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Ring-Opening Reactions of Aminocyclopropanes and Aminocyclobutanes

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par

Mingming WANG

Acceptée sur proposition du jury

Prof. N. Cramer, président du jury
Prof. J. Waser, directeur de thèse
Prof. S. Rousseaux, rapporteuse
Prof. A. Studer, rapporteur
Prof. J. Zhu, rapporteur

École polytechnique fédérale de Lausanne

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À mes parents,
À Qi,
À Bonbon

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Abstract

Nitrogen-containing compounds are an important class of molecules in medicinal chemistry, chemical biology, biochemistry, material sciences or environmental sciences. Organic nitrogen occurs in many forms, ranging from small building blocks such as urea, amino acids, nucleotides, to complex natural products, drug molecules, proteins, nucleic acids, among others. The transformation of easily-accessed nitrogen-containing building blocks into more complex nitrogen-containing structures is therefore important for the synthesis of bioactive compounds or functional materials.

Interested in donor-acceptor aminocyclopropanes and aminocyclobutanes, we first developed a Lewis-acid catalyzed formal [4+1] cycloaddition of donor-acceptor aminocyclobutanes with isocyanides, which resulted in the formation of cyclopentene-1,2-diamines. We then attempted to develop a formal [3+2] cycloaddition of donor-acceptor aminocyclopropanes with electron-deficient alkenes, which was mechanistically inspired by the Morita-Baylis-Hillman reaction.

Apart from the donor-acceptor system, we were also attracted by simple aminocyclopropanes without electron-withdrawing group at vicinal position. We anticipated that the incorporation of cyclopropylamine into carboxylic-containing compounds followed by ring opening functionalization reactions could be used for the synthesis of more complex products. Therefore, we first disclosed an oxidative ring-opening strategy to transform acyl, sulfonyl or carbamate protected aminocyclopropanes into 1,3-dielectrophilic carbon intermediates bearing a halide atom (Br, I) and a N,O-acetal. Replacing the alkoxy group of the N,O-acetal was achieved under acidic conditions via an elimination-addition pathway, while substitution of the halides by nucleophiles was done under basic conditions via a S_N2 pathway, generating a wide range of 1,3-difunctionalized propylamines. A proof of concept for asymmetric induction was realized using a chiral phosphoric acid as catalyst, highlighting the potential of the method in enantioselective synthesis of important building blocks.

Based on the transformation described above, we further discovered an efficient synthesis of 4-amino thiochromans starting from simple aminocyclopropanes and thiophenols through a formal [3+3] annulation reaction. This reaction proceeds under mild conditions with good functional group tolerance. The thiochroman core was formed with complete regioselectivity and modification of complex drug molecules containing an aminocyclopropane was also realized.

Next, we developed an oxidative ring-opening strategy to transform cyclopropylamides and cyclobutylamides into fluorinated imines. The imines can be isolated in their more stable hemiaminal form, with the fluorine atom installed selectively at the γ or δ position. Both cheap benzophenone with UV A light or organic and inorganic dyes with blue light could be used as photoredox catalysts to promote this process. Various fluorinated amines were then obtained by nucleophilic attack on the hemiaminals in one pot, giving access to a broad range of useful building blocks for medicinal chemistry.

Finally, we turned our attention to the synthesis of diamines, which are essential building blocks for the synthesis of agrochemicals, drugs and organic materials, yet their synthesis remains challenging, as both nitrogen moieties need to be differentiated and diverse substitution patterns (1,2-, 1,3 or 1,4) are required. We described herein a new strategy giving access to 1,2-, 1,3- and 1,4- amido azides as orthogonally protected diamines based on the nitrogen-directed diazidation of alkenes, cyclopropanes and cyclobutanes. Commercially available copper thiophene-2-carboxylate (CuTc, 2 mol%) as catalyst promoted the diazidation of both π and σ C-C bonds within 10 minutes in presence of readily available oxidants and trimethylsilyl azide. Selective substitution of the formed α-amino azide by carbon nucleophiles (electron-rich aromatic compounds, malonate, organosilicon, organoboron, organozinc and

organomagnesium compounds) was achieved in a one-pot fashion, leading to the formation of 1,2-, 1,3- and 1,4-diamines with the amino groups protected orthogonally as an amide/carbamate and an azide.

In summary, one new synthetic method based on the use of donor-acceptor substituted strained rings, as well as four novel transformations of simple aminocyclopropanes have been developed in this thesis: a formal [4+1] cycloaddition of donor-acceptor aminocyclobutanes with isocyanides; a ring-opening halogenation (iodination, bromination) inspired by the Hofmann-Löffler-Freytag reaction; an efficient synthesis of 4-amino thiochromans through a formal [3+3] cycloaddition; an oxidative fluorination enabled by photoredox catalysis; An efficient synthesis of 1,2-, 1,3- and 1,4-diamines from enamides, aminocyclopropanes and aminocyclobutanes by a copper-catalyzed diazidation-nucleophilic substitution strategy. Other unsuccessful efforts over the last four years have also been described, together with some preliminary results of ring-opening cyanation and arylation reactions.

Keywords: aminocyclopropanes, ring-opening, halogenation, thiochromans, photoredox catalysis, copper catalysis, diamines.

Résumé

Les molécules azotées sont une classe importante de composés en chimie médicinale, biologie chimique, biochimie, sciences des matériaux et sciences de l'environnement. L'atome d'azote est retrouvé sous diverses formes, allant de petits éléments tels que l'urée, les acides aminés, les nucléotides, à des produits naturels complexes, des composés bioactifs, des protéines, des acides nucléiques etc. La transformation de synthons azotés facilement accessibles en structures plus complexes est donc primordiale pour la synthèse de composés bioactifs ou de matériaux fonctionnels.

Avec l'intérêt de notre groupe de recherche pour les aminocyclopropanes et les aminocyclobutanes donneurs-accepteurs, nous avons d'abord développé une cycloaddition formelle [4+1] d'aminocyclobutanes donneurs-accepteurs avec des isocyanures catalysée par un acide de Lewis, afin de générer des cyclopentène-1,2-diamines. Nous avons ensuite tenté de développer une cycloaddition formelle [3+2] d'aminocyclopropanes donneurs-accepteurs avec des alcènes déficients en électrons. Le mécanisme de la réaction de Morita-Baylis-Hillman nous a directement inspiré pour le développement de cette méthodologie.

Nous avons également été attirés par les aminocyclopropanes. Nous avons pensé que l'incorporation de cyclopropylamine dans des composés contenant des groupes carboxyliques suivie de réactions de fonctionnalisation par ouverture de cycle puisse être utilisée pour la synthèse de produits plus complexes. En effet, nous avons d'abord développé une stratégie d'ouverture de cycle oxydative afin de transformer des aminocyclopropanes, protégés par des groupements acyl, sulfonyl ou carbamate, en intermédiaires carbonés 1,3-diélectrophiles portant un atome d'halogénure (Br, I) et un N,O-acétal. Le remplacement du groupe alcoxy du N,O-acétal a pu être réalisé dans des conditions acides via une séquence d'élimination-addition, tandis que la substitution des halogénures par des nucléophiles a pu être effectuée dans des conditions basiques via une réaction de type S_N2, générant une large gamme de 1,3 -propylamines difonctionnalisées. Une preuve de concept pour l'induction asymétrique a été réalisée en utilisant un acide phosphorique chiral comme catalyseur, mettant en évidence le potentiel de la méthode dans la synthèse énantiosélective de synthons importants.

Sur la base de la transformation décrite ci-dessus, nous avons développé une synthèse efficace de 4-amino thiochromanes via une réaction d'annulation formelle[3+3] de simples aminocyclopropanes et thiophénols. Cette réaction se déroule dans des conditions douces avec une bonne tolérance aux groupes fonctionnels. Le thiochromane est formé avec une régiosélectivité complète. Une modification de molécules bioactives complexes contenant un aminocyclopropane a également été réalisée.

Ensuite, nous avons développé une stratégie d'ouverture de cycle oxydative afin de transformer des cyclopropylamides et des cyclobutylamides en imines fluorées. Les imines peuvent être isolées sous leur forme hémiaminale plus stable, l'atome de fluor étant installé sélectivement en position γ ou δ. La benzophénone, compose peu cher, en présence de lumière UV A ou les colorants organiques et inorganiques en présence de lumière bleue ont été utilisés comme catalyseurs photoredox afin de promouvoir ce processus. Diverses amines fluorées ont été obtenues par attaque nucléophile sur les hémiamines générées, sans isolation de l'intermédiaire, donnant accès à une large gamme de synthons utiles pour la chimie médicinale.

Enfin, nous avons porté notre attention sur la synthèse de diamines, éléments constitutifs essentiels de la synthèse de produits agrochimiques, de médicaments et de matières organiques. Cependant, leur synthèse reste difficile car les deux parties azotées doivent être différenciées et divers modèles de substitution (1,2 -, 1,3 ou 1,4) sont requis. Nous avons décrit une nouvelle stratégie donnant accès aux azotures 1,2-, 1,3- et 1,4-amido en tant que diamines orthogonalement protégées basée sur la diazidation dirigée par l'azote d'alcènes, de cyclopropanes et de cyclobutanes. La présence de thiophène-2-carboxylate de cuivre disponible dans le commerce (CuTc, 2 % en moles) en quantités catalytiques permet de réaliser la diazidation des liaisons C-C π et σ en 10 minutes en présence d'oxydants facilement

disponibles et d'azoture de triméthylsilyle. La substitution sélective de l'azoture -aminé formé par des nucléophiles carbonés (composés aromatiques, malonates, organosiliciés, organoborés, organozinciques et organomagnésiens riches en électrons) a ensuite été réalisée dans le même pot, conduisant à la formation de 1,2-, 1 ,3- et 1,4-diamines avec les groupes amino protégés orthogonalement sous la forme d'un amide/carbamate et d'un azoture.

En résumé, une nouvelle méthode de synthèse basée sur l'utilisation de cycles contraints substitués par des groupements donneurs-accepteurs, et quatre nouvelles transformations d'aminocyclopropanes simples ont été développées dans cette thèse : une cycloaddition formelle [4+1] d'aminocyclobutanes donneurs-accepteurs avec des isocyanures ; une halogénation par ouverture de cycle (iodation, bromation) inspirée de la réaction d'Hofmann-Löffler-Freytag ; une synthèse efficace de 4-amino thiochromanes par une cycloaddition formelle [3+3] ; une fluoration oxydative permise par catalyse photoredox ; la synthèse de 1,2-, 1,3- et 1,4-diamines à partir d'énamides, d'aminocyclopropanes et d'aminocyclobutanes par une stratégie de diazidation-substitution nucléophile catalysée par le cuivre. D'autres efforts infructueux, ainsi que quelques résultats préliminaires de réactions de cyanation et d'arylation par ouverture de cycle sont également discutés dans ce manuscript.

Mots clés : aminocyclopropanes, ouverture de cycle, halogénation, thiochromanes, catalyse photoredox, catalyse au cuivre, diamines.

Table of Contents

Abbreviations, Acronyms and Symbols

Å	angstrom
A	acceptor
Ac	acetyl
APCI	atmospheric-pressure chemical ionization
aq	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butyloxycarbonyl
BOX	bisoxazoline
br	broad
Bu	butyl
°C	degrees centigrade
calcd	calculated
cat	catalytic
δ	NMR chemical shift in ppm
D	donor
d	doublet
DA	donor-acceptor substituted
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicycloundec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DYKAT	dynamic kinetic asymmetric transformation
d.r.	diastereomeric ratio
EDG	electron-donating group
EI	electron impact ionization
equiv	equivalent
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group

g	gram
GC	gas chromatography
h	hour(s)
HIV	human immunodeficiency virus
HPLC	High Pressure Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
Hz	hertz
J	coupling constant
Kcal	kilo calories
L	liter
m	multiplet
*m*CPBA	*meta*-chloroperoxybenzoic acid
m/z	mass per electronic charge
M	molarity
Me	methyl
mg	milligram
min	minute(s)
mL	milliliter
µL	microliter
mmol	millimole
µmol	micromole
Mp	melting point
MS	molecular sieves
ν	frequency (cm^{-1})
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
OTf	triflate
p	para
Ph	phenyl
Phth	phthalimide
Piv	pivaloyl
PPA	Polyphosphoric acid
Pr	propyl
q	quartet

quant	quantitative
R_f	retention factor
rs	regioselectivity
rt	room temperature
s	singlet
S_N	nucleophilic Substitution
Succ	succinimide
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBHP	*tert*-buty hydroperoxide
*t*Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TCNE	tetracyanoethene
Teoc	2-(Trimethylsilyl)ethoxycarbonyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TMEDA	tetramethylethylenediamine
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSOTf	Trimethylsilyltrifluoromethanesulfonate
Tr	Triphenylmethyl

1

Introduction

1. Introduction

Organic chemistry plays a fundamental role in the development of modern society, which lays the foundation and inspired numerous innovations in other areas such as medicinal chemistry, chemical biology and polymer science. This discipline has matured to a brilliant and vibrant field, in just less than two centuries since the synthesis of urea from inorganic materials in 1828.[1] However, organic chemists are still faced with significant challenges, especially when in a pursuit for synthetic, material and energy efficiency. To this end, innovative new synthetic methods have been continuously developed, which may help to improve reaction results, develop alternative synthetic routes, find cheap and environmentally-benign reagents, thus leading to the formation of target molecules at minimum economic and ecological costs.

Given the prevalence of the nitrogen element in organisms, drug molecules as well as materials, novel methodologies involving the conversion of nitrogen-containing compounds to higher value-added products would be desired and valuable. Compared with introduction of an external amino group by amination reaction, the direct conversion of nitrogen-containing compounds has several advantages: first, nitrogen-containing compounds as cheap building blocks can be found in numerous organic or bio-molecules, from amino acids or nucleic acids to small molecules such as anilines, amines and nitrogen-containing heterocycles; second, the pre-existing nitrogen atom can usually act as activating group, which facilitates further transformations. Therefore, tremendous efforts have been devoted in the past for studying the conversion of nitrogen-containing compounds and many classical reactions have been discovered and named after the discoverers or developers, such as the Hofmann-Löffler-Freytag reaction, the Kulinkovich-de Meijere reaction, the Minisci reaction, aza-Wittig rearrangement, the Meisenheimer rearrangement, the Hofmann rearrangement, the Ciamician-Dennstedt rearrangement, the Sommelet-Hauser rearrangement along with others.

Our group has been particularly interested in studying the reactions of strained rings with an amino group, and progress has been achieved in the last decade in the area of Donor-Acceptor aminocyclopropanes (DA aminocyclopropanes).[2] For example, DA aminocyclopropanes have been shown to act as nitrogen-substituted 1,3-zwitterions in the presence of a Lewis acid, which can readily participate in annulations with carbonyls and enol ethers etc., or be involved in ring-opening transformations with nucleophiles. Enantioselective transformations using DA aminocyclopropanes as substrates have also been described several times by exploiting copper/chiral ligand catalytic systems. However, only limited success has been obtained for the conversion of DA aminocyclobutanes. Our group has reported an efficient synthesis of DA aminocyclobutanes as well as subsequent [4+2] annulations with carbonyls and enol ethers.

We first tried to expand the type of reactions for DA aminocyclobutanes by developing a novel [4+1] annulation with isocyanides. Inspired by the classical Baylis-Hillman reaction, we also exploited the possibility of developing a formal [3+2] cycloaddition of DA aminocyclopropanes with electron-deficient alkenes. On the other side, although DA aminocyclopropanes and aminocyclobutanes exhibit excellent reactivities, it takes extra steps to remove the acceptor groups or to transform them into other functionalities. Having this in mind, we tried to get rid of these acceptor groups by developing novel transformations for acyl-protected aminocyclopropanes and aminocyclobutanes.

[1] Clayden, J.; Greeves, N.; Warren, S. (2012). Organic Chemistry (2nd ed.). Oxford University Press.
[2] de Nanteuil, F.; De Simone, F.; Frei, R.; Benfatti, F.; Serrano, E.; Waser, J. *Chem. Commun.* **2014**, *50*, 10912.

Therefore, in this thesis I will describe the ring-opening transformations involving nitrogen-substituted cyclopropanes and cyclobutanes. In the introduction part, I will first give a brief description about the properties of cyclopropane and cyclobutane (section 1.1), followed by an in-depth introduction of DA aminocyclopropanes and aminocyclobutanes (section 1.2). Subsequently, I will focus on the current methodologies for the activation of simple aminocyclopropanes (section 1.3), and finally on the generation and reactivity of nitrogen-centered radical (section 1.4). The main part will discuss about annulations of DA aminocyclopropanes/aminocyclobutanes (Chapter 2), followed by ring-opening difunctionalization reactions of simple aminocyclopropanes/aminocyclobutanes (Chapter 3). After a short conclusion and outlook section, the last two chapters of the thesis will be a comprehensive experimental part.

1.1 Cyclopropane and cyclobutane

Cyclopropane was first discovered and assigned with the correct molecular formula C_3H_6 in 1882 by August Freundand. It is an anaesthetic but has now been superseded by other agents.[3] Cyclobutane was first synthesized in 1907 by James Bruce and Richard Willstätter.[4] Derivatives of both cyclopropane and cyclobutane are important in organic, medicinal and polymer chemistry. For example, abacavir (**1**) is a medication used to prevent and treat HIV/AIDS;[5] saxagliptin (**2**) is part of a class of dipeptidyl peptidase-4 (DPP-4) inhibitors;[6] cyclobut-G (**3**) has potential utility for the therapy of AIDS;[7] and lannotinidine F (**4**) is a natural product (Figure 1).[8]

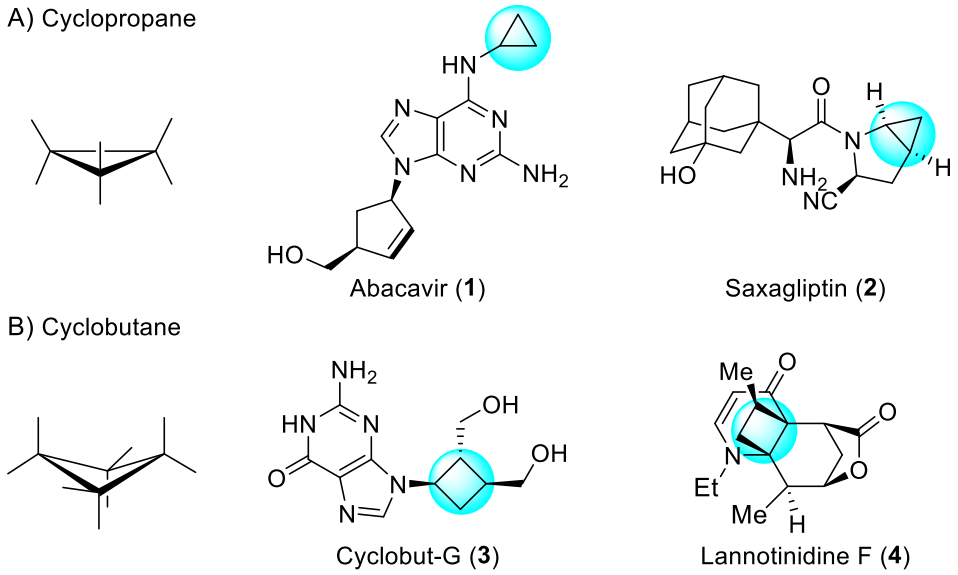

Figure 1. Conformation of cyclopropane/cyclobutane and selected compounds with biological activities.

Among the large family of cycloalkanes, cyclopropanes and cyclobutanes are two distinct members because of the ring strain as well as the rigid structure, which allow conformation control and selective

[3] The Chemistry of the Cyclopropyl Group (Ed.:Z. Rappoport), Wiley, New York, **1987**.
[4] The Chemistry of the Cyclobutanes (Eds.:Z. Rappoport, J. F. Liebman), Wiley, Chichester, **2005**.
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[6] Ali, S.; Fonseca, V. *Expert. Opin. Drug. Saf.* **2013**, *12*, 103.
[7] Norbeck, D, W.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J. J.; Erickson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya. H. *J. Med. Chem.* **1990**, *33*, 1281.
[8] Koyama, K.; Morita, H.; Hirasawa, Y.; Yoshinaga, M.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Tetrahedron* **2005**, *61*, 3681.

interaction with biomolecules. In cycloalkanes, the carbon atoms are sp^3 hybridized, which means the ideal bond angle is 109.5º. However, for cyclopropane, the bond angle is 60º. The strain energy of cyclopropane is 27.5 kcal/mol, the majority of which results from the deviation of bond angles from their normal values, but there is also expected to be a significant contribution from the eclipsing C-H interactions across C-C bonds forced by the planar structure.[9]

To explain the high reactivity of cyclopropane, thermodynamics analysis is not sufficient and three different models can be taken into account in order to describe its electronic configuration:

- The Coulson-Moffitt model describes cyclopropane as formed by three sp^3-hybridized methylene groups, which are pointed ca. 22° outwards from the axis connecting the nuclei, resulting in poorer overlap in comparison to the C-C bond of ethane (Figure 2A).[10] For this reason, the bonds are often called "bent".
- The Walsh model considers cyclopropane as made up of three sp^2-hybridized methylene groups (Figure 2B).[11] In this model, the molecular orbital diagram is constructed by combining sp^2 orbitals with three p-orbitals. The poor overlap of the CH_2 orbitals is an explanation of the angular strain and the olefin-like reactivity.
- The Dewar model considers the six electron of the C-C bonds as aromatic.[12] This explains properties such as the upfield NMR shift of the protons of cyclopropane, or its reactivity towards electrophiles.

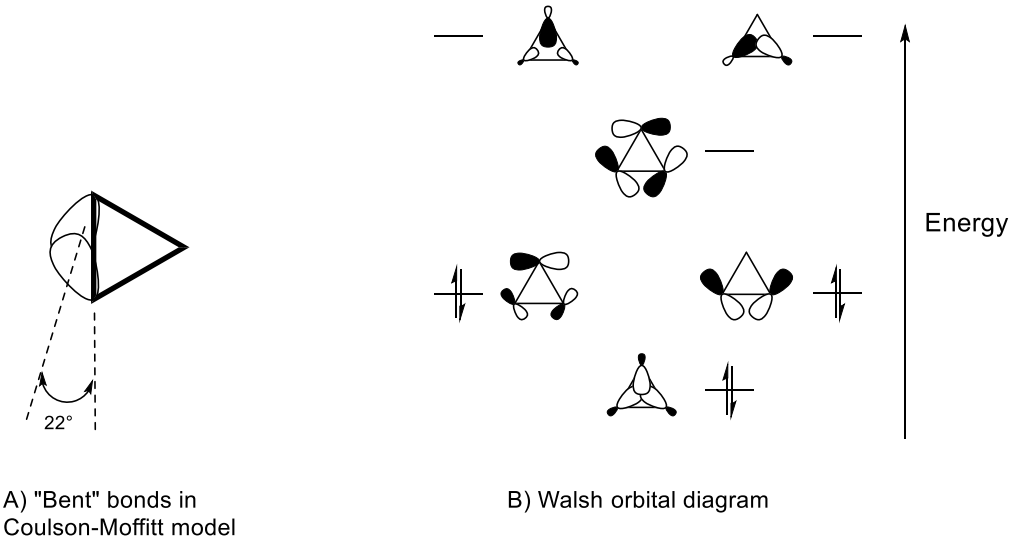


Figure 2. Models describing bonding in cyclopropane: A) Coulson-Moffitt. B) Walsh.

For cyclobutane, the bond angle is 88º rather than 90º as expected in a square planar structure. This implies that the four carbon atoms are not coplanar. Instead the ring typically adopts a folded or 'puckered' conformation (Figure 3A).[13] In this way some of the eclipsing interactions are reduced. The strain energy of cyclobutane is 26.5 kcal/mol, slightly lower than that of cyclopropane. The Coulson-Moffitt model can also be applied to cyclobutane but the deviation angle is much smaller than that of cyclopropane, with a value of 6.7° (Figure 3B). In contrast to cyclopropane, which has shorter bond

[9] Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*. **2006**, 100.
[10] Coulson, C. A.; Moffitt, W. E., *J. Chem. Phys.* **1947**, *15*, 151.
[11] a) Walsh, A. D., *Nature* **1947**, *159*, 712. b) Walsh, A. D., *Trans. Far. Soc.* **1949**, *45*, 179.
[12] Dewar, M. J. S., *J. Am. Chem. Soc.* **1984**, *106*, 669.
[13] Bartell, L. S.; Andersen, B. *J. Chem. Soc. Chem. Commun.* **1973**, 786.

length than linear alkanes, cyclobutane has longer bond length and this can be explained by the presence of C-C transannular interactions (Figure 3C).

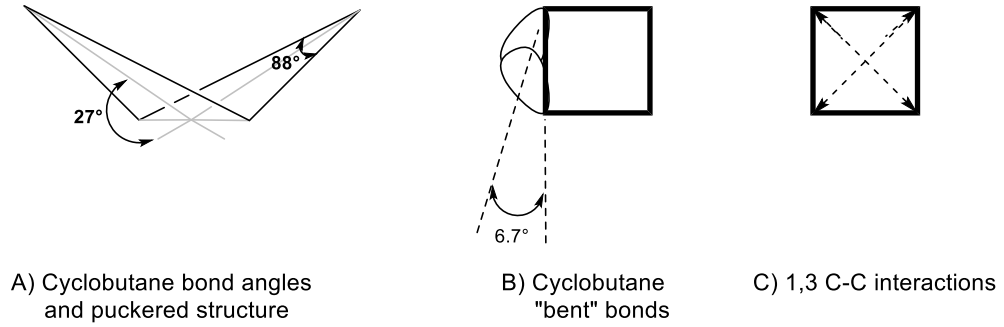


Figure 3. Structure of cyclobutane.

The strained energy inherent to cyclopropanes and cyclobutanes is a very powerful driving force for ring-opening reactions. However, under standard conditions of temperature and pressure, these molecules stay relatively inert. Therefore, finding new methodologies for activation of cyclopropanes and cyclobutanes is crucial in order to harness the ring strain. For more than one decade, our group has been working on the development of new catalytic reactions involving strained rings, with a particular interest in the use of a nitrogen atom as activating substituent, i.e., aminocyclopropanes and aminocyclobutanes.

1.2 Background of DA aminocyclopropanes/aminocyclobutanes

For a fast entry into molecular complexity, ring expansion of cyclopropanes and cyclobutanes is an attractive strategy because of the formation of multiple bonds after the cleavage of one C-C bond. Nevertheless, unsubstituted cyclopropanes and cyclobutanes are still inert and their reactivity needs to be further increased by the introduction of substituents on the ring. In order to make the heterolysis of C-C bonds easier to take place, polarization of the bond could be achieved simply by introducing electron-withdrawing groups and electron-donating groups on each side of the C-C bond (Figure 4). In this way, 1,2 donor-acceptor substituted ring systems are created (DA cyclopropanes and DA cyclobutanes). When it comes to the chemistry of DA cyclobutanes, DA cyclopropanes should always be referred to first because they share some similarities in reactivity and moreover, the chemistry of cyclopropanes is more thoroughly studied. In the presence of a Lewis acid catalyst, 1,3-formal dipoles could be generated from DA cyclopropanes, which could be further trapped by dipolarophiles to form cyclic products, or trapped by separate nucleophiles and electrophiles to form acyclic products (Figure 4a).[14] Similarly, 1,4-formal dipoles are expected to be generated from DA cyclobutanes (Figure 4b). In general, fewer types of donor and acceptor groups have been reported for DA cyclobutanes when compared to the chemistry of DA cyclopropanes.

[14] a) Reissig, H.-U.; Hirsch, E. *Angew. Chem. Int. Ed.* **1980**, *19*, 813. b) Reissig, H.-U.; Zimmer, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 5009. c) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321.

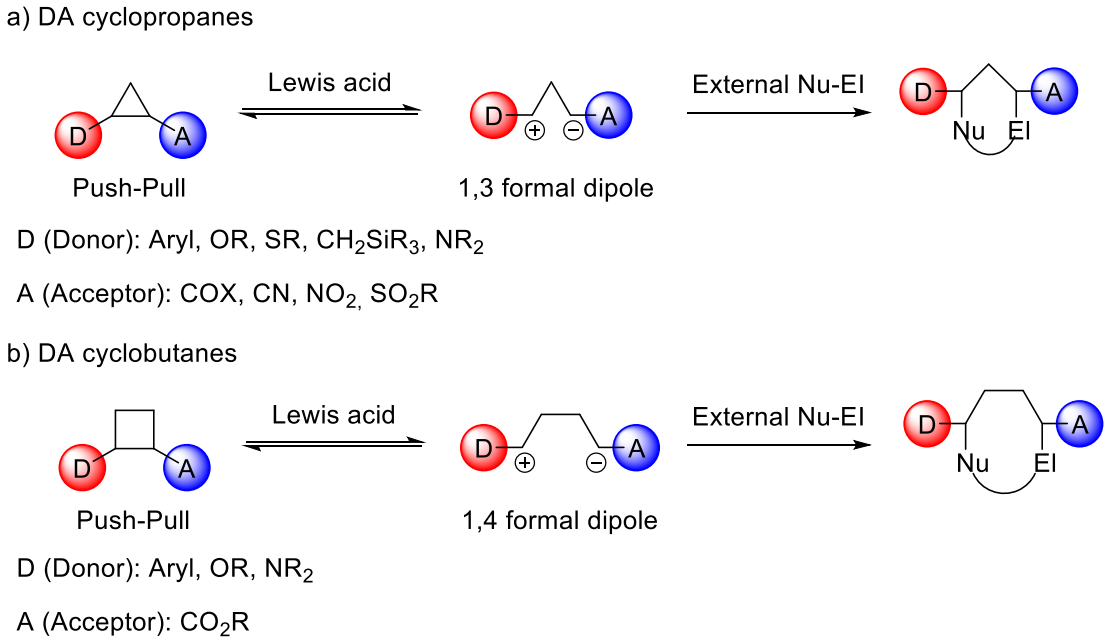


Figure 4. Activation and annulation of DA cyclopropanes and cyclobutanes.

1.2.1 Synthesis and reactivity of DA aminocyclopropanes[15]

The chemistry of donor-acceptor substituted cyclopropanes (DA cyclopropanes)[16] has underwent an impressive renaissance in the last two decades because of their versatility either as building blocks in organic synthesis[17] or as substrates for asymmetric catalysis.[18] As a subclass of DA cyclopropanes, DA cyclopropanes with an amino group as donor (DA aminocyclopropanes) share many reactivity similarities with aryl- and alkoxy-substituted DA cyclopropanes. In addition, the importance of the nitrogen atom in biomolecules and pharmaceutical compounds makes aminocyclopropanes (acceptor-substituted or not) attractive starting materials for accessing more value-added products[2,19]. For example, with the formal [3+2] cycloaddition methods described in this chapter, cyclopentanes with an amino group can be synthesized. Such structures can be found in many bioactive compounds such as the anti-HIV drug Abacavir (**5**), and Ramipril (**6**), which is used to treat high blood pressure, heart failure and diabetic kidney disease. Natural products can also be accessed by using DA aminocyclopropanes as key

[15] This section has been adapted as a book chapter titled "Donor-Acceptor Cyclopropanes with an Amino Group as Donor", which is an invited contribution for the Wiley book "Donor-Acceptor Cyclopropanes in Organic Synthesis".

[16] a) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504. b) O'Connor, N. R.; Wood, J. L.; Stoltz, B. M. *Isr. J. Chem.* **2016**, *56*, 431.

[17] a) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73. b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. c) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. d) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447. e) Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Biomol. Chem.* **2015**, *13*, 655. f) Reiser, O. *Isr. J. Chem.* **2016**, *56*, 531. g) Ivanova, O. A.; Trushkov, I. V. *Chem. Rec.* **2019**, *19,* 2189. h) Werz, D. B.; Biju, A. T. *Angew. Chem. Int. Ed.* **2020**, *59,* 3385.

[18] a) Wang, L.; Tang, Y. *Isr. J. Chem.* **2016**, *56*, 463. b) Pirenne, V.; Muriel, B.; Waser, J. *Chem. Rev.* **2021**, *121,* 227. c) Xia, Y.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed.* **2021**, *60,* 9192. d) Cohen, Y. A.; Marek, I. *Chem. Rev.* **2021**, *121,* 140.

[19] a) Rassadin, V. A.; Six, Y. *Tetrahedron* **2016**, *72*, 4701. b) Sokolova, O. O.; Bower, J. F. *Chem. Rev.* **2021**, *121,* 80.

intermediates in cyclization and annulation reactions, such as the alkaloids Goniomitine (**7**) and Aspidospermidine (**8**) (Figure 5).[20]

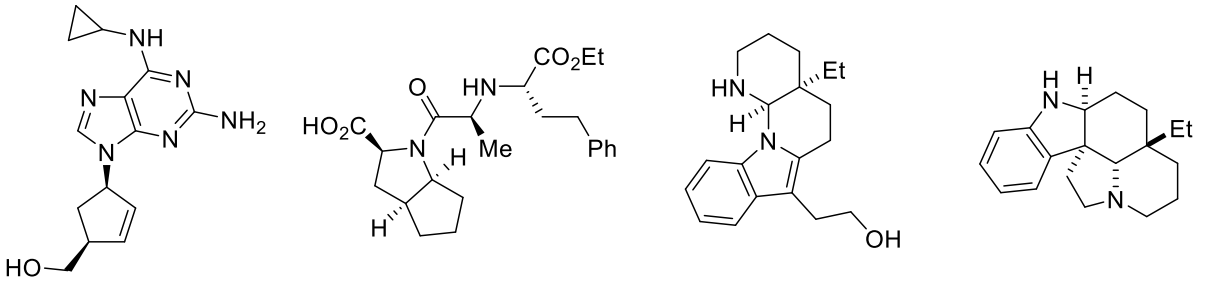


Figure 5. Examples of nitrogen-containing synthetic bioactive compounds and natural products.

In general, based on the distribution of donor and acceptor groups on the cyclopropyl ring, DA aminocyclopropanes can be divided into two different types: geminal DA aminocyclopropanes and vicinal DA aminocyclopropanes (Figure 6A).

The former lacks synergistic activation for the C-C bond of the cyclopropyl ring and is of importance mostly as rigid non-natural amino acid cores,[21] so it will not be covered in this chapter. The vicinal DA aminocyclopropanes can be considered as 1,3-dipolar synthons because C1-C2 bond is activated due to the electronic push pull effect. 2-Amino cyclopropanecarboxylic acid (**10**),[22] the simplest example of vicinal DA aminocyclopropanes, has two stereogenic centers and therefore four isomeric forms.[23] The high reactivity of vicinal DA aminocyclopropanes can compromise their stability. For example, **10** is prone to undergo ring opening, leading to aldehyde **11** in the presence of water (Figure 6B).[24] Therefore, protection of the nitrogen atom to reduce its electron density is necessary in order to have a good balance between reactivity and stability. Common protecting groups include succinimide, phthalimide, an acyl group, carbamates, sulfonamides, imines, nitrogen-containing heterocycles etc. The acceptor is usually one or two electron-withdrawing groups, which can be an ester, an aldehyde/ketone, a cyanide, a nitro group etc. Based on the number of donor/acceptor groups and their distribution on the cyclopropyl ring, DA aminocyclopropanes described in this chapter can be classified as mono-acceptor aminocyclopropane, *gem*-di-acceptor aminocyclopropane, *vic*-di-acceptor aminocyclopropane or *meso* aminocyclopropane (Figure 6C).

[20] De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem. Int. Ed.* **2010***, 49*, 5767.

[21] a) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493. b) Cativiela, C.; Ordonez, M. *Tetrahedron Asymmetry* **2009**, *20*, 1.

[22] Fulop, F. *Chem. Rev.* **2001**, *101*, 2181.

[23] Gnad, F.; Reiser, O. *Chem. Rev.* **2003***, 103*, 1603.

[24] Gu, P.; Wu, X.-P.; Su, Y.; Xue, P.; Li, X.-Q.; Gong, B.-L.; Li, R. *Tetrahedron Lett.* **2013**, *54*, 4957.

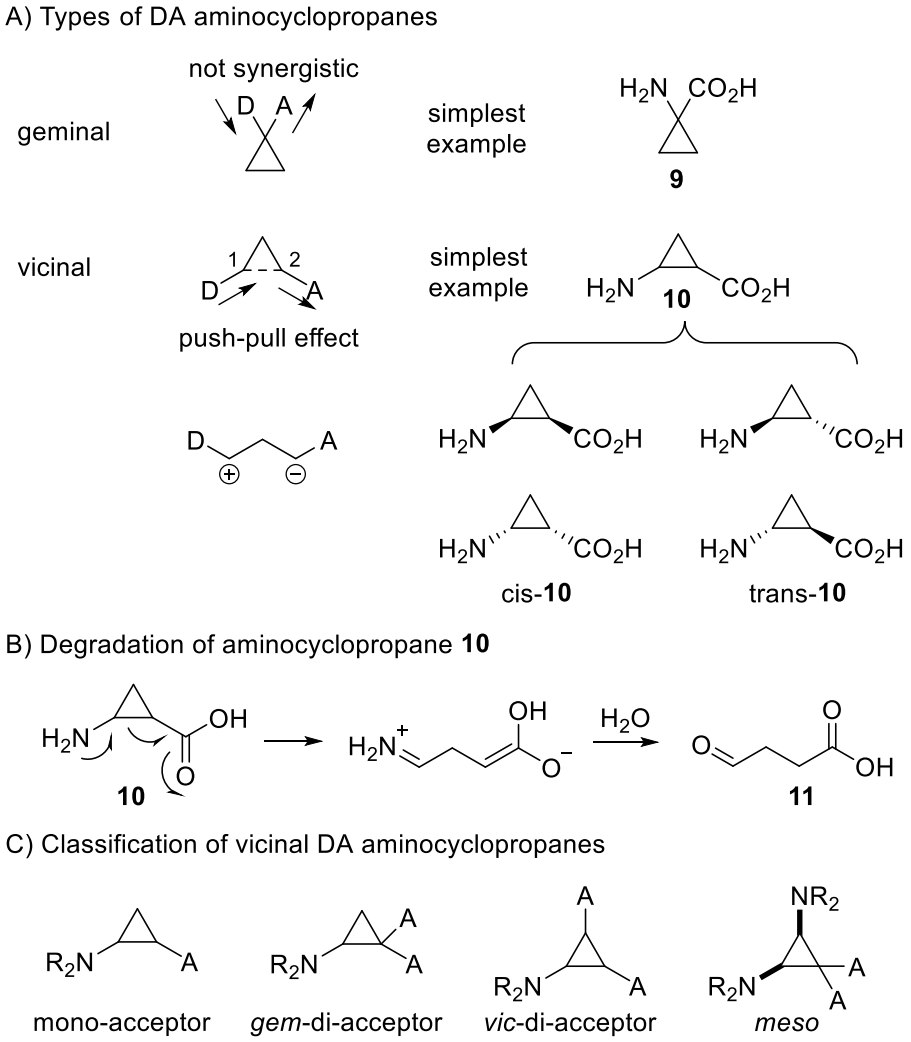


Figure 6. A general description of DA aminocyclopropanes.

We will start by giving a brief summary of the synthetic methods to access DA aminocyclopropanes (1.2.1.1). Their use as starting materials either in ring opening reactions (1.2.1.2) or in formal cycloadditions (1.2.1.3) will then be described in details.

1.2.1.1 Synthesis of DA aminocyclopropanes

DA cyclopropanes are most commonly prepared by addition of carbenes or their equivalents to alkenes, namely formal [2+1] cycloaddition or cyclopropanation. In this case, there are three different routes for constructing a cyclopropyl ring with alkene partners being β-dehydroamino acids (disconnection a), enamines (disconnection b) or acrylates (disconnection c)[23]. It is also possible that all three carbon atoms come from one reaction partner, in which case there are two disconnections for introducing either an amino group (disconnection d) or an acceptor (disconnection e). For the introduction of an amino group, there are two reported routes depending on the substrate: a cyclopropene bearing an acceptor group (disconnection d1) or 2-haloethylidene malonate (disconnection d2). Therefore, based on the starting materials, there are currently six straightforward routes for the synthesis of DA aminocyclopropanes (Figure 7). Each route will be briefly introduced below with selected examples.

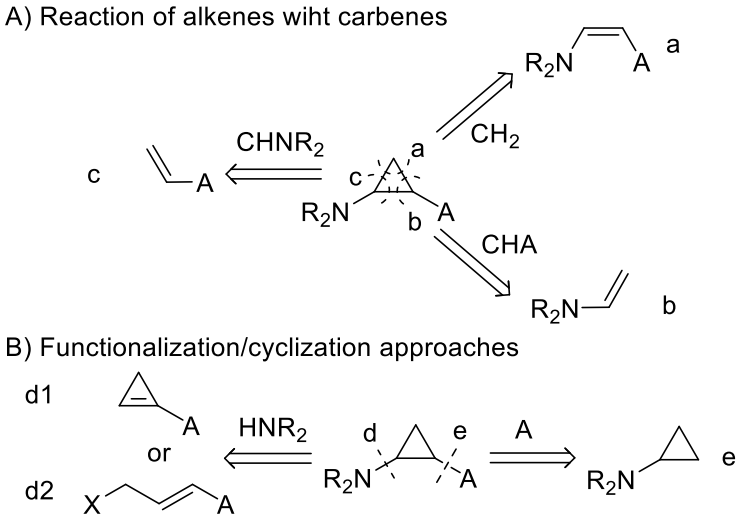
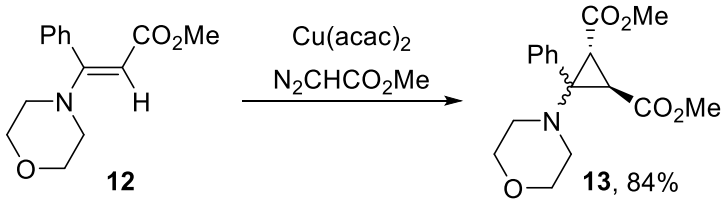


Figure 7. Retro-synthetic analysis of DA aminocyclopropanes.

Route a: Synthesis of DA aminocyclopropanes from β-dehydroamino acids

This cyclopropanation of donor-acceptor-substituted olefins - β-dehydroamino acids - with a carbene gives DA aminocyclopropanes. The most convenient source of carbene equivalents is diazo compounds, which readily generate a carbenoid after reaction with a transition metal catalyst. Acceptor-substituted diazoalkanes were frequently used for the synthesis of DA cyclopropanes, because they can be prepared easily and subsequent cyclopropanation with electron-rich alkenes is efficient. For example, *vic*-di-acceptor aminocyclopropane **13** can be synthesized by the copper-catalyzed cyclopropanation of **12** with diazoester in an intermolecular fashion (Eq. 1).[25] Intramolecular cyclopropanation has also been reported for producing bicyclic *vic*-di-acceptor aminocyclopropanes.[26]

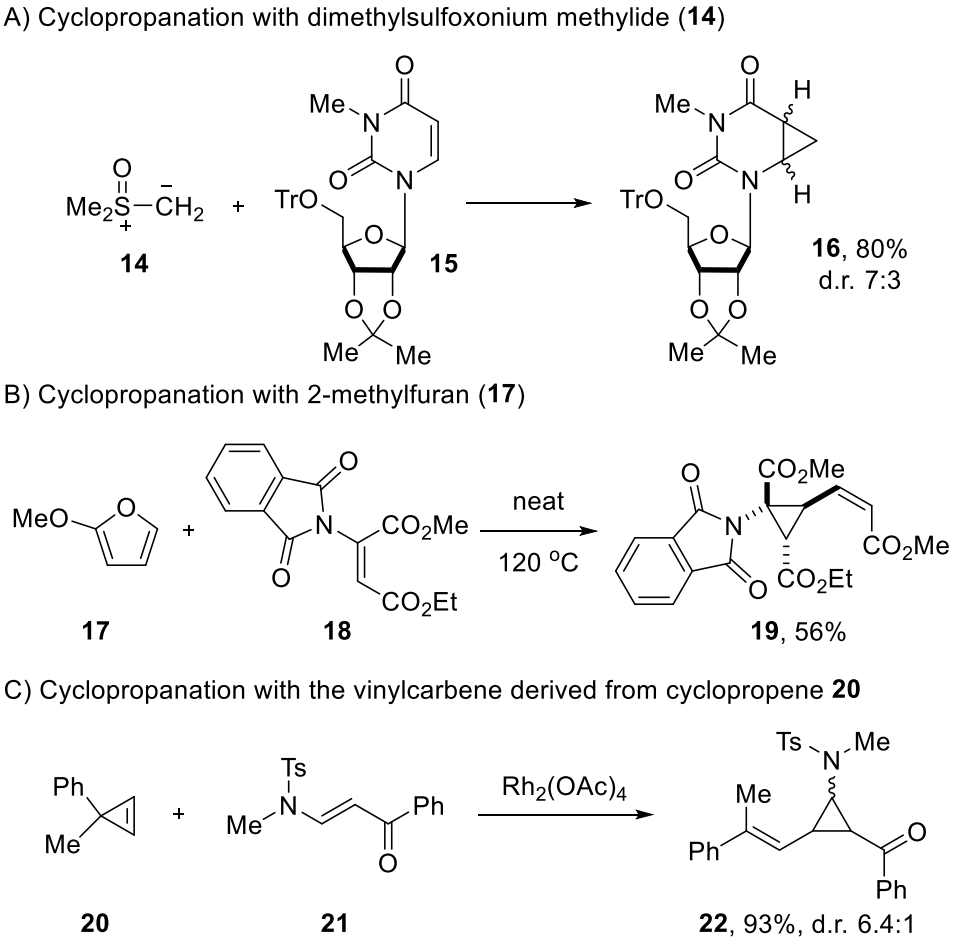


Equation 1. Copper-catalyzed cyclopropanation of **12**.

A Corey-Chaykovsky reaction with dimethylsulfoxonium methylide **14** can also be used to construct the cyclopropyl ring. For example, starting from protected uridine **15**, uridine analog **16** containing a cyclopropyl ring was synthesized and isolated in 80% yield as a mixture of diastereoisomers in a ratio of 7:3 (Scheme 1A).[27] 2-Methoxyfuran **17** has also been studied for the cyclopropanation with electron-deficient olefins[28] such as substrate **18**,[29] although no synthetic utility of the corresponding products has been disclosed so far (Scheme 1B). In 2019, the Loh group reported a cyclopropanation reaction of enaminone **21** with a vinylcarbene intermediate, which was generated *in situ* from cyclopropene **20**

[25] Maas, G.; Mueller, A. *J. Prakt. Chem*. **1998**, *340*, 315.
[26] Gharpure, S. J.; Vijayasree, U.; Reddy, S. R. B. *Org. Biomol. Chem.* **2012**, *10*, 1735.
[27] Kunieda, T.; Witkop, B. *J. Am. Chem. Soc.* **1969**, *91*, 7751.
[28] Huisgen, R.; Mloston, G. *Tetrahedron Lett.* **1994**, *35*, 4981.
[29] Manabe, A.; Matsumoto, R.; Shinada, T. *Synlett* **2015**, *26*, 1710.

(Scheme 1C).[30] The obtained product **22** was then subject to hydrolysis under acidic conditions and α–vinyl aldehyde was formed after ring opening.



Scheme 1. Cyclopropanation of *β*-dehydroamino acids with different reagents.

Route b: Synthesis of DA aminocyclopropanes from enamines

Cyclopropanation of enamines with acceptor-substituted diazoalkanes is a straightforward way for synthesizing DA aminocyclopropanes. *N*-protected pyrroles **23** were versatile starting materials to react with diazoacetates for the synthesis of DA aminocyclopropanes **24**-**25** and exclusive formation of the *exo* diastereoisomer was observed when using carbamate protecting groups (Scheme 2A).[31] Asymmetric versions of this reaction under different catalytic systems were also reported by the Reiser group.[32] In 2012, the Boysen group reported an enantioselective cyclopropanation of *N*-Boc indole **26** by using CuOTf as catalyst together with a carbohydrate-based ligand 3-*O*-Ac glucoBOX (Scheme 2B).[33] As the result, the corresponding indole-derived DA aminocyclopropane **27** was obtained in good enantioselectivity In 2017, an intramolecular enantioselective cyclopropanation of indoles was reported

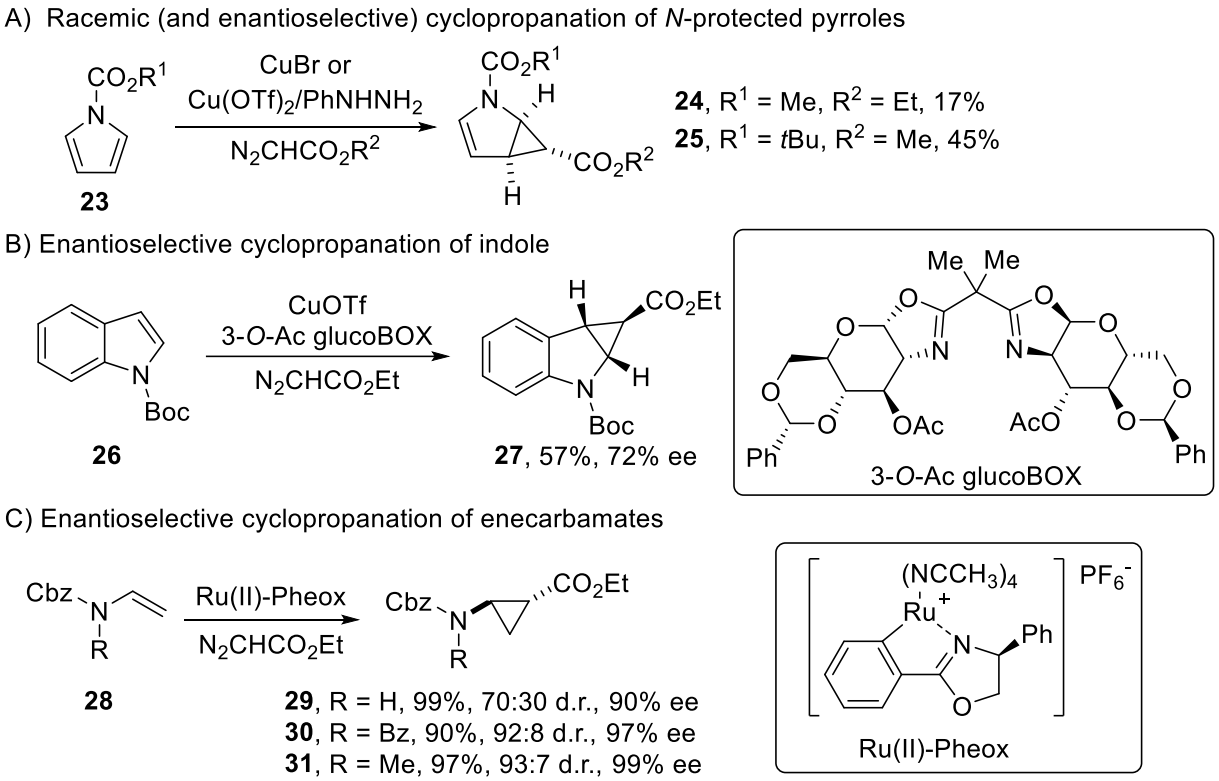
[30] Chen, J.; Guo, P.; Zhang, J.; Rong, J.; Sun, W.; Jiang, Y.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2019**, *58*, 12674.

[31] a) Tanny, S. R.; Grossman, J.; Fowler, F. W. *J. Am. Chem. Soc.* **1972**, *94*, 6495. b) Bubert, C.; Cabrele, C.; Reiser, O. *Synlett* **1997**, *1997*, 827.

[32] a) Schinnerl, M.; Böhm, C.; Seitz, M.; Reiser, O. *Tetrahedron Asymmetry* **2003**, *14*, 765. b) Pilsl, L. K. A.; Ertl, T.; Reiser, O. *Org. Lett.* **2017**, *19*, 2754. c) Fu, J.; Wurzer, N.; Lehner, V.; Reiser, O.; Davies, H. M. L. *Org. Lett.* **2019**, *21*, 6102. d) Liu, W.; Babl, T.; Röther, A.; Reiser, O.; Davies, H. M. L. *Chem. Eur. J.* **2020**, *26*, 4236.

[33] Özüduru, G.; Schubach, T.; Boysen, M. M. K. *Org. Lett.* **2012**, *14*, 4990.

by the Zhu and Zhou groups by using copper or iron complexes with chiral spiro BOX ligands as catalysts.[34] The asymmetric cyclopropanation of acyclic vinylcarbamates **28** with diazoesters was also realized by the Iwasa group in 2013 by using a Ru(II)-Pheox catalyst, giving products such as **29**-**31** in excellent enantioselectivity (Scheme 2C).[35] However, the diastereoselectivity of the reaction depended greatly on the substrates, with higher diastereoselectivity observed for *N*,*N*-disubstituted vinylamines compared to *N*-monosubstituted vinylamines.



Scheme 2. Diastereoselective and enantioselective cyclopropanation of enamides with diazo compounds.

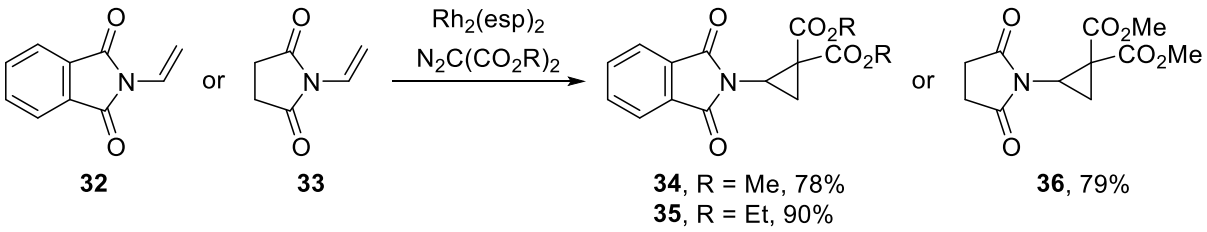
Achieving high diastereoselectivity can be difficult for the cyclopropanation of certain enamines.[36] Switching to diazomalonates allows to avoid diastereoselectivity issues, and leads to the formation of *gem*-di-acceptor aminocyclopropanes. For example, starting from *N*-vinyl-phthalimide **32** or *N*-vinyl-succinimide **33** and dialkyl diazomalonates, DA aminocyclopropanes **34**-**36** were synthesized in gram scale using 0.1 mol% $Rh_2(esp)_2$ as catalyst (Eq. 2).[37] The key point here is to adjust the push effect by using phthalimide or succinimide as donor, which decreases the electron density on nitrogen atom and therefore endows DA aminocyclopropanes **34**-**36** with good stability.

[34] Xu, H.; Li, Y.-P.; Cai, Y.; Wang, G.-P.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2017**, *139*, 7697.

[35] Chanthamath, S.; Nguyen, D. T.; Shibatomi, K.; Iwasa, S. *Org. Lett.* **2013**, *15*, 772.

[36] a) Kaufman, M. D.; Grieco, P. A. *J. Org. Chem.* **1994**, *59*, 7197. b) Dutta, P. K.; J. Chauhan, Ravva, M. K.; Sen, S. *Org. Lett.* **2019**, *21*, 2025.

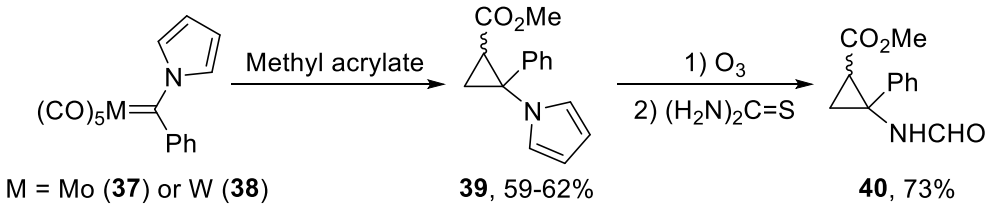
[37] a) de Nanteuil, F.; Waser, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 12075. b) de Nanteuil, F.; Serrano, E.; Perrotta, D.; Waser, J. *J. Am. Chem. Soc.* **2014**, *136*, 6239.



Equation 2. Synthesis of *gem*-di-acceptor aminocyclopropanes **34**-**36**.

Route c: Synthesis of DA aminocyclopropanes from acrylates

Synthesis of DA aminocyclopropanes starting from acrylates requires the use of aminocarbenes to assemble the cyclopropyl ring. As donor-type diazo compound having an α-amino group does not exist,[38] precedence is focused on Fischer carbenes. Amino-substituted Fischer carbenes can be easily prepared by replacing alkoxy group of alkoxycarbene complexes with amines.[39] However, the reaction between most aminocarbene complexes and electron-deficient alkenes gave only byproducts, which arose from [2+2+1] cycloaddition or ring-opening isomerization.[40] DA aminocyclopropane **39** was obtained only when using pyrrolocarbene complexes **37** or **38**, with pyrrole acting as a masked amino group.[41] Conversion of the pyrrole into other nitrogen-containing functionalities has been demonstrated by ozonolysis-reduction sequence, which provided a formamide group in **40** (Eq. 3).



Equation 3. Synthesis of DA aminocyclopropane **39** from Fischer carbenes **37**-**38**.

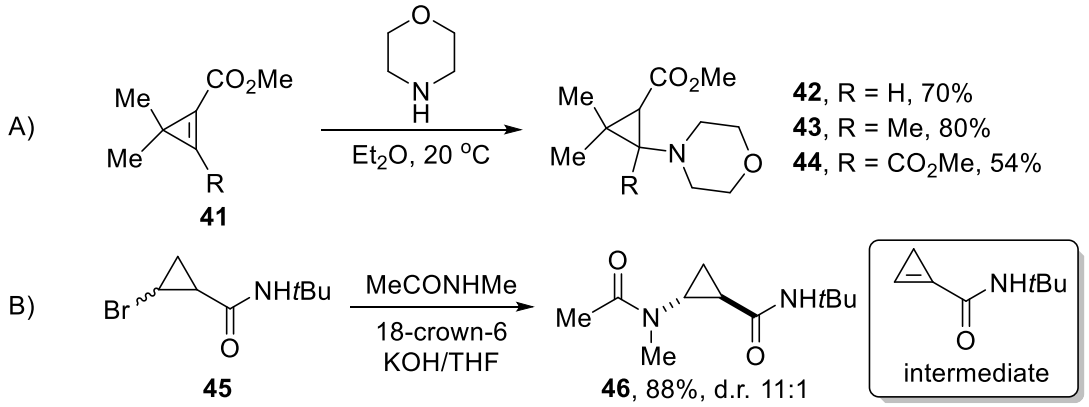
Other synthetic routes starting from simple acrylates involved several functional group interconversions, such as cyclopropanation followed by reduction of a nitro group or Curtius rearrangement of a carboxylic group.[42] These examples of multi-step syntheses from simple acrylates are less efficient and will not be discussed here.

Route d1: Synthesis of DA aminocyclopropanes from cyclopropene

In 1988, it was reported that 1,4-addition of morpholine to cyclopropene carboxylates **41** occurred readily under mild conditions to form DA aminocyclopropanes such as **42**-**44** (Scheme 3A).[43] The required cyclopropene can also be formed *in situ* from bromocyclopropane **45** after 1,2-elimination, and addition of *N*-methylacetamide furnished then DA aminocyclopropane **46** in good yield and high

[38] Zhu, D.; Chen, L.; Fan, H.; Yao, Q.; Zhu, S. *Chem. Soc. Rev.* **2020**, *49*, 908.
[39] Grotjahn, D. B.; Dötz, K. H. *Synlett* **1991**, *1991*, 381.
[40] a) Sierra, M. A.; Soderberg, B.; Lander, P. A.; Hegedus, L. S. *Organometallics* **1993**, *12*, 3769. b) Sierra, M. A.; Mancheño, M. J.; Sáez, E.; del Amo, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 6812.
[41] Merino, I.; Hegedus, L. S. *Organometallics* **1995**, *14*, 2522.
[42] a) Fan, R.; Ye, Y.; Li, W.; Wang, L. *Adv. Synth. Catal.* **2008**, *350*, 2488. b) Wheeler, J. W.; Shroff, C. C.; Stewart, W. S.; Uhm, S. J. *J. Org. Chem.* **1971**, *36*, 3356.
[43] Franck-Neumann, M.; Miesch, M.; Kempf, H. *Tetrahedron* **1988**, *44*, 2933.

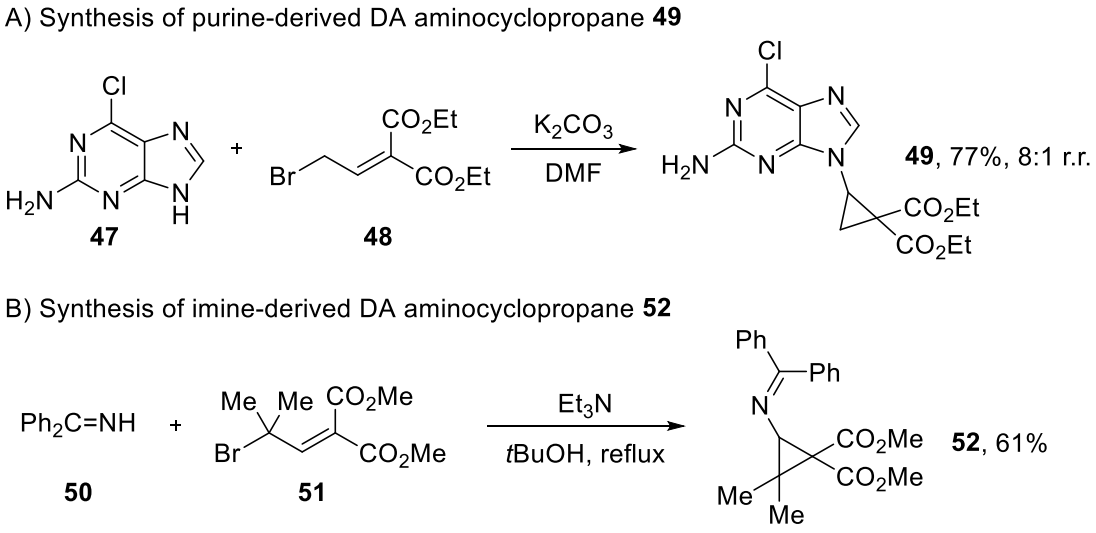
diastereoselectivity as reported by the Rubin group in 2013 (Scheme 3B).[44] In addition to amides, nitrogen-containing heterocycles, such as pyrrole, indole, pyrazole, and anilines were well tolerated in this formal substitution reaction.



Scheme 3. Addition of amines to (*in situ* formed) cyclopropenes.

Route d2: Synthesis of DA aminocyclopropanes from 2-haloethylidene malonates

2-Haloethylidene malonates could be used for a cyclopropanation reaction via an addition-substitution mechanism under basic conditions with amine nucleophiles. An elegant synthesis of purine derived DA aminocyclopropane **49** was reported by the Geen group in 1992 by mixing 2-amino-6-chloropurine **47** with 2-bromoethylidene malonate **48** under basic conditions in DMF (Scheme 4A).[45] Treating diphenylmethylidenamine **50** with 2-bromoethylidene malonate **51** in the presence of triethylamine provided **52** as a different class of DA aminocyclopropanes, as reported by the De Kimpe group in 2005 (Scheme 4B).[46]



Scheme 4. Synthesis of DA aminocyclopropanes from 2-bromoethylidene malonates.

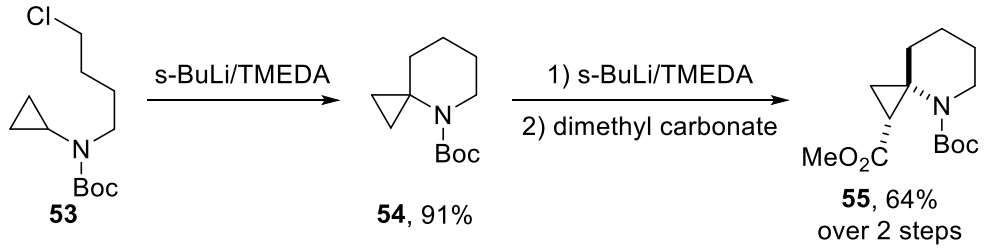
[44] Banning, J. E.; Gentillon, J.; Ryabchuk, P. G.; Prosser, A. R.; Rogers, A.; Edwards, A.; Holtzen, A.; Babkov, I. A.; Rubina, M.; Rubin, M. *J. Org. Chem.* **2013**, *78*, 7601.

[45] Geen, G. R.; Kincey, P. M.; Choudary, B. M. *Tetrahedron Lett.* **1992**, *33*, 4609.

[46] Mangelinckx, S.; De Kimpe, N. *Synlett* **2005**, *2005*, 1521.

Route e: Synthesis of DA aminocyclopropanes from cyclopropylamines

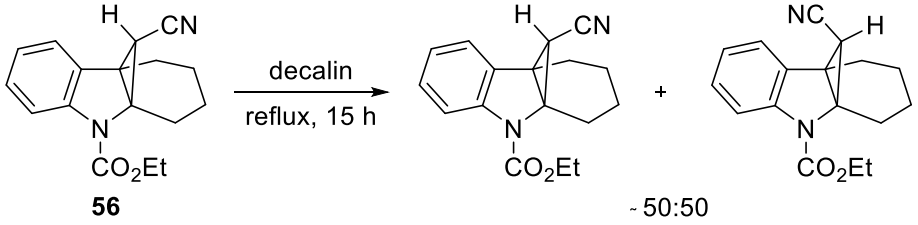
Lithiation at the β position of cyclopropylcarbamate **53** has been observed after the α position was blocked, and further treatment of dimethyl carbonate for introducing the ester group as acceptor produced DA aminocyclopropane **55**, as reported by the Beak group in 1996 (Eq. 4).[47] In contrast to other synthetic routes as shown above, *cis* DA aminocyclopropanes were obtained rather than *trans* products. This is because the β-lithiation is stereospecific: the deprotonation is directed by the carbamate group and the carbanion is stabilized by complexation of the lithium ion with the carbamate, therefore the new substituent is introduced *cis* to the carbamate group.



Equation 4. Synthesis of DA aminocyclopropane **55** by lithiation from aminocyclopropane **53**.

1.2.1.2 Ring-opening reactions of DA aminocyclopropanes

Similar to other types of DA cyclopropanes, heterolytic cleavage of the C1-C2 bond is a facile process, leading to the formation of 1,3-formal dipoles. Thermal epimerization of compounds such as **56** indicated that the ring-opening step can be reversible (Eq. 5).[48]



Equation 5. Thermal epimerization of DA aminocyclopropane **56**.

Depending on the addition of external nucleophiles or not, this section is divided into two parts describing the ring opening reactions of DA aminocyclopropanes in an intramolecular fashion or an intermolecular fashion respectively.

Intramolecular ring opening

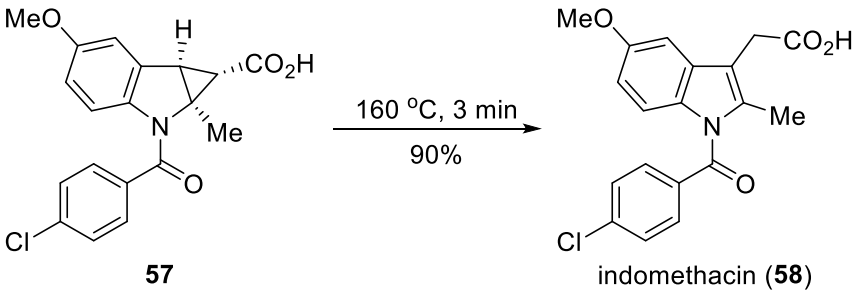
The simplest ring-opening reaction of DA aminocyclopropanes is the isomerization into enamine products. Depending on the substituents on the nitrogen atom, the isomerization can take place spontaneously with dialkyl substituents,[49] or requires some activation if the electron density on nitrogen

[47] Park, Y. S.; Beak, P. *Tetrahedron* **1996**, *52*, 12333.

[48] Ikeda, M.; Matsugashita, S.; Tabusa, F.; Tamura, Y. *J. Chem. Soc. Perkin Trans. I*, **1977**, 1166.

[49] Martin, D.; Canac, Y.; Lavallo, V.; Bertrand, G. *J. Am. Chem. Soc.* **2014**, *136*, 5023.

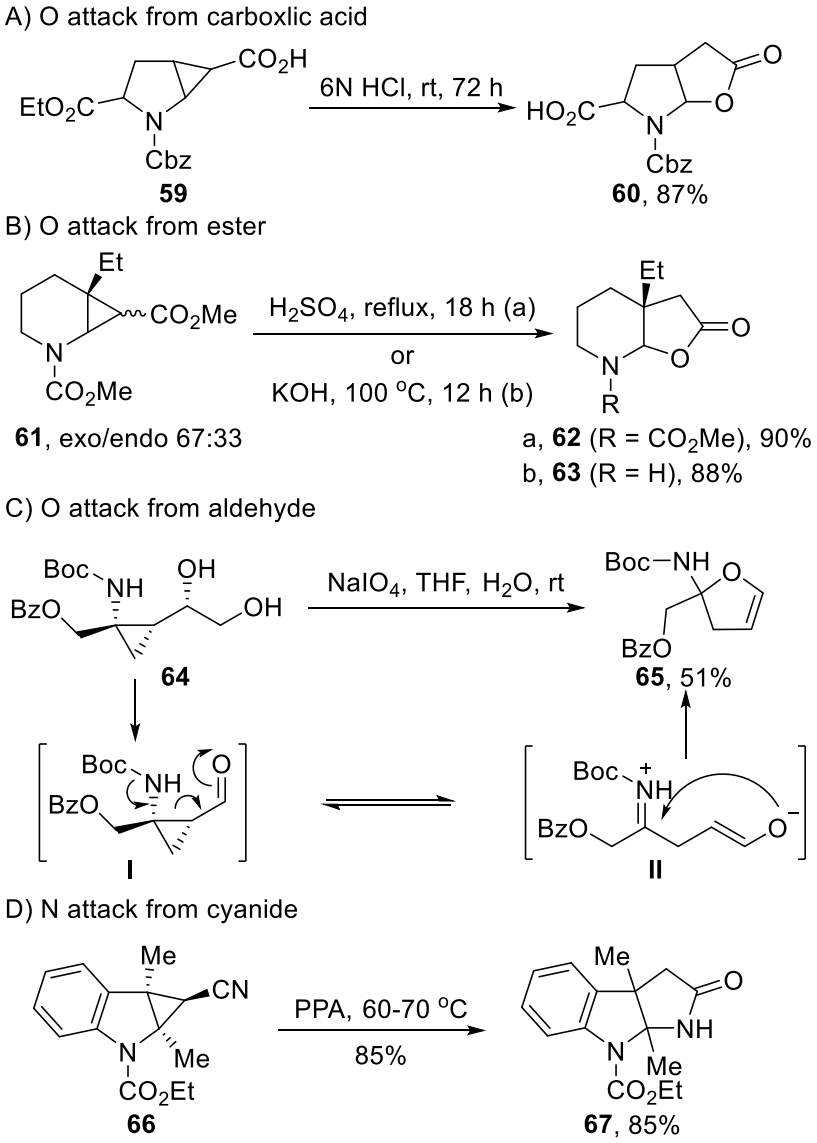
atom is decreased.[50] For example, the isomerization of DA aminocyclopropane **57** to indomethacin (**58**) was reported to occur efficiently at 160 °C (Eq. 6).



Equation 6. Thermal rearrangement of DA aminocyclopropane **57** into indomethacin.

Although some ring opening reactions took place under mild basic conditions, acidic conditions were more frequently used for the activation of DA aminocyclopropanes. In some cases of DA aminocyclopropane synthesis, the desired product was accompanied with the formation of ring-opened byproducts because of the presence of the catalyst, which could also act as Lewis acid to activate DA aminocyclopropanes.[51] Apart from isomerization into enamine, the iminium species after ring opening can also undergo deprotonation to form an imine product[33] or can be trapped by nucleophiles. Nucleophiles can be internal functional groups: DA aminocyclopropane **59** readily underwent rearrangement to givethe N,O-acetal **60**, with the carboxylic group acting as nucleophile (Scheme 5A);[52] hydrolysis of the ester group in DA aminocyclopropane **61** can also facilitate this rearrangement, resulting in the formation of **62** under acidic conditions or **63** under basic conditions (Scheme 5B);[53] After the oxidative cleavage of diol **64** by $NaIO_4$, the in-situ formed aldehyde **I** underwent rearrangement spontaneously to give **65** as product (Scheme 5C);[54] the cyanide group of **66** can also act as nucleophile under acidic conditions, leading to the formation of polycyclic product **67** (Scheme 5D).[55]

[50] a) Welstead, W. J.; Stauffer, H. F.; Sancilio, L. F. *J. Med. Chem.* **1974**, *17*, 544. b) Novikov, M. S.; Rostovskii, N. V.; Koronatov, A. N.; Zavyalov, K. V.; Zubakin, G. V.; Khlebnikov, A. F.; Starova, G. *J. Org. Chem.* **2017**, *82*, 13396.
[51] a) Salim, M.; Capretta, A. *Tetrahedron* **2000**, *56*, 8063. b) Zhang, B.; Wee, A. G. H. *Org. Biomol. Chem.* **2012**, *10*, 4597.
[52] Arenare, L.; De Caprariis, P.; Marinozzi, M.; Natalini, B.; Pellicciari, R. *Tetrahedron Lett.* **1994**, *35*, 1425.
[53] Wenkert, E.; Hudlicky, T.; Showalter, H. D. H. *J. Am. Chem. Soc.* **1978**, *100*, 4893.
[54] a) Rifé, J.; Ortuño, R. M. *Tetrahedron Asymmetry* **1999**, *10*, 4245. b) Kaschel, J.; Schneider, T. F.; Schirmer, P.; Maaß, C.; Stalke, D.; Werz, D. B. *Eur. J. Org. Chem.* **2013**, *2013*, 4539.
[55] Ikeda, M.; Matsugashita, S.; Tamura, Y. *J. Chem. Soc. Perkin Trans. I*, **1977**, 1770.



Scheme 5. Ring opening followed by reaction with internal nucleophiles.

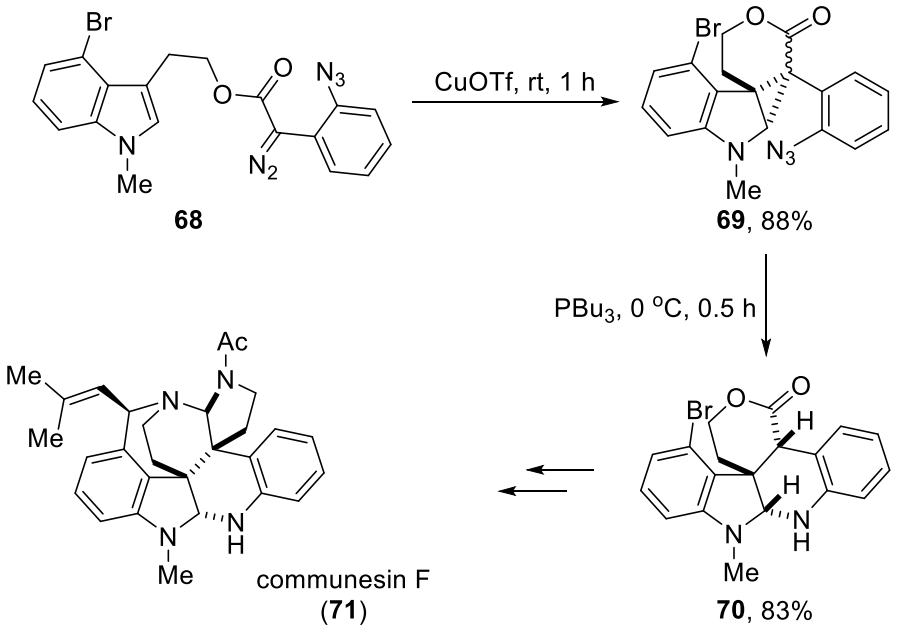
It is important to note that these ring-opening reactions can be applied in the synthesis of complex molecules. For example, based on the reaction illustrated in Scheme 5B, the Wenkert group reported in the 1978 the total synthesis of the natural products Eburnamonine and Aspidospermidine.[53] By extending this reaction to the oxygen analogue, the Wenkert group reported in 1981 the total synthesis of quebrachamine and vincadine and epivincadine.[56]

The use of other internal nucleophiles to react with the *in situ* generated iminium intermediates continues to be developed. For example, the Qin group reported in 2006 that after copper-catalyzed intramolecular cyclopropanation of **68**, reduction of a pendant azido group in **69** by tributylphosphine released a free amino group, which then attacked the iminium after cyclopropane ring opening (Scheme 6).[57] The desired product **70** was obtained in 83% yield as a single diastereoisomer, which was a key intermediate in the total synthesis of the natural product communesin F (**71**). This application showcased the potential

[56] Wenkert, E.; Halls, T. D. J.; Kwart, L. D.; Magnusson, G.; Showalter, H. D. H. *Tetrahedron* **1981**, *37*, 4017.

[57] a) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin, Y. *Org. Lett.* **2006**, *8*, 2187. b) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794.

of DA aminocyclopropanes towards the synthesis of complex molecules. Since 2020, this strategy has also been utilized by the Sen group for the synthesis of spirocyclic indole derivatives.[58]



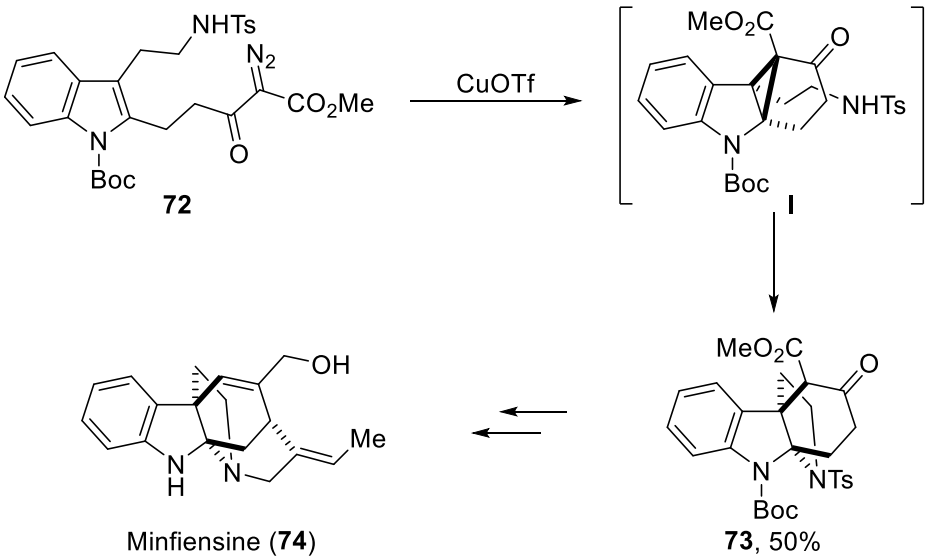
Scheme 6. Ring-opening cyclization with azide as masked amino group.

The pendant nucleophile can also be a sulfonamide or carbamate group. With these protecting groups, the nitrogen atom is deactivated and therefore interference with the cyclopropanation step was avoided. The Qin group demonstrated that structural complexity can be increased in one step by developing cascade reactions involving cyclopropanation and ring opening reaction using a pendant amino group as nucleophile, with DA aminocyclopropanes as non-isolated intermediates. For example, starting from a tryptamine derivative **72**, a copper catalyzed cyclopropanation-ring opening-cyclization sequence provided directly the tetracyclic product **73** in 50% yield, showing the efficiency of this cascade reaction (Scheme 7).[59] This reaction was a key step in the total synthesis of natural products Minfiensine (**74**) and Vincorine. Starting from L-tryptophan, a good diastereoselectivity can be achieved by performing the cascade reaction at low temperature, which was later applied in the total synthesis of the indole alkaloid (−)-Ardeemin.[60]

[58] a) Chauhan, J.; Ravva, M. K.; Gremaud, L.; Sen, S. *Org. Lett.* **2020**, *22*, 4537. b) Guha, S.; Gadde, S.; Kumar, N.; Black, D. S.; Sen, S. *J. Org. Chem.* **2021**, *86*, 5234.

[59] a) Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 3618. b) Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013.

[60] a) Song, H.; Yang, J.; Chen, W.; Qin, Y. *Org. Lett.* **2006**, *8*, 6011. b) He, B.; Song, H.; Du, Y.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 298.



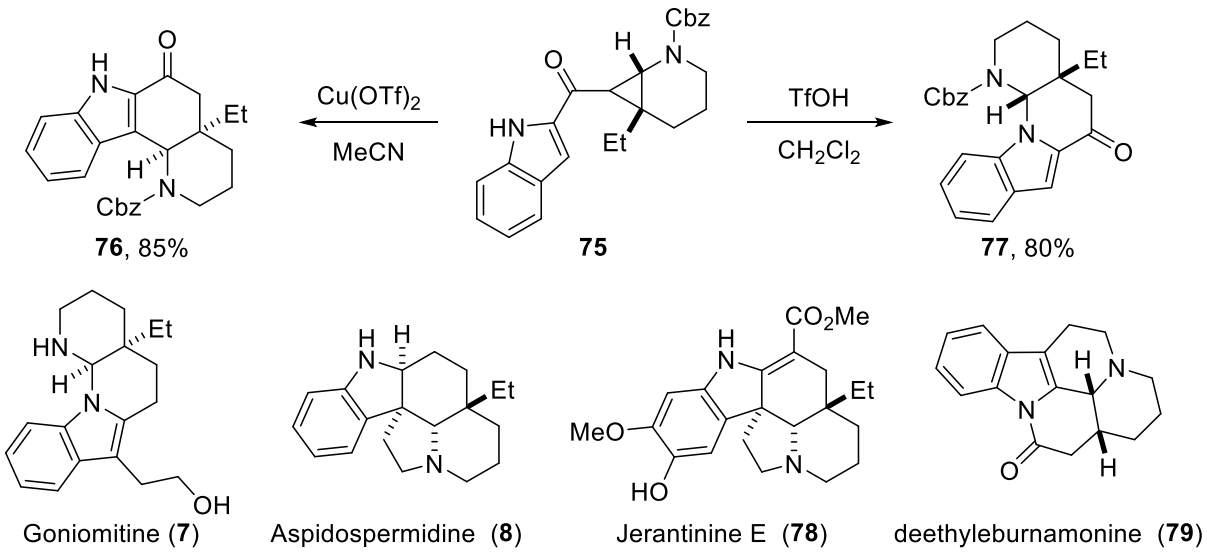
Scheme 7. Cyclopropanation and ring opening cascade with pendant sulfonamide as nucleophile.

When the side chain contains an electron rich aromatic ring, it can react as carbon nucleophile with the iminium intermediate to form a new C-C bond. In several cases, an indole was attached to the acceptor carbonyl group as an internal carbon nucleophile. In 2011, our group studied thoroughly this reaction with an acyl indole substituted DA aminocyclopropane **75**. Ring opening and subsequent cyclization occurred at either the C3 or at the N1 position of the indole, if the nitrogen was not protected.[61] We found that the use of $Cu(OTf)_2$ in MeCN strongly favored the formation of **76** as a result of alkylation at C3 position, while switching to TfOH in dichloromethane gave predominantly **77** as product (Scheme 8). Our group also successfully applied this selective cyclization as a key step for the total synthesis of the natural product Goniomitine (**7**), the formal synthesis of Aspidospermidine (**8**)[20] and the total synthesis of Jerantinine E (**78**).[62] In 2012, this strategy was also used in the total synthesis of deethyleburnamonine (**79**) by the France group.[63]

[61] De Simone, F.; Saget, T.; Benfatti, F.; Almeida, S.; Waser, J. *Chem. Eur. J.* **2011**, *17*, 14527.

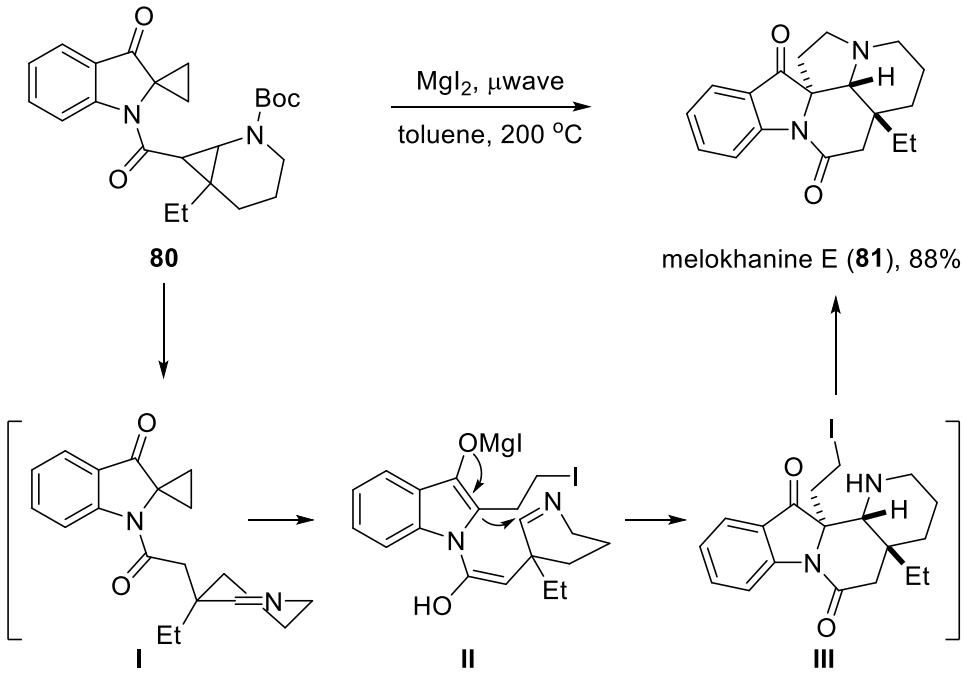
[62] Frei, R.; Staedler, D.; Raja, A.; Franke, R.; Sasse, F.; Gerber-Lemaire, S.; Waser, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 13373.

[63] Patil, D. V.; Cavitt, M. A.; France, S. *Heterocycles* **2012**, *84*, 1363.



Scheme 8. Ring opening with a pendant indole and its application in total synthesis of indole alkaloids.

In addition, the formed imine can also be engaged in a formal [3+2] cycloaddition with a cyclopropane, as demonstrated by the Pierce group in the total synthesis of melokhanine E (Scheme 9).[64] Starting from compound **80**, melokhanine E (**81**) was formed in 88% yield under microwave heating in the presence of MgI_2. This reaction involved a sequence of Boc-deprotection/cyclopropane opening to form intermediate **I**, which underwent stepwise imine addition/nitrogen alkylation to eventually produce the product **81**.

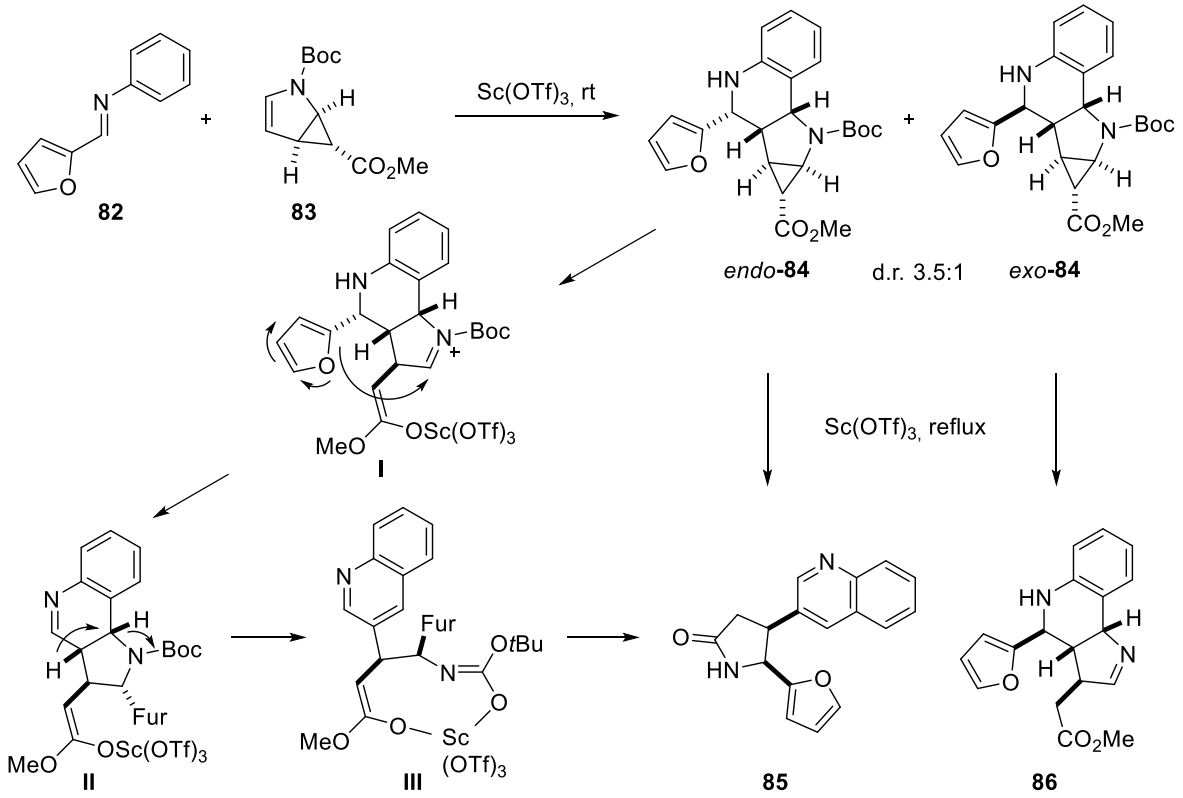


Scheme 9. Ring opening cascade with enolate for the synthesis of melokhanine E (**81**).

In a rare example reported in 2012 by the Reiser group, a furan migration product **85** was isolated for *endo*-**84** after a Povarov reaction between **82** and **83**, while only isomerization into polycyclic imine **86**

[64] A. E. Cholewczynski, P. C. Williams, J. G. Pierce, *Org. Lett.* **2020***, 22*, 714.

was observed for *exo*-**84** (Scheme 10).[65] The authors proposed a plausible mechanism which involves formation of intermediate **I** in the presence of $Sc(OTf)_3$ and subsequent furan migration to **II** via a spiroannulated intermediate. The unusual C-N bond cleavage is compensated by the rearomatization of a quinoline ring in the intermediate **III**, which further undergoes *N*-Boc hydrolysis and lactamization to form **85**. However, other aromatic substituents instead of furan, including *para*-methoxyphenyl, 1-naphthyl and 2-thionyl gave only polycyclic imines without migration, indicating that both a furan moiety and the specific conformational arrangement of *endo*-**84** are necessary for the rearrangement to proceed.



Scheme 10. A rare example of furan migration after the Lewis-acid catalyzed ring opening of *endo*-**84**.

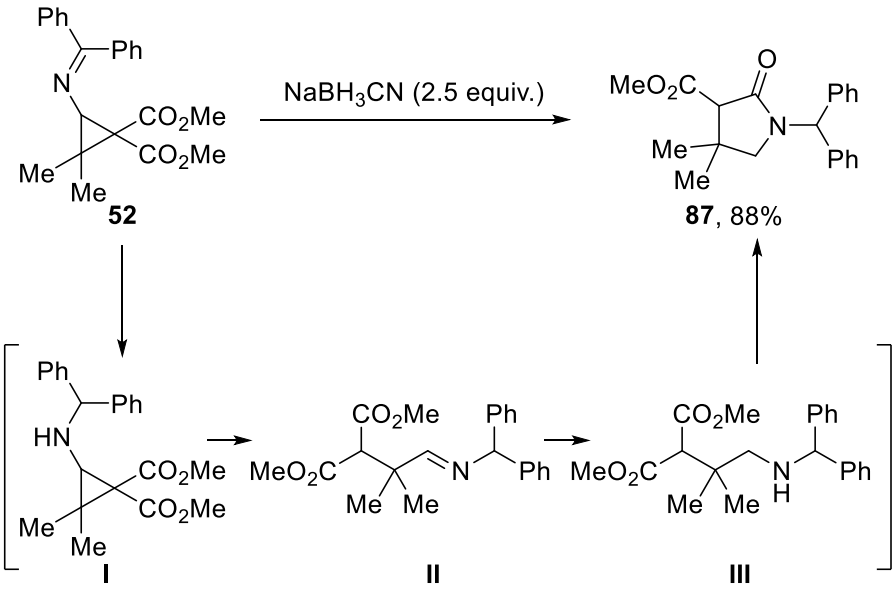
Intermolecular ring opening

External nucleophiles can also be employed to convert the iminium intermediate into amine products. The smallest nucleophile is a hydride, resulting in the reduction of DA aminocyclopropanes. For example, $NaBH_4$ was used as reductant in a one-pot synthesis of γ-aminobutyric acid (GABA) amides.[66] A pyrrolidin-2-one **87** was obtained when the reduction was carried out on **52**, which resulted from two subsequent reductions and an intramolecular condensation (Scheme 11).[46] The cyclopropanation and ring-opening reduction cascade is useful to construct cyclic systems and can thereby find applications in the synthesis of complex molecules. For example, a domino cyclopropanation-ring opening-reduction has been applied as key step in the total synthesis of Lyconesidine B, which was accomplished by the Takemoto group.[67]

[65] Roy, S.; Reiser, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 4722.

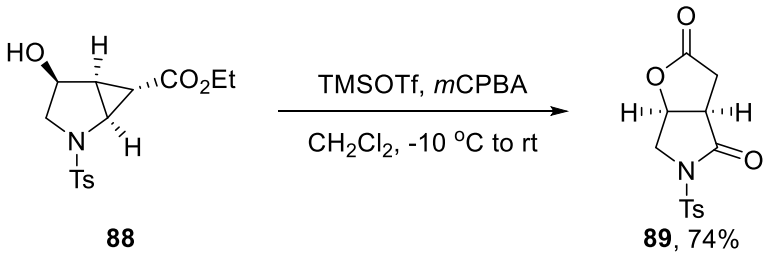
[66] Maslivetc, V. A.; Rubina, M.; Rubin, M. *Org. Biomol. Chem.* **2015**, *13*, 8993.

[67] Kurose, T.; Tsukano, C.; Nanjo, T.; Takemoto, Y. *Org. Lett.* **2021**, *23*, 676.



Scheme 11. Reduction of imine-substituted DA aminocyclopropane **52**.

When water was employed as nucleophile, an aldehyde was usually formed as a result of hydrolysis of the iminium intermediate,[30] which is most often an undesired side reaction because of the loss of nitrogen. With alcohols as nucleophiles, the *in situ* formed iminium intermediate can be stabilized in the form of an N,O-acetal, and the Qin group used this strategy in 2017 for the total synthesis of *Kopsia* indole alkaloids.[68] Similar to alcohols, the Gharpure group reported in 2014 that thiophenol was a good nucleophile as well, which afforded an N,S-acetal as product after ring opening.[26] In 2019, the Saha group reported a $Sc(OTf)_3$-catalyzed ring opening of DA cyclopropanes by hydrogen peroxide.[69] Extension of this reaction to DA aminocyclopropanes with amino group varying from phthalimide (**34**), succinimide (**36**) to even maleimide was successful, resulting in the formation of α-amino peroxides as products. When treating DA aminocyclopropanes with a peracid such as *m*CPBA, there is one example in which case the iminium intermediate from **88** was oxidized to pyrrolidin-2-one **89** (Eq. 7).[26]

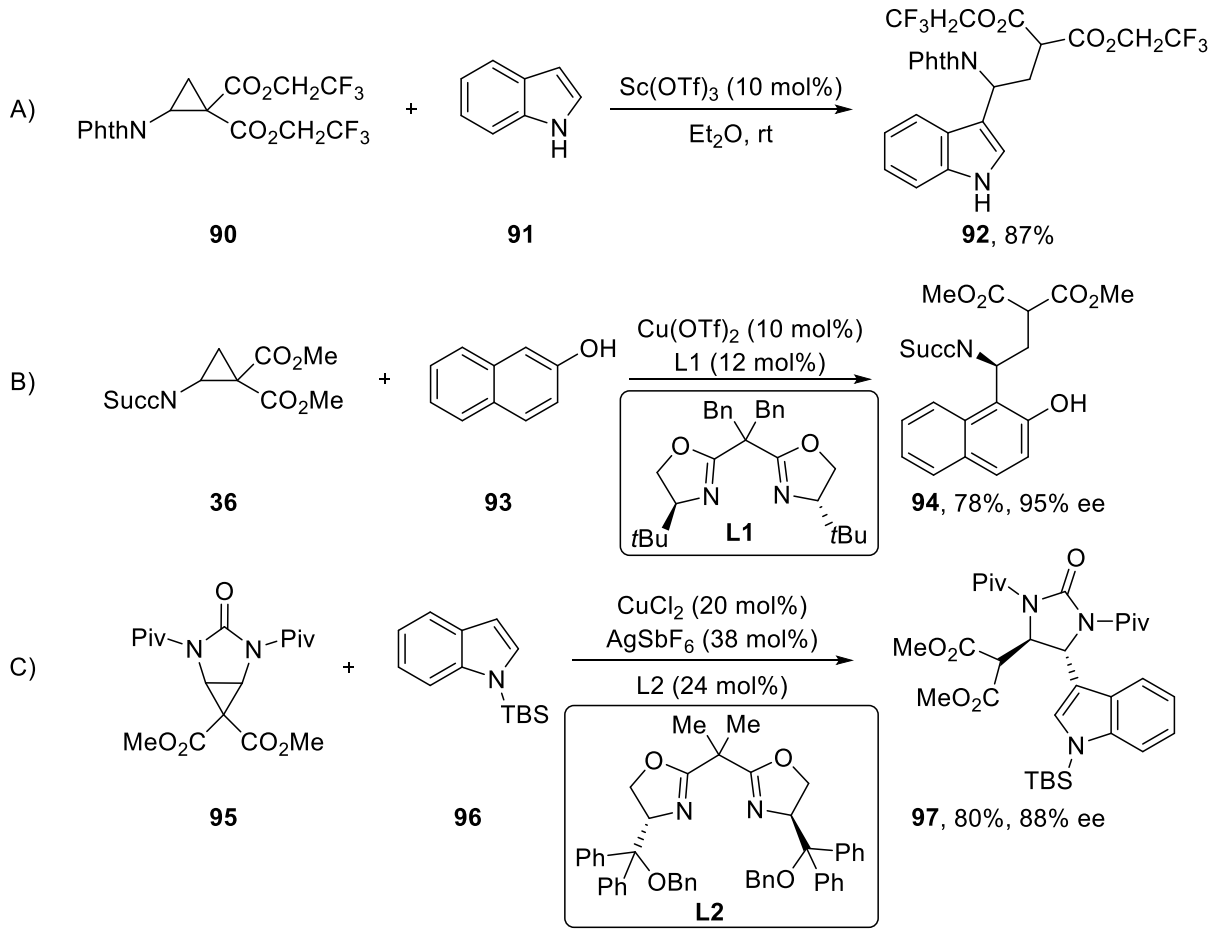


Equation 7. Oxidation of DA aminocyclopropane **88** with *m*CPBA.

Carbon nucleophiles have also been successfully incorporated into the α-amino position in the presence of Lewis acid catalysts. In 2013, our group reported a Friedel-Crafts reaction between DA aminocyclopropane **90** and indole **91**, leading to the formation of indole C3 alkylation product **92**

[68] Leng, L.; Zhou, X.; Liao, Q.; Wang, F.; Song, H.; Zhang, D.; Liu, X.-Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 3703.
[69] Singh, K.; Bera, T.; Jaiswal, V.; Biswas, S.; Mondal, B.; Das, D.; Saha, J. *J. Org. Chem.* **2019**, *84*, 710.

(Scheme 12A).[70] In the presence of C3-substituted indoles, C2 alkylation was observed. Pyrroles were also tested and the regioselectivity between C2/C3 alkylation can be tuned by changing the protecting group on the pyrrole nitrogen atom. Other electron-rich aromatic compounds, such as anisole or phenol, can also be used as nucleophiles but a mixture of products in poorer regioselectivity was usually formed. The Gharpure group reported one example of nucleophilic attack by 1,3,5-trimethoxybenzene on **88** in the presence of Lewis acid TMSOTf, forming a Friedel-Crafts alkylation product in high yield and diastereoselectivity.[26] In 2018, the Wang and Guo group optimized the conditions for the Friedel-Crafts alkylation reaction of DA aminocyclopropane **36** with 2-naphthol **93** as nucleophile (Scheme 12B).[71] With the help of $Cu(OTf)_2$ and BOX ligand **L1**, GABA derivative **94** was obtained in good yield and enantioselectivity by using 2-naphthol as limiting reagent. They also showed that this is a kinetic resolution process, and unreactive **36** can be recovered in excellent enantioselectivity by decreasing the ratio between **36** and 2-naphthol to 1:1. In 2018, our group also reported an example of enantioselective desymmetrization based on the previously described Friedel-Crafts alkylation reaction (Scheme 12C).[72] Starting from 1*H*-imidazol-2(3*H*)-one, *meso*-diaminocyclopropane **95** was prepared by cyclopropanation with diazo malonate using $Rh_2(OAc)_4$ as catalyst. The combination of a copper catalyst and the fine-tuned BOX ligand **L2** enabled the conversion of **95** into an enantioenriched, diastereomerically pure urea derivative **97**.



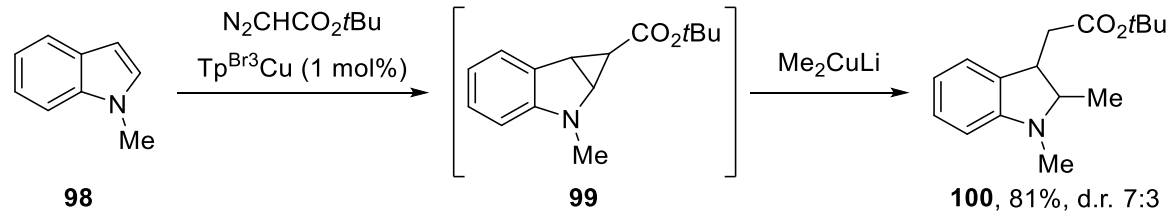
Scheme 12. Friedel-Crafts reaction between DA aminocyclopropanes and indoles or 2-naphthols.

[70] de Nanteuil, F.; Loup, J.; Waser, J. *Org. Lett.* **2013**, *15*, 3738.

[71] Zhu, M.; Wang, D.-C.; Xie, M.-S.; Qu, G.-R.; Guo, H.-M. *Chem. Eur. J.* **2018**, *24*, 15512.

[72] Perrotta, D.; Wang, M.-M.; J. Waser, *Angew. Chem. Int. Ed.* **2018**, *57*, 5120.

In addition to aromatic compounds, organometallic reagent can be used as nucleophile too. For instance, Me_2CuLi was used to introduce a methyl group by the Prieto and Pérez group in 2014 for C2, C3-difunctionalization of 1-methylindole **98** via an unstable indole-derived DA aminocyclopropane **99** (Eq. 8).[73]



Equation 8. Ring-opening reaction using Me_2CuLi as nucleophile.

Apart from monofunctionalization of the DA aminocyclopropanes, 1,3-difunctionalization has also been reported in the presence of an electrophile. In 2014, the Werz group reported a 1,3-dichlorination of DA cyclopropanes by iodobenzene dichloride under mild conditions (Scheme 13A).[74] The donor group could vary from succinimide, phthalimide to alkyl or aryl substituents, and the acceptors were usually diesters or dinitriles. A radical pathway, rather than an ionic process, was proposed as the mechanism of this reaction. Following this work, the Werz group reported a 1,3-halochalcogenation with magnesium iodide as Lewis acid catalyst (Scheme 13B).[75] The strongly polarized bonds of sulfenyl or selenyl halides were exploited for the incorporation of a chalcogen and a halogen atom into the nucleophilic and electrophilic sites of **34** respectively, forming **104** or **105** in good yields. A similar strategy was utilized by the Studer group in 2017 for the ring opening 1,3-aminobromination[76] of **35** as well as by the Saha group in 2019 for 1,3-haloperoxygenation[69] of **34** (Scheme 13C). In these cases, *p*-toluenesulfonamide or *tert*-butyl hydrogen peroxide were used as nucleophiles for the ring opening reaction with the help of a Lewis acid catalyst, leading to the formation of **106** or **107**. In 2020, the Saha group also reported a bisarylation reaction of **34**, using 1-methylindole and an arylbismuth(V) reagent as nucleophile and electrophilic arylating agents respectively (Scheme 13D).[77]

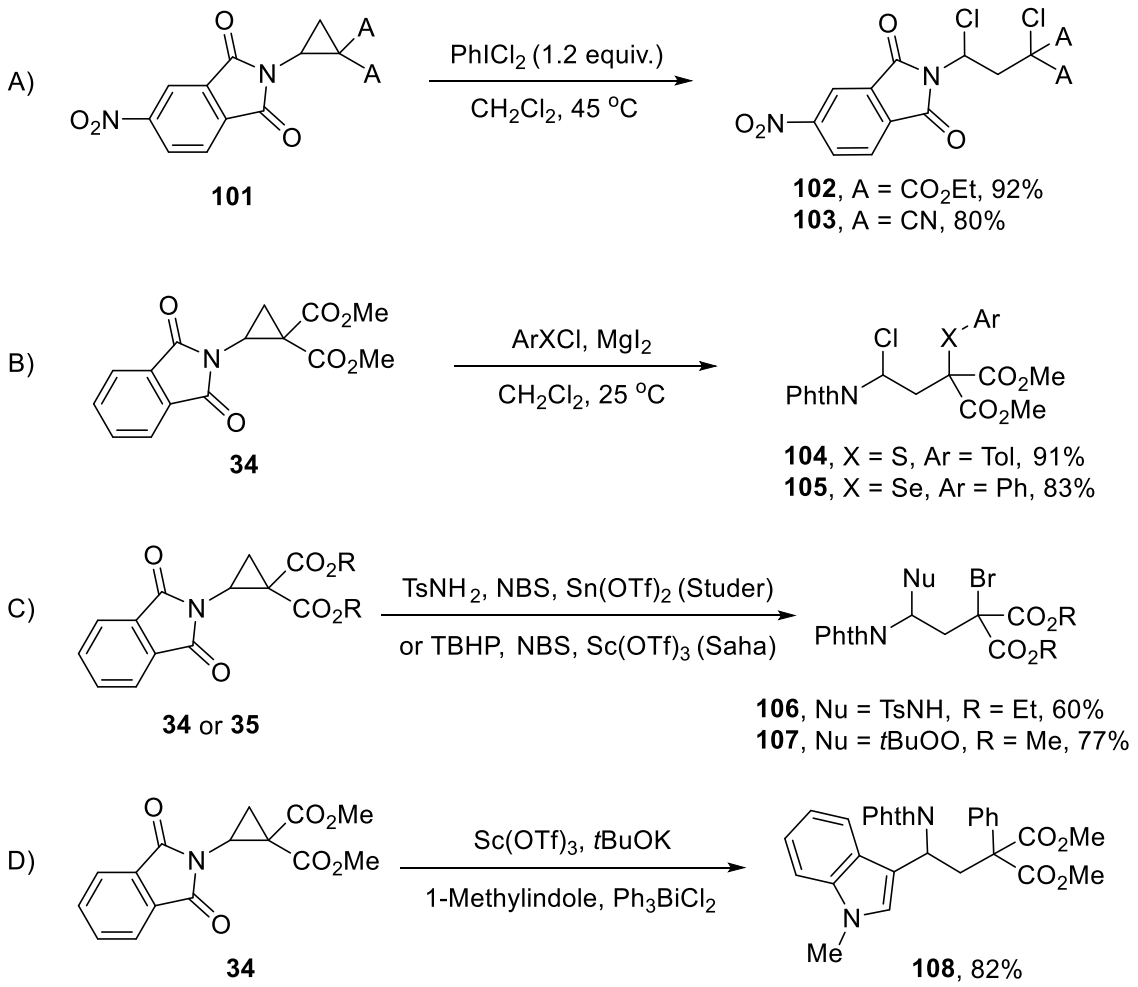
[73] Delgado-Rebollo, M.; Prieto, A.; Pérez, P. J. *ChemCatChem* **2014**, *6*, 2047.

[74] Garve, L. K. B.; Barkawitz, P.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2014**, *16*, 5804.

[75] Wallbaum, J.; Garve, L. K. B.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2017**, *19*, 98.

[76] Das, S.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2017**, *56*, 11554.

[77] Mondal, B.; Das, D.; Saha, J. *Org. Lett.* **2020**, *22*, 5115.



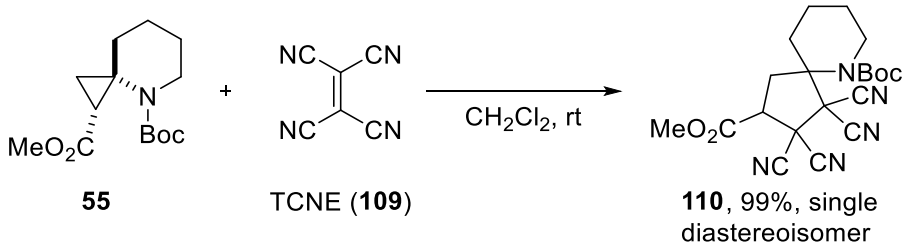
Scheme 13. Ring-opening 1,3-difunctionalization reactions with electrophiles.

To summarize this section, ring opening reactions of DA aminocyclopropanes have been discussed, including isomerization, cyclization, monofunctionalization as well as 1,3-difunctionalization. In all these cases only classic bond-cleavage involving the C1-C2 bond was observed. In addition to these reports, rare examples of ring opening reactions involving non-classic bond cleavage were also disclosed.[78]

1.2.1.3 Formal cycloaddition of DA aminocyclopropanes

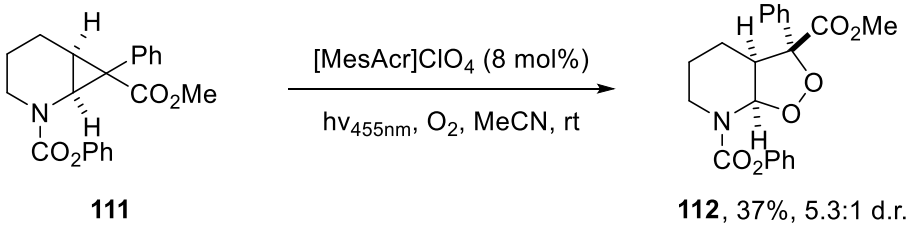
In 1996, the Beak group reported a formal [3+2] cycloaddition between DA aminocyclopropane **55** and tetracyanoethylene (TCNE, **109**) (Eq. 9).[47] In an attempt to broaden the synthetic utility of this reaction, less activated electrophiles including fumaronitrile, dimethyl maleate and acrylonitrile were tested. However, no corresponding products were observed and only the starting material **55** was recovered. This may suggest that the first elementary step with tetracyanoethylene could be single electron transfer.[19a]

[78] a) Gheorghe, A.; Schulte, M.; Reiser, O. *J. Org. Chem.* **2006**, *71*, 2173. b) Yedoyan, J.; Wurzer, N.; Klimczak, U.; Ertl, T.; Reiser, O. *Angew. Chem. Int. Ed.* **2019**, *58*, 3594. c) Sonnleitner, C. M.; Park, S.; Eckl, R.; Ertl, T.; Reiser, O. *Angew. Chem. Int. Ed.* **2020**, *59*, 18110. d) McClure, C. K.; Kiessling, A. J.; Link, J. S. *Org. Lett.* **2003**, *5*, 3811.



Equation 9. Formal [3+2] cycloaddition of DA aminocyclopropane **55** with tetracyanoethylene.

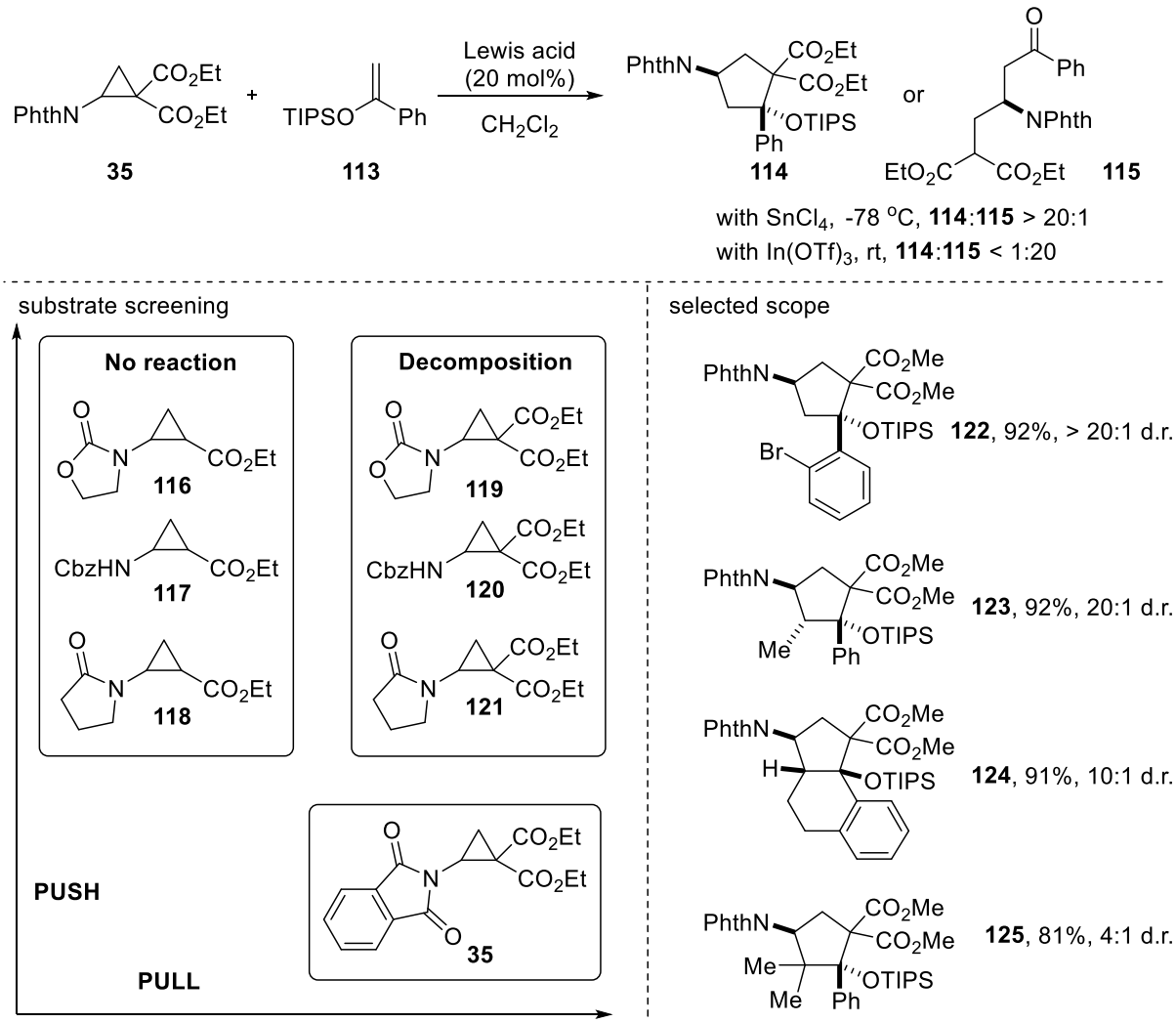
In 2020, the Reiser group explored the possibility of activating DA aminocyclopropanes by single-electron oxidation. By using Fukuzumi dye as catalyst with blue light irradiation, A polycyclic endoperoxide **112** was formed as a result of formal [3+2] cycloaddition between DA aminocyclopropane **111** and molecular oxygen (Eq. 10).[79] The obtained endoperoxides were tested for antimalarial activity given their close analogy to the active principle of approved drugs such as artemisinin



Equation 10. Formal [3+2] cycloadditions of **111** with molecular oxygen.

While examples of DA aminocyclopropanes activation involving a radical pathway remain scarce, polar mechanism has been widely exploited for developing cycloaddition reactions. In 2011, our group reported a catalytic [3+2] annulation of DA aminocyclopropanes with silyl/alkyl enol ethers (Scheme 14).[37a] Several DA aminocyclopropanes have been synthesized to compare their reactivity and stability. It was found that mono-acceptor aminocyclopropanes **116-118** were not reactive under the examined conditions, while *gem*-di-acceptor aminocyclopropanes **119-121** were not stable and decomposed directly after cyclopropanation. In the end, a balance between reactivity and stability was found when the nitrogen atom was protected as a phthalimide group to reduce its electron density, leading to the formation of DA aminocyclopropane **35**. After the [3+2] annulation of **35** with enol ether **113**, cyclopentylamine **114** was obtained in 98% yield and more than 20:1 diastereoselectivity using $SnCl_4$ as catalyst at -78 ^{o}C, while an acyclic product **115** arising from nucleophilic ring opening was formed when $In(OTf)_3$ was used as catalyst. This reaction was stereospecific in relation to the configuration of enol ether and enantiospecific. The size of the silyl group on the enol ether and the substituent on the benzene ring of the aminocyclopropane almost had no influence on the yield or selectivity of the products, as shown in the case of **122**. For trisubstituted or tetrasubstituted enol ether, a drop in diastereoselectivity in the final products **123-125** was observed. In all the cases products having the nitrogen in *anti* relationship with the oxygen were determined as the major diastereoisomer except in the case of product **124** where the opposite diastereoisomer was formed.

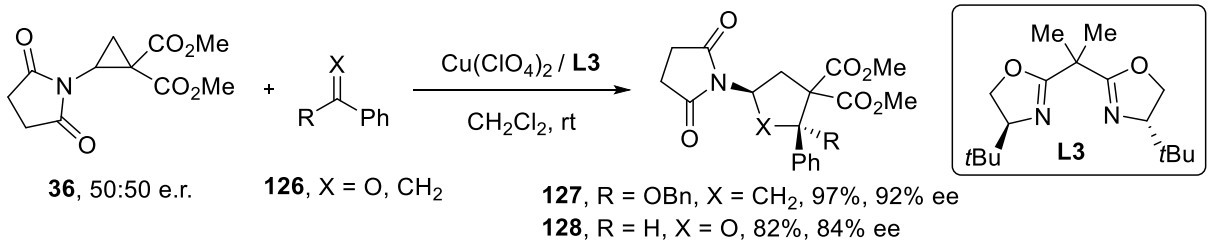
[79] Budde, S.; Goerdeler, F.; Floß, J.; Kreitmeier, P.; Hicks, E. F.; Moscovitz, O.; Seeberger, P. H.; Davies, H. M. L.; Reiser, O. *Org. Chem. Front.* **2020**, *7*, 1789.



Scheme 14. Catalyst-tuned ring opening/cycloaddition with enol ether.

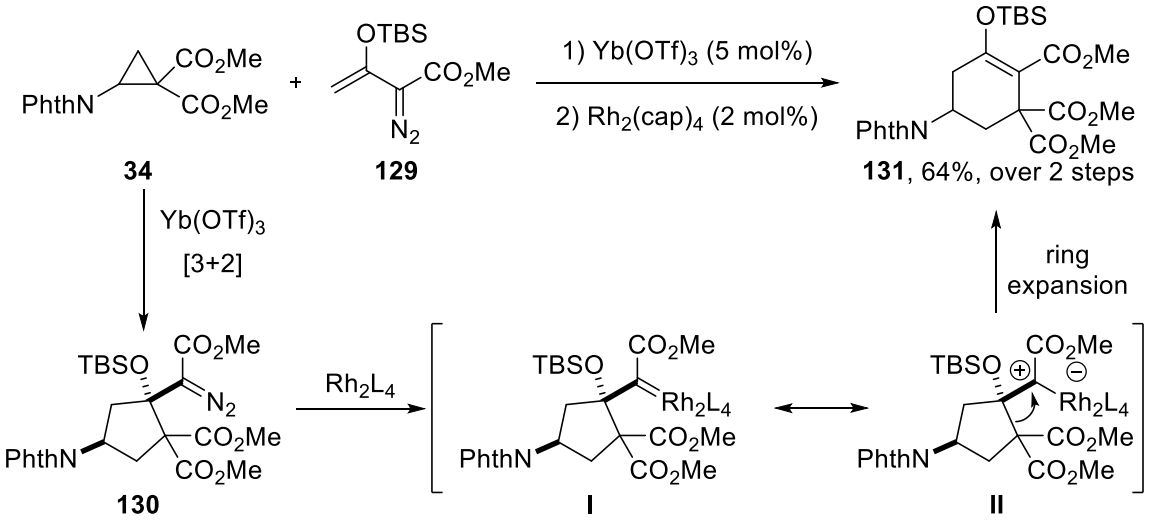
In 2012, our group also reported catalytic [3+2] annulations between DA aminocyclopropanes and aldehydes or ketones, giving access to aminotetrahydrofurans.[80] Based on these results, our group further reported in 2014 a dynamic kinetic asymmetric (DYKAT) [3+2] annulation reaction of DA aminocyclopropane **36** with enol ethers or aldehydes **126** to form five-membered cyclic compounds such as **127** and **128** (Eq. 11).[37b] The combination of a copper catalyst and the commercially available bisoxazoline ligand **L3** was key to success for this reaction, which provided products in high yield, good diastereoselectivity and excellent enantioselectivity under mild conditions. The dynamic process can be speculated to proceed via reversible ring opening/closing, as racemization of enantio-enriched **36** was observed in the absence of enol ether. This DYKAT process is a straightforward approach to convert easily accessible racemic DA aminocyclopropanes into enantiopure cyclopentylamines.

[80] a) Benfatti, F.; de Nanteuil, F.; Waser, J. *Org. Lett.* **2012**, *14*, 386. b) Benfatti, F.; de Nanteuil, F.; Waser, J. *Chem. Eur. J.* **2012**, *18*, 4844.



Equation 11. Dynamic kinetic asymmetric [3+2] annulation reaction of **36**.

In 2015, the Doyle group reported a formal [3+3] cycloaddition of enoldiazoacetate **129** with DA cyclopropanes, which was extended successfully to DA aminocyclopropane **34** (Scheme 15).[81] This reaction was realized by a tandem reaction first with a Lewis acid-catalyzed [3+2] cycloaddition to form **130**, followed by a subsequent rhodium-catalyzed ring expansion to afford the six-membered cyclic compound **131** as final product.



Scheme 15. Formal [3+3] cycloaddition of **34** with enoldiazoacetate **129**.

In addition to enol ethers/aldehydes/ketones, formal [3+2] cycloadditions with thioalkynes and ynamides were also reported.[82] Based on our previous studies on hypervalent iodine chemistry, thioalkynes were easily synthesized from thiophenols and ethynylbenziodoxolones (EBX reagents).[83] The annulation reaction of **34** with triethylsilyl substituted thioalkyne gave access to highly substituted cyclopentene **132** in high yield and regioselectivity (Scheme 16A) while a different product was formed with aliphatic thioalkynes.[82a] 1-Alkynyltriazenes were synthesized by the Severin group and their synthetic utility was demonstrated in several types of transformation, including the [3+2] annulation with **34** to form cyclopentene **133** (Scheme 16B).[82b] In 2014, the Studer group reported a formal [3+2] cycloaddition of **35** with nitrosobenzene to form **134** (Scheme 16C).[84] The Werz group reported in 2016 a formal [4+3] cycloaddition of **34** with amphiphilic benzodithioloimine as surrogate for ortho-bisthioquinone to give **135** (Scheme 16D) as well as a formal [3+2] cycloaddition of **34** with

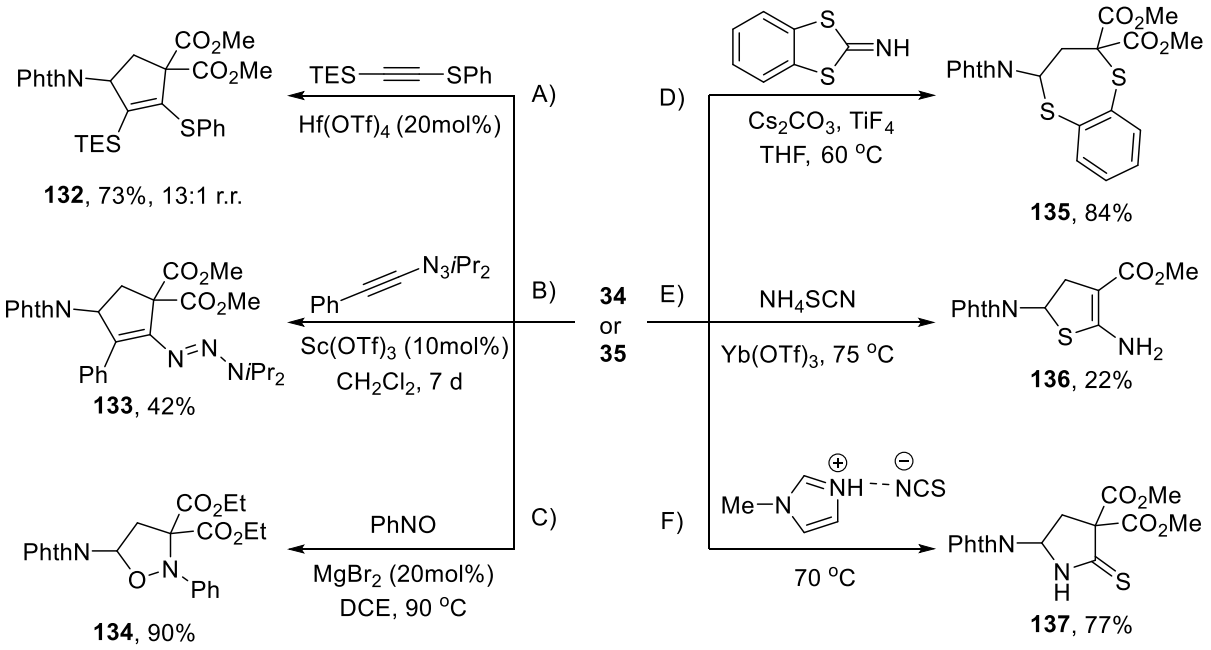
[81] Cheng, Q.-Q.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2015**, *17*, 3568.

[82] a) Racine, S.; Hegedüs, B.; Scopelliti, R.; Waser, J. *Chem. Eur. J.* **2016**, *22*, 11997. b) Perrin, F. G.; Kiefer, G.; Jeanbourquin, L.; Racine, S.; Perrotta, D.; Waser, J.; Scopelliti, R.; Severin, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 13393.

[83] Frei, R.; Waser, J. *J. Am. Chem. Soc.* **2013**, *135*, 9620.

[84] Chakrabarty, S.; Chatterjee, I.; Wibbeling, B.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 5964.

selenocyanate or thiocyanate to form **136** (Scheme 16E).[85] In 2021, the Trushkov group in collaboration with the Werz group reported a formal [3+2] cycloaddition of **34** with isothiocyanic acid to produce **137**, in which case an untypical *N*-attack took place (Scheme 16F).[86]



Scheme 16. Formal cycloaddition with thioalkyne, ynamide, nitrosobenzene, benzodithioloimine, thiocyanate or isothiocyanic acid.

Apart from annulations of DA aminocyclopropanes with dipolarophiles mentioned above, dearomative [3+2] annulation reactions have also been studied. In 2017, our group described a dearomative [3+2] annulation of N-heterocycles with DA aminocyclopropanes (Scheme 17A).[87] In this case, DA aminocyclopropanes such as **34** exhibited superior reactivity compared to aryl or alkoxy substituted DA cyclopropanes, giving product **139** in high yield. Several different N-heterocycles, including pyridines, quinolines and isoquinolines, were well tolerated. An asymmetric dearomative [3+2] cycloaddition reaction of DA aminocyclopropane **140** with benzazole **141** was later disclosed by the Guo and You group, forming tricyclic product **142** in good yield and enantioselectivity (Scheme 17B).[88] In 2019, the Guo group successfully extended the asymmetric dearomative [3+2] cycloaddition to purines.[89]

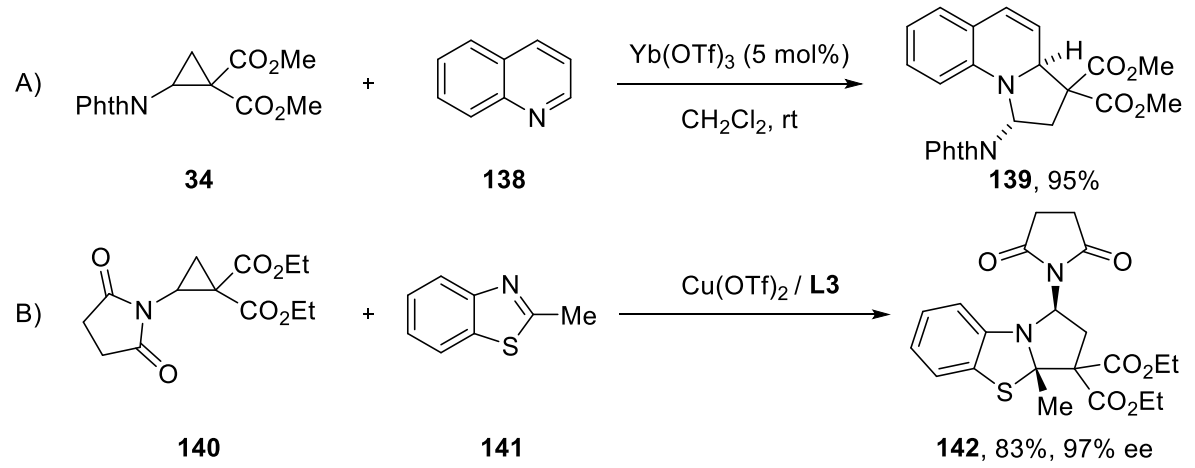
[85] a) Garve, L. K. B.; Pawliczek, M.; Wallbaum, J.; Jones, P. G.; Werz, D. B. *Chem. Eur. J.* **2016**, *22*, 521. b) Jacob, A.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2020**, *22*, 8720. c) Jacob, A.; Barkawitz, P.; Andreev, I. A.; Ratmanova, N. K.; Trushkov, I. V.; Werz, D. B. *Synlett* **2021**, *32*, 901.

[86] Andreev, I. A.; Ratmanova, N. K.; Augustin, A. U.; Ivanova, O. A.; Levina, I. I.; Khrustalev, V. N.; Werz, D. B.; Trushkov, I. V. *Angew. Chem. Int. Ed.* **2021**, *60*, 7927.

[87] Preindl, J.; Chakrabarty, S.; Waser, J. *Chem. Sci.* **2017**, *8*, 7112.

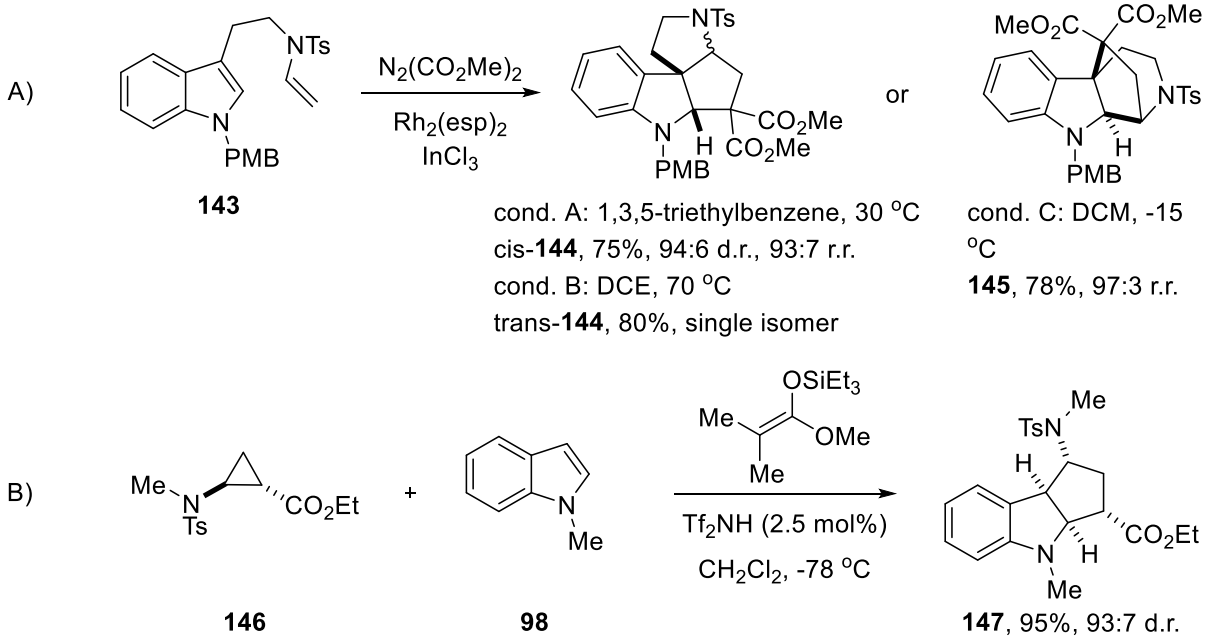
[88] Zhang, M.-C.; Wang, D.-C.; Xie, M.-S.; Qu, G.-R.; Guo, H.-M.; You, S.-L. *Chem* **2019**, *5*, 156.

[89] Hao, E.-J.; Fu, D.-D.; Wang, D.-C.; Zhang, T.; Qu, G.-R.; Li, G.-X.; Lan, Y.; Guo, H.-M. *Org. Chem. Front.* **2019**, *6*, 863.



Scheme 17. Dearomative [3+2] cycloaddition reactions.

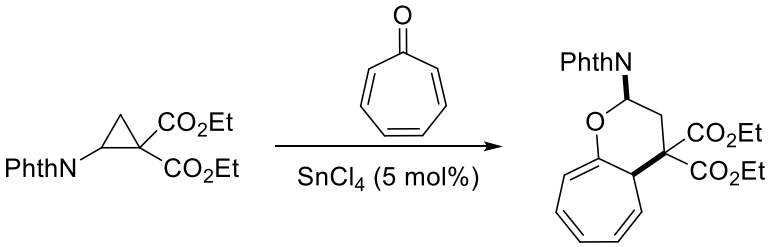
In 2019, the Wang group developed a cooperative Rh^{II}/In^{III} catalytic system for the cyclopentannulations of indole **143** to synthesize tetracyclic indolines (Scheme 18A).[90] By tuning carefully the reaction parameters such as solvent and temperature, three structurally divergent tetracyclic indolines, cis-**144**, trans-**144** and **145**, were synthesized in good yield and excellent selectivity. Mechanistic studies indicated an intramolecular annulation of the indole with an *in situ* formed aminocyclopropane. In 2021, our group reported a catalytic [3+2] dearomative annulation reaction between mono-acceptor aminocyclopropanes and indoles (Scheme 18B).[91] Getting rid of one ester was not easy, as a balance between reactivity and stability needed to be found. We found that protecting the amino group with a tosyl group and a methyl group, as shown in the case of **146**, offered an optimal reactivity. The choice of the *in situ* formed triethylsilyl triflimide as catalyst was also very important and led to the formation of tricyclic indoline product **147** in excellent yield and stereoselectivity.



Scheme 18. Intra- and intermolecular dearomative [3+2] annulations of indoles.

[90] Liu, H.-K.; Wang, S. R.; Song, X.-Y.; Zhao, L.-P.; Wang, L.; Tang, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 4345.
[91] Pirenne, V.; Robert, E. G. L.; Waser, J. *Chem. Sci.* **2021**, *12*, 8706.

Dearomatization annulation with other aromatic systems was also explored. For example, the Sierra group reported in 2013 a formal [8+3] cycloaddition between **35** and tropone, which produced amino-substituted tetrahydrocyclohepta[b]pyran **148** with complete regio- and diastereoselectivity (Eq. 12).[92] Density Functional Theory (DFT) calculations revealed that the transformation proceeds stepwise through a zwitterionic intermediate, which is stabilized by some degree of π-aromaticity of the tropyl cation. The regio- and diastereoselectivity are controlled in the ring closure step. In the same year, the Adrio and Carretero group also reported a nickel-catalyzed [8+3] cycloaddition reaction of tropone with **34**.[93]



35 **148**, 61%

Equation 12. Formal [3+2] cycloaddition of **35** with tropone.

Besides the commonly used imide-substituted DA cyclopropanes, our group developed also an efficient synthesis of thymine/uracil-substituted DA cyclopropanes **149** and their subsequent formal [3+2] cycloaddition with enol ethers/aldehydes/ketones **150** for the synthesis of nucleoside analogues **151** (Scheme 19A).[94] Based on the recent progress in the synthesis of alkenyltriazene **152**,[95] the Severin group in collaboration with our group has synthesized triazene-derived DA cyclopropane **153** by cyclopropanation with diazomalonate (Scheme 19B).[96] We also demonstrated the reactivities of **153** by developing ring-opening reaction with methanol to form an N,O-acetal **154** or by developing formal [3+2] cycloadditions with TCNE or enol ether to form five-membered cyclic product **155** or **156** respectively.

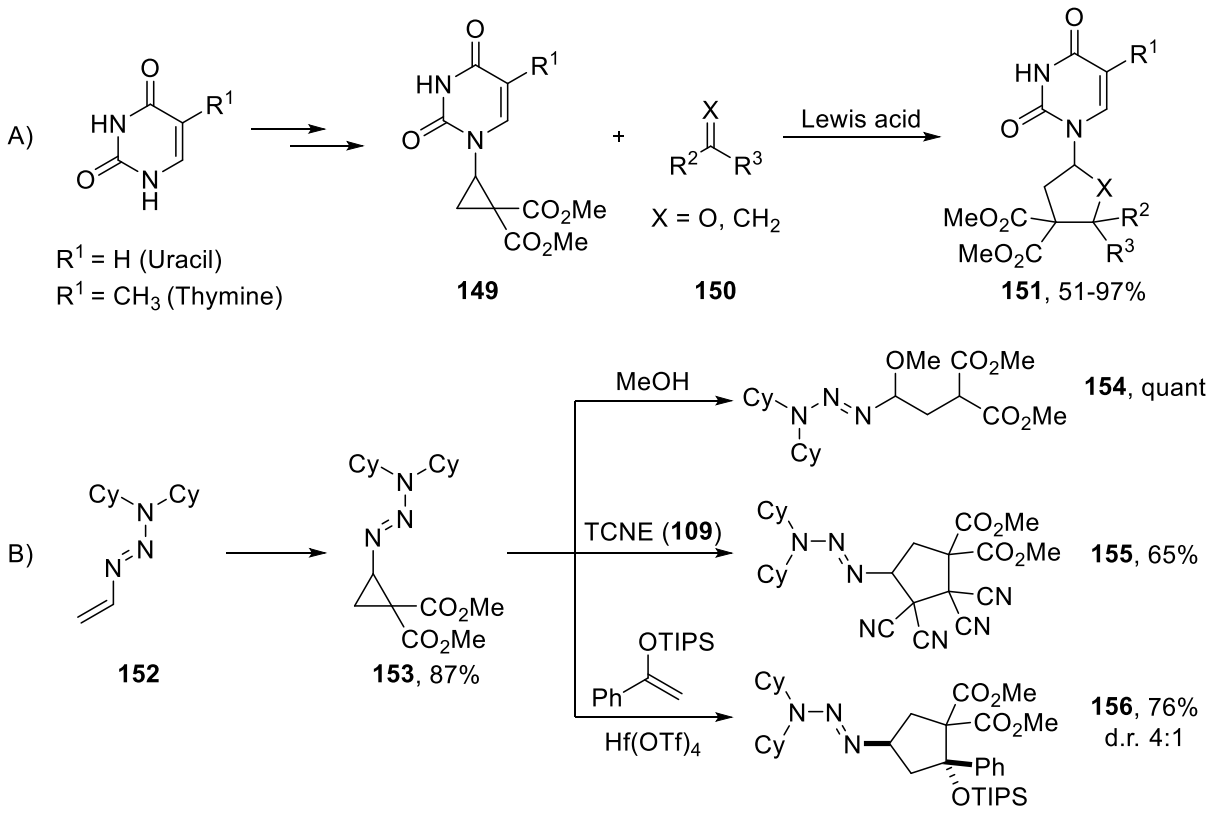
[92] Rivero, A. R.; Fernández, I.; Sierra, M. Á. *Org. Lett.* **2013**, *15*, 4928.

[93] Tejero, R.; Ponce, A.; Adrio, J.; Carretero, J. C. *Chem. Commun.* **2013**, *49*, 10406.

[94] a) Racine, S.; de Nanteuil, F.; Serrano, E.; Waser, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 8484. b) Racine, S.; Vuilleumier, J.; Waser, J. *Isr. J. Chem.* **2016**, *56*, 566.

[95] Kiefer, G.; Riedel, T.; Dyson, P. J.; Scopelliti, R.; Severin, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 302.

[96] Suleymanov, A. A.; Le Du, E.; Dong, Z.; Muriel, B.; Scopelliti, R.; Fadaei-Tirani, F.; Waser, J.; Severin, K. *Org. Lett.* **2020**, *22*, 4517.



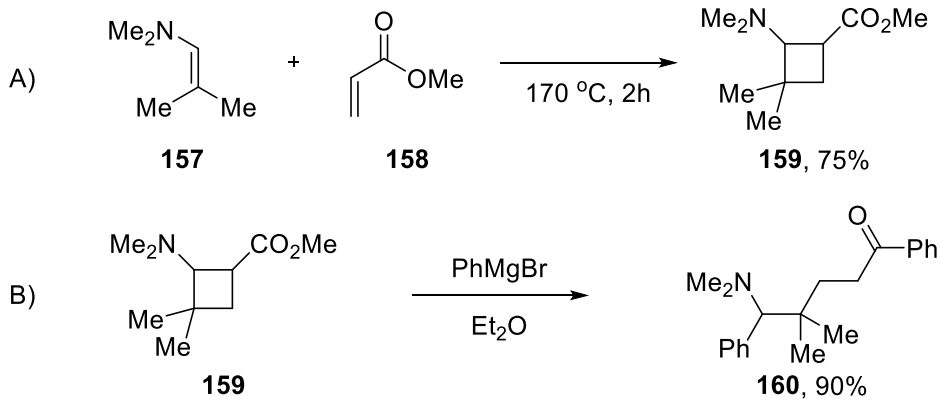
Scheme 19. Thymine/uracil- and triazene-substituted DA cyclopropanes.

1.2.2 Synthesis and reactivity of DA aminocyclobutanes

Compared to the numerous reactions of DA cyclopropanes, transformations of DA cyclobutanes are much less explored. Only a few synthetic routes have been developed for accessing DA aminocyclobutanes.

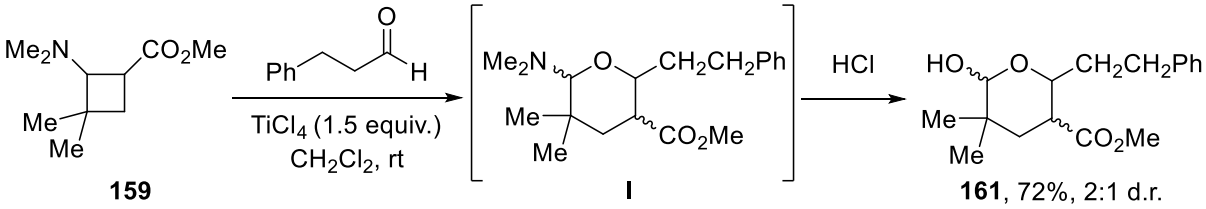
In 1961, Brannock *et al.* reported the synthesis of a DA aminocyclobutanes **159** through a formal [2+2] cycloaddition of enamine **157** and methyl acrylate (**158**) under thermal conditions (Scheme 20A).[97] In combination with the Hofmann elimination and hydogenation, this cycloaddition was first used for the synthesis of cyclobutanecarboxylic acids. In 1964, Weintraub *et al*. reported the Grignard reagent-induced ring opening reaction of **159**, in which case phenyl ketone **160** was obtained as product instead of the expected carbinol (Scheme 20B).[98]

[97] Brannock, K.; Bell, A.; Burpitt, R.; Kelly, C. *J. Org. Chem.* **1961**, *26*, 625.
[98] Weintraub, L.; Wilson, A.; Goldhamer, D. L.; Hollis, D. P. *J. Am. Chem. Soc.* **1964**, *86*, 4880.



Scheme 20. Studies of the DA aminocyclobutane **159** in 1960s.

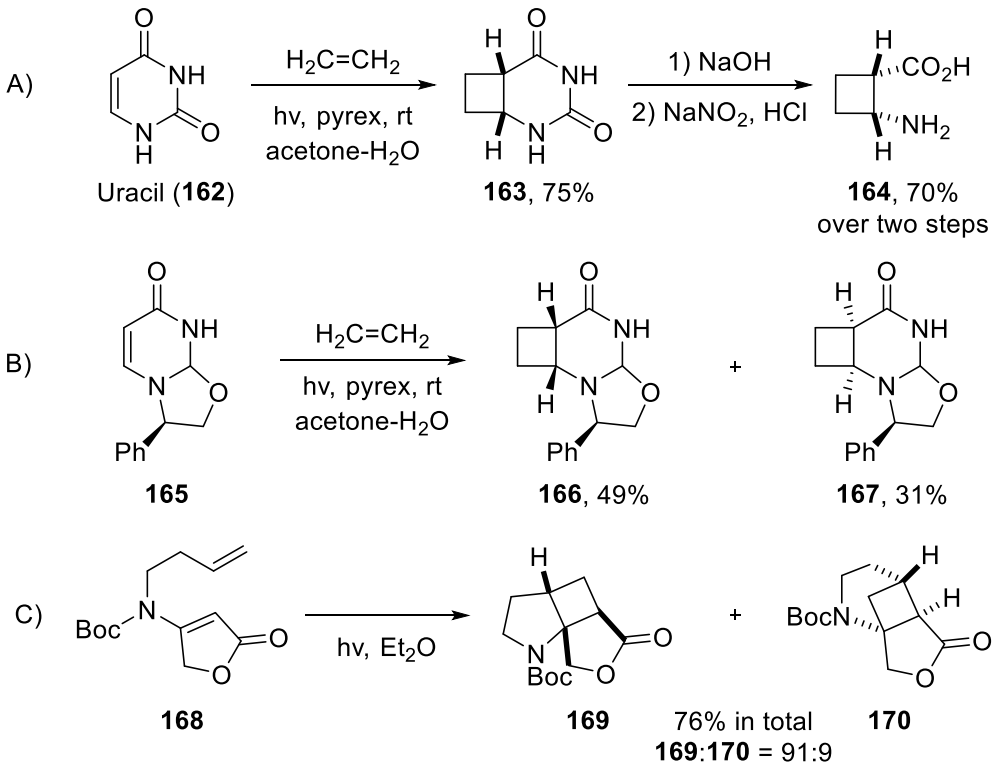
There was almost no progress in this research area until 1991, when the first [4+2] annulation of **159** with carbonyl compounds was reported by the Saigo group (Eq. 13).[99] The major drawbacks of this reaction were the loss of the nitrogen moiety as well as the requirement for a stoichiometric amount of $TiCl_4$, while other Lewis acids either gave products in lower yields or did not promote the reaction at all.



Equation 13. $TiCl_4$-mediated formal [4+2] cycloaddition of **159** with carbonyl compounds.

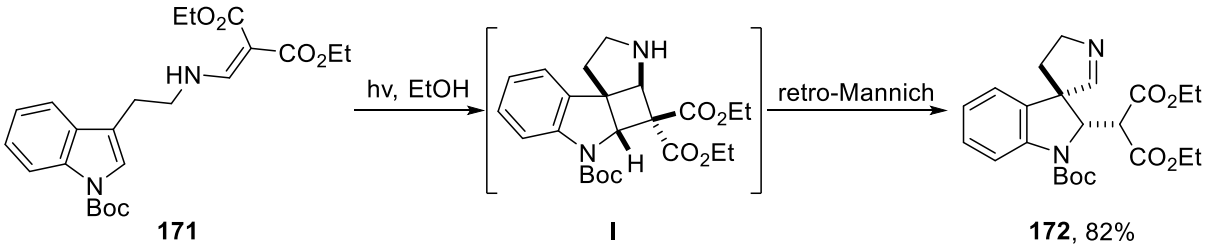
Photocatalyzed [2+2] cycloaddition reactions between two alkenes have also been developed to access other types of DA aminocyclobutanes, either in an intermolecular or in an intramolecular way. In 2002, the Aitken group described the cycloaddition between uracil (**162**) and ethylene (Scheme 21A).[100] After hydrolysis of the heterocyclic moiety of **163** and further decarbamoylation, *cis*-2-cyclobutanecarboxylic acid **164** was synthesized with an overall yield of 52% starting from uracil. In 2004, the Aitken group further reported the enantioselective version of this synthesis by using the chiral uracil equivalent **165** as substrate (Scheme 21B).[101] After the cycloaddition reaction, **166** and **167** were obtained as a pair of separable diastereoisomers, which afforded (+)-(1*S*,2*R*) and (-)-(1*R*,2*S*) **164** in >97% *ee* after the hydrolysis-decarbamoylation sequence. An intramolecular [2+2] cycloaddition was reported by the Bach group in 2005 as an efficient way to prepare tricyclic constrained scaffolds such as **169** (Scheme 21C).[102] In all three examples here, attention has mainly been put on the synthesis of DA aminocyclobutanes and no ring-opening reactions involving the C1-C2 bond cleavage were reported.

[99] Shimada, S.; Saigo, K.; Nakamura, H.; Hasegawa, M. *Chem. Lett.* **1991**, *20*, 1149.
[100] Aitken, D. J.; Gauzy, C.; Pereira, E. *Tetrahedron Lett.* **2002**, *43*, 6177.
[101] Gauzy, C.; Pereira, E.; Faure, S.; Aitken, D. J. *Tetrahedron Lett.* **2004**, *45*, 7095.
[102] Basler, B.; Schuster, O.; Bach, T. *J. Org. Chem.* **2005**, *70*, 9798.



Scheme 21. Photocatalyzed [2+2] cycloaddition for the synthesis of DA aminocyclobutanes.

In 2010, the White group developed a tandem intramolecular photocycloaddition-retro Mannich Fragmentation reaction of a tryptamine derivative **171** (Eq. 14), which was a key step for the synthesis of a few natural products such as horsfiline, coerulescine and elacomine.[103] Due to the presence of a second ester, which strengthened the electron pull effect, intermediate **I** underwent retro Mannich reaction spontaneously to give the spirocyclic product **172**.

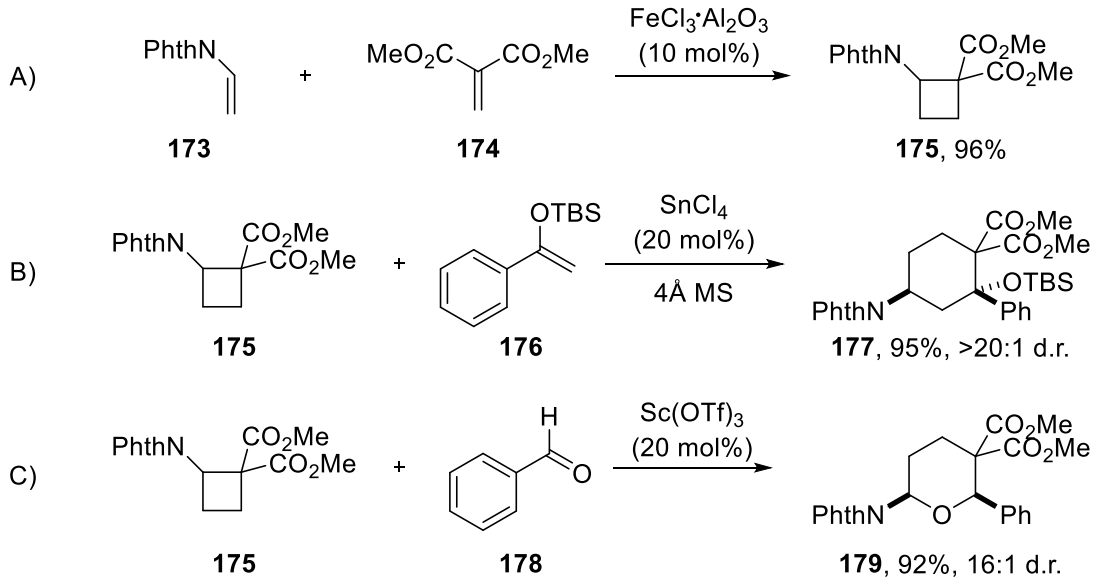


Equation 14. [2+2] cycloaddition-retro Mannich sequence of the tryptamine derivative **171**.

In 2013, our group developed a Lewis acid-catalyzed [2+2] alkene-alkene cycloaddition to access DA aminocyclobutanes (Scheme 22A).[104] Similar to DA aminocyclopropanes such as **34** and **35**, phthalimide was shown as a suitable protecting group in this case, which reduced the electron density on nitrogen and thus stabilized the *vic*-di-acceptor aminocyclobutane **175**. It is important to note that a catalytic [4+2] cycloaddition between **175** and silyl enol ether **176** has been demonstrated with 20 mol%

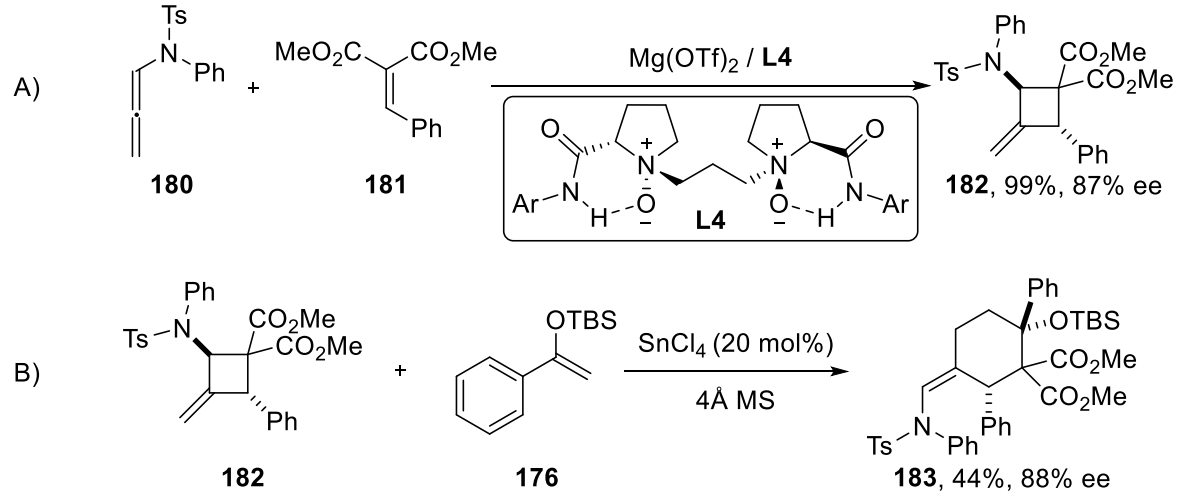
[103] White, J. D.; Li, Y.; Ihle, D. C. *J. Org. Chem.* **2010**, *75*, 3569.
[104] de Nanteuil, F.; Waser, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 9009.

$SnCl_4$ as catalyst (Scheme 22B). Aldehydes can also be reaction partner for the [4+2] cycloaddition, yielding tetrahydropyrans such as **179** in the presence of 20 mol% $Sc(OTf)_3$ (Scheme 22C).[105]



Scheme 22. Synthesis of DA aminocyclobutane **175** and subsequent [4+2] annulation reactions.

In 2018 a highly enantioselective [2+2] cycloaddition reaction of alkylidene malonate **181** with the internal C=C bond of N-allenamide **180** was developed by the Feng group with a Mg^{II}/N,N'-dioxide **L4** complex as a catalyst (Scheme 23A).[106] A highly substituted DA aminocyclobutane **182** was obtained in excellent yield and high enantioselectivity. **182** was also submitted to the [4+2] reaction conditions with silyl enol ether **176** in the presence of $SnCl_4$, and the product **183** was formed in moderate yield along with a maintained *ee* value (Scheme 23B).

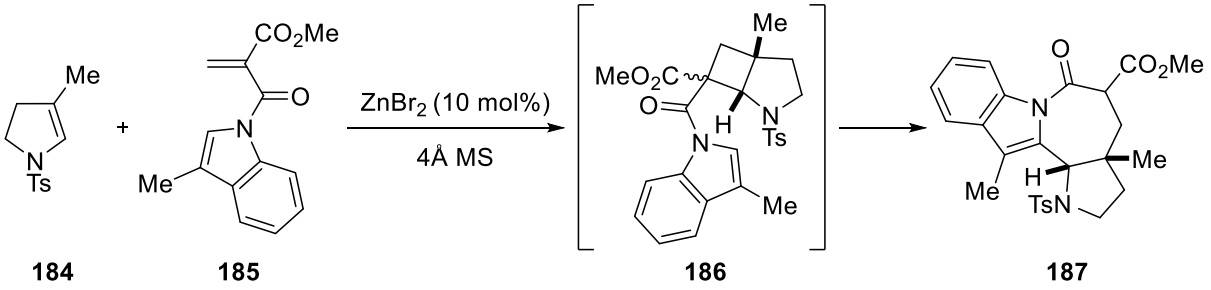


Scheme 23. Enantioselective [2+2] cycloaddition of N-allenamide **180** with alkylidene malonate **181** and further [4+2] cycloaddition with **176**.

[105] Perrotta, D.; Racine, S.; Vuilleumier, J.; de Nanteuil, F.; Waser, J. *Org. Lett.* **2015**, *17*, 1030.

[106] Zhong, X.; Tang, Q.; Zhou, P.; Zhong, Z.; Dong, S.; Liu, X.; Feng, X. *Chem. Commun.* **2018**, *54*, 10511.

In 2019, the Tang group also reported a copper-catalyzed [2+2] cycloaddition of N-sulfonyl enamides with dimethyl methylenemalonate **174**.[107] Based on this finding, they further reported in 2020 a formal [5+2] cycloaddition by replacing **174** with N-acryloyl indole **185** (Eq. 15).[108] The [2+2] cycloadduct **186** has been shown to be an important intermediate for the formation of **187** as supported by thorough mechanistic studies.



184 **185** **186** **187**

Equation 15. A formal [5+2] cycloaddition of N-sulfonyl enamide **184** with N-acryloyl indole **185**.

To sum up this section, various types of reactions have been developed for DA aminocyclopropanes while only a handful of reactions for DA aminocyclobutanes have been reported so far. It encouraged us to put more efforts into this relatively immature area in order to make DA cyclobutanes comparable to DA cyclopropanes in terms of reaction types. To this end, a Lewis acid-catalyzed [4+1] annulation between DA aminocyclobutane and isocyanide has been developed, which will be described in details in section 2.1.

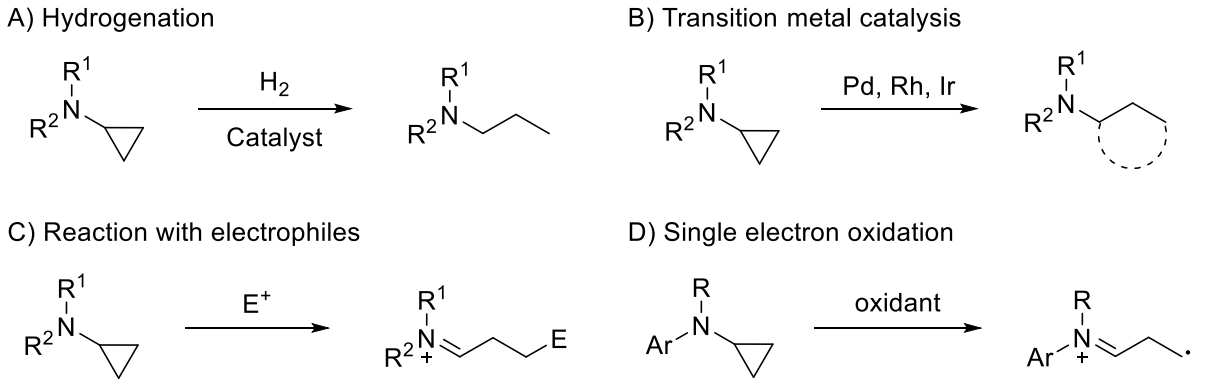
1.3 Reactivity of simple aminocyclopropanes and aminocyclobutanes

Due to the lack of electron-withdrawing groups at vicinal position, simple aminocyclopropanes are less reactive than DA aminocyclopropanes. However, due to the π-character of the strained carbon-carbon σ bonds, the bonding properties of cyclopropane derivatives are reminiscent of those of alkenes, which makes simple aminocyclopropanes still reactive under some circumstances.[109] For example, hydrogenation of simple aminocyclopropanes to produce propylamines is known to be thermodynamically favorable.[110]

Depending on the substituents on the nitrogen atom, simple aminocyclopropanes can be classified as electron-rich aminocyclopropanes (e.g. *N*-cyclopropyl amines with alkyl, aryl substituents) and electron-deficient aminocyclopropanes (e.g. *N*-cyclopropyl amides, *N*-cyclopropyl carbamates and *N*-cyclopropyl ureas). Transition-metal catalysis has been a general strategy for activating the cyclopropyl C-C bonds of both electron-rich aminocyclopropanes and electron-deficient aminocyclopropanes, leading to the formation of products through hydrogenation (Scheme 24A) or other transformations (Scheme 24B).[19] For electron-rich aminocyclopropanes, reaction with electrophiles (Scheme 24C) and single electron oxidation (Scheme 24D) are the two major ways for the C-C bond cleavage. For electron-deficient aminocyclopropanes, which are less reactive due to the delocalization of the lone pair of the nitrogen atom into the carbonyl group, their reactions with electrophiles or oxidants are much less

[107] Wei, S.; Yin, L.; Wang, S. R.; Tang, Y. *Org. Lett.* **2019**, *21*, 1458.
[108] Wei, S.; Zheng, L.; Wang, S. R.; Tang, Y. *Org. Lett.* **2020**, *22*, 1013.
[109] de Meijere, A. *Angew. Chem. Int. Ed.* **1979**, *18*, 809.
[110] Kuehne, M. E.; King, J. C. *J. Org. Chem.* **1973**, *38*, 304.

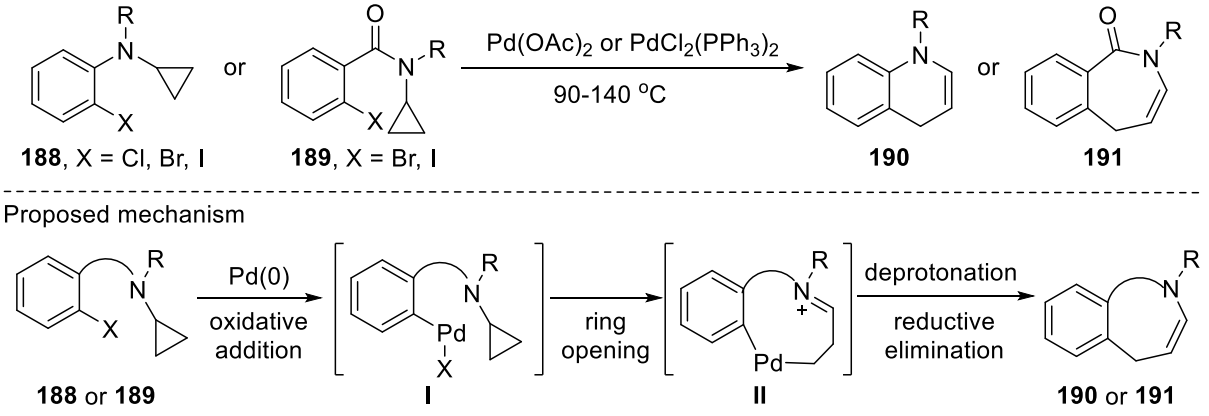
documented. As the products from hydrogenation are usually less interesting than the starting materials, I will summarize here the recent progress achieved by adopting the last three strategies.



Scheme 24. Major strategies for the activation of *N*-cyclopropyl amines.

1.3.1 Transition-metal catalyzed ring opening

In presence of transition-metal catalysts, versatile transformations can take place as they can stabilize ring-opening intermediates via formation of metallocycle species. In 2012, Rousseaux *et al.* and Dos Santos *et al.* independently reported the palladium-catalyzed intramolecular arylation of cyclopropylamine derivatives including *N*-cyclopropyl *ortho*-haloaniline compounds **188** as well as *N*-cyclopropyl *ortho*-iodobenzamides **189**, which were prepared conveniently by the Ugi reaction (Scheme 25).[111] In 2013 the Charette group extended the reaction to *N*-cyclopropyl *ortho*-bromobenzamides as substrates.[112] It is believed that this transformation proceeds via oxidative addition of palladium (0) into the C-X bond of **188** or **189** to generate the electrophilic Pd(II) intermediate **I**, which then triggers the ring opening and forms the intermediate **II**. In the end, after proton loss and reductive elimination, arylation product **190** or **191** could be obtained with good regioselectivity.



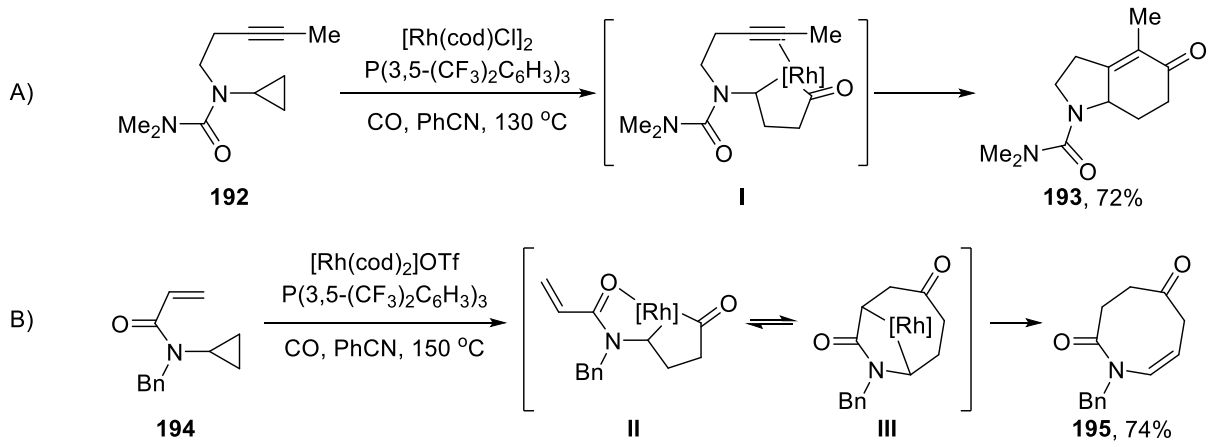
Scheme 25. Palladium-catalyzed intramolecular arylation and ring-expansion processes.

The Bower group has been investigating systematically the rhodium-catalyzed carbonylative cycloaddition processes of aminocyclopropanes since 2013. A strong Lewis-basic carbonyl substituent on the nitrogen atom is essential for directing C-C activation. They first reported a rhodium-catalyzed

[111] a) Rousseaux, S.; Liégault, B.; Fagnou, K. *Chem. Sci.* **2012**, *3*, 244. b) Dos Santos, A.; El Kaïm, L.; Grimaud, L.; Ramozzi, R. *Synlett* **2012**, 438.

[112] Ladd, C. L.; Roman, D. S.; Charette, A. B. *Tetrahedron* **2013**, *69*, 4479.

carbonylative [3+2+1] cyclization of **192** as a proof-of-principle transformation (Scheme 26A).[113] Mechanistic studies suggest that C-C bond activation was directed by the protecting group, then followed by CO insertion to form the rhodacyclopentanone intermediate **I**. Trapping of **I** with the tethered alkyne then provides a flexible access to *N*-heterobicyclic compound **193**. In 2015 the Bower group expanded the substrate scope to *N*-carbamate protected aminocyclopropanes with tethered alkene substituents under slightly different conditions.[114] Interestingly, when using *N*-cyclopropyl acrylamide **194** as substrate, only azocane derivative **195** was isolated rather than the expected bicyclic products[115]. The mechanism of this reaction involves a sequence of oxidative addition, CO insertion to form the intermediate **II**, alkene insertion to form the intermediate **III**, β-hydride elimination and reductive elimination (Scheme 26B).



Scheme 26. Rhodium-catalyzed carbonylative cyclizations of aminocyclopropanes.

More recently, they found that rhodacyclopentanones can also be captured by pendant nucleophiles such as urea N-H bonds or C(sp^2)-H bonds, forming 1,3-diazapanes or azepines respectively.[116] In the former case, the choice of substituent on the cyclopropylamine nitrogen controls the oxidation level of the product and C4-C5 unsaturated products like **197** or saturated products like **198** can be accessed selectively (Scheme 27A). In the latter case, when the two N-substituents of substrates such as **199** are a carbamate and an aryl/vinyl group, the rhodacyclopentanones can engage in C(sp^2)-H metalation and subsequently the C(sp^2)-C(sp^2) bond was formed via reductive elimination (Scheme 27B). For *trans*-1,2-disubstituted cyclopropanes, e.g. **201**, formation of a C3-substituted azepine arising from activation of the less-substituted C-C bond **a** was favored and >25:1 regioselectivity was observed with $P(C_6F_5)_3$ as ligand. By changing the pendant nucleophiles on the N-substituent, they further applied this methodology for the synthesis of diverse polyheterocycles.[117] In 2020 they also reported an example of

[113] Shaw, M. H.; Melikhova, E. Y.; Kloer, D. P.; Wittingham, W. G.; Bower, J. F. *J. Am. Chem. Soc.* **2013***, 135*, 4992.

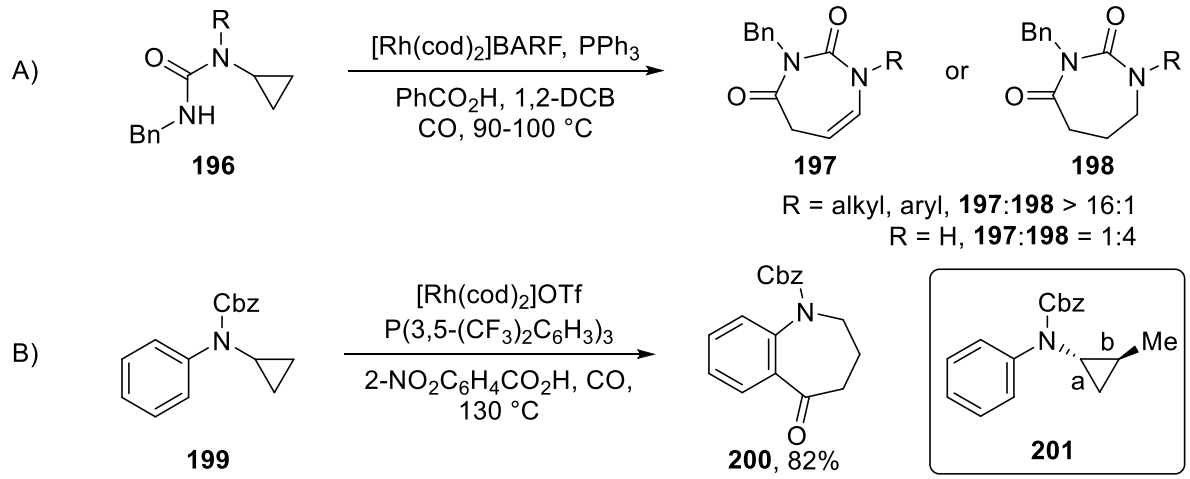
[114] Shaw, M. H.; McCreanor, N. G.; Wittingham, W. G.; Bower, J. F. *J. Am. Chem. Soc.* **2015***, 137*, 463.

[115] Shaw, M. H.; Croft, R. A.; Wittingham, W. G.; Bower, J. F. *J. Am. Chem. Soc.* **2015***, 137*, 8054.

[116] a) McCreanor, N. G.; Stanton, S.; Bower, J. F. *J. Am. Chem. Soc.* **2016***, 138*, 11465. b) Wang, G.-W.; Bower, J. F. *J. Am. Chem. Soc.* **2018***, 140*, 2743.

[117] a) Boyd, O.; Wang, G.-W.; Sokolova, O. O.; Calow, A. D. J.; Bertrand, S. M.; Bower, J. F. *Angew. Chem. Int. Ed.* **2019***, 58*, 18844. b) Wang, G.-W.; Boyd, O.; Young, T. A.; Bertrand, S. M.; Bower, J. F. *J. Am. Chem. Soc.* **2020***, 142*, 1740.

the carbonylative C-C bond activation of aminocyclopropanes by using isocyanate as a temporary directing group.[118]



Scheme 27. Rhodium-catalyzed synthesis of 1,3-diazepanes or azepines from aminocyclopropanes.

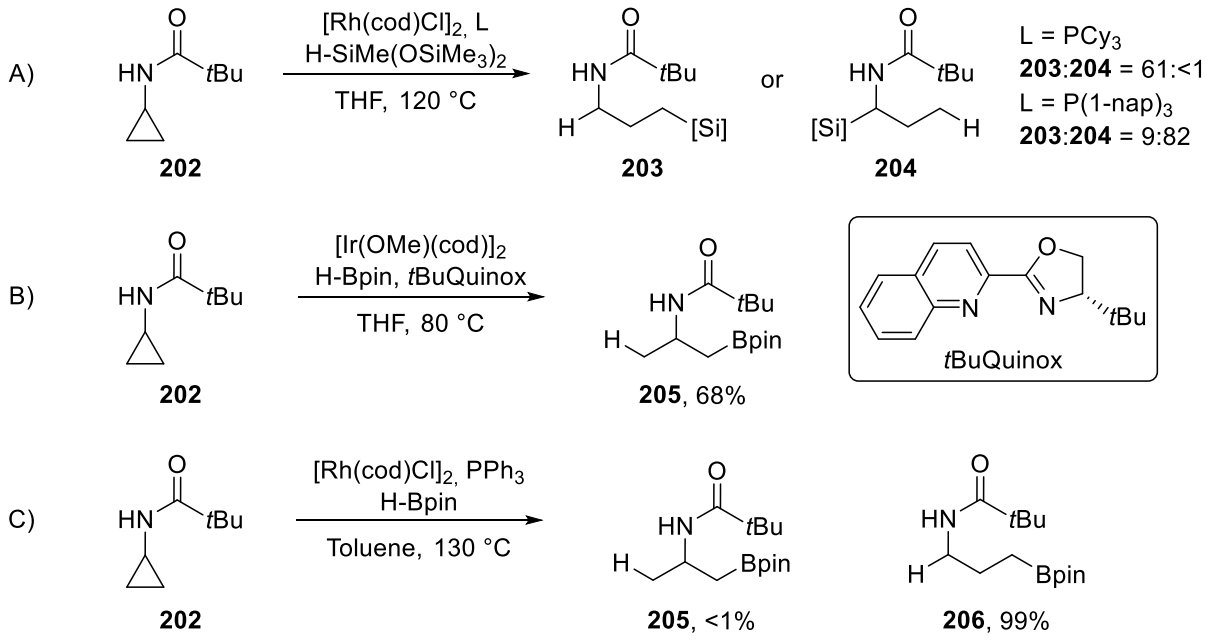
In addition to these heterocyclic products above, transition-metal catalysis has also been exploited for the synthesis of linear products starting from aminocyclopropanes. In 2017, the Yamaguchi group reported the ligand-controlled regiodivergent hydrosilylation of acyl aminocyclopropanes (Scheme 28A).[119] With PCy_3 as ligand, the silyl group was predominantly installed at the terminal position as shown in product **203**; with tri(naphthalen-1-yl)phosphine as ligand, the silyl group was introduce preferentially to the α-amino position as shown in **204**. In 2020, the same group also disclosed an iridium-catalyzed hydroboration reaction of aminocyclopropanes, and β-amino borates such as **205** were isolated as a result of the unexpected C2-C3 bond cleavage (Scheme 28B).[120] The use of *t*BuQuinox as ligand was essential for this transformation. By computing the activation energy, the authors found that the selective bond activation could be attributed to the ligand effect: the distances between the methyl group in Bpin and the methyl group in **202** vary with different ligands, which creates the steric repulsion. The Shi group reported in 2021 a rhodium-catalyzed hydroboration reaction of **202**, which was complementary to the iridium-catalyzed hydroboration reaction as linear boronate **206** was formed exclusively (Scheme 28C).[121]

[118] Wang, G.-W.; Sokolova, O. O.; Young, T. A.; Christodoulou, E. M. S.; Butts, C. P.; Bower, J. F. *J. Am. Chem. Soc.* **2020***, 142*, 19006.

[119] Kondo, H.; Itami, K.; Yamaguchi, J. *Chem. Sci.* **2017***, 8*, 3799.

[120] Kondo, H.; Miyamura, S.; Matsushita, K.; Kato, H.; Kobayashi, C.; Arifin; Itami, K.; Yokogawa, D.; Yamaguchi, J. *J. Am. Chem. Soc.* **2020***, 142*, 11306.

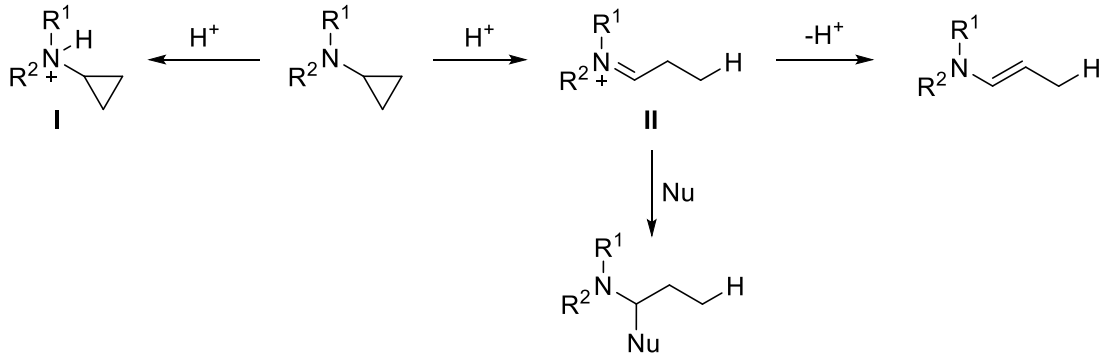
[121] Wang, Y.; Bai, J.; Yang, Y.; Zhao, W.; Liang, Y.; Wang, D.; Zhao, Y.; Shi, Z. *Chem. Sci.* **2021***, 12*, 3599.



Scheme 28. Rhodium- or iridium-catalyzed hydrosilylation and hydroboration of aminocyclopropane **202**.

1.3.2 Reaction with electrophiles

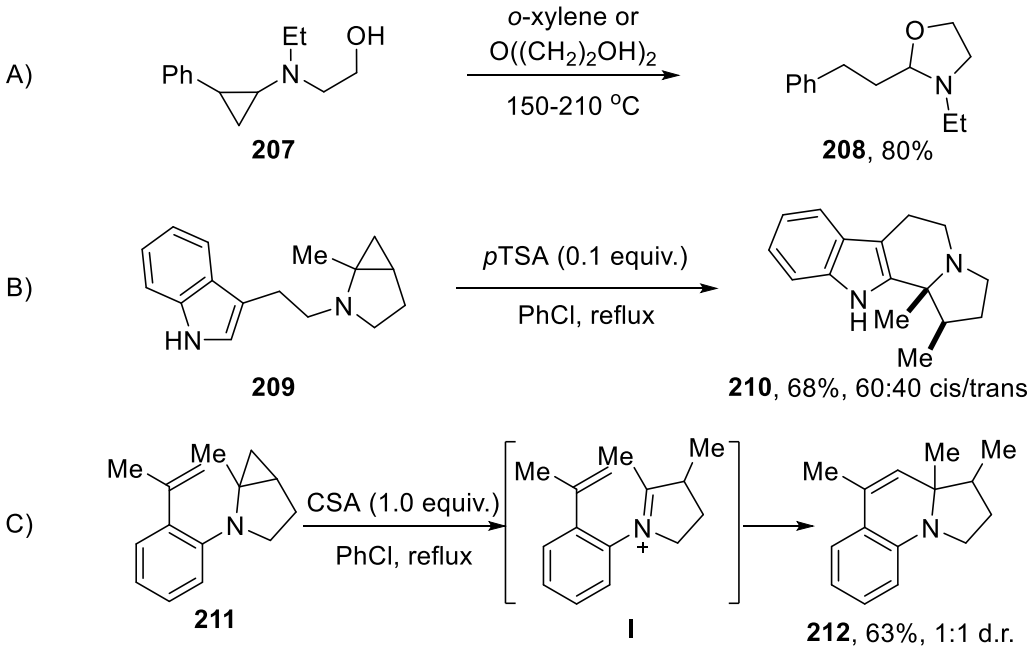
The simplest example of this type of transformations is protonation. However, unlike cyclopropanols which undergo ring opening under acidic conditions,[122] aminocyclopropanes are much more resistant because ammonium salts **I** could preferentially be formed rather than the ring-opened iminium species **II** (Scheme 29). In order to trigger the ring opening, heat is necessary especially when there is no other activating groups on the cyclopropyl ring. Once the iminium intermediates are formed, there are two possibilities to move forward: the first one is deprotonation to form enamine, which could also be seen as the result of thermal isomerization; the other possibility is addition of a nucleophile to form a stable product.



Scheme 29. Protonation of aminocyclopropanes.

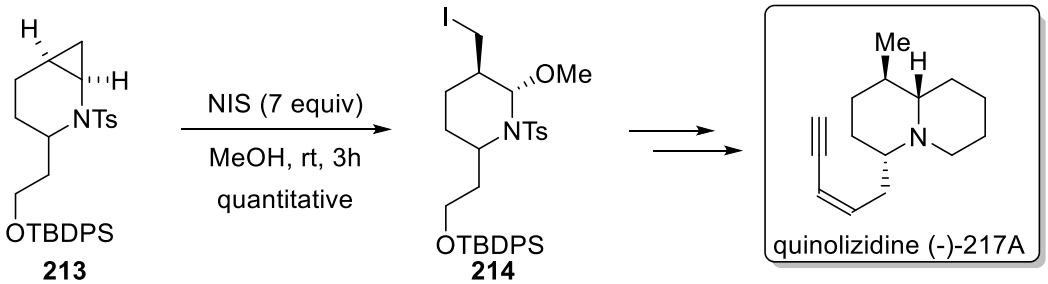
[122] Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597.

Pendant hydroxyl groups (Scheme 30A), electron-rich aryl groups (Scheme 30B) or vinyl groups (Scheme 30C) have been demonstrated to be good nucleophiles to trap the iminium, but all these examples are limited to intramolecular reactions and harsh conditions are usually required.[123]



Scheme 30. Trapping the ring-opening intermediates of aminocyclopropanes by a pendant nucleophile.

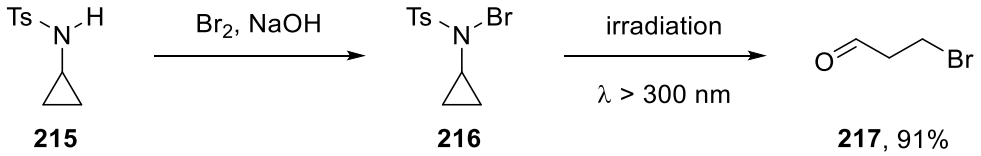
Apart from Brønsted acid, electrophilic halogenating agents could also act as electrophiles to trigger the ring opening of aminocyclopropanes, though only one example had been reported before I started my thesis work: in 2011, during the total synthesis of the amphibian alkaloid quinolizidine (-)-217A, the Harrity group disclosed that 2-tosyl-2-azabicyclo[4.1.0]heptane derivative **213** underwent ring-opening iodination with *N*-iodosuccinimide (NIS) to afford the hemiaminal ether **214** (Eq. 16).[124] NBS was also tested in this article but only afforded a dibromination byproduct. Though the ring-opening halogenation took place readily under mild conditions, this article did not provide any mechanistic insights on the facile ring-opening process.



Equation 16. Ring-opening of aminocyclopropane **213** by NIS.

[123] a) Bolesov, I. G.; Surmina, L. S.; Abramova, G. M.; Avezov, I. B.; Ustynyuk, Y. A.; Levina, R. Y. *Zh. Org. Khim.* **1974**, *10*, 2107. b) Larquetoux, L.; Ouhamou, N.; Chiaroni, A.; Six, Y. *Eur. J. Org. Chem.* **2005**, 4654. c) Wasilewska, A.; Wozniak, B, A.; Doridot, G.; Piotrowska, K.; Witkowska, N.; Retailleau, P.; Six, Y. *Chem. Eur. J.* **2013**, *19*, 11759.
[124] Mancey, N. C.; Sandon, N.; Auvidet, A.-L.; Butlin, R. J.; Czechtizky, W.; Harrity, J. P. A. *Chem. Commun.* **2011**, *47*, 9804.

By searching carefully in the literature, we found one example of photolysis of *N*-cycloalkyl-*N*-halosulfonamides such as **216**, which was reported by Dekker *et al*. in 1978.[125] In this work the authors first prepared **216** by the bromination of **215**, and irradiation of **216** in a pyrex reaction vessel at -10 °C and -80 °C then gave 3-bromopropanal (**217**) in high yield (Eq. 17). Based on these two reports, we wondered if we can develop a general method for the activation of simple aminocyclopropanes and meanwhile gain deeper understandings on the ring opening process. Related efforts will be described in section 3.1.

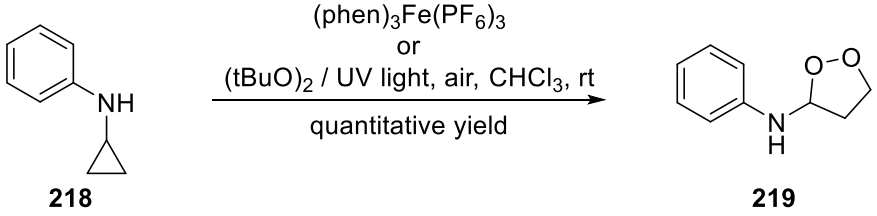


Equation 17. Photolysis of *N*-bromination aminocyclopropane **216**.

1.3.3 Single-electron oxidation

It is known that amino groups can be easily oxidized to radical cation species. The cyclopropyl group could then be opened up quickly to release ring strain and to form a distonic cation radical, which can be trapped by an alkene, an alkyne or molecular oxygen as shown below.

In the presence of molecular oxygen, single electron oxidation of aminocyclopropanes could result in the formation of 1,2-dioxolane species, which were first proposed as likely intermediates in 1975.[126] However, 1,2-dioxolanes such as **219** were not isolated until 2001 when the Wimalasena group employed an iron(III) catalyst as single-electron oxidizing reagent for this formal [3+2] cycloaddition (Eq. 18). [127] Interestingly, the Six group found in 2003 that purification of *N*-(4-phenoxyphenyl)aminocyclopropane by flash column chromatography on silica gel can also afford α-amino endoperoxide, probably due to the activating effect of silica gel.[128] Electrochemical aerobic oxidation was later developed by the Six group to realize the same transformation, and the advantage of this method is that the applied potential can be finely adjusted for each substrate.[129]

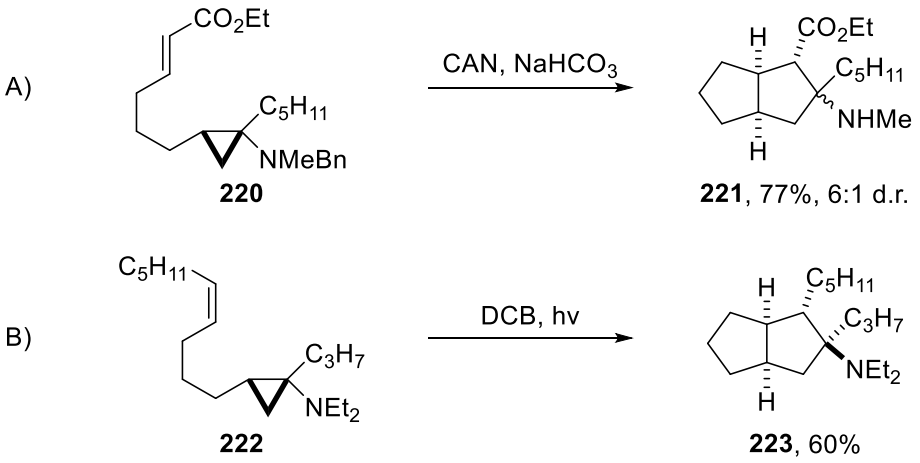


Equation 18. Single electron oxidation of N-cyclopropyl aniline **218** for the synthesis of 1,2-dioxolanes.

In 1998, the Iwata group and the Cha group independently reported intramolecular [3+2] annulations between cyclopropyl ring substituted with dialkylamino group and a pendant π C = C bond.[130] The Iwata group used several equivalents of ceric ammonium nitrate (CAN) as oxidant (Scheme 31A), while the

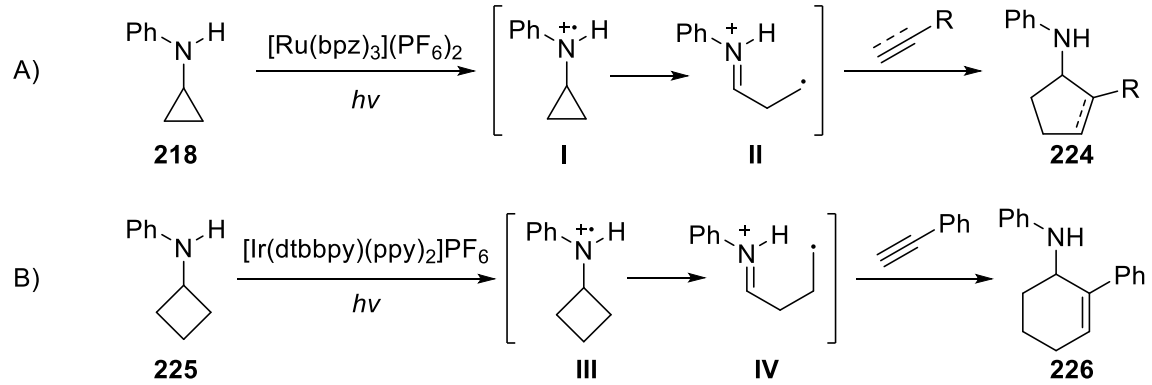
[125] Dekker, E. E. J.; Engberts, J. B. F. N.; de Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 39.
[126] Itoh, T.; Kanda, K.; Teranishi, S. *Tetrahedron Lett*. **1975**, *16*, 2801.
[127] Wimalasena, K.; Wickman, H. B.; Mahindaratne, M. P. D. *Eur. J. Org. Chem.* **2001**, 3811.
[128] Ouhamou, N.; Six, Y. *Org. Biomol. Chem.* **2003**, *1*, 3007.
[129] Madelaine, C.; Six, Y.; Buriez, O. *Angew. Chem. Int. Ed.* **2007**, *46*, 8046.
[130] a) Takemoto, Y.; Yamagata, S.; Furuse, S.; Hayase, H.; Echigo, T.; Iwata, C. *Chem. Commun.* **1998**, 651. b) Ha, J. D.; Lee, J.; Blackstock, S. C.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 8510.

Cha group used 1.5 equivalents of 1,4-dicyanobenzene (DCB) under irradiation with a medium-pressure mercury lamp as the oxidizing system (Scheme 31B).



Scheme 31. Intramolecular [3+2] annulation of dialkylamino cyclopropanes with a tethered alkene.

In 2012, the Zheng group reported a catalytic [3+2] annulation of cyclopropyl aniline **218** and alkenes, which is enabled by visible-light photocatalysis (Scheme 32A).[131] In 2014, under similar conditions they extended this transformation to the cycloaddition of cyclopropyl anilines with alkynes.[132] By using an iridium polypyridyl complex as photocatalyst, the Zheng group also reported similar intermolecular [4+2] cycloadditions of cyclobutyl anilines with alkynes (Scheme 32B).[133]



Scheme 32. Formal [3+2]/[4+2] cycloadditions enabled by photoredox catalysis.

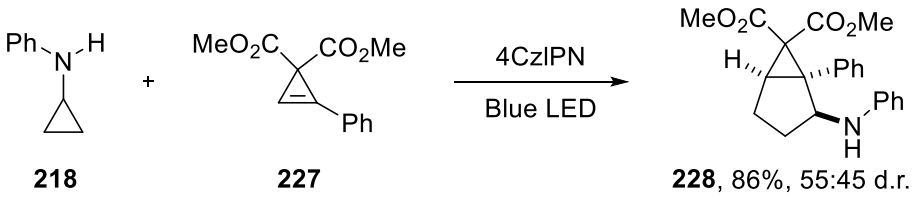
Inspired by the work from the Zheng group, our group reported in 2019 an intermolecular [3+2] annulation of cyclopropyl aniline **218** with cyclopropenes such as **227** for the synthesis of bicyclo[3.1.0]hexane **228** (Eq. 19).[134]

[131] Maity, S.; Zhu, M.; Shinabery, R. S.; Zheng, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 222.

[132] Nguyen, T. H.; Maity, S.; Zheng, N. *Beilstein J. Org. Chem.* **2014**, *10*, 975.

[133] a) Wang, J.; Zheng, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 11424. b) Wang, Q.; Zheng, N. *ACS. Catal.* **2017**, *7*, 4197.

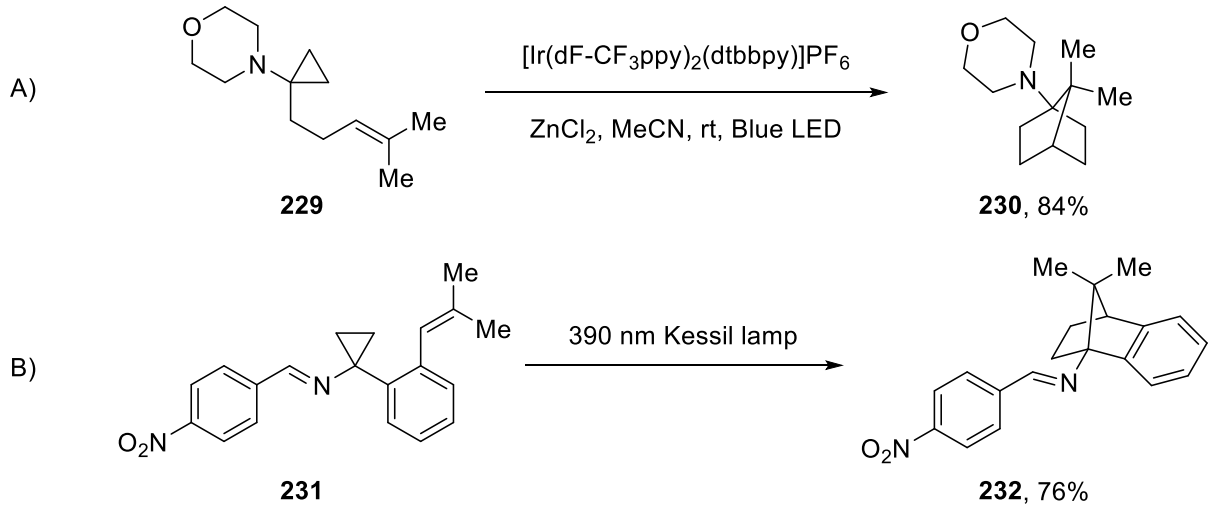
[134] Muriel, B.; Gagnebin, A.; Waser, J. *Chem. Sci.* **2019**, *10*, 10716.



218 **227** **228**, 86%, 55:45 d.r.

Equation 19. Photoredox catalyzed [3+2] cycloaddition of **218** with cyclopropenes.

Interestingly, by tethering the alkene to the C1 position of aminocyclopropane and modifying the length of alkyl chain, the Stephenson group has recently synthesized 1-aminonorbornanes via a formal [3+2] cycloaddition (Scheme 33A).[135] The combination of a commonly-used iridium complex and the Lewis acid $ZnCl_2$ provided product **230** in 84% yield under blue light irradiation. In 2019, they also reported another method for the synthesis of 1-aminonorbornanes by exploiting imine photochemistry for masked N-centered radical reactivity (Scheme 33B).[136] This process utilized violet light to excite imine **231** in order to get an excited state diyl, whose nitrogen-centered radical character was employed to facilitate the homolytic fragmentation of the cyclopropane ring. Subsequent radical cyclization then formed two new C-C bonds as shown in the product **232**. These two reports represent to date the most efficient and flexible access to 1-aminonorbornanes, which can be potentially useful in medicinal chemistry.



229 **230**, 84%

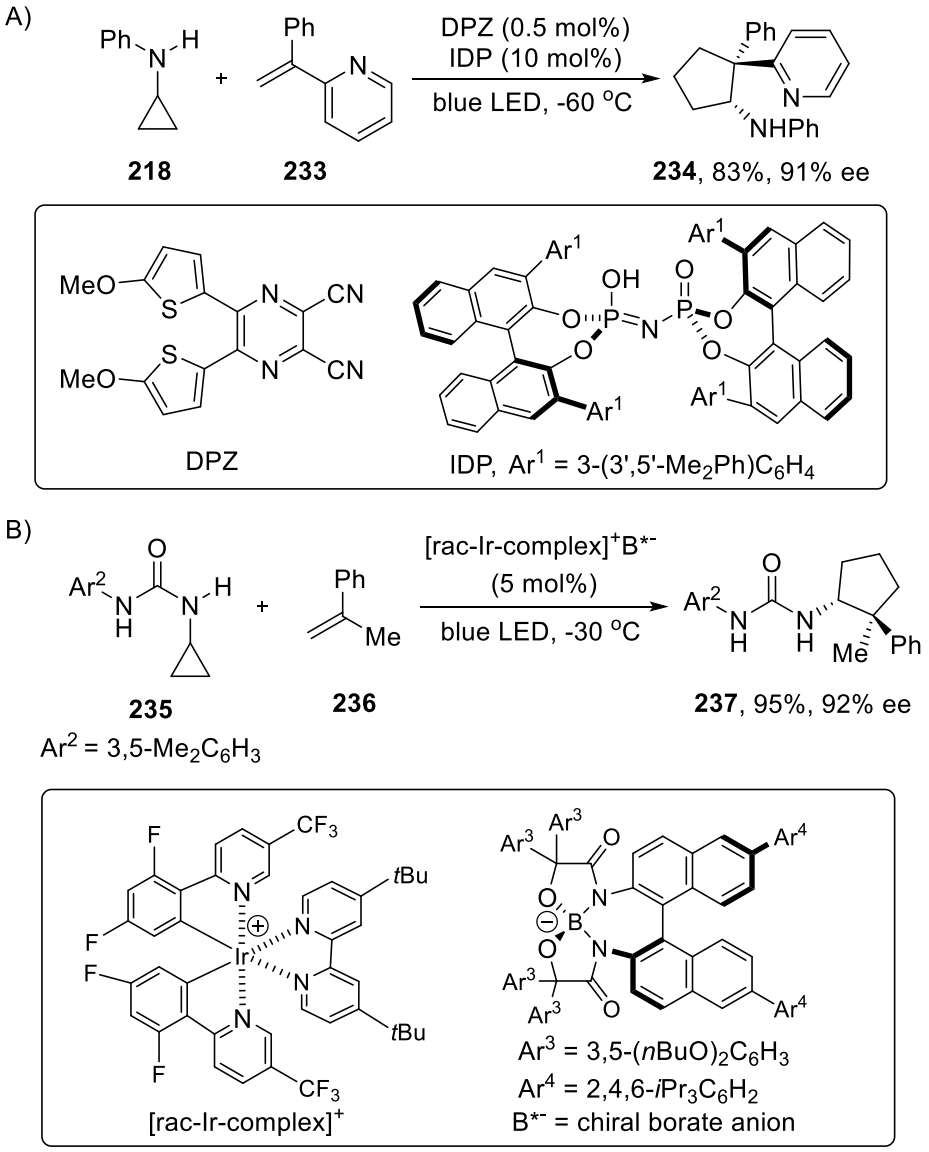
231 **232**, 76%

Scheme 33. Intramolecular [3+2] cycloadditions developed by the Stephenson group.

In 2020, the Jiang group reported an asymmetric version of the formal [3+2] cycloaddition between **218** and 2-(1-phenylvinyl)pyridine **233** under cooperative photoredox and chiral Brønsted acid catalysis (Scheme 34A).[137] The use of a rigid and confined C_2-symmetric iminodiphosphoric acid (IDP), in combination with a dicyanopyrazine-derived chromophore DPZ as photoredox catalyst, enables a high enantioselectivity for this asymmetric [3+2] cycloaddition. The azaarene in the alkene partner, for example the pyridine in **233**, plays a crucial rule because in the transition state the coordination of azaarene as well as the iminium functionality with the bifunctional catalyst IDP controls the stereoselectivity. Almost at the same time, the Ooi group also reported an asymmetric [3+2]

[135] Staveness, D.; Sodano, T. M.; Li, K.; Burnham, E. A.; Jackson, K. D.; Stephenson, C. J. *Chem* **2019**, *5*, 215.
[136] Staveness, D.; Collins III, J. L.; McAtee, R. C.; Stephenson, C. J. *Angew. Chem. Int. Ed.* **2019**, *58*, 19000.
[137] Yin, Y.; Li, Y.; Gonçalves, T. P.; Zhan, Q.; Wang, G.; Zhao, X.; Qiao, B.; Huang, K.-W.; Jiang, Z. *J. Am. Chem. Soc.* **2020**, *142*, 19451.

cycloaddition between aminocyclopropanes and 1,1-disubstituted alkenes (Scheme 34B).[138] Protecting cyclopropylamine with an anion-binding urea group, together with the use of an ion pair comprising an iridium complex and a weakly coordinating chiral borate anion, led to the successful implementation of this asymmetric radical cycloaddition.

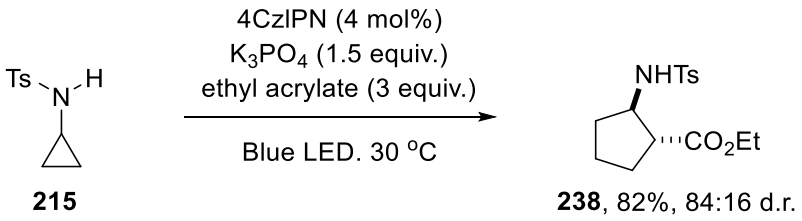


Scheme 34. Asymmetric [3+2] cycloadditions between aminocyclopropanes and alkenes.

In 2021, the Aggarwal group also reported a diastereoselective photoredox-catalyzed [3+2] cycloaddition of *N*-sulfonyl cyclopropylamines with ethyl acrylate (Eq. 20).[139] Considering the high oxidation potential of *N*-tosyl cyclopropylamine **215** ($E_{1/2}^{red}$ = 2.24 V vs SCE in CH_3CN), this reaction probably proceeded via oxidation of the deprotonated form of **215** as evidenced by the cyclic voltammetry experiments.

[138] a) Uraguchi, D.; Kimura, Y.; Ueoka, F.; Ooi, T. *J. Am. Chem. Soc.* **2020***, 142*, 19462. b) Kimura, Y.; Uraguchi, D.; Ooi, T. *Org. Biomol. Chem.* **2021***, 19*, 1744.

[139] White, D. H.; Noble, A.; Booker-Milburn, K. I.; Aggarwal, V. K. *Org. Lett.* **2021***, 23*, 3038.



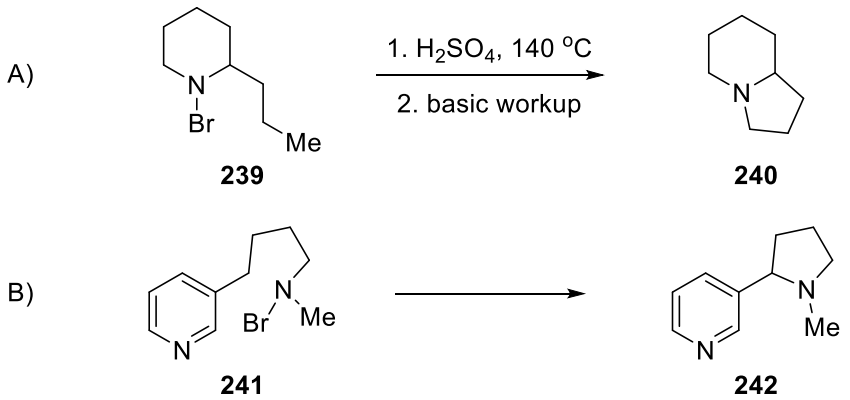
Equation 20. Diastereoselective photoredox-catalyzed [3+2] cycloaddition of **215**.

1.4 Nitrogen-centered radicals

From a synthetic perspective, nitrogen-centered radicals have been relatively underutilized compared to carbon-centered radicals. This can be attributed to a lack of convenient methods for generating these reactive species, which limited their broad applicability.[140] A general approach for the generation of nitrogen-centered radicals involves the cleavage of N-X bonds, where X can be a halogen, a nitrogen, an oxygen or a sulfur group.[141] In this part, homolytic cleavage of nitrogen-halogen bonds (known as Hoffmann–Löffler–Freytag reaction, HLF reaction) and nitrogen-hydrogen bonds (enabled by proton-coupled electron transfer, PCET) to form nitrogen-centered radicals, will be introduced in details since these two methods do not require pre-functionalization of N-H bonds and are more related to my thesis. Activation of N-fluorinated compounds will also be introduced because it gives some insights into the mechanism of the oxidative ring-opening fluorination project described in section 3.3.

1.4.1 Hofmann–Löffler–Freytag reaction

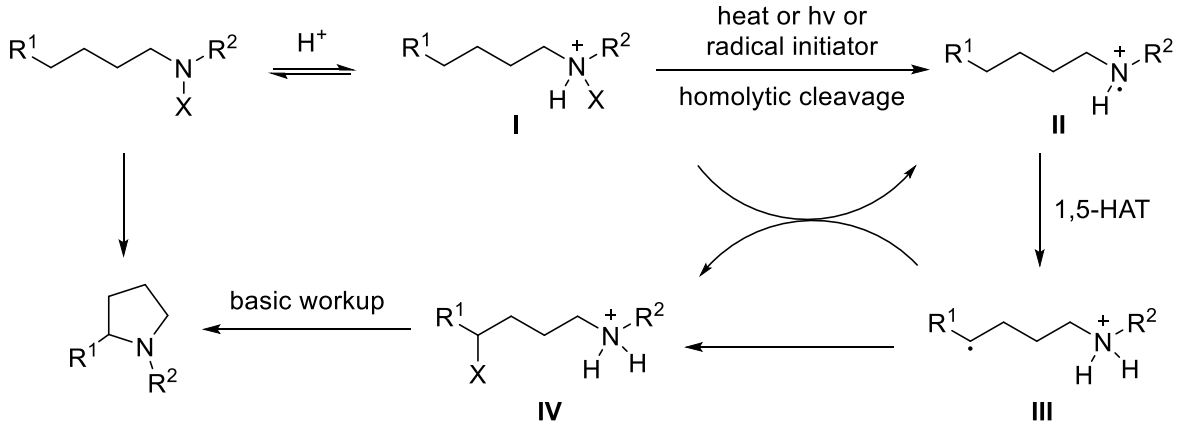
Early in 1880s, A. W. Hofmann reported the synthesis of a tertiary amine which was later known as δ-coneceine **240** from an N-bromo precursor **239** under acidic and reflux conditions (Scheme 35A).[142] In 1909, K. Löffler and C. Freytag extended the scope of this transformation and demonstrated the synthetic utility of the process as exemplified by their elegant synthesis of nicotine **242** (Scheme 35B). The mechanism of the HLF reaction was first investigated by the Wawzonek group in 1950 and more detailed studies were reported in 1960 by the Corey group to elucidate the mechanism.[143]



Scheme 35. Discovery of the HLF reaction.

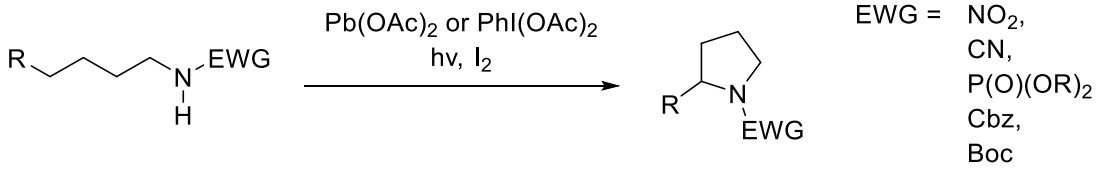
[140] a) Zard, S. Z. *Chem. Soc. Rev.* **2008**, *37*, 1603. b) Kärkäs, M. D. *ACS Catal*. **2017**, *7*, 4999.
[141] Xiong, T.; Zhang, Q. *Chem. Soc. Rev.* **2016**, *45*, 3069.
[142] Kumar, G.; Pradhan, S.; Chatterjee, I. *Chem. Asian. J.* **2020**, *15*, 651.
[143] a) Wawzonek, S.; Thelen, P. J. *J. Am. Chem. Soc.* **1950**, *72*, 2118. b) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960**, *82*, 1657.

The generally accepted mechanism involves the protonation of the halogenated amine in the first step, followed by homolytic cleavage of the N-X bond of **I** under the influence of heat or chemical initiation to afford nitrogen-centered radical cation **II**. Intramolecular 1,5-hydrogen atom transfer (1,5-HAT) then produces carbon-centered radical **III** which subsequently abstracts a halogen atom to form intermediate **IV** through a radical chain reaction. After basic workup, **IV** undergoes deprotonation and further intramolecular S_N2 reaction to yield the pyrrolidine product (Scheme 36).



Scheme 36. Mechanism of the HLF reaction.

The application of the original HLF reaction for the synthesis of complex molecules was rather limited due to the strongly acidic reaction conditions. Therefore, many variations of the HLF reaction were introduced, among which the Suárez modification is the most important one. In 1980s, the Suárez group discovered that when putting an electron-withdrawing group on the nitrogen atom, these substrate can undergo HLF reaction under very mild neutral conditions (Eq. 21).[144] The use of an electron-deficient substituent on nitrogen promotes the 1,5-HAT process through a polarized aminyl radical intermediate and avoids the need of strongly acidic conditions. Notable features of the Suárez modification are: 1) the N-I bond was formed in situ; 2) the homolysis of the N-I bond proceeds at low temperature (20-40 ^oC) or by irradiation with visible light.



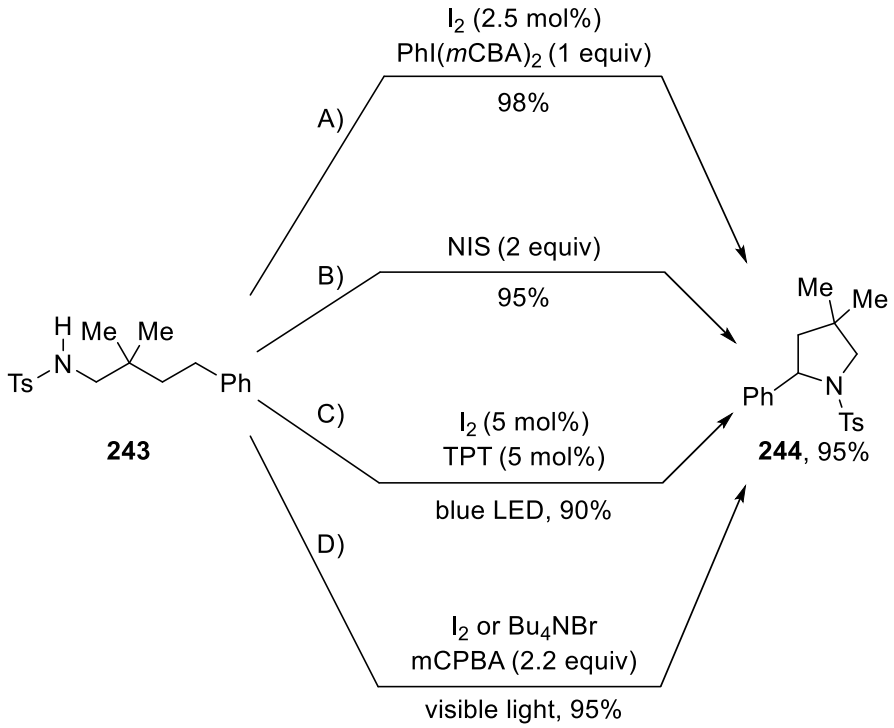
Equation 21. Suárez modification of the HLF reaction.

The Suárez modification allowed the use of HLF reaction with more sensitive molecules, thus greatly extended its application in synthesis. Nonetheless, the need to use stoichiometric amount of I_2 has pushed chemists to find either a catalytic solution or other alternative reagents. In 2015, the Muñiz group reported a catalytic HLF reaction by modification of the iodine (III) reagent (Scheme 37A).[145] The

[144] a) Betancor, C.; Concepcion, J. I.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1983**, *48*, 4430. b) de Armas, P.; Carrau, R.; Concepcion, J. I.; Francisco, C. G.; Hernández, R.; Suárez, E. *Tetrahedron Lett*. **1985**, *26*, 2493. c) Carrau, R.; Hernández, R.; Suárez, E.; Betancor, C. *J. Chem. Soc., Perkin Trans. 1,* **1987**, 937. d) de Armas, P.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Chem. Soc., Perkin Trans. 1,* **1988**, 3255. e) Francisco, C. G.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2003**, *68*, 1012.

[145] Martínez, C.; Muñiz, K. *Angew. Chem., Int. Ed.* **2015***, 54*, 8287.

amount of I_2 could be lowered to 2.5 mol% without loss in yield by simply replacing the oxidant $PhI(OAc)_2$ with $PhI(mCBA)_2$. In 2016, the Muñiz group reported an *N*-iodosuccinimide (NIS) promoted HLF reaction under visible light irradiation,[146] in which case visible light was believed to induce the homolytic cleavage of the N-I bond and initiate the radical chain process (Scheme 37B). This discovery directly inspired us when we looked for an efficient approach to activate simple aminocyclopropanes. Further progress in this area includes: a triiodide-mediated approach for HLF reaction which was reported by the Nagib group in 2016;[147] a photoredox approach using 2,4,6-triphenylpyrylium tetrafluoroborate (TPT) as catalyst and air as terminal oxidant, which was reported by the Muñiz group in 2017 (Scheme 37C);[148] an iodine catalysis or bromine catalysis system by using *m*CPBA as terminal oxidant under visible light irradiation, as reported by the Muñiz group in 2018 (Scheme 37D).[149]

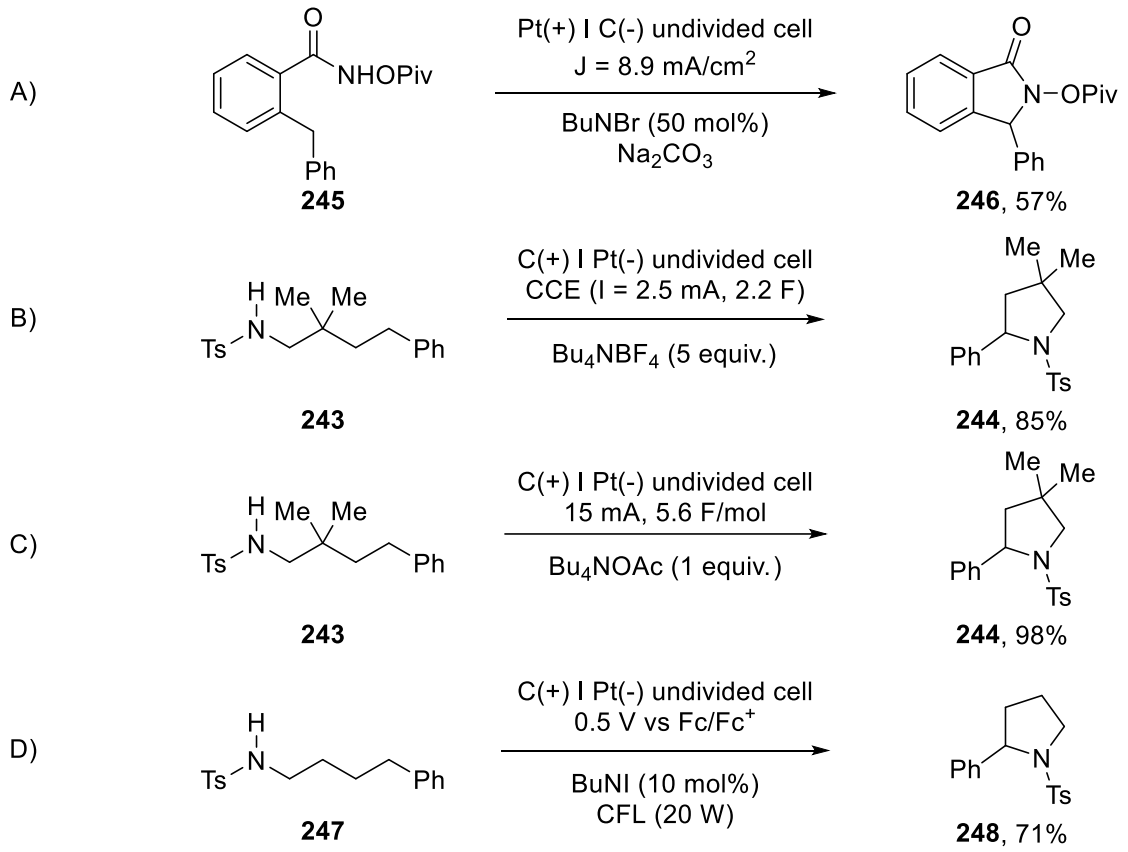


Scheme 37. Modifications of the HLF reaction by the Muñiz group.

Electrochemical methods for the HLF reaction have also been explored by several groups independently: 1) Zhang *et al*. reported in 2018 the electrochemical generation of N-acyloxy amidyl radicals and their application in intramolecular amination of sp^2 and sp^3 C-H bonds (Scheme 38A). Tetrabutylammonium bromide was used as electrolyte and generation of the N-centered radical was proposed through the homolytic cleavage of *in-situ* formed N-Br bond;[150] 2) In 2018, the Muñiz group disclosed a direct anodic benzylic C-H amination strategy for the synthesis of pyrrolidines, though the proposed mechanism is different from the classical HLF reaction as the N-centered radical might not be formed due to the use of tetrabutylammonium tetrafluoroborate as electrolyte. High potentials were applied in order to activate the benzylic C-H bond for generating a benzylic cation, which was then trapped by a

[146] O'Broin, C. Q.; Fernandez, P.; Martínez, C.; Muñiz, K. *Org. Lett.* **2016***, 18*, 436.
[147] Wappes, E. A.; Fosu, S. C.; Chopko, T. C.; Nagib, D. A. *Angew. Chem. Int. Ed.* **2016***, 55*, 9974.
[148] Becker, P.; Duhamel, T.; Stein, C. J.; Reiher, M.; Muñiz, K. *Angew. Chem. Int. Ed.* **2017***, 56*, 8004.
[149] a) Duhamel, T.; Stein, C. J.; Reiher, M.; Muñiz, K. *ACS Catal.* **2018***, 8*, 3918. b) Becker, P.; Duhamel, T.; Martínez, C.; Muñiz, K. *Angew. Chem. Int. Ed.* **2018***, 57*, 5166.
[150] Zhang, S.; Li, L.; Xue, M.; Zhang, R.; Xu, K.; Zeng, C. *Org. Lett.* **2018***, 20*, 3443.

nitrogen nucleophile (Scheme 38B);[151] 3) Also in 2018 the Lei group realized an electrochemical HLF reaction by using tetrabutylammonium acetate as electrolyte, and as a plausible mechanism, they proposed the generation of a N-centered radical after the formation of a hydrogen bonding complex between the substrate and acetate (Scheme 38C); [152] 4) In 2019, a combined electrochemical/photochemical method was reported by the Stahl group (Scheme 38D), in which case the anodic potentials, as compared to the three abovementioned examples, were significantly reduced by using tetrabutylammonium iodide as electrolyte (Figure 8).[153]



Scheme 38. Electrochemical methods for realizing the HLF reaction.

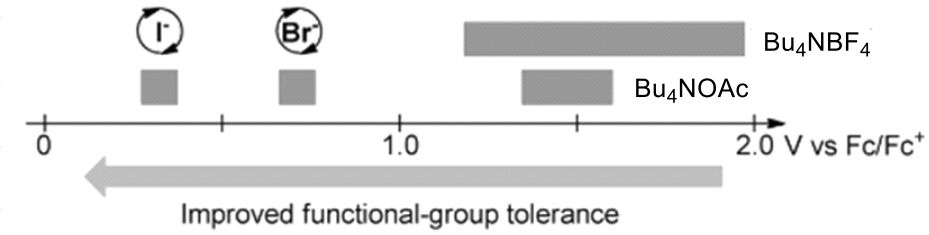


Figure 8. Comparing the anodic potentials of the abovementioned electrochemical methods.

To conclude this part, the HLF reaction represents a uniquely effective protocol for the formation of pyrrolidines by exploiting the *in-situ* formed N-X bonds (X = I, Br or Cl) for the generation of N-centered radicals. However, it is important to note that the reactivity of N-halogenated intermediates

[151] Herold, S.; Bafaluy, D.; Muñiz, K. *Green Chem.* **2018***, 20*, 3191.
[152] Hu, X.; Zhang, G.; Bu, F.; Nie, L.; Lei, A. *ACS Catal.* **2018***, 8*, 9370.
[153] Wang, F.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2019***, 58*, 6385.

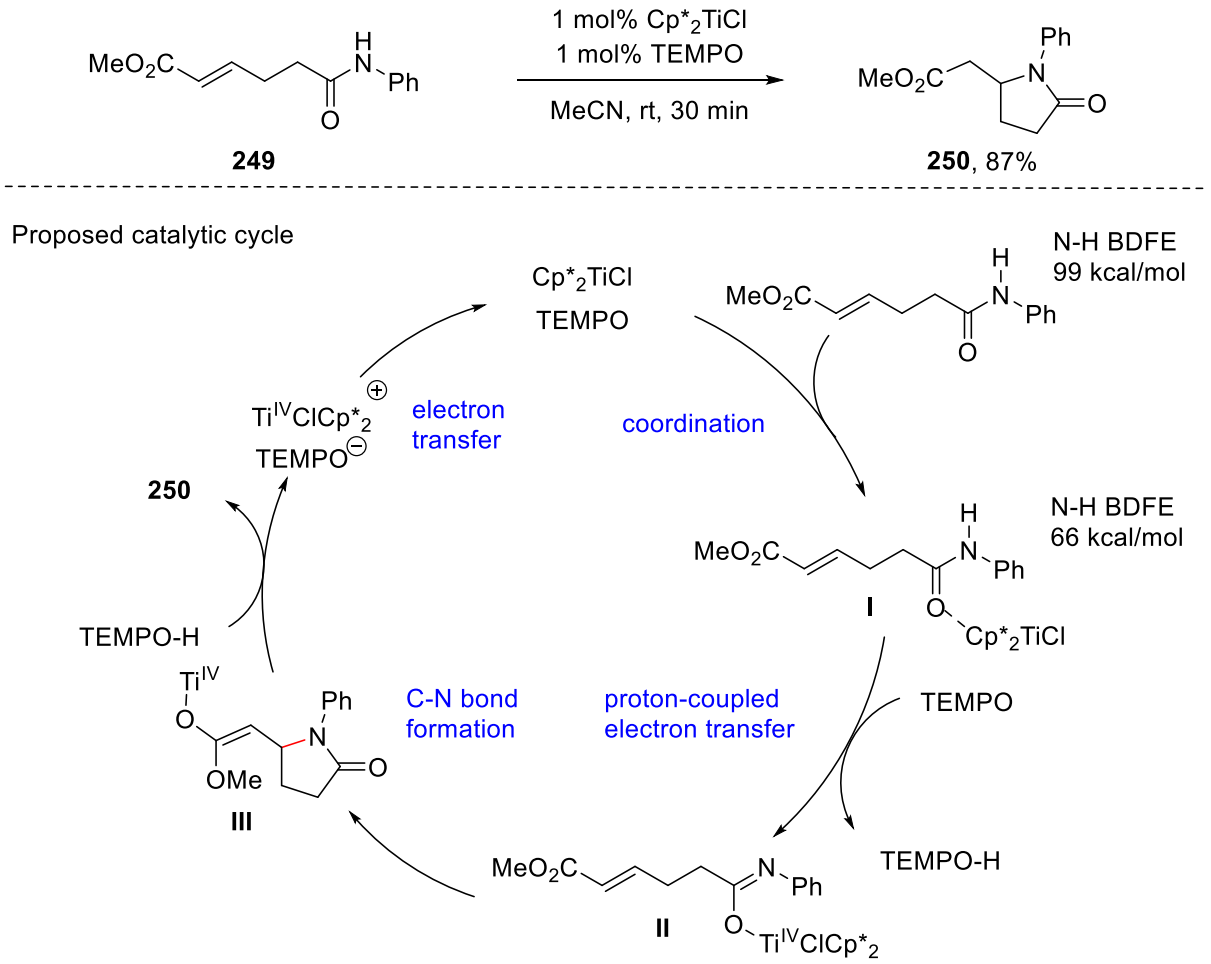
generally decreases in the order of I>Br>Cl>F. This is in line with the facts that N-I and N-Br bonds readily undergo visible light–induced homolysis, while the activation of an N-Cl bond requires a photoredox catalyst[154] and the N-F bond is entirely stable under photochemical conditions.[155] The activation of N-F bond by transition-metal catalysis for generating N-centered radicals will be discussed in section 1.4.3.

1.4.2 Generation of nitrogen-centered radical by PCET

Proton-coupled electron transfer (PCET) is an unconventional redox process in which both proton and electron are transferred, often in a concerted elementary step.[156] Recognized as an important mechanism in biological redox processes and inorganic energy conversion technologies, PCET has recently been exploited in organic synthesis. Activating amide N-H bonds by PCET is a straightforward way to generate nitrogen-centered radicals, which are usually challenging to produce by classical hydrogen atom transfer (HAT) based approaches because of the high bond dissociation free energies (BDFEs) of amide N-H bonds (~110 kcal/mol).[157] PCET studies often require the combination of an outer-sphere oxidant and a base, to remove an electron and a proton simultaneously. However, a common problem is the incompatibility of the oxidant and the base, because the former is electron deficient while the latter is electron rich.[158]

The Knowles group has been pioneering this research field since 2015, when they first reported a complexation-induced bond-weakening strategy for the homolysis of N-H bonds (Scheme 39).[159] In this conjugate amination reaction, coordination of the amide carbonyl group to the titanocene complex helps to reduce the N-H bond strength of *N*-aryl amide **249** by 33 kcal/mol, which enables its soft homolysis to afford a closed-shell, Ti^{IV} aza-enolate intermediate **II** by using TEMPO as H-atom acceptor. **II** then undergoes addition to an electron-deficient olefin to form a C-N bond and generate a new titanium enolate **III**, which could be protonated by TEMPO-H to give product **250**. The highly reducing nitroxide anion would then reduce Ti^{IV} to Ti^{III} and close the catalytic cycle.

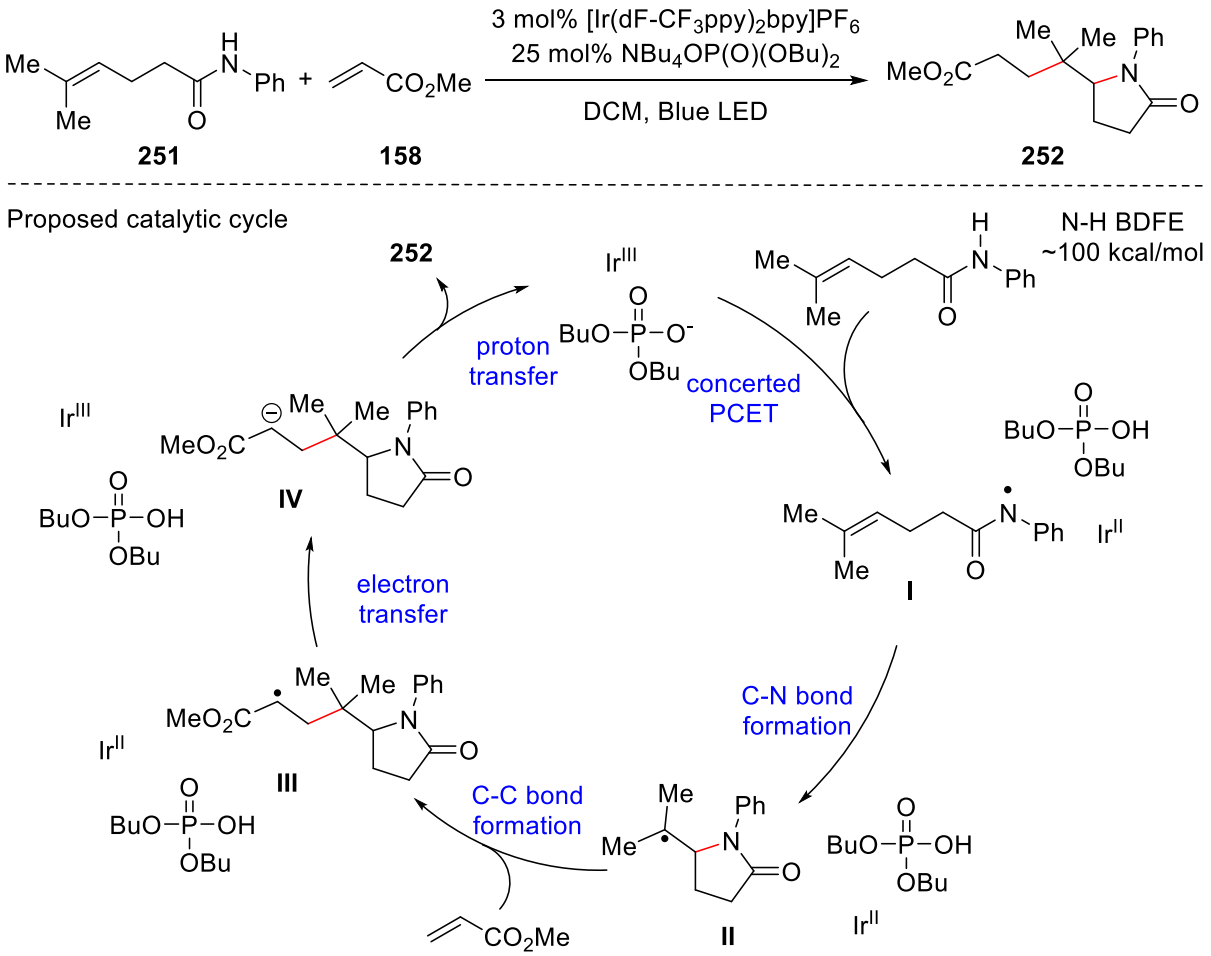
[154] Qin, Q.; Yu, S. *Org. Lett.* **2015**, *17*, 1894.
[155] Bosnidou, A. E.; Duhamel, T.; Muñiz, K. *Eur. J. Org. Chem.* **2020**, *2020*, 6361.
[156] a) Miller, D, C.; Tarantino, K. T.; Knowles, R. R. *Top. Curr. Chem.* **2016**, *374*, 30. b) Gentry, E. C.; Knowles, R. R. *Acc. Chem. Res.* **2016**, *49*, 1546.
[157] Nguyen, L. Q.; Knowles, R. R. *ACS Catal.* **2016**, *6*, 2894.
[158] Waidmann, C. R.; Miller, A. J. M.; Ng, C.-W. A.; Scheuermann, M. L.; Porter, T. R.; Tronic, T. A.; Mayer, J. M. *Energy Environ. Sci.* **2012**, *5*, 7771.
[159] Tarantino, K. T.; Miller, D, C.; Callon, T. A.; Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 6440.



Scheme 39. Bond-weakening strategy for the homolysis of N-H bonds.

Also in 2015, the Knowles group reported another strategy for the selective homolysis of strong N-H bonds: an oxidative PCET process (Scheme 40).[160] With the help of Mayer's effective bond strength formalism,[161] they found that Ir(III) photocatalyst/dibutyl phosphate catalyst pair with blue light irradiation enables high yielding carboamination reactions. It is proposed that the formation of a hydrogen bond between phosphate and the secondary amide substrate **251**, together with the excited Ir(III) photocatalyst, could facilitate the PCET process. The amidyl radical **I** would then add to the pendant double bond to form a C-N bond as well as a carbon-centered radical, which could undergo intermolecular addition to methyl acrylate to form a C-C bond and an α-carbonyl radical. Intermediate **III** could then take one electron from the Ir(II) species and form an enolate **IV**, which would be protonated to form product **252** and regenerate the catalytically active forms of the oxidant/base pair.

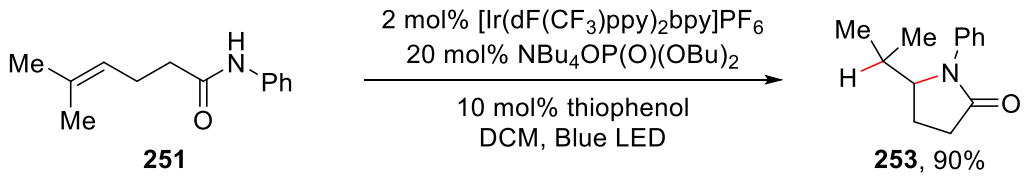
[160] Choi, G. J.; Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 9226.
[161] Warren, J. J.; Tronic, T. A. Mayer, J. M. *Chem. Rev.* **2010**, *110*, 6961.



Scheme 40. Catalytic alkene carboaminations enabled by oxidative PCET.

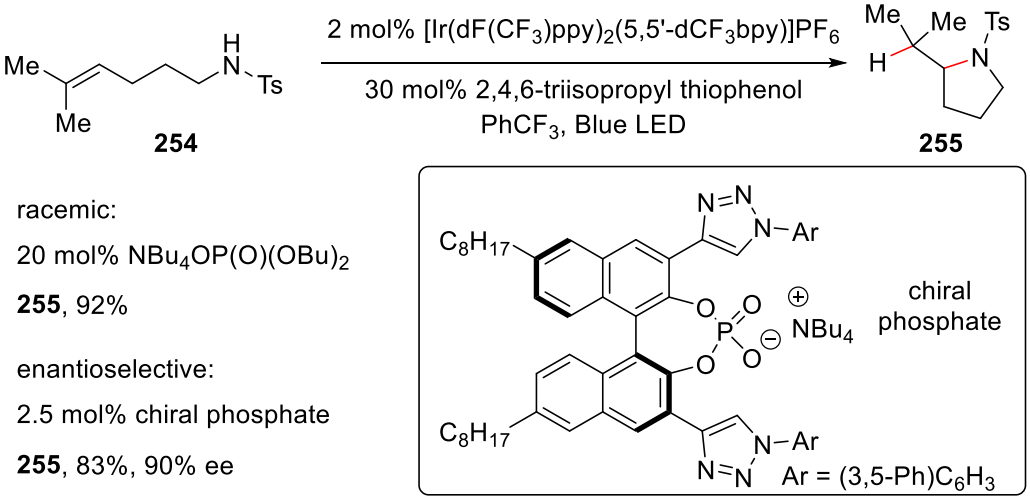
Based on the achievements in the oxidative PCET process, the Knowles group also reported an intramolecular hydroamidation reaction of unactivated alkenes with amides by adding thiophenol as H-atom donor instead of trapping the carbon-centered radical by acrylates (Eq. 22).[162] Kinetic studies were performed in order to elucidate the factors that control the chemoselectivity in these hydroamination reactions.[163] It was found that the driving force for both PCET reactions increases as the reduction potential of the Ir photocatalyst becomes more positive. However, since $k_{PCET\text{-}amide}$ is more sensitive to changes in the driving force than $k_{PCET\text{-}thiol}$, a more efficient hydroamidation can be realized by using a stronger oxidant. These findings can be used to predict reactivity trends, rationalize the selective activation of amide N-H bonds in the presence of much weaker thiol S-H bonds, and deliver strategies for further improvement of thiol co-catalyzed PCET reactions.

[162] a) Miller, D, C.; Choi, G. J.; Orbe, H. S.; Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 13492. b) Nguyen, S. T.; Zhu, Q.; Knowles, R. R. *ACS. Catal.* **2019**, *9*, 4502.
[163] Qiu, G.; Knowles, R. R. *J. Am. Chem. Soc.* **2019**, *141*, 16574.



Equation 22. Catalytic intramolecular hydroamidation of olefin **251** enabled by PCET.

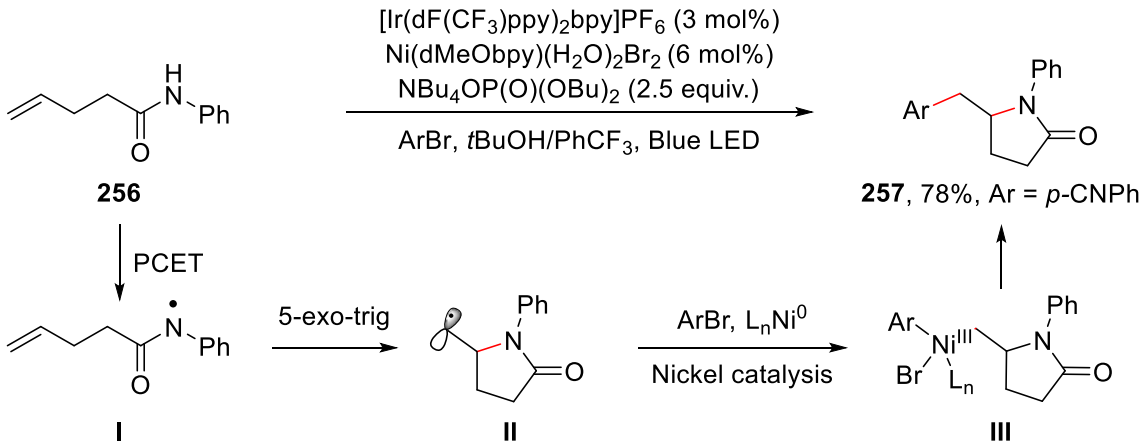
In 2018, the intra- and intermolecular hydroamination reactions of unactivated alkenes with sulfonamides were reported by the Knowles group with 30 mol% 2,4,6-triisopropyl thiophenol as co-catalyst.[164] Interestingly, by using a BINOL-derived chiral phosphate, they further reported in 2020 an enantioselective hydroamination of alkenes with sulfonamides (Scheme 41). [165] Noncovalent interactions between the neutral sulfonamidyl radical and a chiral phosphoric acid generated in the PCET event were hypothesized to serve as the basis for asymmetric induction in a subsequent C-N bond forming step, leading to the formation of **255** in high enantioselectivity.



Scheme 41. Racemic and asymmetric intramolecular hydroamidation of sulfonamide **254** enabled by PCET.

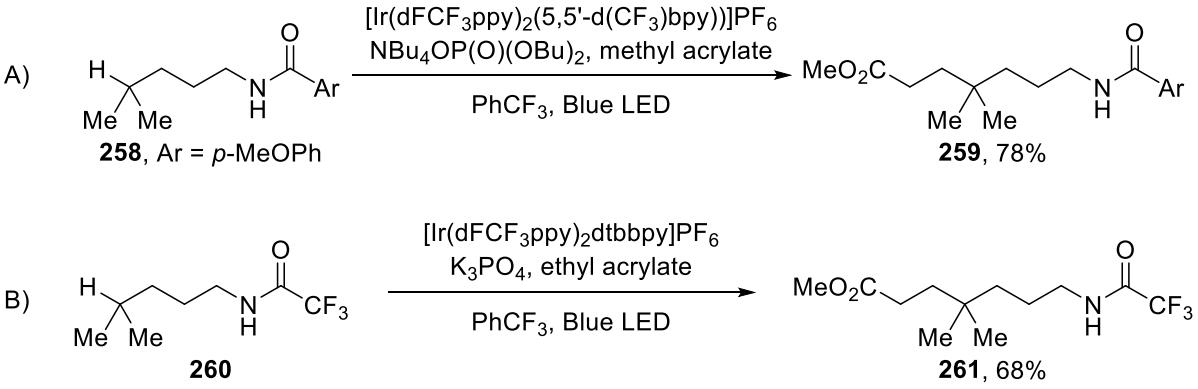
In addition to trapping the *in-situ* formed carbon-centered radical by acrylates or thiophenols, nickel catalysis has also been merged with photoredox PCET process to stabilize the carbon-centered radical, which can then participate in the nickel-catalyzed cross-coupling reactions. In 2019, the Molander group disclosed a photoredox PCET and nickel dual-catalysed amidoarylation of unactivated olefins such as **256** with aryl bromides, thus forging five-membered heterocyclic compound **257** under mild conditions (Scheme 42).[166] In 2020 they further extended the coupling partner to acyl chlorides, which readily afforded the amidoacylation products under CO-free conditions.[167]

[164] Zhu, Q.; Graff, D. E.; Knowles, R. R. *J. Am. Chem. Soc.* **2018**, *140*, 741.
[165] Roos, C. B.; Demaerel, J.; Graff, D. E.; Knowles, R. R. *J. Am. Chem. Soc.* **2020**, *142*, 5974.
[166] Zheng, S.; Gutiérrez-Boent, Á.; Molander, G. A. *Chem* **2019**, *5*, 339.
[167] Zheng, S.; Zhang, S.-Q.; Saeednia, B.; Zhou, J.; Anna, J. M.; Hong, X.; Molander, G. A. *Chem. Sci.* **2020**, *11*, 4131.



Scheme 42. Photoredox PCET/nickel dual catalysis for amidoarylation of olefin **256**.

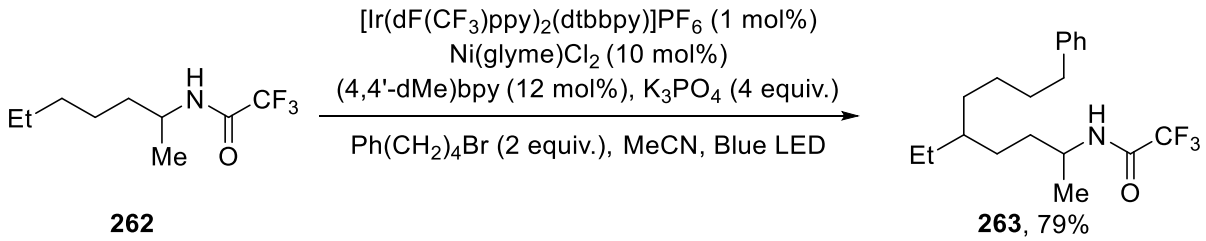
In 2016, the Knowles group reported a remote C-H alkylation reaction by utilizing the amidyl radical to promote the 1,5-HAT process (Scheme 43A).[168] During the same period the Rovis group also reported the same type of reaction under slightly different conditions (Scheme 43B).[169] These findings together addressed the regioselectivity issue in aliphatic C-H bond functionalization by developing an amide-directed photoredox-catalyzed C-C bond formation at unactivated C(sp^3)-H bonds. In 2017, the Rovis group applied the same strategy for the directed γ-C(sp^3)-H alkylation of carboxylic acid derivatives.[170]



Scheme 43. Catalytic alkylations of remote C-H bonds enabled by PCET.

In 2019, the Rovis group also described the use of a combined photoredox and nickel catalytic system for the regioselective C(sp^3)-C(sp^3) coupling between unactivated C(sp^3)-H bonds and alkyl bromides (Eq. 23).[171] Interception of the carbon-centered radical by a nickel catalyst allows distal alkylation to occur in good yield and excellent selectivity, which would otherwise be difficult to realize.

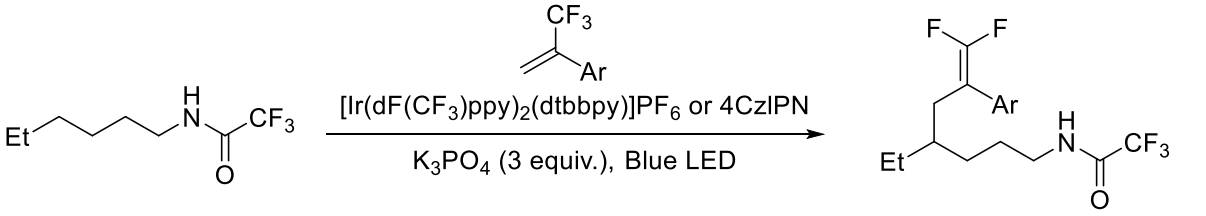
[168] Choi, G. J.; Zhu, Q.; Miller, D, C.; Gu, C. J.; Knowles, R. R. *Nature* **2016**, *539*, 268.
[169] Chu, J. C. K.; Rovis, T. *Nature* **2016**, *539*, 272.
[170] Chen, D.-F.; Chu, J. C. K.; Rovis, T. *J. Am. Chem. Soc.* **2017**, *139*, 14897.
[171] Thullen, S. M.; Treacy, S. M.; Rovis, T. *J. Am. Chem. Soc.* **2019**, *141*, 14062.



262 **263**, 79%

Equation 23. Photoredox PCET/nickel dual catalysis for regioselective alkylation of amide **262**.

Moreover, the Martin group and the Pan group both found in 2021 that CF_3-substituted alkenes can also be good radical acceptors to trap the carbon-centered radical, leading to the formation of δ-defluorinative alkylation products **265-266** for secondary trifluoroacetamides such as **264** using either an iridium complex or the organic dye 4CzIPN as photocatalyst (Eq. 24).[172]



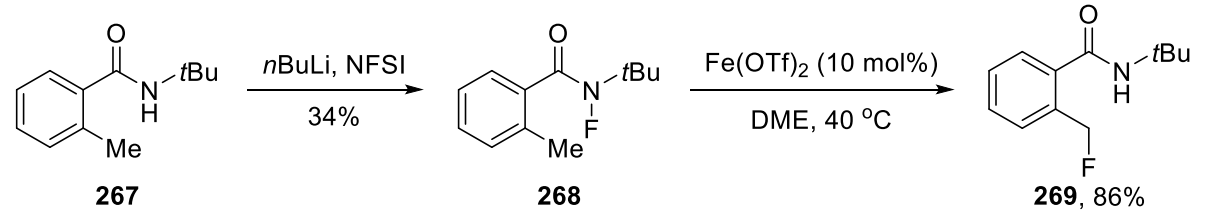
264

265, Ar = Ph, 78% (Martin)
266, Ar = *p*MeOPh, 67% (Pan)

Equation 24. Defluorinative C(sp^3)-H alkylation of secondary amide **264**.

1.4.3 Generation of N-centered radicals by the activation of N-F bonds

As mentioned in section 1.4.1, the activation of N-F bonds for the generation of N-centered radicals is less straightforward as it requires an extra step to synthesize the N-fluorinated substrates from the corresponding N-H amides. Moreover, transition metal catalysts need to be employed since the N-F bond is rather stable under photochemical conditions. In 2016, the Cook group reported an iron-catalyzed fluorine transfer reaction on the N-F amide **268** (Eq. 25).[173] DFT calculations revealed that upon cleavage of the N-F bond by iron, the N-centered radical undergoes 1,5-HAT and the resulting benzylic radical then recombines the F atom from the $Fe^{III}F$ species to form the C-F bond in **269**.



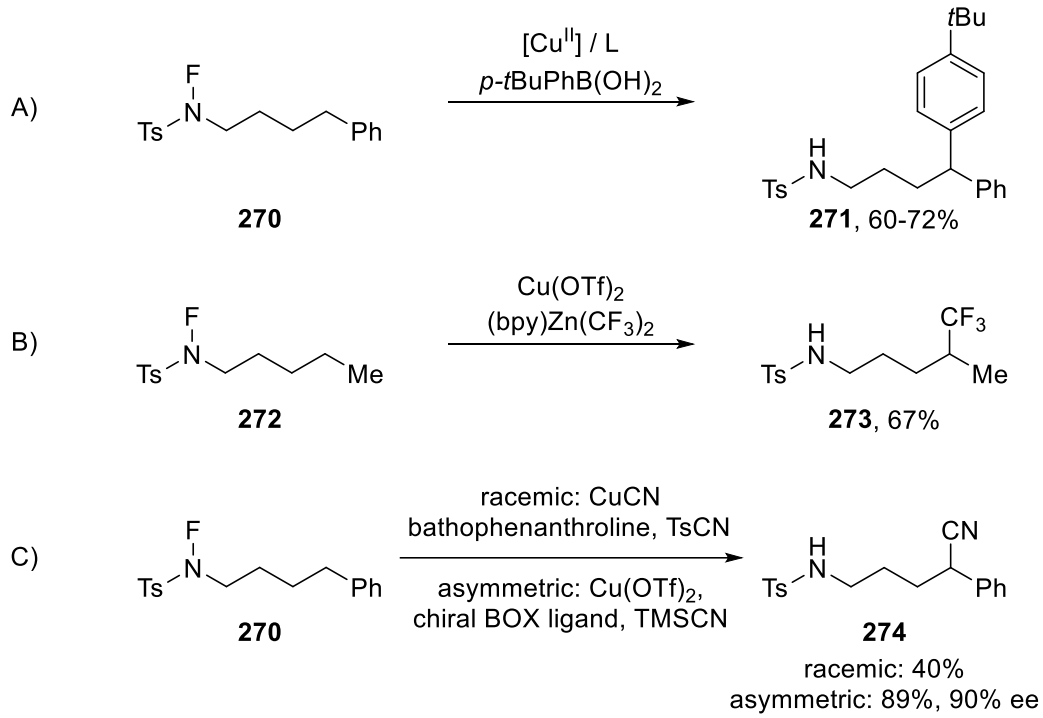
267 **268** **269**, 86%

Equation 25. Iron-catalyzed fluorine transfer reaction of N-F amide **268**.

Inspired by this work, other remote C-H functionalization reactions have been realized with high site-selectivity by intercepting the fluorine recombination step. For example, in 2018 the Zhu group and the Nagib group independently reported a copper-catalyzed arylation of the N-fluorinated carboxamides or

[172] a) Yue, W.-J.; Day, C. S.; Martin, R. *J. Am. Chem. Soc.* **2021**, *143*, 6395. b) Hu, Q.-P.; Cheng, J.; Wang, Y.; Shi, J.; Wang, B.-Q.; Hu, P.; Zhao, K.-Q.; Pan F. *Org. Lett.* **2021**, *23*, 4457.
[173] Groendyke, B. J.; AbuSalim, D. I.; Cook, S. P. *J. Am. Chem. Soc.* **2016**, *138*, 12771.

sulfonamides (Scheme 44A).[174] By employing (bpy)Zn$(CF_3)_2$ as the CF_3 reagent, the Li group reported in 2019 a copper-catalyzed trifluoromethylation reaction (Scheme 44B).[175] Cyanation reactions on similar substrates have also been realized in both racemic and asymmetric fashions. The Zhang group disclosed a racemic copper-catalyzed cyanation by using TsCN as the radical CN source, while the Nagib group found that the use of TMSCN in combination with $Cu(OTf)_2$ and a chiral bisoxazoline ligand could deliver **274** in high yield and enantioselectivity (Scheme 44C).[176] This strategy has also been utilized for the incorporation of other functional groups[177] or for the synthesis of pyrrolidines.[178]



Scheme 44. Site-selective remote C-H functionalization of N-Fluorinated sulfonamides.

1.4.4 Conclusion

To summarize this part, nitrogen-centered radicals have been generated in different ways, such as homolysis of weak nitrogen-halogen bond (HLF reaction), direct cleavage of strong N-H bond (PCET process) as well as other methods for the activation of pre-functionalized substrates such as N-fluorinated amides. Other types of pre-functionalized substrates including hydroxylamine derivatives[179] and oxime derivatives[180] etc., were not discussed here as they are less relevant to the topic of my thesis.

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[174] a) Li, Z.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 13288. b) Zhang, Z.; Stateman, L. M.; Nagib, D. A. *Chem. Sci.* **2019**, *10*, 1207.

[175] Liu, Z.; Xiao, H.; Zhang, B.; Shen, H.; Zhu, L.; Li, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 2510.

[176] a) Zhang, H.; Zhou, Y.; Tian, P.; Jiang, C. *Org. Lett.* **2019**, *21*, 1921. b) Zhang, Z.; Zhang, X.; Nagib, D. A. *Chem* **2019**, *5*, 3127.

[177] a) Muñoz-Molina, J. M.; Belderrain, T. R.; Pérez, P. J. *Synthesis* **2021**, *53*, 51. b) Guo, Q.; Peng, Q.; Chai, H.; Huo, Y.; Wang, S; Xu, Z. *Nat. Commun.* **2020**, *11*, 1463. c) Min, Q.-Q.; Yng, J.-W.; Pang, M.-J.; Ao, G.-Z.; Liu, F. *Org. Chem. Front.* **2021**, *8*, 249. d) Zhang, H.; Yu, F.; Li, C.; Tian, P.; Zhou, Y.; Cao, Z.-Y. *Org. Lett.* **2021**, *23*, 4721.

[178] a) Bafaluy, D.; Muñoz-Molina, J. M.; Funes-Ardoiz, I.; Herold, S.; de Aguirre, A. J.; Zhang, H.; Maseras, F.; Belderrain, T. R.; Pérez, P. J.; Muñiz, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 8912. b) Ji, Y.-X.; Li, J.; Li, C.-M.; Qu, S.; Zhang, B. *Org. Lett.* **2021**, *23*, 207.

[179] Davies, J.; Svejstrup, T. D.; Fernandez Reina, D.; Sheikh, N. S.; Leonori, D. *J. Am. Chem. Soc.* **2016**, *138*, 8092.

[180] Jiang, H.; An, X.; Tong, K.; Zheng, T.; Zhang, Y.; Yu, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 4055.

Once nitrogen-centered radicals are formed, they can add to alkenes or participate in 1,5-HAT process to provide carbon-centered radicals, which can then be quenched by thiophenols, by Michael acceptors to furnish Giese-type reaction products, or by a nickel catalyst to produce cross-coupling products with different electrophiles such as aryl halides, alkyl halides or acyl halides.

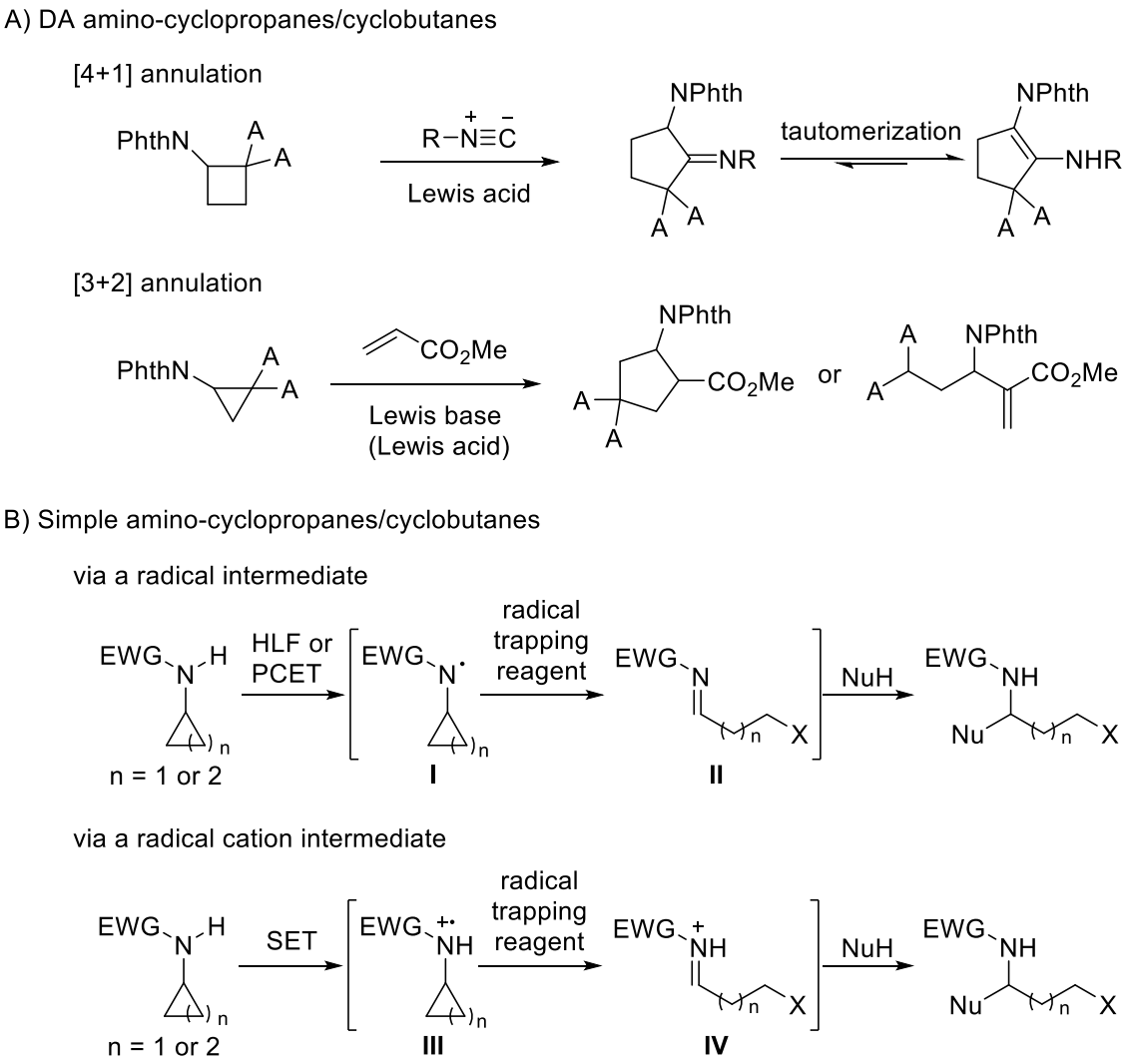
1.5 Goal of the project

As already described in the introduction, our group has focused on the studies of DA aminocyclopropanes for more than one decade and efforts to apply this chemistry to the total synthesis of indole alkaloids have also been made. Extension to their four-membered counterparts, namely DA aminocyclobutanes, has also been achieved successfully although the subsequent transformation of DA aminocyclobutanes was limited to formal [4+2] cycloadditions with enol ethers or aldehydes.

Our first goal was to develop other transformations of DA aminocyclobutanes. We attempted to develop a formal [4+1] cycloaddition between DA aminocyclobutanes and isocyanides, which would afford a highly functionalized cyclopentene as product after tautomerization. Meanwhile, inspired by the Morita-Baylis-Hillman reaction, we also tried to turn electrophilic acrylates into a nucleophile to facilitate the ring-opening reactions of DA aminocyclopropanes (Scheme 45A).

Donor-Acceptor systems can activate three- or four-membered rings by polarizing the C1-C2 bond to form 1,3 or 1,4 formal dipoles, however, the synthetic utility could be limited to some extent as both donor and acceptor groups needed to be finely tuned and in some cases it required extra steps to remove the acceptor group(s). Therefore, we were wondering if we could get rid of the acceptor group and activate directly simple aminocyclopropanes or aminocyclobutanes.

To achieve this second goal, we aimed to seek a radical approach for the activation of simple acyl-protected aminocyclopropanes. This can be done either by generating a nitrogen-centered radical via the HLF-type reaction or the PCET pathway, or by direct oxidation of the amidyl nitrogen to a radical cation species. The advantage of ring-opening transformation of aminocyclopropanes via a radical pathway is the formation of an imine/iminium intermediate, to which a variety of nucleophiles could then be added to yield α,γ-difunctionalized amines (Scheme 45B). Similarly, extension to aminocyclobutanes would then provide α,δ-difunctionalized amines. As cheap building blocks, simple aminocyclopropanes and aminocyclobutanes have been surprisingly undervalued in organic synthesis. However, ring-opening difunctionalization of these strained cyclic amines, if achieved, could give an easy access to diverse amine products, which exist widely as intermediates towards the synthesis of many pharmaceutical compounds.



Scheme 45. Developing novel annulation reactions for DA amino-cyclopropanes/cyclobutanes and ring-opening difuntionalizations of simple amino-cyclopropanes/cyclobutanes via a radical pathway.

2

Lewis Acid Catalyzed [4+1] Annulation of DA Aminocyclobutanes and Lewis Base Catalyzed [3+2] Annulation of DA Aminocyclopropanes

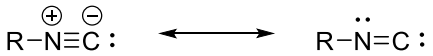
2. Lewis acid catalyzed [4+1] annulation of DA aminocyclobutanes and Lewis base catalyzed [3+2] annulation of DA aminocyclopropanes

When I began my doctoral studies, I spent the first four months on the enantioselective desymmetrization of DA *meso*-diaminocyclopropanes (Scheme 12C), in collaboration with senior PhD student Daniele Perrotta.[72] As it is not the main part of my PhD thesis and is already thoroughly described in the thesis of Dr. Daniele Perrotta,[181] this project will not be further discussed here. After finishing this desymmetrization project, I was interested in developing a formal [4+1] cycloaddition for DA aminocyclobutanes, in an effort to expand their reaction types. I reasoned that isocyanide could be a suitable C1 block for this transformation and the efforts for developing this reaction are summarized in section 2.1. In section 2.2, I described some fruitless results on a formal [3+2] cycloaddition of DA aminocyclopropanes with electron-deficient alkenes.

2.1 Lewis acid catalyzed [4+1] annulation of DA aminocyclobutanes with isocyanides

2.1.1 Reactivity of isocyanides

An isocyanide (also called isonitrile) is an organic compound with the functional group –N≡C. It is the isomer of the related cyanide (–C≡N). The organic fragment is connected to the isocyanide group via the nitrogen atom, not the carbon atom. The first isocyanide compound was obtained by Lieke in 1859.[182] The C-N distance in isocyanides is very short, 1.158 Å in methyl isocyanide. The C-N-C is almost linear since the bond angles are near 180°.[183] Akin to carbon monoxide, isocyanides are described by two resonance structures (Eq. 26): one has a triple bond between the nitrogen atom and the carbon atom (zwiterrionic representation by Lindemann and Wiegrebe) while the other one has a double bond between them (carbene representation by Nef). How to best describe the electronic structure of isocyanides: whether as carbenes, as zwitterions, or as a mixture of both? This question is still open.[184]



Equation 26. The resonance structure of isocyanides.

Isocyanides have been mainly exploited as a valuable C1 building block for the synthesis of nitrogen-containing compounds. Because of their unique feature of exhibiting both nucleophilicity and electrophilicity, they are mostly involved in multicomponent reactions, such as the Ugi reaction and the Passerini reaction (Scheme 46).[185] It is not difficult to understand why isocyanides can be both nucleophilic and electrophilic, when considering the first resonance structure.

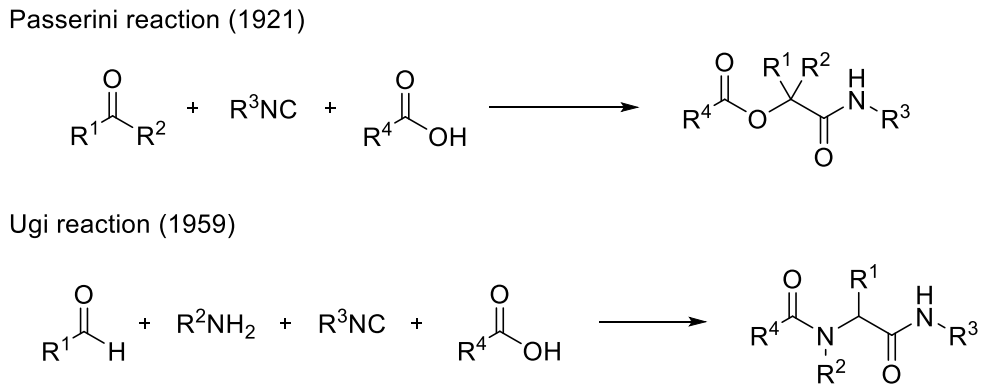
[181] Perrotta, D. **2018**. Developing reactions of strained rings: enantioselective desymmetrization of meso-diaminocyclopropanes and annulation of donor-acceptor aminocyclobutanes. Doctoral dissertation, EPFL, thesis number 8579, Lausanne.

[182] Lieke, W. *Justus Liebigs Ann. Chem.* **1859**, *112*, 316.

[183] Kessler, M.; Ring, H.; Trambarulo, R.; Gordy, W. *Phy. Rev.* **1950**, *79*, 54.

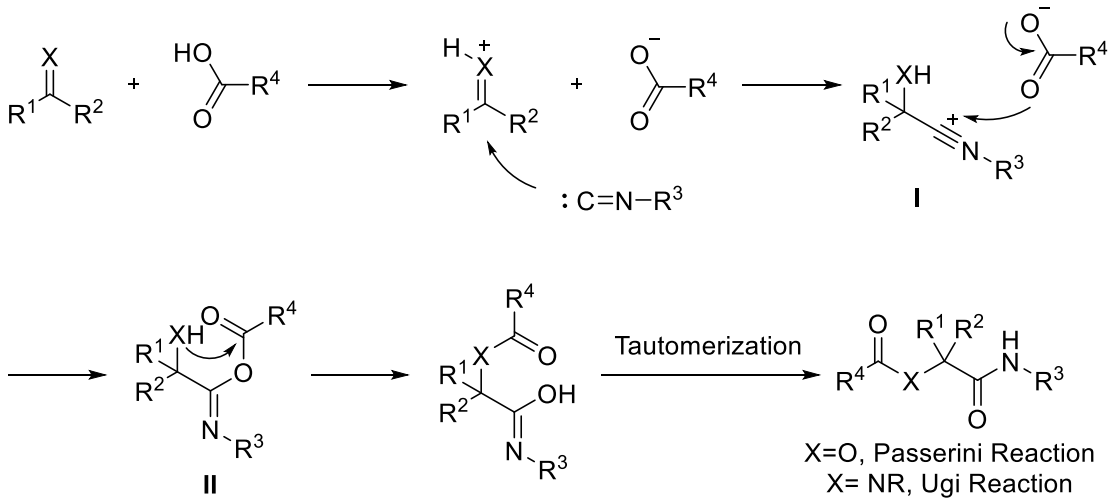
[184] Ramozzi, R.; Chéron, N.; Braïda, B.; Hiberty, P. C.; Fleurat-Lessard, P. *New J. Chem.* **2012**, *36*, 1137.

[185] a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. b) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53. c) Zhu, J. *Eur. J. Org. Chem*. **2003**, 1133. d) Dömling, A. *Chem. Rev*. **2006**, *106*, 17. e) Lygin, A. V.; de Meijere, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 9094.



Scheme 46. Multicomponent reactions involving isocyanide.

The mechanism of the Passerini reaction and the Ugi reaction involves protonation of carbonyls or *in-situ* formed imines followed by nucleophilic addition of the isocyanide to give a nitrilium ion **I**, which is then attacked by the carboxylate to form intermediate **II**. Subsequent acyl group transfer and amide tautomerization eventually give the corresponding products (Scheme 47). In recent years, asymmetric versions of both the Passerini reaction[186] and the Ugi reaction[187] have been realized by different catalytic systems.



Scheme 47. Mechanism of the Passerini reaction and the Ugi reaction.

However, other reactivities of isocyanides, such as isocyanide insertion reactions (also called imidoylative reactions),[188] have been relatively undervalued. The isocyanide insertion reactions can be divided into two different types depending on the substrates: 1) annulation with acyclic substrates, in which case the nucleophilic part and electrophilic part are linked; 2) annulation with cyclic substrates, which contain a polarized bond and can be seemed as formal dipoles upon activation. Based on the

[186] a) Kusebauch, U.; Beck, B.; Messer, K.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 4021. b) Andreana, P. R.; Liu, C. C.; Schreiber, S. L. *Org. Lett.* **2004**, *6*, 4231. c) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 388. d) Zhang, J.; Lin, S.-X.; Cheng, D.-J.; Liu, X.-Y.; Tan, B. *J. Am. Chem. Soc*. **2015**, *137*, 14039.
[187] Zhang, J.; Yu, P.; Li, S.-Y.; Sun, H.; Xiang, S.-H.; Wang, J.; Houk, K. N.; Tan, B. *Science* **2018**, *361*, 1087.
[188] Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257.

number of atoms of the linkage, isocyanide insertion reactions can also be classified as formal [4+1], [3+1+1], or even higher order such as [8+2+1] cycloadditions.[189]

Annulation with acyclic substrates

Diverse heterocycles have been synthesized by adopting a formal [4+1] cycloaddition between isocyanides and acyclic substrates. For example, α,β-unsaturated imines for the synthesis of pyrroles (Figure 9A), nitroolefins for the synthesis of oxazoles (Figure 9B), vinylketenes for the synthesis of pentenones (Figure 9C), hydrazones for the synthesis of pyrazoles (Figure 9D), α,β-unsaturated ketones for the synthesis of furans (Figure 9E), 2-amino pyridines and aldehydes for the synthesis of imidazoles (Figure 9F) have been well documented.[190]

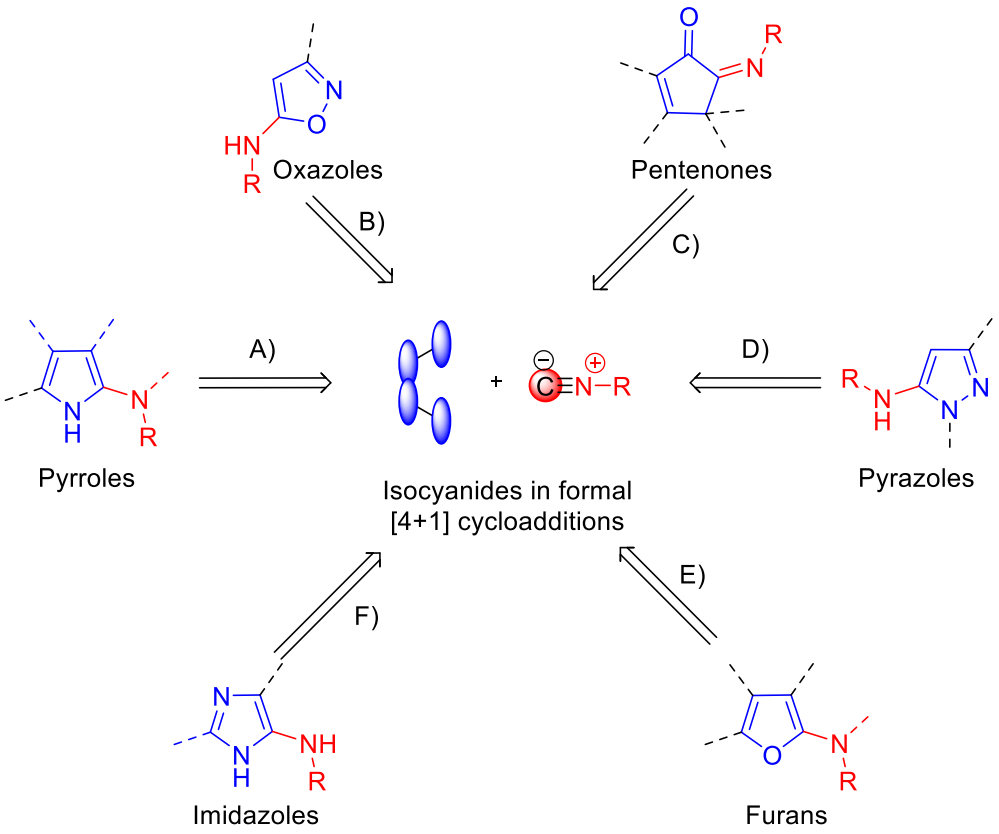


Figure 9. Synthesis of diverse heterocycles involving isocyanides in formal [4+1] annulations.

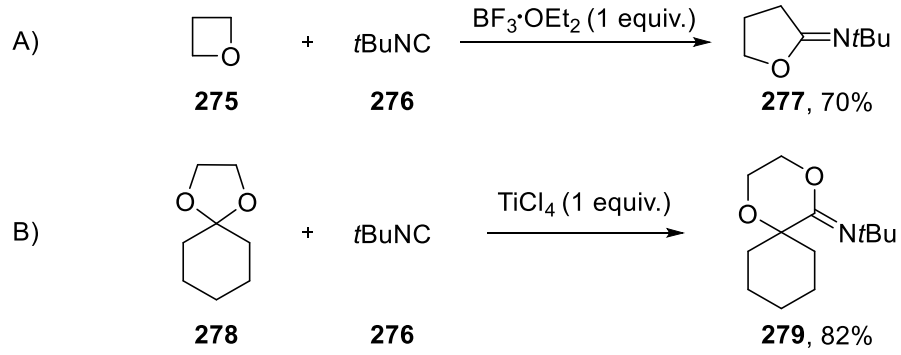
Annulation with cyclic substrates

Isocyanides can also insert into cyclic compounds in the presence of Lewis-acid catalysts. So far, great progress in isocyanide insertion into carbon-heteroatom and carbon-carbon bonds has been achieved, catalyzed by either Lewis acid catalyst or transition metal catalyst. Details about previous work on the insertion of isocyanides into C-X and C-C bonds will be given in this section because they are closely relevant to my current project.

[189] Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. *Chem. Rev.* **2015**, *115*, 5301.

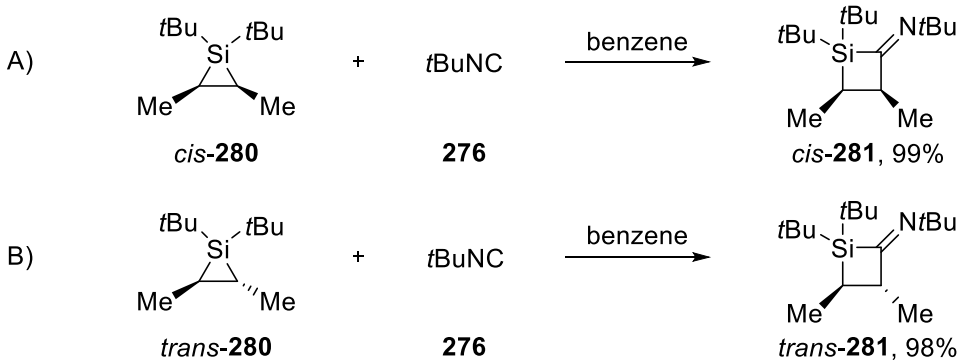
[190] a) Kaur, T., Wadhwa, P.; Bagchi, S.; Sharma, A. *Chem. Commun.* **2016**, *52*, 6958. b) Senadi, G. C.; Hu, W.-P.; Lu, T.-Y.; Garkhedkar, A. M.; Vandavasi, J. K.; Wang, J.-J. *Org. Lett.*, **2015**, *17*, 1521.

In 1971, the Ito and Saegusa group reported the first example of isocyanide insertion into the C-O bond of oxetane **275** in the presence of boron trifluoride diethyl etherate (Scheme 48A).[191] In 1984, the same group reported another example of isocyanide insertion into the C-O bond of ketal **278** in the presence of $TiCl_4$ (Scheme 48B).[192] Later, catalytic isocyanide insertion into the C-O bond of epoxides or ketals was achieved by utilizing $GaCl_3$ or TfOH as catalyst.[193] For epoxides, 2,3-diiminofurans were usually obtained as product resulting from double insertion. In 2008, the Chatani group also extended the substrate scope for isocyanide insertion to the C-S bond of dithioacetals by using $GaCl_3$ or $TiCl_4$ as catalyst.[194]



Scheme 48. Isocyanide insertion into oxetane **275** or ketal **278**.

In 1999, stereospecific insertion of isocyanide into the C-Si bond of silirane **280** was reported by the Woerpel group (Scheme 49).[195] Unlike the insertion into epoxides, only one isocyanide molecule was involved in this reaction, yielding a new type of four-membered compound **281**. This reaction was stereospecific: *cis*-**281** was exclusively obtained from *cis*-**280** (Scheme 49A) and *trans*-**281** was formed from *trans*-**280** (Scheme 49B). The stereospecificity indicates that homolysis or heterolysis of a C-Si bond prior to C-C bond formation is unlikely. In this work, regiospecific insertion of isocyanide into the more substituted C-Si bond of mono-substituted siliranes was also disclosed.



Scheme 49. Stereospecific insertion of isocyanide **276** into silirane **280**.

[191] a) Saegusa, T.; Takaishi, N.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1971**. *44*, 2473. b) Saegusa, T.; Takaishi, N.; Takami, M.; Ito, Y. *Synth. Commun.* **1971***, 1*, 99.

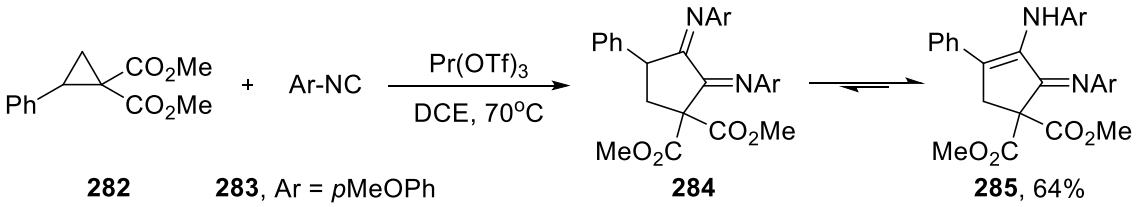
[192] Ito, Y.; Segoe, K.; Saegusa, T. *Chem. Lett*. **1984**, 937.

[193] a) Bez, G.; Zhao, C.-G. *Org. Lett*. **2003**, *5*, 4991. b) Yoshioka, S.; Oshita, M.; Tobisu, M.; Chatani, N. *Org. Lett*. **2005**, *7*, 3697. c) Tobisu, M.; Kitajima, A.; Yoshioka, S.; Hyodo, I.; Oshita, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 11431.

[194] Tobisu, M.; Ito, S.; Kitajima, A.; Chatani, N. *Org. Lett*. **2008**, *10*, 5223.

[195] Nguyen, P. T.; Palmer, W. S.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1843.

Though isocyanide insertion into several types of carbon-heteroatom bonds was well documented, only one example of isocyanide insertion into C-C bonds has been reported so far: a formal [3+1+1] cycloaddition of DA cyclopropane **282** and isocyanide **283** from the de Meijere group in 2006 (Eq. 27).[196] After intensive screening of Lewis acid catalysts, $Pr(OTf)_3$ was found as the most efficient catalyst for this reaction. Similar to the insertion into epoxides, double insertion of isocyanides was observed, leading to the formation of a stable 2,3-diiminocyclopentane-1,1-dicarboxylate **284** or its tautomer **285**. In fact, only **285** was observed and isolated.



Equation 27. A formal [3+1+1] cycloaddition of DA cyclopropane **282** and isocyanide **283**.

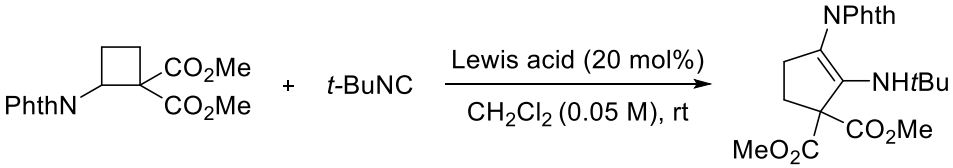
2.1.2 Discovery of the [4+1] annulation and optimization

As already described in the introduction (section 1.2.2), the transformations involving DA aminocyclobutanes are still limited to [4+2] annulation reactions.[197] Therefore, developing other types of annulation reaction for DA aminocyclobutanes, such as a formal [4+1] cycloaddition, can be an interesting goal as it will give a quick access to five-membered cyclic products. Based on the progress in the research area of isocyanides, a Lewis acid catalyzed [4+1] annulation of DA aminocyclobutane **175** with *tert*-butyl isocyanide **276** was tested, which would allow us to prepare otherwise not easily accessed cyclopentene-1,2-diamines like **286**. The synthesis of **175** has been previously reported by our group, as shown in Scheme 22A.

We started this project by screening different Lewis acid catalysts first, with a focus on metal triflates as they usually are optimal catalysts for such transformations involving DA cycloalkanes (Table 1).[2] To our delight, the desired product **286** was observed and isolated in 42% yield when using $Sc(OTf)_3$ as catalyst (entry 1). The polarity of product **286** is similar to that of the starting material **175**, thus causing difficulties for the purification. When using $Hf(OTf)_4$ as catalyst, full conversion of **175** was observed, though **286** was isolated in only 40% yield (entry 2). This can be attributed to the retro [2+2] cycloaddition in the presence of Lewis acid catalyst, which led to the formation of 2-vinylisoindoline-1,3-dione as by-product. Other metal triflates (entries 3-7) as well as Tin(IV) chloride (entry 8), or the Brønsted acid TfOH (entry 9), failed to catalyze this reaction. A control experiment confirmed that no reaction took place without any catalyst (entry 10).

[196] Korotkov, V. S.; Larionov, O. V.; de Meijere, A. *Synthesis* **2006**, *21*, 3542.
[197] De, N.; Yoo, E. J. *ACS Catal.* **2018**, *8*, 48.

Table 1. Screening catalysts for the [4+1] annulation of DA aminocyclobutane **175** with isocyanide **276**.



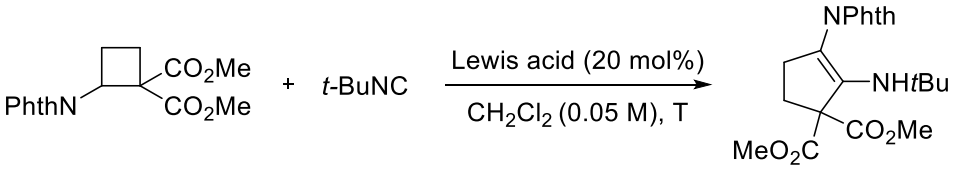
175 **276** **286**

Entry[a]	Lewis acid	Yield of **286** (%)	Recovery of **175** (%)
1	$Sc(OTf)_3$	42[b]	17
2	$Hf(OTf)_4$	40[b]	0
3	$La(OTf)_3$	trace	>90
4	$Yb(OTf)_3$	trace	>90
5	$Gd(OTf)_3$	0	100
6	$Cu(OTf)_2$	0	100
7	$In(OTf)_3$	0	100
8	$SnCl_4$	0	100
9	TfOH	0	100
10	-	0	100

(a) Reaction conditions: 0.05 mmol **175**, 0.1 mmol **276**, 20 mol% catalyst, 1 mL CH_2Cl_2, room temperature, 12 h. The yield was determined by ^1H NMR yield using CH_2Br_2 as internal standard. (b) Isolated yield.

In order to inhibit the decomposition of **175**, the reaction temperature was lowered to -40 °C and -78 °C for both $Sc(OTf)_3$ and $Hf(OTf)_4$, but unfortunately no improvement in terms of yield for **286** was observed (Table 2, entries 1-4).

Table 2. Screening temperature for the [4+1] annulation of DA aminocyclobutane **175** with isocyanide **276**.



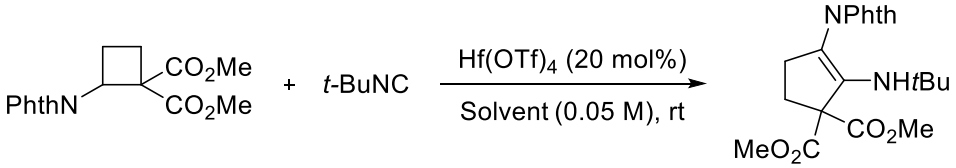
175 **276** **286**

Entry[a]	Conditions	Yield of **286** (%)	Recovery of **175** (%)
1	$Sc(OTf)_3$, -78 °C	16	80
2	$Hf(OTf)_4$, -78 °C	30	28
3	$Sc(OTf)_3$, -40 °C	6	80
4	$Hf(OTf)_4$, -40 °C	16	32

(a) Reaction conditions: 0.05 mmol **175**, 0.1 mmol **276**, 20 mol% catalyst, 1 mL CH_2Cl_2, 12 h. The yield was determined by ^1H NMR yield using CH_2Br_2 as internal standard.

Then different solvents were tested by focusing on $Hf(OTf)_4$ as catalyst (Table 3). DCM was found to be the optimal solvent (entry 1) and DCE gave similar results (entry 2), while Et_2O and MeCN gave much lower yields (entries 3 and 4). Therefore, we continued to use DCM as solvent for the screening of catalyst loading.

Table 3. Screening solvents for the [4+1] annulation of DA aminocyclobutane **175** with isocyanide **276**.



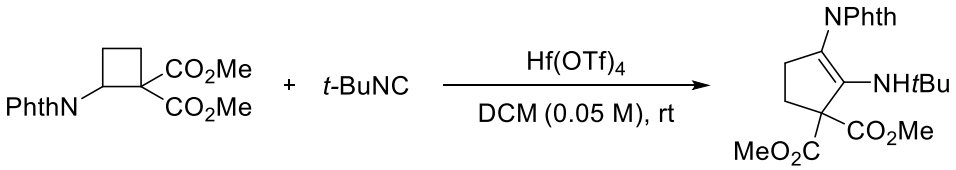
175 **276** **286**

Entry[a]	Solvent	Yield of **286** (%)	Recovery of **175** (%)
1	DCM	40[b]	-
2	DCE	40[b]	5
3	Et_2O	4	12
4	MeCN	16	13

(a) Reaction conditions: 0.05 mmol **175**, 0.1 mmol **276**, 20 mol% $Hf(OTf)_4$, 1 mL solvent, room temperature, 12 h. The yield was determined by ^1H NMR yield using CH_2Br_2 as internal standard. (b) Isolated yield.

Lower catalyst loading led to incomplete conversion of **175**, so 20 mol% of $Hf(OTf)_4$ is still necessary in order to obtain the product in higher yield (Table 4, entries 1-3).

Table 4. Screening catalyst loadings for the [4+1] annulation of DA aminocyclobutane **175** with isocyanide **276**.



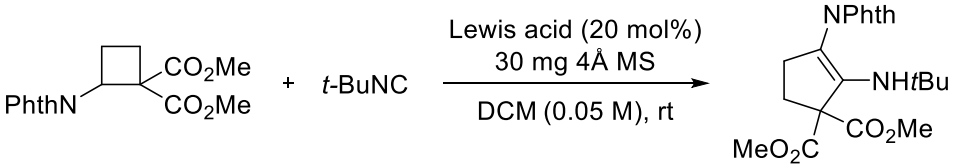
175 **276** **286**

Entry[a]	$Hf(OTf)_4$ (%)	Yield of **286** (%)	Recovery of **175** (%)
1	5	4	90
2	10	18	56
3	20	40	-

(a) Reaction conditions: 0.05 mmol **175**, 0.1 mmol **276**, $Hf(OTf)_4$, 1 mL DCM, room temperature, 12 h. The yield was determined by ^1H NMR yield using CH_2Br_2 as internal standard.

As yields were not improved by changing the parameters above, we tried to introduce some additives such as 4Å MS (Table 5), which is an essential additive to improve both yield and diastereoselectivity as illustrated in our previous [4+2] annulations of DA aminocyclopropanes with enol ethers.[104] To our delight, the yield of **286** was indeed improved to 64% by adding 30 mg 4Å MS when using $Sc(OTf)_3$ as catalyst (entry 1), which is the best yield to date. Adding 4Å MS is less effective in the case of $Hf(OTf)_4$ as the yield was only improved from 40% to 46% (entry 2). Therefore, further studies should focus on using $Sc(OTf)_3$ as catalyst in the following optimization. However, before more efforts were devoted to further optimizing this formal [4+1] cycloaddition, we briefly screened the substrate scope for both reaction partners.

Table 5. Adding 4Å MS as additive to the [4+1] annulation of DA aminocyclobutane **175** with isocyanide **276**.



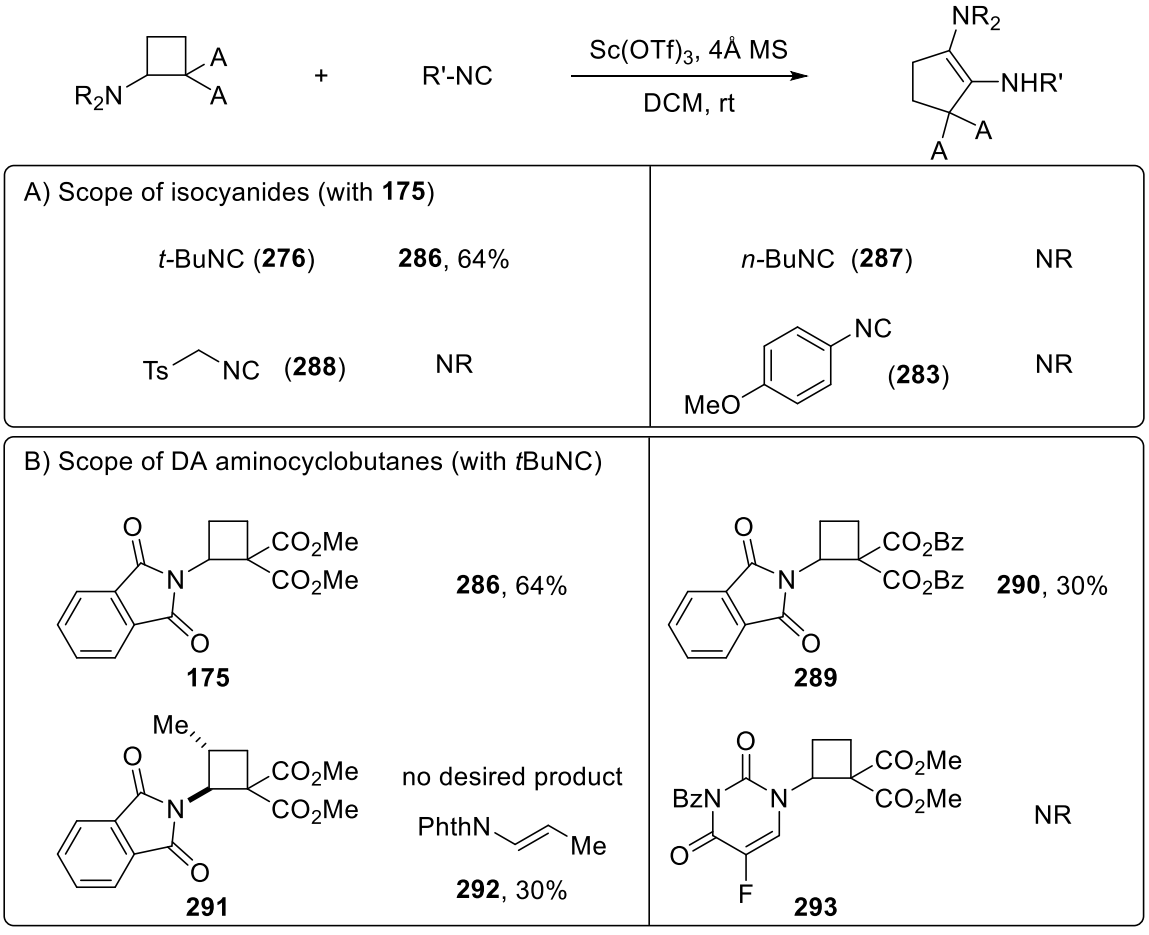
175 **276** **286**

Entry[a]	Lewis acid	Yield of **286** (%)[b]	Recovery of **175** (%)[b]
1	$Sc(OTf)_3$	64	30
2	$Hf(OTf)_4$	46	14

(a) Reaction conditions: 0.05 mmol **175**, 0.1 mmol **276**, 20 mol% $Sc(OTf)_3$ or $Hf(OTf)_4$, 30 mg 4Å MS, 1 mL DCM, room temperature, 12h. (b) Isolated yield.

2.1.3 Preliminary substrate scope of the [4+1] annulation

As we can see from Scheme 50A, other alkyl isocyanides **287**-**288** or aryl isocyanide **283** were unfortunately not tolerated in this reaction, showing no reactivity at all. For DA aminocyclobutanes: moving from methyl ester **175** to benzyl ester **289** provided the corresponding product **290** in lower yield; with a methyl substituent at 3 position, **291** mainly underwent retro-[2+2] annulation to give enamide **292**; and no reactivity of uracil-substituted DA aminocyclopropane **293** was observed under the standard conditions (Scheme 50B).



Scheme 50. Substrate scope of the [4+1] annulation of DA aminocyclobutanes with isocyanides.

Since the scope of this reaction seemed a little bit narrow, we decided to temporarily put this project on hold in order to focus on the development of other transformations involving strained rings. To conclude, we have developed a novel [4+1] annulation of DA aminocyclobutanes with isocyanides, which readily gave cyclopentene-1,2-diamines as products under mild conditions.

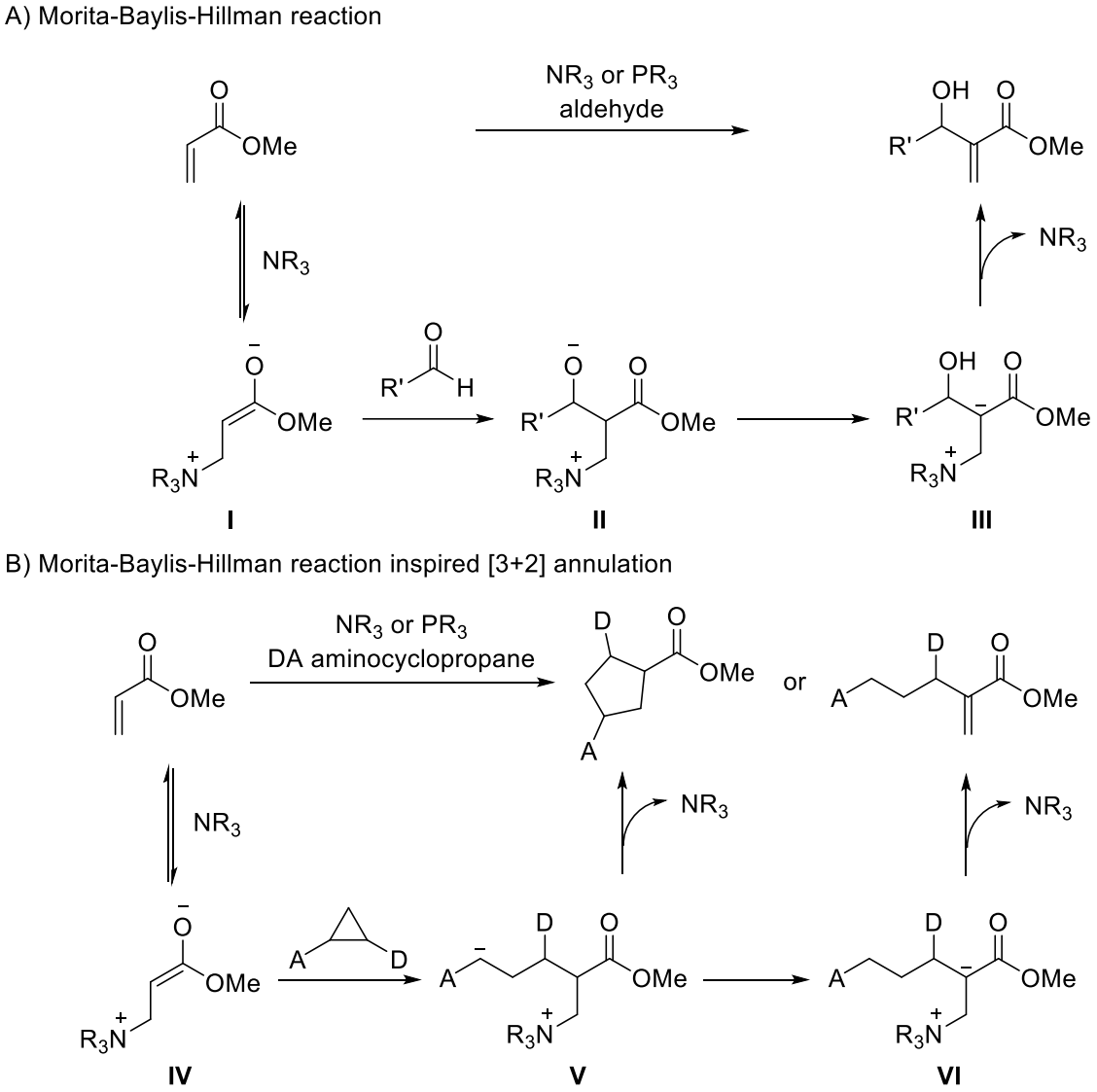
2.2 Lewis base catalyzed [3+2] annulation of DA aminocyclopropanes

Along with efforts on developing Lewis acid catalyzed transformations of DA aminocyclopropanes with nucleophiles, we were also interested in exploring the possibility of using Lewis base to promote the ring opening process. This inspiration came from the classical Morita-Baylis-Hillman reaction (MBH reaction), which is a carbon-carbon bond forming reaction between the α-position of an activated alkene and a carbon electrophile such as an aldehyde.[198] A tertiary amine or phosphine is usually employed as nucleophilic catalyst to activate the alkene, e.g. methyl acrylate, to form the zwitterionic intermediate **I**, which adds to the aldehyde via an aldol reaction to form **II**. After intramolecular proton shift and subsequent elimination, a densely functionalized allyl alcohol could then be formed as product (Scheme 51A).

In 2004, the Gaunt group reported an enantioselective cyclopropanation reaction of an acrylate with phenylacyl bromide by using cinchona alkaloid catalysts, resulting from an intramolecular S_N2 reaction.[199] Inspired by these examples, we wondered if we could replace aldehydes or phenylacyl bromide with other electrophiles such as DA aminocyclopropanes. As DA aminocyclopropanes have been demonstrated to be good electrophiles reacting with nucleophiles, we envisioned that **V** would be formed after ring opening by **IV**. A five-membered cyclic product would then be accessed through an intramolecular S_N2 reaction from intermediate **V**; alternatively, the proton shift of **V** might also occur, leading to the formation of **VI** and eventually the formation of a similar MBH adduct after elimination of the tertiary amine catalyst (Scheme 51B).

[198] Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

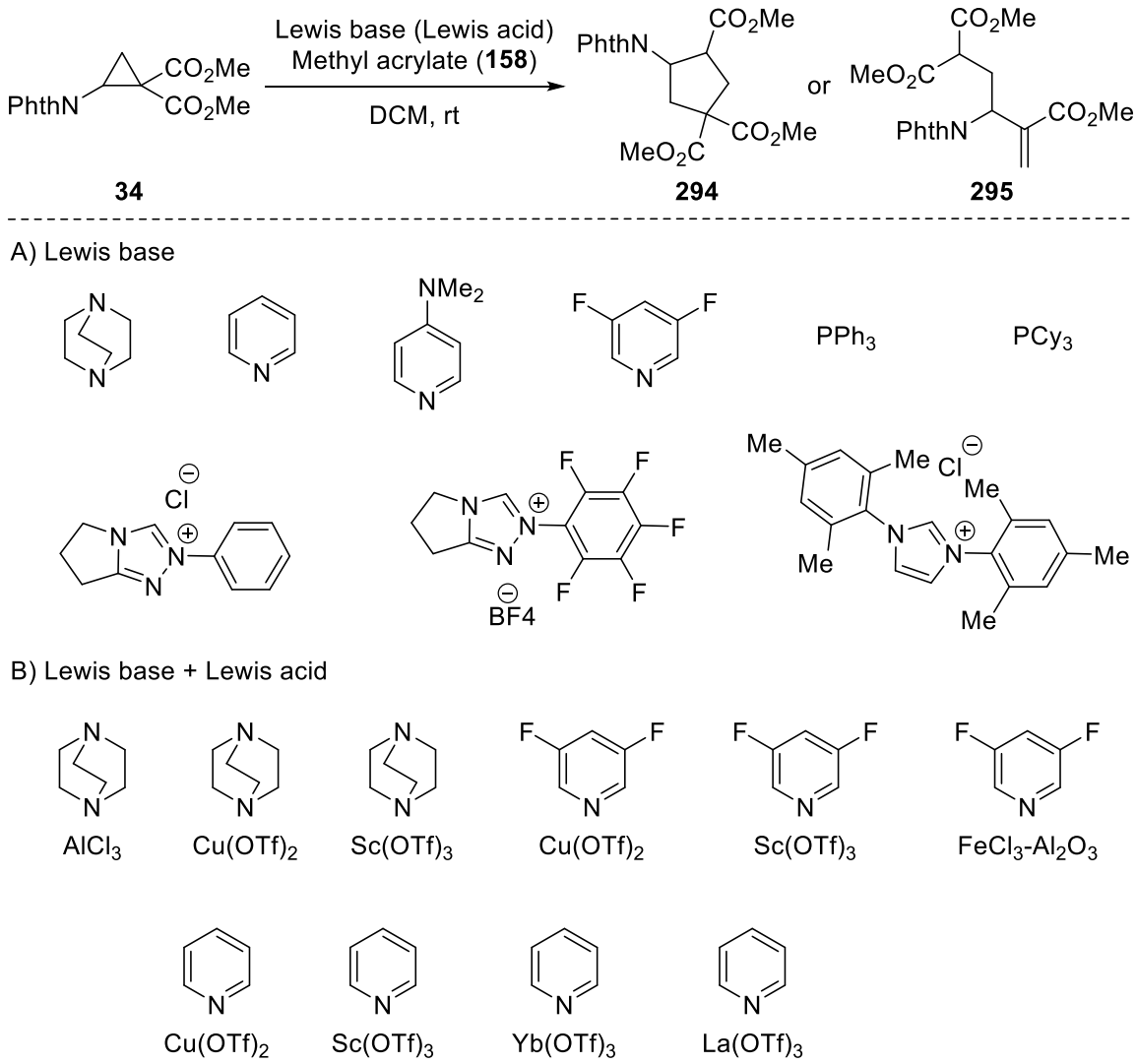
[199] Papageorgiou, C. D.; de Dios, M. A. C.; Ley, S. V.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4641.



Scheme 51. The MBH reaction and a proposed [3+2] annulation inspired by it.

We tested this hypothesis by screening different Lewis bases, such as tertiary amine DABCO, pyridines, phosphines, as well as several N-heterocyclic carbene (NHC) catalysts.[200] However, no conversion of **34** was observed based on the ^{1}H NMR spectra (Scheme 52A). We reasoned that perhaps **34** was not activated under these conditions as it usually required Lewis acid for its activation. Therefore, we tested a few combinations of Lewis acid/base pairs. Nevertheless, no desired products have been observed so far in all these cases (Scheme 52B).

[200] He, L.; Jian, T.-Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466.



Scheme 52. No formation of desired product in the case of Lewis base catalyst or Lewis base-Lewis acid pair for the [3+2] annulation. Reaction conditions: 0.1 mmol **34**, 0.2 mmol **158**, 0.1 mmol Lewis base, (20 mol% Lewis acid), 0.5 mL DCM, room temperature, 16 h.

Although no positive results have been obtained so far for this Lewis base catalyzed [3+2] annulation reaction, we will spend some more time investigating other parameters in order to realize this transformation. The first challenge here would be to find a pair of Lewis acid and Lewis base which activate independently DA aminocyclopropane **34** and methyl acrylate but should not form a deactivated adduct between themselves. In this sense, turning attention to the research field of frustrated Lewis pair (FLP)[201] could potentially help to solve this issue. On the other side, the use of **34** as substrate may not be a good choice since the negative charge in intermediate **V** would be stabilized by two ester groups, causing difficulties to the formation of **VI** through proton shift. Therefore, mono-acceptor aminocyclopropanes should be synthesized and tested in this reaction.

[201] Stephan, D. W. *J. Am. Chem. Soc.* **2015**, *137*, 10018.

3

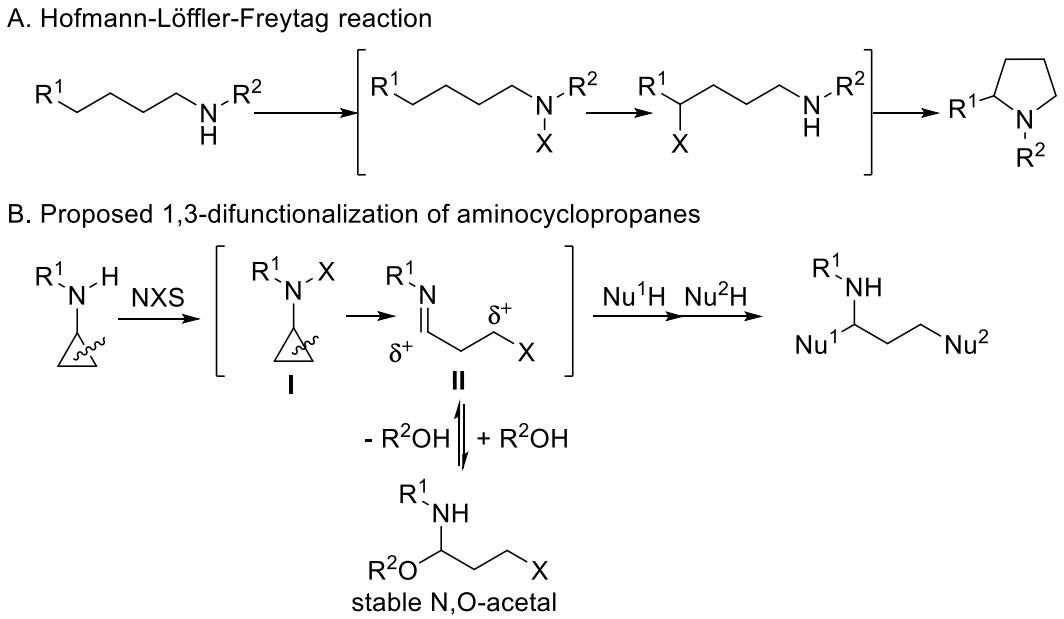
Oxidative Ring-Opening Difunctionalization of Simple Aminocyclopropanes and Aminocyclobutanes

3. Oxidative ring-opening difunctionalization of simple aminocyclopropanes and aminocyclobutanes

In this chapter, I will present the oxidative activation of simple aminocyclopropanes and aminocyclobutanes as a general strategy, which includes: 1) a halogenation (iodination & bromination) of aminocyclopropanes inspired by the HLF reaction (section 3.1); 2) an efficient synthesis of 4-amino thiochromans, as an application to demonstrate the synthetic utility of the HLF reaction-inspired halogenation reaction (section 3.2); 3) an oxidative ring-opening fluorination of aminocyclopropanes and aminocyclobutanes enabled by organic photoredox catalysis (section 3.3); 4) a copper-catalyzed diazidation of aminocyclopropanes, aminocyclobutanes as well as enamides for the synthesis of diamines (section 3.4).

3.1 Halogenation of aminocyclopropanes inspired by the HLF reaction[202]

As already described in the introduction (section 1.4.1), the HLF reaction is an efficient way for the synthesis of pyrrolidines, and it can now be carried out under mild conditions by virtue of modern modifications such as the Suárez modification, the contributions from the Muñiz group and among others (Scheme 53A). Inspired by the recent progress in this area, we, with a particular interest in the conversion of strained rings, wondered if we can generate a nitrogen-centered radical and initiate ring-opening reactions for aminocyclopropanes by the homolytic cleavage of an *in-situ* formed N-X bond. We anticipated that halogenation of simple aminocyclopropanes would give the intermediate **I**, which would undergo homolysis and ring opening to provide a dielectrophilic intermediate **II**. To this dielectrophilic intermediate two different nucleophiles can be added sequentially for the synthesis of 1,3-difunctionalized amines. In case of stability issue, **II** can be masked in the form of an N,O-acetal, which preserves the reactivity of **II** and readily release an iminium ion under acidic conditions (Scheme 53B).

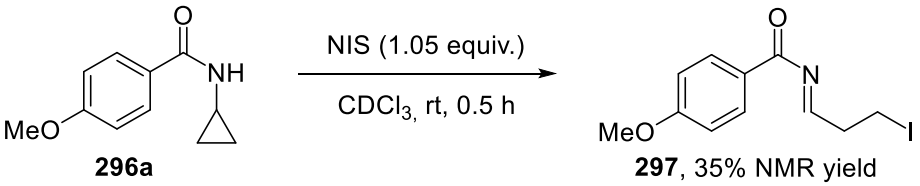


Scheme 53. HLF reaction inspired 1,3-difunctionalization of aminocyclopropanes.

[202] Wang, M.-M.; Waser, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 13880.

3.1.1 Discovery and optimization of the ring-opening halogenation reaction

We started our investigation by reacting aminocyclopropane **296a** with a stoichiometric amount of NIS in $CDCl_3$ (Eq. 28). To our delight, formation of an imine product **297** was observed in 35% yield based on ^{1}H NMR, though accompanied by degradation. Due to the instability issue, **297** could not be isolated in a pure form.

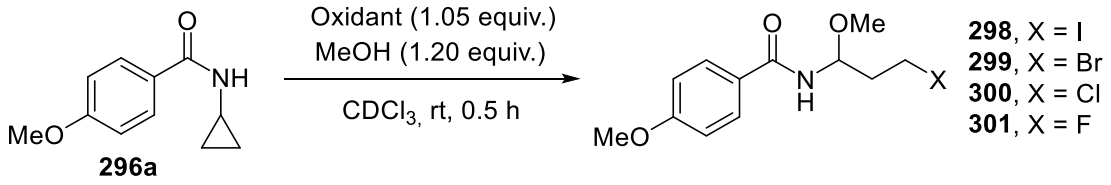


296a **297**, 35% NMR yield

Equation 28. Activation of aminocyclopropane **296a** with NIS.

Since N,O-acetals are stable precursors of imines,[203] we then tried to convert **297** into N,O-acetal **298** by adding methanol as nucleophile. To our delight, **298** was formed in 86% NMR yield with NIS as oxidant (Table 6, entry 1). NBS also promoted ring opening, giving **299** in 65% yield (Table 6, entry 2). In contrast, *N*-chloro-succinimide (NCS) and N-fluorobenzenesulfonimide (NFSI) failed to yield the ring-opening products **300** and **301** (Table 6, entries 3 and 4). The yield of **298** could be improved to 88% by performing the reaction in MeCN and further to 92% by adding 10 mol% $(PhO)_2PO_2H$ (Table 6, entries 5 and 6). N,O-acetal **298** was stable enough to be isolated in 84% yield. The role of $(PhO)_2PO_2H$ as additive could be: 1) to accelerate the nucleophilic addition of MeOH to imine; 2) to enhance the reactivity of NIS through protonation of its carbonyl group.[204] Under these conditions, bromide **299** was isolated with an improved yield of 90% (Table 6, entry 7).

Table 6. Optimization of the ring-opening of aminocyclopropane **296a**.



296a

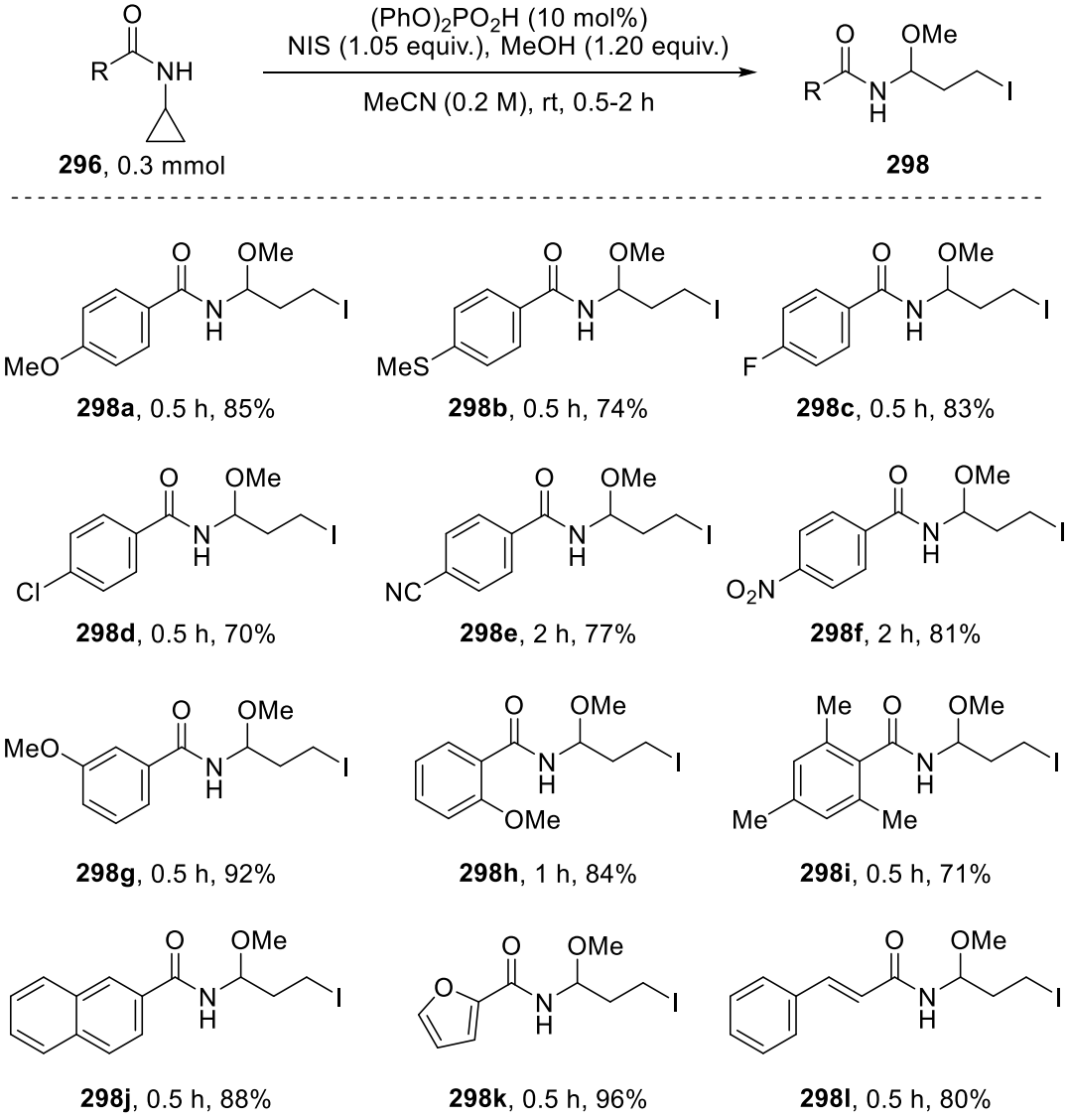
Entry[a]	Oxidant	^{1}H NMR Yield (%)
1	NIS	86
2	NBS	65
3	NCS	0
4	NFSI	0
5	NIS, in MeCN	88
6	NIS with 10 mol% $(PhO)_2PO_2H$, in MeCN	92 (84 isolated)
7	NBS with 10 mol% $(PhO)_2PO_2H$, in MeCN	90

(a) Reaction conditions: reactions were run on a 0.10 mmol scale in 0.50 mL of CD_3Cl at room temperature for 0.5 h. The yield was determined by ^{1}H NMR yield using CH_2Br_2 as internal standard.

[203] Huang, Y.-Y.; Cai, C.; Yang, X.; Lv, Z.-C.; Schneider, U. *ACS Catal.* **2016**, *6*, 5747.
[204] Mori, K.; Ichikawa, Y.; Kobayashi, M.; Shibata, Y.; Yamanaka, M. Akiyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3964.

3.1.2 Substrate scope of the ring-opening iodination reaction

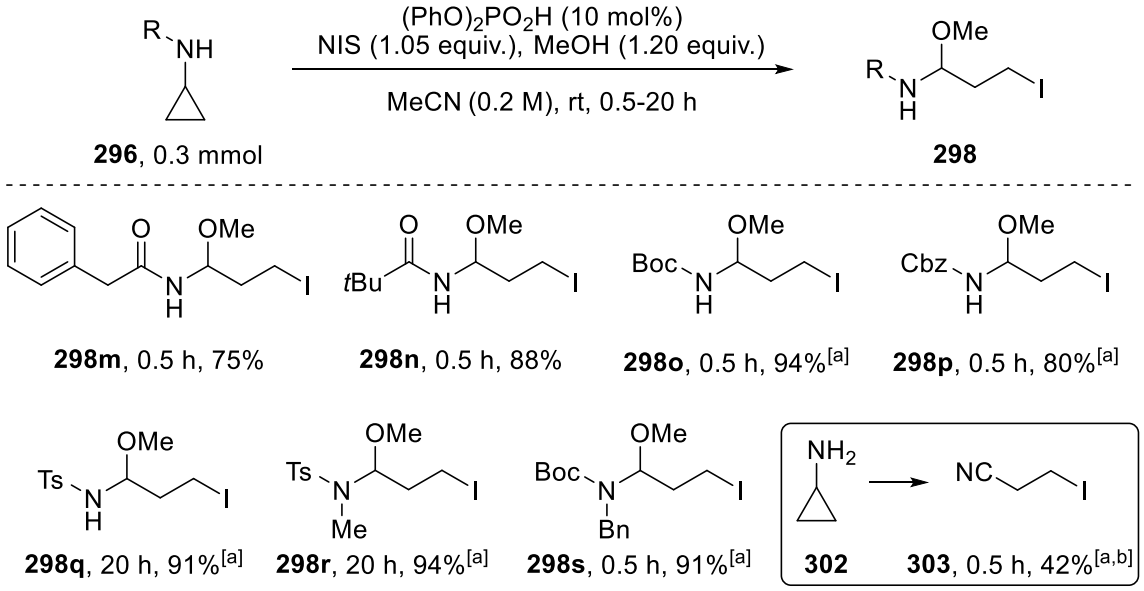
With the optimal conditions in hand, we then examined the substrate scope of the reaction (Scheme 54). A library of cyclopropylamides has been prepared by following the reported procedure on condensation between cyclopropylamine and the corresponding acyl chlorides.[205] Cyclopropyl benzamides with electron-withdrawing or electron-donating groups in the *para* position of the benzene ring all underwent the ring-opening well to give products **298a-f** in yields ranging between 70 and 85%. With substituents on the *ortho*, *meta* or 2,4,6-positions, no erosion of the yield was observed (products **298g-i**). Naphthoyl and furyl-substituted amides **298j-k** were obtained in 88% and 96% yield respectively. With a cinnamoyl protected aminocyclopropane, N,O-acetal **298l** was isolated in 80% yield with the double bond staying untouched.



Scheme 54. Scope of aminocyclopropanes in the ring-opening iodination reaction.

