# Novel Synthetic Methods for the Preparation of Heterocycles and Alkynes via Carbenoids

**BY**

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**THESIS**

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This thesis is dedicated to my mother, Marie-Céline Ventadour, and my sister, Valérie Droin-Helan, without whom I would not have had the strength to go through this journey.

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Finally, I would like to thank the UIC department of chemistry staff, especially Ms. Silvia Solis and Ms. Rhonda Staudohar.

## CONTRIBUTION OF AUTHORS

Chapter 1 represents a series of my own experiments directed to determine whether Lewis acids could efficiently catalyze the fragmentation of tetrazoles into alkylidenecarbenes. Chapter 2 represents a published paper (Gulevich, A. V.; Helan, V.; Wink, D. J.; Gevorgyan, V. *Org. Lett.* **2013**, *15*, 956) for which I was the second author. I generated all tables and schemes in this chapter except Schemes 12 and 18 by Dr. Anton Gulevich. The X-ray analysis (Figures 4-6) was performed by Professor Donald Wink. I played a large role in the writing of the manuscript along with Dr. Gulevich and Professor Vladimir Gevorgyan. Chapter 3 represents a published paper (Helan, V.; Gulevich, A. V.; Gevorgyan, V. *Chem. Sci.* **2015**, *6*, 1928) for which I was the primary author and major contributor of the research. Dr. Gulevich defined the research question and assisted in the synthesis of copper acetylide for the mechanistic investigation (Scheme 26). Professor Gevorgyan and Dr. Gulevich contributed to the writing of the manuscript. Chapter 4 represents also a series of my own experiments directed to synthesize small molecule inhibitors of influenza A virus. I anticipate that both research projects described in chapters 1 and 4 will be continued after I leave and that these works will be ultimately published as part of a co-authored manuscript.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| Å | angstrom |
| Ar | aryl |
| Bn | benzyl |
| Boc | *tert*-butyloxycarbonyl protecting group |
| Bu | butyl |
| br. s. | broad singlet (NMR) |
| ºC | degree Celsius |
| Calcd | calculated |
| Cbz | carboxybenzyl protecting group |
| Cy | cyclohexyl |
| δ | chemical shifts (in ppm) downfield from tetramethylsilane (NMR) |
| d | doublet (NMR) |
| DBU | 1,8-diazabicyclo[5.4.0]undec–7–ene |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |
| DIC | diisopropylcarbodiimide |
| DMAP | 4-dimethylaminopyridine |
| DMF | *N*,*N*-dimethylformamide |
| dr | diastereomeric ratio |
| EI | Electron Impact Ionization |
| equiv | molar equivalent |
| Et | ethyl |

## LIST OF ABBREVIATIONS (continued)

| | |
|---|---|
| EtOAc | ethyl acetate |
| FBW | Fritsch-Buttenberg-Wiechell rearrangement |
| h | hour(s) |
| Hz | Hertz |
| HRMS | high-resolution mass spectrometry |
| $IC_{50}$ | half maximal inhibitory concentration |
| *J* | spin-spin coupling constant (NMR) |
| LDA | lithium diisopropylamide |
| logP | logarithm of partition coefficient |
| µ | micro |
| µW | microwave irradiation |
| m | multiplet (NMR) |
| M | molar, metal |
| [M]+ | molecular ion |
| Me | methyl |
| MeOH | methanol |
| mg | milligram |
| MHz | MegaHertz |
| mL | milliliter |
| mmol | millimole |
| m.p. | melting point |
| Ms | methanesulfonyl (mesyl) |

## LIST OF ABBREVIATIONS (continued)

| | |
|---|---|
| MS | molecular sieves |
| MsCl | methanesulfonyl chloride |
| NIS | *N*-iodosuccinimide |
| NMP | 1-methyl-2-pyrrolidinone |
| NMR | nuclear magnetic resonance |
| Nphth | phthalimide protecting group |
| N.R. | no reaction |
| Ph | phenyl |
| $pK_a$ | logarithmic acidity constant |
| ppm | parts per million |
| Rf | retention factor (TLC) |
| rt | room temperature |
| s | singlet (NMR) |
| STD | saturation transfer difference (NMR) |
| t | triplet (NMR) |
| T | temperature in degrees Celsius |
| *t*-Bu | *tert*-butyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| Tol | tolyl |

## LIST OF ABBREVIATIONS (continued)

| | |
|---|---|
| Ts | 4-toluenesulfonyl (tosyl) |
| TsOH | *p*-toluenesulfonic acid |
| WaterLOGSY | water ligand observed via gradient spectroscopy |

## SUMMARY

The first three chapters of this thesis concern the development of distinct synthetic methodologies, which exploit the reactivity of metal carbenoids and unencumbered alkylidenecarbenes for the preparation of *N*-fused heterocycles (imidazo[1,2-*a*]pyridines, indolizines) and alkynes, respectively. In the concluding chapter, the design and synthesis of a family of small molecules that inhibit the fusion of influenza A virus with mammalian cells is described.

The Lewis acid-mediated dehydrative fragmentation of 5-hydroxyalkyl-1*H*-tetrazole as a means to generate alkylidenecarbenes has been investigated. Previous studies showed that treatment of these substrates with a range of carbodiimindes or high temperatures leads to the extrusion of two molar equivalents of dinitrogen and the concomitant formation of a reactive alkylidenecarbene. We screened various Lewis acids in order to find mild, catalytic conditions for the formation of alkylidenecarbenes from tetrazoles. These carbenes are also known to spontaneously undergo various transformations including 1,2-shifts to form alkynes. Optimization of the reaction conditions revealed that $CuCl/Cu(OTf)_2$ efficiently catalyzed the fragmentation of the tetrazole substrates and the corresponding alkyne was formed almost quantitatively.

Three-component coupling (3-CC) reactions represent an attractive opportunity to develop atom-economical transformations, which generate molecules with a high degree of complexity. A Lewis acid-catalyzed 3-CC reaction employing 2-aminoazines, aromatic aldehydes, and diazo-compounds was developed; β-amino-α-diazocarbonyl compounds were produced in moderate to good yields even though the imine generated by addition of the 2-aminoazine to the aldehyde did not bear an electron-withdrawing group. Moreover, the pyridine

group on the imine acted as a proton shuttle leading to the conservation of the diazo group in the final products. These diazo-compounds were found to be valuable building blocks for the preparation of β-amino acid derivatives, imidazo[1,2-*a*]pyridines, and pyrido[1,2-*a*]pyrimidine-4-ones.

Optimization studies on the transannulation reaction of pyridotriazoles and terminal alkynes to generate indolizines were also conducted in order to replace the rhodium catalyst commonly employed in the reaction of 1,2,3-triazoles with a more abundant and less expensive catalyst. Through screening of the reaction conditions, it was found that $Cu(MeCN)_4PF_6$ efficiently catalyzed the transannulation reaction. Aerobic conditions were now tolerated and a broader reaction scope of pyridotriazoles and terminal alkynes was developed.

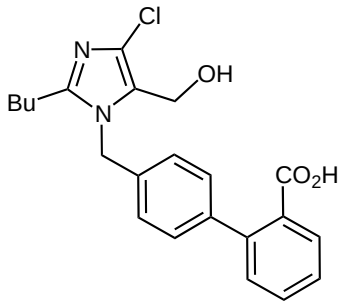
In a collaborative effort with the laboratories of Caffrey and Lavie at UIC, a novel family of small molecule inhibitors of H5 HA influenza A viruses have been developed. While MBX2546 was previously characterized as fusion inhibitor of H5 HA, additional crystallographic data were needed to confirm the binding to the viral protein. We therefore designed analogs of MBX2546 to improve the solubility of the H5 HA complex with the inhibitor in the X-ray crystallography experiments. Two batches of analogs were produced in good yields following a 4-step synthetic route. Preliminary results showed that the analog bearing the chlorine substituents could bind the same binding site as MBX2546 but with lower affinity.

# CHAPTER ONE: DEHYDRATIVE FRAGMENTATION OF 5-HYDROXYALKYL-1*H*-TETRAZOLES INTO ALKYNES

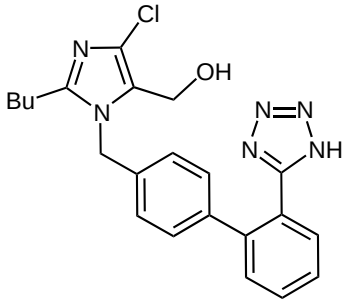
## 1 - INTRODUCTION

### 1.1 Tetrazoles as Isosteres of Carboxylic Acids

In the past four decades, 5-substituted-1*H*-tetrazoles have gathered great attention in the pharmaceutical industry because they act as non-classical isosteres of carboxylic acids;[1] both functional groups show similar ranges of acidity ($pK_a$ = 4.2–4.9) with the ionized form predominant at physiological pH (7.4). In addition, compounds bearing tetrazolyl groups exhibit greater lipophilicity than their carboxylic acid analogs, which represents an important advantage when designing drugs (Figure 1). Moreover, switching a carboxylic acid with a tetrazole in a drug generally leads to slower biological, metabolic degradation, which provides drugs with longer half-lives.




**1**

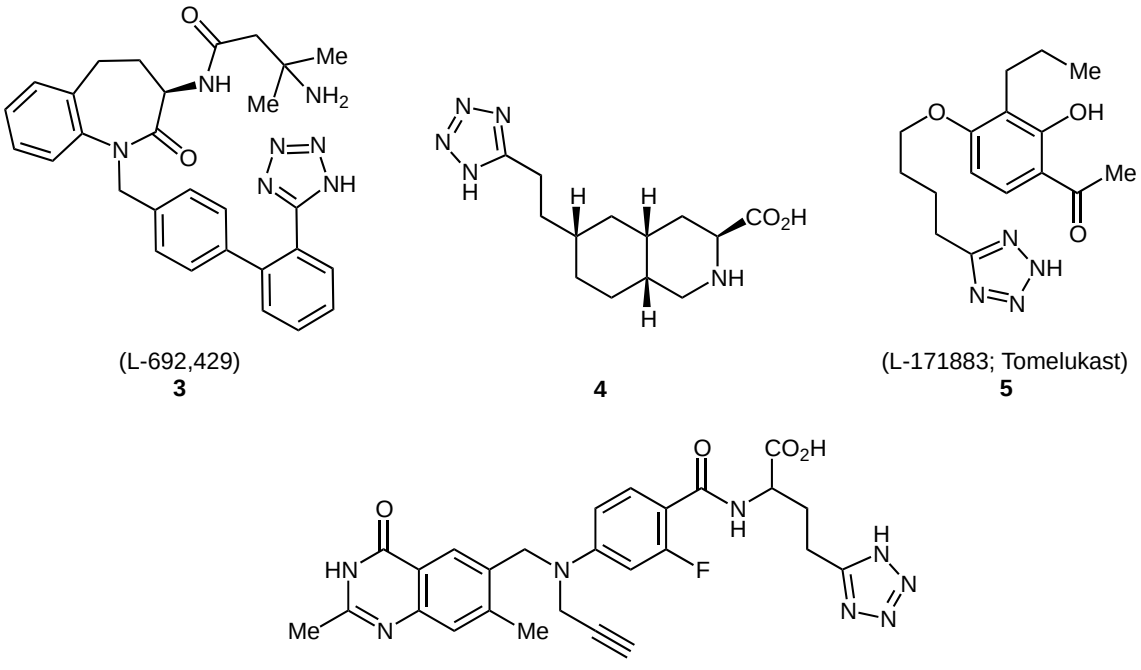



(Losartan)
**2**

| | |
|---|---|
| $pK_a$ = 4.5 | $pK_a$ = 5.0 |
| $IC_{50}$ = 0.23 μM | $IC_{50}$ = 0.02 μM |
| logP = 1.2 | logP = 4.5 |

**Figure 1.** Analytical Properties of Carboxylic Acid **1** and its Tetrazole Isostere **2**.

Arguably, the most successful example of such isosterism was the discovery of Losartan (**2**) by DuPont researchers in 1994. Compound **2** is an angiotensin II receptor antagonist used in the treatment of hypertension. Substitution of the carboxylic acid by the tetrazole group revealed a dramatic increase in oral potency ($IC_{50}$ = 0.02 μM) and lipophilicity (logP = 4.5) (Figure 1).[1a] Subsequently, numerous analogs of Losartan have been synthesized and studied by various research groups.[1] Other examples in medicinal chemistry include both aryl and aliphatic 5-substituted-1*H*-tetrazoles (Figure 2). These molecules were tested as leads in clinical trials for various targets, e.g. peptidomimetic of growth hormone (GHRP-6) (**3**), glutamate receptor antagonist (**4**), cysteinyl leukotriene $D_4$ ($LTD_4$) receptor antagonist (**5**) or thymidylate synthase inhibitor (**6**).[2] However, these compounds did not reach the market due to negative side effects,[3] poor solubility or because additional studies were needed.



(L-692,429)
**3**

**4**

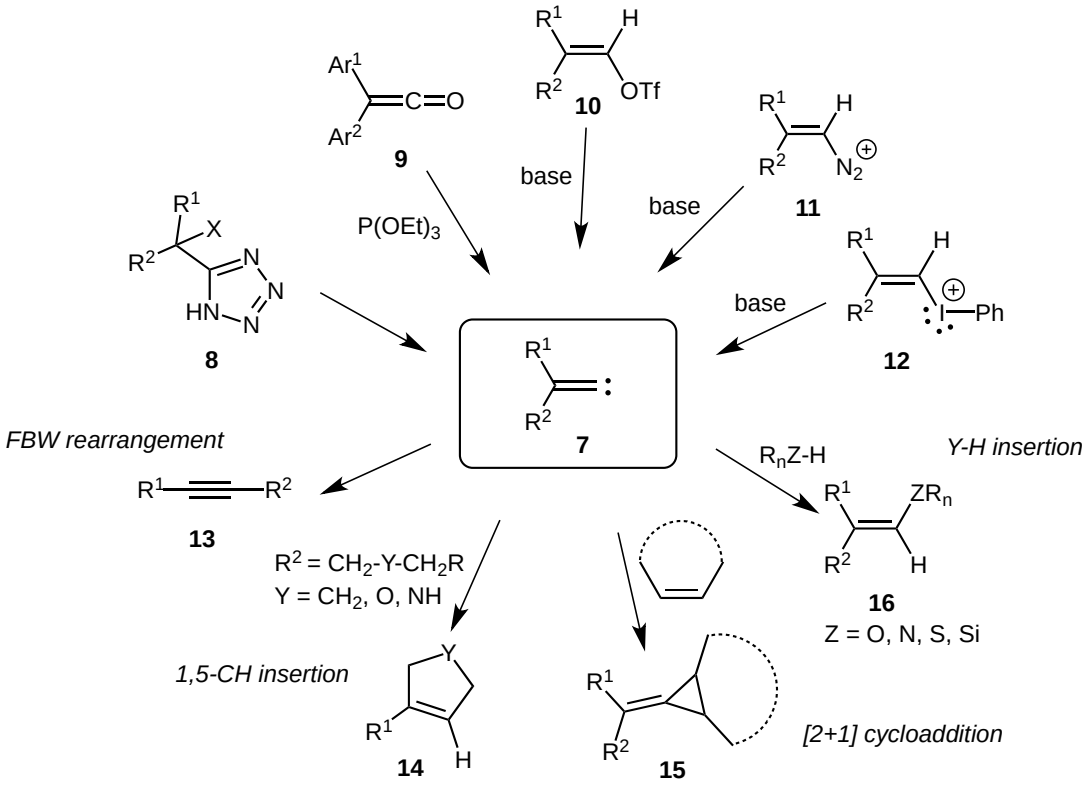
(L-171883; Tomelukast)
**5**

(ZD9331)
**6**

**Figure 2.** Examples of 5-Substituted-1*H*-tetrazoles Evaluated in Human Clinical Trials

## 1.2 Generation and Reactivity of Alkylidenecarbenes

In addition to the aforementioned pharmaceutical properties, 5-substituted-1*H*-tetrazoles are also reported as precursors of alkylidenecarbenes **7**.[4] Alkylidenecarbenes are unsaturated singlet carbenes with the divalent carbon bound to an $sp^2$ hybridized carbon atom. Compared to saturated carbenes, intensive investigations of the properties and reactivity of unsaturated carbenes started in the mid-1970s with the works of Apeloig and Stang.[5] Alkylidenecarbenes **7** can be generated from a variety of precursors, including, ketenes **9**, alkenyl triflates **10**, diazoalkenes **11** or alkenyl iodonium salts **12**, upon pyrolysis or reaction with a strong base (RLi, ROLi, *t*BuOK) (Scheme 1).[4b]



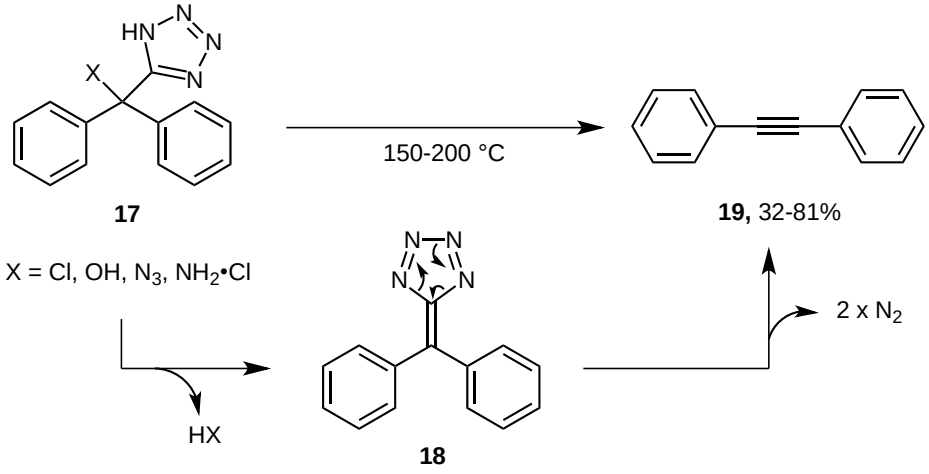

**Scheme 1.** Overview of Generation and Applications of Alkylidenecarbenes.

Although alkylidenecarbenes are too unstable to be isolated, computational and deuterium-labeling studies have confirmed the identity of this type of carbene as an intermediate in various transformations (Scheme 1).[5f,6] Indeed, alkylidenecarbenes can undergo Fritsch-Buttenberg-Wiechell (FBW) rearrangement to produce alkynes **13**,[4b,6a,7] and intramolecular cyclization *via* 1,5-CH insertion to yield cyclopentenes, dihydrofurans or pyrrolines **14**.[8] The latter transformation has been applied in the total syntheses of various natural products.[9] Moreover, like saturated carbenes, alkylidenecarbenes can also react with alkenes to form cyclopropyl adducts **15**,[4b,5a,5e,10] and insert into X-H bonds (X = O, N, Si, S) by reaction with alcohols,[11] amines,[12] silanes[4b] or thiols.[5d] Studies have demonstrated that the outcome of the reaction of alkylidenecarbenes depends both on the reaction conditions and on the type of substituents on the *beta* carbon. Thus, alkylidenecarbenes bearing long alkyl chain preferentially undergo 1,5-CH bond insertion instead of FBW rearrangement, while the opposite is observed when at least one aryl, alkenyl group or hydrogen atom is present at the *beta* position.[4b] However, no strong and general conclusion has been drawn on the migratory aptitude of substituents in the FBW rearrangement of alkylidenecarbenes.[4b,13]

For this project, we were particularly interested in the fragmentation of tetrazoles **8** into alkylidenecarbenes **7** and the subsequent Fritsch-Buttenberg-Wiechell (FBW) rearrangement of **7** to produce alkynes **13**. While many synthetic methods to produce alkynes have been reported over the past century,[14] the drive for mild, sustainable, and atom economical methodologies made tetrazoles an attractive substrate for this reaction.

### 1.3 Fragmentation of 5-Hydroxymethyl-1*H*-tetrazoles

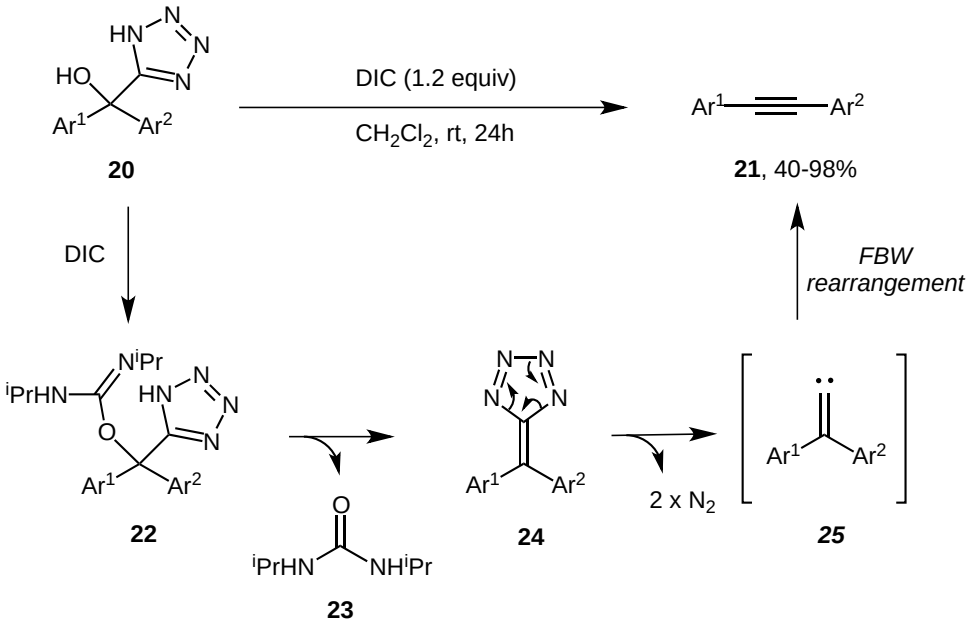
In 1966, Behringer and Matner were the first to observe that the pyrolysis of various 5-methyl-1*H*-tetrazoles **17** provided both internal and terminal alkynes in low to good yields (32-81%) (Scheme 2).[4a] They hypothesized that upon elimination of a leaving group on the *beta* carbon of the tetrazole (X = Cl, OH, $N_3$, $NH_2$•HCl), tetraazafulvene 18 would be generated in situ. It was proposed that after extrusion of two molecules of dinitrogen, followed by 1,2-shift rearrangement, the corresponding alkyne 19 would be formed. However, temperatures greater than 150 ºC were required for the reaction to occur, the scope was limited to a few examples, and no rearrangement was observed for cyclic disubstituted tetrazoles. It was therefore important to develop a method to access alkynes from 5-substituted-1H-tetrazoles 8 under mild conditions, i.e. under low temperatures and in the absence of strong bases or acids.




**Scheme 2.** Pyrolysis of 5-Substituted-1*H*-tetrazoles **17**

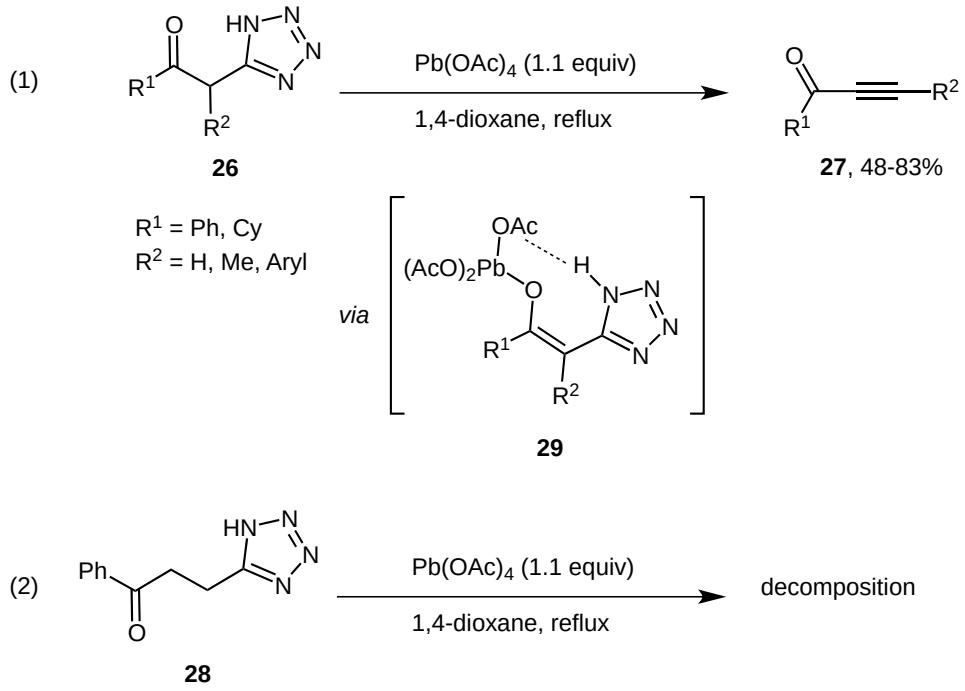
Surprisingly, very few reports of such transformation of tetrazoles have been since published in the literature. In 2012, Wardrop and Komenda reported an elegant dehydrative

fragmentation of 5-hydroxyalkyl-1*H*-tetrazoles **20** into internal alkynes **21** under mild conditions (Scheme 3).[15] The reaction occurred at room temperature in presence of a stoichiometric amount of carbodiimide. The scope of the reaction showed that both symmetrical and unsymmetrical alkynes were obtained in good to excellent yields. Based on Behringer's previous work, the proposed mechanism (Scheme 3) starts with nucleophilic attack of the carbodiimide by the hydroxyl group of tetrazole **20**. Upon elimination of urea **23**, tetraazafulvene **24** can be generated. Then, the extrusion of molecular nitrogen would lead to the formation of alkylidenecarbene intermediate **25**, which would undergo FBW rearrangement to yield the corresponding alkyne **21**. This methodology was then applied to the total synthesis of biologically active Combretastatin A4.




**Scheme 3.** DIC-Mediated Fragmentation of 5-Hydroxyalkyl-1*H*-tetrazoles **20**

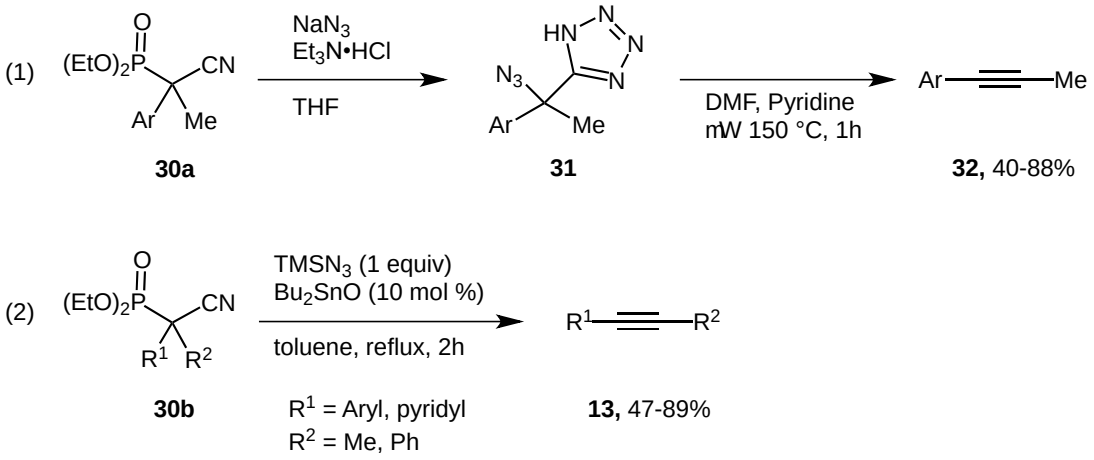
Encouraged by these results, we decided to further investigate the development of mild conditions for the dehydrative fragmentation of tetrazole **20** into **21**. We turned our attention to the employment of Lewis acid as a metal catalyst to trigger the fragmentation/FBW rearrangement under neutral conditions. In 2001, Fetter and co-workers showed that treatment of tetrazoylacetate **26** with a stoechiometric amount of lead tetraacetate ($Pb(OAc)_4$) produced ynones **27** in moderate to good yields (Scheme 4, eq.1).[16] The presence of an alkylidenecarbene as a reaction intermediate was confirmed by trapping of the carbene with acetic acid. Interestingly, homologated ketone **28** underwent decomposition (Scheme 4, eq. 2) and *N*-substituted tetrazole failed to react, suggesting Lewis acid chelates **29** as a reaction intermediate. However, this method is limited to substrate **26** with a benzoyl group at the beta position of the tetrazole.




**Scheme 4.** $Pb(OAc)_4$-Mediated Fragmentation of Tetrazolylacetate **26**

Finally, while we were conducting this project, Yoneyama and co-workers published a fragmentation of 5-substituted-1*H*-tetrazoles **31** (**8** with X= $N_3$) performed with microwave irradiation.[17] The prop-1-yn-1-ylbenzene derivatives **32** were obtained in moderate to high yields (Scheme 5, eq. 1). The tetrazole was initially generated by reaction of a cyanohydrin-*O*-phosphate **30a** with $NaN_3$. Moreover, when a catalytic amount of $Bu_2SnO$ was added to the reaction mixture of cyanophosphate **30b** and $TMSN_3$ (Wittenberger conditions[18]) alkyne **13** was directly obtained in one step (Scheme 5, eq. 2). This second method expanded the scope to various heterocyclic aryl substituents and one example of cyclic alkyne was presented.

Therefore, we decided to develop a mild, general, Lewis acid-catalyzed fragmentation of 5-hydroxyalkyl-1*H*-tetrazoles **20** into alkylidenecarbenes to produce alkynes.



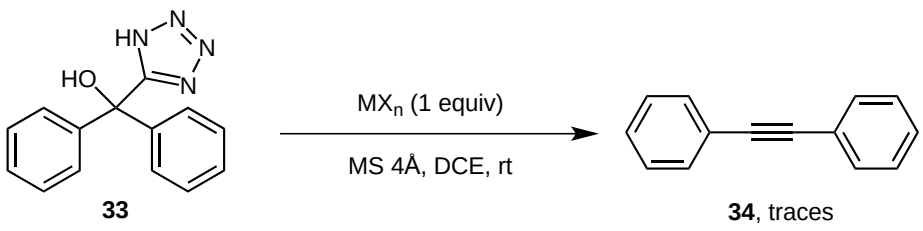

**Scheme 5.** Fragmentation of Tetrazole **31** under microwave irradiation or with $Bu_2SnO$

# 2 - OPTIMIZATION OF LEWIS ACID MEDIATED FRAGMENTATION OF 5-HYDROXYALKYL-1*H*-TETRAZOLES

## 2.1 Reaction Conditions Screening

Diphenyl(1*H*-tetrazol-5-yl)methanol **33**, readily prepared in two steps from benzophenone, was chosen to conduct the optimization of the reaction. Also, diphenylacetylene (**34**) produced after fragmentation of the tetrazole **33** and subsequent FBW rearrangement can easily be observed with gas-liquid chromatography (GC). However, we found that due to the high temperature of the GC column the tetrazole starting material **33** underwent spontaneous fragmentation into the alkyne and both compounds would appear under a single peak on the GC spectrum. So, it was necessary to quench the reaction mixtures with a basic solution and then analyze only the organic phase to obtain a GC yield of alkyne **34**.

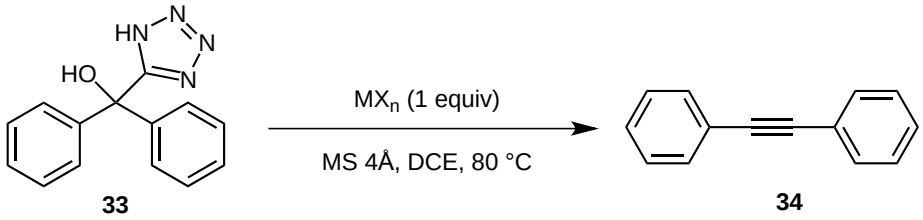
We started the investigation of Lewis acid-mediated dehydrative fragmentation of 5-hydroxyalkyl-1*H*-tetrazoles by screening various Lewis acids ($CuBr_2$, CuCl, CuI, $ZnBr_2$, $ZnI_2$, $Sc(OTf)_3$, $Ti(OBu)_4$, $BF_3{\bullet}Et_2O$, $FeCl_3$, $AgOCOCF_3$) at room temperature. Unfortunately, only traces of the desired diphenylacetylene **34** were obtained (Scheme 6), which confirmed that higher temperatures were necessary for the elimination of the leaving group, in this case water, in presence of a Lewis acid.




