.6 mmol) of 2-bromopropylamine hydrobromide and 900 mg (13.8 mmol) of sodium azide are dissolved in 5 mL of water and stirred at 80 °C for 19 h. After the reaction mixture has cooled to room temperature, 1.8 g of potassium hydroxide are added in small portions. After the reaction mixture has cooled to rt it is extracted thrice with 20, 15 and 15 mL of diethylether. The combined organic phases are dried over magnesium sulfate, filtered and most of the solvent removed *in vacuo* (the potential explosion hazard and low boiling point of the product bars the complete removal of solvent in a rotary evaporator without losing significant amounts of the product) to yield a yellow liquid (642 mg of a ethereous solution containing 308 mg of the title compound, 67 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (t, *J* = 6.7 Hz, 2H), 2.81 (t, *J* = 6.8 Hz, 2H), 1.74 (p, *J* = 6.8 Hz, 2H), 1.25 (s (br), 2H).

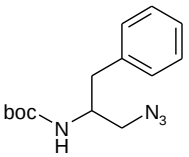
Synthesis of (1-benzyl-2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester (III)



In a 100 mL round bottom flask with nitrogen atmosphere 2.01 g (13.2 mmol) of phenylalaninol are dissolved in 40 mL dry dichloromethane and cooled in an ice bath to 0 °C. 3.31 g (15.2 mmol) of di-*tert*-butylcarbonate are added to this solution and stirred overnight in the melting ice bath for 18 hours. Then the mixture is washed with 50 mL of 10 % citric acid in water and 40 mL of brine. Evaporation of the solvent in a rotavap yields 3.35 g of the title compound as an off-white solid (100 %).

MS (ESI): 274.0 ($M+Na^+$, 100), 196.0 (90), 152.0 (60), 116.8 (34).

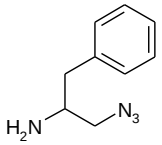
Synthesis of (2-azido-1-benzyl-ethyl)-carbamic acid *tert*-butyl ester (IV)



In a 100 mL round bottom flask with nitrogen atmosphere 3.35 g (13.2 mmol) of (1-benzyl-2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester are dissolved in 30 mL of dry dichloromethane and 3.70 mL (2.67 g, 26.4 mmol) of triethylamine are added. This mixture is then cooled to 0 °C and 1.23 mL (1.81 g, 15.8 mmol) of methanesulfonyl chloride are added which changes the color of the solution from yellow to light brown and leads to a white precipitate within a few minutes. After 15 minutes at 0 °C, the mixture is stirred for another 105 minutes at room temperature, and then evaporated to dryness. The remaining solid is taken up in 45 mL of dry *N,N*-dimethylformamide, 4.50 g (69.2 mmol) of sodium azide are added and this mixture is then stirred at 80 °C for 2.5 hours. After diluting with 50 mL of water the mixture is extracted with 3× 100 mL of diethylether, the combined organic phases are washed with 100 mL brine, dried over magnesium sulfate, filtered and evaporated to dryness in a rotavap. The crude product was further purified by column chromatography (3 × 40 cm silica, 100 % chloroform, product-R_f = 0.40) to yield 1.38 g of the title compound (38 %).

MS (ESI): 299.0 ($M+Na^+$, 100), 249.0 (81), 193.0 (52), 119.9 (70).

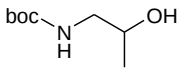
Synthesis of 2-azido-1-benzyl-ethylamine (V)



In a 100 mL round bottom flask 1.38 g of (2-azido-1-benzyl-ethyl)-carbamic acid *tert*-butyl ester are dissolved in 2 mL of dichloromethane and 10 mL of 5-6 N HCl in isopropanol and stirred at room temperature for 2 hours. The mixture is then reduced *in vacuo* to a few mL, diluted with 10 mL dichloromethane, extracted with 10 mL saturated sodium carbonate solution, and washed with 3× 10 mL dichloromethane. The combined organic phases are dried over magnesium sulfate, filtered and evaporated to dryness in a rotavap to yield 713 mg of the title compound (91 %).

MS (ESI): 218.0 ($M+H^+$+MeCN, 67), 177.0 ($M+H^+$, 26), 119.9 (100).

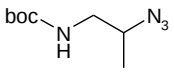
Synthesis of (2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (VI)



In a 100 mL round bottom flask with nitrogen atmosphere 2.19 g (29.2 mmol) of 2-(methylamino)-ethanol are dissolved in 40 mL dry dichloromethane and cooled in an ice bath to 0 °C. 7.00 g (32.1 mmol) of di-*tert*-butylcarbonate are added to this solution and stirred overnight in the melting ice bath for 18 hours. Then the mixture is washed with 40 mL of 10 % citric acid in water and 40 mL of brine. Evaporation of the solvent in a rotavap yields 4.64 g of the title compound as an off-white solid (91 %).

^{1}H NMR ($CDCl_3$) δ 5.02 (s (br), 1H), 3.90 (s (br), 1H), 3.36 – 3.21 (m, 1H), 3.04 – 2.97 (m, 1H), 2.63 (s, 1H), 1.45 (s, 9H), 1.18 (d, J = 6.3 Hz, 3H).

Synthesis of (2-azido-propyl)-carbamic acid *tert*-butyl ester (VII)

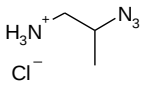


In a 100 mL round bottom flask with nitrogen atmosphere 4.14.g (23.6 mmol) of (2-hydroxy-propyl)-carbamic acid *tert*-butyl ester are dissolved in 40 mL of dry dichloromethane and 8.20 mL (5.95 g, 58.8 mmol) of triethylamine are added. This mixture is then cooled to 0 °C and 2.75 mL (4.07 g, 35.4 mmol) of methanesulfonyl chloride are added which leads to a white precipitate within a few minutes and changes the color of the solution to yellow. After 60 minutes at 0 °C the mixture is stirred for another 120 minutes at room temperature, and then evaporated to dryness. The remaining solid is taken up in 50 mL of dry *N,N*-dimethylformamide, 9.57 g (147 mmol) of sodium azide are added and this mixture is then stirred at 80 °C for 17 hours. After diluting with 50 mL of water the mixture is extracted with 3× 100 mL of diethylether, the combined organic phases are dried over magnesium sulfate, filtered and evaporated to dryness in a rotavap to yield 3.95 g (84 %) of the title compound.

^{1}H NMR ($CDCl_3$) δ 4.83 (s (br), 1H), 3.74 – 3.59 (m, 1H), 3.40 – 3.25 (m, 1H), 3.06 – 2.92 (m, 1H), 1.45 (s, 9H), 1.25 (d, J = 6.6 Hz, 3H).

Synthesis of 2-azido-propyl-ammonium chloride (VIII)

[NOTE OF CAUTION: Low molecular weight azides can be explosive and must be handled accordingly!]

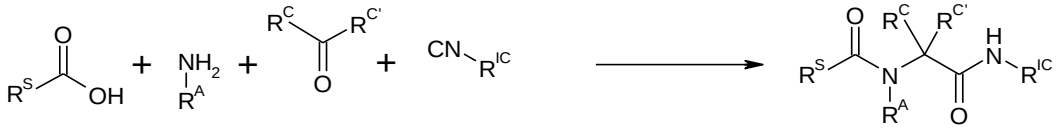


In a 50 mL round bottom flask 3.95 g of (2-azido-propyl)-carbamic acid *tert*-butyl ester are dissolved in 8 mL of 5-6 N HCl in isopropanol and stirred at room temperature for 2.5 hours. The mixture is then evaporated *in vacuo* to yield 2.56 g (95 %) of the title compound as a yellow solid.

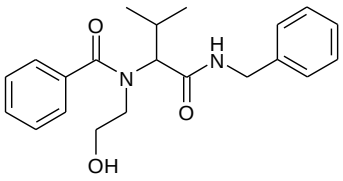
^{1}H NMR (DMSO) δ 8.37 (s (br), 3H), 3.95 (ddq, J = 9.0, 4.2, 6.6 Hz, 1H), 2.98 – 2.87 (m, 1H), 2.80 – 2.69 (m, 1H), 1.28 (d, J = 6.6 Hz, 3H).

^{13}C NMR (DMSO) δ 55.4, 43.6, 17.4.

Syntheses of Ugi products (1a', 1a – 20a)



Synthesis of *N*-(1-benzylcarbamoyl-2-methyl-propyl)-*N*-(2-hydroxy-ethyl)-benzamide (1a')

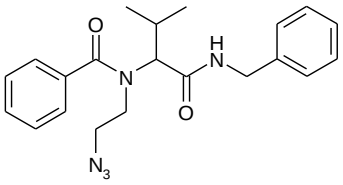


1a' was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 60.4 µL (61.1 mg, 1.00 mmol) of 2-aminoethanol, 122 mg (1.00 mmol) of benzoic acid and 116 mg (0.99 mmol) of benzyl isocyanide. Purification by flash chromatography (ethyl acetate/hexane, grad 0-50 in 100 CV, product elutes from 68 to 85 CV) yielded 254 mg (72 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B=5/1) δ 7.77 (s (br), 1H, A), 7.46 – 7.21 (m, 2×10H, AB), 6.09 (s (br), 1H, B), 4.56 – 4.39 (m, 2H+1H, AB), 4.34 – 3.47 (m (br), 5H+6H, AB), 2.68 (s (br), 1H, A), 2.33 (s (br), 1H, B), 1.98 (s, 2×1H, AB), 1.04 (d, *J* = 6.4 Hz, 3H, A), 1.01 (d, *J* = 6.4 Hz, 3H, A), 0.92 (d, *J* = 5.4 Hz, 3H, B), 0.81 (d, *J* = 5.5 Hz, 3H, B).

MS (ESI): 376.9(48, M+Na$^+$), 354.9 (7, M+H$^+$), 248.0 (100), 148.9 (72), 104.7 (5), 98.0 (5).

***Synthesis of N*-(2-azido-ethyl)-*N*-(1-benzylcarbamoyl-2-methyl-propyl)-benzamide (1a)**



Method A: To a solution of 48.7 mg (0.14 mmol) of **1a'** in 4.0 mL of dry tetrahydrofuran in a dried 10 ml round bottom flask with nitrogen atmosphere, 52.4 µL (38.0 mg, 0.38 mmol) of triethylamine and 14.5 µL (21.5 mg, 0.19 mmol) of methanesulfonyl chloride were added. The resulting mixture was stirred at room temperature for 1 hour (after a few minutes a precipitate had formed) and then evaporated to dryness. in a rotavap. The remaining solid is taken up in 4.0 mL of dry *N,N*-dimethylformamide, 188 mg (2.89 mmol) of sodium azide are added and this mixture is then stirred at room temperature for 6 hours. The solvent was removed in a rotavap *in vacuo* and the residue taken up in 5.0 mL of dichloromethane and washed with 5.0 mL of water. After separation, the aqueous phase was reextracted with 3× 5.0 mL dichloromethane, the combined organic phases were dried over magnesium sulfate, filtered and evaporated to dryness in a rotavap to yield 42.2 mg (81 %) of the title compound.

Method B: 1a was prepared according to *GRP1* with 1.0 mL of methanol, , 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 93.2 mg (1.00 mmol) of 2-azidoethylamine, 125 mg (1.02 mmol) of benzoic acid and 121 µL (117 mg, 1.00 mmol) of benzyl isocyanide. Purification by column chromatography (1.5 × 20 cm silica, ethyl acetate/hexane = 1/4, product-R_f = 0.13) yielded 343 mg (90 %) of the title compound.

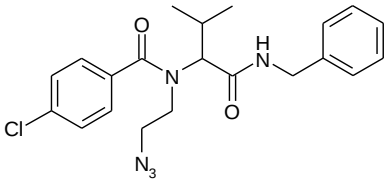
^{1}H NMR ($CDCl_3$) δ 7.68 (s (br), 1H), 7.43 – 7.42 (m, 2H), 7.35 – 7.28 (m, 8H), 4.47 (d, *J* = 5.6 Hz, 2H), 4.22 (d, *J* = 5.9 Hz, 1H), 3.57 – 3.41 (m, 2H), 3.25 – 3.04 (m, 2H), 2.62 (s (br), 1H), 1.06 (d, *J* = 5.9 Hz, 3H), 1.02 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 170.7, 138.2, 135.8, 130.1, 128.8, 128.6, 127.7, 127.4, 126.8, 49.1, 43.4, 26.2, 20.0, 19.0.

HRMS: 402.1900 (M+Na$^+$, calc.), 402.1894 (found).

MS (ESI): 402.0 (13, M+Na$^+$), 273.0 (100), 104.8 (7).

Synthesis of *N*-(2-azido-ethyl)-*N*-(1-benzylcarbamoyl-2-methyl-propyl)-4-chloro-benzamide (2a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 114 mg of a 77 % etherous solution of 2-azidoethylamine (1.02 mmol), 158 mg (1.01 mmol) of 4-chlorobenzoic acid and 123 µL (118 mg, 1.01 mmol) of benzyl isocyanide. Purification by flash chromatography (SF15-12g, ethyl acetate/hexane, grad. 0-5 in 5 CV, iso 5 for 5 CV, grad 5-30 in 50 CV, product elutes from 31-44 CV) yielded 353 mg (85 %) of the title compound.

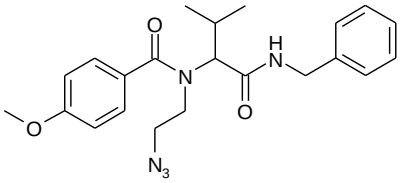
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s (br), 1H), 7.48 – 7.15 (m, 9H), 4.46 (s (br), 2H), 4.19 (d (br), *J* = 6.0 Hz, 1H), 3.48 (s (br), 3H), 3.24 (s (br), 2H), 2.60 (s (br), 1H), 1.05 (d, *J* = 5.6 Hz, 3H), 1.00 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 170.5, 138.2, 136.2, 134.1, 129.1, 128.6, 128.4, 127.7, 127.4, 49.1, 43.5, 26.2, 20.0, 19.0.

HRMS: 436.1511($M+Na^+$, calc.), 436.1506 (found).

MS (ESI): 436.0 (36, $M+Na^+$), 306.9 (100), 138.8 (42).

Snthesis of *N*-(2-azido-ethyl)-*N*-(1-benzylcarbamoyl-2-methyl-propyl)-4-methoxy-benzamide (3a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 118 mg of a 77 % etherous solution of 2-azidoethylamine (1.06 mmol), 158 mg (1.04 mmol) of 4-methoxybenzoic acid and 122 µL (117 mg, 1.00 mmol) of benzyl isocyanide. Purification by column chromatography (1.5 × 20 cm silica, ethyl acetate/hexane = 1/3 → ½, product-R_f = 0.27 [ethyl acetate/hexane = 1/2]) yielded 378 mg (92 %) of the title compound.

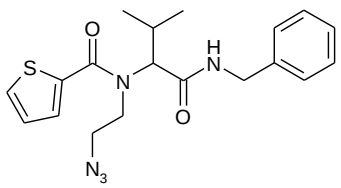
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s (br), 1H), 7.45 – 7.18 (m, 7H), 6.91 (d, *J* = 7.3 Hz, 2H), 4.45 (d, *J* = 4.8 Hz, 2H), 4.17 (s (br), 1H), 3.82 (s, 3H), 3.53 (s (br), 2H), 3.16 (s (br), 2H), 2.59 (s (br), 1H), 1.03 (s (br), 3H), 0.99 (s (br), 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 128.8, 128.6, 127.7, 127.4, 114.1, 55.4, 49.1, 43.4, 20.0, 19.1.

HRMS: 432.2006 ($M+Na^+$, calc.), 432.2002 (found).

MS (ESI): 432.0 (8, $M+Na^+$), 303.0 (100), 134.9 (26).

Synthesis of thiophene-2-carboxylic acid (2-azido-ethyl)-(1-benzylcarbamoyl-2-methyl-propyl)-amide (4a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 120 mg of a 81 % etherous solution of 2-azidoethylamine (1.13 mmol), 154 mg (1.20 mmol) of thiophene-2-carboxylic acid and 122 µL (117 mg, 1.00 mmol) of benzyl isocyanide. Purification by flash chromatography (SF15-15g, ethyl acetate/hexane, grad 0-5 in 5 CV, iso 5 for 5 CV, grad 5-50 in 50 CV, product elutes from 27-35 CV) yielded 324 mg (84 %) of the title compound.

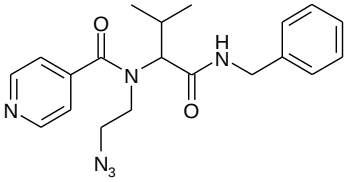
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.37 (d, *J* = 3.3 Hz, 1H), 7.35 – 7.20 (m, 5H), 7.06 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.51 – 4.34 (m, 2H), 4.22 (s (br), 1H), 3.87 (dt, *J* = 14.2, 6.9 Hz, 1H), 3.66 (dt, *J* = 14.3, 7.0 Hz, 1H), 3.30 (s (br), 1H), 2.54 (s, 1H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 166.7, 138.1, 136.7, 129.5, 129.4, 128.6, 127.7, 127.4, 127.1, 67.4, 49.0, 46.6, 43.4, 26.6, 19.9, 19.0.

HRMS: 408.1465 ($M+Na^+$, calc.), 408.1461 (found).

MS (ESI): 407.9 (30, $M+Na^+$), 278.9 (100), 110.8 (13).

Synthesis of *N*-(2-azido-ethyl)-*N*-(1-benzylcarbamoyl-2-methyl-propyl)-isonicotinamide (5a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 116 mg of a 81 % etherous solution of 2-azidoethylamine (1.09 mmol), 125 mg (1.02 mmol) of isonicotinic acid and 122 µL (117 mg, 1.00 mmol) of benzyl isocyanide. Purification by flash chromatography (SF15-15g, ethyl acetate/hexane, grad 0-5 in 5 CV, iso 5 for 5 CV, grad 5-44 in 43 CV, grad 44-100 in 27 CV, product elutes from 56-74 CV) yielded 341 mg (90 %) of the title compound.

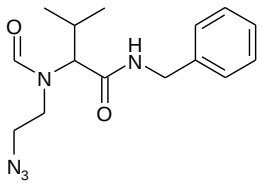
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 5.8 Hz, 2H), 7.56 (s (br), 1H), 7.39 – 7.24 (m, 5H), 7.21 (d, *J* = 5.8 Hz, 2H), 4.50 (dd, *J* = 14.9, 6.0 Hz, 1H), 4.44 (dd, *J* = 14.9, 5.9 Hz, 1H), 4.24 (d, *J* = 9.8 Hz, 1H), 3.43 (td, *J* = 6.0, 2.4 Hz, 2H), 3.32 (td, *J* = 6.1, 2.4 Hz, 2H), 2.67 – 2.52 (m, 1H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 170.1, 150.4, 143.4, 138.1, 128.7, 127.7, 127.5, 121.0, 68.6, 49.1, 43.5, 26.2, 19.9, 19.0.

HRMS: 403.1853 ($M+Na^+$, calc.), 403.1850 (found).

MS (ESI): 403.0 (5, $M+Na^+$), 381.0 (100, $M+H^+$).

Synthesis of 2-[(2-azido-ethyl)-formyl-amino]-*N*-benzyl-3-methyl-butyramide (6a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 118 mg of a 77 % etherous solution of 2-azidoethylamine (1.06 mmol), 37.7 µL (46.0 mg, 1.00 mmol) of formic acid and 122 µL (117 mg, 1.00 mmol) of benzyl isocyanide. Purification by column chromatography (1.5 × 20 cm silica, ethyl acetate/hexane = 1/3 → 1/1, product-R_f = 0.18 and 0.30 [ethyl acetate/hexane = 1/2]) yielded 239 mg (79 %) of the title compound.

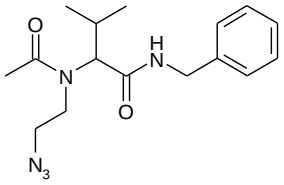
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.36 – 7.29 (m, 2H), 7.29 – 7.22 (m, 3H), 7.09 (s (br), 1H), 4.46 (dd, *J* = 14.8, 6.0 Hz, 1H), 4.36 (dd, *J* = 14.8, 5.7 Hz, 1H), 4.12 (d, *J* = 11.3 Hz, 1H), 3.53 – 3.21 (m, 4H), 2.52 – 2.37 (m, 1H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 164.6, 137.8, 128.7, 127.9, 127.7, 63.7, 50.1, 45.6, 43.5, 26.1, 19.6, 18.8.

HRMS: 326.1587 ($M+Na^+$, calc.), 326.1585 (found).

MS (ESI): 326.0 (12, $M+Na^+$), 304.0 (100, $M+H^+$).

Synthesis of 2-[acetyl-(2-azido-ethyl)-amino]-*N*-benzyl-3-methyl-butyramide (7a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 120 mg of a 77 % etherous solution of 2-azidoethylamine (1.07 mmol), 57.2 µL (60.1 mg, 1.00 mmol) of acetic acid and 122 µL (117 mg, 1.00 mmol) of benzyl isocyanide. Purification by column chromatography (1.5 × 20 cm silica, ethyl acetate/hexane = 1/3 → 1/1, product-R_f = 0.27 [ethyl acetate/hexane = 1/2]) yielded 278 mg (87 %) of the title compound.

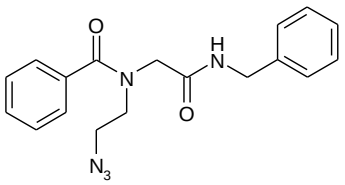
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.15 (m, 6H), 4.44 (dd, *J* = 14.9, 6.1 Hz, 1H), 4.35 (dd, *J* = 14.9, 5.7 Hz, 1H), 4.27 (s (br), 1H), 3.53 – 3.45 (m, 2H), 3.44 – 3.35 (m, 2H), 2.53 – 2.35 (m, 1H), 2.17 (s, 3H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 170.7, 138.1, 128.6, 127.7, 127.4, 49.6, 43.4, 26.2, 22.1, 19.8, 18.8.

HRMS: 340.1744 ($M+Na^+$, calc.), 340.1742 (found).

MS (ESI): 340.0 (92, $M+Na^+$), 318.0 (28, $M+H^+$), 211.0 (100), 112.9 (37).

Synthesis of *N*-(2-azido-ethyl)-*N*-(benzylcarbamoyl-methyl)-benzamide (8a)



The compound was prepared according to *GRP1* with 1.0 mL of 2,2,2-trifluoroethanol, 32.4 mg (1.08 mmol) of paraformaldehyde, 120 mg of a 77 % etherous solution of 2-azidoethylamine (1.07 mmol), 122 mg (1.02 mmol) of benzoic acid and 122 µL (117 mg, 1.00 mmol) of benzyl isocyanide. Purification by flash chromatography (SF15-12g, ethyl acetate/hexane, grad 0-5 in 5 CV, iso 5 for 5 CV, grad 5-70 in 40 CV, product elutes from 37-46 CV) yielded 301 mg (89 %) of the title compound.

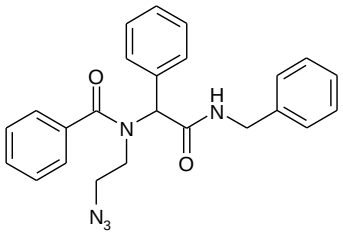
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.13 (m, 10H), 7.12 (s (br), 1H), 4.43 (d, *J* = 5.7 Hz, 2H), 4.23 – 3.89 (m, 2H), 3.75 – 3.25 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$, 2 rotamers) δ 173.1, 168.7, 137.9, 135.0, 130.1, 128.7, 128.7, 127.7, 127.6, 126.8, 54.4, 50.7, 49.9, 49.2, 47.3, 43.6.

HRMS: 360.1431 ($M+Na^+$, calc.), 360.1428 (found).

MS (ESI): 359.9 (57, $M+Na^+$), 338.0 (100, $M+H^+$), 230.9 (19), 104.9 (12).

Synthesis of *N*-(2-azido-ethyl)-*N*-(benzylcarbamoyl-phenyl-methyl)-benzamide (9a)

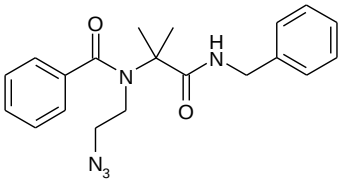


The compound was prepared according to *GRP1* with 1.0 mL of methanol, 102 µL (106 mg, 1.00 mmol) of benzaldehyde, 117 mg of a 77 % etherous solution of 2-azidoethylamine (1.05 mmol), 126 mg (1.03 mmol) of benzoic acid and 122 µL (117 mg, 1.00 mmol) of benzyl isocyanide. Purification by flash chromatography (SF15-12g, ethyl acetate/hexane, grad 0-5 in 5 CV, iso 5 for 5 CV, grad 5-25 in 40 CV, product elutes from 24-29 CV) yielded 351 mg (85 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.17 (m, 15H), 6.46 (s (br), 1H), 5.76 (s (br), 1H), 4.64 – 4.37 (m, 2H), 3.72 – 2.58 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 137.8, 135.8, 134.7, 130.0, 129.2, 129.0, 128.8, 128.7, 127.8, 127.6, 126.6, 43.8. *N.b.*: Due to the existence of rotamers giving rise to broad signals some peaks are very weak or missing.

Synthesis of *N*-(2-azido-ethyl)-*N*-(1-benzylcarbamoyl-1-methyl-ethyl)-benzamide (10a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 73.4 µL (58.1 mg, 1.00 mmol) of acetone, 113 mg of a 77 % etherous solution of 2-azidoethylamine (1.01 mmol), 159 mg (1.30 mmol) of benzoic acid and 122 µL (117 mg, 1.00 mmol) of benzyl isocyanide. Purification by column chromatography (1.5 × 25 cm silica, chloroform/methanol = 97/3, product-R_f = 0.23) yielded 319 mg (87 %) of the title compound.

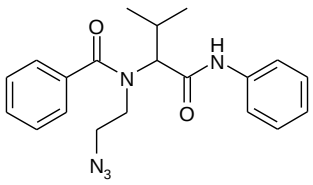
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 3H), 7.38 – 7.23 (m, 7H), 6.59 (s (br), 1H), 4.50 (d, *J* = 5.5 Hz, 2H), 3.58 (t, *J* = 6.8 Hz, 2H), 3.37 (t, *J* = 6.7 Hz, 2H), 1.67 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 173.2, 138.5, 137.1, 129.7, 128.7, 128.7, 127.9, 127.4, 126.5, 62.3, 51.1, 45.2, 44.1, 25.1.

HRMS: 388.1744 ($M+Na^+$, calc.), 388.1741 (found).

MS (ESI): 388.0 (9, $M+Na^+$), 259.0 (100), 231.0 (5), 104.8 (8).

Synthesis of *N*-(2-azido-ethyl)-*N*-(2-methyl-1-phenylcarbamoyl-propyl)-benzamide (11a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 115 mg of a 77 % etherous solution of 2-azidoethylamine (1.03 mmol), 124 mg (1.02 mmol) of benzoic acid and 114 mg (1.11 mmol) of phenyl isocyanide. Purification by flash chromatography (SF15-12g, ethyl acetate/hexane, grad 0-5 in 5 CV, iso 5 for 5 CV, grad 5-30 in 40 CV, product elutes from 25-35 CV) yielded 234 mg (64 %) of the title compound.

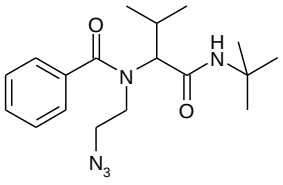
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s (br), 1H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.45 (s, 5H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 4.27 (s (br), 1H), 3.57 (s (br), 2H), 3.47 – 3.13 (m, 2H), 2.73 (s (br), 1H), 1.11 (d, *J* = 6.1 Hz, 3H), 1.08 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 169.1, 138.0, 135.5, 130.4, 129.0, 128.8, 127.0, 124.3, 120.0, 49.2, 26.4, 20.1, 19.1.

HRMS: 388.1744 ($M+Na^+$, calc.), 388.1741 (found).

MS (ESI): 387.9 (81, $M+Na^+$), 273.0 (100), 104.9 (20).

Synthesis of *N*-(2-azido-ethyl)-*N*-(1-*tert*-butylcarbamoyl-2-methyl-propyl)-benzamide (12a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 115 mg of a 77 % etherous solution of 2-azidoethylamine (1.03 mmol), 136 mg (1.11 mmol) of benzoic acid and 113 µL (83.1 mg, 1.00 mmol) of *tert*.-butyl isocyanide. Purification by flash chromatography (SF15-12g, ethyl acetate/hexane, grad 0-5 in 5 CV, iso 5 for 5 CV, grad 5-30 in 50 CV, product elutes from 25-40 CV) yielded 208 mg (60 %) of the title compound.

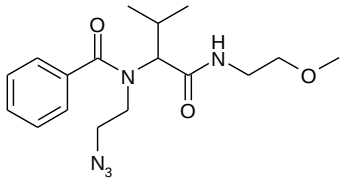
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.33 (m, 5H), 7.11 (s (br), 1H), 4.08 (s (br), 1H), 3.72 – 3.47 (m, 2H), 3.45 – 3.23 (m, 2H), 2.57 (s (br), 1H), 1.38 (s, 9H), 1.04 (d, *J* = 5.7 Hz, 3H), 1.00 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, 2 rotamers) δ 173.9, 170.0, 136.0, 133.2, 130.0, 130.0, 128.8, 128.4, 126.8, 51.2, 49.4, 47.0, 28.6, 26.4, 19.9, 19.0.

HRMS: 368.2057 ($M+Na^+$, calc.), 368.2060 (found).

MS (ESI): 368.0 (59, $M+Na^+$), 346.1 (55, $M+H^+$), 272.9 (100), 104.9 (27).

Synthesis of *N*-(2-azido-ethyl)-*N*-[1-(2-methoxy-ethylcarbamoyl)-2-methyl-propyl]-benzamide (13a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 115 mg of a 77 % etherous solution of 2-azidoethylamine (1.03 mmol), 132 mg (1.08 mmol) of benzoic acid and 86,1 µL (85.1 mg, 1.00 mmol) of 2-methoxyethylisocyanide. Purification by flash chromatography (SF15-12g, ethyl acetate/hexane, grad 0-5 in 5 CV, iso 5 for 5 CV, grad 5-40 in 40 CV, product elutes from 33-42 CV) yielded 206 mg (59 %) of the title compound.

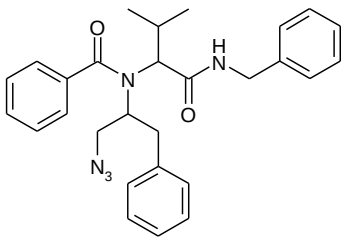
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.34 (m, 6H), 4.24 (d (br), *J* = 8.6 Hz, 1H), 3.59 – 3.22 (m, 11H), 2.60 (s (br), 1H), 1.12 – 0.92 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$, 2 rotamers) δ 173.9, 171.0, 135.9, 133.1, 130.0, 128.8, 128.3, 126.8, 70.9, 68.8, 66.3, 58.8, 49.3, 47.0, 41.9, 39.2, 28.3, 26.3, 19.9, 19.0.

HRMS: 370.1850 ($M+Na^+$, calc.), 370.1846 (found).

MS (ESI): 370.0 (36, $M+Na^+$), 348.0 (19, $M+H^+$), 273.0 (100), 104.8 (22).

Synthesis of *N*-(2-azido-1-benzyl-ethyl)-*N*-(1-benzylcarbamoyl-2-methyl-propyl)-benzamide (14a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 180 mg of 2-azido-1-benzylethylamine (1.02 mmol), 124 mg (1.02 mmol) of benzoic acid and 122 µL (117 mg, 1.00 mmol) of benzyl isocyanide. Purification by flash chromatography (SF15-15g, chloroform/hexane, iso 0 for 4 CV, grad 0-100 in 50 CV, product elutes from 27-33 CV) yielded 435 mg (93 %) of the title compound.

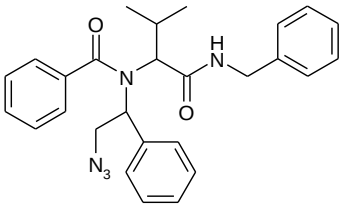
^{1}H NMR (400 MHz, $CDCl_3$, 2 diastereomers A/B = 1/1) δ 9.04 (t, *J* = 5.4 Hz, 1H, A), 8.86 (s (br), 1H, B), 7.55 – 7.02 (m, 2×14H, AB), 6.95 – 6.87 (m, 1H, A), 6.83 (d, *J* = 6.2 Hz, 1H, B), 4.62 (dd, *J* = 15.1, 5.8 Hz, 1H, A), 4.58 (dd, *J* = 15.8, 5.8 Hz, 1H, B), 4.51 (dd, *J* = 15.2, 5.7 Hz, 1H, A), 4.35 (dd, *J* = 14.8, 5.5 Hz, 1H, B), 4.13 (dt, *J* = 13.2, 6.3 Hz, 1H, B), 3.98 (tt, *J* = 11.3, 3.4 Hz, 1H, A), 3.74 (dd, *J* = 12.2, 11.6 Hz, 1H, A), 3.64 (dd, *J* = 12.7, 7.9 Hz, 1H, B), 3.50 – 3.34 (m, 1H+2H, AB), 3.25 – 2.99 (m, 2×2H, AB), 2.94 – 2.74 (m, 2H+1H, AB), 1.13 – 1.07 (m, 2×6H, AB).

^{13}C NMR (101 MHz, $CDCl_3$, 2 diastereomers) δ 174.6, 174.5, 172.3, 172.1, 138.5, 136.7, 136.6, 136.0, 130.2, 129.9, 129.0, 128.9, 128.9, 128.7, 128.5, 128.5, 127.6, 127.4, 127.2, 127.1, 126.8, 126.5, 126.4, 70.2, 70.0, 62.2, 62.0, 52.2, 50.5, 43.5, 43.4, 37.9, 37.1, 27.4, 27.0, 20.6, 20.3, 20.2, 20.0.

HRMS: 492.2370 ($M+Na^+$, calc.), 492.2367 (found).

MS (ESI): 492.1 (28, $M+Na^+$), 470.1 (3, $M+H^+$), 363.0 (100), 307.0 (7), 104.9 (10).

Synthesis of *N*-(2-azido-1-phenyl-ethyl)-*N*-(1-benzylcarbamoyl-2-methyl-propyl)-benzamide (15a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 199 mg of 2-azido-1-phenylethylamine (1.23 mmol), 126 mg (1.03 mmol) of benzoic acid and 122 µL (117 mg, 1.00 mmol) of benzyl isocyanide. Purification by flash chromatography (SF15-12g, ethyl acetate/hexane, grad 0-5 in 5 CV, iso 5 for 5 CV, grad 5-20 in 50 CV, product elutes from 27-36 CV (diastereomer 1)and 49-61 CV (diastereomer 2)) yielded 245 mg (d1; 54 %) and 164 mg (d2; 36 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, diastereomer 1) δ 8.79 (t, *J* = 5.4 Hz, 1H), 7.59 – 7.44 (m, 5H), 7.41 – 7.30 (m, 7H), 7.29 – 7.20 (m, 3H), 4.98 (dd, *J* = 10.8, 4.6 Hz, 1H), 4.60 (dd, *J* = 14.9, 5.9 Hz, 1H), 4.50 (dd, *J* = 15.0, 5.7 Hz, 1H), 4.29 (dd, *J* = 12.5, 11.0 Hz, 1H), 3.63 (dd, *J* = 12.7, 4.7 Hz, 1H), 3.34 (d, *J* = 11.1 Hz, 1H), 3.03 – 2.84 (m, 1H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.28 (d, *J* = 6.6 Hz, 3H).

^{1}H NMR (400 MHz, $CDCl_3$, diastereomer 2) δ 8.44 (s (br), 1H), 7.60 – 7.40 (m, 5H), 7.36 – 6.92 (m, 10H), 5.10 (s (br), 1H), 4.21 – 3.83 (m, 4H), 3.32 (d, *J* = 9.2 Hz, 1H), 3.05 (s (br), 1H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.00 (s (br), 3H).

^{13}C NMR (101 MHz, $CDCl_3$, diastereomer 1) δ 174.2, 172.3, 138.6, 137.0, 135.1, 129.5, 129.2, 128.9, 128.8, 128.5, 127.5, 127.1, 126.6, 68.6, 62.0, 51.2, 43.5, 27.1, 19.8, 19.2.

^{13}C NMR (101 MHz, $CDCl_3$, diastereomer 2) δ 174.5, 171.1, 138.5, 136.4, 135.1, 130.3, 130.0, 129.0, 128.7, 128.5, 127.7, 127.5, 127.0, 127.0, 70.3, 61.5, 50.6, 43.0, 27.1, 20.7, 20.1.

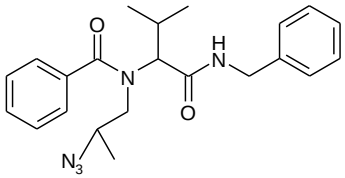
HRMS: diastereomer 1: 478.2213 ($M+Na^+$, calc.), 478.2209 (found).

diastereomer 2: 478.2213 ($M+Na^+$, calc.), 478.2210 (found).

MS (ESI): diastereomer 1: 478.1 (48, $M+Na^+$), 349.0 (100).

diastereomer 2: 478.1 (46, $M+Na^+$), 456.1 (11, $M+H^+$), 349.0 (100).

Synthesis of *N*-(2-azido-propyl)-*N*-(1-benzylcarbamoyl-2-methyl-propyl)-benzamide (16a)



To 1.0 mL of methanol in a 10 mL round bottom flask 140 mg (1.03 mmol) of 2-azido-propylammonium chloride, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde and 139 µL (101 mg, 1.00 mmol) of triethylamine are added and stirred at room temperature for 30 minutes. Then 130 mg (1.07 mmol) benzoic acid and 122 µL (117 mg, 1.00 mmol) of benzyl isocyanide. Purification by flash chromatography (SF15-15g, ethyl acetate/hexane, grad 0-5 in 5 CV, iso 5 for 5 CV, grad 5-50 in 45 CV, product elutes from 23-27 CV (diastereomer 1)and 28-34 CV (diastereomer 2)) yielded 80.9 mg (d1; 21 %) and 85.4 mg (d2; 22 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$, diastereomer 1) δ 7.83 (s (br), 1H), 7.50 – 7.20 (m, 10H), 4.62 (dd, *J* = 14.4, 5.2 Hz, 1H), 4.45 – 4.31 (m, 2H), 3.93 (s (br), 1H), 3.53 – 3.37 (m, 1H), 3.25 (d (br), *J* = 12.3 Hz, 1H), 2.57 (s (br), 1H), 1.08 (d, *J* = 4.9 Hz, 3H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.96 (d, *J* = 5.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, diastereomer 1) δ 174.6, 170.8, 169.9, 138.1, 135.9, 133.3, 130.0, 128.6, 128.3, 127.6, 127.3, 65.8, 55.4, 52.7, 43.5, 25.8, 20.1, 19.1, 17.0.

^{1}H NMR (400 MHz, $CDCl_3$, diastereomer 2) δ 8.52 (s (br), 1H), 7.48 – 7.26 (m, 10H), 4.60 – 4.42 (m, 2H), 3.92 (s (br), 1H), 3.68 (m, 1H), 3.50 (dd, *J* = 14.1, 9.9 Hz, 1H), 3.16 (dd, *J* = 14.2, 3.5 Hz, 1H), 2.96 – 2.79 (m, 1H), 1.05 (d, *J* = 6.3 Hz, 6H), 0.97 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, diastereomer 2) δ 173.9, 171.3, 169.5, 138.4, 136.1, 133.3, 130.1, 128.7, 128.6, 128.4, 127.6, 127.2, 127.2, 72.9, 57.4, 55.3, 43.5, 26.9, 19.9, 19.6, 16.9.

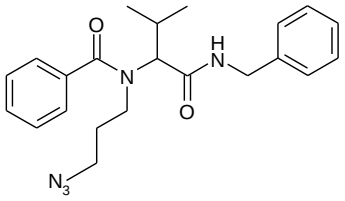
HRMS: diastereomer 1: 416.2057 ($M+Na^+$, calc.), 416.2056 (found).

diastereomer 2: 416.2057 ($M+Na^+$, calc.), 416.2061 (found).

MS (ESI): diastereomer 1: 415.9 (25, $M+Na^+$), 394.0 (10, $M+H^+$), 287.0 (100), 104.8 (17).

diastereomer 2: 415.9 (19, $M+Na^+$), 287.0 (100), 104.8 (14).

Synthesis of *N*-(3-azido-propyl)-*N*-(1-benzylcarbamoyl-2-methyl-propyl)-benzamide (17a)



The compound was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 225 mg of 48 % etherous solution of 2-azidopropylamine (1.08 mmol), 126 mg (1.03 mmol) of benzoic acid and 122 µL (118 mg, 1.01 mmol) of benzyl isocyanide. Purification by flash chromatography (SF15-12g, ethyl acetate/hexane, grad 0-5 in 5CV, iso 5 for 5 CV, grad 5-30 in 50 CV, product elutes from 33-48 CV) yielded 340 mg (86 %) of the title compound.

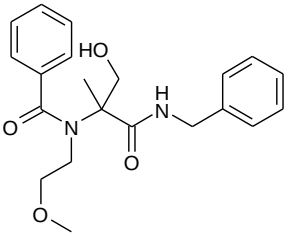
^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers A/B ≈7/1) δ 7.74 (s (br), 1H, A), 7.54 – 7.08 (m, 2×10H, AB), 5.47 (s (br), 1H, B), 4.64 – 4.29 (m, 2×2H, AB), 4.19 (s (br), 1H, A), 3.83 (s (br), 1H, B), 3.49 – 3.27 (m, 2H+4H, AB), 2.95 – 2.81 (m, 2H, A), 2.64 (s (br), 1H, A), 2.37 (s (br), 1H, B), 2.04 (s (br), 1H, B), 1.91 (s (br), 1H, B), 1.70 – 1.50 (m, 1H, A), 1.50 – 1.35 (m, 1H, A), 1.14 – 0.75 (m, 2×6H, AB).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 170.8, 138.4, 136.0, 130.1, 128.7, 128.6, 127.8, 127.4, 126.5, 48.5, 43.3, 28.2, 26.3, 20.0, 19.1.

HRMS: 416.2057 ($M+H^+$, calc.), 416.2053 (found).

MS (ESI): 416.0 (26, $M+Na^+$), 394.0 (6, $M+H^+$), 287.0 (100), 231.0 (5), 104.9 (10).

Synthesis of *N*-(1-benzylcarbamoyl-2-hydroxy-1-methyl-ethyl)-*N*-(2-methoxy-ethyl)-benzamide (18a')

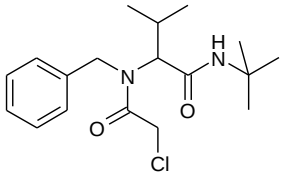


18a' was prepared according to *GRP1* with 1 ml of MeOH, 79.7 µL (92.5 mg, 1.00 mmol), of chloracetone, 86.9 µL (75.1 mg, 1.00 mmol) of 2-methoxyethylamine, 141 mg (1.15 mmol) benzoic acid and 123 mg (1.05 mmol) of benzyl isocyanide. Purification by flash chromatography (ethyl acetate/hexane , grad 0-50 in 100 CV, product elutes from 63 to 81 CV) yielded 48.2 mg (13 %) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.97 (t (br), *J* = 5.6 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.59 – 7.53 (m, 1H), 7.46 – 7.37 (m, 2H), 7.35 – 7.22 (m, 5H), 4.62 – 4.55 (m, 2H), 4.52 (dd, *J* = 14.8, 6.2 Hz, 1H), 4.41 (dd, *J* = 14.7, 5.8 Hz, 1H), 3.40 (t, *J* = 4.9 Hz, 2H), 3.19 (s, 3H), 2.75 (t, *J* = 4.9 Hz, 2H), 1.43 (s, 3H).

MS (ESI): 393.0 (3, $M+Na^+$), 371.0 (100, $M+H^+$), 249.0 (12), 236.0 (8), 141.9 (13), 116.0 (3).

Synthesis of 2-[benzyl-(2-chloro-acetyl)-amino]-*N*-*tert*-butyl-3-methyl-butyramide (20a')



20a' was prepared according to *GRP1* with 1.0 mL of methanol, 91.3 µL (72.1 mg, 1.00 mmol) of isobutyraldehyde, 109 µL (107 mg, 1.00 mmol) of benzylamine, 96.4 mg (1.02 mmol) of chloracetic acid and 113 µL (83.1 mg, 1.00 mmol) of *tert.*-butyl isocyanide. Purification by column chromatography (1.0 × 20 cm silica, ethyl acetate/hexane = 1/7 → 1/3,

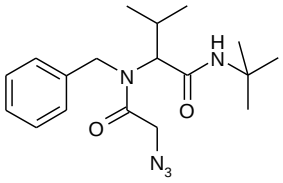
product-R_f = 0.43 [ethyl acetate/hexane = 1/3]) yielded 255 mg (75 %) of the title compound.

^{1}H NMR ($CDCl_3$, 2 rotamers A/B = 10/1, main rotamer only) δ 7.32 – 7.22 (m, 3H), 7.16 (d, *J* = 7.2 Hz, 2H), 6.34 (s (br), 1H), 4.97 (d, *J* = 17.4 Hz, 1H), 4.64 (d, *J* = 17.4 Hz, 1H), 4.47 (d, *J* = 10.8 Hz, 1H), 3.96 (d, *J* = 12.6 Hz, 1H), 3.82 (d, *J* = 12.6 Hz, 1H), 2.43 – 2.34 (m, 1H), 1.29 (s, 9H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$) δ 169.0, 168.6, 137.2, 128.8, 127.5, 126.0, 65.7, 51.4, 48.2, 42.1, 28.5, 27.8, 19.5, 18.7.

MS (ESI): 360.9 (16, M+Na$^+$), 339.0 (97, M+H$^+$), 265.9 (75), 162.0 (100), 90.8 (24).

Synthesis of 2-[(2-azido-acetyl)-benzyl-amino]-*N*-*tert*-butyl-3-methyl-butyramide (20a)



In a 10 mL round bottom flask with nitrogen atmosphere 101 mg (0.30 mmol) of **20a'** are dissolved in 2.0 mL of dry *N*,*N*-dimethylformamide, 152 mg (2.34 mmol) of sodium azide are added and this mixture is then stirred at room temperature for 20 hours. Afterwards the mixture is diluted with 10 mL of dichloromethane, washed with 10 mL of water, the aqueous phase reextracted with 3× 10 mL dichloromethane, the combined organic phases are dried over magnesium sulfate, filtered and evaporated to dryness to yield 100 mg (99 %) of the title compound.

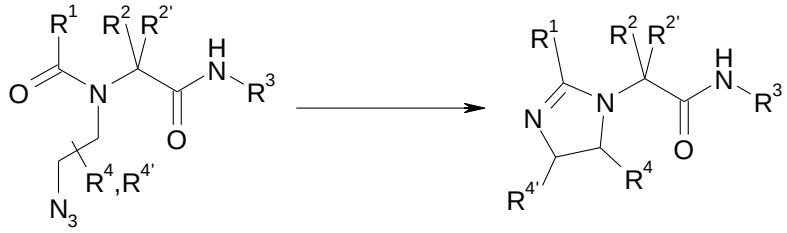
^{1}H NMR ($CDCl_3$, 2 rotamers A/B = 10/1, main rotamer only) δ 7.32 – 7.22 (m, 3H), 7.13 (d, *J* = 7.2 Hz, 2H), 6.19 (s (br), 1H), 4.91 (d, *J* = 17.6 Hz, 1H), 4.48 (d, *J* = 10.8 Hz, 1H), 4.43 (d, *J* = 17.6 Hz, 1H), 3.81 (d, *J* = 15.8 Hz, 1H), 3.60 (d, *J* = 15.8 Hz, 1H), 2.41 – 2.32 (m, 1H), 1.31 (s, 9H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR ($CDCl_3$) δ 170.0, 168.6, 136.8, 128.8, 127.6, 126.0, 65.6, 51.6, 51.2, 47.8, 28.6, 27.5, 19.4, 18.8.

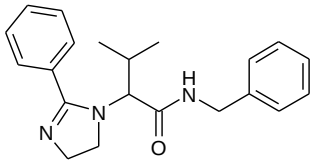
HRMS: 346.2238(M+H$^+$, calc.), 346.2236 (found).

MS (ESI): 346.0 (96, M+H$^+$), 273.0 (100), 162.0 (25), 90.8 (8).

<u>Syntheses of imidazolines (1b – 16b)</u>



Synthesis of *N*-benzyl-3-methyl-2-(2-phenyl-4,5-dihydro-imidazolyl)-butyramide (1b)



The compound was prepared according to GRP*2* with 24.0 mg (0.064 mmol) of **1a** and 62.6 mg polystyrene bound triphenylphosphine in 4.0 ml of dry toluene and yielded 21.0 mg (99 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.25 (m, 8H), 7.22 – 7.15 (m, 2H), 5.29 (t, *J* = 5.4 Hz, 1H), 4.42 (dd, *J* = 14.6, 6.2 Hz, 1H), 4.22 (dd, *J* = 14.6,

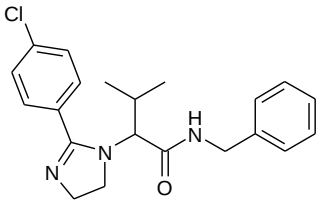
5.2 Hz, 1H), 3.99 – 3.74 (m, 3H), 3.66 – 3.47 (m, 1H), 3.33 (d, *J* = 10.6 Hz, 1H), 2.29 (dhept, *J* = 10.6, 6.6 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 1H), 0.85 (d, *J* = 6.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 166.2, 137.8, 131.2, 130.1, 128.8, 128.8, 128.3, 127.8, 127.7, 66.3, 52.91, 45.2, 43.3, 27.9, 19.7, 19.3.

HRMS: 336.2070 ($M+H^+$, calc.), 336.2068 (found).

MS (ESI): 336.0 (100, $M+H^+$), 146.9 (55).

Synthesis of *N-b*enzyl-2-[2-(4-chloro-phenyl)-4,5-dihydro-imidazolyl]-3-methyl-butyramide (2b)



The compound was prepared according to GRP*2* with 51.7 mg (0.12 mmol) of **2a** and 115 mg polystyrene bound triphenylphosphine in 4.0 ml of dry toluene and yielded 45.7 mg (99 %).

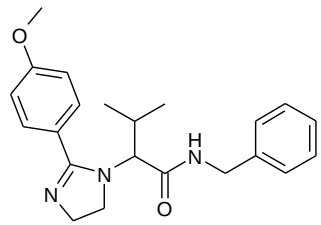
^{1}H NMR (400 MHz, $cdcl_3$) δ 7.49 – 7.21 (m, 7H), 7.18 (d, *J* = 6.7 Hz, 2H), 5.13 (s (br), 1H), 4.47 (dd, *J* = 14.5, 6.4 Hz, 1H), 4.20 (dd, *J* = 14.5, 4.9 Hz, 1H), 4.05 – 3.73 (m, 3H), 3.68 – 3.44 (m, 1H), 3.25 (d, *J* = 10.6 Hz, 1H), 2.29 (dhept, *J* = 10.6, 6.6 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 165.0, 137.7, 136.0, 130.1, 129.7, 129.1, 128.8, 127.8, 66.5, 53.7, 45.2, 43.4, 28.0, 19.7, 19.4.

HRMS: 370.1681 ($M+H^+$, calc.), 370.1677 (found).

MS (ESI): 372.0 (35, $M+H^+$), 370.0 (100, $M+H^+$), 180.9 (10).

Synthesis of *N-b*enzyl-2-[2-(4-methoxy-phenyl)-4,5-dihydro-imidazolyl]-3-methyl-butyramide (3b)



The compound was prepared according to GRP*2* with 95.0 mg (0.23 mmol) of **3a** and 200 mg polystyrene bound triphenylphosphine in 6.0 ml of dry toluene and yielded 83.6 mg (99 %).

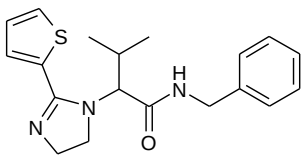
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.25 (m, 5H), 7.18 (d, *J* = 6.7 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.32 (t (br), *J* = 5.0 Hz, 1H), 4.44 (dd, *J* = 14.6, 6.3 Hz, 1H), 4.20 (dd, *J* = 14.6, 5.1 Hz, 1H), 3.99 – 3.66 (m, 6H), 3.62 – 3.48 (m, 1H), 3.37 (d, *J* = 10.6 Hz, 1H), 2.28 (dhept, *J* = 10.8, 6.6 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 165.9, 160.8, 137.9, 129.8, 128.7, 127.8, 127.7, 123.4, 114.1, 66.4, 55.3, 53.2, 45.1, 43.3, 27.9, 19.7, 19.3.

HRMS: 366.2176 ($M+H^+$, calc.), 366.2172 (found).

MS (ESI): 366.0 (100, $M+H^+$), 177.0 (19).

Synthesis of *N-b*enzyl-3-methyl-2-(2-thiophen-2-yl-4,5-dihydro-imidazolyl)-butyramide (4b)



The compound was prepared according to GRP*2* with 50.7 mg (0.13 mmol) of **4a** and 125 mg polystyrene bound triphenylphosphine in 2.0 ml of dry toluene. The crude product was purified by column chromatography (1.5 × 15 cm basic aluminum oxide, ethyl acetate/hexane = 1/1 → 100 % ethyl acetate) and yielded 31.0 mg (69 %).

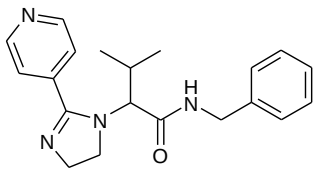
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 4.9 Hz, 1H), 7.37 – 7.26 (m, 4H), 7.20 (d, *J* = 7.0 Hz, 2H), 7.05 (dd, *J* = 4.9, 3.6 Hz, 1H), 5.51 (s (br), 1H), 4.42 (dd, *J* = 14.7, 5.7 Hz, 1H), 4.33 (dd, *J* = 14.7, 5.4 Hz, 1H), 3.96 – 3.77 (m, 3H), 3.74 (d, *J* = 10.5 Hz, 1H), 3.66 – 3.50 (m, 1H), 2.33 (dhept, *J* = 10.6, 6.6 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 160.1, 137.8, 131.6, 129.0, 128.7, 128.4, 127.7, 127.6, 127.5, 66.3, 52.5, 45.6, 43.4, 27.8, 19.7, 19.3.

HRMS: 342.1635 ($M+H^+$, calc.), 342.1632 (found).

MS (ESI): 342.0 (100, $M+H^+$), 152.9 (34).

Synthesis of *N*-benzyl-3-methyl-2-(2-pyridin-4-yl-4,5-dihydro-imidazolyl)-butyramide (5b)



The compound was prepared according to GRP*2* with 51.8 mg (0.14 mmol) of **5a** and 141 mg polystyrene bound triphenylphosphine in 5.0 ml of dry toluene and yielded 42.1 mg (92 %).

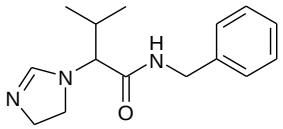
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 5.8 Hz, 2H), 7.36 – 7.28 (m, 3H), 7.21 – 7.12 (m, 5H), 4.54 (dd, *J* = 14.5, 6.5 Hz, 1H), 4.21 – 4.07 (m, 2H), 4.04 – 3.82 (m, 2H), 3.61 (dt, *J* = 11.4, 8.9 Hz, 1H), 3.27 (d, *J* = 10.6 Hz, 1H), 2.41 – 2.23 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 163.7, 149.3, 140.3, 138.1, 128.7, 128.0, 127.7, 122.9, 66.3, 54.0, 45.3, 43.2, 28.2, 19.6, 19.6.

HRMS: 337.2023 ($M+H^+$, calc.), 337.2020 (found).

MS (ESI): 337.0 (100, $M+H^+$), 147.9 (33).

Synthesis of *N*-benzyl-2-(4,5-dihydro-imidazolyl)-3-methyl-butyramide (6b)



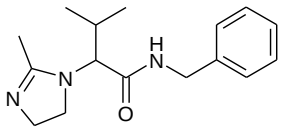
The compound was prepared according to GRP*2* with 48.0 mg (0.16 mmol) of **6a** and 140 mg polystyrene bound triphenylphosphine in 5.0 ml of dry toluene. The reaction time was 20 minutes.

*Due to the lability of the title compound the following analytical data was extracted from the crude product (mixture of **6b** and **6c**)!*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 5H), 7.21 – 7.09 (m, 1H), 6.93 (s (br), 1H), 4.45 (dd, *J* = 14.7, 5.8 Hz, 1H), 4.37 (dd, *J* = 14.7, 5.5 Hz, 1H), 3.72 (t, *J* = 9.9 Hz, 2H), 3.40 (q, *J* = 9.3 Hz, 1H), 3.37 (d, *J* = 10.1 Hz, 1H), 3.23 (q, *J* = 9.5 Hz, 1H), 2.33 – 2.20 (m, 1H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H).

MS (ESI): 260.0 (100, $M+H^+$).

Synthesis of *N*-benzyl-3-methyl-2-(2-methyl-4,5-dihydro-imidazolyl)-butyramide (7b)



The compound was prepared according to GRP*2* with 75.0 mg (0.24 mmol) of **7a** and 200 mg polystyrene bound triphenylphosphine in 6.0 ml of dry toluene. The reaction time was 40 minutes. The crude product was purified by column chromatography (1.5 × 5 cm silica, ethyl acetate → methanol, product-R_f = 0.07 [methanol]) and yielded 39.1 mg (64 %).

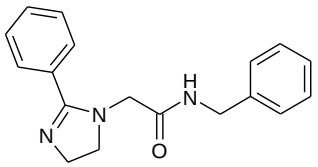
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 5H), 6.75 (t (br), *J* = 4.2 Hz, 1H), 4.45 (dd, J = 14.7, 5.8 Hz, 1H), 4.34 (dd, J = 14.7, 5.5 Hz, 1H), 3.76 – 3.52 (m, 3H), 3.46 – 3.29 (m, 2H), 2.29 (dhept, *J* = 10.2, 6.6 Hz, 1H), 1.88 (s, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 162.7, 138.1, 128.7, 127.8, 127.6, 65.6, 51.7, 45.4, 43.4, 27.7, 19.7, 19.2, 14.7.

HRMS: 274.1914 ($M+H^+$, calc.), 274.1912 (found).

MS (ESI): 274.0 (100, $M+H^+$), 84.9 (3).

Synthesis of *N*-benzyl-2-(2-phenyl-4,5-dihydro-imidazolyl)-acetamide (8b)



The compound was prepared according to GRP*2* with 48.0 mg (0.14 mmol) of **8a** and 200 mg polystyrene bound triphenylphosphine in 5.0 ml of dry toluene and yielded 60.7 mg (99 %).

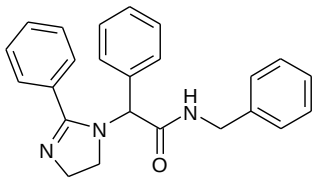
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.21 (m, 11H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.86 (t, *J* = 9.7 Hz, 2H), 3.67 (s, 2H), 3.40 (t, J = 9.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 166.9, 138.1, 130.3, 130.1, 128.7, 128.6, 127.9, 127.6, 127.6, 54.1, 53.8, 53.2, 43.3.

HRMS: 294.1601 ($M+H^+$, calc.), 294.1597 (found).

MS (ESI): 294.0 (100, $M+H^+$).

Synthesis of *N*-benzyl-2-phenyl-2-(2-phenyl-4,5-dihydro-imidazolyl)-acetamide (9b)



The compound was prepared according to GRP*2* with 53.0 mg (0.13 mmol) of **9a** and 177 mg polystyrene bound triphenylphosphine in 6.0 ml of dry toluene and yielded 46.4 mg (99 %).

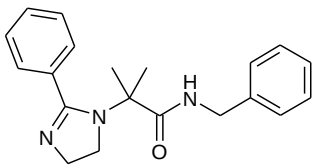
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.12 (m, 13H), 7.11 – 7.05 (m, 2H), 6.85 (t, *J* = 5.7 Hz, 1H), 5.31 (s, 1H), 4.49 (dd, *J* = 14.7, 6.1 Hz, 1H), 4.41 (dd, *J* = 14.7, 5.8 Hz, 1H), 3.83 – 3.67 (m, 1H), 3.66 – 3.36 (m, 2H), 3.12 – 2.92 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.71, 166.3, 138.1, 135.1, 131.1, 130.1, 129.0, 128.8, 128.7, 128.3, 128.2, 127.7, 127.6, 125.3, 64.2, 53.6, 46.2, 43.5.

HRMS: 370.1914 ($M+H^+$, calc.), 370.1909 (found).

MS (ESI): 370.0 (100, $M+H^+$), 146.9 (13).

Synthesis of *N*-benzyl-2-(2-phenyl-4,5-dihydro-imidazolyl)-isobutyramide (10b)



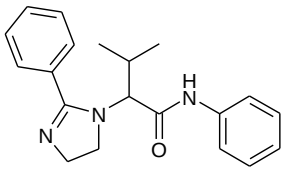
The compound was prepared according to GRP*2* with 55.0 mg (0.15 mmol) of 10**a** and 126 mg polystyrene bound triphenylphosphine in 5.0 ml of dry toluene. The reaction time was 20 minutes.

*Due to the lability of the title compound the following analytical data was extracted from the crude product (mixture of **10b** and **10c**)!*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.13 (m, 10H), 6.61 (t, *J* = 5.1 Hz, 1H), 4.29 (d, *J* = 5.7 Hz, 2H), 3.79 (t, *J* = 9.4 Hz, 2H), 3.51 (t, *J* = 9.5 Hz, 2H), 1.29 (s, 6H).

MS (ESI): 322.0 (100, $M+H^+$), 146.9 (36).

Synthesis of *N*-benzyl-3-methyl-2-(2-thiophen-2-yl-4,5-dihydro-imidazolyl)-butyramide (11b)



The compound was prepared according to GRP*2* with 55.0 mg (0.15 mmol) of **11a** and 130 mg polystyrene bound triphenylphosphine in 5.0 ml of dry toluene and yielded 43.5 mg (99 %).

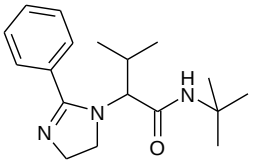
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.40 (m, 5H), 7.36 – 7.20 (m, 4H), 7.12 – 7.01 (m, 1H), 6.93 (s (br), 1H), 4.01 – 3.73 (m, 3H), 3.66 – 3.52 (m, 1H), 3.47 (d, *J* = 10.5 Hz, 1H), 2.32 (dhept, *J* = 10.8, 6.6 Hz, 1H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 165.9, 137.2, 131.7, 130.2, 129.0, 128.4, 124.6, 119.8, 67.0, 53.3, 45.2, 28.0, 19.7, 19.3.

HRMS: 321.1914 ($M+H^+$, calc.), 322.1913 (found).

MS (ESI): 322.0 (100, $M+H^+$), 147.0 (15).

Synthesis of *N*-*tert*-butyl-3-methyl-2-(2-phenyl-4,5-dihydro-imidazolyl)-butyramide (12b)



The compound was prepared according to GRP*2* with 36.0 mg (0.10 mmol) of **12a** and 90.0 mg polystyrene bound triphenylphosphine in 5.0 ml of dry toluene. The crude product was purified by column chromatography (1 × 17 cm silica, ethyl acetate + 5 % triethylamine, product R_f = 0.43) and yielded 24.8 mg (79 %).

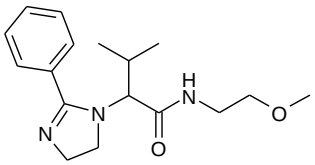
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.37 (m, 5H), 4.57 (s (br), 1H), 4.03 – 3.70 (m, 3H), 3.60 – 3.46 (m, 1H), 3.16 (d, *J* = 10.6 Hz, 1H), 2.21 (dhept, *J* = 10.6, 6.6 Hz, 1H), 1.23 (s, 9H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 166.2, 131.9, 130.0, 128.8, 128.5, 66.9, 53.6, 51.4, 45.1, 28.6, 27.8, 19.7, 19.3.

HRMS: 302.2227 ($M+H^+$, calc.), 302.2223 (found).

MS (ESI): 302.0 (100, $M+H^+$), 146.9 (12).

Synthesis of *N*-(2-methoxy-ethyl)-3-methyl-2-(2-phenyl-4,5-dihydro-imidazolyl)-butyramide (13b)



The compound was prepared according to GRP*2* with 28.1 mg (0.081 mmol) of **13a** and 70.8 mg polystyrene bound triphenylphosphine in 5.0 ml of dry toluene. The crude product was purified by column chromatography (1 × 18 cm silica, ethyl acetate + 5 % triethylamine, product R_f = 0.14) and yielded 17.7 mg (72 %).

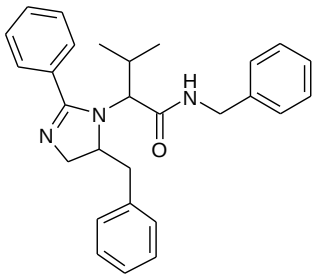
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.39 (m, 5H), 5.39 (s (br), 1H), 4.02 – 3.68 (m, 3H), 3.56 (ddd, *J* = 11.2, 9.2, 8.0 Hz, 1H), 3.48 – 3.18 (m, 8H), 2.27 (dhept, *J* = 10.6, 6.6 Hz, 1H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 166.2, 131.8, 129.9, 128.8, 128.3, 71.0, 66.2, 58.7, 53.5, 45.1, 38.8, 27.7, 19.6, 19.2.

HRMS: 304.2020 ($M+H^+$, calc.), 304.2017 (found).

MS (ESI): 304.0 (100, $M+H^+$), 146.9 (22).

Synthesis of *N*-benzyl-2-(5-benzyl-2-phenyl-4,5-dihydro-imidazolyl)-3-methyl-butyramide (14b)



The compound was prepared according to *GRP2* with 60.0 mg (0.13 mmol) of **14a** and 120 mg polystyrene bound triphenylphosphine in 5.0 ml of dry toluene. The crude product was purified by column chromatography (1 × 20 cm silica, ethyl acetate + 5 % triethylamine, product R_f = 0.58 and 0.72) and yielded 41.7 mg (77 %).

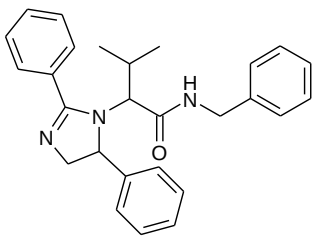
^{1}H NMR (400 MHz, $CDCl_3$, racemic mixture) δ 7.55 – 7.05 (m, 2× 15H), 5.96 (t, *J* = 5.5 Hz, 1H), 5.16 (t, *J* = 5.5 Hz, 1H), 4.65 (tt, *J* = 9.2, 4.6 Hz, 1H), 4.58 – 4.41 (m, 3H), 4.24 – 4.12 (m, 2H), 3.85 – 3.79 (m, 2H), 3.72 (dd, *J* = 15.4, 9.5 Hz, 1H), 3.62 (dd, *J* = 15.4, 4.8 Hz, 1H), 3.31 (d, *J* = 10.6 Hz, 1H), 3.27 (d, *J* = 11.1 Hz, 1H), 3.18 (dd, *J* = 13.3, 4.1 Hz, 1H), 3.06 (dd, *J* = 12.9, 2.9 Hz, 1H), 2.73 (dd, *J* = 13.3, 10.7 Hz, 1H), 2.61 (dd, *J* = 12.9, 10.1 Hz, 1H), 2.54 (ddd, *J* = 13.2, 6.6, 4.1 Hz, 1H), 2.41 (dtt, *J* = 14.3, 7.8, 3.8 Hz, 1H), 1.27 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.79 (d, *J* = 6.4 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 170.2, 166.8, 166.7, 138.1, 137.9, 137.9, 137.7, 132.0, 131.4, 130.5, 130.2, 129.7, 129.4, 128.9, 128.8, 128.8, 128.7, 128.7, 128.6, 128.5, 128.3, 127.8, 127.8, 127.7, 127.7, 126.4, 126.2, 68.1, 67.0, 60.0, 60.0, 58.2, 58.0, 43.6, 43.3, 42.5, 41.1, 28.7, 28.4, 20.1, 19.9, 19.9, 18.7.

HRMS: 426.2540 ($M+H^+$, calc.), 426.2538 (found).

MS (ESI): 426.1 (100, $M+H^+$).

Synthesis of *N*-benzyl-2-(2,5-diphenyl-4,5-dihydro-imidazolyl)-3-methyl-butyramide (15b)



15b-d1 was prepared according to GRP*2* with 54.0 mg (0.12 mmol) of **15a-d1** and 106 mg polystyrene bound triphenylphosphine in 5.0 ml of dry toluene and yielded 44.7 mg (99 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.48 (m, 2H), 7.46 – 7.18 (m, 13H), 5.35 (dd, *J* = 10.9, 5.6 Hz, 1H), 5.19 (t (br), *J* = 5.5 Hz, 1H), 4.51 (dd, *J* = 14.6, 6.5 Hz, 1H), 4.35 (dd, *J* = 15.3, 10.9 Hz, 1H), 4.16 (dd, *J* = 14.6, 5.0 Hz, 1H), 3.81 (dd, *J* = 15.3, 5.6 Hz, 1H), 3.35 (d, *J* = 10.9 Hz, 1H), 2.10 – 1.90 (m, 1H), 0.74 (d, *J* = 6.5 Hz, 3H), 0.67 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 166.7, 145.7, 137.8, 131.4, 130.5, 128.9, 128.7, 128.6, 128.6, 127.7, 127.7, 127.2, 126.9, 68.5, 65.2, 60.9, 43.3, 28.4, 19.8, 19.5.

HRMS: 412.2383 ($M+H^+$, calc.), 412.2379 (found).

MS (ESI): 412.1 (100, $M+H^+$), 223.0 (4).

15b-d2: In a 15 mL microwave vial with nitrogen atmosphere 49.0 mg (0.11 mmol) of **15a-d2** are dissolved in 5 mL of dry toluene and 98.0 mg of resin bound triphenylphosphine (1.2-1.5 mmol/g, crosslinked with 1 % DVB, mesh 200-400)) are added and stirred for 19 hours. The reaction mixture is then placed into the microwave reactor and heated to 150 °C for 10 minutes. The polymer is filtered off, washed with 5 ml of dichloromethane and the combined filtrates are evaporated to dryness. The crude product was purified by preparative column chromatography (column: YMC Pack 150 x 10 mm ID ODS-A 120Å, 5µm; eluent A: H_2O/MeCN (9/1) + 0.5 % TFA; eluent B: MeCN + 0.5 % TFA; 3 ml/min, grad 30-100 in 15 min; t_R = 7.4 min) and yielded after lyophilization 20.7 mg (TFA salt, 36 %).

^{1}H NMR (400 MHz, $CDCl_3$, TFA salt) δ 7.84 (d, *J* = 7.6 Hz, 2H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.47 – 7.42 (m, 3H), 7.37 – 7.33 (m, 2H), 7.29 – 7.24 (m, 3H), 7.02 – 7.00 (m, 2H), 6.41 (t, *J* = 5.0 Hz, 1H), 5.38 (dd, *J* = 5.8 Hz, *J* = 11.4 Hz, 1H), 4.49 (t, *J* = 12.2 Hz, 1H), 3.97 (dd, *J* = 6.0 Hz, *J* = 14.4 Hz,

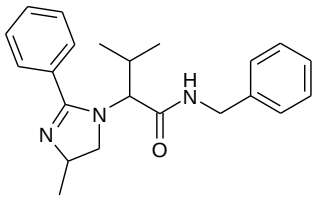
1H), 3.89 (dd, *J* = 6.2 Hz, *J* = 12.6 Hz, 1H), 3.81 (d, *J* = 11.2 Hz, 1H), 3.64 (dd, *J* = 4.8 Hz, *J* = 9.6 Hz, 1H), 2.37 (dhept, *J* = 10.8 Hz, *J* = 6.4 Hz, 1H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, TFA salt) δ 169.3, 165.7, 137.8, 136.6, 134.4, 129.9, 129.7, 129.5, 129.1, 128.8, 127.8, 127.8, 126.4, 122.2, 67.4, 63.1, 53.0, 43.8, 28.0, 19.1, 18.9.

HRMS: 412.2383 ($M+H^+$, calc.), 412.2378 (found).

Synthesis of *N*-benzyl-2-(2,5-diphenyl-4,5-dihydro-imidazolyl)-3-methyl-butyramide (16b)

16b-d1 was prepared according to GRP*2* with 30.0 mg (0.076 mmol) of **16a-d1** and 70.2 mg polystyrene bound triphenylphosphine in 6.3 ml of dry toluene. The crude product was purified by column chromatography (1 × 20 cm silica, ethyl acetate + 5 % triethylamine, product R_f = 0.49) and yielded 19.8 mg (74 %).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 8H), 7.23 – 7.16 (m, 2H), 5.20 (t, *J* = 5.1 Hz, 1H), 4.43 (dd, *J* = 14.6, 6.2 Hz, 1H), 4.28 – 4.17 (m, 2H), 3.93 (t, *J* = 10.1 Hz, 1H), 3.31 (d, *J* = 10.6 Hz, 1H), 3.13 (dd, *J* = 9.6, 7.1 Hz, 1H), 2.37 – 2.17 (m, 1H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 164.5, 137.8, 131.5, 129.9, 128.8, 128.7, 128.4, 127.8, 127.7, 66.0, 59.8, 52.1, 43.3, 27.7, 22.7, 19.6, 19.2.

HRMS: 350.2227 ($M+H^+$, calc.), 350.2223 (found).

MS (ESI): 350.0 (100, $M+H^+$), 161.0 (10).

16b-d2 was prepared according to GRP*2* with 58.0 mg (0.15 mmol) of **16a-d2** and 160 mg polystyrene bound triphenylphosphine in 6.0 ml of dry toluene and yielded 50.1 mg (97 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 8H), 7.23 – 7.14 (m, 2H), 5.12 (t, *J* = 5.2 Hz, 1H), 4.49 (dd, *J* = 14.6, 6.5 Hz, 1H), 4.23 – 4.09 (m, 2H), 3.67 (t, *J* = 10.0 Hz, 1H), 3.36 (t, *J* = 9.3 Hz, 1H), 3.31 (d, *J* = 10.6 Hz, 1H), 2.35 – 2.20 (m, 1H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 164.6, 137.8, 131.5, 129.9, 128.8, 128.7, 128.4, 127.9, 127.8, 66.4, 60.1, 52.1, 43.3, 27.8, 22.7, 19.7, 19.3.

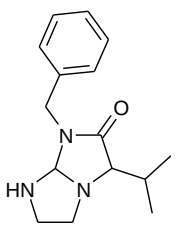
HRMS: 350.2227 ($M+H^+$, calc.), 350.2220 (found).

MS (ESI): 350.0 (100, $M+H^+$), 161.0 (10).

<u>Syntheses of ortho-amidines (6c, 10c, 15c-d2)</u>

Synthesis of 1-benzyl-3-isopropyl-tetrahydro-imidazo[1,2-a]imidazol-2-one (6c)

6c formed during the synthesis of **6b** in varying amounts and upon standing of **6b** in $CDCl_3$ at room temperature.



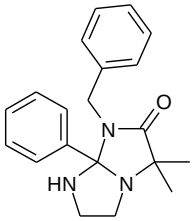
*Due to the lability of the title compound the following analytical data were extracted from the crude product (mixture of **6b** and **6c**)!*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 5H), 5.20 (d, *J* = 1.5 Hz, 1H), 4.95 (d, *J* = 14.7 Hz, 1H), 4.05 (d, *J* = 14.7 Hz, 1H), 3.18 (s(br), 1H), 3.03 – 2.93 (m, 1H), 2.98 (d, *J*

= 8.1 Hz, 1H), 2.83 – 2.68 (m, 2H), 2.24 – 2.08 (m, 2H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H).

Synthesis of 1-benzyl-3,3-dimethyl-7a-phenyl-tetrahydro-imidazo[1,2-a]imidazol-2-one (10c)

10c formed during the synthesis of **10b** in varying amounts.

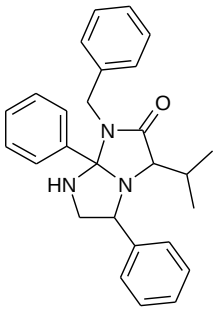


*Due to the lability of the title compound the following analytical data were extracted from the crude product (mixture of **10b** and **10c**)!*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 2H), 7.39 – 7.10 (m, 8H), 4.80 (d, *J* = 15.0 Hz, 1H), 3.96 (d, *J* = 15.0 Hz, 1H), 3.12 (ddd, *J* = 11.3, 6.9, 5.0 Hz, 1H), 3.05 – 2.90 (m, 2H), 2.84 (dt, *J* = 11.1, 6.8 Hz, 1H), 2.07 (s(br), 1H), 1.35 (s, 3H), 1.30 (s, 11H).

Synthesis of 1-benzyl-3-isopropyl-5,7a-diphenyl-tetrahydro-imidazo[1,2-a]imidazol-2-one (15c-d2)

15c-d2 formed during the synthesis of **15b-d2**.



*Due to the lability of the title compound the following analytical data were extracted from the crude product (mixture of **15b-d2** and **15c-d2**)!*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.9, 1.5 Hz, 3H), 7.50 – 7.10 (m, 10H), 6.98 (dd, *J* = 7.4, 1.9 Hz, 2H), 4.76 (d, *J* = 14.8 Hz, 1H), 3.95 – 3.91 (m, 1H), 3.92 (d, *J* = 14.7 Hz, 1H), 3.44 (dd, *J* = 11.6, 7.0 Hz, 1H), 3.21 (d, *J* = 6.3 Hz, 1H), 2.93 (dd, *J* = 11.5, 7.1 Hz, 1H), 2.70 (s(br), 1H), 2.07 – 1.92 (m, 1H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H).

7. Abstract

In this thesis several **novel postmodifiactions of regular Ugi-4CR products**, mostly cyclizations, have been examined. Their scope and limitations were tested both by permutating the required functionalities around the Ugi scaffold and by synthesizing small compound libraries for those permutations which could be successfully cyclized. The great majority of Ugi-4CRs was successful and gave the desired products in good to excellent yields.

1. **Radical cyclizations** of Ugi-4CR products bearing *o*-halogenoaryl substituents and an alkene were examined. The Ugi-4CR scaffold was found to be stable under radical cylization conditions with Bu_3SnH as H-donor but not with $(Me_3Si)_3SiH$. Out of seven Ugi products with permutated functionalities three were successfully cyclized to the corresponding indolone, dihydroisoquinolinone or tetrahydroisoquinoline, respectively, but the cyclization proved to be unreliable and the separation of tin byproducts was tedious.
2. Four different types of enynes were synthesized by Ugi-4CRs. One of them could be further modified by **$Pd^{II/IV}$ catalyzed oxidative cyclization** leading to substituted 3-aza-bicyclo[3.1.0]hexan-2-ones. This represents the first example of a postmodification by $Pd^{II/IV}$ catalysis. Subjecting an analogue Passerini 3CR product to the same conditions led to transesterification and addition of the solvent.
3. **Three known cyclizations strategies for tetrazol-Ugi-4CR products** (S_NAr, intramolecular alkylation, intramolecular ester aminolysis) were tried to be **transferred to their hydrazine analogues**. While the Ugi reaction was uneventful, both cyclization and deprotection of the Ugi products proved to be difficult and led only in one instance to the desired product.
4. An **improved synthesis of highly substituted indazolones** was developed. It requires less synthetic steps, offers superior yields and adds a fourth point of diversity. The cyclization can be effected either by palladium or copper catalysis and can be applied to both BOC protected, alkyl substituted and free hydrazides. The copper protocol is operationally simple and robust, requires only copper(I)iodide and no extra ligand and can be run at room temperature. Cleavage of the BOC protecting group (necessary during the Ugi-4CR) can be accomplished concomitantly by running the cyclization at elevated temperatures. Ugi products of α-unsubstituted isocyanides undergo under the reaction conditions of the copper catalysis a second cyclization to form hitherto undescribed hydroxytriazafluoren-diones. In this second cyclization the BOC group acts as CO source. It was found that this unusual behaviour is bound to the presence of the indazolone (simple BOC hydrazides do not enter into this reaction) and is independent of Cu but requires a polar solvent and a base.
5. Finally Ugi-4CR products derived from 2-azidoethylamine were formed surprisingly quickly (within a few minutes) and in high yield. They were further cyclized to substituted 2-(acetamid-2-yl)-imidazolines with up to five points of diversity by means of a **Staudinger/aza-Wittig** reaction sequence utilizing the tertiary amide (formed during the Ugi-4CR) as carbonyl component. By employing polymerbound phosphane and microwave heating the cyclization was operationally very easy: In most cases only filtration and washing was required to give the pure imidazolines in often near quantitative yields. In some cases the formation of the corresponding *ortho*-amidines was observed.

8. Zusammenfassung

In dieser Arbeit wurden mehrere neuartige, meist zyklisierende Postmodifikationen von Produkten der Ugi-4CR untersucht. Ihre Möglichkeiten und Grenzen wurden durch 1. das Permutieren der notwendigen funktionellen Gruppen um das Ugigrundgerüst herum und 2. durch Synthese von kleinen Substanzbibliotheken für die erfolgreichen Permutationen getestet. Der Großteil der Ugi-4CR lieferte die gewünschten Produkte in guten bis hervorragenden Ausbeuten.

1. Zu Beginn wurden **radikalische Zyklisierungen von Ugi-4CR-Produkten mit *ortho*-Halogenaryl- und Alkensubstituenten** untersucht. Das Grundgerüst der Ugi-4CR erwies sich unter den radikalischen Reaktionsbedingungen als stabil, wenn Bu_3SnH als H-Donor verwendet wurde, nicht aber bei $(Me_3Si)_3SiH$. Von sieben Ugiprodukten mit unterschiedlichem Substitutionsmuster konnten drei erfolgreich zu Indolonen, Dihydroisoquinolinonen bzw. Tetrahydroisoquinolinonen zyklisiert werden. Diese Zyklisierungen erwiesen sich bei genauerer Untersuchung aber als unzuverlässig. Erschwerend kam hinzu, daß die Abtrennung von überschüssigem Stannan und dessen Reaktionsprodukten äußerst mühsam und oft unvollständig war.
2. Vier verschiedene Typen von Eninen wurden durch Ugi-4CRs synthetisiert. Einer davon konnte in einer **$Pd^{II/IV}$ katalysierten oxidativen Zyklsierung** weiter zu substituierten 3-Azabizyklo[3.1.0]hexan-2-onen umgesetzt werden. Dies stellt das erste Beispiel einer Post-modifikation mittels $Pd^{II/IV}$-Katalyse dar. Eine analoges Passerini-3CR-Produkt, das denselben Reaktionsbedingungen unterworfen wurde, lieferte Umesterungs- und Additionsprodukte des Lösungsmittel statt des erhofften Laktons.
3. Eine **verbesserte Synthese von hochsubstituierten Indazolonen** wurde entwickelt. Sie benötigt weniger Reaktionsschritte, liefert bessere Ausbeuten und ermöglicht einen vierten Diversitätspunkt. Die Zyklisierung kann entweder mit Palladium- oder Kupferkatalyse bewerkstelligt werden, und kann sowohl auf BOC-geschützte, alkylsubstituierte oder freie Hydrazide angewendet werden. Das Kupferprotokoll ist einfach handzuhaben und zuverlässig, erfordert nur Kupfer(I)iodid als Katalysator, keine weiteren Liganden und kann bei Raumtemperatur gefahren werden. Die Abspaltung der BOC-Schutzgruppe (nötig während der Ugi-4CR) kann nach Wunsch *in situ* erfolgen, dazu ist lediglich eine höhere Reaktionstemperatur nötig. Ugiprodukte von α-unsubstituierten Isocyaniden bzw. die davon abgeleiteten BOC-geschützten Indazolone zyklisieren unter den Reaktionsbedingungen der Kupferkatalyse weiter zu den bis dato unbekannten Hydroxytriazafluorendionen. In dieser zweiten Zyklisierung dients die BOC-Gruppe als CO-Donor. Es konnte gezeigt werden, daß diese ungewöhnliche Reaktivität dem Indazolon geschuldet ist (einfache Boc-Hydrazide gehen diese Reaktion nicht ein) und nicht von der Gegenwart von Kupfer abhängt.
4. Drei bekannte Zyklisierungsstrategien für Produkte der Tetrazol-Ugi-4CR (S_NAr, intramolekulare Alkylierung, intramolekulare Esteraminolyse) sollten auf die entsprechenden von (BOC-)Hydrazin abgeleiteten Ugi-4CR-Produkte übertragen werden. Während die Ugireaktionen ohne Komplikationen vonstatten gingen, erwiesen sich die sowohl die direkte Zyklisierung als auch die Entschützung als ausgesprochen heikel und führten nur in einem Falle zum gewünschten Produkt.
5. Abschließend wurden Ugi-4CR-Produkte des 2-Azidoethylamins, die sich überraschend schnell (innerhalb weniger Minuten) und in sehr guten Ausbeuten bildeten, in einer **Staudinger/aza-Wittig-Reaktion** weiter zu substituierten 2-Acetamid-2-yl-imidazolinen mit insgesamt fünf Diversitätspunkten umgesetzt werden. Dabei diente das in der Ugi-4CR

entstandene tertiäre Amid als Carbonylkomponente. Durch die Verwendung von polymergebundenem Triphenylphosphan und Mikrowellenheizung ist die Zyklisierung sehr einfach durchzuführen und aufzuarbeiten: In vielen Fällen reichte einfaches Waschen und Filtrieren aus, um das Reinprodukt in oftmals nahezu quantitativer Ausbeute zu erhalten. In einigen Fällen wurde die Bildung der entsprechenden o*rtho*-Amidine beobachtet.

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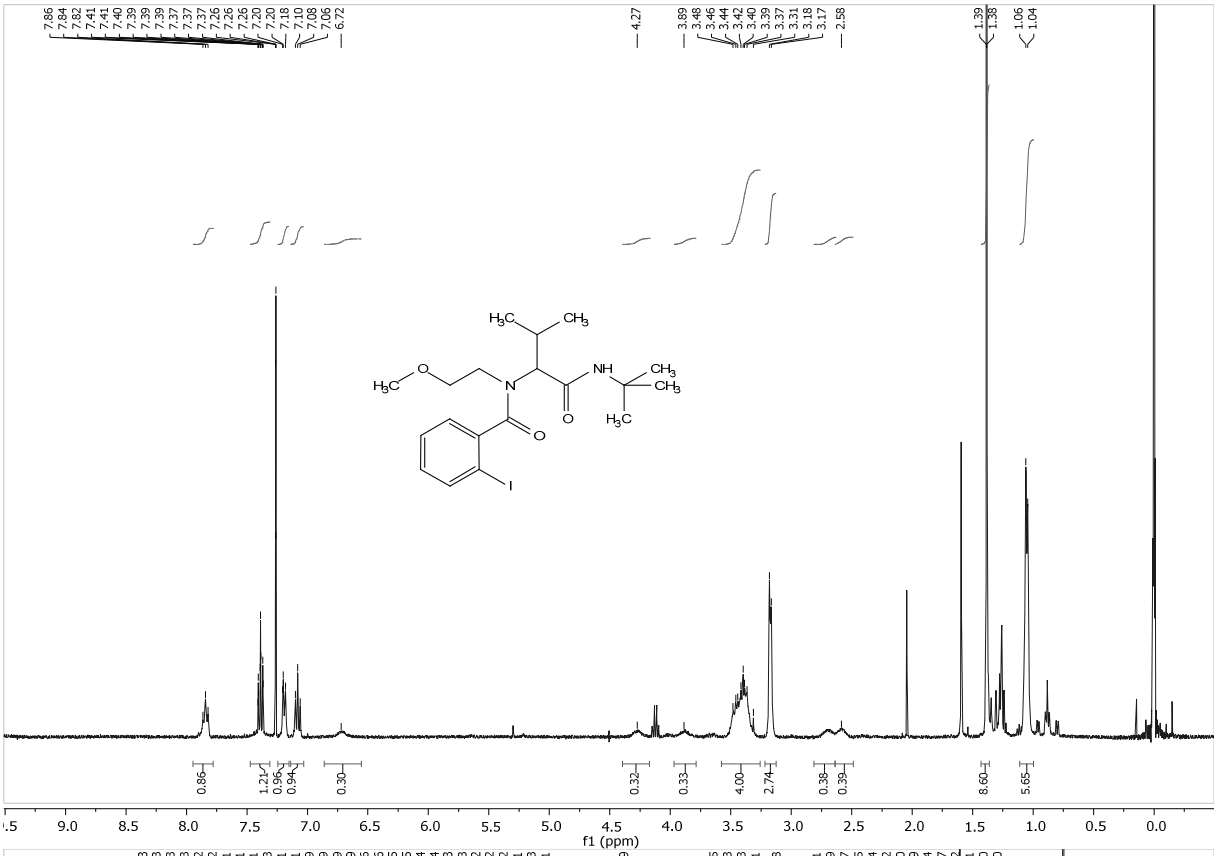
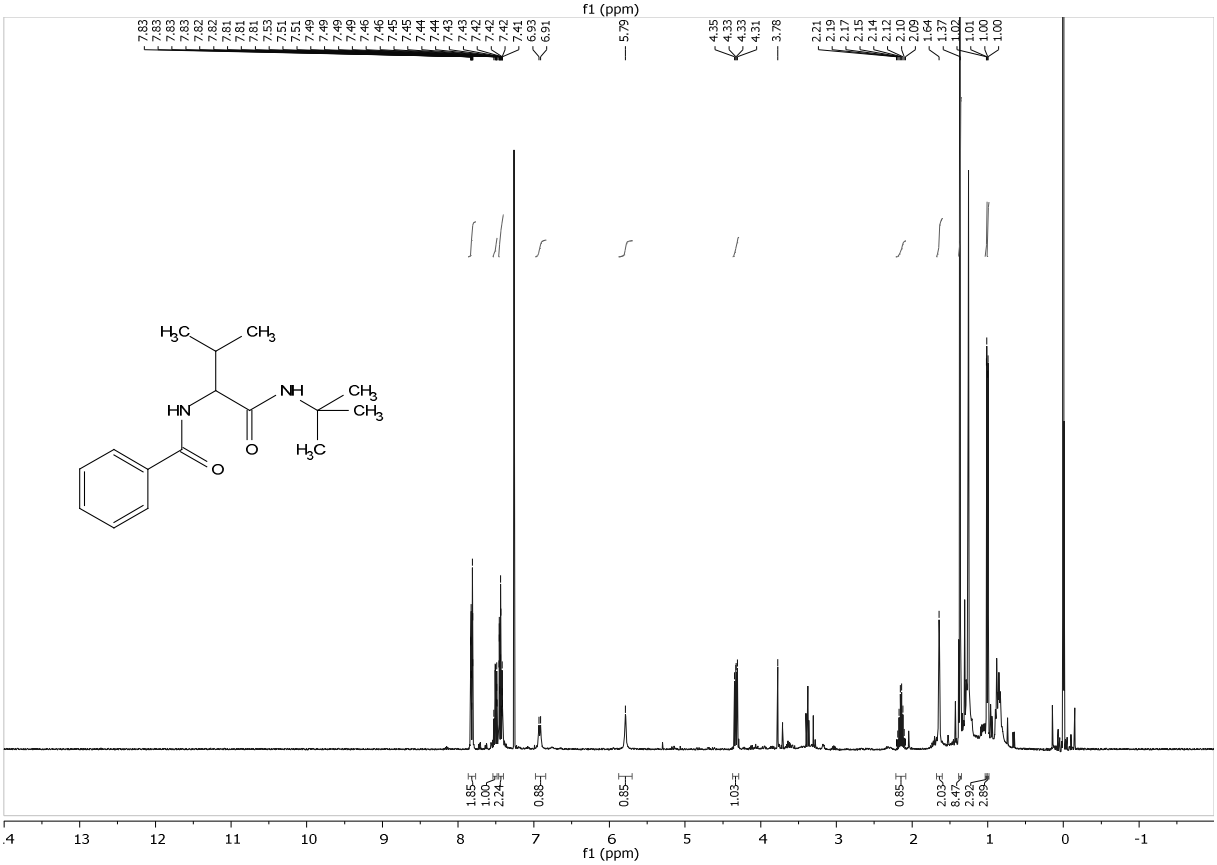
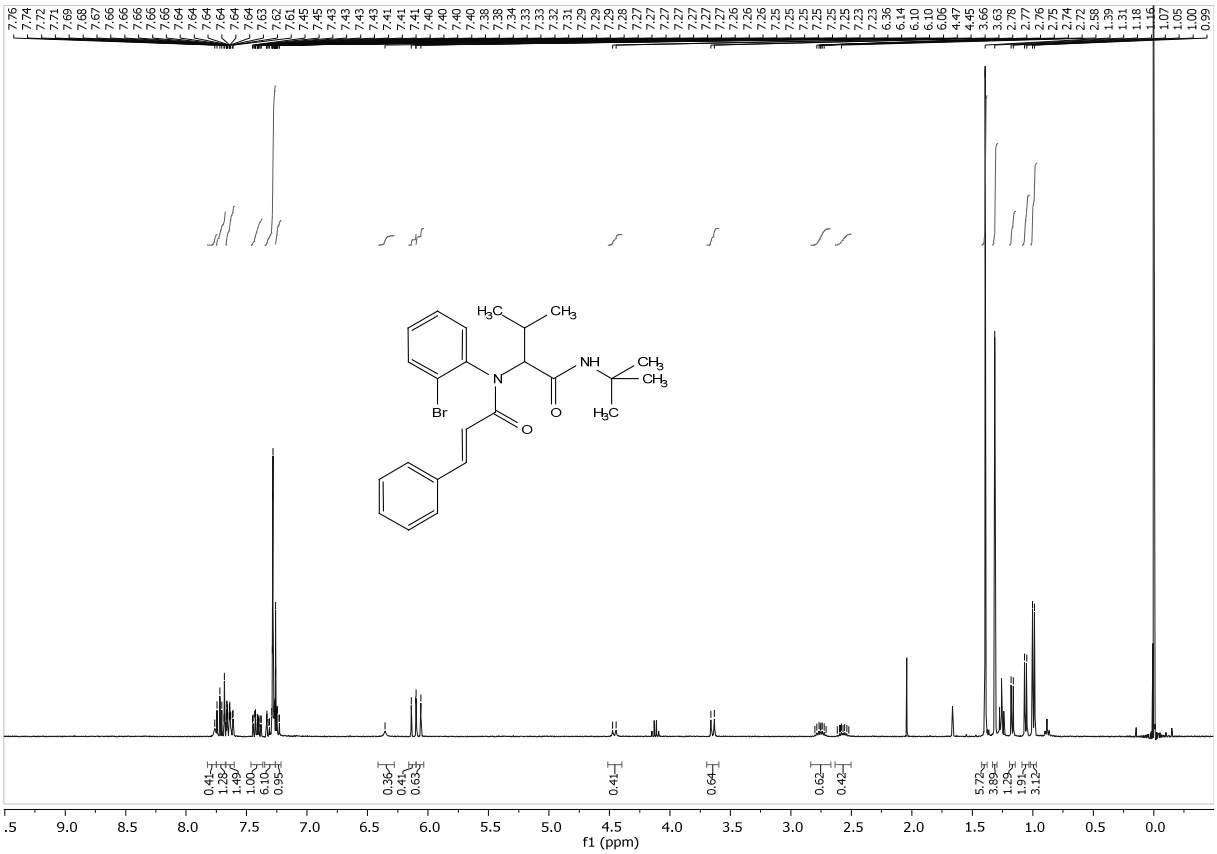
10. Appendix

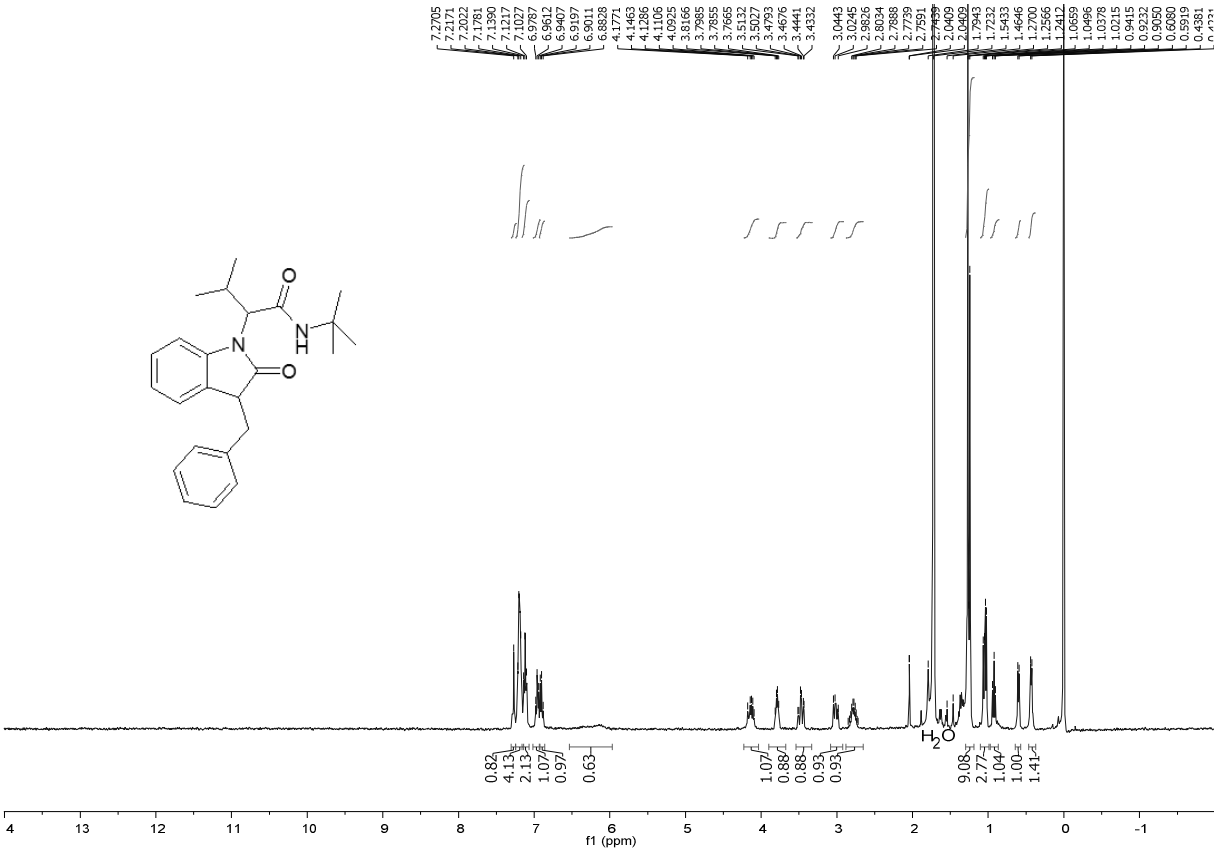
10.1. NMR Spectra

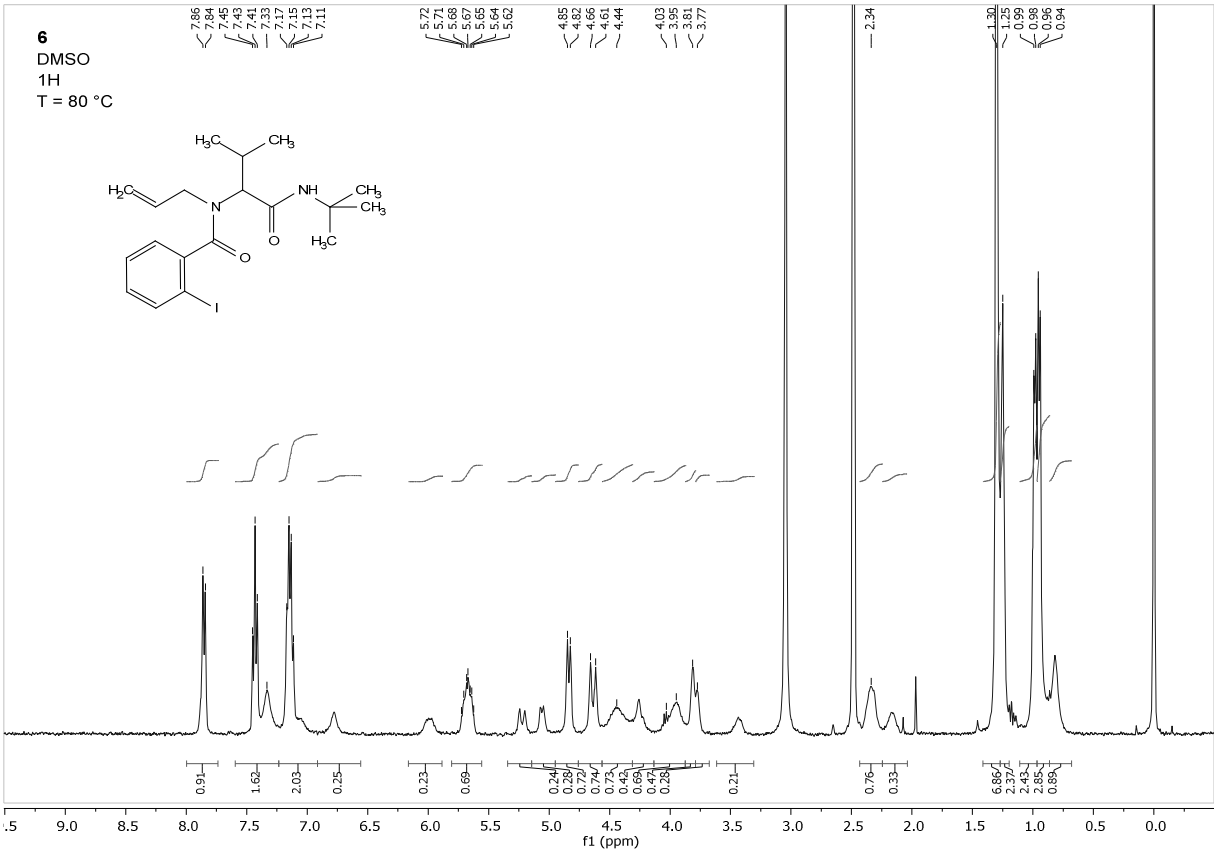
10.1.1. Ugi/Radical cyclizations (chapter 6.1)

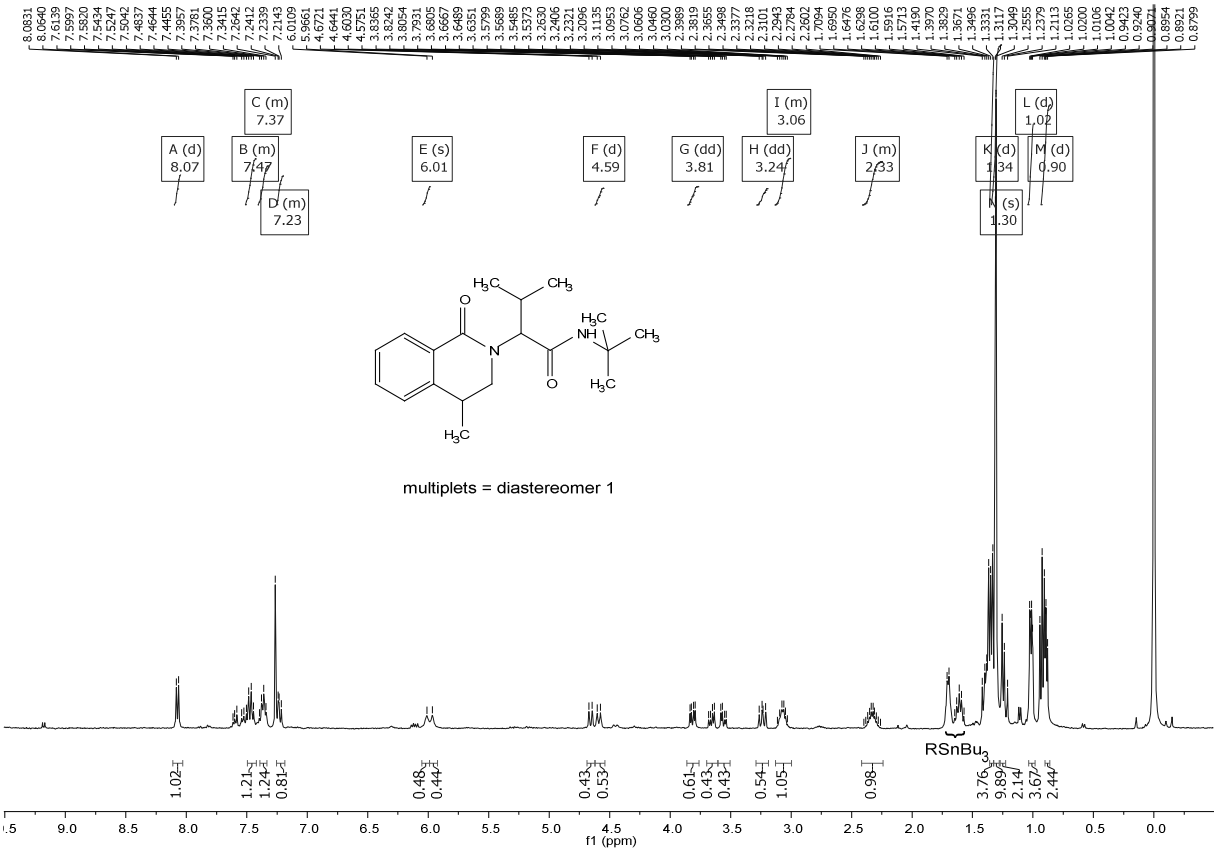


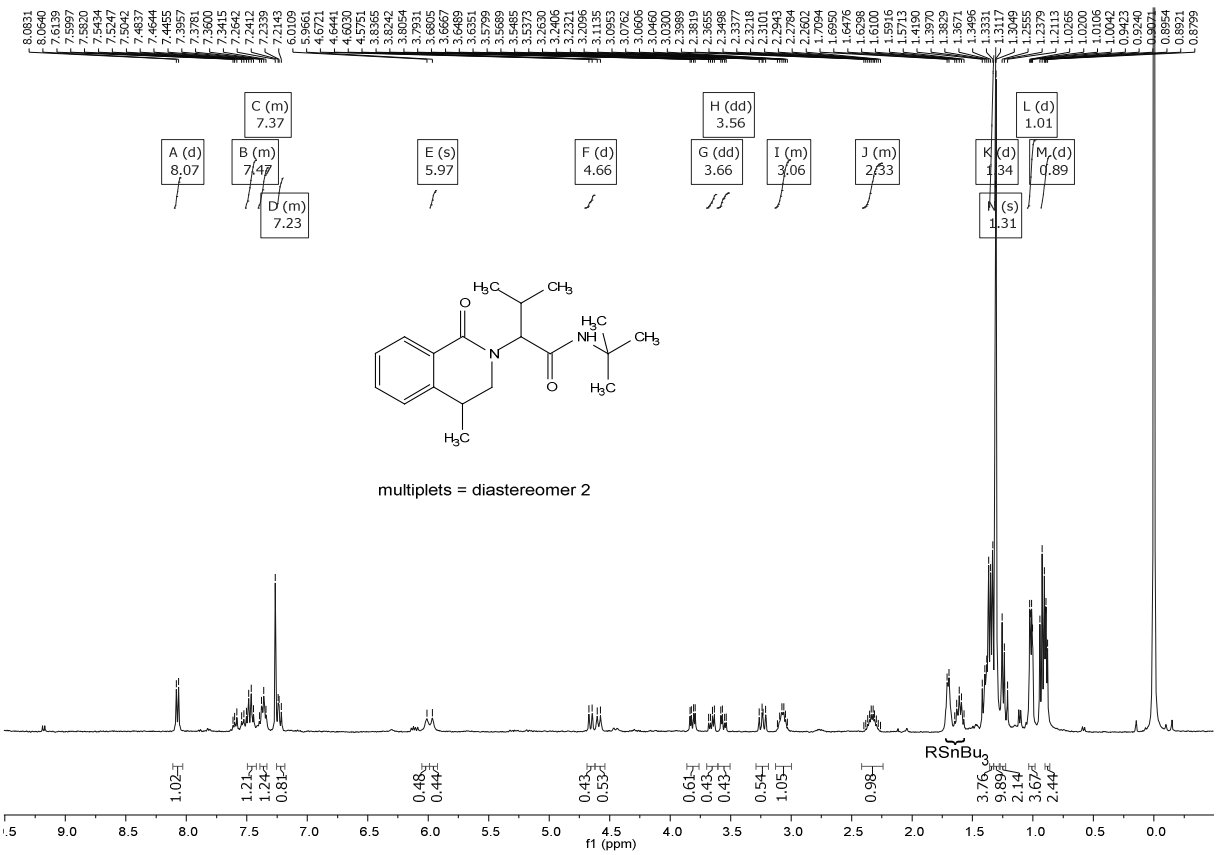


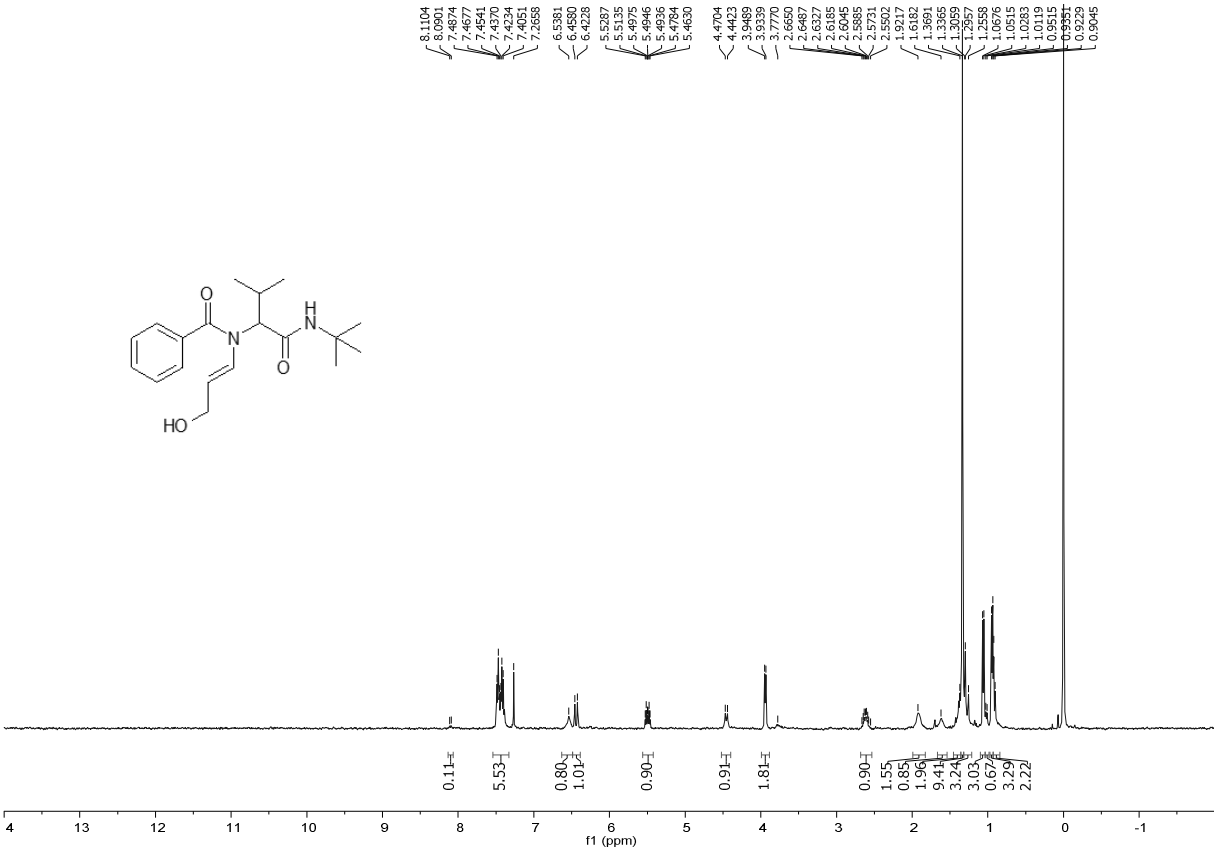

H3C
CH3
NH
CH3
CH3
N
Br
O
O
H3C
f1 (ppm)