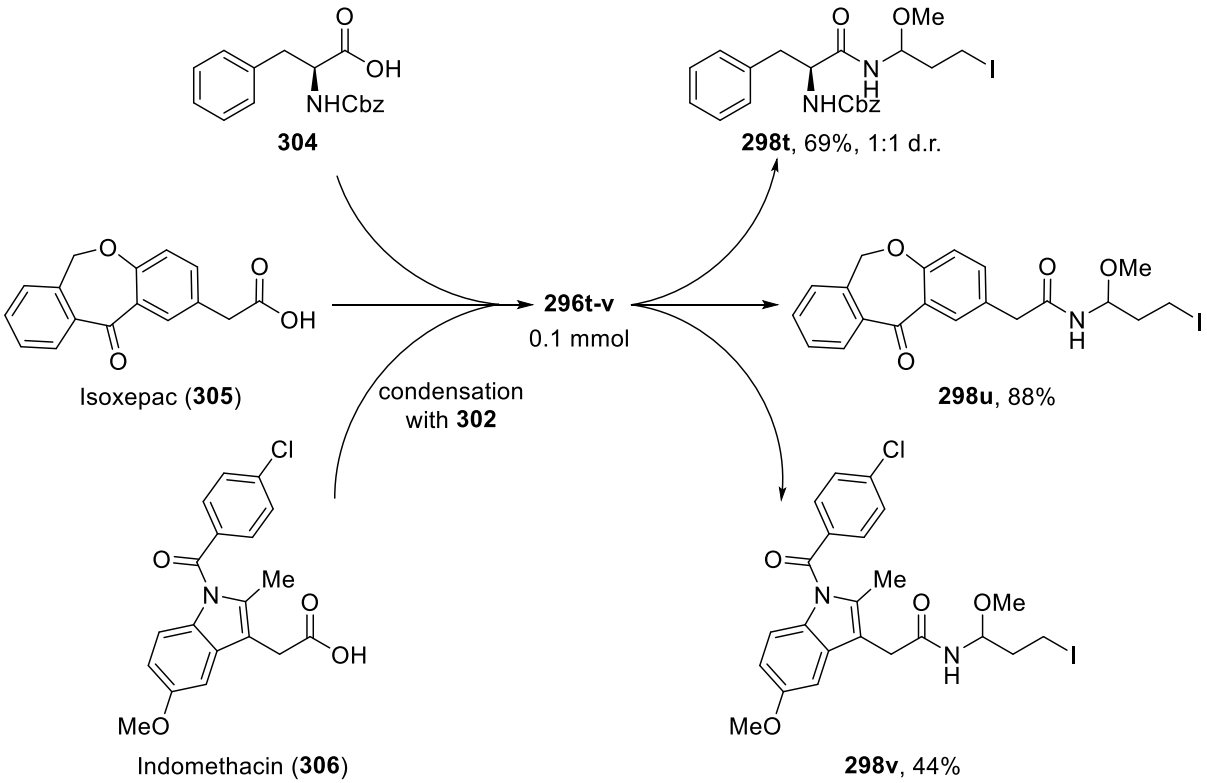
[205] Baburajan, P.; Elango, K. P. *Tetrahedron Lett.* **2014**, *55*, 1006.

Substrates with an alkyl substituent on the acyl protecting group rather than aryl or alkenyl substituent, such as 2-phenylacetoyl and pivaloyl amides, were also well tolerated and gave products **298m-n** in 75-88% yield under the standard conditions (Scheme 55). In addition to these *N*-cyclopropyl amides, carbamate substituted cyclopropanes could also be used as substrates, giving products **298o-p** in 80-94% yield even without the addition of diphenyl phosphate. *N*-Cyclopropyl sulfonamide also underwent the reaction though the reaction time had to be extended to 20 hours in order to improve the yield of **298q**. *N*,*N*-disubstituted aminocyclopropanes were also converted into the corresponding products **298r** and **298s** in high yield. For non-protected aminocyclopropane (**302**), the ring was also cleaved, but the imine intermediate was further oxidized to give cyanide **303** in 42% yield under the standard conditions.



Scheme 55. Scope of aminocyclopropanes in the ring-opening iodination reaction. [a] No diphenyl phosphate. [b] Reaction scale: 0.10 mmol.

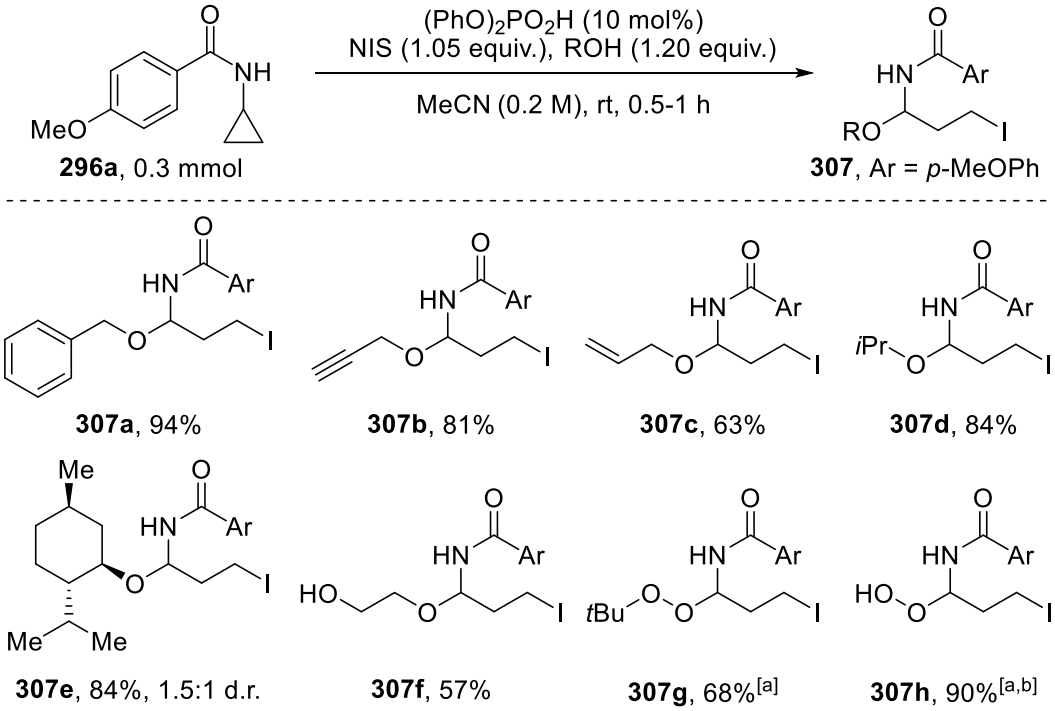
More complex aminocyclopropanes were investigated for this reaction (Scheme 56). The amide substituted cyclopropanes needed for the annulation are easily accessed by standard amide bond formation between a carboxylic acid and commercial aminocyclopropane. Cyclopropylamine **302** was first incorporated into the amino acid **304**, drug molecules such as isoxepac (**305**) and indomethacin (**306**) to give aminocyclopropanes **296t-v**. Starting from **296t-v**, the ring-opening iodination reaction readily gave N,O-acetals **298t-v** in 44-88% yield. These results on complex molecules showed the potential utility of this method in the late-stage functionalization of bioactive compounds.



Scheme 56. Scope of the ring-opening iodination reaction with complex substrates.

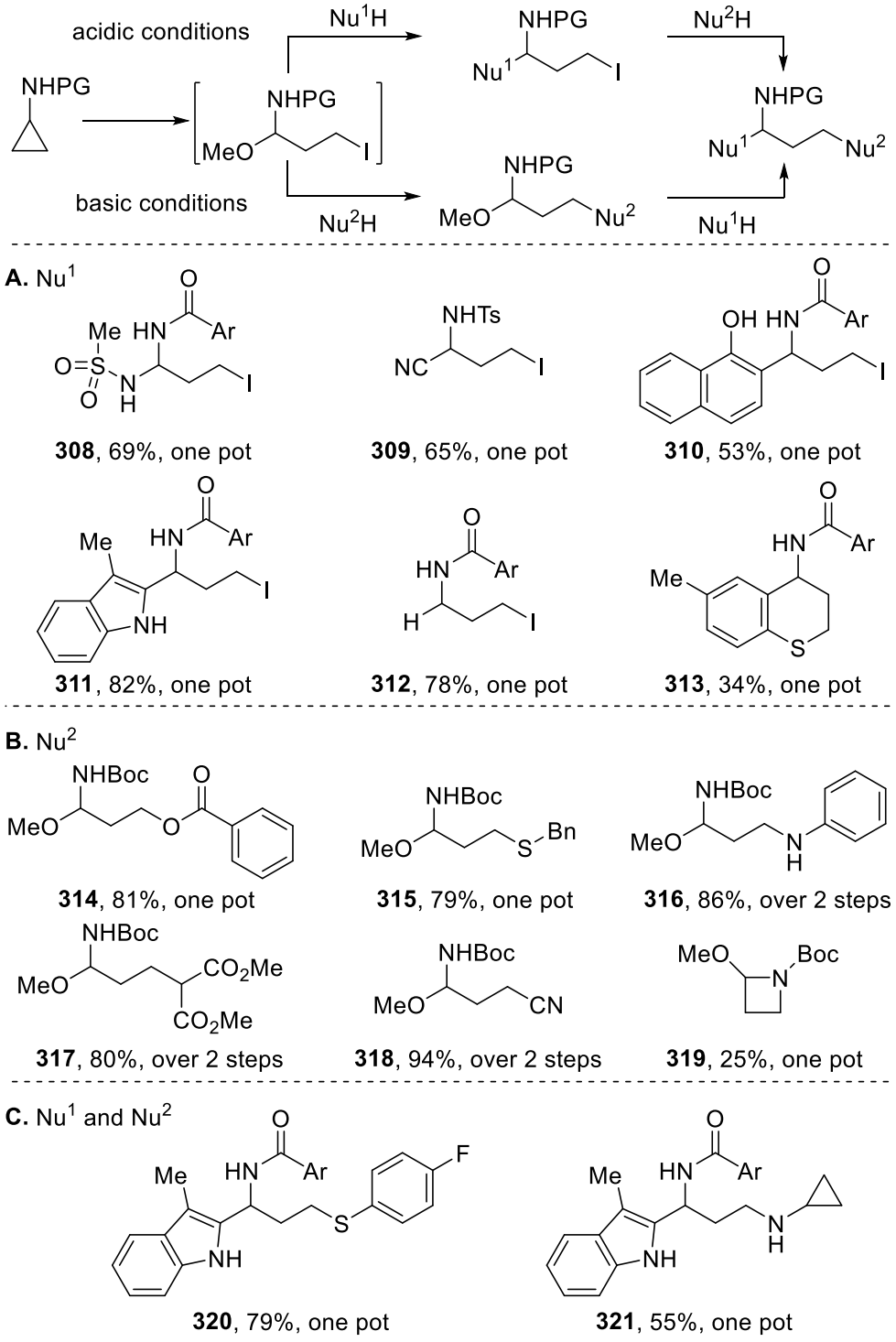
We then explored the scope for the O-nucleophiles (Scheme 57). Apart from methanol, other primary alcohols (products **307a-c**), secondary alcohols (products **307d-e**) or even a diol (product **307f**) were compatible with the reaction conditions. For optically pure menthol, the reaction proceeded with good yield albeit with poor diastereoselectivity to give product **307e**. Simple peroxides were also tested as nucleophiles in this reaction for the production of complex peroxides, which are an important class of bioactive compounds.[206] For *tert*-butyl hydroperoxide (TBHP), molecular iodine was used instead of NIS and a better yield of α-amino peroxide **307g** was obtained. The reaction also worked for hydrogen peroxide, and increasing the amount of H_2O_2 to two equivalents can improve the yield of **307h** to 90%.

[206] Casteel, D, A. *Nat. Prod. Rep.* **1999***, 16*, 55.



Scheme 57. Scope of O-nucleophiles for the ring-opening iodination reaction. [a] I_2 (1.1 equiv.) was used instead of NIS. [b]With 2.0 equivalents of H_2O_2.

Our next objective was to exploit the full potential of the dielectrophilic synthons **298** by adding a broad variety of other nucleophiles for the synthesis of α,γ-difunctionalized amines. However, when other nucleophiles including $MsNH_2$, 1-naphthol, 3-methylindole and thiophenol were used to replace methanol, the corresponding products were obtained in very low yields due to the side reactions between NIS and those nucleophiles. Therefore, one-pot addition of nucleophiles to the N,O-acetals under acidic conditions was attempted (Scheme 58A). The addition of $MsNH_2$ to the crude reaction mixture provided N,N-aminal **308** in 69% yield. The use of C-nucleophiles including TMSCN, 2-naphthol and 3-methyl indole was also successful, with the corresponding products **309-311** isolated in 53-82% yield. When adding $NaBH_3CN$, N,O-acetal **298a** was reduced to give **312** in 78% yield. Interestingly, an unexpected 4-amino thiochroman **313** was formed in 34% yield when adding 4-methylthiophenol to the crude mixture of **298a**, and I will give more details about this transformation in section 3.2.

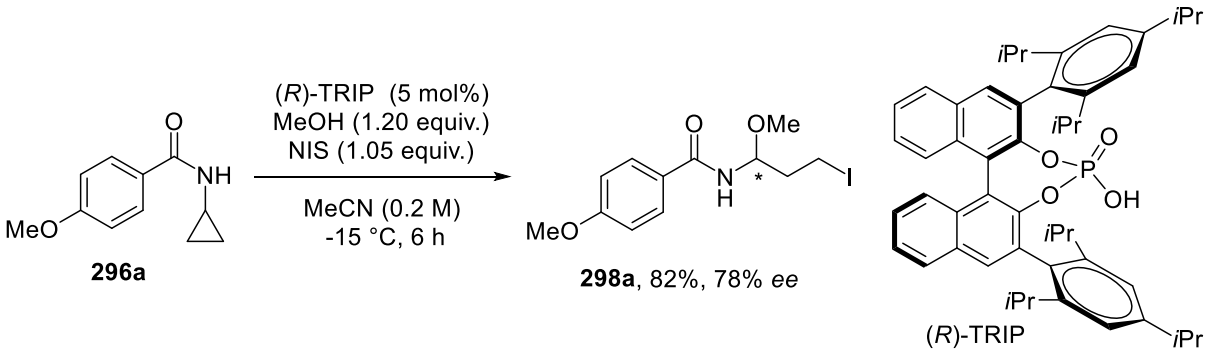


Scheme 58. Conversion of aminocyclopropanes into a variety of α,γ-difunctionalized amines. Ar = *p*-MeOPh.

Next, the iodide was replaced by nucleophiles through an S_N2 reaction (Scheme 58B). Depending on the strength of the external nucleophile compared with that of succinimide, this nucleophilic substitution can be carried out either in a one-pot procedure or in two steps after isolation of the N,O-acetal. For the one-pot procedure, the crude reaction mixture was concentrated under reduced pressure once the first step was done, and then it was dissolved in DMF. Different nucleophiles were added to the DMF solution along with the addition of potassium carbonate as base to promote the S_N2 reaction. For benzoic acid and benzyl thiol, no isolation of the N,O-acetal was necessary. Ester **314** and thioether **315** were isolated

in 81% and 79% yield respectively. When using aniline as nucleophile, N,O-acetal **298o** had to be isolated and purified, otherwise addition of succinimide originating from NIS rather than aniline was observed. Nevertheless, amine **316** was obtained in an excellent 86% yield over two steps. The same procedure was successful for malonate and NaCN, giving products **317** and **318** in good yields. In absence of external nucleophiles, α-methoxy azetidine **319**, which is an interesting building block for the synthesis of α-substituted azetidine derivatives,[207] was obtained in 25% yield. The low yield is due to the formation of a 6-membered ring side product by attack of the oxygen of the carbamate. Finally, the one-pot addition of two different nucleophiles was investigated. Addition of 3-methyl-indole and a thiol or cyclopropylamine gave products **320** and **321** in 79% and 55% yield respectively (Scheme 58C).

Enantioselective addition of alcohols or peroxides to imines has been explored mainly by using two different types of catalysts: chiral phosphoric acids (CPA) and cinchona alkaloid derivatives.[208] In order to obtain the product with enantiomeric excess, we utilized 5 mol% of a commonly used CPA (*R*)-TRIP as shown in Eq. 29. By decreasing reaction temperature and prolonging reaction time, N,O-acetal **298a** could be obtained in 82% yield and 78% ee, which is highly promising for the future development of enantioselective transformations.

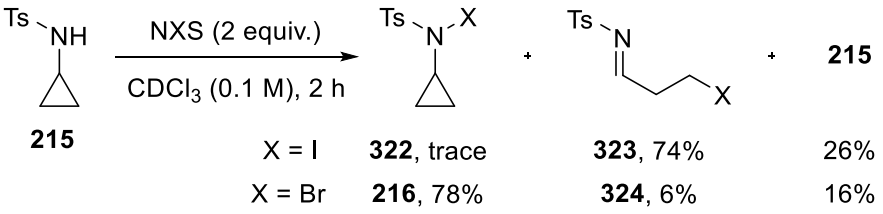


Equation 29. Enantioselective ring-opening of cyclopropane **296a** using (*R*)-TRIP as catalyst.

3.1.3 Mechanistic studies and conclusion of the ring-opening halogenation reaction

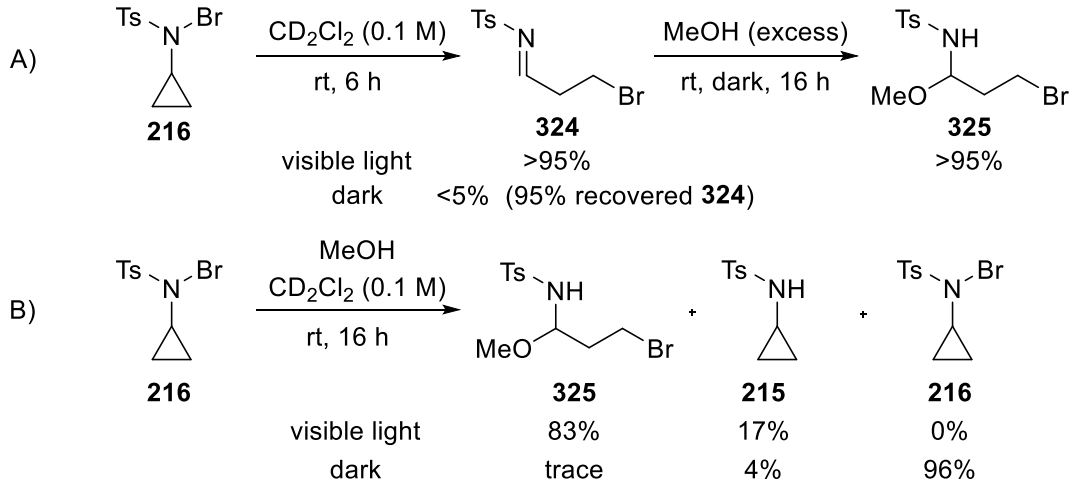
In order to understand the mechanism better, we designed and performed several mechanistic experiments. When mixing **215** and NIS in $CDCl_3$ for two hours, we observed mostly the formation of an imine **323** but it was not stable enough to be isolated in a pure form; while in the case of NBS, only few conversion of the brominated aminocyclopropane **216** into **324** was observed after two hours (Eq. 30). In the latter case, prolonging reaction time only led to non-reproducible results, with varying amounts of **324** being formed. Compound **216** was isolated in 80% yield by flash column chromatography, accompanied by **324** as a major impurity. Although the synthesis of **216** has been reported as shown in Eq. 17, its NMR spectra were not given in the original paper.[125] Therefore, we synthesized **216** in a pure form by following the reported protocol and found that the ^{1}H NMR data of **216** in this case corresponded well to that of crude reaction mixture of **215** with NBS.

[207] Faust, M. R.; Hofner, G.; Pabel, J.; Wanner, K. T. *Eur. J. Med. Chem.* **2010**, *45*, 2453.
[208] a) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216. b) Zheng, W.; Wojtas, L.; Antilla, J. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6589. c) Nakamura, S.; Takahashi, S. *Org. Lett.* **2015**, *17*, 2590.



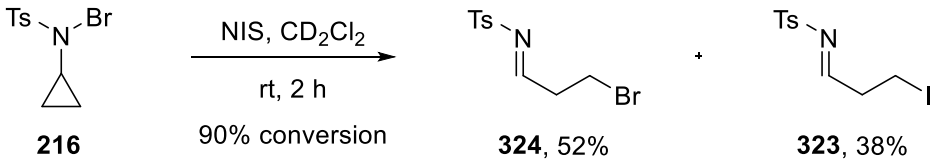
Equation 30. ^{1}H NMR following experiments of mixing aminocyclopropane **215** with NIS or NBS.

The pure compound **216** was converted quantitatively to **324** in 6 h under ambient light irradiation (Scheme 59A). In contrast, nearly no conversion was observed in the dark. The fact that the reaction of the *N*-bromo compound is mediated by light could rationalize the low reproducibility of the results obtained in the one-pot transformation. Imine **324** could then be transformed to N,O acetal **325** in the dark. The addition of methanol since the beginning of the reaction produced similar results, with **325** formed in 83% yield along with a small amount of **215** resulting from the competing debromination (Scheme 59B). Again, almost no reaction was observed in absence of light.



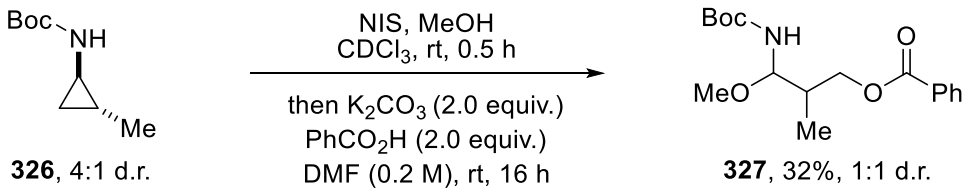
Scheme 59. Determining the role of light during the conversion of **216** into **324**/**325**.

Interestingly, when **216** was treated with NIS, the formation of both bromination and iodination products **324** and **323** was observed, indicating that a cross-over pathway is operative (Eq. 31).



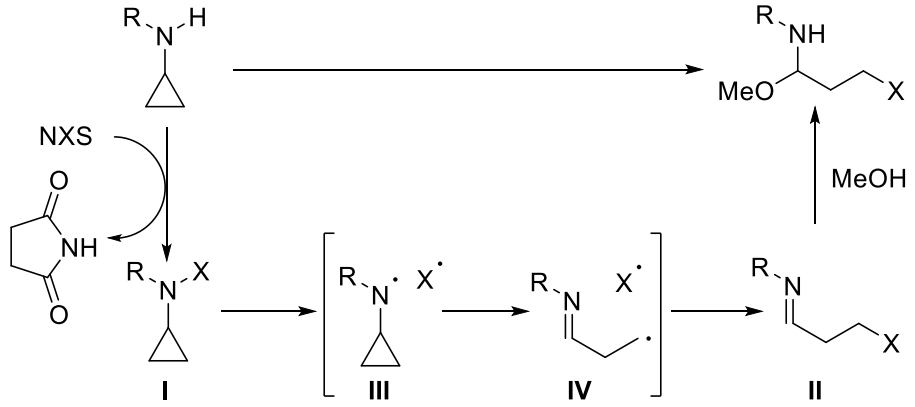
Equation 31. A crossover experiment of **216** with NIS.

Finally, when using 2-methyl substituted aminocyclopropane **326** (d.r. = 4:1), products involving C-C bond cleavage of the more and less substituted C-C bonds were observed in a 1:1 ratio by ^{1}H NMR of the crude reaction mixture. The observed 1:1 ratio is surprising when considering the relative stability of secondary and primary radicals, but may be due to a very early transition state originating from high ring-strain. The iodides were too unstable to be isolated in pure form. Therefore, the in situ S_N2 reaction with benzoate was performed, in which case the secondary iodide decomposed and only **327** was isolated as a mixture of two diastereoisomers in a 1:1 ratio (Eq. 32).



Equation 32. Results of the reaction on 2-methyl substituted aminocyclopropane **326**.

Based on those results, we propose the mechanism depicted in Scheme 60. Halogenation of the aminocyclopropane by NXS provides N-X cyclopropane **I**, which undergoes homolytic cleavage of the N-X bond to form a nitrogen-centered radical and a halogen radical species (**III**). Due to the ring strain of the cyclopropane, ring-opening occurs to form the primary alkyl radical which recombines with the halogen radical (**IV**) to give imine **II**. A radical chain process with the primary radical reacting with a further molecule of **I** can be envisaged. The incorporation of iodine in presence of NIS further support the presence of a primary radical such as **IV**. However, it is not possible at this stage to exclude other reaction mechanisms, such as direct halogenation of the C-C bond or a concerted rearrangement of **I** to **II**. Further studies will be needed to better establish the reaction mechanism. In the presence of MeOH, the N,O-acetal product is then formed. This last step can be accelerated by a Brønsted acid catalyst.



Scheme 60. Speculative reaction mechanism of the ring-opening halogenation reaction.

In summary, we have developed a practical and general strategy for the ring-opening and 1,3-difunctionalization of aminocyclopropanes. A series of stable 3-iodo N,O-acetal products were isolated. From these 1,3-dielectrophiles, a wide range of α,γ-difunctionalized products were rapidly accessed in one pot or in two steps. By using a chiral phosphoric acid as catalyst, a proof-of-concept for asymmetric induction was achieved. Based on the simple reaction procedure and the structural diversity of nitrogen-containing building blocks obtained, we believe that this new methodology will be useful in synthetic and medicinal chemistry.

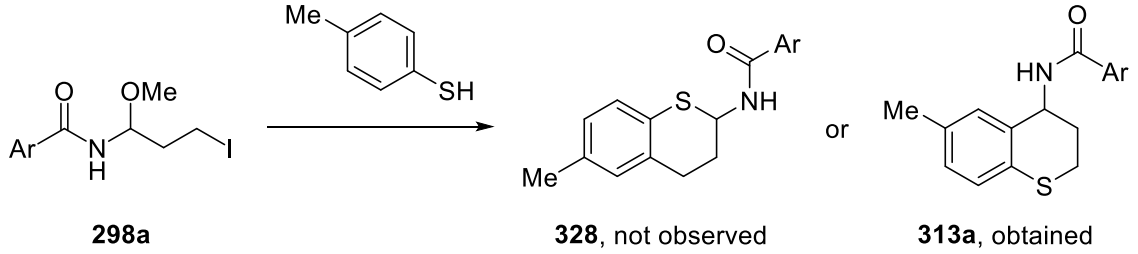
3.2 Synthesis of 4-amino thiochromans by a formal [3+3] cycloaddition[209]

3.2.1 Discovery and optimization of the formal [3+3] cycloaddition

During our investigation on the reaction of the biscationic synthons with nucleophiles as described in section 3.1.2, we isolated an unexpected 4-amino thiochroman product **313a** with exclusive regioselectivity after addition of 4-methylthiophenol (Eq. 33). Based on the favored reaction of

[209] Wang, M.-M.; Jeon, S.; Waser, J. *Org. Lett.* **2020**, *22*, 9123.

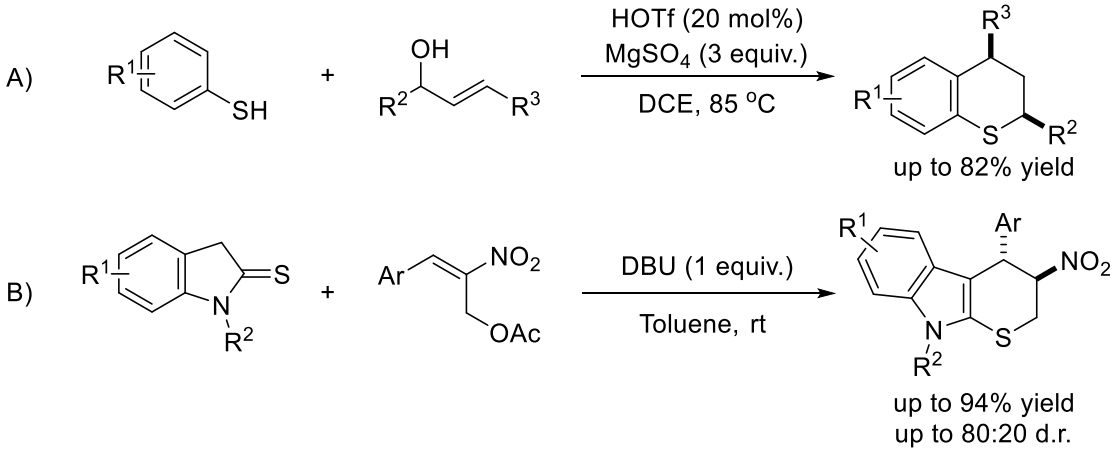
nucleophiles at the acetal position, we expected the formation of 2-amino thiochroman **328** via N,S-acetal. However, 2D NMR spectra indicated that 4-amino thiochroman **313a** had been formed. This non-classical regioselectivity arose our interest and motivated us to investigate the scope of this highly regioselective [3+3] annulation as well as the reaction mechanism.



298a **328**, not observed **313a**, obtained

Equation 33. A highly regioselective formal [3+3] cycloaddition for the synthesis of 4-amino thiochroman **313a**. Ar = *p*-MeOPh.

Although thiochroman and its derivatives have exhibited biological activities,[210] efficient methods for the construction of the thiochroman core remain rare.[211] To the best of our knowledge, there are only two reports disclosing [3+3] annulations for the efficient synthesis of thiochromans from thiophenols. In 2018, Pullarkat and coworkers realized a triflic acid catalyzed tandem allylic substitution–cyclization reaction for the synthesis of 1,4-disubstituted thiochromans (Scheme 61A).[212] High reaction temperature was necessary to force the ring closure. More recently, Namboothiri and coworkers reported the synthesis of thiochromans by using indoline-2-thiones as starting material (Scheme 61B).[213] It is therefore of high interest to develop a formal [3+3] cycloaddition between simple aminocyclopropanes and thiophenols for accessing 4-amino thiochromans.



Scheme 61. Two examples of one-step thiochroman synthesis from thiophenols or thiones.

---

[210] a) Brown, M. J.; Carter, P. S.; Fenwick, A. E.; Fosberry, A. P.; Hamprecht, D. W.; Hibbs, M. J.; Jarvest, R. L.; Mensah, L.; Milner, P. H.; O'Hanlon, P. J.; Pope, A. J.; Richardson, C. M.; West, A.; Witty, D. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3171. b) Geng, H.-J.; Xing, Z.-B.; Luo, W.; Cong, L.; Li, X.-Y.; Guo, C. *Lett. Drug. Des. Discov.* **2012**, *9*, 797. c) Song, Y.-L.; Dong, Y.-F.; Yang, T.; Zhang, C.-C.; Su, L.-M.; Huang, X.; Zhang, D.-N.; Yang, G.-L.; Liu, Y.-X. *Bioorg. Med. Chem.* **2013**, *21*, 7624.

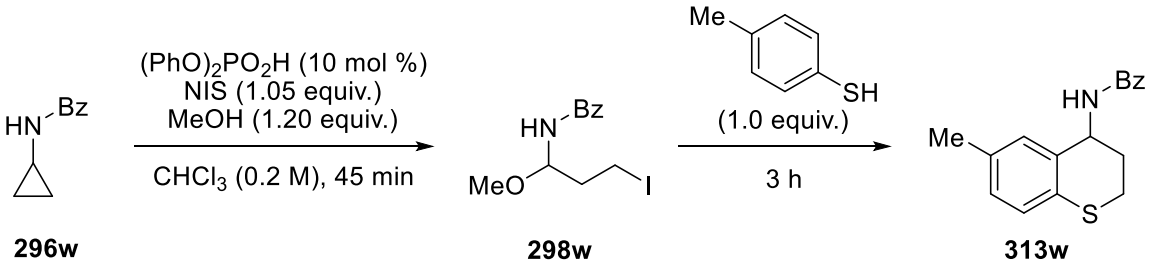
[211] Selected examples depicting two-step synthesis of thiochroman derivatives from thiophenols: a) Niermann, A.; Grössel, J. E.; Reissig, H.-U. *Synlett* **2013**, *24*, 177. b) Mao, H.; You, B.-X.; Zhou, L.-J.; Xie, T.-T.; Wen, Y.-H.; Lv, X.; Wang, X.-X. *Org. Biomol. Chem.* **2017**, *15*, 6157.

[212] Vu, M. D.; Foo, C. Q.; Sadeer, A.; Shand, S. S.; Li, Y.; Pullarkat, S. A. *ACS Omega* **2018**, *3*, 8945.

[213] Basu, P.; Hazra, C.; Baiju, T. V.; Namboothiri, I. N. N. *New J. Chem.* **2020**, *44*, 1389.

Based on our preliminary results, we chose N-cyclopropylbenzamide **296w** as starting material for the preparation of the biscationic synthon intermediate **298w** by reaction with NIS under acidic conditions in chloroform (Table 7). After formation of **298w**, 4-methylbenzenethiol was added to the reaction mixture and **313w** was obtained in good yield (entry 1). Running the reaction in other solvents like dichloromethane or acetonitrile was also possible (entries 2 and 3). The reaction took place even in the absence of diphenyl phosphate, giving **313w** in 70% yield (entry 4). However, adding 4-methylbenzenethiol at the beginning of the reaction gave a low yield, probably due to decomposition of 4-methylbenzenethiol mediated by NIS (entry 5). With NBS as electrophile instead of NIS, the first step was efficient, but only 38% of **313w** was formed during the second step (entry 6).

Table 7. Optimization of reaction conditions for the formation of thiochromans.



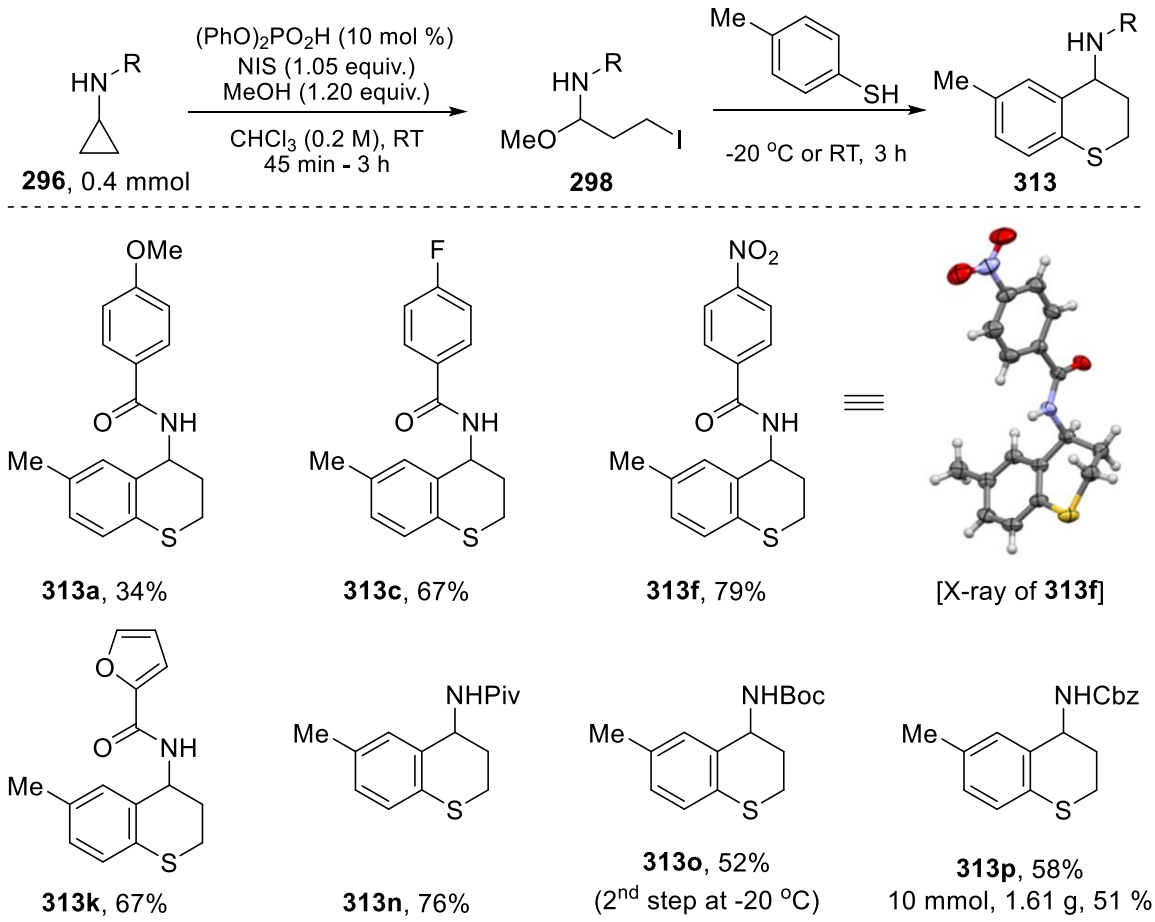
296w **298w** **313w**

Entry[a]	Deviation from standard condition	^{1}H NMR Yield (%)
1	none	79
2	DCM as solvent	78
3	MeCN as solvent	48
4	w/o $(PhO)_2PO_2H$	70
5	Adding thiophenol at the beginning	10
6	NBS instead of NIS	38

(a) Reaction conditions: 0.10 mmol scale for 45 min in the 1st step, then 4-methylbenzenethiol was added and the reaction mixture was kept stirring for 3 hours. Yield was determined by ^{1}H NMR using CH_2Br_2 as internal standard.

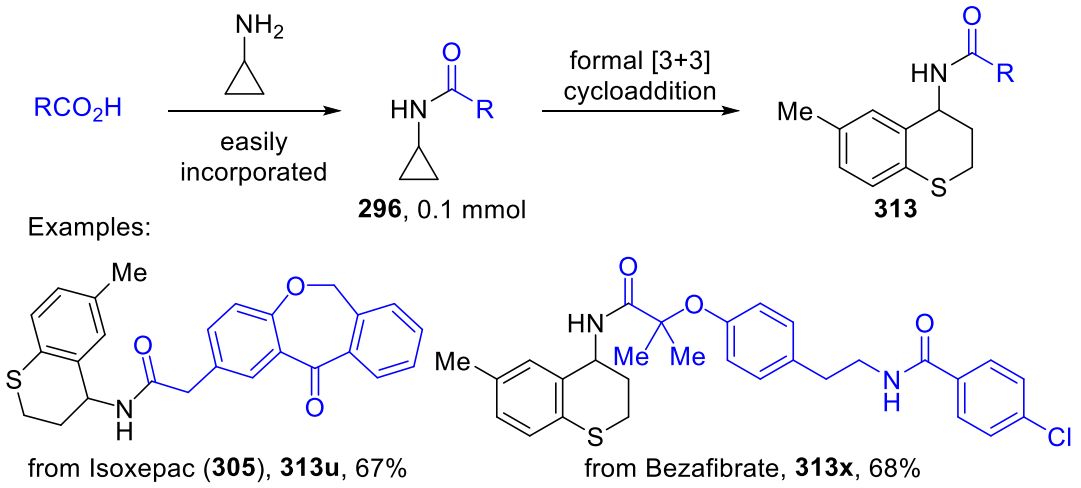
3.2.2 Substrate scope and limitations of the formal [3+3] cycloaddition

With the optimal conditions in hand, we then examined the scope of aminocyclopropanes with different protecting groups (Scheme 62). With electron-donating substituents such as a 4-methoxy group on the benzene ring, the product **313a** was isolated in low yield, possibly due to polymerization of the intermediate. With electron-withdrawing groups on the benzene ring like 4-fluoro or 4-nitro, products **313c** and **313f** were formed in 67% and 79% yield. The structure of **313f** was confirmed by X-ray diffraction. A 2-furoyl group on the aminocyclopropane was well tolerated, giving product **313k** in 67% yield. With a pivalate protecting group, product **313n** was isolated in 76% yield. Carbamate-substituted cyclopropanes can also undergo this transformation, giving the desired products **313o** and **313p** in 52% and 58% yield. The synthesis of **313p** was scaled up to 10 mmol and 1.61 grams of product (51% yield) were obtained.



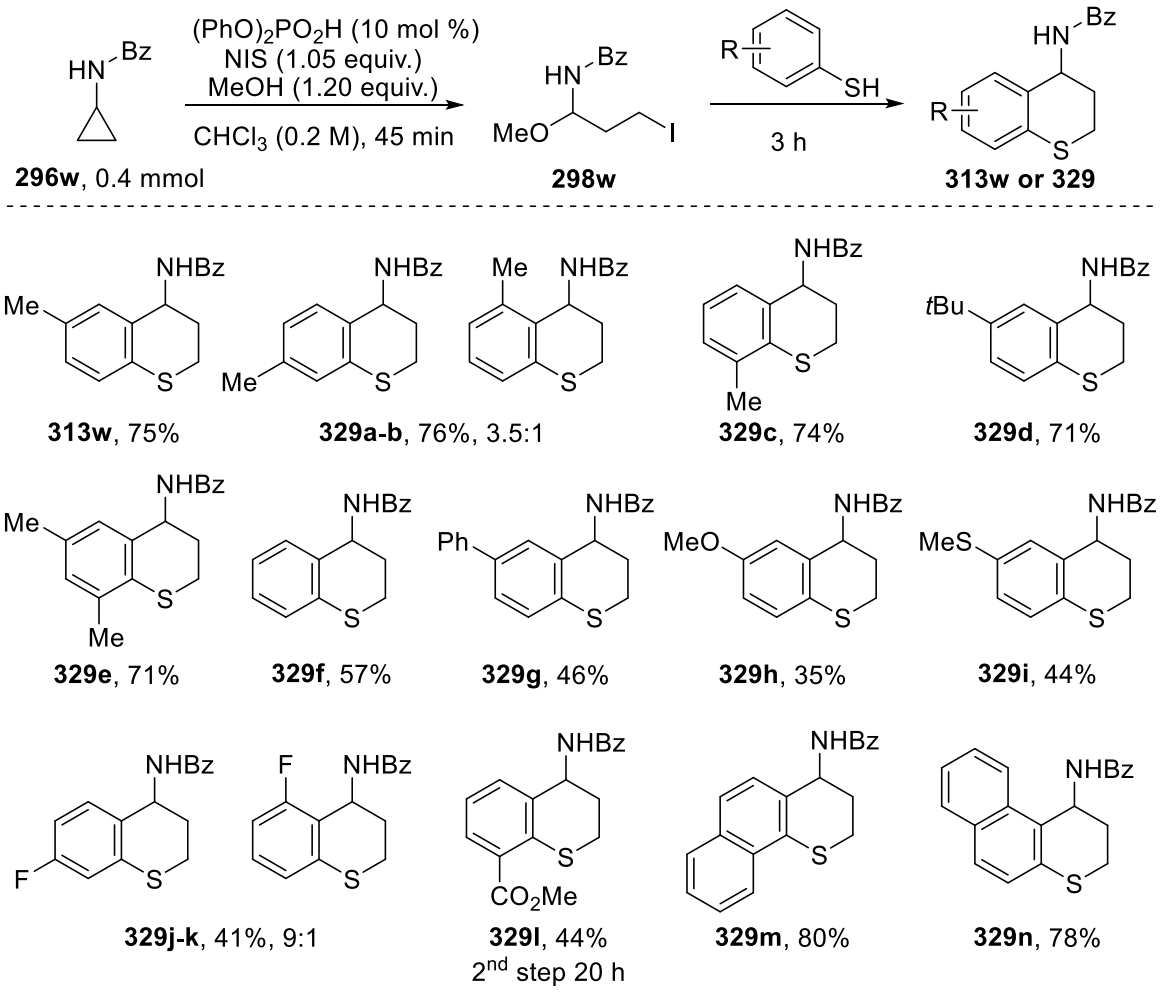
Scheme 62. Scope of aminocyclopropanes for the formal [3+3] cycloaddition.

The formal [3+3] cycloaddition can also be used for the late-stage modification of drugs containing a carboxylic group. This strategy was applied to the lipid-lowering agent bezafibrate and the anti-inflammatory drug isoxepac. Cyclopropylamine was easily incorporated into these carboxylic group-containing compounds to yield cyclopropylamides **296**. After the formal [3+3] cycloaddition, the corresponding thiochroman products **313u** and **313x** were isolated in 67% and 68% yield respectively (Scheme 63).



Scheme 63. Late stage modification of the formal [3+3] cycloaddition on drug derivatives.

We then explored the reaction scope for thiophenols using **296w** as the model substrate (Scheme 64). A series of thiophenols with a methyl substituent at *para/meta/ortho* positions gave the corresponding thiochromans **313w** and **329a-c** with a methyl group at 6/7(5)/8 position in good yields. With 4-*tert* butyl or 2,4-dimethyl substituted thiophenols, **329d** and **329e** were obtained in 71% yield. A slightly lower yield was observed for **329f** when using unsubstituted thiophenol as reaction partner. With a phenyl or electron-donating substituents like a methoxy or a methylthio group at the *para* position, products **329g-i** were obtained in yields ranging from 35% to 46%. Electron poor thiophenols like 3-fluorothiophenol or methyl 2-mercaptobenzoate were also tolerated, affording products **329j-k** and **329l** in 41% and 44% yield respectively. Naphthalene-1-thiol and naphthalene-2-thiol gave the corresponding products **329m** and **329n** in 80% and 78% yield.

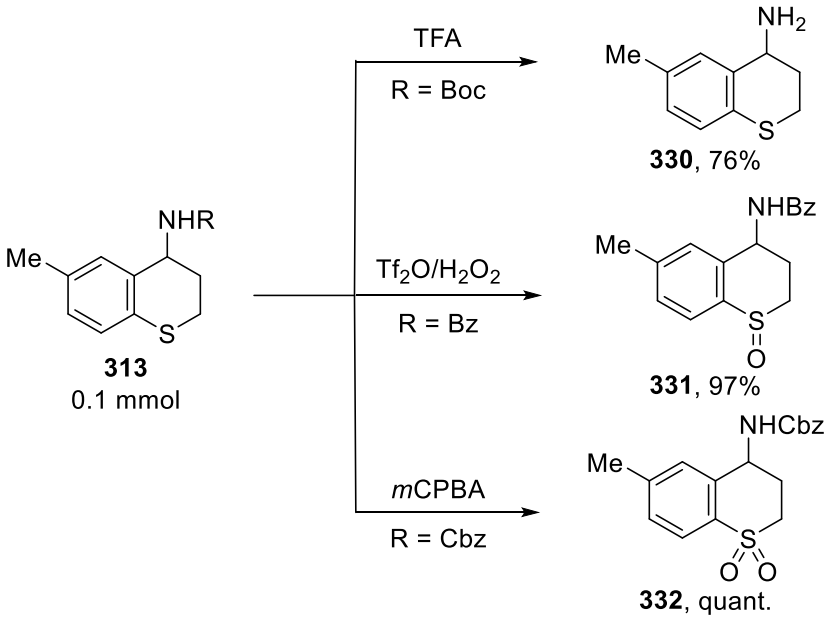


Scheme 64. Scope of thiophenols for the formal [3+3] cycloaddition.

To highlight the synthetic utility of our 4-amino thiochroman products, a series of transformations were performed (Scheme 65). With Boc as protecting group, free amine **330** was easily obtained from **313o** in 76% yield. The thiochroman product can also be oxidized to sulfoxide **331** (97% yield from **313w**) or sulfone **332** (quantitative yield from **313p**) respectively. It is important to note that 4-amino thiochroman derivatives were reported to be potent aldose reductase inhibitors[214] or sirtuin 5 (SIRT5)

[214] Sarges, R.; Schnur, R. C.; Belletire, J. L.; Peterson, M. J. *J. Med. Chem.* **1988**, *31*, 230.

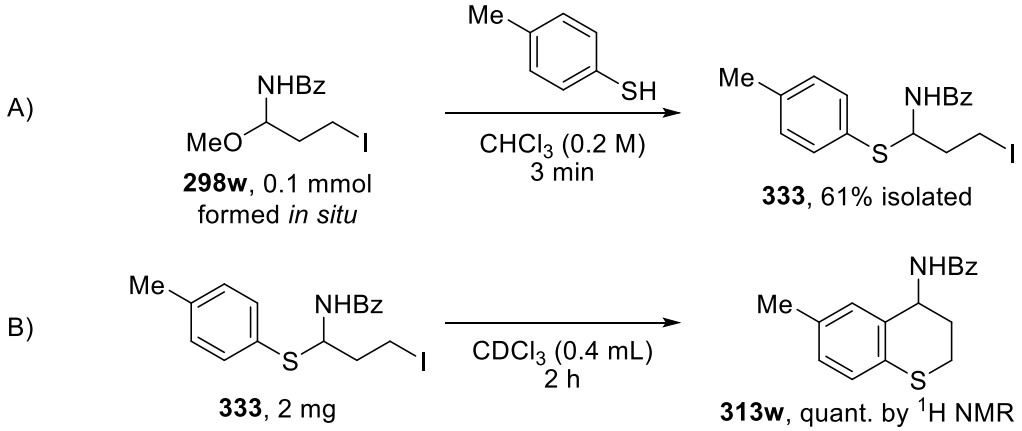
inhibitors.[215] They were also reported to have excellent selective antagonistic activity on an α_{1D} adrenergic receptor.[216]



Scheme 65. Late-stage modification and functionalization of the thiochroman products.

3.2.3 Mechanistic studies of the formal [3+3] cycloaddition

The unexpected formation of 4-amino thiochromans motivated us to perform a series of experiments in order to gain some insight into the mechanism. By performing the standard reaction in $CDCl_3$ and following the reaction progress by ^1H NMR, we observed the conversion of **298w** into a first intermediate, which was isolated in 61% yield and was identified as N,S-acetal **333** after purification by column chromatography (Scheme 66A). The transformation of **333** into thiochroman **313w** was spontaneous in $CDCl_3$ and was complete in 2 hours, indicating the formation of **313w** is via N,S-acetal **333** (Scheme 66B).



Scheme 66. Identification of reaction intermediates for the formal [3+3] cycloaddition.

[215] Rajabi, N.; Auth, M.; Troelsen, K. R.; Pannek, M.; Bhatt, D. P.; Fontenas, M.; Hirschey, M. D.; Steegborn, C.; Madsen, A. S.; Olsen, C. A. *Angew. Chem. Int. Ed.* **2017**, *56*, 14836.
[216] Masato, Y.; Yasuhisa, K.; Nobuki, S.; Ayumu, S. **2009**, WO2009131135 (A1).

An unknown intermediate, which can be stabilized by adding excess K_2CO_3 to the solution, was observed by ^1H NMR during the transformation from **333** to **313w** (Figure 10). However, attempts to isolate this intermediate failed as it was formed only in a small ratio.

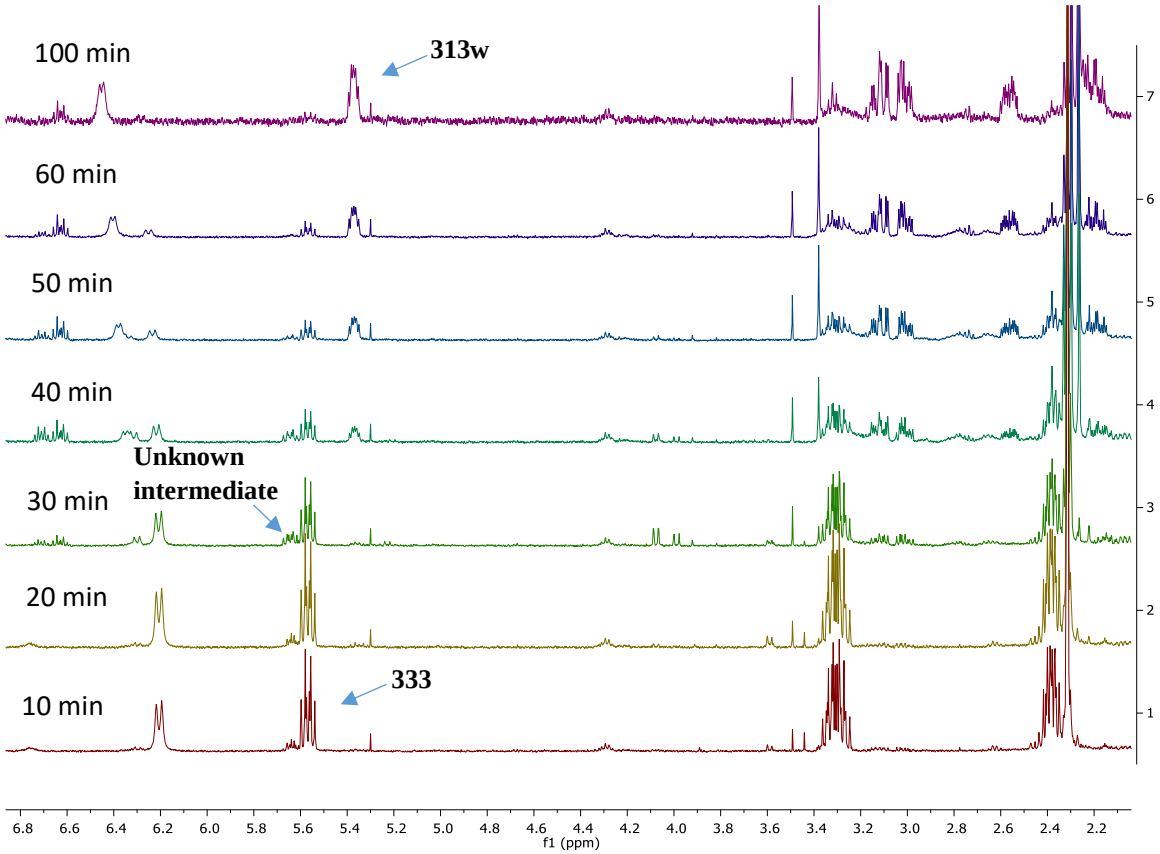
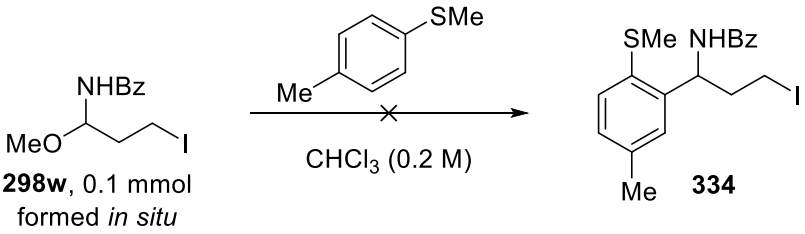


Figure 10. ^1H NMR (400 MHz, $CDCl_3$) following experiments starting from N,S-acetal **333**.

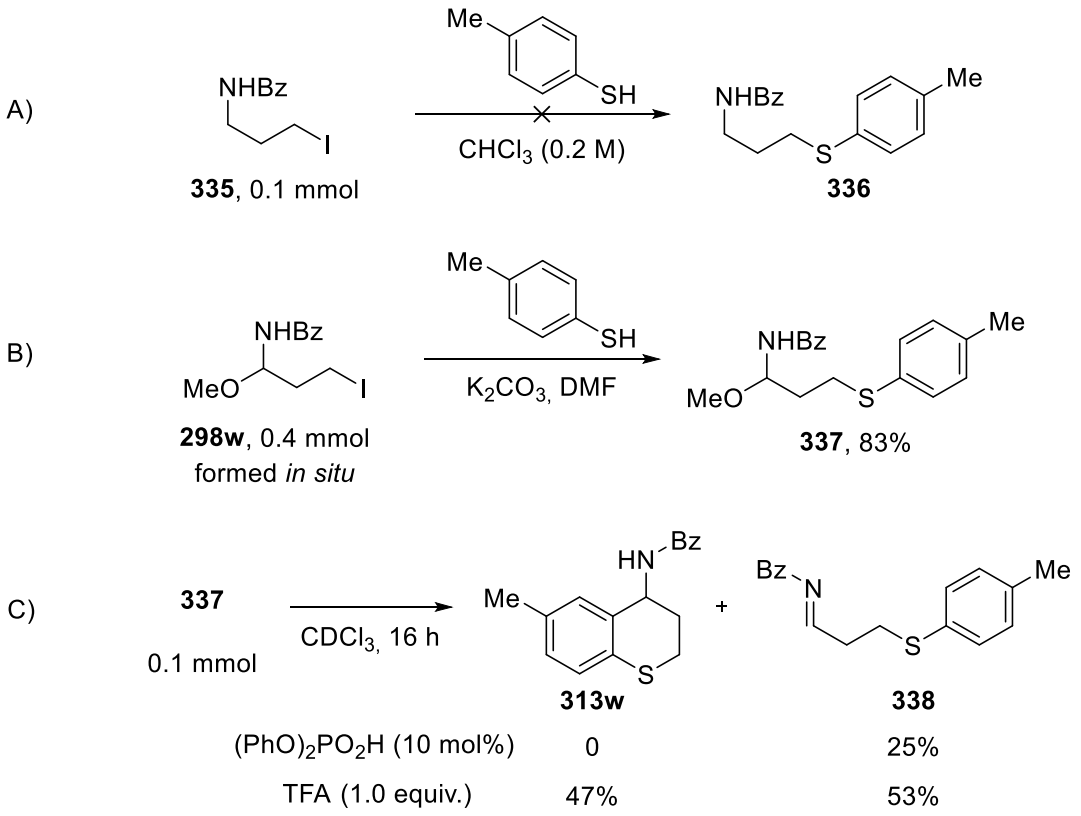
When mixing N,O-acetal **298w** with methyl *p*-tolyl sulfide, the product **334** resulting from an intermolecular Friedel-Crafts reaction was not observed (Eq. 34). This suggests that the free thiol group is more reactive than the ortho position in the nucleophilic substitution step, and again the formation of N,S-acetal is an important step for this reaction.



Equation 34. Reaction of N,O-acetal **298w** with methyl *p*-tolyl sulfide.

We also designed some experiments to rule out the possibility of forming first a C-S bond through an intermolecular S_N2 pathway followed by an intramolecular Friedel-Crafts reaction. Compound **298w** was reduced to give the alkyl iodide **335** and as expected, no reaction was observed between 4-methylbenzenethiol and **335** under neutral or acidic conditions (Scheme 67A). Indeed, the S_N2 reaction took place efficiently only under basic conditions, giving **337** in 83% yield (Scheme 67B). We then added diphenyl phosphate to the solution of **337** in $CDCl_3$ but no formation of thiochroman product **313w** has been recorded for 16 hours. The conversion of the **337** into **313w** was not very efficient even

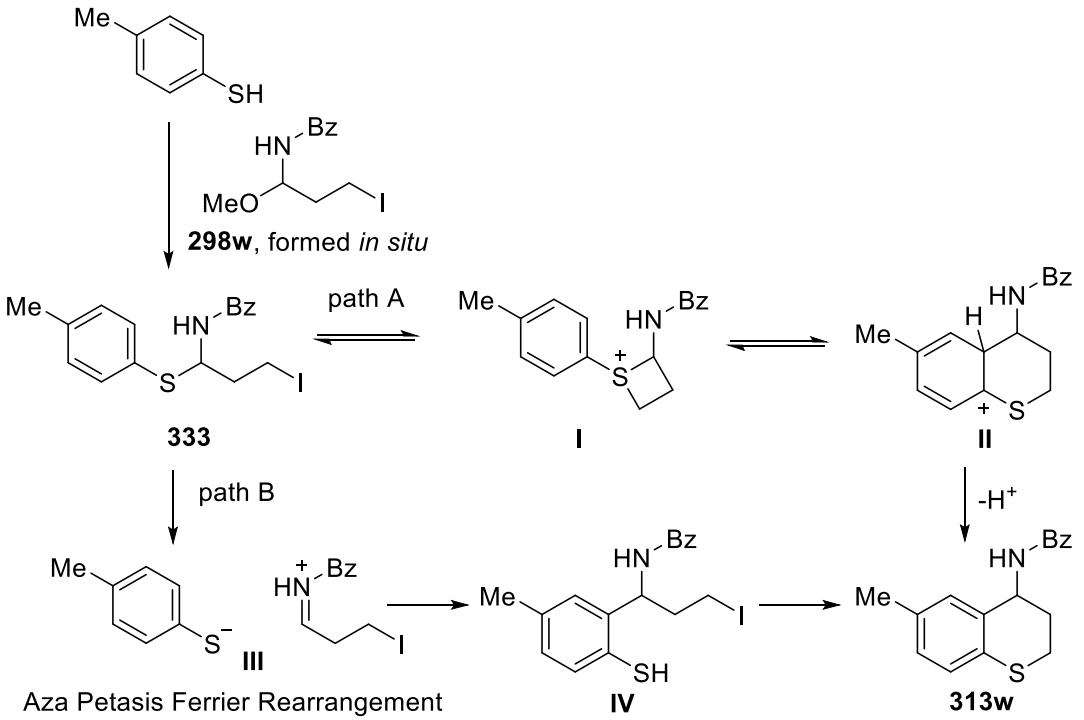
in the presence of 1.0 equiv TFA, and it was accompanied by the formation of imine intermediate **338** (Scheme 67C).



Scheme 67. Mechanistic experiments for probing the S_N2 - intramolecular Friedel-Crafts pathway.

Based on these experiments, we propose a speculative mechanism as depicted in Scheme 68. Once 4-methylbenzenethiol was added, the N,S-acetal **333** was formed as the first intermediate. Due to the nucleophilicity of the sulfur atom, an intramolecular S_N2 reaction would take place to form the sulfonium salt **I**, which might be the unknown intermediate observed from ^1H NMR experiments (path A). The following steps involving ring opening of the four-membered cycle, intramolecular Friedel-Crafts reaction and deprotonation of **II** should be fast, as no other intermediates were observed from ^1H NMR experiments. A mechanism involving a 1,3-shift can also be considered for explaining the transition from **I** to **II**, as imine **338** was not observed. Another possibility to explain the migration of the sulfur atom from the N,S-acetal carbon atom to the terminal carbon atom would involve an aza-Petasis Ferrier rearrangement[217] via ion pair **III** to give **IV**, followed by an intramolecular S_N2 reaction (path B). Nevertheless, path A seems more reasonable, considering the stability of the unknown intermediate in the presence of K_2CO_3, which would be expected to accelerate a S_N2 process.

[217] a) Terada, M.; Toda, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6354. b) Terada, M.; Komuro, T.; Toda, Y.; Korenaga, T. *J. Am. Chem. Soc.* **2014**, *136*, 7044.



Scheme 68. Proposed speculative reaction mechanism for the thiochroman formation.

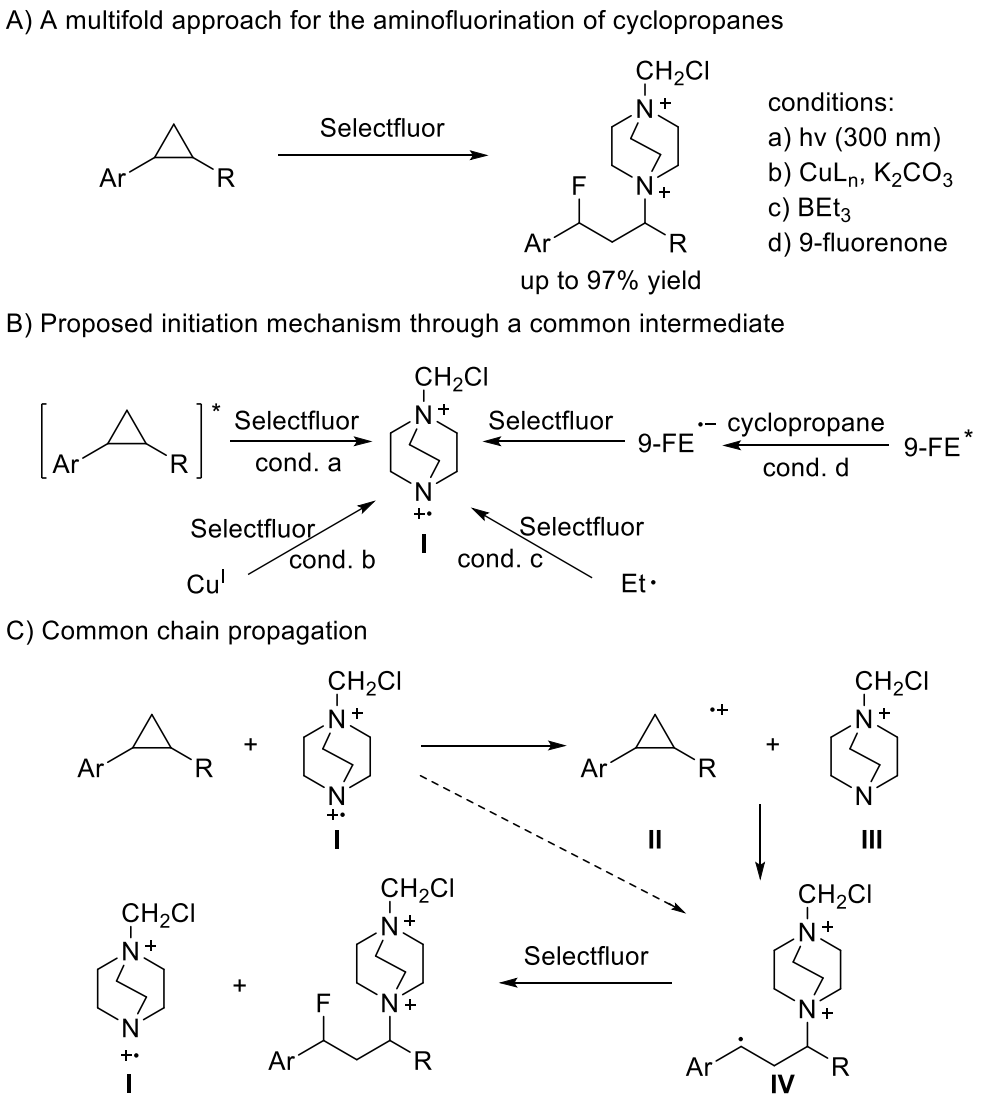
In summary, we have developed an efficient and regioselective [3+3] annulation for the synthesis of 4-amino thiochromans. Good functional group tolerance was observed for electron-donating and electron-withdrawing substituents on both thiophenols and aminocyclopropanes. Late-stage modification of drug derivatives containing an aminocyclopropane was successful and deprotection of the amino group was demonstrated. An enantioselective synthesis as well as other annulations involving dielectrophilic synthons derived from aminocyclopropanes will be investigated by other members from our group.

3.3 Fluorination of aminocyclopropanes/cyclobutanes through photoredox catalysis[218]

Tremendous efforts have been devoted to the development of site-selective fluorination methods, given the significance of fluorinated compounds in medicine and agrochemistry.[219] Among these methods, the formation of C(sp^3)-F bonds via ring opening fluorination of carbocycles is an attractive route.[220] In 2016 the Lectka group disclosed four sets of conditions for the generation of the same aminofluorinated adducts by using an electrophilic fluorinating reagent such as Selectfluor (Scheme 69A).[221] The aminofluorination reaction can be initiated by direct photoexcitation under the irradiation of light at 300 nm (condition a), metal initiation with a copper (I) complex (condition b), radical initiation with triethylborane (condition c) or photosensitization with 9-fluorenone (9-FE) as photosensitizer (condition d). A common intermediate (Selectfluor-derived radical cation, **I**) is formed during these diverse ways

[218] Wang, M.-M.; Waser, J. *Angew. Chem. Int. Ed.* **2020**, *59*, 16420.
[219] a) Organofluorine chemistry (Eds.: R. E. Banks, B. E. Smart, J. C. Tatlow) Springer US: Boston, MA, **1994**. b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. c) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073. d) Cheng, Q.; Ritter, T. *Trends Chem.* **2019**, *1*, 461. e) Szpera, R.; Moseley, D. F. J.; Smith, L. B.; Sterling, A. J.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2019**, *58*, 14824.
[220] a) Yan, H.; Zhu, C. *Sci. China Chem.* **2017**, *60*, 214. b) Wu, X.; Zhu, C. *Chem. Rec.* **2018**, *18*, 587. c) Liu, Y.; Wang, Q.-L.; Chen, Z.; Zhou, C.-S.; Xiong, B.-Q.; Zhang, P.-L.; Yang, C.-A.; Zhou, Q. *Beilstein J. Org. Chem.* **2019**, *15*, 256; d) Morcillo, S. P. *Angew. Chem., Int. Ed.* **2019**, *58*, 14044.
[221] Pitts, C. R.; Ling, B.; Snyder, J. A.; Bragg, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2016**, *138*, 6598.

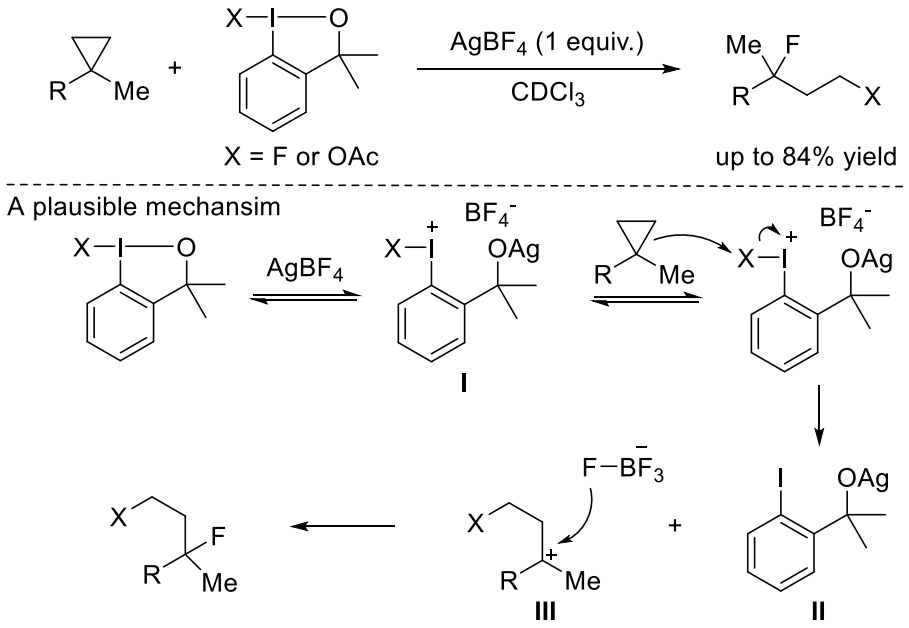
of initiation (Scheme 69B), which is predicted to oxidize arylcyclopropanes very efficiently to form an arylcyclopropane radical cation **II** (Scheme 69C). The formed tertiary amine **III** then acts as nucleophile for the ring opening of the arylcyclopropane radical cation, resulting in the formation of intermediate **IV**. The oxidation of arylcyclopropanes with **I** and subsequent nucleophilic substitution toward **IV** can also occur simultaneously in a concerted way. Then **IV** abstracts a fluorine atom from Selectfluor to yield the aminofluorinated adduct and regenerates **I**. In this way the chain propagates.



Scheme 69. Aminofluorination of cyclopropanes through a common intermediate.

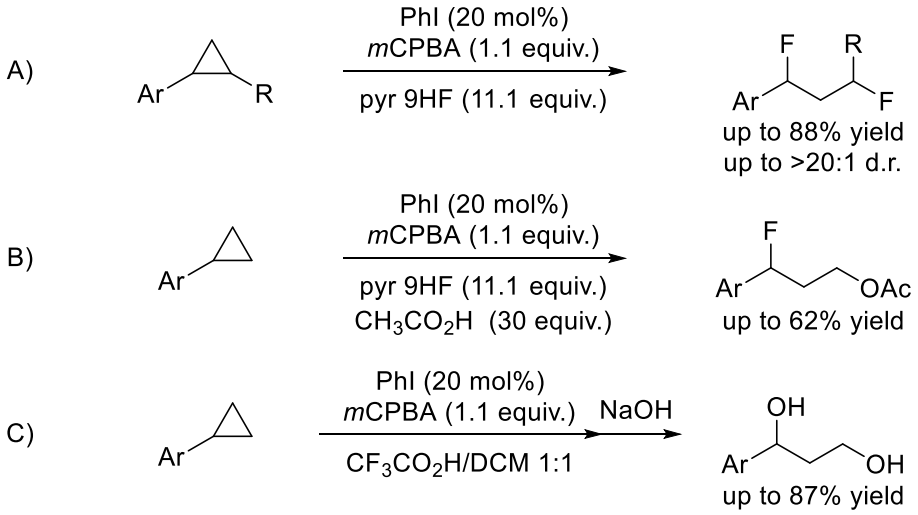
In 2017, the Szabó group reported a difluorination and a 1,3-oxyfluorination of 1,1-disubstitued cyclopropanes by using hypervalent iodine reagents (Scheme 70).[222] Stoichiometric amount of $AgBF_4$ was used to activate hypervalent iodine reagents by coordinating to the oxygen atom of the benziodoxole ring. Then intermediate **I** underwent side-attack of the cyclopropyl ring to afford iodoarene **II** and a carbocation intermediate **III**. Nucleophilic attack by fluorine from the BF_4^- counterion eventually gave difluorination or 1,3-oxyfluorination products, depending on the functional group on the iodine atom of the hypervalent iodine reagents.

[222] Ilchenko, N. O.; Hedberg, M.; Szabó, K. J. *Chem. Sci.* **2017**, *8*, 1056.



Scheme 70. Difluorination and oxyfluorination of cyclopropanes by hypervalent iodine reagents.

In 2017, by using aryl iodide (I-III) catalysis, the Jacobsen group reported a range of 1,3-difunctionalization reactions for cyclopropanes including difluorination (Scheme 71A), 1,3-oxyfluorination (Scheme 71B), dihydroxylation (Scheme 71C) and among others.[223] Different from Szabó's work, they realized the oxidative ring opening of cyclopropanes in a catalytic form by employing *m*CPBA for the generation of an electrophilic iodine (III) species *in situ* from PhI.

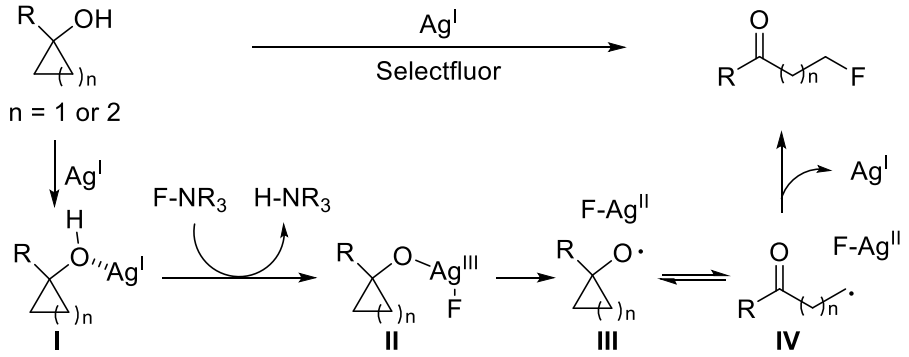


Scheme 71. Difluorination, oxyfluorination and dihydroxylation of cyclopropanes by aryl iodine (I-III) catalysis.

Regarding to cyclopropanols and and cyclobutanols, there are also a few reports on their ring-opening fluorination. In 2015, the Zhu group, the Murakami group and the Loh group reported independently almost at the same time a silver-catalyzed ring-opening strategy for the synthesis of β- and γ-fluorinated ketones (Scheme 72).[224] The Zhu group proposed a plausible mechanism as illustrated below: oxidation

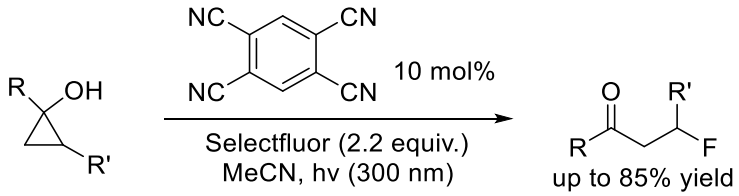
[223] Banik, S. M.; Mennie, K. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2017**, *139*, 9152.
[224] a) Zhao, H.; Fan, X.; Yu, J.; Zhu, C. *J. Am. Chem. Soc.* **2015**, *137*, 3490. b) Ishida, N.; Okumura, S.; Nakanishi, Y.; Murakami, M. *Chem. Lett.* **2015**, *44*, 821. c) Ren, S.; Feng, C.; Loh, T.-P. *Org. Biomol. Chem.* **2015**, *13*, 5105.

of a cyclobutanol-Ag^{I} complex **I** by Selectfluor gives the Ag^{III} complex **II**, which undergoes homolysis to form a F-Ag^{II} species and a cyclobutoxy radical. After the O-centered radical initiated ring opening, the alkyl radical **III** reacts with F-Ag^{II} to finally form the product. The Murakami group and the Loh group proposed a similar mechanism in which the Ag^{I} is first oxidized to Ag^{III} species before interacting with the cyclic alcohol substrates.



Scheme 72. The silver-catalyzed ring-opening fluorination of cyclic tertiary alcohols and a proposed mechanism.

In 2015, shortly after the three reports on silver-catalyzed fluorination of cyclic alcohols, the Lectka group reported a photocatalyzed ring-opening fluorination of cyclopropanols using 1,2,4,5-tetracyanobenzene (TCB) as photosensitizer and Selectfluor as oxidant (Eq. 35).[225] In the proposed mechanism, the photoexcited TCB takes one electron from the cyclopropanol to generate a TCB radical anion and a cyclopropanol radical cation. Next, the cyclopropanol radical cation undergoes ring opening and abstracts one fluorine atom from Selectfluor. The Selectfluor-derived radical cation retrieves one electron from the TCB radical anion and closes the catalytic cycle. One drawback of this reaction is the irradiation with 300 nm wavelength, which could limit its substrate scope and require the use of quartz vials as reaction container.



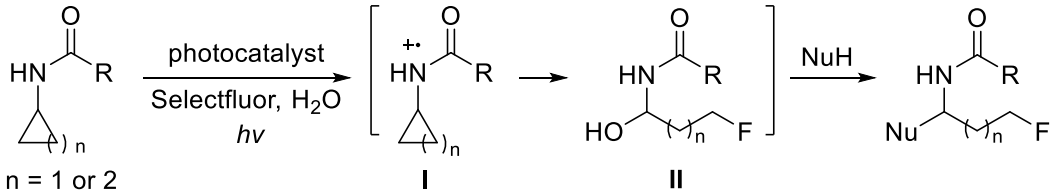
Equation 35. A photocatalyzed ring-opening fluorination of cyclopropanols.

In 2017, the Mohr group revisited the ring-opening fluorination of cyclopropanols and they employed a commercially available AgF_2 as both oxidant and fluorine atom source.[226] Also in 2017, the Kananovich group reported a copper-catalyzed ring-opening functionalization of cyclopropanols by using sulfinate salts as fluoroalkylating reagents.[227] Though no fluorination was demonstrated, several fluoroalkyl groups (e.g. CF_3, CF_2CH_3 and CH_2F) have been incorporated into the terminal position after ring opening.

While much success has been achieved in ring opening fluorination of arylcyclopropanes, cyclopropanols and cyclobutanols, their nitrogen-substituted counterparts were not studied yet, despite the importance of nitrogen-containing fluorinated drugs and agrochemicals. As mentioned in the section

[225] Bloom, S.; Bume, D. D.; Pitts, C. R.; Lectka, T. *Chem. Eur.J.* **2015**, *21*, 8060.
[226] Deng, Y.; Kauser, N. I.; Islam, S. M.; Mohr, J. T. *Eur. J. Org. Chem.* **2017**, *2017*, 5872.
[227] Konik, Y. A.; Kudrjashova, M.; Konrad, N.; Kaabel, S.; Järving, I.; Lopp, M.; Kananovich, D. G. *Org. Biomol. Chem.* **2017**, *15*, 4635.

3.1.1, the HLF reaction-inspired ring-opening halogenation of aminocyclopropanes failed in the case of fluorination no matter which electrophilic fluorinating reagent was employed (e.g. Selectfluor and NFSI). Therefore, we looked for other radical approaches for the activation of aminocyclopropanes. We envisioned that a highly oxidizing excited photocatalyst should be able to activate cyclopropylamides via single electron transfer (SET) oxidation to give amidium radical **I** (Scheme 73).[228] After ring-opening, the formed alkyl radical could be trapped by a fluorination reagent, and the imine stabilized as a hemiaminal **II**. We described here the successful implementation of this strategy, using either cheap benzophenone with black light (365 nm) or organic/inorganic dyes with blue LEDs and Selectfluor acting as both oxidant and fluorination reagent.



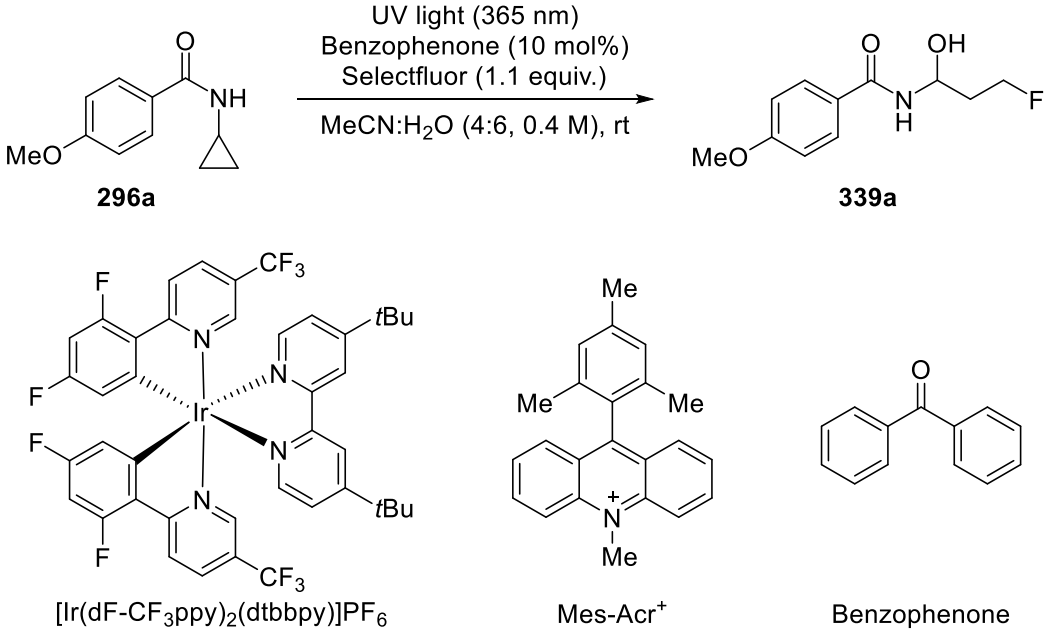
Scheme 73. Proposed ring-opening fluorination of cyclopropylamides and cyclobutylamides.

3.3.1 Discovery and optimization of the ring-opening fluorination reaction

With benzamide cyclopropane **296a** as substrate, the combination of benzophenone and Selectfluor under irradiation at 365 nm in MeCN/H_2O was optimal, yielding 3-fluorinated hemiaminal **339a** in 74% yield (Table 8, entry 1). It is interesting to note that standard borosilicate glass tubes can be used in this reaction, as less than 10% light is absorbed at 365 nm. Control experiments showed no conversion in the absence of benzophenone or irradiation (Table 8, entries 2 and 3). 9-Fluorenone, which is efficient for the ring-opening fluorination of arylcyclopropanes,[221] failed to catalyze this reaction (Table 8, entry 4). Other commonly-used photocatalysts such as [Ir(dF-CF_3ppy)$_2$(dtbbpy)]PF_6 and Mes-Acr^+ can also be utilized to achieve similar results under blue LED irradiation (Table 8, entries 5 and 6).

[228] McManus, J. B.; Onuska, N. P. R.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2018**, *140*, 9056.

Table 8. Optimization of the conditions for the oxidative fluorination of aminocyclopropane **296a**.

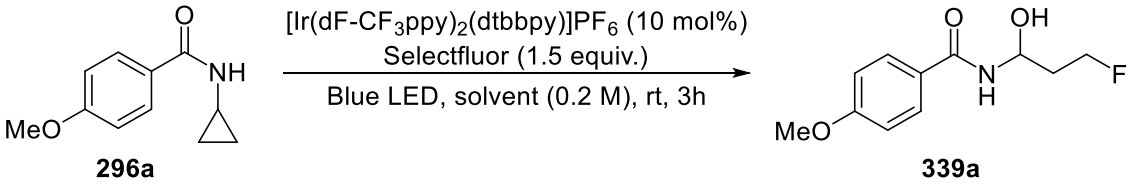


Entry[a]	Deviation from standard condition	^{1}H NMR Yield (%)
1	none	74 isolated
2	no benzophenone	0
3	no irradiation	0
4	9-fluorenone instead of benzophenone	6
5	$[Ir(dF\text{-}CF_3ppy)_2(dtbbpy)]PF_6$ with blue LED[b]	76
6	Mes-Acr$^+$ with blue LED[c]	75

(a) Reaction conditions: 0.30 mmol scale for 45 min. Yield was determined by ^{1}H NMR using CH_2Br_2 as internal standard. (b) With 1 mol% $[Ir(dF\text{-}CF_3ppy)_2(dtbbpy)]PF_6$ and 1.5 equiv. Selectfluor for 1 h. (c) With 2 mol% 9-mesityl-10-methylacridiniumperchlorate (Mes-Acr$^+$) and 1.5 equiv. Selectfluor for 3 h.

With $[Ir(dF\text{-}CF_3ppy)_2(dtbbpy)]PF_6$ system, we then screened the solvent effect for this oxidative ring-opening fluorination reaction. We used deuterated solvents in order to simplify the yield determination by directly submitting the crude reaction mixture to ^{1}H NMR analysis. In CD_2Cl_2, DMSO-d_6 or methanol-d_4, no conversion was observed and **296a** was fully recovered (Table 9, entries 1-3). In deuterated acetonitrile, trace amount of product **339a** was observed but no fluorinated imine was formed (Table 9, entry 4). In deuterated acetone, **339a** was formed in 10% yield (Table 9, entry 5). By comparing with the results using MeCN-H_2O mixture as solvent (shown in Table 8), we reasoned that water does not only act as a nucleophile to stabilize the fluorinated imine intermediate, but also facilitate the reaction probably by solubilizing Selectfluor. Therefore, we further tested a few combinations of organic solvent and water. In acetone-H_2O mixture, **339a** was formed in 53% yield (Table 9, entry 6). In CD_2Cl_2-H_2O or DMSO-H_2O mixture, however, the conversion was not improved compared with anhydrous conditions (Table 9, entries 7-8).

Table 9. Solvent screening for the oxidative fluorination of aminocyclopropane **296a**.

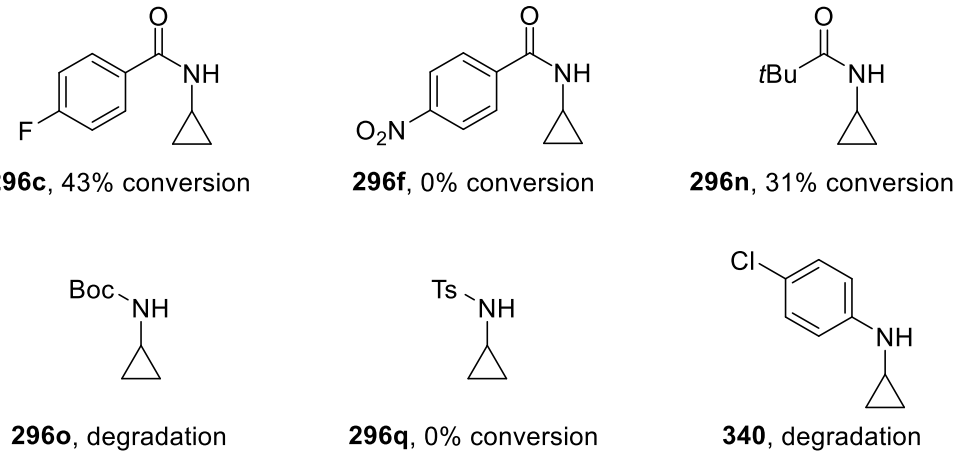


296a **339a**

Entry[a]	Solvent	^{1}H NMR Yield (%)
1	CD_2Cl_2	0
2	DMSO-d_6	0
3	Methanol-d_4	0
4	CD_3CN	<5
5	Acetone-d_6	10
6	Acetone-H_2O (4:6)	53
7	CD_2Cl_2-H_2O (4:6)	<5
8	DMSO-H_2O (4:6)	0

(a) Reaction conditions: 0.10 mmol scale for 3 h. Yield was determined by ^{1}H NMR using fluorobenzene as internal standard.

We then screened the protecting groups on the cyclopropylamine (Scheme 74). For aminocyclopropane **296c**, 43% of the substrate was converted into the corresponding product. No conversion was observed for substrates with a strong electron-withdrawing substituent such as a nitrobenzene (**296f**). With pivaloyl group protected substrate **296n**, the fluorinated hemiaminal was formed in 31% yield. With a Boc group as shown in **296o**, no product was isolated due to fast decomposition of the hemiaminal. With the tosyl protected aminocyclopropane (**296q**), no conversion was observed probably because electron density on the nitrogen atom was too low. When mixing 4-chloro-N-cyclopropylaniline **340** with Selectfluor, fast degradation was observed even prior to UV irradiation.



296c, 43% conversion **296f**, 0% conversion **296n**, 31% conversion

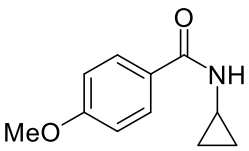
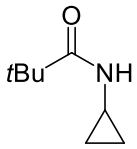
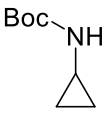
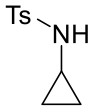
296o, degradation **296q**, 0% conversion **340**, degradation

Scheme 74. Screening protecting groups for the ring-opening fluorination of aminocyclopropanes.

In order to rationalize the reactivity difference of the substrates as shown in Scheme 69, we measured the redox potentials of some representative aminocyclopropanes by cyclic voltammetry experiments

(Table 10). Based on the experimental results, the redox potential value increases in the order **296a** < **296n** < **296o** < **296q**, which corresponds well to their reactivity in this oxidative fluorination reaction. For cyclopropyl anilines, their redox potentials are substantially lower than **296a**,[131] which may explain why **340** is not compatible with Selectfluor.

Table 10. Redox potentials of some representative aminocyclopropanes.

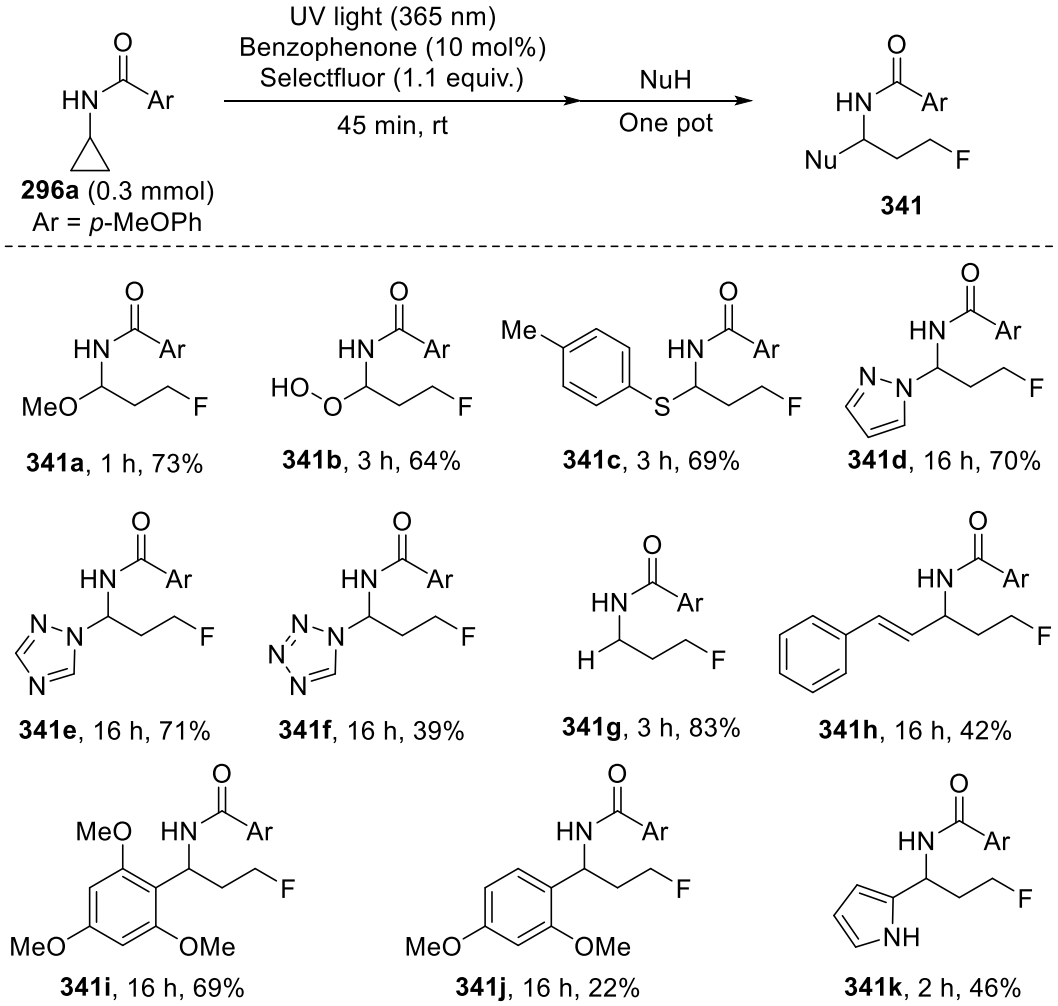
Substrate		$E_{1/2}^{red}$ (vs SCE in MeCN)
	**296a**	+1.67 V
	**296n**	+1.92 V
	**296o**	+2.0 V
	**296q**	+2.23 V

Conditions: voltammograms were performed with a scan rate of 50 mV/s, a concentration of electrolyte Bu_4NPF_6 = 0.1 M, and a concentration of **296** = 5 mM.

3.3.2 One-pot nucleophilic substitution following the ring-opening fluorination reaction

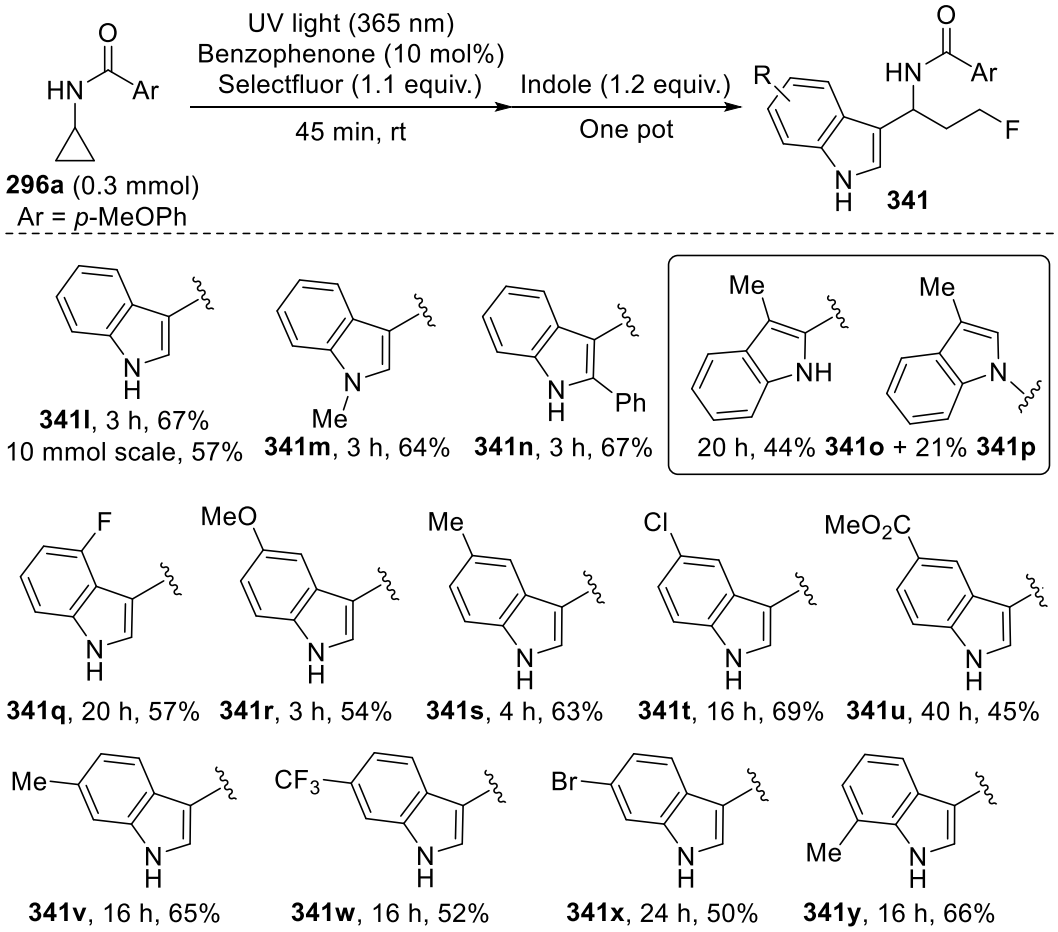
We then focused on using **296a** as model substrate in order to develop a one pot protocol for the hydroxy group substitution. Benzophenone was selected because of its broad availability and low price. By simply adding nucleophiles to the crude reaction mixture after the first step was done, we replaced the hydroxy group by many different nucleophiles (Scheme 75). *N*,*O*- or *N*,*S*- or *N*,*N*- acetals can be accessed in 39-73% yield (products **341a-f**). The hemiaminal can also be reduced by $NaBH_3CN$, affording **341g** in 83% yield. A Petasis reaction[229] gave allylic amine **341h** in 42% yield. 1,3,5-Trimethoxybenzene afforded **341i** in 69% yield while only 22% yield of **341j** was observed when using 1,3-dimethoxybenzene. With pyrrole, C2 addition product **341k** was isolated in 46% yield.

[229] Carrera, D. E. *Chem. Commun.* **2017**, *53*, 11185.



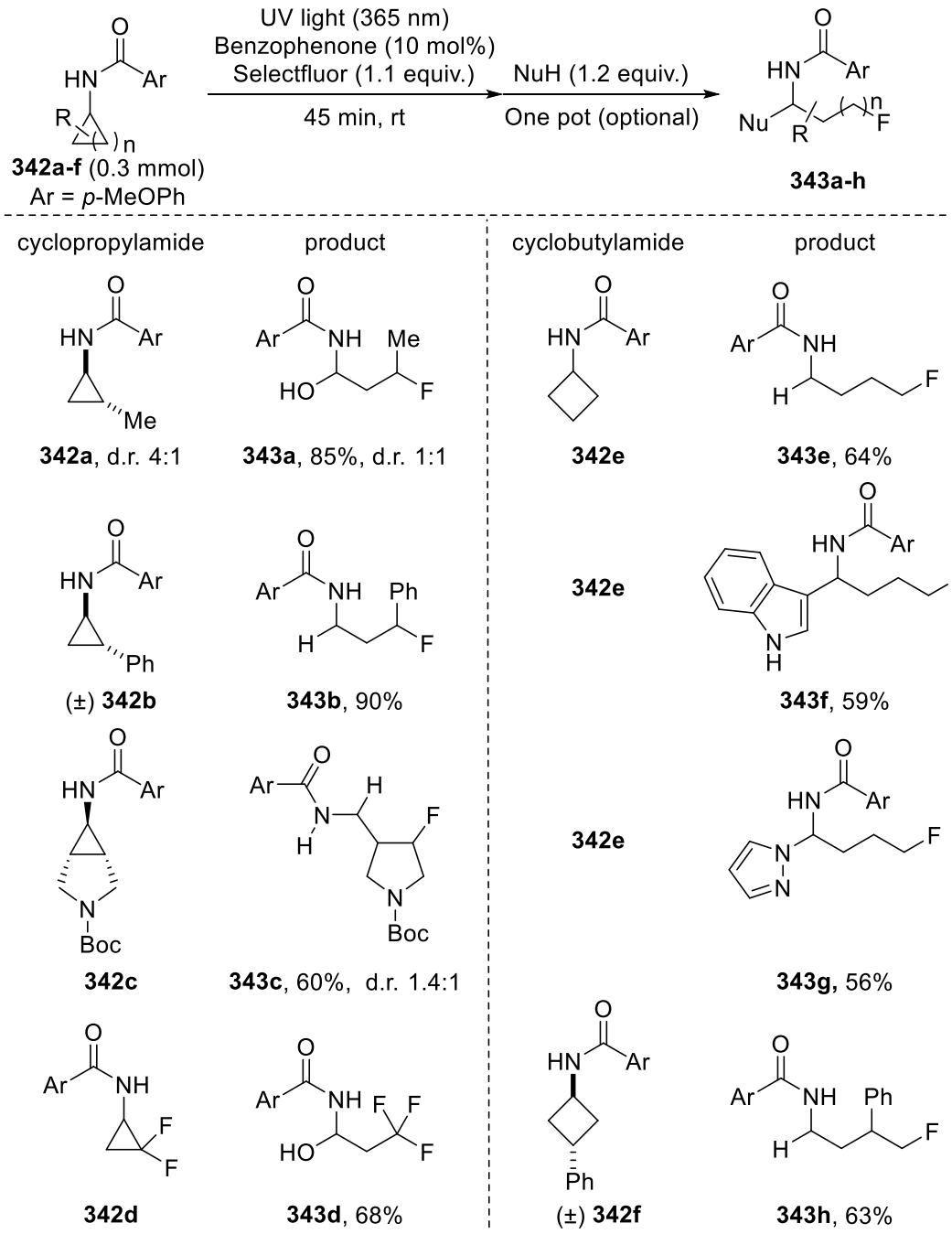
Scheme 75. Scope of nucleophiles in the one-pot ring-opening fluorination reaction.

The addition of indole provided an indole derivative **341l** in 67% yield (Scheme 76). Upon scaling up this reaction to 10 mmol, 1.86 grams (57% yield) of **341l** were obtained. Indoles bearing a *N*-methyl or a 2-phenyl group provided the corresponding products **341m** and **341n** in 64 and 67% yield. With 3-methyl indole, **341o** and **341p** resulting from *C* and *N* alkylation were isolated in 65% yield in 2:1 ratio. 4-Fluoro indole was well tolerated, giving **341q** in 57% yield. Indoles bearing electron-donating substituents like methoxy (**341r**) and methyl (**341s**), as well as electron-withdrawing substituents like a chloro (**341t**) and an ester groups (**341u**) at the C5 position gave yields ranging from 45% to 69%. A methyl (**341v**), a CF_3 (**341w**) and a bromo (**341x**) group at C6 or a methyl at C7 position (**341y**) led to product formation in 50-66% yield.



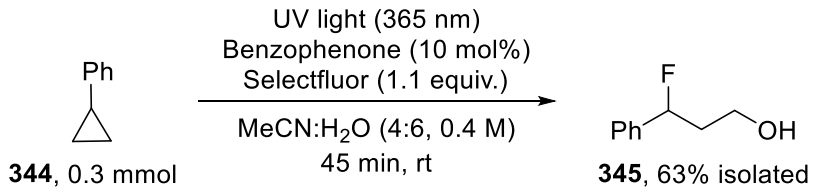
Scheme 76. Scope of indoles in the one-pot ring-opening fluorination reaction.

We then examined the scope of aminocyclopropanes and aminocyclobutanes (Scheme 77). When using 2-methyl substituted aminocyclopropane **342a** (d.r. = 4:1), product **343a** was isolated as a mixture of two diastereoisomers in a 1:1 ratio. With 2-phenyl substituted aminocyclopropane **342b**, **343b** was obtained in 90% yield after reduction by $NaBH_3CN$. When using bicyclic compound **342c**, a mixture of two diastereoisomers in a ratio of 1.4:1 was isolated in 60% yield. 2,2-Difluoro aminocyclopropane **342d** afforded trifluoromethyl hemiaminal **343d** in 68% yield. With aminocyclobutane **342e**, a series of products **343e-g** was obtained in 56-64% yield, by simply adding different nucleophiles (hydride, indole or pyrazole) for the second step. When using 3-phenyl aminocyclobutane **342f**, product **343h** resulting from selective C1-C2 bond cleavage next to nitrogen was obtained in 63% yield, while the byproduct arising from C3-C4 bond cleavage, if formed, was only in trace amount as analyzed by ^{19}F NMR of the reaction mixture.



Scheme 77. Scope of substituted cycloalkylamines in the ring-opening fluorination reaction.

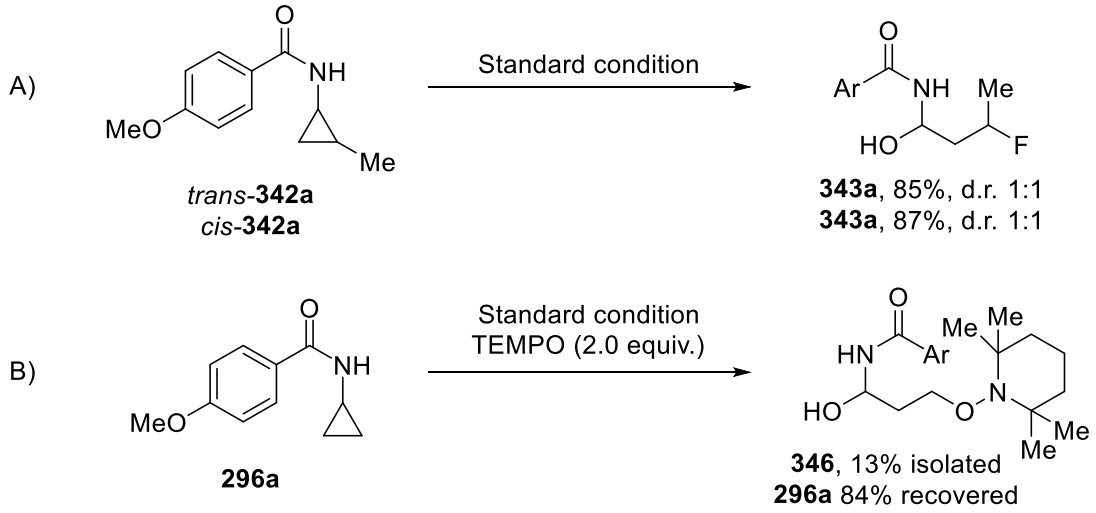
With cyclopropylbenzene (**344**) as substrate, the oxyfluorination product **345** was isolated in 63% yield with completely opposite regioselectivity when compared to **339a** (Eq. 36). However, the regioselectivity was in line with the aminofluorination of arylcyclopropanes shown in Scheme 69 as in both cases the fluorine atom was installed in the benzylic position. This shows that the regioselectivity for this ring-opening fluorination is substrate controlled and not originating from our different reaction conditions.



Equation 36. Oxy-fluorination of cyclopropylbenzene (**344**).

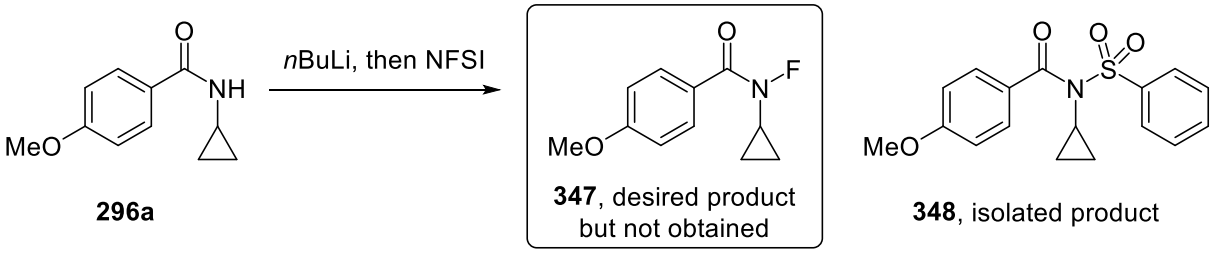
3.3.3 Mechanistic studies of the ring-opening fluorination reaction

In order to better understand the mechanism, we performed several control experiments. When the *trans* and the *cis* isomers of **342a** were submitted separately to the reaction conditions, the same diastereomeric ratio was observed for product **343a**, supporting the formation of a ring-opened intermediate (Scheme 78A). When adding TEMPO as the radical trapping reagent, we obtained the product **346** in 13% yield and recovered 84% **296a**, suggesting that a primary alkyl radical was formed (Scheme 78B).



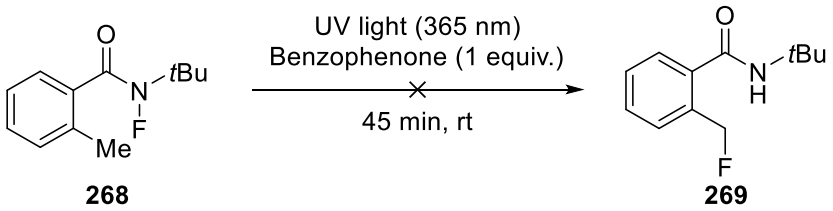
Scheme 78. Mechanistic investigations to support a radical pathway for the ring-opening fluorination.

Although we did not observe any *N*-fluorination when mixing **296a** with Selectfluor, we still tried to synthesis *N*-cyclopropyl-*N*-fluoro-4-methoxybenzamide **347** in order to exclude the possibility of its involvement as an intermediate. However, this goal was not achieved when we followed a reported protocol from the Cook group and **348** was isolated as a major product (Eq. 37). It is also indicated in their paper that their protocol for *N*-fluorination is limited to *N-tert* butyl amides since less-hindered amides undergo *N*-sulfonation when treated with NFSI.[173]



Equation 37. Attempts for synthesizing N-fluorinated amide **347**.

Nevertheless, we were still curious about the stability of *N*-fluoroamides under our reaction conditions. Therefore, we synthesized **268** by following the reported protocol from the Cook group and then tested its stability under UV light irradiation with stoichiometric amount of benzophenone. However, no conversion of **268** was observed based on the $^{1}H/^{19}F$ NMR (Eq. 38). As a result, this indicates that N-H fluorination as a first step is highly improbable.



268 **269**

Equation 38. Photostability of N-fluorinated amide **268**.

Light–dark interval experiments were performed in order to see whether there is an efficient chain process or not. We can see the light is essential to the consumption of the starting material **296a** (Figure 11). Although these results cannot exclude the chain process totally, its contribution to the conversion should be small even if there is some chain propagation after stopping of irradiation.

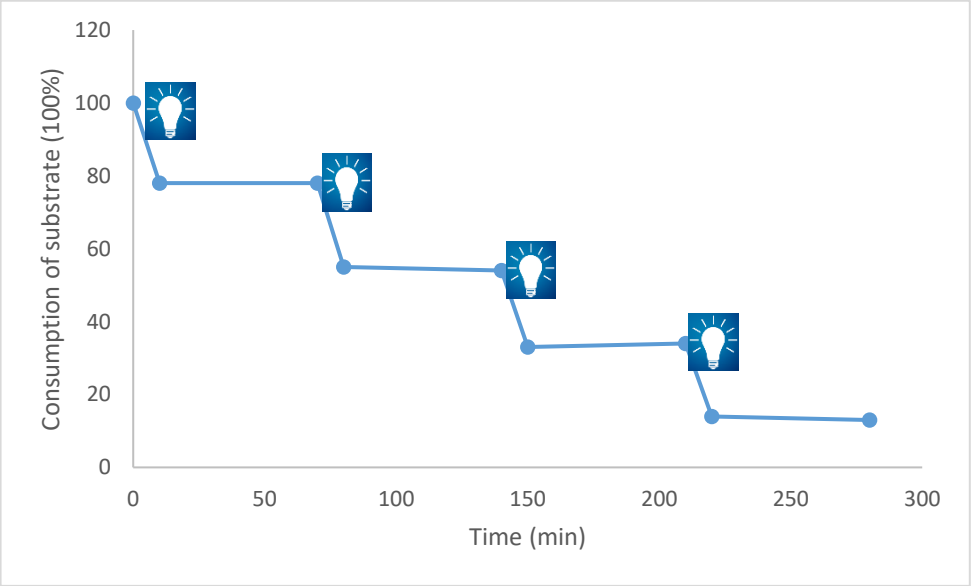


Figure 11. Light–dark interval experiments on **296a**.

To determine the quenching step unambiguously, Stern-Volmer fluorescence quenching experiments were conducted. In the case of $[Ir(dF\text{-}CF_3ppy)_2(dtbbpy)]PF_6$ as photocatalyst, the quenching of fluorescence emitted by its excited state was observed with Selectfluor while **296a** can barely quench the fluorescence signal (Figure 12).

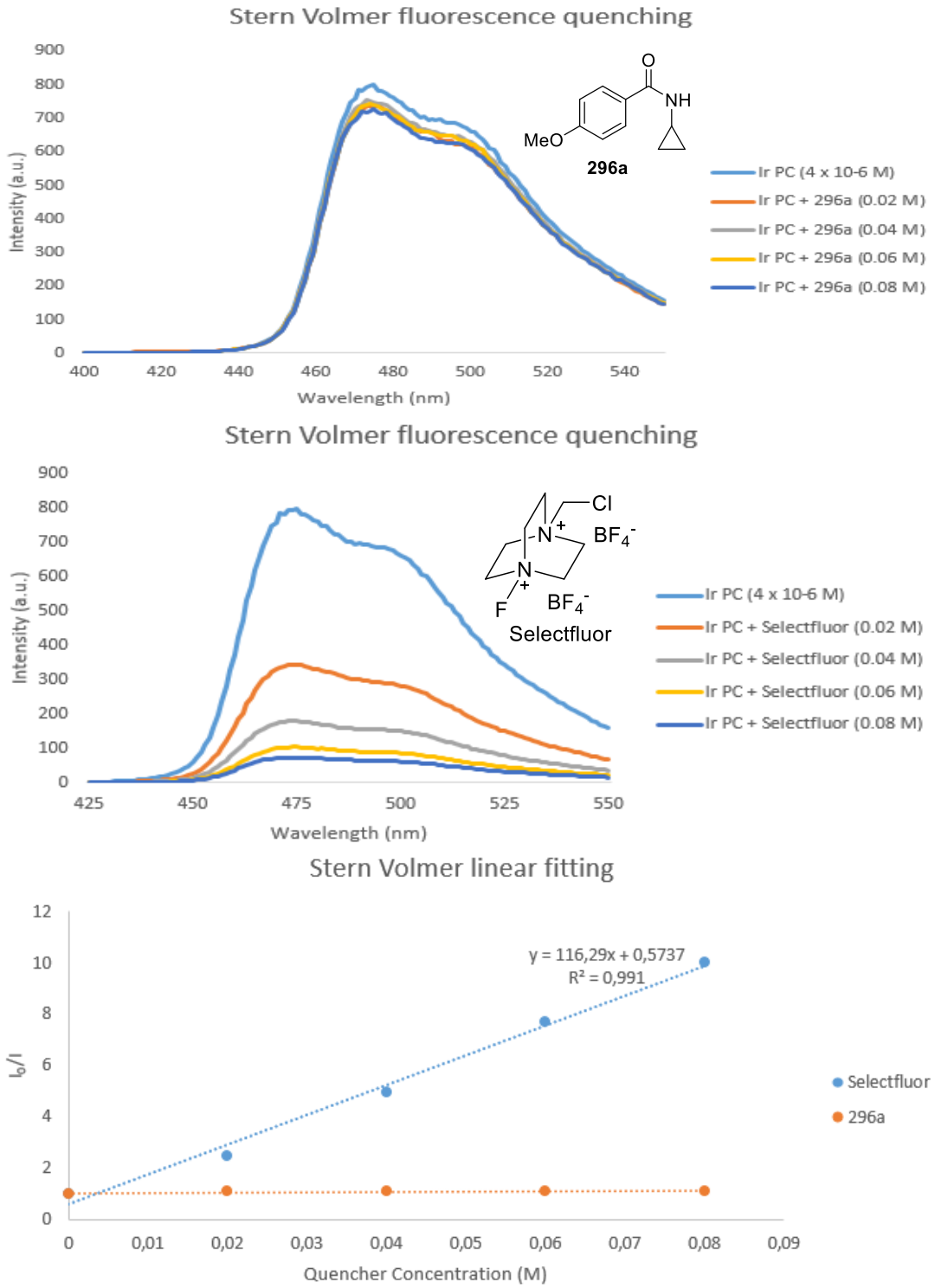


Figure 12. Stern-Volmer fluorescence quenching experiments with $[Ir(dF\text{-}CF_3ppy)_2(dtbbpy)]PF_6$.

In the case of benzophenone as photocatalyst, it is more complicated since it is well known that fluorescence of excited state benzophenone can be quenched by multifunctional aromatics due to the formation of exciplexes.[230] Therefore, we performed the Stern-Volmer quenching experiments of

[230] Yamada, T. K. (1989) Photochemistry of aromatic ketones. I. Quenching of the benzophenone triplet state by multifunctional aromatics. II. Sensitized fluorescence of 9,10-dibromoanthracene and 1,3-dibromo-9,10-bis(phenylethynyl) anthracene by energy transfer from the triplet state of benzophenone and acetophenone. Doctoral dissertation. University of Southern California.

benzophenone with substrate **296n**, and the results showed no obvious quenching of fluorescence of the excited state benzophenone by **296n**. Selectfluor can efficiently quench the fluorescence of the excited benzophenone photocatalyst (Figure 13).

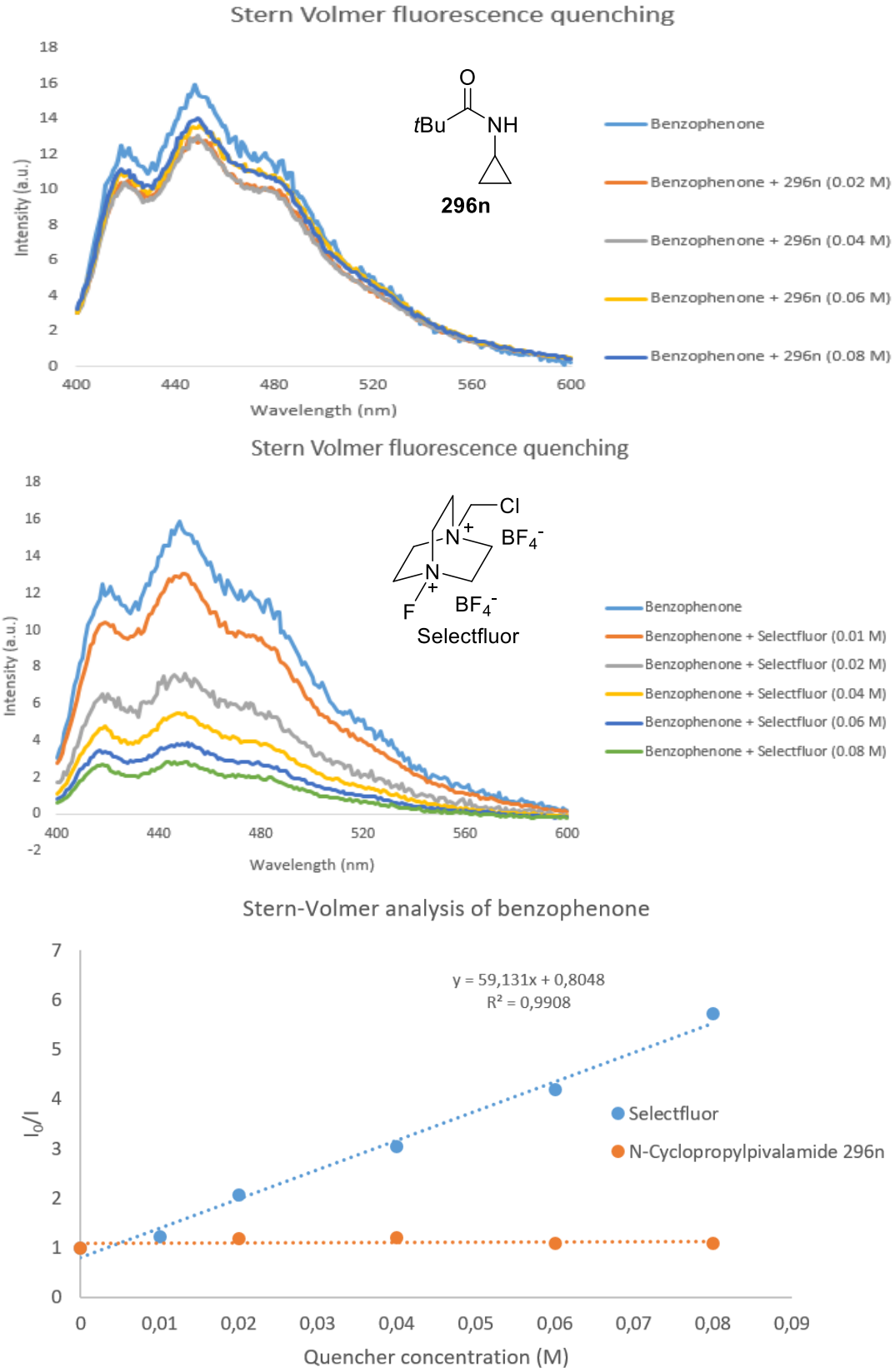
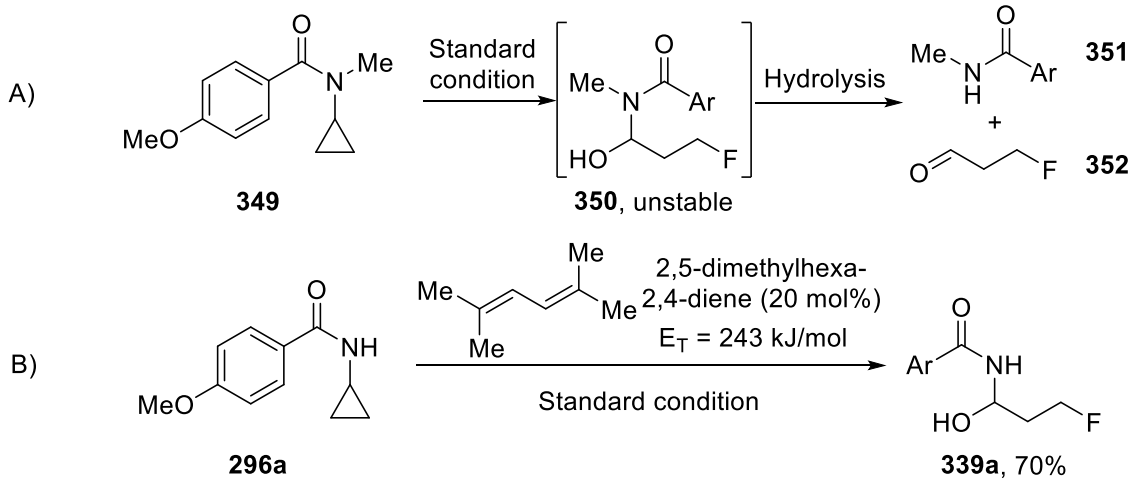


Figure 13. Stern-Volmer fluorescence quenching experiments with benzophenone.

The photochemical properties of diaryl ketones have played a vital role for the foundation of modern molecular photochemistry.[231] Diaryl ketones such as benzophenone (**BP**) are known to have a long-lived triplet state (τ_{BP} = 6.5 μs) generated by the excitation of an electron from a nonbonding orbital at the C=O bond to a corresponding π* orbital (n, π*) followed by the intersystem crossing.[232] Photo-excited diaryl ketones in their triplet state can initiate processes such as hydrogen atom transfer (HAT),[233] triplet energy transfer (EnT)[234] and single electron transfer (SET).[235] In order to exclude initiation by hydrogen atom transfer (HAT) to form a neutral amidyl radical, we tested the reaction of N-cyclopropyl-4-methoxy-N-methylbenzamide (**349**). Products **351** and **352** were obtained, resulting probably from the hydrolysis of unstable hemiaminal intermediate **350** (Scheme 79A). Therefore, HAT process could be ruled out based on the positive results with the substrate **349**. In order to distinguish the SET process from the EnT process, we added 2,5-dimethylhexa-2,4-diene (E_T = 243 kJ/mol) which is known to be able to quench triplet state benzophenone (E_T = 287 kJ/mol) by energy transfer.[234a] The formation of product **339a** was still observed in 70% yield, which suggests that EnT is less probable in this case (Scheme 79B).

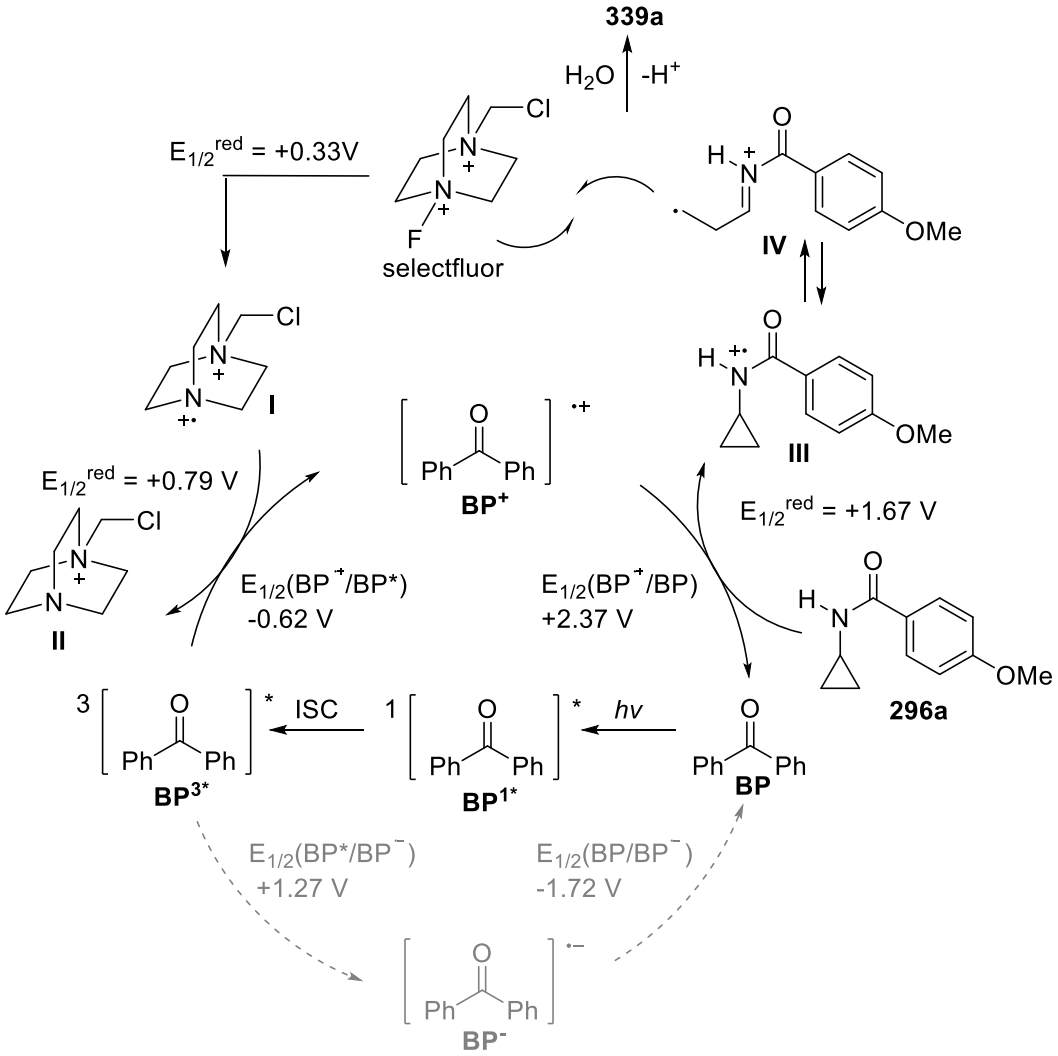


Scheme 79. Reaction on N-methyl cyclopropylamide **349** and quenching experiment of **296a** with a triplet quencher.

Based on these results and literature precedence, we proposed a first speculative reaction mechanism (Scheme 80). By comparing the reduction potentials of cyclopropylamide **296a**, Selectfluor and triplet state benzophenone (**BP**^{3*}), neither Selectfluor ($E_{1/2}^{red}$ = +0.33 V vs SCE in MeCN)[236] nor triplet state

[231] Turro, N. J.; Ramamurthy, V.; Scaiano, J. C. Modern Molecular Photochemistry of Organic Molecules; University Science Books: Sausalito, CA, **2010**.
[232] Clark, W. D. K.; Litt, A. D.; Steel, C. *J. Am. Chem. Soc*. **1969**, *91*, 5413.
[233] a) Kamijo, S.; Hoshikawa, T.; Inoue, M. *Org. Lett.* **2011**, *13*, 5928. b) Hoshikawa, T.; Kamijo, S.; Inoue, M. *Org. Biomol. Chem.* **2013**, *11*, 164. c) Masuda, Y.; Ishida, N.; Murakami, M. *J. Am. Chem. Soc.* **2015**, *137*, 14063. d) Ishida, N.; Masuda, Y.; Uemoto, S.; Murakami, M. *Chem. Eur. J.* **2016**, *22*, 6524. e) Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200. f) Ishida, N.; Masuda, Y.; Imamura, Y.; Yamazaki, K.; Murakami, M. *J. Am. Chem. Soc.* **2019**, *141*, 19611.
[234] a) Arceo, E.; Montroni, E.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2014**, *53*, 12064; b) Tröster, A.; Alonso, R.; Bauer, A.; Bach, T. *J. Am. Chem. Soc.* **2016**, *138*, 7808.
[235] a) Schaefer, C. G.; Peters, K. S. *J. Am. Chem. Soc.* **1980**, *102*, 7566. b) Li, L.; Mu, X.; Liu, W.; Wang, Y.; Mi, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2016**, *138*, 5809. c) Tripathi, C. B.; Ohtani, T.; Corbett, M. T.; Ooi, T. *Chem. Sci.* **2017**, *8*, 5622. d) Cai, X.; Han, Z.; Yao, S.; Lin, N. *Sci. China, Ser. B* **2001**, *44*, 582; e) Ohkubo, K.; Nanjo, T.; Fukuzumi, S. *Org. Lett.* **2005**, *7*, 4265.
[236] Ventre, S.; Petronijevic, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 5654.

benzophenone ($E_{1/2}^{BP*/BP-}$ = +1.27 V vs SCE in MeCN)[237] are able to oxidize cyclopropylamide **296a** (measured $E_{1/2}^{red}$ = +1.67 V vs SCE in MeCN). However, Selectfluor or the Selectfluor-derived radical cation (**I**, $E_{1/2}^{red}$ = +0.79 V vs SCE in MeCN)[238] could oxidize triplet state benzophenone (**BP**^{3*}, $E_{1/2}^{BP+/BP*}$ = -0.62 V vs SCE in MeCN) to the benzophenone radical cation **BP**$^{+}$, which is oxidizing enough to convert **296a** to radical cation intermediate **III** ($E_{1/2}^{BP+/BP}$ = +2.37 V vs SCE in MeCN). In the case of [Ir(dF-CF_3ppy)$_2$(dtbbpy)]PF_6, it can be oxidized in its excitation state by Selectfluor or Selectfluor-derived radical cation to an Ir(IV) species, which is then oxidative enough to take one electron form **296a** ($E_{1/2}^{Ir(III)*/Ir(II)}$ = +1.21 V, $E_{1/2}^{Ir(III)*/Ir(IV)}$ = -0.89 V and $E_{1/2}^{Ir(IV)/Ir(III)}$ = +1.69 V vs SCE in MeCN).[236] For the stronger oxidizing Mes-Acr^{+} dye ($E_{1/2}^{red}$ = +2.06 V vs SCE in MeCN),[239] its excitation state can readily oxidize **296a**. After SET oxidation, **III** would undergo ring opening to form **IV**, followed by radical fluorination with Selectfluor[219c] and nucleophilic addition of water to the iminium to yield **339a**. The reversal of regiochemistry observed compared to the work of Lectka can be tentatively attributed to the low stability of **III** leading to ring-opening, whereas the radical cation obtained from arylcyclopropanes is more stable and undergoes first nucleophilic addition.



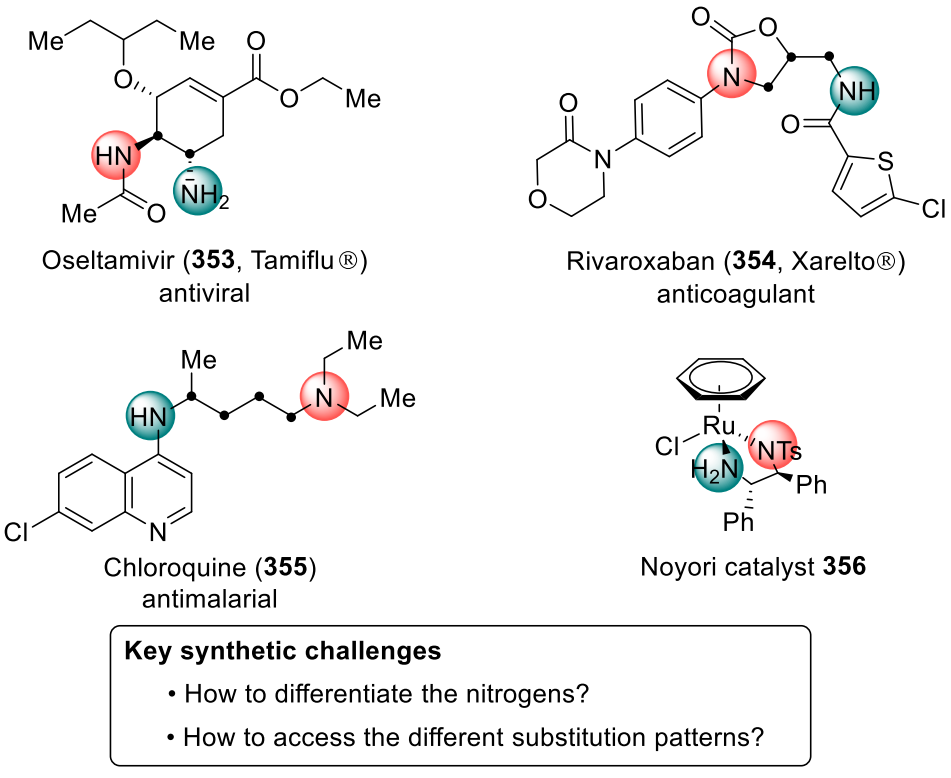
Scheme 80. Speculative reaction mechanism of the benzophenone-catalyzed ring-opening fluorination reaction.

[237] Wallace, W. L.; Van Duyne, R. P.; Lewis, F. D. *J. Am. Chem. Soc.* **1976**, *98*, 5319.
[238] Yan, D.-M.; Zhao, Q.-Q.; Rao, L.; Chen, J.-R.; Xiao, W.-J. *Chem. Eur. J.* **2018**, *24*, 16895.
[239] Margrey, K. A.; Nicewicz, D. A. *Acc. Chem. Res.* **2016**, *49*, 1997.

In summary, we have developed an oxidative strategy for the ring-opening fluorination of cyclopropylamides and cyclobutylamides by using cheap benzophenone as organophotoredox catalyst. The reaction is complementary to the method of Lectka for the synthesis of fluorinated amines (Scheme 69) as a reversed regioselectivity is observed for fluorination compared with arylcyclopropanes. The hemiaminal products can be converted to other building blocks by substituting the hydroxy group with diverse nucleophiles. Based on the simple reaction procedure and the structural diversity of nitrogen- and fluorine-containing building blocks obtained, we believe that this methodology will be useful in synthetic and medicinal chemistry.

3.4 Diamine synthesis via the nitrogen-directed azidation of σ- and π- C-C bonds[240]

Diamines are an important class of compounds found in pharmaceuticals such as Oseltamivir (**353**), Rivaroxaban (**354**) or Chloroquine (**355**), organocatalysts, chiral ligands, as in Noyori catalyst **356**, and materials (Scheme 81).[241] Two key challenges currently hamper access towards these building blocks: 1) A way to differentiate the two nitrogen functionalities and 2) A general access towards the different substitution patterns (1,2, 1,3 or 1,4), which are currently synthesized using fundamentally different disconnections.

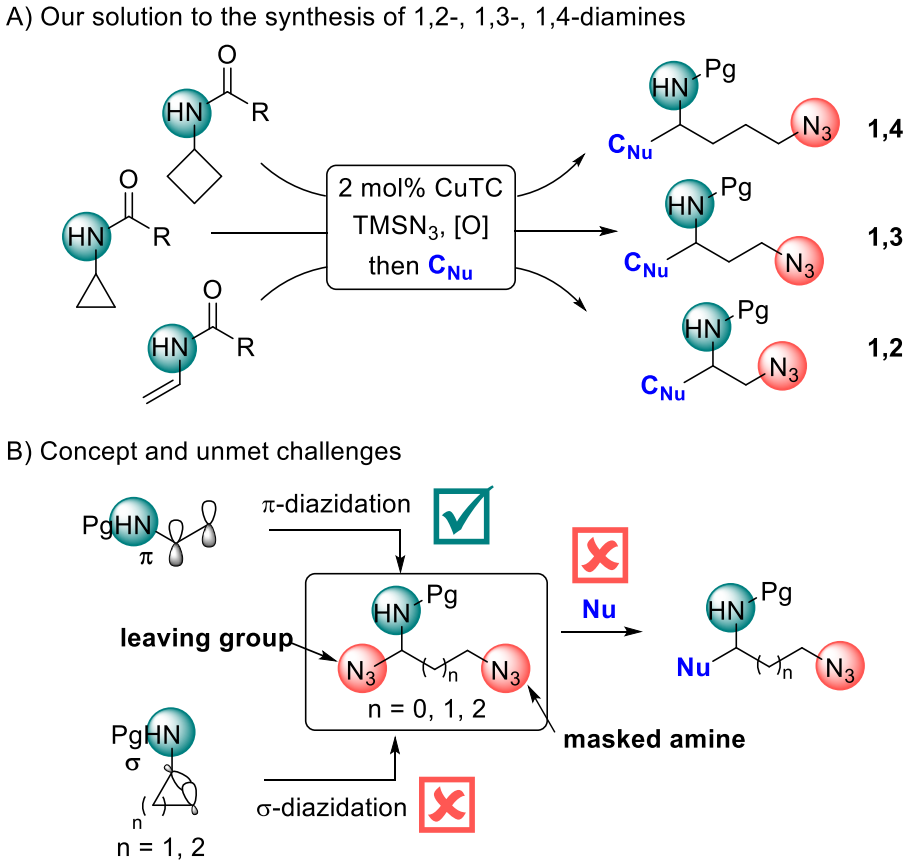


Scheme 81. Diamines: essential building blocks, but a synthetic challenge.

To answer these challenges, we considered a unified approach based on the azidation-nucleophilic substitution of nitrogen-substituted alkenes and strained rings (Scheme 82A). The amine in the starting material would play a key role in this strategy: First, it will act as an activating group to promote the diazidation of an adjacent π or σ C-C bond. Second, it will accelerate the dissociation of the azide at the

[240] Wang, M.-M.; Nguyen, T. V. T.; Waser, J. *J. Am. Chem. Soc.* **2021**, *143*, 11969.
[241] a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580. b) Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140. c) Grygorenko, O. O.; Radchenko, D. S.; Volochnyuk, D. M.; Tolmachev, A. A.; Komarov, I. V. *Chem. Rev.* **2011**, *111*, 5506. d) Ji, X.; Huang, H. *Org. Biomol. Chem.* **2016**, *14*, 10557.

aminal position for the introduction of nucleophiles. Finally, it will remain in the product as an orthogonally protected amine, whereas the second nitrogen functionality would be in the form of an azide, one of the synthetically most useful functional groups (Scheme 82B).[242]

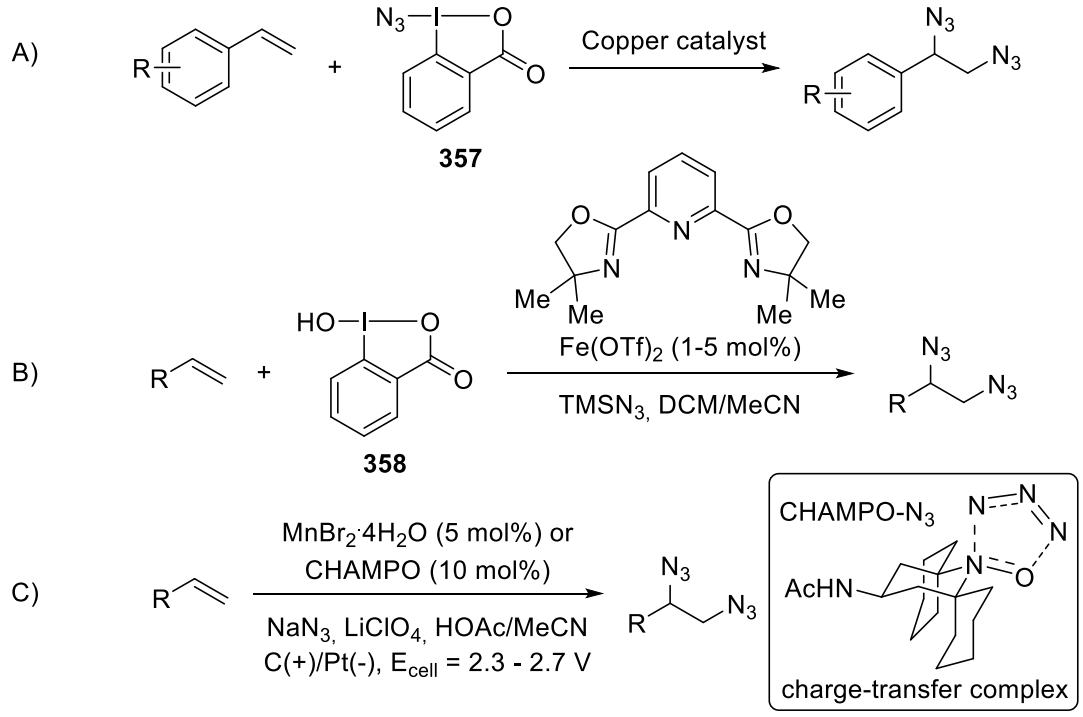


Scheme 82. A unified strategy for the synthesis of 1,2-, 1,3- and 1,4- diamines.

When considering precedence for our strategy, only the π-diazidation step has been realized so far.[243] In 2015, the Greaney group and the Loh group independently reported a copper-catalyzed diazidation of alkenes by using an azidoiodine(III) reagent **357** (Scheme 83A).[244] In 2017 the Bao group improved the copper-catalyzed diazidation by using tert-butyl peroxybenzoate (TBPB) as oxidant and $TMSN_3$ as azide source, which alleviated the necessity of synthesizing the azidoiodine(III) reagent.[245] In 2016 the Xu group reported an iron-catalyzed diazidation of unactivated alkenes by using a bench-stable benziodoxole **358** as oxidant and $TMSN_3$ as azide source (Scheme 83B).[246] This method tolerates a wide range of unfunctionalized or functionalized olefins and provides a convenient access to vicinal diamines after reduction. In 2018, the same group reported a modification of the iron-catalyzed diazidation method by switching to TBPB as oxidant and a bidentate pyridine-oxazoline as ligand.[247] In 2017, the Lin group disclosed a manganese-catalyzed electrochemical method for the diazidation of unactivated

[242] a) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188. b) Sivaguru, P.; Ning, Y.; Bi, X. *Chem. Rev.* **2021**, *121*, 4253.
[243] Schäfer, H. *Angew. Chem. Int. Ed.* **1970**, *9*, 158.
[244] a) Fumagalli, G.; Rabet, P. T. G.; Boyd, S.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2015**, *54*, 11481. b) Lu, M.-Z.; Wang, C.-Q.; Loh, T.-P. *Org. Lett.* **2015**, *17*, 6110.
[245] Zhou, H.; Jian, W.; Qian, B.; Ye, C.; Li, D.; Zhou, J.; Bao, H. *Org. Lett.* **2017**, *19*, 6120.
[246] Yuan, Y.-A.; Lu, D.-F.; Chen, Y.-R.; Xu, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 534.
[247] Shen, S.-J.; Zhu, C.-L.; Lu, D.-F.; Xu, H. *ACS Catal.* **2018**, *8*, 4473.

alkenes and they further reported in 2019 that an aminoxyl radical (CHAMPO) can replace the manganese salt as catalyst for this reaction by forming a charge transfer complex CHAMPO-N_3 (Scheme 83C).[248]

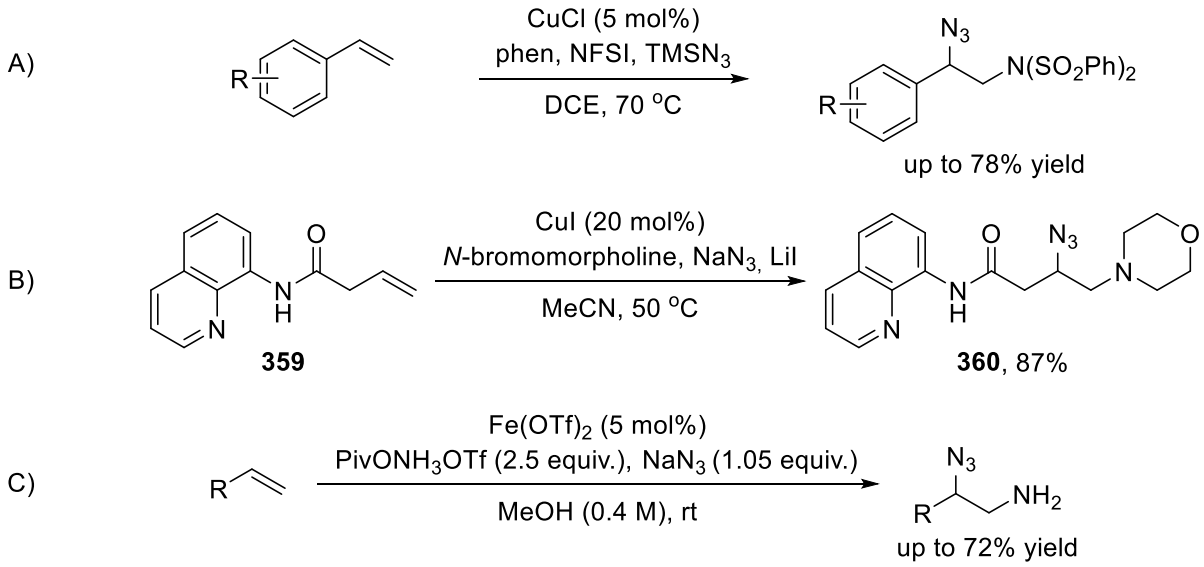


Scheme 83. Diazidation of alkenes by transition-metal catalysis.

Diazidation of alkenes is attractive because of a quick access to diamines after reduction, but selective reaction of one of the two azido groups is difficult.[249] Introducing simultaneously an azide and another nitrogen functionality on an alkene is promising, but has been realized only in a few reports. In 2014, the Studer group described a copper-catalyzed aminoazidation of styrenes by using NFSI as both oxidant and the aminating reagent (Scheme 84A).[250] As for the plausible mechanism, the oxidation of Cu(I) by NFSI is proposed to form a Cu(III) species or a copper-stabilized N-centered radical, which adds to the alkene to generate a benzylic radical along with a Cu(II) species. Two possible pathways were suggested to explain the formation of final aminoazidation product: 1) through radical rebound to form a Cu(III) species followed by ligand exchange and reductive elimination; 2) through oxidation to benzylic cation followed by nucleophilic attack of $TMSN_3$. In 2019 the Guan/Bi/Fu group developed a copper-catalyzed aminoazidation for unactivated alkenes with an 8-aminoquinoline directing group, such as **359** (Scheme 84B).[251] N-bromodialkylamines were used for generating an aminyl radical upon reaction with Cu(I)-substrate complex via single electron transfer. After migratory-insertion of the olefin into the aminyl radical-Cu(II) complex, a Cu(III) species is formed through radical rebound. Product **360** is formed eventually after ligand exchange and reductive elimination. This pathway is supported by mechanistic studies and theoretical calculations. In 2020, the Morandi group described a direct synthesis of

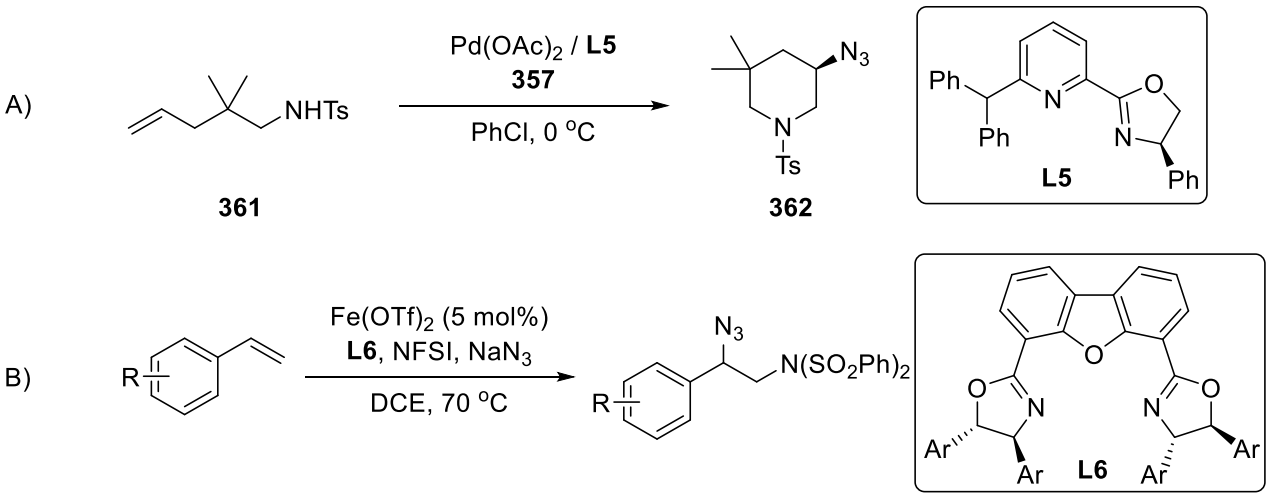
[248] a) Fu, N.; Sauer, G. S.; Saha, A.; Loo, A.; Lin, S. *Science* **2017**, *357*, 575. b) Siu, J. C.; Parry, J. B.; Lin, S. *J. Am. Chem. Soc.* **2019**, *141*, 2825.
[249] a) Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 10773. b) Udumula, V.; Nazari, S. H.; Burt, S. R.; Alfindee, M. N.; Michaelis, D. J. *ACS Catal.* **2016**, *6*, 4423.
[250] Zhang, B.; Studer, A. *Org. Lett.* **2014**, *16*, 1790.
[251] Li, Y.; Liang, Y.; Dong, J.; Deng, Y.; Zhao, C.; Su, Z.; Guan, W.; Bi, X.; Liu, Q.; Fu, J. *J. Am. Chem. Soc.* **2019**, *141*, 18475.

unprotected 2-azidoamines through an iron-catalyzed aminoazidation of alkenes (Scheme 84C).[252] With an easily-accessed O-pivaloyl hydroxylamine triflic acid as the aminating reagent,[253] a free amino group was transferred to the product.



Scheme 84. Copper- or iron-catalyzed aminoazidation of alkenes.

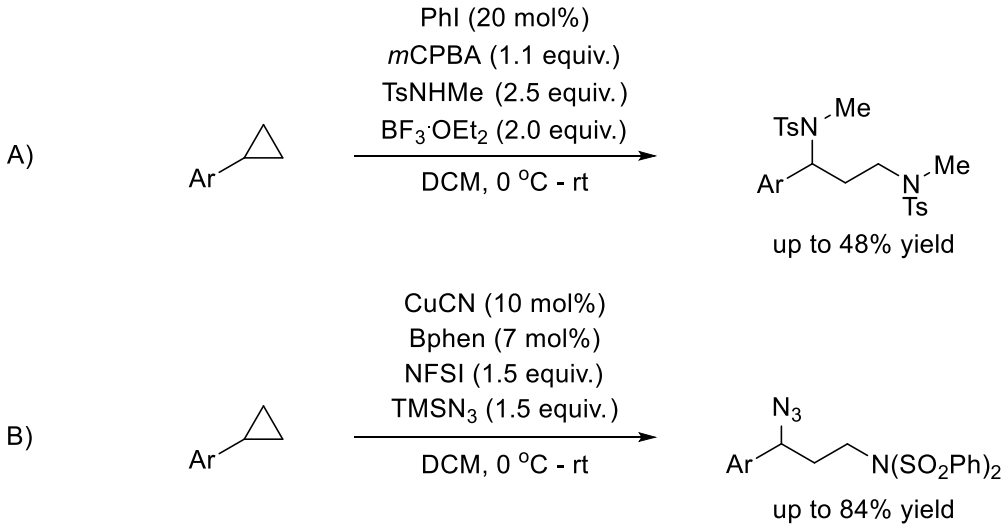
Enantioselective aminoazidation has also been reported recently by developing different catalytic systems. In 2020, the Liu group reported a palladium-catalyzed enantioselective azidation of alkenes with a pendant sulfonamide group (Scheme 85A).[254] The use of azidoiodine(III) reagent **357** as an electrophilic azidating reagent is crucial for the asymmetric azidation because the palladium catalyst is deactivated by azide anions. In 2021, the Bao group also developed an iron-catalyzed enantioselective aminoazidation or diazidation of styrenes, which was enabled by the use of a unique class of BOX ligand such as L6 (Scheme 85B).[255]



Scheme 85. Palladium- or iron-catalyzed enantioselective aminoazidation of alkenes.

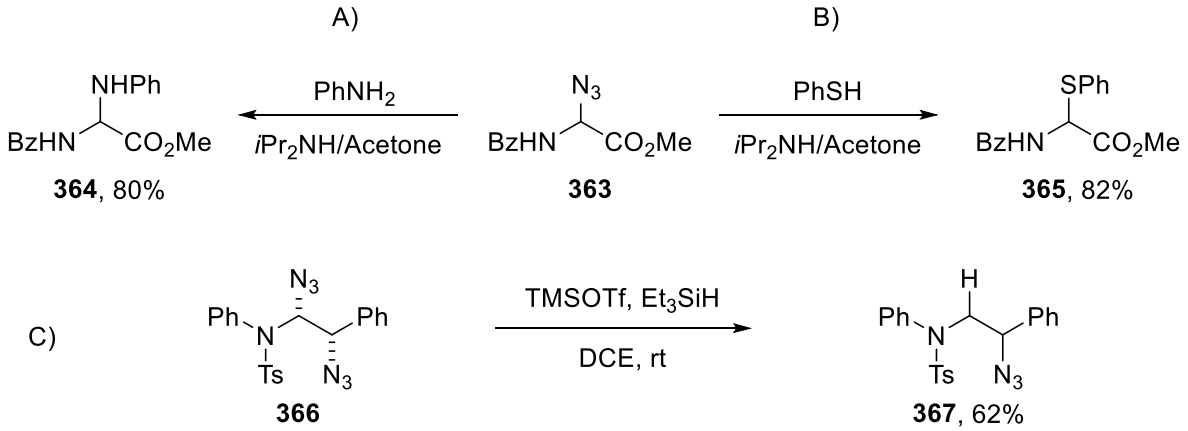
[252] Makai, S.; Falk, E.; Morandi, B. *J. Am. Chem. Soc.* **2020**, *142*, 21548.
[253] Makai, S.; Falk, E.; Morandi, B. *Org. Synth.* **2020**, *97*, 207.
[254] Li, X.; Qi, X.; Hou, C.; Chen, P.; Liu, G. *Angew. Chem. Int. Ed.* **2020**, *59*, 17239..
[255] Lv, D.; Sun, Q.; Zhou, H.; Ge, L.; Qu, Y.; Li, T.; Ma, X.; Li, Y.; Bao, H. *Angew. Chem. Int. Ed.* **2021**, *60*, 12455.

In contrast to the diazidation of π bonds, the envisaged σ bond diazidation of cyclopropanes or cylobutanes to give either 1,3- or 1,4-diazides was unprecedented. Only the diaminations of arylcyclopropanes to form 1,3-ditosylamides (Scheme 86A)[223] or 1,3-azidoimides (Scheme 86B)[256] have been reported. This may be due to the lower reactivity of cyclopropane/cyclobutane σ bonds compared to alkene π bonds.



Scheme 86. Synthesis of 1,3-diamines from arylcyclopropanes.

Among recent efforts in ring-opening reactions of aminocyclopropanes and aminocylobutanes, oxidative ring-opening approaches have been used by our group and others to access multi-functionalized building blocks (see section 1.3.3). For extending this strategy to the diazidation of aminocyclopropanes, two challenges needed to be considered: 1) the choice of a catalyst to promote both oxidative ring-opening and azide transfer; 2) the functionalization of α-azido amides by carbon nucleophiles, which was unprecedented. Indeed, only three examples have been reported by using amine (Scheme 87A),[257] thiophenol (Scheme 87B)[258] and silyl hydride (Scheme 87C)[259] as hetero nucleophiles, forming products **364**, **365** and **367** respectively.

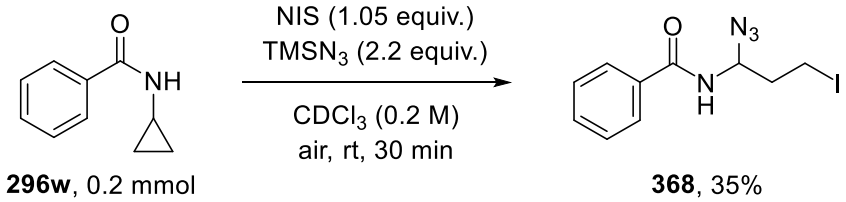


Scheme 87. Replacement of α-amino azide group by hetero nucleophiles.

[256] Wang, L.; Wang, X.; Zhang, G.; Yang, S.; Li, Y.; Zhang, Q. *Org. Chem. Front.* **2019**, *6*, 2934.
[257] Houssine, M. E.; Abdelrhani, E.; Anouar, A.; Abdelilah, E. H. *Molecules* **2010**, *15*, 9354.
[258] Mabrouk, E.; Elachqar, A.; Alami, A.; Hallaoui, A. E.; Hajji, S. E. *Orient. J. Chem.* **2010**, *26*, 1249.
[259] Nocquet-Thibault, S.; Rayar, A.; Retailleau, P.; Cariou, K.; Dodd, R. H. *Chem. Eur. J.* **2015**, *21*, 14205.

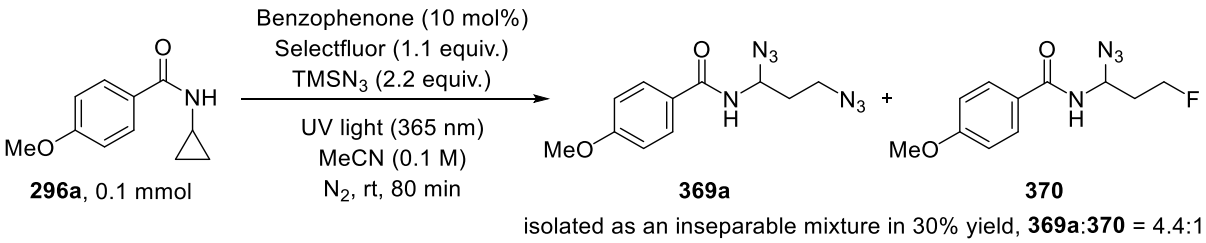
3.4.1 Discovery and optimization of the azidation reaction

Based on our previous work, aminocyclopropane **296w** was selected as the model substrate for the ring-opening azidation reaction with $TMSN_3$ as azide source. At first we tried to intercept the ring-opening iodination reaction as described in section 3.1, but α-azidation product **368** was isolated instead of the desired γ- azidation product (Eq. 39). Indeed, the desired terminal azidation product could theoretically be obtained in a following S_N2 step under basic conditions, but this would be less straightforward and less efficient.



Equation 39. Azidation attempts on cyclopropylamide **296w** via an intercepted HLF reaction.

We then tested photoredox conditions on substrate **296a** using benzophenone as catalyst and Selectfluor as oxidant, an inseparable mixture of diazidation product **369a** and fluorination byproduct **370** was obtained (Eq. 40). Unable to further improve the selectivity of azidation over fluorination, we turned our attention to transition-metal catalysis since some metal catalysts (e.g. copper, iron, manganese salts) are well known to be capable of delivering an azide group efficiently.[260]

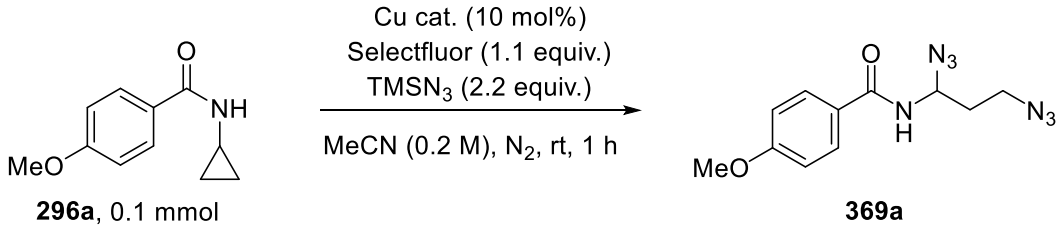


Equation 40. Azidation attempts on cyclopropylamide **296a** under photoredox conditions.

When copper catalysts were used, diazidation product **369a** was formed in medium to high yield and no fluorination byproduct **370** was observed from ^{19}F NMR in all these cases (Table 10). In the case of copper (II) triflate and copper acetate, product **369a** was formed in 74% yield (Table 10, entries 1 and 2). For copper (I) triflate benzene complex, the yield of **369a** dropped to 32% (Table 10, entry 3). Copper (II) acetate outcompeted other copper salts for the diazidation of **296a** and further reducing its loading to 2 mol% led to the formation of **369a** in 93% yield (Table 10, entries 4 and 5).

[260] Goswami, M.; de Bruin, B. *Eur. J. Org. Chem.* **2017**, *2017*, 1152.

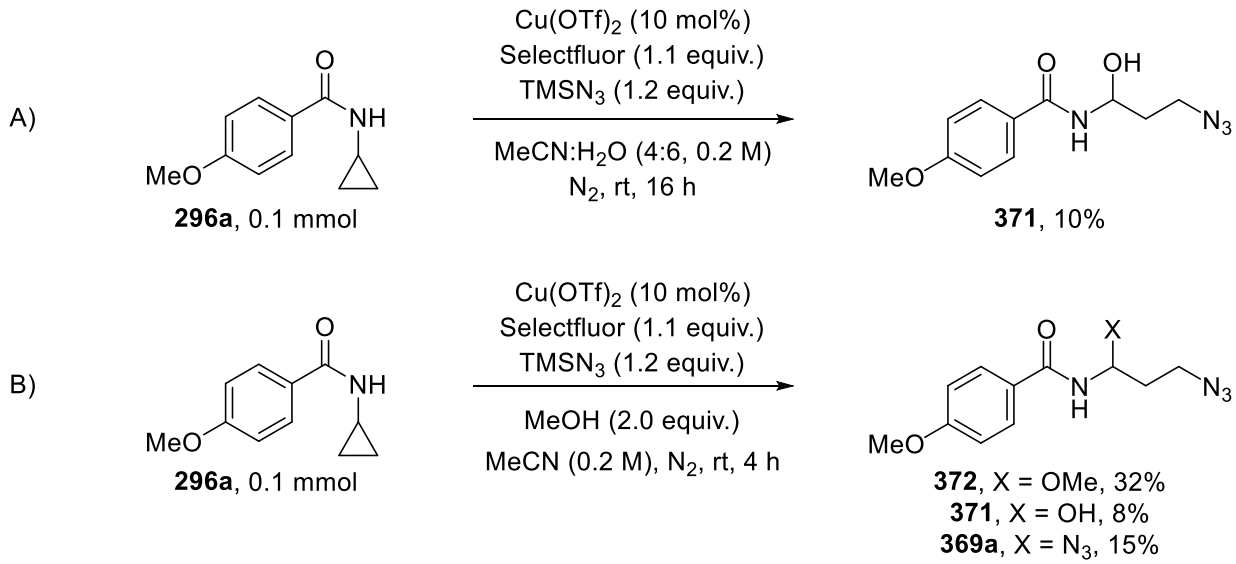
Table 10. Azidation attempts on cyclopropylamide **296a** with copper catalysts.



Entry[a]	Catalyst	^{1}H NMR Yield (%)
1	$Cu(OTf)_2$	74
2	CuOAc	74
3	$(CuOTf)_2$ Benzene complex (5 mol%)	32
4	$Cu(OAc)_2$	87
5	$Cu(OAc)_2$ (2 mol%)	93

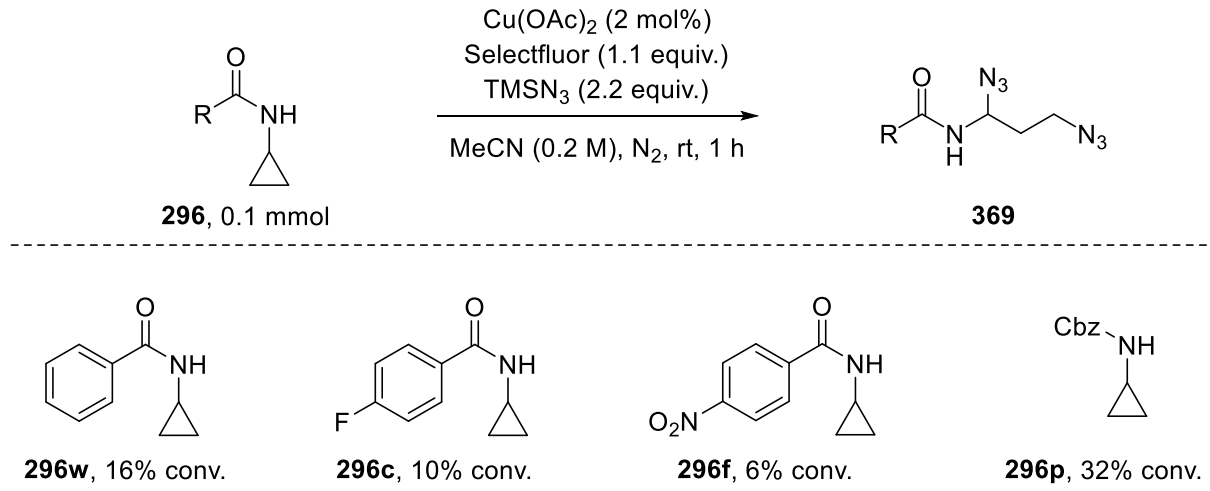
(a) Reaction conditions: 0.10 mmol scale for 1 h. Yield was determined by ^{1}H NMR using CH_2Br_2 as internal standard.

Two different O-nucleophiles were than tested in order to reduce the amount of $TMSN_3$ by forming N,O-acetals. In the case of water as nucleophile, low conversion of **296a** was observed even after prolonged reaction time (Scheme 77A). In the case of methanol, good conversion of **296a** was observed but three different products were isolated, showing the nucleophilicity of methanol is comparable to that of $TMSN_3$ in this case (Scheme 77B). Therefore, when compared to the two oxy-azidation reactions, the diazidation reaction was more promising in terms of conversion, selectivity and yield.



Scheme 88. Water or methanol as nucleophile for the ring-opening azidation of **296a**.

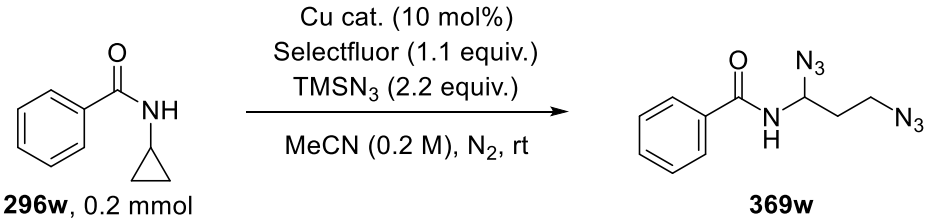
However, poor conversion was encountered for other substrates when using $Cu(OAc)_2$ as catalyst (Scheme 89). This indicated that the optimal conditions for **296a** were not general enough for all substrates. Therefore, a second round of optimization was conducted using **296w** as substrate.



Scheme 89. Substrate scope of aminocyclopropanes for the ring-opening diazidation when using $Cu(OAc)_2$ as catalyst.

The yield of **369w** varied between 16% and 32% when different copper(I) salts were employed as catalyst for the diazidation of **296w** (Table 11, entries 1-5). Among the several copper catalysts tested so far, CuTc exhibited a highest catalytic efficiency, giving the product **369w** in 48% yield (Table 11, entry 6). Reducing the catalyst loadings of CuTc to 2 mol% can further improve the yield of **369w** to 78% (Table 11, entries 7 and 8). This can be attributed to the inhibition of a competing side-reaction between Selectfluor and $TMSN_3$ catalyzed by CuTc. As evidenced by a control experiment in the absence of **296w**, this side-reaction was very fast, usually complete within minutes. Therefore, reducing catalyst loadings can avoid the non-productive consumption of Selectfluor and $TMSN_3$.

Table 11. Screening of catalysts for the ring-opening diazidation of cyclopropylamide **296w**.

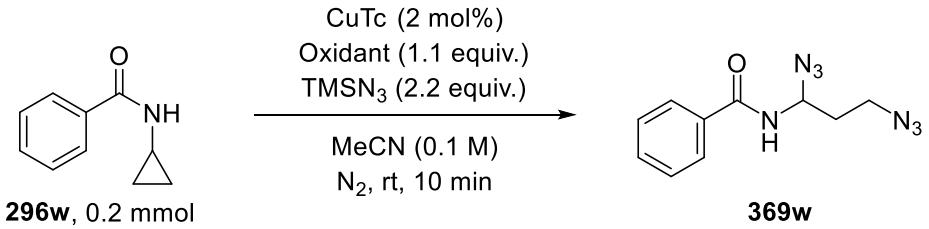


Entry[a]	Catalyst	^{1}H NMR Yield (%)
1	CuBr	26
2	CuCl	16
3	CuCN	20
4	$Cu(MeCN)_4BF_4$	24
5	$(CuOTf)_2$ Benzene complex	32
6	CuTc (20 mol%)	48
7	CuTc (5 mol%)	74
8	CuTc (2 mol%), MeCN (0.1 M)	78

(a) Reaction conditions: 0.20 mmol scale for 10 min. Yield was determined by ^{1}H NMR using CH_2Br_2 as internal standard.

Different oxidants were also screened for this ring-opening diazidation reaction (Table 12). The reaction also proceeded albeit with low conversion when NFSI was used instead of Selectfluor (Table 12, entry 2). Other oxidants including PIDA, NCS, *m*CPBA, $K_2S_2O_8$ and TBHP failed to afford **369w** (Table 12, entries 3-7). Interestingly, the use of a stoichiometric amount of CuF_2 as oxidant resulted in no conversion of **296w**, suggesting that Cu(II) may not be efficient enough to oxidize **296w**.

Table 12. Screening of oxidants for the ring-opening diazidation of cyclopropyl amide **296w**.



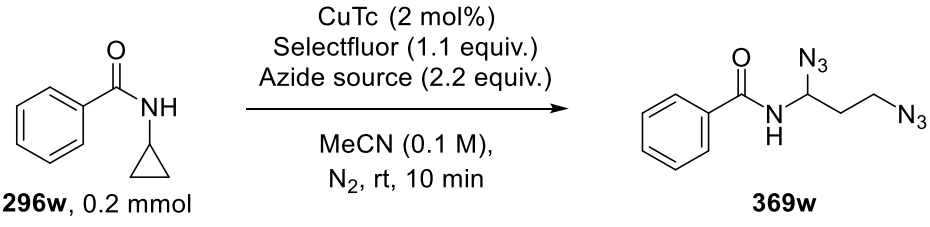
296w, 0.2 mmol — **369w**

Entry[a]	Oxidant	^{1}H NMR Yield (%)
1	Selectfluor	78
2	NFSI	13
3	PIDA	0
4	NCS	0
5	*m*CPBA	0
6	$K_2S_2O_8$	0
7	TBHP	0
8	CuF_2	0

(a) Reaction conditions: 0.20 mmol scale for 10 min. Yield was determined by ^{1}H NMR using CH_2Br_2 as internal standard.

Different azide sources were then screened for this ring-opening diazidation reaction (Table 13). In addition to $TMSN_3$, NaN_3 readily afforded **359w** in 18% yield without any optimization of the reaction conditions while tetrabutylammonium azide did not promote the reaction at all (Table 13, entries 2-3).

Table 13. Screening of azide sources for the ring-opening diazidation of cyclopropyl amide **296w**.



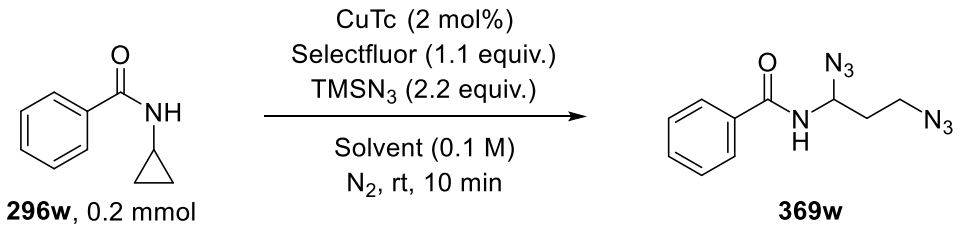
296w, 0.2 mmol — **369w**

Entry[a]	Azide source	^{1}H NMR Yield (%)
1	$TMSN_3$	78
2	NaN_3	18
3	Bu_4NN_3	0

(a) Reaction conditions: 0.20 mmol scale for 10 min. Yield was determined by ^{1}H NMR using CH_2Br_2 as internal standard.

Besides MeCN, we also tried the diazidation reaction in other solvents such as dichloromethane, acetone, nitromethane and DMF. However, no reaction took place in these solvents (Table 14, entries 2-5).

Table 14. Screening of solvents for the ring-opening diazidation of cyclopropyl amide **296w**.

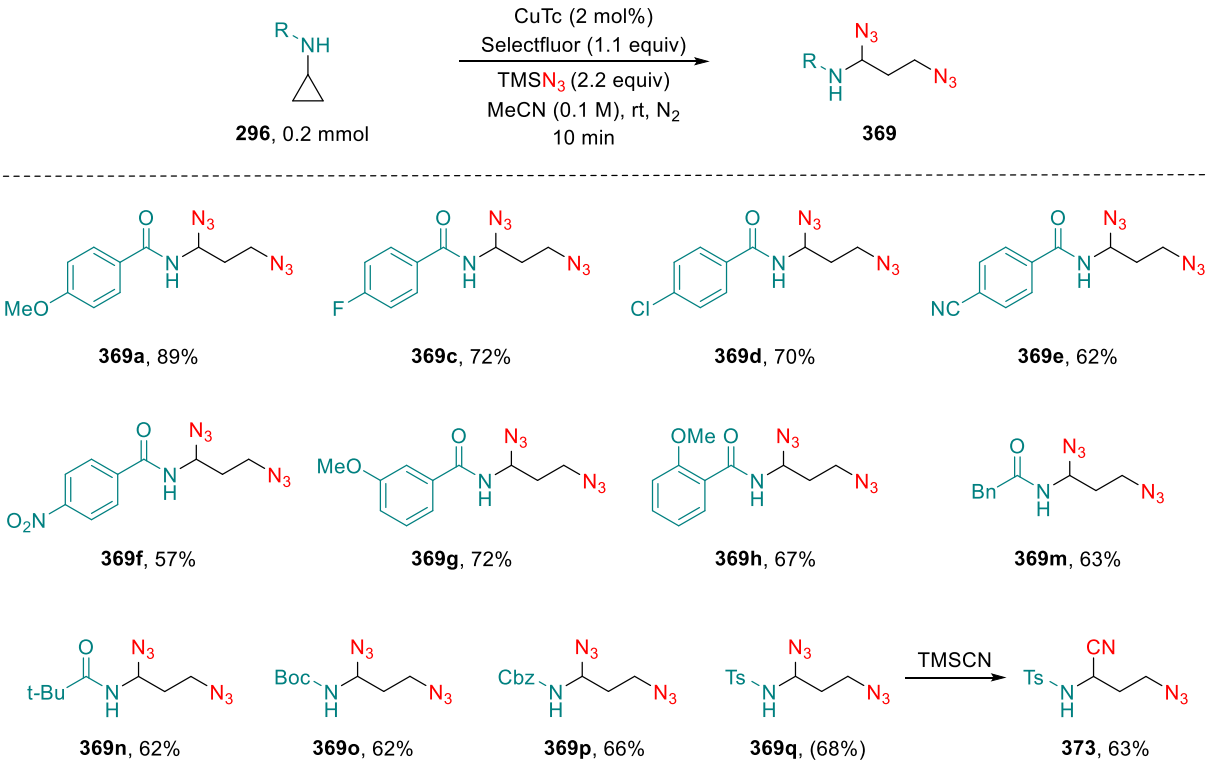


Entry	Solvent	^{1}H NMR Yield (%)
1	MeCN	78
2	DCM	0
3	Acetone	0
4	CH_3NO_2	0
5	DMF	0

(a) Reaction conditions: 0.20 mmol scale for 10 min. Yield was determined by ^{1}H NMR using CH_2Br_2 as internal standard.

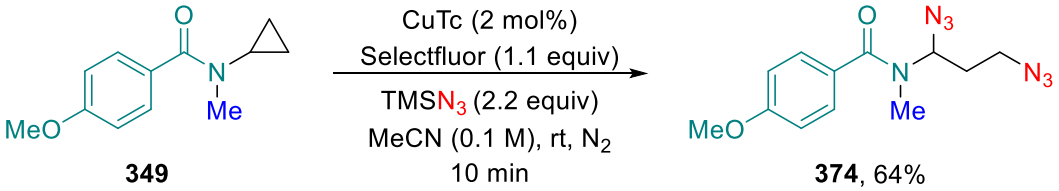
3.4.2 Substrate scope and further nucleophilic substitution of the azidation reaction

After the second round of screening, we then examined the scope of substituents on the nitrogen atom under the optimal conditions with CuTc as catalyst (Scheme 90). The substrate **296a** also underwent the reaction under the standard conditions, giving **369a** in 89% yield. Other cyclopropyl benzamides with substituents in *para* position of the benzene ring were also well tolerated in this reaction, giving products **369c-f** in 57-72% yield. With a methoxy group at the *meta* or *ortho* position, the corresponding diazides **369g** and **369h** were obtained in 72% and 67% yield respectively. Substrates bearing alkyl amides underwent diazidation to give **369m-n** in 62-63% yield. Carbamate protected aminocyclopropanes afforded products **369o** and **369p** in 62% and 66% yield respectively. From tosyl protected substrate **296q**, diazidation product **369q** was observed by ^{1}H NMR, but purification by column chromatography led to decomposition. Addition of TMSCN into the crude mixture of **369q** resulted in the formation of a stable cyano-azidation product **373** in 63% yield.



Scheme 90. Scope of aminocyclopropanes with different protecting groups for the ring-opening diazidation.

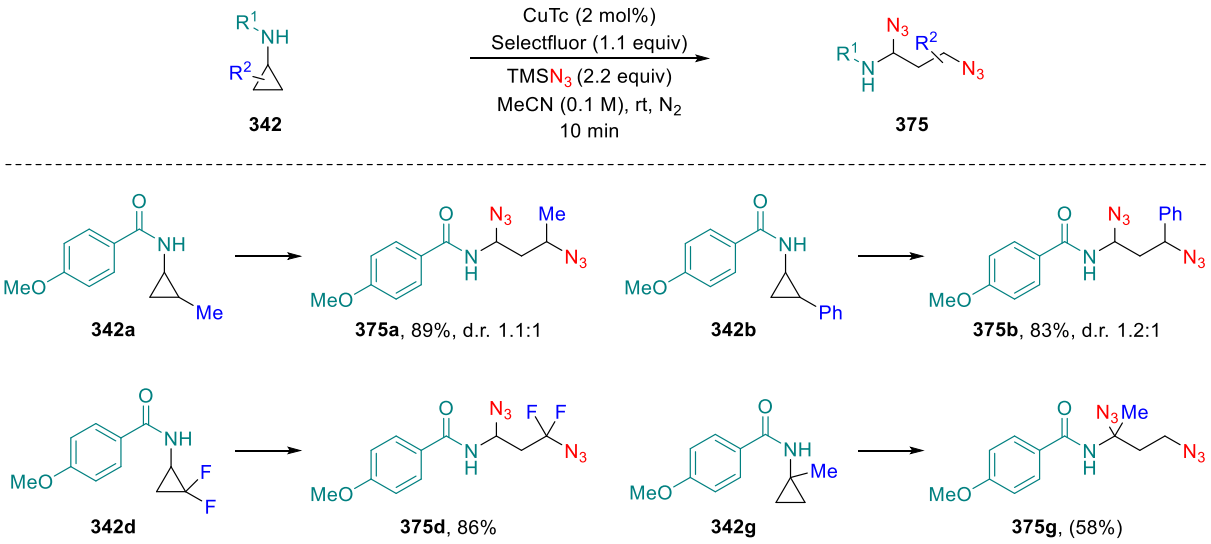
This diazidation is not limited to N-H cyclopropylamides as an N-methyl substituted cyclopropyl benzamide **349** also gave diazide **374** in 64% yield (Eq. 41). This result also precluded the possibility of ring opening via a HAT pathway promoted by the Selectfluor-derived radical cation.[261]



Equation 41. Diazidation of the N,N-disubstituted aminocyclopropane **349**.

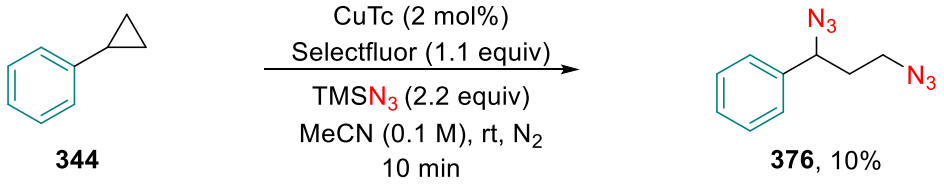
Importantly, the transformation was not limited to unsubstituted small rings (Scheme 92). 2-Methyl and 2-phenyl substituted aminocyclopropanes **342a** and **342b** gave the diazide products **375a** and **375b** in 83-89% yield. From *gem*-difluoro aminocyclopropane **342d**, difluoroazide **375d** was obtained in 86% yield. For 1-methyl substituted aminocyclopropane **342g**, product **375g** was observed by ^{1}H NMR, but it was not stable enough to be isolated. For all substrates, selective cleavage of the more-substituted σ-bond to give the more stable radical was observed.

[261] Troyano, F. J. A.; Merkens, K.; Gómez-Suárez, A. *Asian J. Org. Chem.* **2020**, *9*, 992.



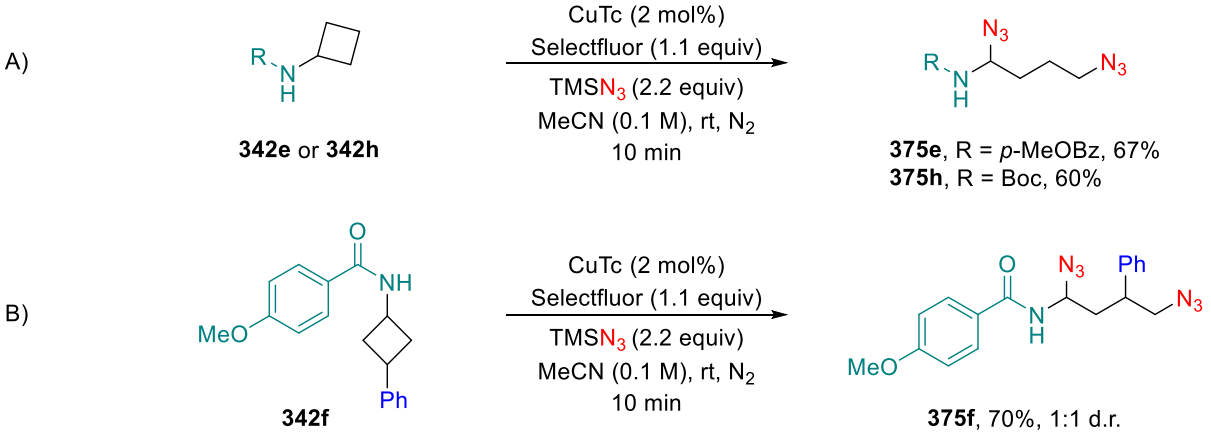
Scheme 92. Scope of aminocyclopropanes with different substituents for the ring-opening diazidation.

Cyclopropylbenzene **344** was also tolerated under standard conditions, affording the diazidation product **376** in 10% yield (Eq. 42). In contrast, only the aminoazidation product for the same substrate had been observed in Zhang's previous work using NFSI as oxidant.[256]



Equation 42. Diazidation of cyclopropylbenzene **344**.

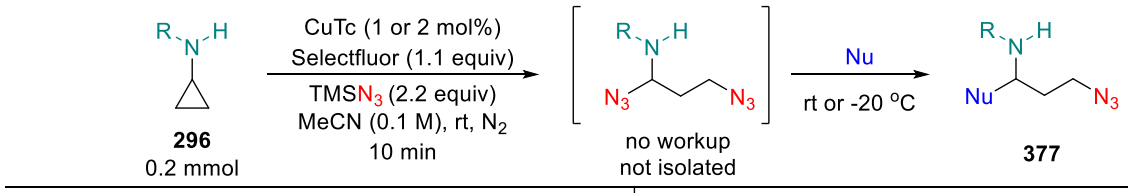
The reaction conditions were also successful in the case of aminocyclobutanes such as **342e** and **342h**, leading to 1,4-diazides **375e** and **375h** in 67% and 60% yield (Scheme 93 A). Ring strain was shown to be an essential driving force for this reaction, as further extension to aminocyclopentane did not work. 3-Phenyl substituted aminocyclobutane **342f** underwent the diazidation with only C1-C2 bond cleavage product **375f** observed and isolated in 70% yield (Scheme 93 B).

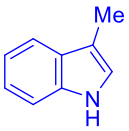
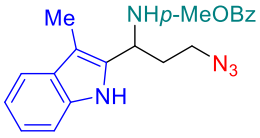
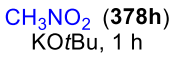
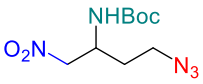
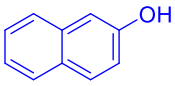
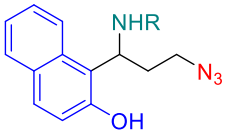
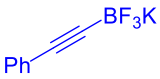
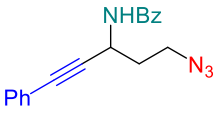
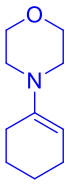
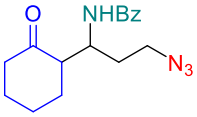
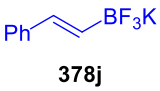
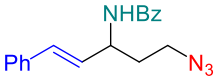
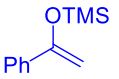
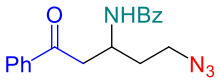
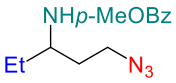
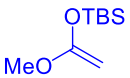
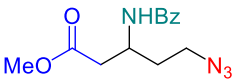
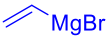
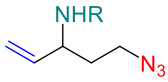
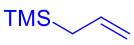
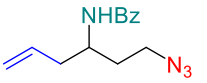
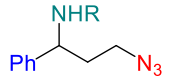
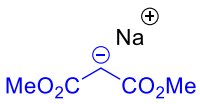
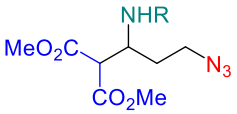
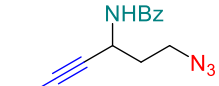
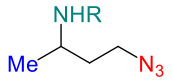


Scheme 93. Scope of aminocyclobutanes for the ring-opening diazidation.

We then turned towards the one-pot nucleophilic substitution of the α-amino azide. After the diazidation step was complete, carbon nucleophiles[262] were added directly to the reaction mixture (Scheme 94). To our delight, the α-amino azide was readily replaced by numerous nucleophiles with or without Lewis acid activation. Friedel-Crafts reactions took place in 46-74% yield with 3-methylindole (**378a**) or 2-naphthol (**378b**) and boron trifluoride etherate as Lewis acid to give diamines **377a** and **377ba**/**377bb**. Mannich-type reactions with enamine **378c** or enol ethers **378d** and **378e** gave products **377c-e** in 58-79% yield. Allyltrimethylsilane (**378f**) was also a good nucleophile in presence of titanium tetrachloride, forming the Sakurai-type product **377f** in 64% yield. More reactive nucleophiles, such as malonate **378g** and nitronate **378h**, reacted directly with the α-amino azide without the need for Lewis acid activation and afforded products **377ga**/**377gb** and **377h** in 54-77% yield. A Petasis-type reaction using tetrafluoroborate salts **378i** and **378j** as nucleophiles led to the formation of propargylic amine **377i** and allylic amine **377j** in 48 and 50% yield in presence of boron trifluoride etherate. Diethylzinc **378k** could be used to introduce an ethyl group as illustrated in **377k** without Lewis acid activation. Similarly, a series of commercially available organomagnesium reagents enabled the introduction of vinyl, aryl, alkynyl and alkyl substituents (products **377l-o**).

[262] Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626.

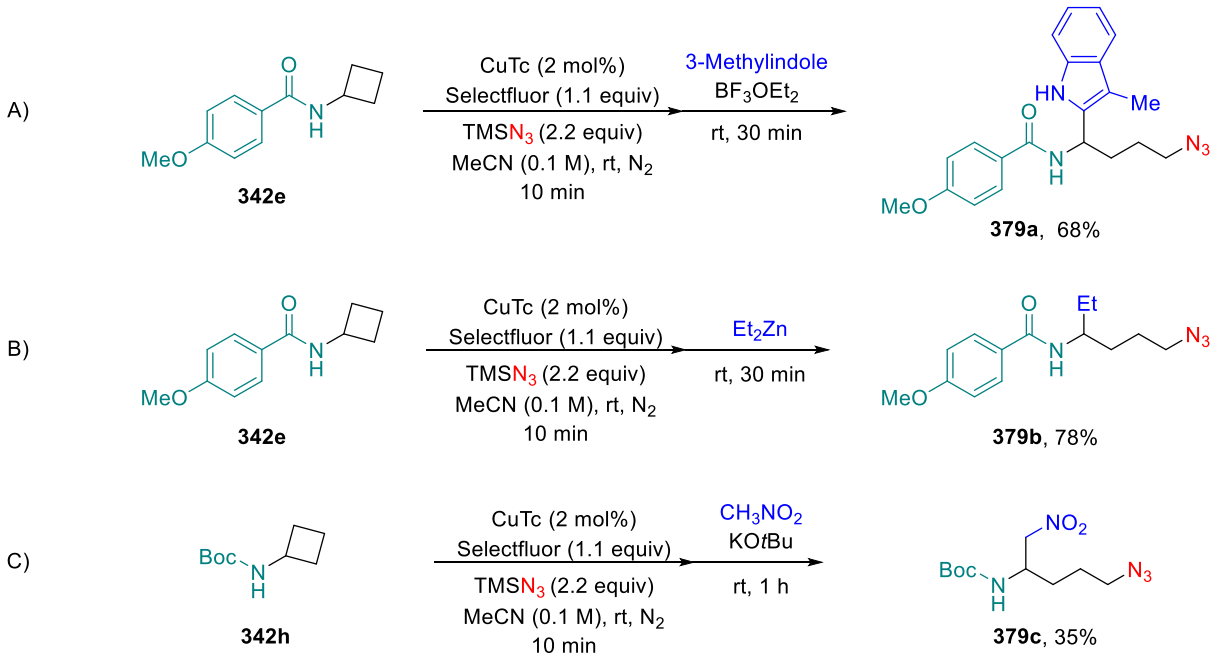


nucleophile	product	nucleophile	product
 **378a** BF_3OEt_2, 30 min	 **377a**, 65%	 CH_3NO_2 (**378h**) KO*t*Bu, 1 h	 **377h**, 54%
 **378b** BF_3OEt_2, 30 min	 **377ba**, R = *p*-MeOBz, 74% **377bb**, R = Cbz, 46%	 **378i** BF_3OEt_2, 2 h	 **377i**, 48%
 **378c** BF_3OEt_2, 1 h	 **377c**, 58%	 **378j** BF_3OEt_2, 1 h	 **377j**, 50%
 **378d** TMSOTf, 30 min	 **377d**, 79%	 **378k** 30 min	 **377k**, 85%
 **378e** 4 h	 **377e**, 62%	 **378l** 30 min	 **377la**, R = Bz, 57% **377lb**, R = Boc, 44%
 **378f** $TiCl_4$, 1 h	 **377f**, 64%	 **378m** 30 min	 **377ma**, R = Bz, 71% **377mb**, R = Boc, 44%
 **378g** 10 min	 **377ga**, R = Bz, 77% **377gb**, R = Boc, 64%	 **378n** 30 min	 **377n**, 65%
		 **378o** 30 min	 **377oa**, R = Bz, 52% **377ob**, R = Cbz, 46%

Scheme 94. One-pot diazidation-nucleophilic substitution for 1,3-diamine synthesis.

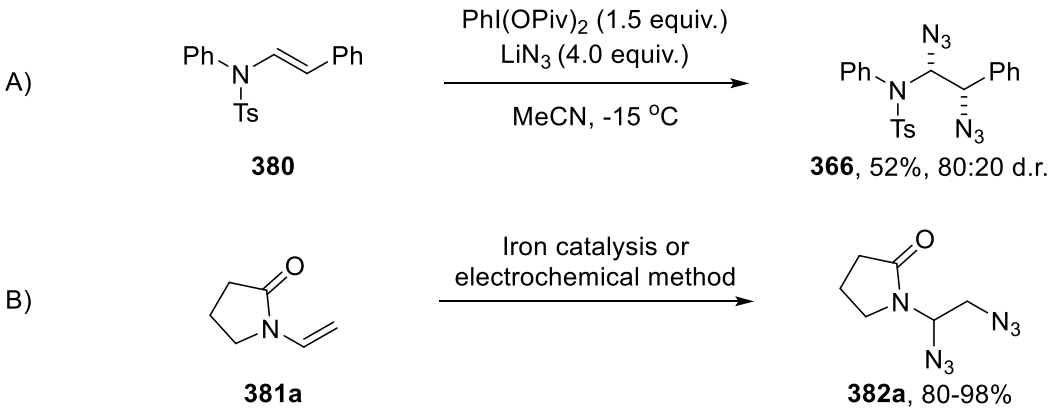
This diazidation-nucleophilic substitution process was successfully extended to aminocyclobutanes (Scheme 95). Starting from **342e**, adding 3-methylindole as well as boron trifluoride etherate to the crude diazidation mixture resulted in the formation of **379a** in 68% yield (Scheme 95A). Using diethyl zinc instead gave **379b** in 78% yield (Scheme 95B). For Boc-protected aminocyclobutane **342h**,

nitromethane was employed as nucleophile in the presence of potassium *tert*-butoxide, which led to the formation of **379c** with three nitrogen moieties in different oxidation states (Scheme 95C).



Scheme 95. One-pot diazidation-nucleophilic substitution for 1,4-diamine synthesis.

We expected that our nucleophilic substitution protocol with carbon nucleophiles would be also successful in the case of diazides derived from enamides. If successful, we can have a quick access to 1,2-diamines. Instead of using the reported methods to access the diazides form enamides, i.e. an iodine(III)-mediated diazidation of enamides (Scheme 96A),[259] an iron-catalyzed or an electrochemical method for the diazidation of enamide **381a** (Scheme 96B),[246-248] we wondered if our copper-catalyzed diazidation method could be applied for the synthesis of diazide **382a**.

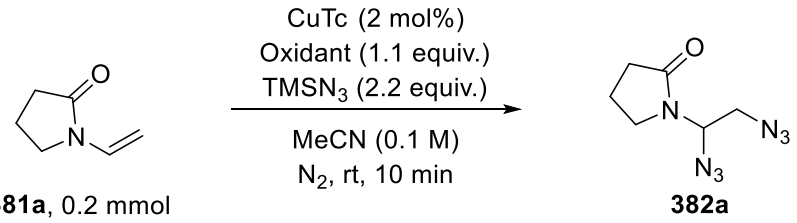


Scheme 96. Reported protocols for the diazidation of enamides.

However, under the standard conditions developed for aminocyclopropanes, only degradation was observed for enamide **381a** (Table 15, entry 1). Switching to NFSI resulted in a complex mixture which was hard to be analyzed (Table 15, entry 2). No conversion was observed in the case of TBHP and potassium persulfate (Table 15, entries 2-3). A fast screening of oxidants revealed that NCS, *m*CPBA and PIDA can give the diazidation product **382a** in 30-70% yield (Table 15, entries 4-7). Increasing the amount of PIDA to 1.3 equivalents further improved the results, with **382a** isolated in 95% yield (Table

15, entry 8). The reaction proceeded even without CuTc, although the isolated yield decreased to 78% (Table 15, entry 9).

Table 15. Screening of oxidants for the diazidation of enamide **381a**.

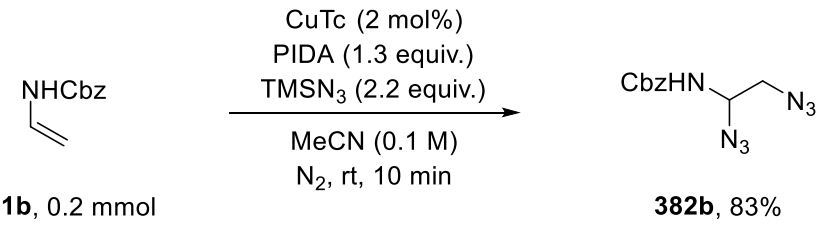


381a, 0.2 mmol — **382a**

Entry[a]	Oxidant	^{1}H NMR Yield (%)
1	Selectfluor	degradation
2	NFSI	messy
3	TBHP	No reaction
4	$K_2S_2O_8$	No reaction
5	NCS	50
6	*m*CPBA	30
7	PIDA	70
8	PIDA (1.3 equiv.)	88 (95)
9	PIDA (1.3 equiv.), without CuTc	78

(a) Reaction conditions: 0.20 mmol scale for 10 min. Yield was determined by ^{1}H NMR using CH_2Br_2 as internal standard. Isolated yield was shown in parentheses.

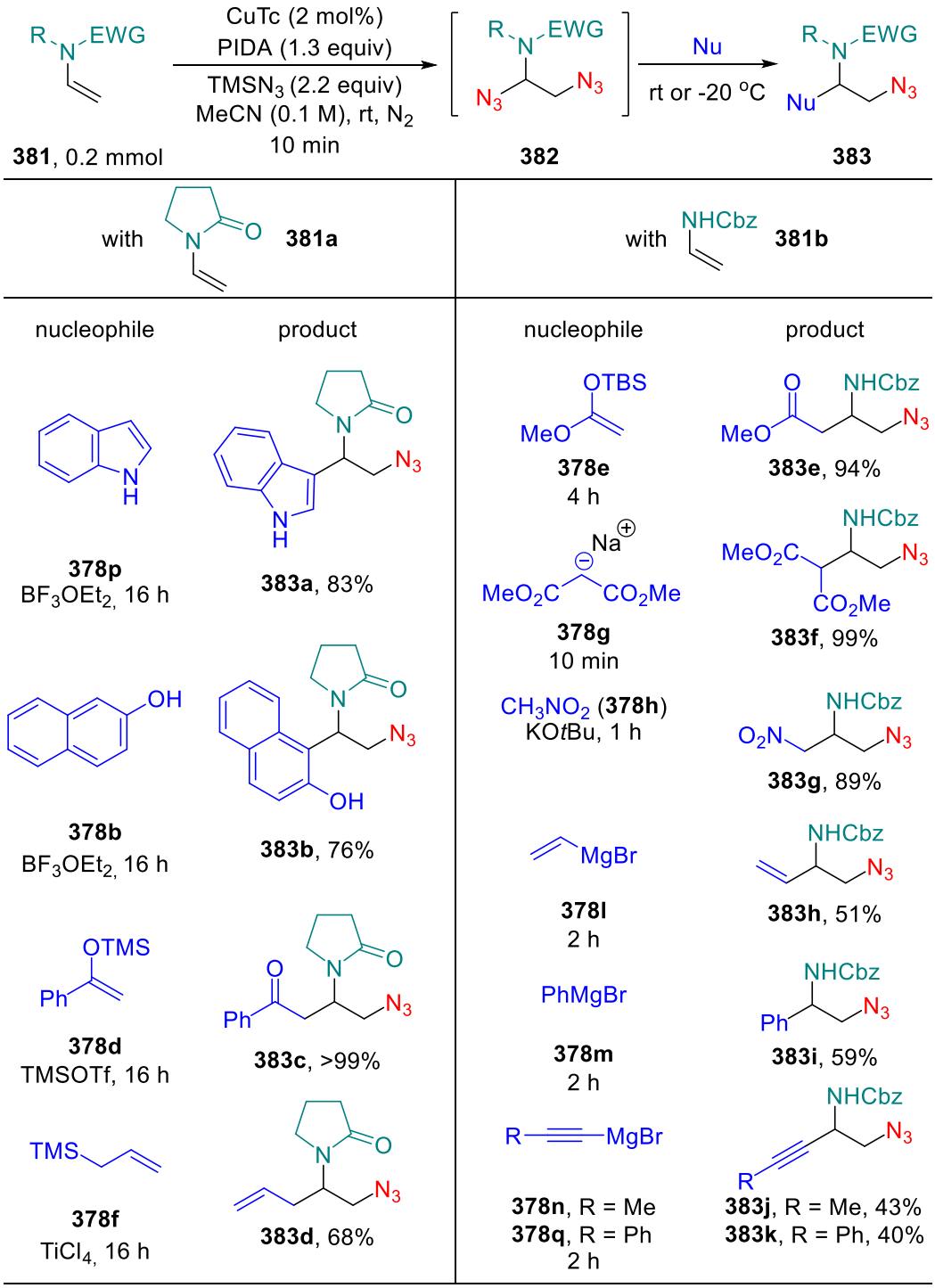
These conditions were also suitable for enecarbamate **381b** and the corresponding product **382b** was isolated in 83% yield in the presence of CuTc, compared to 67% in the absence of CuTc (Eq. 43).



381b, 0.2 mmol — **382b**, 83%

Equation 43. Dizidation of enecarbamate **381b**.

Different nucleophiles were then incorporated into the α-amino position (Scheme 97). For enamide **367a**, Friedel-Crafts reactions with indole (**366p**) and 2-naphthol (**366b**) gave **369a** and **369b** in 83% and 76% yield respectively. Enol ether (**366d**) and allyltrimethylsilane (**366f**) were also good nucleophiles. For enecarbamate **367b**, β-amino acid derivative **369e** was obtained by using an enol ether as nucleophile. Sodium malonate gave **369f** in 99% yield. When nitromethane was used as nucleophile, 1,2,3-trifunctionalized propane **369g** bearing three nitrogen atoms in different oxidation states was formed. Different organomagnesium reagents were also examined and isolated yields for products **369h-369k** ranged from 40% to 59%.



Scheme 97. One-pot diazidation-nucleophilic substitution for enamides.

The structure of products **377a** and **383b** was confirmed by X-ray diffraction analysis (Figure 14).

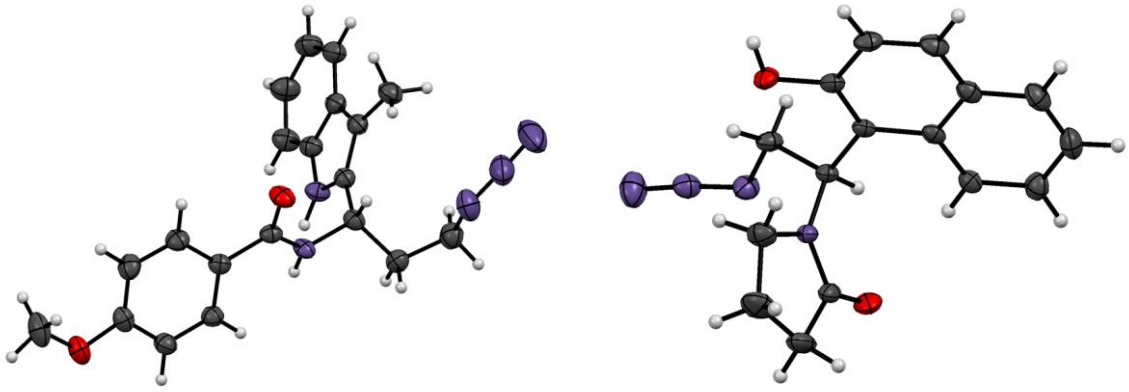
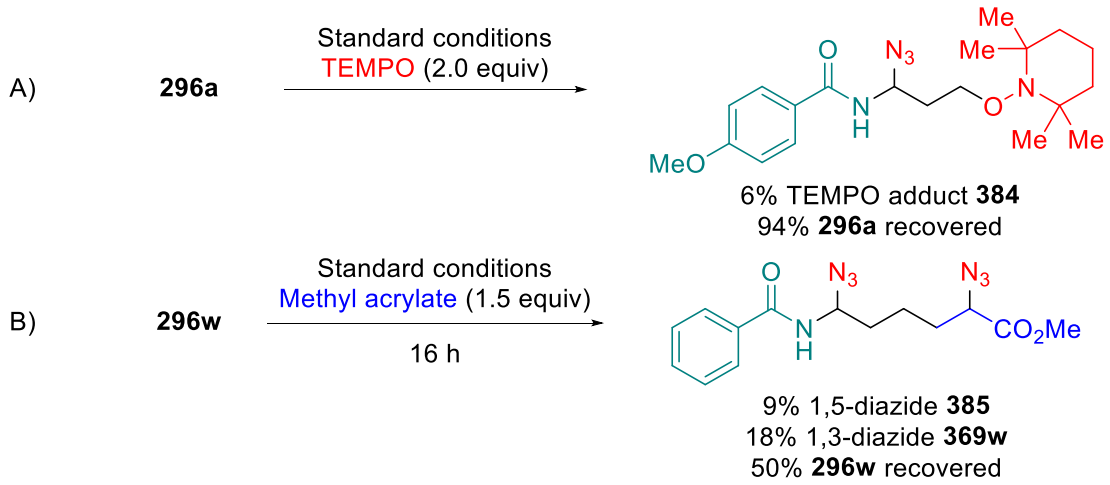


Figure 14. Structure of **377a** and **383b** determined by X-ray diffraction analysis.

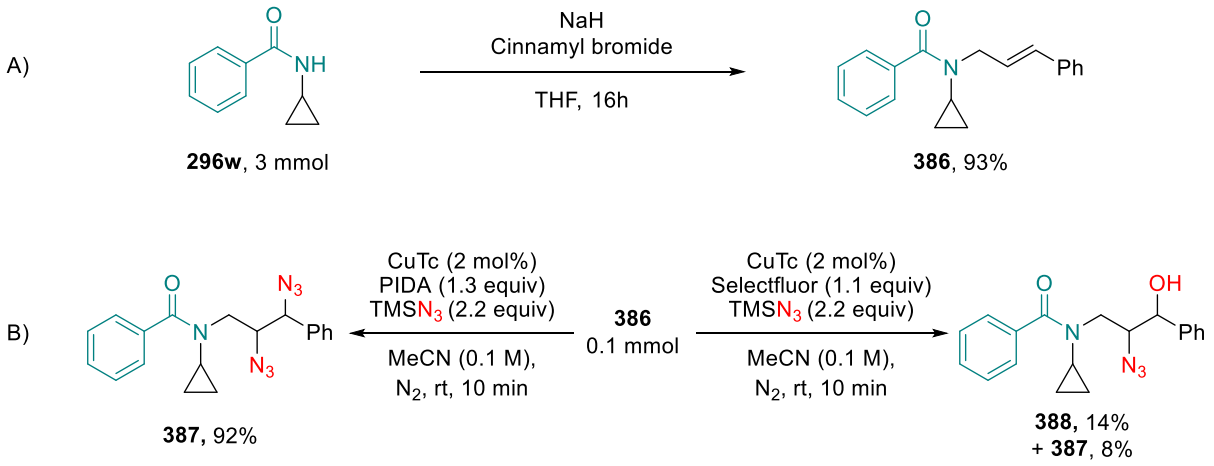
3.4.3 Mechanistic studies of the azidation reaction

Preliminary mechanistic experiments were then performed in order to obtain some deeper insights about the reaction mechanism. In the presence of the radical inhibitor 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 6% of TEMPO adduct **370** could be isolated, while 94% of **296a** was recovered (Scheme 84A). When methyl acrylate was added under the standard conditions, 1,5-diazide product **371** was isolated in 9% yield, accompanied with the isolation of the 1,3-diazide product **359w** and 50% recovery of **296w** (Scheme 84B). These results indicated that the diazidation of aminocyclopropanes goes through the formation of a primary alkyl radical intermediate.



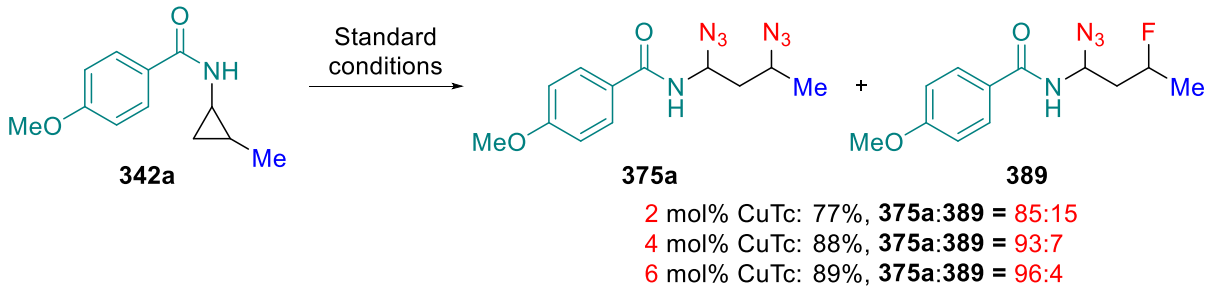
Scheme 98. Mechanistic studies for the diazidation of aminocyclopropanes with radical-trapping reagents.

In order to compare the reactivity of the σ and π bonds, we synthesized substrate **386** bearing a cyclopropyl ring and a cinnamyl group on the nitrogen (Scheme 99A). Using PIDA/$TMSN_3$, 92% of alkene diazidation product **387** was isolated; with Selectfluor/$TMSN_3$, 8% of **387** as well as 14% alkene hydroxy-azidation byproduct **388** were isolated (Scheme 99B). In both cases, no ring-opening product was observed, which indicated the higher reactivity of π bonds over σ bonds.



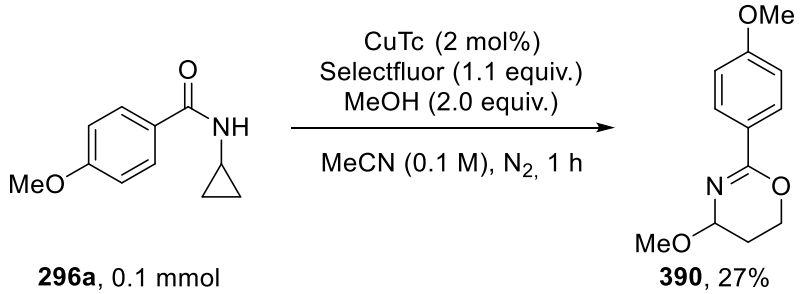
Scheme 99. Synthesis of **386** for comparing reactivity of cyclopropyl ring with C=C bond toward diazidation.

When the 2-methyl substituted aminocyclopropane **342a** was used as substrate, a small amount of fluorination side product **389** was observed in addition to **375a**. Interestingly, the ratio between **375a** and **389** was increased simply by adding more CuTc, indicating that the copper catalyst played a role for azido group transfer (Eq. 44).



Equation 44. Improvement of selectivity of azidation over fluorination by increasing catalyst loadings.

We also attempted the reaction without $TMSN_3$ in dry MeCN: full conversion of **296a** was observed after the reaction mixture was stirred for 1 hour, but crude ^1H NMR indicated complete degradation and no products could be isolated. Nevertheless, with the addition of MeOH (2 equiv.) as nucleophile, a six-membered cyclic compound **390** was isolated and characterized (Eq. 45).

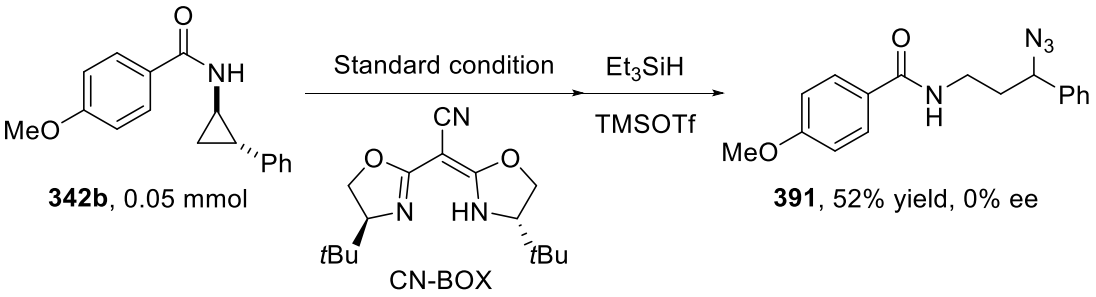


Equation 45. Formation of compound **390** in the absence of $TMSN_3$.

Finally, inspired by the recent progress on copper-catalyzed asymmetric azidation reactions,[263] we tried also to make the ring-opening azidation product in an enantioselective manner. However, when using a

[263] Wu, L.; Zhang, Y.; Wu, D.; Wang, F.; Chen, P.; Lin, Z.; Liu, G. *Angew. Chem. Int. Ed.* **2021**, *60*, 6997.

chiral CN-BOX as ligand, no asymmetric induction was observed in the final product **391**, which was formed after reduction of the diazidation product from substrate **342b** (Eq. 46).



Equation 46. Asymmetric azidation attempts on 2-phenyl substituted aminocyclopropane **342b**.

Based on these results, together with literature precedence on Selectfluor-oxidized Cu(III) species,[264] we preferred a Cu(III) catalyzed pathway for explaining the reaction mechanism. However, it is known that the elusive Cu(III) species has only been isolated and characterized when coordinating to multidentate ligands.[265] We tried to use online ESI-MS to monitor the reaction process, especially to detect the high-valent copper species. However, we only observed the disappearance of the copper signal as soon as Selectfluor was added into the reaction mixture containing stoichiometric amount of CuTc. Even in the presence of neocuproine or the CN-BOX as ligand, no other copper signals have been detected.

We then performed some cyclic voltammetry experiments in order to study the reaction mechanism. Based on the measurement results, CuTc has two oxidation peaks, with the redox potential being 0.86 V (Cu^{I}/Cu^{II}) and 2.28V (Cu^{II}/Cu^{III}) respectively (just before solvent oxidation, as shown from the background voltamogramm). For aminocyclopropane **296a**, its redox potential was determined to be 1.67 V after the calibration of reference electrode with ferrocene. When mixing CuTc with **296a**, we observed two oxidation peaks, 0.86 V and 1.67 V which corresponded to the first peak of CuTc and the oxidation peak of **296a** respectively, but the second peak of CuTc was not observed. In addition, a catalytic current of 0.08 mA was observed when comparing the currents of CuTc+**296a** (0.24 mA), CuTc (0.04 mA) and **296a** (0.12 mA) respectively at the potential of the oxidation peak for **296a**, which may indicate the oxidation of substrate **296a** by a high valent Cu species (Figure 15).[266]

[264] a) Jin, Z.; Xu, B.; Hammond, G. B. *Tetrahedron Lett.* **2011**, *52*, 1956. b) Xiong, T.; Li, Y.; Bi, X.; Lv, Y.; Zhang, Q. *Angew. Chem. Int. Ed.* **2011**, *50*, 7140. c) Michaudel, Q.; Thevenet, D.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 2547. d) Sathyamoorthi, S.; Lai, Y.-H.; Bain, R. M.; Zare, R. N. *J. Org. Chem.* **2018**, *83*, 5681.

[265] DiMucci, I. M.; Lukens, J. T.; Chatterjee, S.; Carsch, K. M.; Titus, C. J.; Lee, S. J.; Nordlund, D.; Betley, T. A.; MacMillan, S. N.; Lancaster, K. M. *J. Am. Chem. Soc.* **2019**, *141*, 18508.

[266] a) Saravanan, N.; Gandhi, M.; Kumar, A. S. *J. Electroanal. Chem.* **2020**, *874*, 1572. b) Abudayyeh, A. M.; Schott, O.; Feltham, H. L. C.; Hanan, G. S.; Brooker, S. *Inorg. Chem. Front*. **2021**, *8*, 1015.

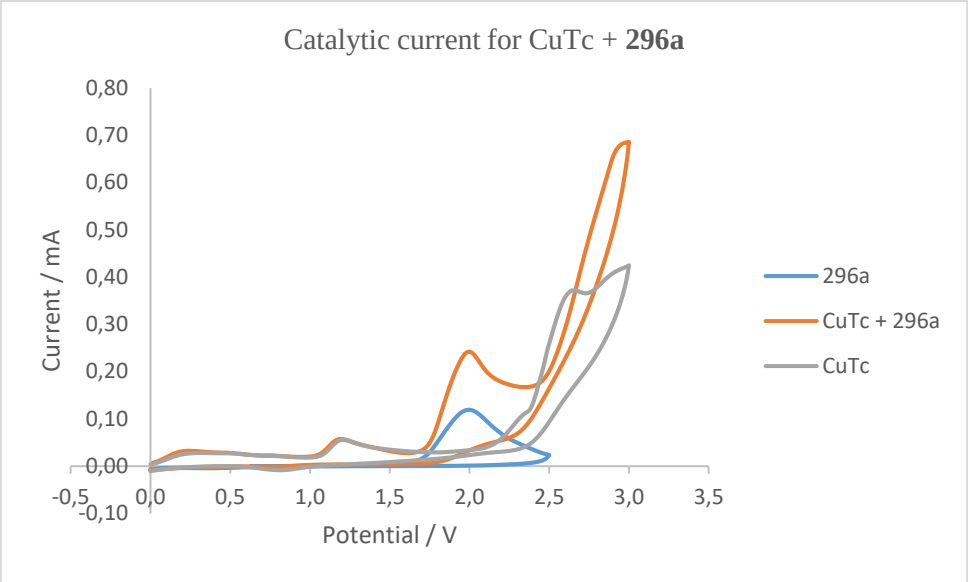


Figure 15. Overlay of the cyclic voltammograms of CuTc, **296a** and the mixture of CuTc and **296a** showing a catalytic current. Voltammograms performed with a scan rate of 50 mV/s, a concentration of electrolyte Bu_4NPF_6 = 0.1 M, and a concentration of **296a** = 5 mM.

With IR spectroscopy, we first mesasured the spectra of $TMSN_3$ and the azide signal was found at 2138 cm^{-1} (Figure 16).By simply mixing CuTc and $TMSN_3$, we observed the shift of azide signal to 2077 and 2047 cm^{-1} (Figure 17). A similar value has been reported previously in the literature for a copper azide complex.[267] Based on these results we can assume the formation of one or more copper-azide species.

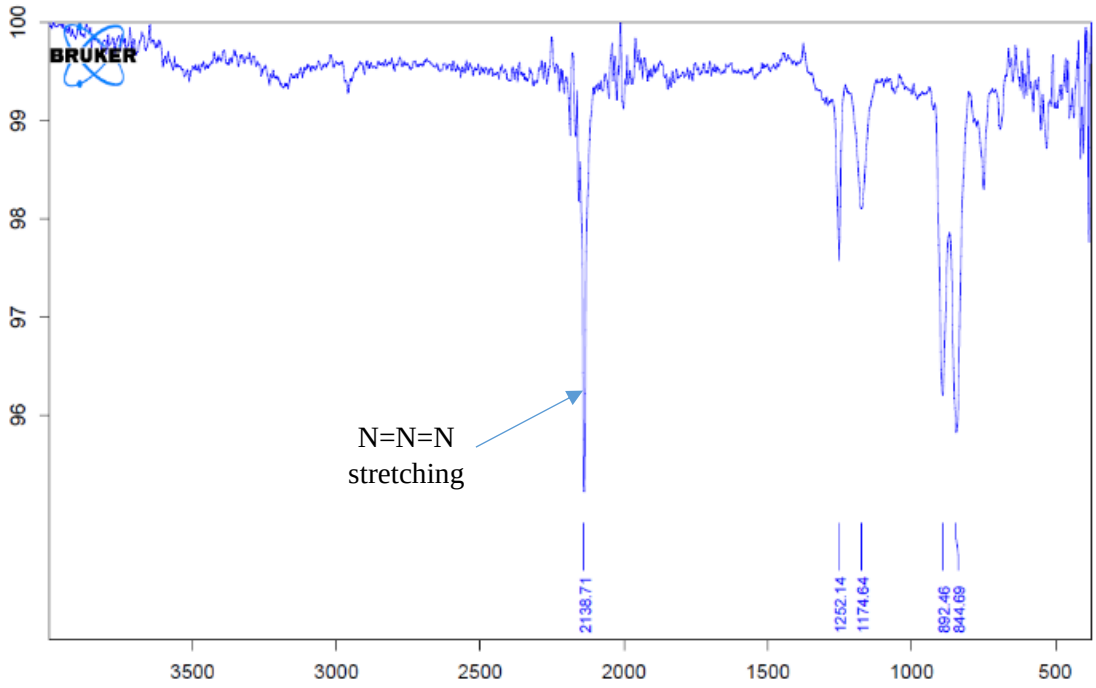


Figure 16. IR spectra of the solution of $TMSN_3$ in MeCN.

[267] Hossain, A.; Vidyasagar, A.; Eichinger, C.; Lankes, C.; Phan, J.; Rehbein, J.; Reiser, O. *Angew. Chem. Int. Ed.* **2018**, *57*, 8288.

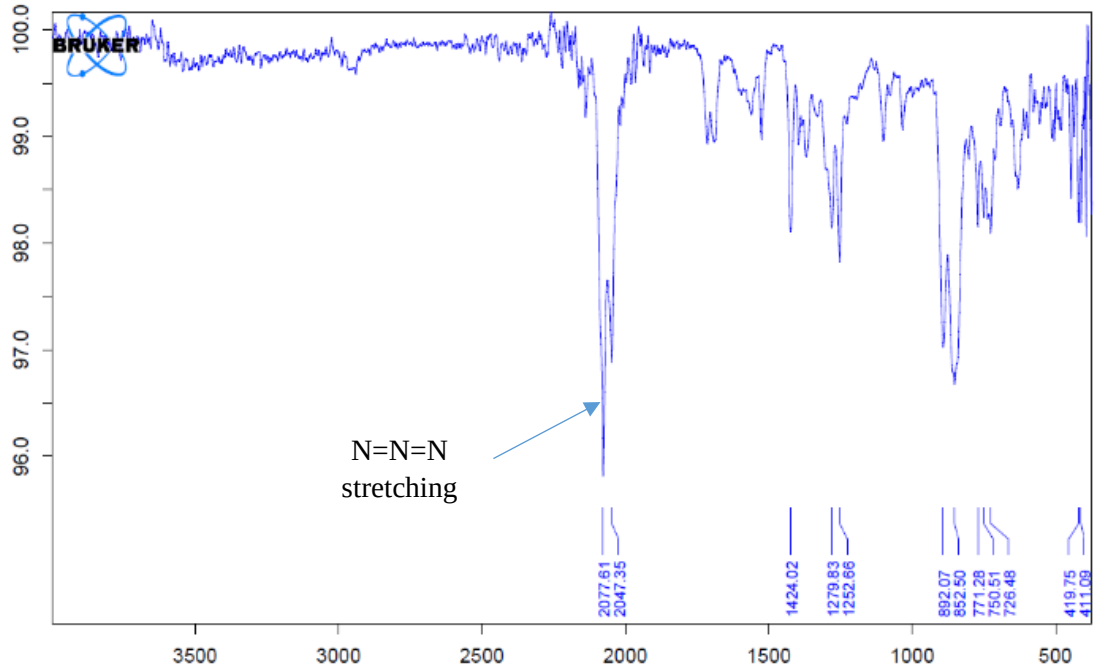


Figure 17. IR spectra of the solution of $TMSN_3$ and CuTc in MeCN.

However, once Selectfluor was added to the CuTc/$TMSN_3$ mixture, the azide peak disappeared (Figure 18).

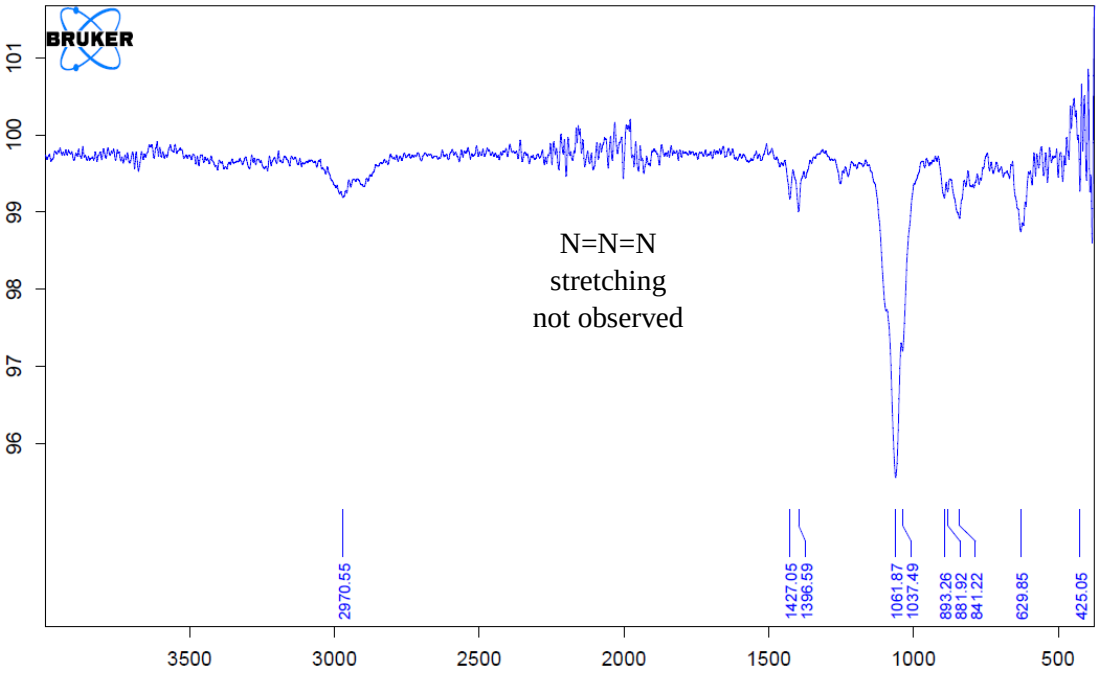


Figure 18. IR spectra of the solution of $TMSN_3$, CuTc and Selectfluor in MeCN.

Although we can support the formation of a copper azide complex under the reaction conditions, no well-defined complex could be isolated. In order to further support the role of a Cu-N_3 species as somophillic azide source, we synthesized the reported complex $[(BPhen)Cu^{II}(N_3)(\mu\text{-}N_3)]_2PhCl$ by

following the literature procedure.[268] The synthesis was successful, as the structure of our complex was confirmed by X-ray crystallography and matched well with the reported data (Figure 19).

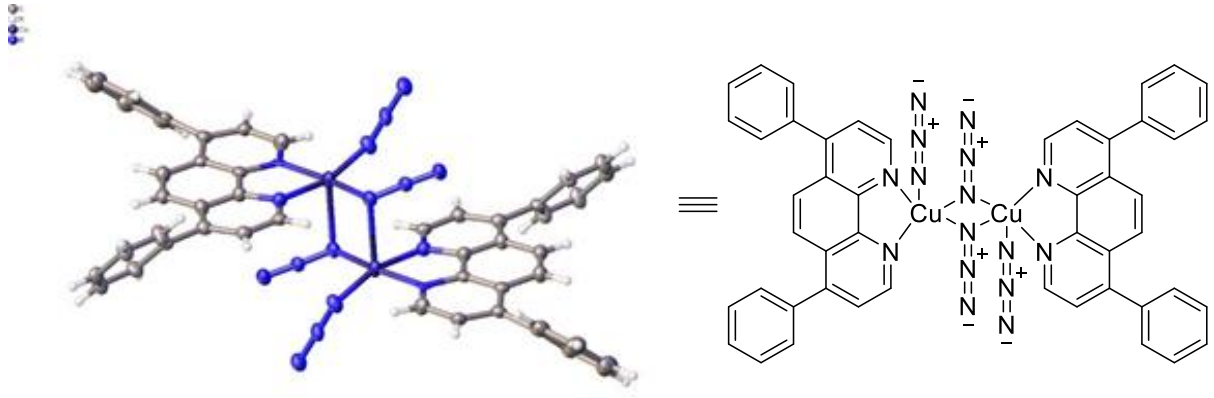
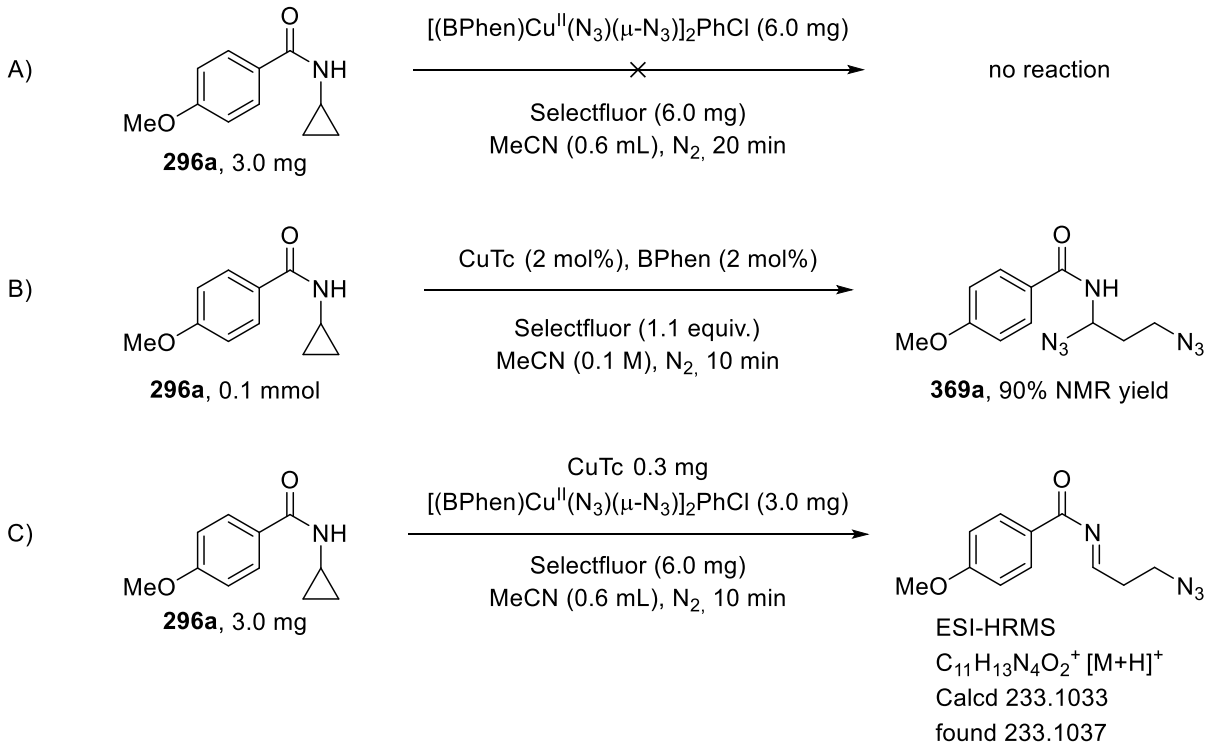


Figure 19. Crystal structure of our synthesized [(BPhen)$Cu^{II}(N_3)(\mu\text{-}N_3)]_2$PhCl complex confirmed by X-ray.

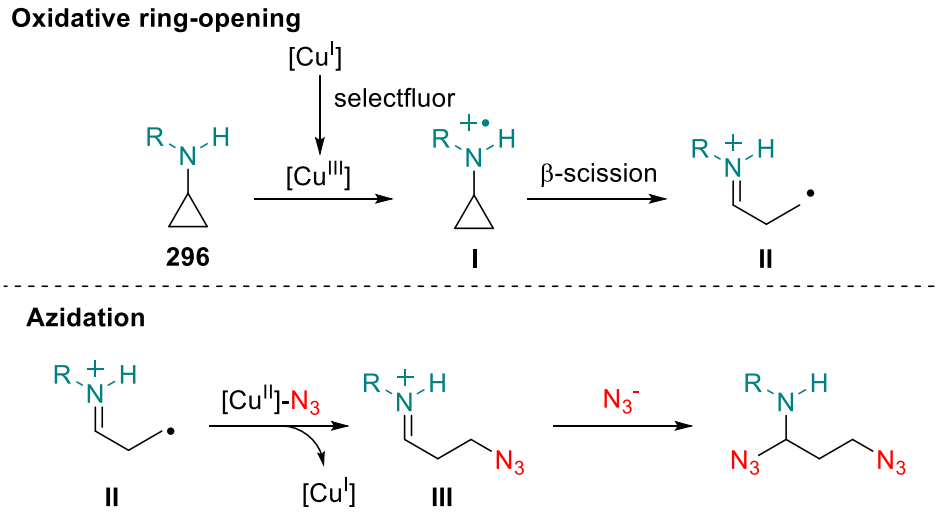
We then mixed this complex with **296a** and Selectfluor in MeCN for 20 minutes, but no reaction was observed (**296a** remained untouched, and [(BPhen)$Cu^{II}(N_3)(\mu\text{-}N_3)]_2$PhCl remained as a dark green precipitate due to poor solubility in MeCN) (Scheme 85A). An individual experiment with BPhen showed that BPhen does not shut down the reaction (Scheme 85B). With addition of CuTc, formation of an azidated imine was observed, which was not stable enough to be isolated, but could be observed by HRMS (Scheme 85C). These experiments indicated that the Cu-N_3 species was not an active catalyst, but it could transfer azido group to a primary alkyl radical.



Scheme 100. Control experiments with [(BPhen)$Cu^{II}(N_3)(\mu\text{-}N_3)]_2$PhCl.

[268] Suh, S.-E.; Chen, S.-J.; Mandal, M.; Guzei, I. A.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2020**, *142*, 11388.

Combining all the results together, we propose a speculative mechanism for explaining the azidation step of aminocyclopropanes as illustrated in Scheme 101. The reaction would be initiated by oxidation of CuTc by Selectfluor to form a fleeting Cu(III) species,[264] which then oxidizes aminocyclopropane **296** to give a radical cation species **I**. Carbon radical **II** is then formed after β-scission. In a second step, the azide could be transferred from a Cu(II)-N_3 complex to **II**, regenerating a Cu(I) complex. In principle, a rebound-type mechanism with a Cu(III)-N_3 complex first oxidizing **296** and then transferring the azide to **II** can be considered, although we have no experimental support for it at this stage. Alternatively, the generation of a free azide radical that recombines with **II** can also be envisaged, though less likely. The azidation of **II** would then lead to iminium **III**, which would be intercepted by an azide nucleophile to deliver the diazidation product.



Scheme 101. A speculative mechanism for the azidation of aminocyclopropanes.

In summary, we have developed an efficient diazidation-nucleophilic substitution sequence for the synthesis of orthogonally protected 1,2-, 1,3-, and 1,4-diamines starting from enamides/enecarbamates, aminocyclopropanes and aminocyclobutanes respectively. The first step was enabled by a copper-catalyzed diazidation proceeding in high yields within 10 minutes at room temperature using commercially available reagents. The obtained α-amino azides functioned then as masked imines for accessing a broad range of protected diamines in the form of an amide/carbamate and an azide by addition of carbon-based nucleophiles. Our new strategy to access diamines further highlights the potential of C-C functionalizations of strained carbocycles for the selective synthesis of multi-functionalized building blocks, as well as shines light on the potential of α-amido azides as masked imines.

4

Conclusions and Outlook

4. Conclusions and Outlook

The research work presented in this thesis was aimed at the development of novel transformations involving cyclopropanes and cyclobutanes. Two fundamentally different approaches have been utilized for the activation of two classes of substrates: 1) Lewis acid activation was used for the activation of DA aminocyclopropanes and DA aminocyclopropanes; 2) a radical strategy was explored for activating simple aminocyclopropanes and aminocyclopropanes.

In the area of donor-acceptor systems, we first tried to develop a formal [4+1] cycloaddition of DA aminocyclobutanes with isocyanides (Figure 20). Preliminary results were obtained when using 20 mol% $Sc(OTf)_3$ as catalyst, with a cyclopentene-1,2-diamine isolated as product in 64% yield in the presence of 4Å MS. However, this reaction suffered from poor substrate scope for both DA aminocyclobutanes and isocyanides. More efforts need to be made in order to establish optimal conditions for this reaction.

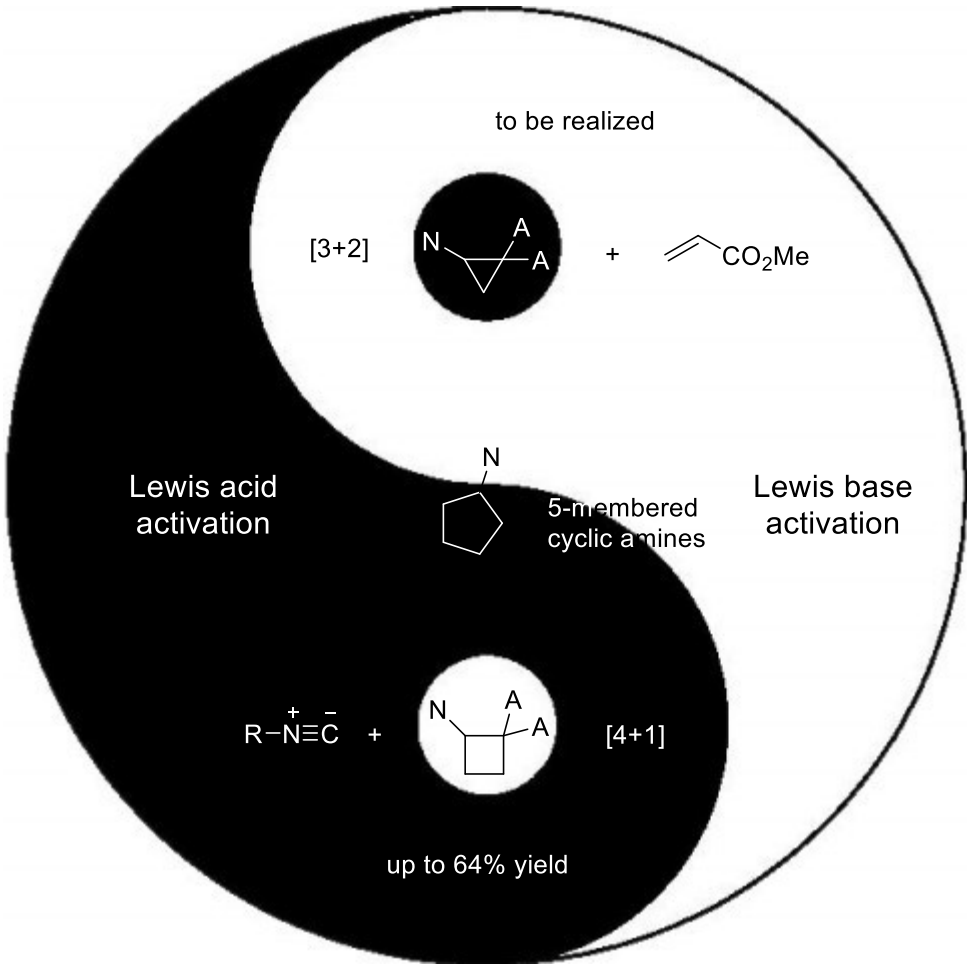


Figure 20. Synthesis of 5-membered cyclic amines from DA aminocyclopropanes or DA aminocyclobutanes.

We also attempted to develop another route for the synthesis of five-membered cyclic amines through a formal [3+2] cycloaddition of DA aminocyclopropanes with electron-deficient alkenes. Inspired by the classical Morita-Baylis-Hillman reaction, we used Lewis bases such as pyridine or DABCO to activate methyl acrylate, which would then behave as a nucleophile for the ring-opening of DA aminocyclopropanes. Despite no positive results have been obtained so far, other members from the Waser group will possibly put some more time on this project in the future.

Though installing one or two electron-withdrawing groups to the vicinal position of aminocyclopropanes makes the cyclopropyl C1-C2 bond polarized, extra synthetic steps are necessary to incorporate these acceptor groups into simple aminocyclopropanes or to remove them if they are not wanted in the final products. Therefore, we turned our attention to the direct activation of simple aminocyclopropanes, in particular the acyl or carbamate protected ones.

Inspired by the recent progress in the HLF reaction, we first developed ring-opening halogenation reactions (iodination, bromination) under mild conditions (Figure 21). Stabilized in the form of N,O-acetals, the alkyl iodides/bromides can be seen as biscationic synthons, which gave 1,3-difunctionalized propylamines upon sequential treatment with two nucleophiles. When thiophenols were used as nucleophile, the biscationic synthons were converted into 4-amino thiochromans efficiently with exclusive regioselectivity. Intrigued by the unexpected regioselectivity, we then further studied the scope as well as the mechanism for this formal [3+3] cycloaddition reaction. Late-stage modification of complex drug molecules containing an aminocyclopropane was also realized.

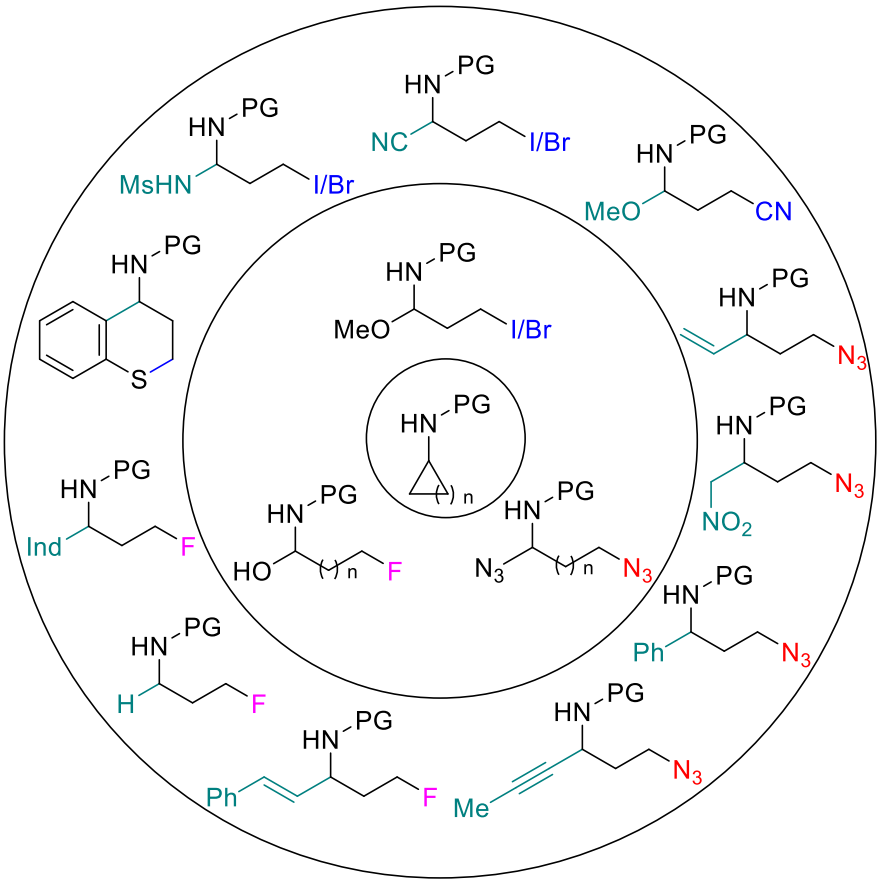


Figure 21. Representative products obtained by the ring-opening transformations of simple aminocyclopropanes and aminocyclobutanes.

One limitation of this HLF-inspired ring-opening halogenation is that it failed in the case of fluorination. Considering the importance of fluorine in medicinal chemistry, we then developed an oxidative fluorination reaction enabled by photoredox catalysis. When using Selectfluor as oxidant, both cheap benzophenone with UV light (365 nm) and an acridinium salt or an iridium complex with blue light could be used as photoredox catalysts to promote this process. As the reaction was performed in MeCN-H_2O, the fluorinated products were stabilized in the form of hemiaminal, which could undergo one-pot

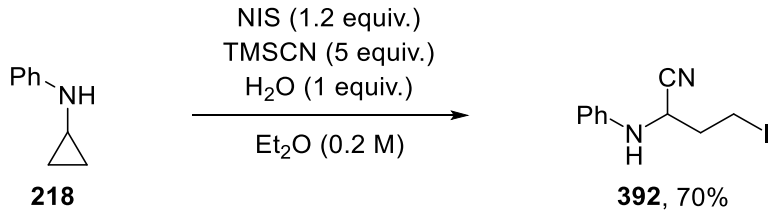
nucleophilic substitution of the hydroxy group. Extension of this reaction to aminocyclobutanes was also successful.

Diamines are essential building blocks for the synthesis of agrochemicals, drugs, and organic materials, yet their synthesis remains challenging, as both nitrogens need to be differentiated and diverse substitution patterns (1,2, 1,3, or 1,4) are required. We developed a new strategy giving access to 1,2, 1,3, and 1,4 amido azides as orthogonally protected diamines based on the nitrogen-directed diazidation of alkenes, cyclopropanes, and cyclobutanes. Commercially available copper thiophene-2-carboxylate as catalyst promoted the diazidation of both π and σ C–C bonds within 10 min in the presence of readily available oxidants and trimethylsilyl azide. Selective substitution of the formed α-amino azide by carbon nucleophiles (electron-rich aromatic compounds, malonate, organosilicon, organoboron, organozinc, and organomagnesium compounds) was then achieved in a one-pot fashion, leading to the formation of 1,2-, 1,3-, and 1,4-diamines with the amino groups protected orthogonally as an amide/carbamate and an azide.

Conclusions can be drawn that in this thesis only limited success has been achieved in the research area of DA aminocyclopropanes and DA aminocyclopropanes, but several ring-opening transformations involving simple aminocyclopropanes and aminocyclobutanes have been realized by a radical approach. Initiating the ring-opening process with a nitrogen-centered radical or a radical cation species is especially efficient, leading to the formation of an imine/iminium with an alkyl radical which can be trapped by different somophiles to yield the iodination/bromination, fluorination or azidation products. The imine/iminium group was stabilized in the form of N,O-acetal or N,N-aminal, which allows nucleophilic substitution with a broad range of nucleophiles in a one-pot fashion. Efforts to incorporate other functional groups by a similar strategy are currently ongoing in our lab.

Outlook:

In 2019, four months after we published the HLF-inspired ring-opening iodination/bromination of cyclopropylamides, the Zheng group reported also a difunctionalization of cyclopropylamines with NIS or the *in situ* formed ICN (Eq. 47).[269] They studied the reaction with cyclopropylanilines as substrate, and they proposed a two-electron pathway rather than single electron transfer for explaining the cyclopropyl ring opening, given the much lower redox potential value of **218** compared to that of cyclopropylamides.



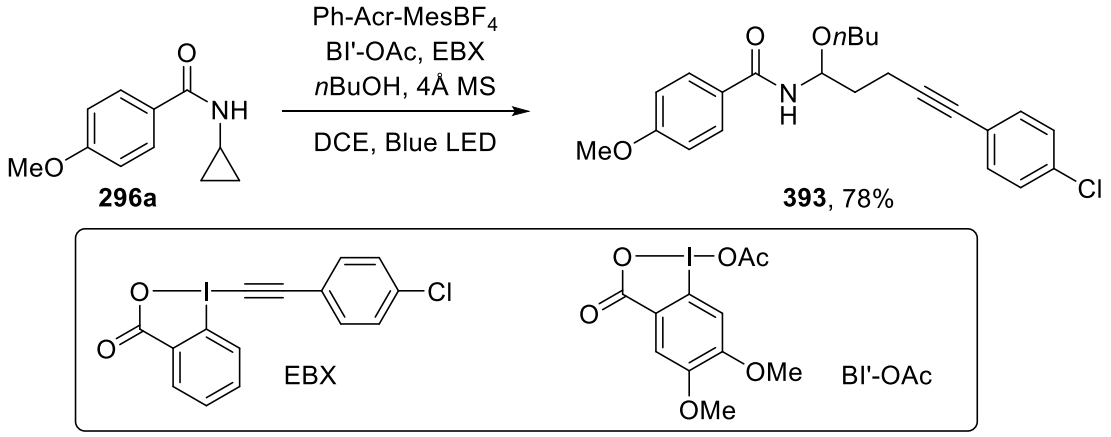
218 **392**, 70%

Equation 47. Difunctionalization of N-cyclopropylaniline **218** with NIS.

In 2021, the Chen group reported a ring-opening alkynylation reaction of cyclopropylamides under mild photoredox catalysis conditions (Scheme 102).[270] Supported by a series of mechanistic experiments, they found that a catalytic amount of the cyclic iodine(III) reagent BI'-OAc facilitated the single electron oxidation as well as the ring-opening alkynylation of cycloalkylamides. Inspired by our work, they used

[269] Wang, Q.; Zheng, N. *Org. Lett.* **2019**, *21*, 9999.
[270] Liu, Z.; Wu, S.; Chen, Y. *ACS Catal.* **2021**, *11*, 10565.

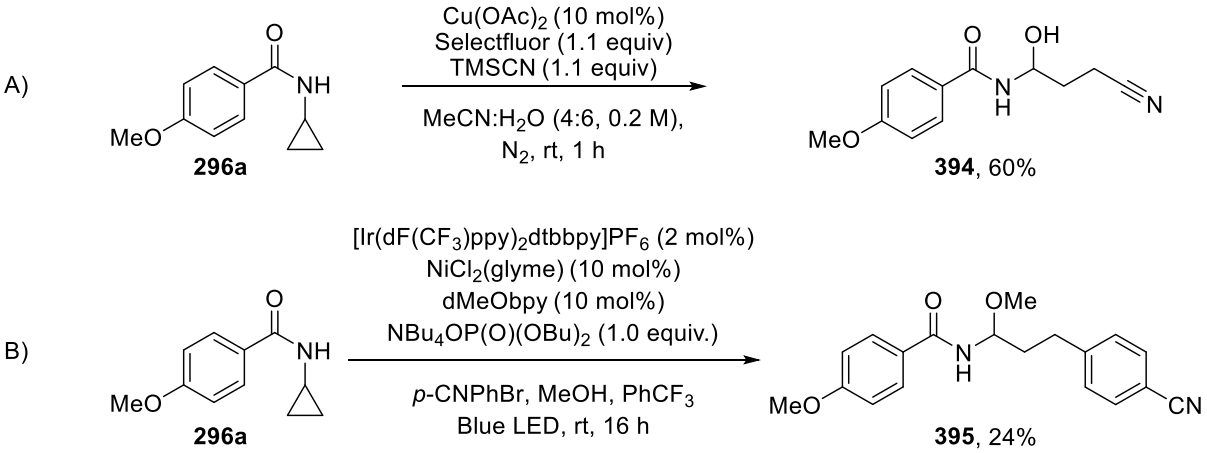
butanol to mask the imine intermediate and further nucleophilic substitution of the butoxy group has been realized by using indole, 1-naphthol, thiophenol etc. as nucleophiles.



Scheme 102. Ring-opening alkynylation of aminocyclopropane **296a**.

The Aggarwal group also reported a diastereoselective photoredox-catalyzed [3+2] cycloaddition of N-sulfonyl protected aminocyclopropanes with ethyl acrylate in 2021 (Eq. 20).[139]

I am also trying to construct a C-C bond for the ring-opening transformations of cyclopropyl amides and some promising results have been obtained. For example, a cyanide group can be introduced to the terminal carbon atom by copper catalysis (Scheme 103A), or an aryl group can be introduced by photoredox PCET and nickel dual catalysis (Scheme 103B). Following the same strategy as shown before, we may replace the OH/OMe group by various nucleophiles in a one-pot manner.

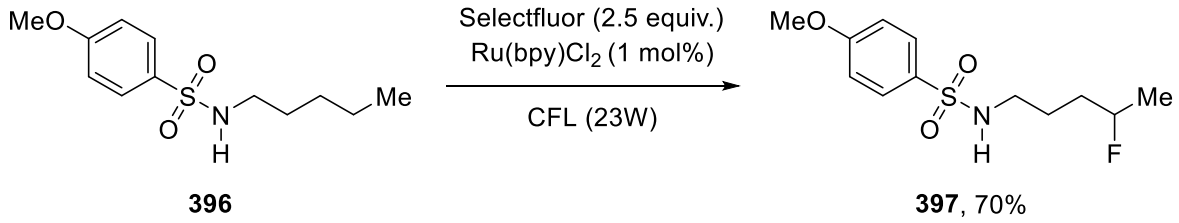


Scheme 103. Preliminary results of ring-opening cyanation and arylation reactions on cyclopropylamide **296a**.

I can envisage that in the future the research field of aminocyclopropanes will experience continuous growth with different transformations to be developed in a racemic or even asymmetric form. The progress in oxidative ring-opening functionalization of cyclopropylamides in turn can also inspire the development in other fields such as remote C(sp3)-H functionalization of linear amides or oxidative ring-opening functionalization of arylcyclopropanes.

For example, based on my benzopheneone catalyzed fluorination project, I found the reaction can be successfully extended to the direct δ-C(sp3)-H fluorination of compound **267** without the necessity of

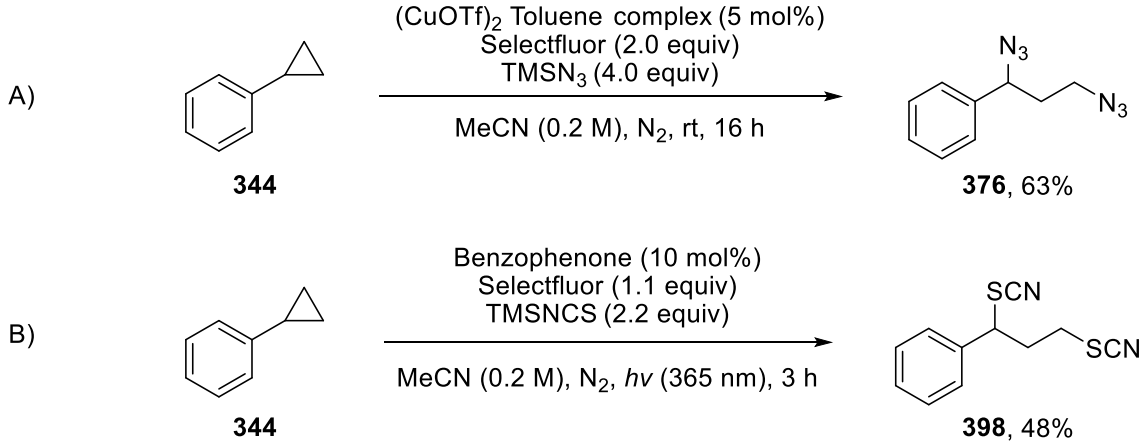
synthesizing N-fluorinated amide **268**. However, I stopped this project after a similar reaction was recently published by the Chen group (Eq. 48).[271]



396 **397**, 70%

Equation 48. Remote C(sp3)-H fluorination of N-sulfonamide **396**.

In the end, I also have some preliminary results on the difunctionalization of cyclopropylbenzene (**344**). As described in the section 3.4.2, diazide **376** was obtained in 10% yield under the standard conditions for the diazidation of aminocyclopropanes. I spent some time optimizing the reaction conditions and the best yield so far was 63% (Scheme 104A). I also found that a dithiocyanide product **398** could be obtained under irradiation conditions when TMSNCS was used instead of $TMSN_3$ (Scheme 104B).



344 **376**, 63%

344 **398**, 48%

Scheme 104. Preliminary results of ring-opening diazidation and dithiocyanation of **344**.

I do hope that these methodologies developed in this thesis can inspire scientists in other fields and eventually find applications in the synthesis of some nitrogen-containing compounds with biological activities or other properties.

[271] Deng, Z.; Zhao, Z.; He, G.; Chen, G. *Org. Lett.* **2021**, *23*, 3631.

5

Experimental Part

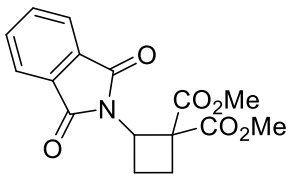
5. Experimental Part

5.1. General Methods

All reactions were carried out in oven- or flame- dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash column chromatography, distilled technical grade solvents were used. THF, Et_2O, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 7 ppm, Karl-Fischer titration). All chemicals were purchased and used as received unless stated otherwise. Chromatographic purification was performed as flash column chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC plastic or aluminium plates and visualized with UV light, permanganate, CAN or *p*-anisaldehyde stains. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. ^{1}H-NMR spectra were recorded at room temperature on a Brucker DPX-400 400 MHz spectrometer in $CDCl_3$, DMSO-d_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm and the internal methanol signal at 3.31 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, p = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration, interpretation). ^{13}C-NMR spectra were recorded with 1H-decoupling on a Brucker DPX-400 100 MHz spectrometer in $CDCl_3$ or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm or CD_3OD signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 or a Bruker Alpha-P spectrophotometer with an ATR device and a ZnSe prism and are reported as cm-1 (w = weak, m = medium, s = strong). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurements were done on an Agilent 1260 Infinity autosampler using a CHIRALPAK IA, IB, IC or IF column from DAICEL Chemical. Fluorescence quenching experiment was conducted on a Varian Cary Eclipse machine. UV/Vis spectroscopy was performed on an Agilent Cary 60 UV-Vis machine. Cyclic voltammetry was performed with a Biologic SP-150 Potentiostat. For reactions under the irradiation of UV light (365 nm), reactions were performed in 12*75 mm borosilicate glass tubes which were placed around 7 cm far away from lamps (CAMAG UV Lamp 4, long-wave UV light 365 nm) in Rayonet RPR-100 photochemical reactor. For reactions under the irradiation of blue light, reactions were performed in 12*75 mm borosilicate glass tubes which were hold using a rack for test tubes placed at the center of a crystallization flask. On this flask were attached the blue LEDs (Ruban LED avec câble à extrémités ouvertes Barthelme Y51516414 182405 24 V 502 cm bleu 1 pc(s), bought directly on www.conrad.ch/fr). The distance between the LEDs and the test tubes was approximatively 3 to 4 cm. Long irradiation for more than 2 h resulted in temperature increasing up to 34 °C.

5.2. [4+1] Annulation of DA aminocyclobutanes with isocyanides

Dimethyl 2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (175)



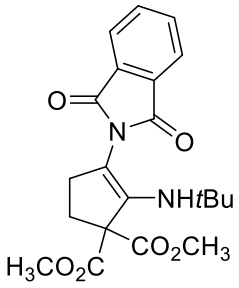
Following a reported procedure,[104] dimethyl malonate (1.32 mL, 11.6 mmol, 2.0 equiv.), diisopropylamine 2,2,2-trifluoroacetate (2.49 g, 11.6 mmol, 2.0 equiv.), paraformaldehyde (0.695 mg, 23.1 mmol, 4.0 equiv.) and trifluoroacetic acid (89.0 µL, 1.16 mmol, 0.2 equiv.) were added to tetrahydrofuran (20 mL). A condenser was added and the suspension was stirred at reflux for 2 h. Paraformaldehyde (0.695 mg, 23.1 mmol, 4.0 equiv.) was added and the reflux was continued for 6 h. The reaction was cooled to room temperature and the tetrahydrofuran was removed under reduced pressure (300 to 50 mbar at 45°C). The crude was dissolved in diethyl ether (25 mL) and filtered through cotton in a separatory funnel. The organic layer was washed twice with 1 M HCl (25 mL). The aqueous layers were combined and extracted with diethyl ether (25 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give dimethyl 2-methylenemalonate crude as colorless oil.

The iron trichloride supported on alumina (1.00 mmol/g, 289 mg, 0.289 mmol, 0.05 equiv.) was weighted in an oven-dry flask in a glovebox. The flask was closed with a silicon septum, taken out of the glovebox and put under positive pressure of nitrogen and dichloromethane (5 mL) was added. 2-vinylisoindoline-1,3-dione (1.00 g, 5.77 mmol, 1.0 equiv.) was dissolved in dichloromethane (5 mL) and added to the yellow suspension. Finally, the crude dimethyl 2-methylenemalonate was dissolved in dichloromethane (5 mL) and added to the reaction in one portion. The reaction was stirred at room temperature for 16 h and then filtered over a basic alumina plug, eluting with ethyl acetate. The solvents were evaporated and the brown solid was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 50 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **175** (1.55 g, 4.89 mmol, 85%) as a colorless solid.

R_f: 0.45 (1:1 hexane/ethyl acetate); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.93 (m, 2 H, Ar*H*), 7.80 (m, 2 H, Ar*H*), 5.17 (t, 1 H, *J* = 10.9 Hz, NC*H*), 3.16 (s, 3 H, CO_2CH_3), 2.98 (s, 3 H, CO_2CH_3), 2.58 (m, 1 H, CH_2), 2.25 (m, 1 H, CH_2), 1.48 (m, 1 H, CH_2), 1.33 (dt, 1 H, *J* = 13.6, 10.4 Hz, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.6, 168.7, 168.3, 134.3, 131.9, 123.5, 59.0, 53.2, 53.0, 47.9, 24.7, 21.9.

Data match literature report.[104]

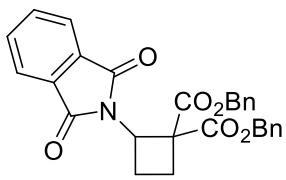
Dimethyl 2-(*tert*-butylamino)-3-(1,3-dioxoisoindolin-2-yl)cyclopent-2-ene-1,1-dicarboxylate (286)



In a flame dried microwave vial, $Sc(OTf)_3$ (4.90 mg, 10.0 µmol, 0.2 equiv.) and 4Å MS (30.0 mg) were added in the glove box. Then dimethyl 2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate **175** (15.9 mg, 50.0 µmol, 1.0 equiv.) and *tert*-butyl isocyanide (8.30 mg, 100 µmol, 2.0 equiv.) were dissolved in 1.0 mL dry CH_2Cl_2 and added dropwise under N_2. The mixture was stirred at room temperature for 12 h, and then filtered over a pad of basic alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, 3:7 pentanes/ethyl acetate) affording dimethyl 2-(*tert*-butylamino)-3-(1,3-dioxoisoindolin-2-yl)cyclopent-2-ene-1,1-dicarboxylate **286** (12.8 mg, 32.0 µmol, 64%) as a yellow solid.

R_f: 0.35 (7:3 pentanes/ethyl acetate); **Mp:** 82-86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.86 (dd, J = 5.5, 3.1 Hz, 2H, Ar*H*), 7.72 (dd, J = 5.5, 3.1 Hz, 2H, Ar*H*), 3.81 (s, 6H, CO_2CH_3), 2.65 – 2.58 (m, 2H, CH_2), 2.56 – 2.49 (m, 2H, CH_2), 1.02 (s, 9H, $C(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.7, 167.0, 139.3, 134.1, 132.3, 123.4, 108.2, 66.6, 52.9, 52.7, 30.2, 29.8, 28.6; **IR** (film): $\tilde{\nu}$ = 2956 (w), 1785 (w), 1718 (s), 1465 (w), 1434 (w), 1385 (m), 1268 (m), 1212 (m), 1163 (m), 1058 (m), 1034 (m), 880 (w), 793 (w), 720 (s); **HRMS** (ESI) calcd. for $C_{21}H_{25}N_2O_6^+$ $[M+H]^+$ 401.1707; found 401.1712.

Dibenzyl 2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (289)



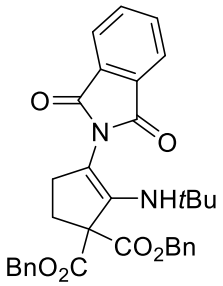
Following a reported procedure,[104] dibenzyl malonate (2.89 mL, 11.6 mmol, 2.0 equiv.), diisopropylamine 2,2,2-trifluoroacetate (2.49 g, 11.6 mmol, 2.0 equiv.), paraformaldehyde (0.695 mg, 23.1 mmol, 4.0 equiv.) and trifluoroacetic acid (89.0 µL, 1.16 mmol, 0.2 equiv.) were added to tetrahydrofuran (20 mL). A condenser was added and the suspension was stirred at reflux for two hours. Paraformaldehyde (0.695 mg, 23.1 mmol, 4.0 equiv.) was added and the reflux was continued for 6 hours. The reaction was cooled to room temperature and the tetrahydrofuran was removed under reduced pressure. The crude was retaken in diethyl ether (25 mL) and filtered through cotton in a separatory funnel. The organic layer was washed twice with 1M HCl (25 mL). The aqueous layers were combined and extracted with diethyl ether (25 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give dibenzyl 2-methylenemalonate crude as colorless oil.

The iron catalyst (289 mg, 0.289 mmol, 0.05 equiv.) was weighted in an oven-dry flask in a glovebox. The flask was closed with a silicon septum, taken out of the glovebox and put under a positive pressure of nitrogen. Dichloromethane (5 mL) was added. The reaction was cooled to 0 °C and 2-vinylisoindoline-1,3-dione (1.00 g, 5.77 mmol, 1.0 equiv.) was dissolved in dichloromethane (5 mL) and added to the yellow suspension dropwise. Finally, the crude dibenzyl 2-methylenemalonate was dissolved in dichloromethane (5 mL) and added to the reaction mixture dropwise. The reaction mixture was stirred at room temperature for 2 hours and then filtered over a basic alumina plug, eluting with ethyl acetate. The solvents were evaporated and the brown solid was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 50 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **289** (2.60 g, 5.54 mmol, 96 %) as a colorless oil that solidify upon storage at 4°C.

R_f 0.45 (hexane/Ethyl acetate 6/4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.74 – 7.68 (m, 2H, Ar*H*), 7.68 – 7.61 (m, 2H, Ar*H*), 7.34 – 7.26 (m, 5H, Ar*H*), 7.14 – 7.07 (m, 1H, Ar*H*), 7.06 – 7.00 (m, 2H, Ar*H*), 6.97 – 6.91 (m, 2H, Ar*H*), 5.50 (td, *J* = 9.5, 0.9 Hz, 1H, NC*H*), 5.17 (q, *J* = 12.3 Hz, 2H, CH_2Ph), 5.02 – 4.87 (m, 2H, CH_2Ph), 3.34 – 3.16 (m, 1H, CH_2), 3.02 (dddd, *J* = 11.7, 10.5, 3.8, 1.0 Hz, 1H, CH_2), 2.32 (dtd, *J* = 11.2, 9.1, 3.7 Hz, 1H, CH_2), 2.18 (dt, *J* = 11.6, 8.8 Hz, 1H, CH_2).

Data match literature report.[104]

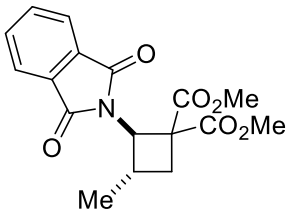
Dibenzyl 2-(*tert*-butylamino)-3-(1,3-dioxoisoindolin-2-yl)cyclopent-2-ene-1,1-dicarboxylate (290)



In a flame dried microwave vial, $Sc(OTf)_3$ (4.90 mg, 10.0 µmol, 0.2 equiv.) and 4Å MS (30.0 mg) were added in the glove box. Then dibenzyl 2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate **289** (23.5 mg, 50.0 µmol, 1.0 equiv.) and *tert*-butyl isocyanide (8.30 mg, 100 µmol, 2.0 equiv.) were dissolved in 1.0 mL dry CH_2Cl_2 and added dropwise under N_2. The mixture was stirred at 60 °C for 16 h, and then filtered over a pad of basic alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, 3:7 pentanes:ethyl acetate) affording dibenzyl 2-(*tert*-butylamino)-3-(1,3-dioxoisoindolin-2-yl)cyclopent-2-ene-1,1-dicarboxylate **290** (8.3 mg, 15.0 µmol, 30%) as a yellow solid.

R_f: 0.30 (7:3 pentanes/ethyl acetate); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.89 – 7.83 (m, 2H, Ar*H*), 7.73 (dt, *J* = 5.5, 3.5 Hz, 2H, Ar*H*), 7.35 – 7.28 (m, 10H, Ar*H*), 5.20 (s, 4H, C*H*$_2$Ph), 2.66 – 2.57 (m, 2H, C*H*$_2$), 2.57 – 2.48 (m, 2H, C*H*$_2$), 0.94 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9, 167.1, 139.2, 135.2, 134.1, 132.4, 128.5, 128.3, 128.2, 123.4, 106.8, 67.4, 66.8, 52.4, 30.1, 30.0, 28.6.

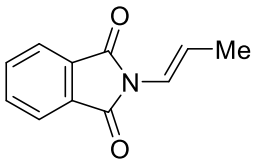
Dimethyl 2-(1,3-dioxoisoindolin-2-yl)-3-methylcyclobutane-1,1-dicarboxylate (291)



Dimethyl malonate (1.22 mL, 10.7 mmol, 2.0 equiv.), diisopropylamine 2,2,2-trifluoroacetate (2.30 g, 10.7 mmol, 2.0 equiv.), paraformaldehyde (0.640 mg, 21.4 mmol, 4.0 equiv.) and trifluoroacetic acid (82.0 µl, 1.07 mmol, 0.2 equiv.) were added to tetrahydrofuran (20 mL). A condenser was added and the suspension was stirred at reflux for two hours. Paraformaldehyde (0.640 mg, 21.4 mmol) was added and the reflux was continued for 6 hours. The reaction was cooled to room temperature and the tetrahydrofuran was removed under reduced pressure. The crude was dissolved in diethyl ether (25 mL) and filtered through cotton in a separatory funnel. The organic layer was washed twice with 1M HCl (25 mL). The aqueous layers were combined and extracted with diethyl ether (25 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give dimethyl 2-methylenemalonate crude as colorless oil.

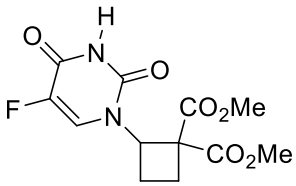
The iron catalyst (267 mg, 0.267 mmol, 0.05 equiv.) was weighted in an oven-dry flask in a glovebox. The flask was closed with a silicon septum, taken out of the glovebox and put under a positive pressure of nitrogen. Dichloromethane (5 mL) was added. The reaction was cooled to 0 °C and (*E*)-2-(prop-1-en-1-yl)isoindoline-1,3-dione (1.00 g, 5.34 mmol, 1.0 equiv.) was dissolved in dichloromethane (5 mL) and added to the yellow suspension dropwise. Finally, the crude dimethyl 2-methylenemalonate was dissolved in dichloromethane (5 mL) and added to the reaction mixture dropwise. The reaction mixture was stirred at room temperature for 4 hours and then filtered over a basic alumina plug, eluting with ethyl acetate. The solvents were evaporated and the brown solid was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 50 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **291** (1.53 g, 4.62 mmol, 86 %) as a colorless solid.

(*E*)-2-(prop-1-en-1-yl)isoindoline-1,3-dione (292)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (dd, 2 H, *J* = 5.2, 3.1 Hz, Ar*H*), 7.72 (dd, 2 H, *J* = 5.2, 3.0 Hz, Ar*H*), 6.64-6.54 (m, 2 H, CH=CH), 1.85 (d, 3 H, *J* = 5.1 Hz, CH_3).

Dimethyl 2-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclobutane-1,1-dicarboxylate (293)



Following an modified procedure,[105] 5-fluoro-1-vinylpyrimidine-2,4(1H, 3H)-dione (0.60 g, 3.8 mmol, 1.0 equiv.) and iron trichloride supported on alumina (1.0 mmol/g, 0.77 g, 0.77 mmol, 0.2 equiv.) were added in a flame dried microwave vial under nitrogen atmosphere. Then, dry dichloromethane (8 mL) and a solution of crude freshly prepared dimethyl 2-methylenemalonate (2.2 g, 15 mmol, 4.0 equiv.) in dichloromethane (2 mL) were added into the vial and the reaction mixture was stirred at room temperature for 14 hours. The reaction mixture was filtrated over a pad of alumina eluting with ethyl acetate (50 mL) and concentrated under reduced pressure. The crude mixture was purified via column chromatography, eluting with a mixture of pentanes/ethyl acetate (5:5 to 2:8). The pure product **293** (0.78 g, 2.6 mmol, 67%) was obtained as a colorless oil.

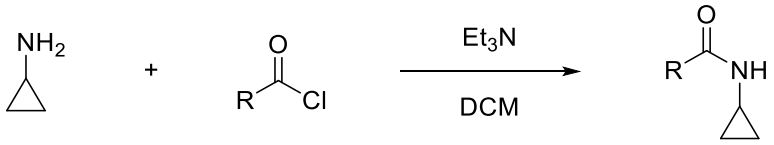
^{1}H NMR (400 MHz, Chloroform-*d*) δ = 9.54 (s, 1 H, N*H*), 7.36 (d, *J* = 6.1 Hz, 1 H, uracil C=C*H*), 5.28 (t, *J* = 9.0 Hz, 1 H, NC*H*), 3.78 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 2.68 – 2.61 (m, 2 H, CH_2), 2.41 – 2.32 (m, 1 H, CH_2), 2.32 – 2.25 (m, 1 H, CH_2).

Data match literature report.[105]

5.3. Ring-opening difunctionalization of simple aminocyclopropanes and aminocyclobutanes

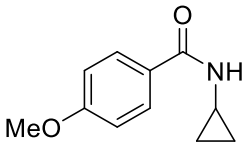
5.3.1 Preparation of the starting materials

General Procedure A (GP A):



Following a modified version of a reported procedure,[205] to a solution of cyclopropylamine (0.70 mL, 10 mmol, 1.1 equiv.) and triethylamine (1.40 mL, 10.0 mmol, 1.1 equiv.) in dichloromethane (10 mL) was slowly added a solution of acyl chloride (9.09 mmol, 1.0 equiv.) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at room temperature usually for 16 hours. Upon completion, the mixture was quenched by the addition of 1 N HCl (10 mL). The aqueous layer was then extracted with dichloromethane. The organic extract was washed with 1 M NaOH (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. In most cases, the crude product was pure enough to be used as such, without further purification.

***N*-Cyclopropyl-4-methoxybenzamide** (**296a**)

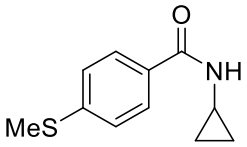


Following GP A, using 4-methoxybenzoyl chloride (1.55 g, 9.09 mmol), *N*-cyclopropyl-4-methoxybenzamide (**296a**) was obtained as a white solid (1.90 g, 8.99 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.66 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.94 – 6.85 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.21 (s, 1H, N*H*), 3.84 (s, 3H, OCH_3), 2.88 (tq, *J* = 7.1, 3.6 Hz, 1H, C*H*), 0.85 (td, *J* = 7.0, 5.3 Hz, 2H, CH_2), 0.65 – 0.55 (m, 2H, CH_2).

^{1}H NMR data correspond to the reported values.[205]

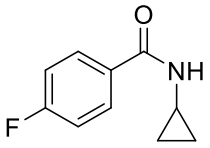
***N*-Cyclopropyl-4-(methylthio)benzamide** (**296b**)



Following GP A, using 4-(methylthio)benzoyl chloride (1.70 g, 9.09 mmol), N-cyclopropyl-4-(methylthio)benzamide (**296b**) was obtained as an off-white solid (1.41 g, 6.80 mmol, 75%).

R_f: 0.33 (silica, pentanes:ethyl acetate 1:1); **Mp:** 158-160 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.68 – 7.61 (m, 2H, Ar*H*), 7.25 – 7.20 (m, 2H, Ar*H*), 6.24 (s, 1H, N*H*), 2.89 (dq, *J* = 7.0, 3.4 Hz, 1H, C*H*), 2.50 (s, 3H, SCH_3), 0.91 – 0.80 (m, 2H, CH_2), 0.66 – 0.54 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.3, 143.4, 130.4, 127.2, 125.3, 23.1, 15.0, 6.8; **IR** (film): $\tilde{\nu}$ = 3271 (m), 3006 (w), 1622 (s), 1556 (s), 1486 (m), 1315 (m), 1121 (w), 840 (m), 761 (m); **HRMS** (ESI) calcd. for $C_{11}H_{13}NNaOS^+$ $[M+Na]^+$ 230.0610; Found 230.0613.

***N*-Cyclopropyl-4-fluorobenzamide** (**296c**)

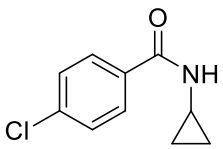


Following GP A, using 4-fluorobenzoyl chloride (1.44 g, 9.09 mmol), *N*-cyclopropyl-4-fluorobenzamide (**296c**) was obtained as a white solid (1.50 g, 8.36 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 – 7.70 (m, 2H, Ar*H*), 7.12 – 7.01 (m, 2H, Ar*H*), 6.37 (s, 1H, N*H*), 2.87 (tq, *J* = 7.1, 3.6 Hz, 1H, C*H*), 0.84 (td, *J* = 7.0, 5.3 Hz, 2H, CH_2), 0.65 – 0.56 (m, 2H, CH_2).

^{1}H NMR data correspond to the reported values.[119]

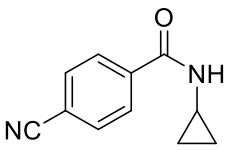
4-Chloro-*N*-cyclopropylbenzamide (**296d**)



Following GP A, using 4-chlorobenzoyl chloride (1.59 g, 9.09 mmol), 4-chloro-*N*-cyclopropylbenzamide (**296d**) was obtained as a white solid (1.65 g, 8.43 mmol, 93%).

R_f: 0.59 (silica, pentanes:ethyl acetate 2:3); **Mp:** 133-135 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.70 – 7.64 (m, 2H, Ar*H*), 7.41 – 7.35 (m, 2H, Ar*H*), 6.27 (s, 1H, N*H*), 2.88 (tt, *J* = 7.1, 3.5 Hz, 1H, C*H*), 0.90 – 0.83 (m, 2H, CH_2), 0.66 – 0.55 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.8, 137.7, 132.7, 128.8, 128.3, 23.2, 6.8; **IR** (film): $\tilde{\nu}$ = 3309 (m), 1639 (s), 1528 (m), 1484 (m), 1312 (m), 1093 (m), 847 (m); **HRMS** (ESI) calcd. for $C_{10}H_{10}ClNNaO^+$ $[M+Na]^+$ 218.0343; Found 218.0344.

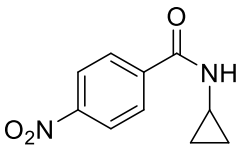
4-Cyano-*N*-cyclopropylbenzamide (**296e**)



Following GP A, using 4-cyanobenzoyl chloride (1.51 g, 9.09 mmol), 4-cyano-*N*-cyclopropylbenzamide (**296e**) was obtained as a white solid (1.60 g, 8.59 mmol, 95%).

R_f: 0.33 (silica, pentanes:ethyl acetate 1:1); **Mp:** 159-161 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.77 – 7.64 (m, 2H, Ar*H*), 6.34 (d, *J* = 38.4 Hz, 1H, N*H*), 2.91 (tq, *J* = 7.0, 3.6 Hz, 1H, C*H*), 1.09 – 0.73 (m, 2H, CH_2), 0.70 – 0.52 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.0, 138.3, 132.4, 127.6, 118.0, 115.1, 23.3, 6.8; **IR** (film): $\tilde{\nu}$ = 3275 (m), 3015 (w), 2230 (m), 1632 (s), 1532 (s), 1499 (m), 1313 (m), 1284 (m), 1018 (w), 858 (m); **HRMS** (ESI) calcd. for $C_{11}H_{11}N_2O^+$ $[M+H]^+$ 187.0866; Found 187.0862.

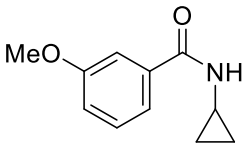
***N*-Cyclopropyl-4-nitrobenzamide** (**296f**)



Following GP A, using 4-nitrobenzoyl chloride (1.69 g, 9.09 mmol), *N*-cyclopropyl-4-nitrobenzamide (**296f**) was obtained as a pale yellow solid (1.71 g, 8.27 mmol, 91%).

R_f: 0.31 (silica, pentanes:ethyl acetate 1:1); **Mp:** 176-177 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.30 – 8.22 (m, 2H, Ar*H*), 7.94 – 7.86 (m, 2H, Ar*H*), 6.41 (s, 1H, N*H*), 2.92 (tq, *J* = 7.2, 3.7 Hz, 1H, C*H*), 0.91 (td, *J* = 7.1, 5.4 Hz, 2H, CH_2), 0.70 – 0.59 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.8, 149.6, 139.9, 128.0, 123.8, 23.4, 6.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3280 (m), 1639 (s), 1597 (w), 1533 (m), 1514 (s), 1350 (m), 1308 (m); **HRMS** (APCI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{11}N_2O_3^+$ 207.0764; Found 207.0761.

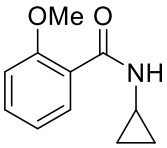
***N*-Cyclopropyl-3-methoxybenzamide** (**296g**)



Following GP A, using 3-methoxybenzoyl chloride (1.55 g, 9.09 mmol), *N*-cyclopropyl-3-methoxybenzamide (**296g**) was obtained as a pale yellow solid (1.88 g, 8.90 mmol, 98%).

R_f: 0.31 (silica, pentanes:ethyl acetate 1:1); **Mp:** 74-76 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.29 (s, 1H, Ar*H*), 7.23 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.19 (d, *J* = 7.7 Hz, 1H, Ar*H*), 6.96 (ddd, *J* = 8.0, 2.7, 1.2 Hz, 1H, Ar*H*), 6.39 (s, 1H, N*H*), 3.78 (s, 1H, OCH_3), 2.84 (tt, *J* = 7.2, 3.5 Hz, 1H, C*H*), 0.92 – 0.69 (m, 2H, CH_2), 0.65 – 0.43 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.8, 159.7, 135.8, 129.4, 118.6, 117.6, 112.2, 55.4, 23.1, 6.7; **IR** (film): $\tilde{\nu}$ = 3295 (w), 1638 (m), 1582 (m), 1527 (m), 1485 (m), 1286 (m), 1247 (m), 1040 (m), 732 (s); **HRMS** (ESI) calcd. for $C_{11}H_{13}NNaO_2^+$ $[M+Na]^+$ 214.0838; Found 214.0842.

***N*-Cyclopropyl-2-methoxybenzamide** (**296h**)

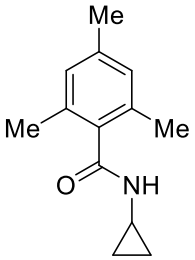


Following GP A, using 2-methoxybenzoyl chloride (0.853 g, 5.00 mmol), *N*-cyclopropyl-3-methoxybenzamide (**296h**) was obtained as a colorless solid (0.586 g, 3.06 mmol, 61%) after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.36 (silica, pentanes:ethyl acetate 1:1); **Mp:** 56-58 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.19 (dq, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 7.89 (s, 1H, N*H*), 7.40 (ddq, *J* = 8.7, 7.3, 1.6 Hz, 1H, Ar*H*), 7.04 (ddt, *J* = 8.9, 7.6,

1.5 Hz, 1H, Ar*H*), 6.92 (dq, *J* = 8.3, 1.2 Hz, 1H, Ar*H*), 3.91 (s, 3H, OCH_3), 2.91 (tq, *J* = 7.4, 3.8 Hz, 1H, C*H*), 0.86 – 0.78 (m, 2H, CH_2), 0.61 – 0.52 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.5, 157.3, 132.6, 132.1, 121.3, 121.2, 111.2, 55.8, 22.7, 6.7; **IR** (film): $\tilde{\nu}$ = 3393 (w), 3002 (w), 1651 (s), 1600 (m), 1525 (s), 1484 (s), 1295 (m), 1240 (s), 1020 (m), 756 (m); **HRMS** (ESI) calcd. for $C_{11}H_{13}NNaO_2^+$ $[M+Na]^+$ 214.0838; Found 214.0843.

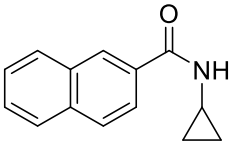
***N*-Cyclopropyl-2,4,6-trimethylbenzamide (296i)**



Following GP A, using 2,4,6-trimethylbenzoyl chloride (1.66 g, 9.09 mmol), *N*-cyclopropyl-2,4,6-trimethylbenzamide (**296i**) was obtained as a white solid (1.70 g, 8.36 mmol, 92%).

R_f: 0.40 (silica, dichloromethane); **Mp:** 133-135 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.81 (s, 2H, Ar*H*), 5.76 (s, 1H, N*H*), 2.90 (dqd, *J* = 7.2, 3.5, 1.4 Hz, 1H, C*H*), 2.25 (s, 9H, CH_3), 0.92 – 0.79 (m, 2H, CH_2), 0.63 – 0.52 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.0, 138.4, 134.6, 134.1, 128.1, 22.6, 21.0, 19.0, 6.8; **IR** (film): $\tilde{\nu}$ = 3223 (w), 1633 (m), 1536 (m), 1310 (w), 1265 (m), 856 (m), 734 (s); **HRMS** (ESI) calcd. for $C_{13}H_{17}NNaO^+$ $[M+Na]^+$ 226.1202; Found 226.1206.

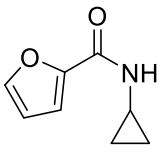
***N*-Cyclopropyl-2-naphthamide (296j)**



Following GP A, using 2-naphthoyl chloride (1.73 g, 9.09 mmol), *N*-cyclopropyl-2-naphthamide (**296j**) was obtained as a white solid (1.90 g, 8.99 mmol, 99%).

R_f: 0.32 (silica, dichloromethane); **Mp:** 179-181 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 1.7 Hz, 1H, Ar*H*), 7.92 – 7.83 (m, 3H, Ar*H*), 7.80 (dd, *J* = 8.5, 1.8 Hz, 1H, Ar*H*), 7.54 (pd, *J* = 6.9, 1.6 Hz, 2H, Ar*H*), 6.45 (s, 1H, N*H*), 2.97 (tq, *J* = 7.2, 3.7 Hz, 1H, C*H*), 0.90 (td, *J* = 7.0, 5.2 Hz, 2H, CH_2), 0.77 – 0.59 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.9, 134.7, 132.6, 131.6, 128.9, 128.4, 127.7, 127.6, 127.2, 126.7, 123.5, 23.2, 6.8; **IR** (film): $\tilde{\nu}$ = 3243 (m), 3056 (w), 1623 (s), 1538 (s), 1314 (m), 1043 (w), 870 (m), 782 (m); **HRMS** (ESI) calcd. for $C_{14}H_{13}NNaO^+$ $[M+Na]^+$ 234.0889; Found 234.0890.

***N*-Cyclopropylfuran-2-carboxamide (296k)**

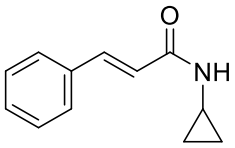


Following GP A, using 2-furoyl chloride (1.19 g, 9.09 mmol), *N*-cyclopropylfuran-2-carboxamide (**296k**) was obtained as an off-white solid (1.31 g, 8.67 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (t, *J* = 3.1 Hz, 1H, Ar*H*), 7.13 – 7.03 (m, 1H, Ar*H*), 6.53 – 6.40 (m, 2H, Ar*H*, N*H*), 2.85 (tq, *J* = 7.2, 3.7 Hz, 1H, C*H*), 0.84 (tt, *J* = 6.7, 4.1 Hz, 2H, CH_2), 0.66 – 0.54 (m, 2H, CH_2).

^{1}H NMR data correspond to the reported values.[119]

N-Cyclopropylcinnamamide (**296l**)

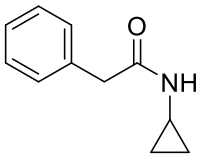


Following GP A, using cinnamoyl chloride (1.52 g, 9.09 mmol), N-cyclopropylcinnamamide (**296l**) was obtained as a white solid (1.25 g, 6.68 mmol, 73%) after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.32 (silica, pentanes:ethyl acetate 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 15.6 Hz, 1H, vinyl*H*), 7.51 – 7.45 (m, 2H, Ar*H*), 7.38 – 7.31 (m, 3H, Ar*H*), 6.35 (d, *J* = 15.6 Hz, 1H, vinyl*H*), 5.90 (brs, 1H, N*H*), 2.86 (tq, *J* = 7.1, 3.6 Hz, 1H, C*H*), 0.87 – 0.80 (m, 2H, CH_2), 0.62 – 0.52 (m, 2H, CH_2).

^{1}H NMR data correspond to the reported values.[272]

***N*-Cyclopropyl-2-phenylacetamide** (**296m**)

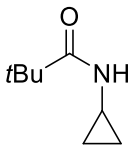


Following GP A, using 2-phenylacetyl chloride (1.41 g, 9.09 mmol), *N*-cyclopropyl-2-phenylacetamide (**296m**) was obtained as a white solid (1.52 g, 8.67mmol, 95%).

R_f: 0.36 (silica, dichloromethane:ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.38 – 7.27 (m, 3H, Ar*H*), 7.23 (dd, *J* = 6.8, 1.8 Hz, 2H, Ar*H*), 5.44 (s, 1H, N*H*), 3.54 (s, 2H, CH_2), 2.66 (tq, *J* = 7.1, 3.6 Hz, 1H, C*H*), 0.75 – 0.67 (m, 2H, CH_2), 0.44 – 0.33 (m, 2H, CH_2).

^{1}H NMR data correspond to the reported values.[273]

***N*-Cyclopropylpivalamide** (**296n**)

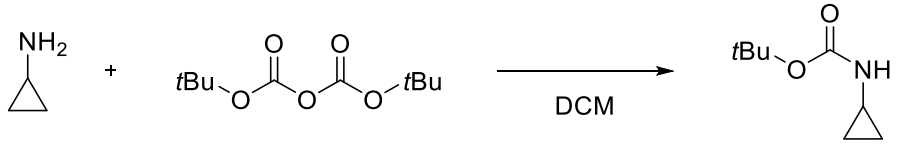


Following GP A, using pivaloyl chloride (1.32 g, 11.0 mmol), *N*-cyclopropylpivalamide (**296n**) was obtained as a white solid (0.90 g, 6.37 mmol, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71 (s, 1H, N*H*), 2.76 – 2.60 (m, 1H, C*H*), 1.16 (s, 9H, CH_3), 0.86 – 0.71 (m, 2H, CH_2), 0.57 – 0.36 (m, 2H, CH_2).

^{1}H NMR data correspond to the reported values.[274]

***tert*-Butyl cyclopropylcarbamate** (**296o**)



Following a modified version of a reported procedure,[275] to a solution of cyclopropylamine (1.40 mL, 20.0 mmol, 1.0 equiv.) in dichloromethane (20 mL) was slowly added a solution of di-*tert*-butyl dicarbonate

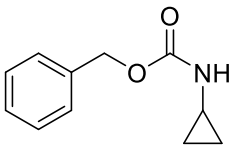
[272] Zhang, B.; Feng, P.; Cui, Y.; Jiao, N. *Chem. Commun.* **2012**, *48*, 7280.
[273] Tam, E.; Rita.; Liu, Y.; Chen, A. *Eur. J. Org. Chem.* **2015**, 1100.
[274] Miyamura, S.; Araki, M.; Suzuki, T.; Yamaguchi, J.; Itami. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 846.
[275] Tars, K.; Leitan, J.; Kazaks, A.; Zelencova, D.; Liepinsh, E.; Kuka, J.; Makrecka, M.; Lola, D.; Andrianovs, V.; Gustina, D.; Grinberga, S.; Liepinsh, E.; Kalvinsh, I.; Dambrova, M.; Loza, E.; Pugovics, O. *J. Med. Chem.* **2014**, *57*, 2213.

(4.85 g, 22.0 mmol, 1.1 equiv.) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at for 16 hours room temperature. Upon completion, the mixture was quenched by addition of 1 N HCl (10 mL). The aqueous layer was then extracted with dichloromethane. The organic layer was washed with 1 M NaOH (10 mL) and brine (10 mL), and dried over Na_2SO_4, filtered and concentrated *in vacuo*. *tert*-Butyl cyclopropylcarbamate (**296o**) was obtained as a white solid (3.11 g, 19.8 mmol, 99%), which was pure enough to be used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.70 (brs, 1H, N*H*), 2.57 – 2.47 (m, 1H, C*H*), 1.44 (s, 9H, CH_3), 0.72 – 0.63 (m, 2H, CH_2), 0.53 – 0.39 (m, 2H, CH_2).

^{1}H NMR data correspond to the reported values.[275]

Benzyl cyclopropylcarbamate (296p)

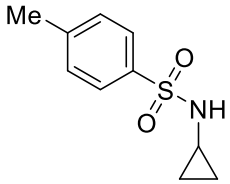


Following GP A, using benzyl chloroformate (1.55 g, 9.09 mmol), benzyl cyclopropylcarbamate (**296p**) was obtained as a colorless solid (1.72 g, 9.00 mmol, 99%).

^{1}H NMR (400 MHz, CDCl3): δ = 7.41 – 7.29 (m, 5H, Ar*H*), 5.10 (s, 2H, CH_2), 5.01 – 4.80 (m, 1H, N*H*), 2.60 (ttd, *J* = 7.0, 3.6, 2.0 Hz, 1H, C*H*), 0.76 – 0.69 (m, 2H, CH_2), 0.55 – 0.49 (m, 2H, CH_2).

^{1}H NMR data correspond to the reported values.[114]

***N*-cyclopropyl-4-methylbenzenesulfonamide** (**296q**)

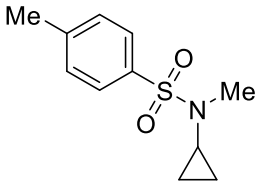


Following GP A, using tosyl chloride (1.73 g, 9.09 mmol), *N*-cyclopropyl-4-methylbenzenesulfonamide (**296q**) was obtained as a colorless solid (1.90 g, 9.00 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.32 (d, *J* = 8.0 Hz, 2H, Ar*H*), 4.94 (s, 1H, N*H*), 2.43 (s, 3H, CH_3), 2.23 (tt, *J* = 6.6, 3.7 Hz, 1H, C*H*), 0.65 – 0.52 (m, 4H, CH_2).

^{1}H NMR data correspond to the reported values.[276]

N-Cyclopropyl-N,4-dimethylbenzenesulfonamide (296r)



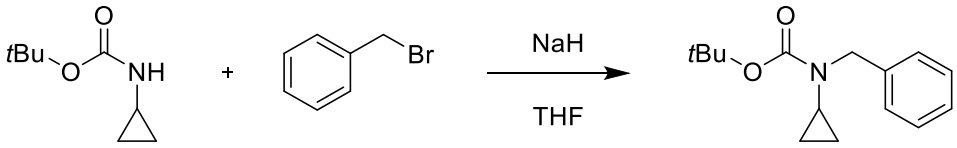
Following GP A, using *N*-cyclopropyl-methylamine hydrochloride (0.323 g, 3.00 mmol, 1.1 equiv.), triethylamine (0.84 mL, 6.0 mmol, 2.2 equiv.) and tosyl chloride (0.535 g, 2.80 mmol, 1.0 equiv.), *N*-cyclopropyl-*N*,4-dimethylbenzenesulfonamide (**296r**) was obtained as a yellow solid (0.580 g, 2.58 mmol, 92%).

R_f: 0.60 (silica, pentanes:ethyl acetate 3:1); **Mp:** 73-76 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.34 (d, *J* = 7.7 Hz, 2H, Ar*H*), 2.73 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 1.78 (tt, *J* = 6.9, 3.6 Hz, 1H, C*H*), 0.90 – 0.83 (m, 2H, CH_2), 0.72 – 0.64 (m, 2H, CH_2); **^{13}C NMR**

[276] O'Sullivan, S.; Doni, E.; Tuttle, T.; Murphy. J. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 474.

(101 MHz, $CDCl_3$): δ = 143.5, 132.8, 129.5, 128.0, 37.5, 32.1, 21.5, 7.5; **IR** (film): $\tilde{\nu}$ = 2963 (w), 1596 (w), 1456 (m), 1365 (m), 1338 (s), 1151 (s), 1089 (s), 1034 (m), 817 (s), 691 (s); **HRMS** (ESI) calcd. for $C_{11}H_{15}NNaO_2S^+$ $[M+Na]^+$ 248.0716; Found 248.0721.

***tert*-Butyl benzyl(cyclopropyl)carbamate** (**296s**)

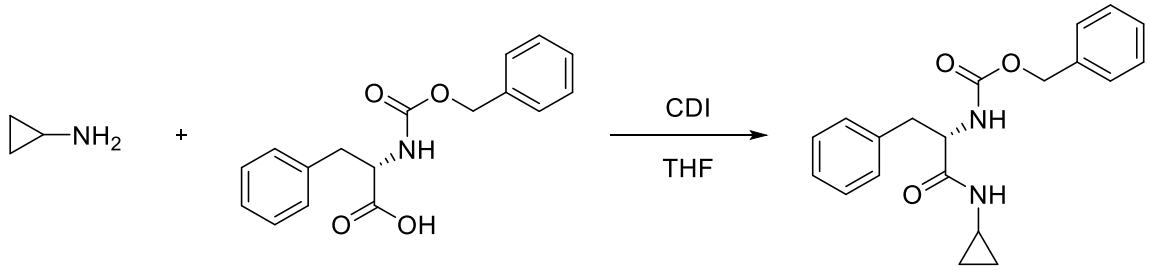


Following a modified version of a reported procedure,[47] to a solution of benzyl bromide (0.616 g, 3.60 mmol, 1.2 equiv.) and NaH (60% dispersion in mineral oil, 156 mg, 3.90 mmol, 1.3 equiv.) in DMF (10 mL) was slowly added a solution of *tert*-butyl cyclopropylcarbamate (0.472 g, 3.00 mmol, 1.0 equiv.) in DMF (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours. Upon completion, the mixture was quenched by addition of 1 N HCl (10 mL). The aqueous layer was then extracted with dichloromethane. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. *tert*-Butyl benzyl(cyclopropyl)carbamate (**296s**) was obtained as a bright yellow oil (0.540 g, 2.18 mmol, 73%) after purification by column chromatography on silica using 8:1 pentanes:ethyl acetate as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.15 (m, 5H, Ar*H*), 4.39 (s, 2H, NCH_2), 2.42 (s, 1H, C*H*), 1.42 (s, 9H, CH_3), 0.74 – 0.53 (m, 4H, CH_2).

^{1}H NMR data correspond to the reported values.[47]

Benzyl (S)-(1-(cyclopropylamino)-1-oxo-3-phenylpropan-2-yl)carbamate (**296t**)



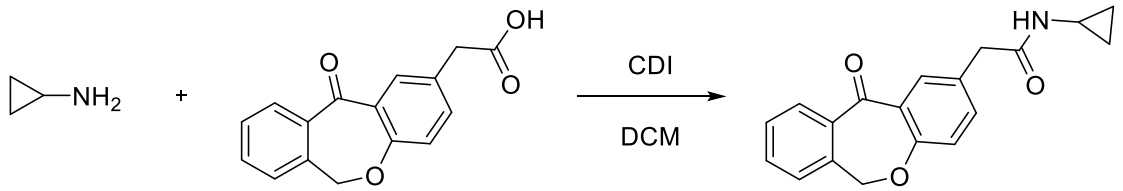
Following a modified version of a reported procedure,[277] Boc-L-phenylalanine (898 mg, 3.00 mmol, 1.0 equiv.) and CDI (486 mg, 3.00 mmol, 1.0 equiv.) were suspended in THF (15 mL). The resulting mixture was stirred for 2 hour before adding cyclopropylamine (185 mg, 3.30 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for another 16 hours. Upon completion, the mixture was quenched by addition of 2 M NaOH (5 mL x 2). The aqueous layer was then extracted with dichloromethane. The organic layer was washed with 1 N HCl (10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Benzyl (S)-(1-(cyclopropylamino)-1-oxo-3-

[277] Shang, M.; Wang, M.-M.; Saint-Denis, T. G.; Li, M.-H.; Dai, H.-X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2017**, *56*, 5317.

phenylpropan-2-yl)carbamate (**296t**) was obtained as a white solid (480 mg, 1.44 mmol, 48%) after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.35 (silica, pentane:ethyl acetate 1:1); **Mp:** 161-163 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.38 – 7.22 (m, 8H, Ar*H*), 7.17 (d, *J* = 7.2 Hz, 2H, Ar*H*), 5.69 (s, 1H, N*H*), 5.43 (d, *J* = 8.1 Hz, 1H, N*H*), 5.07 (s, 2H, OCH_2), 4.28 (q, *J* = 7.6 Hz, 1H, C*H*N), 3.11 (dd, *J* = 13.6, 6.1 Hz, 1H, CH_2), 2.96 (dd, *J* = 13.6, 8.1 Hz, 1H, CH_2), 2.58 (tq, *J* = 7.1, 3.6 Hz, 1H, C*H*N), 0.72 – 0.60 (m, 2H, CH_2), 0.34 – 0.19 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.9, 155.8, 136.5, 136.1, 129.3, 128.7, 128.5, 128.2, 128.0, 127.1, 67.1, 56.3, 38.9, 22.4, 6.5, 6.3; **IR** (film): $\tilde{\nu}$ =3298 (m), 1690 (m), 1652 (s), 1533 (m), 1286 (w), 1261 (w), 1040 (w), 747 (w), 698 (w); **HRMS** (APPI) calcd. for $C_{20}H_{22}N_2NaO_3^+$ $[M+Na]^+$ 361.1523; Found 361.1518.

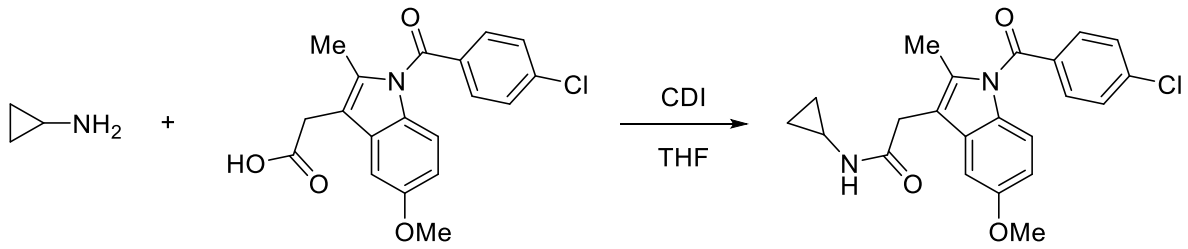
N-Cyclopropyl-2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetamide (**296u**)



Following a modified version of a reported procedure,[277] Isoxepac (536 mg, 2.00 mmol, 1.0 equiv.) and CDI (324 mg, 2.00 mmol, 1.0 equiv.) were suspended in DCM (10 mL). The resulting mixture was stirred for 1 hour before adding cyclopropylamine (123 mg, 2.20 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for another 2 hours. Upon completion, the mixture was quenched by addition of 2 M NaOH (5 mL x 2). The aqueous layer was then extracted with dichloromethane. The organic layer was washed with 1 N HCl (10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. N-Cyclopropyl-2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetamide (**296u**) was obtained as a white solid (550 mg, 1.79 mmol, 90%), which was found pure enough to be used without further purification.

R_f: 0.35 (silica, pentane:ethyl acetate 1:3); **Mp:** 161-163 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 2.3 Hz, 1H, Ar*H*), 7.88 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.57 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.48 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.43 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar*H*), 7.37 (d, *J* = 7.4 Hz, 1H, Ar*H*), 7.04 (d, *J* = 8.4 Hz, 1H, Ar*H*), 5.72 (s, 1H, N*H*), 5.19 (s, 2H, OCH_2), 3.53 (s, 2H, CH_2), 2.68 (tq, *J* = 7.3, 3.6 Hz, 1H, C*H*), 0.73 (td, *J* = 7.1, 5.3 Hz, 2H, CH_2), 0.52 – 0.35 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 190.8, 172.1, 160.5, 140.3, 136.3, 135.4, 132.9, 132.3, 129.4, 129.3, 128.6, 127.9, 125.2, 121.5, 73.6, 42.5, 22.9, 6.6; **IR** (film): $\tilde{\nu}$ = 3272 (w), 3057 (w), 1643 (s), 1609 (m), 1541 (m), 1487 (s), 1412 (m), 1300 (s), 1138 (m), 1016 (m), 801 (w), 735 (m); **HRMS** (ESI) calcd. for $C_{19}H_{17}NNaO_3^+$ $[M+Na]^+$ 330.1101; Found 330.1104.

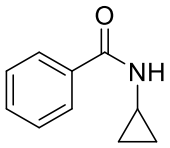
2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)-N-cyclopropylacetamide (**296v**).



Following a modified version of a reported procedure,[277] indomethacin (1.07 g, 3.00 mmol, 1.0 equiv.) and CDI (486 mg, 3.00 mmol, 1.0 equiv.) were suspended in THF (10 mL). The resulting mixture was stirred for 2 hours before adding cyclopropylamine (188 mg, 3.30 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for another 2 hours. Upon completion, the mixture was quenched by addition of 2 M NaOH (5 mL x 2). The aqueous layer was extracted with dichloromethane. The combined organic layers were then washed with 1 N HCl (10 mL) and extracted with dichloromethane. The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. 2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)-N-cyclopropylacetamide (**296v**) was obtained as a yellow solid (1.14 g, 2.88 mmol, 96%), which was found pure enough to be used without further purification.

R_f: 0.20 (silica, pentanes:ethyl acetate 3:7); **Mp:** 166-168 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.48 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.88 – 6.82 (m, 2H, Ar*H*), 6.69 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 5.70 (s, 1H, N*H*), 3.82 (s, 3H, OCH_3), 3.61 (s, 2H, CH_2), 2.65 (tq, *J* = 7.1, 3.6 Hz, 1H, C*H*), 2.36 (s, 3H, CH_3), 0.76 – 0.68 (m, 2H, CH_2), 0.42 – 0.33 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.3, 168.3, 156.3, 139.6, 136.2, 133.5, 131.2, 130.8, 130.2, 129.2, 115.1, 112.8, 112.3, 100.7, 55.7, 32.2, 22.7, 13.2, 6.7; **IR** (film): $\tilde{\nu}$ = 3268 (w), 3006 (w), 2929 (w), 1676 (s), 1644 (s), 1541 (m), 1476 (s), 1356 (s), 1314 (s), 1223 (s), 1147 (m), 1088 (m), 908 (m), 832 (m), 730 (s); **HRMS** (APPI) calcd. for $C_{22}H_{21}ClN_2O_3^+$ $[M]^+$ 396.1235; Found 396.1242.

***N*-Cyclopropylbenzamide** (**296w**)

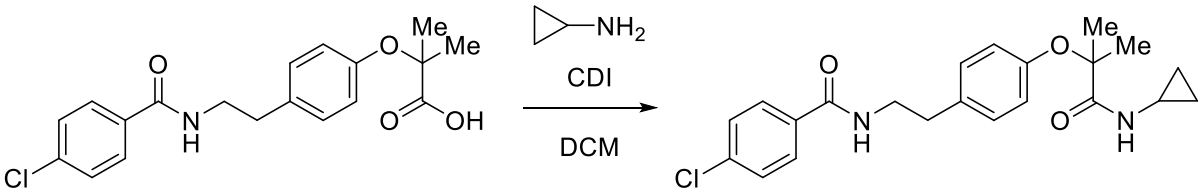


Following GP A, using benzoyl chloride (1.28 g, 9.09 mmol), *N*-cyclopropylbenzamide (**296w**) was obtained as a white solid (1.38 g, 8.57 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 – 7.67 (m, 2H, Ar*H*), 7.49 – 7.43 (m, 1H, Ar*H*), 7.41 – 7.34 (m, 2H, Ar*H*), 6.46 (s, 1H, N*H*), 2.88 (tq, *J* = 7.1, 3.7 Hz, 1H, C*H*), 0.87 – 0.78 (m, 2H, CH_2), 0.66 – 0.50 (m, 2H, CH_2).

^{1}H NMR data correspond to the reported values.[278]

4-Chloro-N-(4-((1-(cyclopropylamino)-2-methyl-1-oxopropan-2-yl)oxy)phenethyl)benzamide (**296x**)



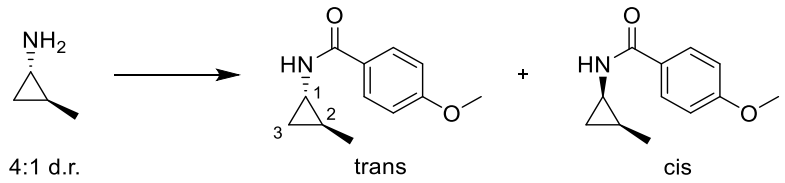
Following a modified procedure,[277] bezafibrate (722 mg, 2.00 mmol, 1.0 equiv.) and CDI (324 mg, 2.00 mmol, 1.0 equiv.) were suspended in DCM (10 mL) and stirred for 1 hour before adding cyclopropylamine (123 mg, 2.20 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for another 2 hours. Upon completion, the mixture was washed with 2 M NaOH (5 mL x 2) and extracted with dichloromethane. The organic layer was then washed with 1 N HCl (10 mL) and and extracted with dichloromethane. The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in*

[278] Sureshbabu, P.; Sadaf, A.; Chaudhary, P.; Kandasamy, J. *Org. Biomol. Chem.* **2019***, 17*, 845.

vacuo. 4-chloro-N-(4-((1-(cyclopropylamino)-2-methyl-1-oxopropan-2-yl)oxy)phenethyl)benzamide (**296x**) was obtained as a white solid (768 mg, 1.92 mmol, 96%) without further purification.

R_f: 0.40 (silica, pentane:ethyl acetate 1:2); **Mp:** 182-184 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.68 – 7.56 (m, 2H, Ar*H*), 7.45 – 7.31 (m, 2H, Ar*H*), 7.17 – 7.05 (m, 2H, Ar*H*), 6.90 – 6.80 (m, 2H, Ar*H*), 6.72 (s, 1H, N*H*), 6.12 (s, 1H, N*H*), 3.67 (td, *J* = 7.0, 5.8 Hz, 2H, NCH_2), 2.88 (t, *J* = 7.0 Hz, 2H, ArCH_2), 2.76 (tq, *J* = 7.3, 3.8 Hz, 1H, C*H*), 1.47 (s, 6H, CH_3), 0.88 – 0.68 (m, 2H, CH_2), 0.59 – 0.39 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 176.1, 166.3, 152.9, 137.7, 133.6, 132.9, 129.5, 128.8, 128.2, 121.5, 81.4, 41.2, 34.8, 25.0, 22.4, 6.4; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3294 (m), 2987 (w), 2926 (w), 2868 (w), 1640 (s), 1596 (m), 1550 (s), 1506 (s), 1228 (s), 1150 (s), 850 (m), 753 (m); **HRMS** (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{26}ClN_2O_3^+$ 401.1626; Found 401.1632.

4-Methoxy-*N*-2-methylcyclopropyl)benzamide (**342a**)



Following a modified version of a reported procedure,[205] to a solution of 2-methylcyclopropan-1-amine (250 mg, 3.52 mmol, 4:1 d.r., ordered from Fluorochem) and Et_3N (0.54 mL, 3.9 mmol, 1.1 equiv.) in dichloromethane (10 mL) was slowly added a solution of 4-methoxybenzoyl chloride (658 mg, 3.87 mmol, 1.1 equiv.) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature usually for 16 hours. Upon completion, the mixture was quenched by the addition of 1 N HCl (10 mL). The aqueous layer was then extracted with dichloromethane. The organic extract was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. 4-Methoxy-*N*-2-methylcyclopropyl)benzamide **342a** was obtained as a white solid (655 mg, 3.20 mmol, 4:1 d.r., 91%) after first purification by column chromatography on silica using 3:2 pentanes:ethyl acetate as eluent. Second purification was performed by column chromatography on silica using 3:2 pentanes:ethyl acetate as eluent, ***trans*-342a** (272 mg) and ***cis*-342a** (79 mg) were obtained separately, together with the rest of product **342a** recovered as a mixture of diastereomers.

4-Methoxy-*N*-*trans*-2-methylcyclopropyl)benzamide (***trans*-342a**)

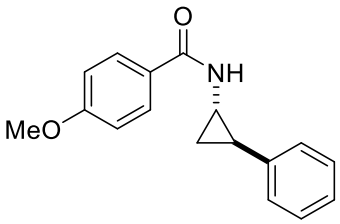
R_f: 0.37 (silica, pentanes:ethyl acetate 1:1); **Mp:** 94-96 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.75 – 7.62 (m, 2H, Ar*H*), 6.94 – 6.83 (m, 2H, Ar*H*), 6.20 (s, 1H, N*H*), 3.83 (s, 3H, OCH_3), 2.56 (dq, *J* = 6.9, 3.4 Hz, 1H, NC*H*), 1.13 (d, *J* = 6.1 Hz, 3H, CH_3), 0.95 (ddt, *J* = 12.2, 6.2, 3.2 Hz, 1H, C*H*CH_3), 0.73 (ddd, *J* = 9.2, 5.4, 3.8 Hz, 1H, CH_2), 0.61 (dt, *J* = 7.2, 5.7 Hz, 1H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.1, 162.1, 128.6, 126.7, 113.6, 55.4, 30.4, 17.2, 14.9 (signals of C2 and C3 are overlapped); **IR** (film): $\tilde{\nu}$ = 3274 (m), 3003 (w), 2952 (w), 1624 (s), 1606 (s), 1574 (m), 1541 (s), 1254 (s), 1031 (m), 843 (m); **HRMS** (APCI) calcd. for $C_{12}H_{15}NNaO_2^+$ $[M+Na]^+$ 228.0995; Found 228.0993.

4-Methoxy-*N*-*cis*-2-methylcyclopropyl)benzamide (***cis*-342a**)

R_f: 0.26 (silica, pentanes:ethyl acetate 1:1); **Mp:** 89-91 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.76 – 7.69 (m, 2H, Ar*H*), 6.92 – 6.87 (m, 2H, Ar*H*), 6.07 (s, 1H, N*H*), 3.84 (s, 3H, OCH_3), 2.90 (dddd, *J* = 9.9, 7.0, 4.0,

3.0 Hz, 1H, NC*H*), 1.15 – 1.07 (m, 4H, CH_3 + CH_2), 1.03 (dddd, *J* = 8.8, 5.4, 3.2, 1.2 Hz, 1H, CH_2), 0.26 – 0.15 (m, 1H, C*H*CH$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.7, 162.1, 128.6, 126.9, 113.7, 55.4, 27.5, 13.2, 12.5, 11.7; **IR** (film): $\tilde{\nu}$ = 3292 (m), 2958 (w), 1631 (s), 1606 (s), 1499 (s), 1252 (s), 1178 (m), 1028 (m), 844 (m); **HRMS** (APCI) calcd. for $C_{12}H_{15}NNaO_2^+$ $[M+Na]^+$ 228.0995; Found 228.0993.

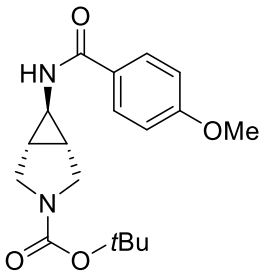
4-Methoxy-*N*-(*trans*-2-phenylcyclopropyl)benzamide (**342b**)



Following GP A, using *trans*-2-phenylcyclopropylamine hydrochloride (635 mg, 3.74 mmol, 1.1 equiv., ordered from Acros), triethylamine (1.0 mL, 7.2 mmol, 2.0 equiv.) and 4-methoxybenzoyl chloride (607 mg, 3.56 mmol, 1.0 equiv.), 4-Methoxy-*N*-(*trans*-2-phenylcyclopropyl)benzamide (**342b**) was obtained as a white solid (0.92 g, 3.4 mmol, 97%).

R_f: 0.50 (silica, pentanes:ethyl acetate 1:1); **Mp:** 153-155 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 – 7.65 (m, 2H, Ar*H*), 7.31 – 7.26 (m, 2H, Ar*H*), 7.24 – 7.15 (m, 3H, Ar*H*), 6.97 – 6.83 (m, 2H, Ar*H*), 6.39 (s, 1H, N*H*), 3.84 (s, 3H, OCH_3), 3.06 (tt, *J* = 7.4, 3.4 Hz, 1H, NC*H*), 2.16 (ddd, *J* = 9.8, 6.3, 3.4 Hz, 1H, PhC*H*), 1.38 – 1.20 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.1, 162.2, 140.4, 128.7, 128.4, 126.6, 126.5, 126.1, 113.7, 55.4, 32.5, 24.9, 16.3; **IR** (film): $\tilde{\nu}$ = 3291 (w), 1632 (s), 1606 (s), 1500 (s), 1255 (s), 1029 (m), 845 (m); **HRMS** (ESI) calcd. for $C_{17}H_{17}NNaO_2^+$ $[M+Na]^+$ 290.1151; Found 290.1151.

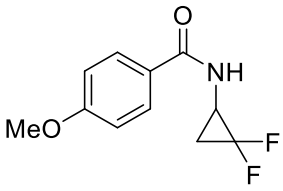
(1*R*,5*S*,6*S*)-*tert*-Butyl 6-(4-methoxybenzamido)-3-azabicyclo[3.1.0]hexane-3-carboxylate (**342c**)



Following GP A, using (1*R*,5*S*,6*S*)-*tert*-butyl 6-amino)-3-azabicyclo[3.1.0] hexane-3-carboxylate (495 mg, 2.50 mmol, 1.0 equiv.), triethylamine (0.40 mL, 2.9 mmol, 1.1 equiv.) and 4-methoxybenzoyl chloride (470 mg, 2.76 mmol, 1.1 equiv.), (1*R*,5*S*,6*S*)-*tert*-butyl 6-(4-methoxybenzamido)-3-azabicyclo[3.1.0]hexane-3-carboxylate (**342c**) was obtained as a beige solid (740 mg, 2.23 mmol, 89%) after purification by column chromatography on silica using 2:3 pentanes:ethyl acetate as eluent.