**Scheme 6.** Preliminary Trials at Room Temperature of Lewis Acid-Fragmentation of **33**

We then examined the reaction raised at 80 ºC, but we found that the reaction remained inefficient in the presence of iron, aluminum, titanium, and silver Lewis acids (Table 1, entries 1-5). Use of $BF_3$•$Et_2O$ (entry 6) and $Sc(OTf)_3$ (entry 7) led to the formation of **34** in moderate yields. We then turned our attention to copper Lewis acids. While most copper compounds tested failed to mediate the fragmentation of the tetrazole (entries 8-12), we were delighted to observe that $Cu(OTf)_2$ (entry 13) and $(MeCN)_4CuBF_4$ (entry 14) provided the alkyne in moderate to good yields. Increasing the reaction time to six hours and avoiding the use of 4Å molecules sieves led to a better yield (entry 15). We also tested the influence of carbodiimide (entry 16) and urea (entry 17) in presence $Cu(OTf)_2$ but the yield decreased. Finally, a combination of Cu(I)/Cu((II) Lewis acids efficiently mediated the reaction (entry 18). Also, it should be noted that small amounts of benzophenone **36** (1-8%) were also observed in the reaction mixtures. This can be rationalized by a retro-addition reaction on **33** (Scheme 7).

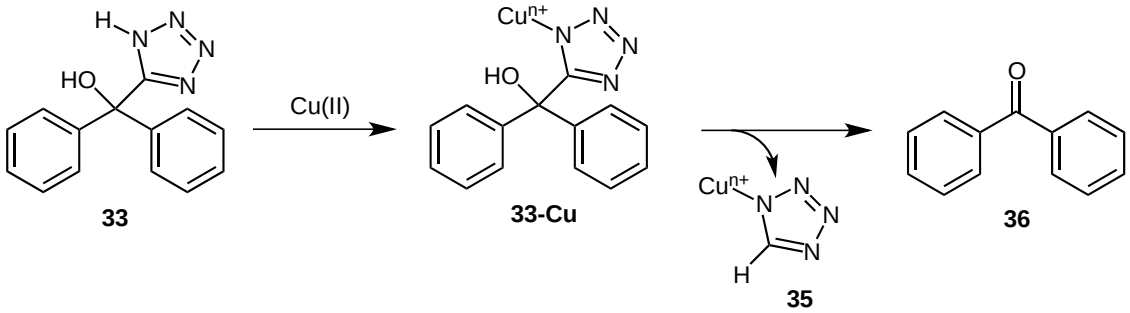
**Table 1.** Screening of Lewis Acids for the Fragmentation Reaction[a]




**33** **34**

| Entry | Lewis Acid | Time (h) | Yield (%) of **34**[b] |
|---|---|---|---|
| 1 | $Fe(OTf)_2$ | 3 | 7 |
| 2 | $FeCl_3$ | 3 | 4 |
| 3 | $AlCl_3$ | 3 | 5 |
| 4 | $Ti(OBu)_4$ | 3 | 2 |
| 5 | $AgOCOCF_3$ | 3 | 11 |
| 6 | $BF_3$•$OEt_2$ | 3 | 21 |
| 7 | $Sc(OTf)_3$ | 3 | 27 |
| 8 | $CuCl_2$ | 3 | 3 |
| 9 | CuCl | 3 | 3 |
| 10 | CuI | 3 | 3 |
| 11 | CuOAc | 3 | 4 |
| 12 | $(MeCN)_4CuOTf$ | 3 | 11 |
| 13 | $Cu(OTf)_2$ | 3 | 36 |
| 14[c] | $(MeCN)_4CuBF_4$ | 6 | 54 |
| 15[c] | $Cu(OTf)_2$ | 6 | 50 |
| 16[c,d] | $Cu(OTf)_2$ /urea | 6 | 35 |
| 17[c] | $Cu(OTf)_2$ /DIC | 6 | 18 |
| 18[c,d] | $Cu(OTf)_2$ /CuCl | 6 | 62 |

[a]Conditions: tetrazole (1 equiv.), Lewis acid (1 equiv.), MS 4Å (200 mg/mmol), DCE (0.2 M) in a vial under nitrogen atmosphere. [b]GC yields. [c]The reaction was run without 4Å molecular sieves. [d]$Cu(OTf)_2$ (0.5 equiv) and additive (0.5 equiv) were added.

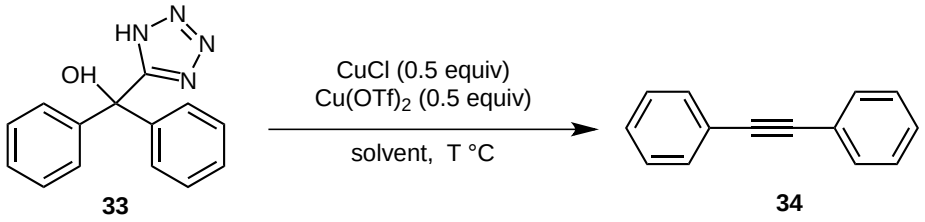



**33** **33-Cu** **35** **36**

**Scheme 7.** Rationalization of the Formation of Benzophenone **36**

We now continued to optimize the reaction conditions by screening the reaction time, temperature and solvent. We were pleased to observe that after 15 h, alkyne **34** was obtained in excellent yield (90%) (Table 2, entry 2). Decreasing the temperature was inefficient (entries 3-4) and other solvents, such as DCM, NMP and toluene led to poor or moderate yields.

**Table 2.** Optimization of Reaction Time, Temperature and Solvent[a]




**33** **34**

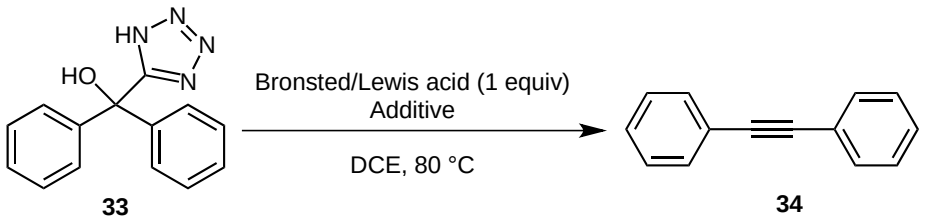
| Entry | Solvent | Reaction time (h) | T (ºC) | Yield (%) of **34**[b] |
|---|---|---|---|---|
| 1 | DCE | 6 | 80 | 62 |
| 2 | DCE | 15 | 80 | 95 (90)[c] |
| 3 | DCE | 15 | 60 | 57 |
| 4 | DCE | 15 | rt | 23 |
| 5 | DCM | 15 | rt | 5 |
| 6 | NMP | 15 | 80 | 16 |
| 7 | toluene | 5 | 80 | 38 |

[a]Conditions: tetrazole (1 equiv.), CuCl (0.5 equiv.), $Cu(OTf)_2$ (0.5 equiv.), DCE (0.2 M) in a vial under nitrogen atmosphere. [b]GC yields. [c]Isolated yield.

Finally, to better understand the catalytic system identified for this transformation (CuCl/ $Cu(OTf)_2$), we decided to verify if $Cu(OTf)_2$ was the true catalyst or whether triflic acid (TfOH), formed *in situ*, was involved. We observed that the reaction was completely inhibited when the proton scavenger (2,4,6-tri-tert-butylpyrimidine, TTBP) was added (entries 1-3).[19] This observation suggested that triflic acid may play an important role in the fragmentation reaction

and use of TfOH alone produced the alkyne **34** in good yields (entries 4-6). However, a combination of CuCl and TfOH was less efficient than CuCl/$Cu(OTf)_2$ (entry 7).

**Table 3.** Comparison of Brønsted and Lewis Acids[a]




**33** **34**

| Entry | Brønsted / Lewis Acid | Additive | Time (h) | Yield (%) of **34**[b] |
|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ | none | 5 | 50 |
| 2[c] | $Cu(OTf)_2$ | TTBP | 5 | 3 |
| 3[c] | $Cu(OTf)_2$ | TTBP + MS 4Å | 5 | 1 |
| 4 | TfOH | MS 4Å | 9 | 53 |
| 5 | TfOH | none | 15 | 55 |
| 6[d] | TfOH | none | 15 | 47 |
| 7[e] | CuCl/TfOH | none | 15 | 52 |

[a]Conditions: tetrazole (1 equiv.), Brønsted/Lewis acid (1 equiv.), MS 4Å (200 mg/mmol), DCE (0.2 M) in a vial under nitrogen atmosphere. [b]GC yields. [c]One equivalent of TTBP was added. [d]0.5 equivalent of TfOH were added. [e]CuCl (0.5 equiv.) and TfOH (0.5 equiv) were used.

## 2.2 Summary

In conclusion, we developed a new Lewis acid mediated dehydrative fragmentation of 5-hydroxyalkyl-1*H*-tetrazole towards alkynes. Based on previous works, it is hypothesized that upon elimination of water a tetraazafulvene intermediate is formed. After extrusion of molecular nitrogen, the alkylidenecarbene generated undergoes FBW rearrangement into the alkyne. We were pleased to find that a combination of copper(I) and copper(II) Lewis acids (CuCl/$Cu(OTf)_2$) led to the formation of diphenylacetylene in excellent yield. While triflic acid was found to

mediate the reaction it was not as efficient as $Cu(OTf)_2$ in presence of CuCl. With the optimized conditions in hand, we will continue and develop the scope of this reaction.

# 3 - EXPERIMENTAL SECTION

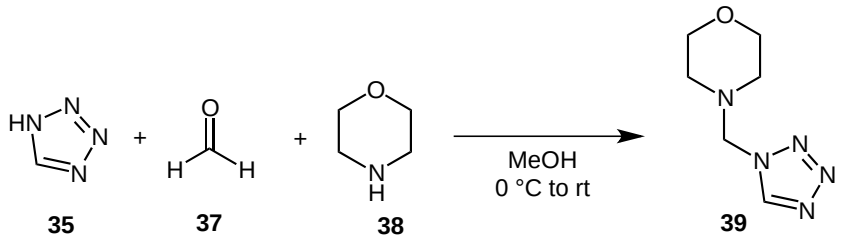
## 3.1 General Information

GC analysis was performed on a GC-2010 Plus SHIMAZU. Column chromatography was carried out employing Silicycle Silica-P flash silica gel (40-63 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz) or DPX-400 (400 MHz) instrument. Anhydrous solvents purchased from Sigma-Aldrich were additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system and/or stored over calcium hydride or MS 4Å. MS 4Å were purchased from Sigma Aldrich, ground and activated under reduced pressure (200 ºC /1 torr, 12 h). All manipulations with transition metal catalysts were conducted in oven-dried glassware under inert atmosphere inside the glovebox. The starting materials were purchased from Sigma Aldrich, Acros or Oakwood Chemicals.

## 3.2 Synthesis of 5-Hydroxyalkyl-1*H*-tetrazoles Starting Material

The following 2-step synthesis of tetrazole **33** was developed in our lab.[20]

**Synthesis of 4-((1*H*-Tetrazol-1-yl)methyl)morpholine (39)**



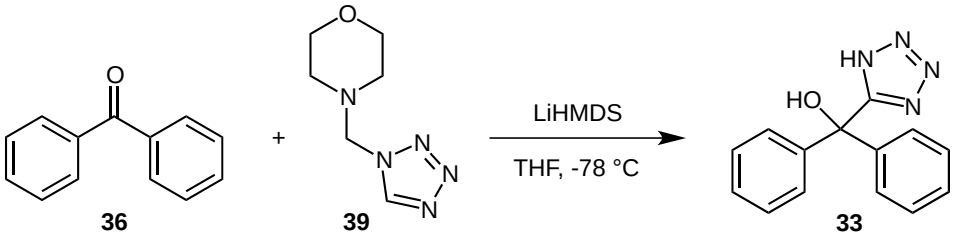

**35** **37** **38** **39**

*Operation Conducted Behind Safety Screen!*

To a cold (0 °C) stirred solution of 1H-tetrazole **35** (2.00 g, 28.5 mmol) in methanol (20 mL) was added morpholine **38** (2.74 mL, 31.4 mmol, 1.1 equiv) and the mixture stirred for 15

min. An aqueous solution of formaldehyde **37** (2.8 mL, 37%, 34 mmol, 1.2 equiv) was added dropwise and the mixture stirred for 12 h at room temperature. The reaction mixture was then concentrated under reduced pressure behind a safety screen to provide a residue, which was recrystallized from mixture of hexanes and $CH_2Cl_2$ (1:2) to give **39** (4.75 g, 28.1 mmol, 99%): white, crystalline solid; mp 81-82 °C (lit. mp 80.0-82.0 °C); Two tautomers (A & B): $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 8.70 (s, 0.2H from B), 8.52 (s, 0.9H from A), 5.49 (s, 2H from A), 5.29 (s, 0.5H from B), 3.67 (t, J = 4.4 Hz, 5H), 2.62 (t, J = 4.8 Hz, 4 H from A), 2.58 (t, J = 4.4 Hz, 1.0 H from B). Two tautomers: $^{13}$C NMR (100 MHz, $CDCl_3$) δ ppm 153.0 (A), 143.2 (B), 74.4 (A), 70.2 (B), 67.0 (A), 66.8 (B), 50.1. HMRS-ESI calcd for $C_6H_1N_5O$: 169.0964, found 169.0965.

**Synthesis of Diphenyl(1*H*-tetrazol-5-yl)methanol (33)**




**36** **39** **33**

To a flame-dried flask was added the tetrazole **39** (1.93 g, 11 mmol, 2 equiv) and benzophenone **36** (1 g, 5.5 mmol, 1 equiv) dissolved in anhydrous THF (20 mL) and cooled to -78 °C. Dropwise, LiHMDS (1.93 g, 11.5 mmol, 2.1 equiv) dissolved in THF (7.5 mL) was added by syringe and the solution was kept at -78 °C for 2 hours before being allowed to reach room temperature overnight (~14 hours). Upon completion, the reaction was concentrated in vacuo. The white residue was then dissolved in 1M HCl (~50 mL) and stirred for an hour. The acid layer was extracted with EtOAc and the organics were combined, dried with sodium sulfate,

filtered, and concentrated in vacuo. Tetrazole **33** was obtained as a beige-pale yellow solid in 92% yield (1.28 g, 5.07 mmol). The NMR data matched the literature.[15]

### 3.3 General Procedure for the Acid-Mediated Fragmentation of Tetrazole

In a vial under nitrogen atmosphere was added the tetrazole (25.2 mg, 1 equiv, 0.1 mmol), Lewis acid (1 equiv), any additive (1 equiv), 4Å MS (20 mg), and dodecane (30 μL) in freshly distilled solvent (0.5 mL, 0.2 M). The reaction mixture was stirred at room temperature or 80 ºC. The reaction mixture was quenched with an aqueous solution of NaOH (2.5 M, 0.5 mL). The organic layer was then extracted with pentane and analyzed with GC. The alkyne was isolated through column chromatography on silica gel (5% EtOAc/Hexanes).

Dodecane was used as GC standard for calibration purposes.

# CHAPTER TWO: PYRIDINE GROUP ASSITED ADDITION OF DIAZO-COMPOUNDS TO IMINES IN THE 3-CC REACTION OF 2-AMINOPYRIDINES, ALDEHYDES AND DIAZO-COMPOUNDS

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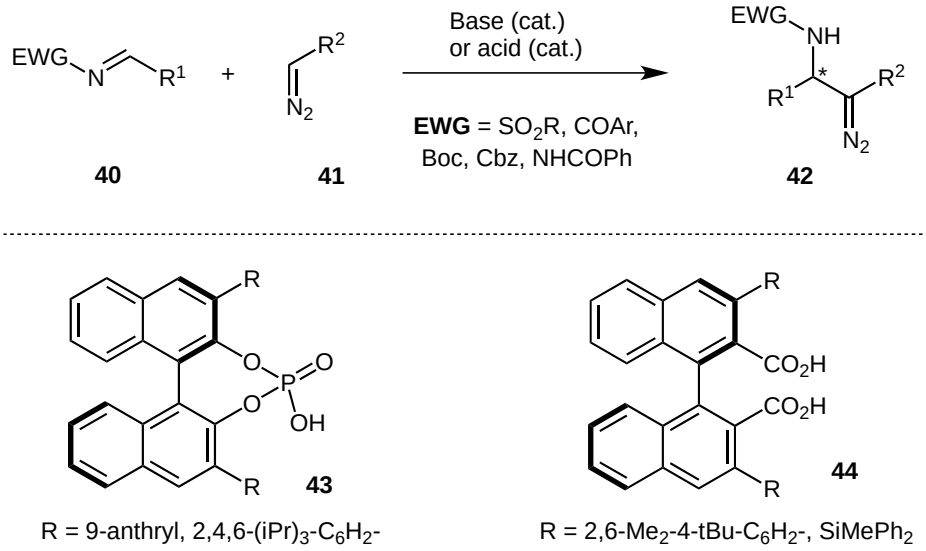
## 1 - INTRODUCTION

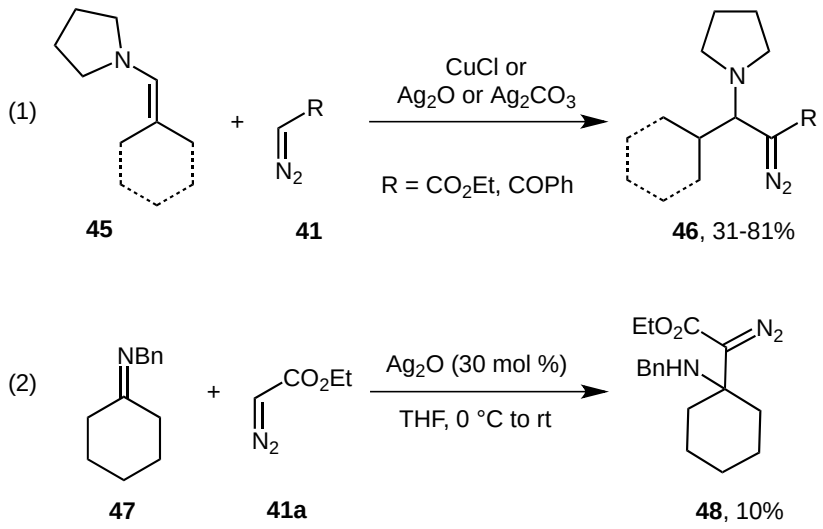
### 1.1 Addition of Diazoesters to Non-Activated Imines

Nucleophilic addition of diazo-compounds to activated imines bearing strong electron-withdrawing groups at the nitrogen atom represents an important method of C–C bond formation, employed in the synthesis of β-amino acid derivatives, as well as other valuable products.[21] Wang and co-workers reported a base-promoted (LDA, NaH, DBU) reaction of *N*-tosyl imines **40** with diazocarbonyl **41** ($R^2$ = $CO_2Et$, COAr) producing *β*-amino-*α*-diazocarbonyl compounds **42** in high yields (Scheme 8).[22] Moreover, this reaction could be executed in a diasteroselective fashion with a chiral diazoamide bearing Evans' oxazolidinone (dr 95:5).[23] Similarly, Terada, Maruoka, and others have reported Brønsted acid-catalyzed addition of diazo-compounds **41** to *N*-COAr and *N*-Boc imines **40**.[24] The employment of chiral binaphthol monophosphoric acids **43** or 1,1'-binaphthyl-2,2'-dicarboxylic acids **44** gave access to enantiopure *β*-amino-*α*-diazocarbonyl compounds **42**. Also, Kantam and co-workers found that Mg/La mixed oxide could catalyze, heterogeneously, this type reaction in water.[25] However, these methods are limited to activated imines only.




**Scheme 8.** Addition of Diazo-compounds to Activated Imines

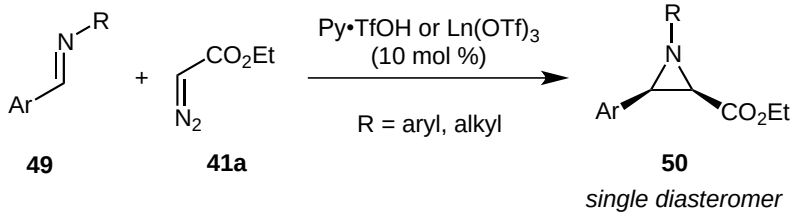
To the best of our knowledge, a single Lewis acid-mediated addition of ethyl diazoacetate (EDA) to non-activated imine towards $\beta$-amino-$\alpha$-diazocarbonyl compounds was reported.[26] Indeed, Wenkert et al. initially studied the condensation of enamine **45** derived from *N*-pyrrolidine and ketone with ethyl diazoacetate **41a**. In the absence of any base or acid catalyst, only traces of expected diazo product were observed and they isolated instead an isopyrazole in 60% yield formed via 1,3-dipolar cycloaddition. Then, screening of metal salts showed that CuCl, $Ag_2O$ and $AgCO_3$ could catalyze the nucleophilic addition of enamine **45** to **41** but diazo-compound **46** was obtained in either low or good yields (Scheme 9, eq. 1). When they adapted their best conditions ($Ag_2O$ as catalyst) to the addition of non-activated imine **47** to EDA, the product was formed in low yield (Scheme 9, eq. 2) and no other examples were reported.




**Scheme 9.** Example of Addition of Diazo-Compounds to Non-Activated Imines

In addition, the acid-catalyzed addition of EDA to *N*-aryl or *N*-alkyl aldimines **49** usually led to the formation of aza-Darzens aziridination product **50** (Scheme 10).[27] In presence of both Brønsted (pyridinium triflate) and Lewis acids (Lanthanide triflates), *cis* aziridines **50** were isolated as a single diasteromer in high yields.

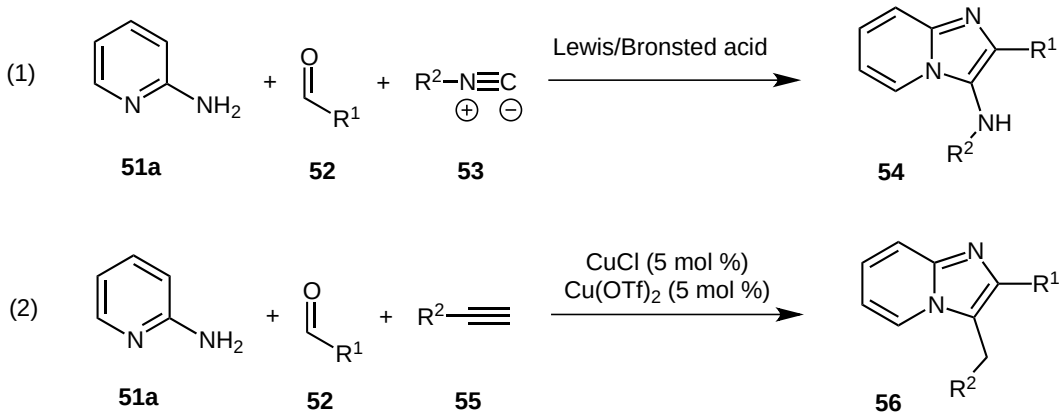
Therefore, we decided to develop a general Lewis acid –catalyzed addition of diazoesters to pyridine-containing imines to produce *β*-amino-*α*-diazocarbonyl compounds.




**Scheme 10.** Aziridine Synthesis *via* Addition of Diazoacetate to Non-Activated Imines

## 1.2 Synthesis of Imidazopyridines via Multicomponent Reaction

As part of the Chicago Tri-Institutional Center for Chemical Methods and Library Development (CCMLD), our group was interested in the development of multicomponent synthetic methods towards *N*-containing heterocycles.[28] Indeed, multicomponent reactions represent an attractive opportunity to design atom-economical transformations while creating molecules with a high degree of complexity in a single step.[29] In 1998, the Groebke,[30] Blackburn,[31] and Bienaymé[32] research groups reported simultaneously related three-component coupling (3-CC) reactions of 2-aminoazines **51a**, aldehydes **52** and isocyanides **53** for the synthesis of 3-amino imidazo[1,2-*a*]pyridines **54** (Scheme 11, eq.1). The bicyclic products were obtained in high yields under mild conditions in presence of Lewis or Brønsted acids (AcOH, $Sc(OTf)_3$ and $HClO_4$, respectively). Notably, the imidazo[1,2-*a*]pyridine scaffold was found in many biologically active molecules like Zolpidem (**56a**), Zolimidine (**56d**) or minodronic acid (**56e**) (Figure 3),[33] hence the necessity to continue to develop new methods to access these molecules. Later, Chernyak and Gevorgyan proposed a modification to this transformation by replacing isocyanide **53** with terminal alkyne **55**.[28b] They presented an efficient copper-catalyzed 3-CC reaction of 2-aminopyridines, aldehydes and terminal alkynes leading to the formation of 3-alkyl imidazopyridines **56** in good to excellent yields (Scheme 11, eq. 2). This reaction also showed a broad reaction scope.




**Scheme 11.** 3-CC Reactions Towards Imidazo[1,2-*a*]pyridines

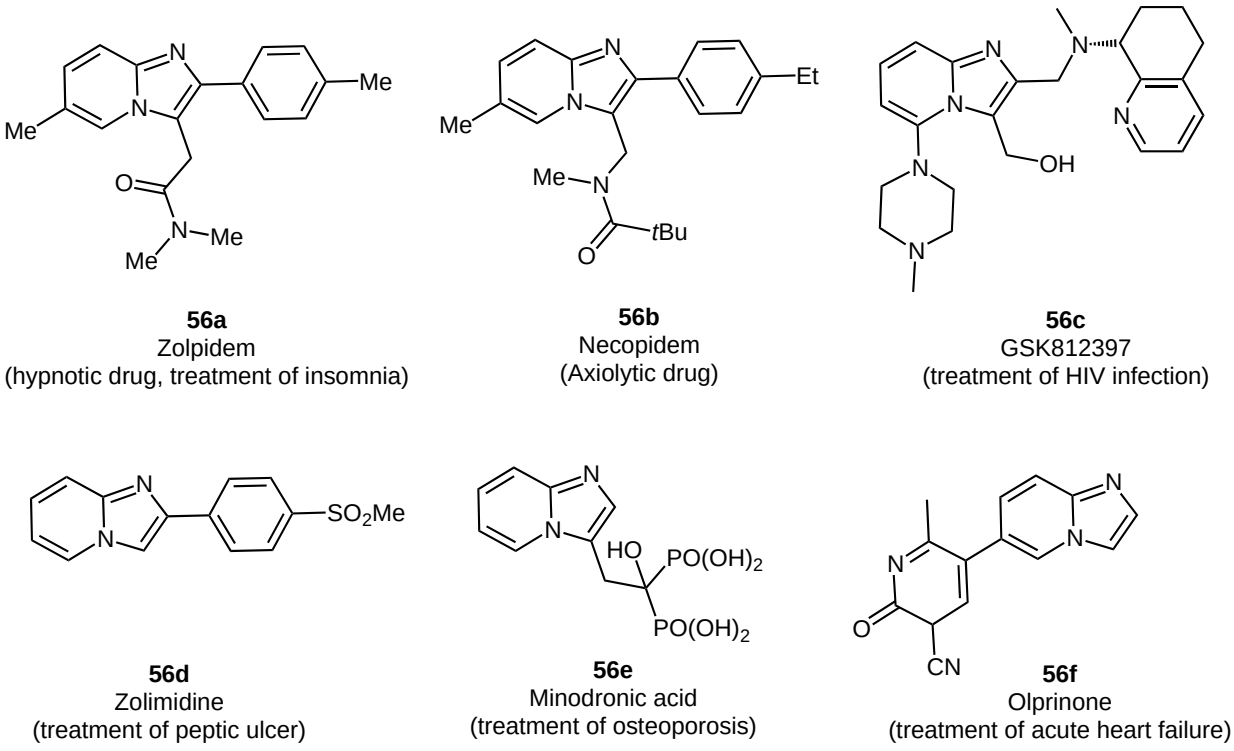



**Figure 3.** Examples of Bioactive Molecules with an Imizado[1,2-a]pyridine Core

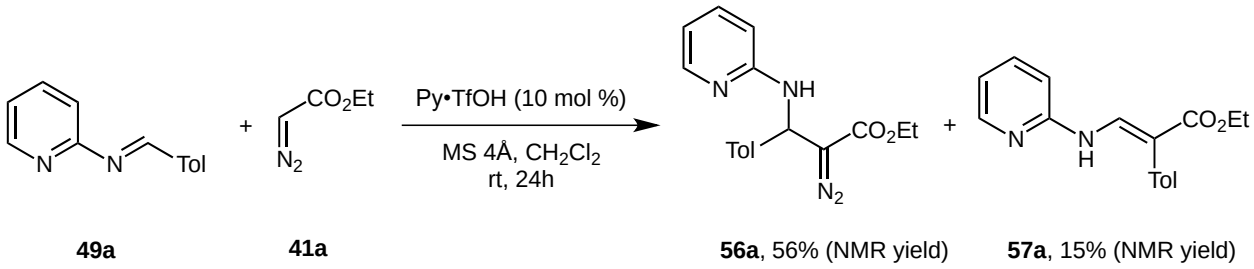
In order to introduce an electron-withdrawing substituent at the C3 position of the imidazopyridine, we explored a three-component coupling reaction of a 2-aminopyridine **51a**, an

aldehyde **52**, and diazoesters **41**.[34] We hypothesized that condensation of imine derived from **51a** and **52** with diazoester **41** would generate a $\beta$-amino-$\alpha$-diazocarbonyl compounds, which would cyclize to afford the corresponding imidazopyridine.

# 2 - DEVELOPMENT OF 3-CC REACTION TOWARDS DIAZO-COMPOUNDS 56

## 2.1 Optimization and Scope of the 3-CC Reaction

We started with screening both Brønsted and Lewis acids for the 2-CC reaction of the imine of 2-aminopyridine **51a** with ethyl diazoacetate (EDA) **41a**. We found that in the presence of Py•TfOH (10 mol %) diazocompound **56a** was produced along with some amounts of enamine **57a**, a product of the 1,2-aryl shift (Scheme 12). Notably, no imidazopyridine or aziridine was observed. The presence of the diazo-group was confirmed with X-ray analysis (analog compound **56j** was crystallized) (figure 4). We considered this outcome to be quite interesting, as it represents the first efficient addition of diazo-compounds to an imine that does not possess a strong electron-withdrawing group at the nitrogen atom.