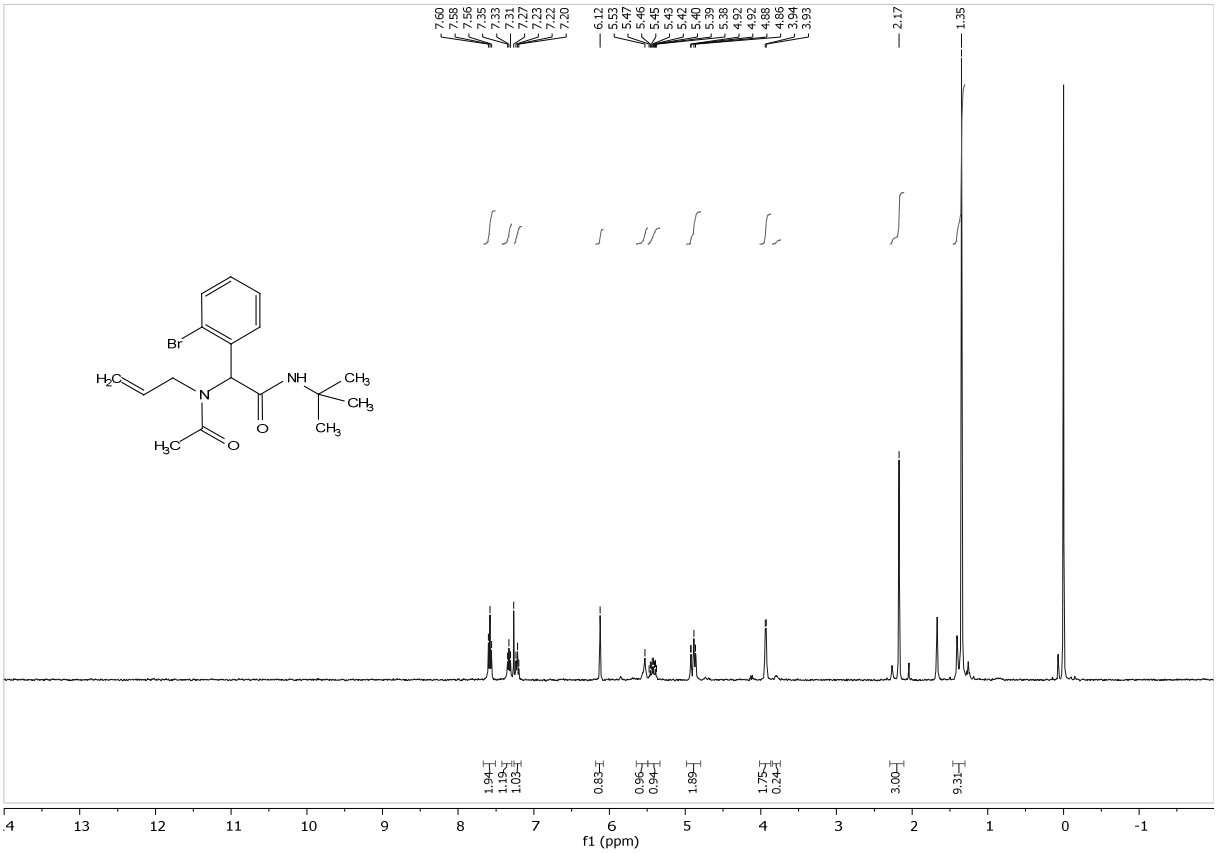

O
N
H
N
O
H2O
f1 (ppm)

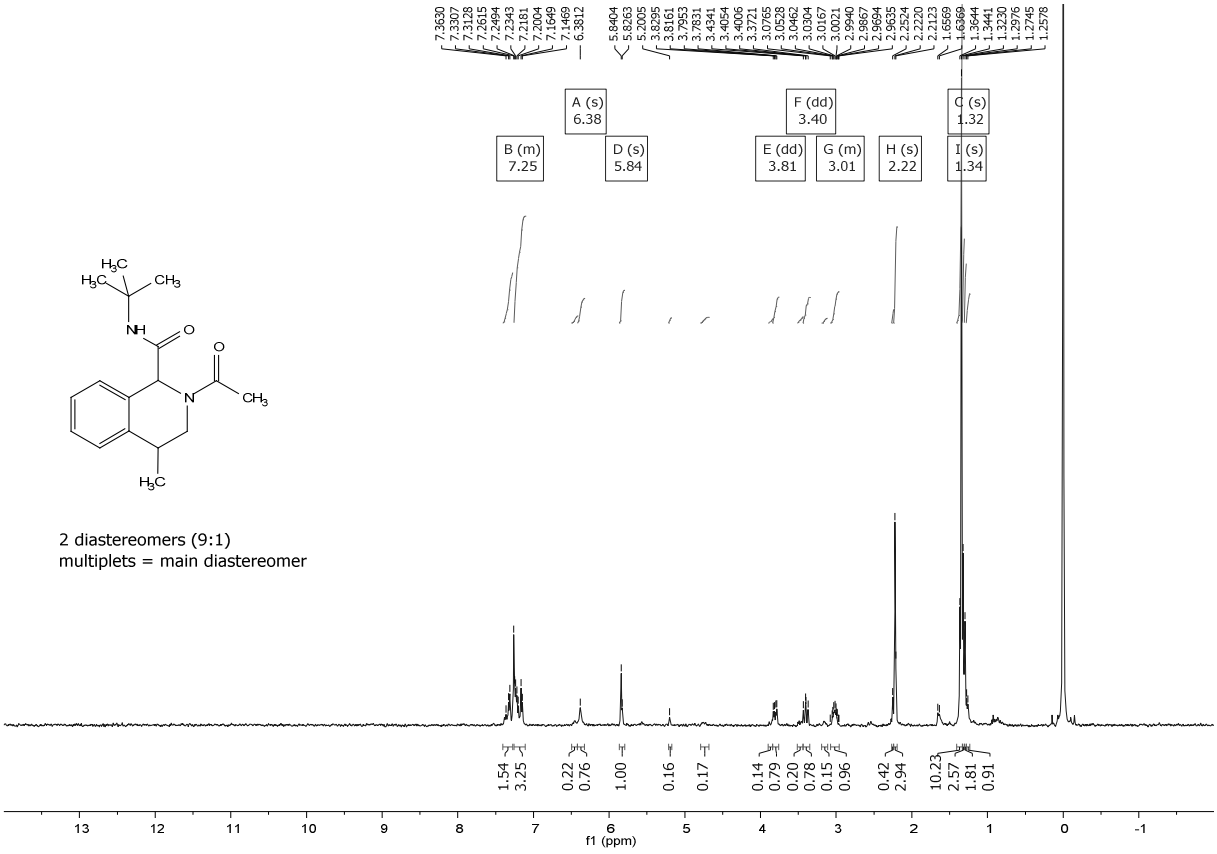

6
DMSO
1H
T = 80 °C
f1 (ppm)

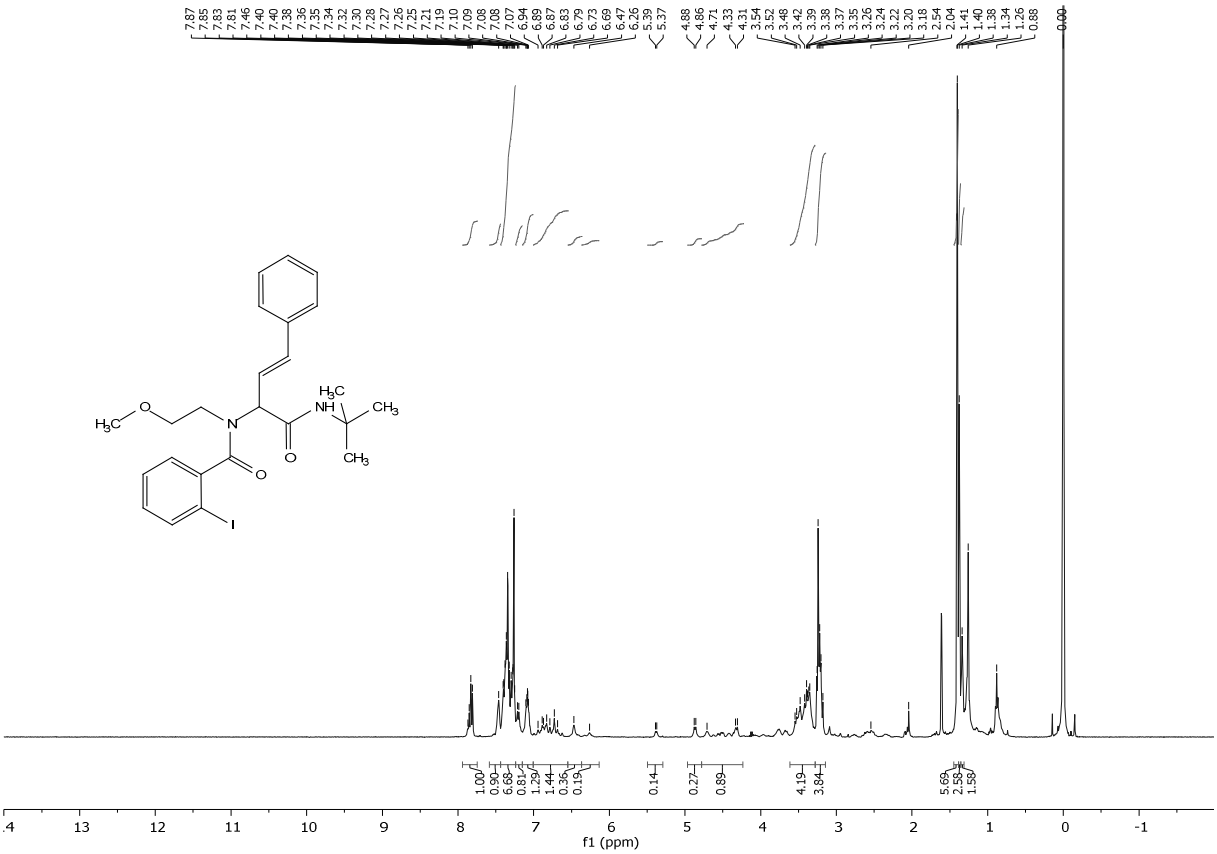

A (d) 8.07
B (m) 7.47
C (m) 7.37
D (m) 7.23
E (s) 6.01
F (d) 4.59
G (dd) 3.81
H (dd) 3.24
I (m) 3.06
J (m) 2.33
K (d) 1.34
L (d) 1.02
M (d) 0.90
N (s) 1.30
multiplets = diastereomer 1
RSnBu3
f1 (ppm)

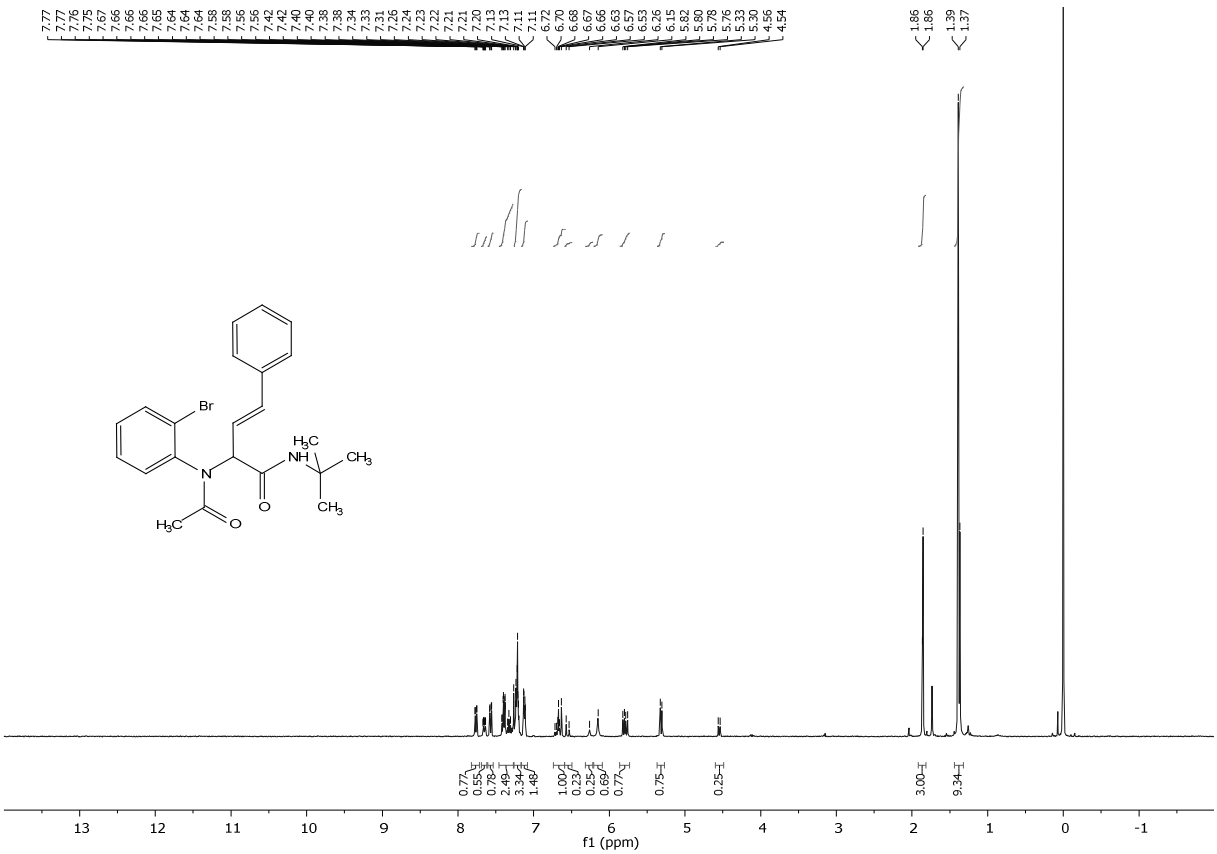

A (d) 8.07
B (m) 7.47
C (m) 7.37
D (m) 7.23
E (s) 5.97
F (d) 4.66
G (dd) 3.66
H (dd) 3.56
I (m) 3.06
J (m) 2.33
K (d) 1.34
L (d) 1.01
M (d) 0.89
N (s) 1.31
multiplets = diastereomer 2
RSnBu3
f1 (ppm)

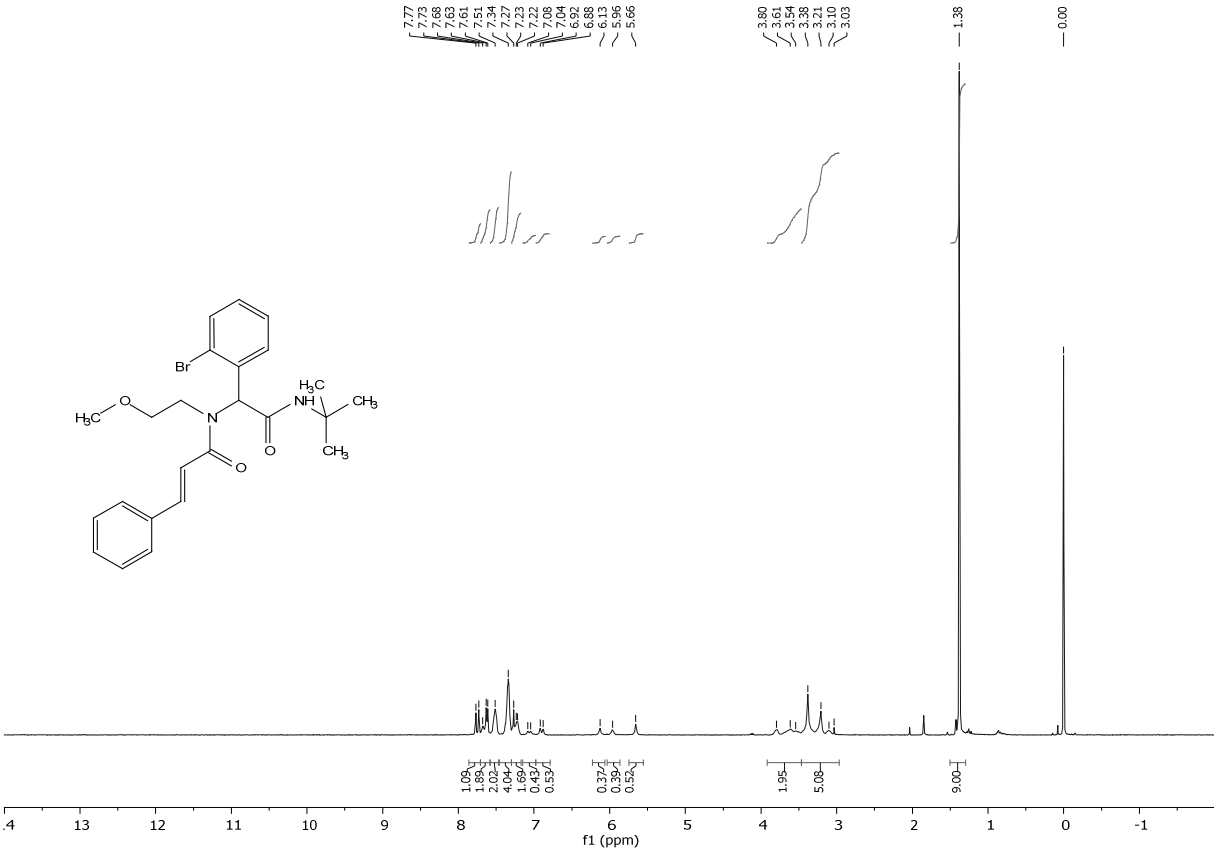

HO
f1 (ppm)


7.60
7.58
7.56
7.35
7.33
7.31
7.27
7.23
7.22
7.20
6.12
5.53
5.47
5.46
5.45
5.43
5.42
5.40
5.39
5.38
4.92
4.88
4.86
3.94
3.93
2.17
1.35
Br
H2C
N
NH
CH3
CH3
CH3
O
H3C
O
1.94
1.19
1.03
0.83
0.96
0.94
1.89
1.75
0.24
3.00
9.31
f1 (ppm)


7.3630
7.3307
7.3128
7.2615
7.2494
7.2343
7.2181
7.2004
7.1649
7.1469
6.3812
5.8404
5.8263
5.2005
3.8295
3.8161
3.7953
3.7831
3.4434
3.4404
3.4006
3.3721
3.0765
3.0528
3.0462
3.0304
3.0167
3.0021
2.9940
2.9867
2.9694
2.9635
2.2524
2.2220
2.2123
1.6569
1.6369
1.3644
1.3441
1.3230
1.2976
1.2745
1.2578
A (s) 6.38
B (m) 7.25
D (s) 5.84
F (dd) 3.40
E (dd) 3.81
G (m) 3.01
H (s) 2.22
C (s) 1.32
I (s) 1.34
H3C
H3C
CH3
NH
O
O
N
CH3
H3C
2 diastereomers (9:1)
multiplets = main diastereomer
1.54
3.25
0.22
0.76
1.00
0.16
0.17
0.14
0.79
0.20
0.78
0.15
0.96
0.42
2.94
10.23
2.57
1.81
0.91
f1 (ppm)


f1 (ppm)


f1 (ppm)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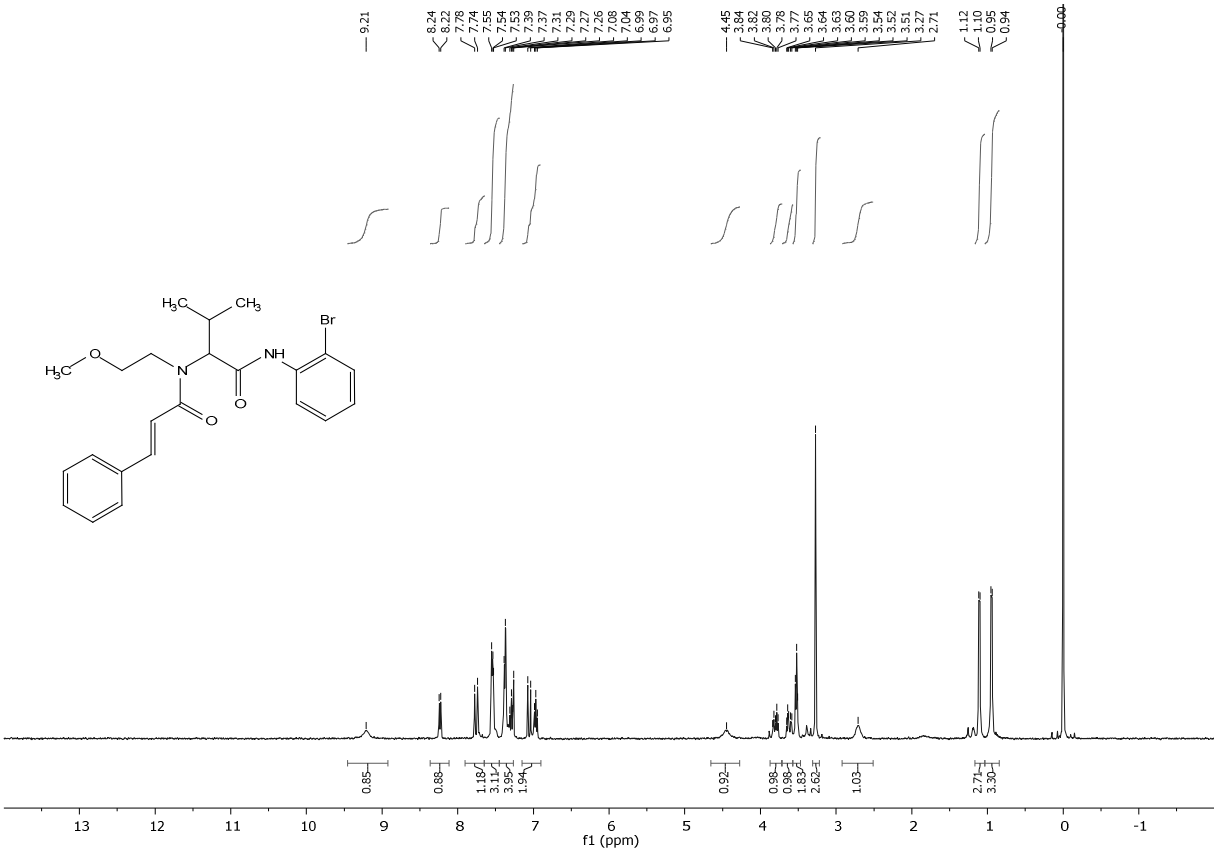
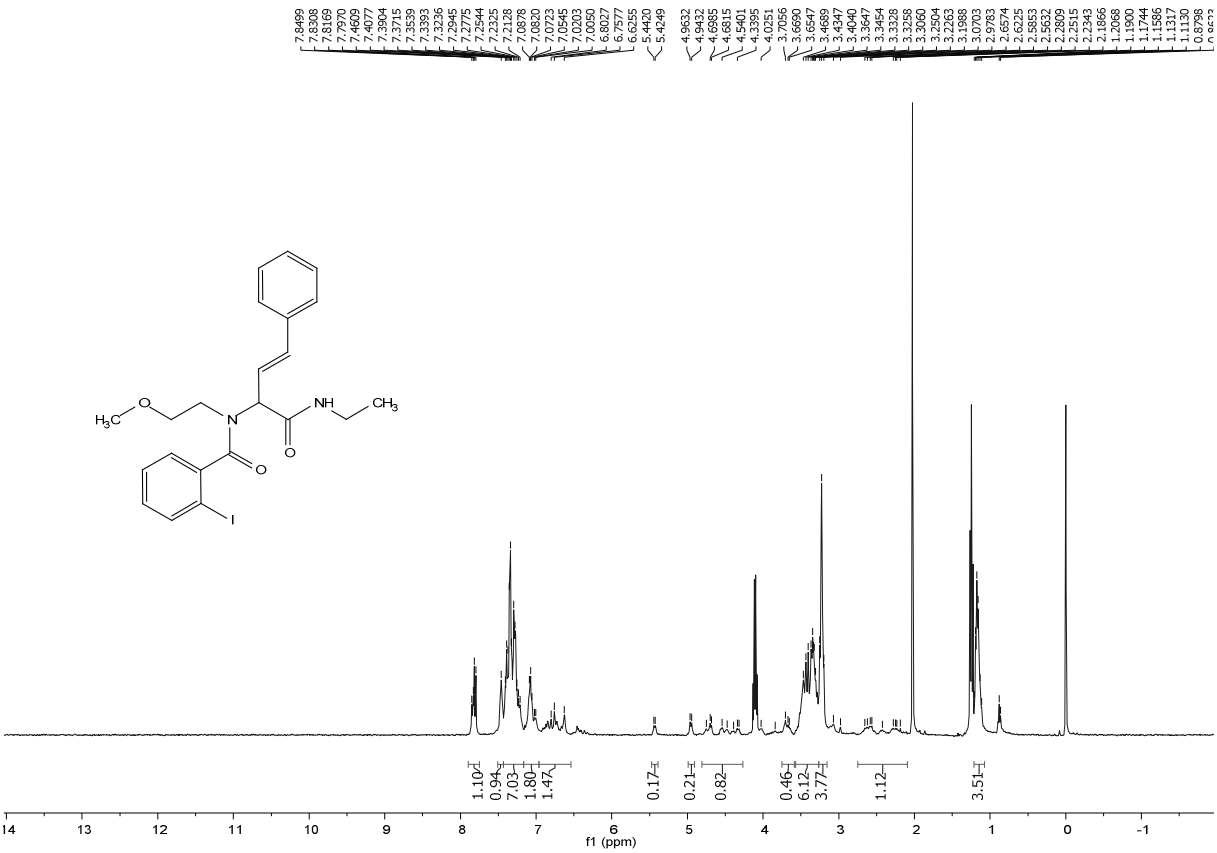
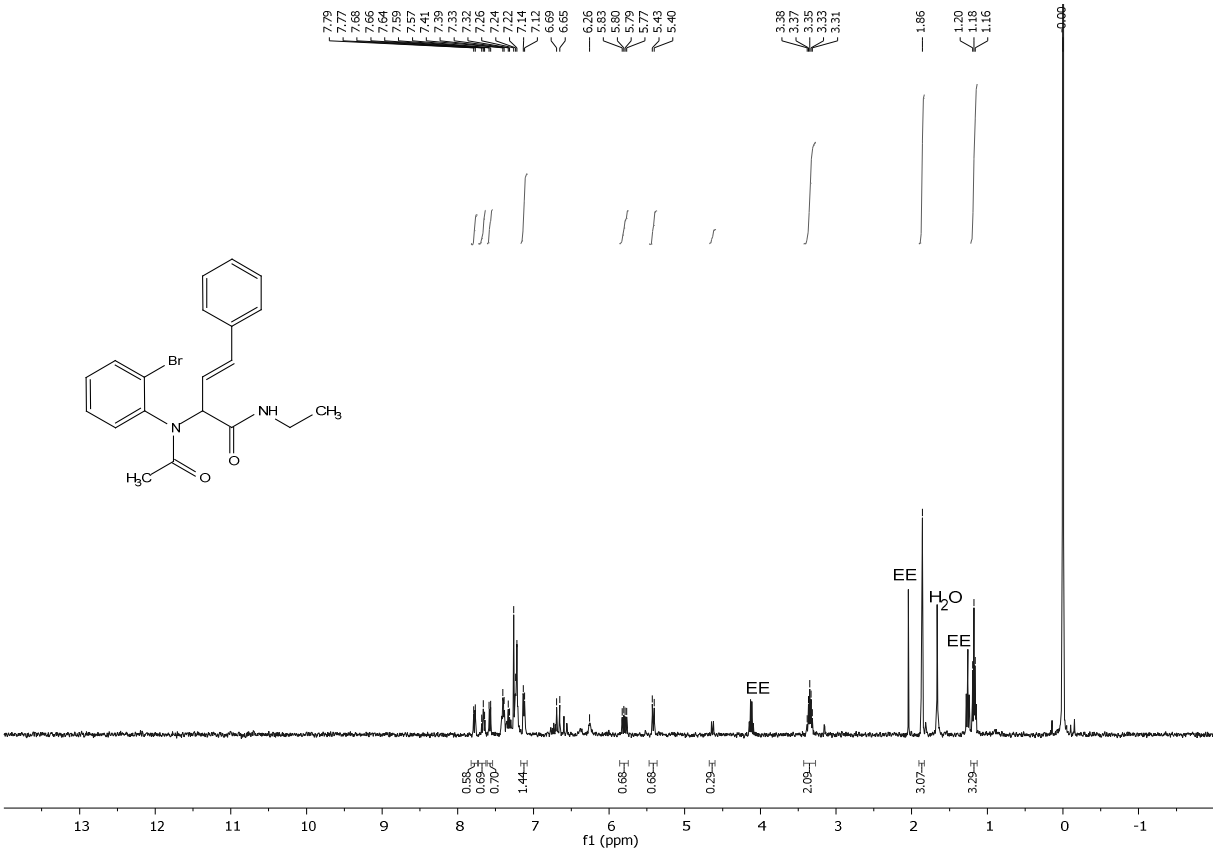
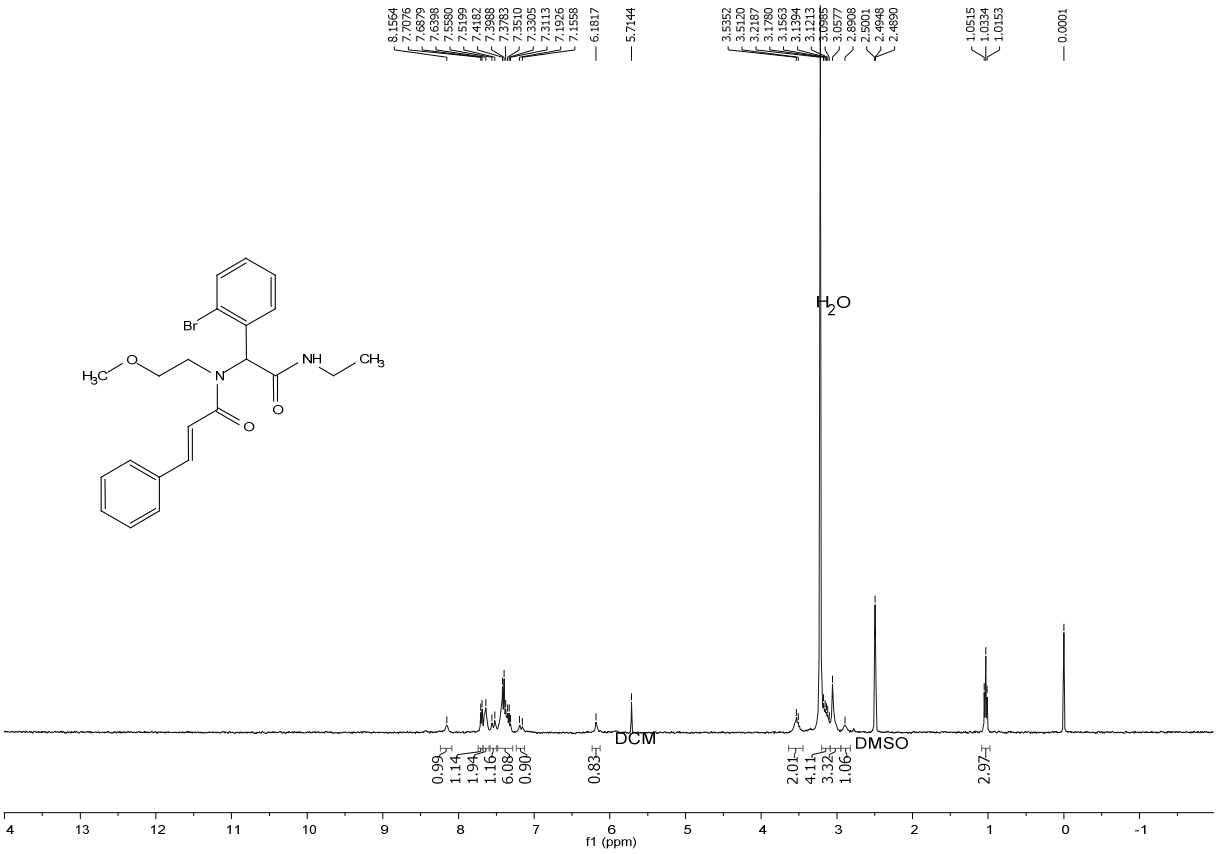
7.73
7.68
7.63
7.61
7.51
7.34
7.27
7.23
7.22
7.08
7.04
6.92
6.88
6.13
5.96
5.66
3.80
3.61
3.54
3.38
3.21
3.10
3.03
1.38
0.00
Br
H3C
O
N
NH
CH3
O
O
CH3
1.09
1.89
2.02
4.04
1.69
0.43
0.53
0.37
0.39
0.52
1.95
5.08
9.00
f1 (ppm)


9.21
8.24
8.22
7.78
7.74
7.55
7.54
7.53
7.39
7.37
7.31
7.29
7.27
7.26
7.08
7.04
6.99
6.97
6.95
4.45
3.84
3.82
3.80
3.79
3.77
3.65
3.64
3.63
3.60
3.59
3.54
3.52
3.51
3.27
2.71
1.12
1.10
0.95
0.94
0.00
H3C
CH3
Br
O
NH
N
O
O
0.85
0.88
1.18
3.11
3.95
1.94
0.92
0.98
0.98
1.83
2.62
1.03
2.71
3.30
f1 (ppm)


f1 (ppm)


EE
H2O
EE
EE
f1 (ppm)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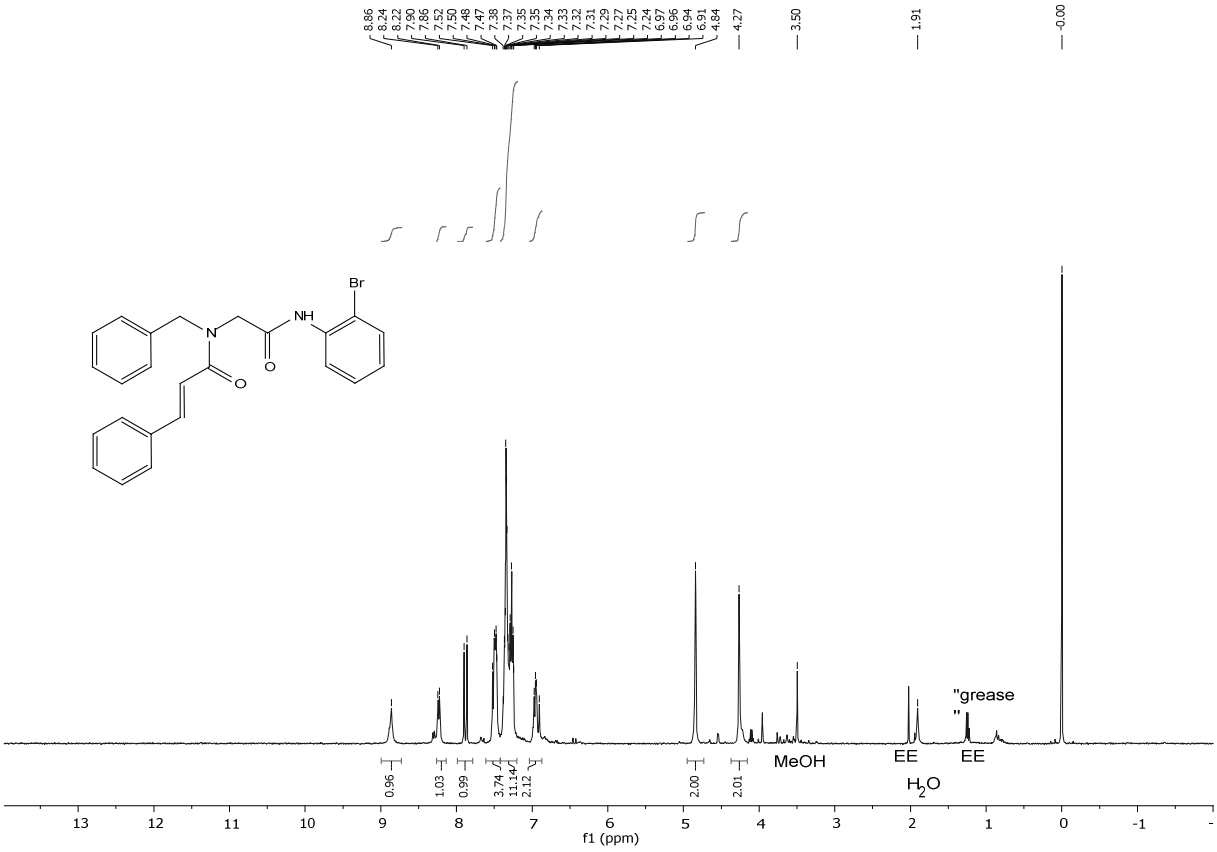
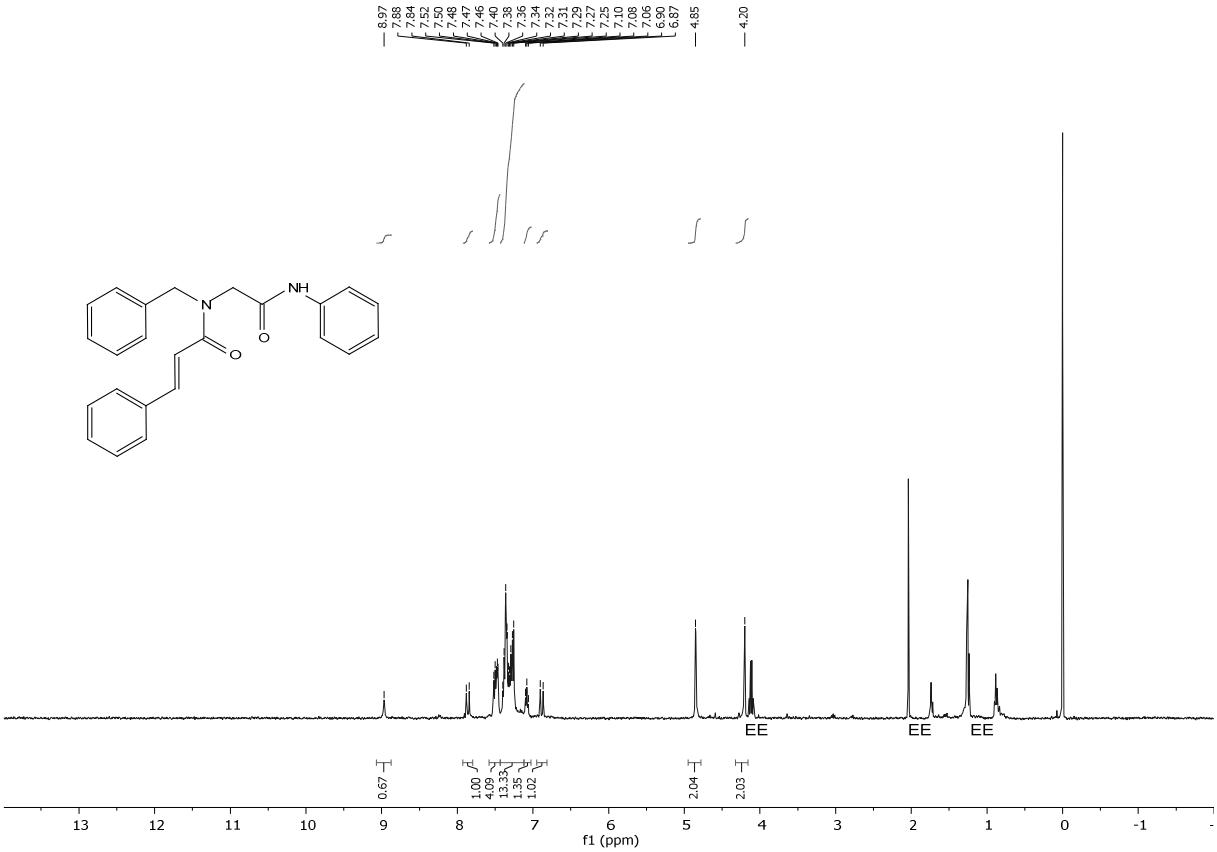
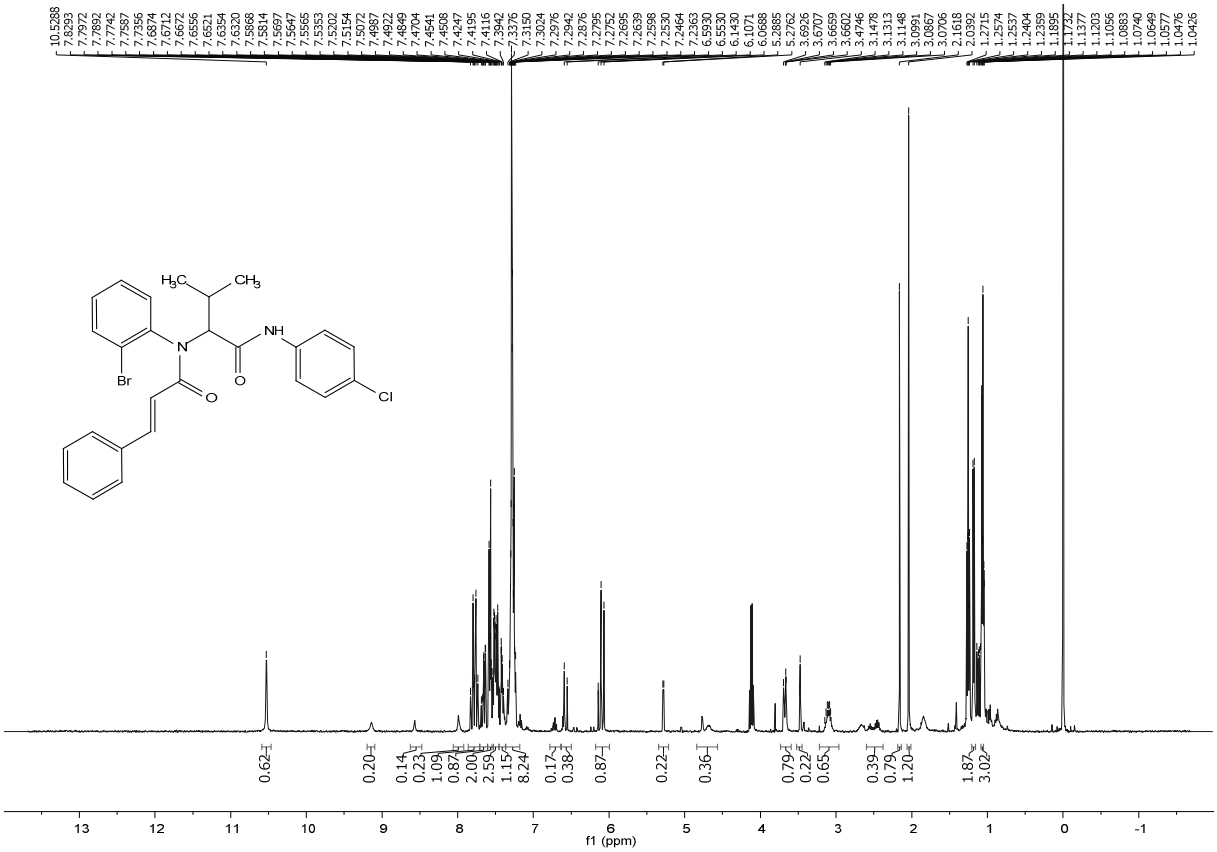
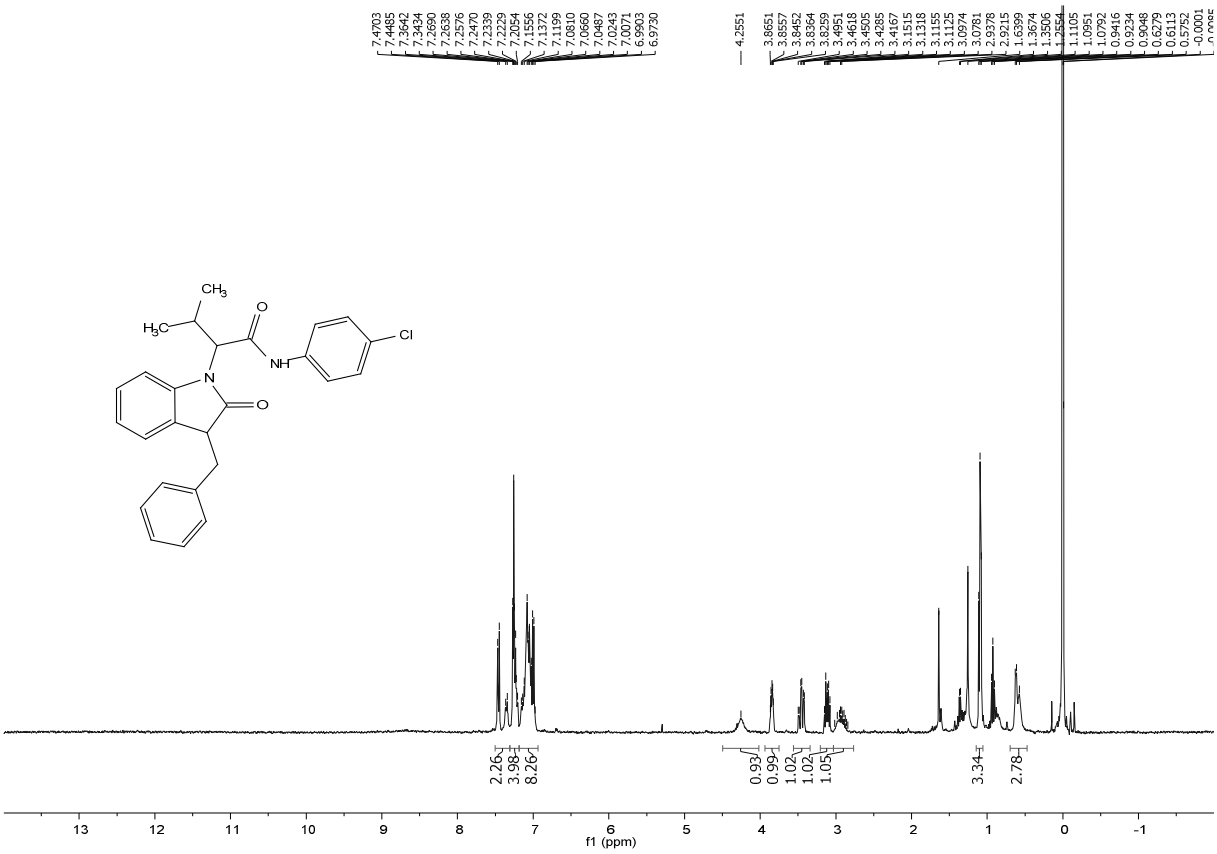
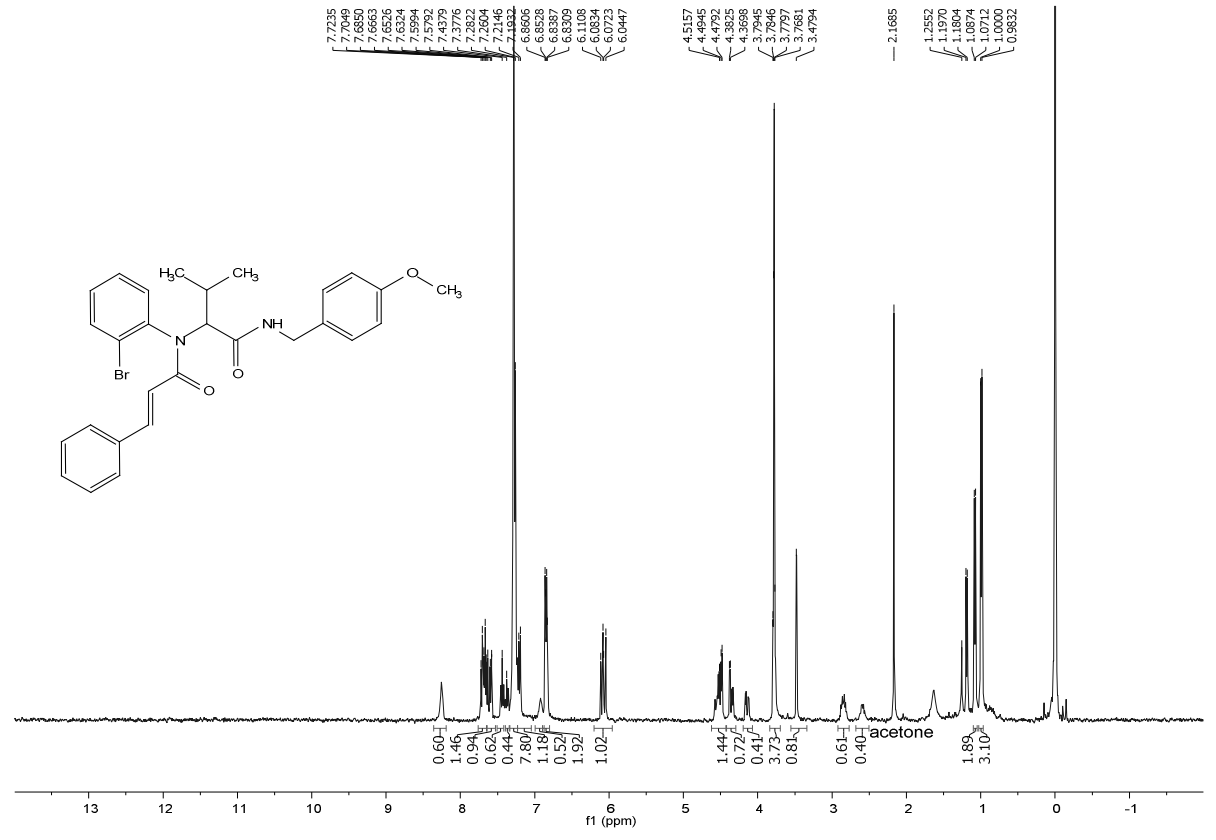
7.3783
7.3510
7.3305
7.3113
7.1926
7.1558
6.1817
5.7144
3.5352
3.5120
3.2187
3.1780
3.1563
3.1394
3.1213
3.0985
3.0577
2.8908
2.5001
2.4948
2.4690
1.0515
1.0334
1.0153
0.0001
H2O
DCM
DMSO
0.99
1.14
1.94
1.16
6.08
0.90
0.83
2.01
4.11
3.32
1.06
2.97
f1 (ppm)


8.86
8.24
8.22
7.90
7.86
7.52
7.50
7.48
7.47
7.38
7.37
7.35
7.35
7.34
7.33
7.32
7.31
7.29
7.27
7.25
7.24
6.97
6.96
6.94
6.91
4.84
4.27
3.50
1.91
-0.00
"grease
"
MeOH
EE
EE
H2O
0.96
1.03
0.99
3.74
11.14
2.12
2.00
2.01
f1 (ppm)


8.97
7.88
7.84
7.52
7.50
7.48
7.47
7.46
7.40
7.38
7.36
7.34
7.32
7.31
7.29
7.27
7.25
7.10
7.08
7.06
6.90
6.87
4.85
4.20
NH
N
O
O
EE
EE
EE
0.67
1.00
4.09
13.33
1.35
1.02
2.04
2.03
f1 (ppm)


H3C
CH3
NH
N
Br
O
O
Cl
0.62
0.20
0.14
0.23
1.09
0.87
2.00
2.59
1.15
8.24
0.17
0.38
0.87
0.22
0.36
0.79
0.22
0.65
0.39
0.79
1.20
1.87
3.02
f1 (ppm)


7.4703
7.4485
7.3642
7.3434
7.2690
7.2638
7.2376
7.2470
7.2339
7.2229
7.2054
7.1595
7.1372
7.1199
7.0810
7.0660
7.0487
7.0243
7.0071
6.9903
6.9730
4.2551
3.8651
3.8557
3.8452
3.8364
3.8259
3.4951
3.4618
3.4585
3.4285
3.4167
3.1515
3.1318
3.1155
3.1025
3.0781
2.9378
2.9215
1.6399
1.3674
1.3506
1.2554
1.1105
1.0951
1.0792
0.9416
0.9234
0.9048
0.6279
0.6113
0.5752
-0.0001
CH3
H3C
O
NH
Cl
N
O
2.26
3.98
8.26
0.93
0.99
1.02
1.02
1.05
3.34
2.78
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)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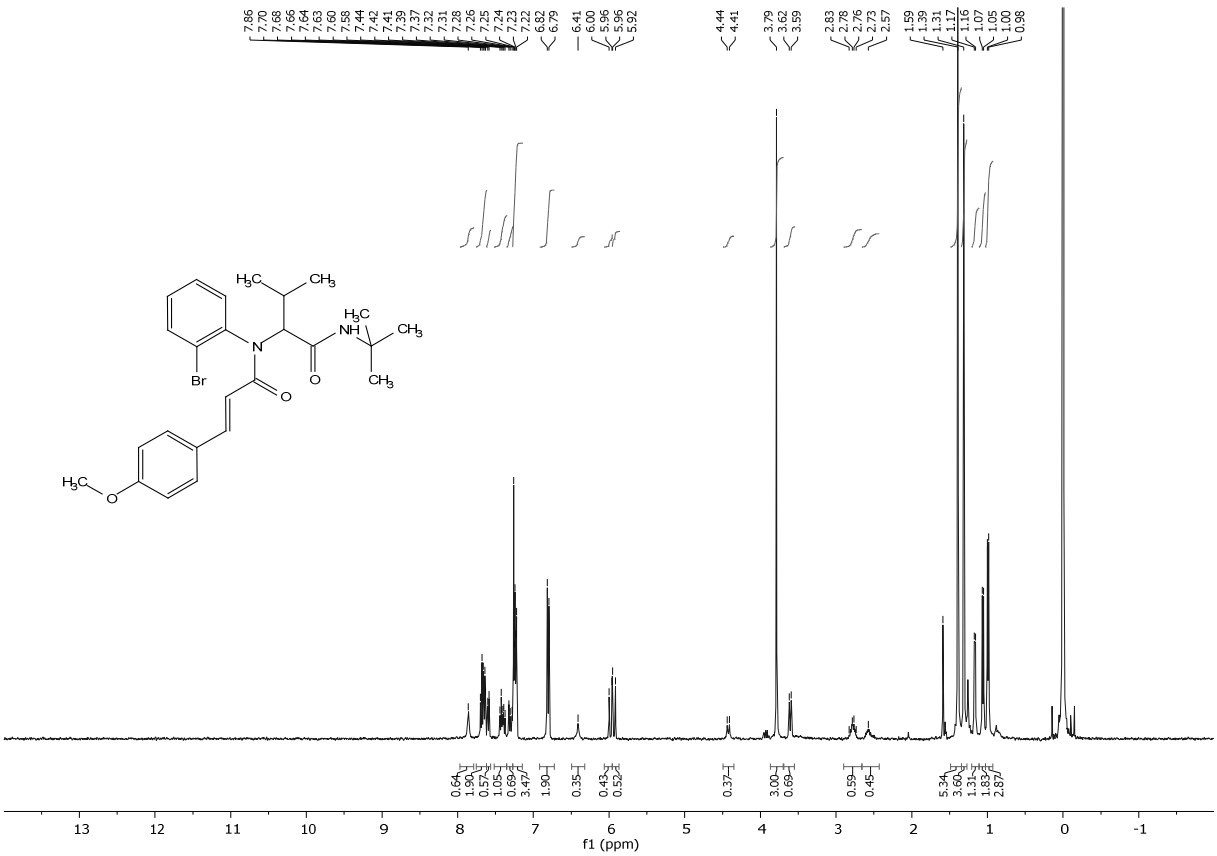
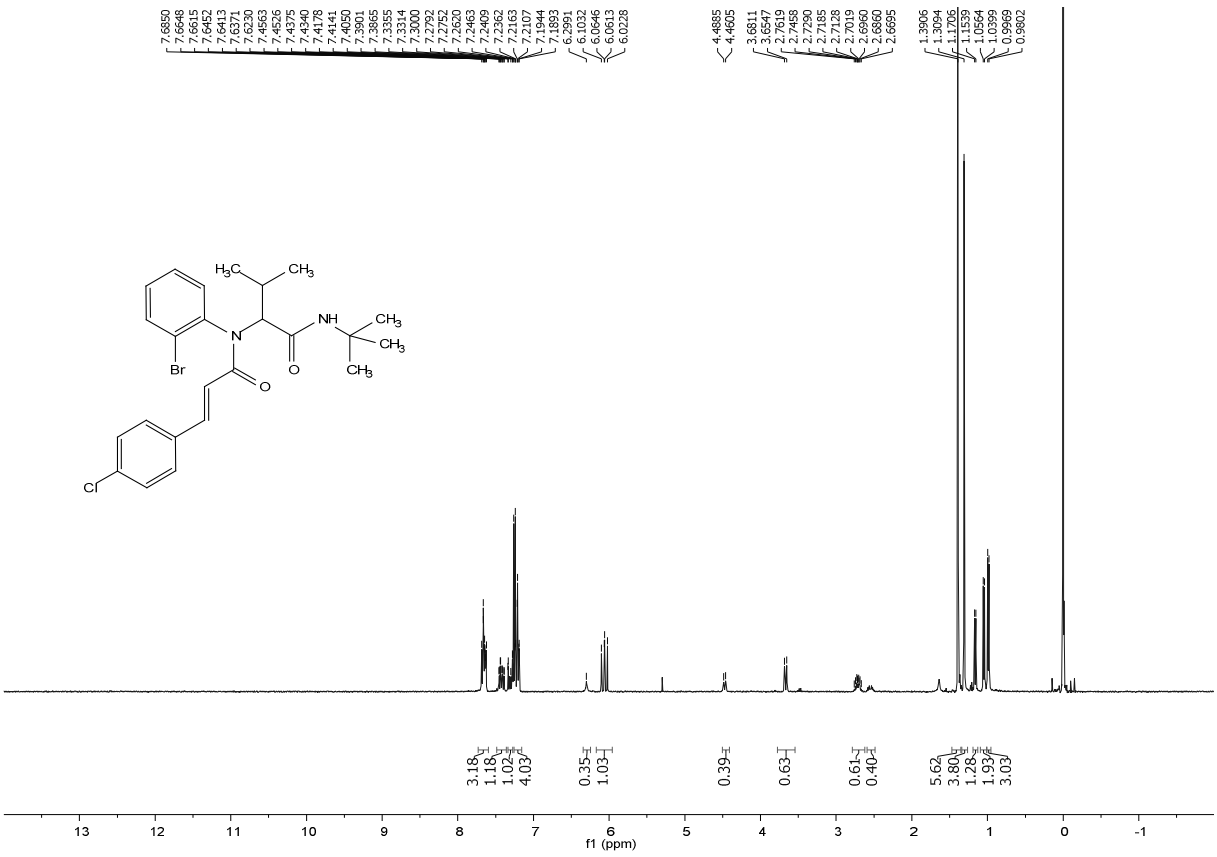
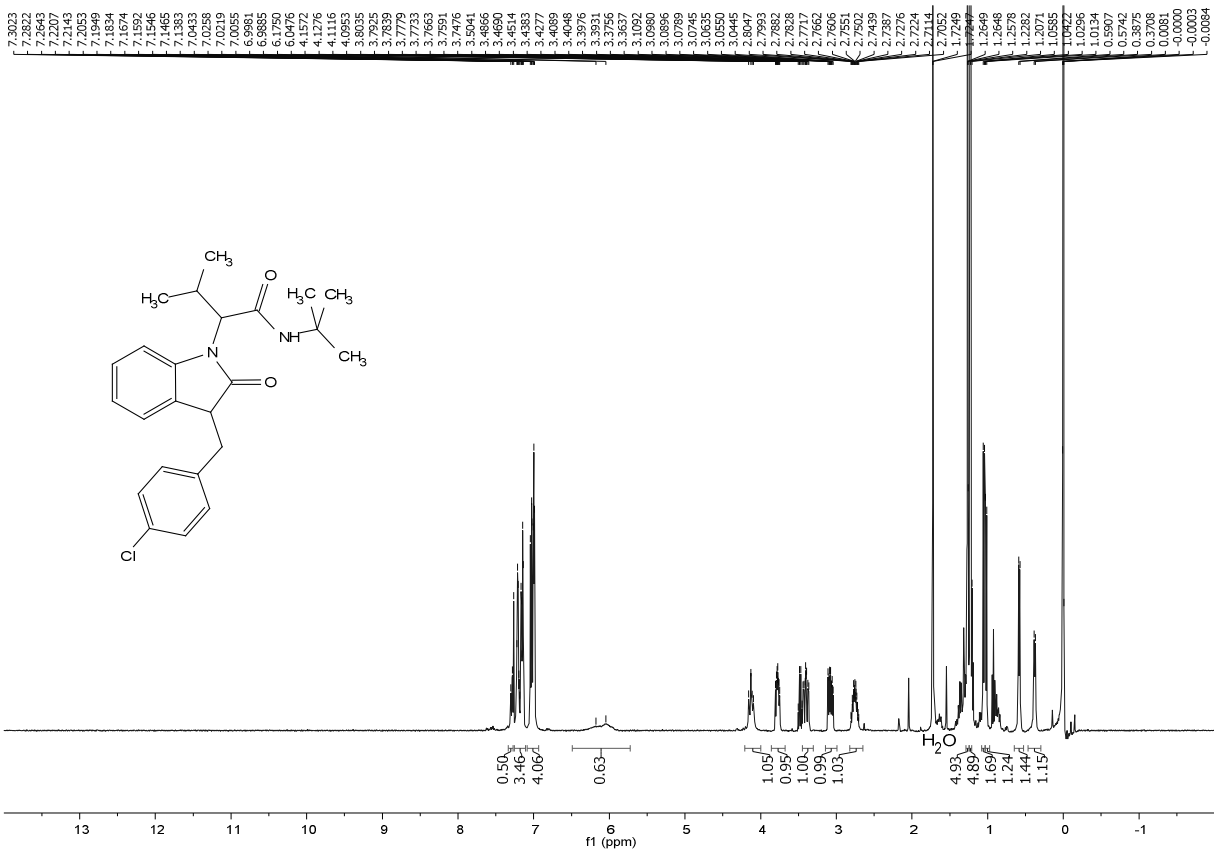
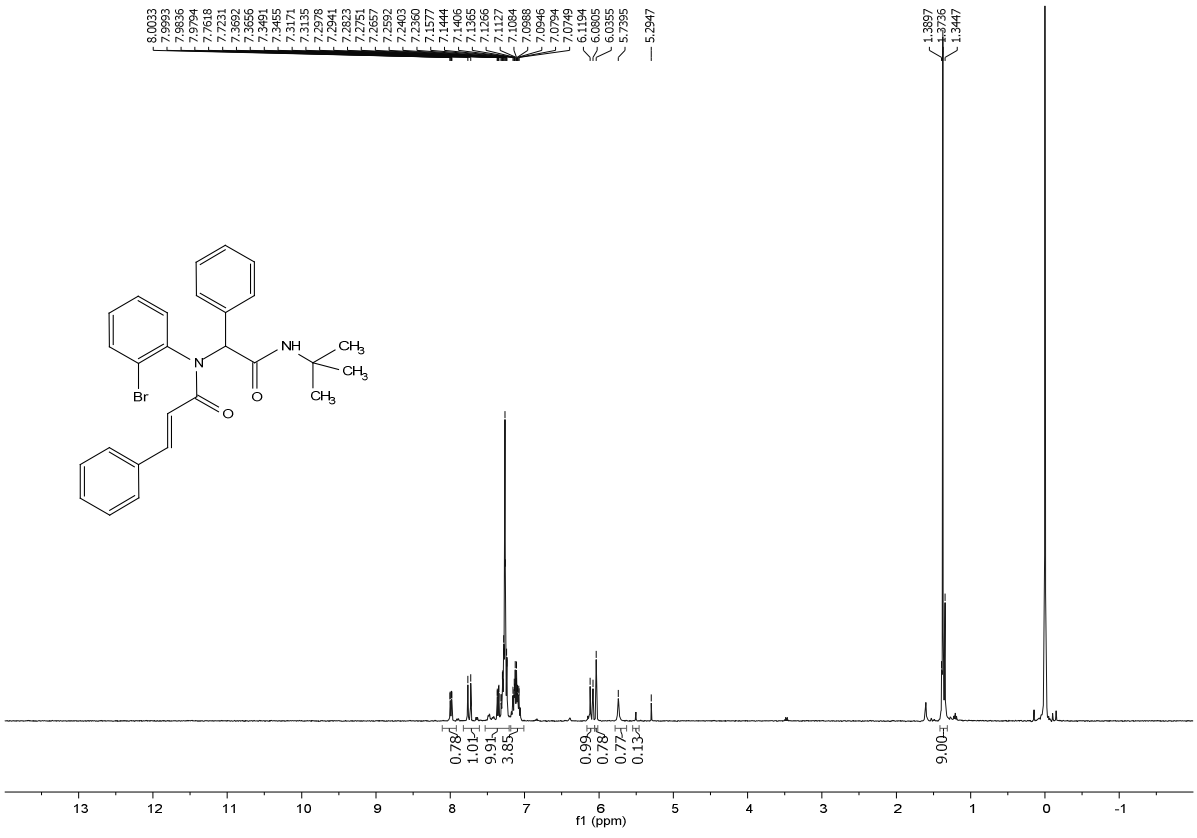
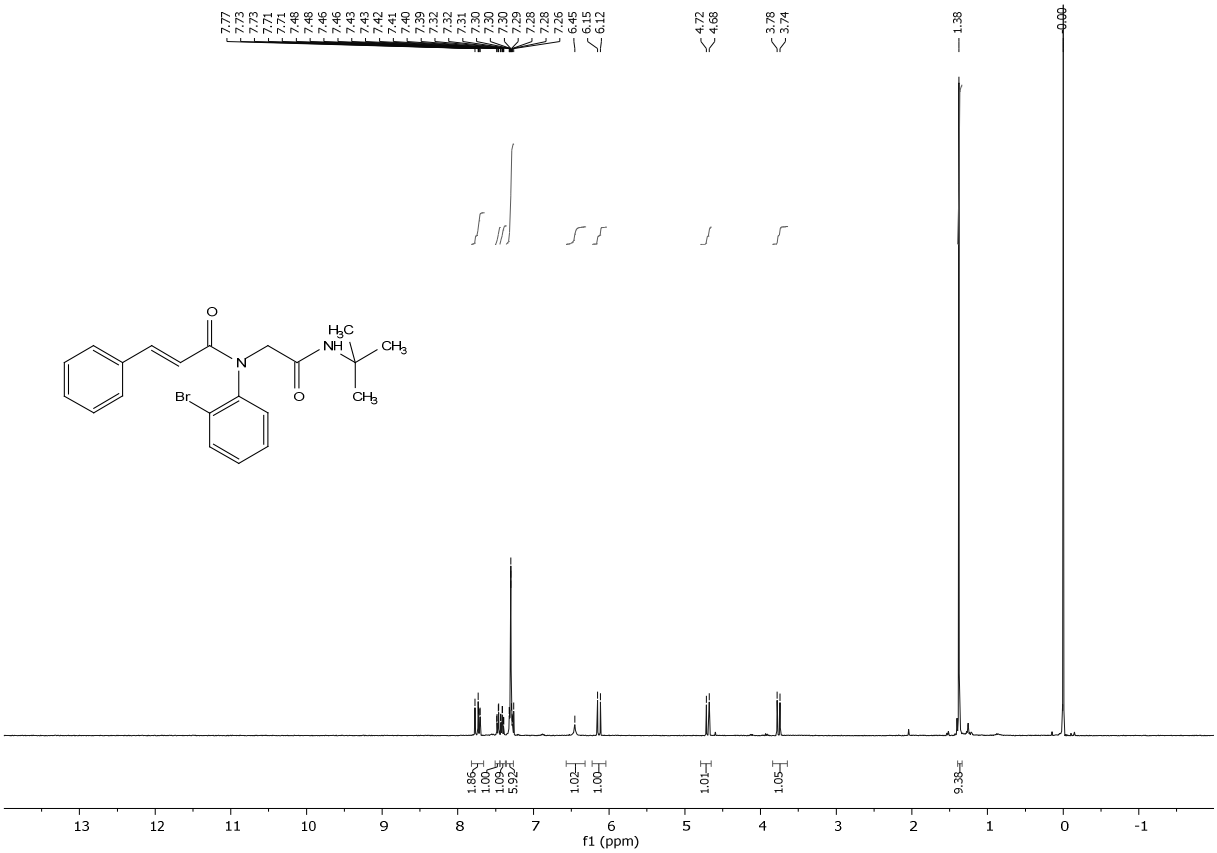
7.7049
7.6850
7.6663
7.6526
7.6324
7.5994
7.5792
7.4379
7.3776
7.2822
7.2604
7.2146
7.1932
6.8606
6.8528
6.8387
6.8309
6.1108
6.0834
6.0723
6.0447
4.5157
4.4945
4.4792
4.3825
4.3698
3.7945
3.7846
3.7797
3.7681
3.4794
2.1685
1.2552
1.1970
1.1804
1.0874
1.0712
1.0000
0.9832
H3C
CH3
O
CH3
NH
N
Br
O
O
0.60
1.46
0.94
0.62
0.44
7.80
1.18
0.52
1.92
1.02
1.44
0.72
0.41
3.73
0.81
0.61
0.40
acetone
1.89
3.10
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


7.86
7.70
7.68
7.66
7.64
7.63
7.60
7.58
7.44
7.42
7.41
7.39
7.37
7.32
7.31
7.28
7.26
7.25
7.24
7.23
7.22
6.82
6.79
6.41
6.00
5.96
5.96
5.92
4.44
4.41
3.79
3.62
3.59
2.83
2.78
2.76
2.73
2.57
1.59
1.39
1.31
1.17
1.16
1.07
1.05
1.00
0.98
0.64
1.90
0.57
1.05
0.69
3.47
1.90
0.35
0.43
0.52
0.37
3.00
0.69
0.59
0.45
5.34
3.60
1.31
1.83
2.87
f1 (ppm)


7.6850
7.6648
7.6615
7.6452
7.6413
7.6371
7.6230
7.4563
7.4536
7.4375
7.4340
7.4178
7.4141
7.4050
7.3901
7.3865
7.3355
7.3314
7.3000
7.2792
7.2752
7.2620
7.2463
7.2409
7.2362
7.2163
7.2107
7.1944
7.1893
6.2991
6.1032
6.0646
6.0613
6.0228
4.4885
4.4605
3.6811
3.6547
2.7619
2.7458
2.7290
2.7185
2.7128
2.7019
2.6960
2.6860
2.6695
1.3906
1.3094
1.1706
1.1539
1.0564
1.0399
0.9969
0.9802
3.18
1.18
1.02
4.03
0.35
1.03
0.39
0.63
0.61
0.40
5.62
3.80
1.28
1.93
3.03
f1 (ppm)


CH3
H3C
O
H3C CH3
NH
CH3
N
O
Cl
H2O
f1 (ppm)


NH
CH3
CH3
CH3
N
Br
O
O
f1 (ppm)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7.73
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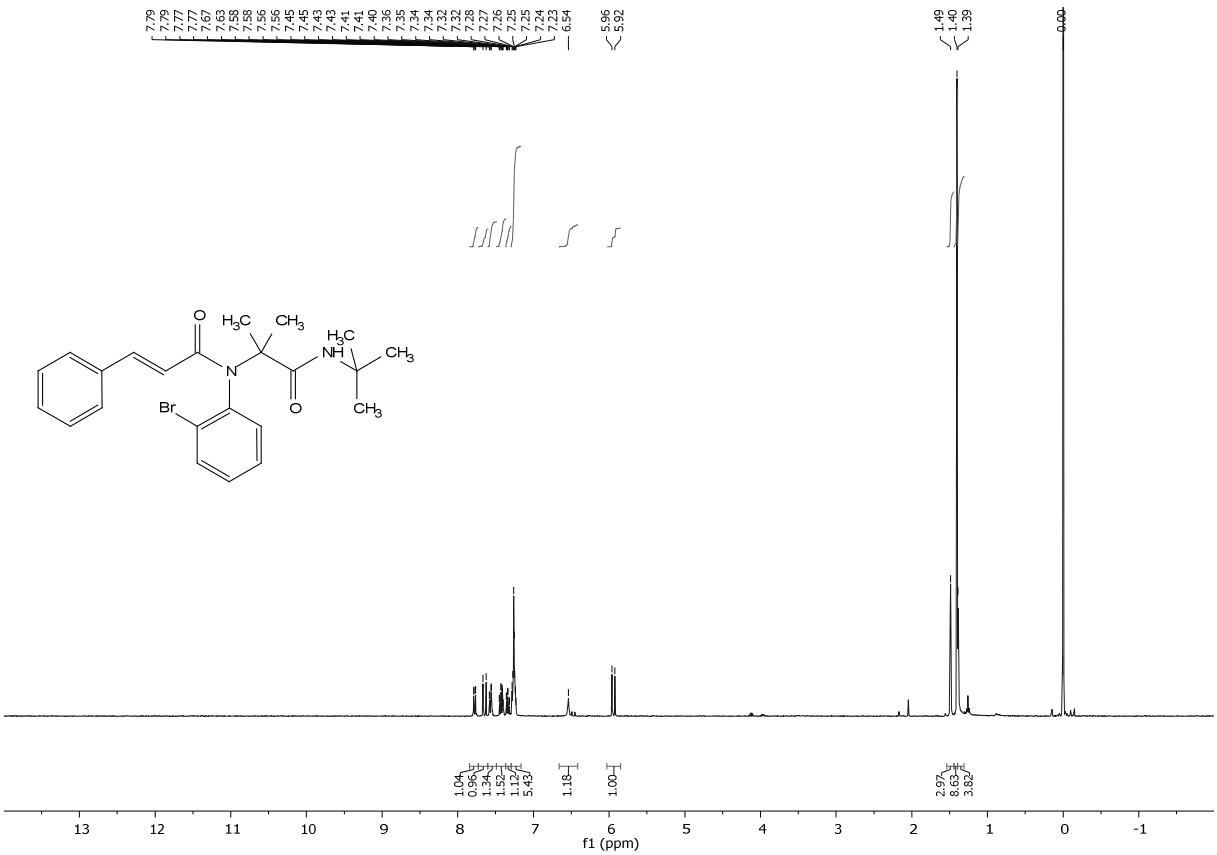
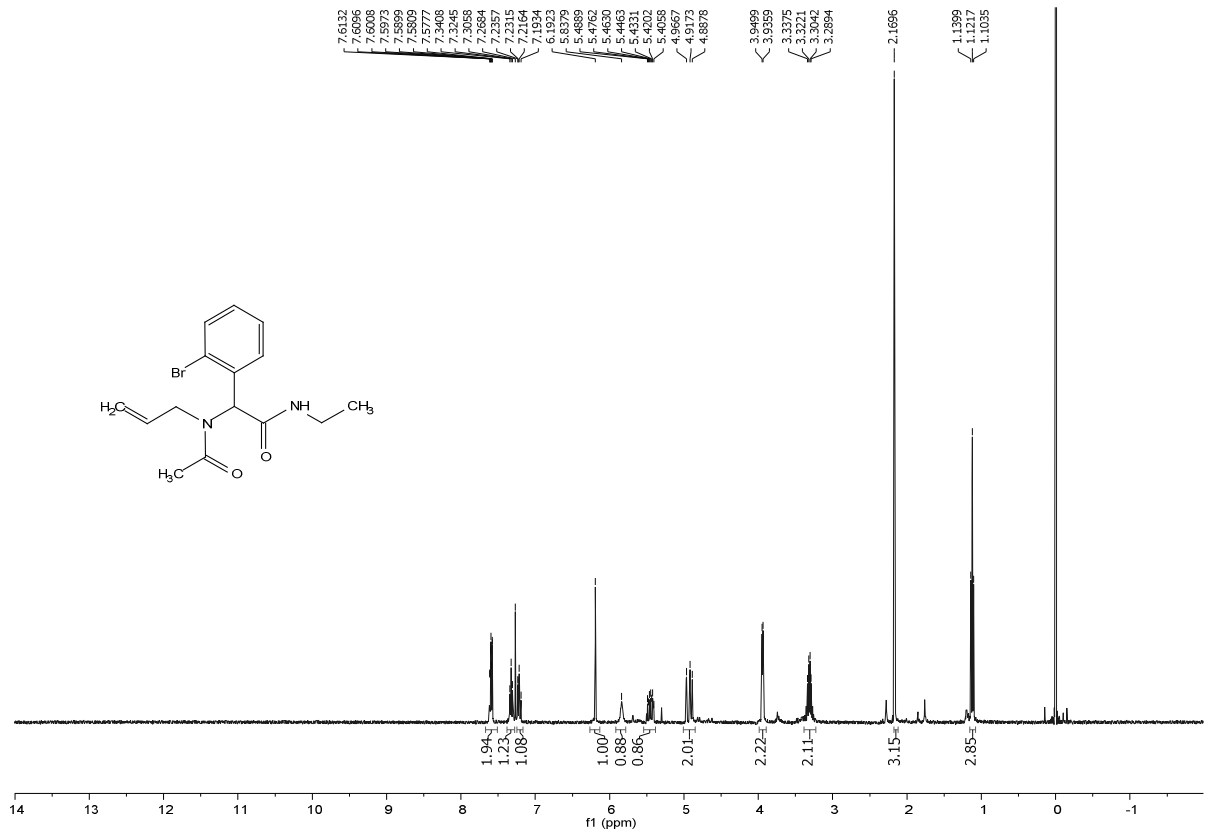
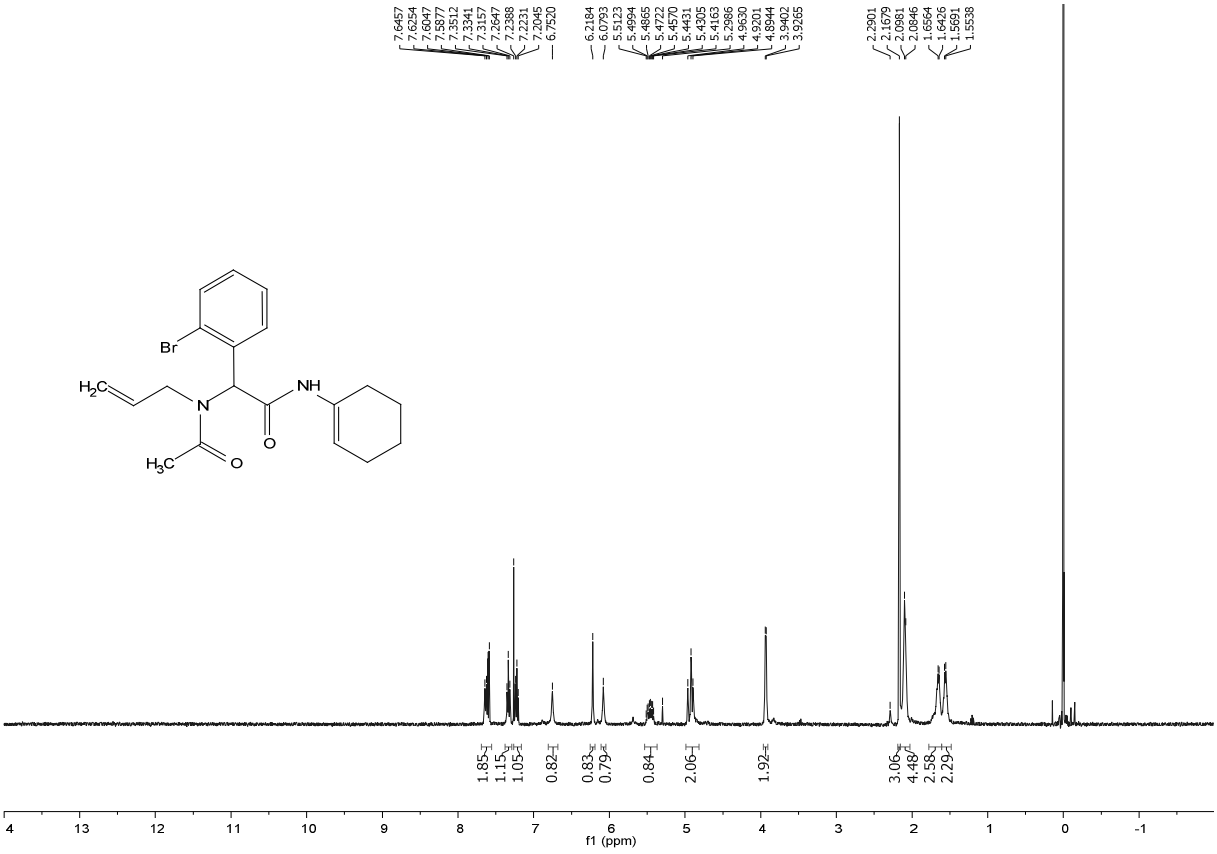
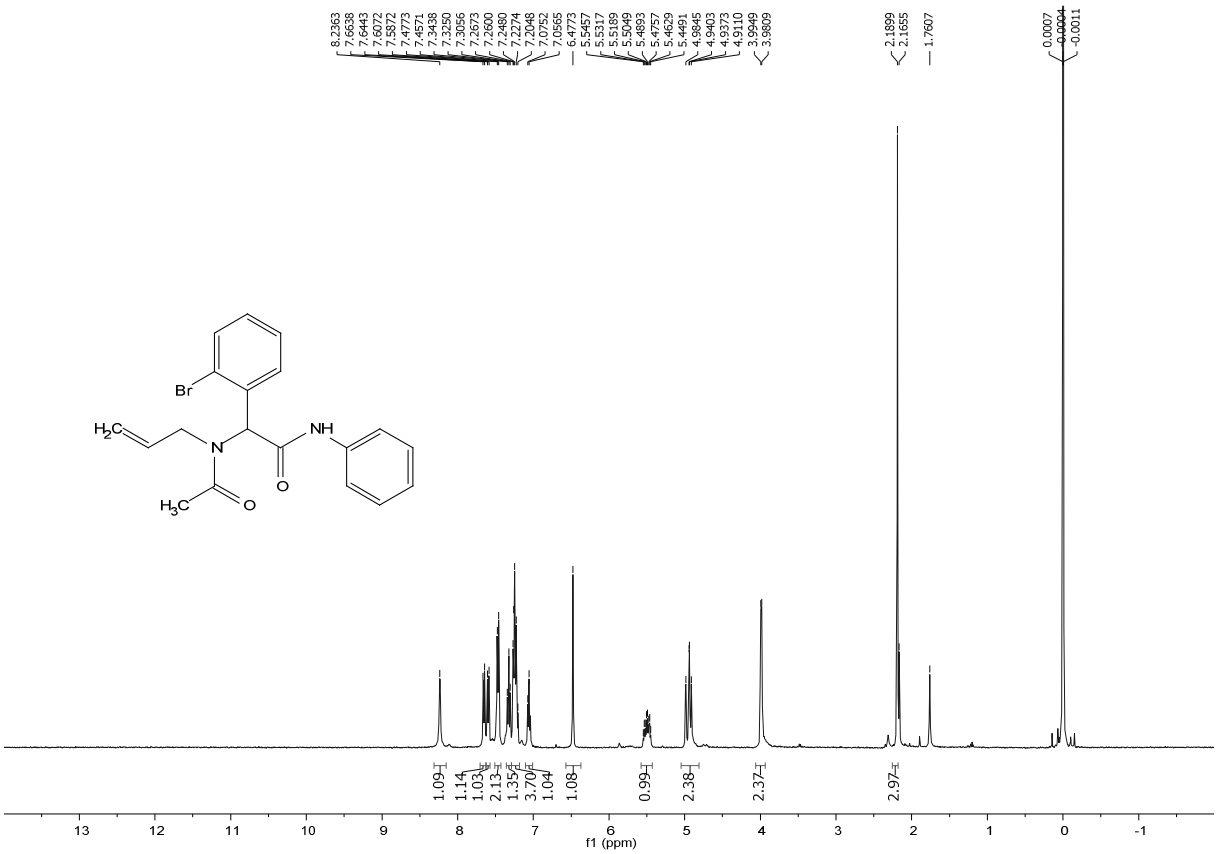
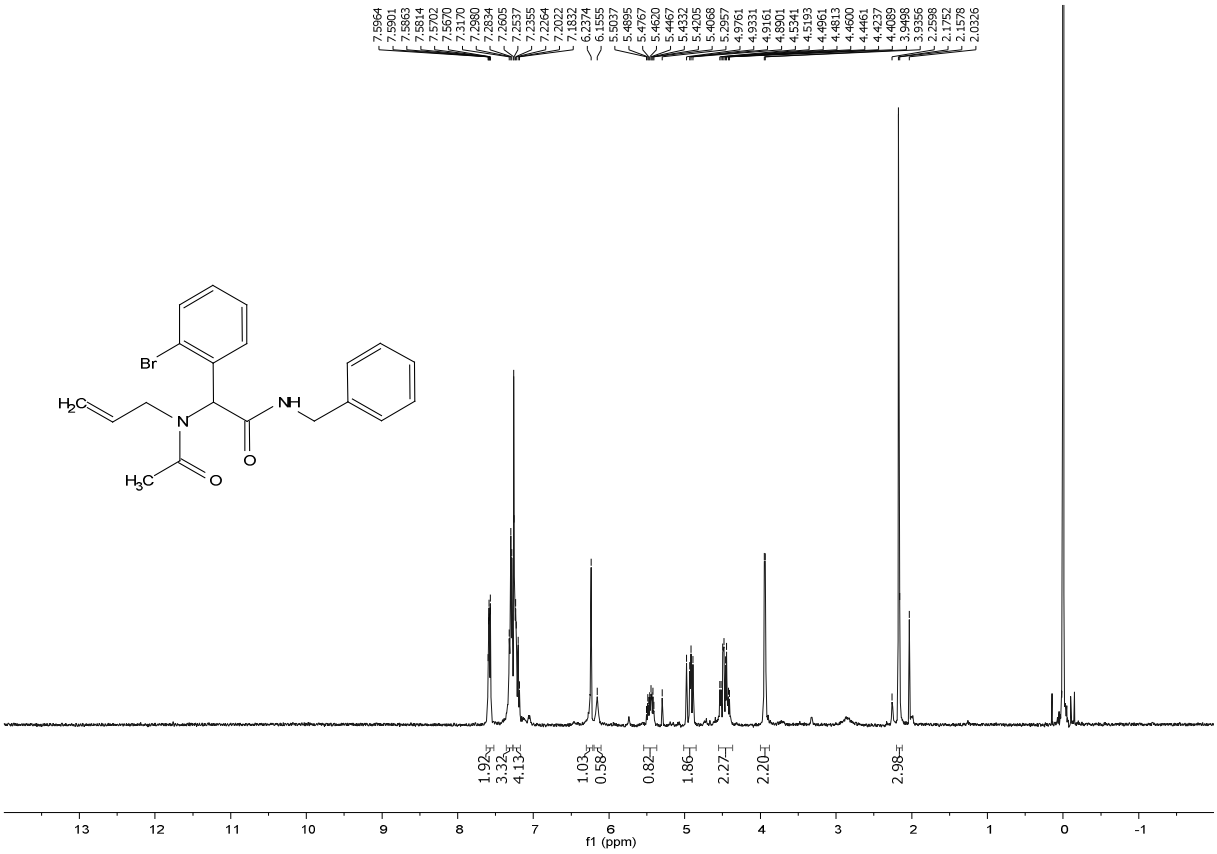
7.71
7.48
7.48
7.46
7.46
7.43
7.43
7.42
7.41
7.40
7.39
7.32
7.32
7.31
7.30
7.30
7.30
7.29
7.28
7.28
7.26
6.45
6.15
6.12
4.72
4.68
3.78
3.74
1.38
0.00
O
N
NH
H3C
CH3
O
CH3
Br
1.85
1.00
1.09
5.92
1.02
1.00
1.01
1.05
9.38
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

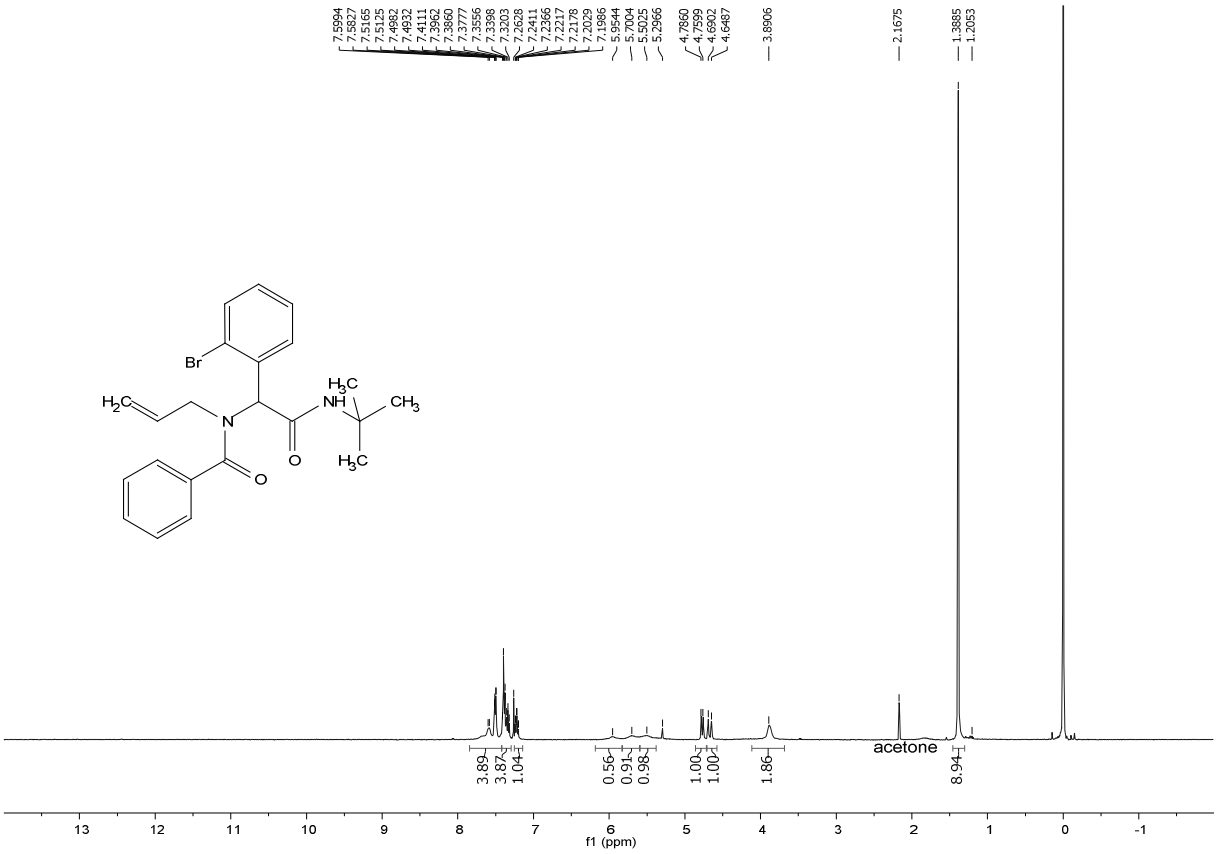

7.79
7.79
7.77
7.77
7.67
7.63
7.58
7.58
7.56
7.56
7.45
7.45
7.43
7.43
7.41
7.41
7.40
7.36
7.35
7.34
7.34
7.32
7.32
7.28
7.27
7.26
7.25
7.25
7.24
7.23
6.54
5.96
5.92
1.49
1.40
1.39
0.00
O
H3C
CH3
N
NH
H3C
CH3
O
CH3
Br
1.04
0.95
1.34
1.52
1.12
5.43
1.18
1.00
2.97
8.63
3.82
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

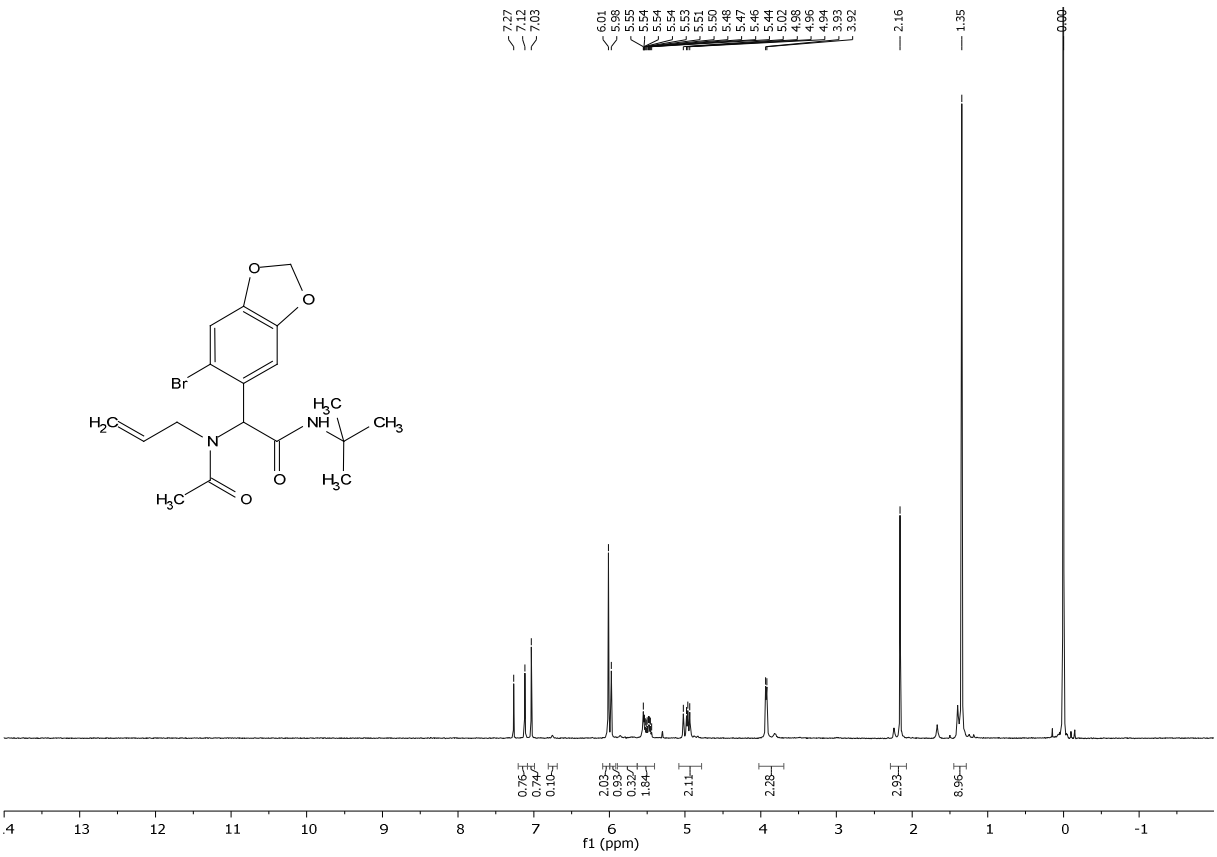

Br
H2C
N
NH
CH3
O
H3C
O
f1 (ppm)

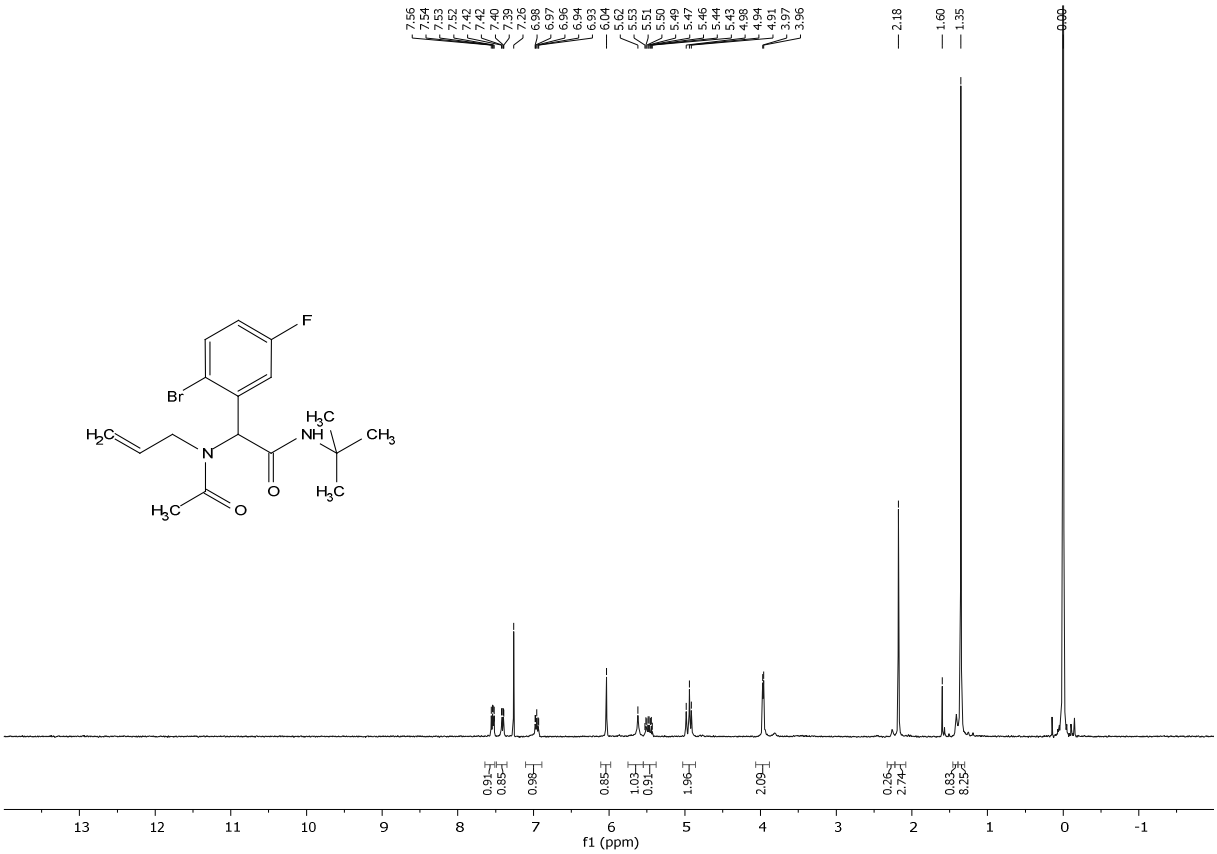

Br
H2C
N
NH
O
H3C
O
f1 (ppm)

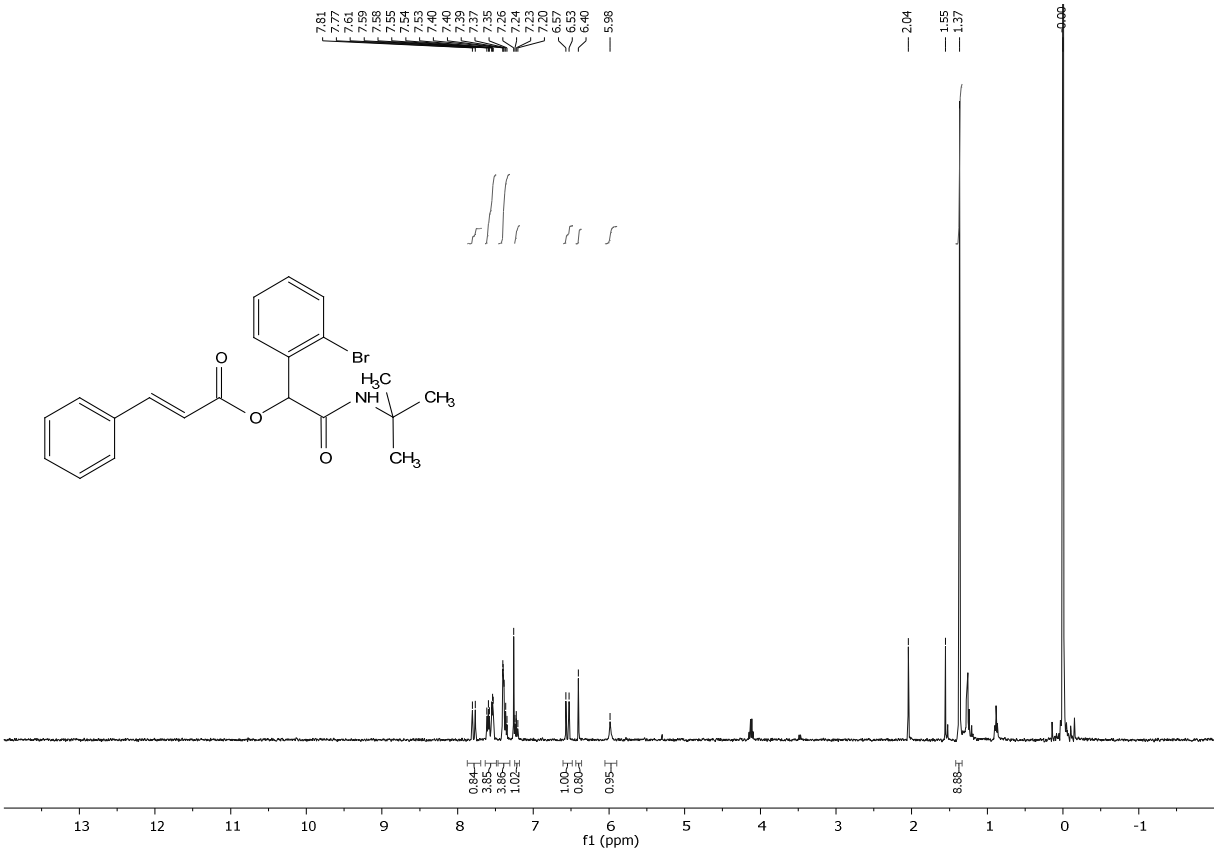

8.2363
7.6638
7.6443
7.6072
7.5872
7.4773
7.4571
7.3438
7.3250
7.3056
7.2673
7.2600
7.2480
7.2274
7.2048
7.0752
7.0565
6.4773
5.5457
5.5317
5.5189
5.5049
5.4993
5.4757
5.4659
5.4491
4.9845
4.9403
4.9373
4.9110
3.9849
3.9809
2.1899
2.1655
1.7607
0.0007
0.0000
-0.0011
Br
H2C
N
NH
O
H3C
O
1.09
1.14
1.03
2.13
1.35
3.70
1.04
1.08
0.99
2.38
2.37
2.97
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


7.5964
7.5901
7.5863
7.5814
7.5702
7.5670
7.3170
7.2980
7.2834
7.2605
7.2537
7.2355
7.2264
7.2022
7.1832
6.2374
6.1555
5.5037
5.4895
5.4767
5.4620
5.4467
5.4232
5.4205
5.4068
5.2957
4.9761
4.9331
4.9161
4.8901
4.5341
4.5193
4.4961
4.4813
4.4600
4.4461
4.4237
4.4089
3.9498
3.9356
2.2598
2.1752
2.1578
2.0326
Br
H2C
N
NH
O
H3C
O
1.92
3.32
4.13
1.03
0.58
0.82
1.86
2.27
2.20
2.98
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

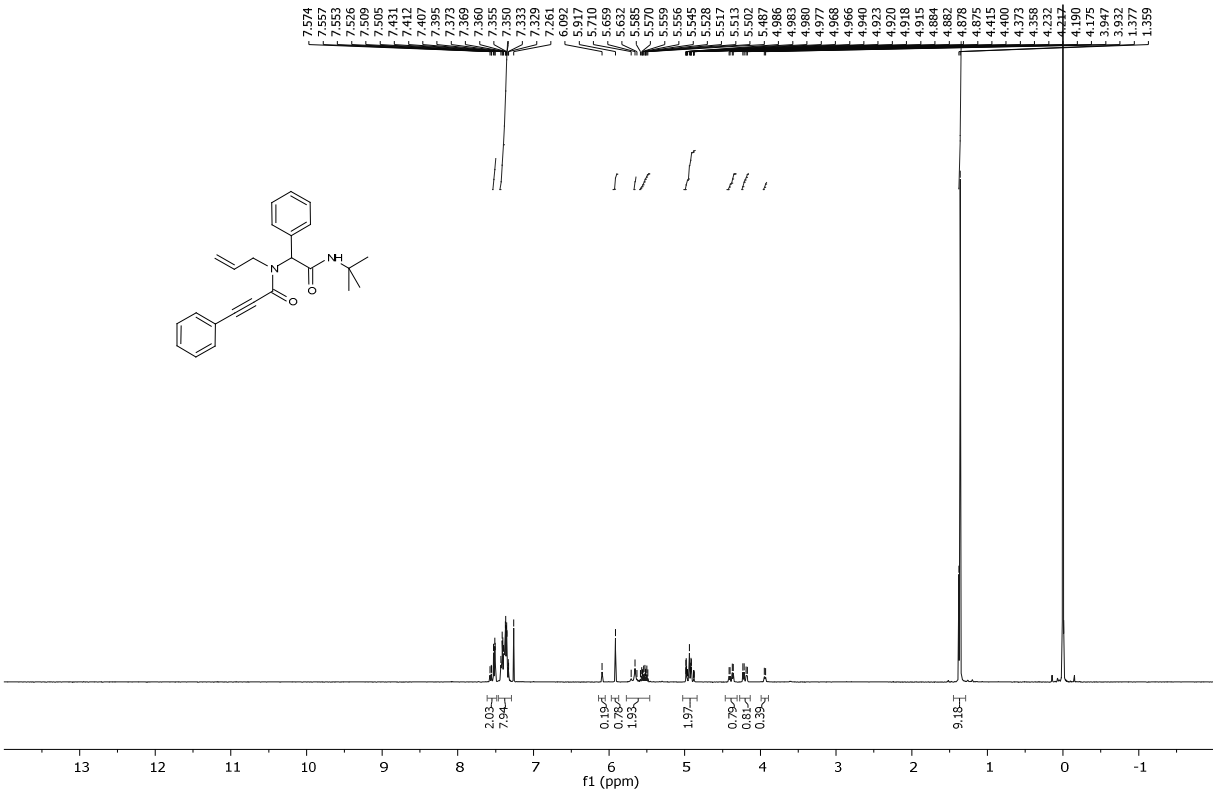

7.5994
7.5827
7.5165
7.5125
7.4982
7.4932
7.4111
7.3962
7.3860
7.3777
7.3556
7.3398
7.3203
7.2628
7.2411
7.2366
7.2217
7.2178
7.2029
7.1986
5.9944
5.7004
5.5025
5.2966
4.7860
4.7599
4.6902
4.6487
3.8906
2.1675
1.3885
1.2053
Br
H2C
N
NH
H3C
CH3
O
O
H3C
acetone
3.89
3.87
1.04
0.56
0.91
0.98
1.00
1.00
1.86
8.94
f1 (ppm)