R_f: 0.29 (silica, pentanes:ethyl acetate 2:3); **Mp:** 160-162 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.74 – 7.64 (m, 2H, Ar*H*), 6.93 – 6.82 (m, 2H, Ar*H*), 6. 41 – 6.24 (m, 1H, N*H*), 3.82 (d, *J* = 1.9 Hz, 3H, OCH_3), 3.77 – 3.65 (m, 2H, CH_2), 3.45 – 3.34 (m, 2H, CH_2), 2.60 – 2.55 (m, 1H, NC*H*), 1.79 – 1.68 (m, 2H, C*H*), 1.42 (d, *J* = 1.4 Hz, 9H, CH_3); Mixture of 2 rotamers with almost 1:1 ratio. They are not completely resolved; **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.0, 162.2, 154.5, 128.7, 126.3, 113.7, 79.5, 55.4, 47.8, 47.5, 33.1, 28.4, 25.2, 23.7; Mixture of 2 rotamers with almost 1:1 ratio. They are not completely resolved; **IR** (film): $\tilde{\nu}$ = 3302 (w), 2974 (w), 2931 (w), 2873 (w), 1694 (s), 1606 (s), 1502 (s), 1393 (s), 1253 (s), 1172 (s), 1115 (s), 1029 (m), 844 (w), 769 (w), 730 (w); **HRMS** (ESI) calcd. for $C_{18}H_{24}N_2NaO_4^+$ $[M+Na]^+$ 355.1628; Found 355.1631.

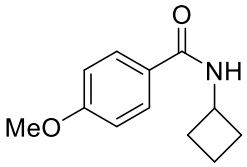
N-(2,2-Difluorocyclopropyl)-4-methoxybenzamide (**342d**)



Following GP A, using 2,2-difluorocyclopropylamine hydrochloride (250 mg, 1.93 mmol, 1.0 equiv., ordered from Fluorochem), triethylamine (0.60 mL, 4.3 mmol, 2.2 equiv.) and 4-methoxybenzoyl chloride (370 mg, 2.17 mmol, 1.1 equiv.), *N*-(2,2-difluorocyclopropyl)-4-methoxybenzamide (**342d**) was obtained as a white solid (320 mg, 1.41 mmol, 73%) after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.25 (silica, pentanes:ethyl acetate 2:1); **Mp:** 128-129 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.91 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.39 (s, 1H, N*H*), 3.84 (s, 3H, OCH_3), 3.51 (dtq, *J* = 12.1, 5.9, 3.4, 3.0 Hz, 1H, C*H*), 1.87 (dtd, *J* = 13.5, 9.3, 6.4 Hz, 1H, CH_2), 1.50 – 1.35 (m, 1H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.8, 162.6, 128.9, 125.5, 113.8, 111.1 (dd, *J* = 291.4, 284.3 Hz), 55.4, 30.8 (dd, *J* = 15.0, 9.4 Hz), 19.3 (t, *J* = 9.9 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -131.2 (d, *J* = 162.2 Hz, 1F), -143.6 (d, *J* = 162.2 Hz, 1F); **IR** (film): $\tilde{\nu}$ = 3307 (m), 1638 (s), 1608 (m), 1500 (s), 1471 (m), 1257 (s), 1222 (s), 1014 (m), 845 (m); **HRMS** (ESI) calcd. for $C_{11}H_{12}F_2NO_2^+$ $[M+H]^+$ 228.0831; Found 228.0843.

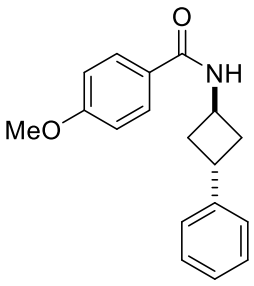
***N*-Cyclobutyl-4-methoxybenzamide** (**342e**)



Following GP A, using cyclobutylamine (523 mg, 7.40 mmol, 1.1 equiv.) and 4-methoxybenzoyl chloride (1.19 g, 7.00 mmol, 1.0 equiv.), *N*-cyclobutyl-4-methoxybenzamide (**342e**) was obtained as a white solid (1.08 g, 5.27 mmol, 75%).

R_f: 0.44 (silica, pentanes:ethyl acetate 1:1); **Mp:** 126-128 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.84 – 7.61 (m, 2H, Ar*H*), 7.00 – 6.82 (m, 2H, Ar*H*), 6.16 (s, 1H, N*H*), 4.58 (h, *J* = 8.1 Hz, 1H, C*H*), 3.84 (s, 3H, OCH_3), 2.53 – 2.32 (m, 2H, $CH_2CH_2CH_2$), 2.02 – 1.86 (m, 2H, CH_2), 1.76 (tt, *J* = 11.4, 6.5 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.0, 162.1, 128.6, 126.8, 113.7, 55.4, 45.1, 31.4, 15.2; **IR** (film): $\tilde{\nu}$ = 3305 (w), 2941 (w), 1628 (s), 1607 (s), 1503 (s), 1253 (s), 1030 (m), 844 (m); **HRMS** (ESI) calcd. for $C_{12}H_{16}NO_2^+$ $[M+H]^+$ 206.1176; Found 206.1175.

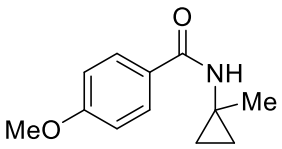
4-Methoxy-*N*-(*trans*-3-phenylcyclobutyl)benzamide (**342f**)



Following GP A, using *trans*-3-phenylcyclobutan-1-amine (250 mg, 1.70 mmol, 1.0 equiv., ordered from Fluorochem), triethylamine (0.27 mL, 1.9 mmol, 1.1 equiv.) and 4-methoxybenzoyl chloride (320 mg, 1.88 mmol, 1.1 equiv.), 4-methoxy-*N*-(*trans*-3-phenylcyclobutyl)benzamide **342f** was obtained as a white solid (448 mg, 1.59 mmol, 94%) after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.50 (silica, pentanes:ethyl acetate 1:1); **Mp:** 164-166 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.83 – 7.71 (m, 2H, Ar*H*), 7.39 – 7.26 (m, 4H, Ar*H*), 7.26 – 7.17 (m, 1H, Ar*H*), 6.98 – 6.87 (m, 2H, Ar*H*), 6.36 (d, *J* = 6.9 Hz, 1H, N*H*), 4.71 (ddtd, *J* = 14.2, 7.9, 6.3, 1.3 Hz, 1H, NC*H*), 3.86 (s, 3H, OCH_3), 3.71 – 3.57 (m, 1H, PhC*H*), 2.74 – 2.61 (m, 2H, CH_2), 2.55 – 2.43 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.5, 162.1, 144.8, 128.7, 128.5, 126.8, 126.5, 126.0, 113.7, 55.4, 43.7, 36.9, 34.6; **IR** (film): $\tilde{\nu}$ = 3338 (m), 2938 (w), 1628 (s), 1605 (m), 1499 (s), 1251 (s), 1031 (m); **HRMS** (ESI) calcd. for $C_{18}H_{20}NO_2^+$ $[M+H]^+$ 282.1489; Found 282.1480.

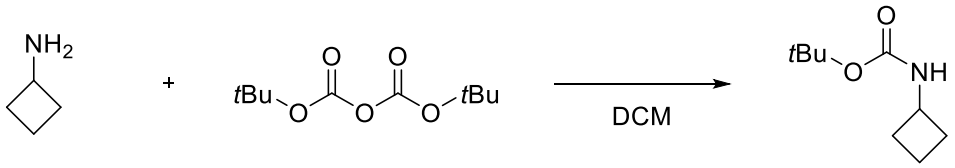
4-Methoxy-*N*-(1-methylcyclopropyl)benzamide (**342g**)



Following GP A, using 1-methylcyclopropan-1-amine hydrochloride (396 mg, 3.68 mmol, 1.1 equiv.), triethylamine (1.0 mL, 7.2 mmol, 2.1 equiv.) and 4-methoxybenzoyl chloride (586 mg, 3.43 mmol, 1.0 equiv.), 4-Methoxy-*N*-(1-methylcyclopropyl)benzamide **342g** (689 mg, 3.36 mmol, 98%) was obtained as a white solid.

R_f: 0.44 (silica, pentanes:ethyl acetate 2:3); **Mp:** 130-132 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.75 – 7.63 (m, 2H, Ar*H*), 6.92 – 6.85 (m, 2H, Ar*H*), 6.53 – 6.35 (m, 1H, N*H*), 3.83 (d, *J* = 1.5 Hz, 3H, OCH_3, due to rotamers), 1.46 (s, 3H, CH_3), 0.86 – 0.80 (m, 2H, CH_2), 0.74 – 0.68 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.1, 162.0, 128.6, 127.1, 113.6, 55.4, 29.5, 22.9, 14.6; **IR** (film): $\tilde{\nu}$ = 3286 (m), 2962 (w), 1634 (s), 1605 (s), 1499 (s), 1252 (s), 1029 (m), 841 (m); **HRMS** (ESI) calcd. for $C_{12}H_{15}NNaO_2^+$ $[M+Na]^+$ 228.0995; Found 228.0996.

***tert*-Butyl cyclobutylcarbamate** (**342h**)

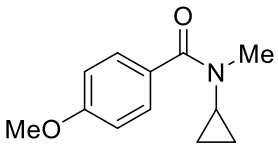


Following a modified version of a reported procedure,[275] to a solution of cyclobutylamine (1.70 mL, 20.0 mmol, 1.0 equiv.) in dichloromethane (20 mL) was slowly added a solution of di-*tert*-butyl dicarbonate (4.85 g, 22.0 mmol, 1.1 equiv.) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at for 16 hours room temperature. Upon completion, the mixture was quenched by addition of 1 N HCl (10 mL). The aqueous layer was then extracted with dichloromethane. The organic layer was washed with 1 M NaOH (10 mL) and brine (10 mL), and dried over Na_2SO_4, filtered and concentrated *in vacuo*. *tert*-Butyl cyclobutylcarbamate **342h** was obtained as a white solid (3.41 g, 19.9 mmol, 99%), which was pure enough to be used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.66 (s, 1H, N*H*), 4.29 – 3.91 (m, 1H, C*H*), 2.30 (q, *J* = 8.8 Hz, 2H, CH_2), 1.88 – 1.72 (m, 2H, CH_2), 1.72 – 1.53 (m, 2H, CH_2), 1.43 (s, 9H, CH_3).

^{1}H NMR data correspond to the reported values.[279]

***N*-Cyclopropyl-4-methoxy-*N*-methylbenzamide** (**349**)



Following GP A using *N*-cyclopropyl-methylamine hydrochloride (323 mg, 3.00 mmol, 1.1 equiv.), triethylamine (0.84 mL, 6.0 mmol, 2.1 equiv.) and 4-methoxybenzoyl chloride (478 mg, 2.80 mmol, 1.0 equiv.), *N*-cyclopropyl-4-methoxy-*N*-methylbenzamide (**349**) was obtained as a yellow oil (560 mg, 2.73 mmol, 97%) which solidified during storage.

[279] Li, P.; Ma, N.; Wang, Z.; Dai, Q.; Hu, C. *J. Org. Chem.* **2018**, 83, 8233.

R_f: 0.40 (silica, pentanes:ethyl acetate 2:3); **Mp:** 59-61 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.55 – 7.43 (m, 2H, Ar*H*), 6.94 – 6.82 (m, 2H, Ar*H*), 3.83 (s, 3H, OCH_3), 3.07 (s, 3H, NCH_3), 2.82 (tt, *J* = 7.0, 3.9 Hz, 1H, C*H*), 0.63 (d, *J* = 6.7 Hz, 2H, CH_2), 0.47 (p, *J* = 5.8, 5.0 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.2, 160.6, 129.4, 129.4, 113.1, 55.2, 35.6, 33.1, 9.4; **IR** (film): $\tilde{\nu}$ = 3010 (w), 2936(w), 1626 (s), 1607 (s), 1381 (s), 1250 (s), 1172 (m), 1027 (m), 842 (m); **HRMS** (ESI) calcd. for $C_{12}H_{15}NNaO_2^+$ $[M+Na]^+$ 228.0995; Found 228.0999.

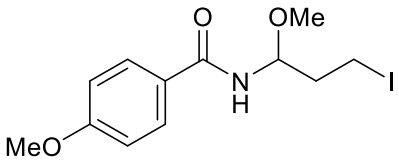
5.3.2 Halogenation of aminocyclopropanes inspired by the HLF reaction

General Procedure B (GP B):

In a glass vial, the correspondent aminocyclopropane (0.300 mmol, 1.0 equiv.), N-Iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.), methanol (14.4 μL, 0.360 mmol, 1.2 equiv.) and diphenyl phosphate (7.5 mg, 0.030 mmol, 0.10 equiv.) were dissolved in 1.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes, if not specified otherwise. After the completion of the reaction, the crude product was directly submitted to column chromatography on silica using pentanes and ethyl acetate as eluent.

Note: The obtained products were found heat-sensitive; in order to avoid their degradation, they were concentrated maintaining the heating bath of the rotatory evaporator below 30 °C and they were stored at -20 °C in the freezer. It is recommended that they are used for further transformations following a one-pot protocol, without isolation.

N-(3-Iodo-1-methoxypropyl)-4-methoxybenzamide (**298a**)

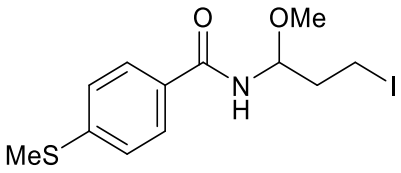


Following GP B, starting from N-cyclopropyl-4-methoxy benzamide **296a** (57.3 mg, 0.300 mmol), N-(3-iodo-1-methoxy propyl)-4-methoxybenzamide **298a** (88.8 mg, 0.255 mmol, 85%) was obtained as a yellow solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

For enantioselective version: in an oven dried microwave vial, N-cyclopropyl-4-methoxybenzamide **296a** (19.1 mg, 0.100 mmol, 1.0 equiv.), N-Iodosuccinimide (23.6 mg, 0.105 mmol, 1.05 equiv.), methanol (4.8 μL, 0.12 mmol, 1.2 equiv.) and (*R*)-TRIP (3.8 mg, 0.0050 mmol, 0.05 equiv.) were dissolved in 0.5 mL of MeCN (0.20 M). The reaction mixture was stirred at -15 °C in a cryostat for 6 hours. After the completion of the reaction, N-(3-iodo-1-methoxypropyl)-4-methoxybenzamide **298a** (28.6 mg, 0.0819 mmol, 82%) was obtained as a yellow solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent. Chiral HPLC conditions: er = 88.9:11.1; Chiralpak IC 90:10 Hexane/iPrOH, 1.0 mL/min, 31 min. t_r (minor) = 17.4 min. and t_r (major) = 19.9 min. λ = 260 cm^{-1}.

R_f: 0.30 (silica, pentanes:ethyl acetate 3:1); **Mp:** 92-95 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.80 – 7.74 (m, 2H, Ar*H*), 6.96 – 6.90 (m, 2H, Ar*H*), 6.36 (d, *J* = 9.5 Hz, 1H, N*H*), 5.44 (ddd, *J* = 9.6, 7.0, 5.3 Hz, 1H, C*H*), 3.85 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.29 – 3.17 (m, 2H, CH_2I), 2.25 (dddd, *J* = 17.7, 12.0, 7.4, 3.2 Hz, 2H, CH_2CH_2I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.8, 162.6, 128.9, 125.7, 113.8, 81.6, 56.2, 55.4, 39.5, -0.9; **IR** (film): $\tilde{\nu}$ = 3308 (w), 2933 (w), 2836 (w), 1641 (s), 1606 (s), 1532 (m), 1502 (s), 1307 (m), 1255 (s), 1175 (s), 1104 (m), 844 (m), 768 (w); **HRMS** (ESI) calcd. for $C_{12}H_{16}INNaO_3^+$ $[M+Na]^+$ 372.0067; Found 372.0066.

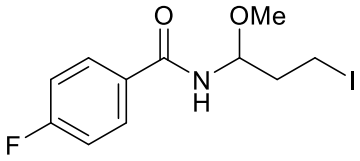
N-(3-Iodo-1-methoxypropyl)-4-(methylthio)benzamide (**298b**)



Following GP B, starting from N-cyclopropyl-4-(methylthio) benzamide **296b** (62.1 mg, 0.300 mmol), N-(3-iodo-1-methoxy propyl)-4-methoxybenzamide **298b** (81.4 mg, 0.223 mmol, 74%) was obtained as a yellow solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.31 (silica, pentanes:ethyl acetate 3:1); **Mp:** 99-102 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.27 (d, *J* = 8.0 Hz, 2H, Ar*H*), 6.32 (d, *J* = 9.6 Hz, 1H, N*H*), 5.45 (dt, *J* = 9.7, 6.2 Hz, 1H, C*H*), 3.42 (s, 3H, OCH_3), 3.30 – 3.19 (m, 2H, CH_2I), 2.51 (s, 3H, SCH_3), 2.26 (ddd, *J* = 13.9, 8.8, 6.7 Hz, 2H, CH_2CH$_2$I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.8, 144.3, 129.5, 127.4, 125.4, 81.7, 56.3, 39.5, 15.0, -1.0; **IR** (film): $\tilde{\nu}$ = 3317 (w), 2928 (w), 1644 (s), 1596 (m), 1520 (s), 1488 (m), 1318 (w), 1107 (m), 837 (w); **HRMS** (ESI) calcd. for $C_{12}H_{16}INNaO_2S^+$ $[M+Na]^+$ 387.9839; Found 387.9842.

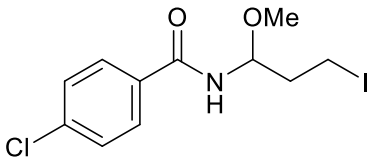
4-Fluoro-N-(3-iodo-1-methoxypropyl)benzamide (**298c**)



Following GP B, starting from N-cyclopropyl-4-fluorobenzamide **296c** (62.1 mg, 0.300 mmol), 4-fluoro-N-(3-iodo-1-methoxypropyl) benzamide **298c** (83.6 mg, 0.248 mmol, 83%) was obtained as a yellow solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.48 (silica, pentanes:ethyl acetate 3:1); **Mp:** 78-81 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.87 – 7.77 (m, 2H, Ar*H*), 7.12 (t, *J* = 8.6 Hz, 2H, Ar*H*), 6.48 (d, *J* = 9.5 Hz, 1H, N*H*), 5.43 (ddd, *J* = 9.5, 7.1, 5.2 Hz, 1H, C*H*), 3.41 (s, 3H, OCH_3), 3.30 – 3.15 (m, 2H, CH_2I), 2.34 – 2.16 (m, 2H, CH_2CH$_2$I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.3, 165.0 (d, *J* = 252.8 Hz), 129.7 (d, *J* = 3.1 Hz), 129.4 (d, *J* = 9.0 Hz), 115.7 (d, *J* = 21.9 Hz), 81.8, 56.3, 39.4, -1.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -107.1; **IR** (film): $\tilde{\nu}$ = 3292 (w), 2933 (w), 1643 (s), 1602 (s), 1530 (m), 1496 (s), 1285 (m), 1233 (s), 1157 (s), 1100 (s), 1064 (s), 848 (s); **HRMS** (ESI) calcd. for $C_{11}H_{13}FINNaO_2^+$ $[M+Na]^+$ 359.9867; Found 359.9868.

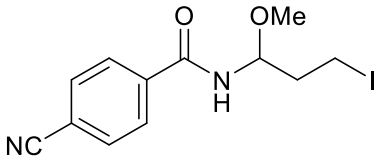
4-Chloro-N-(3-iodo-1-methoxypropyl)benzamide (**298d**)



Following GP B, starting from 4-chloro-N-cyclopropylbenzamide **296d** (58.5 mg, 0.300 mmol), 4-chloro-N-(3-iodo-1-methoxypropyl) benzamide **298d** (74.5 mg, 0.211 mmol, 70%) was obtained as an off-white solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.48 (silica, pentanes:ethyl acetate 3:1); **Mp:** 110-114 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.44 (dd, *J* = 8.5, 1.9 Hz, 2H, Ar*H*), 6.29 (d, *J* = 11.6 Hz, 1H, N*H*), 5.50 – 5.38 (m, 1H, C*H*), 3.43 (d, *J* = 1.2 Hz, 3H, CH_3), 3.32 – 3.15 (m, 2H, CH_2), 2.33 – 2.18 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.3, 138.4, 132.0, 129.0, 128.5, 81.8, 56.4, 39.4, -1.2; **IR** (film): $\tilde{\nu}$ = 3209 (w), 2930 (w), 1645 (s), 1594 (m), 1527 (s), 1485 (s), 1314 (m), 1092 (s), 1065 (m), 844 (m); **HRMS** (ESI) calcd. for $C_{11}H_{13}ClINNaO_2^+$ $[M+Na]^+$ 375.9572; Found 375.9577.

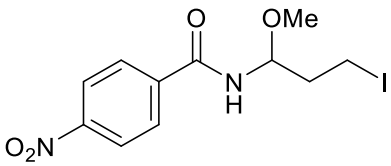
4-Cyano-N-(3-iodo-1-methoxypropyl)benzamide (**298e**)



Following GP B, starting from 4-cyano-N-cyclopropylbenzamide **296e** (55.8 mg, 0.300 mmol) and after stirring for 2 hours, N-(3-iodo-1-methoxypropyl)-4-nitrobenzamide **298e** (79.6 mg, 0.231 mmol, 77%) was obtained as a yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.35 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.77 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.44 (d, *J* = 9.5 Hz, 1H, N*H*), 5.45 (ddd, *J* = 9.5, 6.9, 5.2 Hz, 1H, C*H*), 3.44 (s, 3H, OCH_3), 3.31 – 3.18 (m, 2H, CH_2I), 2.33 – 2.20 (m, 2H, CH_2CH_2I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.6, 137.5, 132.6, 127.7, 117.8, 115.6, 82.0, 56.6, 39.2, -1.3; **IR** (film): $\tilde{\nu}$ = 3307 (m), 2927 (m), 2853 (w), 2231 (m), 1651 (s), 1531 (s), 1496 (s), 1312 (m), 1284 (m), 1104 (m), 1065 (m), 856 (m), 764 (m); **HRMS** (ESI) calcd. for $C_{11}H_{10}IN_2O^+$ $[M\text{-}OCH_3]^+$ 312.9832; Found 312.9835.

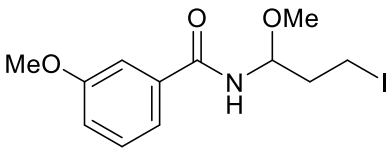
N-(3-Iodo-1-methoxypropyl)-4-nitrobenzamide (**298f**)



Following GP B, starting from N-cyclopropyl-4-nitrobenzamide **296f** (61.8 mg, 0.300 mmol) and after stirring for 2 hours, N-(3-iodo-1-methoxypropyl)-4-nitrobenzamide **298f** (88.0 mg, 0.242 mmol, 81%) was obtained as a yellow solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.50 (silica, pentanes:ethyl acetate 3:1); **Mp:** 65-68 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.34 – 8.29 (m, 2H, Ar*H*), 8.00 – 7.96 (m, 2H, Ar*H*), 6.48 (d, *J* = 9.4 Hz, 1H, N*H*), 5.47 (ddd, *J* = 9.4, 6.9, 5.2 Hz, 1H, C*H*), 3.45 (s, 3H, OCH_3), 3.30 – 3.20 (m, 2H, CH_2I), 2.33 – 2.23 (m, 2H, CH_2CH_2I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.3, 149.9, 139.1, 128.3, 123.9, 82.1, 56.7, 39.2, -1.3; **IR** (film): $\tilde{\nu}$ = 3293 (w), 2930 (w), 1652 (m), 1601 (m), 1522 (s), 1487 (m), 1346 (s), 1105 (m), 1065 (m), 868 (m), 838 (m); **HRMS** (APCI) calcd. for $C_{10}H_{10}IN_2O_3^+$ $[M\text{-}OCH_3]^+$ 332.9731; Found 332.9733.

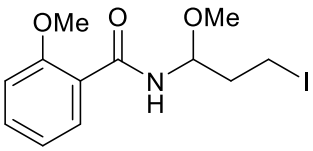
N-(3-Iodo-1-methoxypropyl)-3-methoxybenzamide (**298g**)



Following GP B, starting from N-cyclopropyl-3-methoxybenzamide **296g** (57.3 mg, 0.300 mmol), N-(3-iodo-1-methoxypropyl)-3-methoxybenzamide **298g** (96.0 mg, 0.275 mmol, 92%) was obtained as a yellow oil after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.36 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.38 (s, 1H, Ar*H*), 7.32 (d, *J* = 4.9 Hz, 2H, Ar*H*), 7.04 (td, *J* = 4.9, 2.7 Hz, 1H, Ar*H*), 6.61 (d, *J* = 9.5 Hz, 1H, N*H*), 5.42 (ddd, *J* = 9.5, 7.1, 5.2 Hz, 1H, C*H*), 3.82 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.27 – 3.14 (m, 2H, CH_2I), 2.30 – 2.17 (m, 2H, CH_2CH_2I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.3, 159.8, 135.0, 129.6, 118.7, 118.1, 112.5, 81.7, 56.2, 55.4, 39.3, -1.0; **IR** (film): $\tilde{\nu}$ = 3297 (w), 2934 (w), 2833 (w), 1645 (s), 1583 (s), 1524 (s), 1485 (s), 1358 (w), 1310 (m), 1290 (m), 1251 (m), 1103 (m), 1145 (s), 994 (w), 746 (m); **HRMS** (ESI) calcd. for $C_{12}H_{16}INNaO_3^+$ $[M+Na]^+$ 372.0067; Found 372.0069.

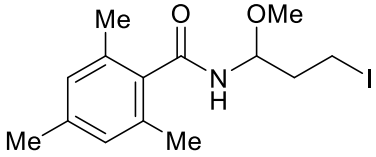
N-(3-Iodo-1-methoxypropyl)-2-methoxybenzamide (**298h**)



Following GP B, starting from N-cyclopropyl-2-methoxybenzamide **296h** (57.3 mg, 0.300 mmol) and after stirring for 1 hour, N-(3-iodo-1-methoxypropyl)-2-methoxybenzamide **298h** (87.5 mg, 0.251 mmol, 84%) was obtained as a yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.45 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.19 (dd, *J* = 7.8, 1.9 Hz, 1H, Ar*H*), 7.99 (d, *J* = 9.4 Hz, 1H, Ar*H*), 7.48 (ddd, *J* = 8.8, 7.4, 1.9 Hz, 1H, Ar*H*), 7.09 (t, *J* = 7.6 Hz, 1H, Ar*H*), 6.99 (d, *J* = 8.3 Hz, 1H, N*H*), 5.47 (ddd, *J* = 9.3, 7.0, 5.3 Hz, 1H, C*H*), 3.97 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.30 – 3.18 (m, 2H, CH_2I), 2.34 – 2.19 (m, 2H, CH_2CH_2I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.5, 157.5, 133.3, 132.5, 121.4, 120.8, 111.4, 81.5, 56.2, 56.0, 39.9, -0.9; **IR** (film): $\tilde{\nu}$ = 3376 (w), 2932 (w), 2834 (w), 1656 (s), 1600 (m), 1516 (s), 1482 (s), 1464 (m), 1293 (m), 1237 (s), 1098 (s), 1019 (m), 843 (w), 755 (s); **HRMS** (ESI) calcd. for $C_{12}H_{16}INNaO_3^+$ $[M+Na]^+$ 372.0067; Found 372.0078.

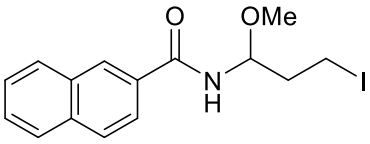
N-(3-Iodo-1-methoxypropyl)-2,4,6-trimethylbenzamide (**298i**)



Following GP B, starting from N-cyclopropyl-2,4,6-trimethylbenzamide **296i** (61.0 mg, 0.300 mmol) and after stirring for 1 hour, N-(3-iodo-1-methoxypropyl)-2,4,6-trimethylbenzamide **298i** (76.7 mg, 0.212 mmol, 71%) was obtained as a pale yellow solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.50 (silica, pentanes:ethyl acetate 3:1); **Mp:** 97-99 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.85 (s, 2H, Ar*H*), 5.84 (d, *J* = 9.5 Hz, 1H, N*H*), 5.40 (ddd, *J* = 9.7, 6.8, 5.6 Hz, 1H, C*H*), 3.52 (s, 3H, OCH_3), 3.23 (td, *J* = 7.5, 7.1, 1.5 Hz, 2H, CH_2I), 2.31 (s, 6H, CH_3), 2.27 (s, 3H, CH_3), 2.19 (qd, *J* = 7.4, 2.0 Hz, 2H, CH_2CH_2I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.6, 138.7, 134.4, 133.8, 128.3, 81.4, 56.7, 39.6, 21.0, 19.3, -1.2; **IR** (film): $\tilde{\nu}$ = 3252 (w), 2924 (m), 2854 (w), 1644 (s), 1523 (s), 1442 (m), 1310 (w), 1176 (m), 1099 (m), 1067 (m), 847 (w); **HRMS** (ESI) calcd. for $C_{14}H_{20}INNaO_2^+$ $[M+Na]^+$ 384.0431; Found 384.0436.

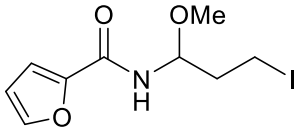
N-(3-Iodo-1-methoxypropyl)-2-naphthamide (**298j**)



Following GP B, starting from N-cyclopropyl-2-naphthamide **296j** (63.4 mg, 0.300 mmol), N-(3-iodo-1-methoxypropyl)-2-naphthamide **298j** (97.5 mg, 0.264 mmol, 88%) was obtained as a yellow solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.58 (silica, pentanes:ethyl acetate 3:1); **Mp:** 96-98 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.32 (s, 1H, Ar*H*), 7.95 – 7.83 (m, 4H, Ar*H*), 7.57 (pd, *J* = 6.9, 1.5 Hz, 2H, Ar*H*), 6.54 (d, *J* = 9.6 Hz, 1H, N*H*), 5.52 (ddd, *J* = 9.6, 7.0, 5.2 Hz, 1H, C*H*), 3.47 (s, 3H, OCH_3), 3.34 – 3.20 (m, 2H, CH_2I), 2.39 – 2.24 (m, 2H, CH_2CH_2I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.4, 134.9, 132.5, 130.8, 129.0, 128.7, 128.0, 127.8, 127.7, 126.9, 123.4, 81.8, 56.4, 39.6, -1.0; **IR** (film): $\tilde{\nu}$ = 3296 (w), 3058 (w), 2925 (m), 2852 (w), 1645 (s), 1527 (s), 1503 (m), 1309 (m), 1066 (m), 863 (w); **HRMS** (ESI) calcd. for $C_{15}H_{16}INNaO_2^+$ $[M+Na]^+$ 392.0118; Found 392.0115.

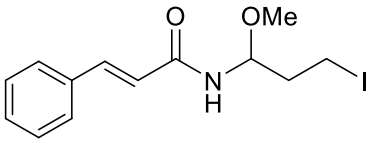
N-(3-Iodo-1-methoxypropyl)furan-2-carboxamide (**298k**)



Following GP B, starting from N-cyclopropylfuran-2-carboxamide **296k** (45.3 mg, 0.300 mmol), N-(3-iodo-1-methoxypropyl)furan-2-carboxamide **298k** (88.7 mg, 0.287 mmol, 96%) was obtained as a yellow oil after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.29 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.49 – 7.43 (m, 1H, Ar*H*), 7.16 (d, *J* = 3.1 Hz, 1H, Ar*H*), 6.57 (d, *J* = 9.9 Hz, 1H, N*H*), 6.52 (dd, *J* = 3.5, 1.8 Hz, 1H, Ar*H*), 5.37 (ddd, *J* = 9.8, 7.2, 5.2 Hz, 1H, C*H*), 3.39 (s, 3H, OCH_3), 3.25 – 3.14 (m, 2H, CH_2I), 2.33 – 2.15 (m, 2H, CH_2CH_2I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 158.2, 147.1, 144.3, 115.3, 112.4, 80.9, 56.2, 39.5, -1.1; **IR** (film): $\tilde{\nu}$ = 3285 (w), 2930 (w), 1650 (w), 1589 (s), 1512 (s), 1471 (s), 1310 (m), 1291 (m), 1174 (s), 1103 (s), 1065 (s), 1010 (s); **HRMS** (ESI) calcd. for $C_9H_{12}INNaO_3^+$ $[M+Na]^+$ 331.9754; Found 331.9762.

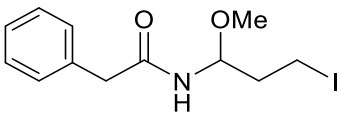
N-(3-Iodo-1-methoxypropyl)cinnamamide (**298l**)



Following GP B, starting from N-cyclopropylcinnamamide **296l** (56.2 mg, 0.300 mmol), N-(3-iodo-1-methoxypropyl)cinnamamide **298l** (83.1 mg, 0.241 mmol, 80%) was obtained as a yellow solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.40 (silica, pentanes:ethyl acetate 3:1); **Mp:** 93-95 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 15.6 Hz, 1H, vinyl*H*), 7.51 (dd, *J* = 6.6, 2.9 Hz, 2H, Ar*H*), 7.42 – 7.33 (m, 3H, Ar*H*), 6.41 (d, *J* = 15.6 Hz, 1H, vinyl*H*), 5.91 (d, *J* = 9.8 Hz, 1H, N*H*), 5.38 (ddd, *J* = 9.7, 7.1, 5.3 Hz, 1H, C*H*), 3.41 (s, 3H, OCH_3), 3.27 – 3.16 (m, 2H, CH_2I), 2.21 (ddt, *J* = 14.3, 11.9, 6.7 Hz, 2H, CH_2CH_2I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.9, 142.6, 134.4, 130.0, 128.9, 127.9, 119.8, 81.3, 56.3, 39.6, -1.0; **IR** (film): $\tilde{\nu}$ = 3264 (m), 3028 (w), 2926 (m), 2853 (w), 1657 (s), 1623 (s), 1530 (s), 1449 (m), 1358 (m), 1336 (m), 1203 (s), 1110 (s), 1068 (s), 976 (m), 862 (w), 765 (m); **HRMS** (ESI) calcd. for $C_{13}H_{16}INNaO_2^+$ $[M+Na]^+$ 368.0118; Found 368.0118.

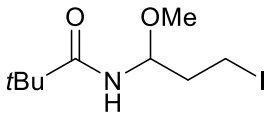
N-(3-Iodo-1-methoxypropyl)-2-phenylacetamide (**298m**)



Following GP B, starting from N-cyclopropyl-2-phenylacetamide **296m** (52.6 mg, 0.300 mmol), N-(3-iodo-1-methoxypropyl)-2-phenylacetamide **298m** (75.0 mg, 0.225 mmol, 75%) was obtained as a yellow solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.40 (silica, pentanes:ethyl acetate 3:1); **Mp:** 84-87 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.40 – 7.34 (m, 2H, Ar*H*), 7.33 – 7.28 (m, 1H, Ar*H*), 7.26 (dd, *J* = 6.1, 2.3 Hz, 2H, Ar*H*), 5.60 (d, *J* = 9.5 Hz, 1H, N*H*), 5.19 (ddd, *J* = 9.6, 7.1, 5.2 Hz, 1H, C*H*), 3.61 (d, *J* = 3.7 Hz, 2H, CH_2), 3.29 (s, 3H, OCH_3), 3.08 (td, *J* = 7.6, 7.1, 1.4 Hz, 2H, CH_2I), 2.10 – 1.97 (m, 2H, CH_2CH_2I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.3, 134.3, 129.3, 129.2, 127.6, 81.2, 56.1, 43.9, 39.2, -1.3; **IR** (film): $\tilde{\nu}$ = 3279 (w), 3062 (w), 3030 (w), 2930 (w), 1654 (s), 1535 (m), 1496 (m), 1176 (m), 1111 (m), 1068 (m), 724 (m); **HRMS** (ESI) calcd. for $C_{12}H_{16}INNaO_2^+$ $[M+Na]^+$ 356.0118; Found 356.0123.

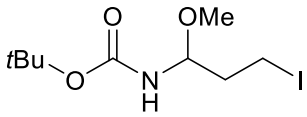
N-(3-Iodo-1-methoxypropyl)pivalamide (**298n**)



Following GP B, starting from N-cyclopropylpivalamide **296n** (42.4 mg, 0.300 mmol), N-(3-iodo-1-methoxypropyl)pivalamide **298n** (78.6 mg, 0.263 mmol, 88%) was obtained as a dark yellow solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.48 (silica, pentanes:ethyl acetate 3:1); **Mp:** 76-78 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.81 (d, *J* = 9.5 Hz, 1H, N*H*), 5.23 (ddd, *J* = 9.5, 7.1, 5.2 Hz, 1H, C*H*), 3.33 (s, 3H, OCH_3), 3.26 – 3.05 (m, 2H, CH_2I), 2.21 – 2.08 (m, 2H, CH_2CH_2I), 1.22 (s, 9H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 178.7, 81.1, 56.0, 39.5, 38.9, 27.5, -1.1; **IR** (film): $\tilde{\nu}$ = 3329 (w), 2961 (m), 2934 (m), 1650 (s), 1518 (s), 1367 (w), 1190 (m), 1110 (m), 1069 (m); **HRMS** (ESI) calcd. for $C_9H_{18}INNaO_2^+$ $[M+Na]^+$ 322.0274; Found 322.0282.

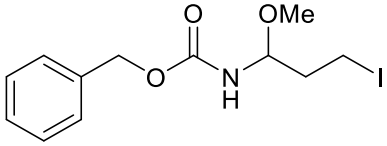
***tert*-Butyl (3-iodo-1-methoxypropyl)carbamate** (**298o**)



Following GP B, starting from *tert*-butyl cyclopropylcarbamate **296o** (47.2 mg, 0.300 mmol) and without the addition of diphenyl phosphate, *tert*-butyl (3-iodo-1-methoxypropyl)carbamate **298o** (89.0 mg, 0.282 mmol, 94%) was obtained as a pale yellow oil after purification by column chromatography on silica using 4:1 pentanes:ethyl acetate as eluent. K_2CO_3 (0.300 mmol, 1.00 equiv.) has to be added to the reaction mixture before purification.

R_f: 0.45 (silica, pentanes:ethyl acetate 6:1); **^{1}H NMR** (400 MHz, Methanol-d_4): δ = 4.85 – 4.80 (m, 2H, N*H* + C*H*), 3.27 (s, 3H, OCH_3), 3.16 (td, *J* = 7.1, 2.5 Hz, 2H, CH_2I), 2.12 – 2.03 (m, 1H, CH_2CH_2I), 1.95 (dtd, *J* = 14.4, 7.4, 5.7 Hz, 1H, CH_2CH_2I), 1.42 (s, 9H, CH_3); **^{13}C NMR** (101 MHz, Methanol-d_4): δ = 157.9, 84.2, 80.5, 55.5, 39.7, 28.6, 0.4; **IR** (film): $\tilde{\nu}$ = 3335 (w), 2977 (w), 2931 (w), 2832 (w), 1698 (s), 1513 (m), 1366 (m), 1244 (s), 1161 (s), 1086 (m), 994 (m), 865 (m); **HRMS** (ESI) calcd. for $C_9H_{18}INNaO_3^+$ $[M+Na]^+$ 338.0224; Found 338.0226.

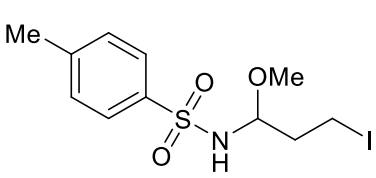
Benzyl (3-iodo-1-methoxypropyl)carbamate (**298p**)



Following GP B, starting from benzyl cyclopropylcarbamate **296p** (57.4 mg, 0.300 mmol) and without the addition of diphenyl phosphate, benzyl (3-iodo-1-methoxypropyl)carbamate **298p** (84.0 mg, 0.241 mmol, 80%) was obtained as a colorless oil after purification by column chromatography on silica using 4:1 pentanes:ethyl acetate as eluent. K_2CO_3 (0.300 mmol, 1.00 equiv.) has to be added to the reaction mixture before purification.

R_f: 0.40 (silica, pentanes:ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.48 – 7.28 (m, 5H, Ar*H*), 5.13 (s, 2H, OCH_2), 5.07 (d, *J* = 10.0 Hz, 1H, N*H*), 4.99 (td, *J* = 10.3, 8.6, 5.8 Hz, 1H, C*H*), 3.38 (s, 3H, OCH_3), 3.17 (t, *J* = 7.1 Hz, 2H, CH_2I), 2.14 (tt, *J* = 14.1, 7.8 Hz, 2H, CH_2CH_2I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.8, 136.0, 128.6, 128.3, 128.1, 83.6, 67.0, 55.9, 39.4, -0.7; **IR** (film): $\tilde{\nu}$ = 3317 (w), 3033 (w), 2934 (w), 2831 (w), 1698 (s), 1521 (s), 1453 (m), 1227 (s), 1200 (s), 1089 (s), 1036 (s), 979 (s), 855 (w), 735 (m), 696 (s); **HRMS** (ESI) calcd. for $C_{12}H_{16}INNaO_3^+$ $[M+Na]^+$ 372.0067; Found 372.0078.

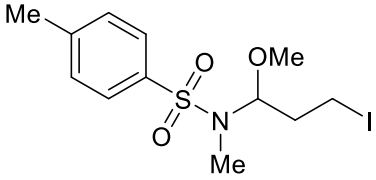
N-(3-Iodo-1-methoxypropyl)-4-methylbenzenesulfonamide (**298q**)



Following GP B, starting from N-cyclopropyl-4-methyl benzenesulfonamide **296q** (63.4 mg, 0.300 mmol), without the addition of diphenyl phosphate. After stirring for 20 hours, N-(3-iodo-1-methoxypropyl)-4-methylbenzenesulfonamide **298q** (101 mg, 0.274 mmol, 91%) was obtained as a yellow oil after purification by column chromatography on silica using 4:1 pentanes:ethyl acetate as eluent.

R_f: 0.29 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, Methanol-d_4): δ = 7.72 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.33 (d, *J* = 7.9 Hz, 2H, Ar*H*), 4.52 (dd, *J* = 7.5, 4.9 Hz, 1H, C*H*), 3.17 (s, 3H, OCH_3), 3.09 – 2.96 (m, 2H, CH_2I), 2.39 (s, 3H, CH_3), 2.00 (dddd, *J* = 14.1, 7.5, 6.5, 5.6 Hz, 1H, CH_2CH$_2$I), 1.71 (dddd, *J* = 14.5, 8.3, 7.0, 5.0 Hz, 1H, CH_2CH$_2$I), N*H* signal was not resolved; **^{13}C NMR** (101 MHz, Methanol-d_4): δ = 144.7, 140.6, 130.7, 127.8, 87.3, 55.4, 40.2, 21.4, 0.4; **IR** (film): $\tilde{\nu}$ = 3272 (m), 2932 (w), 2832 (w), 1598 (w), 1495 (w), 1449 (m), 1324 (m), 1245 (w), 1155 (s), 1114 (m), 1032 (m), 985 (m), 860 (m), 812 (m); **HRMS** (ESI) calcd. for $C_{11}H_{16}INNaO_3S^+$ $[M+Na]^+$ 391.9788; Found 391.9792.

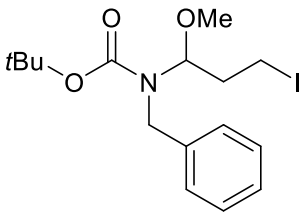
N-(3-Iodo-1-methoxypropyl)-N,4-dimethylbenzenesulfonamide (**298r**)



Following GP B, starting from N-cyclopropyl-N,4-dimethyl benzenesulfonamide **296r** (67.6 mg, 0.300 mmol), without the addition of diphenyl phosphate. After stirring for 20 hours, N-(3-iodo-1-methoxy propyl)-N,4-dimethylbenzenesulfonamide **298r** (104 mg, 0.282 mmol, 94%) was obtained as a pale yellow oil after purification by column chromatography on silica using 4:1 pentanes:ethyl acetate as eluent.

R_f: 0.50 (silica, pentanes:ethyl acetate 6:1); **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 7.77 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.44 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.10 (dd, *J* = 8.3, 4.4 Hz, 1H, C*H*), 3.21 (s, 3H, OCH_3), 3.19 – 3.13 (m, 2H, CH_2I), 2.68 (s, 3H, NCH_3), 2.43 (s, 3H, ArCH_3), 2.12 (ddd, *J* = 14.2, 8.2, 5.9 Hz, 1H, CH_2CH$_2$I), 1.68 (dtd, *J* = 14.6, 7.9, 4.4 Hz, 1H, CH_2CH$_2$I); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 144.4, 138.0, 130.6, 127.9, 89.3, 56.0, 37.4, 27.5, 21.4, 1.3; **IR** (film): $\tilde{\nu}$ = 2938 (w), 2831 (w), 1597 (w), 1494 (w), 1449 (w), 1340 (s), 1216 (m), 1185 (m), 1153 (s), 1099 (m), 932 (s), 814 (m); **HRMS** (ESI) calcd. for $C_{12}H_{18}INNaO_3S^+$ $[M+Na]^+$ 405.9944; Found 405.9960.

***tert*-Butyl benzyl(3-iodo-1-methoxypropyl)carbamate** (**298s**)

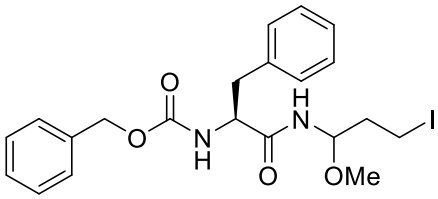


Following GP B, starting from *tert*-butyl benzyl(cyclopropyl)carbamate **296s** (74.2 mg, 0.300 mmol) and without the addition of diphenyl phosphate, *tert*-butyl benzyl(3-iodo-1-methoxypropyl)carbamate **298s** (110 mg, 0.271 mmol, 90%) was obtained as a colorless oil after purification by column chromatography on silica using 6:1 pentanes:ethyl acetate as eluent. K_2CO_3 (0.300 mmol, 1.00 equiv.) was added to the crude mixture before purification.

R_f: 0.44 (silica, pentanes:ethyl acetate 8:1); **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 7.47 – 7.14 (m, 5H, Ar*H*), 5.61 – 5.34 (m, 1H, C*H*), 4.62 – 4.42 (m, 1H, ArCH_2), 4.24 (d, *J* = 16.2 Hz, 1H, ArCH_2), 3.10 (m, 5H, OCH_3 + CH_2I), 2.06 – 2.02 (m, 1H, CH_2), 1.97 – 1.85 (m, 1H, CH_2), 1.59 – 1.31 (m, 9H, CH_3); **^{13}C NMR** (101 MHz, Acetone-d_6): δ =^{13}C NMR (101 MHz,) δ 156.4, 140.9, 129.1, 129.0, 128.4, 128.2, 127.8, 127.5, 88.7, 87.5, 80.8, 80.6, 55.7, 45.1, 44.3, 38.5, 28.4, 1.9, 1.6; Mixture of 2 rotamers with almost 1:1 ratio.

They are not completely resolved. **IR** (film): $\tilde{\nu}$ = 2975 (w), 2933 (w), 1695 (s), 1453 (w), 1403 (m), 1379 (m), 1366 (m), 1252 (m), 1158 (s), 1074 (m), 956 (w), 889 (w); **HRMS** (ESI) calcd. for $C_{16}H_{24}INNaO_3^+$ $[M+Na]^+$ 428.0693; Found 428.0700.

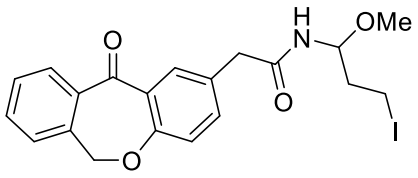
Benzyl ((2S)-1-((3-iodo-1-methoxypropyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**298t**)



Following GP B, starting from benzyl (S)-(1-(cyclopropylamino)-1-oxo-3-phenylpropan-2-yl)carbamate **296t** (33.8 mg, 0.100 mmol), N-Iodosuccinimide (23.6 mg, 0.105 mmol, 1.05 equiv.), methanol (4.8 µL, 0.120 mmol, 1.2 equiv.) and diphenyl phosphate (2.5 mg, 0.010 mmol, 0.10 equiv.) were dissolved in 0.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 3 hours. Benzyl ((2S)-1-((3-iodo-1-methoxypropyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **298t** (34.2 mg, 0.0690 mmol, 69%) was obtained as a beige solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.30 (silica, pentanes:ethyl acetate 3:1); **Mp:** 120-122 °C; **^{1}H NMR** (400 MHz, Acetone-d_6; mixture of diastereoisomers in a 1 :1 ratio: the signals corresponding to the two diastereoisomers are partially resolved): δ = 7.56 (d, *J* = 9.4 Hz, 1H, N*H*), 7.50 (d, *J* = 9.5 Hz, 1H, N*H*), 7.39 – 7.15 (m, 10H, Ar*H*), 6.59 (d, *J* = 8.1 Hz, 1H, N*H*), 6.53 (d, *J* = 8.4 Hz, 1H, N*H*), 5.20 – 5.08 (m, 1H, C*H*), 5.02 (s, 2H, OCH_2), 4.41 (dtd, *J* = 20.8, 8.4, 6.2 Hz, 1H, C*H*), 3.28 – 3.17 (m, 3H, OCH_3), 3.18 – 3.10 (m, 2H, PhCH_2), 3.10 – 3.03 (m, 1H, CH_2I), 3.02 – 2.93 (m, 1H, CH_2I), 2.19 – 2.10 (m, 1H, CH_2CH$_2$I), 2.09 – 2.07 (m, 1H, CH_2CH$_2$I), 1.97 – 1.85 (m, 1H, CH_2CH$_2$I); **^{13}C NMR** (101 MHz, Acetone-d_6; mixture of two diastereoisomers in a 1 :1 ratio: the signals corresponding to the two diastereoisomers are partially resolved): δ = 172.7, 172.6, 156.8, 138.5, 138.4, 138.2, 138.1, 130.2, 129.2, 129.2, 129.1, 128.6, 128.6, 128.6, 128.5, 127.4, 127.4, 81.9, 81.6, 66.7, 66.7, 57.7, 57.7, 55.7, 55.7, 40.0, 39.8, 38.8, 38.7, 1.0, 0.9; **IR** (film): $\tilde{\nu}$ =3289 (m), 3030 (w), 2932 (w), 1664 (s), 1537 (s), 1256 (m), 1066 (m), 745 (m), 698(m); **HRMS** (APPI) calcd. for $C_{21}H_{25}IN_2NaO_4^+$ $[M+Na]^+$ 519.0751; Found 519.0751.

N-(3-Iodo-1-methoxypropyl)-2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetamide (**298u**)

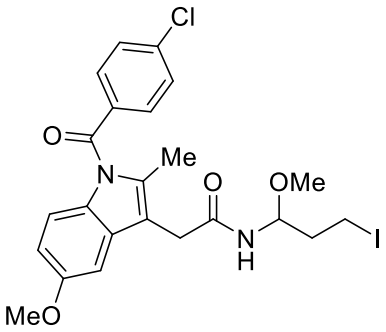


Following GP B, starting from N-cyclopropyl-2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetamide **296u** (30.7 mg, 0.100 mmol), N-Iodosuccinimide (23.6 mg, 0.105 mmol, 1.05 equiv.), methanol (4.8 µL, 0.120 mmol, 1.2 equiv.) and diphenyl phosphate (2.5 mg, 0.010 mmol, 0.10 equiv.) were dissolved in 0.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 1 hour. N-(3-Iodo-1-methoxypropyl)-2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetamide **298u** (40.7 mg, 0.0880 mmol, 88%) was obtained as a yellow oil after purification by column chromatography on silica, using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.50 (silica, pentanes:ethyl acetate 1:1); **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 8.09 (s, 1H, Ar*H*), 7.84 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.69 – 7.58 (m, 2H, Ar*H*), 7.58 – 7.49 (m, 3H, Ar*H* + N*H*), 7.04 (d, *J* = 8.4 Hz, 1H, Ar*H*), 5.29 (s, 2H, OCH_2), 5.18 (dt, *J* = 9.4, 6.3 Hz, 1H, C*H*), 3.61 (d, *J* = 2.4 Hz, 2H, CH_2), 3.31 – 3.16 (m, 5H, OCH_3 + CH_2I), 2.17 (dd, *J* = 14.0, 6.9 Hz, 1H, CH_2CH$_2$I), 2.11 – 2.06 (m, 1H, CH_2CH$_2$I); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 190.8, 171.6, 161.1, 141.4, 137.2, 137.1, 133.7, 132.7, 130.8, 129.9, 129.9,

128.9, 125.9, 121.5, 81.7, 74.1, 55.8, 42.7, 40.0, 1.0; **IR** (film): $\tilde{\nu}$ = 3292 (w), 2930(w), 1647 (s), 1609 (m), 1530 (m), 1487 (s), 1378 (m), 1299 (s), 1253 (m), 1120 (m), 1069 (m), 1015 (m), 831 (w), 760 (m); **HRMS** (APCI) calcd. for $C_{20}H_{20}INNaO_4^+$ $[M+Na]^+$ 488.0329; Found 488.0335.

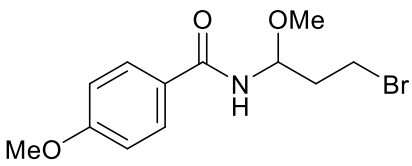
2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)-N-(3-iodo-1-methoxypropyl)acetamide (**298v**)



Following GP B, starting from 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)-N-cyclopropylacetamide **296v** (39.6 mg, 0.100 mmol), N-Iodosuccinimide (47.3 mg, 0.210 mmol, 2.1 equiv.), methanol (4.8 µL, 0.120 mmol, 1.2 equiv.) and diphenyl phosphate (2.5 mg, 0.010 mmol, 0.10 equiv.) were dissolved in 0.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 4 hours. 2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)-N-(3-iodo-1-methoxypropyl)acetamide **298v** (24.4 mg, 0.0440 mmol, 44%) was obtained as a pale yellow solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.30 (silica, pentanes:ethyl acetate 2:1); **Mp:** 135-138 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 7.77 – 7.72 (m, 2H, Ar*H*), 7.66 – 7.61 (m, 2H, Ar*H*), 7.47 (d, *J* = 10.0 Hz, 1H, N*H*), 7.14 (d, *J* = 2.6 Hz, 1H, Ar*H*), 7.02 (d, *J* = 9.0 Hz, 1H, Ar*H*), 6.71 (dd, *J* = 9.0, 2.6 Hz, 1H, Ar*H*), 5.24 – 5.14 (m, 1H, C*H*), 3.81 (s, 3H, OCH_3), 3.68 (s, 2H, ArCH_2), 3.25 (s, 3H, OCH_3), 3.20 (t, *J* = 7.2 Hz, 2H, CH_2I), 2.33 (s, 3H, CH_3), 2.12 (dt, *J* = 13.8, 7.0 Hz, 1H, CH_2CH$_2$I), 2.03 – 1.97 (m, 1H, CH_2CH$_2$I); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 171.0, 168.8, 157.1, 139.2, 136.6, 135.6, 132.1, 131.9, 131.8, 129.9, 115.7, 114.6, 112.5, 102.2, 81.8, 55.9, 55.8, 39.9, 32.5, 13.7, 1.0; **IR** (film): $\tilde{\nu}$ = 3296 (w), 2931 (w), 2832 (w), 1680 (s), 1591 (w), 1521 (w), 1477 (s), 1358 (m), 1321 (s), 1224 (m), 1088 (m), 835 (w); **HRMS** (APPI) calcd. for $C_{23}H_{24}ClIN_2O_4^+$ $[M]^+$ 554.0464; Found 554.0463.

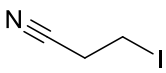
N-(3-Bromo-1-methoxypropyl)-4-methoxybenzamide (**299**)



In a glass vial, N-cyclopropyl-4-methoxybenzamide **296a** (0.300 mmol, 1.0 equiv.), N-bromosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.), methanol (14.4 µL, 0.360 mmol, 1.2 equiv.) and diphenyl phosphate (7.5 mg, 0.030 mmol, 0.10 equiv.) were dissolved in 1.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the crude was directly submitted to column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent. N-(3-Bromo-1-methoxypropyl)-4-methoxybenzamide **299** (81.2 mg, 0.270 mmol, 90%) was obtained as a white solid.

R_f: 0.29 (silica, pentanes:ethyl acetate 2:1); **Mp:** 76-78 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.94 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.42 (d, *J* = 9.6 Hz, 1H, N*H*), 5.53 (ddd, *J* = 9.6, 6.7, 5.3 Hz, 1H, C*H*), 3.85 (s, 3H, OCH_3), 3.54 – 3.46 (m, 2H, CH_2Br), 3.42 (s, 3H, OCH_3), 2.34 – 2.20 (m, 2H, CH_2CH$_2$Br); **^{13}C NMR** (101 MHz, CDCl3): δ = 166.8, 162.6, 128.9, 125.8, 113.9, 80.0, 56.2, 55.4, 38.6, 27.9; **IR** (film): $\tilde{\nu}$ = 3304 (w), 2936 (w), 2837 (w), 1641 (m), 1605 (s), 1532 (m), 1501 (s), 1310 (m), 1252 (s), 1177 (m), 1106 (m), 1030 (m), 844 (m), 769 (m); **HRMS** (ESI) calcd. for $C_{12}H_{16}BrNNaO_3^+$ $[M+Na]^+$ 324.0206; Found 324.0206.

3-Iodopropanenitrile (**303**)



Following GP B, starting from cyclopropyl amine (7.0 µL, 0.10 mmol), N-Iodosuccinimide (23.6 mg, 0.105 mmol, 1.05 equiv.) and methanol (4.8 µL, 0.12 mmol, 1.2 equiv.) were dissolved in 0.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 0.5 hour. 3-Iodopropanenitrile **303** (7.6 mg, 0.042 mmol, 42%) was obtained as a pale yellow oil after purification by column chromatography on silica, using 4:1 pentanes:ethyl acetate as eluent.

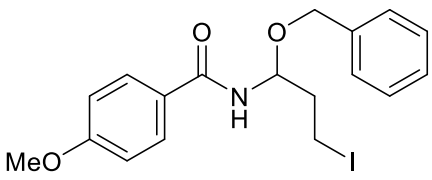
R_f: 0.40 (silica, pentanes:ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.28 (t, *J* = 7.1 Hz, 2H, C*H*$_2$I), 3.01 (t, *J* = 7.1 Hz, 2H, C*H*$_2$CN); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 118.1, 22.5, -6.9; **IR** (film): $\tilde{\nu}$ = 2957 (w), 2921 (m), 2852 (w), 2252 (w), 1413 (s), 1250 (s), 1174 (s), 883 (s).

^{13}C NMR and IR data correspond to the reported values.[280]

General Procedure C (GP C):

In a glass vial, N-cyclopropyl-4-methoxybenzamide **296a** (57.3 mg, 0.300 mmol, 1.0 equiv.), N-Iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.), alcohol (0.360 mmol, 1.2 equiv.) and diphenyl phosphate (7.5 mg, 0.030 mmol, 0.10 equiv.) were dissolved in 1.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes, if not specified otherwise. After the completion of the reaction, the crude product was directly submitted to column chromatography on silica using pentanes:ethyl acetate as eluent.

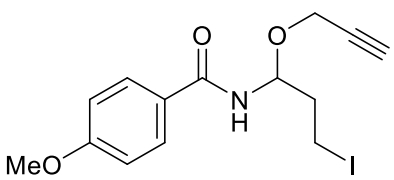
N-(1-(Benzyloxy)-3-iodopropyl)-4-methoxybenzamide (**307a**)



Following GP C, using from phenylmethanol (38.9 mg, 0.360 mmol, 1.2 equiv.), N-(1-(benzyloxy)-3-iodopropyl)-4-methoxy benzamide **307a** (120 mg, 0.282 mmol, 94%) was obtained as a yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.33 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.40 – 7.26 (m, 5H, Ar*H*), 6.94 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.36 (d, *J* = 9.7 Hz, 1H, N*H*), 5.68 (ddd, *J* = 9.7, 7.3, 4.9 Hz, 1H, C*H*), 4.72 – 4.60 (m, 2H, C*H*$_2$), 3.86 (s, 3H, OC*H*$_3$), 3.32 – 3.13 (m, 2H, C*H*$_2$I), 2.40 – 2.21 (m, 2H, C*H*$_2$CH$_2$I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.7, 162.6, 137.8, 128.9, 128.5, 127.9, 127.8, 125.7, 113.9, 80.1, 70.8, 55.5, 39.8, -0.8; **IR** (film): $\tilde{\nu}$ = 3306 (w), 3030 (w), 2938 (w), 2837 (w), 1640 (s), 1606 (s), 1532 (m), 1501 (s), 1307 (m), 1255 (s), 1177 (s), 1100 (m), 1063 (m), 1028 (s), 844 (m), 737 (m); **HRMS** (ESI) calcd. for $C_{18}H_{20}INNaO_3^+$ $[M+Na]^+$ 448.0380; Found 448.0384.

N-(3-Iodo-1-(prop-2-yn-1-yloxy)propyl)-4-methoxybenzamide (**307b**)



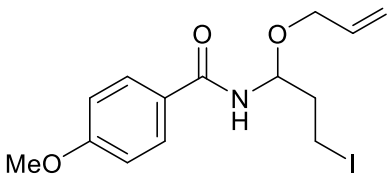
Following GP C, using from prop-2-yn-1-ol (20.2 mg, 0.360 mmol, 1.2 equiv.) and after stirring for 1 hour, N-(3-iodo-1-(prop-2-yn-1-yloxy)propyl)-4-methoxybenzamide **307b** (91.2 mg, 0.244 mmol, 81%)

[280] Irifune, S.; Kibayashi, T.; Ishii, Y.; Ogawa, M. *Synthesis* **1998**, *5*, 366.

was obtained as a yellow solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.40 (silica, pentanes:ethyl acetate 3:1); **Mp:** 78-80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.94 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.39 (d, *J* = 9.6 Hz, 1H, N*H*), 5.67 (ddd, *J* = 9.6, 7.3, 5.0 Hz, 1H, C*H*), 4.34 – 4.24 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 3.33 – 3.16 (m, 2H, CH_2I), 2.43 (t, *J* = 2.4 Hz, 1H, alkynyl*H*), 2.38 – 2.22 (m, 2H, CH_2CH$_2$I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.8, 162.7, 129.0, 125.5, 113.9, 80.1, 79.7, 74.4, 56.3, 55.5, 39.5, -1.3; **IR** (film): $\tilde{\nu}$ = 3291 (w), 2957 (w), 2924 (w), 2854 (w), 1642 (m), 1605 (s), 1530 (m), 1498 (s), 1307 (m), 1253 (s), 1176 (s), 1062 (s), 1029 (s), 909 (w), 843 (m), 607 (m); **HRMS** (ESI) calcd. for $C_{14}H_{16}INNaO_3^+$ $[M+Na]^+$ 396.0067; Found 396.0077.

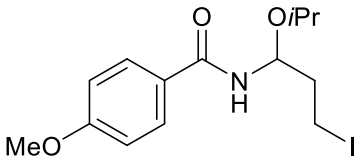
N-(1-(Allyloxy)-3-iodopropyl)-4-methoxybenzamide (**307c**)



Following GP C, using from prop-2-en-1-ol (20.9 mg, 0.360 mmol, 1.2 equiv.) and after stirring for 1 hour, N-(1-(allyloxy)-3-iodopropyl)-4-methoxybenzamide **307c** (71.1 mg, 0.189 mmol, 63%) was obtained as a yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.41 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.9 Hz, 2H, Ar*H*), 6.94 (d, *J* = 8.9 Hz, 2H, Ar*H*), 6.38 (d, *J* = 9.6 Hz, 1H, N*H*), 5.91 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H, vinyl*H*), 5.58 (ddd, *J* = 9.6, 7.2, 5.1 Hz, 1H, C*H*), 5.29 (dq, *J* = 17.2, 1.7 Hz, 1H, vinyl*H*), 5.18 (dq, *J* = 10.4, 1.4 Hz, 1H, vinyl*H*), 4.21 – 4.05 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.33 – 3.14 (m, 2H, CH_2I), 2.41 – 2.14 (m, 2H, CH_2CH$_2$I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.7, 162.6, 134.1, 128.9, 125.7, 117.4, 113.9, 79.9, 69.5, 55.4, 39.7, -0.9; **IR** (film): $\tilde{\nu}$ = 3305 (w), 2933 (w), 2839 (w), 1640 (s), 1606 (s), 1532 (m), 1501 (s), 1308 (m), 1255 (s), 1178 (s), 1032 (s), 927 (w), 844 (m), 768 (w); **HRMS** (ESI) calcd. for $C_{14}H_{18}INNaO_3^+$ $[M+Na]^+$ 398.0224; Found 398.0224.

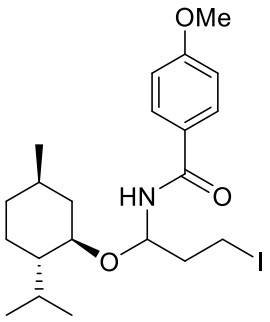
N-(3-Iodo-1-isopropoxypropyl)-4-methoxybenzamide (**307d**)



Following GP C, using from propan-2-ol (21.6 mg, 0.360 mmol, 1.2 equiv.), N-(3-iodo-1-isopropoxypropyl)-4-methoxybenzamide **307d** (94.6 mg, 0.251 mmol, 84%) was obtained as a yellow oil after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.40 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.92 (d, *J* = 8.9 Hz, 2H, Ar*H*), 6.40 (d, *J* = 9.3 Hz, 1H, N*H*), 5.60 (ddd, *J* = 9.4, 7.4, 5.0 Hz, 1H, C*H*), 3.90 (p, *J* = 6.1 Hz, 1H, C*H*), 3.84 (s, 3H, OCH_3), 3.29 – 3.14 (m, 2H, CH_2I), 2.22 (qd, *J* = 7.4, 5.3 Hz, 2H, CH_2CH$_2$I), 1.22 (d, *J* = 6.1 Hz, 3H, CH_3), 1.13 (d, *J* = 6.2 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.4, 162.5, 128.8, 125.9, 113.8, 78.1, 69.5, 55.4, 40.0, 23.4, 21.8, -0.4; **IR** (film): $\tilde{\nu}$ = 3303 (w), 2969 (w), 2933 (w), 2838 (w), 1638 (s), 1606 (s), 1532 (m), 1501 (s), 1442 (w), 1336 (w), 1255 (s), 1175 (s), 1033 (s), 844 (m); **HRMS** (ESI) calcd. for $C_{14}H_{20}INNaO_3^+$ $[M+Na]^+$ 400.0380; Found 400.0388.

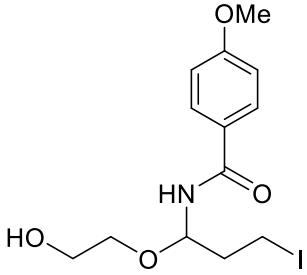
N-(3-Iodo-1-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)propyl)-4-methoxybenzamide (**307e**)



Following GP C, using from (-)-menthol (56.3 mg, 0.360 mmol, 1.2 equiv.), N-(3-iodo-1-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)propyl)-4-methoxybenzamide **307e** (120 mg, 0.253 mmol, 84%) was obtained as an off-white solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.45 (silica, pentanes:ethyl acetate 4:1); **Mp:** 89-91 °C; **^{1}H NMR** (400 MHz, $CDCl_3$; mixture of diastereoisomers in a 1.5 :1 ratio: the signals corresponding to the two distereoisomers are partially resolved): δ = 7.79 – 7.70 (m, 4H, Ar*H, major+minor*), 6.99 – 6.86 (m, 4H, Ar*H, major+minor*), 6.31 (d, *J* = 9.4 Hz, 1H, N*H minor*), 6.25 (d, *J* = 9.4 Hz, 1H, N*H major*), 5.70 – 5.52 (m, 2H, C*H, major+minor*), 3.85 (d, *J* = 1.2 Hz, 6H, OCH_3, *major+minor*), 3.48 (td, *J* = 10.5, 4.3 Hz, 1H, OC*H* ring *minor*), 3.36 (td, *J* = 10.5, 4.3 Hz, 1H, OC*H* ring *major*), 3.29 – 3.09 (m, 4H, CH_2I, *major+minor*), 2.40 – 2.07 (m, 8H, CH_2CH_2I *major+minor* + CH_2 ring, *major+minor*), 2.01 – 1.93 (m, 1H, C*H* ring *minor*), 1.69 – 1.55 (m, 6H, CH_2 ring, *major+minor* + CH_2 ring *minor*), 1.44 – 1.27 (m, 3H, C*H major+minor* + C*H ring major*), 1.22 – 1.12 (m, 2H, CH_2 ring *major*), 1.00 – 0.94 (m, 2H, C*H major+minor*), 0.92 (d, *J* = 6.0 Hz, 6H, CH_3, *major+minor*), 0.88 (d, *J* = 7.1 Hz, 6H, CH_3, *major+minor*), 0.80 (d, *J* = 6.5 Hz, 3H, CH_3 *minor*), 0.62 (d, *J* = 6.9 Hz, 3H, CH_3 *major*); **^{13}C NMR** (101 MHz, $CDCl_3$; mixture of diastereoisomers in a 1.5 :1 ratio: the signals corresponding to the two distereoisomers are partially resolved): δ = 166.4, 166.0, 162.5, 128.8, 126.2, 125.9, 113.9, 113.8, 81.0, 79.5, 75.7, 55.4, 55.4, 49.1, 47.8, 43.3, 40.9, 40.7, 40.3, 34.4, 34.2, 31.6, 31.3, 25.5, 25.4, 22.9, 22.8, 22.3, 21.3, 21.1, 16.1, 15.9, -0.5, -0.9; **IR** (film): $\tilde{\nu}$ = 3317 (w), 2953 (m), 2922 (m), 2868 (w), 1636 (m), 1606 (s), 1501 (m), 1257 (s), 1178 (m), 1026 (m), 844 (m); **HRMS** (ESI) calcd. for $C_{21}H_{32}INNaO_3^+$ $[M+Na]^+$ 496.1319; Found 496.1323.

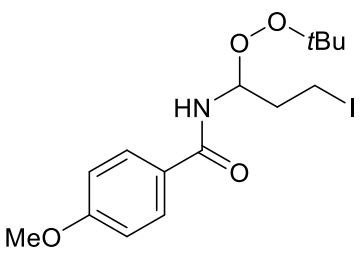
N-(1-(2-Hydroxyethoxy)-3-iodopropyl)-4-methoxybenzamide (**307f**)



Following GP C, using from ethane-1,2-diol (22.3 mg, 0.360 mmol, 1.2 equiv.) and after stirring for 1 hour, N-(1-(2-hydroxyethoxy)-3-iodopropyl)-4-methoxybenzamide **307f** (65.0 mg, 0.171 mmol, 57%) was obtained as a yellow oil after purification by column chromatography on silica using 2:3 pentanes:ethyl acetate as eluent.

R_f: 0.22 (silica, pentanes:ethyl acetate 2:3); **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 7.98 – 7.81 (m, 3H, Ar*H* + N*H*), 7.05 – 6.93 (m, 2H, Ar*H*), 5.55 (ddd, *J* = 9.2, 7.2, 5.4 Hz, 1H, C*H*), 3.86 (s, 3H, OCH_3), 3.70 – 3.59 (m, 4H, OCH_2CH_2O), 3.35 (t, *J* = 7.2 Hz, 2H, CH_2I), 2.35 (dq, *J* = 13.9, 6.9 Hz, 1H, CH_2CH$_2$I), 2.26 – 2.16 (m, 1H, CH_2CH$_2$I); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 167.3, 163.4, 130.2, 127.3, 114.3, 81.3, 70.6, 62.0, 55.8, 40.1, 1.5; **IR** (film): $\tilde{\nu}$ =3307 (w), 2934 (w), 2872 (w), 2839 (w), 1708 (m), 1640 (m), 1605 (s), 1534 (m), 1501 (s), 1255 (s), 1177 (s), 1106 (m), 1027 (s), 844 (m), 768 (w); **HRMS** (ESI) calcd. for $C_{13}H_{18}INNaO_4^+$ $[M+Na]^+$ 402.0173; Found 402.0181.

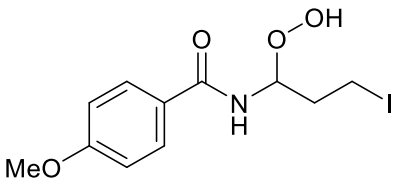
N-(1-(*tert*-Butylperoxy)-3-iodopropyl)-4-methoxybenzamide (**307g**)



In a glass vial, N-cyclopropyl-4-methoxybenzamide **296a** (0.300 mmol, 1.0 equiv.), iodine (83.8 mg, 0.330 mmol, 1.1 equiv.), a *tert*-butyl hydroperoxide solution, 5.0-6.0 M in decane (72.0 µL, 0.360 mmol, 1.2 equiv.) and diphenyl phosphate (7.5 mg, 0.030 mmol, 0.10 equiv.) were dissolved in 1.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the crude product was directly submitted to column chromatography on silica using 4:1 pentanes:ethyl acetate as eluent. N-(1-(*tert*-Butylperoxy)-3-iodopropyl)-4-methoxybenzamide **307g** (83.2 mg, 0.204 mmol, 68%) was obtained as a yellow oil.

R_f: 0.38 (silica, pentanes:ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.93 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.58 (d, *J* = 8.8 Hz, 1H, N*H*), 5.91 (ddd, *J* = 8.9, 7.1, 5.7 Hz, 1H, C*H*), 3.85 (s, 3H, OCH_3), 3.30 – 3.16 (m, 2H, CH_2I), 2.51 – 2.39 (m, 1H, CH_2CH$_2$I), 2.35 – 2.24 (m, 1H, CH_2CH$_2$I), 1.23 (s, 9H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.4, 162.5, 129.0, 126.0, 113.8, 83.7, 80.9, 55.4, 37.2, 26.4, -1.6; **IR** (film): $\tilde{\nu}$ = 3312 (w), 2976 (m), 2933 (w), 2838 (w), 1647 (s), 1606 (s), 1534 (m), 1503 (s), 1363 (m), 1255 (s), 1177 (s), 1031 (m), 845 (m); **HRMS** (ESI) calcd. for $C_{15}H_{22}INNaO_4^+$ $[M+Na]^+$ 430.0486; Found 430.0483.

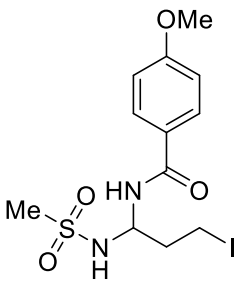
N-(1-Hydroperoxy-3-iodopropyl)-4-methoxybenzamide (**307h**)



In a glass vial, N-cyclopropyl-4-methoxybenzamide **296a** (57.3 mg, 0.300 mmol, 1.0 equiv.), iodine (83.8 mg, 0.330 mmol, 1.1 equiv.), a hydrogen peroxide 30% aqueous solution (61.3 µL, 0.600 mmol, 2.0 equiv.) and diphenyl phosphate (7.5 mg, 0.030 mmol, 0.10 equiv.) were dissolved in 1.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, the crude product was directly submitted to column chromatography on silica using 3:2 pentanes:ethyl acetate as eluent. N-(1-Hydroperoxy-3-iodopropyl)-4-methoxybenzamide **307h** (94.6 mg, 0.269 mmol, 90%) was obtained as a grey solid.

R_f: 0.30 (silica, pentanes:ethyl acetate 3:2); **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 10.94 (s, 1H, OO*H*), 8.08 (d, *J* = 8.9 Hz, 1H, N*H*), 7.93 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.99 (d, *J* = 8.8 Hz, 2H, Ar*H*), 5.90 (dt, *J* = 8.8, 6.7 Hz, 1H, C*H*), 3.86 (s, 3H, OCH_3), 3.34 (t, *J* = 7.2 Hz, 2H, CH_2I), 2.52 (dq, *J* = 14.0, 7.0 Hz, 1H, CH_2CH$_2$I), 2.27 (dq, *J* = 14.2, 7.5 Hz, 1H, CH_2CH$_2$I); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 167.0, 163.4, 130.3, 127.4, 114.3, 85.5, 55.8, 36.8, 0.9; **IR** (film): $\tilde{\nu}$ = 3280 (w), 2963 (w), 2837 (w), 1635 (m), 1605 (s), 1500 (s), 1254 (s), 1176 (s), 1027 (m), 842 (m), 768 (m); **HRMS** (ESI) calcd. for $C_{11}H_{14}INNaO_4^+$ $[M+Na]^+$ 373.9860; Found 373.9857.

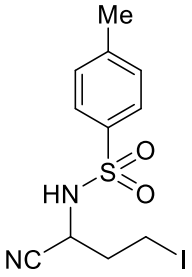
N-(3-Iodo-1-(methylsulfonamido)propyl)-4-methoxybenzamide (**308**)



In a glass vial, N-cyclopropyl-4-methoxybenzamide **296a** (57.3 mg, 0.300 mmol, 1.0 equiv.), N-iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.), diphenyl phosphate (7.5 mg, 0.030 mmol, 0.1 equiv.), and methanol (14.4 μL, 0.360 mmol, 1.2 equiv.) were dissolved in 1.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. Methanesulfonamide (85.6 mg, 0.900 mmol, 3.0 equiv.) was then added and the reaction mixture was stirred at room temperature for another 10 minutes. After the completion of the reaction, the crude product was directly submitted to column chromatography on silica using 2:3 pentanes:Et_2O as eluent. N-(3-Iodo-1-(methylsulfonamido) propyl)-4-methoxybenzamide **308** (84.9 mg, 0.206 mmol, 69%) was obtained as a pale yellow solid.

R_f: 0.26 (silica, pentanes:diethyl ether 2:3); **Mp:** 102-105 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.86 – 7.65 (m, 2H, Ar*H*), 7.03 – 6.83 (m, 2H, Ar*H*), 6.24 (d, *J* = 9.6 Hz, 1H, N*H*), 5.45 (ddd, *J* = 9.6, 7.0, 5.3 Hz, 1H, C*H*), 3.86 (s, 3H, OCH_3), 3.42 (s, 3H, CH_3), 3.32 – 3.15 (m, 2H, CH_2I), 2.37 – 2.14 (m, 2H, CH_2CH_2I); 1 NH is not resolved. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.8, 162.6, 128.9, 125.8, 113.9, 81.6, 56.3, 55.5, 39.6, -1.0; **IR** (film): $\tilde{\nu}$ = 3308 (w), 2933 (w), 2835 (w), 1642 (s), 1606 (s), 1532 (m), 1502 (s), 1255 (s), 1176 (m), 1104 (m), 1066 (m), 844 (m); **HRMS** (ESI) calcd. for $C_{12}H_{17}IN_2NaO_4S^+$ $[M+Na]^+$ 434.9846; Found 434.9855.

N-(1-Cyano-3-iodopropyl)-4-methylbenzenesulfonamide (**309**)

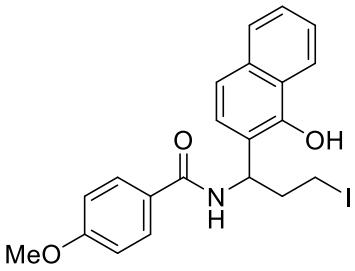


Starting from N-cyclopropyl-4-methylbenzenesulfonamide **296q** (21.1 mg, 0.100 mmol, 1.0 equiv.), N-iodosuccinimide (23.6 mg, 0.105 mmol, 1.05 equiv.) and methanol (4.8 μL, 0.12 mmol, 1.2 equiv.) were dissolved in 0.5 mL of $CDCl_3$ (0.20 M). After stirring for 20 hours at room temperature, TMSCN (18.8 μL, 0.150 mmol, 1.5 equiv.) was added to the reaction crude and kept stirring at room temperature for another 20 hours. N-(1-Cyano-3-iodopropyl)-4-methylbenzenesulfonamide **309** (23.5 mg, 0.0650 mmol, 65%) was obtained as a beige solid after purification by preparative TLC on silica using 4:1 pentanes:ethyl acetate as eluent.

Note: It was later found that N-(1-cyano-3-iodopropyl)-4-methylbenzenesulfonamide **309** can be synthesized simply by replacing methanol with TMSCN. Starting from N-cyclopropyl-4-methylbenzenesulfonamide **296q** (84.4 mg, 0.400 mmol, 1.0 equiv.), NIS (108 mg, 0.480 mmol, 1.2 equiv.) and TMSCN (75.1 μL, 0.600 mmol, 1.5 equiv.) were dissolved in 2.0 mL of $CHCl_3$ (0.20 M). After stirring at room temperature for 24 hours, N-(1-cyano-3-iodopropyl)-4-methylbenzenesulfonamide **309** (109 mg, 0.300 mmol, 75%) was obtained as a beige solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.25 (silica, pentanes:ethyl acetate 4:1); **Mp:** 132-133 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.38 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.49 (d, *J* = 9.8 Hz, 1H, N*H*), 4.40 (dt, *J* = 9.9, 7.4 Hz, 1H, C*H*), 3.21 (t, *J* = 6.7 Hz, 2H, CH_2I), 2.45 (s, 3H, CH_3), 2.29 (q, *J* = 6.9 Hz, 2H, CH_2CH_2I); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.9, 135.6, 130.2, 127.3, 116.6, 45.1, 37.2, 21.7, -2.5; **IR** (film): $\tilde{\nu}$ = 3267 (w), 1436 (w), 1337 (m), 1164 (s), 1090 (m), 936 (w), 819 (w), 757 (m); **HRMS** (ESI) calcd. for $C_{11}H_{13}IN_2NaO_2S^+$ $[M+Na]^+$ 386.9635; Found 386.9633.

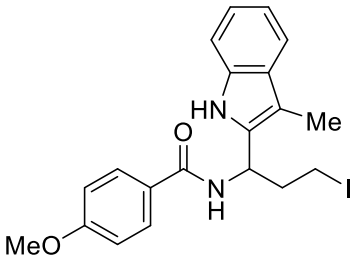
N-(1-(1-Hydroxynaphthalen-2-yl)-3-iodopropyl)-4-methoxybenzamide (**310**)



In a glass vial, N-cyclopropyl-4-methoxybenzamide **296a** (57.3 mg, 0.300 mmol, 1.0 equiv.), diphenyl phosphate (7.5 mg, 0.030 mmol, 0.1 equiv.), N-iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.) and methanol (14.4 µL, 0.360 mmol, 1.2 equiv.) were dissolved in 1.5 mL of $CHCl_3$ (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. 1-Naphthol (47.2 mg, 0.360 mmol, 1.2 equiv.) and TFA (23.0 µL, 0.300 mmol, 1.0 equiv.) were added and the reaction mixture was stirred at room temperature for another 1 hour. After the completion of the reaction, the crude product was directly submitted to column chromatography on silica using 2:1 pentanes: ethyl acetate as eluent. N-(3-Iodo-1-(3-methyl-1H-indol-2-yl)propyl)-4-methoxybenzamide **310** (73.0 mg, 0.159 mmol, 53%) was obtained as a yellow oil.

R_f: 0.44 (silica, pentanes:ethyl acetate 2:1); **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 10.64 (s, 1H, O*H*), 8.61 (d, *J* = 8.1 Hz, 1H, N*H*), 8.43 – 8.25 (m, 1H, Ar*H*), 7.92 (d, *J* = 8.9 Hz, 2H, Ar*H*), 7.82 – 7.72 (m, 1H, Ar*H*), 7.50 – 7.36 (m, 4H, Ar*H*), 6.98 (d, *J* = 8.9 Hz, 2H, Ar*H*), 5.65 (td, *J* = 8.5, 6.3 Hz, 1H, C*H*), 3.83 (s, 3H, OCH_3), 3.51 – 3.29 (m, 2H, CH_2I), 2.98 – 2.86 (m, 1H, CH_2CH$_2$I), 2.64 (dq, *J* = 14.1, 7.0 Hz, 1H, CH_2CH$_2$I); **^{13}C NMR** (101 MHz, Acetone-d_6): δ =169.7, 163.7, 152.5, 135.2, 130.4, 128.1, 127.4, 127.2, 126.0, 125.9, 124.8, 123.9, 121.9, 120.5, 114.5, 55.8, 50.0, 37.5, 3.2; **IR** (film): $\tilde{\nu}$ = 3253 (brs), 3055 (w), 1695 (w), 1605 (s), 1500 (s), 1257 (s), 1178 (s), 1028 (m), 843 (w); **HRMS** (ESI) calcd. for $C_{21}H_{21}INO_3^+$ $[M+H]^+$ 462.0561; Found 462.0557.

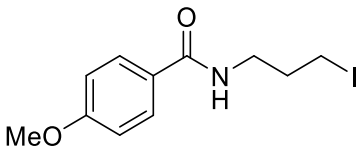
N-(3-Iodo-1-(3-methyl-1H-indol-2-yl)propyl)-4-methoxybenzamide (**311**)



In a glass vial, N-cyclopropyl-4-methoxybenzamide **296a** (57.3 mg, 0.300 mmol, 1.0 equiv.), diphenyl phosphate (7.5 mg, 0.030 mmol, 0.1 equiv.), N-iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.) and methanol (14.4 µL, 0.360 mmol, 1.2 equiv.) were dissolved in 1.5 mL of $CHCl_3$ (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. 3-Methylindole (47.2 mg, 0.360 mmol, 1.2 equiv.) and TFA (23.0 µL, 0.300 mmol, 1.0 equiv.) were added and the reaction mixture was stirred at room temperature for another 20 minutes. After the completion of the reaction, the crude product was directly submitted to column chromatography on silica using 2:1 pentanes: ethyl acetate as eluent. N-(3-Iodo-1-(3-methyl-1H-indol-2-yl)propyl)-4-methoxybenzamide **311** (110 mg, 0.246 mmol, 82%) was obtained as a dark yellow solid.

R_f: 0.33 (silica, pentanes:ethyl acetate 2:1); **Mp:** 83-86 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 9.99 (s, 1H, indole-N*H*), 8.04 (d, *J* = 7.6 Hz, 1H, N*H*), 7.91 – 7.83 (m, 2H, Ar*H*), 7.47 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.30 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.08 – 7.03 (m, 1H, Ar*H*), 7.02 – 6.97 (m, 1H, Ar*H*), 6.96 – 6.89 (m, 2H, Ar*H*), 5.63 (q, *J* = 7.7 Hz, 1H, C*H*), 3.81 (s, 3H, OCH_3), 3.30 (ddd, *J* = 9.8, 7.6, 6.5 Hz, 1H, CH_2I), 3.21 (dt, *J* = 9.7, 7.2 Hz, 1H, CH_2I), 2.65 (ddt, *J* = 26.6, 14.3, 6.9 Hz, 2H, CH_2CH$_2$I), 2.39 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 166.7, 163.1, 136.9, 135.0, 130.0, 129.8, 127.7, 122.2, 119.5, 119.2, 114.3, 111.7, 108.5, 55.8, 48.0, 39.5, 9.0, 2.9; **IR** (film): $\tilde{\nu}$ = 3303 (m), 2959 (w), 2924 (m), 2854 (w), 1606 (s), 1539 (m), 1504 (s), 1460 (m), 1302 (m), 1256 (s), 1177 (m), 1130 (m), 907 (m), 842 (m); **HRMS** (ESI) calcd. for $C_{20}H_{21}IN_2NaO_2^+$ $[M+Na]^+$ 471.0540; Found 471.0546.

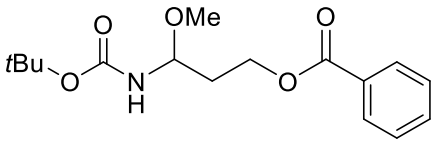
N-(3-Iodopropyl)-4-methoxybenzamide (**312**)



In a glass vial, N-cyclopropyl-4-methoxybenzamide **296** (57.3 mg, 0.300 mmol, 1.0 equiv.), N-iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.) and methanol (14.4 μL, 0.360 mmol, 1.2 equiv.) were dissolved in 1.5 mL of acetic acid (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. Sodium cyanoborohydride (28.3 mg, 0.450 mmol, 1.5 equiv.) was added and the reaction mixture was stirred at room temperature for another 30 minutes. After the completion of the reaction, the crude product was directly submitted to column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent. N-(3-Iodopropyl)-4-methoxybenzamide **312** (75.0 mg, 0.235 mmol, 78%) was obtained as a pale yellow solid.

R_f: 0.34 (silica, pentanes:ethyl acetate 1:1); **Mp:** 84-86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.92 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.27 (s, 1H, N*H*), 3.85 (s, 3H, OCH_3), 3.54 (q, *J* = 6.4 Hz, 2H, CH_2), 3.24 (t, *J* = 6.8 Hz, 2H, CH_2), 2.15 (p, *J* = 6.7 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.2, 162.2, 128.7, 126.5, 113.8, 55.4, 40.5, 32.9, 3.4; **IR** (film): $\tilde{\nu}$ = 3289 (w), 2932 (w), 1633 (m), 1606 (s), 1543 (m), 1504 (s), 1299 (m), 1254 (s), 1179 (m), 1029 (w), 844 (w); **HRMS** (APCI) calcd. for $C_{11}H_{15}INO_2^+$ $[M+H]^+$ 320.0142; Found 320.0138.

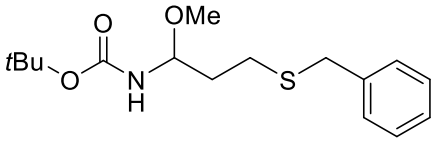
3-((*tert*-Butoxycarbonyl)amino)-3-methoxypropyl benzoate (**314**)



In a glass vial, *tert*-butyl cyclopropylcarbamate **296o** (47.1 mg, 0.300 mmol, 1.0 equiv.), N-iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.) and methanol (14.4 μL, 0.360 mmol, 1.2 equiv.) were dissolved in 1.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, K_2CO_3 (82.8 mg, 0.600 mmol, 2.0 equiv.) was added to the reaction mixture and then solvent was removed under reduced pressure. The crude was dissolved in 1.5 mL of DMF, and benzoic acid (73.2 mg, 0.600 mmol, 2.0 equiv.) was added. The resulting mixture was stirred at room temperature for 16 hours and then diluted with brine (10.0 mL). The aqueous layer was extracted with EtOAc (10.0 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent. 3-((*tert*-Butoxycarbonyl)amino)-3-methoxypropyl benzoate **314** (75.1 mg, 0.243 mmol, 81%) was obtained as a yellow oil.

R_f: 0.33 (silica, pentanes:ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.4 Hz, 2H, Ar*H*), 7.55 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.43 (t, *J* = 7.6 Hz, 2H, Ar*H*), 5.12 – 4.83 (m, 2H, N*H* + C*H*), 4.42 (t, *J* = 6.2 Hz, 2H, OCH_2), 3.36 (s, 3H, OCH_3), 2.08 – 2.04 (m, 2H, CH_2CH_2O), 1.43 (s, 9H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.4, 155.3, 133.0, 130.1, 129.6, 128.4, 80.4, 79.9, 61.1, 55.5, 34.6, 28.2; **IR** (film): $\tilde{\nu}$ = 3354 (w), 2977 (w), 2933 (w), 1716 (s), 1513 (m), 1367 (m), 1274 (s), 1167 (s), 1114 (m), 861 (w), 712 (s); **HRMS** (APCI) calcd. for $C_{16}H_{23}NNaO_5^+$ $[M+Na]^+$ 332.1468; Found 332.1469.

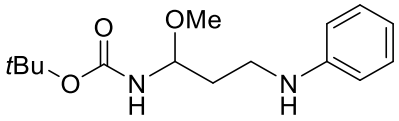
***tert*-Butyl (3-(benzylthio)-1-methoxypropyl)carbamate (315)**



In a glass vial, *tert*-butyl cyclopropylcarbamate **296o** (47.1 mg, 0.300 mmol, 1.0 equiv.), N-iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.) and methanol (14.4 µL, 0.360 mmol, 1.2 equiv.) were dissolved in 1.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, K_2CO_3 (82.8 mg, 0.600 mmol, 2.0 equiv.) was added to the reaction mixture and then solvent was removed under reduced pressure. The crude was dissolved in 1.5 mL of DMF, and phenylmethanethiol (52.7 µL, 0.450 mmol, 1.5 equiv.) was added. The resulting mixture was stirred at room temperature for 3 hours and then diluted with brine (10.0 mL). The aqueous layer was extracted with EtOAc (10.0 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica using 4:1 pentanes:ethyl acetate as eluent. *tert*-Butyl (3-(benzylthio)-1-methoxypropyl)carbamate **315** (74.1 mg, 0.238 mmol, 79%) was obtained as a colorless oil.

R_f: 0.37 (silica, pentanes:ethyl acetate 6:1); **^{1}H NMR** (400 MHz, Acetonitrile-d_3): 7.33 – 7.26 (m, 4H, Ar*H*), 7.23 (h, *J* = 4.3 Hz, 1H, Ar*H*), 5.61 (d, *J* = 10.0 Hz, 1H, N*H*), 4.78 (dt, *J* = 10.2, 6.4 Hz, 1H, C*H*), 3.69 (s, 2H, PhCH_2), 3.19 (s, 3H, OCH_3), 2.40 (t, *J* = 7.4 Hz, 2H, SCH_2), 1.81 (dt, *J* = 14.0, 7.0 Hz, 1H, CH_2CH$_2$S), 1.69 (dq, *J* = 14.0, 7.3 Hz, 1H, CH_2CH$_2$S), 1.40 (s, 9H, CH_3); **^{13}C NMR** (101 MHz, Acetonitrile-d_3): δ = 156.5, 139.9, 129.8, 129.4, 127.8, 82.7, 79.7, 55.2, 36.5, 35.5, 28.5, 27.5; **IR** (film): $\tilde{\nu}$ = 3337 (w), 2977 (w), 2930 (w), 1703 (s), 1495 (s), 1453 (m), 1366 (s), 1248 (m), 1163 (s), 1047 (m), 700 (m); **HRMS** (ESI) calcd. for $C_{16}H_{25}NNaO_3S^+$ $[M+Na]^+$ 334.1447; Found 334.1455.

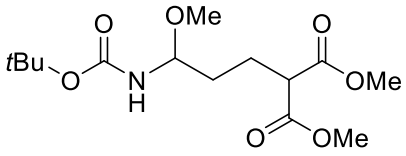
***tert*-Butyl (1-methoxy-3-(phenylamino)propyl)carbamate (316)**



In a glass vial, *tert*-butyl cyclopropylcarbamate **296o** (47.1 mg, 0.300 mmol, 1.0 equiv.), N-iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.) and methanol (14.4 µL, 0.360 mmol, 1.2 equiv.) were dissolved in 1.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, K_2CO_3 (41.4 mg, 0.300 mmol, 1.0 equiv.) was added to the mixture before purification by column chromatography on silica using 4:1 pentanes:ethyl acetate as eluent. The obtained *tert*-butyl (3-iodo-1-methoxypropyl)carbamate **4o** was then dissolved in 1.5 mL of DMF, K_2CO_3 (82.8 mg, 0.600 mmol, 2.0 equiv.) and aniline (54.8 µL, 0.600 mmol, 2.0 equiv.) were added. The resulting mixture was stirred at room temperature for 16 hours and then diluted with brine (10.0 mL). The aqueous layer was extracted with EtOAc (10.0 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent. *tert*-Butyl (1-methoxy-3-(phenylamino)propyl)carbamate **316** (72.1 mg, 0.258 mmol, 86%) was obtained as a pale yellow oil.

R_f: 0.45 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.18 (t, *J* = 7.8 Hz, 2H, Ar*H*), 6.70 (t, *J* = 7.3 Hz, 1H, Ar*H*), 6.62 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.06 – 4.80 (m, 2H, N*H* + C*H*), 3.94 (s, 1H, N*H*), 3.36 (s, 3H, OCH_3), 3.25 (td, *J* = 6.5, 3.4 Hz, 2H, NCH_2), 1.99 – 1.82 (m, 2H, CH_2CH$_2$N), 1.46 (s, 9H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.4, 148.1, 129.2, 117.4, 112.9, 81.8, 80.0, 55.5, 40.1, 35.1, 28.3; **IR** (film): $\tilde{\nu}$ = 3377 (w), 2977 (w), 2932 (w), 2832 (w), 1699 (s), 1603 (s), 1504 (s), 1366 (m), 1251 (m), 1168 (s), 1080 (m), 749 (m); **HRMS** (APCI) calcd. for $C_{15}H_{24}N_2NaO_3^+$ $[M+Na]^+$ 303.1679; Found 303.1677.

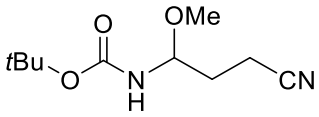
Dimethyl 2-(3-((*tert*-butoxycarbonyl)amino)-3-methoxypropyl)malonate (**317**)



In a glass vial, *tert*-butyl cyclopropylcarbamate **296o** (47.1 mg, 0.300 mmol, 1.0 equiv.), N-iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.) and methanol (14.4 μL, 0.360 mmol, 1.2 equiv.) were dissolved in 1.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, K_2CO_3 (41.4 mg, 0.300 mmol, 1.0 equiv.) was added to the mixture before purification by column chromatography on silica using 4:1 pentanes:ethyl acetate as eluent. The obtained *tert*-butyl (3-iodo-1-methoxypropyl)carbamate **298o** was then dissolved in 1.5 mL of DMF, K_2CO_3 (82.8 mg, 0.600 mmol, 2.0 equiv.) and dimethyl malonate (70.0 μL, 0.600 mmol, 2.0 equiv.) were added. The resulting mixture was stirred at room temperature for 16 hours and then diluted with brine (10.0 mL). The aqueous layer was extracted with EtOAc (10.0 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent. Dimethyl 2-(3-((*tert*-butoxycarbonyl)amino)-3-methoxypropyl)malonate **317** (76.6 mg, 0.240 mmol, 80%) was obtained as a pale yellow oil.

R_f: 0.35 (silica, pentanes:ethyl acetate 3:1) $KMnO_4$; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 6.33 (d, *J* = 9.9 Hz, 1H, N*H*), 4.78 (dt, *J* = 10.0, 6.4 Hz, 1H, C*H*), 3.69 (s, 6H, CO_2CH_3), 3.45 (t, *J* = 7.5 Hz, 1H, C*H*), 3.25 (s, 3H, OCH_3), 1.97 – 1.85 (m, 2H, CH_2), 1.75 – 1.65 (m, 1H, CH_2), 1.62 – 1.54 (m, 1H, C*H*), 1.42 (s, 9H, CH_3); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 170.3, 170.2, 156.5, 83.3, 79.1, 55.0, 52.6, 51.7, 33.3, 28.5, 25.5; **IR** (film): $\tilde{\nu}$ = 3367 (w), 2977 (w), 2955 (w), 2833 (w), 1733 (s), 1717 (s), 1511 (m), 1437 (m), 1366 (m), 1245 (m), 1162 (m), 1110 (m), 1048 (m), 863 (w); **HRMS** (ESI) calcd. for $C_{14}H_{25}NNaO_7^+$ $[M+Na]^+$ 342.1523; Found 342.1530.

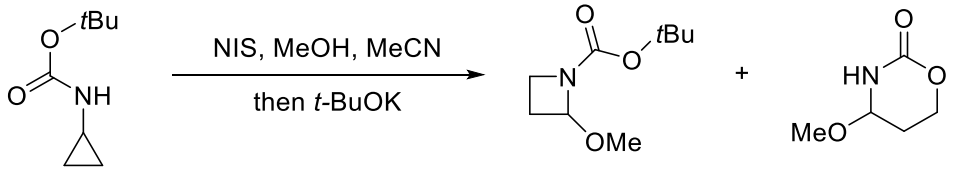
***tert*-Butyl (3-cyano-1-methoxypropyl)carbamate** (**318**)



In a glass vial, *tert*-butyl cyclopropylcarbamate **296o** (47.1 mg, 0.300 mmol, 1.0 equiv.), N-iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.) and methanol (14.4 μL, 0.360 mmol, 1.2 equiv.) were dissolved in 1.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, K_2CO_3 (41.4 mg, 0.300 mmol, 1.0 equiv.) was added to the mixture before purification by column chromatography on silica using 4:1 pentanes:ethyl acetate as eluent. The obtained *tert*-butyl (3-iodo-1-methoxypropyl)carbamate **296o** was then dissolved in 1.5 mL of DMF. K_2CO_3 (82.8 mg, 0.600 mmol, 2.0 equiv.) and NaCN (29.4 mg, 0.600 mmol, 2.0 equiv.) were added. The resulting mixture was stirred at room temperature for 2 hours and then diluted with EtOAc (10.0 mL) and extracted with brine (10.0 mL x 6). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. *tert*-Butyl (3-cyano-1-methoxypropyl)carbamate **318** (60.4 mg, 0.282 mmol, 94%) was obtained as a colorless oil without any further purification.

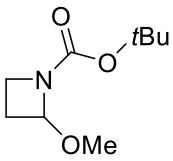
R_f: 0.48 (silica, pentanes:ethyl acetate 2:1) $KMnO_4$; **Mp:** 49-52 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.90 (dt, *J* = 12.6, 6.1 Hz, 1H, C*H*), 4.80 (d, *J* = 10.5 Hz, 1H, N*H*), 3.35 (s, 3H, OCH_3), 2.44 (td, *J* = 7.4, 4.6 Hz, 2H, CH_2CN), 1.93 (q, *J* = 7.1 Hz, 2H, CH_2CH_2CN), 1.46 (s, 9H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.1, 119.0, 81.3, 80.3, 55.6, 31.4, 28.2, 13.3; **IR** (film): $\tilde{\nu}$ = 3341 (w), 2979 (w), 2936 (w), 2834 (w), 2247 (w), 1700 (s), 1515 (s), 1367 (s), 1214 (m), 1169 (s), 1050 (s), 892 (w); **HRMS** (APCI) calcd. for $C_{10}H_{18}N_2NaO_3^+$ $[M+Na]^+$ 237.1210; Found 237.1214.

***tert*-Butyl 2-methoxyazetidine-1-carboxylate (319)**



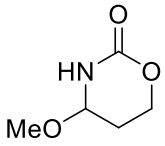
In a glass vial, *tert*-butyl cyclopropylcarbamate **296o** (47.1 mg, 0.300 mmol, 1.0 equiv.), N-iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.) and methanol (14.4 µL, 0.360 mmol, 1.2 equiv.) were dissolved in 1.5 mL of MeCN (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. After the completion of the reaction, *t*-BuOK (101 mg, 0.900 mmol, 3.0 equiv.) was added. The resulting mixture was stirred at room temperature for 16 hours and then diluted with brine (10.0 mL). The aqueous layer was extracted with DCM (10.0 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on basic aluminium oxide. *tert*-Butyl 2-methoxyazetidine-1-carboxylate **319** (14.1 mg, 0.075 mmol, 25%) was obtained as a pale yellow oil by using dichloromethane as eluent. 4-Methoxy-1,3-oxazinan-2-one **319'** (11.8 mg, 0.090 mmol, 30%) was obtained as a yellow oil by using 20:1 dichloromethane:methanol as eluent.

***tert*-Butyl 2-methoxyazetidine-1-carboxylate (319)**



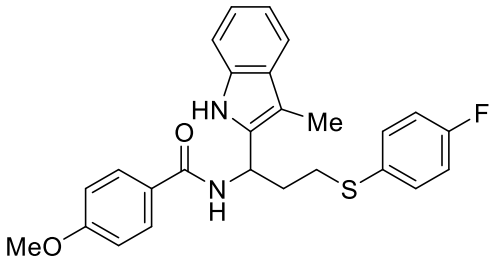
R_f: 0.50 (silica, pentanes:ethyl acetate 6:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.17 (dd, *J* = 6.8, 4.0 Hz, 1H, C*H*), 3.74 (dt, *J* = 8.7, 4.3 Hz, 1H, NCH_2), 3.64 (td, *J* = 8.5, 6.2 Hz, 1H, NCH_2), 3.49 (s, 3H, OCH_3), 2.42 (dddd, *J* = 12.2, 8.9, 6.8, 5.4 Hz, 1H, CH_2), 2.17 – 2.08 (m, 1H, CH_2), 1.46 (s, 9H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.4, 91.2, 80.0, 56.2, 43.5, 28.3, 24.8; **IR** (film): $\tilde{\nu}$ = 2974(w), 2931 (w), 2900 (w), 1702 (s), 1456 (w), 1381 (m), 1349 (m), 1257 (w), 1154 (m), 1092 (s), 999 (w), 925 (w), 853 (w); **HRMS** (ESI) calcd. for $C_9H_{17}NNaO_3^+$ $[M+Na]^+$ 210.1101; Found 210.1107.

4-Methoxy-1,3-oxazinan-2-one (319')



R_f: 0.37 (silica, dichloromethane:methanol 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.70 (s, 1H, N*H*), 4.57 (q, *J* = 3.6 Hz, 1H, C*H*), 4.49 (ddd, *J* = 12.6, 10.9, 2.9 Hz, 1H, OCH_2), 4.26 (dddd, *J* = 10.9, 4.8, 2.5, 1.1 Hz, 1H, OCH_2), 3.36 (s, 3H, OCH_3), 2.05 – 1.99 (m, 1H, CH_2), 1.97 – 1.90 (m, 1H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 153.8, 79.8, 63.1, 54.6, 26.9; **IR** (film): $\tilde{\nu}$ = 3269 (w), 2939 (w), 2182 (w), 1698 (s), 1284 (s) 1087 (s); **HRMS** (ESI) calcd. for $C_5H_{10}NO_3^+$ $[M+H]^+$ 132.0655; Found 132.0651.

N-(3-((4-Fluorophenyl)thio)-1-(3-methyl-1H-indol-2-yl)propyl)-4-methoxybenzamide (320)

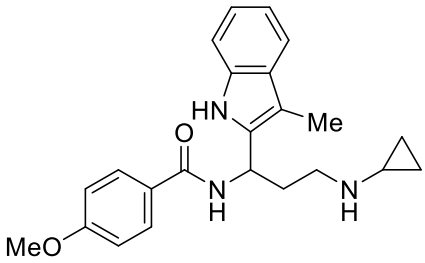


In a glass vial, N-cyclopropyl-4-methoxybenzamide **296a** (57.3 mg, 0.300 mmol, 1.0 equiv.), diphenyl phosphate (7.5 mg, 0.030 mmol, 0.1 equiv.), N-iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.) and methanol (14.4 µL, 0.360 mmol, 1.2 equiv.) were dissolved in 1.5 mL of $CHCl_3$ (0.20 M). The reaction mixture was stirred at room temperature for 30 minutes. 3-Methylindole (47.2 mg, 0.360 mmol, 1.2 equiv.)

and TFA (23.0 μL, 0.300 mmol, 1.0 equiv.) were added to the reaction mixture and the reaction mixture was stirred at room temperature for another 20 minutes. Then the solvent was removed under reduced pressure. K_2CO_3 (124 mg, 0.900 mmol, 3.0 equiv.), 4-fluorobenzenethiol (64.0 μL, 0.600 mmol, 2.0 equiv.) and 1.5 mL of DMF were added to the residue. After stirring at room temperature for 16 hours, the crude product was diluted with DCM (20.0 mL) and extracted with brine (20.0 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent. N-(3-((4-Fluorophenyl)thio)-1-(3-methyl-1H-indol-2-yl)propyl)-4-methoxybenzamide **320** (106 mg, 0.240 mmol, 79%) was obtained as a pale yellow solid.

R_f: 0.41 (silica, pentanes:ethyl acetate 2:1); **Mp:** 143-146 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.01 (s, 1H, indole-N*H*), 7.73 – 7.62 (m, 2H, Ar*H*), 7.51 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.30 (ddd, *J* = 8.7, 5.4, 2.7 Hz, 2H, Ar*H*), 7.27 – 7.25 (m, 1H, Ar*H*), 7.15 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H, Ar*H*), 7.11 – 7.06 (m, 1H, Ar*H*), 6.99 – 6.91 (m, 2H, Ar*H*), 6.89 – 6.83 (m, 2H, Ar*H*), 6.69 (d, *J* = 7.4 Hz, 1H, N*H*), 5.28 (q, *J* = 7.5 Hz, 1H, C*H*), 3.81 (s, 3H, OCH_3), 2.86 (t, *J* = 7.0 Hz, 2H, CH_2S), 2.55 (dq, *J* = 14.3, 7.1 Hz, 1H, CH_2CH$_2$S), 2.38 (dt, *J* = 14.0, 7.3 Hz, 1H, CH_2CH$_2$S), 2.31 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.6, 162.4, 161.9 (d, *J* = 246.7 Hz), 135.4, 133.4, 132.6 (d, *J* = 8.0 Hz), 130.4 (d, *J* = 3.4 Hz), 128.8, 128.6, 126.2, 122.1, 118.9 (d, *J* = 51.0 Hz), 116.2, 116.0, 113.8, 111.0, 108.2, 55.4, 47.1, 33.1, 32.1, 8.8; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -115.1; **IR** (film): $\tilde{\nu}$ = 3313 (m), 2924 (w), 2856 (w), 1606 (s), 1540 (m), 1490 (s), 1460 (m), 1306 (m), 1255 (s), 1178 (m), 1029 (m), 832 (m), 734 (m); **HRMS** (ESI) calcd. for $C_{26}H_{25}FN_2NaO_2S^+$ $[M+Na]^+$ 471.1513; Found 471.1505.

N-(3-(Cyclopropylamino)-1-(3-methyl-1H-indol-2-yl)propyl)-4-methoxybenzamide (**321**)

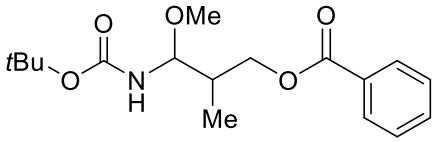


In a glass vial, N-cyclopropyl-4-methoxybenzamide **296a** (57.3 mg, 0.300 mmol, 1.0 equiv.), diphenyl phosphate (7.5 mg, 0.030 mmol, 0.1 equiv.), N-iodosuccinimide (70.8 mg, 0.315 mmol, 1.05 equiv.) and methanol (14.4 μL, 0.360 mmol, 1.2 equiv.) were dissolved in 1.5 mL of $CHCl_3$ (0.20 M). The reaction mixture was stirred for 30 minutes. 3-Methylindole (47.2 mg, 0.360 mmol, 1.2 equiv.) and TFA (23.0 μL, 0.300 mmol, 1.0 equiv.) were added to the reaction mixture and the reaction mixture was stirred for another 20 minutes. Then the solvent was removed under reduced pressure, K_2CO_3 (124 mg, 0.900 mmol, 3.0 equiv.), cyclopropyl amine (42.0 μL, 0.600 mmol, 2.0 equiv.) and 1.5 mL of DMF were added to the residue. After stirring at room temperature for 16h, the crude product was diluted with DCM (20.0 mL) and extracted with brine (20.0 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica using 8:1 dichloromethane:methanol as eluent. N-(3-(Cyclopropylamino)-1-(3-methyl-1H-indol-2-yl)propyl)-4-methoxybenzamide **321** (62.2 mg, 0.165 mmol, 55%) was obtained as a yellow solid.

R_f: 0.28 (silica, dichloromethane:methanol 8:1); **Mp:** 177-179 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 10.19 (s, 1H, indole-N*H*), 8.45 (d, *J* = 7.6 Hz, 1H, N*H*), 7.93 – 7.84 (m, 2H, Ar*H*), 7.45 (d, *J* = 7.1 Hz, 1H, Ar*H*), 7.27 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.02 (td, *J* = 8.0, 7.5, 1.4 Hz, 1H, Ar*H*), 6.99 – 6.96 (m, 1H, Ar*H*), 6.96 – 6.92 (m, 2H, Ar*H*), 5.67 – 5.54 (m, 1H, C*H*), 3.83 (s, 3H, OCH_3), 2.84 (t, *J* = 6.3 Hz, 2H, CH_2N), 2.31 (s, 3H, CH_3), 2.24 (qd, *J* = 6.5, 1.7 Hz, 2H, CH_2CH$_2$N), 2.21 – 2.15 (m, 1H, C*H*), 0.47 – 0.33 (m, 4H, CH_2); 1 N*H* was not resolved. **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 166.3, 163.0, 136.4, 136.3, 130.0,

129.9, 127.9, 121.7, 119.2, 118.9, 114.2, 111.6, 107.0, 55.7, 47.0, 46.1, 34.8, 31.1, 8.8, 6.2, 6.2; **IR** (film): $\tilde{\nu}$ = 3296 (m), 2933 (w), 1606 (s), 1504 (S), 1256 (s), 1179 (m), 1030 (m), 844 (m), 742 (m); **HRMS** (ESI) calcd. for $C_{23}H_{28}N_3O_2^+$ $[M+H]^+$ 378.2176; Found 378.2171.

3-((*tert*-Butoxycarbonyl)amino)-3-methoxy-2-methylpropyl benzoate (**327**)



In a glass vial, *tert*-butyl (2-methylcyclopropyl)carbamate **326** (17.1 mg, 0.100 mmol, 1.0 equiv.), N-iodosuccinimide (23.6 mg, 0.105 mmol, 1.05 equiv.) and methanol (4.8 μL, 0.12 mmol, 1.2 equiv.) were dissolved in 0.5 mL of dichloromethane (0.20 M). The reaction mixture was stirred for 30 minutes. After the completion of the reaction, K_2CO_3 (27.6 mg, 0.200 mmol, 2.0 equiv.) was added to the reaction mixture and then solvent was removed under reduced pressure. The crude was dissolved in 0.5 mL of DMF, and benzoic acid (24.4 mg, 0.200 mmol, 2.0 equiv.) was added. The resulting mixture was stirred at room temperature for 16 hours. The crude was then diluted with brine (5.0 mL). The aqueous layer was extracted with EtOAc (5.0 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by preparative TLC on silica using 3:1 pentanes:ethyl acetate as eluent. 3-((*tert*-Butoxycarbonyl)amino)-3-methoxy-2-methylpropyl benzoate **327** (10.3 mg, 0.032 mmol, 32%) was obtained as a colorless oil.

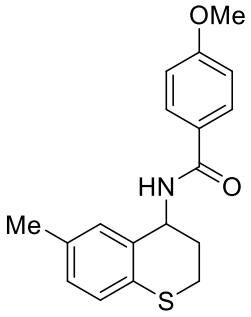
R_f: 0.30 (silica, pentanes:ethyl acetate 6:1); **^{1}H NMR** (400 MHz, $CDCl_3$; mixture of two diastereoisomers in a 1:1 ratio: the signals corresponding to the two diastereoisomers are not resolved): δ = 8.09 – 7.99 (m, 2H, Ar*H*), 7.60 – 7.53 (m, 1H, Ar*H*), 7.45 (dd, *J* = 8.4, 7.0 Hz, 2H, Ar*H*), 5.09 (dd, *J* = 20.7, 10.4 Hz, 1H, N*H*), 4.89 (ddd, *J* = 13.2, 10.4, 5.3 Hz, 1H, C*H*), 4.41 – 4.22 (m, 2H, OCH_2), 3.35 (d, *J* = 1.0 Hz, 3H, OCH_3), 2.19 (dq, *J* = 13.2, 6.4 Hz, 1H, C*H*CH_3), 1.45 (d, *J* = 2.6 Hz, 9H, CH_3), 1.07 (dd, *J* = 7.0, 1.8 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$; mixture of two diastereoisomers in a 1:1 ratio: the signals corresponding to the two diastereoisomers are partially resolved): δ = 166.4, 155.6, 133.0, 130.2, 130.1, 129.5, 128.4, 84.1, 83.8, 79.8, 66.0, 55.8, 55.7, 38.0, 37.7, 28.3, 12.8, 12.2; **IR** (film): $\tilde{\nu}$ = 3355 (w), 2977 (w), 2932 (w), 1718 (s), 1508 (m), 1367 (m), 1273 (s), 1170 (s), 1083 (m), 712 (m); **HRMS** (ESI) calcd. for $C_{17}H_{25}NNaO_5^+$ $[M+Na]^+$ 346.1625; Found 346.1634.

5.3.3 Synthesis of 4-amino thiochromans by a formal [3+3] cycloaddition

General Procedure D (GP D):

In a glass vial, the corresponding aminocyclopropane (0.400 mmol, 1.0 equiv.), N-iodosuccinimide (94.0 mg, 0.420 mmol, 1.05 equiv.), methanol (19.4 μL, 0.480 mmol, 1.20 equiv.), and diphenyl hydrogen phosphate (10.0 mg, 0.0400 mmol, 0.10 equiv.) were dissolved in chloroform (2.0 mL, 0.2 M). The reaction mixture was stirred at room temperature for 45 minutes if not specified otherwise. The corresponding thiophenol (0.400 mmol, 1.0 equiv.) was then added to the reaction mixture (minimum amount of chloroform was added beforehand to dissolve the thiophenols if they are viscous) and the mixture was stirred at room temperature for another 3 hours if not specified otherwise. Upon completion, the mixture was quenched by the addition of saturated aqueous solution of sodium thiosulfate (2 mL). The aqueous layer was then extracted with dichloromethane. The organic extract was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, pentanes/EtOAc).

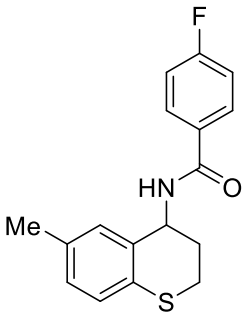
4-Methoxy-N-(6-methylthiochroman-4-yl)benzamide (313a)



Following GP D, starting from N-cyclopropyl-4-methoxybenzamide (**296a**) (76.4 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 4-methylbenzenethiol (49.7 mg, 0.400 mmol, 1.0 equiv.), 4-methoxy-N-(6-methylthiochroman-4-yl)benzamide (**313a**) (42.5 mg, 0.136 mmol, 34%) was obtained as a white solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.33 (silica, pentanes:ethyl acetate 3:1); **Mp:** 177-179 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.80 – 7.67 (m, 2H, Ar*H*), 7.10 (s, 1H, Ar*H*), 7.05 (d, *J* = 8.1 Hz, 1H, Ar*H*), 6.99 (d, *J* = 6.5 Hz, 1H, Ar*H*), 6.96 – 6.87 (m, 2H, Ar*H*), 6.25 (s, 1H, N*H*), 5.35 (dt, *J* = 8.2, 4.5 Hz, 1H, C*H*), 3.85 (s, 3H, OCH_3), 3.11 (ddd, *J* = 12.9, 11.2, 3.2 Hz, 1H, ArSCH_2), 2.99 (ddd, *J* = 12.9, 6.0, 3.7 Hz, 1H, ArSCH_2), 2.54 (dtd, *J* = 13.9, 5.6, 3.0 Hz, 1H, ArCHCH_2), 2.26 (s, 3H, CH_3), 2.17 (ddt, *J* = 14.5, 11.2, 3.7 Hz, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.8, 162.3, 134.3, 132.4, 131.2, 129.9, 129.2, 128.8, 126.8, 126.4, 113.8, 55.4, 47.2, 28.4, 22.8, 20.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3672 (w), 3323 (w), 2939 (m), 1641 (s), 1497 (s), 1257 (s), 1041 (m); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{19}NNaO_2S^+$ 336.1029; Found 336.1023.

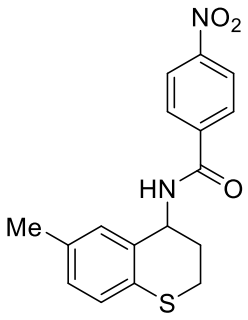
4-Fluoro-N-(6-methylthiochroman-4-yl)benzamide (**313c**)



Following GP D, starting from N-cyclopropyl-4-fluorobenzamide (**296c**) (71.7 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 4-methylbenzenethiol (49.7 mg, 0.400 mmol, 1.0 equiv.), 4-fluoro-N-(6-methylthiochroman-4-yl)benzamide (**313c**) (80.9 mg, 0.269 mmol, 67%) was obtained as a white solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 10:1 to 5:1).

R_f: 0.35 (silica, pentanes:ethyl acetate 6:1); **Mp:** 174-176 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85 – 7.72 (m, 2H, Ar*H*), 7.16 – 7.07 (m, 3H, Ar*H*), 7.05 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.00 (dd, *J* = 8.1, 1.9 Hz, 1H, Ar*H*), 6.30 (d, *J* = 7.5 Hz, 1H, N*H*), 5.34 (dt, *J* = 8.1, 4.4 Hz, 1H, C*H*), 3.11 (ddd, *J* = 12.9, 11.3, 3.3 Hz, 1H, ArSCH_2), 3.04 – 2.96 (m, 1H, ArSCH_2), 2.59 – 2.50 (m, 1H, ArCHCH_2), 2.26 (s, 3H, CH_3), 2.17 (ddt, *J* = 13.9, 11.3, 3.7 Hz, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.3, 164.8 (C-F, 1JC-F = 252.3 Hz), 134.4, 132.1, 131.1, 130.4 (C-F, 4JC-F = 3.2 Hz), 129.9, 129.4, 129.3(C-F, 3JC-F = 9.0 Hz), 126.9, 115.7 (C-F, 2JC-F = 21.9 Hz), 47.4, 28.3, 22.7, 20.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -107.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3672 (w), 3275 (w), 2987 (s), 2903 (s), 1629 (m), 1497 (m), 1401 (m), 1233 (m), 1053 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{16}FNNaOS^+$ 324.0829; Found 324.0834.

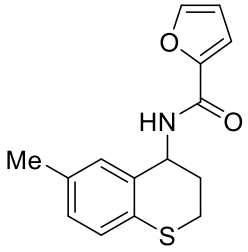
N-(6-Methylthiochroman-4-yl)-4-nitrobenzamide (313f)



Following GP D, starting from N-cyclopropyl-4-nitrobenzamide (**296f**) (82.4 mg, 0.400 mmol, 1.0 equiv.), the first step was kept for 3 hours before the addition of 4-methylbenzenethiol (49.7 mg, 0.400 mmol, 1.0 equiv.). N-(6-methylthiochroman-4-yl)-4-nitrobenzamide (**313f**) (103.9 mg, 0.317 mmol, 79%) was obtained as a yellow solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 10:1 to 4:1).

R_f: 0.26 (silica, pentanes:ethyl acetate 6:1); **Mp:** 128-131 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.33 – 8.23 (m, 2H, Ar*H*), 7.98 – 7.88 (m, 2H, Ar*H*), 7.09 (dq, *J* = 2.0, 0.7 Hz, 1H, Ar*H*), 7.06 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.01 (dd, *J* = 8.1, 1.9 Hz, 1H, Ar*H*), 6.47 (d, *J* = 7.5 Hz, 1H, N*H*), 5.36 (dt, *J* = 8.1, 4.3 Hz, 1H, C*H*), 3.11 (ddd, *J* = 12.9, 11.3, 3.4 Hz, 1H, ArSCH_2), 3.01 (dddd, *J* = 12.9, 5.7, 3.9, 0.6 Hz, 1H, ArSCH_2), 2.57 (dddd, *J* = 14.0, 5.6, 4.9, 3.3 Hz, 1H, ArCHCH_2), 2.27 (s, 3H, CH_3), 2.24 – 2.15 (m, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.3, 149.7, 139.7, 134.6, 131.6, 131.1, 130.0, 129.6, 128.2, 127.0, 123.8, 47.8, 28.1, 22.6, 20.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3299 (w), 2927 (w), 1641 (m), 1521 (s), 1341 (m), 836 (w), 728 (m); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{16}N_2NaO_3S^+$ 351.0774; Found 351.0777.

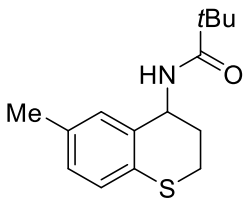
N-(6-Methylthiochroman-4-yl)furan-2-carboxamide (313k)



Following GP D, starting from N-cyclopropylfuran-2-carboxamide (**296k**) (60.4 mg, 0.400 mmol, 1.0 equiv.), the first step was kept for 3 hours before the addition of 4-methylbenzenethiol (49.7 mg, 0.400 mmol, 1.0 equiv.). N-(6-Methylthiochroman-4-yl)furan-2-carboxamide (**313k**) (72.7 mg, 0.266 mmol, 67%) was obtained as a beige solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.39 (silica, pentanes:ethyl acetate 3:1); **Mp:** 119-120 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.41 (dd, *J* = 1.8, 0.8 Hz, 1H, Ar*H*), 7.16 (dd, *J* = 3.5, 0.8 Hz, 1H, Ar*H*), 7.10 (dq, *J* = 2.0, 0.7 Hz, 1H, Ar*H*), 7.05 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.02 – 6.96 (m, 1H, Ar*H*), 6.58 (d, *J* = 8.0 Hz, 1H, N*H*), 6.51 (dd, *J* = 3.5, 1.8 Hz, 1H, Ar*H*), 5.33 (tt, *J* = 4.7, 3.6 Hz, 1H, C*H*), 3.11 (ddd, *J* = 12.9, 11.2, 3.1 Hz, 1H, ArSCH_2), 2.99 (dddd, *J* = 12.9, 6.1, 3.6, 0.7 Hz, 1H, ArSCH_2), 2.49 (dddd, *J* = 13.9, 6.1, 5.3, 3.1 Hz, 1H, ArCHCH_2), 2.26 (d, *J* = 0.7 Hz, 3H, CH_3), 2.18 (ddt, *J* = 13.9, 11.2, 3.7 Hz, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.3, 147.7, 143.9, 134.3, 132.0, 131.2, 129.9, 129.3, 126.8, 114.6, 112.2, 46.4, 28.6, 22.7, 20.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3287 (m), 2927 (w), 1641 (s), 1521 (s), 1281 (m), 1185 (m), 752 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{15}NNaO_2S^+$ 296.0716; Found 296.0719.

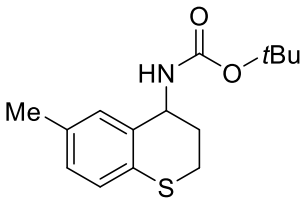
N-(6-Methylthiochroman-4-yl)pivalamide (313n)



Following GP D, starting from N-cyclopropylpivalamide (**296n**) (56.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 4-methylbenzenethiol (49.7 mg, 0.400 mmol, 1.0 equiv.), N-(6-methylthiochroman-4-yl)pivalamide (**313n**) (80.1 mg, 0.304 mmol, 76%) was obtained as a white solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 10:1 to 5:1).

R_f: 0.32 (silica, pentanes:ethyl acetate 6:1); **Mp:** 132-134 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.10 – 6.89 (m, 3H, Ar*H*), 5.80 (d, *J* = 7.4 Hz, 1H, N*H*), 5.12 (ddd, *J* = 7.6, 5.5, 3.9 Hz, 1H, C*H*), 3.05 – 2.91 (m, 2H, ArSCH_2), 2.37 (dtd, *J* = 13.8, 5.5, 4.0 Hz, 1H, ArCHCH_2), 2.26 (s, 3H, CH_3), 2.12 – 2.03 (m, 1H, ArCHCH_2), 1.21 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 177.5, 134.3, 132.7, 130.8, 129.8, 129.1, 126.7, 46.6, 38.7, 28.3, 27.6, 22.8, 20.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3672 (w), 3323 (m), 2987 (m), 2891 (w), 1629 (s), 1521 (s), 1209 (m), 1053 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{21}NNaOS^+$ 286.1236; Found 286.1245.

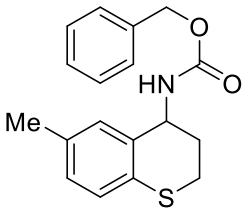
***tert*-Butyl (6-methylthiochroman-4-yl)carbamate (313o)**



Following GP D, starting from *tert*-butyl cyclopropylcarbamate (**296o**) (62.9 mg, 0.400 mmol, 1.0 equiv.), the first step was kept for 1 hour before the addition of 4-methylbenzenethiol (49.7 mg, 0.400 mmol, 1.0 equiv.) at -20 °C (The reaction mixture was pre-cooled for 10 minutes; temperature control is crucial as the intermediate is very reactive). *tert*-Butyl (6-methylthiochroman-4-yl)carbamate (**313o**) (58.3 mg, 0.209 mmol, 52%) was obtained as a white solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 20:1 to 10:1).

R_f: 0.45 (silica, pentanes:ethyl acetate 10:1); **Mp:** 109-111 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.14 – 7.05 (m, 1H, Ar*H*), 7.03 – 6.89 (m, 2H, Ar*H*), 4.93 – 4.63 (m, 2H, N*H* + C*H*), 3.08 (ddd, *J* = 12.8, 11.0, 3.2 Hz, 1H, ArSCH_2), 2.94 (ddd, *J* = 12.8, 6.2, 3.6 Hz, 1H, ArSCH_2), 2.40 – 2.30 (m, 1H, ArCHCH_2), 2.27 (s, 3H, CH_3), 2.13 – 2.02 (m, 1H, ArCHCH_2), 1.47 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.9, 134.1, 132.8, 130.9, 129.6, 129.0, 126.6, 79.7, 47.9, 28.7, 28.4, 22.6, 20.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3333 (w), 3311 (m), 2975 (m), 2925 (w), 1689 (s), 1483 (s), 1390 (m), 1242 (m), 1166 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{21}NNaO_2S^+$ 302.1185; Found 302.1171.

Benzyl (6-methylthiochroman-4-yl)carbamate (313p)

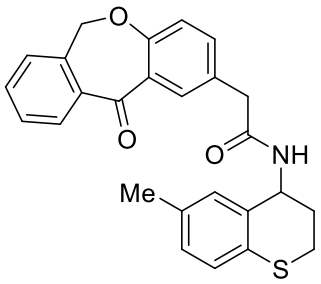


Following GP D, starting from benzyl cyclopropylcarbamate (**296p**) (76.4 mg, 0.400 mmol, 1.0 equiv.), the first step was kept for 1.5 hours before 4-methylbenzenethiol (49.7 mg, 0.400 mmol, 1.0 equiv.) was added. Benzyl (6-methylthiochroman-4-yl)carbamate (**313p**) (73.2 mg, 0.234 mmol, 58%) was obtained as a pale pink solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 10:1 to 5:1).

Scale-up synthesis: In a glass vial, benzyl cyclopropylcarbamate (**296p**) (1.91 g, 10.0 mmol, 1.0 equiv.), N-iodosuccinimide (2.36 g, 10.5 mmol, 1.05 equiv.), methanol (0.48 mL, 12.0 mmol, 1.20 equiv.), and diphenyl hydrogen phosphate (250 mg, 1.00 mmol, 0.10 equiv.) were dissolved in chloroform (50 mL, 0.2 M). The reaction mixture was stirred at room temperature for 1.5 hours before 4-methylbenzenethiol (1.24 g, 10.0 mmol, 1.0 equiv.) was added to the reaction mixture (minimum amount of chloroform was added beforehand to dissolve the 4-methylbenzenethiol). The mixture was stirred at room temperature for another 3 hours. Upon completion, the mixture was quenched by the addition of saturated aqueous solution of sodium thiosulfate (20 mL). The aqueous layer was then extracted with dichloromethane. The organic extract was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, pentanes/EtOAc = 10:1 to 5:1) and benzyl (6-methylthiochroman-4-yl)carbamate (**313p**) (1.61 g, 5.14 mmol, 51%) was obtained.

R_f: 0.38 (silica, pentanes:ethyl acetate 6:1); **Mp:** 136-138 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.47 – 7.27 (m, 5H, Ar*H*), 7.09 (s, 1H, Ar*H*), 7.00 (d, *J* = 8.0 Hz, 1H, Ar*H*), 6.96 (dd, *J* = 8.1, 1.8 Hz, 1H, Ar*H*), 5.14 (s, 2H, OCH_2), 5.01 (d, *J* = 6.9 Hz, 1H, N*H*), 4.91 (d, *J* = 6.9 Hz, 1H, C*H*), 3.07 (ddd, *J* = 12.9, 11.0, 3.2 Hz, 1H, ArSCH_2), 2.95 (ddd, *J* = 12.8, 6.1, 3.7 Hz, 1H, ArSCH_2), 2.39 (td, *J* = 9.3, 8.7, 4.6 Hz, 1H, ArCHCH_2), 2.26 (s, 3H, CH_3), 2.11 (ddt, *J* = 14.3, 11.1, 3.6 Hz, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.3, 136.3, 134.2, 132.3, 130.9, 129.6, 129.2, 128.5, 128.2, 128.1, 126.7, 66.9, 48.5, 28.6, 22.5, 20.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3672 (w), 3311 (m), 2987 (w), 2891 (w), 1701 (s), 1521 (s), 1233 (s), 1041 (m), 812 (m); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{19}NNaO_2S^+$ 336.1029; Found 336.1028.

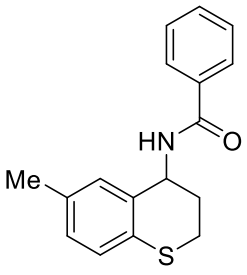
N-(6-Methylthiochroman-4-yl)-2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetamide (313u)



Following GP D, starting from N-cyclopropyl-2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetamide (**296u**) (30.7 mg, 0.100 mmol) followed by the addition of 4-methylbenzenethiol (12.4 mg, 0.100 mmol, 1.0 equiv.), N-(6-methylthiochroman-4-yl)-2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetamide (**313u**) (29.0 mg, 0.0675 mmol, 67%) was obtained as a white solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 6:1 to 1:1).

R_f: 0.50 (silica, pentanes:ethyl acetate 1:1); **Mp:** 167-169 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 2.4 Hz, 1H, Ar*H*), 7.87 (dd, *J* = 7.7, 1.4 Hz, 1H, Ar*H*), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H, Ar*H*), 7.50 – 7.45 (m, 1H, Ar*H*), 7.45 – 7.41 (m, 1H, Ar*H*), 7.39 – 7.34 (m, 1H, Ar*H*), 7.04 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.00 – 6.89 (m, 3H, Ar*H*), 5.74 (d, *J* = 7.9 Hz, 1H, N*H*), 5.19 (s, 2H, OCH_2), 5.15 (ddd, *J* = 8.0, 5.8, 3.8 Hz, 1H, C*H*), 3.60 (s, 2H, C(O)CH_2), 3.01 – 2.87 (m, 2H, ArSCH_2), 2.35 – 2.28 (m, 1H, ArCHCH_2), 2.23 (d, J = 0.9 Hz, 3H, CH_3), 2.16 – 2.03 (m, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 190.7, 169.7, 160.6, 140.3, 136.2, 135.4, 134.3, 132.9, 132.3, 132.2, 130.6, 129.8, 129.5, 129.3, 129.1, 128.5, 127.8, 126.7, 125.3, 121.5, 73.6, 47.0, 42.7, 28.5, 22.8, 20.7; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3666 (m), 2982 (s), 2898 (s), 1639 (w), 1399 (m), 1243 (m), 1063 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{23}NNaO_3S^+$ 452.1291; Found 452.1291.

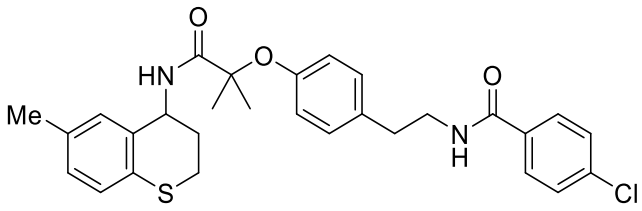
N-(6-Methylthiochroman-2-yl)benzamide (**313w**)



Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 4-methylbenzenethiol (49.7 mg, 0.400 mmol, 1.0 equiv.), N-(6-methylthiochroman-2-yl)benzamide (**313w**) (85.1 mg, 0.300 mmol, 75%) was obtained as a yellow solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.50 (silica, pentanes:ethyl acetate 3:1); **Mp:** 177-179 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 – 7.74 (m, 2H, Ar*H*), 7.54 – 7.48 (m, 1H, Ar*H*), 7.46 – 7.39 (m, 2H, Ar*H*), 7.11 (dd, *J* = 1.8, 0.9 Hz, 1H, Ar*H*), 7.05 (d, *J* = 8.0 Hz, 1H, Ar*H*), 6.99 (dd, *J* = 8.1, 1.9 Hz, 1H, Ar*H*), 6.38 (d, *J* = 7.3 Hz, 1H, N*H*), 5.36 (ddd, *J* = 7.9, 5.2, 3.8 Hz, 1H, C*H*), 3.12 (ddd, *J* = 12.9, 11.2, 3.2 Hz, 1H, ArSCH_2), 3.00 (ddd, *J* = 12.9, 6.0, 3.6 Hz, 1H, ArSCH_2), 2.59 – 2.50 (m, 1H, ArCHCH_2), 2.26 (s, 3H, CH_3), 2.22 – 2.17 (m, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.3, 134.4, 134.2, 132.2, 131.7, 131.2, 129.9, 129.3, 128.6, 127.0, 126.8, 47.3, 28.3, 22.7, 20.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3306 (w), 2921 (w), 1634 (s), 1530 (s), 1484 (m), 807 (w), 695 (w); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{17}NNaOS^+$ 306.0923; Found 306.0929.

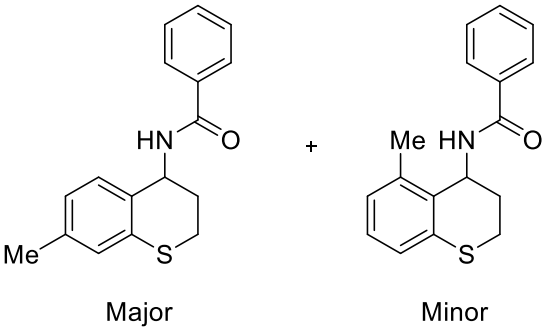
4-Chloro-N-(4-((2-methyl-1-((6-methylthiochroman-4-yl)amino)-1-oxopropan-2-yl)oxy)phenethyl)benzamide (313x)



Following GP D, starting from 4-chloro-N-(4-((1-(cyclopropylamino)-2-methyl-1-oxopropan-2-yl)oxy)phenethyl)benzamide (**296x**) (42.9 mg, 0.100 mmol) for 3 hours, followed by the addition of 4-methylbenzenethiol (12.4 mg, 0.100 mmol, 1.0 equiv.) for another 3 hours, 4-Chloro-N-(4-((2-methyl-1-((6-methylthiochroman-4-yl)amino)-1-oxopropan-2-yl)oxy)phenethyl)benzamide (**313x**) (35.5 mg, 0.0678 mmol, 68%) was obtained as a colorless oil after purification by column chromatography (SiO_2, pentanes/EtOAc = 6:1 to 2:1).

R_f: 0.28 (silica, pentane:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, CD_3CN, 338.1 K, a mixture of rotamers was observed when performing the NMR experiment at 298.1 K which disappears at 338.1 K): δ = 7.74 – 7.70 (m, 2H, Ar*H*), 7.53 – 7.49 (m, 2H, Ar*H*), 7.22 – 7.15 (m, 3H, Ar*H*), 7.13 – 7.04 (m, 1H, N*H*), 6.98 (dd, *J* = 1.7, 0.8 Hz, 1H, Ar*H*), 6.97 – 6.91 (m, 2H, Ar*H* + N*H*), 6.90 – 6.84 (m, 2H, Ar*H*), 5.09 (td, *J* = 7.6, 7.2, 4.3 Hz, 1H, NC*H*), 3.68 (t, *J* = 7.2 Hz, 2H, NCH_2), 2.96 – 2.92 (m, 4H, ArSCH_2 + ArCH_2), 2.28 – 2.21 (m, 1H, ArCHCH_2), 2.20 (s, 3H, CH_3), 2.16 – 2.07 (m, 1H, ArCHCH_2), 1.52 (d, *J* = 2.9 Hz, 6H, gem-CH_3); **^{13}C NMR** (101 MHz, CD_3CN, 338.1 K): δ = 174.8, 154.7, 135.3, 134.6, 134.6, 131.4, 131.3, 131.0, 130.8, 130.6, 130.0, 130.0, 130.0, 129.8, 127.7, 121.7, 82.0, 48.0, 35.2, 30.2, 26.3, 25.4, 24.3, 21.1; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3303 (m), 2982 (w), 2929 (m), 1645 (s), 1532 (s), 1506 (s), 1227 (m), 1153 (m); **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{32}ClN_2O_3S^+$ 523.1817; Found 523.1818.

N-(7-methylthiochroman-4-yl)benzamide (329a, major) & N-(5-methylthiochroman-4-yl)benzamide (329b, minor)

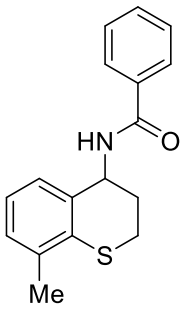


Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 3-methylbenzenethiol (47.6 µL, 0.400 mmol, 1.0 equiv.), a mixture of the two regioisomers N-(7-methylthiochroman-4-yl)benzamide (**329a**, major) and N-(5-methylthiochroman-4-yl)benzamide (**329b**, minor) (85.7 mg, 0.303 mmol, 76%, in a ratio of 3.5:1 based on the integration of the N*H*) was obtained as a beige solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.40 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 – 7.71 (m, 4H, Ar*H*, major + minor), 7.55 – 7.47 (m, 2H, Ar*H*, major + minor), 7.38 – 7.46 (m, 4H, Ar*H*, major + minor), 7.18 (d, *J* = 7.9 Hz, 1H, Ar*H*, major), 7.12 – 7.07 (m, 1H, Ar*H*, minor), 7.03 (dd, *J* = 7.8, 1.3 Hz, 1H, Ar*H*, minor), 7.00 – 6.96 (m, 1H, Ar*H*, major), 6.95 – 6.90 (m, 1H, Ar*H*, minor), 6.90 – 6.85 (m, 1H, Ar*H*, major), 6.32 (d, *J* = 7.5 Hz, 1H, N*H*, major), 6.23 (d, *J* = 7.2 Hz, 1H, N*H*, minor), 5.49 (dt, *J* = 6.6, 3.1 Hz, 1H, NC*H*, minor), 5.36 (dq, *J* = 8.1, 4.1 Hz, 1H, NC*H*, major), 3.23 – 3.07 (m, 2H, ArSCH_2, major + minor), 3.00 (ddd, *J* = 12.9, 6.0, 3.5 Hz, 1H, ArSCH_2, major), 2.94 – 2.85 (m, 1H, ArSCH_2, minor), 2.75 (dq, *J* = 14.1, 3.4 Hz, 1H, ArCHCH_2, minor), 2.61 – 2.49 (m, 1H, ArCHCH_2, major), 2.31 (s, 3H, CH_3, minor), 2.28 (s, 3H, CH_3,

major), 2.23 – 2.14 (m, 1H, ArCHCH_2, major), 2.00 (tt, J = 13.7, 3.3 Hz, 1H, ArCHCH_2, minor); **^{13}C NMR** (101 MHz, $CDCl_3$; mixture of regioisomers in a ratio of 3.5:1, signals corresponding to the two regioisomers are partially resolved): δ 166.4, 166.2, 139.0, 138.2, 134.2, 134.0, 133.5, 133.3, 131.7, 131.6, 130.5, 129.9, 129.5, 128.6, 128.6, 128.1, 127.1, 126.9, 126.7, 125.6, 124.8, 47.1, 43.8, 28.3, 27.6, 22.8, 21.6, 21.0, 18.9 (one aromatic Carbon signal not resolved); **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3666 (w), 3270 (w), 2970 (s), 2910 (s), 1639 (s), 1531 (s), 1255 (m), 1063 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{17}NNaOS^+$ 306.0923; Found 306.0920.

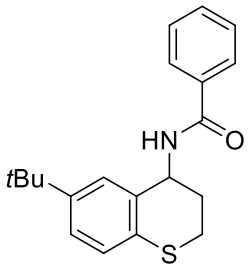
N-(8-Methylthiochroman-4-yl)benzamide (329c)



Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 4-(methylthio)benzenethiol (47.1 µL, 0.400 mmol, 1.0 equiv.), N-(8-methylthiochroman-4-yl)benzamide (**329c**) (83.7 mg, 0.296 mmol, 74%) was obtained as a white solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.50 (silica, pentanes:ethyl acetate 3:1); **Mp:** 179-181 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 – 7.71 (m, 2H, Ar*H*), 7.54 – 7.47 (m, 1H, Ar*H*), 7.46 – 7.38 (m, 2H, Ar*H*), 7.16 (ddt, J = 7.6, 1.4, 0.7 Hz, 1H, Ar*H*), 7.09 (ddd, J = 7.5, 1.6, 0.8 Hz, 1H, Ar*H*), 6.99 (t, J = 7.5 Hz, 1H, Ar*H*), 6.35 (d, J = 7.1 Hz, 1H, N*H*), 5.46 – 5.34 (m, 1H, C*H*), 3.13 (ddd, J = 12.9, 11.4, 3.3 Hz, 1H, ArSCH_2), 3.05 (dddd, J = 12.9, 5.7, 3.8, 0.8 Hz, 1H, ArSCH_2), 2.58 (dtd, J = 14.0, 5.5, 3.3 Hz, 1H, ArCHCH_2), 2.28 (d, J = 0.7 Hz, 3H, CH_3), 2.15 (ddt, J = 13.9, 11.4, 3.7 Hz, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.3, 134.9, 134.2, 133.1, 132.3, 131.7, 129.6, 128.6, 128.2, 126.9, 123.8, 47.8, 27.6, 22.7, 20.0; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3287 (w), 2927 (s), 2855 (m), 1641 (s), 1521 (s), 1281 (m), 704 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{17}NNaOS^+$ 306.0923; Found 306.0927.

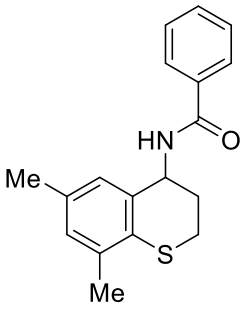
N-(6-(*tert*-Butyl)thiochroman-4-yl)benzamide (329d)



Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 4-(*tert*-butyl)benzenethiol (69.0 µL, 0.400 mmol, 1.0 equiv.), N-(6-(*tert*-butyl)thiochroman-4-yl)benzamide (**329d**) (92.9 mg, 0.286 mmol, 71%) was obtained as a white solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.70 (silica, pentanes:ethyl acetate 3:1); **Mp:** 190-192 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.82 – 7.74 (m, 2H, Ar*H*), 7.55 – 7.47 (m, 1H, Ar*H*), 7.47 – 7.38 (m, 2H, Ar*H*), 7.30 (d, J = 2.2 Hz, 1H, Ar*H*), 7.23 (dd, J = 8.3, 2.2 Hz, 1H, Ar*H*), 7.09 (d, J = 8.4 Hz, 1H, Ar*H*), 6.43 (d, J = 7.4 Hz, 1H, N*H*), 5.38 (dt, J = 7.9, 4.3 Hz, 1H, C*H*), 3.13 (ddd, J = 12.8, 11.6, 3.1 Hz, 1H, ArSCH_2), 3.03 – 2.93 (m, 1H, ArSCH_2), 2.64 – 2.52 (m, 1H, ArCHCH_2), 2.22 – 2.09 (m, 1H, ArCHCH_2), 1.27 (s, 9H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.4, 147.8, 134.3, 131.7, 131.6, 130.2, 128.6, 127.6, 126.9, 126.6, 125.8, 47.6, 34.3, 31.2, 28.1, 22.5; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3318 (w), 2958 (s), 1639 (s), 1519 (s), 1255 (w), 1063 (w), 715 (m); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{23}NNaOS^+$ 348.1393; Found 348.1394.

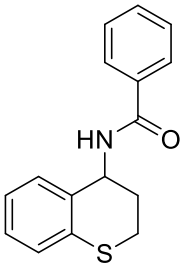
N-(6,8-Dimethylthiochroman-4-yl)benzamide (329e)



Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 2,4-dimethylbenzenethiol (54.0 µL, 0.400 mmol, 1.0 equiv.), N-(6,8-dimethylthiochroman-4-yl)benzamide (**329e**) (84.0 mg, 0.283 mmol, 71%) was obtained as a white solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.56 (silica, pentanes:ethyl acetate 3:1); **Mp:** 177-179 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 – 7.73 (m, 2H, Ar*H*), 7.53 – 7.47 (m, 1H, Ar*H*), 7.46 – 7.38 (m, 2H, Ar*H*), 6.98 (s, 1H, Ar*H*), 6.93 (s, 1H, Ar*H*), 6.40 (d, *J* = 7.2 Hz, 1H, N*H*), 5.36 (dt, *J* = 7.9, 4.2 Hz, 1H, C*H*), 3.12 (ddd, *J* = 12.9, 11.5, 3.2 Hz, 1H, ArSCH_2), 3.02 (ddd, *J* = 12.8, 5.6, 3.7 Hz, 1H, ArSCH_2), 2.57 (dtd, *J* = 13.8, 5.3, 3.2 Hz, 1H, ArCHCH_2), 2.24 (s, 6H, CH_3, the two methyl groups overlapped), 2.12 (ddt, *J* = 13.7, 11.4, 3.7 Hz, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.2, 134.7, 134.3, 133.4, 132.1, 131.6, 130.7, 129.4, 128.8, 128.6, 126.9, 47.7, 27.8, 22.6, 20.6, 19.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3666 (w), 2982 (s), 2898 (s), 1399 (w), 1243 (w), 1063 (s), 883 (w); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{19}NNaOS^+$ 320.1080; Found 320.1085.

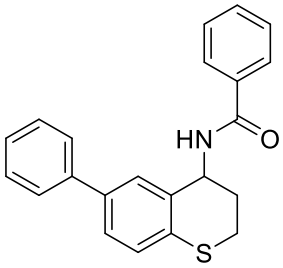
N-(Thiochroman-4-yl)benzamide (329f)



Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of benzenethiol (40.8 µL, 0.400 mmol, 1.0 equiv.), N-(thiochroman-4-yl)benzamide (**329f**) (61.4 mg, 0.228 mmol, 57%) was obtained as a white solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.55 (silica, pentanes:ethyl acetate 3:1); **Mp:** 157-158 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.71 (m, 2H, Ar*H*), 7.52 – 7.43 (m, 1H, Ar*H*), 7.39 (ddt, *J* = 8.2, 6.5, 1.2 Hz, 2H, Ar*H*), 7.26 (dq, *J* = 8.4, 0.8 Hz, 1H, Ar*H*), 7.16 – 7.08 (m, 2H, Ar*H*), 7.03 (ddd, *J* = 7.7, 6.0, 2.6 Hz, 1H, Ar*H*), 6.61 (d, *J* = 7.7 Hz, 1H, N*H*), 5.35 (ddd, *J* = 7.7, 5.5, 3.8 Hz, 1H, C*H*), 3.10 (ddd, *J* = 12.8, 10.9, 3.2 Hz, 1H, ArSCH_2), 3.03 – 2.94 (m, 1H, ArSCH_2), 2.49 (dddd, *J* = 13.9, 6.4, 5.6, 3.2 Hz, 1H, ArCHCH_2), 2.23 – 2.10 (m, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.4, 134.1, 133.6, 132.5, 131.5, 130.4, 128.5, 128.1, 126.9, 126.8, 124.5, 47.2, 28.2, 22.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3660 (w), 3275 (w), 2975 (s), 2903 (s), 1629 (m), 1521 (m), 1245 (w), 1065 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{15}NNaOS^+$ 292.0767; Found 292.0766.

N-(6-Phenylthiochroman-4-yl)benzamide (329g)

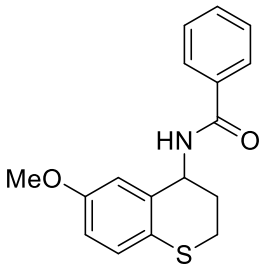


Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of biphenyl-4-thiol (74.5 mg, 0.400 mmol, 1.0 equiv.), N-(6-phenylthiochroman-4-yl)benzamide (**329g**) (63.1 mg, 0.183 mmol, 46%) was obtained as a white solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.50 (silica, pentanes:ethyl acetate 3:1); **Mp:** 212-213 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.83 – 7.73 (m, 2H, Ar*H*), 7.56 – 7.47 (m, 4H, Ar*H*), 7.47 – 7.37 (m, 5H, Ar*H*), 7.35 – 7.29 (m, 1H, Ar*H*), 7.24 (d, *J* = 8.2 Hz, 1H, Ar*H*), 6.41 (d, *J* = 7.5 Hz, 1H, N*H*),

5.55 – 5.40 (m, 1H, C*H*), 3.17 (ddd, *J* = 12.9, 11.4, 3.1 Hz, 1H, ArSCH_2), 3.05 (dddd, *J* = 12.9, 5.9, 3.6, 0.7 Hz, 1H, ArSCH_2), 2.62 (dddd, *J* = 14.0, 5.9, 5.1, 3.1 Hz, 1H, ArCHCH_2), 2.23 (ddt, *J* = 13.9, 11.3, 3.6 Hz, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.4, 140.0, 137.7, 134.1, 132.8, 132.7, 131.7, 129.2, 128.8, 128.6, 127.4, 127.3, 127.0, 127.0, 126.6, 47.5, 28.2, 22.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3275 (m), 3059 (w), 2975 (w), 1641 (s), 1533 (s), 1281 (m), 704 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{19}NNaOS^+$ 368.1080; Found 368.1078.

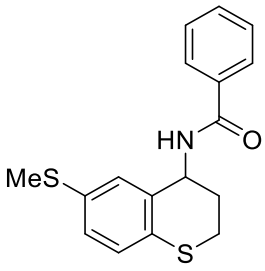
N-(6-methoxythiochroman-4-yl)benzamide (329h)



Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 4-methoxybenzenethiol (49.2 µL, 0.400 mmol, 1.0 equiv.), N-(6-methoxythiochroman-4-yl)benzamide (**329h**) (41.8 mg, 0.140 mmol, 35%) was obtained as a yellow solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.28 (silica, pentanes:ethyl acetate 3:1); **Mp:** 169-170 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 – 7.73 (m, 2H, Ar*H*), 7.59 – 7.45 (m, 1H, Ar*H*), 7.41 (ddd, *J* = 8.2, 6.5, 1.3 Hz, 2H, Ar*H*), 7.05 (d, *J* = 8.7 Hz, 1H, Ar*H*), 6.86 (d, *J* = 2.8 Hz, 1H, Ar*H*), 6.77 (dd, *J* = 8.7, 2.8 Hz, 1H, Ar*H*), 6.52 (d, *J* = 7.7 Hz, 1H, N*H*), 5.40 – 5.31 (m, 1H, C*H*), 3.73 (s, 3H, CH_3), 3.09 (ddd, *J* = 12.9, 10.7, 3.3 Hz, 1H, ArSCH_2), 2.99 (ddd, *J* = 12.9, 6.2, 3.8 Hz, 1H, ArSCH_2), 2.55 – 2.43 (m, 1H, ArCHCH_2), 2.25 – 2.12 (m, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.4, 157.0, 134.1, 133.7, 131.7, 128.6, 127.9, 126.9, 124.2, 115.2, 115.2, 55.4, 47.6, 28.6, 22.9; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3660 (w), 3275 (w), 2975 (s), 2915 (s), 1629 (m), 1533 (m), 1245 (s), 1041 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{17}NNaO_2S^+$ 322.0872; Found 322.0878.

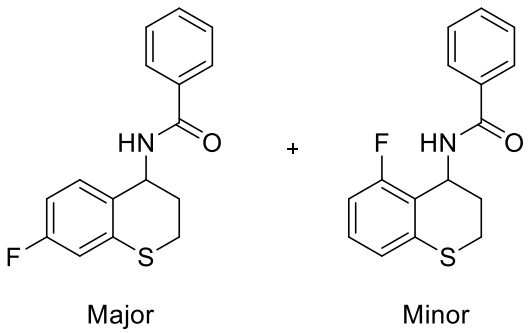
N-(6-(Methylthio)thiochroman-4-yl)benzamide (329i)



Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 4-(methylthio)benzenethiol (62.5 mg, 0.400 mmol, 1.0 equiv.), N-(6-(methylthio)thiochroman-4-yl)benzamide (**329i**) (55.8 mg, 0.177 mmol, 44%) was obtained as a beige solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.37 (silica, pentanes:ethyl acetate 3:1); **Mp:** 182-183 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 – 7.73 (m, 2H, Ar*H*), 7.58 – 7.46 (m, 1H, Ar*H*), 7.43 (ddt, *J* = 8.3, 6.5, 1.4 Hz, 2H, Ar*H*), 7.20 (d, *J* = 1.9 Hz, 1H, Ar*H*), 7.13 – 7.02 (m, 2H, Ar*H*), 6.43 (d, *J* = 7.6 Hz, 1H, N*H*), 5.35 (ddd, *J* = 8.2, 5.2, 3.7 Hz, 1H, C*H*), 3.11 (ddd, *J* = 12.9, 11.0, 3.2 Hz, 1H, ArSCH_2), 3.01 (ddd, *J* = 12.9, 6.1, 3.6 Hz, 1H, ArSCH_2), 2.53 (dtd, *J* = 14.4, 5.8, 3.2 Hz, 1H, ArCHCH_2), 2.42 (s, 3H, CH_3), 2.21 – 2.12 (m, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.5, 134.3, 134.0, 133.1, 131.7, 130.5, 128.9, 128.6, 127.4, 127.0, 47.3, 28.1, 22.8, 16.4 (one aromatic Carbon signal not resolved); **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3672 (w), 2975 (s), 2903 (s), 1401 (w), 1257 (w), 1065 (s), 884 (w); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{17}NNaOS_2^+$ 338.0644; Found 338.0648.

N-(7-fluorothiochroman-4-yl)benzamide (329j, major) & N-(5-fluorothiochroman-4-yl)benzamide (329k, minor)

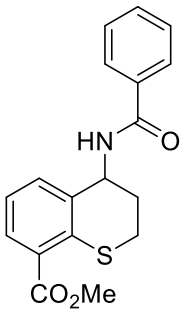


Major Minor

Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 3-fluorobenzenethiol (34.0 μL, 0.400 mmol, 1.0 equiv.), a mixture of the two regioisomers N-(7-fluorothiochroman-4-yl)benzamide (**329j**, major) and N-(5-fluorothiochroman-4-yl)benzamide (**329k**, minor) (46.4 mg, 0.162 mmol, 41%, in a ratio of 9:1 based on the integration of benzylic proton) was obtained as a white solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.51 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$ $CDCl_3$; mixture of two regioisomers in a ratio of 9:1, minor regioisomer omitted for clarity): δ 7.79 – 7.74 (m, 2H, Ar*H*), 7.51 (ddt, *J* = 8.3, 6.6, 1.3 Hz, 1H, Ar*H*), 7.43 (ddt, *J* = 8.2, 6.6, 1.3 Hz, 2H, Ar*H*), 7.29 – 7.23 (m, 1H, Ar*H*), 6.87 (dd, *J* = 9.3, 2.6 Hz, 1H, Ar*H*), 6.75 (td, *J* = 8.3, 2.7 Hz, 1H, Ar*H*), 6.33 (d, J = 7.3 Hz, 1H, N*H*), 5.43 – 5.32 (m, 1H, C*H*), 3.12 (ddd, *J* = 12.9, 11.2, 3.2 Hz, 1H, ArSCH_2), 3.02 (ddd, *J* = 12.9, 6.0, 3.6 Hz, 1H, ArSCH_2), 2.56 (dddd, *J* = 14.3, 6.0, 5.3, 3.1 Hz, 1H, ArCHCH_2), 2.17 (ddt, *J* = 13.9, 11.2, 3.7 Hz, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$; mixture of two regioisomers in a ratio of 9:1, minor regioisomer omitted for clarity): δ 166.4, 162.0 (C-F, 1JC-F = 248.3 Hz), 135.8 (C-F, 3JC-F = 8.6 Hz), 134.0, 132.2 (C-F, 3JC-F = 8.7 Hz), 131.8, 128.6, 128.2 (C-F, 4JC-F = 3.0 Hz), 126.9, 113.2 (C-F, 2JC-F = 23.8 Hz), 112.0 (C-F, 2JC-F = 21.6 Hz), 46.7, 28.0, 22.7; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3660 (m), 2975 (s), 2903 (s), 1629 (w), 1401 (m), 1245 (m), 1065 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}FNNaOS^+$ 310.0672; Found 310.0683.

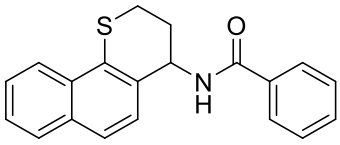
Methyl 4-benzamidothiochromane-8-carboxylate (329l)



Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of methyl thiosalicylate (55.0 μL, 0.400 mmol, 1.0 equiv.), the second step was kept stirring for 20 hours. Methyl 4-benzamidothiochroman-8-carboxylate (**329l**) (57.5 mg, 0.176 mmol, 44%) was obtained as a yellow solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.25 (silica, pentanes:ethyl acetate 3:1); **Mp:** 193-195 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 7.8, 1.6 Hz, 1H, Ar*H*), 7.80 – 7.73 (m, 2H, Ar*H*), 7.54 – 7.38 (m, 4H, Ar*H*), 7.09 (t, *J* = 7.7 Hz, 1H, Ar*H*), 6.51 (d, *J* = 7.7 Hz, 1H, N*H*), 5.46 (dt, *J* = 8.4, 4.4 Hz, 1H, C*H*), 3.89 (s, 3H, CH_3), 3.13 – 2.94 (m, 2H, ArSCH_2), 2.54 (dtd, *J* = 14.2, 5.4, 3.5 Hz, 1H, ArCHCH_2), 2.17 (ddt, *J* = 13.8, 10.8, 3.9 Hz, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.7, 166.4, 138.1, 134.9, 134.2, 134.0, 131.8, 131.5, 128.6, 127.2, 127.0, 123.5, 52.2, 47.9, 27.3, 23.2; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3672 (w), 3299 (w), 2975 (s), 2903 (s), 1713 (m), 1629 (w), 1521 (m), 1269 (m), 1065 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{17}NNaO_3S^+$ 350.0821; Found 350.0822.

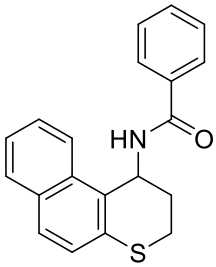
N-(3,4-Dihydro-2H-benzo[h]thiochromen-4-yl)benzamide (329m)



Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 1-naphthalenethiol (56.0 µL, 0.400 mmol, 1.0 equiv.), N-(3,4-dihydro-2H-benzo[h]thiochromen-4-yl)benzamide (**329m**) (102 mg, 0.319 mmol, 80%) was obtained as a pale yellow solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.50 (silica, pentanes:ethyl acetate 3:1); **Mp:** 212-213 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.20 – 8.06 (m, 1H, Ar*H*), 7.78 (tt, *J* = 6.1, 1.5 Hz, 3H, Ar*H*), 7.59 – 7.46 (m, 4H, Ar*H*), 7.42 (tt, *J* = 6.9, 1.6 Hz, 2H, Ar*H*), 7.36 (d, *J* = 8.5 Hz, 1H, Ar*H*), 6.42 (d, *J* = 7.6 Hz, 1H, N*H*), 5.56 (dt, *J* = 7.9, 4.1 Hz, 1H, C*H*), 3.23 (ddd, *J* = 13.0, 11.7, 3.0 Hz, 1H, ArSCH_2), 3.19 – 3.11 (m, 1H, ArSCH_2), 2.74 – 2.60 (m, 1H, ArCHCH_2), 2.27 (ddt, *J* = 13.9, 11.7, 3.8 Hz, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.3, 134.1, 133.0, 131.7, 130.9, 130.4, 129.0, 128.6, 128.4, 128.3, 127.0, 126.6, 126.3, 124.7, 123.5, 47.7, 28.0, 22.5; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3672 (m), 3275 (w), 2987 (s), 2903 (s), 1629 (w), 1533 (w), 1401 (m), 1257 (m), 1065 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{17}NNaOS^+$ 342.0923; Found 342.0925.

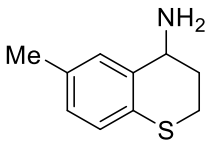
N-(2,3-Dihydro-1H-benzo[f]thiochromen-3-yl)benzamide (329n)



Following GP D, starting from N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.) followed by the addition of 2-naphthalenethiol (64.1 mg, 0.400 mmol, 1.0 equiv.), N-(2,3-dihydro-1H-benzo[f]thiochromen-3-yl)benzamide (**329n**) (99.6 mg, 0.312 mmol, 78%) was obtained as a beige solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 7:1 to 3:1).

R_f: 0.49 (silica, pentanes:ethyl acetate 3:1); **Mp:** 210-211 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.72 (ddd, *J* = 13.0, 8.4, 1.6 Hz, 3H, Ar*H*), 7.64 (d, *J* = 8.7 Hz, 1H, Ar*H*), 7.52 – 7.30 (m, 5H, Ar*H*), 7.17 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.55 (d, *J* = 7.3 Hz, 1H, N*H*), 6.04 (dt, *J* = 6.9, 3.2 Hz, 1H, C*H*), 3.38 – 3.26 (m, 1H, ArSCH_2), 2.99 – 2.88 (m, 1H, ArSCH_2), 2.88 – 2.77 (m, 1H, ArCHCH_2), 2.18 – 2.05 (m, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.1, 133.9, 132.8, 132.1, 131.6, 131.3, 128.7, 128.7, 128.5, 127.6, 127.0, 125.4, 124.9, 124.9, 121.5, 42.5, 27.6, 21.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3672 (w), 3287 (w), 2987 (s), 2903 (s), 1629 (s), 1521 (s), 1257 (m), 1053 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{17}NNaOS^+$ 342.0923; Found 342.0919.

6-Methylthiochroman-4-amine (330)

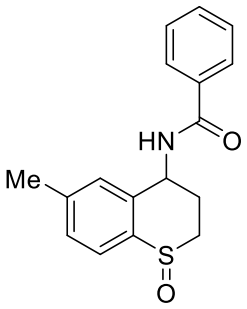


In a glass vial, *tert*-butyl (6-methylthiochroman-4-yl)carbamate (**313o**) (27.9 mg, 0.100 mmol) was dissolved in dichloromethane (0.25 mL) followed by the dropwise addition of trifluoroacetic acid (0.25 mL). The mixture was stirred at room temperature for 20 minutes before being quenched by 2 M NaOH (until pH around 14, checked by pH indicator). Then the mixture was extracted with dichloromethane (5 mL x 3) and the combined extracts were dried over Na_2SO_4 and concentrated in *vacuo*. 6-Methylthiochroman-4-amine (**330**) (13.6 mg, 0.0760 mmol, 76%) was obtained as a yellow oil after purification by column chromatography (SiO_2, dichloromethane:methanol = 40:1 to 10:1).

R_f: 0.35 (silica, dichloromethane:methanol 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.14 (s, 1H, Ar*H*), 7.01 (d, *J* = 8.0 Hz, 1H, Ar*H*), 6.94 (dd, *J* = 8.1, 1.9 Hz, 1H, Ar*H*), 4.08 (t, *J* = 4.4 Hz, 1H, C*H*), 3.23 (ddd, *J* =

12.7, 11.1, 3.6 Hz, 1H, ArSCH_2), 3.13 (s, 2H, NH_2), 2.89 (ddd, *J* = 12.8, 5.8, 4.1 Hz, 1H, ArSCH_2), 2.27 (s, 3H, CH_3), 2.22 (ddd, *J* = 9.1, 7.1, 3.6 Hz, 1H, ArCHCH_2), 2.17 – 2.07 (m, 1H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 134.8, 134.0, 130.2, 129.0, 128.8, 126.7, 48.4, 30.1, 21.9, 20.8; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3348 (br, w), 2918 (s), 2856 (m), 1588 (m), 1481 (s), 1286 (w), 1070 (m), 810 (s); **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_{14}NS^+$ 180.0841; Found 180.0848.

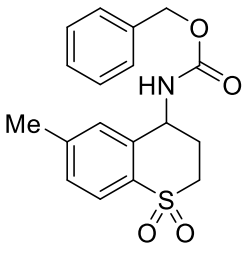
N-(6-Methyl-1-oxidothiochroman-4-yl)benzamide (331)



Following a reported procedure, [281] N-(6-methylthiochroman-2-yl)benzamide (**313w**) (28.3 mg, 0.100 mmol) was suspended in EtOH (0.5 mL). H_2O_2 (30%, 20.0 μL, 0.200 mmol, 2.0 equiv.) and Tf_2O (8.4 μL, 0.050 mmol, 0.5 equiv.) were added and the mixture was stirred at room temperature for 50 minutes. The progress of the reaction was monitored by TLC until no starting material was left. Then the crude mixture was washed with water (5 mL) and extracted by dichloromethane (5 mL x 3). The combined extracts were dried over Na_2SO_4 and concentrated in *vacuo*. N-(6-Methyl-1-oxidothiochroman-4-yl)benzamide (**331**) (29.0 mg, 0.0970 mmol, 97%) was obtained as a beige solid after purification by column chromatography (SiO_2, dichloromethane:methanol = 50:1 to 20:1).

R_f: 0.23 (silica, dichloromethane:methanol 20:1); **Mp:** 75-78 °C; **^{1}H NMR** (400 MHz, $CDCl_3$; mixture of diastereoisomers in a 1.6:1 ratio, the signals corresponding to the two diastereoisomers are partially resolved): δ = 7.90 (d, *J* = 9.1 Hz, 1H, N*H major*), 7.87 – 7.82 (m, 2H, Ar*H major*), 7.79 – 7.74 (m, 2H, Ar*H minor*), 7.64 (d, *J* = 7.9 Hz, 1H, Ar*H minor*), 7.57 (d, *J* = 7.8 Hz, 1H, Ar*H major*), 7.54 – 7.47 (m, 3H, Ar*H minor*), 7.46 – 7.38 (m, 4H, Ar*H major + minor*), 7.37 (s, 1H, Ar*H major*), 7.31 – 7.26 (m, 1H, Ar*H major*), 7.22 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar*H major*), 6.57 (d, *J* = 7.7 Hz, 1H, N*H minor*), 5.62 (dt, *J* = 9.1, 6.6 Hz, 1H, C*H major*), 5.52 (dt, *J* = 7.7, 5.1 Hz, 1H, C*H minor*), 3.40 – 3.22 (m, 2H, ArSCH_2 *major + minor*), 3.10 (ddd, *J* = 13.5, 7.8, 2.4 Hz, 1H, ArSCH_2 *minor*), 2.97 (ddd, *J* = 14.1, 9.9, 5.2 Hz, 1H, ArSCH_2 *major*), 2.85 (dddd, *J* = 15.5, 10.9, 4.9, 2.3 Hz, 1H, ArCHCH_2 *minor*), 2.71 (dddd, *J* = 14.4, 9.9, 7.1, 4.6 Hz, 2H, ArCHCH_2 *major*), 2.37 (s, 6H, CH_3 *major + minor*), 2.36 – 2.23 (m, 2H, ArCHCH_2 *major + minor*); **^{13}C NMR** (101 MHz, $CDCl_3$; mixture of diastereoisomers in a 1.6:1 ratio): δ = 166.8, 166. 6, 144.0, 142.9, 137.1, 136.4, 135.4, 134.8, 133.8, 133.7, 131.9, 131.7, 130.9, 130.7, 130.5, 130.4, 130.1, 129.4, 128.6, 128.6, 127.1, 127.0, 46.6, 46.5, 44.5, 43.3, 21.9, 21.6, 21.4, 20.9; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3275 (m), 3057 (w), 2924 (w), 1637 (s), 1531 (s), 1016 (s), 698 (m); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{17}NNaO_2S^+$ 322.0872; Found 322.0881.

Benzyl (6-methyl-1,1-dioxidothiochroman-4-yl)carbamate (**332**)

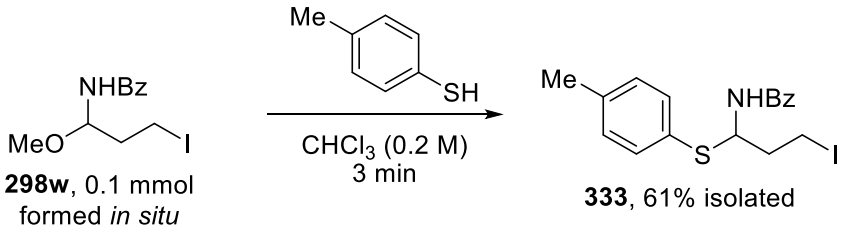


Following a reported procedure,[282] benzyl (6-methylthiochroman-4-yl) carbamate (**313p**) (31.3 mg, 0.100 mmol) and *m*CPBA (43.0 mg, 0.250 mmol, 2.5 equiv.) were dissolved in dichloromethane (0.5 mL). The mixture was stirred at room temperature for 2 hours. Then the crude mixture was submitted directly to column chromatography. Benzyl (6-methyl-1,1-dioxidothiochroman-4-yl)carbamate (**332**)

[281] Khodaei, M. M.; Bahrami, K.; Karimi, A. *Synthesis* **2008**, *11*, 1682.
[282] Herrera, A.; Martinez-Alvarez, R.; Ramiro, P.; Molero, D.; Almy, J. *J. Org. Chem.* **2006**, *71*, 3026.

(34.5 mg, 0.100 mmol, quant.) was obtained as a beige solid after purification by column chromatography (SiO_2, dichloromethane).

R_f: 0.71 (silica, dichloromethane); **Mp:** 111-114 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.43 – 7.32 (m, 5H, Ar*H*), 7.29 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.22 (s, 1H, Ar*H*), 5.26 – 5.12 (m, 3H, OCH_2 + N*H*), 5.11 – 5.00 (m, 1H, C*H*), 3.46 (ddd, *J* = 14.1, 8.8, 3.3 Hz, 1H, ArS(O)$_2$CH_2), 3.34 (ddd, *J* = 13.8, 9.4, 3.3 Hz, 1H, ArS(O)$_2$CH_2), 2.70 (tt, *J* = 8.3, 4.2 Hz, 1H, ArCHCH_2), 2.65 – 2.54 (m, 1H, ArCHCH_2), 2.38 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.7, 143.9, 135.9, 135.6, 130.2, 129.3, 128.6, 128.4, 128.2, 123.8, 67.4, 48.0, 47.9, 27.8, 21.6 (one aromatic Carbon atom not resolved); **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3322 (w), 1694 (s), 1524 (s), 1305 (s), 1284 (s), 1129 (s), 737 (m); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{19}NNaO_4S^+$ 368.0927; Found 368.0932.



The reaction was performed in $CDCl_3$ and monitored by ^{1}H NMR experiments. Spectra were taken before the addition of 1.0 equivalent 4-methylbenzenethiol (0 min) and after the addition of 4-methylbenzenethiol (3/10/30/60 min) respectively. CH_2Br_2 was added as internal standard. At 3 min, it was observed that the in-situ formed N,O-acetal **298w** was almost fully converted into the first intermediate **333** (Figure 22).

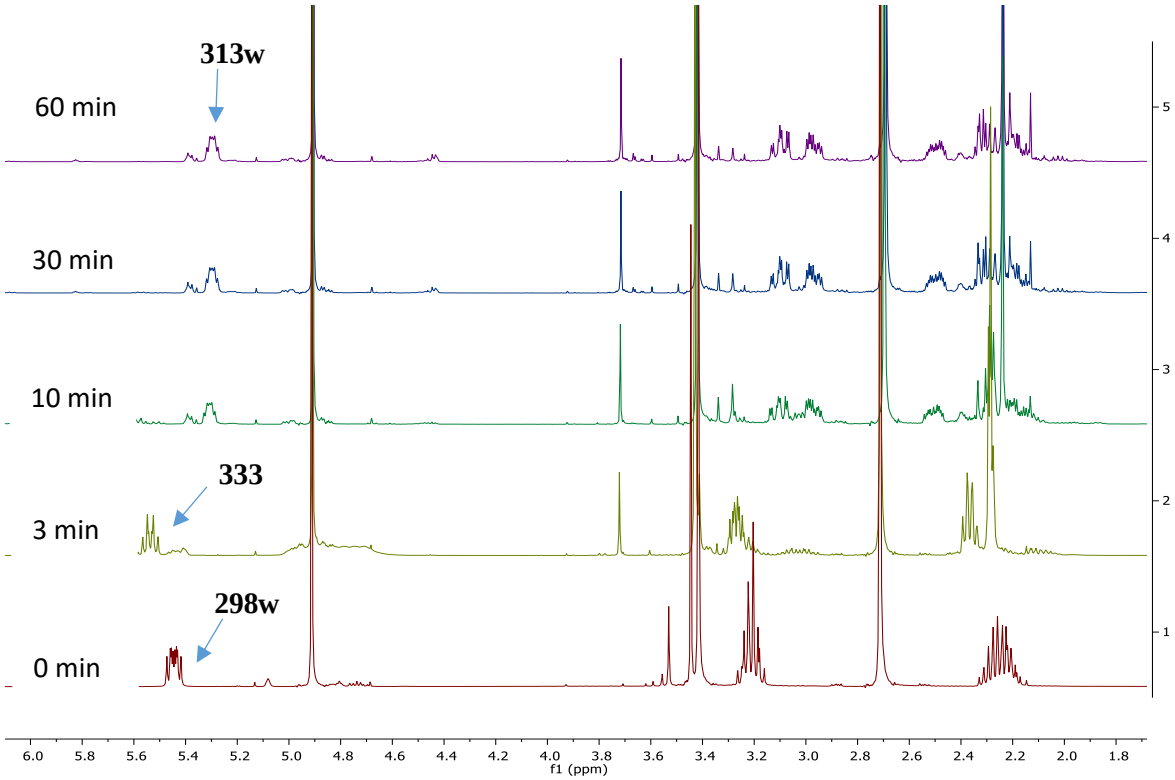
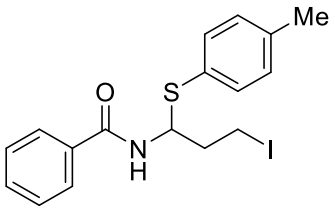


Figure 22. ^{1}H NMR following experiments starting from **298w**.

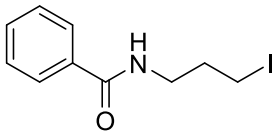
N-(3-Iodo-1-(*p*-tolylthio)propyl)benzamide (**333**)



Following GP D, starting from N-cyclopropylbenzamide (**296w**) (16.1 mg, 0.100 mmol, 1.0 equiv.) followed by the addition of 4-methylbenzenethiol (12.4 mg, 0.100 mmol, 1.0 equiv.), after stirring for 3 minutes, the reaction mixture was quenched by the addition of 1 mL saturated $Na_2S_2O_3$ and was submitted to column chromatography directly. N-(3-Iodo-1-(p-tolylthio)propyl)benzamide (**333**) (25.2 mg, 0.0613 mmol, 61%) was obtained as a white solid after purification by column chromatography (SiO_2, pentanes/EtOAc = 20:1 to 5:1).

R_f: 0.37 (silica, pentanes:ethyl acetate 5:1); **Mp:** 79-80 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ 8.05 (d, *J* = 9.4 Hz, 1H, N*H*), 7.91 – 7.77 (m, 2H, Ar*H*), 7.55 – 7.50 (m, 1H, Ar*H*), 7.49 – 7.36 (m, 4H, Ar*H*), 7.19 – 7.01 (m, 2H, Ar*H*), 5.63 (ddd, *J* = 9.3, 7.9, 6.6 Hz, 1H, C*H*), 3.49 – 3.29 (m, 2H, ICH_2), 2.51 – 2.34 (m, 2H, CH_2), 2.30 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, Acetone-d_6): δ 166.7, 138.9, 135.2, 135.0, 132.3, 130.5, 129.8, 129.1, 128.2, 59.6, 40.3, 21.1, 2.2; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3324 (m), 2916 (w), 1634 (s), 1512 (s), 1487 (s), 1288 (m), 804 (s); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{18}INNaOS^+$ 434.0046; Found 434.0049.

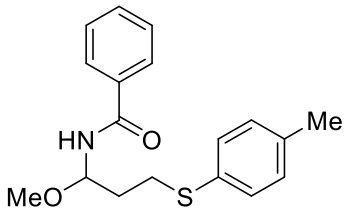
N-(3-Iodopropyl)benzamide (**335**)



In a glass vial, N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.), N-iodosuccinimide (94.0 mg, 0.420 mmol, 1.05 equiv.) and methanol (19.4 μL, 0.480 mmol, 1.2 equiv.) were dissolved in 2.0 mL of acetic acid (0.20 M). The reaction mixture was stirred at room temperature for 45 minutes. Sodium cyanoborohydride (37.7 mg, 0.600 mmol, 1.5 equiv.) was added and the reaction mixture was stirred at room temperature for another 45 minutes. After the completion of the reaction, the mixture was washed with saturated $NaHCO_3$ (5.0 mL). The aqueous layer was extracted with dichloromethane (10.0 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent. N-(3-Iodopropyl)benzamide (**335**) (66.0 mg, 0.228 mmol, 57%) was obtained as a pale yellow solid.

R_f: 0.51 (silica, pentanes:ethyl acetate 1:1); **Mp:** 48-50 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ 7.99 – 7.77 (m, 3H, Ar*H* + N*H*), 7.54 – 7.48 (m, 1H, Ar*H*), 7.48 – 7.39 (m, 2H, Ar*H*), 3.48 (td, *J* = 6.6, 5.7 Hz, 2H, NCH_2), 3.35 (t, *J* = 7.0 Hz, 2H, ICH_2), 2.16 (p, *J* = 6.8 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, Acetone-d_6): δ 167.5, 135.9, 131.9, 129.1, 128.0, 41.1, 34.6, 4.2; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3287 (m), 3059 (w), 1641 (s), 1533 (s), 1293 (s), 1161 (m), 704 (s); **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_{13}INO^+$ 290.0036; Found 290.0038.

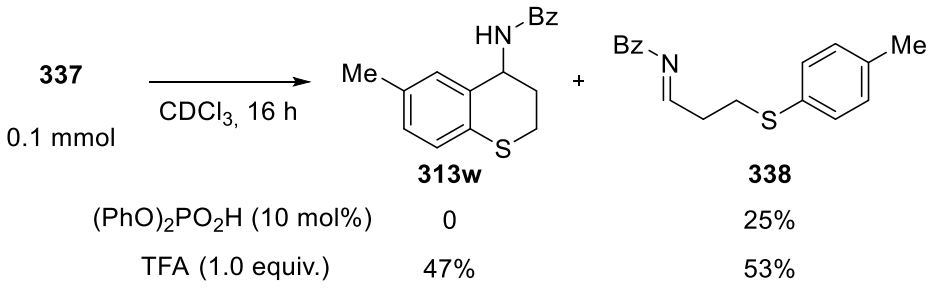
N-(1-Methoxy-3-(*p*-tolylthio)propyl)benzamide (**337**)



In a glass vial, N-cyclopropylbenzamide (**296w**) (64.5 mg, 0.400 mmol, 1.0 equiv.), diphenyl phosphate (10.0 mg, 0.0400 mmol, 0.1 equiv.), N-iodosuccinimide (94.0 mg, 0.420 mmol, 1.05 equiv.) and methanol (19.4 μL, 0.480 mmol, 1.2 equiv.) were dissolved in 2.0 mL of chloroform (0.20 M). The reaction mixture was stirred at room temperature for 45 minutes. After the completion of the reaction, chloroform was evaporated under

reduced pressure. The crude was dissolved in 1.5 mL of DMF, then K_2CO_3 (110 mg, 0.800 mmol, 2.0 equiv.) and 4-methylbenzenethiol (59.6 mg, 0.480 mmol, 1.2 equiv.) were added. The resulting mixture was stirred at room temperature for 16 hours and then diluted with brine (10.0 mL). The aqueous layer was extracted with EtOAc (10.0 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent. N-(1-Methoxy-3-(*p*-tolylthio)propyl)benzamide (**337**) (105 mg, 0.333 mmol, 83%) was obtained as a white solid.

R_f: 0.35 (silica, pentanes:ethyl acetate 3:1); **Mp:** 98-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 – 7.74 (m, 2H, Ar*H*), 7.57 – 7.50 (m, 1H, Ar*H*), 7.49 – 7.41 (m, 2H, Ar*H*), 7. 29 – 7.25 (m, 2H, Ar*H*), 7.15 – 7.03 (m, 2H, Ar*H*), 6.54 (d, *J* = 9.6 Hz, 1H, N*H*), 5.48 (ddd, *J* = 9.7, 6.5, 5.4 Hz, 1H, C*H*), 3.39 (s, 3H, OCH_3), 3.07 (ddd, *J* = 13.3, 8.3, 6.3 Hz, 1H, ArSCH_2), 2.96 (ddd, *J* = 13.3, 8.1, 6.4 Hz, 1H, ArSCH_2), 2.31 (s, 3H, CH_3), 2.12 – 1.92 (m, 2H, ArCHCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.3, 136.6, 133.7, 131.9, 131.7, 130.5, 129.8, 128.7, 127.0, 80.4, 56.1, 35.1, 29.8, 21.0; **IR** (film, cm^{-1}): $\tilde{\nu}$ = 3311 (m), 3059 (w), 2927 (w), 2831 (w), 1653 (s), 1521 (s), 1293 (m), 1101 (s), 800 (m); **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{21}NNaO_2S^+$ 338.1185; Found 338.1186.



The conversion of the isolated product **337** into thiochroman product **313w** was not very efficient even in the presence of 1.0 equiv TFA for 16 hours, as it was accompanied by the formation of imine intermediate **338**.

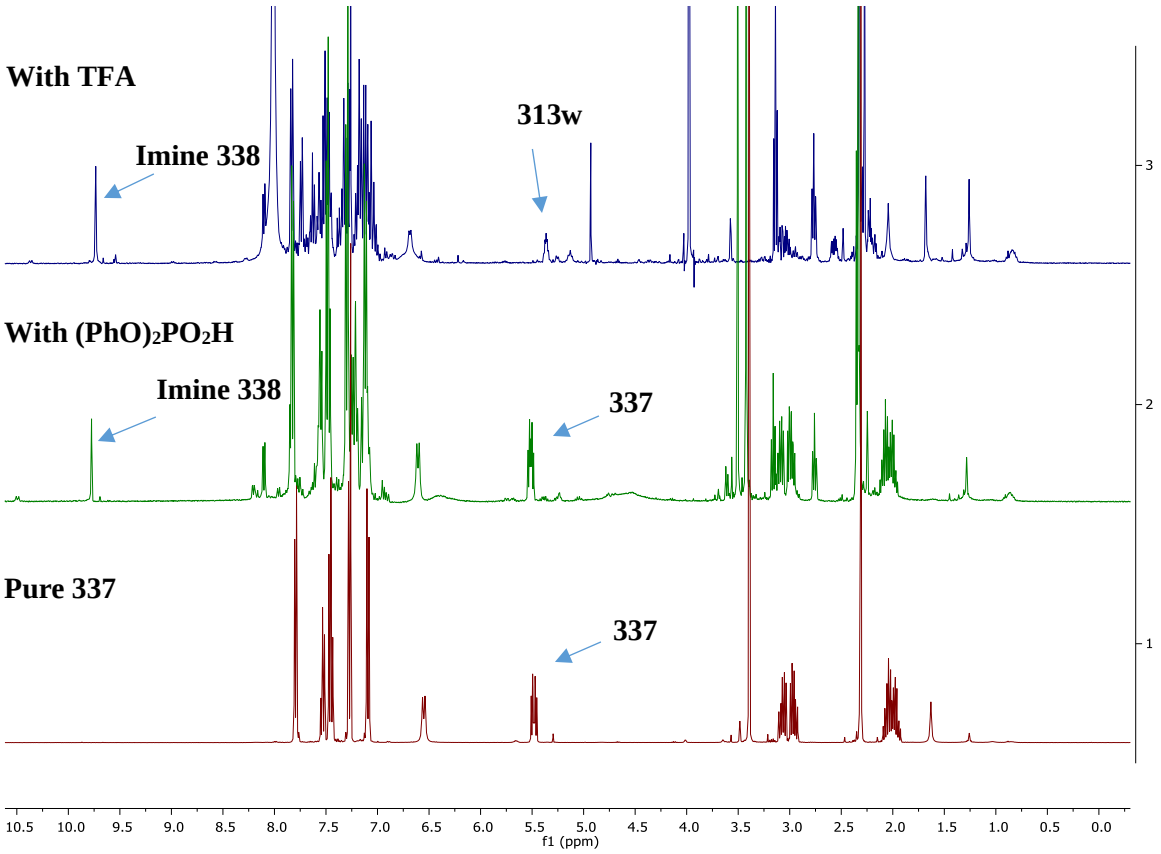


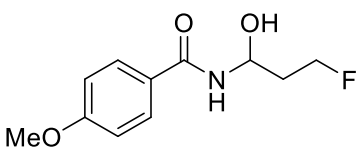
Figure 23. ^{1}H NMR spectra comparison of **337** and crude reaction mixture.

5.3.4 Fluorination of amino-cyclopropanes/cyclobutanes through photoredox catalysis

General Procedure E (GP E):

In a 12*75 mm Borosilicate glass tube, the corresponding aminocyclopropane (0.300 mmol, 1.0 equiv.), selectfluor (117 mg, 0.330 mmol, 1.1 equiv.) and benzophenone (5.4 mg, 0.030 mmol, 0.10 equiv.) were dissolved in 0.75 mL of MeCN-H_2O (v:v 4:6, 0.40 M). The reaction mixture was degassed by three freeze-pump-thaw cycles and backfilled with N_2. The mixture was then stirred at room temperature under 365 nm irradiation in Rayonet Reactor for 45 minutes, if not specified otherwise. The distance between glass tube and lamp was 7 cm. After the completion of the reaction, the crude product was directly submitted to column chromatography on silica using pentanes:ethyl acetate as eluent.

***N*-(3-Fluoro-1-hydroxypropyl)-4-methoxybenzamide** (**339a**)

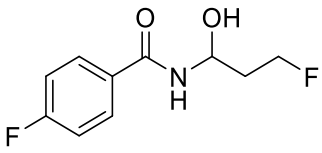


Following GP E, starting from *N*-cyclopropyl-4-methoxybenzamide **296a** (57.3 mg, 0.300 mmol), *N*-(3-fluoro-1-hydroxypropyl)-4-methoxybenzamide **339a** (50.5 mg, 0.222 mmol, 74%) was obtained as a white solid after purification by column chromatography on silica using 3:2 pentanes:ethyl acetate as eluent.

R_f: 0.27 (silica, pentanes:ethyl acetate 1:1); **Mp:** 119-121 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 – 7.69 (m, 2H, Ar*H*), 7.19 – 7.05 (m, 1H, N*H*), 6.96 – 6.87 (m, 2H, Ar*H*), 5.71 (dt, *J* = 7.3, 5.3 Hz, 1H, C*H*), 4.96

– 4.58 (m, 2H, FCH_2), 4.27 (s, 1H, O*H*, peak was not splitted), 3.85 (s, 3H, OCH_3), 2.27 – 2.06 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.1, 162.7, 128.9, 125.5, 113.8, 80.7 (d, *J* = 161.6 Hz), 72.8 (d, *J* = 2.1 Hz), 55.4, 35.1 (d, *J* = 18.8 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -218.0; **IR** (film): $\tilde{\nu}$ = 3318 (br, s), 2968 (w), 1640 (m), 1606 (s), 1503 (s), 1256 (s), 1179 (m), 1029 (m), 846 (m); **HRMS** (APPI) calcd. for $C_{11}H_{14}FNO_3^+$ $[M]^+$ 227.0952; Found 227.0949.

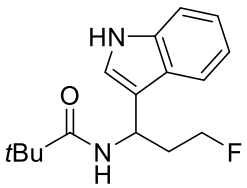
4-Fluoro-*N*-(3-fluoro-1-hydroxypropyl)benzamide (**339c**)



Following GP E, starting from *N*-cyclopropyl-4-fluorobenzamide **296c** (62.1 mg, 0.300 mmol) and after stirring for 4 hours, 4-fluoro-*N*-(3-fluoro-1-hydroxypropyl)benzamide **339c** (27.6 mg, 0.128 mmol, 43%) was obtained as a white solid after purification by column chromatography on silica using 3:2 pentanes:ethyl acetate as eluent.

R_f: 0.42 (silica, pentanes:ethyl acetate 1:1); **Mp:** 80-82 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 (dd, *J* = 8.9, 5.2 Hz, 2H, Ar*H*), 7.20 – 7.08 (m, 3H, Ar*H* + N*H*), 5.72 (dtd, *J* = 7.1, 5.2, 3.2 Hz, 1H, C*H*), 5.11 – 4.43 (m, 2H, FCH_2), 4.17 (d, *J* = 3.2 Hz, 1H, O*H*), 2.44 – 1.92 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.5, 165.1 (d, *J* = 253.0 Hz), 129.5, 129.5 (d, *J* = 9.0 Hz), 115.8 (d, *J* = 21.9 Hz), 80.7 (d, *J* = 161.4 Hz), 72.9 (d, *J* = 8.9 Hz), 35.0 (d, *J* = 18.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -107.0, -217.8; **IR** (film): $\tilde{\nu}$ = 3315 (br, s) 1644 (s), 1604 (s), 1501 (s), 1236 (m), 852 (m); **HRMS** (APCI) calcd. for $C_{10}H_{11}F_2NNaO_2^+$ $[M+Na]^+$ 238.0650; Found 238.0648.

***N*-(3-Fluoro-1-(1*H*-indol-3-yl)propyl)pivalamide** (**339n-indole**)



Following GP E, starting from *N*-cyclopropylpivalamide **296n** (42.3 mg, 0.300 mmol) and after stirring for 10 hours for the first step, 1*H*-indole (42.2 mg, 0.360 mmol, 1.2 equiv.) in 0.5 mL MeCN was then added to the reaction crude. After the reaction mixture was stirred for another 16 hours, *N*-(3-fluoro-1-(1*H*-indol-3-yl)propyl)pivalamide **339n-indole** (8.0 mg, 0.029 mmol, 29%) was obtained as a yellow solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.47 (silica, pentanes:ethyl acetate 1:1); **Mp:** 76-79 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.23 (s, 1H, indole N*H*), 7.59 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.38 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.22 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, Ar*H*), 7.15 – 7.10 (m, 2H, Ar*H*), 6.04 (d, *J* = 7.8 Hz, 1H, N*H*), 5.51 (q, *J* = 7.2 Hz, 1H, C*H*), 4.67 – 4.41 (m, 2H, FCH_2), 2.48 – 2.32 (m, 2H, CH_2), 1.20 (s, 9H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 177.8, 136.6, 125.7, 122.5, 121.7, 119.9, 119.1, 116.2, 111.5, 82.0 (d, *J* = 163.9 Hz), 43.8 (d, *J* = 5.7 Hz), 38.7, 35.4 (d, *J* = 19.2 Hz), 27.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -218.0; **IR** (film): $\tilde{\nu}$ = 3411 (w), 3287 (m), 2965 (m), 1640 (s), 1510 (s), 1197 (w), 1011 (w), 743 (s); **HRMS** (ESI) calcd. for $C_{16}H_{21}FN_2NaO^+$ $[M+Na]^+$ 299.1530; Found 299.1536.

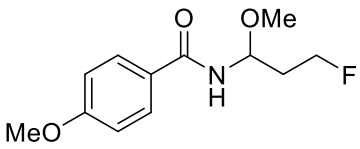
Scope of the nucleophiles for elimination-addition of hemiaminals

General Procedure F (GP F):

In a 12*75 mm borosilicate glass tube, *N*-cyclopropyl-4-methoxybenzamide **296a** (57.3 mg, 0.300 mmol), selectfluor (117 mg, 0.330 mmol, 1.1 equiv.) and benzophenone (5.4 mg, 0.030 mmol, 0.10 equiv.) were

dissolved in 0.75 mL of MeCN-H_2O (v:v 4:6, 0.40 M). The reaction mixture was degassed by three freeze-pump-thaw cycles and backfilled with N_2. The mixture was then stirred at room temperature under 365 nm irradiation in Rayonet Reactor for 45 minutes. Then the tube was taken out from the Rayonet Reactor and a solution of nucleophile (0.360 mmol, 1.2 equiv.) in 0. 50 mL MeCN was added dropwise. The reaction mixture was stirred at room temperature for 3 hours, if not specified otherwise. After the completion of the reaction, the crude product was directly submitted to column chromatography on silica using pentanes:ethyl acetate as eluent.

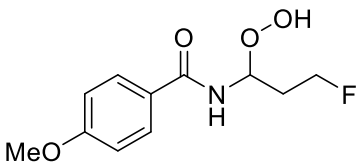
***N*-(3-Fluoro-1-methoxypropyl)-4-methoxybenzamide** (**341a**)



Following GP F, methanol (1.0 mL, 25 mmol, 82 equiv.) was used as nucleophile. After the reaction mixture was stirred for 1 hours, *N*-(3-fluoro-1-methoxypropyl)-4-methoxybenzamide (**341a**) (53.0 mg, 0.220 mmol, 73%) was obtained as a white solid after purification by column chromatography on silica using 3:2 pentanes:ethyl acetate as eluent.

R_f: 0.46 (silica, pentanes:ethyl acetate 1:1); **Mp:** 110-112 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.82 – 7.68 (m, 2H, Ar*H*), 7.01 – 6.85 (m, 2H, Ar*H*), 6.56 (d, *J* = 8.8 Hz, 1H, N*H*), 5.55 (dt, *J* = 10.1, 5.3 Hz, 1H, C*H*), 4.85 – 4.52 (m, 2H, FCH_2), 3.85 (s, 3H, ArOCH_3), 3.42 (s, 3H, OCH_3), 2.24 – 2.01 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.8, 162.5, 128.9, 125.9, 113.8, 80.6 (d, *J* = 162.9 Hz), 78.4 (d, *J* = 3.4 Hz), 56.0, 55.4, 35.9 (d, *J* = 19.0 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -219.3; **IR** (film): $\tilde{\nu}$ = 3304 (w), 2937 (w), 2839 (w), 1642 (s), 1606 (s), 1531 (m), 1503 (s), 1257 (s), 1178 (m), 845 (m); **HRMS** (ESI) calcd. for $C_{12}H_{16}FNNaO_3^+$ $[M+Na]^+$ 264.1006; Found 264.1014.

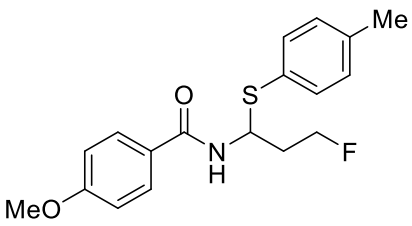
***N*-(3-Fluoro-1-hydroperoxypropyl)-4-methoxybenzamide** (**341b**)



Following GP F, hydrogen peroxide solution 30% (w/w) in water (37 uL, 0.36 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 3 hours, *N*-(3-fluoro-1-hydroperoxypropyl)-4-methoxybenzamide (**341b**) (46.5 mg, 0.191 mmol, 64%) was obtained as a white solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.41 (silica, pentanes:ethyl acetate 2:3); **Mp:** 93-95 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 10.95 (s, 1H, OO*H*), 8.09 (d, *J* = 7.7 Hz, 1H, N*H*), 7.94 – 7.91 (m, 2H, Ar*H*), 7.01 – 6.97 (m, 2H, Ar*H*), 5.95 (dt, *J* = 8.9, 6.8 Hz, 1H, C*H*), 4.69 – 4.51 (m, 2H, FCH_2), 3.86 (s, 3H, OCH_3), 2.39 – 2.09 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 167.0, 163.3, 130.2, 127.4, 114.3, 82.3 (d, *J* = 5.9 Hz), 81.2 (d, *J* = 163.0 Hz), 55.8, 33.7 (d, *J* = 20.0 Hz); **^{19}F NMR** (376 MHz, Acetone-d_6): δ = -221.6; **IR** (film): $\tilde{\nu}$ = 3305 (br, s), 2971 (w), 1644 (s), 1606 (s), 1503 (s), 1258 (s), 1178 (m), 1028 (m), 845 (m); **HRMS** (ESI) calcd. for $C_{11}H_{14}FNNaO_4^+$ $[M+Na]^+$ 266.0799; Found 266.0798.

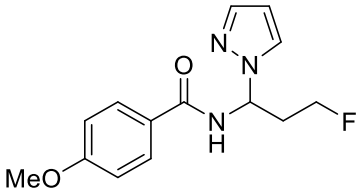
***N*-(3-Fluoro-1-(*p*-tolylthio)propyl)-4-methoxybenzamide** (**341c**)



Following GP F, 4-methylthiophenol (44.6 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 3 hours, *N*-(3-fluoro-1-(*p*-tolylthio)propyl)-4-methoxybenzamide (**341c**) (68.5 mg, 0.206 mmol, 69%) was obtained as a white solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.33 (silica, pentanes:ethyl acetate 3:1); **Mp:** 97-99 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.66 – 7.59 (m, 2H, Ar*H*), 7.40 – 7.33 (m, 2H, Ar*H*), 7.12 – 7.06 (m, 2H, Ar*H*), 6.90 – 6.86 (m, 2H, Ar*H*), 6.45 (d, *J* = 9.4 Hz, 1H, N*H*), 5.69 (ddd, *J* = 9.4, 7.4, 5.7 Hz, 1H, C*H*), 4.86 – 4.52 (m, 2H, FCH_2), 3.83 (s, 3H, OCH_3), 2.39 – 2.09 (m, 5H, CH_3 + CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.8, 162.3, 138.4, 133.9, 129.9, 128.7, 128.2, 126.0, 113.7, 81.2 (d, *J* = 165.6 Hz), 55.4, 55.1 (d, *J* = 3.9 Hz), 36.1 (d, *J* = 19.5 Hz), 21.1; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -218.7; **IR** (film): $\tilde{\nu}$ = 3293 (w), 2963 (w), 1636 (s), 1605 (s), 1500 (s), 1293 (s), 1028 (m), 843 (m), 810 (m); **HRMS** (ESI) calcd. for $C_{18}H_{20}FNNaO_2S^+$ $[M+Na]^+$ 356.1091; Found 356.1095.

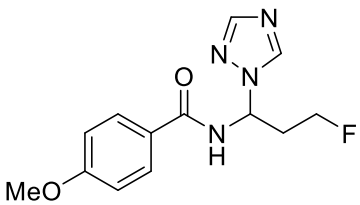
***N*-(3-Fluoro-1-(1*H*-pyrazol-1-yl)propyl)-4-methoxybenzamide** (**341d**)



Following GP F, 1*H*-pyrazole (24.5 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 16 hours, *N*-(3-fluoro-1-(1*H*-pyrazol-1-yl)propyl)-4-methoxybenzamide (**341d**) (58.2 mg, 0.210 mmol, 70%) was obtained as a white solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.26 (silica, pentanes:ethyl acetate 1:1); **Mp:** 146-148 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.77 – 7.71 (m, 2H, Ar*H* + N*H*), 7.71 – 7.66 (m, 2H, Ar*H*), 7.56 (d, *J* = 1.7 Hz, 1H, Ar*H*), 6.84 – 6.79 (m, 2H, Ar*H*), 6.57 (q, *J* = 7.8 Hz, 1H, C*H*), 6.25 (t, *J* = 2.1 Hz, 1H, Ar*H*), 4.63 – 4.07 (m, 2H, FCH_2), 3.80 (s, 3H, OCH_3), 2.72 – 2.54 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.4, 162.5, 140.4, 130.8, 129.1, 125.2, 113.6, 105.2, 79.9 (d, *J* = 165.7 Hz), 62.3 (d, *J* = 3.9 Hz), 55.4, 35.0 (d, *J* = 19.8 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -221.8; **IR** (film): $\tilde{\nu}$ = 3304 (w), 2970 (w), 1645 (m), 1606 (m), 1502 (s), 1252 (s), 1027 (m), 845 (m), 767 (m); **HRMS** (ESI) calcd. for $C_{14}H_{16}FN_3NaO_2^+$ $[M+Na]^+$ 300.1119; Found 300.1124.

***N*-(3-Fluoro-1-(1*H*-1,2,4-triazol-1-yl)propyl)-4-methoxybenzamide** (**341e**)

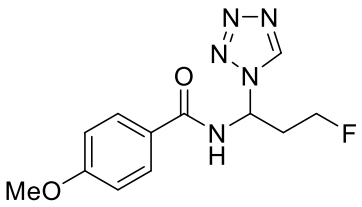


Following GP F, 1,2,4-1*H*-triazole (41.4 mg, 0.600 mmol, 2.0 equiv.) was used as nucleophile. After the reaction mixture was stirred for 16 hours, *N*-(3-fluoro-1-(1*H*-1,2,4-triazol-1-yl)propyl)-4-methoxy benzamide (**341e**) (59.1 mg, 0.213 mmol, 71%) was obtained as a white solid after purification by column chromatography on silica using 100% ethyl acetate as eluent.

R_f: 0.26 (silica, 100% ethyl acetate); **Mp:** 156-158 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 8.60 (d, *J* = 8.4 Hz, 1H, N*H*), 8.55 (s, 1H, Ar*H*), 7.94 – 7.86 (m, 3H, Ar*H*), 7.02 – 6.93 (m, 2H, Ar*H*), 6.61 (q, *J* = 7.7 Hz, 1H, C*H*), 4.75 – 4.33 (m, 2H, FCH_2), 3.85 (s, 3H, OCH_3), 2.69 (ddt, *J* = 25.7, 7.5, 5.7 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 167.1, 163.7, 152.6, 144.9, 130.3, 126.4, 114.4, 80.8 (d, *J* = 163.7

Hz), 61.8 (d, *J* = 5.7 Hz), 55.8, 35.0 (d, *J* = 20.0 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -221.2; **IR** (film): $\tilde{\nu}$ = 3303 (w), 1653 (m), 1606 (m), 1503 (s), 1256 (s), 1178 (m), 1025 (m), 846 (m); **HRMS** (ESI) calcd. for $C_{13}H_{15}FN_4NaO_2^+$ $[M+Na]^+$ 301.1071; Found 301.1064.

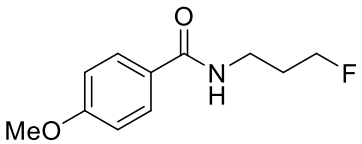
***N*-(3-Fluoro-1-(1*H*-tetrazol-1-yl)propyl)-4-methoxybenzamide** (**341f**)



Following GP F, 1*H*-tetrazole (42.0 mg, 0.600 mmol, 2.0 equiv.) was used as nucleophile. After the reaction mixture was stirred for 16 hours, *N*-(3-fluoro-1-(1*H*-tetrazol-1-yl)propyl)-4-methoxybenzamide (**341f**) (33.0 mg, 0.118 mmol, 39%) was obtained as a white solid after purification by column chromatography on silica using 2:3 pentanes:ethyl acetate as eluent.

R_f: 0.26 (silica, pentanes:ethyl acetate 2:3); **Mp:** 157-159 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 9.30 (s, 1H, Ar*H*), 8.86 (d, *J* = 8.4 Hz, 1H, N*H*), 7.93 – 7.87 (m, 2H, Ar*H*), 7.03 – 6.97 (m, 2H, Ar*H*), 6.87 (q, *J* = 8.1 Hz, 1H, C*H*), 4.85 – 4.49 (m, 2H, FCH_2), 3.85 (s, 3H, OCH_3), 2.89 – 2.79 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 167.3, 163.9, 144.1, 130.4, 126.0, 114.5, 80.7 (d, *J* = 164.3 Hz), 62.5 (d, *J* = 5.2 Hz), 55.9, 35.0 (d, *J* = 20.1 Hz); **^{19}F NMR** (376 MHz, Acetone-d_6): δ = -223.2; **IR** (film): $\tilde{\nu}$ = 3294 (w), 2971 (w), 1650 (m), 1605 (s), 1503 (s), 1256 (s), 1177 (m), 1025 (m), 845 (m); **HRMS** (ESI) calcd. for $C_{12}H_{14}FN_5NaO_2^+$ $[M+Na]^+$ 302.1024; Found 302.1017.

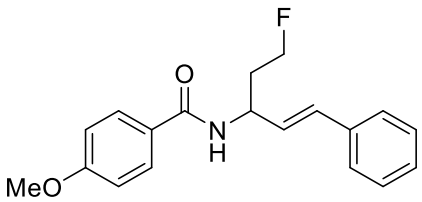
***N*-(3-Fluoropropyl)-4-methoxybenzamide** (**341g**)



Following GP F, $NaBH_3CN$ (22.6 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 3 hours, *N*-(3-fluoropropyl)-4-methoxybenzamide (**341g**) (52.4 mg, 0.248 mmol, 83%) was obtained as a beige solid after purification by column chromatography on silica using 3:2 pentanes:ethyl acetate as eluent.

R_f: 0.28 (silica, pentanes:ethyl acetate 1:1); **Mp:** 71-73 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.79 – 7.64 (m, 2H, Ar*H*), 6.97 – 6.85 (m, 2H, Ar*H*), 6.38 (s, 1H, N*H*), 4.59 (dt, *J* = 47.3, 5.6 Hz, 2H, FCH_2), 3.84 (s, 3H, OCH_3), 3.60 (q, *J* = 6.3 Hz, 2H, NCH_2), 2.03 (dddd, *J* = 28.2, 12.1, 6.5, 5.5 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.1, 162.1, 128.6, 126.7, 113.7, 82.9 (d, *J* = 163.8 Hz), 55.4, 37.1 (d, *J* = 4.2 Hz), 30.2 (d, *J* = 19.1 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -219.9; **IR** (film): $\tilde{\nu}$ = 3298 (m), 2967 (w), 1630 (s), 1607 (s), 1542 (m), 1505 (s), 1299 (m), 1256 (s), 1179 (m), 848 (m); **HRMS** (ESI) calcd. for $C_{11}H_{15}FNO_2^+$ $[M+H]^+$ 212.1081; Found 212.1083.

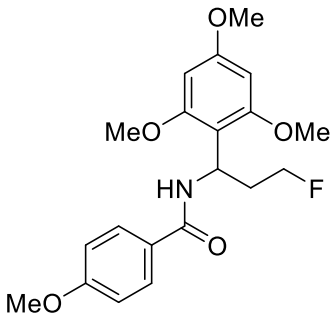
(*E*)-*N*-(5-Fluoro-1-phenylpent-1-en-3-yl)-4-methoxybenzamide (**341h**)



Following GP F, potassium *trans*-styryltrifluoroborate (126 mg, 0.600 mmol, 2.0 equiv.) was used as nucleophile. After the reaction mixture was stirred for 16 hours, (*E*)-*N*-(5-fluoro-1-phenylpent-1-en-3-yl)-4-methoxybenzamide (**341h**) (39.0 mg, 0.125 mmol, 42%) was obtained as a white solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.29 (silica, pentanes:ethyl acetate 2:1); **Mp:** 121-123 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 7.96 – 7.86 (m, 2H, Ar*H*), 7.70 (d, *J* = 8.4 Hz, 1H, N*H*), 7.47 – 7.39 (m, 2H, Ar*H*), 7.36 – 7.27 (m, 2H, Ar*H*), 7.26 – 7.19 (m, 1H, Ar*H*), 7.01 – 6.93 (m, 2H, Ar*H*), 6.65 (dd, *J* = 16.0, 1.2 Hz, 1H, vinyl C*H*), 6.40 (dd, *J* = 16.0, 6.7 Hz, 1H, vinyl C*H*), 4.99 (h, *J* = 7.3, 6.8 Hz, 1H, C*H*), 4.73 – 4.48 (m, 2H, FCH_2), 3.84 (s, 3H, OCH_3), 2.18 (ddt, *J* = 24.8, 7.2, 6.0 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 165.4, 162.1, 137.1, 130.2, 130.1, 129.0, 128.5, 127.4, 127.3, 126.3, 113.4, 81.1 (d, *J* = 163.3 Hz), 54.9, 48.2 (d, *J* = 5.7 Hz), 35.6 (d, *J* = 19.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -220.4; **IR** (film): $\tilde{\nu}$ = 3316 (w), 2963 (w), 1630 (s), 1606 (s), 1538 (m), 1504 (s), 1255 (s), 1178 (m), 1030 (m), 749 (m); **HRMS** (ESI) calcd. for $C_{19}H_{21}FNO_2^+$ $[M+H]^+$ 314.1551; Found 314.1539.

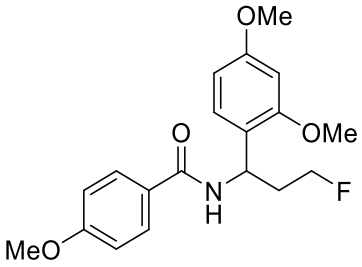
***N*-(3-Fluoro-1-(2,4,6-trimethoxyphenyl)propyl)-4-methoxybenzamide (341i)**



Following GP F, 1,3,5-trimethoxybenzene (60.5 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 16 hours, *N*-(3-fluoro-1-(2,4,6-trimethoxyphenyl)propyl)-4-methoxybenzamide (**341i**) (77.8 mg, 0.206 mmol, 69%) was obtained as a white solid after purification by column chromatography on silica using 3:2 pentanes:ethyl acetate as eluent.

R_f: 0.44 (silica, pentanes:ethyl acetate 3:2); **Mp:** 133-135 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.75 – 7.66 (m, 2H, Ar*H*), 7.55 (d, *J* = 9.6 Hz, 1H, N*H*), 6.95 – 6.85 (m, 2H, Ar*H*), 6.16 (s, 2H, Ar*H*), 5.98 (dt, *J* = 9.6, 7.4 Hz, 1H, C*H*), 4.47 (dt, *J* = 47.1, 6.6 Hz, 2H, FCH_2), 3.88 (s, 6H, OCH_3), 3.84 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.39 – 2.11 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.6, 161.9, 160.5, 158.6, 128.6, 127.4, 113.6, 109.7, 91.1, 82.2 (d, *J* = 164.2 Hz), 55.9, 55.4 (there are two ^{13}C signals for four methoxy groups, meaning signals for the two *para* methoxy groups are overlapped), 41.7 (d, *J* = 8.1 Hz), 36.1 (d, *J* = 19.0 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -218.4; **IR** (film): $\tilde{\nu}$ = 3445 (w), 2962 (w), 2839 (w), 1653 (m), 1606 (s), 1493 (s), 1252 (s), 1124 (s), 1030 (m), 844 (w), 814 (w); **HRMS** (ESI) calcd. for $C_{20}H_{24}FNNaO_5^+$ $[M+Na]^+$ 400.1531; Found 400.1522.

***N*-(1-(2,4-Dimethoxyphenyl)-3-fluoropropyl)-4-methoxybenzamide (341j)**

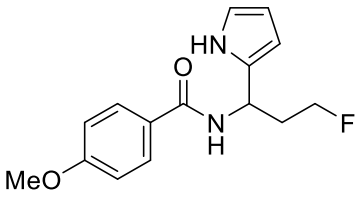


Following GP F, 1,3-dimethoxybenzene (49.7 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 16 hours, *N*-(1-(2,4-dimethoxyphenyl)-3-fluoropropyl)-4-methoxybenzamide (**341j**) (22.4 mg, 0.0646 mmol, 22%) was obtained as a white solid after purification by column chromatography on silica using 3:2 pentanes:ethyl acetate as eluent.

R_f: 0.43 (silica, pentanes:ethyl acetate 1:1); **Mp:** 133-134 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 7.90 – 7.83 (m, 2H, Ar*H*), 7.74 (d, *J* = 8.8 Hz, 1H, N*H*), 7.27 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.01 – 6.91 (m, 2H, Ar*H*), 6.58 (d, *J* = 2.4 Hz, 1H, Ar*H*), 6.48 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar*H*), 5.52 (td, *J* = 8.6, 6.2 Hz, 1H, C*H*), 4.62 – 4.36 (m, 2H, FCH_2), 3.90 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.33 – 2.18 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 166.0, 163.0, 161.2, 159.0, 129.8, 129.2, 128.4, 123.7, 114.3, 105.3, 99.6, 82.4 (d, *J* = 163.3 Hz), 55.9, 55.8, 55.6, 47.3 (d, *J* = 6.1 Hz), 37.0 (d, *J* = 19.4 Hz); **^{19}F NMR** (376 MHz, Acetone-d_6): δ = -220.2; **IR** (film): $\tilde{\nu}$ = 3325 (w), 2962 (w),

1632 (s), 1607 (s), 1504 (s), 1254 (s), 1031 (m), 843 (m); **HRMS** (ESI) calcd. for $C_{19}H_{23}FNO_4^+$ $[M+H]^+$ 348.1606; Found 348.1603.

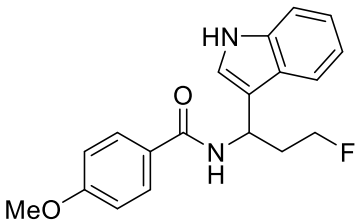
***N*-(3-Fluoro-1-(1*H*-pyrrol-2-yl)propyl)-4-methoxybenzamide (341k)**



Following GP F, 1*H*-pyrrole (24.1 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 2 hours, *N*-(3-fluoro-1-(1*H*-pyrrol-2-yl)propyl)-4-methoxybenzamide (**341k**) (38.2 mg, 0.138 mmol, 46%) was obtained as a red solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.30 (silica, pentanes:ethyl acetate 2:1); **Mp:** 150-152 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.37 (s, 1H, pyrrole N*H*), 7.78 – 7.61 (m, 2H, Ar*H*), 6.98 – 6.82 (m, 2H, Ar*H*), 6.74 (td, *J* = 2.6, 1.5 Hz, 1H, Ar*H*), 6.56 (d, *J* = 7.6 Hz, 1H, N*H*), 6.12 (q, *J* = 2.9 Hz, 1H, Ar*H*), 6.05 (qd, *J* = 2.9, 1.8 Hz, 1H, Ar*H*), 5.31 (dt, *J* = 8.3, 6.2 Hz, 1H, C*H*), 4.87 – 4.52 (m, 2H, FCH_2), 3.84 (s, 3H, OCH_3), 2.65 – 2.31 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.9, 162.4, 132.6, 128.8, 126.1, 118.0, 113.8, 107.5, 104.4, 82.0 (d, *J* = 164.2 Hz), 55.4, 45.5 (d, *J* = 3.5 Hz), 33.3 (d, *J* = 19.5 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -217.2; **IR** (film): $\tilde{\nu}$ = 3320 (br,s), 2965 (w), 1621 (s), 1606 (s), 1533 (m), 1503 (s), 1255 (s), 1178 (m), 1027 (m), 728 (w); **HRMS** (ESI) calcd. for $C_{15}H_{17}FN_2NaO_2^+$ $[M+Na]^+$ 299.1166; Found 299.1174.

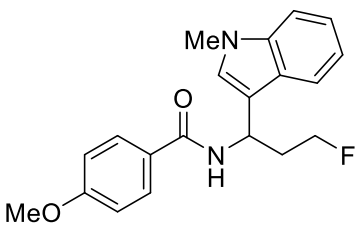
***N*-(3-Fluoro-1-(1*H*-indol-3-yl)propyl)-4-methoxybenzamide (341l)**



Following GP F, 1*H*-indole (42.2 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 3 hours, *N*-(3-fluoro-1-(1*H*-indol-3-yl)propyl)-4-methoxybenzamide (**341l**) (65.2 mg, 0.200 mmol, 67%) was obtained as a dark solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.46 (silica, pentanes:ethyl acetate 1:1); **Mp:** 63-66 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.28 (s, 1H, indole N*H*), 7.74 – 7.69 (m, 2H, Ar*H*), 7.67 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 7.38 (dt, *J* = 8.2, 1.0 Hz, 1H, Ar*H*), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, Ar*H*), 7.16 (dd, *J* = 2.6, 0.7 Hz, 1H, Ar*H*), 7.12 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H, Ar*H*), 6.92 – 6.85 (m, 2H, Ar*H*), 6.48 (d, *J* = 8.0 Hz, 1H, N*H*), 5.72 (q, *J* = 7.1 Hz, 1H, C*H*), 4.75 – 4.46 (m, 2H, FCH_2), 3.82 (s, 3H, OCH_3), 2.59 – 2.42 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.3, 162.2, 136.7, 128.7, 126.7, 125.7, 122.5, 122.0, 120.0, 119.1, 116.0, 113.7, 111.5, 82.0 (d, *J* = 163.9 Hz), 55.4, 44.3 (d, *J* = 5.7 Hz), 35.5 (d, *J* = 19.2 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -218.2; **IR** (film): $\tilde{\nu}$ = 3408 (w), 3292 (m), 2965(w), 1631 (s), 1606 (s), 1499 (s), 1254 (s), 1178 (m), 1029 (m), 745 (m); **HRMS** (ESI) calcd. for $C_{19}H_{19}FN_2NaO_2^+$ $[M+Na]^+$ 349.1323; Found 349.1322.

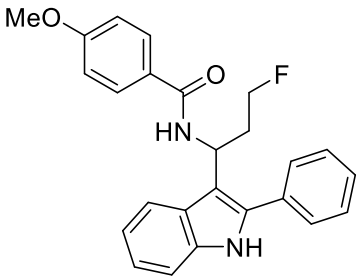
***N*-(3-Fluoro-1-(1-methyl-1H-indol-3-yl)propyl)-4-methoxybenzamide (341m)**



Following GP F, 1-methylindole (47.2 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 3 hours, *N*-(3-fluoro-1-(1-methyl-1H-indol-3-yl)propyl)-4-methoxy benzamide (**341m**) (65.5 mg, 0.193 mmol, 64%) was obtained as a beige solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.40 (silica, pentanes:ethyl acetate 1:1); **Mp:** 168-169 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 7.90 – 7.84 (m, 2H, Ar*H*), 7.72 (dt, *J* = 7.9, 1.0 Hz, 2H, Ar*H* + N*H*), 7.35 (dt, *J* = 8.3, 0.9 Hz, 1H, Ar*H*), 7.27 (d, *J* = 0.8 Hz, 1H, Ar*H*), 7.16 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H, Ar*H*), 7.01 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar*H*), 6.95 – 6.89 (m, 2H, Ar*H*), 5.80 – 5.70 (m, 1H, C*H*), 4.74 – 4.46 (m, 2H, FCH_2), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, NCH_3), 2.63 – 2.30 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 166.2, 162.9, 138.2, 129.9, 128.2, 127.8, 127.5, 122.4, 120.2, 119.7, 116.7, 114.2, 110.3, 82.4 (d, *J* = 163.0 Hz), 55.7, 43.3 (d, *J* = 6.5 Hz), 36.6 (d, *J* = 19.5 Hz), 32.8; **^{19}F NMR** (376 MHz, Acetone-d_6): δ = -220.0; **IR** (film): $\tilde{\nu}$ = 3306 (w), 2961 (m), 1626 (s), 1606 (s), 1502 (s), 1253 (s), 1178 (m), 1030 (m), 743 (m); **HRMS** (ESI) calcd. for $C_{20}H_{21}FN_2NaO_2^+$ $[M+Na]^+$ 363.1479; Found 363.1481.

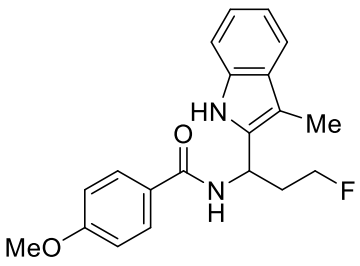
***N*-(3-Fluoro-1-(2-phenyl-1*H*-indol-3-yl)propyl)-4-methoxybenzamide** (**341n**)



Following GP F, 2-phenylindole (69.5 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 3 hours, *N*-(3-fluoro-1-(2-phenyl-1*H*-indol-3-yl)propyl)-4-methoxy benzamide (**341n**) (80.6 mg, 0.200 mmol, 67%) was obtained as a pink solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.31 (silica, pentanes:ethyl acetate 2:1); **Mp:** 105-107 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.32 (s, 1H, indole N*H*), 7.81 – 7.77 (m, 1H, Ar*H*), 7.69 – 7.61 (m, 4H, Ar*H*), 7.50 – 7.44 (m, 2H, Ar*H*), 7.44 – 7.37 (m, 2H, Ar*H*), 7.25 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H, Ar*H*), 7.20 (td, *J* = 7.4, 1.2 Hz, 1H, Ar*H*), 6.90 – 6.83 (m, 2H, Ar*H*), 6.74 (d, *J* = 7.1 Hz, 1H, N*H*), 5.75 (q, *J* = 7.2 Hz, 1H, C*H*), 4.61 – 4.32 (m, 2H, FCH_2), 3.82 (s, 3H, OCH_3), 2.76 – 2.35 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.1, 162.1, 136.2, 136.1, 132.2, 129.1, 128.8, 128.7, 128.5, 126.7, 126.6, 122.5, 120.3, 119.1, 113.7, 111.6, 111.5, 82.0 (d, *J* = 164.3 Hz), 55.4, 45.1 (d, *J* = 5.7 Hz), 36.6 (d, *J* = 19.4 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -218.2; **IR** (film): $\tilde{\nu}$ = 3428 (w), 3274 (w), 2962 (w), 1637 (s), 1605 (s), 1491 (s), 1253 (s), 1177 (m), 1029 (m), 843 (m), 745 (m); **HRMS** (ESI) calcd. for $C_{25}H_{23}FN_2NaO_2^+$ $[M+Na]^+$ 425.1636; Found 425.1631.

***N*-(3-Fluoro-1-(3-methyl-1*H*-indol-2-yl)propyl)-4-methoxybenzamide** (**341o**)

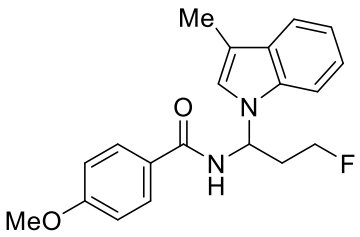


Following GP F, 3-methylindole (47.2 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 20 hours, *N*-(3-fluoro-1-(3-methyl-1*H*-indol-2-yl)propyl)-4-methoxybenzamide (**341o**) (44.8 mg, 0.132 mmol, 44%) and *N*-(3-fluoro-1-(3-methyl-1*H*-indol-1-yl)propyl)-4-methoxybenzamide (**341p**) (21.4 mg, 0.063 mmol, 21%) were obtained as beige solids after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.33 (silica, pentanes:ethyl acetate 2:1); **Mp:** 170-172 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.17 (s, 1H, indole N*H*), 7.76 – 7.68 (m, 2H, Ar*H*), 7.53 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.31 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.16 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, Ar*H*), 7.09 (td, *J* = 7.4, 6.8, 1.1 Hz, 1H, Ar*H*), 6.93 – 6.86 (m, 2H, Ar*H*), 6.81 (d, *J* = 7.1 Hz, 1H, N*H*), 5.25 (q, *J* = 7.2 Hz, 1H, C*H*), 4.67 – 4.38 (m, 2H, FCH_2), 3.84 (s, 3H, OCH_3), 2.77 – 2.45 (m, 2H, CH_2), 2.33 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 165.7, 162.2, 135.9, 134.6, 129.0, 128.9, 126.9, 121.2, 118.5, 118.2, 113.4, 110.8, 107.1, 81.1 (d, *J* = 163.6 Hz), 54.9, 43.0 (d, *J* = 5.5

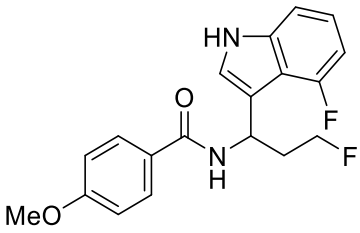
Hz), 35.3 (d, *J* = 19.9 Hz), 7.7; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -220.1; **IR** (film): $\tilde{\nu}$ = 3312 (m), 2963 (w), 2919 (w), 1607 (s), 1504 (s), 1257 (s), 1028 (m), 844 (w), 740 (m); **HRMS** (APCI) calcd. for $C_{20}H_{22}FN_2O_2^+$ $[M+H]^+$ 341.1660; Found 341.1654.

***N*-(3-Fluoro-1-(3-methyl-1*H*-indol-1-yl)propyl)-4-methoxybenzamide (341p)**



R_f: 0.36 (silica, pentanes:ethyl acetate 2:1); **Mp:** 278-280 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.72 – 7.65 (m, 2H, Ar*H*), 7.58 – 7.51 (m, 2H, Ar*H*), 7.26 – 7.20 (m, 1H, Ar*H*), 7.16 – 7.09 (m, 1H, Ar*H*), 7.06 (d, *J* = 1.3 Hz, 1H, Ar*H*), 6.90 – 6.85 (m, 2H, Ar*H*), 6.78 (d, *J* = 8.0 Hz, 1H, N*H*), 6.71 (q, *J* = 7.1 Hz, 1H, C*H*), 4.66 – 4.35 (m, 2H, FCH_2), 3.82 (s, 3H, OCH_3), 2.61 (dddt, *J* = 26.5, 11.2, 6.7, 4.5 Hz, 2H, CH_2), 2.31 (d, *J* = 1.1 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.2, 162.6, 135.7, 129.2, 128.9, 125.6, 122.3, 121.4, 119.5, 119.1, 113.8, 112.3, 109.9, 80.4 (d, *J* = 165.7 Hz), 58.6 (d, *J* = 4.5 Hz), 55.4, 35.4 (d, *J* = 19.9 Hz), 9.7; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -222.2; **IR** (film): $\tilde{\nu}$ = 3282 (w), 2967 (w), 1635 (s), 1606 (s), 1504 (s), 1257 (s), 1177 (m), 1030 (m), 745 (m); **HRMS** (ESI) calcd. for $C_{20}H_{21}FN_2NaO_2^+$ $[M+Na]^+$ 363.1479; Found 363.1469.

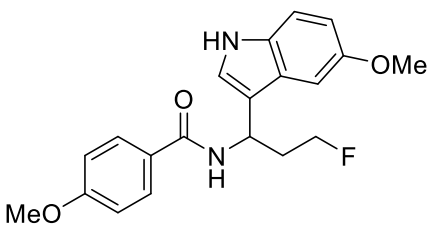
***N*-(3-Fluoro-1-(4-fluoro-1*H*-indol-3-yl)propyl)-4-methoxybenzamide (341q)**



Following GP F, 4-fluoro-1*H*-indole (48.6 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 20 hours, *N*-(3-fluoro-1-(4-fluoro-1*H*-indol-3-yl)propyl)-4-methoxybenzamide (**341q**) (59.2 mg, 0.172 mmol, 57%) was obtained as a beige solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.33 (silica, pentanes:ethyl acetate 2:3); **Mp:** 82-84 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 10.45 (s, 1H, indole N*H*), 7.93 – 7.80 (m, 2H, Ar*H*), 7.59 (d, *J* = 8.4 Hz, 1H, N*H*), 7.42 (s, 1H, Ar*H*), 7.25 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.08 (td, *J* = 8.0, 5.2 Hz, 1H, Ar*H*), 6.99 – 6.92 (m, 2H, Ar*H*), 6.75 (ddd, *J* = 11.6, 7.8, 0.6 Hz, 1H, Ar*H*), 5.76 (q, *J* = 7.8 Hz, 1H, C*H*), 4.73 – 4.40 (m, 2H, FCH_2), 3.83 (s, 3H, OCH_3), 2.52 – 2.34 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 166.1, 162.9, 157.3 (d, *J* = 242.8 Hz), 140.8 (dd, *J* = 15.5, 12.2 Hz), 129.8, 128.3, 124.1 (d, *J* = 15.9 Hz), 122.9 (d, *J* = 8.1 Hz), 115.9 (t, *J* = 4.1 Hz), 115.3 (dd, *J* = 20.8, 2.8 Hz), 114.3, 108.9 (t, *J* = 4.4 Hz), 104.8 (d, *J* = 20.2 Hz), 82.4 (d, *J* = 163.1 Hz), 55.7, 44.8 (d, *J* = 6.4 Hz), 38.1 (dd, *J* = 19.5, 2.8 Hz); **^{19}F NMR** (376 MHz, Acetone-d_6): δ = -121.5, -220.2; **IR** (film): $\tilde{\nu}$ = 3273 (w), 2964 (w), 1634 (s), 1606 (s), 1499 (s), 1255 (s), 1032 (m), 848 (m), 738 (m); **HRMS** (ESI) calcd. for $C_{19}H_{19}F_2N_2O_2^+$ $[M+H]^+$ 345.1409; Found 345.1406.

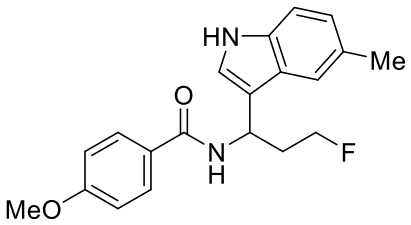
***N*-(3-Fluoro-1-(5-methoxy-1*H*-indol-3-yl)propyl)-4-methoxybenzamide (341r)**



Following GP F, 5-methoxy-1*H*-indole (52.9 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 3 hours, *N*-(3-fluoro-1-(5-methoxy-1*H*-indol-3-yl)propyl)-4-methoxybenzamide (**341r**) (58.0 mg, 0.163 mmol, 54%) was obtained as a beige solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.34 (silica, pentanes:ethyl acetate 1:1); **Mp:** 133-136 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 10.01 (s, 1H, indole N*H*), 7.93 – 7.84 (m, 2H, Ar*H*), 7.70 (d, *J* = 8.8 Hz, 1H, N*H*), 7.33 (d, *J* = 2.1 Hz, 1H, Ar*H*), 7.30 – 7.23 (m, 2H, Ar*H*), 6.97 – 6.91 (m, 2H, Ar*H*), 6.75 (dd, *J* = 8.7, 2.5 Hz, 1H, Ar*H*), 5.75 (td, *J* = 8.6, 6.0 Hz, 1H, C*H*), 4.74 – 4.50 (m, 2H, FCH_2), 3.81 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 2.61 – 2.39 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, Acetone-d_6, mixture of two rotamers, minor rotamer omitted for clarity): δ = 166.4, 162.9, 154.8, 132.9, 129.9, 128.3, 127.8, 123.7, 117.4, 114.2, 112.9, 112.6, 101.8, 82.4 (d, *J* = 162.9 Hz), 55.8, 55.7, 43.4 (d, *J* = 6.6 Hz), 36.3 (d, *J* = 19.8 Hz); **^{19}F NMR** (376 MHz, Acetone-d_6): δ = -219.9; **IR** (film): $\tilde{\nu}$ = 3311 (w), 2962 (w), 1625 (s), 1606 (s), 1500 (s), 1255 (s), 1174 (m), 1029 (m), 844 (m); **HRMS** (ESI) calcd. for $C_{20}H_{21}FN_2NaO_3^+$ $[M+Na]^+$ 379.1428; Found 379.1428.

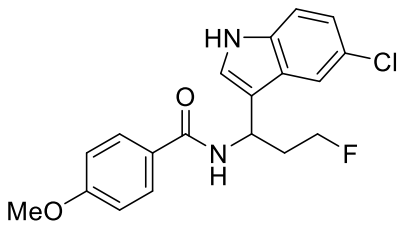
***N*-(3-Fluoro-1-(5-methyl-1*H*-indol-3-yl)propyl)-4-methoxybenzamide** (**341s**)



Following GP F, 5-methyl-1*H*-indole (47.2 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 4 hours, *N*-(3-fluoro-1-(5-methyl-1*H*-indol-3-yl)propyl)-4-methoxybenzamide (**341s**) (64.0 mg, 0.188 mmol, 63%) was obtained as a pink solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.34 (silica, pentanes:ethyl acetate 1:1); **Mp:** 140-142 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.14 (s, 1H, indole N*H*), 7.77 – 7.66 (m, 2H, Ar*H*), 7.44 (s, 1H, Ar*H*), 7.27 (d, *J* = 6.7 Hz, 1H, Ar*H*), 7.13 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.04 (dd, *J* = 8.3, 1.6 Hz, 1H, Ar*H*), 6.92 – 6.85 (m, 2H, Ar*H*), 6.45 (d, *J* = 7.9 Hz, 1H, N*H*), 5.67 (q, *J* = 7.1 Hz, 1H, C*H*), 4.72 – 4.47 (m, 2H, FCH_2), 3.83 (s, 3H, OCH_3), 2.57 – 2.45 (m, 2H, CH_2), 2.43 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.3, 162.1, 135.0, 129.3, 128.7, 126.8, 125.9, 124.2, 122.1, 118.7, 115.4, 113.7, 111.2, 82.0 (d, *J* = 164.0 Hz), 55.4, 44.3 (d, *J* = 5.9 Hz), 35.5 (d, *J* = 19.2 Hz), 21.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -218.2; **IR** (film): $\tilde{\nu}$ = 3407 (w), 3307 (br, m), 2962 (w), 2917 (w), 1630 (s), 1605 (s), 1497 (s), 1254 (s), 1177 (m), 1029 (m), 731 (m); **HRMS** (ESI) calcd. for $C_{20}H_{21}FN_2NaO_2^+$ $[M+Na]^+$ 363.1479; Found 363.1473.

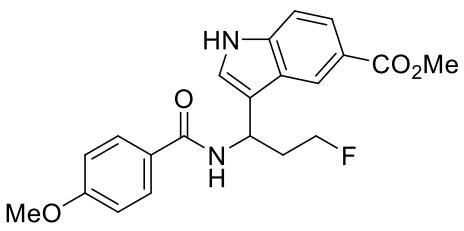
***N*-(1-(5-Chloro-1*H*-indol-3-yl)-3-fluoropropyl)-4-methoxybenzamide** (**341t**)



Following GP F, 5-chloro-1*H*-indole (54.4 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 16 hours, *N*-(1-(5-chloro-1*H*-indol-3-yl)-3-fluoropropyl)-4-methoxybenzamide (**341t**) (74.3 mg, 0.206 mmol, 69%) was obtained as a pink solid after purification by column chromatography on silica using 1:2 pentanes:ethyl acetate as eluent.

R_f: 0.46 (silica, pentanes:ethyl acetate 1:2); **Mp:** 103-105 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.57 (s, 1H, indole N*H*), 7.75 – 7.69 (m, 2H, Ar*H*), 7.60 (s, 1H, Ar*H*), 7.23 (d, *J* = 8.7 Hz, 1H, Ar*H*), 7.11 (dd, *J* = 8.6, 2.0 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.59 (d, *J* = 7.8 Hz, 1H, N*H*), 5.64 (q, *J* = 7.0 Hz, 1H, C*H*), 4.71 – 4.44 (m, 2H, FCH_2), 3.82 (s, 3H, OCH_3), 2.45 (dq, *J* = 26.2, 6.1 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.6, 162.3, 135.0, 128.7, 126.6, 126.5, 125.5, 123.5, 122.7, 118.4, 115.6, 113.8, 112.6, 82.0 (d, *J* = 163.7 Hz), 55.4, 44.5 (d, *J* = 4.6 Hz), 35.4 (d, *J* = 19.2 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -218.0; **IR** (film): $\tilde{\nu}$ = 3430 (w), 3271 (m), 2960 (w), 1630 (s), 1605 (s), 1498 (s), 1253 (s), 1177 (m), 1029 (m), 731 (m); **HRMS** (ESI) calcd. for $C_{19}H_{18}ClFN_2NaO_2^+$ $[M+Na]^+$ 383.0933; Found 383.0930.

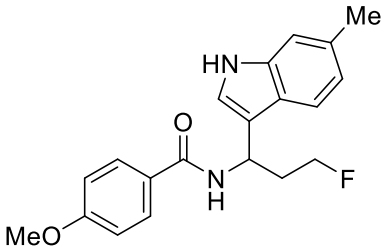
Methyl 3-(3-fluoro-1-(4-methoxybenzamido)propyl)-1*H*-indole-5-carboxylate (**341u**)



Following GP F, methyl-1*H*-indole-5-carboxylate (63.0 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 40 hours, methyl 3-(3-fluoro-1-(4-methoxybenzamido)propyl)-1*H*-indole-5-carboxylate (**341u**) (51.4 mg, 0.134 mmol, 45%) was obtained as a yellow solid after purification by column chromatography on silica using 1:2 pentanes:ethyl acetate as eluent.

R_f: 0.28 (silica, pentanes:ethyl acetate 1:2); **Mp:** 147-149 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 10.56 (s, 1H, indole N*H*), 8.54 (dd, *J* = 1.6, 0.7 Hz, 1H, Ar*H*), 7.96 – 7.90 (m, 1H, N*H*), 7.90 – 7.86 (m, 2H, Ar*H*), 7.81 (dd, *J* = 8.6, 1.6 Hz, 1H, Ar*H*), 7.53 (d, *J* = 0.9 Hz, 1H, Ar*H*), 7.47 (dd, *J* = 8.7, 0.7 Hz, 1H, Ar*H*), 6.96 – 6.90 (m, 2H, Ar*H*), 5.82 (q, *J* = 7.8 Hz, 1H, C*H*), 4.63 (dddt, *J* = 47.1, 37.7, 9.3, 6.0 Hz, 2H, FCH_2), 3.84 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.63 – 2.47 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, Acetone-d_6, mixture of two rotamers, ratio = ca. 1:1): δ = 168.3, 166.6, 162.9, 140.3, 140.1, 129.9, 128.2, 126.9, 126.9, 125.2, 125.0, 123.6, 122.9, 122.1, 119.1, 119.1, 114.2, 112.1, 112.0, 82.3 (d, *J* = 163.2 Hz), 55.7, 51.9, 43.4 (d, *J* = 6.2 Hz), 36.7 (d, *J* = 19.7 Hz); **^{13}C NMR** (151 MHz, Acetonitrile-d_3, 70 °C): δ = 169.0, 167.5, 163.6, 140.6, 130.2, 128.6, 127.2, 125.4, 124.2, 123.0, 122.9, 119.5, 115.0, 112.6, 83.1 (d, *J* = 162.2 Hz), 56.5, 52.5, 44.3 (d, *J* = 5.9 Hz), 37.0 (d, *J* = 19.6 Hz); **^{19}F NMR** (376 MHz, Acetone-d_6): δ = -220.1; **IR** (film): $\tilde{\nu}$ = 3315 (w), 2952 (w), 1695 (s), 1607 (s), 1502 (s), 1435 (m), 1252 (s), 1178 (m), 1112 (m), 770 (m); **HRMS** (ESI) calcd. for $C_{21}H_{21}FN_2NaO_4^+$ $[M+Na]^+$ 407.1378; Found 407.1381.

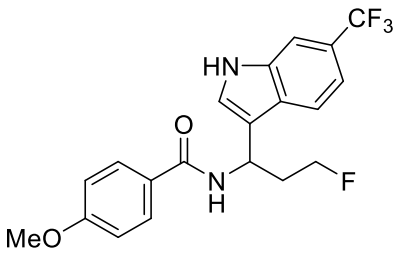
***N*-(3-Fluoro-1-(6-methyl-1*H*-indol-3-yl)propyl)-4-methoxy benzamide** (**341v**)



Following GP F, 6-methyl-1*H*-indole (47.2 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 16 hours, *N*-(3-fluoro-1-(6-methyl-1*H*-indol-3-yl)propyl)-4-methoxy benzamide **341v** (65.8 mg, 0.194 mmol, 65%) was obtained as a red solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.35 (silica, pentanes:ethyl acetate 1:1); **Mp:** 153-156 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 10.01 (s, 1H, indole N*H*), 7.93 – 7.82 (m, 2H, Ar*H*), 7.69 (d, *J* = 8.7 Hz, 1H, N*H*), 7.60 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.28 (dd, *J* = 2.5, 0.8 Hz, 1H, Ar*H*), 7.19 (dt, *J* = 1.6, 0.8 Hz, 1H, Ar*H*), 6.96 – 6.89 (m, 2H, Ar*H*), 6.87 – 6.80 (m, 1H, Ar*H*), 5.75 (td, *J* = 8.6, 6.2 Hz, 1H, C*H*), 4.74 – 4.45 (m, 2H, FCH_2), 3.81 (s, 3H, OCH_3), 2.56 – 2.42 (m, 2H, CH_2), 2.38 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 166.3, 162.9, 138.3, 131.8, 129.9, 128.3, 125.3, 122.4, 121.6, 119.7, 117.4, 114.2, 112.1, 82.4 (d, *J* = 163.0 Hz), 55.7, 43.5 (d, *J* = 6.4 Hz), 36.6 (d, *J* = 19.7 Hz), 21.7; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -219.9; **IR** (film): $\tilde{\nu}$ = 3295 (w), 2963 (w), 1629(s), 1606 (s), 1500 (s), 1254 (s), 1178 (m), 1030 (m), 802 (m); **HRMS** (ESI) calcd. for $C_{20}H_{21}FN_2NaO_2^+$ $[M+Na]^+$ 363.1479; Found 363.1480.

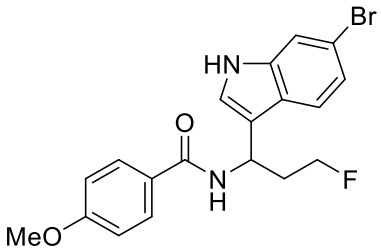
***N*-(3-Fluoro-1-(6-(trifluoromethyl)-1*H*-indol-3-yl)propyl)-4-methoxybenzamide** (**341w**)



Following GP F, 6-trifluoromethyl-1*H*-indole (66.6 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 16 hours, *N*-(3-fluoro-1-(6-(trifluoromethyl)-1*H*-indol-3-yl)propyl)-4-methoxybenzamide **341w** (61.5 mg, 0.156 mmol, 52%) was obtained as a pink solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.36 (silica, pentanes:ethyl acetate 1:1); **Mp:** 78-80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.91 (s, 1H, indole N*H*), 7.76 – 7.69 (m, 3H, Ar*H*), 7.57 (s, 1H, Ar*H*), 7.29 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.21 (d, *J* = 2.5 Hz, 1H, Ar*H*), 6.93 – 6.86 (m, 2H, Ar*H*), 6.63 (d, *J* = 7.5 Hz, 1H, N*H*), 5.73 (q, *J* = 7.1 Hz, 1H, C*H*), 4.74 – 4.44 (m, 2H, FCH_2), 3.82 (s, 3H, OCH_3), 2.56 – 2.37 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.7, 162.4, 135.5, 128.7, 127.9, 126.3, 125.0 (q, *J* = 271.7 Hz), 124.7, 124.4 (q, *J* = 31.9 Hz), 119.3, 116.5 (q, *J* = 3.5 Hz), 116.2, 113.9, 109.1 (q, *J* = 4.4 Hz), 81.9 (d, *J* = 164.0 Hz), 55.4, 44.5 (d, *J* = 4.4 Hz), 35.4 (d, *J* = 19.3 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -60.7, -217.9; **IR** (film): $\tilde{\nu}$ = 3272 (w), 2965 (w), 1628(s), 1606 (s), 1499 (s), 1355 (s), 1255 (s), 1111 (s), 734 (m); **HRMS** (ESI) calcd. for $C_{20}H_{19}F_4N_2O_2^+$ $[M+H]^+$ 395.1377; Found 395.1372.

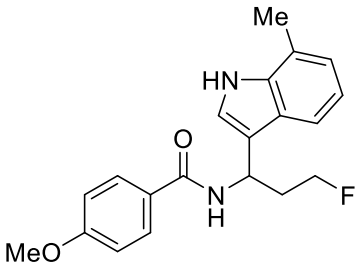
***N*-(1-(6-Bromo-1*H*-indol-3-yl)-3-fluoropropyl)-4-methoxybenzamide** (**341x**)



Following GP F, 6-bromo-1*H*-indole (70.2 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 24 hours, *N*-(1-(6-bromo-1*H*-indol-3-yl)-3-fluoropropyl)-4-methoxybenzamide **341x** (61.0 mg, 0.151 mmol, 50%) was obtained as a yellow solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.33 (silica, pentanes:ethyl acetate 1:1); **Mp:** 175-178 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.34 (s, 1H, indole N*H*), 7.73 – 7.68 (m, 2H, Ar*H*), 7.53 – 7.45 (m, 2H, Ar*H*), 7.18 (dd, *J* = 8.4, 1.7 Hz, 1H, Ar*H*), 7.09 (d, *J* = 2.4 Hz, 1H, Ar*H*), 6.92 – 6.87 (m, 2H, Ar*H*), 6.50 (d, *J* = 8.1 Hz, 1H, N*H*), 5.69 (q, *J* = 7.1 Hz, 1H, C*H*), 4.70 – 4.49 (m, 2H, FCH_2), 3.82 (s, 3H, OCH_3), 2.56 – 2.33 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.5, 162.3, 137.4, 128.7, 126.4, 124.6, 123.2, 122.4, 120.3, 116.3, 116.1, 114.4, 113.8, 81.9 (d, *J* = 164.0 Hz), 55.4, 44.2 (d, *J* = 4.8 Hz), 35.4 (d, *J* = 19.1 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -217.9; **IR** (film): $\tilde{\nu}$ = 3269 (w), 2962 (w), 1630 (s), 1605 (s), 1497 (s), 1254 (s), 1177 (m), 1029 (m), 730 (m); **HRMS** (ESI) calcd. for $C_{19}H_{18}{}^{79}BrFN_2NaO_2^+$ $[M+Na]^+$ 427.0428; Found 427.0424.

***N*-(3-Fluoro-1-(7-methyl-1*H*-indol-3-yl)propyl)-4-methoxybenzamide** (**341y**)



Following GP F, 7-methyl-1*H*-indole (47.2 mg, 0.360 mmol, 1.2 equiv.) was used as nucleophile. After the reaction mixture was stirred for 16 hours, *N*-(3-fluoro-1-(7-methyl-1*H*-indol-3-yl)propyl)-4-methoxybenzamide (**341y**) (67.4 mg, 0.198 mmol, 66%) was obtained as a beige solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

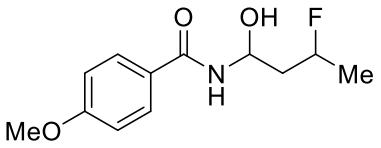
R_f: 0.37 (silica, pentanes:ethyl acetate 1:1); **Mp:** 175-176 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 10.13 (s, 1H, indole N*H*), 7.93 – 7.81 (m, 2H, Ar*H*), 7.70 (d, *J* = 8.7 Hz, 1H, N*H*), 7.57 (dd, *J* = 5.7, 3.5 Hz, 1H, Ar*H*), 7.36 (d, *J* = 2.6 Hz, 1H, Ar*H*), 6.96 – 6.85 (m, 4H, Ar*H*), 5.77 (td, *J* = 8.4, 6.4 Hz, 1H, C*H*), 4.76 – 4.46 (m, 2H, FCH_2), 3.81 (s, 3H, OCH_3), 2.58 – 2.42 (m, 5H, CH_2 + CH_3); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 166.3, 162.9, 137.2, 129.9, 128.3, 127.1, 123.0, 122.8, 121.4, 120.1, 117.9, 117.7, 114.2, 82.4 (d, *J* = 163.1 Hz), 55.7, 43.5 (d, *J* = 6.6 Hz), 36.7 (d, *J* = 19.6 Hz), 16.9; **^{19}F NMR** (376 MHz, Acetone-d_6): δ = -220.0; **IR** (film): $\tilde{\nu}$ = 3293 (w), 2964 (w), 1632 (s), 1606 (s), 1499 (s), 1254 (s), 1177 (m), 1029 (m), 844 (m); **HRMS** (ESI) calcd. for $C_{20}H_{21}FN_2NaO_2^+$ $[M+Na]^+$ 363.1479; Found 363.1480.

Scope of ring-opening fluorination for substituted aminocyclopropanes or aminocyclobutanes

General Procedure G (GP G):

In a 12*75 mm borosilicate glass tube, substituted cyclopropylamides or cyclobutylamides (0.100 mmol, 1.0 equiv.), selectfluor (39.0 mg, 0.110 mmol, 1.1 equiv.) and benzophenone (1.8 mg, 0.010 mmol, 0.10 equiv.) were dissolved in 0.50 mL of MeCN-H_2O (v:v 4:6, 0.20 M). The reaction mixture was degassed by three freeze-pump-thaw cycles and backfilled with N_2. Then the mixture was stirred at room temperature under 365 nm irradiation in Rayonet Reactor until the reaction was complete. The tube was taken out from the Rayonet Reactor and a solution of nucleophile (0.120 mmol, 1.2 equiv.) in 0. 20 mL MeCN was added dropwise. The reaction mixture was stirred at room temperature for 3 hours, if not specified otherwise. After the completion of the reaction, the crude product was directly submitted to column chromatography on silica using pentanes:ethyl acetate as eluent.

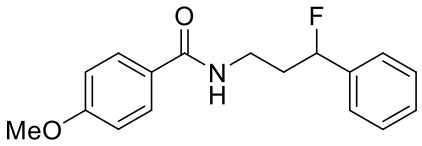
***N*-(3-Fluoro-1-hydroxybutyl)-4-methoxybenzamide** (**343a**)



Following GP G, 4-methoxy-*N*-(2-methylcyclopropyl)benzamide (**342a**) (20.5 mg, 0.100 mmol, 1.0 equiv.) was used as starting material and the reaction was kept stirring under irradiation for 45 minutes. ***N*-**(3-fluoro-1-hydroxybutyl)-4-methoxybenzamide (**343a**) (20.6 mg, 0.0855 mmol, 85%, 1:1 d.r., diastereomeric value was determined by integration of the two peaks in ^{19}F NMR) was obtained as a white solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.29 (silica, pentanes:ethyl acetate 1:1); **Mp:** 136-138 °C; **^{1}H NMR** (400 MHz, Acetone-d_6; mixture of diastereoisomers in a 1:1 ratio: the signals corresponding to the two diastereoisomers are partially resolved): δ = 7.99 (s, 1H, N*H*), 7.93 – 7.81 (m, 2H, Ar*H*), 7.01 – 6.91 (m, 2H, Ar*H*), 5.76 – 5.63 (m, 1H, NC*H*), 5.06 – 4.77 (m, 2H, FC*H* + O*H*), 3.85 (s, 3H, OCH_3), 2.20 – 2.07 (m, 1H, CH_2), 1.99 – 1.88 (m, 1H, CH_2), 1.35 (ddd, *J* = 23.8, 6.2, 4.9 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, Acetone-d_6; mixture of diastereoisomers in a 1:1 ratio: the signals corresponding to the two diastereoisomers are partially resolved): δ = 167.1, 166.9, 163.2, 163.2, 130.0, 130.0, 127.6, 114.3, 114.3, 88.8 (d, *J* = 162.5 Hz), 88.5 (d, *J* = 163.2 Hz), 72.2 (d, *J* = 6.4 Hz), 72.1 (d, *J* = 5.5 Hz), 55.8, 44.0 (d, *J* = 20.6 Hz), 43.5 (d, *J* = 20.6 Hz), 21.5 (d, *J* = 22.4 Hz), 21.2 (d, *J* = 22.4 Hz); **^{19}F NMR** (376 MHz, Acetone-d_6): δ = -173.3, -175.4; **IR** (film): $\tilde{\nu}$ = 3317 (br, s), 2979 (w), 1638 (m), 1606 (s), 1503 (s), 1255 (s), 1029 (m), 846 (w); **HRMS** (APCI) calcd. for $C_{12}H_{16}FNNaO_3^+$ $[M+Na]^+$ 264.1006; Found 264.1001.

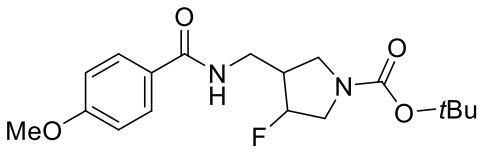
***N*-(3-Fluoro-3-phenylpropyl)-4-methoxybenzamide (343b)**



Following GP G, 4-methoxy-*N*-(trans-2-phenylcyclopropyl) benzamide (**342b**) (26.7 mg, 0.100 mmol, 1.0 equiv.) was used as starting material and the reaction was kept stirring under irradiation for 1 hour. Then $NaBH_3CN$ (7.6 mg, 0.12 mmol, 1.2 equiv.) was added as nucleophile. After the reaction mixture was stirred for 3 hours, *N*-(3-fluoro-3-phenylpropyl)-4-methoxybenzamide (**343b**) (25.8 mg, 0.0900 mmol, 90%) was obtained as a white solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.50 (silica, pentanes:ethyl acetate 1:1); **Mp:** 71-73 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.72 – 7.63 (m, 2H, Ar*H*), 7.42 – 7.28 (m, 5H, Ar*H*), 6.94 – 6.84 (m, 2H, Ar*H*), 6.45 (t, *J* = 5.8 Hz, 1H, N*H*), 5.61 (ddd, *J* = 47.9, 7.3, 5.2 Hz, 1H, C*H*), 3.83 (s, 3H, OCH_3), 3.71 – 3.55 (m, 2H, NCH_2), 2.30 – 2.16 (m, 2H, NCH_2CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.0, 162.1, 139.5 (d, *J* = 19.7 Hz), 128.6, 128.6, 128.4 (d, *J* = 2.0 Hz), 126.7, 125.3 (d, *J* = 7.0 Hz), 113.6, 93.5 (d, *J* = 170.1 Hz), 55.3, 36.7 (d, *J* = 24.8 Hz), 36.6 (d, *J* = 1.8 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -176.3; **IR** (film): $\tilde{\nu}$ = 3315 (w), 2932(w), 1629 (m), 1605 (m), 1542 (m), 1502 (s), 1252 (s), 1178 (m), 1028 (m), 844 (m); **HRMS** (ESI) calcd. for $C_{17}H_{18}FNNaO_2^+$ $[M+Na]^+$ 310.1214; Found 310.1212.

***tert*-Butyl 3-fluoro-4-((4-methoxybenzamido)methyl)pyrrolidine-1-carboxylate (343c)**

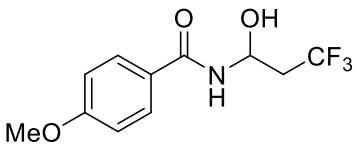


Following GP G, *tert*-Butyl (*1R,5S,6S*)-6-(4-methoxybenzamido)-3-azabicyclo[3.1.0]hexane-3-carboxylate (**342c**) (33.2 mg, 0.100 mmol, 1.0 equiv.) was used as starting material and the reaction was kept stirring under irradiation for 45 minutes. Then $NaBH_3CN$ (7.6 mg, 0.12 mmol, 1.2 equiv.) was added as nucleophile. After the reaction mixture was stirred for 3 hours, *tert*-butyl 3-fluoro-4-((4-methoxybenzamido)methyl)pyrrolidine-1-carboxylate (**343c**) (21.1 mg, 0.0599 mmol, 60%, 1.4:1 d.r., diastereomeric value was determined by integration of FC*H* signals from ^{1}H NMR at 70 °C in CD_3CN) was obtained as a colorless gel which solidified during storage after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.30 (silica, pentanes:ethyl acetate 2:3); **Mp:** 56-59 °C; **^{1}H NMR** (400 MHz, $CDCl_3$; mixture of diastereoisomers and rotamers: the signals corresponding to the two diastereoisomers and two rotamers are partially resolved): δ = 7.86 – 7.63 (m, 2H, Ar*H*), 7.04 – 6.80 (m, 2H, Ar*H*), 6.35 (s, 1H, N*H*), 5.10 (dd, *J* = 53.0, 37.7 Hz, 1H, FC*H*), 3.85 (s, 3H, OCH_3), 3.80 – 3.10 (m, 6H, 3 x NCH_2), 2.69 (t, *J* = 27.2 Hz, 1H, , FCHC*H*), 1.46 (d, *J* = 2.9 Hz, 9H, C(CH_3)$_3$); **^{1}H NMR** (400 MHz, Acetonitrile-d_3, 70 °C; mixture of two diastereoisomers: the signals corresponding to the two diastereoisomers are partially resolved, diastereomeric ratio was determined by integration of FC*H* signals): δ = 7.81 – 7.73 (m, 4H, Ar*H, major + minor*), 7.02 – 6.97 (m, 4H, Ar*H, major + minor*), 6.94 (s, 2H, N*H, major + minor*), 5.17 (dt, *J* = 53.6, 3.3 Hz, 1H, FC*H, major*), 5.07 (ddd, *J* = 50.9, 4.5, 2.4 Hz, 1H, FC*H, minor*), 3.85 (s, 6H, OCH_3, *major + minor*), 3.69 – 3.46 (m, 8H, 2* NCH_2, *major + minor*), 3.41 – 3.27 (m, 2H, NCH_2, major), 3.15 (t, *J* = 10.7 Hz, 2H, NCH_2, minor), 2.74 – 2.55 (m, 2H, FCHC*H, major + minor*), 1.45 (s, 18H, 3* CH_3, *major + minor*); **^{13}C NMR** (101 MHz, $CDCl_3$; mixture of diastereoisomers in a 1.4:1 ratio: the signals corresponding to the two diastereoisomers are partially resolved): δ = 167.4, 167.3, 162.4, 162.3, 154.3, 154.2, 128.7, 128.7,

126.3, 126.1, 113.9, 113.8, 93.6 (d, J = 178.8 Hz), 93.0 (d, J = 177.8 Hz), 79.9, 79.8, 55.4, 52.9 (d, J = 23.3 Hz), 52.5 (d, J = 22.3 Hz), 46.8, 46.6, 43.3 (d, J = 19.4 Hz), 42.5 (d, J = 19.1 Hz), 37.5 (d, J = 6.8 Hz), 37.2 (d, J = 6.5 Hz), 28.4; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -176.1, -177.5, -193.4, -193.5; **IR** (film): $\tilde{\nu}$ = 3339 (w), 2974 (w), 1695 (s), 1606 (s), 1505 (s), 1411 (s), 1255 (s), 1175 (s), 845 (m); **HRMS** (ESI) calcd. for $C_{18}H_{25}FN_2NaO_4^+$ $[M+Na]^+$ 375.1691; Found 375.1698.

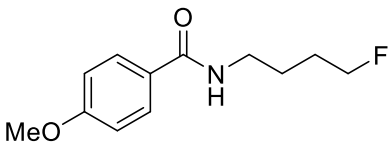
4-Methoxy-*N*-(3,3,3-trifluoro-1-hydroxypropyl)benzamide (**343d**)



Following GP G, *N*-(2,2-difluorocyclopropyl)-4-methoxybenzamide (**342d**) (22.7 mg, 0.100 mmol, 1.0 equiv.) was used as starting material and the reaction was kept stirring under irradiation for 6 hours. 4-methoxy-*N*-(3,3,3-trifluoro-1-hydroxypropyl)benzamide (**343d**) (18.0 mg, 0.0684 mmol, 68%) was obtained as a white solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.26 (silica, pentanes:ethyl acetate 3:2); **Mp:** 104-106 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 8.20 (d, J = 8.3 Hz, 1H, N*H*), 7.91 – 7.83 (m, 2H, Ar*H*), 7.02 – 6.95 (m, 2H, Ar*H*), 5.93 (dtd, J = 8.4, 6.2, 4.6 Hz, 1H, C*H*), 5.33 (d, J = 4.7 Hz, 1H, O*H*), 3.85 (s, 3H, OCH_3), 2.73 (qdd, J = 10.9, 6.3, 1.5 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 166.6, 163.4, 130.0, 127.3, 126.8 (q, J = 277.1 Hz), 114.4, 70.1 (q, J = 4.4 Hz), 55.8, 40.5 (q, J = 27.1 Hz); **^{19}F NMR** (376 MHz, Acetone-d_6): δ = -64.2; **IR** (film): $\tilde{\nu}$ = 3304 (br, s), 1642 (s), 1607 (s), 1505 (s), 1254 (s), 1140 (s), 1029 (m), 843 (m); **HRMS** (ESI) calcd. for $C_{11}H_{12}F_3NNaO_3^+$ $[M+Na]^+$ 286.0661; Found 286.0653.

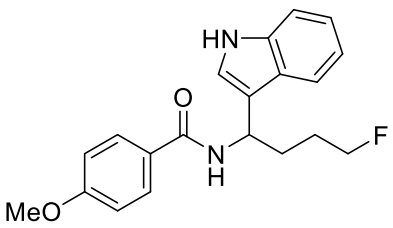
***N*-(4-Fluorobutyl)-4-methoxybenzamide** (**343e**)



Following GP G, *N*-cyclobutyl-4-methoxybenzamide (**342e**) (20.5 mg, 0.100 mmol, 1.0 equiv.) was used as starting material and the reaction was kept stirring under irradiation for 45 minutes. Then $NaBH_3CN$ (7.6 mg, 0.12 mmol, 1.2 equiv.) was added as nucleophile. After the reaction mixture was stirred for 3 hours, *N*-(4-fluorobutyl)-4-methoxybenzamide (**343e**) (14.3 mg, 0.0636 mmol, 64%) was obtained as a colorless oil after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.28 (silica, pentanes:ethyl acetate 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.79 – 7.65 (m, 2H, Ar*H*), 6.98 – 6.83 (m, 2H, Ar*H*), 6.20 (s, 1H, N*H*), 4.55 (t, J = 5.7 Hz, 1H, FCH_2), 4.43 (td, J = 5.6, 4.7, 2.5 Hz, 1H, FCH_2), 3.84 (s, 3H, OCH_3), 3.49 (q, J = 6.7 Hz, 2H, NCH_2), 1.85 – 1.72 (m, 4H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.1, 162.1, 128.6, 126.8, 113.7, 83.8 (d, J = 164.4 Hz), 55.4, 39.4, 27.8 (d, J = 19.9 Hz), 25.8 (d, J = 4.3 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -218.2; **IR** (film): $\tilde{\nu}$ = 3317 (w), 2962 (w), 1632 (s), 1606 (s), 1504 (m), 1254 (s), 1179 (m), 1030 (m), 845 (m); **HRMS** (ESI) calcd. for $C_{12}H_{17}FNO_2^+$ $[M+H]^+$ 226.1238; Found 226.1232.

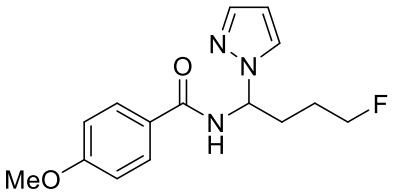
***N*-(4-Fluoro-1-(1*H*-indol-3-yl)butyl)-4-methoxybenzamide (343f)**



Following GP G, *N*-cyclobutyl-4-methoxybenzamide (**342e**) (20.5 mg, 0.100 mmol, 1.0 equiv.) was used as starting material and the reaction was kept stirring under irradiation for 45 minutes. Then 1*H*-indole (14.0 mg, 0.120 mmol, 1.2 equiv.) was added as nucleophile. After the reaction mixture was stirred for 3 hours, *N*-(4-fluoro-1-(1*H*-indol-3-yl)butyl)-4-methoxybenzamide (**343f**) (20.1 mg, 0.0591 mmol, 59%) was obtained as a orange oil after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.43 (silica, pentanes:ethyl acetate 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.39 (s, 1H, indole N*H*), 7.73 – 7.65 (m, 3H, Ar*H*), 7.38 (dt, *J* = 8.2, 0.9 Hz, 1H, Ar*H*), 7.21 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H, Ar*H*), 7.17 – 7.14 (m, 1H, Ar*H*), 7.11 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H, Ar*H*), 6.90 – 6.83 (m, 2H, Ar*H*), 6.31 (d, *J* = 8.2 Hz, 1H, N*H*), 5.56 (q, *J* = 7.6 Hz, 1H, C*H*), 4.62 – 4.38 (m, 2H, FCH_2), 3.81 (s, 3H, OCH_3), 2.23 (dddd, *J* = 15.3, 14.2, 8.6, 4.4 Hz, 2H, CH_2), 1.93 – 1.77 (m, 2H, CH_2CH$_2$F); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.4, 162.1, 136.6, 128.7, 126.7, 126.0, 122.5, 121.8, 119.9, 119.2, 116.5, 113.7, 111.4, 83.9 (d, *J* = 164.6 Hz), 55.4, 46.4, 30.7 (d, *J* = 4.2 Hz), 27.6 (d, *J* = 19.7 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -218.4; **IR** (film): $\tilde{\nu}$ = 3413 (w), 3273 (w), 2960 (w), 1630 (s), 1606 (s), 1498 (s), 1253 (s), 1178 (m), 1030 (m), 745 (m); **HRMS** (ESI) calcd. for $C_{20}H_{21}FN_2NaO_2^+$ $[M+Na]^+$ 363.1479; Found 363.1477.

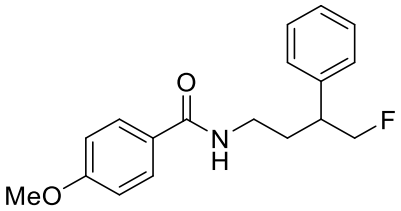
***N*-(4-Fluoro-1-(1*H*-pyrazol-1-yl)butyl)-4-methoxybenzamide (343g)**



Following GP G, *N*-cyclobutyl-4-methoxybenzamide (**342e**) (20.5 mg, 0.100 mmol, 1.0 equiv.) was used as starting material and the reaction was kept stirring under irradiation for 45 minutes. Then 1*H*-pyrazole (8.2 mg, 0.12 mmol, 1.2 equiv.) was added as nucleophile. After the reaction mixture was stirred for 16 hours, *N*-(4-fluoro-1-(1*H*-pyrazol-1-yl)butyl)-4-methoxybenzamide (**343g**) (16.2 mg, 0.0556 mmol, 56%) was obtained as a white solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.36 (silica, pentanes:ethyl acetate 1:1); **Mp:** 157-158 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 8.37 (d, *J* = 8.7 Hz, 1H, N*H*), 7.96 – 7.84 (m, 2H, Ar*H*), 7.81 (dd, *J* = 2.3, 0.7 Hz, 1H, Ar*H*), 7.45 (d, *J* = 1.7 Hz, 1H, Ar*H*), 7.01 – 6.91 (m, 2H, Ar*H*), 6.37 (q, *J* = 7.9 Hz, 1H, C*H*), 6.20 (dd, *J* = 2.3, 1.7 Hz, 1H, Ar*H*), 4.47 (dtd, *J* = 47.4, 6.0, 0.9 Hz, 2H, FCH_2), 3.84 (s, 3H, OCH_3), 2.46 – 2.19 (m, 2H, CH_2), 1.87 – 1.53 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 166.7, 163.4, 139.9, 130.2, 130.1, 126.9, 114.3, 105.3, 84.0 (d, *J* = 163.6 Hz), 66.2, 55.8, 31.0 (d, *J* = 5.2 Hz), 27.3 (d, *J* = 20.0 Hz); **^{19}F NMR** (376 MHz, Acetone-d_6): δ = -219.5; **IR** (film): $\tilde{\nu}$ = 3302 (w), 2965 (w), 1644 (m), 1606 (s), 1503 (s), 1254 (s), 1176 (m), 1031 (m), 762 (m); **HRMS** (ESI) calcd. for $C_{15}H_{18}FN_3NaO_2^+$ $[M+Na]^+$ 314.1275; Found 314.1270.

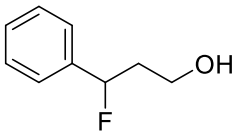
***N*-(4-Fluoro-3-phenylbutyl)-4-methoxybenzamide** (**343h**)



Following GP G, 4-methoxy-*N*-(3-phenylcyclobutyl)benzamide (**342f**) (28.1 mg, 0.100 mmol, 1.0 equiv.) was used as starting material and the reaction was kept stirring under irradiation for 2 hours. Then $NaBH_3CN$ (7.6 mg, 0.12 mmol, 1.2 equiv.) was added as nucleophile. After the reaction mixture was stirred for 3 hours, *N*-(4-fluoro-3-phenylbutyl)-4-methoxybenzamide (**343h**) (19.0 mg, 0.0631 mmol, 63%) was obtained as a colorless oil after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.48 (silica, pentanes:ethyl acetate 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.60 – 7.52 (m, 2H, Ar*H*), 7.38 – 7.32 (m, 2H, Ar*H*), 7.27 (tt, *J* = 7.8, 1.3 Hz, 3H, Ar*H*), 6.93 – 6.83 (m, 2H, Ar*H*), 5.95 (s, 1H, N*H*), 4.66 – 4.40 (m, 2H, FCH_2), 3.83 (s, 3H, OCH_3), 3.55 – 3.31 (m, 2H, NCH_2), 3.06 (dddd, *J* = 24.0, 10.3, 6.8, 5.3 Hz, 1H, PhC*H*), 2.26 – 1.92 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.8, 162.0, 140.1 (d, *J* = 6.1 Hz), 129.0, 128.5, 127.9, 127.3, 126.7, 113.6, 86.9 (d, *J* = 173.8 Hz), 55.4, 44.9 (d, *J* = 18.7 Hz), 38.4, 31.4 (d, *J* = 4.0 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -217.8; **IR** (film): $\tilde{\nu}$ = 3315 (m), 2960 (m), 1630 (s), 1605 (s), 1502 (s), 1253 (s), 1026 (s), 700 (m); **HRMS** (ESI) calcd. for $C_{18}H_{21}FNO_2^+$ $[M+H]^+$ 302.1551; Found 302.1556.

3-Fluoro-3-phenylpropan-1-ol (**345**)



Following GP E, starting from Cyclopropylbenzene **344** (35.4 mg, 0.300 mmol) and after stirring for 45 minutes, 3-fluoro-3-phenylpropan-1-ol **345** (29.1 mg, 0.189 mmol, 63%) was obtained as a colorless oil after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.44 (silica, pentanes:ethyl acetate 2:1, $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.49 – 7.30 (m, 5H, Ar*H*), 5.68 (ddd, *J* = 48.1, 9.1, 4.0 Hz, 1H, FC*H*), 3.94 – 3.74 (m, 2H, OCH_2), 2.32 – 1.97 (m, 2H, CH_2), 1.53 (t, *J* = 5.5 Hz, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 139.9 (d, *J* = 19.6 Hz), 128.5, 128.4 (d, *J* = 1.3 Hz), 125.5 (d, *J* = 6.9 Hz), 92.4 (d, *J* = 169.3 Hz), 59.1 (d, *J* = 4.3 Hz), 39.9 (d, *J* = 23.1 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -177.5; **IR** (film): $\tilde{\nu}$ = 3339 (br,s), 2953 (w), 2926 (w), 1454 (w), 1048 (s), 759 (m), 698 (s).

^{1}H/^{19}F NMR data correspond to the reported values.[283]

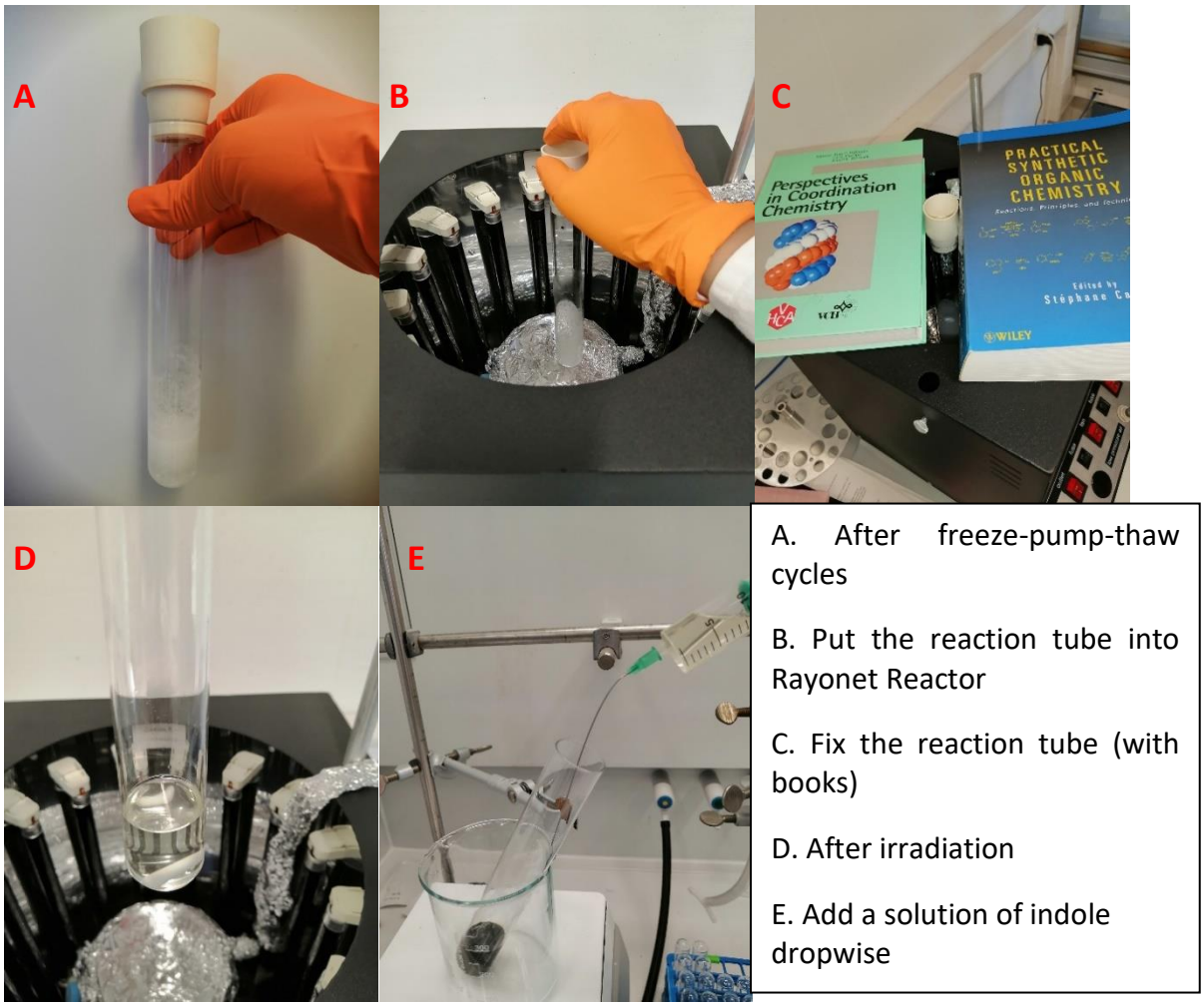
Scale-up synthesis of compound 341l

Procedure:

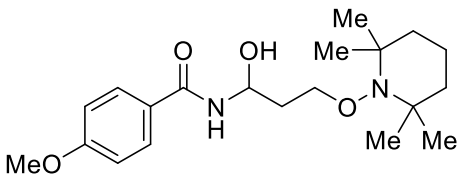
In a 30*200 mm borosilicate glass tube, *N*-cyclopropyl-4-methoxybenzamide **296a** (1.91 g, 10.0 mmol), selectfluor (3.89 g, 11.0 mmol, 1.1 equiv.) and benzophenone (182 mg, 1.00 mmol, 0.10 equiv.) were dissolved in 12.5 mL of MeCN-H_2O (v:v 4:6, 0.40 M). The reaction mixture was degassed by three freeze-pump-thaw cycles and backfilled with N_2. The mixture was then stirred at room temperature under 365 nm irradiation in Rayonet Reactor for 45 minutes. Then the tube was taken out from the Rayonet Reactor and a

[283] Remli, M.; Ayi, A. I.; Condom, R.; Guedj, R. *Bull. Soc. Chim. Fr.* **1986***, 6*, 864.

solution of 1*H*-indole (1.40 g, 12.0 mmol, 1.2 equiv.) in 7. 50 mL MeCN was added dropwise. The reaction mixture was stirred at room temperature for 3 hours. After the completion of the reaction, the crude product was washed with water (30 mL) and extracted with dichloromethane (30 mL x 3). Then the organic phases were combined, dried over Na_2SO_4, concentrated. After purification by column chromatography on silica using pentanes:ethyl acetate as eluent, **341l** (1.86 g, 5.71 mmol, 57%) was obtained as product.



***N*-(1-Hydroxy-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propyl)-4-methoxybenzamide (346)**



In a 12*75 mm borosilicate glass tube, *N*-cyclopropyl-4-methoxybenzamide **296a** (19.1 mg, 0.100 mmol, 1.0 equiv.), selectfluor (39.0 mg, 0.110 mmol, 1.1 equiv.), benzophenone (1.8 mg, 0.010 mmol, 0.10 equiv.) and TEMPO (31.2 mg, 0.200 mmol, 2.0 equiv.) were dissolved in 0.50 mL of MeCN-H_2O (v:v 4:6, 0.20 M). The reaction mixture was degassed by three freeze-pump-thaw cycles and backfilled with N_2. The mixture was then stirred at room temperature under 365 nm irradiation in Rayonet Reactor for 45 minutes. After the completion of the reaction, the crude product was directly submitted to column chromatography on silica using 3:2 pentanes:ethyl acetate as eluent and *N*-(1-Hydroxy-3-((2,2,6,6-tetramethylpiperidin-1-

yl)oxy)propyl)-4-methoxybenzamide **346** (4.7 mg, 0.013 mmol, 13%) was obtained as a white solid. *N*-cyclopropyl-4-methoxybenzamide **296a** (16.0 mg, 0.084 mmol, 84%) was recovered using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.39 (silica, pentanes:ethyl acetate 1:1); **Mp:** 118-121 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 – 7.71 (m, 2H, Ar*H*), 7.58 (d, *J* = 6.5 Hz, 1H, N*H*), 6.95 – 6.86 (m, 2H, Ar*H*), 5.65 (q, *J* = 5.5 Hz, 1H, C*H*), 4.21 (ddd, *J* = 9.6, 8.3, 3.6 Hz, 1H, OCH_2), 4.12 (d, *J* = 2.8 Hz, 1H, O*H*), 3.93 (ddd, *J* = 9.8, 6.1, 3.7 Hz, 1H, OCH_2), 3.85 (s, 3H, OCH_3), 2.10 – 1.95 (m, 2H, OCH_2CH_2), 1.49 – 1.40 (m, 4H, CH_2), 1.33 – 1.24 (m, 2H, $CH_2CH_2CH_2$), 1.23 – 0.99 (m, 12H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.2, 162.5, 129.0, 126.0, 113.7, 74.2, 72.6, 59.8, 55.4, 39.7, 39.6, 33.5, 33.0, 32.9, 20.5, 20.3, 17.0; **IR** (film): $\tilde{\nu}$ = 3341 (m), 2930 (m), 1643 (m), 1606 (m), 1503 (s), 1255 (s), 1177 (m), 987 (m), 845 (w); **HRMS** (ESI) calcd. for $C_{20}H_{33}N_2O_4^+$ $[M+H]^+$ 365.2435; Found 365.2418.

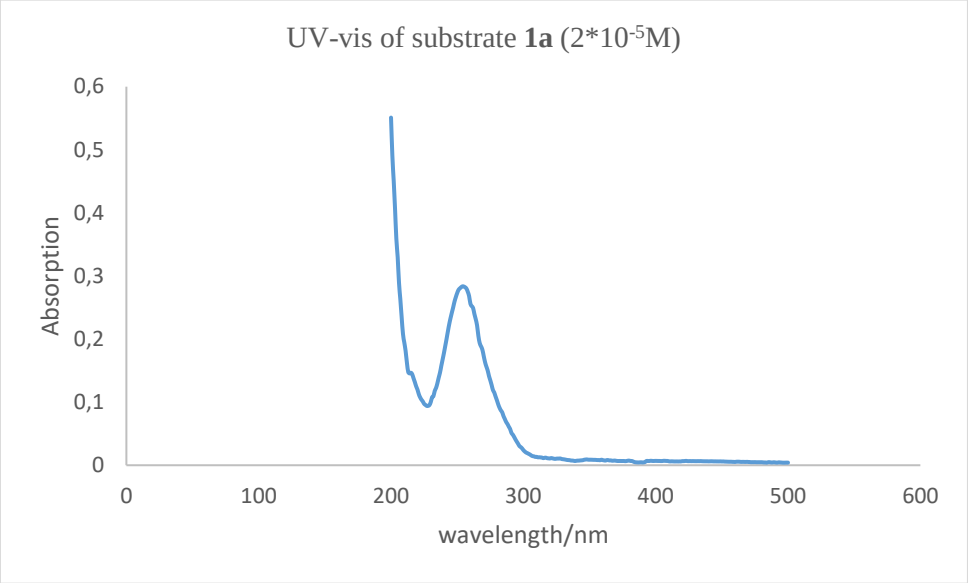
Light-dark interval experiment

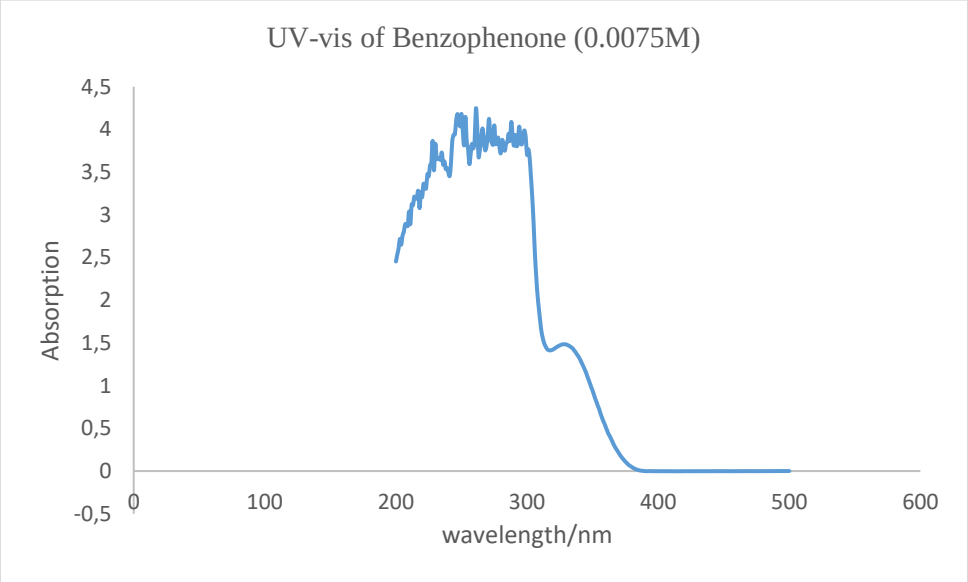
Procedure: The reaction was run similar with the standard procedure, except that fluorobenzene (28.8 mg, 0.300 mmol, 1.0 equiv.) was added as internal standard at the begining. After 10 minutes, 20 μL of the reaction mixture was extracted by micro syringe under N_2 flow. The aliquot was then diluted in 0.4 mL $CDCl_3$ and was then measured the substrate recovery rate (yield of product was not accounted as the hemiaminal could undergo hydrolysis slowly over time) by crude ^{1}H NMR. The reaction mixture was stirred under ambient light for 1 hour and an aliquot was prepared and analyzed by the above mentioned methods. Then the reaction mixture was kept stirring under irradiation in the Rayonet reactor for a second 10 minutes and an aliquot was prepared and analyzed. The reaction mixture was stirred under ambient light for a second hour and an aliquot was prepared and analyzed. Next the reaction mixture was kept stirring under irradiation in the Rayonet reactor for a third 10 minutes and an aliquot was prepared and analyzed. The reaction mixture was stirred under ambient light for a third hour and an aliquot was prepared and analyzed. The reaction mixture was kept stirring under irradiation in the Rayonet reactor for a forth 10 minutes and an aliquot was prepared and analyzed. Finally the reaction mixture was stirred under ambient light for a forth hour and an aliquot was prepared and analyzed.

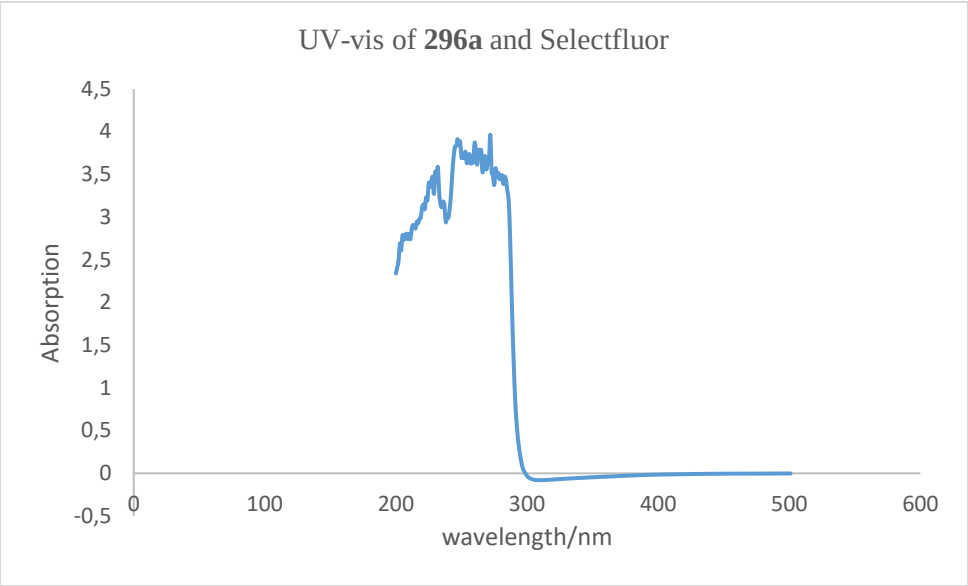
Discussion: The light–dark interval experiments cannot exclude the chain process totally, but from the obtained results, we can see the light is essential to the generation of product. If there is some chain propagation after stopping of irradiation, its contribution to the product should be small.

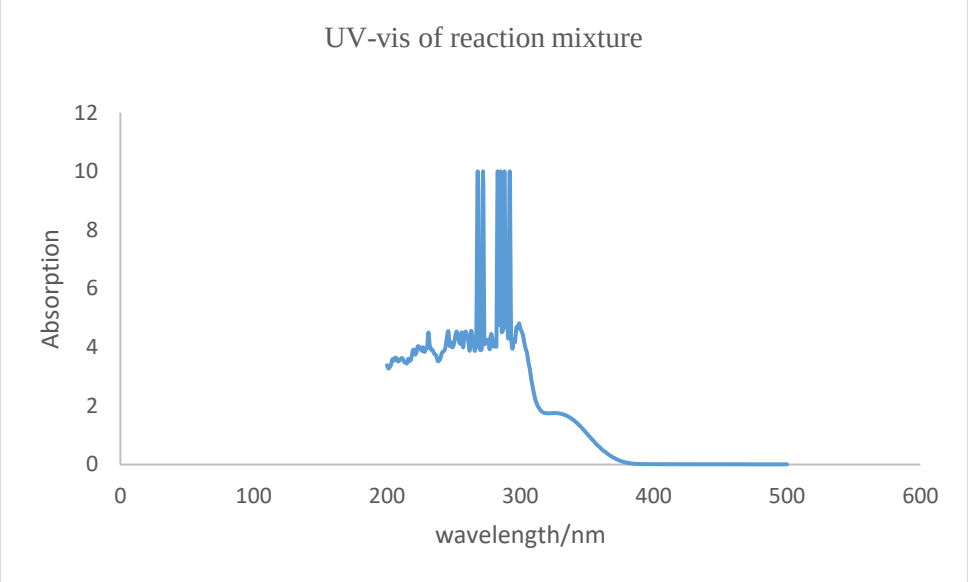
UV-vis spectra

The UV-vis spectra was measured by using the solution of corresponding compound in MeCN-water (v:v 4:6).



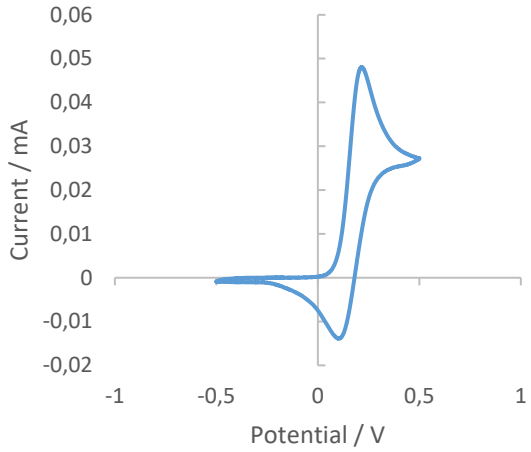



UV-vis of **296a** and Selectfluor
Absorption
wavelength/nm
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
-0,5
0
100
200
300
400
500
600

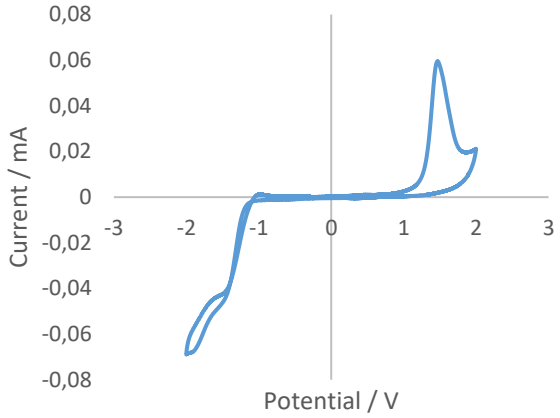

UV-vis of reaction mixture
Absorption
wavelength/nm
12
10
8
6
4
2
0
0
100
200
300
400
500
600

8.4 Cyclic voltammetry experiment

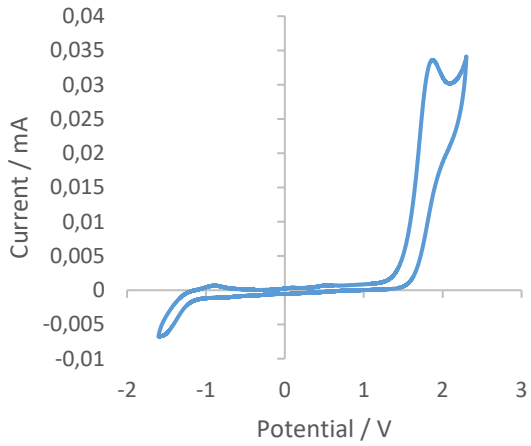
Ferrocene



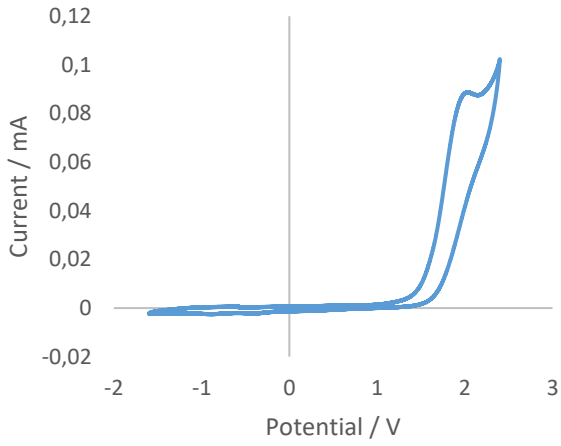
N-Cyclopropyl-4-methoxybenzamide **296a**



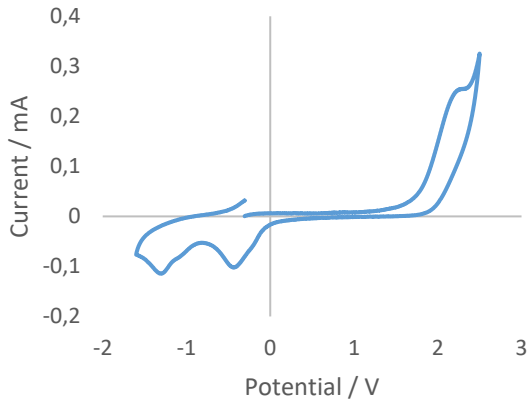
N-Cyclopropylpivalamide **296n**



tert-butyl cyclopropylcarbamate **296o**



N-cyclopropyl-4-methylbenzenesulfonamide **296q**



Procedure: Cyclic voltammetry was performed with a Biologic SP-150 Potentiostat, with a three-electrode cell configuration: a glassy carbon electrode as the working electrode, Pt wire as the counter electrode and a Ag/Ag^+ quasi-reference electrode with 0.01 M $AgBF_4$ in acetonitrile. Bu_4NPF_6 was employed as the electrolyte and acetonitrile was used as solvent. Ferrocene was used to calibrate the potential of Ag/Ag^+ quasi-reference electrode. Conditions: voltammograms were performed with a scan rate of 50 mV/s, a concentration of electrolyte Bu_4NPF_6 = 0.1 M, and a concentration of **296** = 5 mM.

Result:

$E_{1/2}^{red}$(**296a**)= +1.67 V vs SCE in MeCN;

$E_{1/2}^{red}$(**296n**)= +1.92 V vs SCE in MeCN;

$E_{1/2}^{red}$(**296o**)= +2.0 V vs SCE in MeCN;

$E_{1/2}^{red}$(**296q**)= +2.23 V vs SCE in MeCN.

8.5 Stern-Volmer quenching experiments

Procedure: Stern-Volmer fluorescence quenching experiments were conducted on a Varian Cary Eclipse machine. Benzophenone was recrystallized from ethanol. Selectfluor was recrystallized from acetonitrile/diethyl ether. **296a** was recrystallized from ethyl acetate.

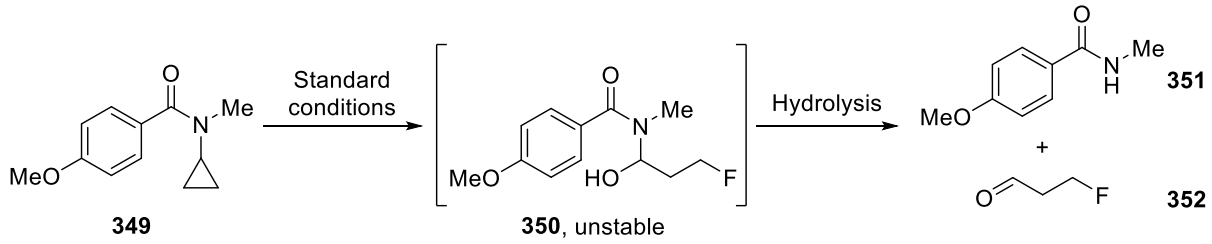
For Ir photocatalyst:

Stock solution of $[Ir(dF\text{-}CF_3ppy)_2(dtbbpy)]PF_6$ (0.45 mg in volumetric flask of 100 mL with MeCN-H_2O v:v 4:6, 4.0×10^{-6} M). Four samples of **296a** (11.5 mg, 22.9 mg, 34.4 mg, 45.8 mg) were measured and dissolved respectively with 3.0 mL stock solution of $[Ir(dF\text{-}CF_3ppy)_2(dtbbpy)]PF_6$ to prepare solutions of **296a** as 0.02 M, 0.04 M, 0.06 M, 0.08 M. Similarly, four samples of selectfluor (21.2 mg, 42.5 mg, 63.7 mg, 85.0 mg) were measured and dissolved respectively with 3.0 mL stock solution of $[Ir(dF\text{-}CF_3ppy)_2(dtbbpy)]PF_6$ to prepare solutions of selectfluor as 0.02 M, 0.04 M, 0.06 M, 0.08 M. The above solutions were transferred to quartz cuvettes and were bubbled with N_2 for 2 minutes before analysis. The solution was excited at 365 nm and the emission intensity was recorded at 475 nm.

For benzophenone photocatalyst:

Stock solution of benzophenone (82.0 mg in volumetric flask of 50.0 mL with MeCN-H_2O v:v 4:6, 0.009 M). Four samples of **296n** (8.5 mg, 16.9 mg, 25.4 mg, 42.3 mg) were measured and dissolved respectively with 3.0 mL stock solution of benzophenone to prepare solutions of **296n** as 0.02 M, 0.04 M, 0.06 M, 0.1 M. Similarly, five samples of Selectfluor (10.6 mg, 21.2 mg, 42.5 mg, 63.7 mg, 85.0 mg) were measured and dissolved respectively with 3.0 mL stock solution of benzophenone to prepare solutions of Selectfluor as 0.01 M, 0.02 M, 0.04 M, 0.06 M, 0.08 M. The above solutions were transferred to quartz cuvettes and were bubbled with N_2 for 2 minutes before analysis. The solution was excited at 365 nm and the emission intensity was recorded at 475 nm.

8.6 Reaction of *N*-Cyclopropyl-4-methoxy-*N*-methylbenzamide (9)



Following GP E, starting from *N*-Cyclopropyl-4-methoxy-*N*-methylbenzamide **349** (20.5 mg, 0.100 mmol), 4-methoxy-N-methylbenzamide **351** (12.0 mg, 0.073 mmol, 73%) was obtained as a white solid after purification by column chromatography on silica using 1:2 pentanes:ethyl acetate as eluent.

R_f: 0.25 (silica, pentanes:ethyl acetate 1:2); **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 7.85 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.58 (s, 1H, N*H*), 7.12 – 6.79 (m, 2H, Ar*H*), 3.84 (s, 3H, OCH_3), 2.88 (d, *J* = 2.9 Hz, 3H, NCH_3).

^{1}H NMR data correspond to the reported values.[284]

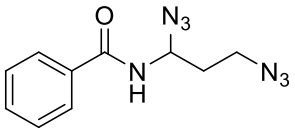
3-Fluoropropanal **352** was observed from crude ^{1}H NMR and peaks correspond to the reported values.[285]

5.3.5 Diamine synthesis via the nitrogen-directed azidation of σ- and π- C-C bonds

General Procedure H (GP H):

In a 12*75 mm Borosilicate glass tube, the corresponding aminocyclopropane (0.200 mmol, 1.0 equiv.), Selectfluor (78.0 mg, 0.220 mmol, 1.1 equiv.) and CuTc (0.8 mg, 0.004 mmol, 0.02 equiv.) were measured on analytical balance. The tube was then closed with a rubber septum and sealed off with parafilm. Evacuate-refill cycle three times with nitrogen were performed to remove O_2 and extra-dry acetonitrile (2.0 mL, 0.1 M) was added under nitrogen atmosphere, followed by the addition of $TMSN_3$ (94% purity purchased from TCI, 62.0 μL, 0.440 mmol, 2.2 equiv.). The reaction mixture was stirred at room temperature for 10 minutes. Upon completion, the mixture was quenched by the addition of water (10 mL). The aqueous layer was then extracted with dichloromethane (10 mL x 3). The organic extract was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, pentanes/EtOAc).

***N*-(1,3-Diazidopropyl)benzamide** (**369w**)

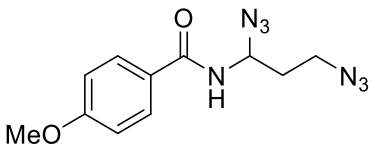


Following GP H, starting from *N*-cyclopropylbenzamide **296w** (32.2 mg, 0.200 mmol), *N*-(1,3-diazidopropyl)benzamide **369w** (39.3 mg, 0.160 mmol, 80%) was obtained as a yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

[284] Xia, Q.; Liu, X.; Zhang, Y.; Chen, C.; Chen, W. *Org. Lett.* **2013**, *15*, 3326-3329.
[285] Linclau, B.; Peron, F.; Bogdan, E.; Wells, N.; Wang, Z.; Compain, G.; Fontenelle, C.; Galland, N.; Le Questel, J.-Y.; Graton, J. *Chem. Eur. J.* **2015**, *21*, 17808-17816.

R_f: 0.41 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85 – 7.79 (m, 2H, Ar*H*), 7.58 – 7.52 (m, 1H, Ar*H*), 7.49 – 7.43 (m, 2H, Ar*H*), 7.19 (d, *J* = 9.0 Hz, 1H, N*H*), 5.92 (dt, *J* = 8.9, 5.8 Hz, 1H, C*H*), 3.66 (dt, *J* = 12.8, 6.5 Hz, 1H, CH_2N_3), 3.54 (dt, *J* = 12.6, 5.8 Hz, 1H, CH_2N_3), 1.95 (q, *J* = 5.9 Hz, 2H, C$H_2CH_2N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.4, 132.9, 132.3, 128.8, 127.1, 65.1, 47.3, 33.2; **IR** (film): $\tilde{\nu}$ = 3672 (w), 3311 (w), 2975 (m), 2903 (m), 2110 (s), 1653 (m), 1521 (m), 1065 (s); **HRMS** (ESI) calcd. for $C_{10}H_{11}N_7NaO^+$ $[M+Na]^+$ 268.0917; Found 268.0920.

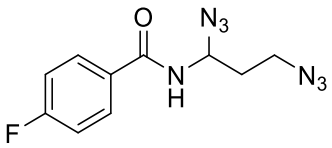
***N*-(1,3-Diazidopropyl)-4-methoxybenzamide** (**369a**)



Following GP H, starting from *N*-cyclopropyl-4-methoxybenzamide **296a** (38.2 mg, 0.200 mmol), *N*-(1,3-diazidopropyl)-4-methoxybenzamide **369a** (49.0 mg, 0.178 mmol, 89%) was obtained as a yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.36 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.82 – 7.75 (m, 2H, Ar*H*), 7.15 (d, *J* = 8.9 Hz, 1H, N*H*), 6.95 – 6.89 (m, 2H, Ar*H*), 5.89 (dt, *J* = 8.9, 5.9 Hz, 1H, C*H*), 3.85 (s, 3H, OCH_3), 3.64 (dt, *J* = 12.9, 6.4 Hz, 1H, CH_2N_3), 3.52 (dt, *J* = 12.6, 5.9 Hz, 1H, CH_2N_3), 1.94 (q, *J* = 6.1 Hz, 2H, C$H_2CH_2N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.9, 162.8, 129.1, 125.0, 113.9, 65.1, 55.4, 47.4, 33.2; **IR** (film): $\tilde{\nu}$ = 2975 (w), 2903 (w), 2110 (s), 1665 (s), 1497 (s), 1269 (s); **HRMS** (ESI) calcd. for $C_{11}H_{13}N_7NaO_2^+$ $[M+Na]^+$ 298.1023; Found 298.1023.

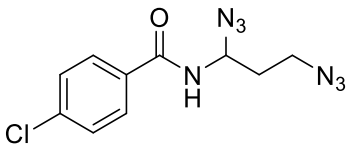
***N*-(1,3-Diazidopropyl)-4-fluorobenzamide** (**369c**)



Following GP H, starting from *N*-cyclopropyl-4-fluorobenzamide **296c** (41.4 mg, 0.200 mmol), *N*-(1,3-diazidopropyl)-4-fluorobenzamide **369c** (37.9 mg, 0.144 mmol, 72%) was obtained as a pale yellow solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.45 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.87 – 7.77 (m, 2H, Ar*H*), 7.22 (d, *J* = 8.9 Hz, 1H, N*H*), 7.13 (t, *J* = 8.5 Hz, 2H, Ar*H*), 5.89 (dt, *J* = 8.9, 5.8 Hz, 1H, C*H*), 3.67 (dt, *J* = 12.8, 6.4 Hz, 1H, CH_2N_3), 3.54 (dt, *J* = 12.2, 5.7 Hz, 1H, CH_2N_3), 1.95 (q, *J* = 6.0 Hz, 2H, C$H_2CH_2N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.4, 165.2 (d, *J* = 253.1 Hz), 129.6 (d, *J* = 9.0 Hz), 129.0 (d, *J* = 3.2 Hz), 115.9 (d, *J* = 22.0 Hz), 65.2, 47.3, 33.1; **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -106.5; **IR** (film): $\tilde{\nu}$ = 3303 (w), 2925 (w), 2095 (s), 1645 (m), 1498 (m), 1234 (s), 882 (m); **HRMS** (ESI) calcd. for $C_{10}H_{10}FN_4O^+$ $[M-N_3]^+$ 221.0833; Found 221.0835.

4-Chloro-*N*-(1,3-diazidopropyl)benzamide (**369d**)

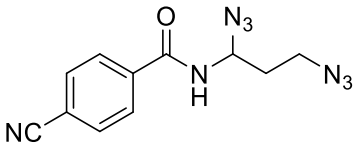


Following GP H, starting from 4-chloro-*N*-cyclopropylbenzamide **296d** (39.0 mg, 0.200 mmol), 4-chloro-*N*-(1,3-diazidopropyl)benzamide **369d** (39.2 mg, 0.141 mmol, 70%) was obtained as a beige solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.52 (silica, pentanes:ethyl acetate 3:1); **Mp:** 81-83 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 – 7.75 (m, 2H, Ar*H*), 7.49 – 7.45 (m, 2H, Ar*H*), 7.21 (d, *J* = 9.0 Hz, 1H, N*H*), 5.92 (dt, *J* = 8.8, 5.7 Hz, 1H, C*H*),

3.71 (dt, *J* = 12.8, 6.5 Hz, 1H, C*H*$_2$N$_3$), 3.57 (dt, *J* = 12.6, 5.8 Hz, 1H, C*H*$_2$N$_3$), 1.98 (q, *J* = 5.9 Hz, 2H, C*H*$_2$CH$_2$N$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.4, 138.7, 131.3, 129.1, 128.6, 65.2, 47.3, 33.1; **IR** (film): $\tilde{\nu}$ = 3292 (w), 2104 (s), 1648 (m), 1527 (m), 1485 (m), 1244 (m), 1091 (m), 846 (m); **HRMS** (ESI) calcd. for $C_{10}H_{10}ClN_7NaO^+$ $[M+Na]^+$ 302.0528; Found 302.0531.

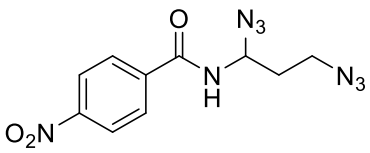
4-Cyano-*N*-(1,3-diazidopropyl)benzamide (**369e**)



Following GP H, starting from 4-cyano-*N*-cyclopropylbenzamide **296e** (37.2 mg, 0.200 mmol), 4-cyano-*N*-(1,3-diazidopropyl)benzamide **369e** (33.5 mg, 0.124 mmol, 62%) was obtained as a pale yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R$_f$: 0.33 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.97 – 7.89 (m, 2H, Ar*H*), 7.80 – 7.74 (m, 2H, Ar*H*), 7.34 (d, *J* = 8.7 Hz, 1H, N*H*), 5.90 (dt, *J* = 8.7, 5.6 Hz, 1H, C*H*), 3.76 – 3.64 (m, 1H, C*H*$_2$N$_3$), 3.57 (dt, *J* = 12.7, 5.6 Hz, 1H, C*H*$_2$N$_3$), 1.97 (dt, *J* = 6.3, 5.5 Hz, 2H, C*H*$_2$CH$_2$N$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.7, 136.8, 132.6, 127.9, 117.8, 115.8, 65.3, 47.2, 32.9; **IR** (film): $\tilde{\nu}$ = 3322 (w), 2232 (w), 2104 (s), 1653 (m), 1530 (m), 1496 (m), 1280 (m), 1244 (m), 857 (m); **HRMS** (APCI) calcd. for $C_{11}H_{10}N_5O^+$ $[M-N_3]^+$ 228.0880; Found 228.0876.

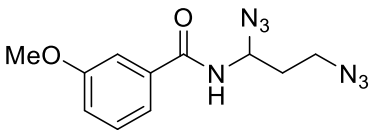
***N*-(1,3-Diazidopropyl)-4-nitrobenzamide** (**369f**)



Following GP H, starting from *N*-cyclopropyl-4-nitrobenzamide **296f** (41.2 mg, 0.200 mmol), *N*-(1,3-diazidopropyl)-4-nitrobenzamide **369f** (33.1 mg, 0.114 mmol, 57%) was obtained as a yellow solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R$_f$: 0.50 (silica, pentanes:ethyl acetate 3:1); **Mp:** 88-91 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.34 – 8.28 (m, 2H, Ar*H*), 8.01 – 7.95 (m, 2H, Ar*H*), 7.38 (d, *J* = 8.7 Hz, 1H, N*H*), 5.92 (dt, *J* = 8.7, 5.6 Hz, 1H, C*H*), 3.73 (dt, *J* = 12.8, 6.2 Hz, 1H, C*H*$_2$N$_3$), 3.58 (dt, *J* = 12.6, 5.5 Hz, 1H, C*H*$_2$N$_3$), 1.98 (dt, *J* = 6.2, 5.4 Hz, 2H, C*H*$_2$CH$_2$N$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.5, 150.0, 138.4, 128.4, 124.0, 65.4, 47.2, 32.9; **IR** (film): $\tilde{\nu}$ = 3294 (w), 2095 (s), 1652 (m), 1522 (s), 1344 (m), 1240 (m), 867 (m); **HRMS** (APCI) calcd. for $C_{10}H_{10}N_5O_3^+$ $[M-N_3]^+$ 248.0778; Found 248.0776.

***N*-(1,3-Diazidopropyl)-3-methoxybenzamide** (**369g**)

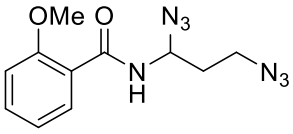


Following GP H, starting from *N*-cyclopropyl-3-methoxybenzamide **296g** (38.2 mg, 0.200 mmol), *N*-(1,3-diazidopropyl)-3-methoxybenzamide **369g** (39.4 mg, 0.143 mmol, 72%) was obtained as a yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R$_f$: 0.45 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 2.7, 1.5 Hz, 1H, Ar*H*), 7.32 – 7.27 (m, 1H, Ar*H*), 7.26 – 7.23 (m, 1H, Ar*H*), 7.09 (d, *J* = 9.1 Hz, 1H, N*H*), 7.04 – 6.99 (m, 1H, Ar*H*), 5.84 (dt, *J* = 8.9, 5.8 Hz, 1H, C*H*), 3.78 (s, 3H, OC*H*$_3$), 3.59 (dt, *J* = 12.8, 6.5 Hz, 1H, C*H*$_2$N$_3$), 3.47 (dt, *J* = 12.7, 5.9 Hz, 1H, C*H*$_2$N$_3$), 1.88 (q, *J* = 6.0 Hz, 2H, C*H*$_2$CH$_2$N$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$):

δ = 167.3, 159.9, 134.3, 129.7, 118.8, 118.6, 112.5, 65.1, 55.5, 47.3, 33.2; **IR** (film): $\tilde{\nu}$ = 3305 (w), 2940 (w), 2099 (s), 1647 (m), 1583 (m), 1523 (m), 1289 (m), 1246 (m); **HRMS** (ESI) calcd. for $C_{11}H_{13}N_7NaO_2^+$ $[M+Na]^+$ 298.1023; Found 298.1029.

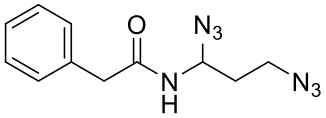
***N*-(1,3-Diazidopropyl)-2-methoxybenzamide** (**369h**)



Following GP H, starting from *N*-cyclopropyl-2-methoxybenzamide **296h** (38.2 mg, 0.200 mmol), *N*-(1,3-diazidopropyl)-2-methoxybenzamide **369h** (37.0 mg, 0.135 mmol, 67%) was obtained as a pale yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.32 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 8.7 Hz, 1H, N*H*), 8.25 – 8.19 (m, 1H, Ar*H*), 7.54 – 7.46 (m, 1H, Ar*H*), 7.10 (ddd, *J* = 8.3, 7.3, 1.0 Hz, 1H, Ar*H*), 7.00 (dd, *J* = 8.4, 1.0 Hz, 1H, Ar*H*), 5.95 (dt, *J* = 8.7, 6.0 Hz, 1H, C*H*), 3.99 (s, 3H, OCH_3), 3.65 – 3.38 (m, 2H, CH_2N_3), 1.95 (q, *J* = 6.3 Hz, 2H, C$H_2CH_2N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.5, 157.7, 133.7, 132.6, 121.5, 120.1, 111.4, 64.6, 56.0, 47.2, 33.5; **IR** (film): $\tilde{\nu}$ = 3362 (w), 2945 (w), 2100 (s), 1658 (m), 1514 (m), 1482 (m), 1240 (m), 1020 (m); **HRMS** (ESI) calcd. for $C_{11}H_{13}N_7NaO_2^+$ $[M+Na]^+$ 298.1023; Found 298.1030.

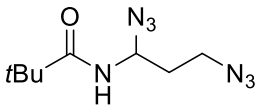
***N*-(1,3-Diazidopropyl)-2-phenylacetamide** (**369m**)



Following GP H, starting from *N*-cyclopropyl-2-phenylacetamide **296m** (35.0 mg, 0.200 mmol), *N*-(1,3-Diazidopropyl)-2-phenylacetamide **369m** (32.5 mg, 0.125 mmol, 63%) was obtained as a yellow solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.30 (silica, pentanes:ethyl acetate 3:1); **Mp:** 54-56 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.42 – 7.37 (m, 2H, Ar*H*), 7.36 – 7.31 (m, 1H, Ar*H*), 7.30 – 7.26 (m, 2H, Ar*H*), 6.36 (d, *J* = 8.7 Hz, 1H, N*H*), 5.67 (dt, *J* = 9.0, 5.6 Hz, 1H, C*H*), 3.71 – 3.61 (m, 2H, PhCH_2), 3.45 (ddd, *J* = 13.0, 7.2, 5.9 Hz, 1H, CH_2N_3), 3.36 (dt, *J* = 12.6, 5.7 Hz, 1H, CH_2N_3), 1.69 (dd, *J* = 6.6, 4.9 Hz, 2H, C$H_2CH_2N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.5, 133.8, 129.5, 129.2, 127.7, 64.4, 46.9, 43.5, 32.7; **IR** (film): $\tilde{\nu}$ = 3277 (w), 2097 (s), 1656 (m), 1532 (m), 1242 (m), 696 (m); **HRMS** (ESI) calcd. for $C_{11}H_{13}N_7NaO^+$ $[M+Na]^+$ 282.1074; Found 282.1073.