**Scheme 12.** Preliminary Result of Addition of Diazoacetate to *N*-Pyridyl Imine

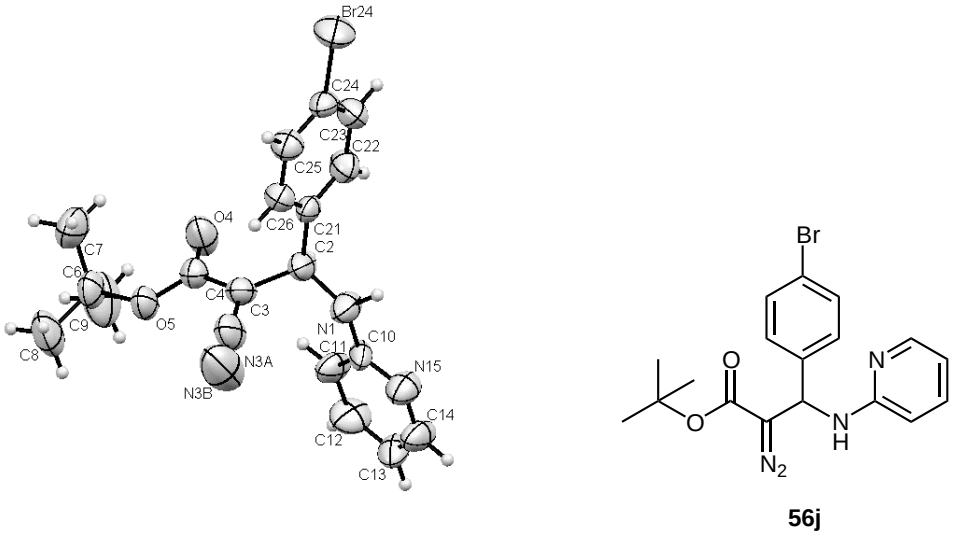
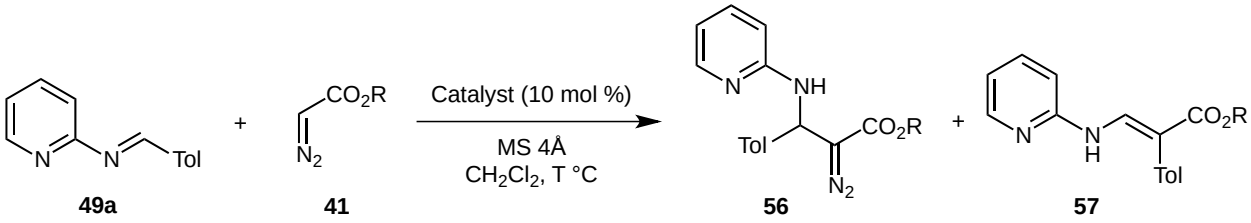



**Figure 4.** ORTEP-style Drawing of Molecule **56j:** the thermal ellipsoids are drawn at the 50% probability level. Drawing produced by Mercury 3.0 (Build RC5)

Accordingly, optimization studies towards a more efficient formation of **56** were performed (Table 4). It was found that strong acids such as TfOH (entry 2), as well as $Tf_2NH$ (entry 3), could catalyze this reaction to produce **56a**, together with a byproduct enamine **57a**. Employment of weaker acids, such as $CF_3CO_2H$ (entry 4), did not give any product, whereas the use of a phenylphosphinic acid catalyst produced the product **56a** selectively, though in moderate yield only (entry 5). We found that the reaction of *tert*-Butyl and cyclohexyl-diazoacetates afforded products **56b** and **56c**, respectively, in slightly better yields. However, formation of significant amounts of enamine **57** was observed (Table 4, entries 6, 7). To our delight, the amount of enamine byproduct **57** was significantly decreased when lanthanide triflates were used (entries 8–11). After this two-component coupling (2-CC) reaction was optimized, we focused on the development of a more synthetically attractive 3-CC reaction. We found that this transformation can indeed be performed in a three-component fashion starting from an aldehyde,

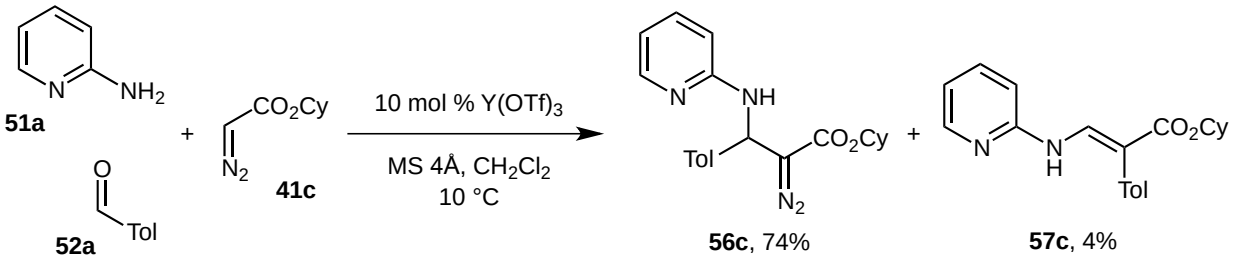
a 2-aminopyridine, and a cyclohexyldiazoacetate, which forms the product **56c** in high yield (Scheme 13).

**Table 4.** Optimization of the 2-CC Reaction Conditions[a]




| Entry | Catalyst | R | T (ºC) | Yield (%) of **56**[b] | Yield (%) of **57**[b] |
|---|---|---|---|---|---|
| 1 | Py•TfOH | Et | rt | 56 | 15 |
| 2 | TfOH | Et | rt | 45 | 15 |
| 3 | $Tf_2NH$ | Et | rt | 55 | 15 |
| 4 | $CF_3CO_2H$ | Et | rt | - | - |
| 5[c] | $PhP(OH)_2$ | Et | rt | 50 | 2 |
| 6 | Py•TfOH | *t*-Bu | rt | 5 | 14 |
| 7 | Py•TfOH | Cy | rt | 63 | 13 |
| 8 | $Sc(OTf)_3$ | Cy | rt | 42 | 14 |
| 9 | $La(OTf)_3$ | Cy | rt | 63 | 10 |
| 10 | $Y(OTf)_3$ | Cy | rt | 52 | 1 |
| 11 | $Y(OTf)_3$ | Cy | 10 | 75 | 3 |

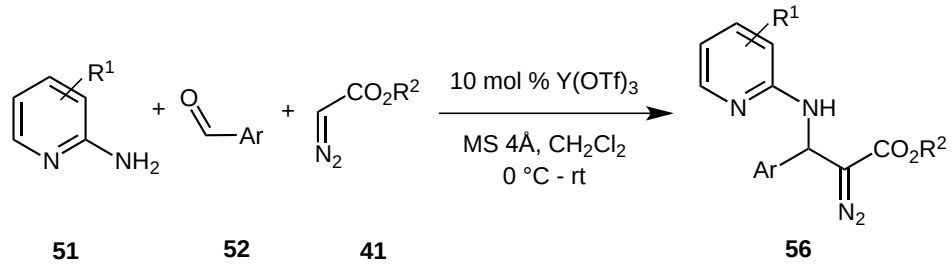
[a] Conditions: imine (1 equiv), diazo-compound (1.2 equiv), catalyst (10 mol %), and MS 4Å (125mg/mmol) in $CH_2Cl_2$ (0.3M). [b] NMR yields after 24 h. [c] Toluene was used as a solvent.



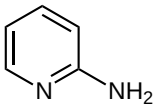
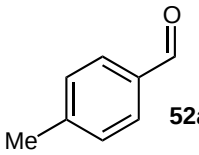
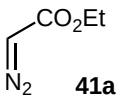
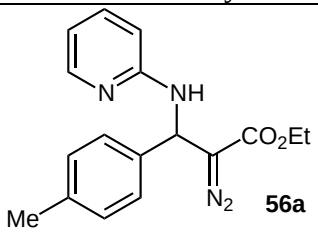
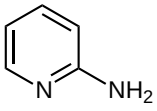
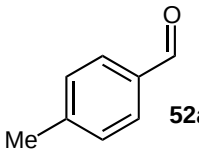
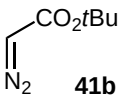
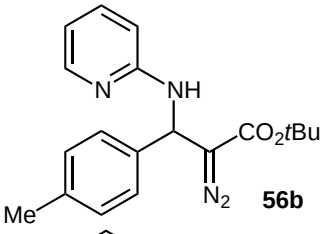
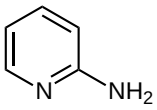
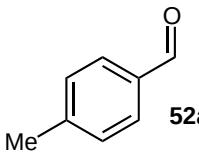
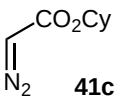
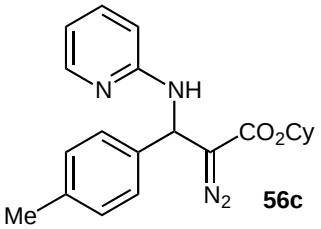
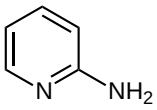
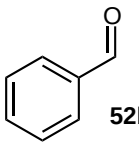
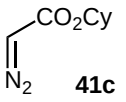
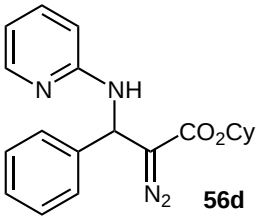
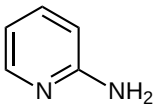
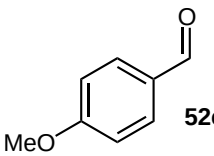
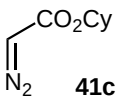
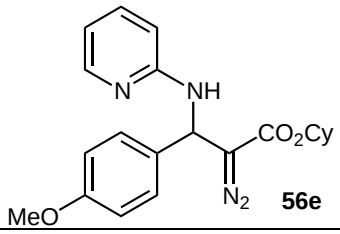

**Scheme 13.** Optimized Conditions for the 3-CC Reaction

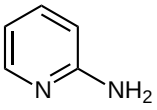
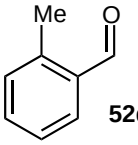
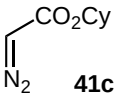
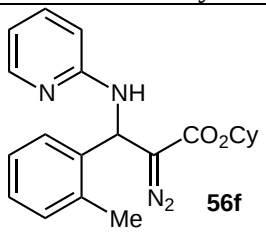
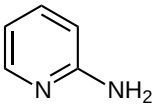
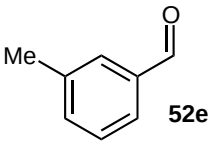
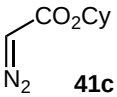
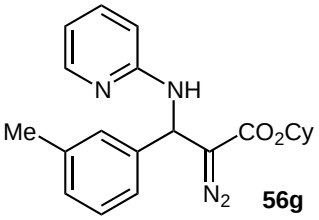
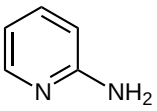
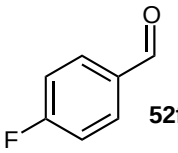
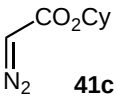
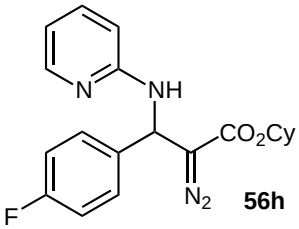
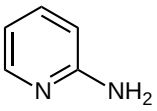
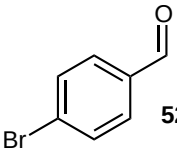
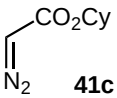
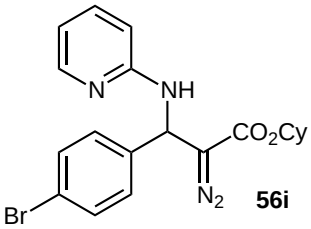
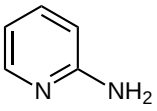
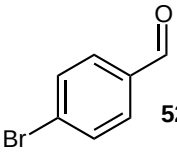
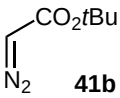
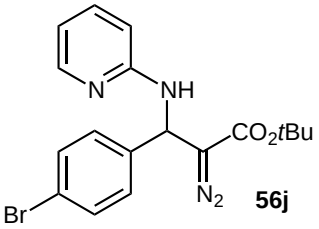
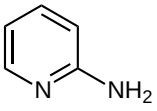
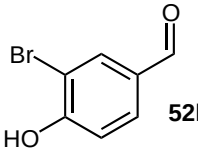
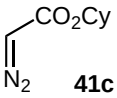
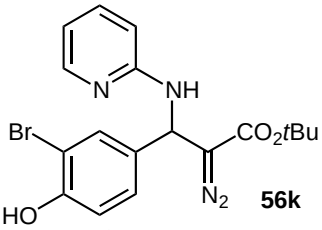
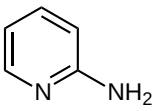
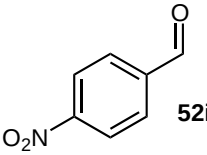
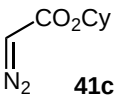
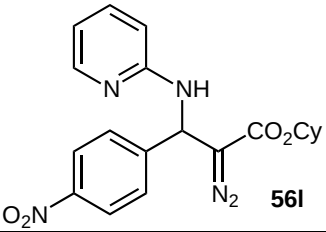
With optimized conditions in hand, we explored the scope of this novel 3-CC reaction. Thus, aromatic aldehydes bearing electron-donating and -neutral groups (Table 5, entries 1–7) at the *ortho*-, *meta*-, and *para*-positions reacted smoothly. Benzaldehydes having electron-withdrawing groups, such as fluoro (entry 8), bromo (entries 9, 10), $NO_2$ (entry 12), and $CF_3$ (entry 13), produced the corresponding diazo esters in slightly lower yields (entries 8–13). In addition, an aldehyde bearing an unprotected hydroxy group (entry 11), as well as a heteroaromatic aldehyde, such as 2-thiophenecarboxaldehyde (entry 14), were tolerated under these reaction conditions. Substituted 2-aminopyridines were also competent partners for this 3-CC reaction (entries 15–18). However, the reaction of 2-aminopyridine, having an electron-withdrawing group, afforded the product in a diminished yield (entry 18). The reaction could also be performed with other 2-aminoazines, namely 2-aminopyrimidine (entry 19), and 2-aminopyrazine (entry 20), as well as with 2-aminothiazole (entry 21), producing the corresponding products in reasonable yields. In addition to diazoesters, diethyl (diazomethyl)-phosphonate could also be employed to form the corresponding β-amino-α-diazo-compounds **56v,w** efficiently (entries 22 and 23). In general, the reaction showed high functional group tolerance with respect to all three components.

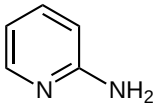
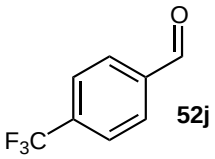
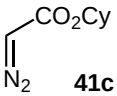
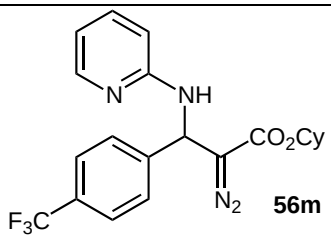
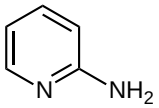
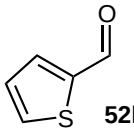
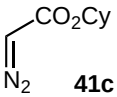
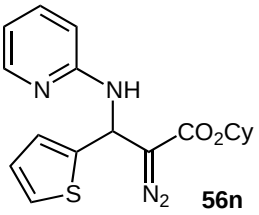
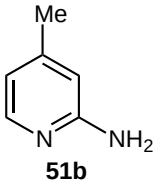
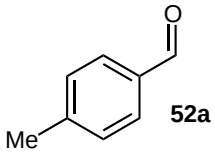
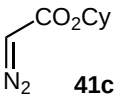
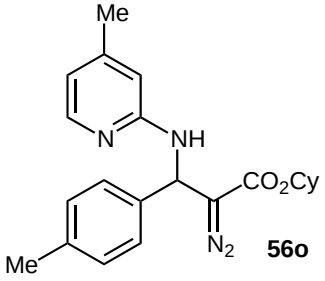
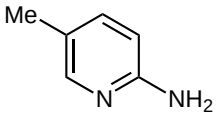
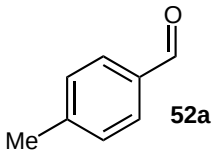
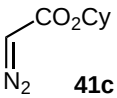
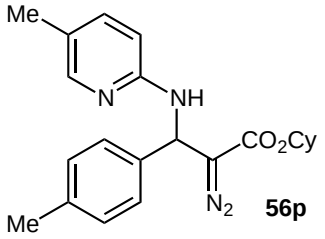
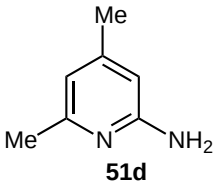
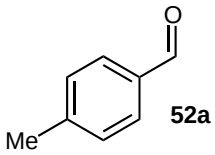
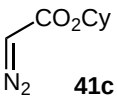
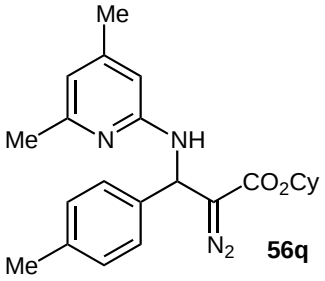
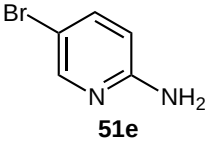
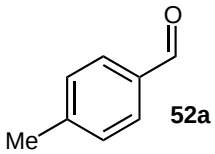
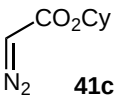
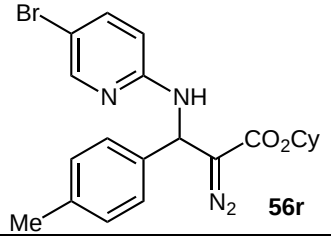
**Table 5.** Scope of the New 3-CC Reaction[a]

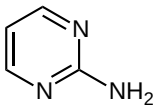
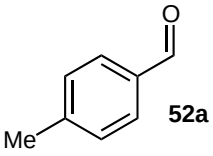
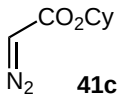
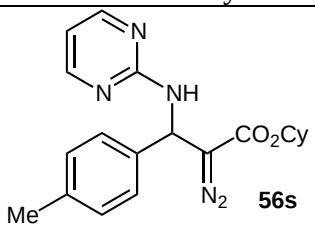
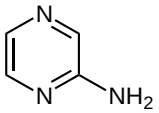
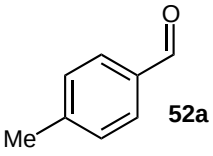
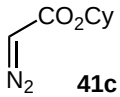
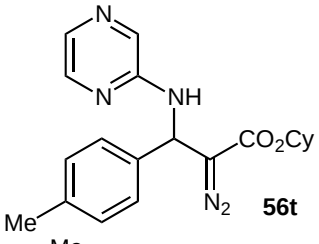
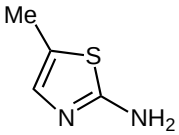
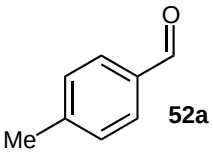
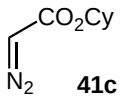
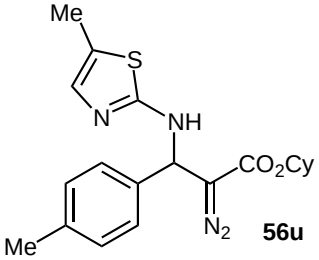
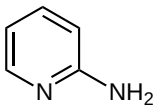
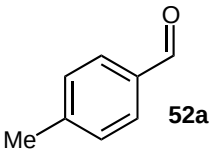
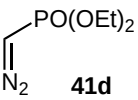
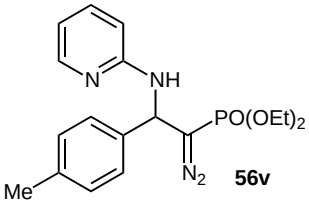
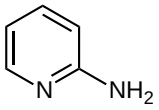
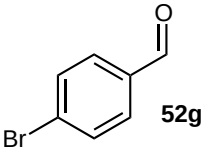
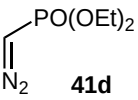
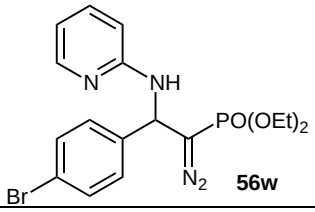



**51** **52** **41** **56**

| Entry | Azine | Aldehyde | Diazo-compound | α-Amino-β-diazocarbonyl | Yield (%) of **56**[b] |
|---|---|---|---|---|---|
| 1 |  **51a** |  **52a** |  **41a** |  **56a** | 60 |
| 2 |  **51a** |  **52a** |  **41b** |  **56b** | 64 |
| 3 |  **51a** |  **52a** |  **41c** |  **56c** | 70 |
| 4 |  **51a** |  **52b** |  **41c** |  **56d** | 71 |
| 5 |  **51a** |  **52c** |  **41c** |  **56e** | 60 |

| Entry | Azine | Aldehyde | Diazo-compound | α-Amino-β-diazocarbonyl | Yield (%) of **56**[b] |
|---|---|---|---|---|---|
| 6 |  **51a** |  **52d** |  **41c** |  **56f** | 66 |
| 7 |  **51a** |  **52e** |  **41c** |  **56g** | 76 |
| 8 |  **51a** |  **52f** |  **41c** |  **56h** | 58 |
| 9 |  **51a** |  **52g** |  **41c** |  **56i** | 65 |
| 10 |  **51a** |  **52g** |  **41b** |  **56j** | 62 |
| 11 |  **51a** |  **52h** |  **41c** |  **56k** | 51 |
| 12[b] |  **51a** |  **52i** |  **41c** |  **56l** | 50 |

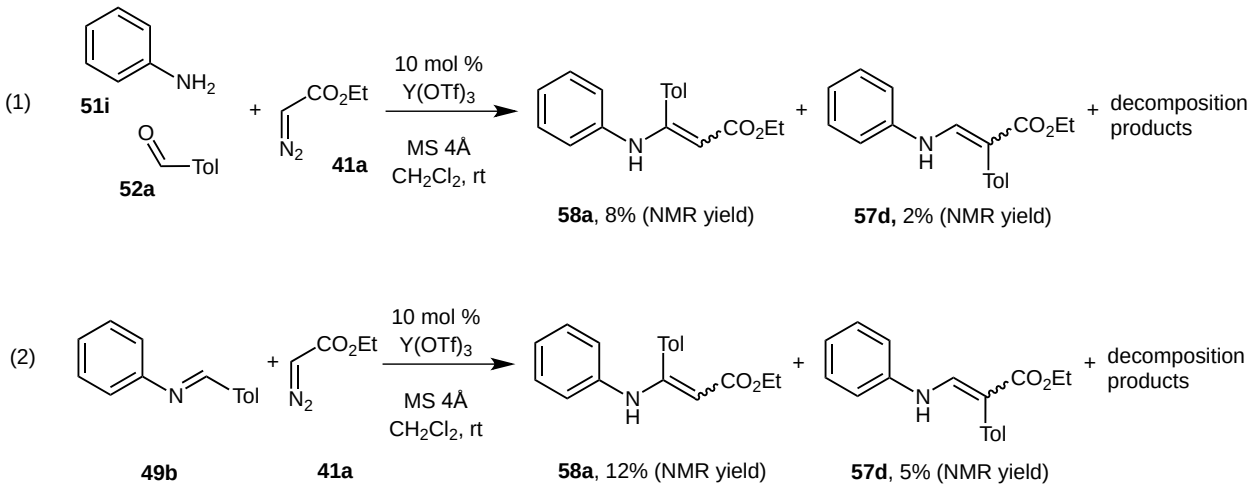
| Entry | Azine | Aldehyde | Diazo-compound | α-Amino-β-diazocarbonyl | Yield (%) of **56**[b] |
|---|---|---|---|---|---|
| 13 |  **51a** |  **52j** |  **41c** |  **56m** | 68 |
| 14 |  **51a** |  **52k** |  **41c** |  **56n** | 45 |
| 15 |  **51b** |  **52a** |  **41c** |  **56o** | 75 |
| 16 |  **51c** |  **52a** |  **41c** |  **56p** | 63 |
| 17 |  **51d** |  **52a** |  **41c** |  **56q** | 50 |
| 18[b] |  **51e** |  **52a** |  **41c** |  **56r** | 45 |

| Entry | Azine | Aldehyde | Diazo-compound | α-Amino-β-diazocarbonyl | % Yield of **56**[b] |
|---|---|---|---|---|---|
| 19 |  **51f** |  **52a** |  **41c** |  **56s** | 42 |
| 20 |  **51g** |  **52a** |  **41c** |  **56t** | 46 |
| 21 |  **51h** |  **52a** |  **41c** |  **56u** | 41 |
| 22 |  **51a** |  **52a** |  **41d** |  **56v** | 67 |
| 23 |  **51a** |  **52g** |  **41d** |  **56w** | 51 |

[a]Unless otherwise noted: aldehyde (1 equiv), 2-aminoazine (1.1 equiv), diazo-compound (1.2 equiv), $Y(OTf)_3$ (10%), and MS 4Å (125 mg/mmol) in $CH_2Cl_2$ (0.3 M). [b]Isolated yields. [c]Preformed imine used.

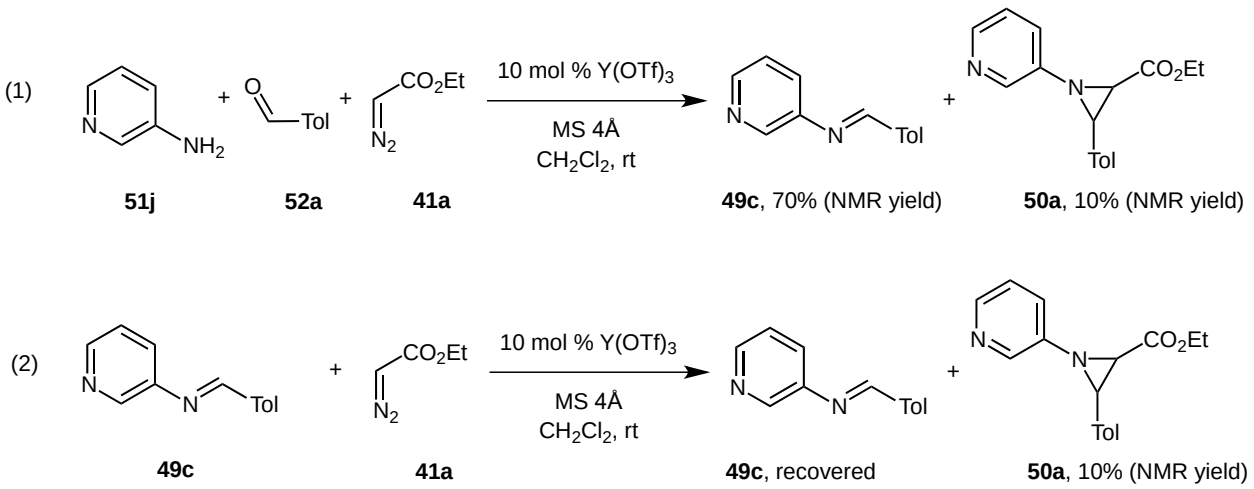
## 2.2 Investigation of the Reaction Mechanism

Next, we decided to test various aryl amines without a nitrogen atom at the $\alpha$-position to better understand the role the pyridine N-atom played in the mechanism of the reaction. Thus, we found that the 3-CC reaction of aniline **51i**, *p*-tolualdehyde **52a** and EDA led to undefined decomposition products along with the formation of small amounts of 1,2-*H*- and 1,2-*Ar* shift products (**58** and **57**, respectively) (Scheme 14, eq. 1). Preforming imine **49b** in the 2-CC reaction also gave the similar result (eq. 2).



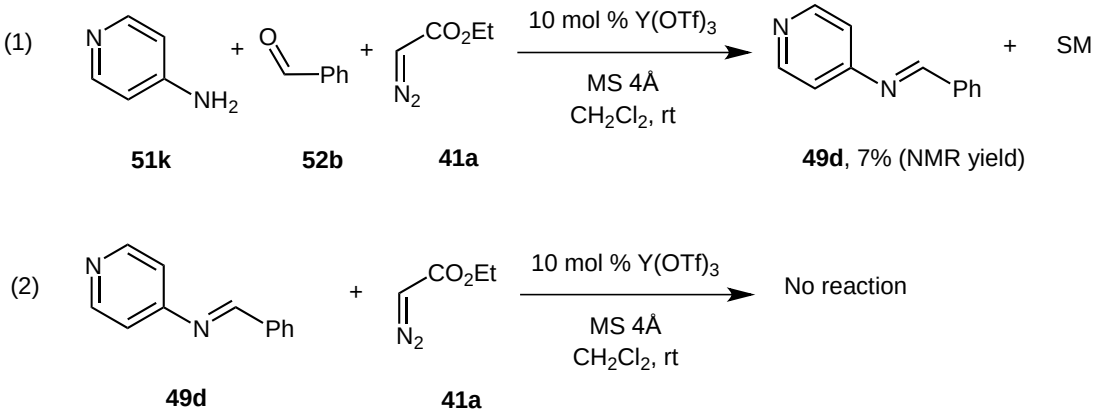

**Scheme 14.** Analysis of Aniline in 3-CC and 2-CC Reactions

Then, when 3-aminopyridine **51j** was employed in the 3-CC reaction with p-tolualdehyde and ethyl diazoacetate, imine **49c** was obtained as the major product along with small amounts of aziridine **50a** (Scheme 15, eq. 1). The corresponding 2-CC reaction with imine **49c** produced small amount of aziridine and unreacted imine **49c** was recovered (eq. 2).



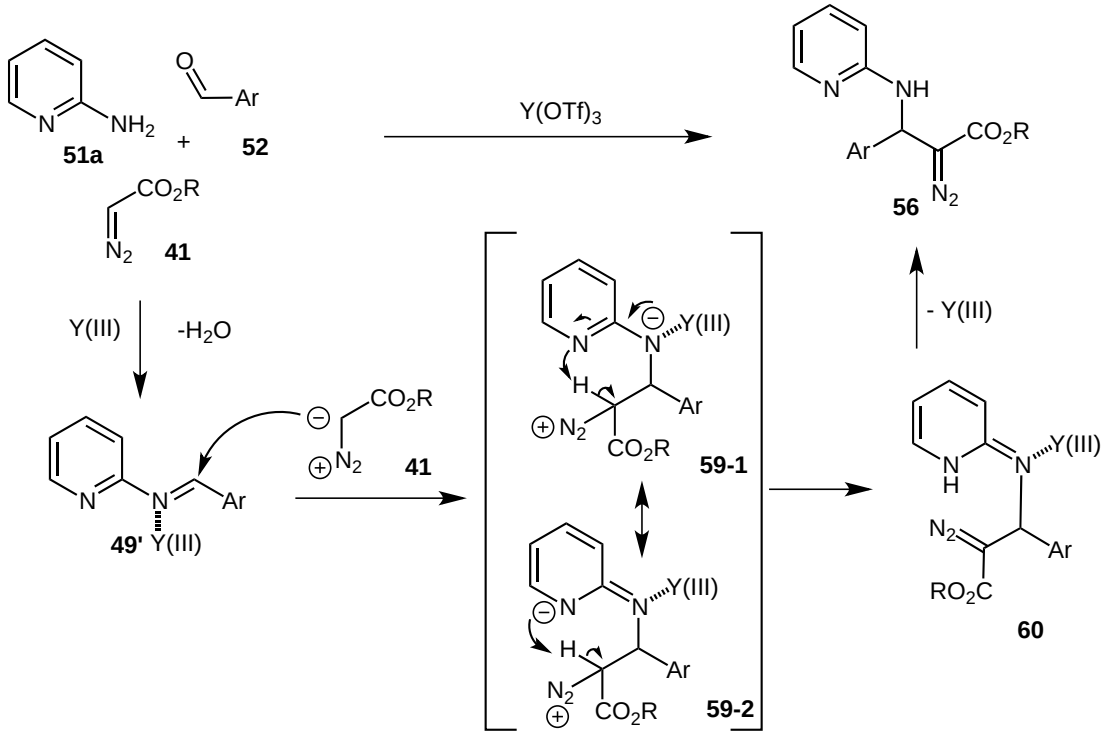

**Scheme 15.** Analysis of 3-Aminopyridine in 3-CC and 2-CC Reactions

Finally, we found that like the two previous aryl amines 4-aminopyridine **51k** was not a good partner for the reaction. Most of the starting materials were recovered in the 3-CC reaction along with small amounts of imine **49d** (Scheme 16, eq. 1). No condensation product was recovered when the 2-CC reaction was performed (eq. 2).




**Scheme 16.** Analysis of 4-Aminopyridine in 3-CC and 2-CC Reactions

We rationalize these observations in the following way (Scheme 17). First, the formed Y(III)-activated imine **49'** undergoes a nucleophilic attack by the diazo-compound **41** to produce zwitterion **59**. It is likely that the nitrogen atom of the pyridine ring serves as an intramolecular proton shuttle. Thus, deprotonation in **59** by the pyridine N-atom leads to diazo-intermediate **60**, producing diazo-compound **56** upon release of a Y(III)-catalyst and tautomerization process. Therefore, the overall process can be considered as a pyridine group assisted addition of diazo-compounds to imines. This mechanism is in good agreement with the fact that aniline, as well as 3- and 4-aminopyridines, which do not possess a properly situated N-atom, do not undergo this addition reaction (Schemes 14-16).

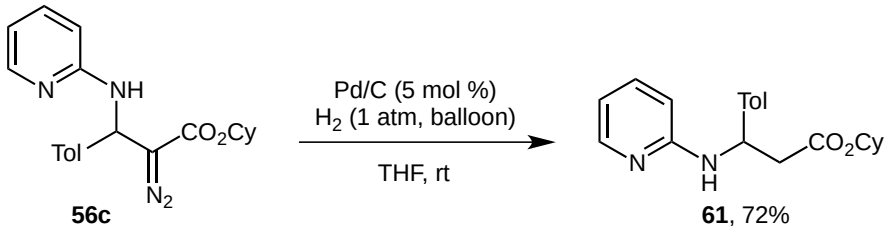



**Scheme 17.** Proposed Mechanism for the 3-CC Reaction

# 3 - SYNTHETIC APPLICATIONS OF DIAZO-COMPOUNDS 56

## 3.1 Reduction and Rearrangement of Diazo-compounds

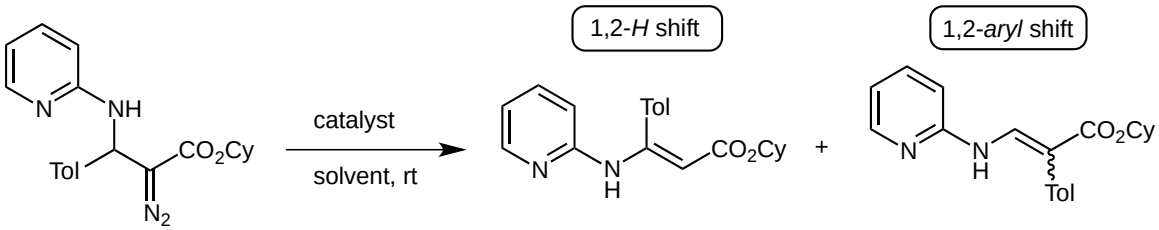
Compounds **56** discussed in section 5 represent a versatile scaffold for various types of transformations. We found that hydrogenation of the diazo-group of **56c** (R = $CO_2Cy$) efficiently converted it to *β*-amino acid derivative **61** (Scheme 18).