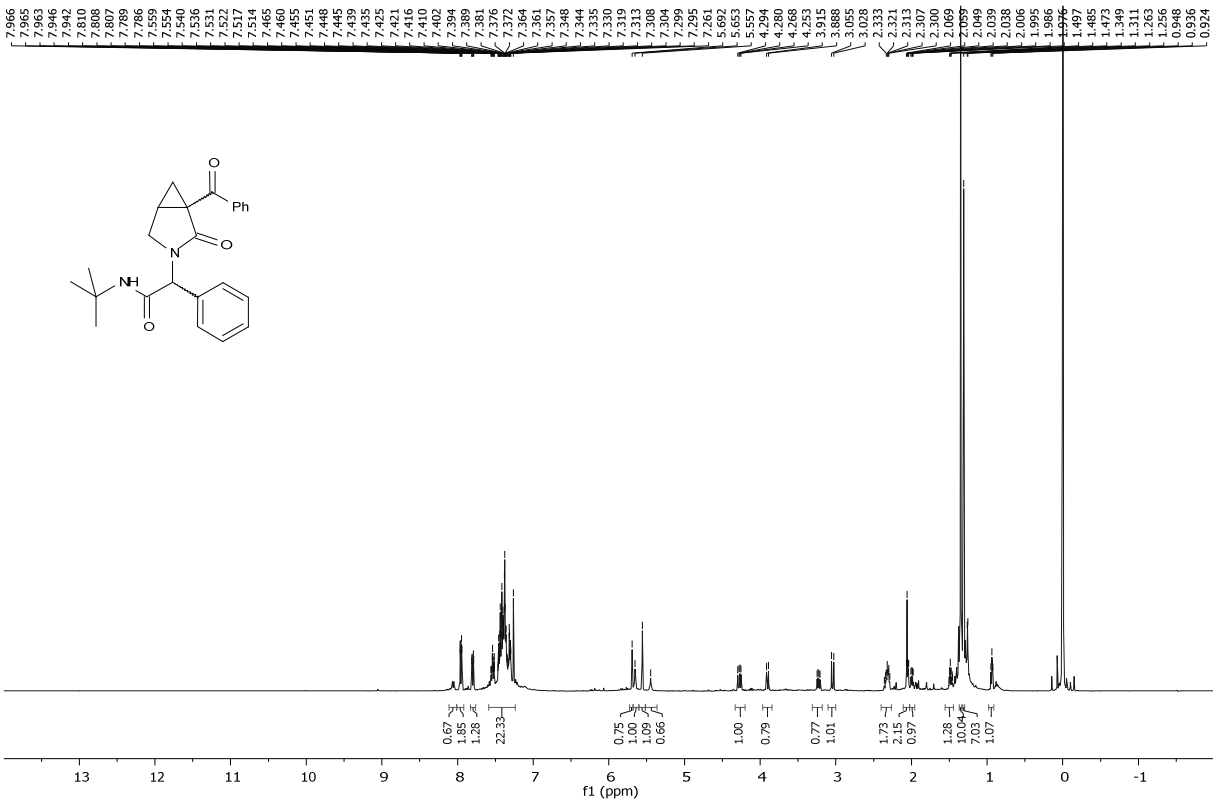

7.27
7.12
7.03
6.01
5.98
5.55
5.54
5.54
5.54
5.53
5.51
5.50
5.48
5.47
5.46
5.44
5.02
4.98
4.96
4.94
3.93
3.92
2.16
1.35
0.00
O
O
Br
H2C
N
NH
H3C
CH3
O
H3C
O
0.76
0.74
0.10
2.03
0.93
0.32
1.84
2.11
2.28
2.93
8.96
f1 (ppm)

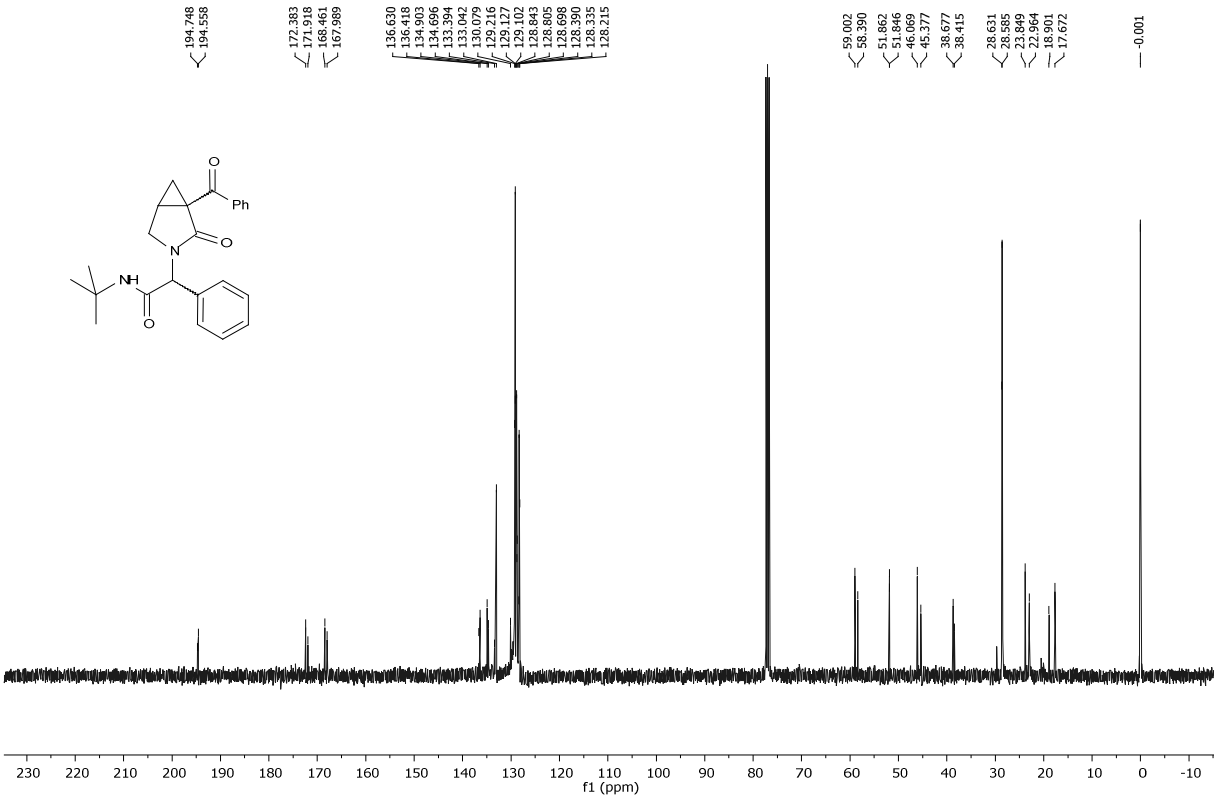

F
Br
H2C
N
H3C
NH
CH3
O
H3C
O
H3C
f1 (ppm)

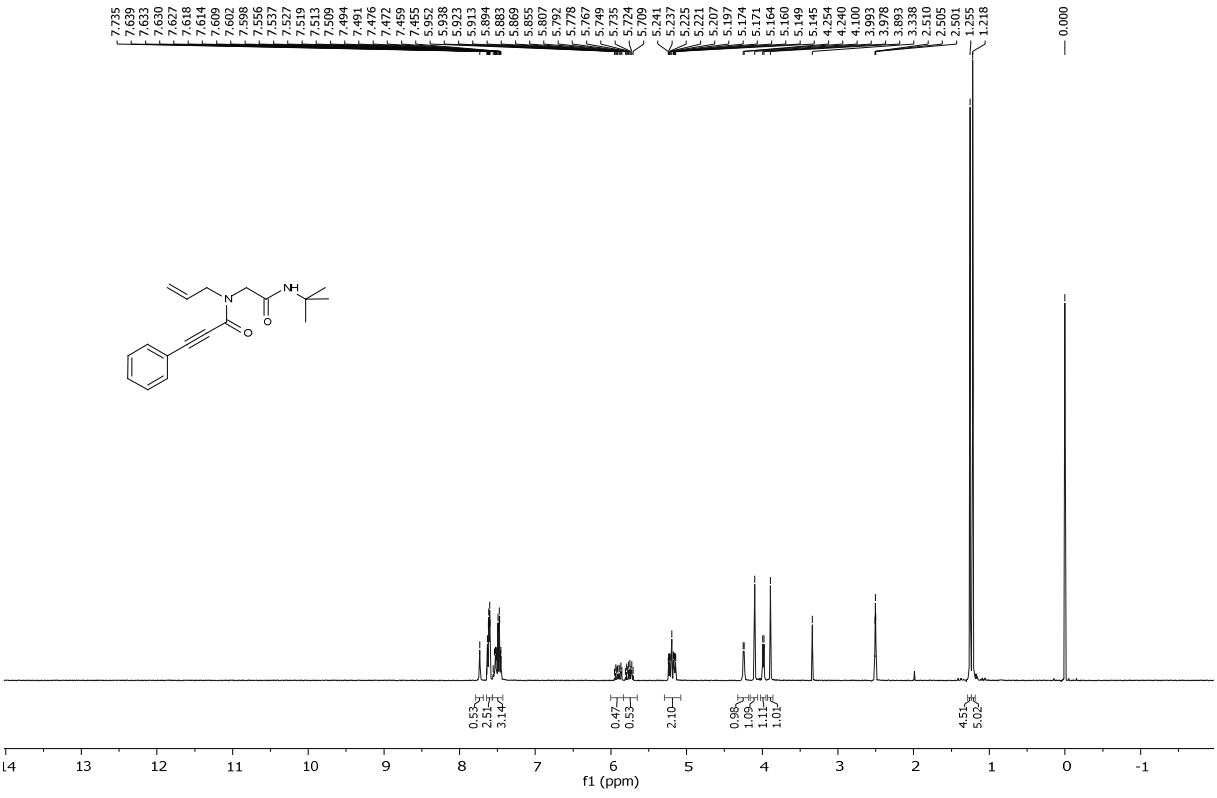

Br
O
O
H3C
NH
CH3
O
CH3
f1 (ppm)

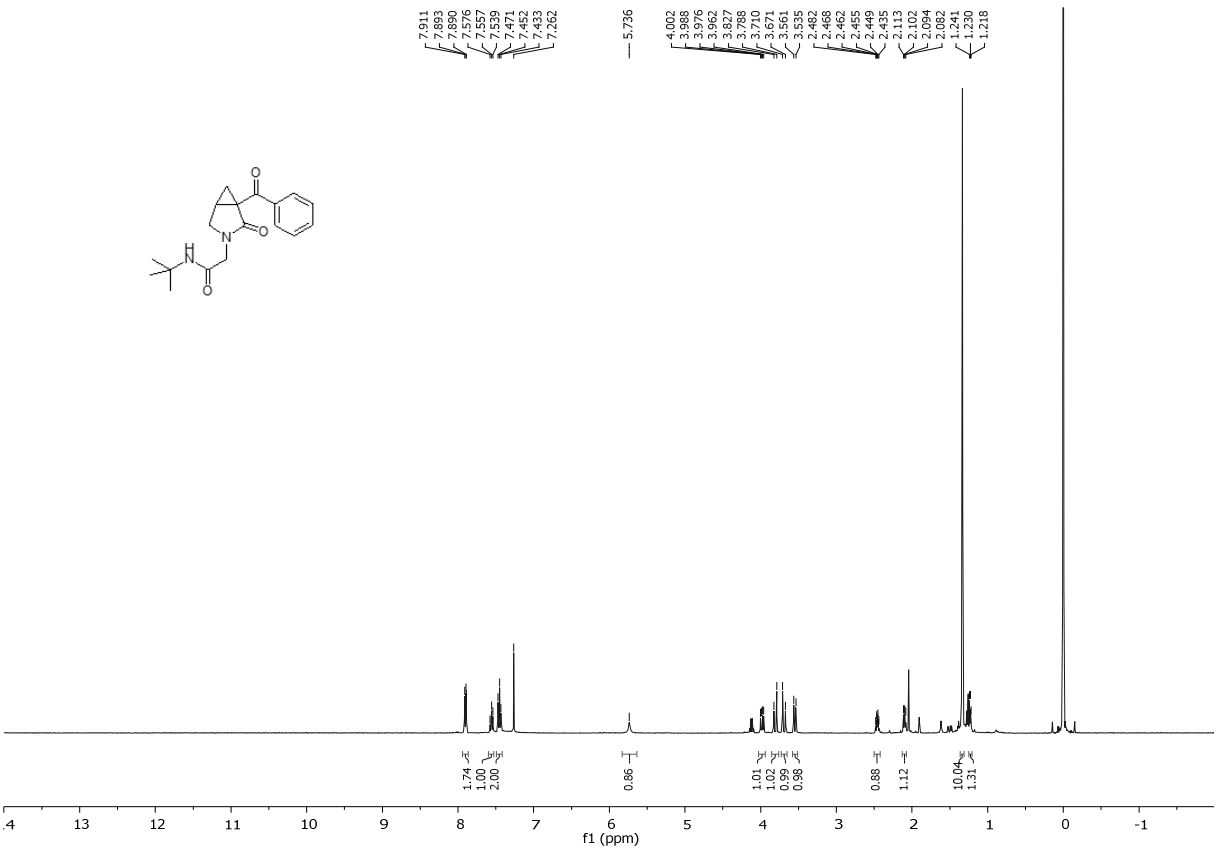
10.1.2. $Pd^{II/IV}$ catalyzed cycloaddition of 1,6-enynes (chapter 6.2)

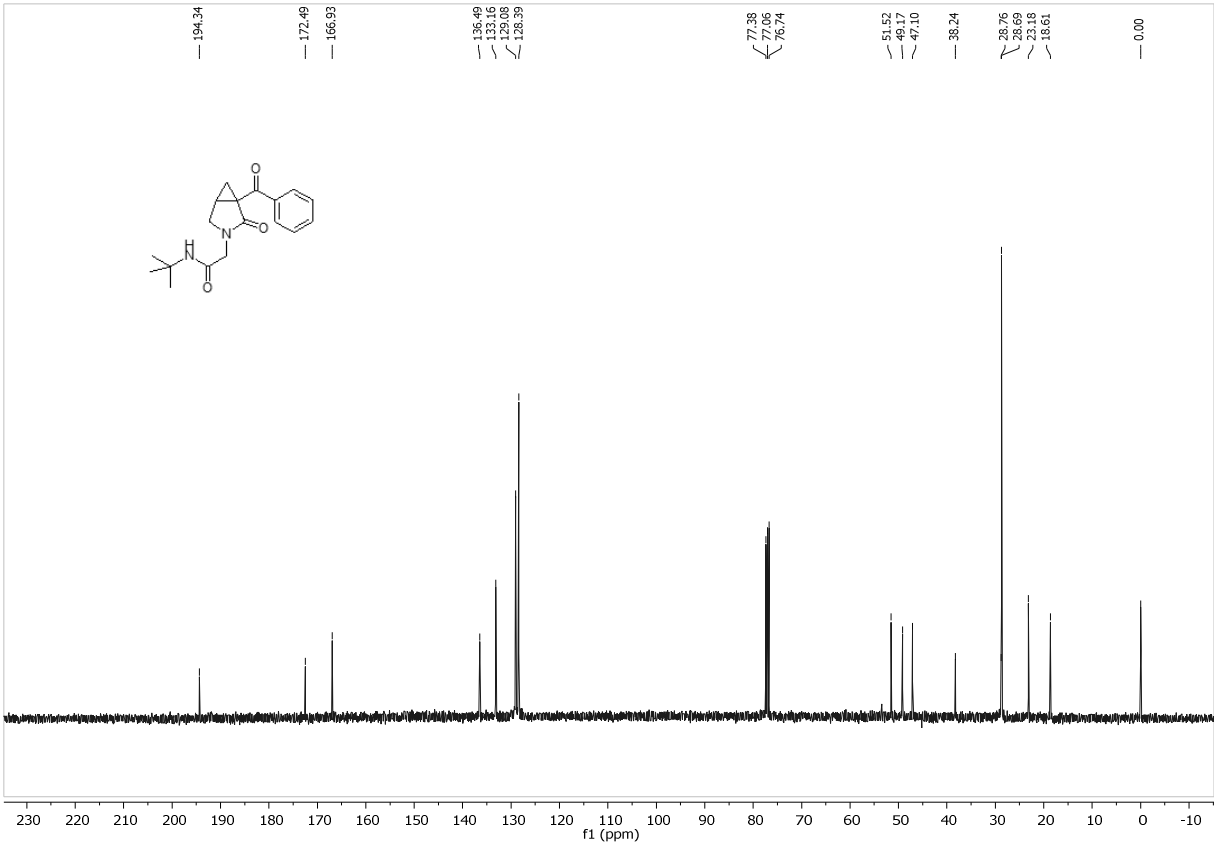


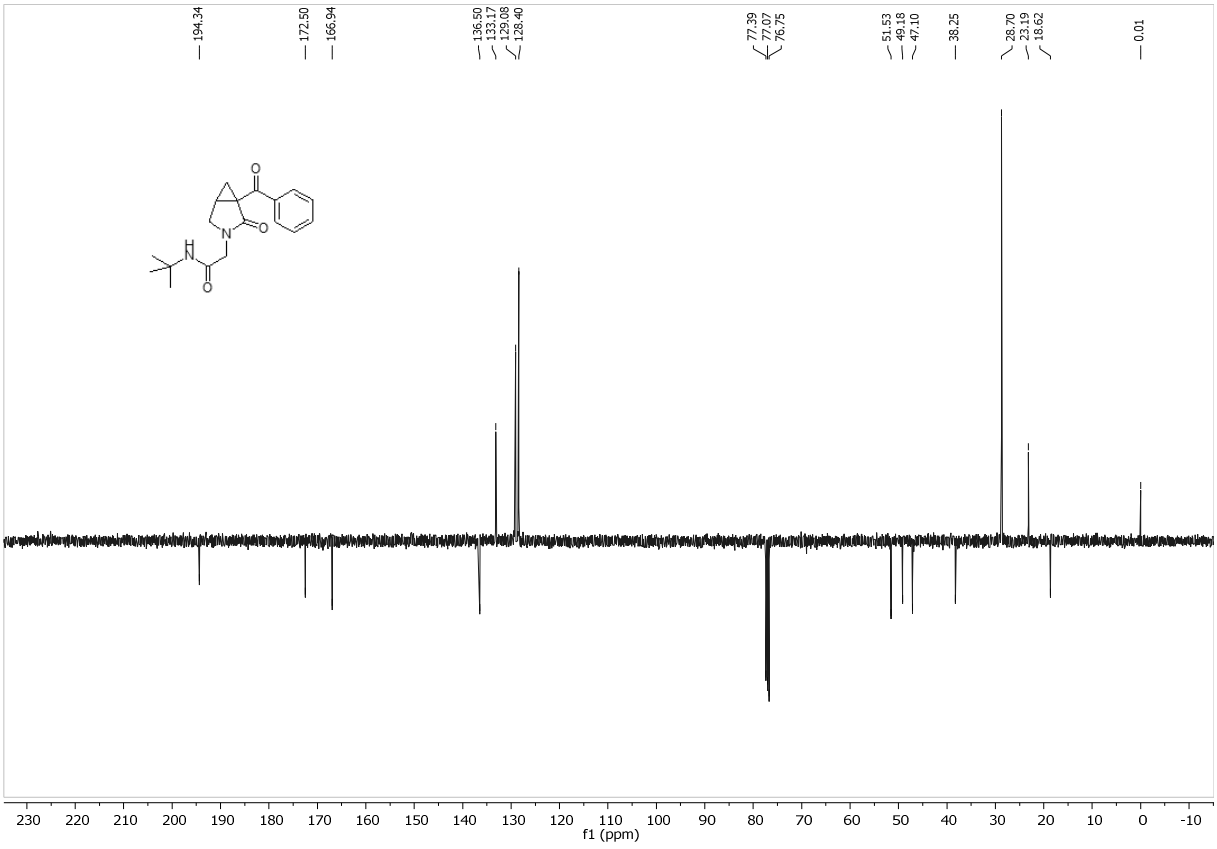


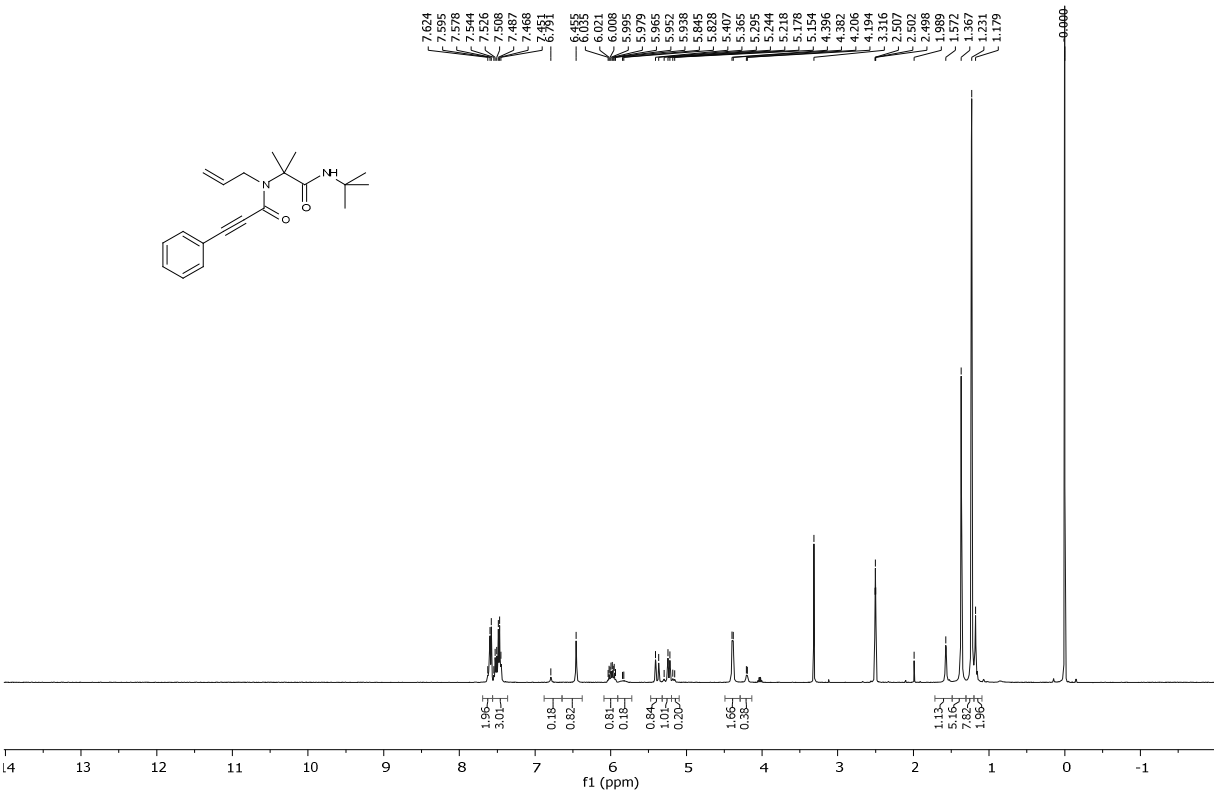

194.748
194.558
172.383
171.918
168.461
167.989
136.630
136.418
134.903
134.696
133.394
133.042
130.079
129.216
129.127
129.102
128.843
128.805
128.698
128.390
128.335
128.215
59.002
58.390
51.862
51.846
46.069
45.377
38.677
38.415
28.631
28.585
23.849
22.964
18.901
17.672
-0.001
O
Ph
O
N
NH
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.735
7.639
7.633
7.630
7.627
7.618
7.614
7.609
7.602
7.598
7.556
7.537
7.527
7.519
7.513
7.509
7.494
7.491
7.476
7.472
7.459
7.455
5.952
5.938
5.923
5.913
5.894
5.883
5.869
5.855
5.807
5.792
5.778
5.767
5.749
5.735
5.724
5.709
5.241
5.237
5.225
5.221
5.207
5.197
5.174
5.171
5.164
5.160
5.149
5.145
4.254
4.240
4.100
3.993
3.978
3.893
3.338
2.510
2.505
2.501
1.255
1.218
0.000
N
NH
O
O
0.53
2.51
3.14
0.47
0.53
2.10
0.98
1.09
1.11
1.01
4.51
5.02
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


7.911
7.893
7.890
7.576
7.557
7.539
7.471
7.452
7.433
7.262
5.736
4.002
3.988
3.976
3.962
3.827
3.788
3.710
3.671
3.561
3.535
2.482
2.468
2.462
2.455
2.449
2.435
2.113
2.102
2.094
2.082
1.241
1.230
1.218
1.74
1.00
2.00
0.86
1.01
1.02
0.99
0.98
0.88
1.12
10.04
1.31
f1 (ppm)


194.34
172.49
166.93
136.49
133.16
129.08
128.39
77.38
77.06
76.74
51.52
49.17
47.10
38.24
28.76
28.69
23.18
18.61
0.00
f1 (ppm)


194.34
172.50
166.94
136.50
133.17
129.08
128.40
77.39
77.07
76.75
51.53
49.18
47.10
38.25
28.70
23.19
18.62
0.01
f1 (ppm)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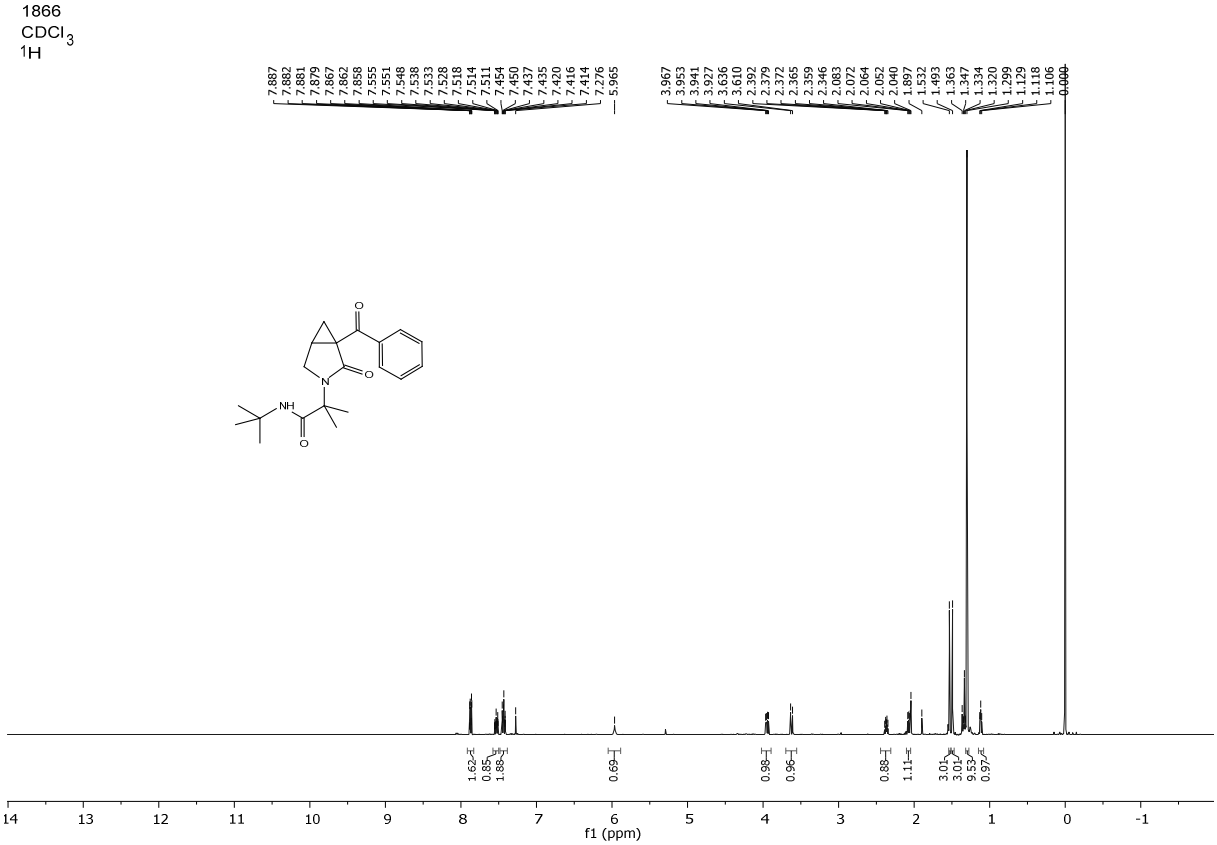
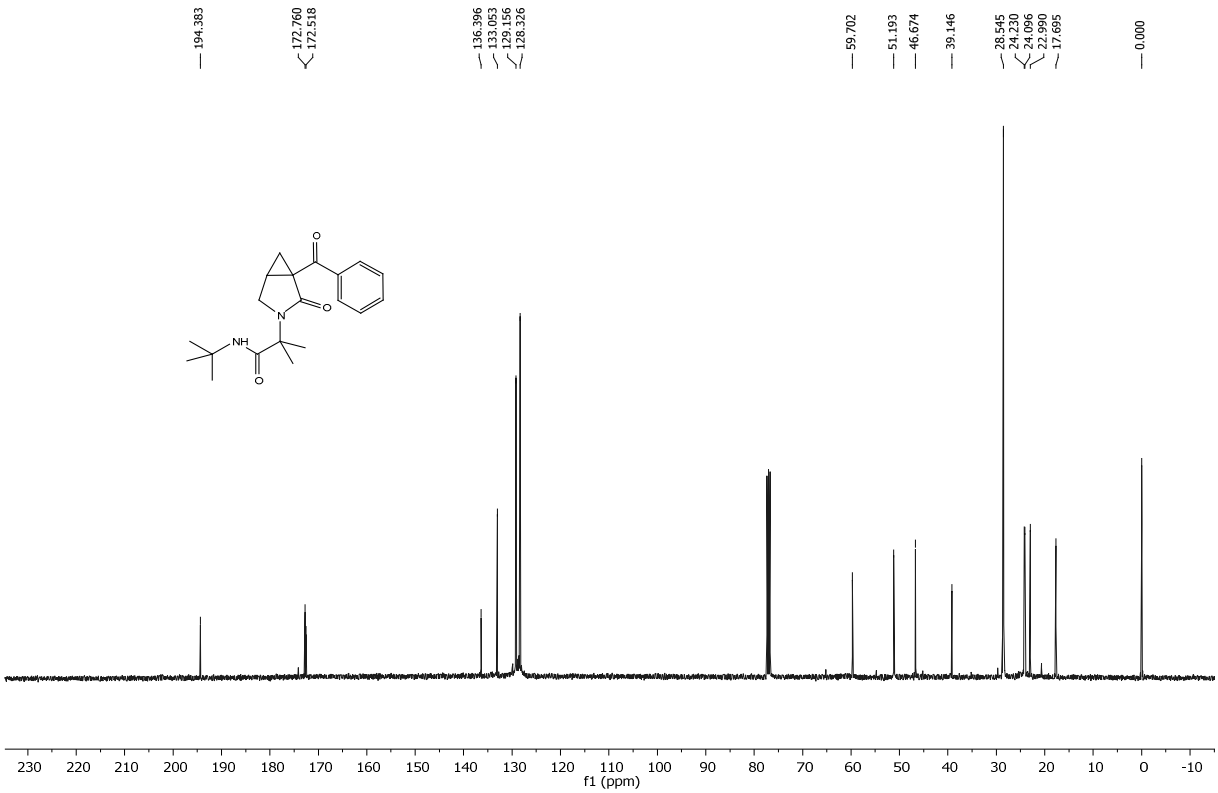
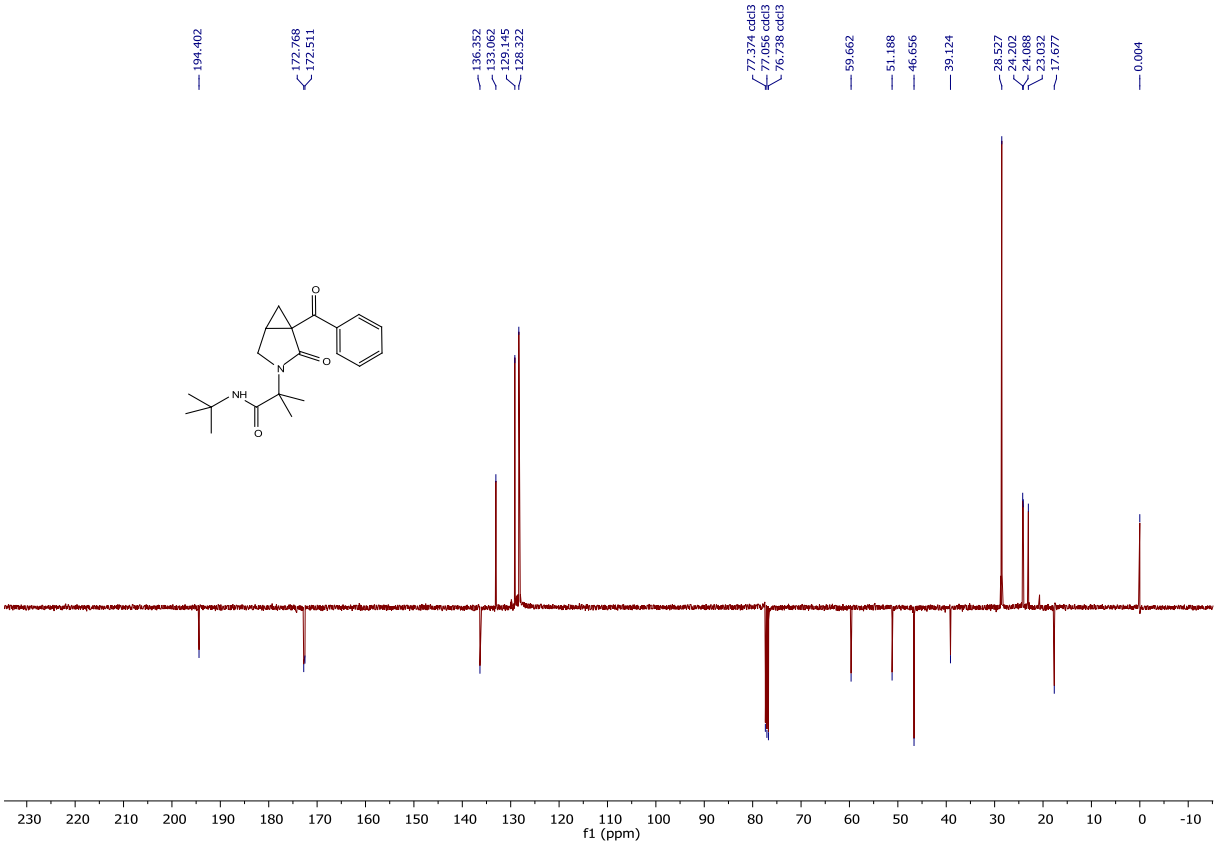
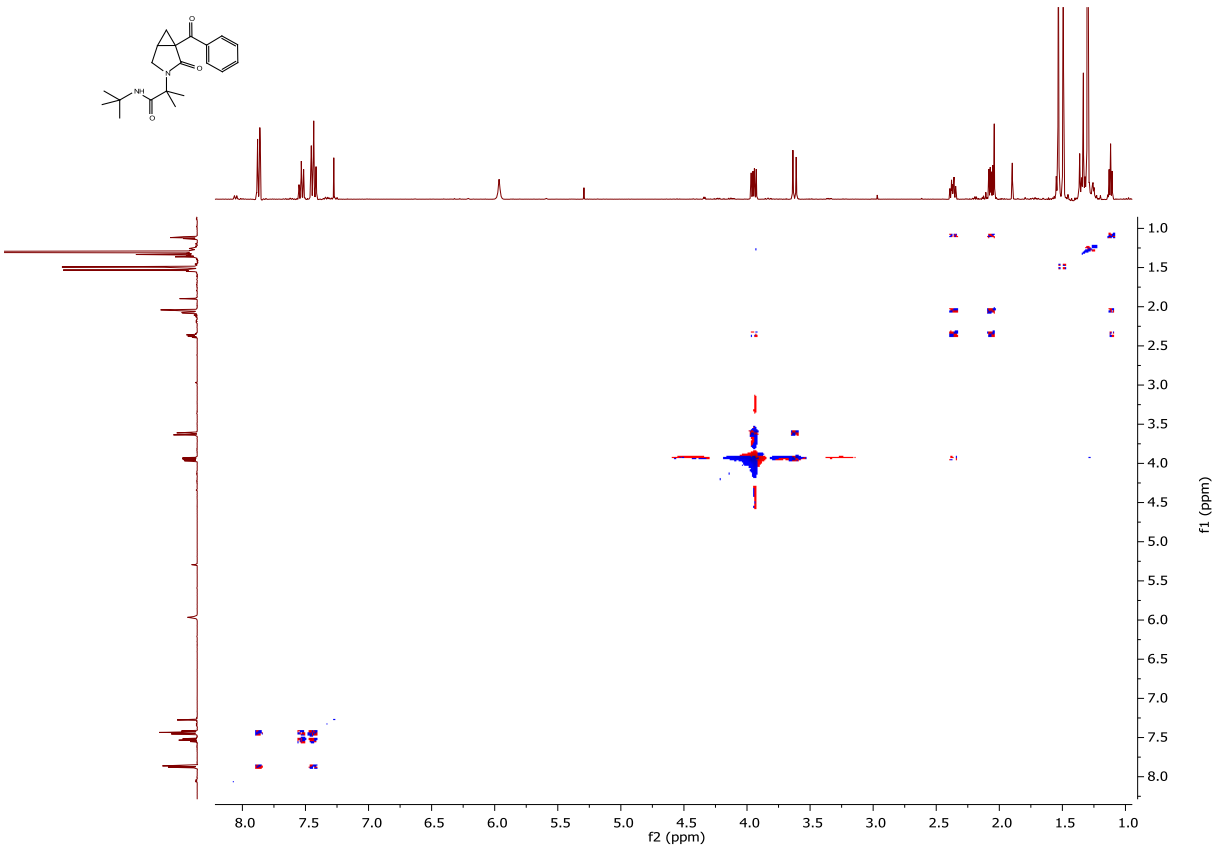
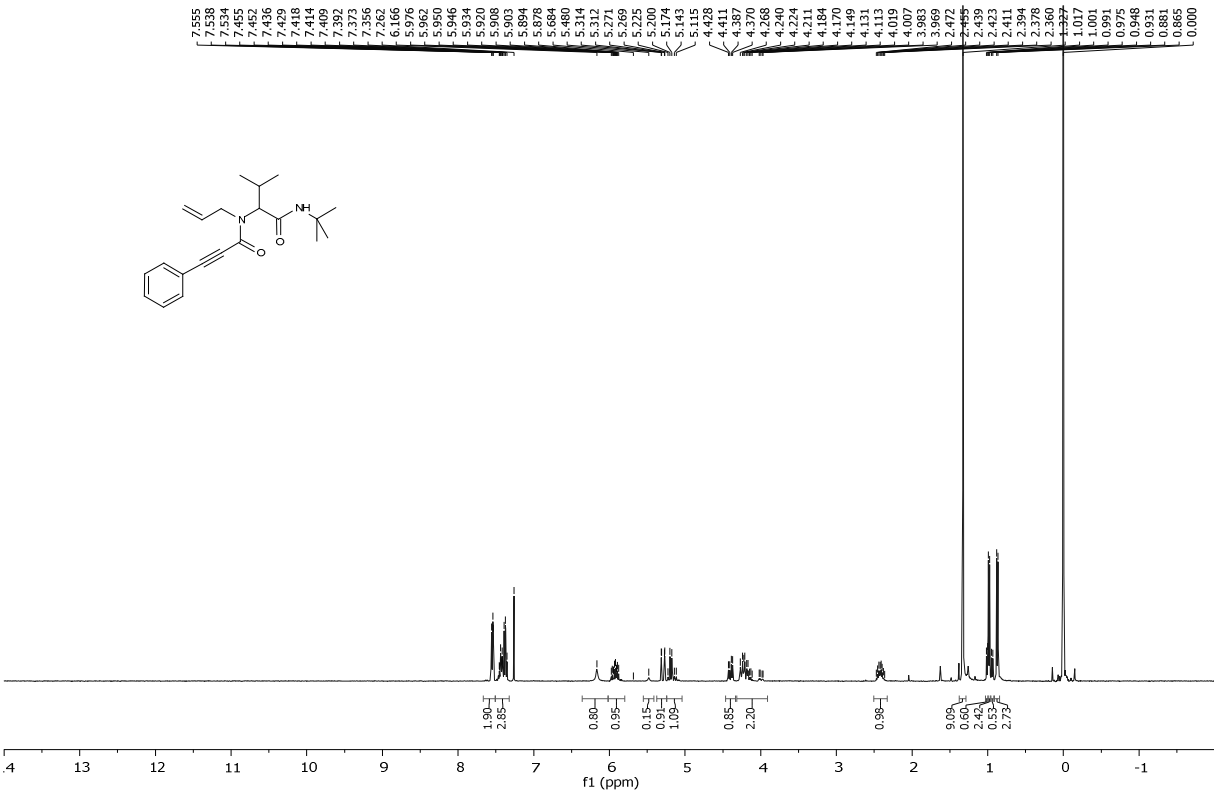
7.595
7.578
7.544
7.526
7.508
7.487
7.468
7.451
6.791
6.455
6.435
6.021
6.008
5.995
5.979
5.965
5.952
5.938
5.845
5.828
5.407
5.365
5.295
5.244
5.218
5.178
5.154
4.396
4.382
4.206
4.194
3.316
2.507
2.502
2.498
1.989
1.572
1.367
1.231
1.179
0.000
1.96
3.01
0.18
0.82
0.81
0.18
0.84
1.01
0.20
1.66
0.38
1.13
5.16
7.82
1.96
f1 (ppm)


1866
CDCl3
1H
7.887
7.882
7.881
7.879
7.867
7.862
7.858
7.555
7.551
7.548
7.538
7.533
7.528
7.518
7.514
7.511
7.454
7.450
7.437
7.435
7.420
7.416
7.414
7.276
5.965
3.967
3.953
3.941
3.927
3.636
3.610
2.392
2.379
2.372
2.365
2.359
2.346
2.083
2.072
2.064
2.052
2.040
1.897
1.532
1.493
1.363
1.347
1.334
1.320
1.299
1.129
1.118
1.106
0.000
O
O
N
NH
O
1.62
0.85
1.88
0.69
0.98
0.96
0.88
1.11
3.01
3.01
9.53
0.97
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


194.383
172.760
172.518
136.396
133.053
129.156
128.326
59.702
51.193
46.674
39.146
28.545
24.230
24.096
22.990
17.695
0.000
O
O
N
NH
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


194.402
172.768
172.511
136.352
133.062
129.145
128.322
77.374 cdcl3
77.056 cdcl3
76.738 cdcl3
59.662
51.188
46.656
39.124
28.527
24.202
24.088
23.032
17.677
0.004
f1 (ppm)


f2 (ppm)
f1 (ppm)


7.555
7.538
7.534
7.455
7.452
7.436
7.429
7.418
7.414
7.409
7.392
7.373
7.356
7.262
6.166
5.976
5.962
5.950
5.946
5.934
5.920
5.908
5.903
5.894
5.878
5.684
5.480
5.314
5.312
5.271
5.269
5.225
5.200
5.174
5.143
5.115
4.428
4.411
4.387
4.370
4.268
4.240
4.224
4.211
4.184
4.170
4.149
4.131
4.113
4.019
4.007
3.983
3.969
2.472
2.455
2.439
2.423
2.411
2.394
2.378
2.360
1.327
1.017
1.001
0.991
0.975
0.948
0.931
0.881
0.865
0.000
1.90
2.85
0.80
0.95
0.15
0.91
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0.85
2.20
0.98
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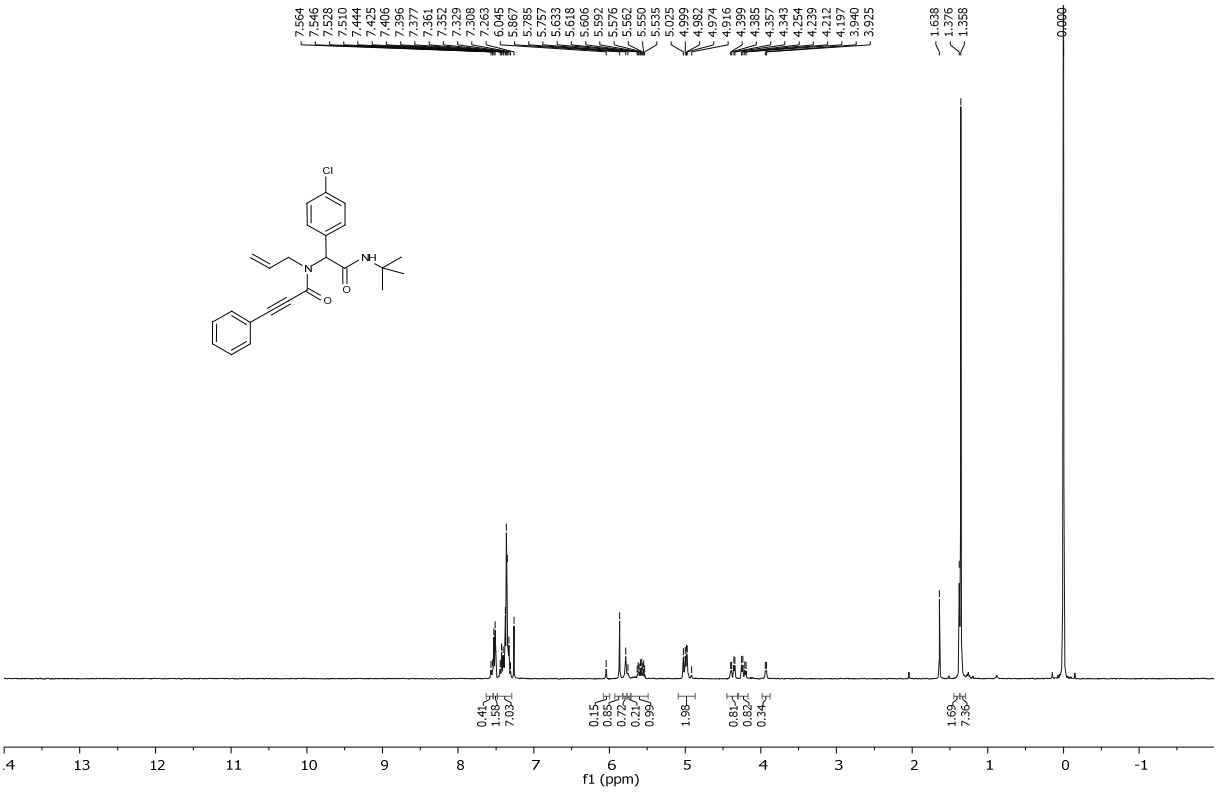
2.42
0.53
2.79
f1 (ppm)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5.757
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5.618
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5.550
5.535
5.025
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4.974
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4.357
4.343
4.254
4.239
4.212
4.197
3.940
3.925
1.638
1.376
1.358
0.000
0.41
1.58
7.03
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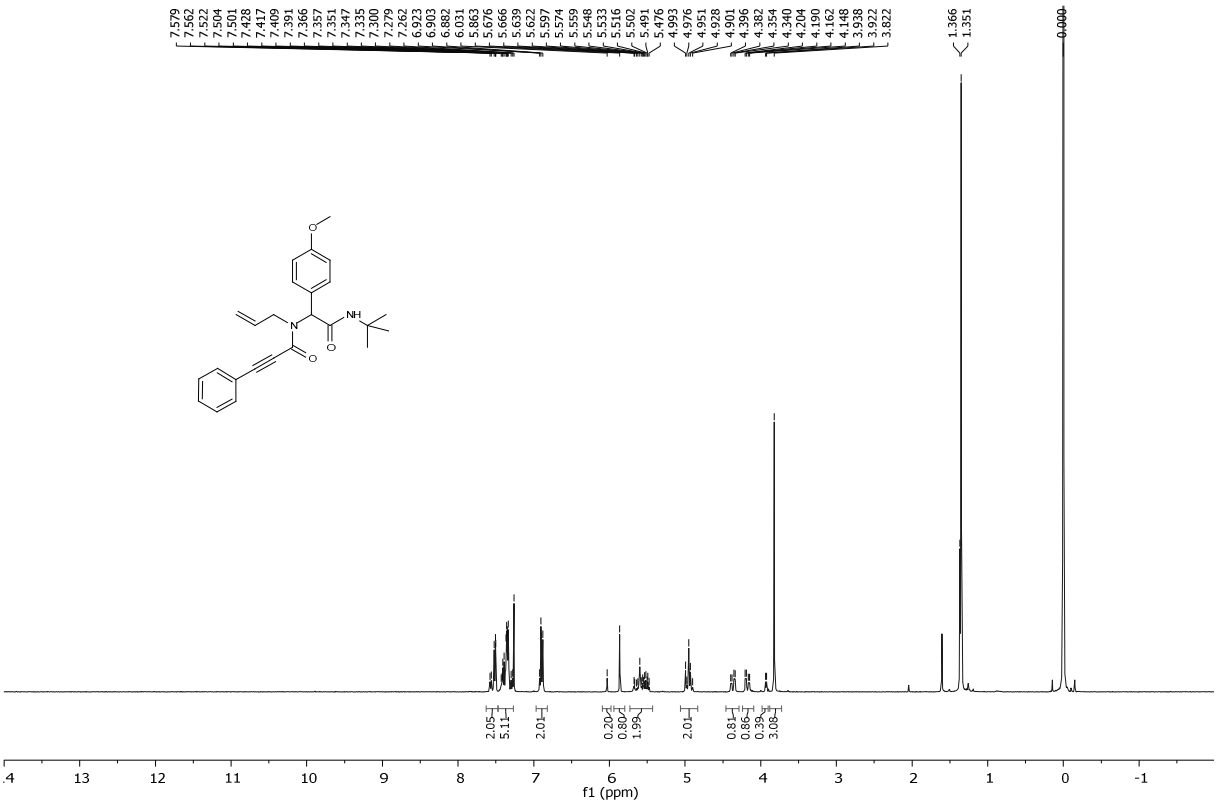
7.36
f1 (ppm)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7.357
7.351
7.347
7.335
7.300
7.279
7.262
6.923
6.903
6.882
6.031
5.863
5.676
5.666
5.639
5.622
5.597
5.574
5.559
5.548
5.533
5.516
5.502
5.491
5.476
4.993
4.976
4.951
4.928
4.901
4.396
4.382
4.354
4.340
4.204
4.190
4.162
4.148
3.938
3.922
3.822
1.366
1.351
0.000
O
N
NH
O
O
2.05
5.11
2.01
0.20
0.80
1.99
2.01
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0.86
0.39
3.08
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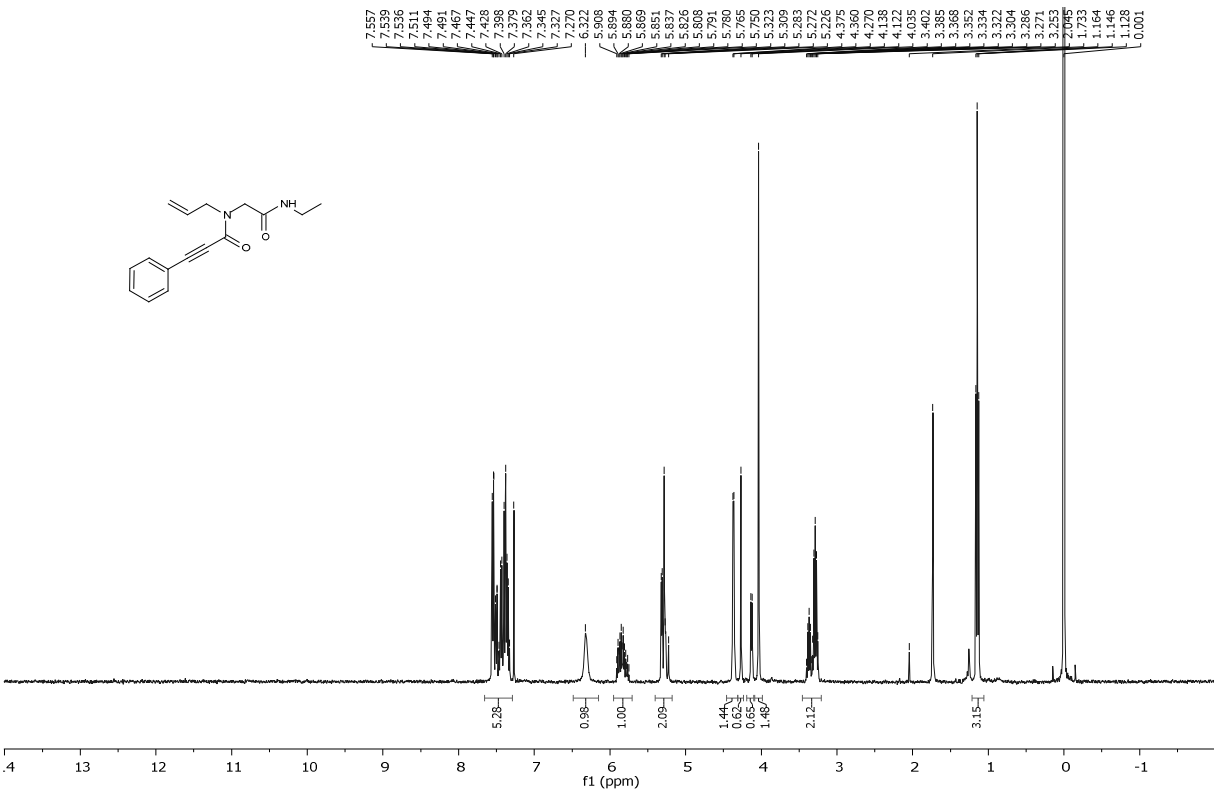
f1 (ppm)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7.362
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7.327
7.270
6.322
5.908
5.894
5.880
5.869
5.851
5.837
5.826
5.808
5.791
5.780
5.765
5.750
5.323
5.309
5.283
5.272
5.226
4.375
4.360
4.270
4.138
4.122
4.035
3.402
3.385
3.368
3.352
3.334
3.322
3.304
3.286
3.271
3.253
2.045
1.733
1.164
1.146
1.128
0.001
N
NH
O
O
5.28
0.98
1.00
2.09
1.44
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0.65
1.48
2.12
3.15
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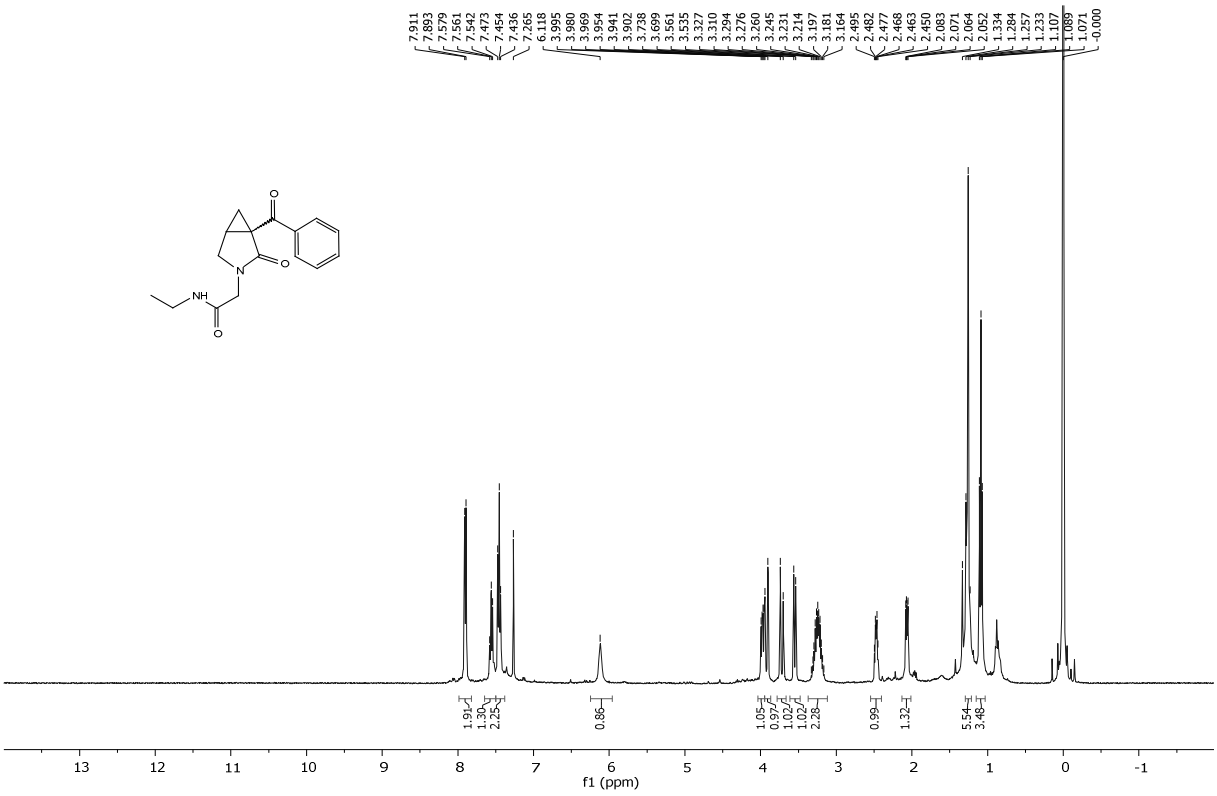
f1 (ppm)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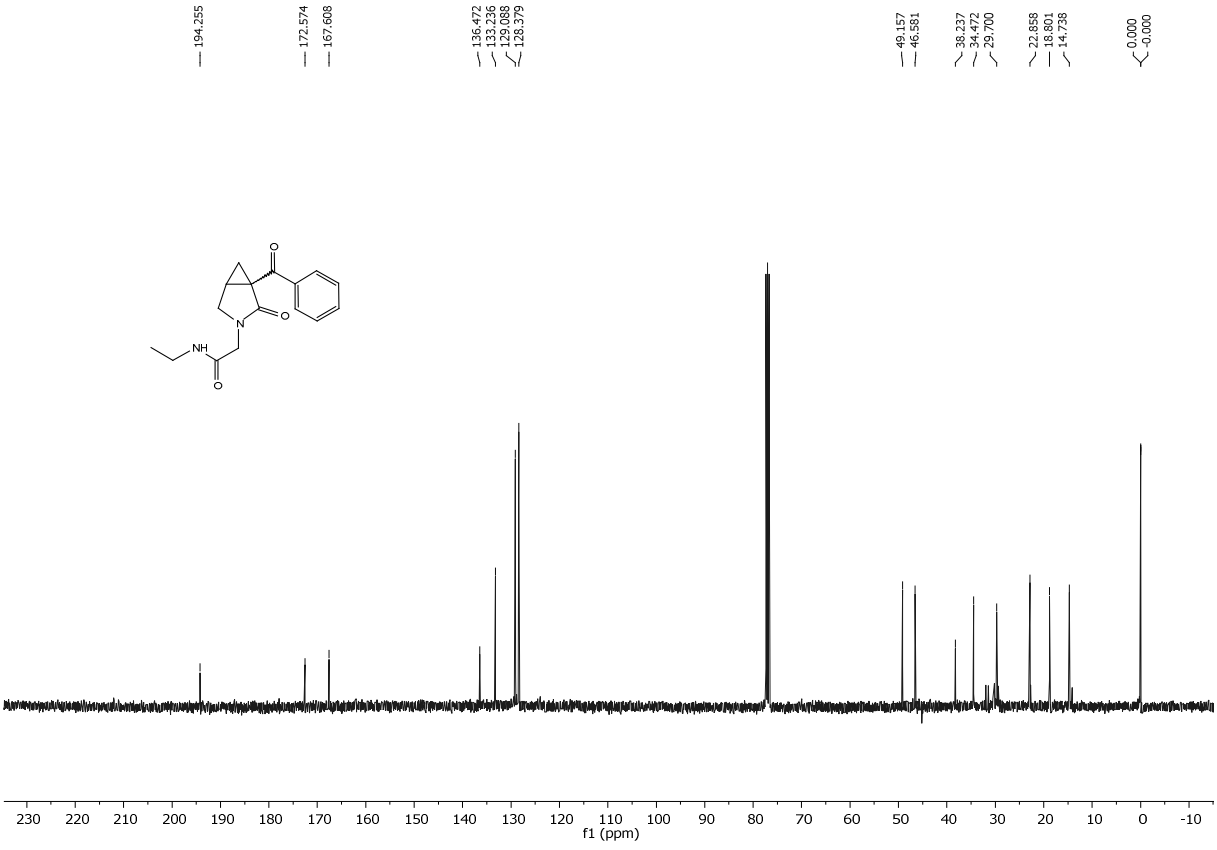
7.454
7.436
7.265
6.118
3.995
3.980
3.969
3.954
3.941
3.902
3.738
3.699
3.561
3.535
3.327
3.310
3.294
3.276
3.260
3.245
3.231
3.214
3.197
3.181
3.164
2.495
2.482
2.477
2.468
2.463
2.450
2.083
2.071
2.064
2.052
1.334
1.284
1.257
1.233
1.107
1.089
1.071
-0.000
1.91
1.30
2.25
0.86
1.05
0.97
1.02
1.02
2.28
0.99
1.32
5.54
3.48
f1 (ppm)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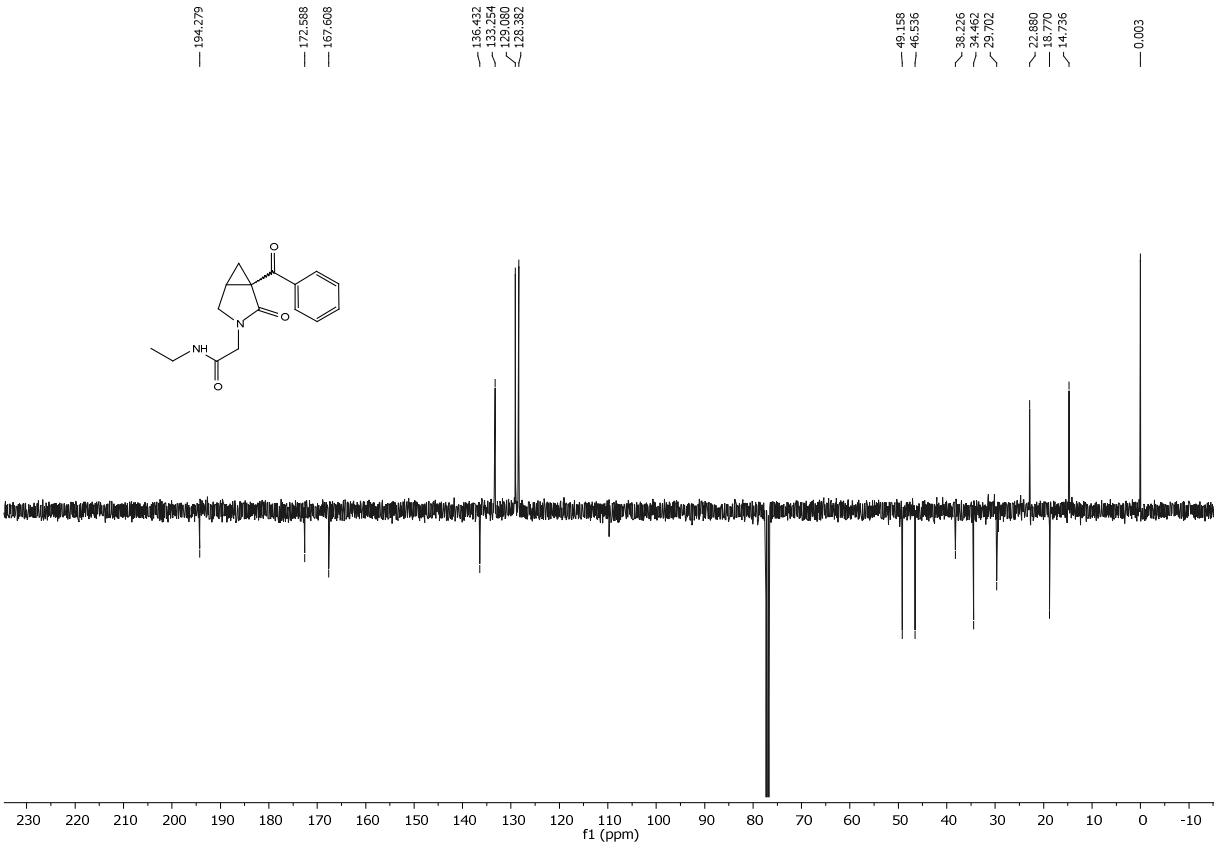
167.608
136.472
133.236
129.088
128.379
49.157
46.581
38.237
34.472
29.700
22.858
18.801
14.738
0.000
-0.000
f1 (ppm)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167.608
136.432
133.254
129.080
128.382
49.158
46.536
38.226
34.462
29.702
22.880
18.770
14.736
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O
N
NH
O
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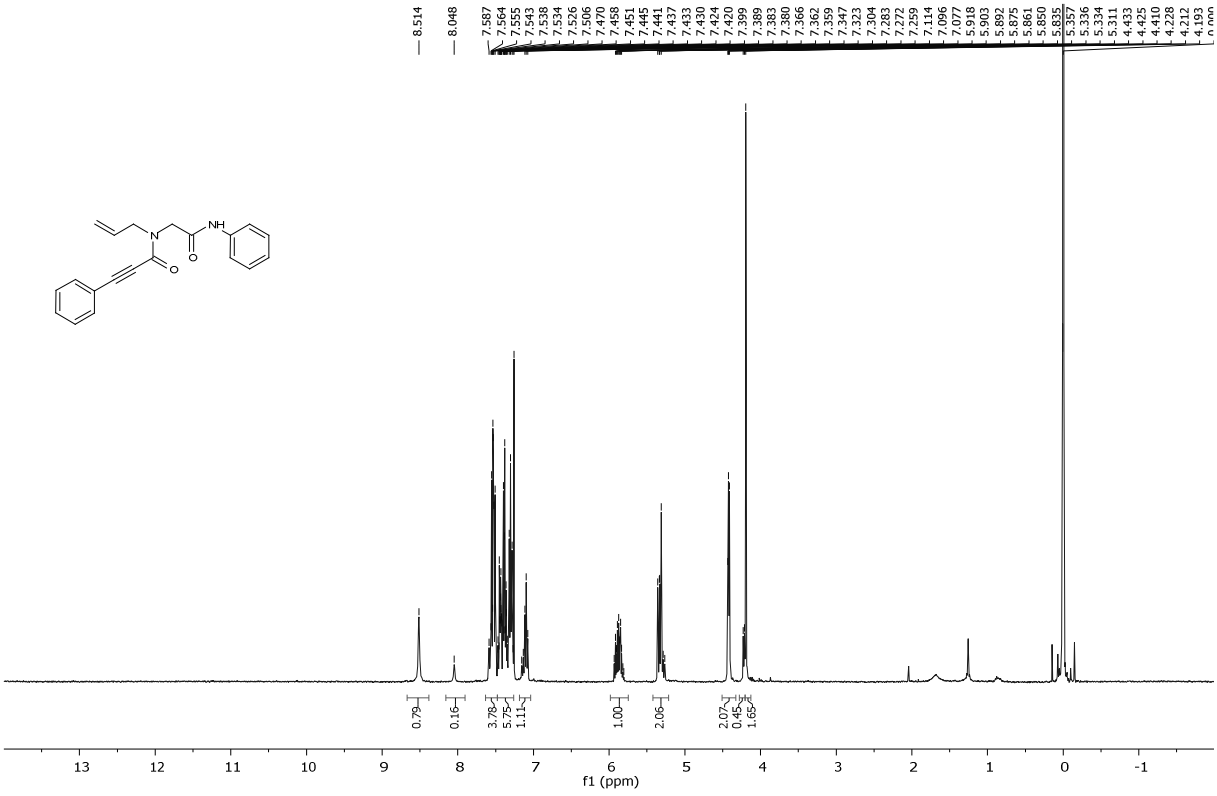
f1 (ppm)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7.587
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7.555
7.543
7.538
7.534
7.526
7.506
7.470
7.458
7.451
7.445
7.441
7.437
7.433
7.430
7.424
7.420
7.399
7.389
7.383
7.380
7.366
7.362
7.359
7.347
7.323
7.304
7.283
7.272
7.259
7.114
7.096
7.077
5.918
5.903
5.892
5.875
5.861
5.850
5.835
5.357
5.336
5.334
5.311
4.433
4.425
4.410
4.228
4.212
4.193
N
NH
O
O
0.79
0.16
3.78
5.75
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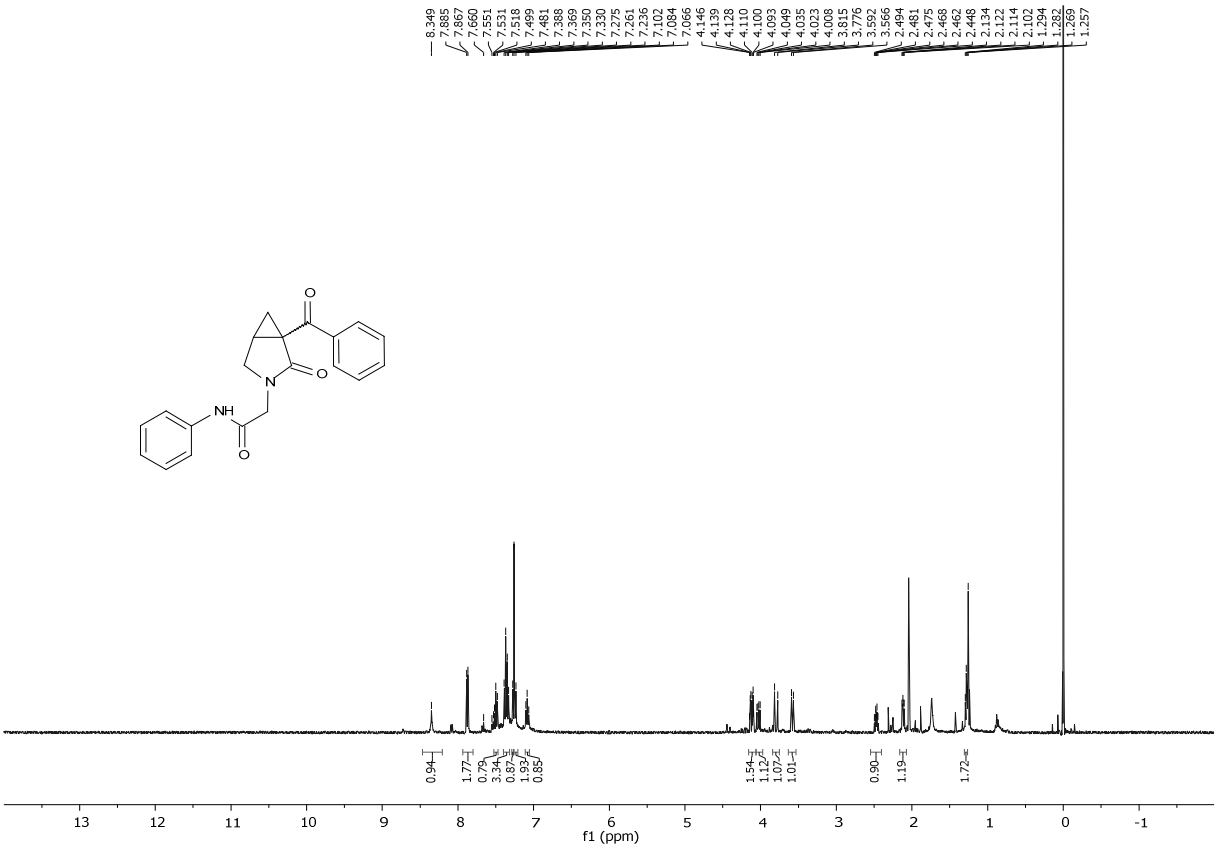
1.00
2.06
2.07
0.45
1.65
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)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7.660
7.551
7.531
7.518
7.499
7.481
7.388
7.369
7.350
7.330
7.275
7.261
7.236
7.102
7.084
7.066
4.146
4.139
4.128
4.110
4.100
4.093
4.049
4.035
4.023
4.008
3.815
3.776
3.592
3.566
2.494
2.481
2.475
2.468
2.462
2.448
2.134
2.122
2.114
2.102
1.294
1.282
1.269
1.257
0.94
1.77
0.79
3.34
0.87
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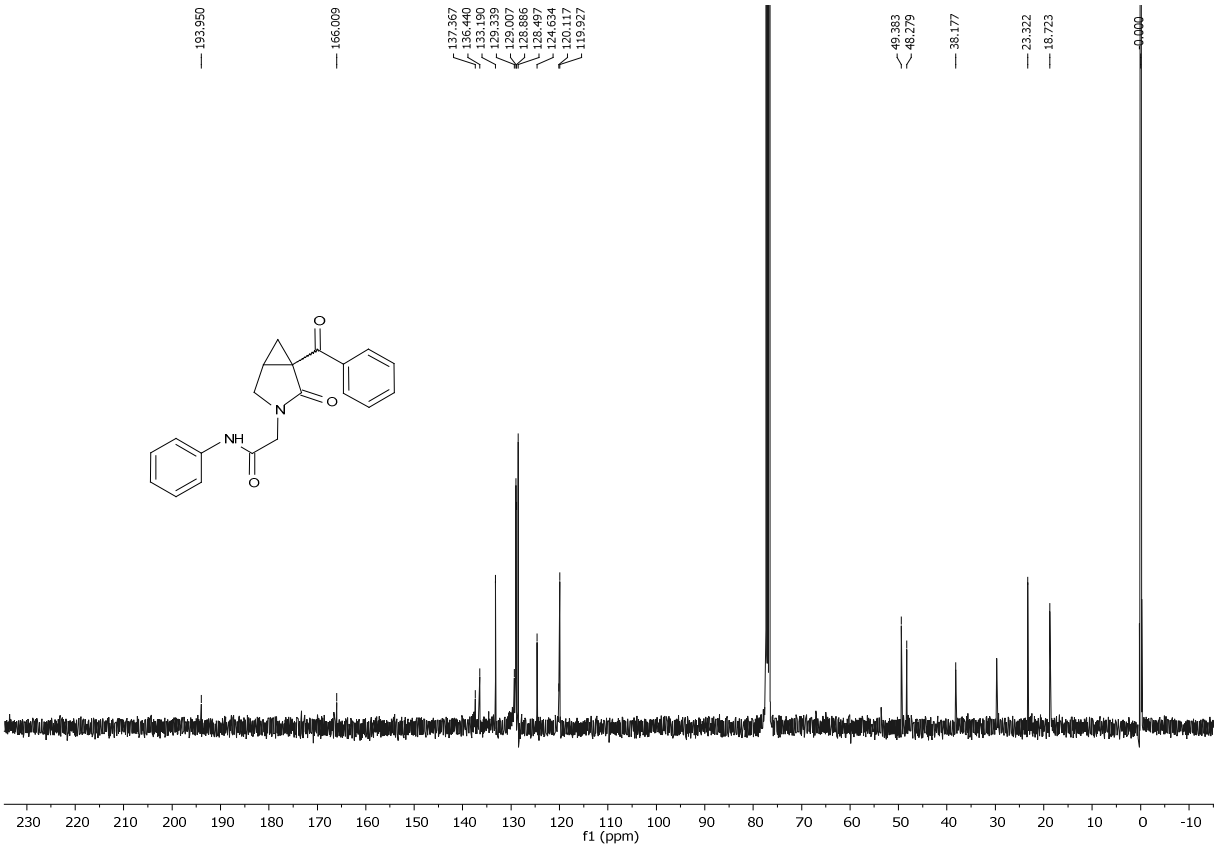
0.85
1.54
1.12
1.07
1.01
0.90
1.19
1.72
f1 (ppm)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137.367
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129.339
129.007
128.886
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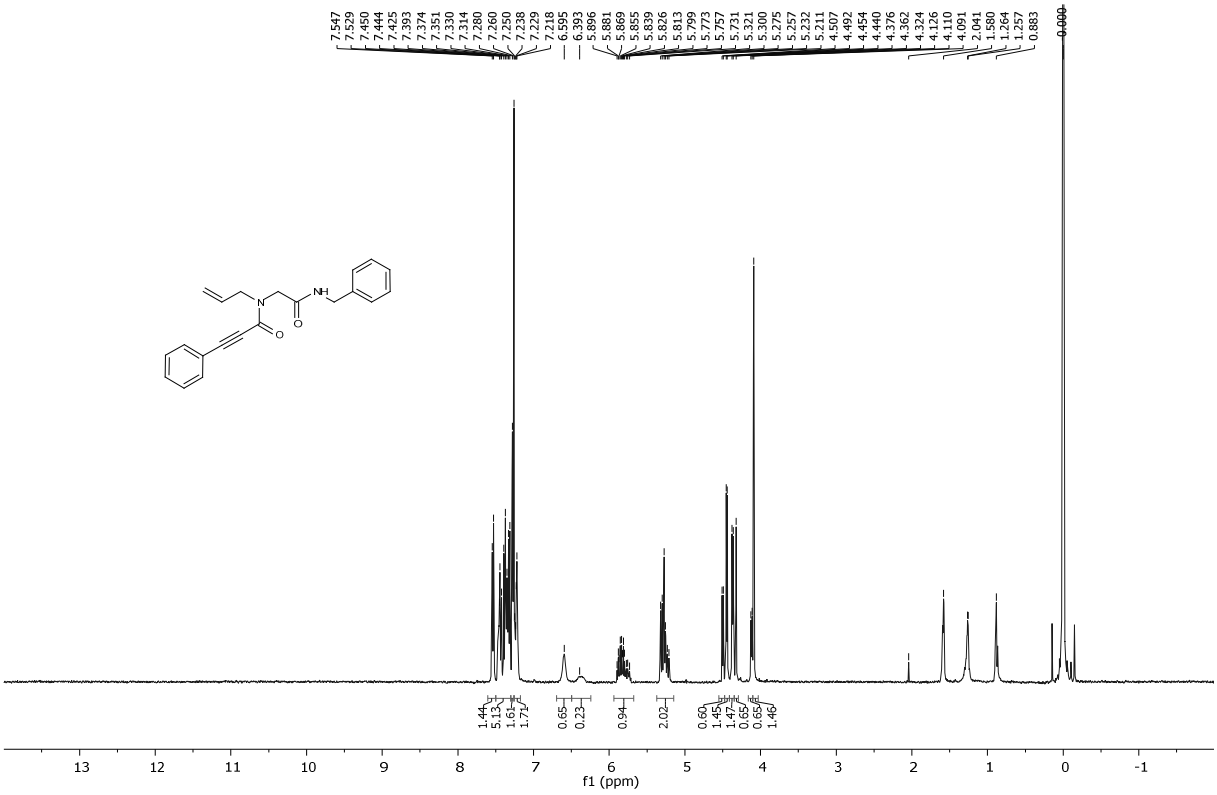
124.634
120.117
119.927
49.383
48.279
38.177
23.322
18.723
0.000
f1 (ppm)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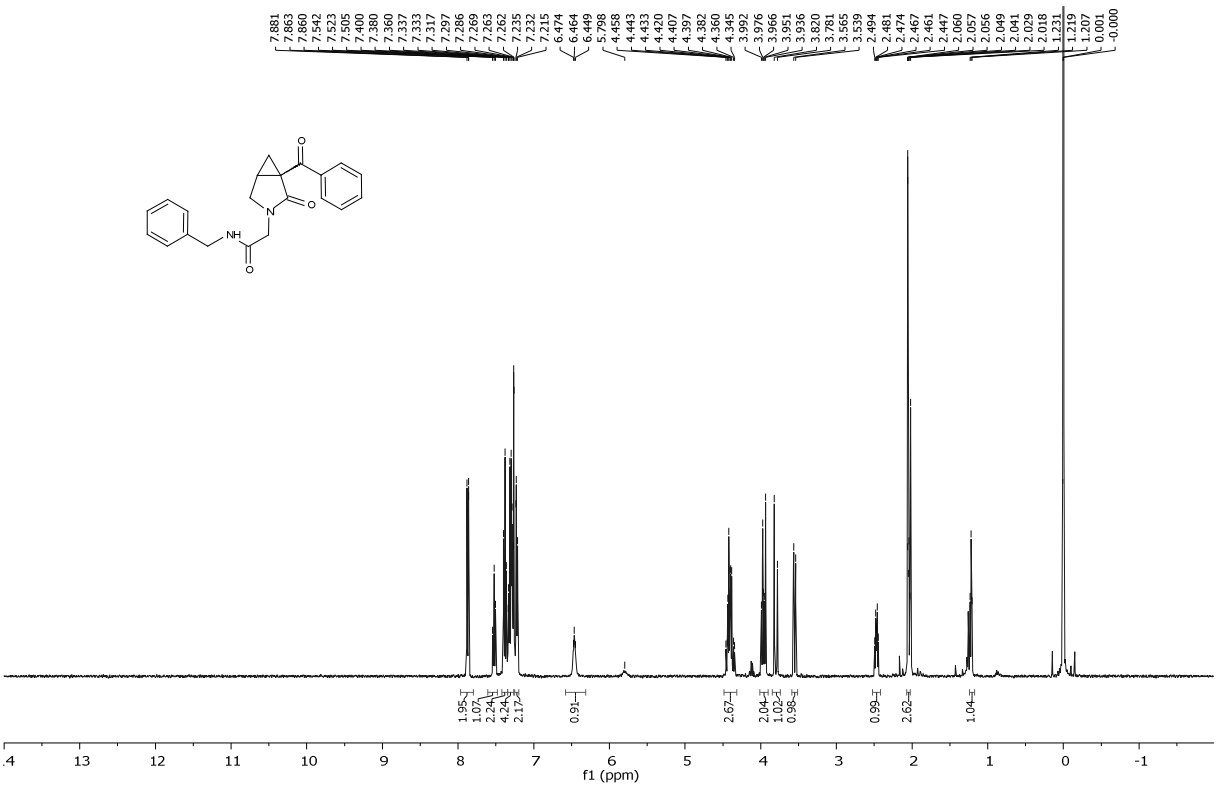
7.529
7.450
7.444
7.425
7.393
7.374
7.351
7.330
7.314
7.280
7.260
7.250
7.238
7.229
7.218
6.595
6.393
5.896
5.881
5.869
5.855
5.839
5.826
5.813
5.799
5.773
5.757
5.731
5.321
5.300
5.275
5.257
5.232
5.211
4.507
4.492
4.454
4.440
4.376
4.362
4.324
4.126
4.110
4.091
2.041
1.580
1.264
1.257
0.883
0.000
1.44
5.13
1.61
1.71
0.65
0.23
0.94
2.02
0.60
1.45
1.47
0.65
0.65
1.46
f1 (ppm)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7.297
7.286
7.269
7.263
7.262
7.235
7.232
7.215
6.474
6.464
6.449
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4.458
4.443
4.433
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4.407
4.397
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4.360
4.345
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3.966
3.951
3.936
3.820
3.781
3.565
3.539
2.494
2.481
2.474
2.467
2.461
2.447
2.060
2.057
2.056
2.049
2.041
2.029
2.018
1.231
1.219
1.207
0.001
-0.000
1.95
1.07
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0.91
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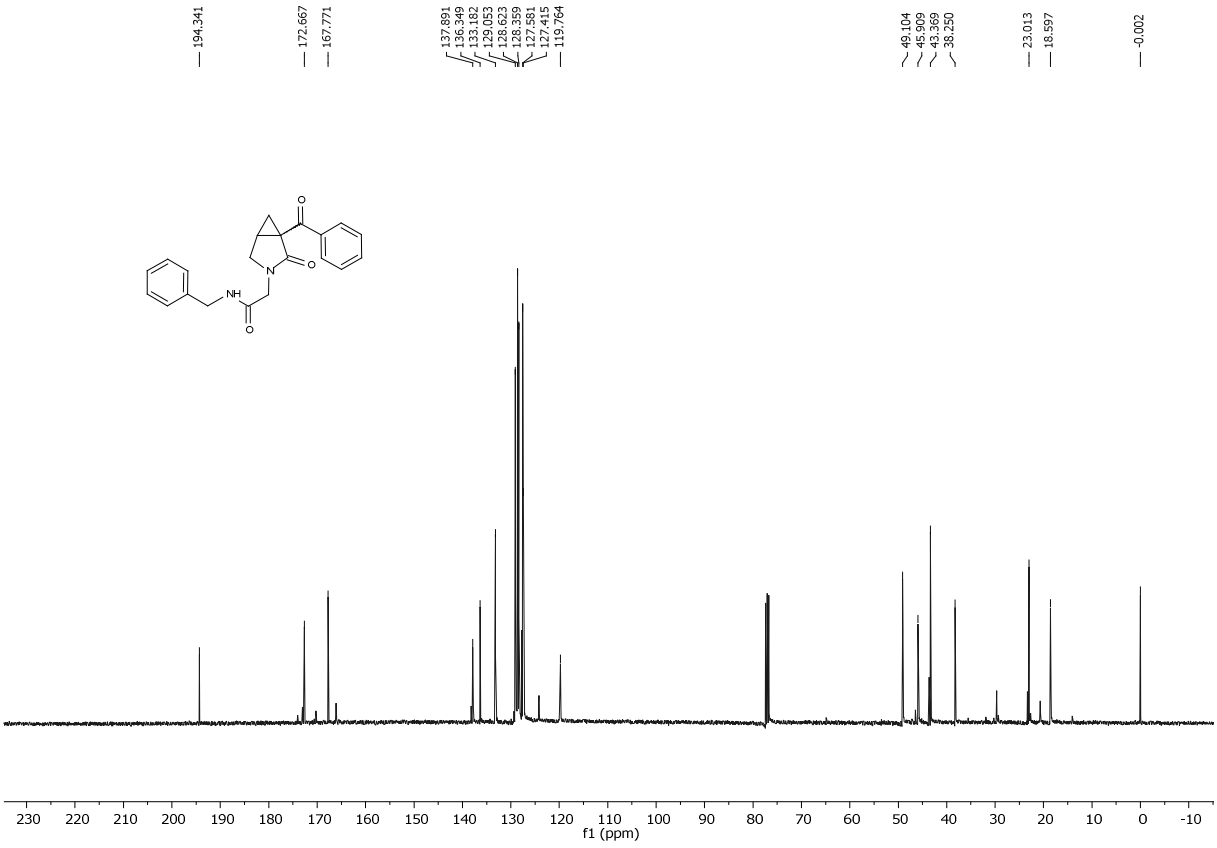
1.02
0.98
0.99
2.62
1.04
f1 (ppm)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128.623
128.359
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43.369
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23.013
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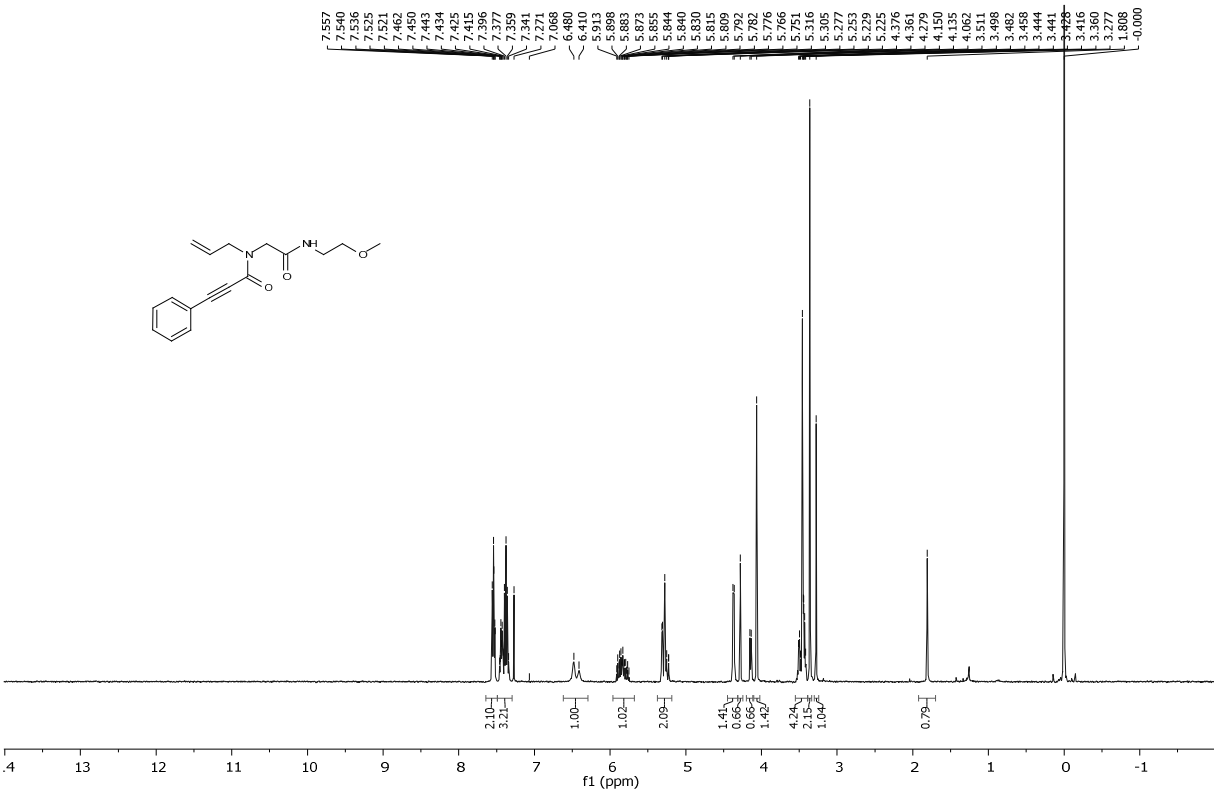
f1 (ppm)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7.521
7.462
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7.443
7.434
7.425
7.415
7.396
7.377
7.359
7.341
7.271
7.068
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6.410
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5.782
5.776
5.766
5.751
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5.305
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5.253
5.229
5.225
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4.361
4.279
4.150
4.135
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3.482
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3.444
3.441
3.428
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3.360
3.277
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3.21
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0.66
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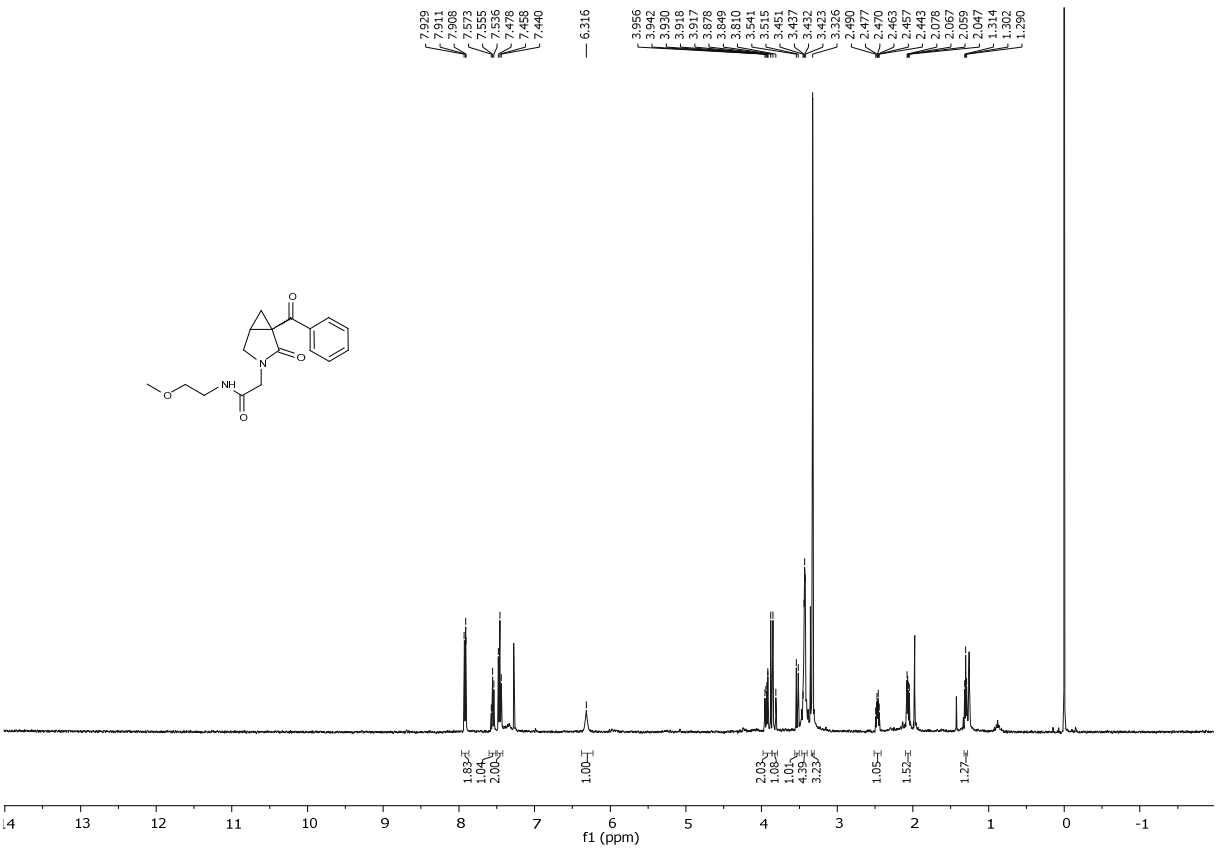
f1 (ppm)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3.917
3.878
3.849
3.810
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3.515
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3.437
3.432
3.423
3.336
2.490
2.477
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2.463
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2.443
2.078
2.067
2.059
2.047
1.314
1.302
1.290
1.83
1.04
2.00
1.00
2.03
1.08
1.01
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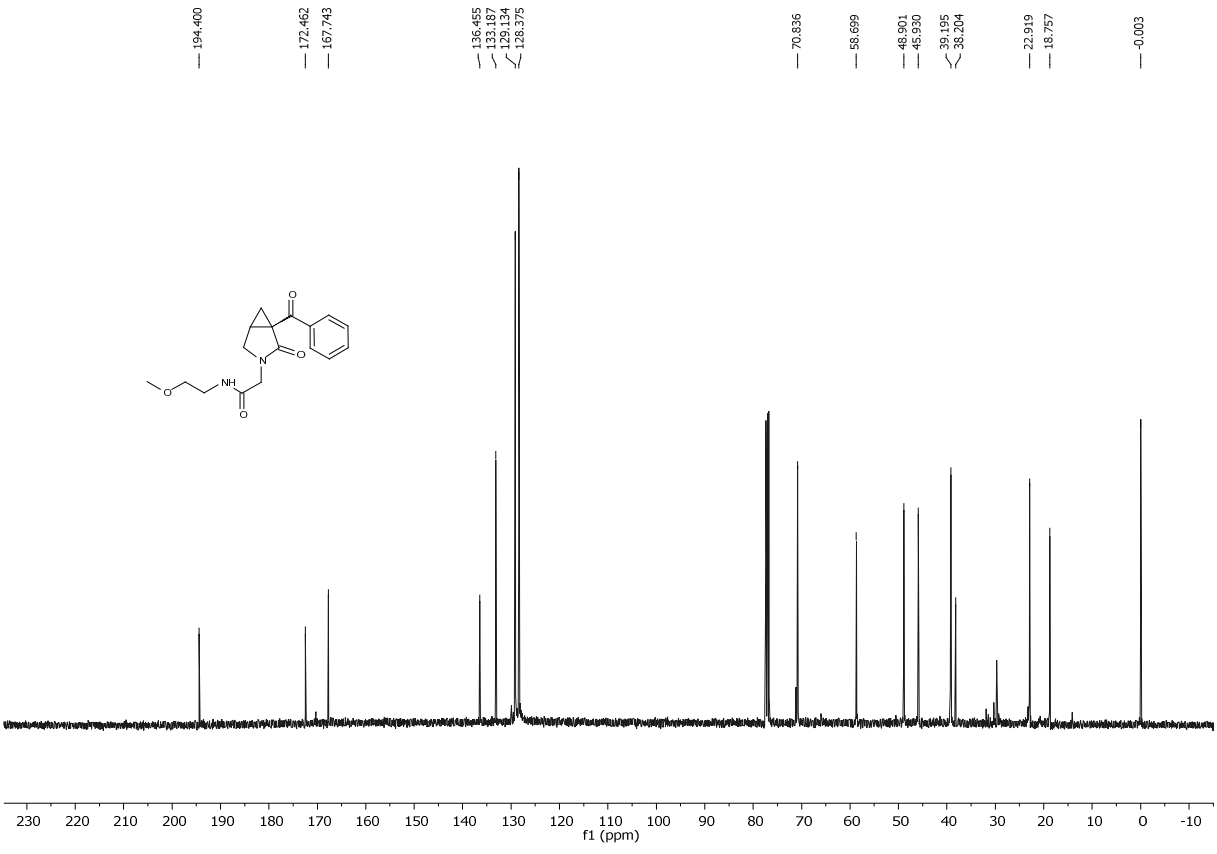
1.05
1.52
1.27
f1 (ppm)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39.195
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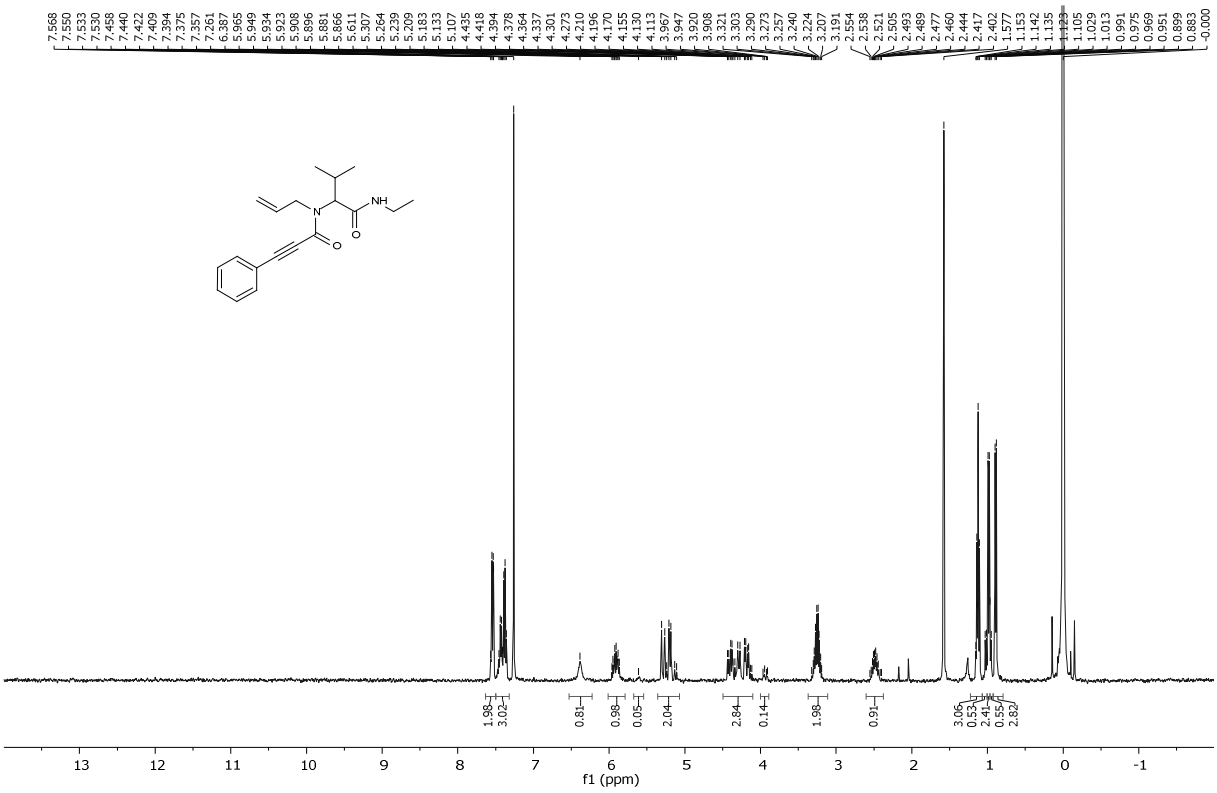
22.919
18.757
-0.003
f1 (ppm)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5.934
5.923
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5.307
5.264
5.239
5.209
5.183
5.133
5.107
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4.394
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4.364
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4.273
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4.155
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4.113
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3.290
3.273
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3.240
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3.207
3.191
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2.538
2.521
2.505
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2.460
2.444
2.417
2.402
1.577
1.153
1.142
1.135
1.123
1.105
1.029
1.013
0.991
0.975
0.969
0.951
0.899
0.883
-0.000
NH
O
O
1.98
3.02
0.81
0.98
0.05
2.04
2.84
0.14
1.98
0.91
3.06
0.53
2.41
0.55
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12
11
10
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8
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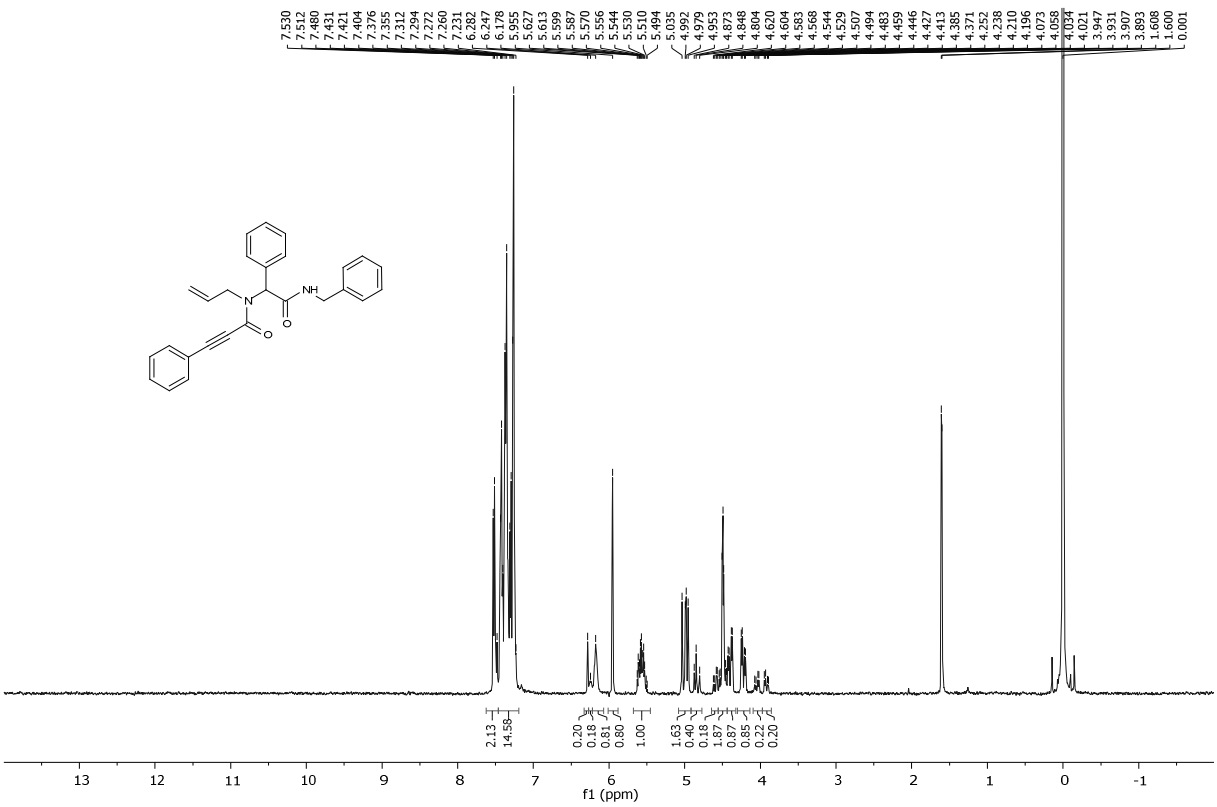
4
3
2
1
0
-1
f1 (ppm)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7.421
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7.272
7.260
7.231
6.282
6.247
6.178
5.955
5.627
5.613
5.599
5.587
5.570
5.556
5.544
5.530
5.510
5.494
5.035
4.992
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4.604
4.583
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4.529
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4.371
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4.238
4.210
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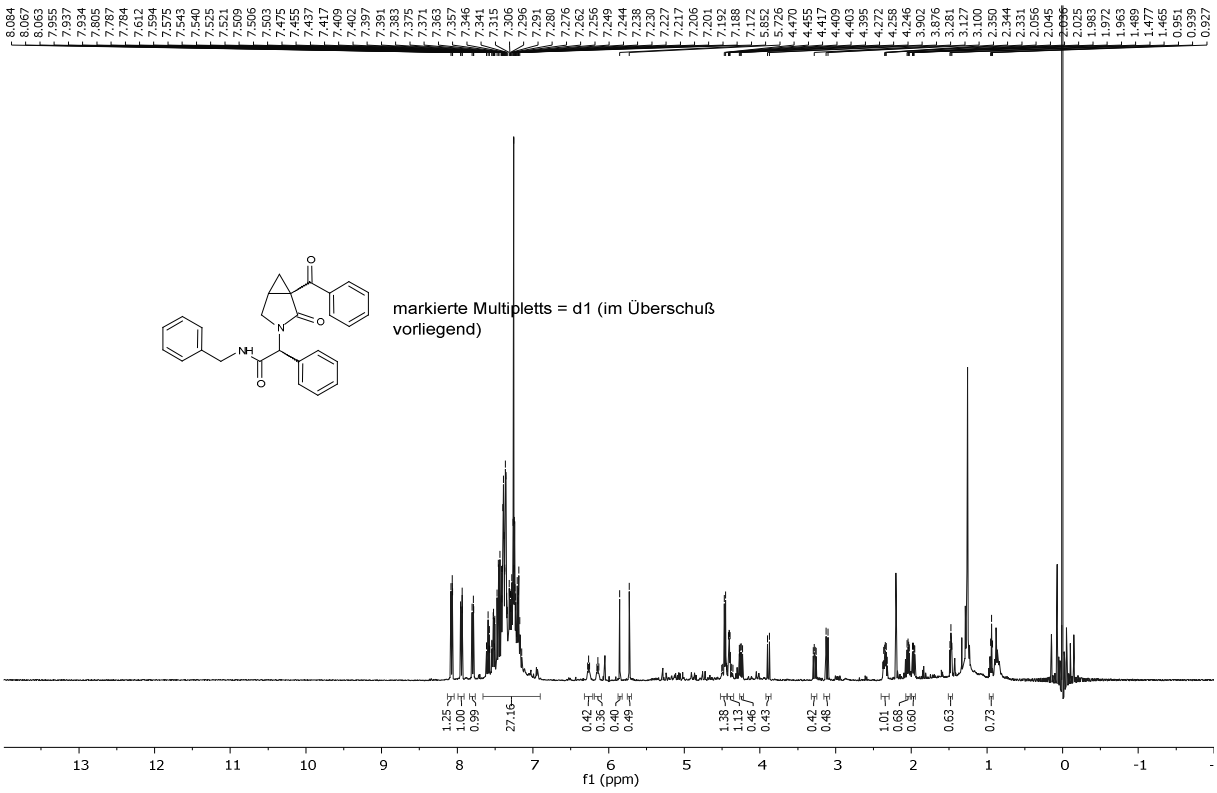
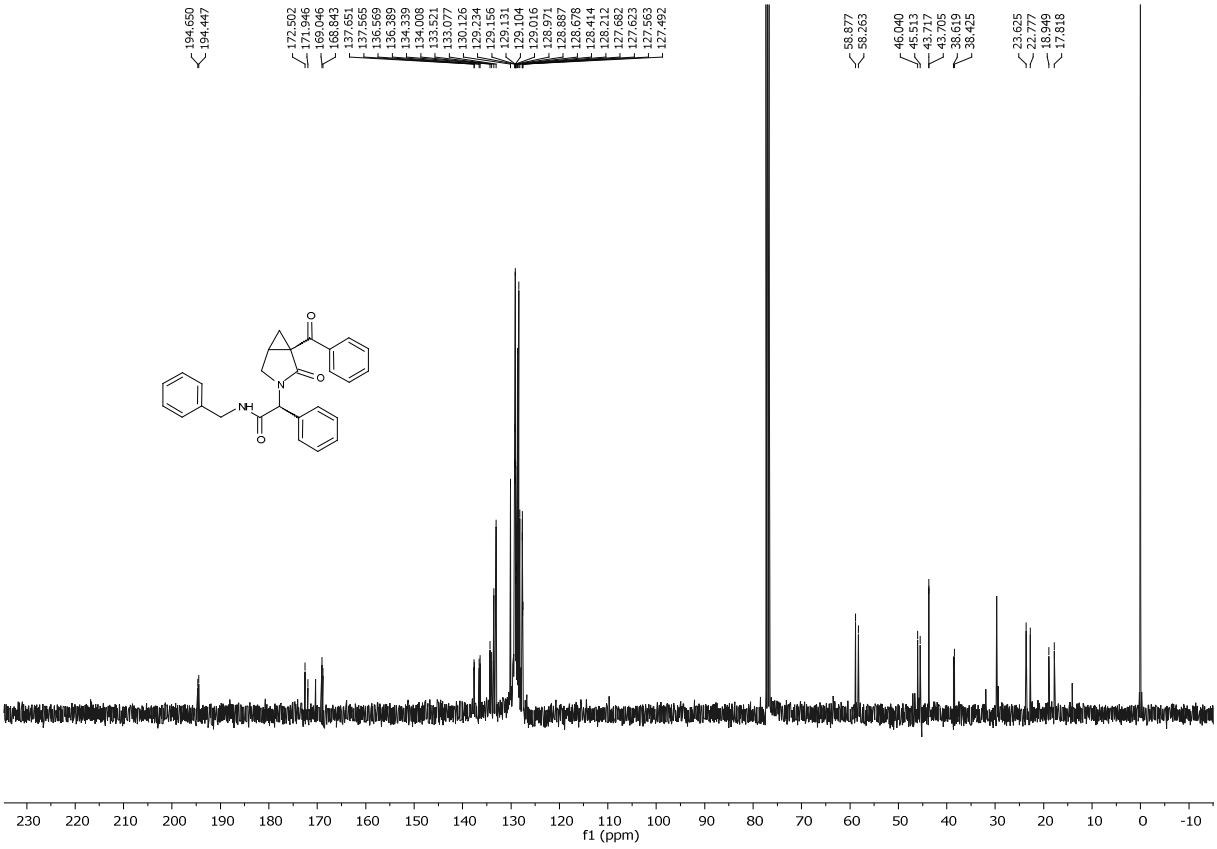
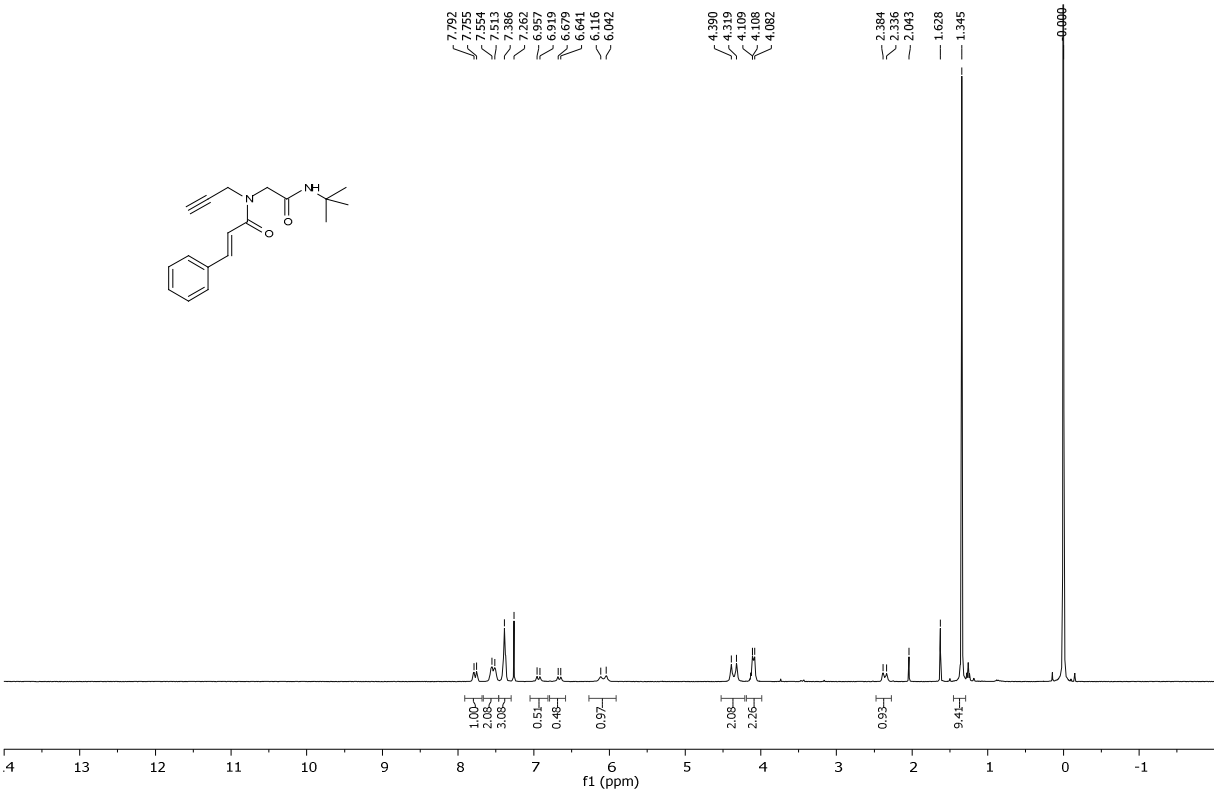
4.073
4.058
4.034
4.021
3.947
3.931
3.907
3.893
1.608
1.600
0.001
NH
O
O
2.13
14.58
0.20
0.18
0.81
0.80
1.00
1.63
0.40
0.18
1.87
0.87
0.85
0.22
0.20
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


markierte Multipletts = d1 (im Überschuß vorliegend)
f1 (ppm)


f1 (ppm)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6.641
6.116
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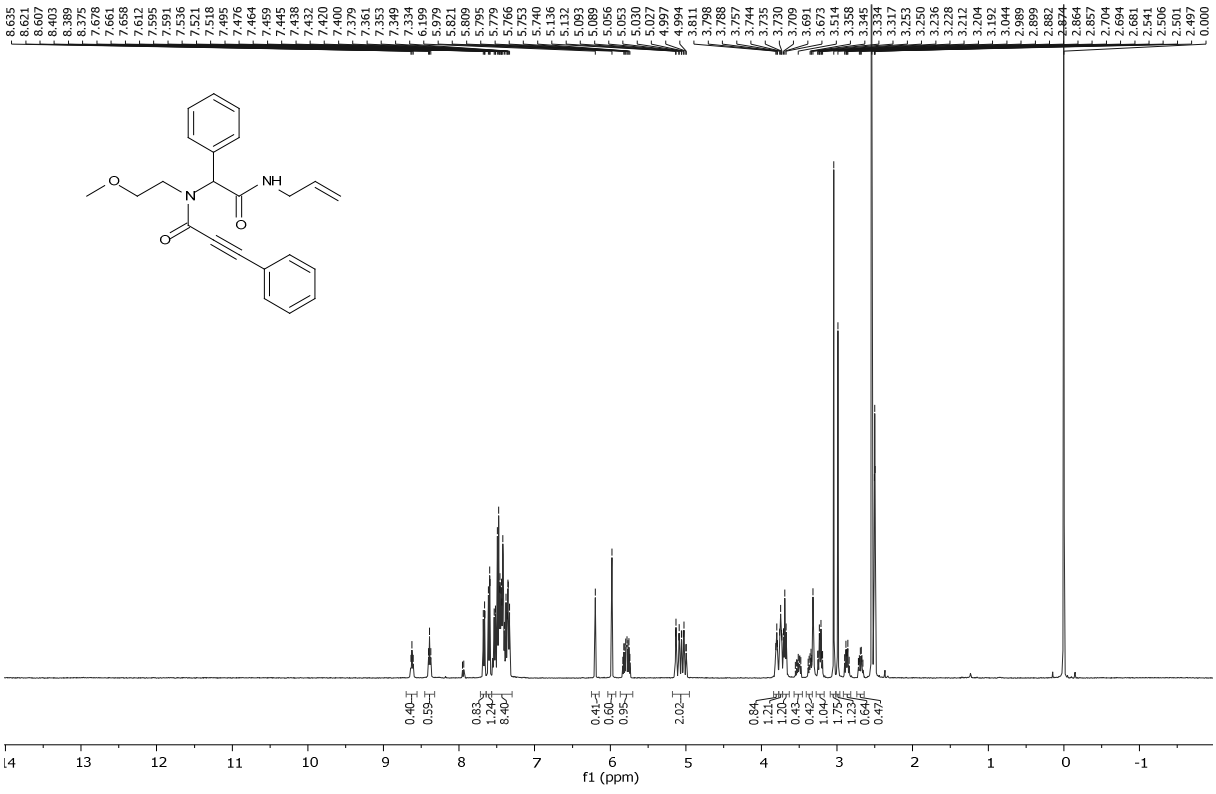
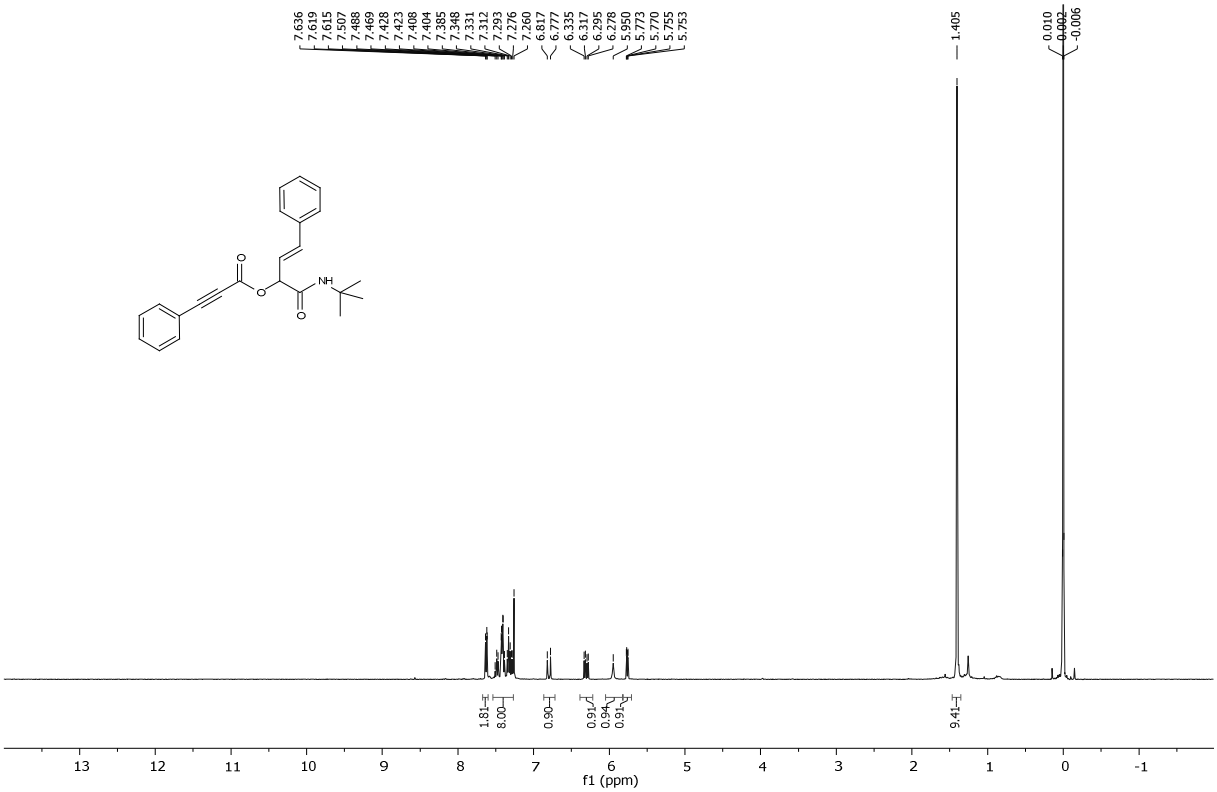
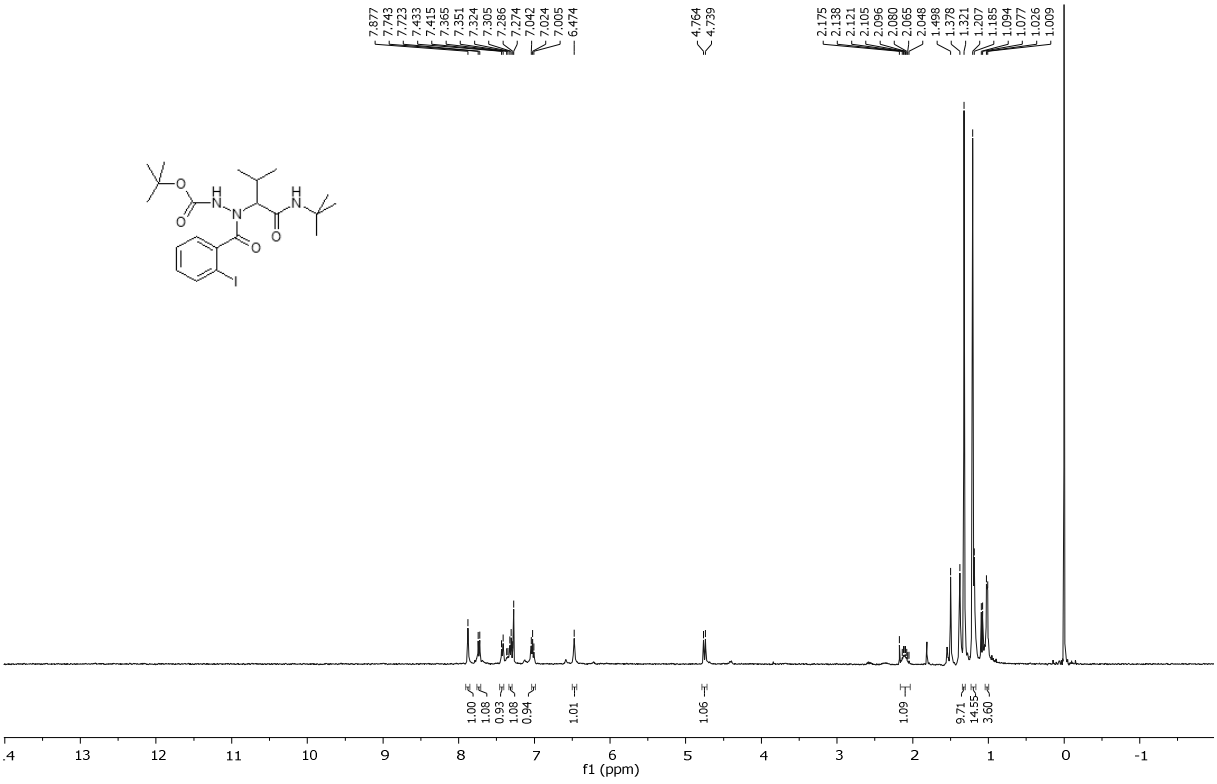
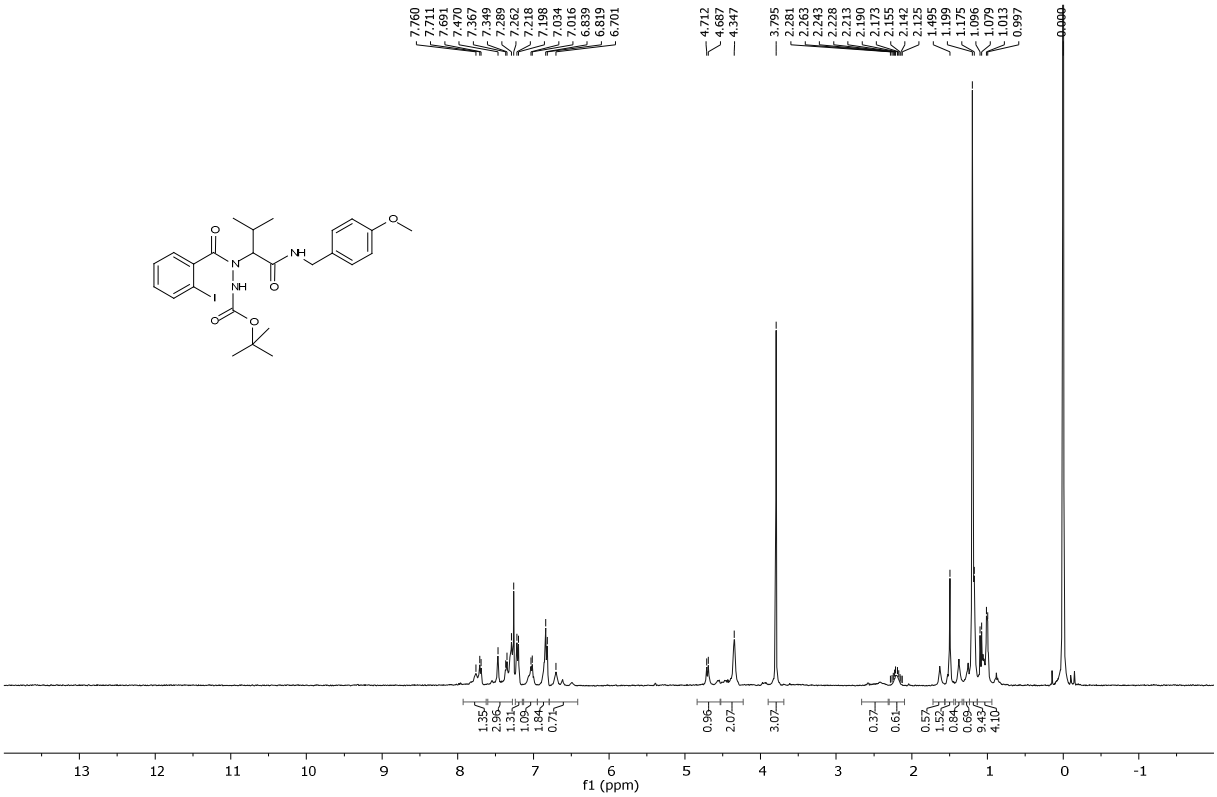
4.390
4.319
4.109
4.108
4.082
2.384
2.336
2.043
1.628
1.345
0.000
1.00
2.08
3.08
0.51
0.48
0.97
2.08
2.26
0.93
9.41
f1 (ppm)