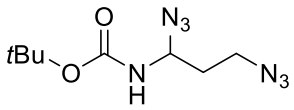
***N*-(1,3-Diazidopropyl)pivalamide** (**369n**)



Following GP H, starting from *N*-cyclopropylpivalamide **296n** (28.2 mg, 0.200 mmol), *N*-(1,3-diazidopropyl)pivalamide **369n** (27.8 mg, 0.124 mmol, 62%) was obtained as a yellow gel after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.33 (silica, pentanes:ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.58 (s, 1H, N*H*), 5.77 – 5.64 (m, 1H, C*H*), 3.60 (dtd, *J* = 12.9, 6.7, 2.4 Hz, 1H, CH_2N_3), 3.47 (dtd, *J* = 13.3, 5.7, 1.5 Hz, 1H, CH_2N_3), 1.84 (q, *J* = 6.0 Hz, 2H, C$H_2CH_2N_3$), 1.24 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 178.9, 64.3, 47.3, 39.0, 33.0, 27.5; **IR** (film): $\tilde{\nu}$ = 3333 (w), 2969 (w), 2098 (s), 1654 (m), 1513 (m), 1246 (m); **HRMS** (ESI) calcd. for $C_8H_{15}N_7NaO^+$ $[M+Na]^+$ 248.1230; Found 248.1230.

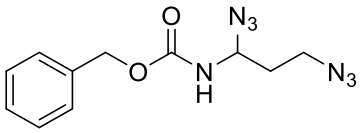
***tert*-Butyl (1,3-diazidopropyl)carbamate** (**369o**)



Following GP H, starting from *tert*-butyl cyclopropylcarbamate **296o** (31.4 mg, 0.200 mmol) with CuTc (0.4 mg, 0.002 mmol, 0.01 equiv.), *tert*-Butyl (1,3-diazidopropyl)carbamate **369o** (29.7 mg, 0.123 mmol, 62%) was obtained as a colorless oil after purification by column chromatography on silica using 10:1 pentanes:ethyl acetate as eluent.

R_f: 0.38 (silica, pentanes:ethyl acetate 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.54 – 5.12 (m, 2H, N*H* + C*H*), 3.46 (qt, *J* = 12.7, 6.4 Hz, 2H, CH_2N$_3$), 1.80 (q, *J* = 6.4 Hz, 2H, CH_2CH$_2$N$_3$), 1.47 (s, 9H, C(CH$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.8, 81.0, 66.5, 47.3, 33.6, 28.1; **IR** (film): $\tilde{\nu}$ = 3323 (w), 2987 (m), 2098 (s), 1701 (s), 1509 (m), 1257 (s), 1161 (s); **HRMS** (ESI) calcd. for $C_8H_{15}N_7NaO_2^+$ $[M+Na]^+$ 264.1179; Found 264.1180.

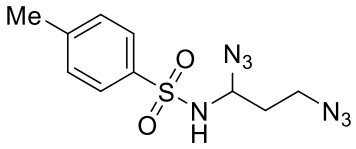
Benzyl (1,3-diazidopropyl)carbamate (**369p**)



Following GP H, starting from benzyl cyclopropylcarbamate **296p** (38.2 mg, 0.200 mmol) with CuTc (0.4 mg, 0.002 mmol, 0.01 equiv.), benzyl (1,3-diazidopropyl)carbamate **369p** (36.2 mg, 0.132 mmol, 66%) was obtained as a colorless oil after purification by column chromatography on silica using 5:1 pentanes:ethyl acetate as eluent.

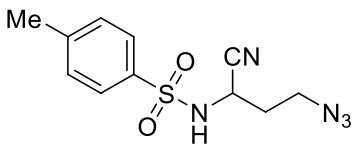
R_f: 0.53 (silica, pentanes:ethyl acetate 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.39 – 7.34 (m, 5H, Ar*H*), 5.63 (d, *J* = 9.7 Hz, 1H, N*H*), 5.48 (p, *J* = 6.7 Hz, 1H, C*H*), 5.16 (s, 2H, OCH_2), 3.54 – 3.40 (m, 2H, CH_2N$_3$), 1.82 (q, *J* = 6.4 Hz, 2H, CH_2CH$_2$N$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.6, 135.6, 128.6, 128.4, 128.3, 67.5, 66.9, 47.1, 33.4; **IR** (film): $\tilde{\nu}$ = 3672 (w), 3323 (w), 2975 (s), 2098 (s), 1713 (s), 1245 (s), 1065 (s); **HRMS** (ESI) calcd. for $C_{11}H_{13}N_7NaO_2^+$ $[M+Na]^+$ 298.1023; Found 298.1028.

***N*-(1,3-diazidopropyl)-4-methylbenzenesulfonamide** (**369q**)



Following GP H, starting from *N*-cyclopropyl-4-methylbenzenesulfonamide **296q** (42.2 mg, 0.200 mmol), N-(1,3-diazidopropyl)-4-methylbenzenesulfonamide **369q** was formed in 68% yield based on crude ^{1}H NMR after workup, but purification by column chromatography on silica led to decomposition. Please refer to compound **373** for one-pot nucleophilic substitution via **369q**.

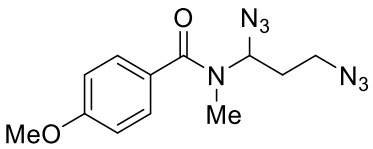
***N*-(3-Azido-1-cyanopropyl)-4-methylbenzenesulfonamide** (**373**)



Following GP H, starting from *N*-cyclopropyl-4-methyl benzenesulfonamide **296q** (42.2 mg, 0.200 mmol), after diazidation step is finished, TMSCN (38.0 µL, 0.300 mmol, 1.5 equiv.) was added to the crude. The reaction mixture was stirred at room temperature for 30 minutes. *N*-(3-Azido-1-cyanopropyl)-4-methylbenzenesulfonamide **373** (35.1 mg, 0.126 mmol, 63%) was obtained as a beige solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.50 (silica, pentanes:ethyl acetate 1:1); **Mp:** 113-116 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.87 – 7.73 (m, 2H, Ar*H*), 7.37 (d, *J* = 8.1 Hz, 2H, Ar*H*), 5.39 (d, *J* = 9.8 Hz, 1H, N*H*), 4.42 (ddd, *J* = 9.8, 7.2, 6.2 Hz, 1H, NC*H*), 3.64 – 3.49 (m, 2H, CH_2N_3), 2.45 (s, 3H, CH_3), 2.02 (dtd, *J* = 7.6, 5.8, 2.4 Hz, 2H, C$H_2CH_2N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.9, 135.7, 130.2, 127.3, 116.7, 46.9, 42.3, 33.0, 21.7; **IR** (film): $\tilde{\nu}$ = 3275 (m), 2929 (w), 2105 (s), 1336 (s), 1161 (s), 1090 (s), 815 (m); **HRMS** (ESI) calcd. for $C_{11}H_{13}N_5NaO_2S^+$ $[M+Na]^+$ 302.0682; Found 302.0684.

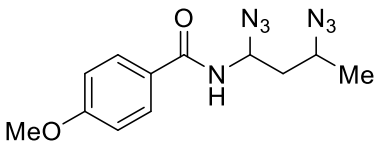
***N*-(1,3-Diazidopropyl)-4-methoxy-N-methylbenzamide (374)**



Following GP H, starting from *N*-cyclopropyl-4-methoxy-*N*-methylbenzamide **349** (41.0 mg, 0.200 mmol), *N*-(1,3-diazidopropyl)-4-methoxy-N-methylbenzamide **374** (37.1 mg, 0.128 mmol, 64%) was obtained as a pale yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.26 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$, 298K): δ = 7.52 – 7.34 (m, 2H, Ar*H*), 6.99 – 6.90 (m, 2H, Ar*H*), 6.36 – 5.51 (br, 1H, C*H*), 3.85 (s, 3H, OCH_3), 3.38 (dd, *J* = 12.4, 5.9 Hz, 2H, CH_2N_3), 2.99 (s, 3H, NCH_3), 2.02 – 1.79 (m, 2H, C$H_2CH_2N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$, 298K): δ = 172.5, 161.3, 129.4, 126.9, 113.9, 55.4, 47.4, 31.7 (two carbon signals are not resolved due to rotamers, which can be observed by measuring NMR experiment in Acetone-d_6 at 261.7 K); **IR** (film): $\tilde{\nu}$ = 2963 (w), 2097 (s), 1641 (m), 1607 (m), 1251 (s), 1064 (m), 1028 (m), 842 (m); **HRMS** (ESI) calcd. for $C_{12}H_{15}N_7NaO_2^+$ $[M+Na]^+$ 312.1179; Found 312.1187.

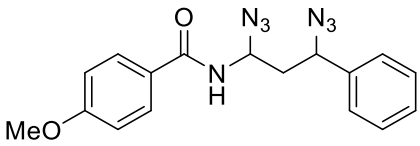
***N*-(1,3-Diazidobutyl)-4-methoxybenzamide (375a)**



Following GP H, starting from 4-methoxy-*N*-(trans-2-methylcyclopropyl)benzamide **342a** (41.0 mg, 0.200 mmol) with CuTc (2.4 mg, 0.012 mmol, 0.06 equiv.), *N*-(1,3-diazidobutyl)-4-methoxybenzamide **375a** (51.6 mg, 0.179 mmol, 89%) was obtained as a yellow gel after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.23 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$; mixture of diastereoisomers in a ratio of 1.1:1, signals corresponding to the two regioisomers are partially resolved): δ = 7.78 (ddd, *J* = 10.1, 4.9, 2.7 Hz, 4H, Ar*H*, major + minor), 7.62 – 7.35 (m, 1H, N*H*, minor), 7.00 – 6.89 (m, 4H, Ar*H*, major + minor), 6.59 (t, *J* = 18.1 Hz, 1H, N*H*, major), 5.96 – 5.81 (m, 2H, NC*H*, major + minor), 3.99 (dd, *J* = 6.5, 3.5 Hz, 1H, MeC*H*, minor), 3.86 (s, 6H, OCH_3, major +minor), 3.75 – 3.66 (m, 1H, MeC*H*, major), 1.96 – 1.71 (m, 4H, CH_2, major +minor), 1.37 (dd, *J* = 8.2, 6.5 Hz, 6H, CH_3, major +minor); **^{13}C NMR** (101 MHz, $CDCl_3$; mixture of diastereoisomers in a ratio of 1.1:1, signals corresponding to the two regioisomers are partially resolved): δ = 166.8, 166.7, 162.8, 162.8, 129.1, 125.2, 114.0, 65.2, 64.7, 55.5, 54.3, 53.7, 41.0, 39.7, 19.6, 19.3; **IR** (film): $\tilde{\nu}$ = 3307(w), 2971 (w), 2098 (s), 1640 (m), 1605 (m), 1500 (s), 1252 (s), 1029 (m); **HRMS** (ESI) calcd. for $C_{12}H_{15}N_7NaO_2^+$ $[M+Na]^+$ 312.1179; Found 312.1180.

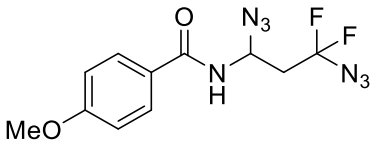
***N*-(1,3-Diazido-3-phenylpropyl)-4-methoxybenzamide** (**375b**)



Following GP H, starting from 4-methoxy-*N*-(trans-2-phenylcyclopropyl)benzamide **342b** (53.4 mg, 0.200 mmol), *N*-(1,3-diazido-3-phenylpropyl)-4-methoxybenzamide **375b** (58.0 mg, 0.165 mmol, 83%) was obtained as a yellow solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.43 (silica, pentanes:ethyl acetate 3:1); **Mp:** 81-84 °C; **^{1}H NMR** (400 MHz, $CDCl_3$; mixture of diastereoisomers in a ratio of 1.2:1, signals corresponding to the two regioisomers are partially resolved): δ = 7.81 – 7.75 (m, 2H, Ar*H*, major), 7.70 – 7.62 (m, 2H, Ar*H*, minor), 7.59 – 7.53 (m, 1H, N*H*, major), 7.46 – 7.30 (m, 10H, Ar*H*, major + minor), 6.97 – 6.92 (m, 2H, Ar*H*, major), 6.92 – 6.87 (m, 2H, Ar*H*, minor), 6.66 (d, *J* = 8.9 Hz, 1H, N*H*, minor), 5.91 (ddd, *J* = 8.9, 7.6, 5.6 Hz, 1H, NC*H*, minor), 5.85 (ddd, *J* = 8.9, 5.8, 4.5 Hz, 1H, NC*H*, major), 4.88 (dd, *J* = 9.2, 5.0 Hz, 1H, PhC*H*, major), 4.71 (dd, *J* = 9.1, 5.2 Hz, 1H, PhC*H*, minor), 3.86 (s, 3H, OCH_3, major), 3.84 (s, 3H, OCH_3, minor), 2.22 – 1.95 (m, 4H, CH_2, major + minor); **^{13}C NMR** (101 MHz, $CDCl_3$; mixture of diastereoisomers in a ratio of 1.2:1, signals corresponding to the two regioisomers are partially resolved): δ = 166.8, 166.8, 162.8, 162.8, 138.5, 137.9, 129.3, 129.2, 129.1, 129.1, 129.0, 128.9, 126.9, 125.1, 125.0, 113.9, 113.8, 65.0, 64.8, 62.3, 62.2, 55.4, 55.4, 40.9, 39.9; **IR** (film): $\tilde{\nu}$ = 3307(w), 2100 (s), 1643 (m), 1605 (m), 1502 (s), 1255 (s), 1177 (m), 1029 (m); **HRMS** (ESI) calcd. for $C_{17}H_{17}N_7NaO_2^+$ $[M+Na]^+$ 374.1336; Found 374.1345.

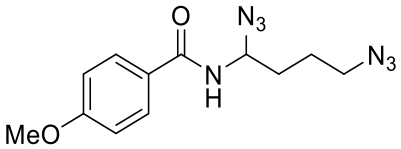
***N*-(1,3-Diazido-3,3-difluoropropyl)-4-methoxybenzamide** (**375d**)



Following GP H, starting from *N*-(2,2-difluorocyclopropyl)-4-methoxybenzamide **342d** (45.4 mg, 0.200 mmol), *N*-(1,3-diazido-3,3-difluoropropyl)-4-methoxybenzamide **375d** (53.8 mg, 0.173 mmol, 86%) was obtained as a beige solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.43 (silica, pentanes:ethyl acetate 3:1); **Mp:** 58-61 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.80 – 7.75 (m, 2H, Ar*H*), 6.97 – 6.93 (m, 2H, Ar*H*), 6.77 (d, *J* = 9.1 Hz, 1H, N*H*), 6.00 (ddd, *J* = 8.8, 7.1, 5.7 Hz, 1H, C*H*), 3.86 (s, 3H, CH_3), 2.43 (tdd, *J* = 11.1, 6.4, 2.9 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.8, 163.0, 129.1, 124.8, 121.9 (t, *J* = 266.9 Hz), 114.0, 62.2 (t, *J* = 4.1 Hz), 55.5, 40.1 (t, *J* = 26.7 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$): δ = -69.1; **IR** (film): $\tilde{\nu}$ = 3312(w), 2936 (w), 2142 (s), 1652 (m), 1601 (s), 1502 (m), 1250 (s), 1171 (s); **HRMS** (ESI) calcd. for $C_{11}H_{11}F_2N_7NaO_2^+$ $[M+Na]^+$ 334.0834; Found 334.0838.

***N*-(1,4-Diazidobutyl)-4-methoxybenzamide** (**375e**)

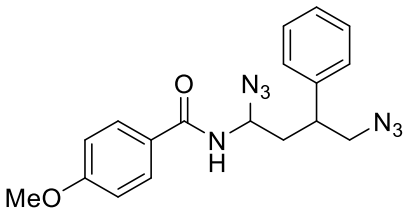


Following GP H, starting from *N*-cyclobutyl-4-methoxybenzamide **342e** (41.0 mg, 0.200 mmol), *N*-(1,4-diazidobutyl)-4-methoxybenzamide **375e** (39.0 mg, 0.135 mmol, 67%) was obtained as a white solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.30 (silica, pentanes:ethyl acetate 3:1); **Mp:** 58-61 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.74 – 7.69 (m, 2H, Ar*H*), 6.89 – 6.85 (m, 2H, Ar*H*), 6.52 (d, *J* = 9.1 Hz, 1H, N*H*), 5.68 (dt, *J* = 8.9, 6.5 Hz, 1H, C*H*),

3.79 (s, 3H, OCH_3), 3.33 – 3.28 (m, 2H, CH_2N$_3$), 1.76 – 1.63 (m, 4H, CH_2CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.9, 162.8, 129.1, 125.1, 113.9, 66.6, 55.5, 50.7, 32.0, 24.7; **IR** (film): $\tilde{\nu}$ = 3296(w), 2933 (w), 2097 (s), 1638 (m), 1605 (s), 1500 (s), 1254 (s), 1177 (m), 1029 (m), 845 (m); **HRMS** (APCI) calcd. for $C_{12}H_{15}N_7NaO_2^+$ $[M+Na]^+$ 312.1179; Found 312.1174.

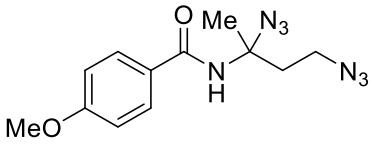
***N*-(1,4-Diazido-3-phenylbutyl)-4-methoxybenzamide (375f)**



Following GP H, starting from 4-methoxy-*N*-(*trans*-3-phenylcyclobutyl)benzamide **342f** (28.1 mg, 0.100 mmol), *N*-(1,4-diazido-3-phenylbutyl)-4-methoxybenzamide **375f** (25.7 mg, 0.070 mmol, 70%) was obtained as a colorless oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

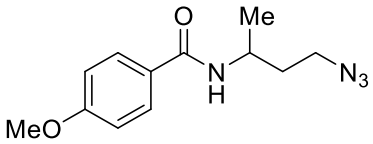
R_f: 0.43 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$; mixture of diastereoisomers in a ratio of 1:1, signals corresponding to the two regioisomers are partially resolved): δ = 7.59 – 7.54 (m, 2H, Ar*H*), 7.43 – 7.37 (m, 4H, Ar*H*), 7.36 – 7.32 (m, 3H, Ar*H*), 7.31 – 7.26 (m, 3H, Ar*H*), 7.25 – 7.22 (m, 2H, Ar*H*), 6.89 – 6.80 (m, 4H, Ar*H*), 6.49 (d, *J* = 8.7 Hz, 1H, N*H*), 6.40 (d, *J* = 9.1 Hz, 1H, N*H*), 5.75 (ddd, *J* = 9.2, 7.1, 4.1 Hz, 1H, C*H*), 5.49 (td, *J* = 8.7, 5.8 Hz, 1H, C*H*), 3.84 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.55 (dt, *J* = 12.1, 7.0 Hz, 2H, N$_3$CH_2), 3.45 (ddd, *J* = 15.1, 12.1, 7.4 Hz, 2H, N$_3$CH_2), 3.14 (ddt, *J* = 10.5, 7.2, 3.7 Hz, 1H, PhC*H*), 3.07 (ddt, *J* = 10.9, 7.0, 3.7 Hz, 1H, PhC*H*), 2.26 – 2.12 (m, 2H, CH_2), 2.06 (tdd, *J* = 13.8, 10.3, 5.0 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$; mixture of diastereoisomers in a ratio of 1:1, signals corresponding to the two regioisomers are partially resolved): δ = 166.7, 166.5, 162.7, 140.7, 140.0, 129.5, 129.2, 129.0, 128.9, 128.8, 127.9, 127.8, 127.7, 127.6, 125.0, 124.9, 113.7, 113.7, 66.0, 65.4, 56.8, 56.6, 55.4, 55.3, 42.4, 41.3, 37.8, 37.5; **IR** (film): $\tilde{\nu}$ = 3303(w), 2934 (w), 2097 (s), 1641 (m), 1605 (m), 1499 (m), 1254 (s), 1176 (m), 1028 (m); **HRMS** (ESI) calcd. for $C_{18}H_{19}N_7NaO_2^+$ $[M+Na]^+$ 388.1492; Found 388.1496.

***N*-(2,4-Diazidobutan-2-yl)-4-methoxybenzamide (375g)**



Following GP H, starting from 4-methoxy-*N*-(1-methylcyclopropyl)benzamide **342g** (41.0 mg, 0.200 mmol), *N*-(2,4-diazidobutan-2-yl)-4-methoxybenzamide **375g** was formed in 58% yield based on crude ^{1}H NMR after workup, but purification by column chromatography on silica led to decomposition.Therefore, one-pot reduction by trimethylsilane was performed as shown below to form **375g'**.

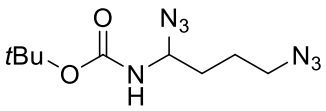
***N*-(4-azidobutan-2-yl)-4-methoxybenzamide (375g')**



Following GP H, starting from 4-methoxy-*N*-(1-methylcyclopropyl)benzamide **342g** (41.0 mg, 0.200 mmol), after diazidation step is finished, triethylsilane (32.0 µL, 0.200 mmol, 1.0 equiv.) and TMSOTf (36.0 µL, 0.200 mmol, 1.0 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 2 hours. *N*-(4-azidobutan-2-yl)-4-methoxybenzamide **375g'** (22.4 mg, 90.3 µmol, 45%) was obtained as a white solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.37 (silica, pentanes:ethyl acetate 1:1); **Mp:** 61-63 °C; **^{1}H NMR** (800 MHz, $CDCl_3$): δ = 7.77 – 7.66 (m, 2H, Ar*H*), 6.96 – 6.86 (m, 2H, Ar*H*), 6.07 (d, *J* = 8.4 Hz, 1H, N*H*), 4.30 (tdd, *J* = 8.2, 6.6, 5.0 Hz, 1H, C*H*), 3.84 (s, 3H, OCH_3), 3.49 – 3.36 (m, 2H, N_3CH_2), 1.90 – 1.75 (m, 2H, $N_3CH_2CH_2$), 1.28 (d, *J* = 6.7 Hz, 3H, CH_3); **^{13}C NMR** (201 MHz, $CDCl_3$): δ = 166.4, 162.1, 128.6, 126.8, 113.7, 55.4, 48.7, 43.8, 35.8, 20.9; **IR** (film): $\tilde{\nu}$ = 3313(w), 2977 (s), 2098 (s), 1631 (s), 1500 (s), 1257 (s), 1045 (s), 852 (m); **HRMS** (ESI) calcd. for $C_{12}H_{16}N_4NaO_2^+$ $[M+Na]^+$ 271.1165; Found 271.1169.

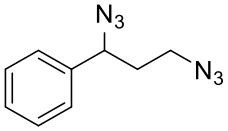
***tert*-Butyl (1,4-diazidobutyl)carbamate** (**375h**)



Following GP H, starting from *tert*-butyl cyclobutylcarbamate **342h** (34.2 mg, 0.200 mmol) with CuTc (0.4 mg, 0.002 mmol, 0.01 equiv.), *tert*-Butyl (1,4-diazidopropyl)carbamate **375h** (30.5 mg, 0.120 mmol, 60%) was obtained as a colorless oil after purification by column chromatography on silica using 8:1 pentanes:ethyl acetate as eluent.

R_f: 0.31 (silica, pentanes:ethyl acetate 8:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.34 – 4.97 (m, 2H, N*H* + C*H*), 3.32 (t, *J* = 6.1 Hz, 2H, CH_2N_3), 1.67 (tdd, *J* = 13.4, 10.2, 6.2 Hz, 4H, CH_2), 1.46 (s, 9H, $C(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.8, 80.8, 68.2, 50.7, 31.9, 28.1, 24.6; **IR** (film): $\tilde{\nu}$ = 3667 (w), 3340 (w), 2973 (s), 2102 (s), 1704 (s), 1508 (m), 1253 (s), 1060 (s); **HRMS** (ESI) calcd. for $C_9H_{17}N_7NaO_2^+$ $[M+Na]^+$ 278.1336; Found 278.1338.

(1,3-Diazidopropyl)benzene (**376**)



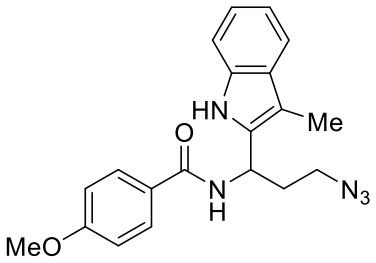
Following GP H, starting from cyclopropylbenzene **344** (25.1 µL, 0.200 mmol), (1,3-diazidopropyl)benzene **376** (4.0 mg, 0.020 mmol, 10%) was obtained as a colorless oil after purification by column chromatography on silica using pentanes as eluent.

R_f: 0.32 (silica, pentanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.41 (ddt, *J* = 8.0, 6.5, 1.3 Hz, 2H, Ar*H*), 7.38 – 7.35 (m, 1H, Ar*H*), 7.32 (tt, *J* = 5.6, 1.4 Hz, 2H, Ar*H*), 4.61 (dd, *J* = 8.6, 5.9 Hz, 1H, C*H*), 3.48 – 3.29 (m, 2H, CH_2N_3), 2.10 – 1.88 (m, 2H, $CH_2CH_2N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 138.6, 129.0, 128.6, 126.9, 63.2, 48.1, 35.5; **IR** (film): $\tilde{\nu}$ = 2963 (m), 2098 (s), 1245 (m), 1053 (m), 908 (m); **HRMS** (ESI) calcd. for $C_9H_{11}N_4^+$ $[M+H-N_2]^+$ 175.0978; Found 175.0965.

General Procedure I (GP I):

In a 12*75 mm Borosilicate glass tube, the corresponding aminocyclopropane (0.200 mmol, 1.0 equiv.), Selectfluor (78.0 mg, 0.220 mmol, 1.1 equiv.) and CuTc (0.8 mg, 0.004 mmol, 0.02 equiv.) were measured on analytical balance. The tube was then closed with a rubber septum and sealed off with parafilm. Evacuate-refill cycle with nitrogen were performed three times to remove O_2 and extra-dry acetonitrile (2.0 mL, 0.1 M) was added under nitrogen atmosphere, followed by the addition of $TMSN_3$ (94% purity purchased from TCI, 62.0 µL, 0.440 mmol, 2.2 equiv.). The reaction mixture was stirred at room temperature for 10 minutes before nucleophile (and if needed the Lewis acid/base) was added. The nucleophilc substitution step was not sensitive to air and nucleophile can be added directly by injection if it is in liquid state or by removing the cap and adding from the top if it is in solid state. The progress of the reaction was monitored by TLC. Upon completion, the mixture was quenched by the addition of water (10 mL). The aqueous layer was then extracted with dichloromethane (10 mL x 3). The organic extract was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, pentanes/EtOAc).

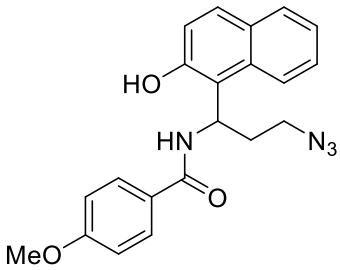
***N*-(3-Azido-1-(3-methyl-1H-indol-2-yl)propyl)-4-methoxybenzamide (377a)**



Following GP I, starting from *N*-cyclopropyl-4-methoxybenzamide **296a** (38.2 mg, 0.200 mmol), after diazidation step is finished, 3-methylindole (39.4 mg, 0.300 mmol, 1.5 equiv.) and boron trifluoride etherate (25.0 µL, 0.200 mmol, 1.0 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 30 minutes. *N*-(3-Azido-1-(3-methyl-1H-indol-2-yl)propyl)-4-methoxybenzamide **377a** (47.3 mg, 0.130 mmol, 65%) was obtained as a yellow solid after purification by column chromatography on silica using 3:2 pentanes:ethyl acetate as eluent.

R_f: 0.45 (silica, pentanes:ethyl acetate 3:2); **Mp:** 152-155 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.13 (s, 1H, indole N*H*), 7.75 – 7.70 (m, 2H, Ar*H*), 7.54 – 7.50 (m, 1H, Ar*H*), 7.32 (dt, *J* = 8.1, 1.0 Hz, 1H, Ar*H*), 7.17 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, Ar*H*), 7.10 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H, Ar*H*), 6.93 – 6.89 (m, 2H, Ar*H*), 6.75 (d, *J* = 7.1 Hz, 1H, N*H*), 5.16 (q, *J* = 7.4 Hz, 1H, C*H*), 3.84 (s, 3H, OCH_3), 3.44 (ddd, *J* = 12.5, 7.0, 5.6 Hz, 1H, CH_2N_3), 3.31 (ddd, *J* = 12.6, 7.2, 5.6 Hz, 1H, CH_2N_3), 2.56 – 2.40 (m, 2H, C$H_2CH_2N_3$), 2.34 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.9, 162.5, 135.4, 133.1, 128.8, 128.5, 126.1, 122.2, 119.2, 118.7, 113.9, 111.0, 108.3, 55.4, 48.8, 46.2, 32.8, 8.7; **IR** (film): $\tilde{\nu}$ = 3672 (w), 3323 (m), 2975 (s), 2098 (s), 1617 (s), 1497 (m), 1257 (s), 1065 (s); **HRMS** (ESI) calcd. for $C_{20}H_{21}N_5NaO_2^+$ $[M+Na]^+$ 386.1587; Found 386.1588.

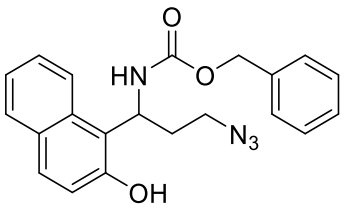
***N*-(3-Azido-1-(2-hydroxynaphthalen-1-yl)propyl)-4-methoxybenzamide (377ba)**



Following GP I, starting from *N*-cyclopropyl-4-methoxybenzamide **296a** (38.2 mg, 0.200 mmol), after diazidation step is finished, 2-naphthol (43.2 mg, 0.300 mmol, 1.5 equiv.) and boron trifluoride etherate (25.0 µL, 0.200 mmol, 1.0 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 30 minutes. *N*-(3-Azido-1-(2-hydroxynaphthalen-1-yl)propyl)-4-methoxybenzamide **377ba** (56.0 mg, 0.149 mmol, 74%) was obtained as a white solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.27 (silica, pentanes:ethyl acetate 1:1); **Mp:** 187-190 °C; **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 9.55 (s, 1H, naphthol O*H*), 8.39 (d, *J* = 8.8 Hz, 1H, N*H*), 8.31 (d, *J* = 8.7 Hz, 1H, Ar*H*), 7.88 – 7.78 (m, 3H, Ar*H*), 7.75 (d, *J* = 8.8 Hz, 1H, Ar*H*), 7.54 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H, Ar*H*), 7.33 (ddd, *J* = 8.0, 6.8, 1.0 Hz, 1H, Ar*H*), 7.26 (d, *J* = 8.9 Hz, 1H, Ar*H*), 7.01 – 6.90 (m, 2H, Ar*H*), 6.34 (q, *J* = 8.1 Hz, 1H, NC*H*), 3.82 (s, 3H, OCH_3), 3.52 (dt, *J* = 12.3, 7.0 Hz, 1H, CH_2N_3), 3.42 (dt, *J* = 12.6, 6.6 Hz, 1H, CH_2N_3), 2.63 – 2.44 (m, 1H, C$H_2CH_2N_3$), 2.28 (dq, *J* = 13.6, 6.8 Hz, 1H, C$H_2CH_2N_3$); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 166.5, 163.1, 154.0, 133.4, 130.1, 130.0, 129.6, 129.5, 128.0, 127.6, 123.9, 123.3, 120.2, 119.5, 114.4, 55.8, 49.8, 45.7, 34.4; **IR** (film): $\tilde{\nu}$ = 3137 (m), 2932 (w), 2097 (s), 1627 (s), 1606 (s), 1501 (s), 1259 (s), 1029 (m); **HRMS** (ESI) calcd. for $C_{21}H_{20}N_4NaO_3^+$ $[M+Na]^+$ 399.1428; Found 399.1426.

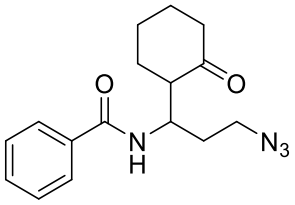
Benzyl (3-azido-1-(2-hydroxynaphthalen-1-yl)propyl)carbamate (**377bb**)



Following GP I, starting from benzyl cyclopropylcarbamate **296p** (38.2 mg, 0.200 mmol), after diazidation step is finished, the crude was cooled down to -20 °C before 2-naphthol (43.2 mg, 0.300 mmol, 1.5 equiv.) and boron trifluoride etherate (25.0 µL, 0.200 mmol, 1.0 equiv.) were added to the crude. The reaction mixture was stirred at -20 °C for 2 hours. Benzyl (3-azido-1-(2-hydroxynaphthalen-1-yl)propyl)carbamate **377bb** (35.0 mg, 0.093 mmol, 46%) was obtained as a white solid after purification by column chromatography on silica using 4:1 pentanes:ethyl acetate as eluent.

R_f: 0.30 (silica, pentanes:ethyl acetate 4:1); **MP:** 149-150 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.04 (s, 1H, Ar*H*), 7.76 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar*H*), 7.65 (d, *J* = 8.8 Hz, 1H, Ar*H*), 7.49 (ddd, *J* = 8.5, 6.7, 1.4 Hz, 1H, Ar*H*), 7.39 – 7.31 (m, 6H, Ar*H*), 7.04 (d, *J* = 8.8 Hz, 1H, Ar*H*), 5.85 (dt, *J* = 9.4, 7.2 Hz, 1H, NC*H*), 5.20 (d, *J* = 9.6 Hz, 2H, PhCH_2), 3.32 (ddt, *J* = 47.1, 12.5, 6.6 Hz, 2H, CH_2N_3), 2.42 – 2.13 (m, 2H, C$H_2CH_2N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.0, 136.0, 131.9, 129.6, 129.0, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.2, 123.3, 121.9, 118.2, 67.5, 48.8, 47.0, 33.9; **IR** (film): $\tilde{\nu}$ = 3277 (m), 2097 (s), 1687 (s), 1516 (s), 1329 (m), 1271 (m); **HRMS** (ESI) calcd. for $C_{21}H_{20}N_4NaO_3^+$ $[M+Na]^+$ 399.1428; Found 399.1435.

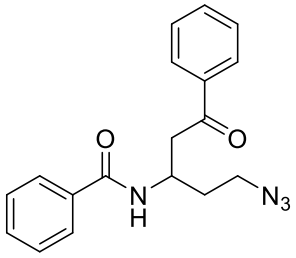
***N*-(3-Azido-1-(2-oxocyclohexyl)propyl)benzamide** (**377c**)



Following GP I, starting from *N*-cyclopropylbenzamide **296w** (32.2 mg, 0.200 mmol), after diazidation step is finished, 1-morpholinocyclohexane (100 µL, 0.600 mmol, 3.0 equiv.) and boron trifluoride etherate (75.0 µL, 0.600 mmol, 3.0 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 1 hour. *N*-(3-Azido-1-(2-oxocyclohexyl)propyl)benzamide **377c** (35.1 mg, 0.117 mmol, 58%) was obtained as a beige solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.30 (silica, pentanes:ethyl acetate 3:1); **Mp:** 93-96 °C; **^{1}H NMR** (400 MHz, CDCl3; mixture of two diastereoisomers in a 1.7:1 ratio: the signals corresponding to the two diastereoisomers are partially resolved): δ = 7.77 (ddd, *J* = 7.6, 6.0, 1.4 Hz, 2H, Ar*H*), 7.54 – 7.47 (m, 1H, Ar*H*), 7.44 (dtd, *J* = 8.7, 4.3, 2.3 Hz, 2H, Ar*H*), 7.09 (d, *J* = 9.8 Hz, 1H, N*H*, major:minor = 1.7:1), 4.31 (qdd, *J* = 11.0, 4.5, 2.6 Hz, 1H, NC*H*), 3.50 – 3.28 (m, 2H, CH_2N_3), 2.72 (dddd, *J* = 17.5, 12.3, 5.4, 1.8 Hz, 1H, C(O)C*H*), 2.48 – 2.01 (m, 5H, CH_2), 2.00 – 1.62 (m, 5H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$; mixture of two diastereoisomers in a 1.7:1 ratio: the signals corresponding to the two diastereoisomers are partially resolved): δ = 214.4, 213.2, 167.1, 166.7, 134.1, 134.1, 131.6, 128.6, 126.9, 54.5, 54.0, 49.0, 48.9, 48.7, 48.2, 43.3, 42.5, 33.7, 33.1, 30.9, 29.5, 28.4, 27.0, 25.1, 24.8; **IR** (film): $\tilde{\nu}$ = 3315 (w), 2936 (m), 2093 (s), 1703 (s), 1636 (s), 1527 (s), 1308 (m), 1258 (m); **HRMS** (ESI) calcd. for $C_{16}H_{20}N_4NaO_2^+$ $[M+Na]^+$ 323.1478; Found 323.1477.

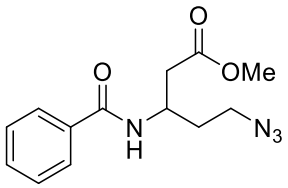
***N*-(5-Azido-1-oxo-1-phenylpentan-3-yl)benzamide (377d)**



Following GP I, starting from *N*-cyclopropylbenzamide **296w** (32.2 mg, 0.200 mmol), after diazidation step is finished, trimethyl((1-phenylvinyl)oxy)silane (82.0 µL, 0.400 mmol, 2.0 equiv.) and TMSOTf (72.0 µL, 0.400 mmol, 2.0 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 30 minutes. *N*-(5-Azido-1-oxo-1-phenylpentan-3-yl)benzamide **377d** (51.1 mg, 0.159 mmol, 79%) was obtained as a yellow solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.32 (silica, pentanes:ethyl acetate 2:1); **Mp:** 81-84 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.00 – 7.94 (m, 2H, Ar*H*), 7.82 – 7.75 (m, 2H, Ar*H*), 7.62 – 7.57 (m, 1H, Ar*H*), 7.46 (ddd, *J* = 19.5, 8.1, 6.5 Hz, 5H, Ar*H*), 7.26 – 7.22 (m, 1H, N*H*), 4.68 (tq, *J* = 9.4, 4.8 Hz, 1H, NC*H*), 3.56 (dd, *J* = 17.6, 4.2 Hz, 1H, C(O)CH_2), 3.47 (dd, *J* = 7.4, 6.0 Hz, 2H, CH_2N$_3$), 3.29 (dd, *J* = 17.6, 5.5 Hz, 1H, C(O)CH_2), 2.20 (ddt, *J* = 14.2, 9.4, 6.0 Hz, 1H, CH_2CH$_2$N$_3$), 1.95 (dtd, *J* = 14.4, 7.4, 4.7 Hz, 1H, CH_2CH$_2$N$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 199.5, 167.0, 136.6, 134.2, 133.7, 131.6, 128.8, 128.6, 128.1, 126.9, 48.9, 45.0, 41.5, 33.0; **IR** (film): $\tilde{\nu}$ = 3310 (w), 3061 (w), 2095 (s), 1682 (s), 1636 (s), 1534 (s), 1306 (m), 690 (s); **HRMS** (ESI) calcd. for $C_{18}H_{19}N_4O_2^+$ $[M+H]^+$ 323.1503; Found 323.1498.

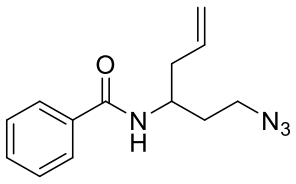
Methyl 5-azido-3-benzamidopentanoate (377e)



Following GP I, starting from *N*-cyclopropylbenzamide **296w** (32.2 mg, 0.200 mmol), after diazidation step is finished, *tert*-butyl[(1-methoxyvinyl)oxy]dimethylsilane (132 µL, 0.600 mmol, 3.0 equiv.) was added to the crude. The reaction mixture was stirred at room temperature for 4 hours. Methyl 5-azido-3-benzamidopentanoate **377e** (34.0 mg, 0.123 mmol, 62%) was obtained as a colorless oil after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.47 (silica, pentanes:ethyl acetate 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.79 (dq, *J* = 8.1, 1.7, 1.2 Hz, 2H, Ar*H*), 7.54 – 7.48 (m, 1H, Ar*H*), 7.44 (ddd, *J* = 8.1, 6.2, 1.3 Hz, 2H, Ar*H*), 7.08 (d, *J* = 9.0 Hz, 1H, N*H*), 4.65 – 4.47 (m, 1H, NC*H*), 3.72 (s, 3H, OCH_3), 3.50 – 3.39 (m, 2H, CH_2N$_3$), 2.79 – 2.65 (m, 2H, CH_2CO$_2$CH$_3$), 2.07 – 1.96 (m, 1H, CH_2CH$_2$N$_3$), 1.94 – 1.82 (m, 1H, CH_2CH$_2$N$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.4, 166.8, 134.1, 131.7, 128.6, 126.9, 51.9, 48.7, 44.3, 37.9, 33.3; **IR** (film): $\tilde{\nu}$ = 3309 (w), 2951 (m), 2098 (s), 1736 (s), 1638 (s), 1534 (s), 1307 (m), 1263 (m); **HRMS** (ESI) calcd. for $C_{13}H_{16}N_4NaO_3^+$ $[M+Na]^+$ 299.1115; Found 299.1114.

***N*-(1-Azidohex-5-en-3-yl)benzamide (377f)**

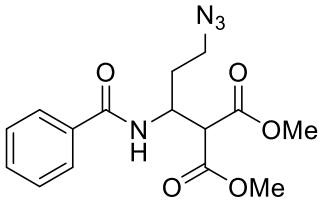


Following GP I, starting from *N*-cyclopropylbenzamide **296w** (32.2 mg, 0.200 mmol), after diazidation step is finished, allyltrimethylsilane (64.0 µL, 0.400 mmol, 2.0 equiv.) and $TiCl_4$ (55.0 µL, 0.500 mmol, 2.5 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 1 hour. *N*-(1-Azidohex-5-en-3-yl)benzamide **377f** (31.2 mg, 0. 128 mmol, 64%) was

obtained as a grey solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.39 (silica, pentanes:ethyl acetate 3:1); **Mp:** 54-57 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.80 – 7.69 (m, 2H, Ar*H*), 7.53 – 7.47 (m, 1H, Ar*H*), 7.46 – 7.38 (m, 2H, Ar*H*), 6.15 (d, *J* = 8.7 Hz, 1H, N*H*), 5.82 (ddt, *J* = 16.5, 10.8, 7.1 Hz, 1H, vinylC*H*), 5.21 – 5.09 (m, 2H, vinylCH_2), 4.31 (ttd, *J* = 8.8, 6.4, 4.5 Hz, 1H, NC*H*), 3.51 – 3.35 (m, 2H, CH_2N_3), 2.47 – 2.30 (m, 2H, allylic CH_2), 1.93 (dtd, *J* = 14.2, 7.5, 4.5 Hz, 1H, C$H_2CH_2N_3$), 1.79 (dddd, *J* = 14.4, 8.9, 7.1, 6.0 Hz, 1H, C$H_2CH_2N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.1, 134.5, 133.7, 131.5, 128.6, 126.8, 118.6, 48.7, 47.1, 39.1, 33.6; **IR** (film): $\tilde{\nu}$ = 3293 (w), 2930 (w), 2094 (s), 1633 (s), 1536 (s), 1305 (m), 917 (w); **HRMS** (ESI) calcd. for $C_{13}H_{17}N_4O^+$ $[M+H]^+$ 245.1397 Found 245.1394.

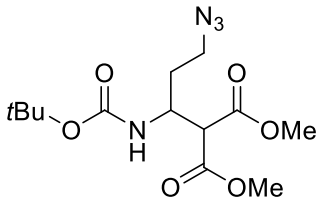
Dimethyl 2-(3-azido-1-benzamidopropyl)malonate (**377ga**)



Following GP I, starting from *N*-cyclopropylbenzamide **296w** (32.2 mg, 0.200 mmol), after diazidation step is finished, a solution of dimethyl malonate (46.0 μL, 0.400 mmol, 2.0 equiv.) and sodium hydride 60% dispersion mineral oil (16.0 mg, 0.400 mmol, 2.0 equiv.) in THF (0.5 mL) was added dropwise to the crude. The reaction mixture was stirred at room temperature for 10 minutes. Dimethyl 2-(3-azido-1-benzamidopropyl)malonate **377ga** (51.2 mg, 0.153 mmol, 77%) was obtained as a grey solid after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

R_f: 0.45 (silica, pentanes:ethyl acetate 1:1); **Mp:** 57-59 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 – 7.73 (m, 2H, Ar*H*), 7.54 – 7.48 (m, 1H, Ar*H*), 7.46 – 7.41 (m, 2H, Ar*H*), 7.33 (d, *J* = 9.5 Hz, 1H, N*H*), 4.90 (tdd, *J* = 9.6, 4.7, 3.8 Hz, 1H, NC*H*), 3.82 (s, 3H, OCH_3), 3.79 (d, *J* = 3.8 Hz, 1H, C*H*), 3.71 (s, 3H, OCH_3), 3.44 (dd, *J* = 7.5, 6.2 Hz, 2H, CH_2N_3), 2.06 – 1.82 (m, 2H, C$H_2CH_3N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.1, 167.8, 167.0, 133.9, 131.7, 128.6, 127.0, 54.3, 53.0, 52.8, 48.5, 47.0, 32.8; **IR** (film): $\tilde{\nu}$ = 3306 (m), 2954 (m), 2096 (s), 1732 (s), 1642 (s), 1523 (s), 1257 (s), 1158 (s), 712 (m); **HRMS** (ESI) calcd. for $C_{15}H_{18}N_4NaO_5^+$ $[M+Na]^+$ 357.1169; Found 357.1179.

Dimethyl 2-(3-azido-1-((*tert*-butoxycarbonyl)amino)propyl)malonate (**377gb**)

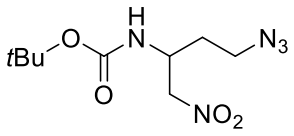


Following GP I, starting from *tert*-butyl cyclopropylcarbamate **296o** (31.4 mg, 0.200 mmol), after diazidation step is finished, a solution of dimethyl malonate (46.0 μL, 0.400 mmol, 2.0 equiv.) and sodium hydride 60% dispersion mineral oil (16.0 mg, 0.400 mmol, 2.0 equiv.) in THF (0.5 mL) was added dropwise to the crude. The reaction mixture was stirred at room temperature for 10 minutes. Dimethyl 2-(3-azido-1-((*tert*-butoxycarbonyl)amino)propyl)malonate **377gb** (42.5 mg, 0.129 mmol, 64%) was obtained as a white solid after purification by column chromatography on silica using 5:1 pentanes:ethyl acetate as eluent.

R_f: 0.30 (silica, pentanes:ethyl acetate 5:1); **Mp:** 78-81 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.37 (d, *J* = 10.0 Hz, 1H, N*H*), 4.34 (td, *J* = 9.8, 4.8 Hz, 1H, NC*H*), 3.77 (d, *J* = 1.4 Hz, 3H, OCH_3), 3.73 (d, *J* = 1.5 Hz, 3H, OCH_3), 3.66 (d, *J* = 4.2 Hz, 1H, C*H*), 3.48 – 3.30 (m, 2H, CH_2N_3), 1.82 (dtd, *J* = 19.4, 7.3, 3.5 Hz, 2H, C$H_2CH_3N_3$), 1.42 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.5, 167.9, 155.3, 79.8, 54.8, 52.8,

52.6, 48.5, 47.9, 32.6, 28.2; **IR** (film): $\tilde{\nu}$ = 3376 (w), 2955 (m), 2097 (s), 1734 (s), 1713 (s), 1500 (m), 1242 (s), 1161 (s); **HRMS** (ESI) calcd. for $C_{13}H_{22}N_4NaO_6^+$ $[M+Na]^+$ 353.1432; Found 353.1432.

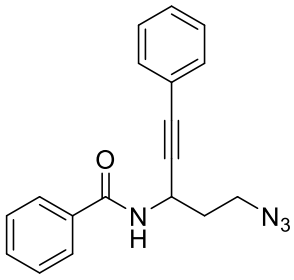
***tert*-Butyl (4-azido-1-nitrobutan-2-yl)carbamate** (**377h**)



Following GP I, starting from *tert*-butyl cyclopropylcarbamate **296o** (31.4 mg, 0.200 mmol), after diazidation step is finished, CH_3NO_2 (22.0 µL, 0.400 mmol, 2.0 equiv.) was added to the crude followed by the addition of KO*t*Bu 1.0M in *t*BuOH (0.40 mL, 0.40 mmol, 2.0 equiv.). The reaction mixture was stirred at room temperature for 1 hour. *tert*-Butyl (4-azido-1-nitrobutan-2-yl)carbamate **377h** (28.0 mg, 0.108 mmol, 54%) was obtained as a white solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.45 (silica, pentanes:ethyl acetate 3:1); **Mp:** 49-53 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 4.97 (d, *J* = 8.7 Hz, 1H, N*H*), 4.63 (dd, *J* = 13.0, 5.7 Hz, 1H, NO_2CH_2), 4.56 (dd, *J* = 13.1, 4.4 Hz, 1H, NO_2CH_2), 4.24 (tt, *J* = 9.5, 4.7 Hz, 1H, NC*H*), 3.47 (dtt, *J* = 17.9, 12.9, 6.9 Hz, 2H, CH_2N_3), 1.97 – 1.78 (m, 2H, $CH_2CH_3N_3$), 1.44 (s, 9H, $C(CH_3)_3$); **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 154.9, 80.6, 77.9, 48.0, 47.0, 30.8, 28.2; **IR** (film): $\tilde{\nu}$ = 3339 (w), 2979 (w), 2100 (s), 1692 (s), 1554 (s), 1367 (s), 1165 (s), 1062 (w); **HRMS** (ESI) calcd. for $C_9H_{17}N_5NaO_4^+$ $[M+Na]^+$ 282.1173; Found 282.1176.

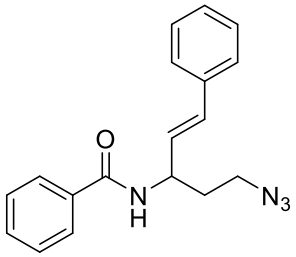
***N*-(5-Azido-1-phenylpent-1-yn-3-yl)benzamide** (**377i**)



Following GP I, starting from *N*-cyclopropylbenzamide **296w** (32.2 mg, 0.200 mmol), after diazidation step is finished, potassium phenylethynyltrifluoroborate (83.2 mg, 0.400 mmol, 2.0 equiv.) and boron trifluoride etherate (100 µL, 0.800 mmol, 4.0 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 2 hours. *N*-(5-Azido-1-phenylpent-1-yn-3-yl)benzamide **377i** (28.8 mg, 0. 095 mmol, 48%) was obtained as a yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.43 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.84 – 7.79 (m, 2H, Ar*H*), 7.55 – 7.51 (m, 1H, Ar*H*), 7.48 – 7.42 (m, 4H, Ar*H*), 7.35 – 7.29 (m, 3H, Ar*H*), 6.60 (d, *J* = 8.2 Hz, 1H, N*H*), 5.37 (dt, *J* = 8.2, 6.3 Hz, 1H, NC*H*), 3.72 – 3.66 (m, 1H, CH_2N_3), 3.60 (dt, *J* = 12.6, 6.4 Hz, 1H, CH_2N_3), 2.23 – 2.07 (m, 2H, $CH_2CH_2N_3$); **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 166.3, 133.7, 131.9, 131.8, 128.7, 128.7, 128.3, 127.0, 122.1, 86.6, 84.5, 48.4, 40.7, 34.7; **IR** (film): $\tilde{\nu}$ = 3293 (m), 3060 (w), 2927 (w), 2096 (s), 1637 (s), 1527 (s), 1443 (m), 1279 (m); **HRMS** (ESI) calcd. for $C_{18}H_{16}N_4NaO^+$ $[M+Na]^+$ 327.1216; Found 327.1222.

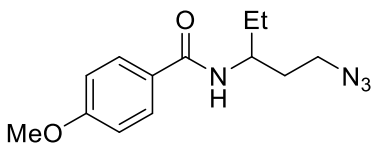
(*E*)-*N*-(5-Azido-1-phenylpent-1-en-3-yl)benzamide (377j)



Following GP I, starting from *N*-cyclopropylbenzamide **296w** (32.2 mg, 0.200 mmol), after diazidation step is finished, potassium trans-styryltrifluoroborate (73.6 mg, 0.400 mmol, 2.0 equiv.) and boron trifluoride etherate (100 µL, 0.800 mmol, 4.0 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 1 hour. (E)-*N*-(5-Azido-1-phenylpent-1-en-3-yl)benzamide **377j** (30.8 mg, 0.100 mmol, 50%) was obtained as a yellow gel after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.37 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.84 – 7.77 (m, 2H, Ar*H*), 7.55 – 7.49 (m, 1H, Ar*H*), 7.48 – 7.41 (m, 2H, Ar*H*), 7.39 – 7.34 (m, 2H, Ar*H*), 7.34 – 7.28 (m, 2H, Ar*H*), 7.27 – 7.24 (m, 1H, Ar*H*), 6.62 (dd, *J* = 15.9, 1.3 Hz, 1H, vinylC*H*), 6.47 (d, *J* = 8.3 Hz, 1H, N*H*), 6.20 (dd, *J* = 15.9, 6.5 Hz, 1H, vinylC*H*), 4.97 (dqd, *J* = 8.0, 6.5, 1.4 Hz, 1H, NLC*H*), 3.59 – 3.41 (m, 2H, CH_2N$_3$), 2.04 (qd, *J* = 6.8, 3.0 Hz, 2H, CH_2CH$_2$N$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.7, 136.2, 134.3, 131.7, 131.6, 128.6, 128.6, 128.1, 127.9, 126.9, 126.5, 49.7, 48.5, 34.1; **IR** (film): $\tilde{\nu}$ = 3301 (w), 3027 (w), 2929 (w), 2096 (s), 1634 (s), 1532 (s), 1304 (m), 966 (m); **HRMS** (ESI) calcd. for $C_{18}H_{18}N_4NaO^+$ $[M+Na]^+$ 329.1373; Found 329.1372.

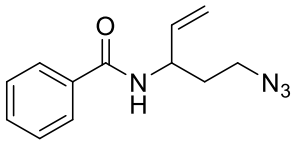
***N*-(1-Azidopentan-3-yl)-4-methoxybenzamide (377k)**



Following GP I, starting from *N*-cyclopropyl-4-methoxybenzamide **296a** (38.2 mg, 0.200 mmol), after diazidation step is finished, diethylzinc solution 1.0M in hexanes (0.30 mL, 0.30 mmol, 1.5 equiv.) was added to the crude. The reaction mixture was stirred at room temperature for 30 minutes. *N*-(1-Azidopentan-3-yl)-4-methoxybenzamide **377k** (44.6 mg, 0.170 mmol, 85%) was obtained as a beige solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.33 (silica, pentanes:ethyl acetate 2:1); **Mp:** 73-76 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 – 7.68 (m, 2H, Ar*H*), 6.96 – 6.86 (m, 2H, Ar*H*), 6.03 (d, *J* = 9.0 Hz, 1H, N*H*), 4.17 – 4.09 (m, 1H, C*H*), 3.84 (s, 3H, OCH_3), 3.41 (tt, *J* = 12.3, 7.0 Hz, 2H, CH_2N$_3$), 1.90 (dtd, *J* = 14.1, 7.6, 4.2 Hz, 1H, CH_2CH$_2$N$_3$), 1.73 (dddd, *J* = 14.3, 8.9, 7.2, 5.8 Hz, 1H, CH_2CH$_2$N$_3$), 1.59 (ddt, *J* = 28.8, 13.8, 7.5 Hz, 2H, CH_2CH$_3$), 0.96 (t, *J* = 7.4 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.8, 162.1, 128.6, 126.8, 113.7, 55.4, 49.1, 48.7, 33.9, 28.0, 10.4; **IR** (film): $\tilde{\nu}$ = 3305 (m), 2964 (m), 2933 (m), 2096 (s), 1629 (s), 1506 (s), 1255 (s), 1029 (m), 841 (m); **HRMS** (ESI) calcd. for $C_{13}H_{18}N_4NaO_2^+$ $[M+Na]^+$ 285.1322; Found 285.1317.

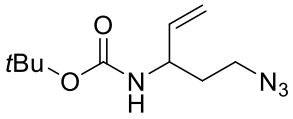
***N*-(5-Azidopent-1-en-3-yl)benzamide (377la)**



Following GP I, starting from *N*-cyclopropylbenzamide **296w** (32.2 mg, 0.200 mmol), after diazidation step is finished, vinylmagnesium bromide solution 1.0 M in THF (0.30 mL, 0.30 mmol, 1.5 equiv.) was added to the crude. The reaction mixture was stirred at room temperature for 30 minutes. *N*-(5-Azidopent-1-en-3-yl)benzamide **377la** (26.3 mg, 0.130 mmol, 57%) was obtained as a yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.32 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 – 7.76 (m, 2H, Ar*H*), 7.52 – 7.47 (m, 1H, Ar*H*), 7.44 – 7.39 (m, 2H, Ar*H*), 6.53 (d, *J* = 8.4 Hz, 1H, N*H*), 5.85 (ddd, *J* = 17.2, 10.4, 5.7 Hz, 1H, vinylC*H*), 5.32 – 5.15 (m, 2H, vinylCH_2), 4.79 (dddt, *J* = 14.6, 7.2, 5.6, 1.6 Hz, 1H, NC*H*), 3.44 (h, *J* = 5.7 Hz, 2H, CH_2N_3), 2.01 – 1.82 (m, 2H, C$H_2CH_2N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.8, 136.9, 134.2, 131.5, 128.5, 126.9, 116.0, 49.9, 48.4, 33.5; **IR** (film): $\tilde{\nu}$ = 3293 (w), 2929 (w), 2094 (s), 1632 (s), 1528 (s), 1290 (s), 921 (m); **HRMS** (ESI) calcd. for $C_{12}H_{15}N_2O^+$ $[M+H]^+$ 203.1179; Found 203.1192.

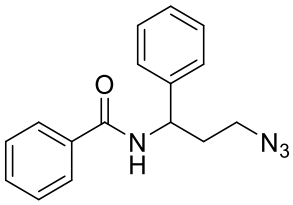
***tert*-Butyl (5-azidopent-1-en-3-yl)carbamate** (**377lb**)



Following GP I, starting from *tert*-butyl cyclopropylcarbamate **296o** (31.4 mg, 0.200 mmol), after diazidation step is finished, the crude was cooled down to -20 °C before vinylmagnesium bromide solution 1.0 M in THF (0.30 mL, 0.30 mmol, 1.5 equiv.) was added dropwise. The reaction mixture was stirred at -20 °C for 2 hours. *tert*-Butyl (5-azidopent-1-en-3-yl)carbamate **377lb** (20.0 mg, 0.088 mmol, 44%) was obtained as a colorless oil after purification by column chromatography on silica using 10:1 pentanes:ethyl acetate as eluent.

R_f: 0.33 (silica, pentanes:ethyl acetate 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.76 (ddd, *J* = 16.6, 10.4, 5.7 Hz, 1H, vinylC*H*), 5.26 – 5.09 (m, 2H, vinylCH_2), 4.55 (s, 1H, N*H*), 4.26 – 4.15 (m, 1H, NC*H*), 3.41 – 3.32 (m, 2H, CH_2N_3), 1.79 (dh, *J* = 28.8, 6.9 Hz, 2H, C$H_2CH_2N_3$), 1.45 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.2, 137.7, 115.4, 79.7, 50.7, 48.3, 34.1, 28.4; **IR** (film): $\tilde{\nu}$ = 3337 (w), 2978 (w), 2097 (s), 1690 (s), 1516 (s), 1366 (s), 1248 (s), 1168 (s); **HRMS** (ESI) calcd. for $C_{10}H_{18}N_4NaO_2^+$ $[M+Na]^+$ 249.1322; Found 249.1325.

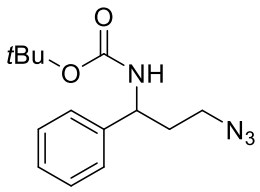
***N*-(3-Azido-1-phenylpropyl)benzamide** (**377ma**)



Following GP I, starting from *N*-cyclopropylbenzamide **296w** (32.2 mg, 0.200 mmol), after diazidation step is finished, phenylmagnesium bromide solution 3.0 M in diethyl ether (0.10 mL, 0.30 mmol, 1.5 equiv.) was added to the crude. The reaction mixture was stirred at room temperature for 30 minutes. *N*-(3-Azido-1-phenylpropyl)benzamide **377ma** (39.5 mg, 0.141 mmol, 71%) was obtained as a beige solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.45 (silica, pentanes:ethyl acetate 3:1); **Mp:** 84-86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 – 7.75 (m, 2H, Ar*H*), 7.53 – 7.48 (m, 1H, Ar*H*), 7.46 – 7.40 (m, 2H, Ar*H*), 7.37 (dtd, *J* = 7.5, 6.5, 1.6 Hz, 4H, Ar*H*), 7.33 – 7.27 (m, 1H, Ar*H*), 6.69 (d, *J* = 7.9 Hz, 1H, N*H*), 5.33 (td, *J* = 7.6, 6.2 Hz, 1H, NC*H*), 3.38 (t, *J* = 6.8 Hz, 2H, CH_2N_3), 2.29 – 2.09 (m, 2H, C$H_2CH_2N_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.7, 140.7, 134.2, 131.6, 129.0, 128.6, 127.8, 126.9, 126.5, 52.0, 48.6, 35.0; **IR** (film): $\tilde{\nu}$ = 3291 (w), 3061 (w), 2093 (s), 1633 (s), 1529 (s), 1292 (s), 696 (s); **HRMS** (ESI) calcd. for $C_{16}H_{16}N_4NaO^+$ $[M+Na]^+$ 303.1216; Found 303.1216.

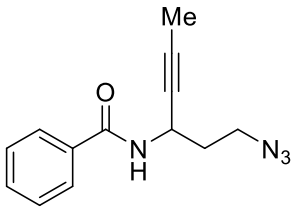
***tert*-Butyl (3-azido-1-phenylpropyl)carbamate (377mb)**



Following GP I, starting from *tert*-butyl cyclopropylcarbamate **296o** (31.4 mg, 0.200 mmol), after diazidation step is finished, the crude was cooled down to -20 °C before phenylmagnesium bromide solution 3.0 M in diethyl ether (0.10 mL, 0.30 mmol, 1.5 equiv.) was added dropwise. The reaction mixture was stirred at -20 °C for 2 hours. *tert*-Butyl (3-azido-1-phenylpropyl)carbamate **377mb** (24.5 mg, 89.0 µmol, 44%) was obtained as a white solid after purification by column chromatography on silica using 10:1 pentanes:ethyl acetate as eluent.

R_f: 0.36 (silica, pentanes:ethyl acetate 10:1); **MP:** 84-84.5 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.38 – 7.25 (m, 5H, Ar*H*), 5.01 – 4.83 (m, 1H, N*H*), 4.83 – 4.65 (m, 1H, NC*H*), 3.29 (tt, *J* = 9.8, 5.0 Hz, 2H, CH_2N$_3$), 2.13 – 1.88 (m, 2H, CH_2CH$_2$N$_3$), 1.42 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.1, 141.5, 128.8, 127.6, 126.3, 79.7, 52.7, 48.5, 35.8, 28.3; **IR** (film): $\tilde{\nu}$ = 3343 (w), 2977 (m), 2096 (s), 1696 (s), 1512 (m), 1167 (s), 700 (m); **HRMS** (ESI) calcd. for $C_{14}H_{20}N_4NaO_2^+$ $[M+Na]^+$ 299.1478; Found 299.1486.

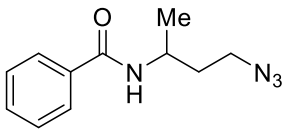
N-(1-Azidohex-4-yn-3-yl)benzamide (377n)



Following GP I, starting from *N*-cyclopropylbenzamide **296w** (32.2 mg, 0.200 mmol), after diazidation step is finished, 1-propynylmagnesium bromide solution 0.5 M in THF (0.60 mL, 0.30 mmol, 1.5 equiv.) was added to the crude. The reaction mixture was stirred at room temperature for 30 minutes. *N*-(1-Azidohex-4-yn-3-yl)benzamide **377n** (31.5 mg, 0.130 mmol, 65%) was obtained as a colorless oil after purification by column chromatography on silica using 4:1 pentanes:ethyl acetate as eluent.

R_f: 0.26 (silica, pentanes:ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 – 7.74 (m, 2H, Ar*H*), 7.52 – 7.47 (m, 1H, Ar*H*), 7.45 – 7.39 (m, 2H, Ar*H*), 6.57 (d, *J* = 8.0 Hz, 1H, N*H*), 5.04 (dddd, *J* = 10.3, 8.1, 5.9, 2.4 Hz, 1H, NC*H*), 3.63 – 3.43 (m, 2H, CH_2N$_3$), 2.09 – 1.93 (m, 2H, CH_2CH$_2$N$_3$), 1.83 (d, *J* = 2.3 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.3, 133.8, 131.7, 128.5, 127.0, 80.5, 76.8, 48.3, 40.3, 34.7, 3.5; **IR** (film): $\tilde{\nu}$ = 3292 (w), 2920 (w), 2092 (s), 1634 (s), 1523 (s), 1263 (s), 1155 (m); **HRMS** (ESI) calcd. for $C_{13}H_{14}N_4NaO^+$ $[M+Na]^+$ 265.1060; Found 265.1059.

N-(4-Azidobutan-2-yl)benzamide (377oa)

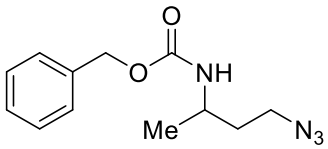


Following GP I, starting from *N*-cyclopropylbenzamide **296w** (32.2 mg, 0.200 mmol), after diazidation step is finished, methylmagnesium bromide solution 3.0 M in THF (0.10 mL, 0.30 mmol, 1.5 equiv.) was added to the crude. The reaction mixture was stirred at room temperature for 30 minutes. *N*-(4-Azidobutan-2-yl)benzamide **377oa** (22.6 mg, 0.104 mmol, 52%) was obtained as a pale yellow oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.29 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 – 7.72 (m, 2H, Ar*H*), 7.51 – 7.46 (m, 1H, Ar*H*), 7.43 – 7.38 (m, 2H, Ar*H*), 6.27 (d, *J* = 8.4 Hz, 1H, N*H*), 4.31 (tdd, *J* = 8.1, 6.7, 5.4 Hz, 1H, NC*H*), 3.49 – 3.36 (m, 2H, CH_2N$_3$), 1.89 – 1.77 (m, 2H, CH_2CH$_2$N$_3$), 1.28 (d, *J* = 6.7 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.9, 134.5, 131.4, 128.5, 126.8, 48.6, 43.9, 35.7, 20.8; **IR** (film):

$\tilde{\nu}$ = 3303 (w), 2971 (w), 2093 (s), 1633 (s), 1535 (s), 1289 (m), 694 (m); **HRMS** (ESI) calcd. for $C_{11}H_{14}N_4NaO^+$ $[M+Na]^+$ 241.1060; Found 241.1062.

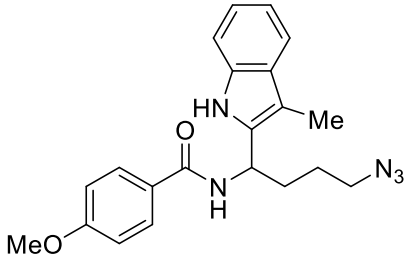
Benzyl (4-azidobutan-2-yl)carbamate (**377ob**)



Following GP I, starting from benzyl cyclopropylcarbamate **296p** (38.2 mg, 0.200 mmol), after diazidation step is finished, the crude was cooled down to -20 °C before methylmagnesium bromide solution 3.0 M in THF (0.10 mL, 0.30 mmol, 1.5 equiv.) was added drpwise. The reaction mixture was stirred at -20 °C for 2 hours. Benzyl (4-azidobutan-2-yl)carbamate **377ob** (23.0 mg, 93.0 µmol, 46%) was obtained as a colorless oil after purification by column chromatography on silica using 4:1 pentanes:ethyl acetate as eluent.

R_f: 0.45 (silica, pentanes:ethyl acetate 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.42 – 7.28 (m, 5H, Ar*H*), 5.09 (s, 2H, PhCH_2), 4.78 – 4.43 (m, 1H, N*H*), 3.85 (p, *J* = 7.1 Hz, 1H, NC*H*), 3.36 (t, *J* = 7.0 Hz, 2H, CH_2N_3), 1.71 (dq, *J* = 14.7, 7.0 Hz, 2H, C$H_2CH_2N_3$), 1.19 (d, *J* = 6.7 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.7, 136.4, 128.5, 128.1, 128.1, 66.7, 48.4, 45.1, 36.0, 21.1; **IR** (film): $\tilde{\nu}$ = 3326 (w), 2969 (m), 2096 (s), 1695 (s), 1529 (m), 1245 (s), 1072 (m); **HRMS** (ESI) calcd. for $C_{12}H_{16}N_4NaO_2^+$ $[M+Na]^+$ 271.1165; Found 271.1167.

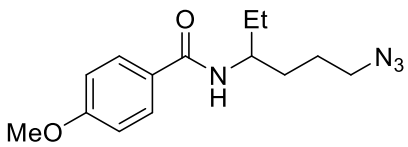
N-(4-Azido-1-(3-methyl-1H-indol-2-yl)butyl)-4-methoxybenzamide (**379a**)



Following GP I, starting from *N*-cyclobutyl-4-methoxybenzamide **342e** (41.0 mg, 0.200 mmol), after diazidation step is finished, 3-methylindole (39.4 mg, 0.300 mmol, 1.5 equiv.) and boron trifluoride etherate (25.0 µL, 0.200 mmol, 1.0 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 30 minutes. *N*-(4-Azido-1-(3-methyl-1H-indol-2-yl)butyl)-4-methoxybenzamide **379a** (51.4 mg, 0.136 mmol, 68%) was obtained as a beige solid after purification by column chromatography on silica using 3:2 pentanes:ethyl acetate as eluent.

R_f: 0.37 (silica, pentanes:ethyl acetate 3:2); **Mp:** 160-164 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.93 (s, 1H, indole N*H*), 7.72 – 7.67 (m, 2H, Ar*H*), 7.52 (dd, *J* = 7.8, 1.2 Hz, 1H, Ar*H*), 7.27 – 7.24 (m, 1H, Ar*H*), 7.15 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H, Ar*H*), 7.09 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, Ar*H*), 6.87 – 6.81 (m, 2H, Ar*H*), 6.79 (d, *J* = 7.5 Hz, 1H, N*H*), 5.22 (q, *J* = 7.8 Hz, 1H, C*H*), 3.80 (s, 3H, OCH_3), 3.29 (t, *J* = 6.6 Hz, 2H, CH_2N_3), 2.33 (s, 3H, CH_3), 2.29 – 2.13 (m, 2H, CH_2), 1.71 – 1.55 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.3, 162.4, 135.4, 133.6, 128.8, 128.7, 126.3, 122.1, 119.2, 118.7, 113.8, 110.9, 108.2, 55.4, 51.1, 47.6, 31.6, 26.0, 8.8; **IR** (film): $\tilde{\nu}$ = 3316 (m), 2938 (w), 2102 (s), 1616 (s), 1500 (s), 1261 (s), 1029 (w); **HRMS** (ESI) calcd. for $C_{21}H_{23}N_5NaO_2^+$ $[M+Na]^+$ 400.1744; Found 400.1745.

N-(6-Azidohexan-3-yl)-4-methoxybenzamide (**379b**)

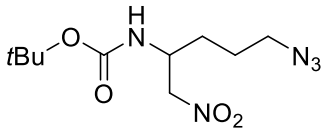


Following GP I, starting from *N*-cyclobutyl-4-methoxybenzamide **342e** (41.0 mg, 0.200 mmol), after diazidation step is finished, diethylzinc solution 1.0 M in hexanes (0.30 mL, 0.30 mmol, 1.5 equiv.) was added to the crude. The reaction mixture was stirred at room temperature for 30 minutes. *N*-(6-Azidohexan-3-yl)-4-

methoxybenzamide **379b** (43.3 mg, 0.157 mmol, 78%) was obtained as a white solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.28 (silica, pentanes:ethyl acetate 2:1); **Mp:** 55-58 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.75 – 7.69 (m, 2H, Ar*H*), 6.94 – 6.91 (m, 2H, Ar*H*), 5.88 – 5.65 (m, 1H, N*H*), 4.08 (qd, *J* = 9.0, 4.5 Hz, 1H, C*H*), 3.85 (s, 3H, OCH_3), 3.33 (td, *J* = 6.3, 3.8 Hz, 2H, CH_2N$_3$), 1.68 (qtd, *J* = 15.2, 7.6, 3.3 Hz, 4H, CH_2), 1.55 – 1.46 (m, 2H, CH_2), 0.97 (t, *J* = 7.4 Hz, 3H, CH_3); **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 166.8, 162.1, 128.5, 126.9, 113.7, 55.4, 51.3, 50.4, 32.2, 28.4, 25.5, 10.4; **IR** (film): $\tilde{\nu}$ = 3307 (w), 2961 (w), 2933 (w), 2093 (s), 1627 (s), 1505 (s), 1250 (s), 1030 (m), 844 (m); **HRMS** (ESI) calcd. for $C_{14}H_{20}N_4NaO_2^+$ $[M+Na]^+$ 299.1478; Found 299.1480.

***tert*-Butyl (5-azido-1-nitropentan-2-yl)carbamate** (**379c**)



Following GP I, starting from *tert*-butyl cyclobutylcarbamate **342h** (34.2 mg, 0.200 mmol), after diazidation step is finished, CH_3NO_2 (22.0 μL, 0.400 mmol, 2.0 equiv.) was added to the crude followed by the addition of KO*t*Bu 1.0 M in *t*BuOH (0.40 mL, 0.40 mmol, 2.0 equiv.). The reaction mixture was stirred at room temperature for 1 hour. *tert*-Butyl (5-azido-1-nitropentan-2-yl)carbamate **379c** (19.0 mg, 0.070 mmol, 35%) was obtained as a colorless oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

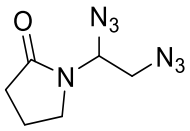
R_f: 0.33 (silica, pentanes:ethyl acetate 6:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.88 (d, *J* = 8.9 Hz, 1H, N*H*), 4.61 – 4.38 (m, 2H, NO_2CH_2), 4.13 (td, *J* = 8.3, 4.0 Hz, 1H, NC*H*), 3.45 – 3.19 (m, 2H, CH_2N$_3$), 1.67 (ddt, *J* = 9.3, 7.2, 3.5 Hz, 4H, CH_2), 1.44 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.0, 80.4, 78.3, 50.7, 48.7, 29.0, 28.2, 25.4; **IR** (film): $\tilde{\nu}$ = 3667 (w), 3340 (m), 2973 (s), 2098 (s), 1697 (s), 1550 (s), 1373 (s), 1253 (s), 1064 (s); **HRMS** (ESI) calcd. for $C_{10}H_{19}N_5NaO_4^+$ $[M+Na]^+$ 296.1329; Found 296.1332.

Diazidation-nucleophilic substitution of enamides

General Procedure J (GP J):

In a 12*75 mm Borosilicate glass tube, the corresponding enamide **381a** or enecarbamate **381b** (0.200 mmol, 1.0 equiv.), (Diacetoxyiodo)benzene (83.7 mg, 0.260 mmol, 1.3 equiv.) and CuTc (0.8 mg, 0.004 mmol, 0.02 equiv.) were measured on analytical balance. The tube was then closed with a rubber septum and sealed off with parafilm. Evacuate-refill cycle three times with nitrogen were performed to remove O_2 and extra-dry acetonitrile (2.0 mL, 0.1 M) was added under nitrogen atmosphere, followed by the addition of $TMSN_3$ (94% purity purchased from TCI, 62.0 μL, 0.440 mmol, 2.2 equiv.). The reaction mixture was stirred at room temperature for 10 minutes. Upon completion, the mixture was quenched by the addition of water (10 mL). The aqueous layer was then extracted with dichloromethane (10 mL x 3). The organic extract was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, pentanes/EtOAc).

1-(1,2-Diazidoethyl)pyrrolidin-2-one (**382a**)

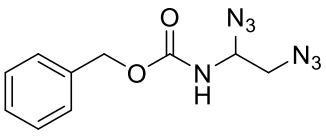


Following GP J, starting from 1-vinylpyrrolidin-2-one **381a** (22.2 mg, 0.200 mmol), 1-(1,2-diazidoethyl)pyrrolidin-2-one **382a** (36.9 mg, 0.189 mmol, 95%) was obtained as a colorless oil after purification by column chromatography on silica using 1:1 pentanes:ethyl acetate as eluent.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (t, *J* = 6.6 Hz, 1H, NC*H*), 3.55 – 3.46 (m, 1H, NCH_2), 3.46 – 3.29 (m, 3H, NCH_2 + N_3CH_2), 2.69 – 2.34 (m, 2H, C(O)CH_2), 2.34 – 1.89 (m, 2H, CH_2).

^{1}H NMR data correspond to the reported values.[246]

Benzyl (1,2-diazidoethyl)carbamate (**382b**)



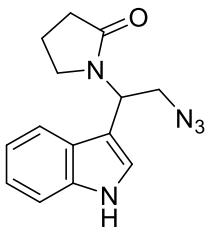
Following GP J, starting from benzyl vinylcarbamate **381b** (35.4 mg, 0.200 mmol), benzyl (1,2-diazidoethyl)carbamate **382b** (43.5 mg, 0.167 mmol, 83%) was obtained as a colorless oil after purification by column chromatography on silica using 6:1 pentanes:ethyl acetate as eluent.

R_f: 0.42 (silica, pentanes:ethyl acetate 6:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.45 – 7.29 (m, 5H, Ar*H*), 5.74 (d, *J* = 9.7 Hz, 1H, N*H*), 5.47 (dt, *J* = 9.7, 4.2 Hz, 1H, NC*H*), 5.17 (s, 2H, benzylic CH_2), 3.47 (dd, *J* = 12.7, 4.0 Hz, 1H, CH_2N_3), 3.33 (dd, *J* = 12.7, 4.5 Hz, 1H, CH_2N_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.4, 135.4, 128.6, 128.5, 128.2, 67.7, 67.2, 53.6; **IR** (film): $\tilde{\nu}$ = 3310 (w), 2097 (s), 1698 (s), 1508 (m), 1213 (s), 1045 (m); **HRMS** (ESI) calcd. for $C_{10}H_{11}N_7NaO_2^+$ $[M+Na]^+$ 284.0866; Found 284.0867.

General Procedure K (GP K):

In a 12*75 mm Borosilicate glass tube, the corresponding enamide **381a** or enecarbamate **381b** (0.200 mmol, 1.0 equiv.), (Diacetoxyiodo)benzene (83.7 mg, 0.260 mmol, 1.3 equiv.) and CuTc (0.8 mg, 0.004 mmol, 0.02 equiv.) were measured on analytical balance. The tube was then closed with a rubber septum and sealed off with parafilm. Evacuate-refill cycle three times with nitrogen were performed to remove O_2 and extra-dry acetonitrile (2.0 mL, 0.1 M) was added under nitrogen atmosphere, followed by the addition of $TMSN_3$ (94% purity purchased from TCI, 62.0 μL, 0.440 mmol, 2.2 equiv.). The reaction mixture was stirred at room temperature for 10 minutes before nucleophile (and if needed the Lewis acid/base) was added. The nucleophilc substitution step was not sensitive to air and nucleophile can be added directly by injection if it is in liquid state or by removing the cap and adding from the top if it is in solid state. The progress of the reaction was monitored by TLC. Upon completion, the mixture was quenched by the addition of water (10 mL). The aqueous layer was then extracted with dichloromethane (10 mL x 3). The organic extract was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, pentanes/EtOAc).

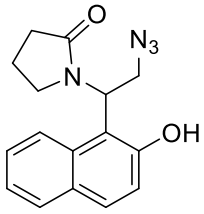
1-(2-Azido-1-(1*H*-indol-3-yl)ethyl)pyrrolidin-2-one (**383a**)



Following GP K, starting from 1-vinyl-2-pyrrolidinone **381a** (22.2 mg, 0.200 mmol), after diazidation step is finished, indole (35.1 mg, 0.300 mmol, 1.5 equiv.) and boron trifluoride etherate (50.0 µL, 0.400 mmol, 2.0 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 16 hours. 1-(2-Azido-1-(1*H*-indol-3-yl)ethyl)pyrrolidin-2-one **383a** (44.9 mg, 0.167 mmol, 83%) was obtained as a dark red solid after purification by column chromatography on silica using ethyl acetate as eluent.

R_f: 0.44 (silica, ethyl acetate); **Mp:** 113-117 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.84 (s, 1H, indole N*H*), 7.60 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.40 (dt, *J* = 8.2, 0.9 Hz, 1H, Ar*H*), 7.22 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, Ar*H*), 7.16 (dd, *J* = 2.6, 0.9 Hz, 1H, Ar*H*), 7.11 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar*H*), 5.81 (ddd, *J* = 8.9, 5.2, 0.9 Hz, 1H, NC*H*), 3.89 (dd, *J* = 12.5, 8.9 Hz, 1H, NCH_2), 3.79 (dd, *J* = 12.5, 5.3 Hz, 1H, NCH_2), 3.32 (ddd, *J* = 9.6, 8.4, 5.4 Hz, 1H, N_3CH_2), 2.98 (ddd, *J* = 9.6, 8.5, 5.9 Hz, 1H, N_3CH_2), 2.56 – 2.36 (m, 2H, C(O)CH_2), 2.04 – 1.90 (m, 1H, CH_2), 1.84 (dddd, *J* = 16.0, 9.5, 4.9, 3.3 Hz, 1H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 175.5, 136.1, 126.2, 122.7, 122.3, 120.1, 119.0, 111.4, 111.2, 51.1, 47.2, 43.4, 31.4, 17.8; **IR** (film): $\tilde{\nu}$ = 3254 (w), 2095 (s), 1658 (s), 1421 (m), 1285 (m), 743 (m); **HRMS** (ESI) calcd. for $C_{14}H_{16}N_5O^+$ $[M+H]^+$ 270.1349; Found 270.1358.

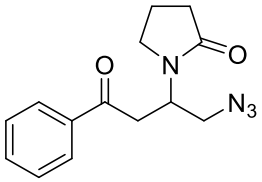
1-(2-Azido-1-(2-hydroxynaphthalen-1-yl)ethyl)pyrrolidin-2-one (**383b**)



Following GP K, starting from 1-vinyl-2-pyrrolidinone **381a** (22.2 mg, 0.200 mmol), after diazidation step is finished, 2-naphthol (57.6 mg, 0.400 mmol, 2.0 equiv.) and boron trifluoride etherate (50.0 µL, 0.400 mmol, 2.0 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 16 hours. 1-(2-Azido-1-(2-hydroxynaphthalen-1-yl)ethyl)pyrrolidin-2-one **383b** (44.8 mg, 0.151 mmol, 76%) was obtained as a white solid after purification by recrystallization in dichloromethane and pentanes.

R_f: 0.23 (silica, pentanes:ethyl acetate 1:1); **Mp:** 210-212 °C; **^{1}H NMR** (500 MHz, Methanol-d_4): δ = 8.13 (d, *J* = 8.7 Hz, 1H, Ar*H*), 7.74 (t, *J* = 7.9 Hz, 2H, Ar*H*), 7.44 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H, Ar*H*), 7.29 (ddd, *J* = 7.9, 6.7, 1.0 Hz, 1H, Ar*H*), 7.10 (d, *J* = 8.9 Hz, 1H, Ar*H*), 6.13 (dd, *J* = 9.1, 5.4 Hz, 1H, NC*H*), 4.41 (dd, *J* = 12.7, 9.2 Hz, 1H, N_3CH_2), 3.97 (dd, *J* = 12.7, 5.3 Hz, 1H, N_3CH_2), 3.75 (ddd, *J* = 10.3, 8.5, 5.4 Hz, 1H, NCH_2), 3.16 (ddd, *J* = 10.3, 8.5, 6.0 Hz, 1H, NCH_2), 2.42 (ddd, *J* = 17.1, 9.6, 6.3 Hz, 1H, CH_2), 2.35 – 2.27 (m, 1H, CH_2), 2.00 (dddd, *J* = 15.4, 12.7, 5.9, 4.3 Hz, 1H, C(O)CH_2), 1.90 – 1.82 (m, 1H, C(O)CH_2); **^{13}C NMR** (126 MHz, Methanol-d_4): δ = 177.6, 156.2, 135.2, 131.9, 130.5, 129.7, 128.2, 124.1, 123.5, 119.3, 113.5, 52.8, 51.7, 45.4, 32.0, 18.9; **IR** (film): $\tilde{\nu}$ = 3064 (w), 2098 (s), 1646 (s), 1435 (m), 1243 (m), 818 (m); **HRMS** (ESI) calcd. for $C_{16}H_{16}N_4NaO_2^+$ $[M+Na]^+$ 319.1165; Found 319.1166.

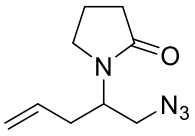
1-(1-Azido-4-oxo-4-phenylbutan-2-yl)pyrrolidin-2-one (**383c**)



Following GP K, starting from 1-vinyl-2-pyrrolidinone **381a** (22.2 mg, 0.200 mmol), after diazidation step is finished, trimethyl((1-phenylvinyl)oxy)silane (82.0 µL, 0.400 mmol, 2.0 equiv.) and TMSOTf (72.0 µL, 0.400 mmol, 2.0 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 16 hours. 1-(1-Azido-4-oxo-4-phenylbutan-2-yl)pyrrolidin-2-one **383c** (54.4 mg, 0.200 mmol, >99%) was obtained as a yellow solid after purification by column chromatography on silica using ethyl acetate as eluent.

R_f: 0.41 (silica, ethyl acetate); **Mp:** 40-42 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.98 – 7.84 (m, 2H, Ar*H*), 7.59 – 7.50 (m, 1H, Ar*H*), 7.44 (dd, *J* = 8.4, 7.0 Hz, 2H, Ar*H*), 4.38 (tt, *J* = 8.0, 5.4 Hz, 1H, NC*H*), 3.83 (dd, *J* = 12.4, 8.4 Hz, 1H, N_3CH_2), 3.62 (dd, *J* = 17.1, 7.7 Hz, 1H, PhC(O)CH_2), 3.58 – 3.52 (m, 1H, NCH_2), 3.52 – 3.41 (m, 2H, N_3CH_2 + NCH_2), 3.20 (dd, *J* = 17.2, 5.8 Hz, 1H, PhC(O)CH_2), 2.39 – 2.26 (m, 2H, C(O)CH_2), 2.03 – 1.95 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 197.0, 175.6, 136.3, 133.5, 128.7, 128.0, 51.9, 50.1, 47.5, 38.1, 31.5, 18.6; **IR** (film): $\tilde{\nu}$ = 2921 (w), 2099 (s), 1684 (s), 1285 (m), 757 (w); **HRMS** (ESI) calcd. for $C_{14}H_{17}N_4O_2^+$ $[M+H]^+$ 273.1346; Found 273.1348.

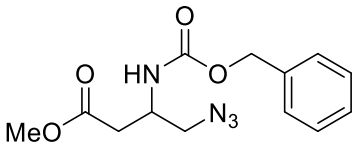
1-(1-Azidopent-4-en-2-yl)pyrrolidin-2-one (**383d**)



Following GP K, starting from 1-vinyl-2-pyrrolidinone **381a** (22.2 mg, 0.200 mmol), after diazidation step is finished, allyltrimethylsilane (63.0 µL, 0.400 mmol, 2.0 equiv.) and $TiCl_4$ (55.0 µL, 0.500 mmol, 2.5 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 16 hours. 1-(1-Azidopent-4-en-2-yl)pyrrolidin-2-one **383d** (26.4 mg, 0.136 mmol, 68%) was obtained as a yellow oil after purification by column chromatography on silica using pentanes:ethyl acetate 2:3 as eluent.

R_f: 0.25 (silica, pentanes:ethyl acetate 2:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.70 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, vinyl C*H*), 5.17 – 5.01 (m, 2H, vinyl CH_2), 4.28 (qd, *J* = 7.7, 4.6 Hz, 1H, NC*H*), 3.45 (dd, *J* = 12.7, 7.9 Hz, 1H, N_3CH_2), 3.41 – 3.29 (m, 3H, N_3CH_2 + NCH_2), 2.39 (ddd, *J* = 8.4, 7.0, 2.6 Hz, 2H, C(O)CH_2), 2.32 (ddt, *J* = 8.0, 6.9, 1.4 Hz, 2H, allyl CH_2), 2.07 – 1.92 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 175.5, 133.6, 118.0, 52.2, 50.6, 43.6, 34.0, 31.2, 18.4; **IR** (film): $\tilde{\nu}$ = 2976 (w), 2098 (s), 1681 (s), 1421 (m), 1284 (m), 920 (w); **HRMS** (ESI) calcd. for $C_9H_{14}N_4NaO^+$ $[M+Na]^+$ 217.1060; Found 217.1065.

Methyl 4-azido-3-(((benzyloxy)carbonyl)amino)butanoate (**383e**)

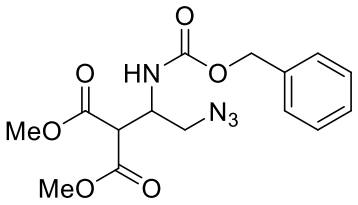


Following GP K, starting from benzyl vinylcarbamate **381b** (35.4 mg, 0.200 mmol), after diazidation step is finished, *tert*-butyl[(1-methoxyvinyl)oxy]dimethylsilane (132 µL, 0.600 mmol, 3.0 equiv.) was added to the crude. The reaction mixture was stirred at room temperature for 4 hours. Methyl 4-azido-3-(((benzyloxy)carbonyl) amino)butanoate **383e** (54.7 mg, 0.187 mmol, 94%) was obtained as a colorless oil after purification by column chromatography on silica using pentanes:ethyl acetate 3:1 as eluent.

R_f: 0.35 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.41 – 7.29 (m, 5H, Ar*H*), 5.42 (s, 1H, N*H*), 5.10 (s, 2H, benzylic CH_2), 4.17 (dt, *J* = 8.7, 5.5 Hz, 1H, NC*H*), 3.68 (s, 3H, OCH_3), 3.60 – 3.43 (m, 2H, N_3CH_2), 2.62 (dd, *J* = 6.0, 2.9 Hz, 2H, C(O)CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.2,

155.5, 136.1, 128.5, 128.2, 128.1, 66.9, 53.4, 51.9, 47.5, 35.8; **IR** (film): $\tilde{\nu}$ = 3329 (w), 2953 (w), 2098 (s), 1697 (s), 1522 (s), 1214 (s), 1050 (s), 737 (m); **HRMS** (ESI) calcd. for $C_{13}H_{16}N_4NaO_4^+$ $[M+Na]^+$ 315.1064; Found 315.1066.

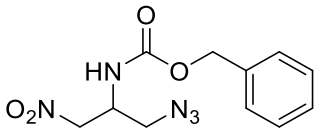
Dimethyl 2-(2-azido-1-(((benzyloxy)carbonyl)amino)ethyl)malonate (**383f**)



Following GP K, starting from benzyl vinylcarbamate **381b** (35.4 mg, 0.200 mmol), after diazidation step is finished, a solution of dimethyl malonate (46.0 µL, 0.400 mmol, 2.0 equiv.) and sodium hydride 60% dispersion mineral oil (16.0 mg, 0.400 mmol, 2.0 equiv.) in THF (0.5 mL) was added dropwise to the crude. The reaction mixture was stirred at room temperature for 10 minutes. Dimethyl 2-(2-azido-1-(((benzyloxy)carbonyl)amino)ethyl)malonate **383f** (69.4 mg, 0.198 mmol, 99%) was obtained as a colorless oil after purification by column chromatography on silica using pentanes:ethyl acetate 3:1 as eluent.

R_f: 0.30 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.41 – 7.28 (m, 5H, Ar*H*), 5.77 (d, *J* = 9.6 Hz, 1H, N*H*), 5.10 (s, 2H, benzylic CH_2), 4.52 – 4.42 (m, 1H, NC*H*), 3.77 (d, *J* = 4.9 Hz, 1H, C*H*), 3.76 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.63 (dd, *J* = 12.3, 5.9 Hz, 1H, N_3CH_2), 3.45 (dd, *J* = 12.4, 6.8 Hz, 1H, N_3CH_2); **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 168.1, 167.4, 155.6, 136.1, 128.5, 128.2, 128.0, 67.0, 53.0, 52.9, 52.5, 51.9, 50.1; **IR** (film): $\tilde{\nu}$ = 3361 (w), 2954 (w), 2101 (s), 1722 (s), 1506 (m), 1218 (s), 1059 (m); **HRMS** (ESI) calcd. for $C_{15}H_{18}N_4NaO_6^+$ $[M+Na]^+$ 373.1119; Found 373.1115.

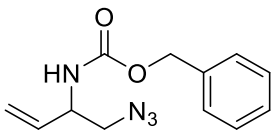
Benzyl (1-azido-3-nitropropan-2-yl)carbamate (**383g**)



Following GP K, starting from benzyl vinylcarbamate **381b** (35.4 mg, 0.200 mmol), after diazidation step is finished, CH_3NO_2 (22.0 µL, 0.400 mmol, 2.0 equiv.) was added to the crude followed by the addition of KO*t*Bu 1.0M in *t*BuOH (0.40 mL, 0.40 mmol, 2.0 equiv.). The reaction mixture was stirred at room temperature for 1 hour. Benzyl (1-azido-3-nitropropan-2-yl)carbamate **383g** (49.7 mg, 0.178 mmol, 89%) was obtained as a colorless oil after purification by column chromatography on silica using pentanes:ethyl acetate 3:1 as eluent.

R_f: 0.39 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.40 – 7.30 (m, 5H, Ar*H*), 5.36 (d, *J* = 8.5 Hz, 1H, N*H*), 5.12 (s, 2H, benzylic CH_2), 4.63 (dd, *J* = 13.3, 6.2 Hz, 1H, NO_2CH_2), 4.53 (dd, *J* = 13.3, 5.3 Hz, 1H, NO_2CH_2), 4.41 (dt, *J* = 8.8, 5.6 Hz, 1H, NC*H*), 3.67 (dd, *J* = 12.6, 5.0 Hz, 1H, N_3CH_2), 3.59 (dd, *J* = 12.6, 6.2 Hz, 1H, N_3CH_2); **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 155.3, 135.6, 128.6, 128.4, 128.2, 75.0, 67.5, 51.3, 48.7; **IR** (film): $\tilde{\nu}$ = 3310 (w), 2106 (s), 1698 (s), 1554 (s), 1259 (m), 1063 (w); **HRMS** (ESI) calcd. for $C_{11}H_{13}N_5NaO_4^+$ $[M+Na]^+$ 302.0860; Found 302.0865.

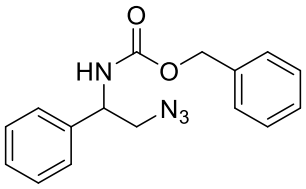
Benzyl (1-azidobut-3-en-2-yl)carbamate (**383h**)



Following GP K, starting from benzyl vinylcarbamate **381b** (35.4 mg, 0.200 mmol), after diazidation step is finished, the crude was cooled down to -20 °C before vinylmagnesium bromide solution 1.0 M in THF (0.30 mL, 0.30 mmol, 1.5 equiv.) was added dropwise. The reaction mixture was stirred at -20 °C for 2 hours. Benzyl (1-azidobut-3-en-2-yl)carbamate **383h** (25.2 mg, 0.102 mmol, 51%) was obtained as a colorless oil after purification by column chromatography on silica using pentanes:ethyl acetate 7:1 as eluent.

R_f: 0.33 (silica, pentanes:ethyl acetate 7:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.42 – 7.33 (m, 5H, Ar*H*), 5.82 (ddd, *J* = 17.3, 10.5, 5.5 Hz, 1H, vinyl C*H*), 5.34 – 5.20 (m, 2H, vinyl CH_2), 5.13 (s, 2H, PhCH_2), 5.08 – 4.79 (m, 1H, N*H*), 4.48 – 4.36 (m, 1H, NC*H*), 3.48 (qd, *J* = 12.5, 4.7 Hz, 2H, CH_2N_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.6, 136.1, 134.9, 128.5, 128.2, 128.1, 117.3, 67.0, 54.6, 52.7; **IR** (film): $\tilde{\nu}$ = 3328 (w), 2099 (s), 1699 (s), 1522 (m), 1241 (m); **HRMS** (ESI) calcd. for $C_{12}H_{14}N_4NaO_2^+$ $[M+Na]^+$ 269.1009; Found 269.1017.

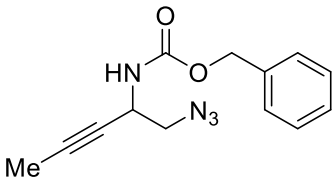
Benzyl (2-azido-1-phenylethyl)carbamate (**383i**)



Following GP K, starting from benzyl vinylcarbamate **381b** (35.4 mg, 0.200 mmol), after diazidation step is finished, the crude was cooled down to -20 °C before phenylmagnesium bromide solution 3.0 M in diethyl ether (0.10 mL, 0.30 mmol, 1.5 equiv.) was added dropwise. The reaction mixture was stirred at -20 °C for 2 hours. Benzyl (2-azido-1-phenylethyl)carbamate **383i** (35.2 mg, 0.119 mmol, 59%) was obtained as a colorless oil after purification by column chromatography on silica using pentanes:ethyl acetate 7:1 as eluent.

R_f: 0.34 (silica, pentanes:ethyl acetate 7:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.42 – 7.30 (m, 10H, Ar*H*), 5.41 (d, *J* = 8.0 Hz, 1H, N*H*), 5.12 (d, *J* = 5.4 Hz, 2H, PhCH_2), 5.02 – 4.83 (m, 1H, NC*H*), 3.65 (t, *J* = 5.8 Hz, 2H, CH_2N_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.6, 138.8, 136.1, 128.9, 128.5, 128.5, 128.2, 128.2, 126.5, 67.1, 55.5, 54.5; **IR** (film): $\tilde{\nu}$ = 3319 (w), 2097 (s), 1693 (s), 1523 (m), 1241 (s), 1043 (m); **HRMS** (ESI) calcd. for $C_{16}H_{16}N_4NaO_2^+$ $[M+Na]^+$ 319.1165; Found 319.1170.

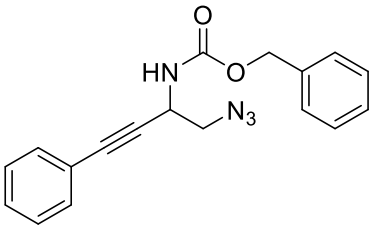
Benzyl (1-azidopent-3-yn-2-yl)carbamate (**383j**)



Following GP K, starting from benzyl vinylcarbamate **381b** (35.4 mg, 0.200 mmol), after diazidation step is finished, the crude was cooled down to -20 °C before 1-propynylmagnesium bromide solution 0.5 M in THF (0.60 mL, 0.30 mmol, 1.5 equiv.) was added dropwise. The reaction mixture was stirred at -20 °C for 2 hours. Benzyl (1-azidopent-3-yn-2-yl)carbamate **383j** (22.0 mg, 85.0 μmol, 43%) was obtained as a colorless oil after purification by column chromatography on silica using pentanes:ethyl acetate 7:1 as eluent.

R_f: 0.38 (silica, pentanes:ethyl acetate 7:1); **^{1}H NMR** (400 MHz, $CDCl_3$; a mixture of rotamers in a ratio of 1:1 was observed, which was partly resolved): δ = 7.40 – 7.30 (m, 5H, Ar*H*), 5.13 (t, *J* = 5.9 Hz, 3H, PhCH_2 + N*H*), 4.63 (s, 1H, NC*H*), 3.43 (t, *J* = 5.2 Hz, 2H, CH_2N_3), 1.83 (d, *J* = 2.3 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.2, 136.0, 128.5, 128.2, 128.1, 81.6, 75.3, 67.1, 55.1, 43.8, 3.5; **IR** (film): $\tilde{\nu}$ = 3327 (w), 2969 (m), 2099 (s), 1700 (s), 1508 (s), 1237 (s), 1051 (m); **HRMS** (ESI) calcd. for $C_{13}H_{14}N_4NaO_2^+$ $[M+Na]^+$ 281.1009; Found 281.1014.

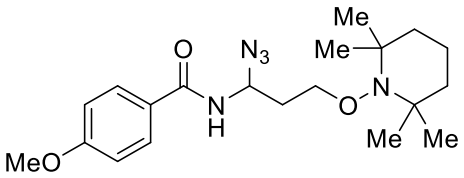
Benzyl (1-azido-4-phenylbut-3-yn-2-yl)carbamate (**383k**)



Following GP K, starting from benzyl vinylcarbamate **381b** (35.4 mg, 0.200 mmol), after diazidation step is finished, the crude was cooled down to -20 °C before 1-propynylmagnesium bromide solution 1.0 M in THF (0.30 mL, 0.30 mmol, 1.5 equiv.) was added dropwise. The reaction mixture was stirred at -20 °C for 2 hours. Benzyl (1-azido-4-phenylbut-3-yn-2-yl)carbamate **383k** (25.7 mg, 80.0 μmol, 40%) was obtained as a colorless oil after purification by column chromatography on silica using pentanes:ethyl acetate 7:1 as eluent.

R_f: 0.38 (silica, pentanes:ethyl acetate 7:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.47 – 7.29 (m, 10H, Ar*H*), 5.29 (d, *J* = 8.6 Hz, 1H, N*H*), 5.22 – 5.12 (m, 2H, PhCH_2), 4.94 (dd, *J* = 8.6, 4.6 Hz, 1H, NC*H*), 3.56 (qd, *J* = 12.2, 4.9 Hz, 2H, CH_2N_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.2, 135.9, 131.8, 128.8, 128.6, 128.3, 128.3, 128.2, 121.8, 85.0, 84.9, 67.3, 55.0, 44.4; **IR** (film): $\tilde{\nu}$ = 3321 (w), 2101 (s), 1702 (s), 1518 (m), 1239 (s), 1046 (m); **HRMS** (ESI) calcd. for $C_{18}H_{16}N_4NaO_2^+$ $[M+Na]^+$ 343.1165; Found 343.1165.

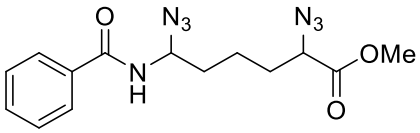
***N*-(1-Azido-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propyl)-4-methoxybenzamide** (**384**)



Following GP H, starting from *N*-cyclopropyl-4-methoxybenzamide **296a** (38.2 mg, 0.200 mmol), TEMPO (62.4 mg, 0.400 mmol, 2.0 equiv.) was added since the beginning. After stirring for 10 minutes, *N*-(1-azido-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propyl)-4-methoxy benzamide **384** (5.0 mg, 0.012 mmol, 6%) was obtained as a white solid after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.44 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.86 – 7.74 (m, 2H, Ar*H*), 7.51 (d, *J* = 8.5 Hz, 1H, N*H*), 6.98 – 6.88 (m, 2H, Ar*H*), 5.93 (ddd, *J* = 8.9, 5.6, 3.8 Hz, 1H, NC*H*), 4.21 (td, *J* = 9.9, 2.8 Hz, 1H, OCH_2), 3.91 – 3.87 (m, 1H, OCH_2), 3.86 (s, 3H, OCH_3), 2.04 (ddt, *J* = 14.1, 10.1, 3.9 Hz, 1H, CH_2CH$_2$O), 1.89 (dtd, *J* = 14.4, 5.2, 2.9 Hz, 1H, CH_2CH$_2$O), 1.57 – 1.45 (m, 6H, CH_2CH_2CH_2), 1.27 – 1.07 (m, 12H, 4 x CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.0, 162.6, 129.1, 125.6, 113.7, 72.7, 65.6, 59.9, 59.8, 55.4, 39.8, 39.6, 33.0, 33.0, 32.7, 20.8, 20.3, 17.0; **IR** (film): $\tilde{\nu}$ = 3308 (w), 2931 (m), 2105 (s), 1644 (m), 1606 (m), 1502 (s), 1256 (s), 1030 (m); **HRMS** (ESI) calcd. for $C_{20}H_{32}N_5O_3^+$ $[M+H]^+$ 390.2500; Found 390.2506.

Methyl 2,6-diazido-6-benzamidohexanoate (**385**)

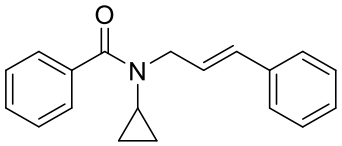


Following GP H, starting from *N*-cyclopropyl-benzamide **296w** (32.2 mg, 0.200 mmol), methyl acrylate (27.0 μL, 0.300 mmol, 1.5 equiv.) was added since the beginning. After stirring for 10 minutes, Methyl 2,6-diazido-6-benzamidohexanoate **385** (6.0 mg, 0.018 mmol, 9%) was obtained as a colorless oil after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.27 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$; mixture of two diastereoisomers in a 1:1 ratio: the signals corresponding to the two diastereoisomers are not resolved): δ = 7.81 (dt, *J* = 8.4,

1.3 Hz, 2H, Ar*H*), 7.60 – 7.53 (m, 1H, Ar*H*), 7.50 – 7.44 (m, 2H, Ar*H*), 6.59 – 6.40 (m, 1H, N*H*), 5.75 (dt, *J* = 9.1, 6.7 Hz, 1H, NC*H*), 3.90 (dd, *J* = 8.2, 5.2 Hz, 1H, N_3CH), 3.80 (d, *J* = 3.5 Hz, 3H, OCH_3), 1.95 – 1.71 (m, 4H, CH_2), 1.62 – 1.55 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$; mixture of two diastereoisomers in a 1:1 ratio: the signals corresponding to the two diastereoisomers are partially resolved): δ = 170.7, 167.4, 133.0, 132.3, 128.8, 127.1, 66.7, 66.7, 61.7, 52.7, 34.1, 30.6, 21.4; **IR** (film): $\tilde{\nu}$ = 3312 (w), 2954 (w), 2102 (s), 1741 (m), 1647 (m), 1523 (s), 1242 (m), 715 (m); **HRMS** (ESI) calcd. for $C_{14}H_{17}N_7NaO_3^+$ $[M+Na]^+$ 354.1285; Found 354.1282.

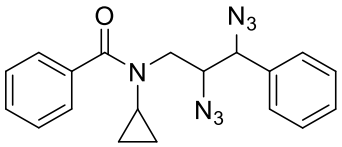
***N*-Cinnamyl-*N*-cyclopropylbenzamide (386)**



Following a modified version of a reported procedure,[47] to a solution of Cinnamyl bromide (709 mg, 3.60 mmol, 1.2 equiv.) and NaH (60% dispersion in mineral oil, 156 mg, 3.90 mmol, 1.3 equiv.) in THF (10 mL) was slowly added a solution of *N*-cyclopropyl-benzamide **296w** (483 mg, 3.00 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours. Upon completion, the mixture was quenched by addition of 1 N HCl (10 mL). The aqueous layer was then extracted with dichloromethane. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. *N*-Cinnamyl-*N*-cyclopropylbenzamide **386** was obtained as a yellow oil (773 mg, 2.79 mmol, 93%) after purification by column chromatography on silica using 3:1 pentanes:ethyl acetate as eluent.

R_f: 0.30 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.55 – 7.46 (m, 2H, Ar*H*), 7.44 – 7.36 (m, 5H, Ar*H*), 7.36 – 7.30 (m, 2H, Ar*H*), 7.28 – 7.25 (m, 1H, Ar*H*), 6.59 (d, *J* = 15.9 Hz, 1H, vinyl C*H*), 6.34 (s, 1H, vinyl C*H*), 4.30 (s, 2H, NCH_2), 2.80 (tt, *J* = 6.9, 4.0 Hz, 1H, C*H*), 0.57 (d, *J* = 34.6 Hz, 4H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.4, 137.3, 136.7, 132.6, 129.5, 128.6, 128.0, 127.7, 127.2, 126.4, 125.2, 49.8, 31.6, 9.7; **IR** (film): $\tilde{\nu}$ = 3025 (w), 1631 (s), 1402 (s), 1289 (m), 965 (m), 697 (s); **HRMS** (ESI) calcd. for $C_{19}H_{19}NNaO^+$ $[M+Na]^+$ 300.1359; Found 300.1372.

***N*-Cyclopropyl-*N*-(2,3-diazido-3-phenylpropyl)benzamide (387)**

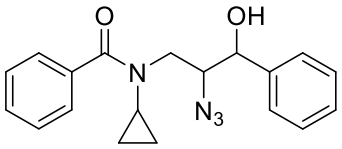


Following GP J, starting from *N*-Cinnamyl-*N*-cyclopropylbenzamide **386** (27.7 mg, 0.100 mmol), *N*-cyclopropyl-*N*-(2,3-diazido-3-phenylpropyl)benzamide **387** (39.2 mg, 0.092 mmol, 92%) was obtained as a colorless oil after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.59 (silica, pentanes:ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$; mixture of two diastereoisomers in a 1.2:1 ratio: the signals corresponding to the two diastereoisomers are partially resolved): δ = 7.57 – 7.30 (m, 10H, Ar*H*), 4.66 (d, *J* = 6.4 Hz, 1H, benzylic C*H* minor), 4.55 (d, *J* = 6.9 Hz, 1H, benzylic C*H* major), 4.25 (q, *J* = 8.9 Hz, 1H, N_3CH), 3.94 (d, *J* = 13.9 Hz, 1H, NCH_2 minor), 3.64 (d, *J* = 13.3 Hz, 1H, NCH_2 major), 3.39 (d, *J* = 9.9 Hz, 1H, NCH_2 major), 3.35 (d, *J* = 9.9 Hz, 1H, NCH_2 minor), 2.95 – 2.78 (m, 1H, C*H*), 0.74 – 0.49 (m, 2H, CH_2), 0.49 – 0.32 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$; mixture of two diastereoisomers in a 1.2:1 ratio: the signals corresponding to the two diastereoisomers are partially resolved): δ = 172.8, 136.8, 136.7, 135.6, 135.3, 129.8, 129.8, 129.2, 129.1, 129.1, 129.0, 128.0, 128.0, 127.6, 127.4, 127.2, 127.1, 68.0, 67.3, 64.2, 63.8, 50.5, 49.5, 33.5, 11.1, 10.3; **IR** (film): $\tilde{\nu}$ = 3062 (w), 2095

(s), 1631 (s), 1401 (m), 1248 (m), 699 (s); **HRMS** (ESI) calcd. for $C_{19}H_{20}N_7O^+$ $[M+H]^+$ 362.1724; Found 362.1722.

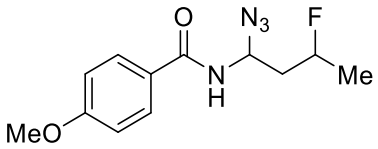
***N*-(2-azido-3-hydroxy-3-phenylpropyl)-*N*-cyclopropylbenzamide** (**388**)



Following GP H, starting from *N*-Cinnamyl-*N*-cyclopropylbenzamide **386** (27.7 mg, 0.100 mmol), N-cyclopropyl-N-(2,3-diazido-3-phenylpropyl)benzamide **387** (3.0 mg, 0.008 mmol, 8%) and *N*-(2-azido-3-hydroxy-3-phenylpropyl)-*N*-cyclopropylbenzamide **388** (5.0 mg, 0.014 mmol, 14%, d.r. 4:1, only the major diastereoisomer was fully characterized) was obtained as a white solid after purification by preparative TLC on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.27 (silica, pentanes:ethyl acetate 2:1); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.54 – 7.31 (m, 10H, Ar*H*), 4.68 (d, *J* = 5.9 Hz, 1H, OC*H*), 4.08 (ddd, *J* = 8.2, 5.9, 1.9 Hz, 1H, N_3C*H*), 4.04 – 3.84 (m, 1H, NCH_2), 3.55 (dd, *J* = 14.3, 1.9 Hz, 1H, NCH_2), 2.78 (tt, *J* = 7.1, 4.0 Hz, 1H, NC*H*), 0.60 – 0.11 (m, 4H, CH_2); **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 175.1, 136.3, 136.3, 130.0, 128.8, 128.5, 128.0, 127.4, 127.4, 75.7, 68.7, 52.5, 34.1, 10.4, 8.7; **IR** (film): $\tilde{\nu}$ = 3343 (w), 2924 (w), 2101 (s), 1614 (m), 1414 (m), 1287 (w), 700 (m); **HRMS** (ESI) calcd. for $C_{19}H_{21}N_4O_2^+$ $[M+H]^+$ 337.1659; Found 337.1668.

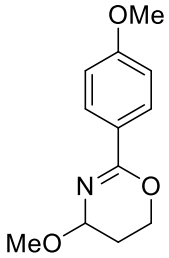
***N*-(1-Azido-3-fluorobutyl)-4-methoxybenzamide (389)**



Following modified GP H, starting from 4-methoxy-*N*-(trans-2-methylcyclopropyl)benzamide **342a** (41.0 mg, 0.200 mmol) with insufficient amount of CuTc catalyst, *N*-(1-Azido-3-fluorobutyl)-4-methoxybenzamide **389** can be observed, which co-eluted with diazidation product **375a** during purification by column chromatography. Therefore, no pure **389** was obtained, but its existence was confirmed by:

^{19}F NMR (376 MHz, $CDCl_3$): δ = -171.6, -174.0; **HRMS**: (ESI) calcd. for $C_{12}H_{15}FN_4NaO_2^+$ $[M+Na]^+$ 289.1071; Found 289.1072.

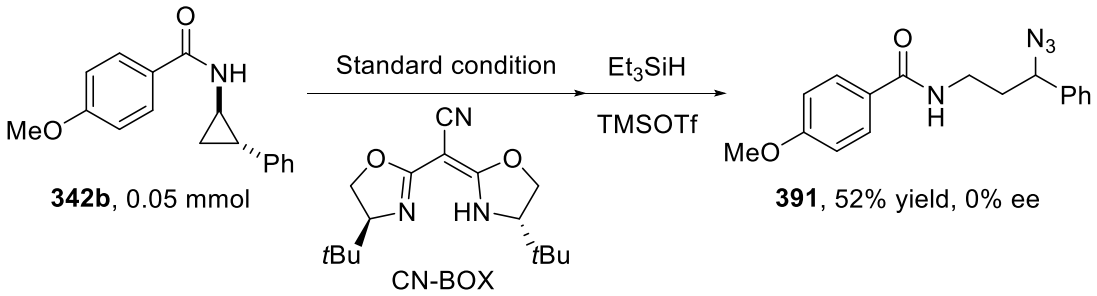
4-Methoxy-2-(4-methoxyphenyl)-5,6-dihydro-4H-1,3-oxazine (390)



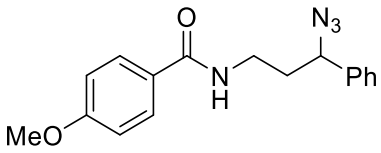
Following GP H, starting from *N*-cyclopropyl-4-methoxybenzamide **296a** (19.1 mg, 0.100 mmol), MeOH (8.0 µL, 0.20 mmol, 2.0 equiv.) was added since the beginning. After stirring for 1 hour, 4-methoxy-2-(4-methoxyphenyl)-5,6-dihydro-4H-1,3-oxazine **390** (6.0 mg, 0.027 mmol, 27%) was obtained as a colorless oil after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.59 (silica, pentanes:ethyl acetate 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$): 7.96 – 7.86 (m, 2H, Ar*H*), 6.93 – 6.83 (m, 2H, Ar*H*), 4.75 (dd, *J* = 7.8, 4.3 Hz, 1H, NC*H*), 4.41 (dt, *J* = 11.1, 4.7 Hz, 1H, OCH_2), 4.28 (td, *J* = 10.8, 3.5 Hz, 1H, OCH_2), 3.83 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 2.15 (dtd, *J* = 13.5, 4.6, 3.5 Hz, 1H, CH_2), 1.97 – 1.88 (m, 1H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.7, 155.3, 129.1, 125.8, 113.2, 82.9, 63.0, 55.3, 54.7, 27.4; **IR** (film): $\tilde{\nu}$ = 2933 (w), 2836 (w), 1648 (s), 1607 (s), 1510 (s), 1249 (s), 840 (m); **HRMS** (ESI) calcd. for $C_{12}H_{16}NO_3^+$ $[M+H]^+$ 222.1125; Found 222.1129.

Asymmetric azidation attempts with CN-BOX ligand



***N*-(3-azido-3-phenylpropyl)-4-methoxybenzamide (391)**

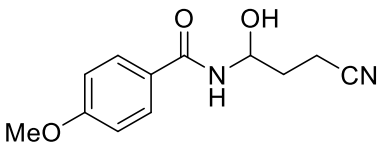


Following modified GP H, CuTc (0.40 mg, 2.0 μmol, 0.04 equiv.), 4-methoxy-*N*-(trans-2-phenylcyclopropyl)benzamide **342b** (13.4 mg, 50.0 μmol) and (*E*)-2-((*S*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)-2-((*S*)-4-(tert-butyl)oxazolidin-2-ylidene)acetonitrile (0.73 mg, 2.5 μmol, 0.05 equiv.) were measured on analytical balance. The tube was then closed with a rubber septum and sealed off with parafilm. Evacuate-refill cycle three times with nitrogen were performed to remove O_2 and extra-dry acetonitrile (0.5 mL) was added under nitrogen atmosphere, followed by the addition of $TMSN_3$ (94% purity purchased from TCI, 16.0 μL, 0.110 mmol, 2.2 equiv.). The mixture was stirred at room temperature for 20 minutes before a solution of Selectfluor (19.5 mg, 55.0 μmol, 1.1 equiv.) in acetonitrile (0.5 mL) was added by syringe. The reaction mixture was stirred at room temperature for 10 minutes. After the diazidation step is finished, triethylsilane (8.0 μL, 0.050 mmol, 1.0 equiv.) and TMSOTf (9.0 μL, 0.050 mmol, 1.0 equiv.) were added to the crude. The reaction mixture was stirred at room temperature for 2 hours. *N*-(3-azido-3-phenylpropyl)-4-methoxybenzamide **391** was obtained as a white solid (8.0 mg, 0.026 mmol, 52%) after purification by preparative TLC on silica using 1:1 pentanes:ethyl acetate as eluent. Chiral HPLC conditions: er = 49.8:50.2; Chiralpak IB 80:20 Hexane/ *i*PrOH, 1.0 mL/min, 31 min. tr (minor) = 20.6 min. and tr (major) = 24.9 min. λ = 260 cm^{-1}.

R_f: 0.28 (silica, pentanes:ethyl acetate 1:1); **Mp:** 81-82 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.70 – 7.61 (m, 2H, Ar*H*), 7.46 – 7.37 (m, 2H, Ar*H*), 7.37 – 7.30 (m, 3H, Ar*H*), 6.97 – 6.83 (m, 2H, Ar*H*), 6.32 – 6.18 (m, 1H, N*H*), 4.60 (t, *J* = 7.1 Hz, 1H, N_3CH), 3.85 (s, 3H, OCH_3), 3.59 – 3.45 (m, 2H, NCH_2), 2.16 – 2.02 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.9, 162.2, 139.0, 129.0, 128.6, 128.6, 126.8, 126.6, 113.7, 64.8, 55.4, 37.4, 35.9; **IR** (film): $\tilde{\nu}$ = 3312 (w), 2932 (w), 2095 (s), 1630 (m), 1503 (s), 1254 (s), 1030 (m); **HRMS** (ESI) calcd. for $C_{17}H_{18}N_4NaO_2^+$ $[M+Na]^+$ 333.1322; Found 333.1328.

5.3.6 Some preliminary results

N-(3-Cyano-1-hydroxypropyl)-4-methoxybenzamide (394)

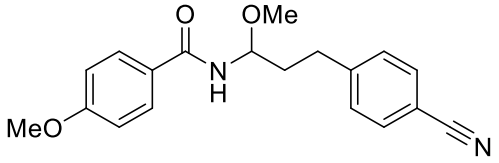


N-cyclopropyl-4-methoxybenzamide **296a** (19.1 mg, 0.100 mmol), $Cu(OAc)_2$ (1.8 mg, 0.010 mmol, 0.1 equiv.) and Selectfluor (38.9 mg, 0.110 mmol, 1.1 equiv.) was added in a 12*75 mm borosilicate glass tube. The tube was closed with a rubber septum and sealed off with parafilm. Evacuate-refill cycle three times with nitrogen were performed to remove O_2 and degassed acetonitrile-water (v:v 4:6, 0.5 mL, 0.2 M) was added under nitrogen

atmosphere, followed by the addition of TMSCN (14.0 μL, 0.110 mmol, 1.1 equiv.). The mixture was then stirred at room temperature for 1 hour. N-(3-Cyano-1-hydroxypropyl)-4-methoxybenzamide **394** (14.0 mg, 60.0 μmol, 60%) was obtained as a white solid after purification by column chromatography on silica using pentanes:ethyl acetate 2:1 as eluent.

R_f: 0.18 (silica, pentanes:ethyl acetate 2:1); **^{1}H NMR** (400 MHz, Acetone-d_6): δ = 8.02 (d, *J* = 6.5 Hz, 1H, N*H*), 7.94 – 7.84 (m, 2H, Ar*H*), 7.02 – 6.94 (m, 2H, Ar*H*), 5.70 – 5.59 (m, 1H, C*H*), 5.13 (d, *J* = 4.3 Hz, 1H, O*H*), 3.85 (s, 3H, OCH_3), 2.61 (td, *J* = 7.3, 1.4 Hz, 2H, CH_2CN), 2.11 – 2.05 (m, 2H, CH_2CH_2CN); **^{13}C NMR** (101 MHz, Acetone-d_6): δ = 167.1, 163.3, 130.1, 127.5, 120.4, 114.3, 73.8, 55.8, 32.4, 13.6.

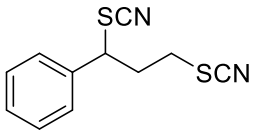
N-(3-(4-Cyanophenyl)-1-methoxypropyl)-4-methoxybenzamide (**395**)



Following a reported procedure,[166] N-cyclopropyl-4-methoxy benzamide **296a** (19.1 mg, 0.100 mmol), 4-bromobenzonitrile (21.7 mg, 0.120 mmol, 1.2 equiv.), $NiCl_2$(glyme) (2.2 mg, 0.010 mmol, 0.1 equiv.), 4,4'-dimethoxy-2,2'-bipyridyl (2.2 mg, 0.010 mmol, 0.1 equiv.), [Ir(dF(CF_3)ppy)$_2$dtbbpy]PF_6 (2.2 mg, 2.0 μmol, 0.02 equiv.), and $NBu_4OP(O)(OBu)_2$ (45.1 mg, 0.100 mmol, 1.0 equiv.) were added in a 12*75 mm borosilicate glass tube, followed by the addition of α,α,α-trifluorotoluene (0.5 mL, 0.2 M) and methanol (8.0 μL, 0.20 mmol, 2.0 equiv.). The reaction mixture was degassed by three freeze-pump-thaw cycles and backfilled with N_2. The mixture was then stirred at room temperature under irradiation of blue light LEDs for 16 hours. N-(3-(4-Cyanophenyl)-1-methoxypropyl)-4-methoxybenzamide **395** (7.8 mg, 0.024 mmol, 24%) was obtained as a white solid after purification by column chromatography on silica using 2:1 pentanes:ethyl acetate as eluent.

R_f: 0.24 (silica, pentanes:ethyl acetate 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.74 – 7.67 (m, 2H, Ar*H*), 7.61 – 7.53 (m, 2H, Ar*H*), 7.35 – 7.28 (m, 2H, Ar*H*), 6.96 – 6.91 (m, 2H, Ar*H*), 6.11 (d, *J* = 9.6 Hz, 1H, N*H*), 5.39 – 5.28 (m, 1H, C*H*), 3.86 (s, 3H, ArOCH_3), 3.39 (s, 3H, OCH_3), 2.93 – 2.72 (m, 2H, ArCH_2), 2.13 – 1.94 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.8, 162.6, 146.9, 132.3, 129.2, 128.8, 125.7, 118.9, 113.9, 110.0, 81.0, 56.0, 55.5, 36.9, 31.5; **IR** (film): $\tilde{\nu}$ = 3317 (w), 2933 (w), 2227 (w), 1643 (m), 1606 (s), 1502 (s), 1255 (s), 1177 (m), 845 (m); **HRMS** (ESI) calcd. for $C_{19}H_{20}N_2NaO_3^+$ $[M+Na]^+$ 347.1366; Found 347.1362.

(1,3-Dithiocyanatopropyl)benzene (**398**)



Following a modified GP E, cyclopropylbenzene **344** (12.5 μL, 0.100 mmol), benzophenone (1.8 mg, 0.010 mmol, 0.1 equiv.) and Selectfluor (38.9 mg, 0.110 mmol, 1.1 equiv.) were measured on analytical balance and added in a 12*75 mm borosilicate glass tube. The tube was closed with a rubber septum and sealed off with parafilm. Evacuate-refill cycle three times with nitrogen were performed to remove O_2 and extra-dry acetonitrile (0.5 mL, 0.2 M) was added under nitrogen atmosphere, followed by the addition of TMSNCS (31.1 μL, 0.220 mmol, 2.2 equiv.). The mixture was then stirred under irradiation of 365 nm UV light at room temperature for 3 hours. (1,3-Dithiocyanatopropyl)benzene **398** (11.3 mg, 0.048 mmol, 48%) was obtained as a colorless oil after purification by column chromatography on silica using pentanes:ethyl acetate 3:1 as eluent.

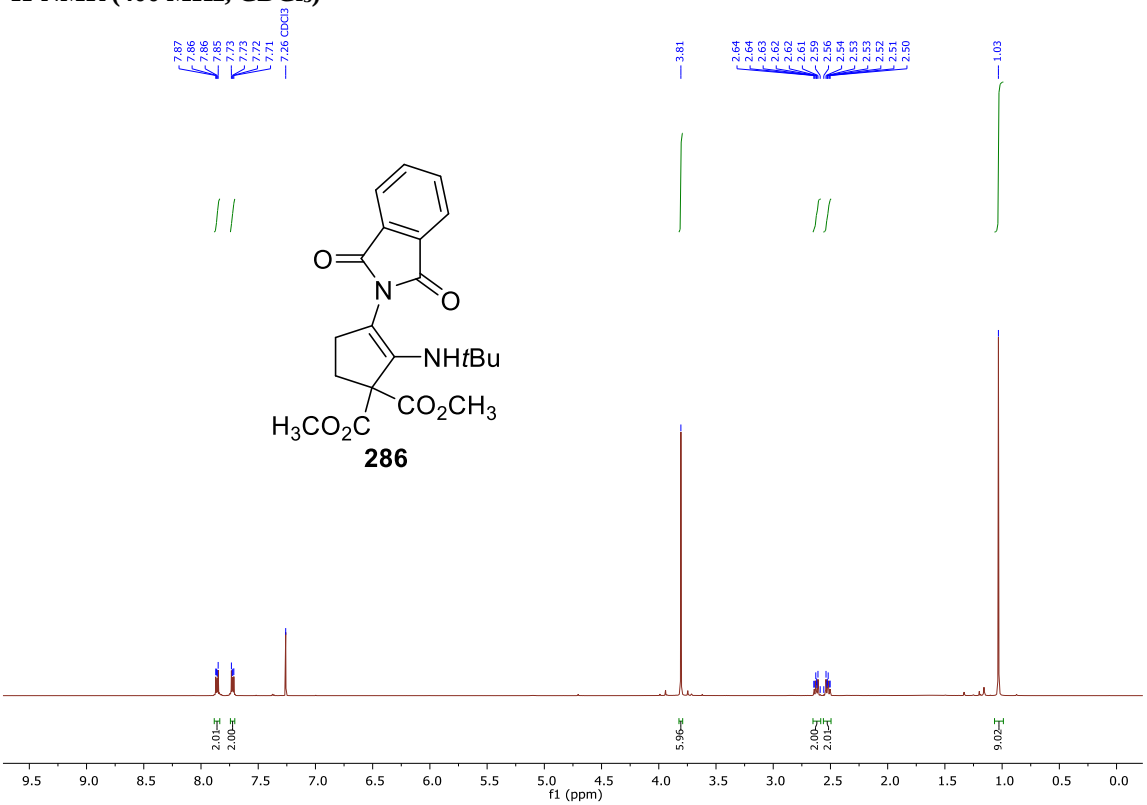
R_f: 0.23 (silica, pentanes:ethyl acetate 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.54 – 7.28 (m, 5H, Ar*H*), 4.50 (dd, *J* = 8.6, 6.9 Hz, 1H, C*H*), 3.01 (ddd, *J* = 13.7, 7.6, 6.3 Hz, 1H, SCH_2), 2.91 (ddd, *J* = 13.4, 7.8, 6.5 Hz, 1H, SCH_2), 2.79 – 2.61 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 136.2, 129.7, 129.6, 127.3, 111.0, 110.4, 50.6, 35.4, 31.0; **IR** (film): $\tilde{\nu}$ = 3063 (w), 2938 (w), 2152 (s), 1494 (m), 1454 (m), 757 (m), 698 (s); **HRMS** (ESI) calcd. for $C_{11}H_{10}N_2NaS_2^+$ $[M+Na]^+$ 257.0178; Found 257.0180.

6

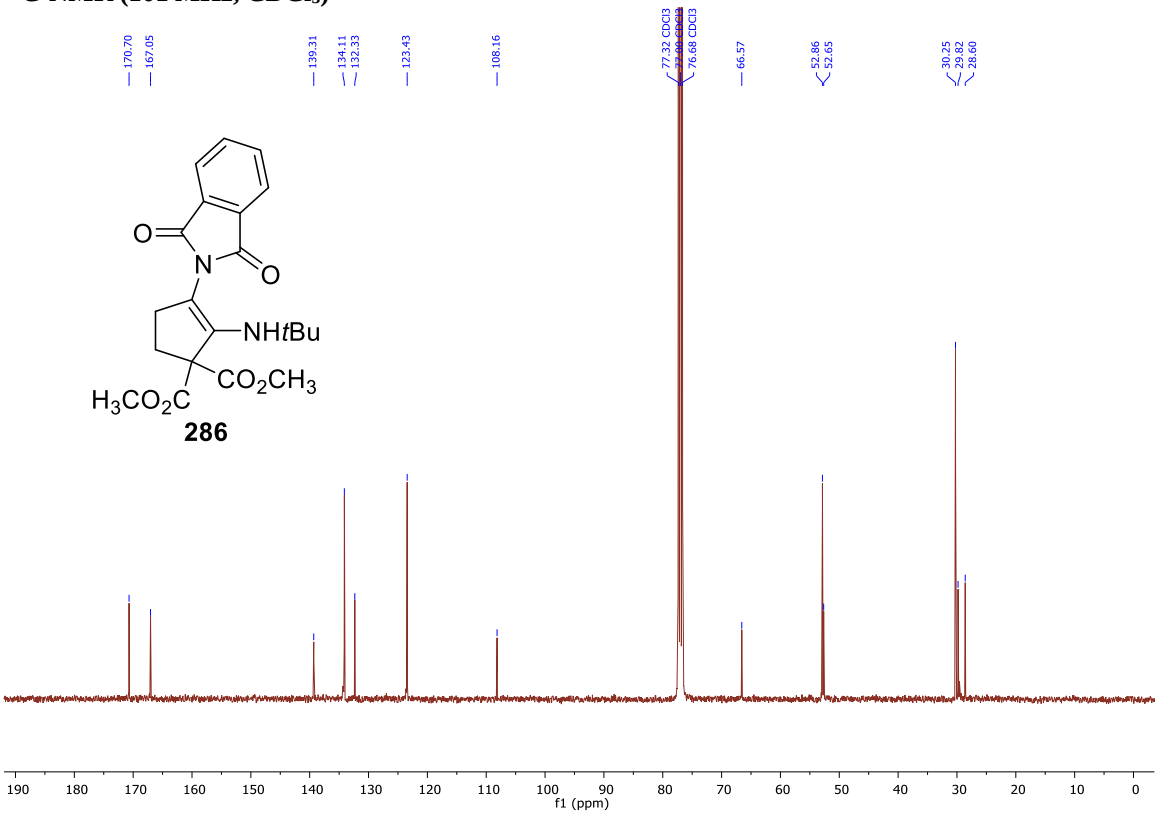
Spectra of New Compounds

6. Spectra of new compounds

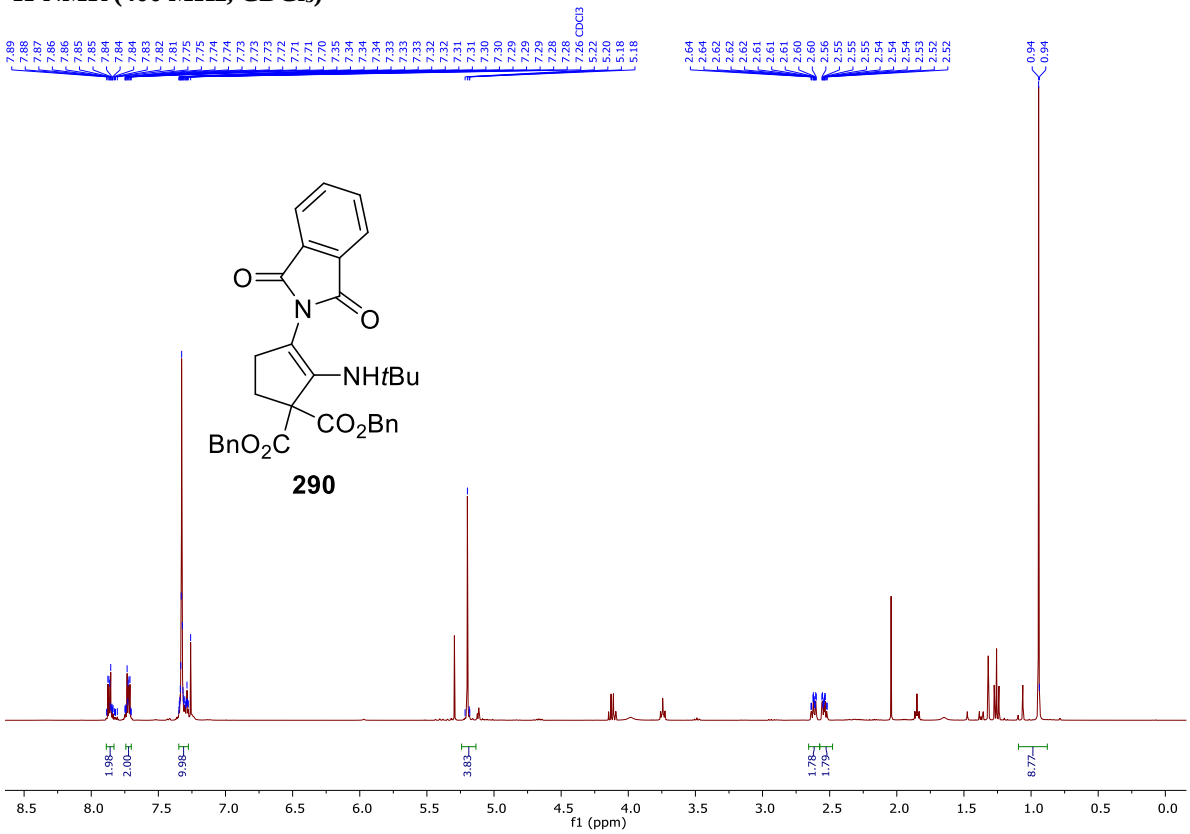
^{1}H-NMR (400 MHz, $CDCl_3$)



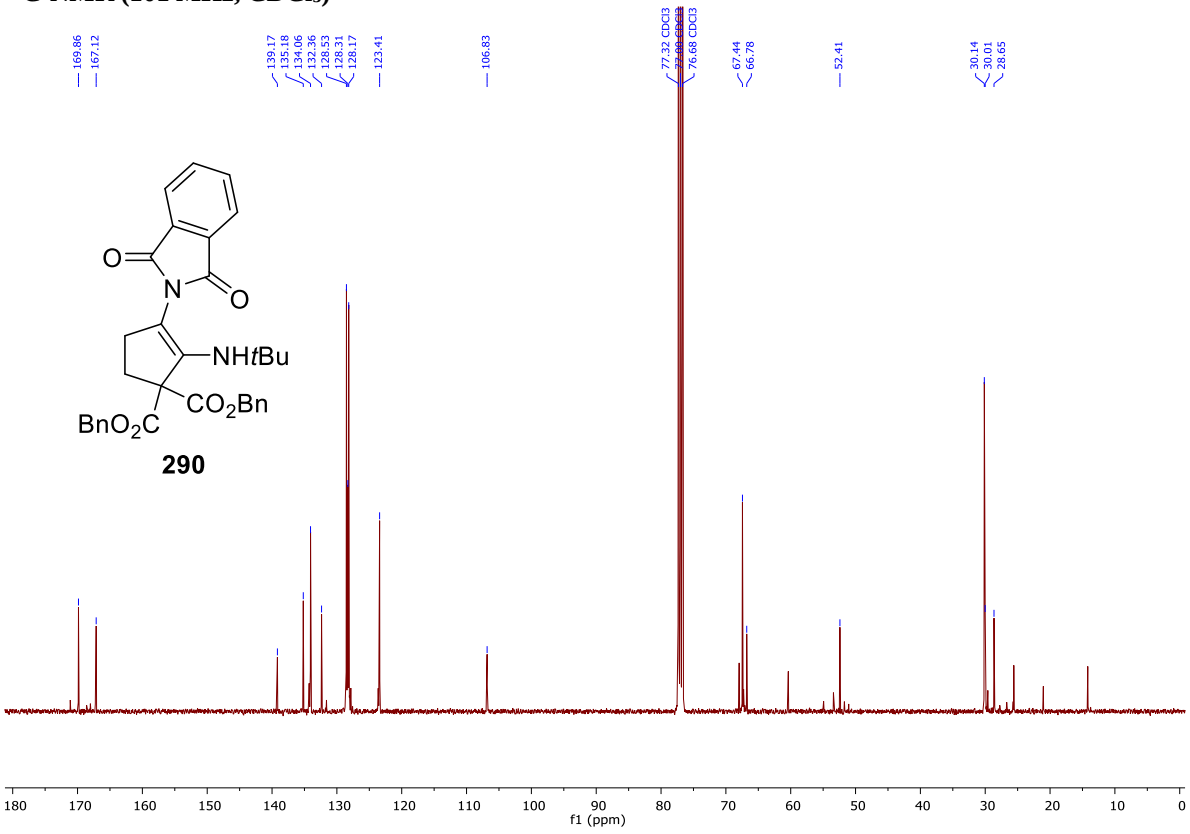
^{13}C-NMR (101 MHz, $CDCl_3$)



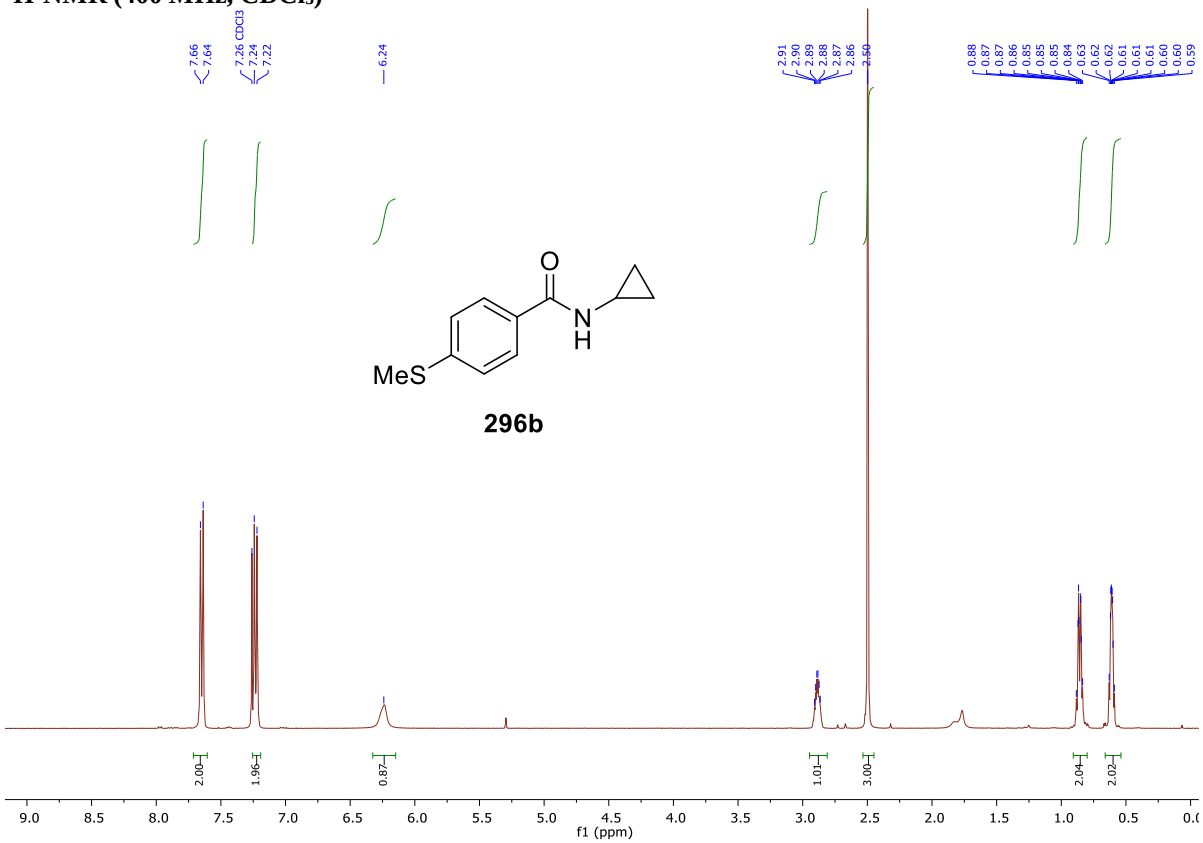
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

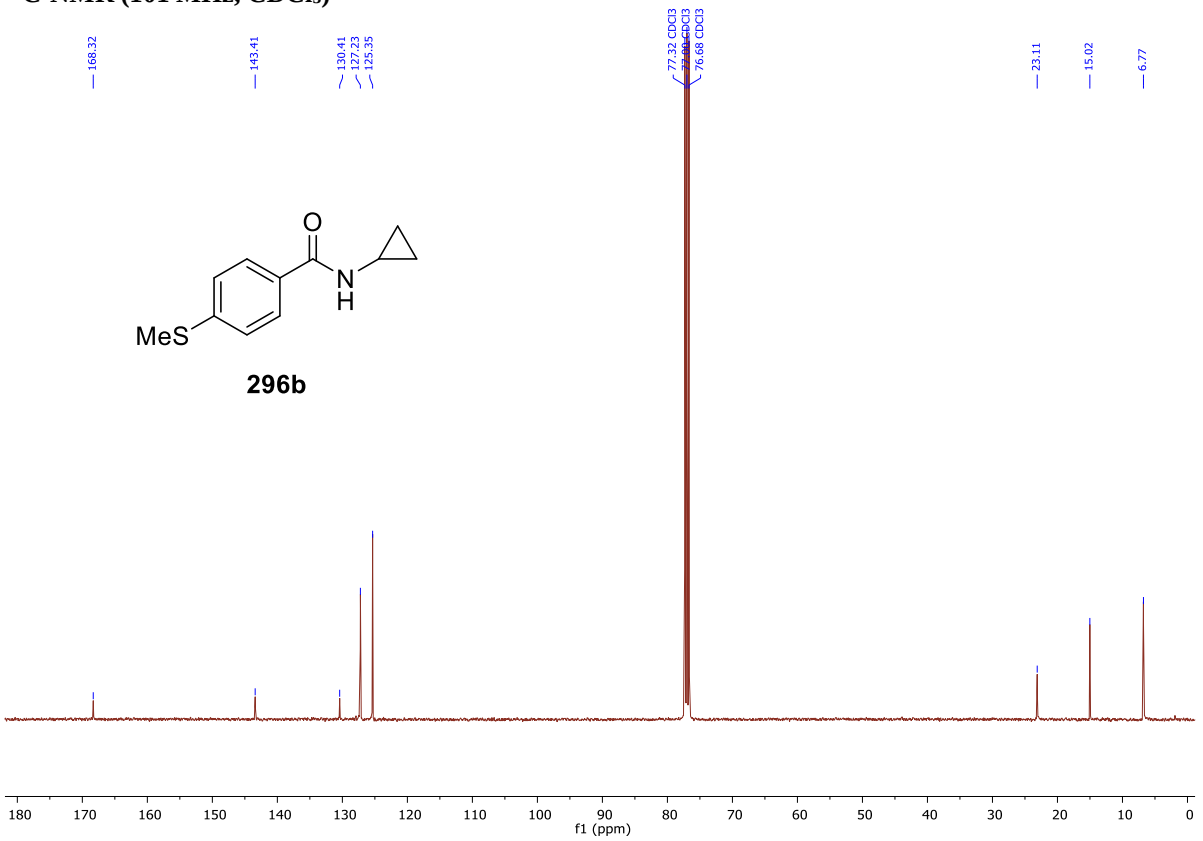


^{1}H-NMR (400 MHz, $CDCl_3$)



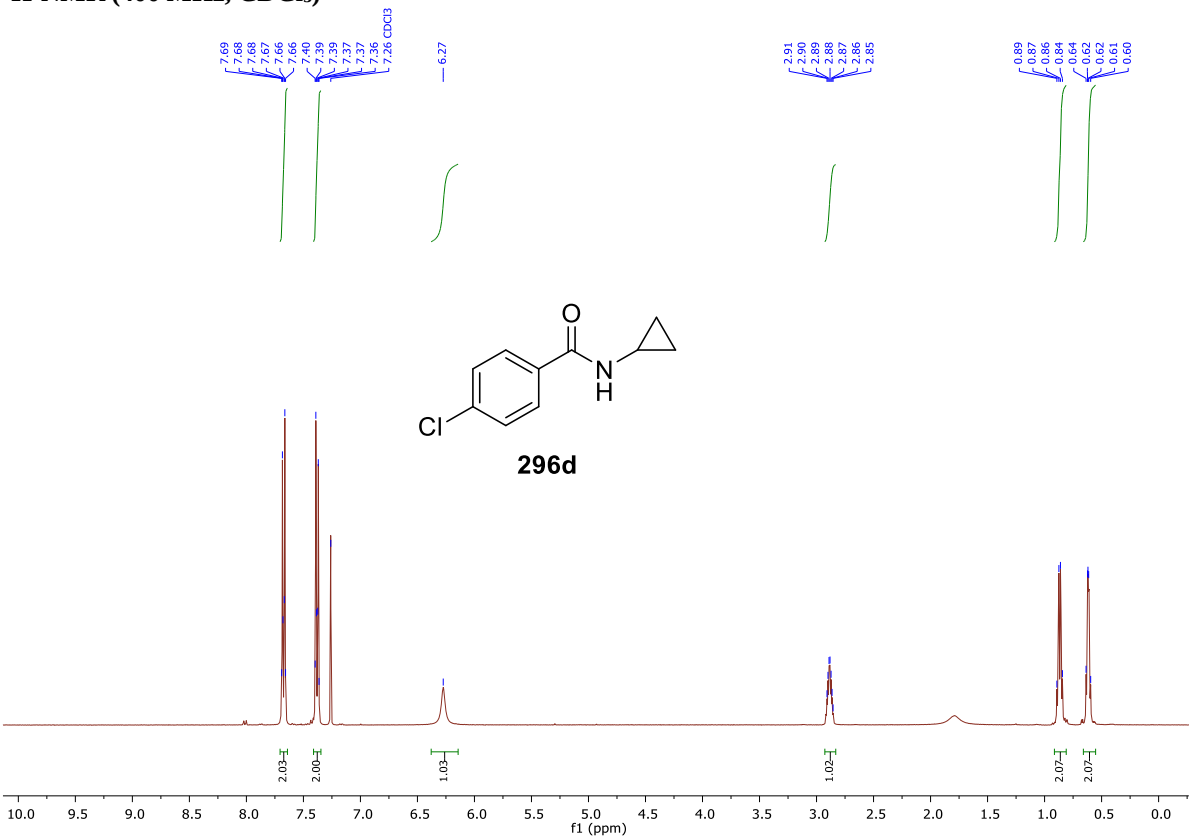
296b

^{13}C-NMR (101 MHz, $CDCl_3$)

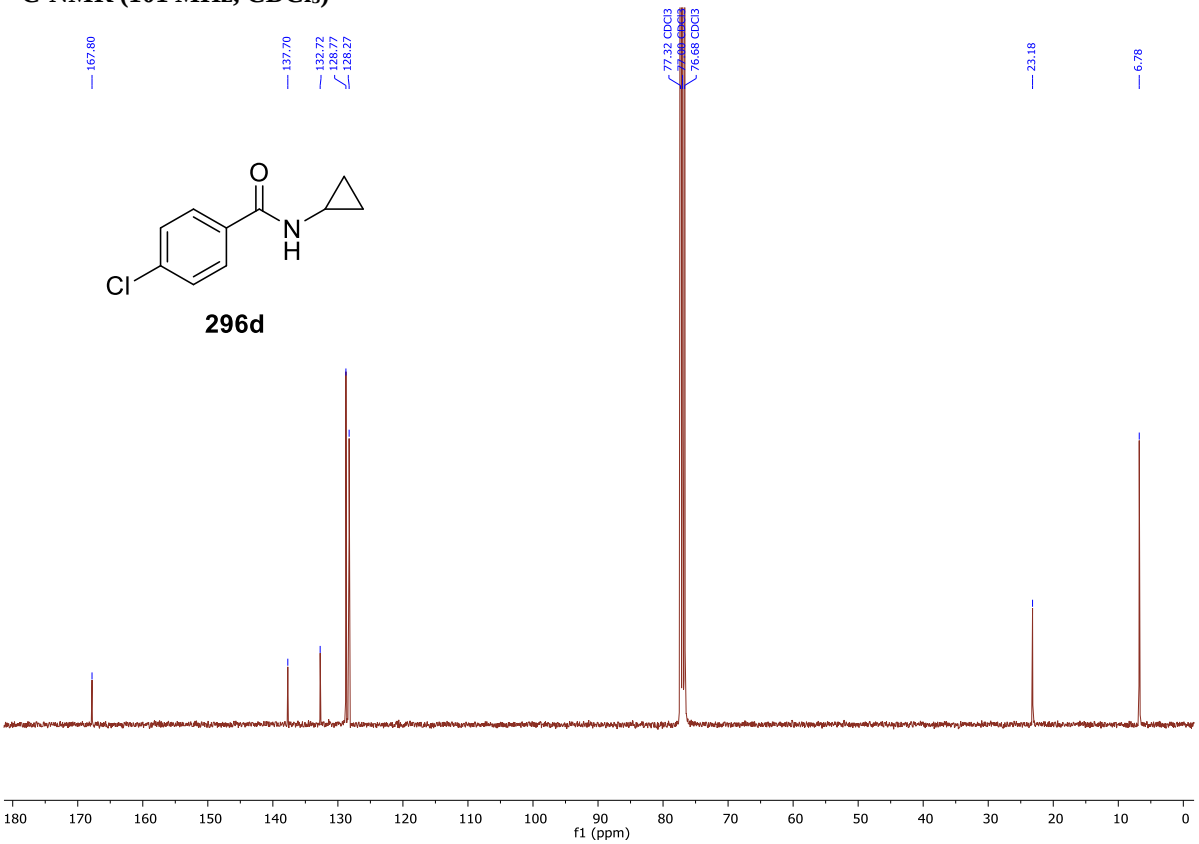


296b

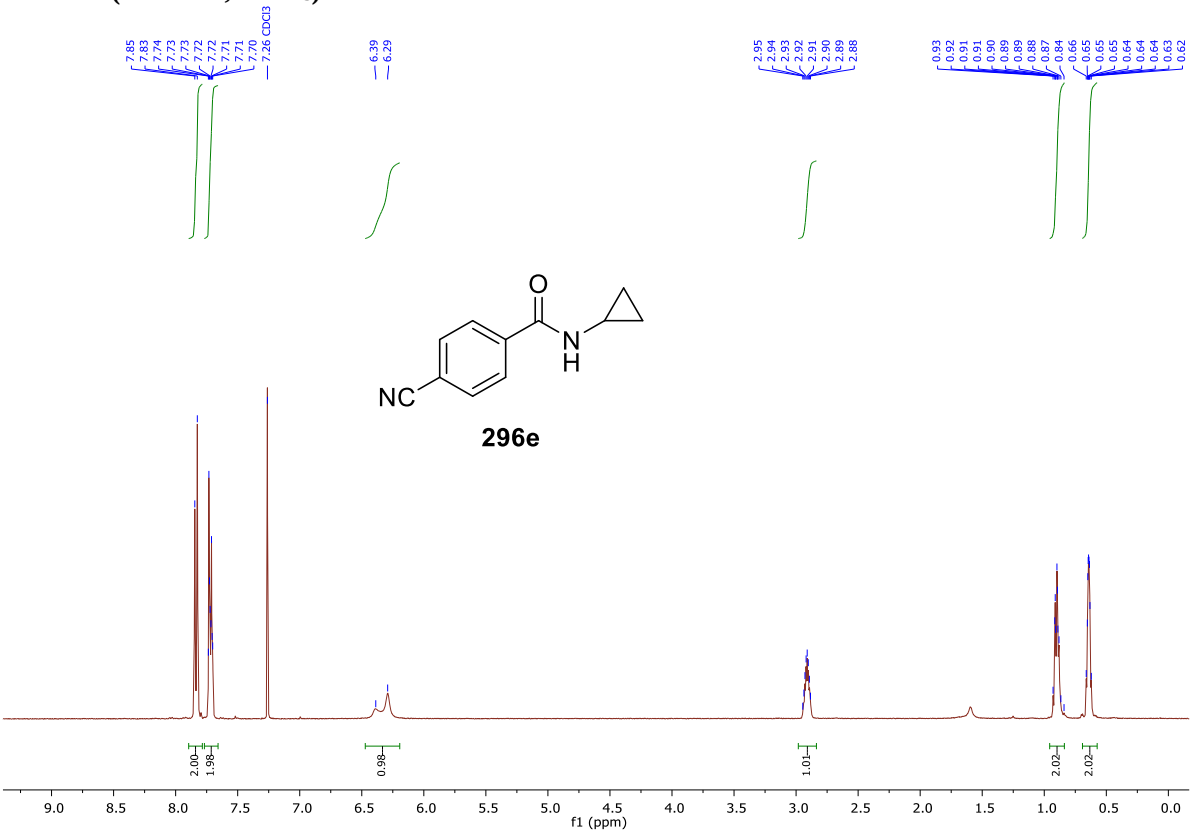
^{1}H-NMR (400 MHz, $CDCl_3$)



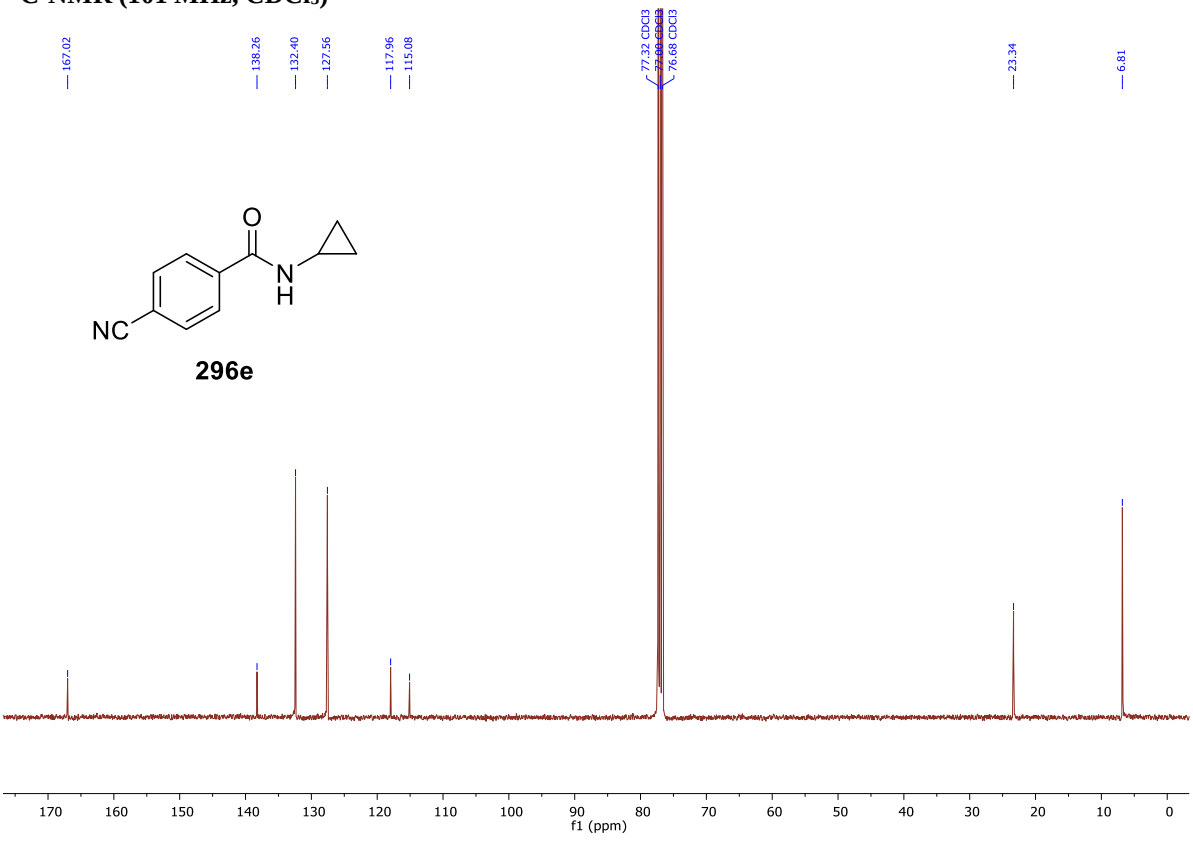
^{13}C-NMR (101 MHz, $CDCl_3$)



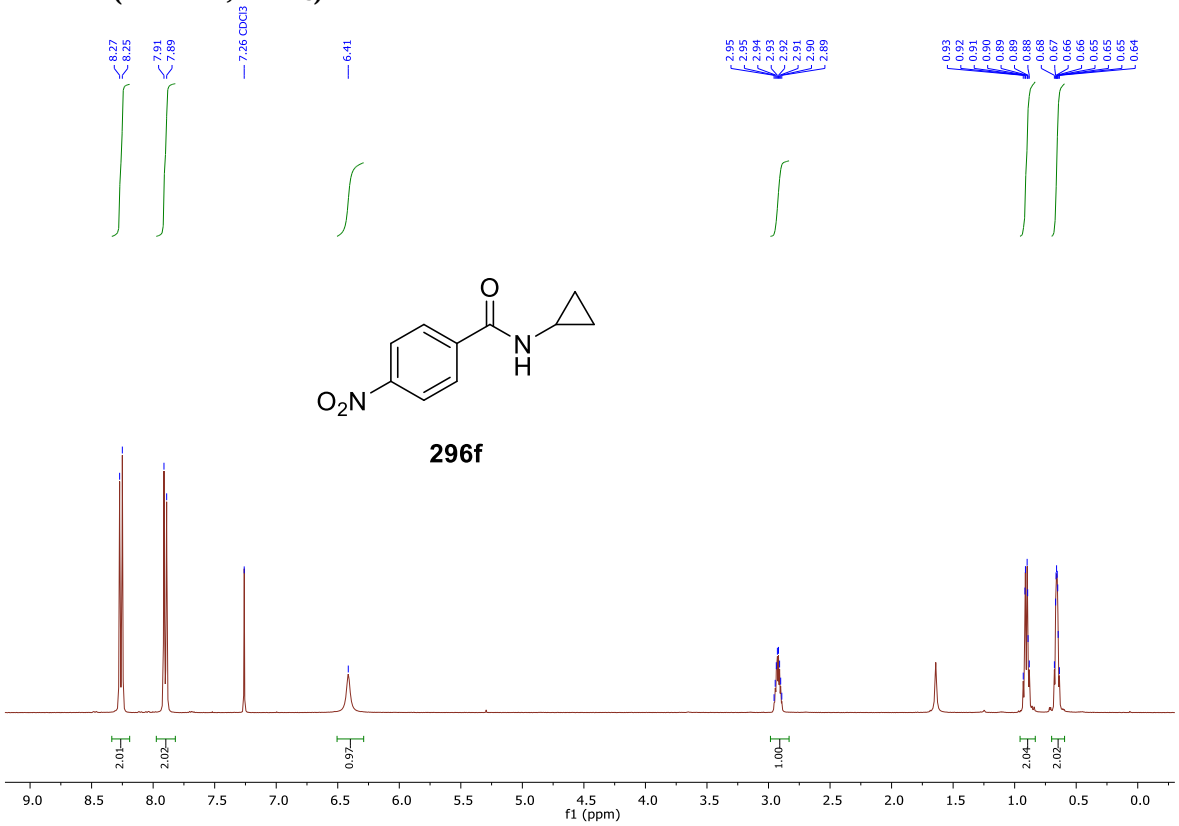
^{1}H-NMR (400 MHz, $CDCl_3$)



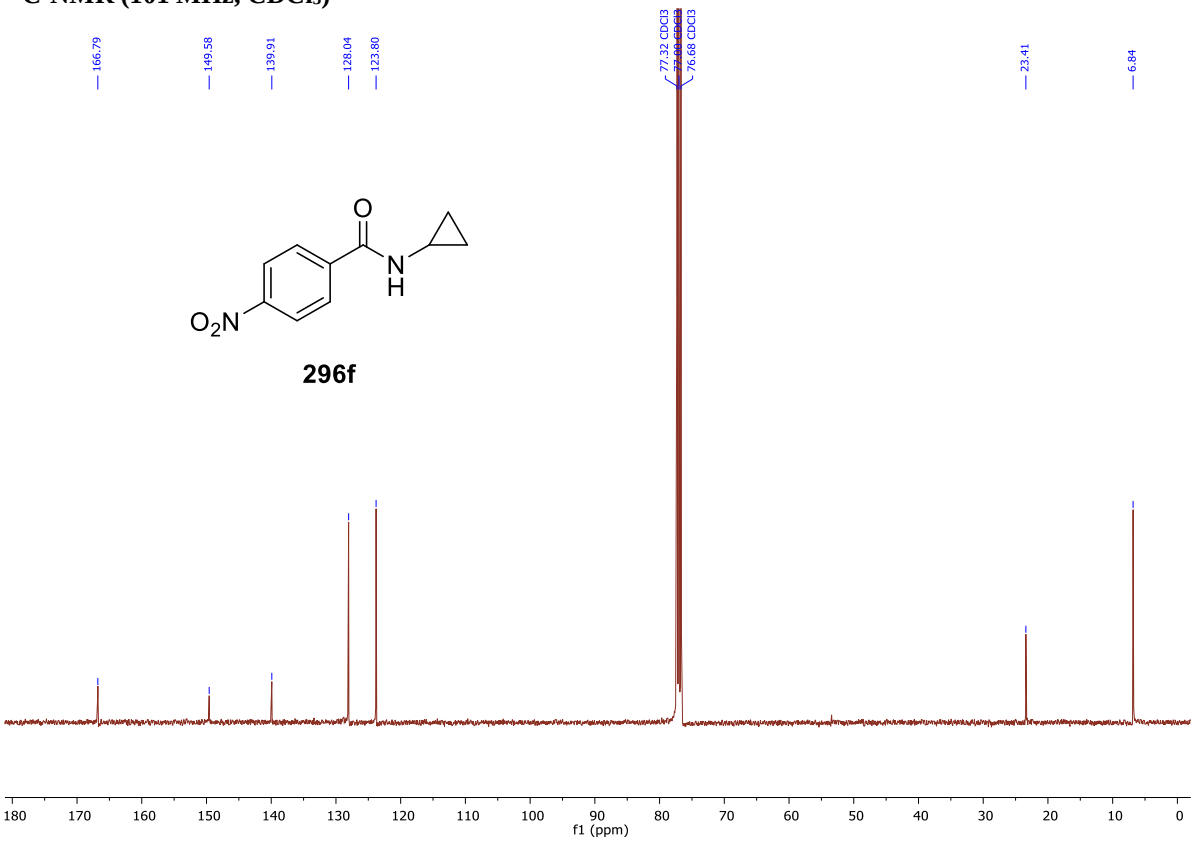
^{13}C-NMR (101 MHz, $CDCl_3$)



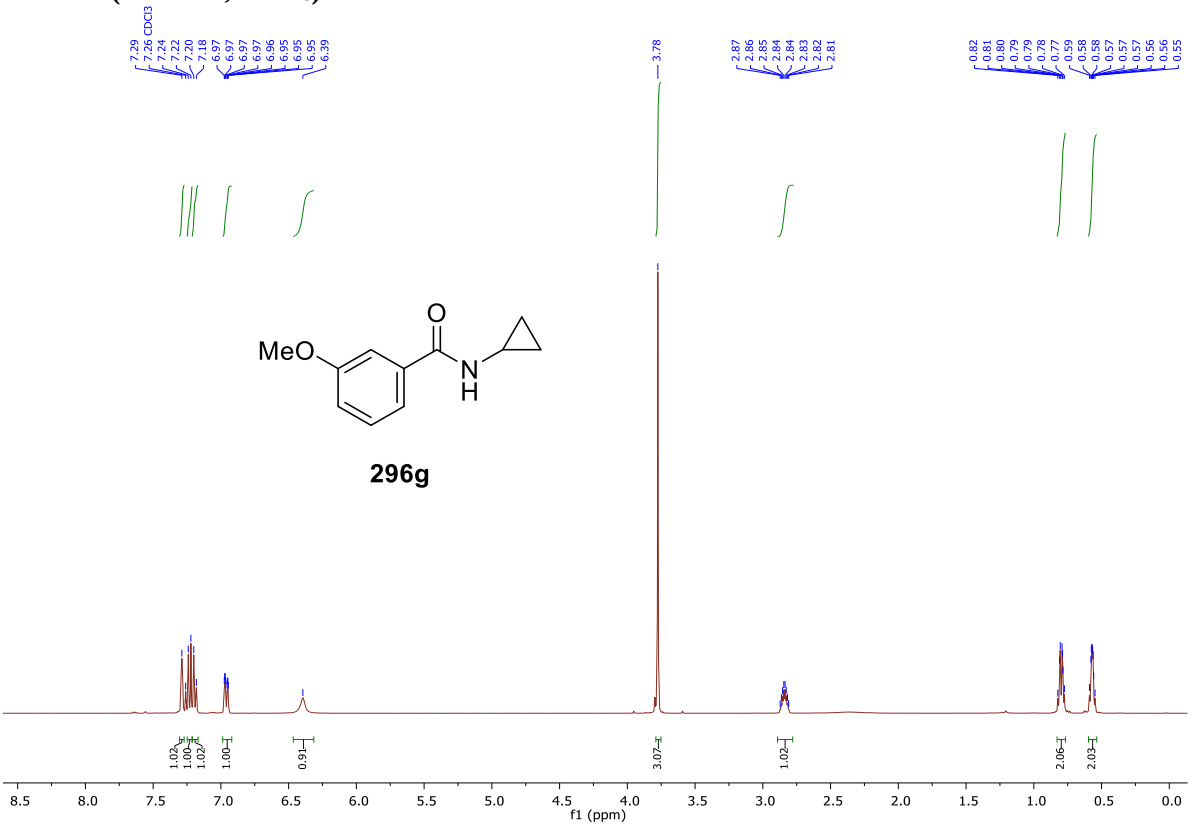
^{1}H-NMR (400 MHz, $CDCl_3$)



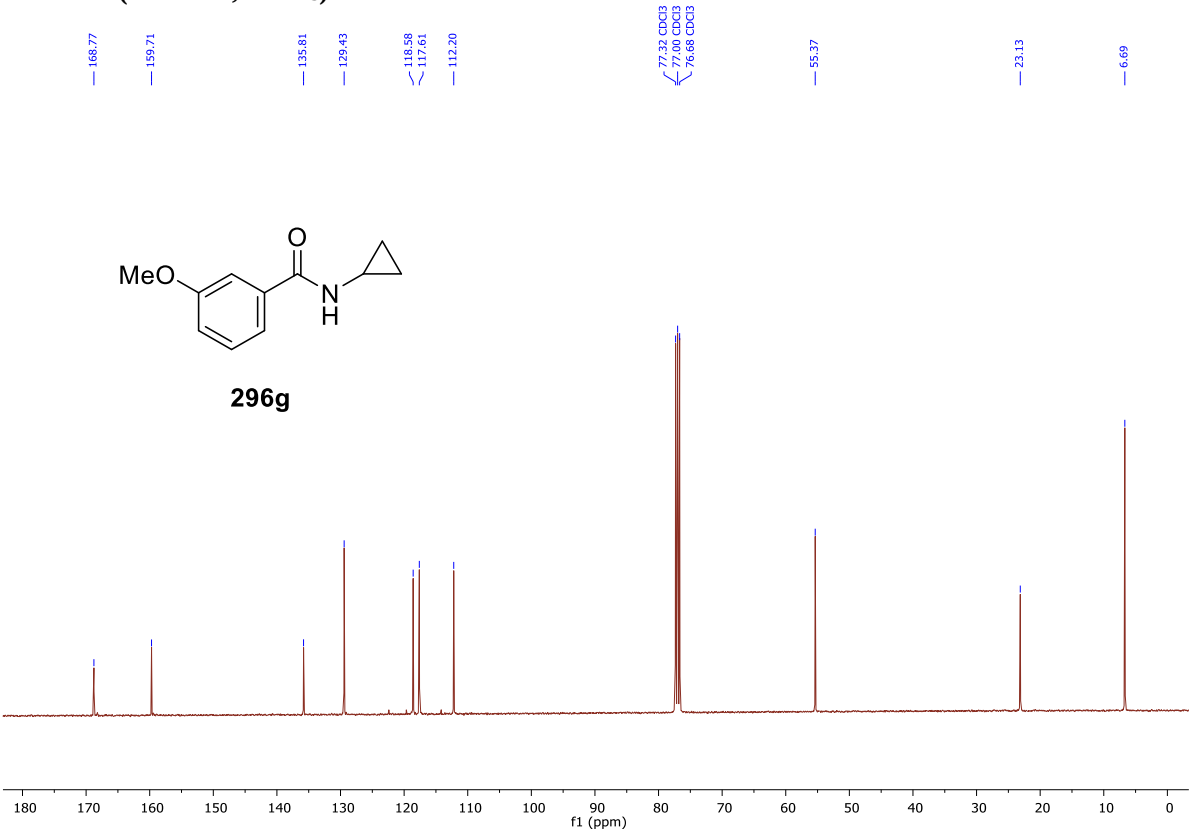
^{13}C-NMR (101 MHz, $CDCl_3$)



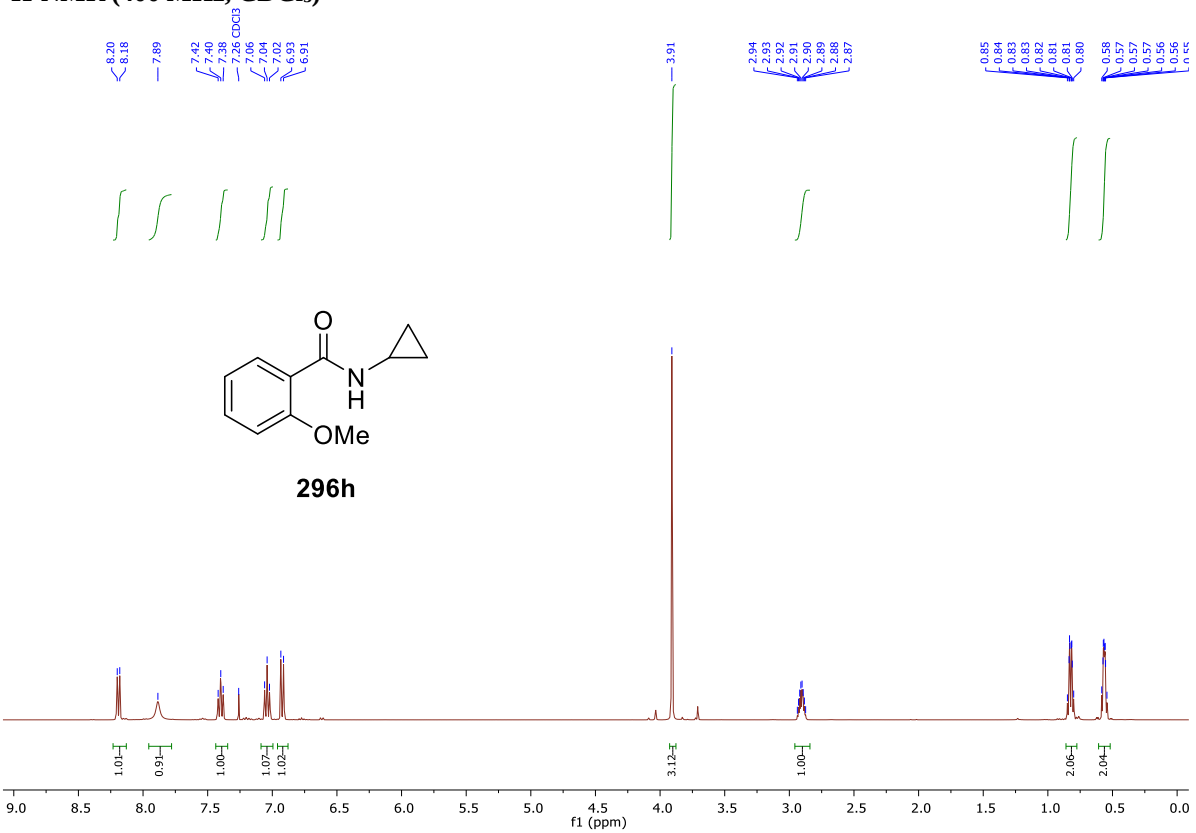
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

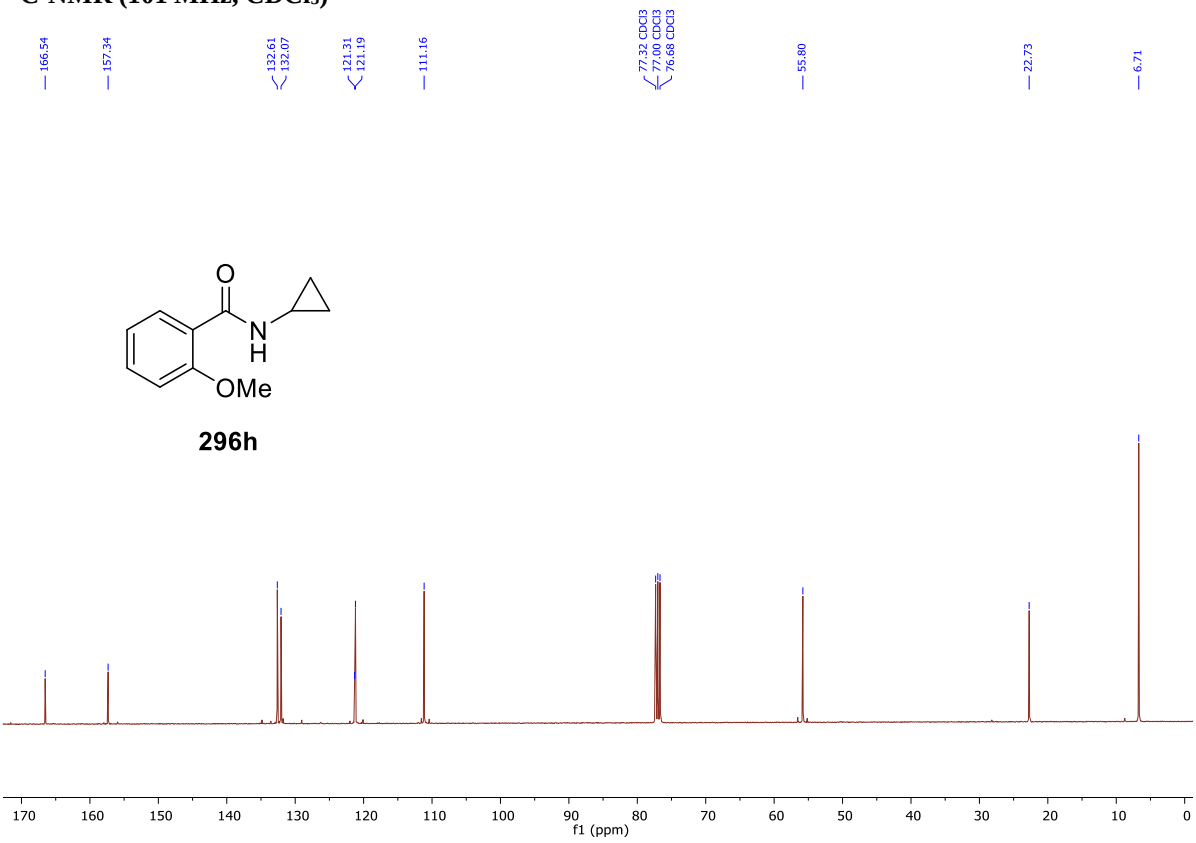


^{1}H-NMR (400 MHz, $CDCl_3$)



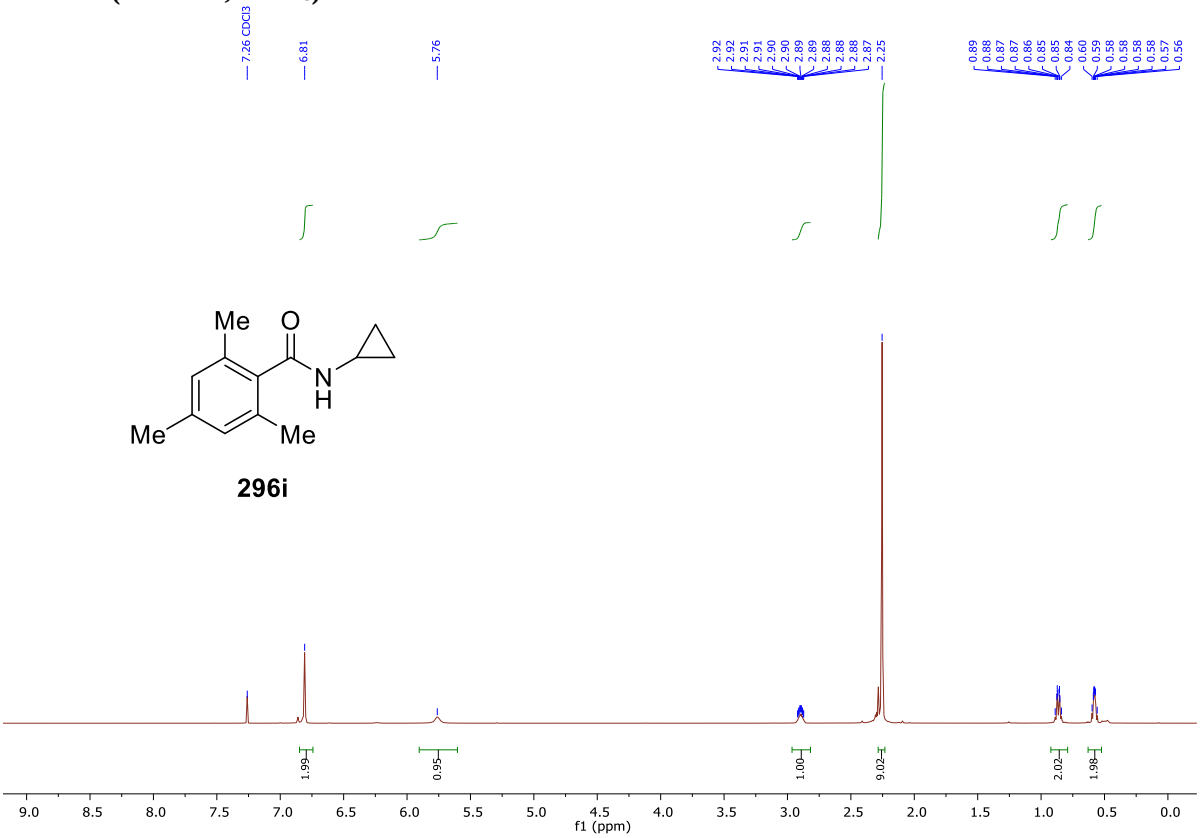
296h

^{13}C-NMR (101 MHz, $CDCl_3$)



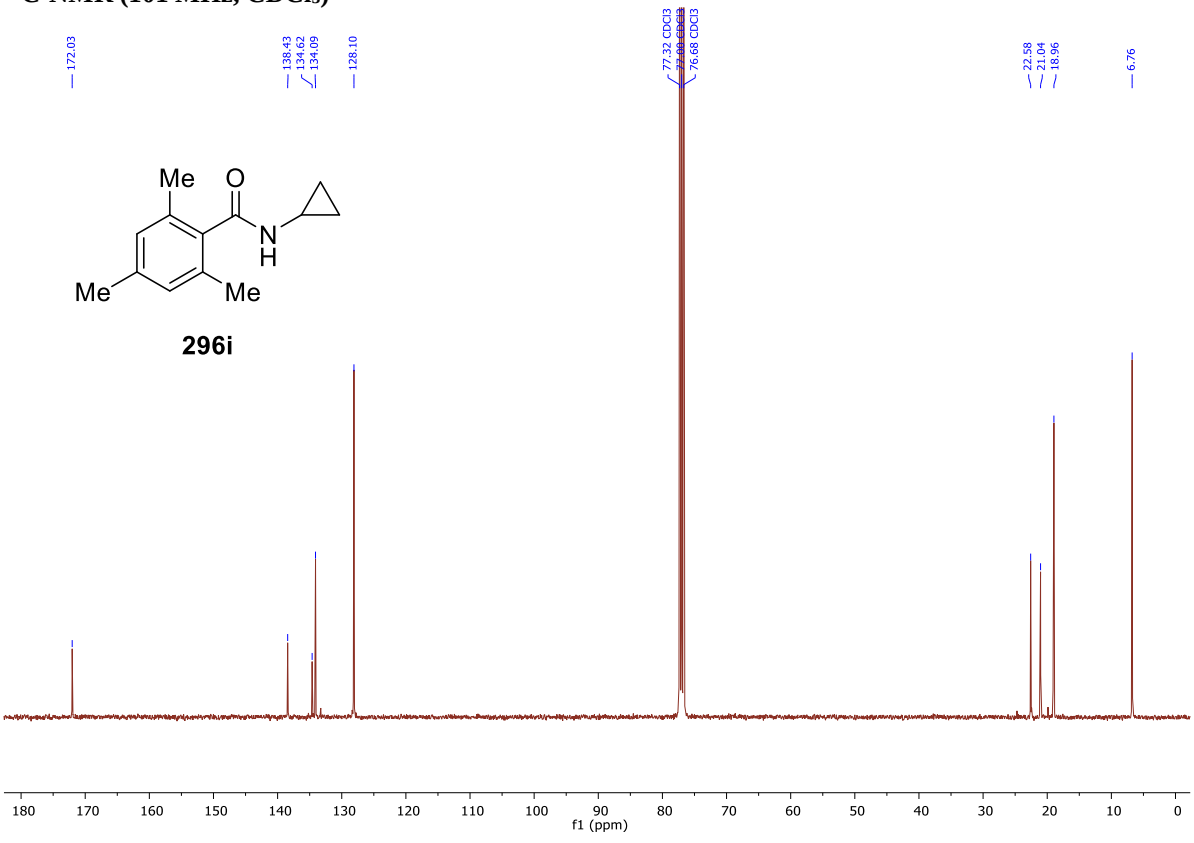
296h

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



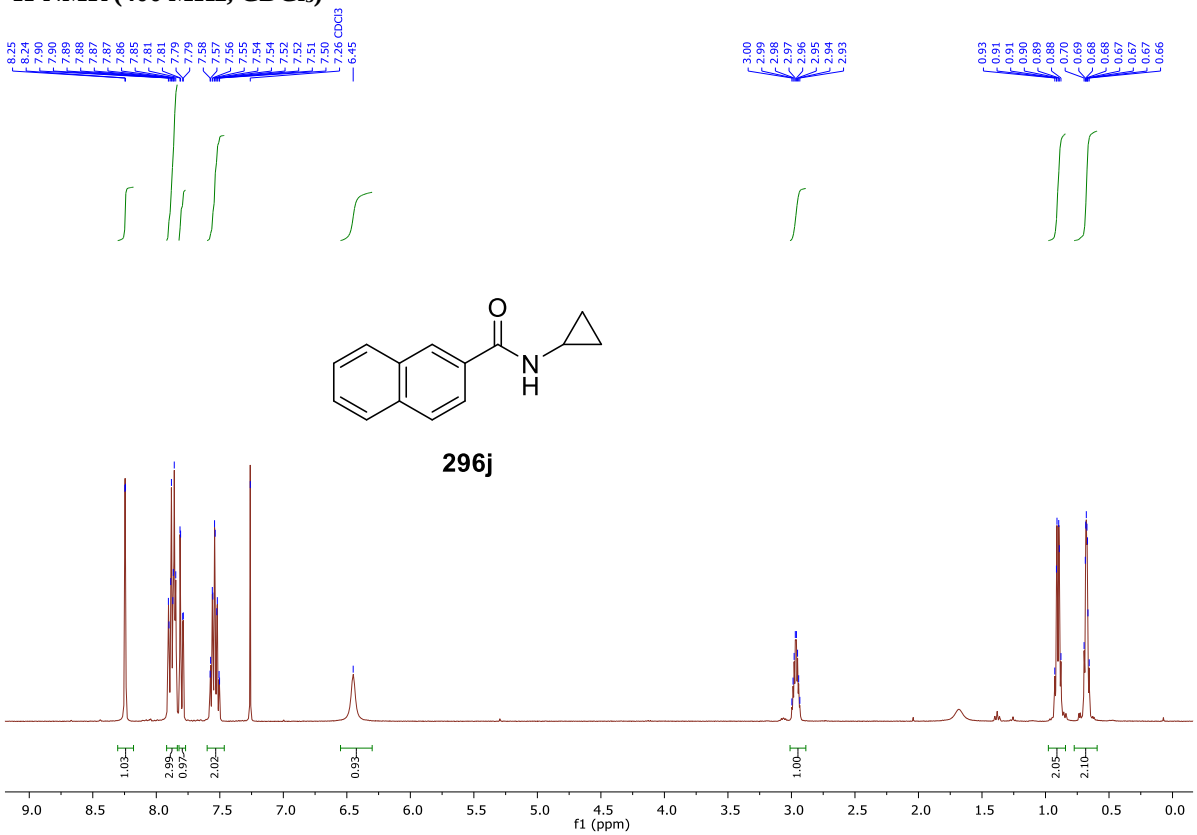
296i

^{13}C-NMR (101 MHz, $CDCl_3$)



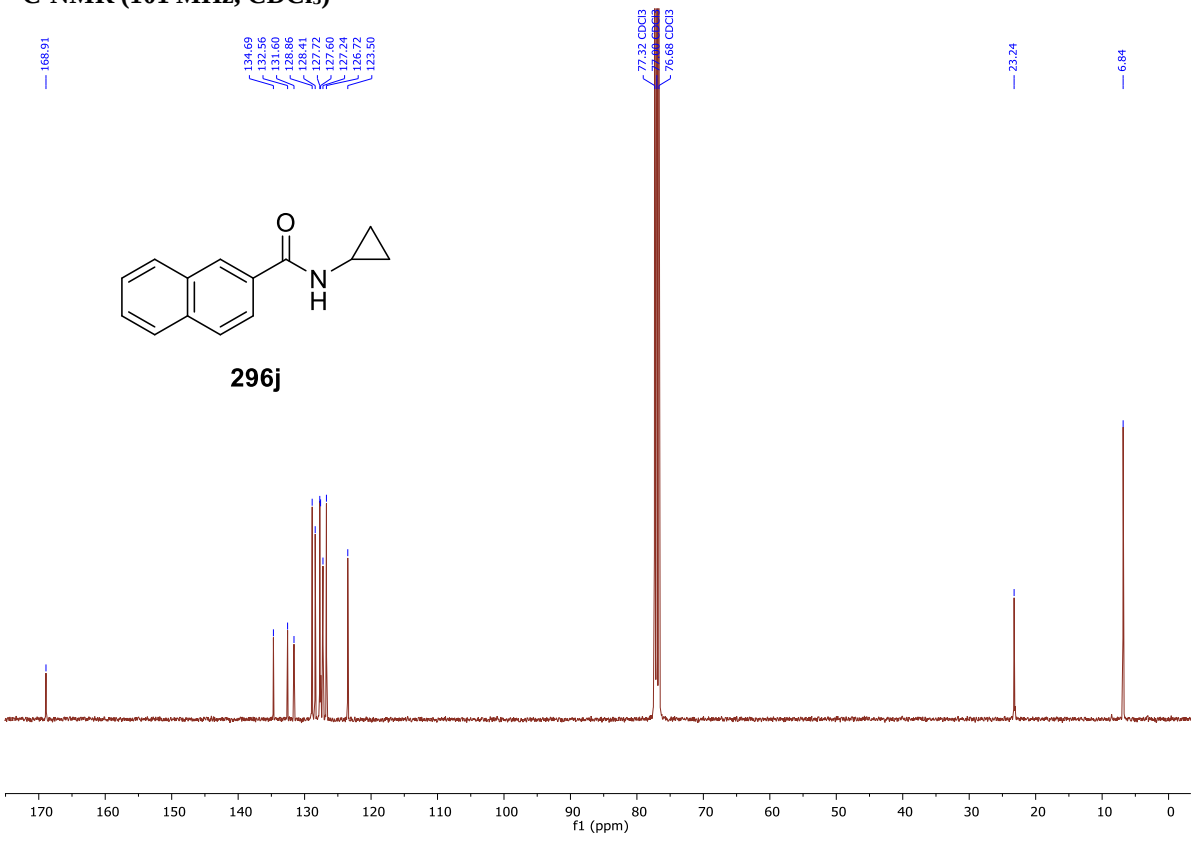
296i

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



296j

^{13}C-NMR (101 MHz, $CDCl_3$)



296j

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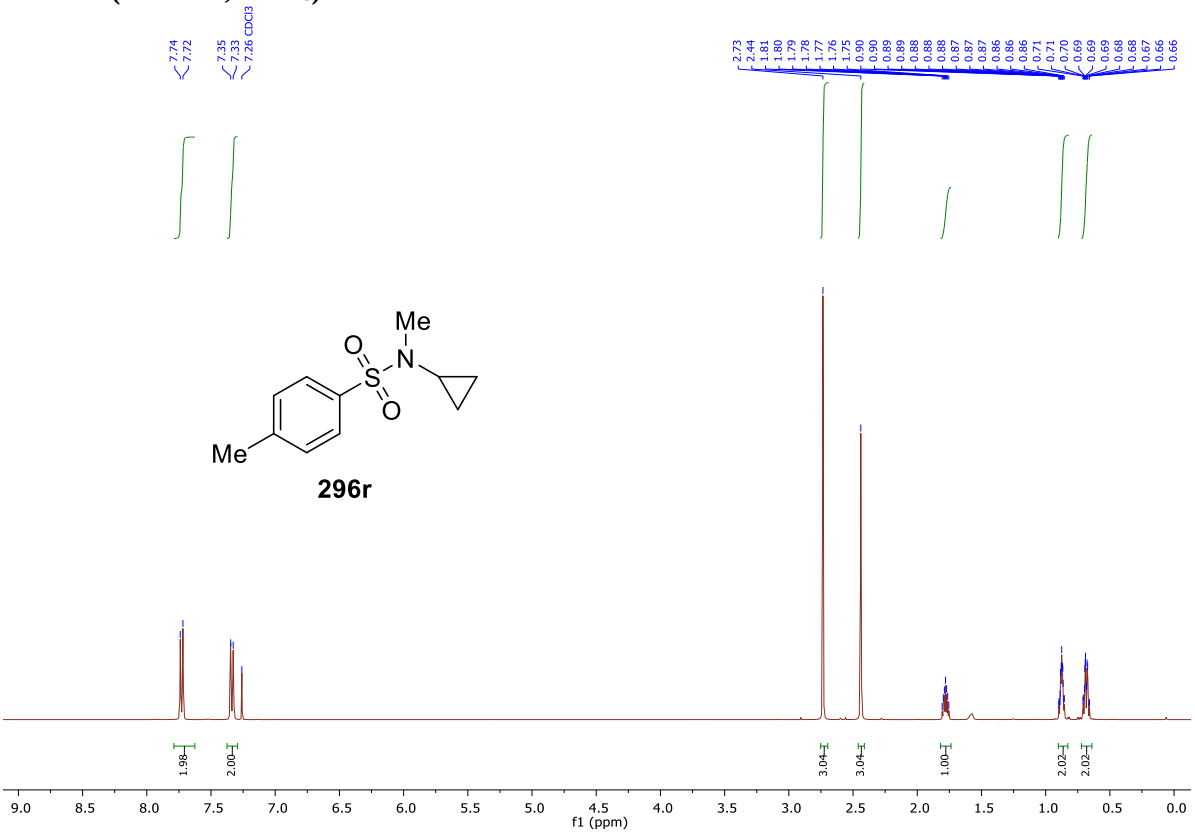
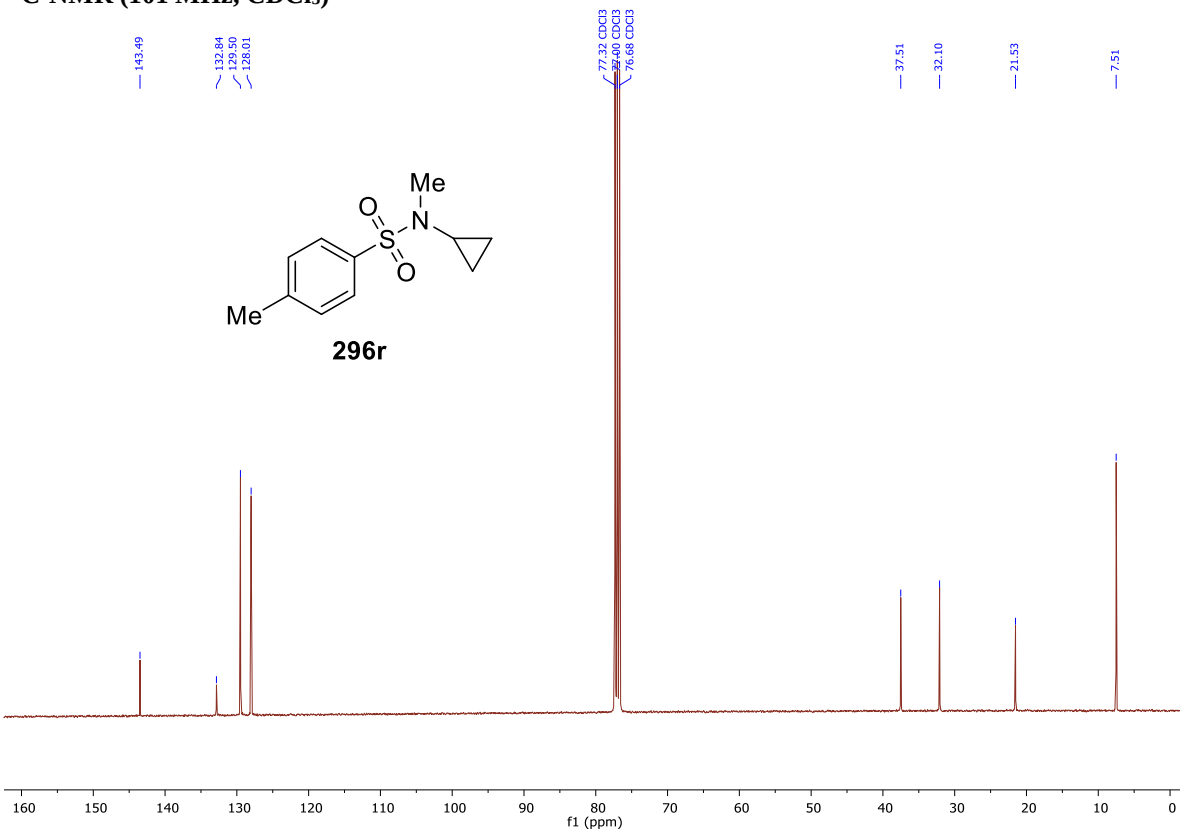
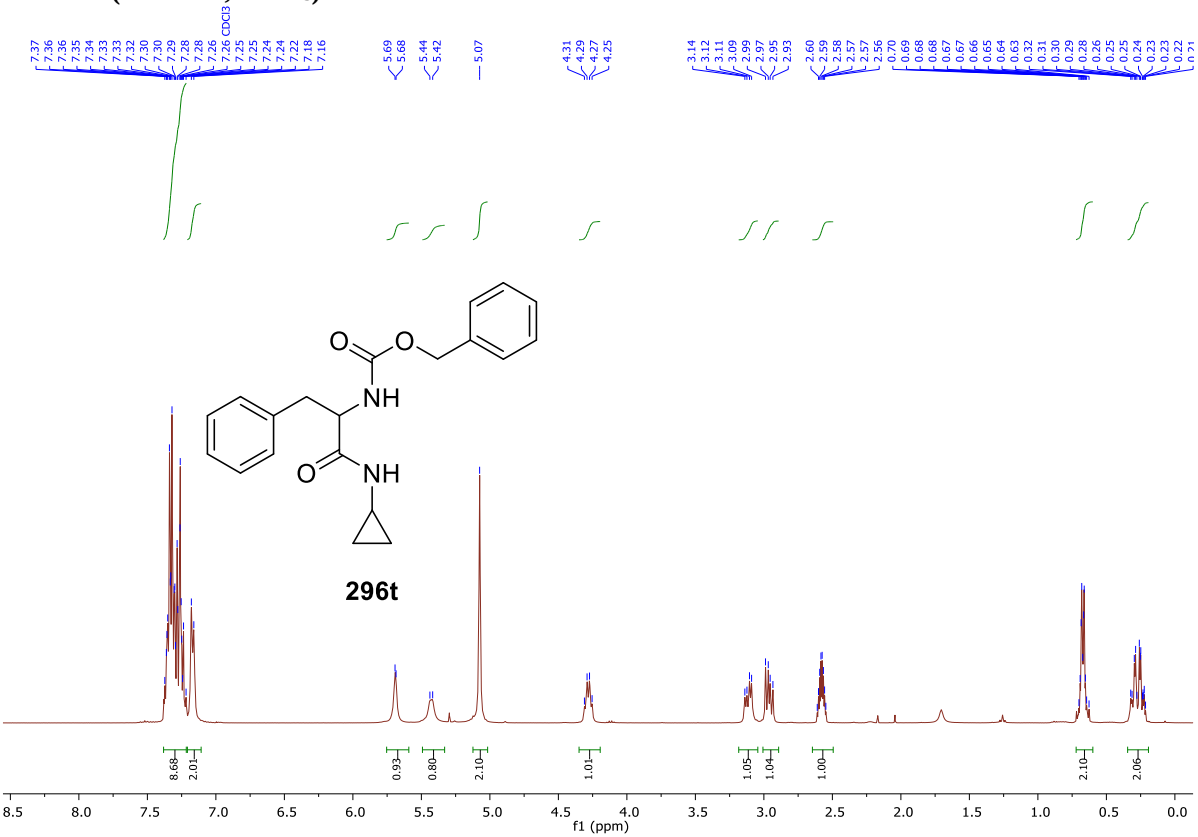


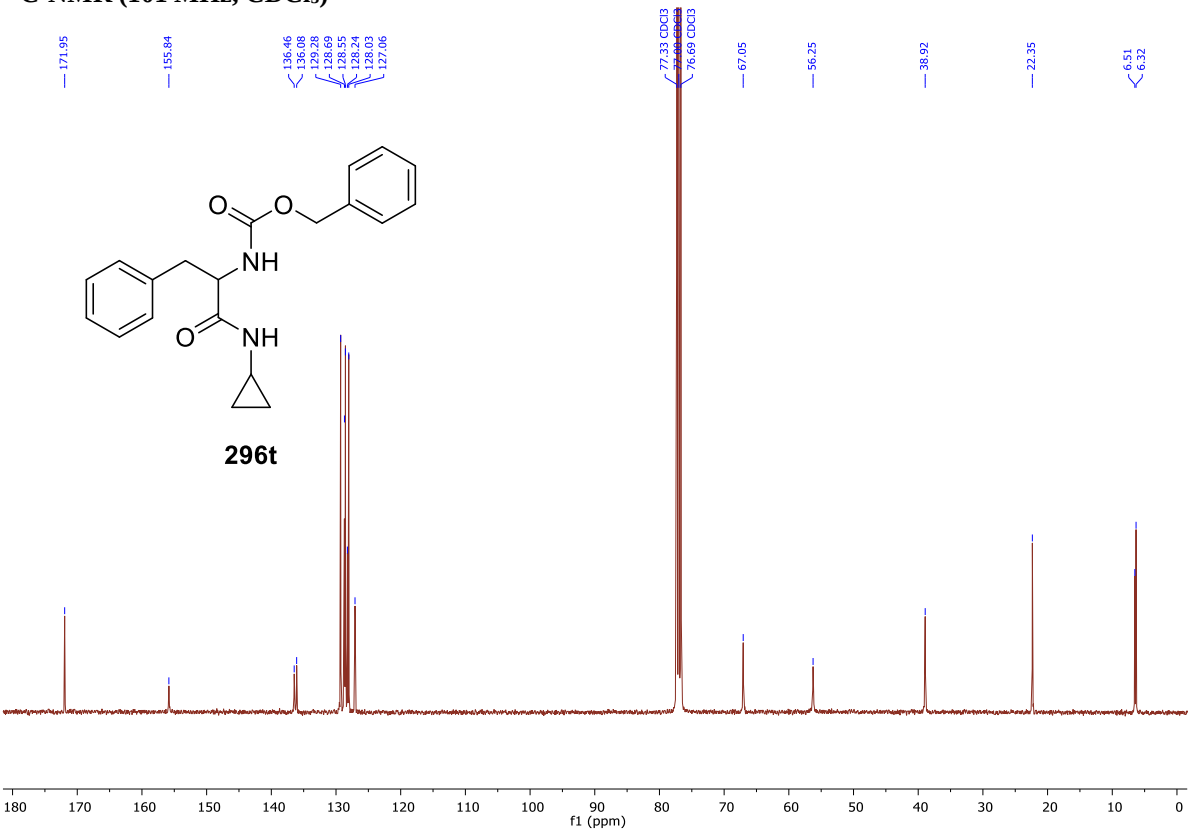
^{13}C-NMR (101 MHz, $CDCl_3$)



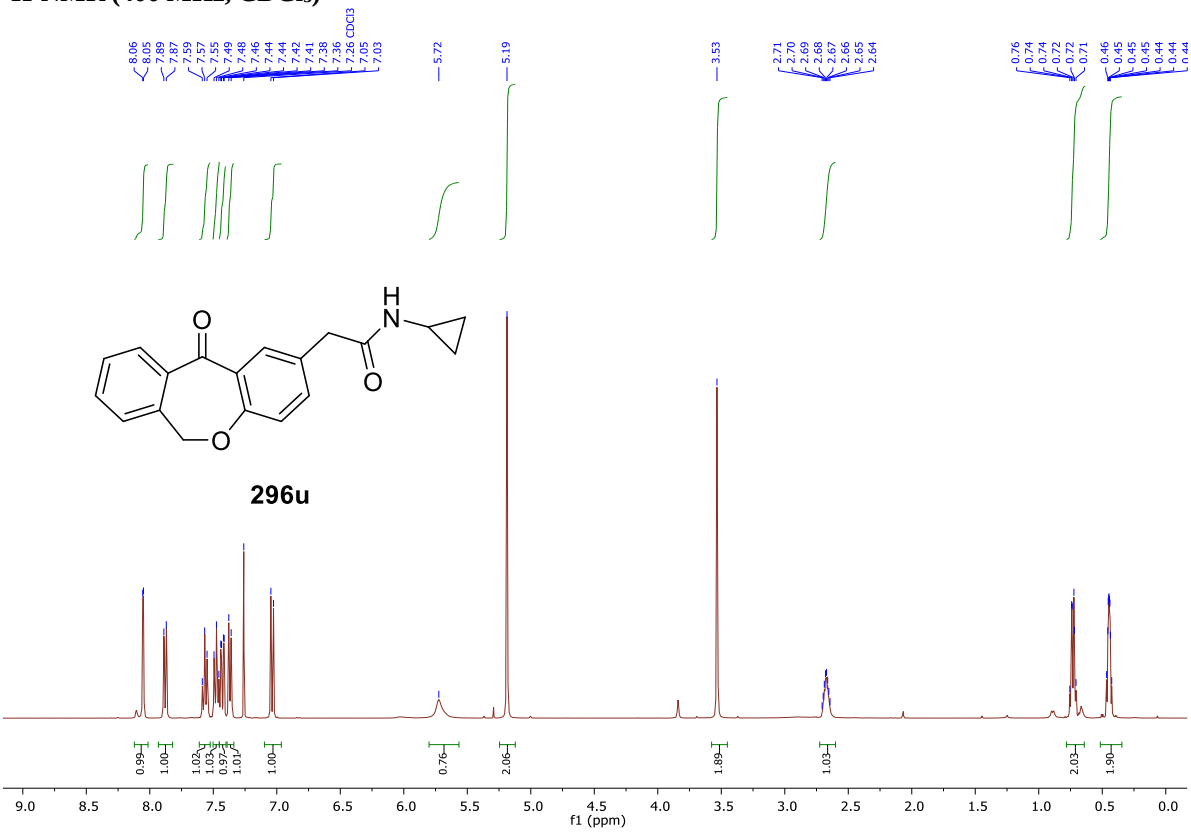
^{1}H-NMR (400 MHz, $CDCl_3$)



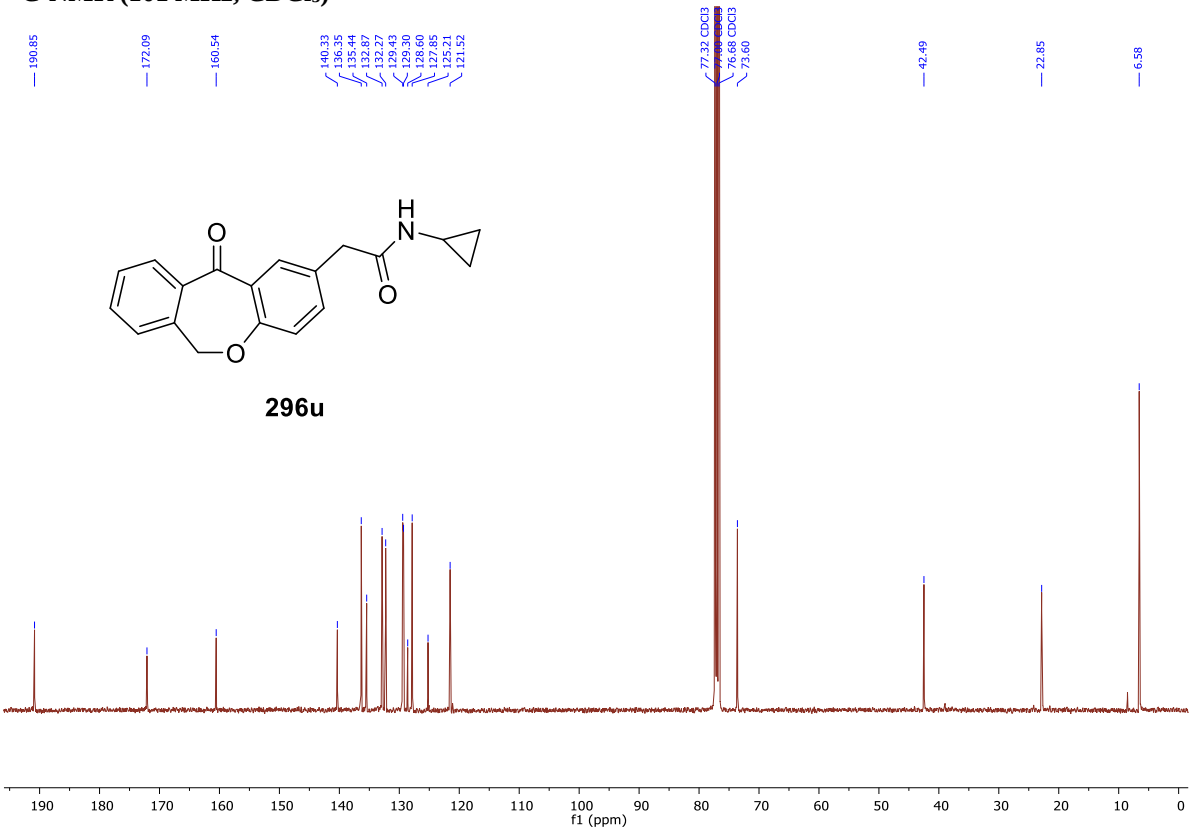
^{13}C-NMR (101 MHz, $CDCl_3$)



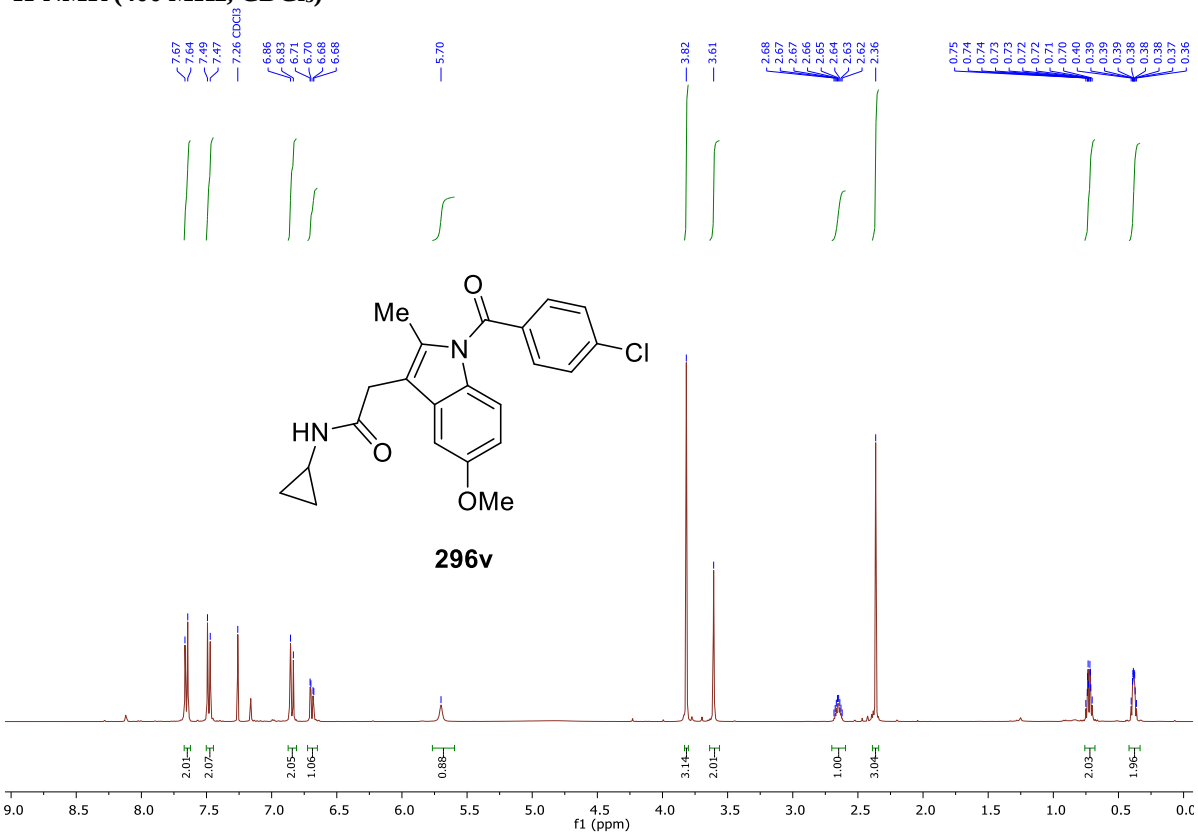
^{1}H-NMR (400 MHz, $CDCl_3$)



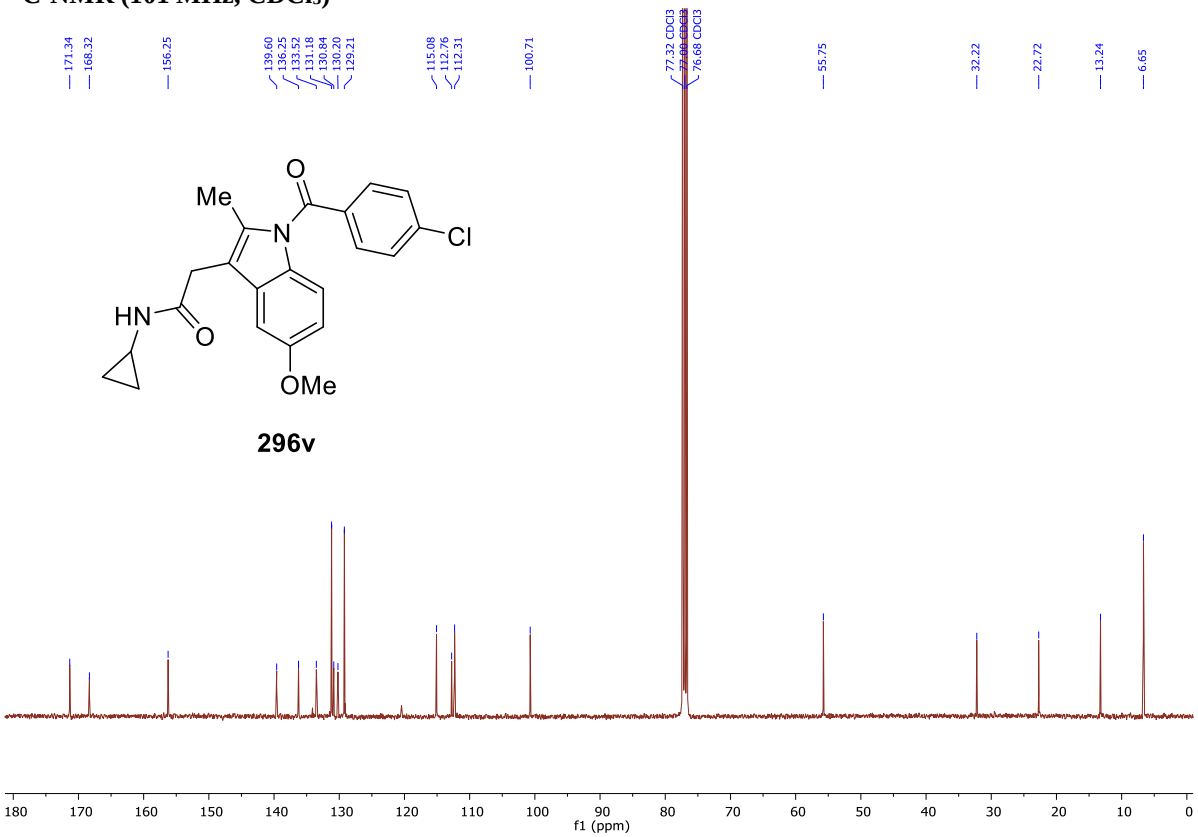
^{13}C-NMR (101 MHz, $CDCl_3$)



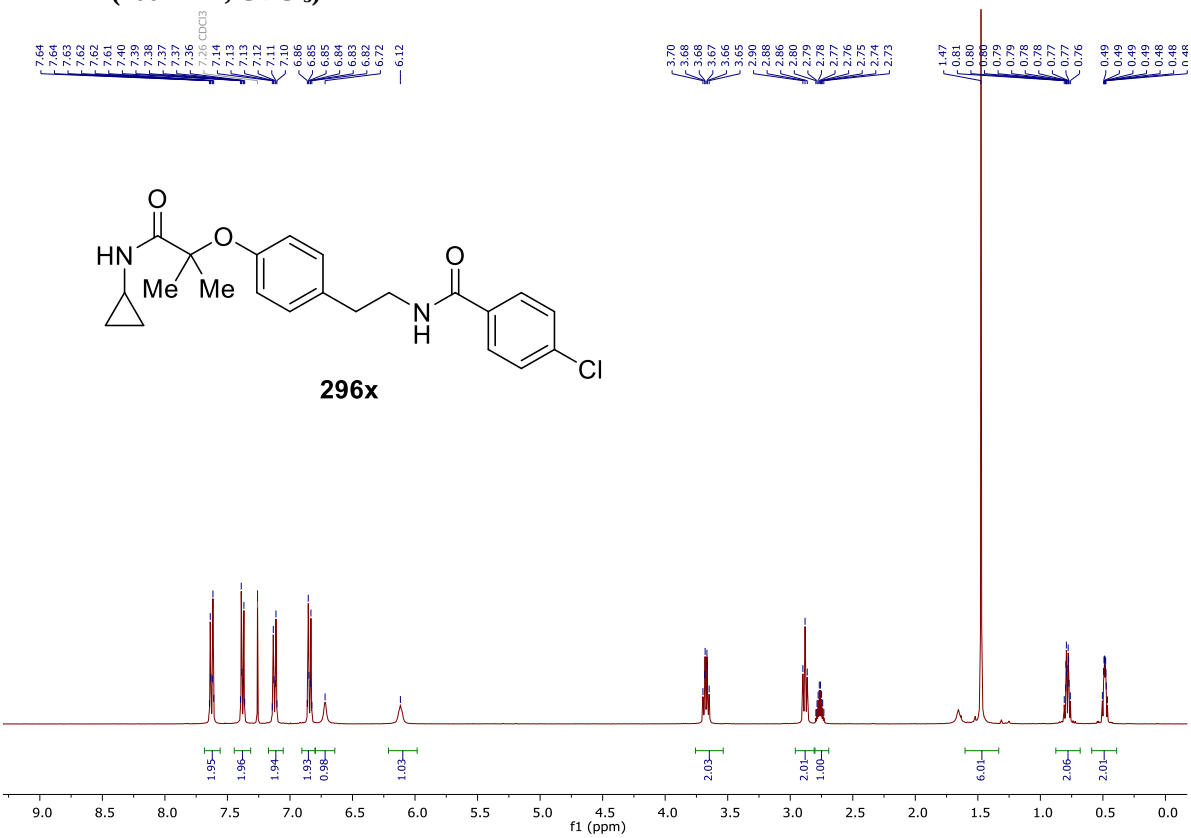
^{1}H-NMR (400 MHz, $CDCl_3$)



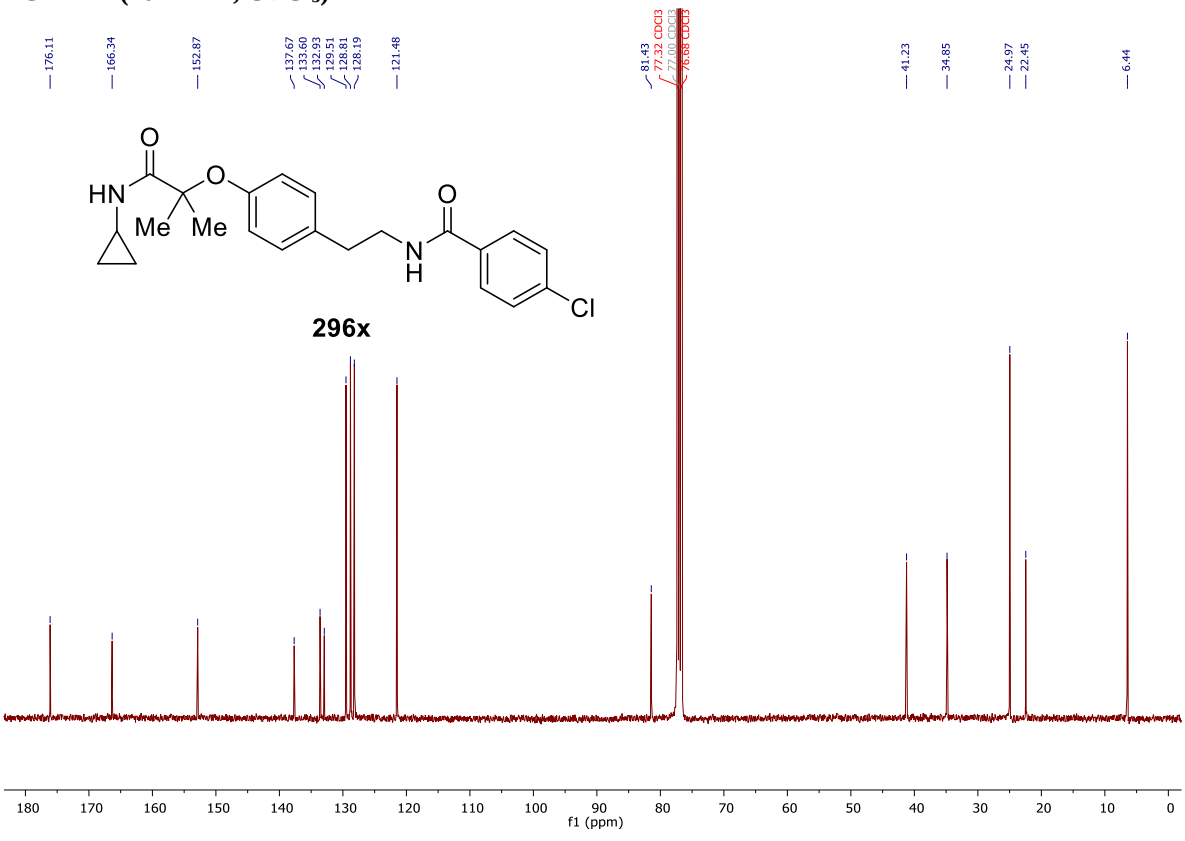
^{13}C-NMR (101 MHz, $CDCl_3$)



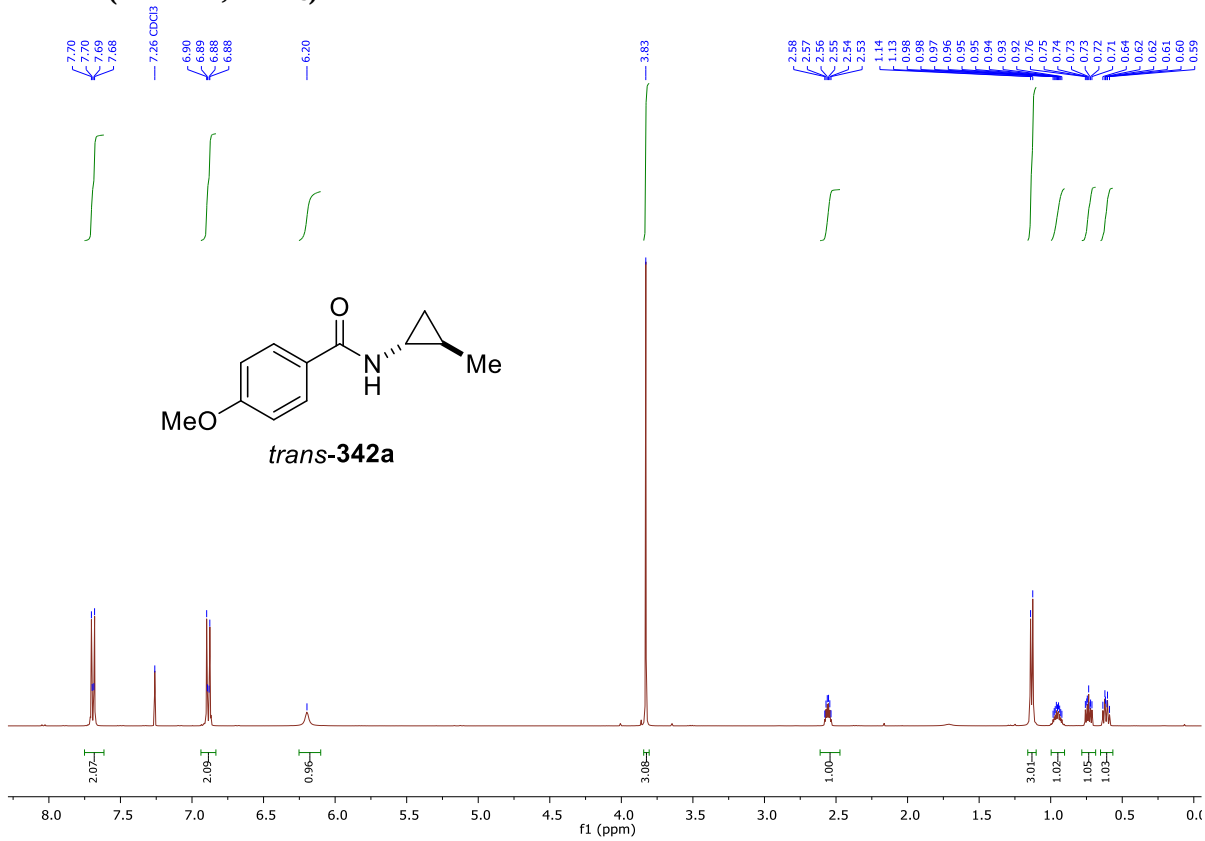
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

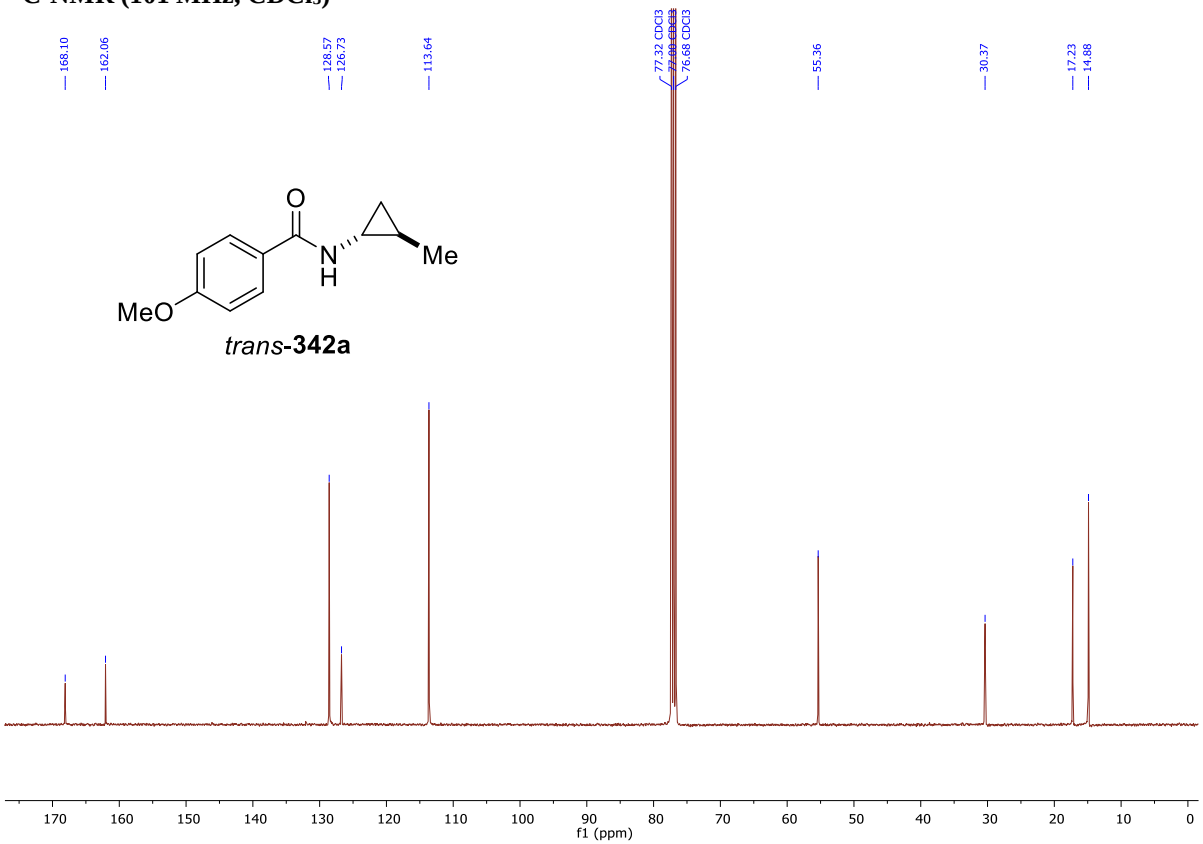


^{1}H-NMR (400 MHz, $CDCl_3$)



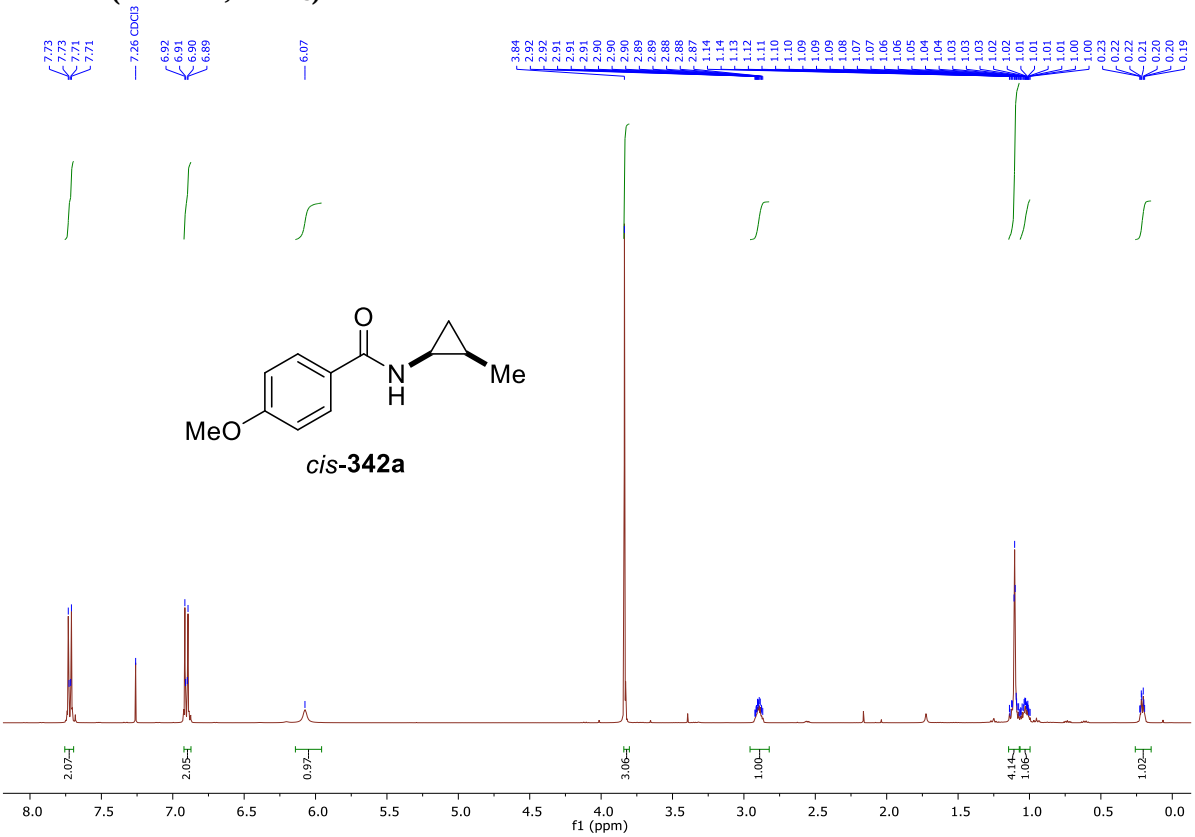
trans-**342a**

^{13}C-NMR (101 MHz, $CDCl_3$)

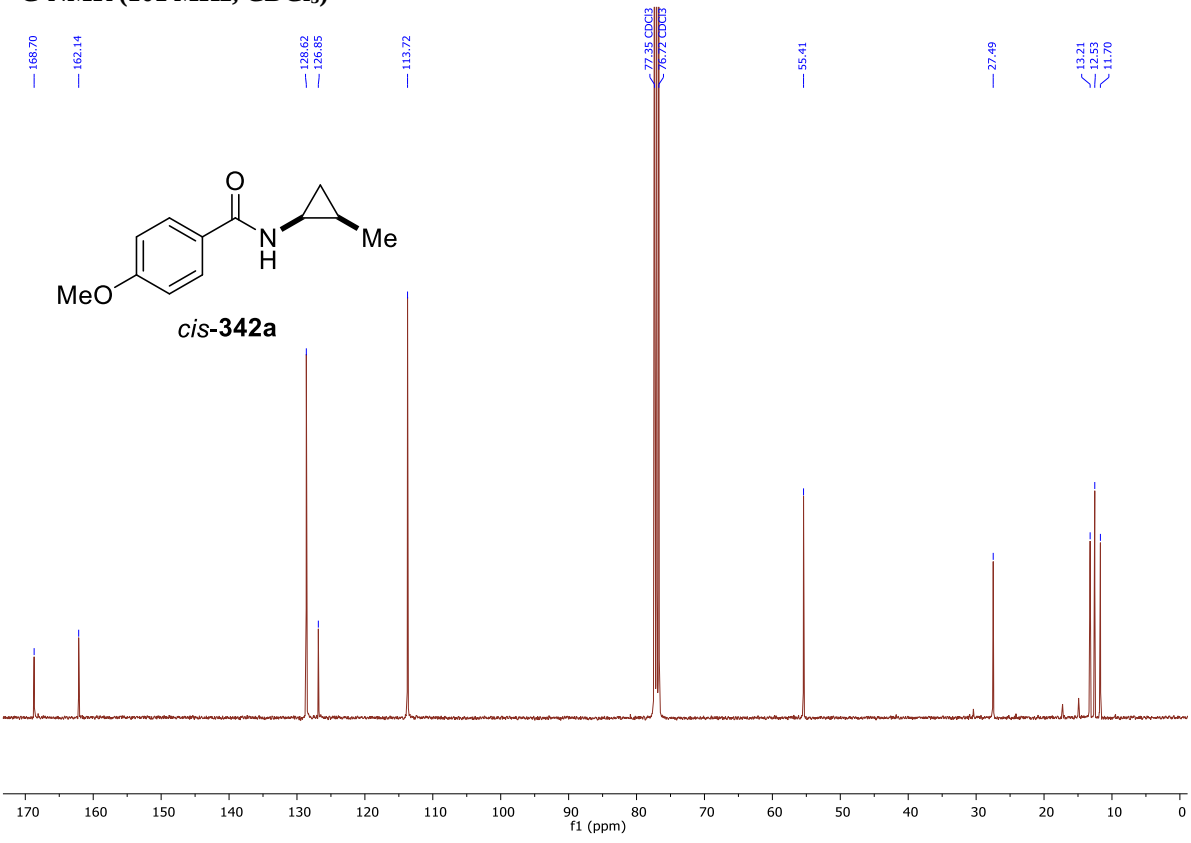


trans-**342a**

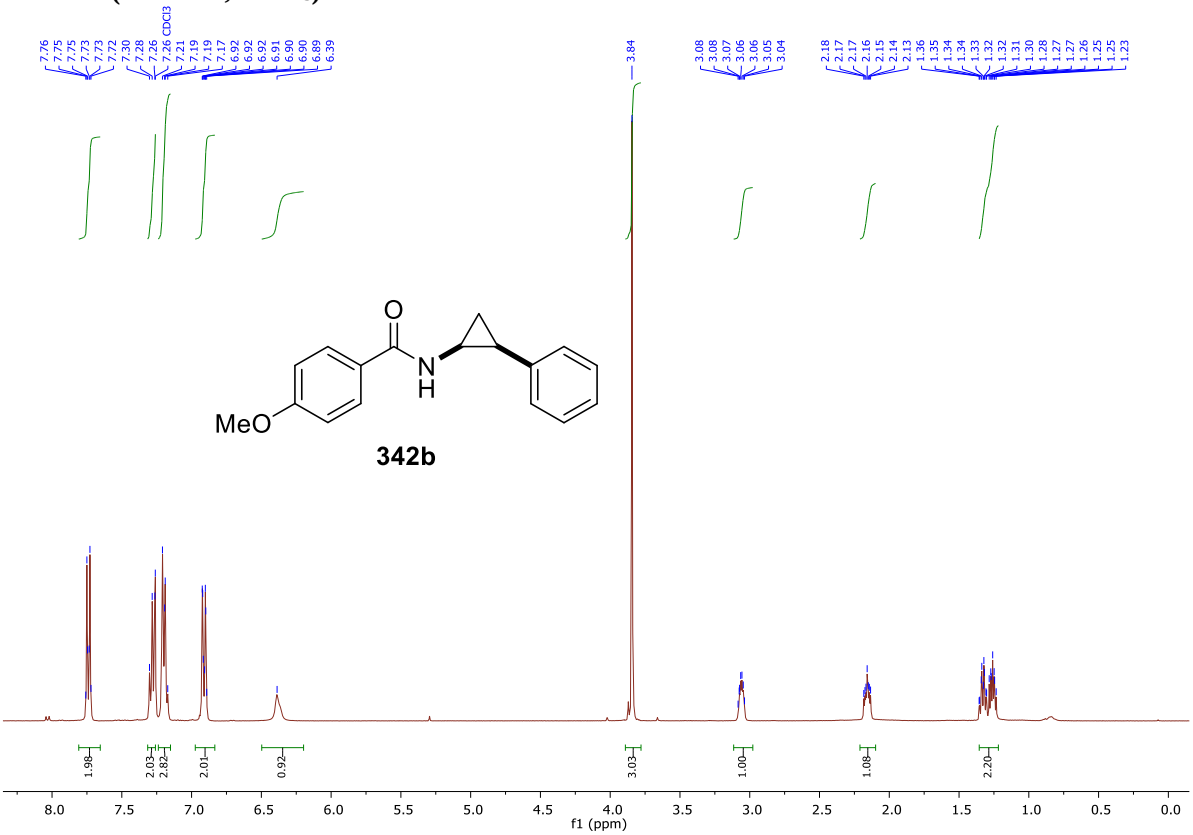
^{1}H-NMR (400 MHz, $CDCl_3$)



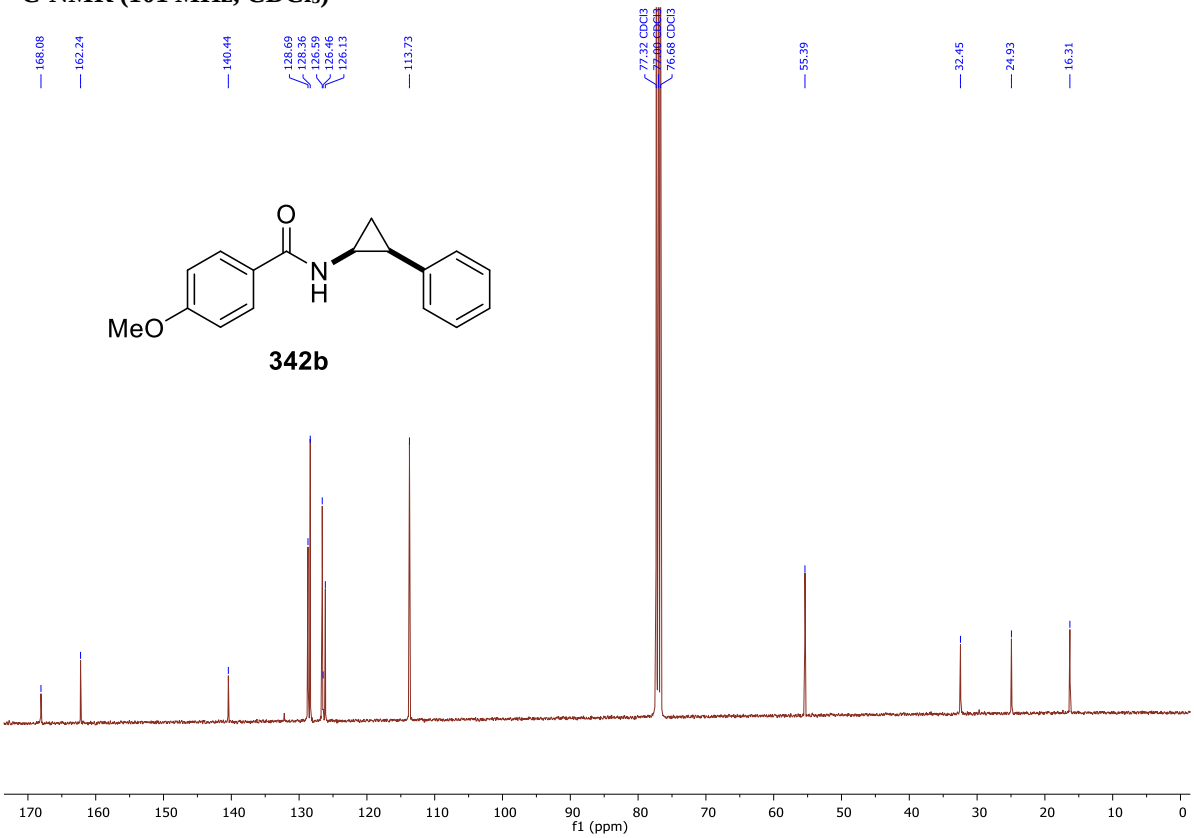
^{13}C-NMR (101 MHz, $CDCl_3$)



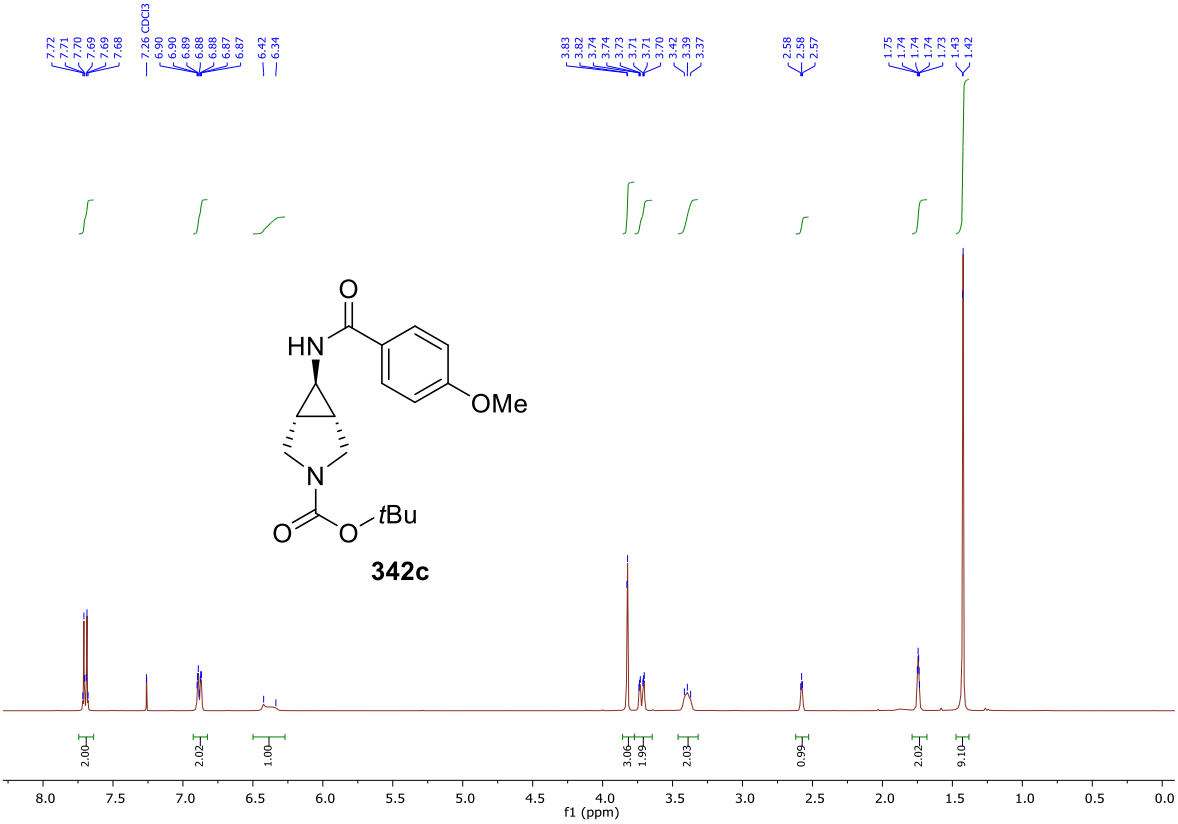
^{1}H-NMR (400 MHz, $CDCl_3$)



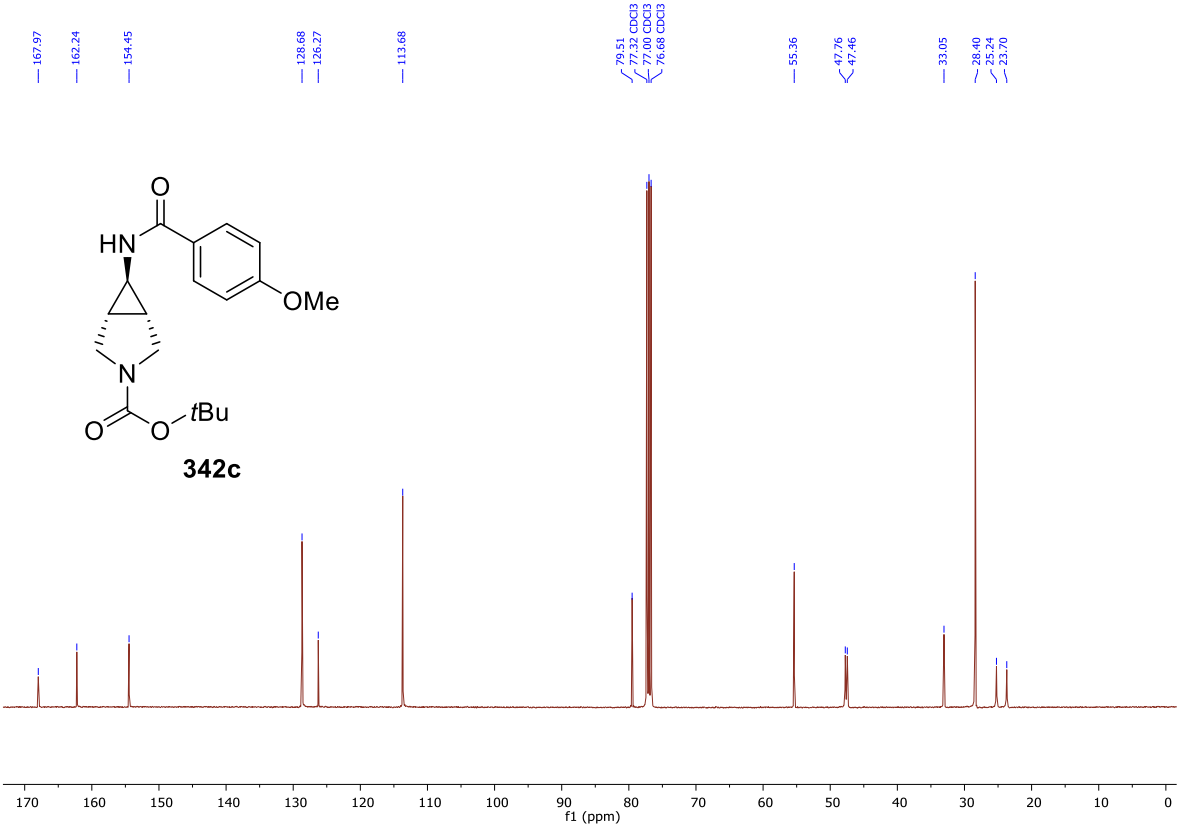
^{13}C-NMR (101 MHz, $CDCl_3$)



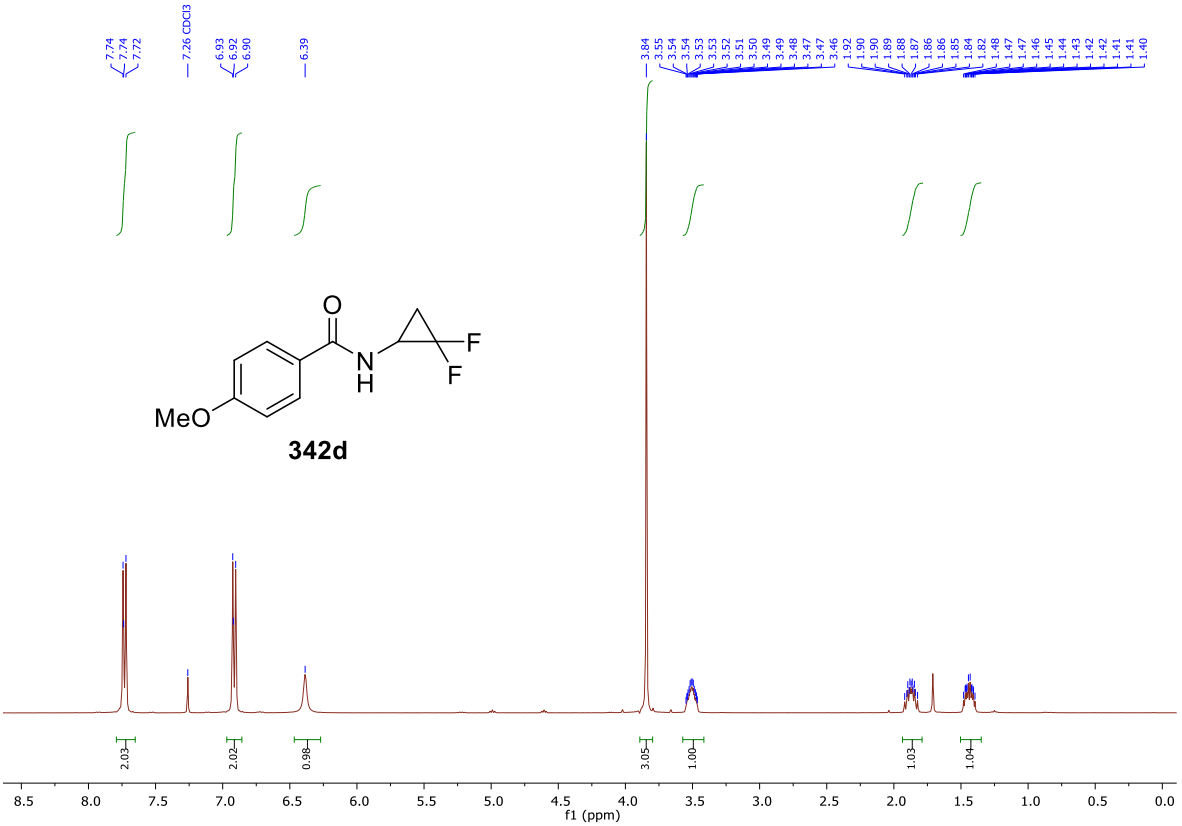
^{1}H-NMR (400 MHz, $CDCl_3$)



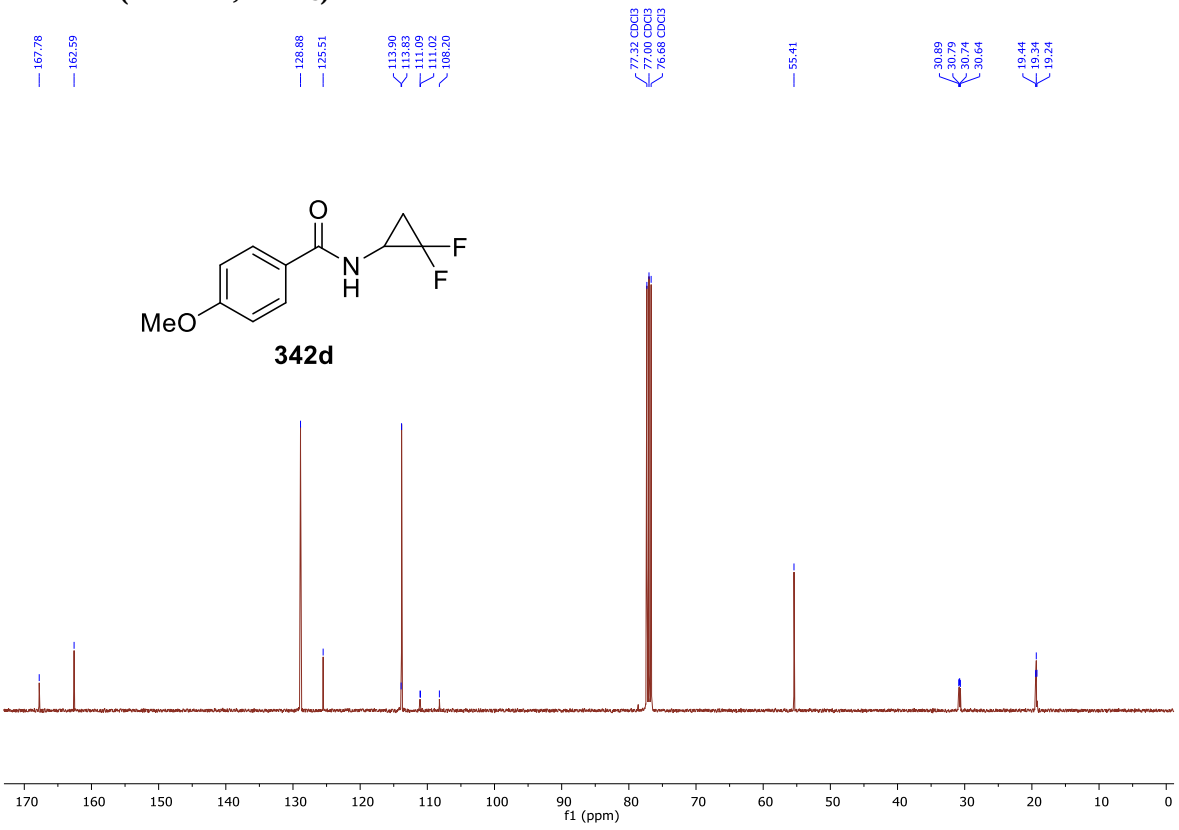
^{13}C-NMR (101 MHz, $CDCl_3$)



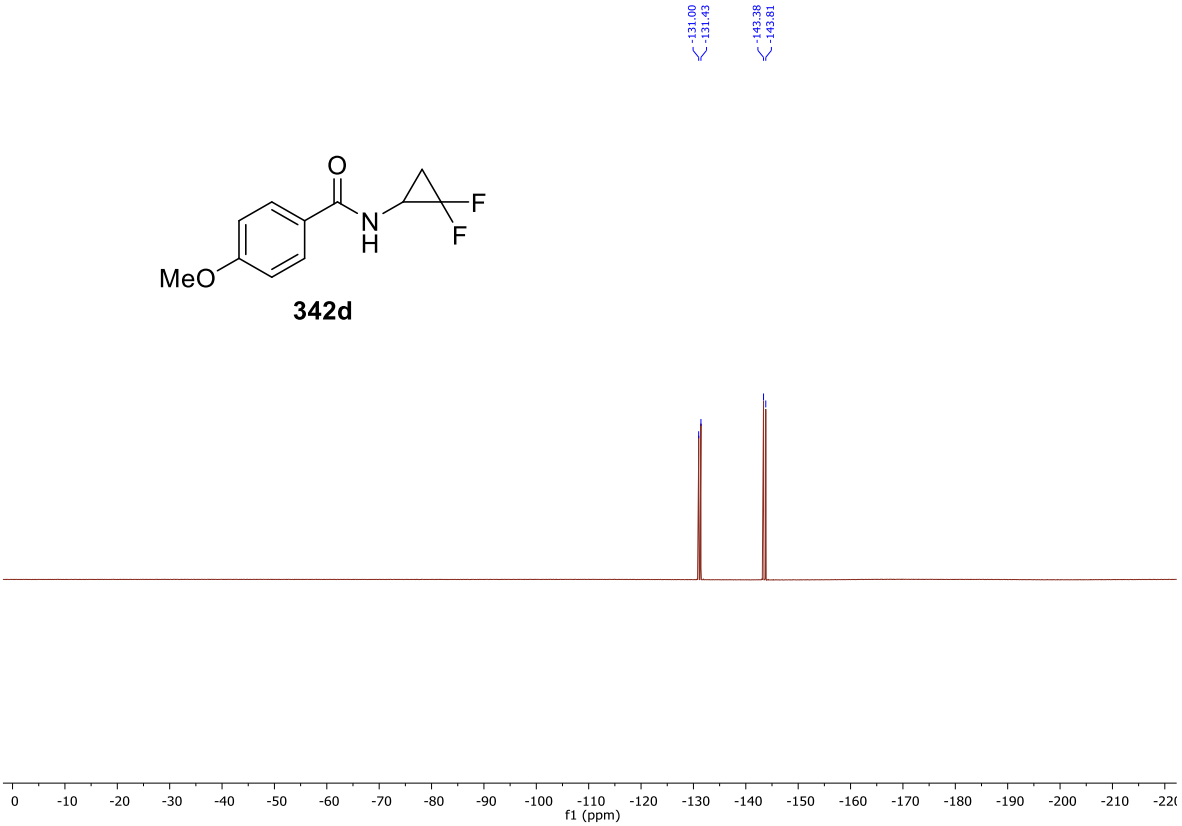
^{1}H-NMR (400 MHz, $CDCl_3$)



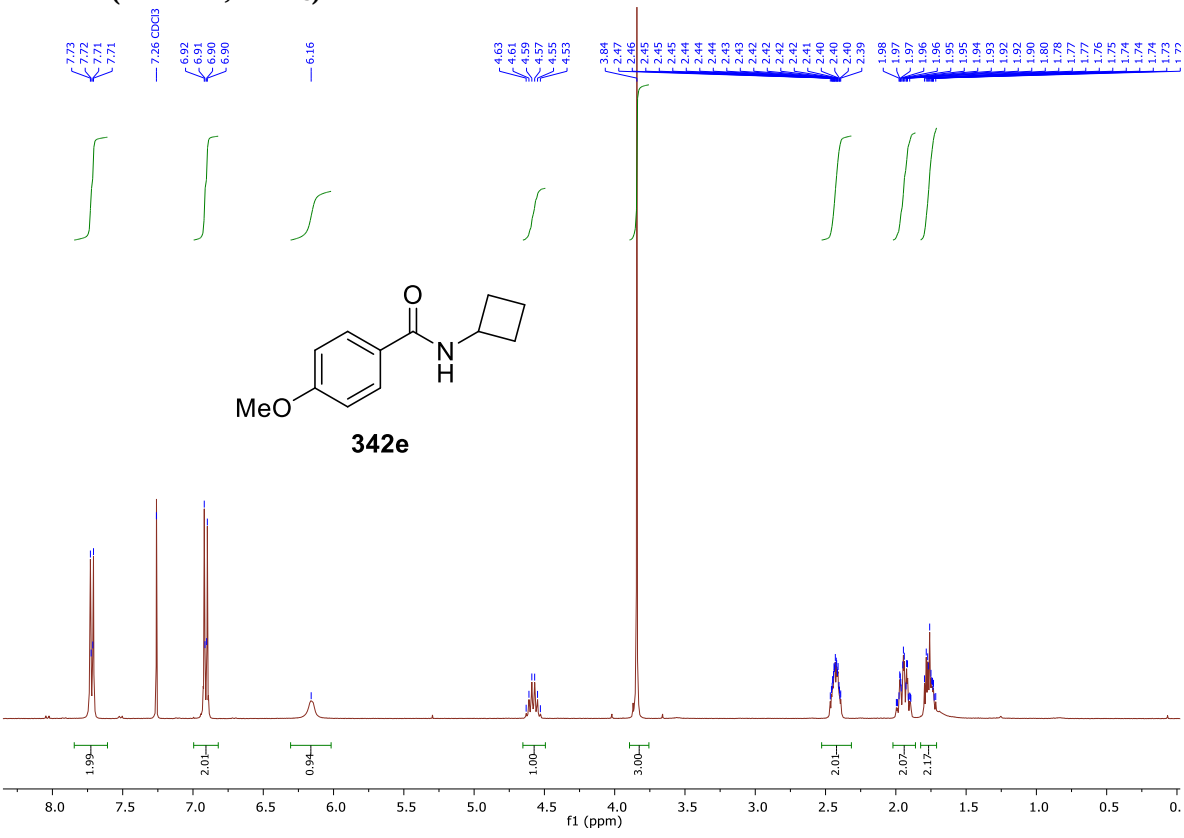
^{13}C-NMR (101 MHz, $CDCl_3$)



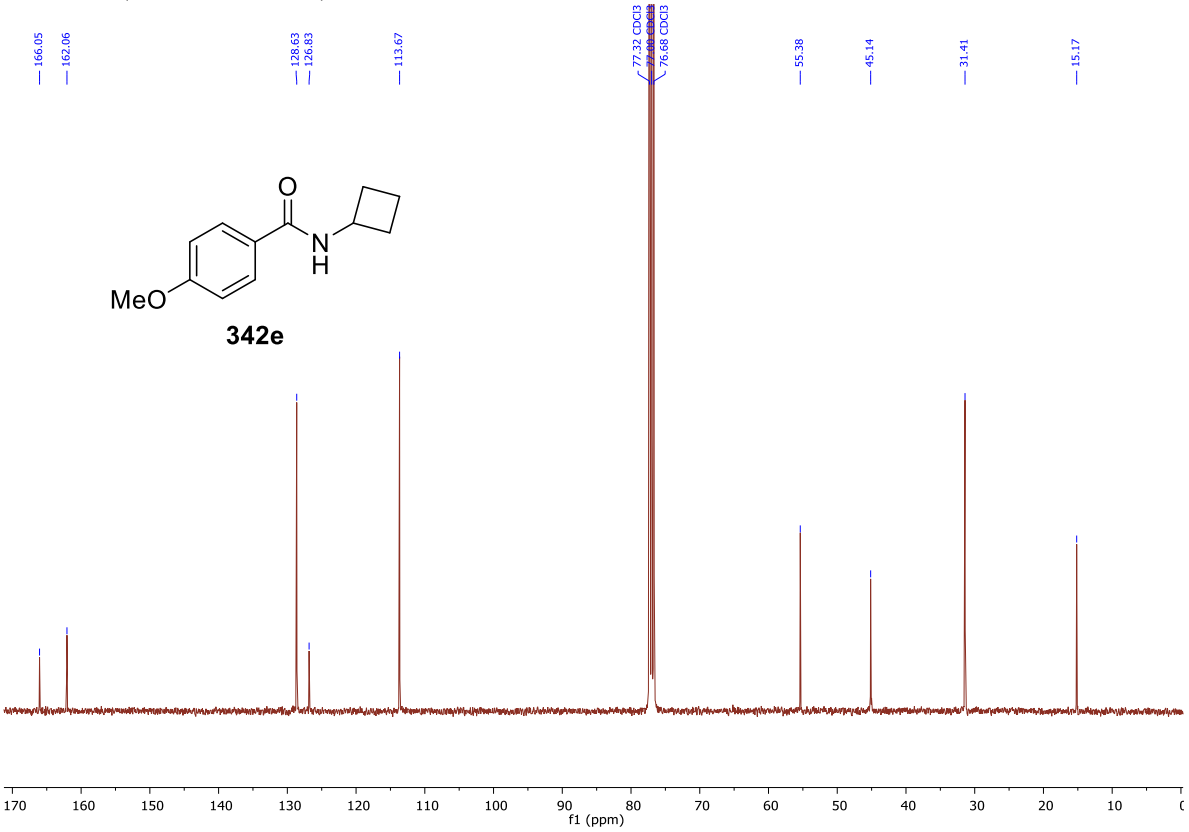
^{19}F-NMR (376 MHz, $CDCl_3$)



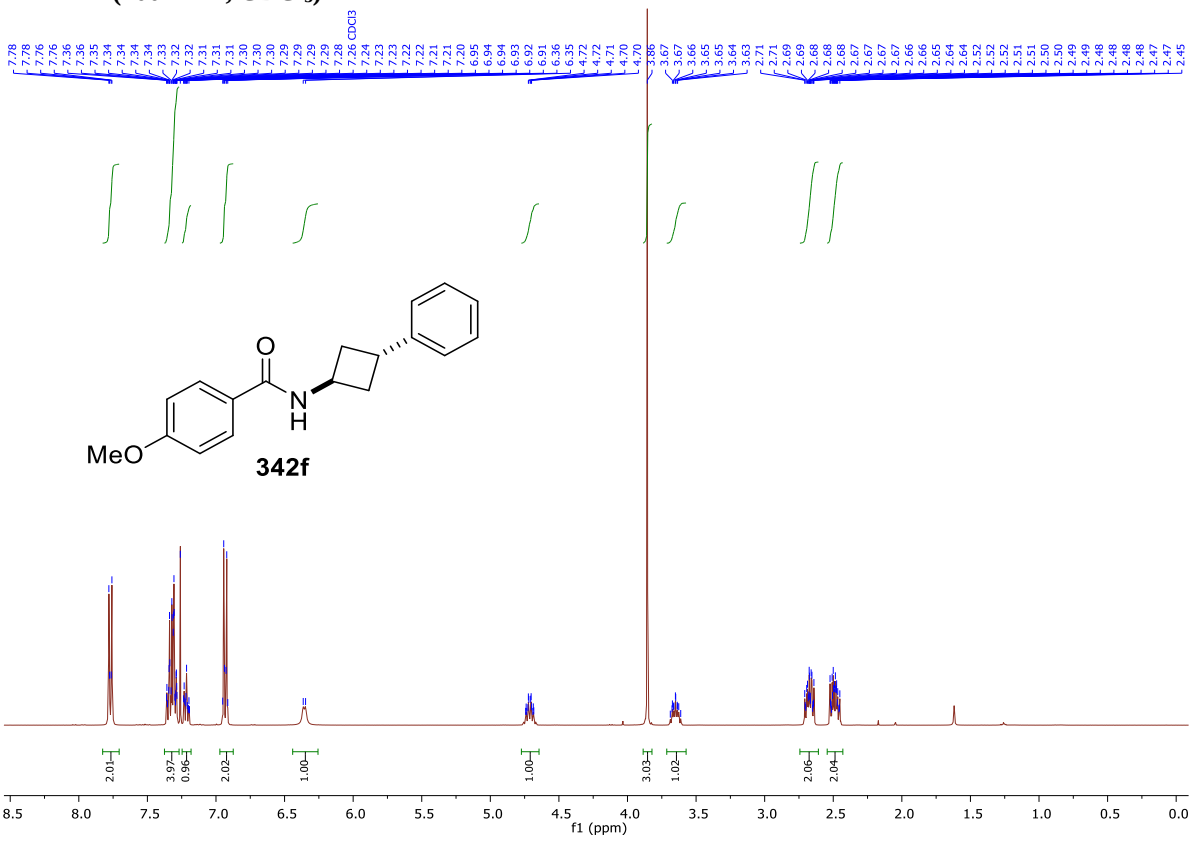
^{1}H-NMR (400 MHz, $CDCl_3$)



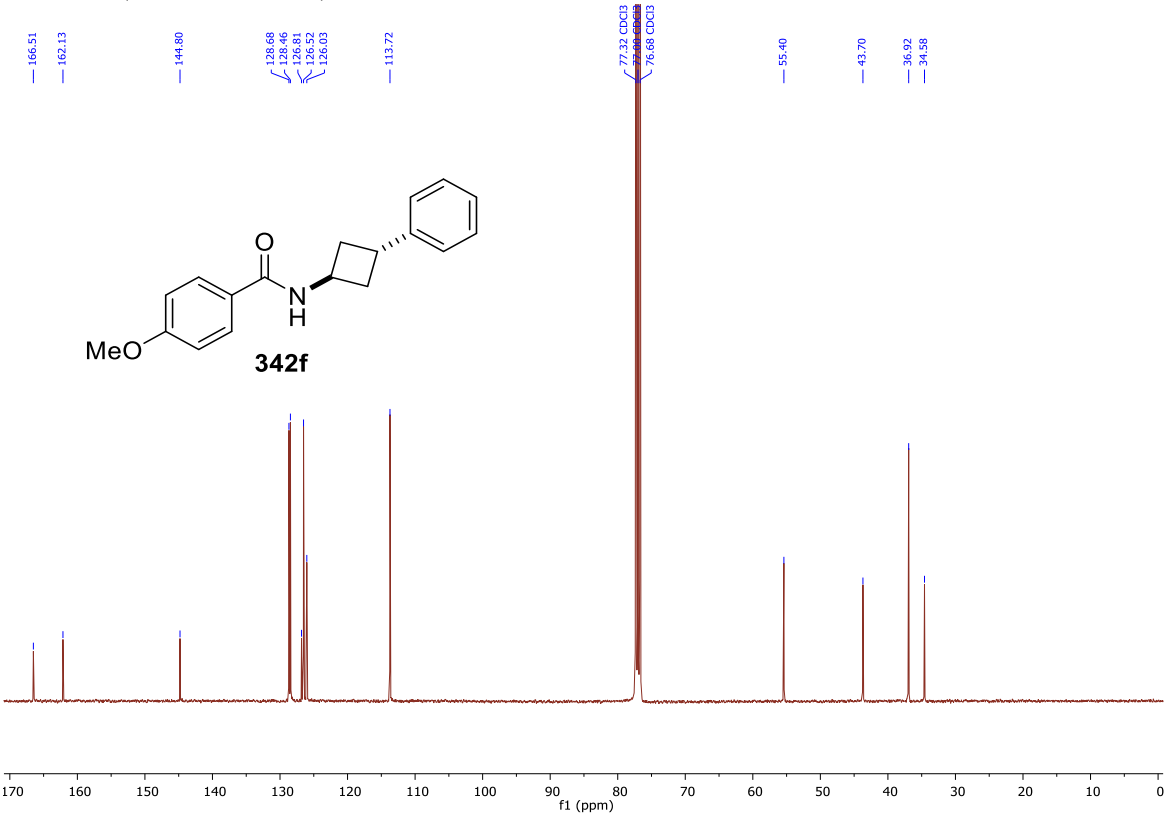
^{13}C-NMR (101 MHz, $CDCl_3$)



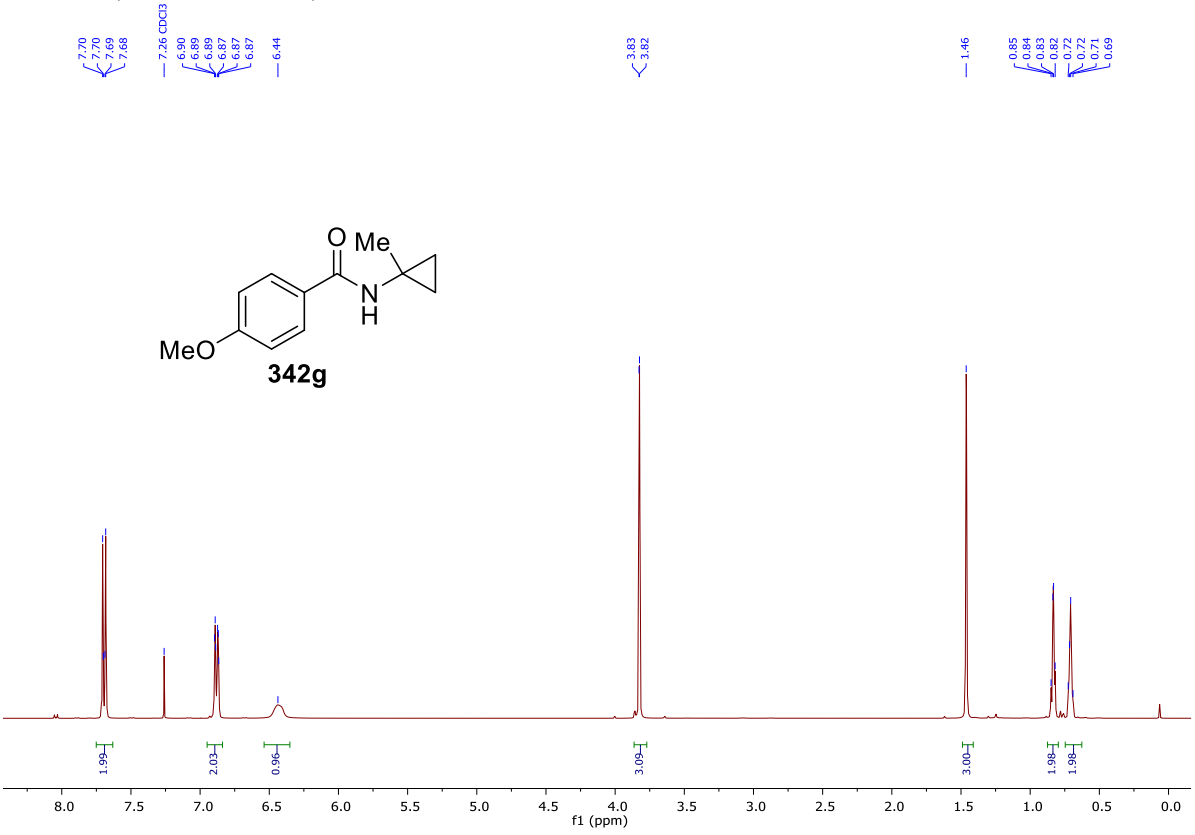
^{1}H-NMR (400 MHz, $CDCl_3$)



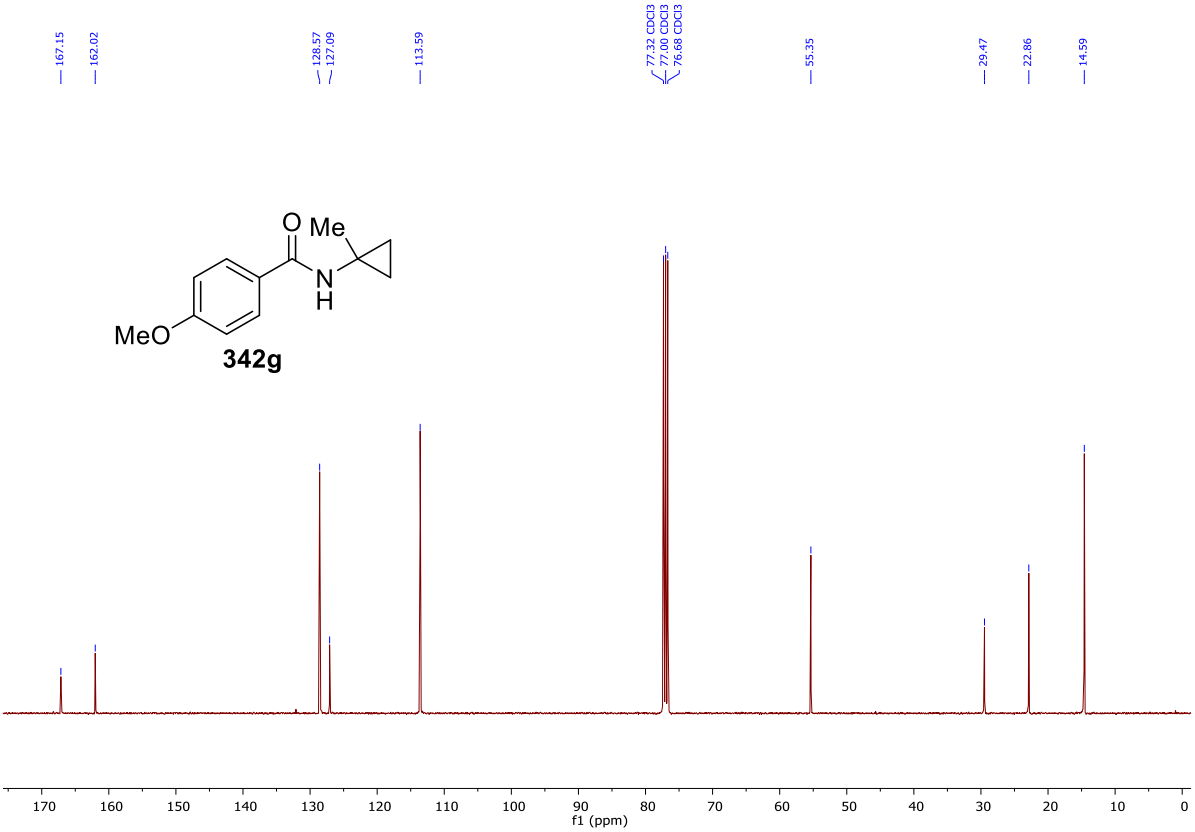
^{13}C-NMR (101 MHz, $CDCl_3$)



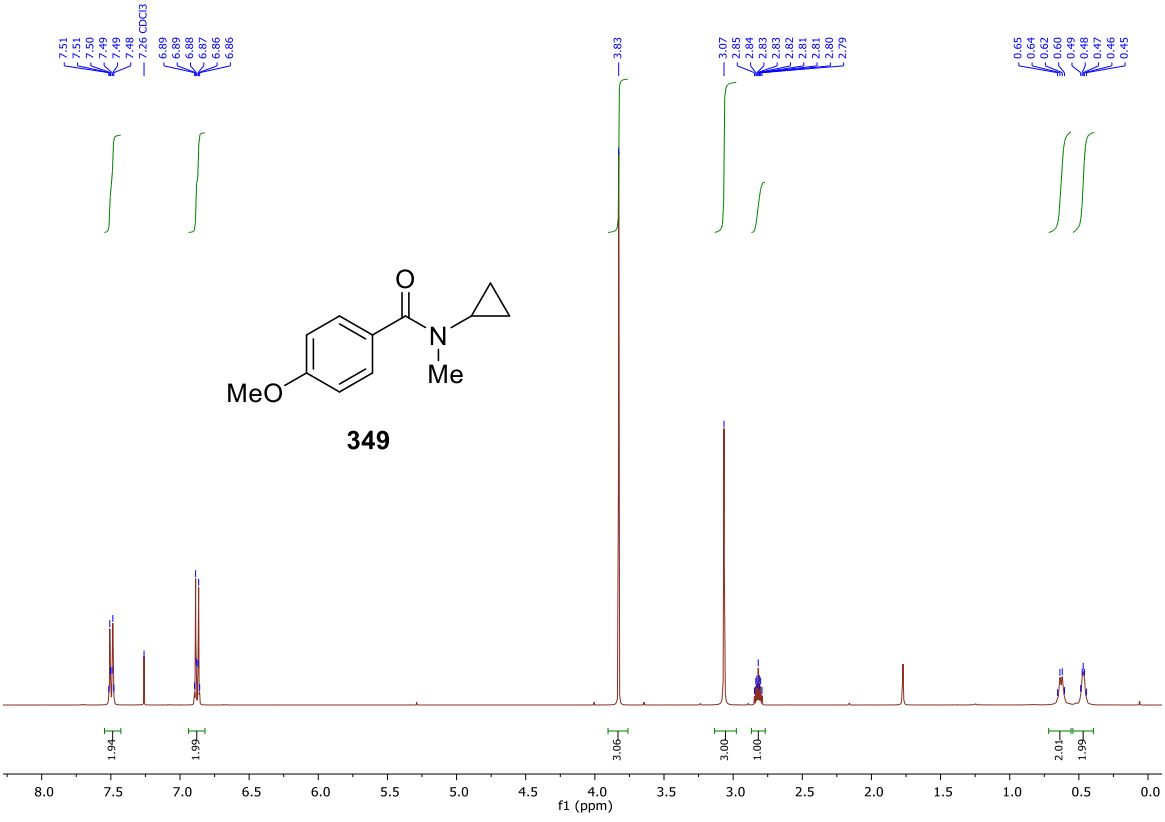
^{1}H-NMR (400 MHz, $CDCl_3$)



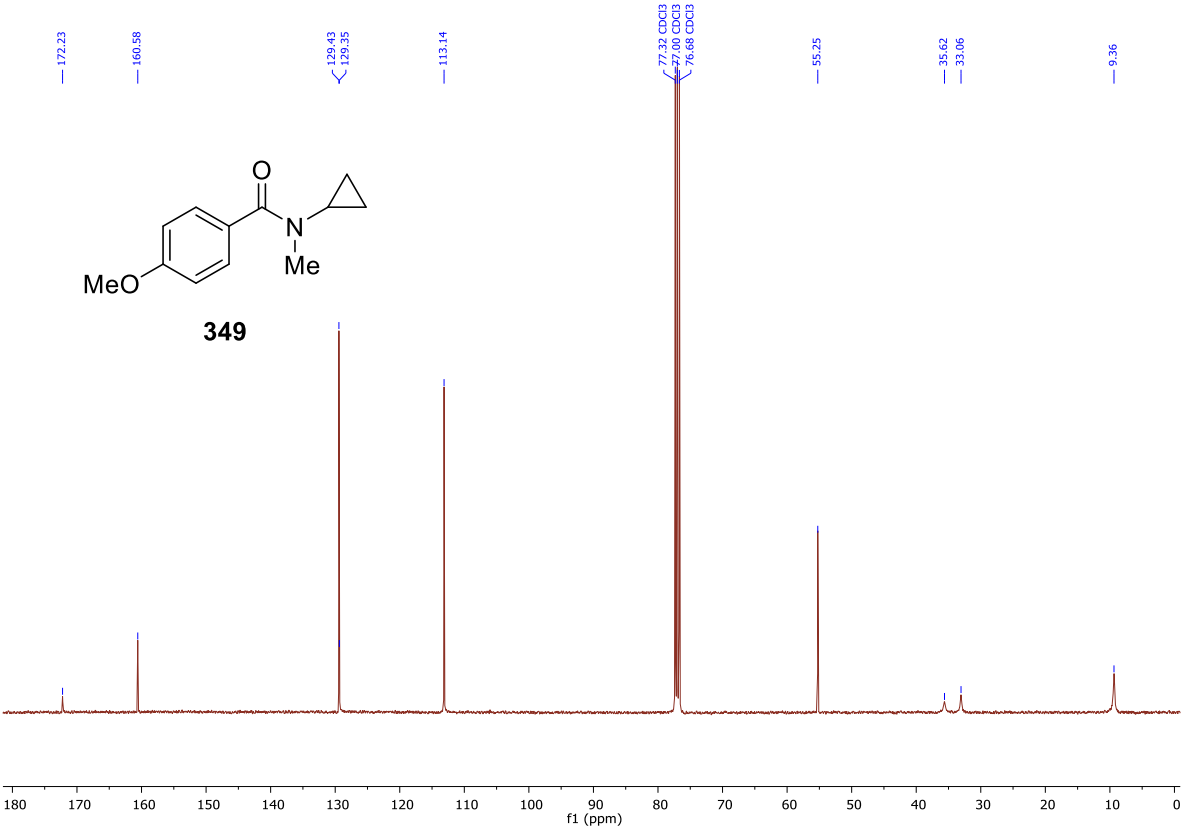
^{13}C-NMR (101 MHz, $CDCl_3$)



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

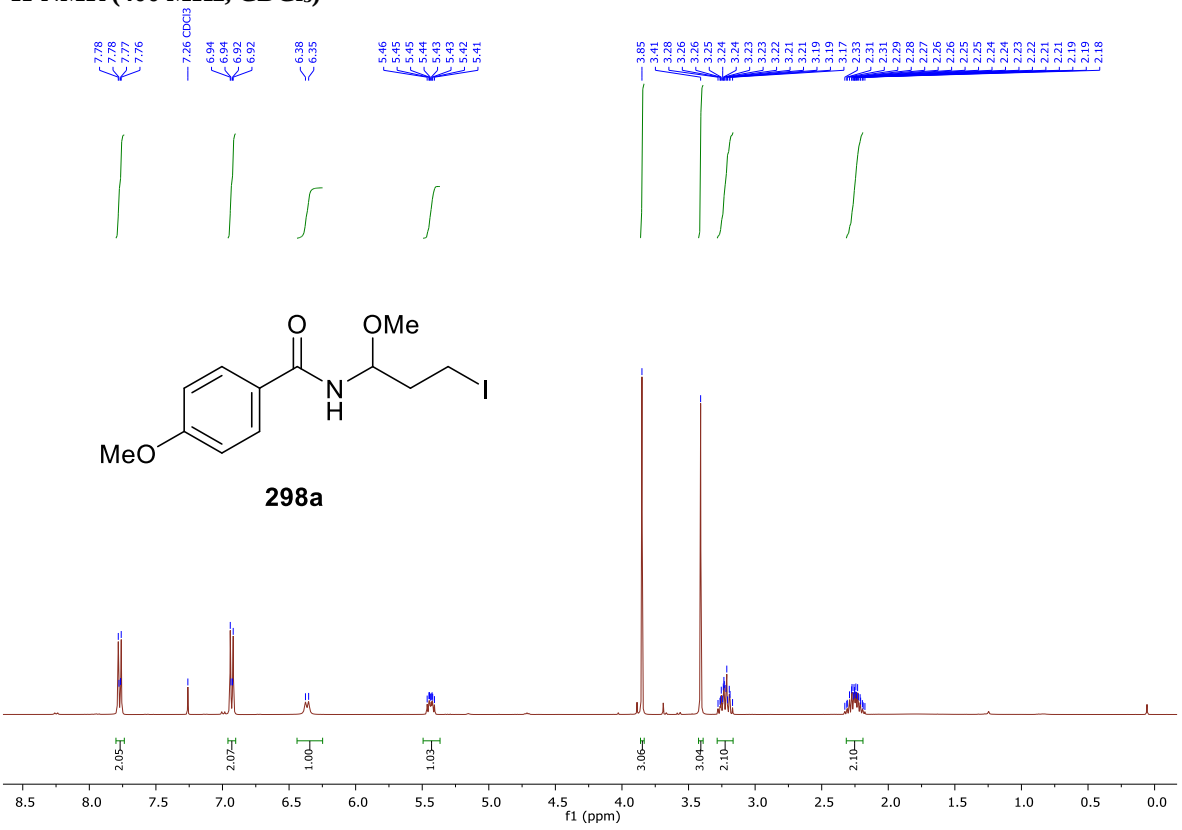


^{13}C-NMR (101 MHz, $CDCl_3$)



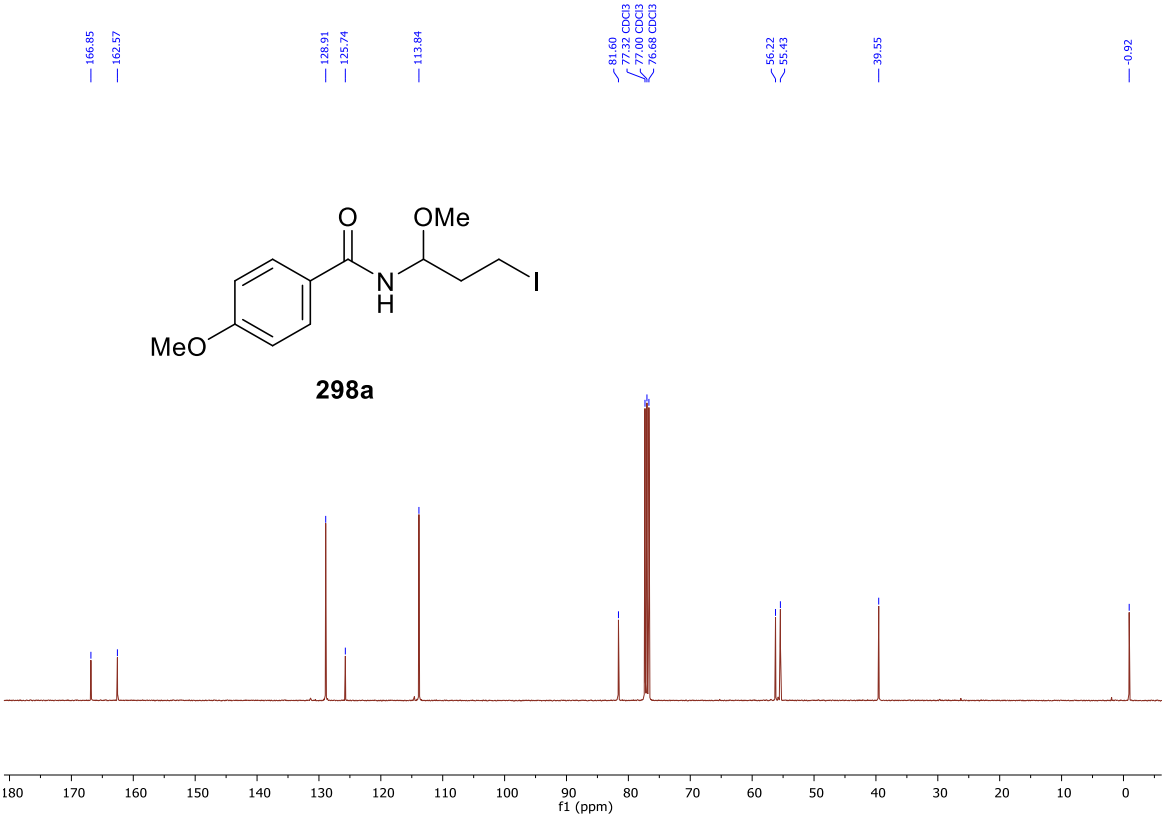
349

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



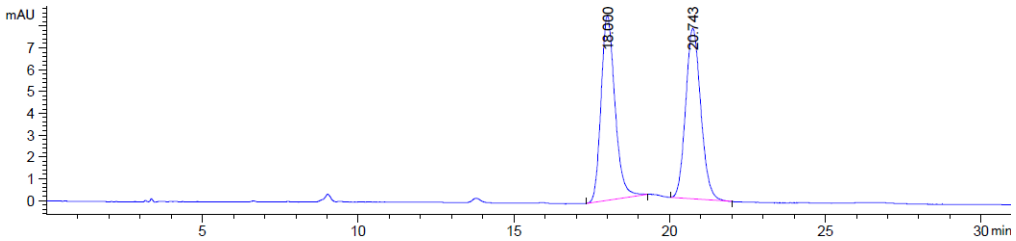
298a

^{13}C-NMR (101 MHz, $CDCl_3$)

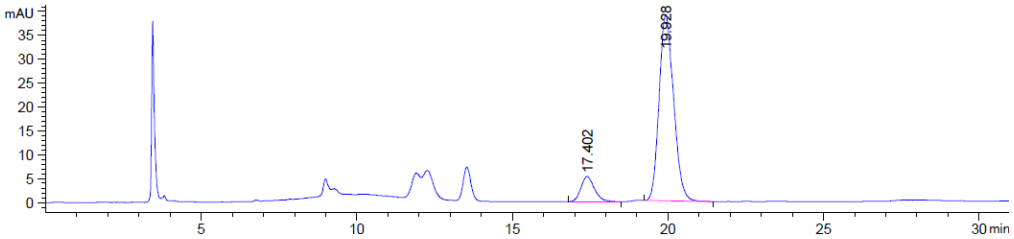


298a

HPLC

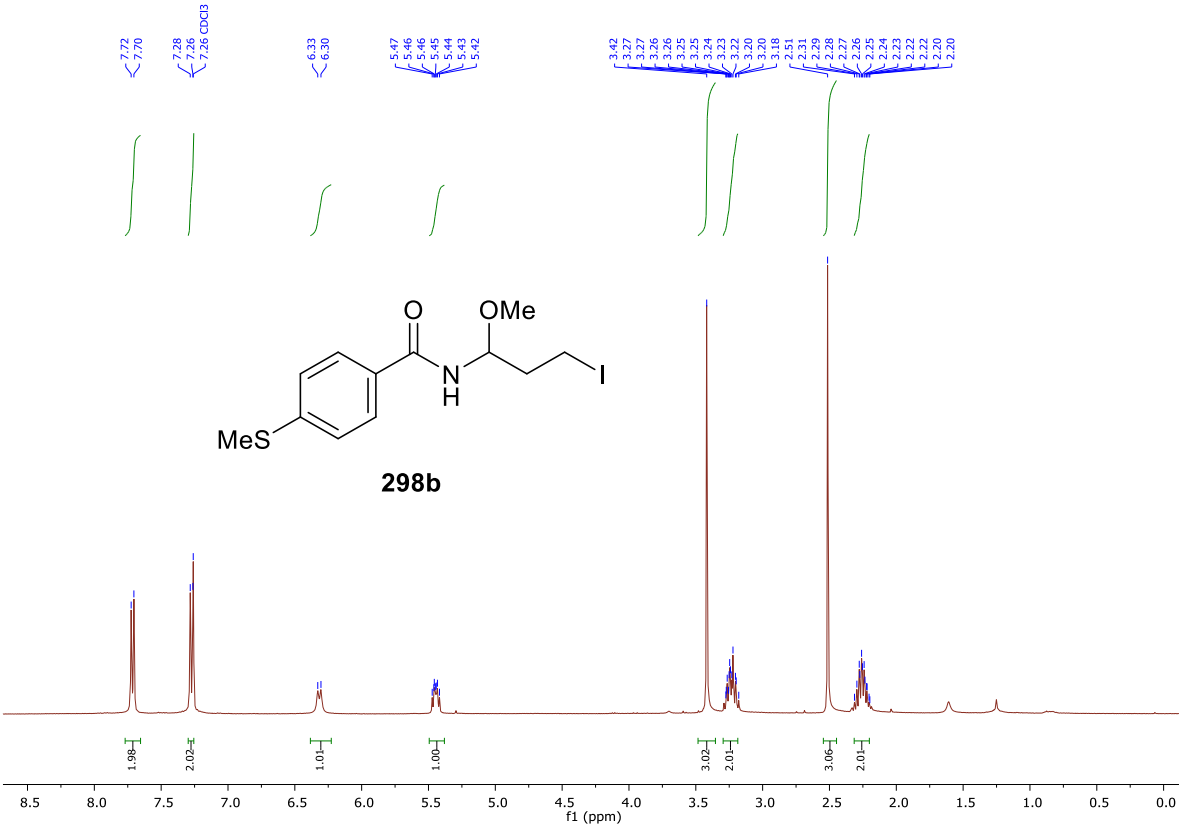


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.000	BB	0.4742	262.42535	8.45173	49.8710
2	20.743	BB	0.5242	263.78317	7.80741	50.1290

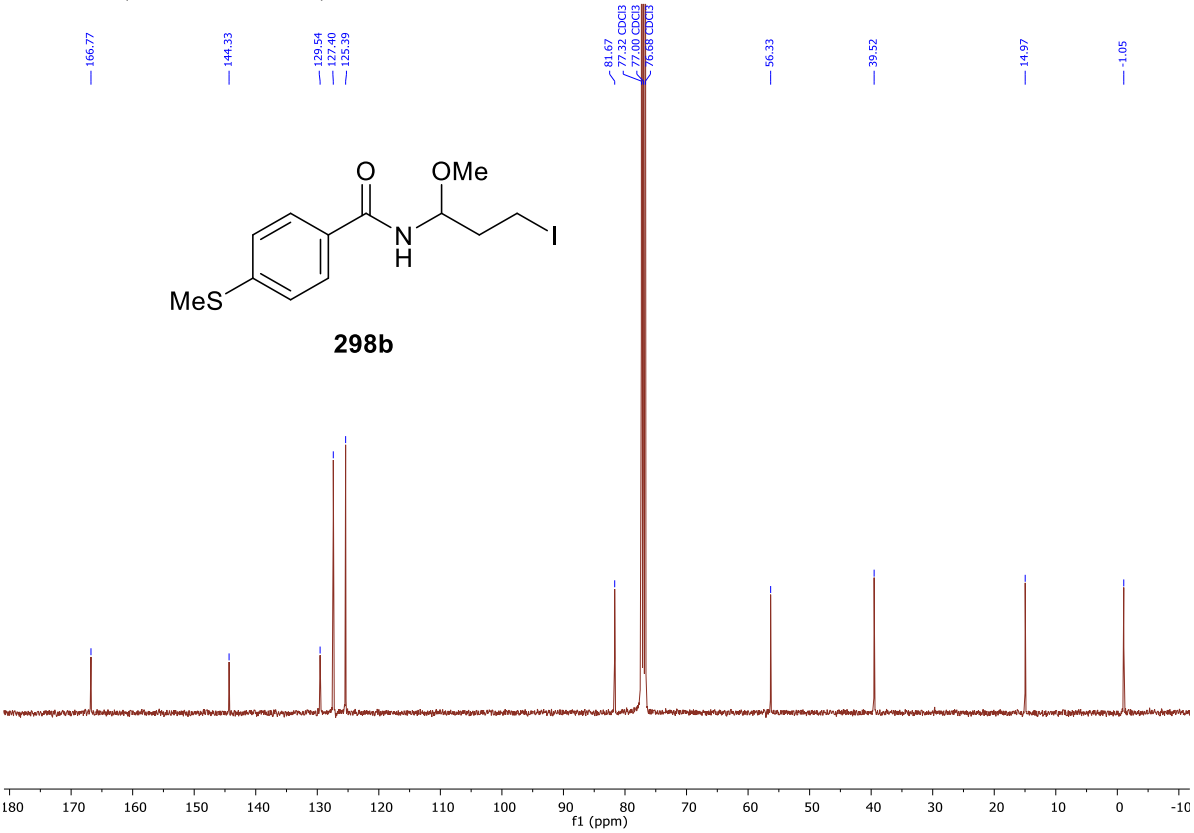


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.402	BB	0.4508	157.17209	5.25709	11.0808
2	19.928	BB	0.4757	1261.24243	38.95499	88.9192

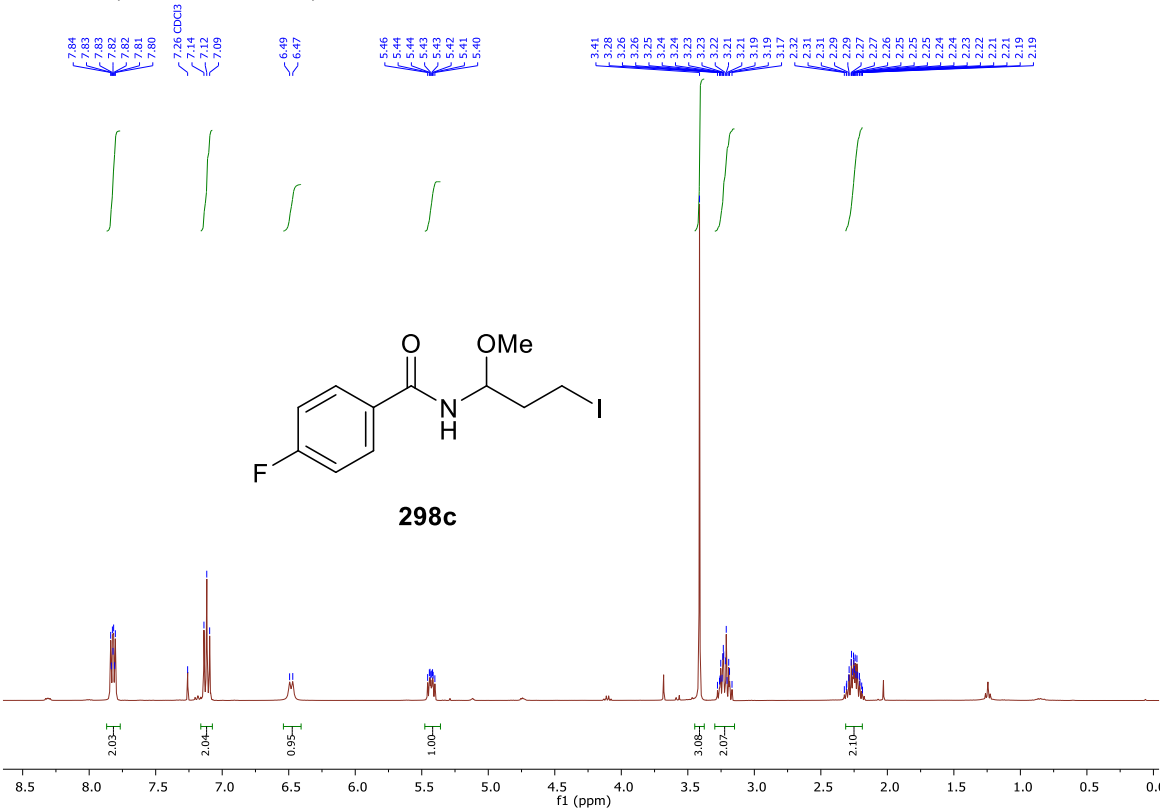
^{1}H-NMR (400 MHz, $CDCl_3$)



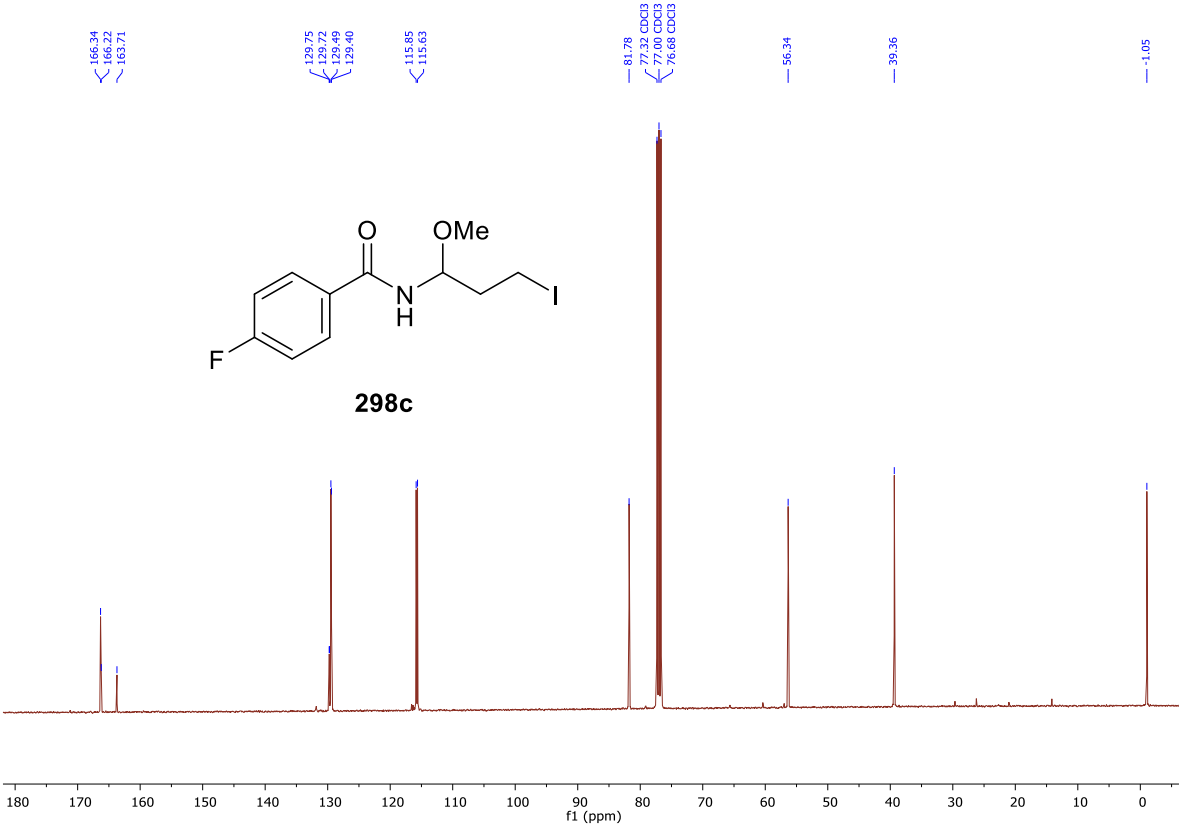
^{13}C-NMR (101 MHz, $CDCl_3$)



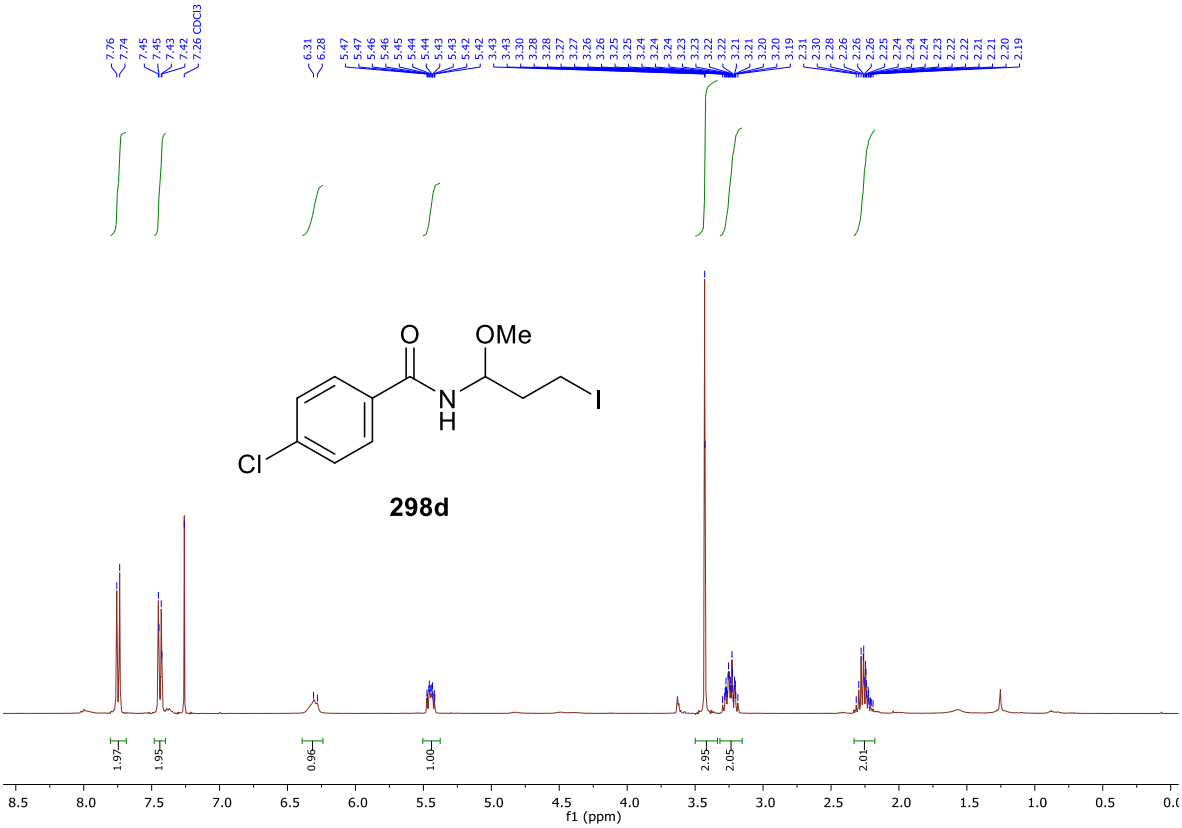
^{1}H-NMR (400 MHz, $CDCl_3$)



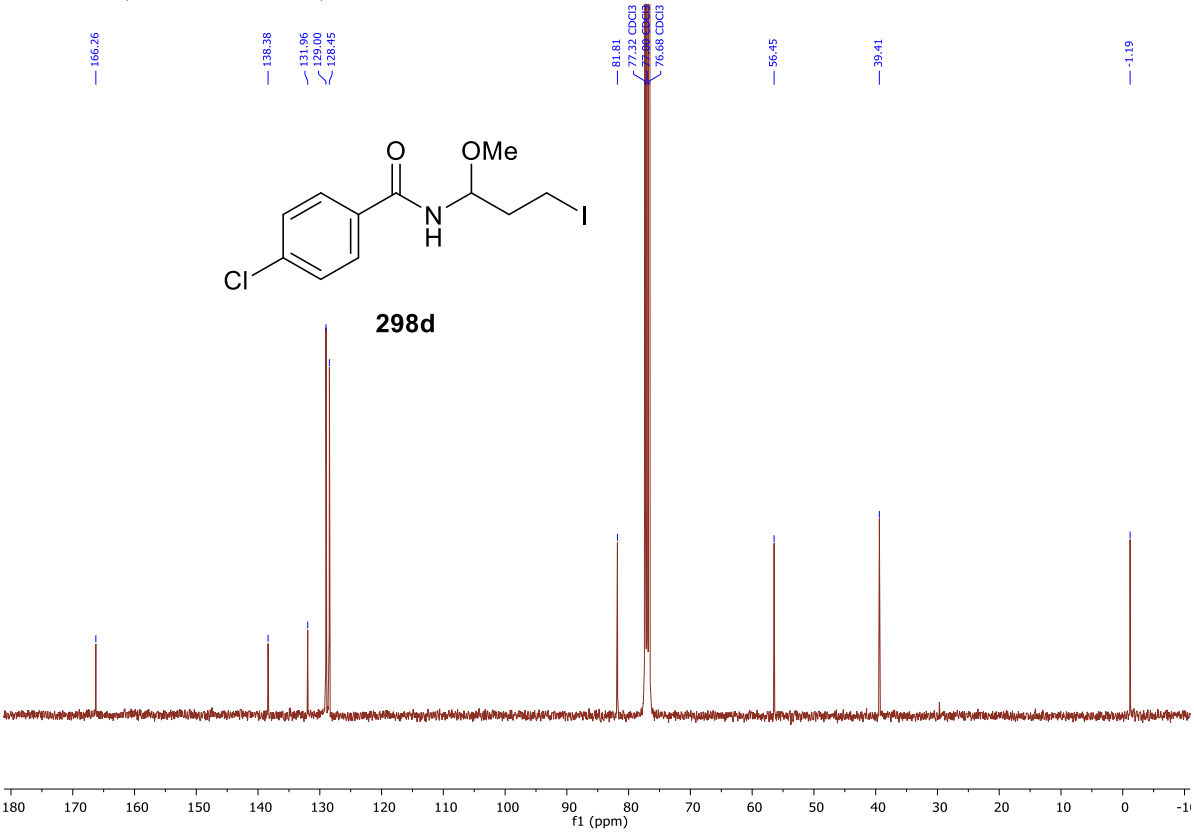
^{13}C-NMR (101 MHz, $CDCl_3$)



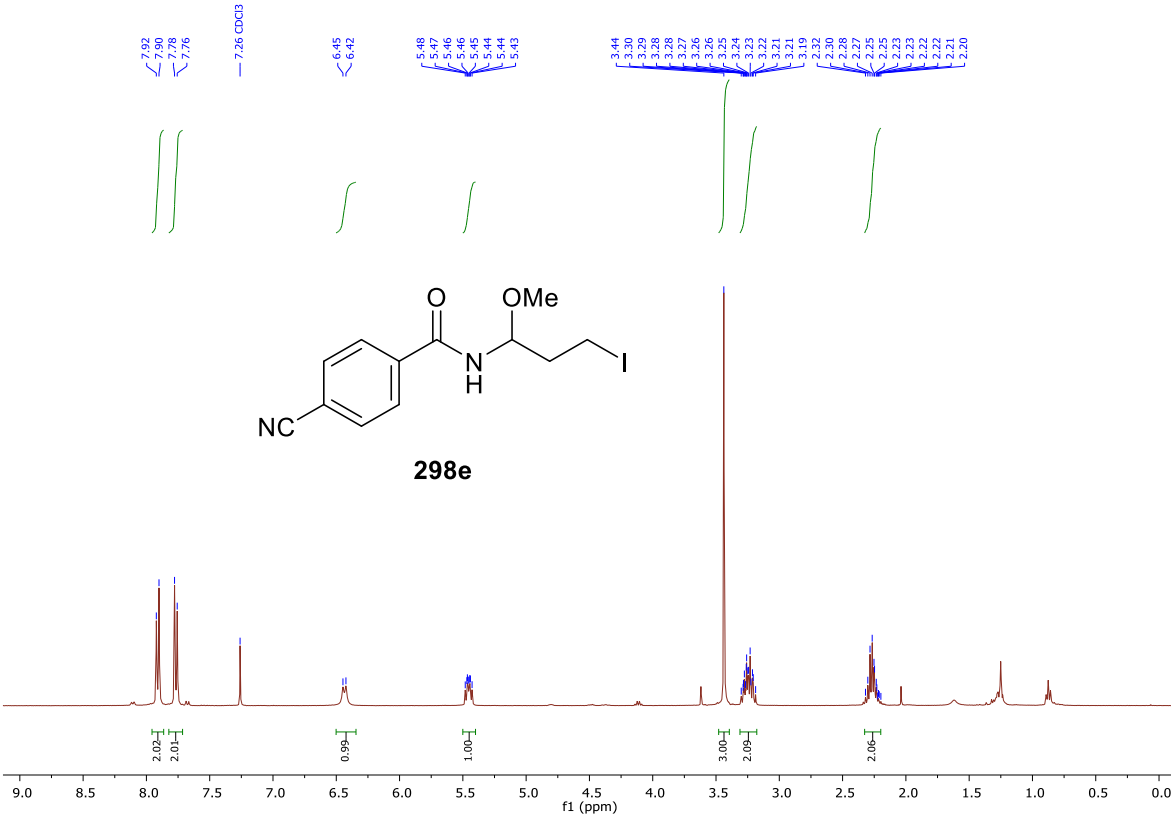
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

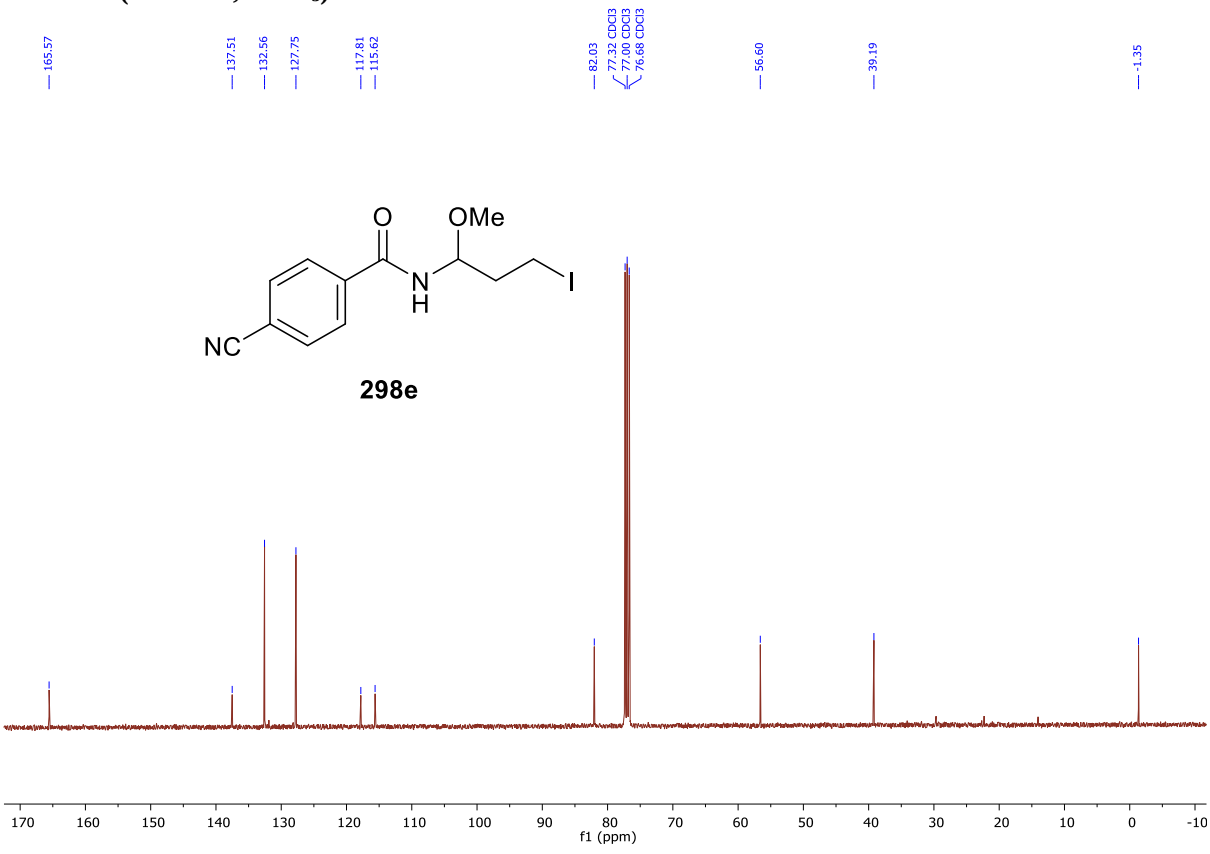


^{1}H-NMR (400 MHz, $CDCl_3$)



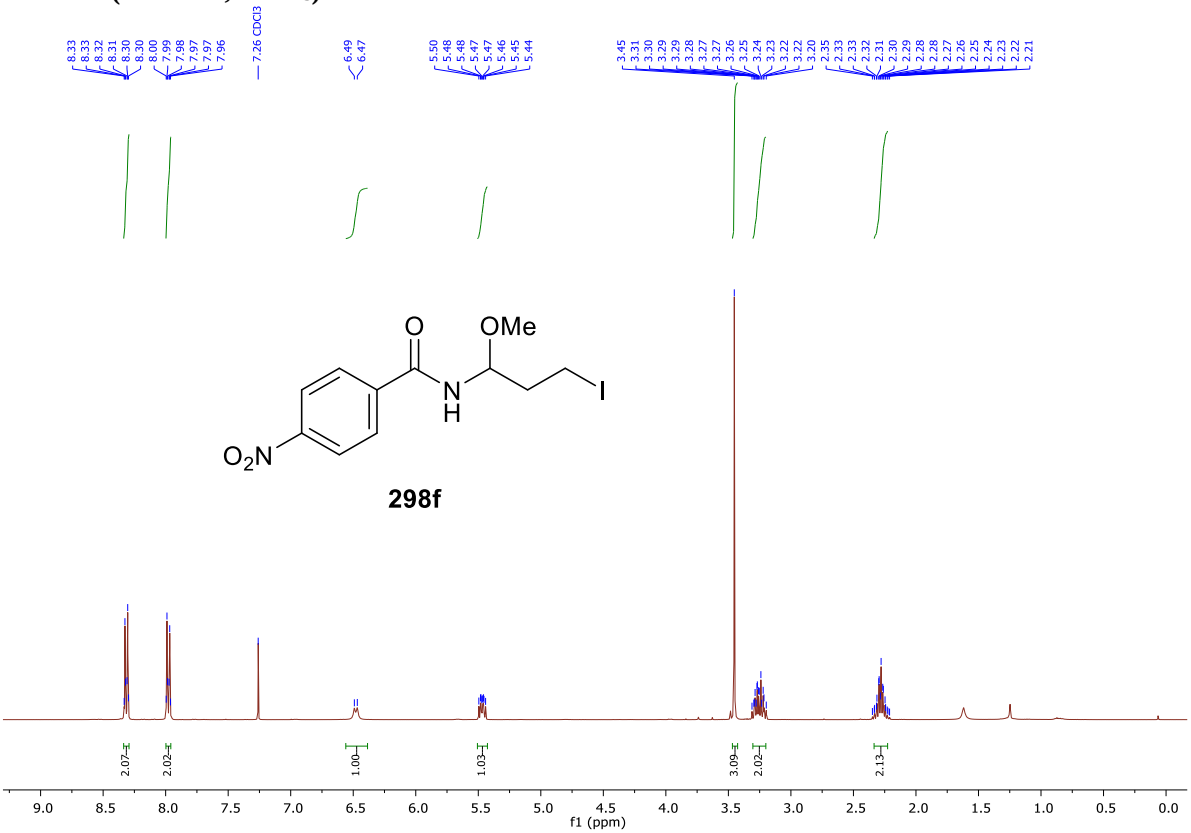
298e

^{13}C-NMR (101 MHz, $CDCl_3$)