**Scheme 18.** Reduction of Diazo Group into *β*-Amino Ester

Wang and co-workers have reported that *β*-amino-*α*-diazo-compounds derived from activated imines (*N*-Ts, *N*-$COCCl_3$) undergo 1,2-migrations (1,2-*H* or 1,2-*aryl* shift) to form enamines.[22a,22c,35] The selectivity of the reaction depended on both electronic and steric effects. Thus, the reaction conditions (metal catalyst, Lewis or Brønsted acid) and the substituents on the amine, aryl group or diazocarbonyl compound influenced the outcome of the reaction. Notably, silver benzoate ($AgO_2CPh$) would selectively catalyze the 1,2-*H* migration.[22a,35b] We therefore decided to investigate the migratory aptitude of *β*-*N*-pyridylamino-*α*-diazoester **56c** in presence of silver catalysts.

**Table 6.** Optimization of 1,2-*H* Shift Conditions.[a]

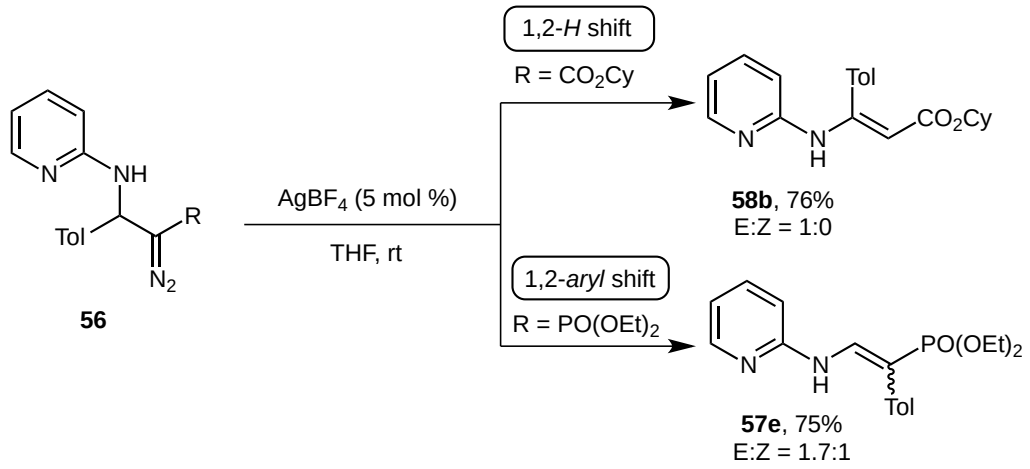



**56c** **58b** **57c**

| Entry | Catalyst | Catalyst loading | Solvent | Ratio **58b**/**57c**[b] |
|---|---|---|---|---|
| 1 | AgOTf | 5 mol % | $CH_2Cl_2$ | 5.2 : 1 |
| 2 | AgOAc | 5 mol % | $CH_2Cl_2$ | 3 : 1 |
| 3 | AgOMs | 5 mol % | $CH_2Cl_2$ | 4.3 : 1 |
| 4 | $AgBF_4$ | 5 mol % | $CH_2Cl_2$ | 6.2 : 1 |
| 5 | $AgSbF_6$ | 5 mol % | $CH_2Cl_2$ | 4 : 1 |
| 6 | $AgPF_6$ | 5 mol % | $CH_2Cl_2$ | 3.9 : 1 |
| 7 | AgF | 5 mol % | $CH_2Cl_2$ | 4 : 1 |
| 8 | $AgNO_3$ | 5 mol % | $CH_2Cl_2$ | 3 : 1 |
| 9 | $AgBF_4$ | 3 mol % | $CH_2Cl_2$ | 6 : 1 |
| 10 | $AgBF_4$ | 10 mol % | $CH_2Cl_2$ | 1.7 : 1 |
| 11 | $AgBF_4$ | 5 mol % | DCE | 6.2 : 1 |
| 12 | $AgBF_4$ | 5 mol % | Toluene | 6 : 1 |
| 13 | $AgBF_4$ | 5 mol % | $CH_3CN$ | 5.6 : 1 |
| 14 | $AgBF_4$ | 5 mol % | THF | 12 : 1 |

[a] Conditions: diazo-compound **56** (1 equiv), silver salt in THF (0.1 M) at room temperature. [b]Ratio **58b**/**57c** was determined using proton NMR (dibromomethane as a standard).

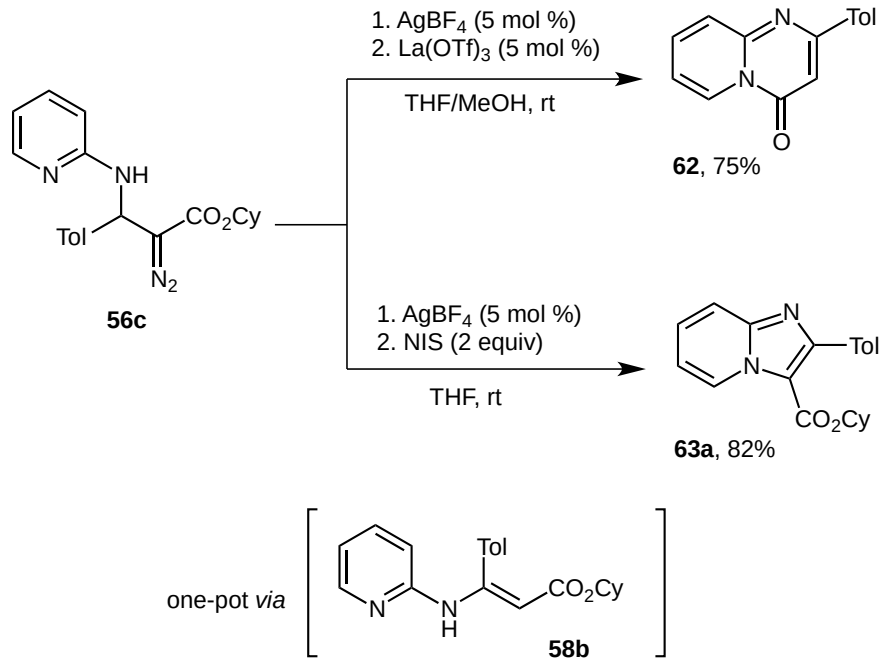
We tested various silver salts to study the chemoselectivity of 1,2-migrations in diazo-compound **56c** (Table 6). While all silver salts formed predominantly the 1,2-*H* shift product **58b** (entries 1-8), the best selectivity was observed in presence of $AgBF_4$ (**58b**/**57c** 6:1). The selectivity of the reaction decreased when we modified the amount of catalyst (entries 9-10) but optimization of the solvent was successful (entries 11-14). Only the 1,2-*H* shift product was observed in THF (**58b**/**57c** 12:1) (entry 14). Interestingly, under these reaction conditions, α-diazoethylphosphonate **56v** (R = $PO(OEt)_2$) underwent an exclusive 1,2-*aryl* shift to form the enamine product **57e** (Scheme 19).[22c]




**Scheme 19.** Chemoselective 1,2-Migrations of Diazo-compound **56**

### 3.2 Synthesis of Imidazopyridinone and Imidazopyridine

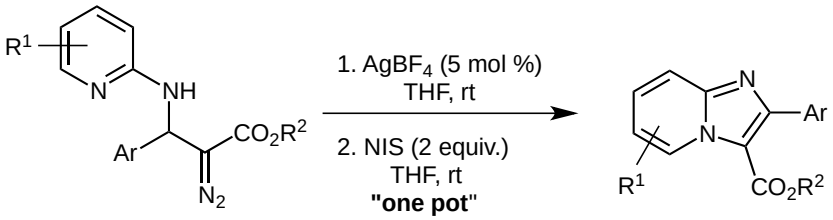
The synthetic usefulness of the diazo-compounds **56** was further demonstrated in an efficient one-pot synthesis of *N*-fused heterocycles *via* cyclization of the *in situ* formed enamine **58b**. Thus, in the presence of $La(OTf)_3$, **58b** underwent lactamization into pyrido[1,2-a]pyrimidine-4-one **62**. On the other hand, NIS-mediated cyclization converted **58b** into imidazo-[1,2-*a*]pyridine **63a** (Scheme 20).



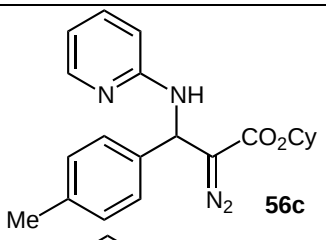
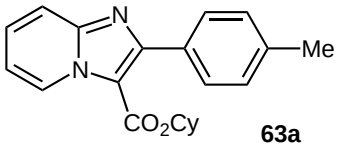
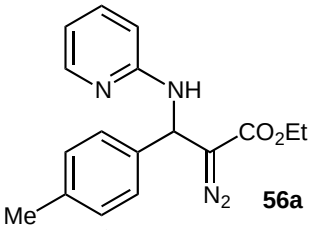
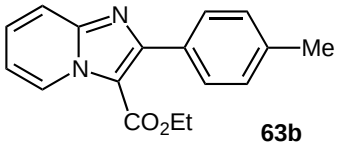
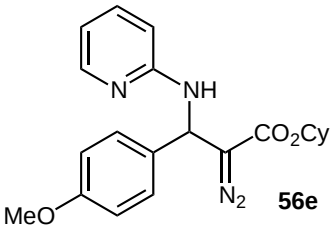
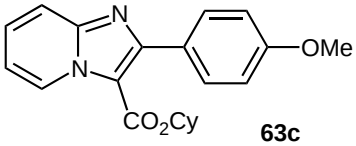
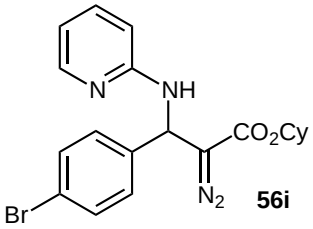
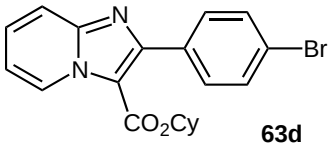
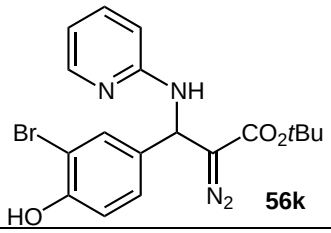
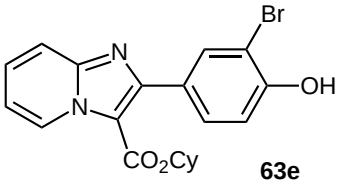

**Scheme 20.** Intramolecular Cyclizations of Diazo-compound **56c**

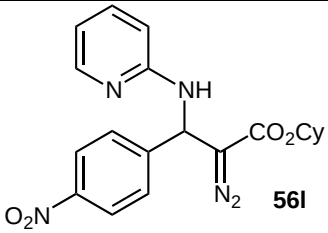
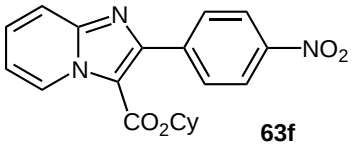
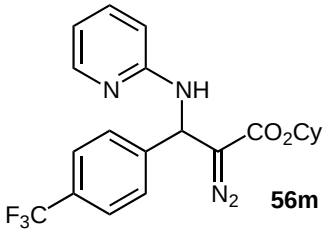
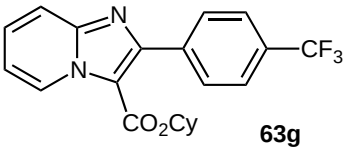
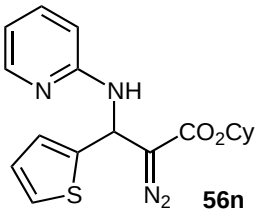
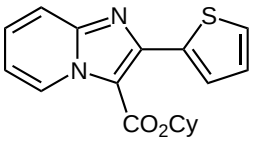
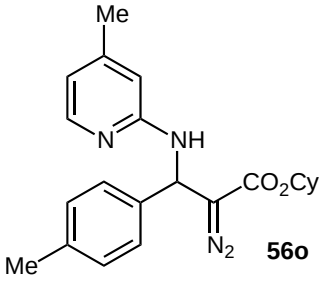
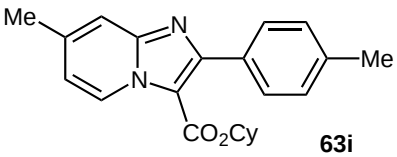
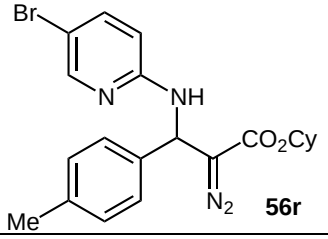
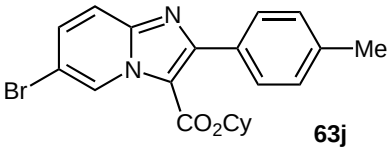
Due to our group's aforementioned interest in the synthesis of imidazopyridines, we developed the scope of the direct transformation of *β*-amino-*α*-diazoesters **56** into imidazo[1,2-*a*]pyridines **63** (Table 7). This reaction demonstrated broad scope and high yields of imidazopyridines **63**. Thus, diazo-compounds **56** bearing various substituents and functional groups such as Br, OH, $NO_2$, $CF_3$ as well as the thiophene residue, were tolerated (Table 7, entries 1-10). It was also shown that not only imidazo[1,2-*a*]pyridine, but also imidazo[1,2-*a*]pyrimidine **63k** (entry 11) and imidazo[1,2-*a*]pyrazine **63l** (entry 12) can be efficiently prepared *via* this protocol. Compared to other approaches towards 2-aryl-imidazo[1,2-*a*]pyridine-3-carboxylates of type **63**,[36] the newly developed protocol features milder reaction conditions and better functional group tolerance.

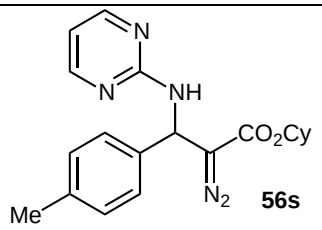
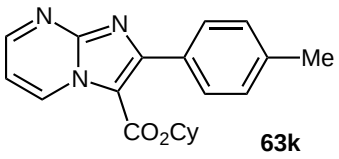
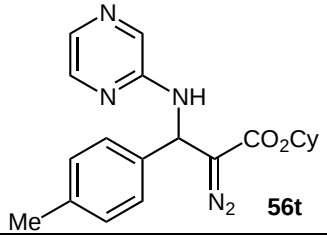
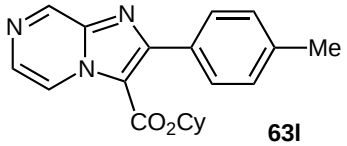
**Table 7.** Scope of One-Pot Synthesis of Imidazopyridines from **56**[a]




**56** **63**

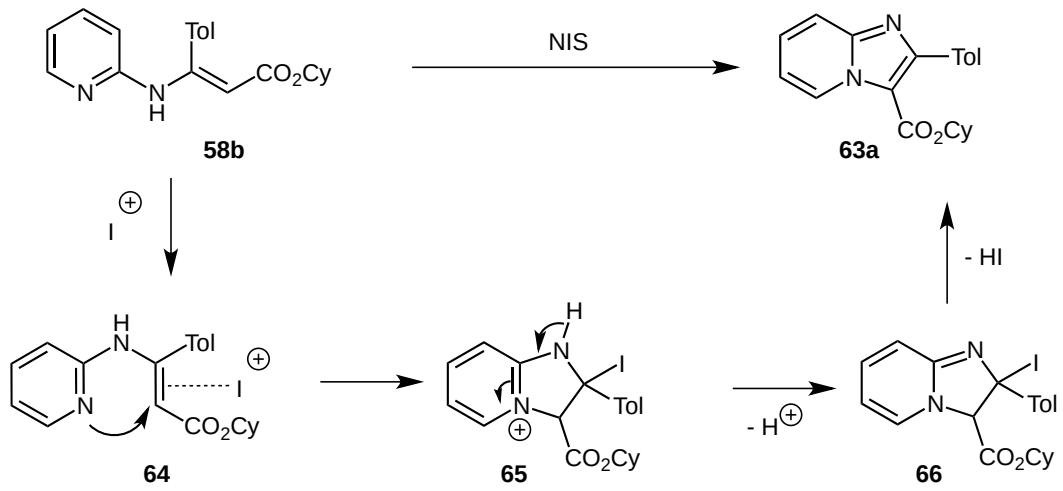
| Entry | Diazo-compound | Product | Yield (%) of **63**[b] |
|---|---|---|---|
| 1 |  **56c** |  **63a** | 82 |
| 2 |  **56a** |  **63b** | 72 |
| 3 |  **56e** |  **63c** | 83 |
| 4 |  **56i** |  **63d** | 65 |
| 5 |  **56k** |  **63e** | 60 |

| Entry | Diazo-compound | Product | Yield (% ) of **63**[b] |
|---|---|---|---|
| 6 |  **56l** |  **63f** | 78 |
| 7 |  **56m** |  **63g** | 77 |
| 8 |  **56n** |  **63h** | 59 |
| 9 |  **56o** |  **63i** | 75 |
| 10 |  **56r** |  **63j** | 79 |

| Entry | Diazo-compound | Product | Yield (% ) of **63**[b] |
|---|---|---|---|
| 11[c] |  **56s** |  **63k** | 66 |
| 12[c] |  **56t** |  **63l** | 70 |

[a] Conditions: diazo-compound **56** (1 equiv), $AgBF_4$ (5 mol %) in THF at room temperature then NIS (2 equiv) in THF at room temperature. [b]Isolated yields. [c]Reaction was run at 60 ºC.

We proposed the following mechanism for the synthesis of imidazopyridines 63 (Scheme 21). Presumably, upon activation of double bond of the enamine **58b** by an electrophilic agent, **64** undergo cyclization *via* intramolecular attack of the pyridine nitrogen at the double bond of the enamine. Imidazopyridine **63** is then formed upon subsequent elimination and tautomerization process.




**Scheme 21.** Proposed Mechanism for the Synthesis of Imidazopyridine **63a**

### 3.3 Summary

In summary, we have developed a novel three-component coupling reaction of 2-aminoazines, aromatic aldehydes, and diazo compounds producing β-amino-α-diazoesters. This reaction features an unprecedented heterocycle-assisted addition of a diazo-compound to an imine. The obtained β-amino-α-diazoesters represent an important polyfunctional synthetic scaffold suitable for useful transformations. Thus, the obtained diazo-compounds could be efficiently converted into valuable heterocyclic molecules such as imidazo[1,2-*a*]-pyridines and pyrido[1,2-*a*]pyrimidine-4-ones, as well as *β*-(2-pyridyl)-amino acid derivatives.

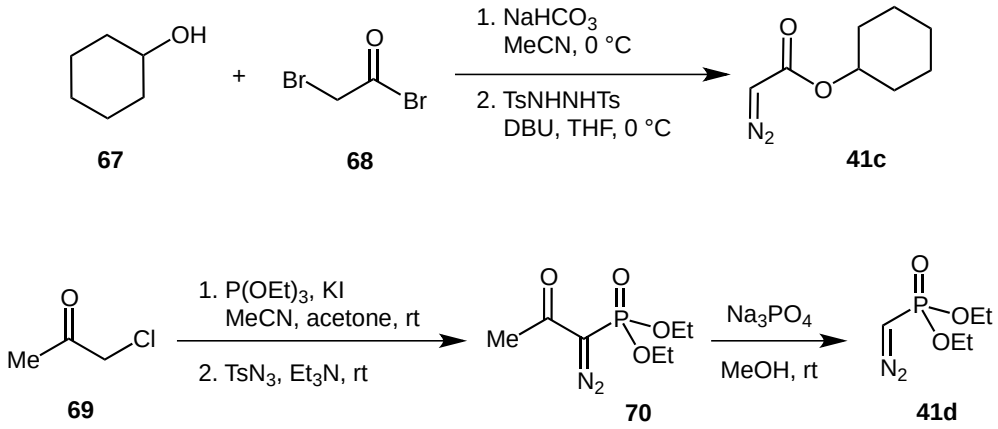
# 4 - EXPERIMENTAL SECTION

## 4.1 General Information

NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz) instrument. $^{1}H$ signals are referenced to residual $CHCl_3$ at 7.26 ppm. $^{13}C$ signals are referenced to $CDCl_3$ at 77.0 ppm. GC/MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Silicycle Silica-P flash silica gel (40-63 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. LRMS and HRMS analyses were performed on Micromass 70 VSE mass spectrometer. Anhydrous solvents purchased from Aldrich were additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system and/or stored over calcium hydride. All starting materials were purchased from Aldrich, TCI America, or Alfa Aesar, or synthesized via known literature procedures. MS 4Å were purchased from Sigma Aldrich, grounded and activated under reduced pressure (200 ºC /1 torr, 12 h). All manipulations with transition metal catalysts were conducted in oven-dried glassware under inert atmosphere using a combination of glovebox and standard Schlenk techniques.

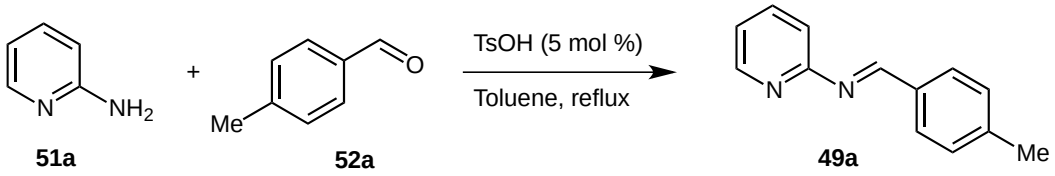
## 4.2 Synthesis of Diazo-compounds 41

Ethyl diazoacetate **41a** and *tert*-butyl diazoacetate **41b** were purchased from Sigma-Aldrich. Cyclohexyl diazoacetate **41c**[37] and (diethyl)diazomethylphosphonate **41d**[38] were prepared according to literature procedures.




### 4.3 General Procedure for the Synthesis of Imines 49

**Synthesis of (*E*)-*N*-(4-Methylbenzylidene)pyridin-2-amine (49a)**

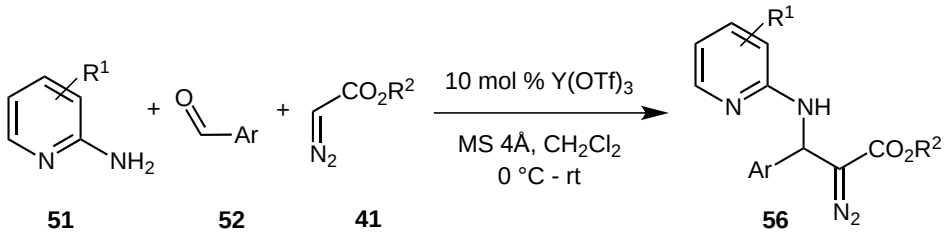



An oven dried 100 mL flask, containing a stirring bar, was charged with 2-amiopyridine (1.974 g, 21 mmol), and 4-methylbenzaldehyde (2.4 g, 20 mmol), TsOH•$H_2O$ (190 mg, 1 mmol) and toluene (50 mL). The flask was equipped with Dean-Stark apparatus and refluxed for 6h. The solvent was removed under a reduced pressure, and the residue was distilled *in vacuo* (135 $^oC$, 1 torr). The product **49a** was obtained in 78% yield (3.05 g, 15.6 mmol) as a white solid. The NMR spectra matched the literature data.[39]

**Synthesis of Imines 49b-f**

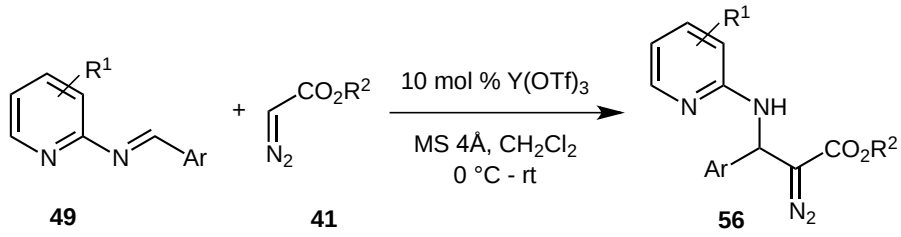
Imines **49b-f** were prepared according to the procedure for the preparation of **49a** above. The NMR spectra of each imine matched the literature data. [39-40]

### 4.4 Synthesis of *α*-Amino-*β*-diazocarbonyl Compounds 56




**51** **52** **41** **56**

**General procedure for 3-CC reaction (GP-1):** An oven dried 5 mL Wheaton V-vial, containing a stirring bar, was charged with 2-amioazine (1.1 mmol), an aldehyde (1 mmol), activated MS 4Å (125 mg), and $Y(OTf)_3$ (56.8 mg, 0.1 mmol) under $N_2$ atmosphere (glovebox). Dry $CH_2Cl_2$ (2.5 mL) was added, and the mixture was stirred 10 min at rt and then cooled to ~8-10 ºC (if needed). Diazo-compound (1.2 mmol) in $CH_2Cl_2$ (0.83 mL) was added, and the reaction mixture was stirred at this temperature upon completion (see particular reaction times below). The resulting mixture was filtered (Celite/ $CH_2Cl_2$) and concentrated under a reduced pressure. The residue was purified by column chromatography on silica gel (hexanes/EtOAc) to afford the corresponding diazo-compound **56**.




**49** **41** **56**

**General procedure for 2-CC reaction (GP-2):** An oven dried 5 mL Wheaton V-vial, containing a stirring bar, was charged with imine **49** (1 mmol), activated MS 4Å (125 mg), and $Y(OTf)_3$ (56.8 mg, 0.1 mmol) under $N_2$ atmosphere (glovebox). Dry $CH_2Cl_2$ (2.5 mL) was added, and the mixture was stirred 10 min at rt and then cooled to ~8-10 ºC. Diazo-compound

(1.2 mmol) in $CH_2Cl_2$ (0.83 mL) was added, and the reaction mixture was stirred at this temperature upon completion (see particular reaction times below). The resulting mixture was filtered (Celite/ $CH_2Cl_2$) and concentrated under a reduced pressure. The residue was purified by column chromatography on silica gel (hexanes/EtOAc) to afford the corresponding diazo-compound **56**.

**Ethyl 2-diazo-3-(4-methylphenyl)-3-(pyridin-2-ylamino)propanoate (56a)**

**56a** was prepared according to GP-1 (the reaction time was 12 h at 8-10 ºC) from 2-aminopyridine (103.4 mg, 1.1 mmol), 4-methylbenzaldehyde (120.2 mg, 1 mmol), and ethyl diazoacetate (136.8 mg, 1.2 mmol) in 60% yield (186 mg, 0.6 mmol) as a yellow viscous oil. Compound **56a** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.12 (d *J* = 4.1 Hz, 1H), 7.40-7.45 (m, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.63-6.68 (m, 1H), 6.46 (d, *J* = 8.8 Hz, 1H), 5.81 (d, *J* = 7.0 Hz, 1H), 5.1 (br. s, 1H), 4.2 (q, *J* = 7.0 Hz), 2.34 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 14.4, 21.1, 51.9, 60.9, 107.7, 114.2, 126.3, 129.6, 136.6, 137.6, 137.8, 148.3, 157.3, 166.2. HRMS (EI) calcd. for $C_{17}H_{18}O_2N_4$ [M]+: 311.1508, found: 311.1506.

***tert*-Buthyl 2-diazo-3-(4-methylphenyl)-3-(pyridin-2-ylamino)propanoate (56b)**

**56b** was prepared according to GP-1 (the reaction time was 16 h at 8-10 ºC) from 2-aminopyridine (103.4 mg, 1.1 mmol), 4-methylbenzaldehyde (120.2 mg, 1 mmol), and *t*- Bu-diazoacetate (170.4 mg, 1.2 mmol) in 64% yield (216 mg, 0.64 mmol) as a yellow solid, m.p. 126-128 ºC. Compound **56b** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.10 (d, *J* = 5.1, 1H), 7.40-

7.45 (m, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.60-6.65 (m, 1H), 6.44 (d, *J* = 8.5 Hz, 1H), 5.74 (d, *J* = 6.6 Hz, 1H), 5.2 (br. s, 1H), 2.33 (s, 3H), 1.43 (s, 9H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.1, 28.3, 52.0, 81.7, 107.5, 114.1, 126.3, 129.6, 136.7, 137.6, 148.2, 157.4, 165.5. HRMS (EI) calcd. for $C_{19}H_{22}O_2N_4$ [M]+: 339.1821, found: 339.1830.

**Cyclohexyl 2-diazo-3-(4-methylphenyl)-3-(pyridin-2-ylamino)propanoate (56c)**

**56c** was prepared according to GP-1 (the reaction time was 16 h at 8-10 ºC) from 2-aminopyridine (103.4 mg, 1.1 mmol), 4-methylbenzaldehyde (120.2 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 70% yield (255 mg, 0.7 mmol) as a yellow solid m.p. 102-104 ºC. Compound **56c** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.12 (d, *J* = 5.2Hz, 1H), 7.40-7.45 (m, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.63- 6.68 (m, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 5.81 (d, *J* = 7.0 Hz, 1H), 5.1 (br. s, 1H), 4.81-4.88 (m, 1H), 2.33 (s, 3H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.0, 23.5, 25.3, 31.7, 52.0, 73.2, 107.6, 114.1, 126.3, 129.6, 136.7, 137.6, 137.7, 148.2, 157.3. HRMS (EI) calcd. for $C_{21}H_{24}O_2N_4$ [M]+: 365.1978, found: 365.1987.

**Cyclohexyl 2-diazo-3-phenyl-3-(pyridin-2-ylamino)propanoate (56d)**

**56d** was prepared according to GP-1 (the reaction time was 16 h at 8-10 ºC) from 2-aminopyridine (103.4 mg, 1.1 mmol), benzaldehyde (106.1 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 71% yield (249 mg, 0.71 mmol) as a yellow viscous oil. Compound **56d** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.10 (d, *J* = 4.0 Hz, 1H), 7.40-7.45 (m, 3H), 7.35-7.40

(m, 2H), 7.26-7.33 (m, 1H), 6.60-6.67 (m, 1H), 6.46 (d, *J* = 8.1 Hz, 1H), 5.88 (d, *J* = 7.0 Hz, 1H), 5.3 (br. s, 1H), 4.80-4.87 (m, 1H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 23.4, 25.3, 31.6, 52.1, 73.3, 107.8, 114.1, 126.4, 128.0, 128.9, 137.6, 139.7, 148.2, 157.3, 165.7. HRMS (EI) calcd. for $C_{20}H_{22}O_2N_4$ [M]+: 351.1821, found: 351.1818.

**Cyclohexyl 2-diazo-3-(4-methoxyphenyl)-3-(pyridin-2-ylamino)propanoate (56e**)

**56e** was prepared according to GP-1 (the reaction time was 48 h at 8-10 ºC) from 2-aminopyridine (103.4 mg, 1.1 mmol), 4-methoxybenzaldehyde (136.2 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 60% yield (228 mg, 0.6 mmol) as a yellow viscous oil. Compound **56e** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.1 (d, *J* = 4.8 Hz, 1H), 7.33-7.45 (m, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.60-6.67 (m, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 5.79 (d, *J* = 6.6 Hz, 1H), 5.1 (br. s, 1H), 4.82-4.87 (m, 1H), 3.79 (s, 3H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 23.5, 25.3, 31.7, 51.7, 55.3, 73.2, 107.7, 114.1, 114.2, 127.6, 131.7, 137.6, 148.3, 157.3, 159.3, 165.4. HRMS (EI) calcd. for $C_{21}H_{24}O_3N_4$ [M]+: 381.1927, found: 381.1930.