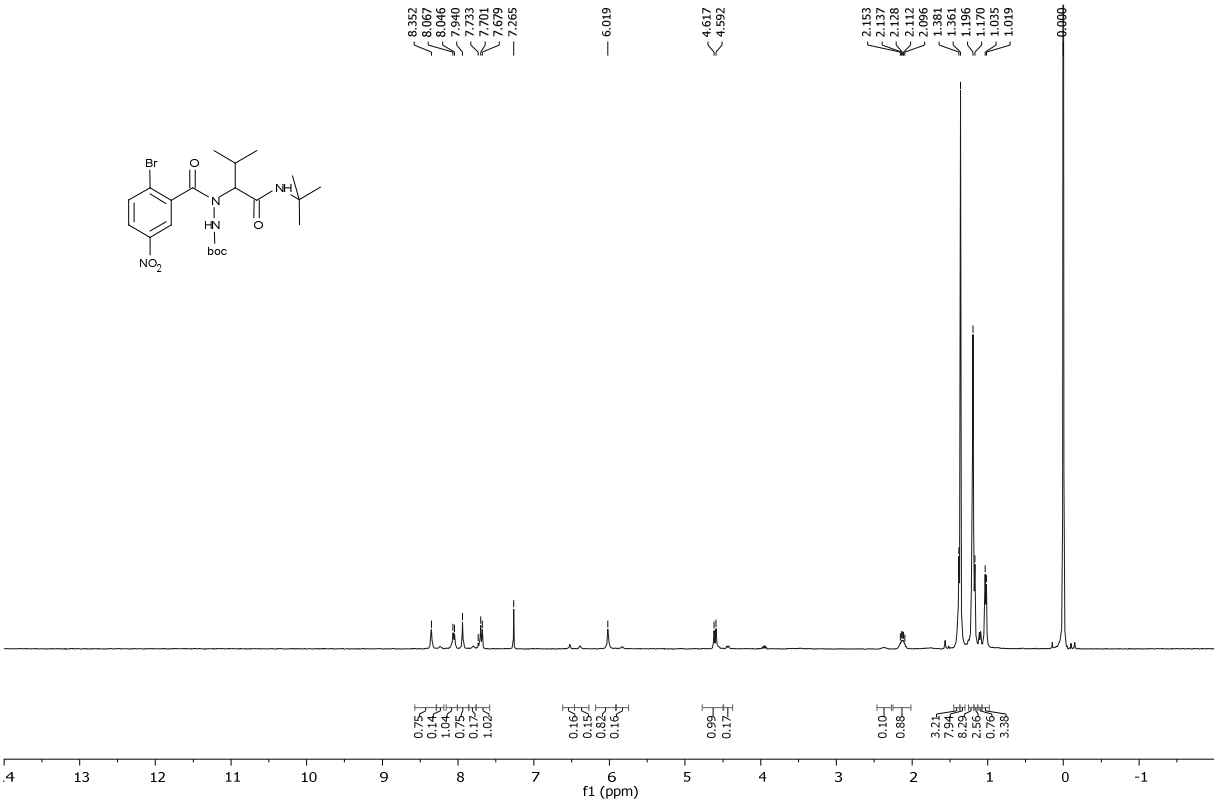

f1 (ppm)

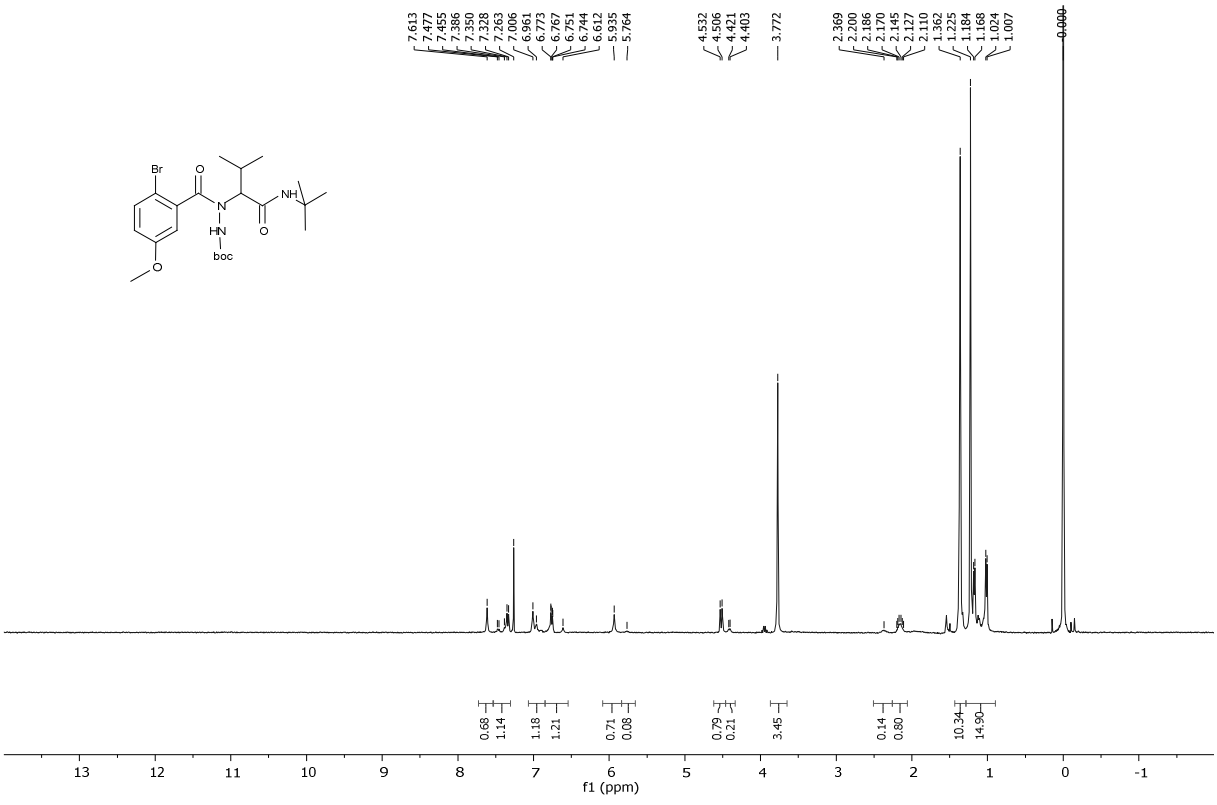

7.636
7.619
7.615
7.507
7.488
7.469
7.428
7.423
7.408
7.404
7.385
7.348
7.331
7.312
7.293
7.276
7.260
6.817
6.777
6.335
6.317
6.295
6.278
5.950
5.773
5.770
5.755
5.753
1.405
0.010
0.002
-0.006
O
O
NH
O
1.81
8.00
0.90
0.91
0.94
0.91
9.41
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

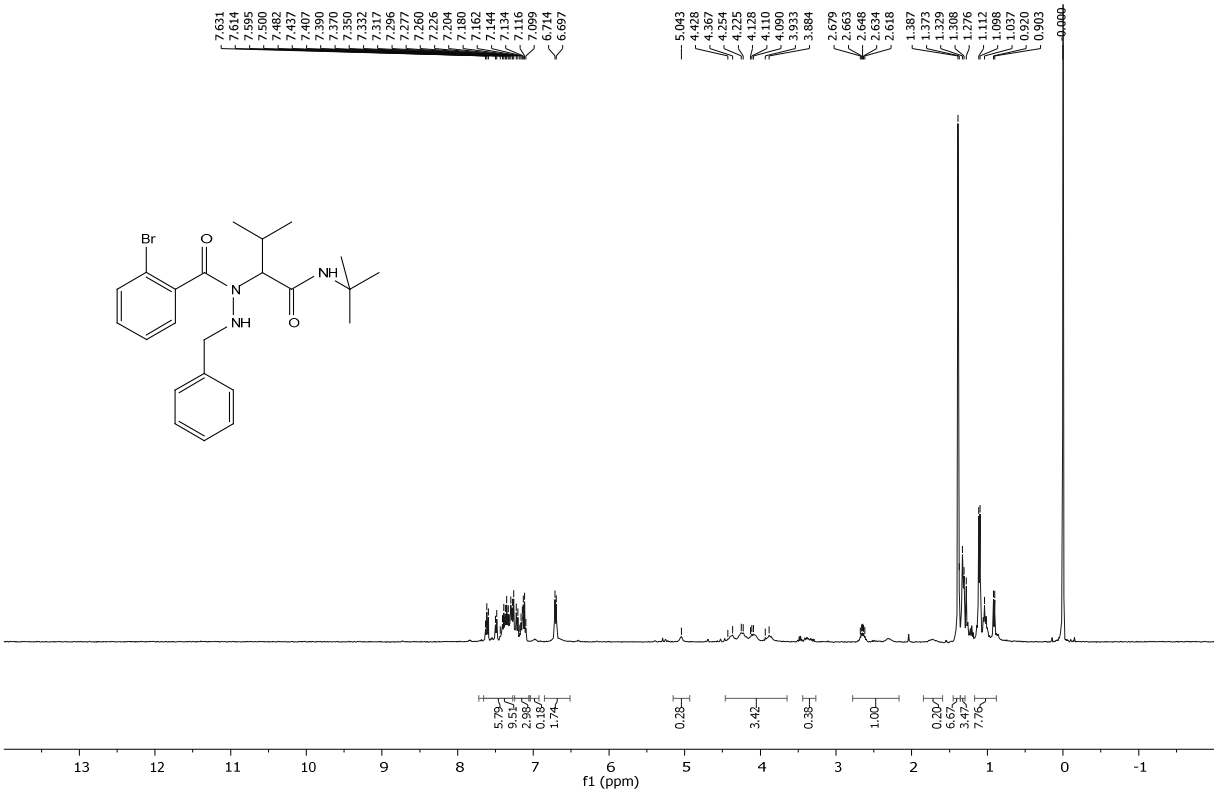
10.1.3. Cyclizations of hydrazine derived Ugi-4CR products (chapter 6.3)

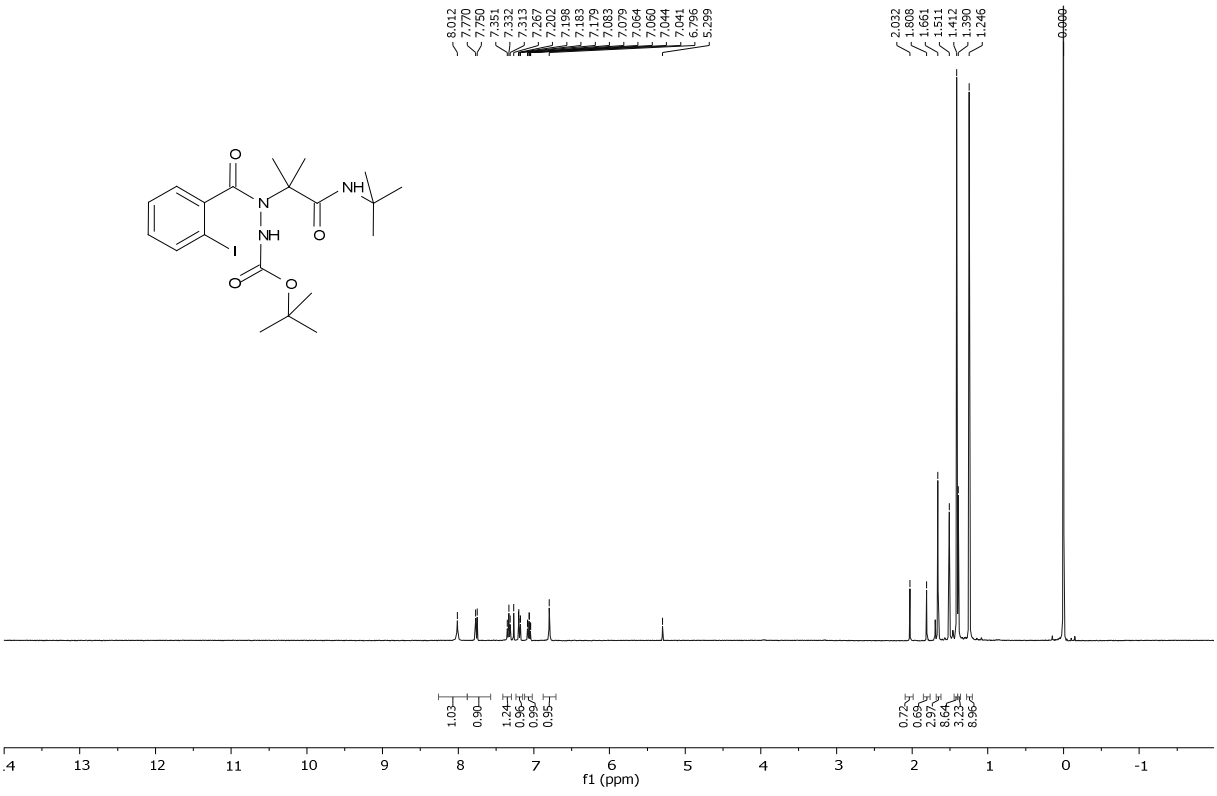


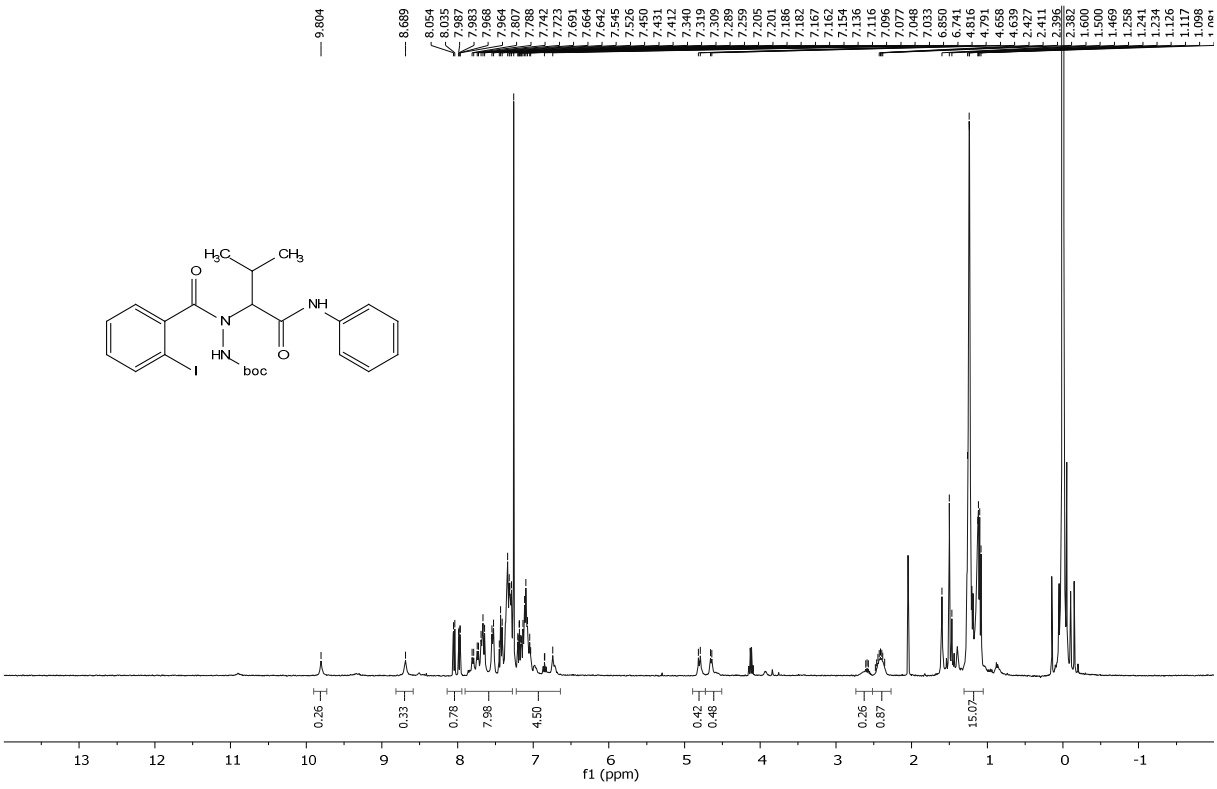


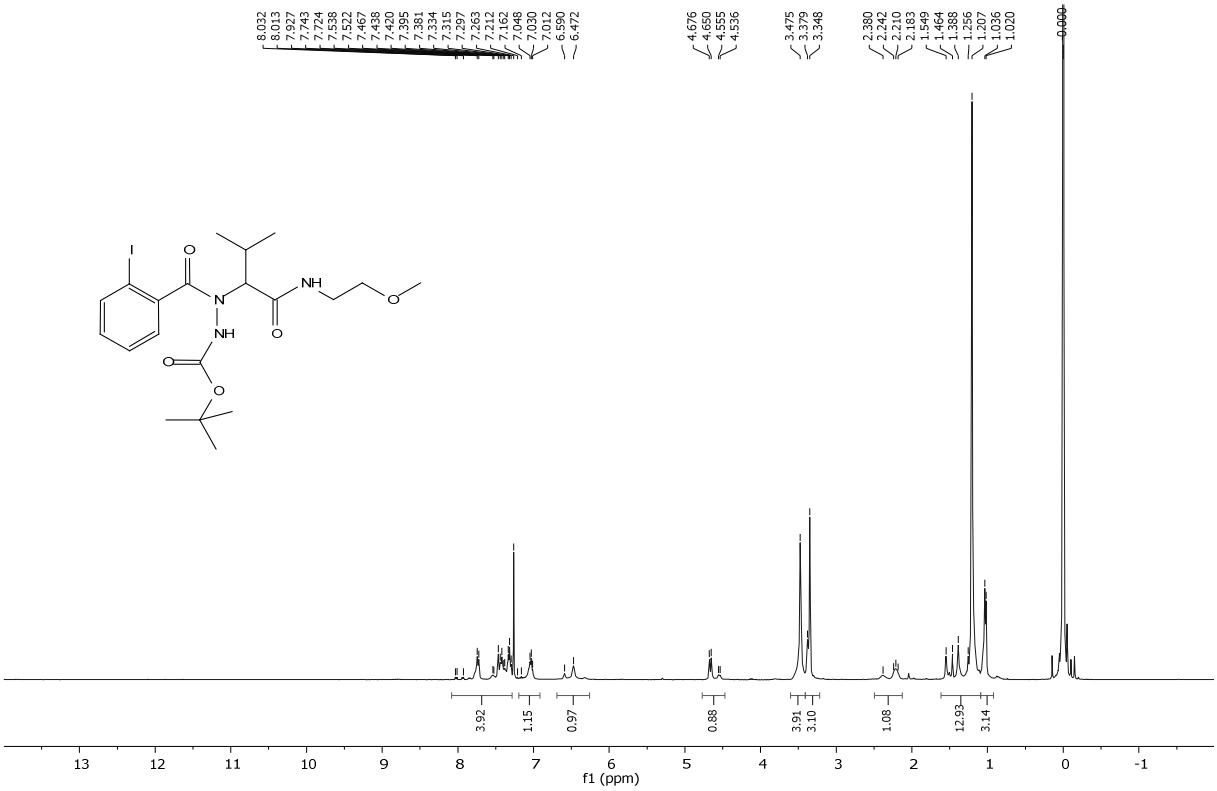

8.352
8.067
8.046
7.940
7.733
7.701
7.679
7.265
6.019
4.617
4.592
2.153
2.137
2.128
2.112
2.096
1.381
1.361
1.196
1.170
1.035
1.019
0.000
Br
O
N
HN
boc
NH
O
NO2
0.75
0.14
1.04
0.75
0.17
1.02
0.16
0.15
0.82
0.16
0.99
0.17
0.10
0.88
3.21
7.44
8.29
2.56
0.76
3.30
f1 (ppm)


7.613
7.477
7.455
7.386
7.350
7.328
7.263
7.006
6.961
6.773
6.767
6.751
6.744
6.612
5.935
5.764
4.532
4.506
4.421
4.403
3.772
2.369
2.200
2.186
2.170
2.145
2.127
2.110
1.362
1.225
1.184
1.168
1.024
1.007
0.000
Br
O
N
HN
boc
NH
O
O
0.68
1.14
1.18
1.21
0.71
0.08
0.79
0.21
3.45
0.14
0.80
10.34
14.90
f1 (ppm)


7.631
7.614
7.595
7.500
7.482
7.437
7.407
7.390
7.370
7.350
7.332
7.317
7.296
7.277
7.260
7.226
7.204
7.180
7.162
7.144
7.134
7.116
7.099
6.714
6.697
5.043
4.428
4.367
4.254
4.225
4.128
4.110
4.090
3.933
3.884
2.679
2.663
2.648
2.634
2.618
1.387
1.373
1.329
1.308
1.276
1.112
1.098
1.037
0.920
0.903
0.000
Br
O
N
NH
NH
O
5.79
9.51
2.98
0.18
1.74
0.28
3.42
0.38
1.00
0.20
6.67
3.47
7.76
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


8.012
7.770
7.750
7.351
7.332
7.313
7.267
7.202
7.198
7.183
7.179
7.083
7.079
7.064
7.060
7.044
7.041
6.796
5.299
2.032
1.808
1.661
1.511
1.412
1.390
1.246
0.000
O
N
NH
NH
O
I
O
O
1.03
0.90
1.24
0.96
0.99
0.95
0.72
0.69
2.97
8.64
3.23
8.96
.4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


9.804
8.689
8.054
8.035
7.987
7.983
7.968
7.964
7.807
7.788
7.742
7.723
7.691
7.664
7.642
7.545
7.526
7.450
7.431
7.412
7.340
7.319
7.309
7.289
7.259
7.205
7.201
7.186
7.182
7.167
7.162
7.154
7.136
7.116
7.096
7.077
7.048
7.033
6.850
6.741
4.816
4.791
4.658
4.639
2.427
2.411
2.396
2.382
1.600
1.500
1.469
1.258
1.241
1.234
1.126
1.117
1.098
H3C
CH3
O
N
HN
boc
NH
O
I
0.26
0.33
0.78
7.98
4.50
0.42
0.48
0.26
0.87
15.07
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)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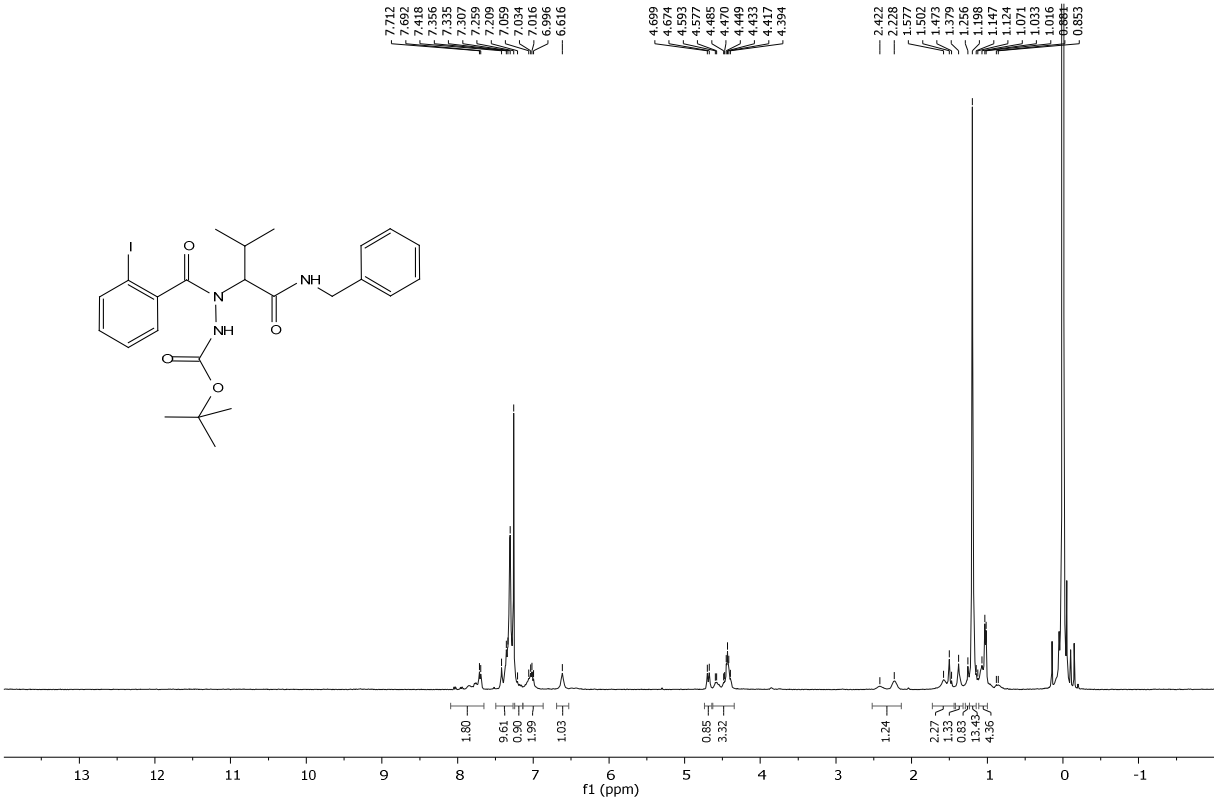
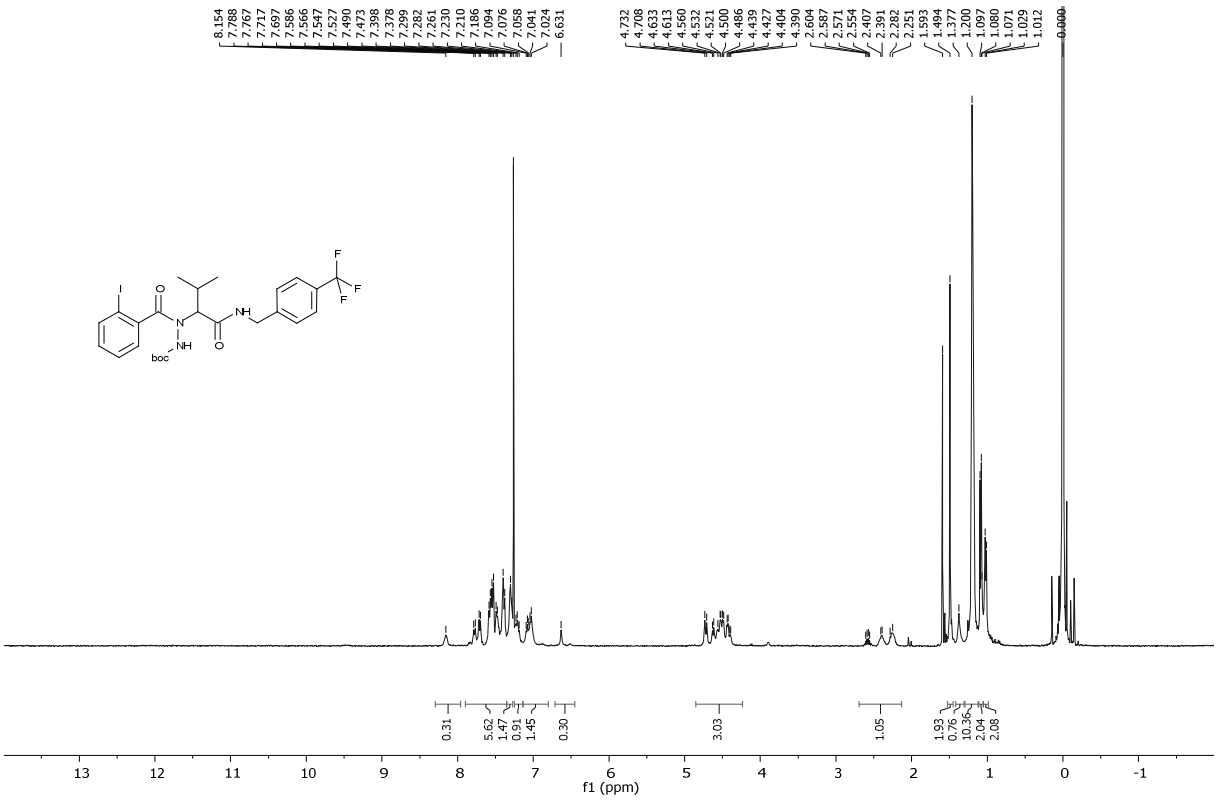
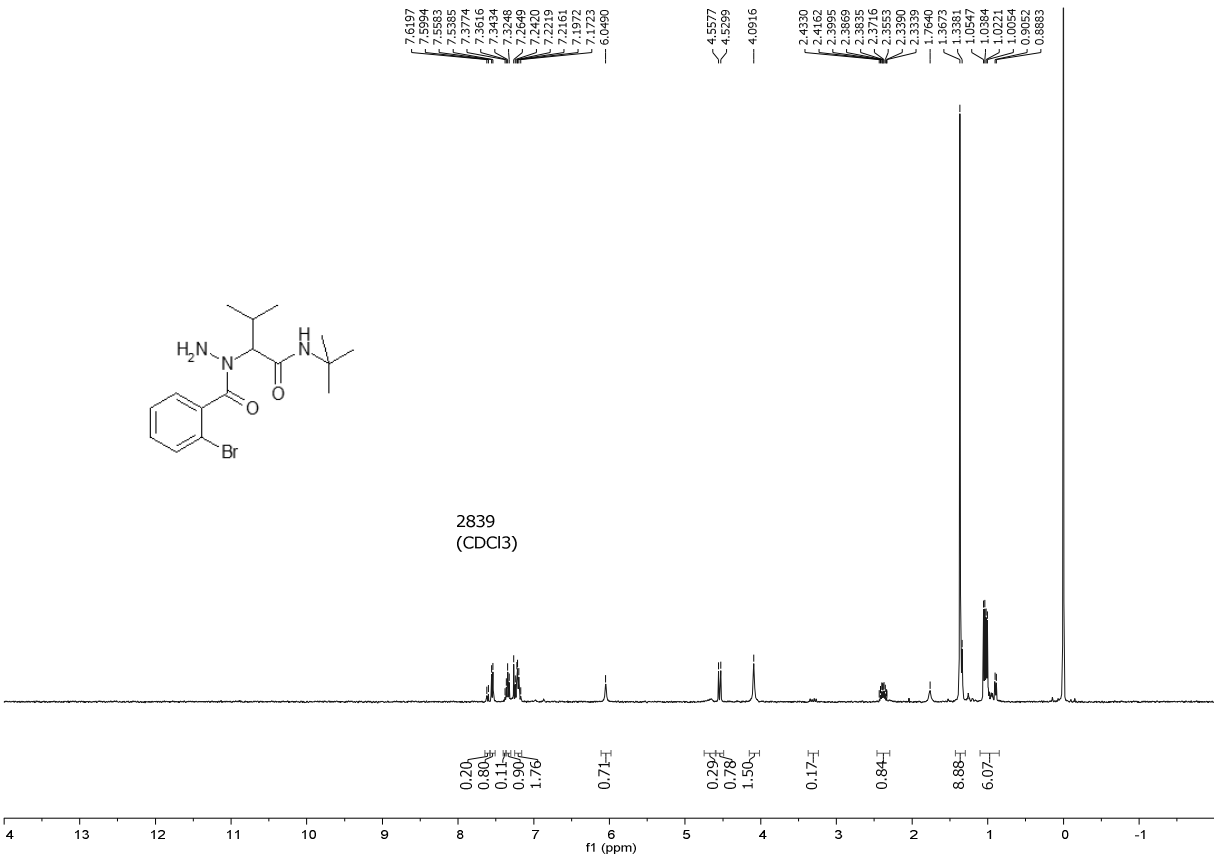
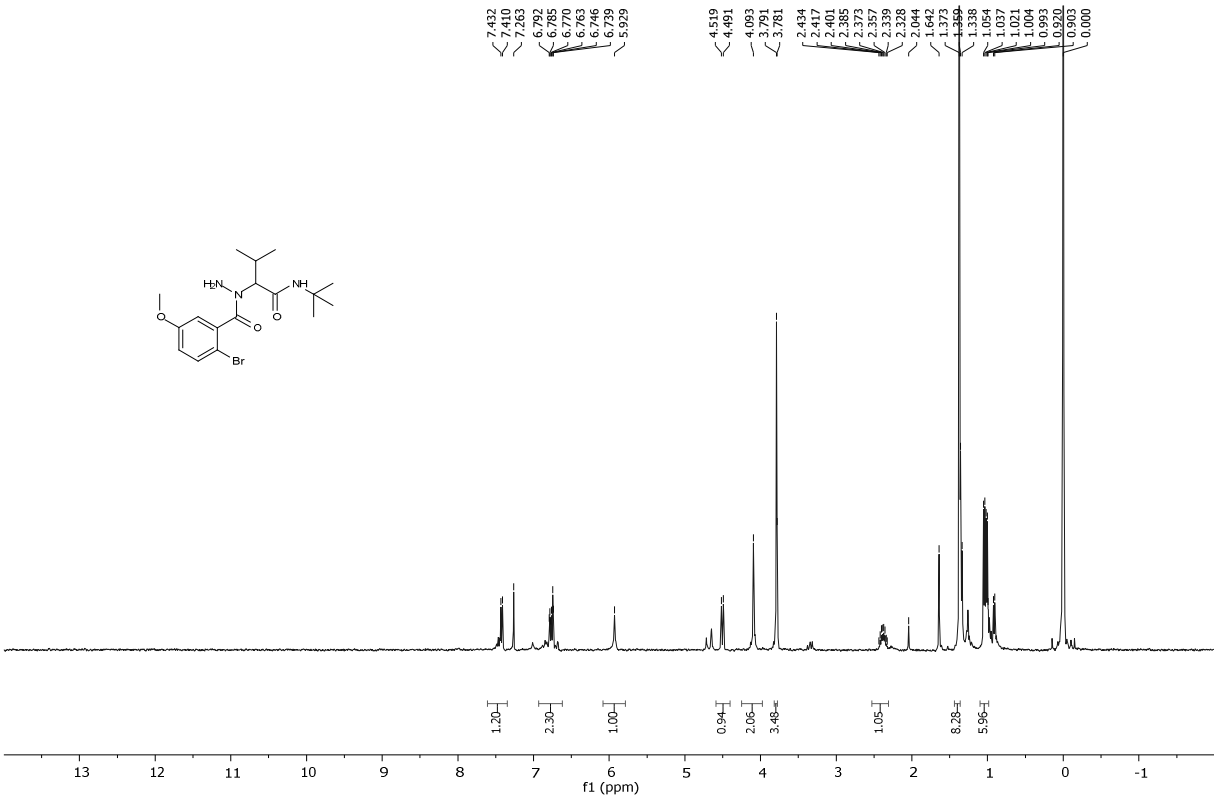
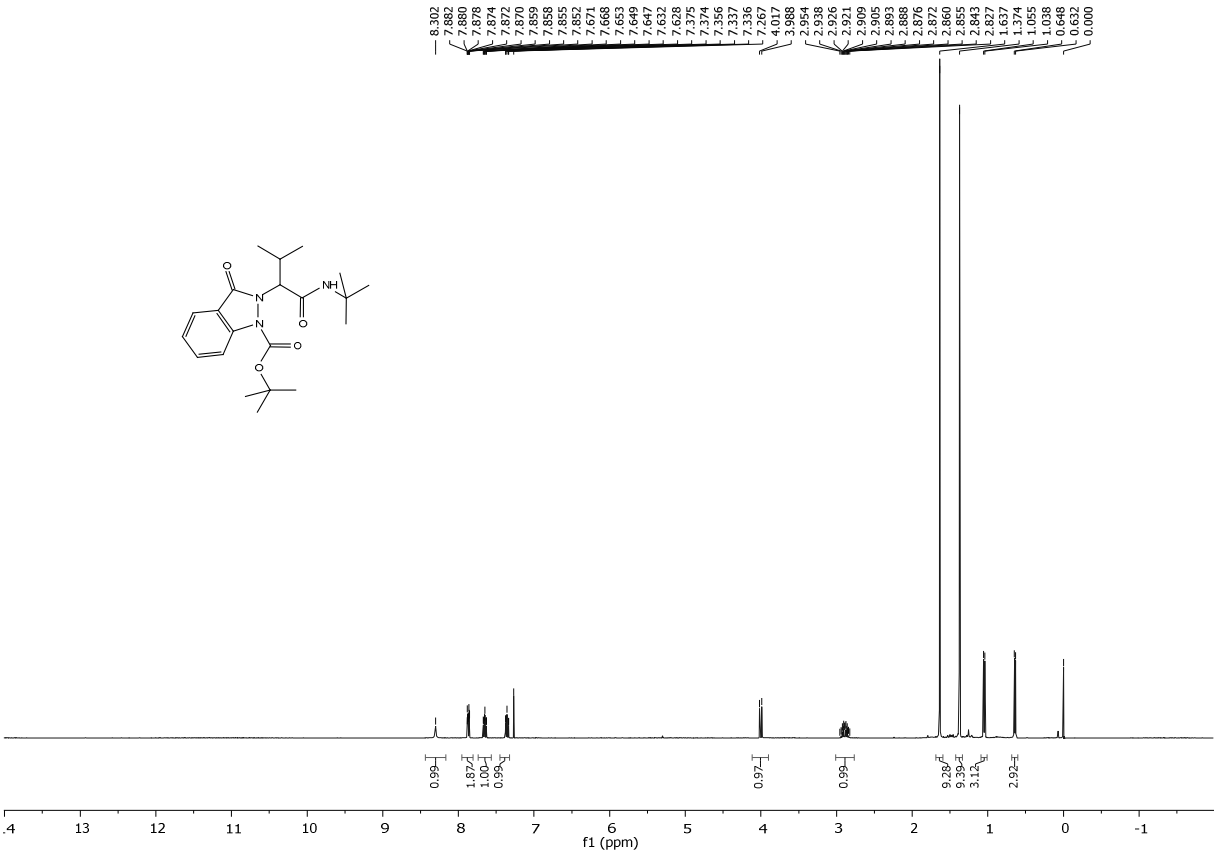
8.013
7.927
7.743
7.724
7.538
7.522
7.467
7.438
7.420
7.395
7.381
7.334
7.315
7.297
7.263
7.212
7.162
7.048
7.030
7.012
6.590
6.472
4.676
4.650
4.555
4.536
3.475
3.379
3.348
2.380
2.242
2.210
2.183
1.549
1.464
1.388
1.256
1.207
1.036
1.020
0.000
I
O
N
NH
O
NH
O
O
O
3.92
1.15
0.97
0.88
3.91
3.10
1.08
12.93
3.14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

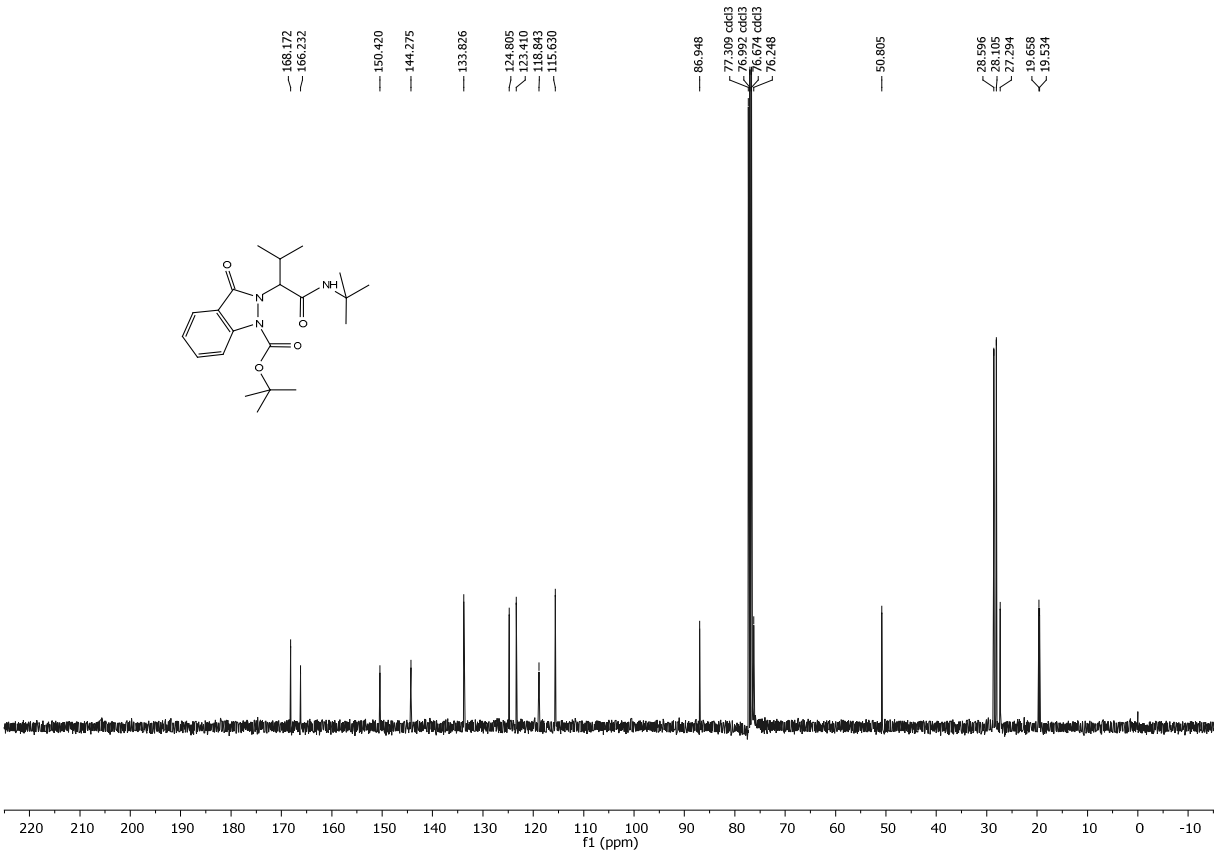

7.712
7.692
7.418
7.356
7.335
7.307
7.259
7.209
7.059
7.034
7.016
6.996
6.616
4.699
4.674
4.593
4.577
4.485
4.470
4.449
4.433
4.417
4.394
2.422
2.228
1.577
1.502
1.473
1.379
1.256
1.198
1.147
1.124
1.071
1.033
1.016
0.881
0.853
I
O
N
NH
O
NH
O
O
O
1.80
9.61
0.90
1.99
1.03
0.85
3.32
1.24
2.27
1.33
0.83
13.43
4.36
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

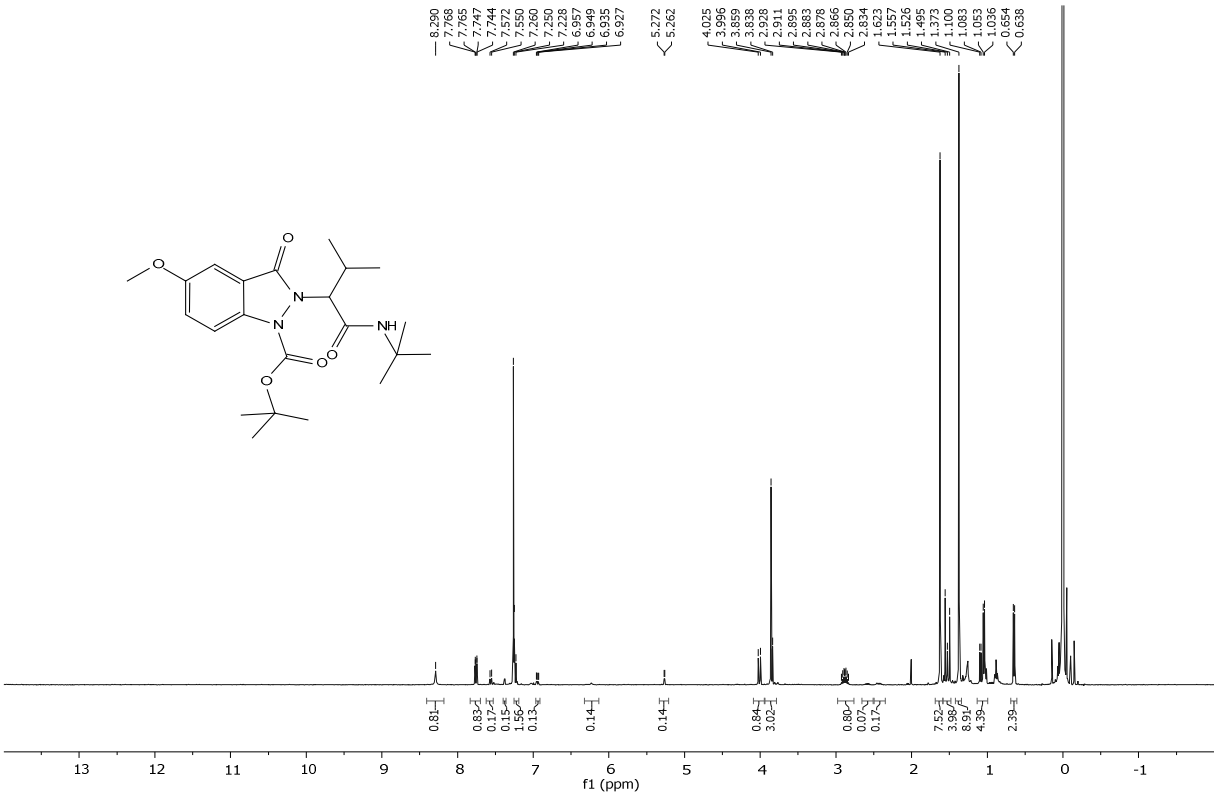

8.154
7.788
7.767
7.717
7.697
7.586
7.566
7.547
7.527
7.490
7.473
7.398
7.378
7.299
7.282
7.261
7.230
7.210
7.186
7.094
7.076
7.058
7.041
7.024
6.631
4.732
4.708
4.633
4.613
4.560
4.532
4.521
4.500
4.486
4.439
4.427
4.404
4.390
2.604
2.587
2.571
2.554
2.407
2.391
2.282
2.251
1.593
1.494
1.377
1.200
1.097
1.080
1.071
1.029
1.012
0.000
I
O
N
NH
boc
O
NH
F
F
F
0.31
5.62
1.47
0.91
1.45
0.30
3.03
1.05
1.93
0.76
10.36
2.04
2.08
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


2839
(CDCl3)
f1 (ppm)


f1 (ppm)


8.302
7.882
7.880
7.878
7.874
7.872
7.870
7.859
7.858
7.855
7.852
7.671
7.668
7.653
7.649
7.647
7.632
7.628
7.375
7.374
7.356
7.337
7.336
7.267
4.017
3.988
2.954
2.938
2.926
2.921
2.909
2.905
2.893
2.888
2.876
2.872
2.860
2.855
2.843
2.827
1.637
1.374
1.055
1.038
0.648
0.632
0.000
0.99
1.87
1.00
0.99
0.97
0.99
9.28
9.39
3.12
2.92
f1 (ppm)


168.172
166.232
150.420
144.275
133.826
124.805
123.410
118.843
115.630
86.948
77.309 cdd3
76.992 cdd3
76.674 cdd3
76.248
50.805
28.596
28.105
27.294
19.658
19.534
f1 (ppm)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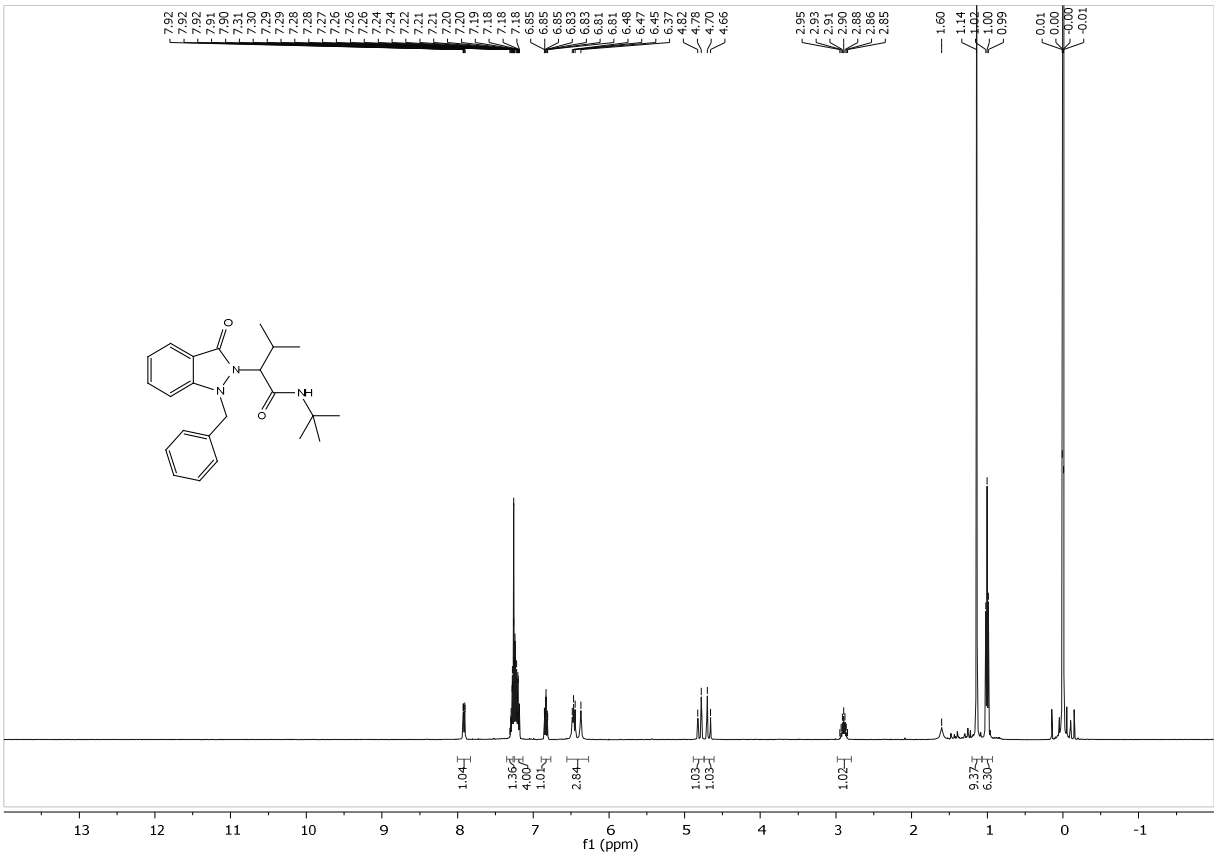
7.768
7.765
7.747
7.744
7.572
7.550
7.260
7.250
7.228
6.957
6.949
6.935
6.927
5.272
5.262
4.025
3.996
3.859
3.838
2.928
2.911
2.895
2.883
2.878
2.866
2.850
2.834
1.623
1.557
1.526
1.495
1.373
1.100
1.083
1.053
1.036
0.654
0.638
O
N
N
NH
O
O
O
0.81
0.83
0.17
0.15
1.56
0.13
0.14
0.14
0.84
3.02
0.80
0.07
0.17
7.52
3.98
8.91
4.39
2.39
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)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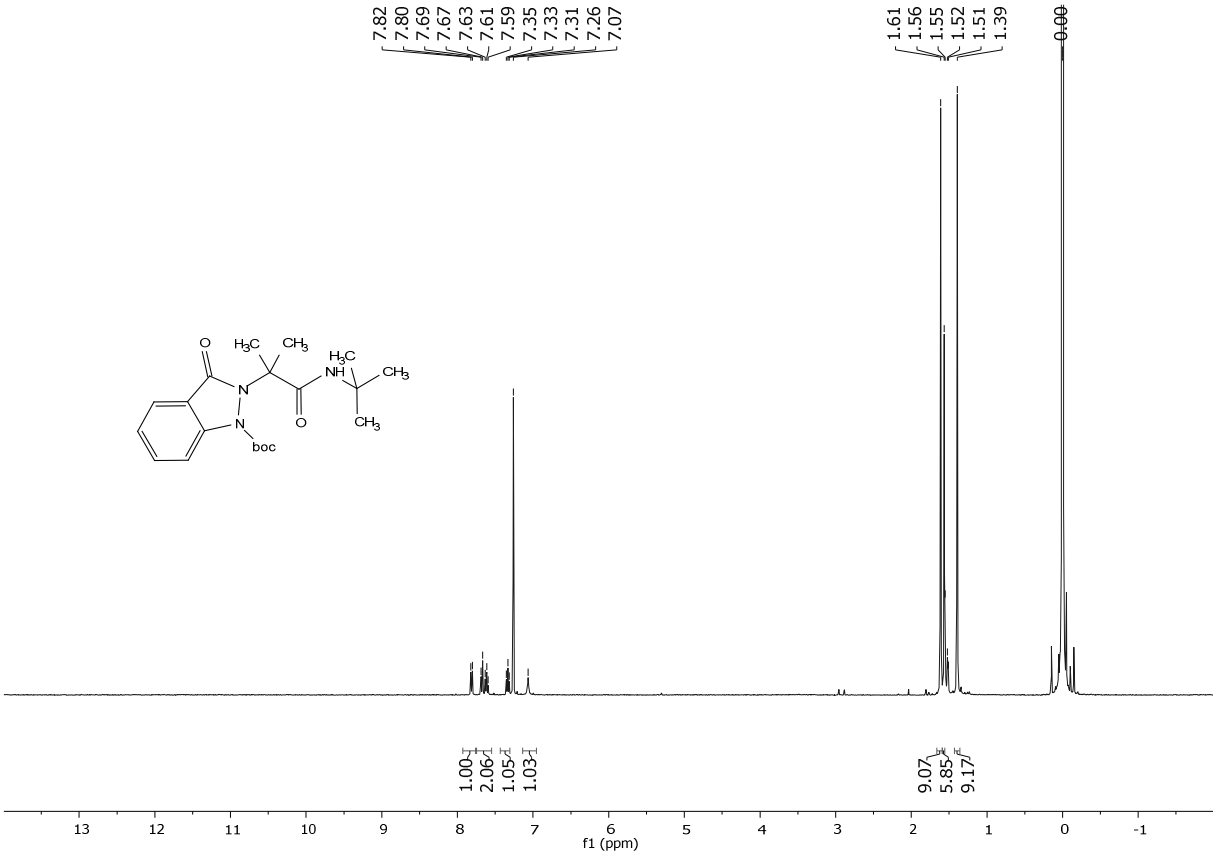
7.92
7.92
7.91
7.90
7.31
7.30
7.29
7.29
7.28
7.28
7.27
7.26
7.26
7.26
7.24
7.24
7.22
7.21
7.21
7.20
7.20
7.19
7.18
7.18
7.18
6.85
6.85
6.85
6.83
6.83
6.81
6.81
6.48
6.47
6.45
6.37
4.82
4.78
4.70
4.66
2.95
2.93
2.91
2.90
2.88
2.86
2.85
1.60
1.14
1.02
1.00
0.99
0.01
0.00
-0.00
-0.01
O
N
N
NH
O
1.04
1.36
4.00
1.01
2.84
1.03
1.03
1.02
9.37
6.30
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)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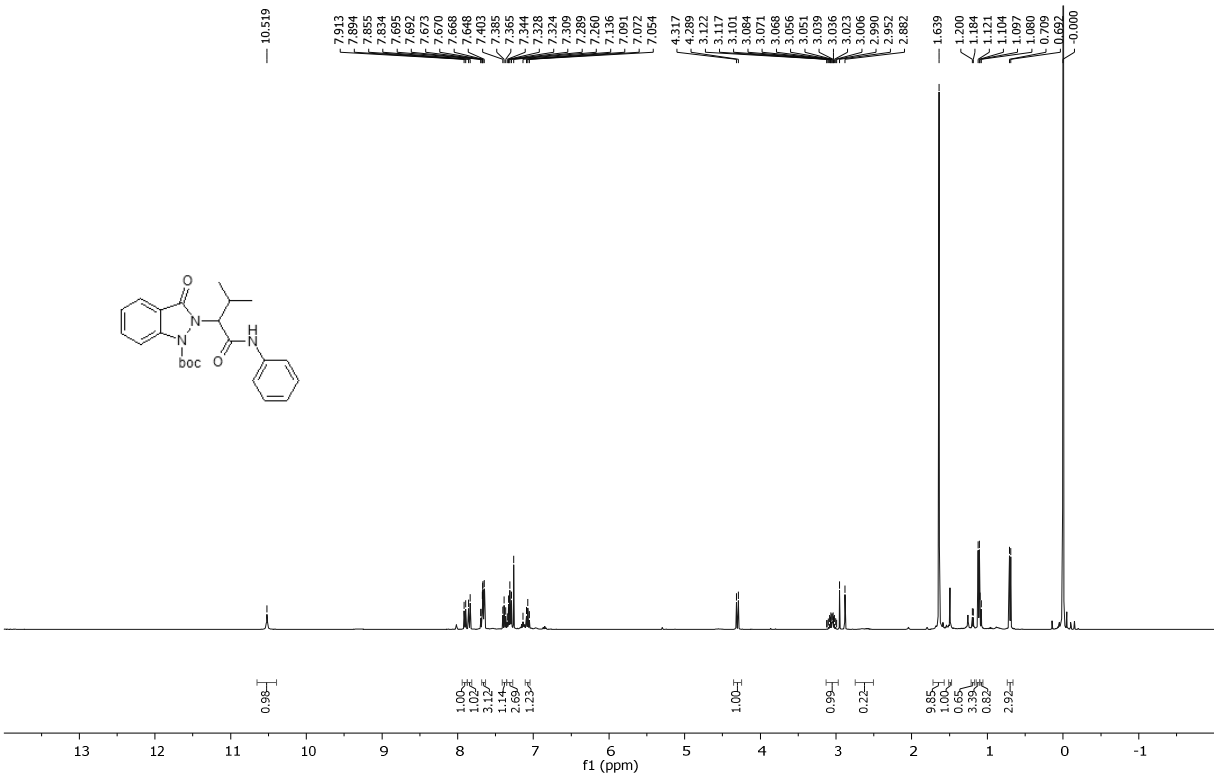
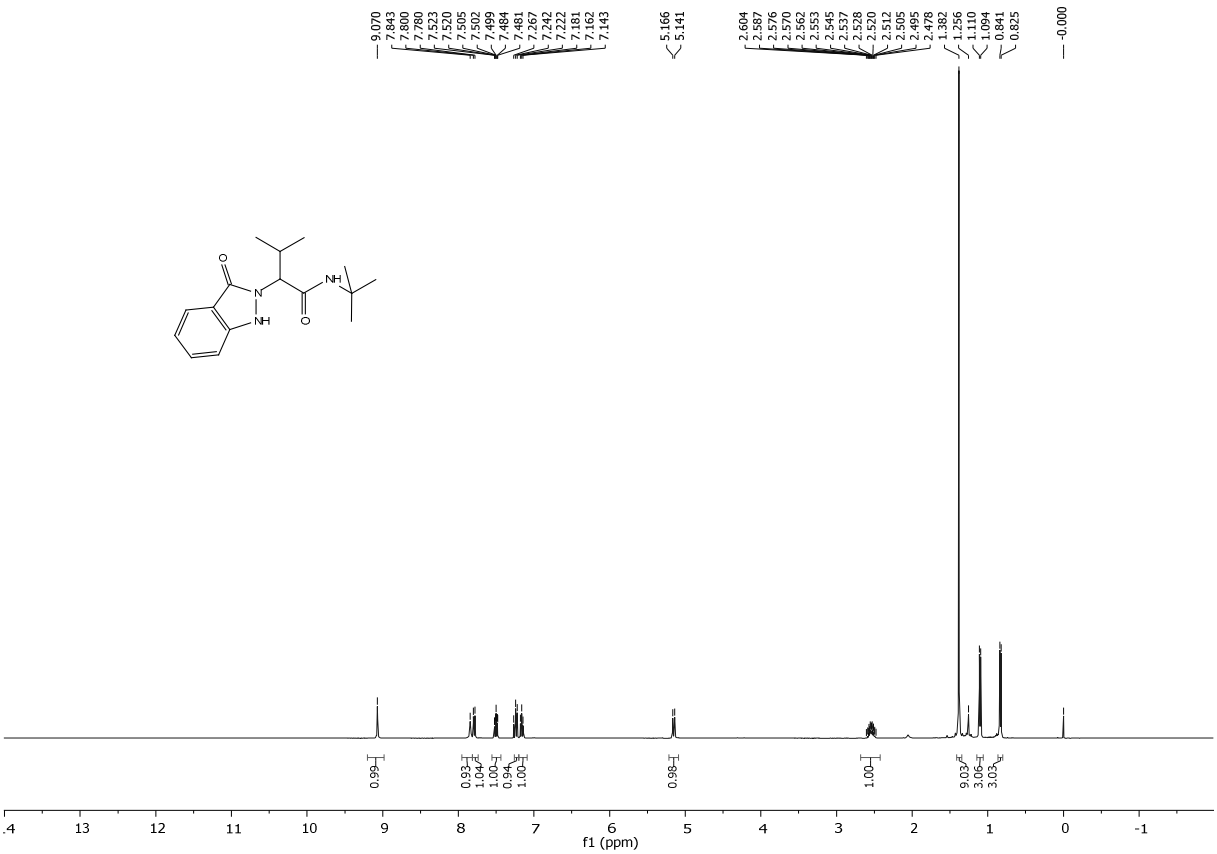
7.80
7.69
7.67
7.63
7.61
7.59
7.35
7.33
7.31
7.26
7.07
1.61
1.56
1.55
1.52
1.51
1.39
0.00
1.00
2.06
1.05
1.03
9.07
5.85
9.17
f1 (ppm)


10.519
7.913
7.894
7.855
7.834
7.695
7.692
7.673
7.670
7.668
7.648
7.403
7.385
7.365
7.344
7.328
7.324
7.309
7.289
7.260
7.136
7.091
7.072
7.054
4.317
4.289
3.122
3.117
3.101
3.084
3.071
3.068
3.056
3.051
3.039
3.036
3.023
3.006
2.990
2.952
2.882
1.639
1.200
1.184
1.121
1.104
1.097
1.080
0.709
0.692
-0.000
0.98
1.00
1.02
3.12
1.14
2.69
1.23
1.00
0.99
0.22
9.85
1.00
0.65
3.39
0.82
2.92
f1 (ppm)


9.070
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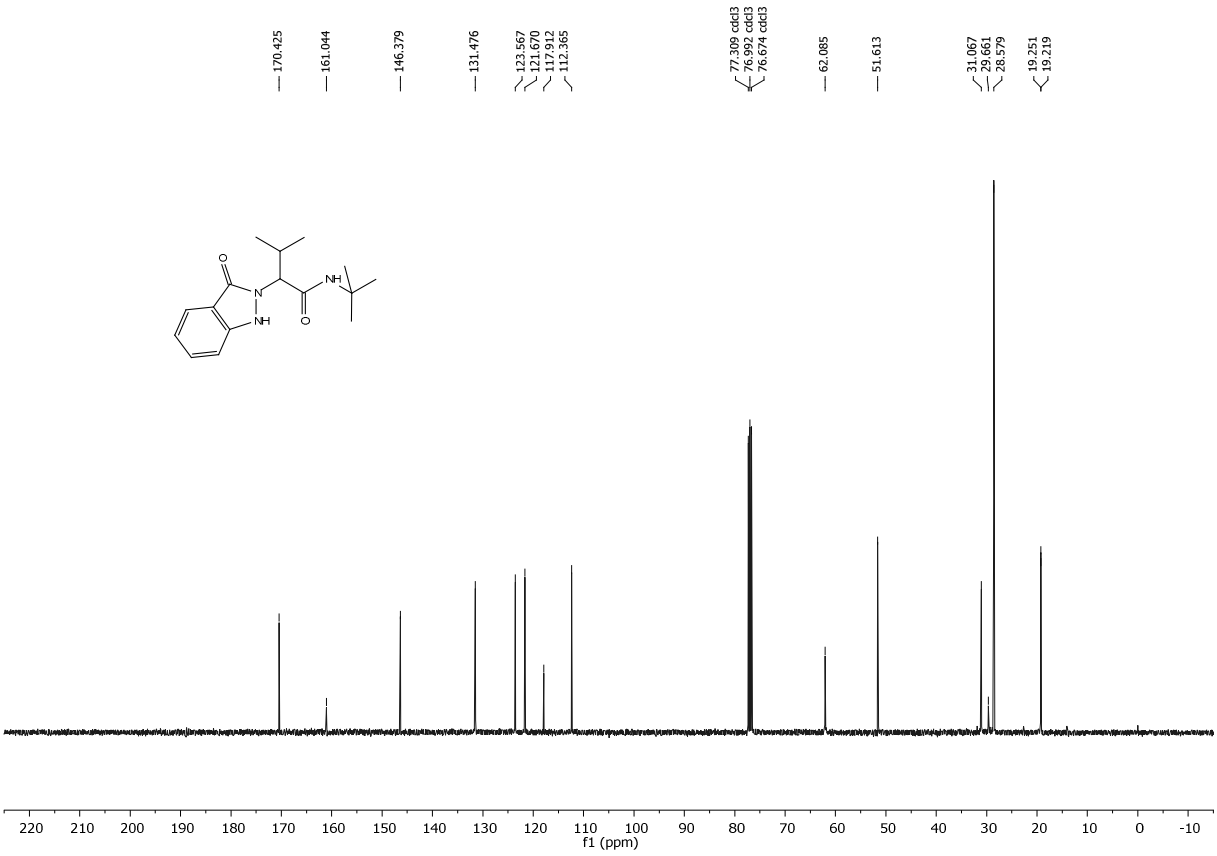
7.800
7.780
7.523
7.520
7.505
7.502
7.499
7.484
7.481
7.267
7.242
7.222
7.181
7.162
7.143
5.166
5.141
2.604
2.587
2.576
2.570
2.562
2.553
2.545
2.537
2.528
2.520
2.512
2.505
2.495
2.478
1.382
1.256
1.110
1.094
0.841
0.825
-0.000
0.99
0.93
1.04
1.00
0.94
1.00
0.98
1.00
9.03
3.06
3.05
f1 (ppm)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121.670
117.912
112.365
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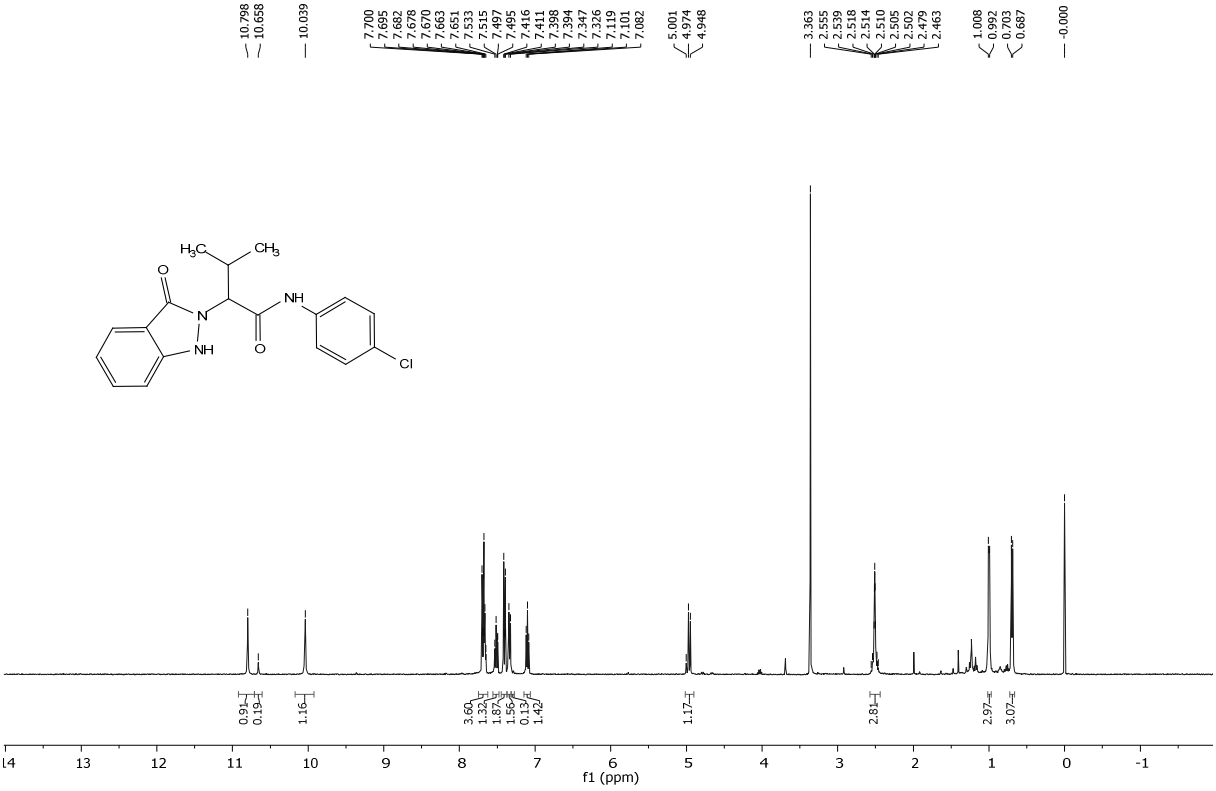
76.992 cdcl3
76.674 cdcl3
62.085
51.613
31.067
29.661
28.579
19.251
19.219
f1 (ppm)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10.039
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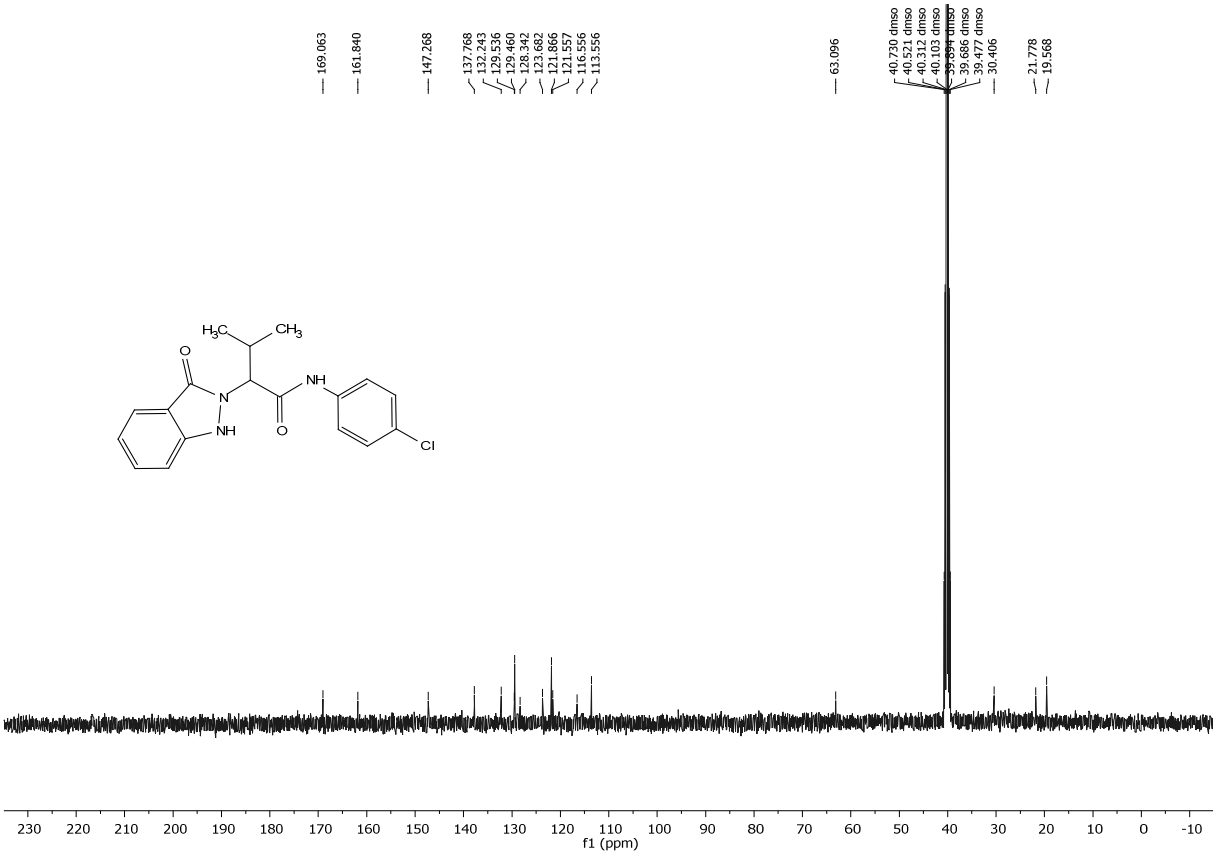
7.695
7.682
7.678
7.670
7.663
7.651
7.533
7.515
7.497
7.495
7.416
7.411
7.398
7.394
7.347
7.326
7.119
7.101
7.082
5.001
4.974
4.948
3.363
2.595
2.539
2.518
2.514
2.510
2.505
2.502
2.479
2.463
1.008
0.992
0.703
0.687
-0.000
H3C
CH3
O
N
NH
O
NH
Cl
0.91
0.19
1.16
3.60
1.32
1.87
1.56
0.13
1.42
1.17
2.81
2.97
3.07
f1 (ppm)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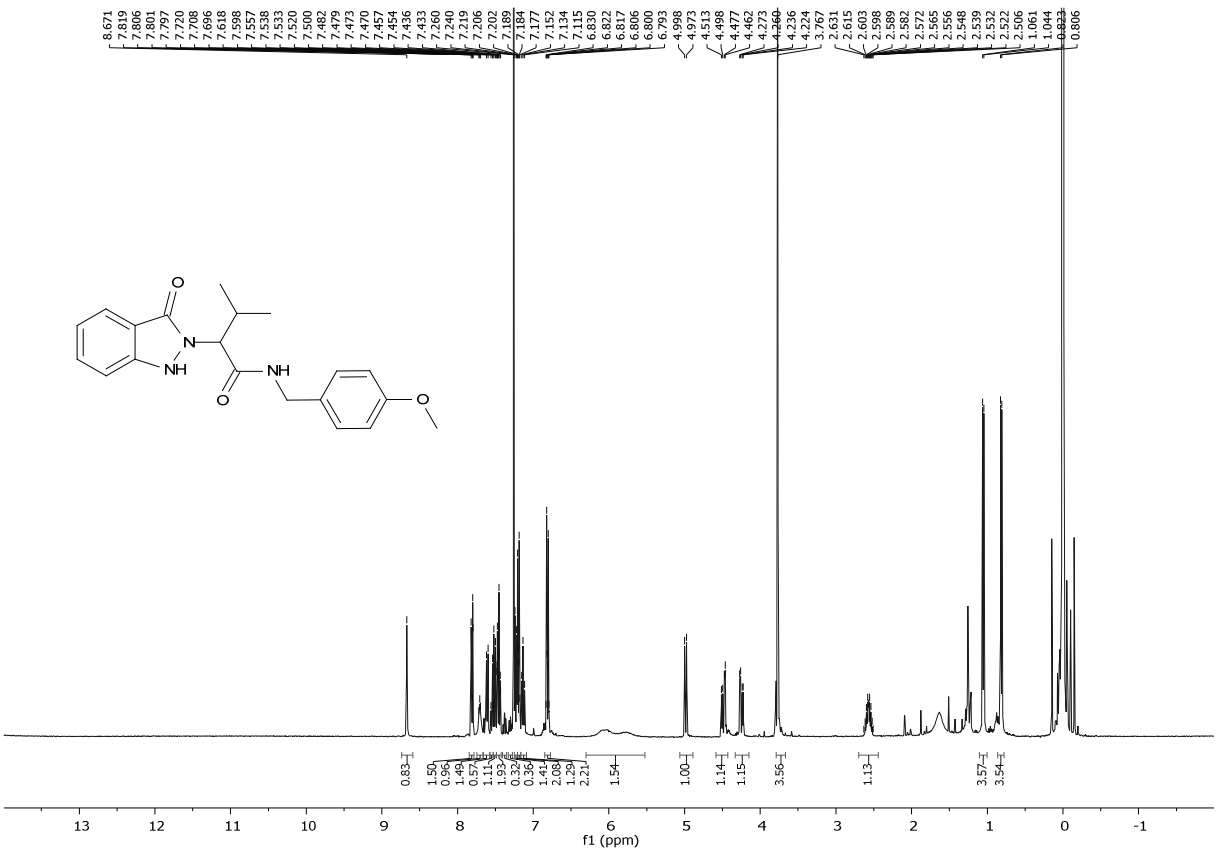
147.268
137.768
132.243
129.536
129.460
128.342
123.682
121.866
121.557
116.556
113.556
63.096
40.730 dmso
40.521 dmso
40.312 dmso
40.103 dmso
39.894 dmso
39.686 dmso
39.477 dmso
30.406
21.778
19.568
H3C
CH3
O
N
NH
O
NH
Cl
f1 (ppm)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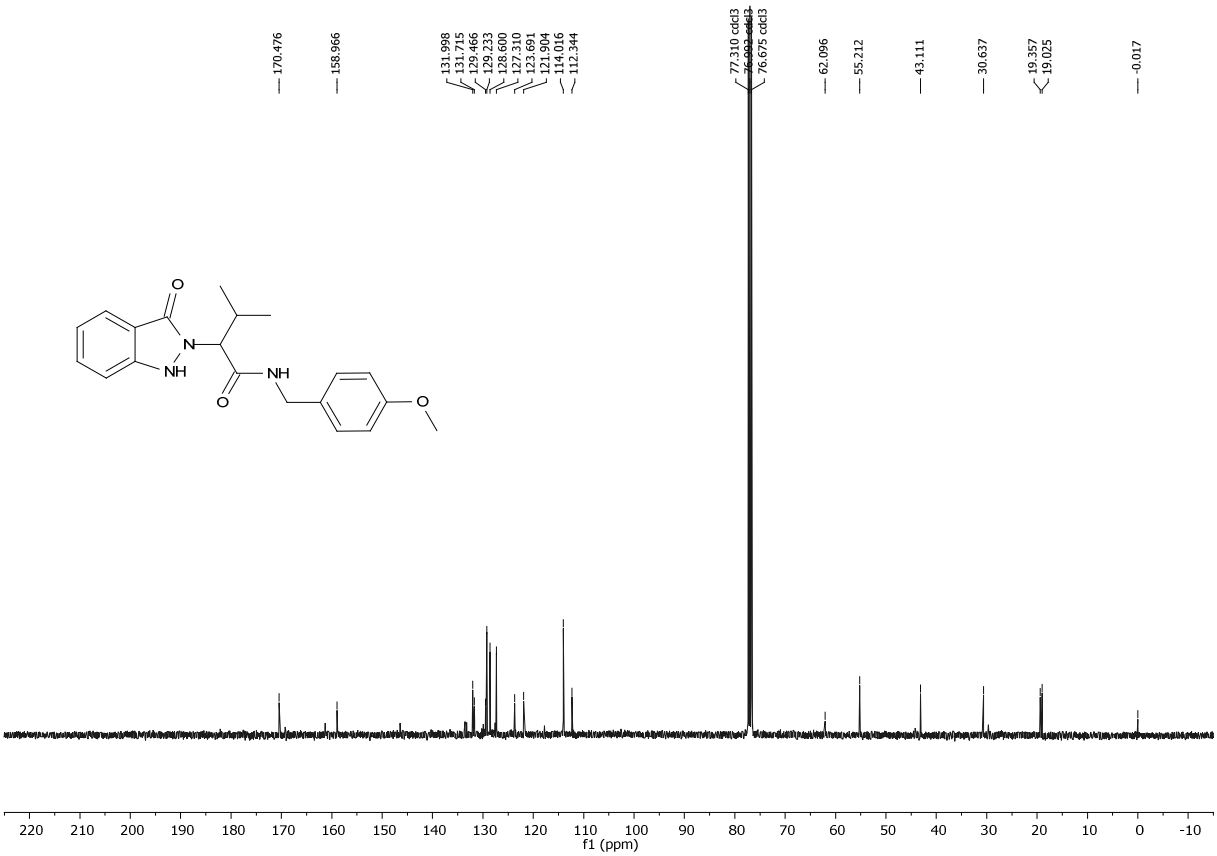
7.797
7.720
7.708
7.696
7.618
7.598
7.557
7.538
7.533
7.520
7.500
7.482
7.479
7.473
7.470
7.457
7.454
7.436
7.433
7.260
7.240
7.219
7.206
7.202
7.189
7.184
7.177
7.152
7.134
7.115
6.830
6.822
6.817
6.806
6.800
6.793
4.998
4.973
4.513
4.498
4.477
4.462
4.273
4.260
4.236
4.224
3.767
2.631
2.615
2.603
2.598
2.589
2.582
2.572
2.565
2.556
2.548
2.539
2.532
2.522
2.506
1.061
1.044
0.883
0.806
O
N
NH
NH
O
O
0.83
1.50
0.95
1.49
0.57
1.11
1.93
0.32
0.36
1.41
2.08
1.29
2.21
1.54
1.00
1.14
1.15
3.56
1.13
3.57
3.54
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)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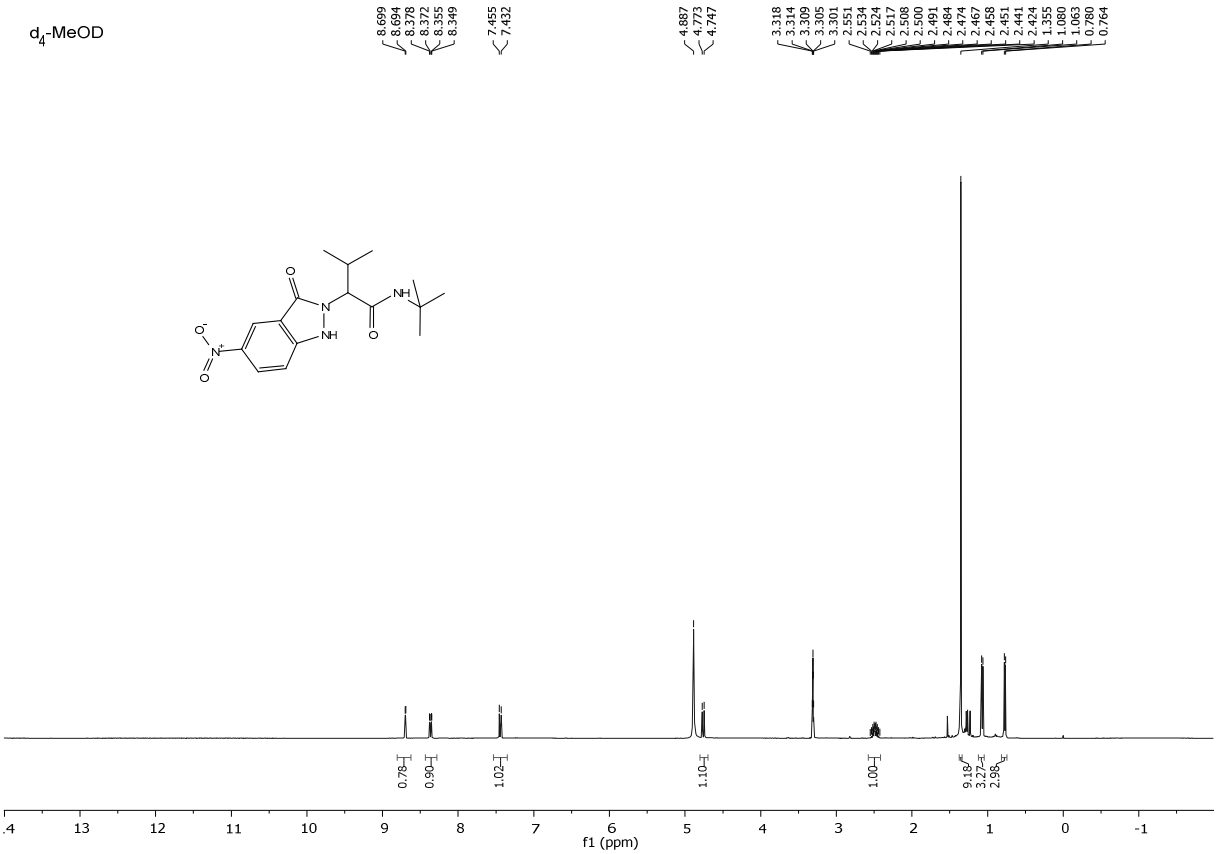
158.966
131.998
131.715
129.466
129.233
128.600
127.310
123.691
121.904
114.016
112.344
77.310 cdcl3
76.993 cdcl3
76.675 cdcl3
62.096
55.212
43.111
30.637
19.357
19.025
-0.017
O
N
NH
NH
O
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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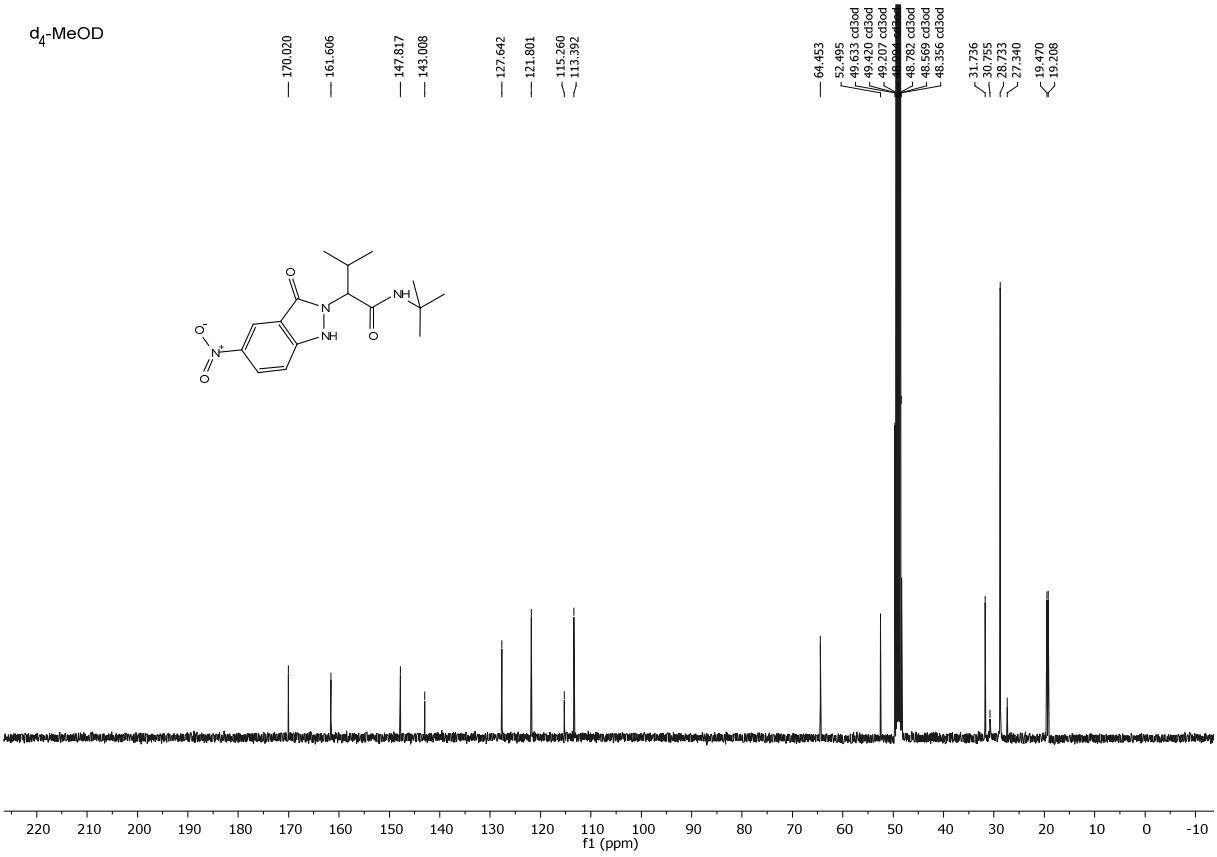
8.694
8.378
8.372
8.355
8.349
7.455
7.432
4.887
4.773
4.747
3.318
3.314
3.309
3.305
3.301
2.551
2.534
2.524
2.517
2.508
2.500
2.491
2.484
2.474
2.467
2.458
2.451
2.441
2.424
1.355
1.080
1.063
0.780
0.764
0.78
0.90
1.02
1.10
1.00
9.18
3.27
2.98
f1 (ppm)