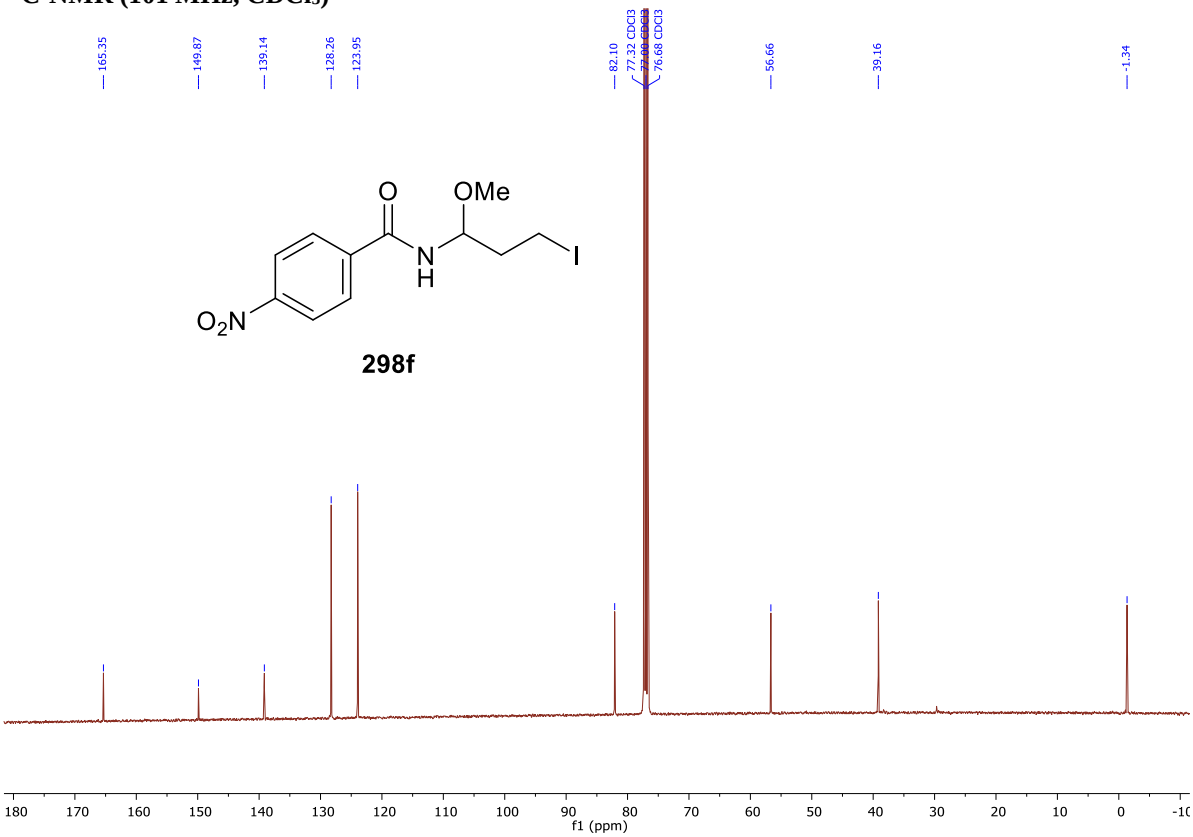


298e

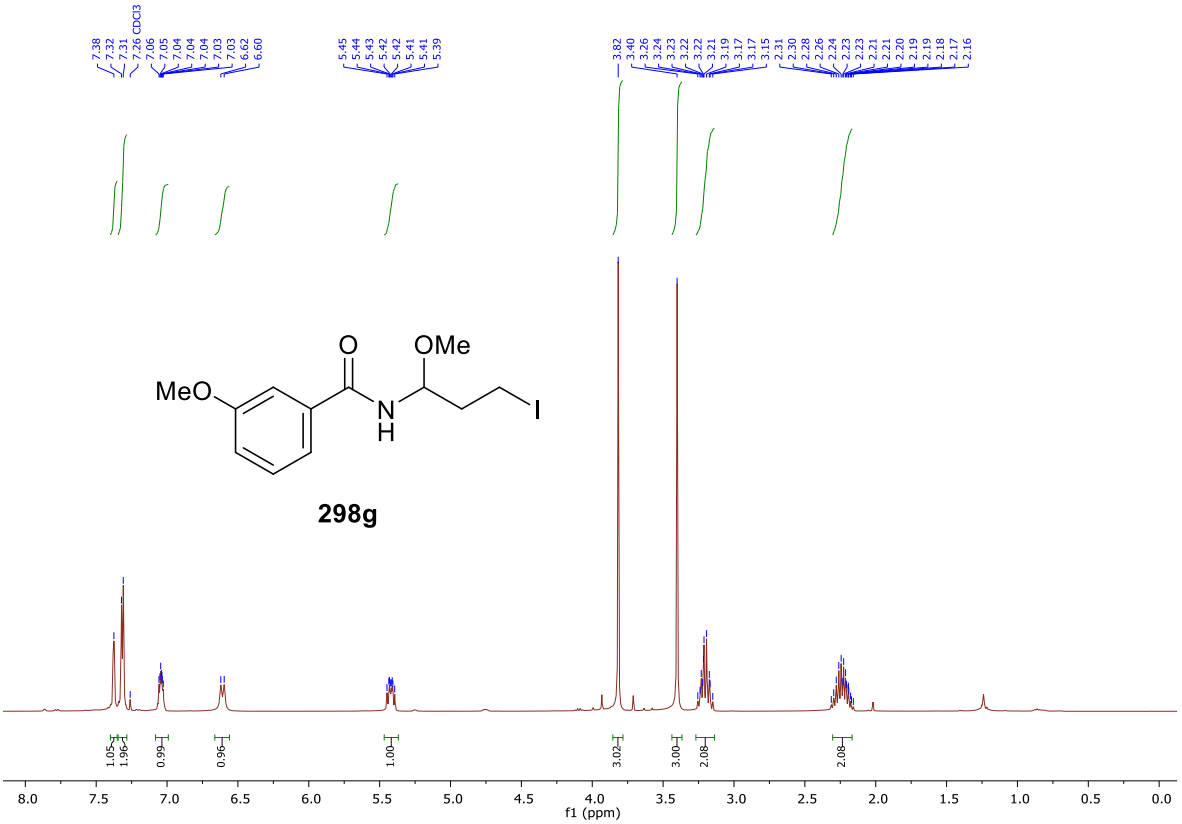
^{1}H-NMR (400 MHz, $CDCl_3$)



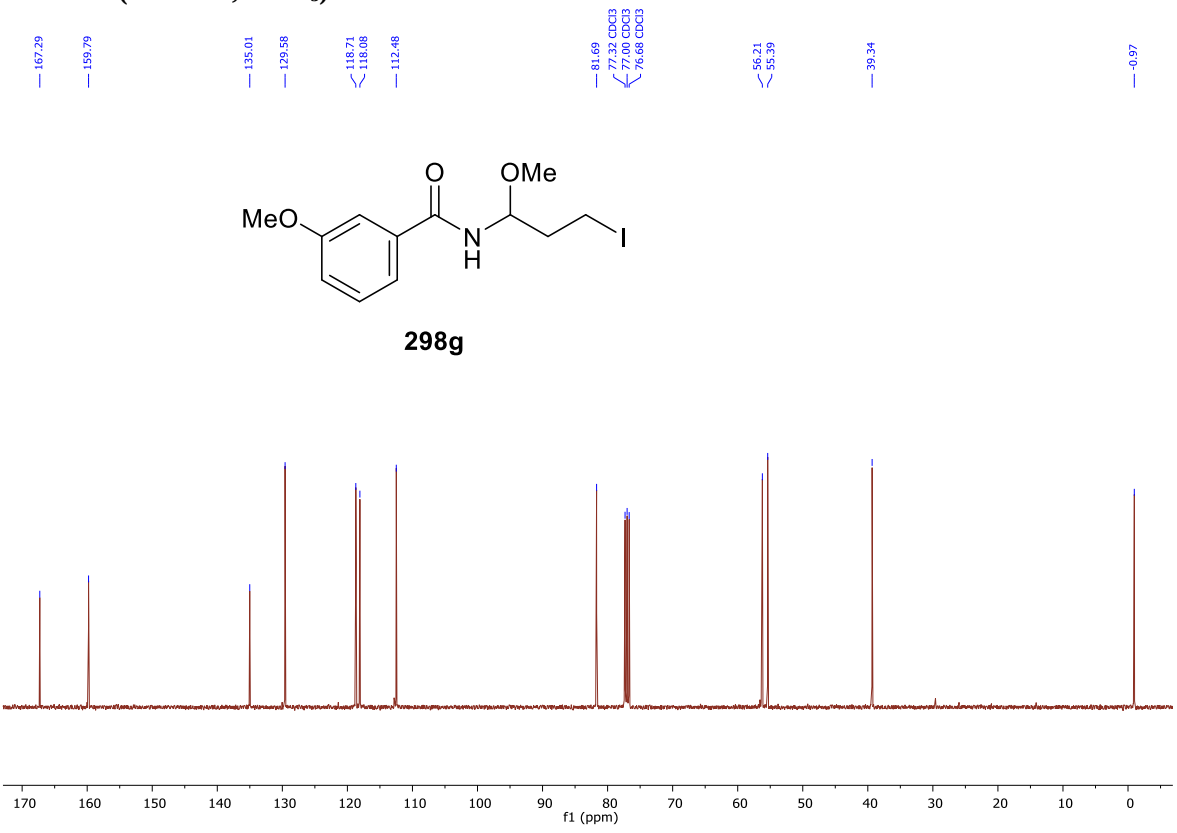
^{13}C-NMR (101 MHz, $CDCl_3$)



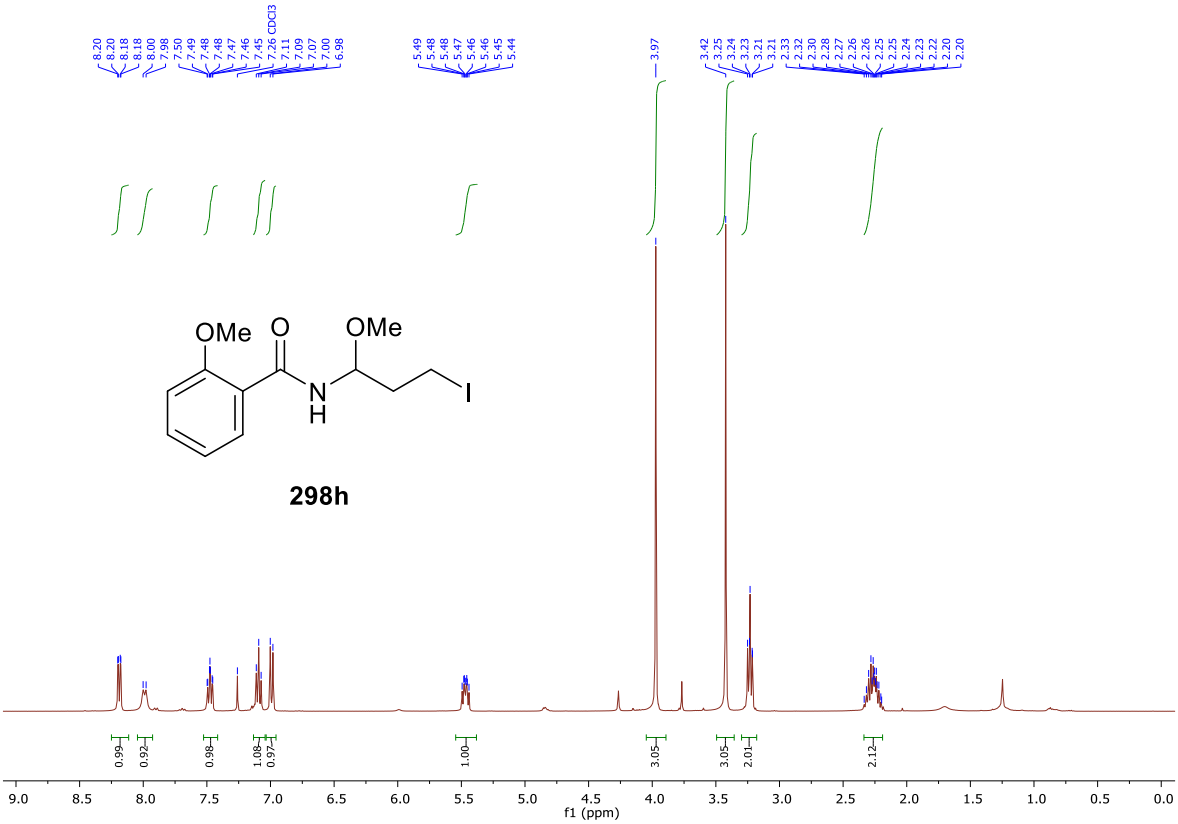
^{1}H-NMR (400 MHz, $CDCl_3$)



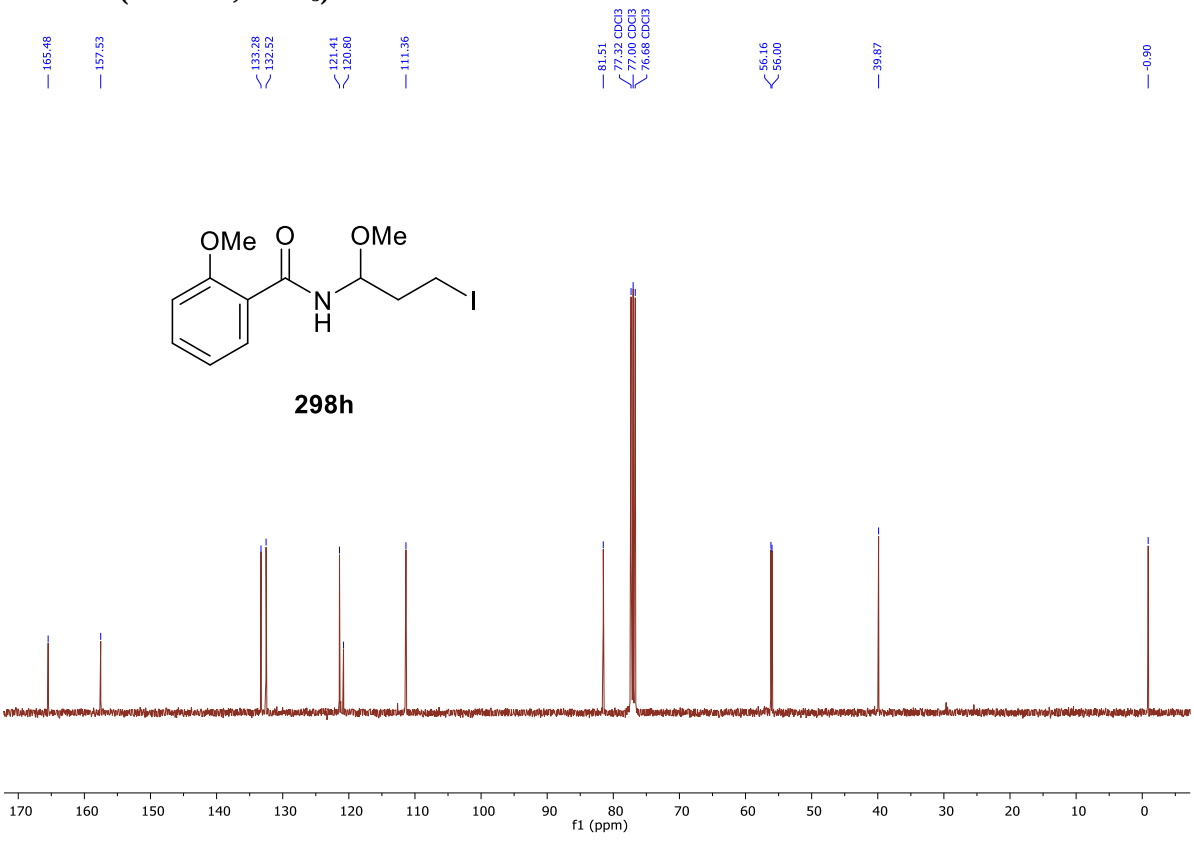
^{13}C-NMR (101 MHz, $CDCl_3$)



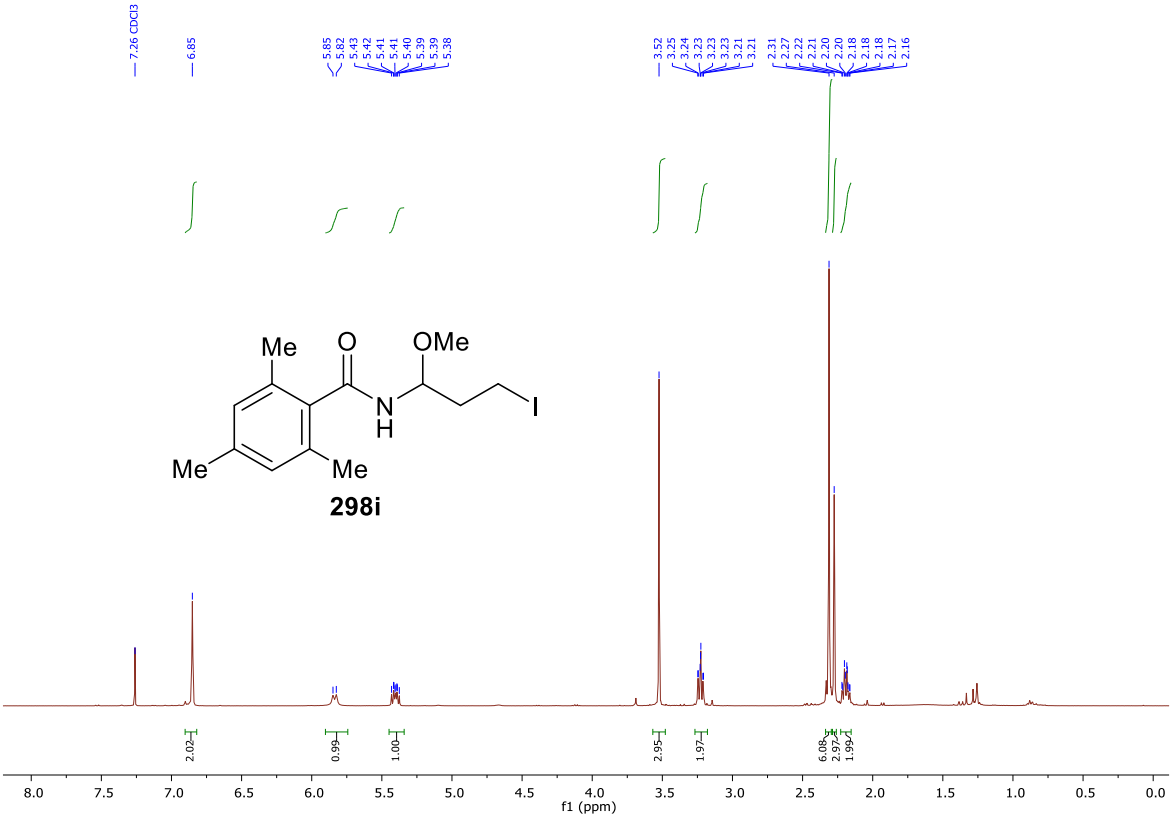
^{1}H-NMR (400 MHz, $CDCl_3$)



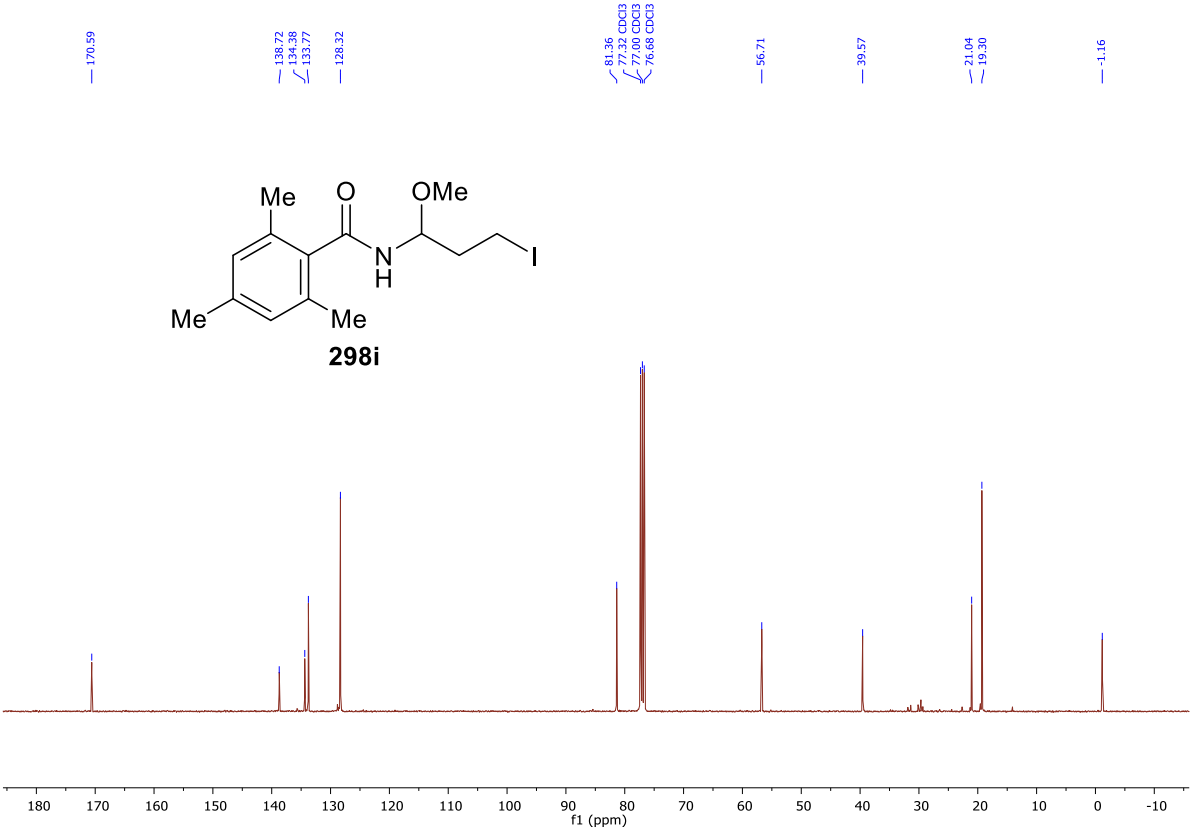
^{13}C-NMR (101 MHz, $CDCl_3$)



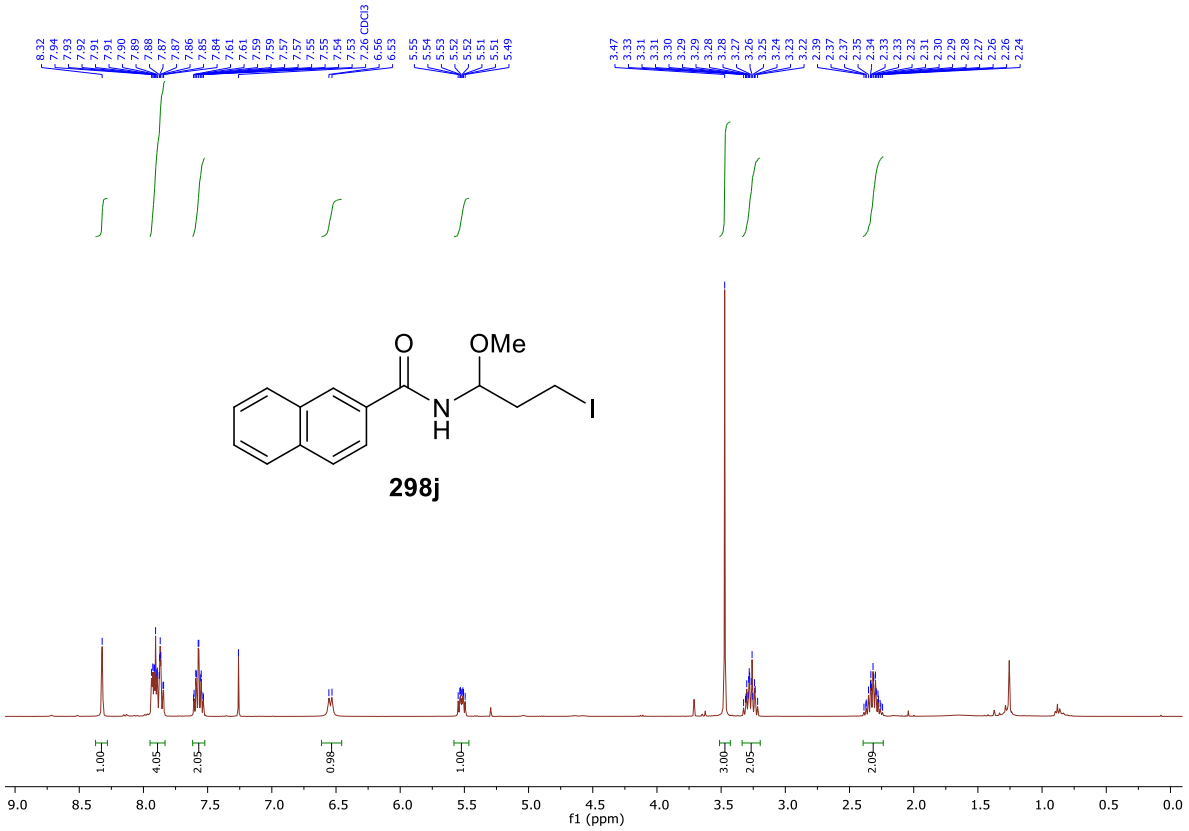
^{1}H-NMR (400 MHz, $CDCl_3$)



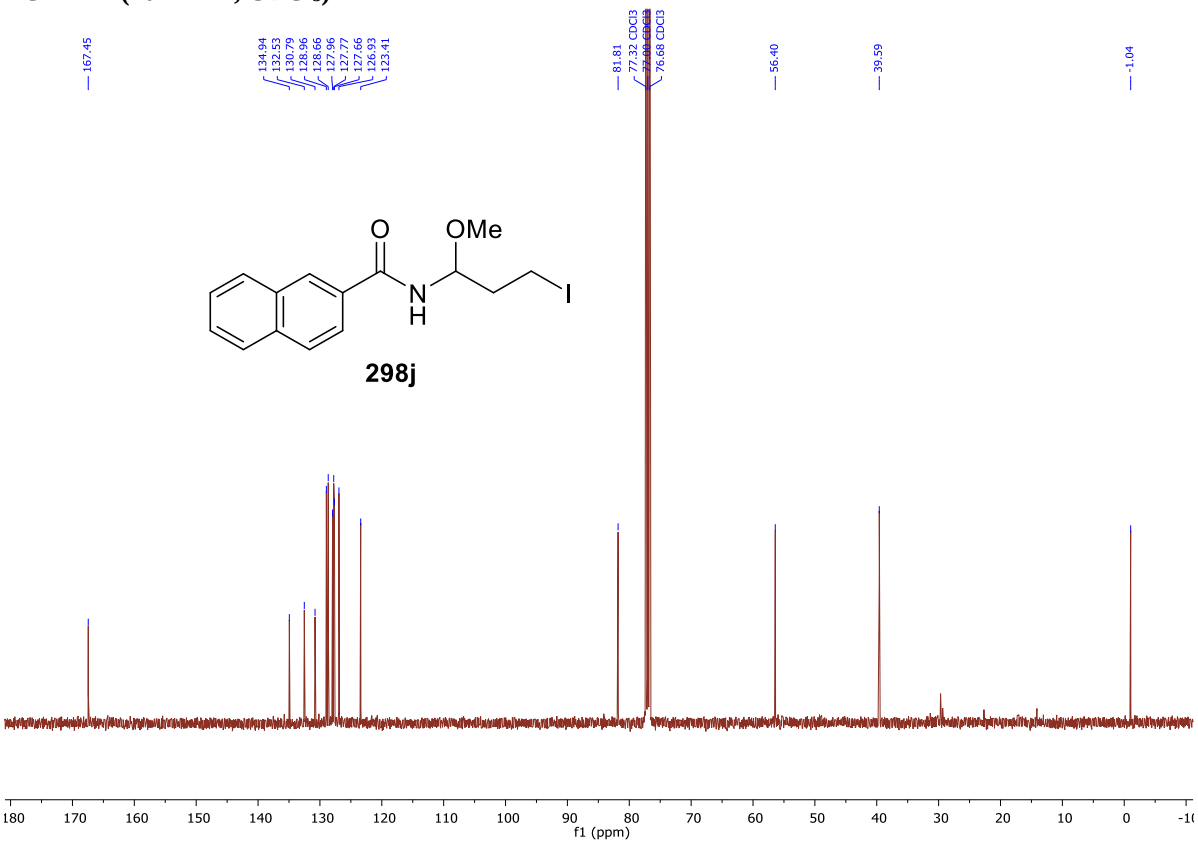
^{13}C-NMR (101 MHz, $CDCl_3$)



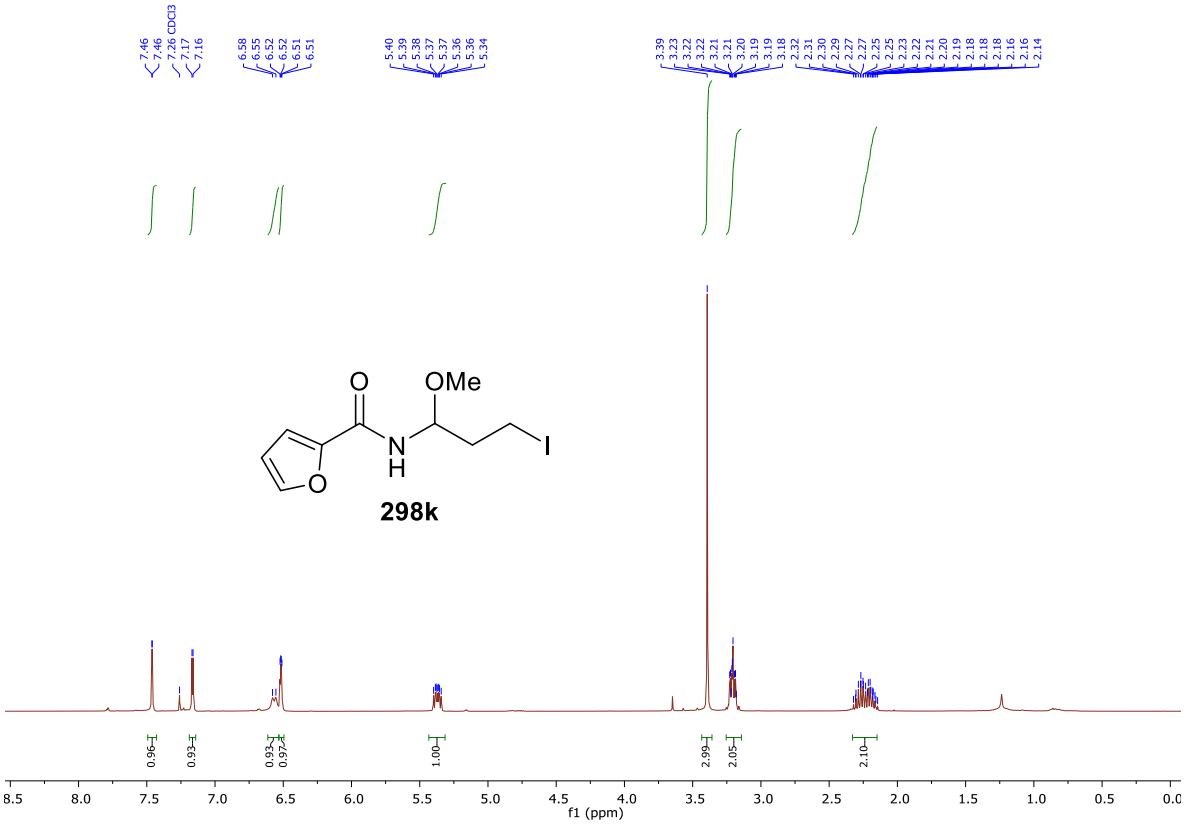
^{1}H-NMR (400 MHz, $CDCl_3$)



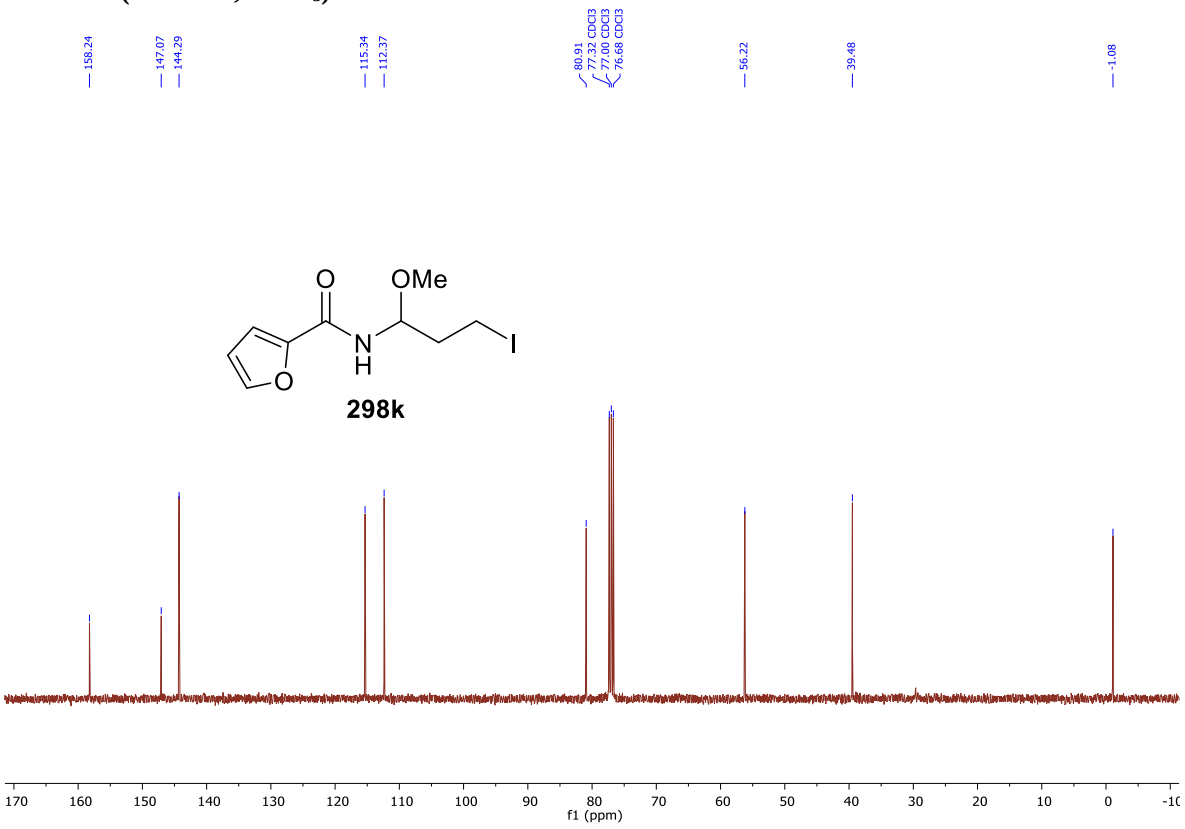
^{13}C-NMR (101 MHz, $CDCl_3$)



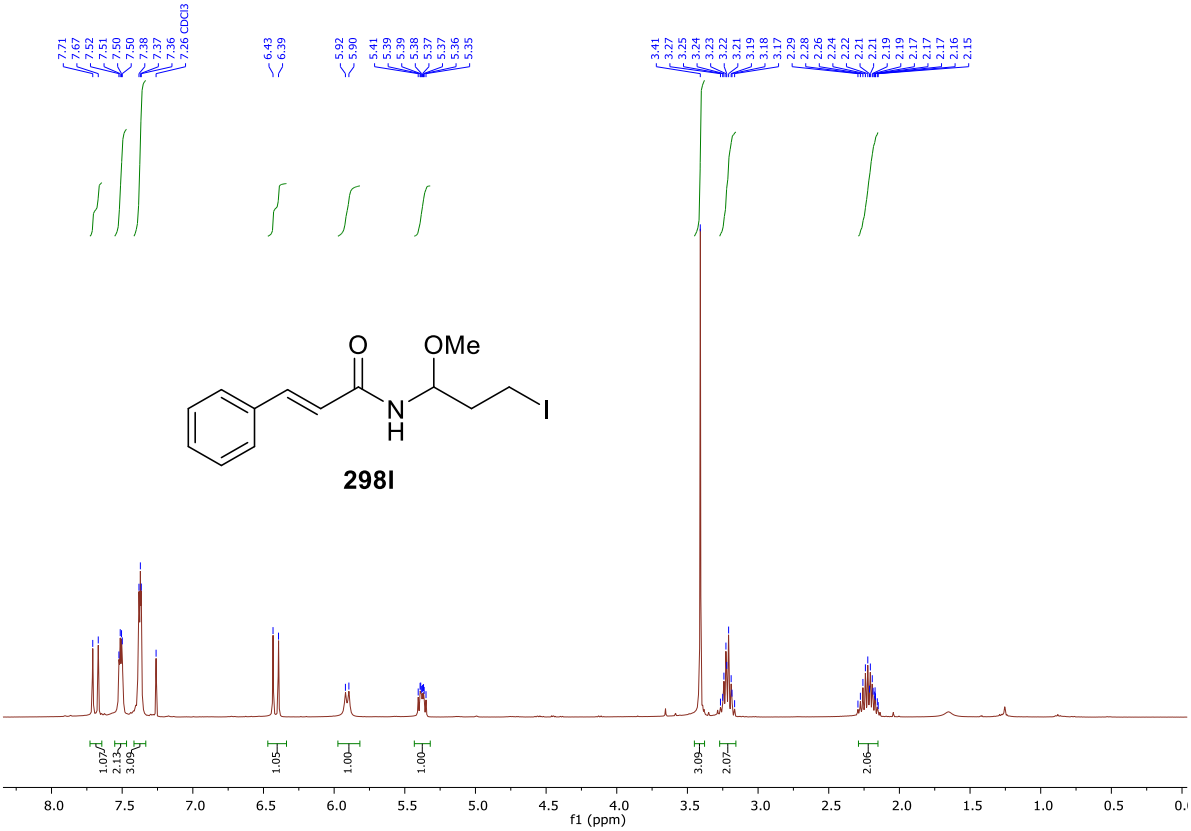
^{1}H-NMR (400 MHz, $CDCl_3$)



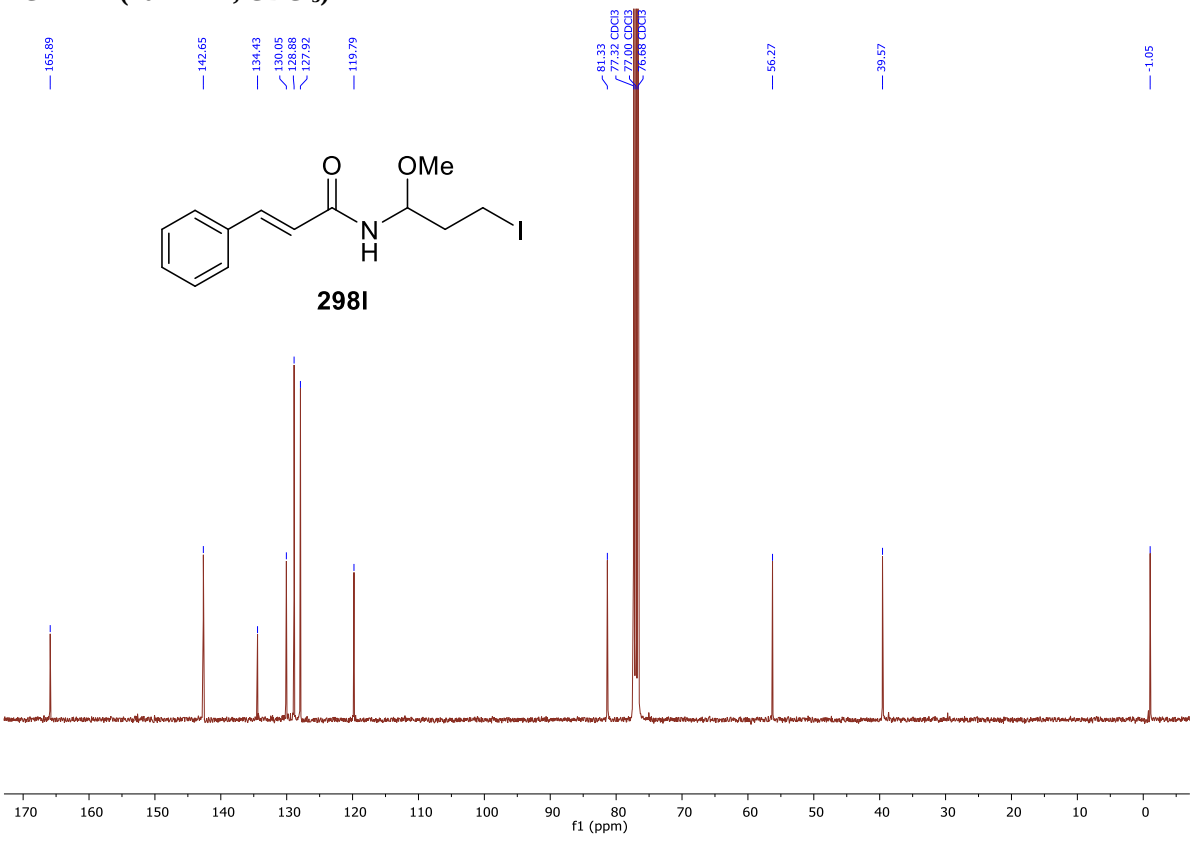
^{13}C-NMR (101 MHz, $CDCl_3$)



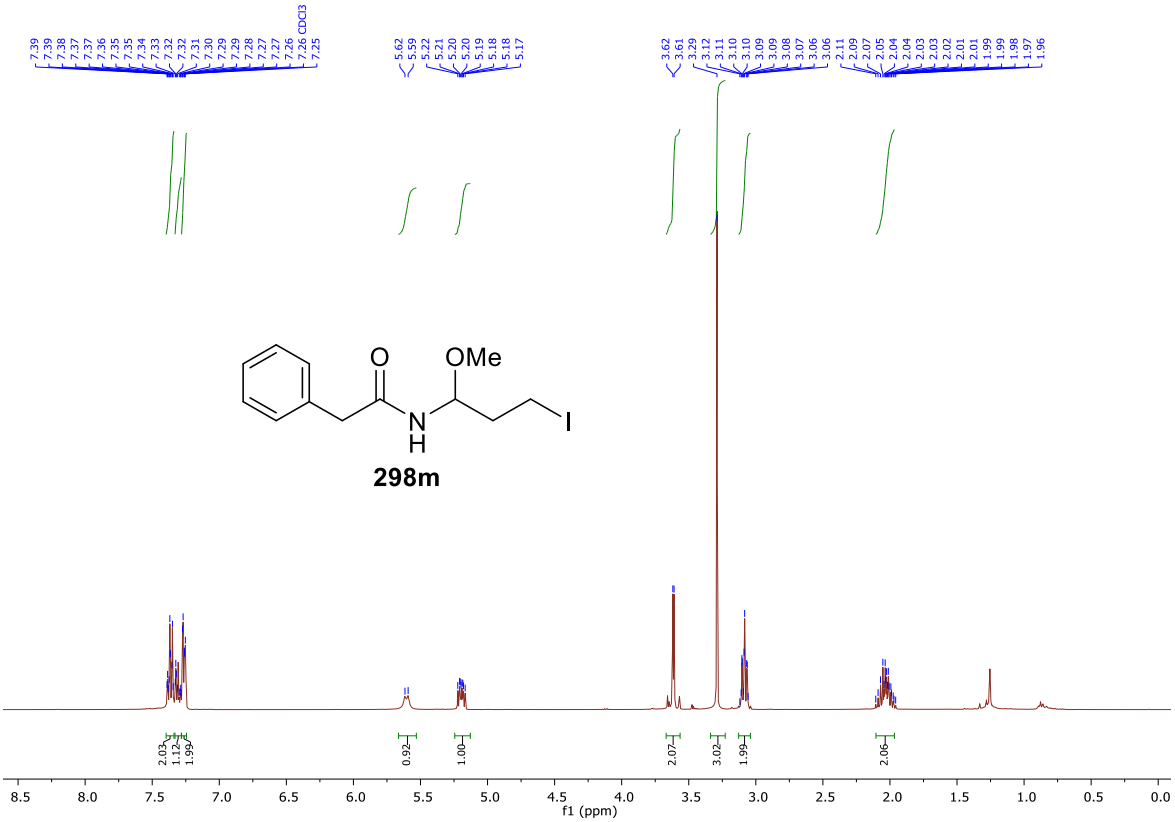
^{1}H-NMR (400 MHz, $CDCl_3$)



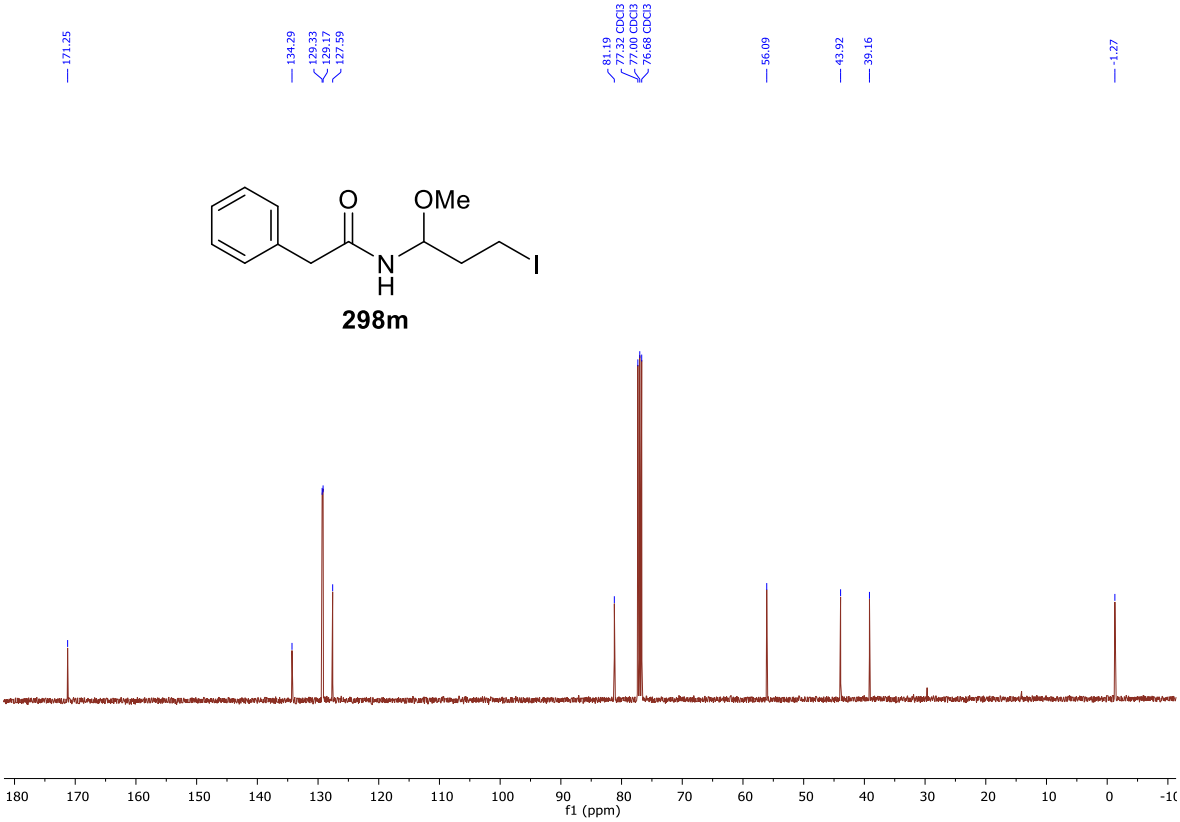
^{13}C-NMR (101 MHz, $CDCl_3$)



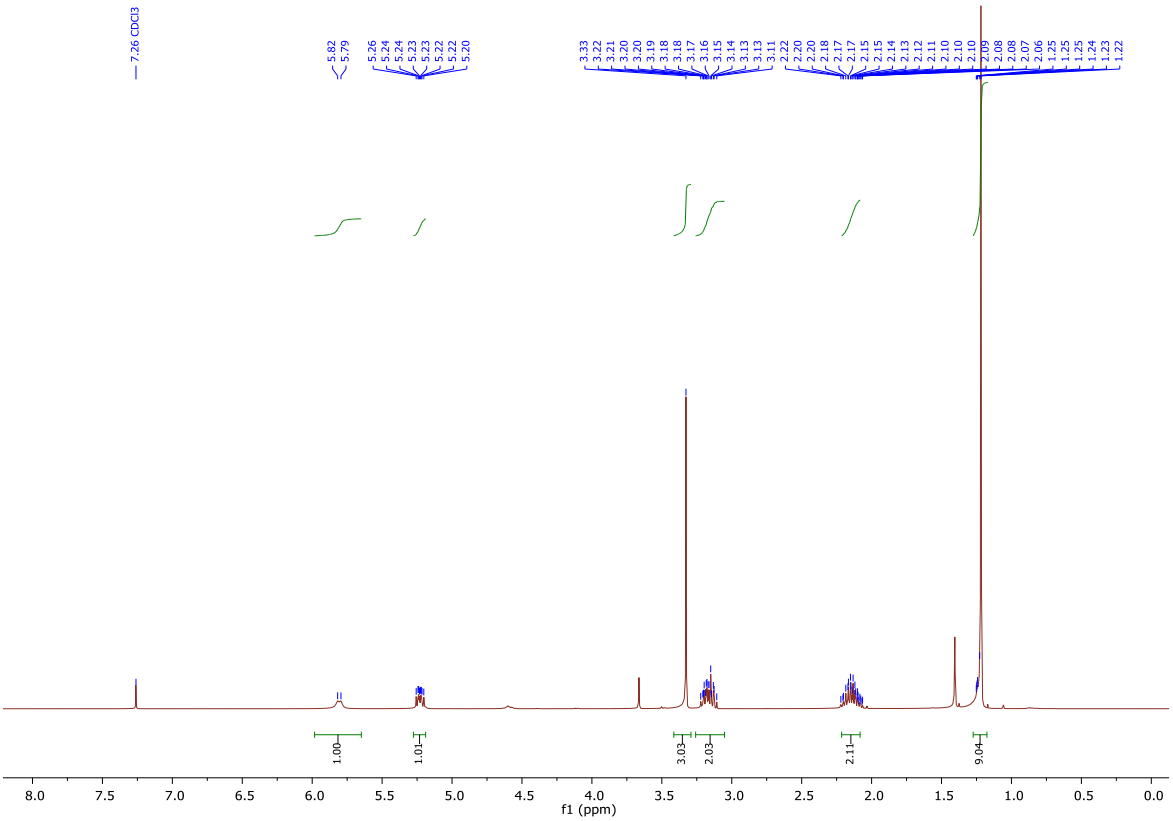
^{1}H-NMR (400 MHz, $CDCl_3$)



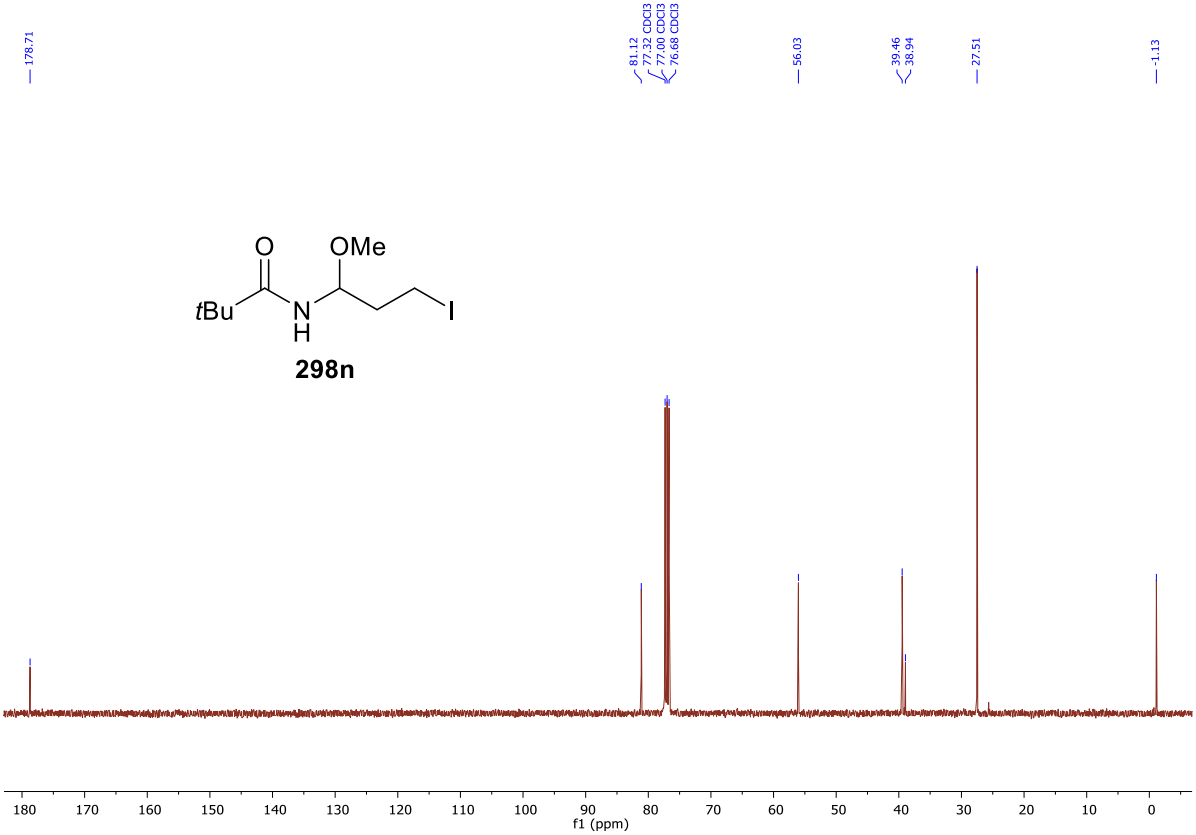
^{13}C-NMR (101 MHz, $CDCl_3$)



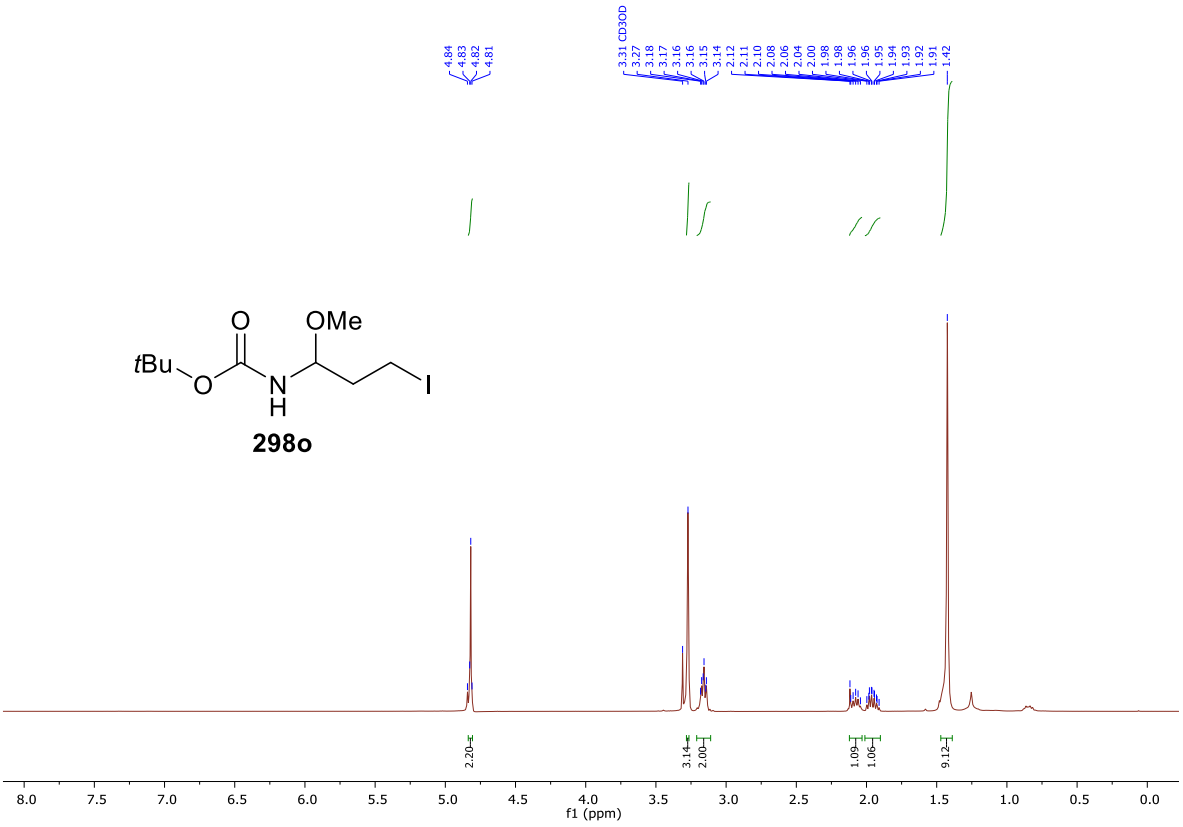
^{1}H-NMR (400 MHz, $CDCl_3$)



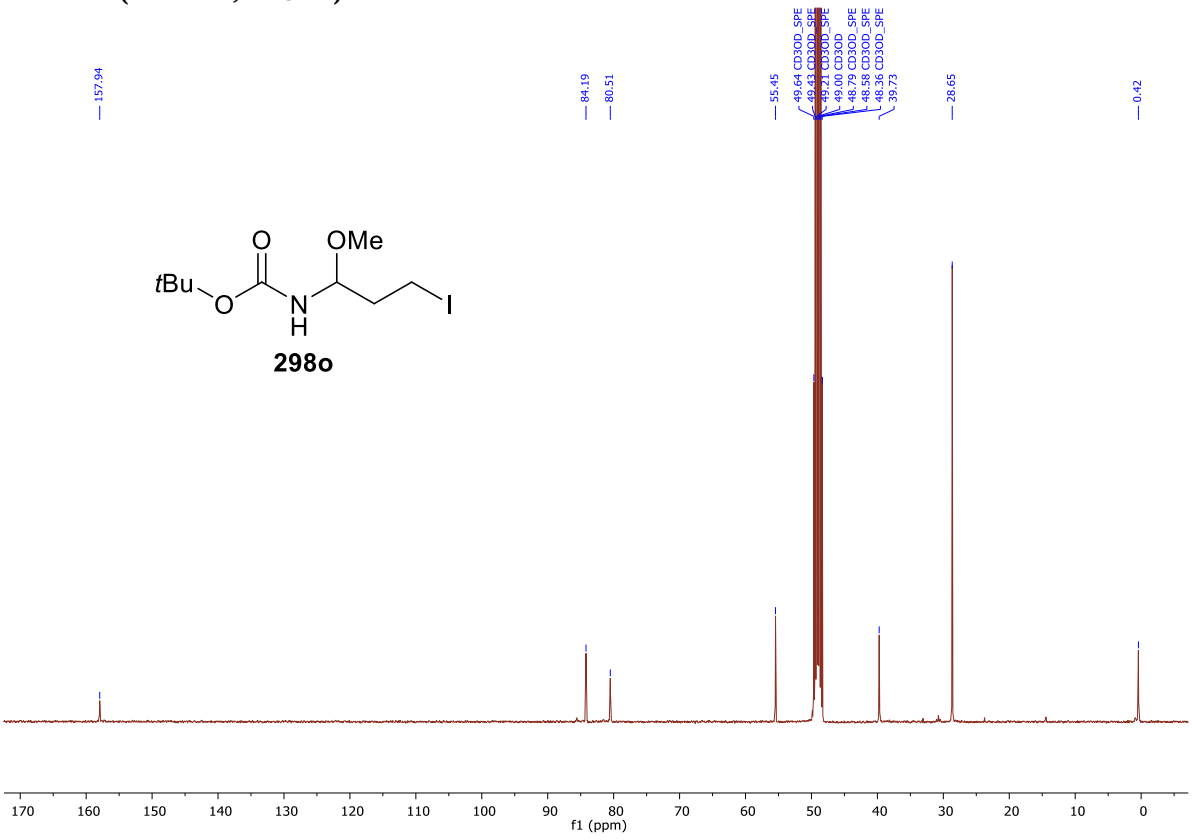
^{13}C-NMR (101 MHz, $CDCl_3$)



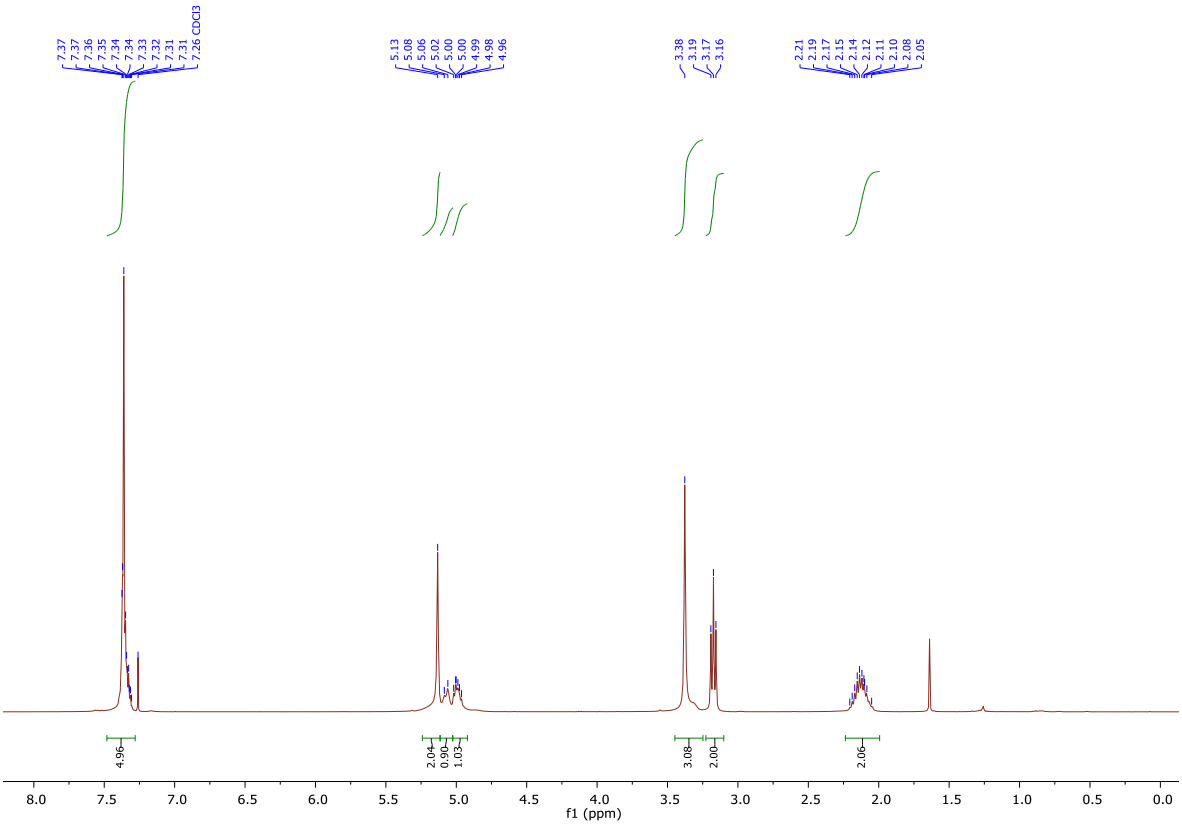
^{1}H-NMR (400 MHz, CD_3OD)



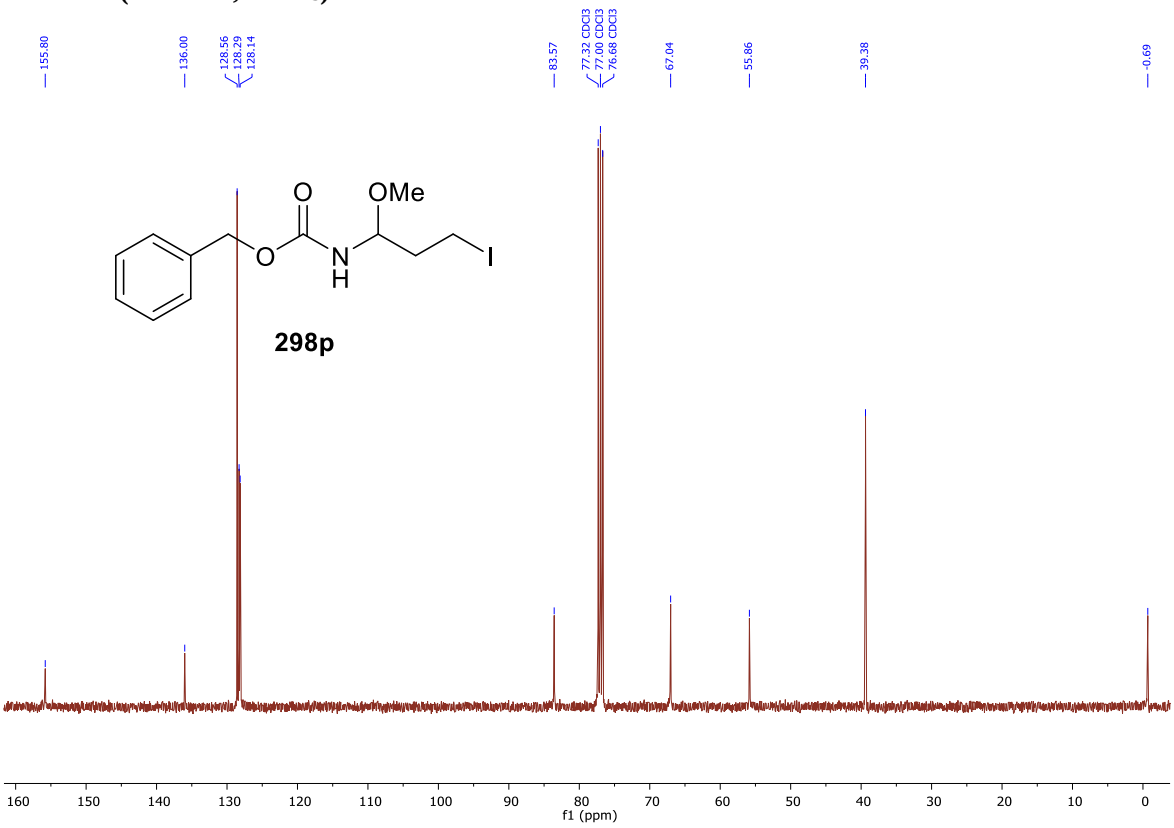
^{13}C-NMR (101 MHz, CD_3OD)



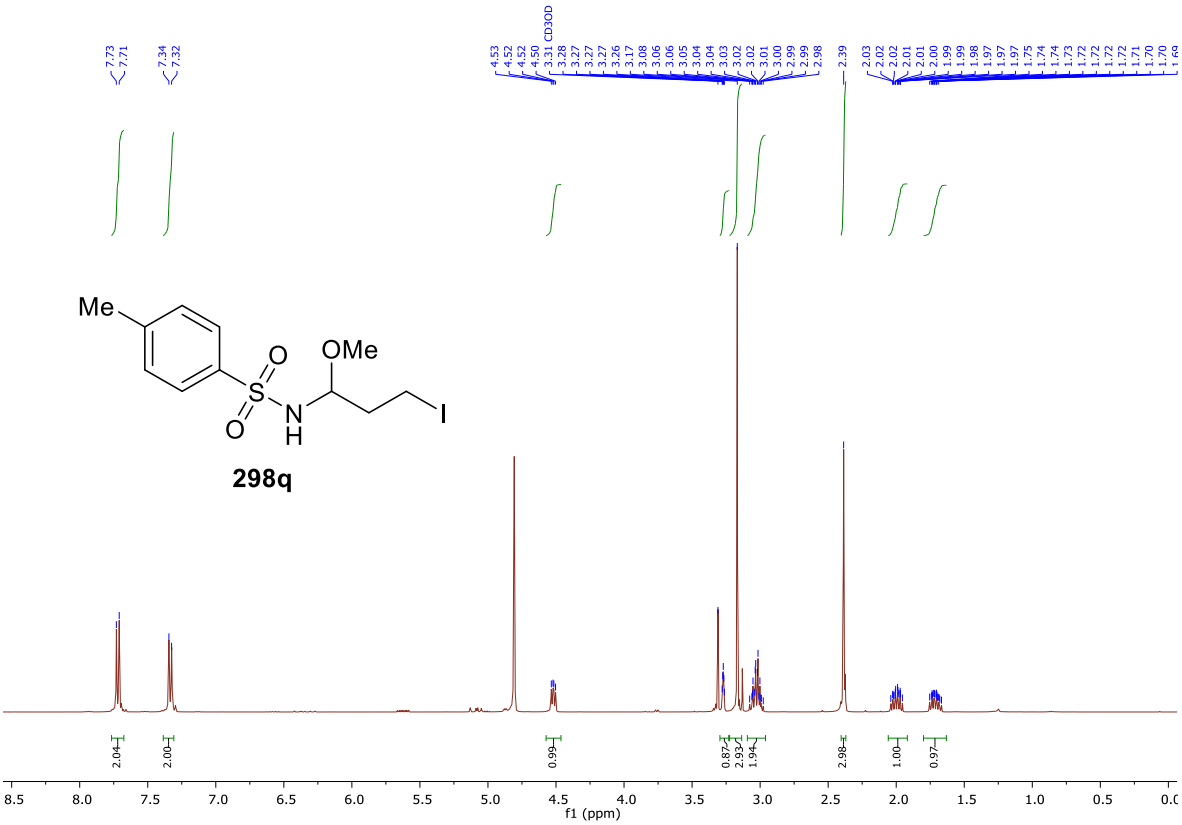
^{1}H-NMR (400 MHz, $CDCl_3$)



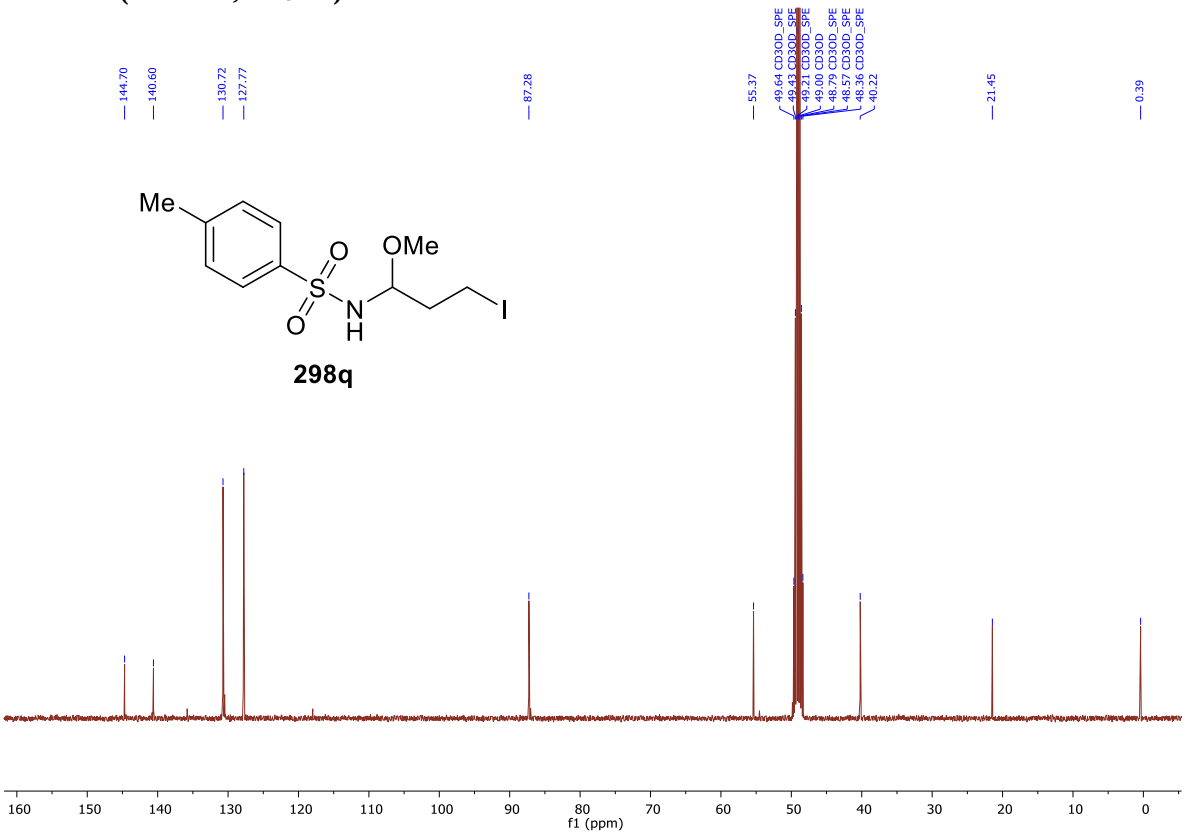
^{13}C-NMR (101 MHz, $CDCl_3$)



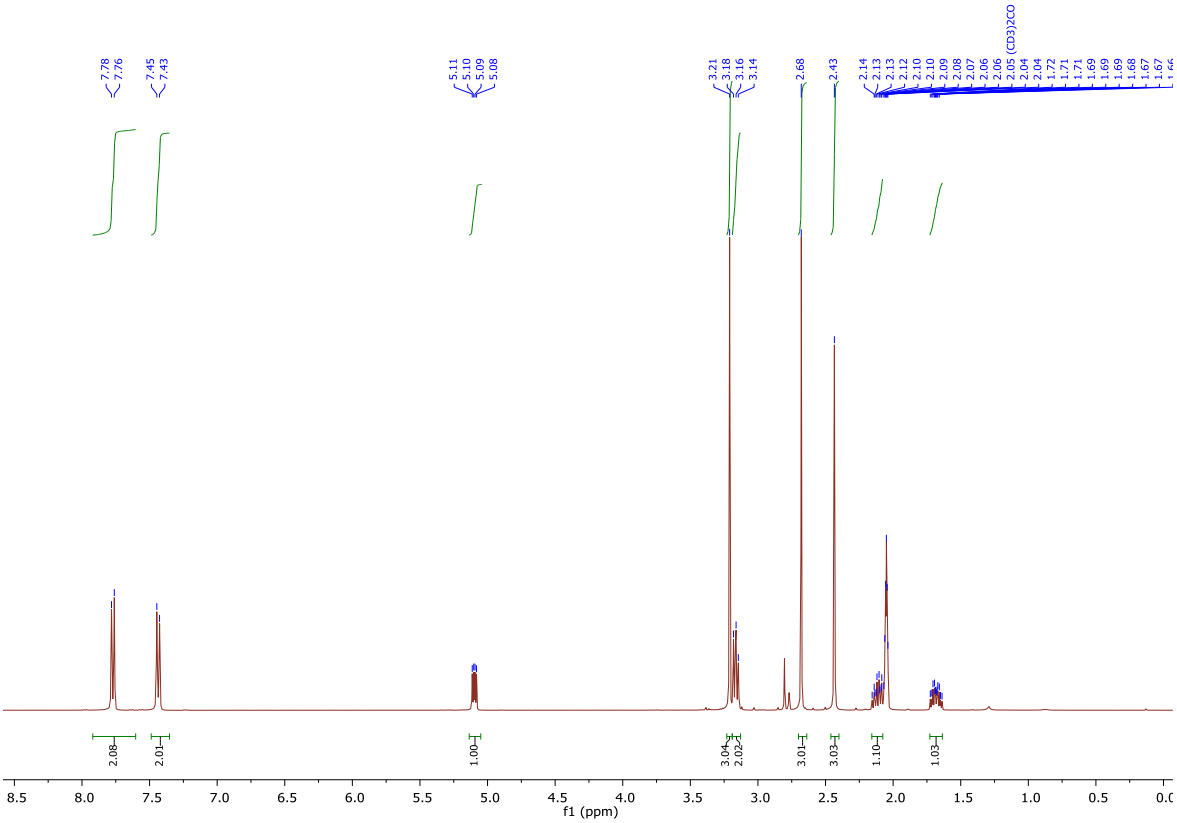
^{1}H-NMR (400 MHz, CD_3OD)



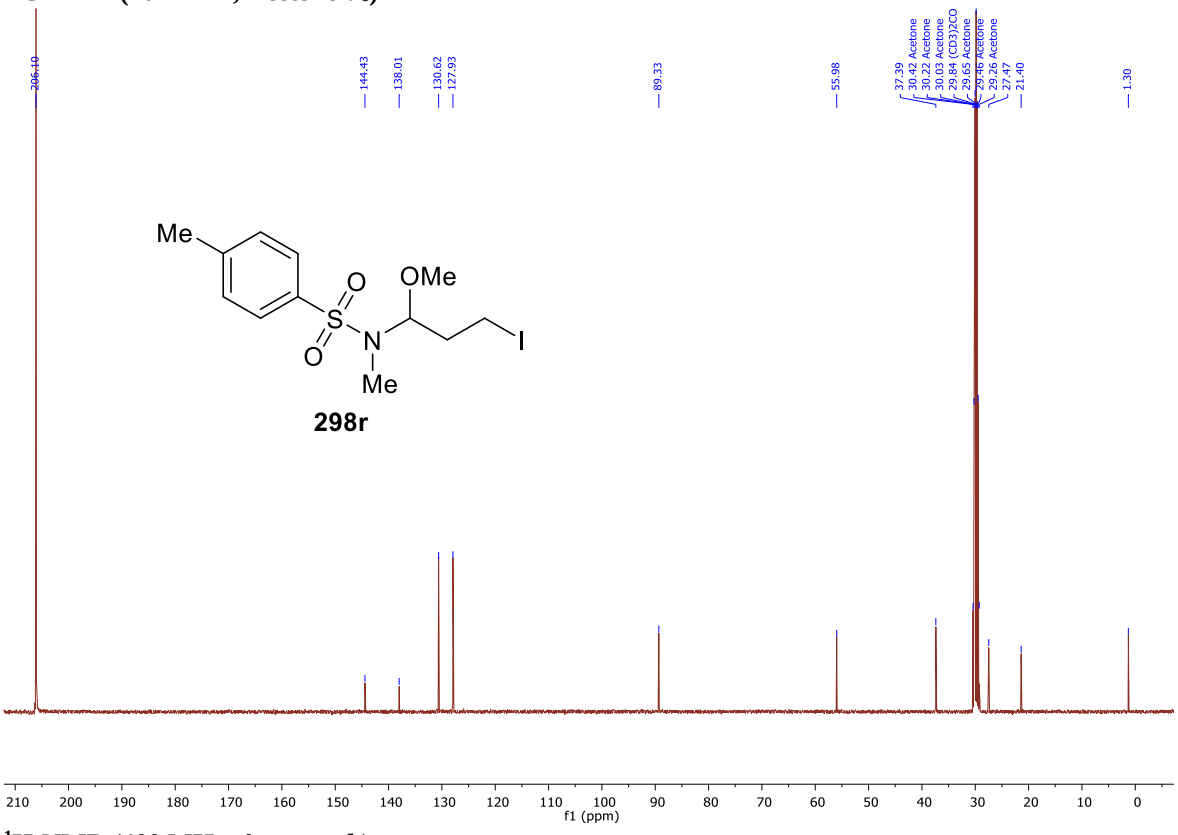
^{13}C-NMR (101 MHz, CD_3OD)



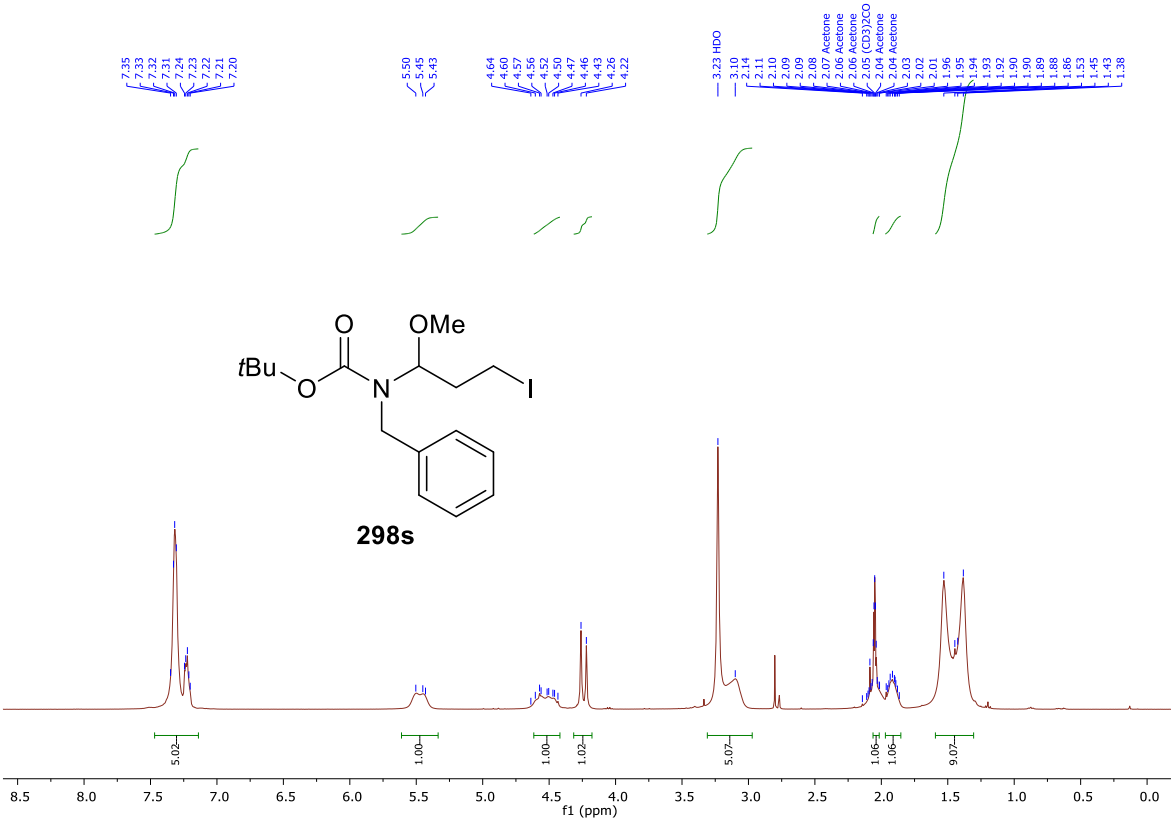
^{1}H-NMR (400 MHz, Acetone-d_6)



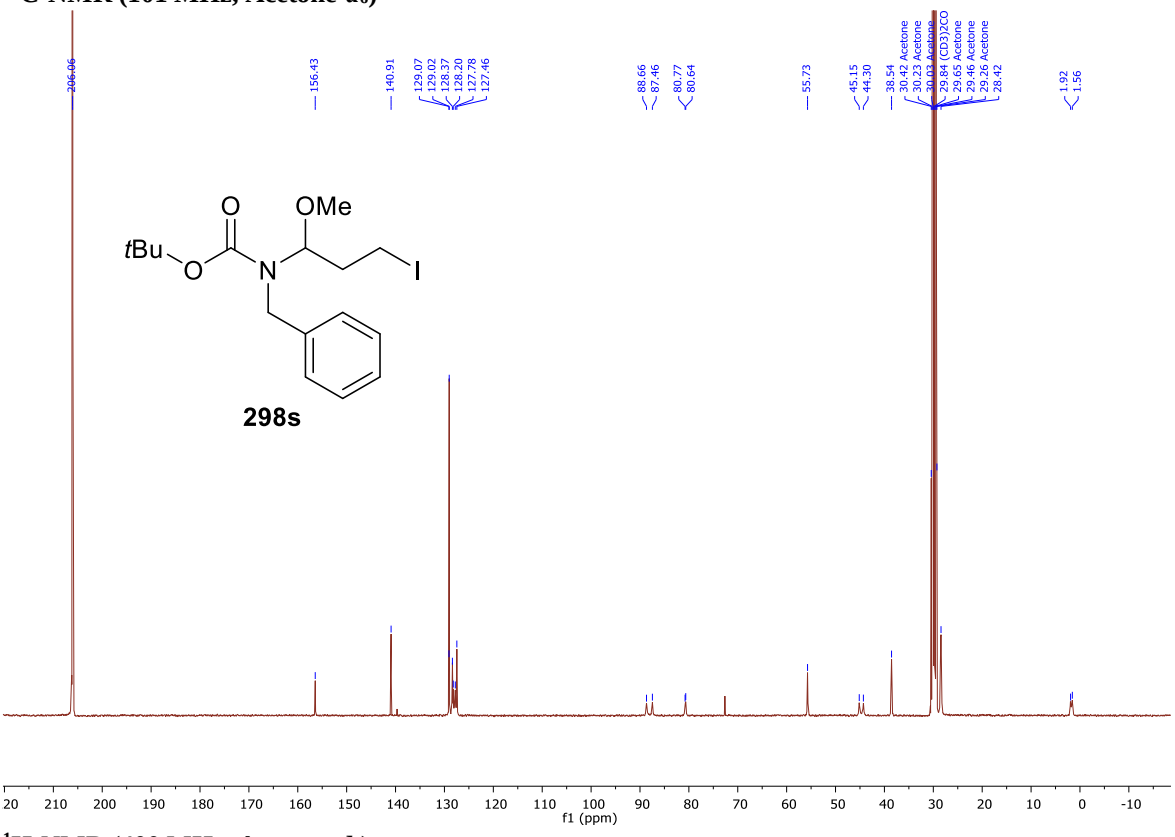
^{13}C-NMR (101 MHz, Acetone-*d*$_6$)



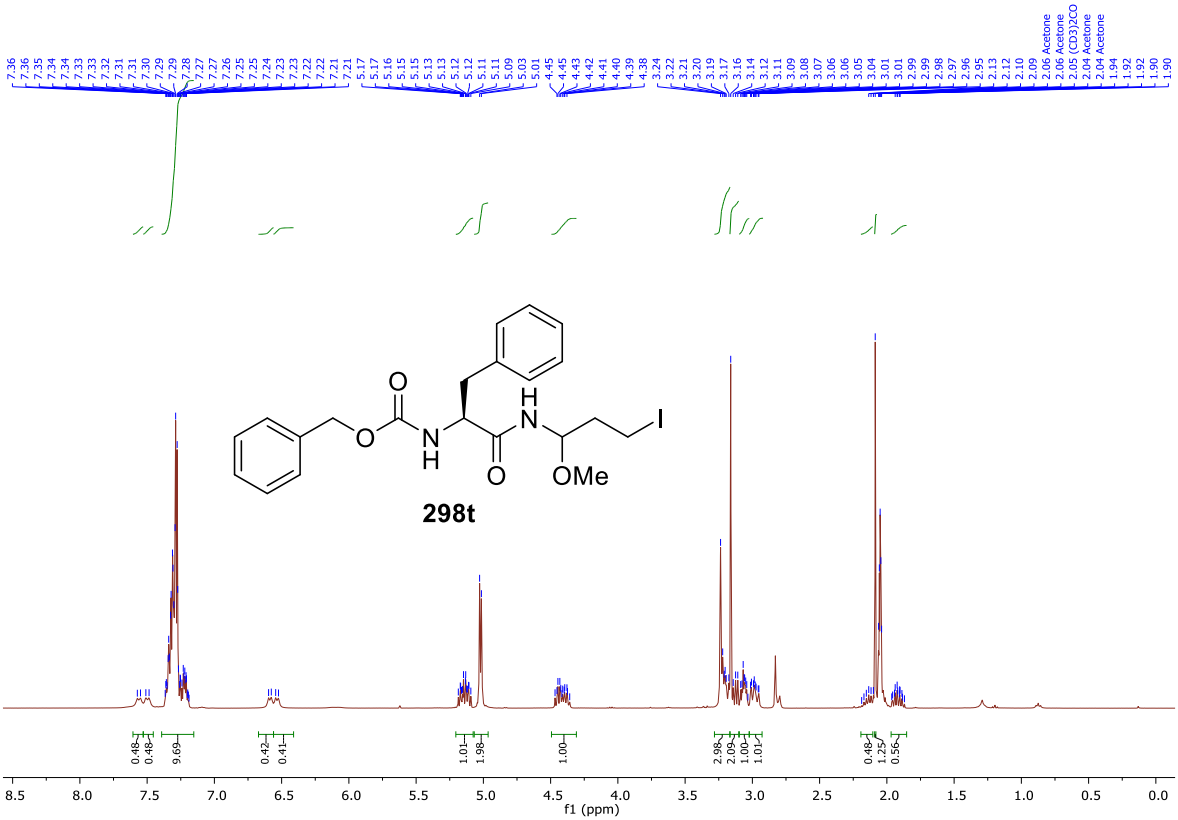
^{1}H-NMR (400 MHz, Acetone-*d*$_6$)



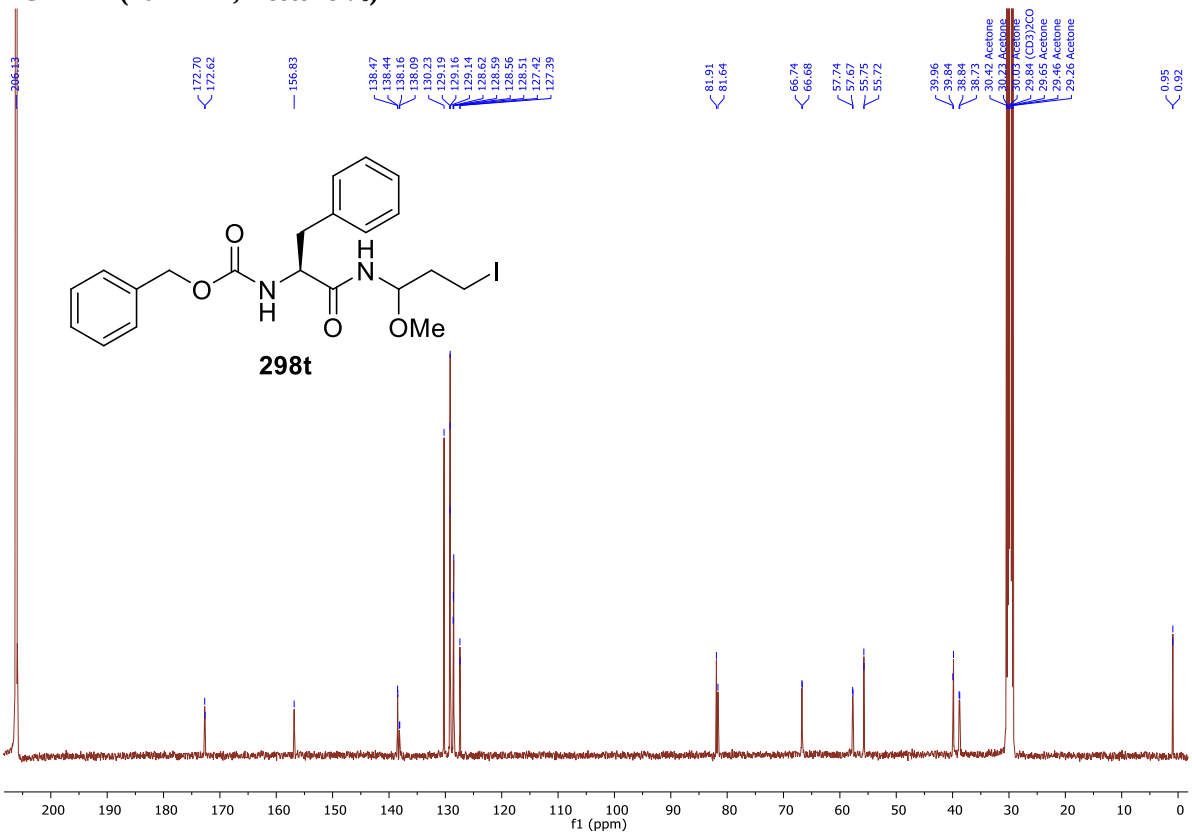
^{13}C-NMR (101 MHz, Acetone-d_6)



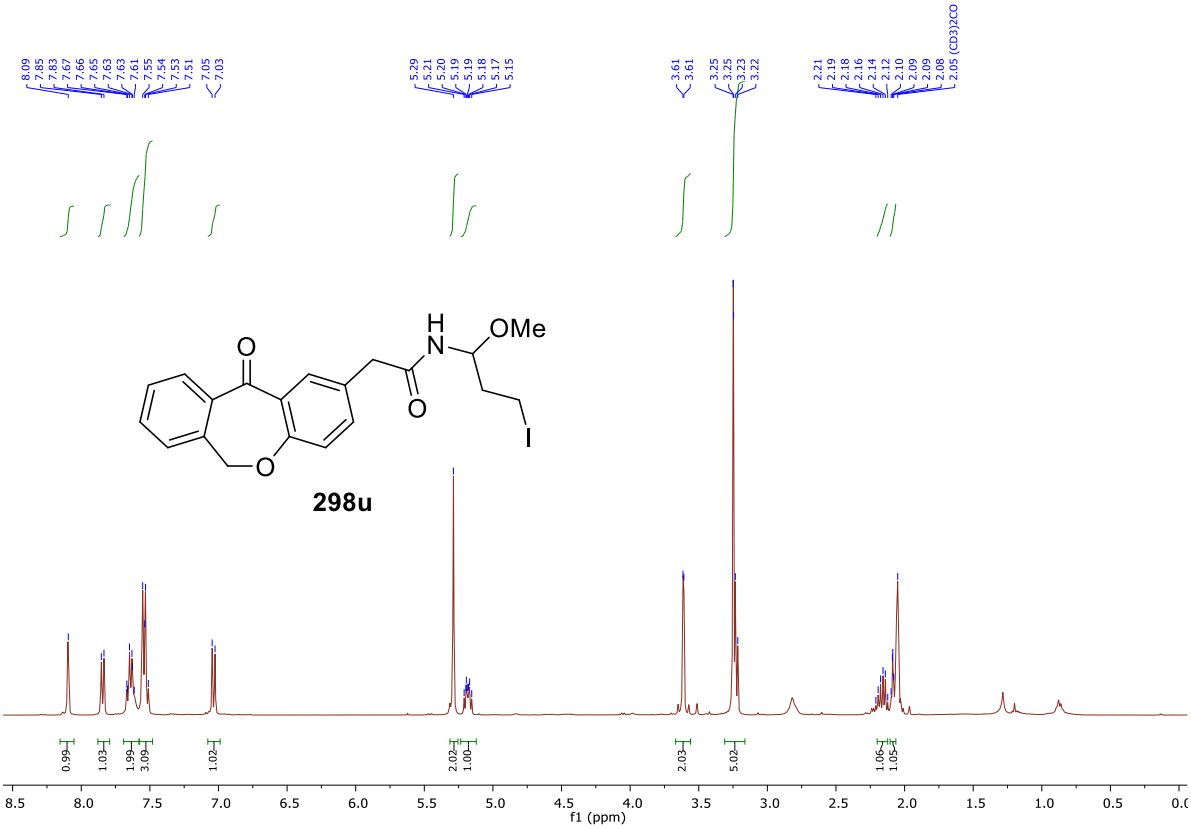
^{1}H-NMR (400 MHz, Acetone-d_6)



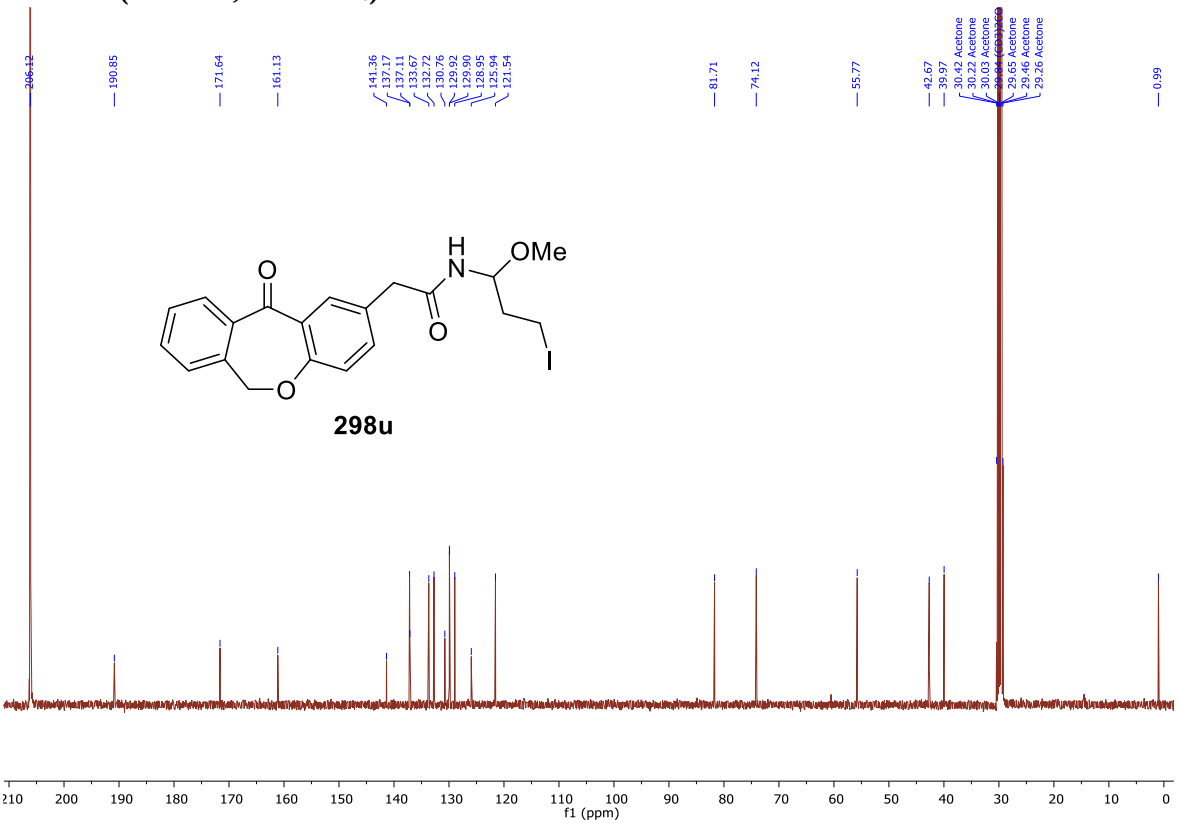
^{13}C-NMR (101 MHz, Acetone-*d*$_6$)



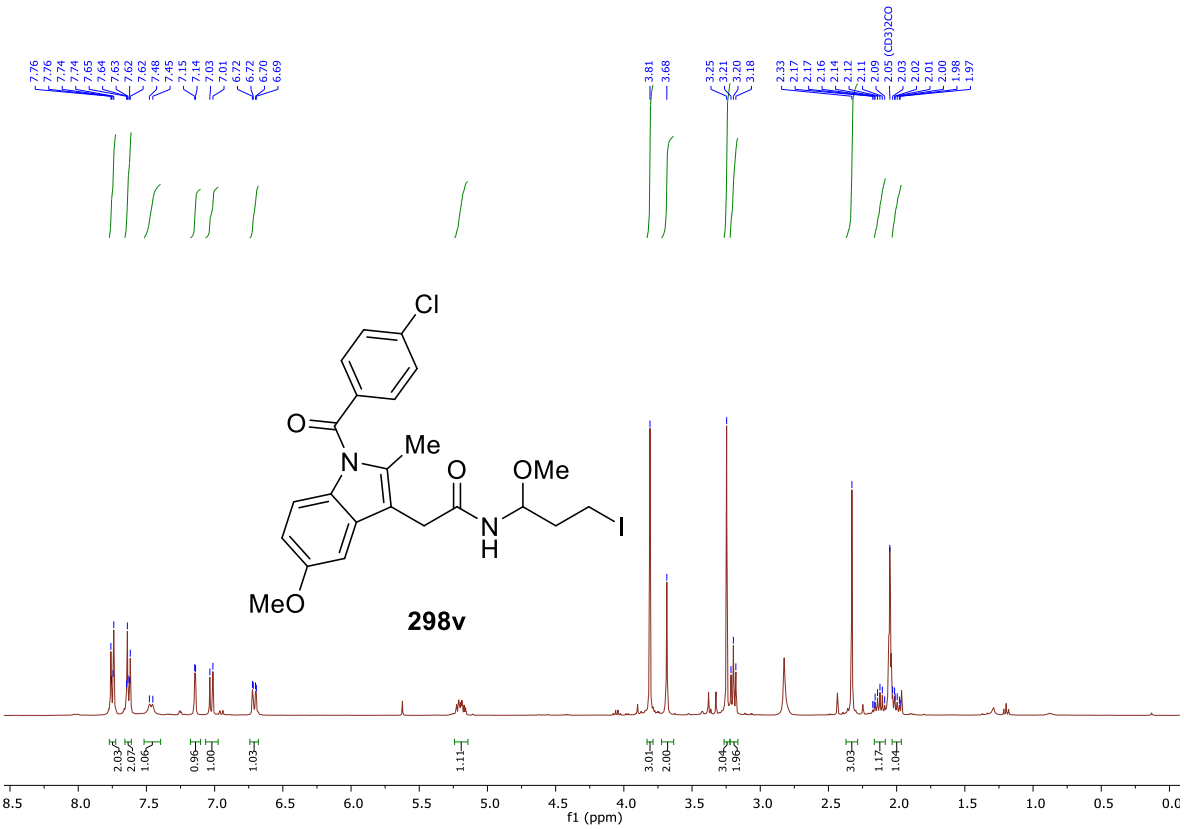
^{1}H-NMR (400 MHz, Acetone-*d*$_6$)



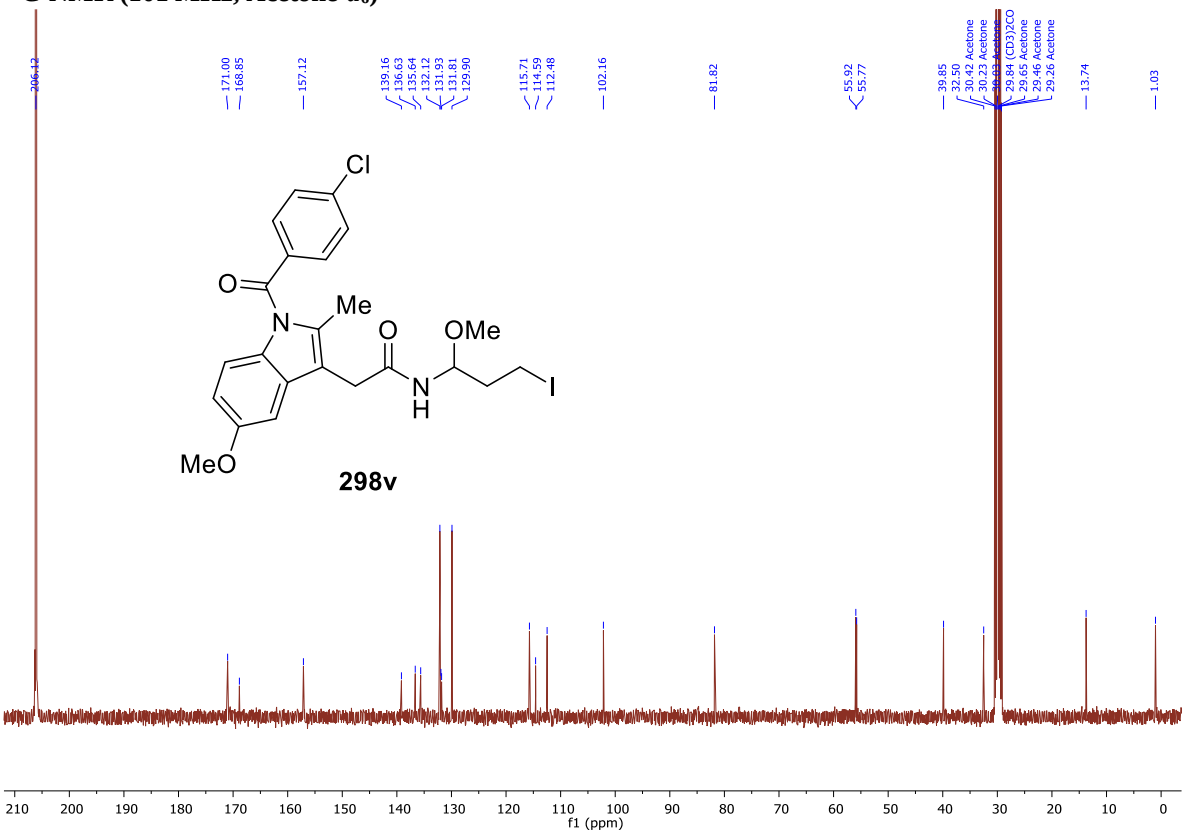
^{13}C-NMR (101 MHz, Acetone-d_6)



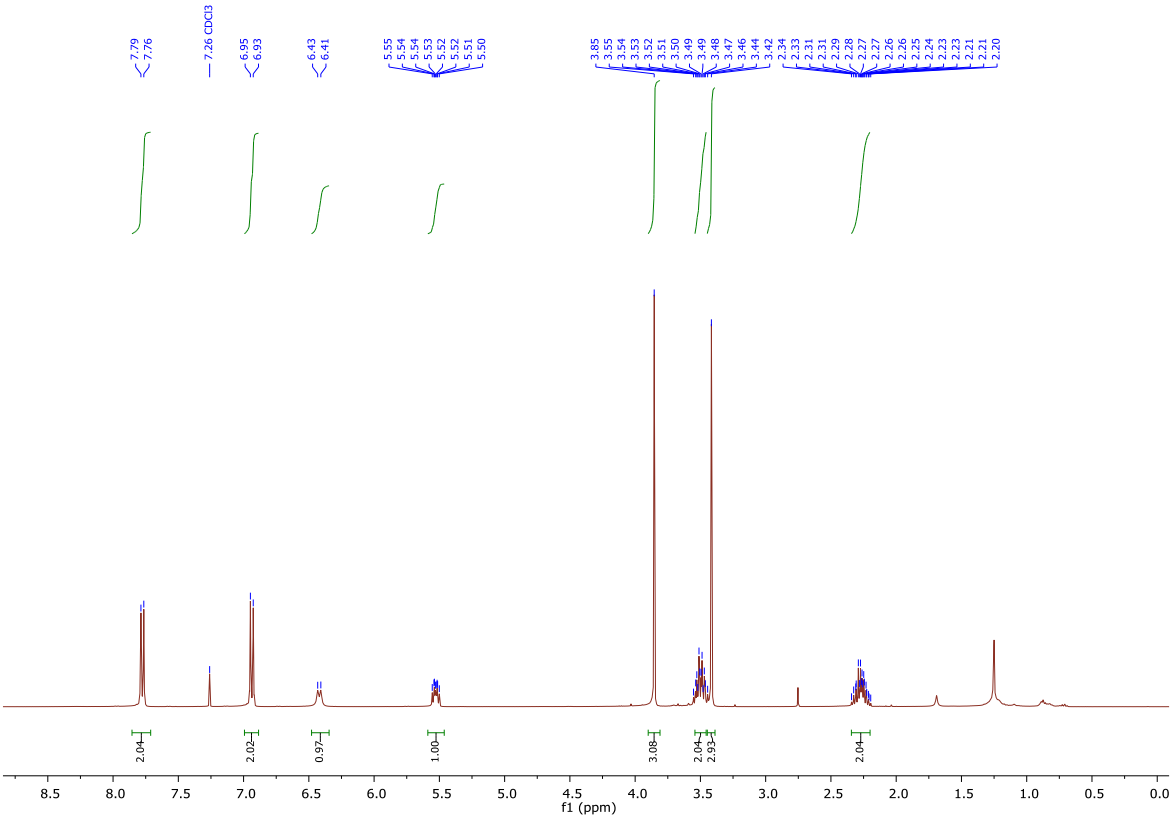
^{1}H-NMR (400 MHz, Acetone-d_6)



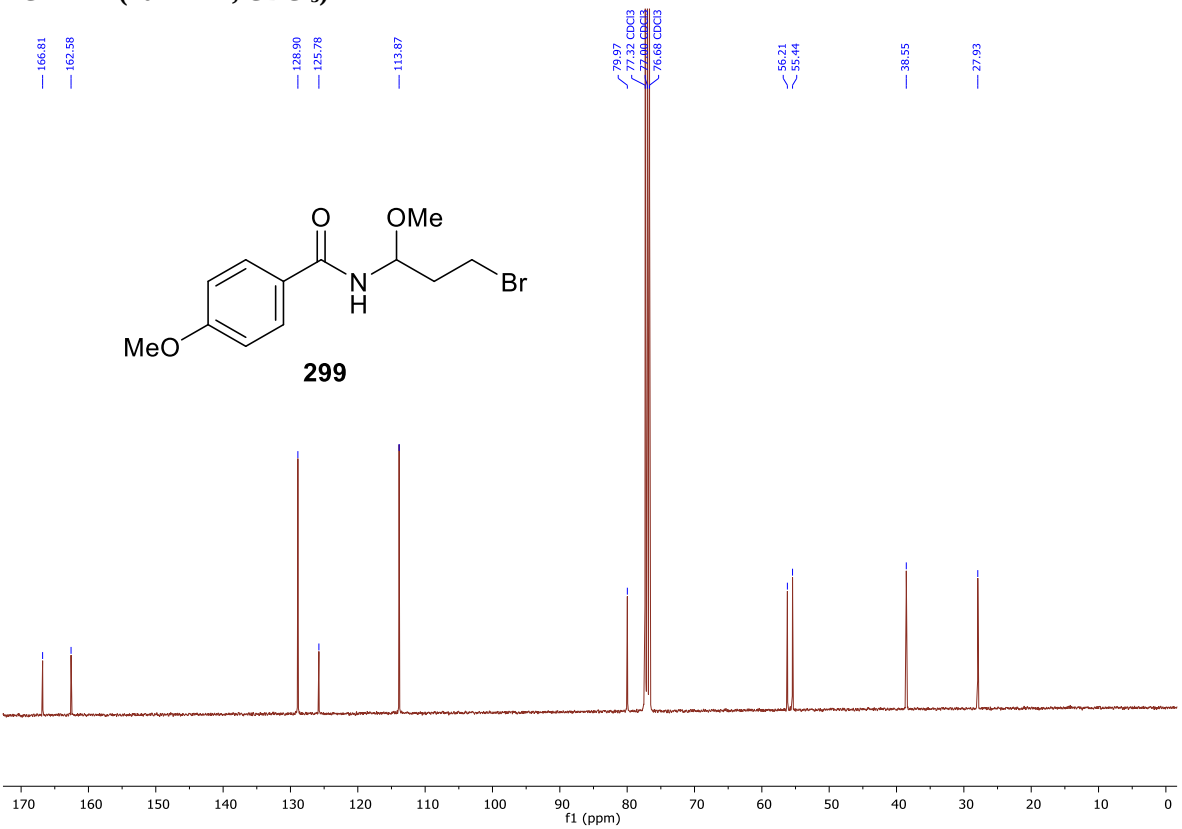
^{13}C-NMR (101 MHz, Acetone-d_6)



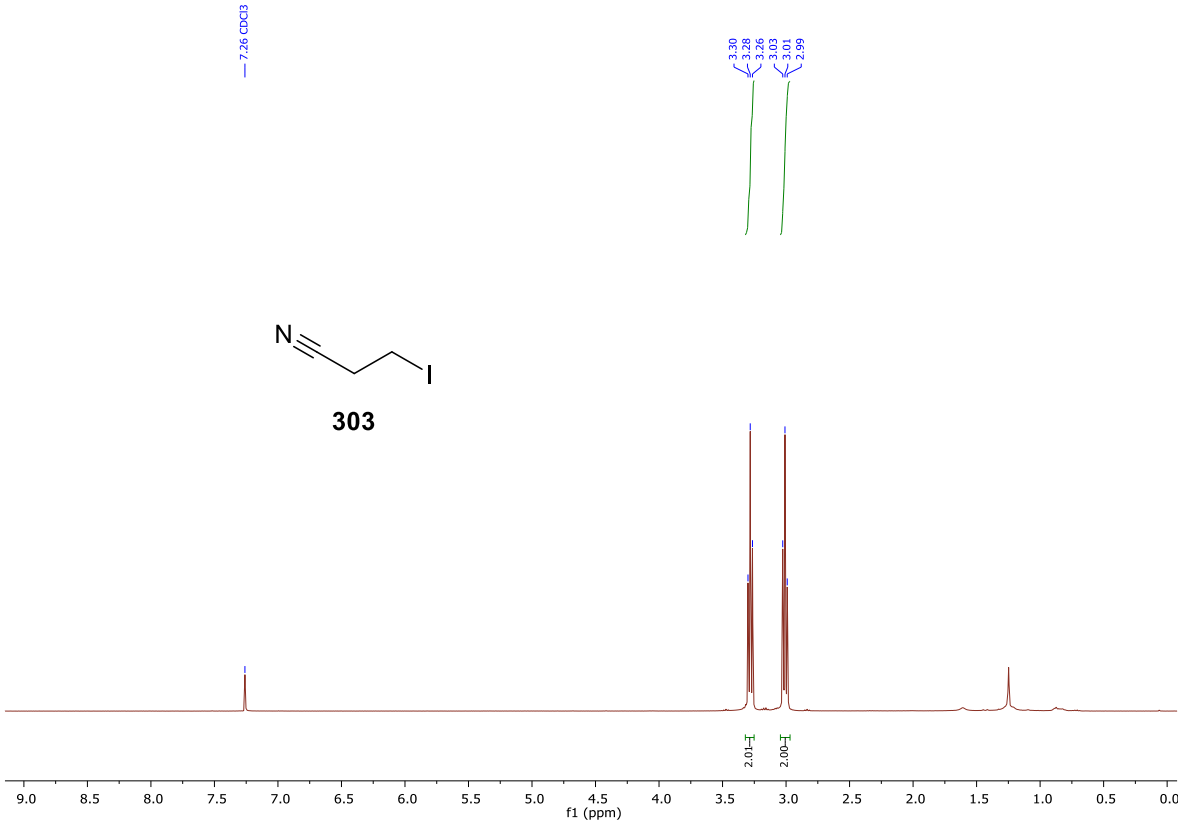
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

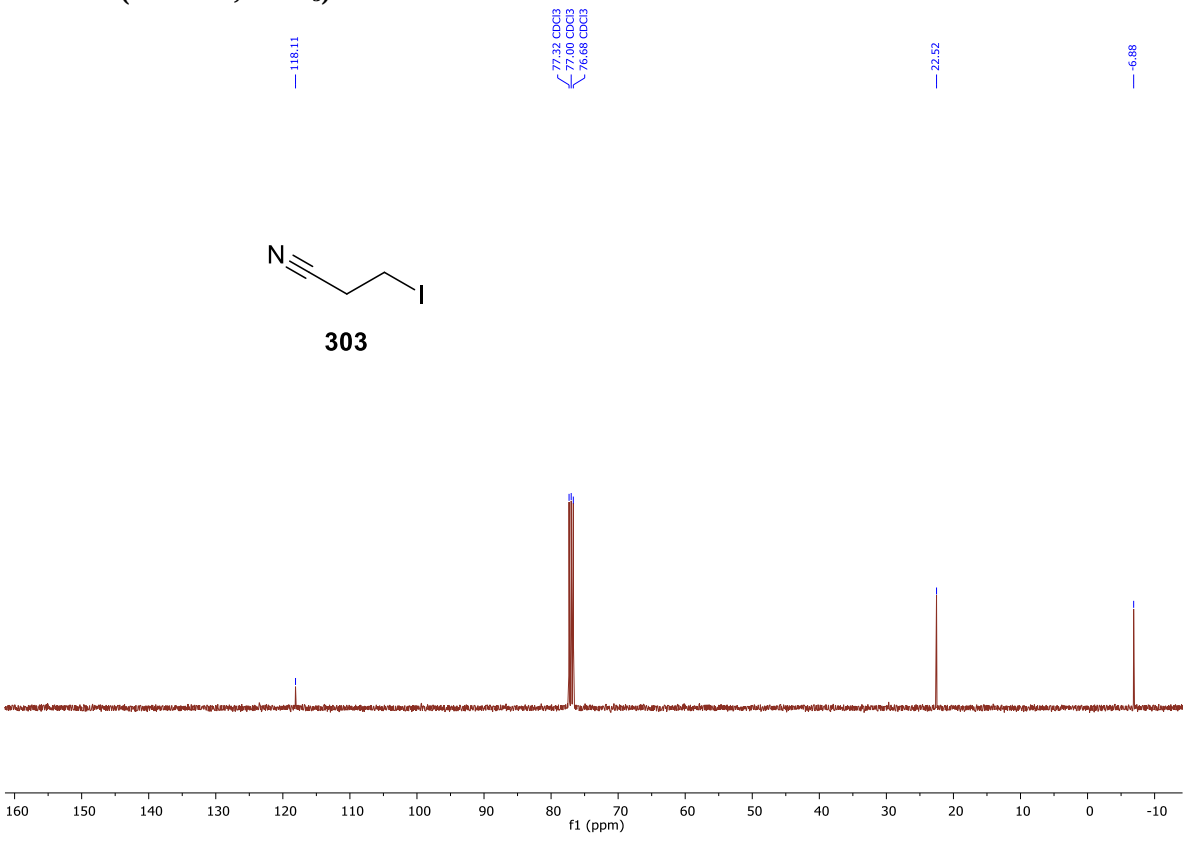


^{1}H-NMR (400 MHz, $CDCl_3$)



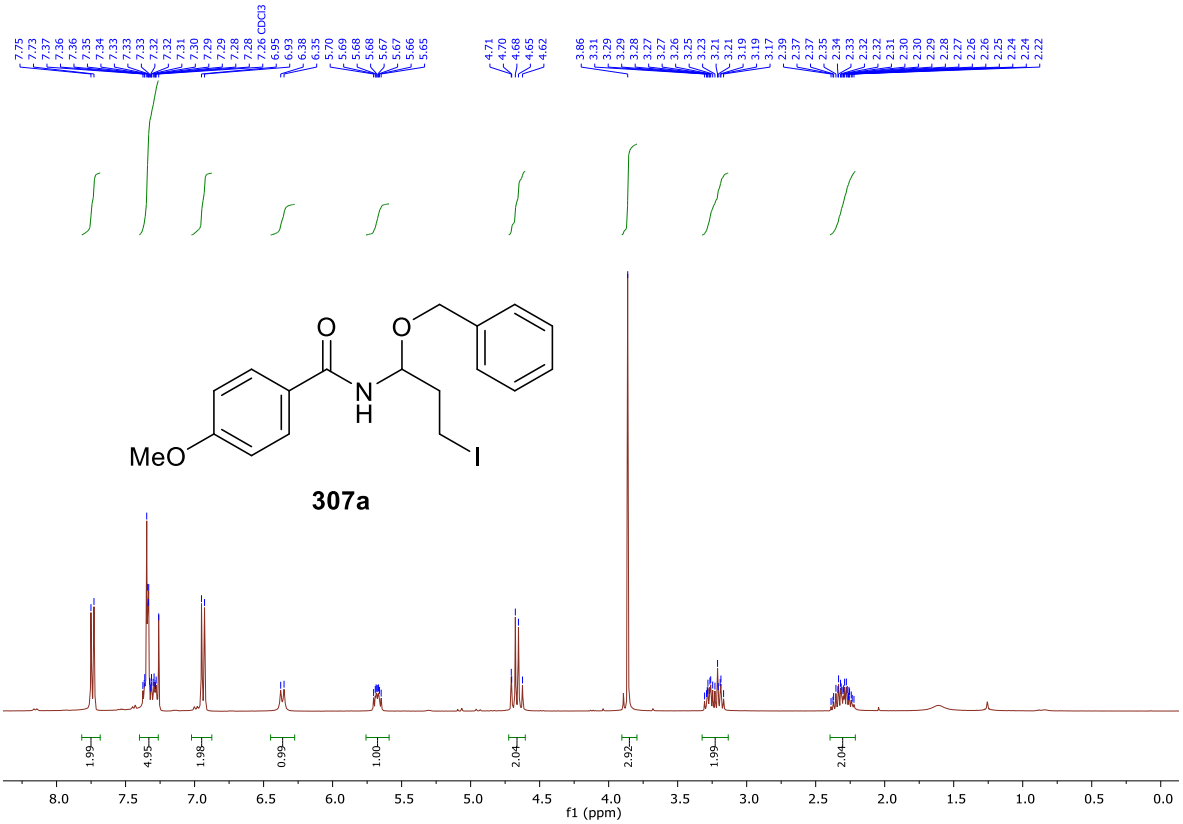
303

^{13}C-NMR (101 MHz, $CDCl_3$)

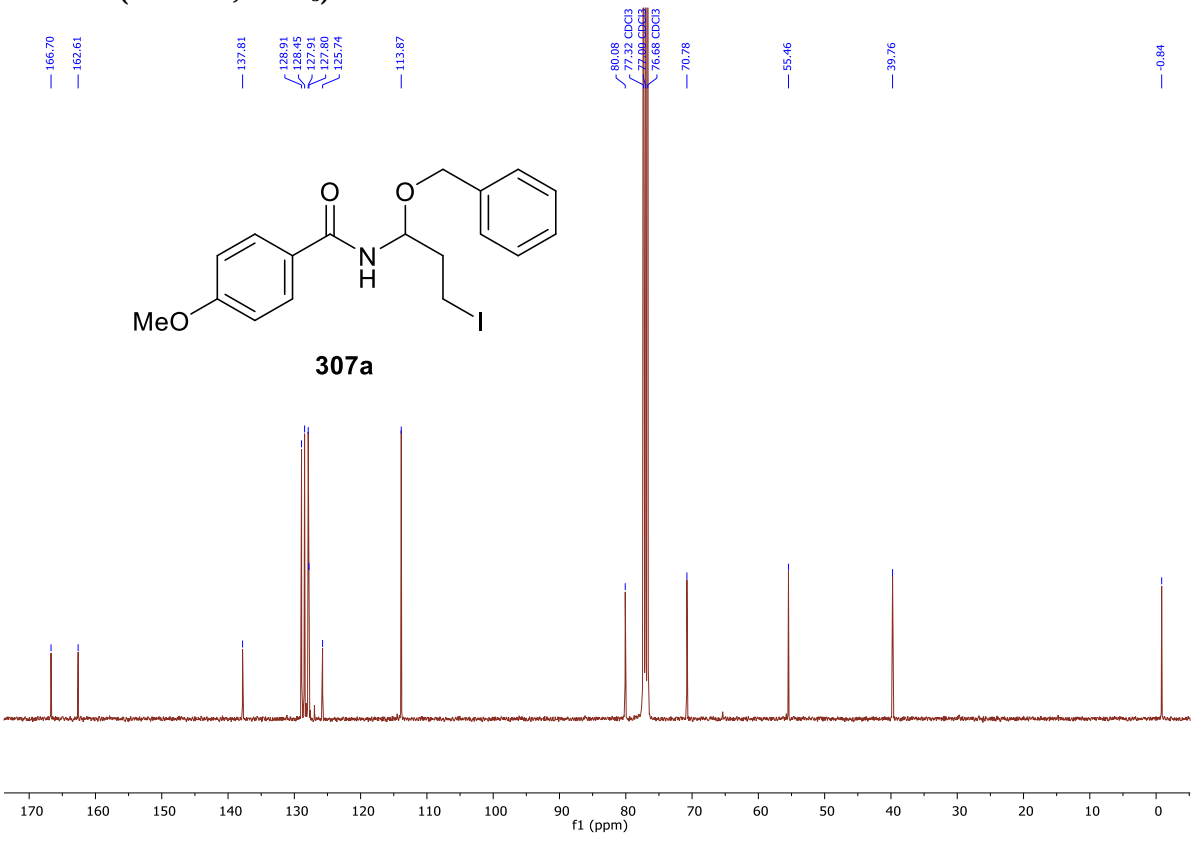


303

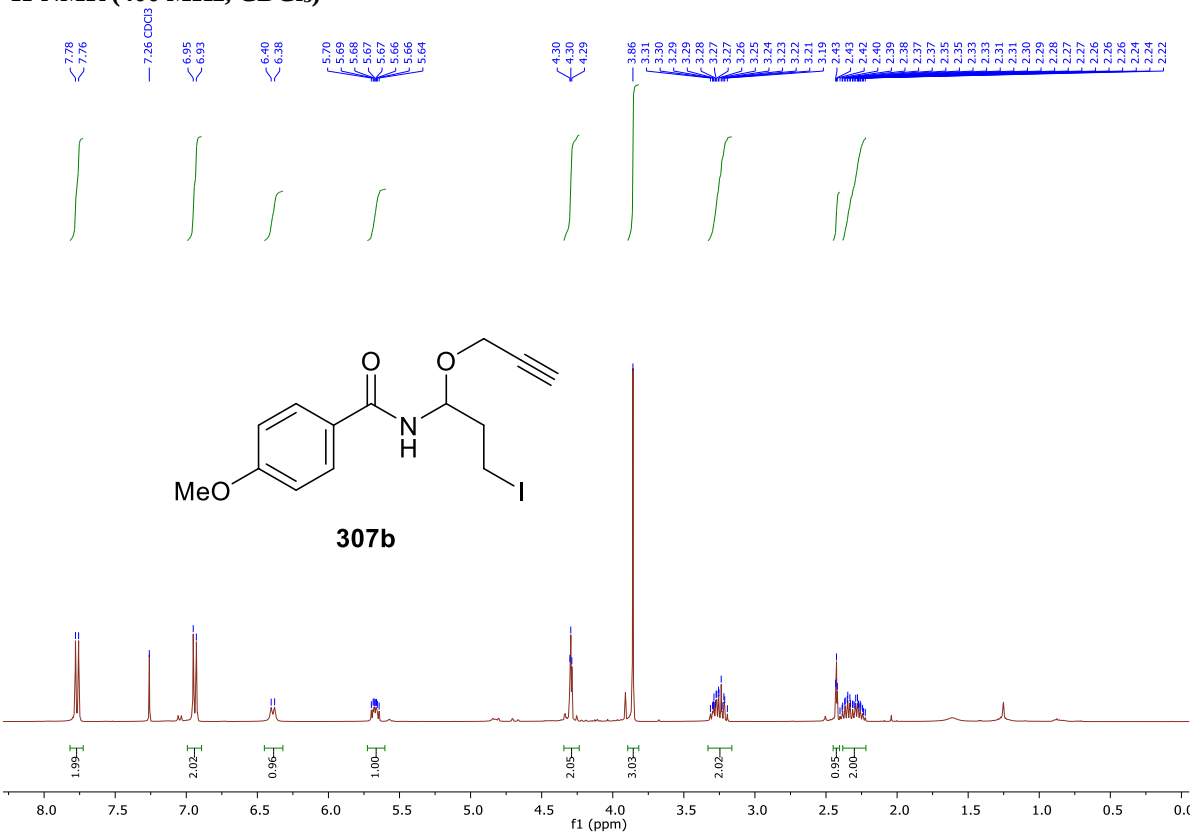
^{1}H-NMR (400 MHz, $CDCl_3$)



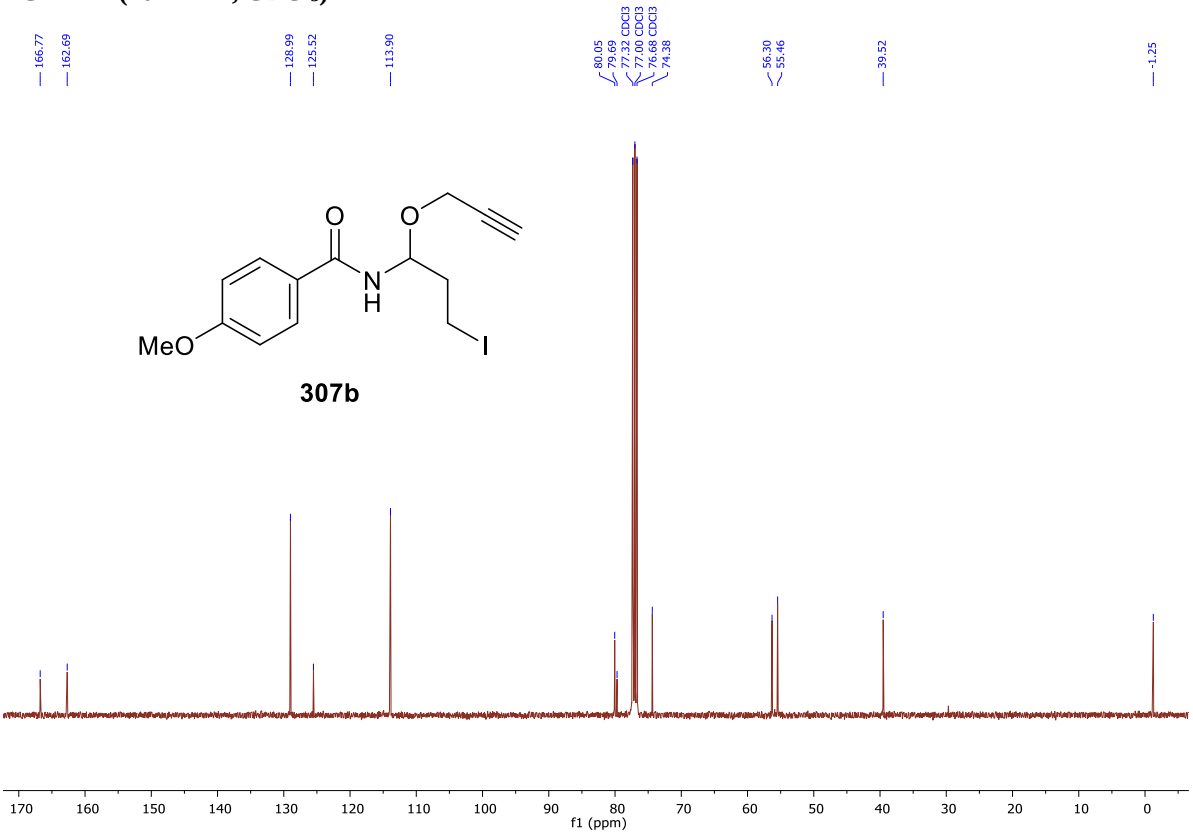
^{13}C-NMR (101 MHz, $CDCl_3$)



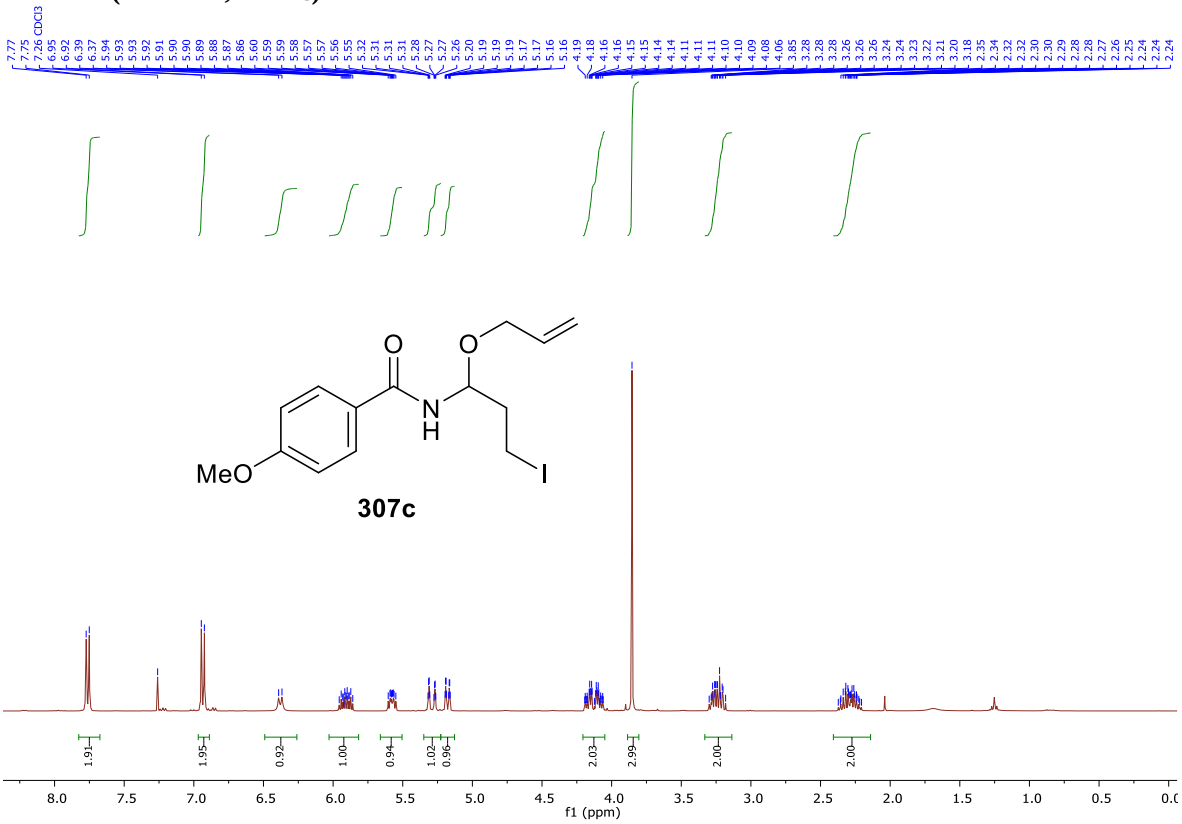
^{1}H-NMR (400 MHz, $CDCl_3$)



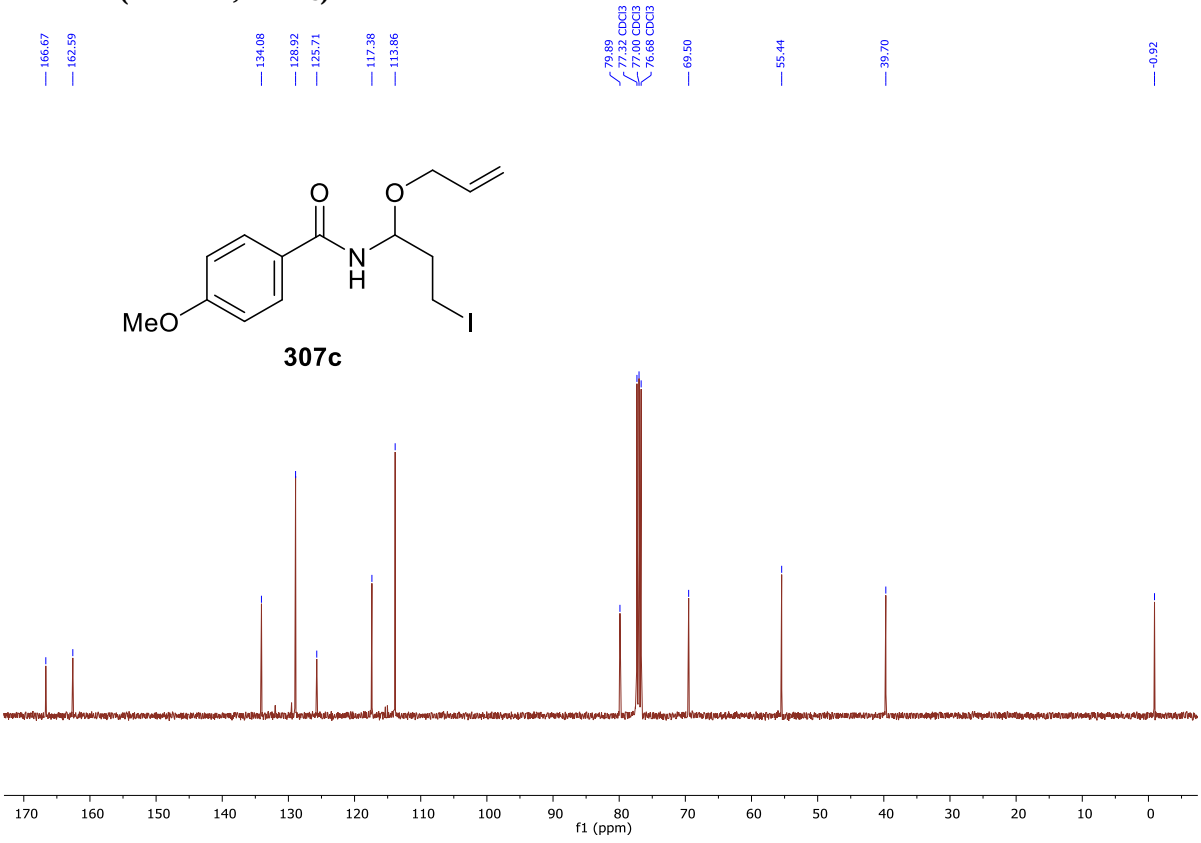
^{13}C-NMR (101 MHz, $CDCl_3$)



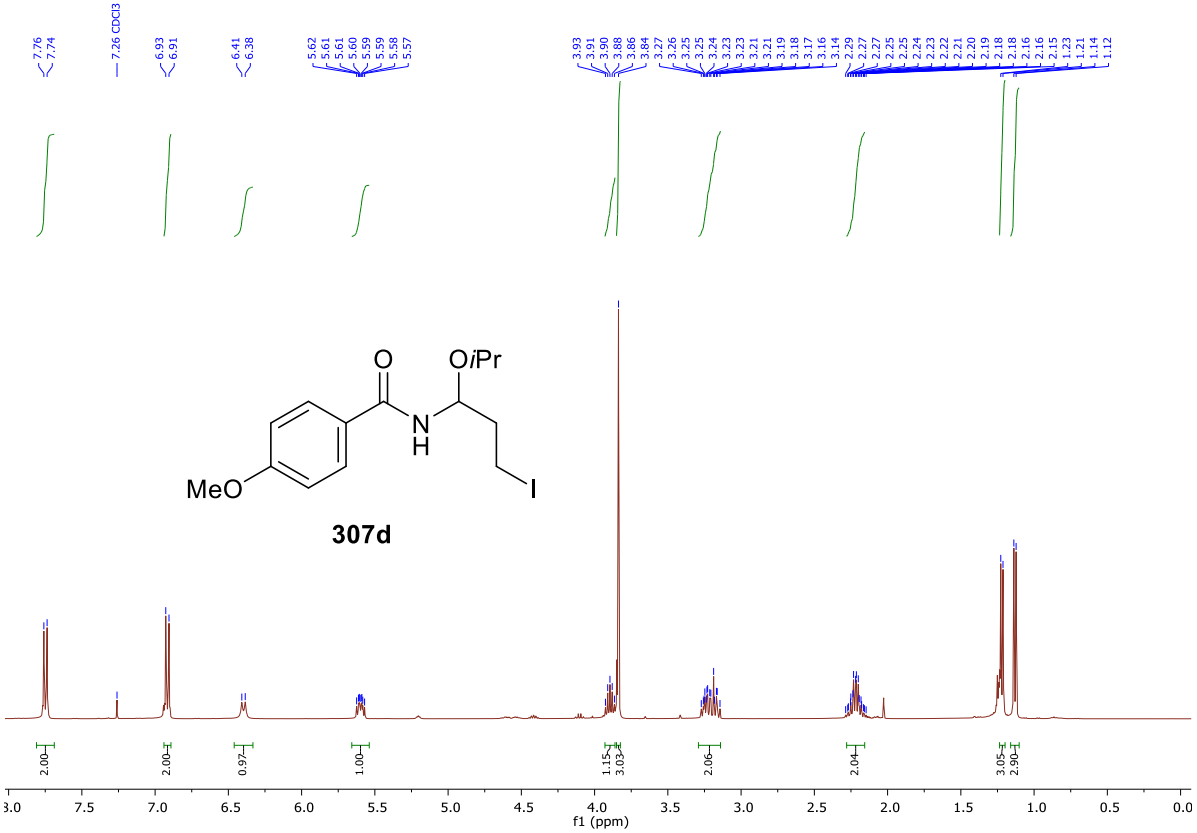
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

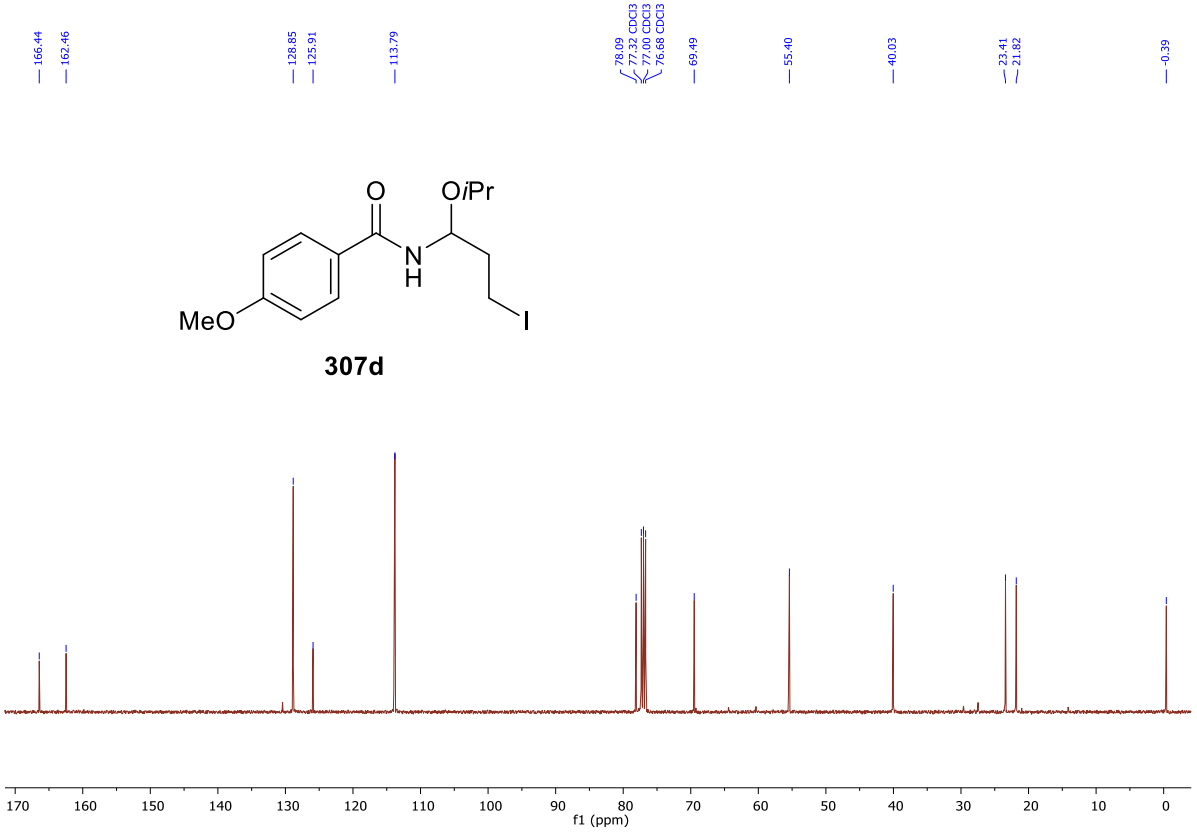


^{1}H-NMR (400 MHz, $CDCl_3$)



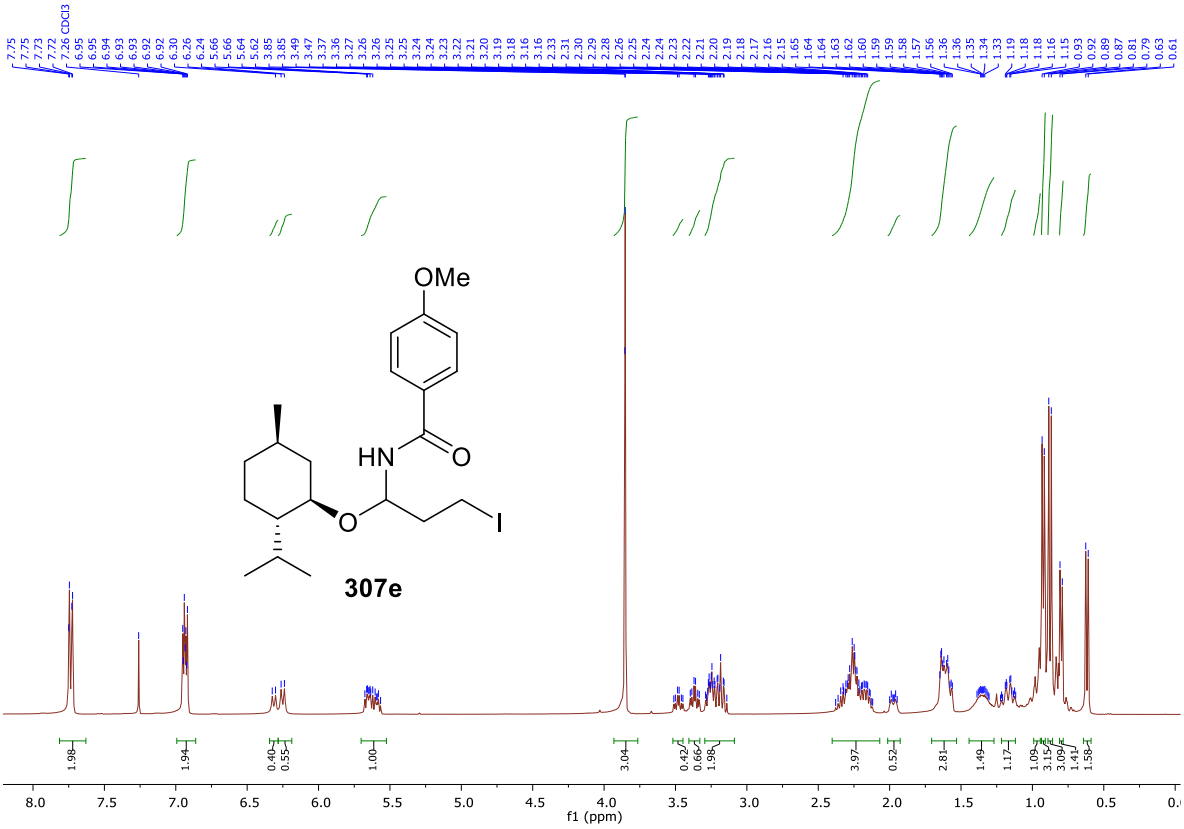
307d

^{13}C-NMR (101 MHz, $CDCl_3$)

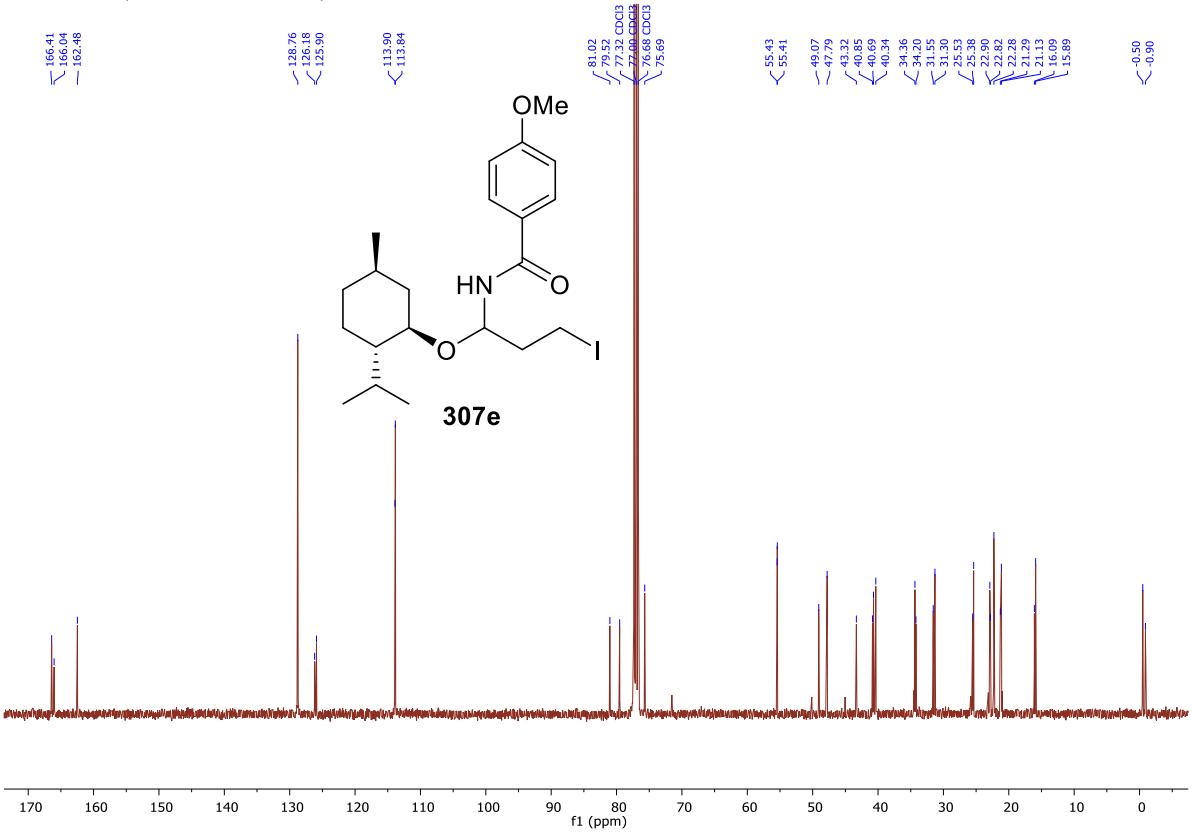


307d

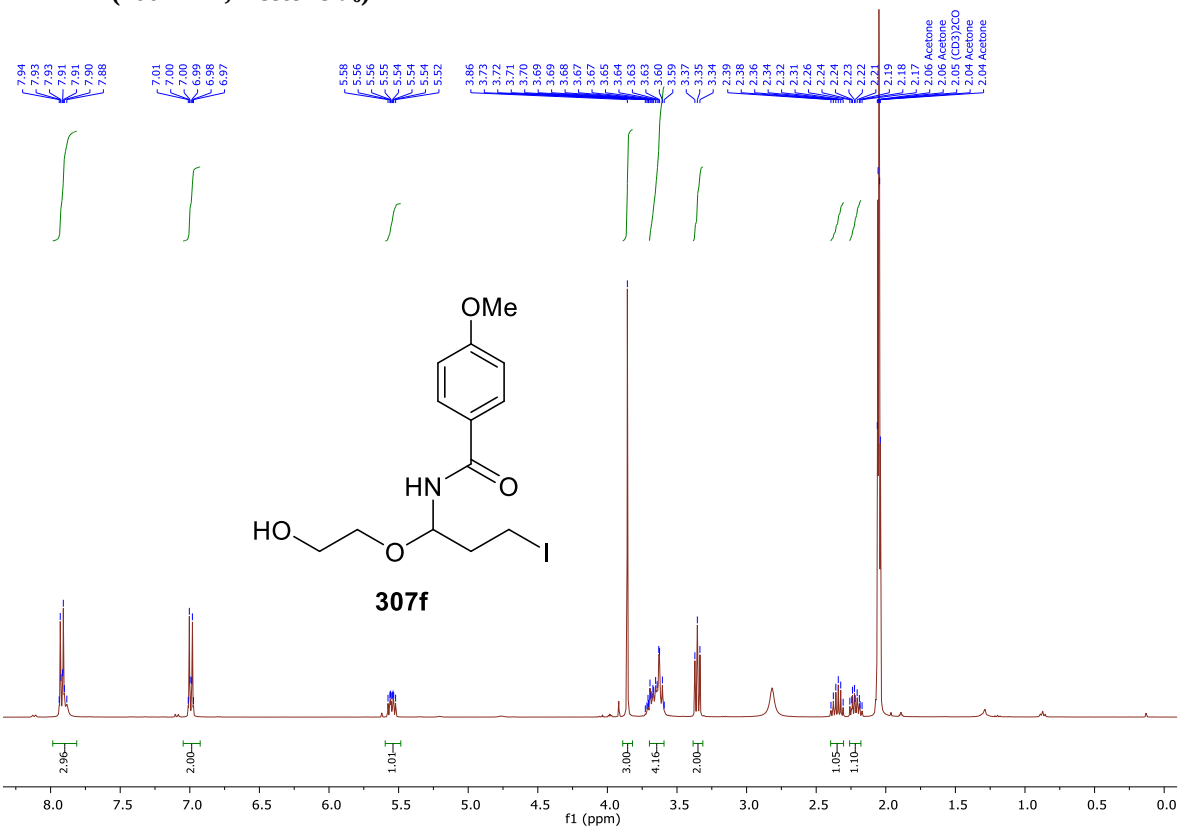
^{1}H-NMR (400 MHz, $CDCl_3$)



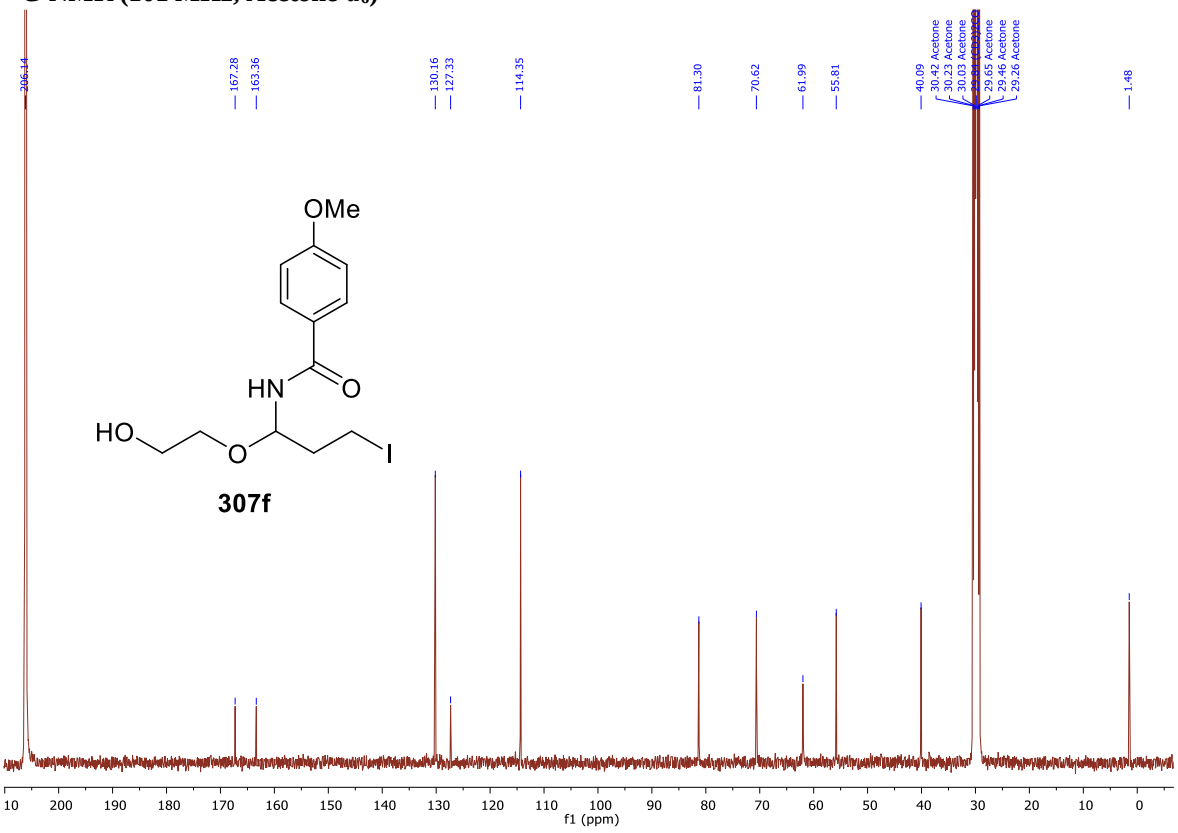
^{13}C-NMR (101 MHz, $CDCl_3$)



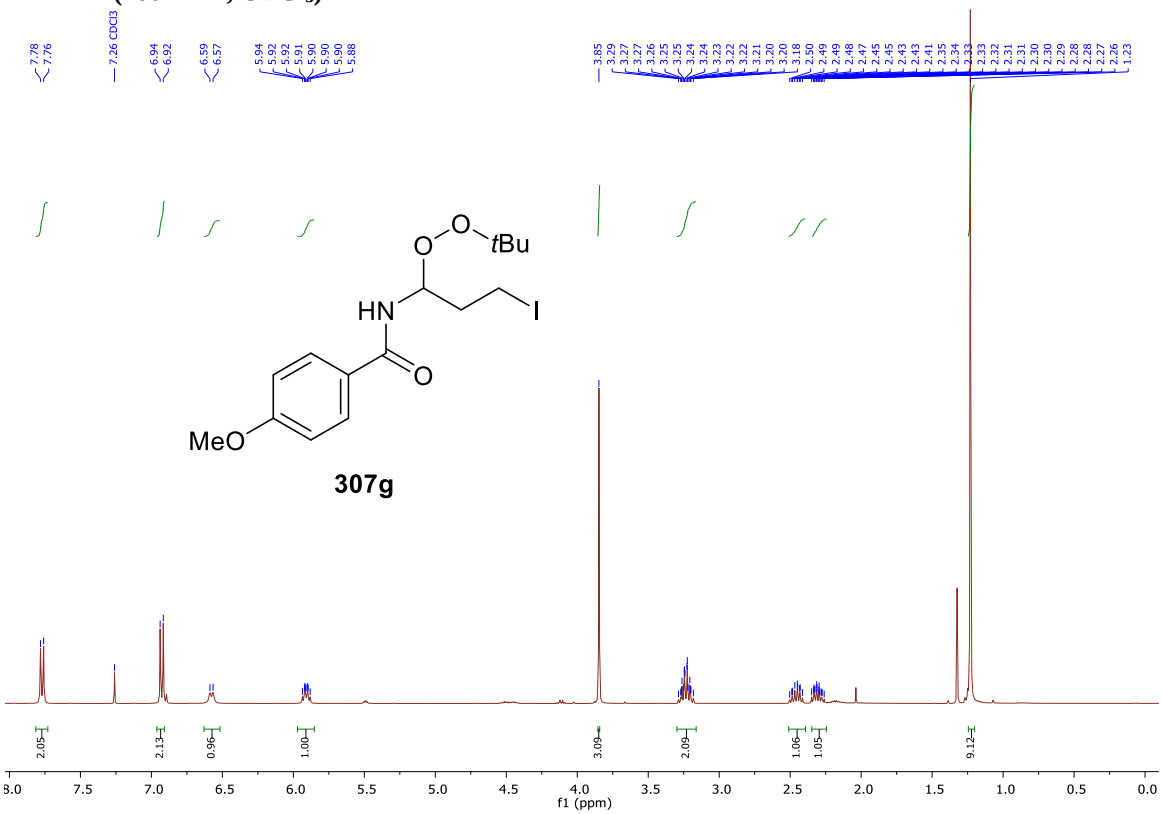
^{1}H-NMR (400 MHz, Acetone-d_6)



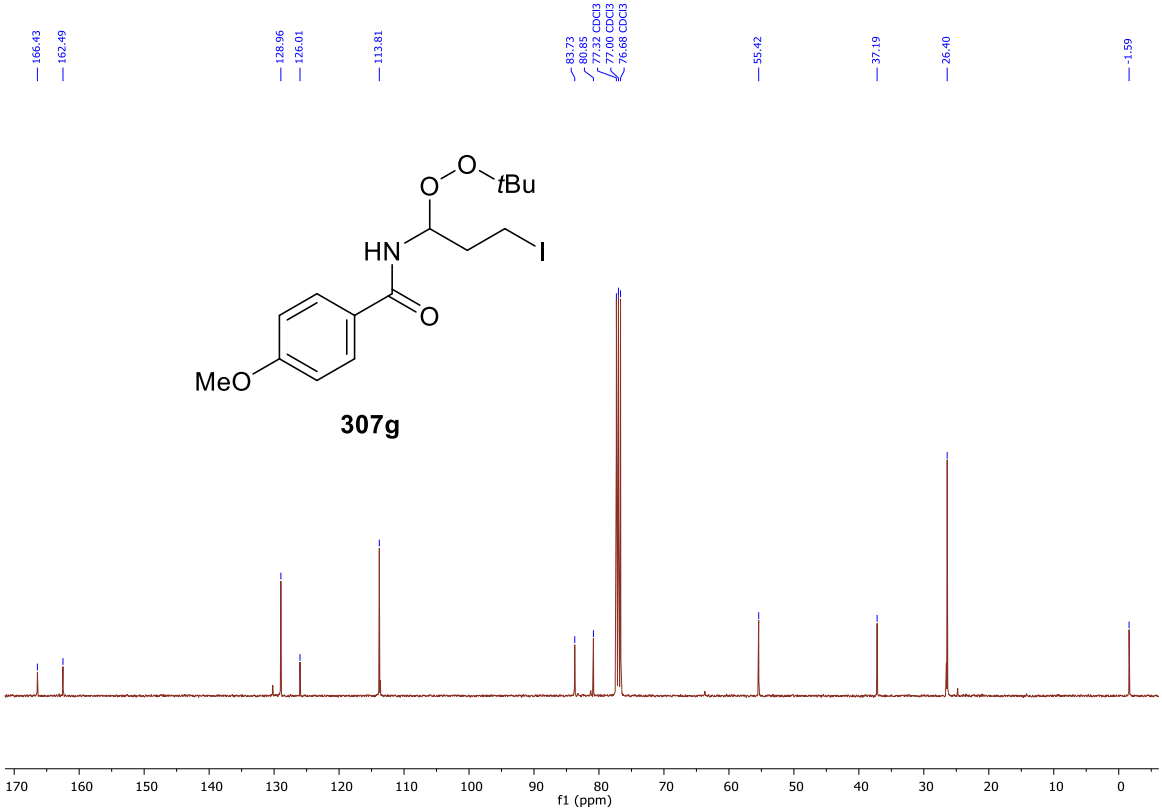
^{13}C-NMR (101 MHz, Acetone-d_6)



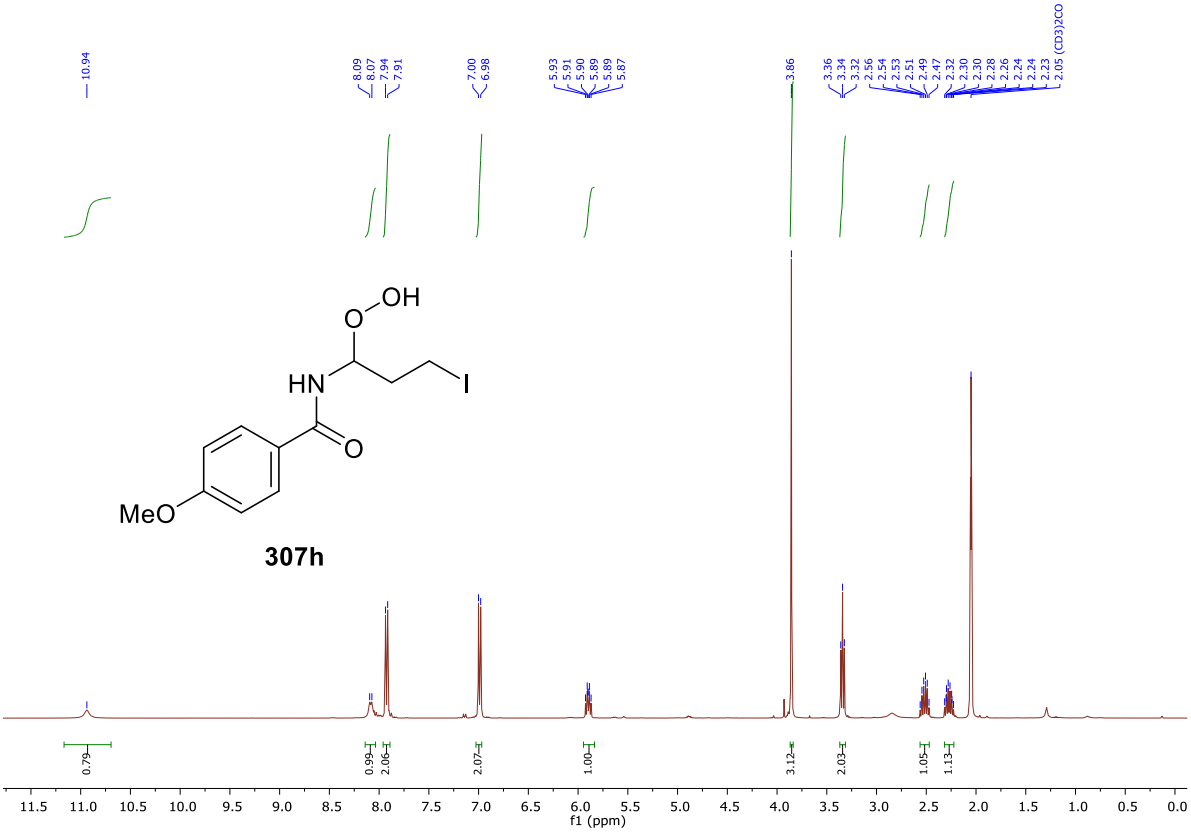
^{1}H-NMR (400 MHz, $CDCl_3$)



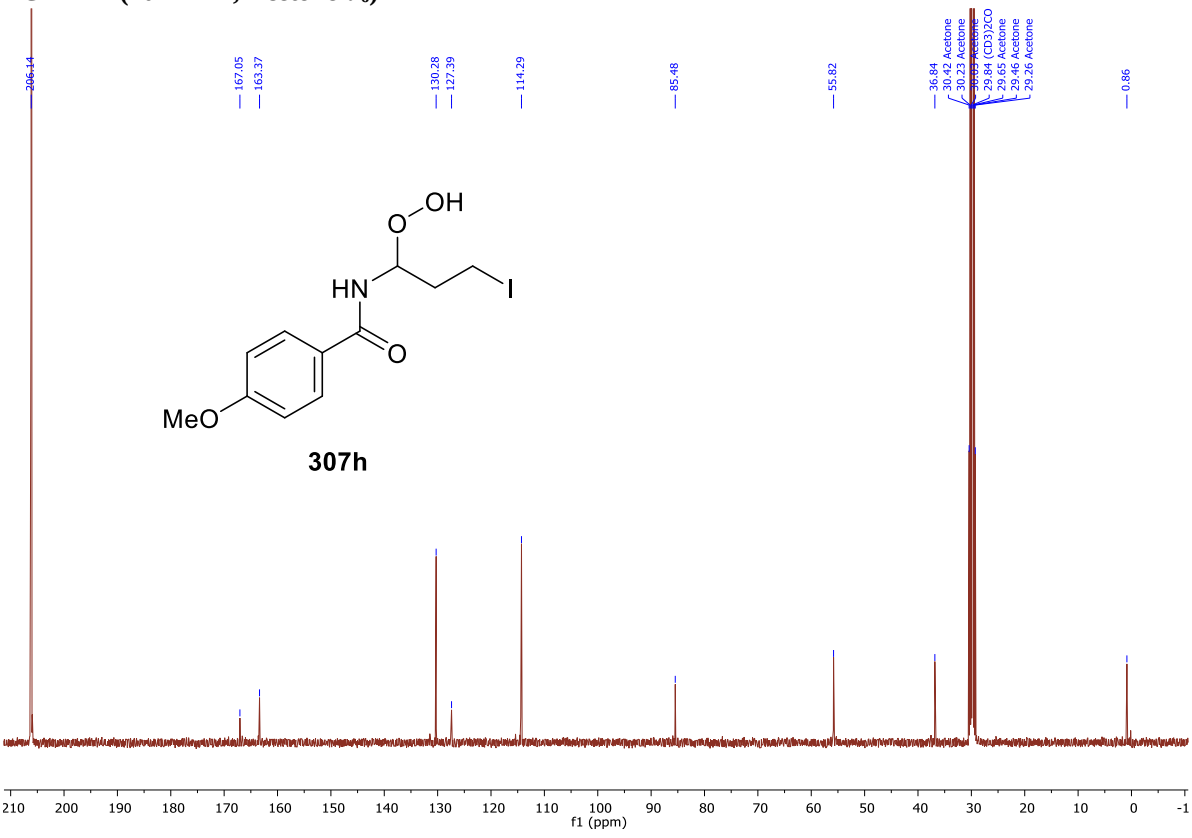
^{13}C-NMR (101 MHz, $CDCl_3$)



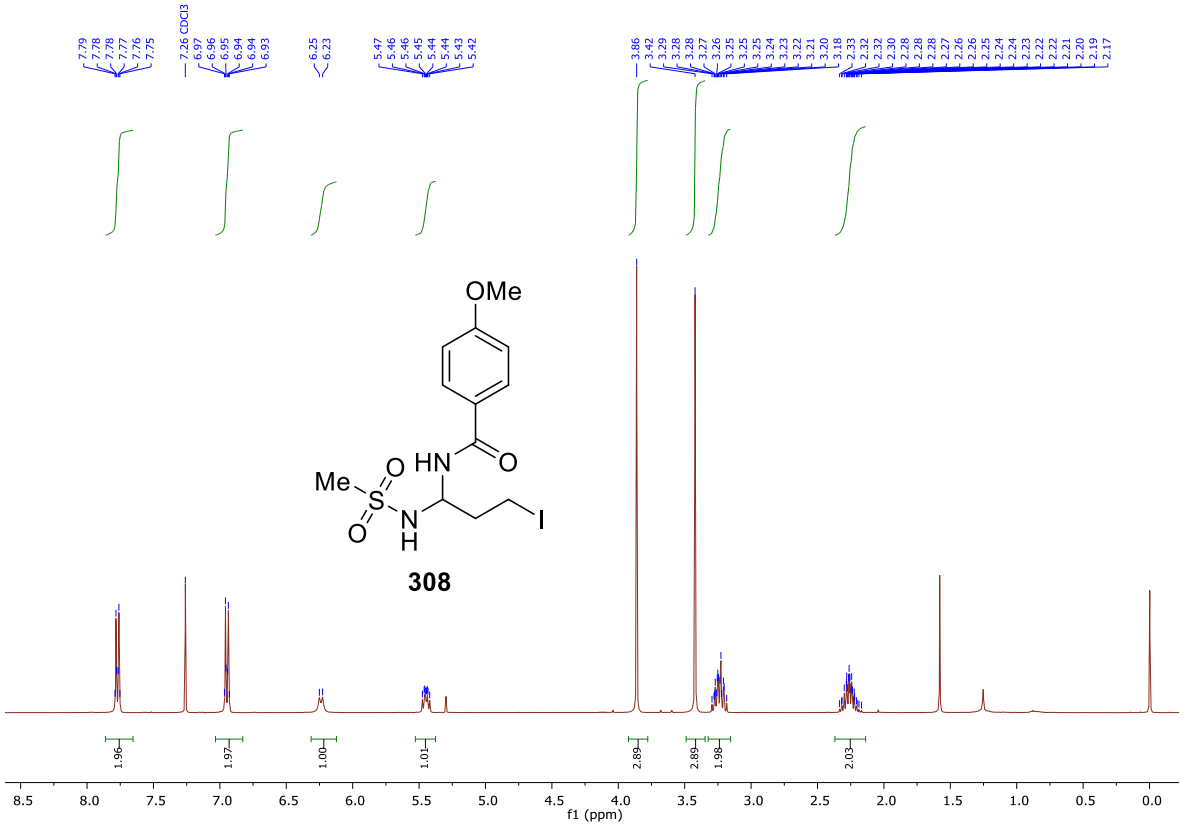
^{1}H-NMR (400 MHz, Acetone-d_6)



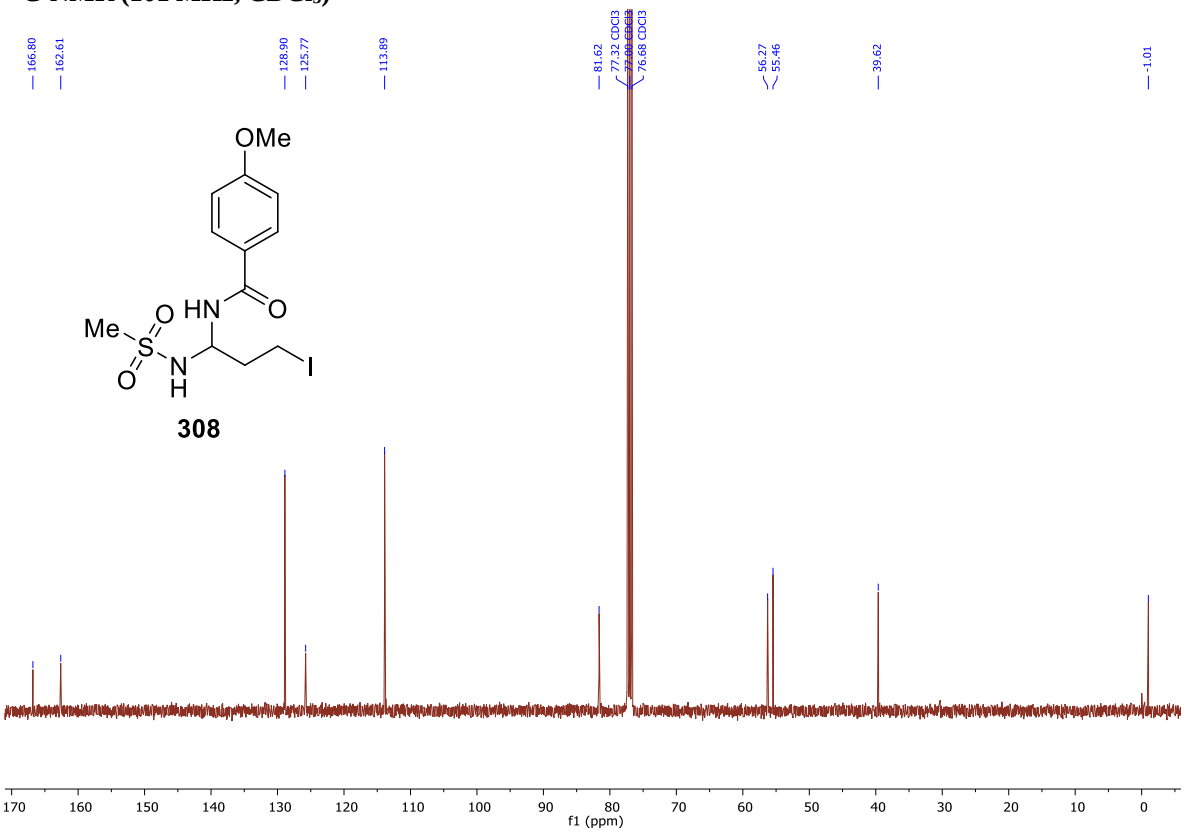
^{13}C-NMR (101 MHz, Acetone-d_6)



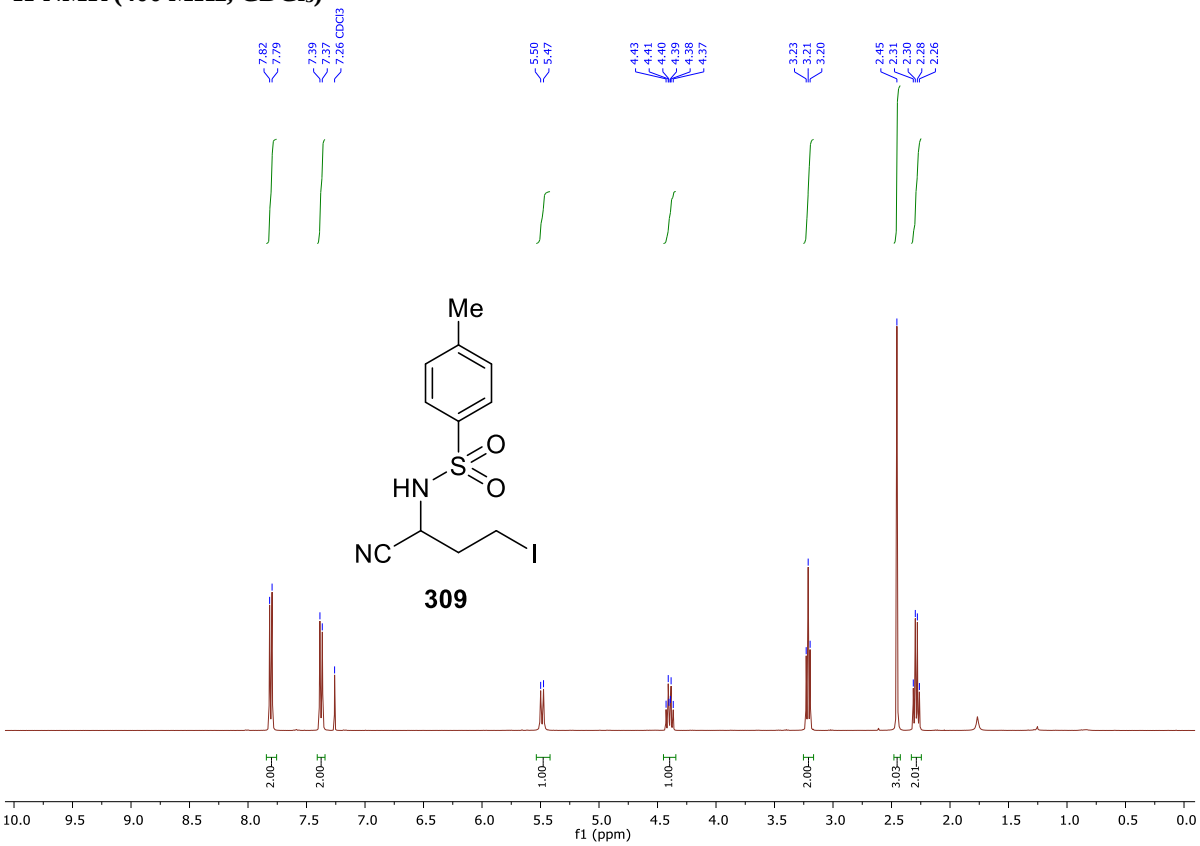
^{1}H-NMR (400 MHz, $CDCl_3$)



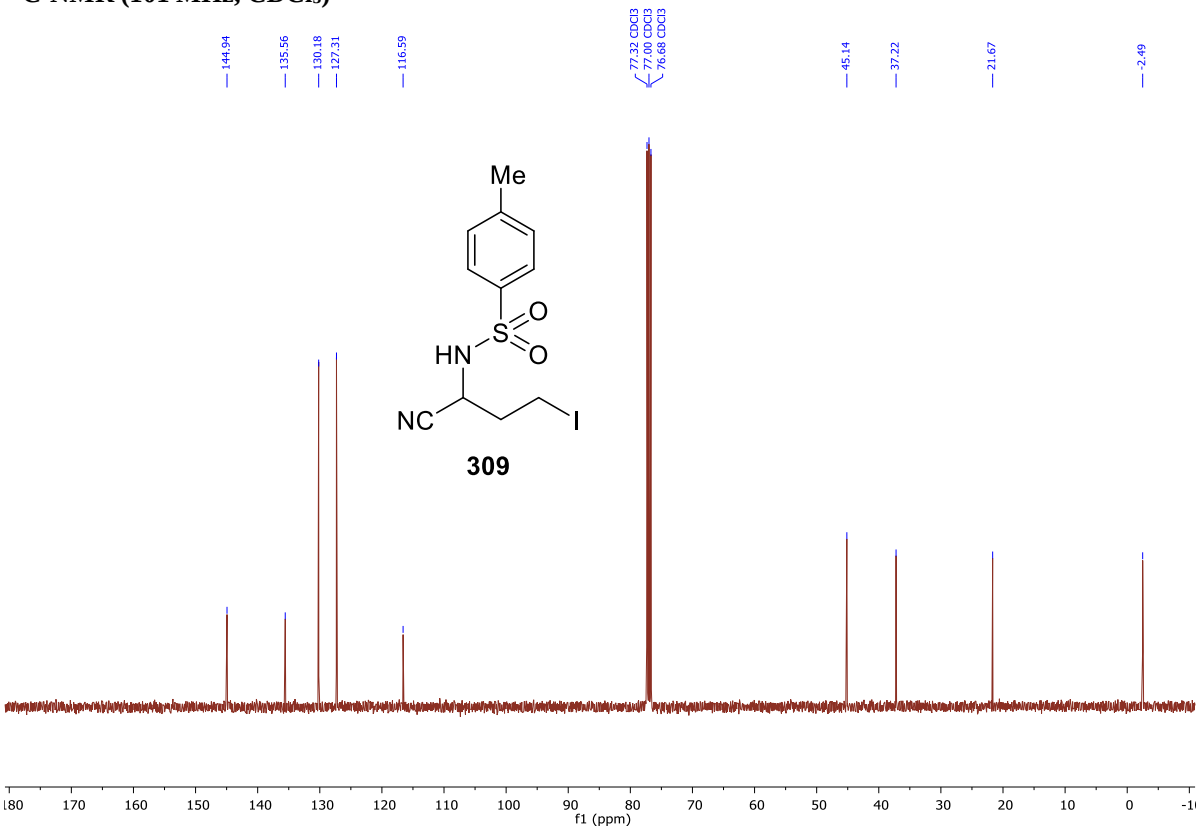
^{13}C-NMR (101 MHz, $CDCl_3$)



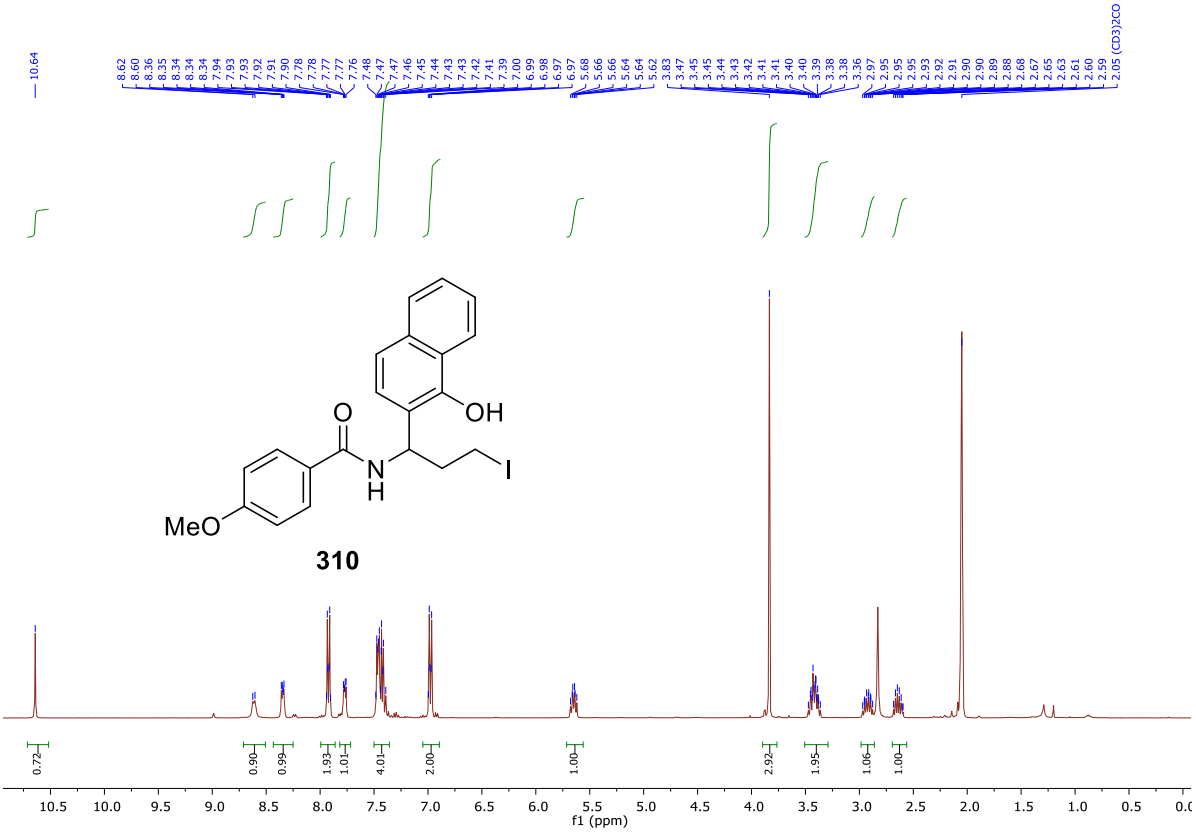
^{1}H-NMR (400 MHz, $CDCl_3$)



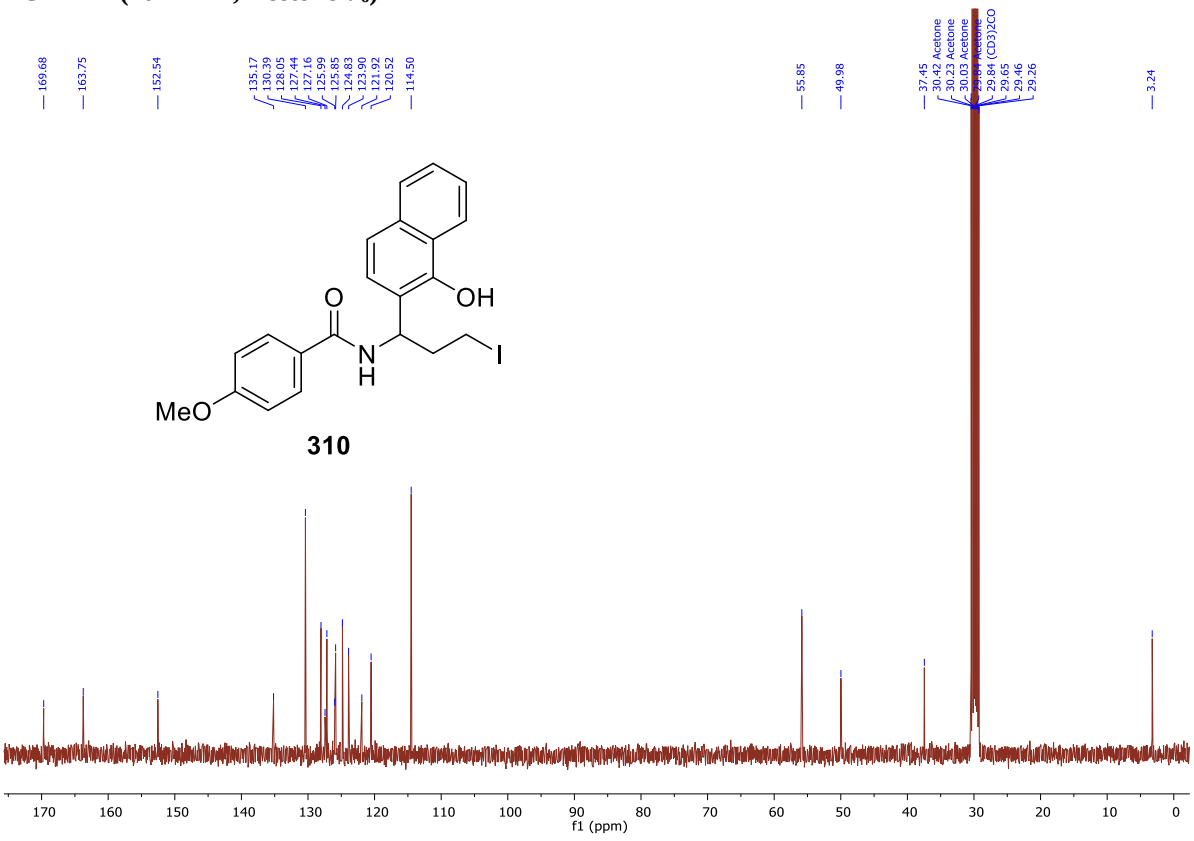
^{13}C-NMR (101 MHz, $CDCl_3$)



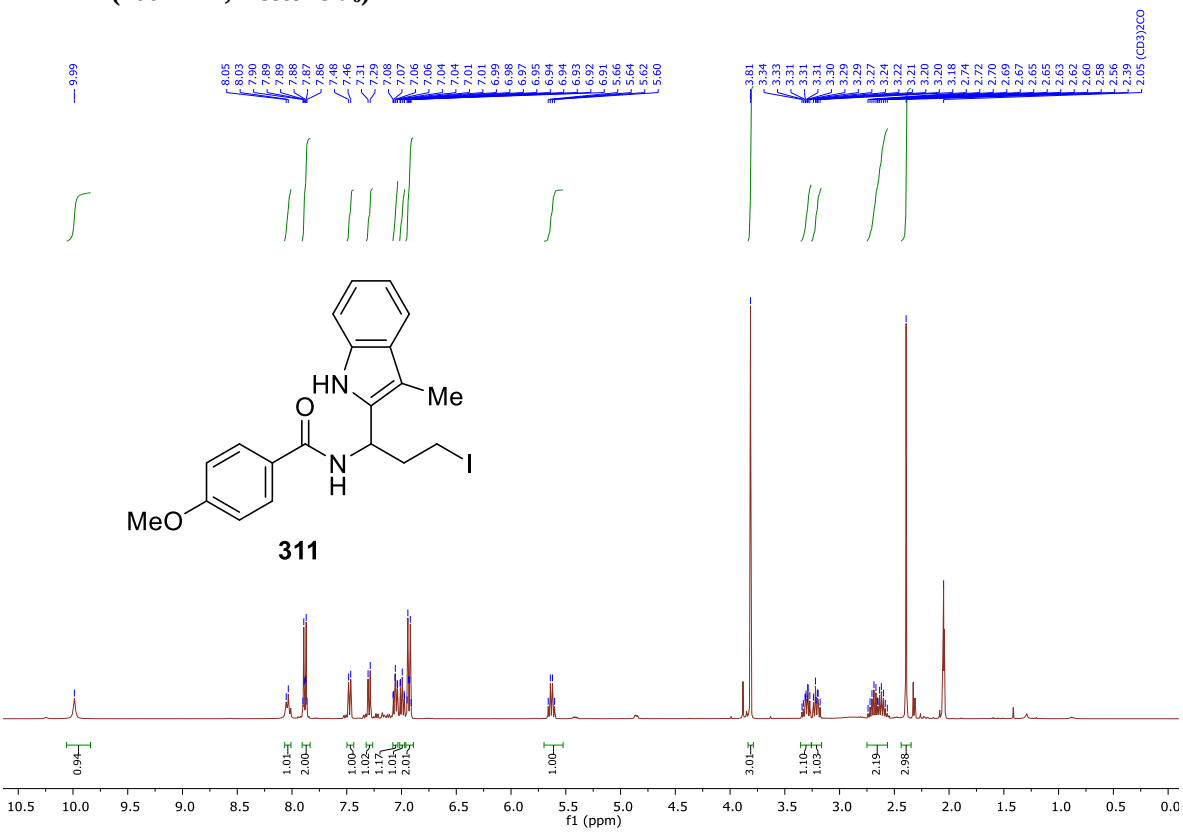
^{1}H-NMR (400 MHz, Acetone-d_6)



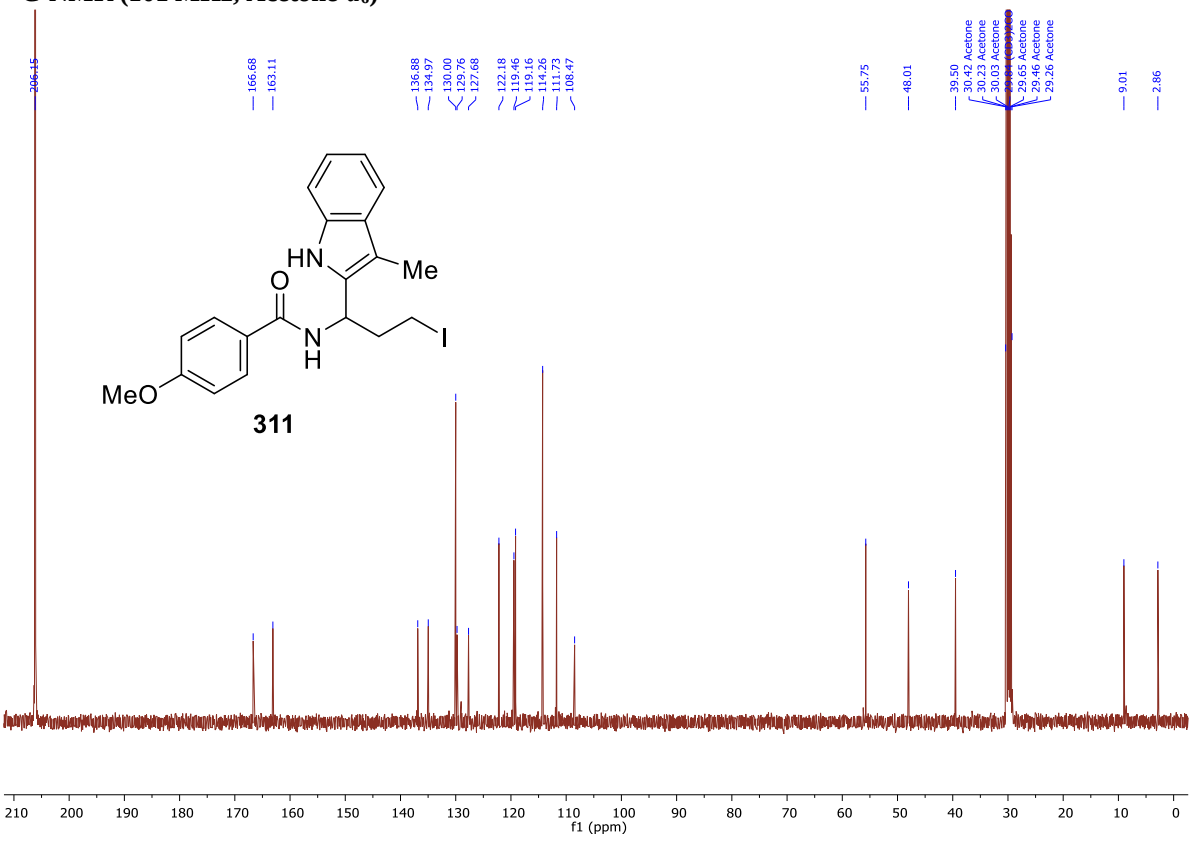
^{13}C-NMR (101 MHz, Acetone-d_6)



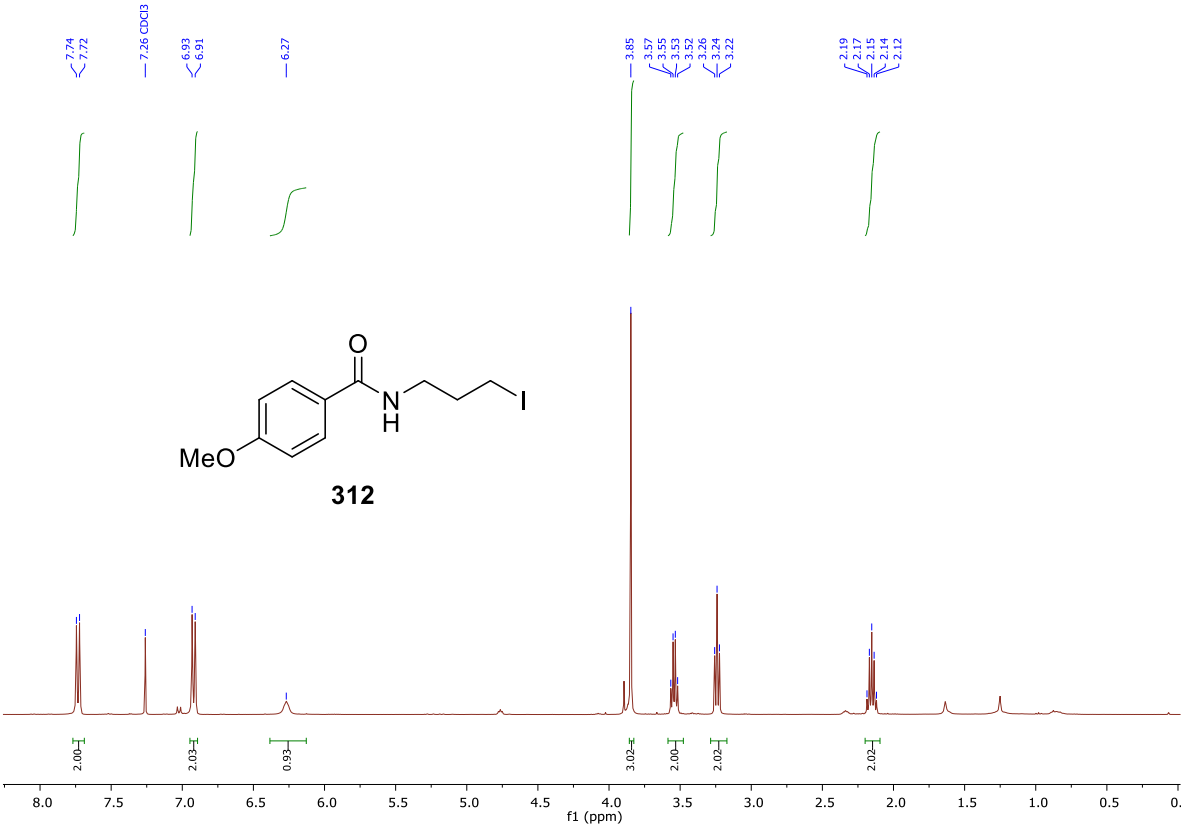
^{1}H-NMR (400 MHz, Acetone-d_6)



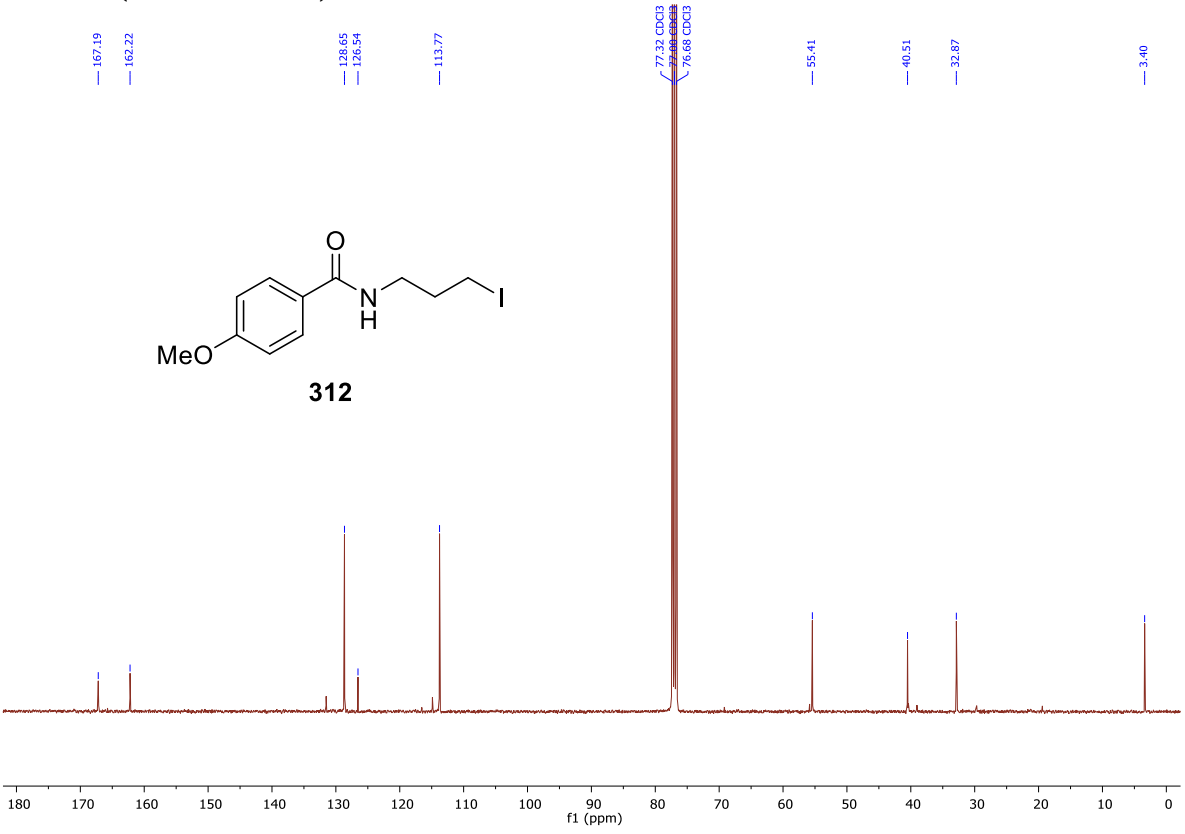
^{13}C-NMR (101 MHz, Acetone-d_6)



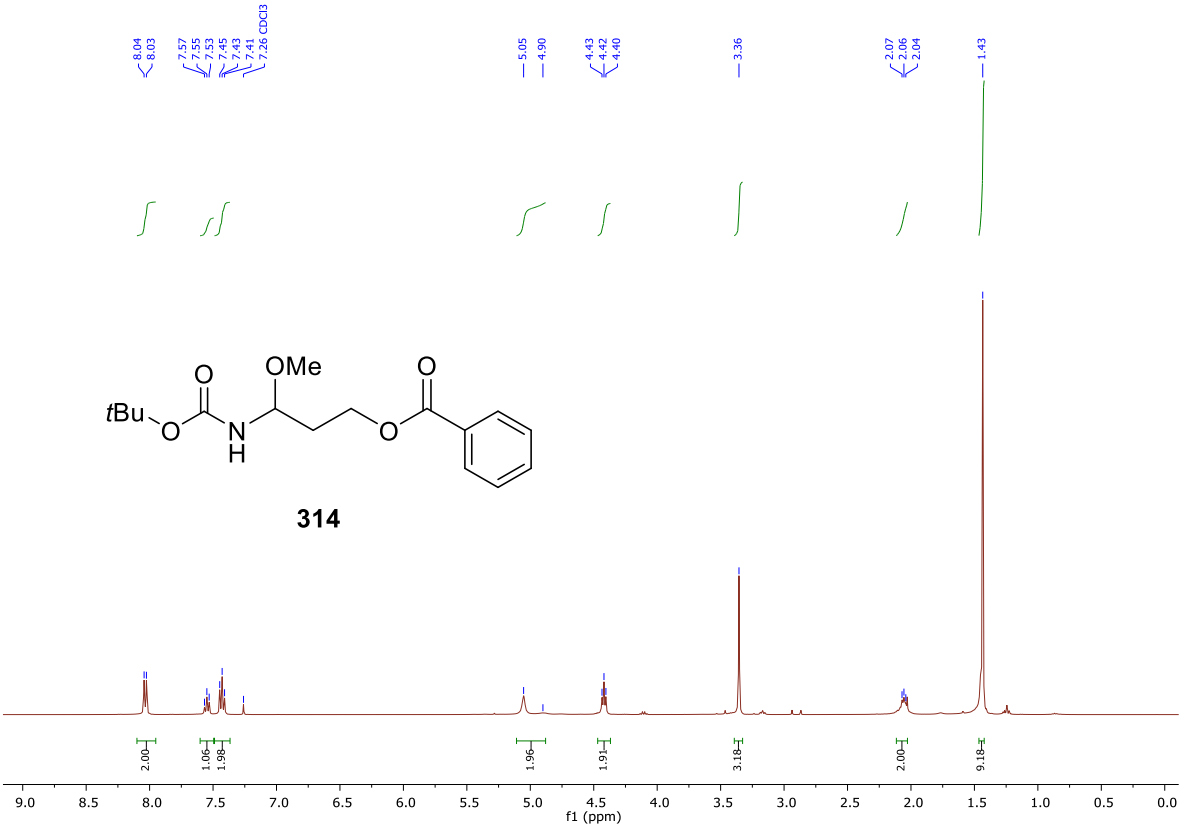
^{1}H-NMR (400 MHz, $CDCl_3$)



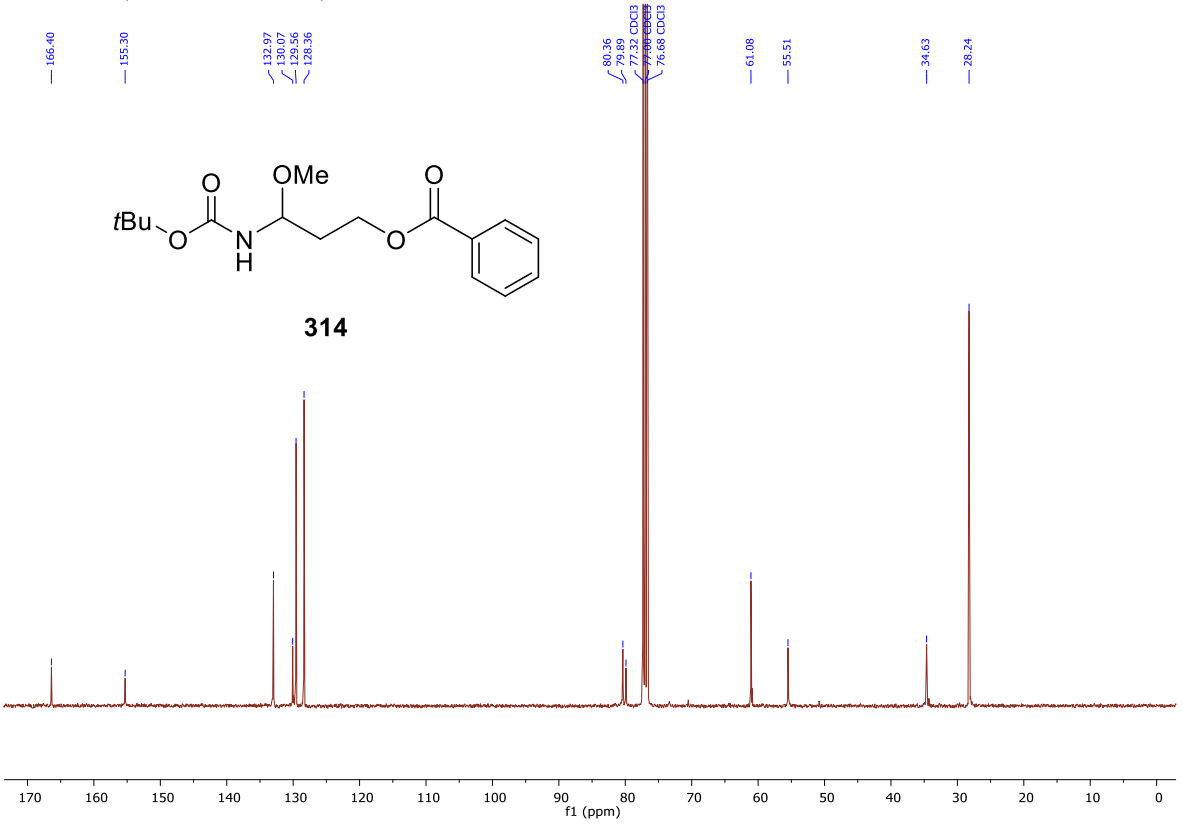
^{13}C-NMR (101 MHz, $CDCl_3$)



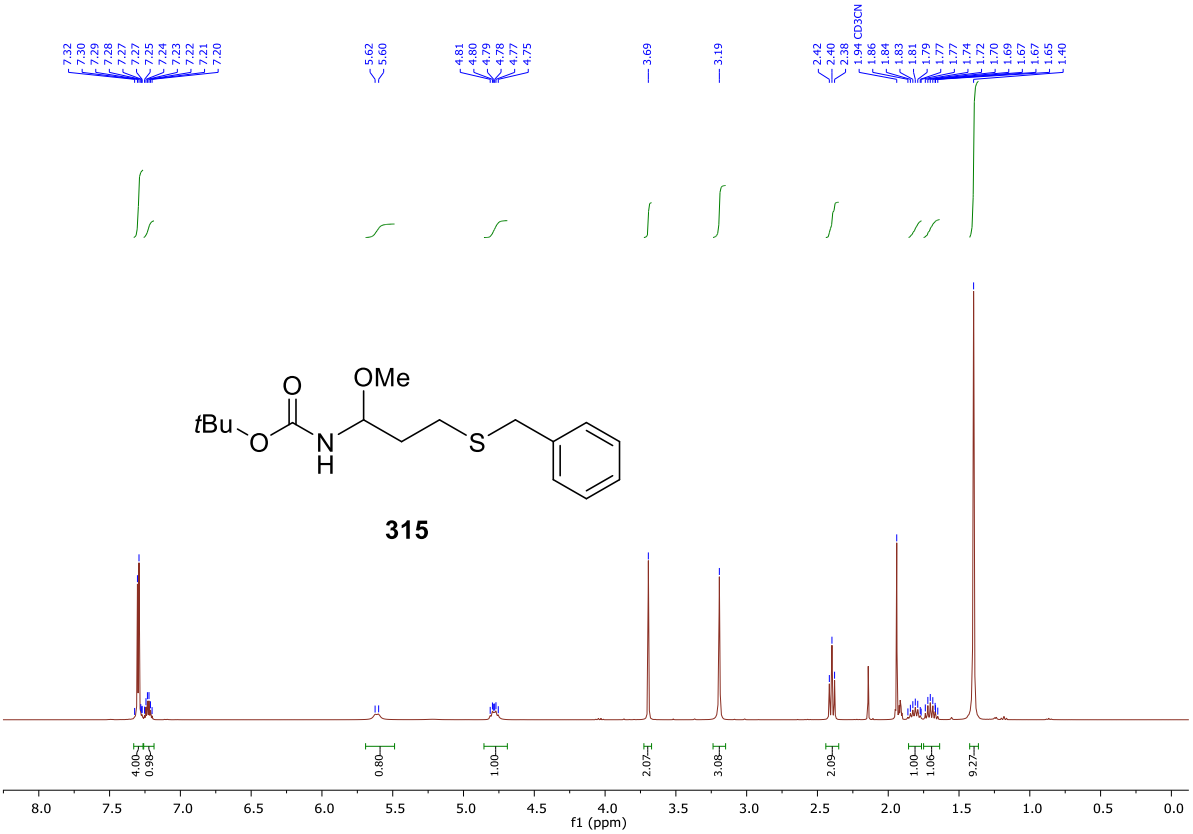
^{1}H-NMR (400 MHz, $CDCl_3$)



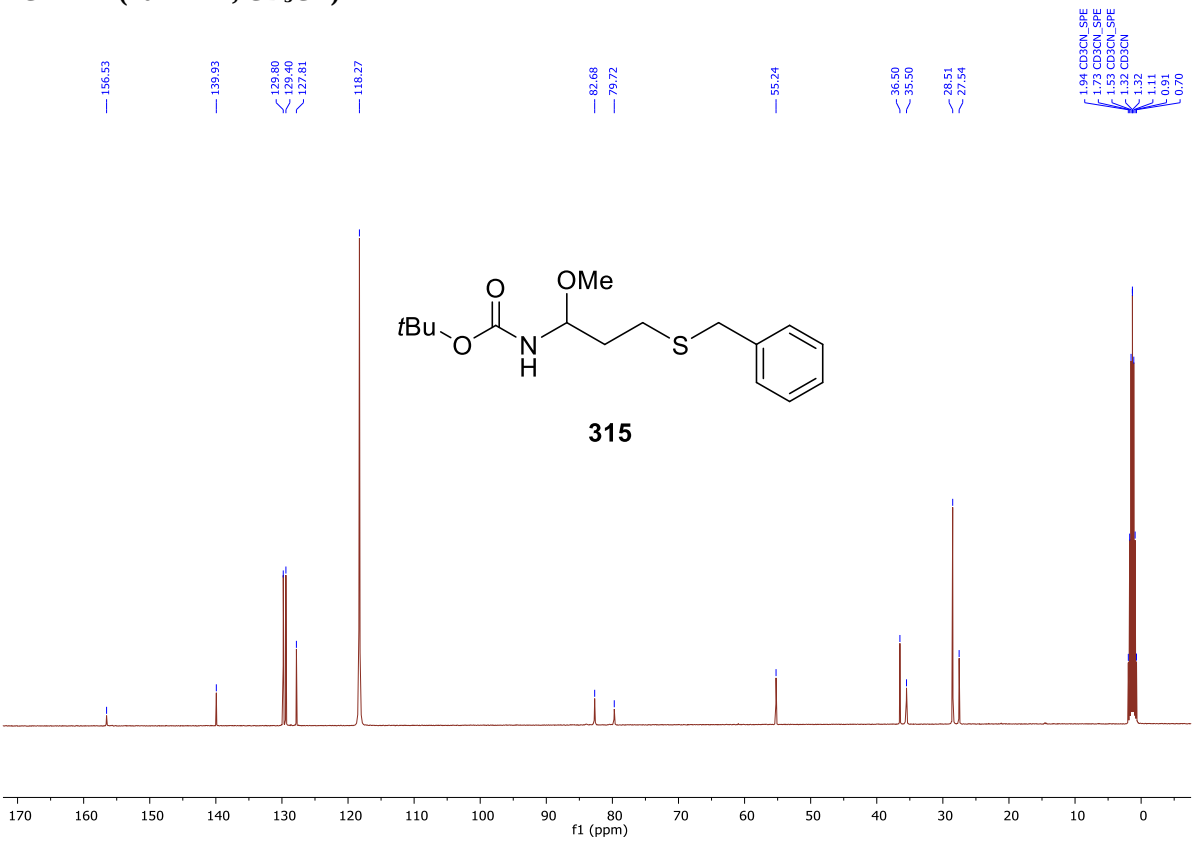
^{13}C-NMR (101 MHz, $CDCl_3$)



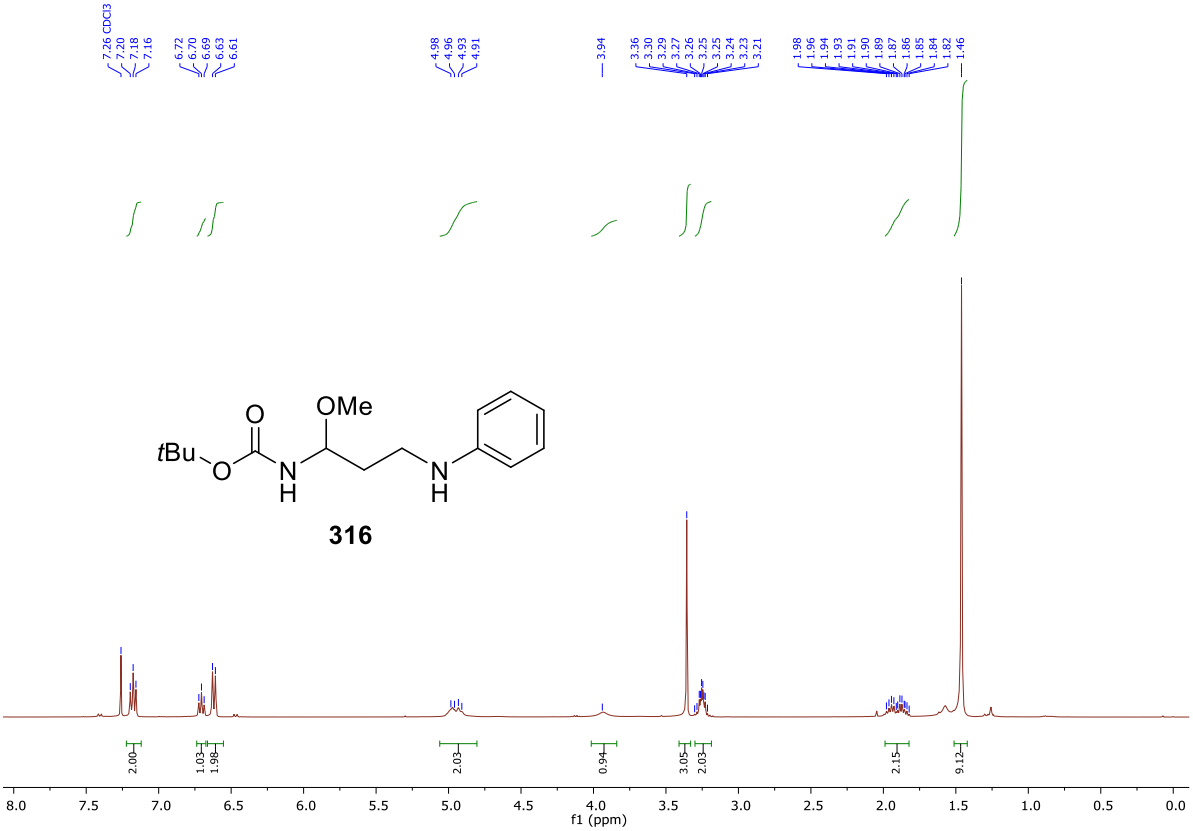
^{1}H-NMR (400 MHz, CD_3CN)



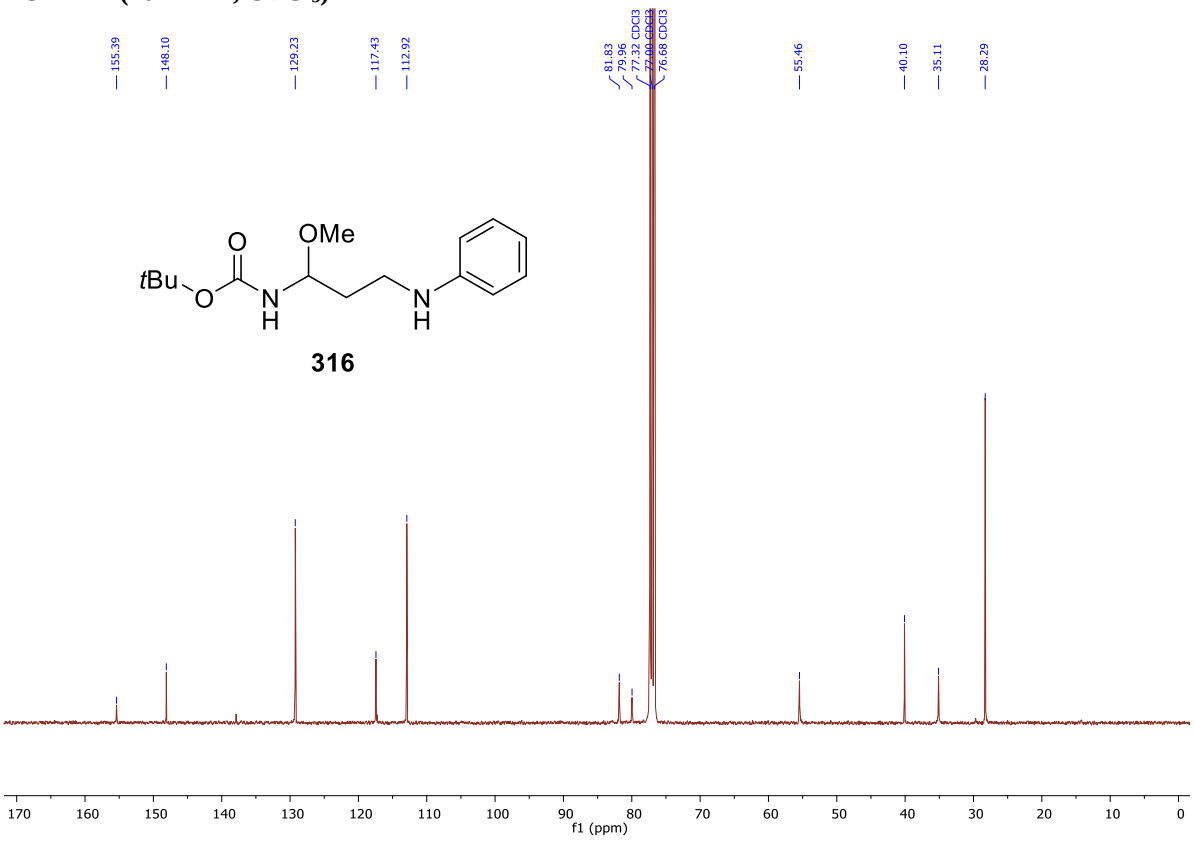
^{13}C-NMR (101 MHz, CD_3CN)



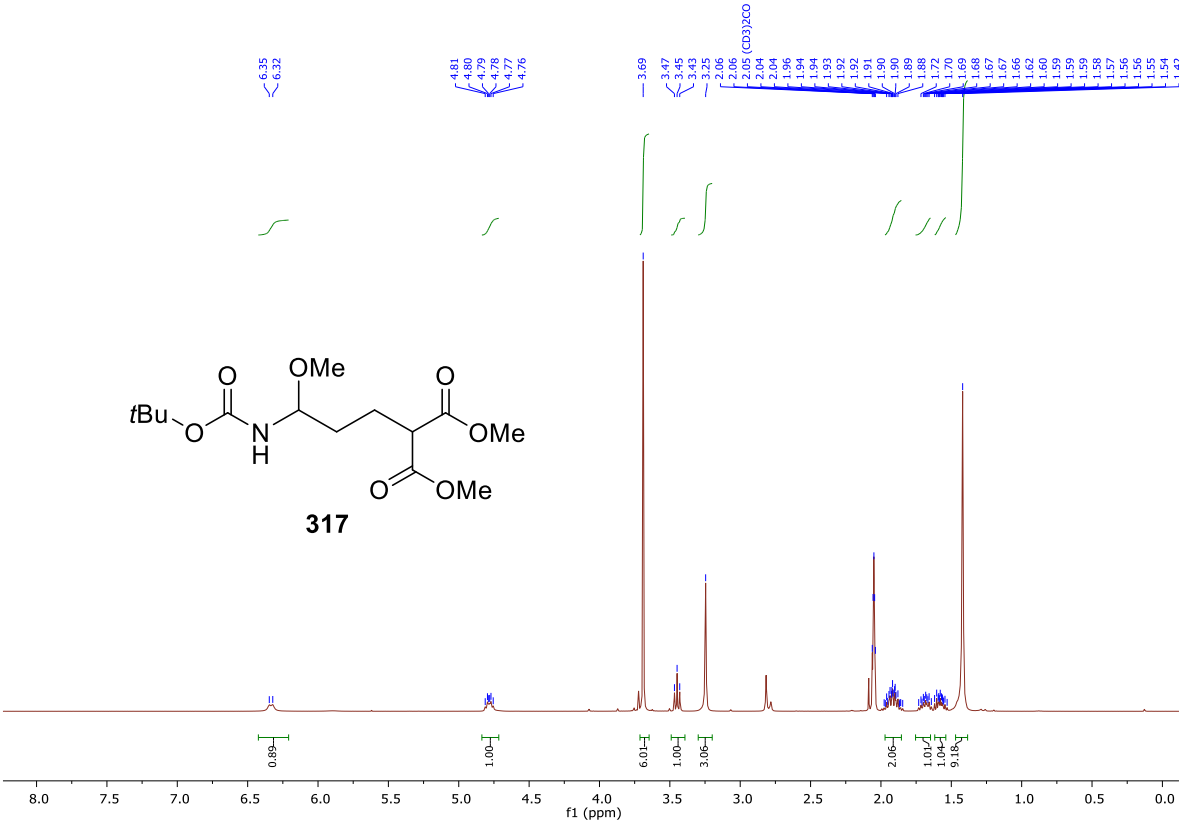
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



^{1}H-NMR (400 MHz, Acetone-d_6)



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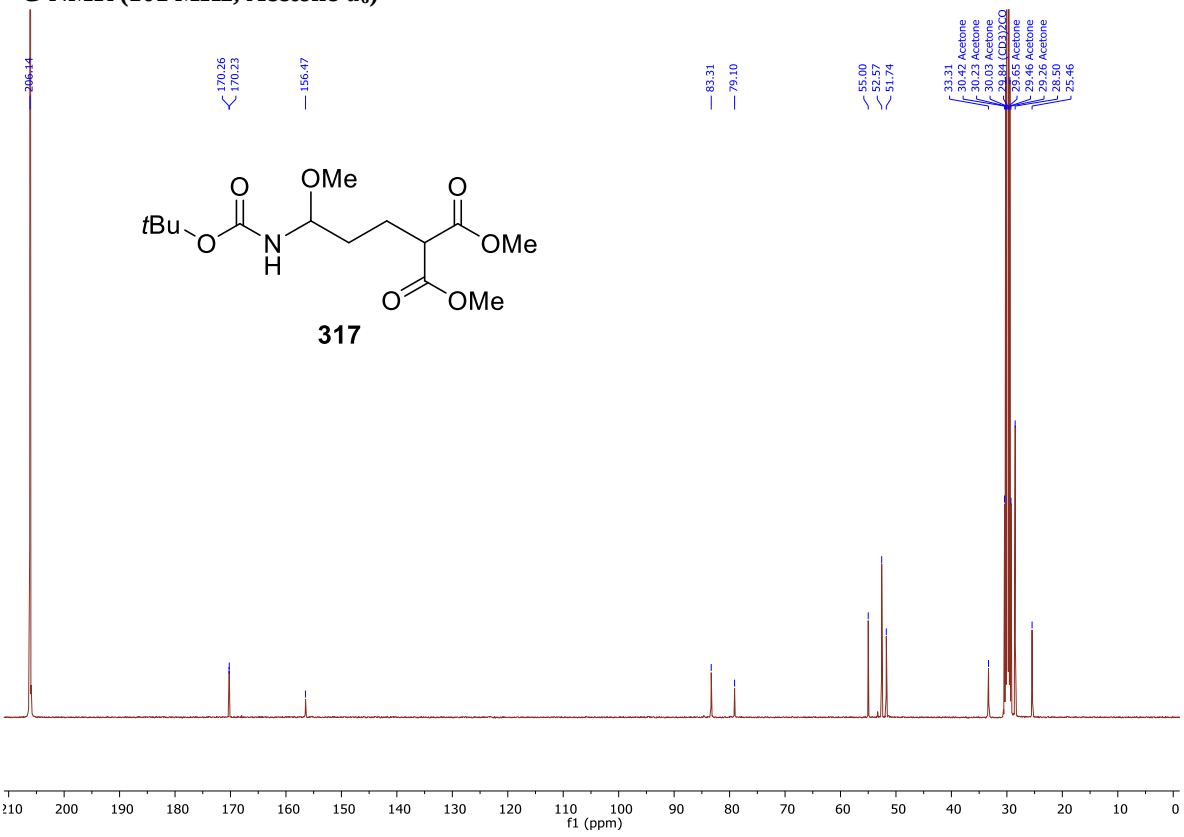
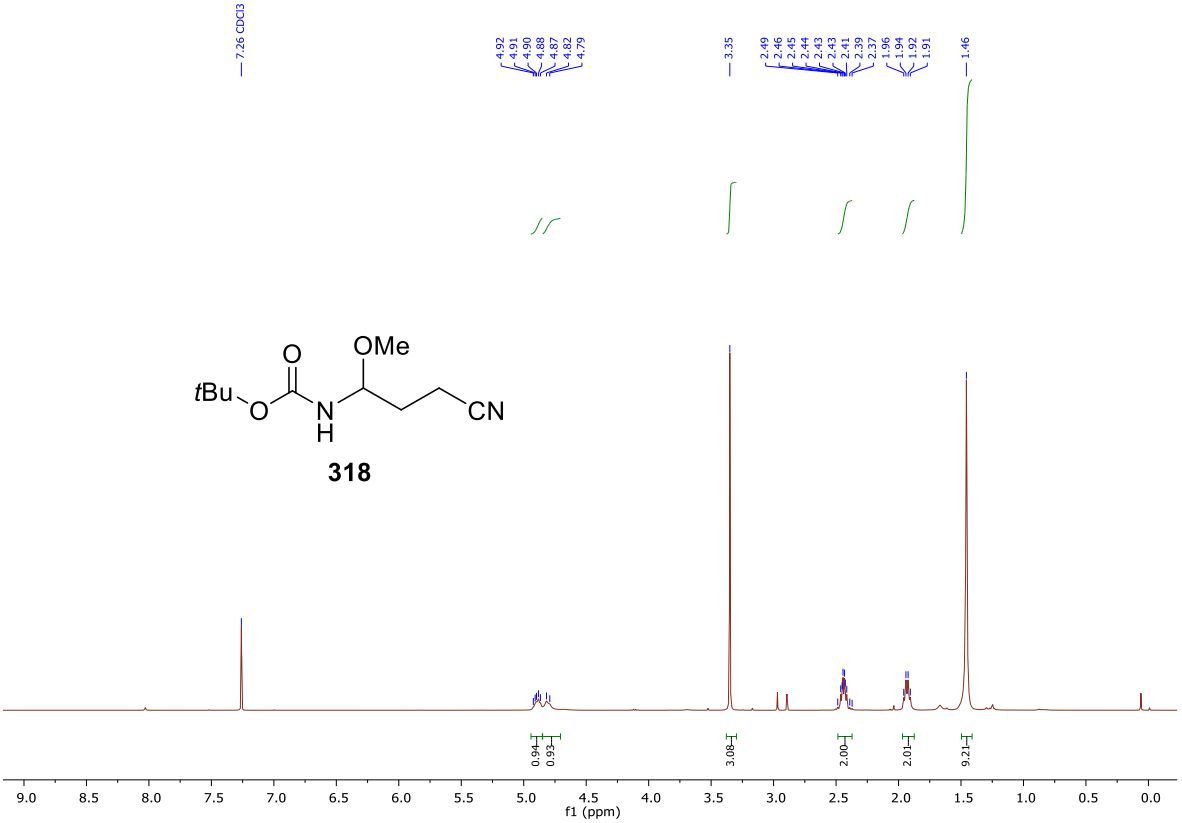
^{13}C-NMR (101 MHz, Acetone-d_6)



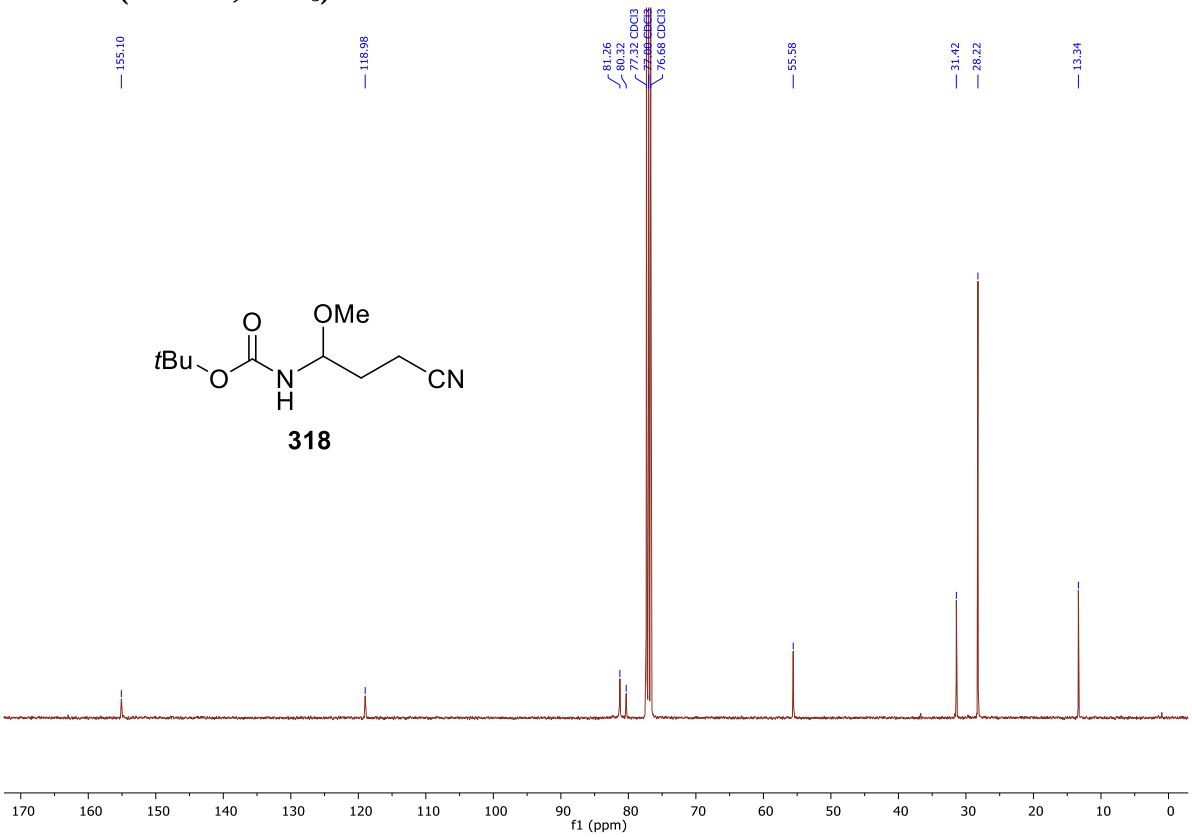
317

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



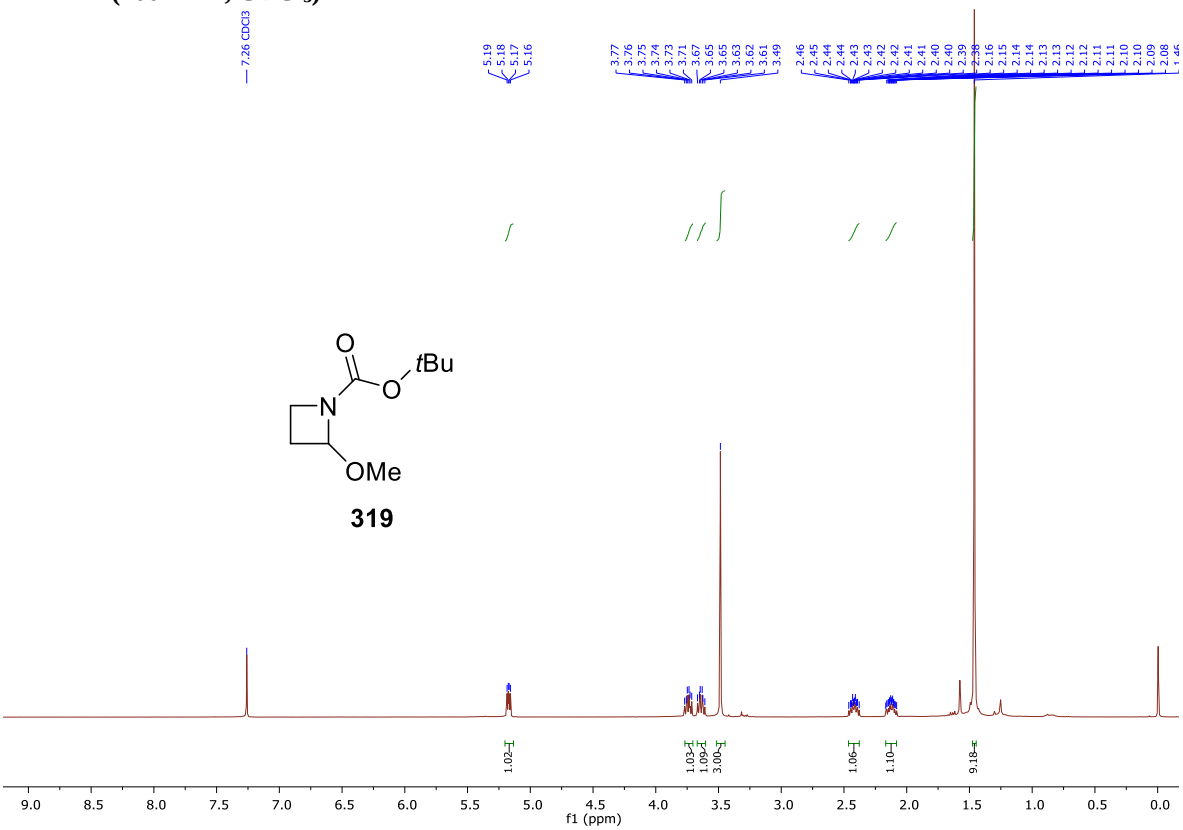
318

^{13}C-NMR (101 MHz, $CDCl_3$)

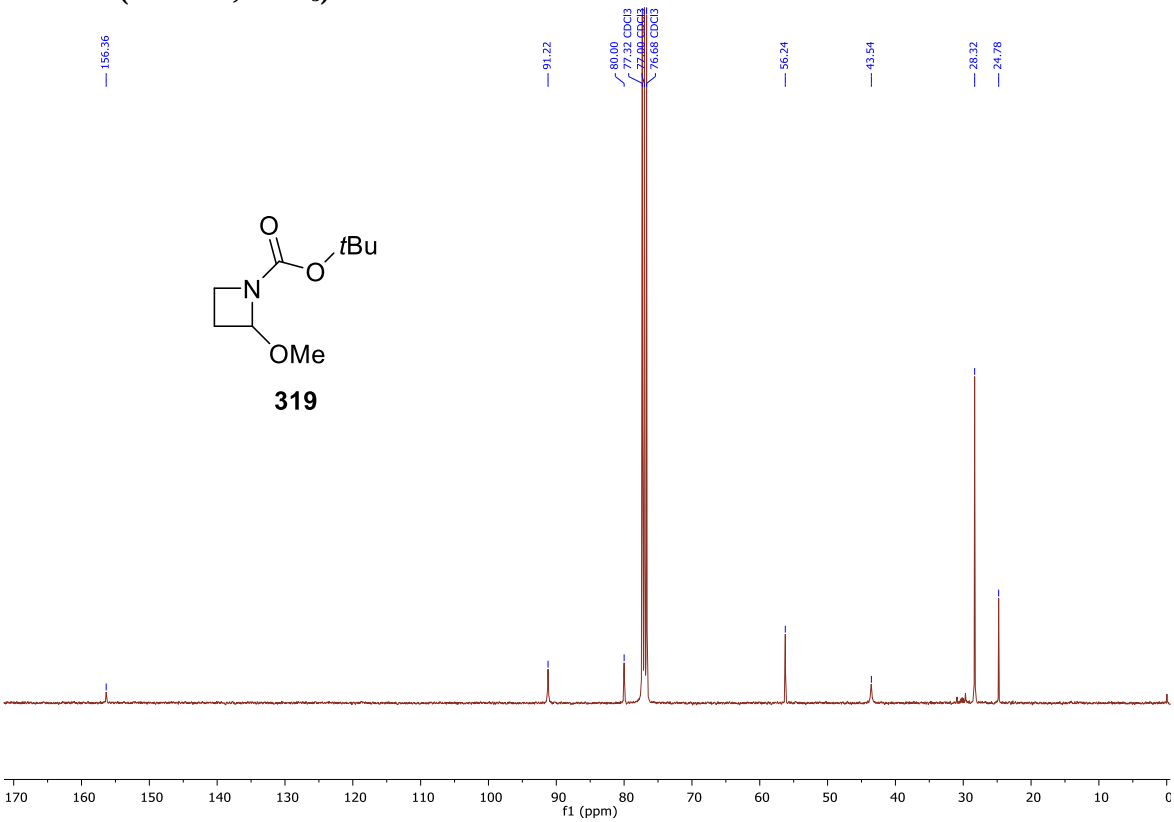


318

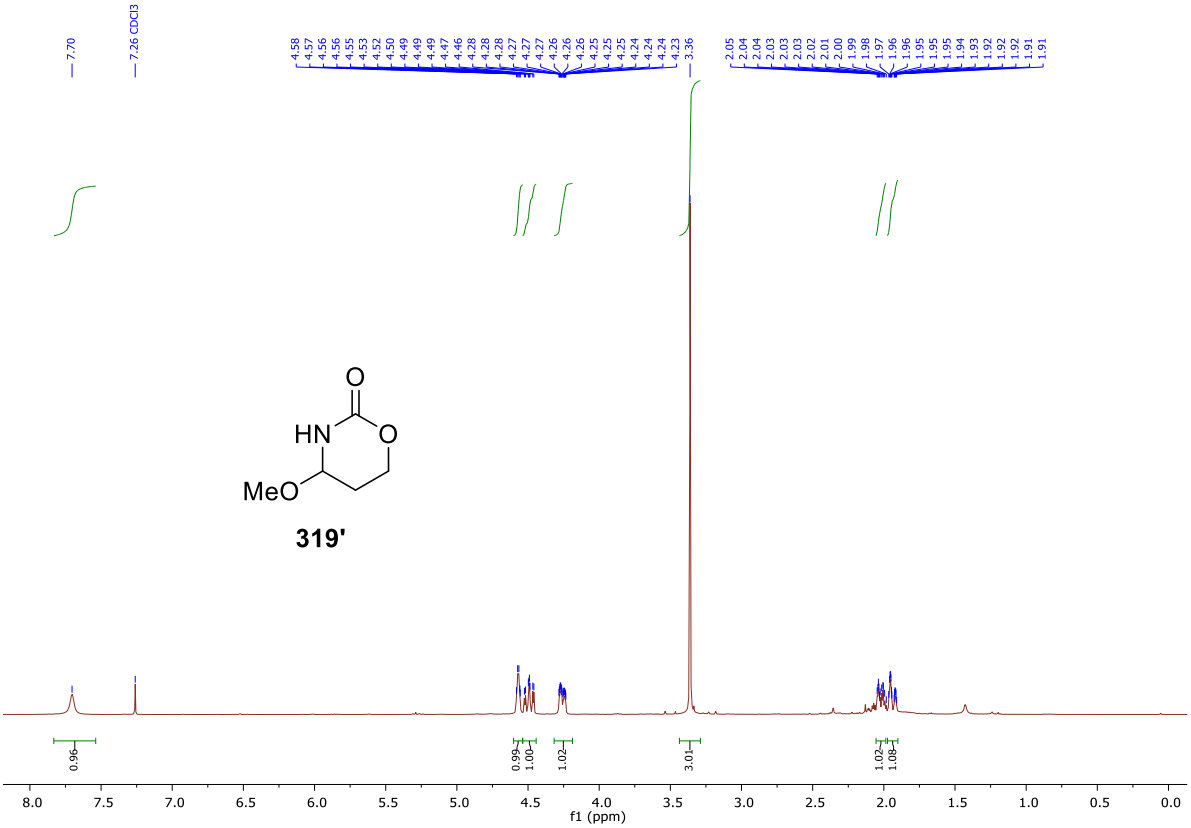
^{1}H-NMR (400 MHz, $CDCl_3$)



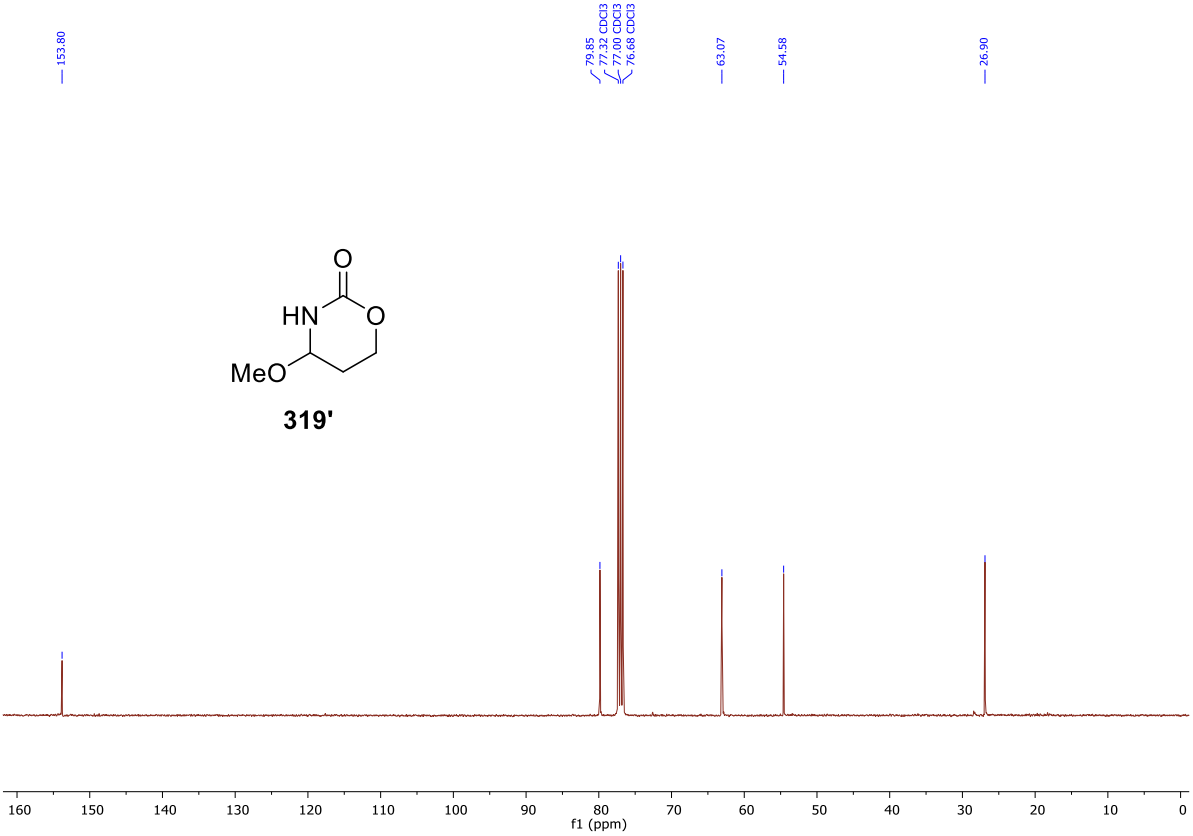
^{13}C-NMR (101 MHz, $CDCl_3$)



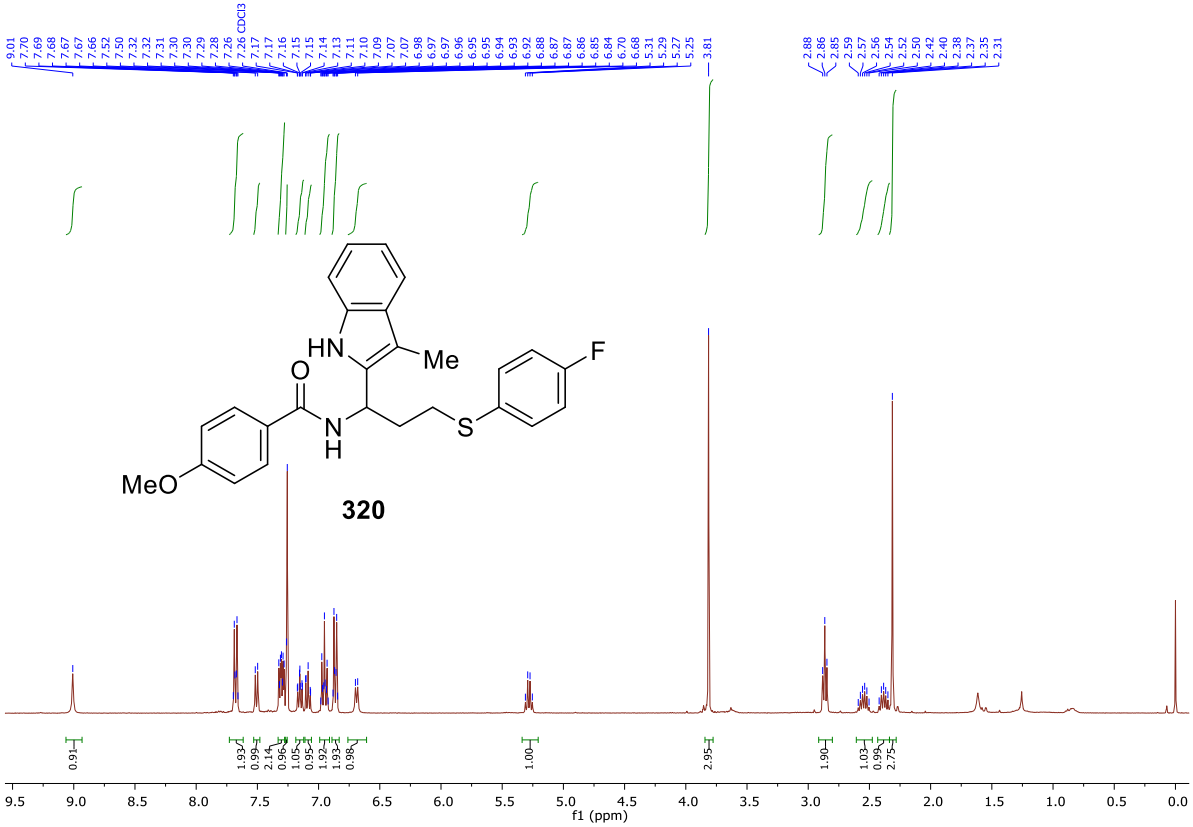
^{1}H-NMR (400 MHz, $CDCl_3$)



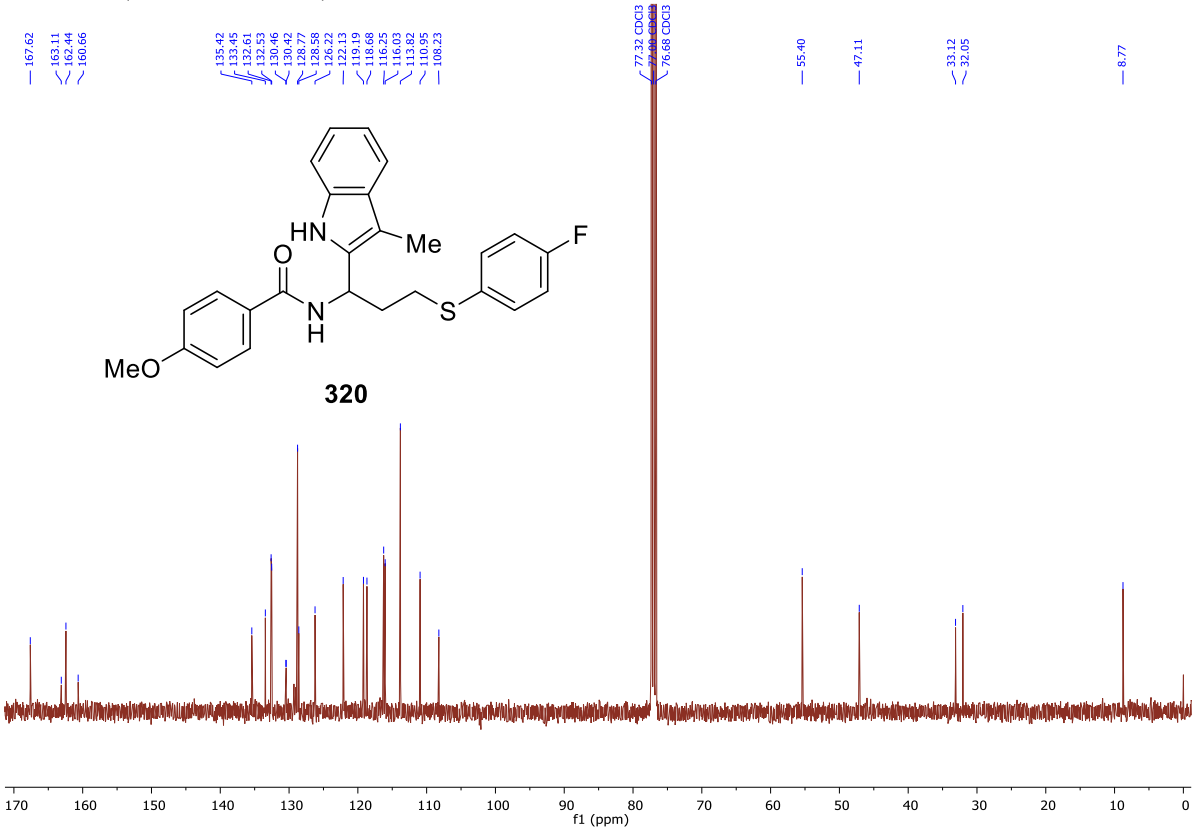
^{13}C-NMR (101 MHz, $CDCl_3$)



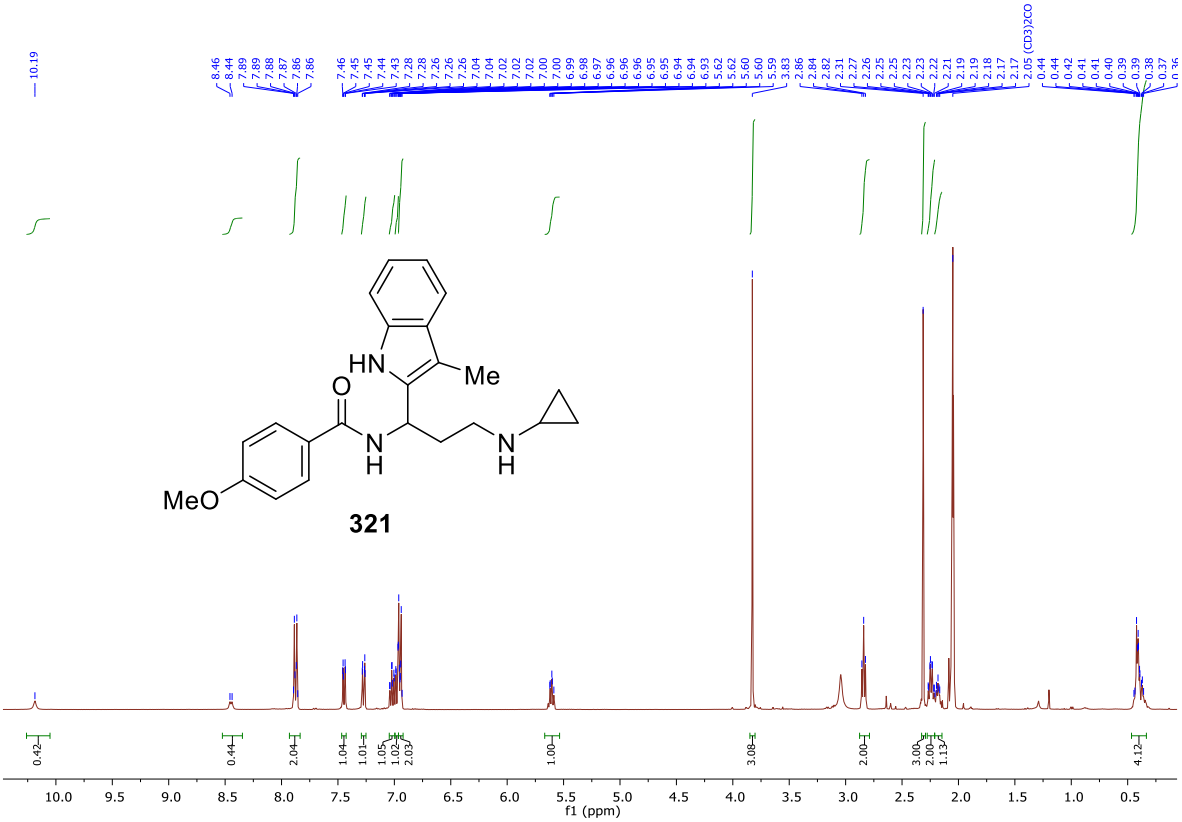
^{1}H-NMR (400 MHz, $CDCl_3$)



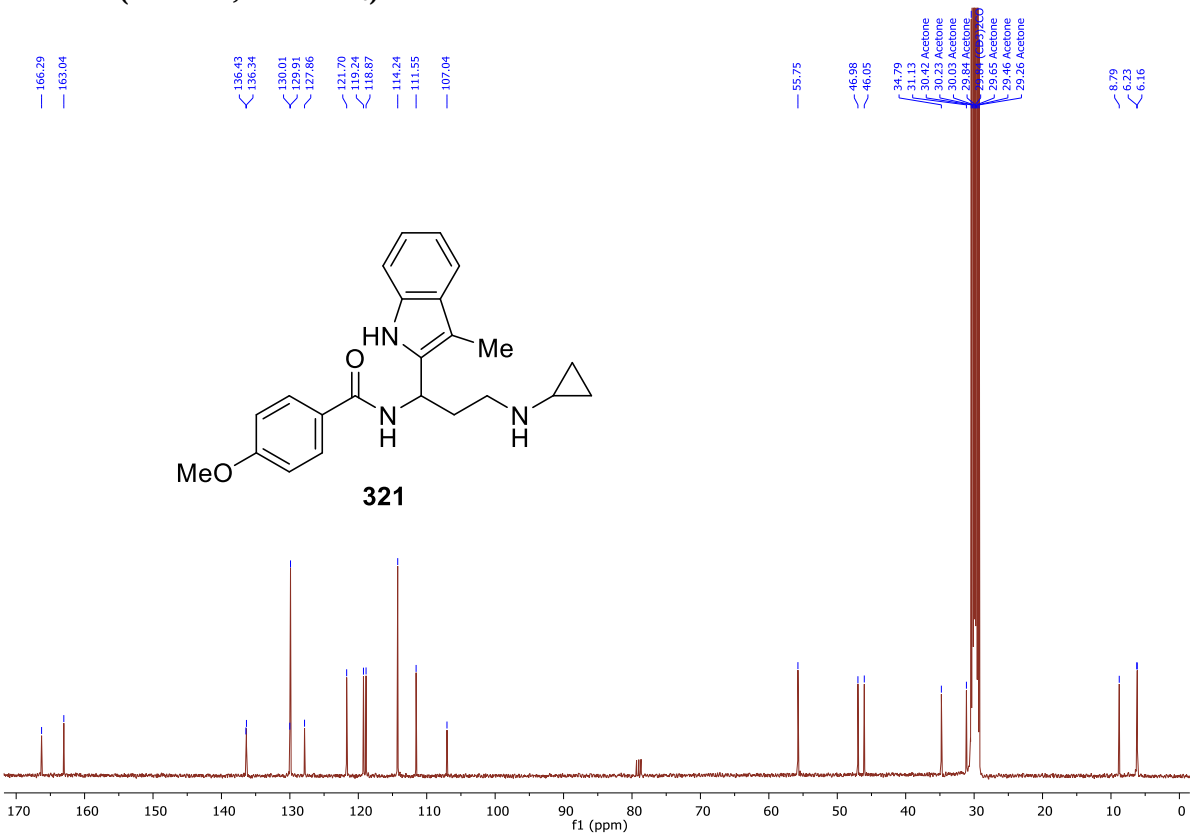
^{13}C-NMR (101 MHz, $CDCl_3$)



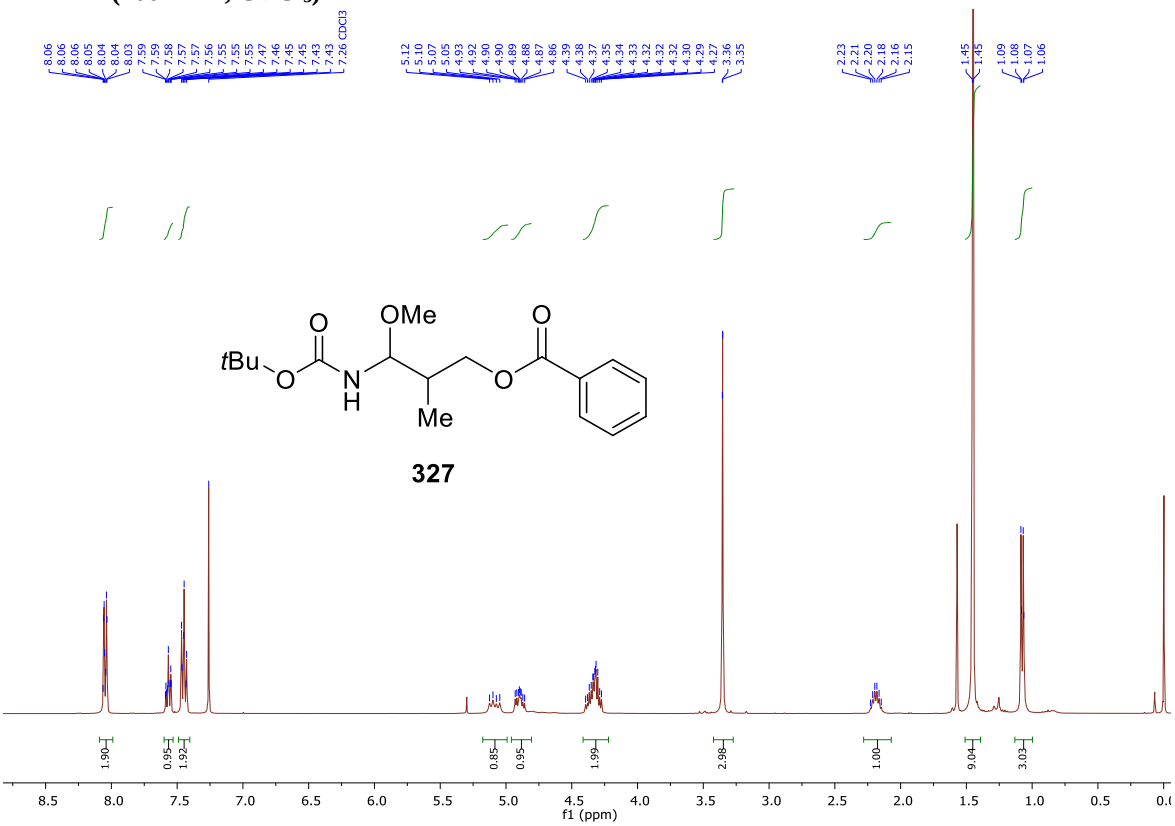
^{1}H-NMR (400 MHz, Acetone-d_6)



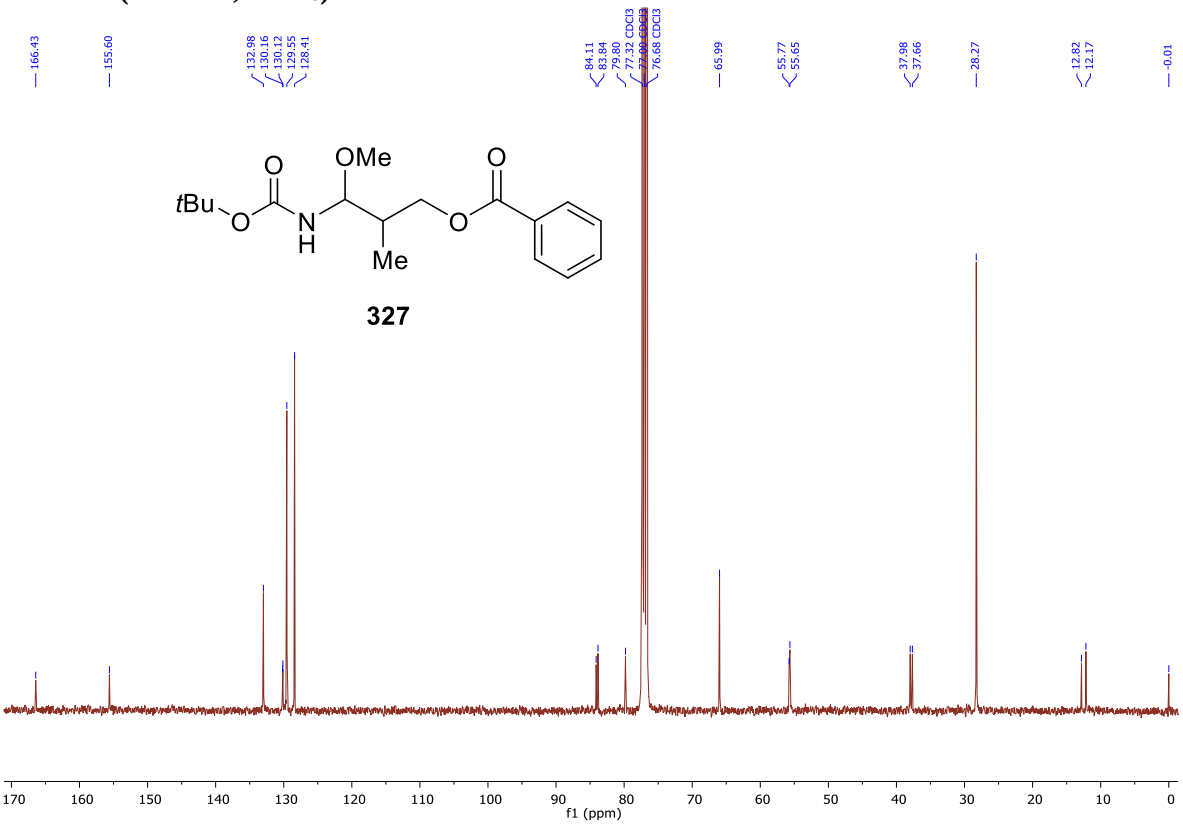
^{13}C-NMR (101 MHz, Acetone-d_6)



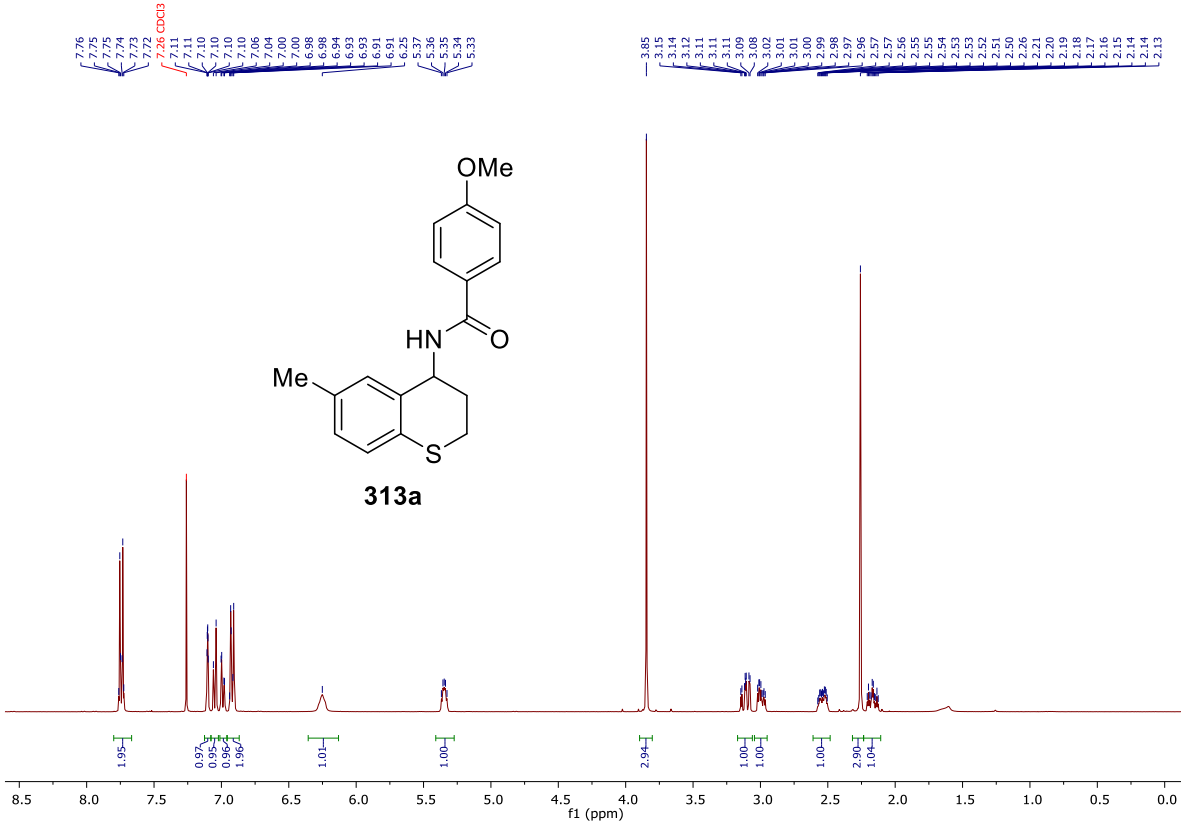
^{1}H-NMR (400 MHz, $CDCl_3$)



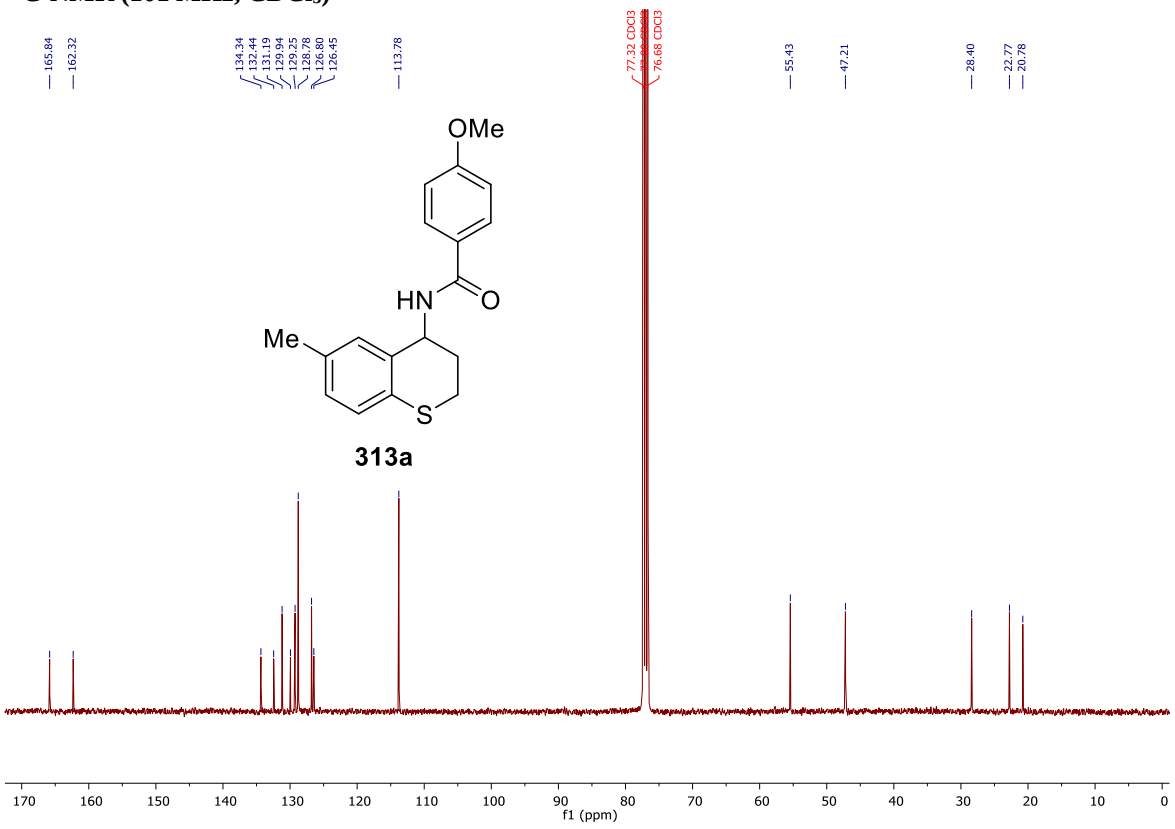
^{13}C-NMR (101 MHz, $CDCl_3$)



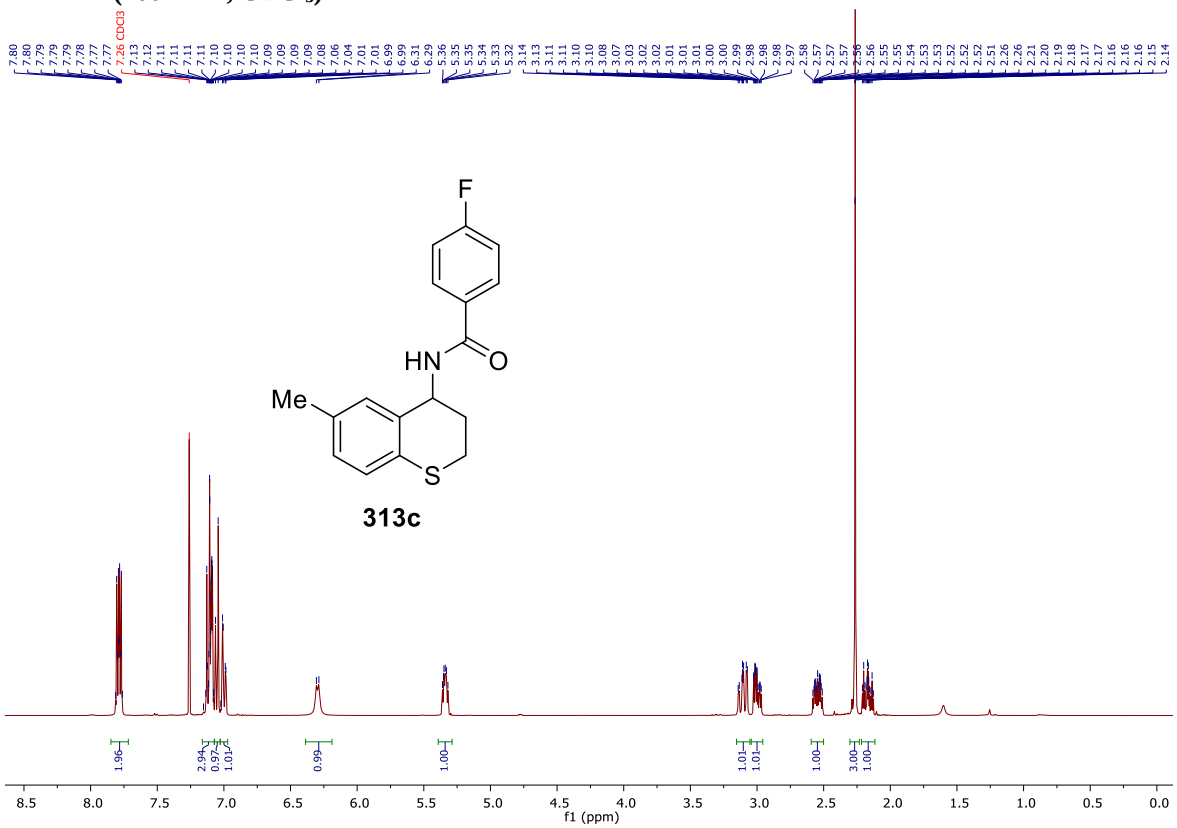
^{1}H-NMR (400 MHz, $CDCl_3$)



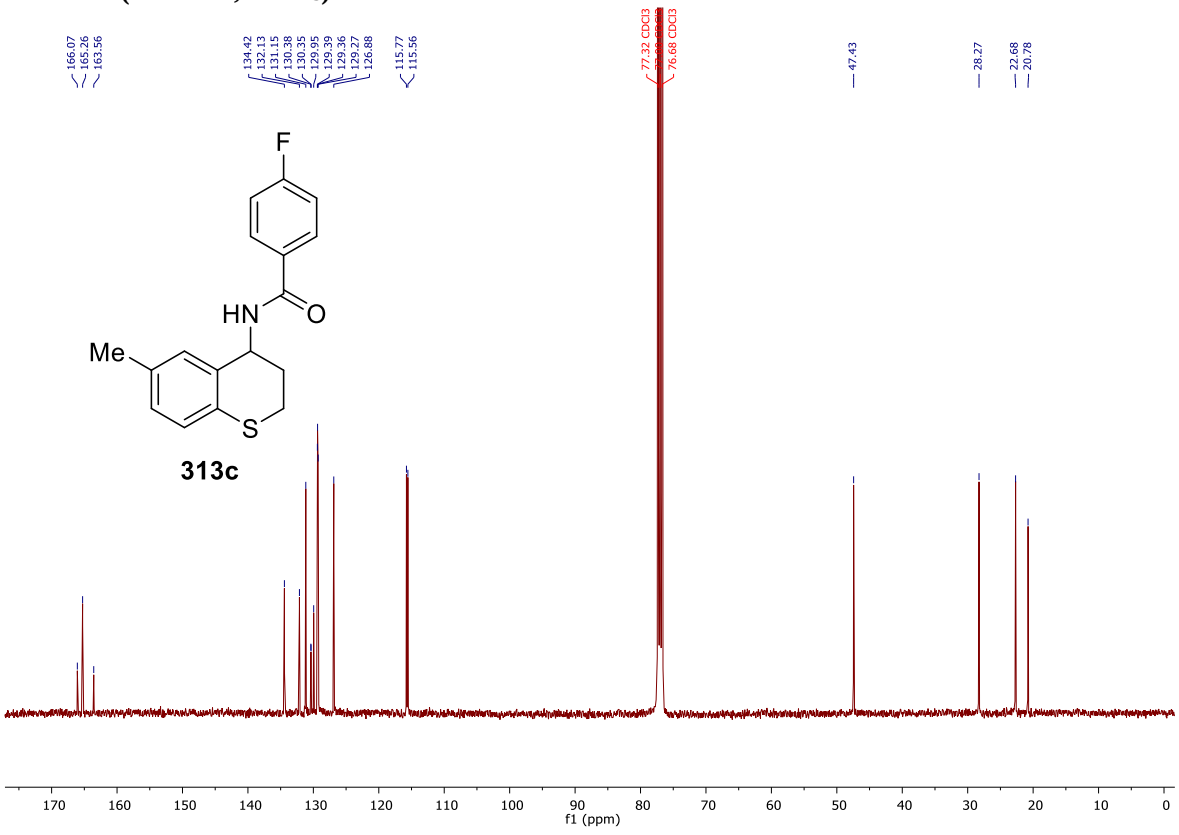
^{13}C-NMR (101 MHz, $CDCl_3$)



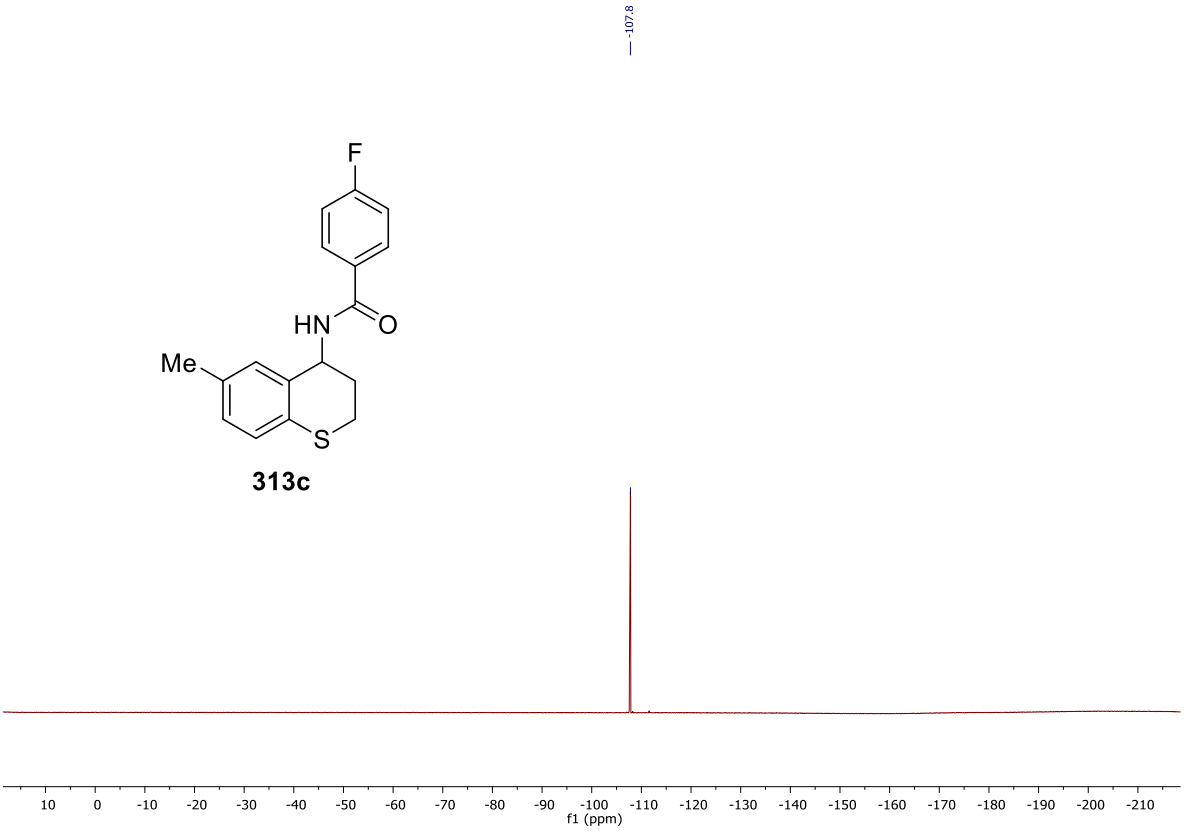
^{1}H-NMR (400 MHz, $CDCl_3$)



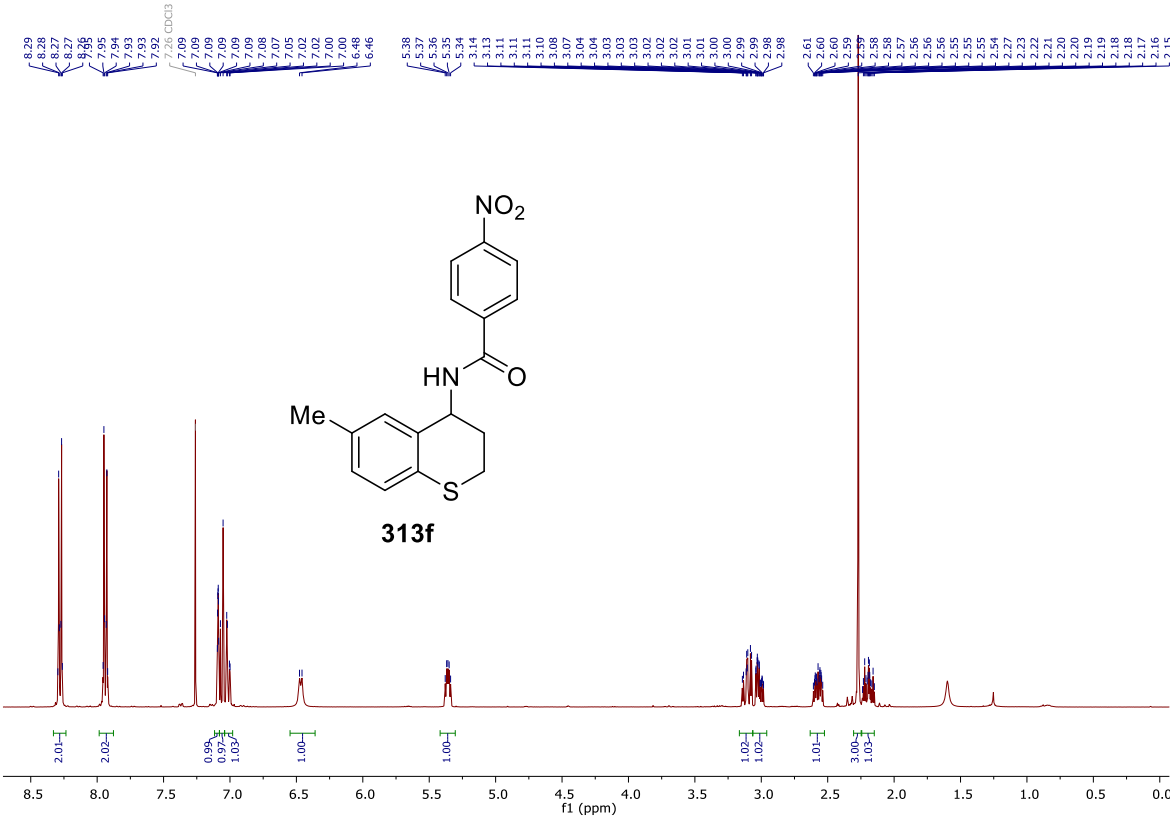
^{13}C-NMR (101 MHz, $CDCl_3$)



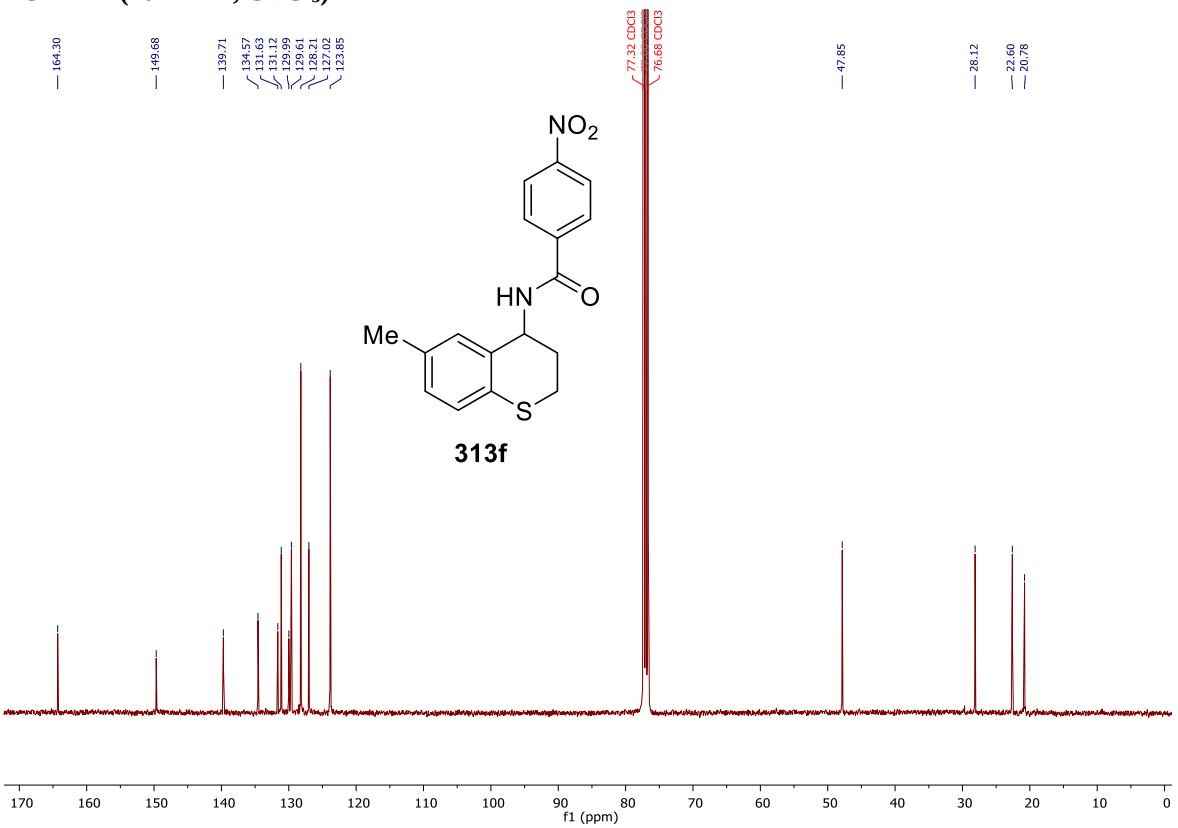
^{19}F-NMR (376 MHz, $CDCl_3$)



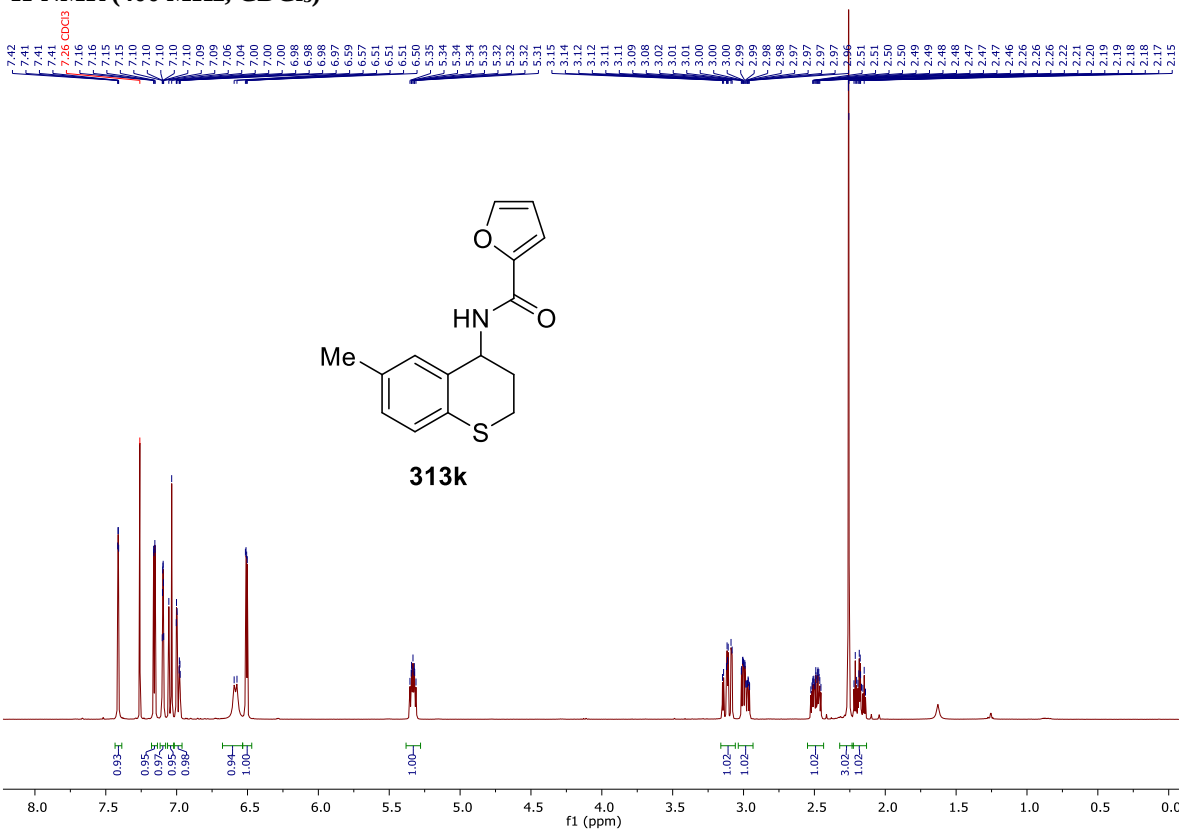
^{1}H-NMR (400 MHz, $CDCl_3$)



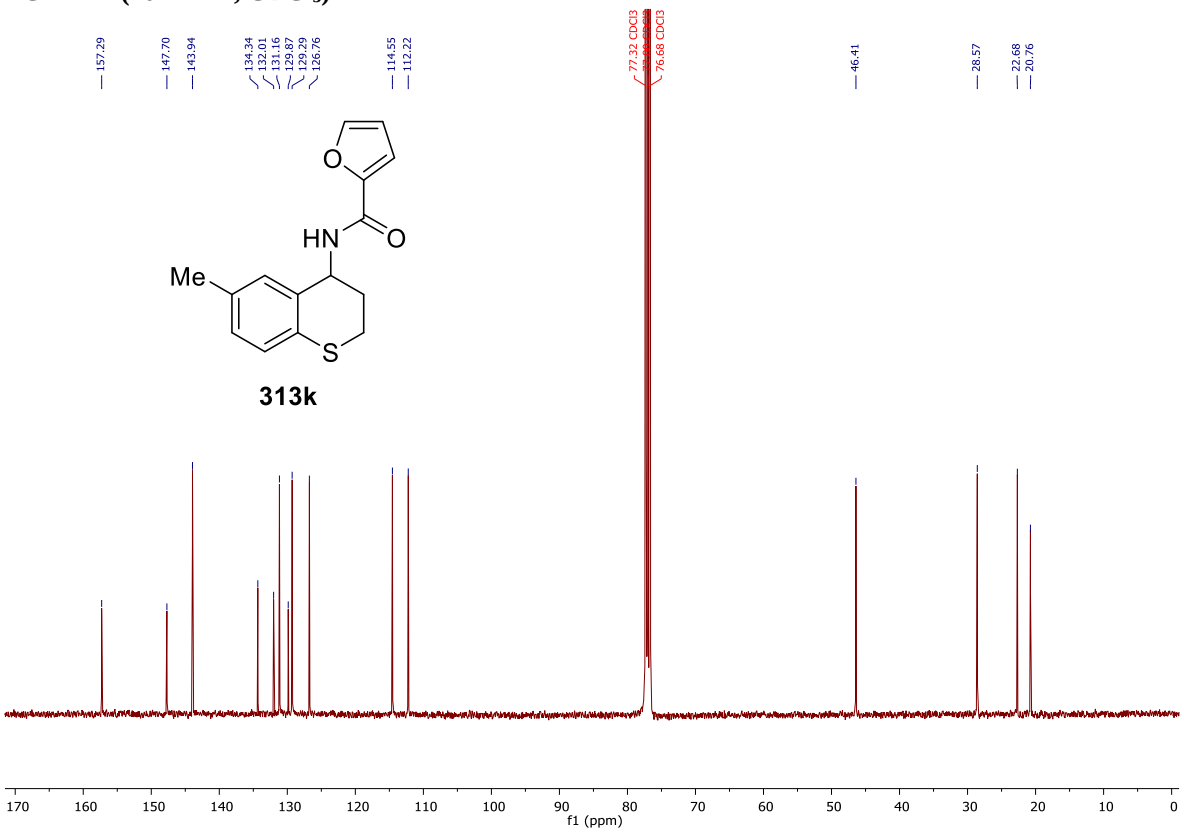
^{13}C-NMR (101 MHz, $CDCl_3$)



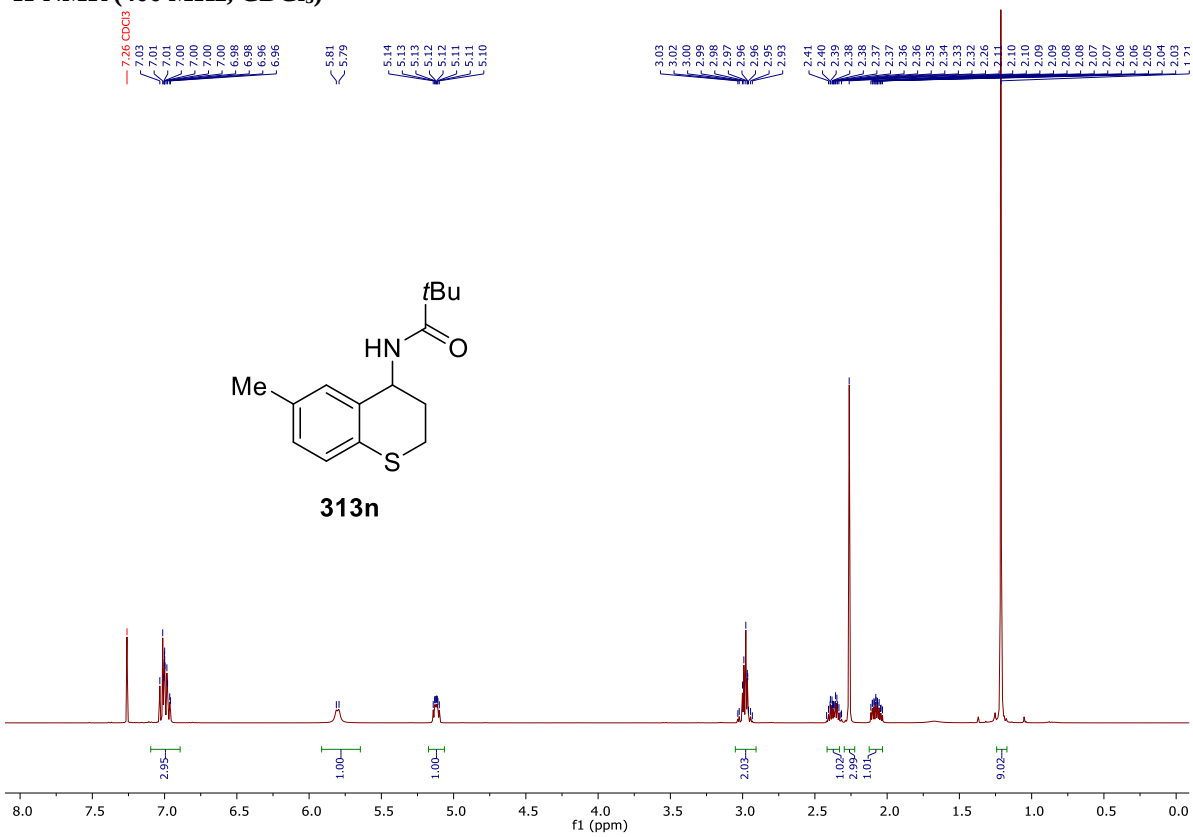
^{1}H-NMR (400 MHz, $CDCl_3$)



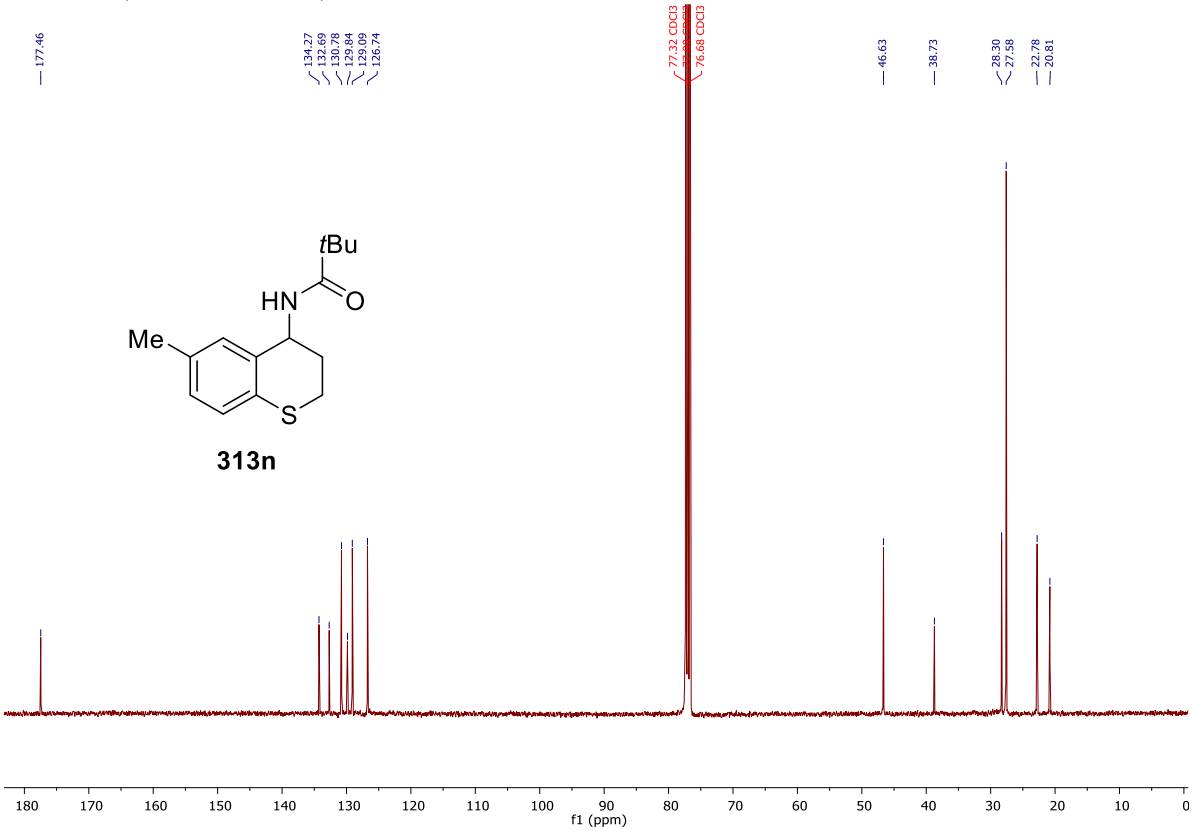
^{13}C-NMR (101 MHz, $CDCl_3$)



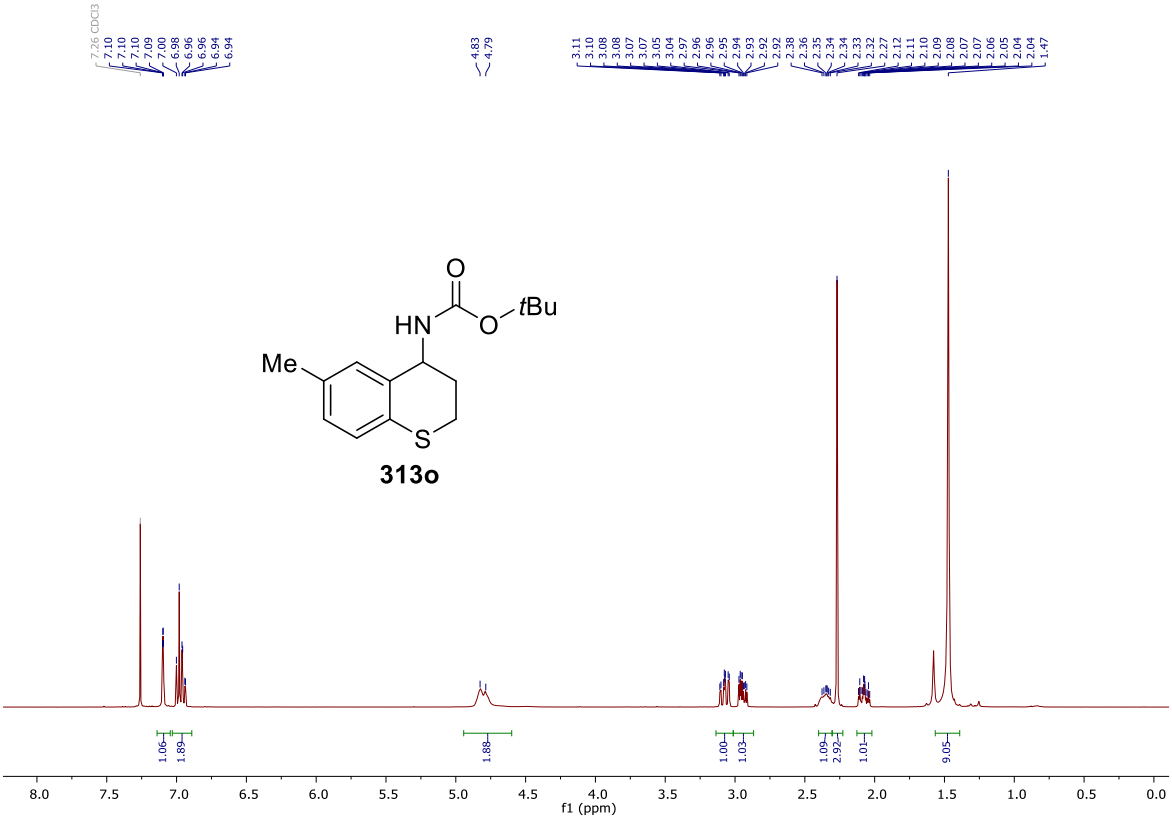
^{1}H-NMR (400 MHz, $CDCl_3$)



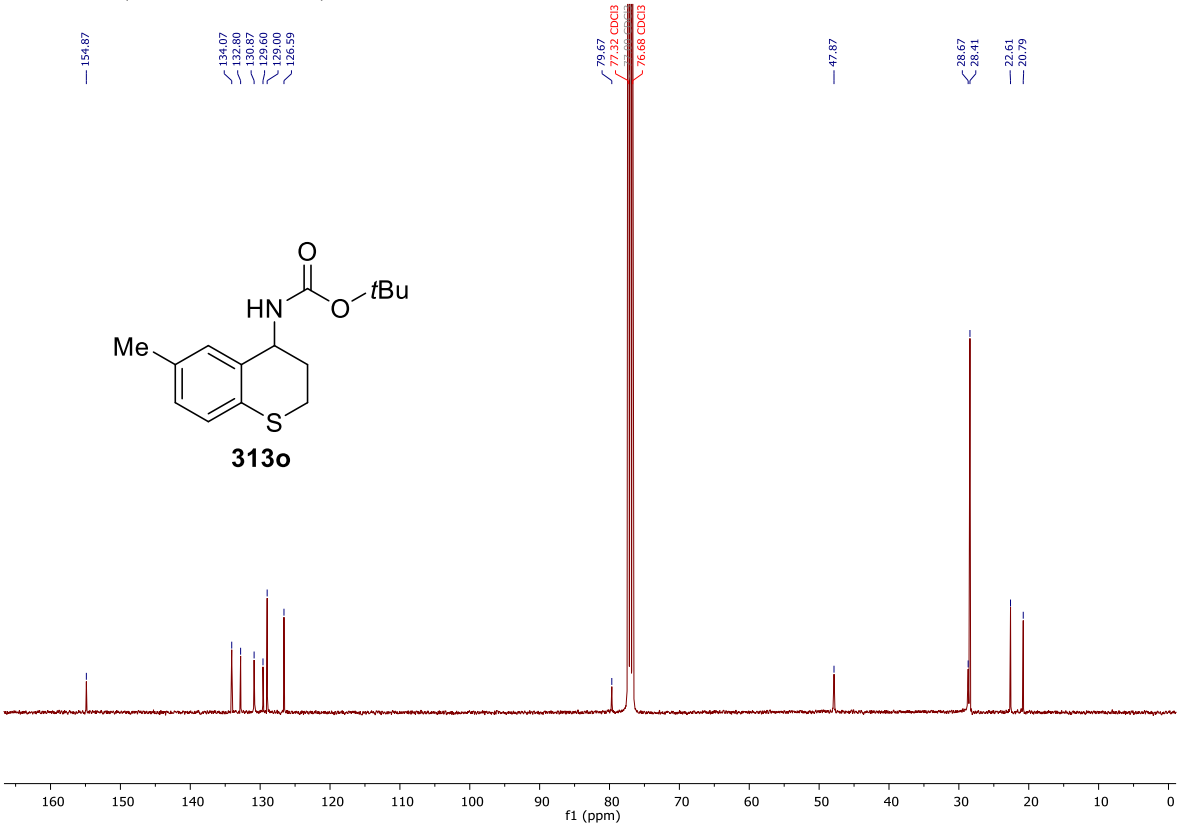
^{13}C-NMR (101 MHz, $CDCl_3$)



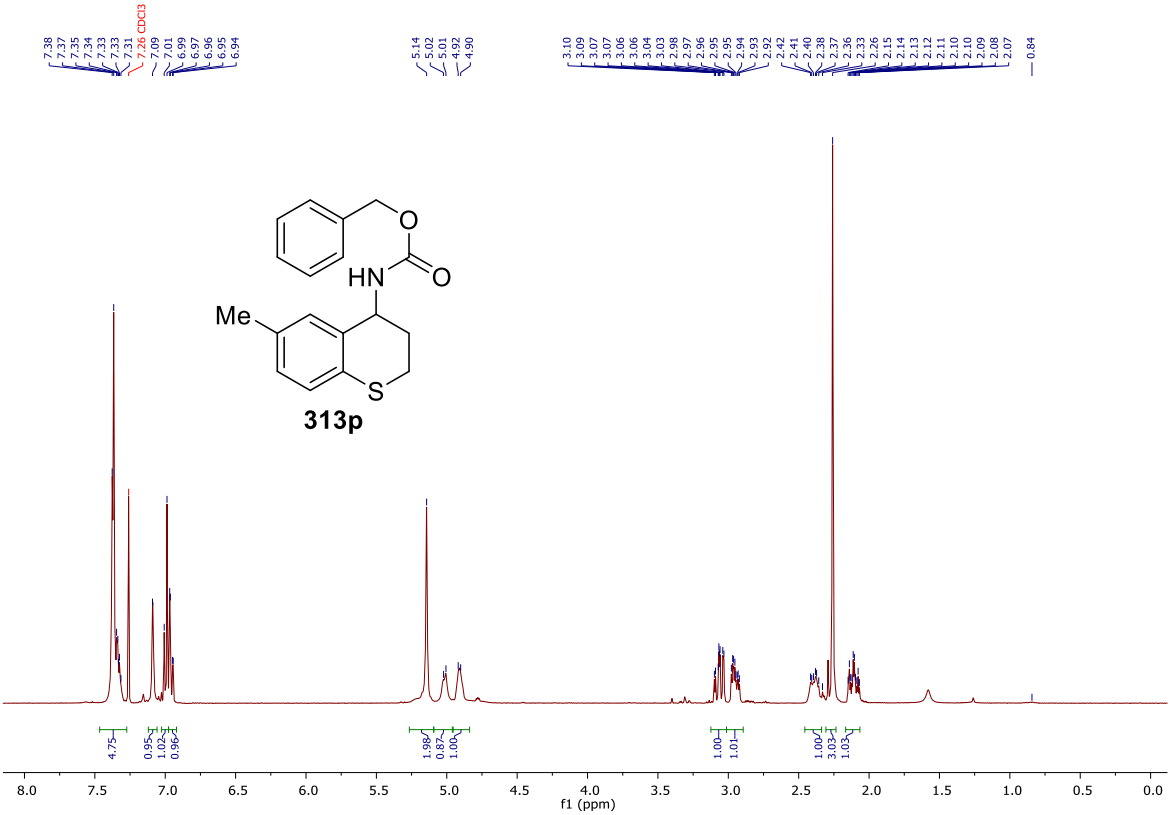
^{1}H-NMR (400 MHz, $CDCl_3$)



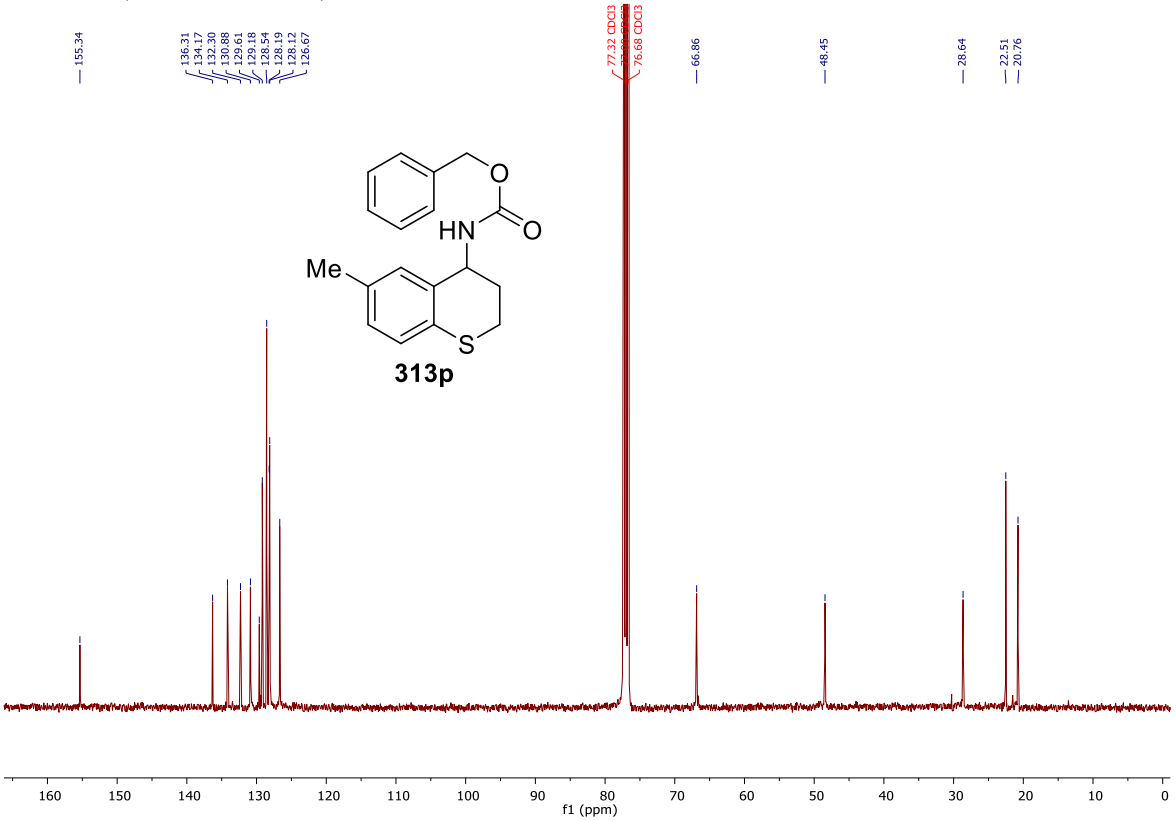
^{13}C-NMR (101 MHz, $CDCl_3$)



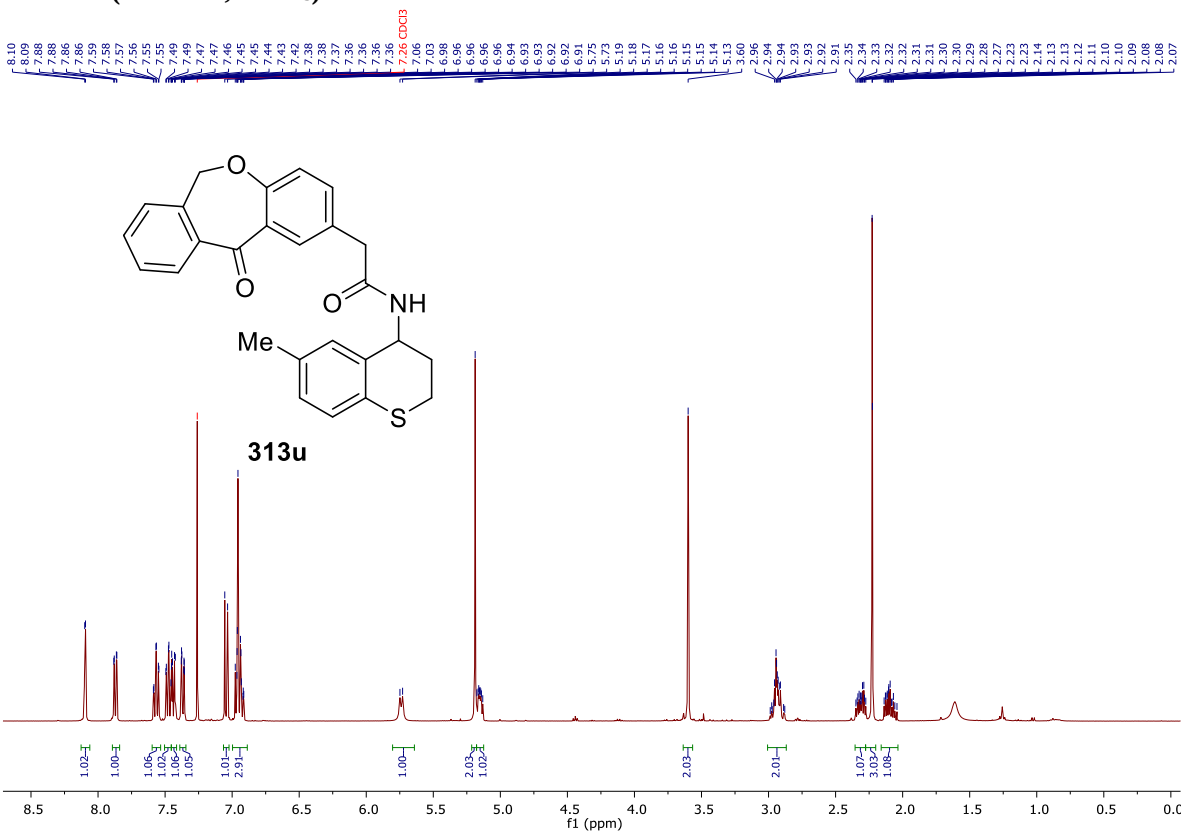
^{1}H-NMR (400 MHz, $CDCl_3$)



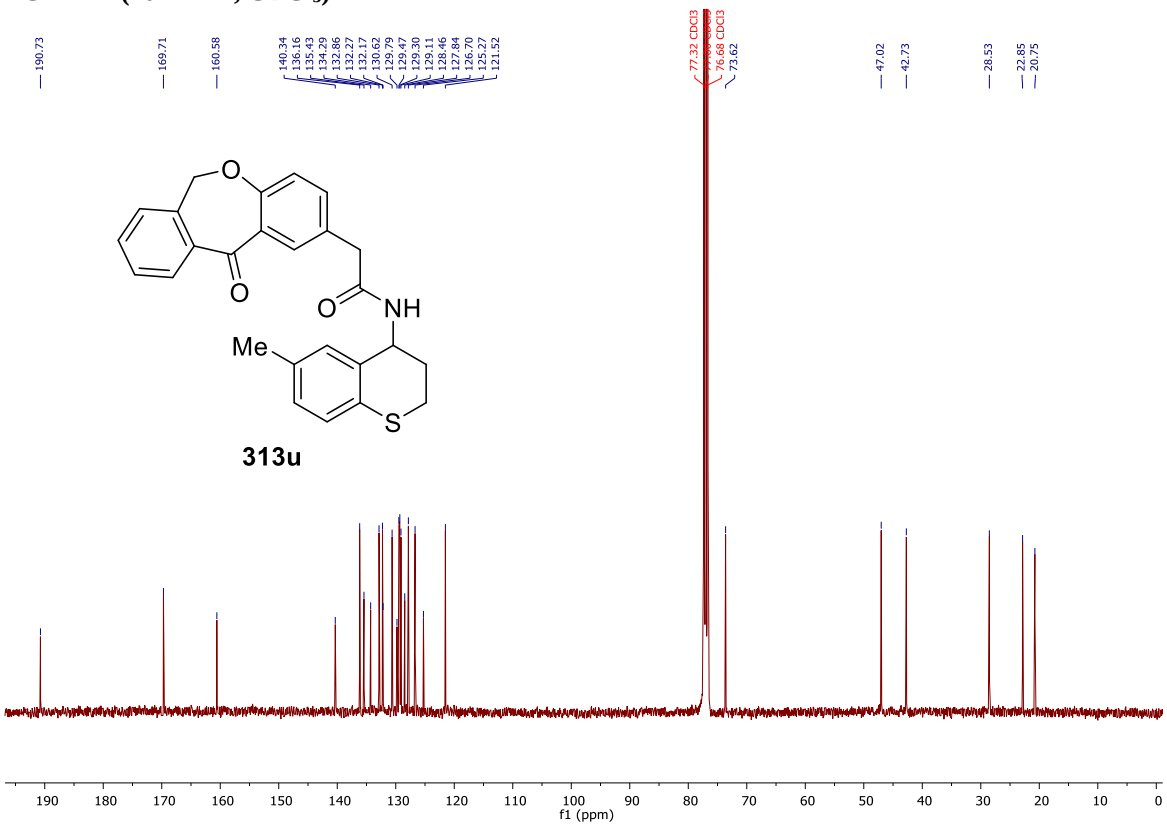
^{13}C-NMR (101 MHz, $CDCl_3$)