**Cyclohexyl 2-diazo-3-(pyridin-2-ylamino)-3-(o-tolyl)propanoate (56f)**

**56f** was prepared according to GP-1 (the reaction time was 72 h at 8-10 ºC) from 2-aminopyridine (103.4 mg, 1.1 mmol), 2-methylbenzaldehyde (120.2 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 66% yield (240 mg. 0.66 mmol) as a yellow viscous oil. Compound **56f** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). 1H NMR (500 MHz, CDCl3): 8.06 (d, *J* = 4.4 Hz, 1H), 7.37-7.45 (m, 2H), 7.18-

7.45 (m, 3H), 6.60-6.65 (m, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 5.91 (d, *J* = 5.6 Hz, 1H), 5.2 (br. s, 1H), 4.80-4.90 (m, 1H), 2.40 (s, 3H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 19.1, 23.4, 25.3,31.7, 49.2, 73.3, 107.1, 114.1, 125.6, 126.4, 128.0, 130.9, 135.7, 137.5, 137.6, 148.3, 157.3. HRMS (EI) calcd. for $C_{21}H_{24}O_2N_4$ [M]+: 365.1978, found: 365.1976.

**Cyclohexyl 2-diazo-3-(pyridin-2-ylamino)-3-(m-tolyl)propanoate (56g)**

**56g** was prepared according to GP-1 (the reaction time was 36 h at 8-10 ºC) from 2-aminopyridine (103.4 mg, 1.1 mmol), 3-methylbenzaldehyde (120.2 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 76% yield (277 mg, 0.76 mmol) as a yellow viscous oil. Compound **56g** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^1$H NMR (500 MHz, $CDCl_3$): 8.1 (d, *J* = 4.8, 1H), 7.40-7.45 (m, 1H), 7.20-7.25 (m, 3H), 7.07-7.12 (m, 1H), 6.60-6.65 (m, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 5.80 (d, *J* = 6.6 Hz, 1H), 5.1 (br. s, 1H), 4.80-4.85 (m, 1H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.5, 23.5, 25.3, 31.7, 52.1, 73.3, 107.7, 114.2, 123.4, 127.1, 128.8, 137.6, 138.7, 139.7, 148.3, 157.3, 165.8. HRMS (EI) calcd. for $C_{21}H_{24}O_2N_4$ [M]+: 365.1978, found: 365.1974.

**Cyclohexyl 2-diazo-3-(4-fluorophenyl)-3-(pyridin-2-ylamino)propanoate (56h)**

**56h** was prepared according to GP-1 (the reaction time was 36 h at 8-10 ºC) from 2-aminopyridine (103.4 mg, 1.1 mmol), *p*-fluorobenzaldehyde (124.1 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 58% yield (213.4 mg, 0.58 mmol) as a yellow viscous oil. Compound **56h** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 7.95 (d, *J* = 4.8 Hz, 1H), 7.40-7.45 (m, 3H), 7.02-7.06 (m, 2H), 6.63-6.68 (m, 1H), 6.45 (d, *J* = 8.1 Hz, 1H), 5.90 (d, *J* = 7.0 Hz, 1H), 5.2 (br. s, 1H),

4.80-4.87 (m, 1H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 23.5, 25.3, 31.6, 31.7, 51.6, 73.4, 108.0, 114.3, 115.7 (d, $^2J$ = 21.3 Hz), 128.2 (d, $^2J$ = 7.4 Hz), 135.6, 137.6, 148.2, 157.1, 162.3 (d, $J$ = 247.9 Hz), 165.7. HRMS (EI) calcd. for $C_{20}H_{21}O_2N_4F$ [M]+: 369.1727, found: 369.1733.

**Cyclohexyl 3-(4-bromophenyl)-2-diazo-3-(pyridin-2-ylamino)propanoate (56i)**

**56i** was prepared according to GP-1 (the reaction time was 36 h at 8-10 ºC) from 2-aminopyridine (103.4 mg, 1.1 mmol), *p*-bromobenzaldehyde (185.0 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 65% yield (278.2 mg, 0.65 mmol) as a yellow viscous oil. Compound **56i** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.1 (d, $J$ = 4.8 Hz, 1H), 7.48 (d, $J$ = 8.4 Hz, 2H), 7.40-7.45 (m, 1H), 7.34 (d, $J$ = 8.4 Hz, 2H), 6.66-6.68 (m, 1H), 6.45 (d, $J$ = 8.4 Hz, 1H), 5.91 (d, $J$ = 7.3 Hz, 1H), 5.2 (br. s, 1H), 4.80-4.85 (m, 1H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 23.5, 25.3, 31.7, 51.7, 73.5, 108.3, 114.4, 121.8, 128.2, 131.9, 137.6, 139.0, 148.2, 157.0, 165.6. HRMS (EI) calcd. for $C_{20}H_{21}O_2N_4Br$ [M]+: 429.0926, found: 429.0935.

***tert*-Butyl 3-(4-bromophenyl)-2-diazo-3-(pyridin-2-ylamino)propanoate (56j)**

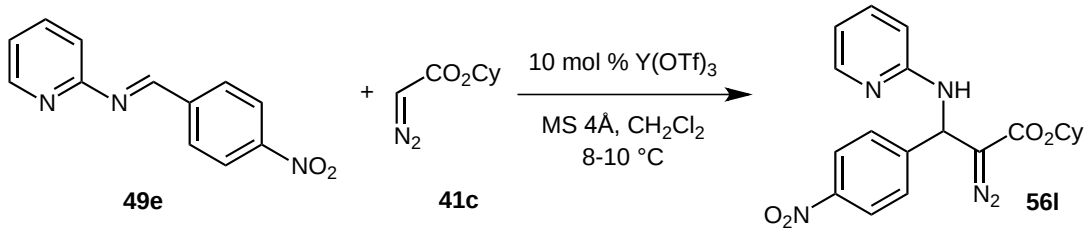
**56j** was prepared according to GP-1 (the reaction time was 36 h at 8-10 ºC) from 2-aminopyridine (103.4 mg, 1.1 mmol), *p*-bromobenzaldehyde (185.0 mg, 1 mmol), and *t*-Bu-diazoacetate (170.4 mg, 1.2 mmol) in 62% yield (249 mg, 0.62 mmol) as a yellow solid, m.p. 126-130 ºC. Compound **56j** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.11 (d, $J$ = 4.8 Hz, 1H), 7.49 (d, $J$ = 8.4 Hz,

2H), 7.42-7.47 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.63-6.69 (m, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 5.86 (d, *J* = 7.4 Hz, 1H), 5.2 (br. s, 1H), 1.44 (s, 9H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 165.3, 157.1, 148.2, 139.0, 137.6, 131.9, 128.2, 121.7, 114.3, 108.1, 82.0, 51.7, 28.3. HRMS (EI) calcd. for $C_{18}H_{19}BrN_4O_2$ [M]+: 403.0770, found: 403.0762.

**Cyclohexyl 2-diazo-3-(4-hydroxy-3-bromophenyl)-3-(pyridin-2-ylamino)propanoate (56k)**

**56k** was prepared according to GP-1 (the reaction time was 72 h at rt) from 2-aminopyridine (103.4 mg, 1.1 mmol), 3-bromo-4-hydroxybenzaldehyde (185.1 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 51% yield (226.4 mg, 0.51 mmol) as a yellow viscous oil. Compound **56k** was purified via column chromatography (silica gel, Hexanes/EtOAc = 5/1 to 1/1). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.0 (d, *J* = 4.1 Hz, 1H), 7.52 (d, *J* = 2.2 Hz, 1H), 7.43-7.50 (m, 1H), 7.20 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.65-6.71 (m, 1H), 6.49 (d, *J* = 8.4 Hz), 5.80 (d, *J* = 6.6 Hz, 1H), 5.2 (br. s, 1H), 4.80-4.90 (m, 1H), 1.30-1.90 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 23.5, 25.3, 31.7, 51.3, 73.5, 108.2, 110.6, 114.4, 116.5, 127.1, 130.3, 132.9, 138.0, 147.9, 152.5, 156.9, 165.6. HRMS (EI) calcd. for $C_{20}H_{21}O_3N_4Br$ [M]+: 445.0797, found: 445.0794.

**Cyclohexyl 2-diazo-3-(4-nitrophenyl)-3-(pyridin-2-ylamino)propanoate (56l)**




**49e** **41c** **56l**

**56l** was prepared according to GP-2 (the reaction time was 72 h at 8-10 ºC) from the corresponding imine **49e** (227.0 mg, 1 mmol)[37] and cyclohexyl diazoacetate (201.6 mg, 1.2

mmol) in 50% yield as a yellow viscous oil. Compound **56l** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.19 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 4.8 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.40-7.48 (m, 1H), 6.63-6.70 (m, 1H), 6.50 (d, *J* = 8.1 Hz, 1H), 6.18 (d, *J* = 7.7 Hz, 1H), 5.4 (br. s, 1H), 4.77-4.85 (m, 1H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 23.5, 25.2, 31.7, 51.6, 73.7, 108.9, 114.6, 123.9, 127.4, 137.6, 147.4, 147.5, 148.0, 156.7, 165.4. HRMS (EI) calcd. for $C_{20}H_{21}N_5O_4$ [M]+: 396.1672, found: 396.1680.

**Cyclohexyl 2-diazo-3-(pyridin-2-ylamino)-3-(4-(trifluoromethyl)phenyl)propanoat (56m)**

**56m** was prepared according to GP-1 from 2-aminopyridine (103.4 mg, 1.1 mmol), 4-$CF_3$-benzaldehyde (174.1 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 68% yield (284.2 mg, 0.68 mmol) as a yellow viscous oil. The reaction time was 48 h at 8-10 ºC. Compound **56m** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.07 (d, *J* = 5.1 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.40-7.50 (m, 1H), 6.63-6.68 (m, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 6.07 (d, *J* = 7.3 Hz, 1H), 5.4 (br. s, 1H), 4.80-4.85 (m, 1H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 23.4, 25.2, 31.7, 51.8, 73.5, 108.5, 114.4, 124.0 (q, $^{1}J$ = 278.4 Hz), 125.7 (m), 126.9, 130.0 (q, $^{2}J$ = 32.4 Hz), 137.6, 144.0, 148.1, 156.9, 165.6. HRMS (EI) calcd. for $C_{21}H_{21}F_3N_4O_2$ [M]+: 419.1695, found: 419.1690.

**Cyclohexyl 2-diazo-3-(pyridin-2-ylamino)-3-(thiophen-2-yl)propanoate (56n)**

**56n** was prepared according to GP-1 (the reaction time was 24 h at 8-10 ºC) from 2-aminopyridine (103.4 mg, 1.1 mmol), 2-thiophenecarboxaldehyde (112.2 mg, 1 mmol), and

cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 45% yield (159.8 mg, 0.45 mmol) as a yellow viscous oil. Compound **56n** was purified via column chromatography (silica gel, Hexanes/EtOAc = 20/1 to 10/1). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 7.95 (d, *J* = 5.1 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.49 (d, *J* = 5.8 Hz, 1H), 6.29 (s, 1H), 5.81 (d, *J* = 7.0 Hz, 1H), 5.3 (br. s, 1H), 4.80-4.90 (m, 1H), 2.33 (s, 3H), 2.21 (s, 3H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 20.1, 21.1, 23.4, 25.2, 31.6, 51.9, 73.1, 107.9, 115.6, 126.2, 129.5, 136.8, 137.6, 147.7, 148.7, 157.5, 165.7. HRMS (EI) calcd. for $C_{18}H_{20}N_4O_2S$ [M]+: 356.1306, found: 356.1308.

**Cyclohexyl 2-diazo-3-((4-methylpyridin-2-yl)amino)-3-(p-tolyl)propanoate (56o)**

**56o** was prepared according to GP-1 (the reaction time was 20 h at 8-10 ºC) from 2-amino-4-methylpyridine (118.9 mg, 1.1 mmol), 4-methylbenzaldehyde (120.2 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 75% yield (184.2 mg, 0.75 mmol) as a yellow viscous oil. Compound **56o** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 7.95 (d, *J* = 5.1 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.49 (d, *J* = 5.8 Hz, 1H), 6.29 (s, 1H), 5.81 (d, *J* = 7.0 Hz, 1H), 5.3 (br. s, 1H), 4.80-4.90 (m, 1H), 2.33 (s, 3H), 2.21 (s, 3H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 20.1, 21.1, 23.4, 25.2, 31.6, 51.9, 73.1, 107.9, 115.6, 126.2, 129.5, 136.8, 137.6, 147.7, 148.7, 157.5, 165.7. HRMS (EI) calcd. for $C_{22}H_{26}N_4O_2$ [M]+: 379.2134, found: 379.2134.

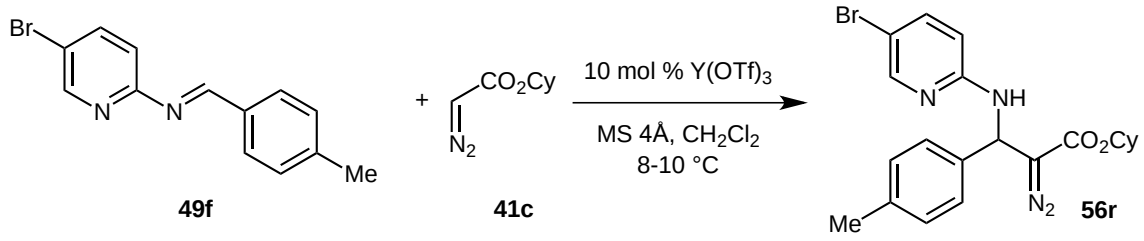
**Cyclohexyl 2-diazo-3-((5-methylpyridin-2-yl)amino)-3-(p-tolyl)propanoate (56p)**

**56p** was prepared according to GP-1 (the reaction time was 60 h at 8-10 ºC) from 2-amino-5-methylpyridine (118.9 mg, 1.1 mmol), 4-methylbenzaldehyde (120.2 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 63% yield (238.1 mg, 0.63 mmol) as a yellow viscous oil. Compound **56p** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 7.90 (s, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.24-7.28 (m, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.49 (d, *J* = 8.4 Hz, 1H), 5.76 (d, *J* = 7.0 Hz, 1H), 5.1 (br. s, 1H), 4.80-4.90 (m, 1H), 2.33 (s, 3H), 2.17 (s, 3H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 17.4, 21.0, 23.4, 25.3, 31.6, 52.2, 73.1, 122.9, 126.3, 129.5, 136.9, 137.6, 138.5, 147.8, 155.5, 165.7. HRMS (EI) calcd. for $C_{22}H_{26}N_4O_2$ [M]+: 379.2134, found: 379.2134.

**Cyclohexyl 2-diazo-3-((4,6-dimethylpyridin-2-yl)amino)-3-(p-tolyl)propanoate (56q)**

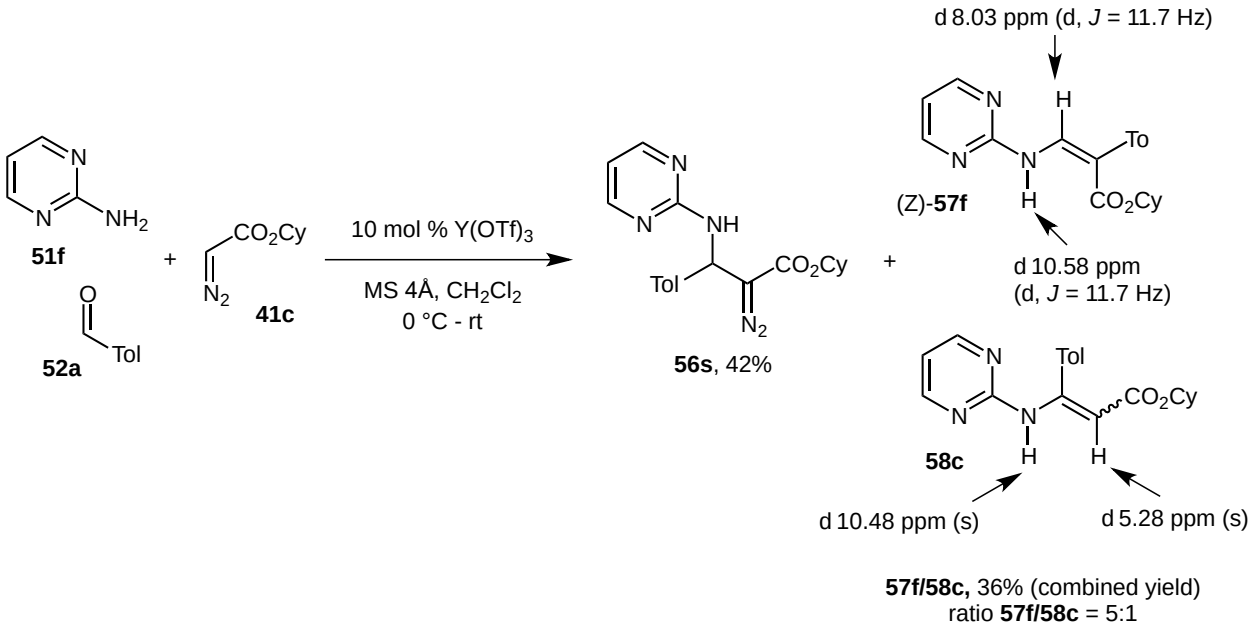
**56q** was prepared according to GP-1 (the reaction time was 48 h at 8-10 ºC) from 2-amino-4,6-dimethylpyridine (134.3 mg, 1.1 mmol), 4-methylbenzaldehyde (120.2 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 50% yield as a yellow viscous oil. Compound **56q** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 7.32 (d, *J* = 7.7 Hz, 2H), 7.16 (d, *J* = 7.7 Hz, 2H), 6.39 (s, 1H), 6.10 (s, 1H), 5.71 (d, *J* = 6.6 Hz, 1H), 5.0 (br. s, 1H), 4.80-4.90 (m, 1H), 2.31 (s, 3H), 2.33 (s, 3H), 2.18 (s, 3H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.0, 21.1, 23.4, 24.0, 25.3, 31.7, 52.2, 73.1, 104.4, 115.0, 126.2, 129.5, 130.1, 136.8, 137.6, 149.0, 156.6, 157.1. HRMS (EI) calcd. for $C_{23}H_{28}N_4O_2$ [M]+: 393.2291, found: 393.2287.

**Cyclohexyl 3-((5-bromopyridin-2-yl)amino)-2-diazo-3-(p-tolyl)propanoate (56r)**



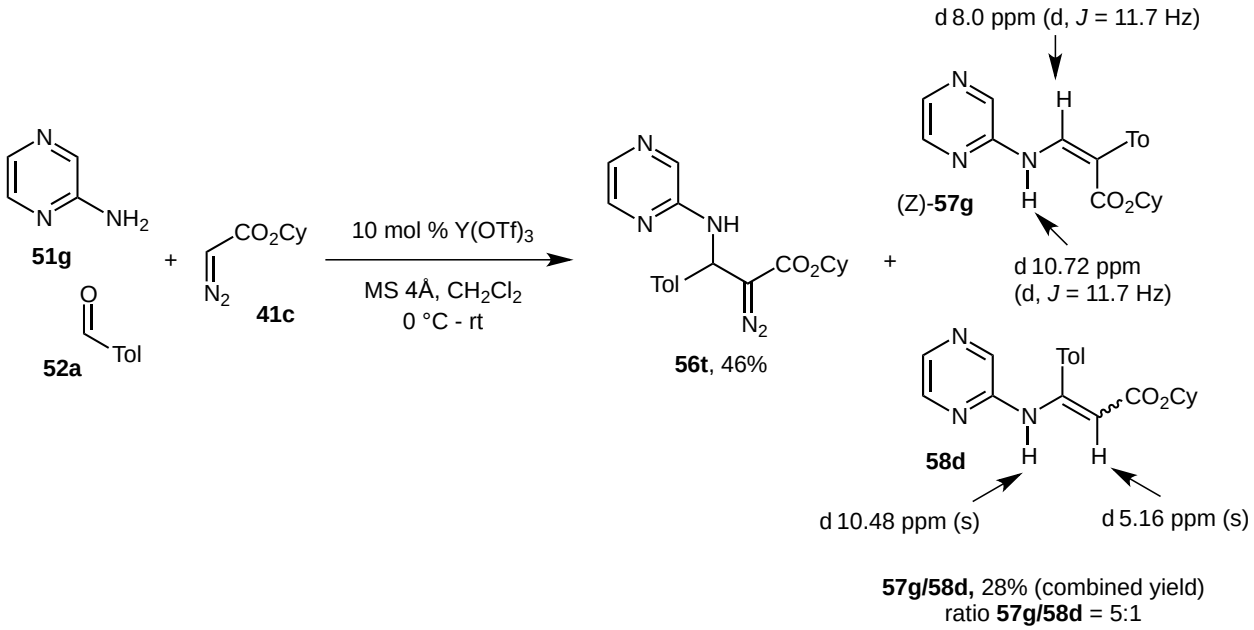

**56r** was prepared according to GP-2 (the reaction time was 24 h at 8-10 ºC) from the corresponding imine **49f** (275.1 mg, 1 mmol)[37] and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 45% (199.0 mg, 0.45 mmol) yield as a yellow viscous oil. Compound **56r** was purified via column chromatography (silica gel, Hexanes/EtOAc = 10/1 to 5/1). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.09 (d, *J* = 2.2 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.38 (d, *J* = 8.8 Hz, 1H), 5.78 (d, *J* = 7.0 Hz, 1H), 5.4 (br. s, 1H), 4.80-4.90 (m, 1H), 2.35 (s, 3H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.1, 23.5, 25.3, 31.7, 52.1, 73.4, 108.5, 109.3, 126.3, 128.8, 129.7, 136.2, 137.9, 139.9, 148.8, 155.9. HRMS (EI) calcd. for $C_{21}H_{23}N_4O_2Br$ [M]+: 443.1083, found: 443.1085.

**Cyclohexyl 2-diazo-3-(pyrimidin-2-ylamino)-3-(p-tolyl)propanoate (56s)**




**56s** was prepared according to GP 1 (the reaction time was 12 h at rt) from 2-aminopyrimidine (104.5 mg, 1.1 mmol), 4-methylbenzaldehyde (120.2 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 42% yield (153.3 mg, 0.42 mmol) as a yellow viscous oil. Compound **56s** was purified via column chromatography (silica gel, Hexanes/EtOAc = 5/1 to 1/1). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.27 (d, *J* = 4.8 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.58 (t, *J* = 4.8 Hz, 1H), 6.12 (d, *J* = 8.1 Hz, 1H), 6.0 (br. s, 1H), 4.80-4.87 (m, 1H), 2.33 (s, 3H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.1, 23.4, 25.3, 31.7, 51.4, 73.2, 111.7, 126.3, 129.5, 136.3, 137.6, 158.1, 161.4. HRMS (EI) calcd. for $C_{20}H_{23}O_2N_5$ [M]+: 366.1930, found: 366.1943.

**Cyclohexyl 2-diazo-3-(pyrazin-2-ylamino)-3-(p-tolyl)propanoate (56t)**




**56t** was prepared according to GP 1 (the reaction time was 20 h at 0 ºC) from 2-aminopyrazine (104.5 mg, 1.1 mmol), 4-methylbenzaldehyde (120.2 mg, 1 mmol), and cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 46% yield (167.99 mg, 0.46 mmol) as a yellow viscous oil. Compound **56t** was purified via column chromatography (silica gel, Hexanes/EtOAc = 5/1 to 1/1). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 7.90-8.00 (m, 1H), 7.93-7.95 (m, 1H), 7.85 (d, *J* = 2.6 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 5.94 (d, *J* = 7.0 Hz, 1H), 5.50 (br. s, 1H), 4.80-4.87 (m, 1H), 2.33 (s, 3H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.1, 23.5, 25.3, 31.6, 31.7, 51.4, 73.4, 126.3, 129.6, 132.7, 134.0, 136.0, 137.9, 142.0, 153.4, 165.6. HRMS (EI) calcd. for $C_{20}H_{23}O_2N_5$ [M]+: 366.1851, found: 366.1855.

**Cyclohexyl 2-diazo-3-((5-methylthiazol-2-yl)amino)-3-(p-tolyl)propanoate (56u)**

**56u** was prepared according to GP-1 (the reaction time was 48 h at 8-10 ºC) from 2-amino-5-methylthiazole (125.6 mg, 1.1 mmol), 4-methylbenzaldehyde (120.2 mg, 1 mmol), and

cyclohexyl diazoacetate (201.6 mg, 1.2 mmol) in 41% yield (157.5 mg, 0.41 mmol) as a yellow viscous oil. Compound **56u** was purified via column chromatography (silica gel, Hexanes/EtOAc = 5/1 to 1/1). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 7.31 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.63 (s, 1H), 6.3 (br. s, 1H), 5.54 (s, 1H), 4.80-4.87 (m, 1H), 2.34 (s, 3H), 2.25 (s, 3H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 11.9, 21.2, 23.5, 25.3, 31.7, 55.3, 73.4, 122.7, 126.3, 129.6, 135.6, 138.1, 165.3, 167.0. HRMS (EI) calcd. for $C_{20}H_{24}O_2N_4S$ [M]+: 384.1620, found: 384.1617.

**Diethyl (1-diazo-2-(pyridin-2-ylamino)-2-(p-tolyl)ethyl)phosphonate (56v)**

**56v** was prepared according to GP-1 (the reaction time was 24 h at 8-10 ºC) from 2-aminopyridine (103.4 mg, 1.1 mmol), 4-methylbenzaldehyde (120.2 mg, 1 mmol), and diethyl diazomethylphosphonate (213.8 mg, 1.2 mmol) in 67% yield as a yellow solid, m.p. 124-126 ºC. Compound **56v** was purified via column chromatography (silica gel, Hexanes/EtOAc = 5/1 to 1/2). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.10 (d, *J* = 4.8 Hz, 1H), 7.40-7.45 (m, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.60-6.67 (m, 1H), 6.50 (d, *J* = 8.1 Hz, 1H), 5.62 (dd, *J* = 7.0, 2.6 Hz, 1H), 5.22 (br. d, *J* = 7.0 Hz, 1H), 3.85-4.10 (m, 4H), 2.34 (s, 9H), 1.17-1.27 (m, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 16.3 (*J* = 7.4 Hz), 21.1, 52.9 (d, *J* = 9.3 Hz), 62.5 (m), 108.0, 114.1, 126.4, 129.5, 137.1, 137.5, 137.8, 148.1, 157.1. HRMS (EI) calcd. for $C_{18}H_{23}O_3N_4P$ [M]+: 375.1586, found: 375.1595.

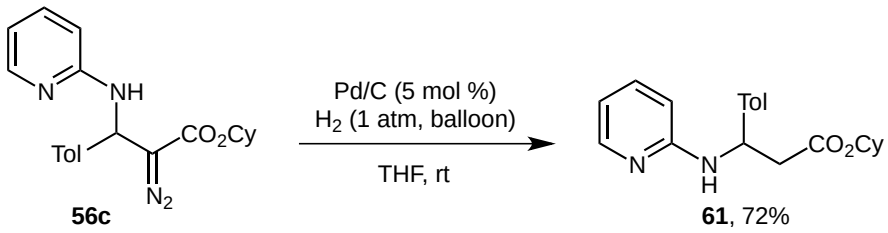
**Diethyl (2-(4-bromophenyl)-1-diazo-2-(pyridin-2-ylamino)ethyl)phosphonate (56w)**

**56w** was prepared according to GP-1 (the reaction time was 48 h at 8-10 ºC) 2-aminopyridine (103.4 mg, 1.1 mmol), 4-bromobenzaldehyde (185.0 mg, 1 mmol), and diethyl

diazomethylphosphonate (213.8 mg, 1.2 mmol) in 51% yield (223.4, 0.51 mmol) as a yellow solid, m.p. 160-164 ºC. Compound **56w** was purified via column chromatography (silica gel, Hexanes/EtOAc = 5/1 to 1/2). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.07 (d, *J* = 5.1 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.37-7.45 (m, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 6.60-6.65 (m, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 5.73 (dd, *J* = 7.3, 4.0 Hz, 1H), 5.75 (br. d, *J* = 7.3 Hz), 3.85-4.10 (m, 4H), 2.34 (s, 9H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 16.0 (t, *J* = 7.4 Hz), 52.7 (d, *J* = 9.2 Hz), 62.7 (m), 108.5, 114.3, 121.8, 128.4, 131.9, 137.5, 139.3, 148.0, 156.8. HRMS (EI) calcd. for $C_{17}H_{20}BrN_4O_3P$ [M]+: 439.0535, found: 439.0544.

### 4.5 Synthesis of Compounds 61, 58b, 57e, 62 and 63

**Synthesis of cyclohexyl 3-(pyridin-2-ylamino)-3-(p-tolyl)propanoate (61)**

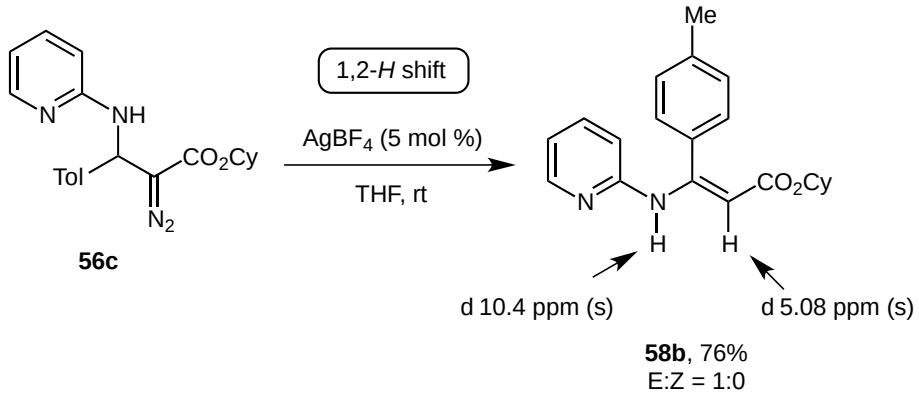



**56c** **61**, 72%

An oven dried 10 mL flask, containing a stirring bar, was charged with 10% Pd on charcoal (10.6 mg, 0.01 mmol) under argon atmosphere (glovebox). The argon atmosphere was evacuated and backfilled with $H_2$ (balloon) 3 times. A solution of diazo-compound **56c** (72.9 mg, 0.2 mmol) in dry THF (5 mL) was then added. The reaction mixture was stirred at rt for 12h, then filtered (Celite®, dichloromethane), and evaporated under a reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc 3/1) to afford the corresponding amino acid derivative **61** (30.4 mg, 72% yield) as a white solid, m.p. 84-86 ºC. $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.03-8.06 (d, *J* = 5.9 Hz, 1H), 7.30-7.35 (m, 1H), 7.25 (d, *J* =

7.7 Hz, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 6.50-6.55 (m, 1H), 6.30 (d, *J* = 8.4 Hz, 1H), 5.30 (br d, *J* = 7.7 Hz, 1H), 5.10-5.20 (m, 1H), 4.65-4.75 (m, 1H), 2.78-2.88 (m, 2H), 2.29 (s, 3H), 1.20-1.75 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.0, 23.6, 25.3, 31.4, 42.6, 52.6, 73.1, 107.2, 113.3, 126.2, 129.3, 137.0, 137.4, 138.8, 148.2, 157.7, 170.5. HRMS (EI) calcd. for $C_{21}H_{26}O_2N_2$ [M]: 338.2000, found: 338.1994.