d4-MeOD
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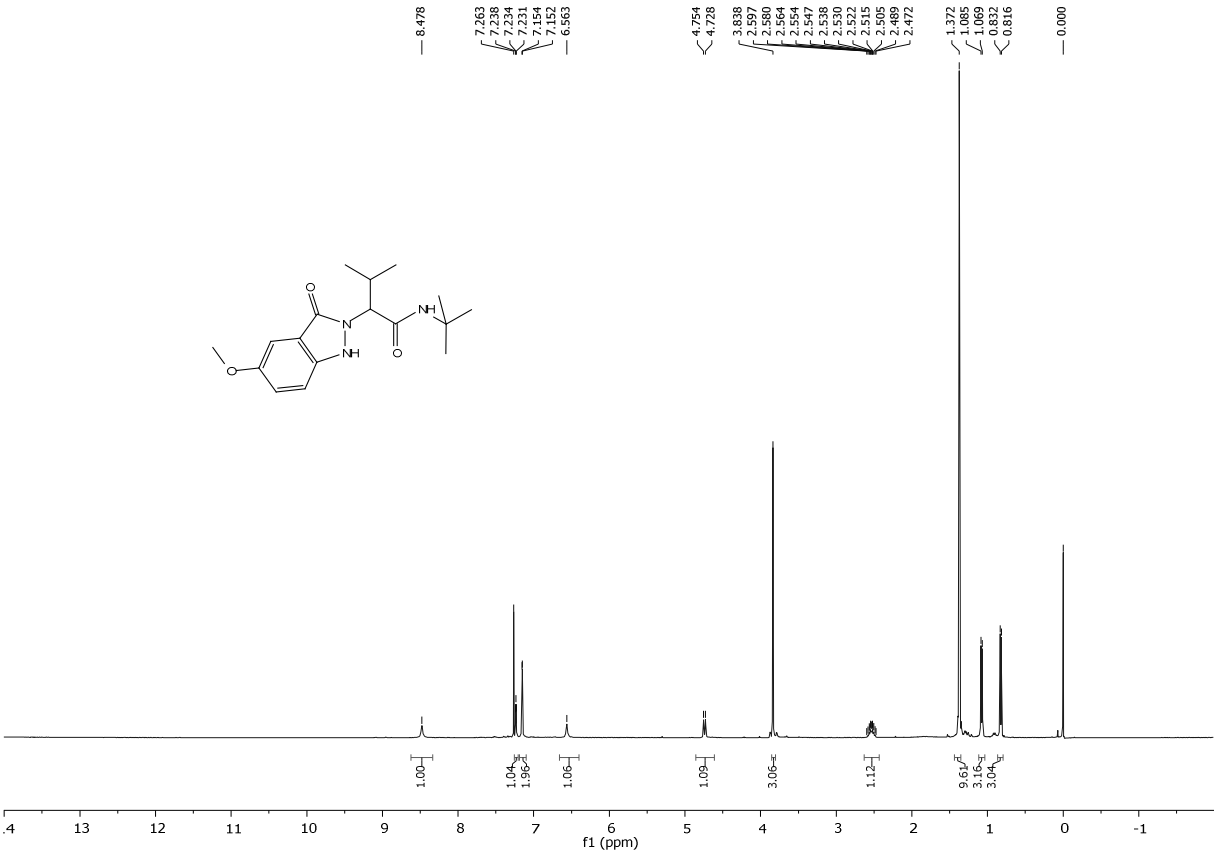
161.606
147.817
143.008
127.642
121.801
115.260
113.392
64.453
52.495
49.633 cd3od
49.420 cd3od
49.207 cd3od
48.782 cd3od
48.569 cd3od
48.356 cd3od
31.736
30.755
28.733
27.340
19.470
19.208
f1 (ppm)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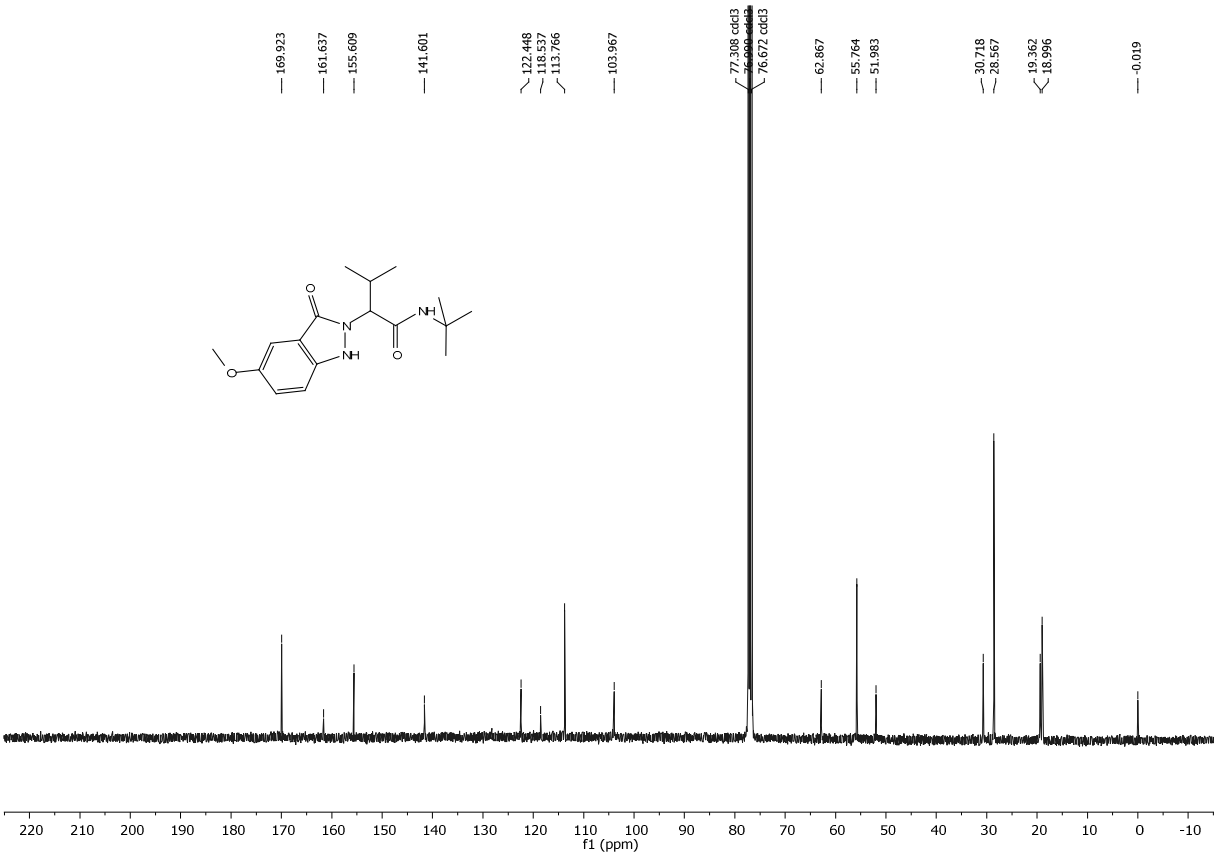
7.263
7.238
7.234
7.231
7.154
7.152
6.563
4.754
4.728
3.838
2.597
2.580
2.564
2.554
2.547
2.538
2.530
2.522
2.515
2.505
2.489
2.472
1.372
1.085
1.069
0.832
0.816
0.000
1.00
1.04
1.96
1.06
1.09
3.06
1.12
9.61
3.16
3.04
f1 (ppm)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161.637
155.609
141.601
122.448
118.537
113.766
103.967
77.308 cdcl3
76.672 cdcl3
62.867
55.764
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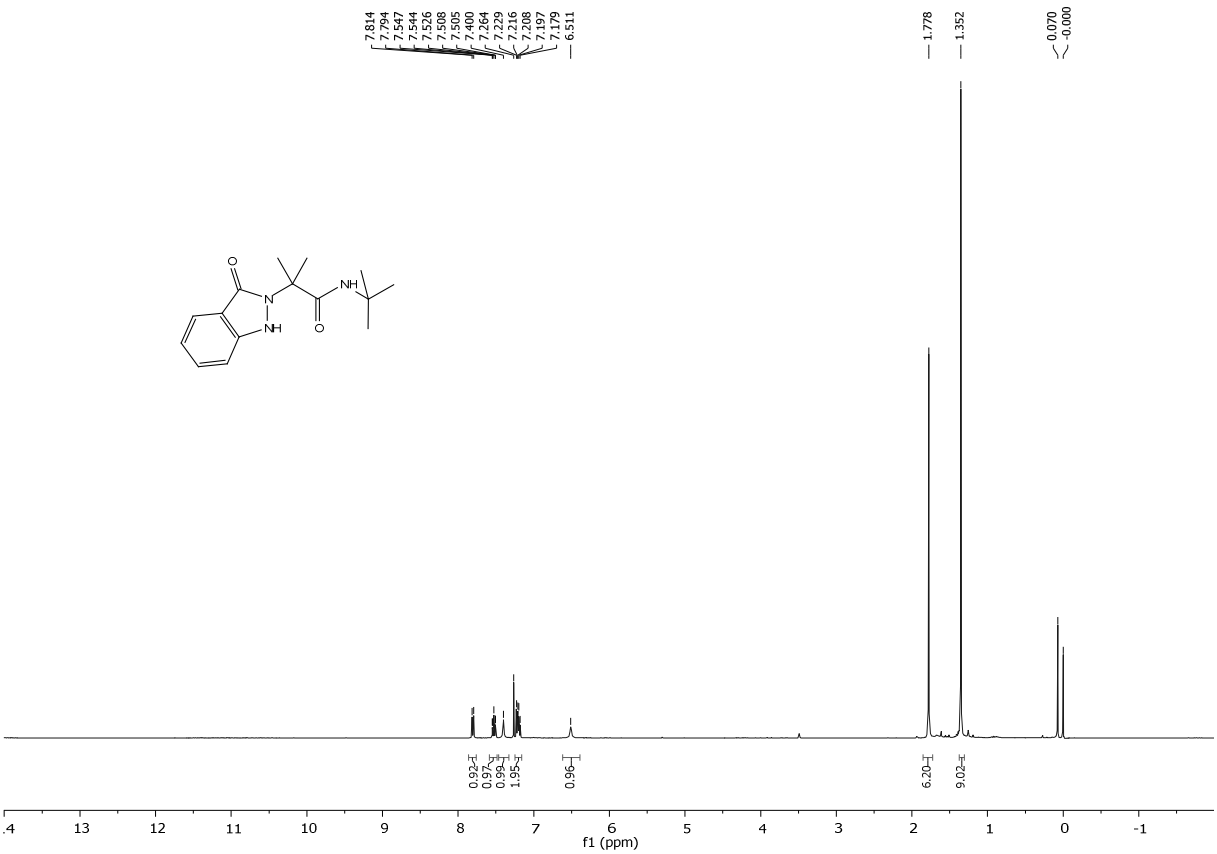
30.718
28.567
19.362
18.996
-0.019
f1 (ppm)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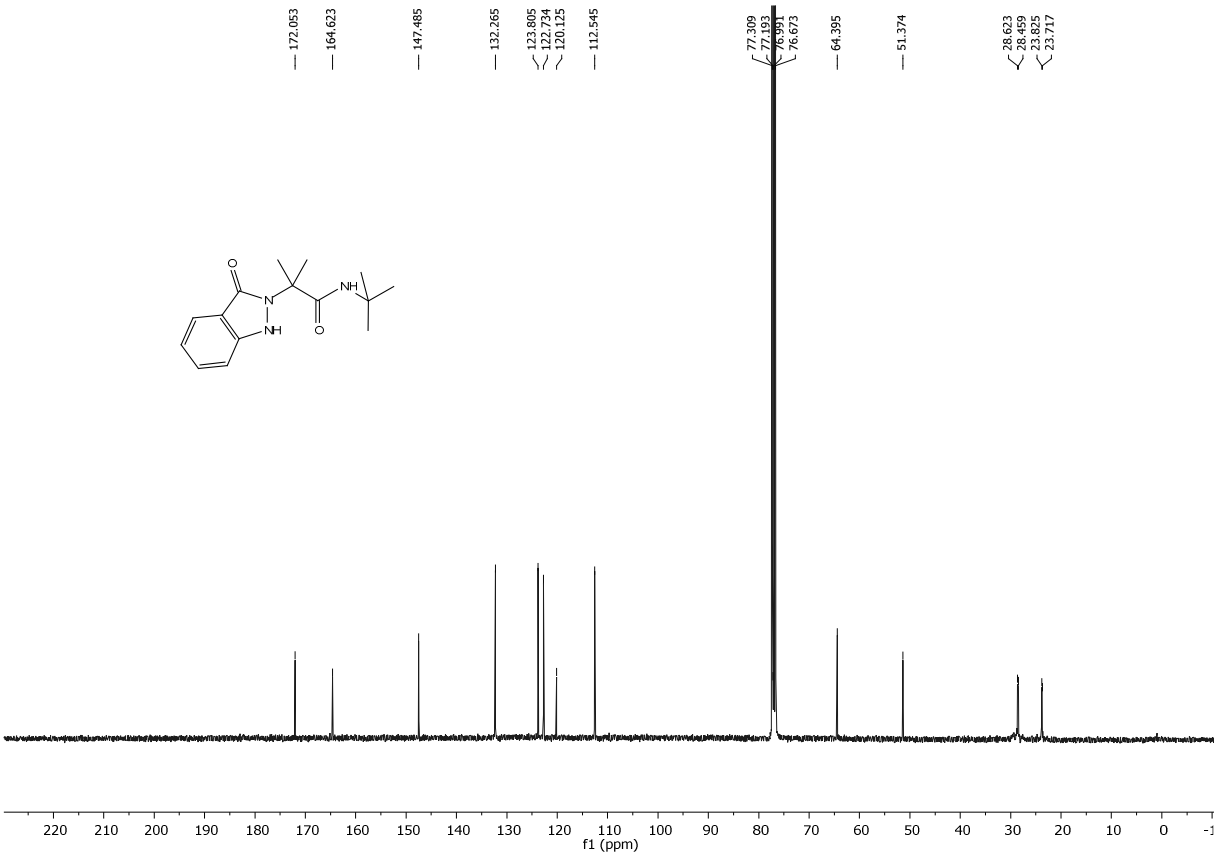
7.794
7.547
7.544
7.526
7.508
7.505
7.400
7.264
7.229
7.216
7.208
7.197
7.179
6.511
1.778
1.352
0.070
-0.000
O
N
NH
NH
O
0.92
0.92
0.94
1.95
0.96
6.20
9.02
f1 (ppm)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132.265
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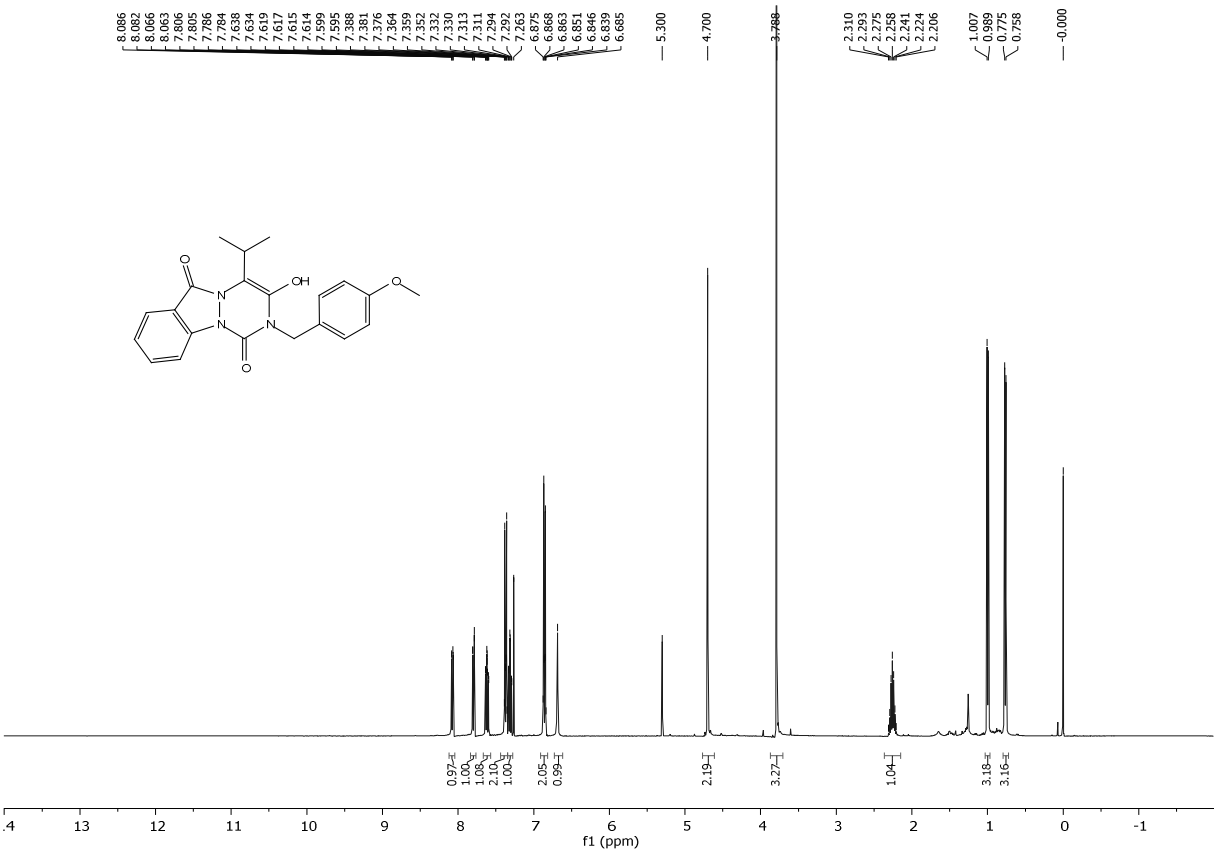
122.734
120.125
112.545
77.309
77.193
76.991
76.673
64.395
51.374
28.623
28.459
23.825
23.717
O
N
NH
NH
O
f1 (ppm)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8.082
8.066
8.063
7.806
7.805
7.786
7.784
7.638
7.634
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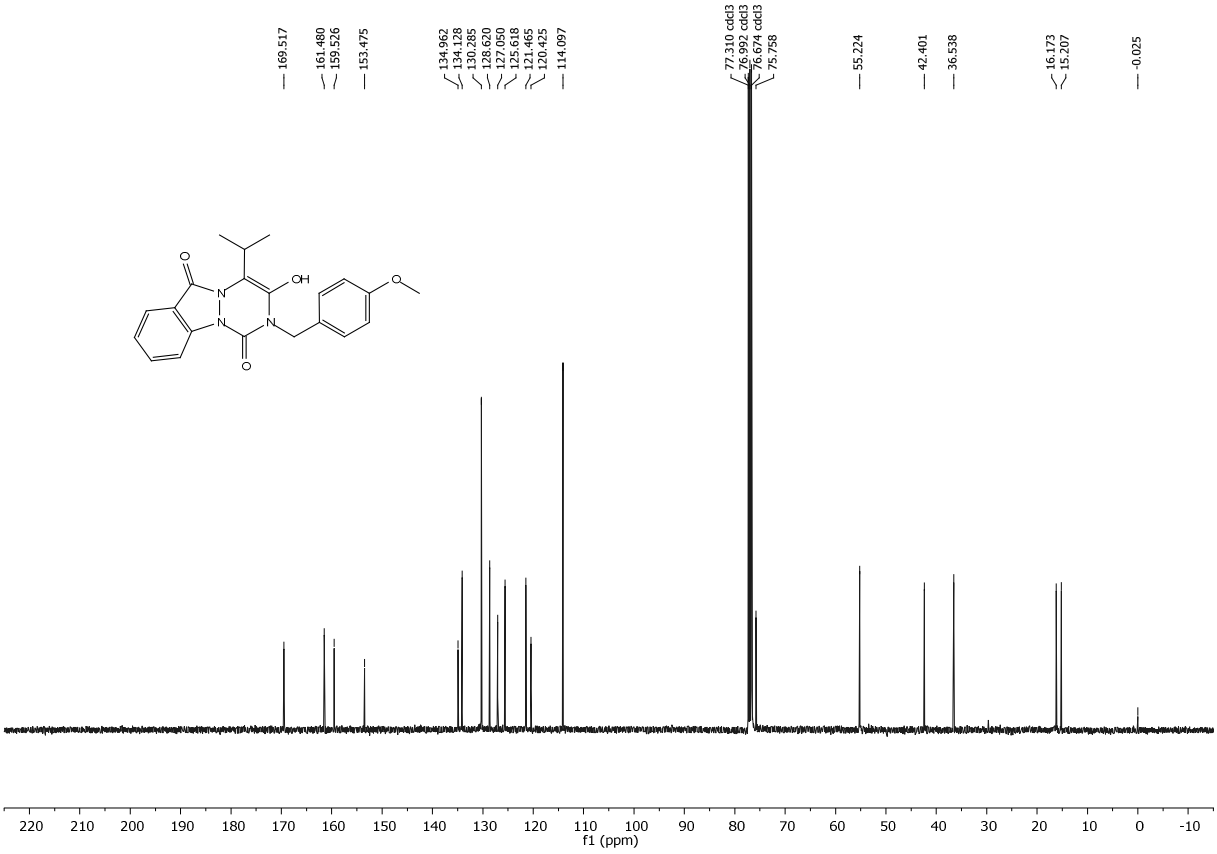
7.617
7.615
7.614
7.599
7.595
7.388
7.381
7.376
7.364
7.359
7.352
7.332
7.330
7.313
7.311
7.294
7.292
7.263
6.875
6.868
6.863
6.851
6.846
6.839
6.685
5.300
4.700
3.788
2.310
2.293
2.275
2.258
2.241
2.224
2.206
1.007
0.989
0.775
0.758
-0.000
OH
O
N
N
N
O
O
0.97
1.00
1.08
2.10
1.00
2.05
0.99
2.19
3.27
1.04
3.18
3.16
f1 (ppm)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159.526
153.475
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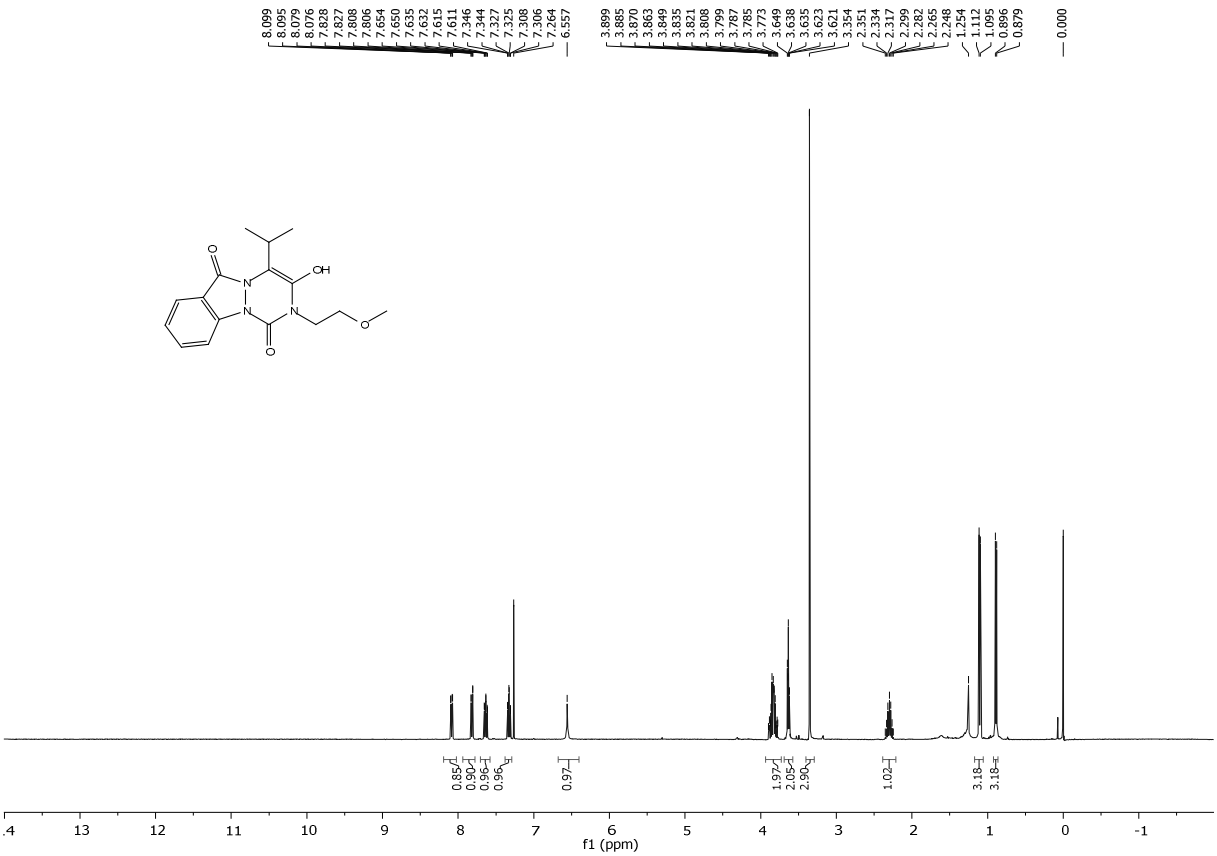
134.128
130.285
128.620
127.050
125.618
121.465
120.425
114.097
77.310 cdcl3
76.992 cdcl3
76.674 cdcl3
75.758
55.224
42.401
36.538
16.173
15.207
-0.025
OH
O
N
N
N
O
O
f1 (ppm)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8.095
8.079
8.076
7.828
7.827
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7.806
7.654
7.650
7.635
7.632
7.615
7.611
7.346
7.344
7.327
7.325
7.308
7.306
7.264
6.557
3.899
3.885
3.870
3.863
3.849
3.835
3.821
3.808
3.799
3.787
3.785
3.773
3.649
3.638
3.635
3.623
3.621
3.354
2.351
2.334
2.317
2.299
2.282
2.265
2.248
1.254
1.112
1.095
0.896
0.879
0.000
OH
O
N
N
N
O
O
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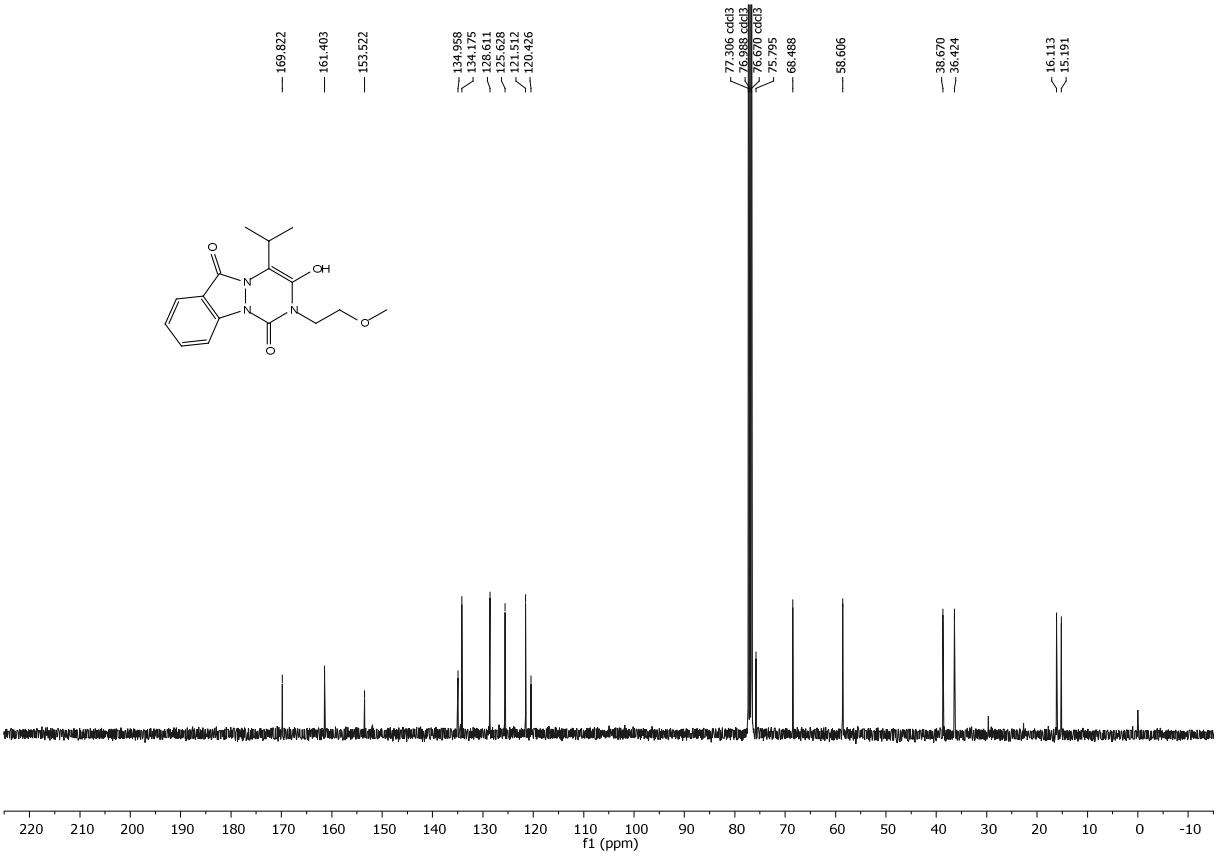
0.96
0.96
0.97
1.97
2.05
2.90
1.02
3.18
3.18
f1 (ppm)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76.988 cdd3
76.670 cdd3
75.795
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38.670
36.424
16.113
15.191
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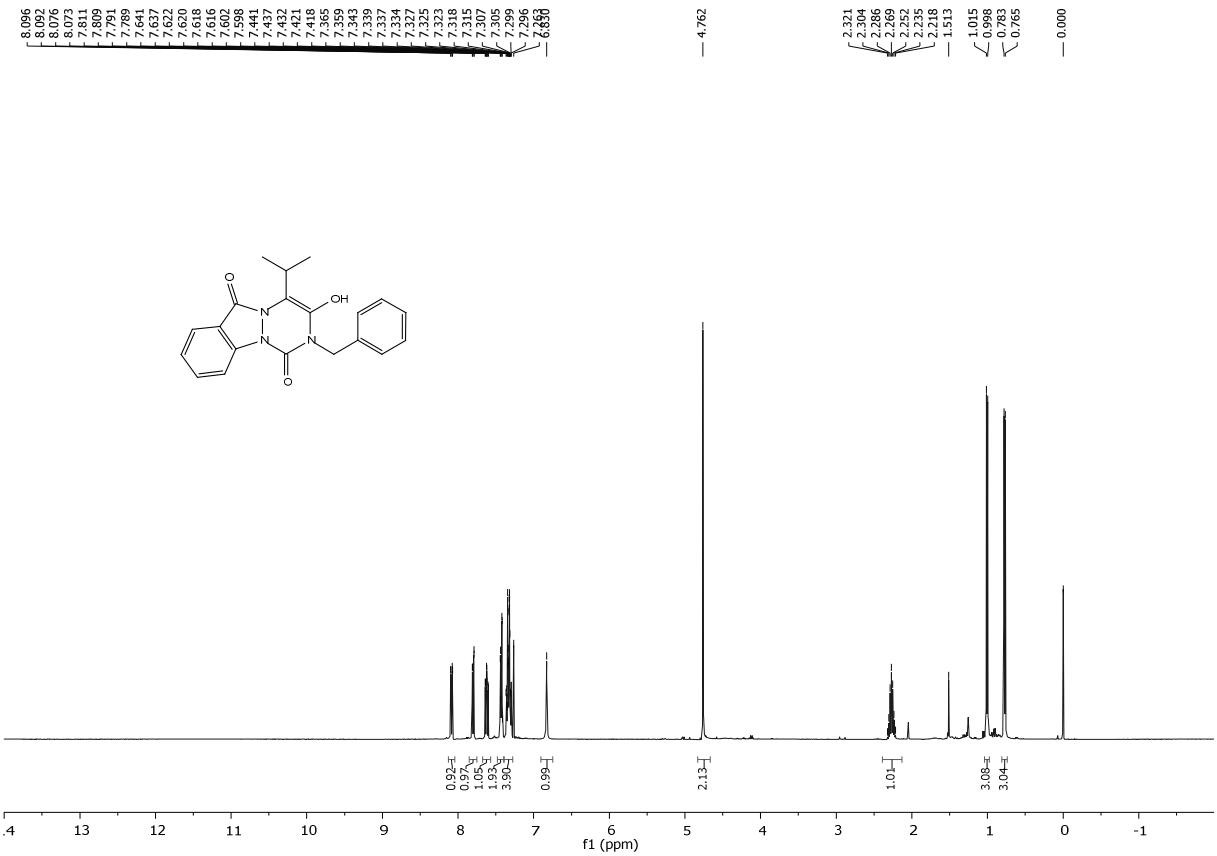
N
N
N
O
O
f1 (ppm)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7.789
7.641
7.637
7.622
7.620
7.618
7.616
7.602
7.598
7.441
7.437
7.432
7.421
7.418
7.365
7.359
7.343
7.339
7.337
7.334
7.327
7.325
7.323
7.318
7.315
7.307
7.305
7.299
7.296
7.263
6.830
4.762
2.321
2.304
2.286
2.269
2.252
2.235
2.218
1.513
1.015
0.998
0.783
0.765
0.000
OH
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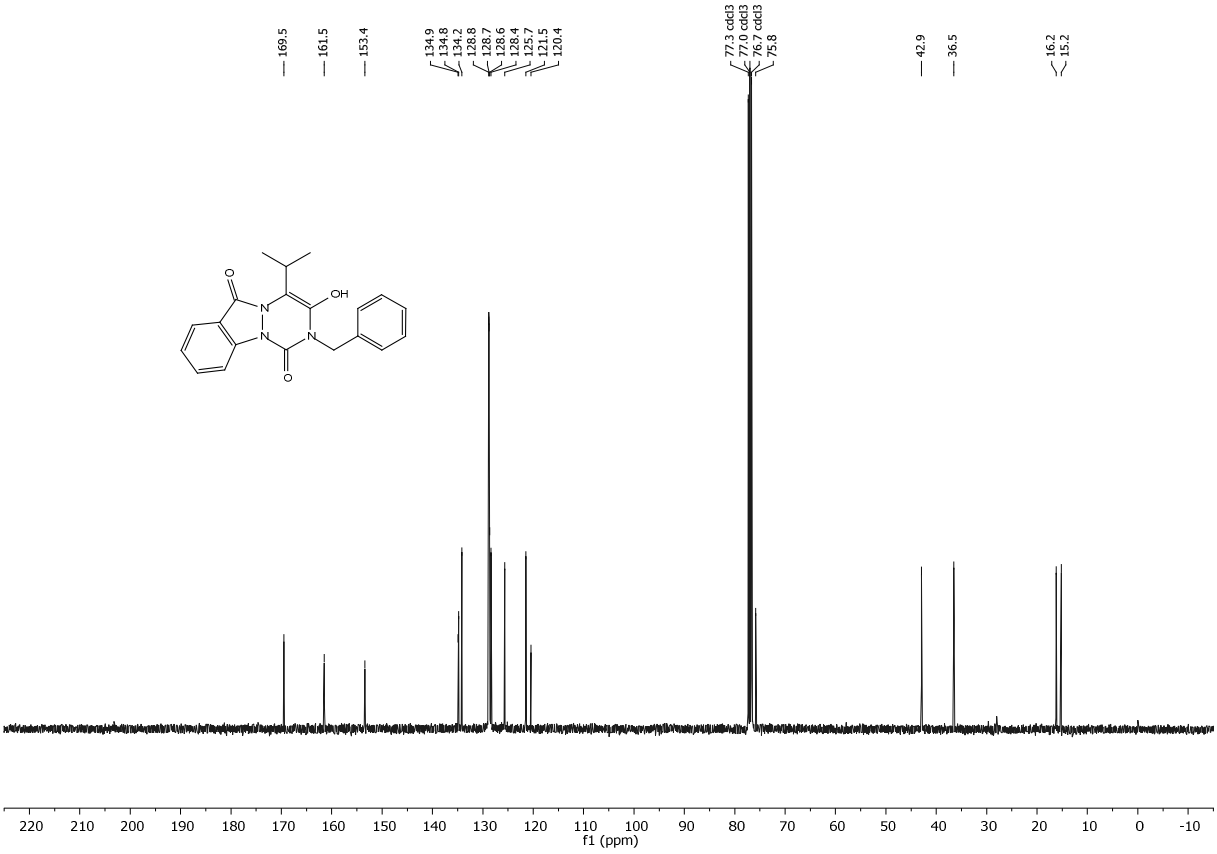
0.97
1.05
1.93
3.90
0.99
2.13
1.01
3.08
3.04
f1 (ppm)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134.8
134.2
128.8
128.7
128.6
128.4
125.7
121.5
120.4
77.3 cdd3
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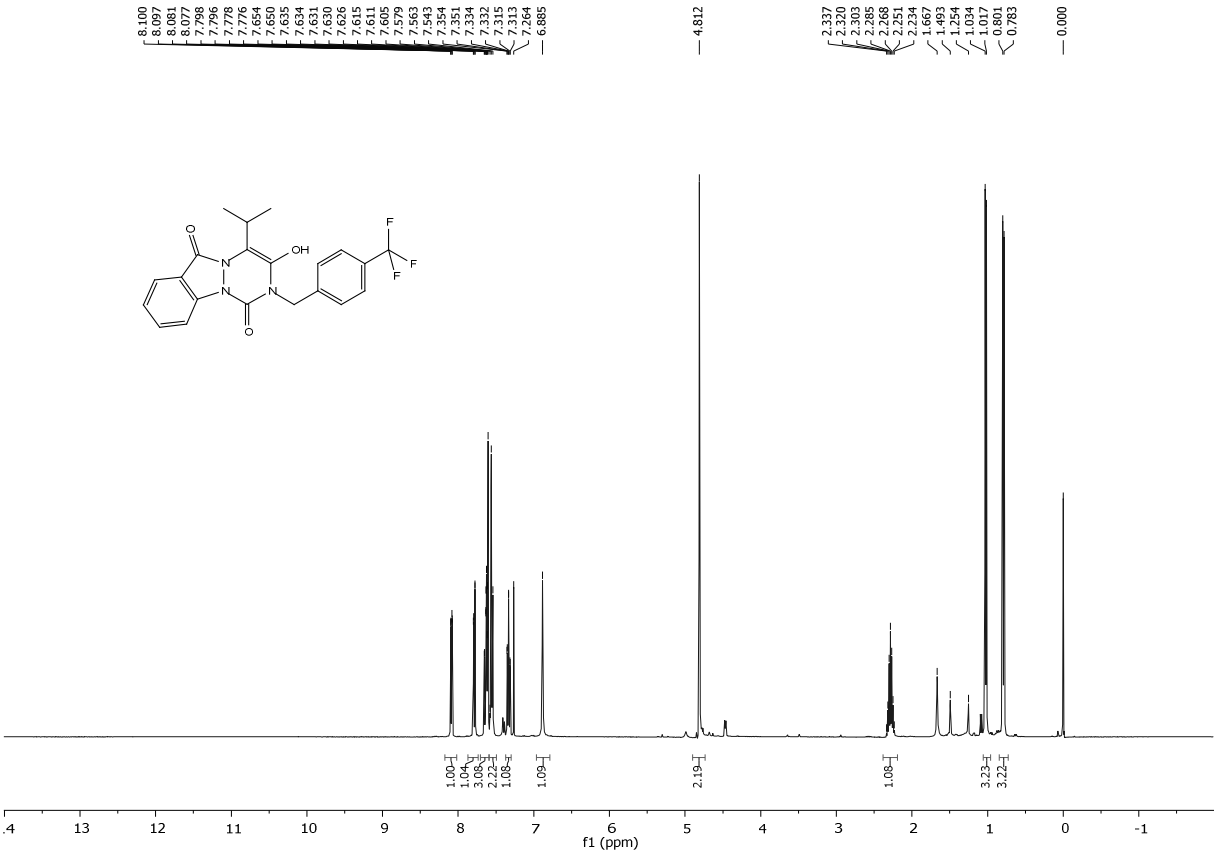
76.7 cdd3
75.8
42.9
36.5
16.2
15.2
OH
f1 (ppm)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8.081
8.077
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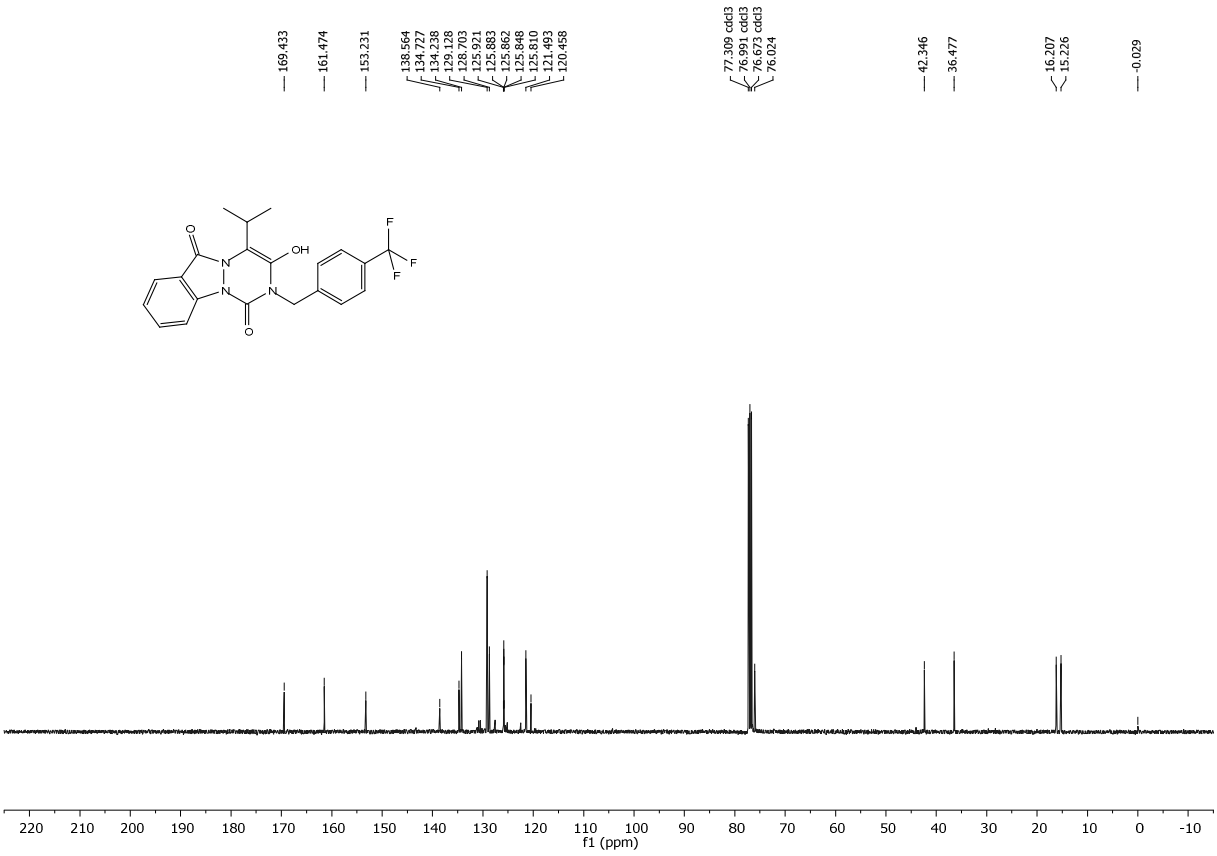
7.778
7.776
7.654
7.650
7.635
7.634
7.631
7.630
7.626
7.615
7.611
7.605
7.579
7.563
7.543
7.354
7.351
7.334
7.332
7.315
7.313
7.264
6.885
4.812
2.337
2.320
2.303
2.285
2.268
2.251
2.234
1.667
1.493
1.254
1.034
1.017
0.801
0.783
0.000
OH
F
F
F
O
O
1.00
1.04
3.08
2.22
1.08
1.09
2.19
1.08
3.23
3.22
f1 (ppm)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128.703
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125.883
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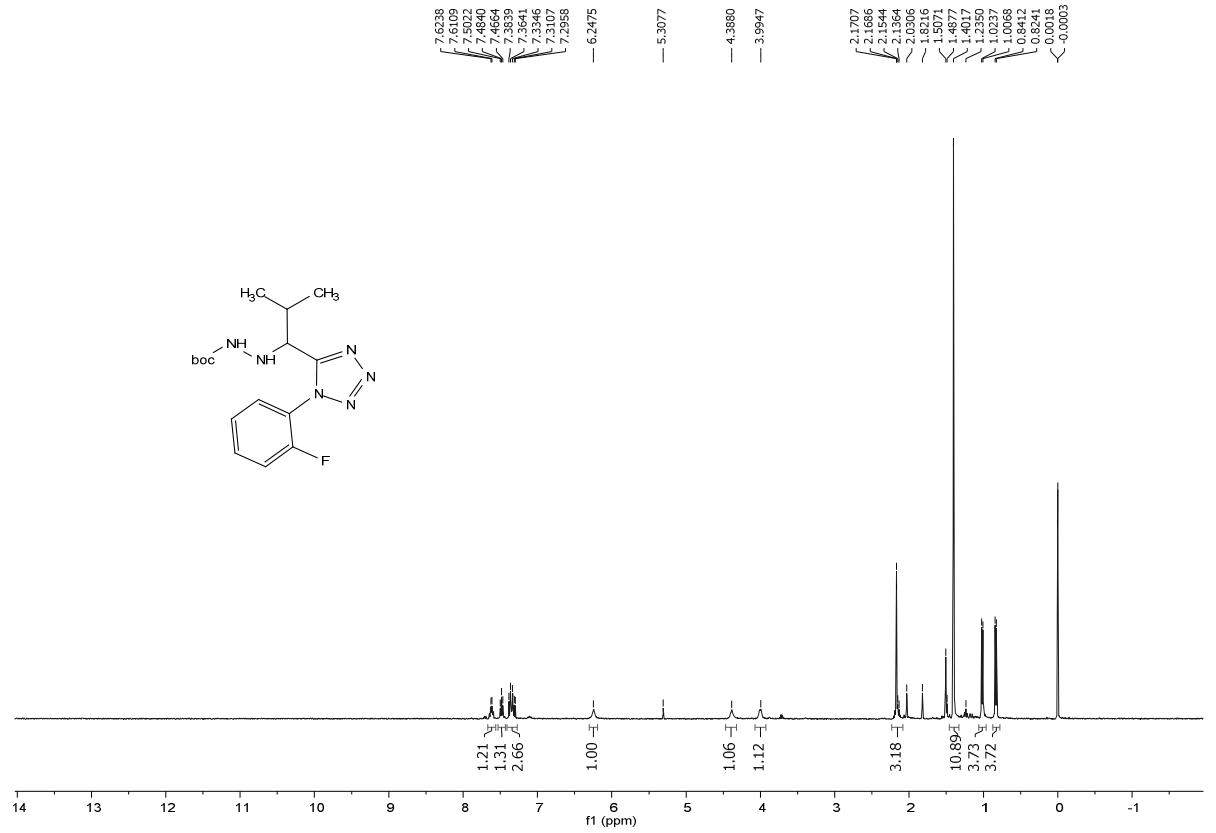
125.810
121.493
120.458
77.309 cdcl3
76.991 cdcl3
76.673 cdcl3
76.024
42.346
36.477
16.207
15.226
-0.029
OH
F
F
F
O
O
f1 (ppm)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7.3107
7.2958
6.2475
5.3077
4.3880
3.9947
2.1707
2.1686
2.1544
2.1364
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1.5071
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1.4017
1.2350
1.0237
1.0068
0.8412
0.8241
0.0018
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1.00
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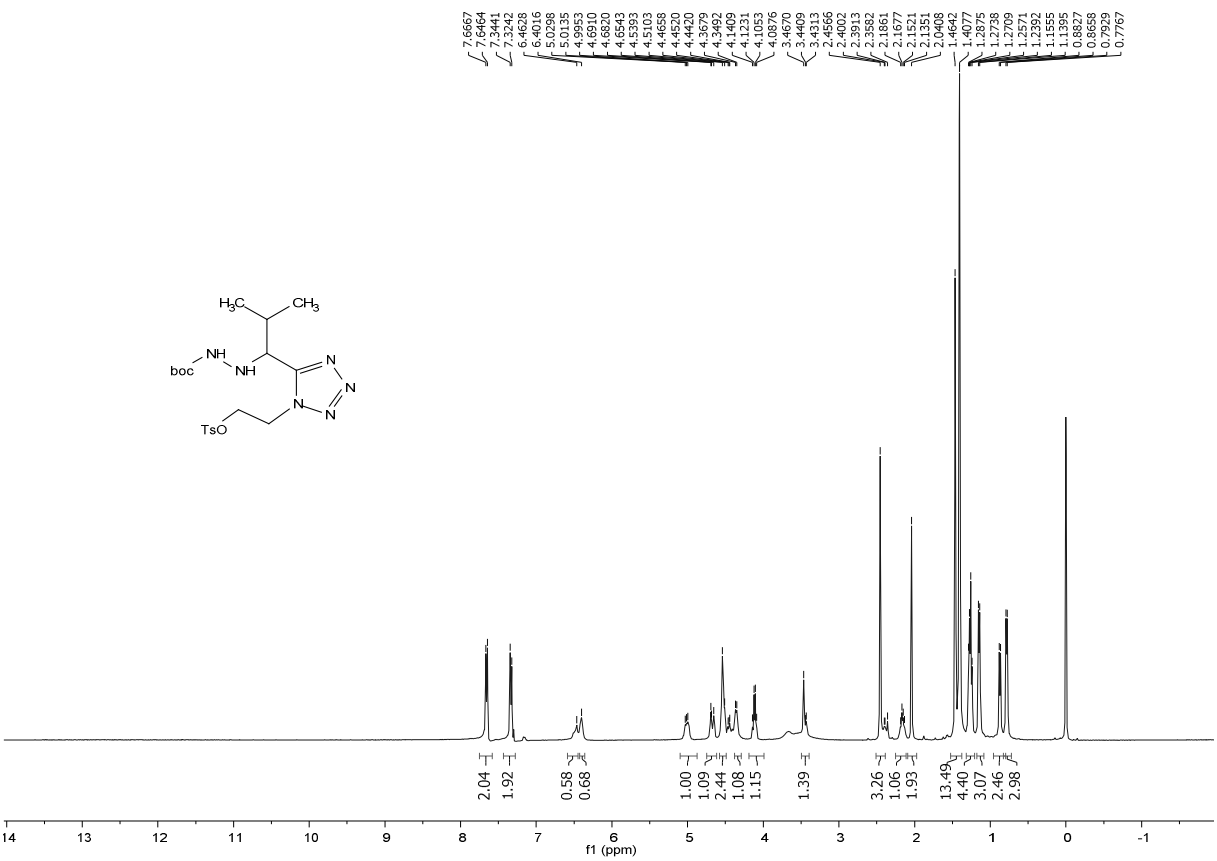
10.89
3.73
3.72
f1 (ppm)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4.5393
4.5103
4.4658
4.4520
4.4420
4.3679
4.3492
4.1409
4.1231
4.1053
4.0876
3.4670
3.4409
3.4313
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2.4002
2.3913
2.3582
2.1861
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2.1521
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1.4077
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1.2738
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1.2392
1.1555
1.1395
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1.92
0.58
0.68
1.00
1.09
2.44
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1.15
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1.06
1.93
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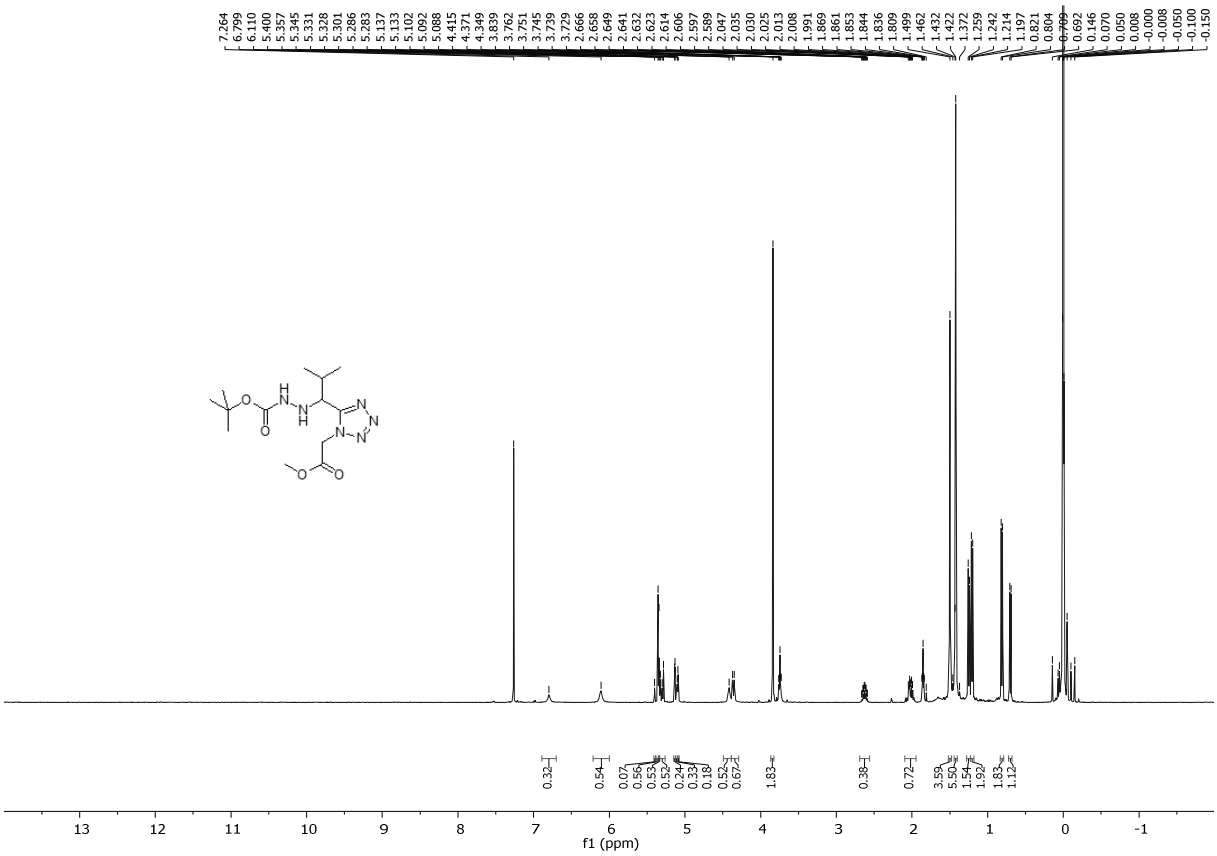
2.46
2.98
f1 (ppm)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5.092
5.088
4.415
4.371
4.349
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3.762
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2.666
2.658
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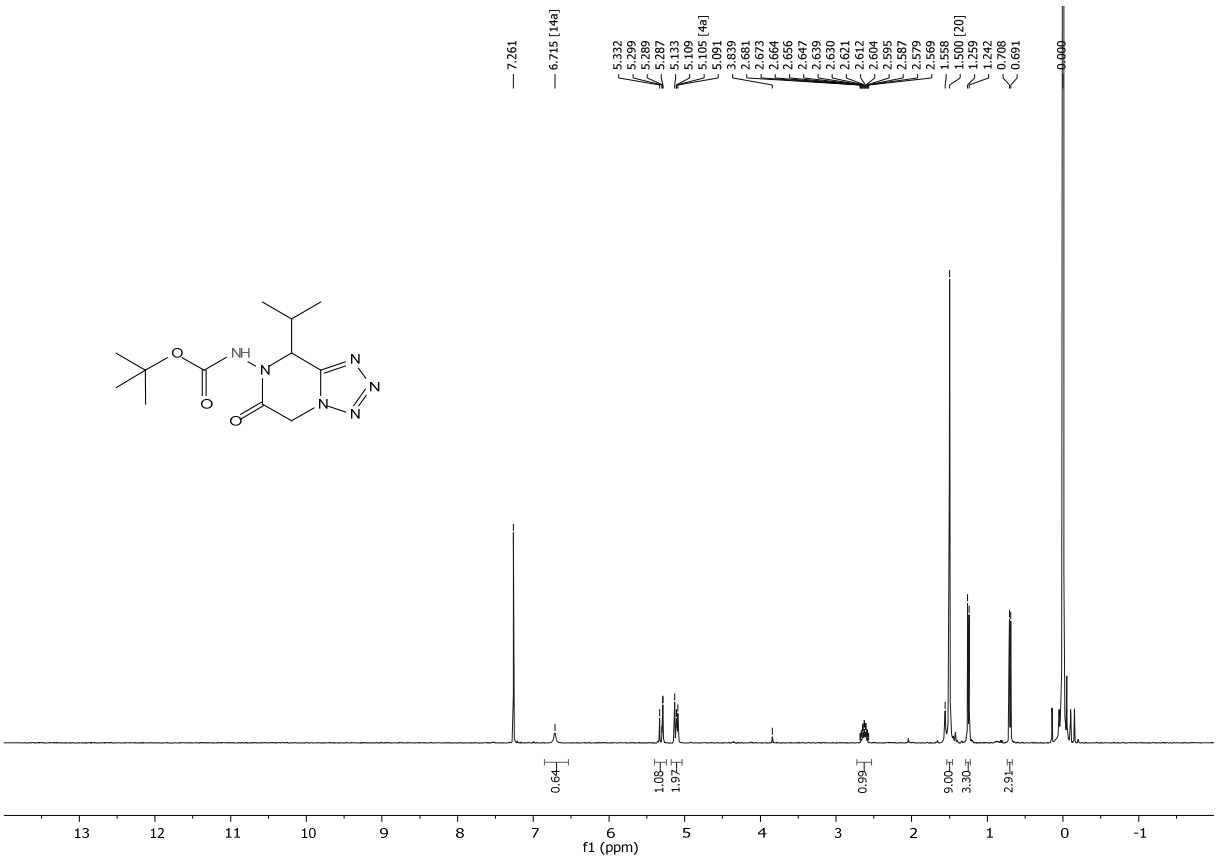
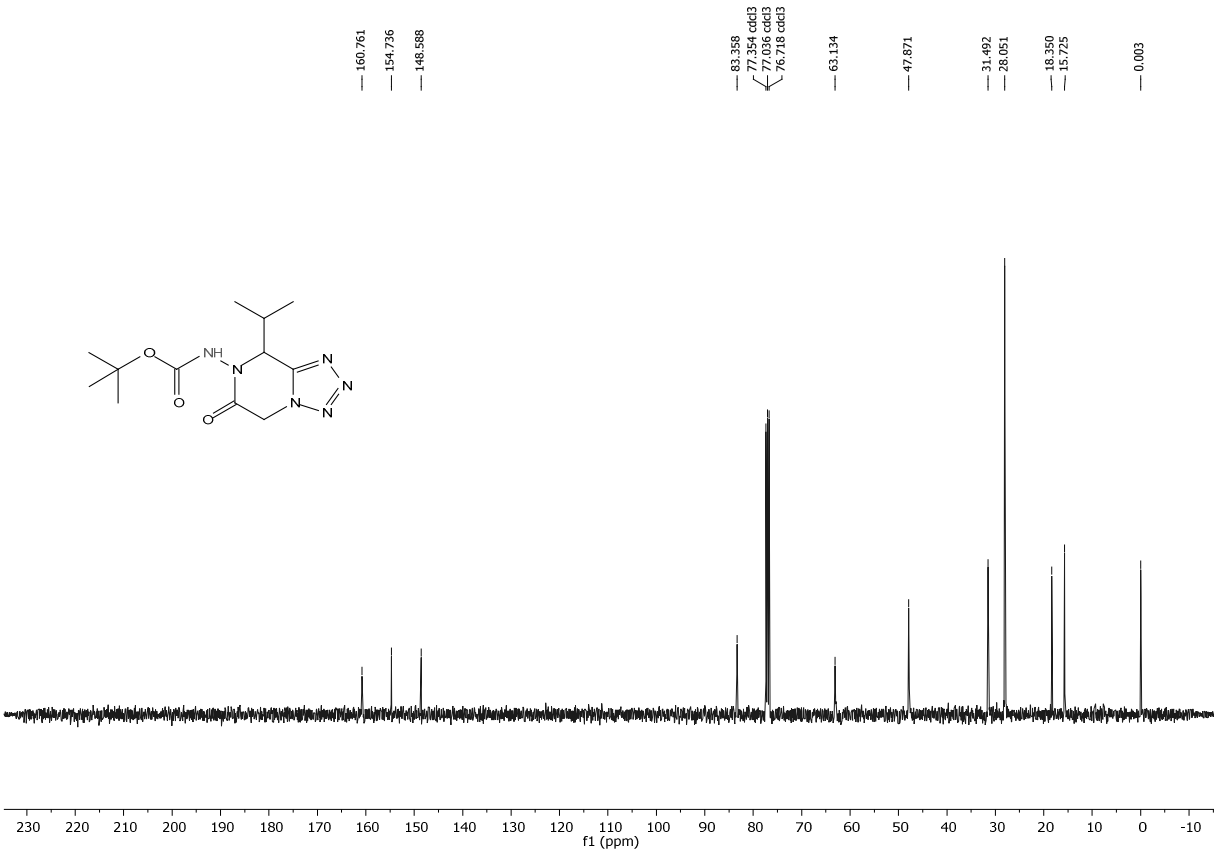
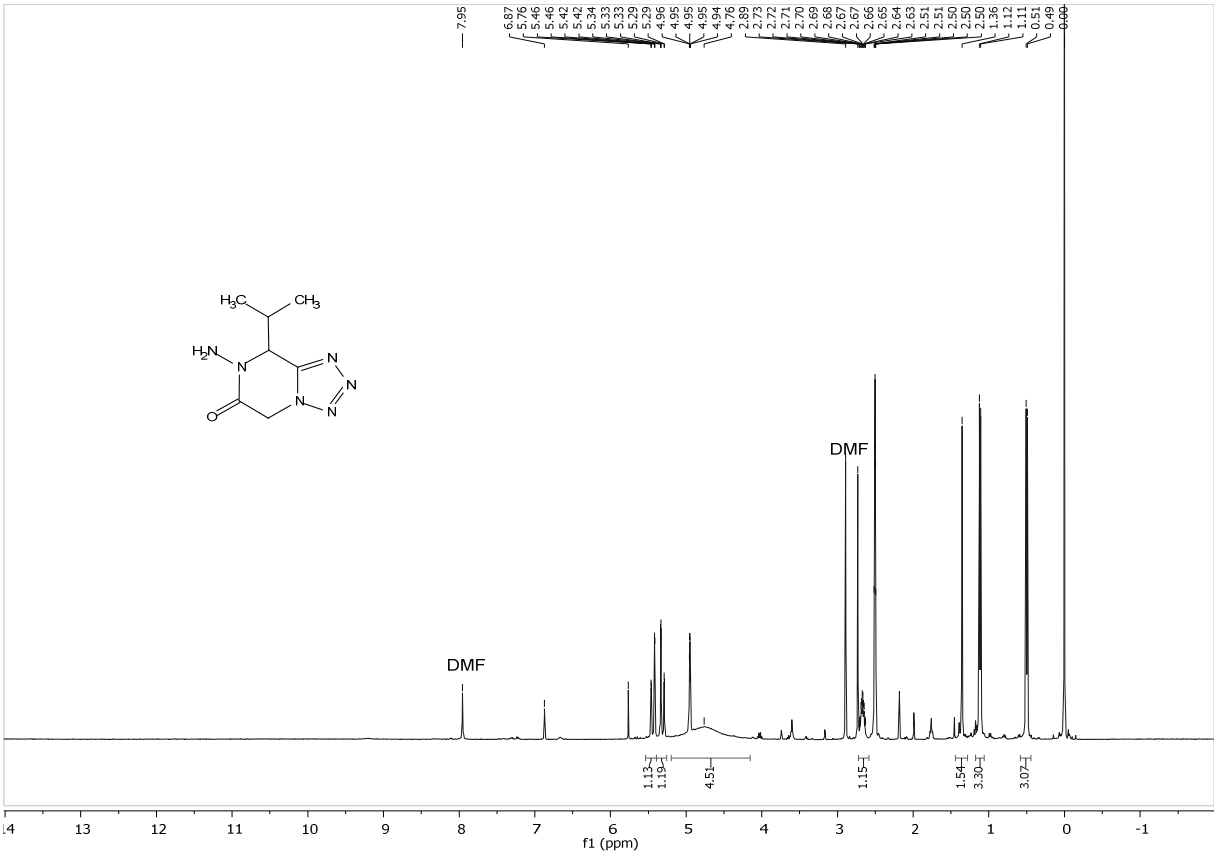
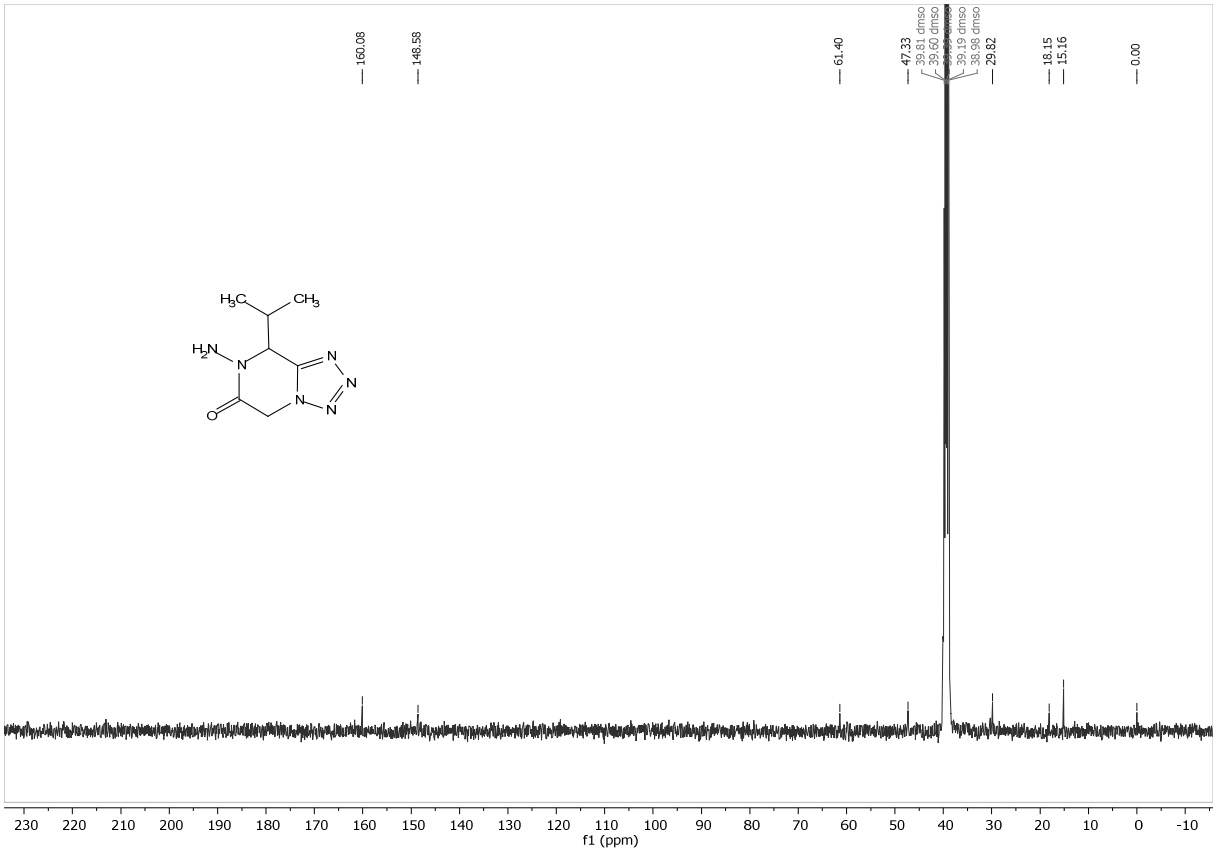
2.641
2.632
2.623
2.614
2.606
2.597
2.589
2.047
2.035
2.030
2.025
2.013
2.008
1.991
1.866
1.861
1.853
1.844
1.836
1.809
1.499
1.462
1.432
1.422
1.372
1.259
1.242
1.214
1.197
0.821
0.804
0.692
0.146
0.070
0.050
0.008
-0.000
-0.008
-0.050
-0.100
-0.150
0.32
0.54
0.07
0.56
0.53
0.52
0.24
0.33
0.18
0.52
0.67
1.83
0.38
0.72
3.59
5.50
1.54
1.92
1.83
1.12
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

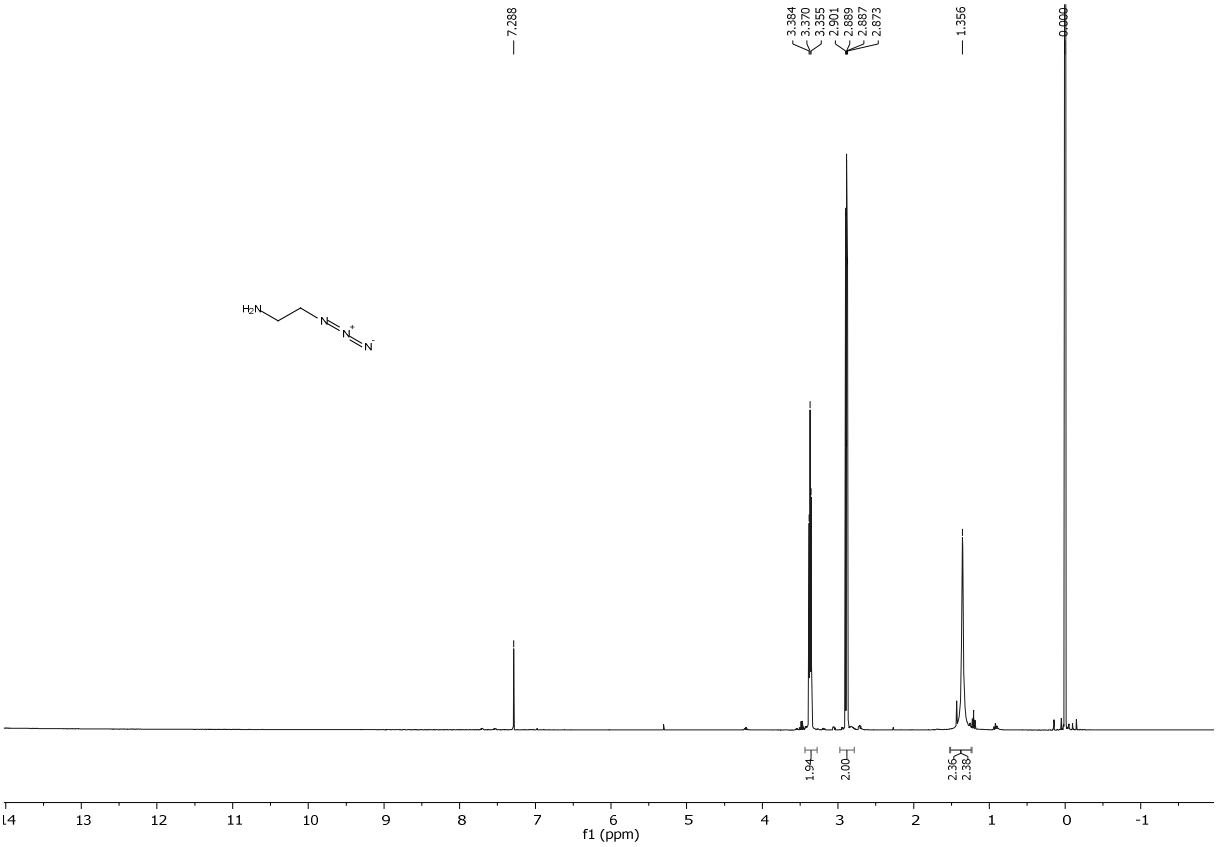

7.261
6.715 [14a]
5.332
5.299
5.289
5.287
5.133
5.109
5.105 [4a]
5.091
3.839
2.681
2.673
2.664
2.656
2.647
2.639
2.630
2.621
2.612
2.604
2.595
2.587
2.579
2.569
1.558
1.500 [20]
1.259
1.242
0.708
0.691
0.000
0.64
1.08
1.97
0.99
9.00
3.30
2.91
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

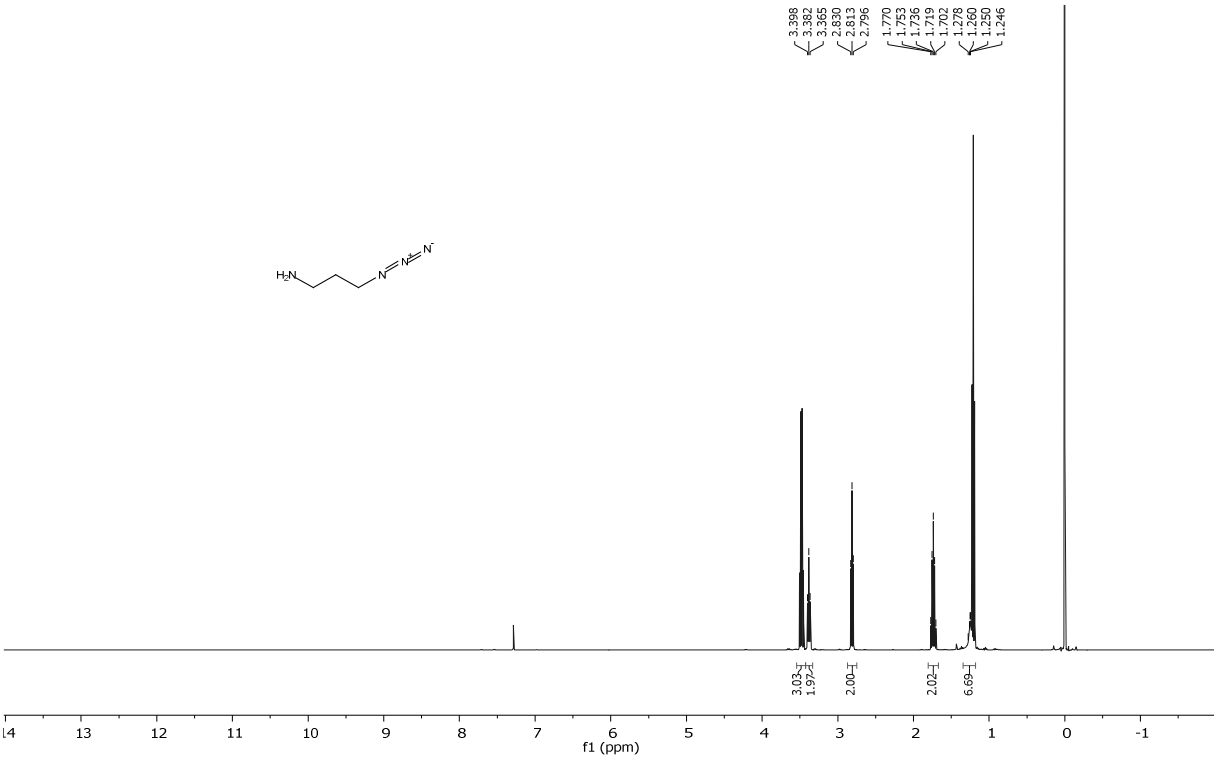

160.761
154.736
148.588
83.358
77.354 cdd3
77.036 cdd3
76.718 cdd3
63.134
47.871
31.492
28.051
18.350
15.725
0.003
NH
O
O
O
N
N
N
N
N
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

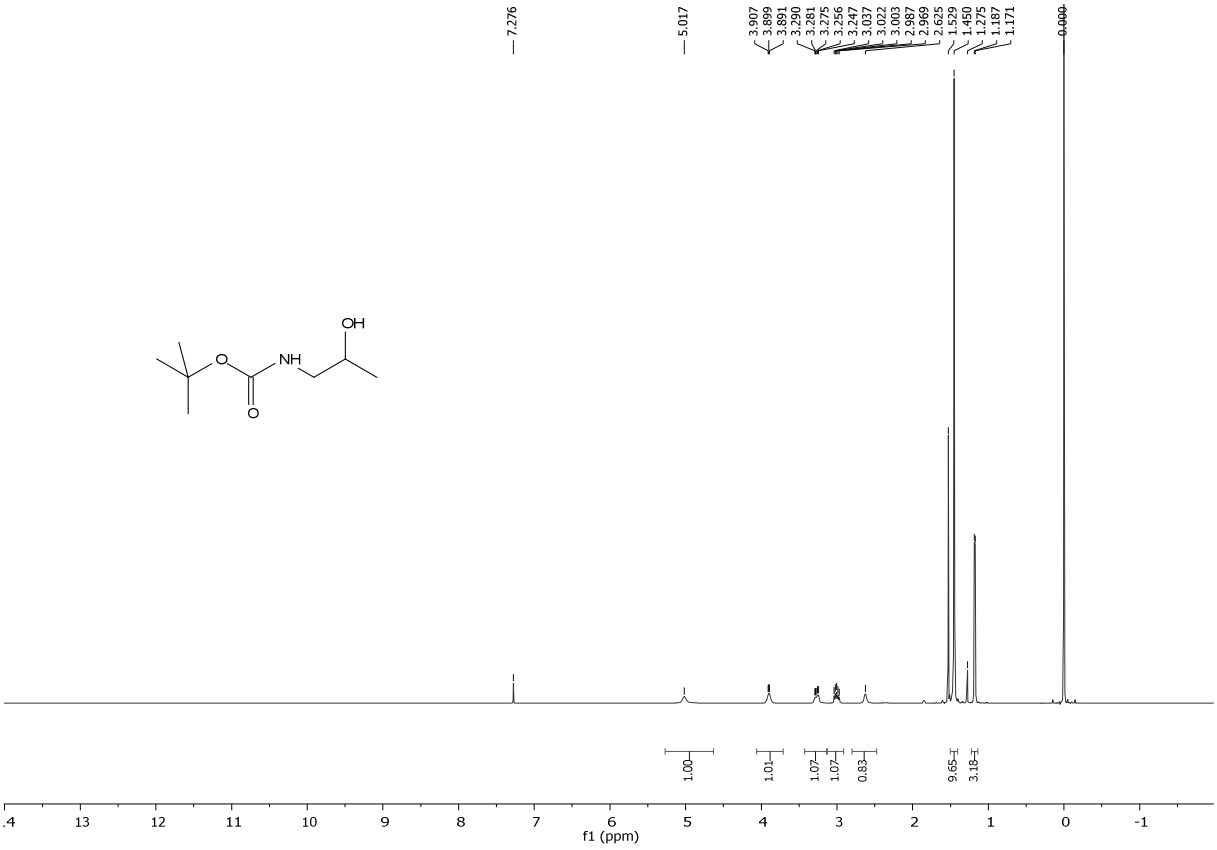

7.95
6.87
5.76
5.46
5.42
5.34
5.33
5.29
4.96
4.95
4.94
4.76
2.89
2.73
2.72
2.71
2.70
2.69
2.68
2.67
2.66
2.65
2.64
2.63
2.51
2.50
1.36
1.12
1.11
0.51
0.49
0.00
H3C
CH3
H2N
N
N
N
N
O
DMF
DMF
1.13
1.19
4.51
1.15
1.54
3.30
3.07
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

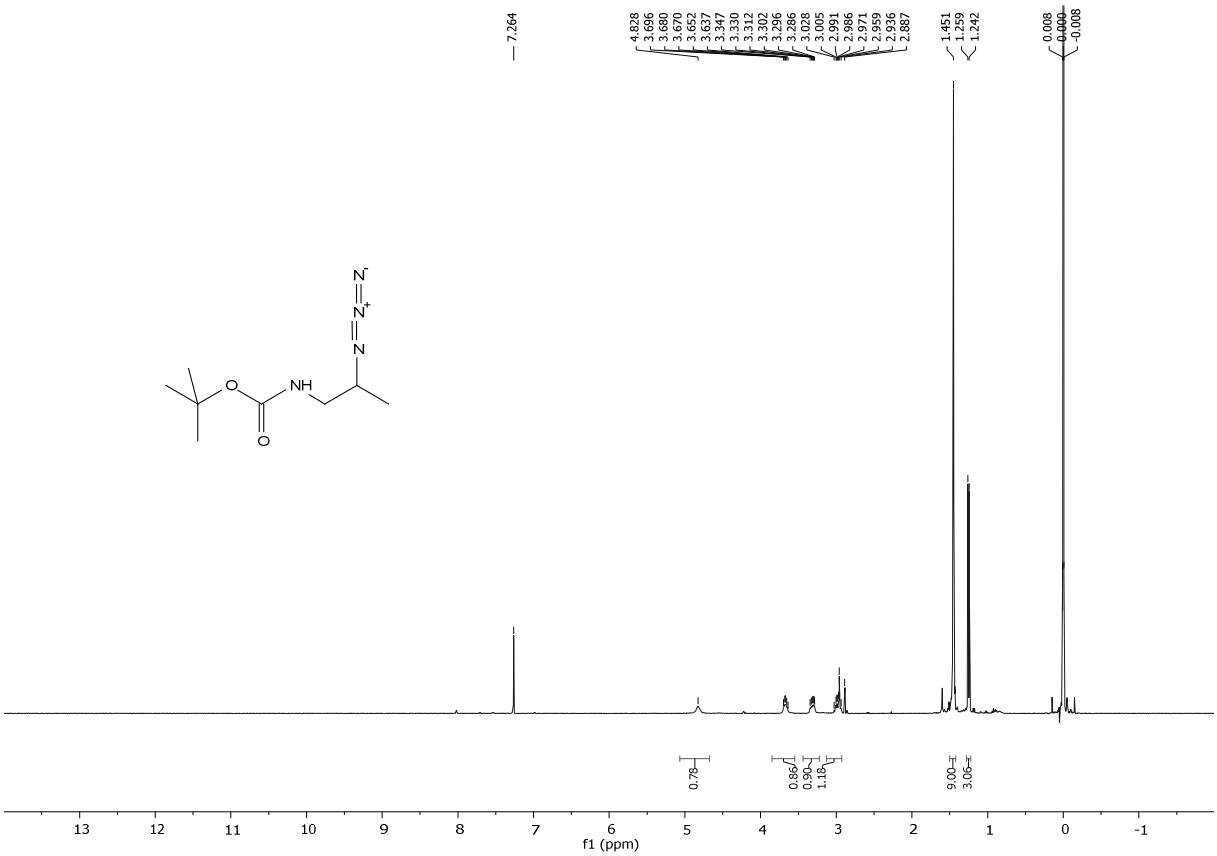

160.08
146.58
61.40
47.33
39.81 dmso
39.60 dmso
39.39 dmso
39.19 dmso
38.98 dmso
29.82
18.15
15.16
0.00
H3C
CH3
H2N
N
N
N
N
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

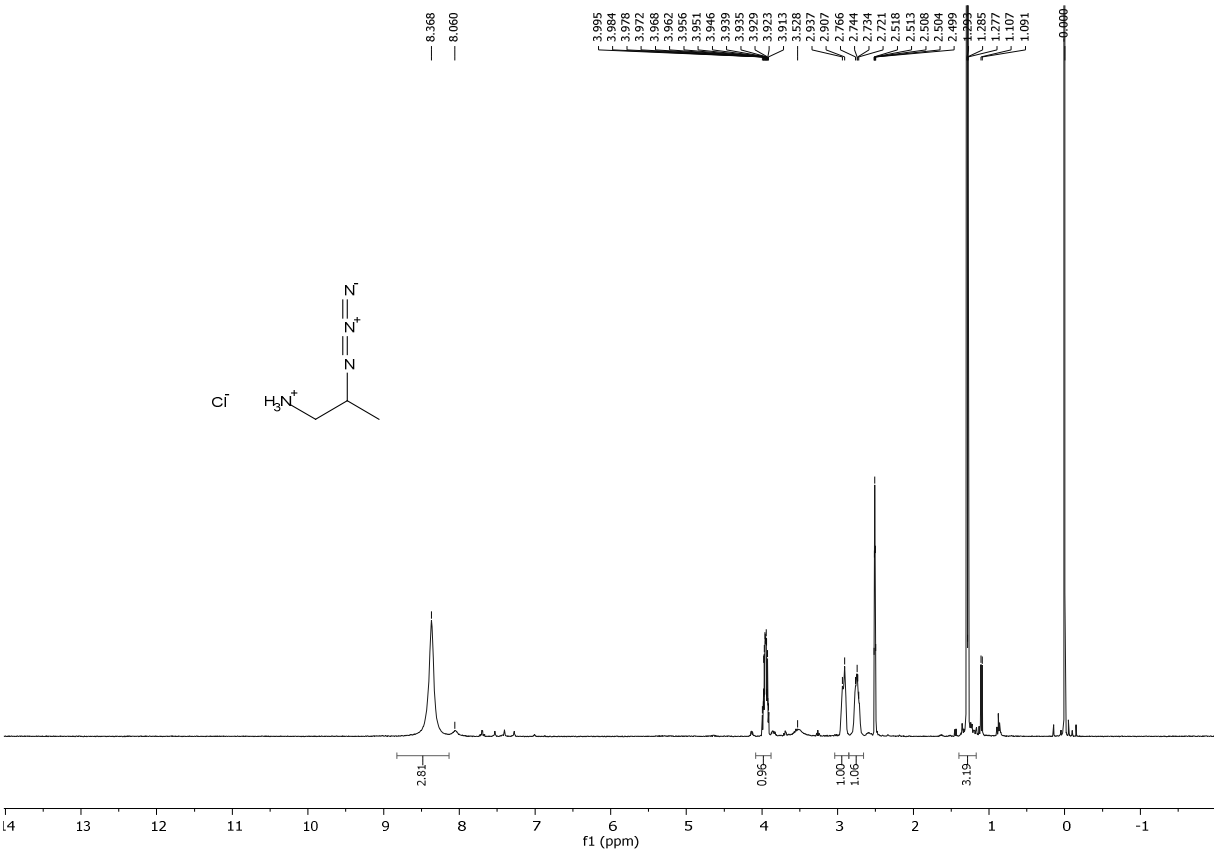
10.1.4. Ugi/Staudinger/aza-Wittig (chapter 6.4)

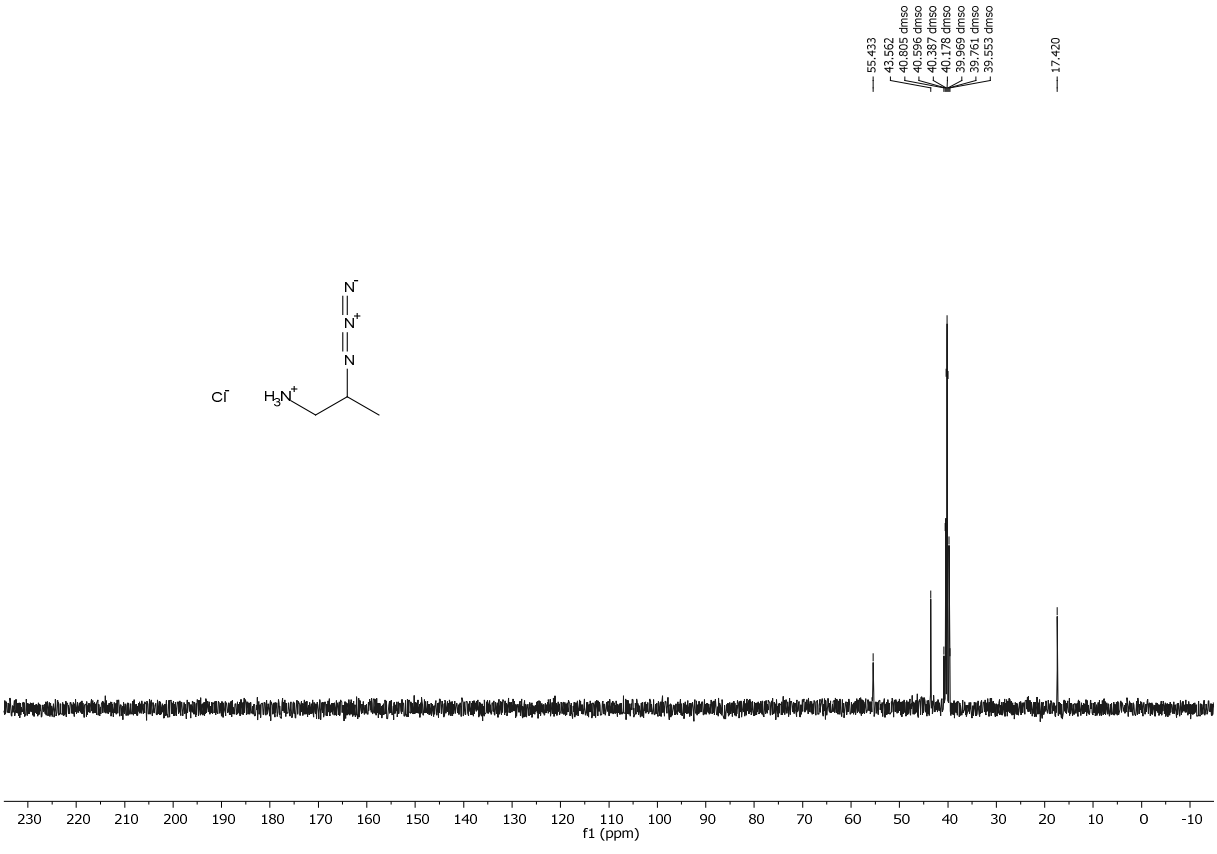


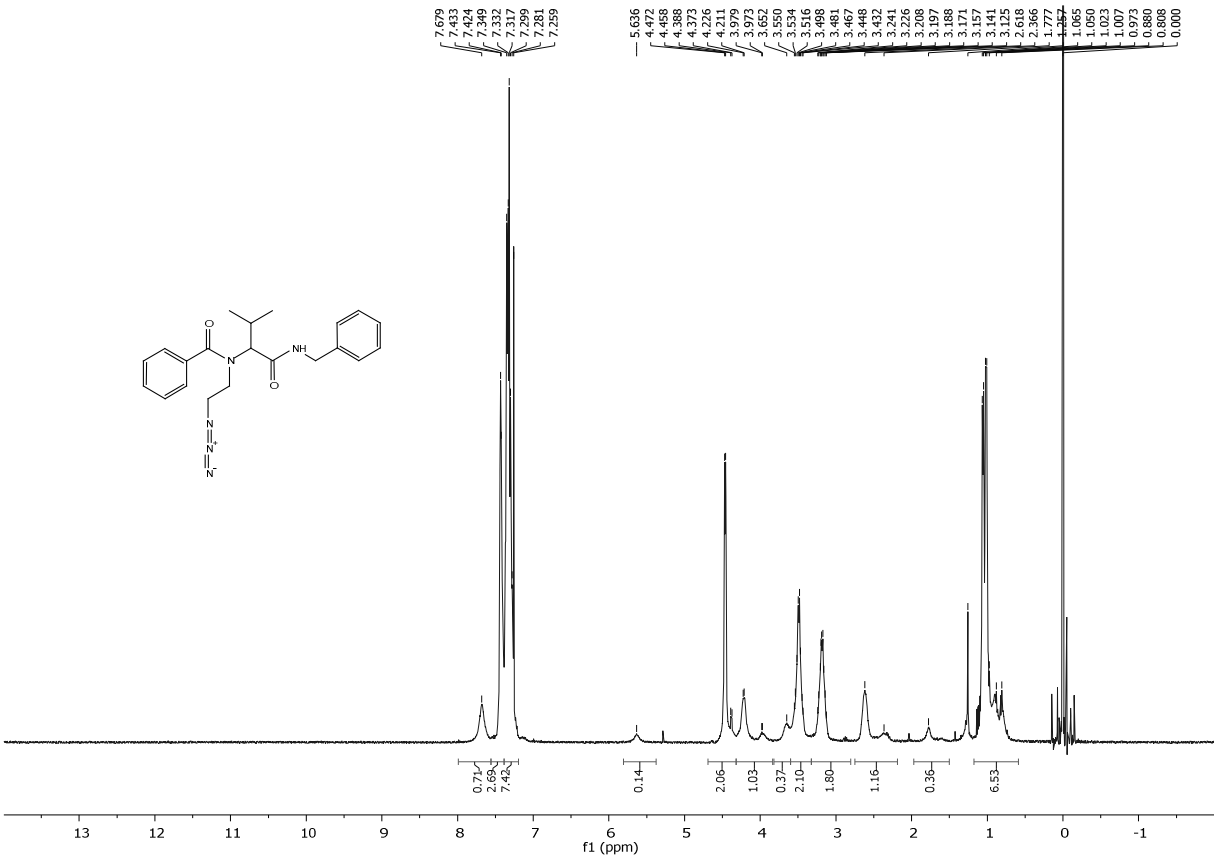


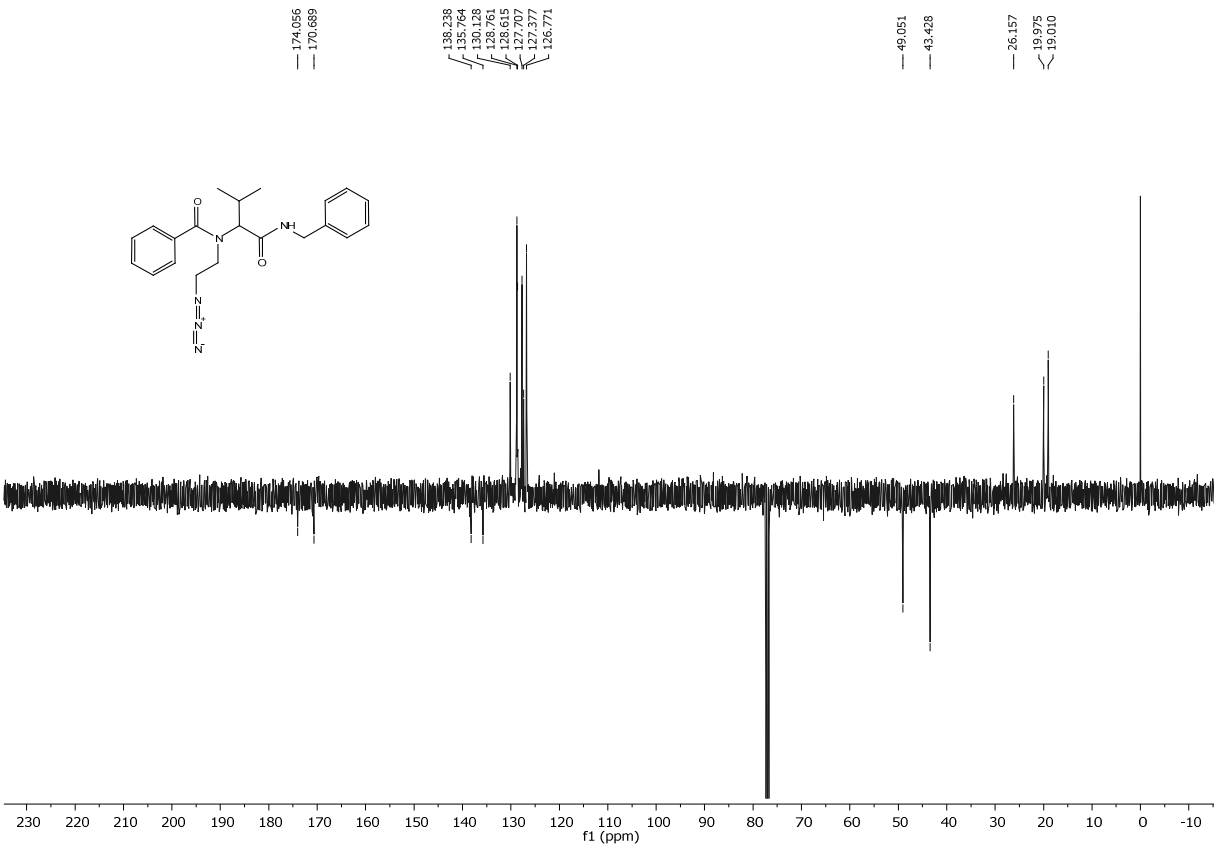

7.276
5.017
3.907
3.899
3.891
3.290
3.281
3.275
3.256
3.247
3.037
3.022
3.003
2.987
2.969
2.625
1.529
1.450
1.275
1.187
1.171
0.000
OH
O
NH
O
1.00
1.01
1.07
1.07
0.83
9.65
3.18
f1 (ppm)

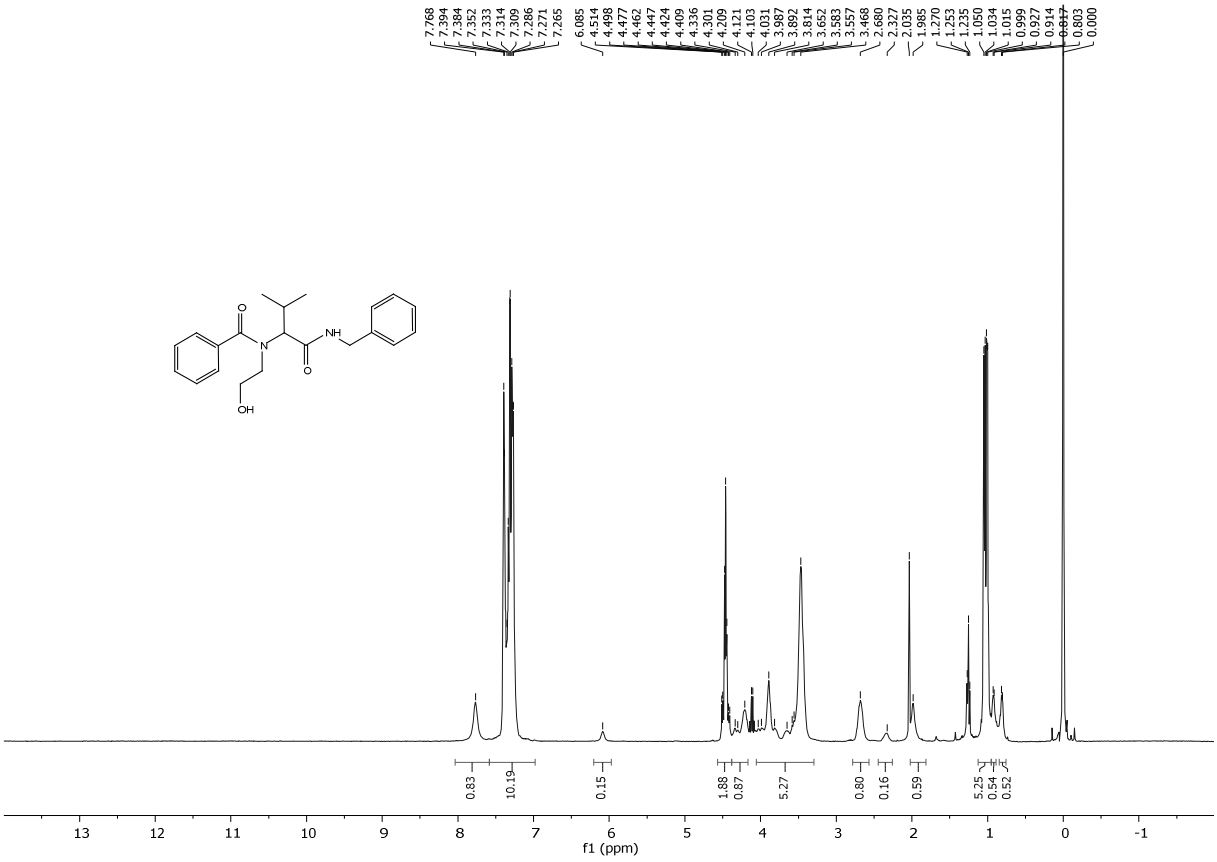

7.264
4.828
3.696
3.680
3.670
3.652
3.637
3.347
3.330
3.312
3.302
3.296
3.286
3.028
3.005
2.991
2.986
2.971
2.959
2.936
2.887
1.451
1.259
1.242
0.008
0.000
-0.008
N
N
N
O
NH
O
0.78
0.86
0.90
1.18
9.00
3.06
f1 (ppm)

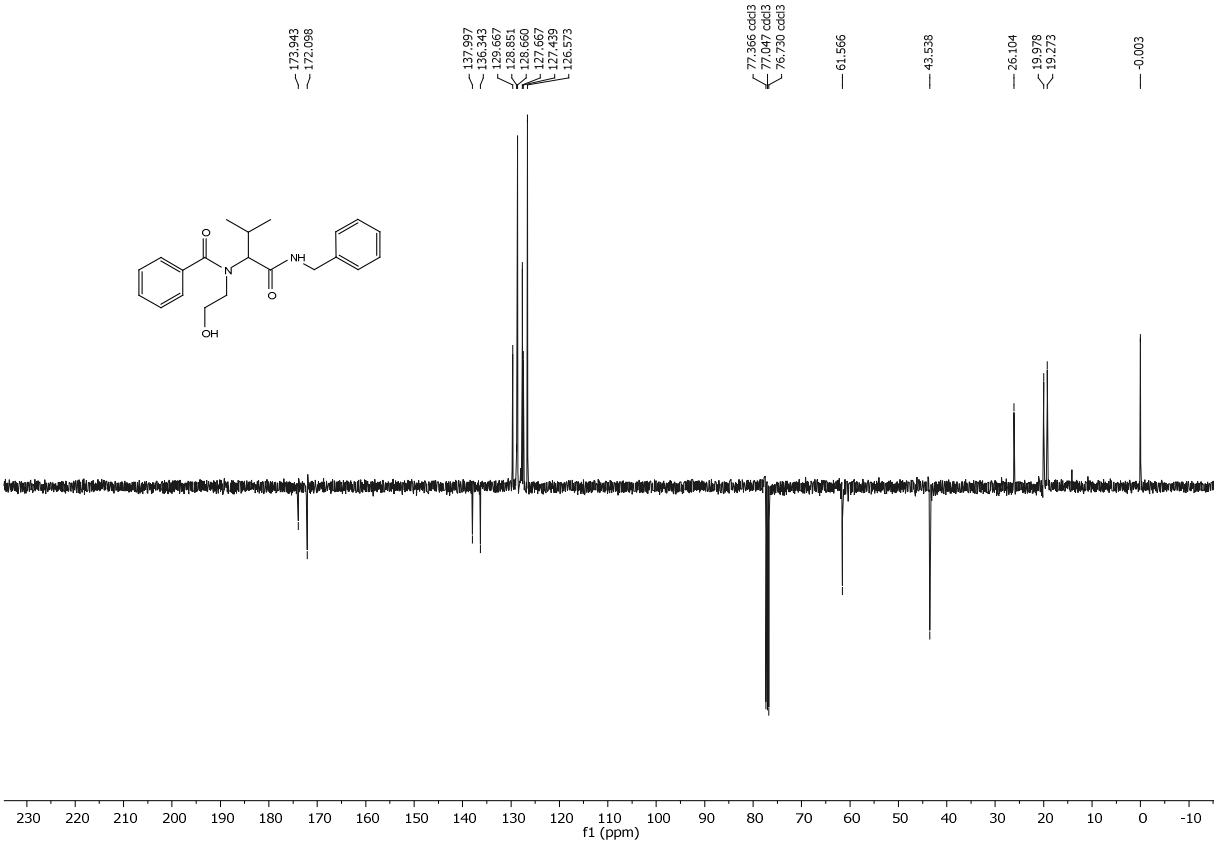

8.368
8.060
3.995
3.984
3.978
3.972
3.968
3.962
3.956
3.951
3.946
3.939
3.935
3.929
3.923
3.913
3.528
2.937
2.907
2.766
2.744
2.734
2.721
2.518
2.513
2.508
2.504
2.499
1.285
1.277
1.107
1.091
0.000
2.81
0.96
1.00
1.06
3.19
f1 (ppm)

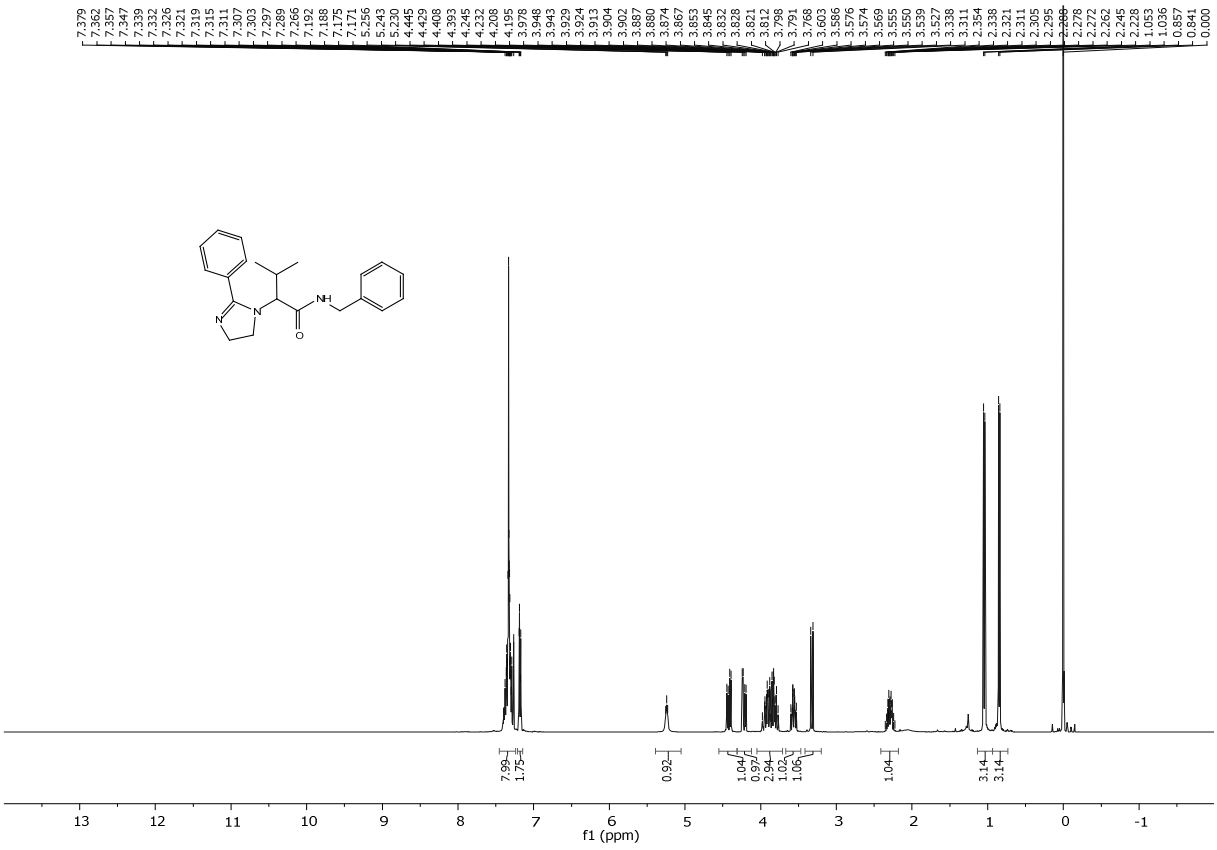

55.433
43.562
40.805 dmso
40.596 dmso
40.387 dmso
40.178 dmso
39.969 dmso
39.761 dmso
39.553 dmso
17.420
f1 (ppm)

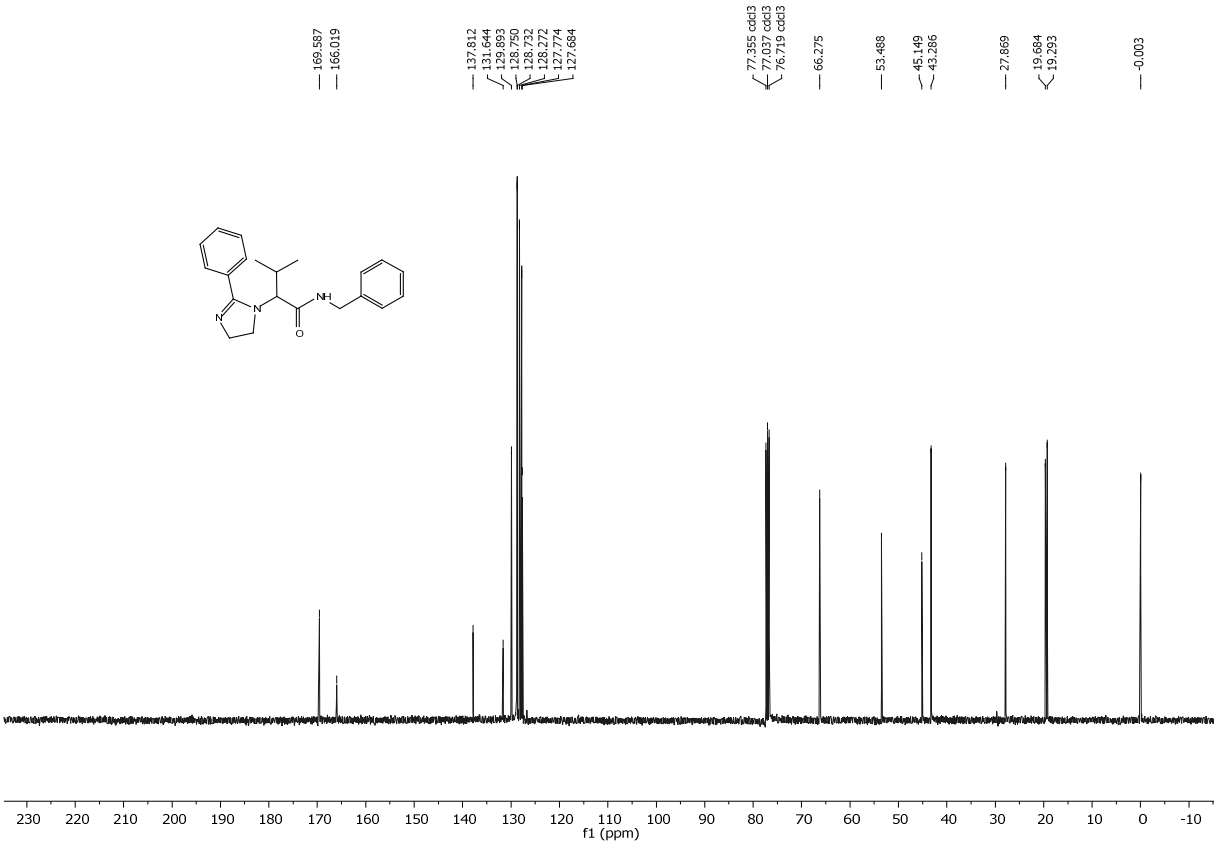

7.679
7.433
7.424
7.349
7.332
7.317
7.299
7.281
7.259
5.636
4.472
4.458
4.388
4.373
4.226
4.211
3.979
3.973
3.652
3.550
3.534
3.516
3.498
3.481
3.467
3.448
3.432
3.241
3.226
3.208
3.197
3.188
3.171
3.157
3.141
3.125
2.618
2.366
1.777
1.252
1.065
1.050
1.023
1.007
0.973
0.880
0.808
0.000
0.71
2.69
7.42
0.14
2.06
1.03
0.37
2.10
1.80
1.16
0.36
6.53
f1 (ppm)

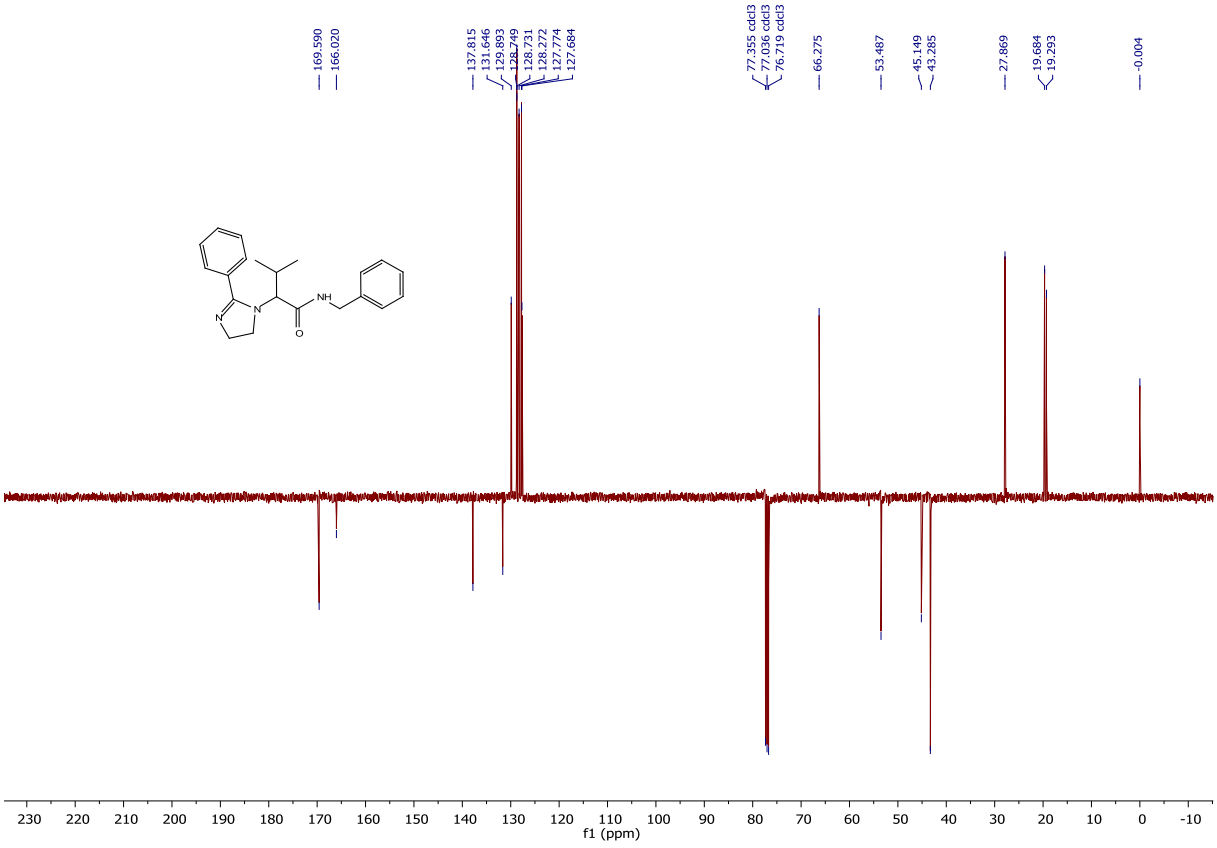

174.056
170.689
138.238
135.764
130.128
128.761
128.615
127.707
127.377
126.771
49.051
43.428
26.157
19.975
19.010
f1 (ppm)

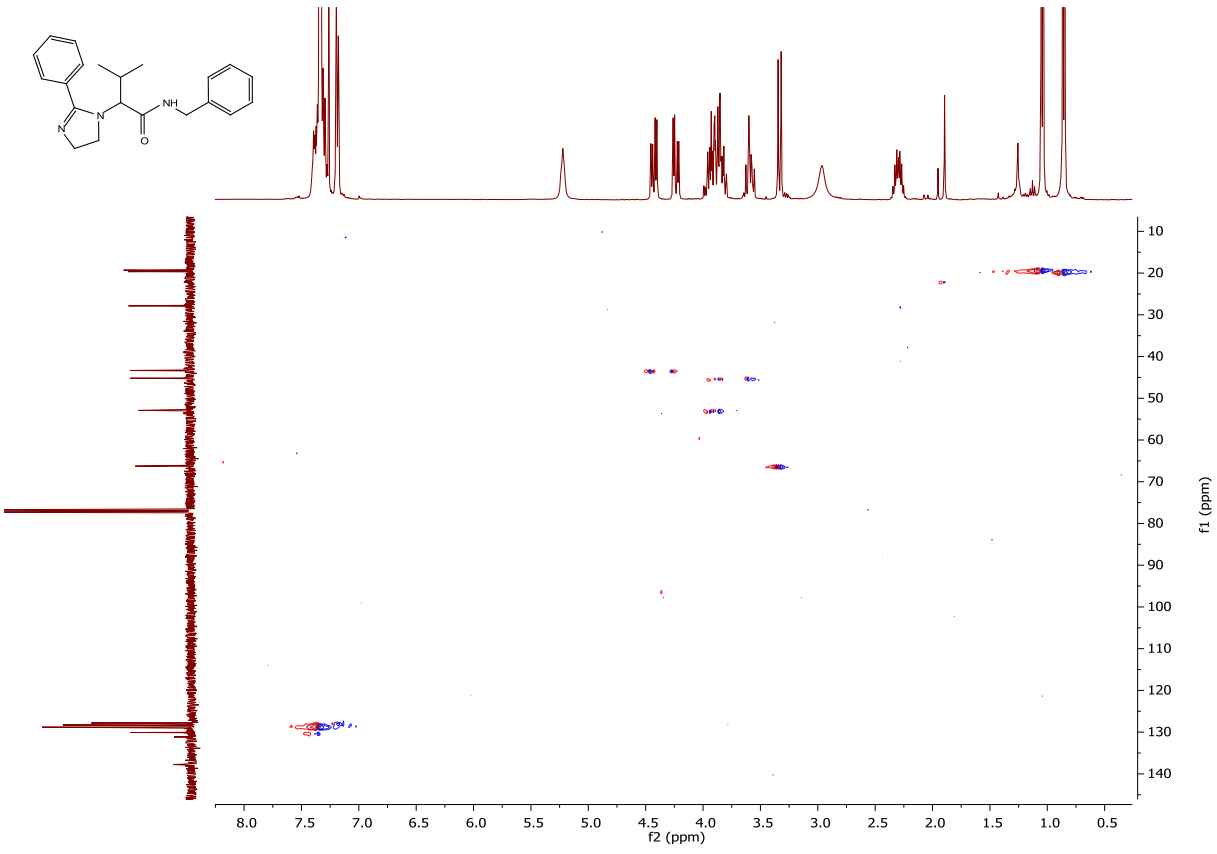

7.768
7.394
7.384
7.352
7.333
7.314
7.309
7.286
7.271
7.265
6.085
4.514
4.498
4.477
4.462
4.447
4.424
4.409
4.336
4.301
4.209
4.121
4.103
4.031
3.987
3.892
3.814
3.652
3.583
3.557
3.468
2.680
2.327
2.035
1.985
1.270
1.253
1.235
1.050
1.034
1.015
0.999
0.927
0.914
0.817
0.803
0.000
0.83
10.19
0.15
1.88
0.87
5.27
0.80
0.16
0.59
5.25
0.54
0.52
f1 (ppm)