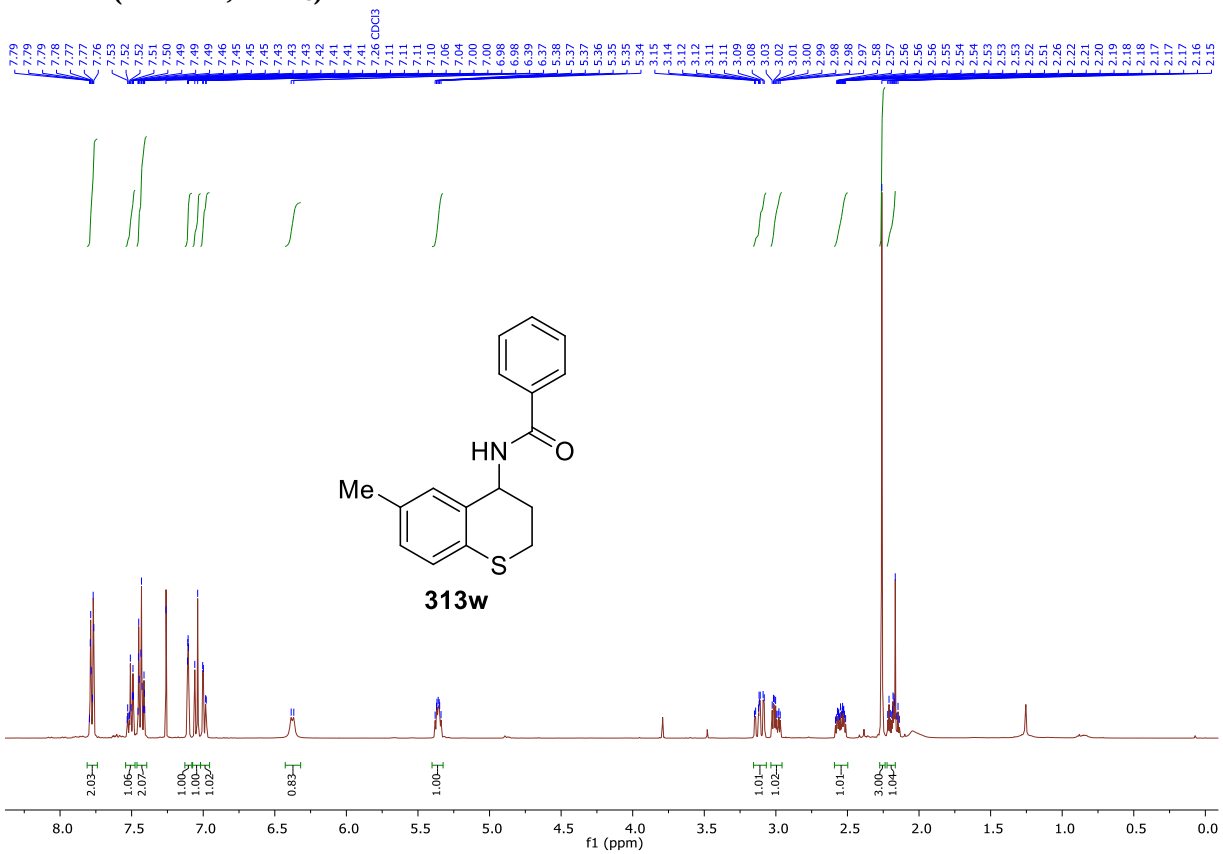
^{1}H-NMR (400 MHz, $CDCl_3$)



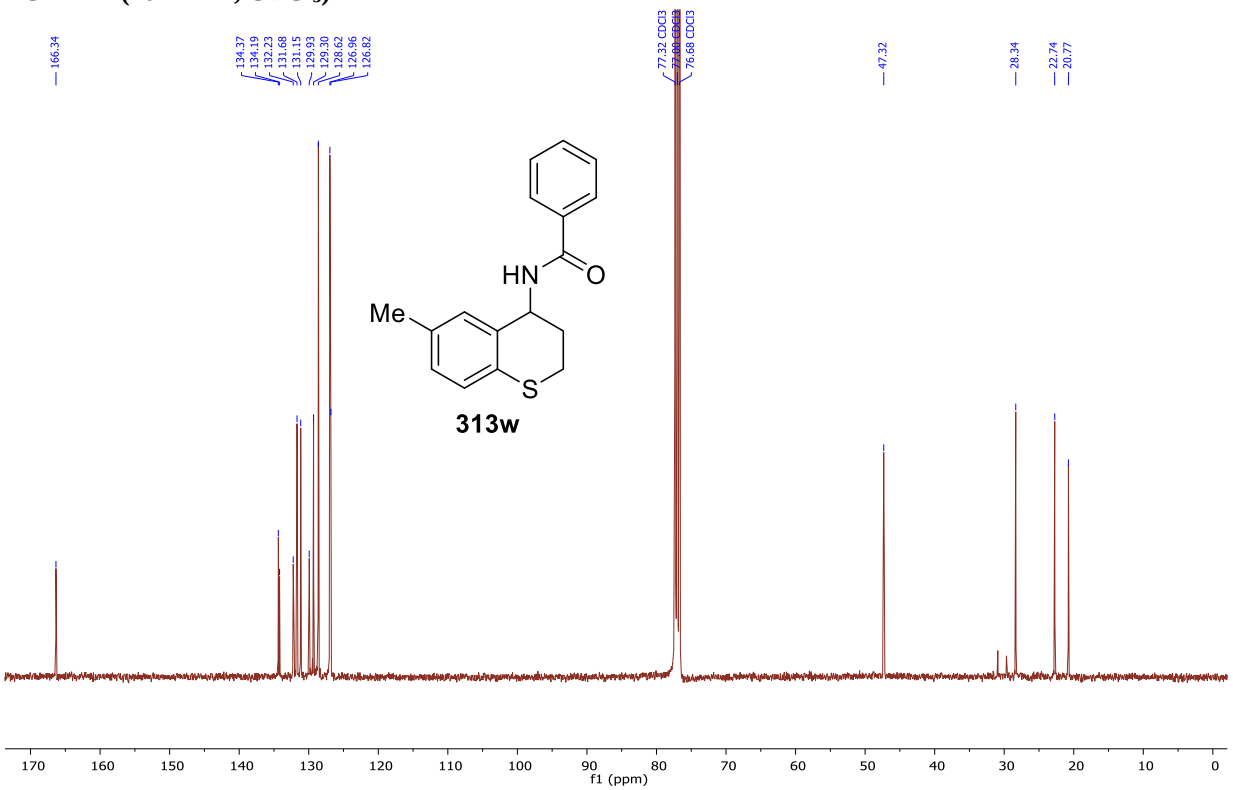
^{13}C-NMR (101 MHz, $CDCl_3$)



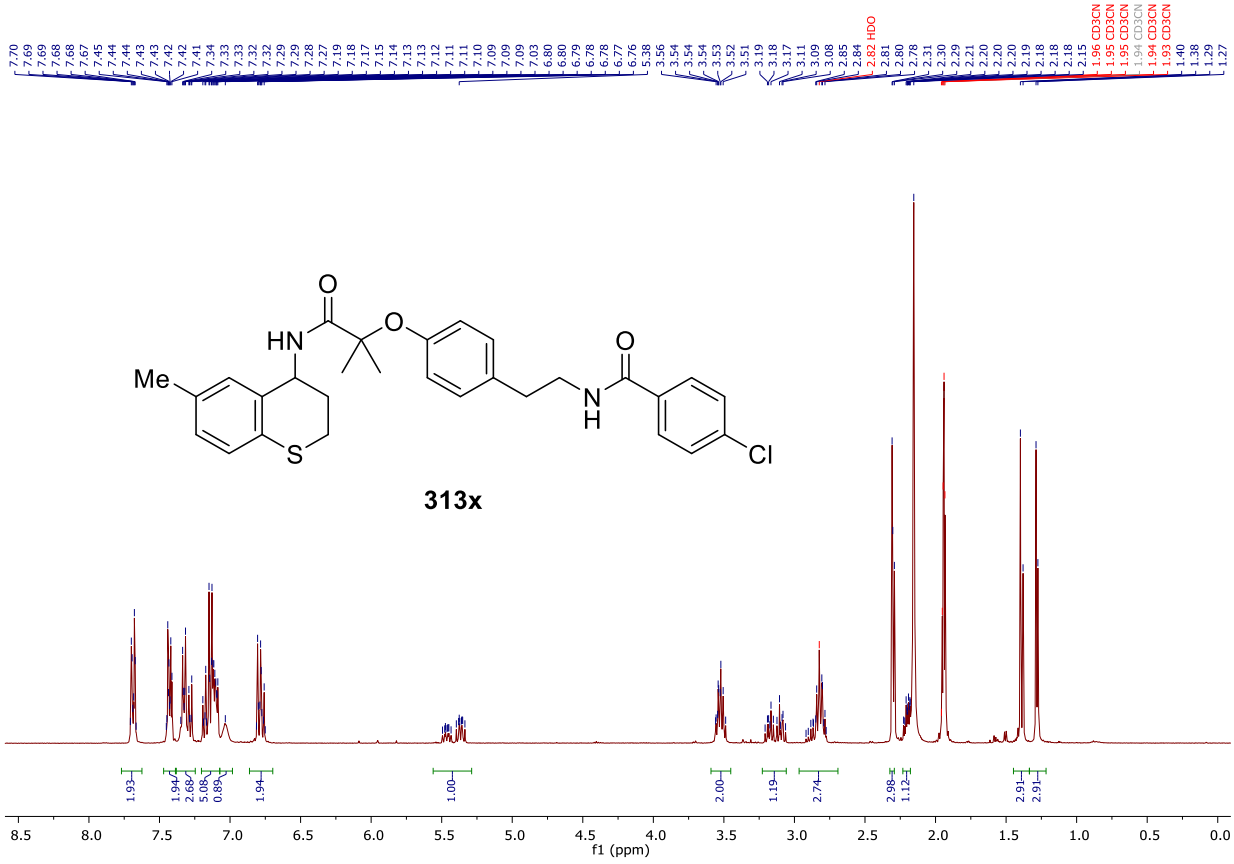
^{1}H-NMR (400 MHz, $CDCl_3$)



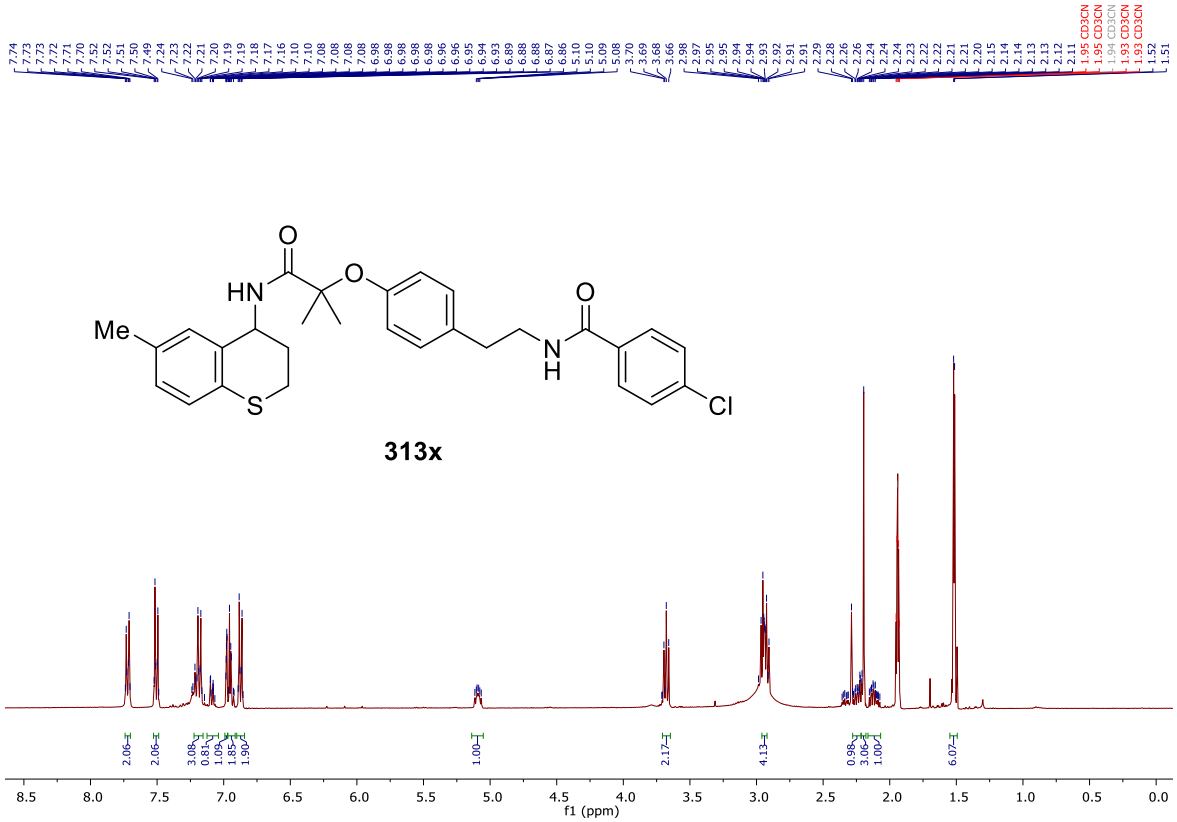
^{13}C-NMR (101 MHz, $CDCl_3$)



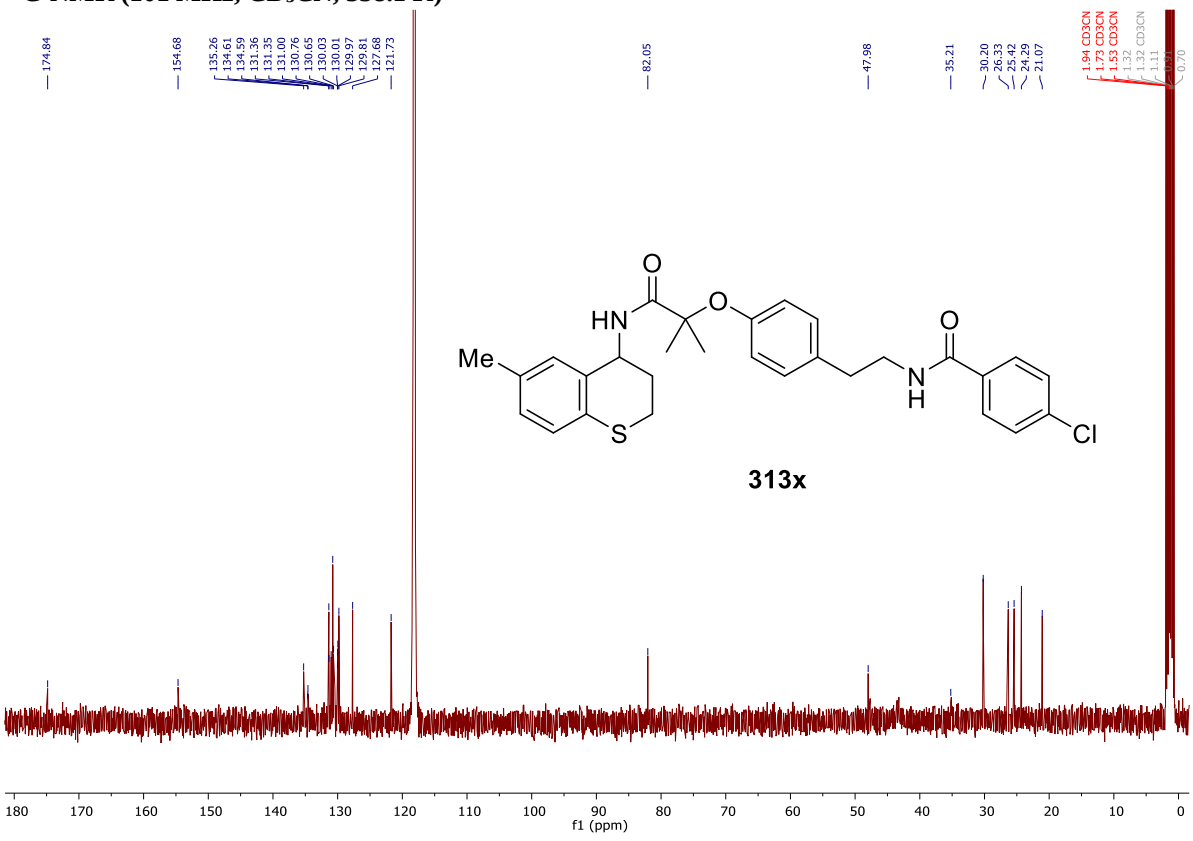
^{1}H-NMR (400 MHz, CD_3CN, 298.1 K)



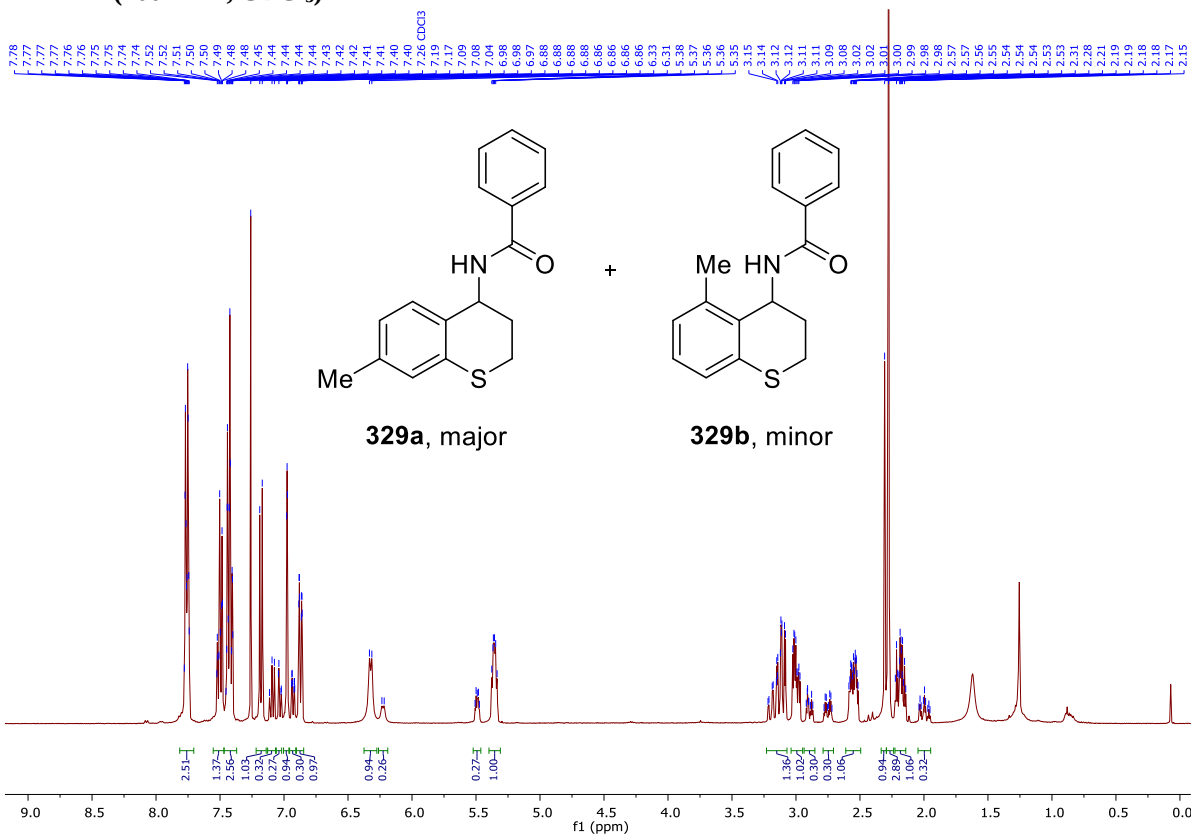
^{1}H-NMR (400 MHz, CD_3CN, 338.1 K)



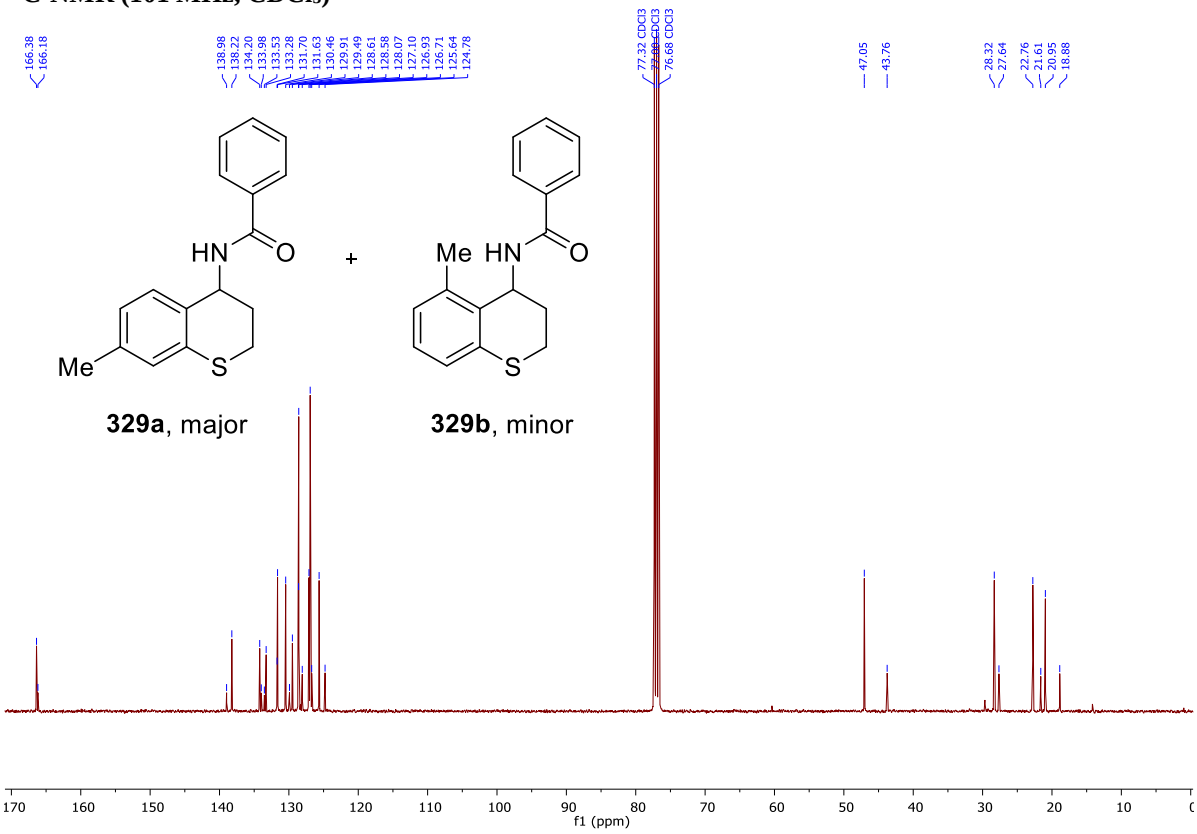
^{13}C-NMR (101 MHz, CD_3CN, 338.1 K)



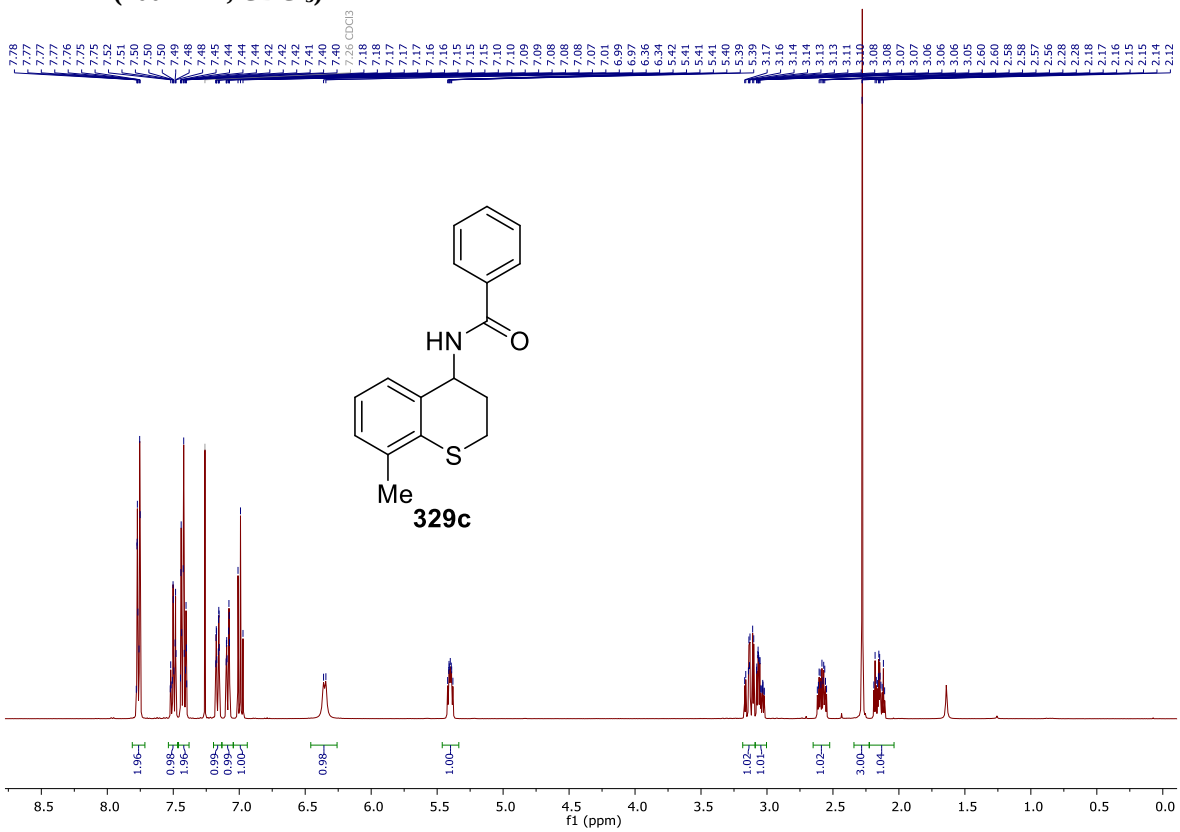
^{1}H-NMR (400 MHz, $CDCl_3$)



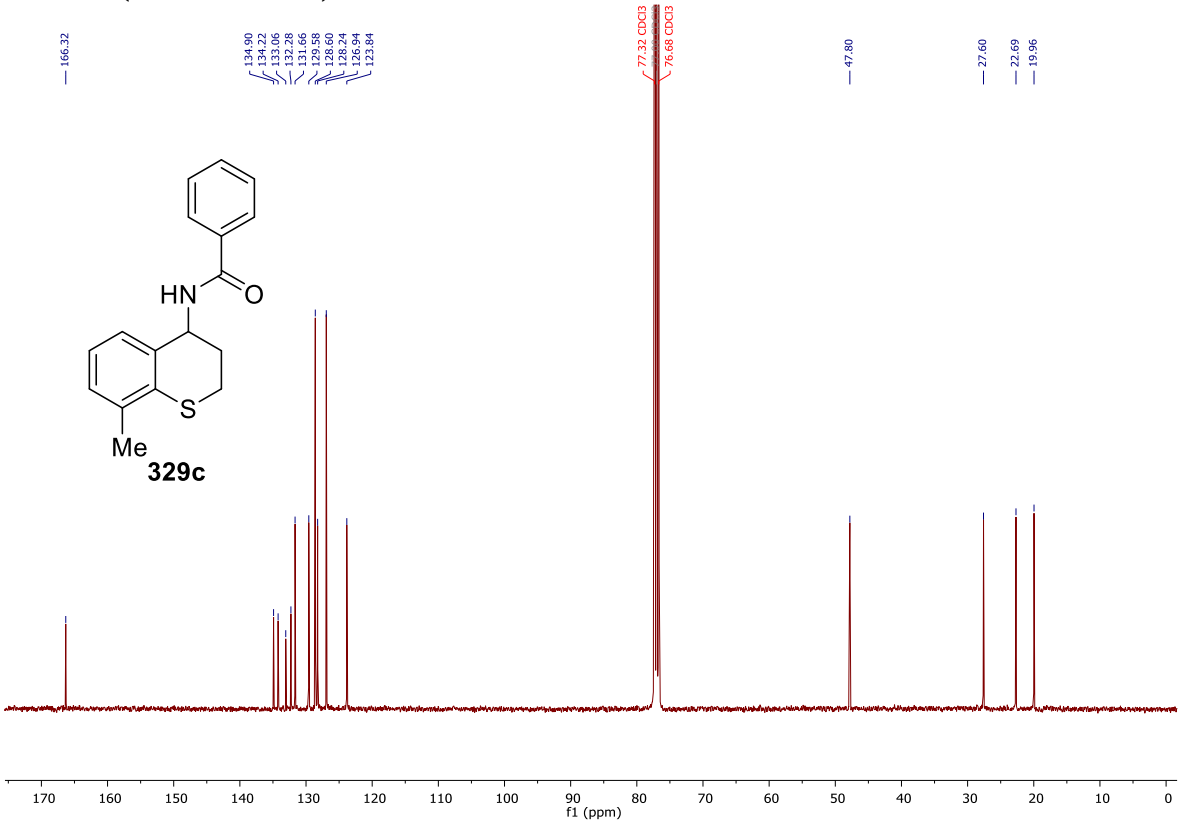
^{13}C-NMR (101 MHz, $CDCl_3$)



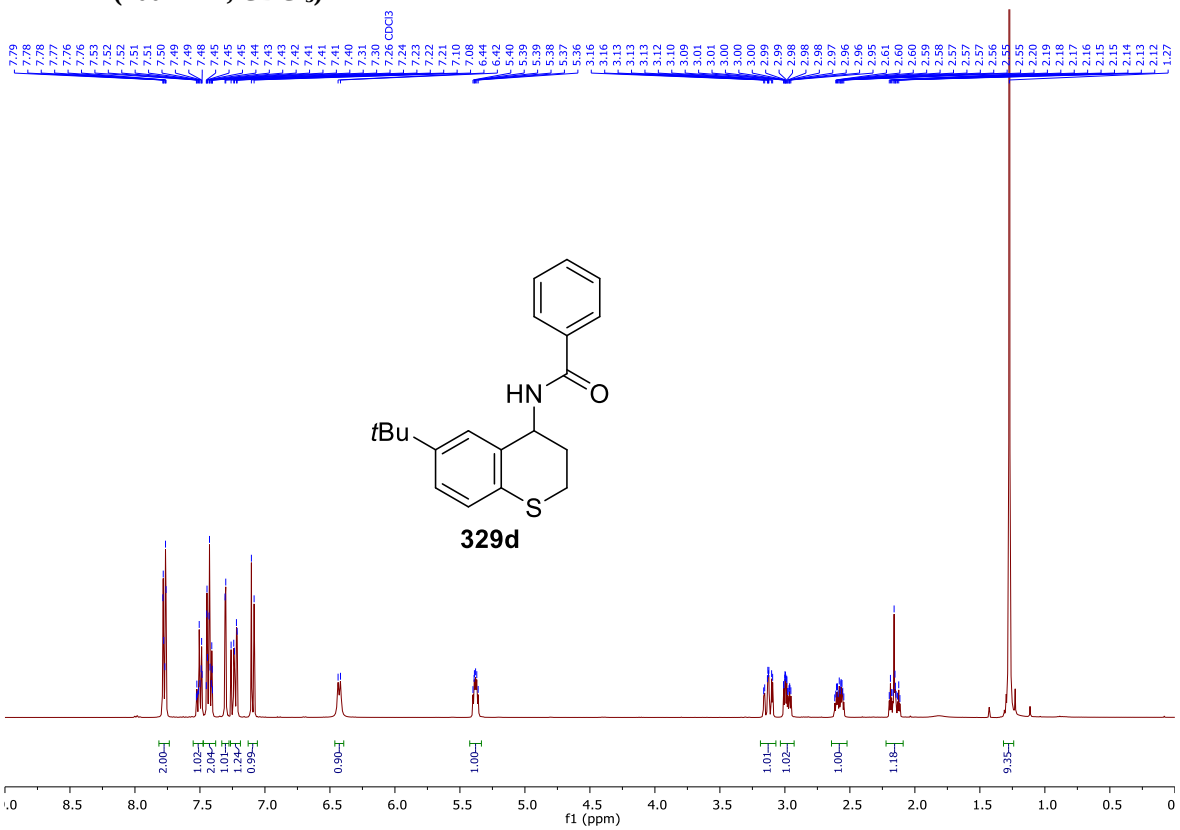
^{1}H-NMR (400 MHz, $CDCl_3$)



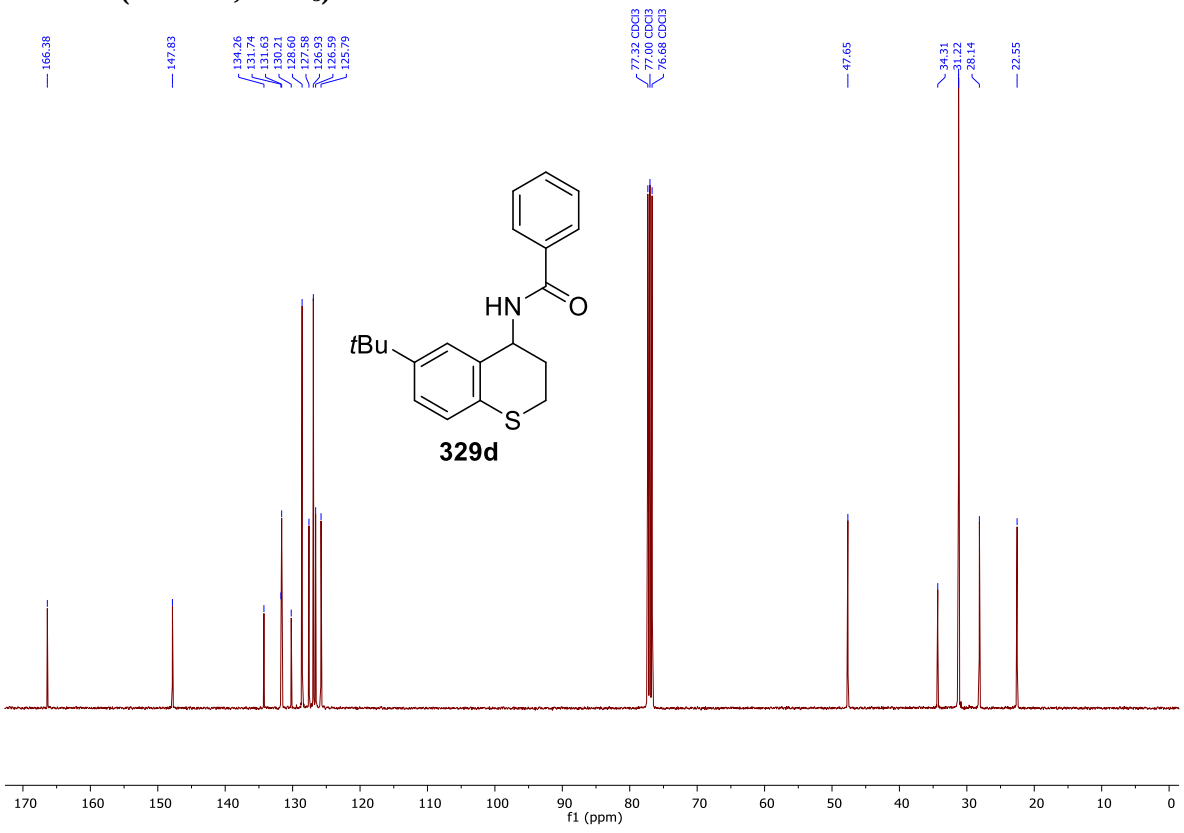
^{13}C-NMR (101 MHz, $CDCl_3$)



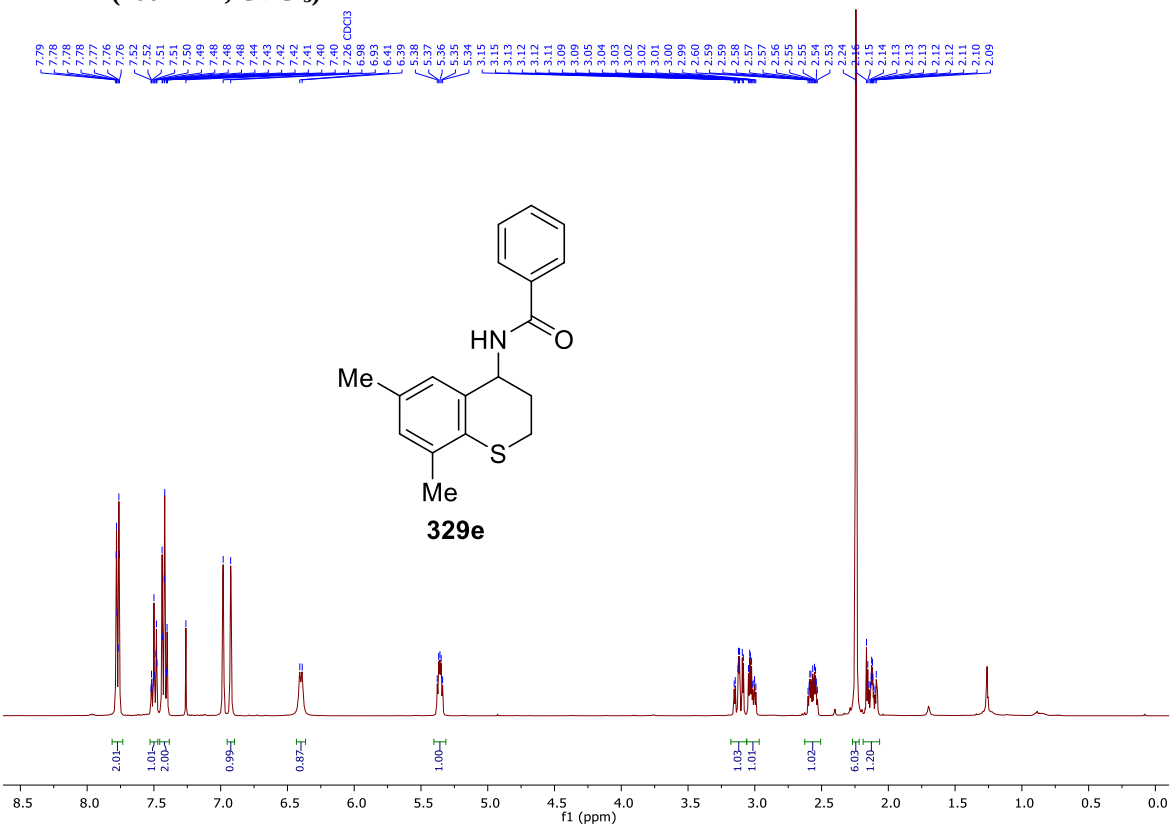
^{1}H-NMR (400 MHz, $CDCl_3$)



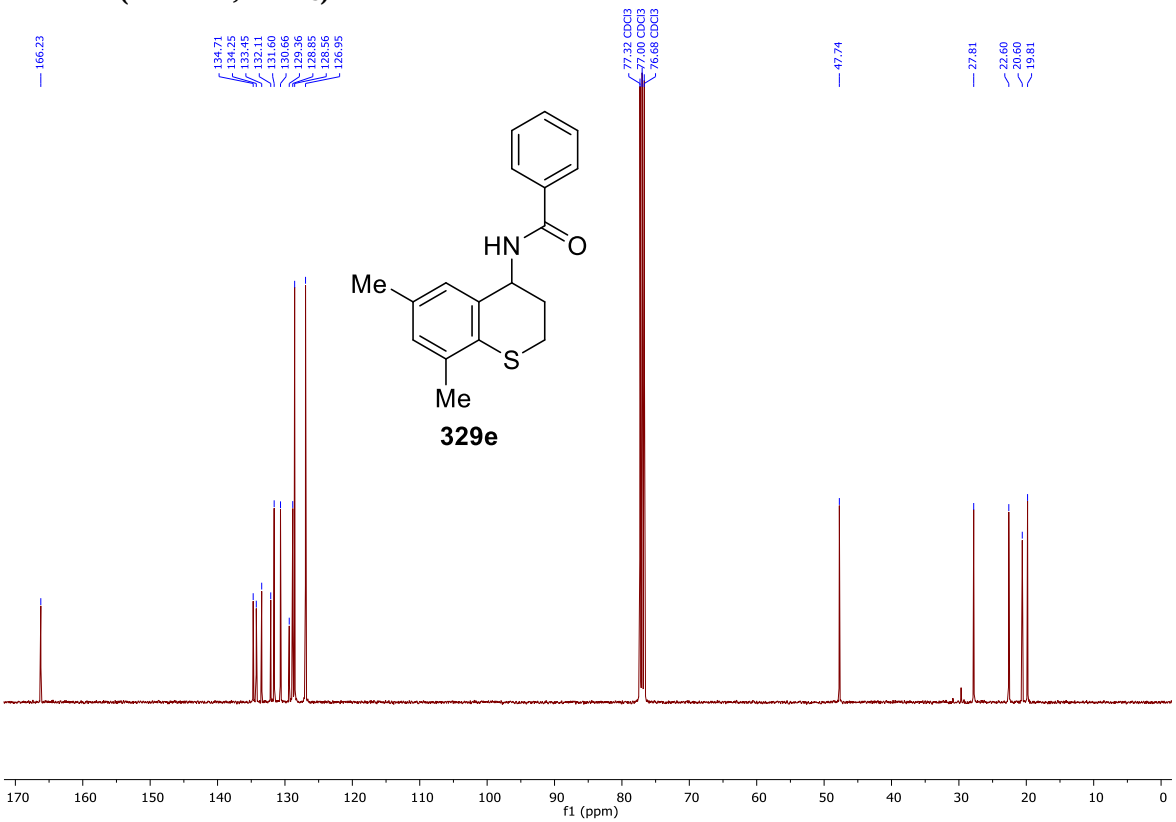
^{13}C-NMR (101 MHz, $CDCl_3$)



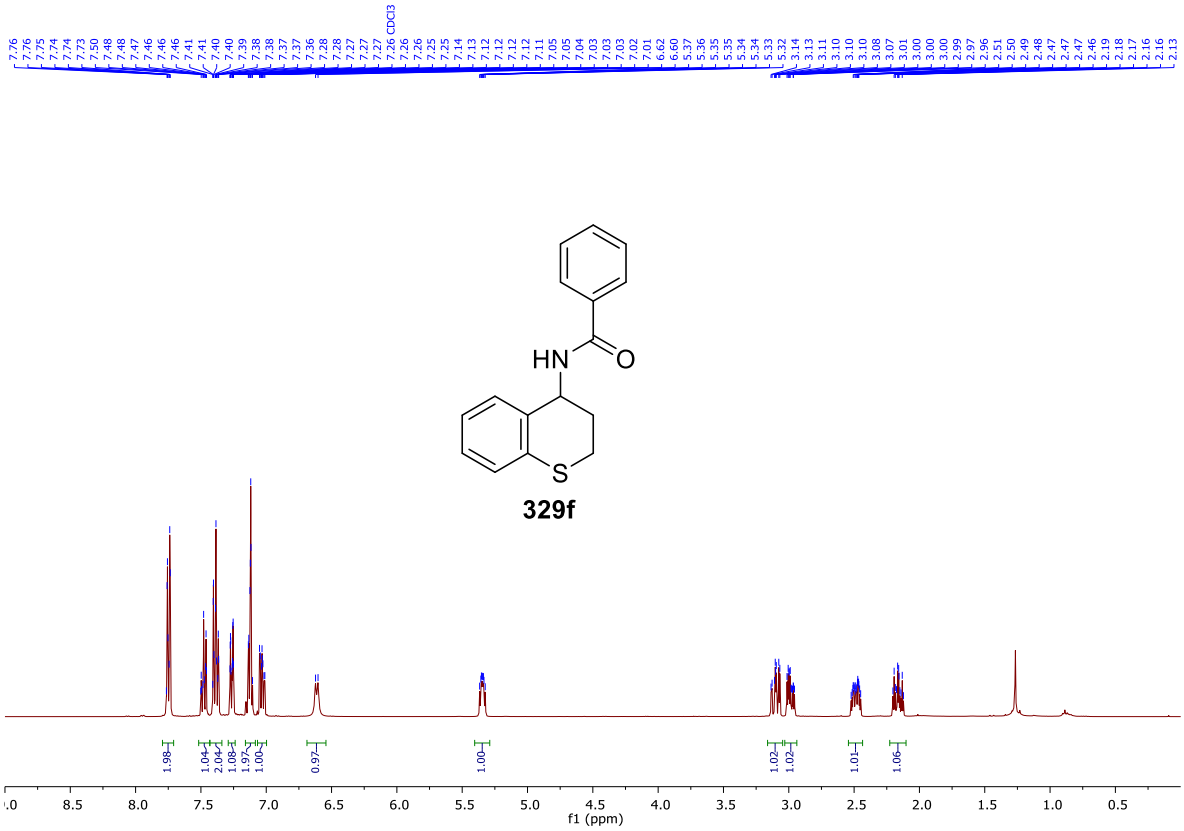
^{1}H-NMR (400 MHz, $CDCl_3$)



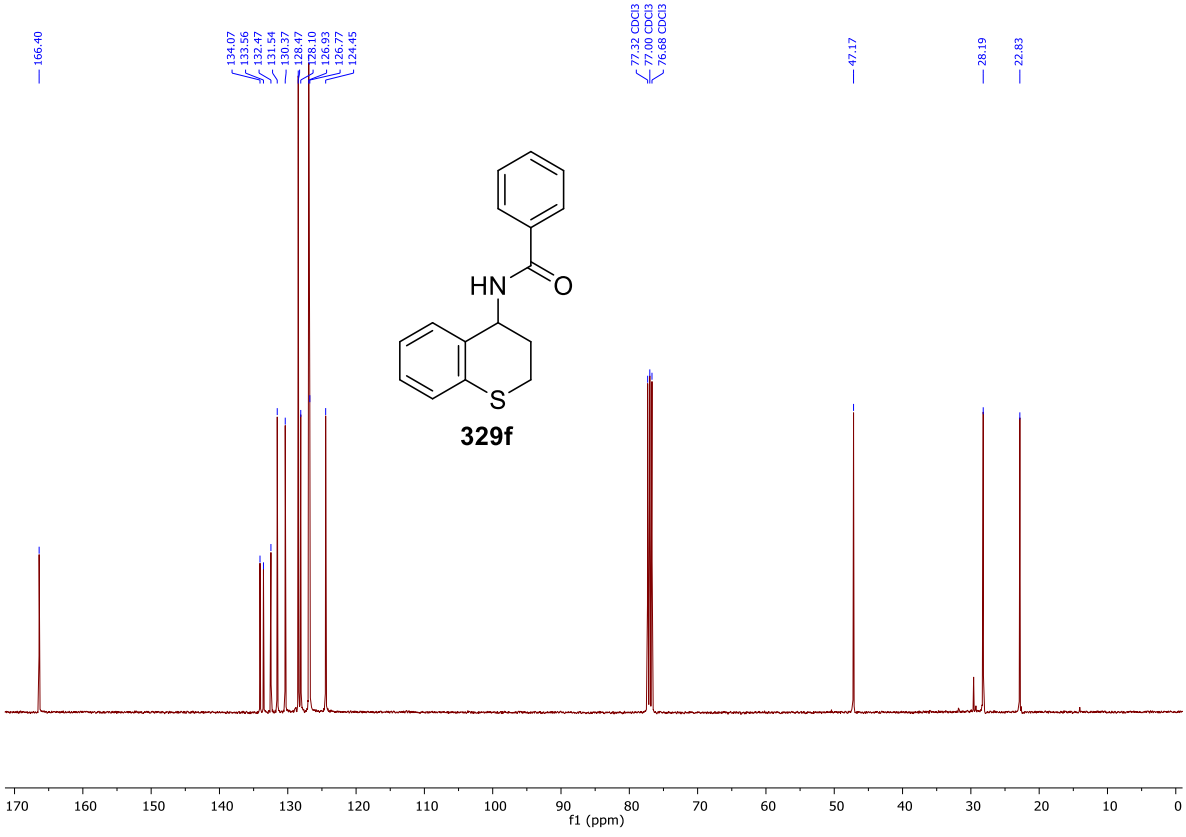
^{13}C-NMR (101 MHz, $CDCl_3$)



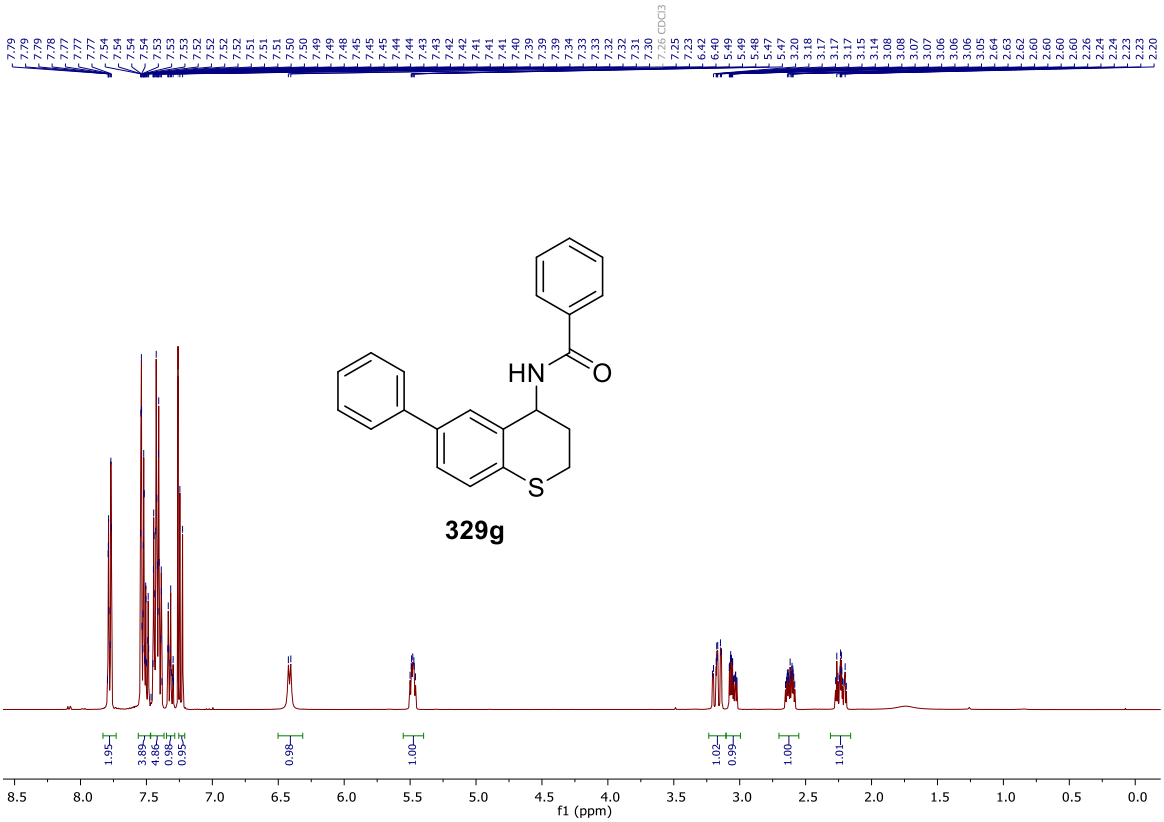
^{1}H-NMR (400 MHz, $CDCl_3$)



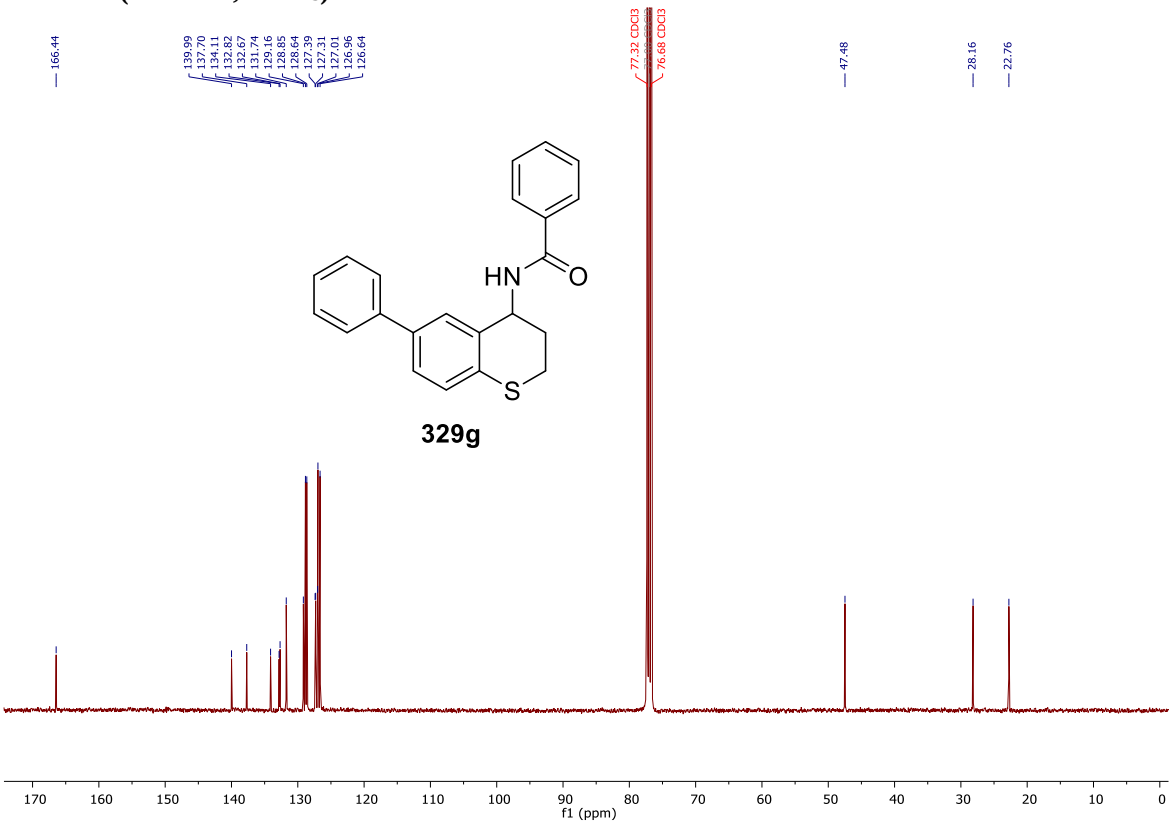
^{13}C-NMR (101 MHz, $CDCl_3$)



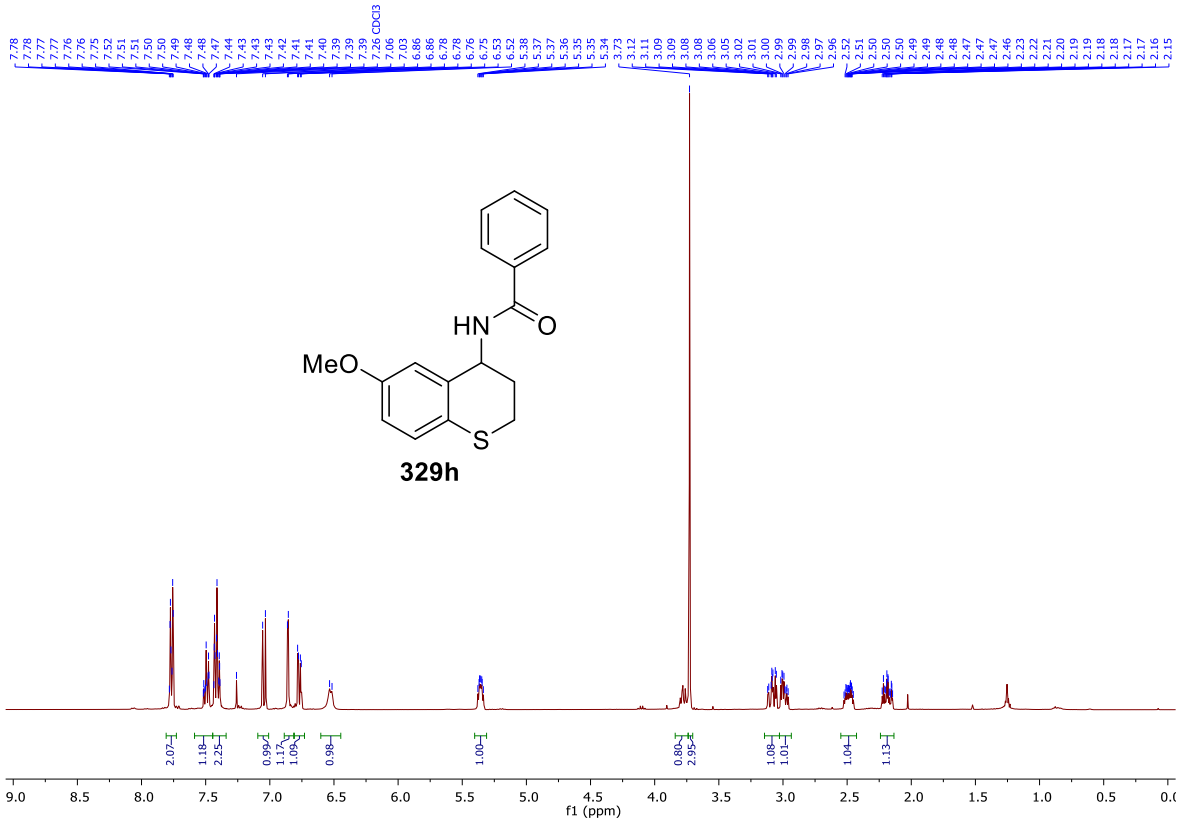
^{1}H-NMR (400 MHz, $CDCl_3$)



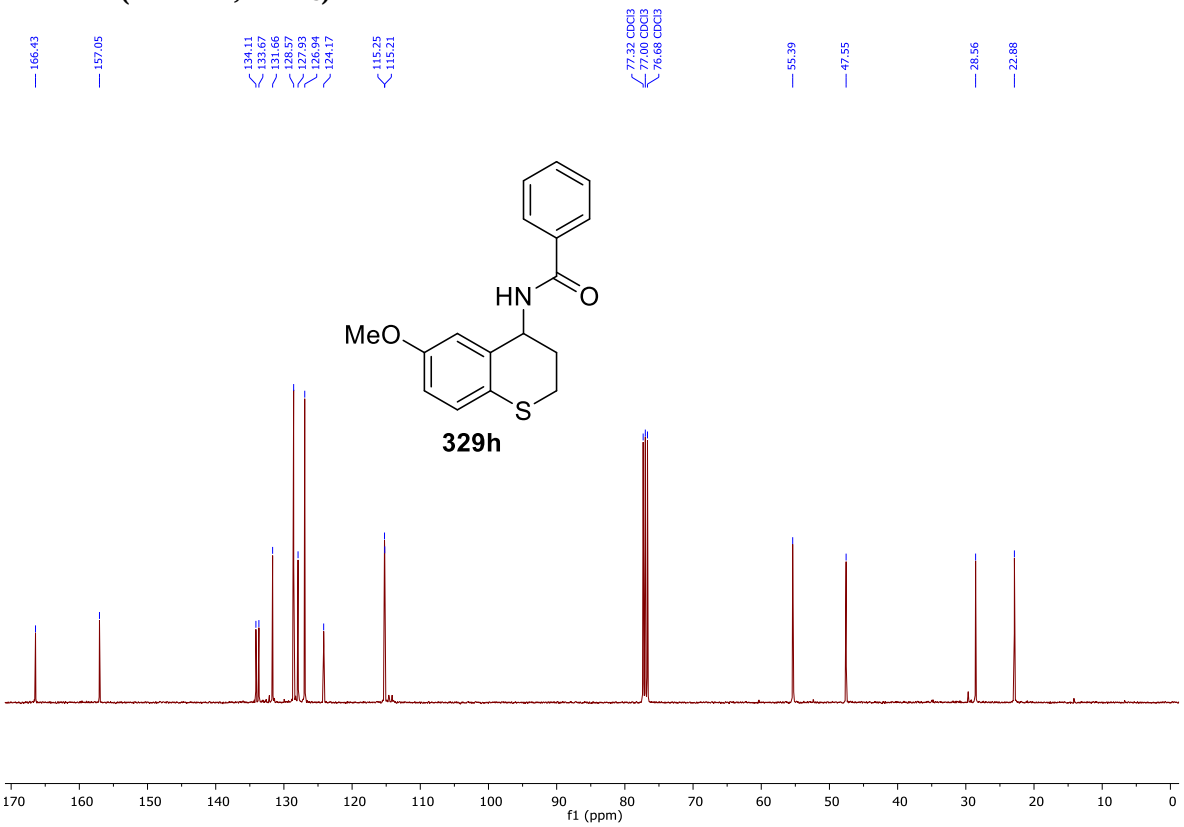
^{13}C-NMR (101 MHz, $CDCl_3$)



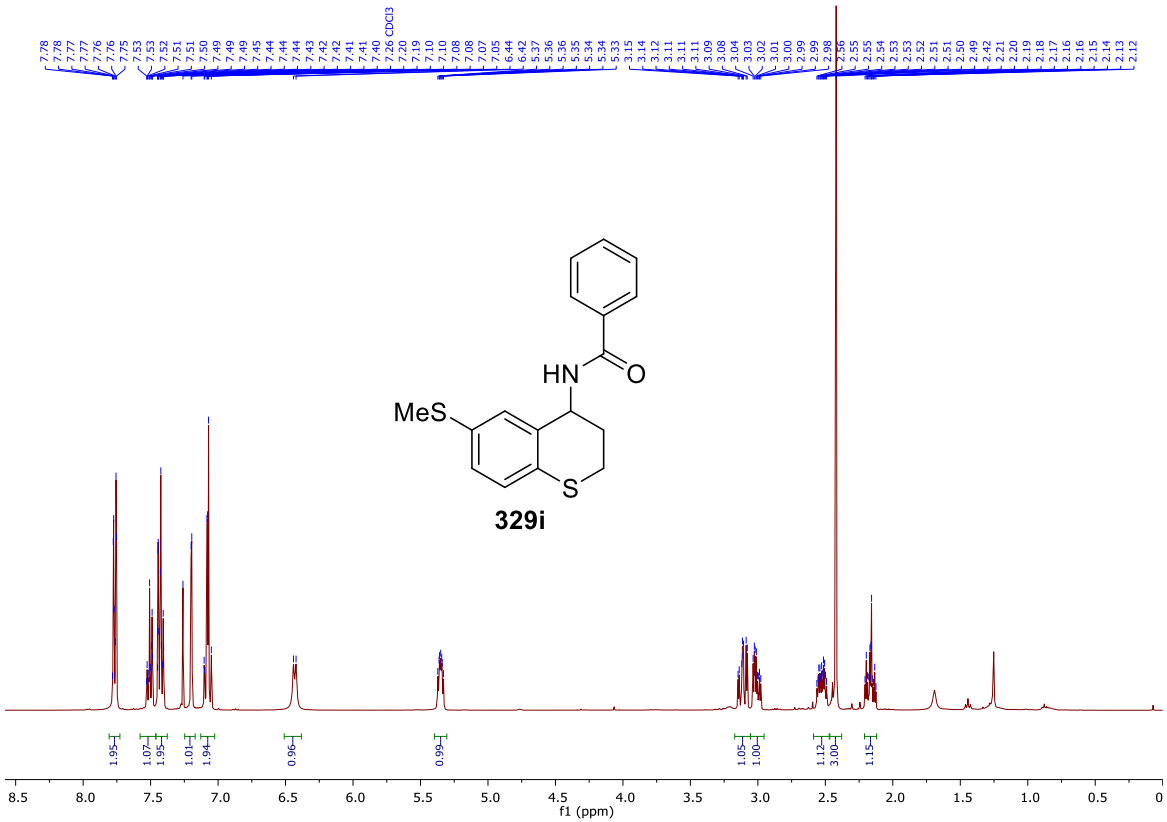
^{1}H-NMR (400 MHz, $CDCl_3$)



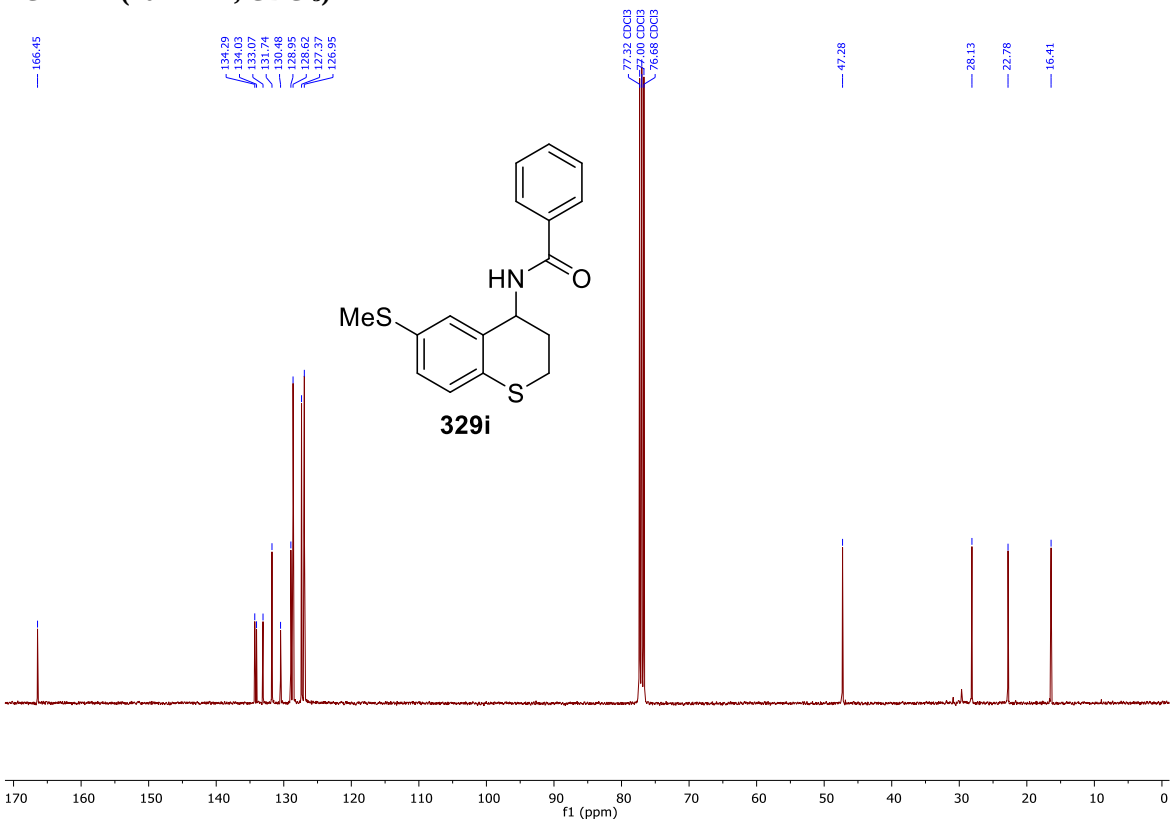
^{13}C-NMR (101 MHz, $CDCl_3$)



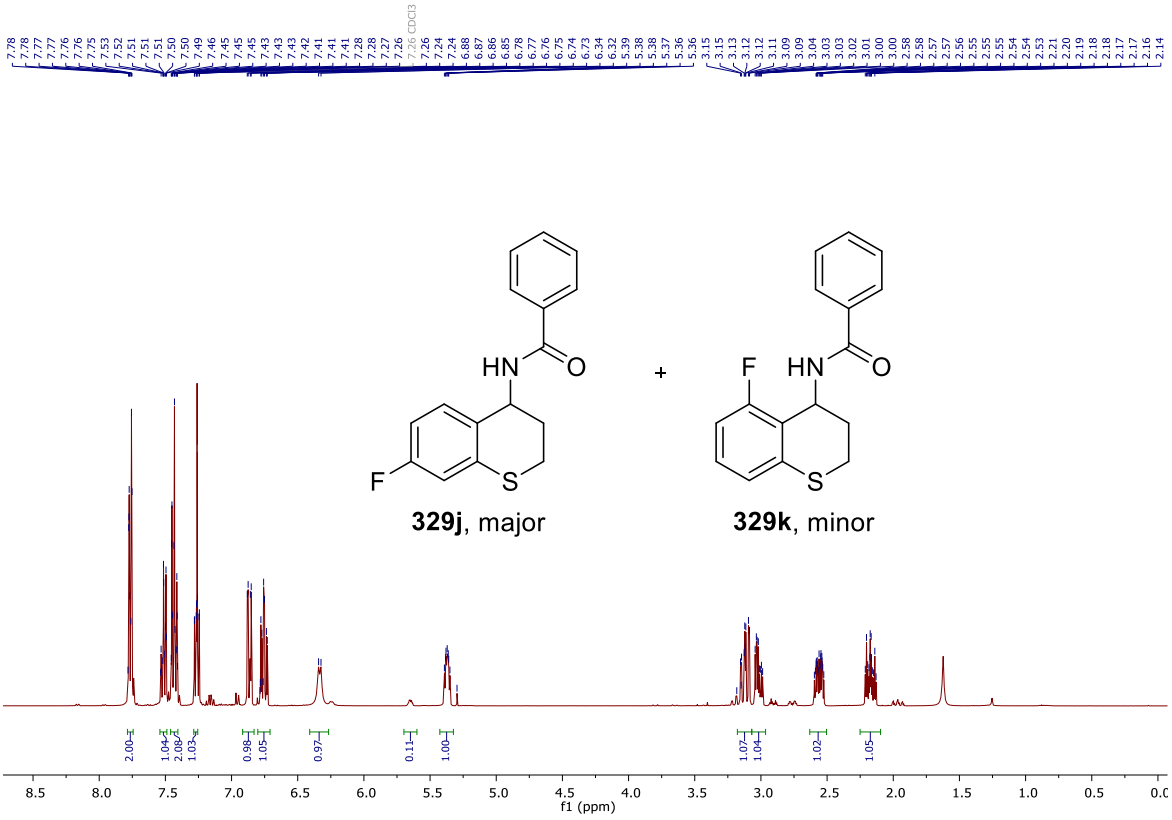
^{1}H-NMR (400 MHz, $CDCl_3$)



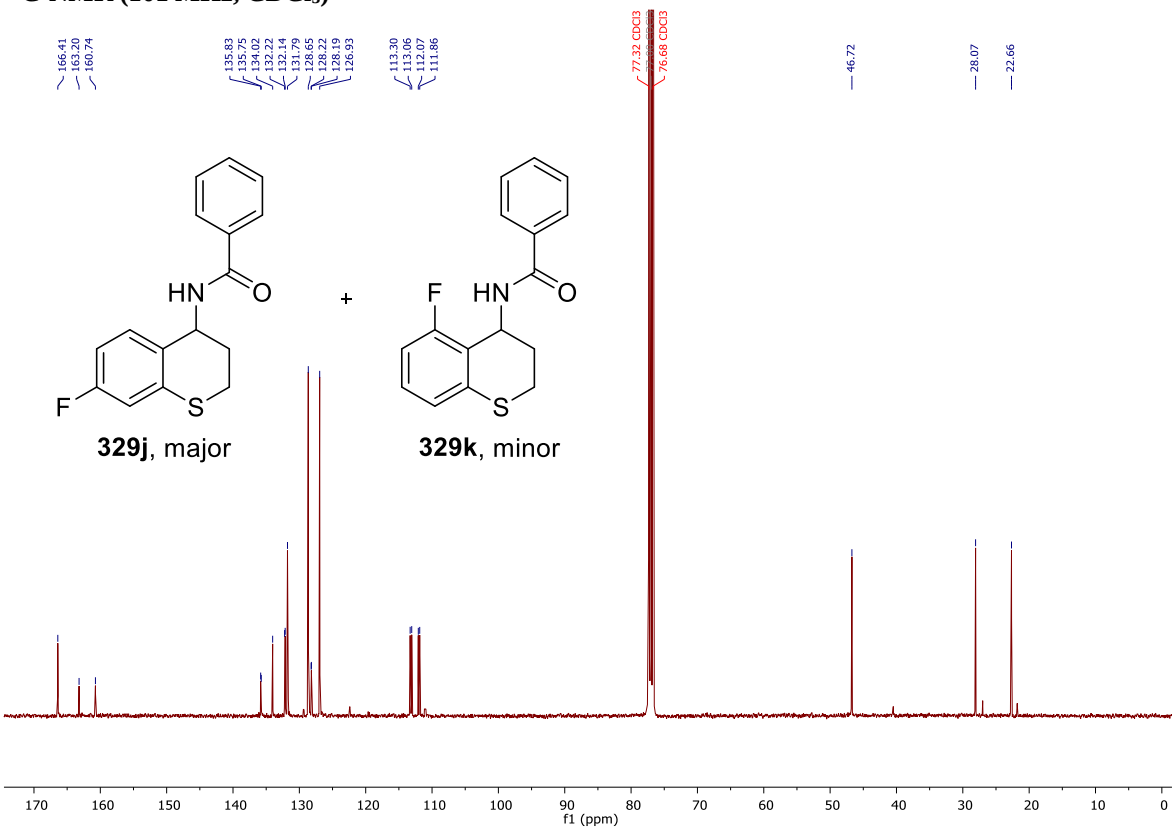
^{13}C-NMR (101 MHz, $CDCl_3$)



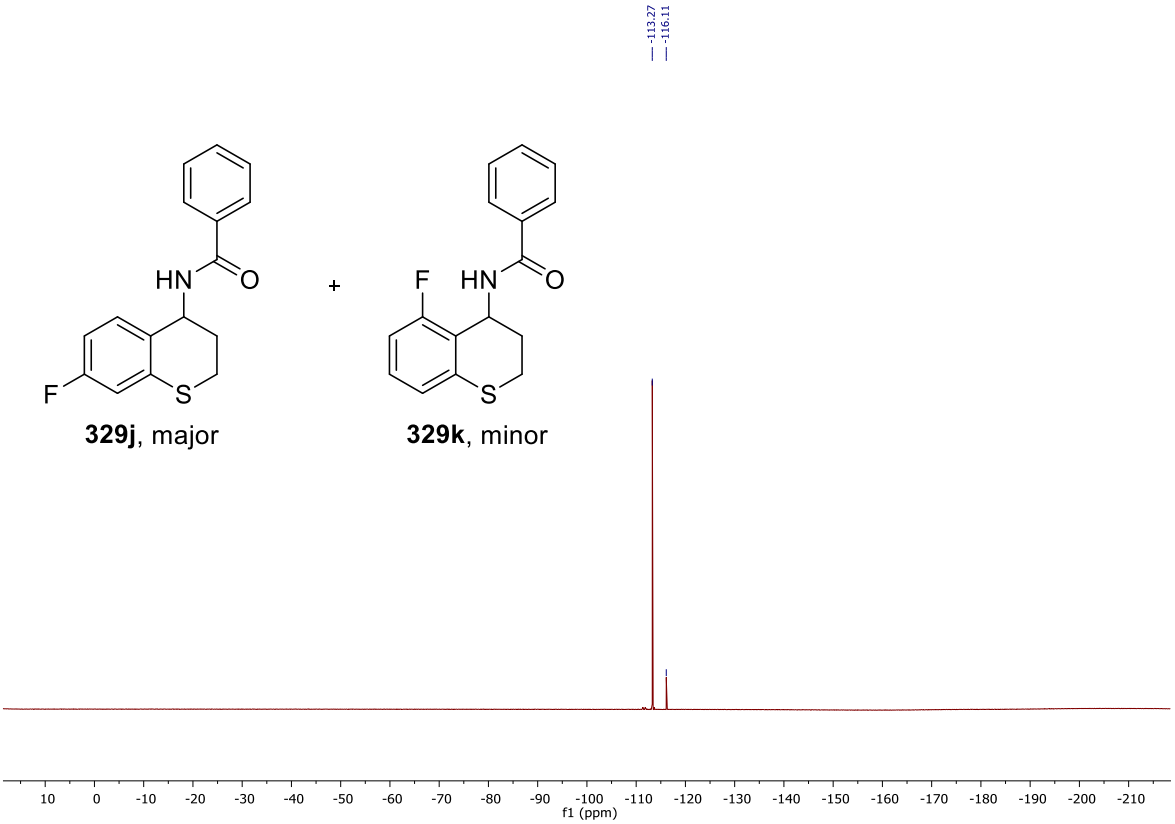
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

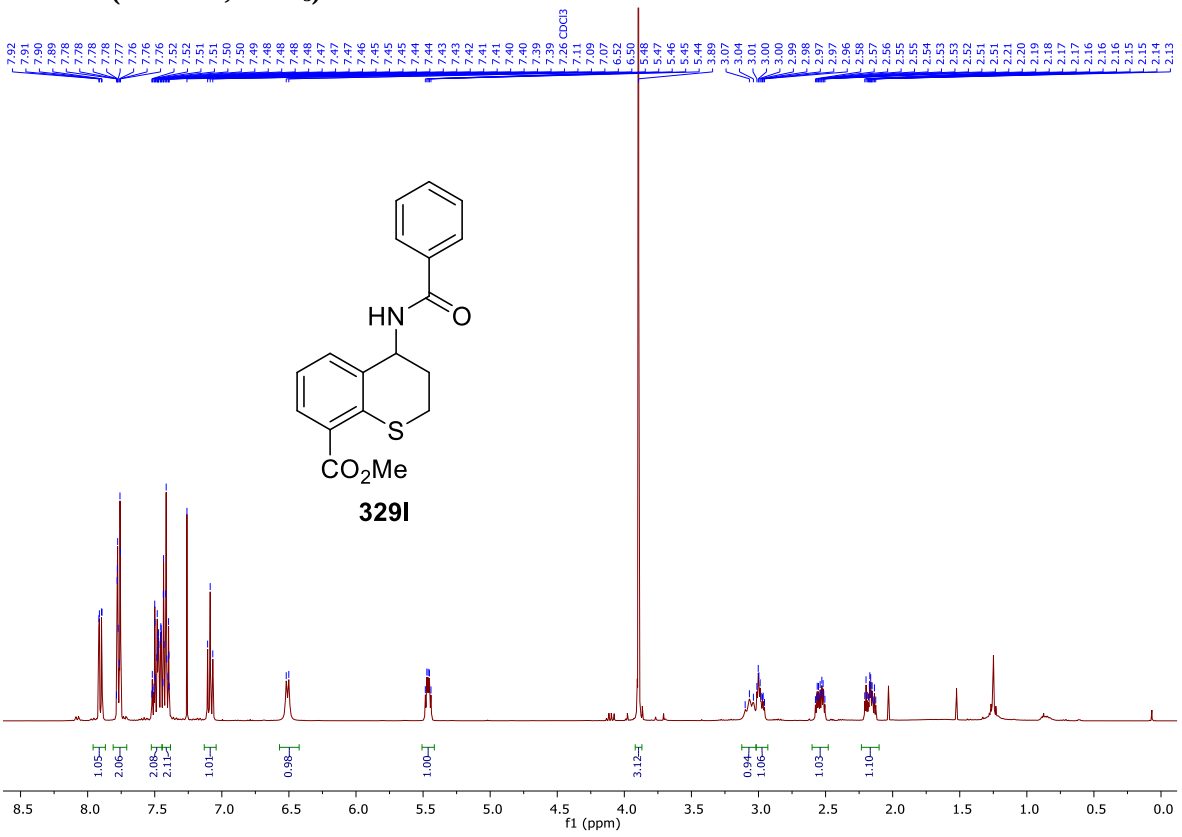


^{19}F-NMR (376 MHz, $CDCl_3$)



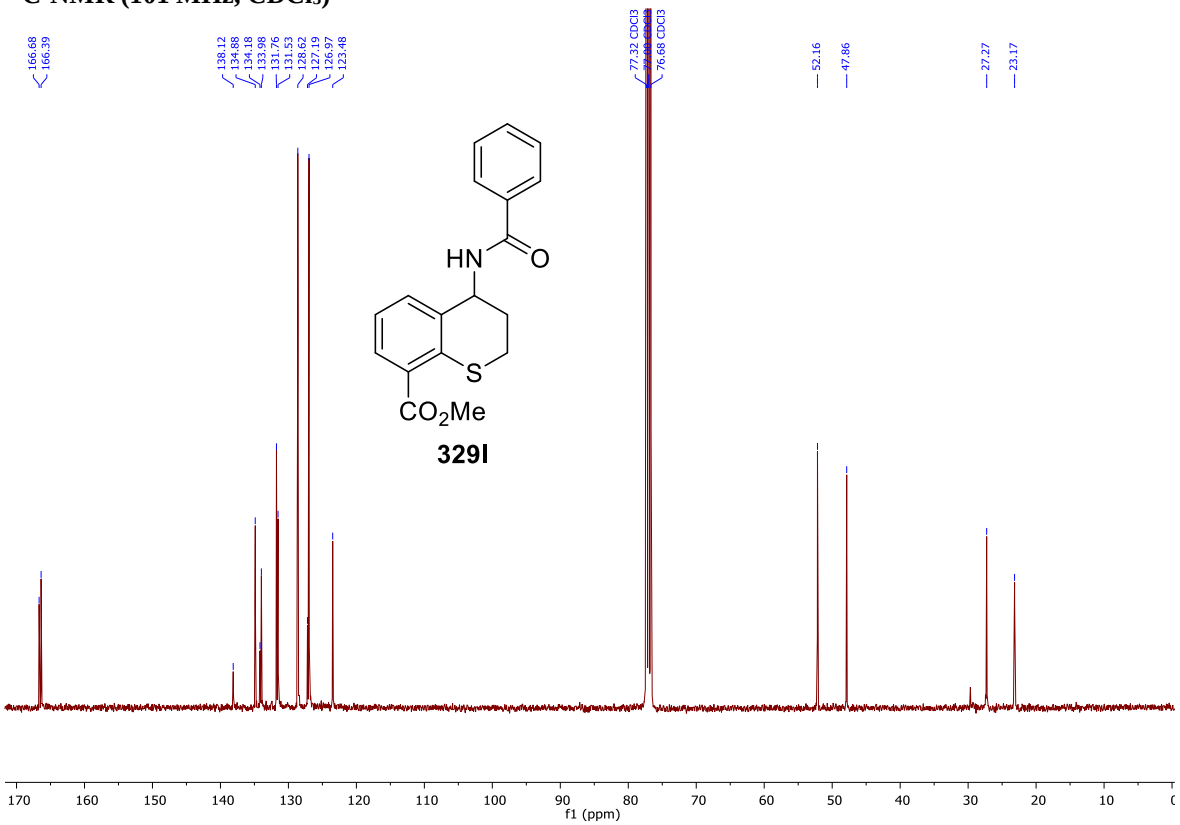
329j, major **329k**, minor

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

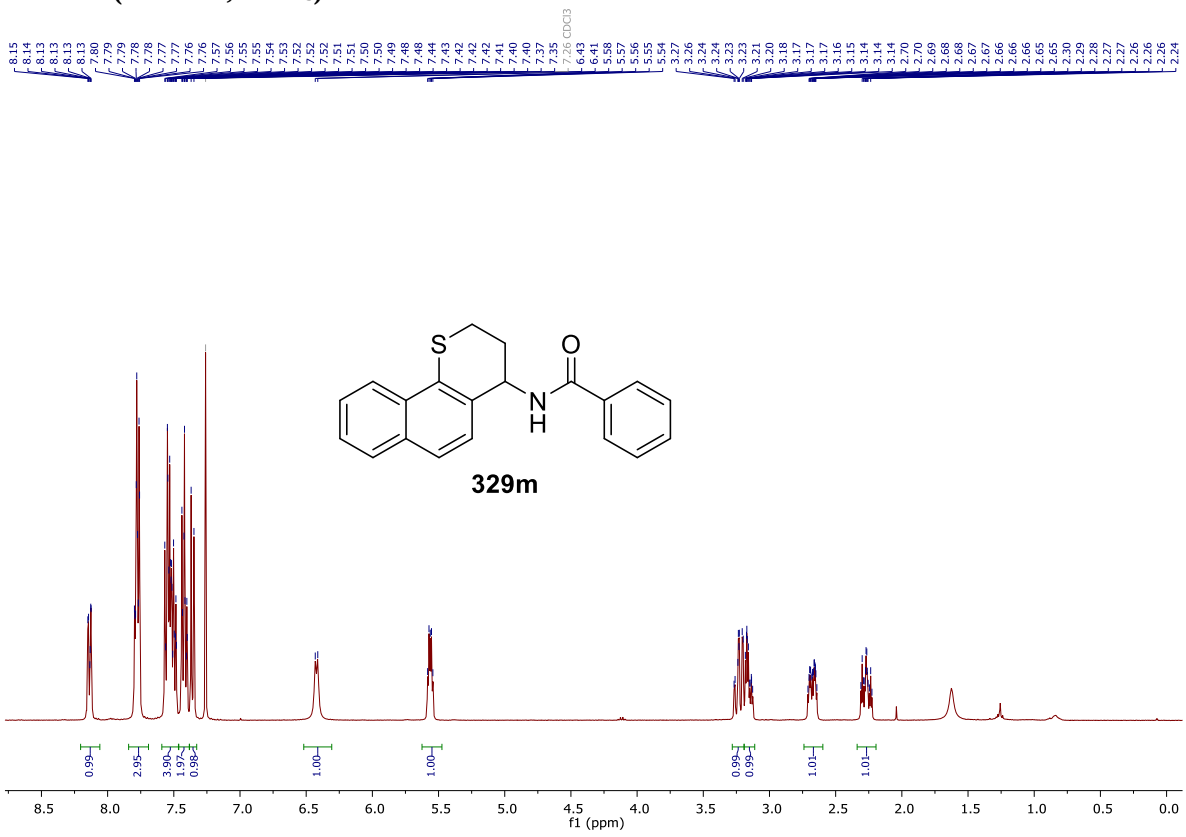


329l

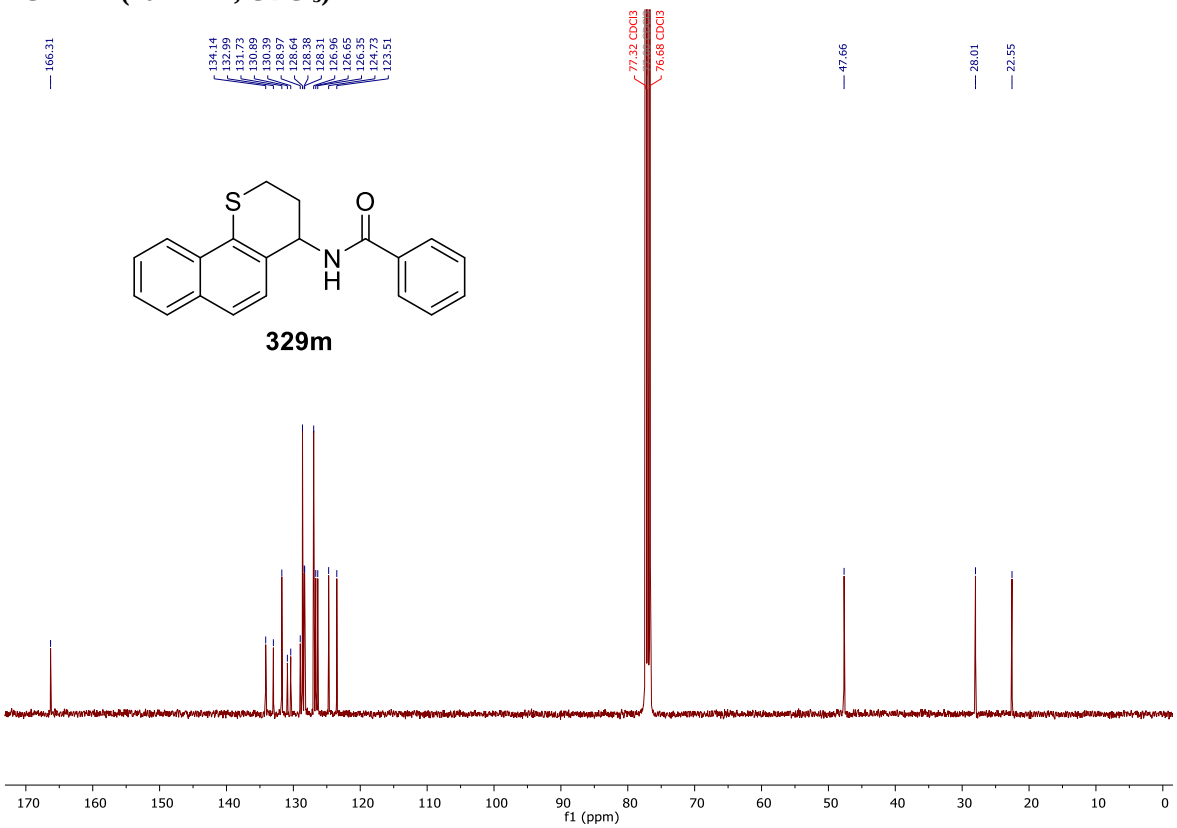
^{13}C-NMR (101 MHz, $CDCl_3$)



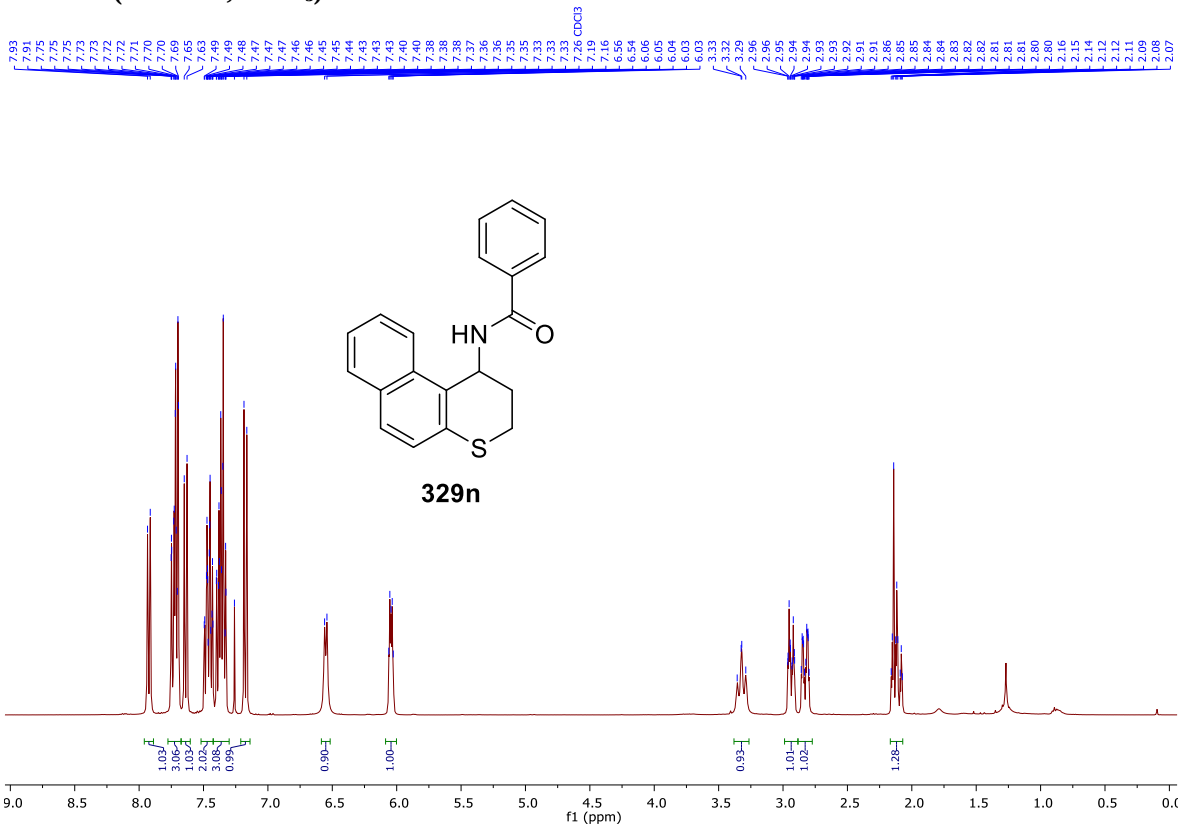
^{1}H-NMR (400 MHz, $CDCl_3$)



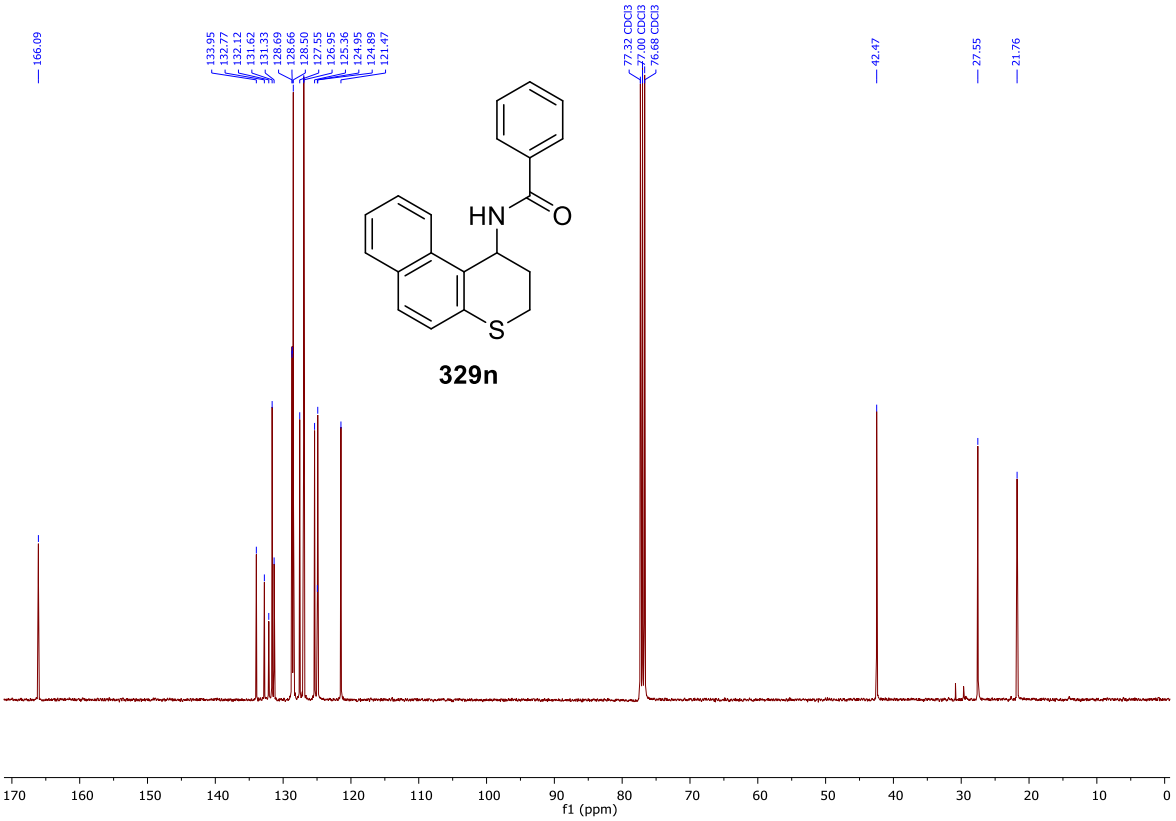
^{13}C-NMR (101 MHz, $CDCl_3$)



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

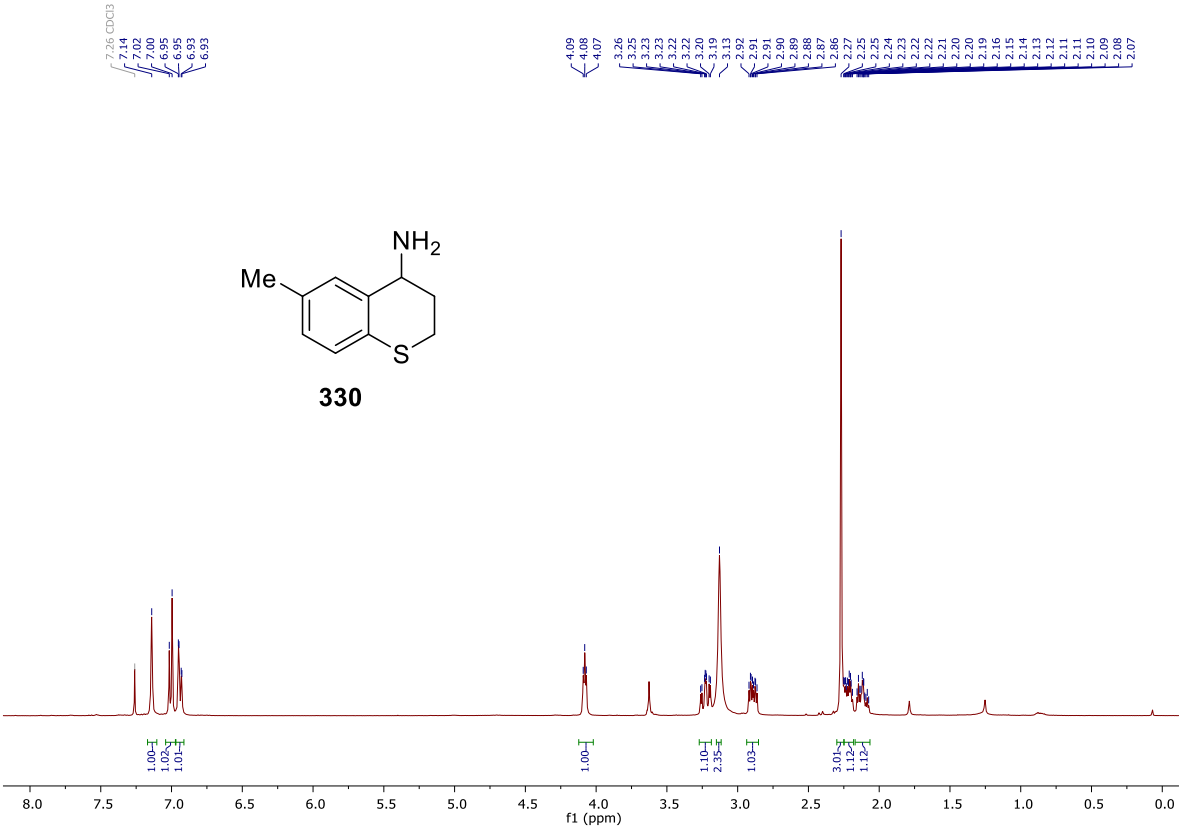


^{13}C-NMR (101 MHz, $CDCl_3$)



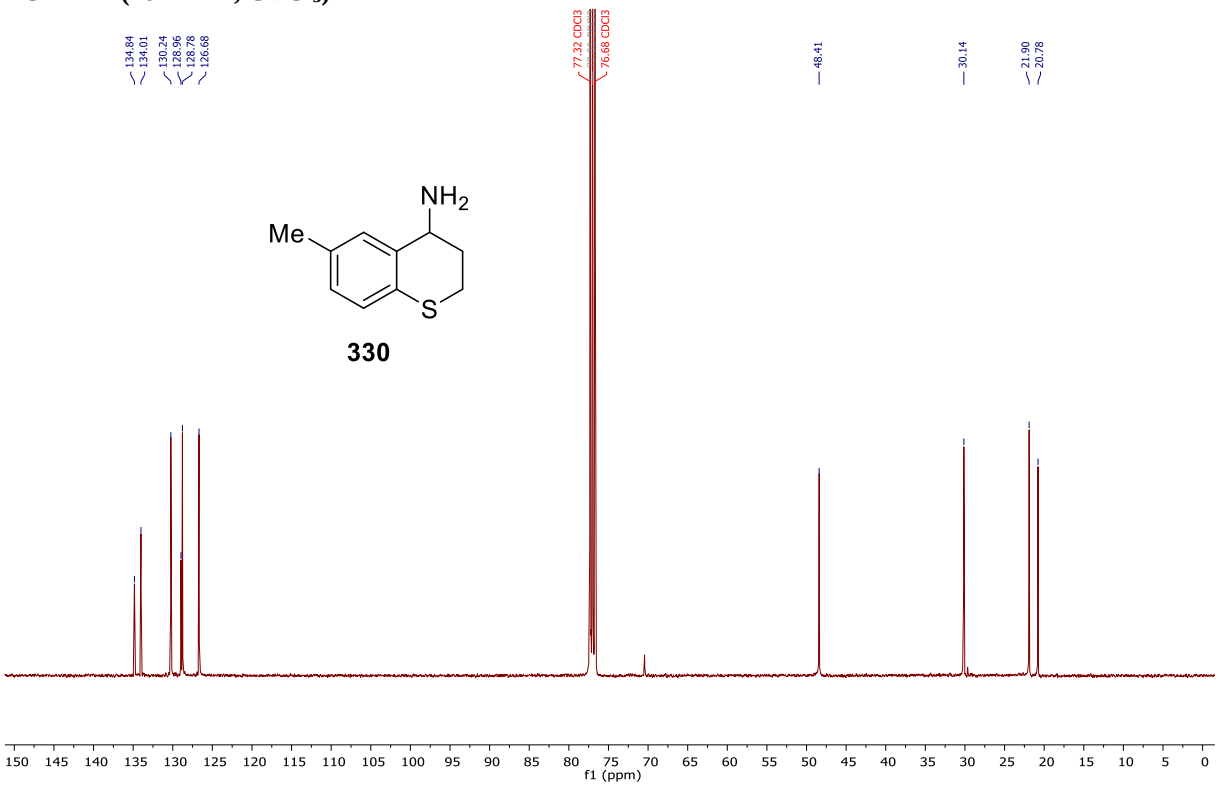
329n

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

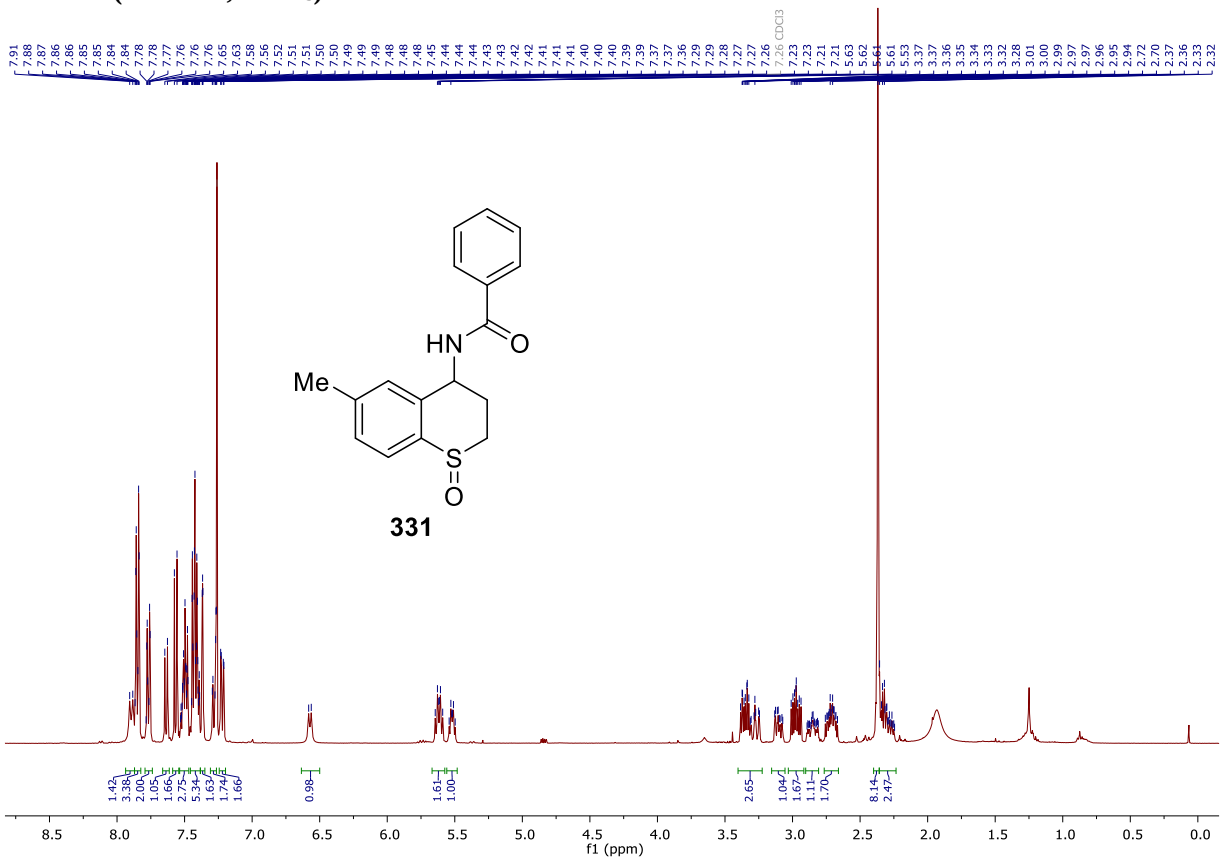


330

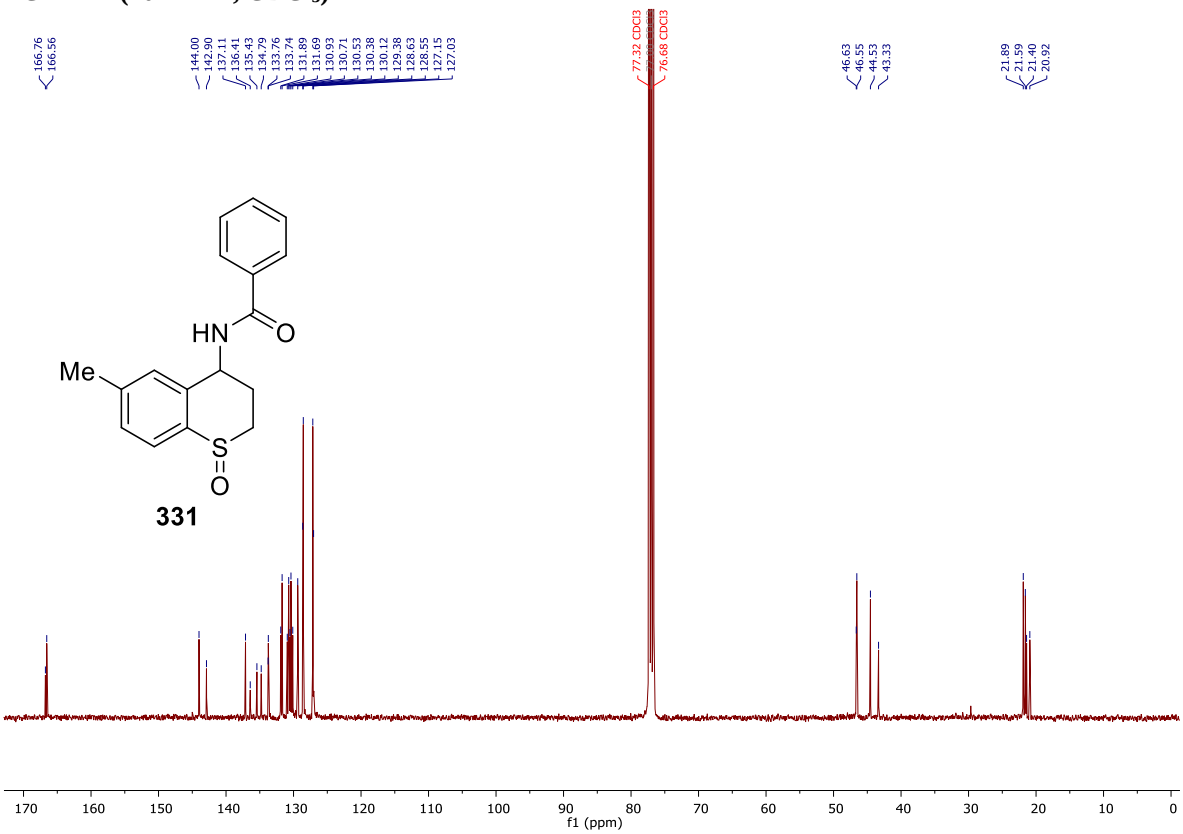
^{13}C-NMR (101 MHz, $CDCl_3$)



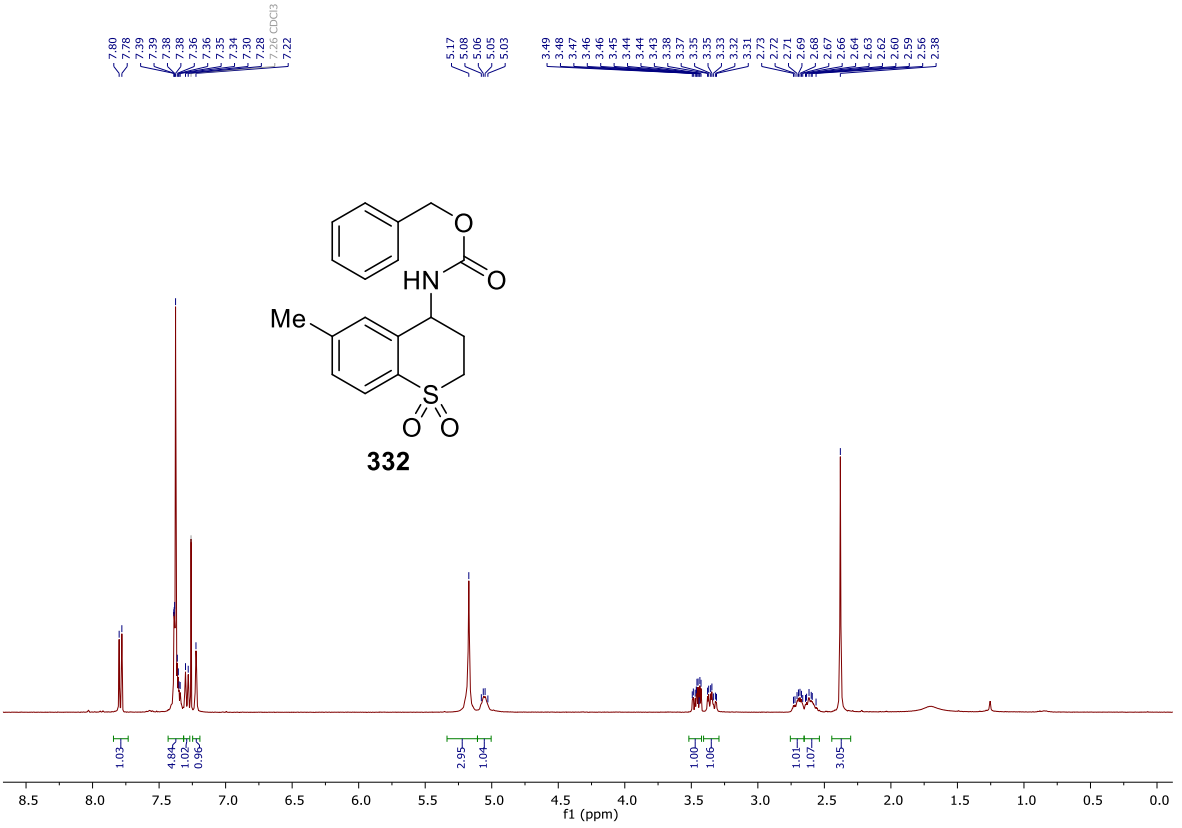
^{1}H-NMR (400 MHz, $CDCl_3$)



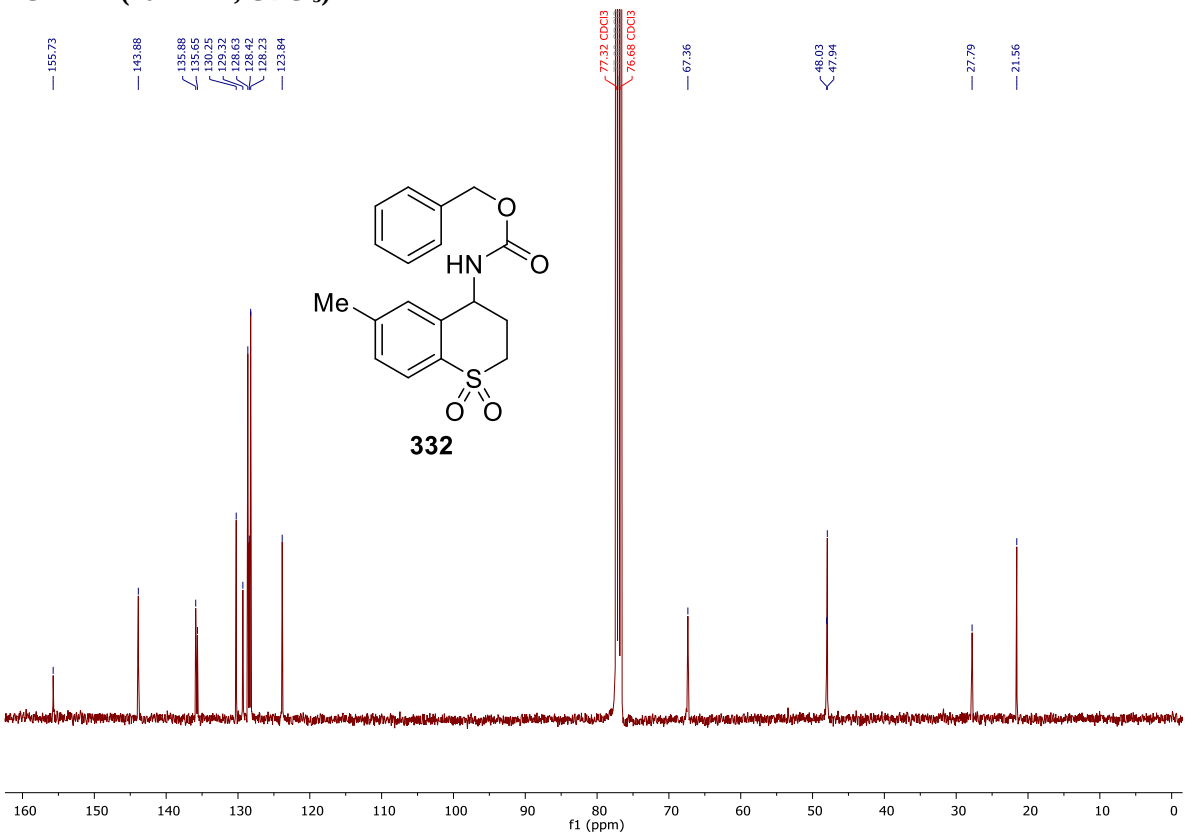
^{13}C-NMR (101 MHz, $CDCl_3$)



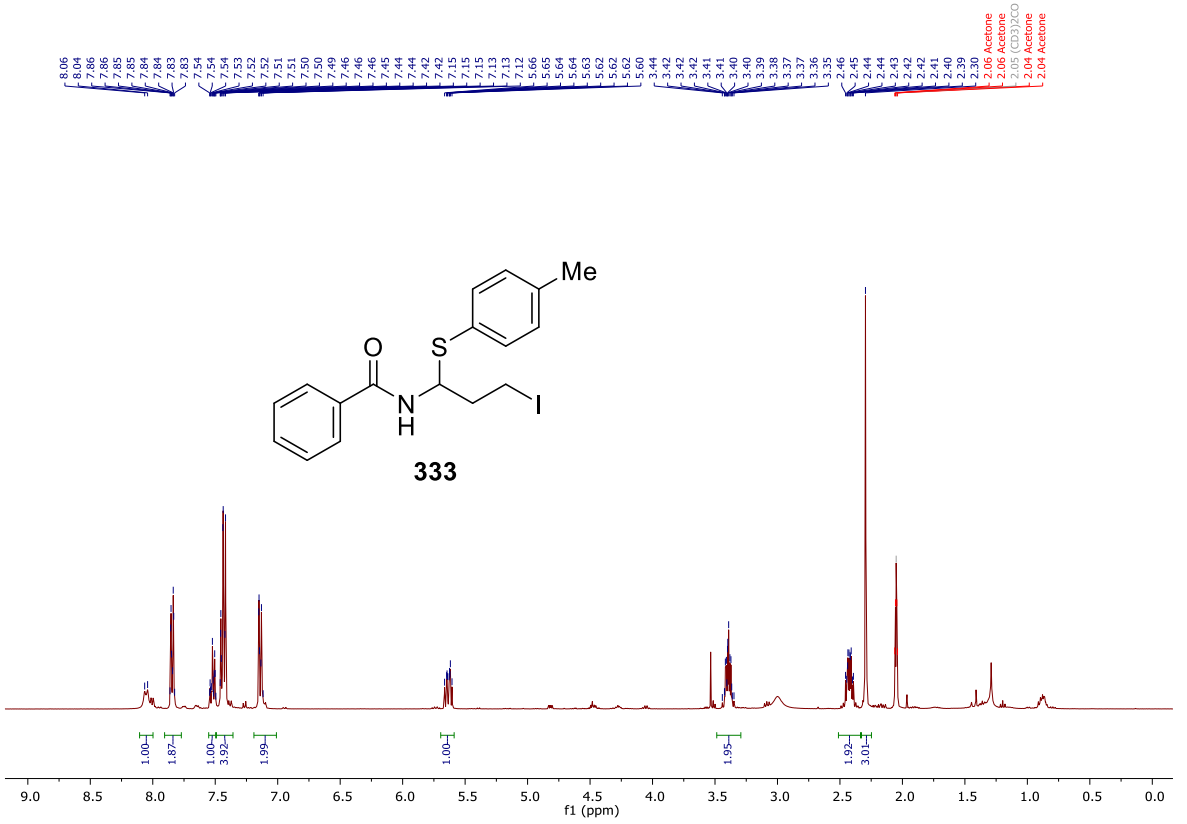
^{1}H-NMR (400 MHz, $CDCl_3$)



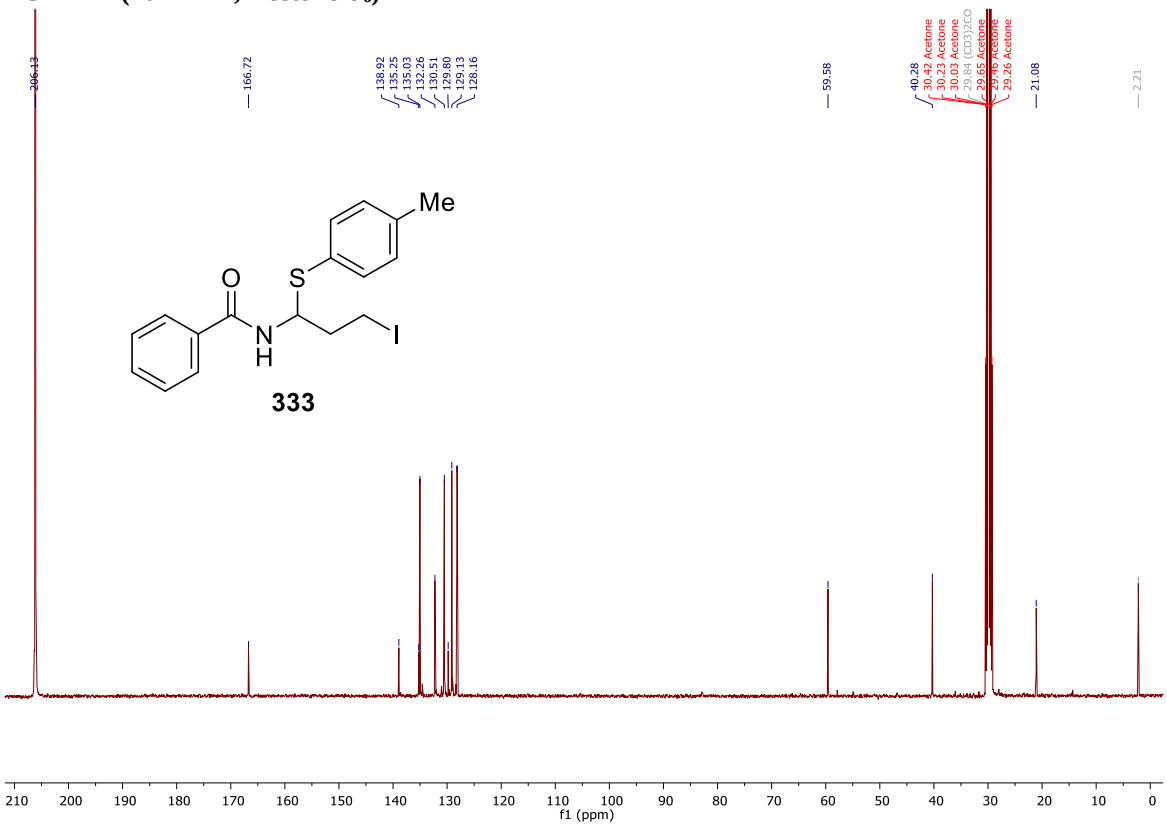
^{13}C-NMR (101 MHz, $CDCl_3$)



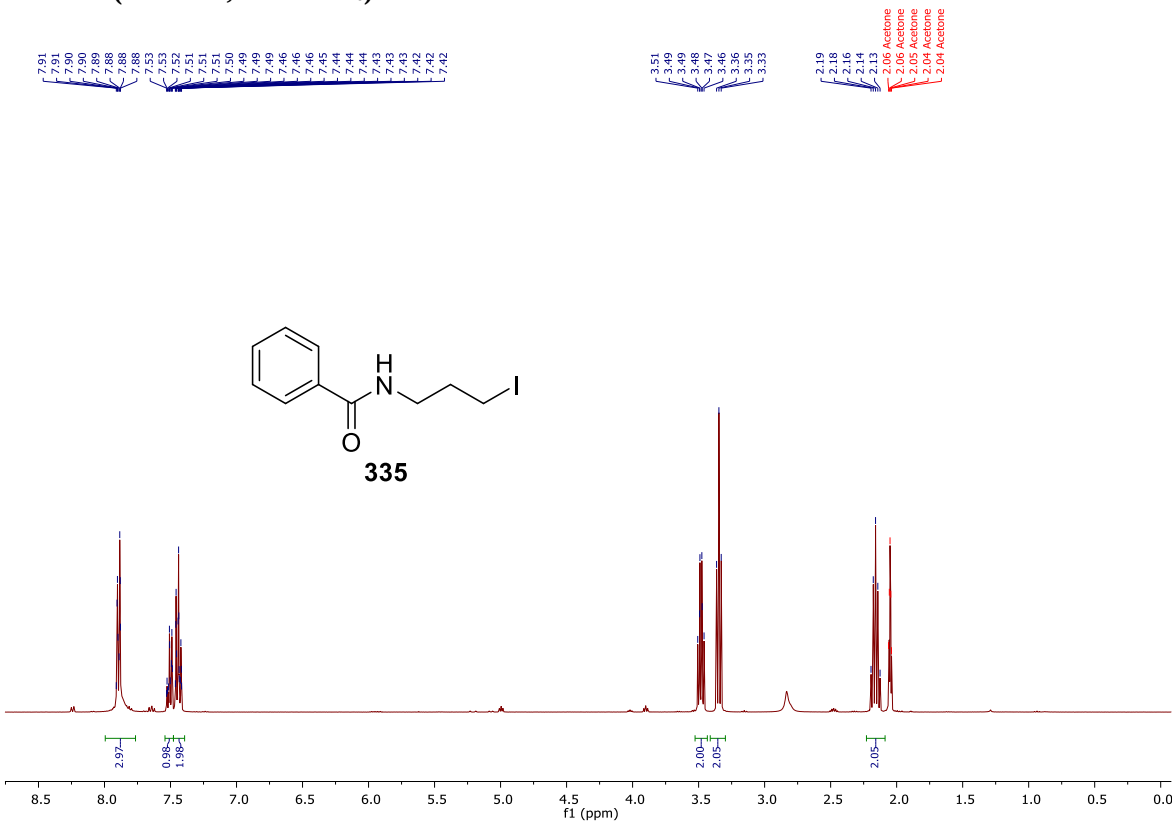
^{1}H-NMR (400 MHz, Acetone-d_6)



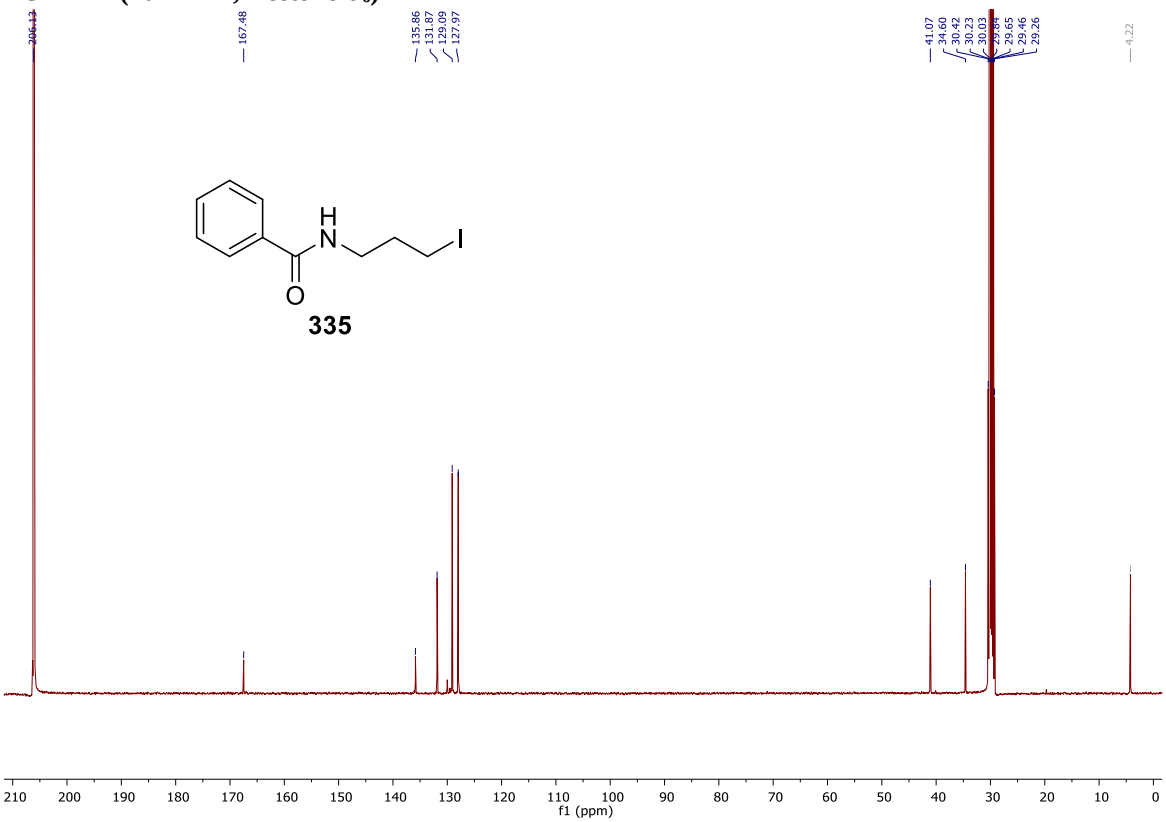
^{13}C-NMR (101 MHz, Acetone-d$_6$)



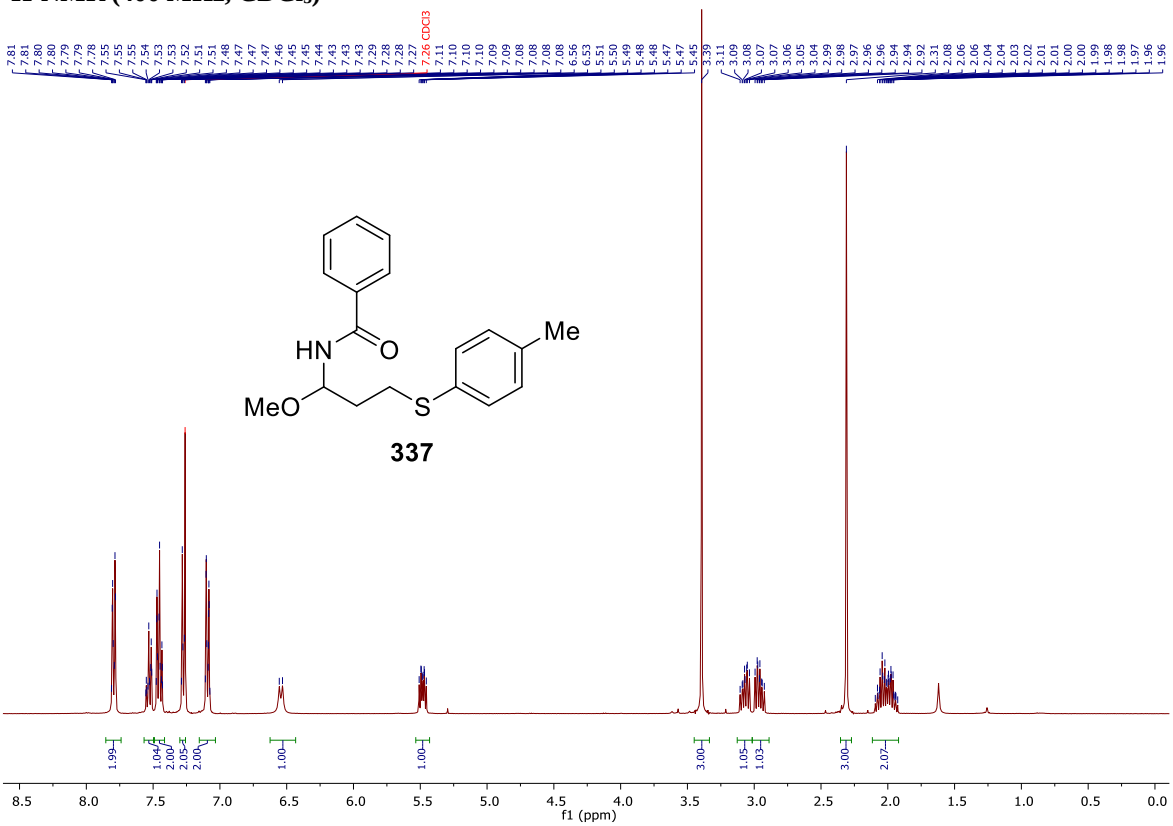
^{1}H-NMR (400 MHz, Acetone-d$_6$)



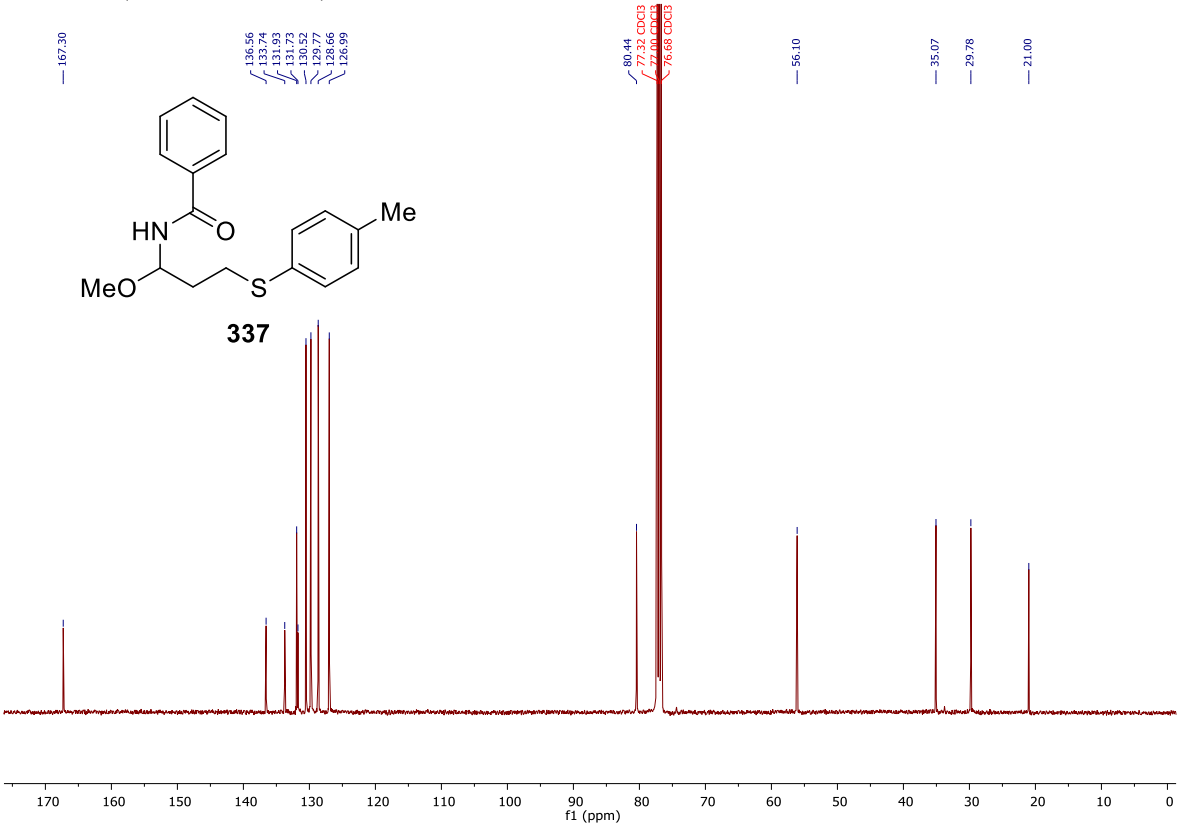
^{13}C-NMR (101 MHz, Acetone-d_6)



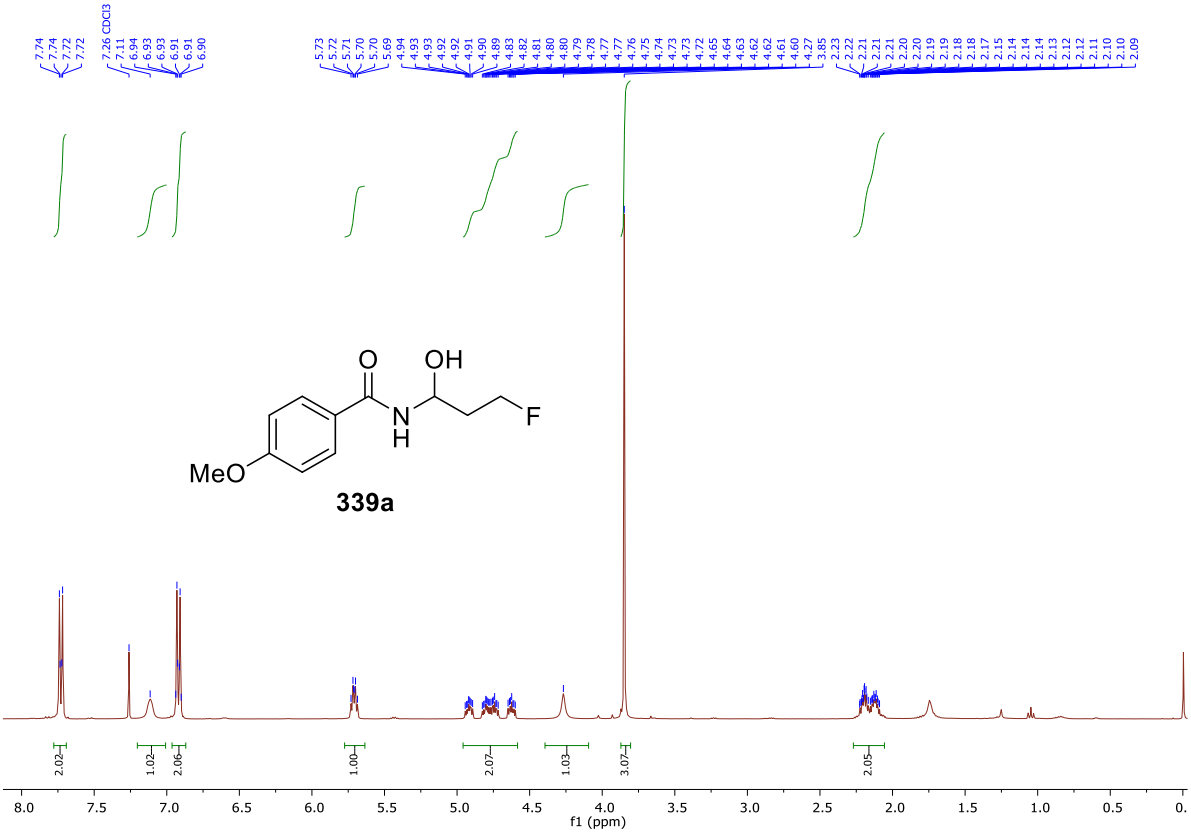
^{1}H-NMR (400 MHz, $CDCl_3$)



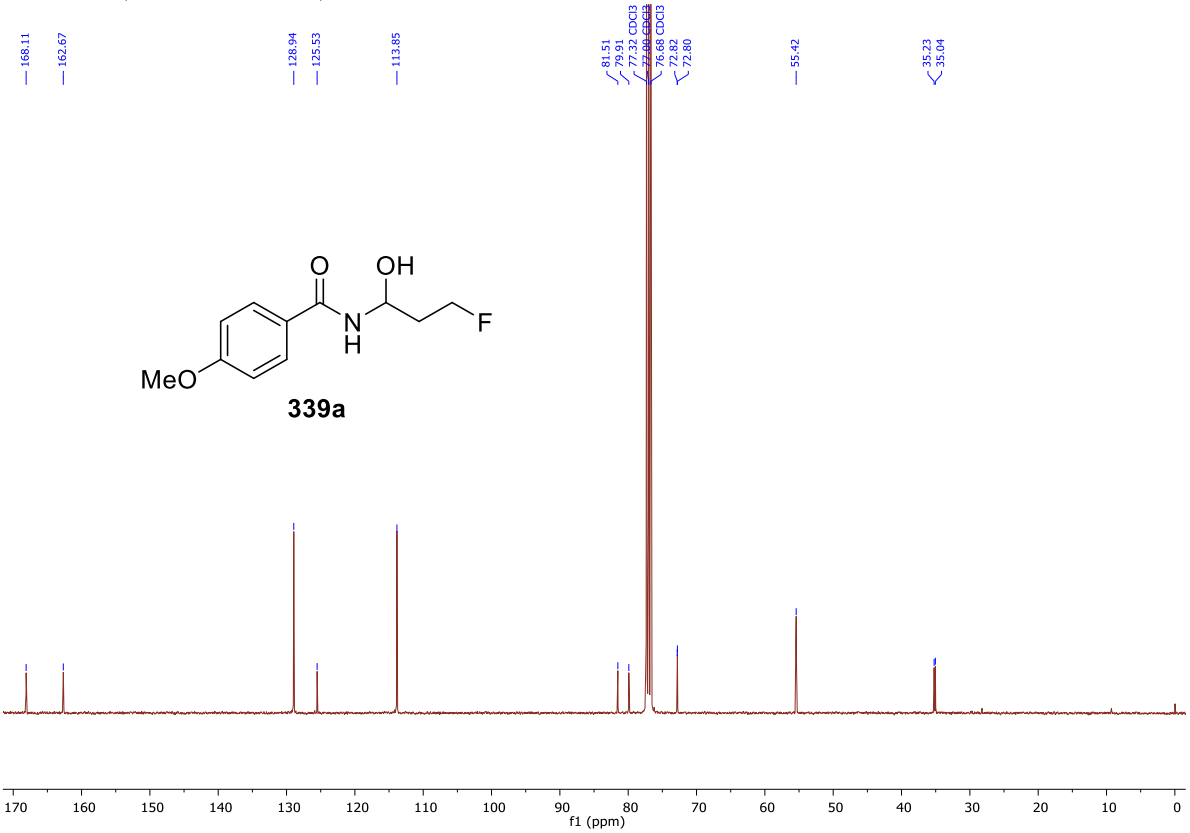
^{13}C-NMR (101 MHz, $CDCl_3$)



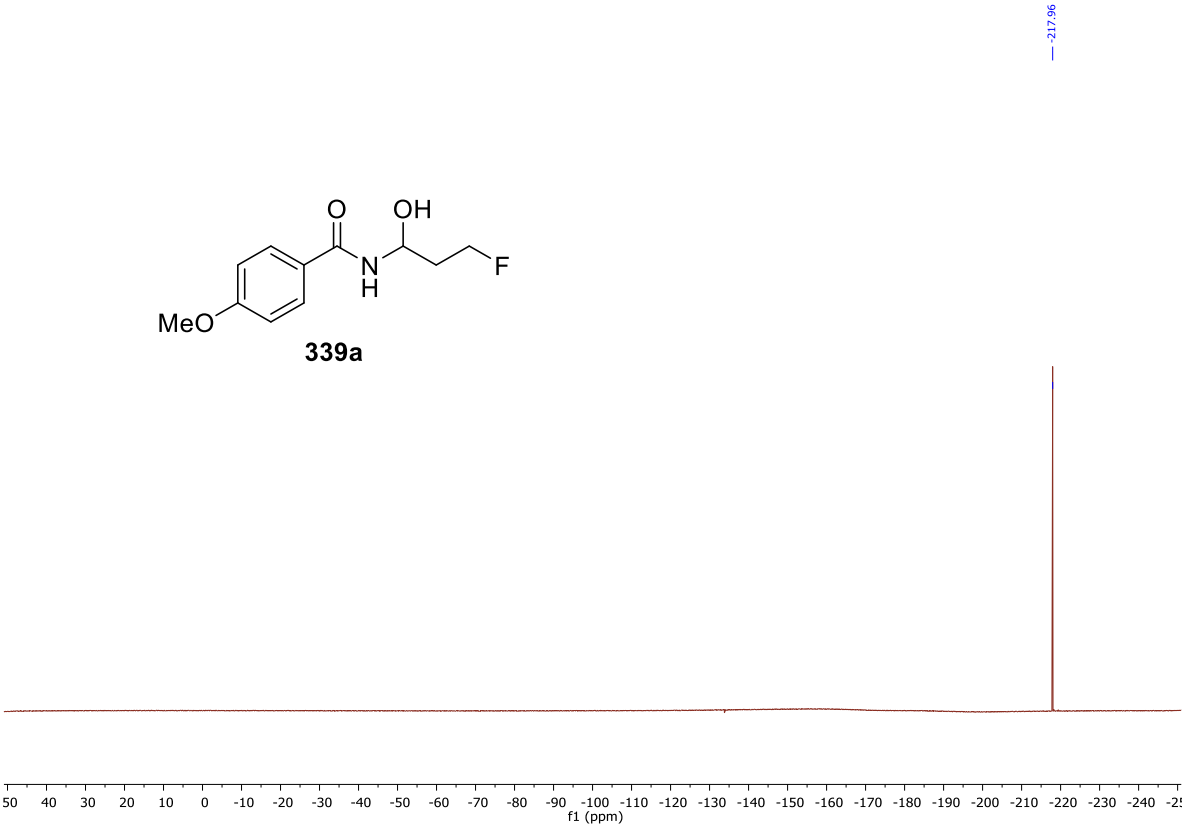
^{1}H-NMR (400 MHz, $CDCl_3$)



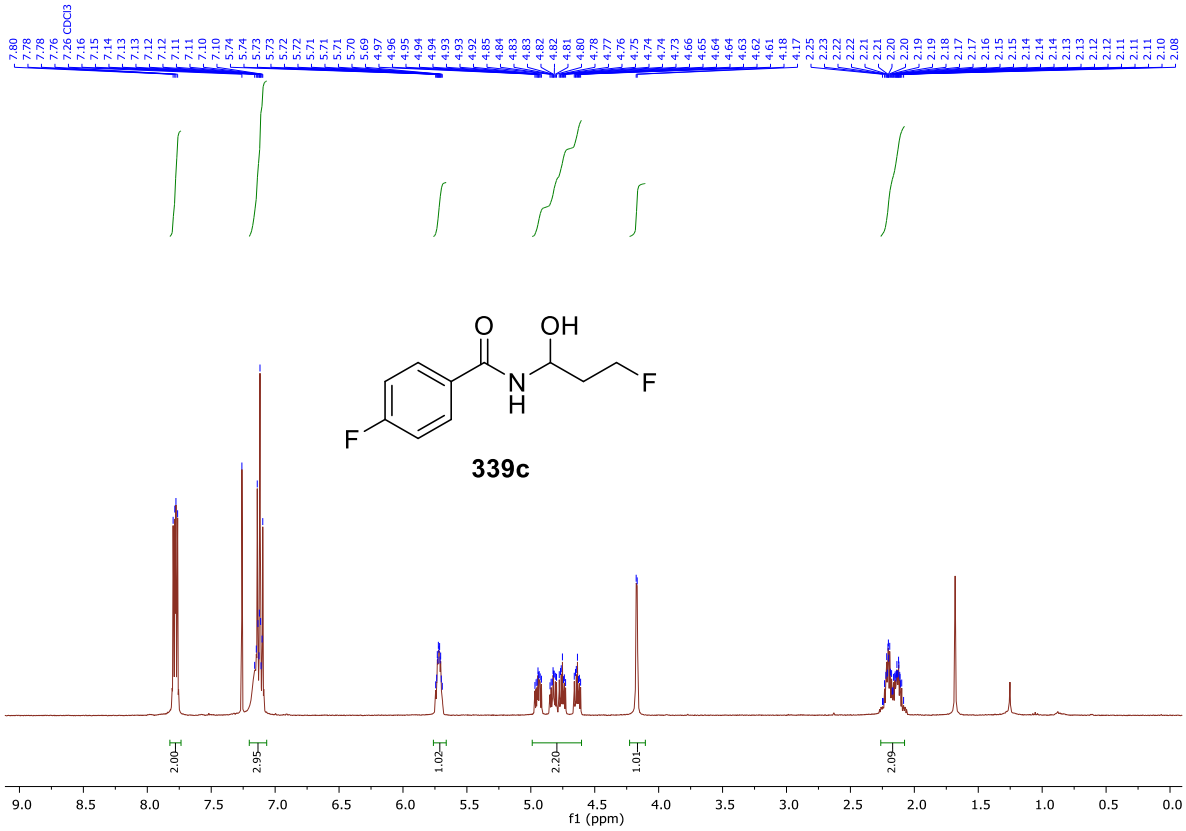
^{13}C-NMR (101 MHz, $CDCl_3$)



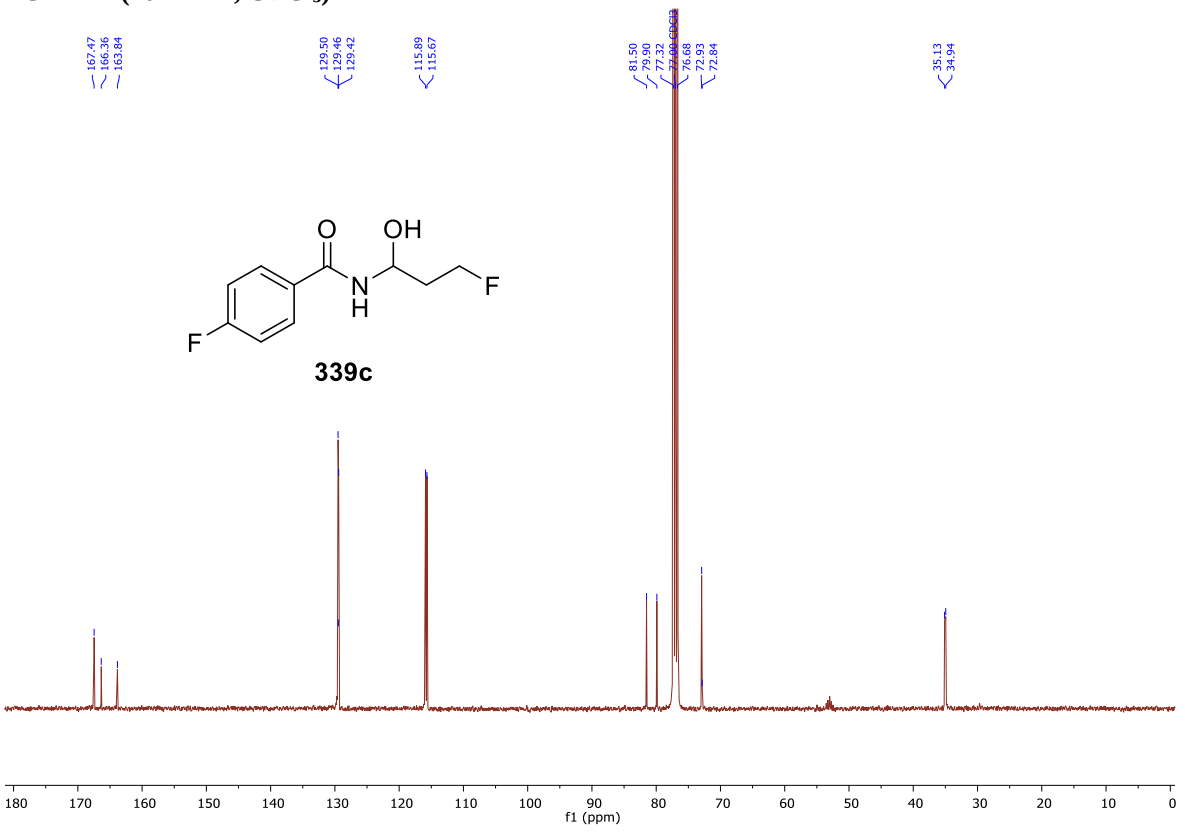
^{19}F-NMR (376 MHz, $CDCl_3$)



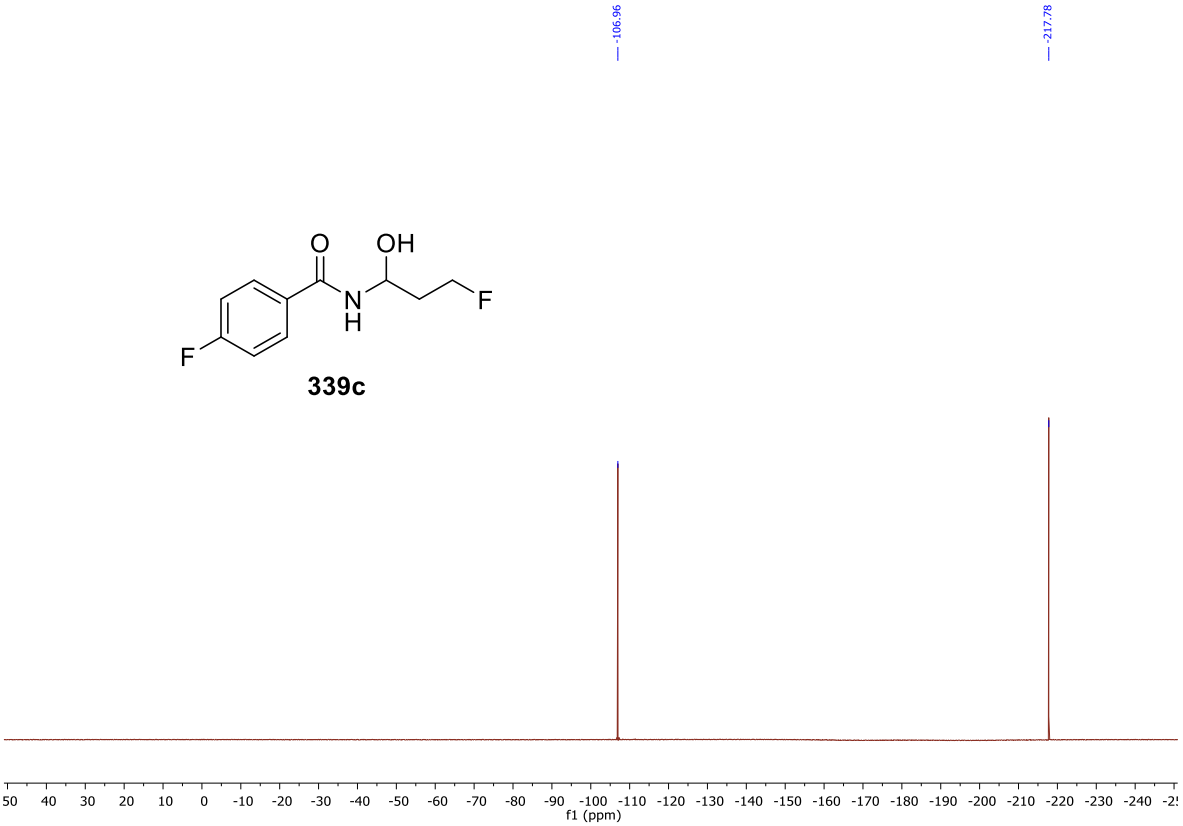
^{1}H-NMR (400 MHz, $CDCl_3$)



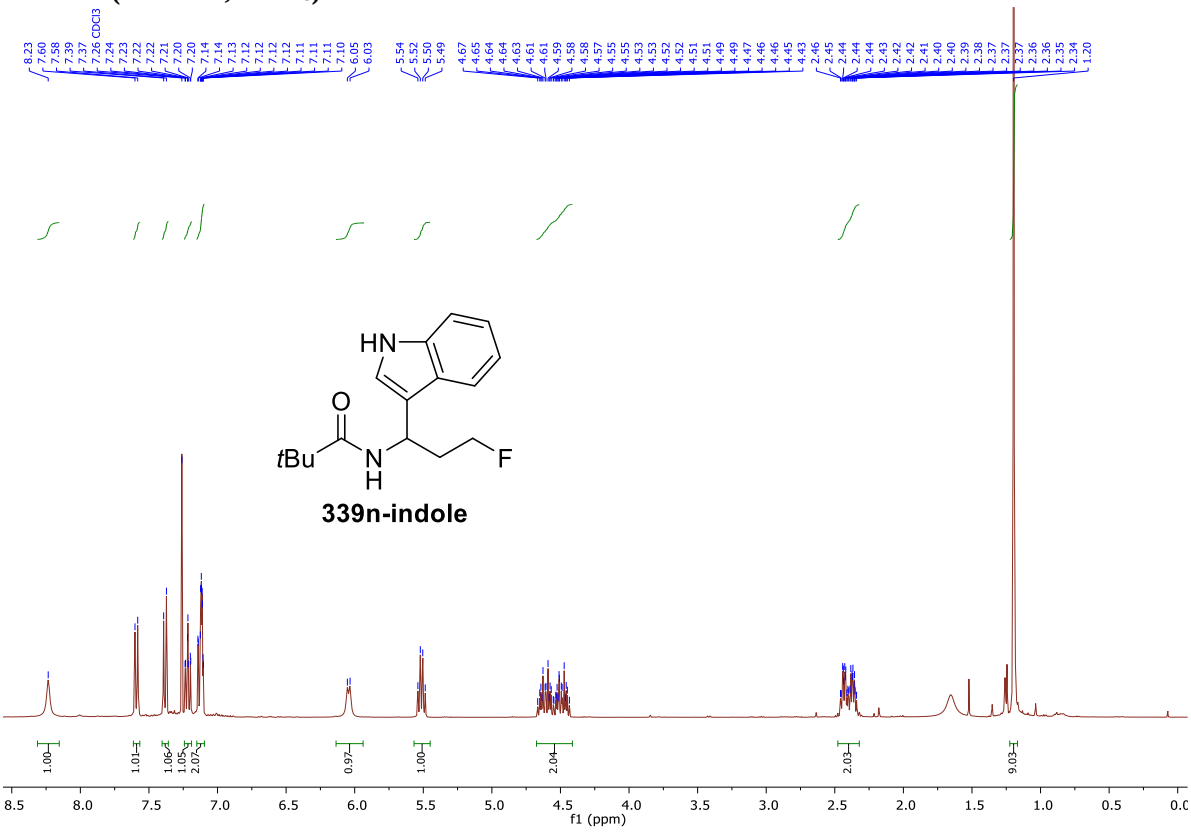
^{13}C-NMR (101 MHz, $CDCl_3$)



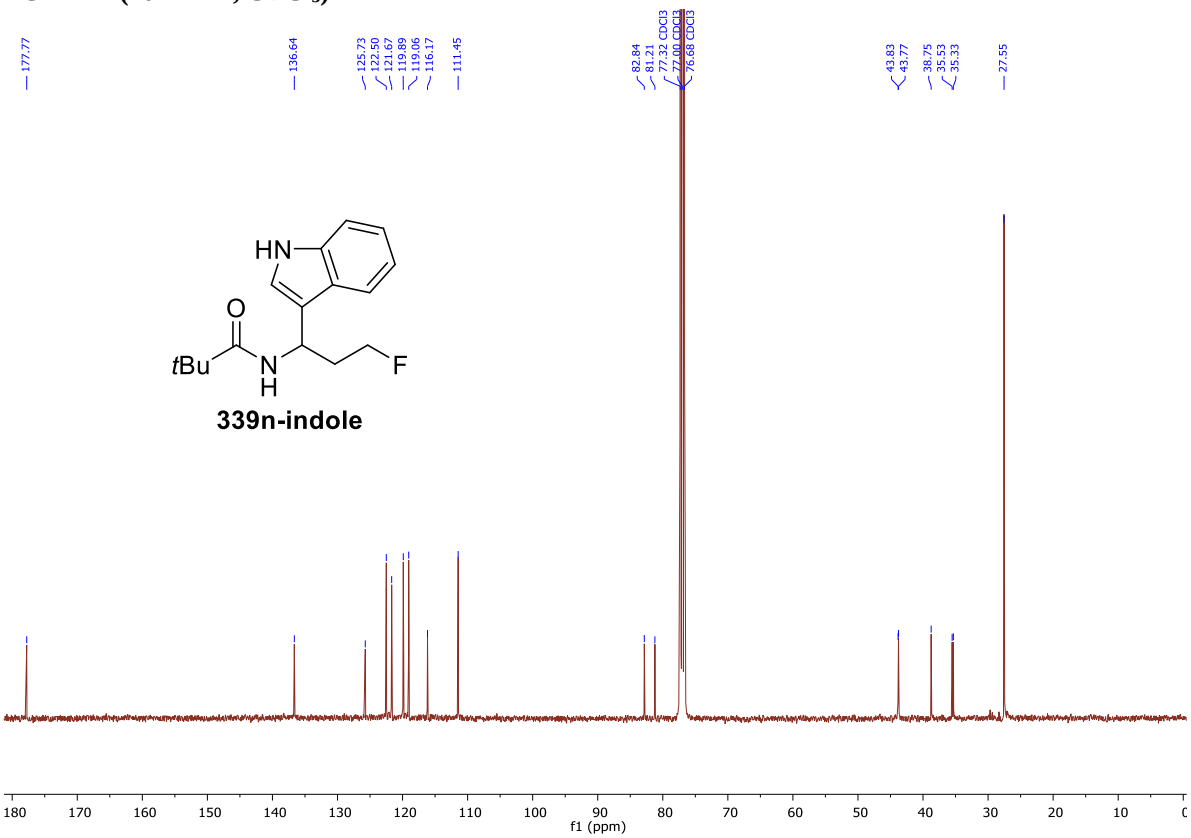
^{19}F-NMR (376 MHz, $CDCl_3$)



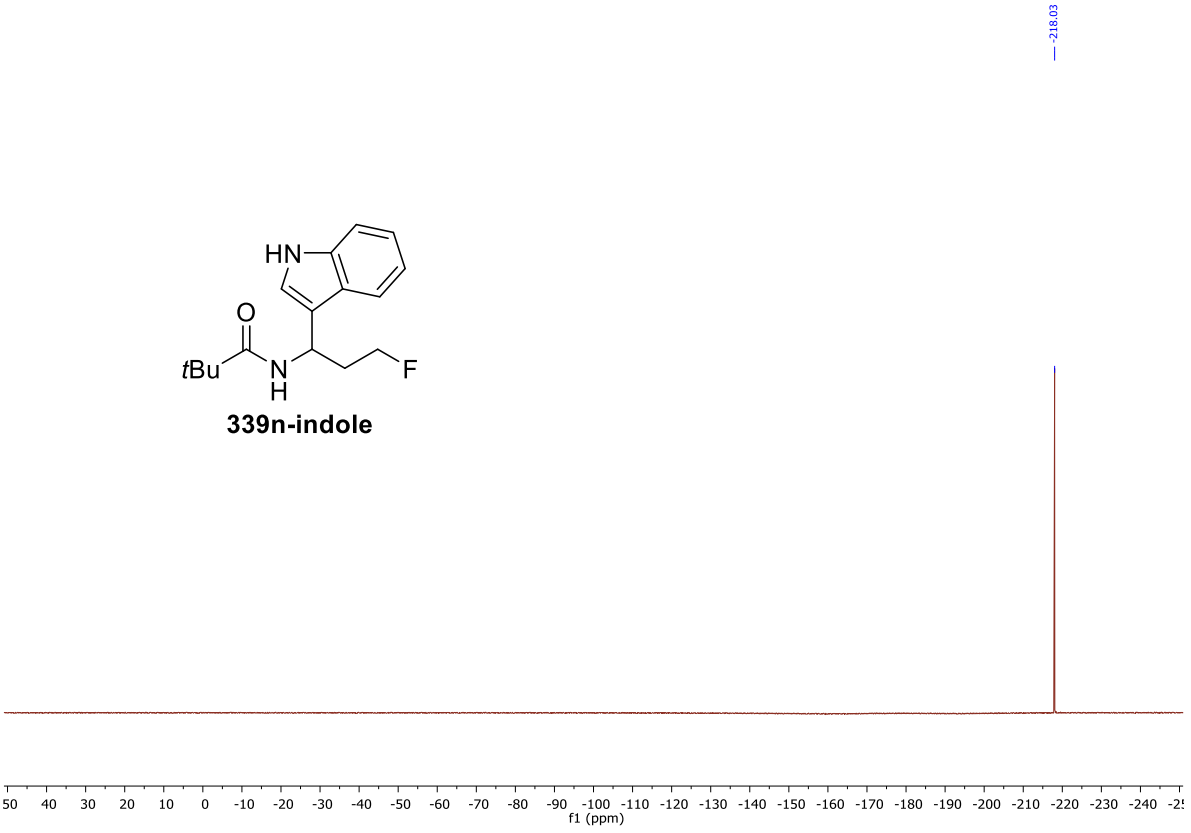
^{1}H-NMR (400 MHz, $CDCl_3$)



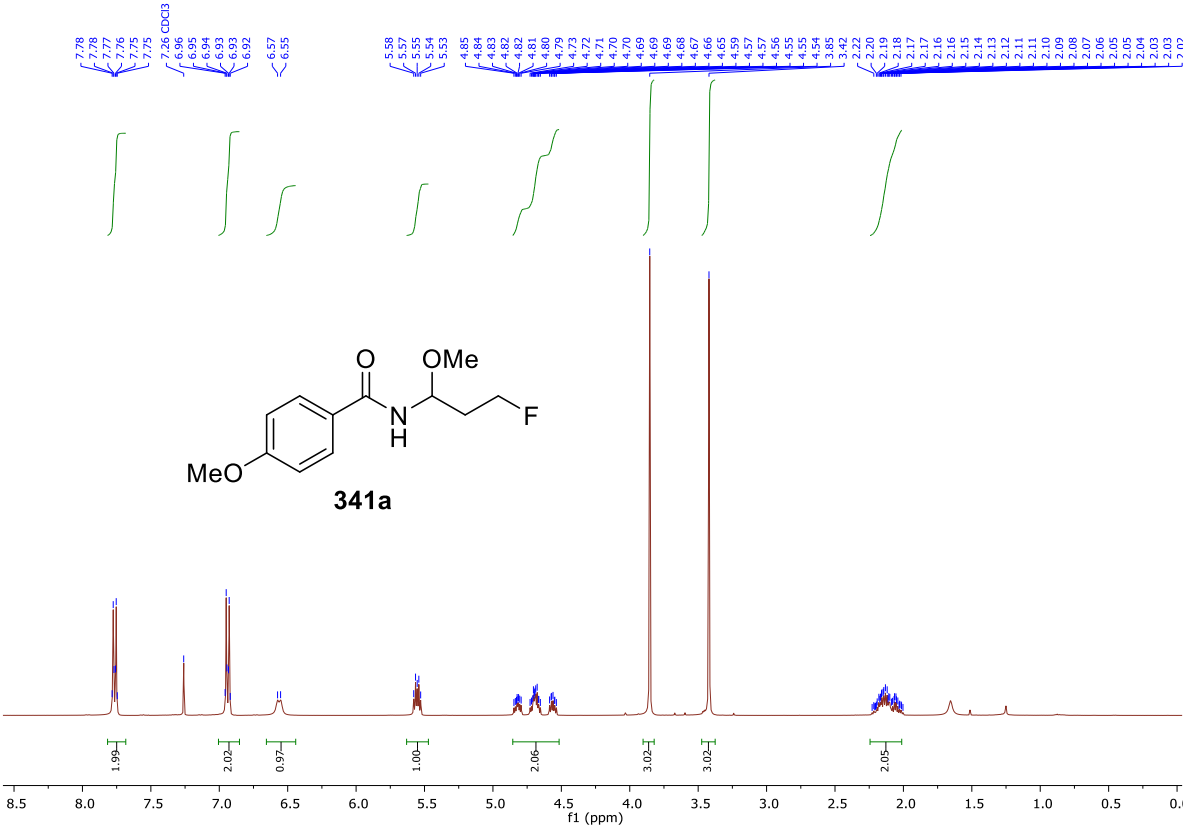
^{13}C-NMR (101 MHz, $CDCl_3$)



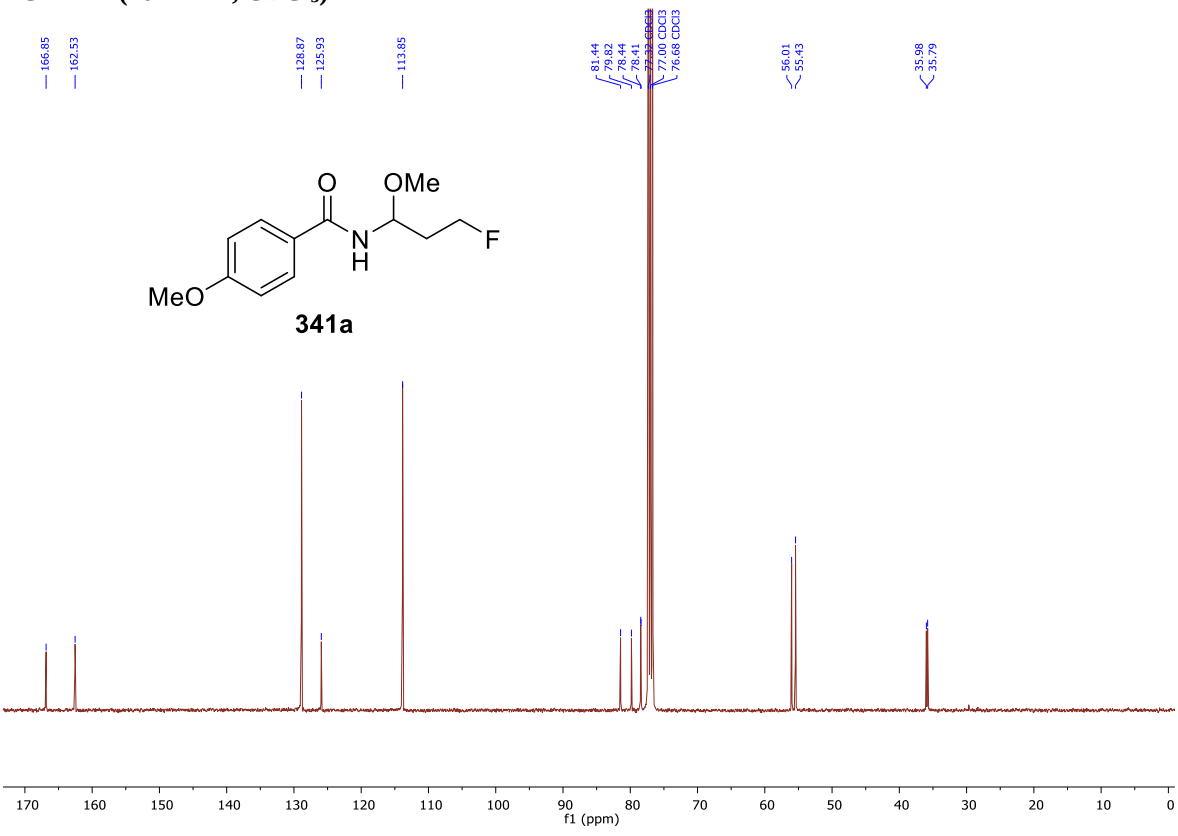
^{19}F-NMR (376 MHz, $CDCl_3$)



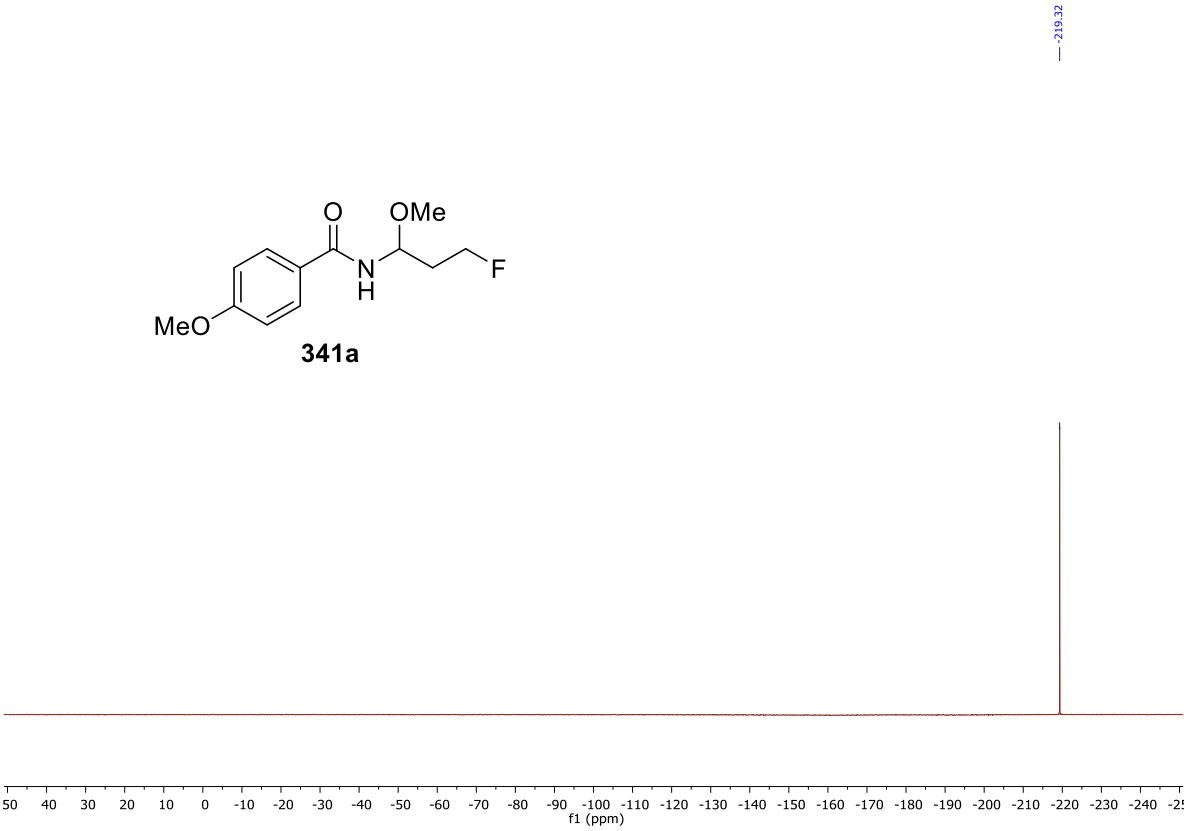
^{1}H-NMR (400 MHz, $CDCl_3$)



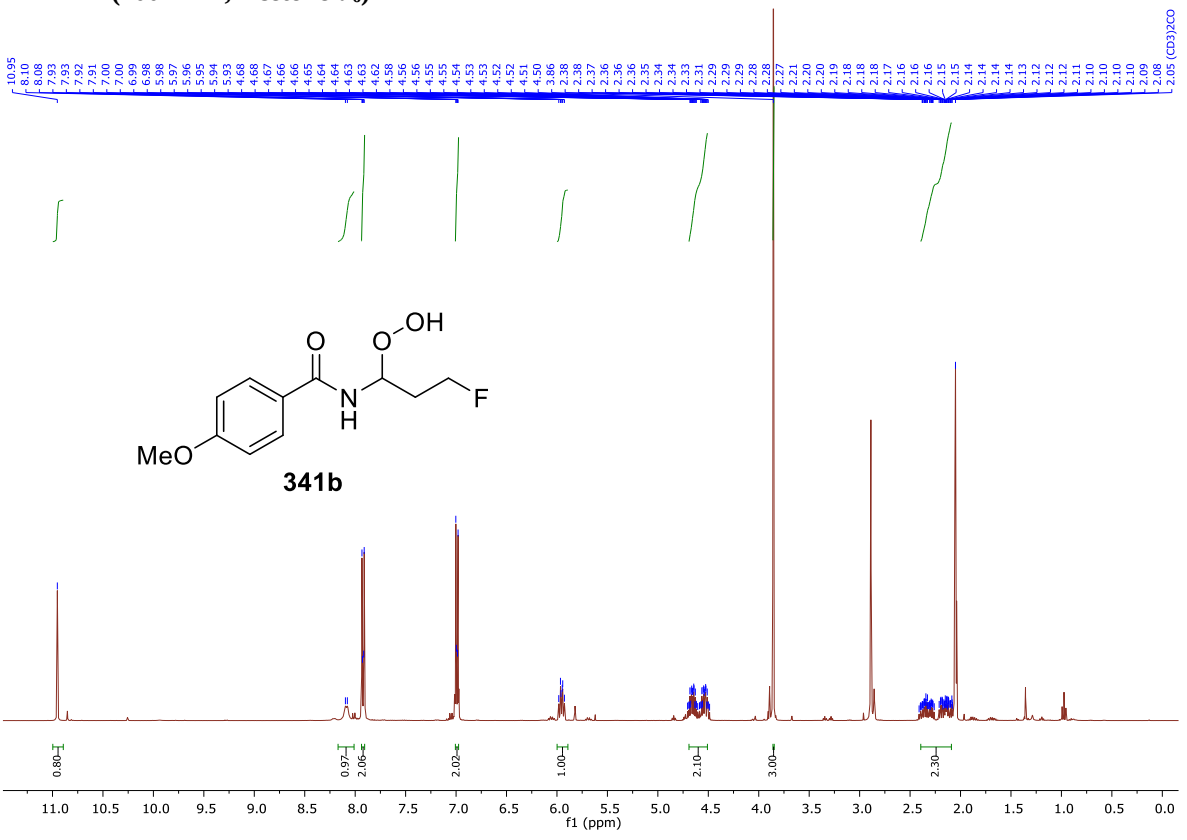
^{13}C-NMR (101 MHz, $CDCl_3$)



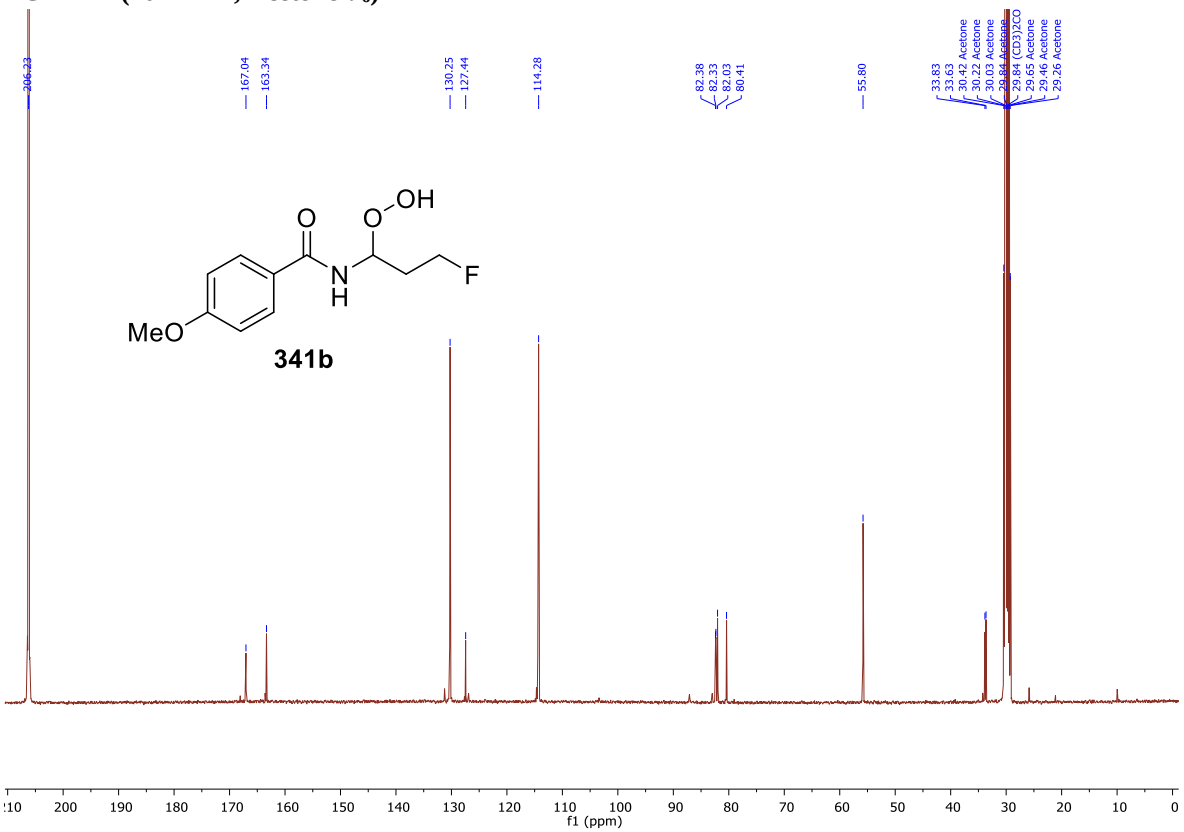
^{19}F-NMR (376 MHz, $CDCl_3$)



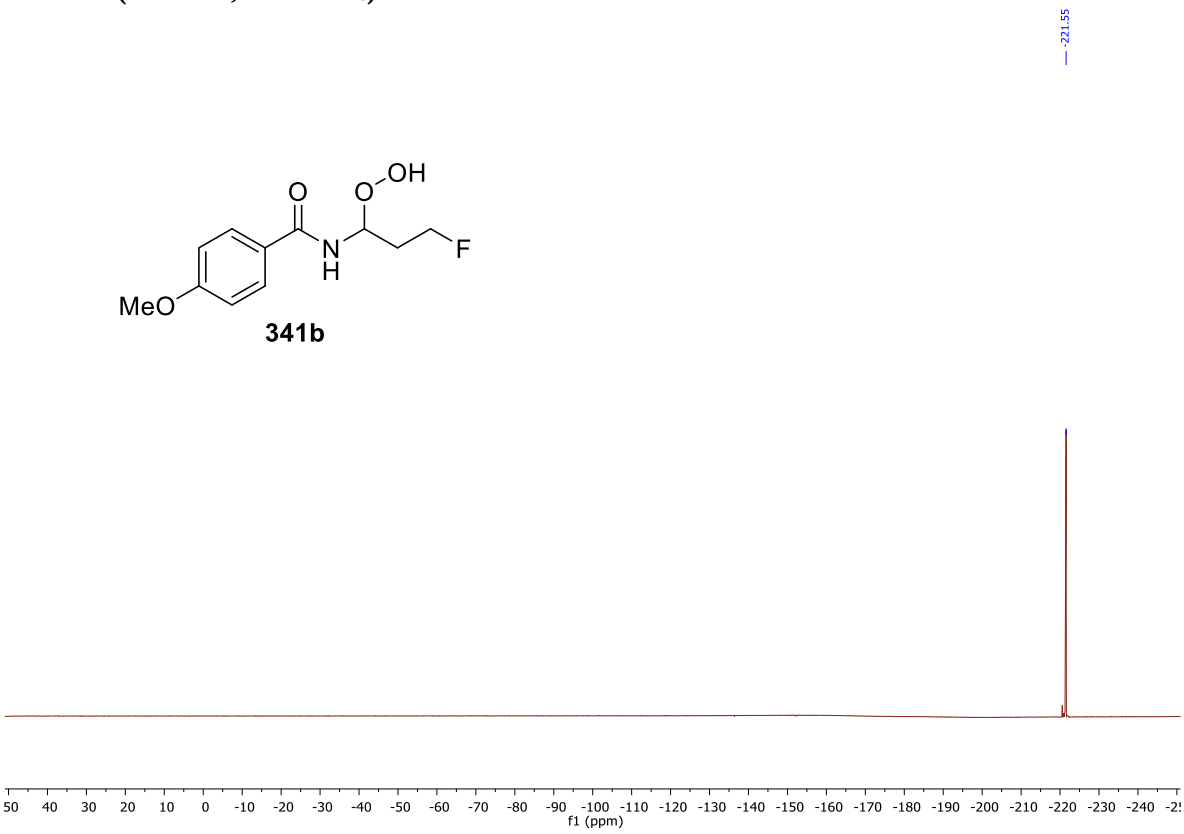
^{1}H-NMR (400 MHz, Acetone-d_6)



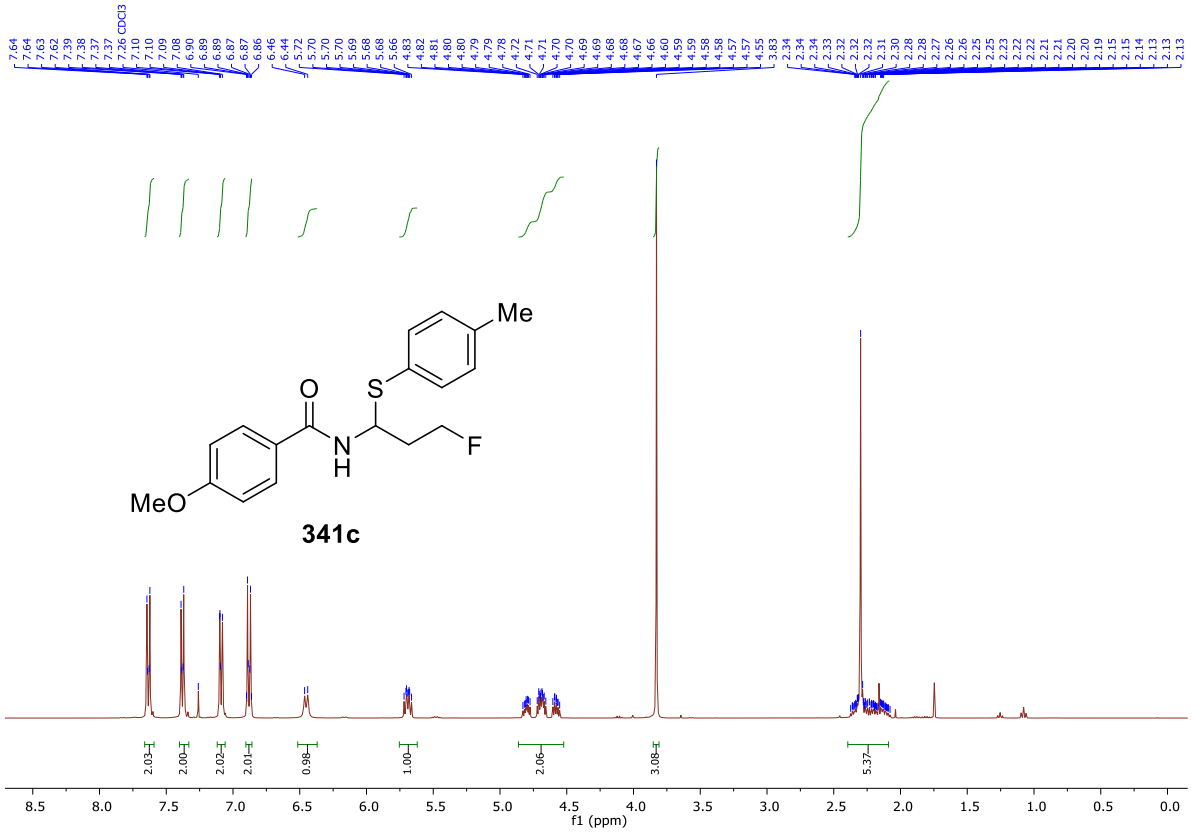
^{13}C-NMR (101 MHz, Acetone-d_6)



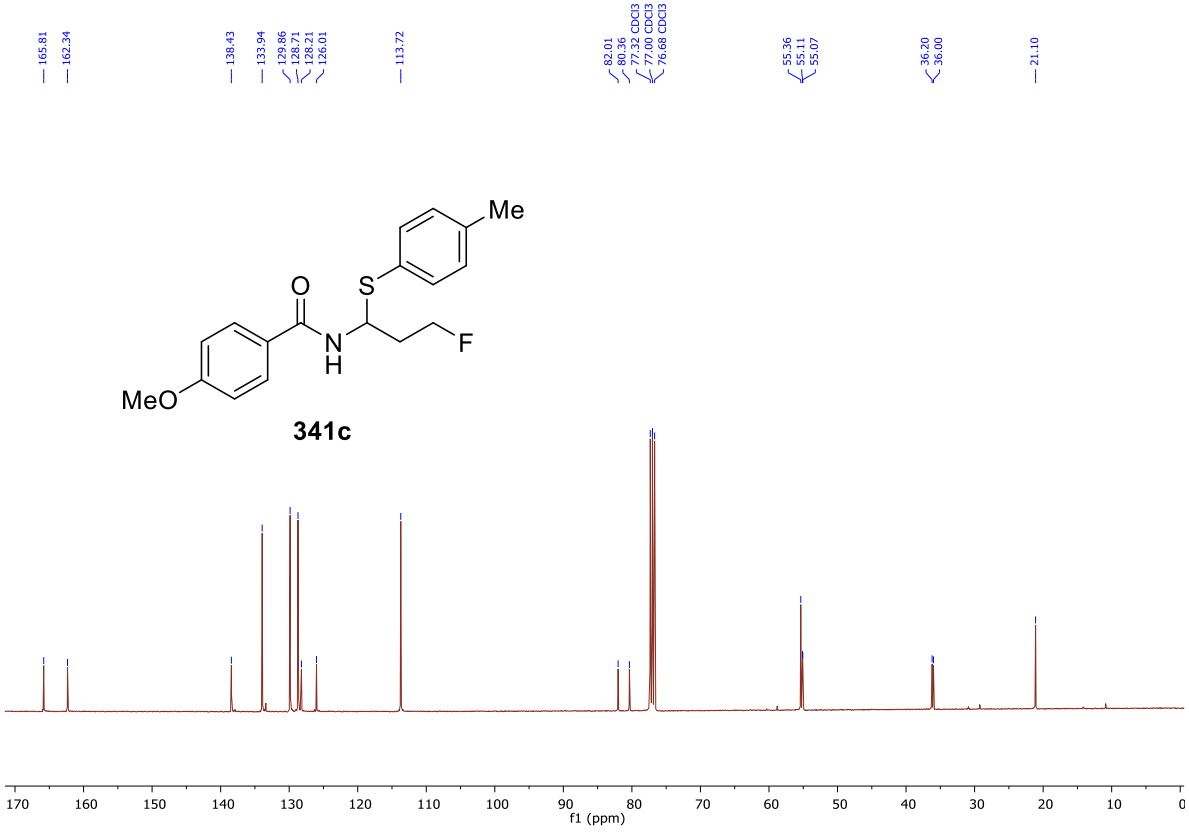
^{19}F-NMR (376 MHz, Acetone-d_6)



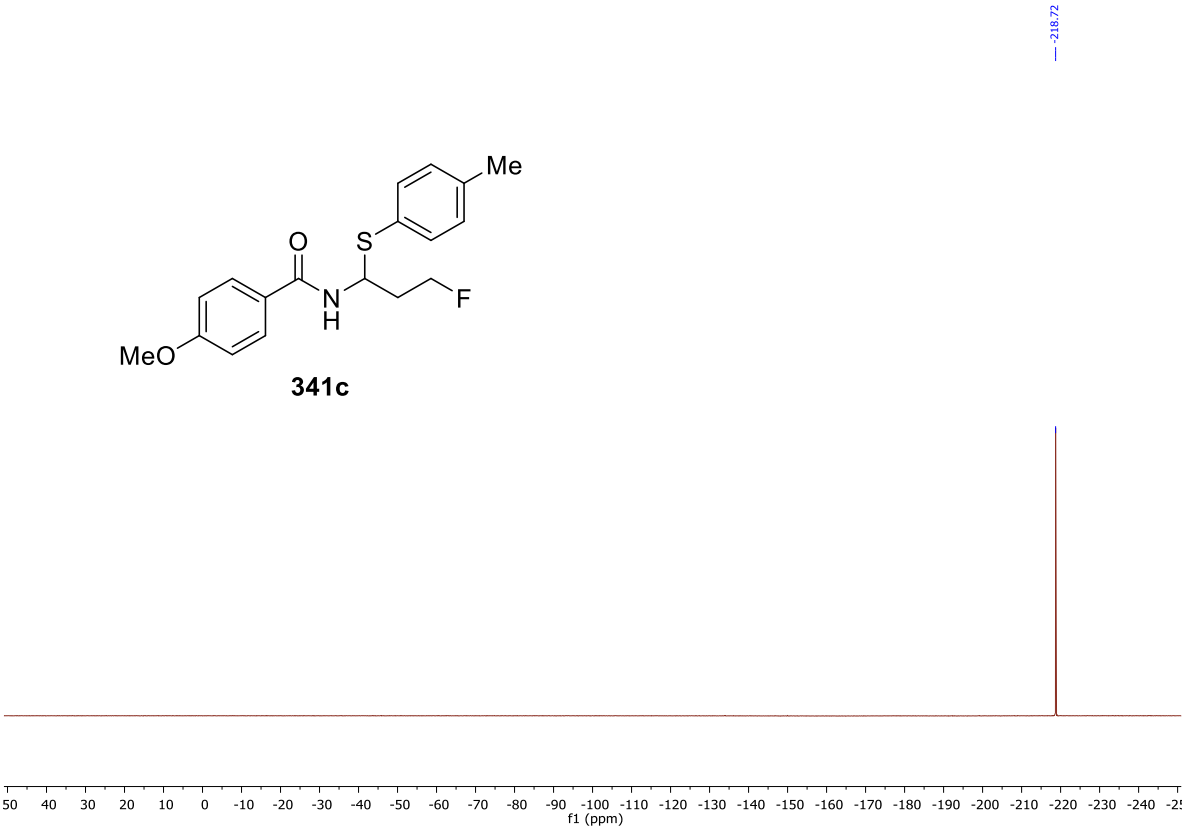
^{1}H-NMR (400 MHz, $CDCl_3$)



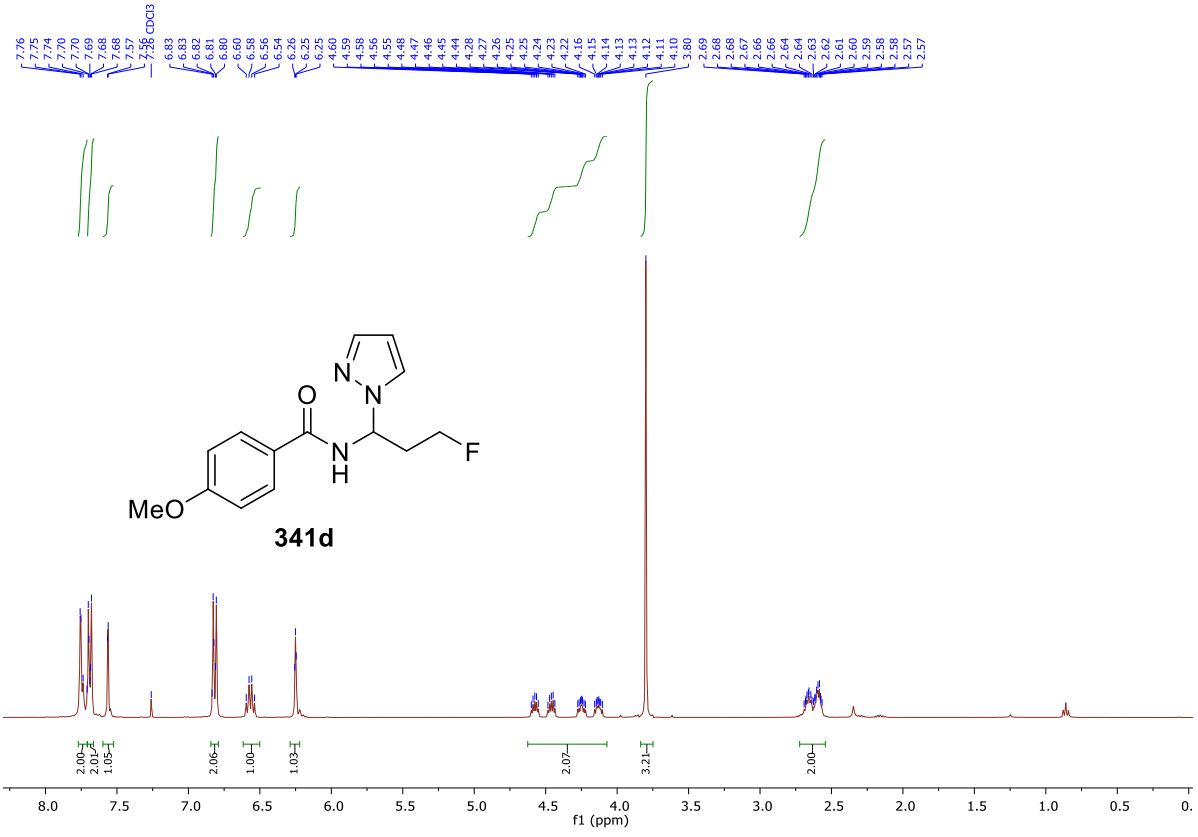
^{13}C-NMR (101 MHz, $CDCl_3$)



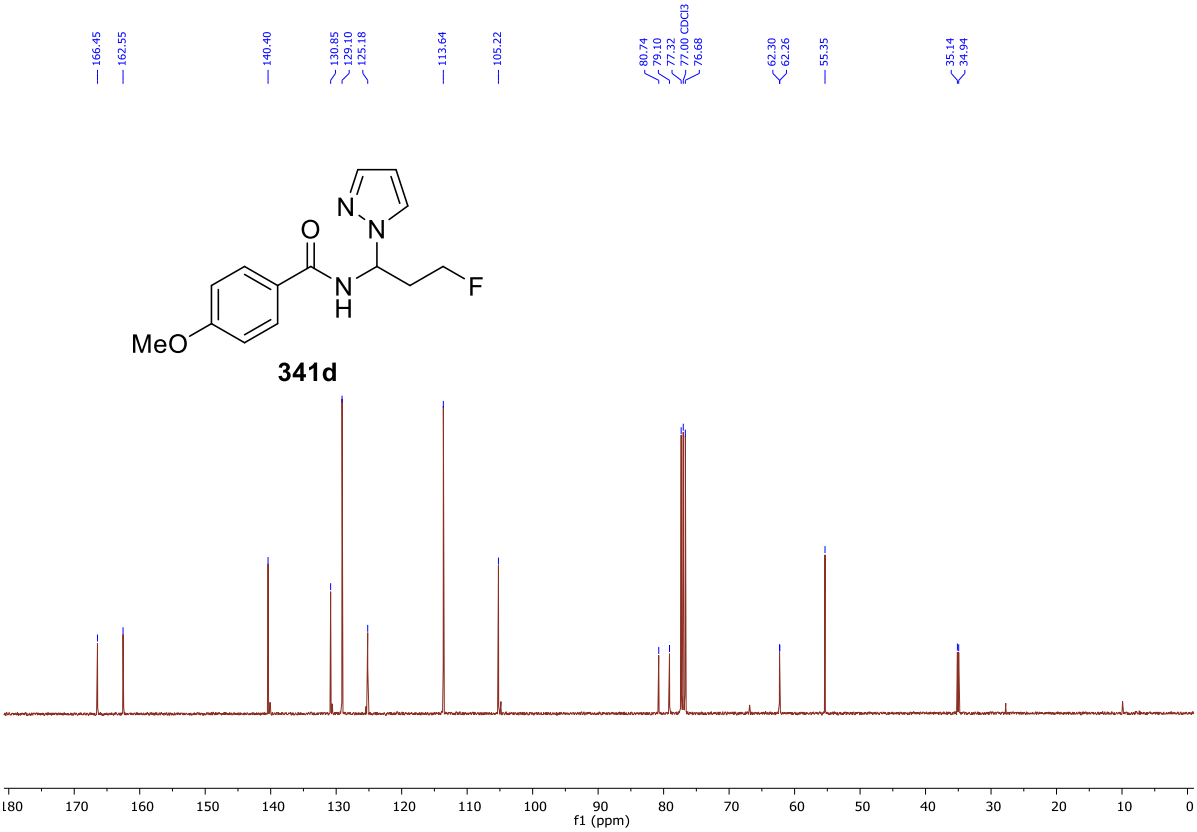
^{19}F-NMR (376 MHz, $CDCl_3$)



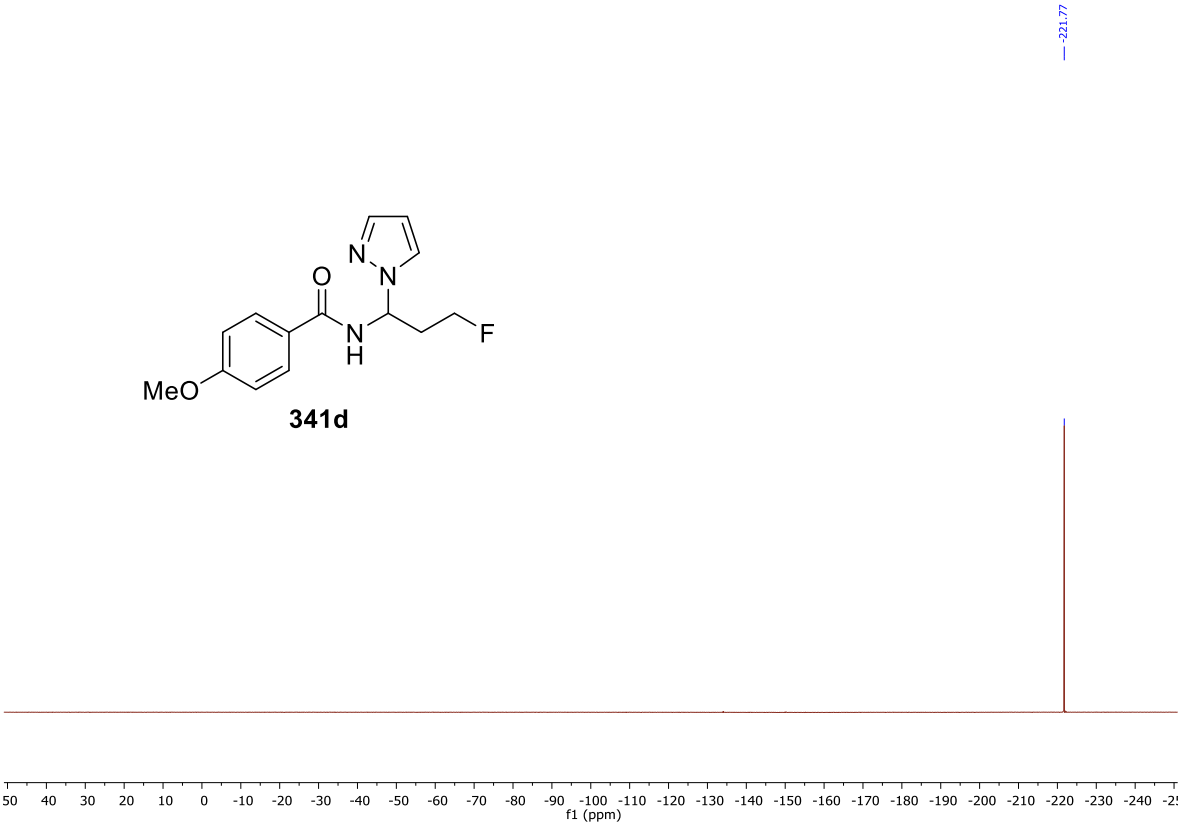
^{1}H-NMR (400 MHz, $CDCl_3$)



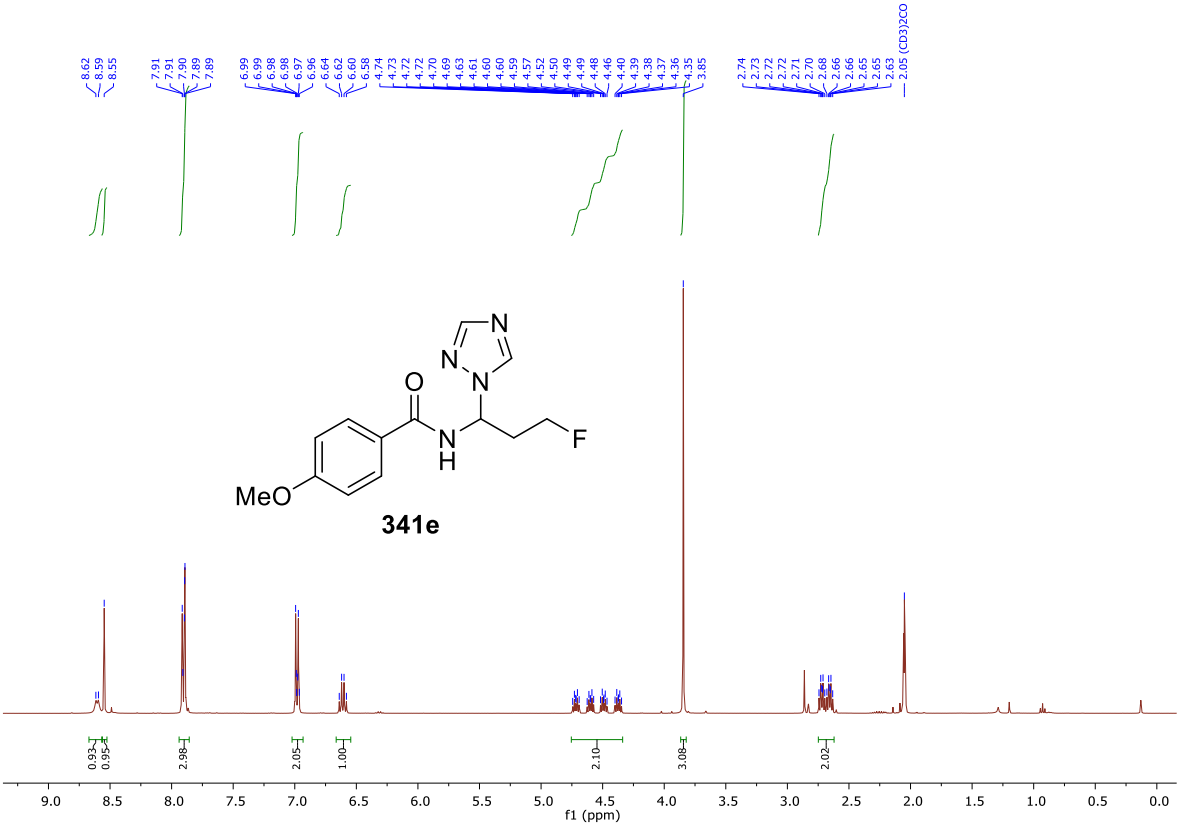
^{13}C-NMR (101 MHz, $CDCl_3$)



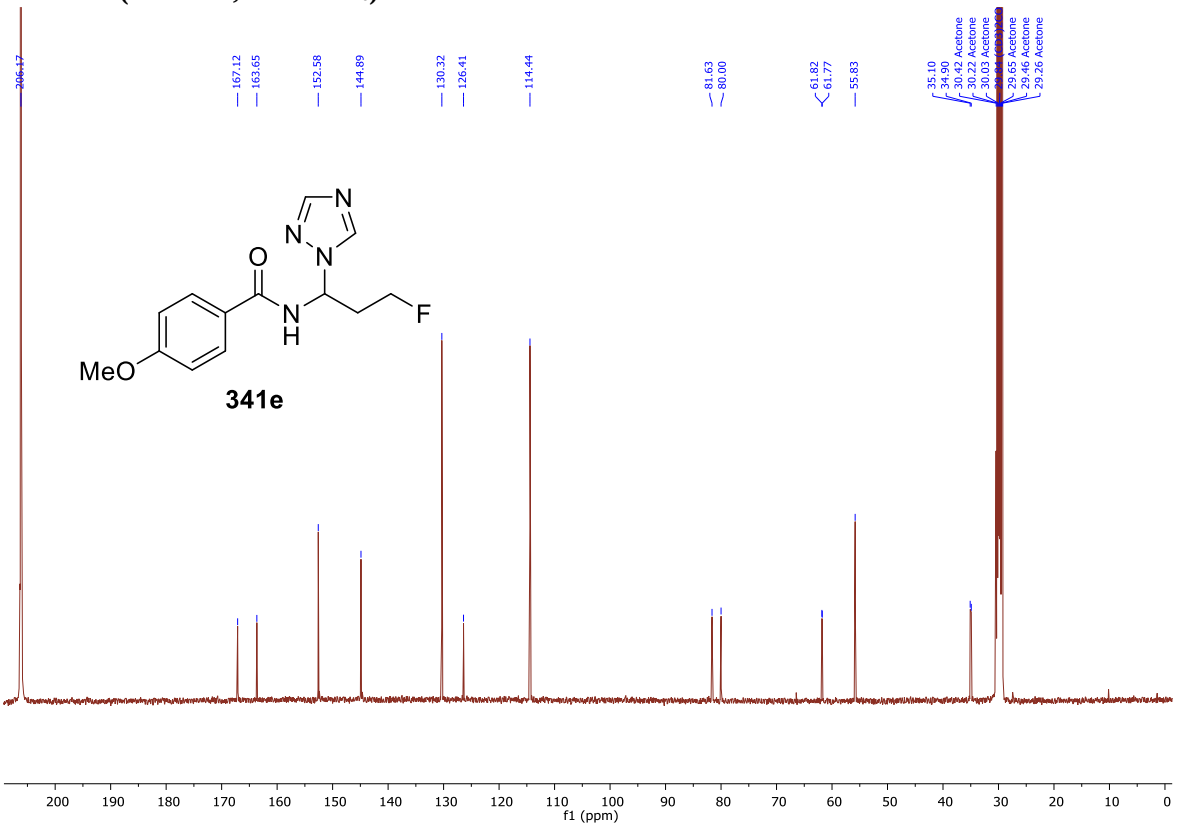
^{19}F-NMR (376 MHz, $CDCl_3$)



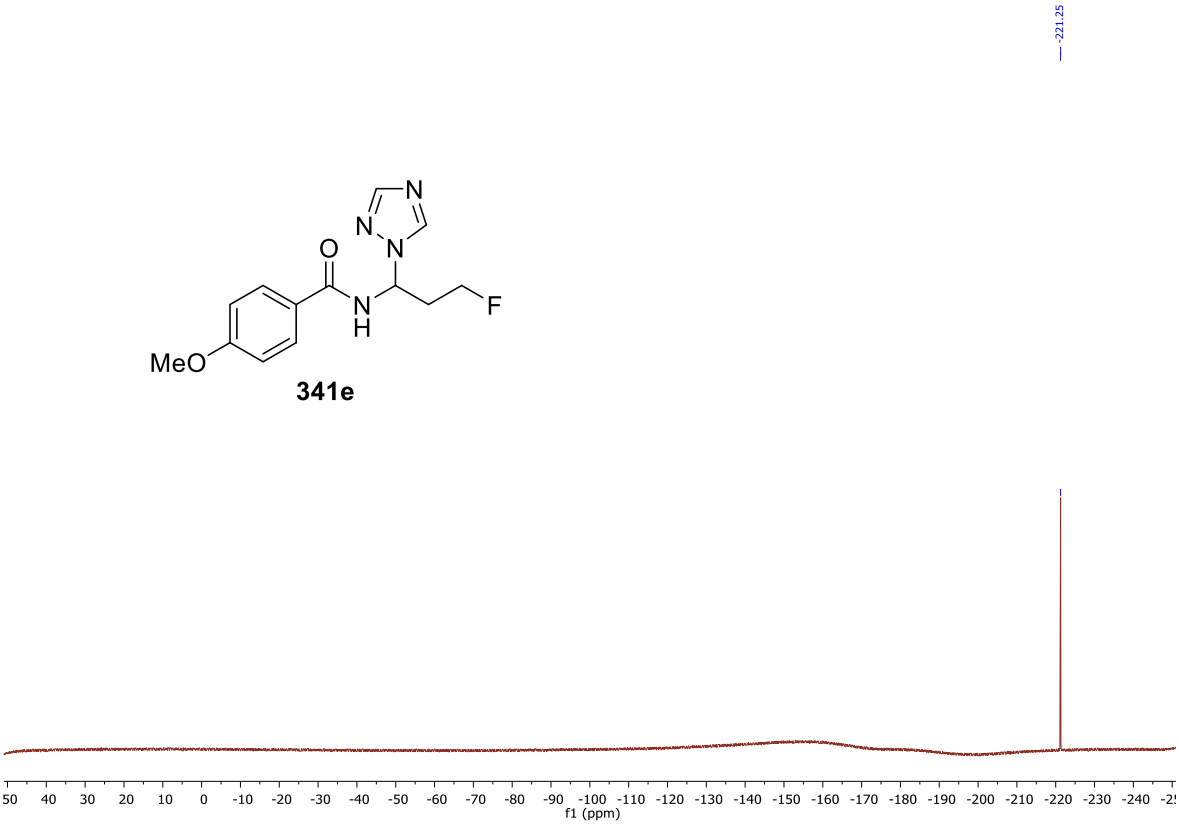
^{1}H-NMR (400 MHz, Acetone-d_6)



^{13}C-NMR (101 MHz, Acetone-d_6)

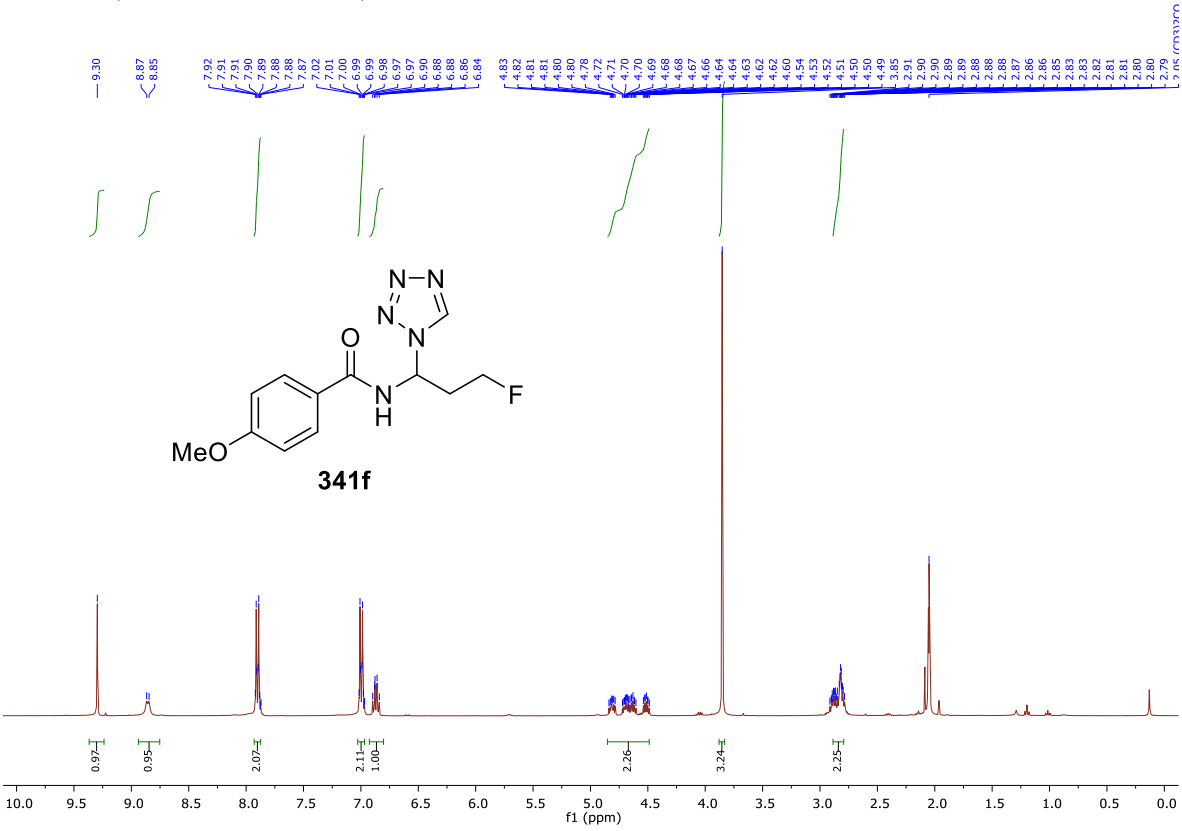


^{19}F NMR (376 MHz, $CDCl_3$)



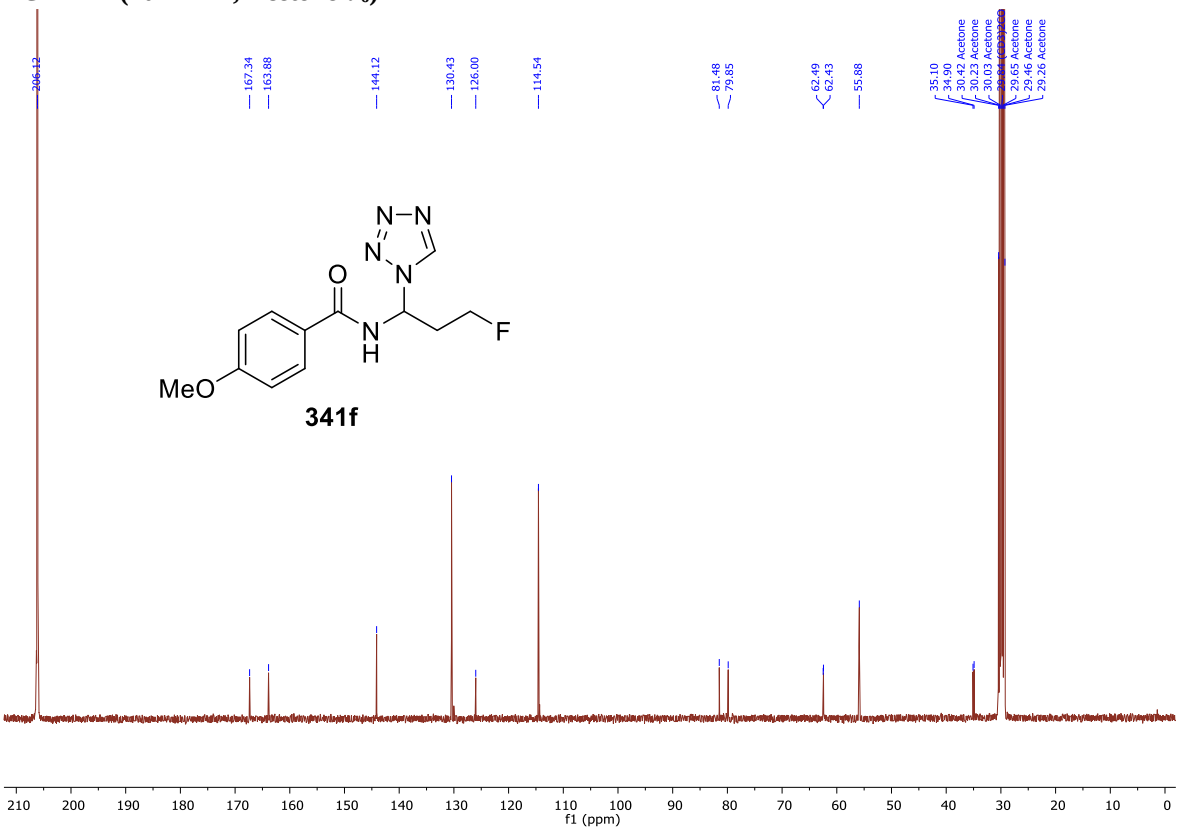
341e

^{1}H-NMR (400 MHz, Acetone-d_6)

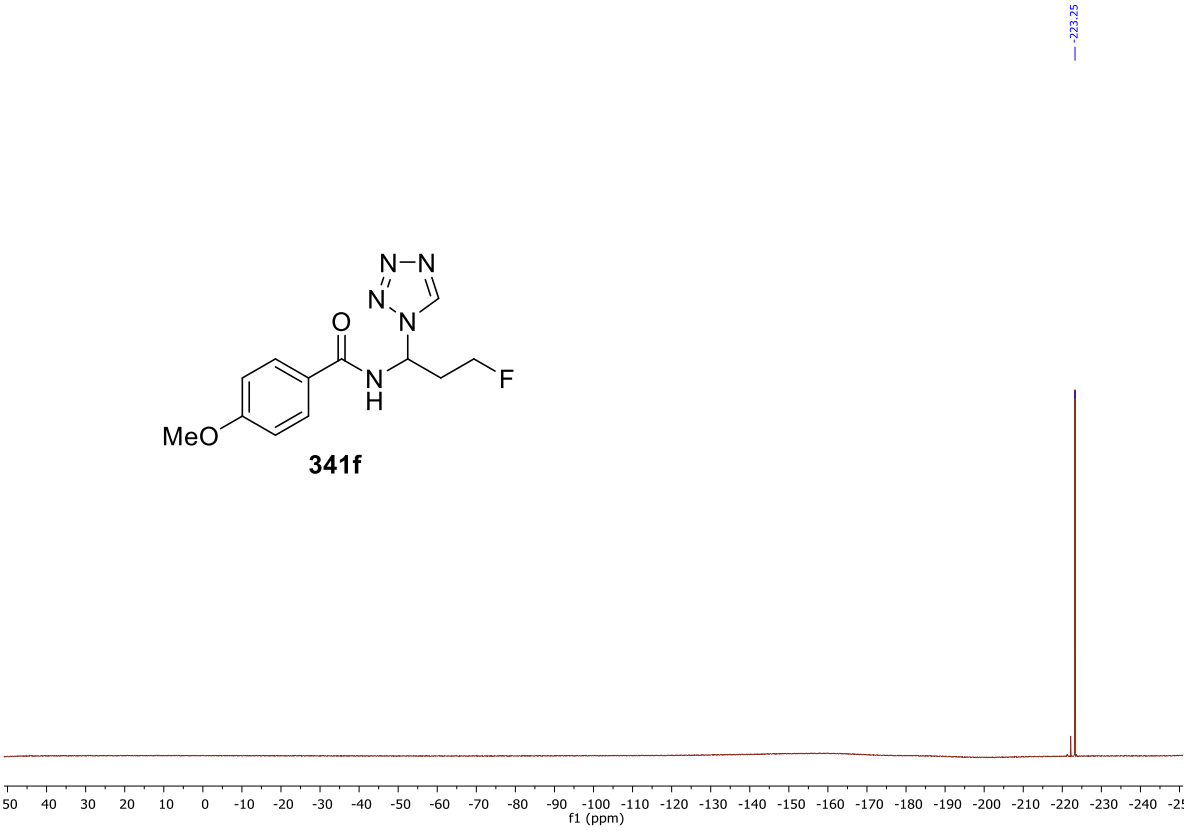


341f

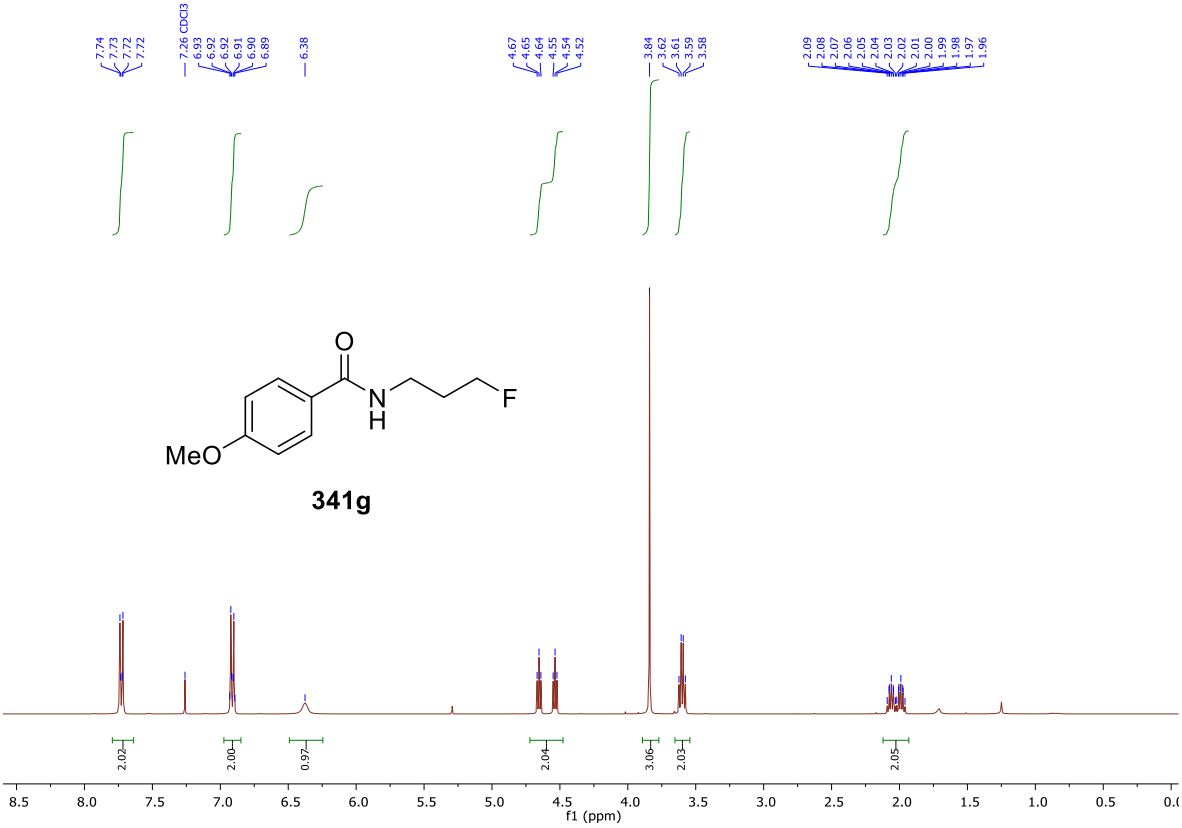
^{13}C-NMR (101 MHz, Acetone-d_6)



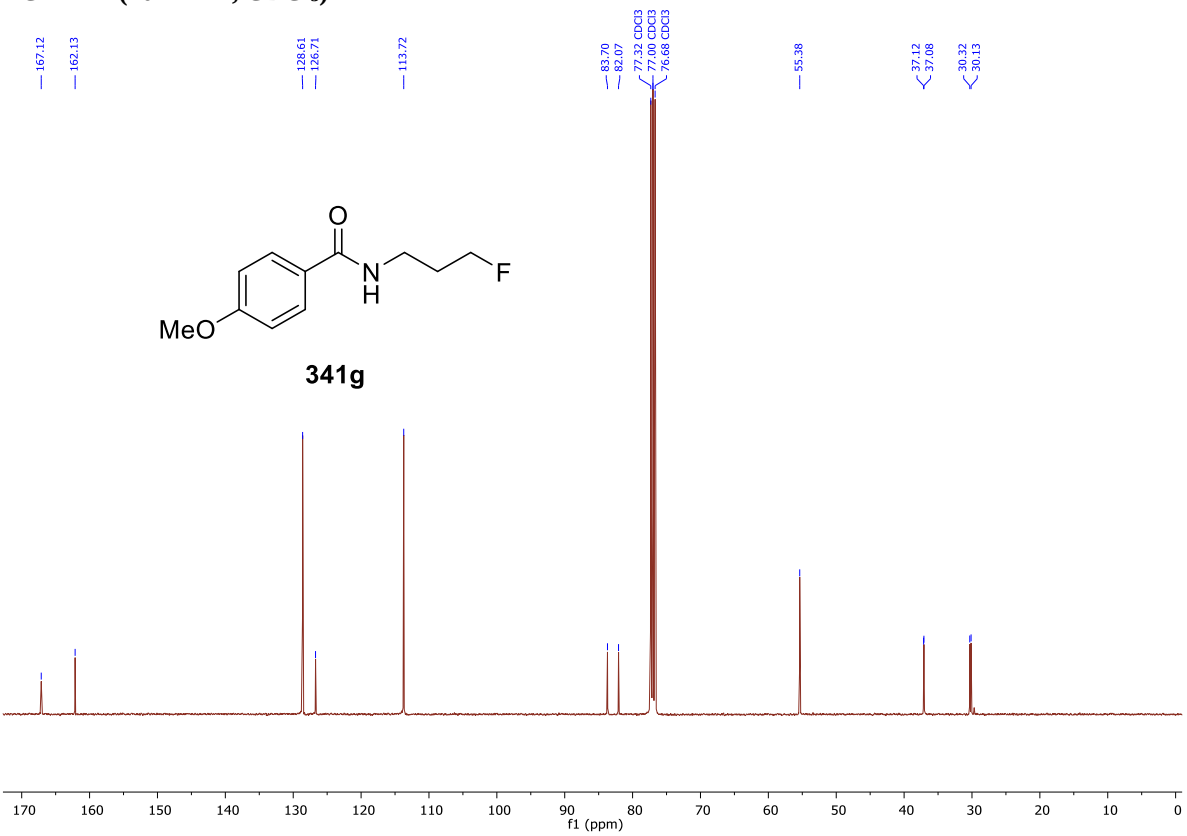
^{19}F NMR (376 MHz, Acetone-d_6)



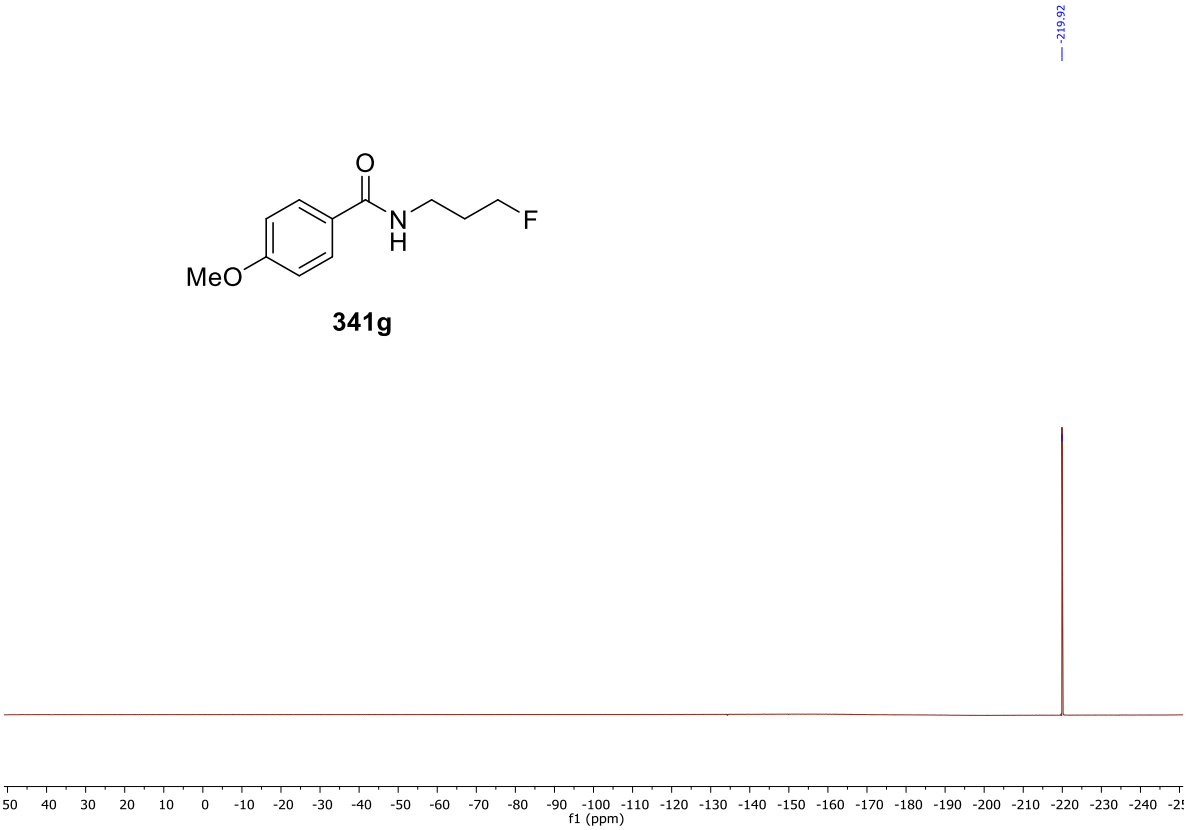
^{1}H-NMR (400 MHz, $CDCl_3$)



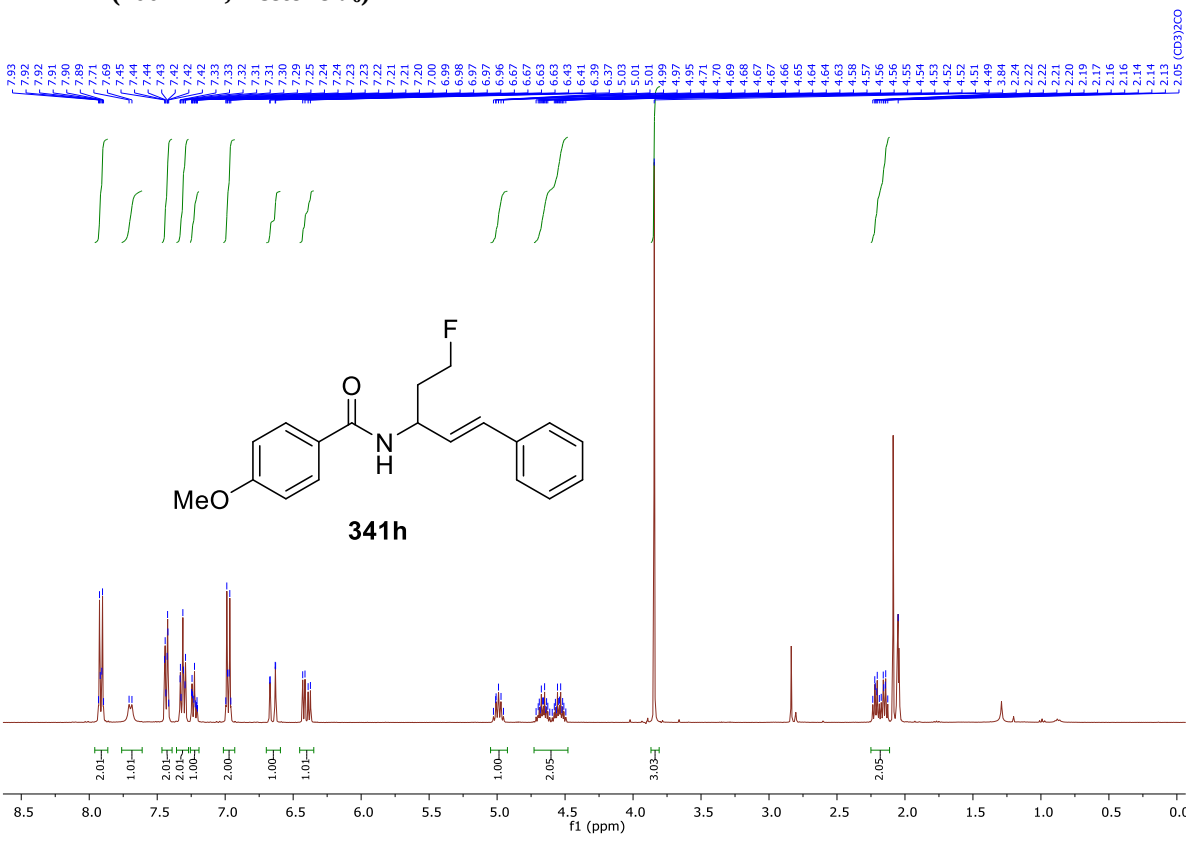
^{13}C-NMR (101 MHz, $CDCl_3$)



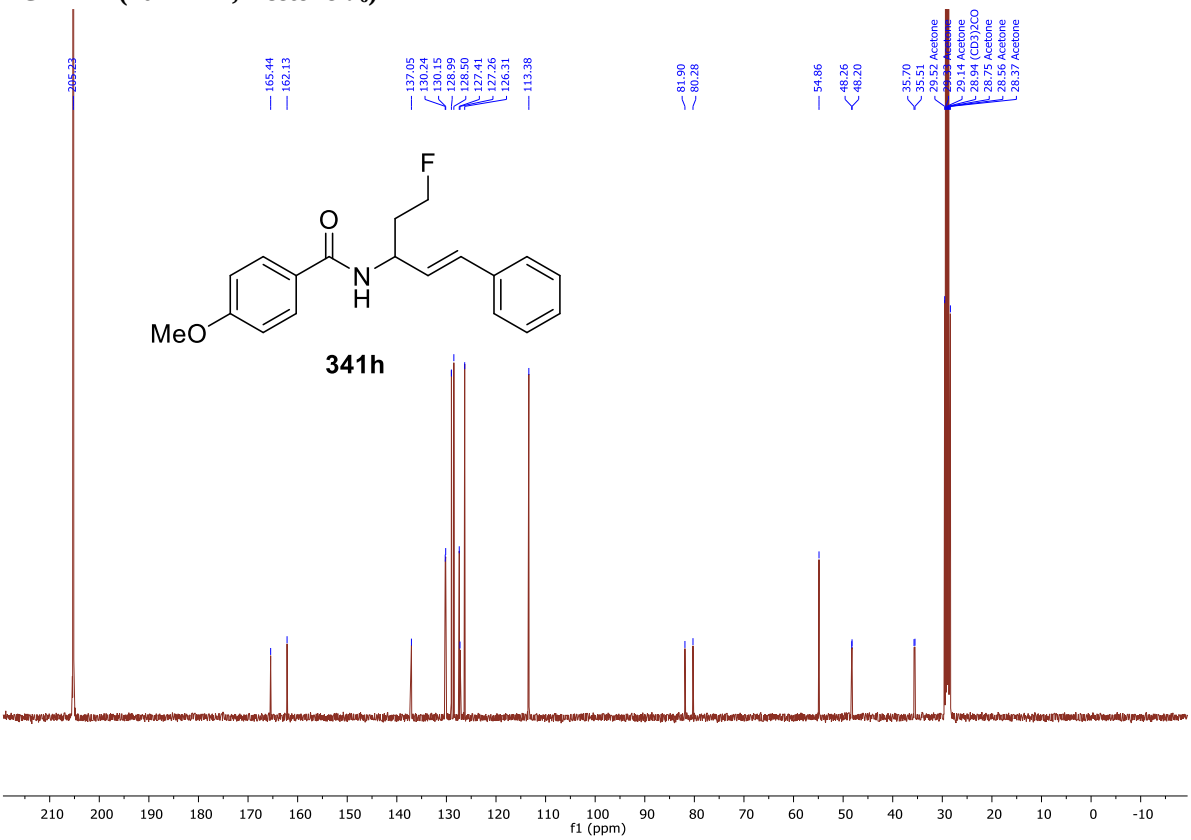
^{19}F-NMR (376 MHz, $CDCl_3$)



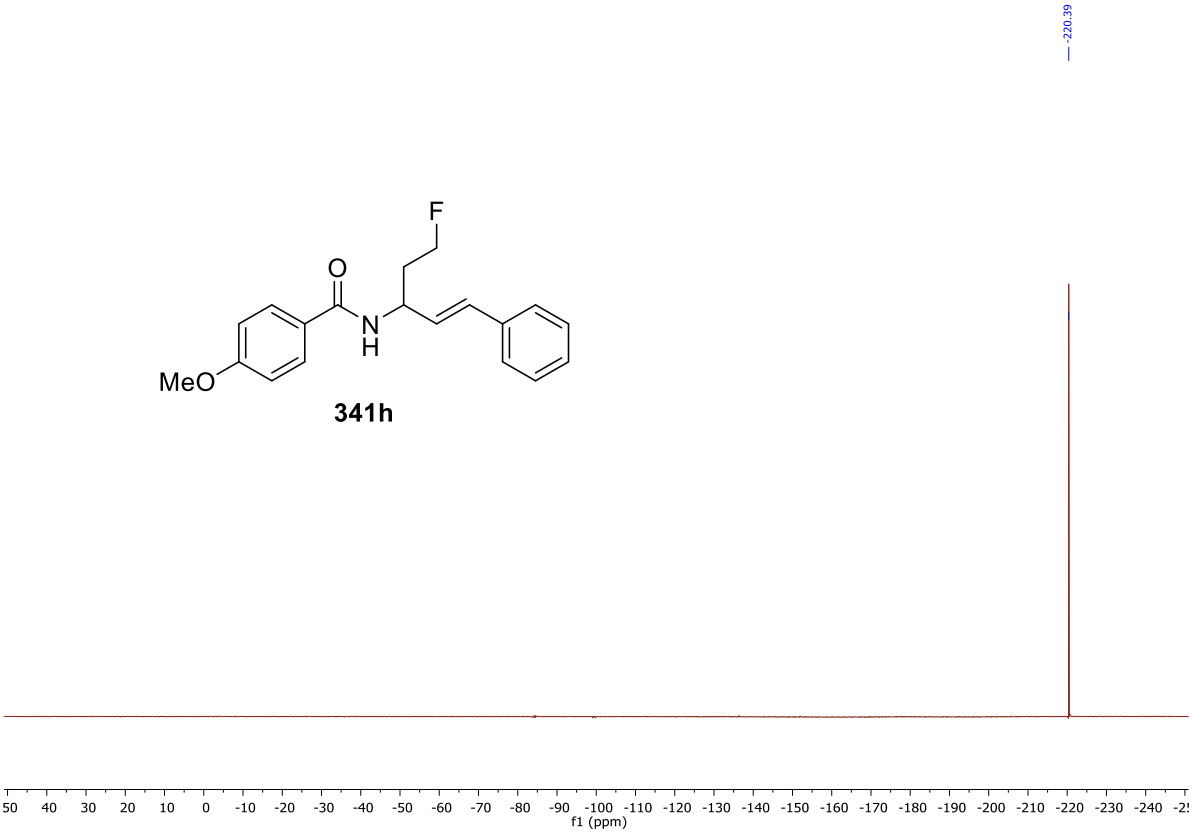
^{1}H-NMR (400 MHz, Acetone-d_6)



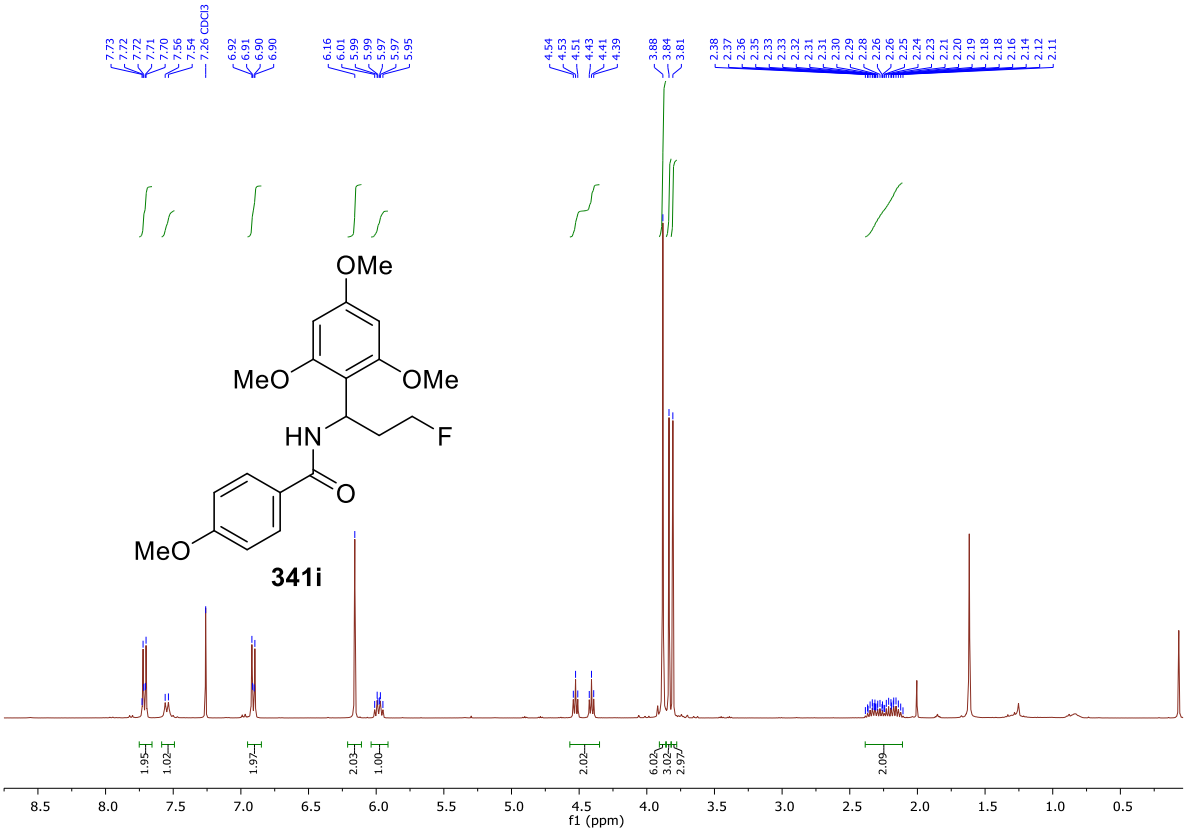
^{13}C-NMR (101 MHz, Acetone-d_6)



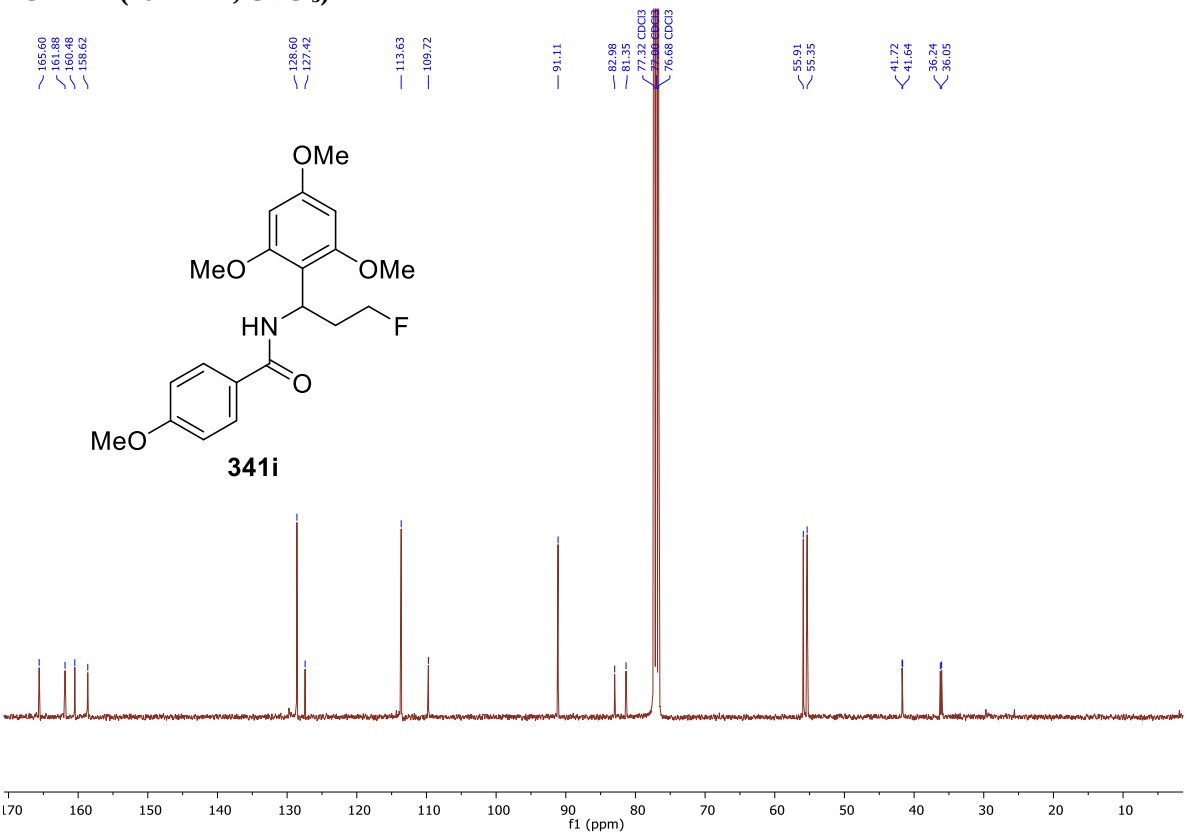
^{19}F-NMR (376 MHz, Acetone-d_6)



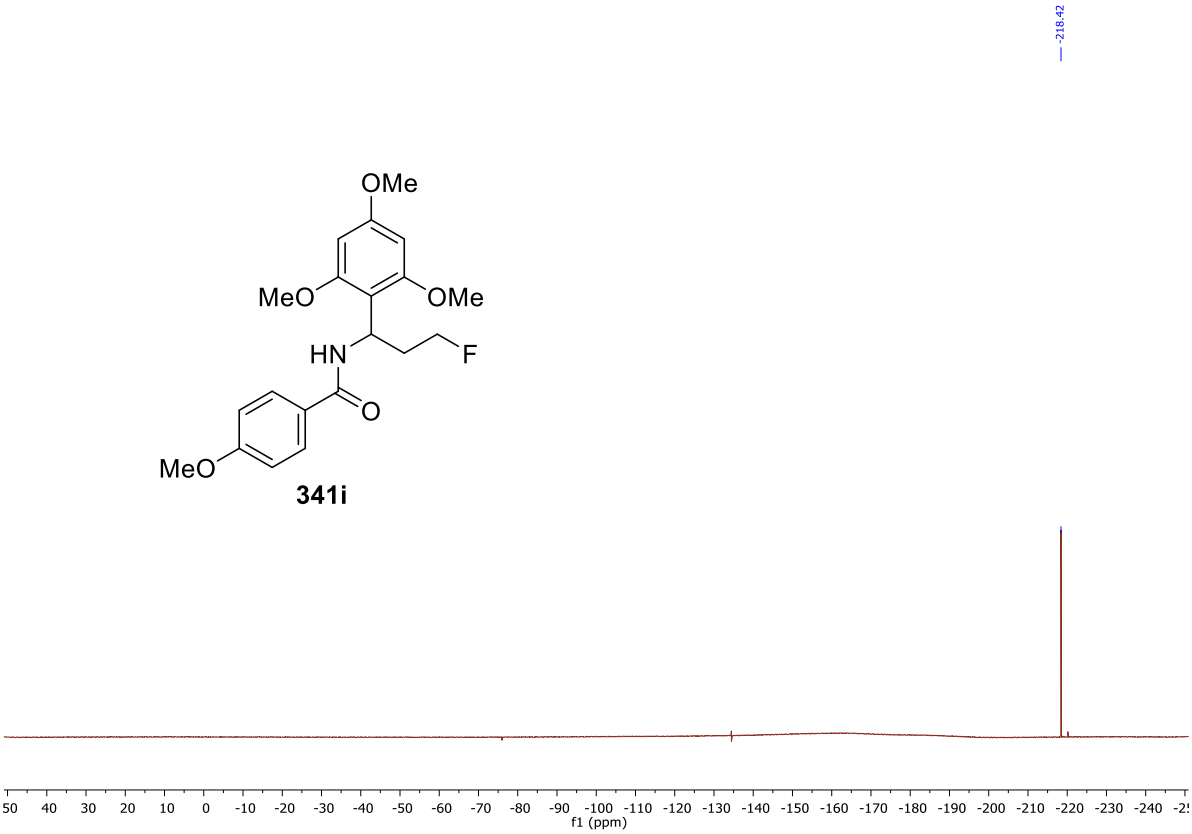
^{1}H-NMR (400 MHz, $CDCl_3$)



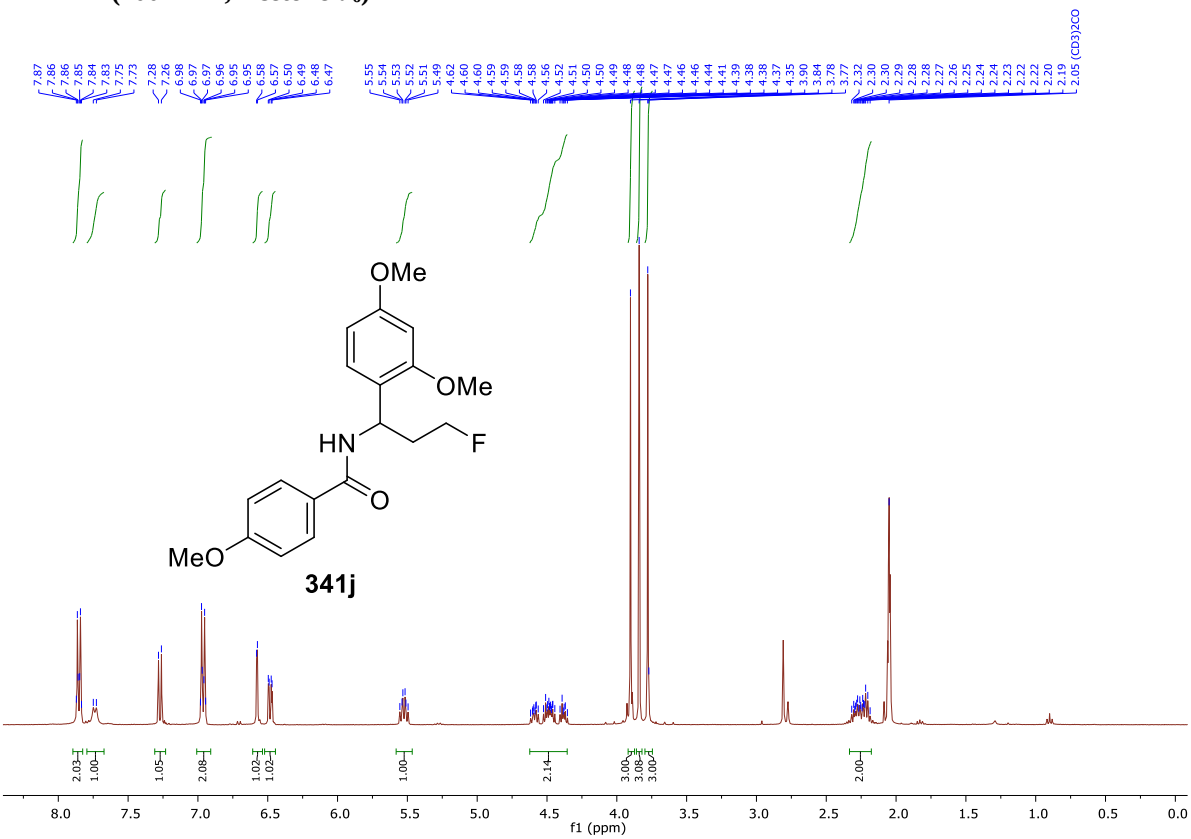
^{13}C-NMR (101 MHz, $CDCl_3$)



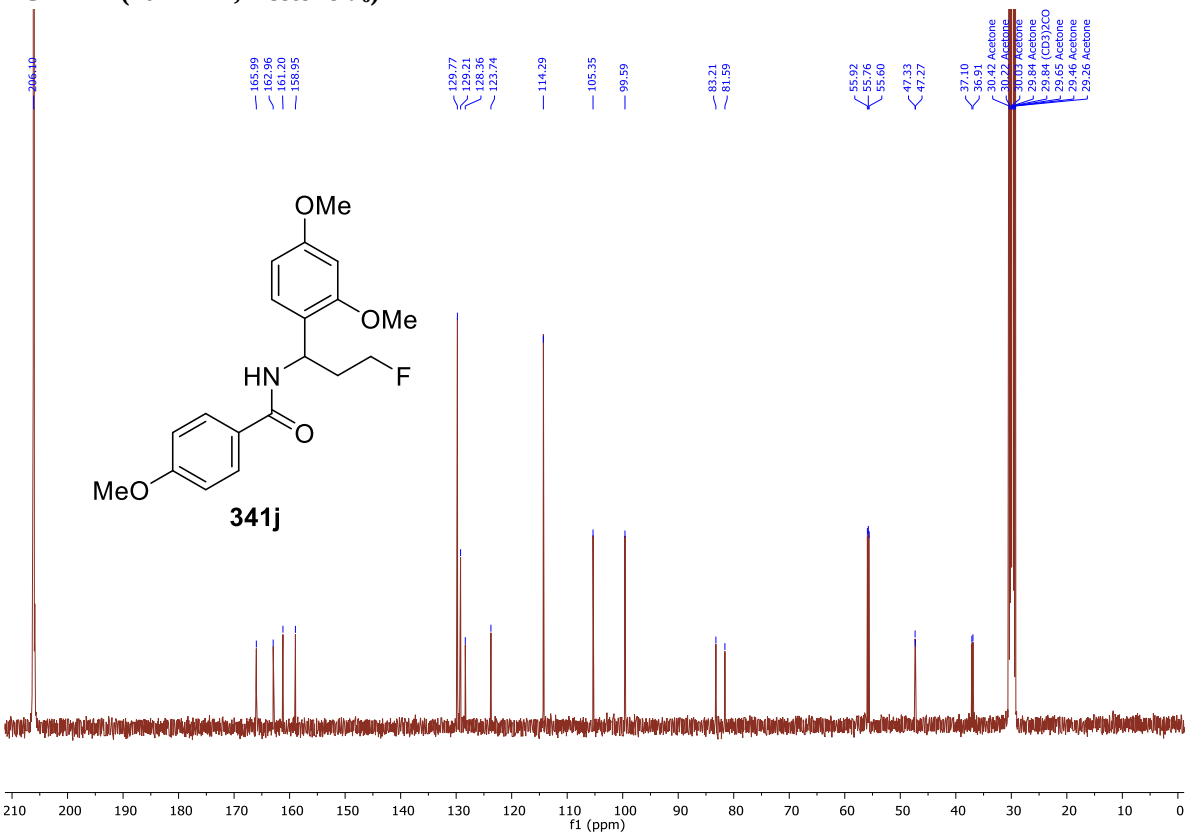
^{19}F-NMR (376 MHz, $CDCl_3$)



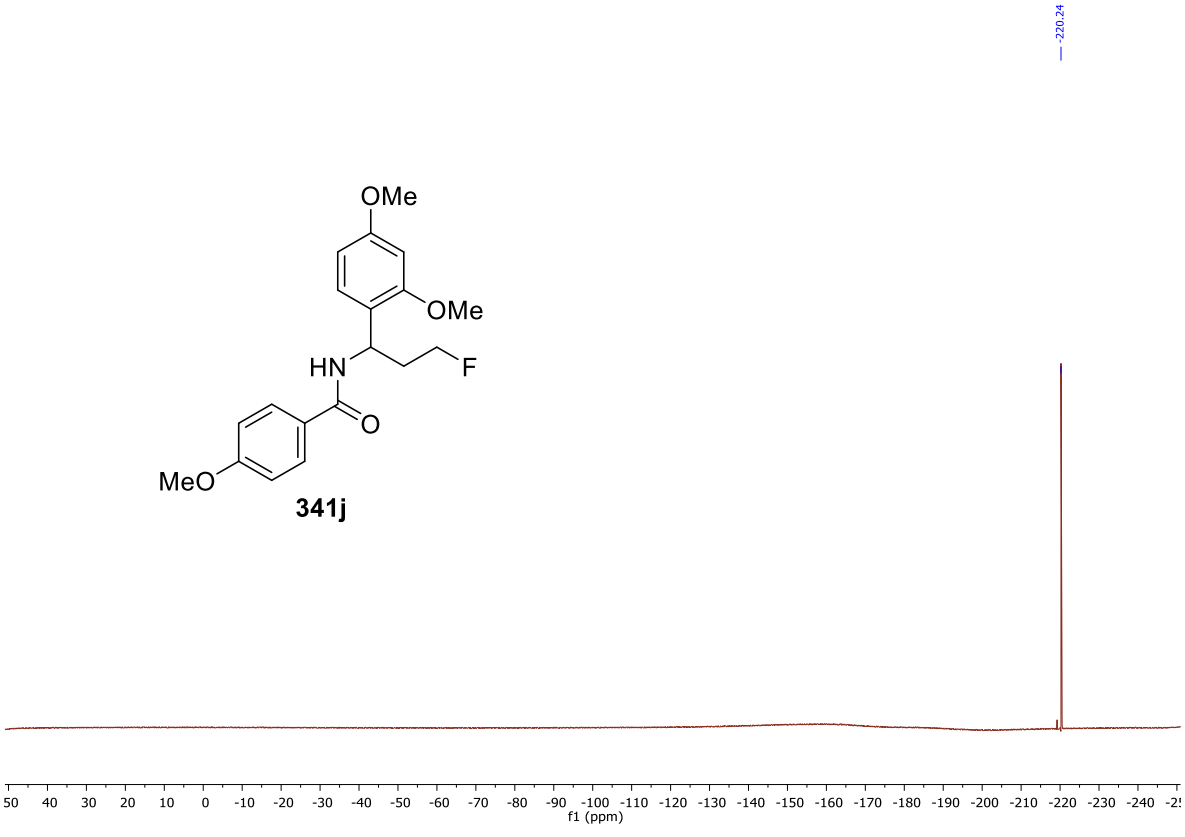
^{1}H-NMR (400 MHz, Acetone-d_6)



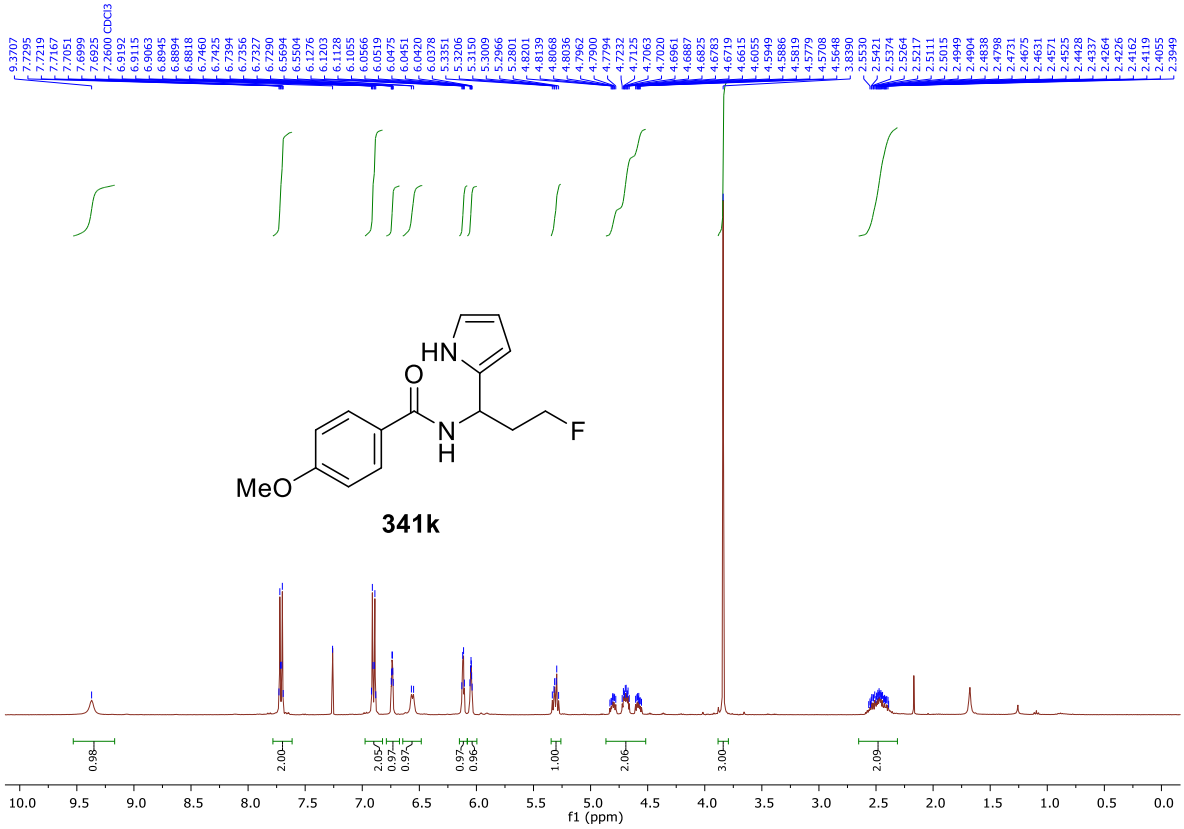
^{13}C-NMR (101 MHz, Acetone-d_6)



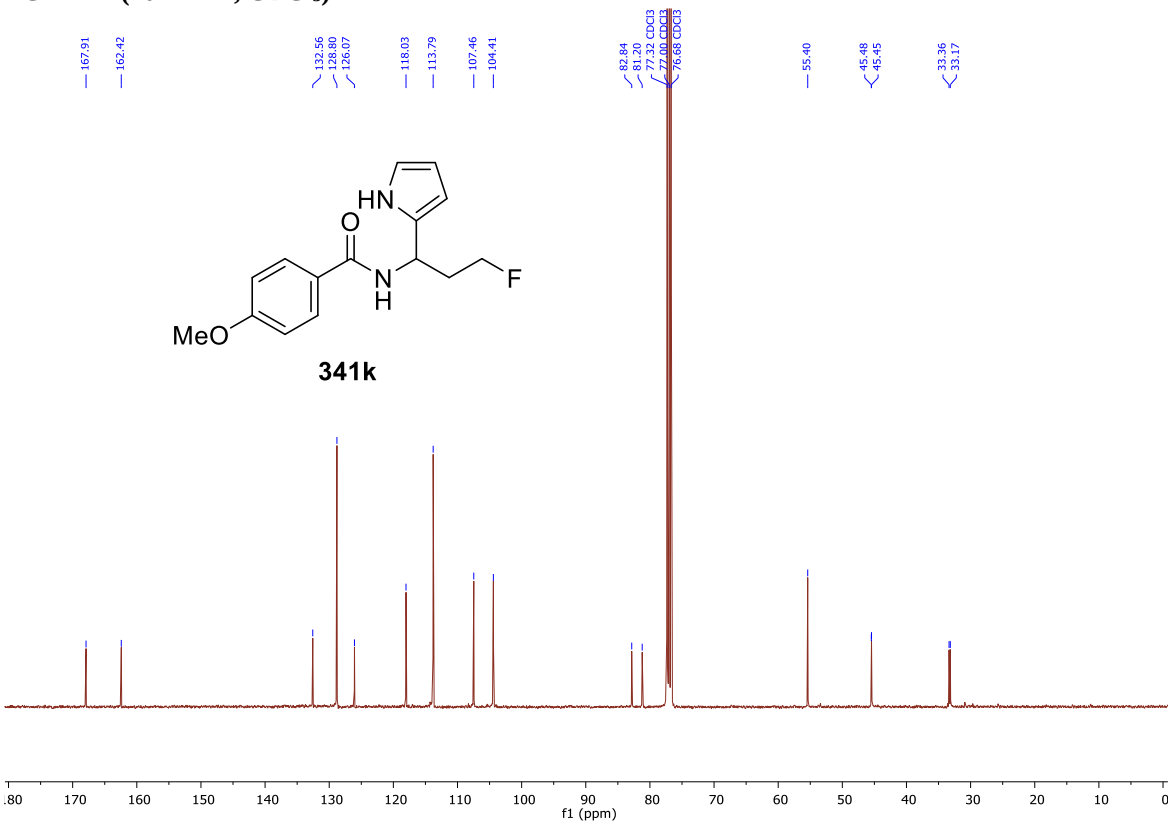
^{19}F-NMR (376 MHz, Acetone-d_6)



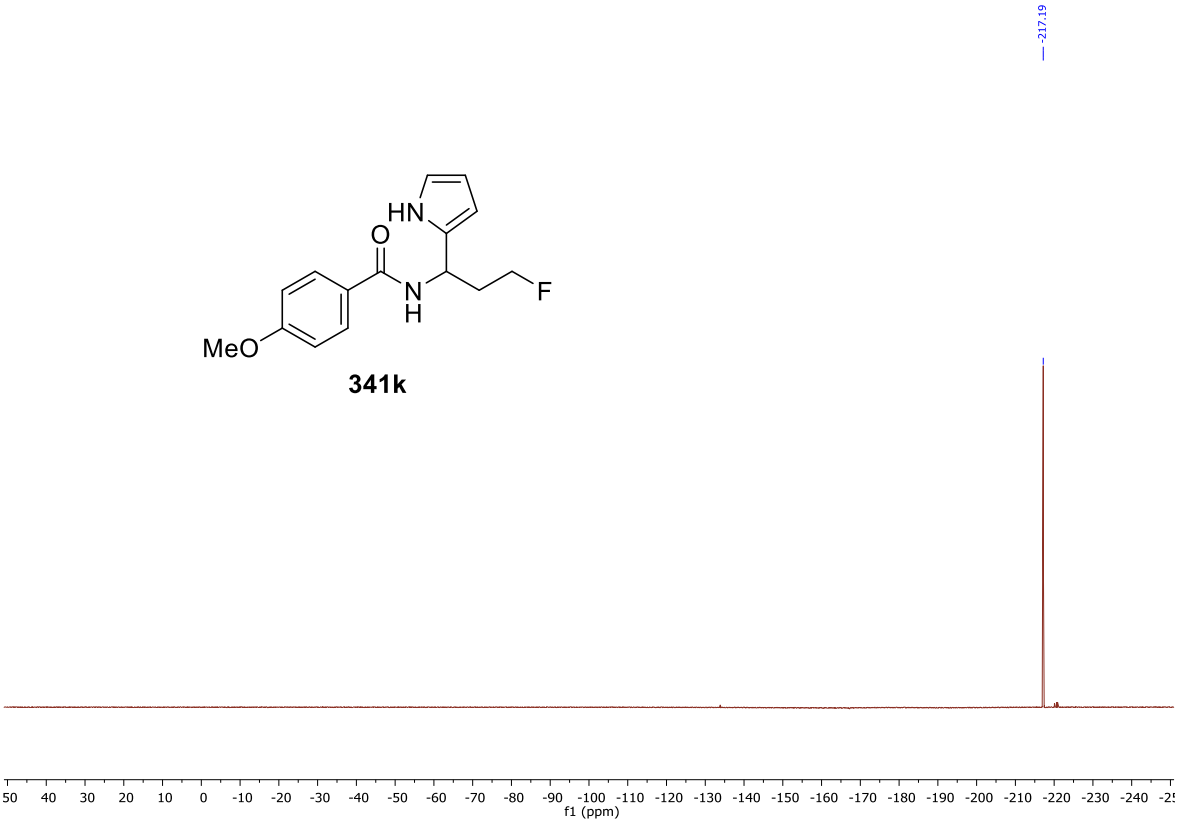
^{1}H-NMR (400 MHz, $CDCl_3$)



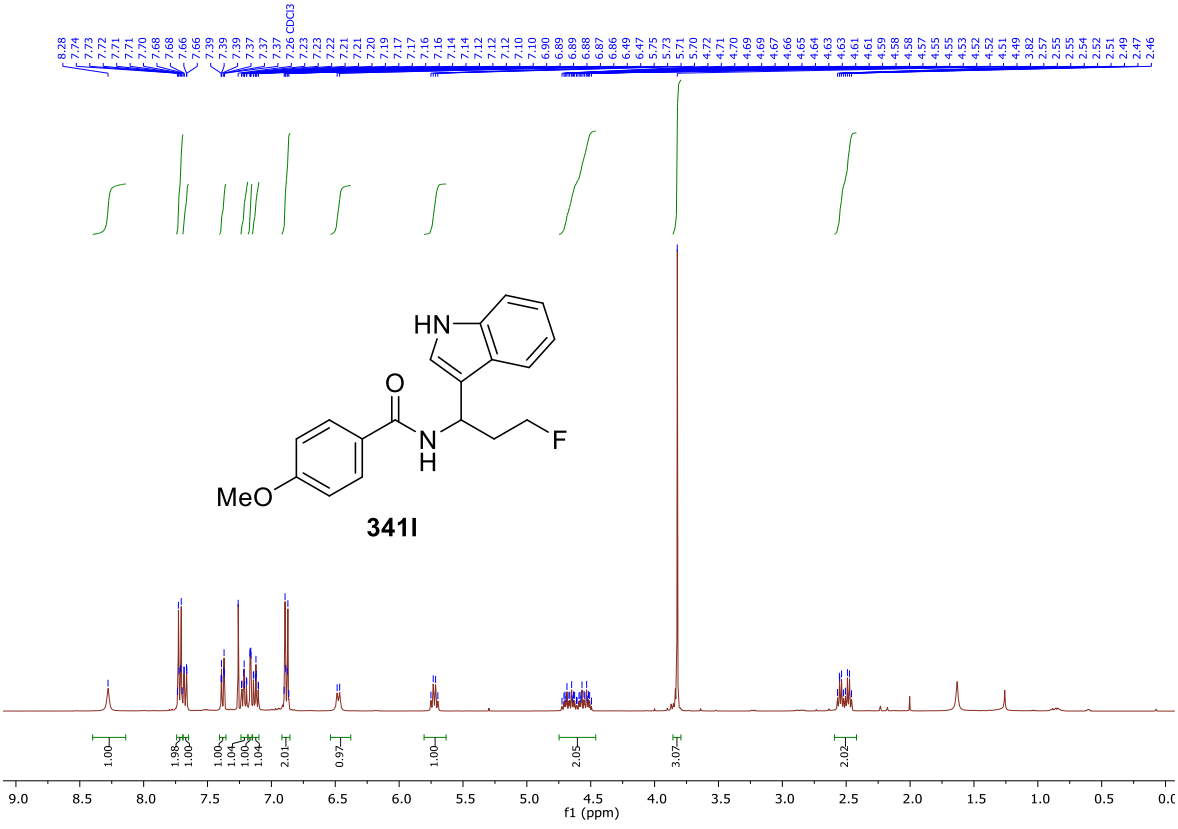
^{13}C-NMR (101 MHz, $CDCl_3$)



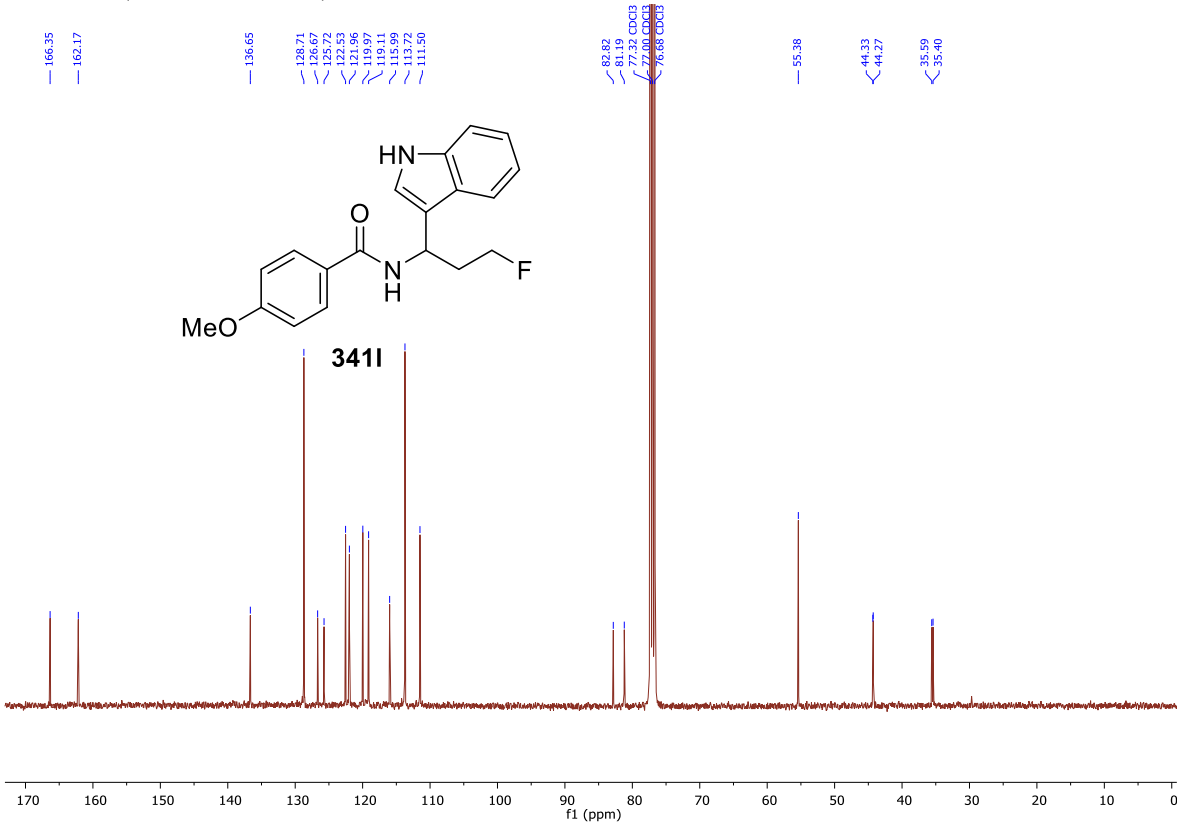
^{19}F-NMR (376 MHz, $CDCl_3$)



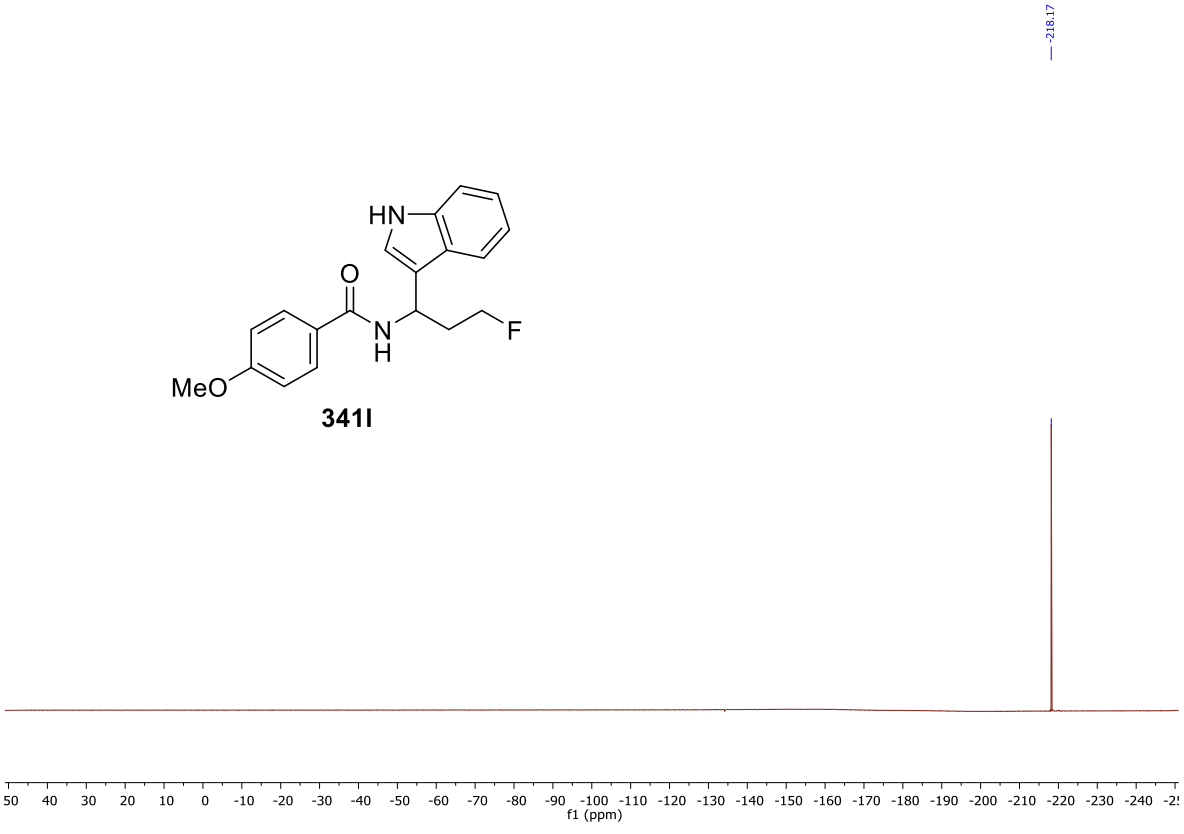
^{1}H-NMR (400 MHz, $CDCl_3$)



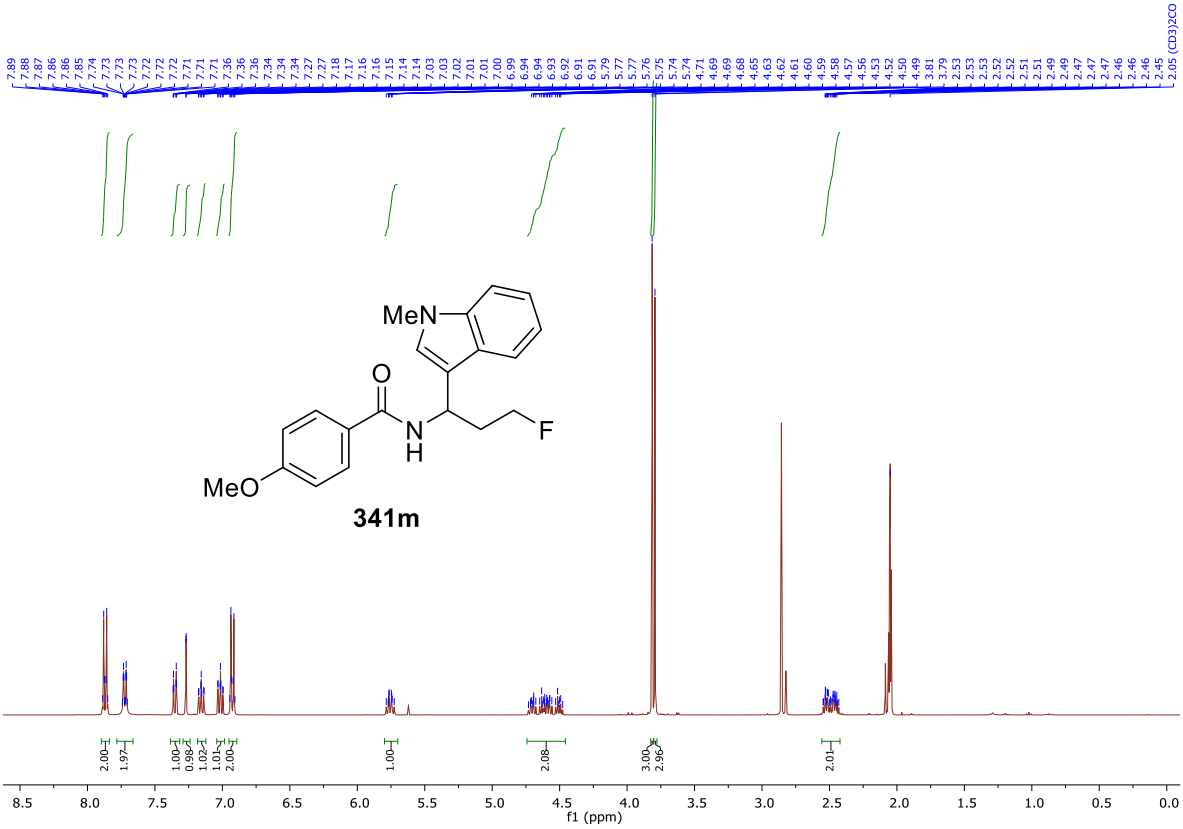
^{13}C-NMR (101 MHz, $CDCl_3$)



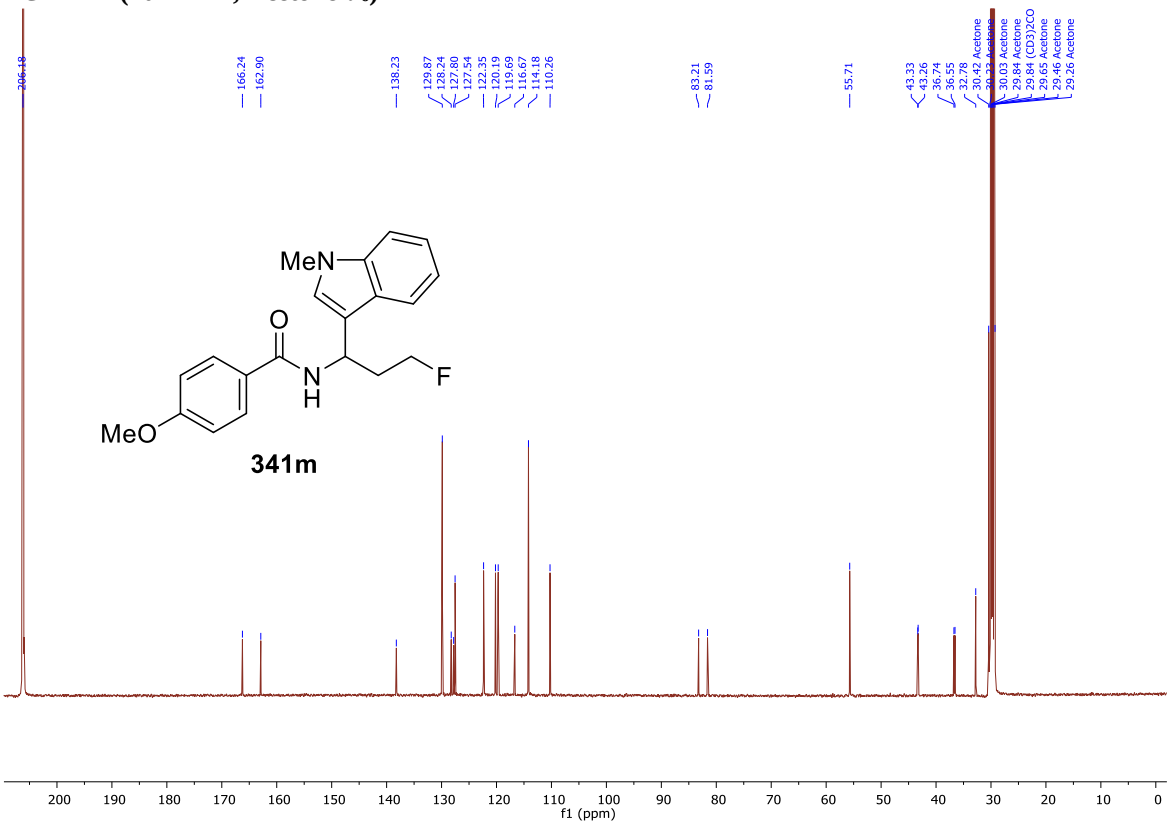
^{19}F-NMR (376 MHz, $CDCl_3$)



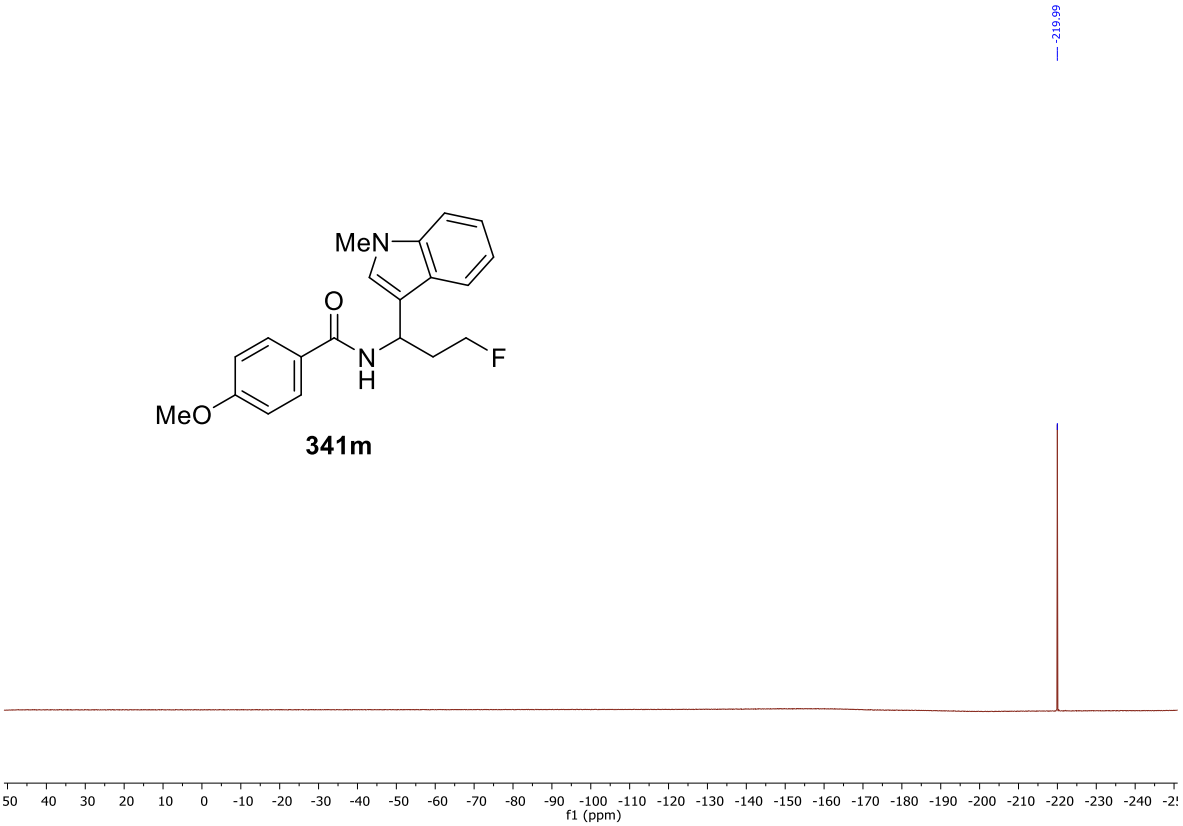
^{1}H-NMR (400 MHz, Acetone-d_6)



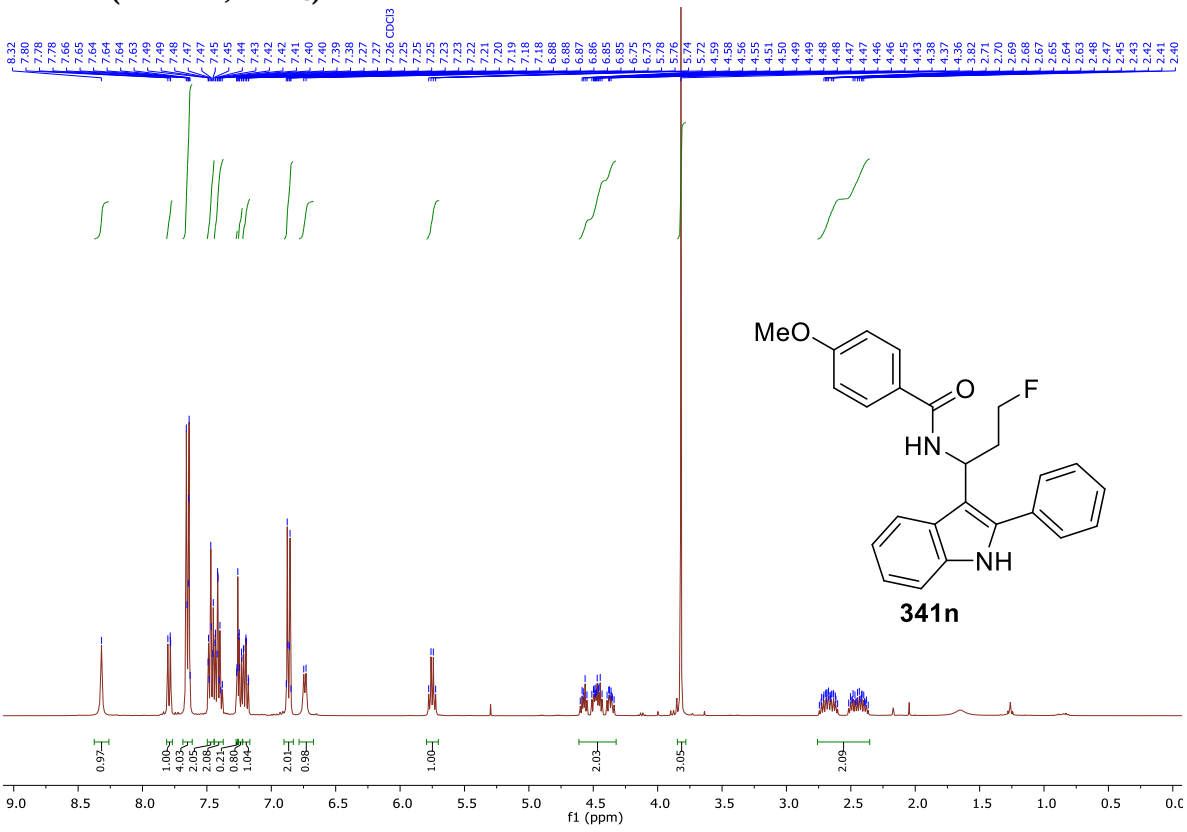
^{13}C-NMR (101 MHz, Acetone-d_6)



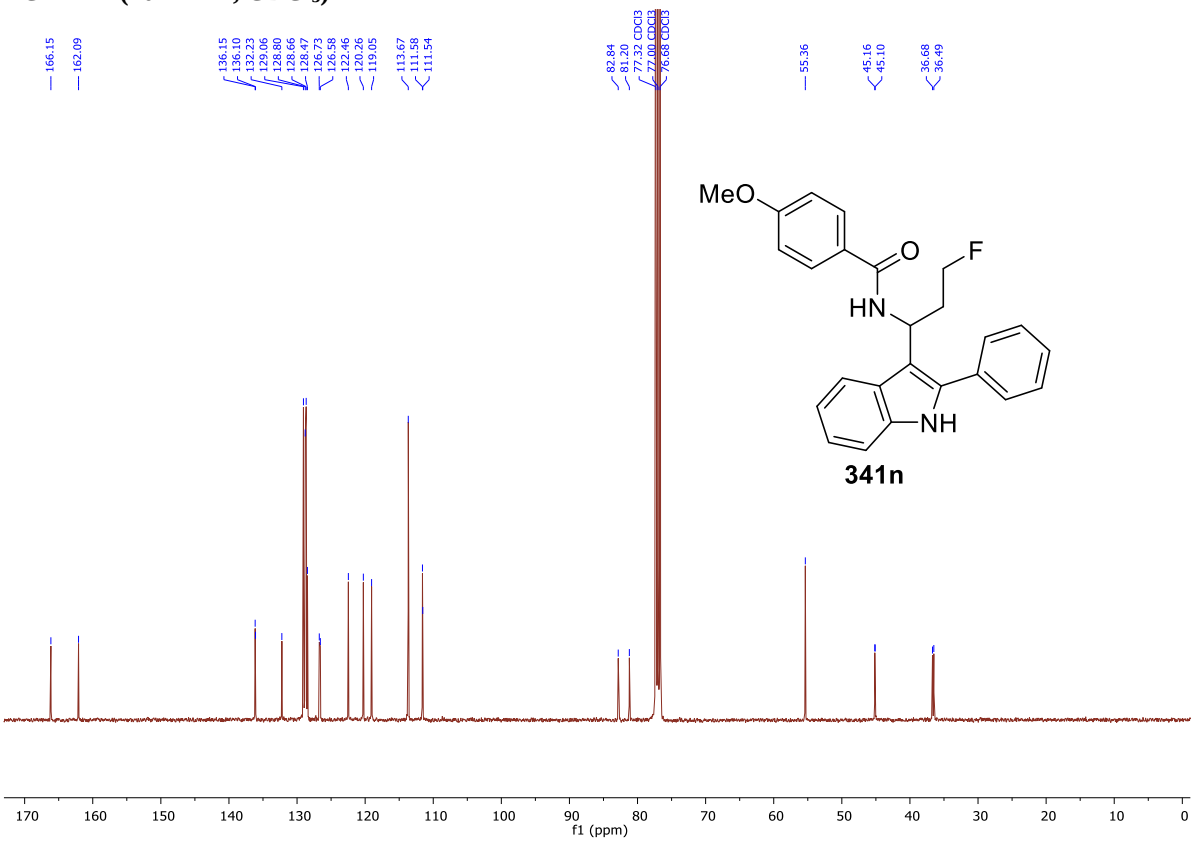
^{19}F-NMR (376 MHz, Acetone-d_6)



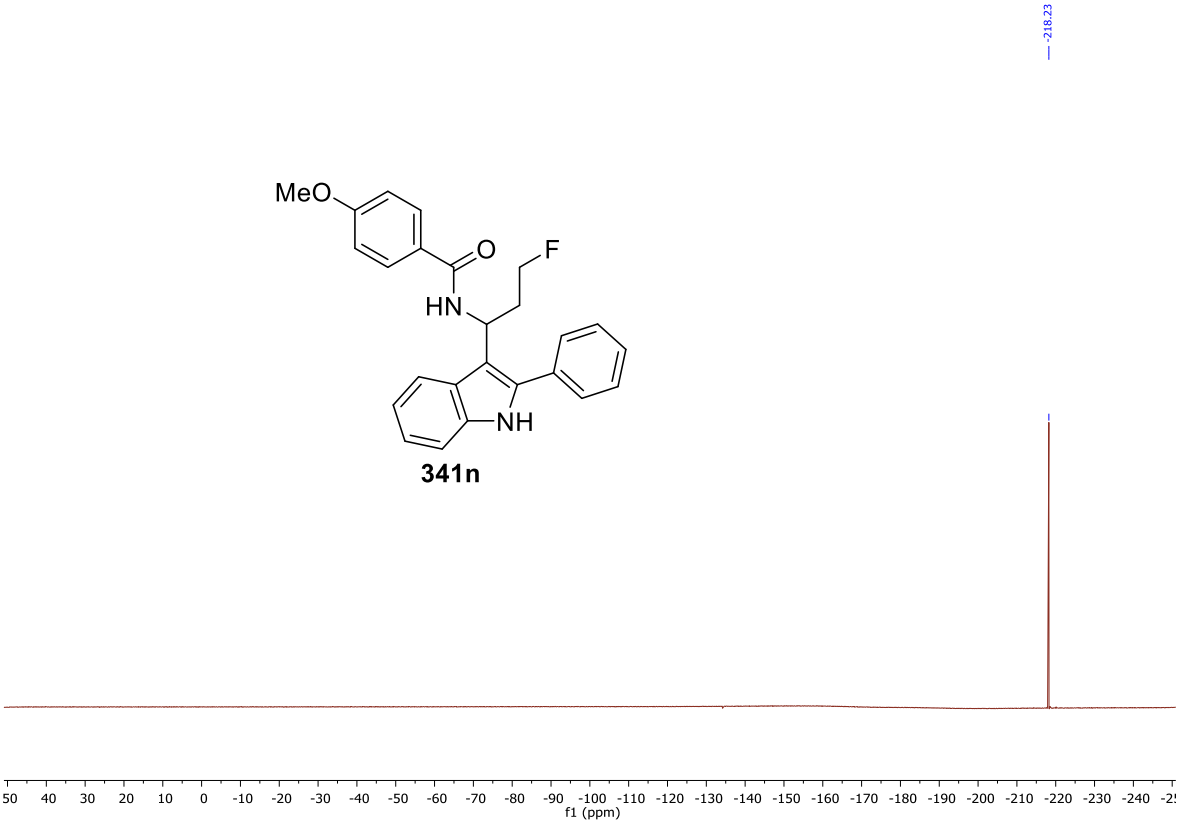
^{1}H-NMR (400 MHz, $CDCl_3$)



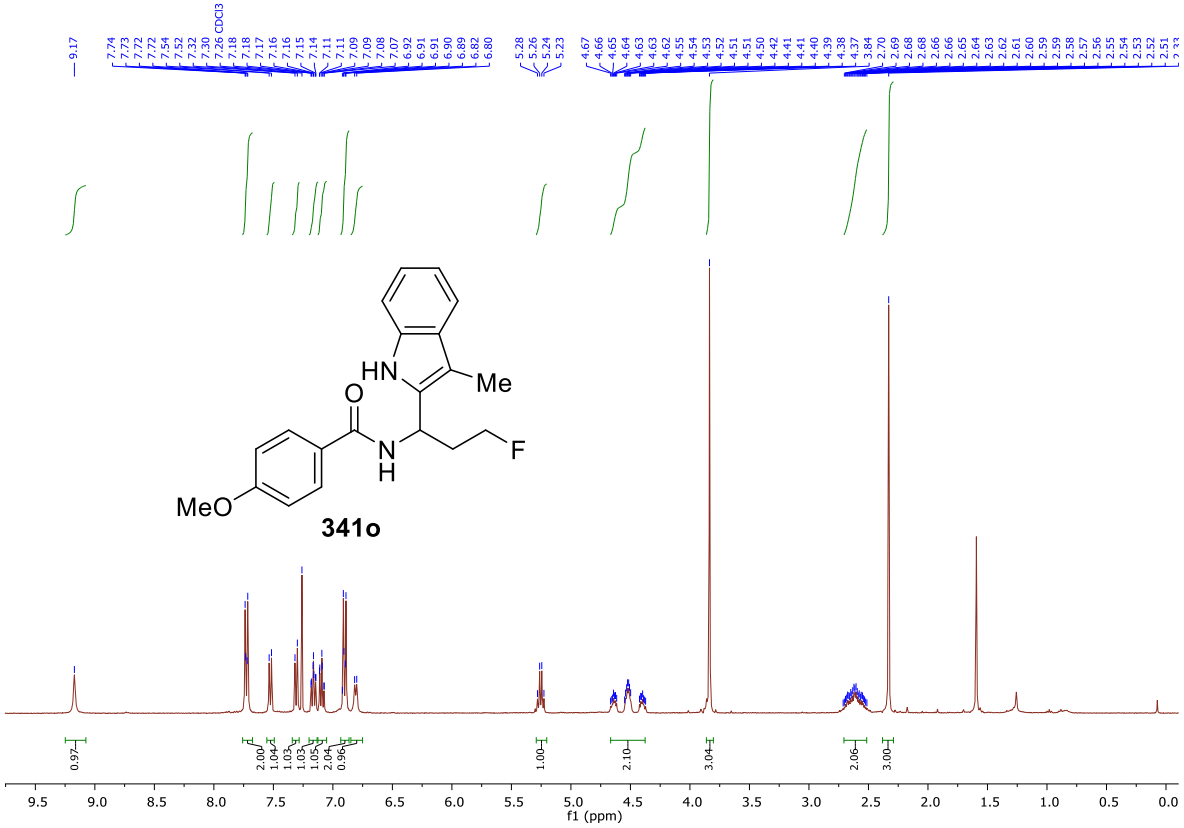
^{13}C-NMR (101 MHz, $CDCl_3$)



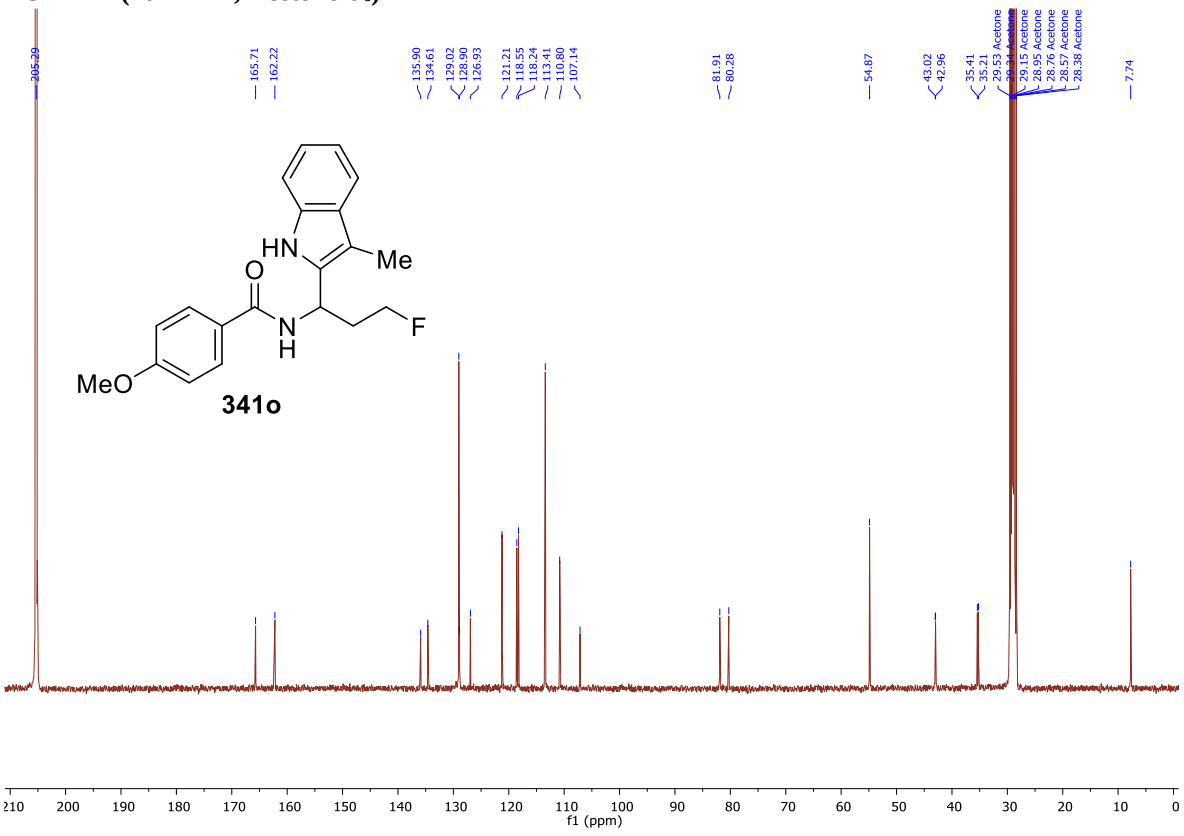
^{19}F-NMR (376 MHz, $CDCl_3$)



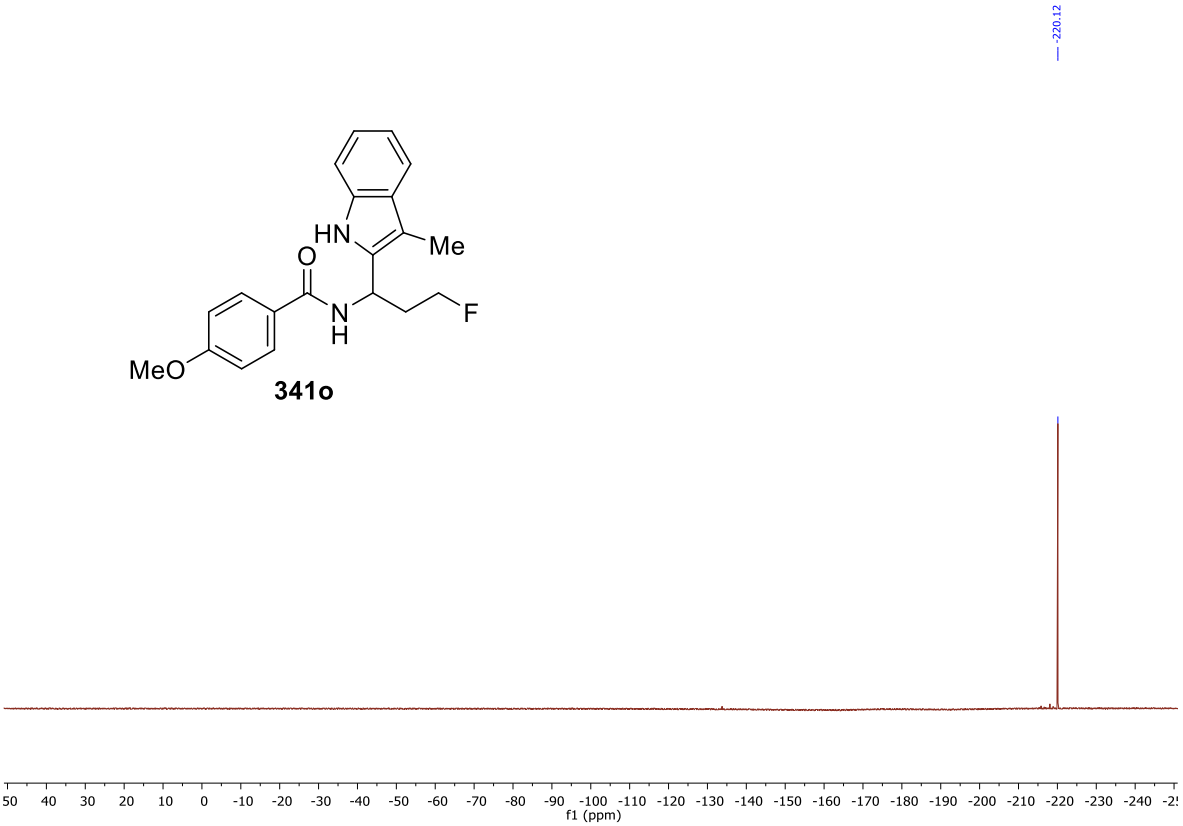
^{1}H-NMR (400 MHz, $CDCl_3$)



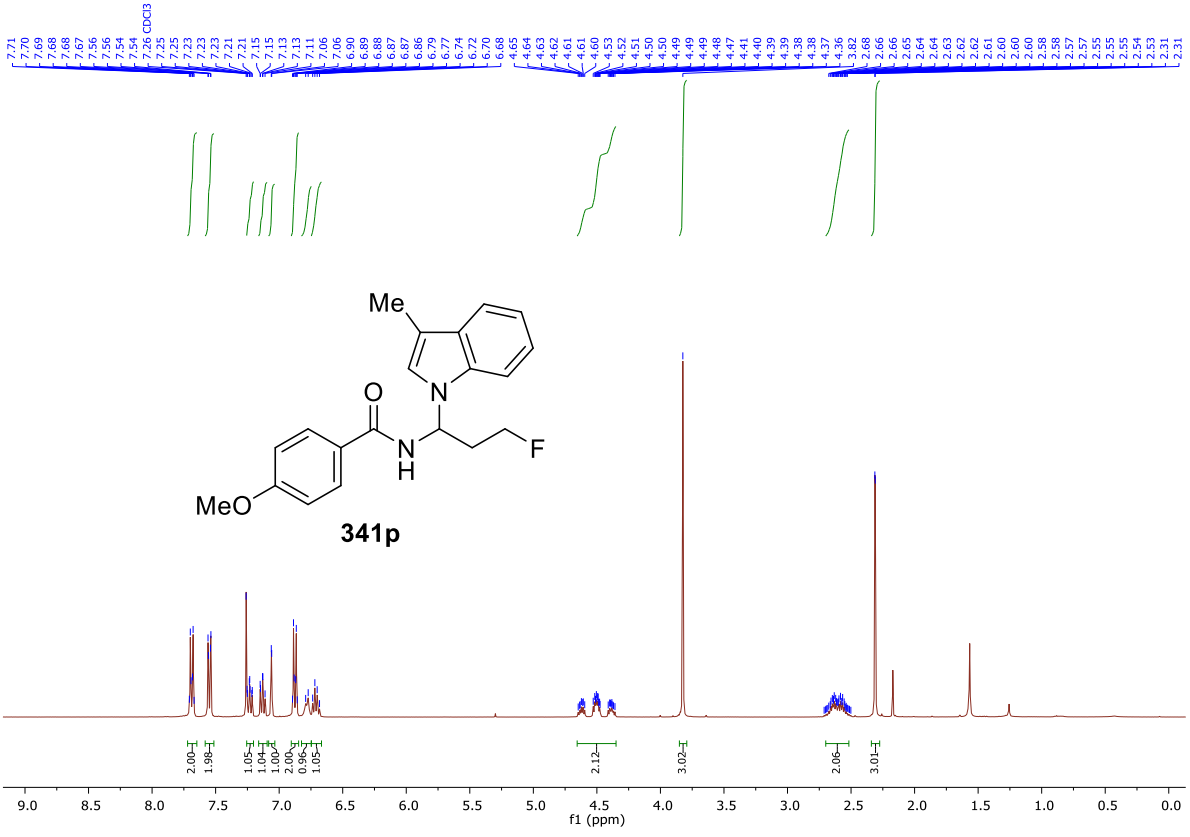
^{13}C-NMR (101 MHz, Acetone-d_6)



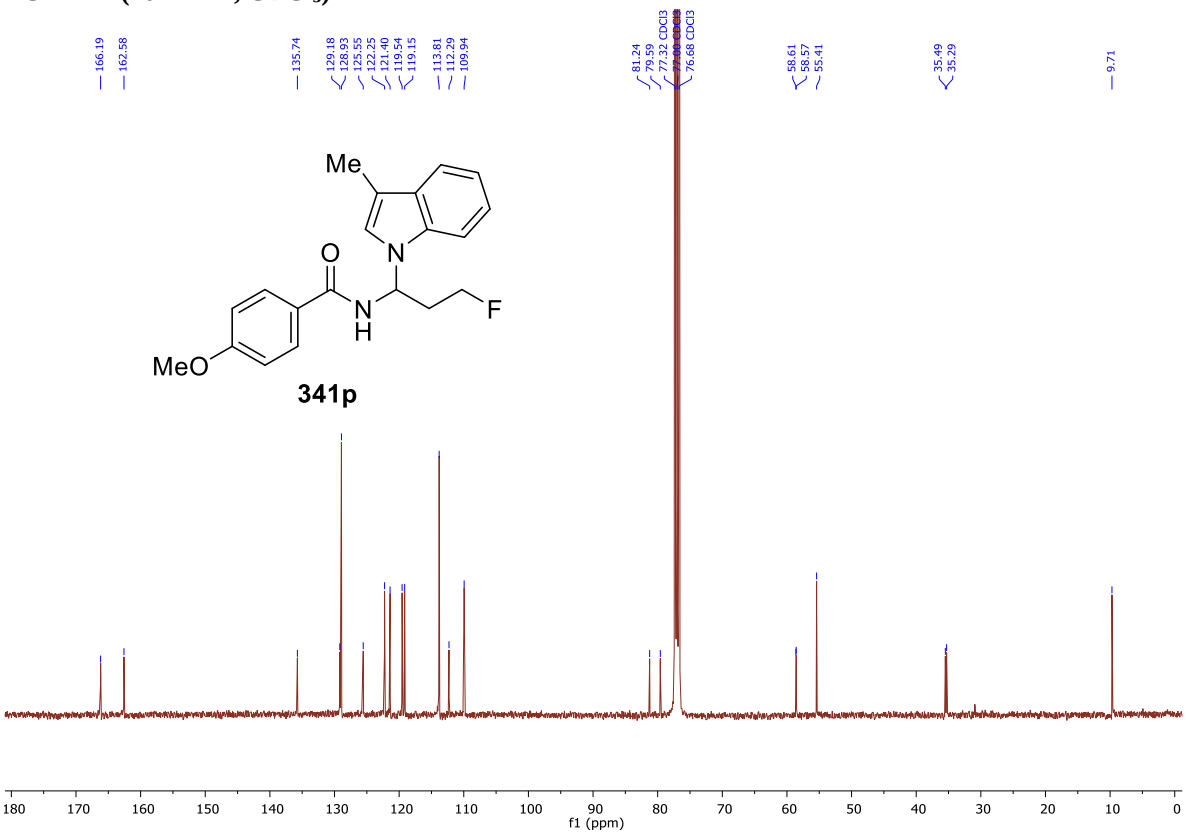
^{19}F-NMR (376 MHz, $CDCl_3$)



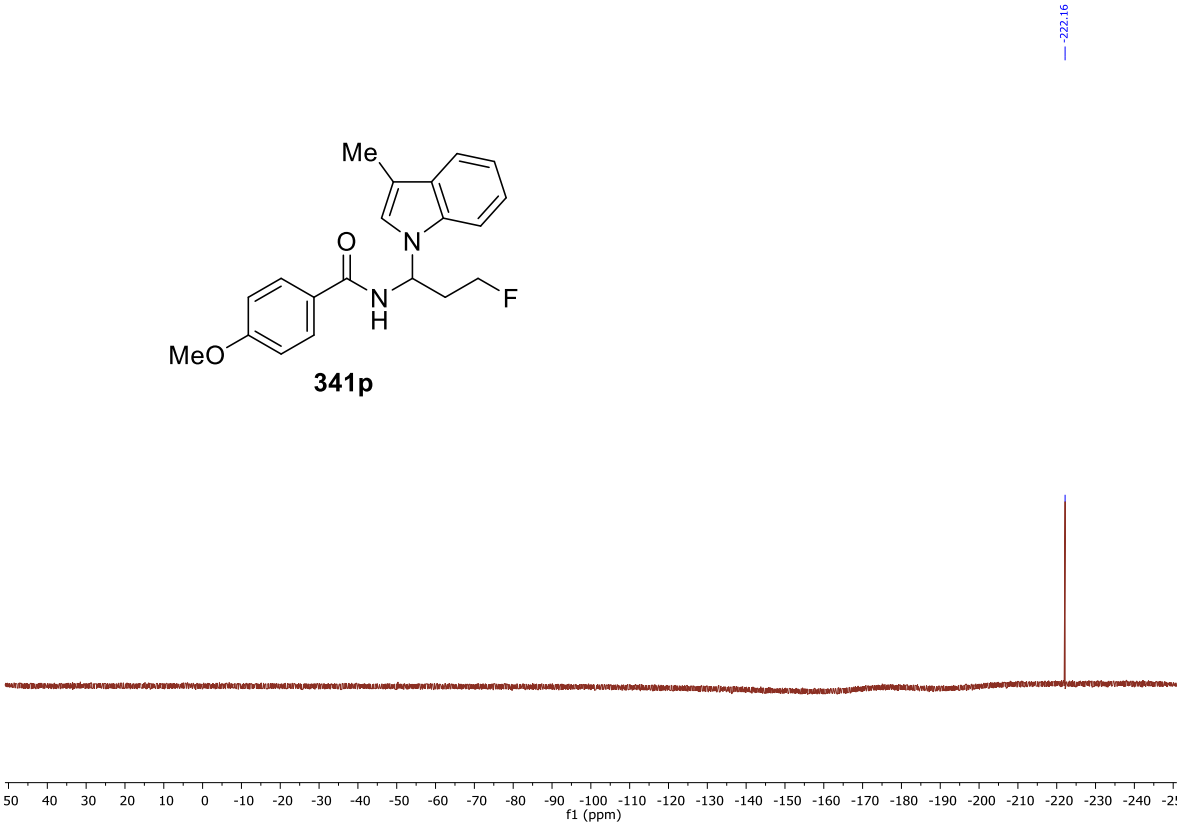
^{1}H-NMR (400 MHz, $CDCl_3$)



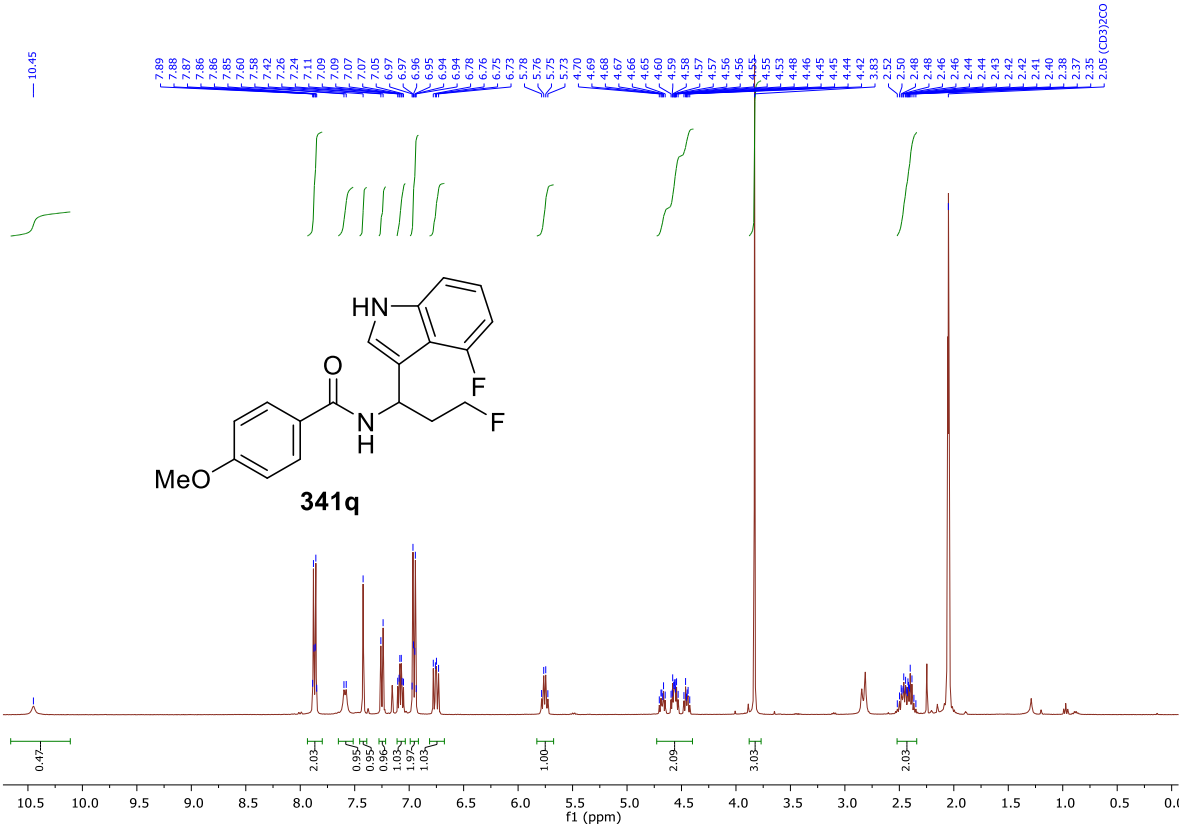
^{13}C-NMR (101 MHz, $CDCl_3$)