**Synthesis of (*E*)-Cyclohexyl 3-(pyridin-2-ylamino)-3-(p-tolyl)acrylate (58b)**

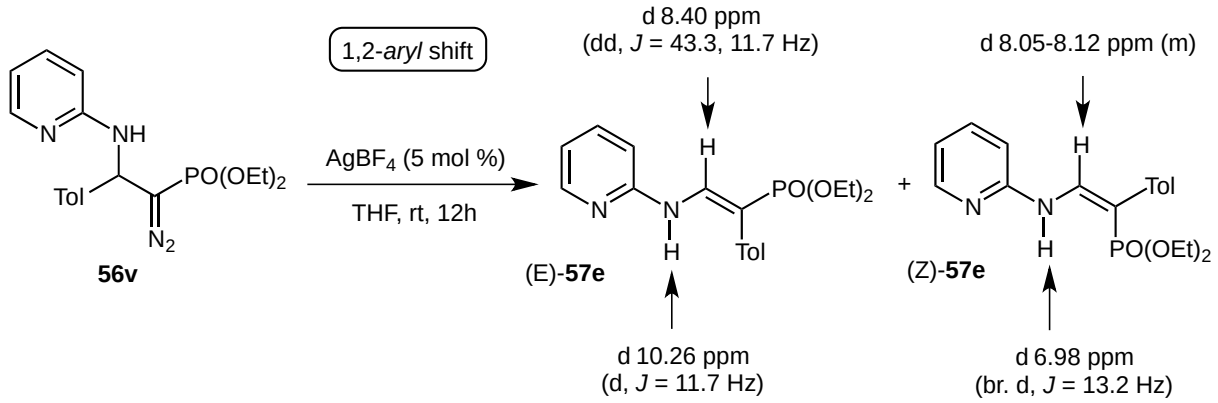



**56c**

**58b**, 76%
E:Z = 1:0

An oven dried 10 mL flask, containing a stirring bar, was charged with $AgBF_4$ (4.8 mg, 0.025 mmol). A solution of diazo-compound **56c** (0.5 mmol, 182.5) in dry THF (5 mL) was then added. The reaction mixture was stirred at room temperature for 5h. The solvent was removed under a reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to afford the corresponding enamine **58b** in 75% yield as a white solid, m.p. 116-119 ºC. $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 10.4 (s, 1H), 8.15-8.17 (m, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.22-7.26 (m, 1H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.72-6.75 (m, 1H), 6.15 (d, *J* = 8.1 Hz, 2H), 5.08 (s, 1H), 4.81-4.86 (m, 1H), 2.34 (s, 3H), 1.20-1.85 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.3, 23.9, 25.5, 31.9, 71.7, 77.2, 95.2, 113.8, 117.2, 127.7, 129.2, 133.4, 136.8, 139.7, 148.4, 153.8, 156.2, 168.7. HRMS (EI) calcd. for $C_{21}H_{24}O_2N_2$ [M]+: 337.1916, found: 337.1916.

**Synthesis of (*E*/*Z*)-Diethyl (2-(pyridin-2-ylamino)-1-(p-tolyl)vinyl)phosphonate (57e)**



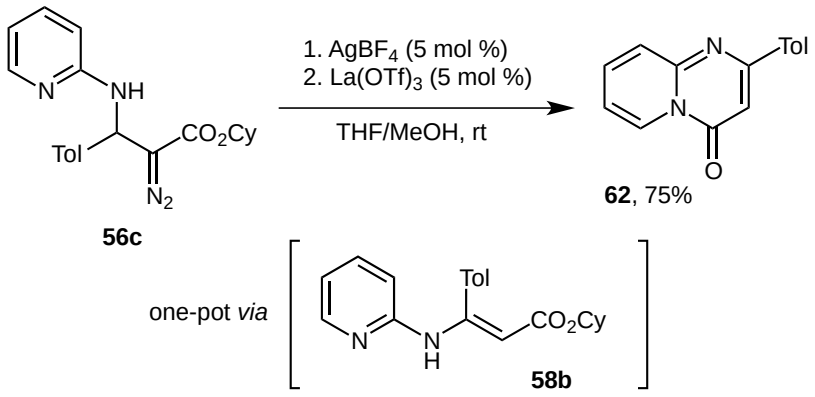

**57e**, 75% (combined yield)
E:Z = 1.7:1

An oven dried 10 mL flask, containing a stirring bar, was charged with $AgBF_4$ (4.8 mg, 0.025 mmol). A solution of diazo-compound **56v** (187.5 mg, 0.5 mmol) in dry THF (5 mL) was then added. The reaction mixture was stirred at rt for 12h. The solvent was removed under a reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to afford the corresponding enamine **57e** as a mixture of stereoisomers (NMR ratio of *E:Z* is 1.7:1) in 75% combined isolated yield. Notably, the ratio of *E:Z* depends on the reaction time.

Isomer (*E*)-**57e**, an upper spot on TLC ($R_f$ ~ 0.5, Hexanes/EtOAc 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 10.26 (d, *J* = 11.7 Hz, 1H), 8.40 (dd, J = 43.3, 12.1 Hz, 1H), 8.18 (d, *J* = 4.8 Hz, 1H), 7.48-7.53 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.77-6.82 (m, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 3.96-4.14 (m, 4H), 2.32 (s, 3H), 1.23-1.30 (m, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 16.2 (d, *J* = 6.5 Hz), 21.0, 61.7 (d, *J* = 4.6 Hz), 96.8 (d, *J* = 179.4 Hz), 111.0, 116.7, 127.4 (d, *J* = 5.6 Hz), 129.1, 135.7, 137.9, 142.6 (d, *J* = 7.4 Hz), 148.1, 152.4, 154.9. HRMS (EI) calcd. for $C_{18}H_{23}O_3N_2P$ [M]: 346.1446, found: 283.1454.

Isomer (*Z*)-**57e**, a bottom spot on TLC ($R_f$ ~ 0.2, Hexanes/EtOAc 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.19 (d, *J* = 5.1 Hz, 1H), 8.05-8.12 (m, 1H), 7.55-7.60 (m, 1H), 7.20-7.30 (m, 4H), 6.98 (br. d, *J* = 13.2 Hz), 6.83-6.87 (m, 1H), 6.82 (br. d, *J* = 8.4 Hz, 2H), 4.06-4.14 (m, 4H), 2.39 (s, 3H), 1.25-1.32 (m, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 16.2 (d, *J* = 6.5 Hz), 21.1, 61.6 (d, *J* = 5.6 Hz), 102.0 (d, *J* = 200.7 Hz), 108.0, 117.2, 129.2 (d, *J* = 12.0 Hz), 129.6 (d, *J* = 5.5 Hz), 130.0, 130.1, 137.8 (d, *J* = 74.9 Hz), 138.2, 148.4, 152.7. HRMS (EI) calcd. for $C_{18}H_{23}O_3N_2P$ [M]: 346.1446, found: 283.1451.

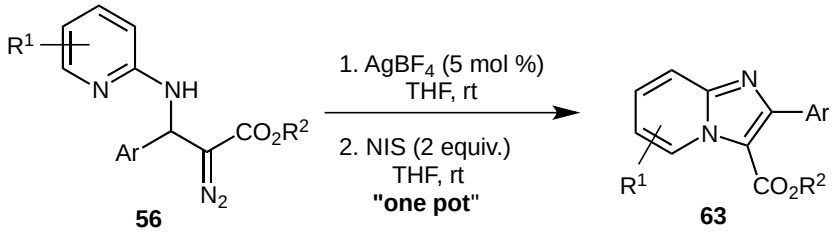
**Synthesis of 2-(*p*-Tolyl)-4H-pyrido[1,2-a]pyrimidin-4-one 62:**




An oven dried 10 mL flask, containing a stirring bar, was charged with $AgBF_4$ (1.9 mg, 0.01 mmol). A solution of diazo-compound **56c** (72.9 mg, 0.2 mmol) in dry THF (2 mL) was then added. The reaction mixture was stirred at rt for 5h. After that, $La(OTf)_3$ (11.7 mg, 0.02 mmol) followed by MeOH (1 mL) was added to the reaction mixture under air atmosphere. The reaction was then stirred at room temperature for 12h. After completion, the solvent was removed under a reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes/EtOAc = 4/1) to afford the corresponding pyrimidin-4-one **62** in 75% yield (35.4 mg, 0.15 mmol) as a white solid, m.p. 162-164 ºC. $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 9.03 (d, *J* = 7.0 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 2H), 7.65-7.72 (m, 1H), 7.28 (d, *J* = 8.1 Hz, 2H),

7.05-7.12 (m, 1H), 6.87 (s, 1H), 2.40 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.4, 99.5, 114.9, 126.7, 127.2, 127.3, 129.5, 134.4, 135.9, 141.0, 150.9, 158.6, 161.9. HRMS (EI) calcd. for $C_{15}H_{12}ON_2$ [M]+: 237.1028, found: 237.1027.

**General Procedure for the Synthesis of Imidazopyridines 63**




**General procedure *GP-3***. An oven dried 10 mL flask, containing a stirring bar, was charged with $AgBF_4$ (4.8 mg, 0.025 mmol). A solution of diazo-compound 2 (0.5 mmol) in dry THF (5 mL) was then added. The reaction mixture was stirred at rt for 5h. Than, the reaction mixture was transferred (via syringe) to another oven-dried 10 mL flask containing NIS (224 mg, 1 mmol). The reaction was stirred overnight at room temperature, quenched ($Na_2S_2O_{3aq}$, 10 mL, 0.1M), extracted (EtOAc, 3×20 mL), dried ($Na_2SO_4$), and concentrated under a reduced pressure. Th recidue was purified by column chromatography (silica gel, hexanes/EtOAc) to afford the corresponding imidazo[1,2-a]pyridine **63**. In the case of imidazo[1,2-a]pyrimidine **63k** and imidazo[1,2-a]pyrazine **63l** the second step was performed at 60 ºC (2 h).

**Cyclohexyl 2-(p-tolyl)imidazo[1,2-a]pyridine-3-carboxylate (63a)**

**63a** was prepared according to GP-3 in 82% yield as a white solid, m.p. 109-112 ºC. $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 9.40 (d, *J* = 7.0 Hz, 1H), 7.70 (d, *J* = 9.2 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 2H), 7.35-7.40 (m, 1H), 7.22 (d, *J* = 7.7 Hz, 2H), 6.96-7.01 (m, 1H), 4.95-5.05 (m, 1H), 2.40 (s, 3H), 1.15-1.90 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.4, 23.5, 25.3, 31.5, 112.2,

113.8, 117.4, 127.6, 128.2, 128.4, 130.1, 131.7, 138.4, 147.0, 153.7, 160.8. HRMS (EI) calcd. for $C_{21}H_{22}O_2N_2$ [M]+: 335.1760, found: 335.1769.

**Ethyl 2-(p-tolyl)imidazo[1,2-a]pyridine-3-carboxylate (63b)**

**63b** was prepared according to GP-3 in 72% yield as a white solid, m.p. 91-93 ºC. $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 9.38 (d, *J* = 7.0 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.35-7.40 (m, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.95-7.00 (m, 1H), 4.30 (q, *J* = 7.3 Hz, 2H), 2.39 (s, 3H), 1.23 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.0, 23.6, 25.3, 31.4, 42.6, 52.6, 73.1, 107.2, 113.3, 126.2, 129.3, 137.0, 137.4, 138.8, 148.2, 157.7, 170.5. HRMS (EI) calcd. for $C_{17}H_{16}O_2N_2$ [M]+: 281.1290, found: 281.1287.

**Cyclohexyl 2-(4-methoxyphenyl)imidazo[1,2-a]pyridine-3-carboxylate (63c)**

**63c** was prepared according to GP-3 in 83% yield as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 9.40 (d, *J* = 7.0 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.37-7.42 (m, 1H), 6.95-7.03 (m, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.97-5.05 (m, 1H), 3.86 (s, 3H), 1.15-1.90 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 23.6, 25.3, 31.6, 55.3, 73.2, 112.0, 113.0, 113.8, 117.3, 127.0, 127.6, 128.4, 131.6, 147.0, 152.3, 160.0, 160.7. HRMS (EI) calcd. for $C_{21}H_{22}O_3N_2$ [M]+: 351.1709, found: 351.1708.

**Cyclohexyl 2-(4-bromophenyl)imidazo[1,2-a]pyridine-3-carboxylate (63d)**

**63d** was prepared according to GP-3 in 65% yield as an yellow solid, m.p. 131-133 ºC. $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 9.39 (d, *J* = 7.0 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.37-7.42 (m, 1H), 6.97-7.03 (m, 1H), 4.96-5.03 (m, 1H), 1.15-

1.90 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 23.5, 25.2, 31.5, 73.4, 112.3, 114.1, 117.4, 122.9, 127.9, 128.3, 130.7, 131.8, 133.6, 147.0, 152.1, 160.4. HRMS (EI) calcd. for $C_{20}H_{19}BrO_2N_2$ [M]+: 399.0708, found: 399.0706.

**Cyclohexyl 2-(3-bromo-4-hydroxyphenyl)imidazo[1,2-a]pyridine-3-carboxylate (63e)**

**63e** was prepared according to GP-3 in 60% yield as a white solid, m.p. 186-188 ºC. $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 9.44 (d, *J* = 7.0 Hz, 1H), 8.08 (d, *J* = 1.8 Hz, 1H), 7.92 (d, *J* = 1.8 Hz, 1H), 7.70-7.72 (d, *J* = 9.2 Hz, 1H), 7.40-7.50 (m, 1H), 7.0-7.10 (m, 1H), 4.95-5.05 (m, 1H), 1.15-1.90 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 23.8, 25.3, 31.8, 73.7, 107.9, 112.2, 114.3, 117.4, 128.3, 128.5, 130.1, 134.6, 140.1, 146.9, 149.7, 151.9, 160.3. HRMS (EI) calcd. for $C_{20}H_{19}BrO_2N_2$ [M]+: 414.0579, found: 414.0566.

**Cyclohexyl 2-(4-nitrophenyl)imidazo[1,2-a]pyridine-3-carboxylate (63f)**

**63f** was prepared according to GP-3 in 78% yield as a yellow solid, m.p. 128-131 ºC. $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 9.42 (d, *J* = 7.3 Hz, 1H), 8.29 (d, *J* = 8.8 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 9.2 Hz, 2H), 7.44-7.52 (m, 1H), 7.05-7.13 (m, 1H), 4.97-5.06 (m, 1H), 1.15-1.90 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 23.6, 25.1, 31.6, 73.9, 112.9, 114.6, 117.7, 122.7, 128.4, 131.3, 141.3, 147.1, 147.8, 150.7, 160.1. HRMS (EI) calcd. for $C_{20}H_{19}O_4N_3$ [M]+: 366.1454, found: 366.1445.

**Cyclohexyl 2-(4-(trifluoromethyl)phenyl)imidazo[1,2-a]pyridine-3-carboxylate (63g)**

**63g** was prepared according to GP-3 in 77% yield as a white solid, m.p. 88-90 ºC. $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 9.41 (d, *J* = 7.3 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 2H),

7.67 (d, *J* = 8.8 Hz, 2H), 7.40-7.47 (m, 1H), 7.00-7.08 (m, 1H), 4.95-5.05 (m, 1H), 1.15-1.90 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 23.3, 25.2, 31.4, 73.4, 112.7, 114.3, 117.6, 124.2 ($^1J$ = 271.9 Hz), 124.5 ($^1J$ = 3.7 Hz), 128.2 ($^2J$ = 37.9 Hz), 130.3, 130.5, 138.4, 147.0, 151.8, 160.3. HRMS (EI) calcd. for $C_{21}H_{19}F_3O_2N_2$ [M]+: 389.1477, found: 389.1472.

**Cyclohexyl 2-(thiophen-2-yl)imidazo[1,2-a]pyridine-3-carboxylate (63h)**

**63h** was prepared according to GP-3 in 59% yield as a pale orange solid, m.p. 97-100 ºC. $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 9.35 (d, *J* = 7.0 Hz, 1H), 8.03 (d, *J* = 3.3 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 5.1 Hz, 1H), 7.35-7.42 (m, 1H), 7.10-7.20 (m, 1H), 6.95-7.01 (m, 1H) 5.10-5.17 (m, 1H), 1.20-2.10 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 24.0, 25.3, 31.9, 74.0, 111.4, 113.9, 117.2, 127.2, 127.9, 128.0, 128.5, 129.9, 136.6, 146.7, 160.3. HRMS (EI) calcd. for $C_{18}H_{18}O_2N_2S$ [M]+: 327.1167, found: 327.1170.

**Cyclohexyl 7-methyl-2-(p-tolyl)imidazo[1,2-a]pyridine-3-carboxylate (63i)**

**63i** was prepared according to GP-3 in 75% yield as a white solid, m.p. 118-120 ºC. $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 9.27 (d, *J* = 7.0 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.46 (s, 3H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.80-6.88 (m, 1H), 4.95-5.05 (m, 1H), 2.45 (s, 3H), 2.41 (s, 3H), 1.15-1.90 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.2, 21.4, 23.5, 25.3, 31.5, 72.9, 111.7, 116.0, 116.3, 127.5, 128.2, 130.0, 131.8, 138.2, 138.9, 147.4, 153.7, 160.8. HRMS (EI) calcd. for $C_{22}H_{24}O_2N_2$ [M]+: 349.1916, found: 349.1912.

**Cyclohexyl 6-bromo-2-(p-tolyl)imidazo[1,2-a]pyridine-3-carboxylate (63j)**

**63j** was prepared according to GP-3 in 79% yield as a yellow oil. $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 9.60 (s, 1H), 7.62 (d, *J* = 7.7 Hz, 2H), 7.57 (d, *J* = 9.5 Hz, 1H), 7.43 (d, *J* = 9.5 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 2H), 4.95-5.05 (m, 1H), 2.39 (s, 3H), 1.15-1.90 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.3, 23.3, 25.2, 31.3, 108.6, 112.4, 117.8, 128.2, 128.5, 130.0, 130.9, 138.6, 145.2, 153.7, 160.4. HRMS (EI) calcd. for $C_{21}H_{21}BrO_2N_2$ [M]+: 413.0865, found: 413.0878.

**Cyclohexyl 2-(p-tolyl)imidazo[1,2-a]pyrimidine-3-carboxylate (63k)**

**63k** was prepared according to GP-3 (second step at 60 ºC) in 66% yield as pale yellow solid, m.p. 110-113 ºC. $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 9.68 (dd, *J* = 7.0, 2.2 Hz, 1H), 8.70 (dd, *J* = 4.0, 2.2 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 8.70 (dd, *J* = 7.0, 4.4 Hz, 1H), 5.00-5.05 (m, 1H), 2.41 (s, 3H), 1.15-1.90 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.4, 23.5, 25.2, 29.5, 31.5, 73.8, 110.0, 110.5, 128.2, 130.3, 130.7, 136.1, 139.0, 149.6, 152.2, 154.8, 160.4. HRMS (EI) calcd. for $C_{20}H_{21}O_2N_3$ [M]+: 336.1712, found: 336.1711.

**Cyclohexyl 2-(p-tolyl)imidazo[1,2-a]pyrazine-3-carboxylate (63l)**

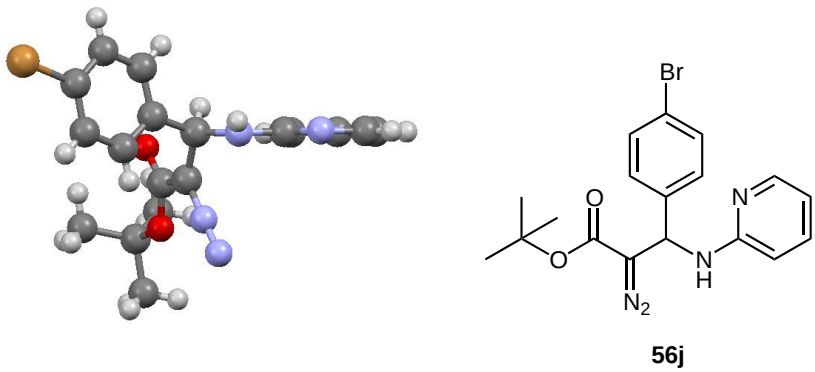
**63l** was prepared according to GP-3 (second step at 60 ºC) in 70% yield as a yellow oil. $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 9.22 (d, *J* = 3.4 Hz, 1H), 9.19 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.00-5.08 (m, 1H), 2.41 (s, 3H), 1.15-1.90 (m, 10H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 21.4, 23.4, 25.1, 31.4, 113.3, 120.6, 128.4, 130.1, 130.5, 131.4, 139.1, 141.2, 143.5, 153.9, 160.1. HRMS (EI) calcd. for $C_{20}H_{21}O_2N_3$ [M]+: 336.1712, found: 336.1719.

### 4.6 X-Ray Analysis of the Compound 56j

Prepared by Donald J. Wink (dwink@uic.edu)

Compound **56j** was crystallized from Hexanes/EtOAc (10:1) at room temperature. CCDC-916523 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

The amine nitrogen, the atoms of they pyridine ring, and the other carbon on the amine nitrogen are present in a planar arrangement with all atoms within 0.05 angstroms of the common plane. The hydrogen on the amine nitrogen, which was refined independently, is 0.28 angstroms from the plane, making the geometry around the amine hydrogen a trigonal plane, not a pyramid (Figure 5). This presumably occurs as a result of the conjugation of the line pair on the nitrogen with the aromatic pi-electrons. The compound crystallizes with a single molecule in the asymmetric unit. Inspection of the crystal packing reveals that the two molecules in the unit cell are bound together by a pair of hydrogen bonds between the pyridine nitrogen on one molecule and the amino hydrogen on the other unit (Figure 6).




**56j**

**Figure 5.** Drawing of Molecule **56j**: the drawing is parallel to the plane formed by the pyridine atoms, the adjacent amino N and the second C on the N, showing the near-trigonal planar geometry around the amino N.

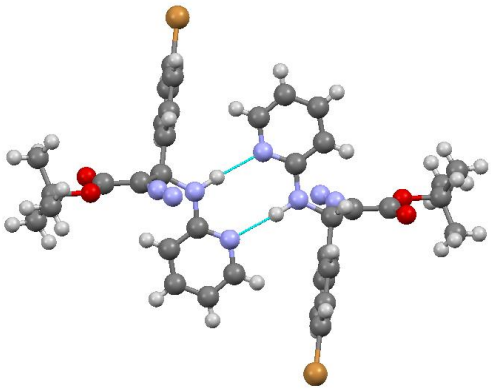


**Figure 6.** Drawing of molecule **56j** showing the H-bonds that connect the two molecules in the unit cell.

**Computing details**

Data collection: *SMART* (Bruker); cell refinement: *SAINT* (Bruker); data reduction: *SAINT* (Bruker); absorption correction: SADABS. Program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997).

**Crystal data**

| | |
|---|---|
| $C_{20}H_{26}BrN_2O_3$ | $F(000) = 712$ |
| $M_r = 403.28$ | $D_x = 1.480$ Mg m$^{-3}$ |
| Monoclinic, $P_1$ | Mo $K\square$ radiation, $\square = 0.71073$ Å |
| a = 6.2016 (7) Å | Cell parameters from 47 reflections |
| b = 11.2171 (12) Å | $\square = 2.19$ mm$^{-1}$ |
| c = 14.3699 (16) Å | $T = 296$ K |
| α = 102.070 (2)° | Block, colorless |
| β = 96.115 (2)° | 0.45 × 0.30 × 0.28 mm |
| γ = 101.230 (2)° | |
| V = 947.45 (18) Å$^3$ | |
| $Z = 3$ | |

**Data collection**

| | |
|---|---|
| CCD area detector diffractometer | 4234 independent reflections |
| Radiation source: fine-focus sealed tube | 2550 reflections with $I > 2\sigma(I)$ |
| Graphite | $R_{int} = 0.050$ |
| phi and $\omega$ scans | $\theta_{max} = 28.3°$, $\theta_{min} = 1.5°$ |
| Absorption correction: multi-scan | $h = -8 \rightarrow 8$ |
| $T_{min} = 0.439$, $T_{max} = 0.579$ | $k = -14 \rightarrow 14$ |
| 8757 measured reflections | $l = -19 \rightarrow 18$ |

**Refinement**

| | |
|---|---|
| Refinement on $F^2$ | Primary atom site location: structure-invariant direct methods |
| Least-squares matrix: full | Secondary atom site location: difference Fourier map |
| $R[F^2 > 2\sigma(F^2)] = 0.046$ | Hydrogen site location: inferred from neighbouring sites or located in difference map (amino hydrogen) |
| $wR(F^2) = 0.106$ | H atoms treated by a mixture of independent and constrained refinement |
| $S = 0.81$ | $w = 1/[\sigma^2(F_o^2) + (0.0411P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$ |
| 4234 reflections | $(\Delta/\sigma)_{max} < 0.001$ |
| 233 parameters | $\Delta\rho_{max} = 0.60$ e Å$^{-3}$ |
| 0 restraints | $\Delta\rho_{min} = -0.28$ e Å$^{-3}$ |

# CHAPTER THREE: COPPER-CATALYZED TRANSANNULATION REACTION OF PYRIDOTRIAZOLES AND TERMINAL ALKYNES TOWARDS INDOLIZINES

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## 1 - INTRODUCTION

### 1.1 Synthesis of Indolizines

In keeping with our group's interest in *N*-fused heterocyclic compounds, we turned our attention to indolizines **71**. The indolizine moiety can be found in several pharmaceutically active molecules and electroluminescent materials (Figure 7),[41] which drives the continuous development of efficient methods to access these molecules.

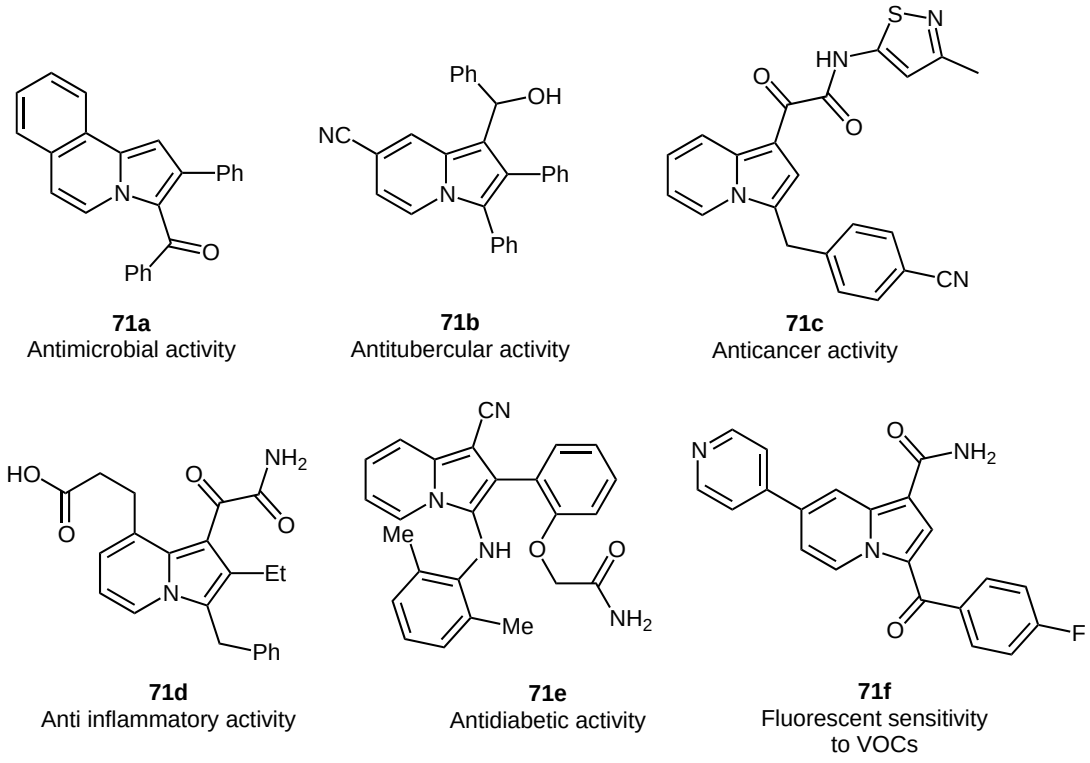
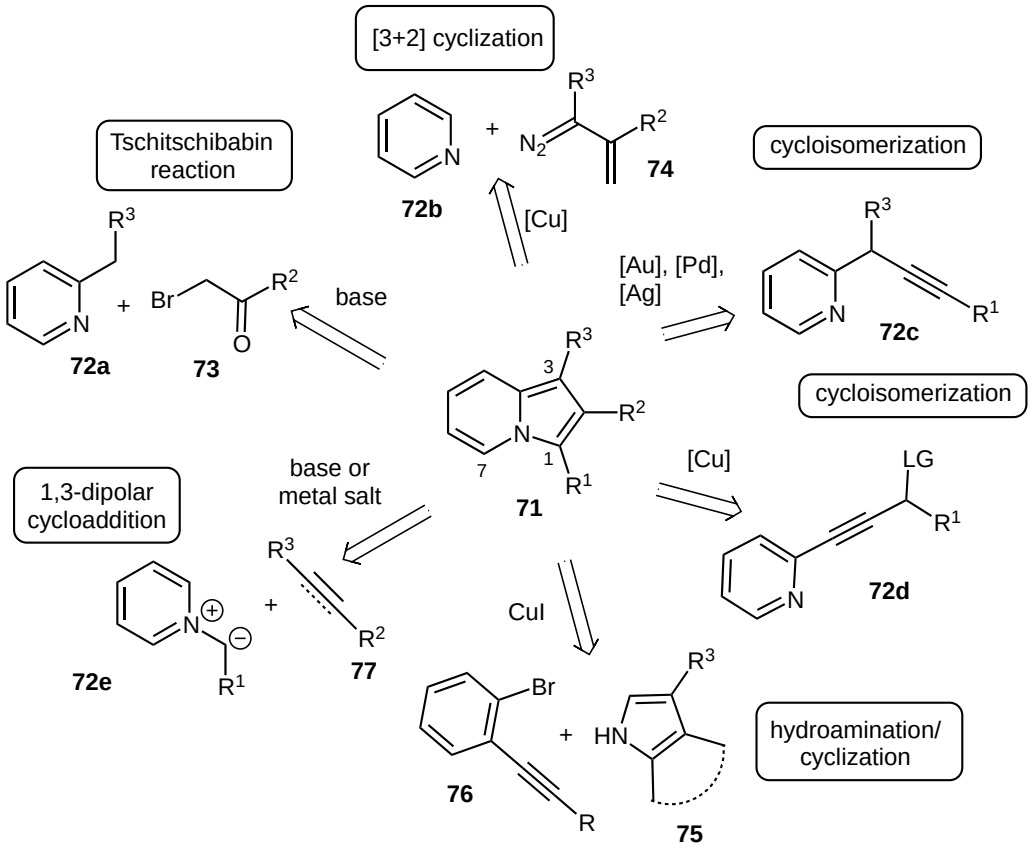



**Figure 7.** Examples of Bioactive Molecules Containing the Indolizine Scaffold

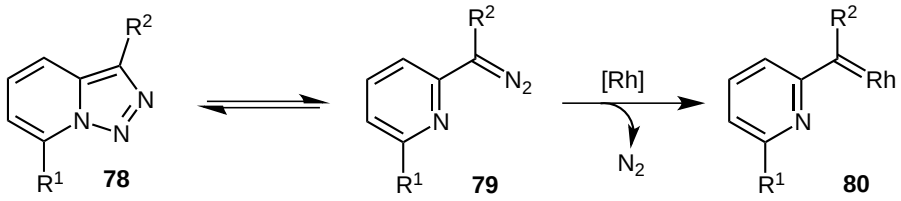
Numerous synthetic routes towards indolizines **71** have been reported over the past century aiming at the formation of either the pyridyl or pyrrolyl ring (Scheme 22).[42] The most common methods are the Tschitschibabin reaction from 2-methylpyridine derivatives, 1,3-dipolar cycloaddition reaction from pyridinium ylides and cycloizomerization of propargylpyridines. However, general, direct, and sustainable methods are still needed to expand the scope of indolizines.




**Scheme 22.** General Methods for the Synthesis of Indolizines

## 1.2 Transannulation of Pyridotriazoles

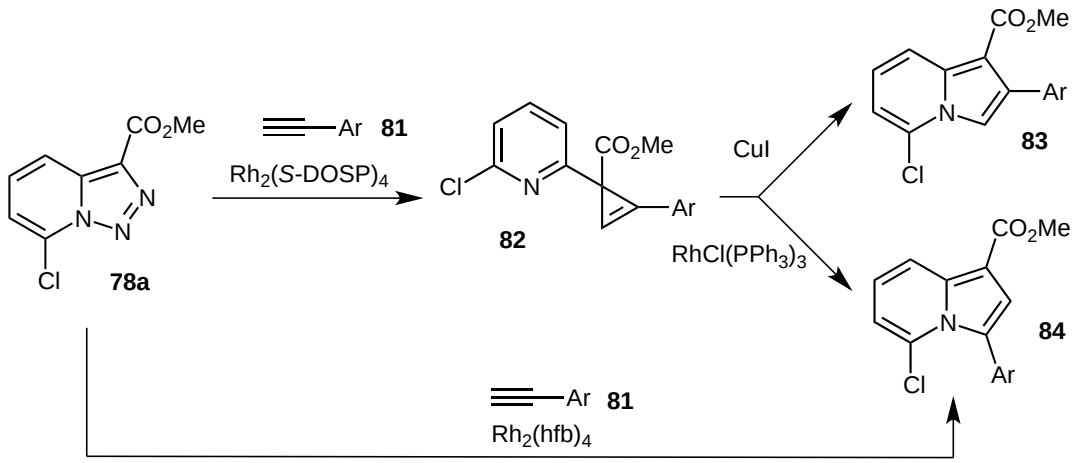
[1,2,3]Triazolo[1,5-*a*]pyridines **78** represent a source of *α*-imino diazo-compounds. Indeed, study of the pyridotriazoles properties showed that upon tautomerization, **78** exists in equilibrium with diazo-form **79** (Scheme 23).[43] While calculations demonstrated that the closed-form of pyridotriazoles was more stable, electronic effect of substituents at C-3 and C-7 positions could shift the equilibrium towards diazo-form **79**.