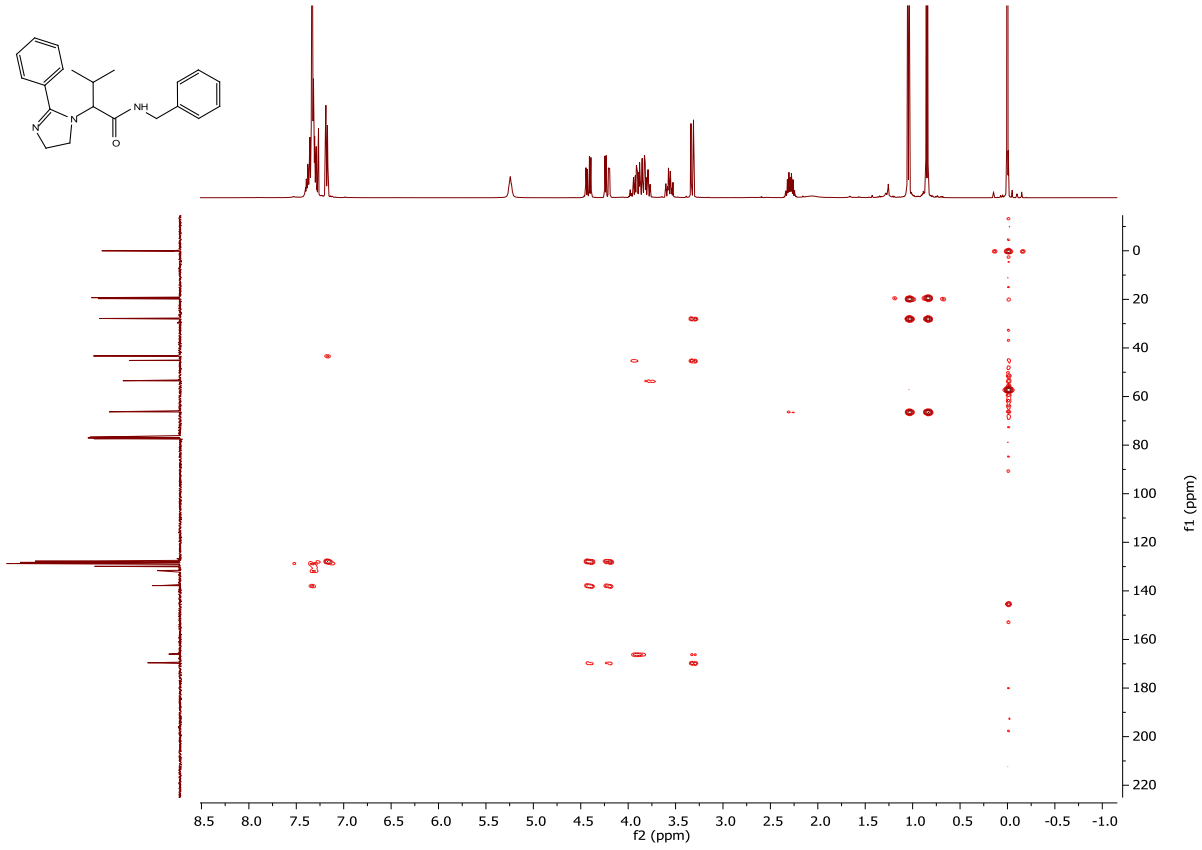

173.943
172.098
137.997
136.343
129.667
128.851
128.660
127.667
127.439
126.573
77.366 cdcl3
77.047 cdcl3
76.730 cdcl3
61.566
43.538
26.104
19.978
19.273
-0.003
f1 (ppm)

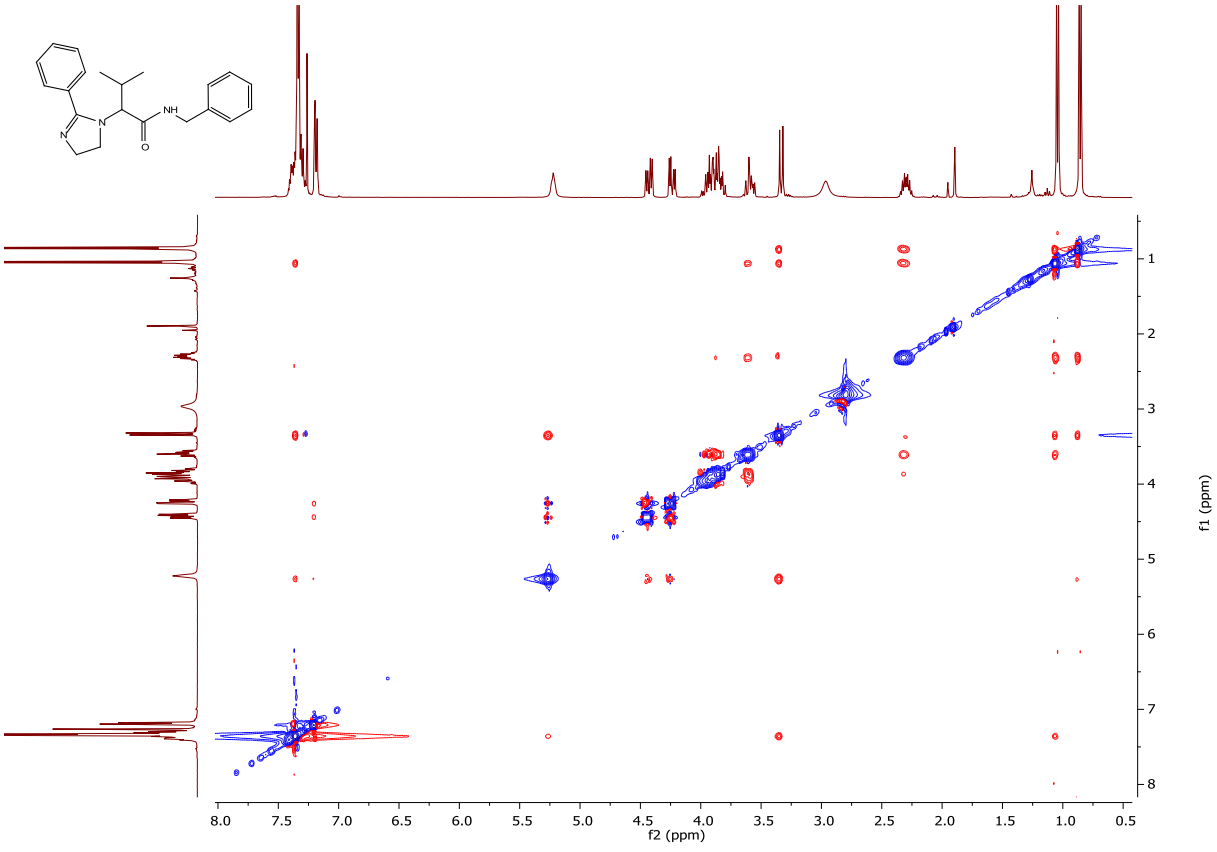

7.379
7.362
7.357
7.347
7.339
7.332
7.326
7.321
7.319
7.315
7.311
7.307
7.303
7.297
7.289
7.266
7.192
7.188
7.175
7.171
5.256
5.243
5.230
4.445
4.429
4.408
4.393
4.245
4.232
4.208
4.195
3.978
3.948
3.943
3.929
3.924
3.913
3.904
3.902
3.887
3.880
3.874
3.867
3.853
3.845
3.832
3.828
3.821
3.812
3.798
3.791
3.768
3.603
3.586
3.576
3.574
3.569
3.555
3.550
3.539
3.527
3.338
3.311
2.354
2.338
2.321
2.311
2.305
2.295
2.280
2.278
2.272
2.262
2.245
2.228
1.053
1.036
0.857
0.841
0.000
NH
O
7.99
1.75
0.92
1.04
0.97
2.94
1.02
1.06
1.04
3.14
3.14
f1 (ppm)

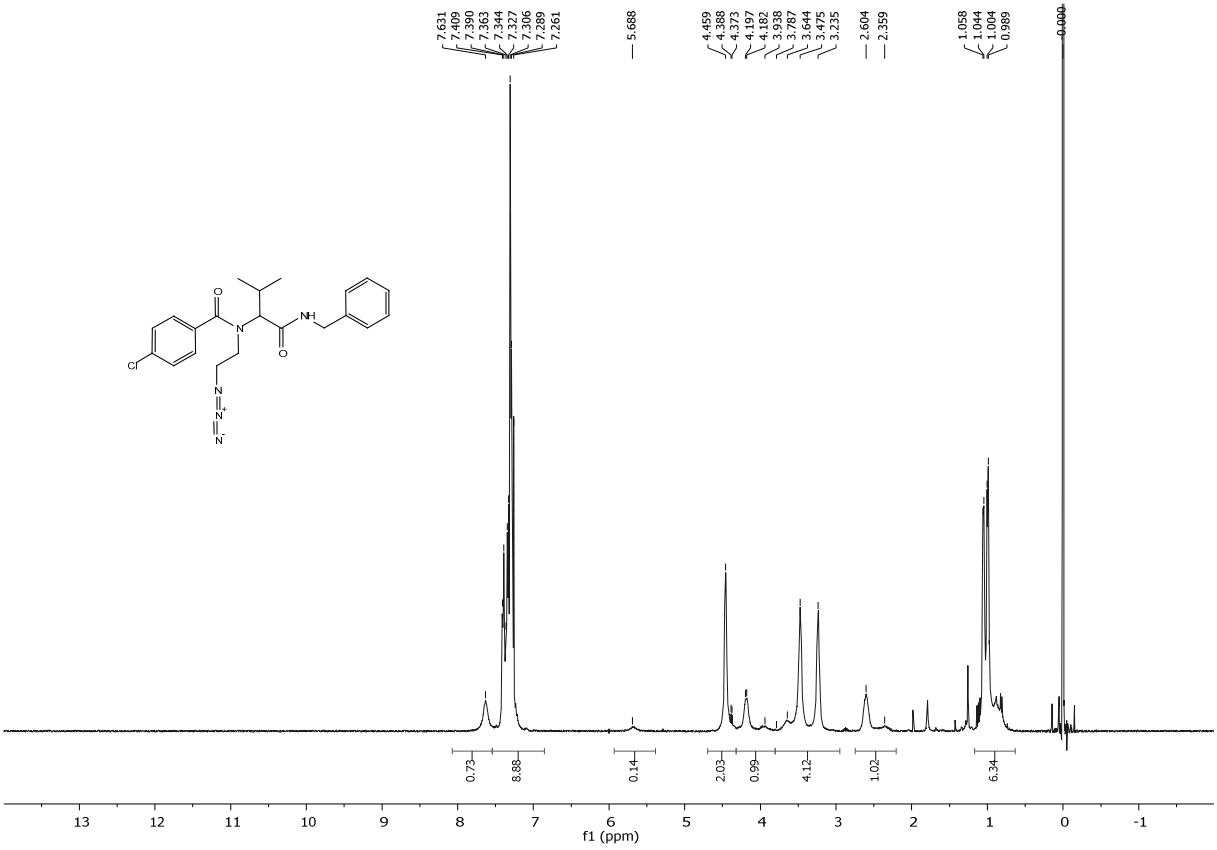

169.587
166.019
137.812
131.644
129.893
128.750
128.732
128.272
127.774
127.684
77.355 cdcl3
77.037 cdcl3
76.719 cdcl3
66.275
53.488
45.149
43.286
27.869
19.684
19.293
-0.003
NH
O
f1 (ppm)


169.590
166.020
137.815
131.646
129.893
128.749
128.731
128.272
127.774
127.684
77.355 cdcl3
77.036 cdcl3
76.719 cdcl3
66.275
53.487
45.149
43.285
27.869
19.684
19.293
-0.004
NH
O
f1 (ppm)


NH
O
f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)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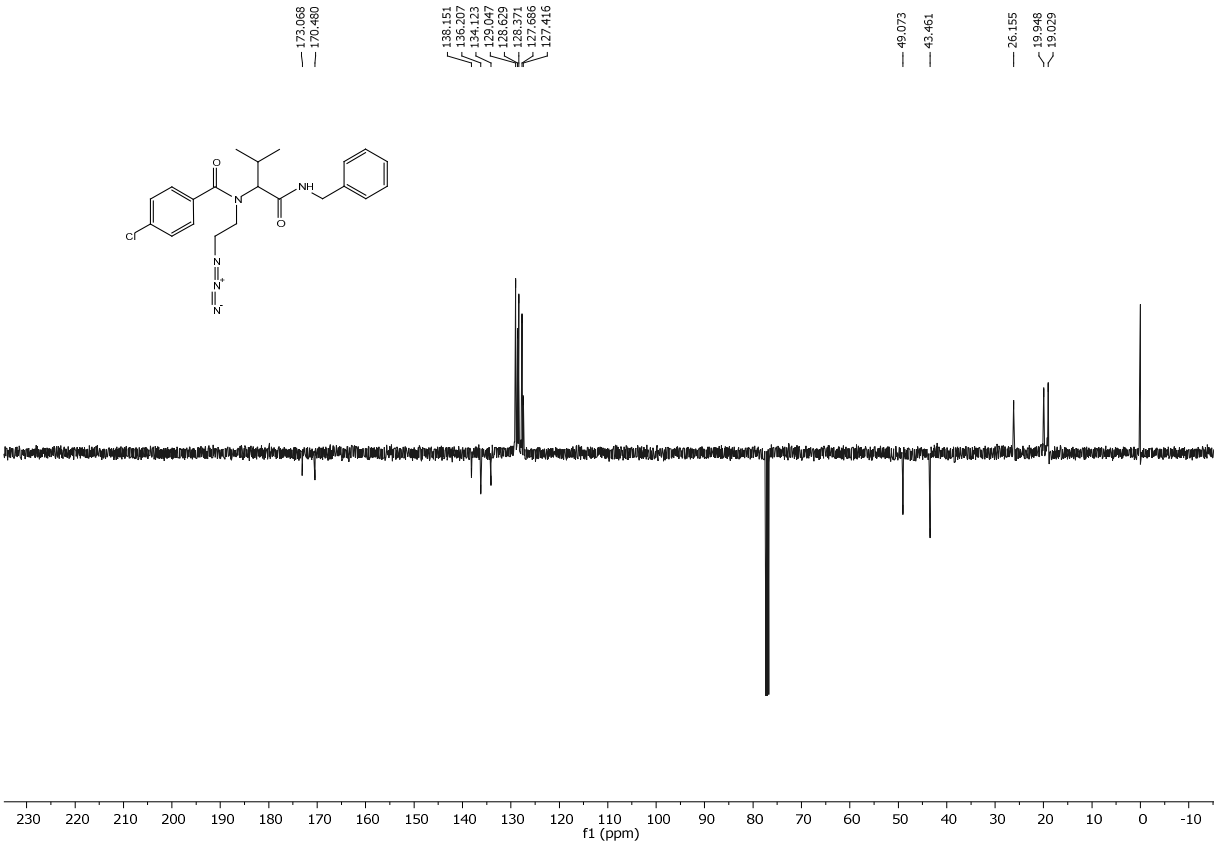
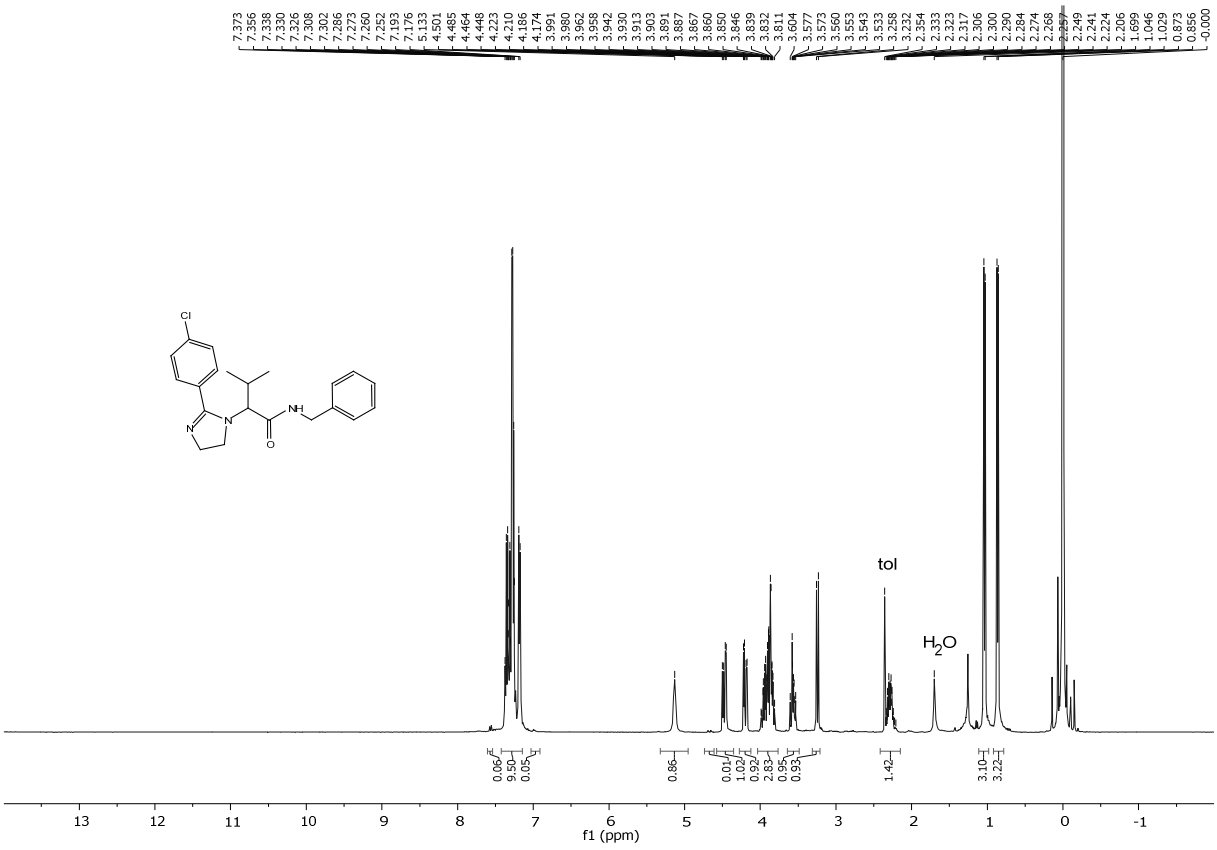
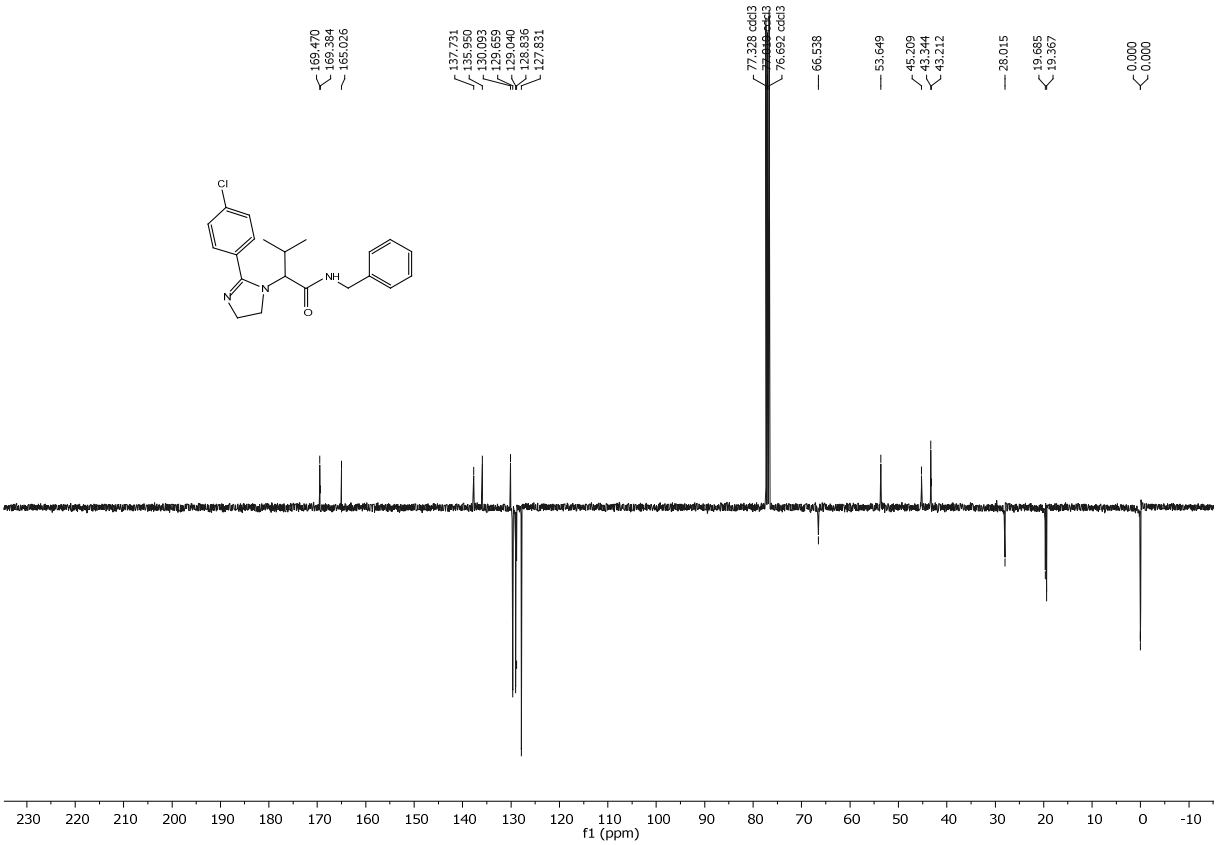
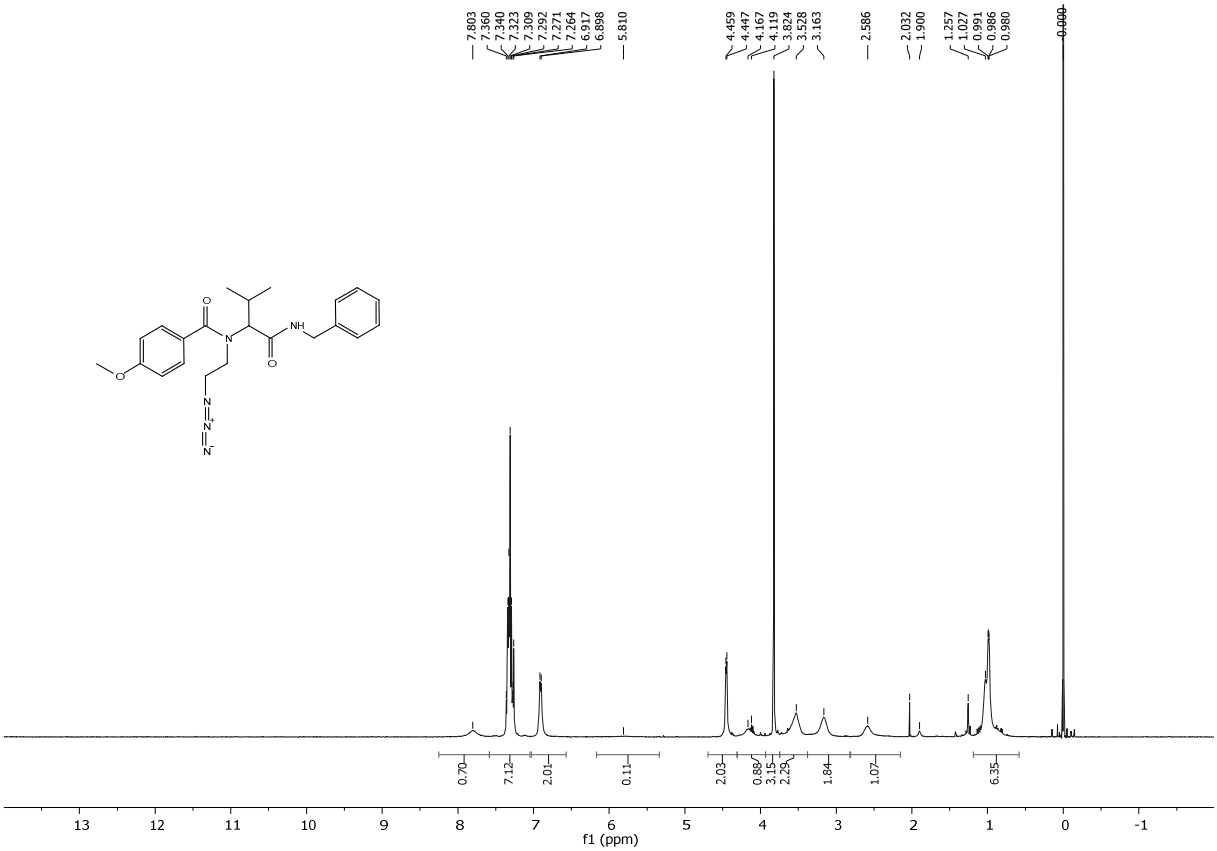
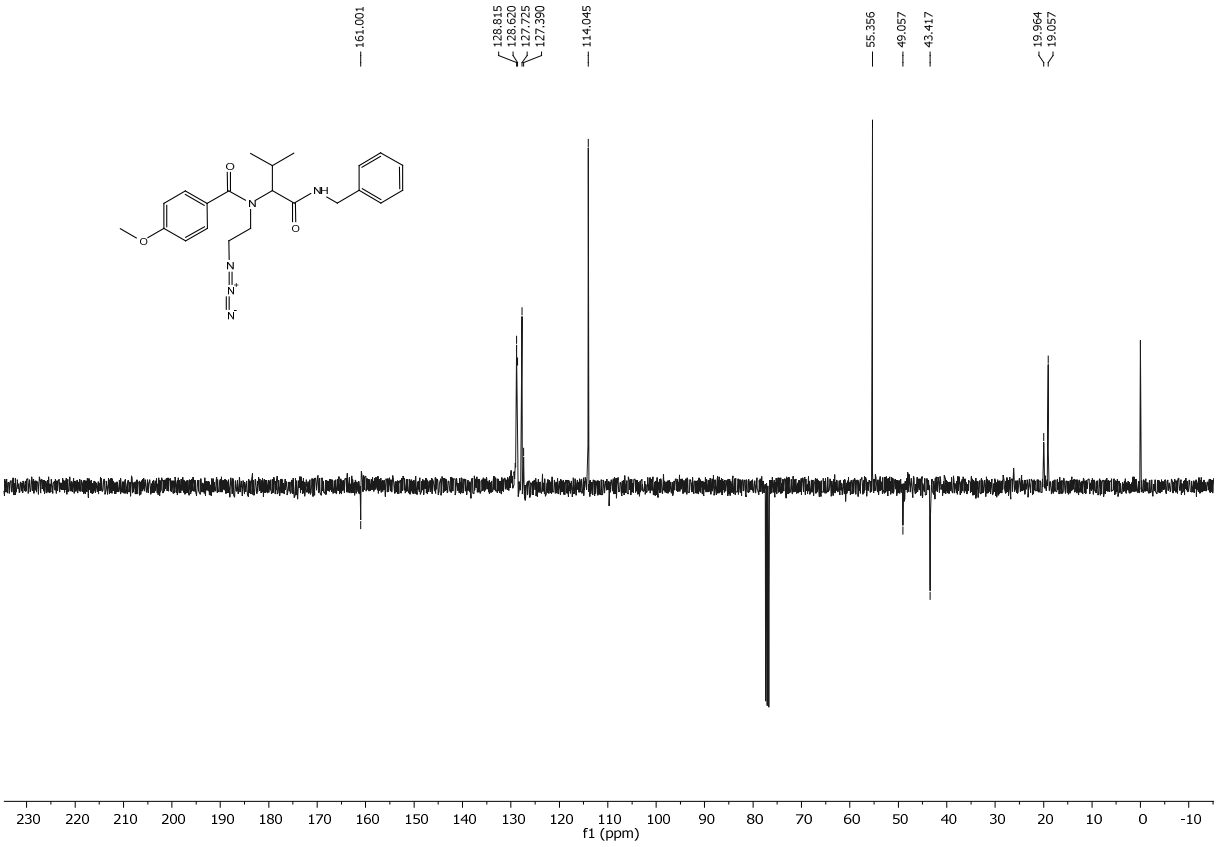
7.363
7.344
7.327
7.306
7.289
7.261
5.688
4.459
4.388
4.373
4.197
4.182
3.938
3.787
3.644
3.475
3.235
2.604
2.359
1.058
1.044
1.004
0.989
0.000
0.73
8.88
0.14
2.03
0.99
4.12
1.02
6.34
f1 (ppm)

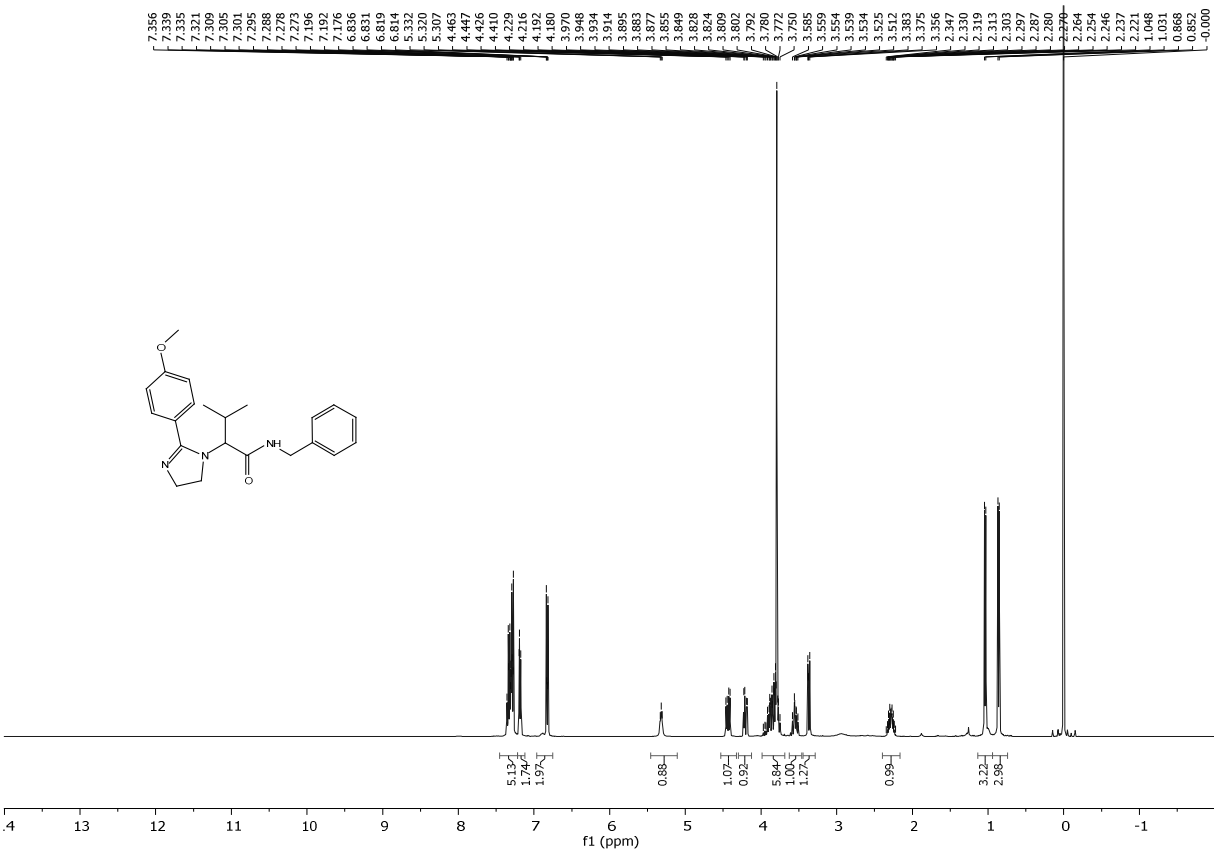

173.068
170.480
138.151
136.207
134.123
129.047
128.629
128.371
127.686
127.416
49.073
43.461
26.155
19.948
19.029
f1 (ppm)


tol
H2O
f1 (ppm)


f1 (ppm)


7.803
7.360
7.340
7.323
7.309
7.292
7.271
7.264
6.917
6.898
5.810
4.459
4.447
4.167
4.119
3.824
3.528
3.163
2.586
2.032
1.900
1.257
1.027
0.991
0.986
0.980
0.000
0.70
7.12
2.01
0.11
2.03
0.88
3.15
2.29
1.84
1.07
6.35
f1 (ppm)


161.001
128.815
128.620
127.725
127.390
114.045
55.356
49.057
43.417
19.964
19.057
f1 (ppm)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7.339
7.335
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7.309
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7.301
7.295
7.288
7.278
7.273
7.196
7.192
7.176
6.836
6.831
6.819
6.814
5.332
5.320
5.307
4.463
4.447
4.426
4.410
4.229
4.216
4.192
4.180
3.970
3.948
3.934
3.914
3.895
3.883
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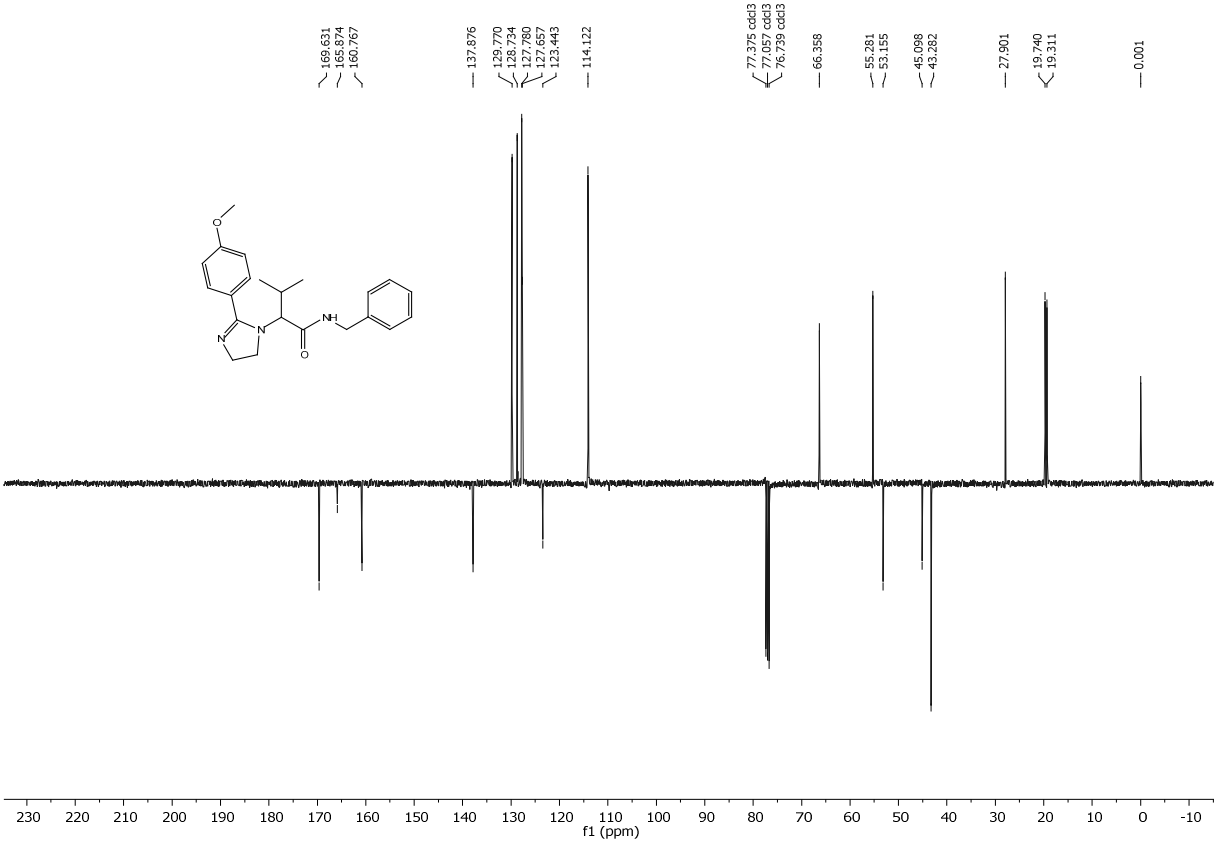
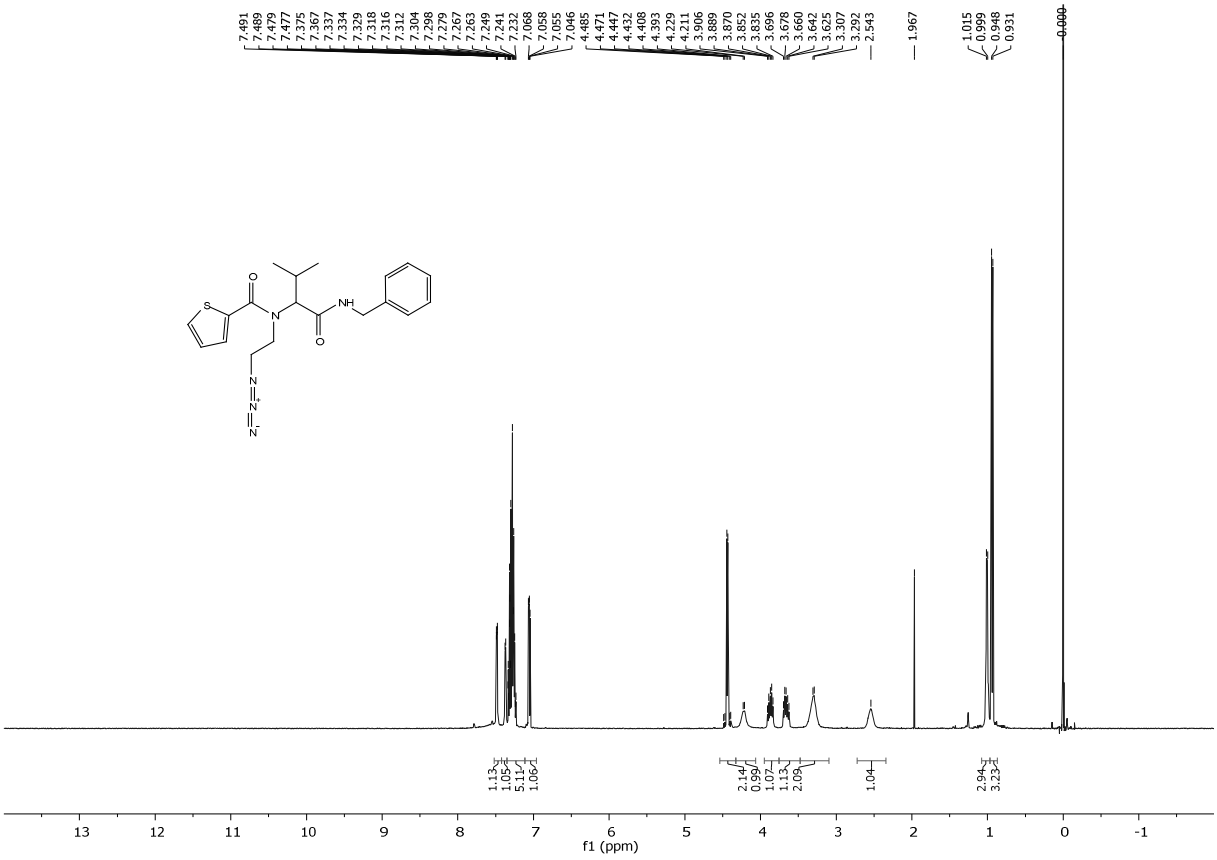
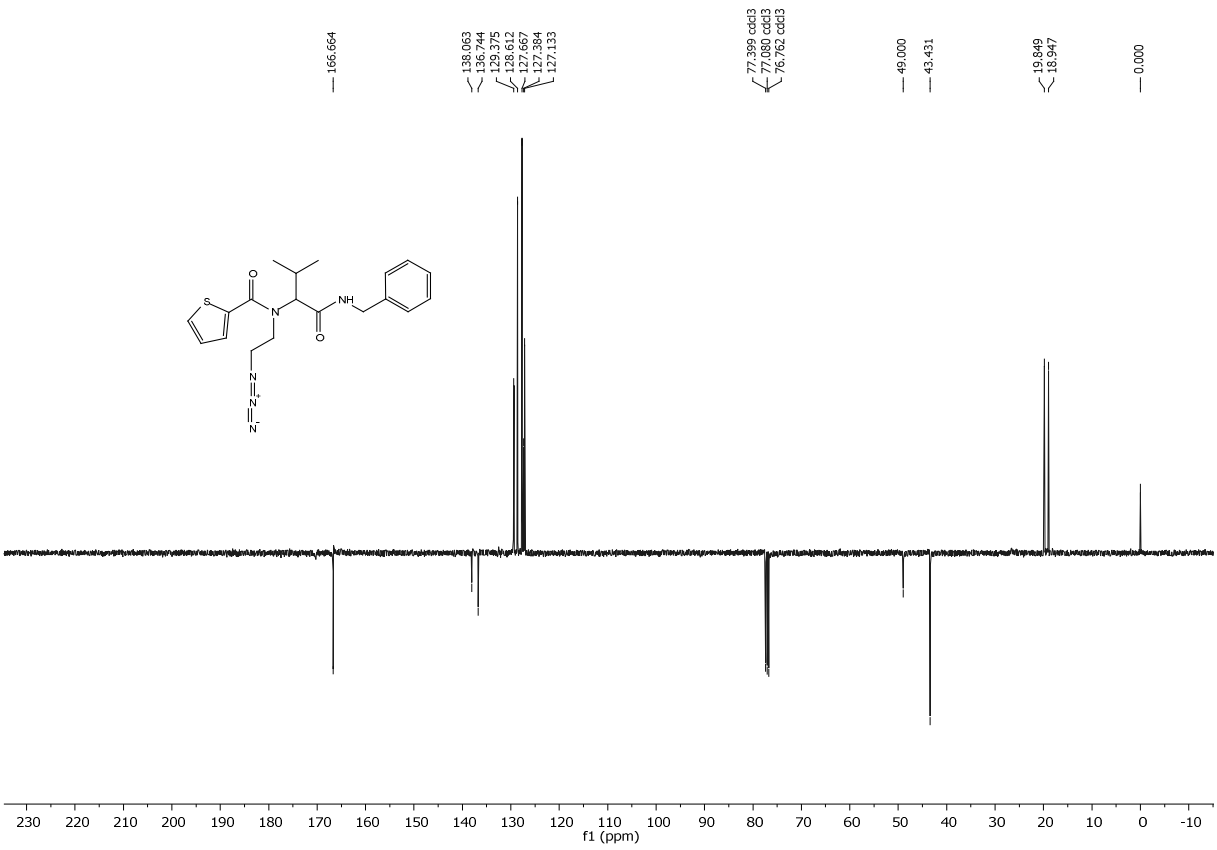
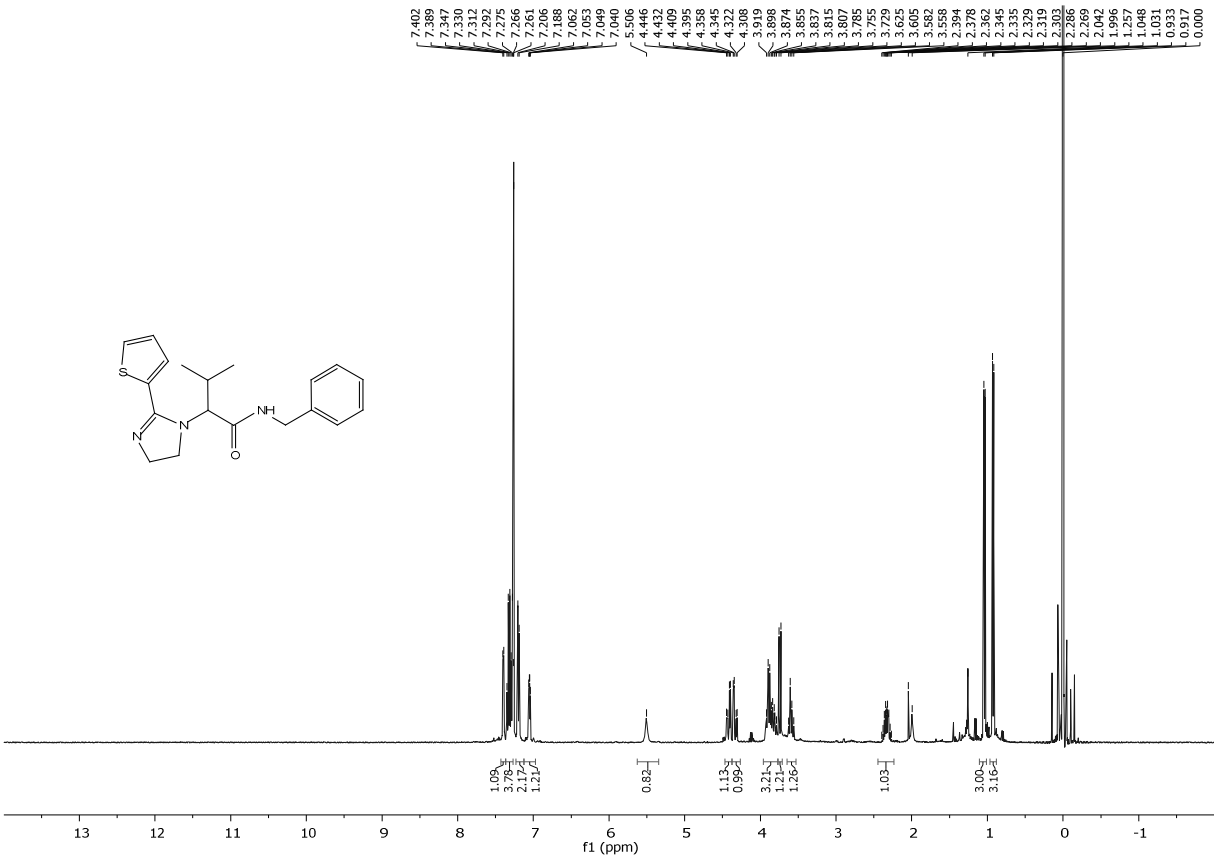
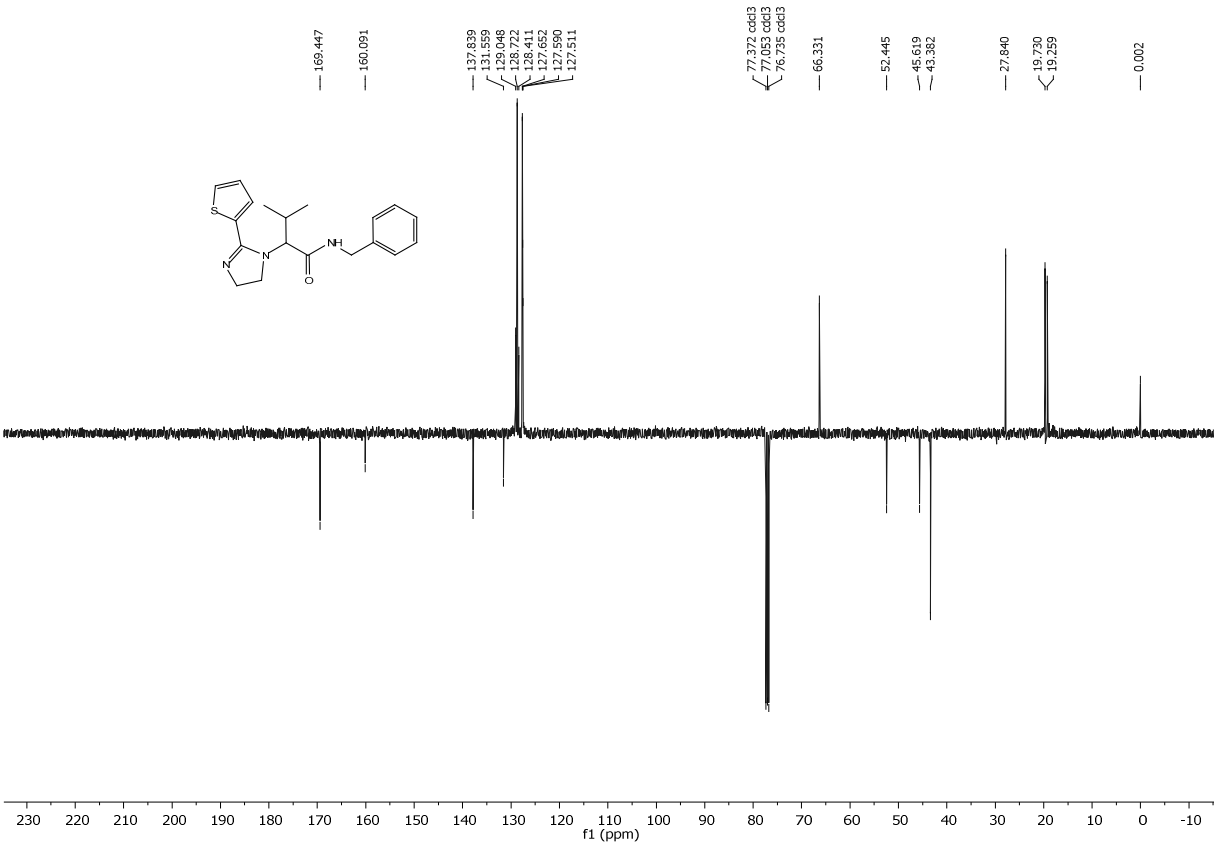
3.855
3.849
3.828
3.824
3.809
3.802
3.792
3.780
3.772
3.750
3.585
3.559
3.554
3.539
3.534
3.525
3.512
3.383
3.375
3.356
2.347
2.330
2.319
2.313
2.303
2.297
2.287
2.280
2.270
2.264
2.254
2.246
2.237
2.221
1.048
1.031
0.868
0.852
-0.000
5.13
1.74
1.97
0.88
1.07
0.92
5.84
1.00
1.27
0.99
3.22
2.98
f1 (ppm)

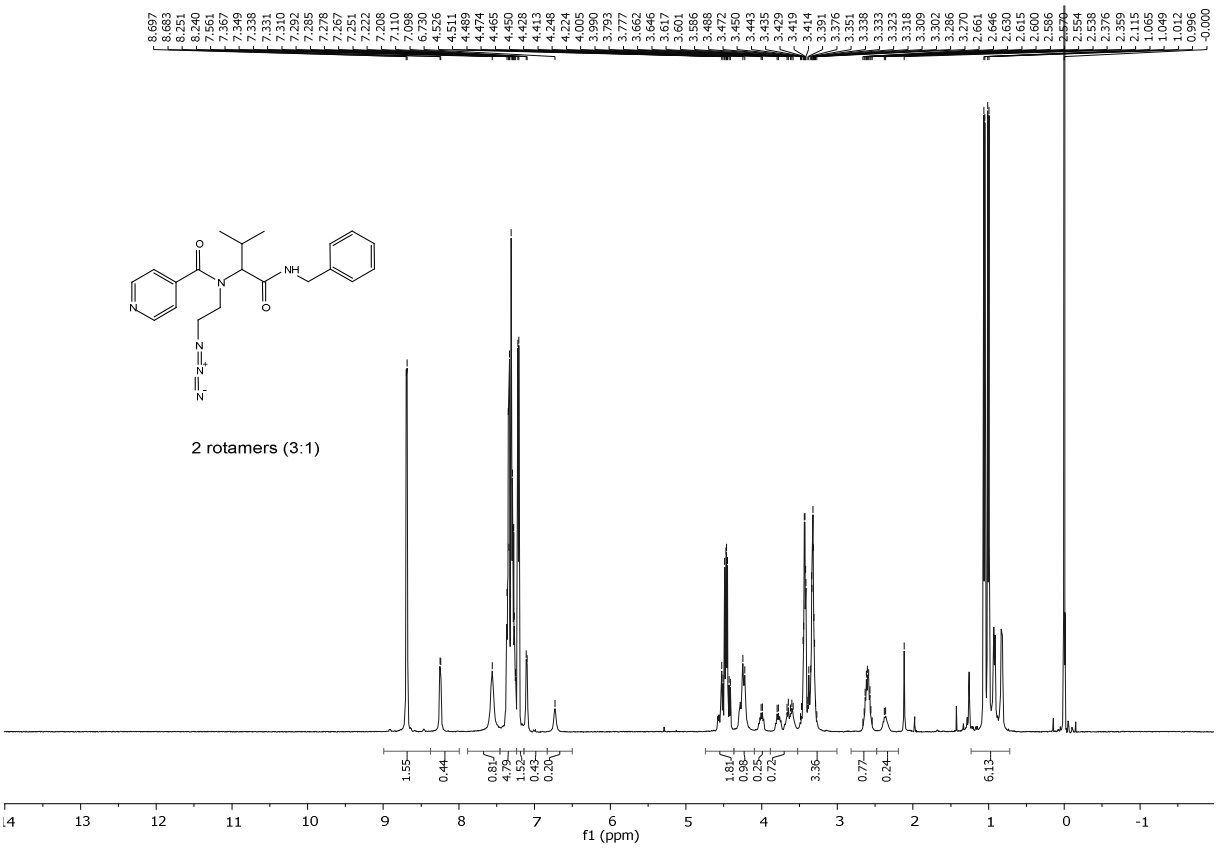

169.631
165.874
160.767
137.876
129.770
128.734
127.780
127.657
123.443
114.122
77.375 cdcl3
77.057 cdcl3
76.739 cdcl3
66.358
55.281
53.155
45.098
43.282
27.901
19.740
19.311
0.001
f1 (ppm)

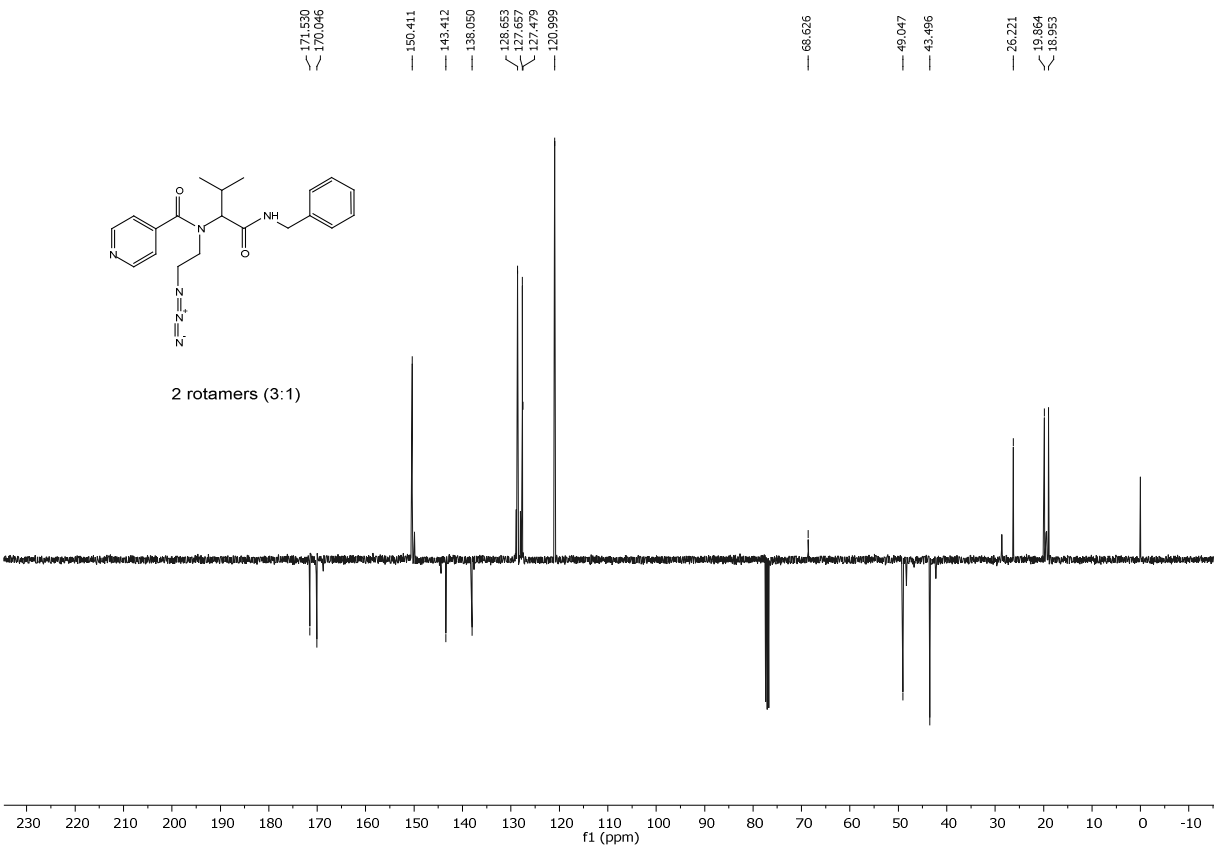

7.491
7.489
7.479
7.477
7.375
7.367
7.337
7.334
7.329
7.318
7.316
7.312
7.304
7.298
7.279
7.267
7.263
7.249
7.241
7.232
7.068
7.058
7.055
7.046
4.485
4.471
4.447
4.432
4.408
4.393
4.229
4.211
3.906
3.889
3.870
3.852
3.835
3.696
3.678
3.660
3.642
3.625
3.307
3.292
2.543
1.967
1.015
0.999
0.948
0.931
0.000
1.13
1.05
5.11
1.06
2.14
0.99
1.07
1.13
2.09
1.04
2.94
3.23
f1 (ppm)

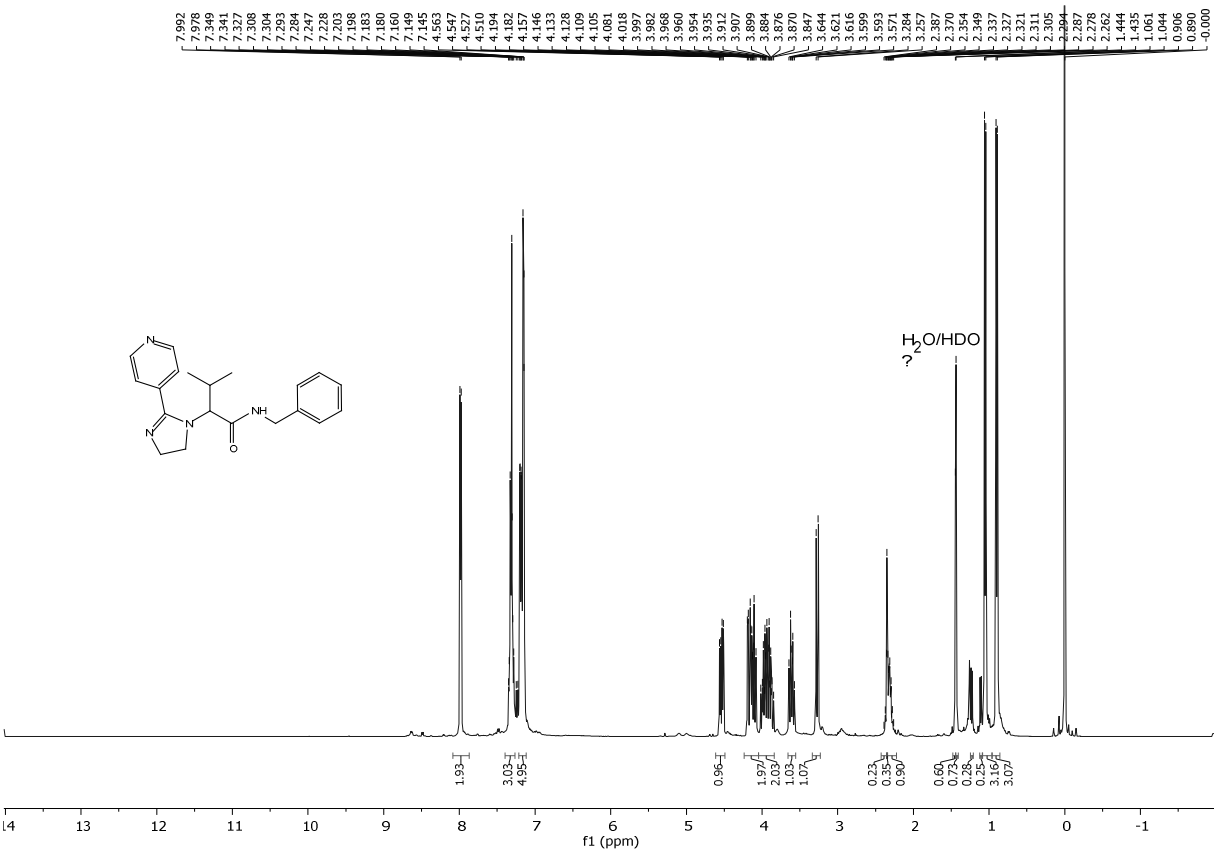

166.664
138.063
136.744
129.375
128.612
127.667
127.384
127.133
77.399 cdcl3
77.080 cdcl3
76.762 cdcl3
49.000
43.431
19.849
18.947
0.000
f1 (ppm)

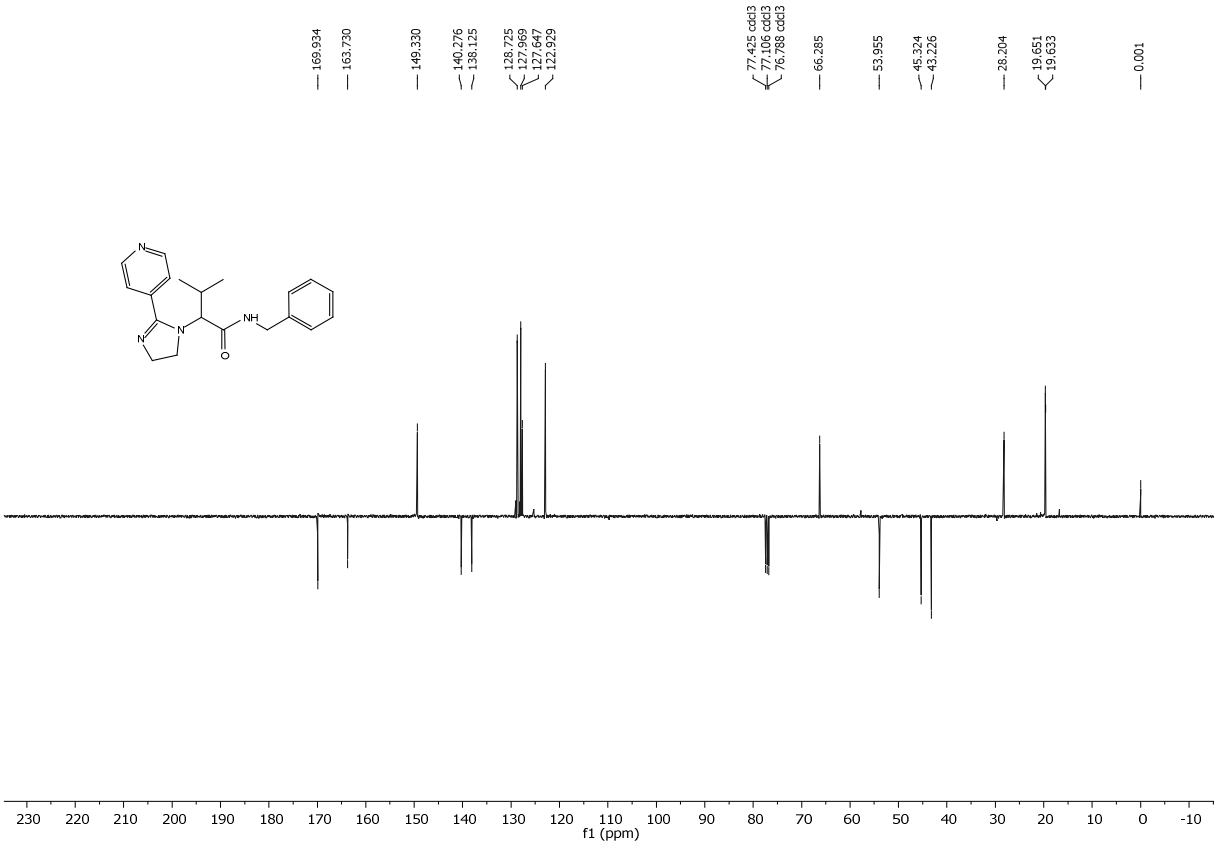

7.402
7.389
7.347
7.330
7.312
7.292
7.275
7.266
7.261
7.206
7.188
7.062
7.053
7.049
7.040
5.506
4.446
4.432
4.409
4.395
4.358
4.345
4.322
4.308
3.919
3.898
3.874
3.855
3.837
3.815
3.807
3.785
3.755
3.729
3.625
3.605
3.582
3.558
2.394
2.378
2.362
2.345
2.335
2.329
2.319
2.303
2.286
2.269
2.042
1.996
1.257
1.048
1.031
0.933
0.917
0.000
1.09
3.78
2.17
1.21
0.82
1.13
0.99
3.21
1.21
1.26
1.03
3.00
3.16
S
N
N
NH
O
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

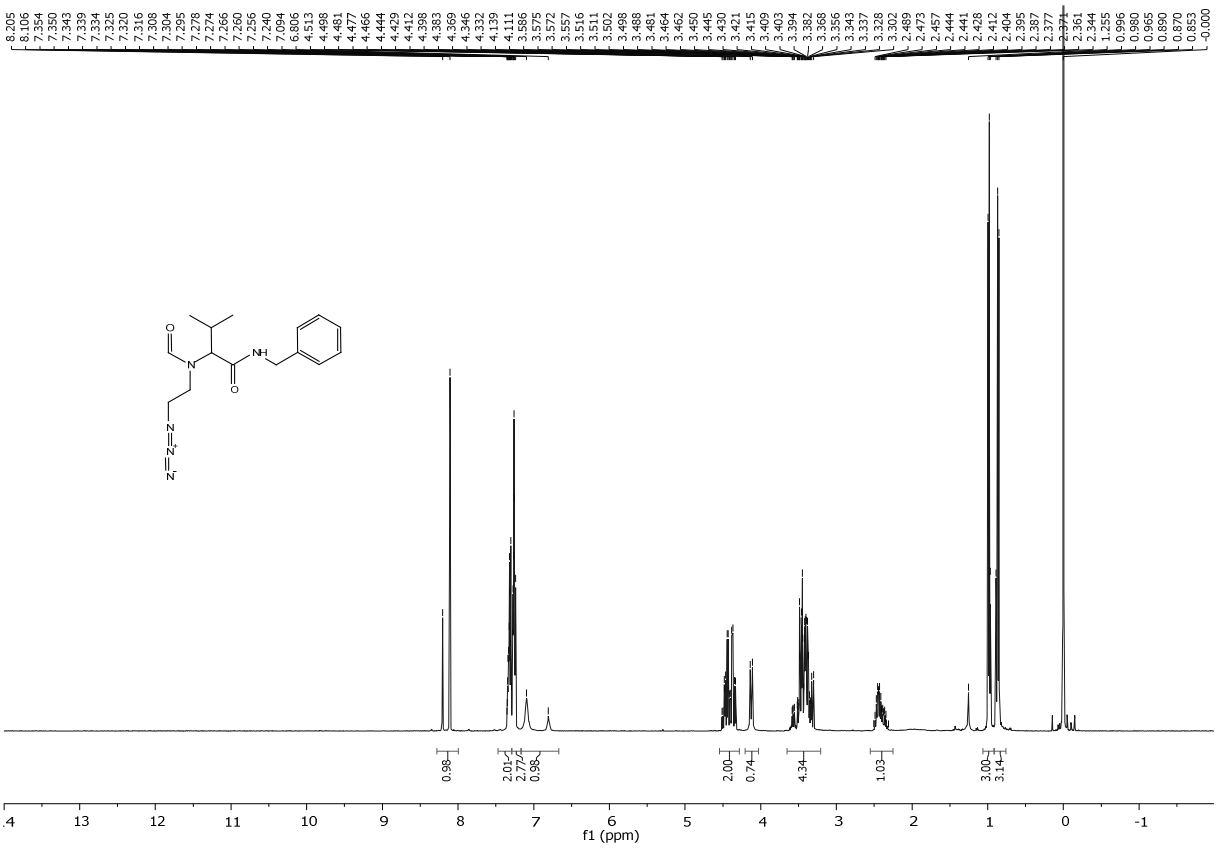

169.447
160.091
137.839
131.559
129.048
128.722
128.411
127.652
127.590
127.511
77.372 cdcl3
77.053 cdcl3
76.735 cdcl3
66.331
52.445
45.619
43.382
27.840
19.730
19.259
0.002
S
N
N
NH
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

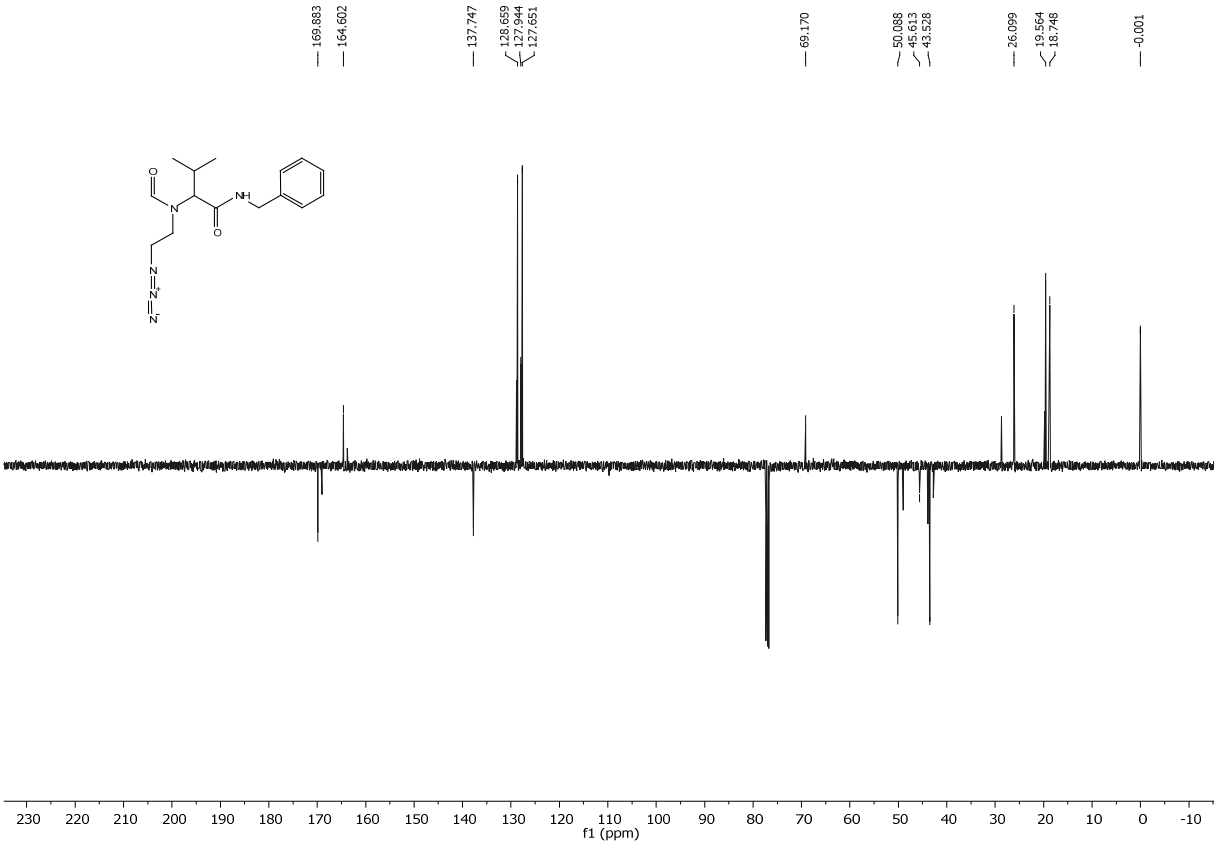

2 rotamers (3:1)
f1 (ppm)

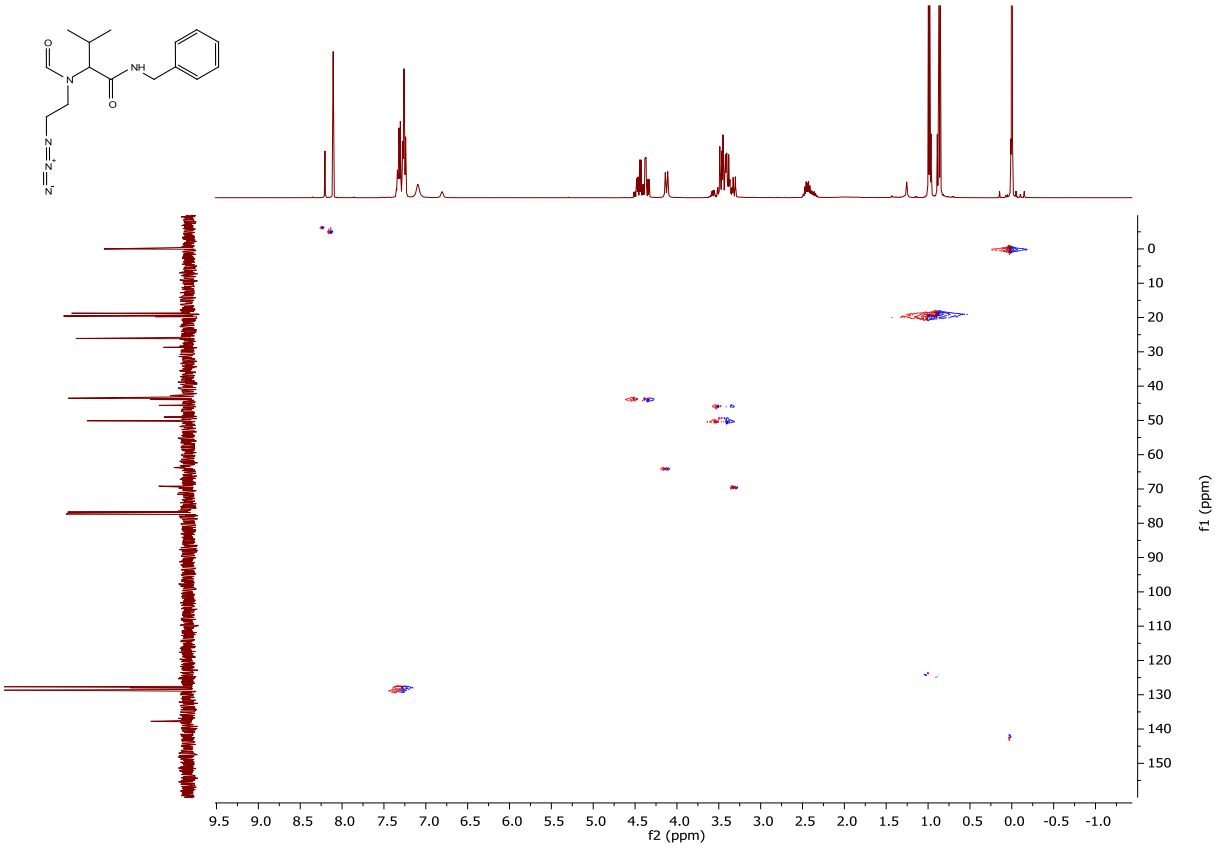

2 rotamers (3:1)
f1 (ppm)

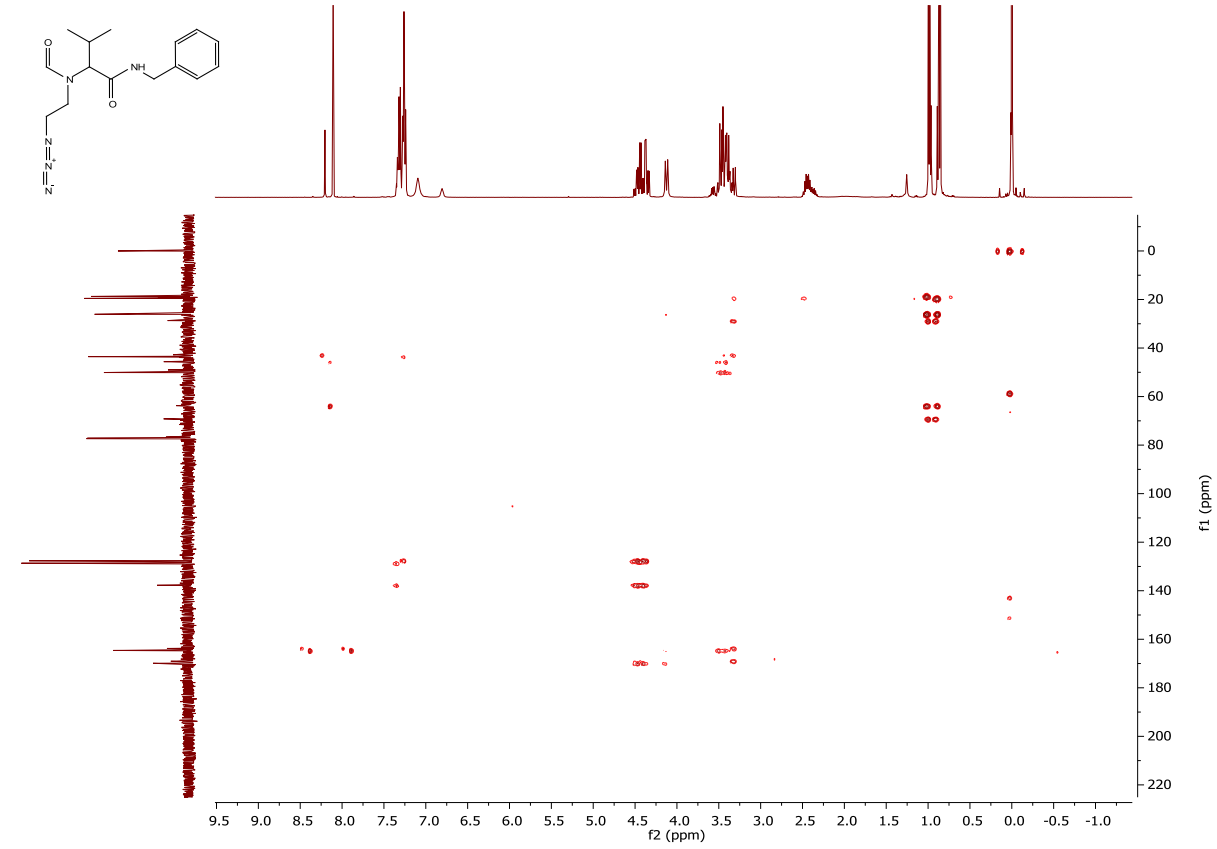

7.992
7.978
7.349
7.341
7.327
7.308
7.304
7.293
7.284
7.247
7.228
7.203
7.198
7.183
7.180
7.160
7.149
7.145
4.563
4.547
4.527
4.510
4.194
4.182
4.157
4.146
4.133
4.128
4.109
4.105
4.081
4.018
3.997
3.982
3.968
3.960
3.954
3.935
3.912
3.907
3.899
3.884
3.876
3.870
3.847
3.644
3.621
3.616
3.599
3.593
3.571
3.284
3.257
2.387
2.370
2.354
2.349
2.337
2.327
2.321
2.311
2.305
2.294
2.287
2.278
2.262
1.444
1.435
1.061
1.044
0.906
0.890
-0.000
H2O/HDO
?
1.93
3.03
4.95
0.96
1.97
2.03
1.03
1.07
0.23
0.35
0.90
0.60
0.73
0.28
0.25
3.16
3.07
f1 (ppm)

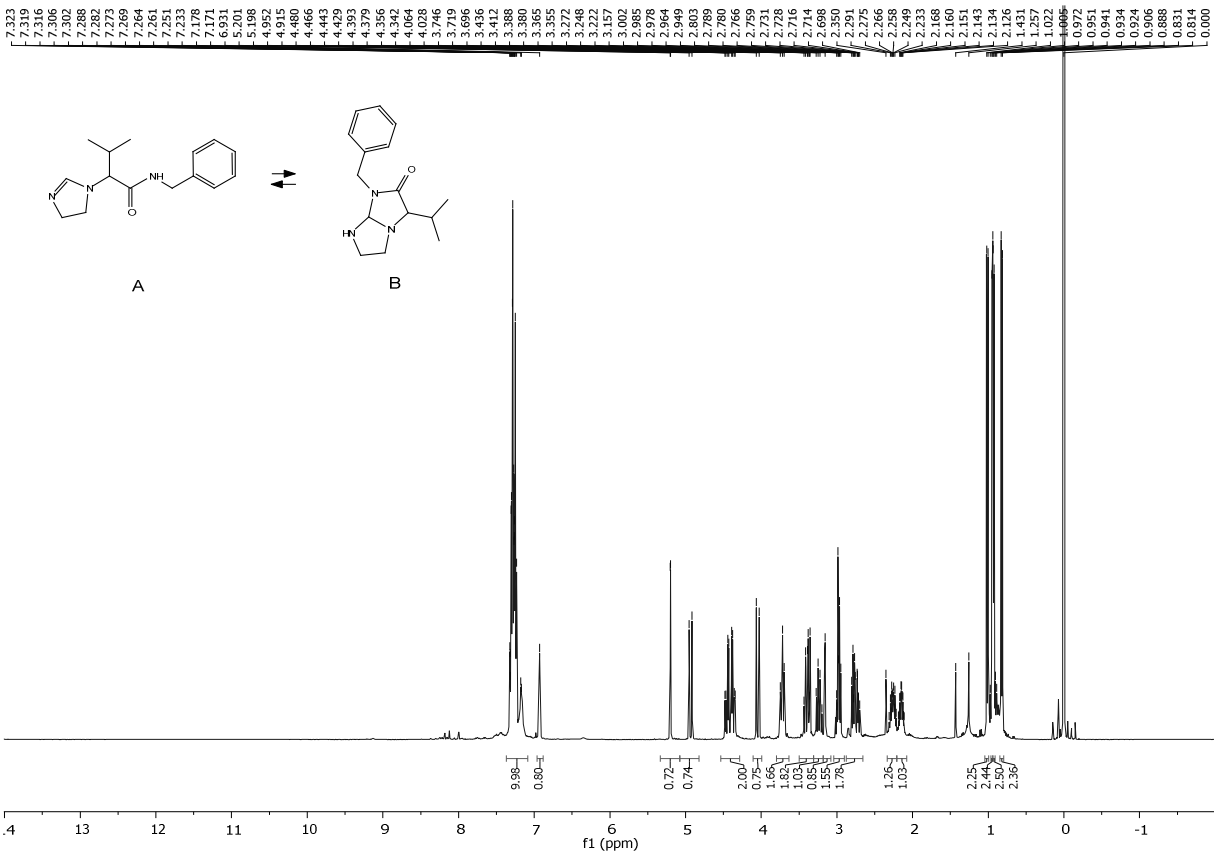

169.934
163.730
149.330
140.276
138.125
128.725
127.969
127.647
122.929
77.425 cdcl3
77.106 cdcl3
76.788 cdcl3
66.285
53.955
45.324
43.226
28.204
19.651
19.633
0.001
f1 (ppm)

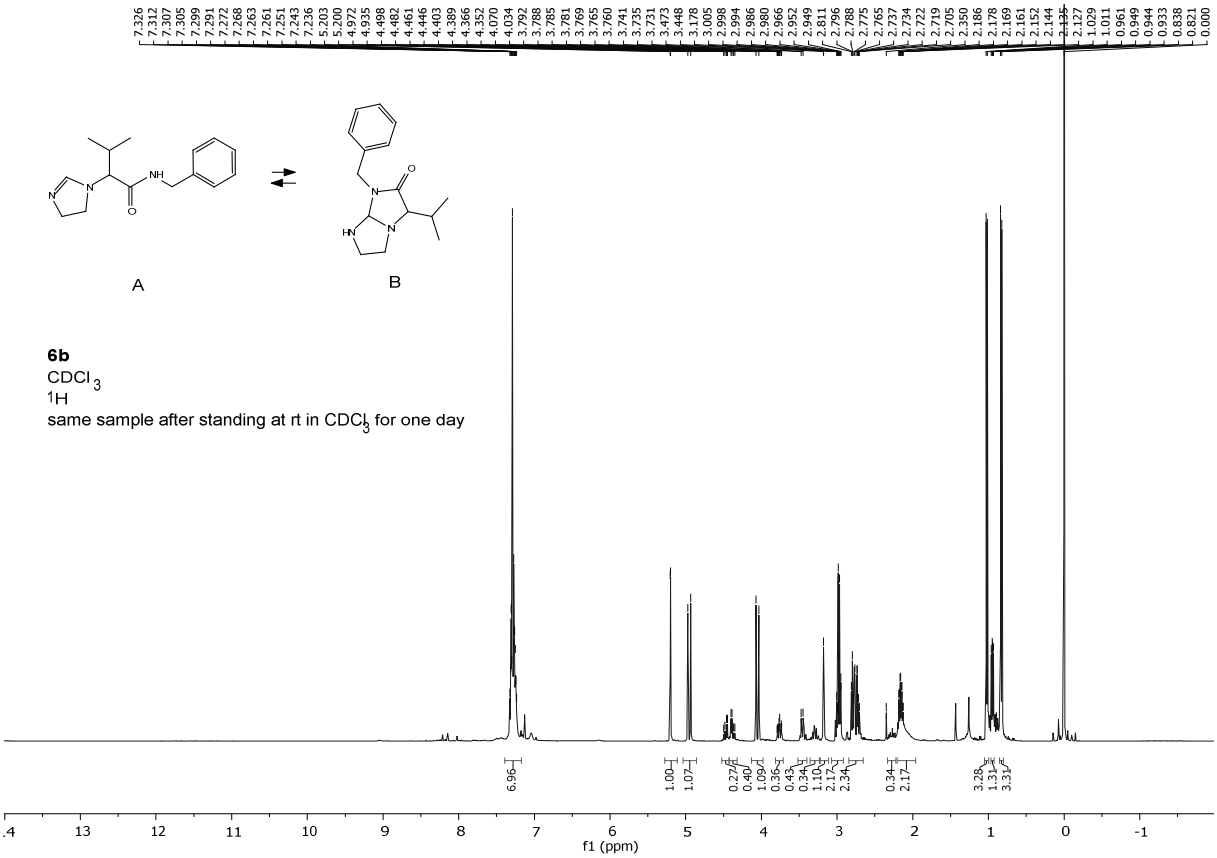

f1 (ppm)


f1 (ppm)

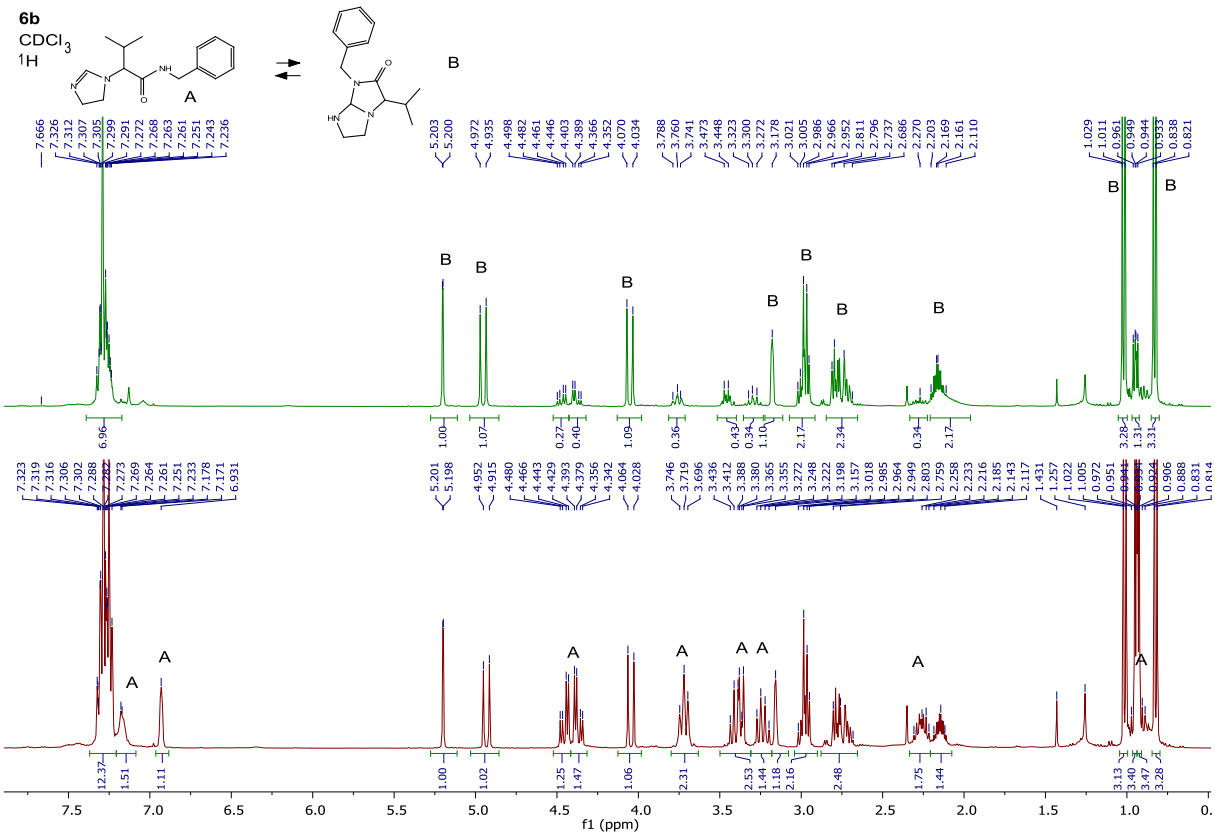

f2 (ppm)
f1 (ppm)

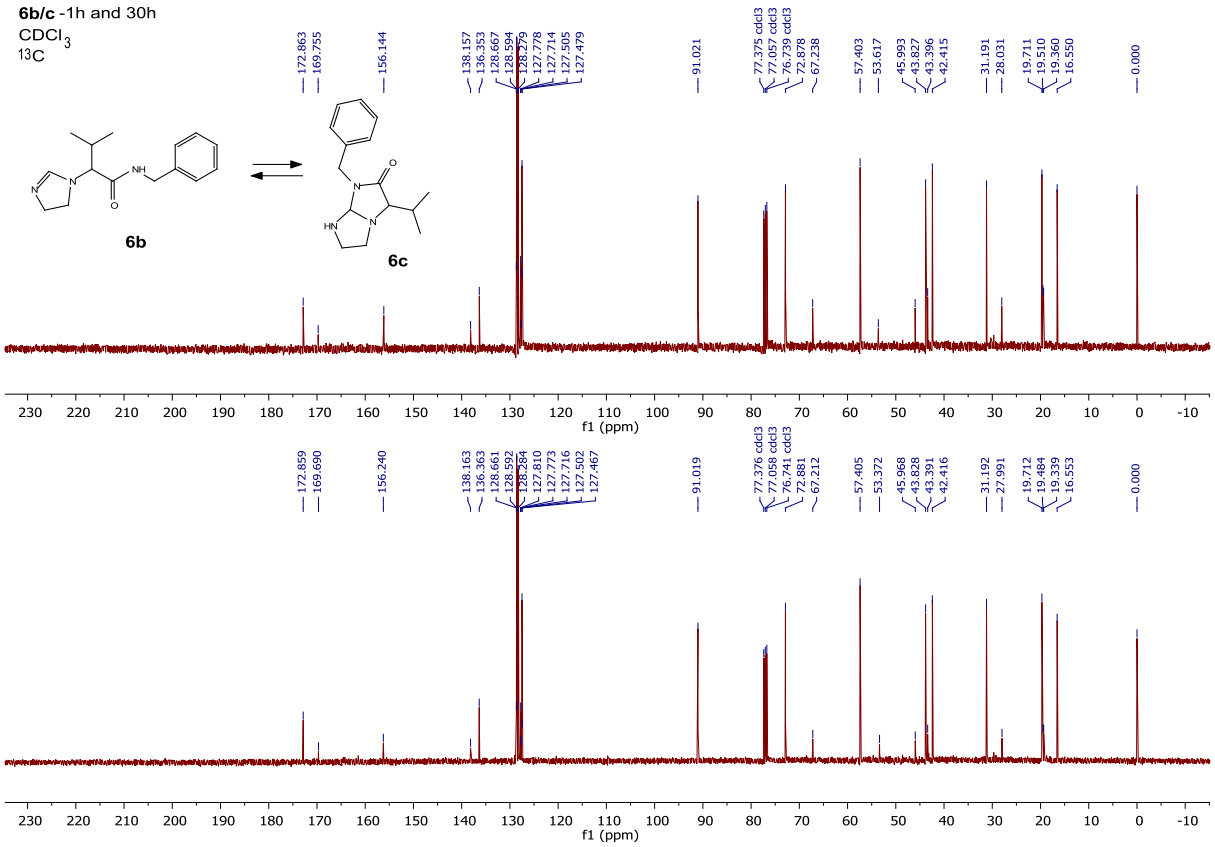

f2 (ppm)
f1 (ppm)

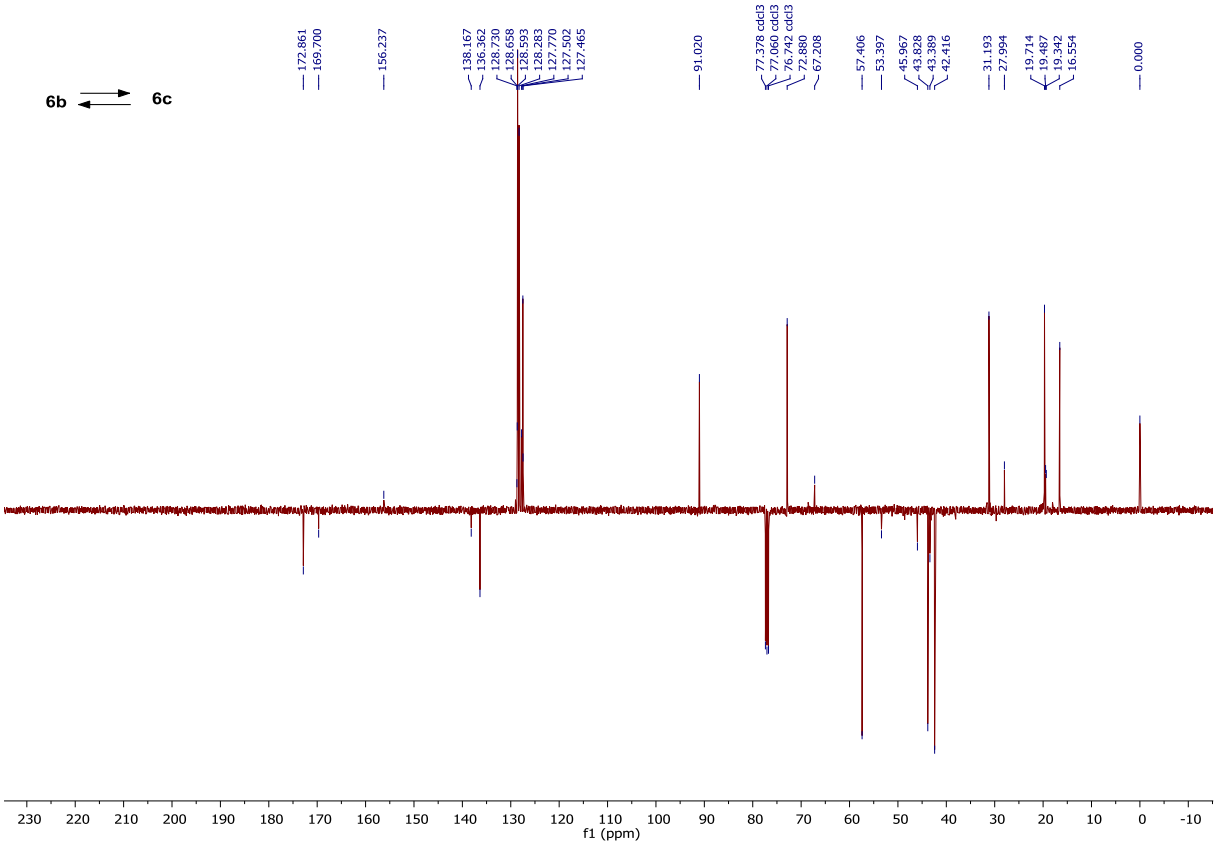


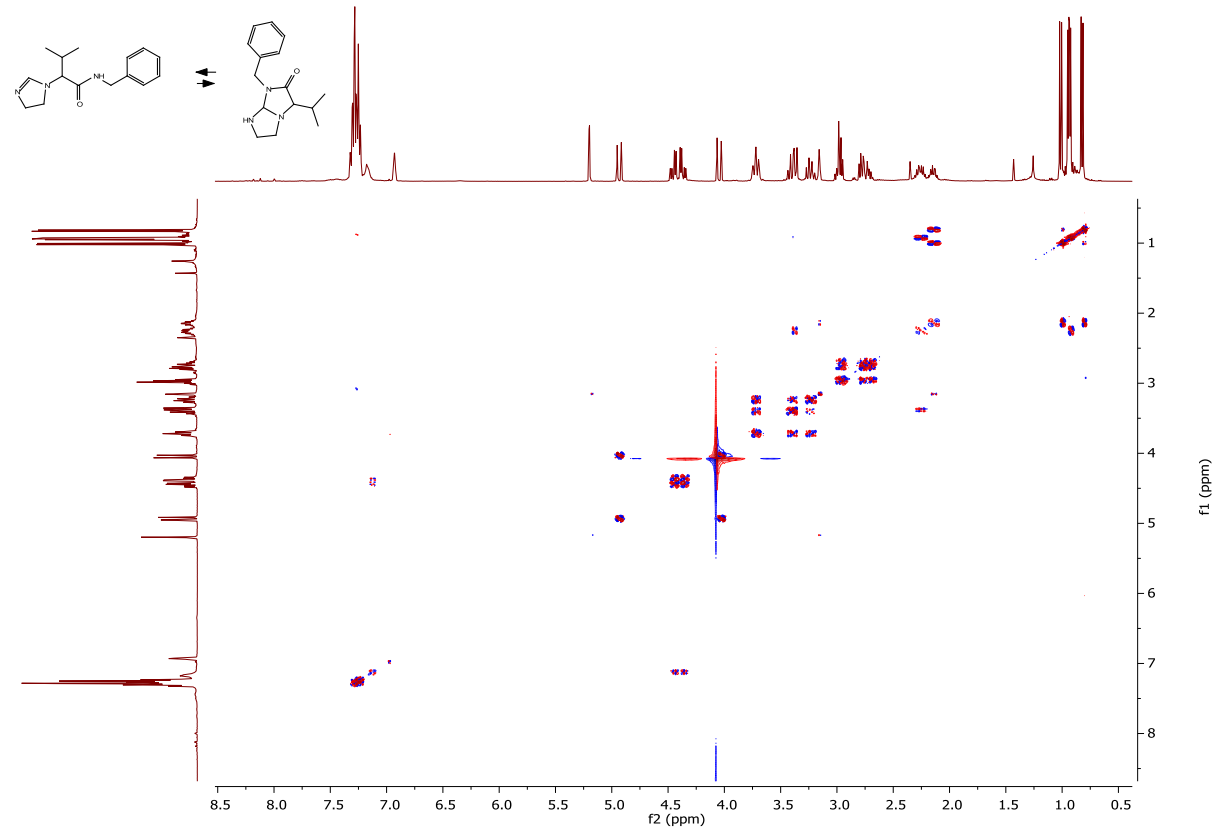


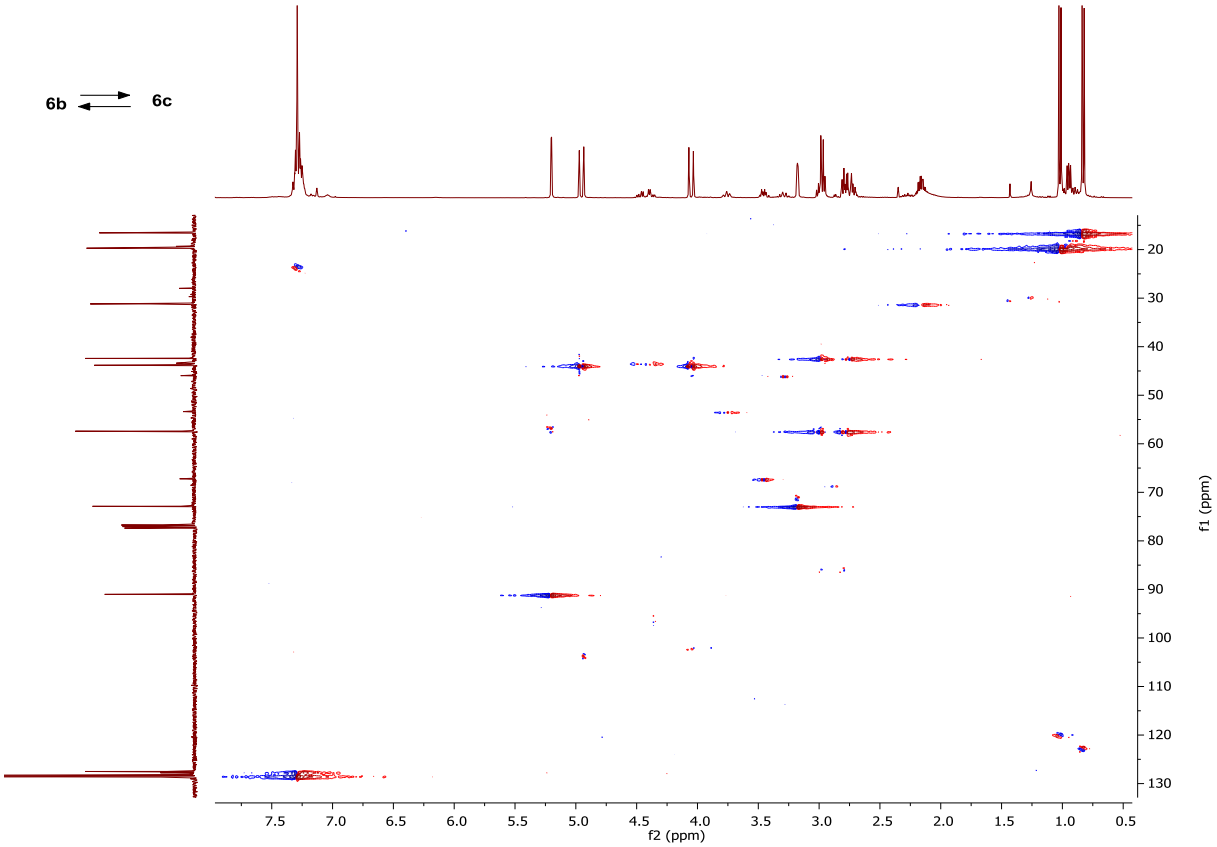
6b
$CDCl_3$
^1H
same sample after standing at rt in $CDCl_3$ for one day

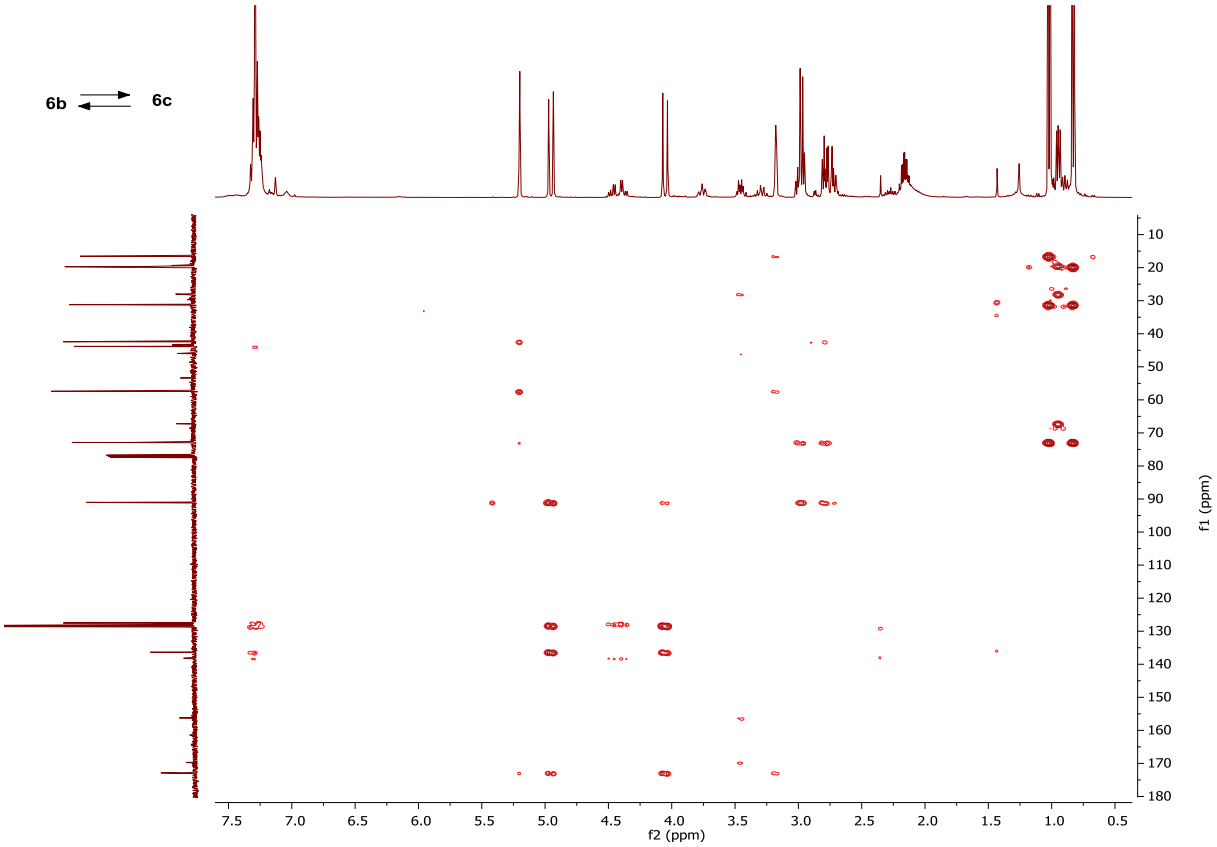

6b
CDCl3
1H
A
B
f1 (ppm)

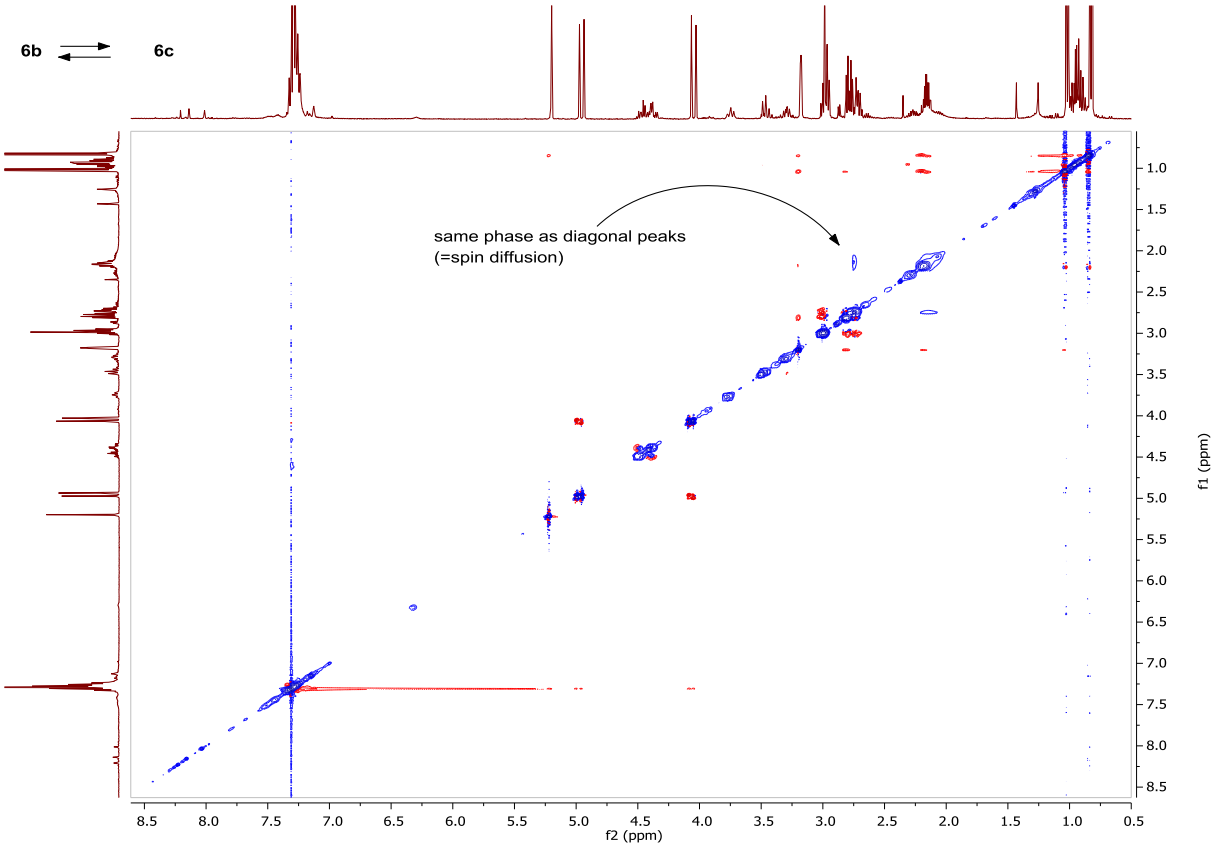

6b/c -1h and 30h
CDCl3
13C
6b
6c
f1 (ppm)