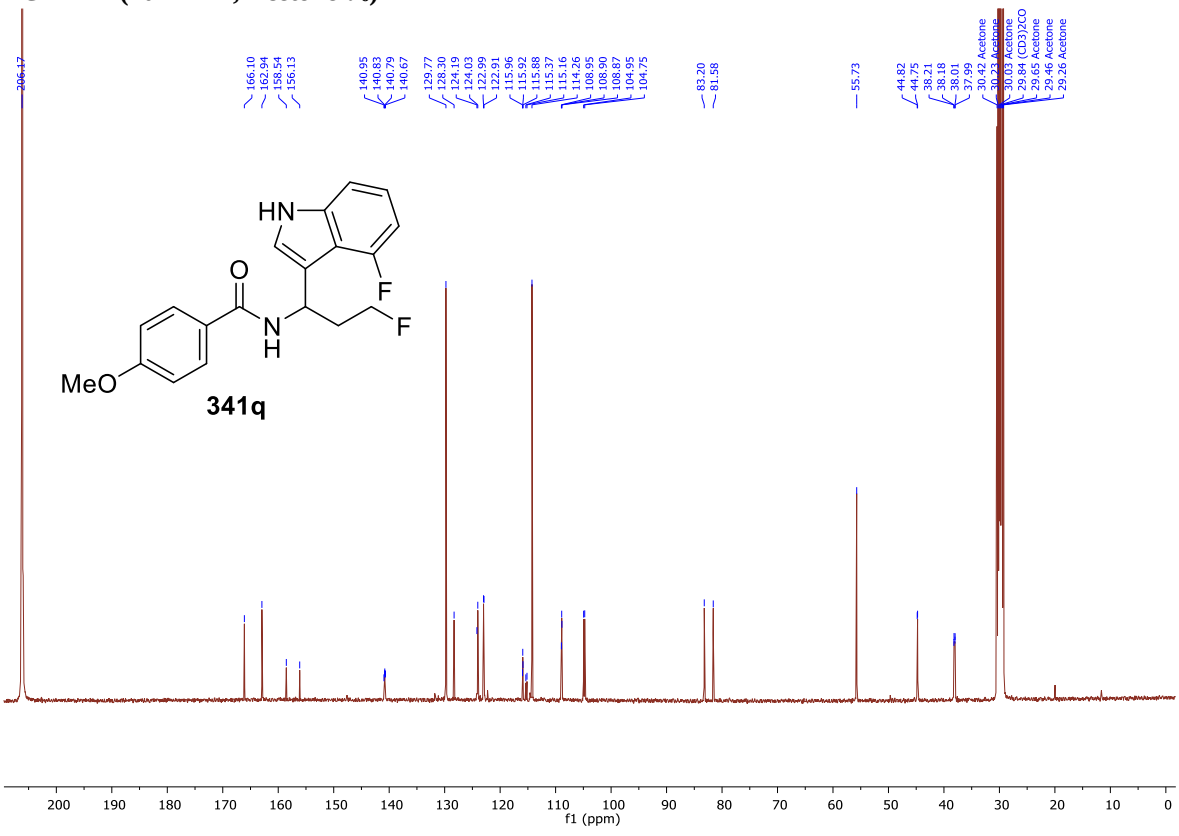
^{19}F-NMR (376 MHz, $CDCl_3$)



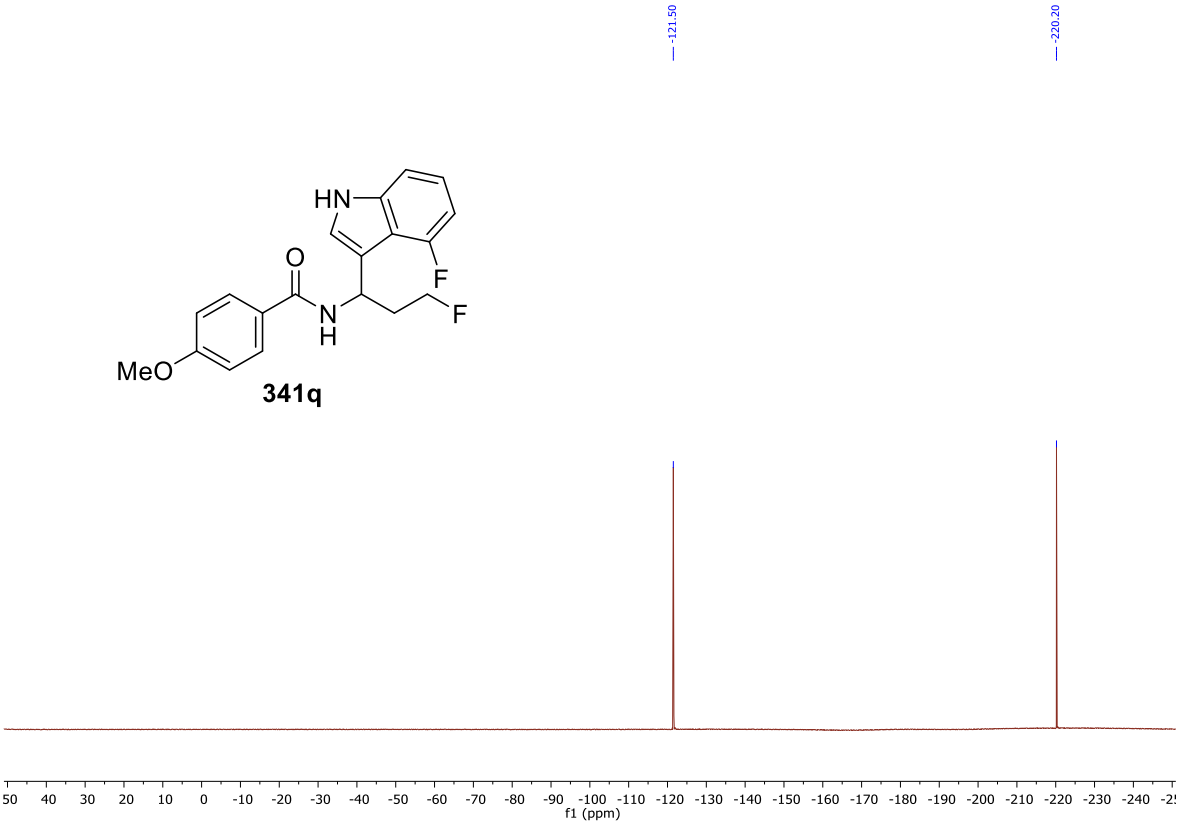
^{1}H-NMR (400 MHz, Acetone-d_6)



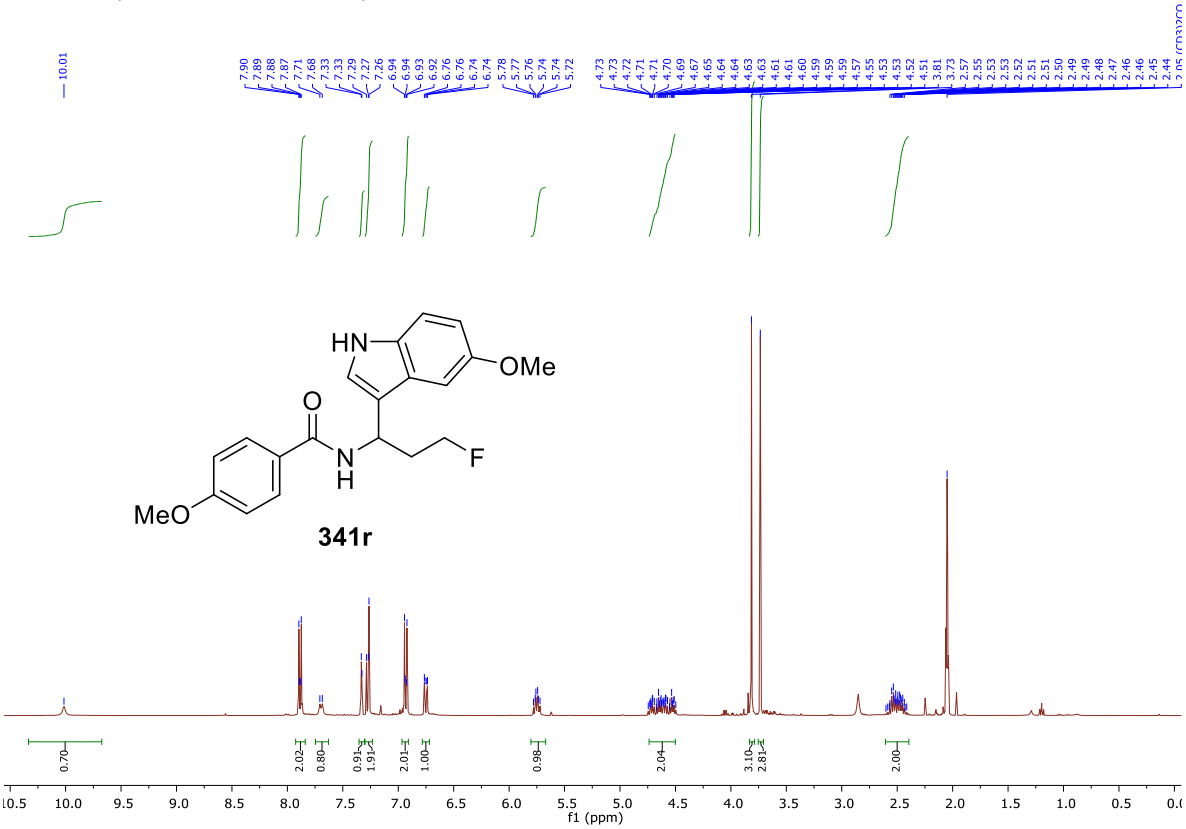
^{13}C-NMR (101 MHz, Acetone-d_6)



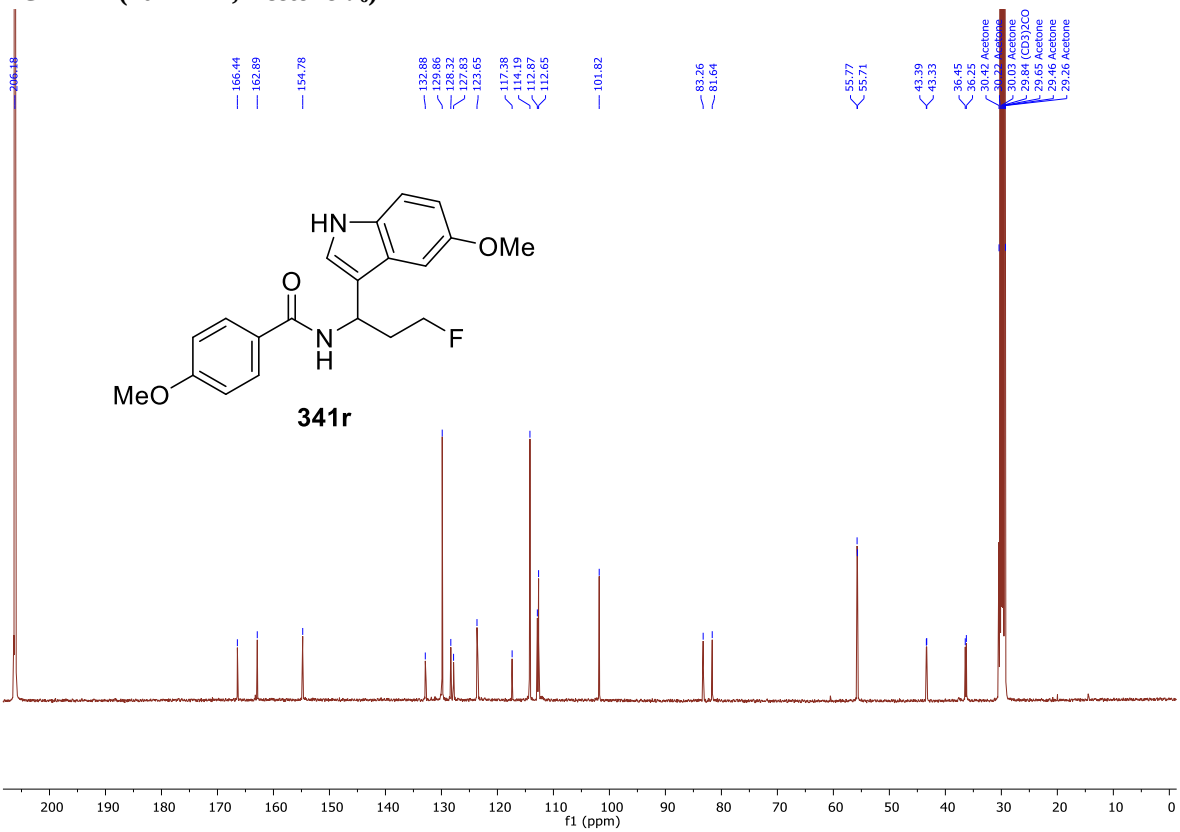
^{19}F-NMR (376 MHz, Acetone-d_6)



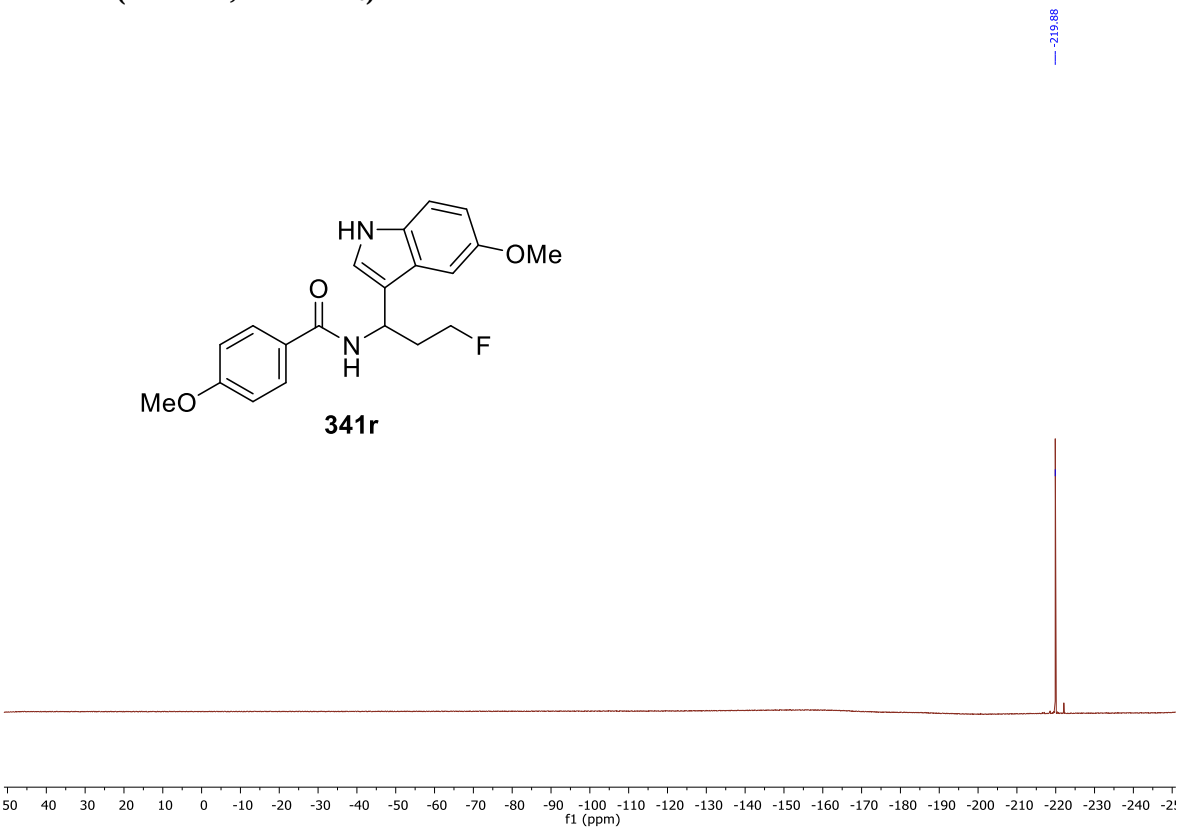
^{1}H-NMR (400 MHz, Acetone-d_6)



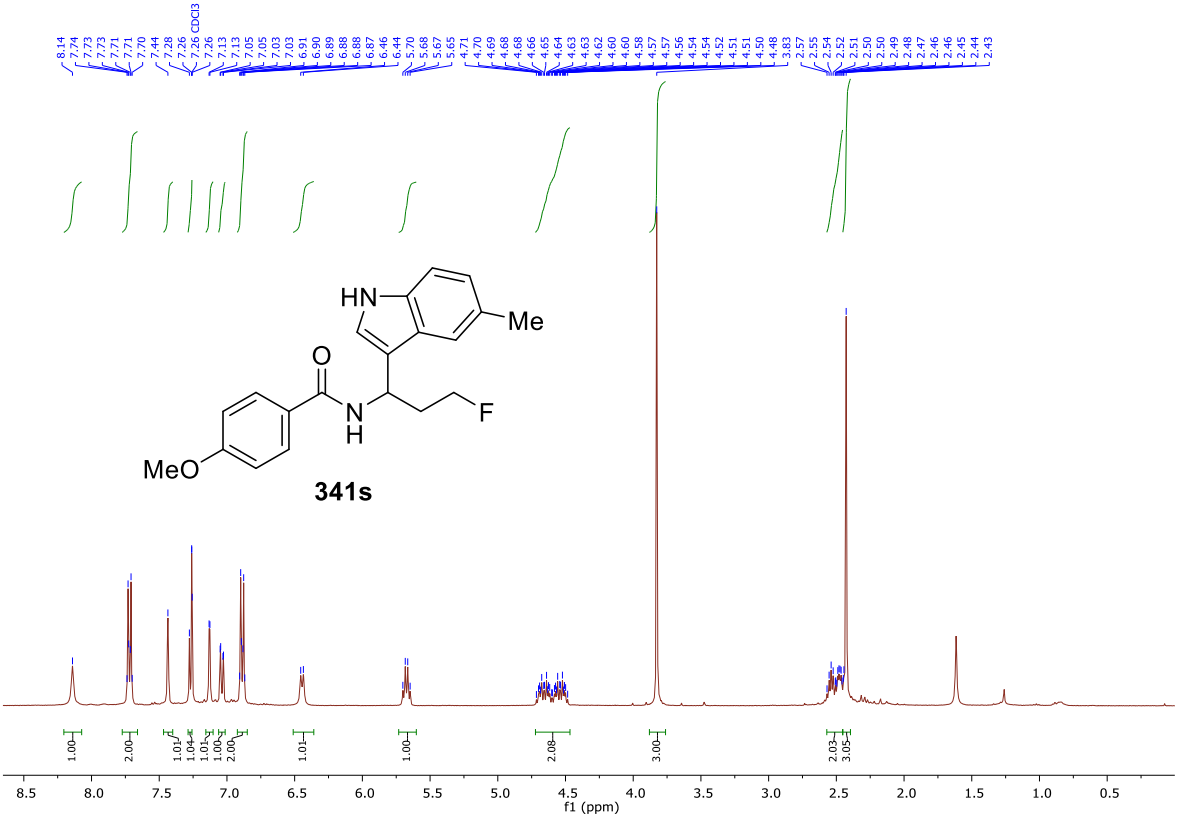
^{13}C-NMR (101 MHz, Acetone-d_6)



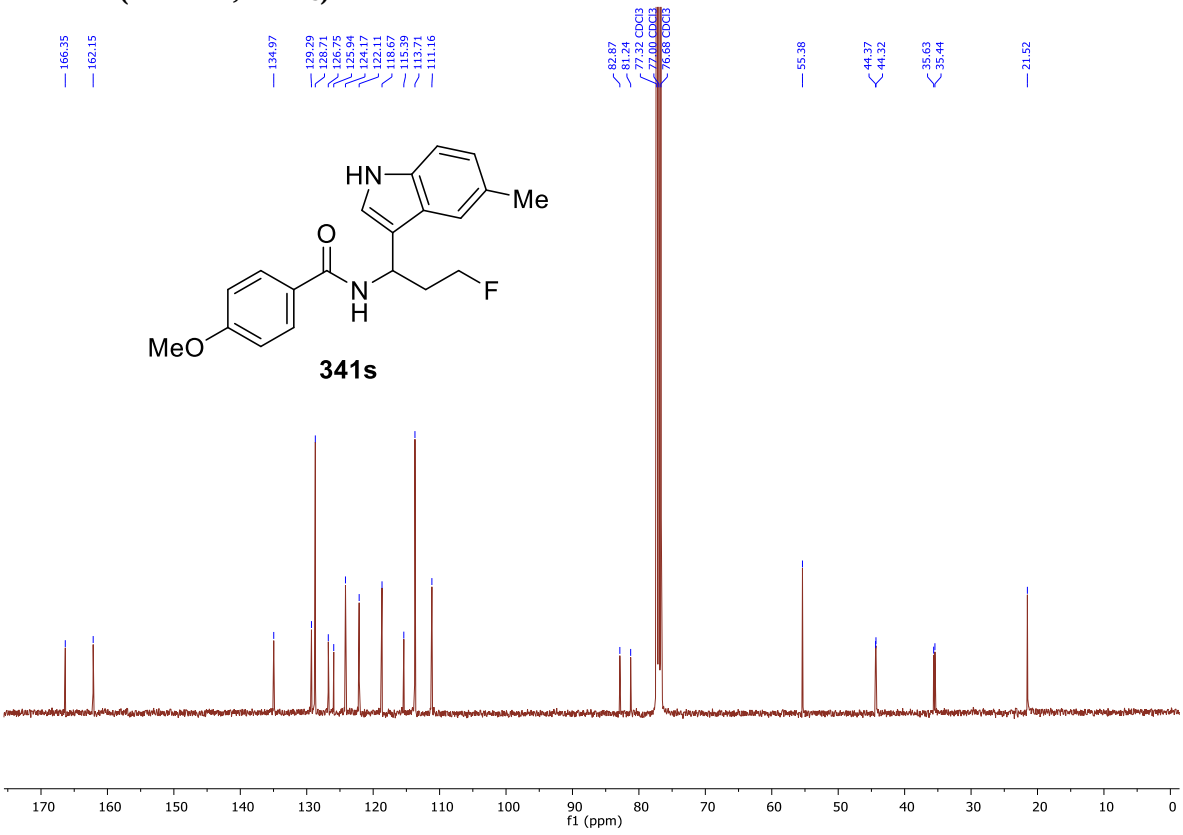
^{19}F-NMR (376 MHz, Acetone-d_6)



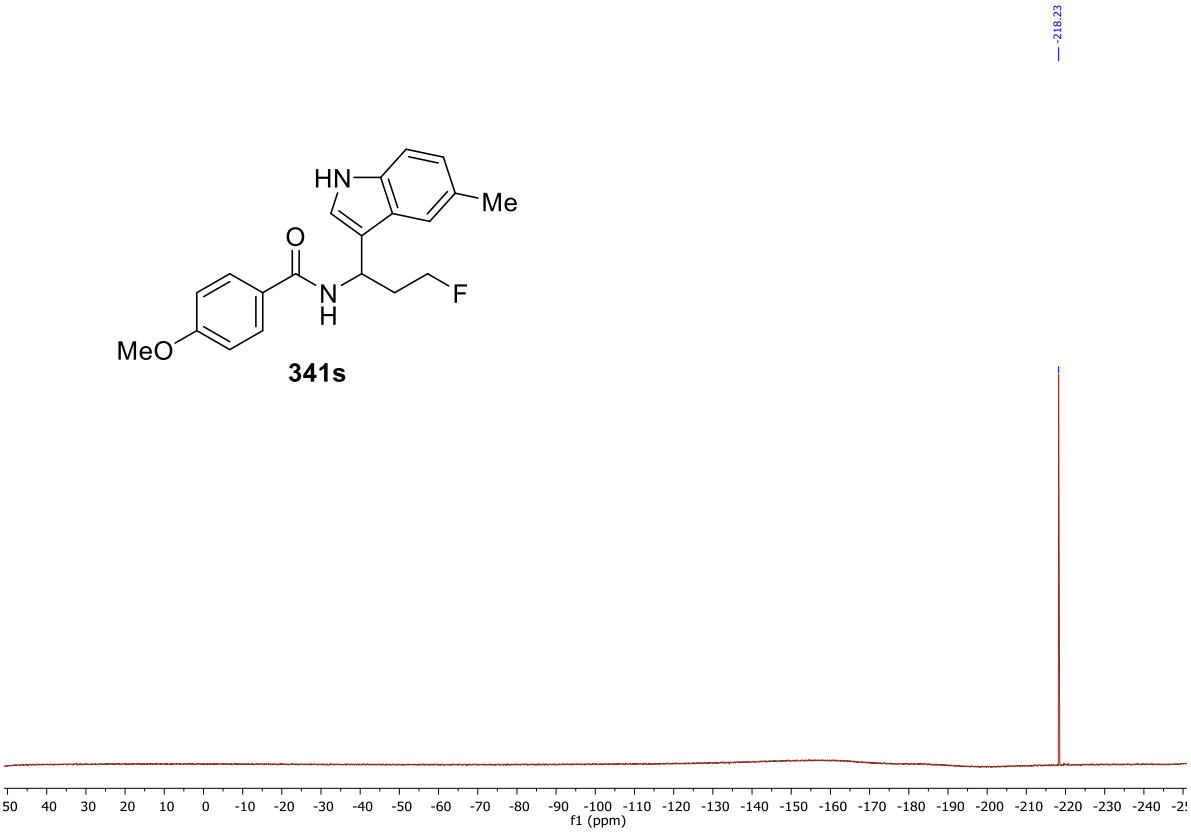
^{1}H-NMR (400 MHz, $CDCl_3$)



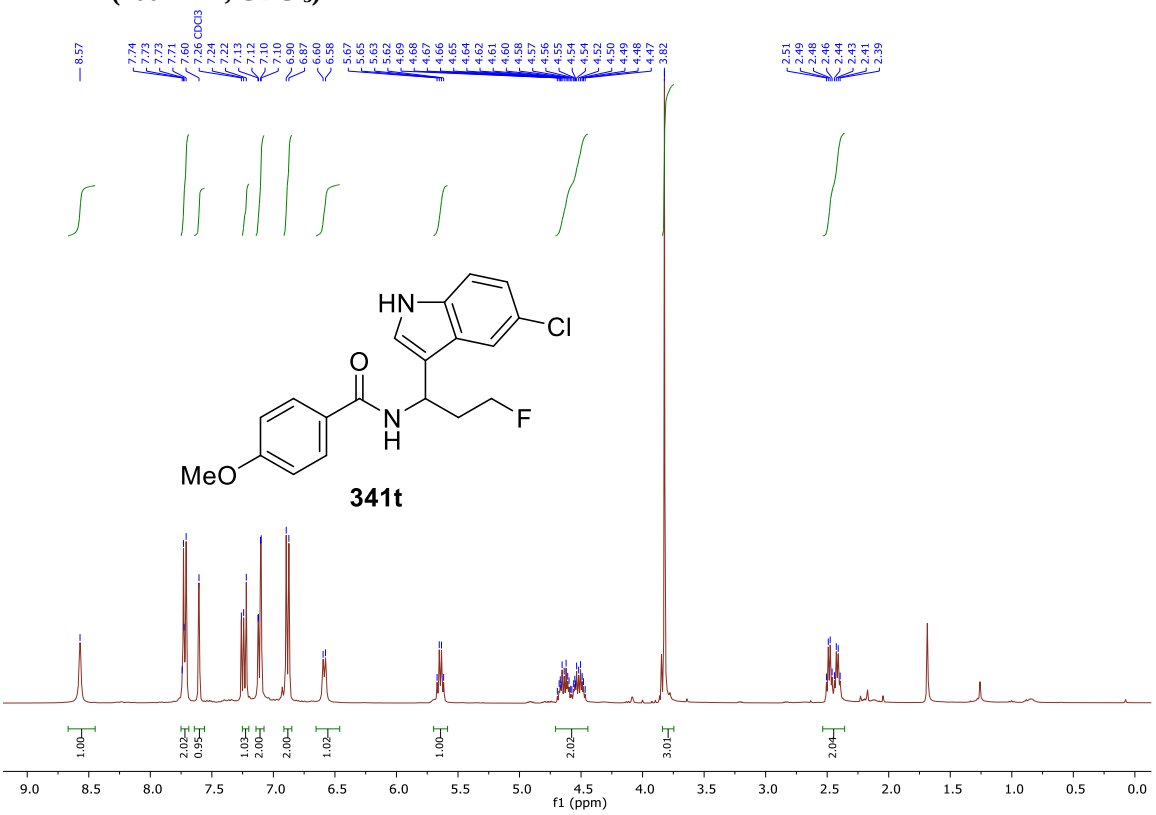
^{13}C-NMR (101 MHz, $CDCl_3$)



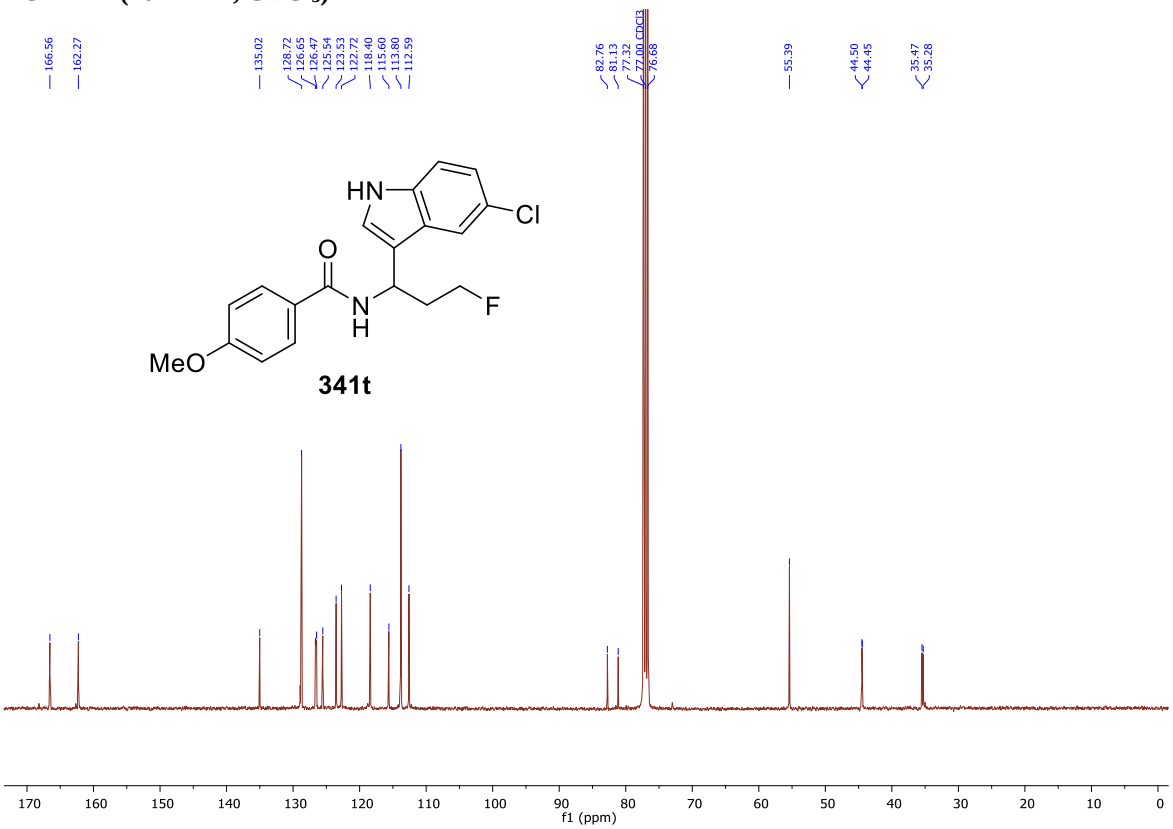
^{19}F-NMR (376 MHz, $CDCl_3$)



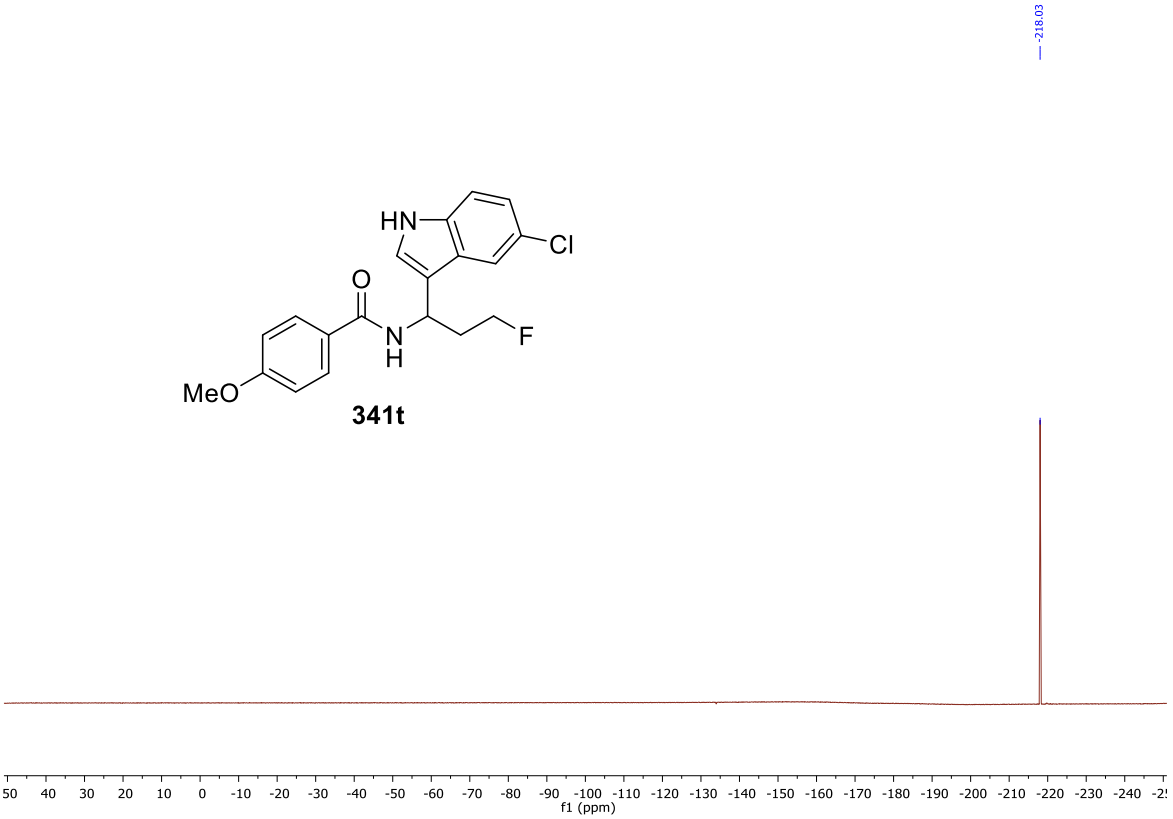
^{1}H-NMR (400 MHz, $CDCl_3$)



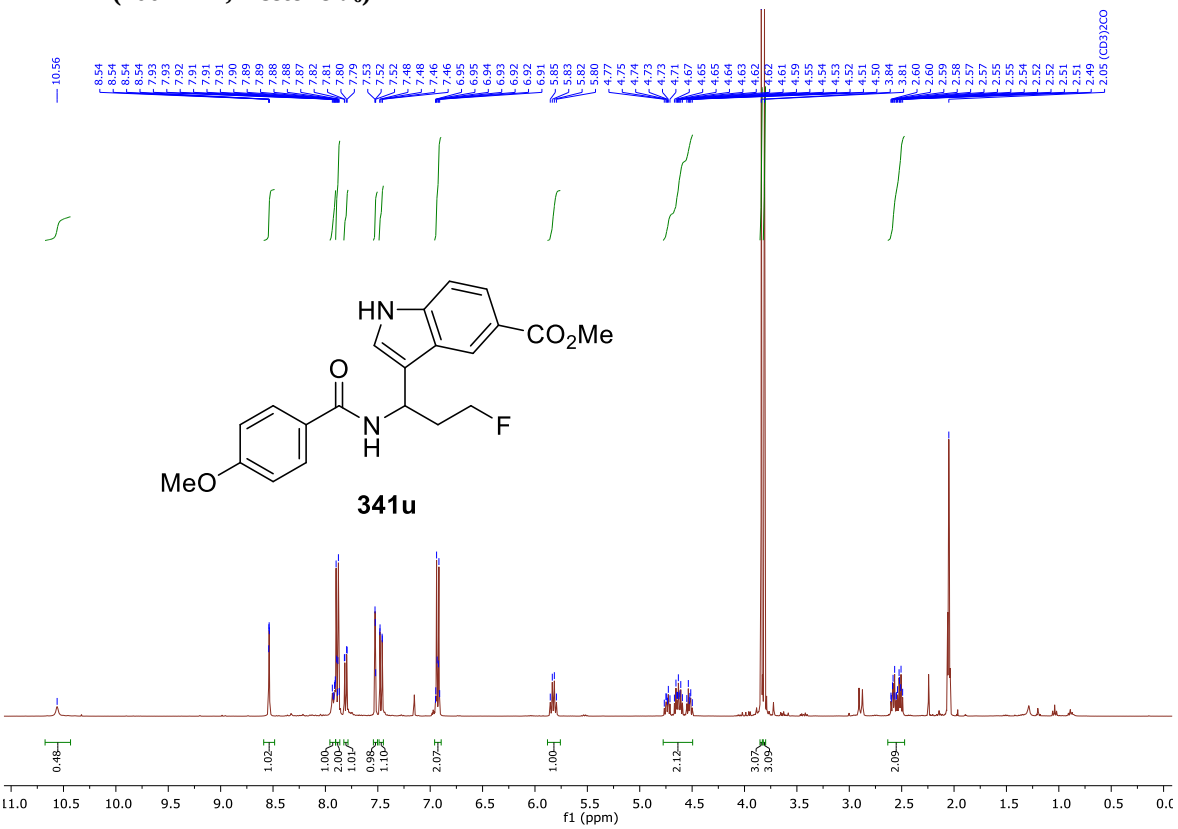
^{13}C-NMR (101 MHz, $CDCl_3$)



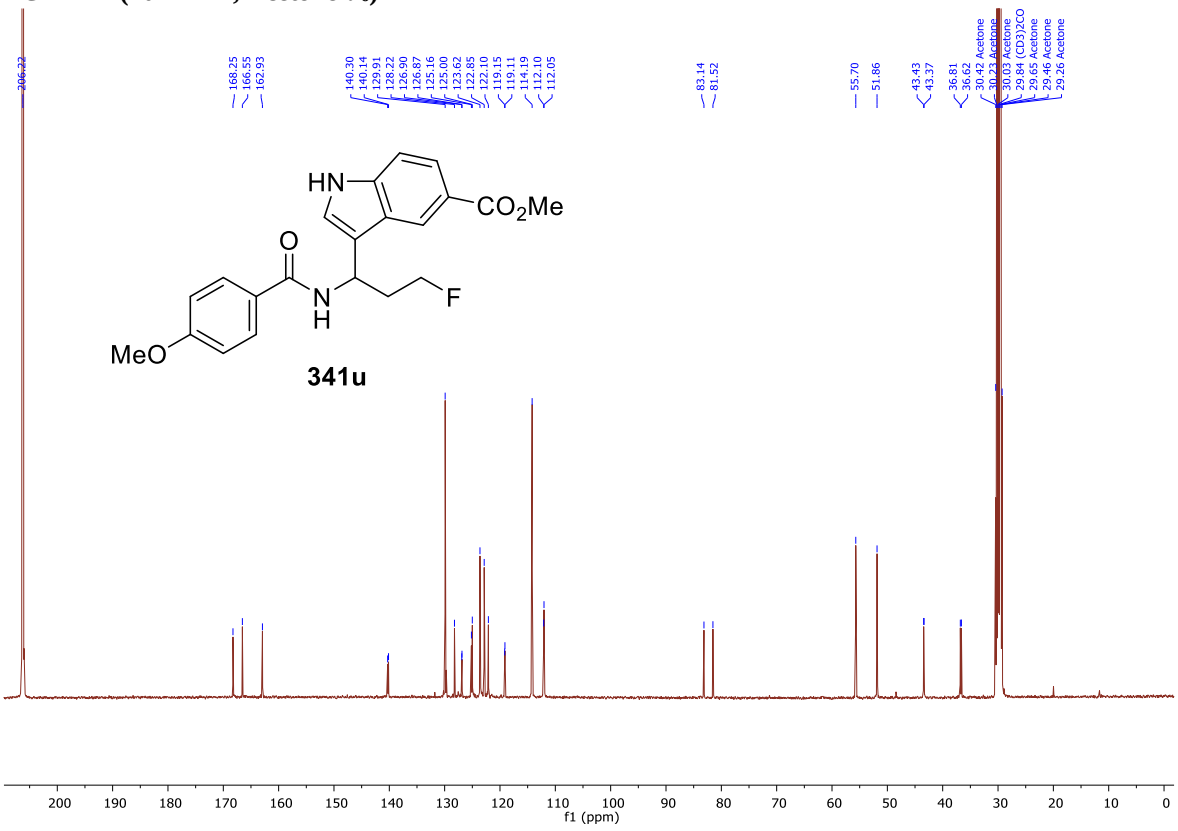
^{19}F-NMR (376 MHz, $CDCl_3$)



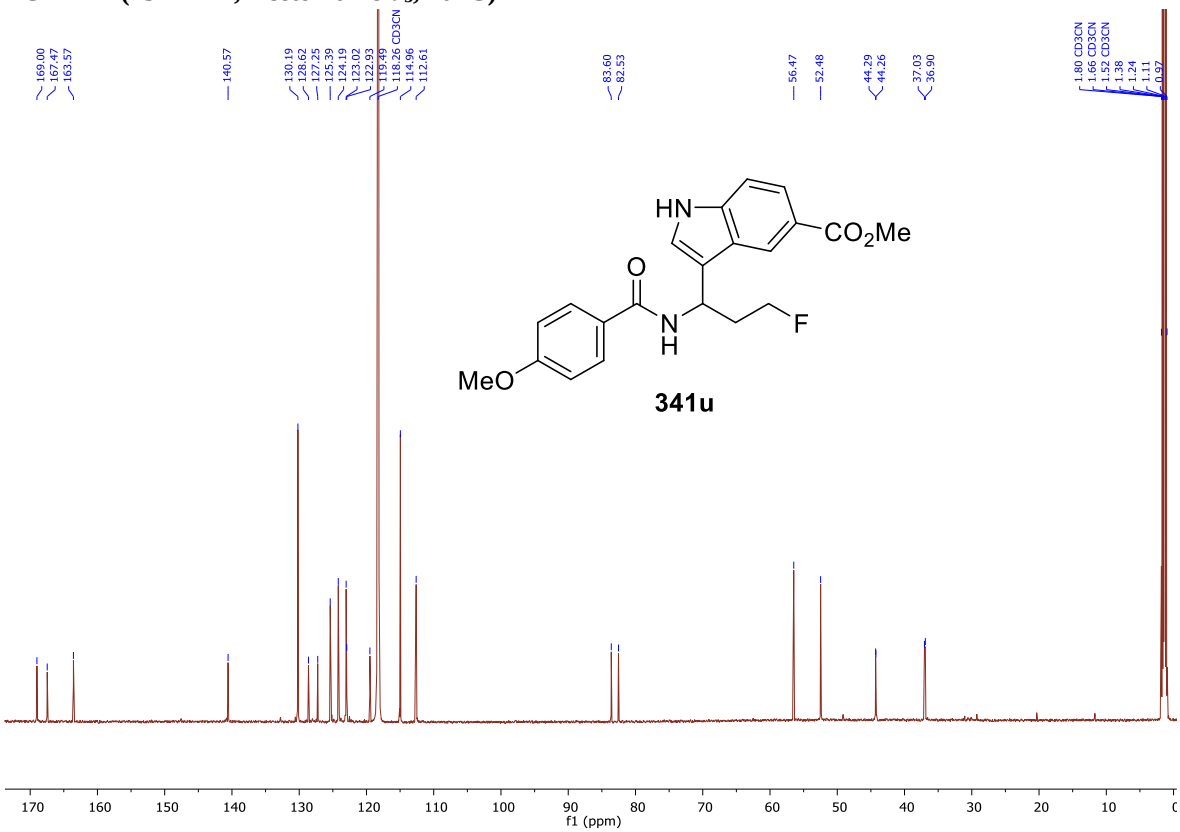
^{1}H-NMR (400 MHz, Acetone-d_6)



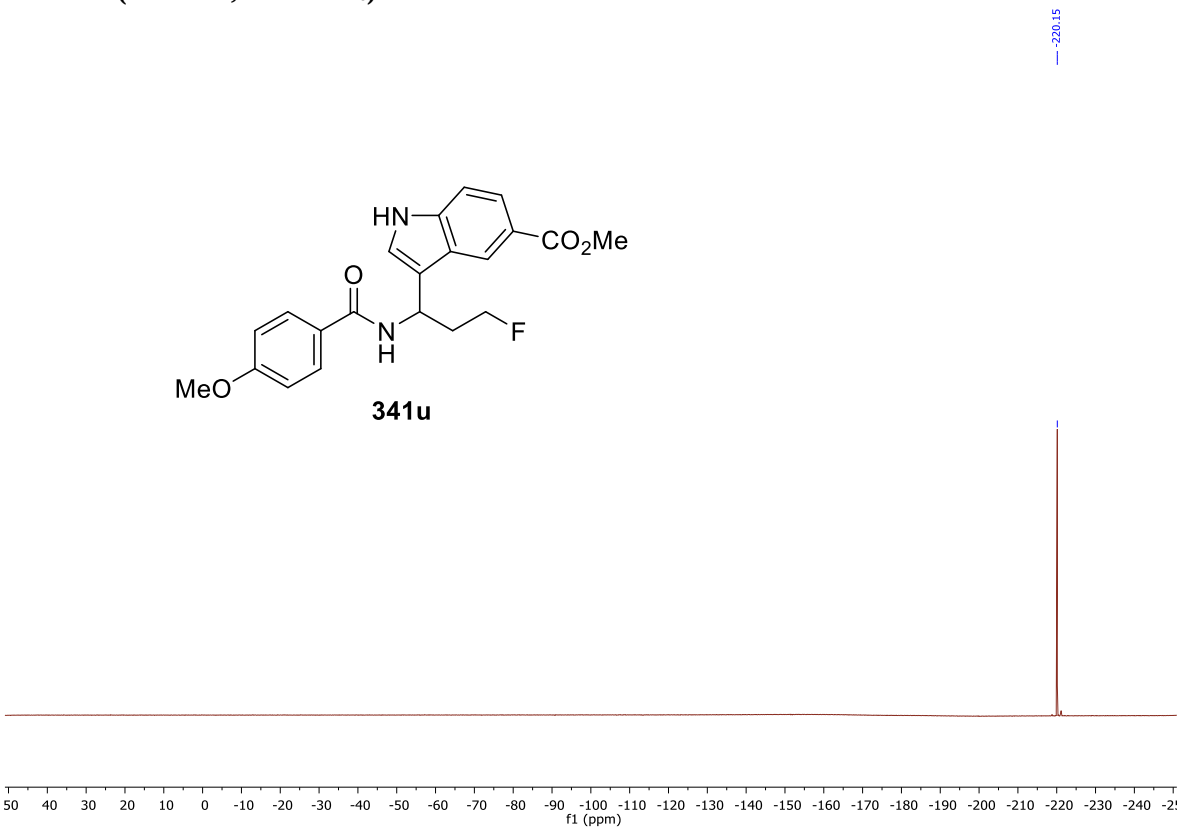
^{13}C-NMR (101 MHz, Acetone-d_6)



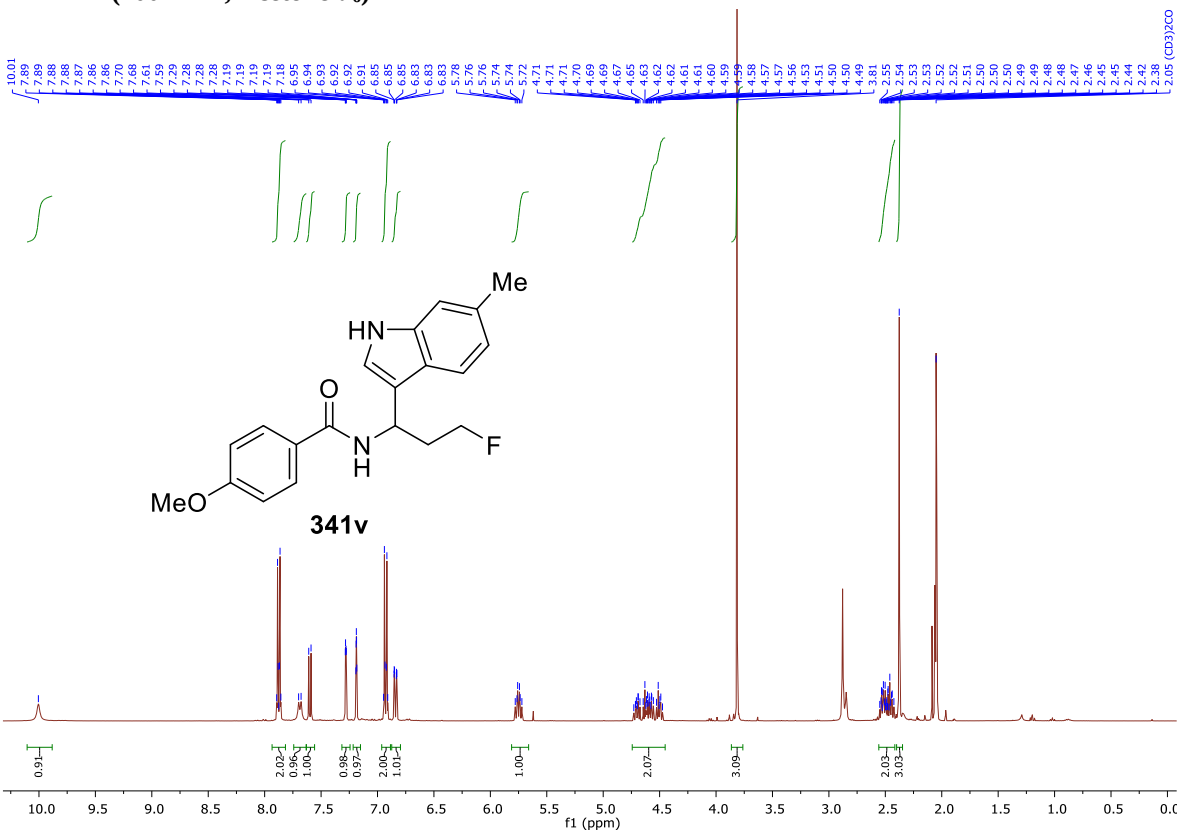
^{13}C-NMR (151 MHz, Acetonitrile-d_3, 70 °C)



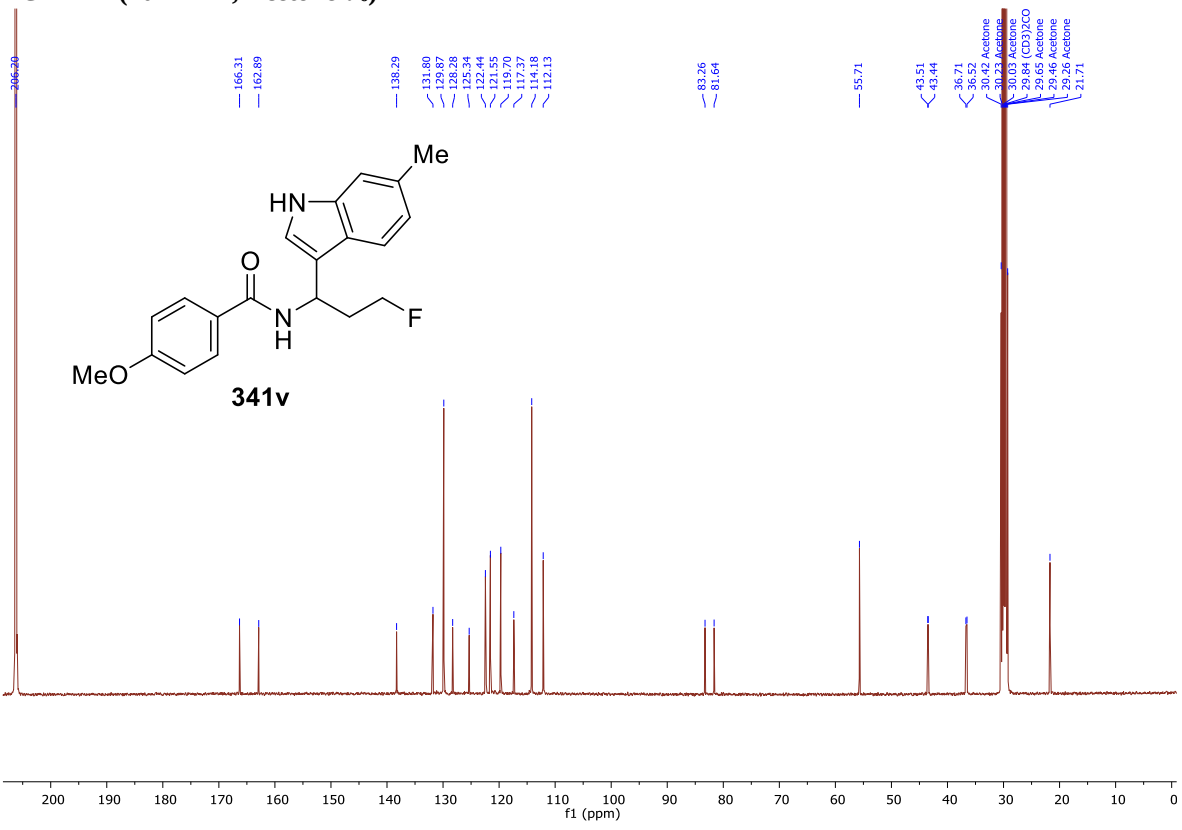
^{19}F-NMR (376 MHz, Acetone-d_6)



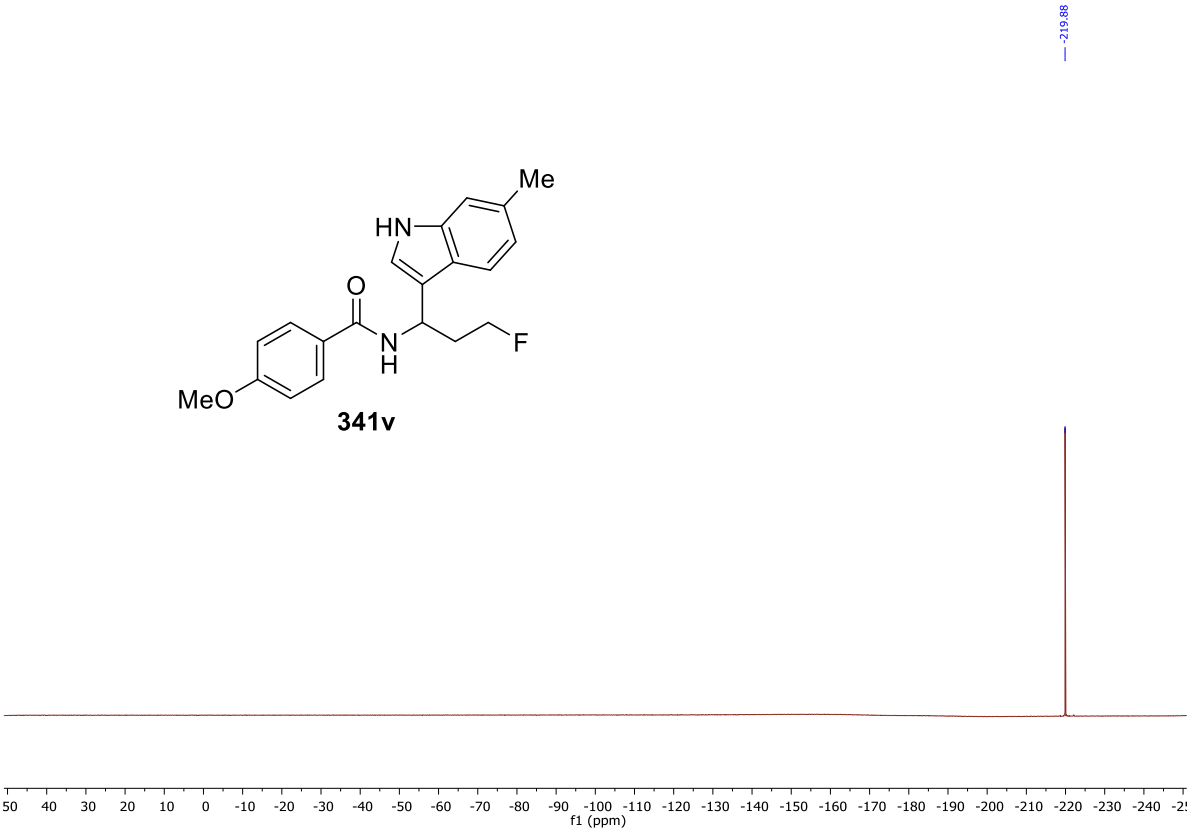
^{1}H-NMR (400 MHz, Acetone-d_6)



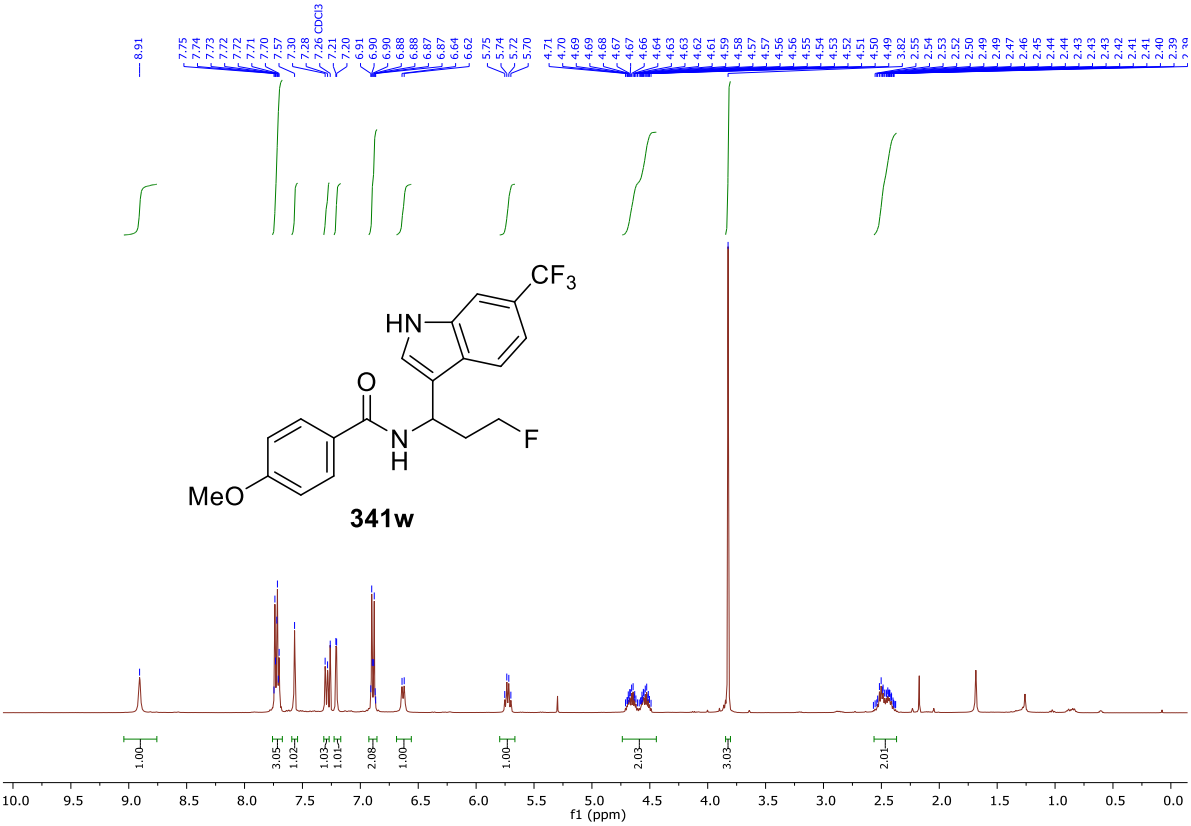
^{13}C-NMR (101 MHz, Acetone-d_6)



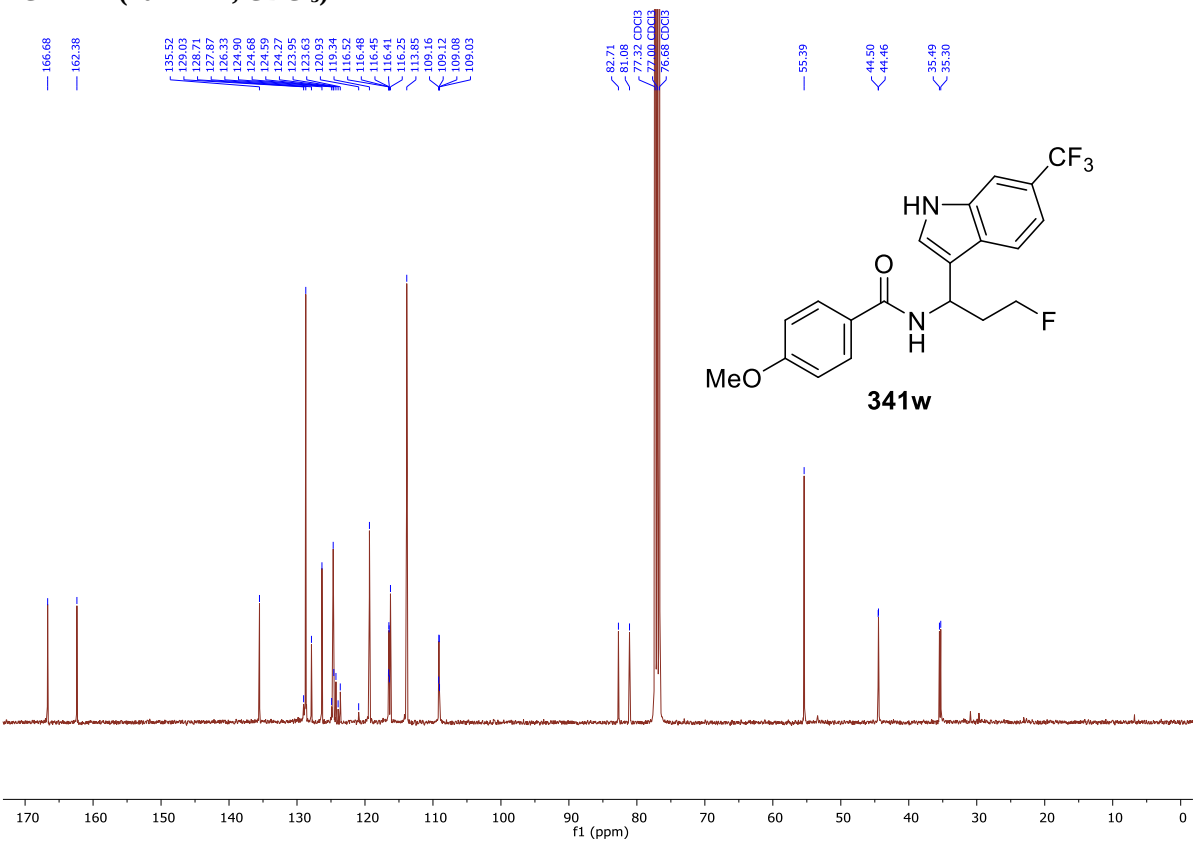
^{19}F-NMR (376 MHz, Acetone-d_6)



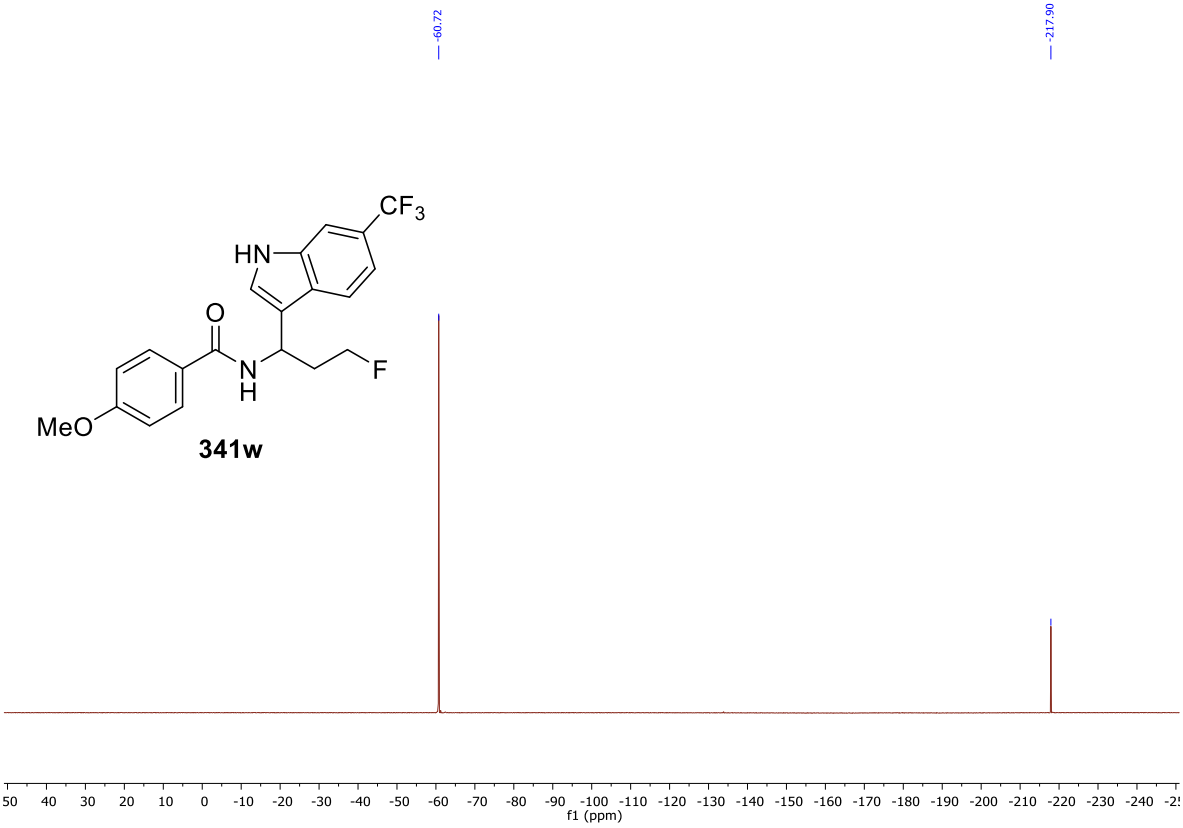
^{1}H-NMR (400 MHz, $CDCl_3$)



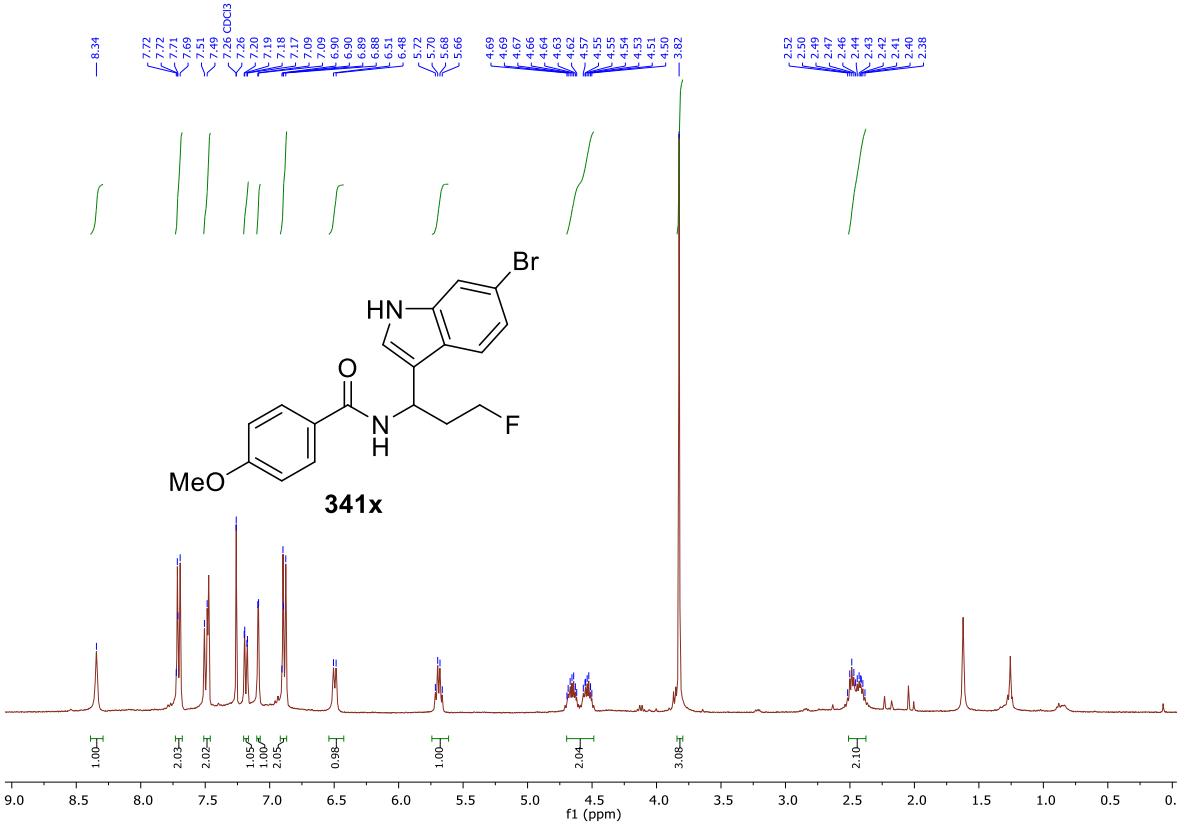
^{13}C-NMR (101 MHz, $CDCl_3$)



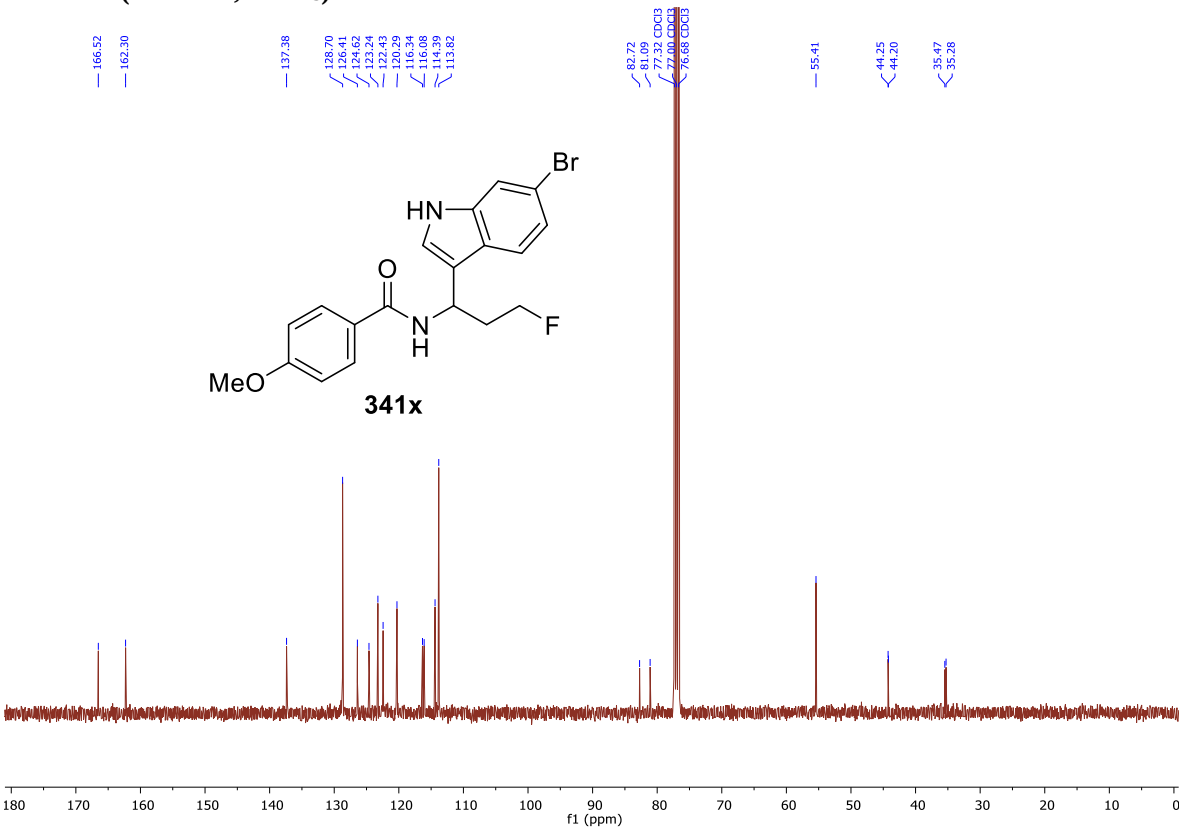
^{19}F-NMR (376 MHz, $CDCl_3$)



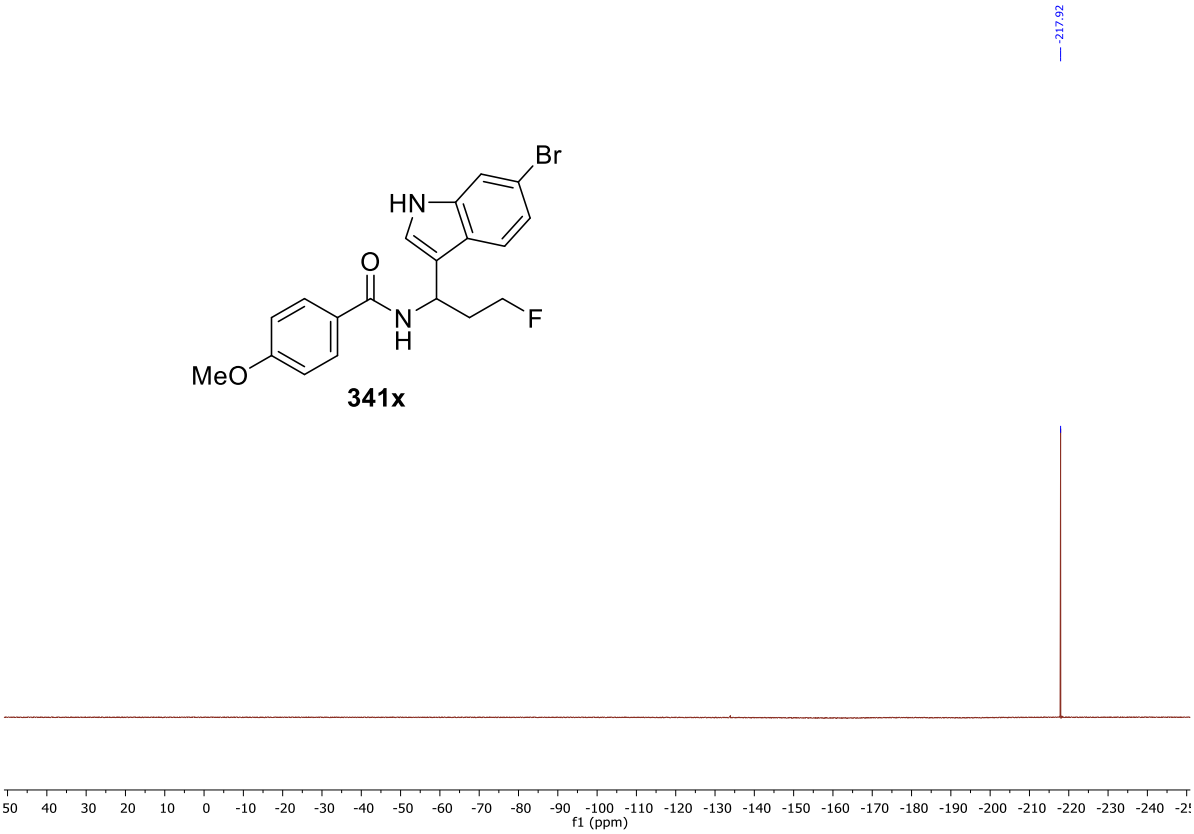
^{1}H-NMR (400 MHz, $CDCl_3$)



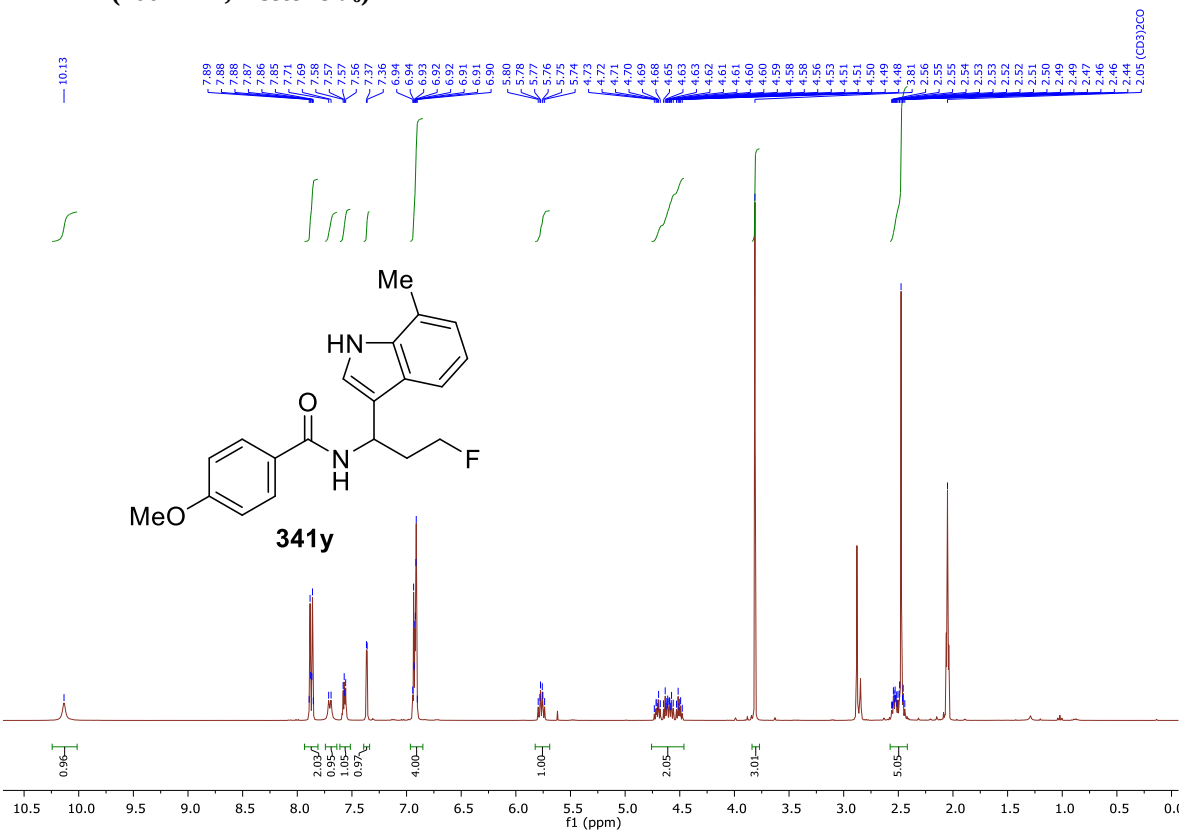
^{13}C-NMR (101 MHz, $CDCl_3$)



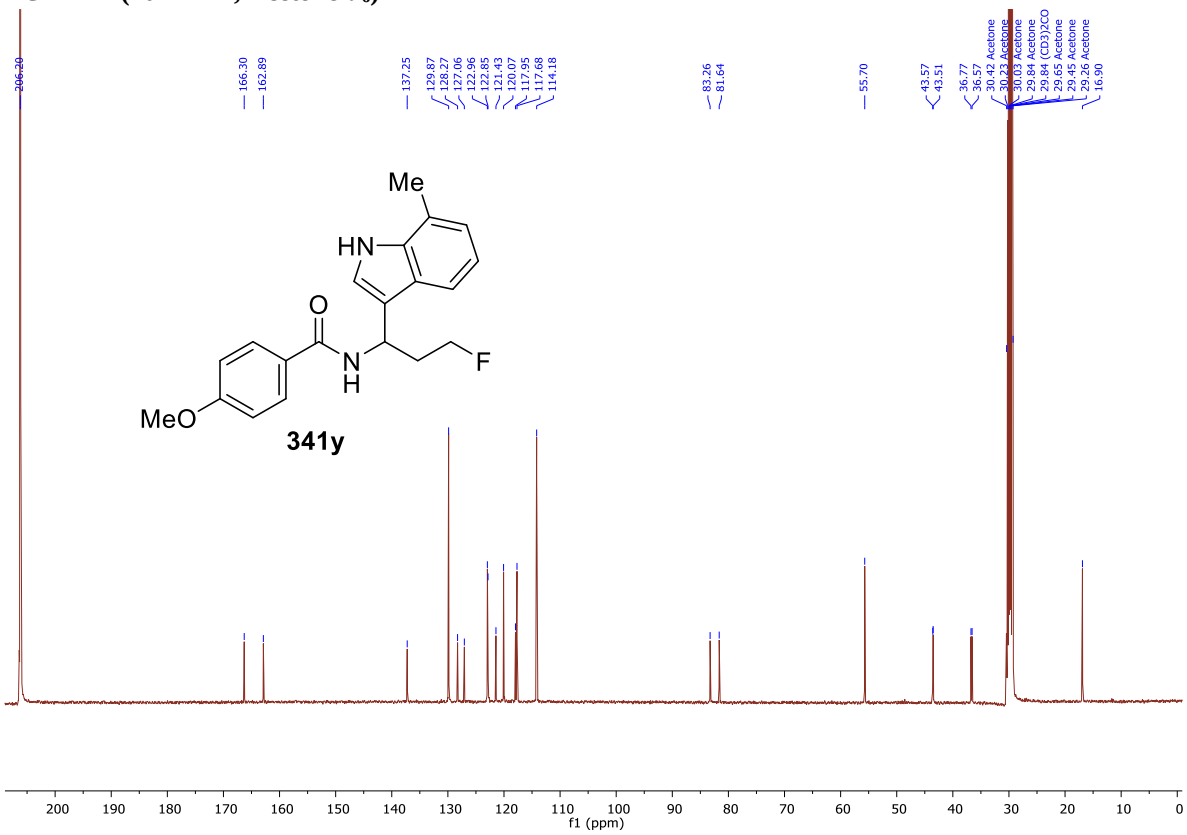
^{19}F-NMR (376 MHz, $CDCl_3$)



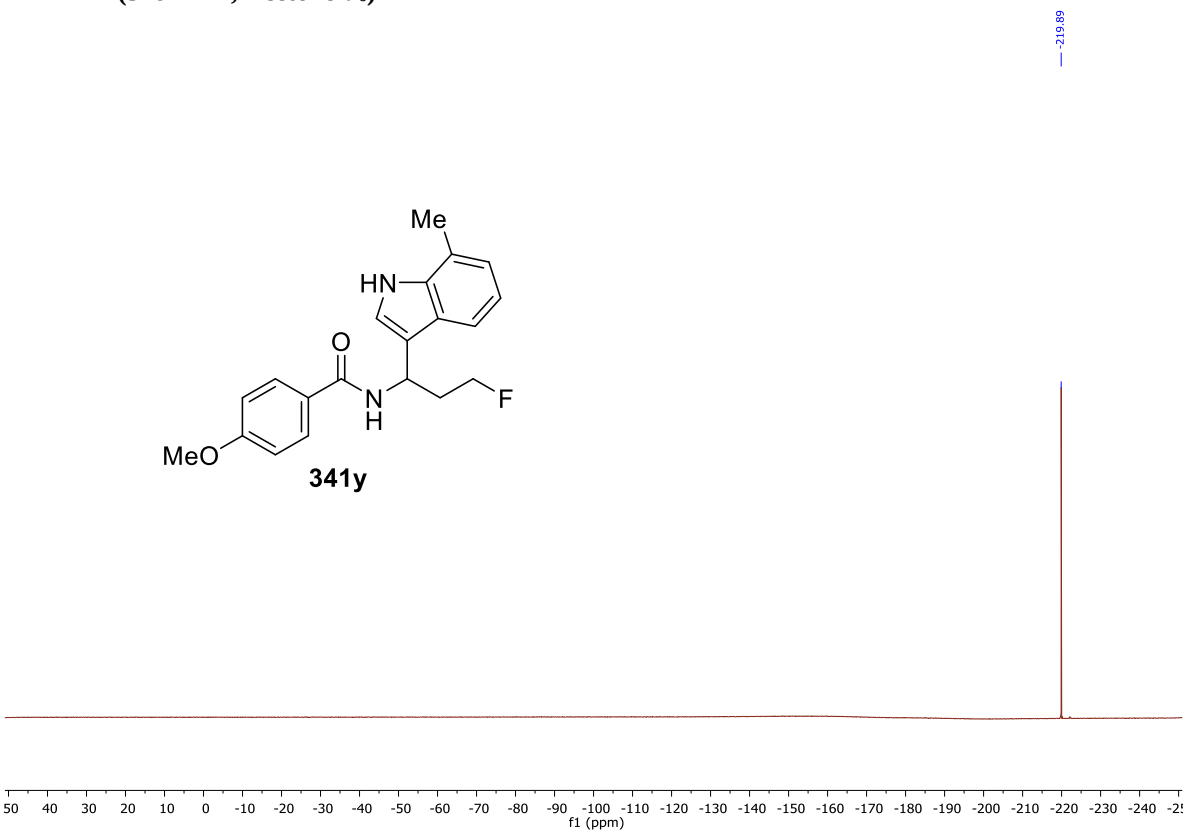
^{1}H-NMR (400 MHz, Acetone-d_6)



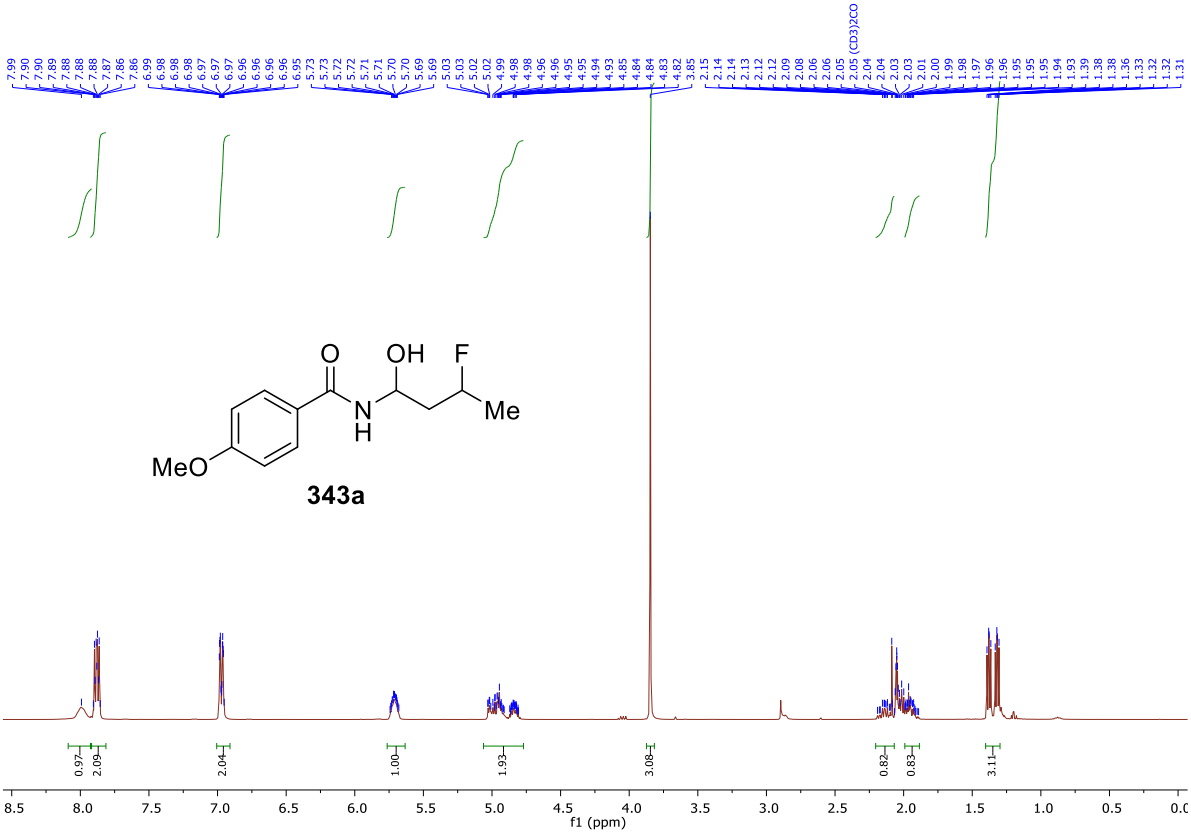
^{13}C-NMR (101 MHz, Acetone-d_6)



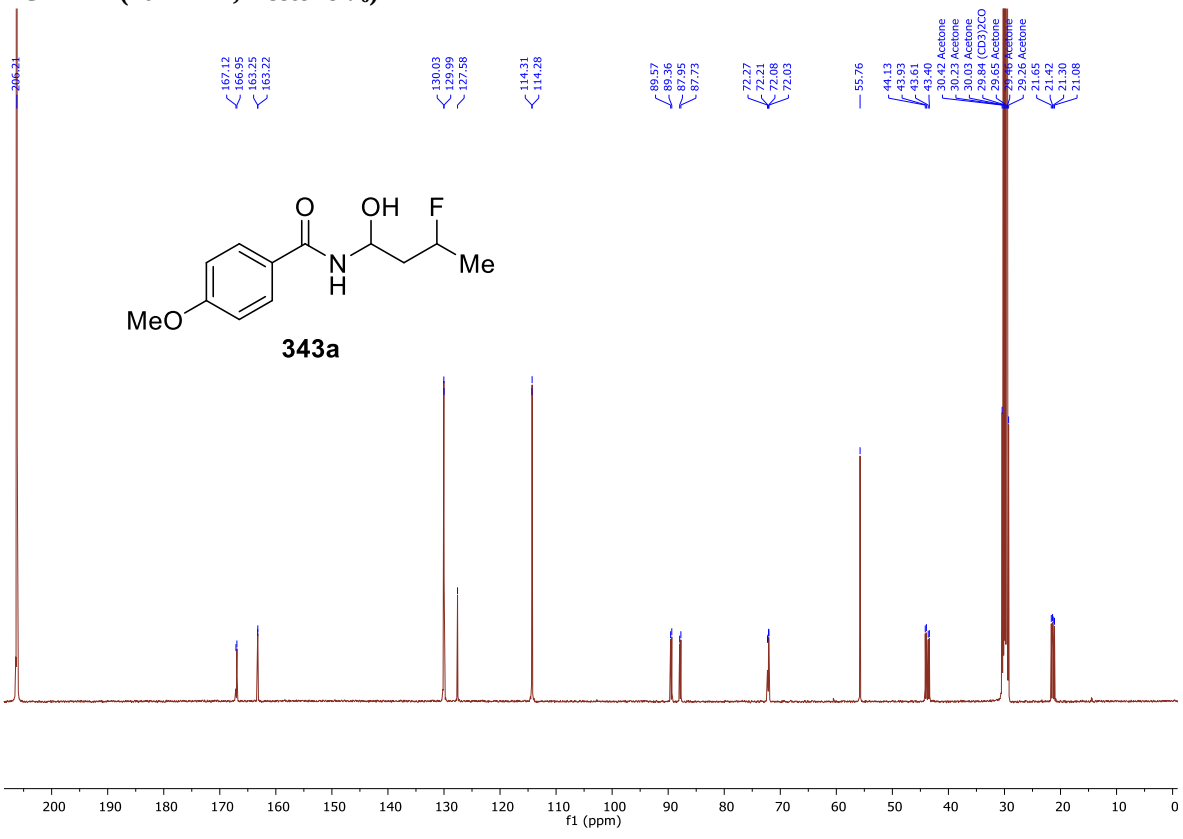
^{19}F-NMR (376 MHz, Acetone-d_6)



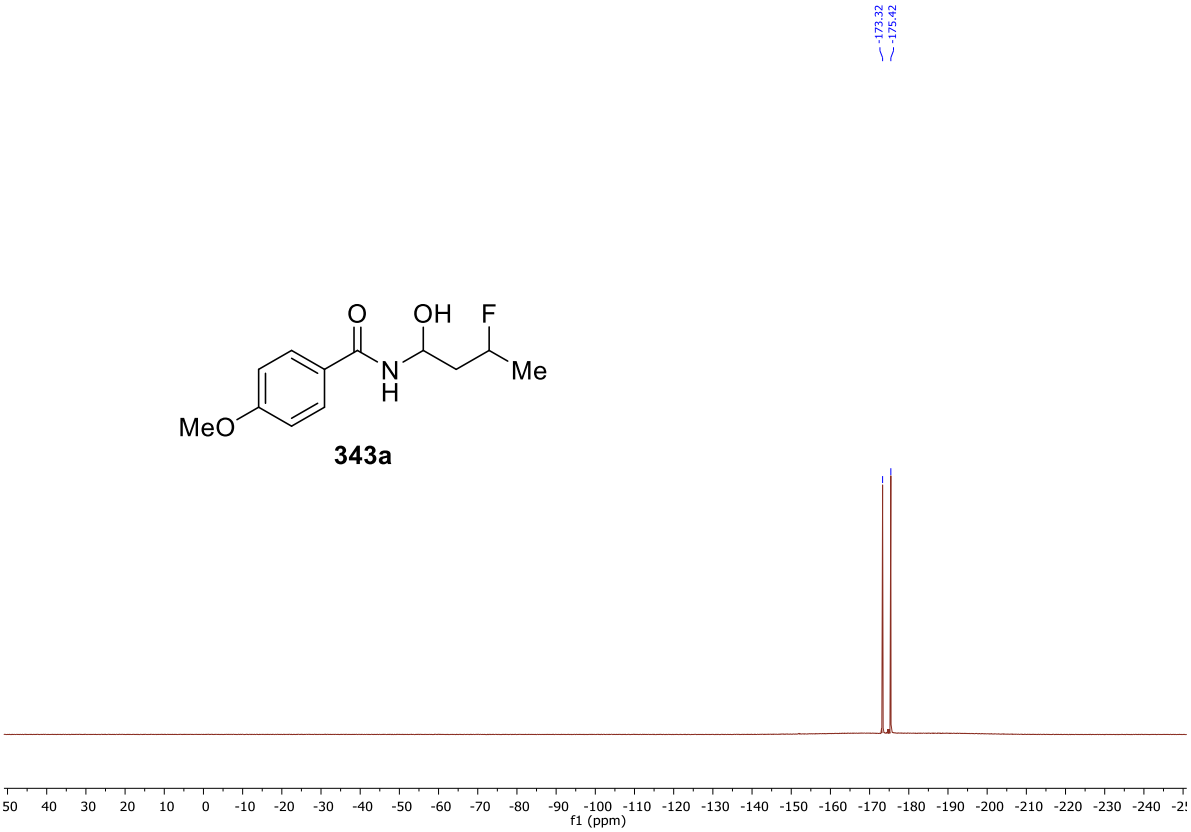
^{1}H-NMR (400 MHz, Acetone-d_6)



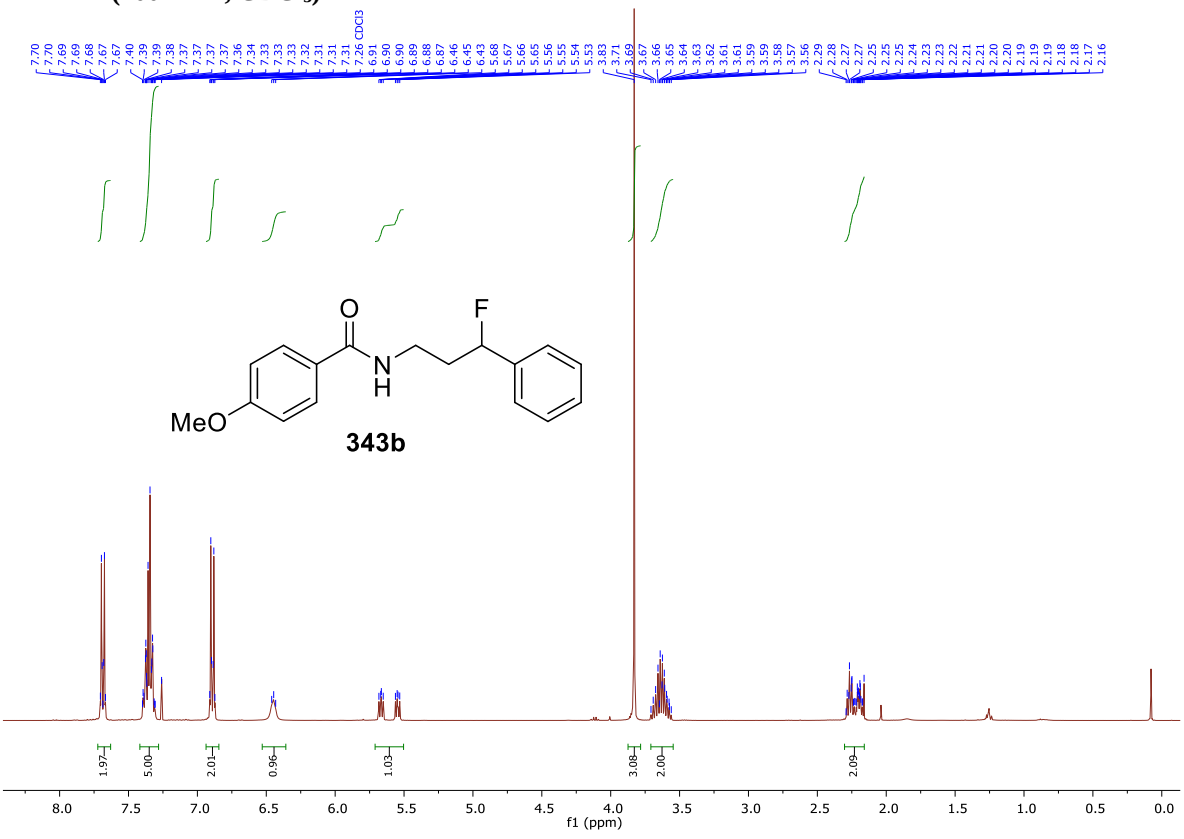
^{13}C-NMR (101 MHz, Acetone-d_6)



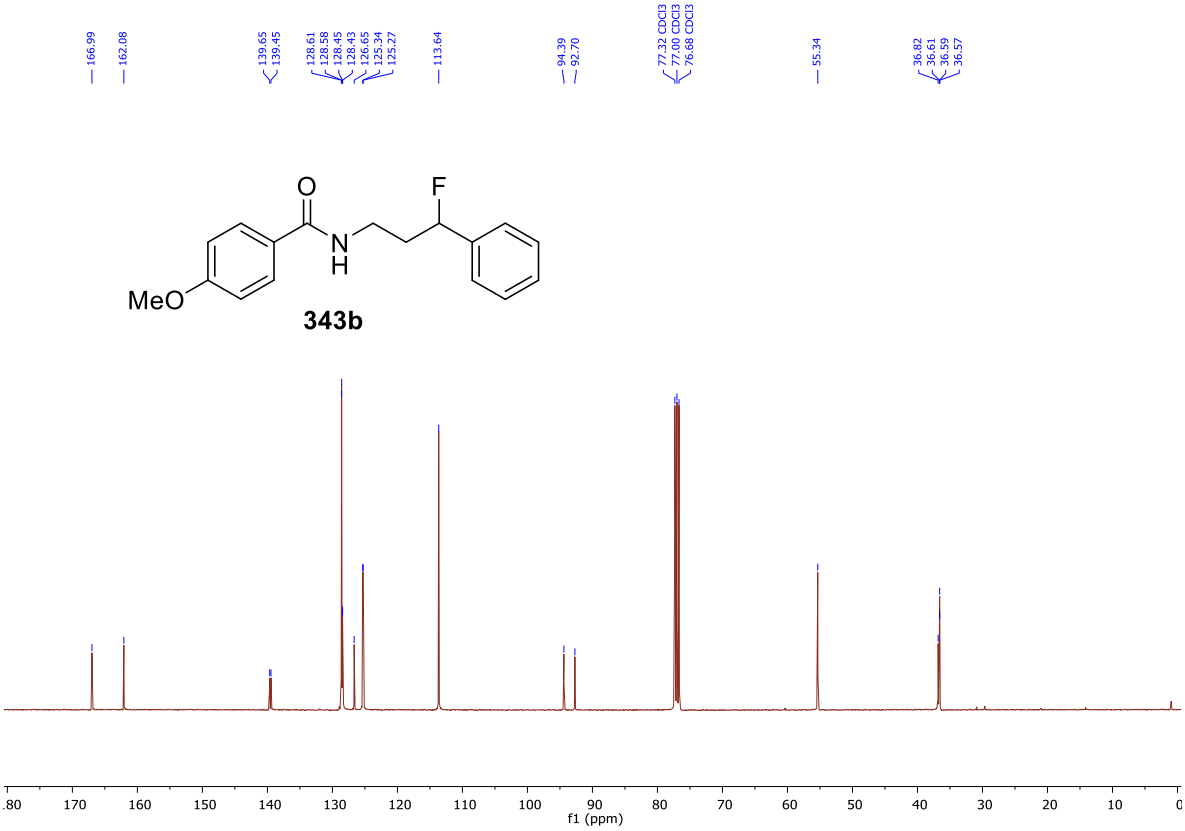
^{19}F-NMR (376 MHz, Acetone-d_6)



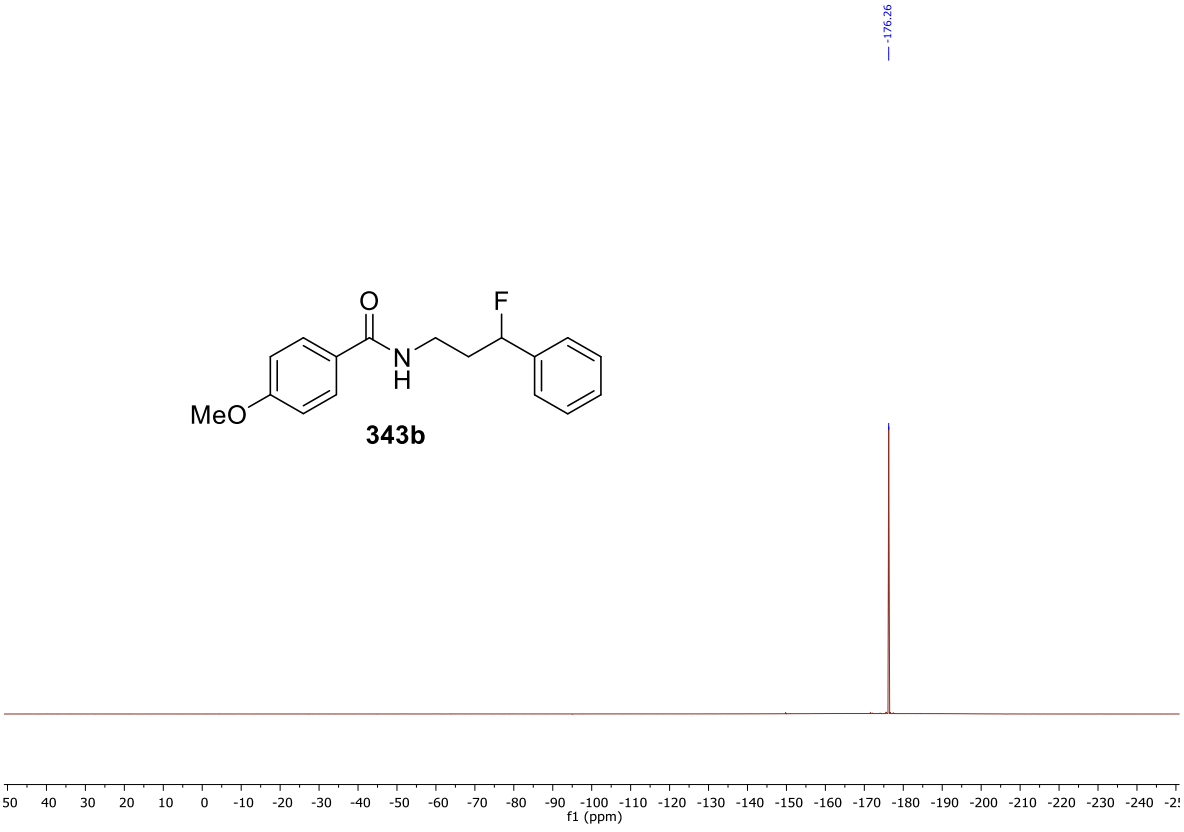
^{1}H-NMR (400 MHz, $CDCl_3$)



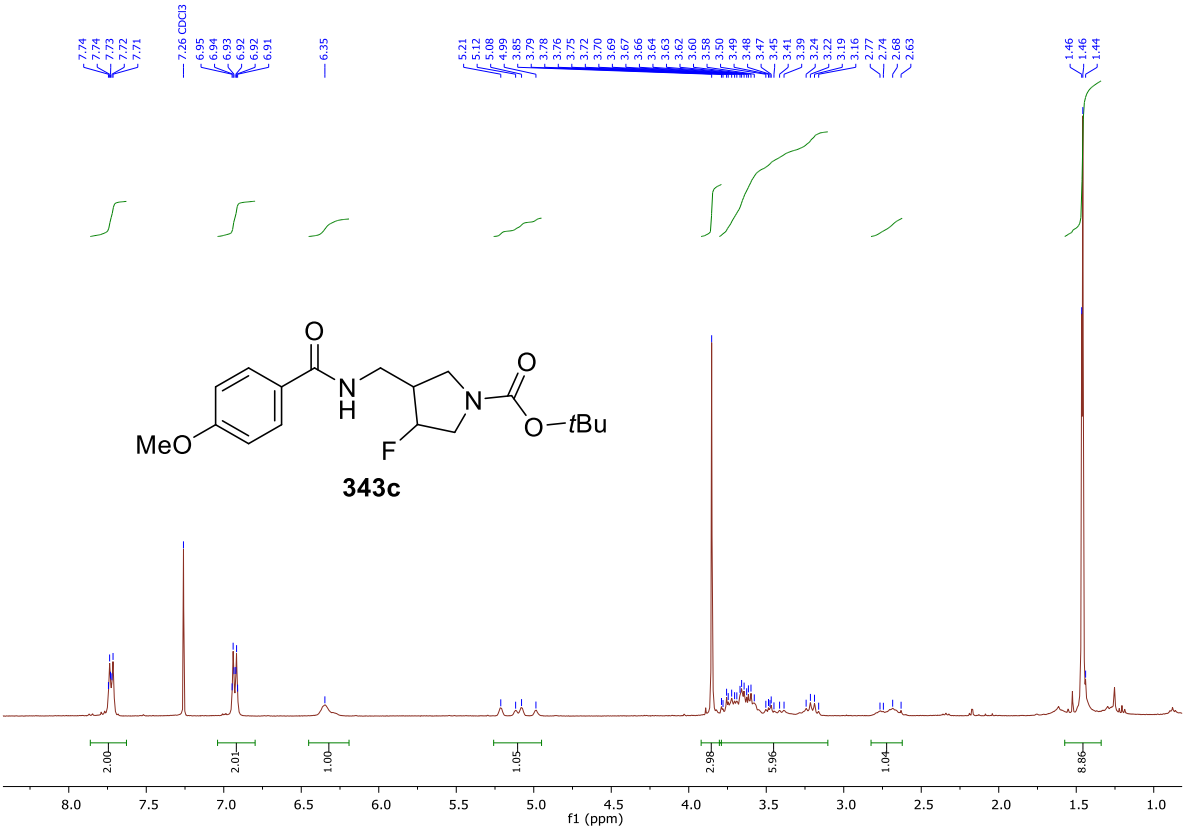
^{13}C-NMR (101 MHz, $CDCl_3$)



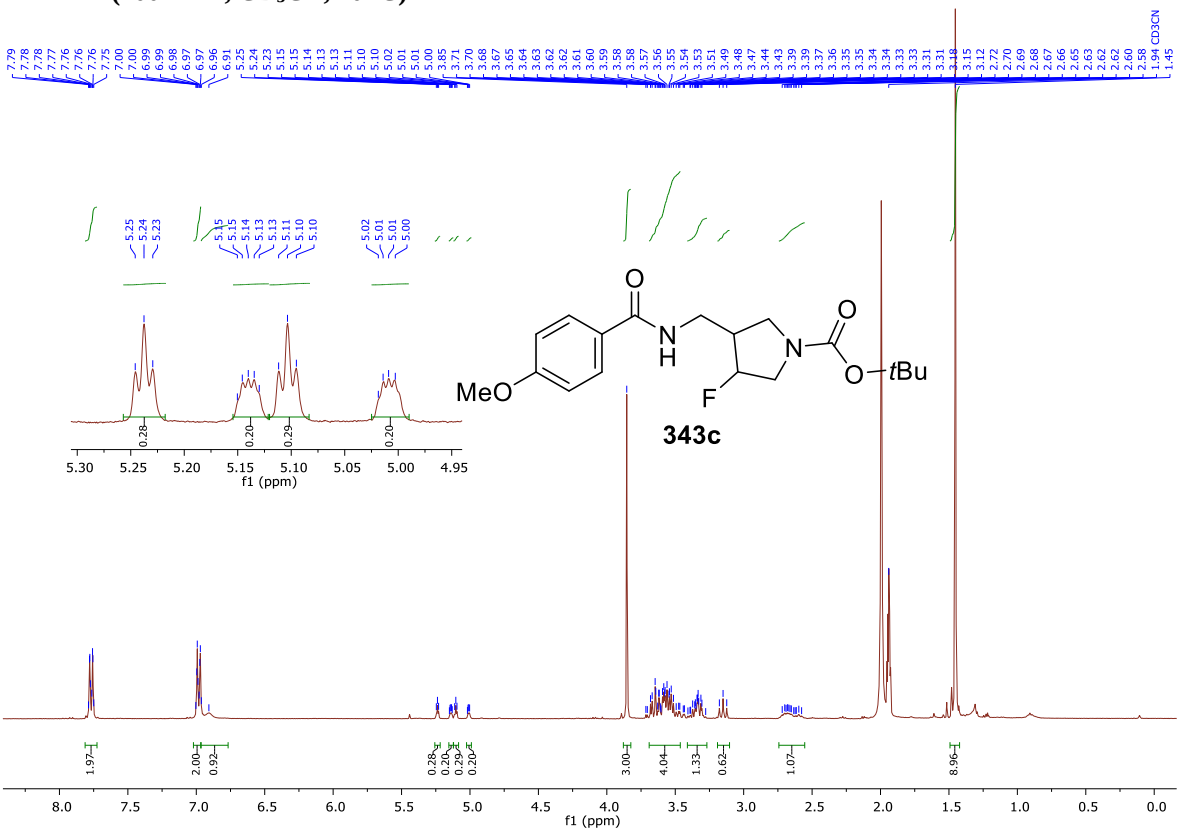
^{19}F-NMR (376 MHz, $CDCl_3$)



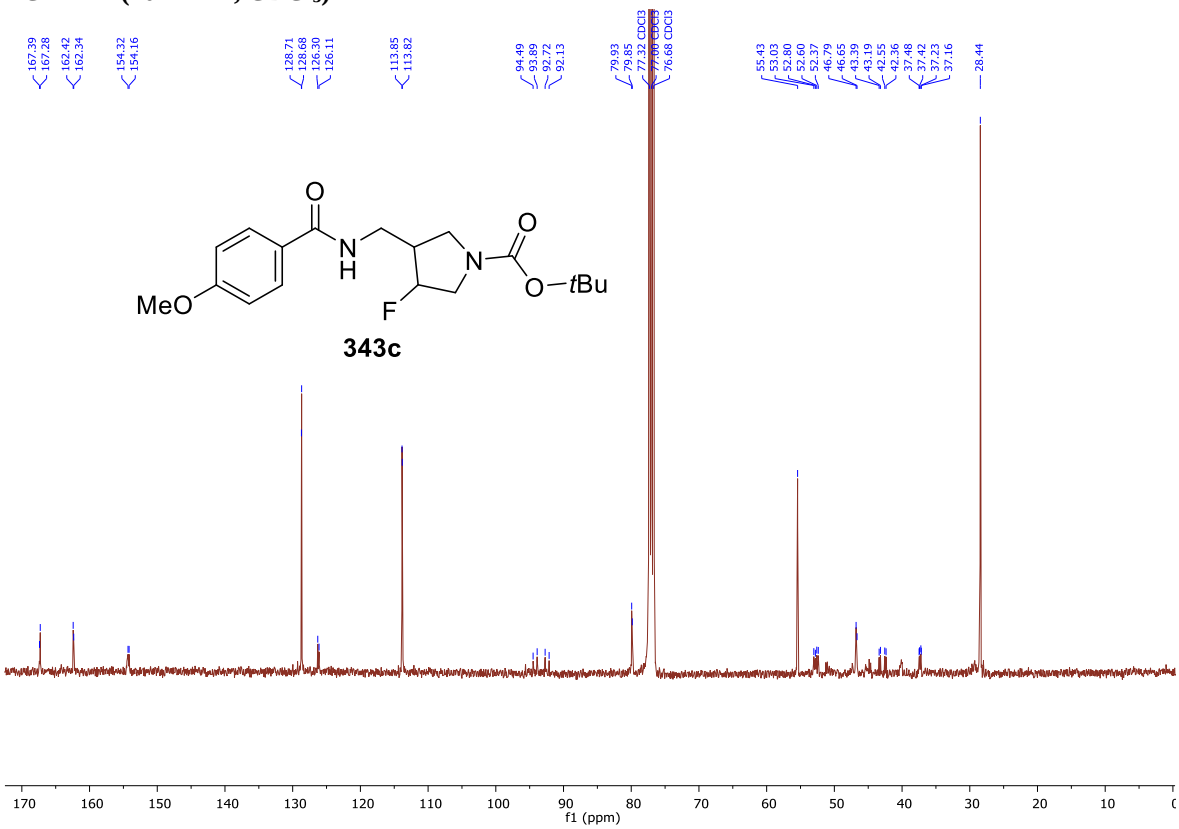
^{1}H-NMR (400 MHz, $CDCl_3$)



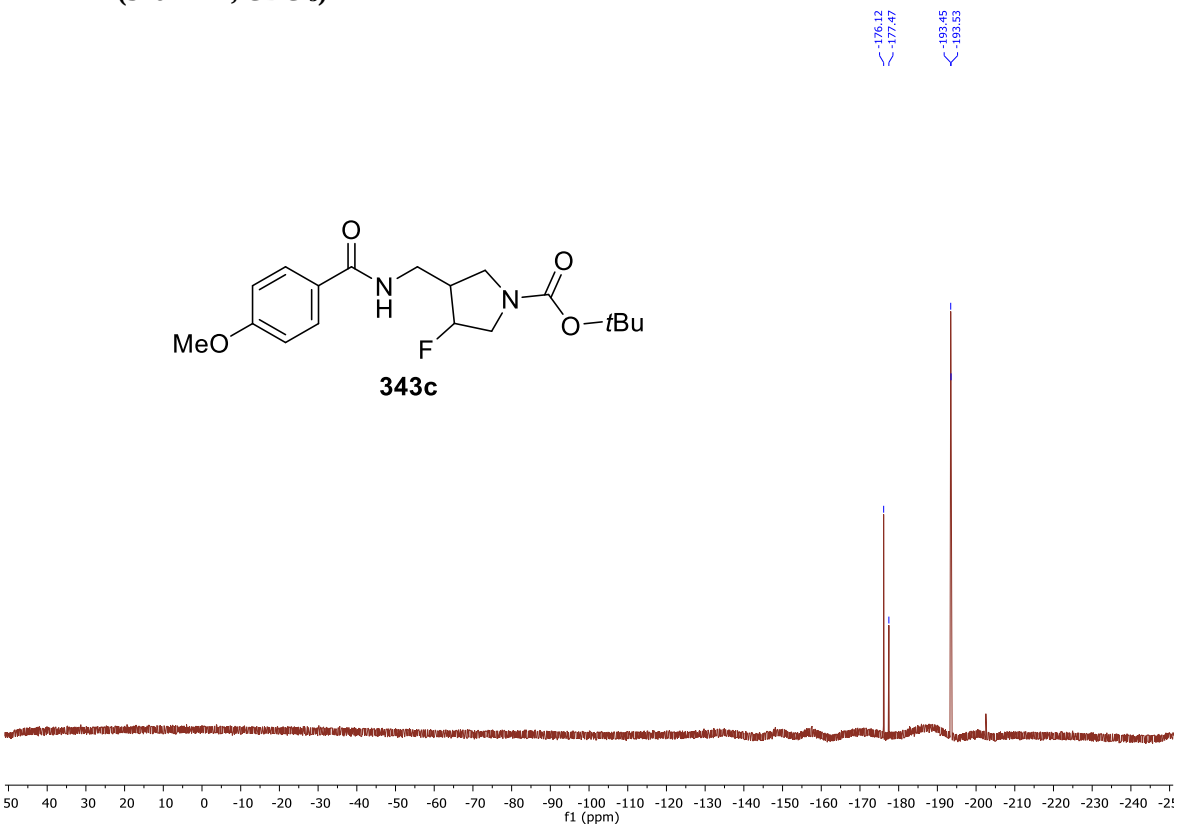
^{1}H-NMR (400 MHz, CD_3CN, 70 ºC)



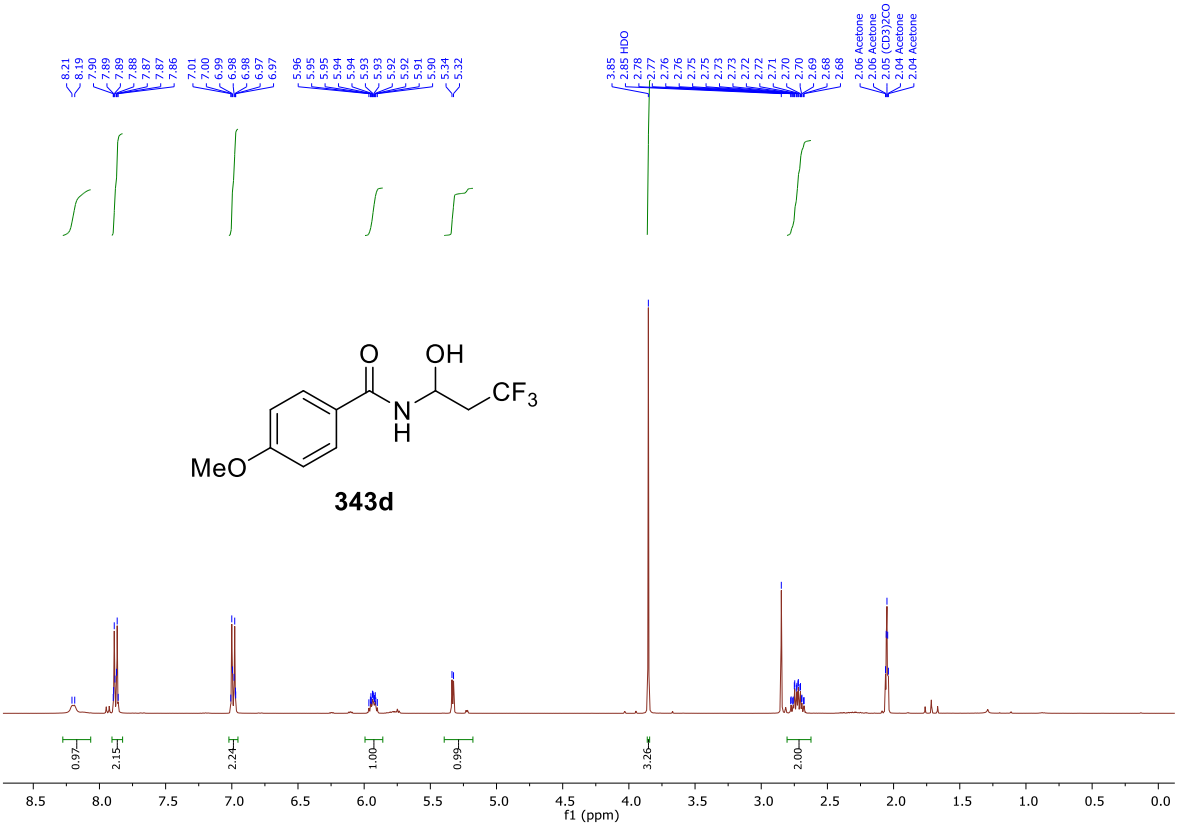
^{13}C-NMR (101 MHz, $CDCl_3$)



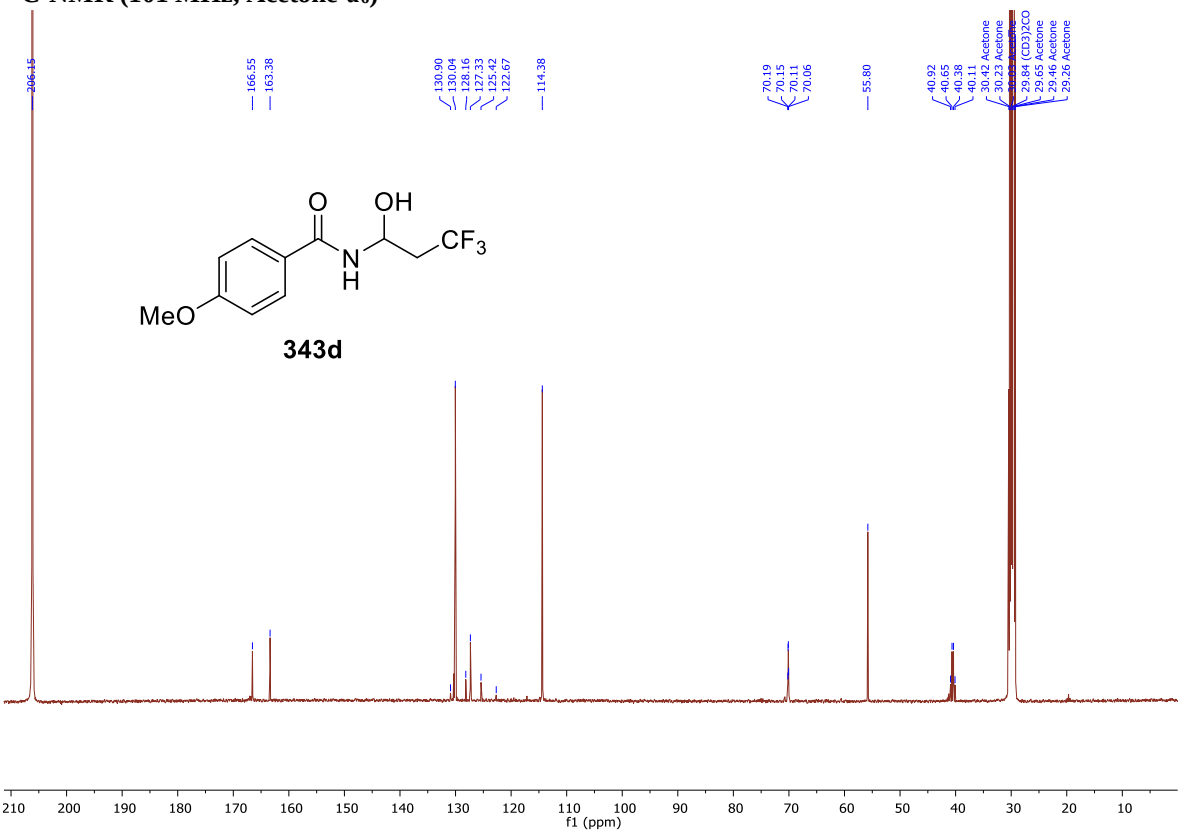
^{19}F-NMR (376 MHz, $CDCl_3$)



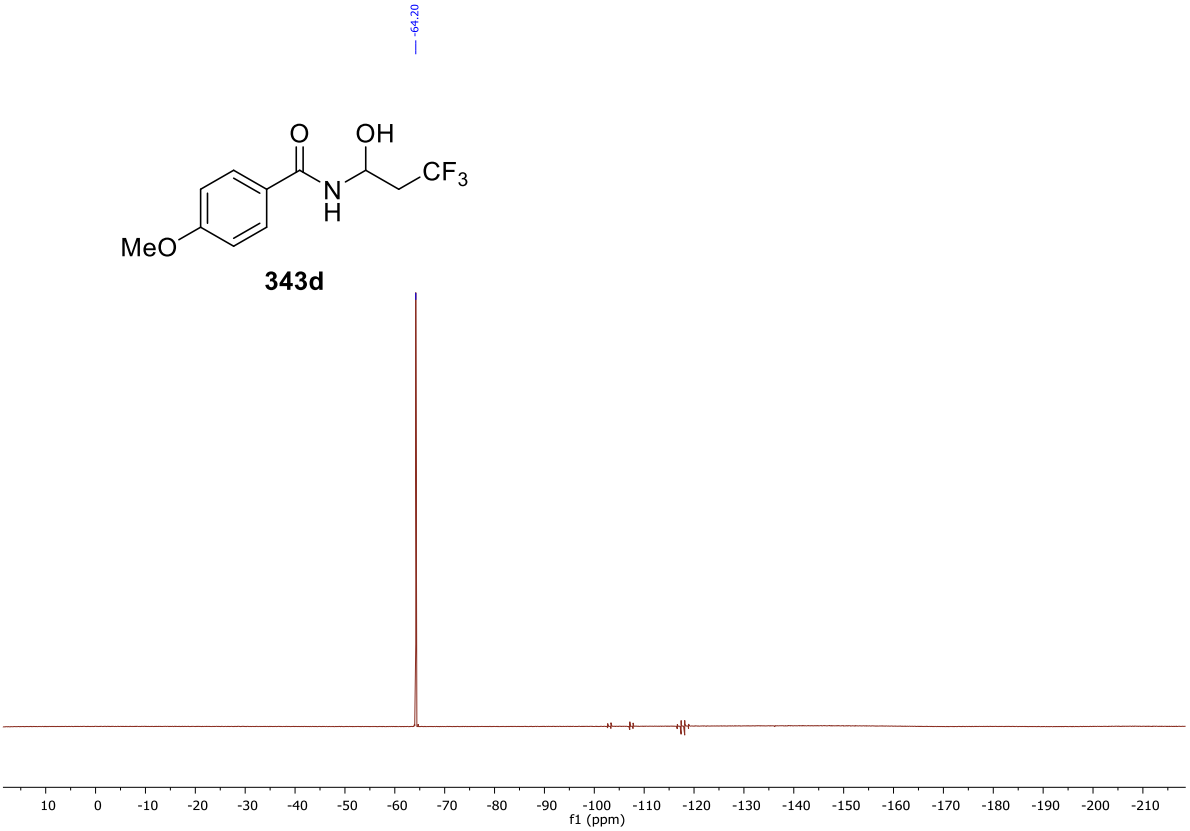
^{1}H-NMR (400 MHz, Acetone-d_6)



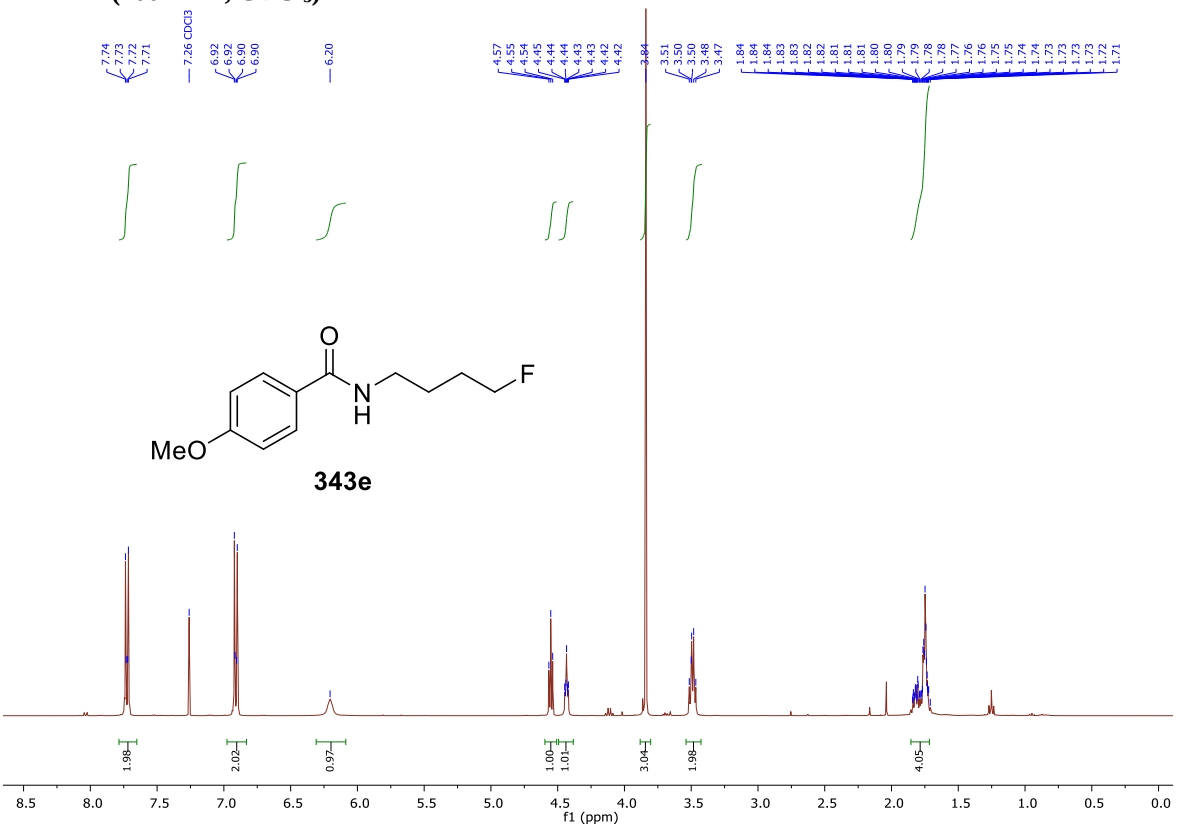
^{13}C-NMR (101 MHz, Acetone-d_6)



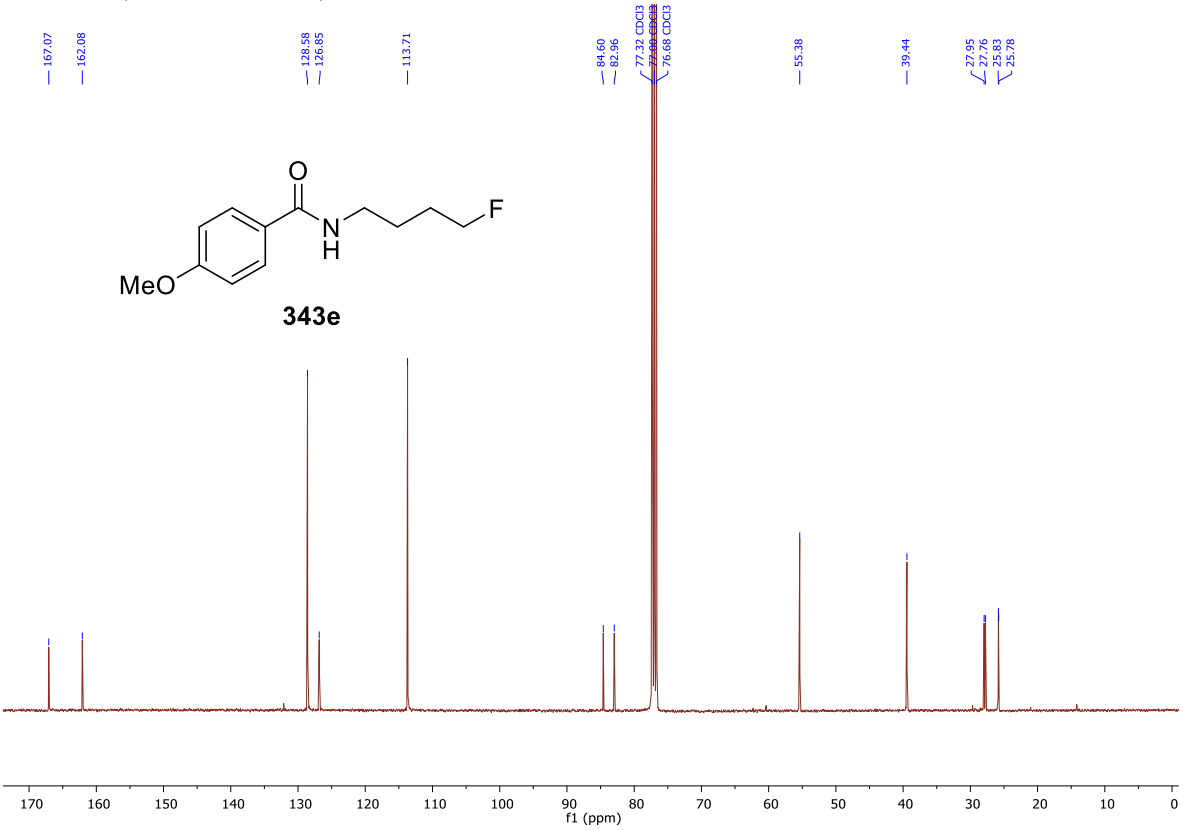
^{19}F-NMR (376 MHz, Acetone-d_6)



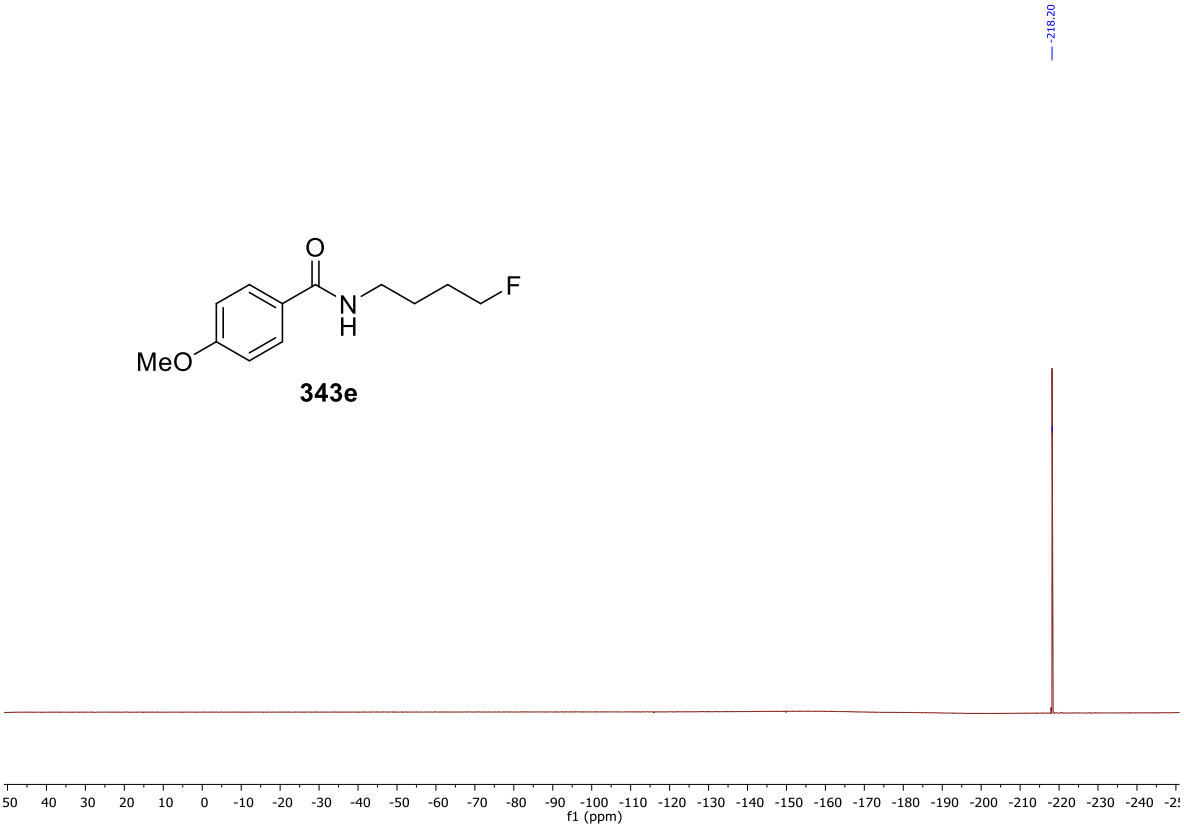
^{1}H-NMR (400 MHz, $CDCl_3$)



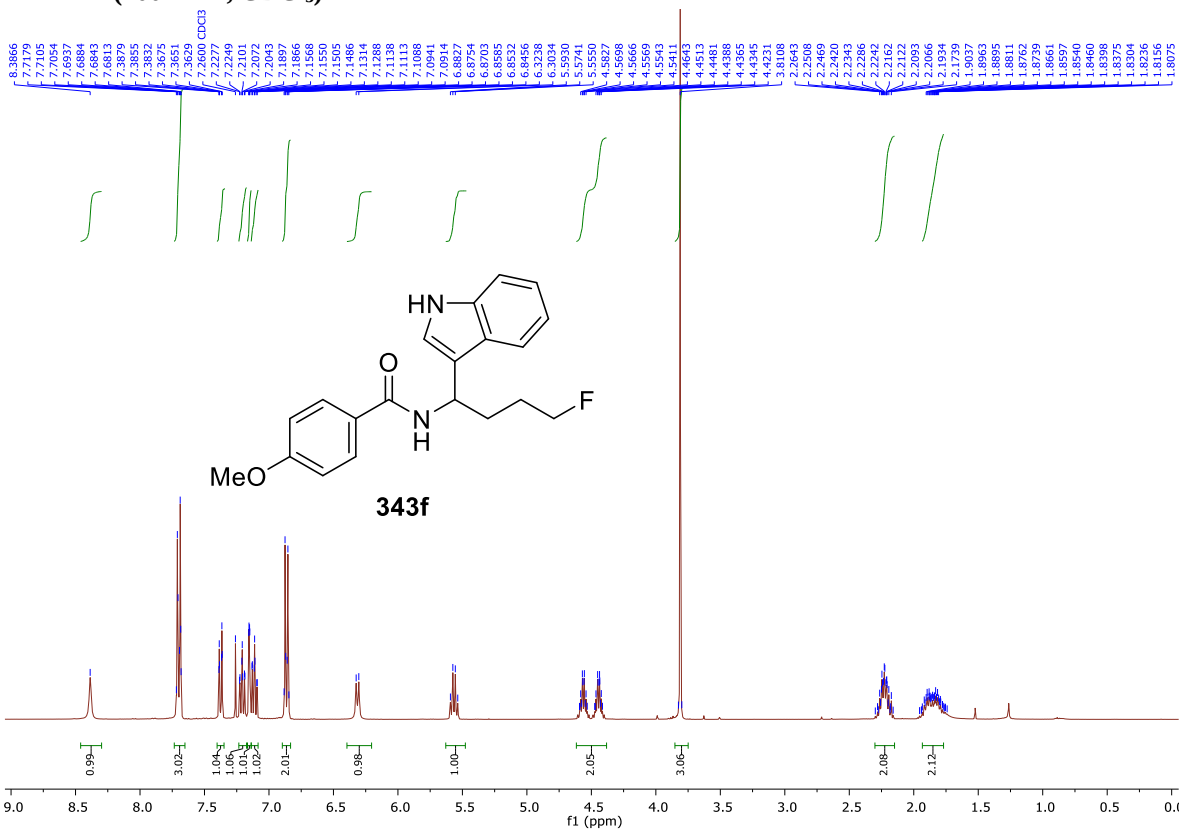
^{13}C-NMR (101 MHz, $CDCl_3$)



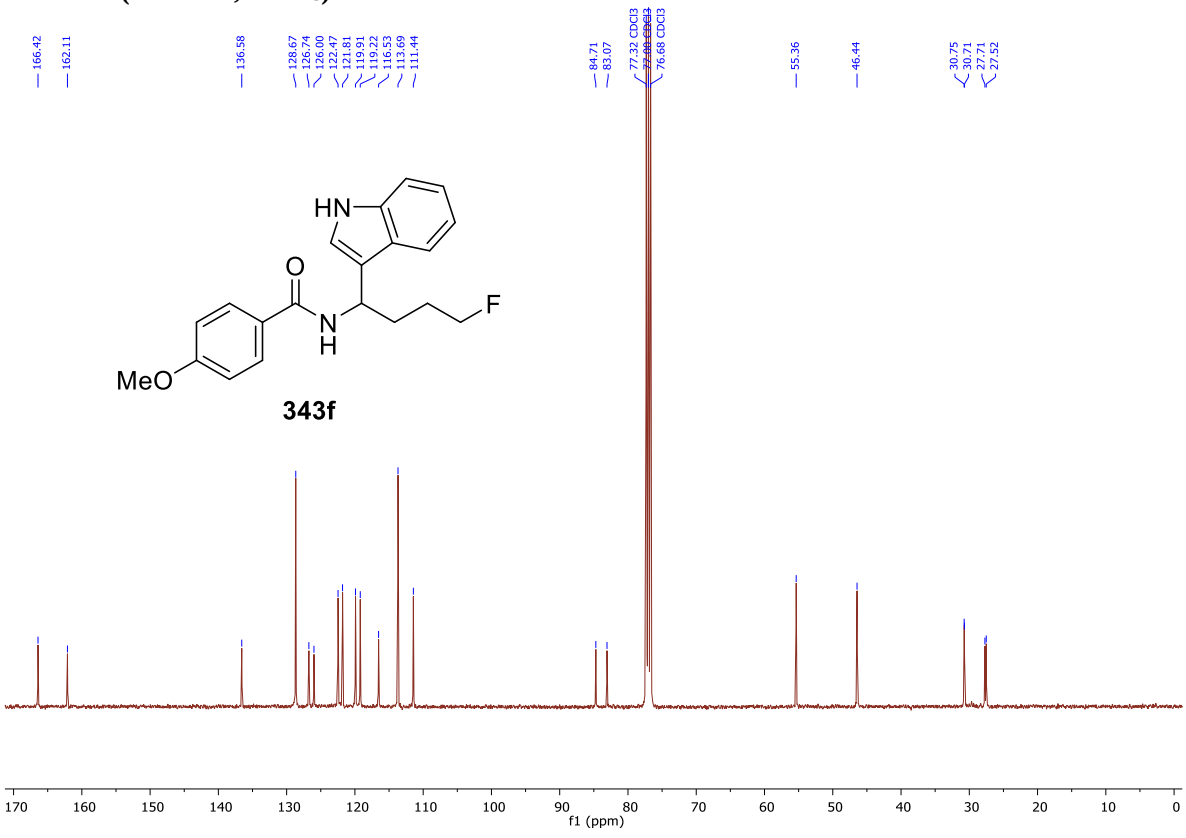
^{19}F-NMR (376 MHz, $CDCl_3$)



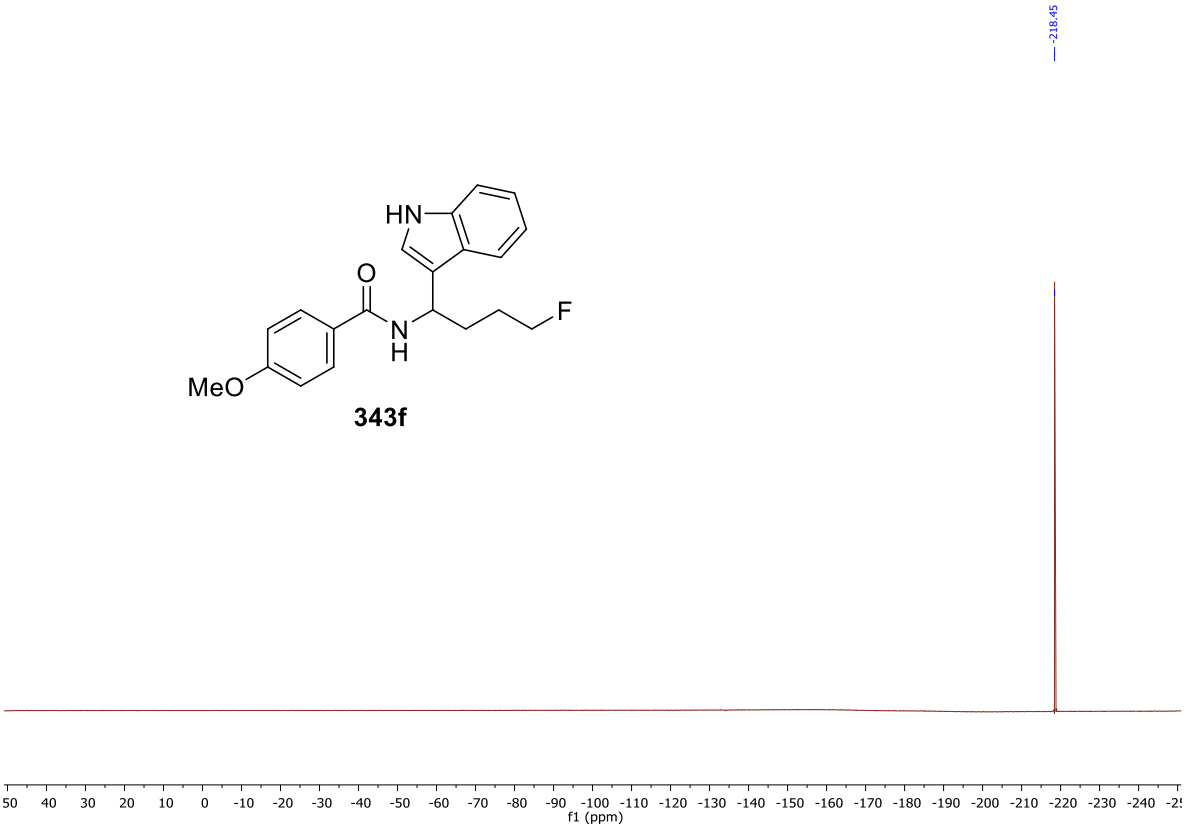
^{1}H-NMR (400 MHz, $CDCl_3$)



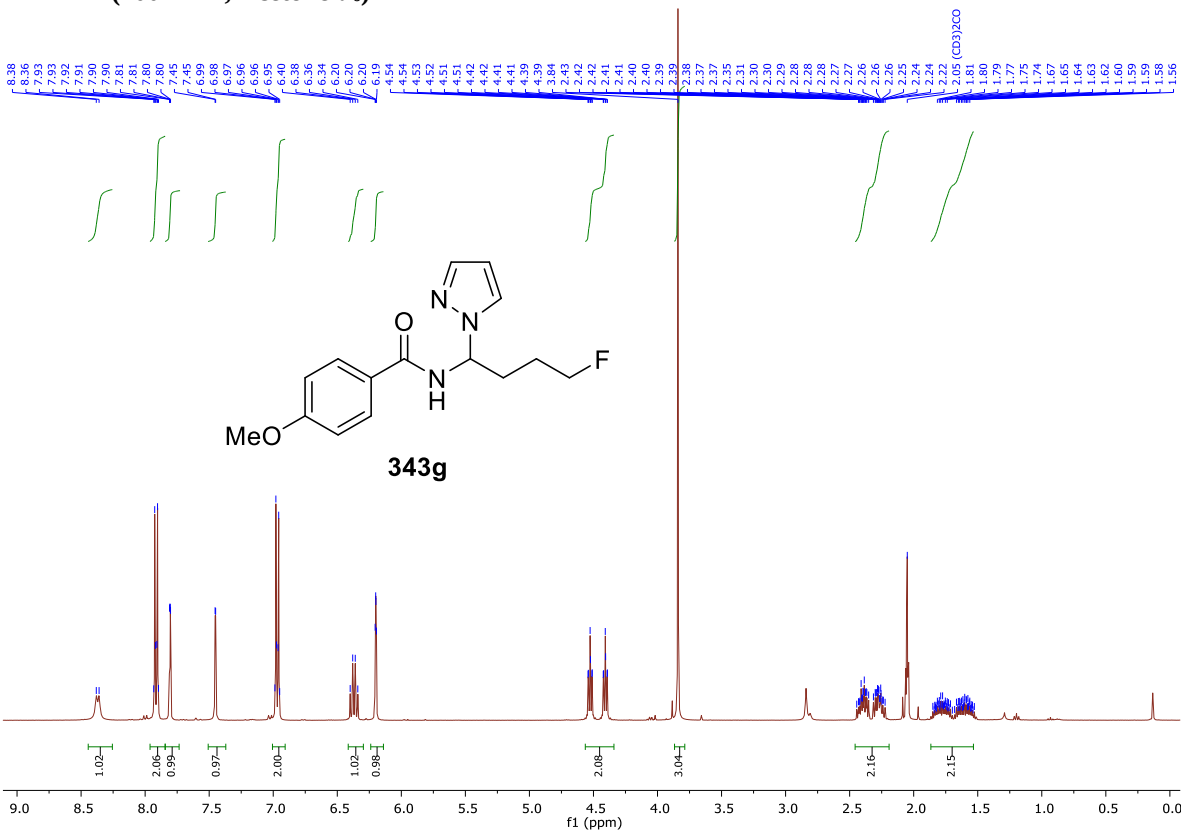
^{13}C-NMR (101 MHz, $CDCl_3$)



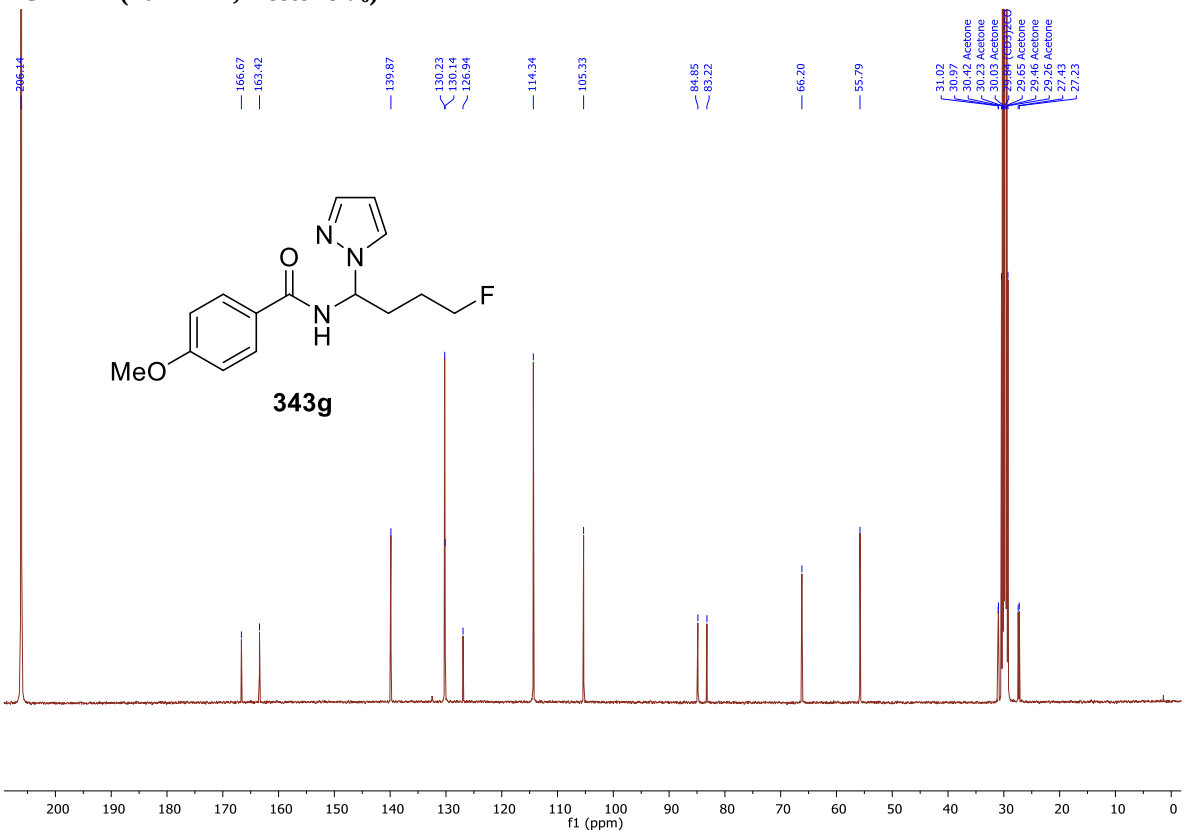
^{19}F-NMR (376 MHz, $CDCl_3$)



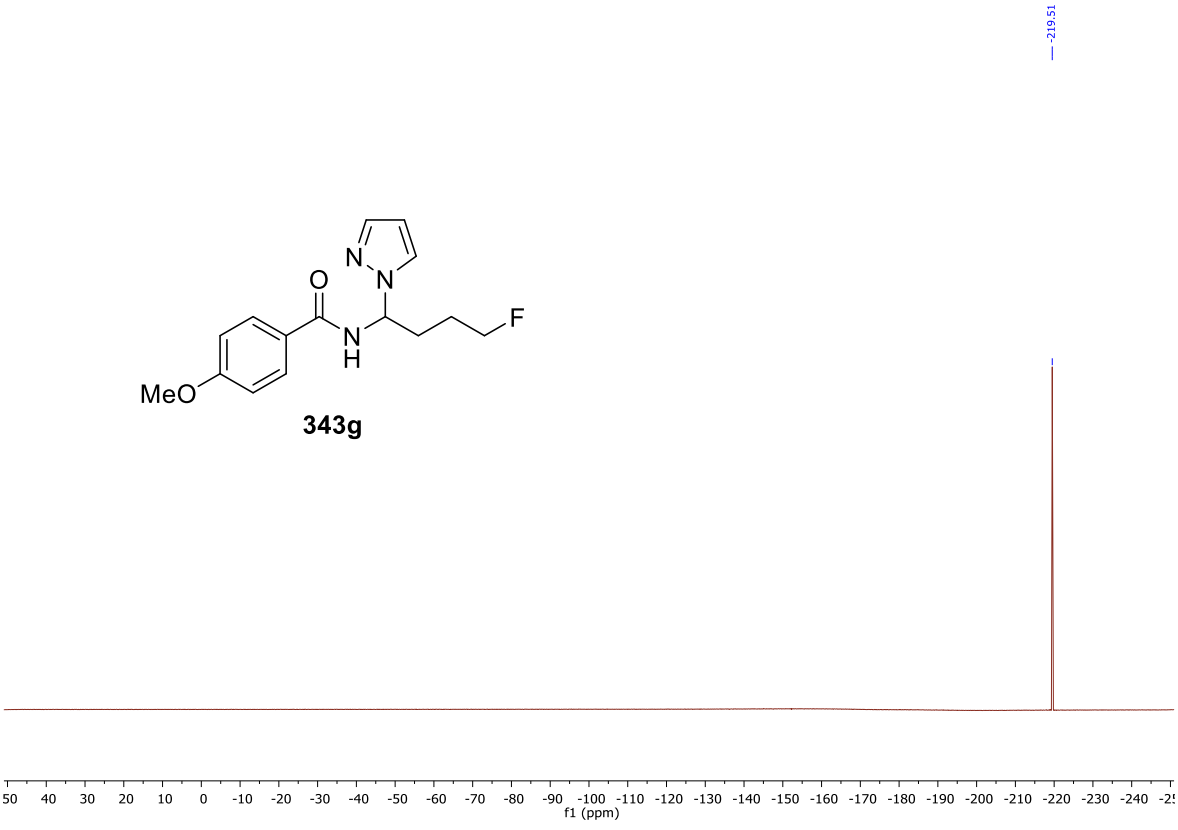
^{1}H-NMR (400 MHz, Acetone-*d*$_6$)



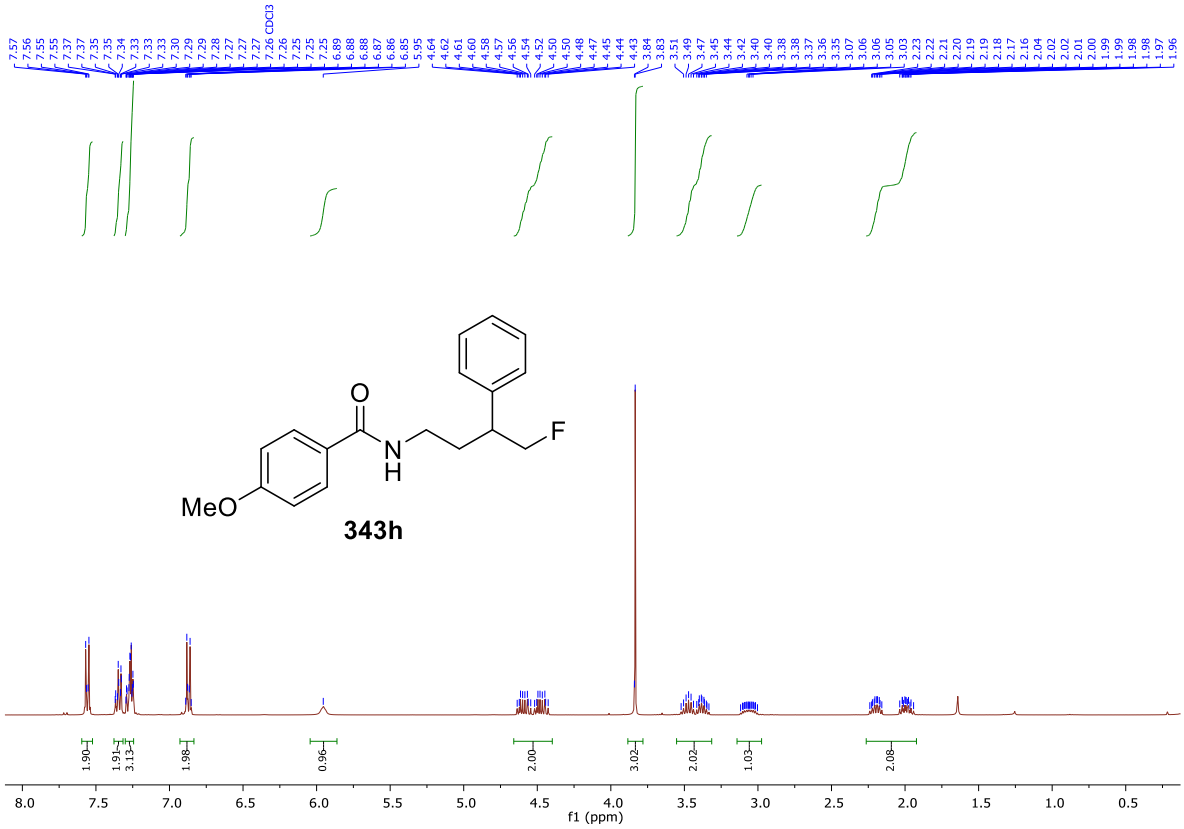
^{13}C-NMR (101 MHz, Acetone-d_6)



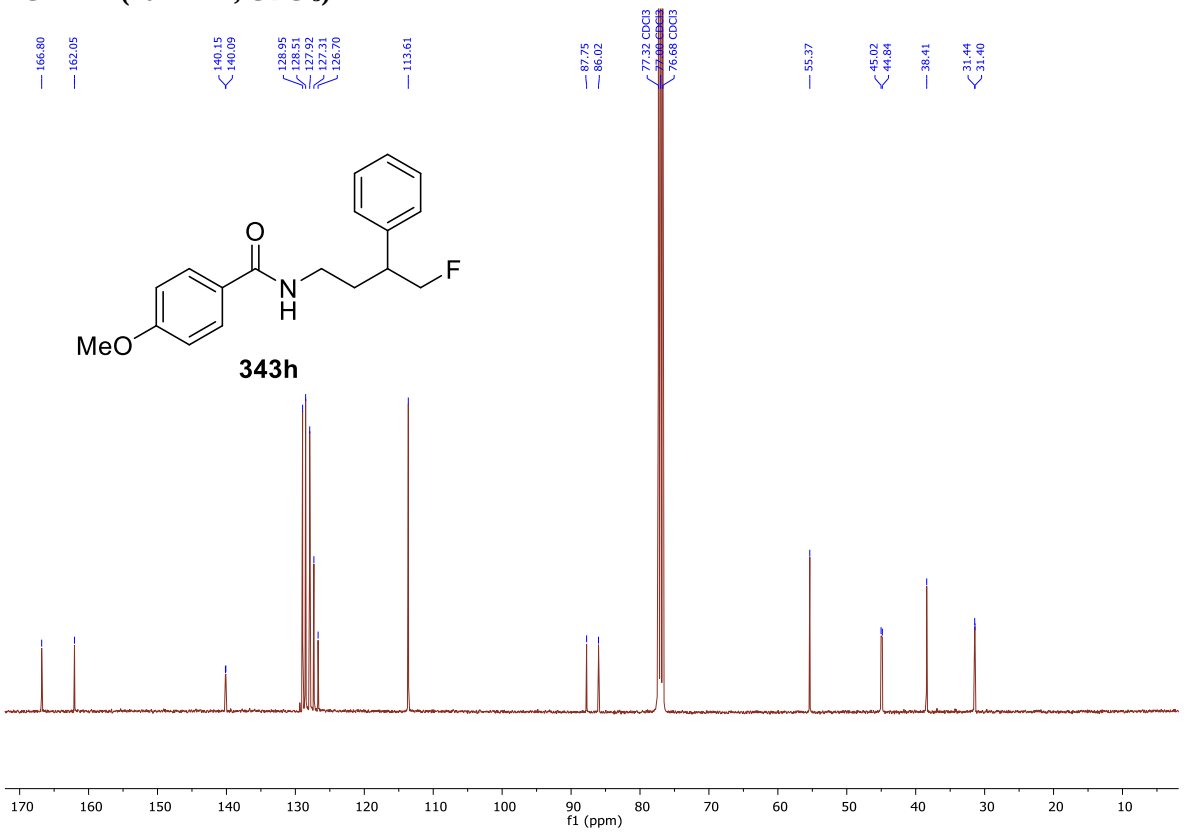
^{19}F-NMR (376 MHz, Acetone-d_6)



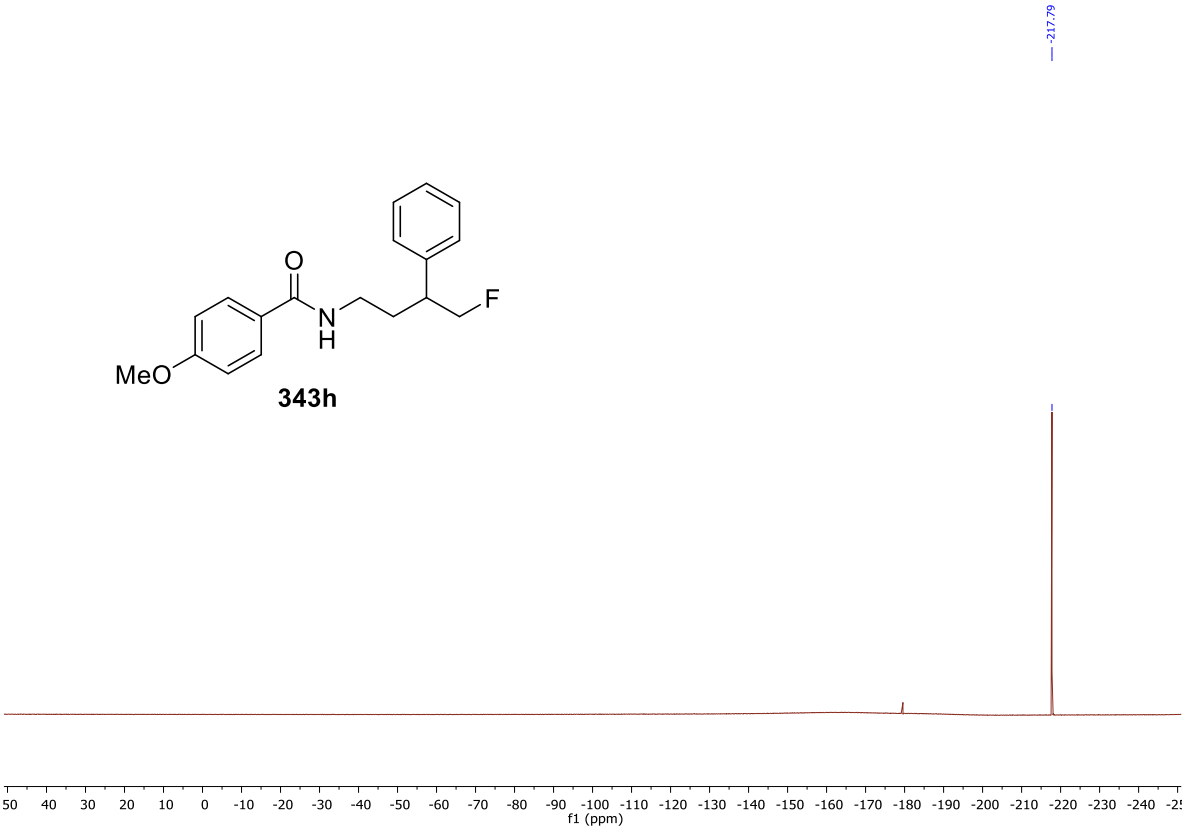
^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)

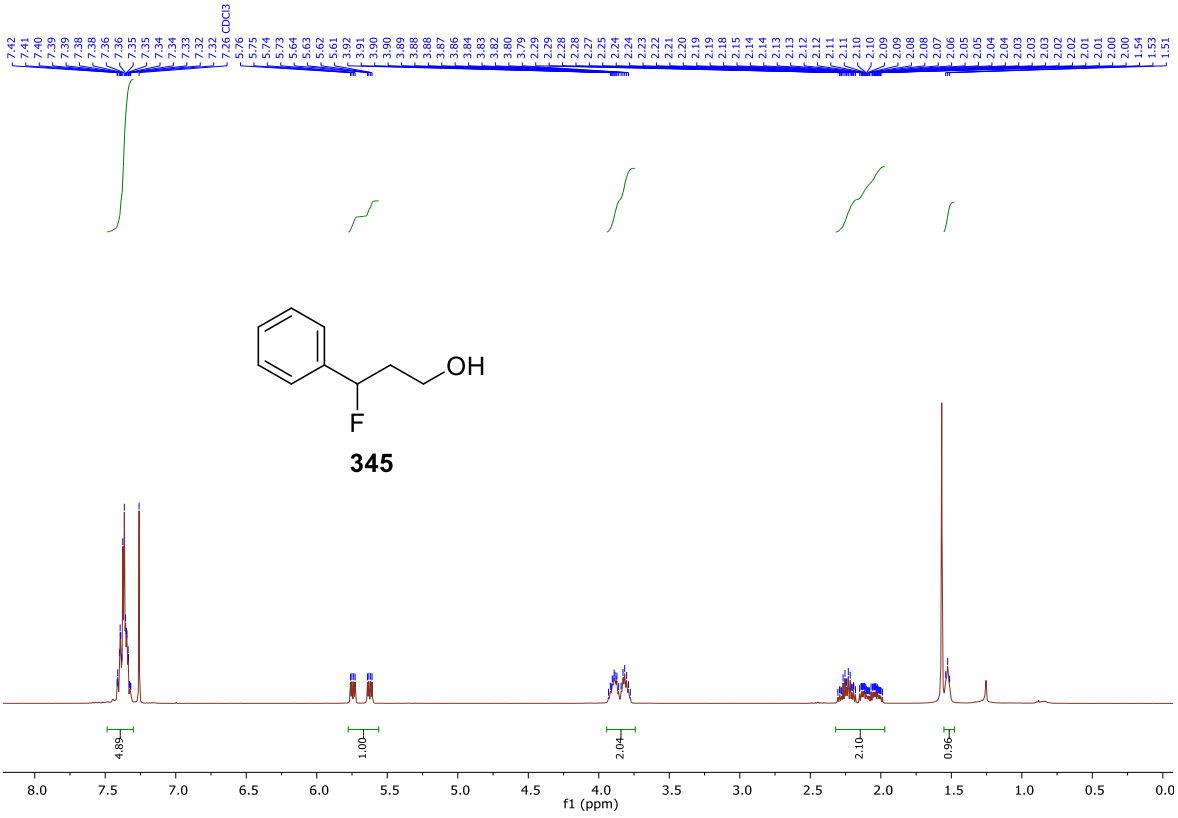


^{19}F-NMR (376 MHz, $CDCl_3$)



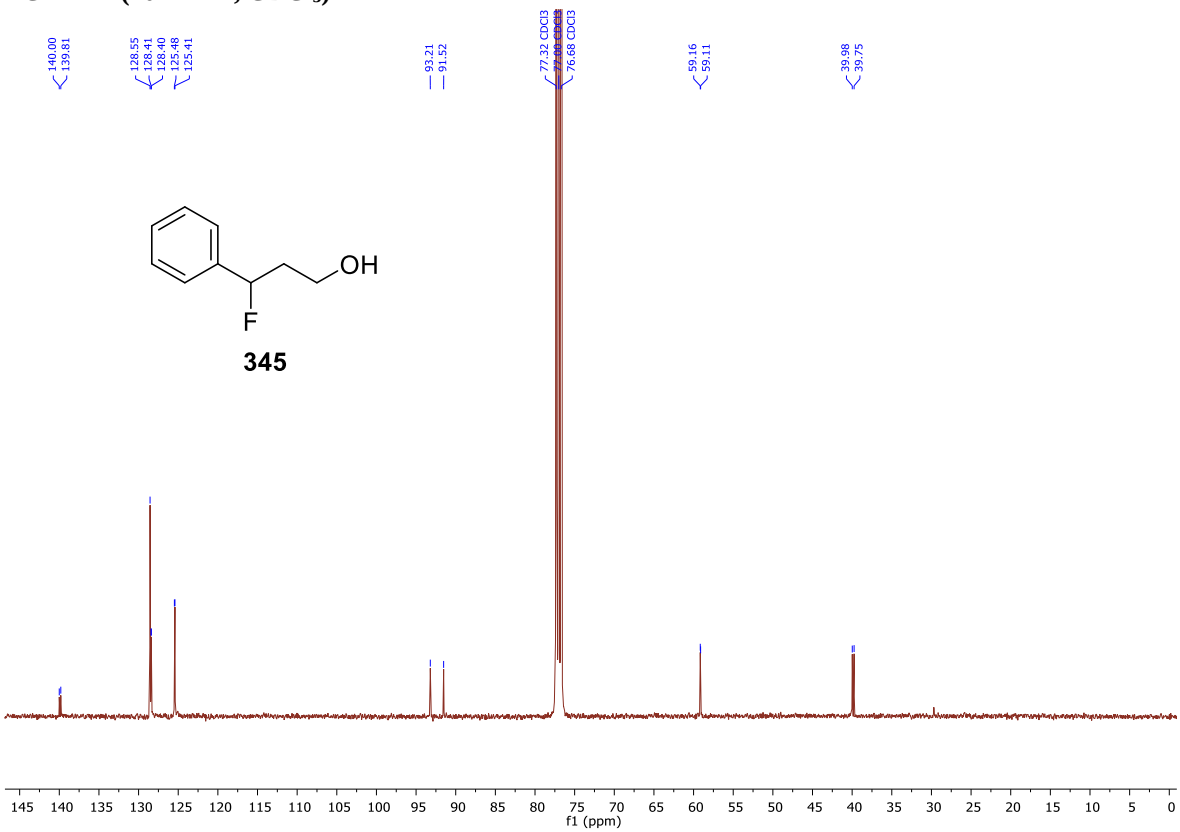
343h

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



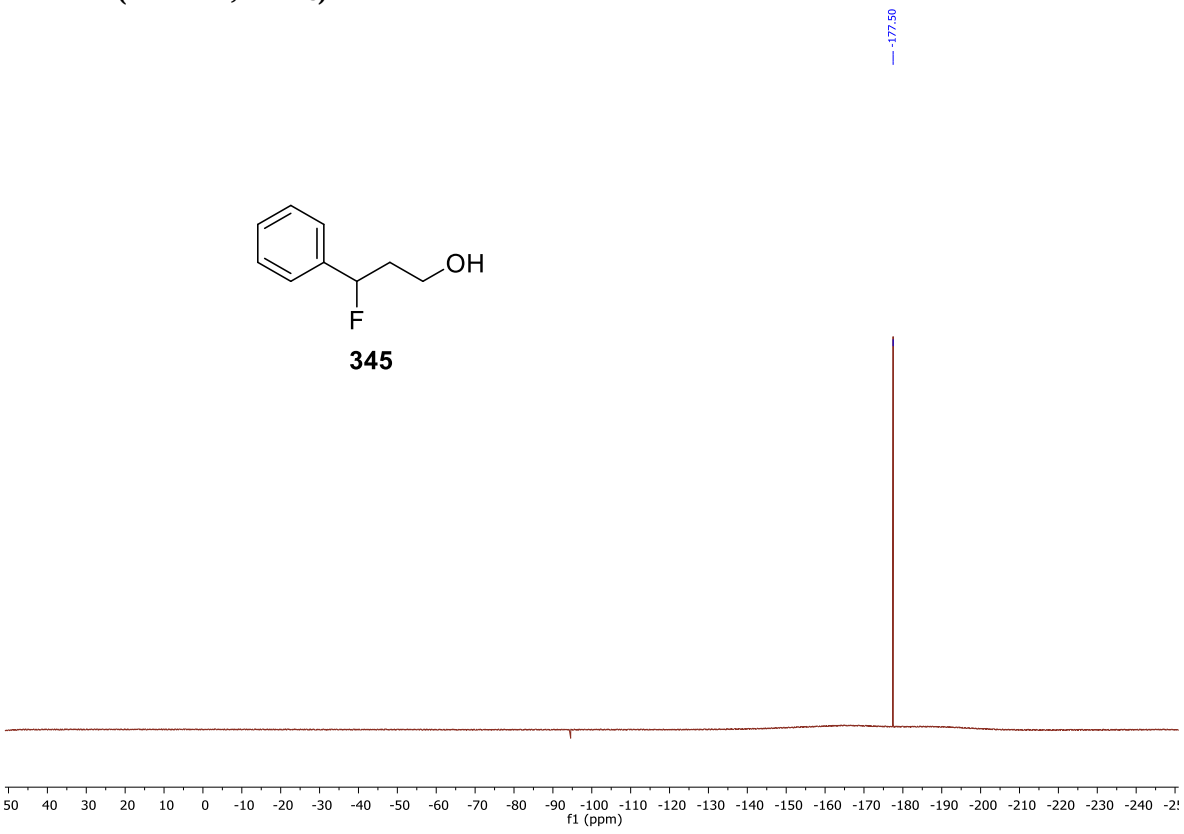
345

^{13}C-NMR (101 MHz, $CDCl_3$)



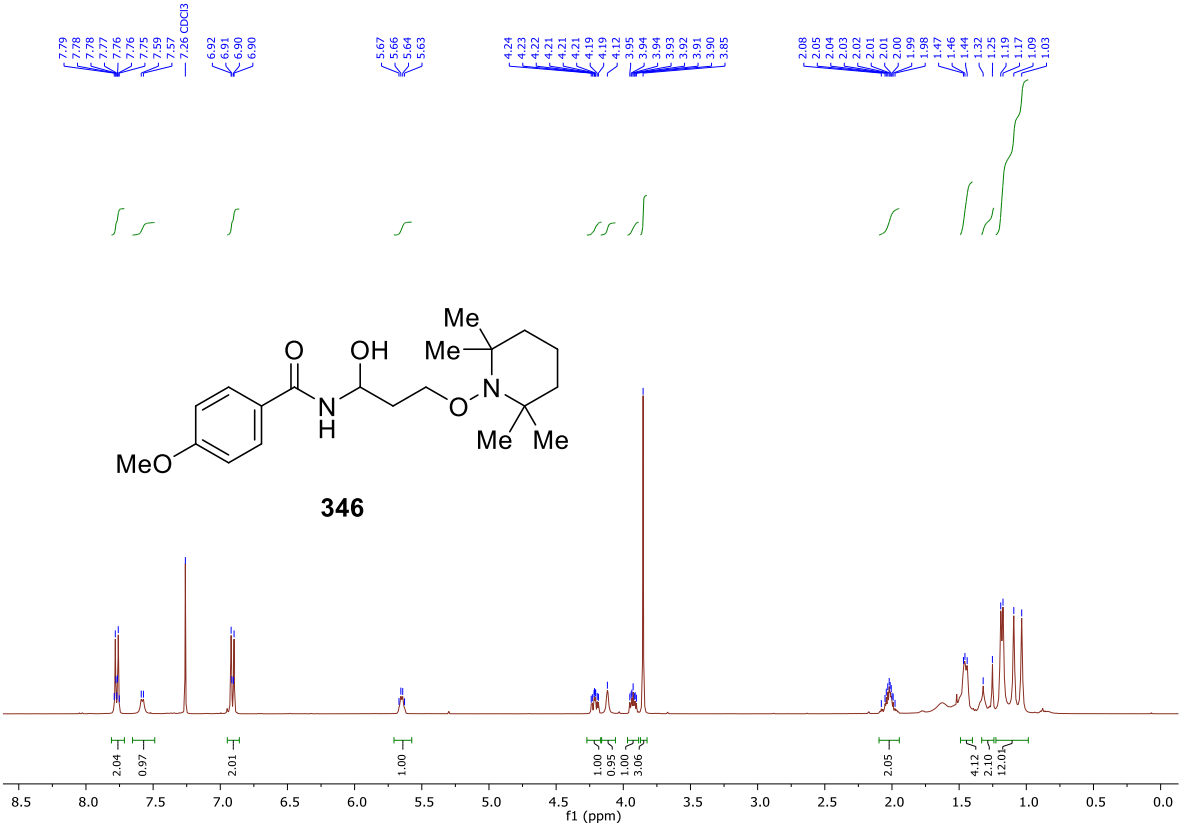
345

^{19}F-NMR (376 MHz, $CDCl_3$)

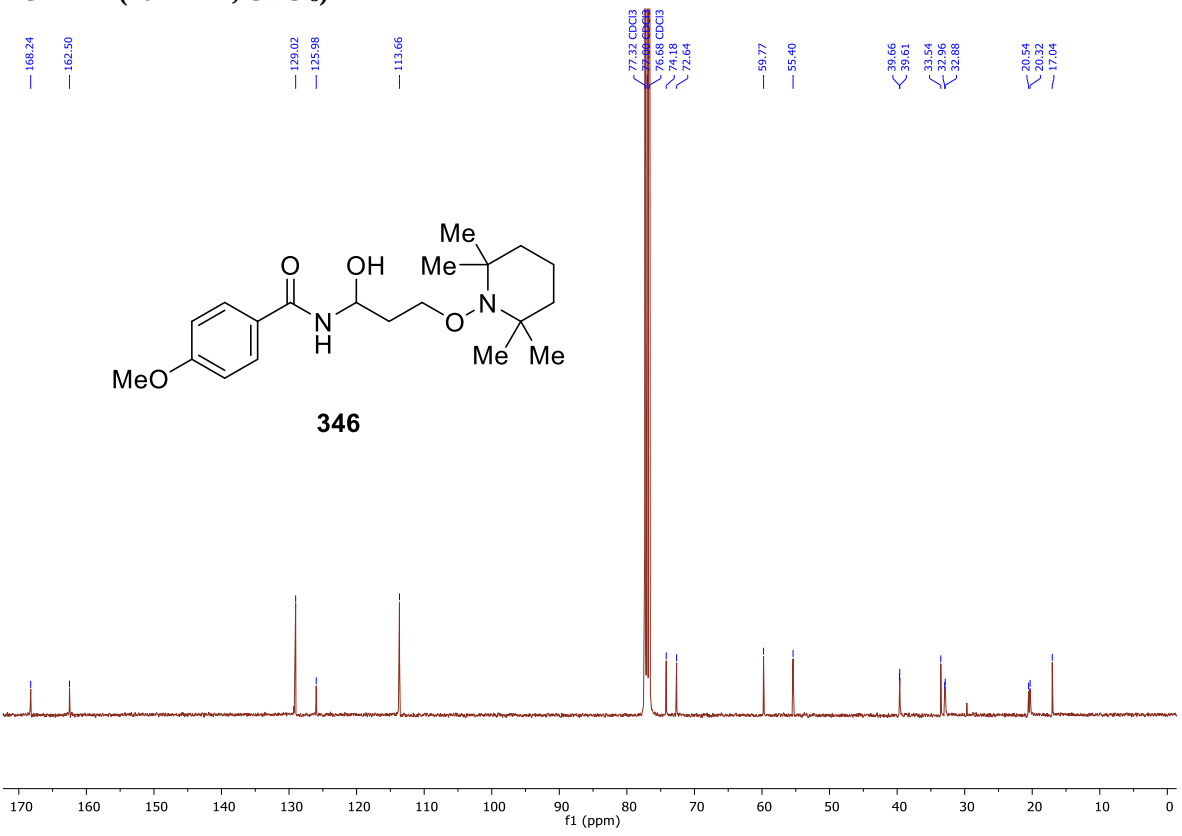


345

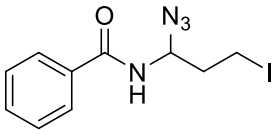
^{1}H-NMR (400 MHz, $CDCl_3$)



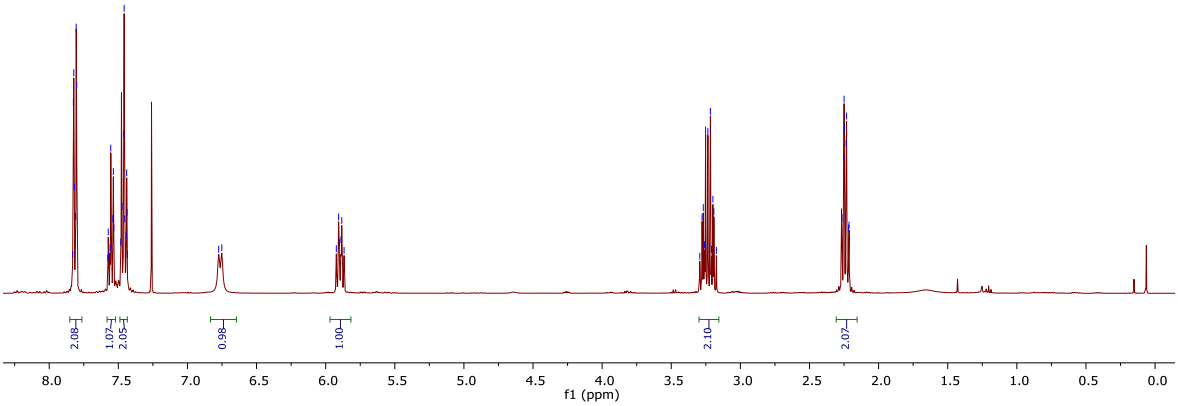
^{13}C-NMR (101 MHz, $CDCl_3$)



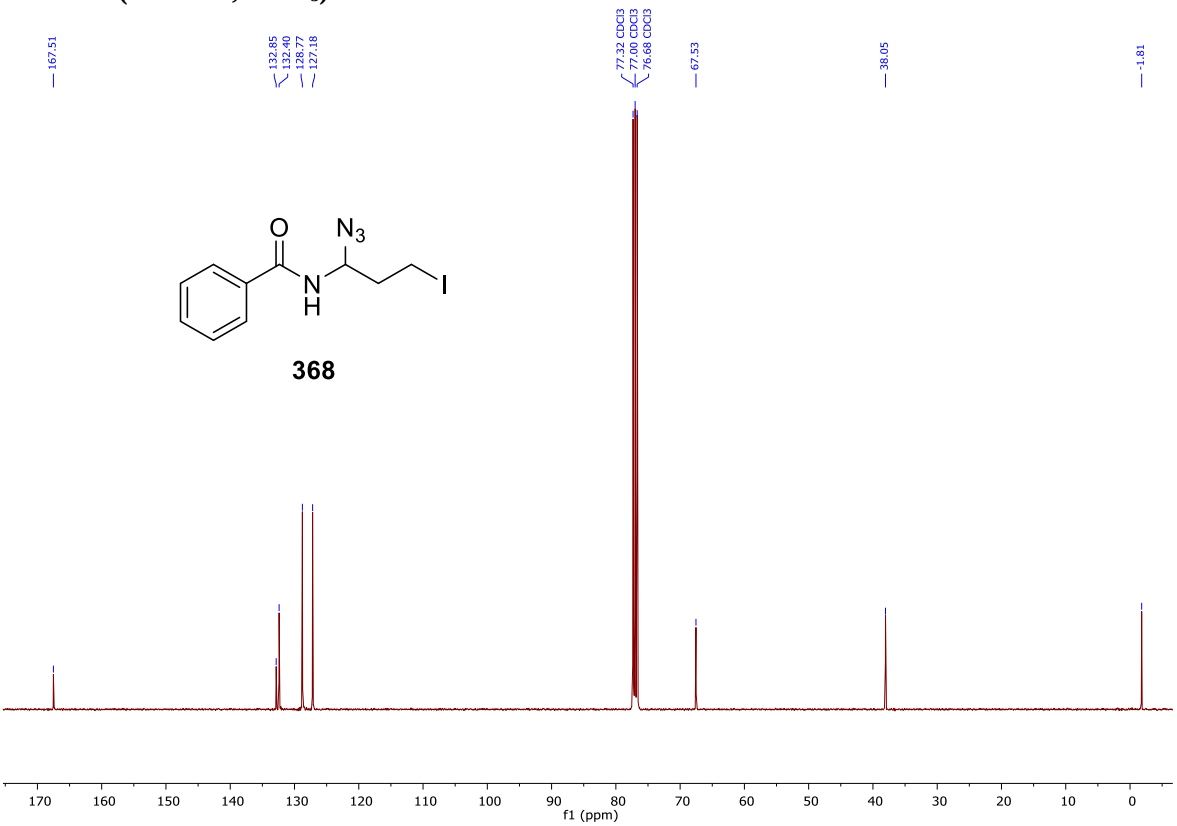
^{1}H-NMR (400 MHz, $CDCl_3$)



368

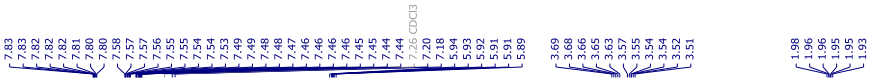


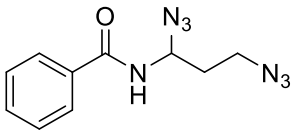
^{13}C-NMR (101 MHz, $CDCl_3$)



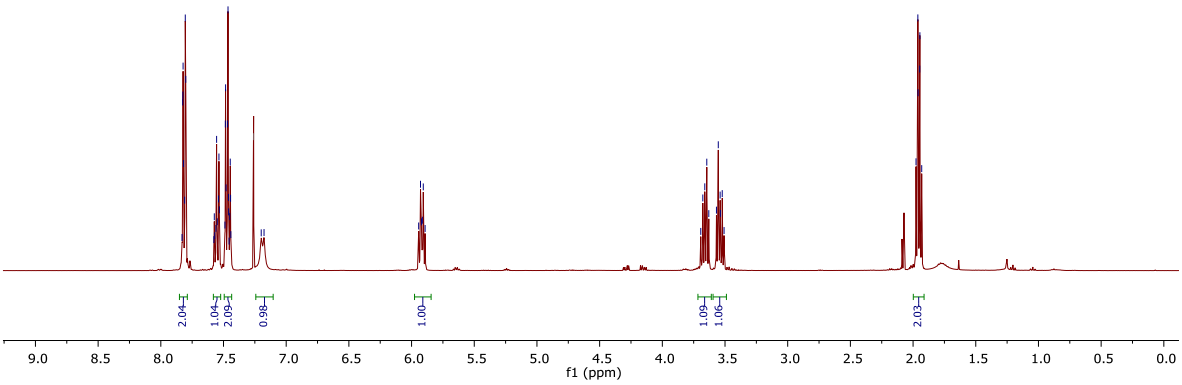
368

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

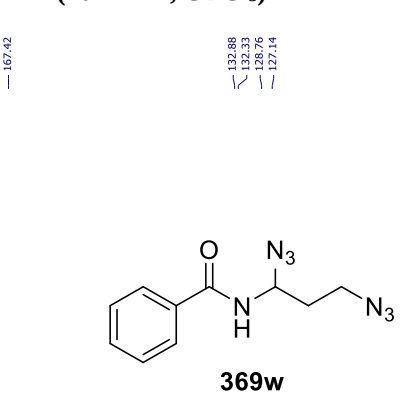




369w

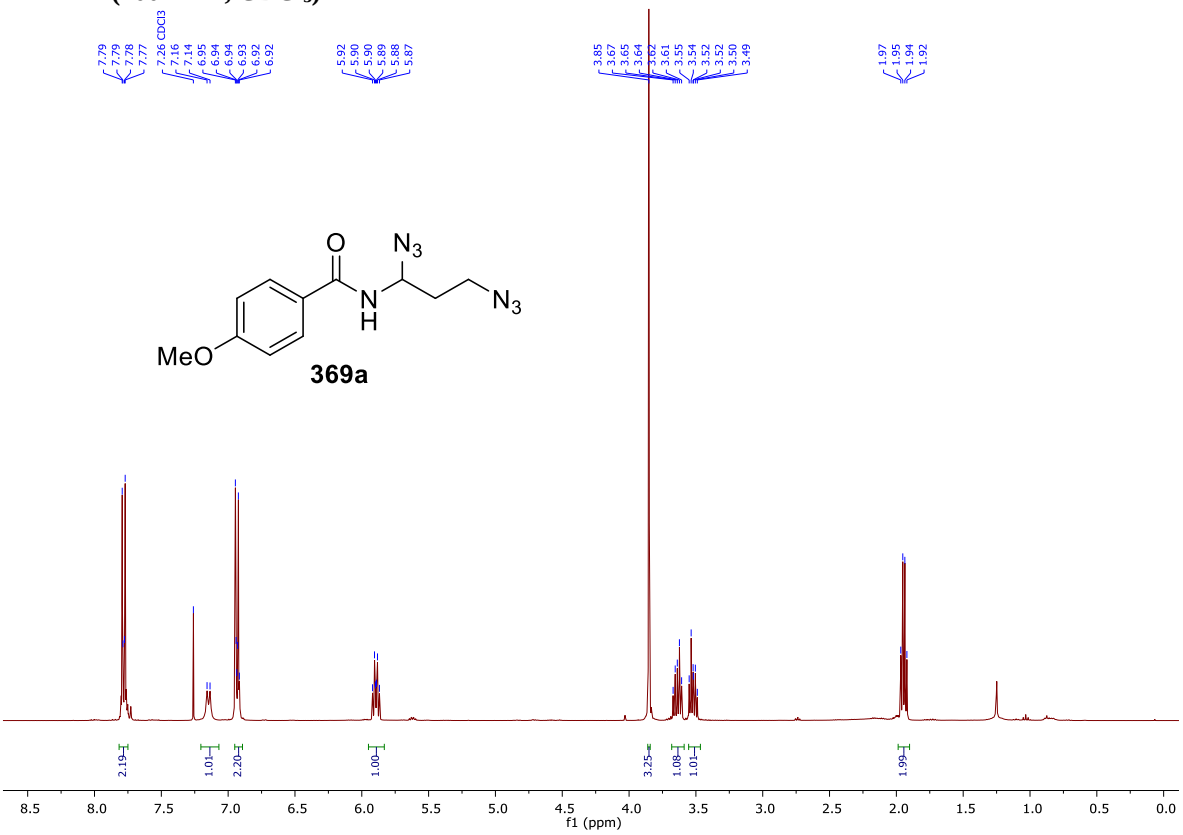


^{13}C-NMR (101 MHz, $CDCl_3$)

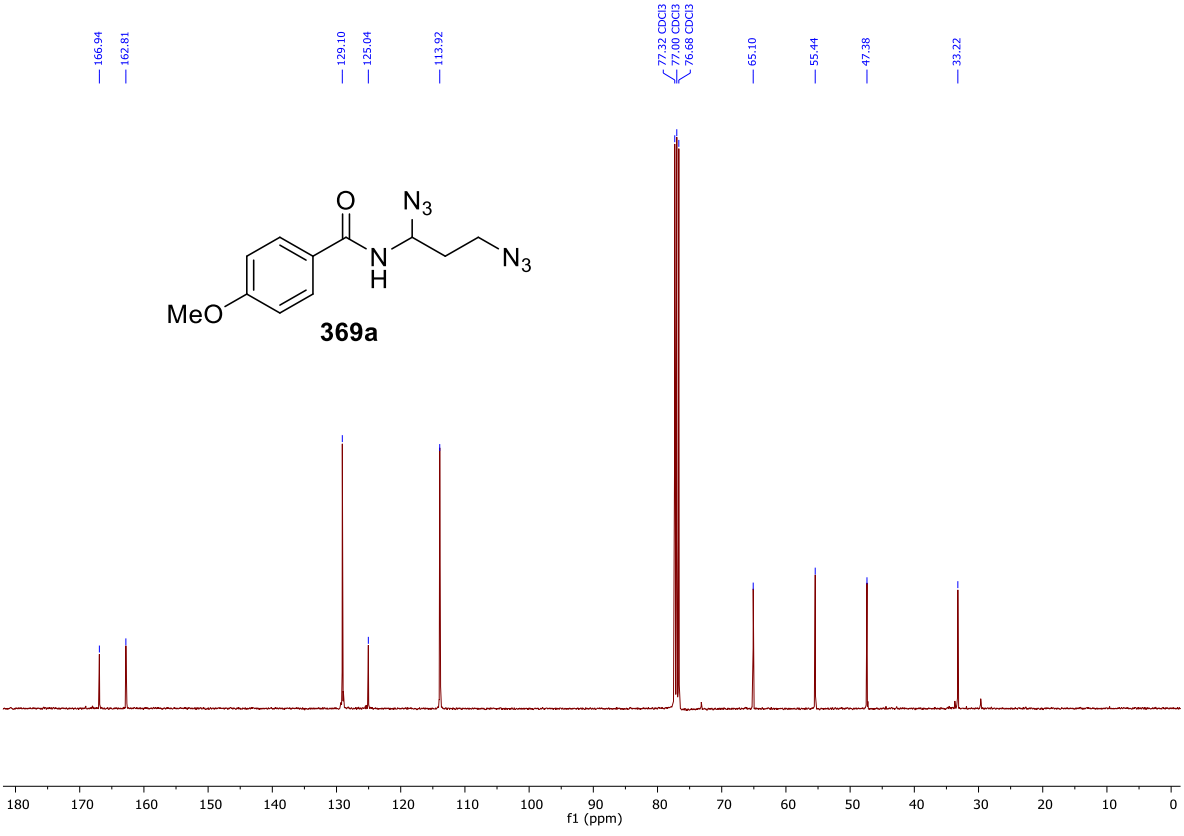


369w

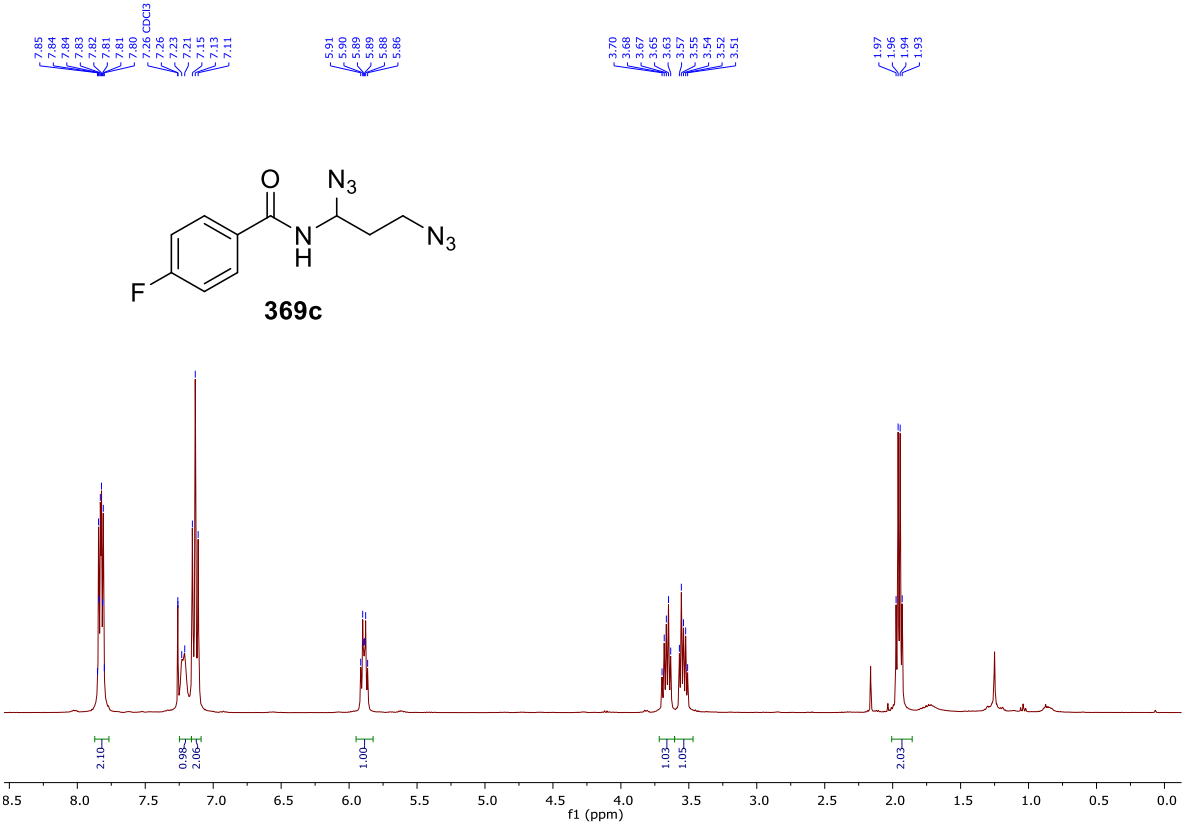
^{1}H-NMR (400 MHz, $CDCl_3$)



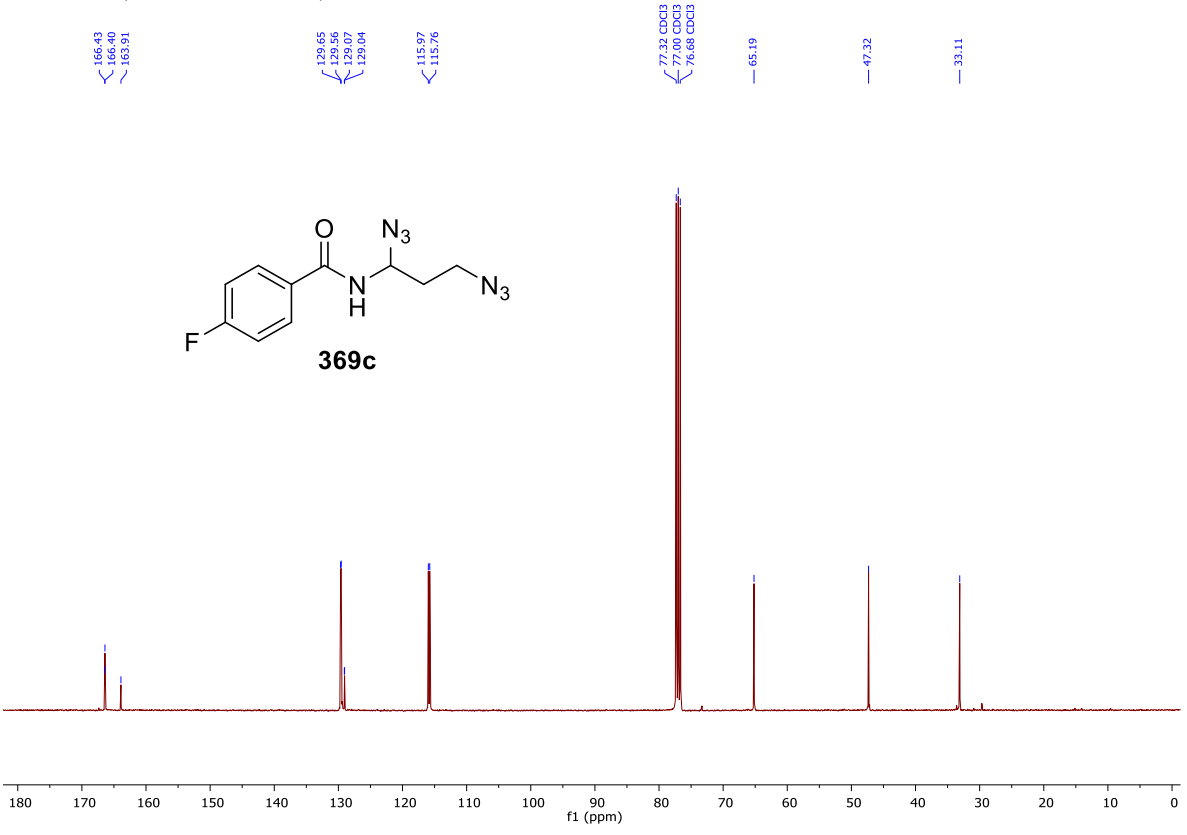
^{13}C-NMR (101 MHz, $CDCl_3$)



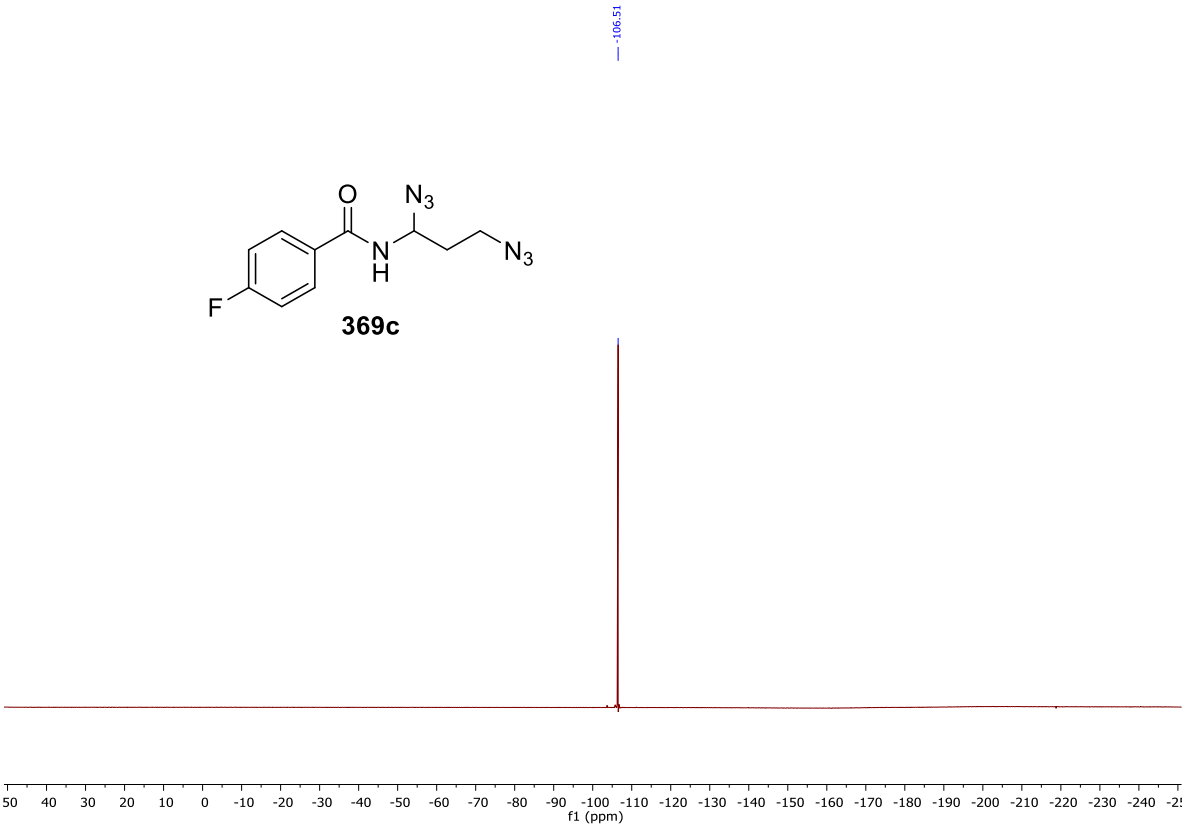
^{1}H-NMR (400 MHz, $CDCl_3$)



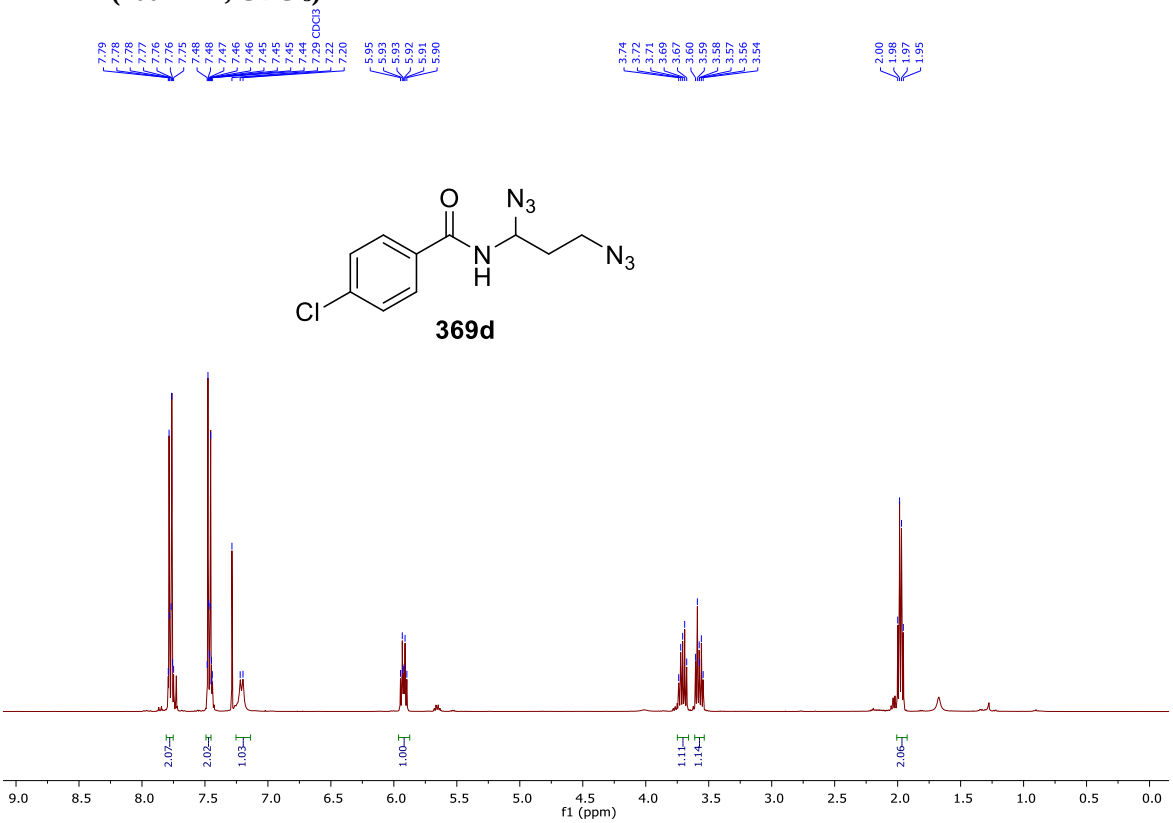
^{13}C-NMR (101 MHz, $CDCl_3$)



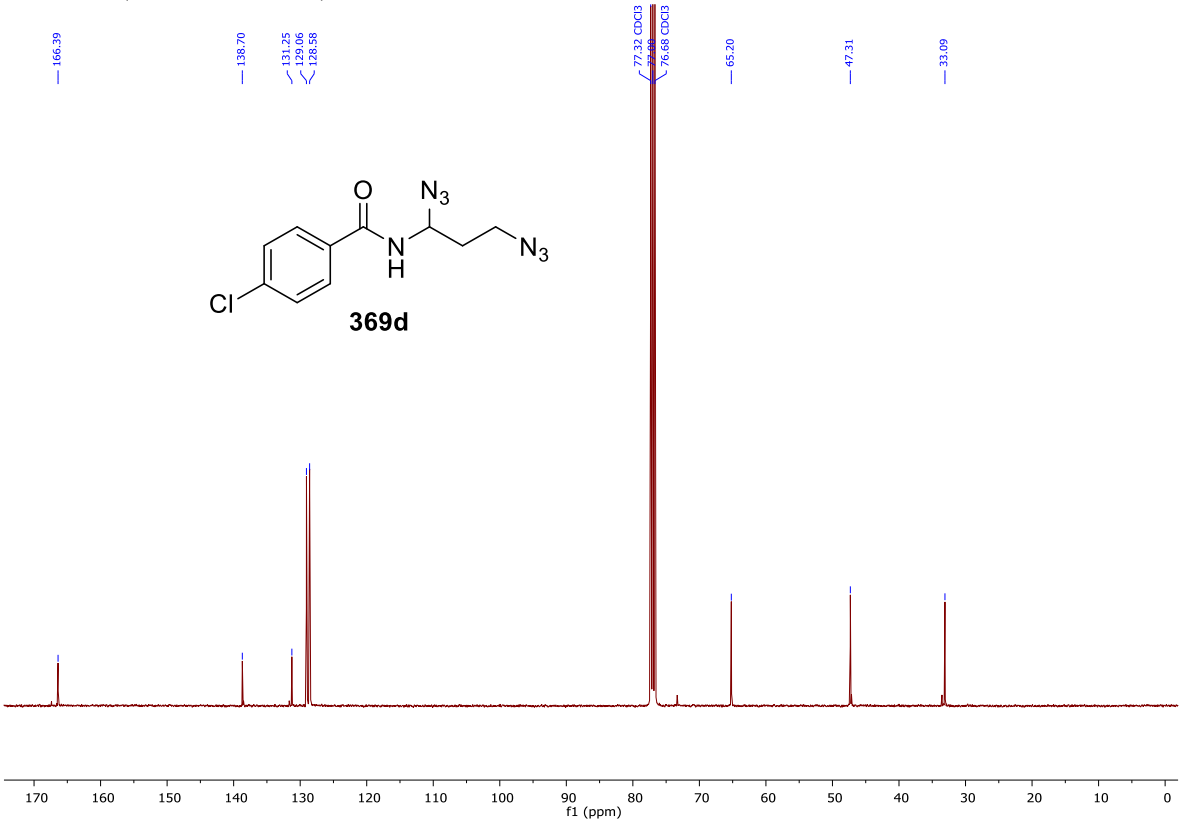
^{19}F-NMR (376 MHz, $CDCl_3$)



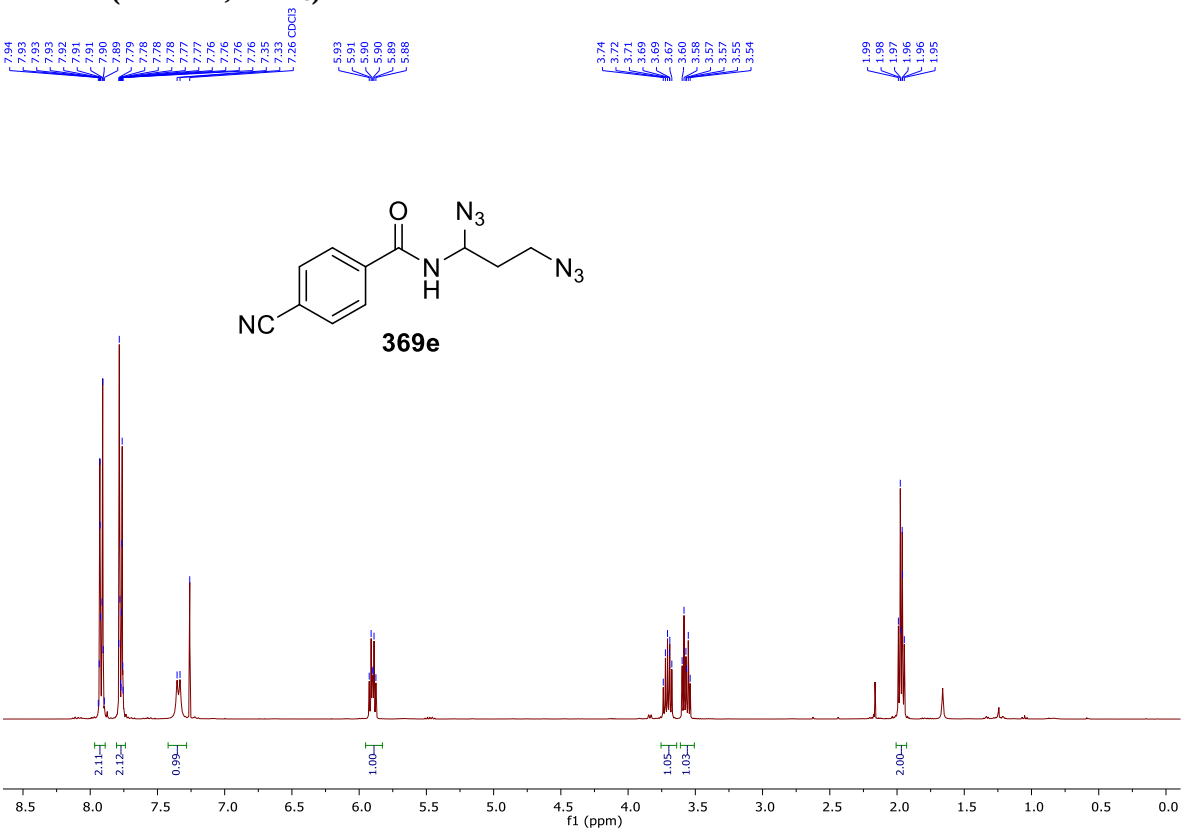
^{1}H-NMR (400 MHz, $CDCl_3$)



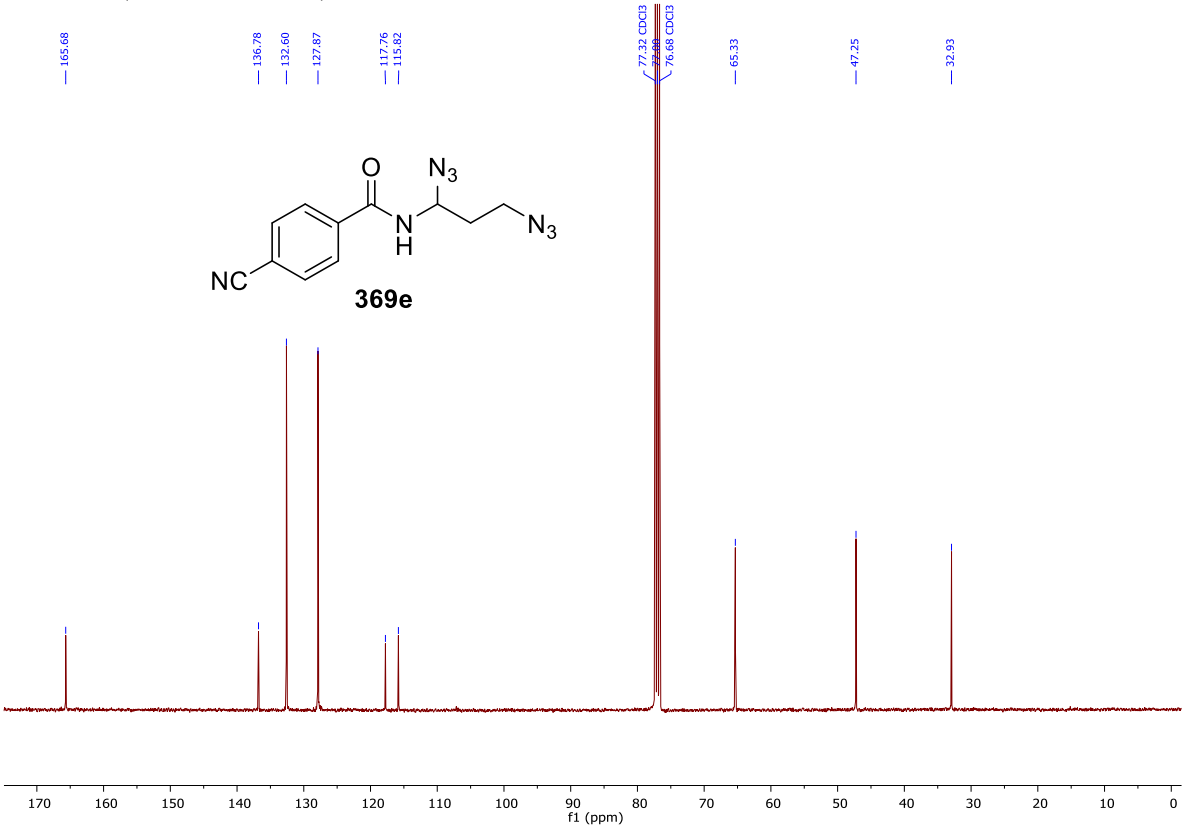
^{13}C-NMR (101 MHz, $CDCl_3$)



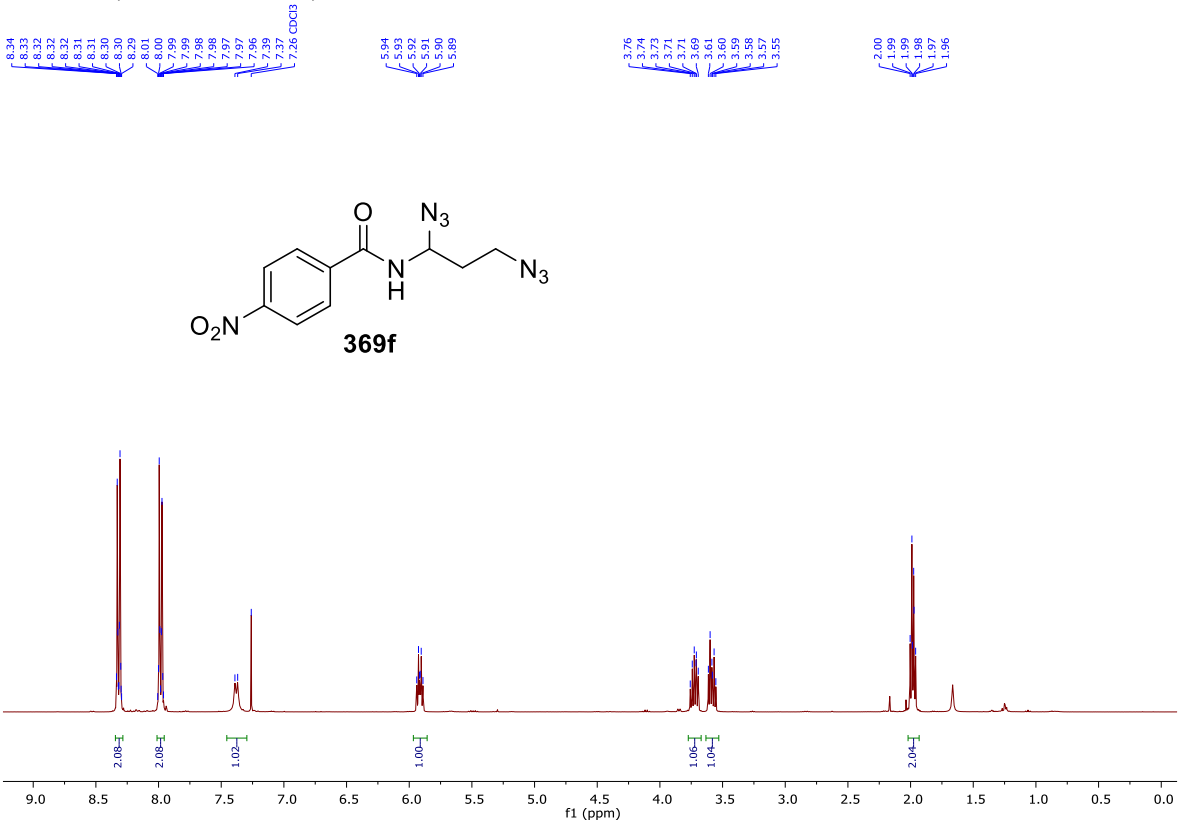
^{1}H-NMR (400 MHz, $CDCl_3$)



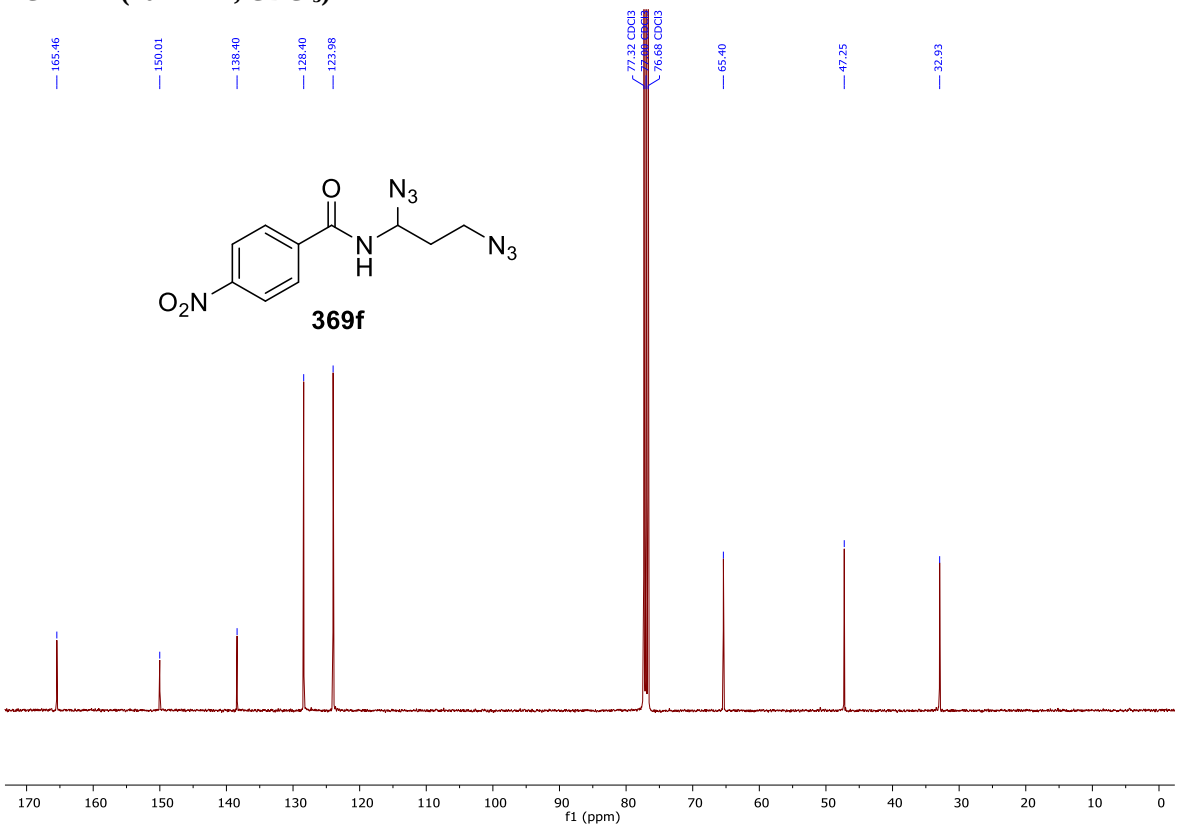
^{13}C-NMR (101 MHz, $CDCl_3$)



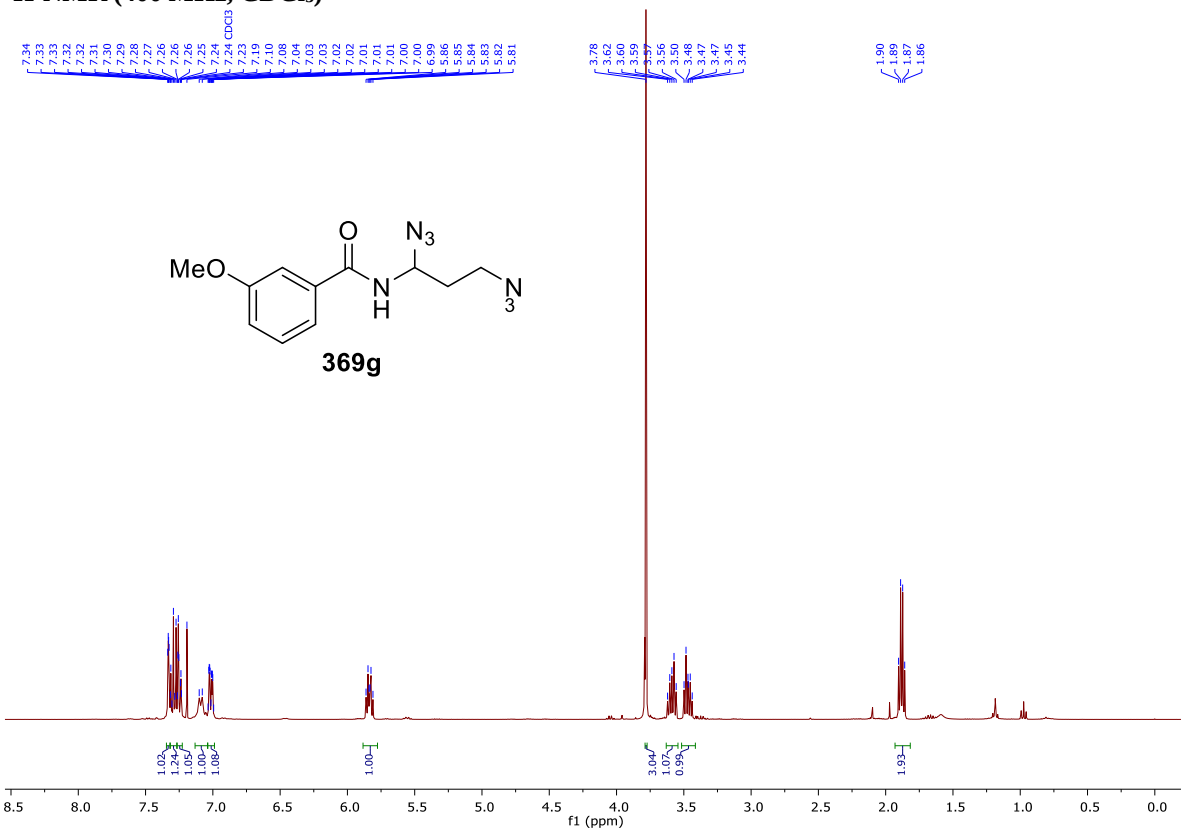
^{1}H-NMR (400 MHz, $CDCl_3$)



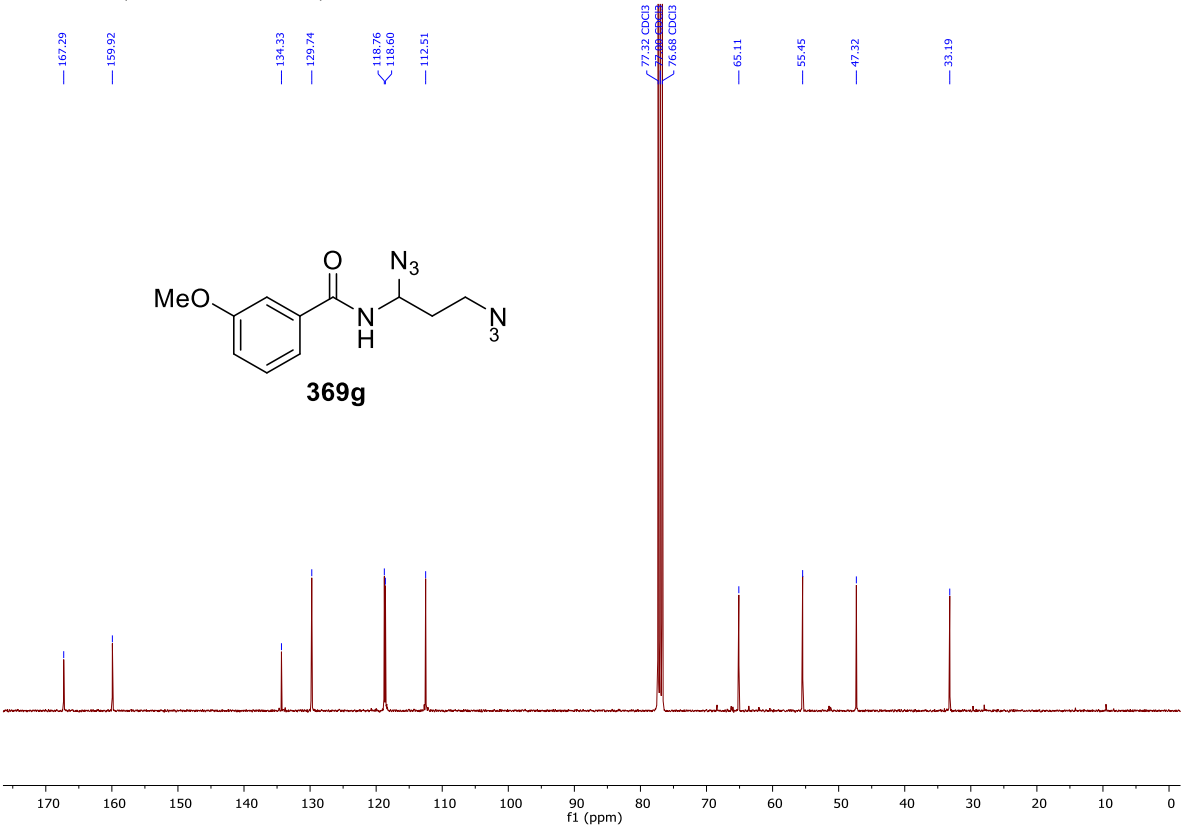
^{13}C-NMR (101 MHz, $CDCl_3$)



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

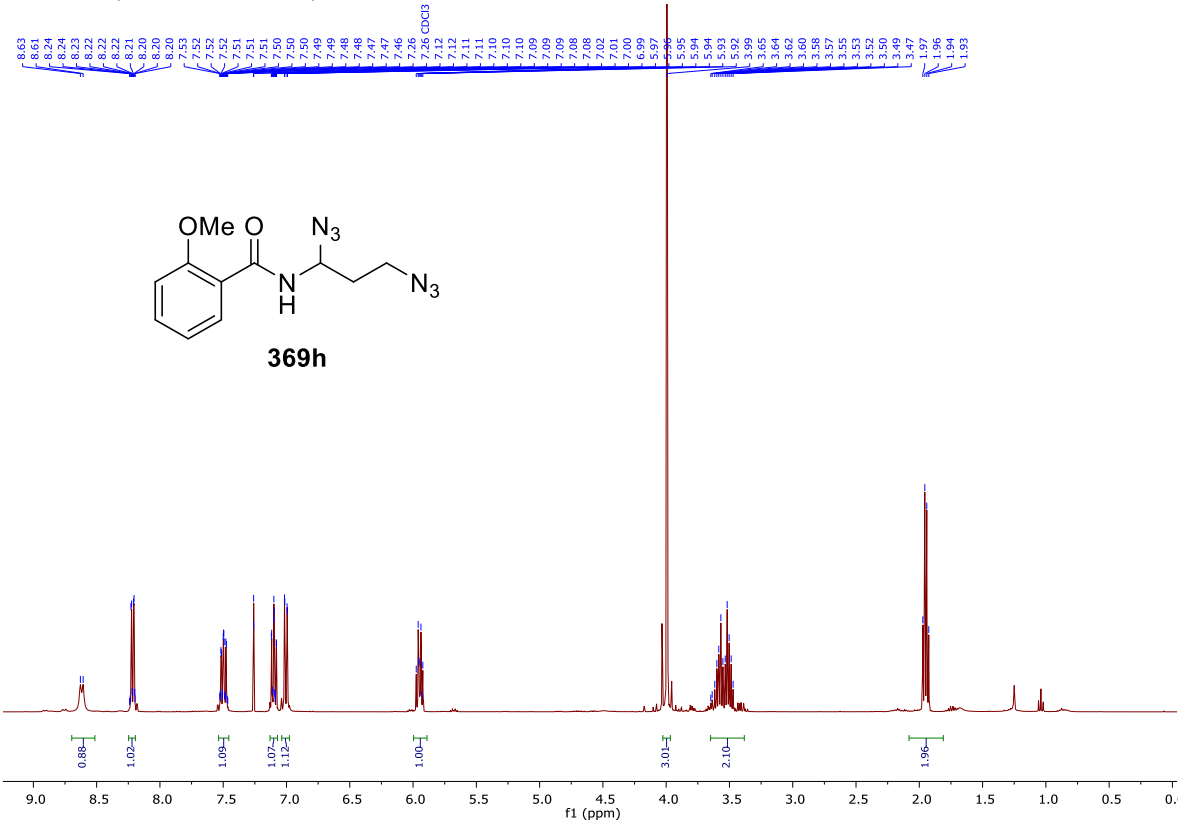


^{13}C-NMR (101 MHz, $CDCl_3$)



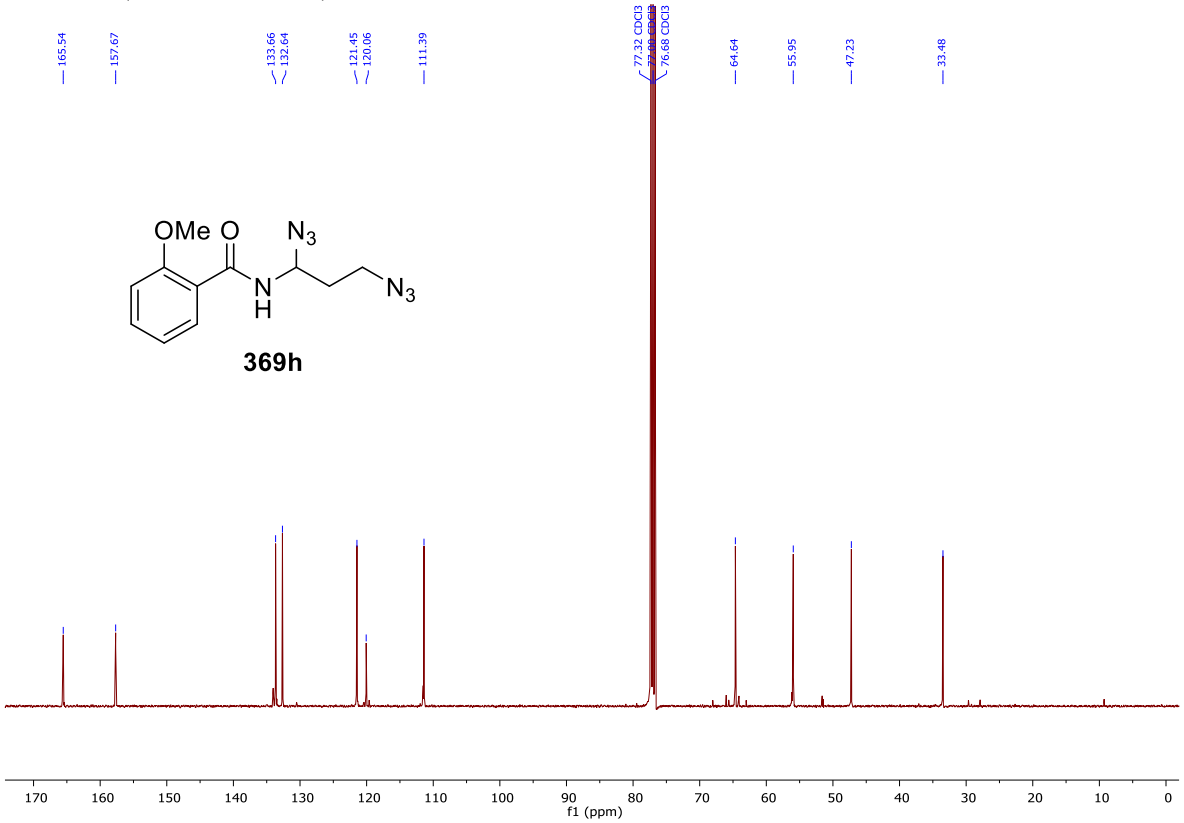
369g

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

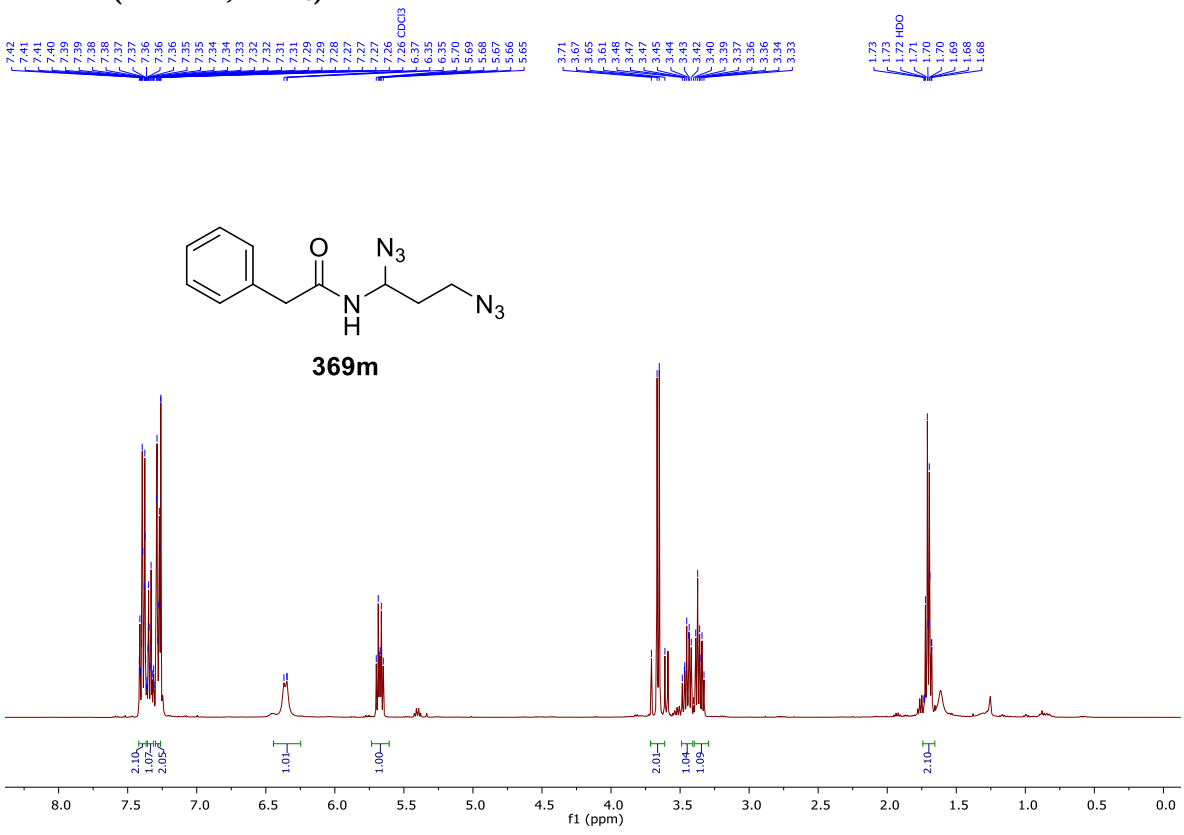


369h

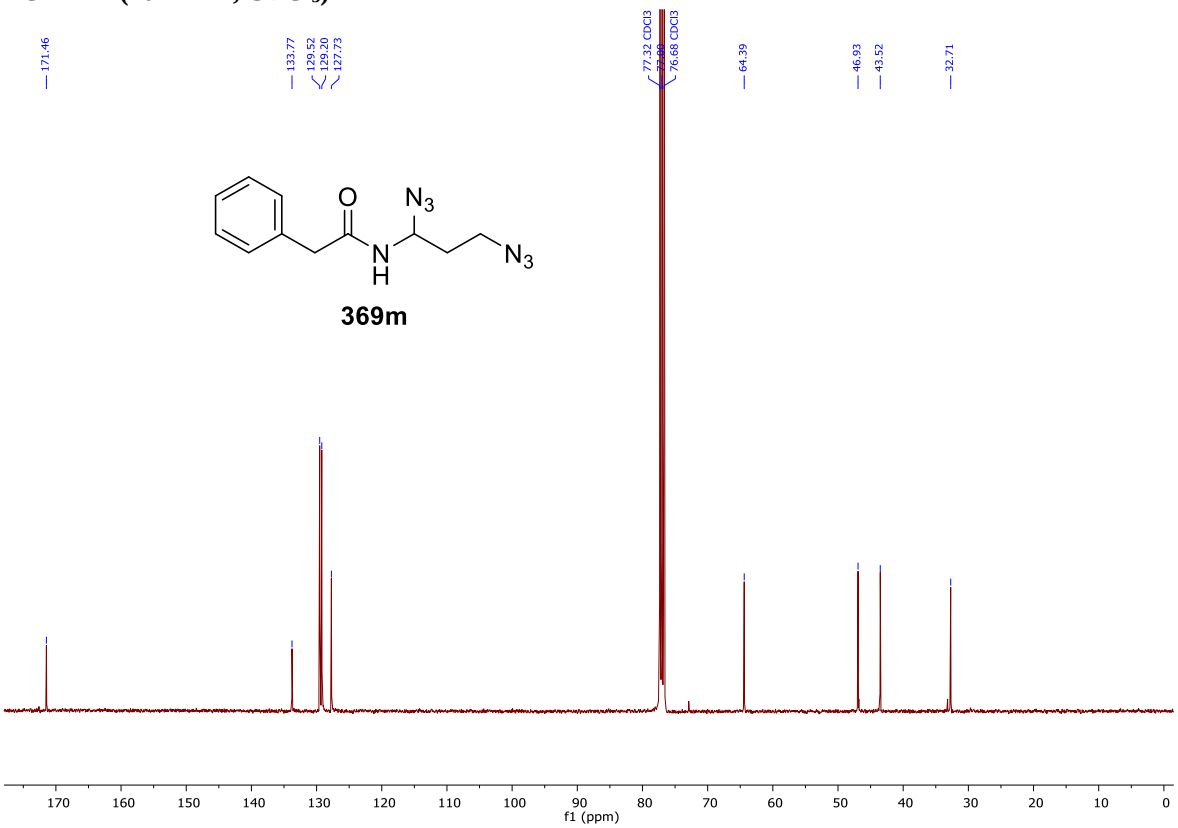
^{13}C-NMR (101 MHz, $CDCl_3$)



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

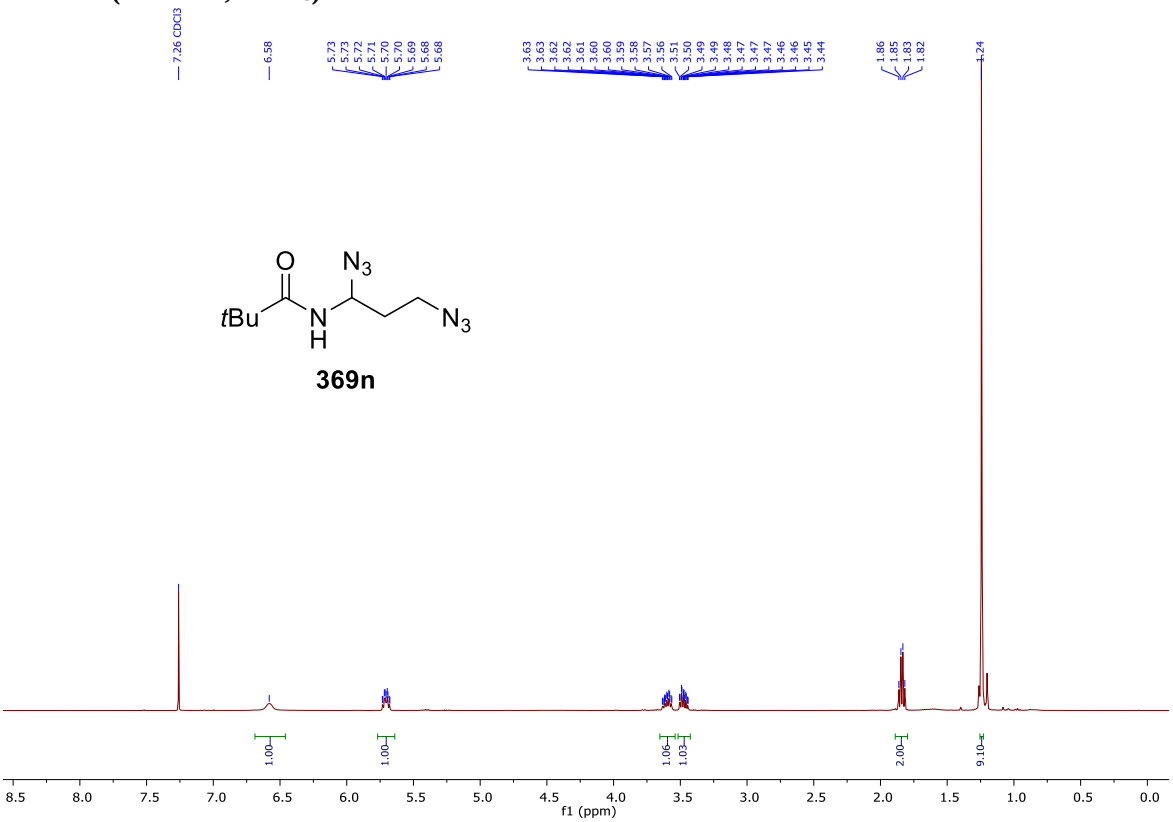


^{13}C-NMR (101 MHz, $CDCl_3$)



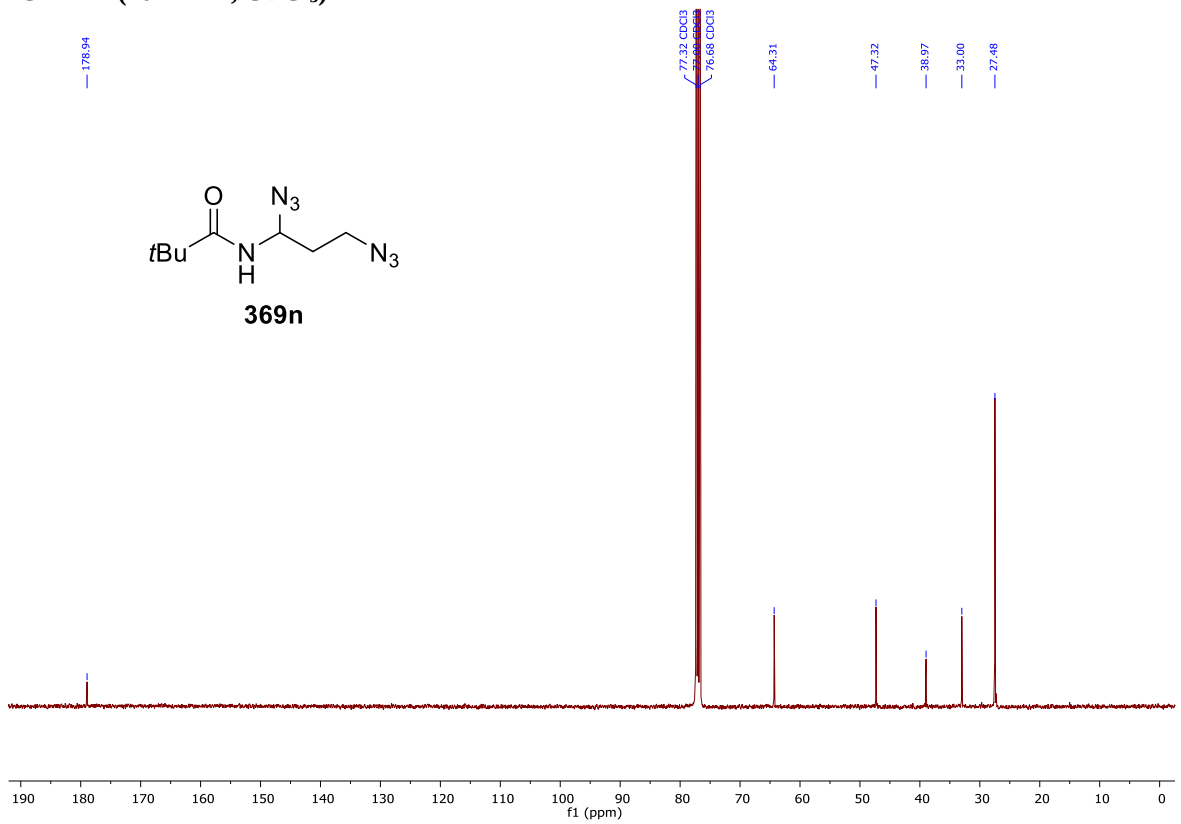
369m

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

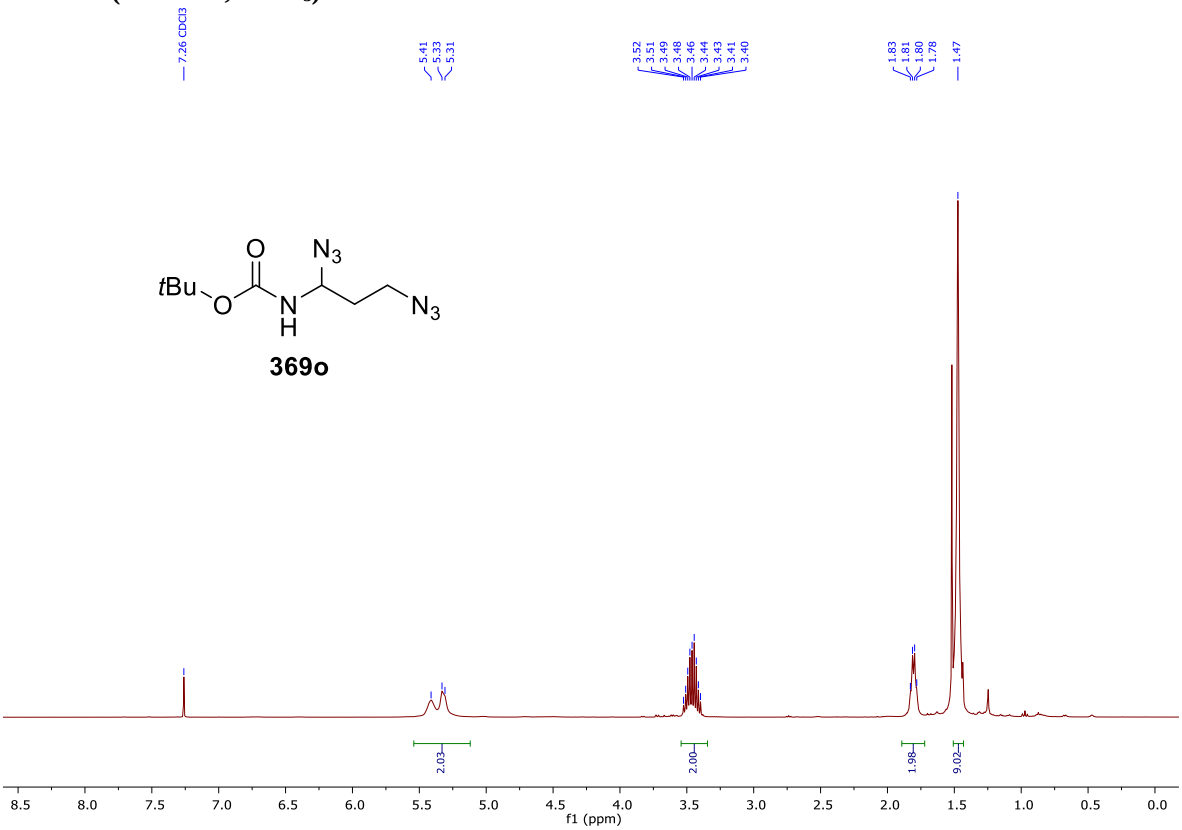


369n

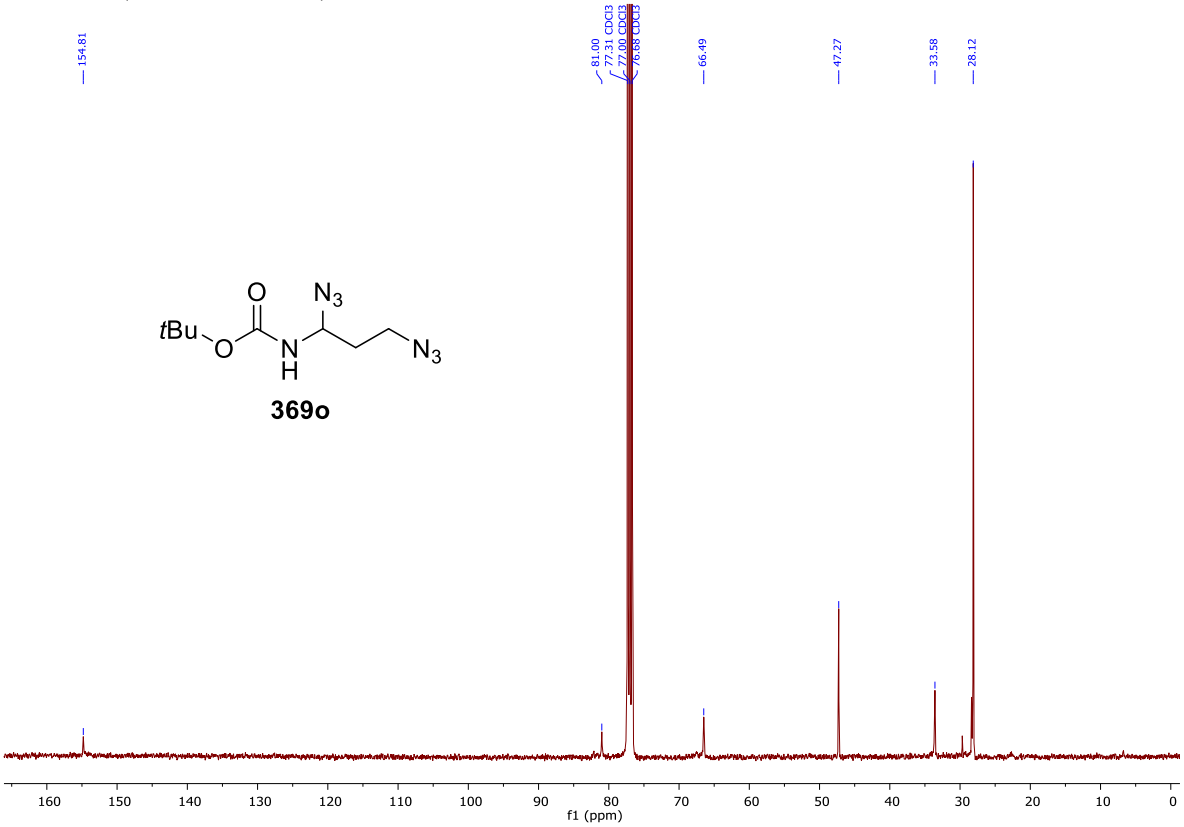
^{13}C-NMR (101 MHz, $CDCl_3$)



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

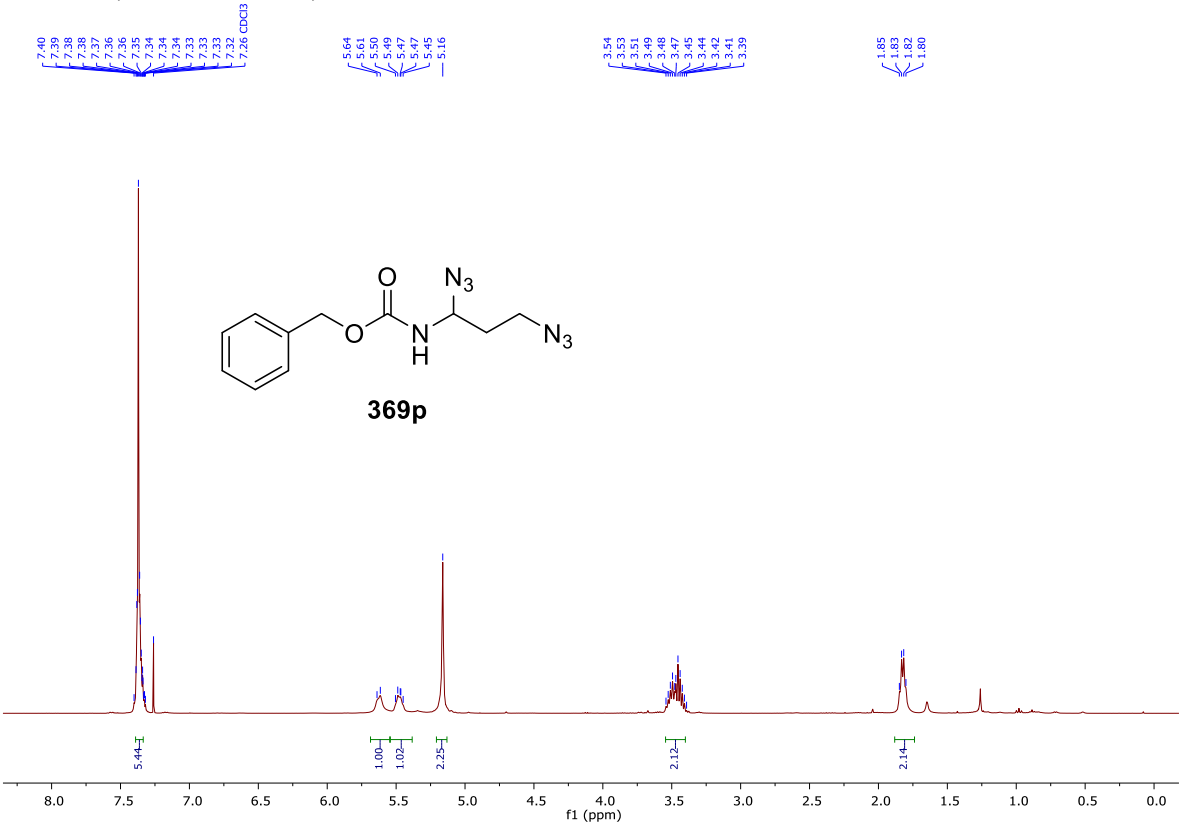


^{13}C-NMR (101 MHz, $CDCl_3$)



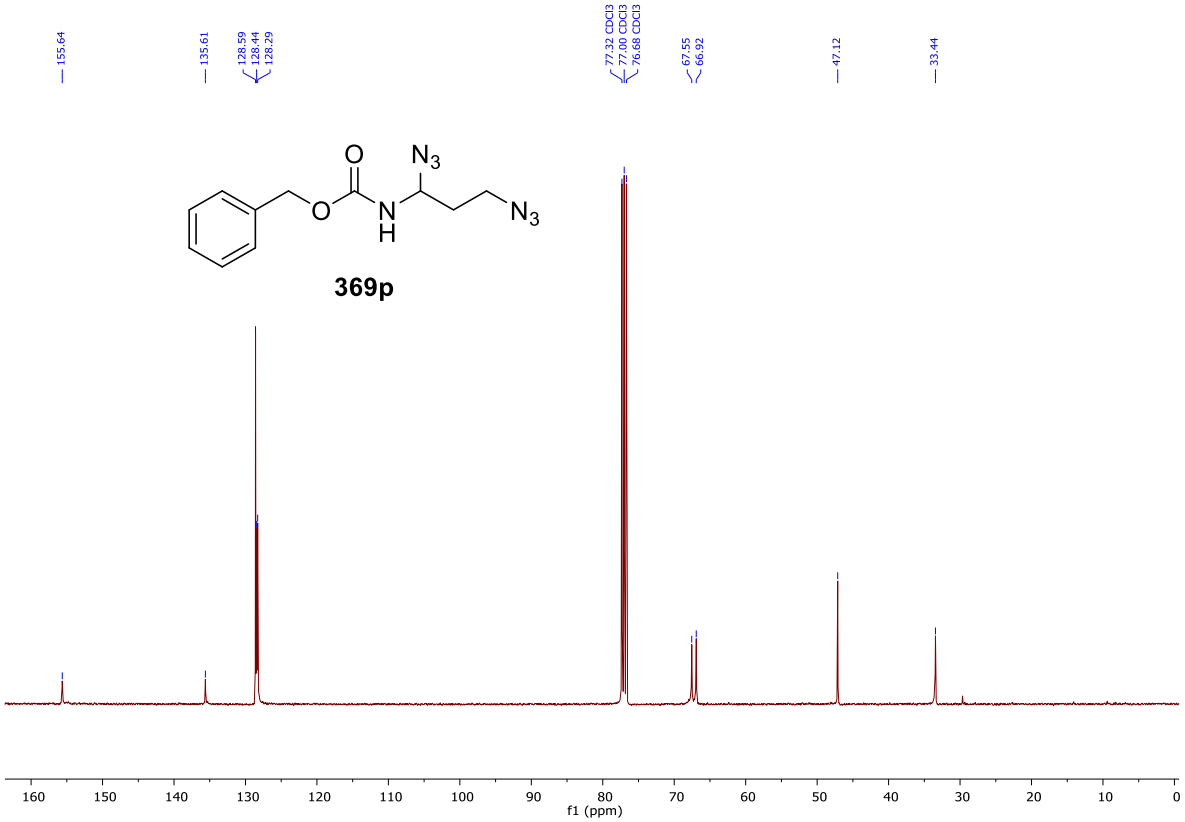
369o

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

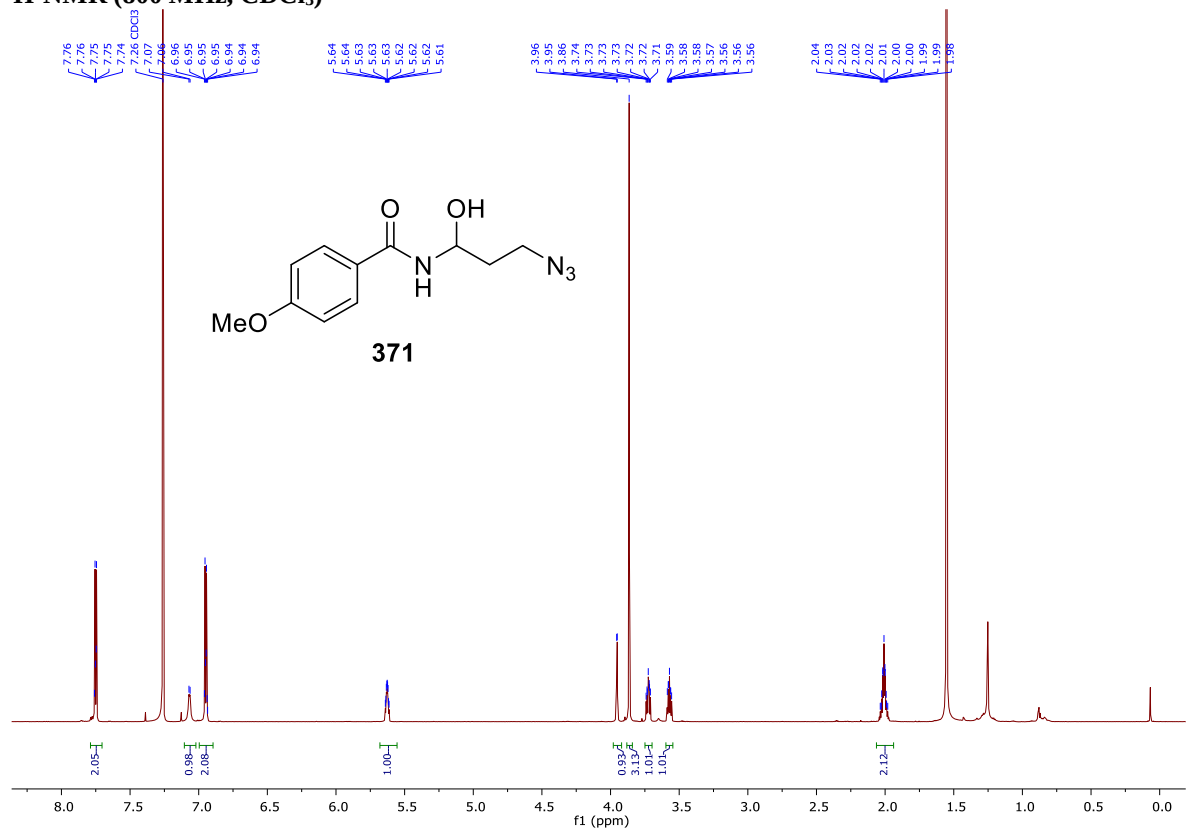


369p

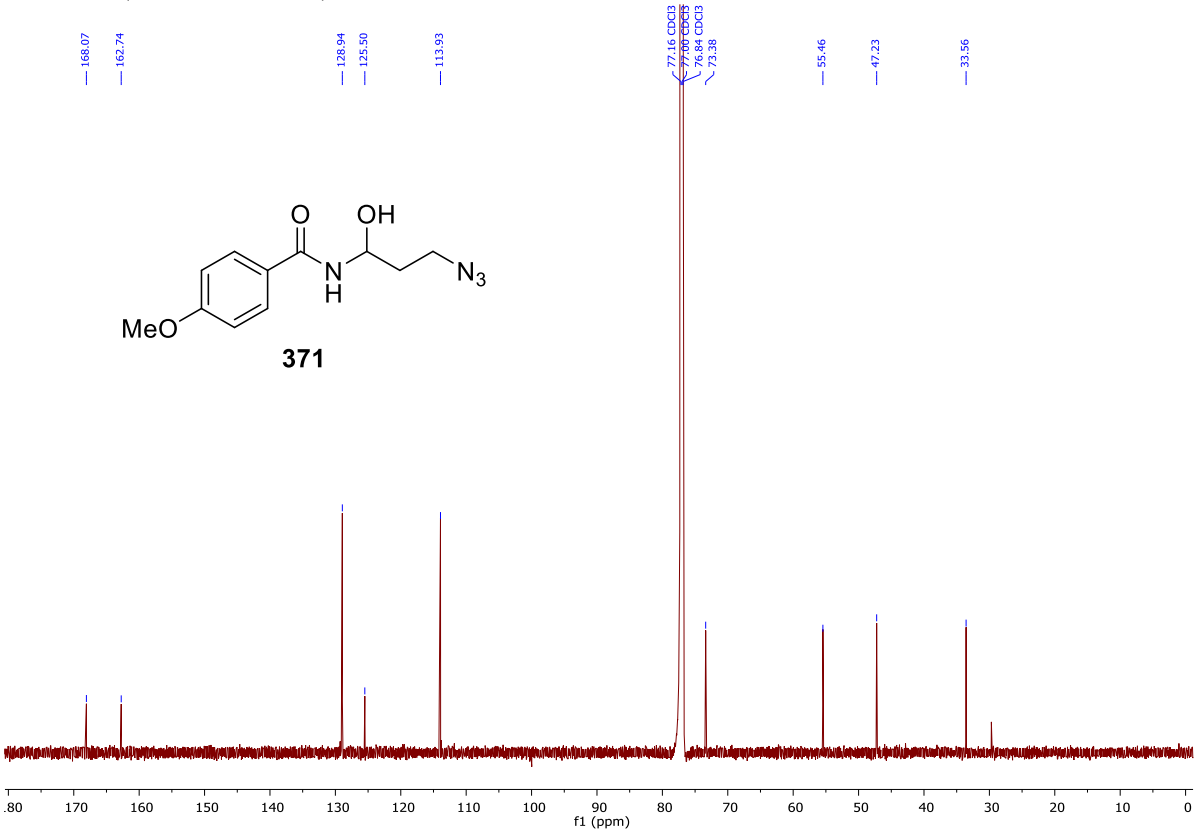
^{13}C-NMR (101 MHz, $CDCl_3$)



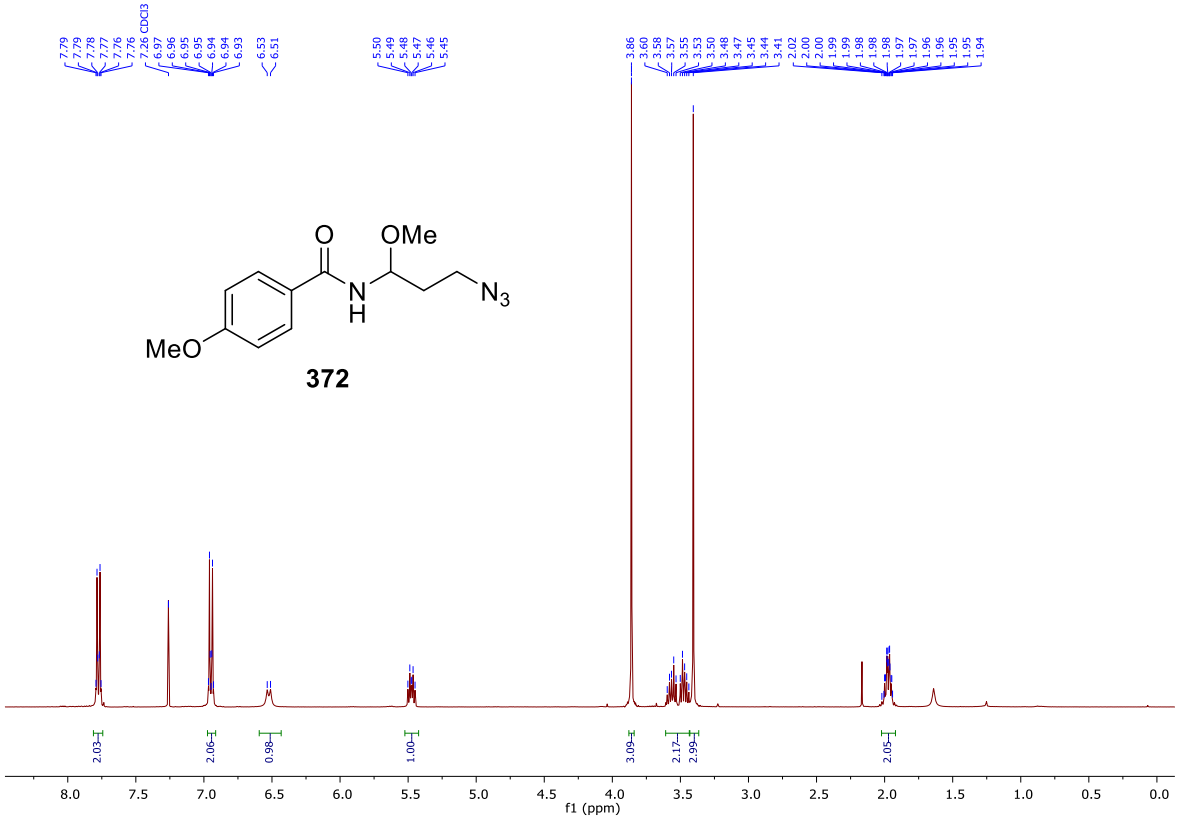
^{1}H-NMR (800 MHz, $CDCl_3$)



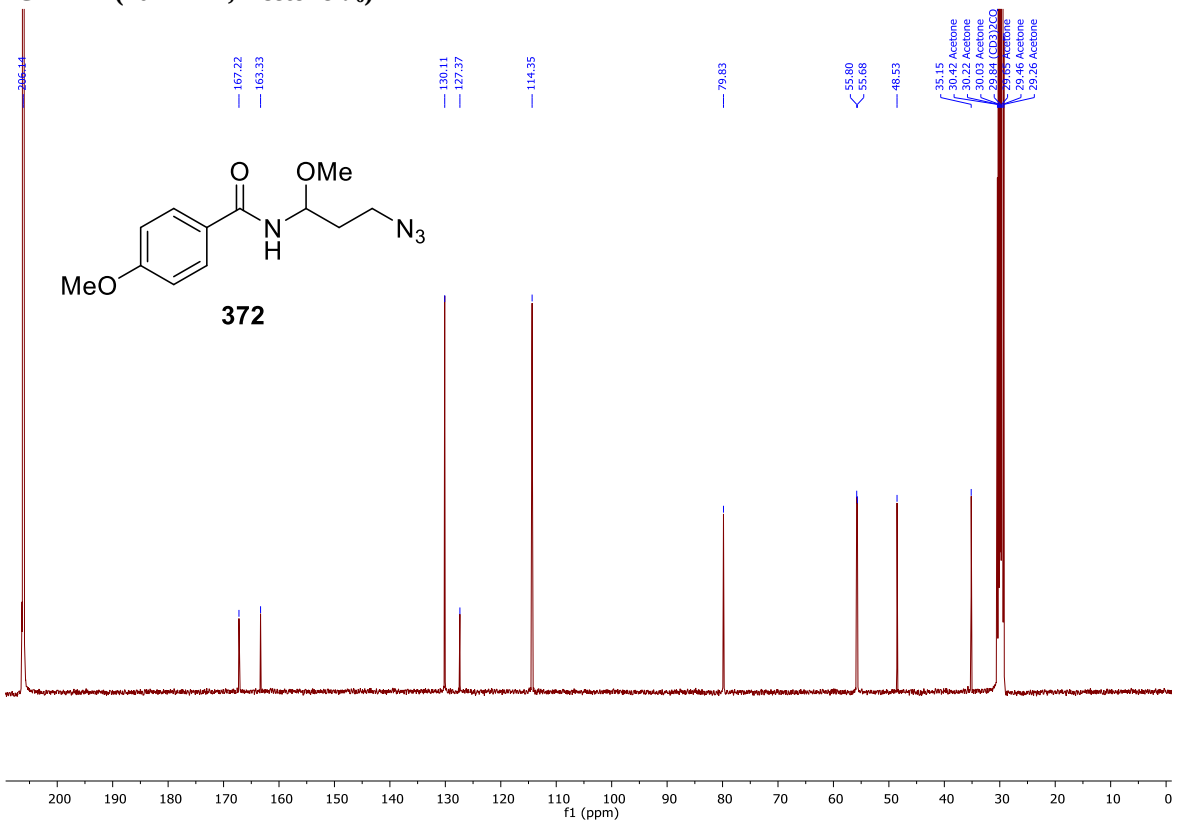
^{13}C-NMR (201 MHz, $CDCl_3$)



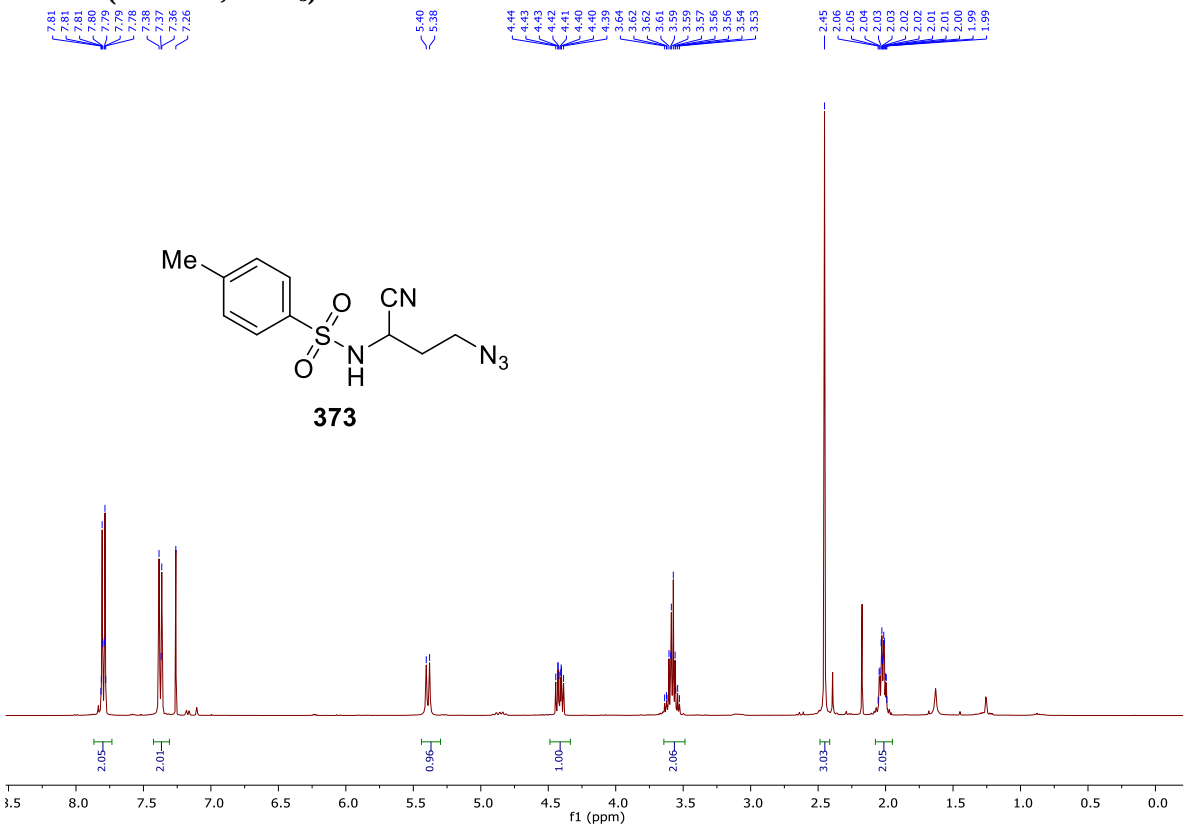
^{1}H-NMR (400 MHz, $CDCl_3$)



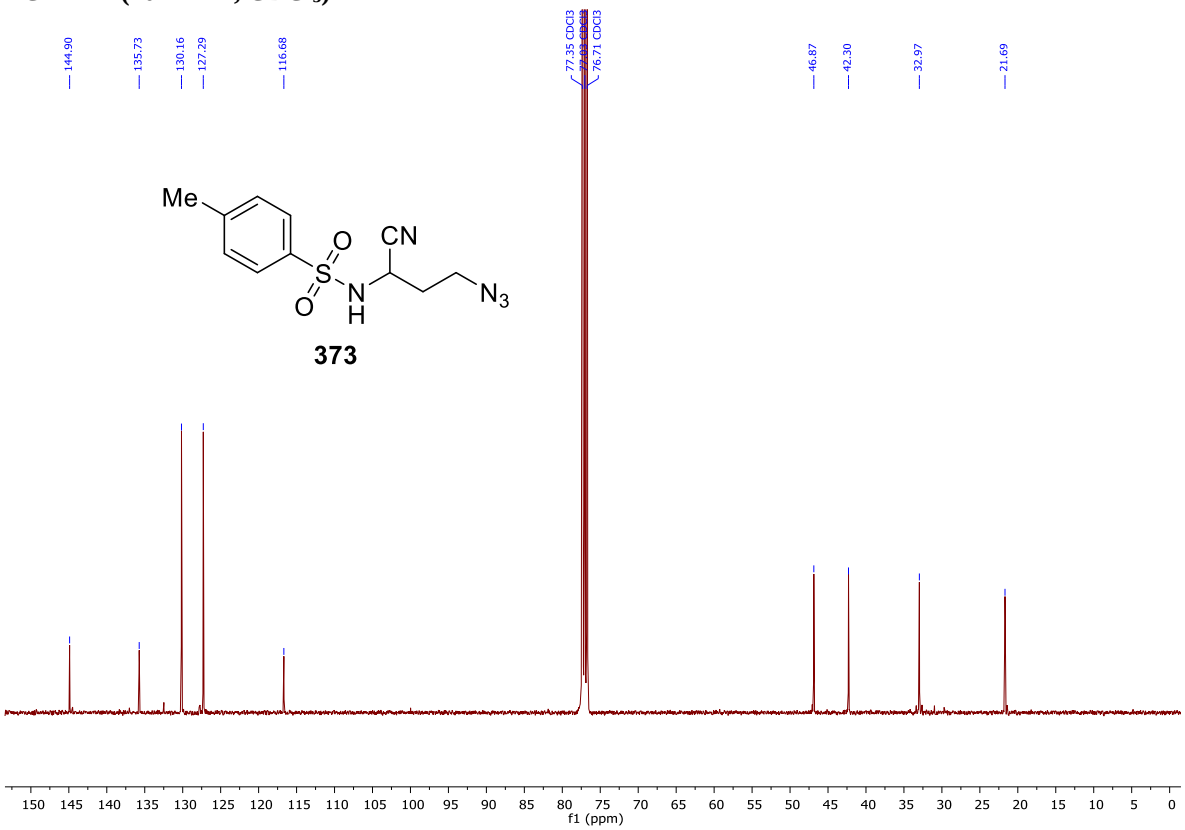
^{13}C-NMR (101 MHz, Acetone-d_6)



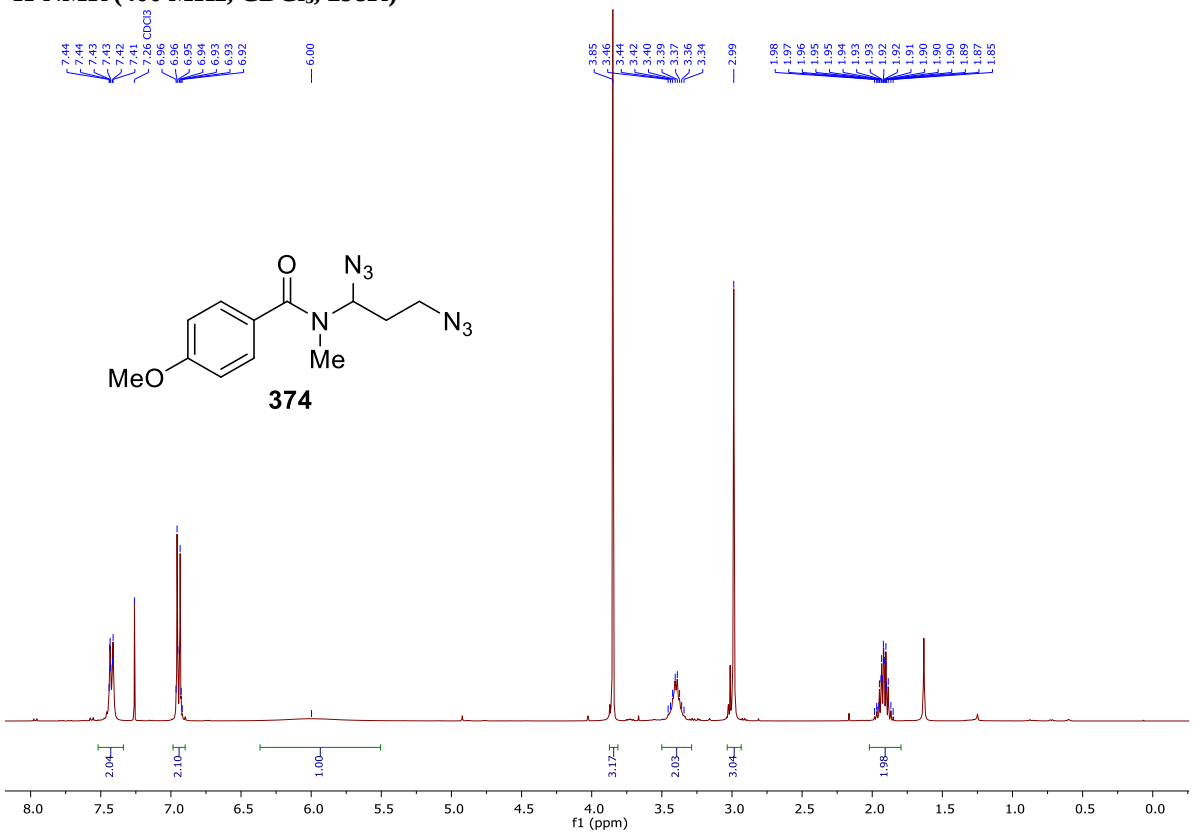
^{1}H-NMR (400 MHz, $CDCl_3$)



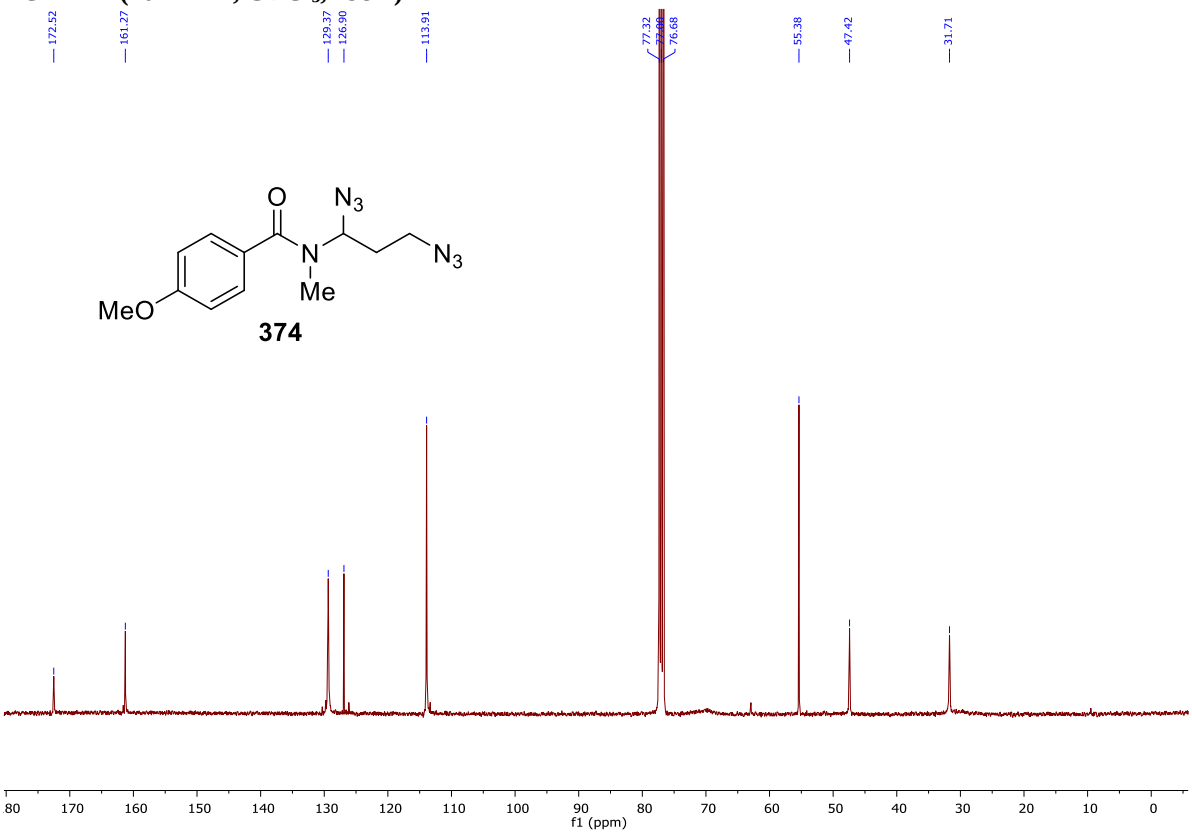
^{13}C-NMR (101 MHz, $CDCl_3$)



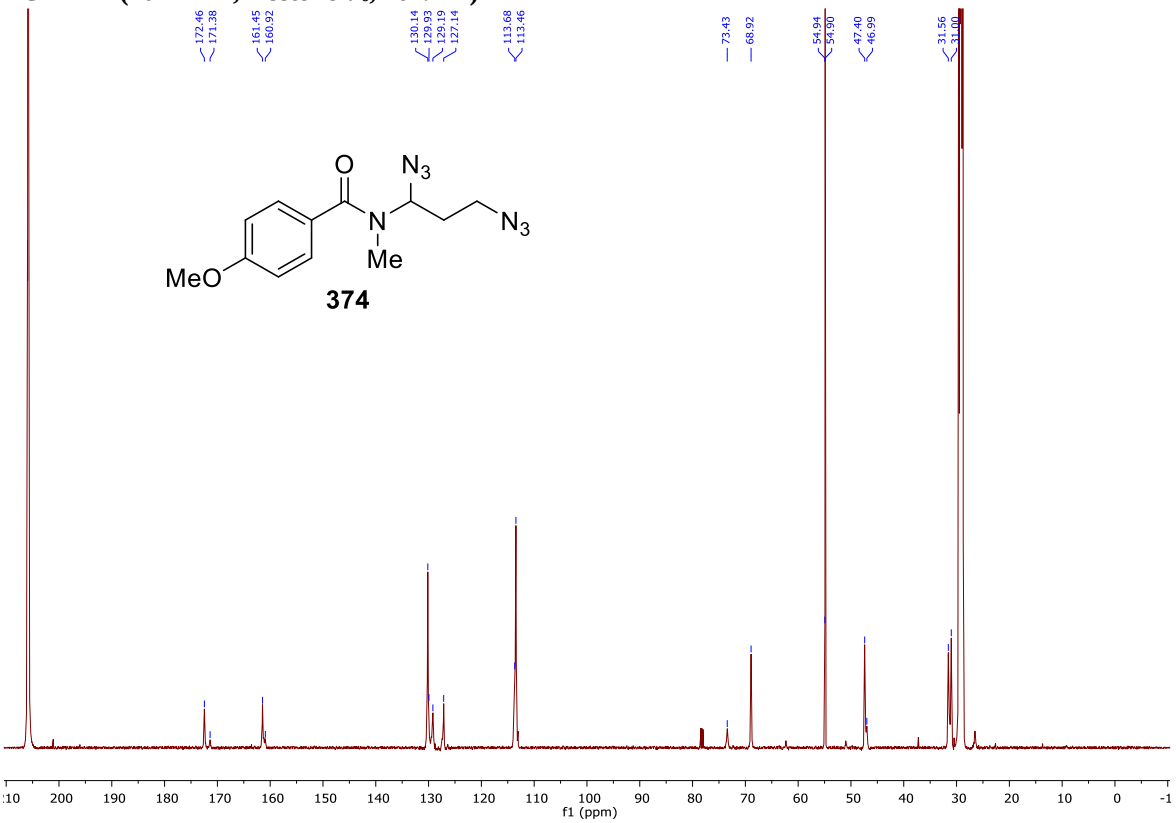
^{1}H-NMR (400 MHz, $CDCl_3$, 298K)



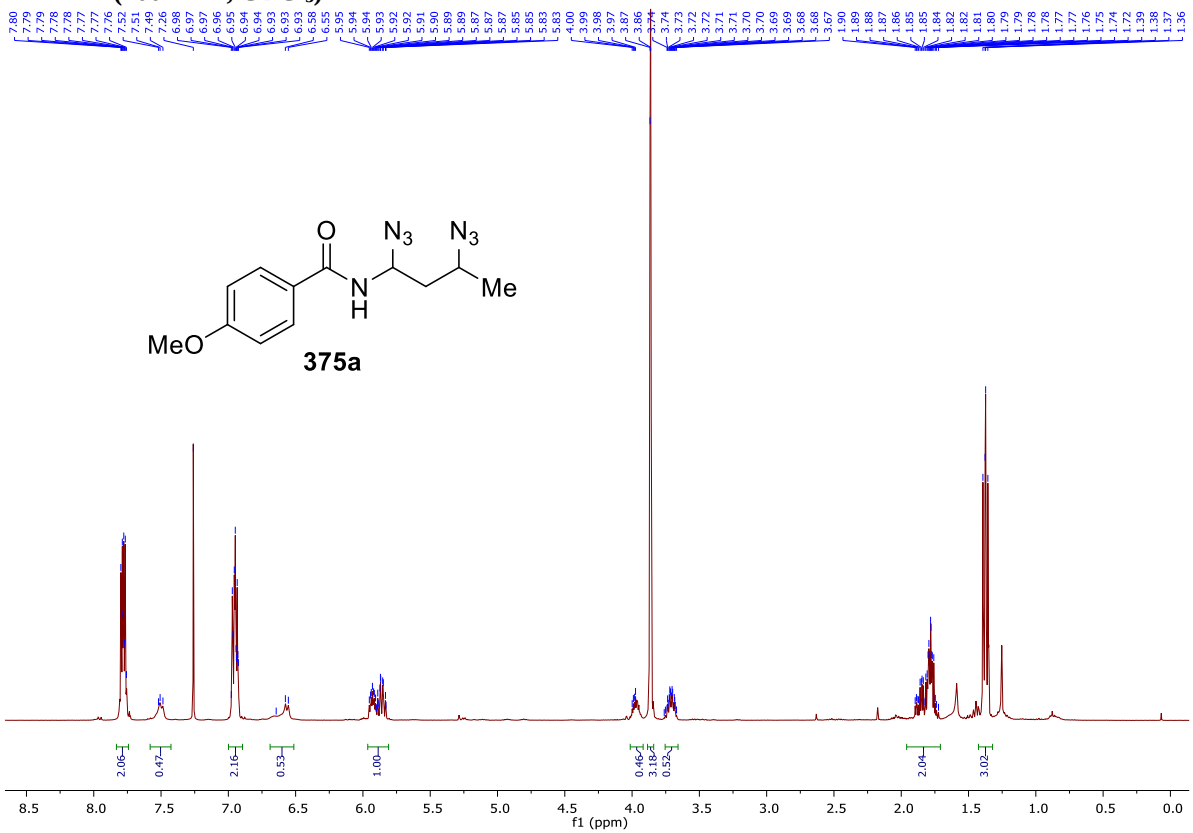
^{13}C-NMR (101 MHz, $CDCl_3$, 298K)



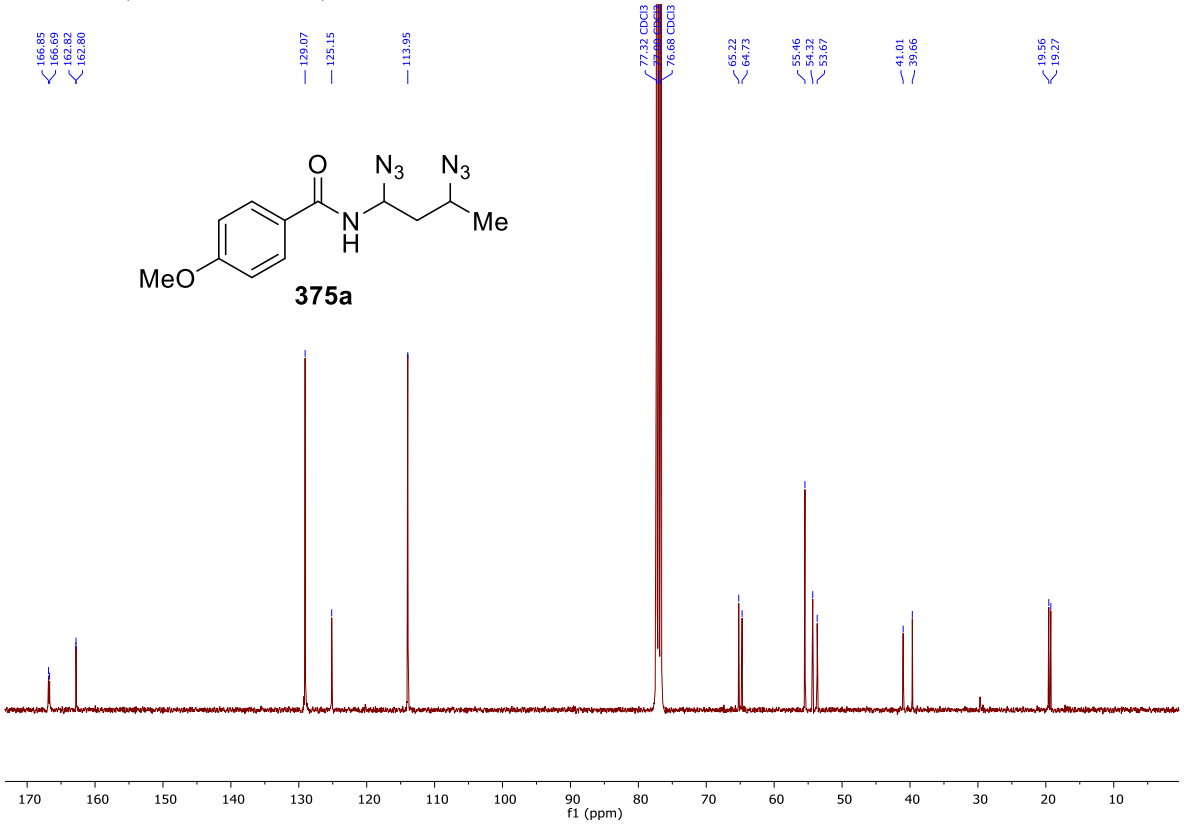
^{13}C-NMR (101 MHz, Acetone-d_6, 261.7 K)



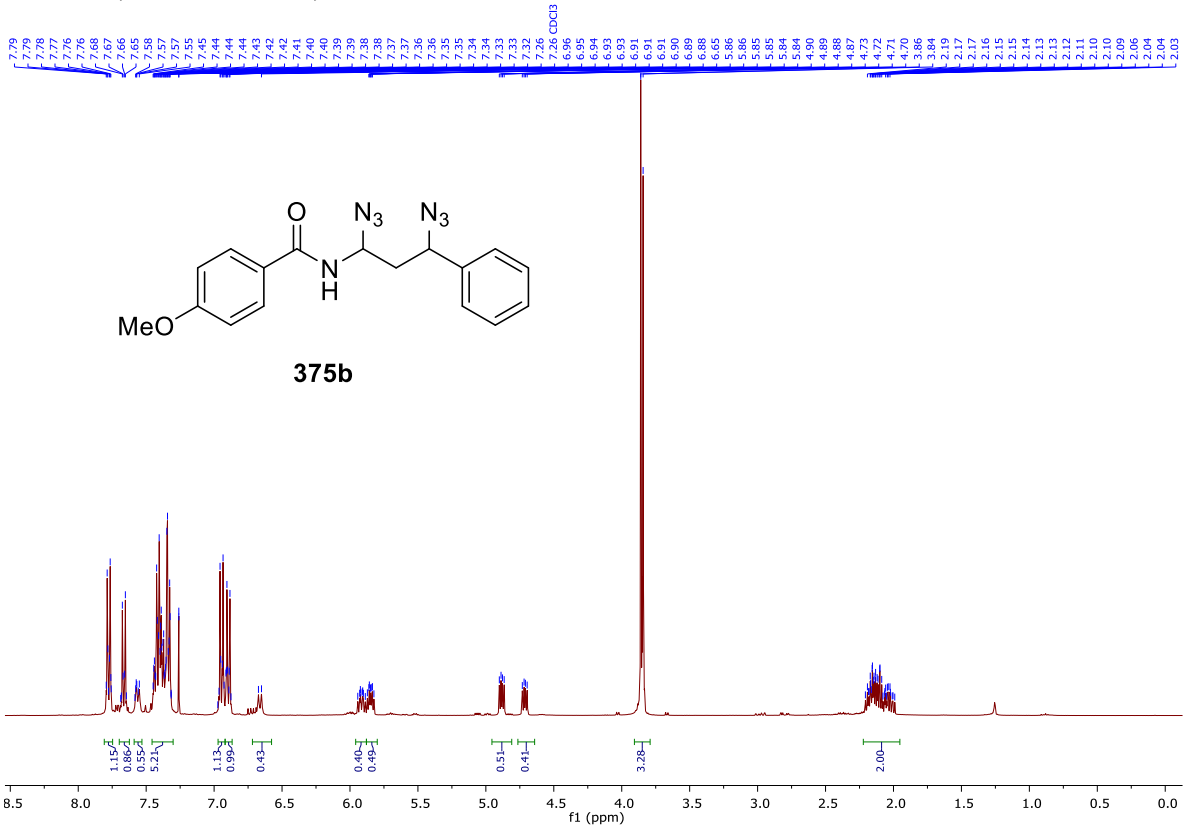
^{1}H-NMR (400 MHz, $CDCl_3$)



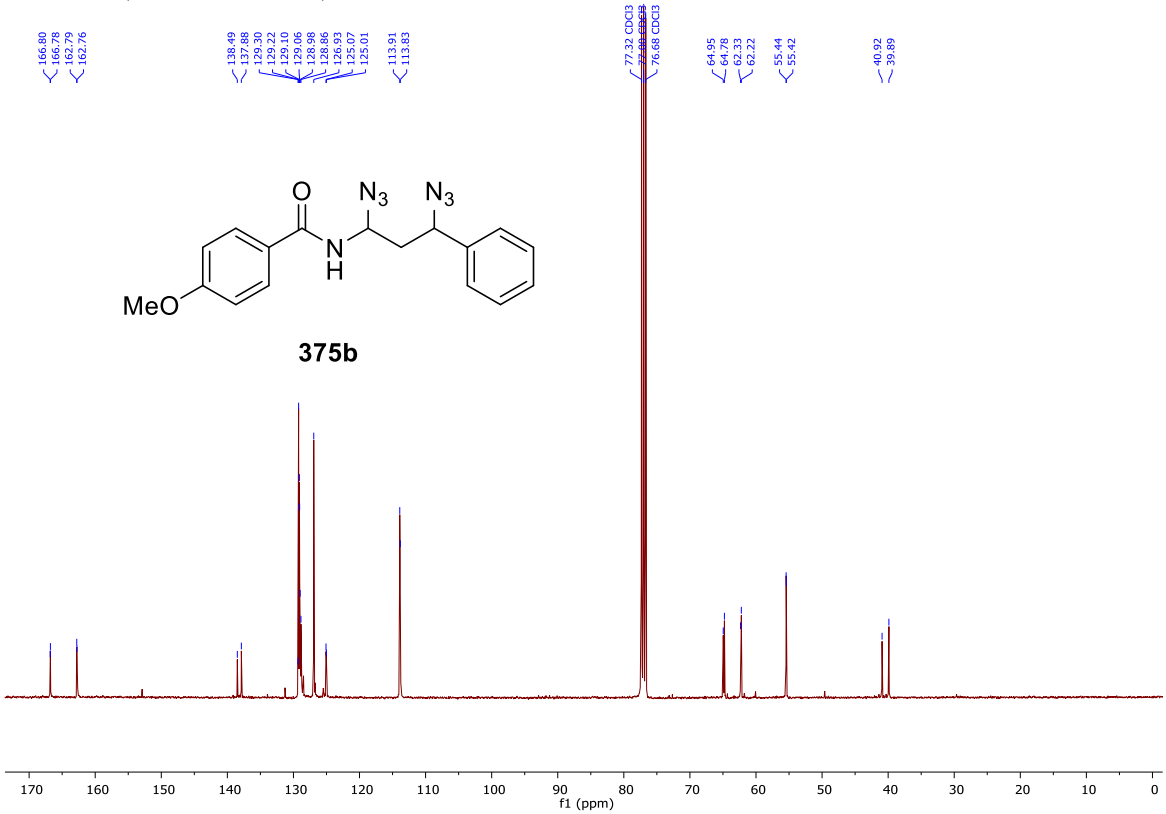
^{13}C-NMR (101 MHz, $CDCl_3$)



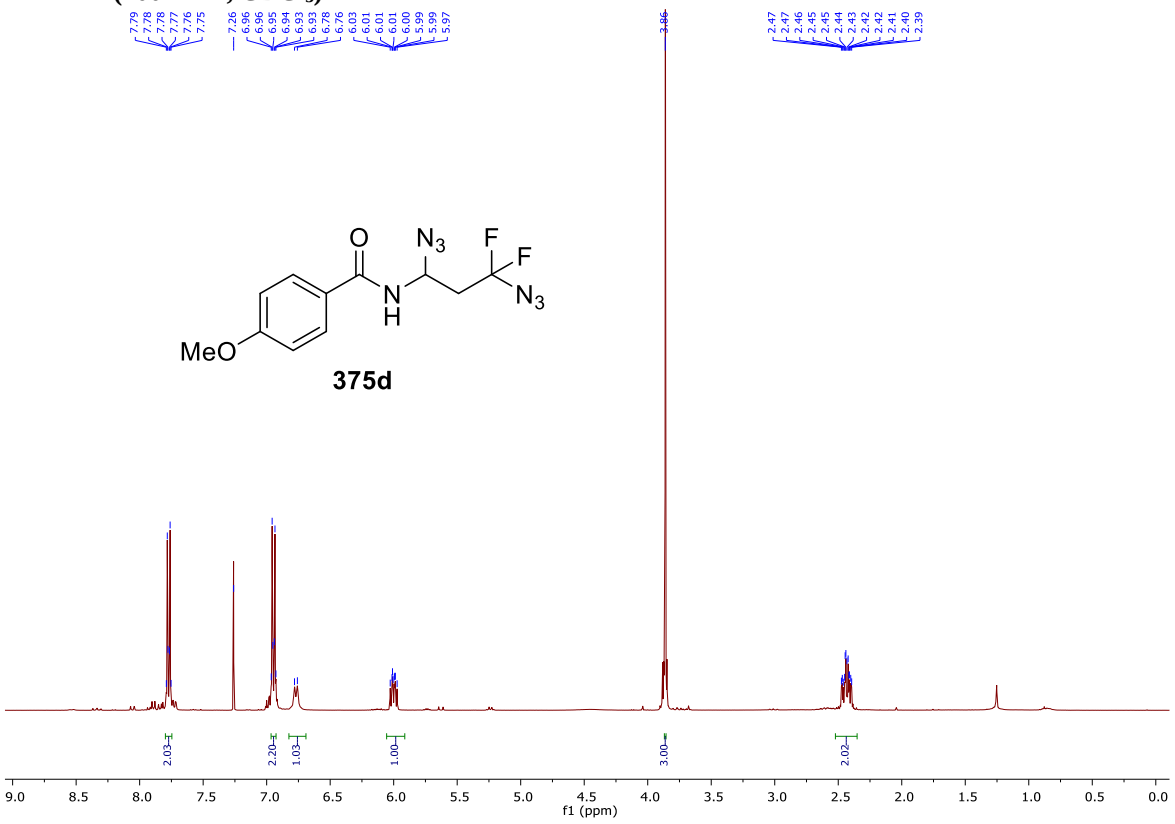
^{1}H-NMR (400 MHz, $CDCl_3$)



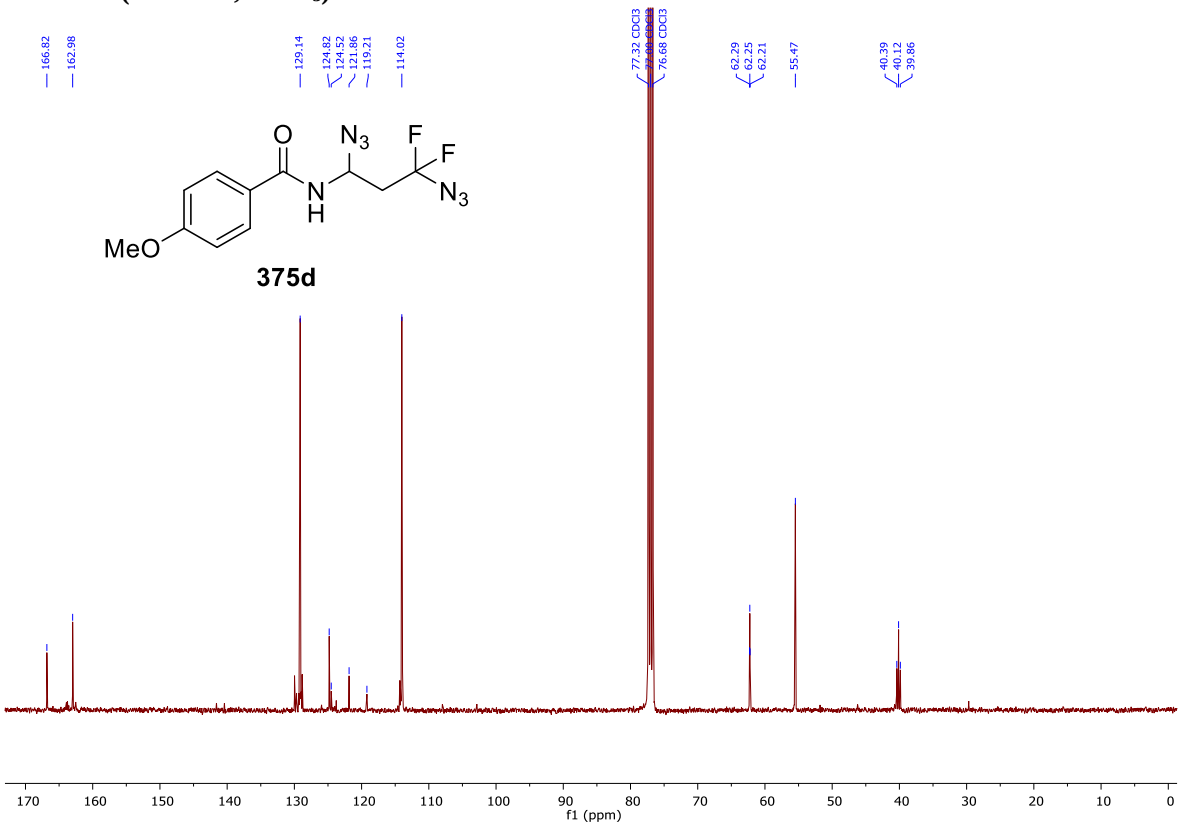
^{13}C-NMR (101 MHz, $CDCl_3$)



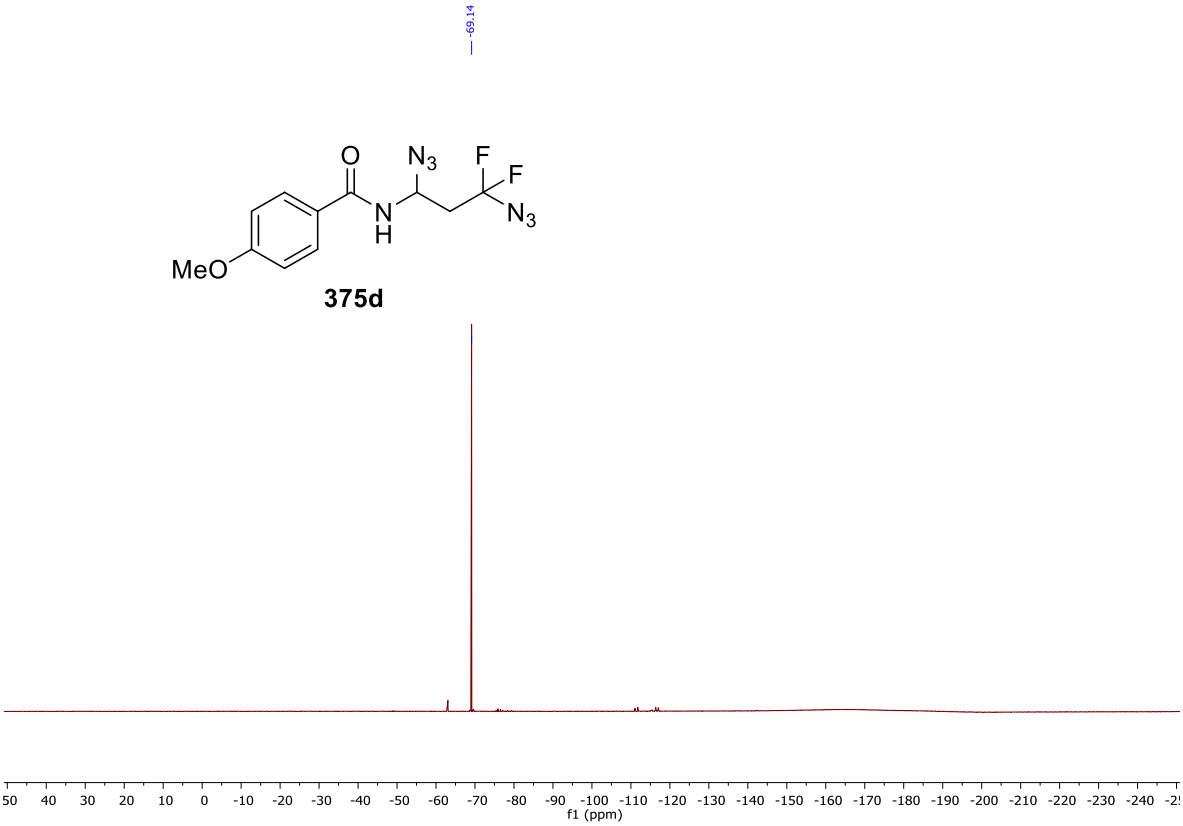
^{1}H-NMR (400 MHz, $CDCl_3$)



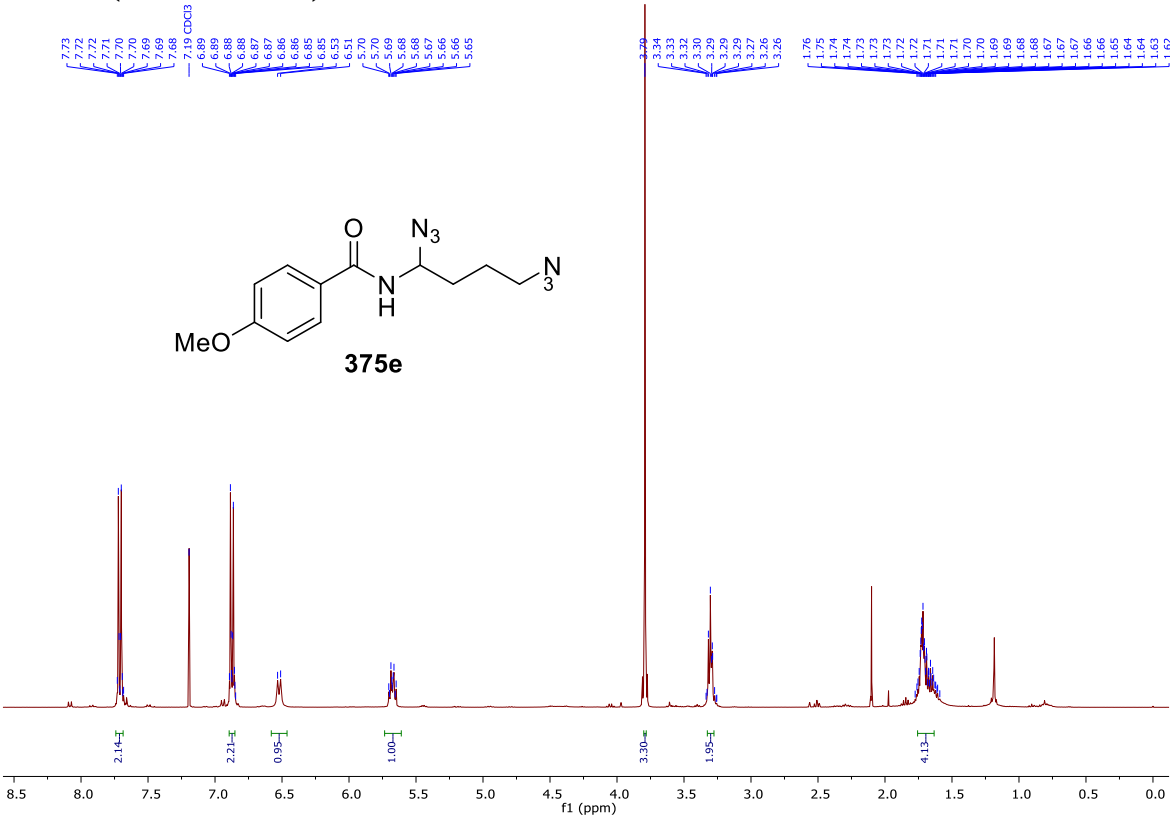
^{13}C-NMR (101 MHz, $CDCl_3$)



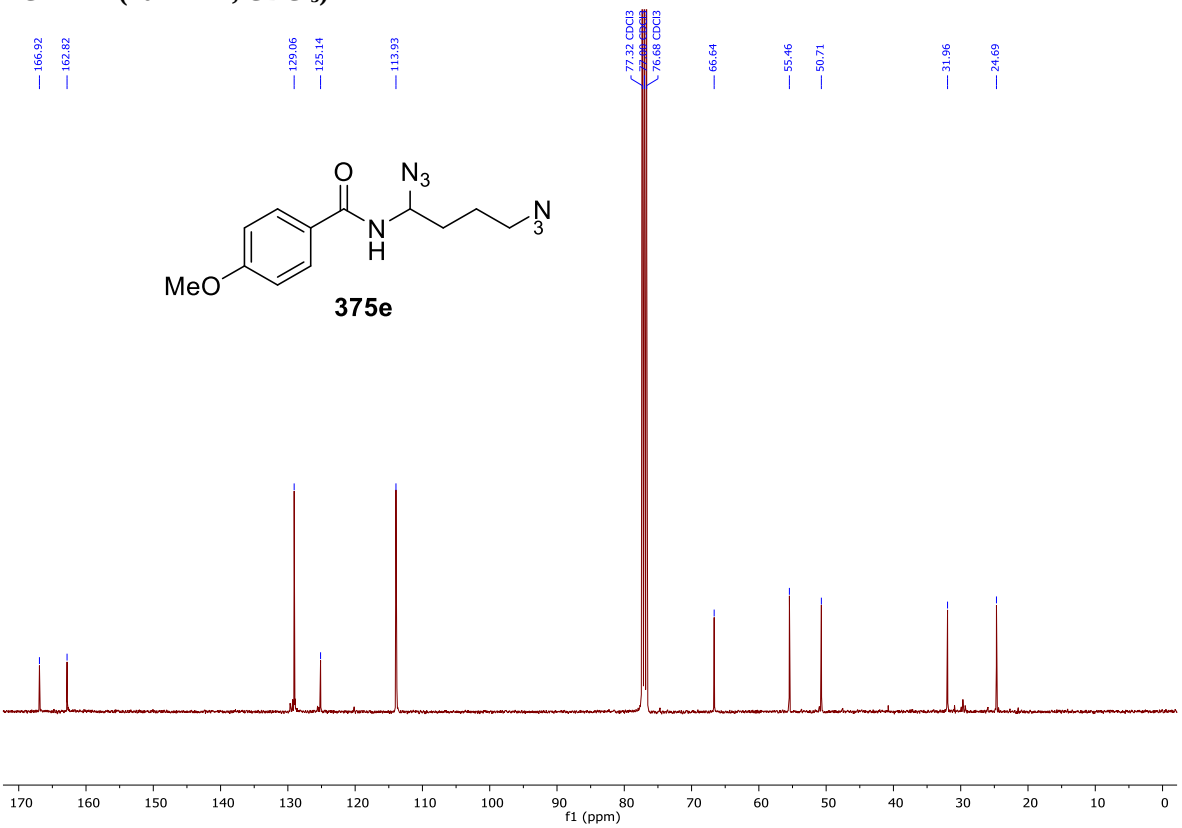
^{19}F-NMR (377 MHz, $CDCl_3$)