**Scheme 23.** Equilibrium Between Closed- and Open-Form of Pyridotriazoles

Thus, taking advantage of the carbene reactivity of pyridotriazoles, the transition metal-catalyzed denitrogenative transannulation of pyridotriazoles **78** represents an efficient method for the synthesis of fused nitrogen-containing heterocycles (Scheme 24).[44] Chuprakov and Gevorgyan showed that Rh(II) could catalyze the reaction of pyridotriazole **78a** with a terminal alkyne to form both cyclopropene **82** and indolizines **84**.[44a] It is hypothesized that the diazo-form **79** would be trapped with Rh(II) to form the reactive pyridiyl carbene intermediate **80**, which is capable of reacting with terminal alkynes to produce **82** and **84**. The regioselectivity of the subsequent isomerization of the cyclopropene into indolizine depended on the metal catalyst employed. Thus, CuI selectively led to the formation of the 1,2-disubstituted indolizine **83** while $RhCl(PPh_3)_3$ provided only the other isomer **84**. Moreover, further screening of the Rh(II)

ligands revealed that indolizine **84** could be selectively accessed in one step from pyridotriazole **78a** in presence of rhodium heptafluorobutyrate ($Rh_2(hfb)_4$).[44b]




**Scheme 24.** Rh(II)-Catalyzed Transannulation Reaction of Pyridotriazole

However, this transannulation reaction had several shortcomings. Thus, a Cl substituent at the C-7 position and an electron withdrawing ester group at the C-3 position of the pyridotriazoles were requisite to facilitate the formation of a sufficient amount of the open form of triazole **79** even at room temperature and subsequently generate indolizines **84**.[43] In addition, the reaction was limited to aryl alkynes **81** only.[44b] Interestingly, Shi and Gevorgyan reported that non-activated pyridotriazoles could undergo Rh(II)-catalyzed N-H insertion producing 2-picolylamine derivatives and imidazo[1,5-*a*]pyridines in high yields.[45] Consequently, we decided to investigate the metal-catalyzed transannulation of non-activated pyridotriazoles **78** ($R^1$ = H) with terminal alkynes **81** to form indolizines **85**.

In addition, the above-mentioned transannulation reaction of pyridotriazoles **78a** (Scheme 24)[44] as well as the further developed and widely used transannulation reactions of N-sulfonyl

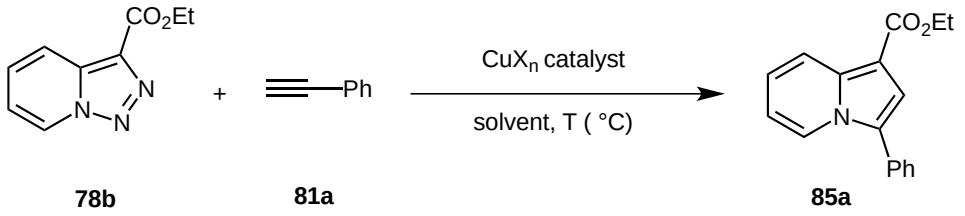
1,2,3-triazoles,[46] require the use of a Rh-catalyst,[47] which is one of the most expensive and rare metals used in catalysis. Naturally, the development of alternative catalysts for transannulation reactions of triazoles would dramatically increase the synthetic applicability of this methodology.[48]

# 2 - OPTIMIZATION OF THE COPPER-CATALYZED TRANSANNULATION

## 2.1 Optimization of Reaction Conditions and Scope

Accordingly, aiming at the discovery of a less expensive catalyst and at expanding the scope of transannulation reactions of pyridotriazoles, we turned our attention to the potential employment of copper catalysts.[21d,49] To ensure sufficient amounts of the open form **79** of the non-activated pyridotriazole **78b**, we tested the potential transannulation reaction at elevated temperatures.[43b,50] Thus, we tested various copper catalysts in the reaction of non-activated pyridotriazole **78b** with phenylacetylene **81a** (Table 8). While copper halides (entries 1-5) and $Cu(OAc)_2$ (entry 6) were found to be inefficient, the use of Cu(I) and Cu(II) triflates led to the formation of the corresponding indolizine **85a** in moderate yields (entries 7 and 8). Delightfully, the more electrophilic $Cu(MeCN)_4PF_6$ catalyst turned out to be even more efficient in the formation of **85a** (entry 9). After optimization of the temperature and solvent (entries 10-13), a virtually quantitative yield of **85a** was achieved (entry 13). Decreasing the catalyst loading was also inefficient (entries 14-15). Finally, we were pleased to find that this reaction works equally efficiently under aerobic conditions (entry 16). As expected, under thermal conditions no reaction occurred (entry 17). Moreover, it was found that $Rh_2(hfb)_4$ is not a capable catalyst for this reaction of non-activated pyridotriazole **78b** (entry 18). Also, the 7-Cl substituted analog pyridotriazole **78a** of produced a complex mixture of products in presence of $Cu(MeCN)_4PF_6$, even at lower temperature.

**Table 8.** Optimization of Transannulation Reaction[a]




**78b** **81a** **85a**

| Entry | Catalyst | | Solvent | T (ºC) | Yield (%) of **85a**[b] |
|---|---|---|---|---|---|
| 1 | CuBr | 15 mol % | toluene | 100 | N.R. |
| 2 | $CuBr_2$ | 15 mol % | toluene | 100 | N.R. |
| 3 | CuCl | 15 mol % | toluene | 100 | N.R. |
| 4 | $CuCl_2$ | 15 mol % | toluene | 100 | N.R. |
| 5 | CuI | 15 mol % | toluene | 100 | N.R. |
| 6 | $Cu(OAc)_2$ | 15 mol % | toluene | 100 | N.R. |
| 7 | $CuOTf•0.5C_6H_6$ | 15 mol % | toluene | 100 | 38 |
| 8 | $Cu(OTf)_2$ | 15 mol % | toluene | 100 | 25 |
| 9 | $Cu(MeCN)_4PF_6$ | 15 mol % | toluene | 100 | 50 |
| 10[c] | $Cu(MeCN)_4PF_6$ | 15 mol % | toluene | 120 | 96 |
| 11[c] | $Cu(MeCN)_4PF_6$ | 15 mol % | DCE | 120 | 89 |
| 12[c] | $Cu(MeCN)_4PF_6$ | 15 mol % | DMA | 120 | 28 |
| 13[c] | $Cu(MeCN)_4PF_6$ | 15 mol % | toluene | 130 | 99 |
| 14[c] | $Cu(MeCN)_4PF_6$ | 10 mol % | toluene | 130 | 91 |
| 15[c] | $Cu(MeCN)_4PF_6$ | 5 mol % | toluene | 130 | 49 |
| 16[d] | $Cu(MeCN)_4PF_6$ | 15 mol % | toluene | 130 | 99 |
| 17 | No catalyst | - | toluene | 100 | N.R. |
| 18 | $Rh_2(hfb)_4$ | 15 mol % | toluene | 100 | N.R [e] |

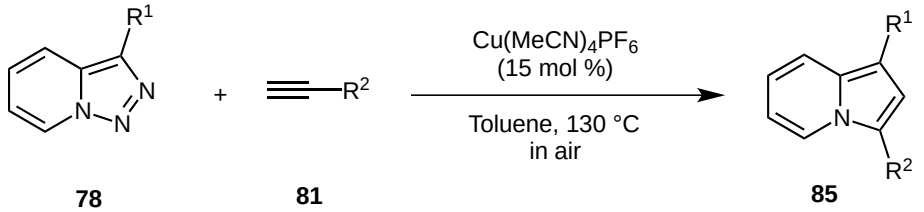
[a] Conditions: triazole (1 equiv), alkyne (3 equiv), catalyst (15 mol %), solvent (1 M). [b]GCMS yields. [c]1.2 equiv of alkyne was used. [d] In air with 1.2 equiv of alkyne. [e]Polymerization of the alkyne was observed. hfb = heptafluorobutyrate.

Having the optimized conditions in hand, we investigated the scope of this Cu-catalyzed transannulation reaction of pyridotriazoles with terminal alkynes (Table 9). A variety of aryl alkynes bearing electron-neutral, electron withdrawing and electron donating substituents at *ortho*-, *meta*- and *para*-positions produced the corresponding indolizines **85** in high yields upon reaction with pyridotriazole **78b** (Table 9, entries 1–10). Heteroaromatic alkynes such as 3-thienyl acetylene and enyne led to the indolizines **85k, l** in reasonable yields (entries 11 and 12).

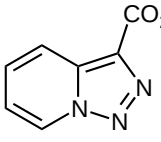
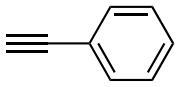
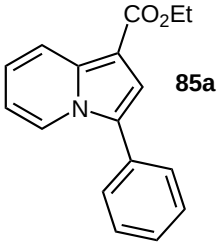
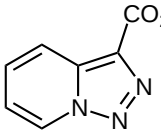
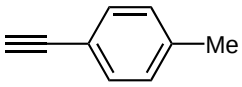
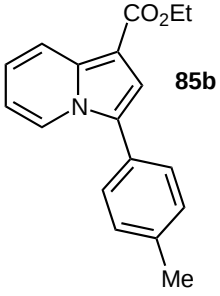
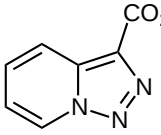
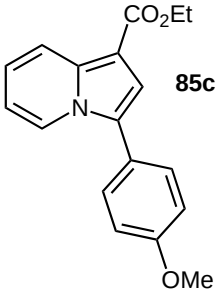
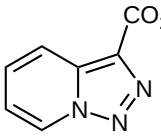
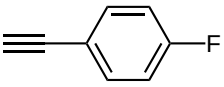
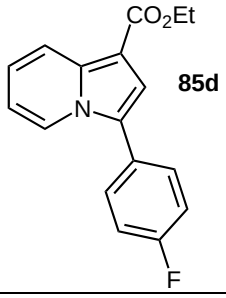
We were pleased to find that in contrast to the previously reported Rh-catalyzed reaction, aliphatic alkynes were also competent reactants. Thus, benzyl-, n-butyl, and c-hexyl acetylenes reacted smoothly to produce the corresponding indolizines in good yields (entries 13–15). To our delight, functional groups including benzyloxy- and *N*-phthalimido were perfectly tolerated under the reaction conditions (entries 16 and 17).

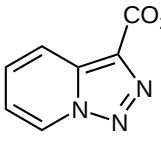
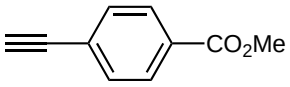
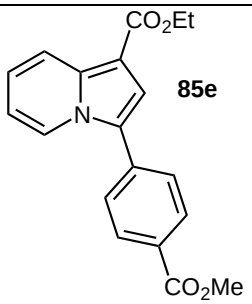
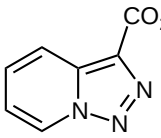
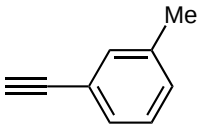
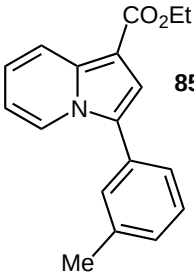
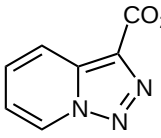
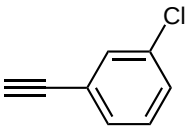
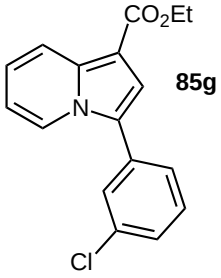
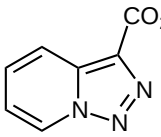
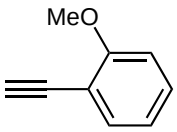
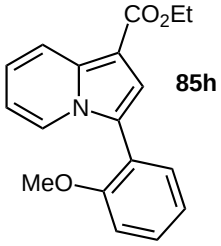
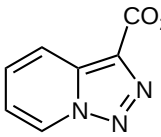
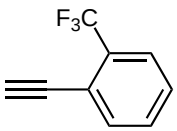
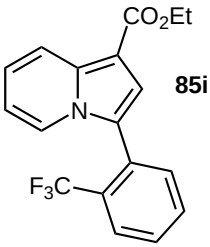
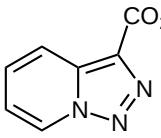
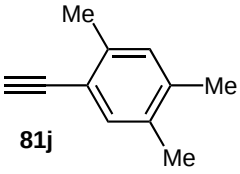
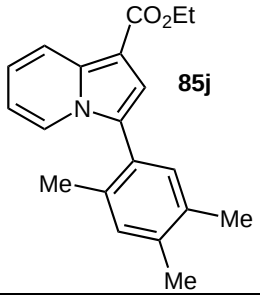
Moreover, while our group previously reported the Rh-catalyzed transannulation reaction of pyridotriazoles with nitriles,[44b] the Cu-catalyzed transannulation showed a strong preference for the alkyne over the nitrile group. Thus, the reaction of pyridotriazole **78b** with 5-hexynenitrile furnished indolizine **85r** with the nitrile group staying intact (entry 18). Notably, pyridotriazoles which did not contain electron-withdrawing groups at the C-3 position were found to be reactive substrates as well. Hence, the indolizines derived from 3-phenyl and 3-methyl pyridotriazoles were produced in reasonable yields (entries 19–23). Remarkably, even a non-substituted pyridotriazole ($R^2$ = H) reacted with phenylacetylene to form indolizine **85x** in a moderate yield. We also tested trialkylsilyl-substituted alkynes, which were either unstable (TMS, TES) or stayed intact (TIPS) under the reaction conditions.

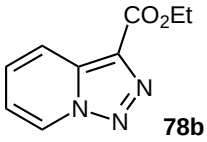
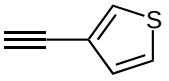
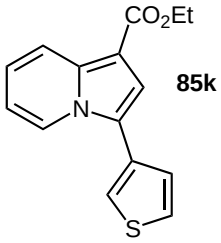
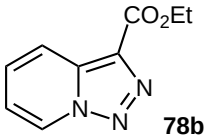
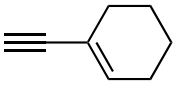
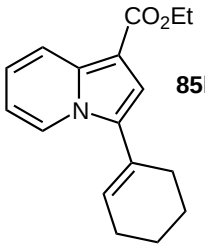
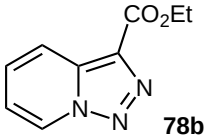
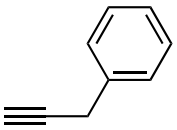
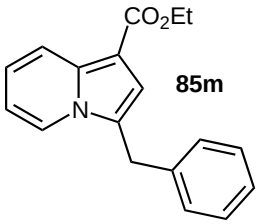
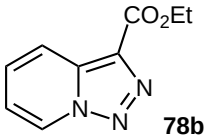
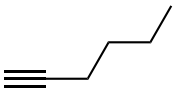
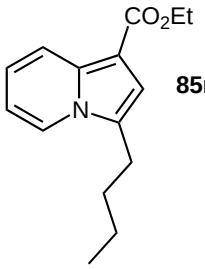
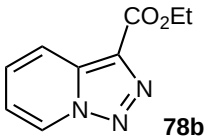
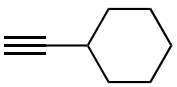
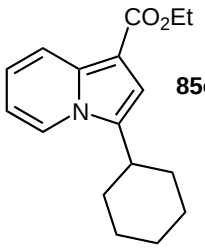
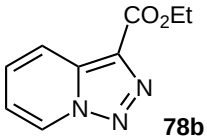
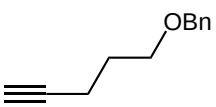
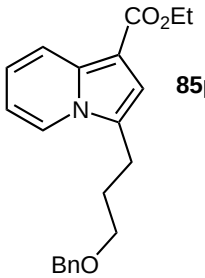
**Table 9.** Scope of Indolizines **85**[a]

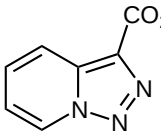
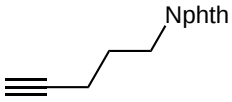
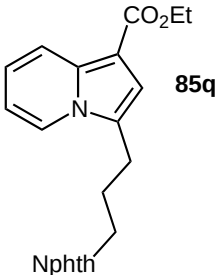
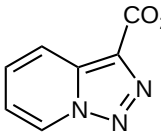
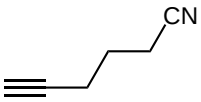
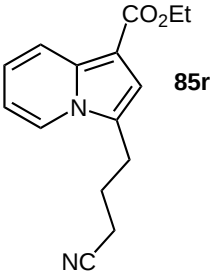
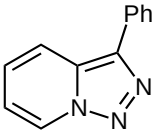
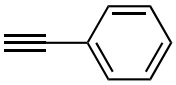
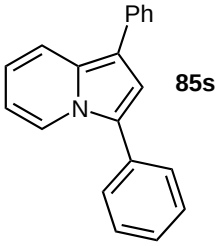
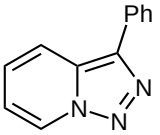
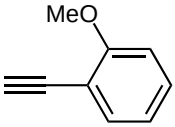
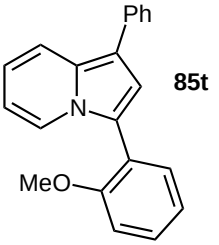
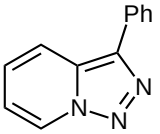
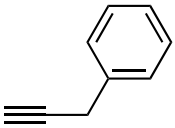
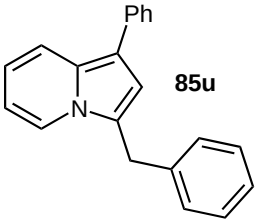
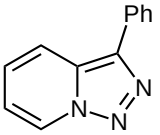
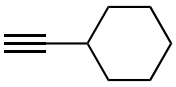
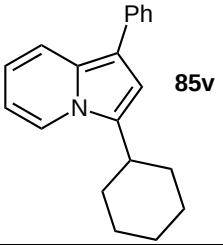


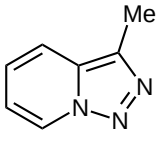
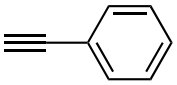
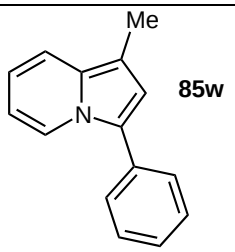
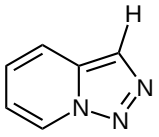
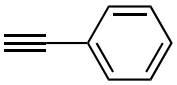
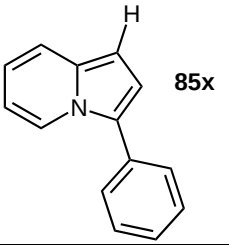

**78** **81** **85**

| Entry | Pyridotriazole | Alkyne | Product | Yield (%) of **85**[b] |
|---|---|---|---|---|
| 1 |  **78b** |  **81a** |  **85a** | 70 |
| 2 |  **78b** |  **81b** |  **85b** | 74 |
| 3 |  **78b** |  **81c** |  **85c** | 65 |
| 4 |  **78b** |  **81d** |  **85d** | 70 |

| Entry | Pyridotriazole | Alkyne | Product | Yield (%) of **85**[b] |
|---|---|---|---|---|
| 5 |  **78b** |  **81e** |  **85e** | 48 |
| 6 |  **78b** |  **81f** |  **85f** | 57 |
| 7 |  **78b** |  **81g** |  **85g** | 60 |
| 8 |  **78b** |  **81h** |  **85h** | 94 |
| 9 |  **78b** |  **81i** |  **85i** | 78 |
| 10 |  **78b** |  **81j** |  **85j** | 75 |

| Entry | Pyridotriazole | Alkyne | Product | Yield (%) of **85**[b] |
|---|---|---|---|---|
| 11 |  **78b** |  **81k** |  **85k** | 33 |
| 12 |  **78b** |  **81l** |  **85l** | 67 |
| 13 |  **78b** |  **81m** |  **85m** | 68 |
| 14 |  **78b** |  **81n** |  **85n** | 82 |
| 15 |  **78b** |  **81o** |  **85o** | 83 |
| 16 |  **78b** |  **81p** |  **85p** | 53 |

| Entry | Pyridotriazole | Alkyne | Product | Yield (%) of **85**[b] |
|---|---|---|---|---|
| 17 |  **78b** |  **81q** |  **85q** | 82 |
| 18 |  **78b** |  **81r** |  **85r** | 66 |
| 19 |  **78c** |  **81a** |  **85s** | 77 |
| 20 |  **78c** |  **81h** |  **85t** | 80 |
| 21 |  **78c** |  **81m** |  **85u** | 67 |
| 22 |  **78c** |  **81o** |  **85v** | 50 |

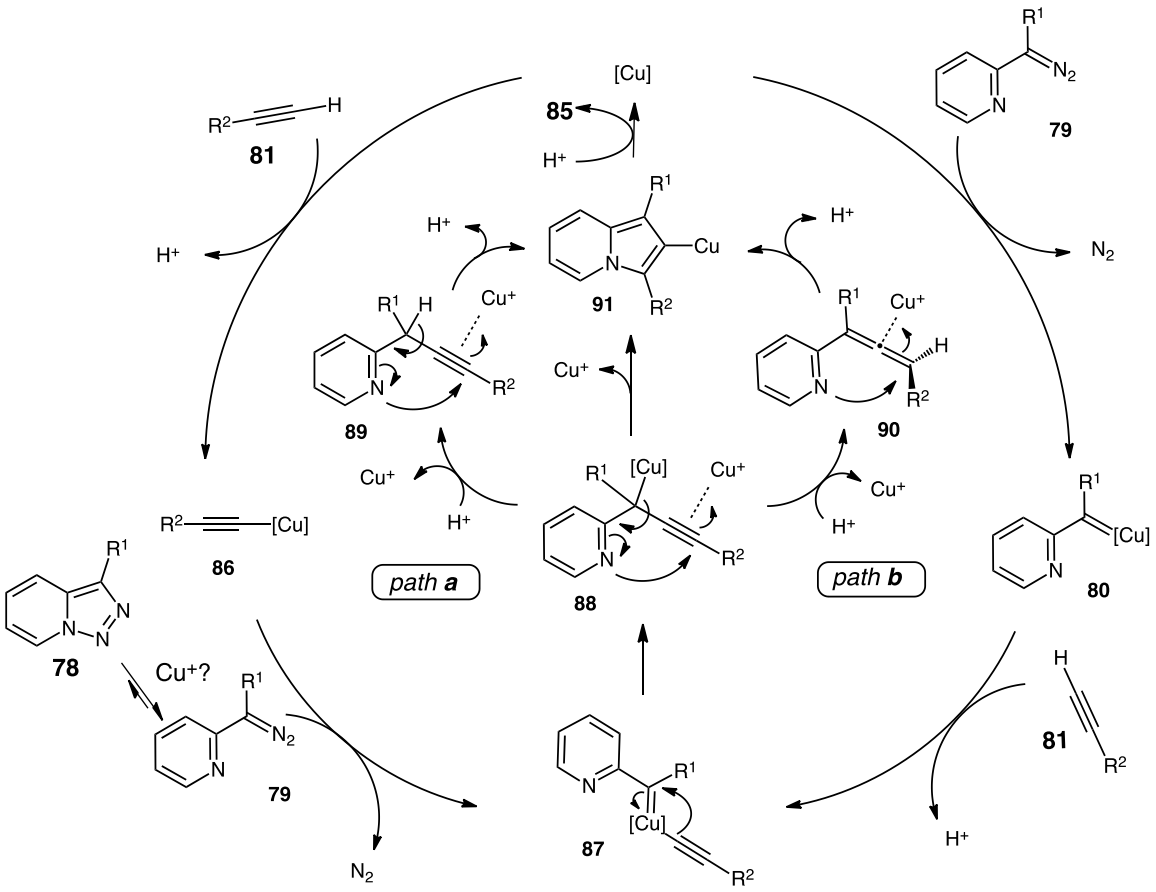
| Entry | Pyridotriazole | Alkyne | Product | Yield (%) of **85**[b] |
|---|---|---|---|---|
| 23 |  **78d** |  **81a** |  **85w** | 41 |
| 24 |  **78e** |  **81a** |  **85x** | 54 |

[a]Conditions: pyridotriazole (1 equiv), alkyne (1.2 equiv), $Cu(MeCN)_4PF_6$ (15 mol %), toluene (1M) at 130 °C for 1-12h in air. [b]Isolated yields.

### 2.2 Mechanistic Investigations

We envisioned two alternative pathways for this Cu-catalyzed transannulation reaction (Scheme 25). First, the copper catalyst can react with the terminal alkyne **81** to form copper acetylide **86**, which would react with the α-imino diazo compound **79** to generate the Cu–carbene complex **87** (path a). Alternatively, the copper–carbene C can be formed via the reaction of alkyne **81** with copper–carbene **80**, which is produced from the diazo compound **79** and the Cu-catalyst (path b). Next, migratory insertion of the alkynyl group at the carbene C-atom of **87** would form the propargyl intermediate **88**.[51] The latter would undergo cyclization via a nucleophilic attack of the pyridine nitrogen at the triple bond activated by the electrophilic Cu-species[52] to produce the triazolyl-copper intermediate **91**. Also, one cannot exclude the formation of propargylic (**89**) or allenic (**90**) intermediates upon protiodemetalation of **88**.

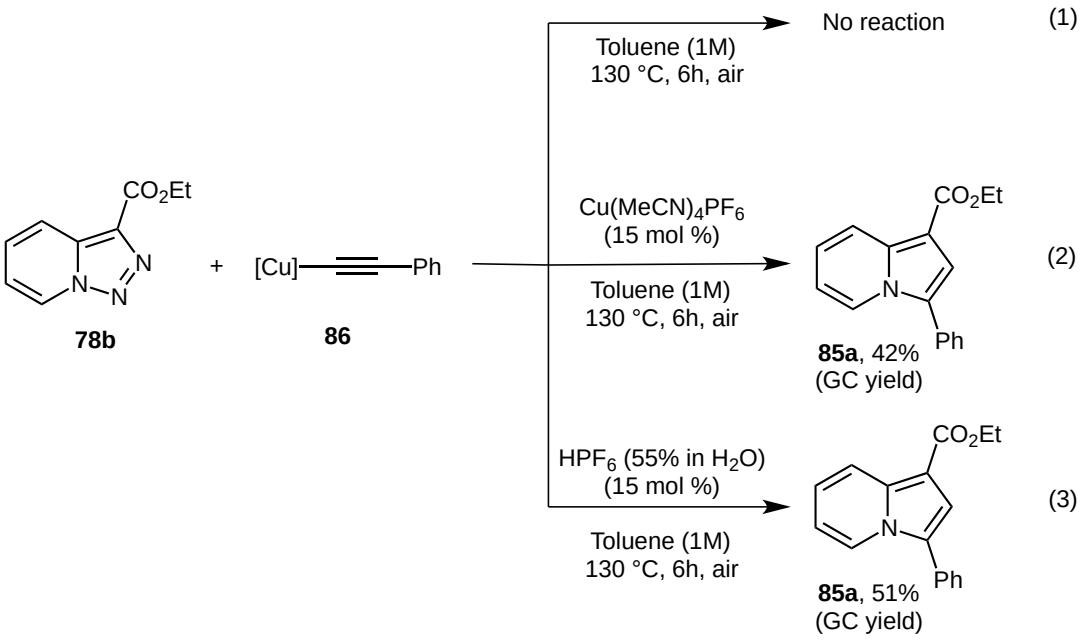
Cycloisomerization of **89** and **90** would form intermediate **91**.[53] A subsequent protiodemetalation of **91** would lead to the indolizine **85**.



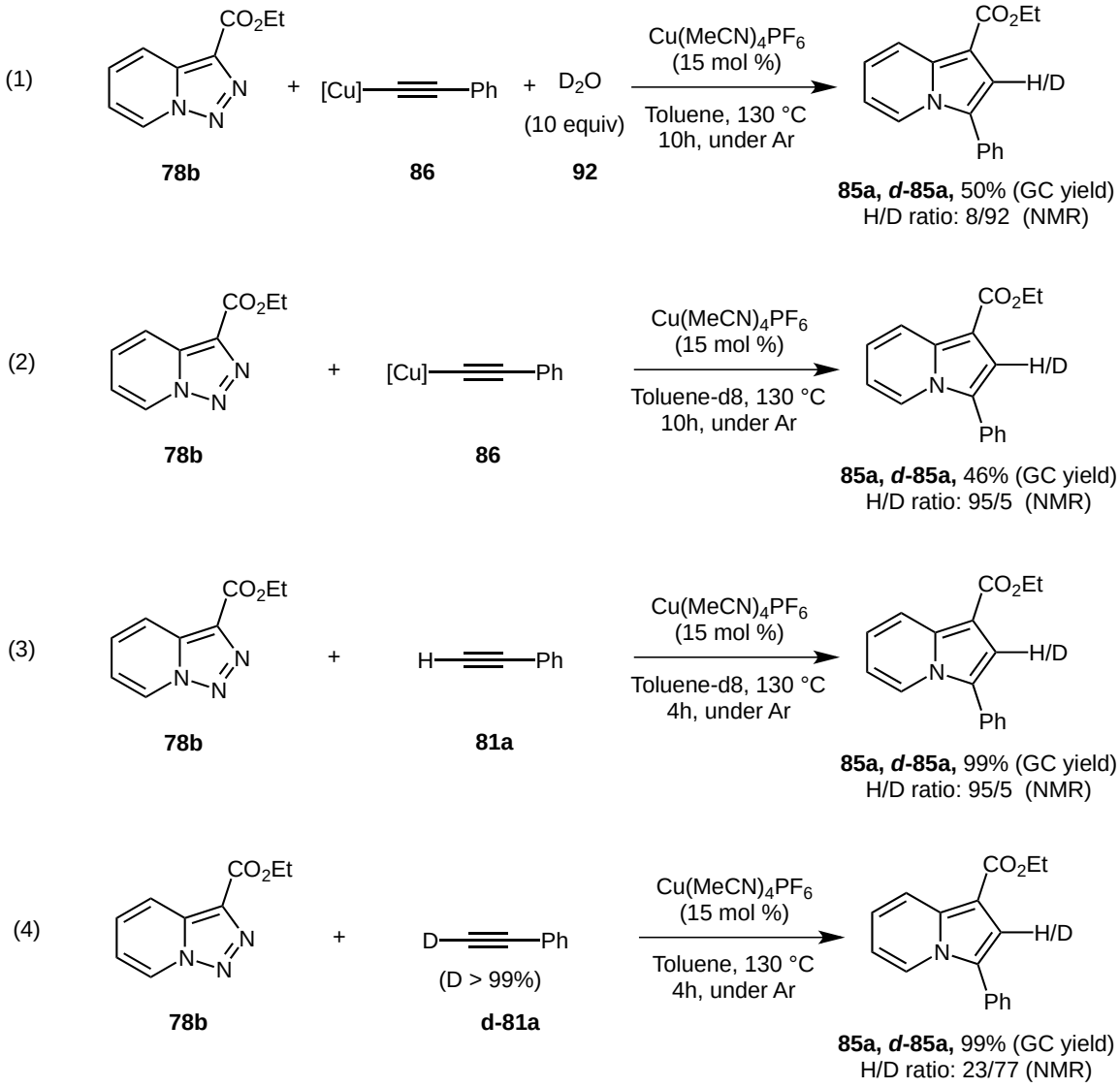

**Scheme 25.** Proposed Mechanism for the Cu-Catalyzed Transannulation Reaction

In order to verify a potential involvement of Cu-acetylide **86** in this transformation, we performed several test experiments. First, it was found that the reaction of pyridotriazole **78b** with **86** did not produce indolizine **85a** (Scheme 26, eq. 1). However, the reaction of **78b** with **86** can be catalyzed by both $Cu(MeCN)_4PF_6$ (eq. 2) and $HPF_6$(aq.) (eq. 3) to furnish indolizine **85a** in good yield. It is believed that $HPF_6$(aq.) liberated catalytic amounts of electrophilic Cu-species

by protonation of copper acetylide. Also, we hypothesized that under normal conditions intermediate **91** was quenched by an eventual proton source. Deuterium-labeling experiments were performed to gain an additional insight into the reaction mechanism (Scheme 27). It was found that addition of $D_2O$ to the reaction of **78b** with **86** produced mainly the deuterium-incorporated product ***d*-85a** (Scheme 25, eq. 1). Moreover, toluene solvent can also act as a marginal proton source (eq. 2-3). Finally, the reaction of **78b** with deuterium-labeled phenylacetylene showed that the $D^+$ released upon formation of copper acetylide **86** (path a, Scheme 25) or copper carbene **87** (path b, Scheme 25) was mainly incorporated in the indolizine product ***d*-85a** (Scheme 27, eq. 4). Notably, scrambling of deuterium-labeled phenylacetylene was observed after 2h with GC/MS (ratio 20:80).