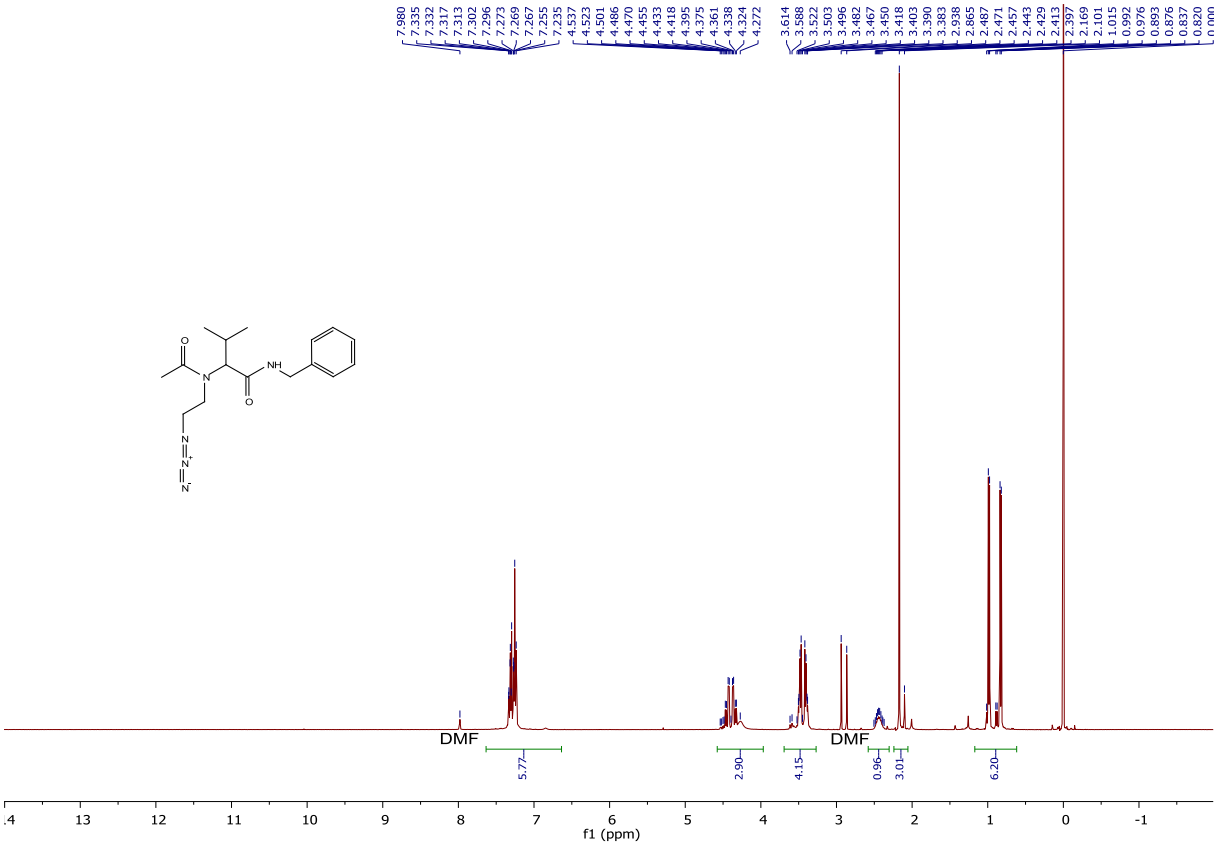

6b
6c
172.861
169.700
156.237
138.167
136.362
128.730
128.658
128.593
128.283
127.770
127.502
127.465
91.020
77.378 cdcl3
77.060 cdcl3
76.742 cdcl3
72.880
67.208
57.406
53.397
45.967
43.828
43.389
42.416
31.193
27.994
19.714
19.487
19.342
16.554
0.000
f1 (ppm)

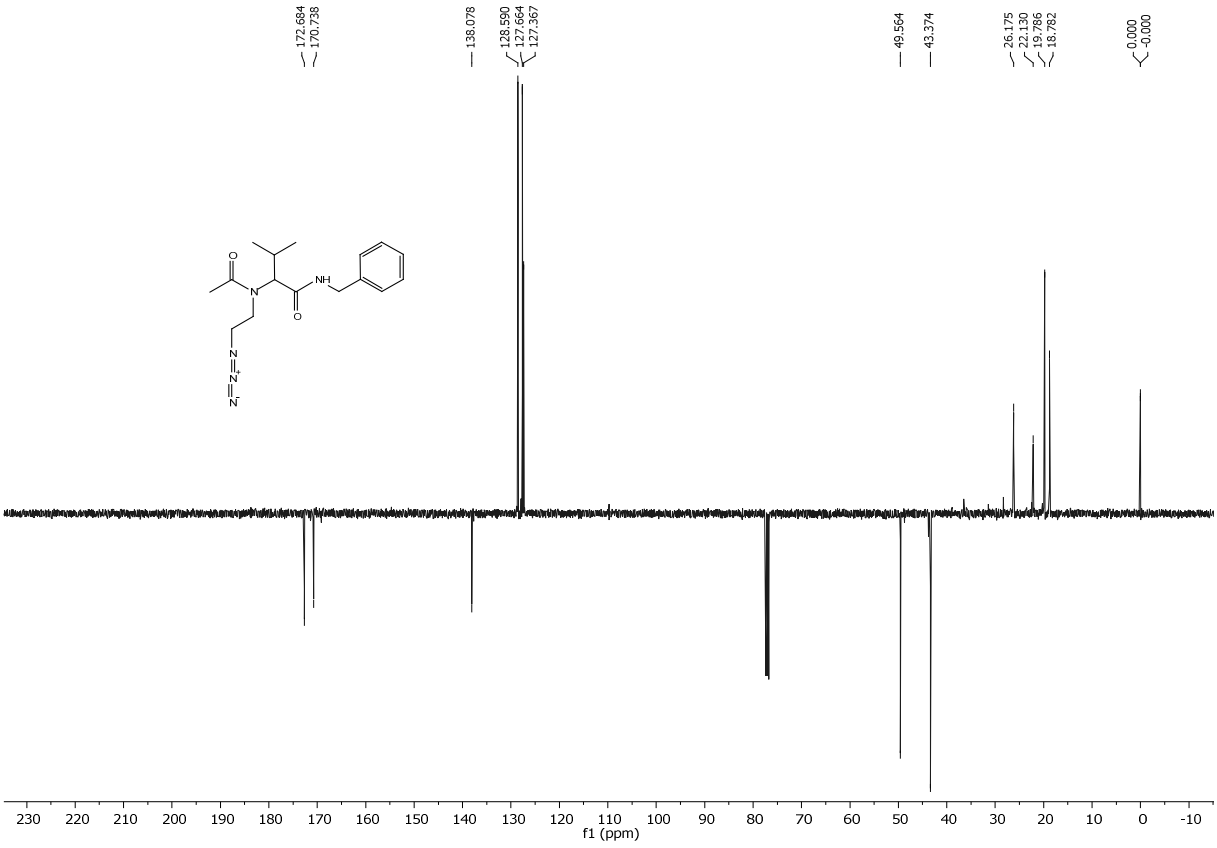

f2 (ppm)
f1 (ppm)

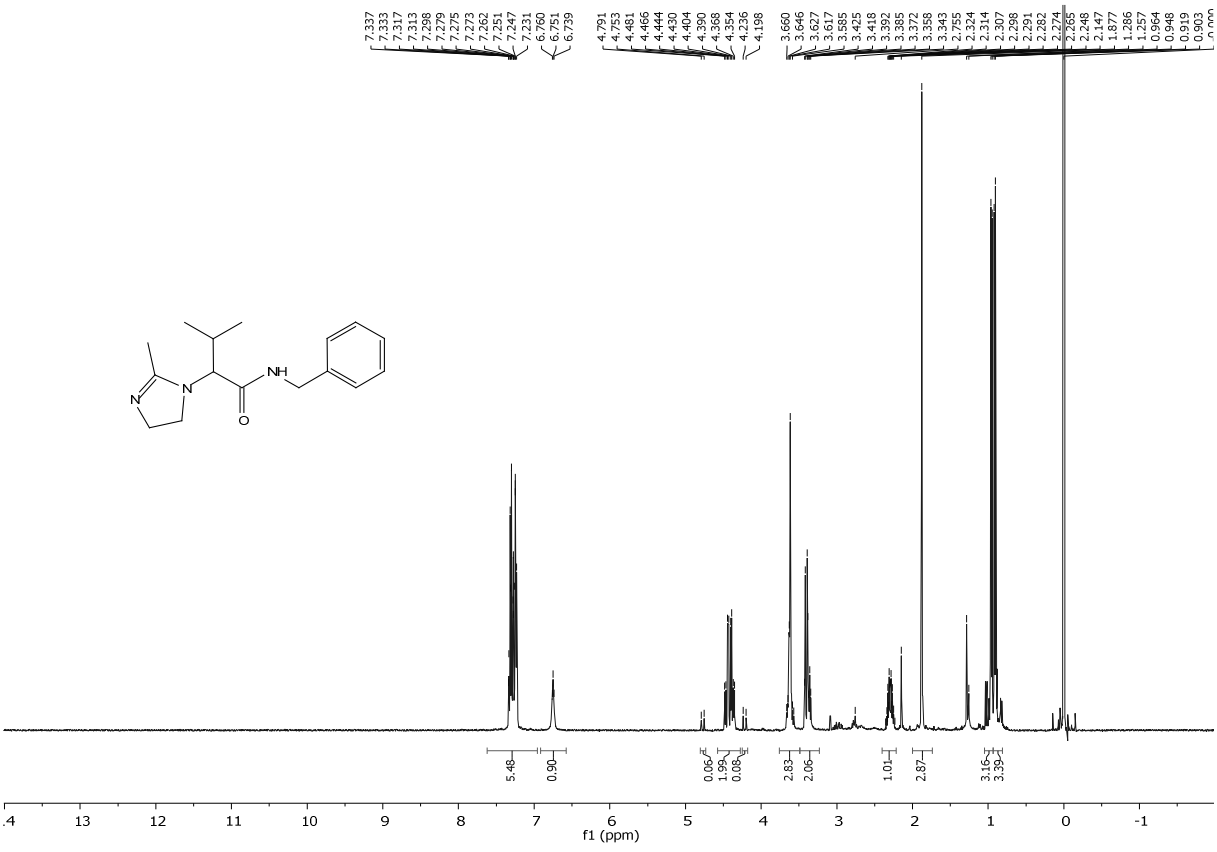

6b
6c
f2 (ppm)
f1 (ppm)

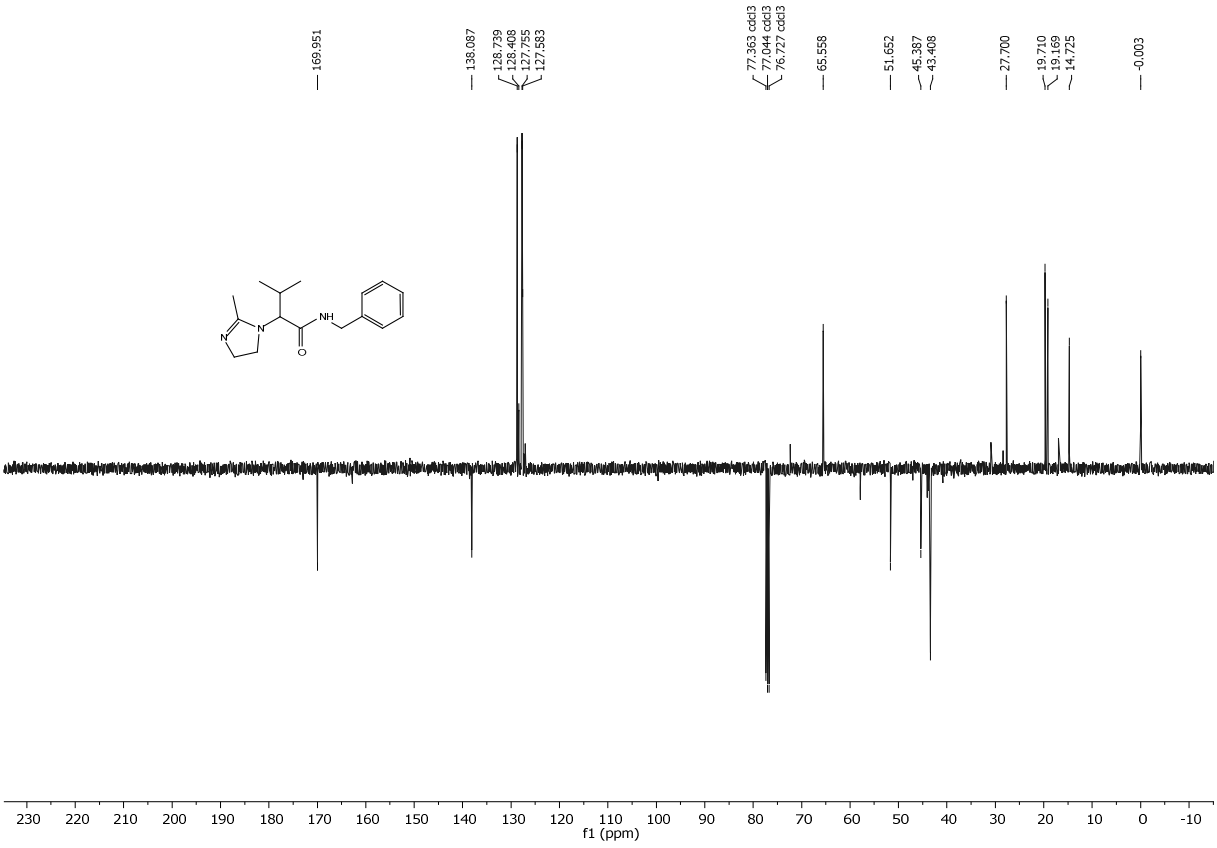

6b
6c
f2 (ppm)
f1 (ppm)

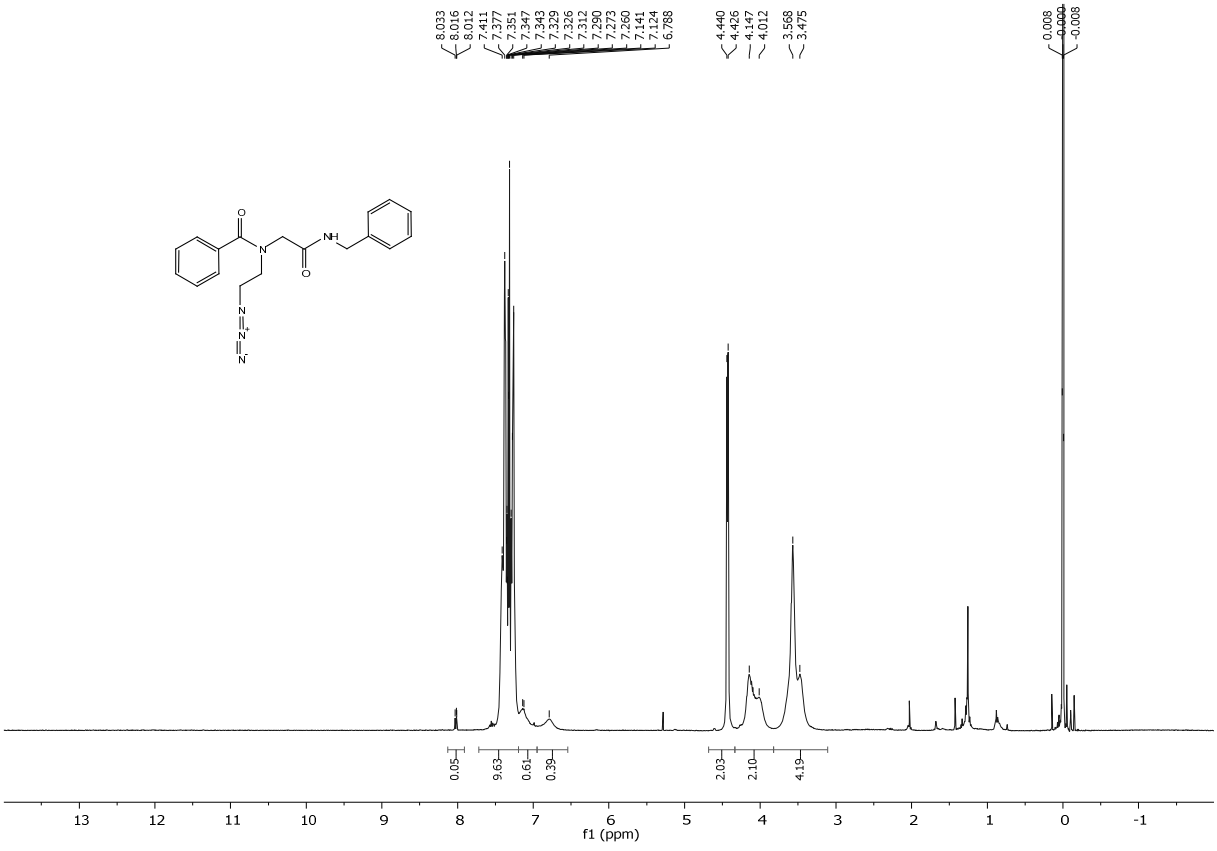

6b
6c
same phase as diagonal peaks
(=spin diffusion)
f2 (ppm)
f1 (ppm)

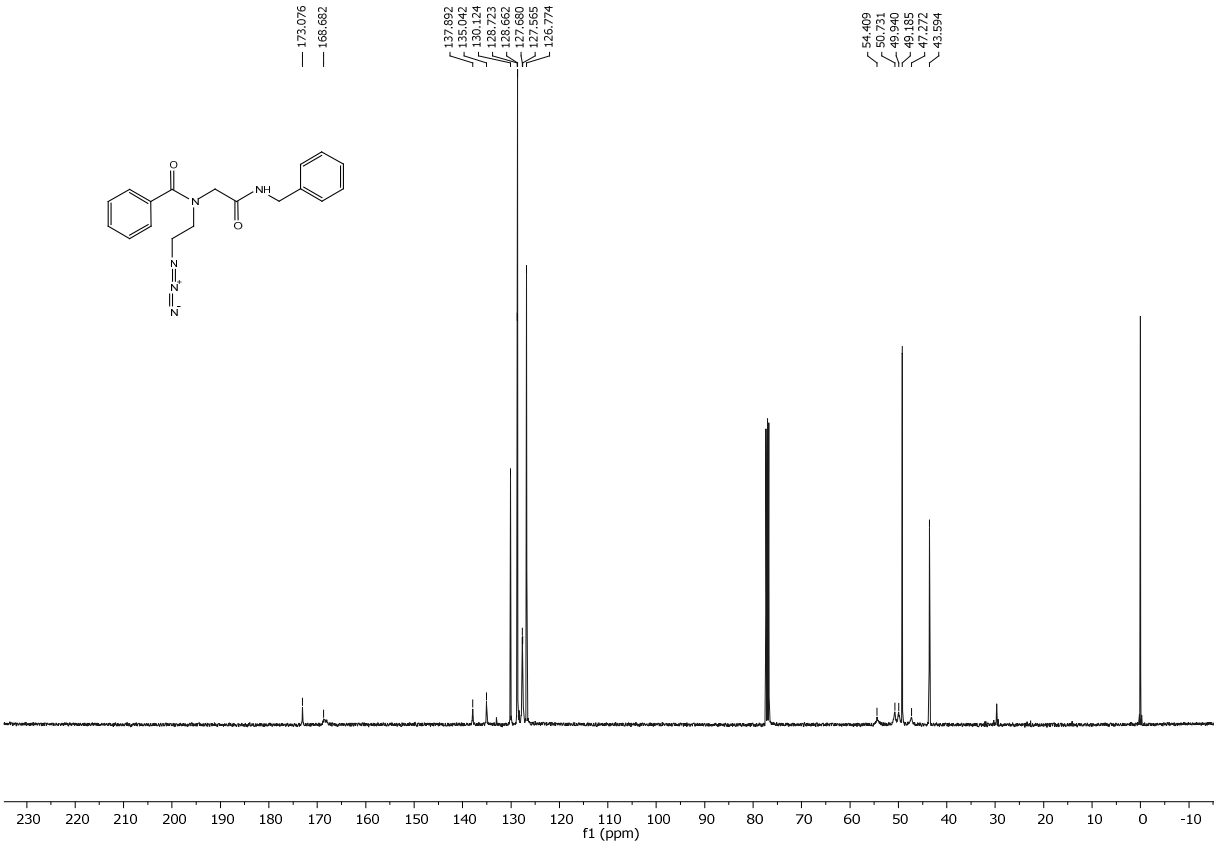

DMF
DMF
f1 (ppm)

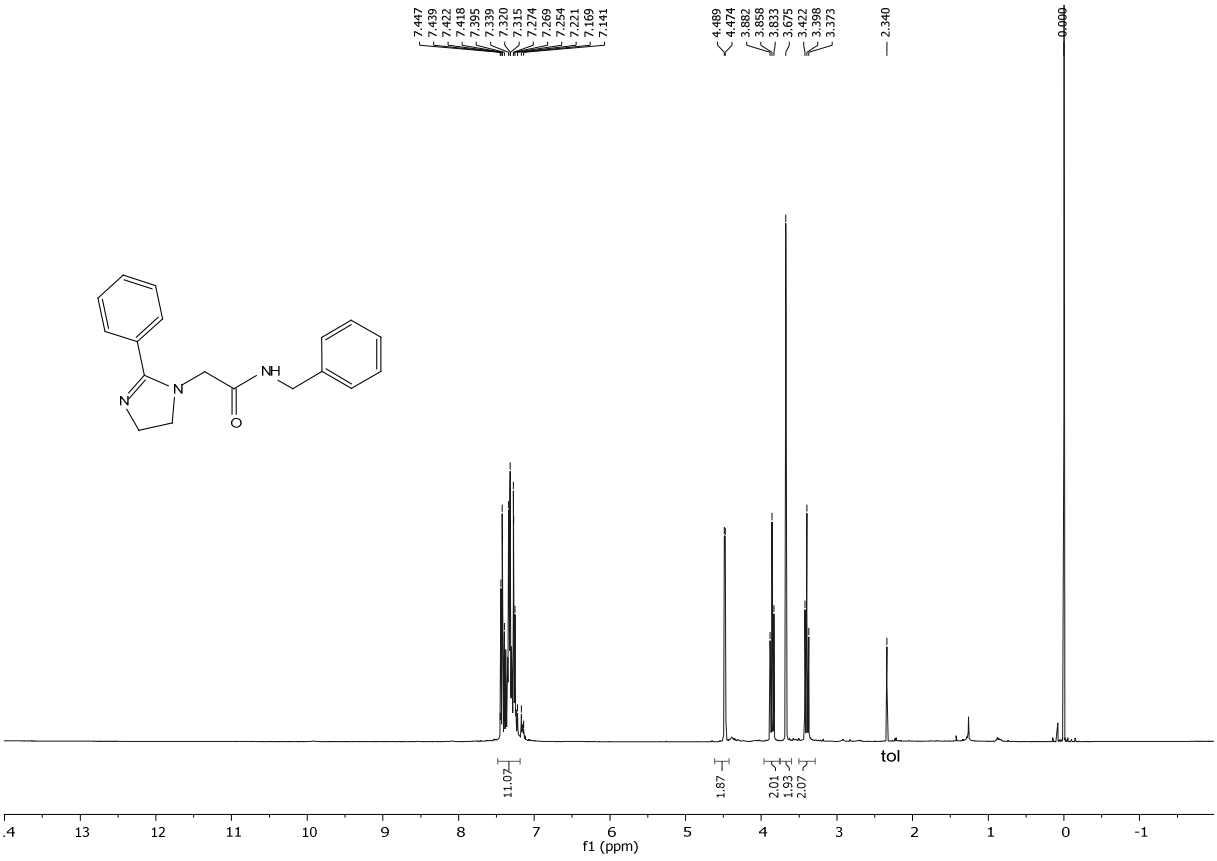

172.684
170.738
138.078
128.590
127.664
127.367
49.564
43.374
26.175
22.130
19.786
18.782
0.000
-0.000
f1 (ppm)

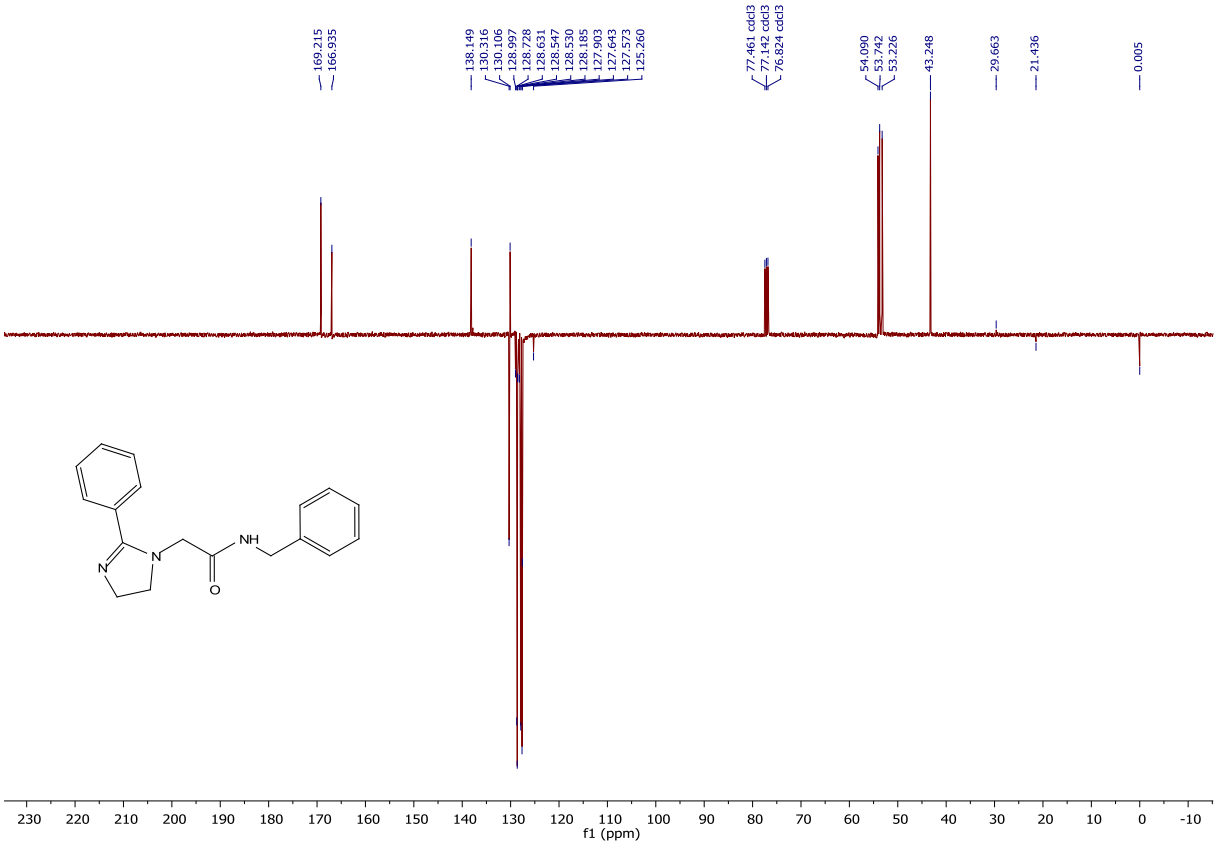

f1 (ppm)

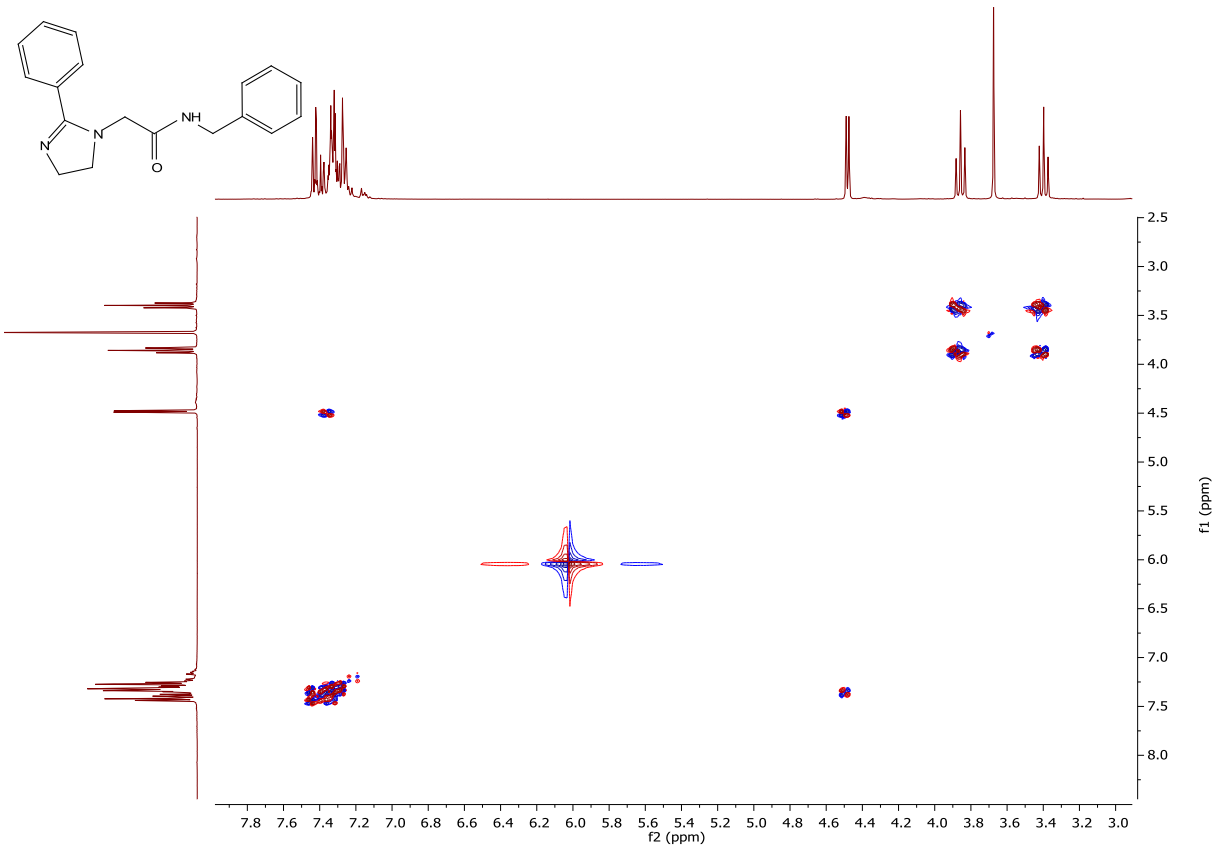

169.951
138.087
128.739
128.408
127.755
127.583
77.363 cdcl3
77.044 cdcl3
76.727 cdcl3
65.558
51.652
45.387
43.408
27.700
19.710
19.169
14.725
-0.003
f1 (ppm)

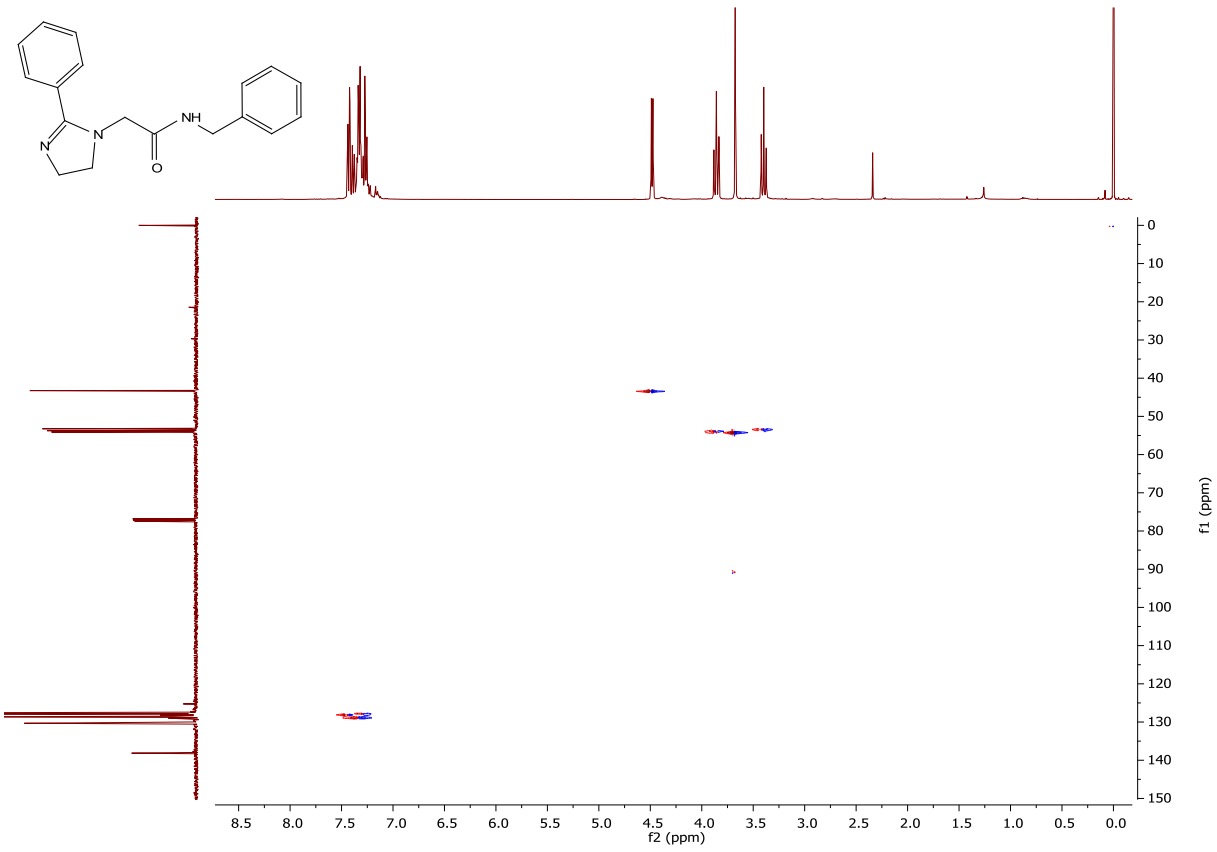

8.033
8.016
8.012
7.411
7.377
7.351
7.347
7.343
7.329
7.326
7.312
7.290
7.273
7.260
7.141
7.124
6.788
4.440
4.426
4.147
4.012
3.568
3.475
0.008
0.000
-0.008
0.05
9.63
0.61
0.39
2.03
2.10
4.19
f1 (ppm)

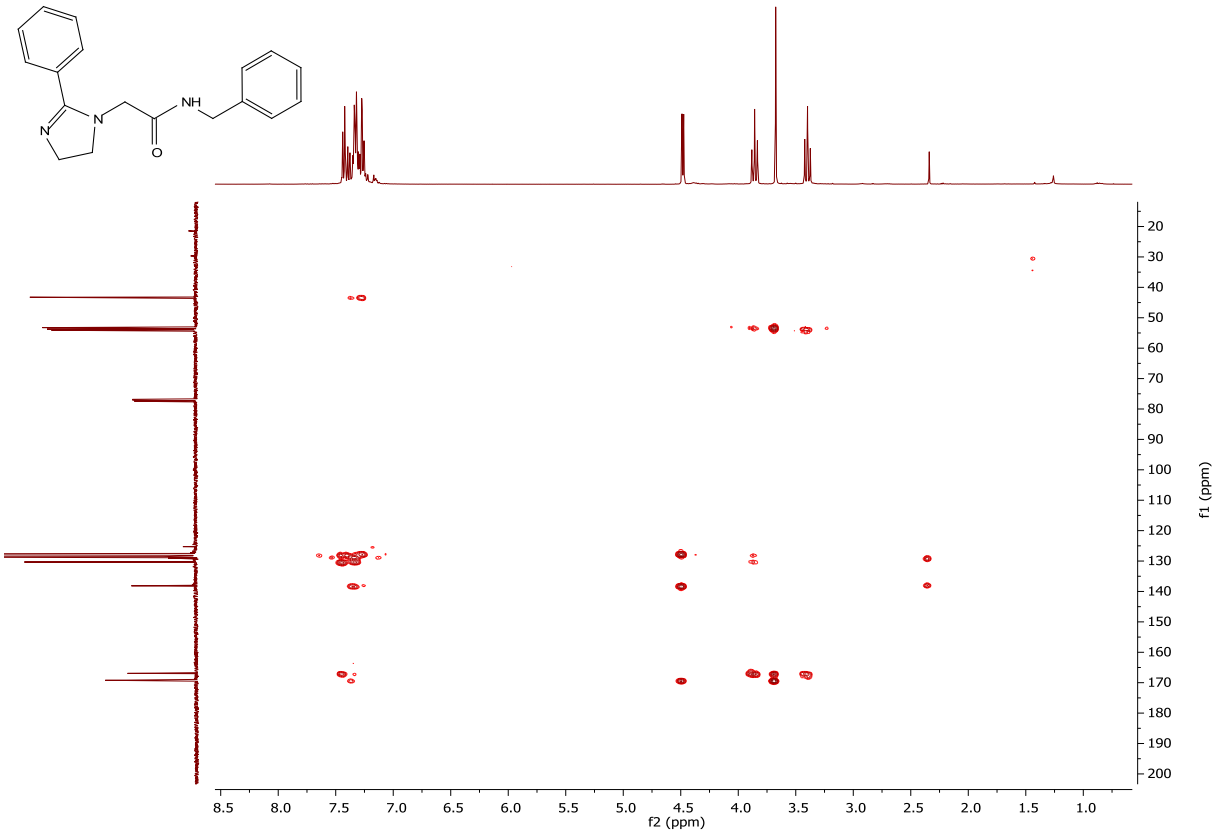

173.076
168.682
137.892
135.042
130.124
128.723
128.662
127.680
127.565
126.774
54.409
50.731
49.940
49.185
47.272
43.594
f1 (ppm)

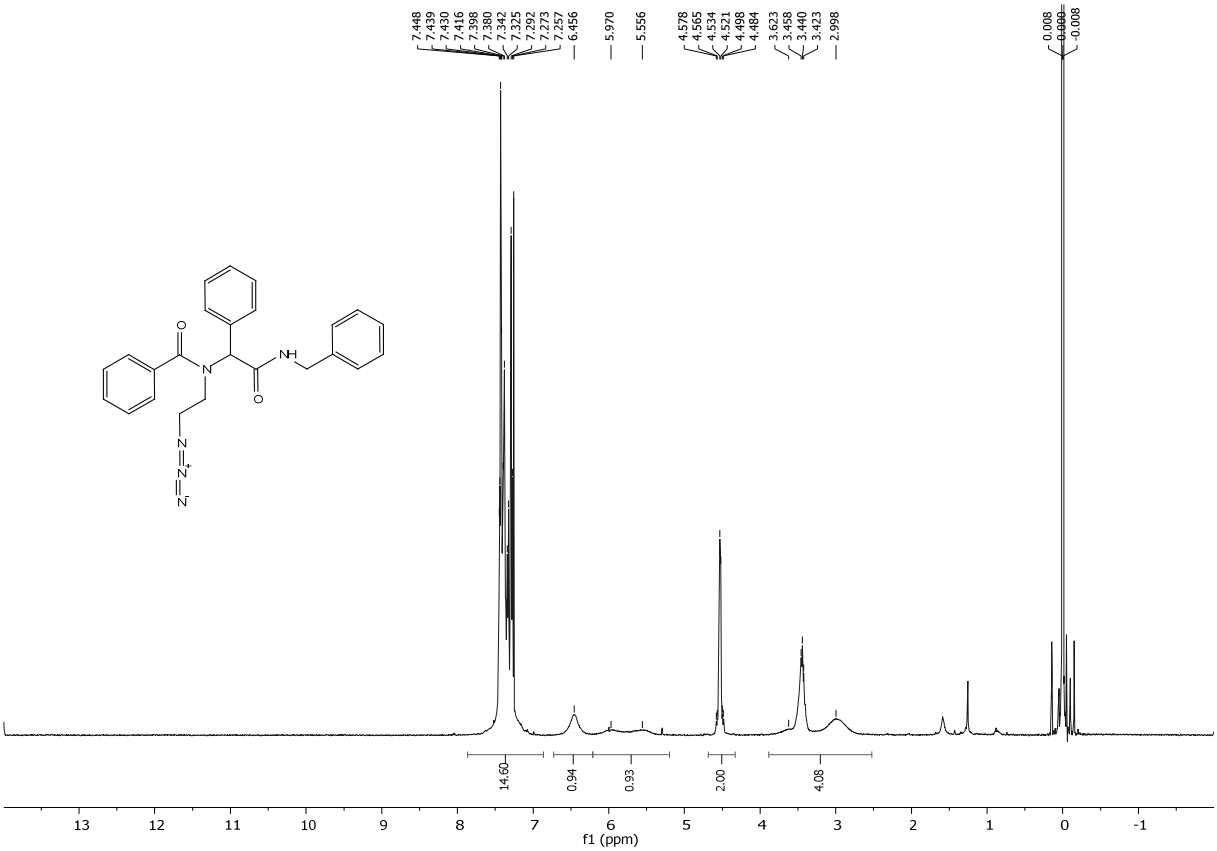

7.447
7.439
7.422
7.418
7.395
7.339
7.320
7.315
7.274
7.269
7.254
7.221
7.169
7.141
4.489
4.474
3.882
3.858
3.833
3.675
3.422
3.398
3.373
2.340
0.000
tol
11.07
1.87
2.01
1.93
2.07
f1 (ppm)


169.215
166.935
138.149
130.316
130.106
128.997
128.728
128.631
128.547
128.530
128.185
127.903
127.643
127.573
125.260
77.461 cdcl3
77.142 cdcl3
76.824 cdcl3
54.090
53.742
53.226
43.248
29.663
21.436
0.005
f1 (ppm)

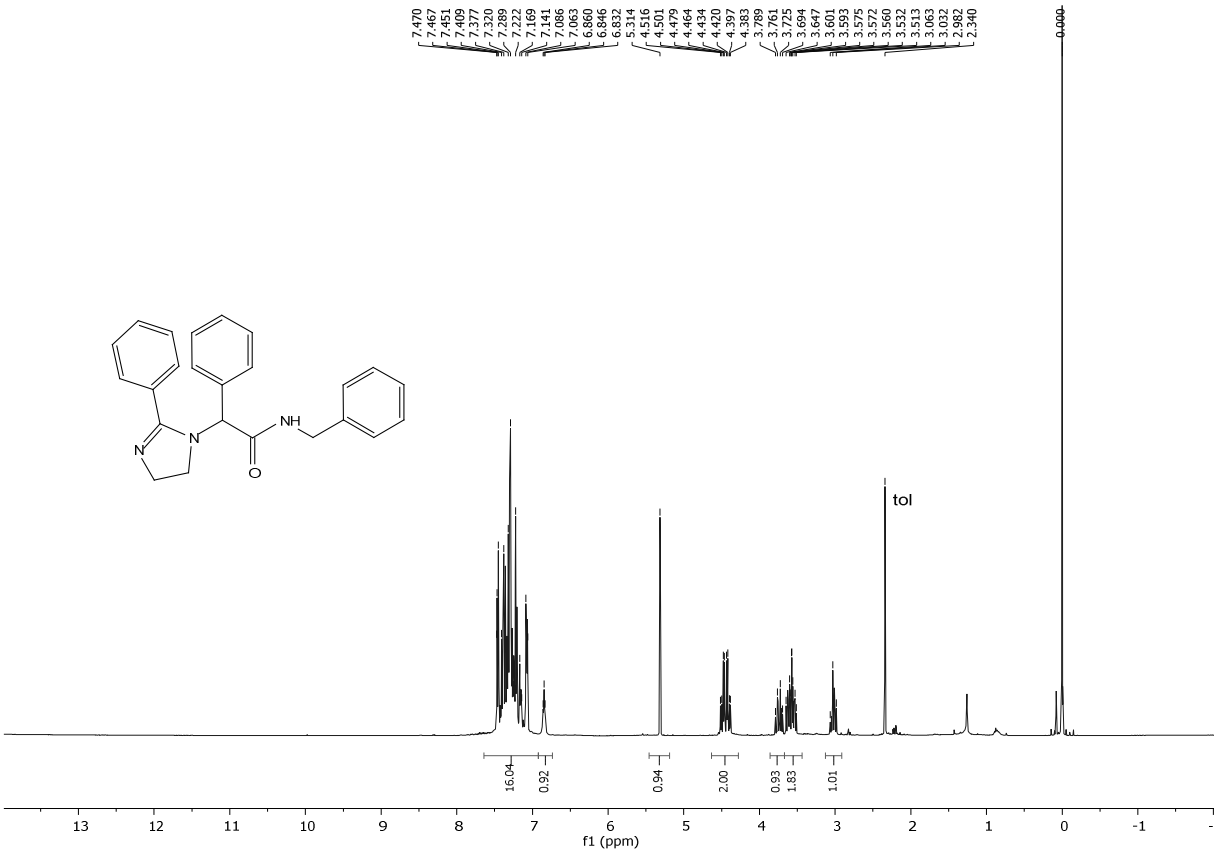

f2 (ppm)
f1 (ppm)


NH
N
N
O
f2 (ppm)
f1 (ppm)


NH
N
N
O
f2 (ppm)
f1 (ppm)


7.448
7.439
7.430
7.416
7.398
7.380
7.342
7.325
7.292
7.273
7.257
6.456
5.970
5.556
4.578
4.565
4.534
4.521
4.498
4.484
3.623
3.458
3.440
3.423
2.998
0.008
0.000
-0.008
14.60
0.94
0.93
2.00
4.08
f1 (ppm)


173.155
137.753
135.806
134.699
130.043
129.181
129.034
128.788
128.735
127.799
127.613
126.638
43.812
f1 (ppm)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7.467
7.451
7.409
7.377
7.320
7.289
7.222
7.169
7.141
7.086
7.063
6.860
6.846
6.832
5.314
4.516
4.501
4.479
4.464
4.434
4.420
4.397
4.383
3.789
3.761
3.725
3.694
3.647
3.601
3.593
3.575
3.572
3.560
3.532
3.513
3.063
3.032
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tol
16.04
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0.94
2.00
0.93
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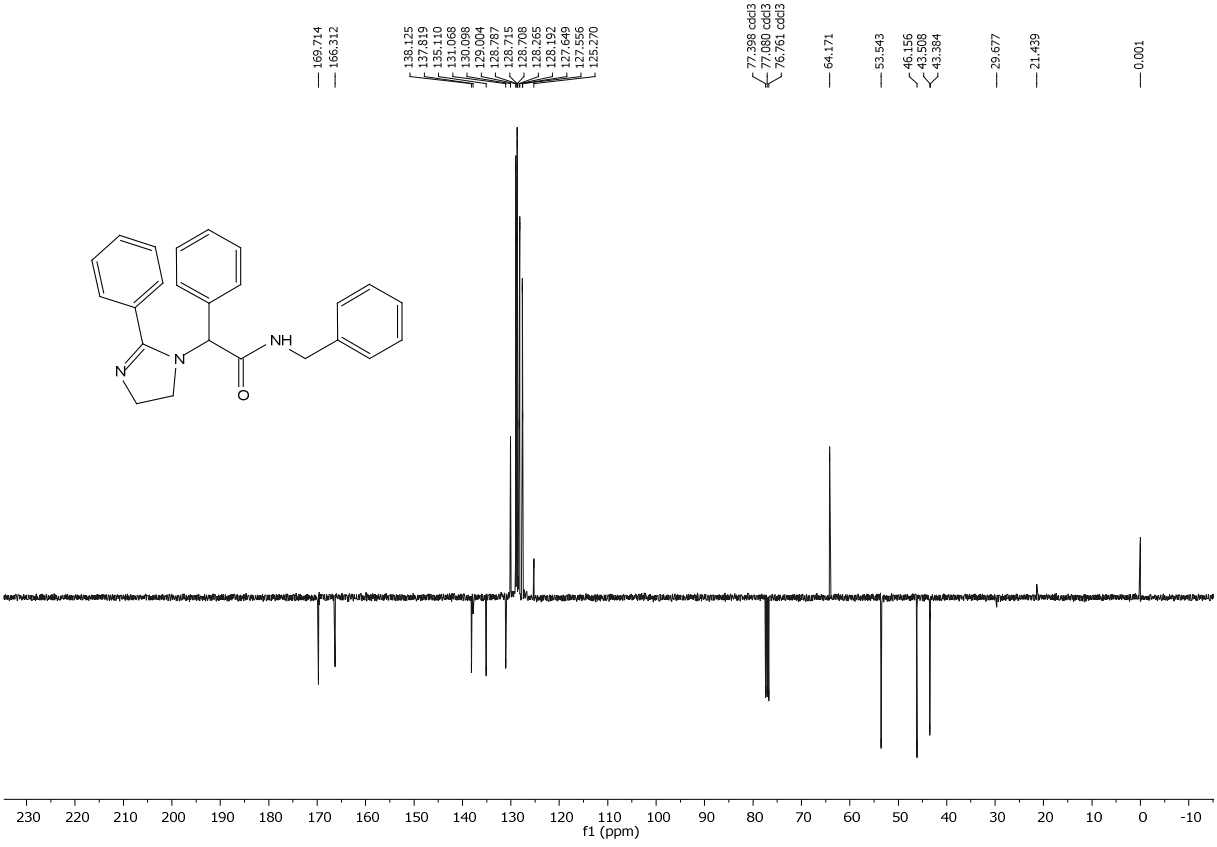
1.01
f1 (ppm)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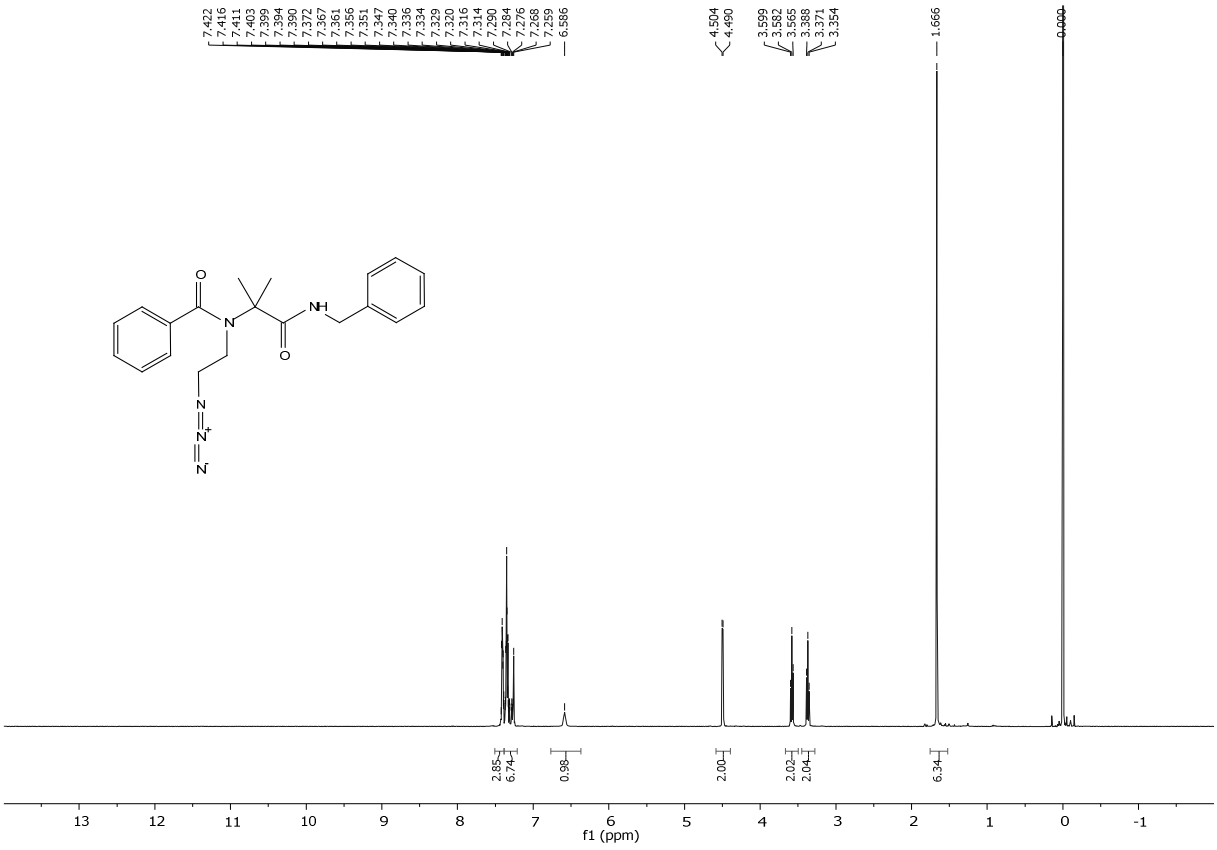
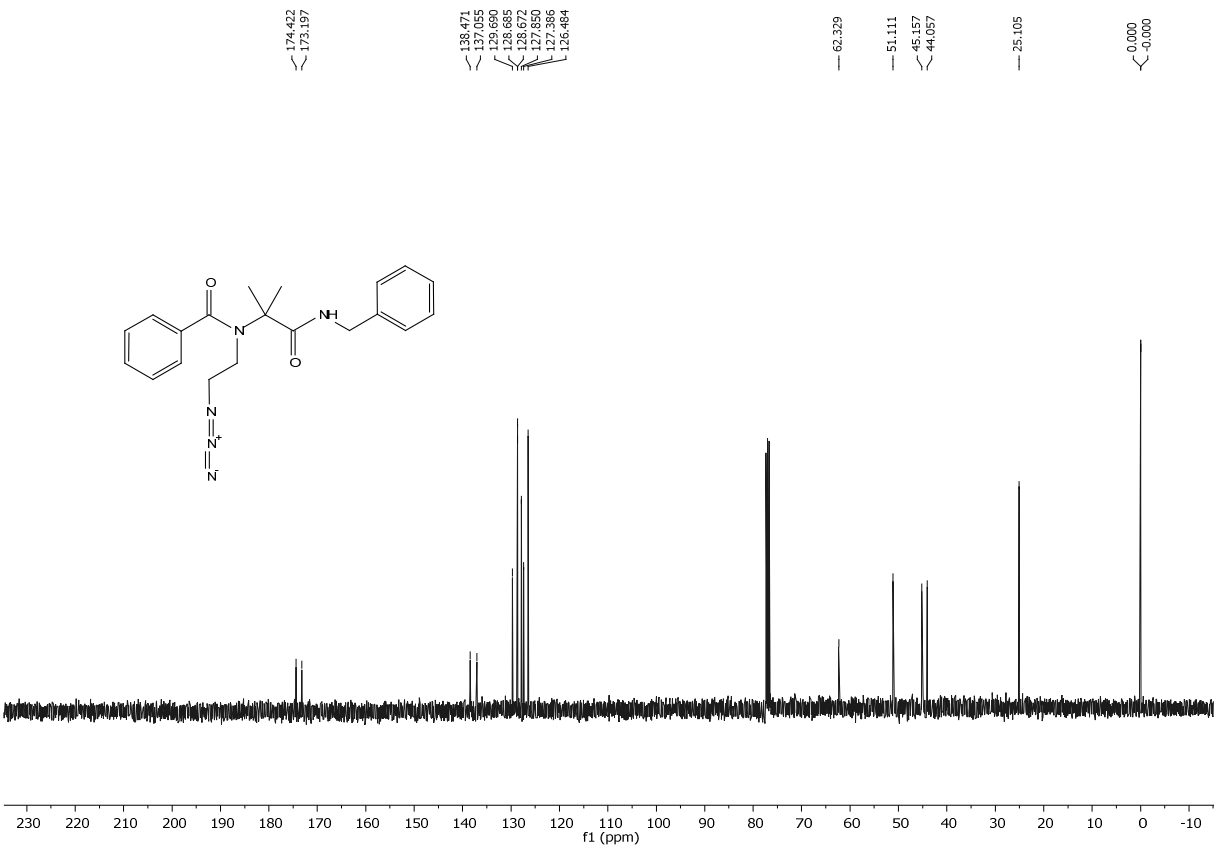
137.819
135.110
131.068
130.098
129.004
128.787
128.715
128.708
128.265
128.192
127.649
127.556
125.270
77.398 cdcl3
77.080 cdcl3
76.761 cdcl3
64.171
53.543
46.156
43.508
43.384
29.677
21.439
0.001
f1 (ppm)


7.422
7.416
7.411
7.403
7.399
7.394
7.390
7.372
7.367
7.361
7.356
7.351
7.347
7.340
7.336
7.334
7.329
7.320
7.316
7.314
7.290
7.284
7.276
7.268
7.259
6.586
4.504
4.490
3.599
3.582
3.565
3.388
3.371
3.354
1.666
0.000
2.85
6.74
0.98
2.00
2.02
2.04
6.34
f1 (ppm)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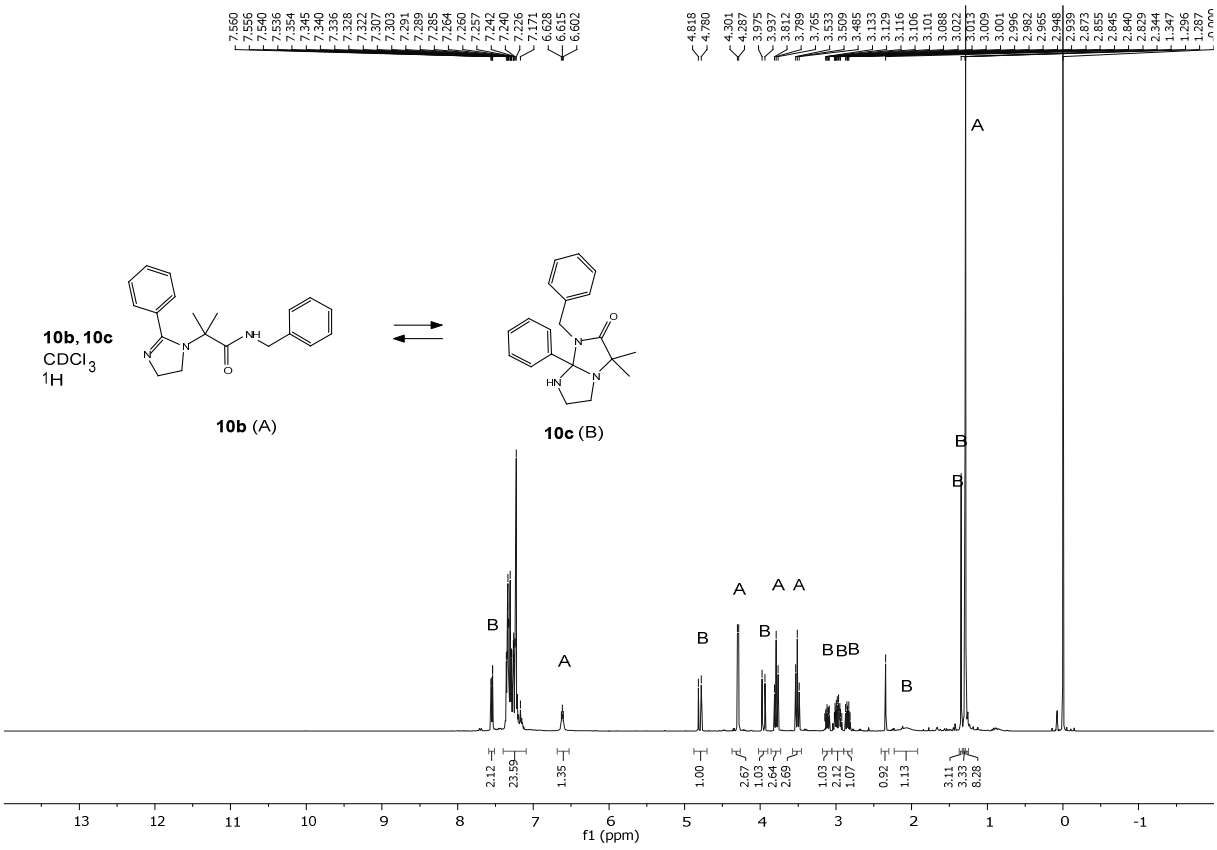
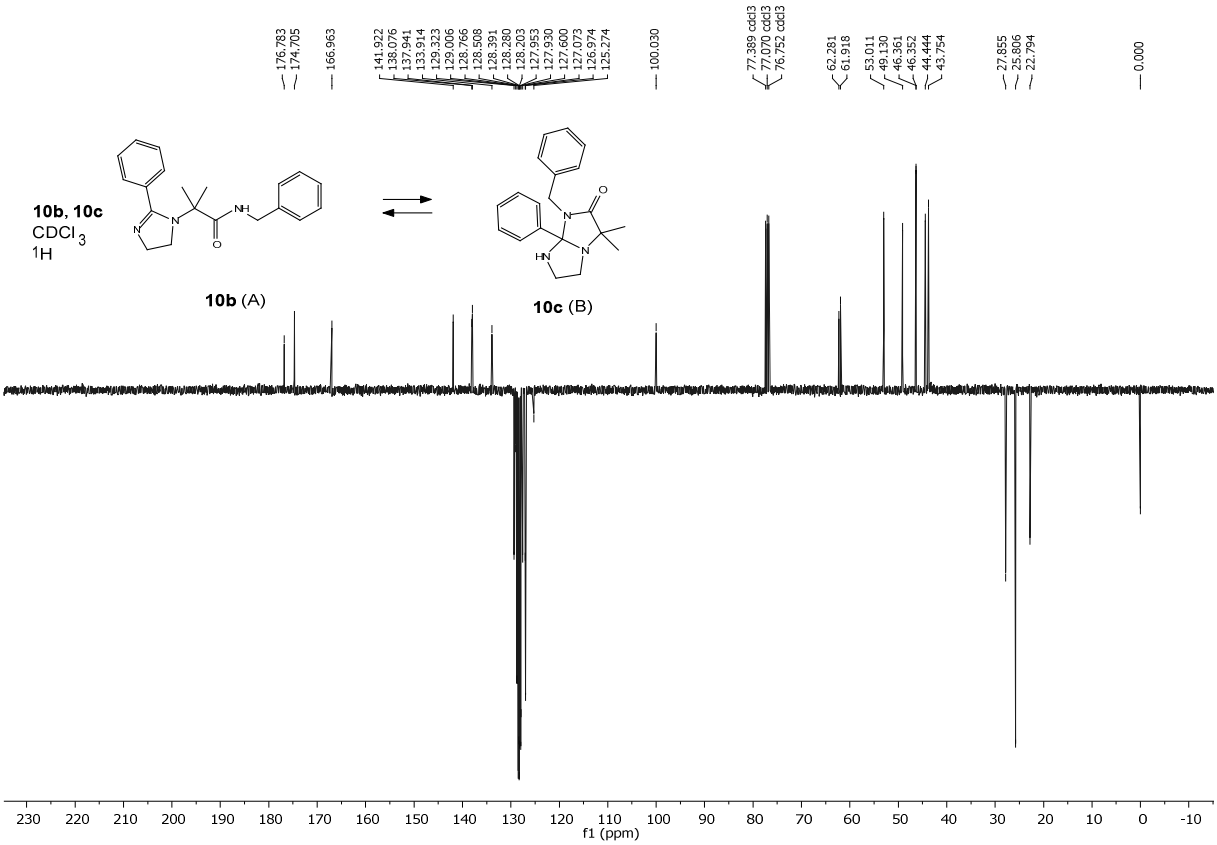
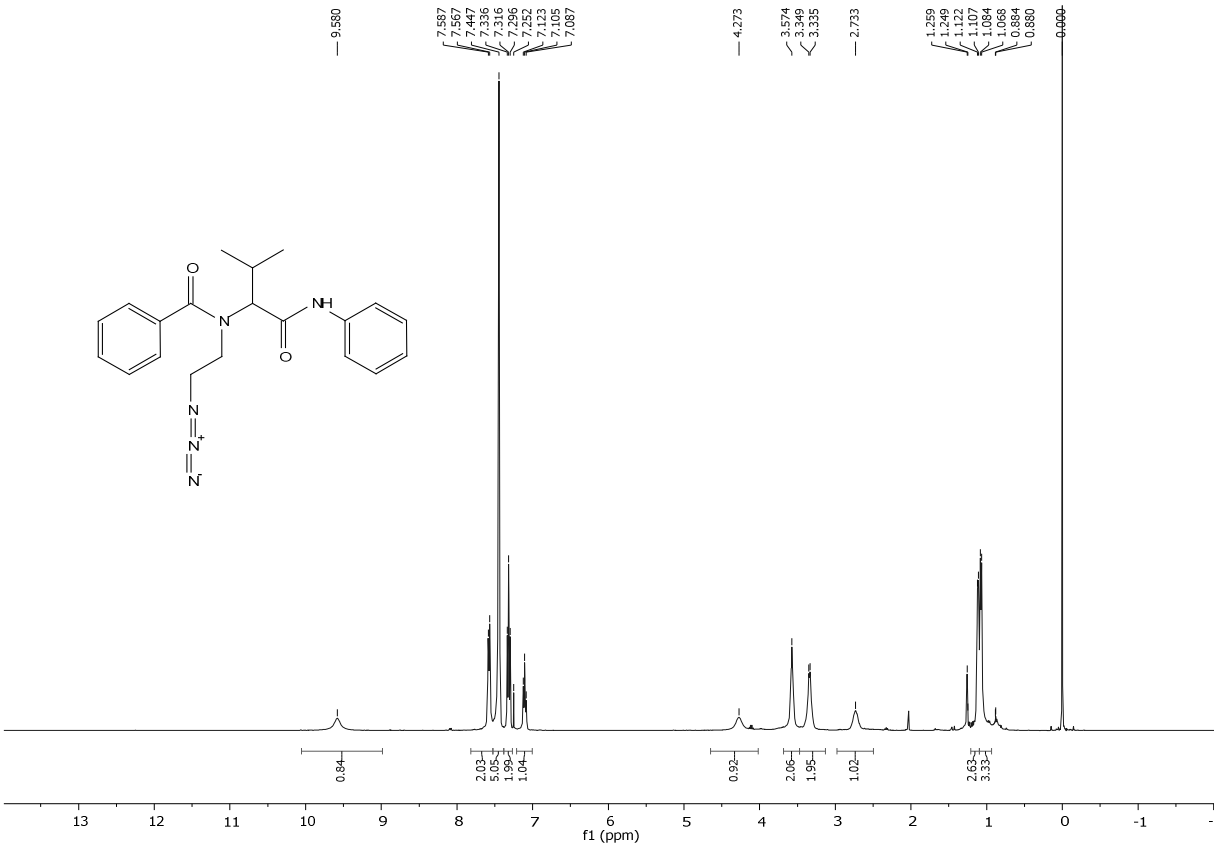
173.197
138.471
137.055
129.690
128.685
128.672
127.850
127.386
126.484
62.329
51.111
45.157
44.057
25.105
0.000
-0.000
f1 (ppm)


10b, 10c
CDCl3
1H
10b (A)
10c (B)
f1 (ppm)


10b, 10c
CDCl3
1H
10b (A)
10c (B)
f1 (ppm)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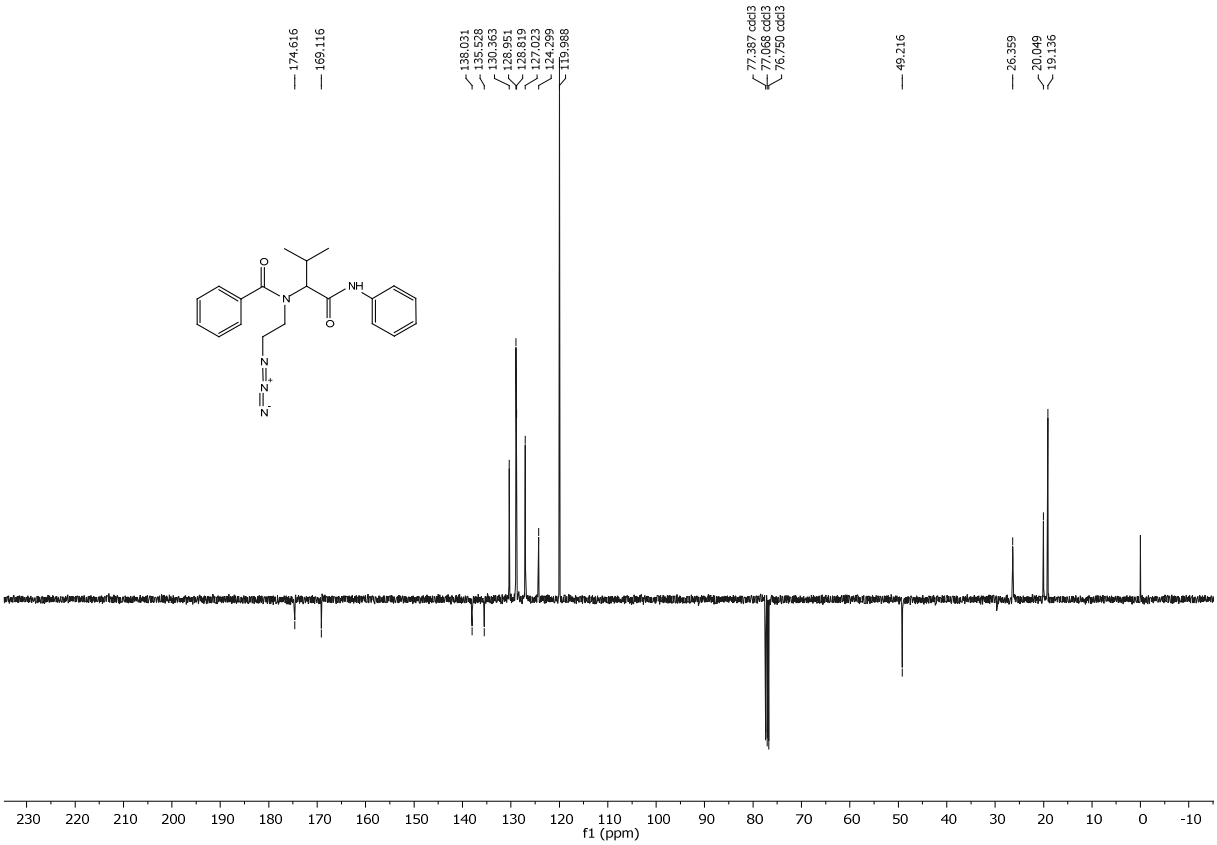
7.587
7.567
7.447
7.336
7.316
7.296
7.252
7.123
7.105
7.087
4.273
3.574
3.349
3.335
2.733
1.259
1.249
1.122
1.107
1.084
1.068
0.884
0.880
0.000
0.84
2.03
5.05
1.99
1.04
0.92
2.06
1.95
1.02
2.63
3.33
f1 (ppm)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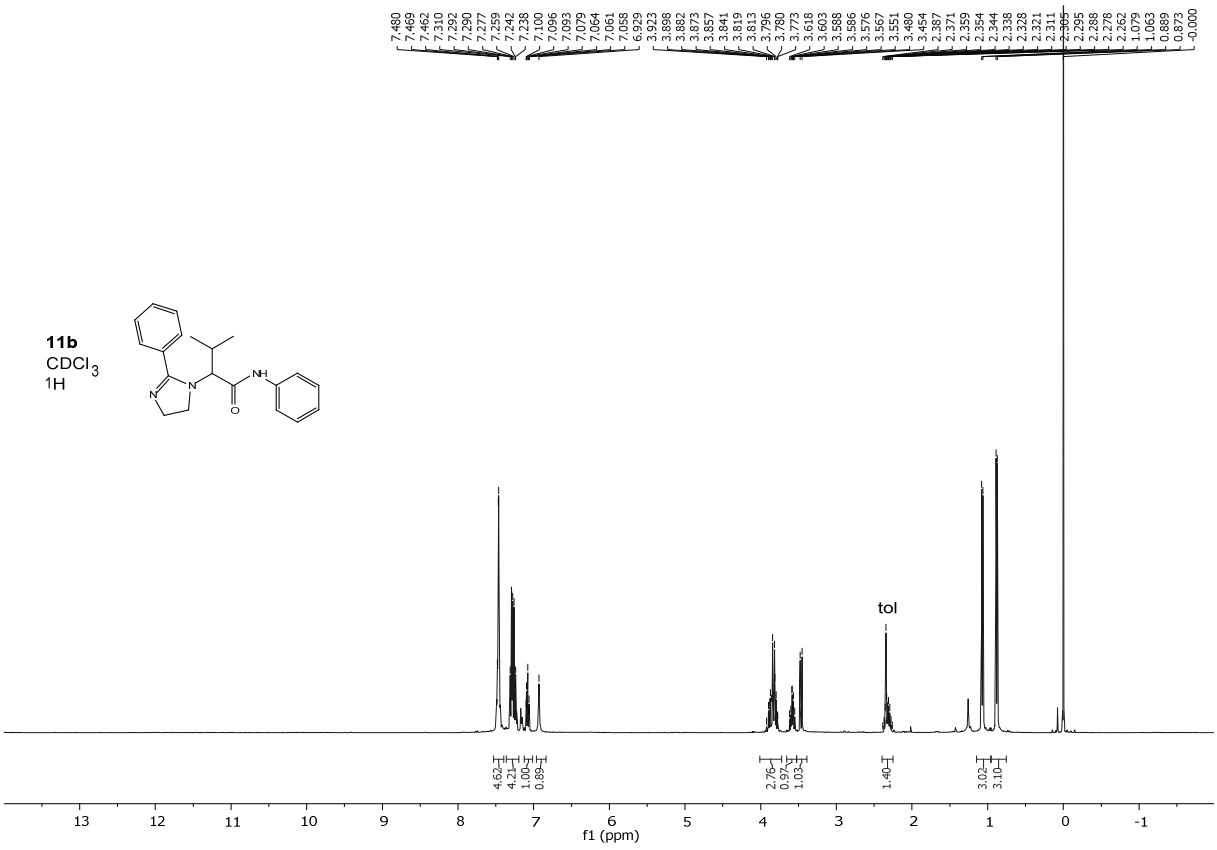
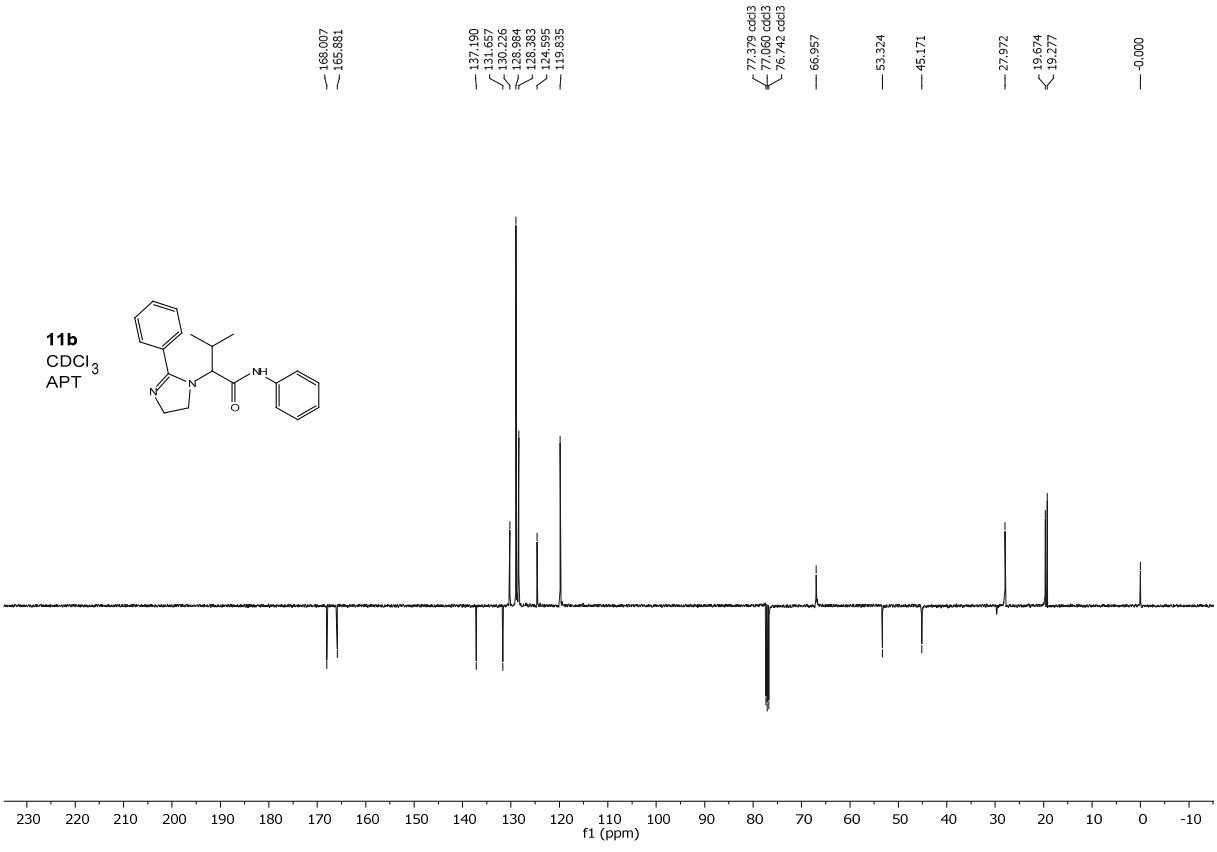
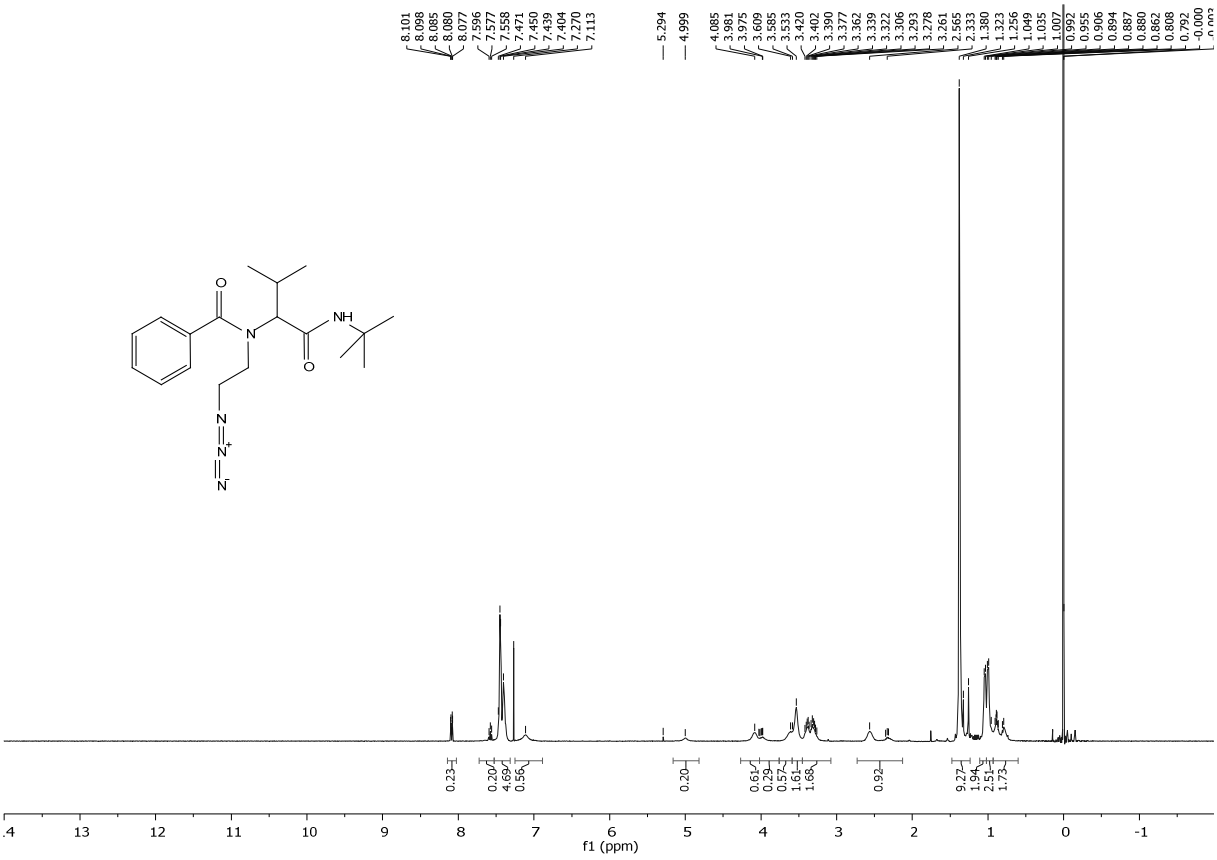
169.116
138.031
135.528
130.363
128.951
128.819
127.023
124.299
119.988
77.387 cdcl3
77.068 cdcl3
76.750 cdcl3
49.216
26.359
20.049
19.136
f1 (ppm)


11b
CDCl3
1H
tol
f1 (ppm)


11b
CDCl3
APT
f1 (ppm)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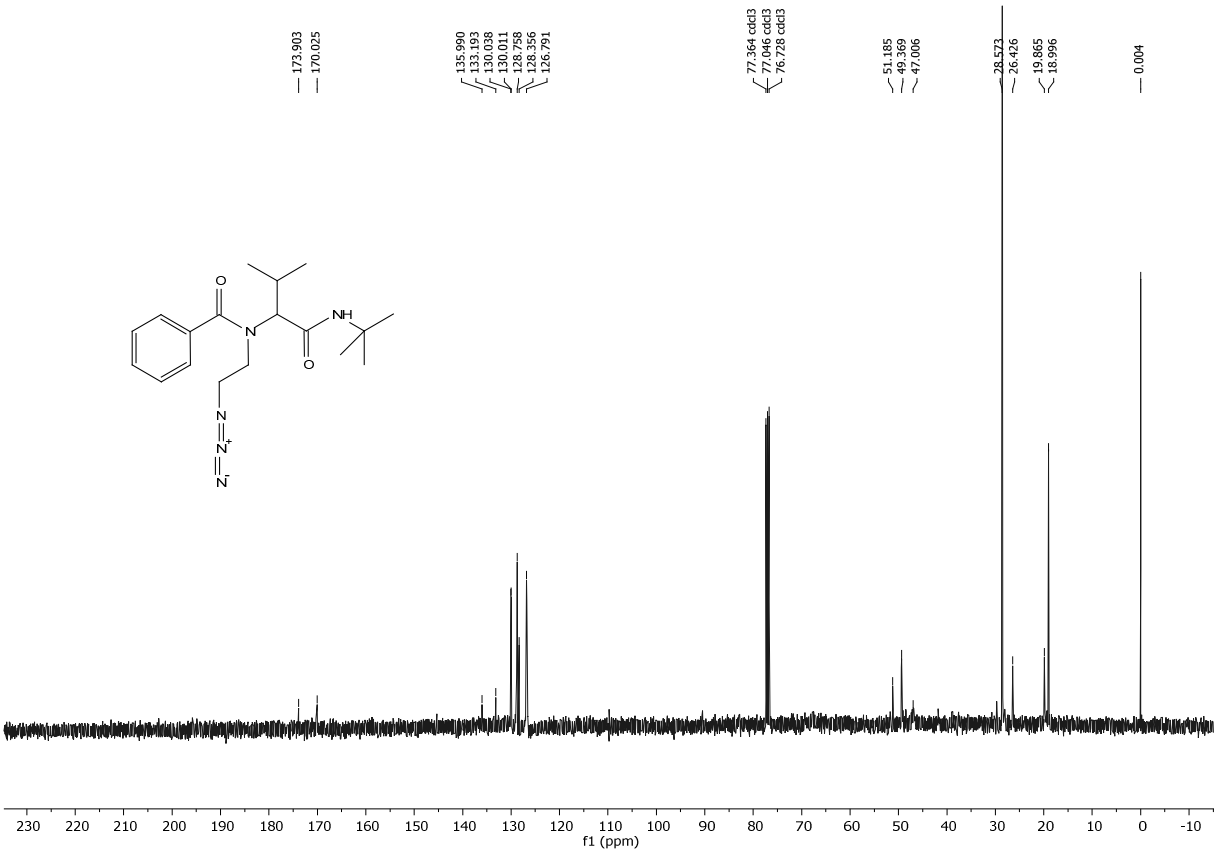
8.098
8.085
8.080
8.077
7.596
7.577
7.558
7.471
7.450
7.439
7.404
7.270
7.113
5.294
4.999
4.085
3.981
3.975
3.609
3.585
3.533
3.420
3.402
3.390
3.377
3.362
3.339
3.322
3.306
3.293
3.278
3.261
2.565
2.333
1.380
1.323
1.256
1.049
1.035
1.007
0.992
0.955
0.906
0.894
0.887
0.880
0.862
0.808
0.792
-0.000
0.23
0.20
4.69
0.56
0.20
0.62
0.29
0.57
1.61
1.68
0.92
9.27
1.94
2.51
1.73
f1 (ppm)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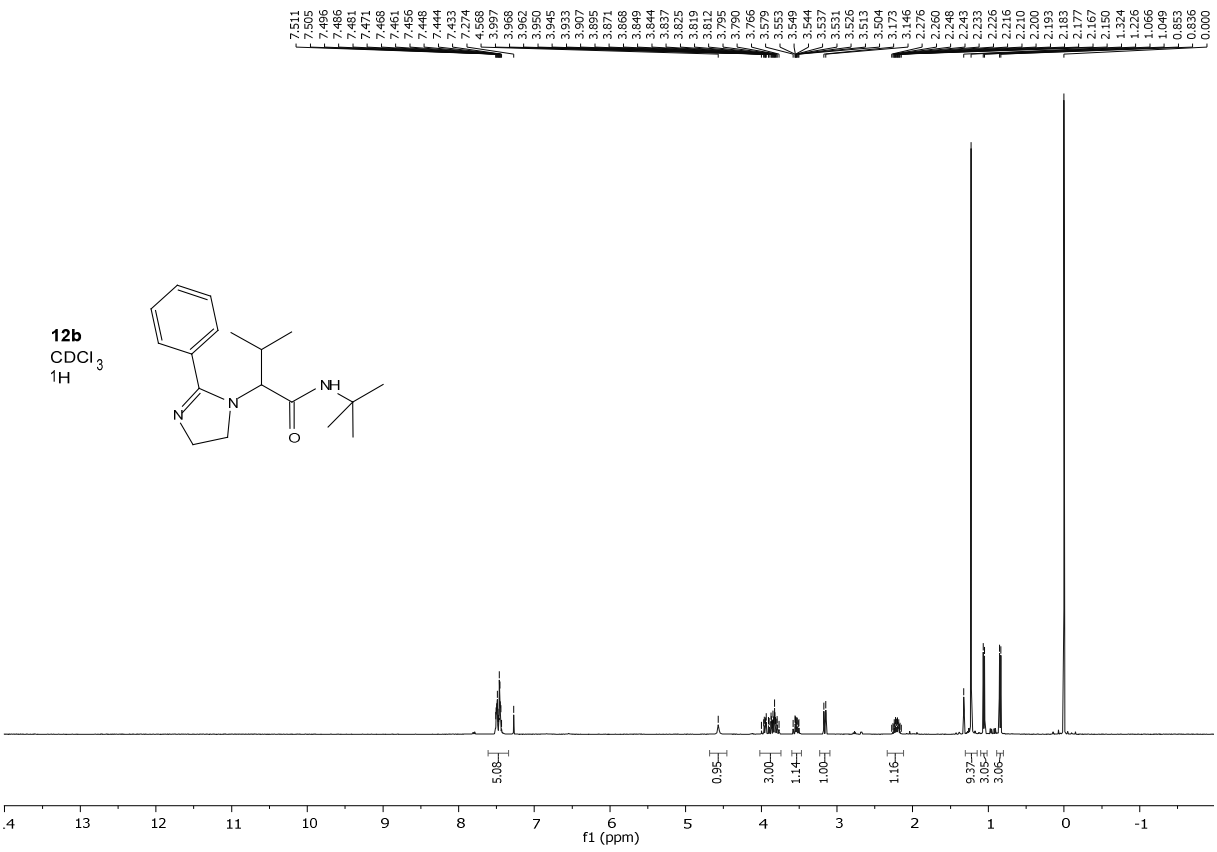
170.025
135.990
133.193
130.038
130.011
128.758
128.356
126.791
77.364 cdcl3
77.046 cdcl3
76.728 cdcl3
51.185
49.369
47.006
28.573
26.426
19.865
18.996
0.004
f1 (ppm)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7.461
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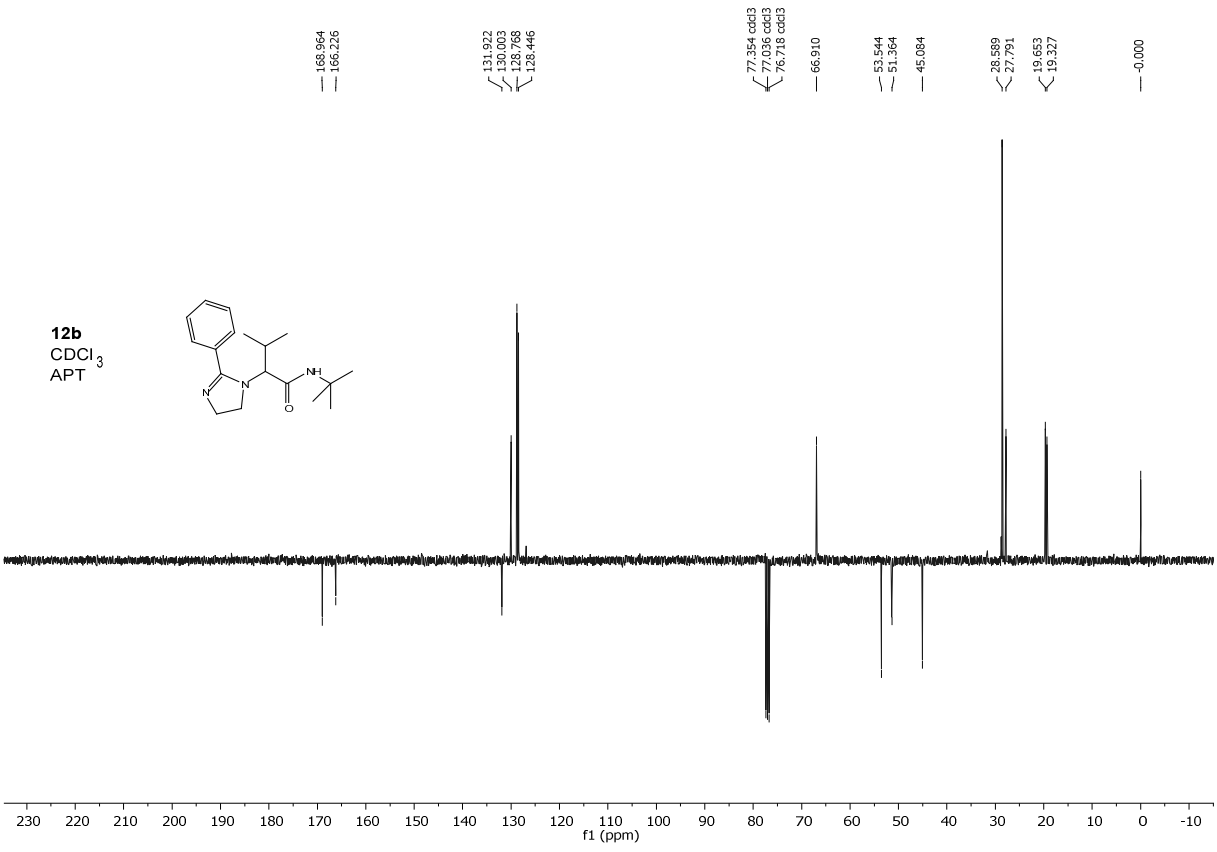
7.448
7.444
7.433
7.274
4.568
3.997
3.968
3.962
3.950
3.945
3.933
3.907
3.895
3.871
3.868
3.849
3.844
3.837
3.825
3.819
3.812
3.795
3.790
3.766
3.579
3.553
3.549
3.544
3.537
3.531
3.526
3.513
3.504
3.173
3.146
2.276
2.260
2.248
2.243
2.233
2.226
2.216
2.210
2.200
2.193
2.183
2.177
2.167
2.150
1.324
1.226
1.066
1.049
0.853
0.836
0.000
12b
CDCl3
1H
NH
N
N
O
5.08
0.95
3.00
1.14
1.00
1.16
9.37
3.05
3.06
f1 (ppm)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130.003
128.768
128.446
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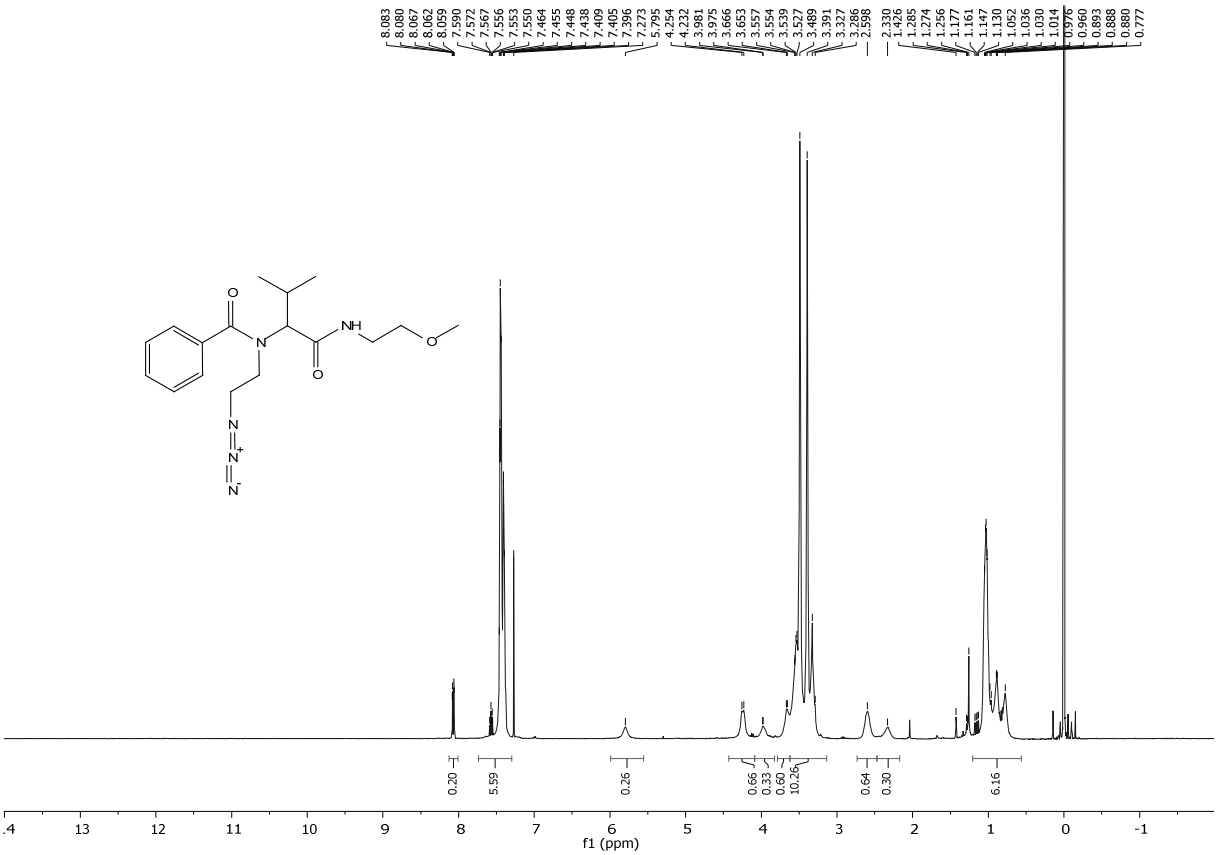
77.036 cdcl3
76.718 cdcl3
66.910
53.544
51.364
45.084
28.589
27.791
19.653
19.327
-0.000
12b
CDCl3
APT
NH
N
N
O
f1 (ppm)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8.062
8.059
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7.572
7.567
7.556
7.553
7.550
7.464
7.455
7.448
7.438
7.409
7.405
7.396
7.273
5.795
4.254
4.232
3.981
3.975
3.666
3.653
3.557
3.554
3.539
3.527
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3.391
3.327
3.286
2.598
2.330
1.426
1.285
1.274
1.256
1.177
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1.147
1.130
1.052
1.036
1.030
1.014
0.976
0.960
0.893
0.888
0.880
0.777
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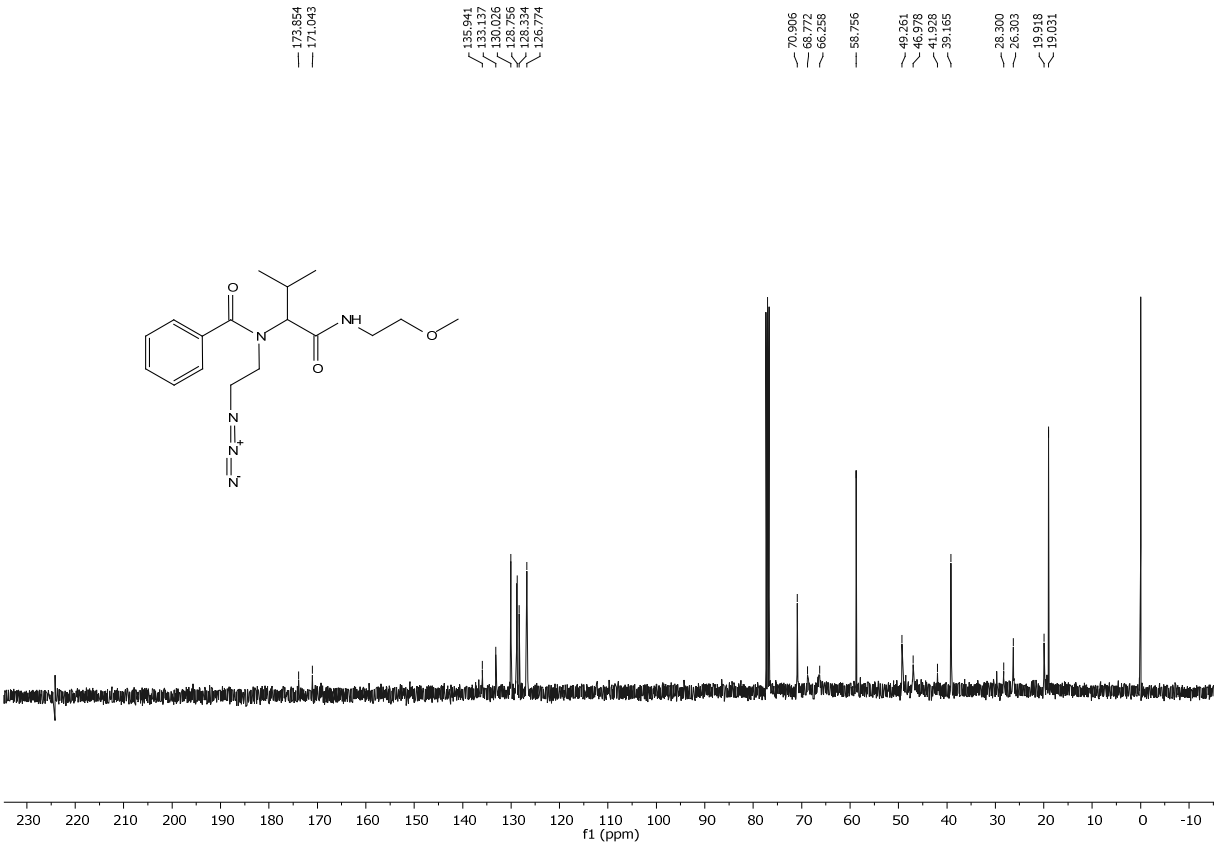
0.33
0.60
10.25
0.64
0.30
6.16
f1 (ppm)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171.043
135.941
133.137
130.026
128.756
128.334
126.774
70.906
68.772
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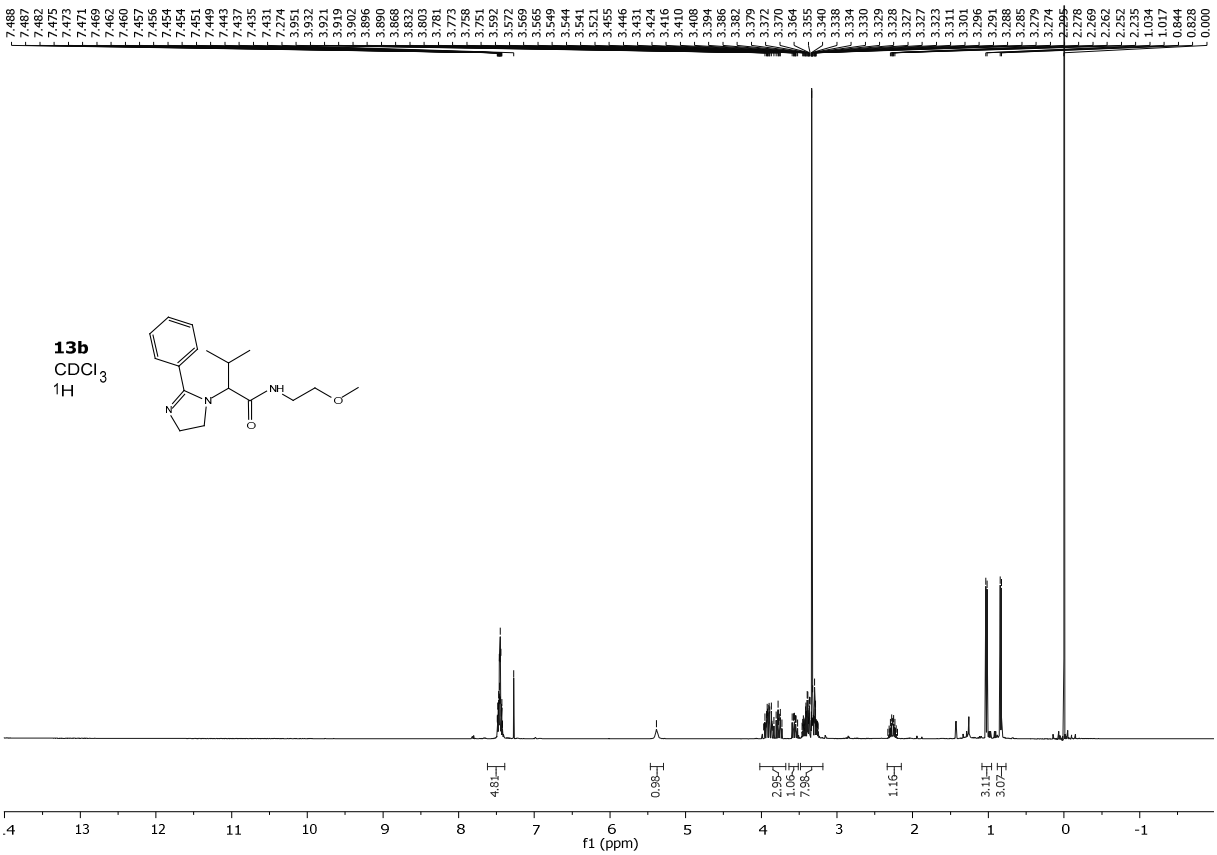
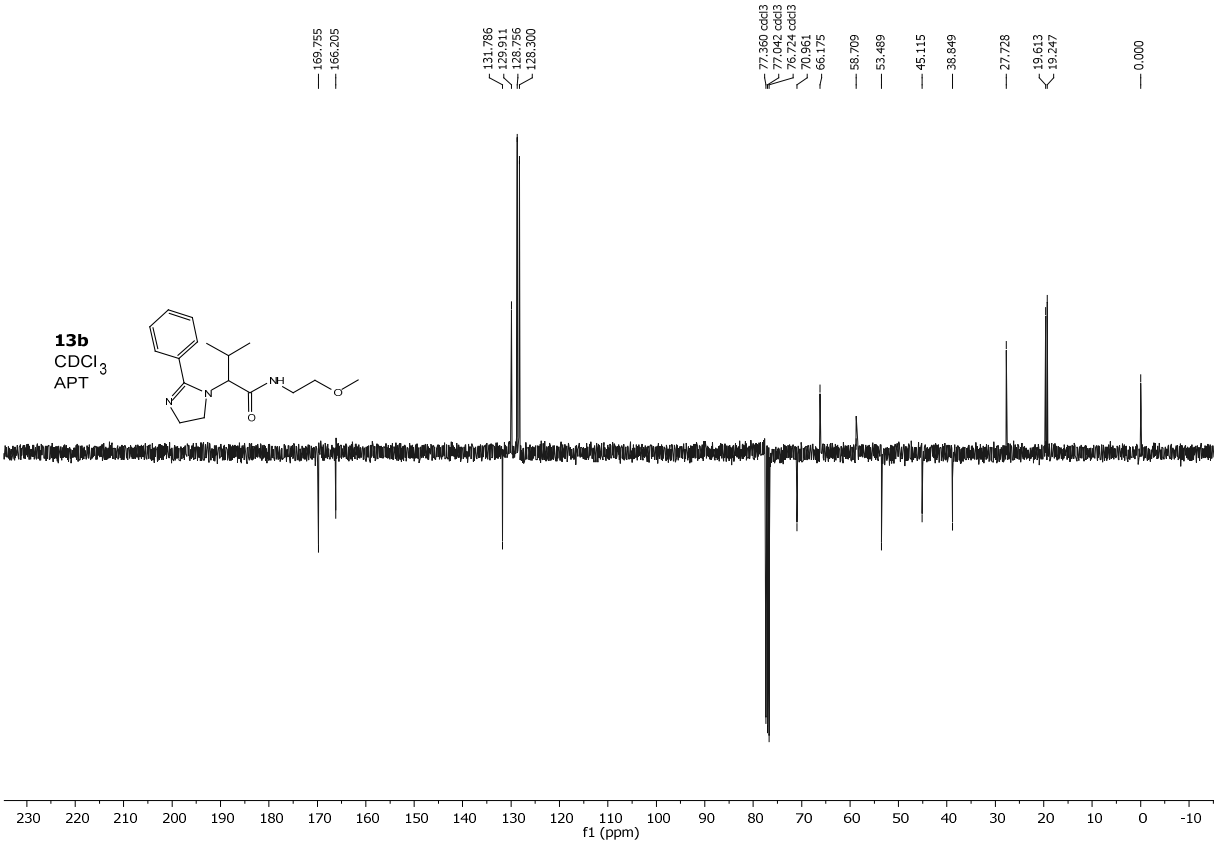
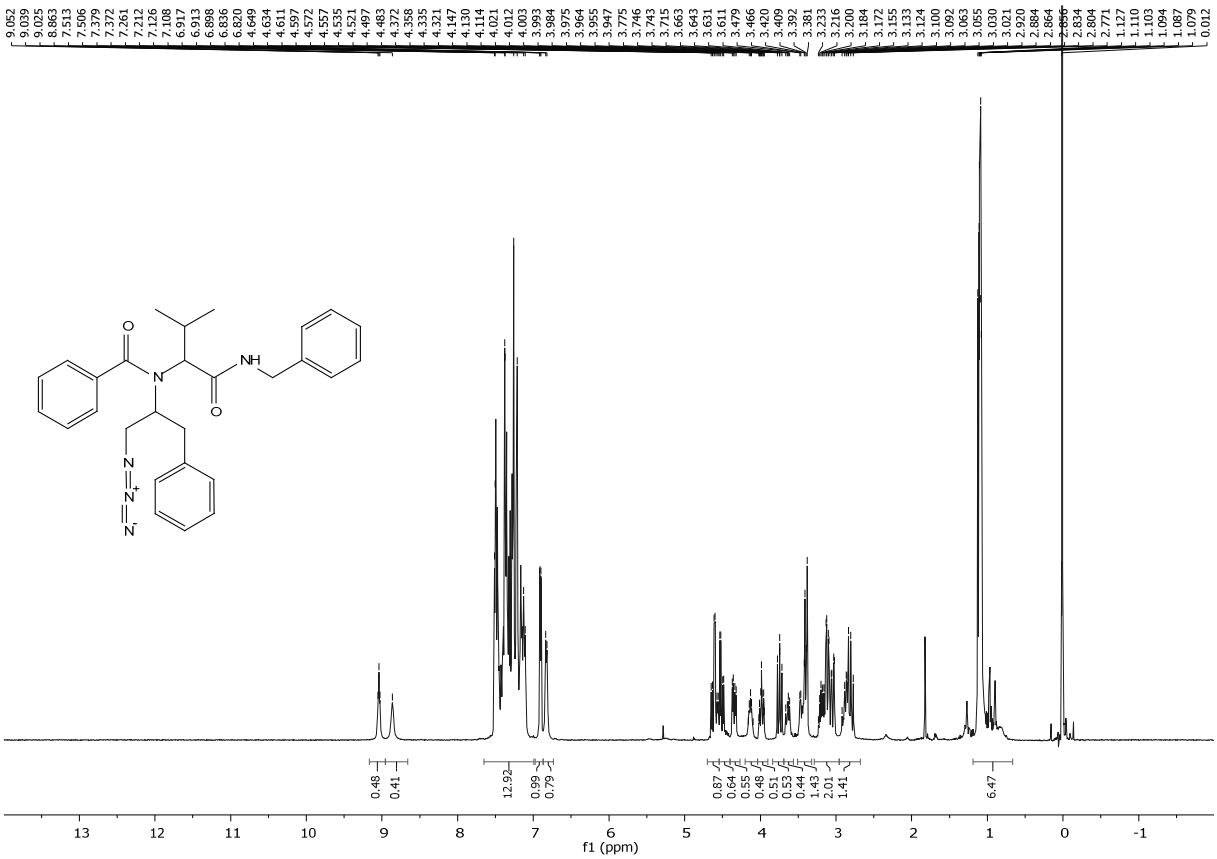
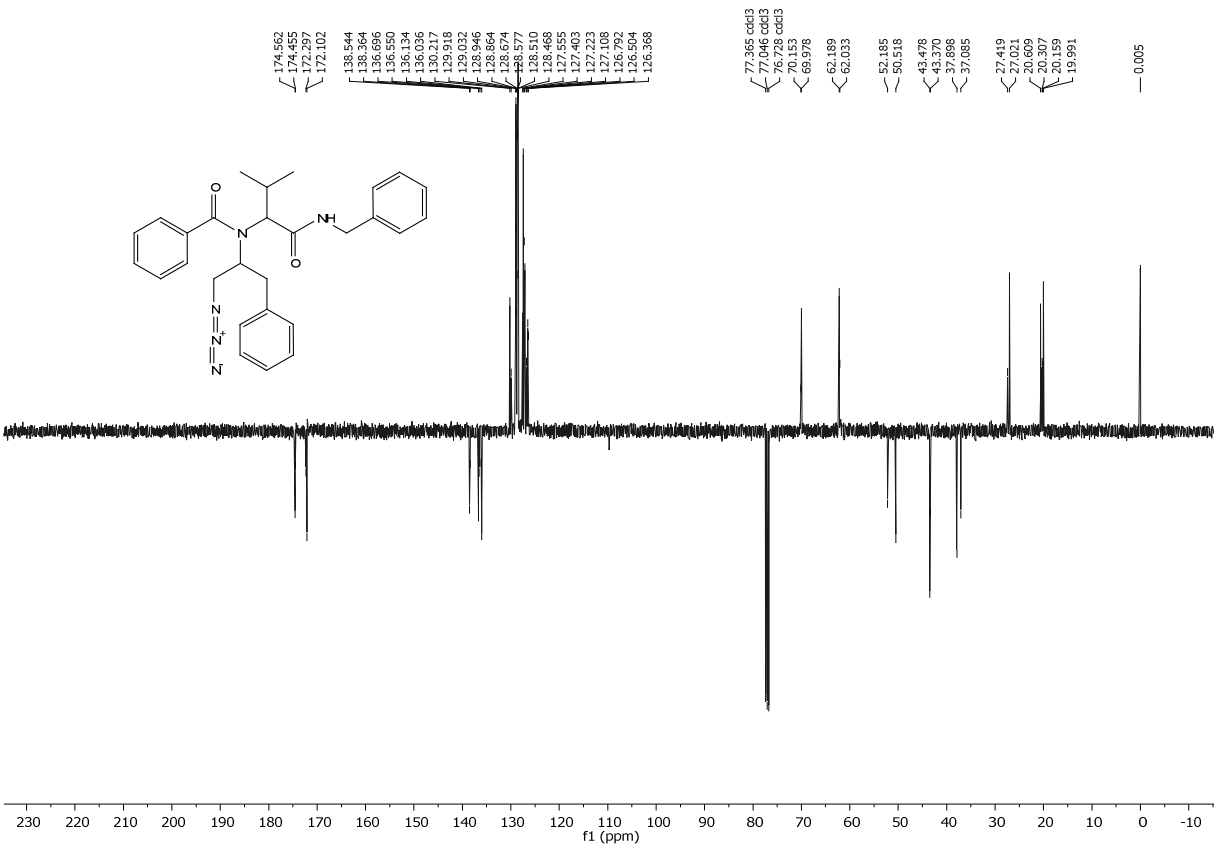
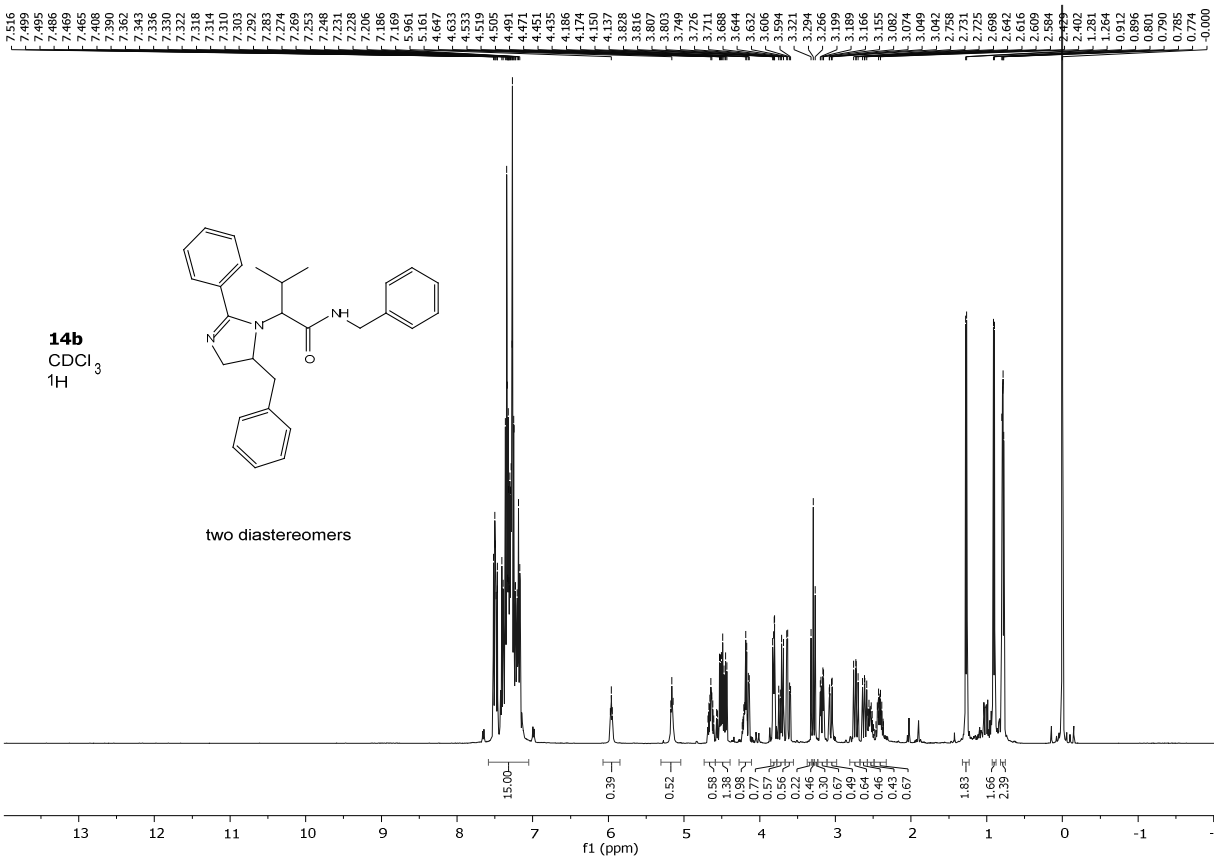
49.261
46.978
41.928
39.165
28.300
26.303
19.918
19.031
f1 (ppm)