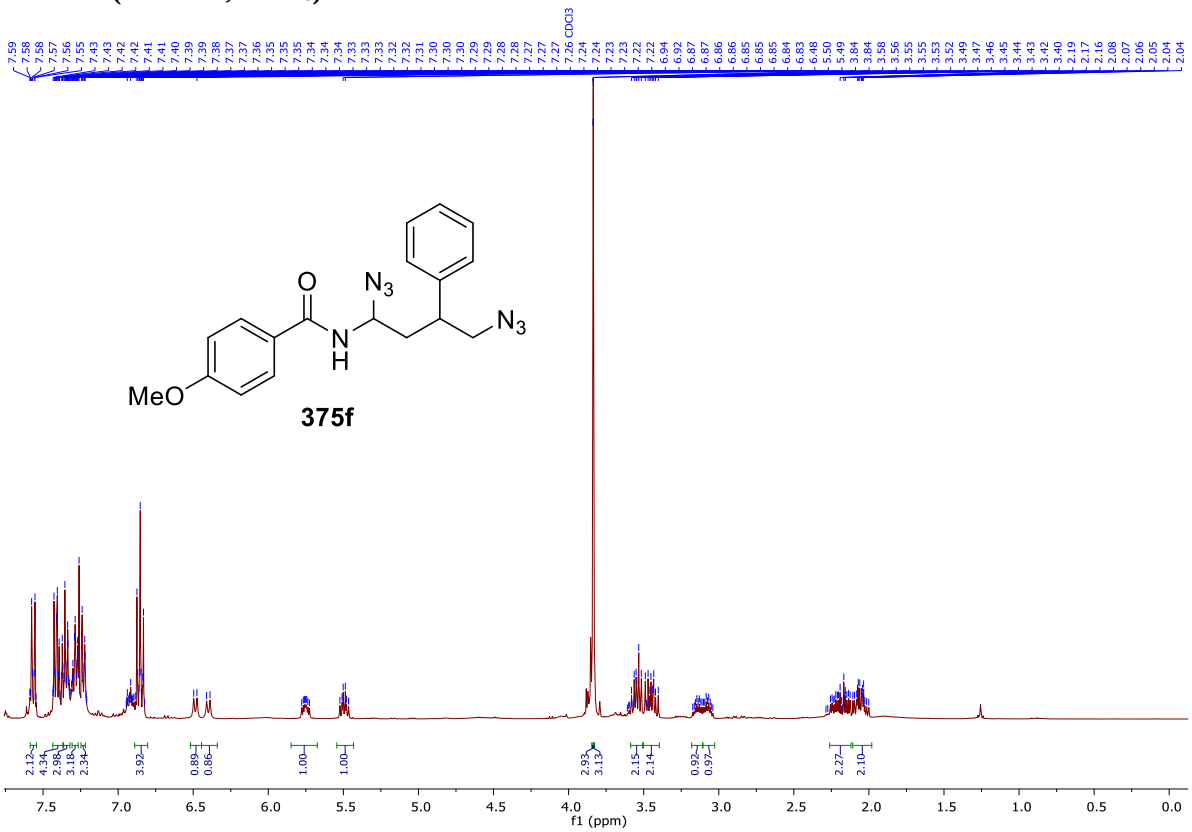
^{1}H-NMR (400 MHz, $CDCl_3$)



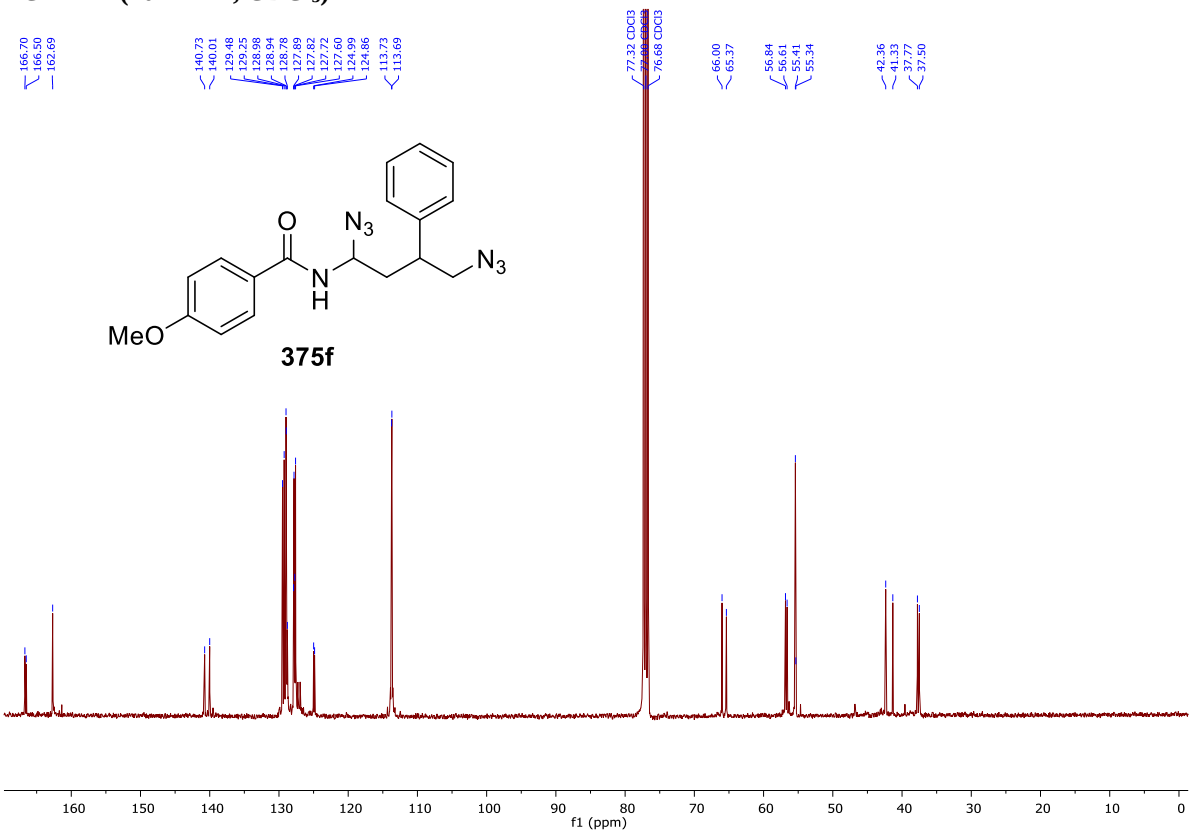
^{13}C-NMR (101 MHz, $CDCl_3$)



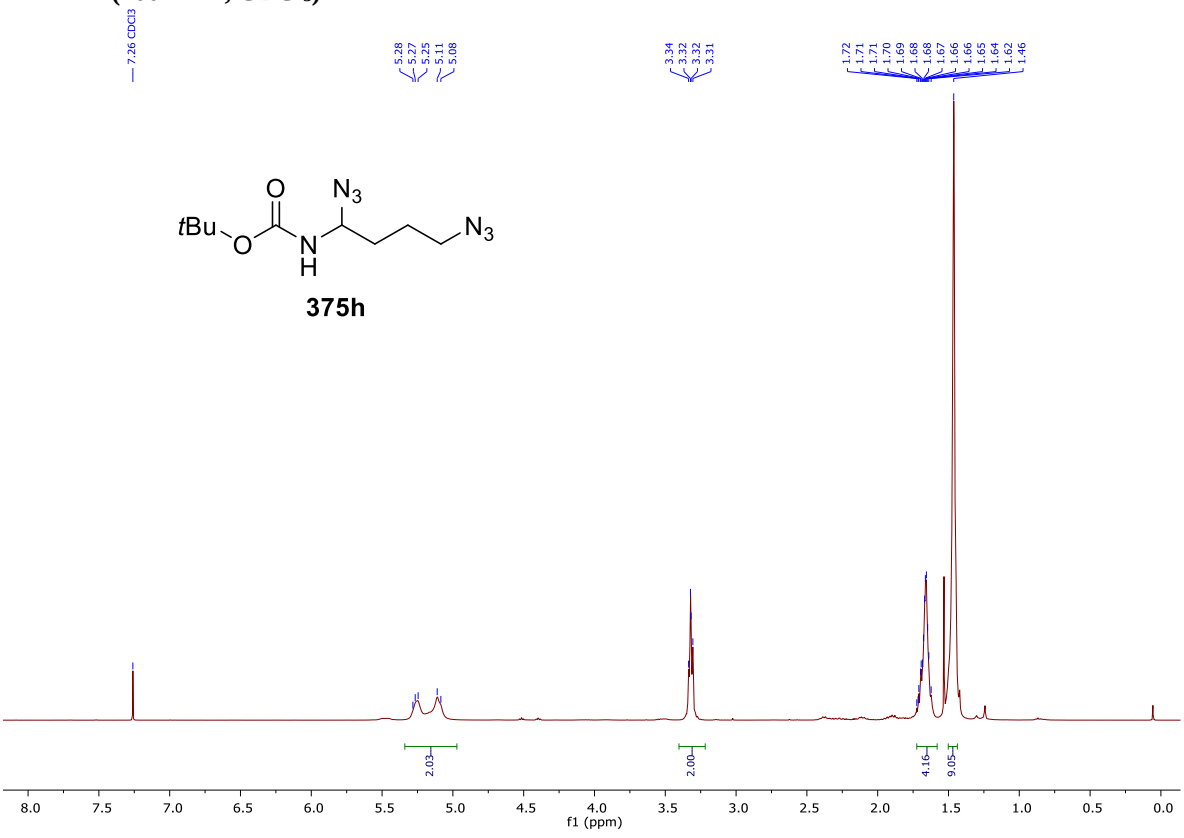
^{1}H-NMR (400 MHz, $CDCl_3$)



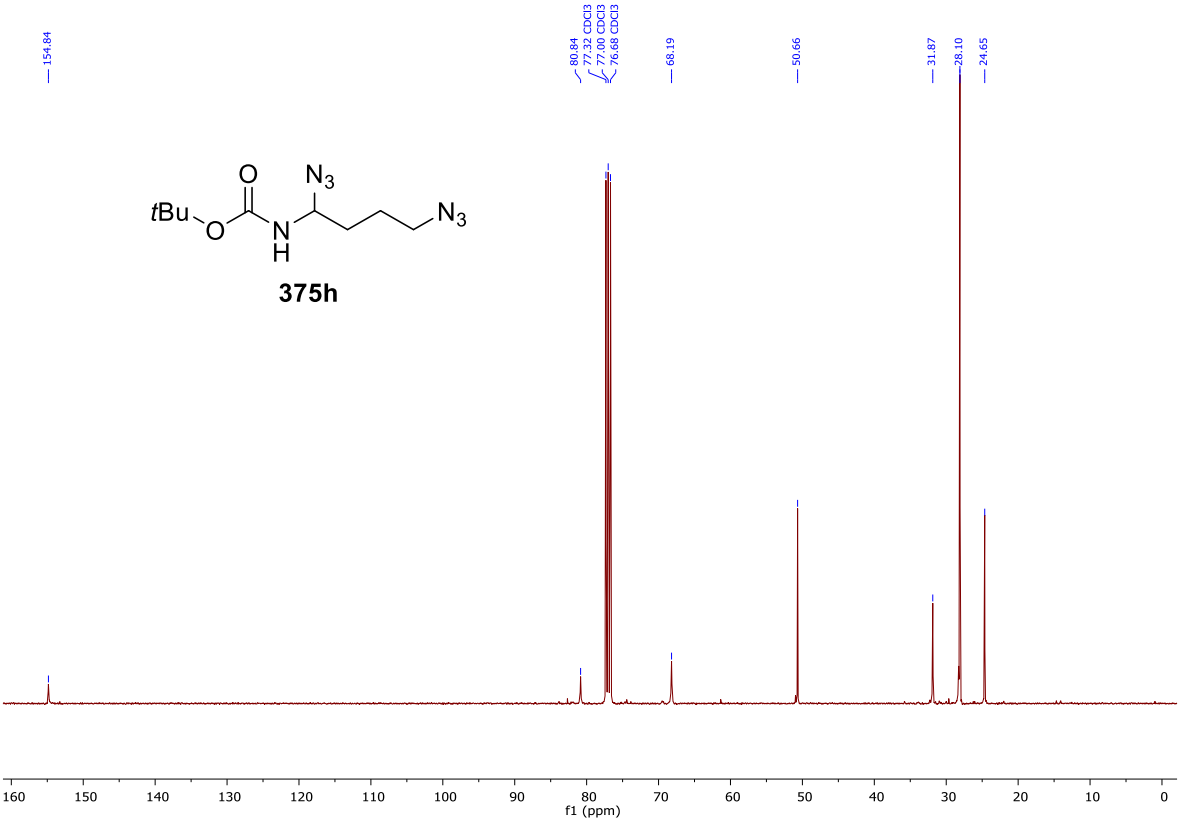
^{13}C-NMR (101 MHz, $CDCl_3$)



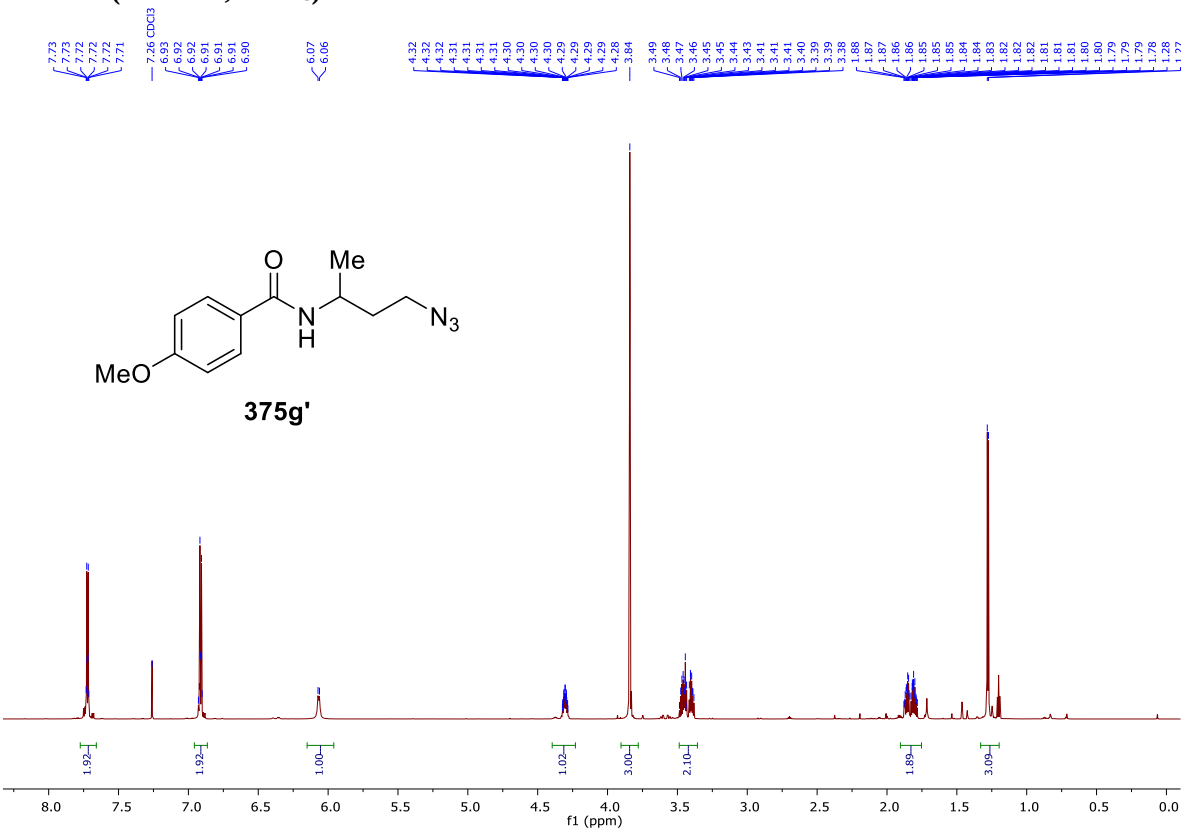
^{1}H-NMR (400 MHz, $CDCl_3$)



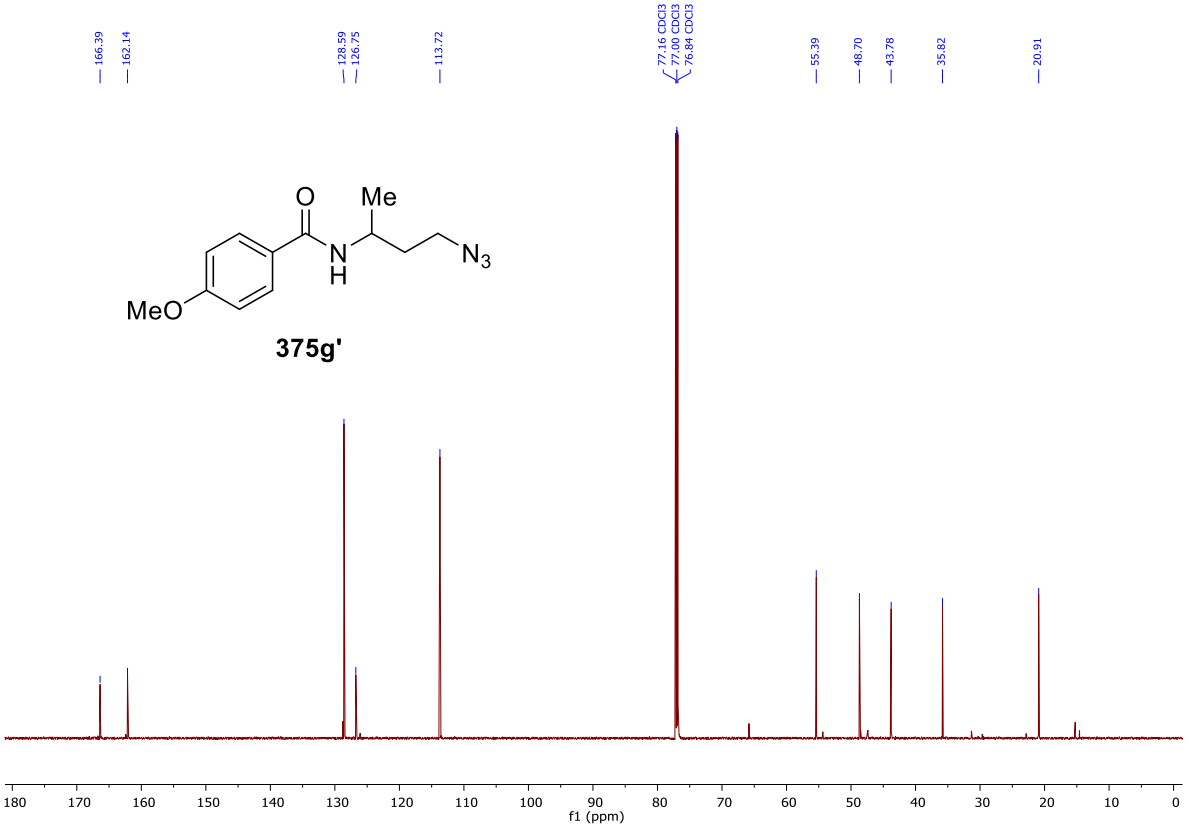
^{13}C-NMR (101 MHz, $CDCl_3$)



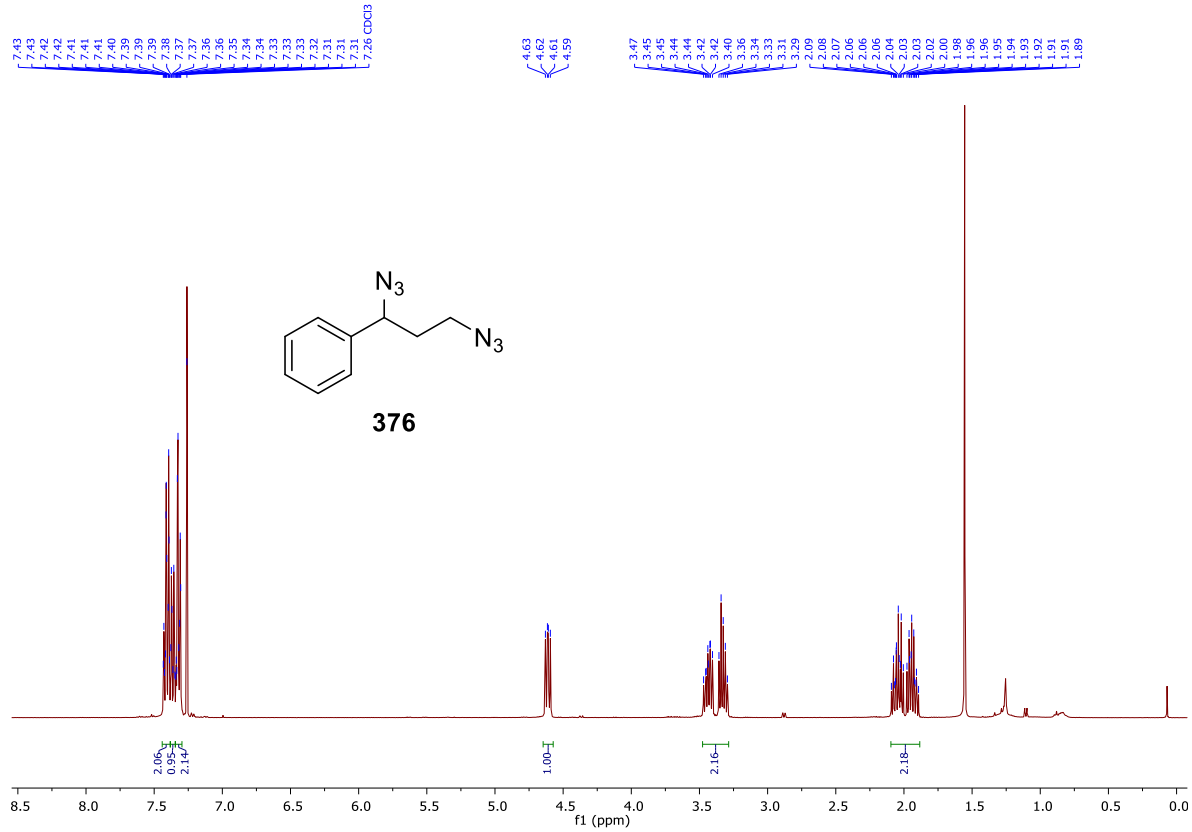
^{1}H-NMR (800 MHz, $CDCl_3$)



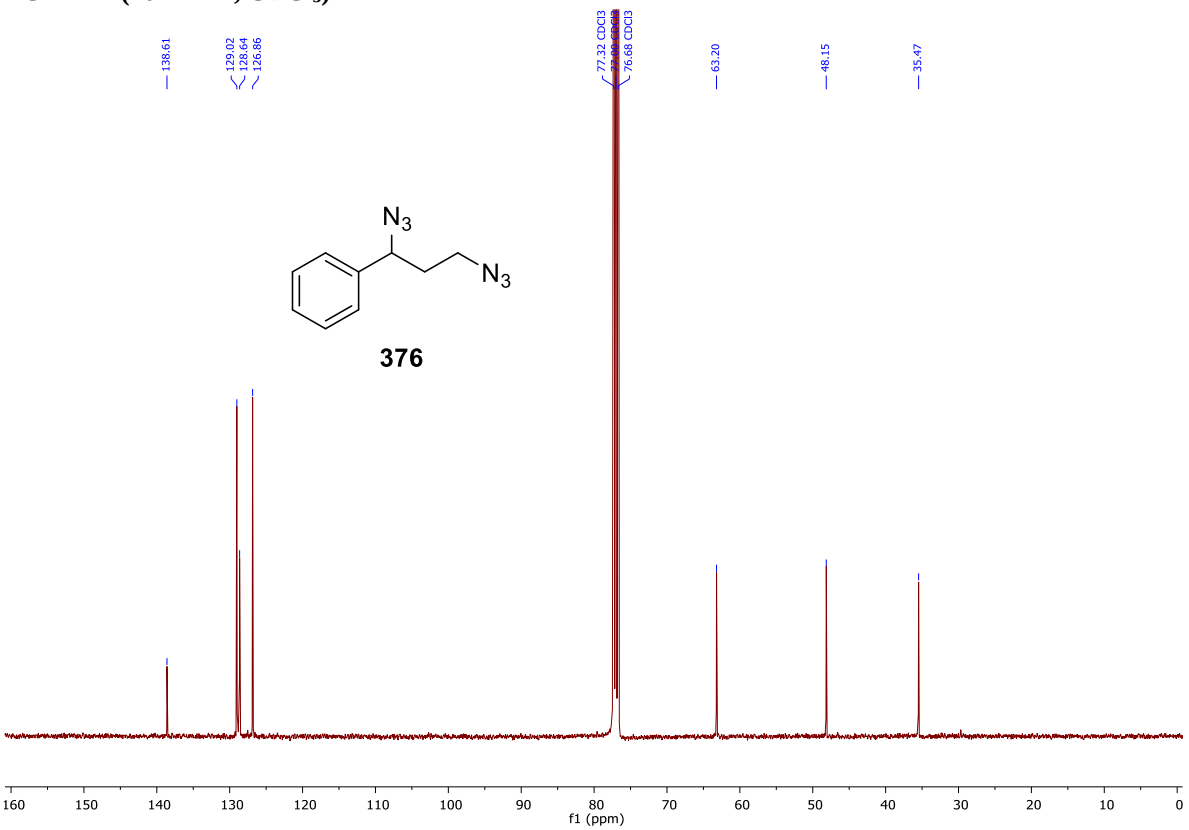
^{13}C-NMR (201 MHz, $CDCl_3$)



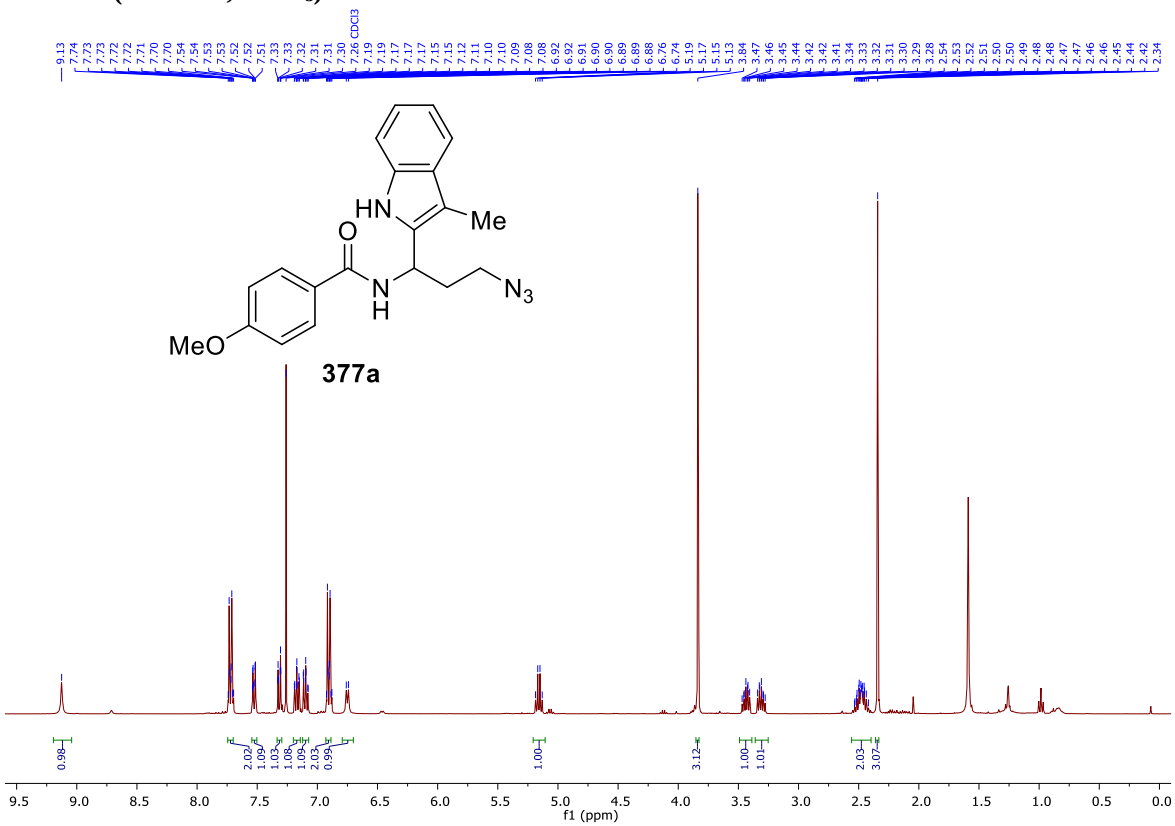
^{1}H-NMR (400 MHz, $CDCl_3$)



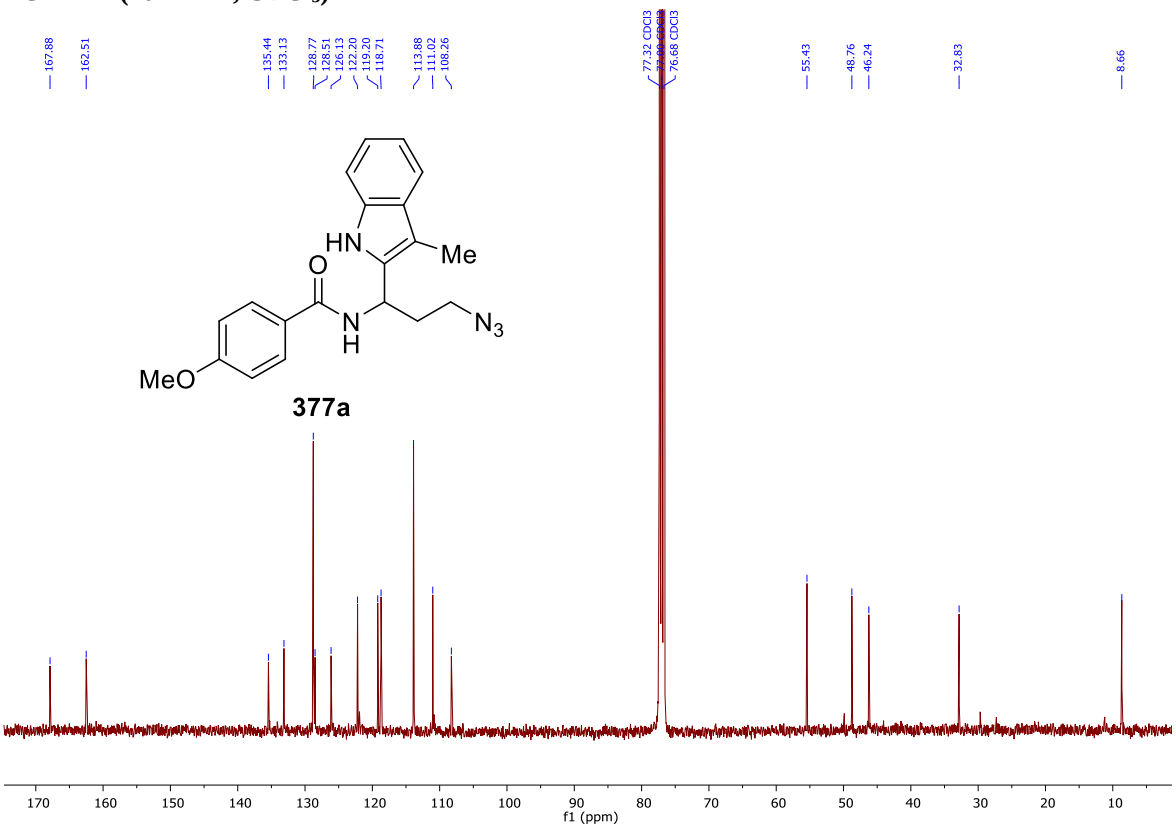
^{13}C-NMR (101 MHz, $CDCl_3$)



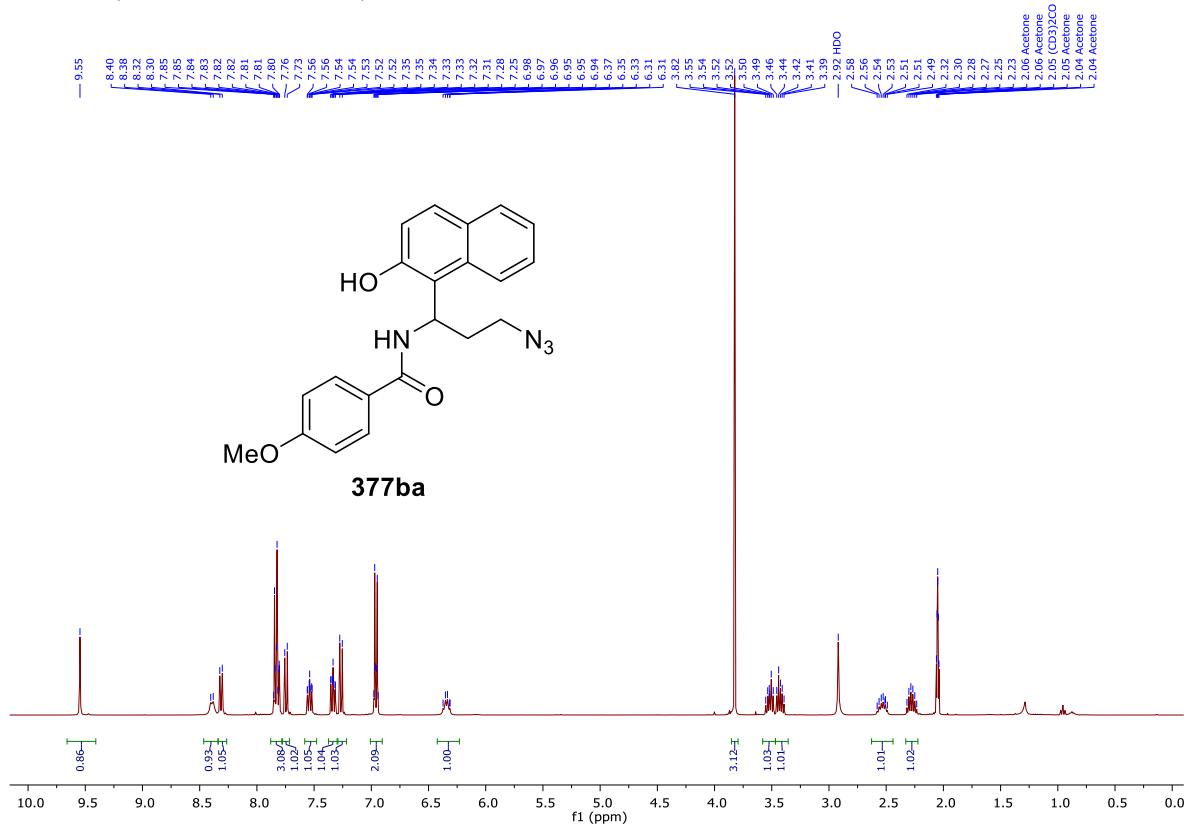
^{1}H-NMR (400 MHz, $CDCl_3$)



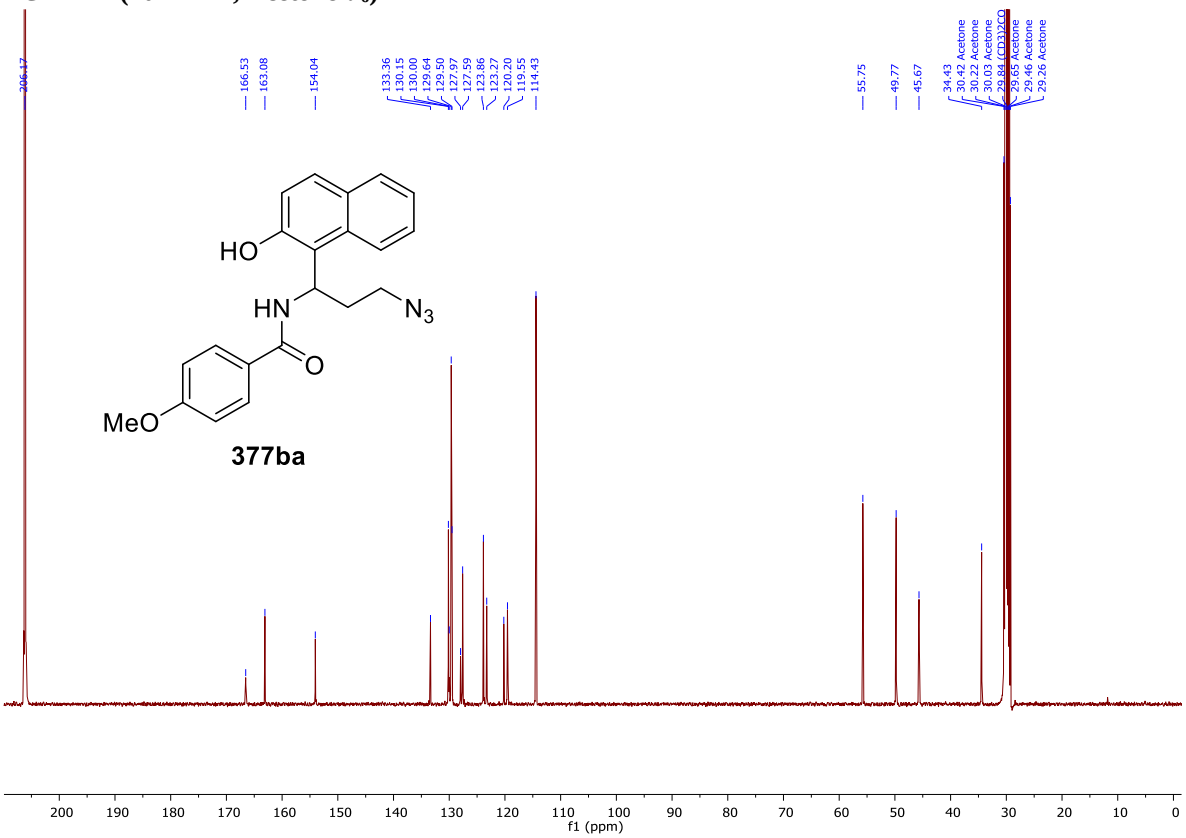
^{13}C-NMR (101 MHz, $CDCl_3$)



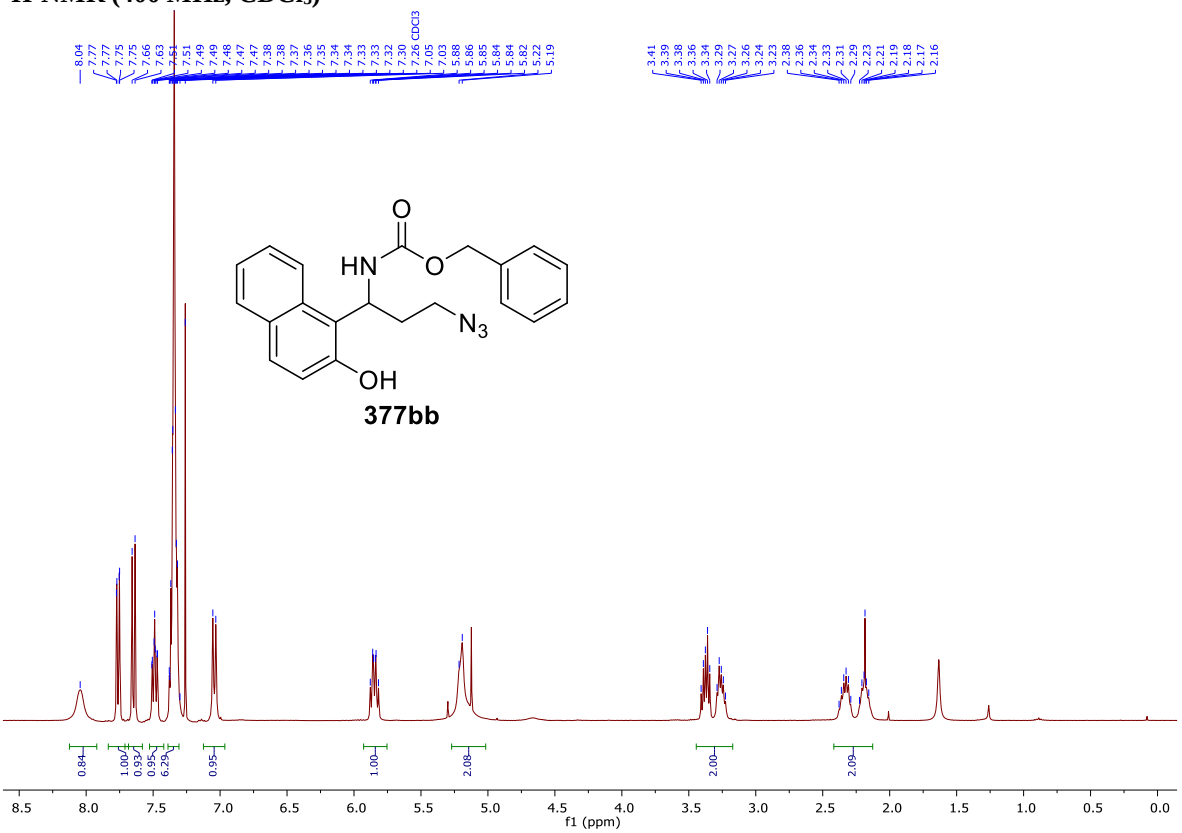
^{1}H-NMR (400 MHz, Acetone-d_6)



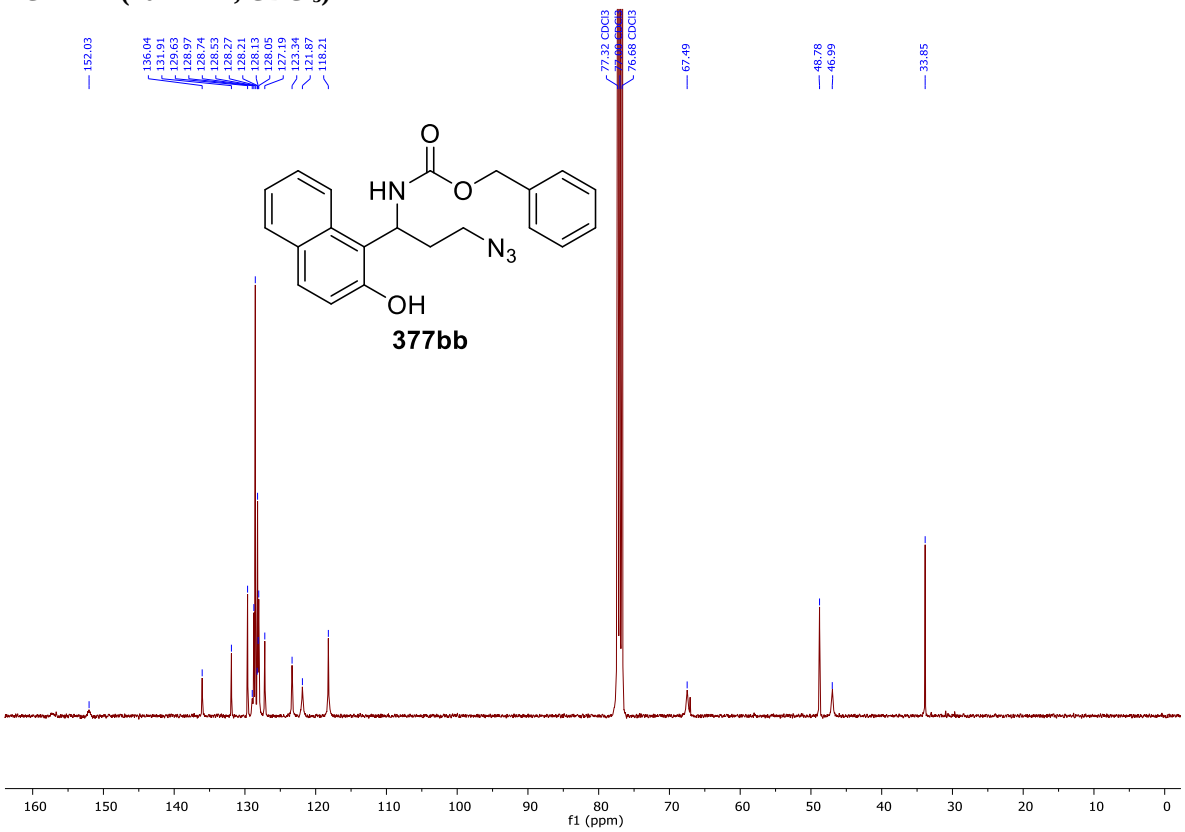
^{13}C-NMR (101 MHz, Acetone-d_6)



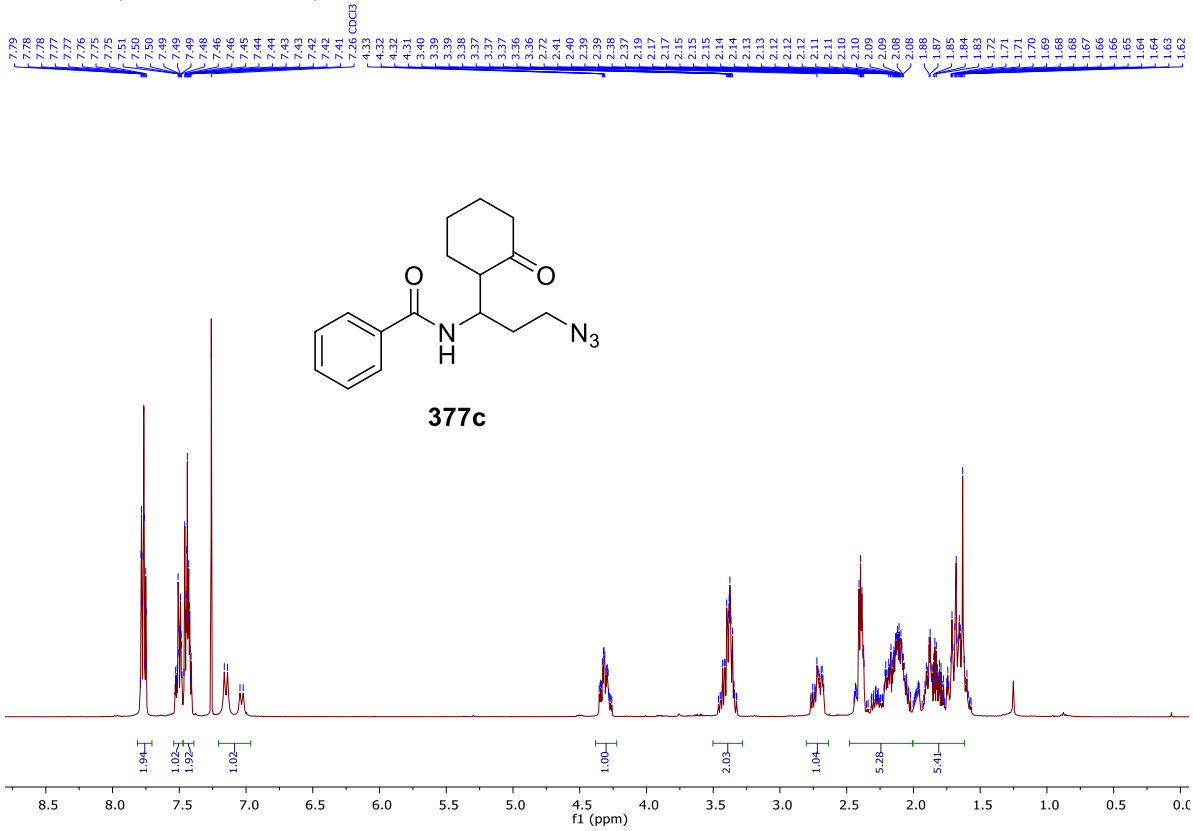
^{1}H-NMR (400 MHz, $CDCl_3$)



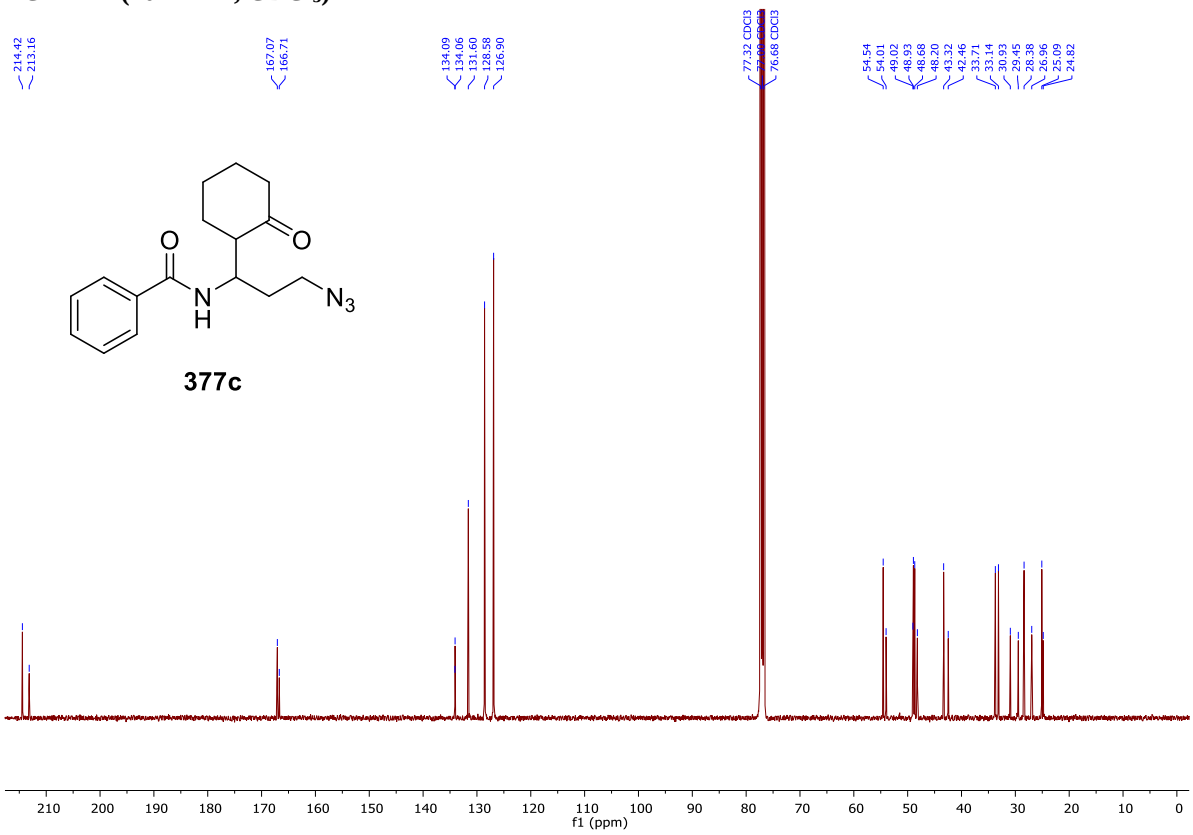
^{13}C-NMR (101 MHz, $CDCl_3$)



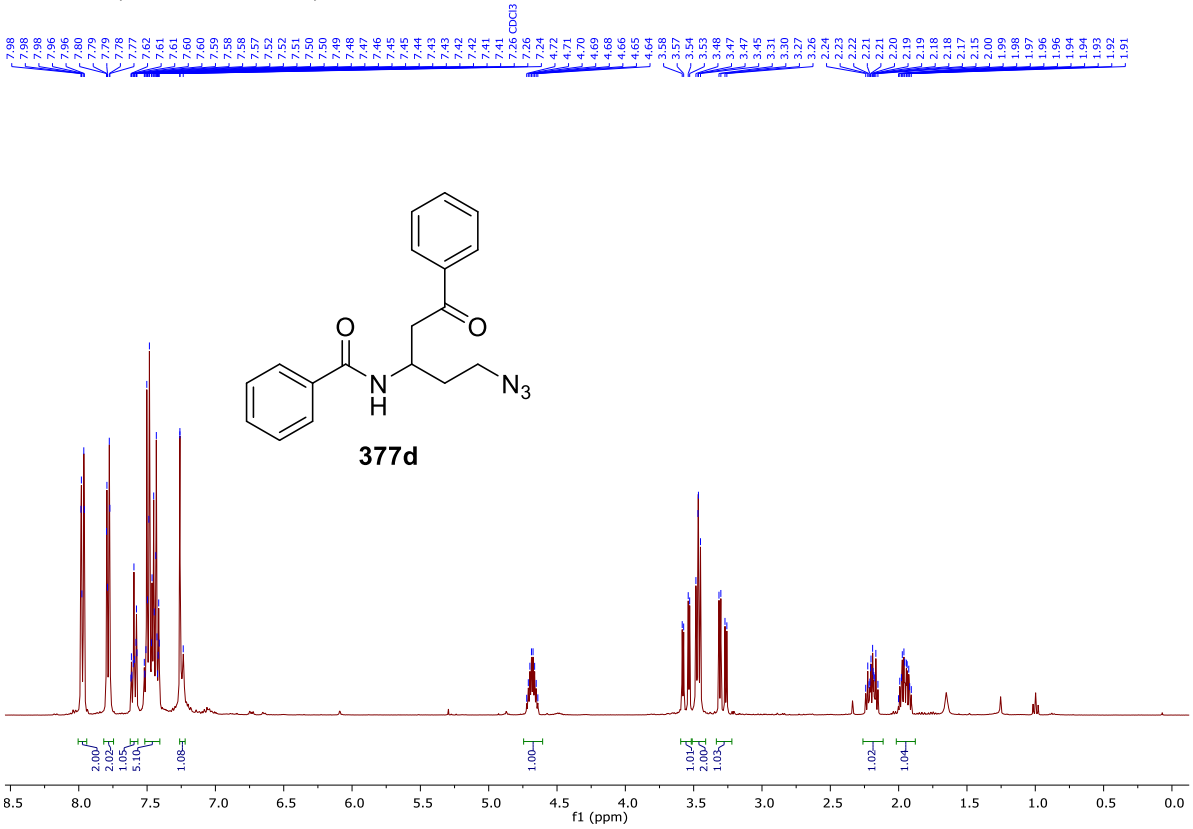
^{1}H-NMR (400 MHz, $CDCl_3$)



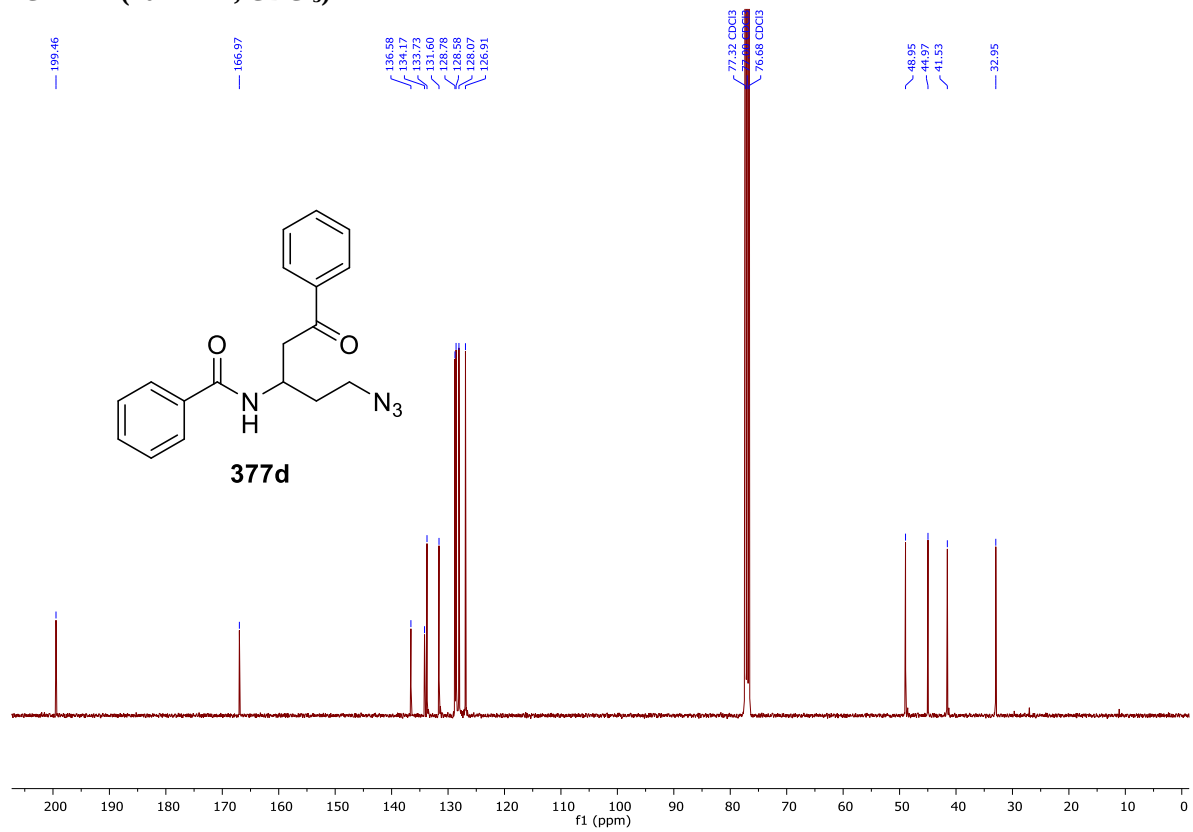
^{13}C-NMR (101 MHz, $CDCl_3$)



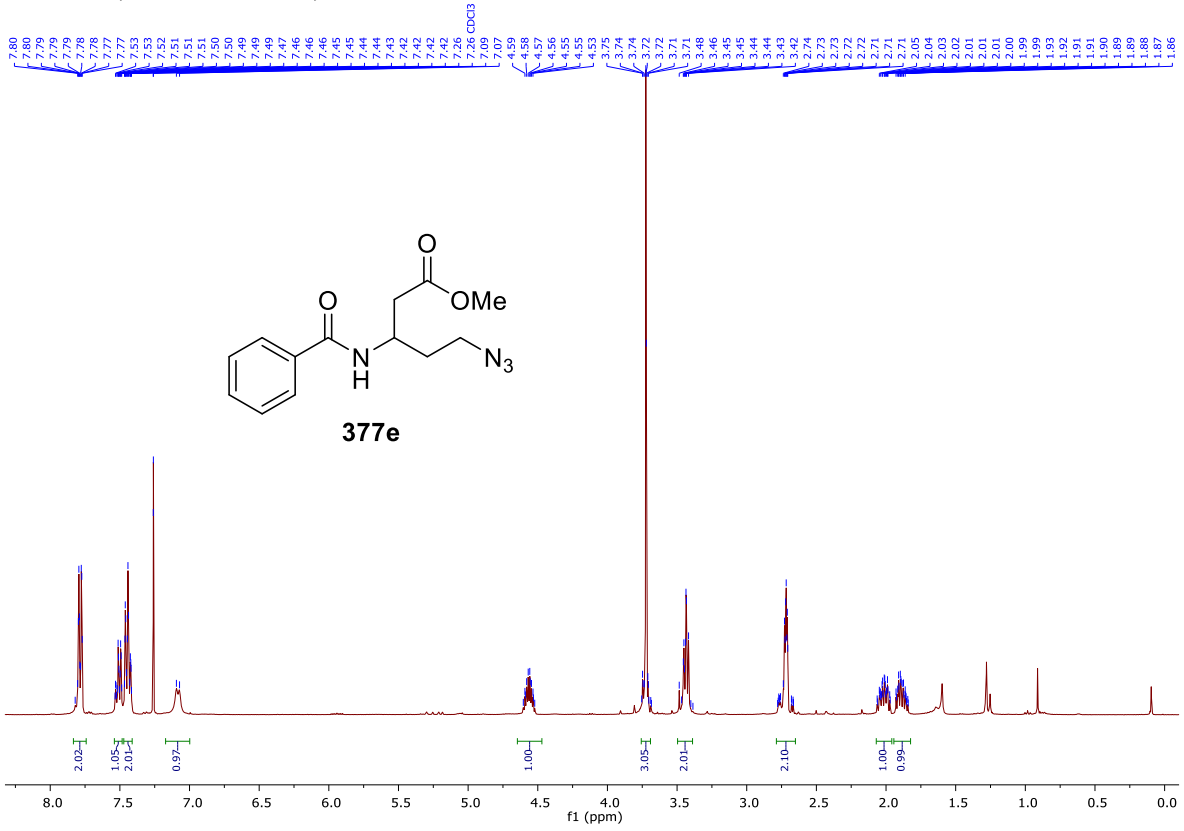
^{1}H-NMR (400 MHz, $CDCl_3$)



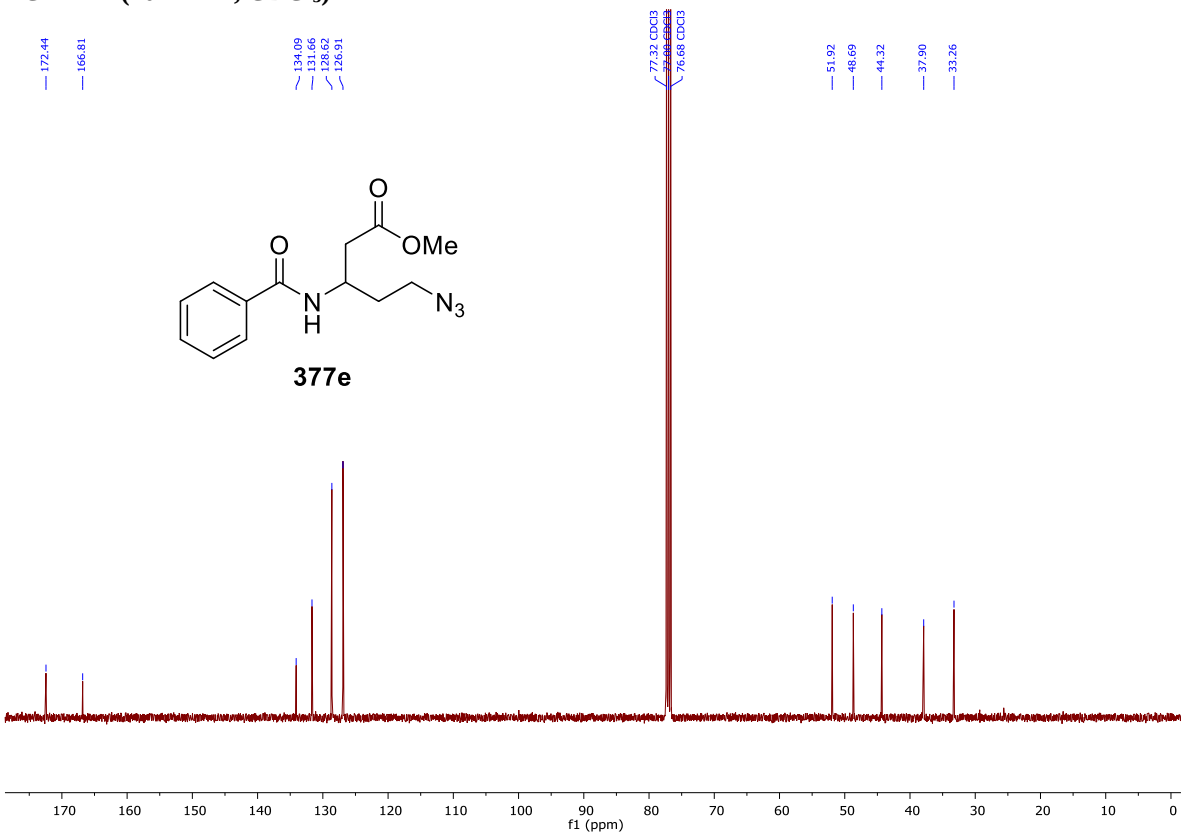
^{13}C-NMR (101 MHz, $CDCl_3$)



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

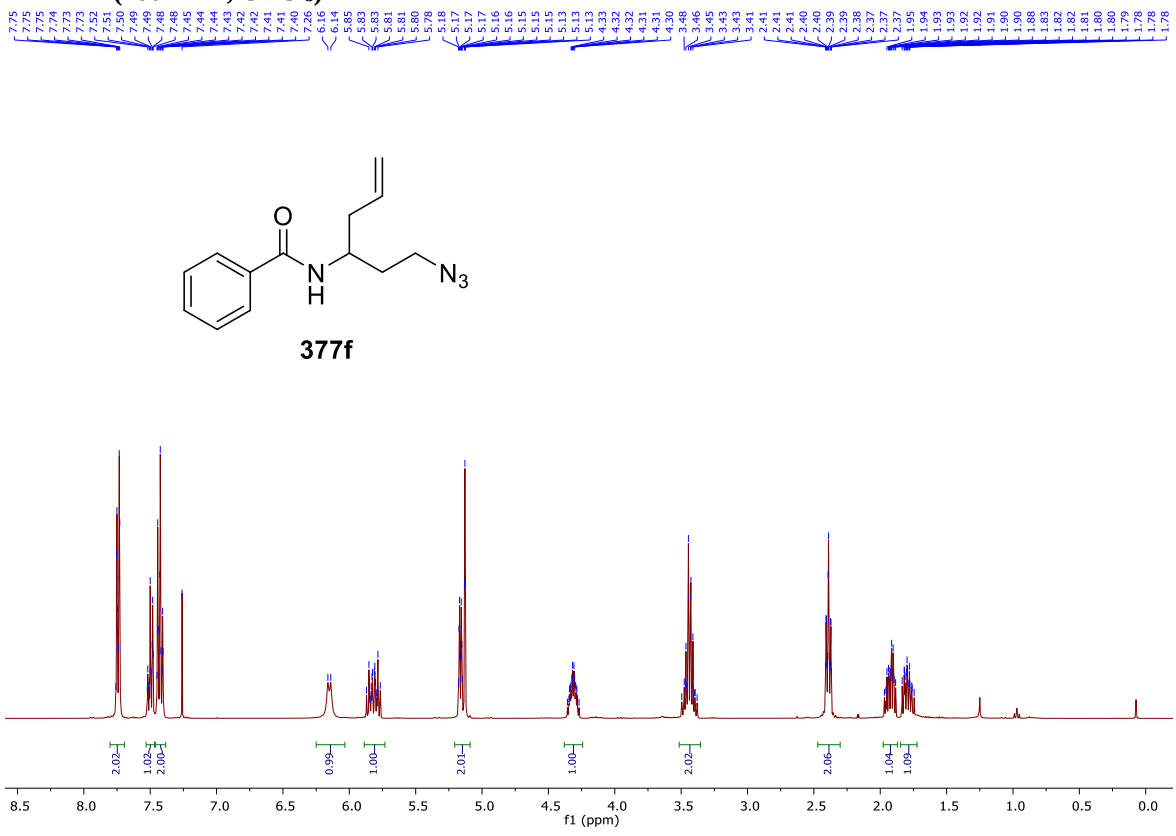


^{13}C-NMR (101 MHz, $CDCl_3$)



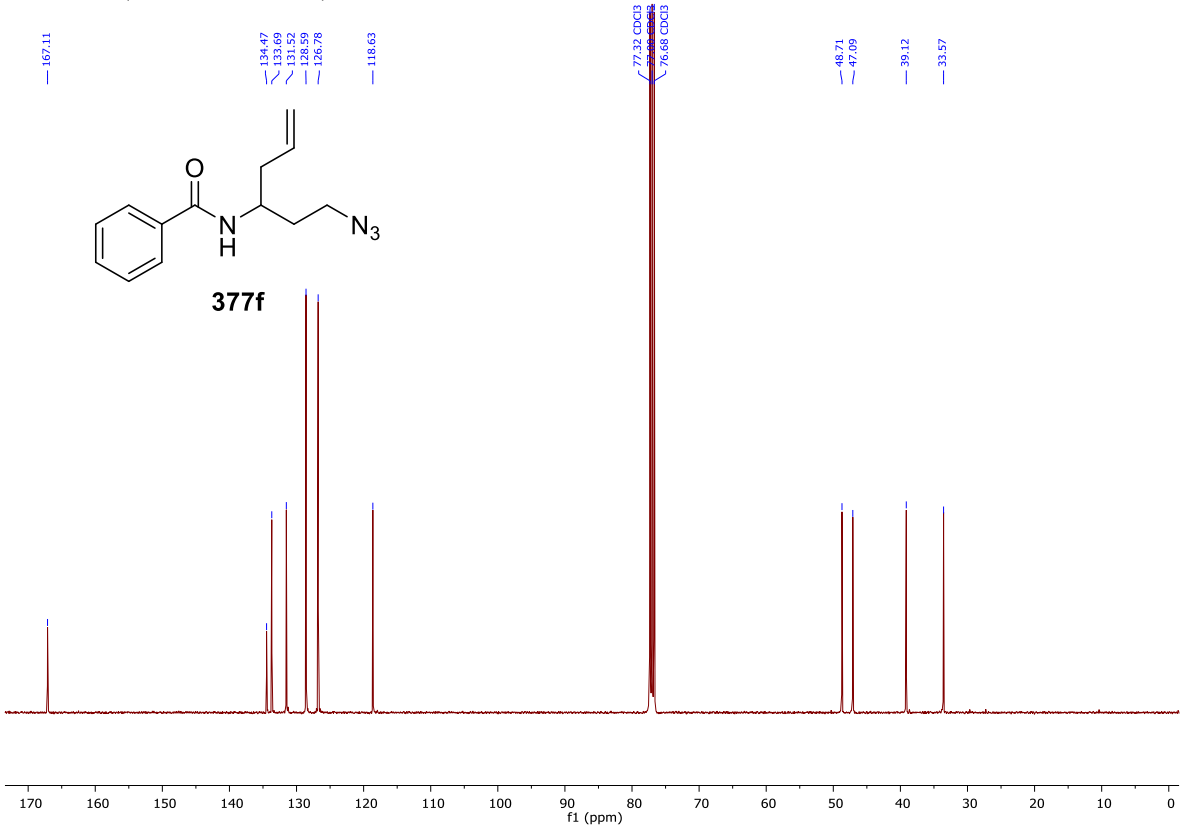
377e

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

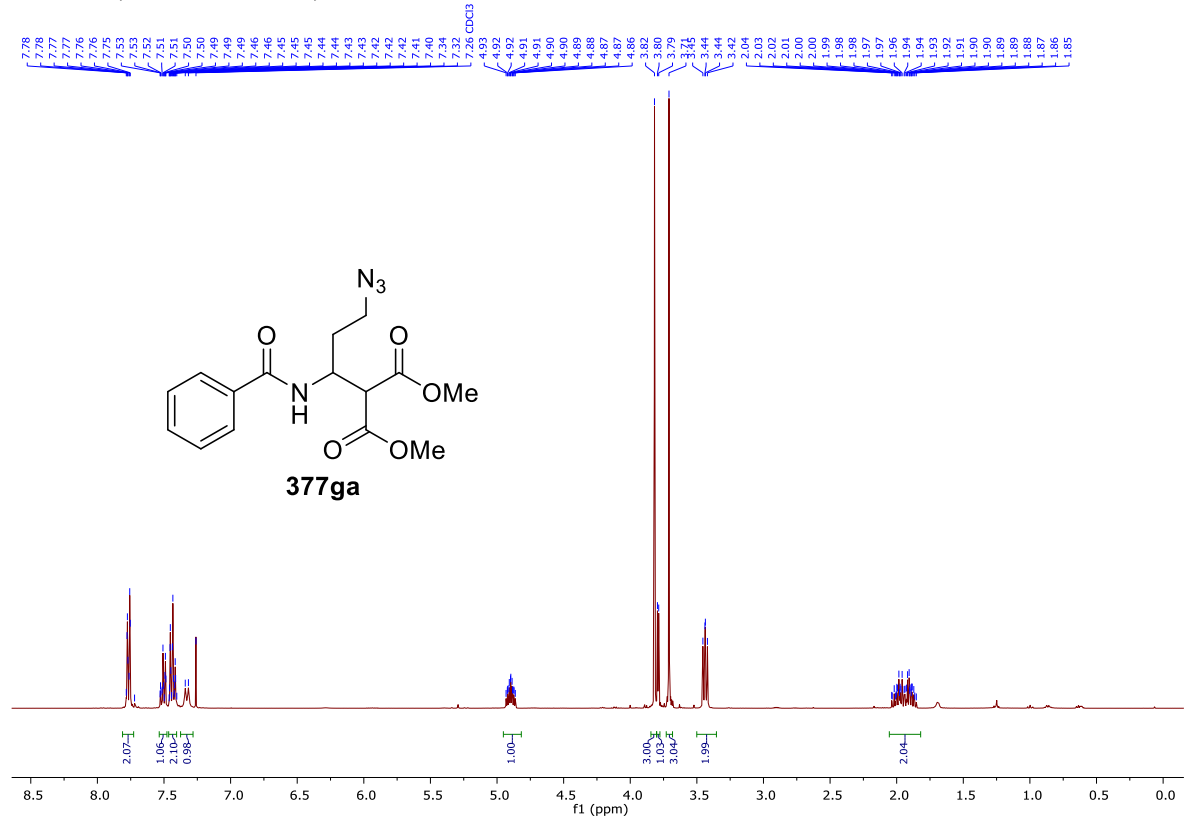


377f

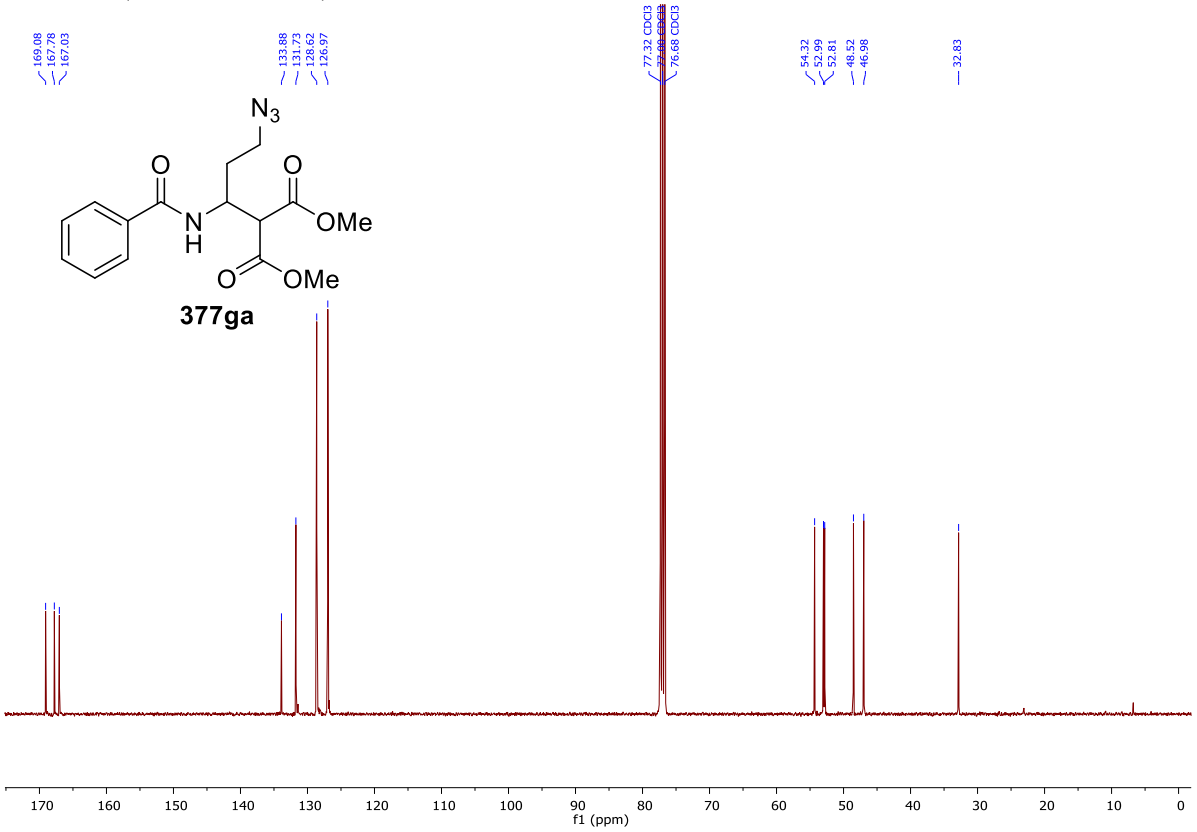
^{13}C-NMR (101 MHz, $CDCl_3$)



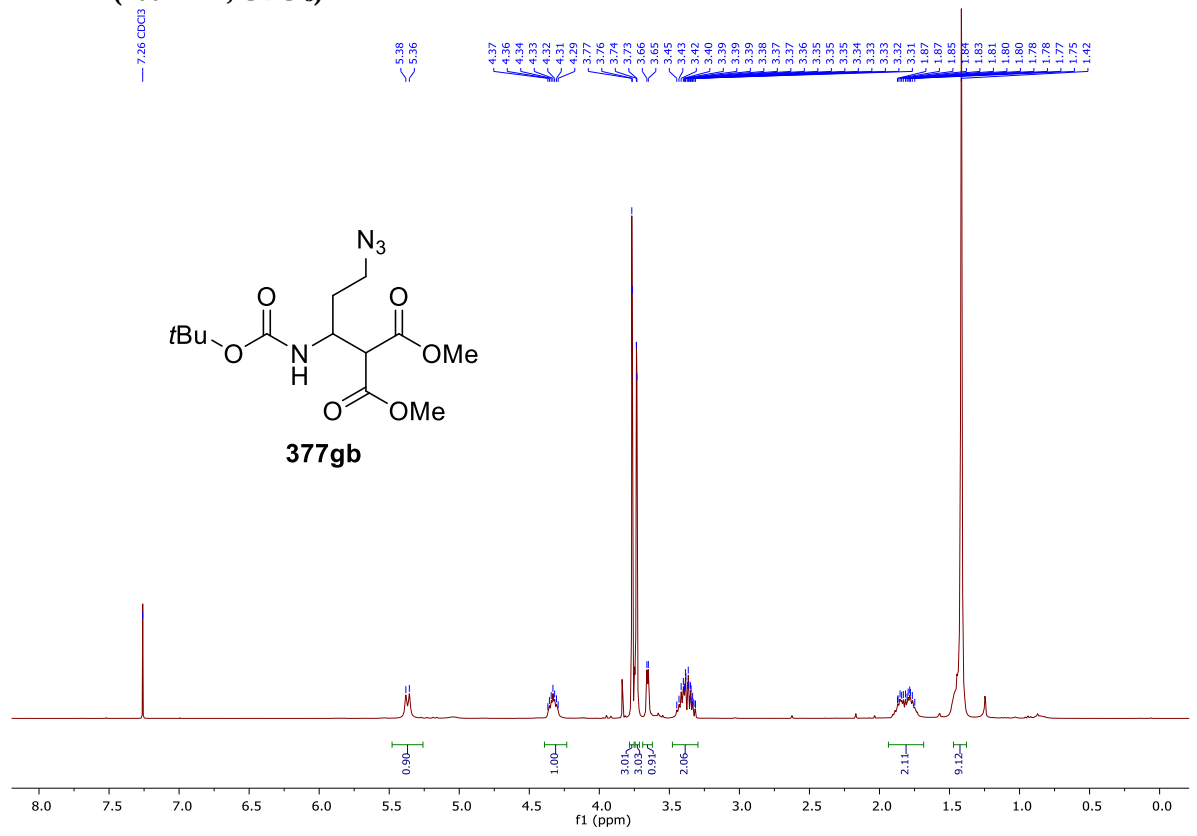
^{1}H-NMR (400 MHz, $CDCl_3$)



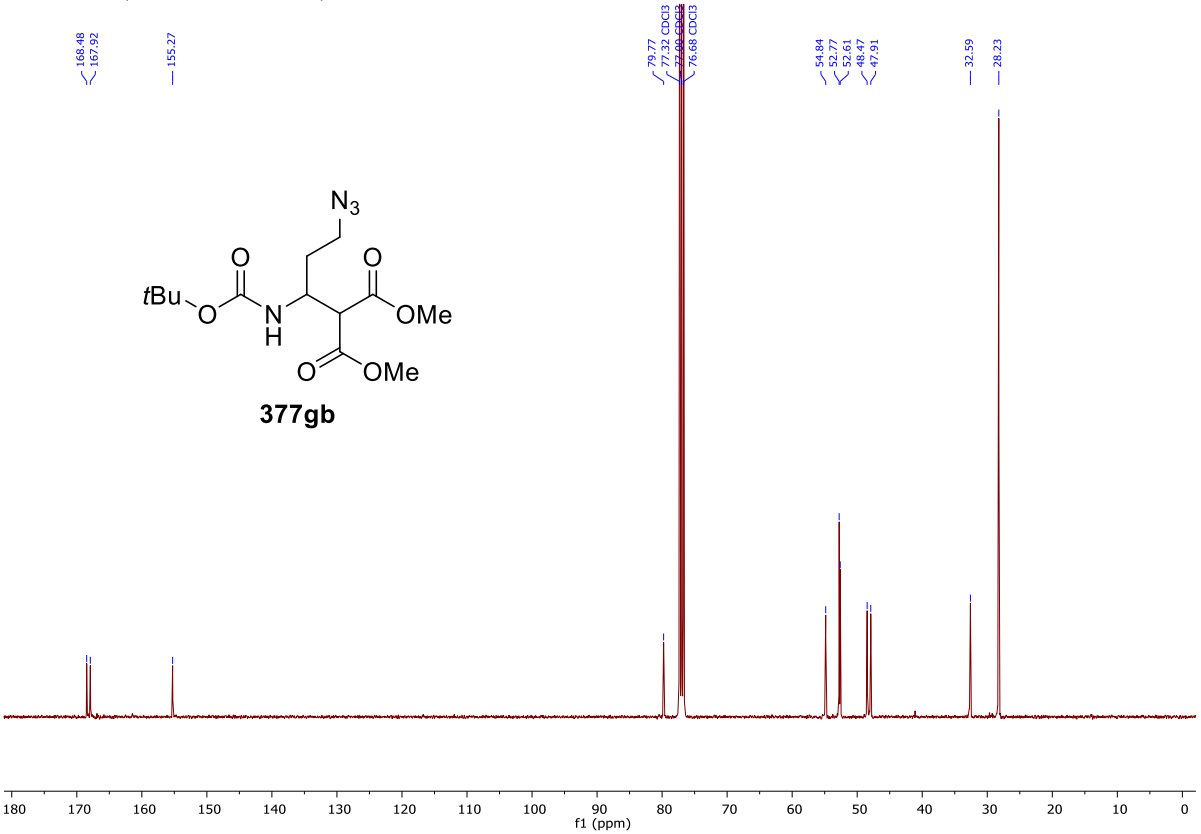
^{13}C-NMR (101 MHz, $CDCl_3$)



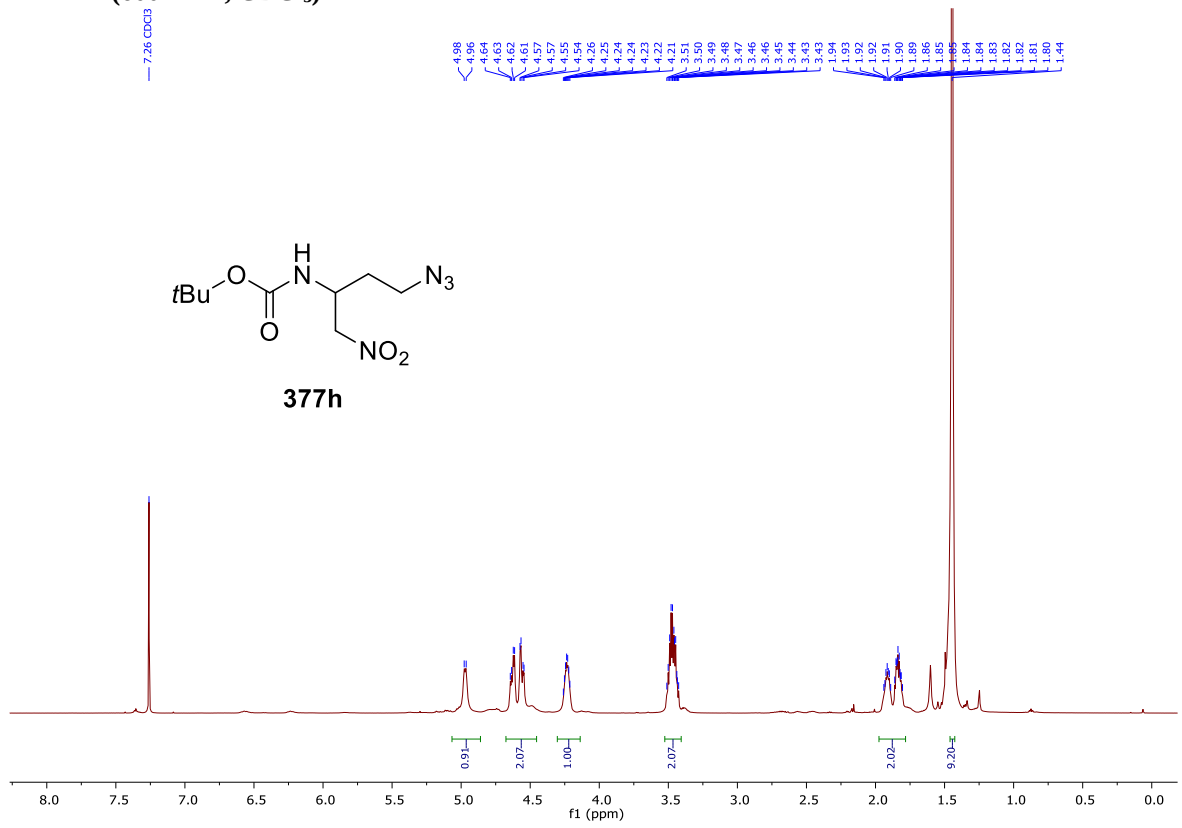
^{1}H-NMR (400 MHz, $CDCl_3$)



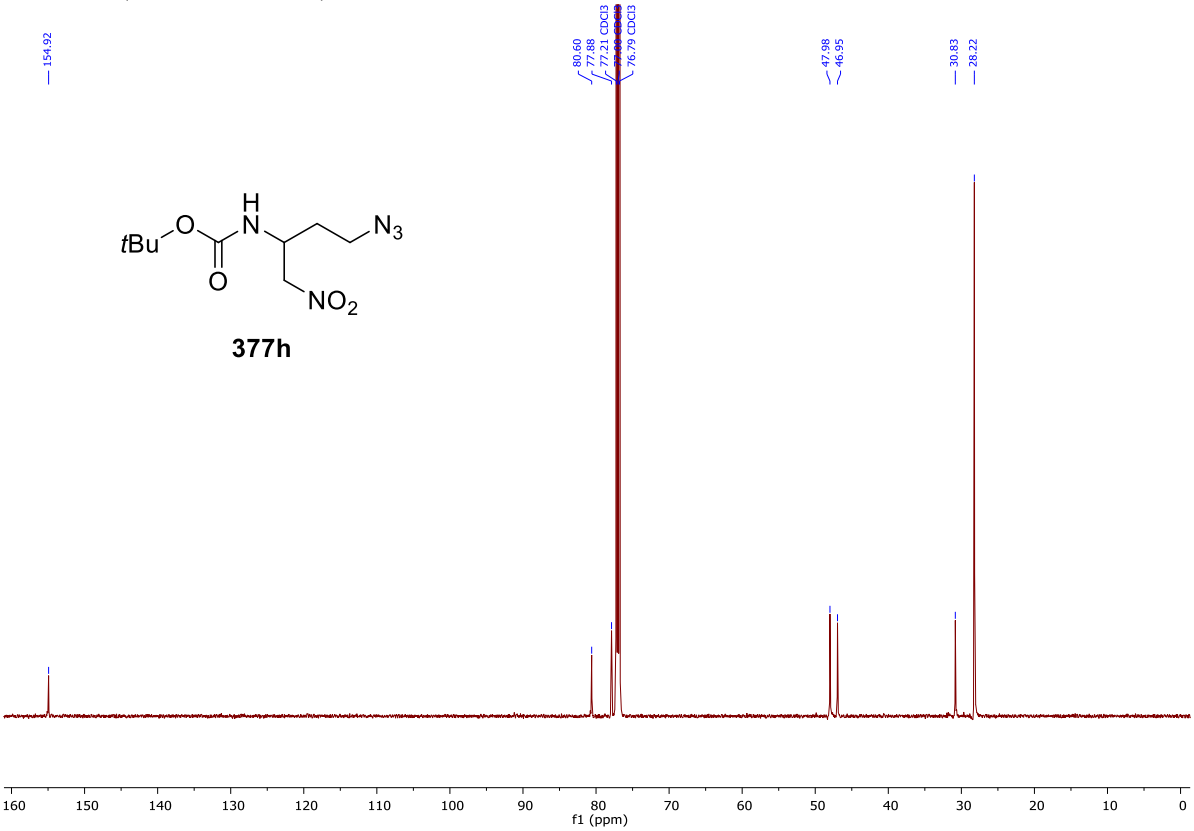
^{13}C-NMR (101 MHz, $CDCl_3$)



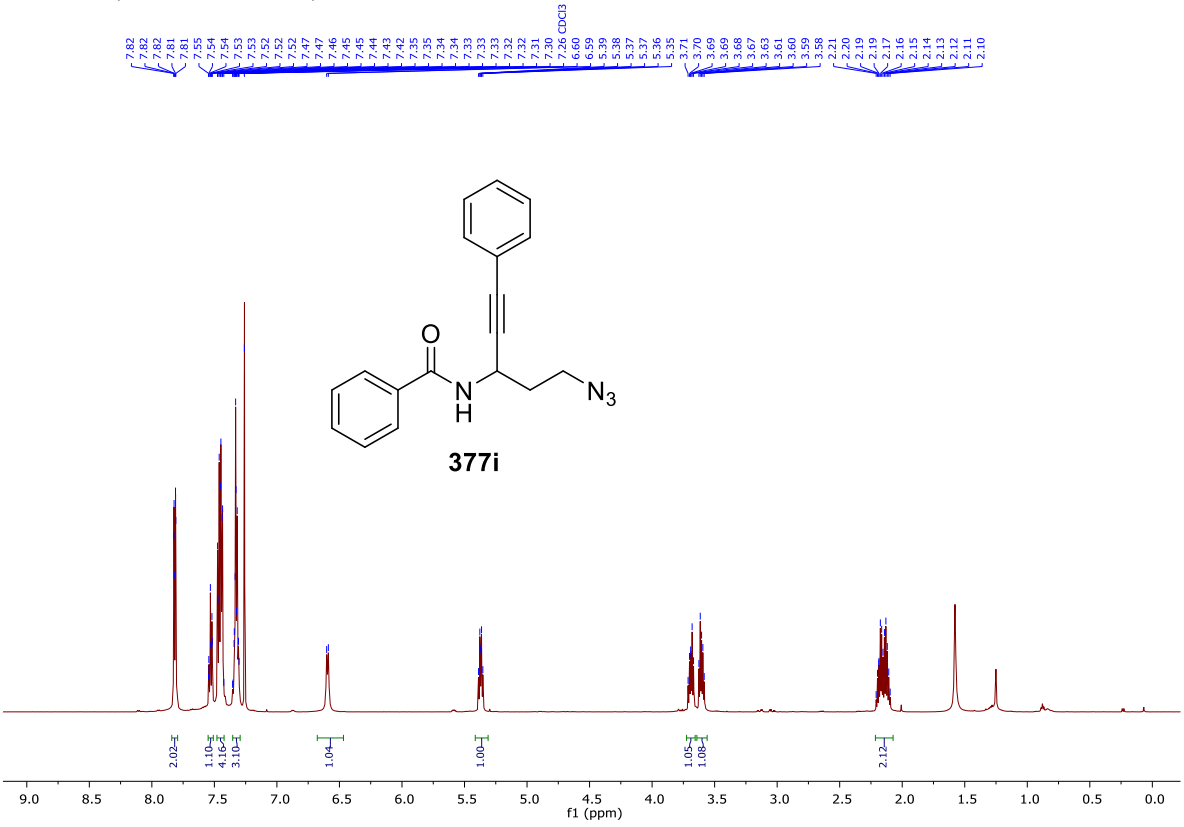
^{1}H-NMR (600 MHz, $CDCl_3$)



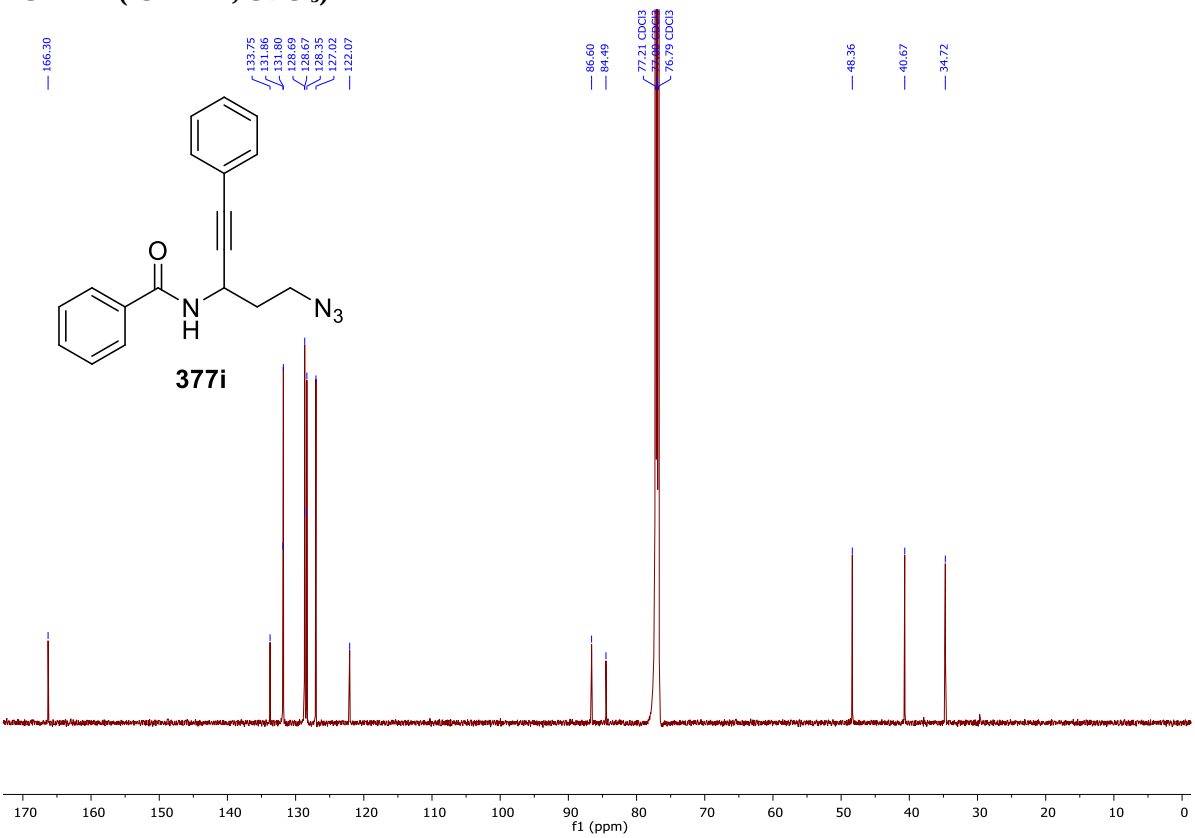
^{13}C-NMR (151 MHz, $CDCl_3$)



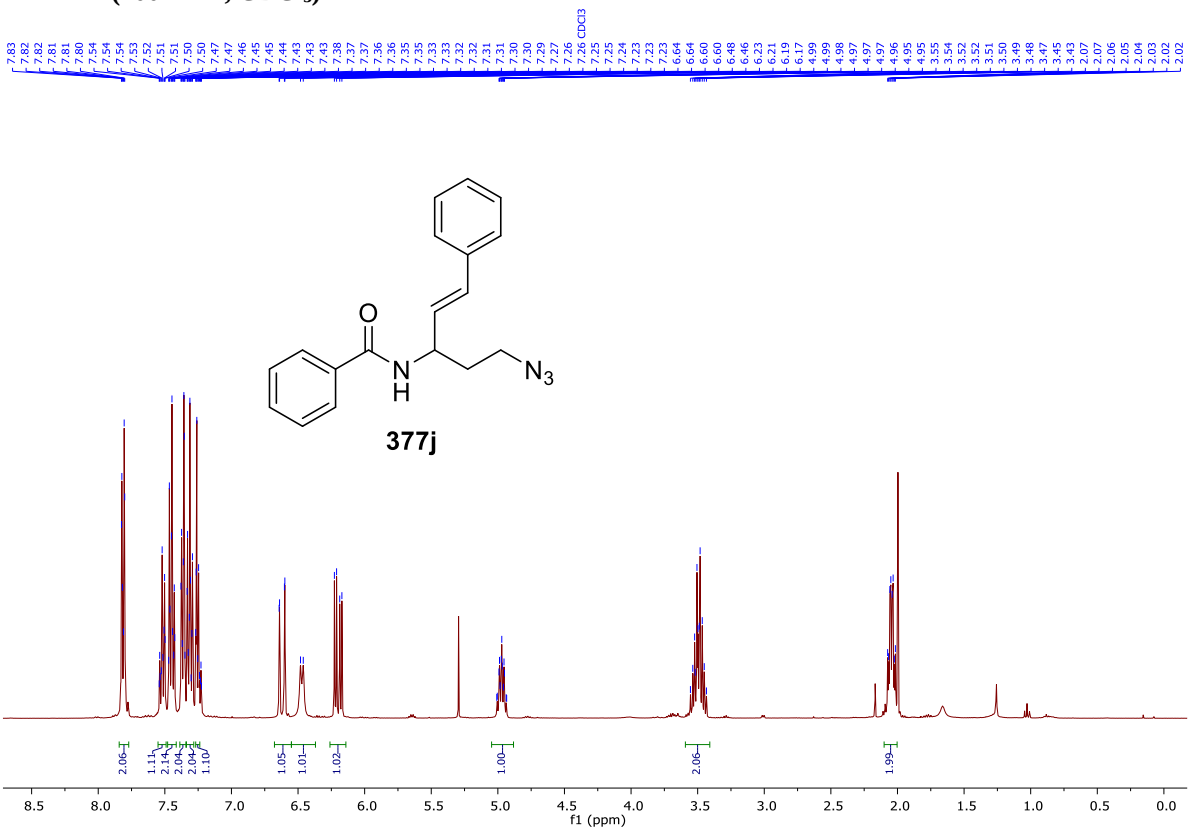
^{1}H-NMR (600 MHz, $CDCl_3$)



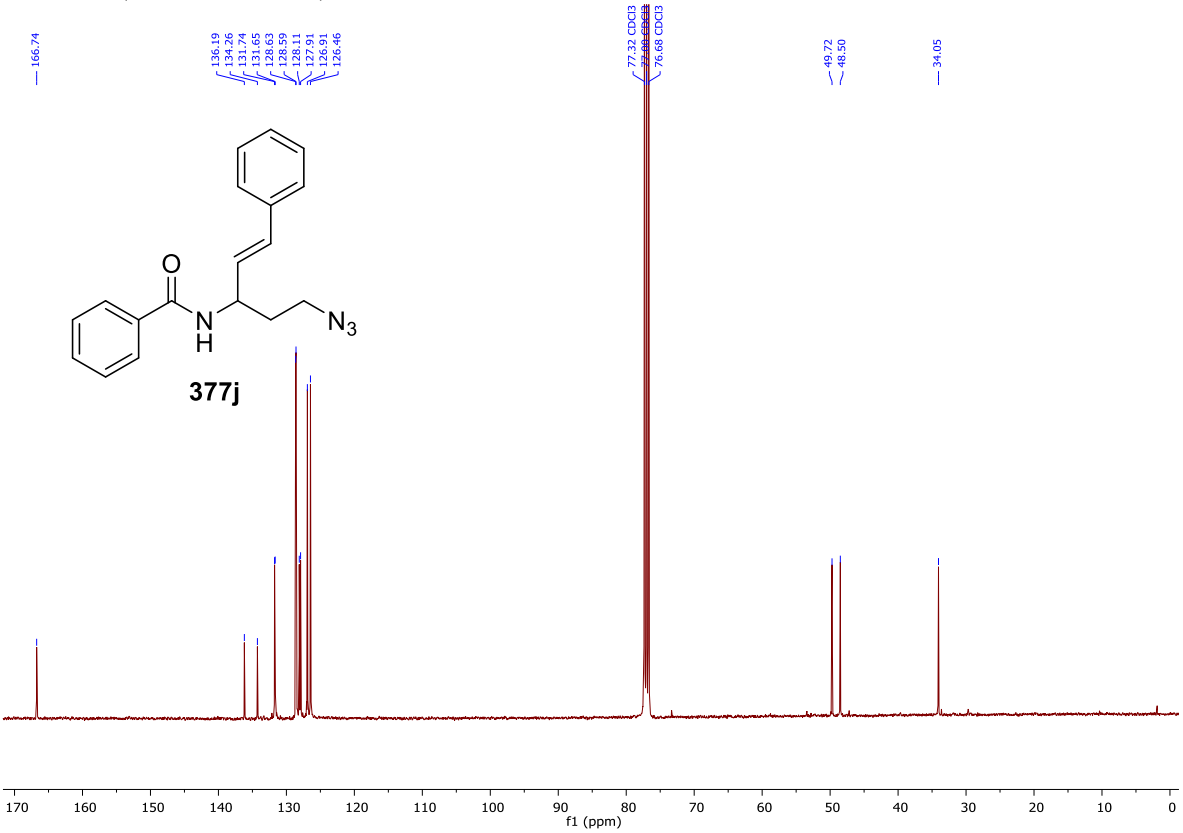
^{13}C-NMR (151 MHz, $CDCl_3$)



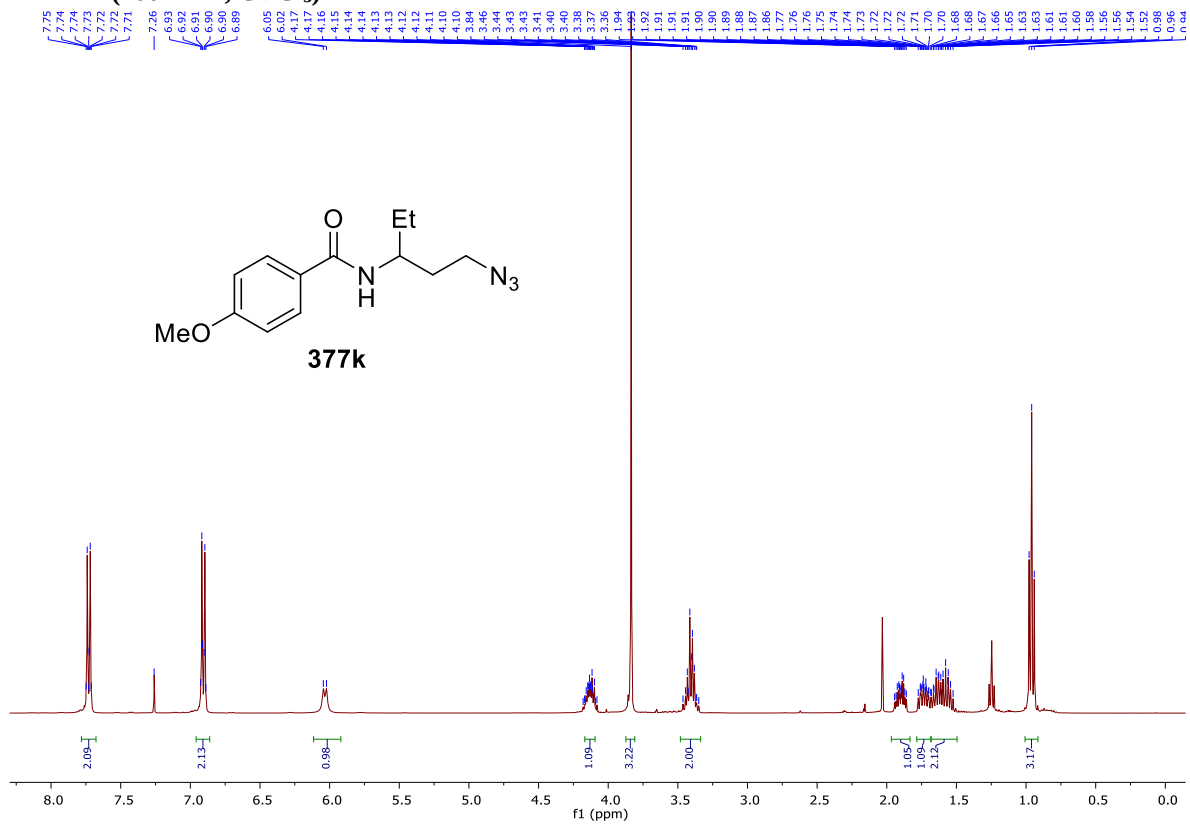
^{1}H-NMR (400 MHz, $CDCl_3$)



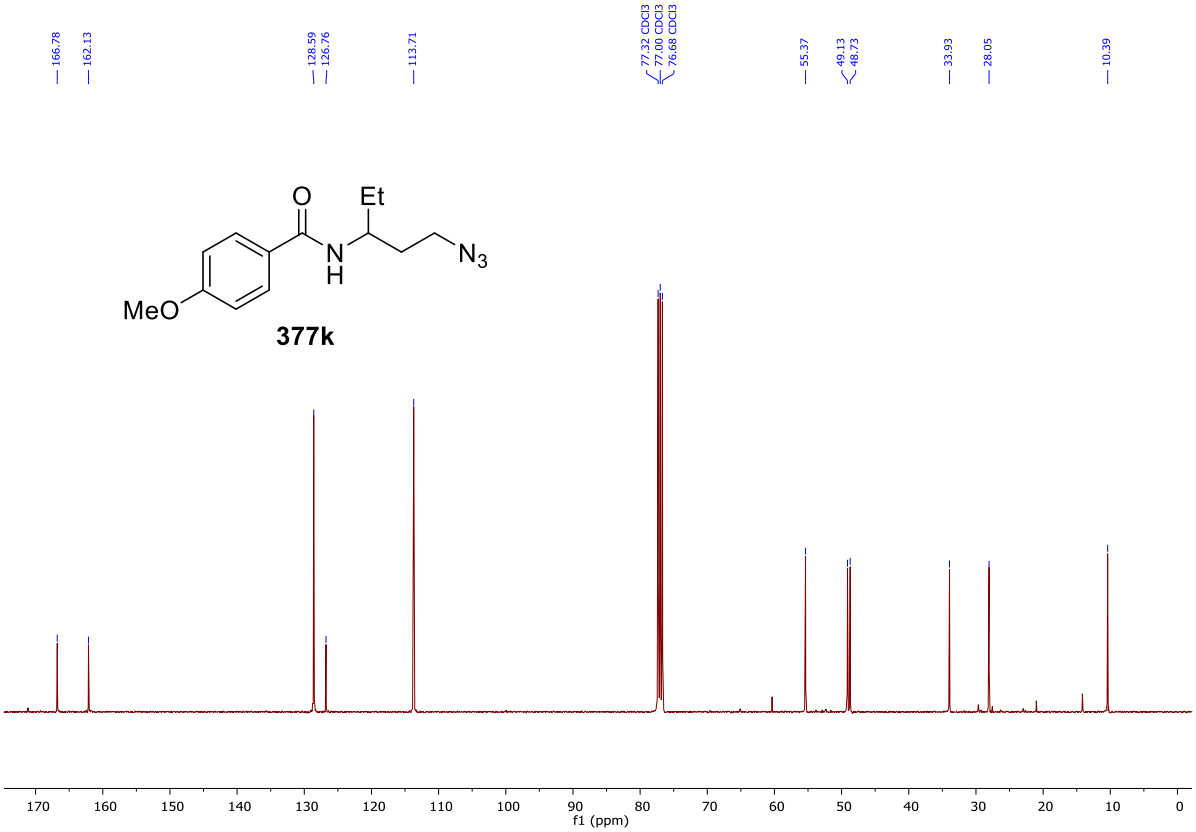
^{13}C-NMR (101 MHz, $CDCl_3$)



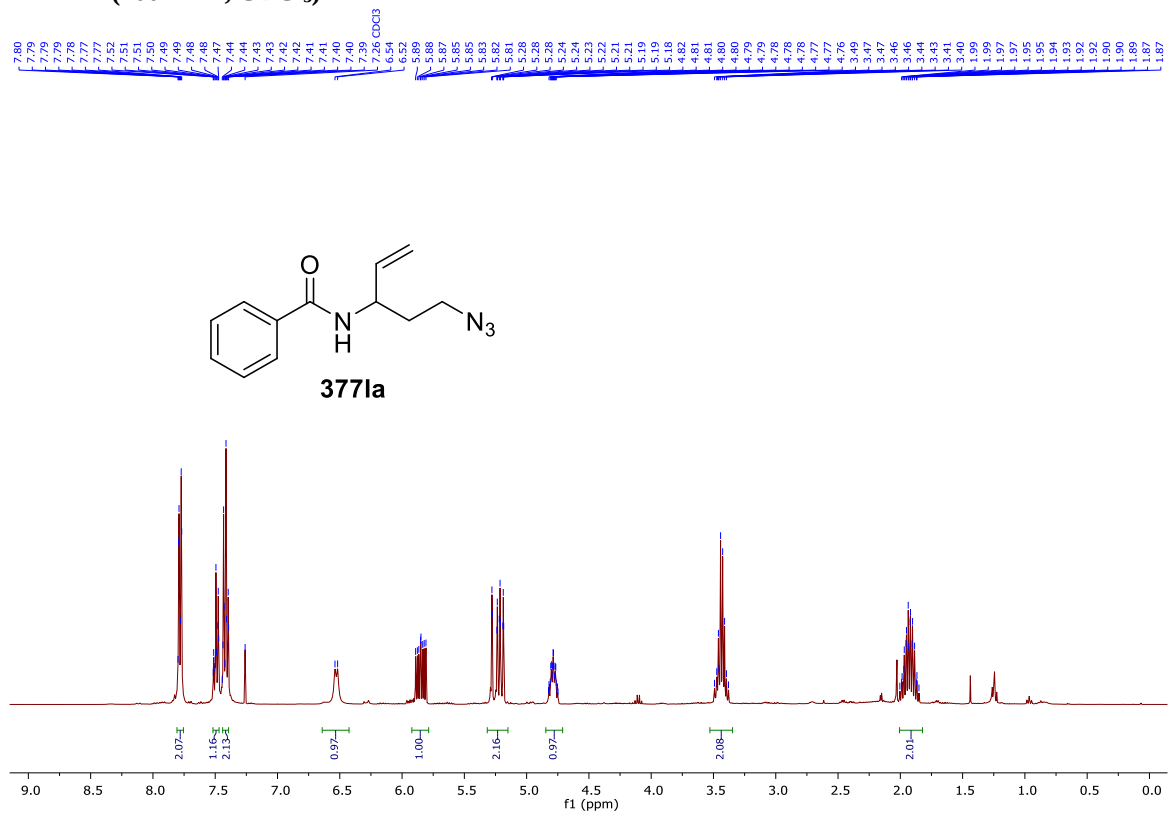
^{1}H-NMR (400 MHz, $CDCl_3$)



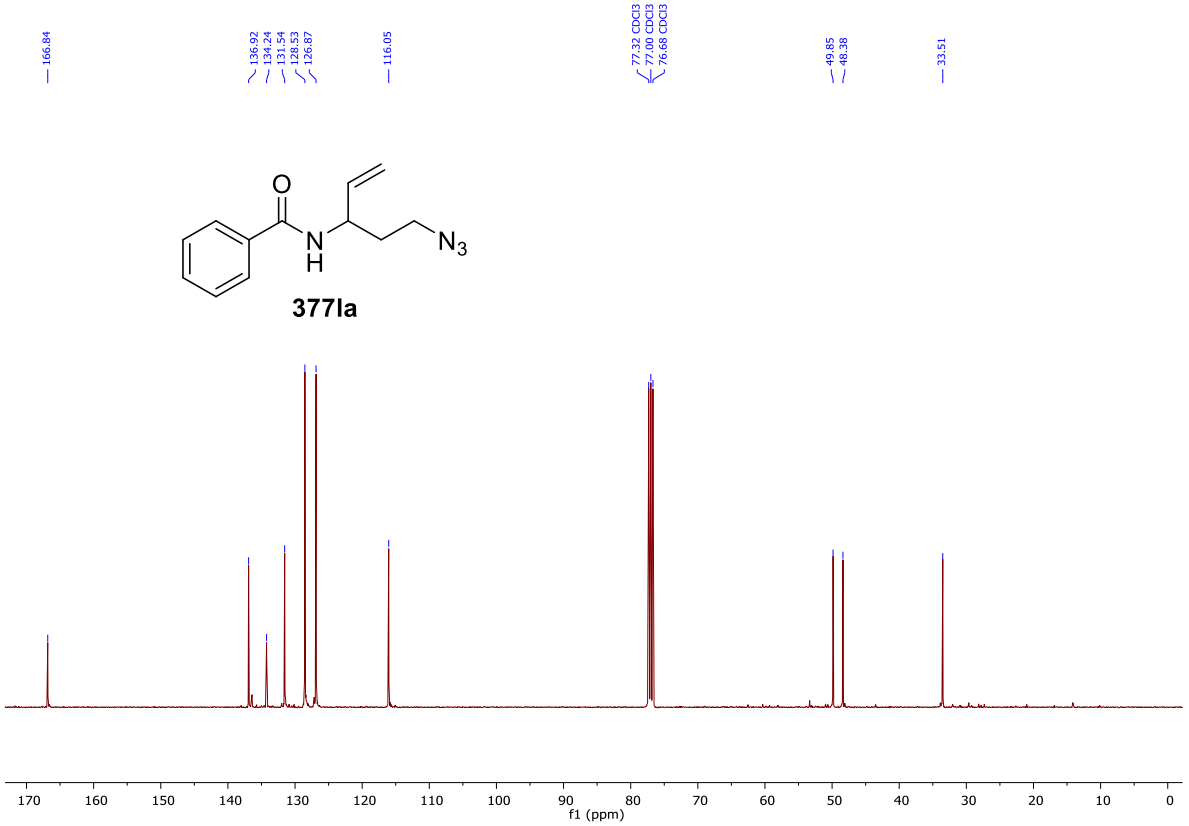
^{13}C-NMR (101 MHz, $CDCl_3$)



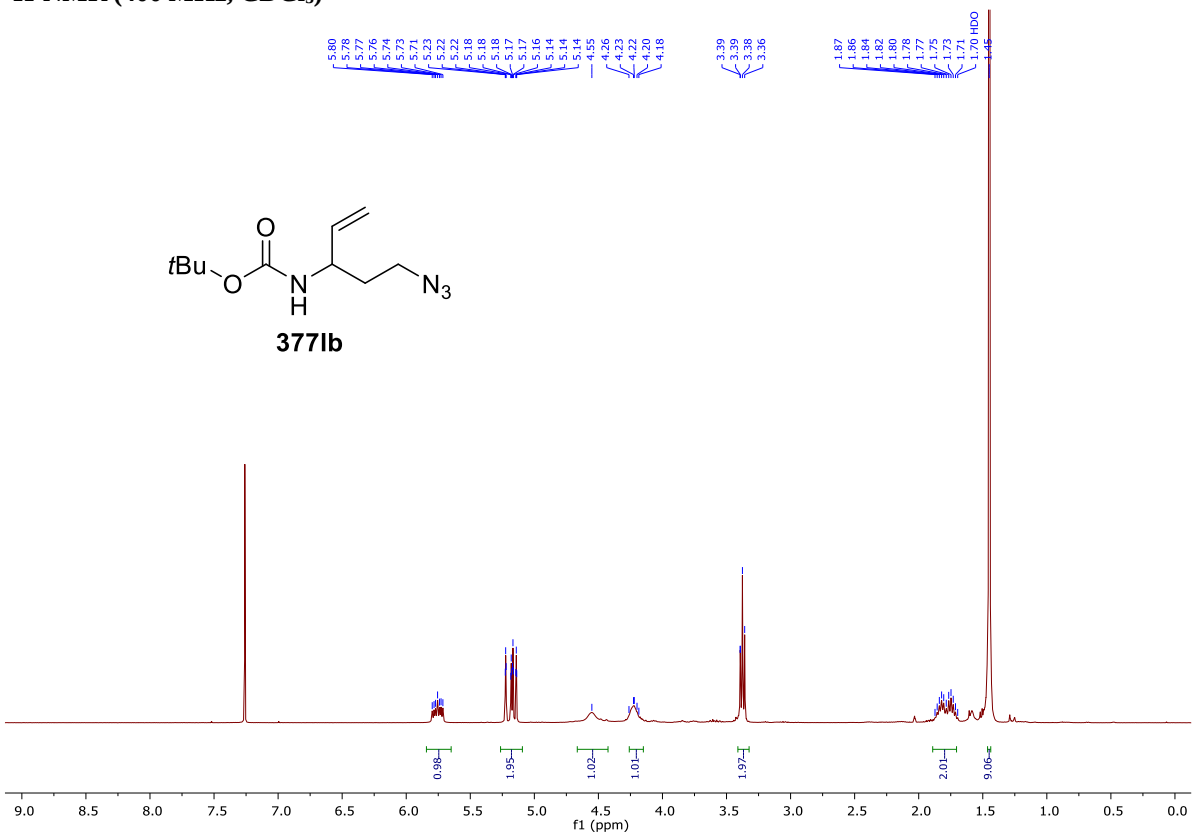
^{1}H-NMR (400 MHz, $CDCl_3$)



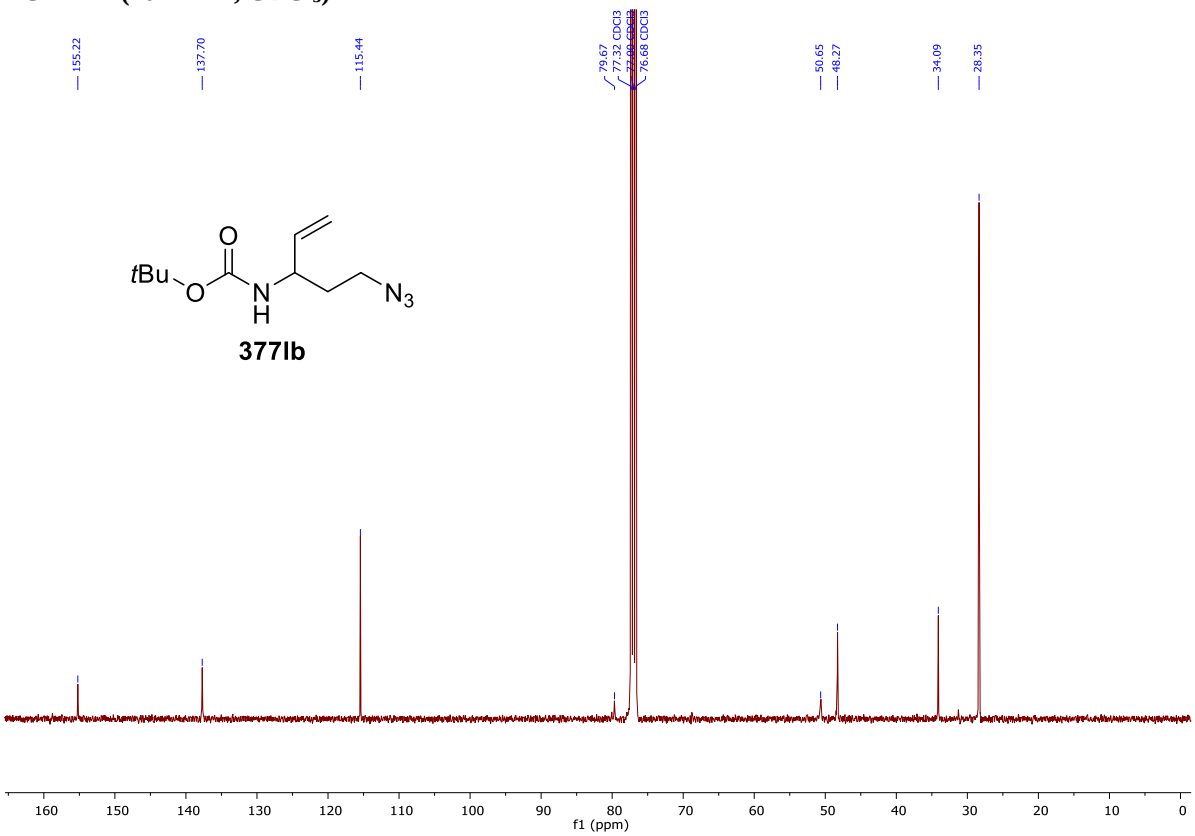
^{13}C-NMR (101 MHz, $CDCl_3$)



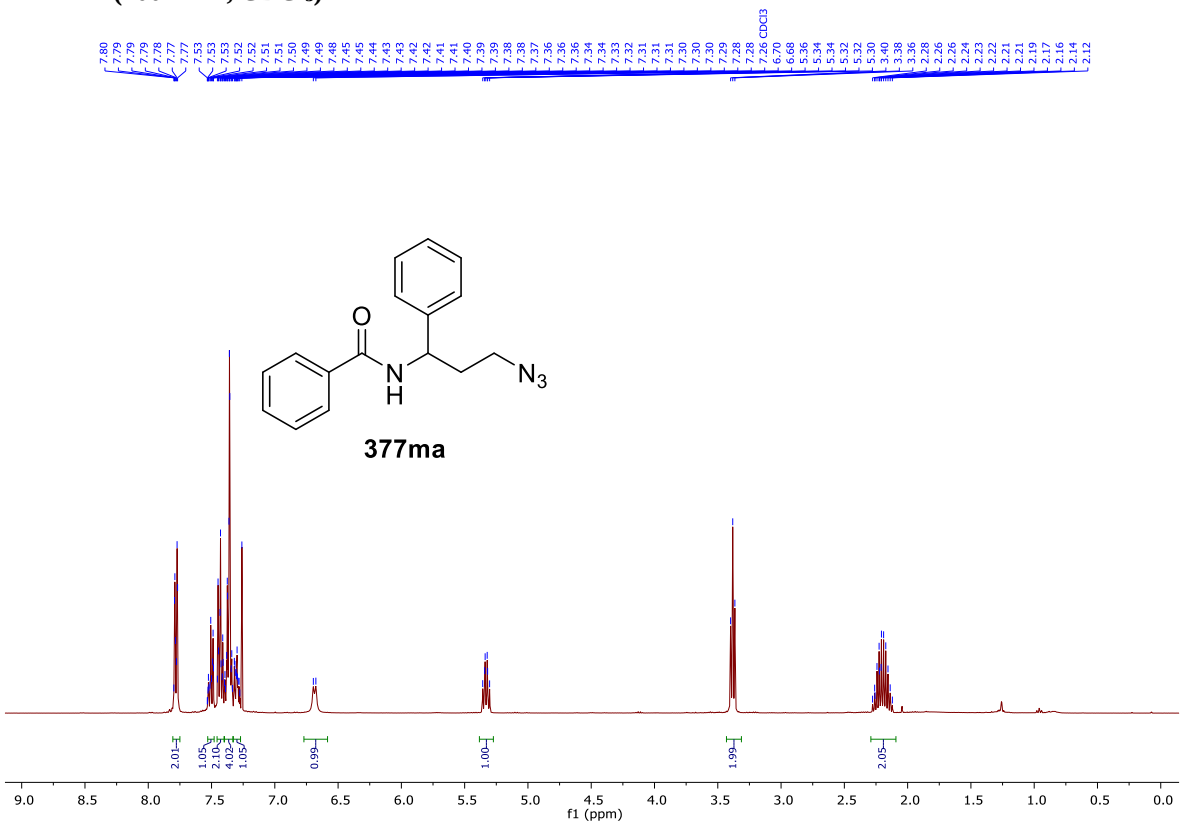
^{1}H-NMR (400 MHz, $CDCl_3$)



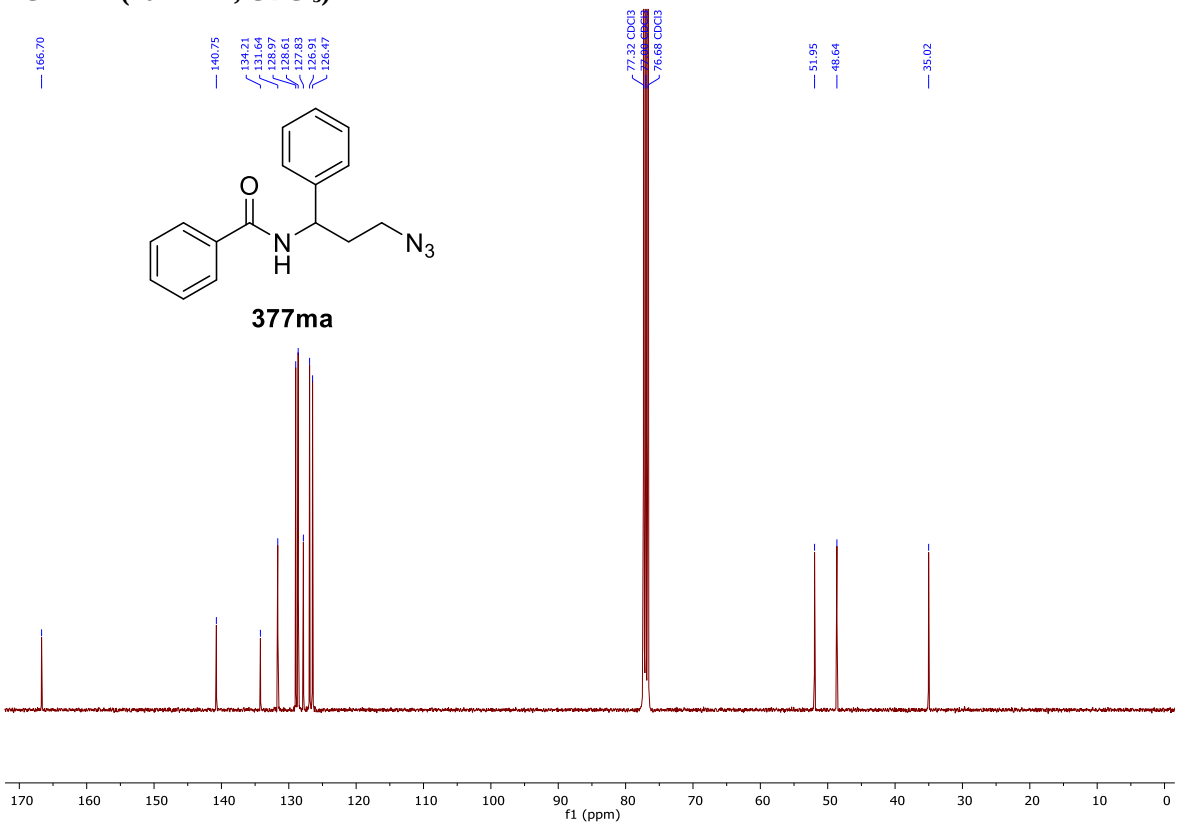
^{13}C-NMR (101 MHz, $CDCl_3$)



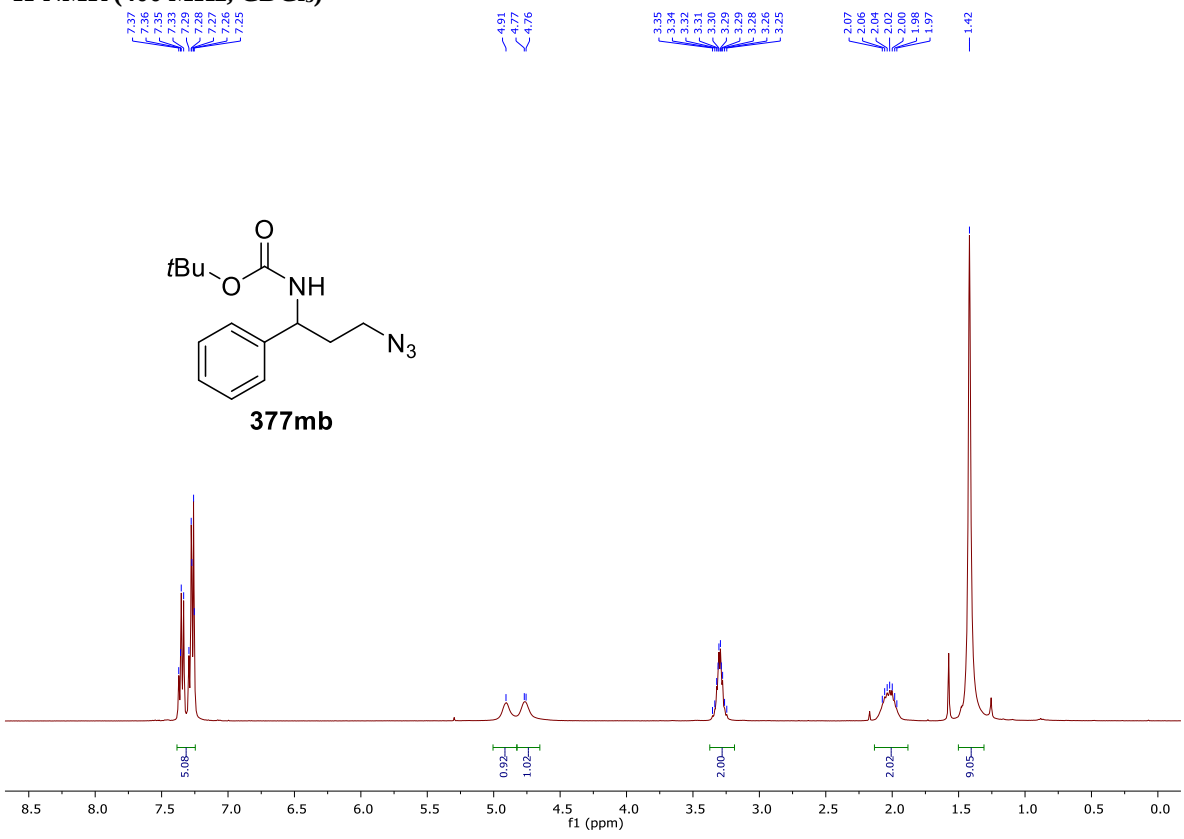
^{1}H-NMR (400 MHz, $CDCl_3$)



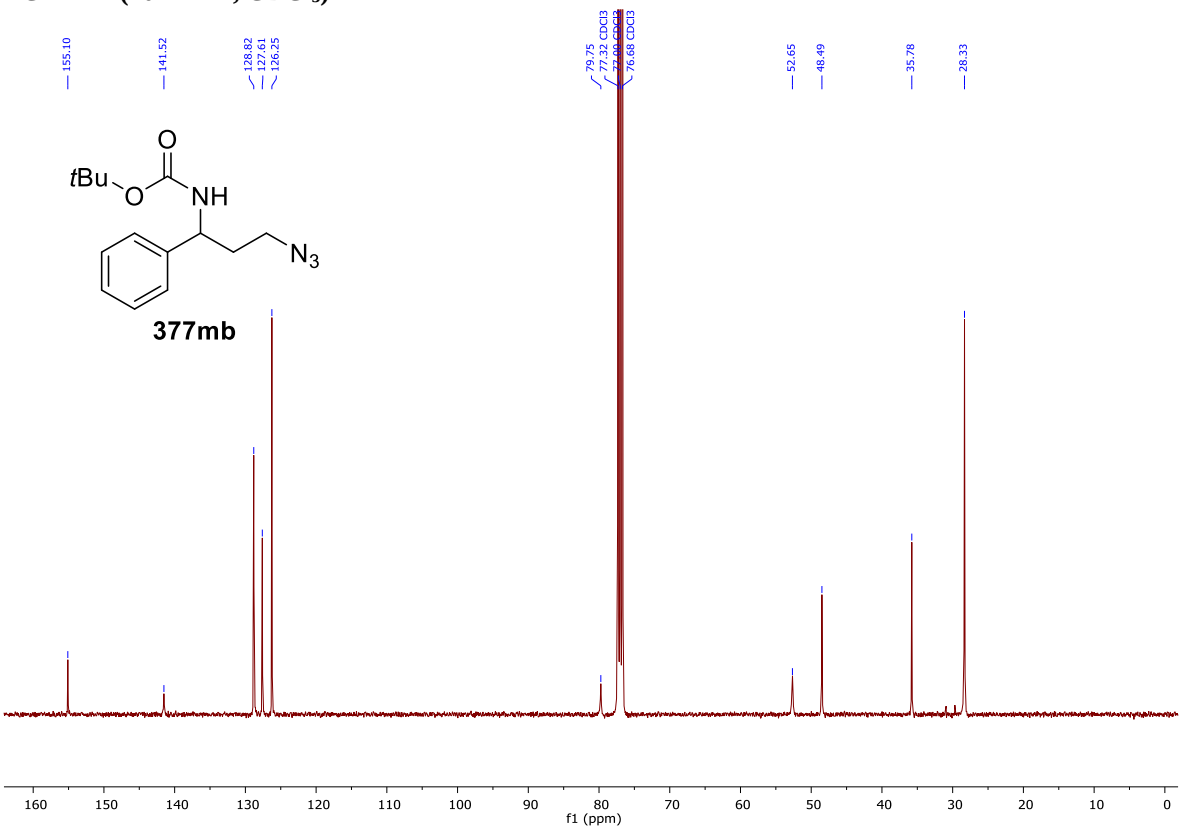
^{13}C-NMR (101 MHz, $CDCl_3$)



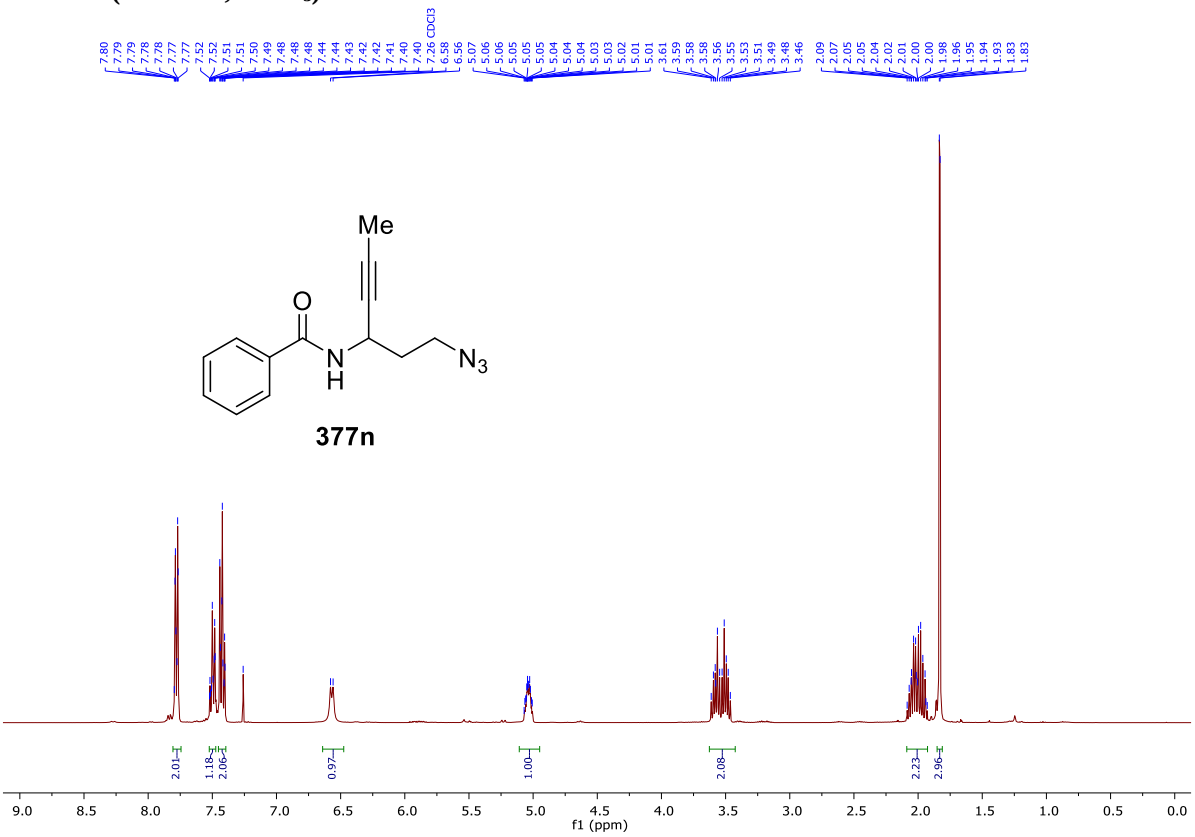
^{1}H-NMR (400 MHz, $CDCl_3$)



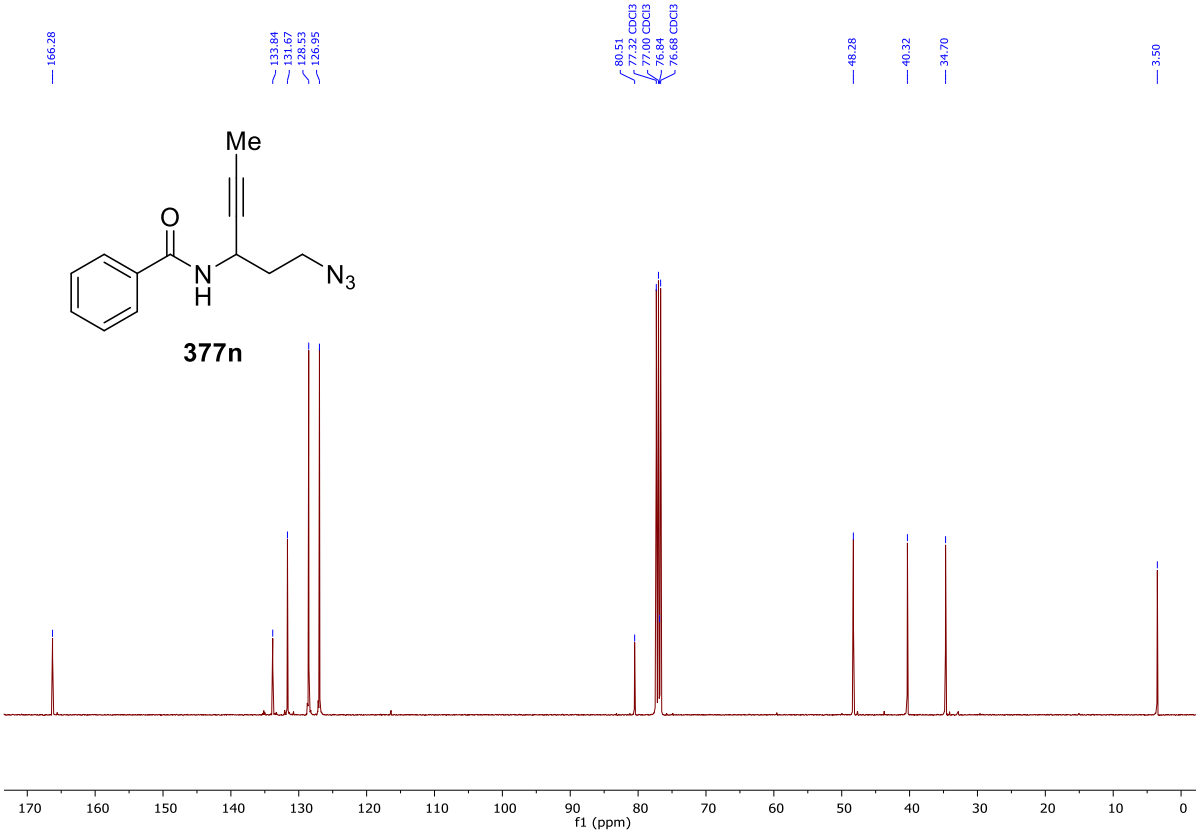
^{13}C-NMR (101 MHz, $CDCl_3$)



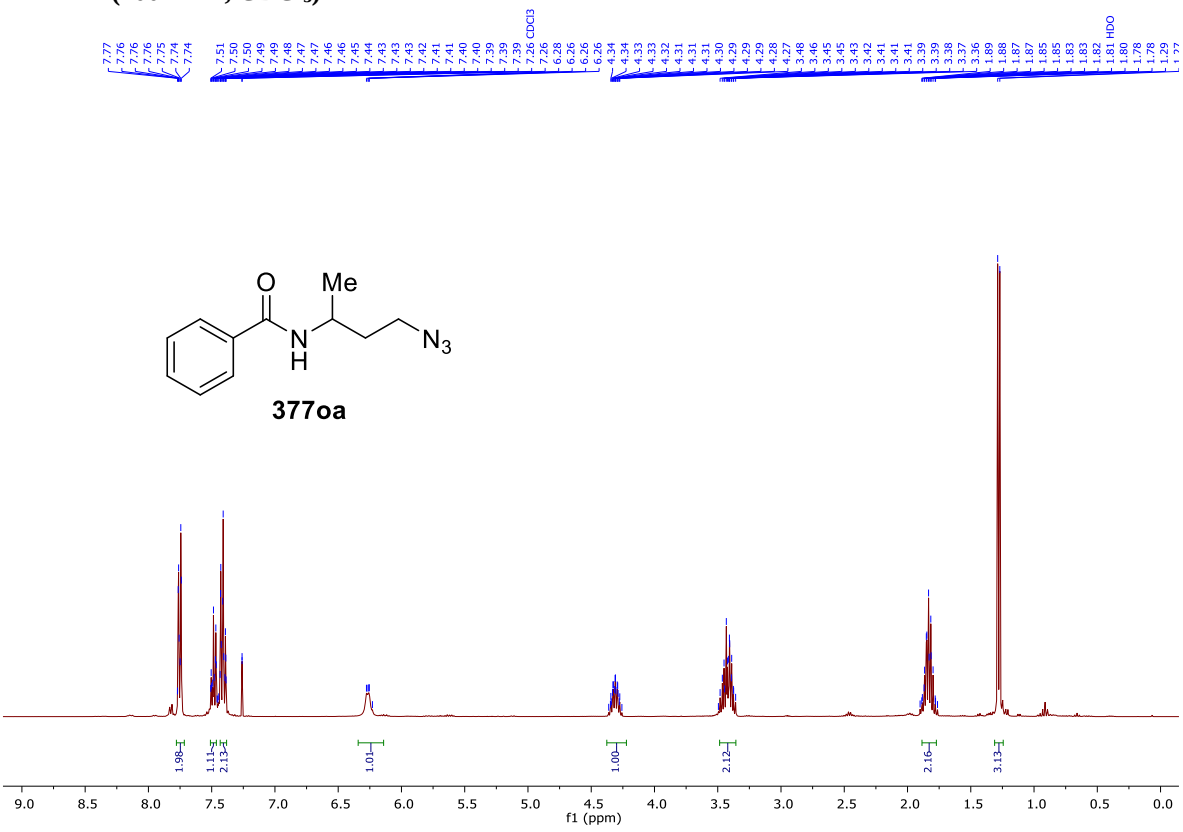
^{1}H-NMR (400 MHz, $CDCl_3$)



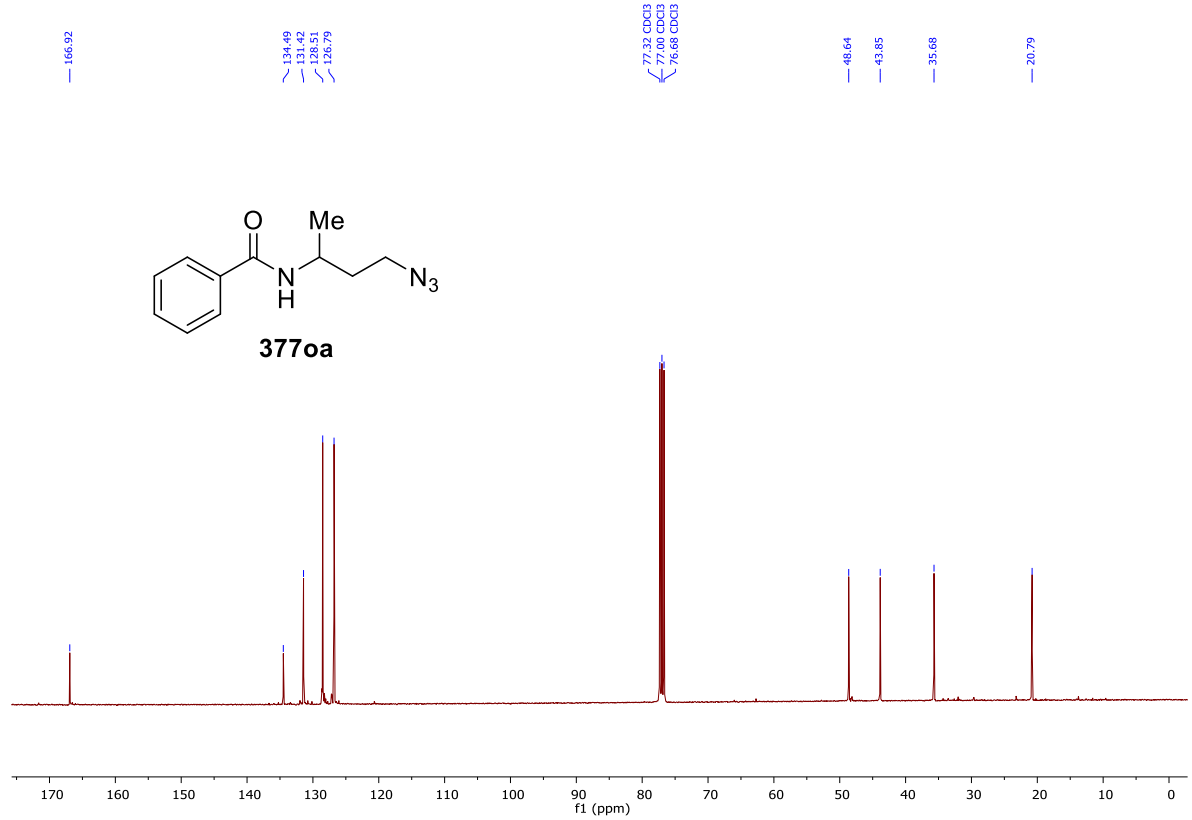
^{13}C-NMR (101 MHz, $CDCl_3$)



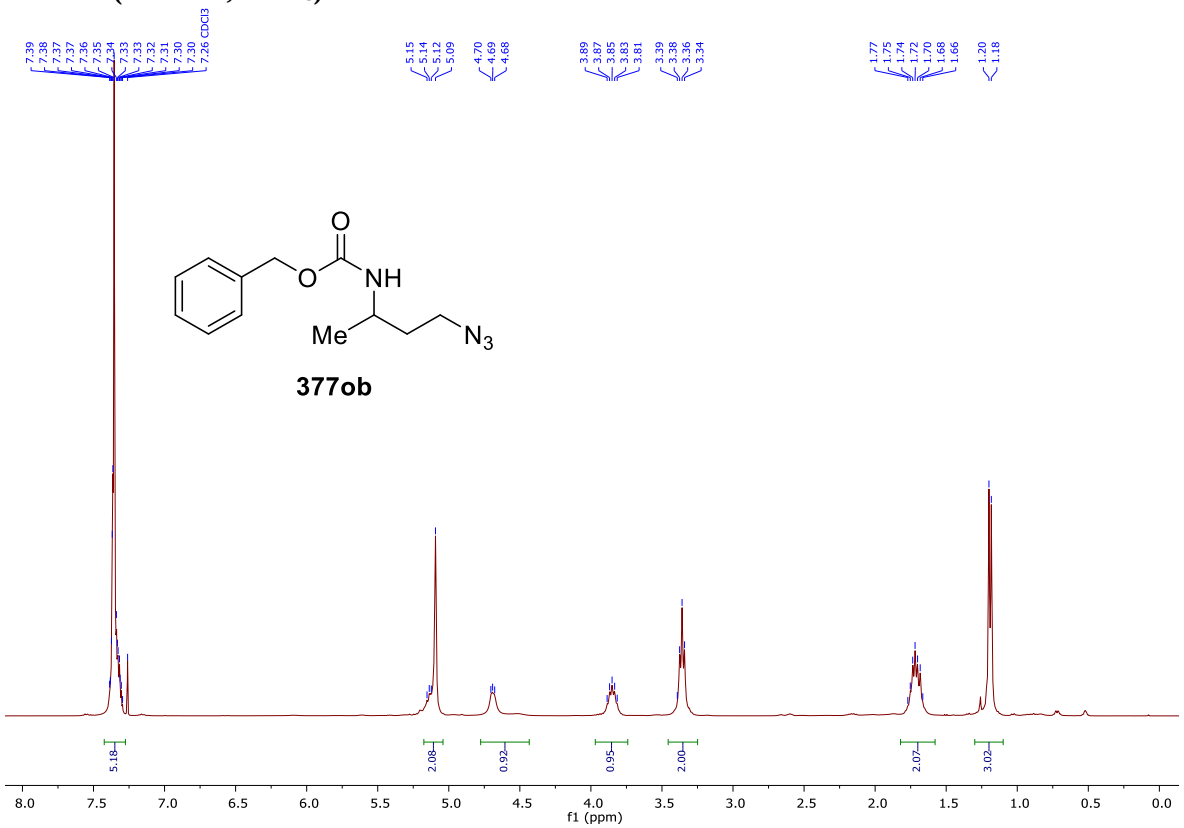
^{1}H-NMR (400 MHz, $CDCl_3$)



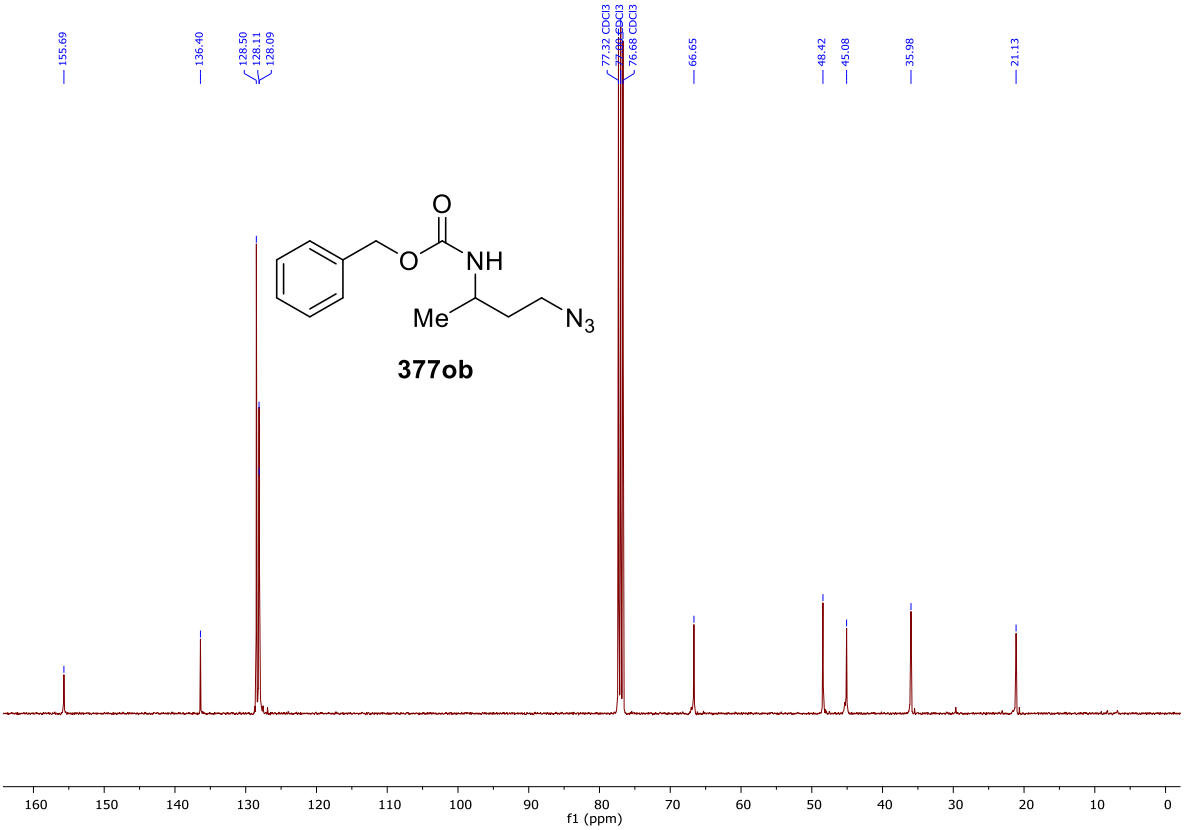
^{13}C-NMR (101 MHz, $CDCl_3$)



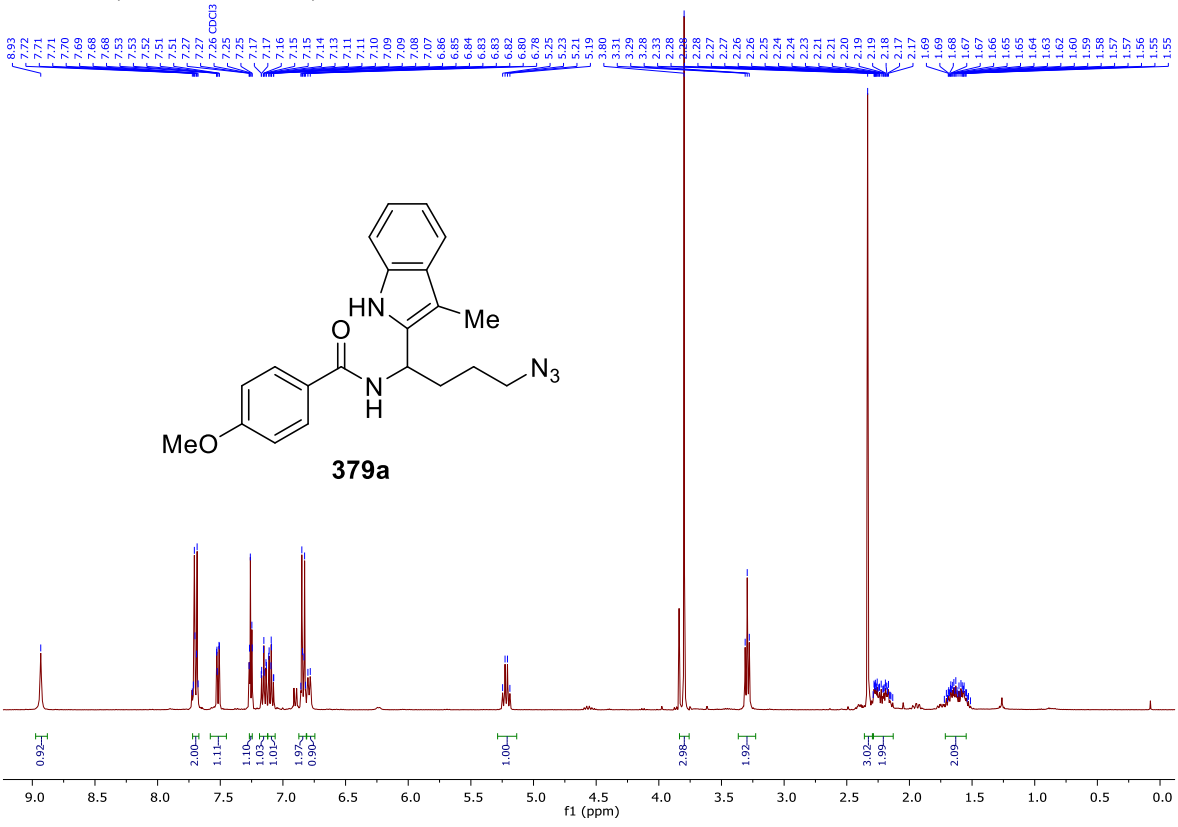
^{1}H-NMR (400 MHz, $CDCl_3$)



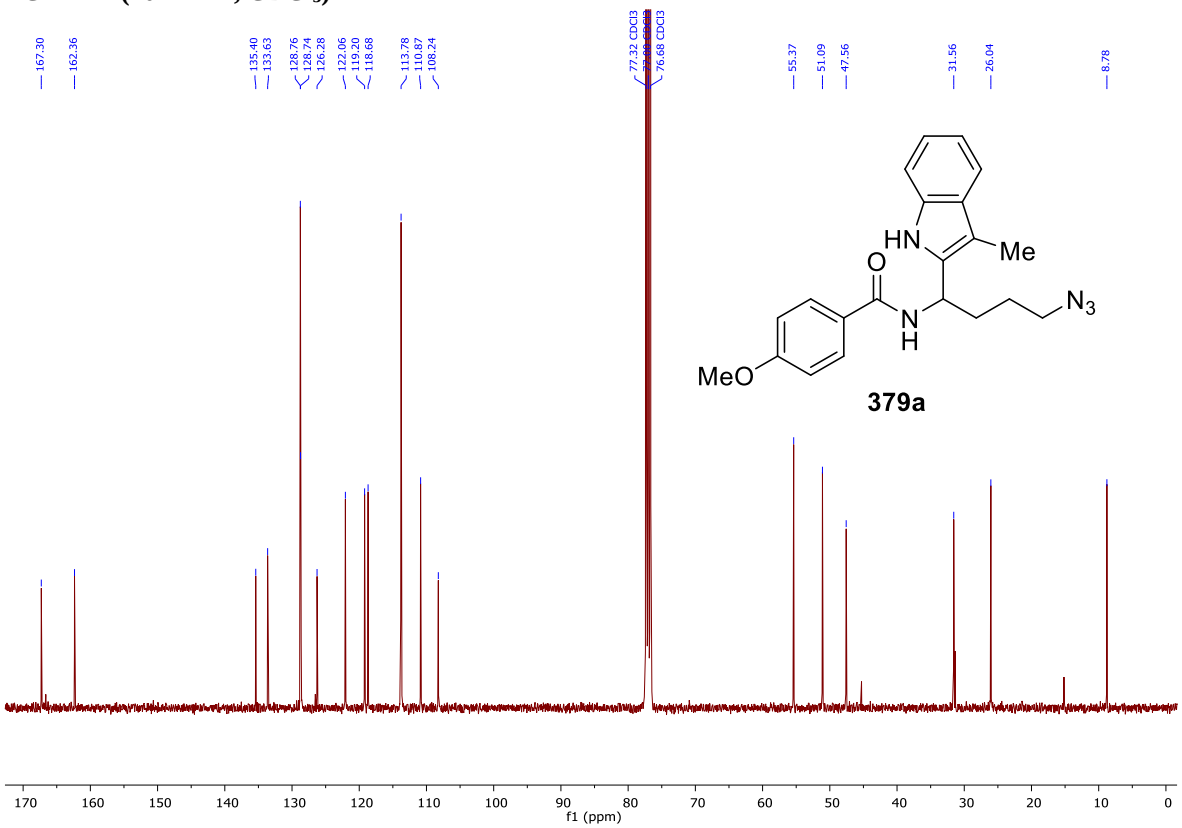
^{13}C-NMR (101 MHz, $CDCl_3$)



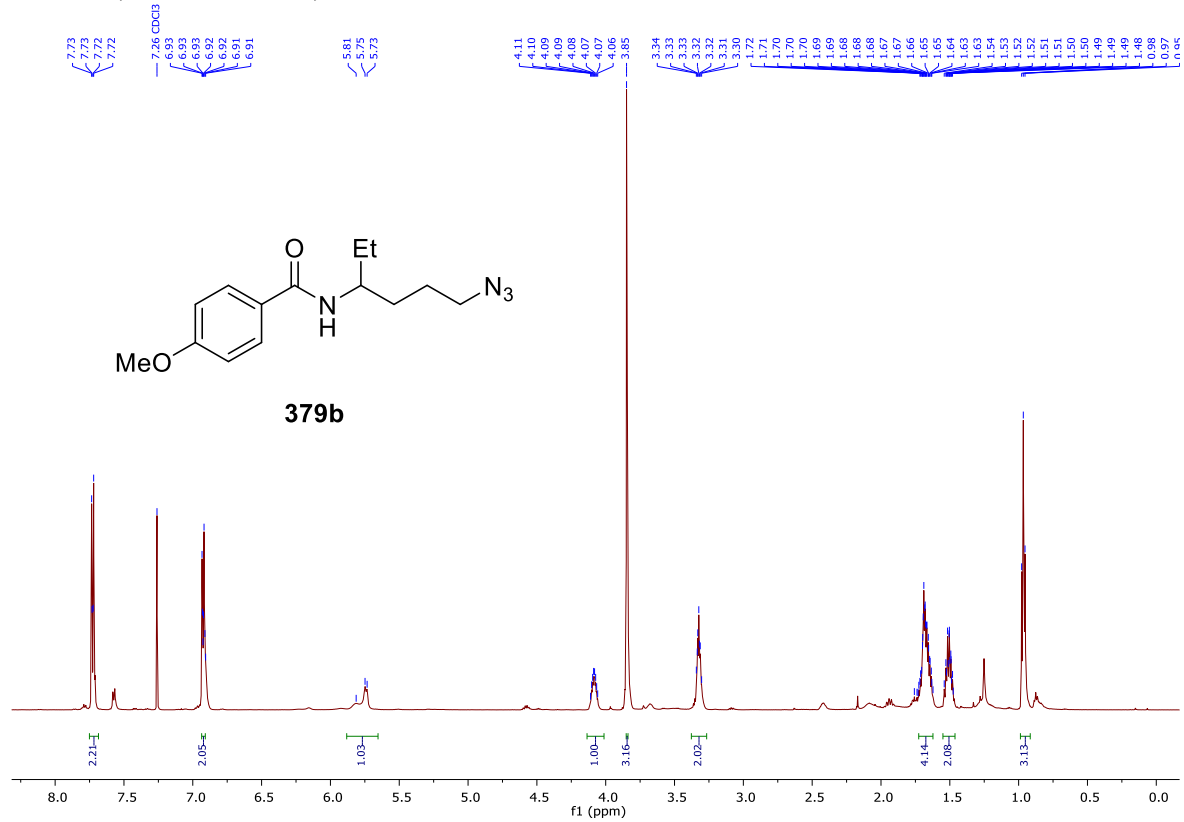
^{1}H-NMR (400 MHz, $CDCl_3$)



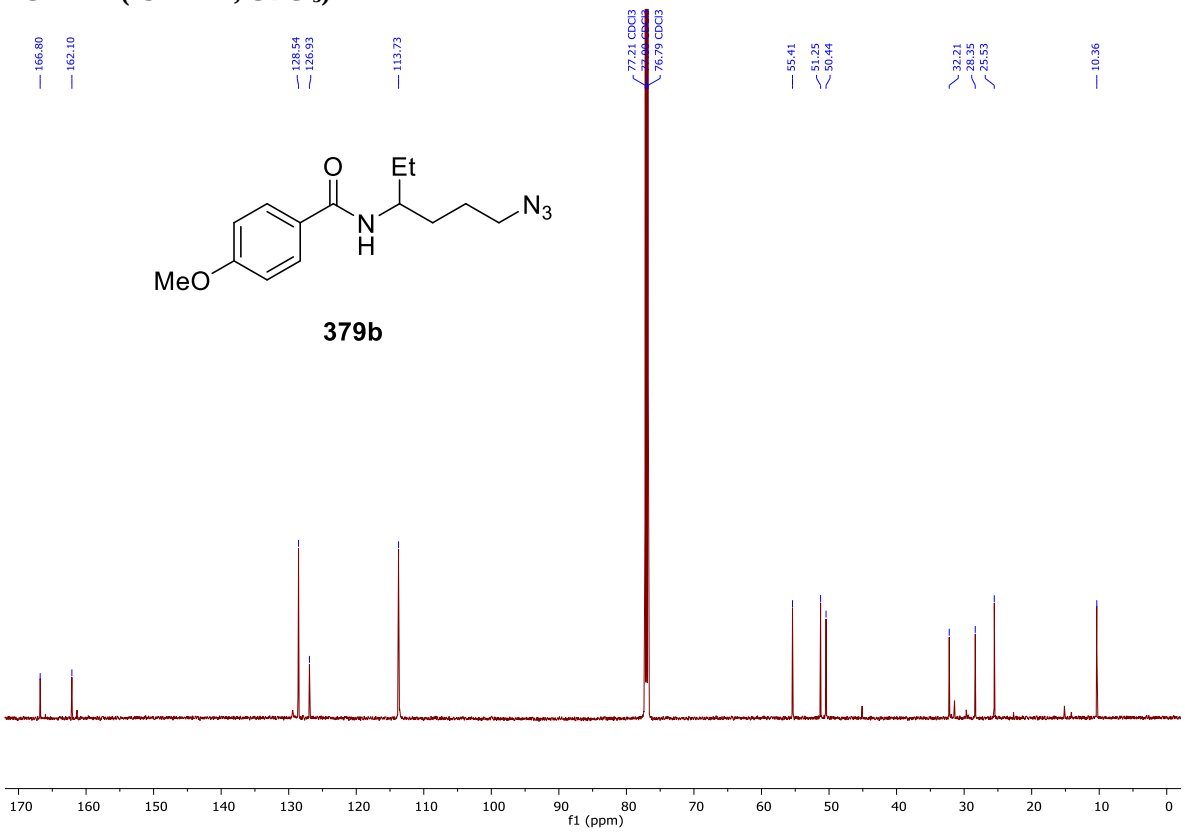
^{13}C-NMR (101 MHz, $CDCl_3$)



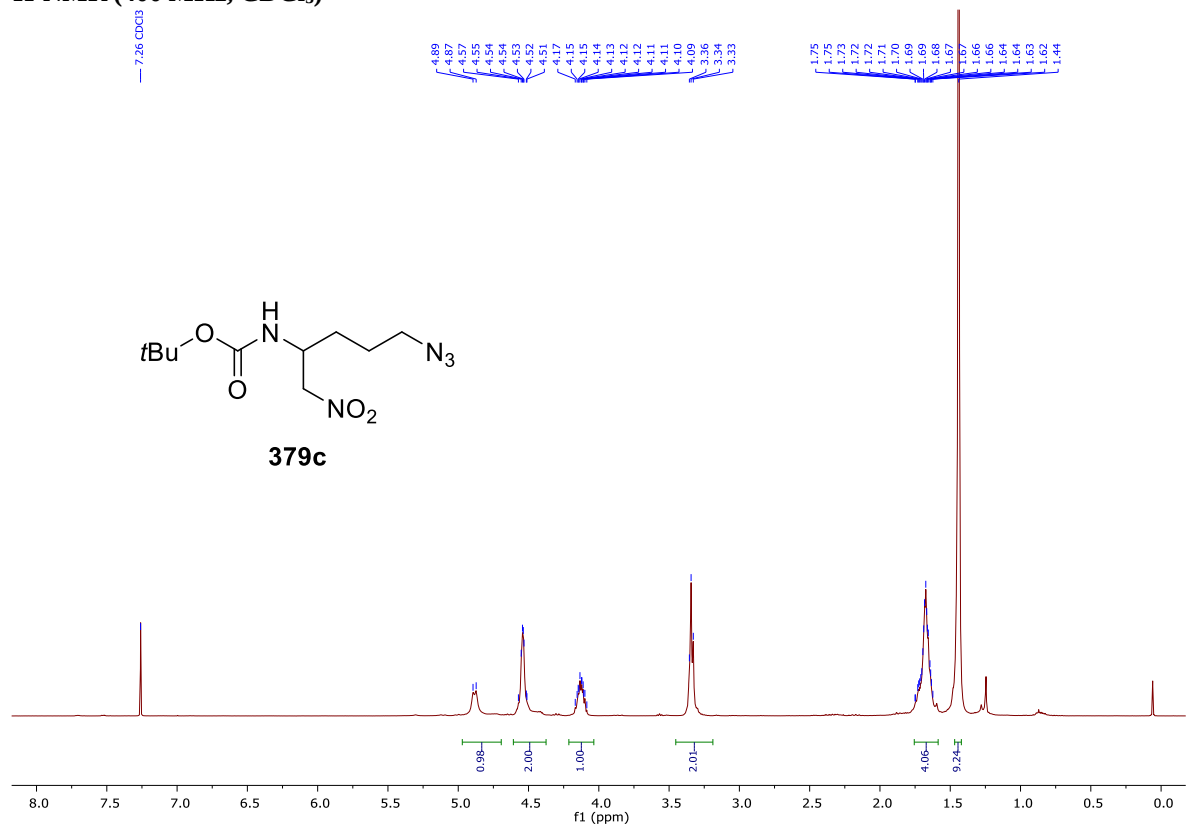
^{1}H-NMR (600 MHz, $CDCl_3$)



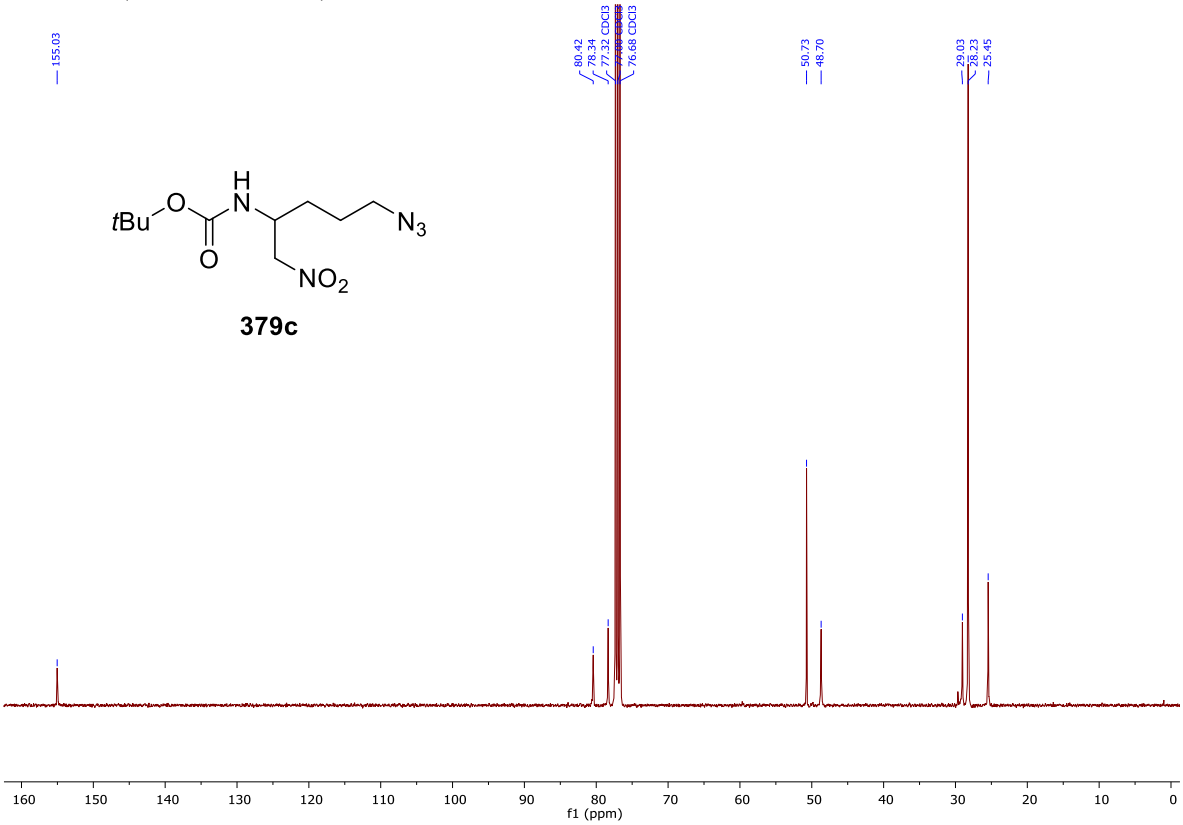
^{13}C-NMR (151 MHz, $CDCl_3$)



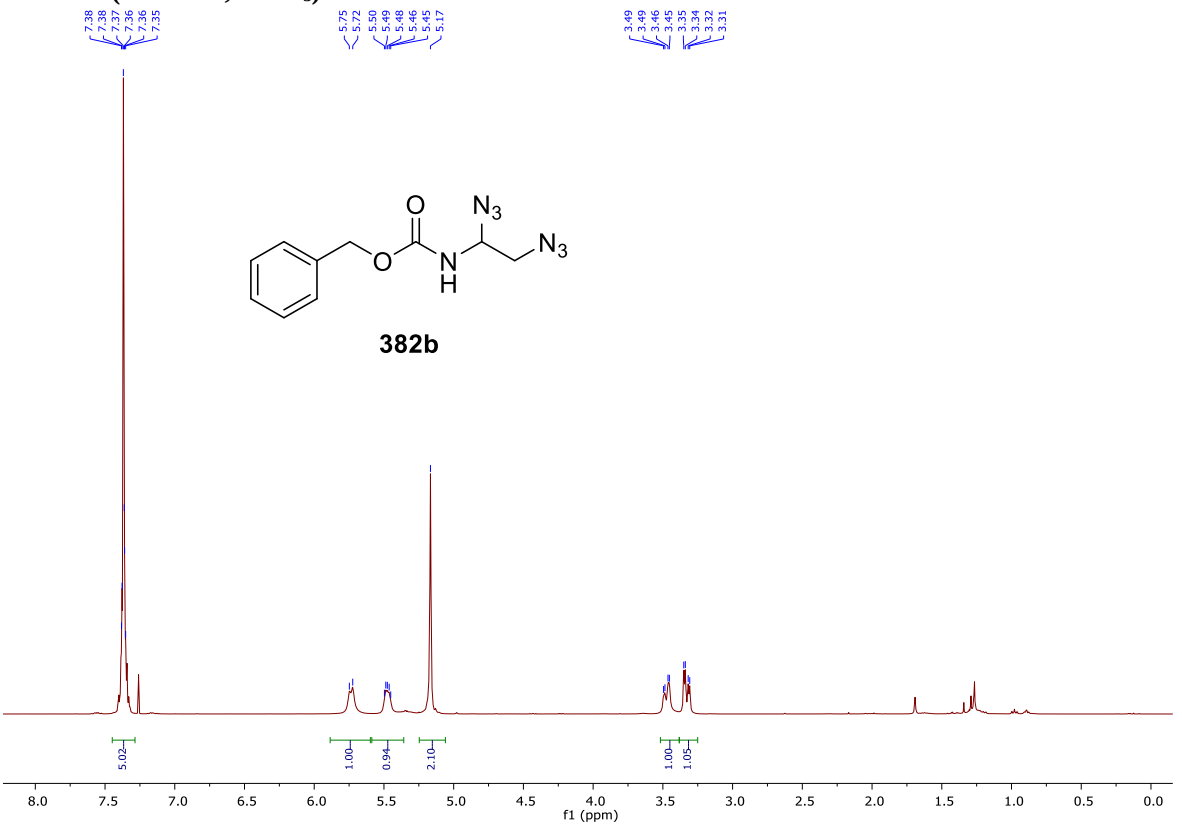
^{1}H-NMR (400 MHz, $CDCl_3$)



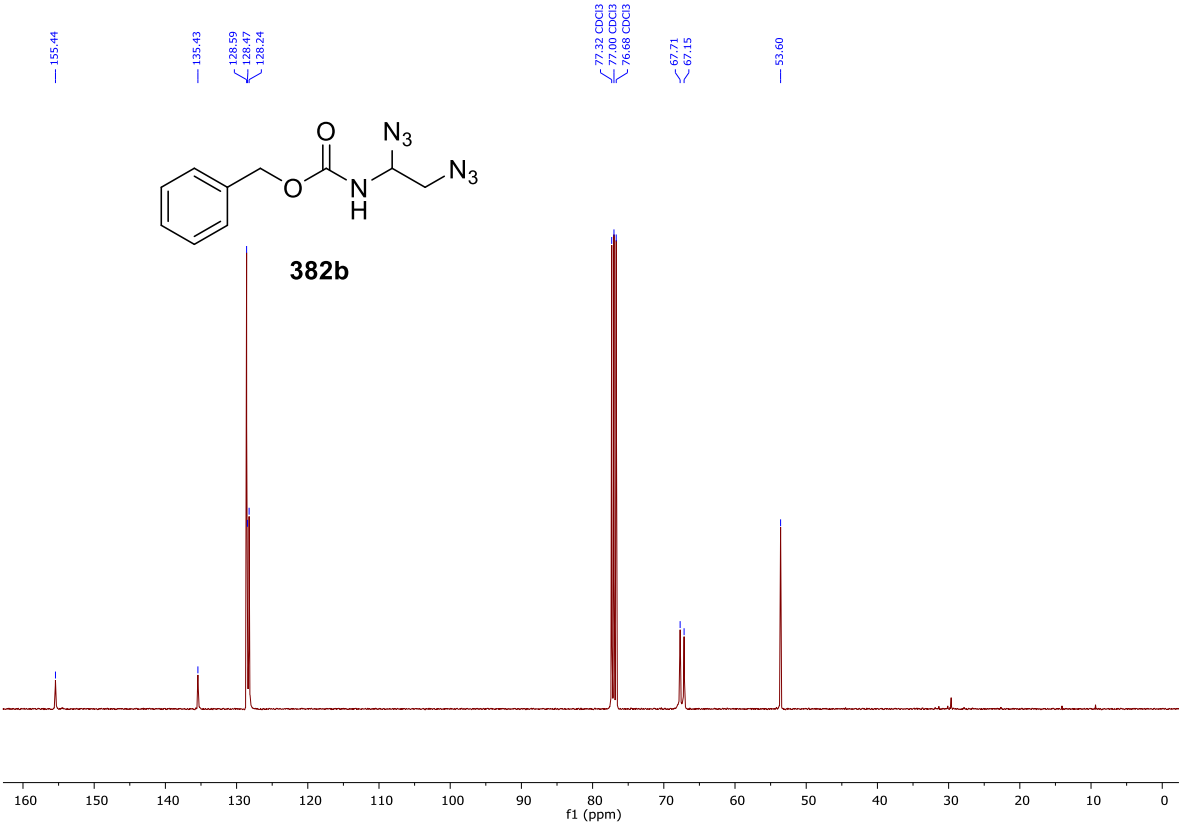
^{13}C-NMR (101 MHz, $CDCl_3$)



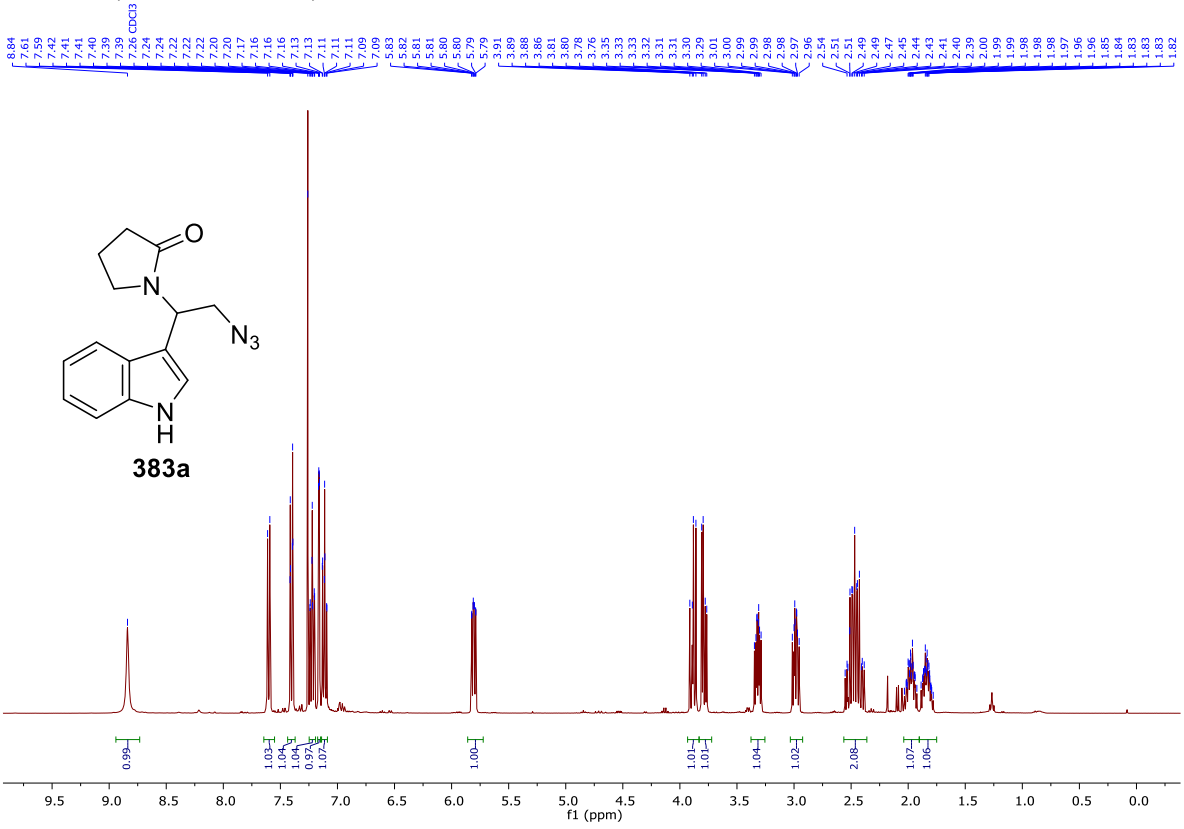
^{1}H-NMR (400 MHz, $CDCl_3$)



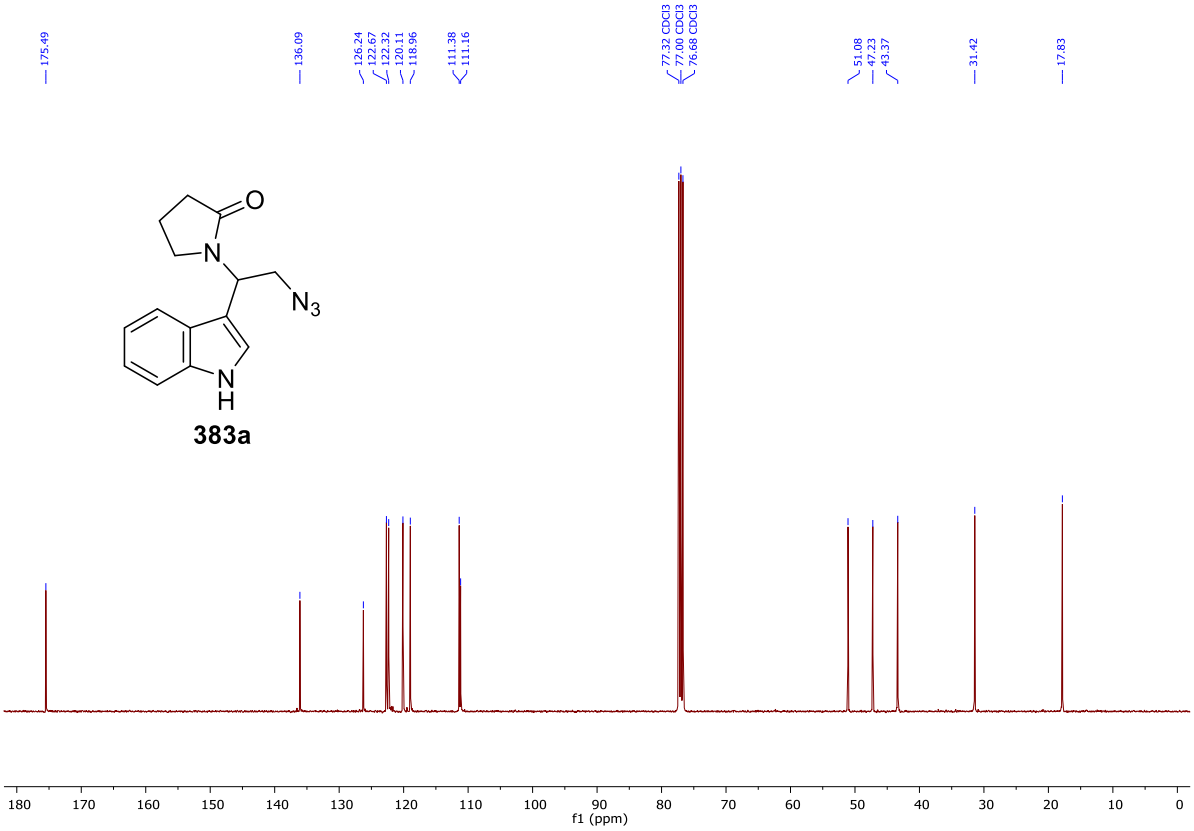
^{13}C-NMR (101 MHz, $CDCl_3$)



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

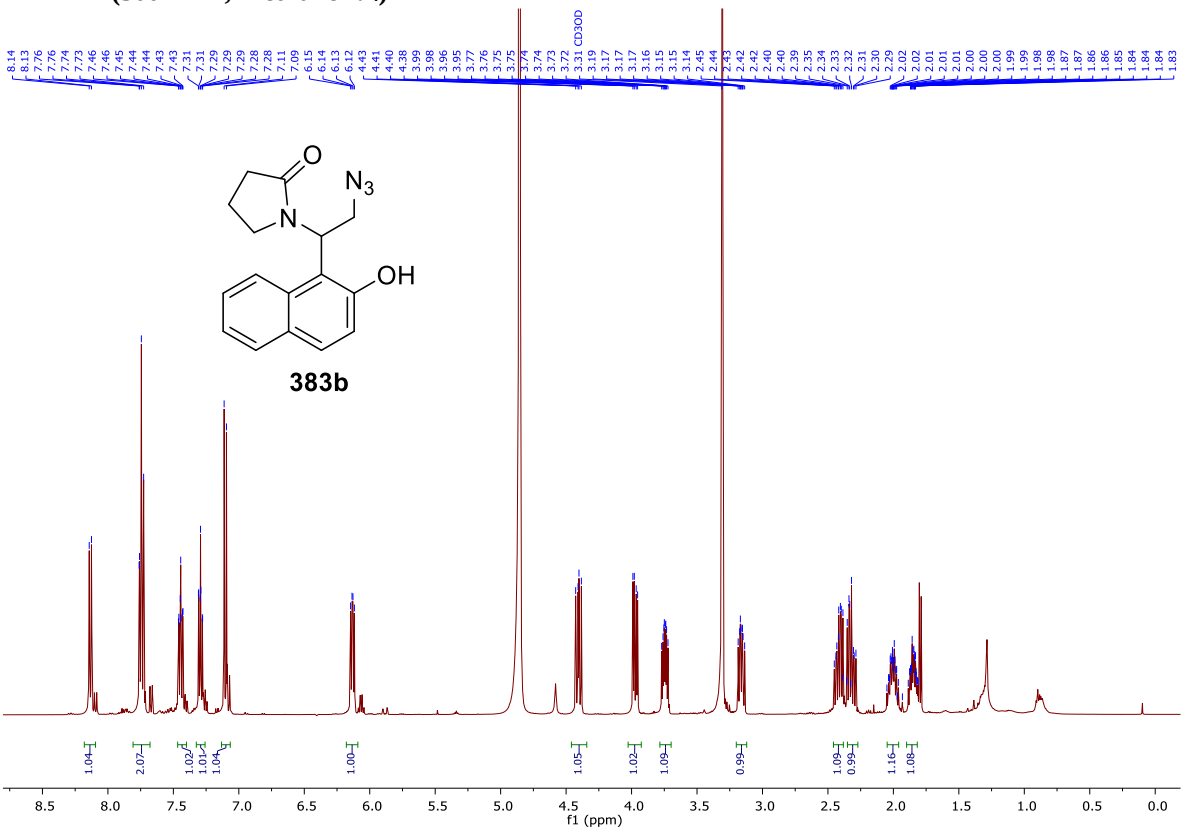


^{13}C-NMR (101 MHz, $CDCl_3$)



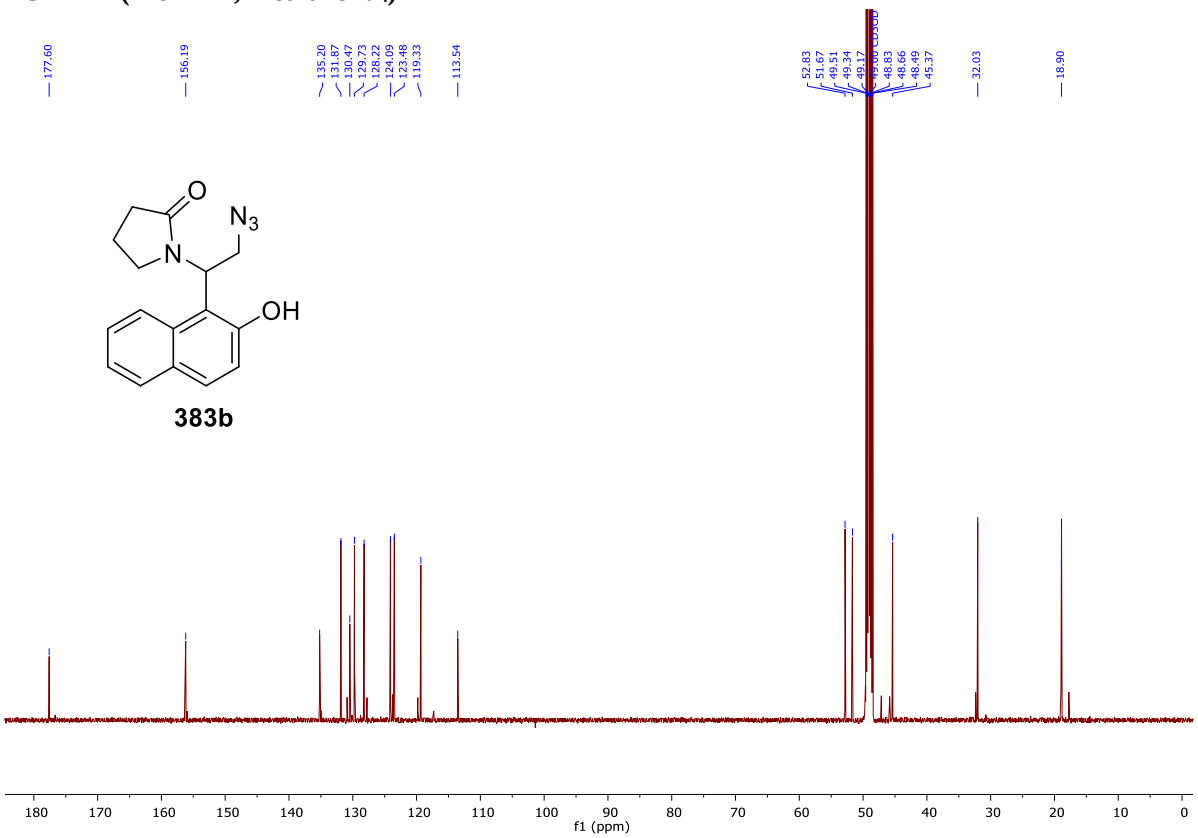
383a

^{1}H-NMR (500 MHz, Methanol-d_4)

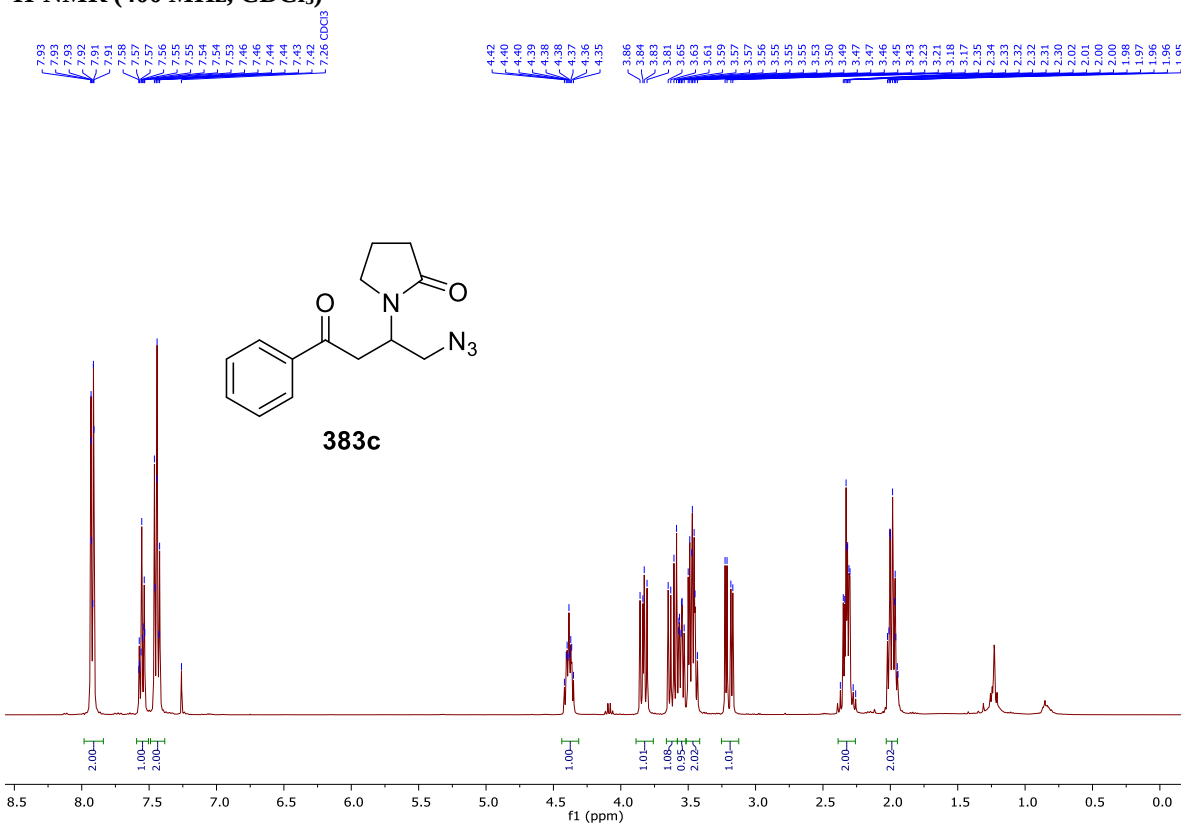


383b

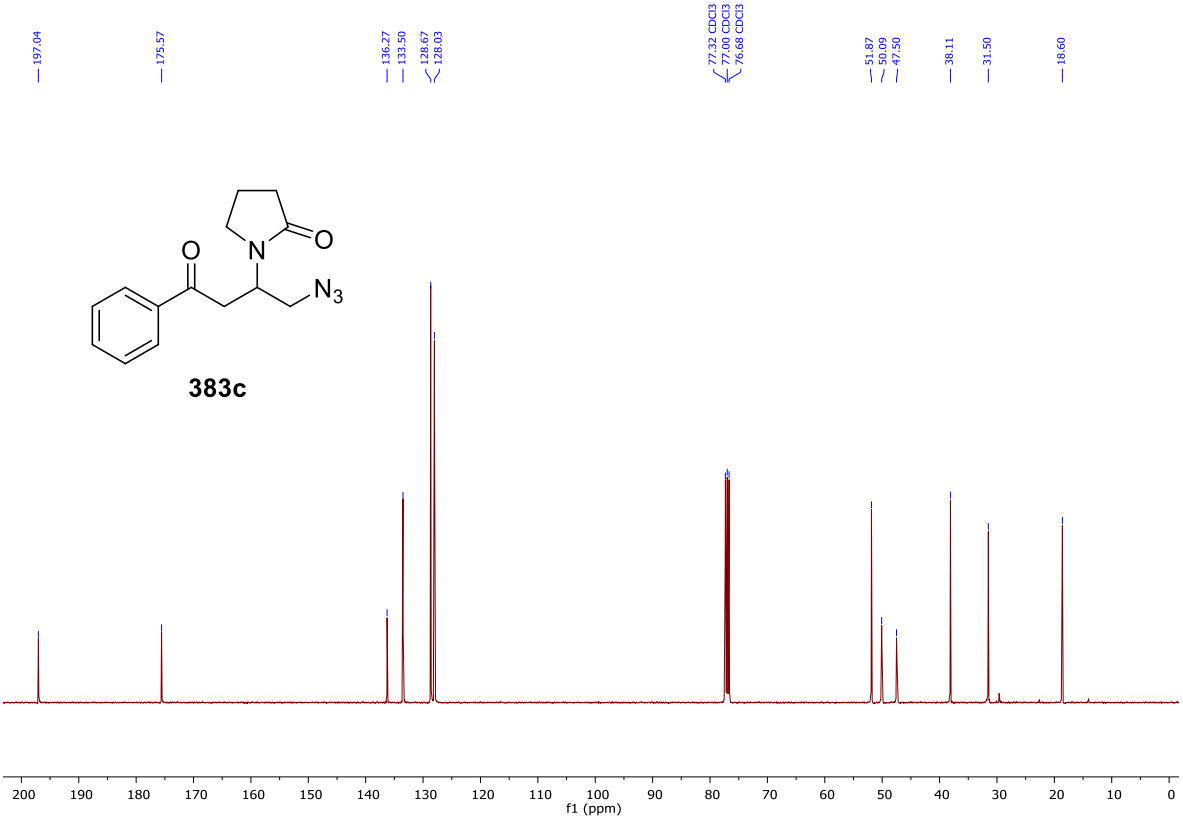
^{13}C-NMR (126 MHz, Methanol-d_4)



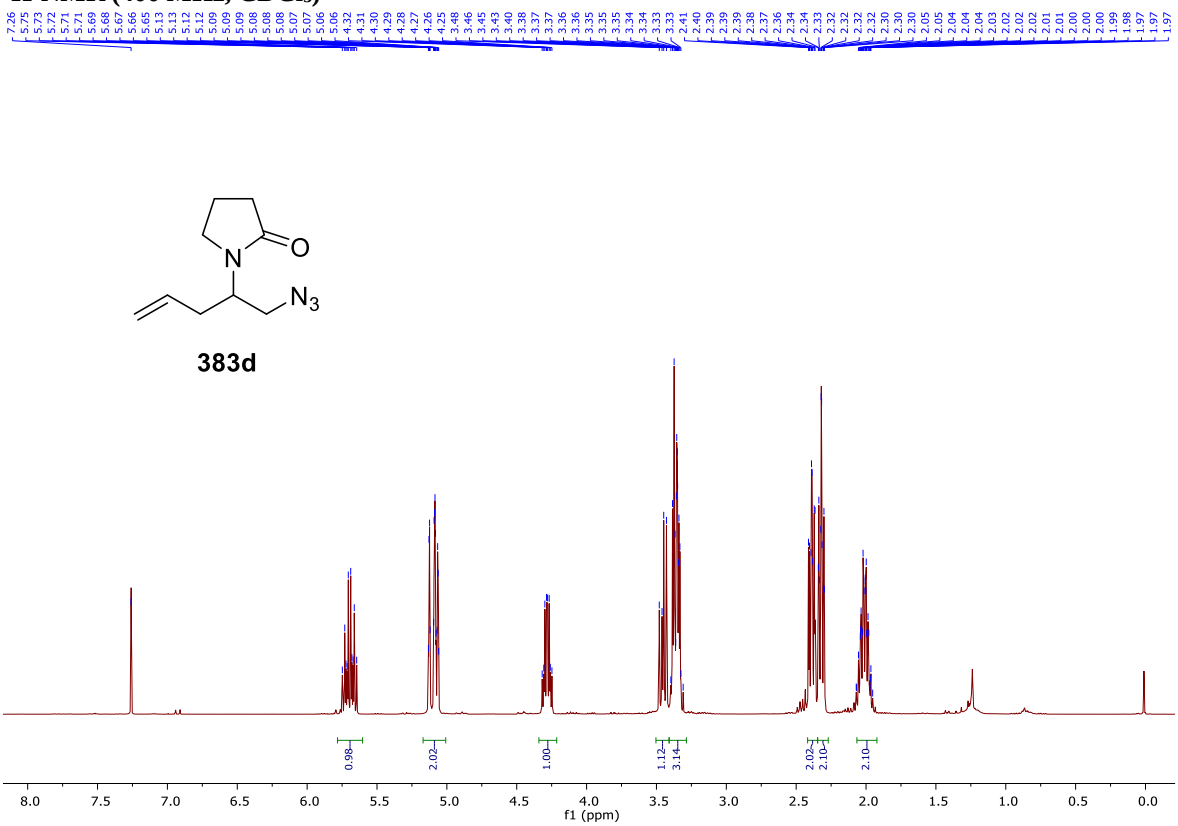
^{1}H-NMR (400 MHz, $CDCl_3$)



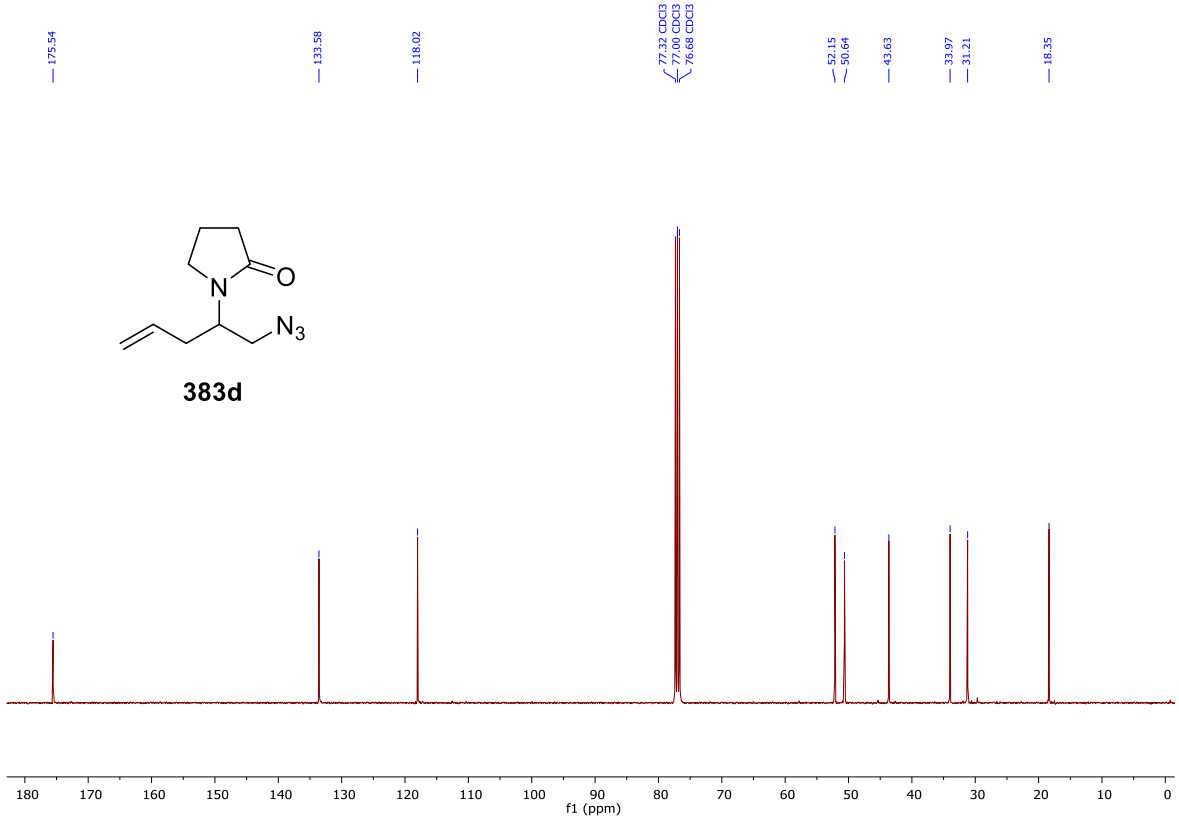
^{13}C-NMR (101 MHz, $CDCl_3$)



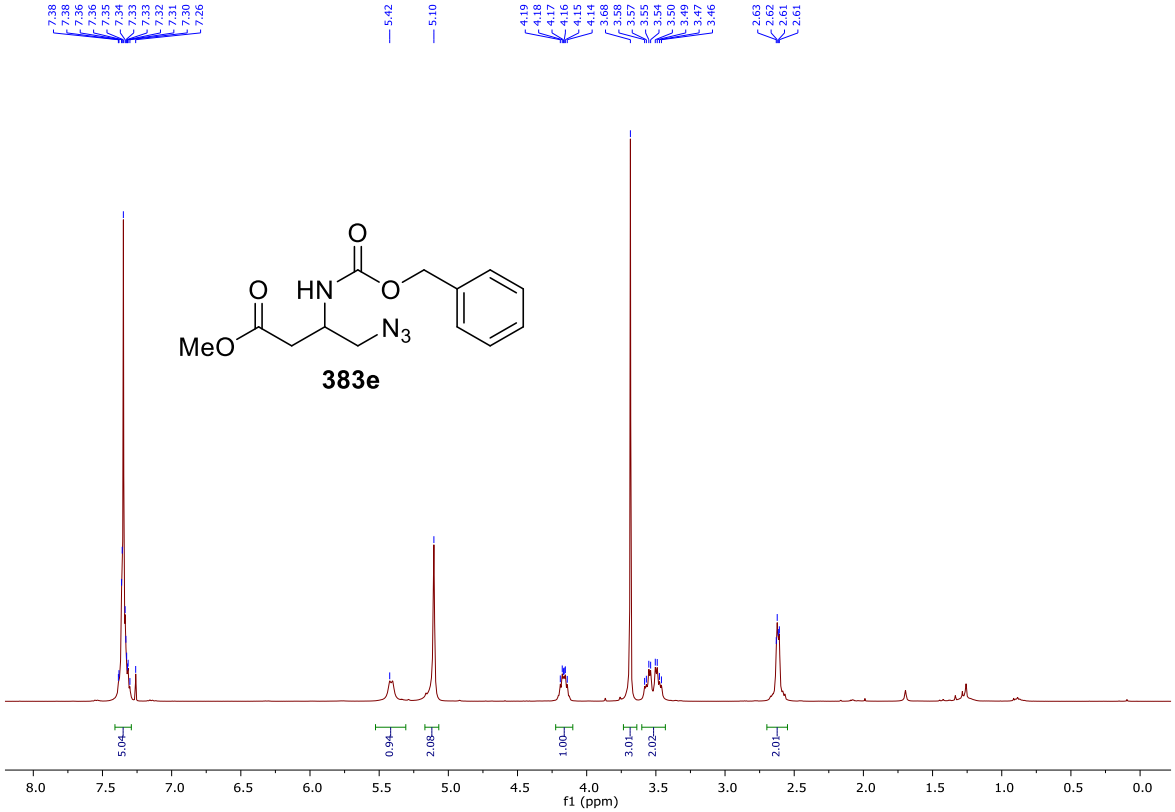
^{1}H-NMR (400 MHz, $CDCl_3$)



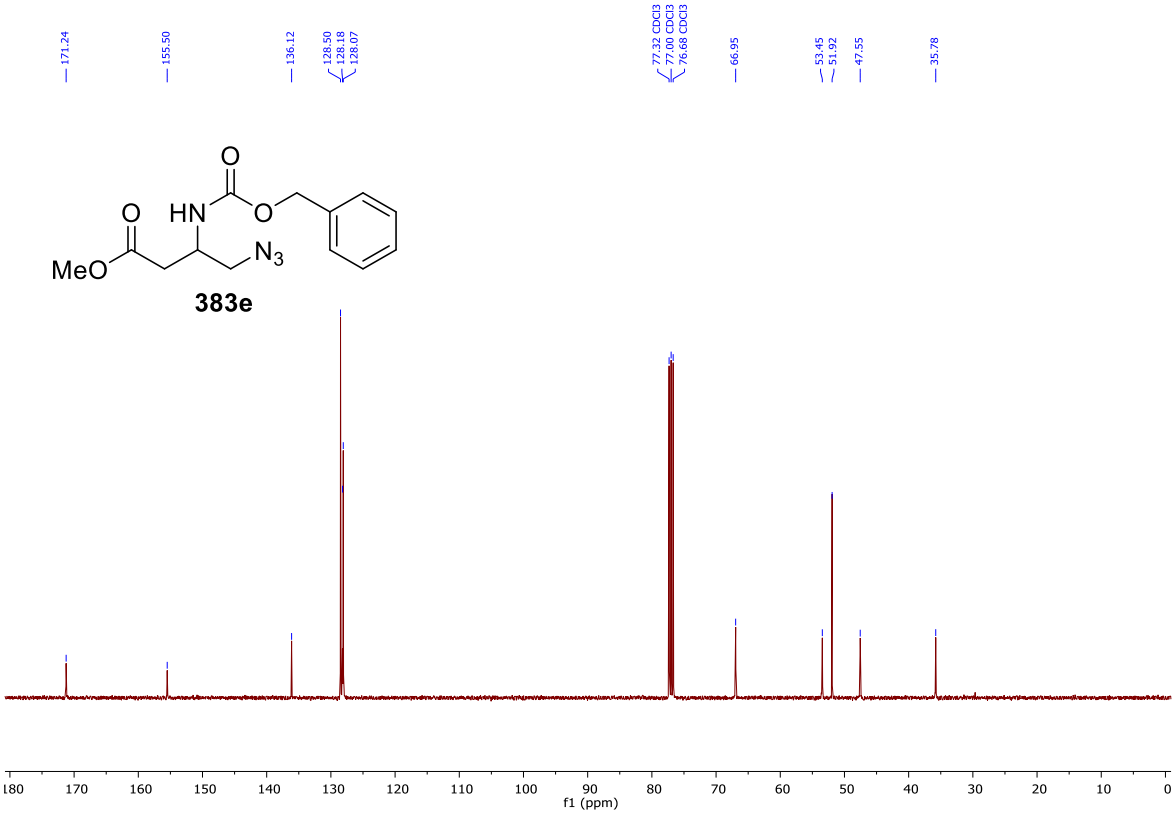
^{13}C-NMR (101 MHz, $CDCl_3$)



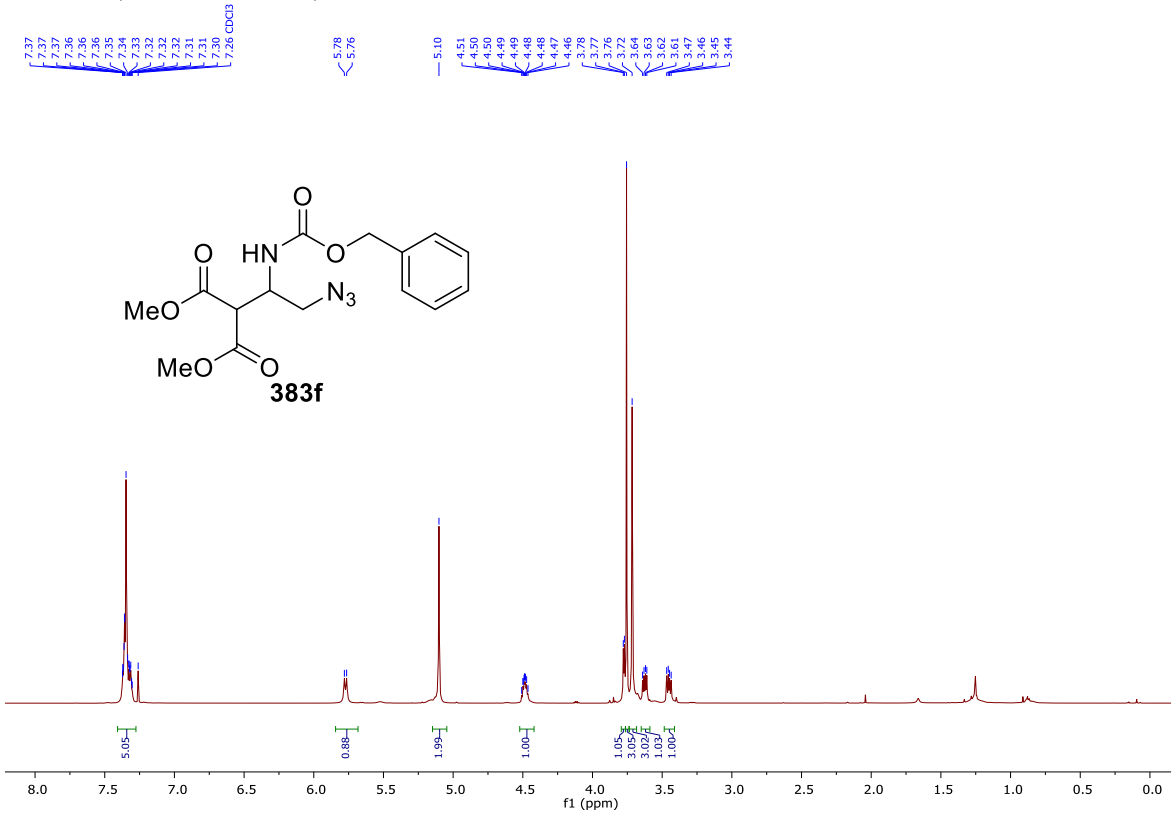
^{1}H-NMR (400 MHz, $CDCl_3$)



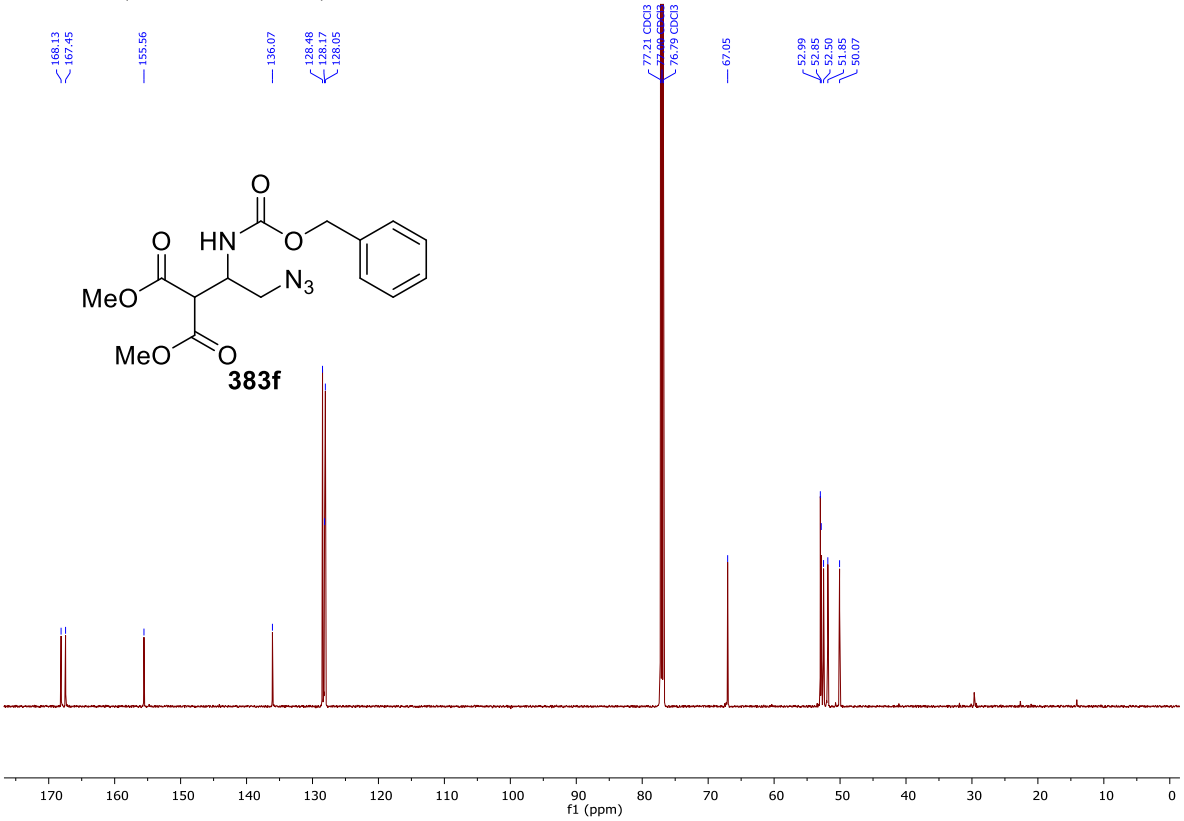
^{13}C-NMR (101 MHz, $CDCl_3$)



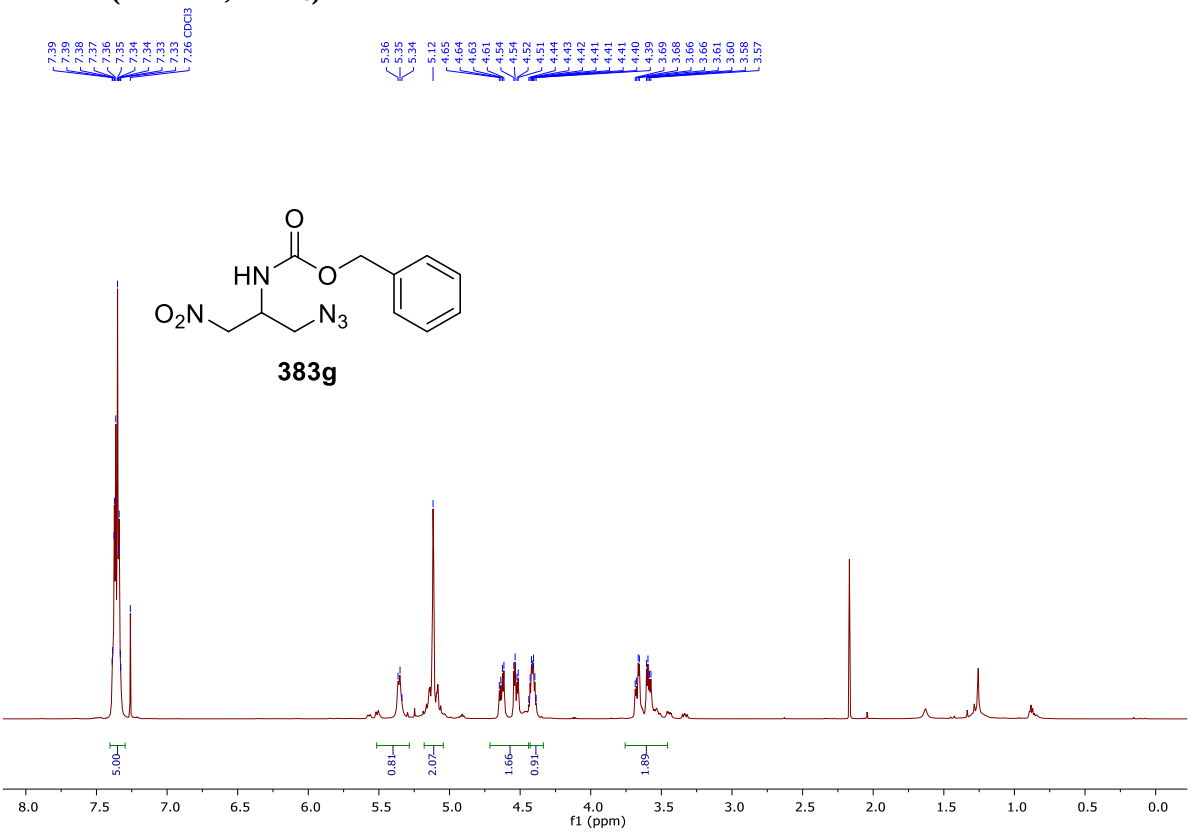
^{1}H-NMR (600 MHz, $CDCl_3$)



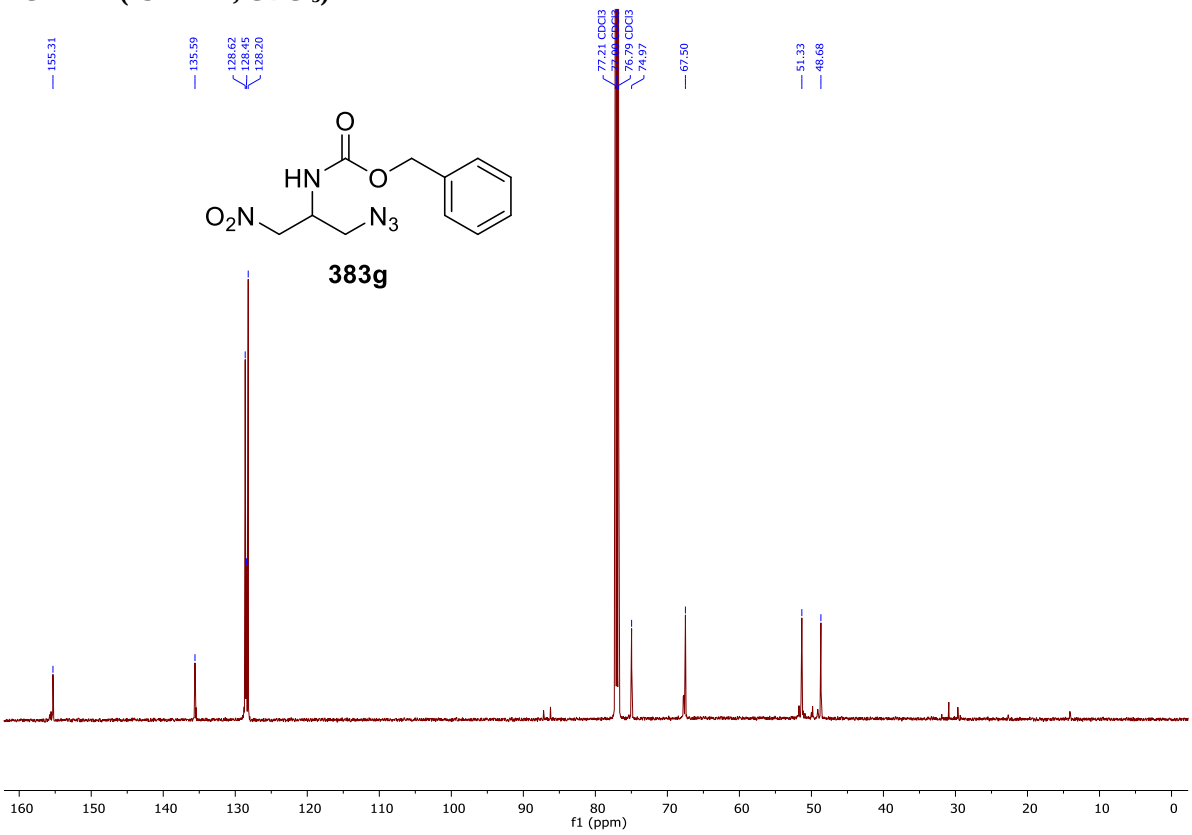
^{13}C-NMR (151 MHz, $CDCl_3$)



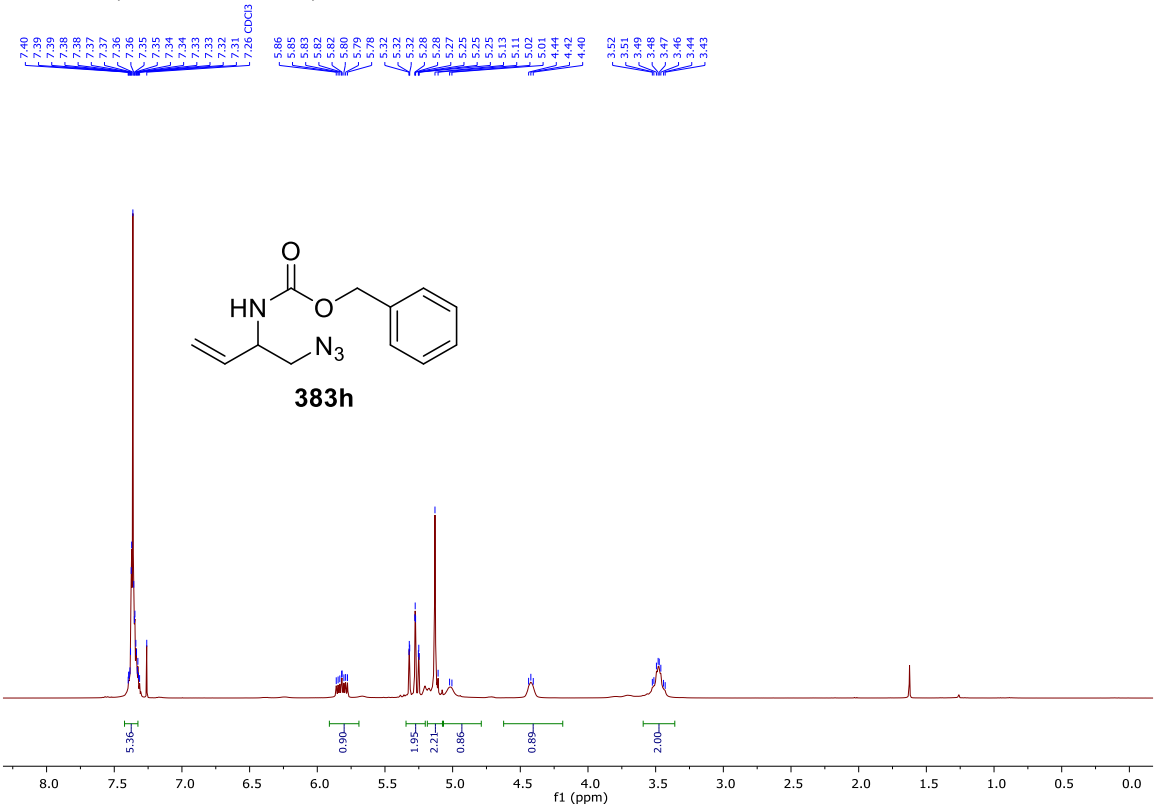
^{1}H-NMR (600 MHz, $CDCl_3$)



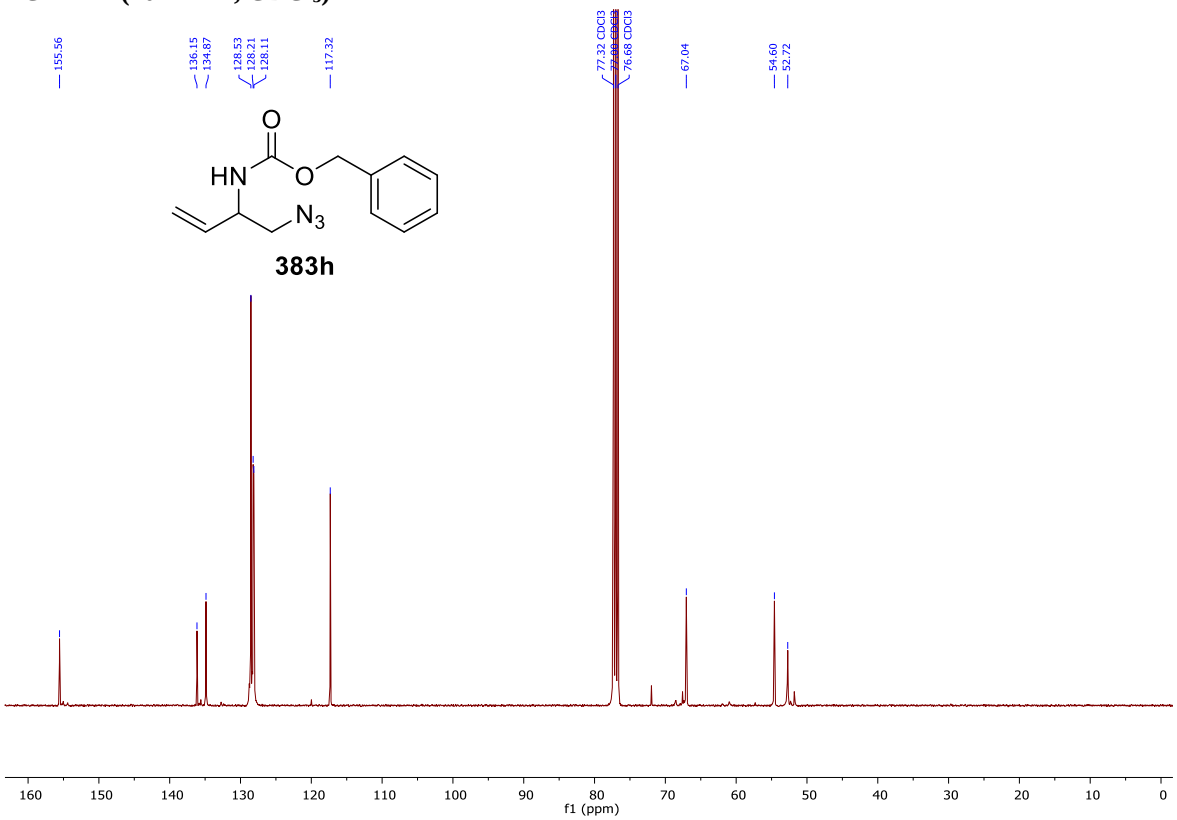
^{13}C-NMR (151 MHz, $CDCl_3$)



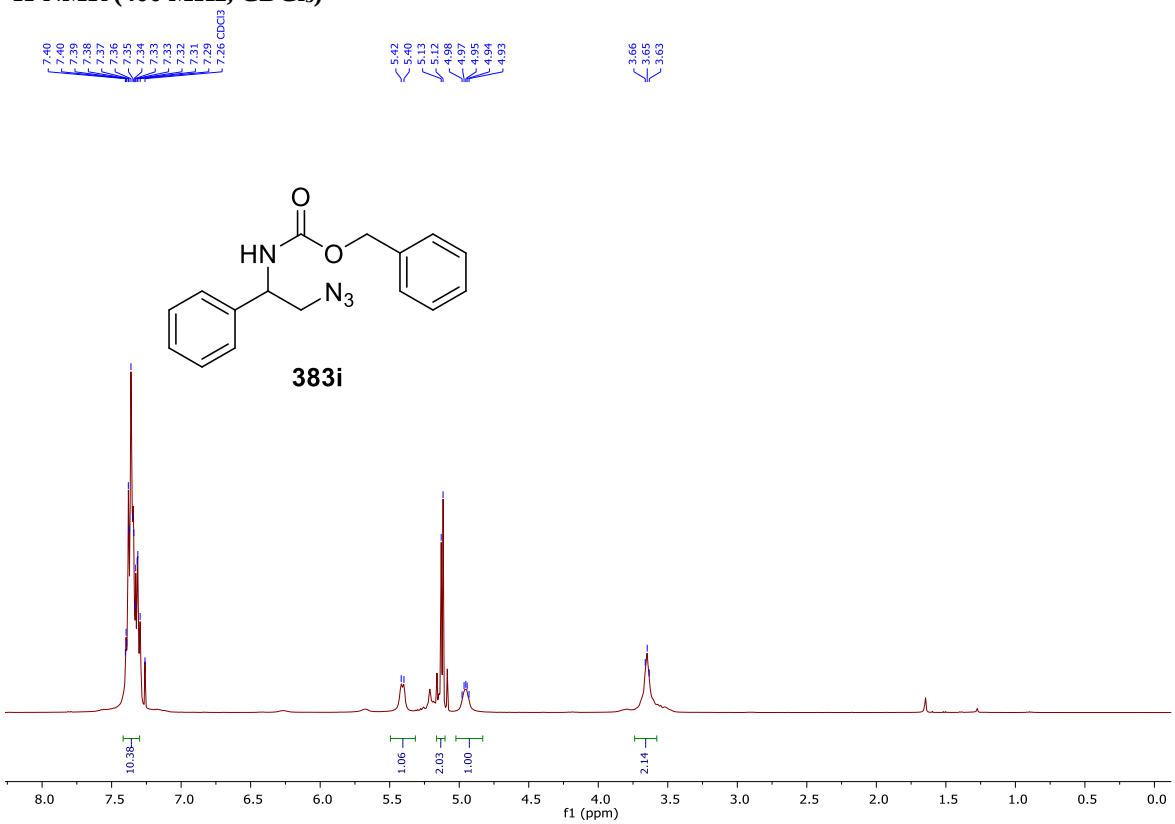
^{1}H-NMR (400 MHz, $CDCl_3$)



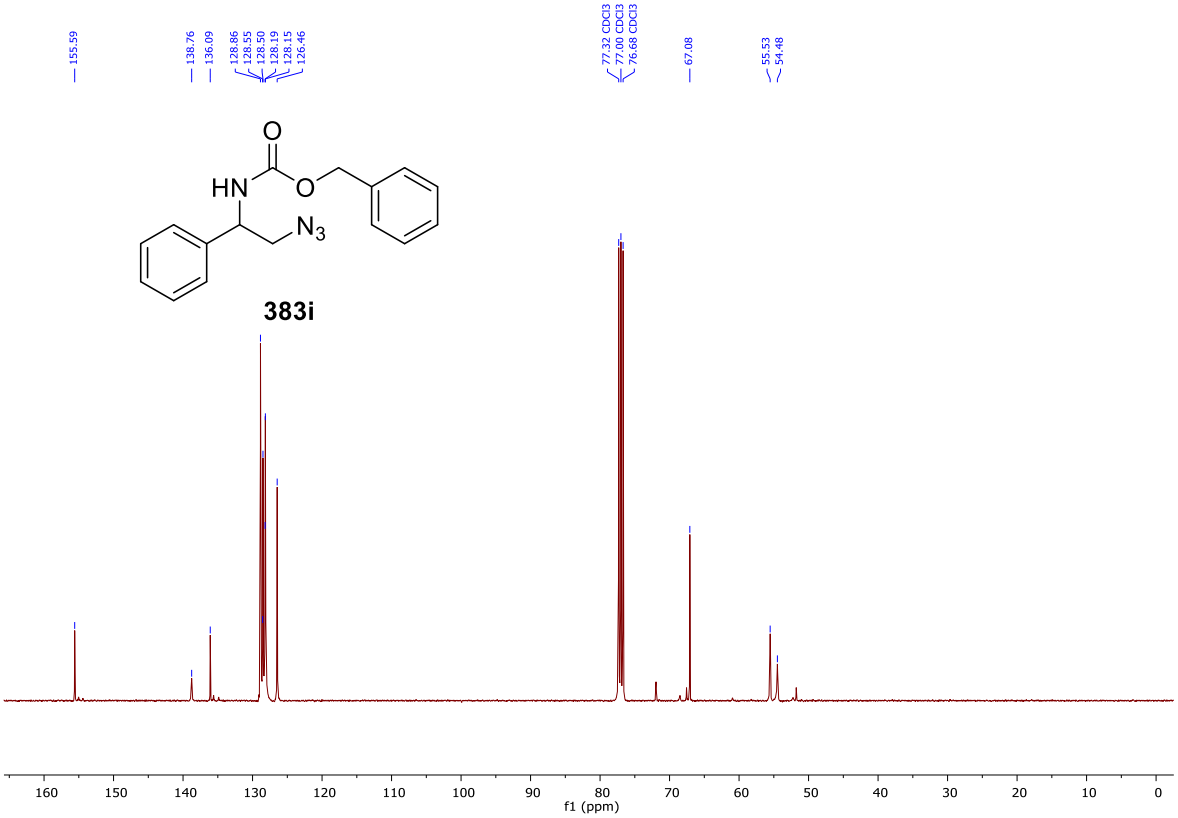
^{13}C-NMR (101 MHz, $CDCl_3$)



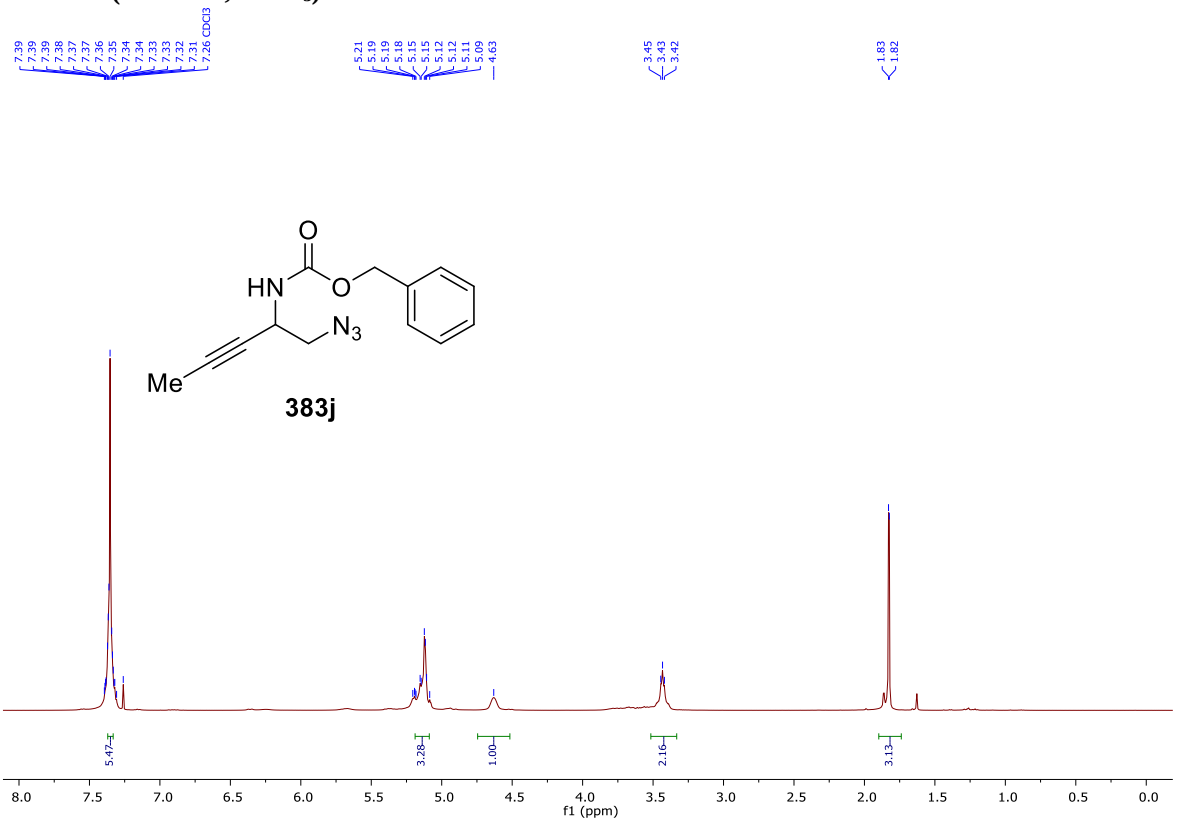
^{1}H-NMR (400 MHz, $CDCl_3$)



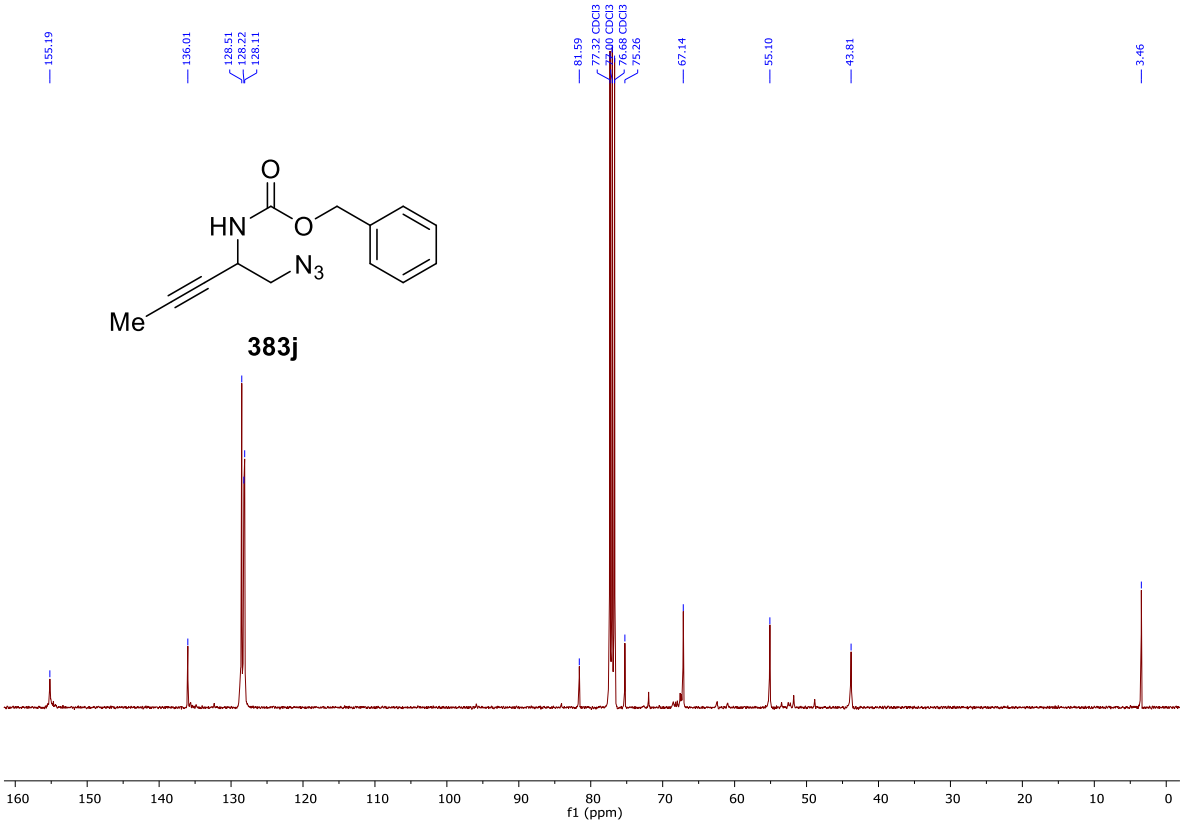
^{13}C-NMR (101 MHz, $CDCl_3$)



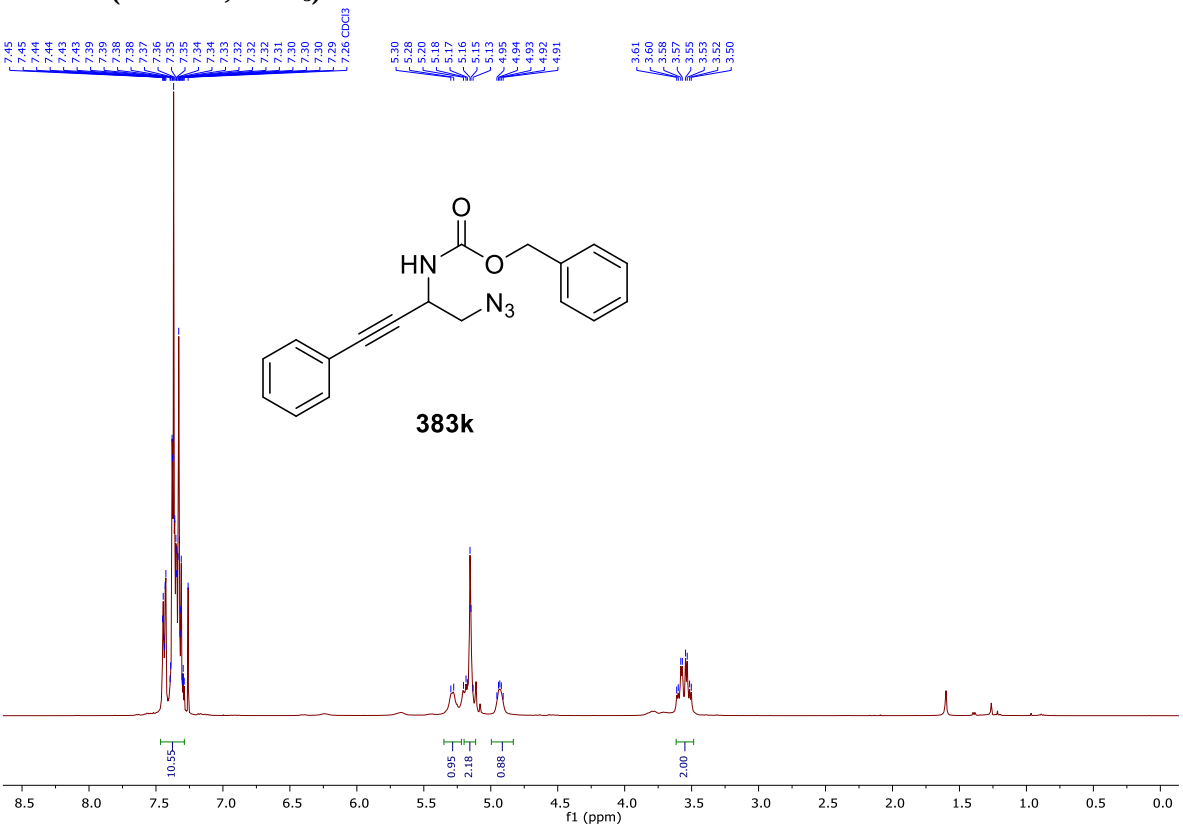
^{1}H-NMR (400 MHz, $CDCl_3$)



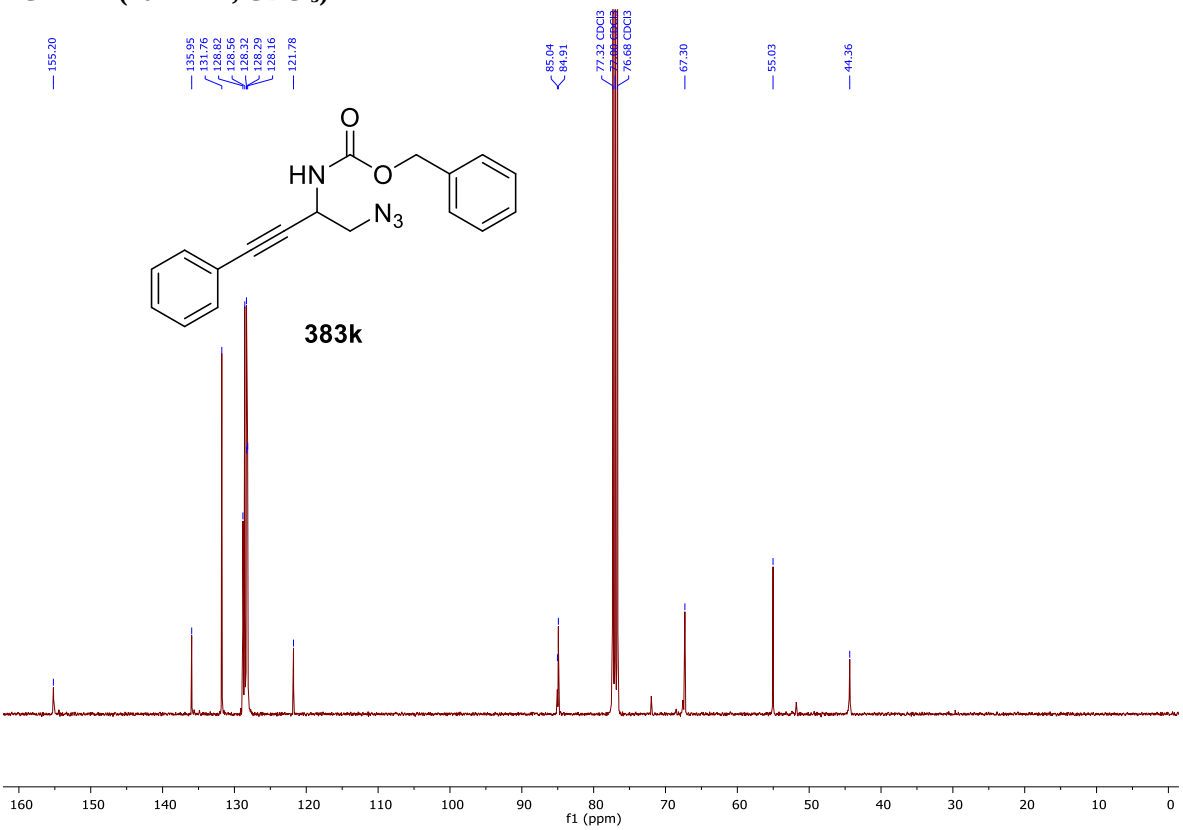
^{13}C-NMR (101 MHz, $CDCl_3$)



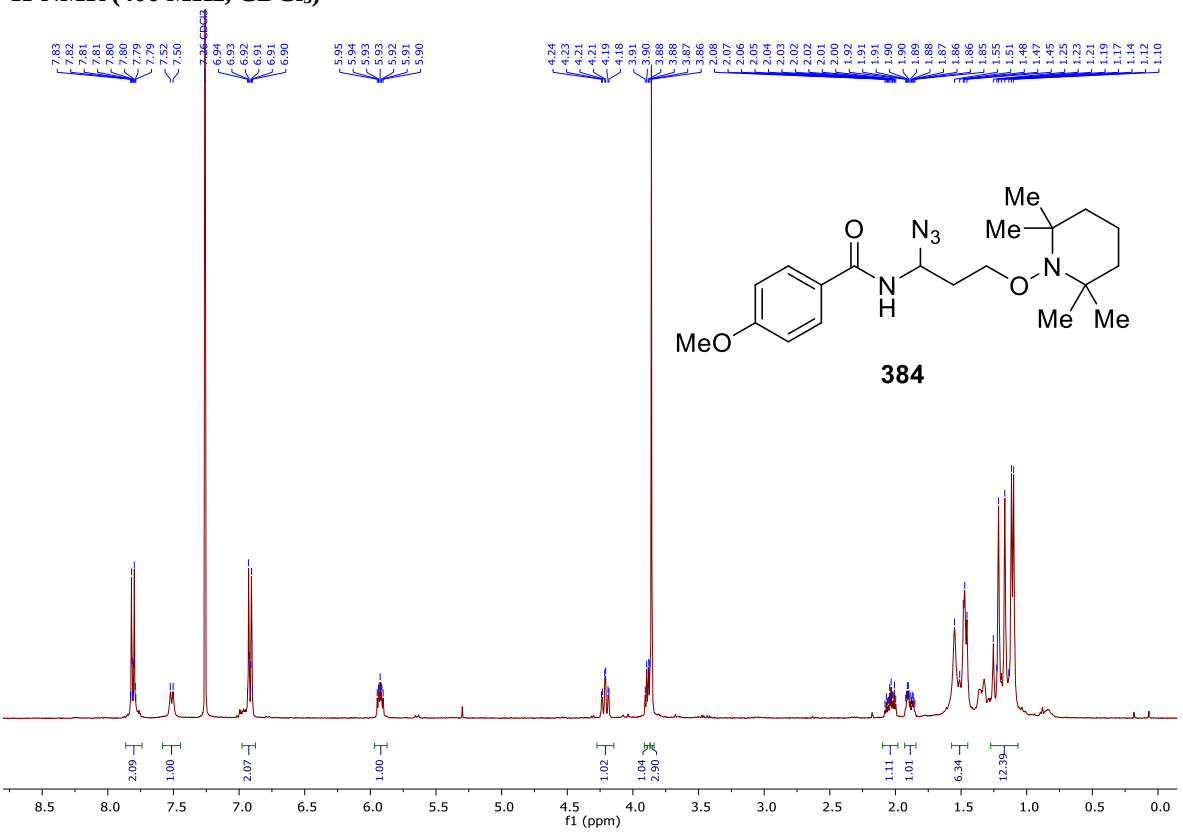
^{1}H-NMR (400 MHz, $CDCl_3$)



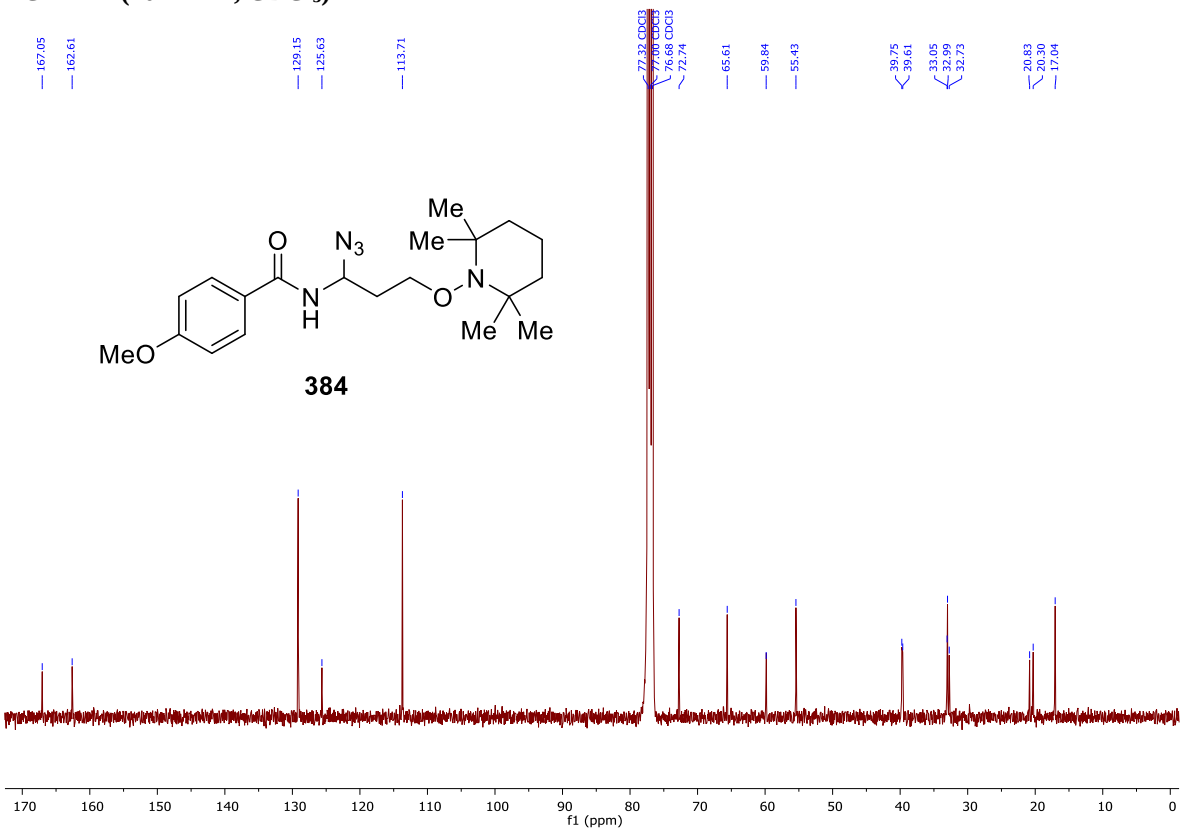
^{13}C-NMR (101 MHz, $CDCl_3$)



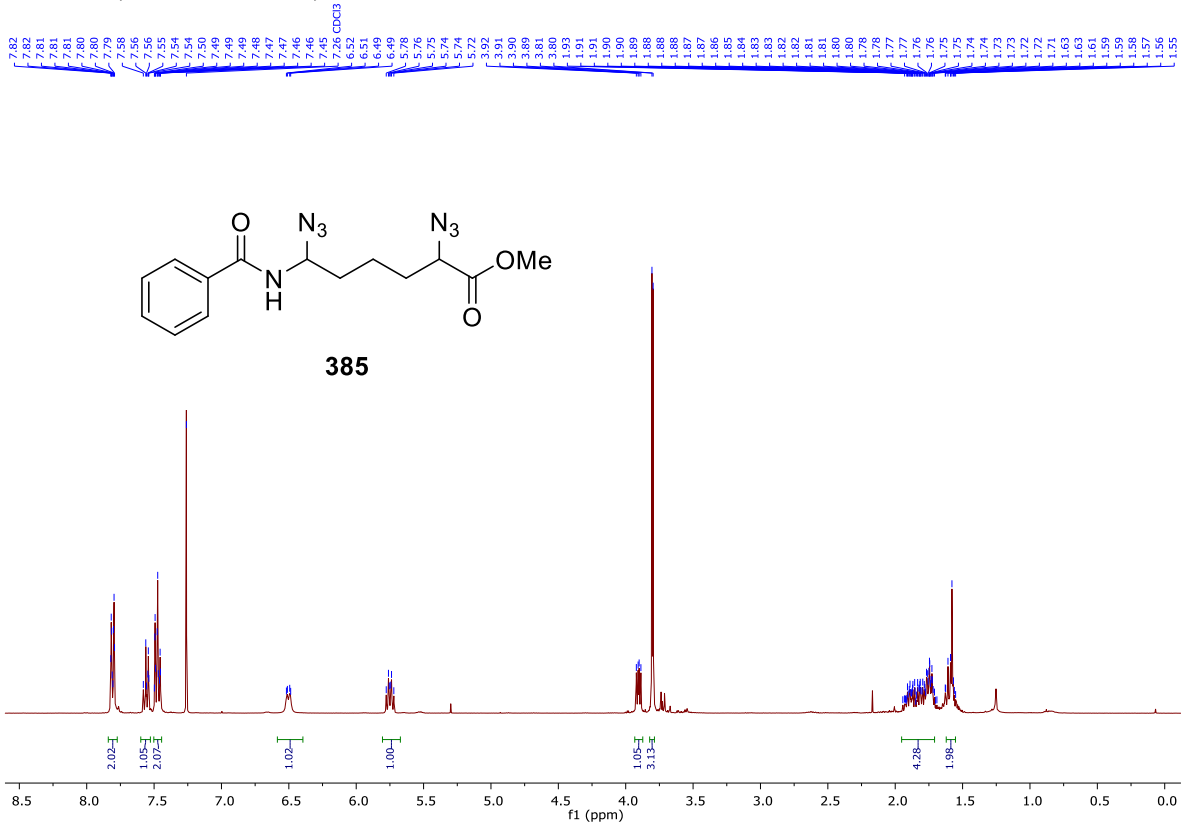
^{1}H-NMR (400 MHz, $CDCl_3$)



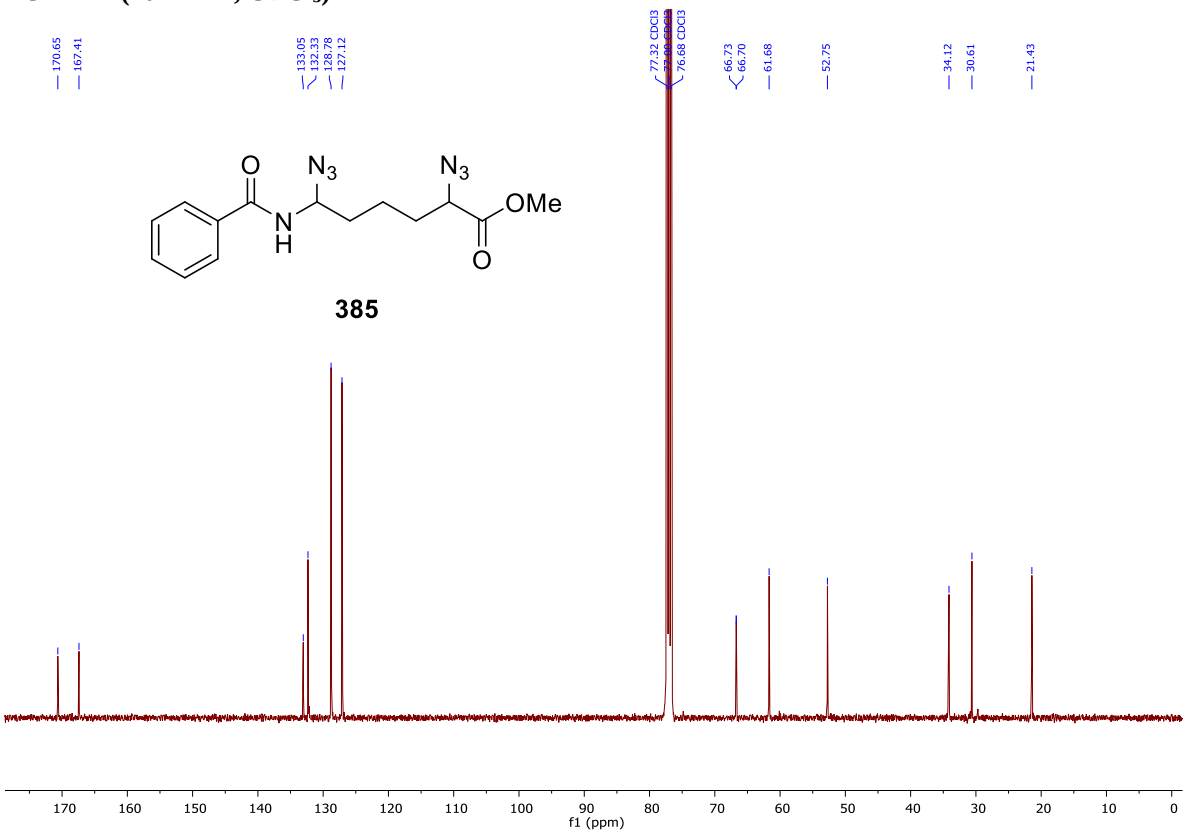
^{13}C-NMR (101 MHz, $CDCl_3$)



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

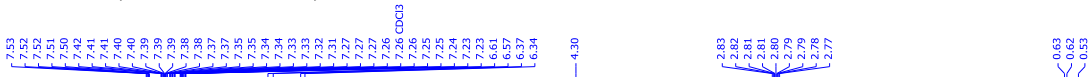


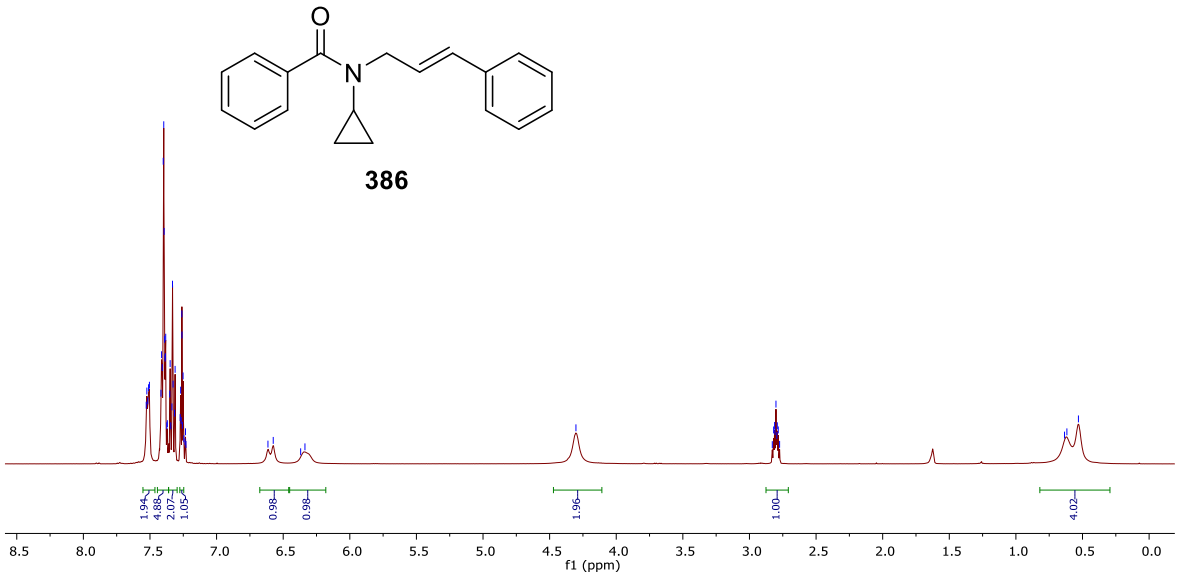
^{13}C-NMR (101 MHz, $CDCl_3$)



385

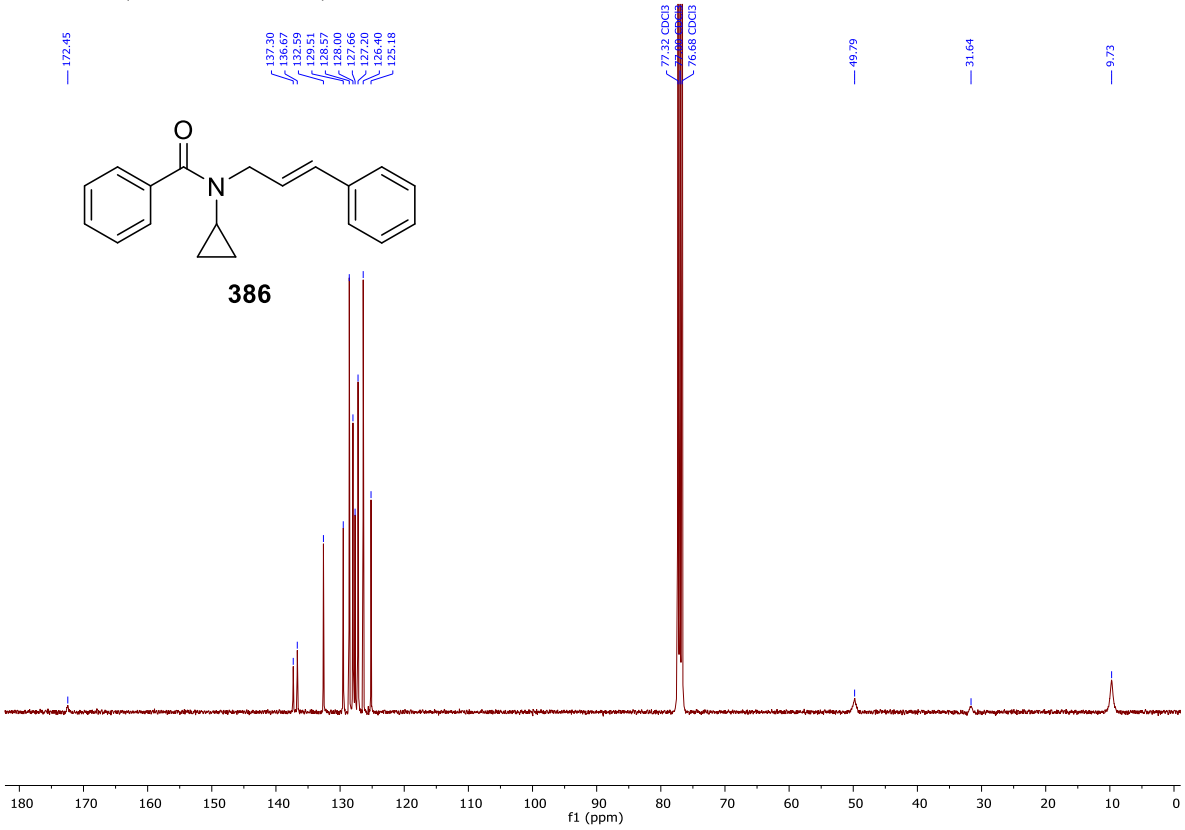
^{1}H-NMR (400 MHz, $CDCl_3$)



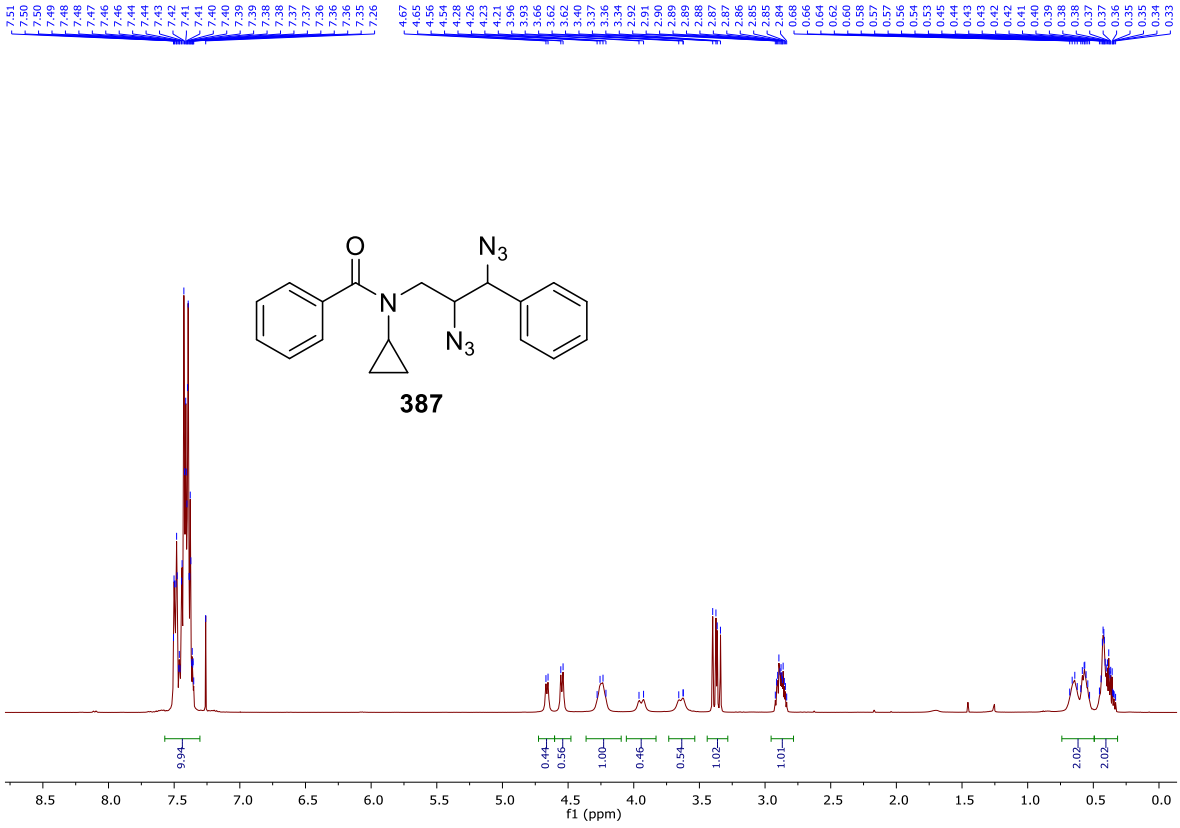


386

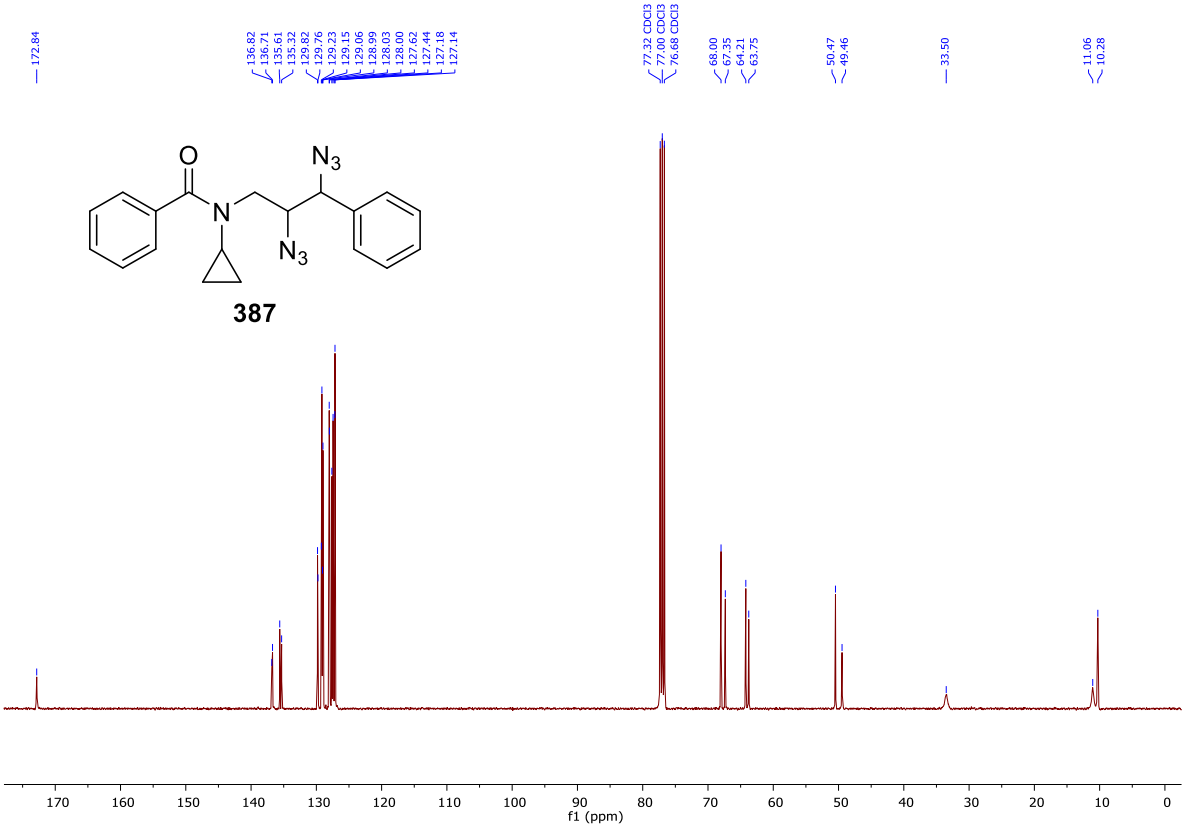
^{13}C-NMR (101 MHz, $CDCl_3$)



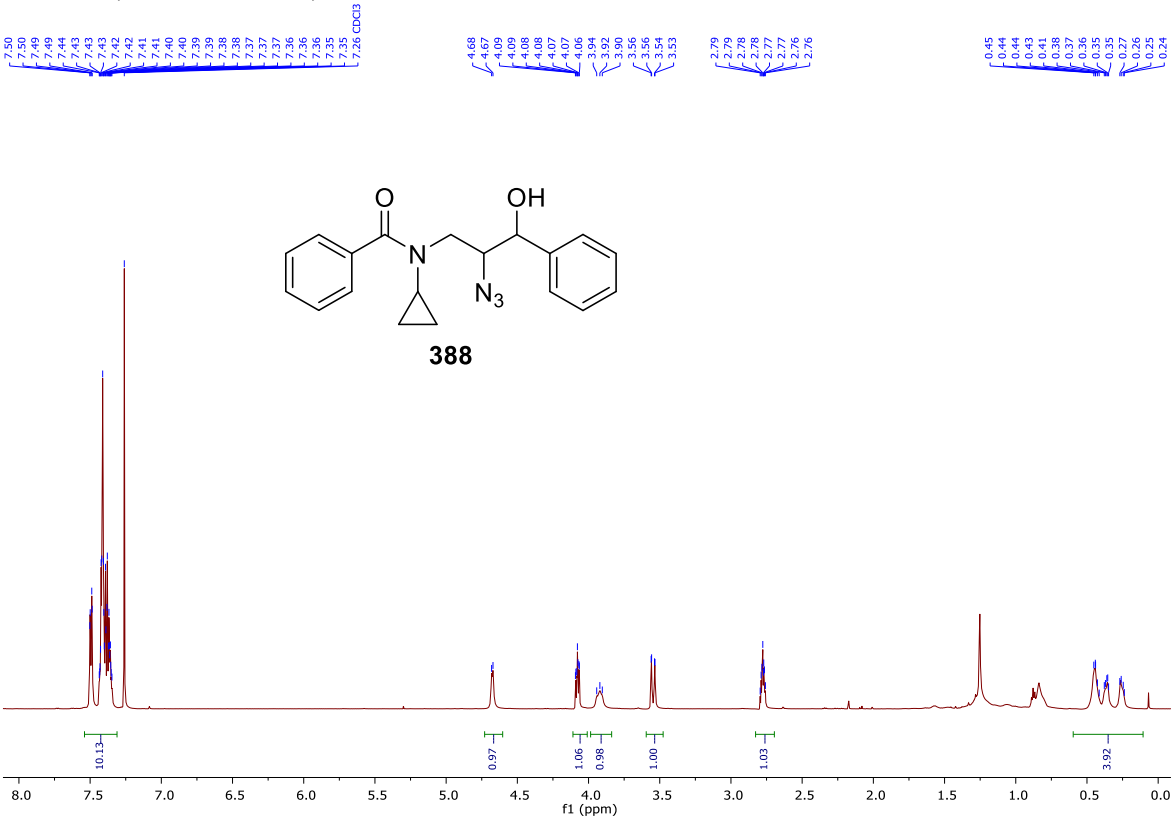
^{1}H-NMR (400 MHz, $CDCl_3$)



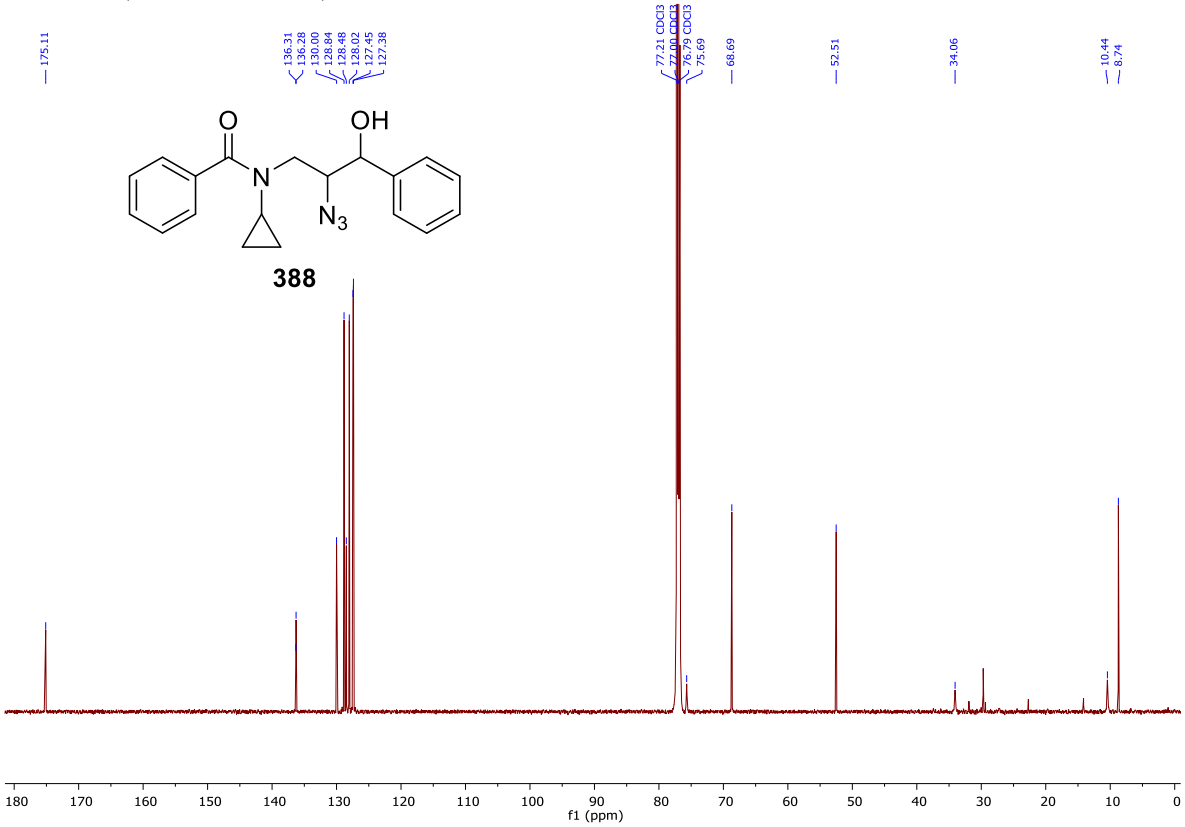
^{13}C-NMR (101 MHz, $CDCl_3$)



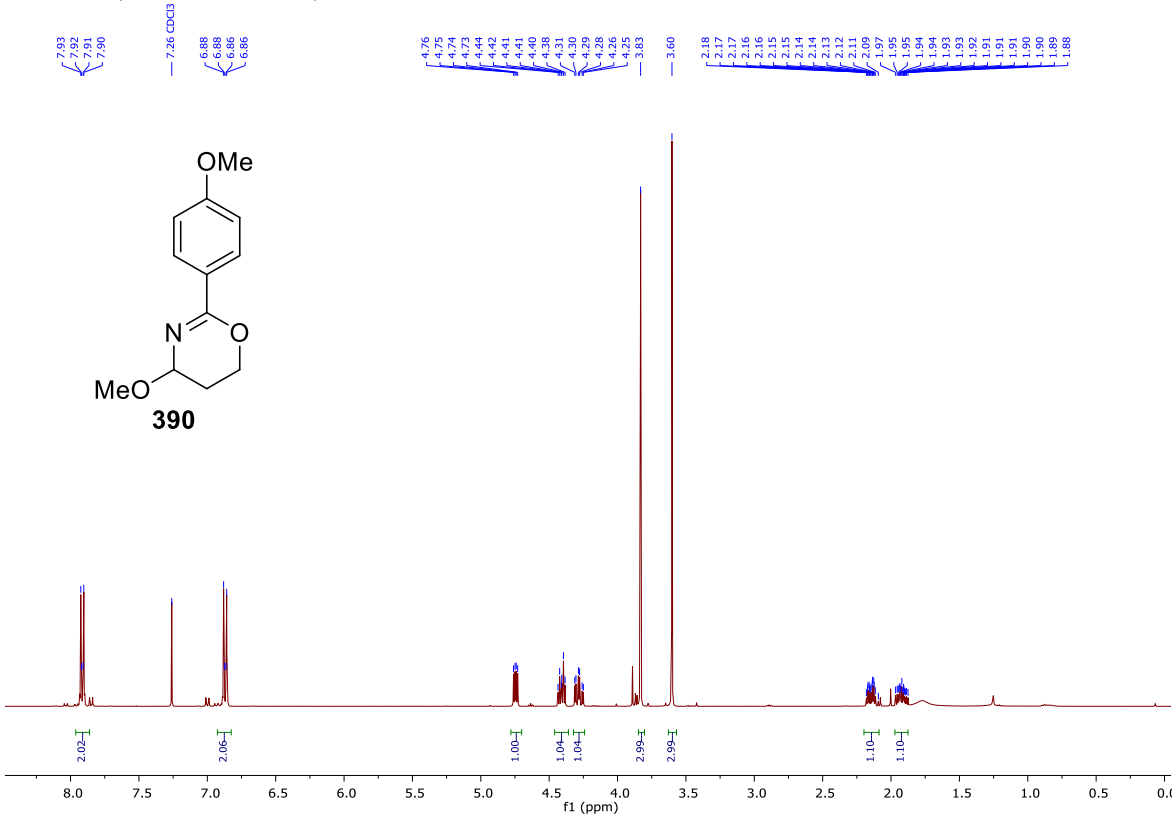
^{1}H-NMR (600 MHz, $CDCl_3$)



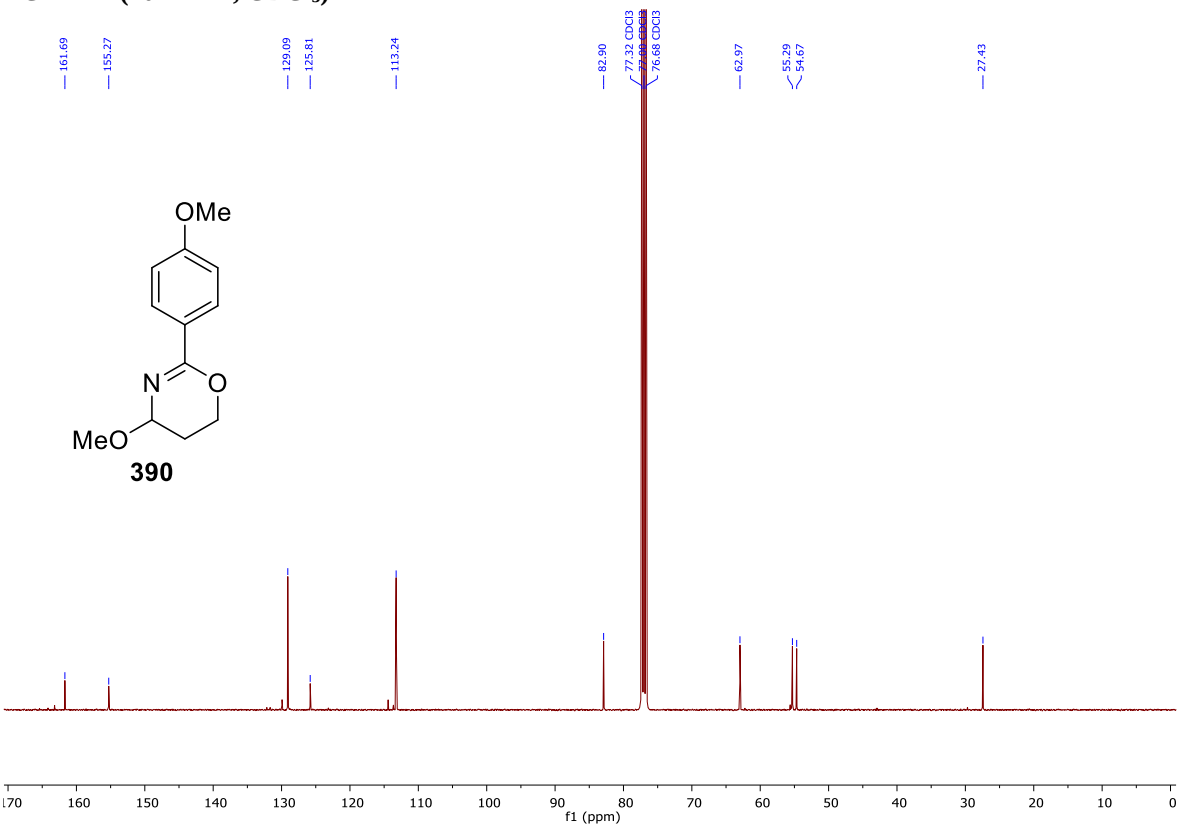
^{13}C-NMR (151 MHz, $CDCl_3$)



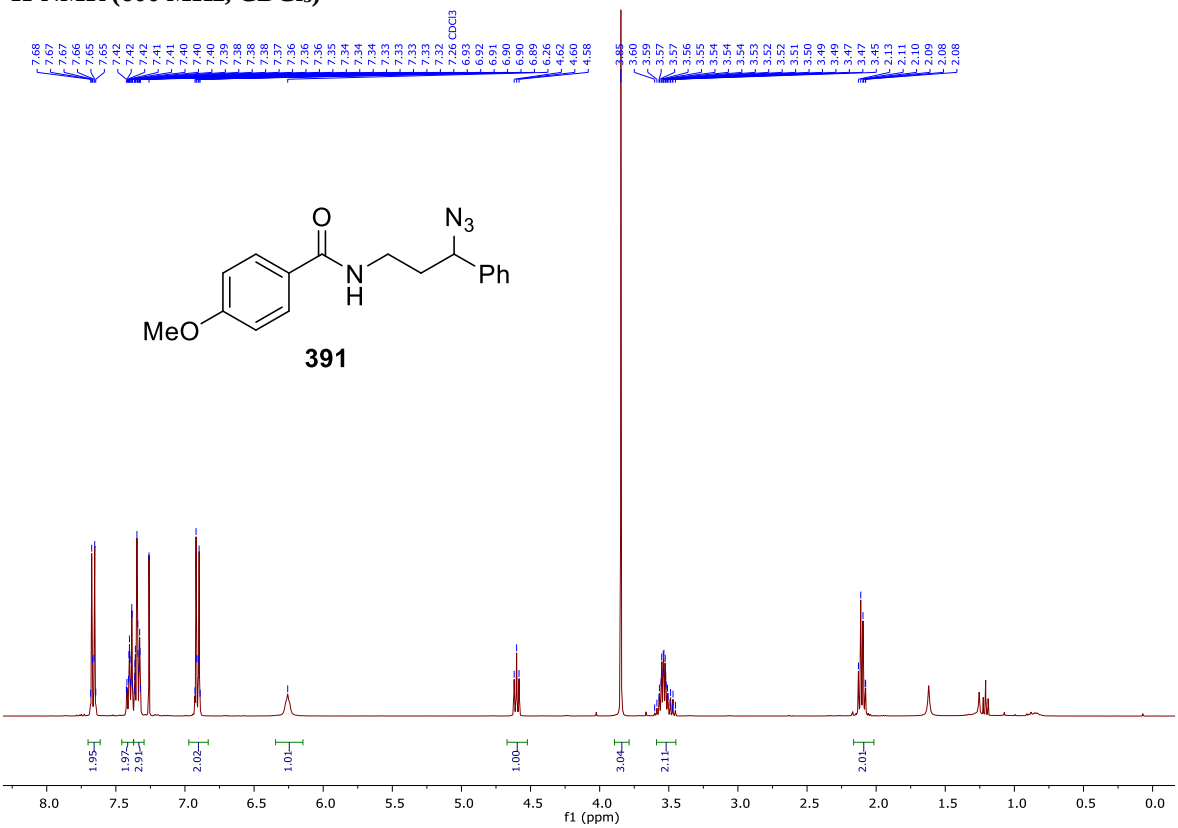
^{1}H-NMR (400 MHz, $CDCl_3$)



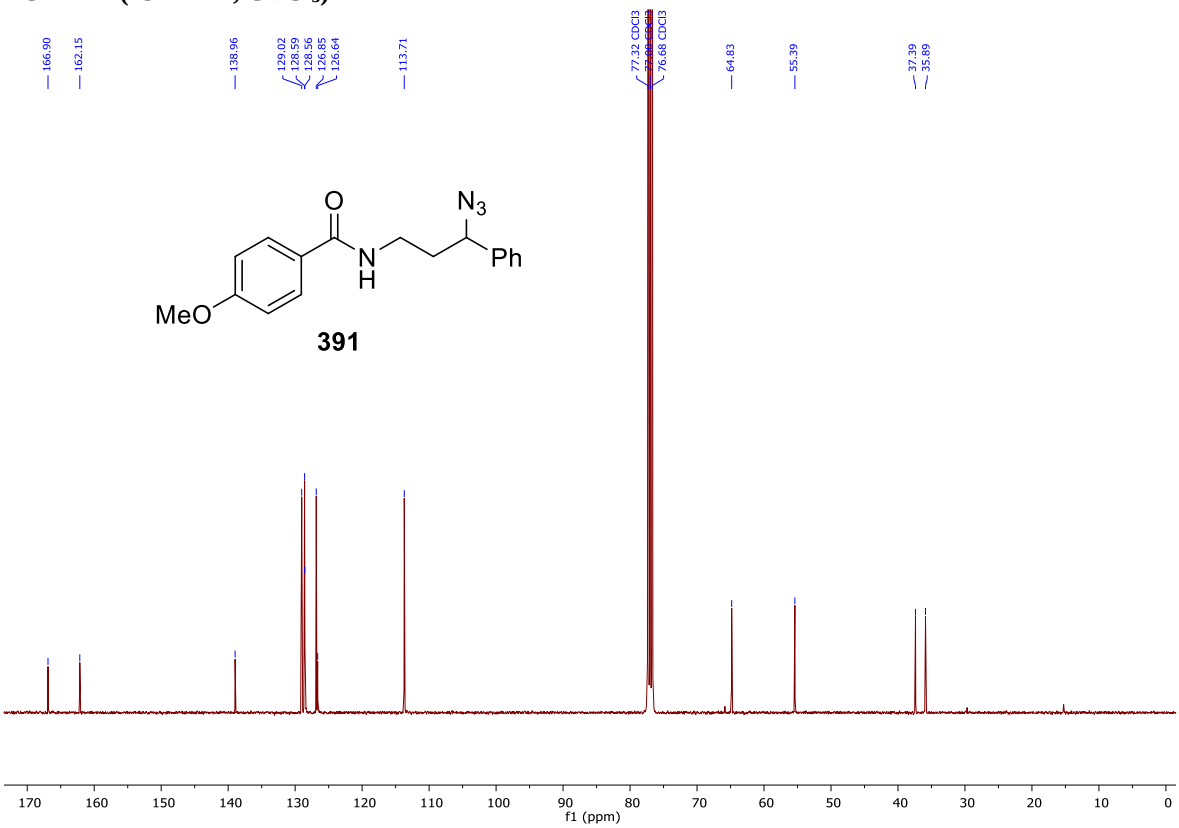
^{13}C-NMR (201 MHz, $CDCl_3$)



^{1}H-NMR (600 MHz, $CDCl_3$)

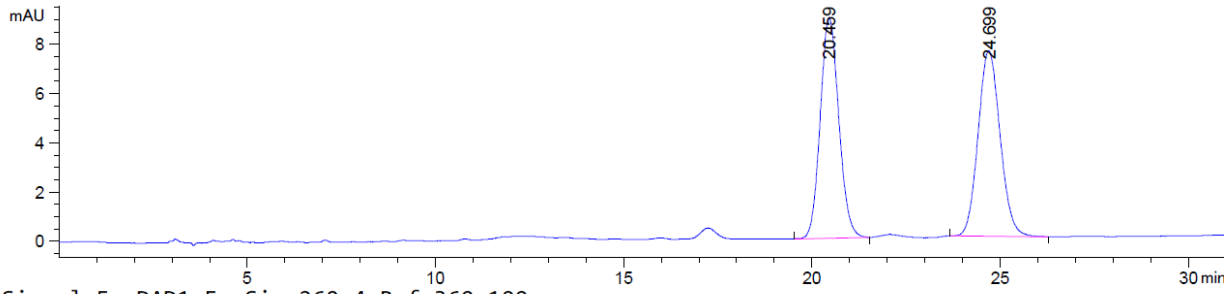


^{13}C-NMR (151 MHz, $CDCl_3$)



HPLC

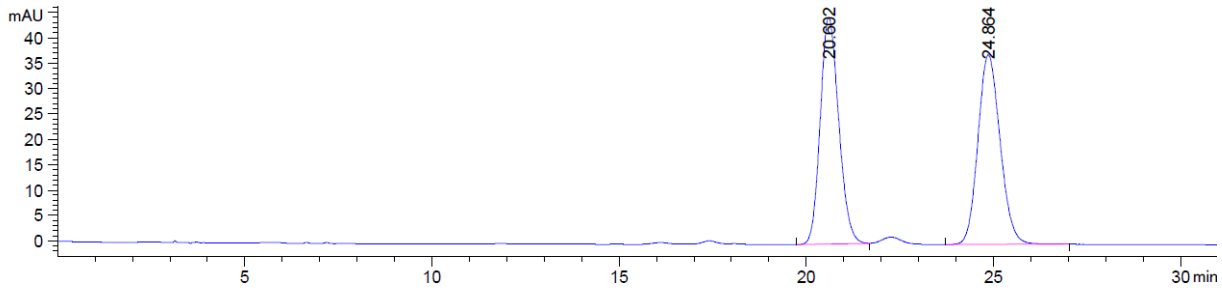
Racemic



Signal 5: DAD1 E, Sig=260,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.459	BB	0.5313	306.83521	8.96500	49.9731
2	24.699	BB	0.6316	307.16583	7.53440	50.0269

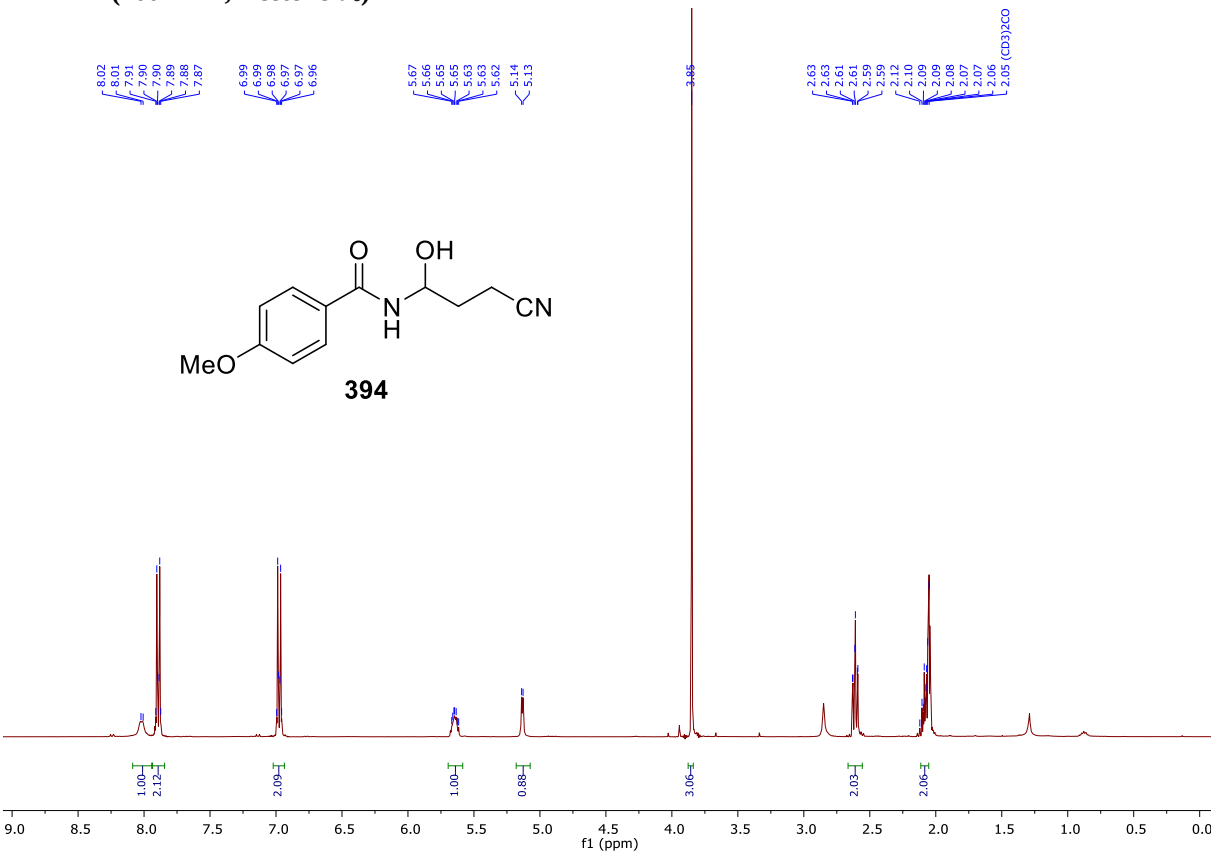
With CN-BOX



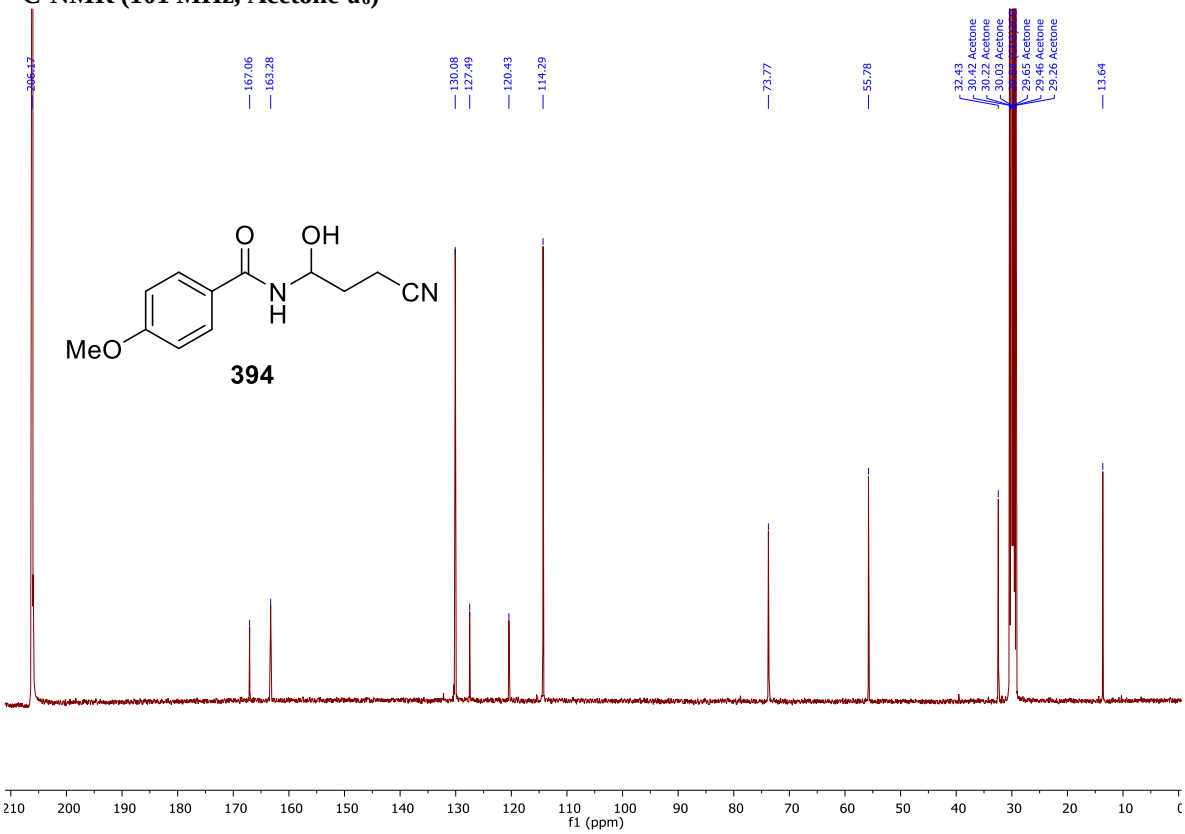
Signal 5: DAD1 E, Sig=260,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.602	BB	0.5300	1527.54224	44.55735	49.8299
2	24.864	BB	0.6410	1537.97205	37.30072	50.1701

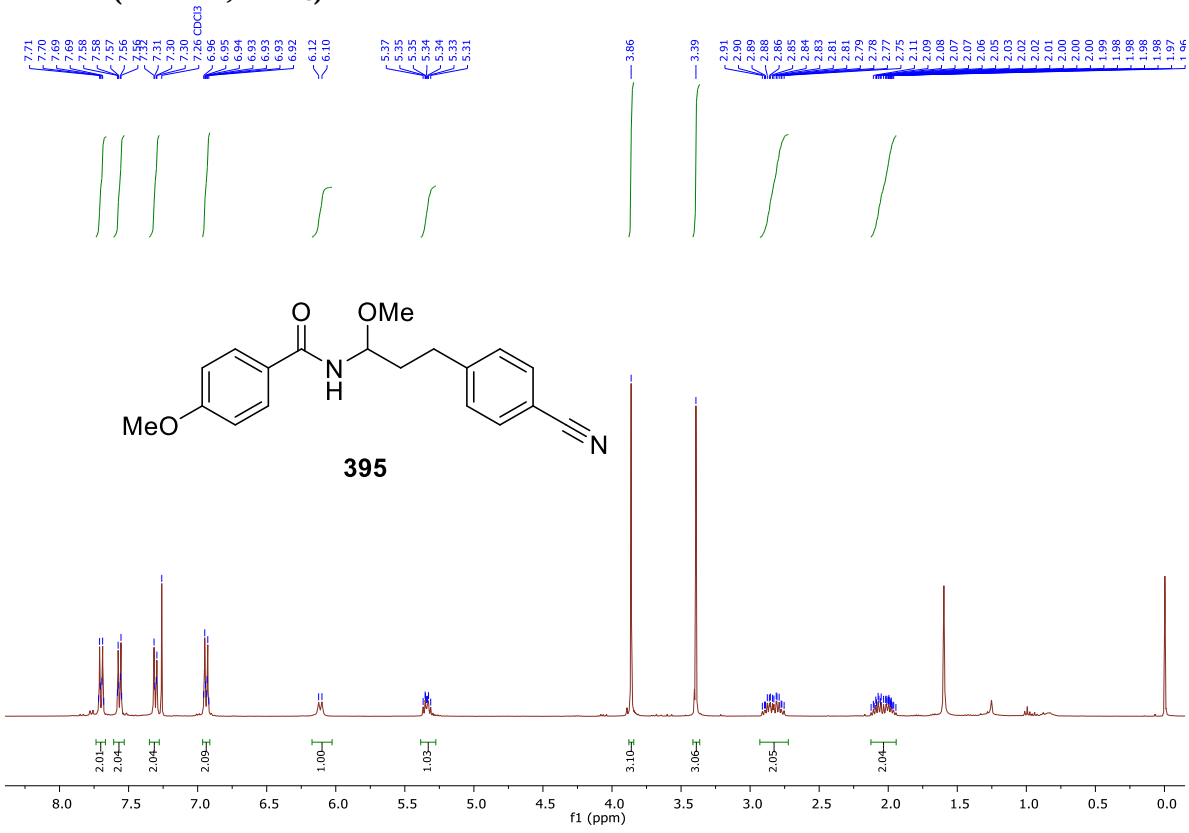
^{1}H-NMR (400 MHz, Acetone-d_6)



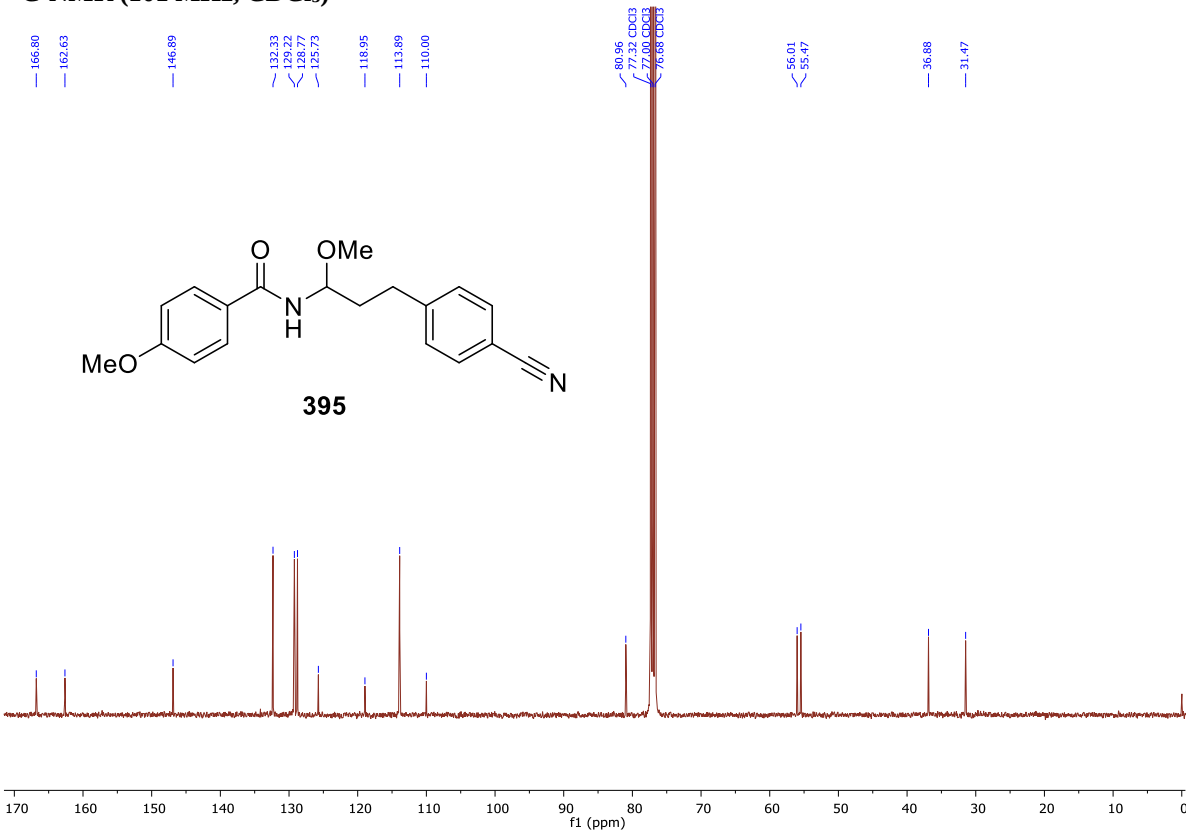
^{13}C-NMR (101 MHz, Acetone-d_6)



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

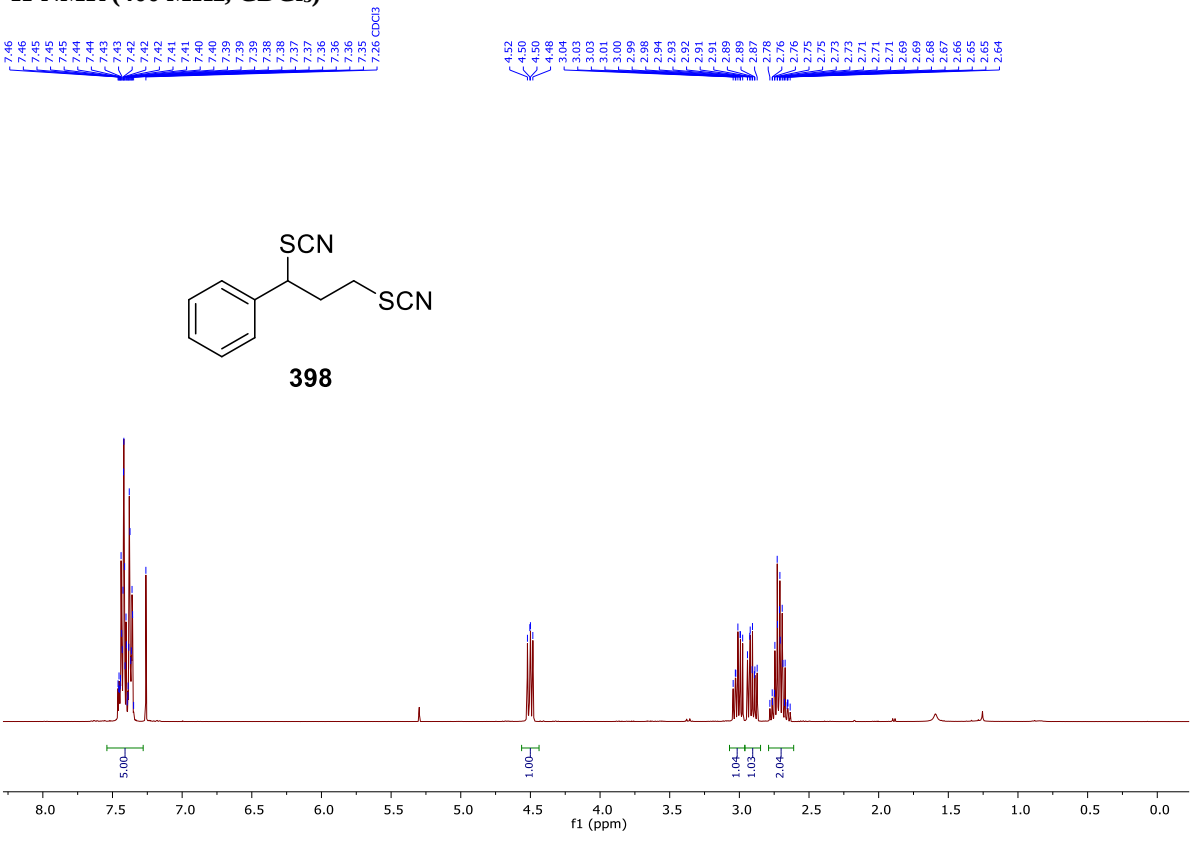


^{13}C-NMR (101 MHz, $CDCl_3$)



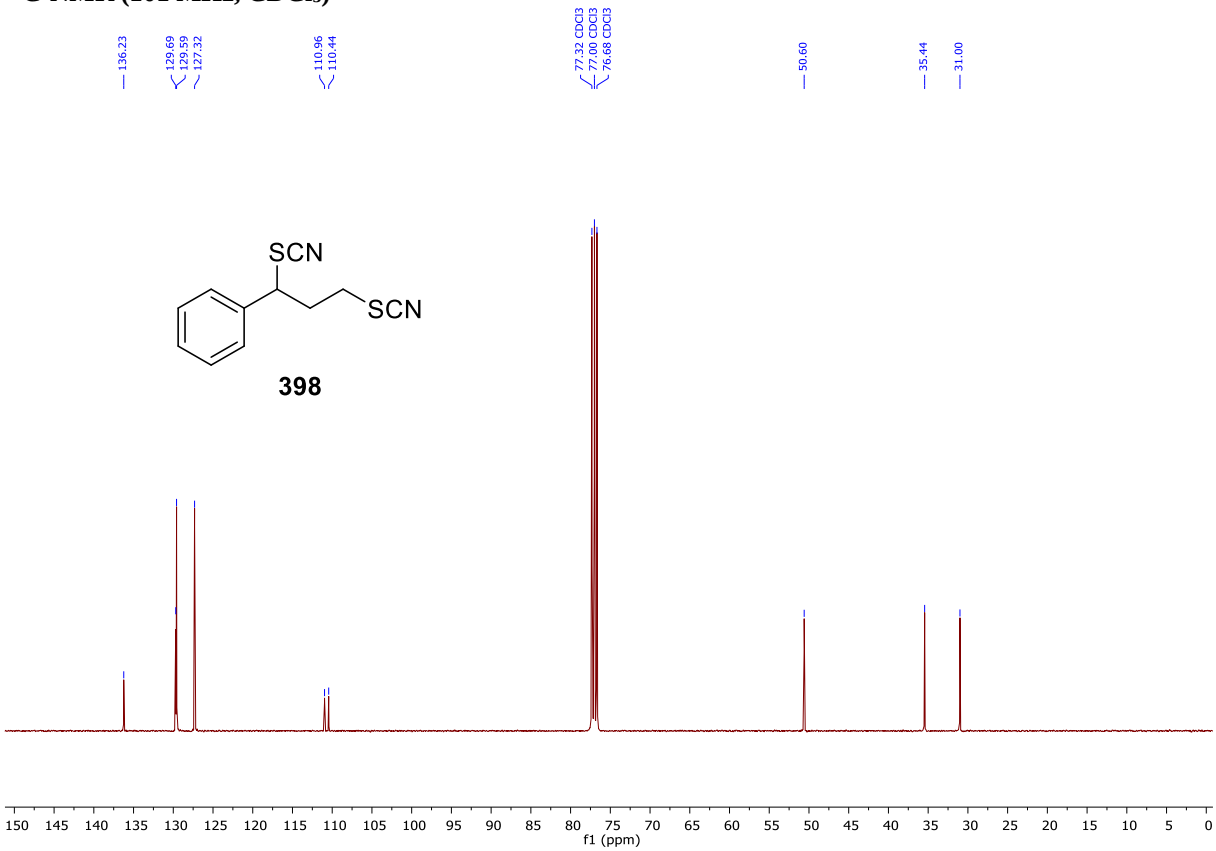
395

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



398

^{13}C-NMR (101 MHz, $CDCl_3$)



Curriculum Vitae

Mingming Wang

Citizenship	Chinese
Date of birth	29/06/1992
Place of birth	Jiangsu
Address	Ch. des Vignes-d'Argent, 1, 1004 Lausanne, Switzerland
Email	mingming.wang@epfl.ch
ORCID	0000-0003-3401-5633

Education and research experience

Since 09/2017	PhD student at École Polytechnique Fédérale de Lausanne (EPFL), Switzerland, under the supervision of Prof. Jérôme Waser.
	Research topic: developing reactions of strained rings.
11/2016 – 12/2016	Master exchange at Leibniz Institute for Catalysis. V. (LIKAT), Germany, under the supervision of Dr. Thomas Werner and Prof. Matthias Beller.
	Research topic: deuteration reaction.
09/2014 – 06/2017	Master's degree in Organic Chemistry at Shanghai Institute of Organic Chemistry (SIOC), China, under the supervision of Prof. Jin-Quan Yu.
	Research topic: copper mediated late-stage C-H functionalization.
09/2010 – 07/2014	Bachelor's degree in Chemistry at Yangzhou University, China

Teaching activities

EPFL Organic chemistry Laboratory – Teaching Assistant (2017-2021)

Preparative chemistry + Chemistry laboratory work (178 hours)

Advanced general chemistry (119 hours)

Project in molecular sciences (112 hours)

Organic chemistry courses and exams (169 hours)

In total: 578 hours

Language skills

Chinese	Native speaker
English	Full proficiency
French	Basic level

Technical skills

Radical chemistry, multi-step synthesis, retrosynthetic analysis, asymmetric catalysis, organometallic chemistry, photoredox catalysis, reaction optimization, glovebox technique, NMR analysis, solvent purification system, GC-MS, analytical chiral HPLC, software (ChemDraw, MestReNova, Endnote, Scifinder, Reaxys).

Award

2020	SCNAT-SCS Chemistry Travel Award
2020	Chinese Government Award for Outstanding Self Finance Students Abroad

Oral presentation

04/2021	ACS Spring 2021 (Virtual)
	"1,3-Difunctionalization of Aminocyclopropanes"

Poster presentation

08/2020	SCS Fall Meeting 2020 (Virtual)
	"Oxidative ring-opening fluorination of cyclopropylamides"
09/2019	SCS Fall Meeting 2019, Zurich
	"1,3-Difunctionalization of Aminocyclopropanes via Dielectrophilic Intermediates"
07/2019	21st European Symposium on Organic Chemistry, Vienna
	"1,3-Difunctionalization of Aminocyclopropanes via Dielectrophilic Intermediates"
09/2018	18th Ischia Advanced School of Organic Chemistry, Naples
	"Lewis Acid Catalyzed Enantioselective Desymmetrization of Donor-Acceptor Meso-Diaminocyclopropanes"

List of publications

- Wang, M.-M.; Nguyen, T. V. T.; Waser J. *J. Am. Chem. Soc.* **2021**, *143*, 11969:
  "Diamine synthesis via the Nitrogen-Directed Azidation of σ- and π- C-C Bonds"

- Wang, M.-M.; Waser J. *Angew. Chem. Int. Ed.* **2020**, *59*, 16420:
  "Oxidative Fluorination of Cyclopropylamides through Organic Photoredox Catalysis"

- Wang, M.-M.; Waser J. *Angew. Chem. Int. Ed.* **2019**, *58*, 13880:
  "1,3-Difunctionalization of Aminocyclopropanes via Dielectrophilic Intermediates"

- Wang, M.-M.; Jeon, S.; Waser J. *Org. Lett.* **2020**, *22*, 9123:
  "Synthesis of Thiochromans via [3+3] Annulation of Aminocyclopropanes with Thiophenols"

- Wang, M.-M.; Waser, J. Invited chapter for the Wiley book "Donor-Acceptor Cyclopropanes in Organic Synthesis", *under revision*:
  "Donor-Acceptor Cyclopropanes with an Amino Group as Donor"

- Perrotta, D.; Wang, M.-M.; Waser, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 5120:
  "Lewis Acid Catalyzed Enantioselective Desymmetrization of Donor-Acceptor *Meso*-Diaminocyclopropanes"

- Shang, M.#; Wang, M.-M.# (co-first author); St Denis, T. G.; Li, M-H.; Dai, H-X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2017**, *56*, 5317:
  "Cu-Mediated Late-Stage Functionalization of Heterocycle-Containing Molecules"

- Li, W.; Wang, M.-M.; Hu, Y.; Werner, T. *Org. Lett.* **2017**, *19*, 5768:
  "$B(C_6F_5)_3$-Catalyzed Regioselective Deuteration of Electron-Rich Aromatic and Heteroaromatic Compounds"

- Kong, W-.J.; Chen, X.; Wang, M.-M.; Dai, H-X.; Yu, J.-Q. *Org. Lett.* **2018**, *20*, 284:
  "Rapid Syntheses of Heteroaryl-Substituted Imidazo[1,5-a]indole and Pyrrolo[1,2-c]imidazole via Aerobic C2-H Functionalizations"