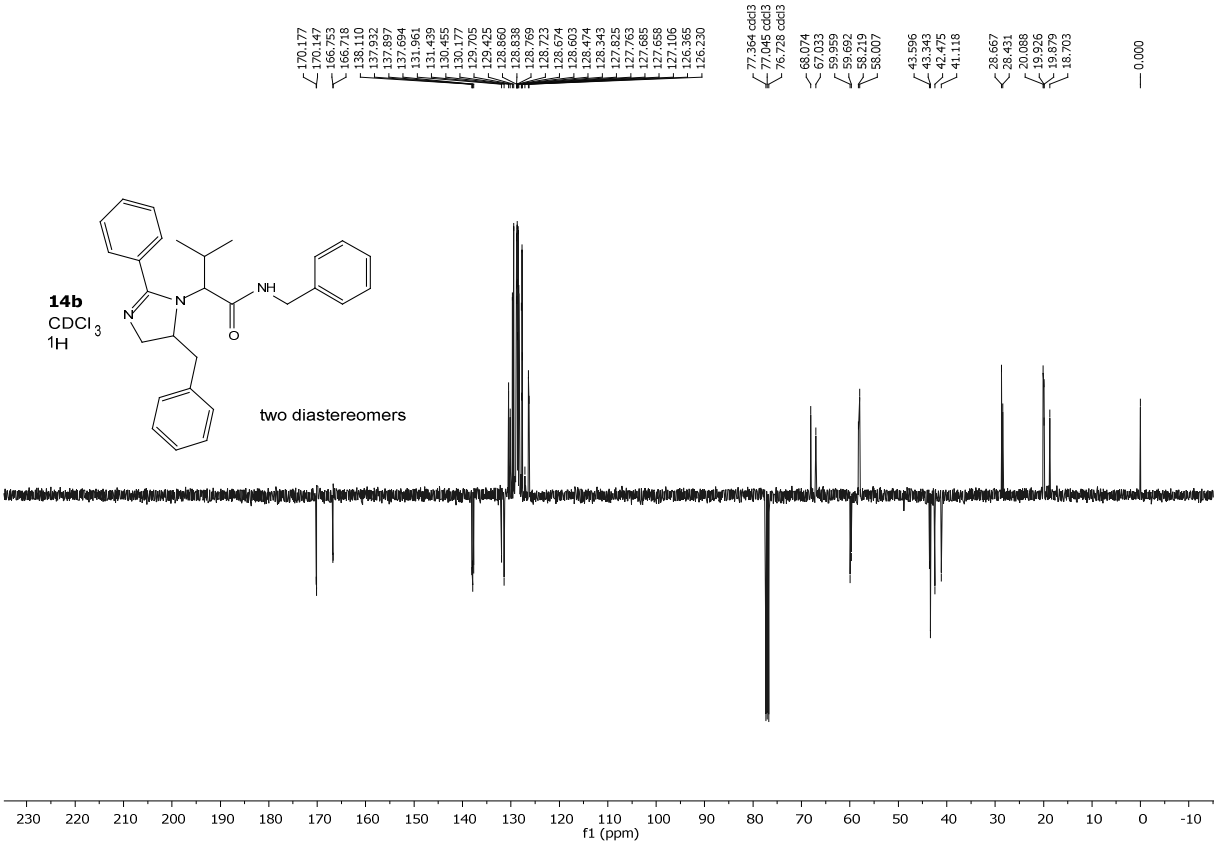

13b
CDCl3
1H
f1 (ppm)

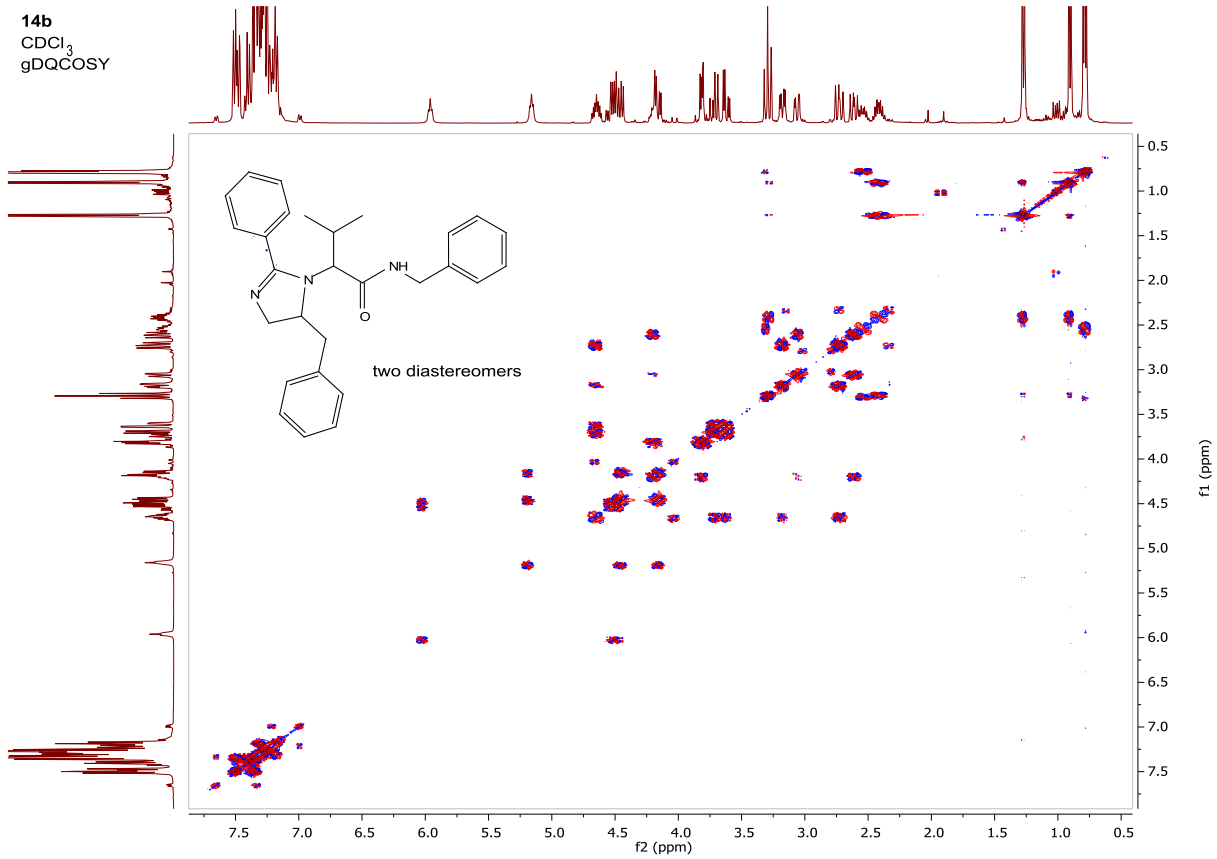

13b
CDCl3
APT
f1 (ppm)

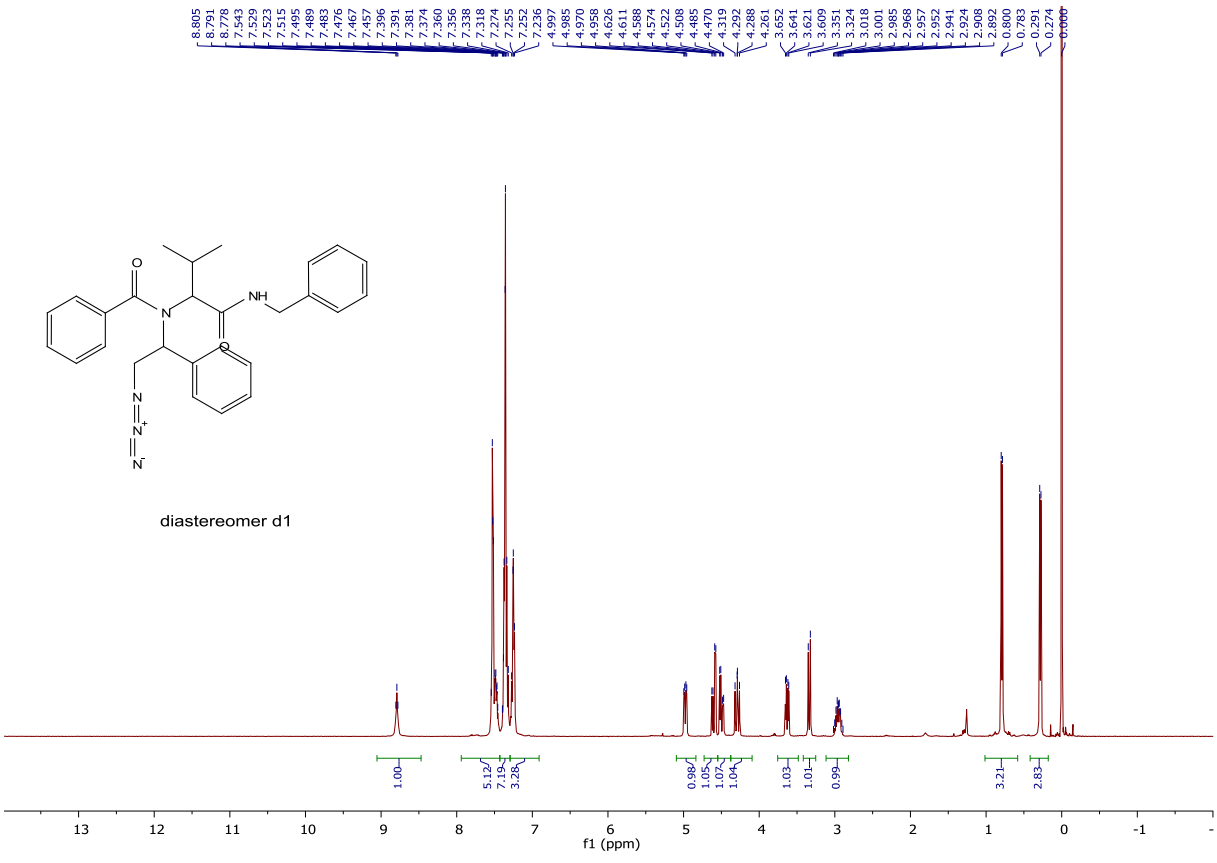

f1 (ppm)

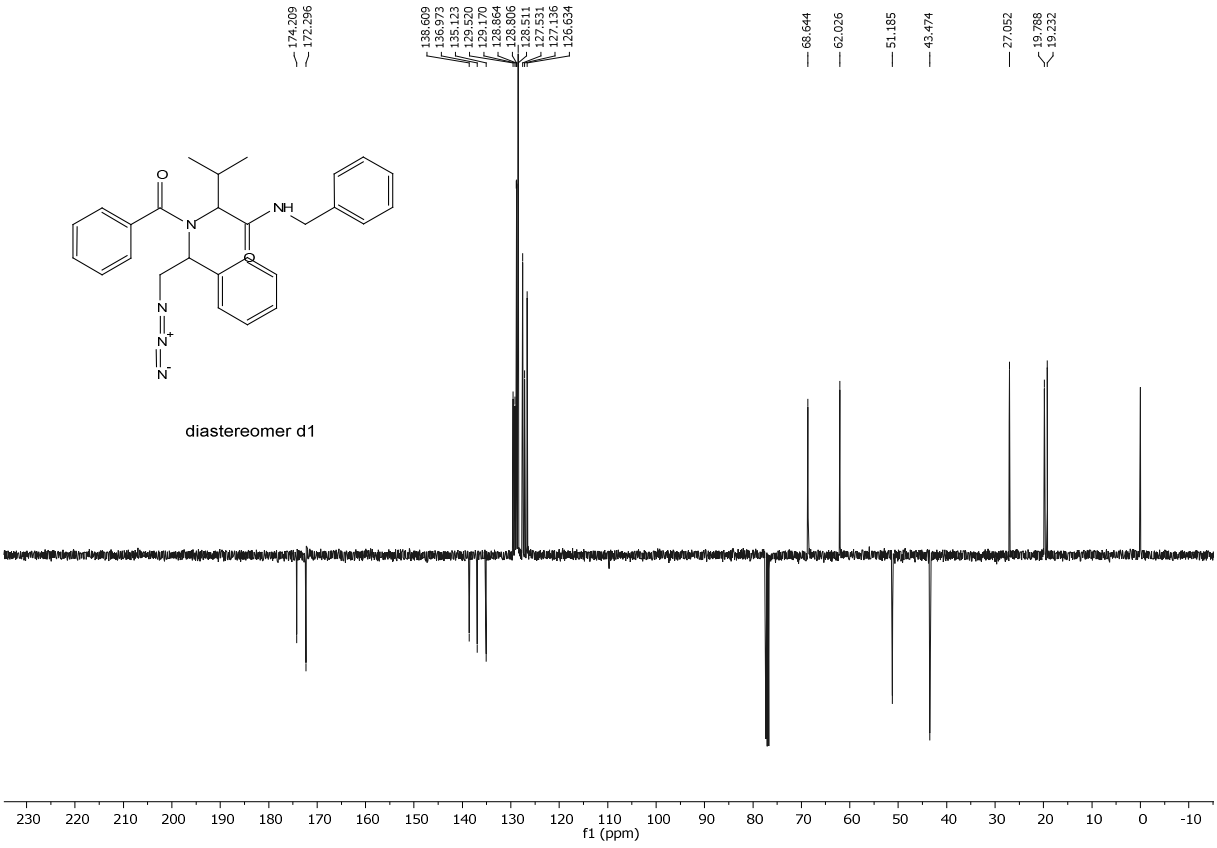

f1 (ppm)


14b
CDCl 3
1H
two diastereomers
f1 (ppm)


14b
CDCl 3
1H
two diastereomers
f1 (ppm)


14b
CDCl3
gDQCOSY
two diastereomers
f2 (ppm)
f1 (ppm)


diastereomer d1
f1 (ppm)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128.511
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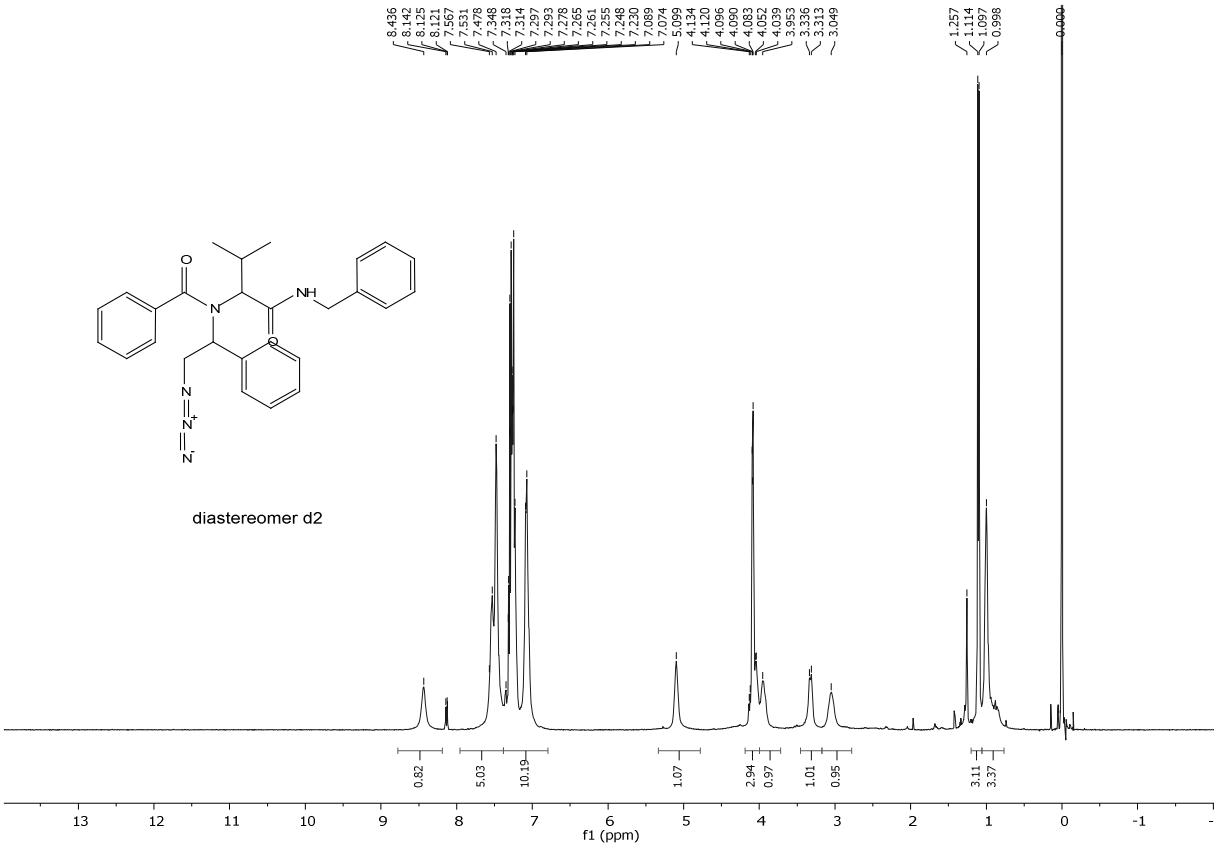
126.634
68.644
62.026
51.185
43.474
27.052
19.788
19.232
O
N
NH
O
N
N+
N-
diastereomer d1
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.265
7.261
7.255
7.248
7.230
7.089
7.074
5.099
4.134
4.120
4.096
4.090
4.083
4.052
4.039
3.953
3.336
3.313
3.049
1.257
1.114
1.097
0.998
0.000
O
N
NH
O
N
N+
N-
diastereomer d2
0.82
5.03
10.19
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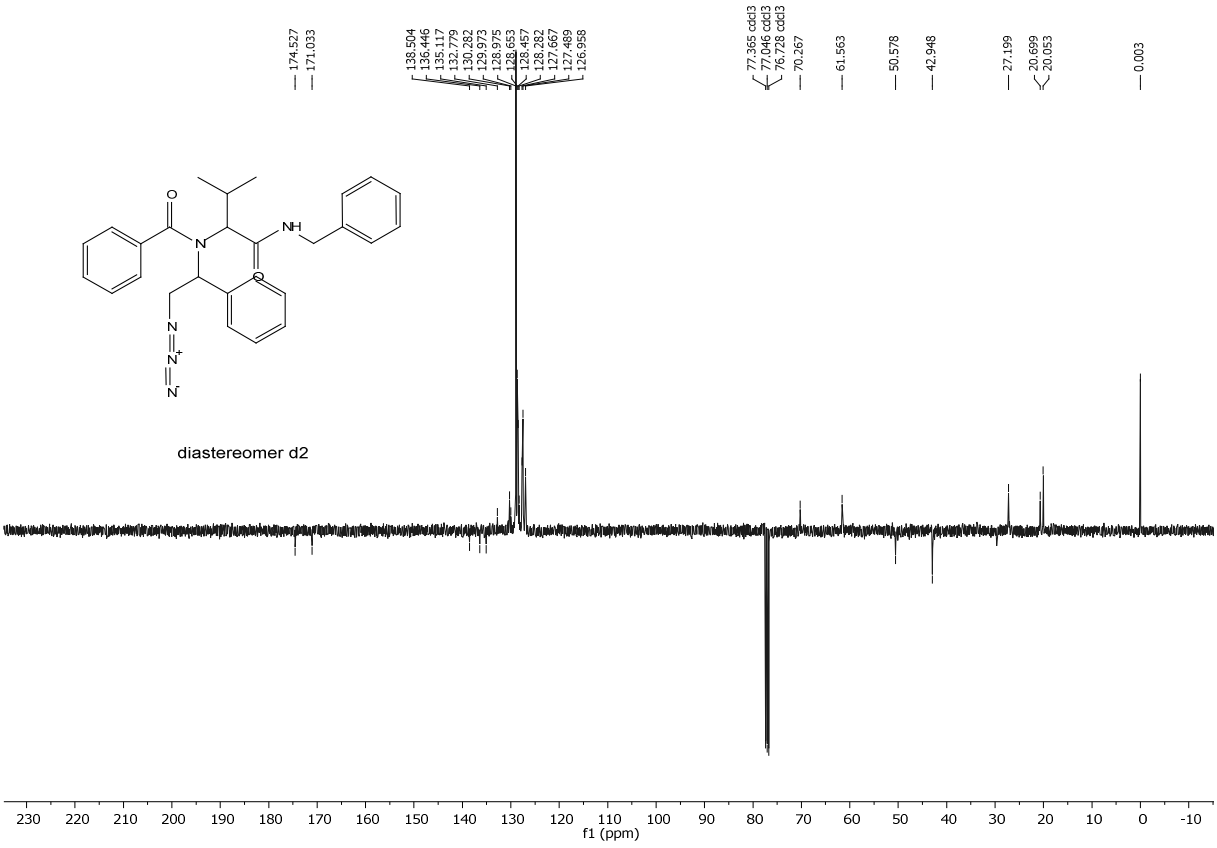
0.97
1.01
0.95
3.11
3.37
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)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138.504
136.446
135.117
132.779
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129.973
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128.457
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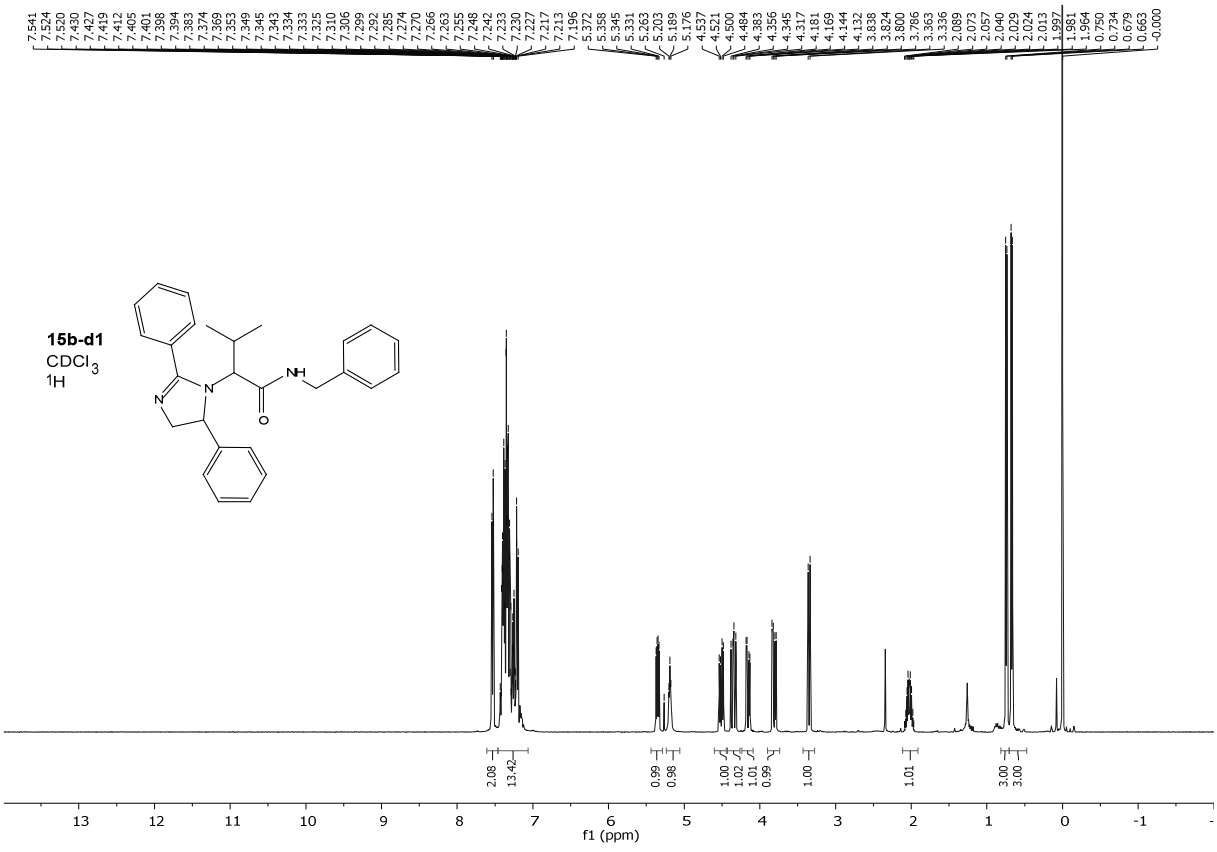
127.667
127.489
126.958
77.365 cdcl3
77.046 cdcl3
76.728 cdcl3
70.267
61.563
50.578
42.948
27.199
20.699
20.053
0.003
diastereomer d2
f1 (ppm)


15b-d1
CDCl3
1H
2.08
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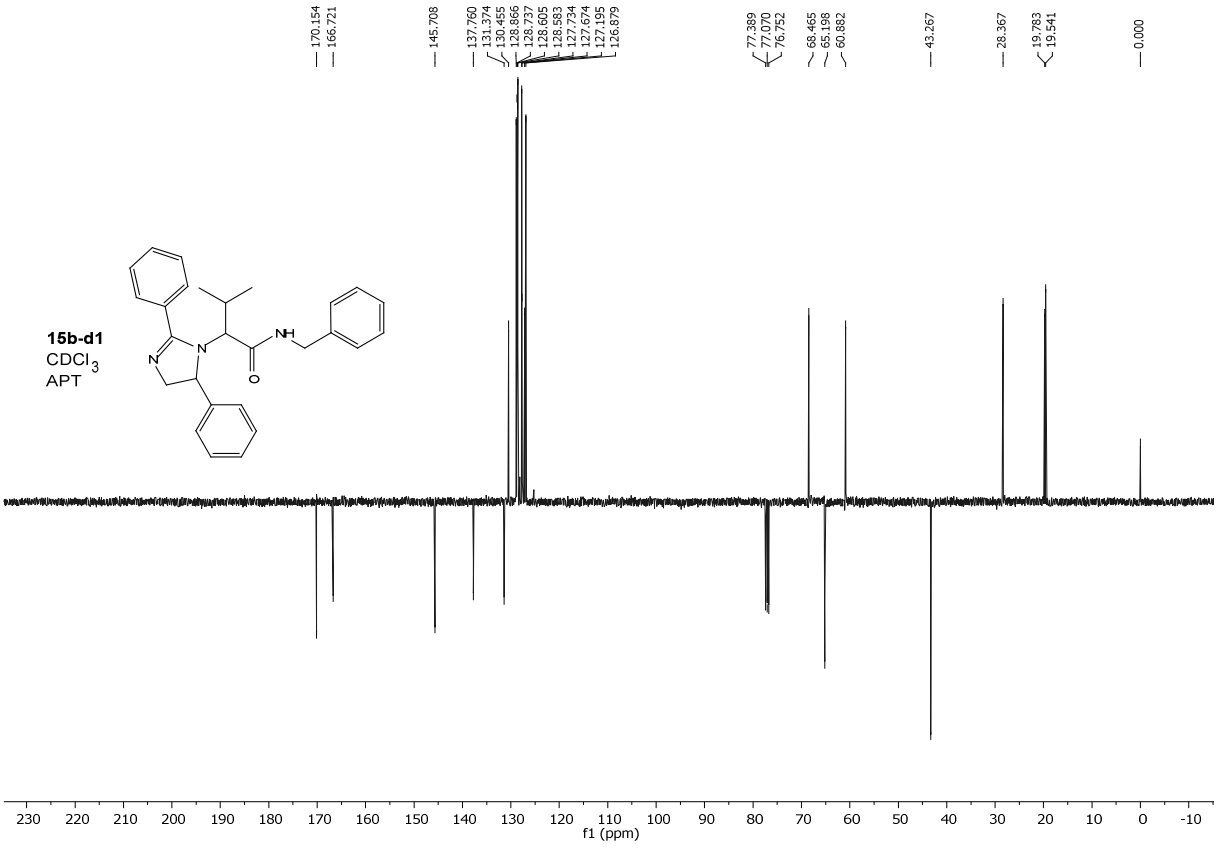
0.98
1.00
1.02
1.01
0.99
1.00
1.01
3.00
3.00
f1 (ppm)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166.721
145.708
137.760
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130.455
128.866
128.737
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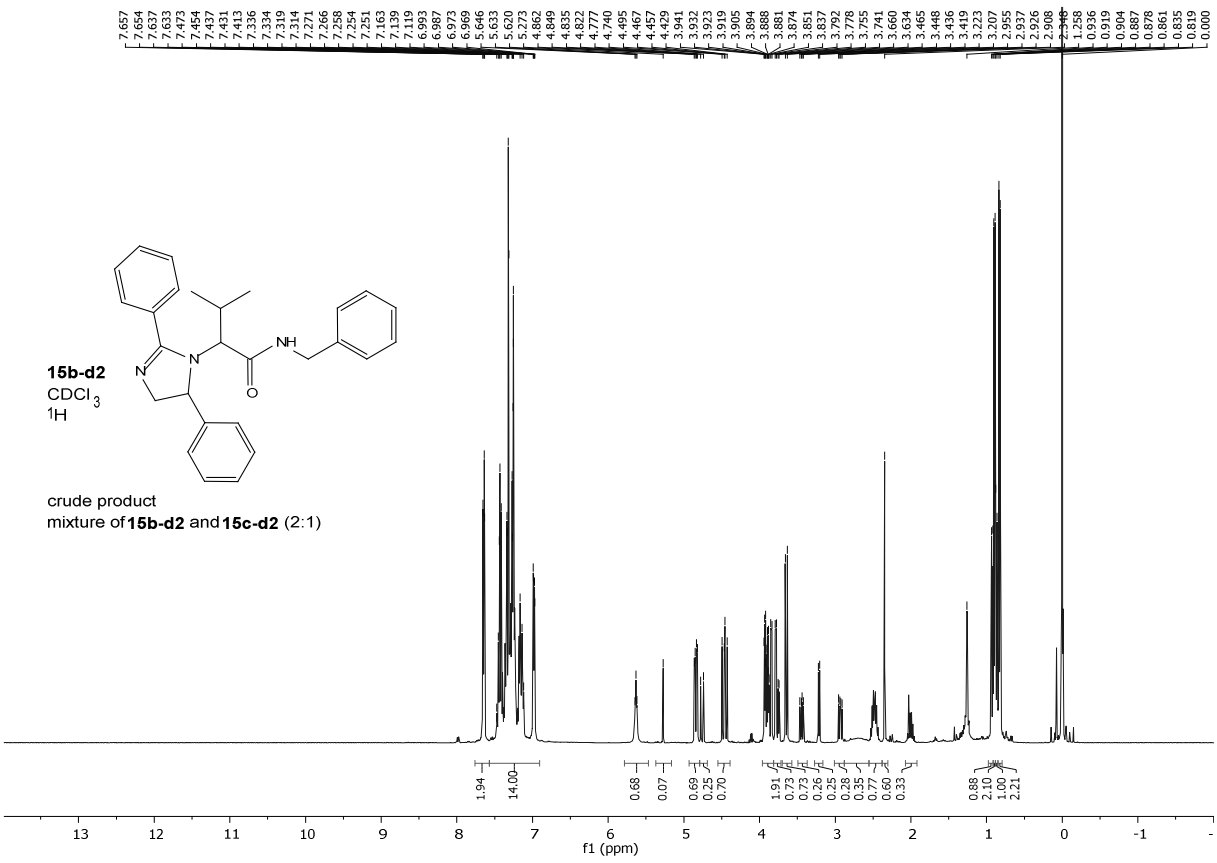
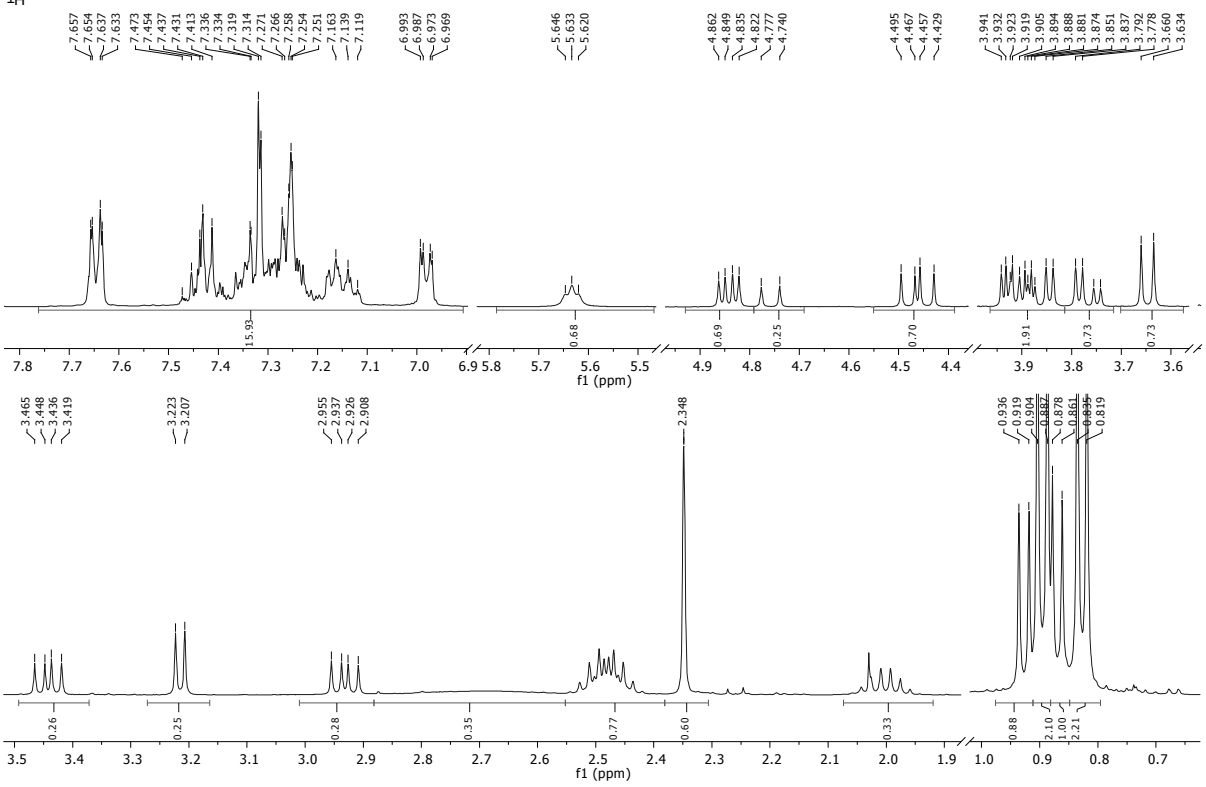
127.734
127.674
127.195
126.879
77.389
77.070
76.752
68.465
65.198
60.882
43.267
28.367
19.783
19.541
0.000
15b-d1
CDCl3
APT
NH
O
f1 (ppm)

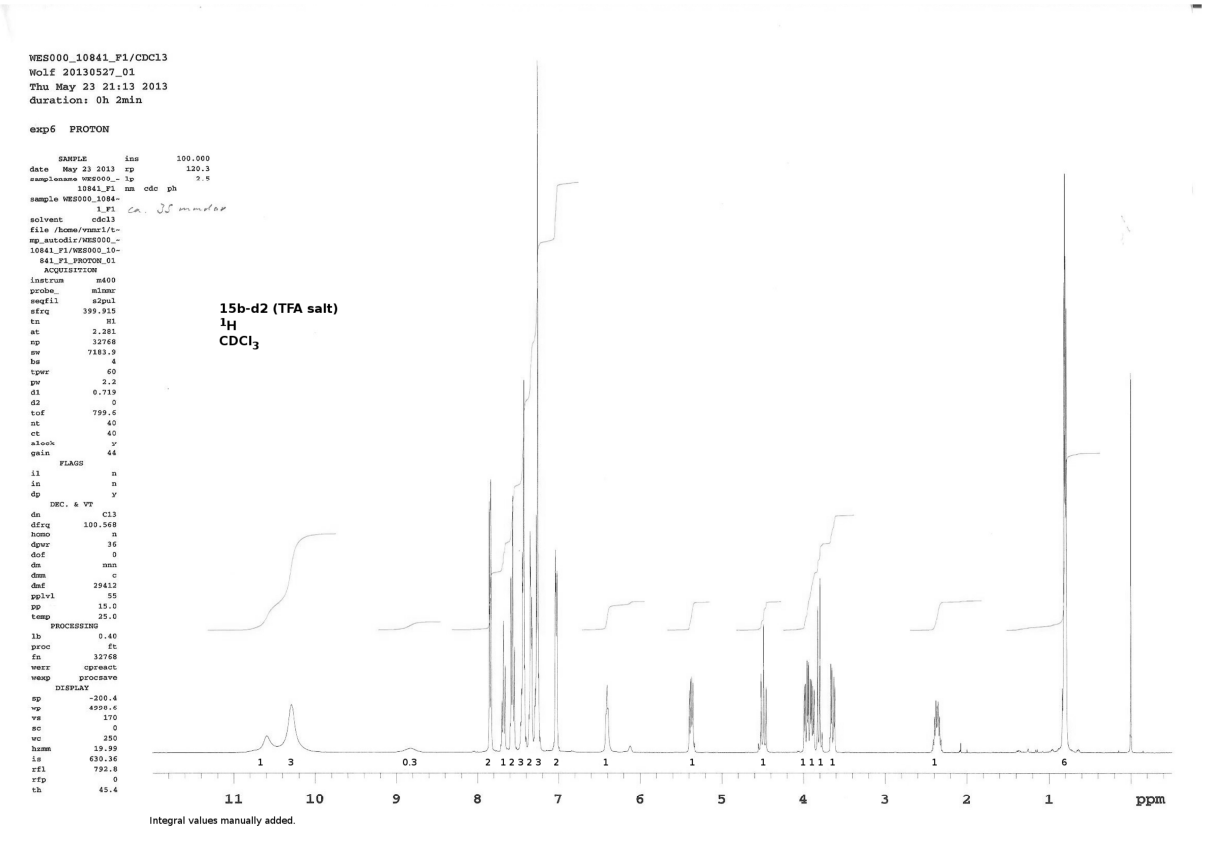

15b-d2
CDCl3
1H
NH
O
crude product
mixture of 15b-d2 and 15c-d2 (2:1)
1.94
14.00
0.68
0.07
0.69
0.25
0.70
1.91
0.73
0.73
0.26
0.25
0.28
0.35
0.77
0.60
0.33
0.88
2.10
1.00
2.21
f1 (ppm)

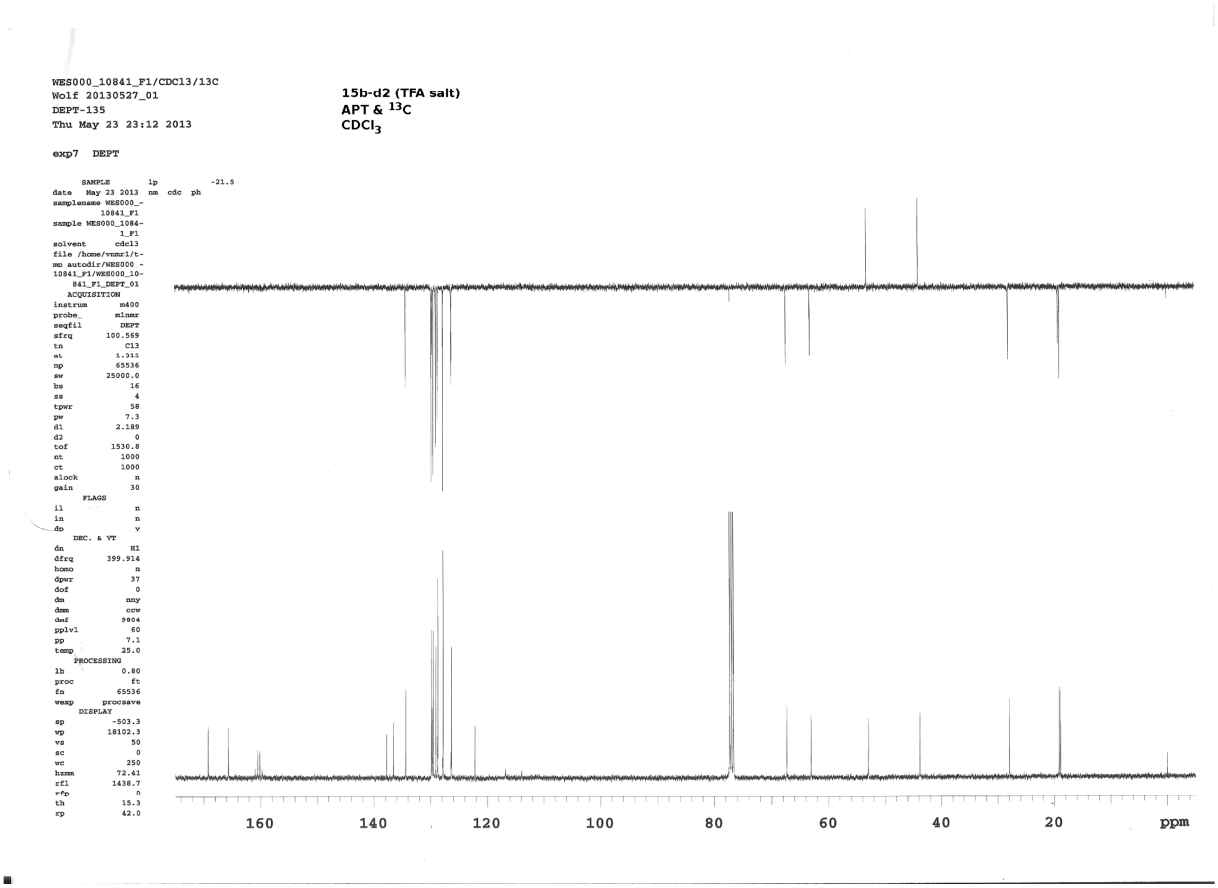
mixture (crude product) of **15b-d2** and **15c-d2** (2:1)

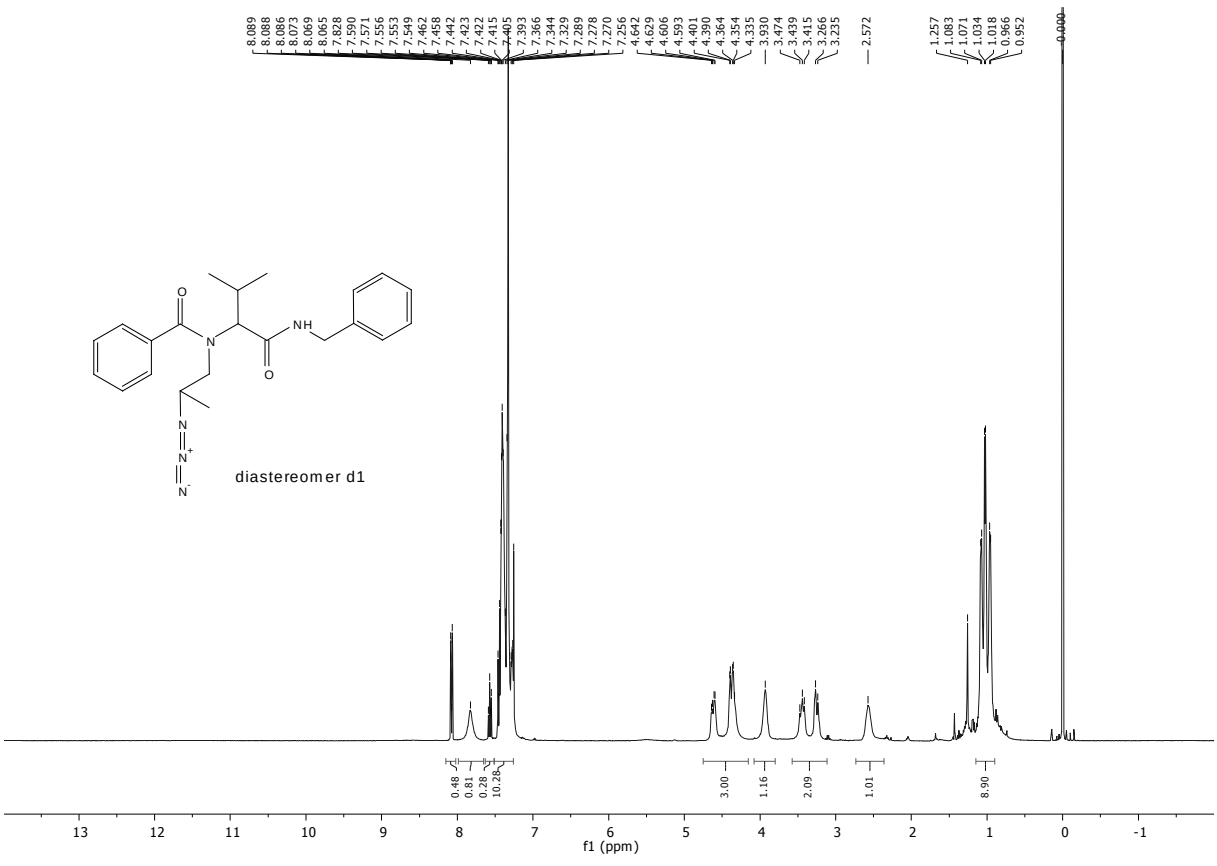
$CDCl_3$

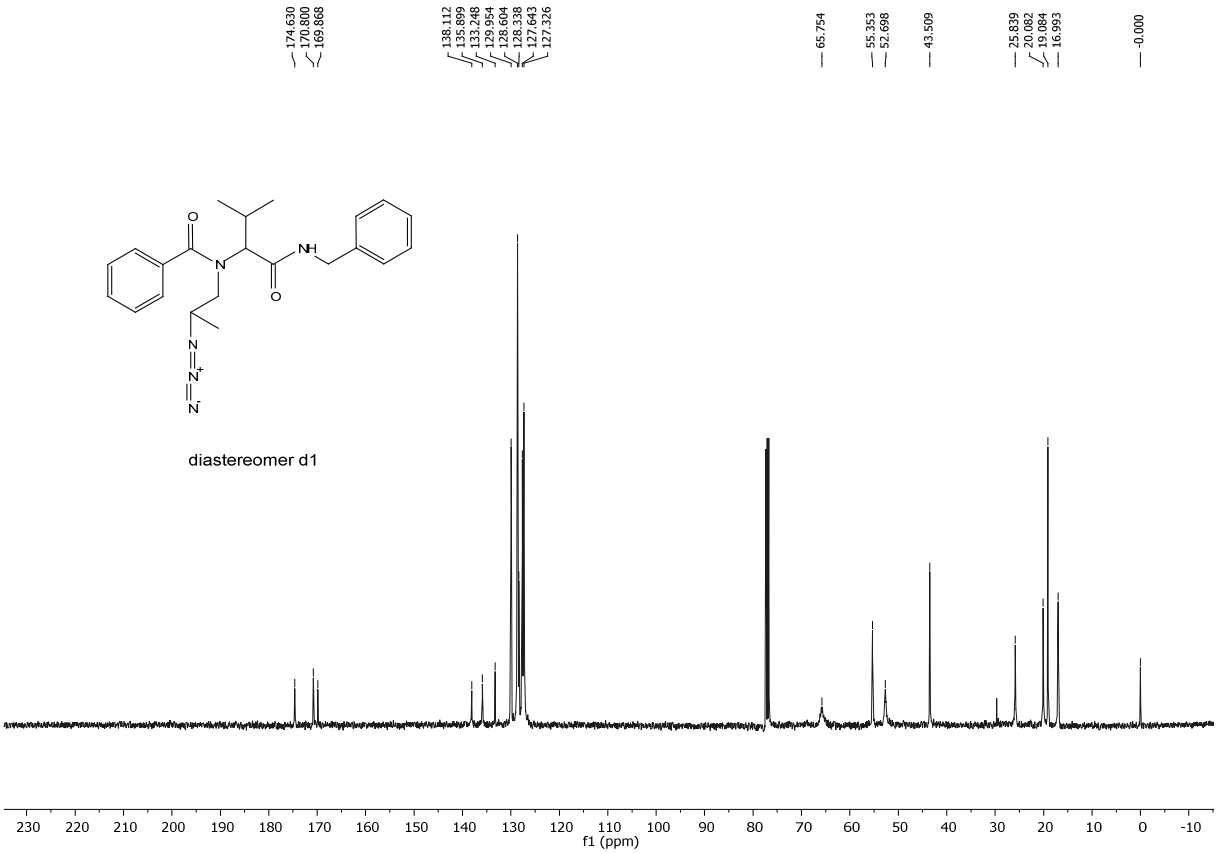
^1H

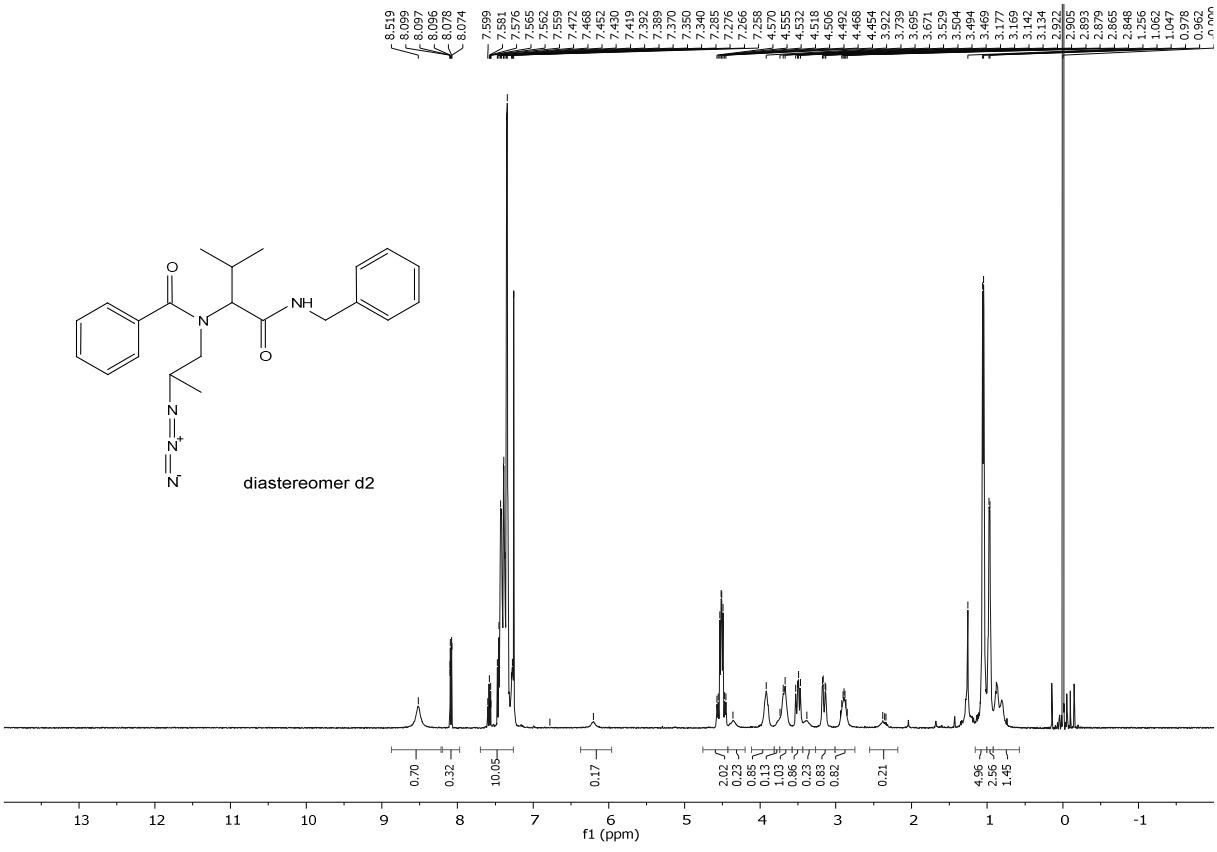


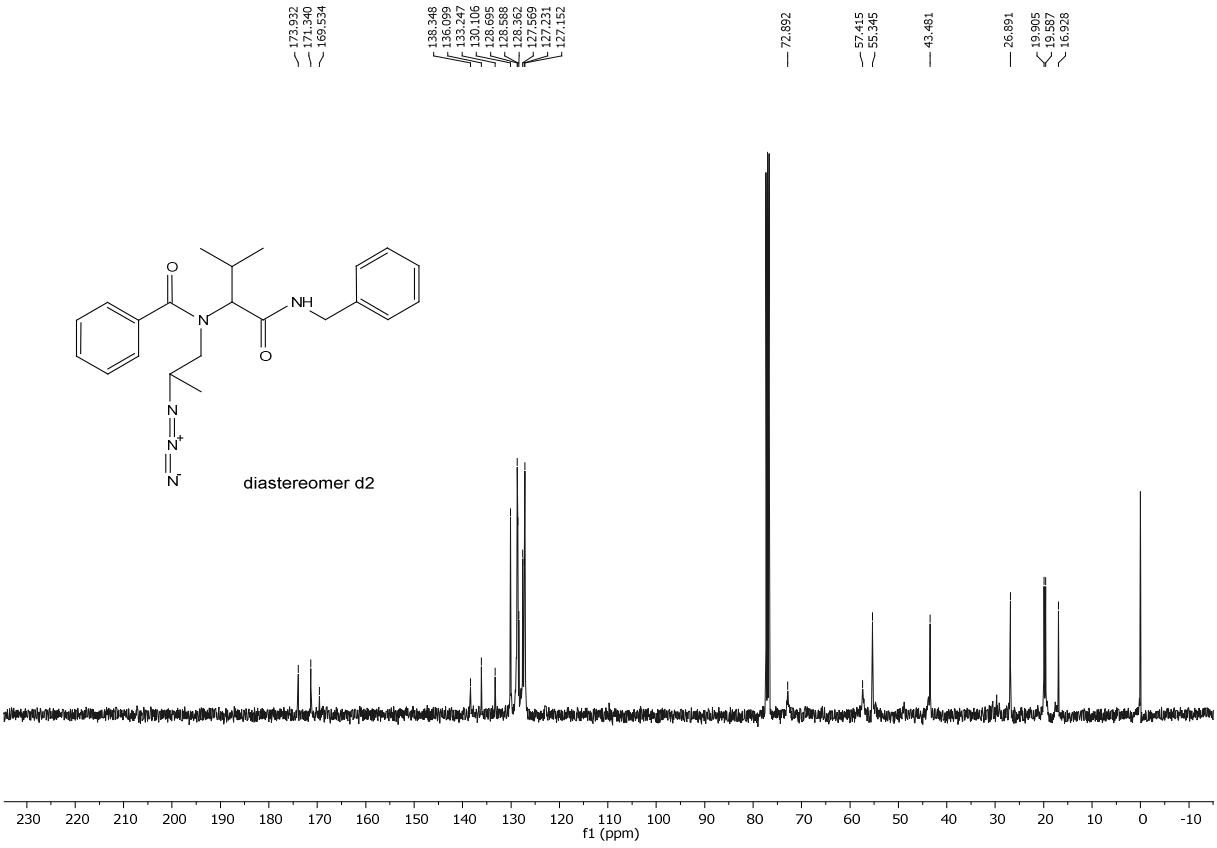


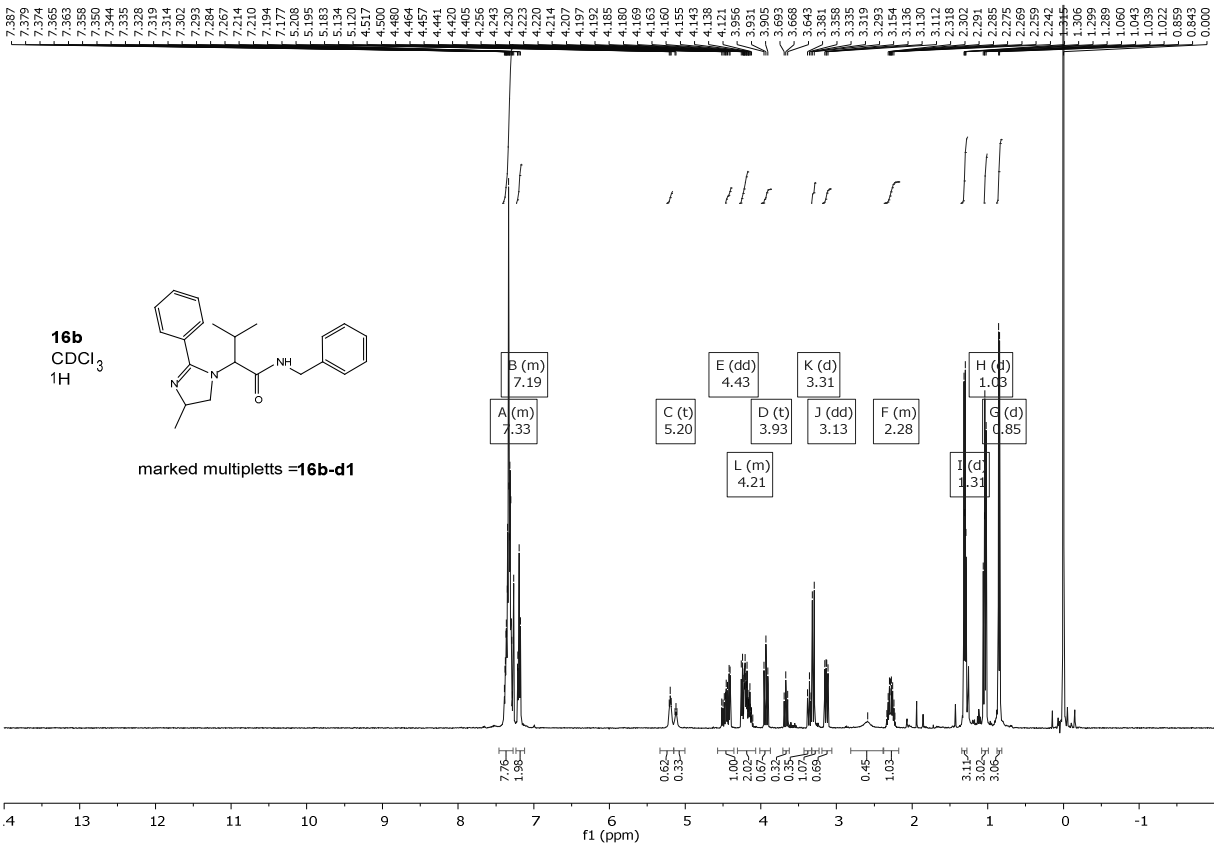

WES000_10841_F1/CDCl3/13C
Wolf 20130527_01
DEPT-135
Thu May 23 23:12 2013
exp7 DEPT
15b-d2 (TFA salt)
APT & 13C
CDCl3
160
140
120
100
80
60
40
20
ppm

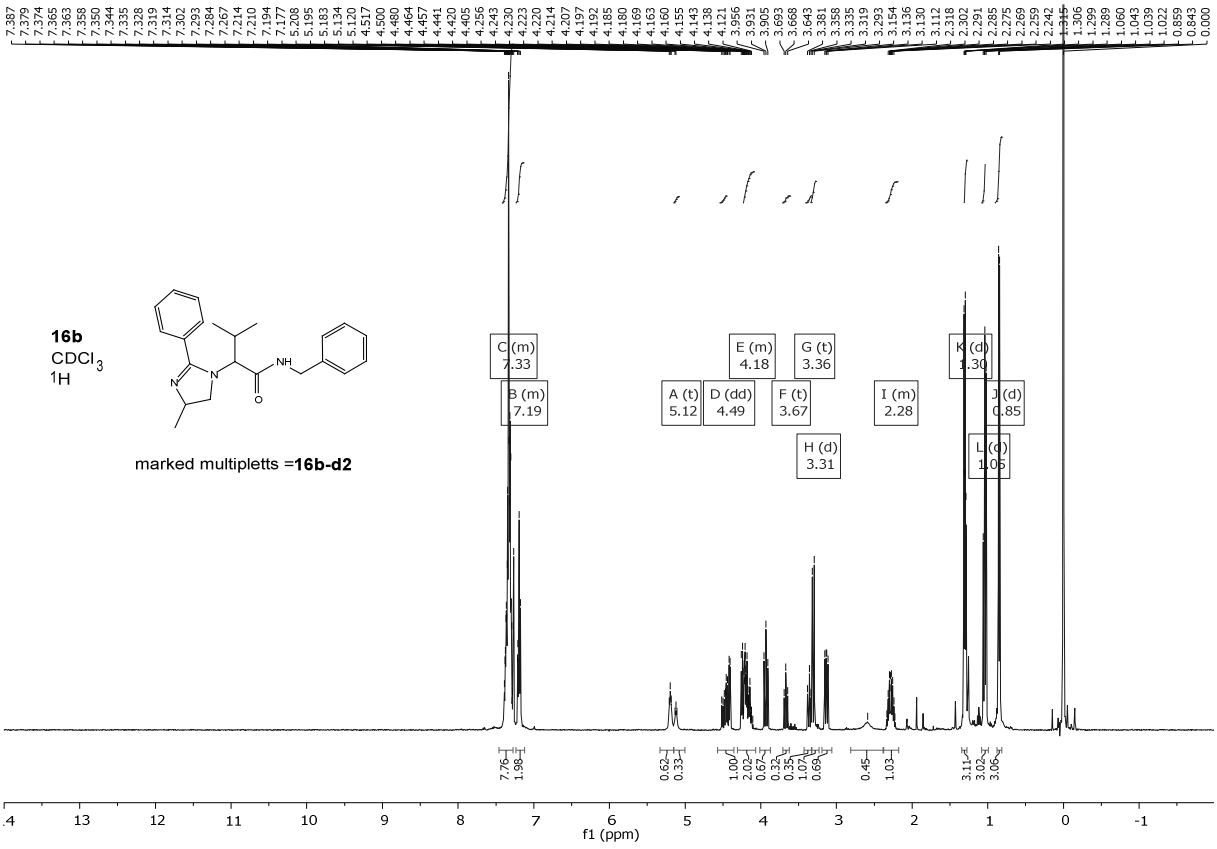

8.089
8.088
8.086
8.073
8.069
8.065
7.828
7.590
7.571
7.556
7.553
7.549
7.462
7.458
7.442
7.423
7.422
7.415
7.405
7.393
7.366
7.344
7.329
7.289
7.278
7.270
7.256
4.642
4.629
4.606
4.593
4.401
4.390
4.364
4.354
4.335
3.930
3.474
3.439
3.415
3.266
3.235
2.572
1.257
1.083
1.071
1.034
1.018
0.966
0.952
0.000
O
N
NH
O
N
N+
N-
diastereomer d1
0.48
0.81
0.28
10.28
3.00
1.16
2.09
1.01
8.90
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

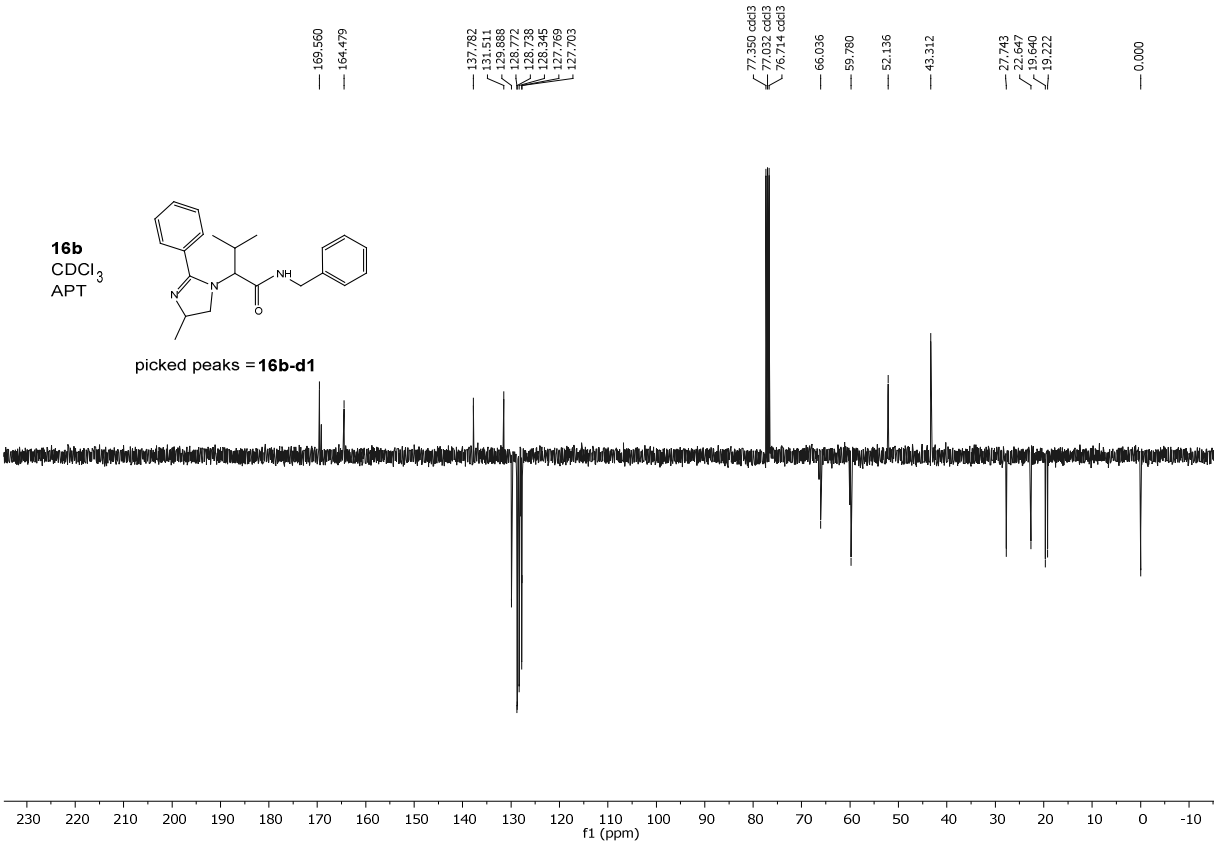

174.630
170.800
169.868
138.112
135.899
133.248
129.954
128.604
128.338
127.643
127.326
65.754
55.353
52.698
43.509
25.839
20.082
19.084
16.993
-0.000
diastereomer d1
f1 (ppm)

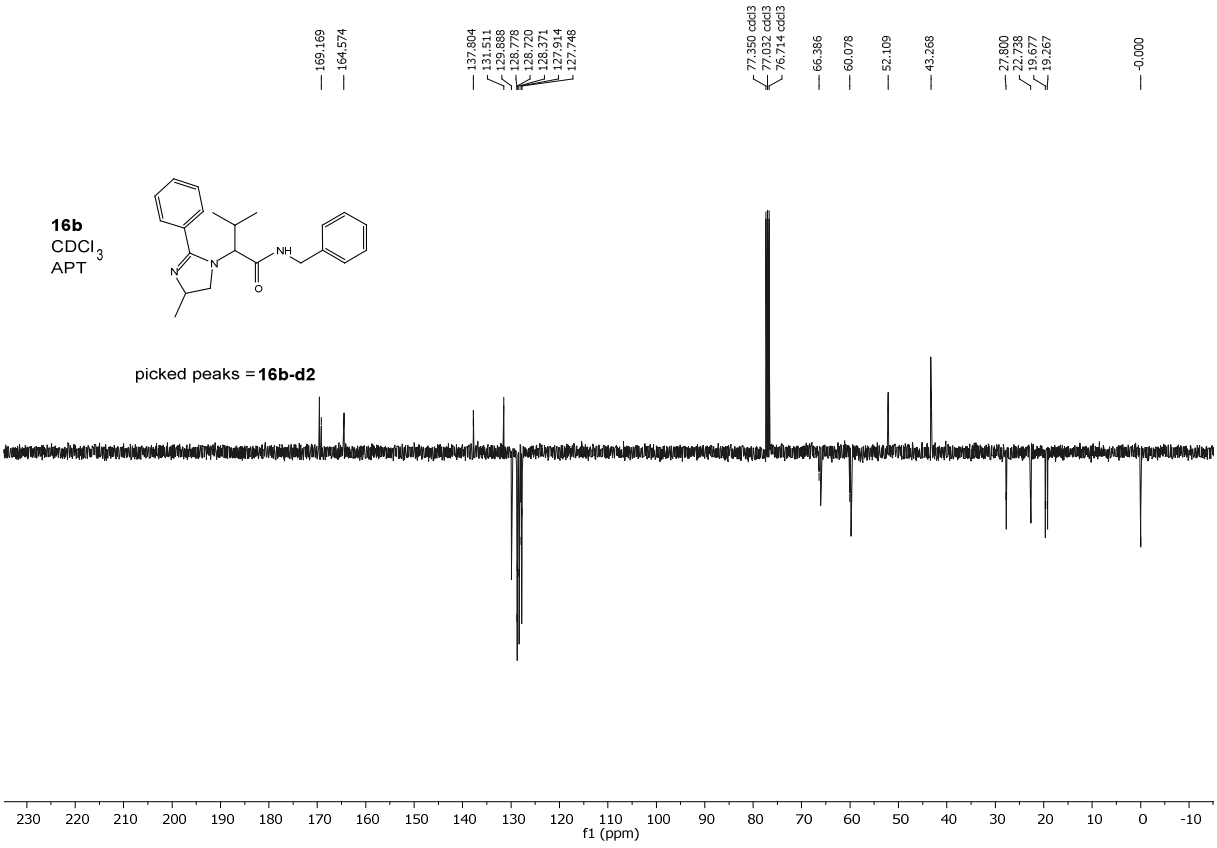

diastereomer d2
0.70
0.32
10.05
0.17
2.02
0.23
0.85
0.13
1.03
0.86
0.23
0.83
0.82
0.21
4.96
2.56
1.45
f1 (ppm)

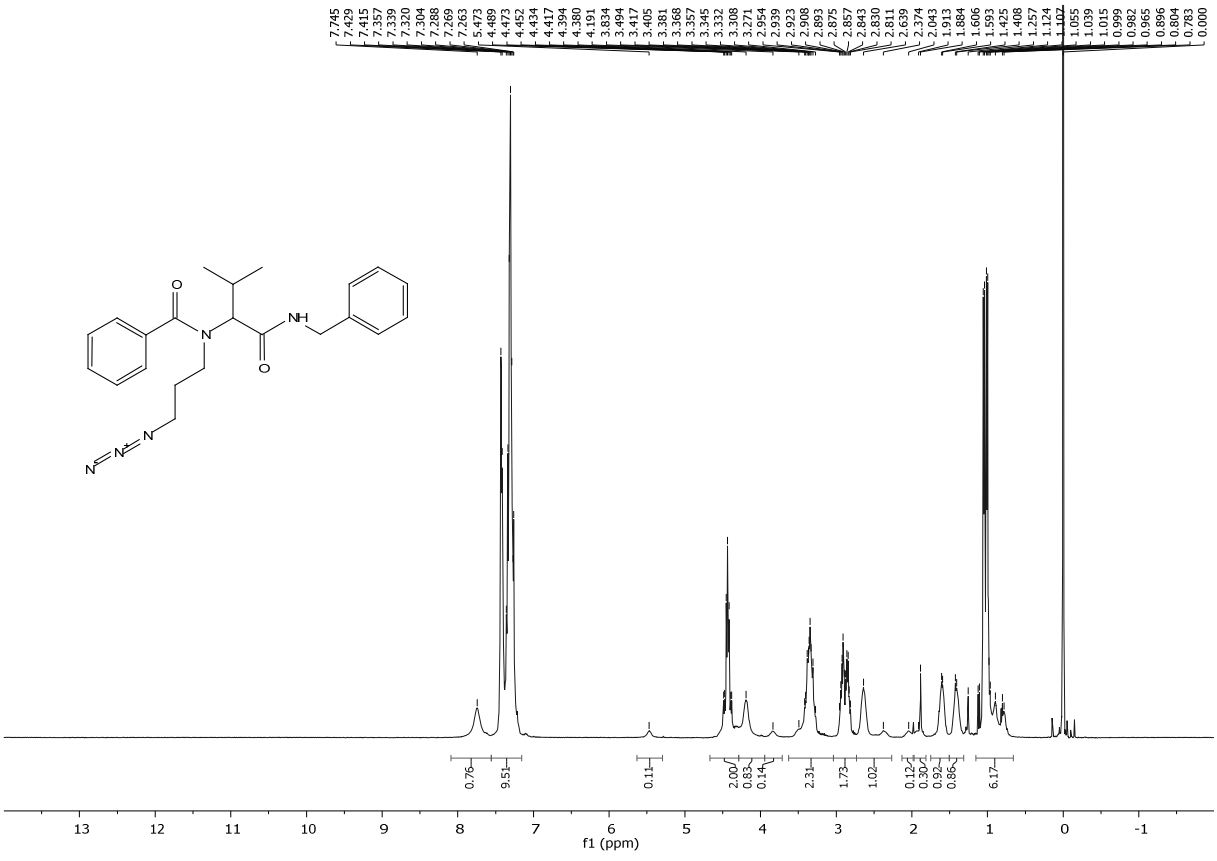

173.932
171.340
169.534
138.348
136.099
133.247
130.106
128.695
128.588
128.362
127.569
127.231
127.152
72.892
57.415
55.345
43.481
26.891
19.905
19.587
16.928
diastereomer d2
f1 (ppm)

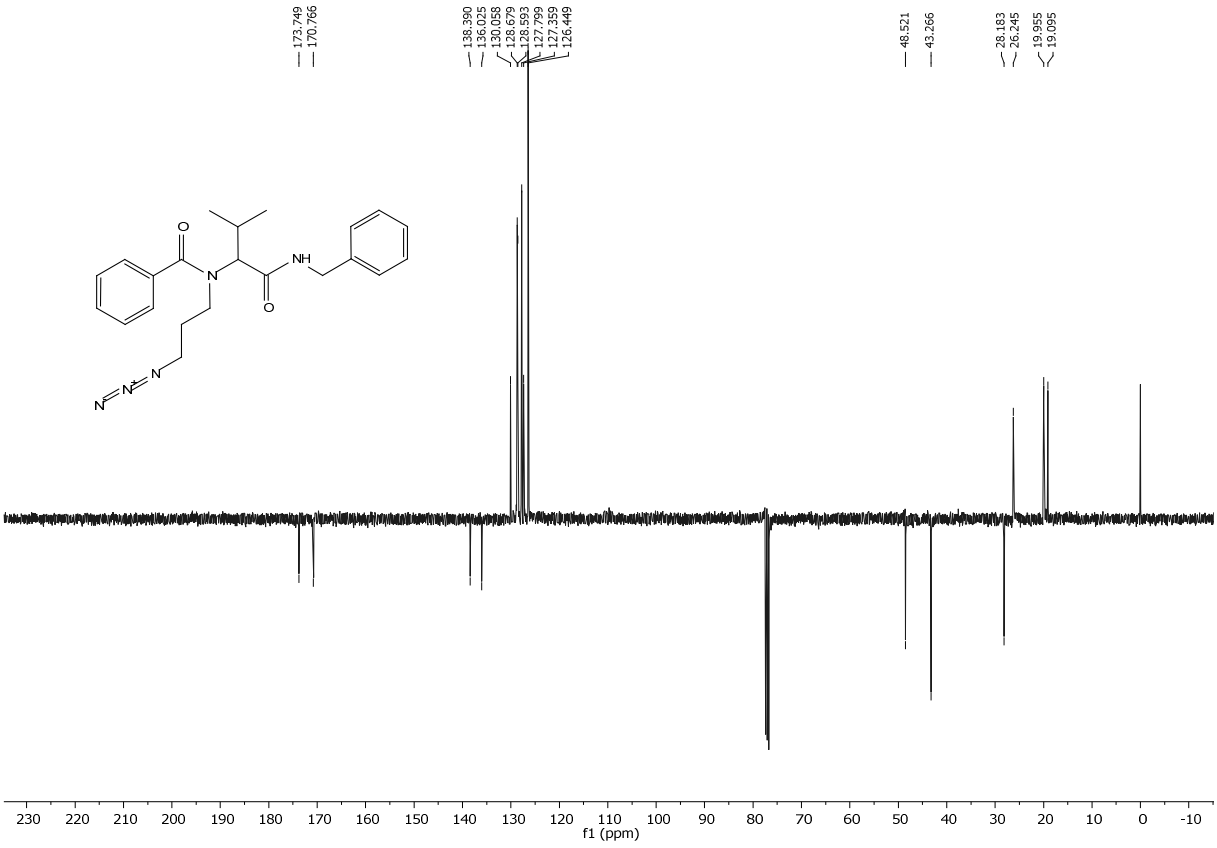

16b
CDCl3
1H
marked multipletts =16b-d1
B (m) 7.19
A (m) 7.33
C (t) 5.20
E (dd) 4.43
D (t) 3.93
L (m) 4.21
K (d) 3.31
J (dd) 3.13
F (m) 2.28
H (d) 1.03
G (d) 0.85
I (d) 1.31
f1 (ppm)

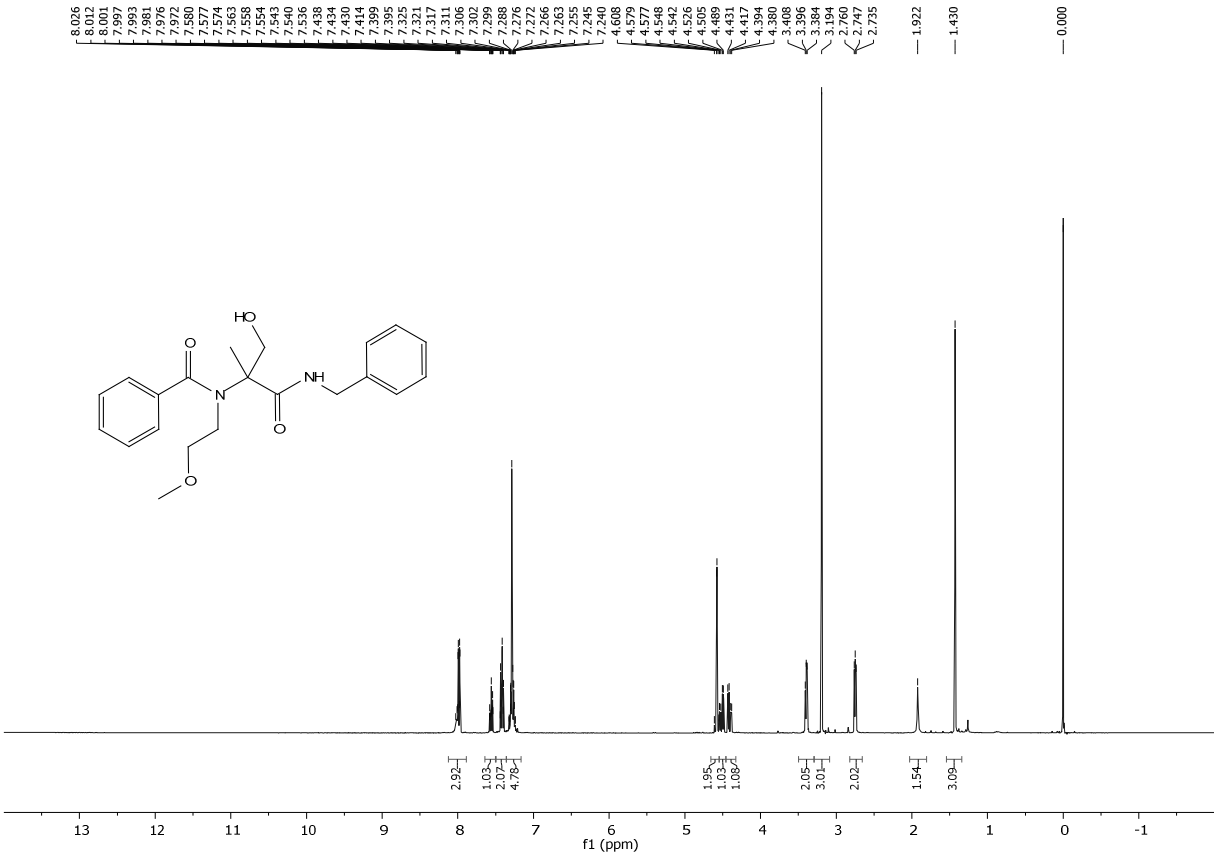

16b
CDCl3
1H
marked multipletts =16b-d2
C (m) 7.33
B (m) 7.19
E (m) 4.18
G (t) 3.36
A (t) 5.12
D (dd) 4.49
F (t) 3.67
H (d) 3.31
I (m) 2.28
K (d) 1.30
J (d) 0.85
L (d) 1.05
f1 (ppm)

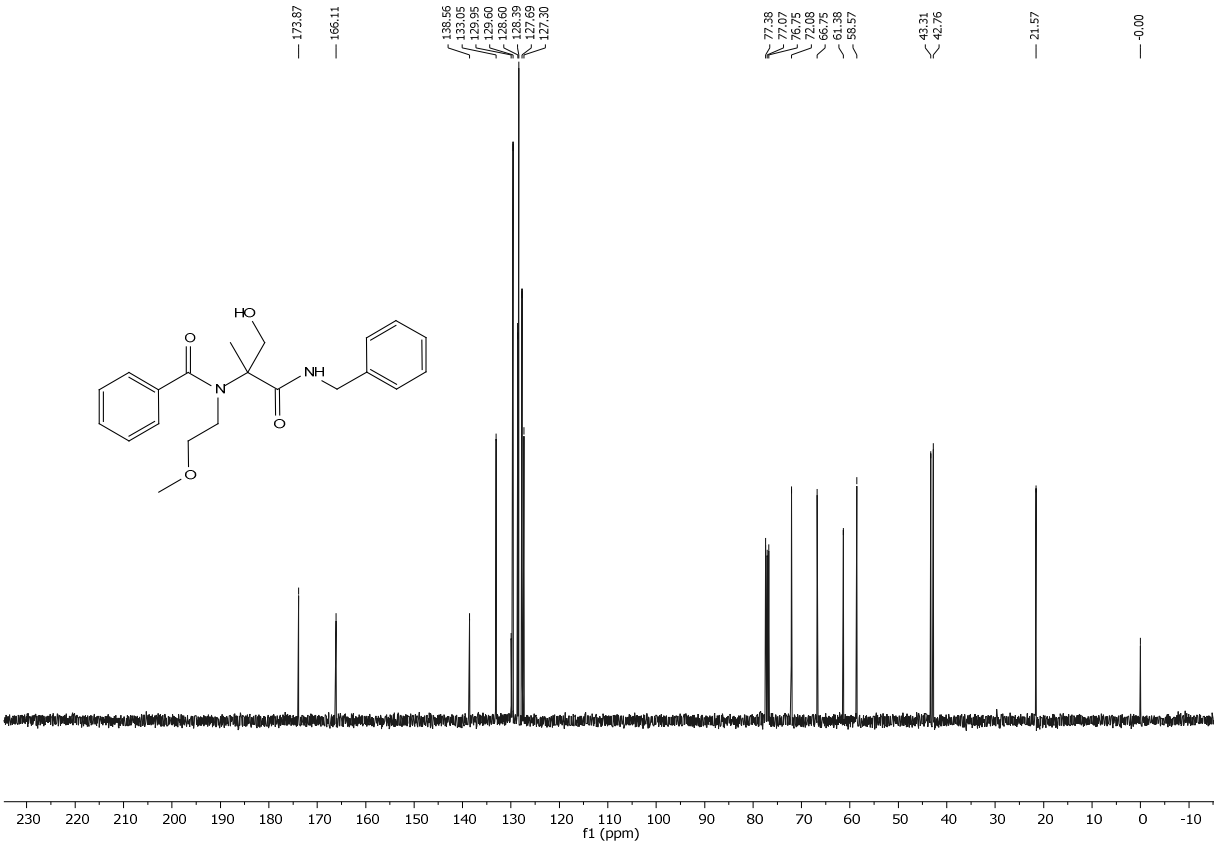

16b
CDCl3
APT
picked peaks =16b-d1
169.560
164.479
137.782
131.511
129.888
128.772
128.738
128.345
127.769
127.703
77.350 cdd3
77.032 cdd3
76.714 cdd3
66.036
59.780
52.136
43.312
27.743
22.647
19.640
19.222
0.000
f1 (ppm)

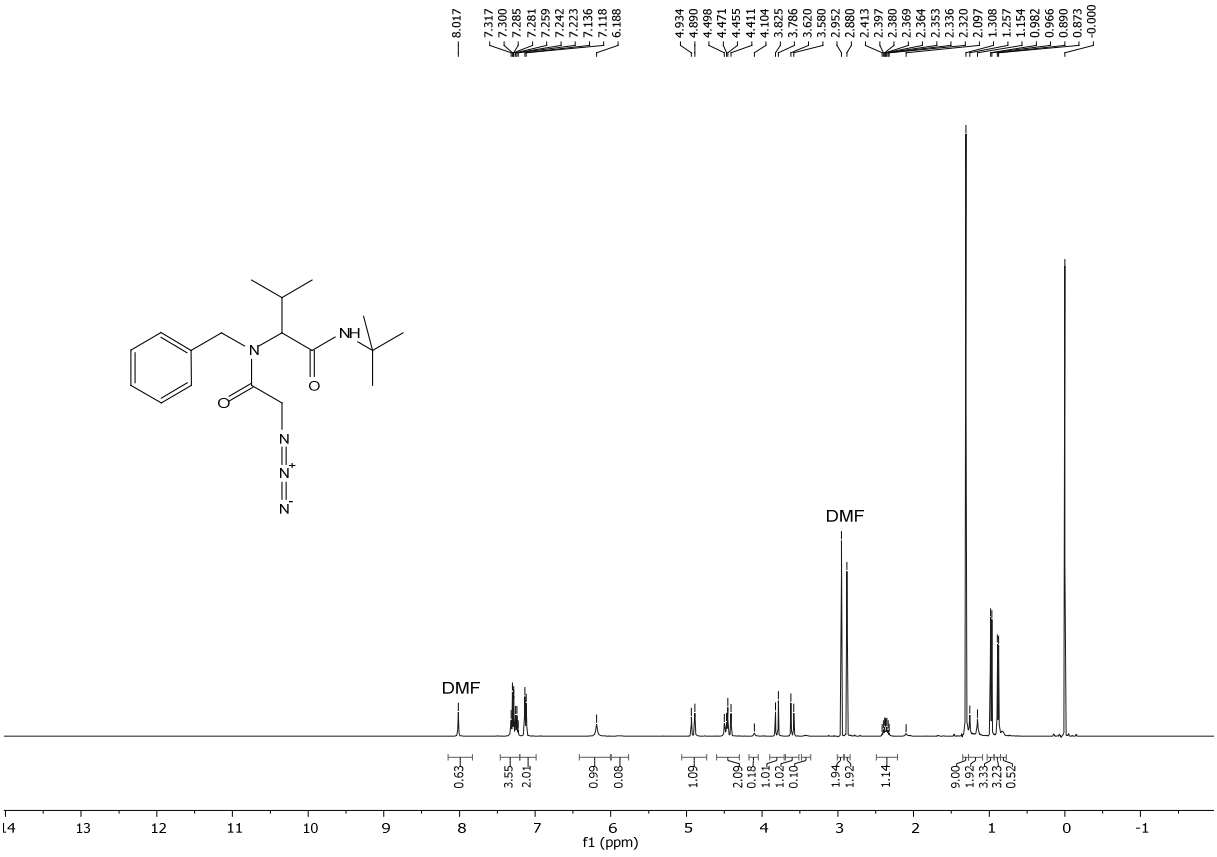

169.169
164.574
137.804
131.511
129.888
128.778
128.720
128.371
127.914
127.748
77.350 cdcl3
77.032 cdcl3
76.714 cdcl3
66.386
60.078
52.109
43.268
27.800
22.738
19.677
19.267
-0.000
16b
CDCl3
APT
picked peaks = 16b-d2
f1 (ppm)

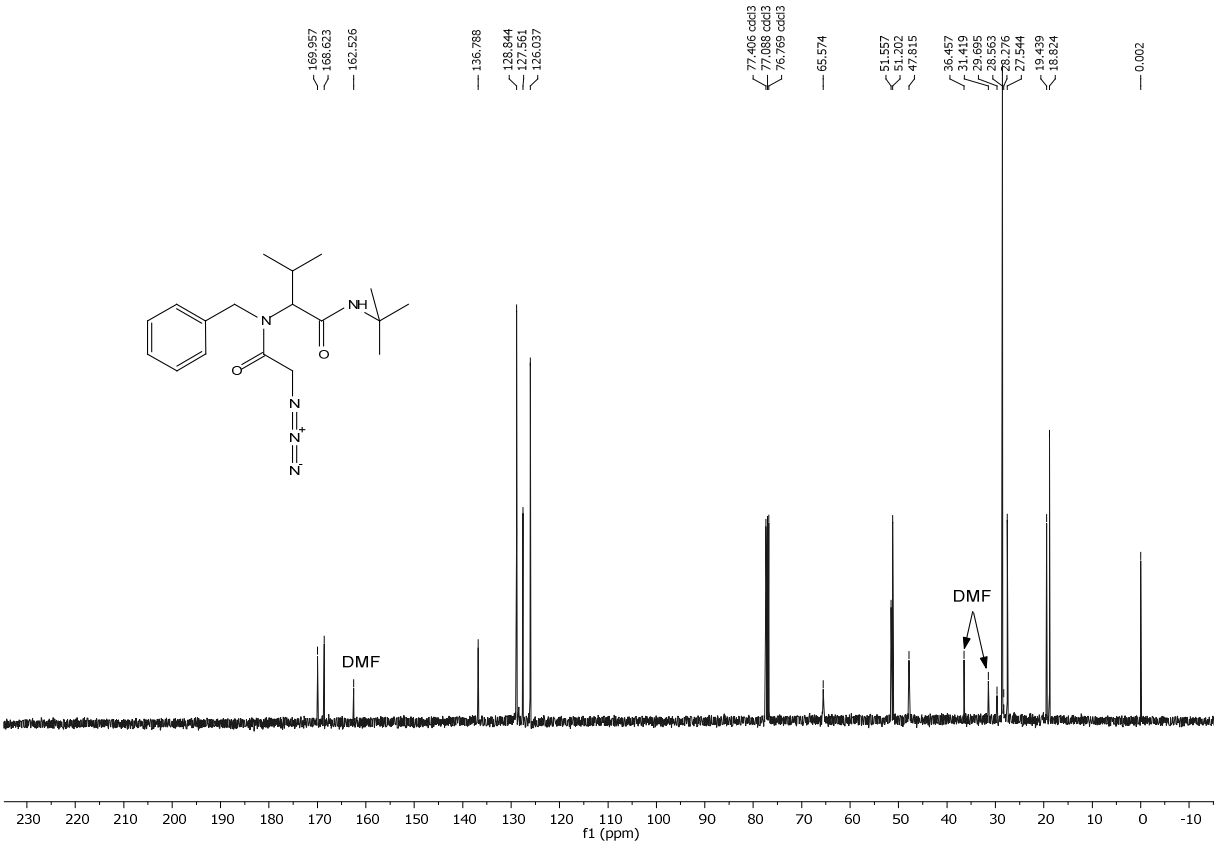

7.745
7.429
7.415
7.357
7.339
7.320
7.304
7.288
7.269
7.263
5.473
4.489
4.473
4.452
4.434
4.417
4.394
4.380
4.191
3.834
3.494
3.417
3.405
3.381
3.368
3.357
3.345
3.332
3.308
3.271
2.954
2.939
2.923
2.908
2.893
2.875
2.857
2.843
2.830
2.811
2.639
2.374
2.043
1.913
1.884
1.606
1.593
1.425
1.408
1.257
1.124
1.102
1.055
1.039
1.015
0.999
0.982
0.965
0.896
0.804
0.783
0.000
0.76
9.51
0.11
2.00
0.83
0.14
2.31
1.73
1.02
0.12
0.30
0.92
0.86
6.17
f1 (ppm)

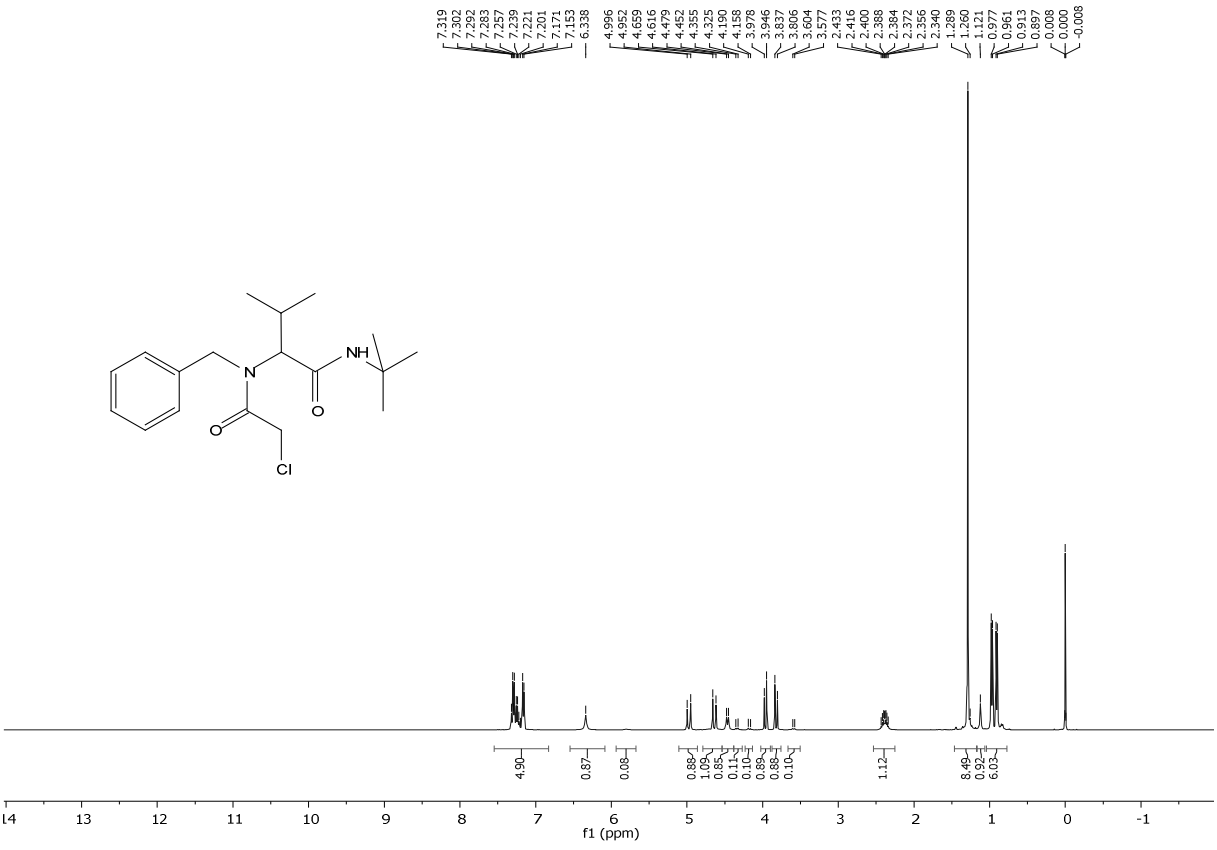

173.749
170.766
138.390
136.025
130.058
128.679
128.593
127.799
127.359
126.449
48.521
43.266
28.183
26.245
19.955
19.095
O
N
NH
O
N
N
N
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

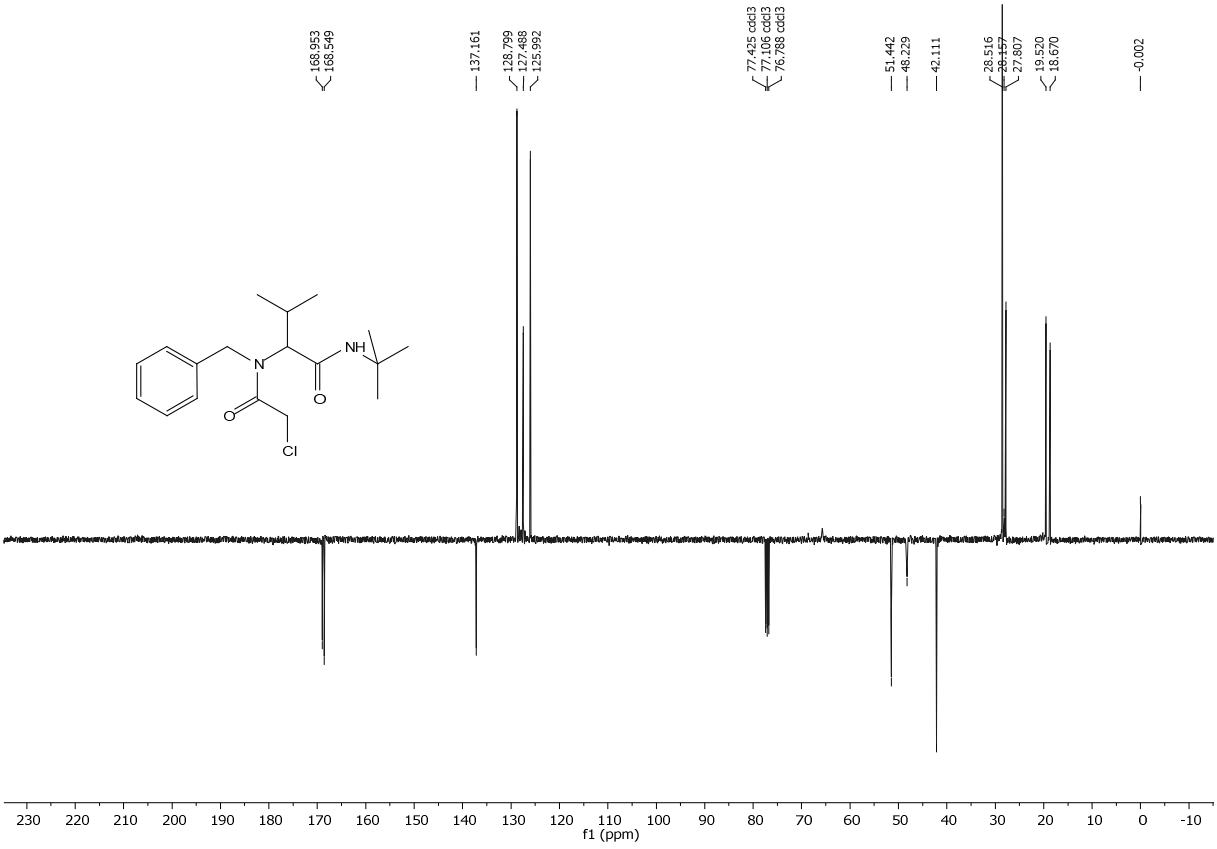

8.026
8.012
8.001
7.997
7.993
7.981
7.976
7.972
7.580
7.577
7.574
7.563
7.558
7.554
7.543
7.540
7.536
7.438
7.434
7.430
7.414
7.399
7.395
7.325
7.321
7.317
7.311
7.306
7.302
7.299
7.288
7.276
7.272
7.266
7.263
7.255
7.245
7.240
4.608
4.579
4.577
4.548
4.542
4.526
4.505
4.489
4.431
4.417
4.394
4.380
3.408
3.396
3.384
3.194
2.760
2.747
2.735
1.922
1.430
0.000
HO
O
N
NH
O
O
2.92
1.03
2.07
4.78
1.95
1.03
1.08
2.05
3.01
2.02
1.54
3.09
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


173.87
166.11
138.56
133.05
129.95
129.60
128.60
128.39
127.69
127.30
77.38
77.07
76.75
72.08
66.75
61.38
58.57
43.31
42.76
21.57
-0.00
HO
O
N
NH
O
O
f1 (ppm)


8.017
7.317
7.300
7.285
7.281
7.259
7.242
7.223
7.136
7.118
6.188
4.934
4.890
4.498
4.471
4.455
4.411
4.104
3.825
3.786
3.620
3.580
2.952
2.880
2.413
2.397
2.380
2.369
2.364
2.353
2.336
2.320
2.097
1.308
1.257
1.154
0.982
0.966
0.890
0.873
-0.000
DMF
DMF
NH
N
O
O
N
N
N
0.63
3.55
2.01
0.99
0.08
1.09
2.09
0.18
1.01
1.02
0.10
1.94
1.92
1.14
9.00
1.92
3.33
3.23
0.52
f1 (ppm)


169.957
168.623
162.526
136.788
128.844
127.561
126.037
77.406 cdcl3
77.088 cdcl3
76.769 cdcl3
65.574
51.557
51.202
47.815
36.457
31.419
29.695
28.563
28.276
27.544
19.439
18.824
0.002
DMF
DMF
NH
O
O
N
N
N
f1 (ppm)


7.319
7.302
7.292
7.283
7.257
7.239
7.221
7.201
7.171
7.153
6.338
4.996
4.952
4.659
4.616
4.479
4.452
4.355
4.325
4.190
4.158
3.978
3.946
3.837
3.806
3.604
3.577
2.433
2.416
2.400
2.388
2.384
2.372
2.356
2.340
1.289
1.260
1.121
0.977
0.961
0.913
0.897
0.008
0.000
-0.008
NH
O
O
N
Cl
4.90
0.87
0.08
0.88
1.09
0.85
0.11
0.10
0.89
0.88
0.10
1.12
8.49
0.92
6.03
f1 (ppm)


168.953
168.549
137.161
128.799
127.488
125.992
77.425 cdcl3
77.106 cdcl3
76.788 cdcl3
51.442
48.229
42.111
28.516
28.157
27.807
19.520
18.670
-0.002
N
NH
O
O
Cl
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

10.2. Correlation of substance numbers

Thesis number	IPB number
Chapter 6.1	
1	WES137
2	WES138
3	WES139
4	WES140
5	WES141
6	WES142
7	WES143
8	WES144
9	WES145
10	WES146
12	WES147
13	WES148
14	WES149
16	WES150
17	WES151
18	WES152
19	WES153
20	WES154
21	WES155
25	WES157
26	WES158
27	WES159
29	WES160
31	WES161
32	WES162
33	WES163
35	WES164
37	WES165
39	WES166
41	WES167
43	WES168
45	WES169
47	WES170
49	WES171
51	WES172
chapter 6.2.	
1a	WES092
1b	WES051
2a	WES096
2b	WES052
3a	WES095
3b	WES053
4a	WES097
4b	WES054
5a	WES110
5b	WES055
6a	WES104
7a	WES108
7b	WES057
8a	WES102
8b	WES058
9a	WES103
9b	WES059
10a	WES109
10b	WES062
11a	WES107
11b	WES060
12a	WES112
13a	WES111
13b	WES061
14	WES100
15	WES173
17	WES094
18	WES099
19	WES098
Chapter 6.3.	
5a	WES174
5a‘	WES077
5b	WES088
5c	WES089
5c‘	WES075
5d	WES086
5e	WES073
5f	WES069
5g	WES079
5h‘	WES074
5i‘	WES063
5k‘	WES066
5l‘	WES067
5m‘	WES071
6a	WES175
6b	WES087
6c	WES090
6e	WES081
6f	WES080
7a	WES0006
7f	WES068
7g	WES078
7h	WES176
7i	WES064
8a	WES005
8b	WES011
8c	WES010
8e	WES008
8f	WES009
8h	WES007
9c	WES001
9k	WES004
9l	WES003
9m	WES002
10	WES177
11	WES178
12	WES179
13	WES180
17	WES181
18	WES182
Chapter 6.4	
I	WES123
II	WES124
III	WES126
IV	WES127
V	WES129
VI	WES132
VII	WES133
VIII	WES136
1a	WES033
1a‘	WES115
1b	WES012
2a	WES034
2b	WES013
3a	WES035
3b	WES014
4a	WES039
4b	WES018
5a	WES038
5b	WES017
6a	WES037
6b	WES016
6c	WES029
7a	WES036
7b	WES015
8a	WES040
8b	WES019
9a	WES041
9b	WES020
10a	WES042
10b	WES021
10c	WES030
11a	WES043
11b	WES022
12a	WES044
12b	WES023
13a	WES045
13b	WES024
14a	WES046
14b	WES025
15a	d1: WES047 d2: WES048
15b	d1: WES026 d2: WES027
15c	WES031
16a	d1: WES049 d2: WES050
16b	WES028 (from d1) WES032 (from d2)
17a	WES125
18a‘	WES116
20a	WES121
20a‘	WES119

10.3. Selbständigkeitserklärung

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbständig und ohne fremde Hilfe verfasst, und keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt habe. Die den benutzten Werken wörtlich oder inhaltlich entnommen Stellen sind als solche kenntlich gemacht.

Bonn, den 15.05.2015

10.4. Lebenslauf

Persönliche Daten	Sebastian Johannes Welsch geb. am 25. November 1979 in Starnberg verheiratet
Okt. 2008 – heute	Dissertation zum Thema „Neue Postmodifikationen von Produkten der Ugi-Reaktion“ unter Betreuung von Prof. Dr. L. Wessjohann (Leibniz-Institut für Pflanzenbiochemie/Martin-Luther-Universität Halle-Wittenberg) bei Priaxon AG, München
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