**Scheme 26.** Reactions of the Cu-Acetylide with Triazole **78b**




**Scheme 27.** Deuterium-labeling Experiments with Triazole **78b**

These observations suggested that the presence of an electrophilic Cu-species was required to activate the alkyne during the cyclization of **88** into **91**,[54] and potentially to shift the equilibrium of the pyridotriazole towards the reactive α-imino diazo compound **79**.[55] Although more detailed studies are required to elucidate the exact mechanism of this transformation, based

on literature data[56] and the above-mentioned observations, it is believed that the reaction most likely proceeds via path a (Scheme 25).

## 2.3 Summary

In summary, we have developed practical and efficient copper-catalyzed denitrogenative transannulation reaction of pyridotriazoles with terminal alkynes into indolizines. Compared to the known Rh-catalyzed transannulation reaction, this newly developed method features not only the use of an inexpensive copper catalyst and aerobic conditions, but also much broader scope of multisubstituted indolizines that now can be accessed from non-activated pyridotriazoles and diverse terminal alkynes.

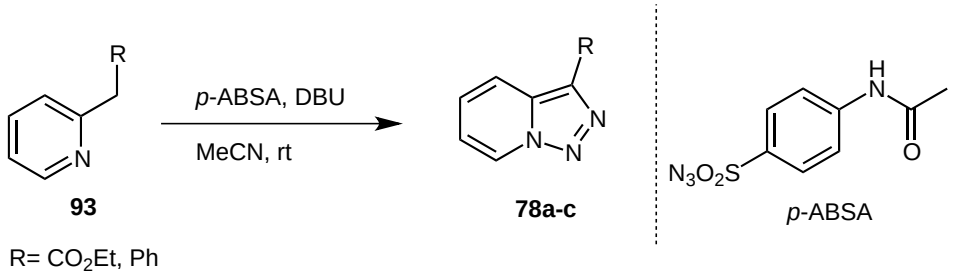
# 3 - EXPERIMENTAL SECTION

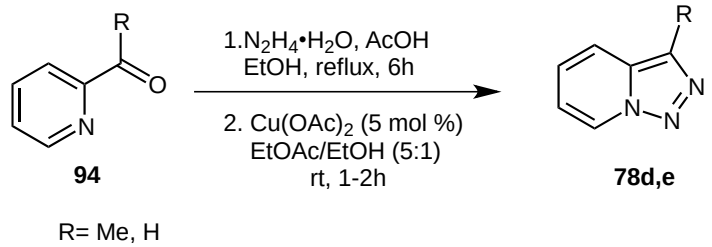
## 3.1 General Information

GC/MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Silicycle Silica-P flash silica gel (40-63 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz) or DPX-400 (400 MHz) instrument. All manipulations with transition metal catalysts were conducted in oven-dried glassware under inert atmosphere using a glovebox unless otherwise noted. Anhydrous solvents purchased from Sigma-Aldrich were additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system and/or stored over calcium hydride. The starting materials were purchased from Sigma-Aldrich and Alfa Aesar.

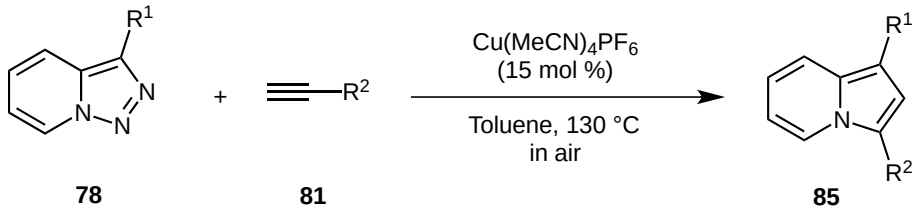
## 3.2 Synthesis of Pyridotriazoles 78

[1,2,3]triazolo[1,5-*a*]pyridines **78a-c**[44b] and **78d,e**[57] were synthesized according to literature procedures.






### 3.3 General Procedure for the Synthesis of Indolizines 85




**General procedure GP-4:** An oven-dried 3 mL Wheaton V-vial capped with a mininert syringe valve, containing a stirring bar, was charged with a pyridotriazole (0.5 mmol, 1 equiv), $Cu(MeCN)_4PF_6$ (28 mg, 0.075 mmol, 15 mol %), dry toluene (0.5 mL, 1 M), and a terminal alkyne (0.6 mmol, 1.2 equiv) in air. The reaction mixture was stirred at 130 °C for 1 to 12 h. The residue was then directly purified by column chromatography on triethylamine-treated silica gel (EtOAc/Hexane) to afford the corresponding indolizine 85.

**Ethyl 3-phenylindolizine-1-carboxylate (85a)**

**85a** was prepared according to GP-4 (the reaction time was 4 h) in 70% yield (0.35 mmol, 93 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/19). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.29-8.27 (m, 2H), 7.54 (d, *J* = 7.1 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.32 (s, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.69 (t, *J* = 6.8 Hz, 1H), 4.40 (q, *J*

= 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 165.02, 136.34, 131.26, 129.08, 128.59, 127.99, 126.41, 123.33, 122.22, 120.17, 116.11, 112.58, 104.27, 59.55, 14.70. HRMS (ES+) calcd. for $C_{17}H_{15}NO_2$ [M]+: 266.1181, found: 266.1182.

**Ethyl 3-(p-tolyl)indolizine-1-carboxylate (85b)**

**85b** was prepared according to GP-4 (reaction time: 4 h) in 74% yield (0.37 mmol, 103 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/19). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.27-8.25 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.28 (s, 1H), 7.05 (dd, *J* = 9.4, 6.6 Hz, 1H), 6.68 (t, *J* = 7.2 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 165.06, 137.93, 136.21, 129.76, 128.56, 128.30, 126.49, 123.39, 122.05, 120.14, 115.80, 112.46, 104.12, 59.51, 21.32, 14.70. HRMS (ES+) calcd. for $C_{18}H_{17}NO_2$ [M]+: 280.1338, found: 280.1334.

**Ethyl 3-(4-methoxyphenyl)indolizine-1-carboxylate (85c)**

**85c** was prepared according to GP-4 (reaction time: 4 h) in 65% yield (0.325 mmol, 96 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/6). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.25 (d, *J* = 9.0 Hz, 1H), 8.20 (d, *J* = 7.1 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.24 (s, 1H), 7.04 (m, 3H), 6.68 (t, *J* = 6.8 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 165.08, 159.45, 136.02, 130.14, 126.23, 123.56, 123.31, 121.95, 120.09, 115.59, 114.51, 112.42, 103.96, 59.49, 55.39, 14.69. HRMS (ES+) calcd. for $C_{18}H_{17}NO_3$ [M]+: 296.1287, found: 296.1282.

**Ethyl 3-(4-fluorophenyl)indolizine-1-carboxylate (85d)**

**85d** was prepared according to GP-4 (reaction time: 4 h) in 70% yield (0.325 mmol, 99 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/19). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.26 (d, *J* = 9.0 Hz, 1H), 8.18 (d, *J* = 7.1 Hz, 1H), 7.50 (dd, *J* = 8.1, 5.4 Hz, 2H), 7.27 (s, 1H), 7.19 (t, *J* = 8.4 Hz, 2H), 7.07 (dd, *J* = 8.3, 7.3 Hz, 1H), 6.71 (t, *J* = 6.8 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 164.94, 163.40, 161.43, 136.23, 130.58, 130.51, 127.33, 127.30, 125.24, 123.08, 122.23, 120.21, 116.26, 116.13, 116.08, 112.70, 104.24, 59.58, 14.67. HRMS (ES+) calcd. for $C_{17}H_{14}FNO_2$ [M]+: 284.1087, found: 284.1085.

**Ethyl 3-(4-(methoxycarbonyl)phenyl)indolizine-1-carboxylate (85e)**

**85e** was prepared according to GP-4 (reaction time: 4 h) in 48% yield (0.34 mmol, 78 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/19). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.35 (d, *J* = 7.1 Hz, 1H), 8.28 (d, *J* = 9.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.39 (s, 1H), 7.10 (dd, *J* = 8.4, 7.2 Hz, 1H), 6.75 (t, *J* = 6.8 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 166.60, 164.77, 136.95, 135.77, 130.39, 129.12, 127.80, 125.26, 123.27, 122.73, 120.36, 117.14, 113.08, 104.93, 59.67, 52.23, 14.64. HRMS (ES+) calcd. for $C_{19}H_{17}NO_4$ [M]+: 324.1236, found:324.1239.

**Ethyl 3-(m-tolyl)indolizine-1-carboxylate (85f)**

**85f** was prepared according to GP-4 (reaction time: 4 h) in 57% yield (0.285 mmol, 76 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/19). $^{1}$H NMR (500

MHz, $CDCl_3$): $\delta$ ppm 8.30 (d, *J* = 7.1 Hz, 1H), 8.27 (d, *J* = 9.1 Hz, 1H), 7.37 (m, 3H), 7.30 (s, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.06 (dd, *J* = 9.0, 6.7 Hz, 1H), 6.70 (t, *J* = 6.8 Hz, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 2.43 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). $^{13}C$ NMR (126 MHz, $CDCl_3$): δ ppm 165.05, 138.84, 136.30, 131.18, 129.33, 128.93, 128.78, 126.57, 125.59, 123.46, 122.12, 120.14, 115.99, 112.49, 104.18, 59.52, 21.49, 14.68. HRMS (ES+) calcd. for $C_{18}H_{17}NO_2$ [M]+: 280.1338, found: 280.1337.

**Ethyl 3-(3-chlorophenyl)indolizine-1-carboxylate (85g)**

**85g** was prepared according to GP-4 (reaction time: 4 h) in 60% yield (0.3 mmol, 90 mg) and was purified via column chromatography (silica gel, EtOAc/Hex = 1/19). $^1H$ NMR (500 MHz, $CDCl_3$): δ ppm 8.28 (d, *J* = 8.7 Hz, 2H), 7.55 (t, *J* = 1.2 Hz, 1H), 7.44-7.41 (m, 2H), 7.37 (dt, *J* = 6.4, 2.4 Hz, 1H), 7.33 (s, 1H), 7.10 (dd, *J* = 9.6, 7.0 Hz, 1H), 6.74 (t, *J* = 6.7 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). $^{13}C$ NMR (126 MHz, $CDCl_3$): δ ppm 164.83, 136.58, 134.99, 133.05, 130.34, 128.41, 127.99, 126.52, 124.81, 123.15, 122.52, 120.29, 116.65, 112.93, 104.58, 59.63, 14.66. HRMS (ES+) calcd. for $C_{17}H_{14}ClNO_2$ [M]+: 300.0791, found: 300.0789.

**Ethyl 3-(2-methoxyphenyl)indolizine-1-carboxylate (85h)**

**85h** was prepared according to GP-4 (reaction time: 4 h) in 94% yield (0.47 mmol, 139 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/6). $^1H$ NMR (500 MHz, $CDCl_3$): δ ppm 8.28 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 7.1 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.31 (s, 1H), 7.08 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.67 (t, *J* = 6.8 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H). $^{13}C$ NMR (126 MHz, $CDCl_3$): δ ppm 165.14, 157.43, 136.18, 132.40, 130.17, 125.21, 123.74, 122.03, 121.04, 119.93,

119.67, 116.61, 111.70, 111.09, 103.77, 59.40, 55.44, 14.74. HRMS (ES+) calcd. for $C_{18}H_{17}NO_3$ [M]+: 296.1287, found: 296.1282.

**Ethyl 3-(2-(trifluoromethyl)phenyl)indolizine-1-carboxylate (85i)**

**85i** was prepared according to GP-4 (reaction time: 4 h) in 78% yield (0.39 mmol, 130 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/9). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.26 (d, *J* = 9.1 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 7.0 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.29 (s, 1H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.64 (t, *J* = 6.8 Hz, 1H), 4.39 (t, *J* = 6.5 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 165.01, 135.73, 133.58, 132.08, 131.40 (q, $^2J$ = 30 Hz), 129.61; 129.37, 126.83 (m); 123.71, 123.58 (q, $^1J$ = 274.9 Hz), 122.23, 121.33, 119.83, 117.61, 112.46, 104.05, 59.57, 14.64. HRMS (ES+) calcd. for $C_{18}H_{14}F_3NO_2$ [M]+: 334.1055, found: 334.1054.

**Ethyl 3-(2,4,5-trimethylphenyl)indolizine-1-carboxylate (85j)**

**85j** was prepared according to GP-4 (reaction time: 4 h) in 75% yield (0.375 mmol, 115 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/19). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.26 (d, *J* = 9.1 Hz, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.20 (s, 1H), 7.13 (s, 1H), 7.10 (s, 1H), 7.06 (dd, *J* = 9.0, 6.6 Hz, 1H), 6.65 (t, *J* = 6.8 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 2.27 (s, 3H), 2.05 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 165.21, 137.55, 135.56, 135.52, 134.33, 132.49, 131.81, 127.64, 125.76, 123.81, 121.80, 119.90, 116.02, 112.20, 103.52, 59.46, 19.55, 19.18, 19.04, 14.71. HRMS (ES+) calcd. for $C_{20}H_{21}NO_2$ [M]+: 308.1651, found: 308.1642.

**Ethyl 3-(thiophen-3-yl)indolizine-1-carboxylate (85k)**

**85k** was prepared according to GP-4 (reaction time: 12 h) in 33% yield (0.165 mmol, 45 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/19). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.28 (d, *J* = 7.1 Hz, 1H), 8.26 (d, *J* = 9.5 Hz, 1H), 7.48 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.46 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.33 (s, 1H), 7.32 (dd, *J* = 5.5, 1.9 Hz, 1H), 7.07 (dd, *J* = 8.4, 7.1 Hz, 1H), 6.74 (t, *J* = 6.8 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 164.96, 136.17, 131.55, 127.56, 126.51, 123.67, 122.67, 122.09, 121.74, 120.11, 116.08, 112.71, 104.04, 59.57, 14.67. HRMS (ES+) calcd. for $C_{15}H_{13}NO_2S$ [$M^+$]: 272.0745, found: 272.0743.

**Ethyl 3-(cyclohex-1-en-1-yl)indolizine-1-carboxylate (85l)**

**85l** was prepared according to GP-4 (reaction time: 5 h) in 67% yield (0.335 mmol, 90 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/9). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.23 (d, *J* = 7.1 Hz, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.10 (s, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.66 (t, *J* = 6.8 Hz, 1H), 6.05 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.35-2.25 (m, 4H), 1.83-1.70 (m, 4H), 1.40 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 165.12, 135.98, 128.39, 128.27, 128.09, 124.45, 121.56, 119.99, 114.15, 112.02, 103.33, 59.39, 29.07, 25.51, 22.88, 22.05, 14.67. HRMS (ES+) calcd. for $C_{17}H_{19}NO_2$ [M]+: 270.1494, found: 270.1495.

**Ethyl 3-benzylindolizine-1-carboxylate (85m)**

**85m** was prepared according to GP-4 (reaction time: 4 h) in 68% yield (0.34 mmol, 95 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/19). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.23 (d, *J* = 9.1 Hz, 1H), 7.72 (d, *J* = 7.0 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 2H),

7.25 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.10 (s, 1H), 7.03 (dd, *J* = 8.5, 7.2 Hz, 1H), 6.65 (t, *J* = 6.8 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.20 (s, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 165.09, 136.89, 136.08, 128.77, 128.37, 126.80, 123.51, 123.06, 121.52, 119.96, 115.95, 112.27, 103.02, 59.45, 32.39, 14.71. HRMS (ES+) calcd. for $C_{18}H_{17}NO_2$ [M]+: 280.1338, found: 280.1335.

**Ethyl 3-butylindolizine-1-carboxylate (85n)**

**85n** was prepared according to GP-4 (reaction time: 5 h) in 82% yield (0.41 mmol, 100 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/19). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.18 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 7.0 Hz, 1H), 7.03 (s, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.72 (t, *J* = 6.8 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 1.74 (quintet, *J* = 7.6 Hz, 2H), 1.45 (q, *J* = 7.5 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 165.17, 135.61, 125.68, 122.67, 121.06, 119.98, 113.61, 112.06, 102.79, 59.34, 28.98, 25.39, 22.55, 14.70, 13.89. HRMS (ES+) calcd. for $C_{15}H_{19}NO_2$ [M]+:246.1494, found: 246.1493.

**Ethyl 3-cyclohexylindolizine-1-carboxylate (85o)**

**85o** was prepared according to GP-4 (reaction time: 5 h) in 83% yield (0.42 mmol, 112 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/19). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.20 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 7.1 Hz, 1H), 7.03 (s, 1H), 7.00 (dd, *J* = 8.6, 7.1 Hz, 1H), 6.72 (t, *J* = 6.3 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.80-2.76 (m, 1H), 2.09 (d, *J* = 8.6 Hz, 2H), 1.89-1.87 (m, 2H), 1.82-1.44 (m, 6H), 1.41 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 165.21, 135.60, 131.11, 122.79, 121.08, 120.15, 111.98, 111.67, 102.86,

59.35, 34.97, 31.61, 26.45, 26.27, 14.71. HRMS (ES+) calcd. for $C_{17}H_{21}NO_2$ [M]+: 272.1651, found: 272.1648.

**Ethyl 3-(3-(benzyloxy)propyl)indolizine-1-carboxylate (85p)**

**85p** was prepared according to GP-4 (reaction time: 10 h) in 53% yield (0.265 mmol, 89 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/6). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.20 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 7.0 Hz, 1H), 7.36 (d, *J* = 4.5 Hz, 4H), 7.30 (dd, *J* = 8.8, 4.6 Hz, 1H), 7.04-7.01 (m, 2H), 6.73 (t, *J* = 6.8 Hz, 1H), 4.53 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.58 (t, *J* = 6.0 Hz, 2H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.08 (dt, *J* = 14.1, 6.8 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 165.15, 138.37, 135.70, 128.42, 127.67, 127.64, 125.03, 122.80, 121.21, 119.96, 113.81, 112.15, 102.87, 73.05, 69.24, 59.39, 27.39, 22.32, 14.70. HRMS (ES+) calcd. for $C_{21}H_{23}NO_3$ [M]+: 338.1756, found: 338.1756.

**Ethyl 3-(3-(1,3-dioxoisoindolin-2-yl)propyl)indolizine-1-carboxylate (85q)**

**85q** was prepared according to GP-4 (reaction time: 12 h) in 82% yield (0.41 mmol, 154 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/9). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 8.16 (d, *J* = 9.0 Hz, 1H), 7.83-7.80 (m, 3H), 7.70 (dd, *J* = 5.1, 5.5 Hz, 2H), 7.07 (s, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.74 (t, *J* = 6.6 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.85 (t, *J* = 6.9 Hz, 2H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.20 (quintet, *J* = 7.4 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 168.36, 164.98, 135.77, 133.99, 131.99, 123.91, 123.24, 122.58, 121.30, 119.96, 113.73, 112.30, 102.95, 59.35, 37.68, 25.85, 23.30, 14.67. HRMS (ES+) calcd. for $C_{22}H_{20}N_2O_4$ [M]+: 377.1501, found: 377.1496.

**Ethyl 3-(3-cyanopropyl)indolizine-1-carboxylate (85r)**

**85r** was prepared according to GP-4 (reaction time: 12 h) in 66% yield (0.33 mmol, 84 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/4). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.21 (d, *J* = 9.1 Hz, 1H), 7.84 (d, *J* = 6.3 Hz, 1H), 7.06 (s, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.78 (t, *J* = 6.8 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.99 (t, *J* = 7.4 Hz, 2H), 2.47 (t, *J* = 6.9 Hz, 2H), 2.13 (quintet, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 164.90, 135.95, 122.42, 121.61, 120.17, 119.12, 114.24, 112.63, 103.21, 59.52, 24.41, 22.85, 16.76, 14.67. HRMS (ES+) calcd. for $C_{15}H_{16}N_2O_2$ [$M^+$]: 257.1290, found: 257.1290.

**1,3-Diphenylindolizine (85s)**

**85s** was prepared according to GP-4 (reaction time: 4 h) in 77% yield (0.358 mmol, 104 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/19). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.31 (d, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 9.1 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 6.9 Hz, 1H), 7.08 (s, 1H), 6.78 (dd, *J* = 9.1, 6.4 Hz, 1H), 6.54 (t, *J* = 7.3 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 136.29, 132.21, 130.21, 129.04, 128.80, 128.26, 127.62, 127.36, 126.34, 125.77, 125.49, 122.68, 118.56, 118.12, 113.87, 111.15. HRMS (ES+) calcd. for $C_{20}H_{15}N$ [M]+: 270.1283, found: 270.1279.

**3-(2-Methoxyphenyl)-1-phenylindolizine (85t)**

**85t** was prepared according to GP-4 (reaction time: 4 h) in 80% yield (0.4 mmol, 120 mg) and was purified via column chromatography (silica gel, EtOAc/Pentane = 1/9). $^{1}$H NMR (500 MHz,

$CDCl_3$): δ ppm 7.82 (d, *J* = 9.1 Hz, 1H), 7.68 (t, *J* = 6.0 Hz, 3H), 7.46 (m, 4H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.11-7.08 (m, 2H), 7.07 (s, 1H), 6.79 (dd, *J* = 9.1, 6.4 Hz, 1H), 6.51 (t, *J* = 6.8 Hz, 1H), 3.85 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 157.24, 136.58, 132.24, 129.96, 129.45, 128.68, 127.61, 125.18, 124.62, 122.82, 120.96, 118.05, 117.80, 114.67, 114.36, 111.11, 110.11, 55.48. HRMS (ES+) calcd. for $C_{21}H_{17}NO$ [M]+: 300.1388, found: 300.1385.

**3-Benzyl-1-phenylindolizine (85u)**

**85u** was prepared according to GP-4 (reaction time: 4 h) in 67% yield (0.34 mmol, 95 mg) and was purified via column chromatography (silica gel, EtOAc/Hexanes = 1/19). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 7.78 (d, *J* = 9.1 Hz, 1H), 7.66 (d, *J* = 7.1 Hz, 1H), 7.62 (d, *J* = 7.1 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.27-7.23 (m, 4H), 6.82 (s, 1H), 6.73 (dd, *J* = 9.1, 6.5 Hz, 1H), 6.49 (t, *J* = 6.8 Hz, 1H), 4.27 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 137.65, 136.55, 129.34, 128.71, 128.68, 128.51, 127.42, 126.59, 125.14, 122.77, 122.33, 118.34, 117.07, 113.61, 110.62, 32.56. HRMS (ES+) calcd. for $C_{21}H_{17}N$ [M]+: 284.1439, found: 284.1445.

**3-Cyclohexyl-1-phenylindolizine (85v)**

**85v** was prepared according to GP-4 (reaction time: 8h) 50% yield (0.25 mmol, 69 mg) and was purified via column chromatography (silica gel, EtOAc/Pentane = 1/19). $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 7.81 (d, *J* = 7.1 Hz, 1H), 7.74 (d, *J* = 9.1 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.78 (s, 1H), 6.69 (dd, *J* = 8.7, 6.8 Hz, 1H), 6.53 (t, *J* = 6.3 Hz, 1H), 2.84 (quintet, *J* = 9.5 Hz, 1H), 2.16-190 (m, 4H), 1.57-1.45 (m, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 136.77, 130.40, 128.65, 127.41, 124.98, 122.11, 116.58, 113.58,

110.30, 109.36, 35.21, 31.77, 26.61, 26.40. HRMS (ES+) calcd. for $C_{20}H_{21}N$ [M]+: 276.1752, found: 276.1748.

**1-Methyl-3-phenylindolizine (85w)**

**85w** was prepared according to GP-4 (reaction time: 12 h) in 41% yield (0.205 mmol, 42 mg) and was purified via column chromatography (silica gel, EtOAc/Pentane = 1/50). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.24 (d, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.74 (s, 1H), 6.63 (dd, *J* = 8.8, 6.5 Hz, 1H), 6.43 (t, *J* = 6.7 Hz, 1H), 2.42 (s, 3H).$^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 132.67, 131.13, 128.92, 127.83, 126.80, 124.16, 122.07, 117.83, 115.42, 115.23, 110.28, 108.92, 10.51. HRMS (ES+) calcd. for $C_{15}H_{13}N$ [M]+: 208.1126, found: 208.1119.

**3-Phenylindolizine (85x)**

**85x** was prepared according to GP-4 (reaction time: 1 h; 54% yield (0.27 mmol, 52 mg) and was purified via column chromatography (silica gel, Hexanes 100%). $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.29 (d, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 9.0 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 3.9 Hz, 1H), 6.68 (t, *J* = 7.8 Hz, 1H), 6.55 (d, *J* = 3.7 Hz, 1H), 6.48 (t, *J* = 6.8 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 133.88, 132.60, 128.93, 128.05, 127.03, 125.42, 122.29, 119.64, 116.88, 114.11, 110.63, 99.78. HRMS (ES+) calcd. for $C_{14}H_{11}N$ [M]+: 194.0970, found: 194.0970.

### 3.4 General Procedure for Deuterium-Labeling Experiments

Cu-acetylide **86** and deuterium phenyl acetylene ***d*-81a**[58] were prepared according to literature procedure.

An oven dried 1 mL Wheaton V-vial capped with a mininert syringe valve, containing a stirring bar, was charged with a pyridotriazole **78b** (38.2 mg, 0.2 mmol, 1 equiv), catalyst (15 mol %), toluene (0.2 mL, 0.1 M), additive, and phenylacetylene derivative (0.24 mmol, 1.2 equiv) under the indicated atmosphere. The reaction mixture was stirred at 130 °C upon completion then was quenched with DCM and analyzed with GC-MS using pentadecane as internal standard. The residue was then purified by column chromatography on triethylamine-treated silica gel (3% EtOAc/Hexane) to afford the corresponding indolizine **85a** and calculate the H/D ratio.

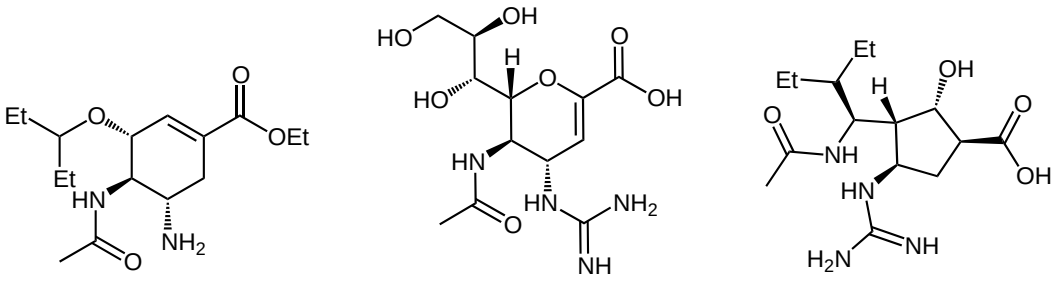
# CHAPTER FOUR: DEVELOPMENT OF ANALOGS OF MBX2546 IN THE STUDY OF INFLUENZA A VIRUS FUSION INHIBITORS

## 1 - INTRODUCTION

### 1.1 Influenza A Virus

Flu epidemics are due to the massive spread of the influenza A virus. Statistics show that each year, 5-20% of the U.S. population is affected by this contagious respiratory infection and that thousands of people (3,000-49,000) die of influenza-related complications.[59] Moreover, over the past centuries, several influenza pandemics have caused the death of millions of people worldwide with the most recent large-scale outbreak occurring in 2009.[60]

If vaccination is presented as the first preventive method against the seasonal flu, the Centers for Disease Control and Prevention (CDC) recommend the use of antiviral drugs for the treatment of influenza. At the moment, there are only three antiviral drugs approved by the U.S. Food and Drug Administration (FDA) on the market to treat influenza: oseltamivir (Tamiflu®), zanamivir (Relenza®), and peramivir (Rapivab®) (Figure 8).[61] However, rapid mutations of the influenza virus and antiviral drug resistance[62] are among the reasons why researchers are constantly seeking a better understanding of the mode of the viral cell entry in order to develop new therapeutic agents.




Oseltamivir
**95**

Zanamivir
**96**

Paramivir
**97**

**Figure 8.** Structures of FDA-Approved Influenza Antiviral Drugs

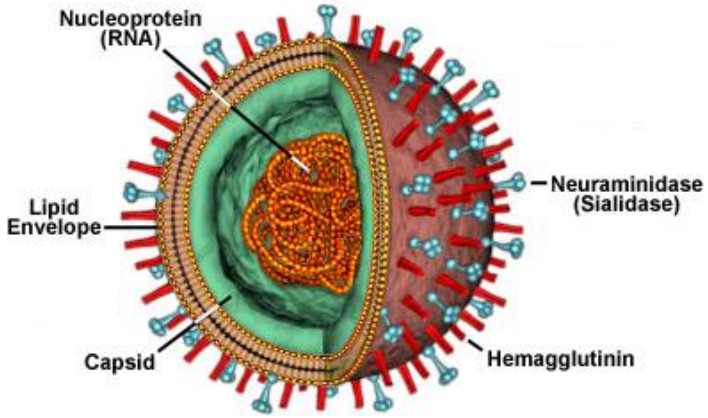



**Figure 9.** Structure of Influenza A Virus[63]

Influenza A is a negative-strand RNA virus (Figure 9) that needs to enter a host cell to replicate and be infectious.[64] Two important proteins located on the membrane of the virus are hemagglutinin (HA) and neuraminidase (NA). HA is known to play a crucial role in the viral entry mechanism, binding and membrane fusion to host cells. NA is involved in the viral cleavage mechanism. While two of the FDA-approved antiviral drugs on the market, Tamiflu® (**95**) and Relenza® (**96**), are NA inhibitors[64] there has been no small molecule inhibitor of HA successfully developed so far.[65] Moreover, resistance to **95** was found in the H5N1 flu virus in

2005[66] and H1N1 virus in 2008.[67] Consequently, inhibiting the function of HA represents an attractive strategy in the development of new therapeutic agents.

### 1.2 Hemagglutinin (HA)

Hemagglutinin has a trimer structure and each monomer contains two segments designated as HA1 and HA2.[68] The receptor binding domain of the hemagglutinin is located in the HA1 head while the fusion peptide is part of the stem domain in HA2 (Figure 10). At low pH or fusion pH (pH ~5), HA undergoes a conformational change leading the N-terminal of the fusion peptide and the C-terminal of the membrane anchor to be aligned.[68]

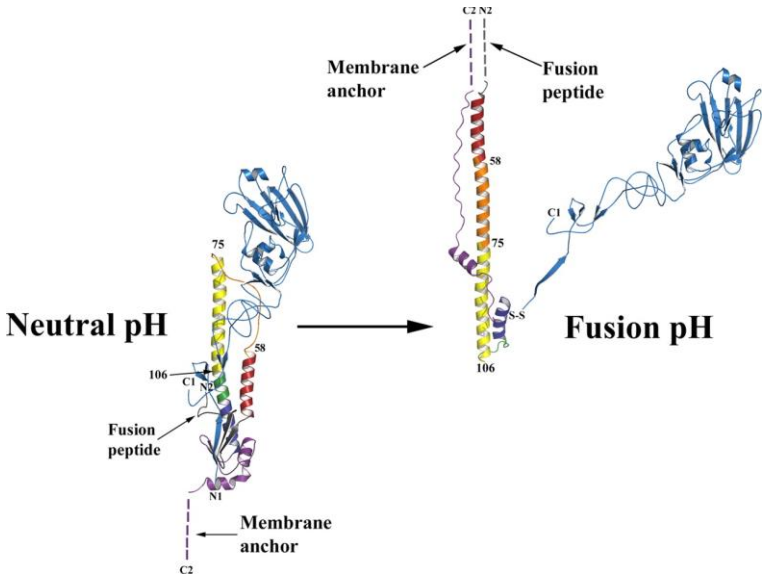



**Figure 10.** Conformational Change of HA During Fusion with Host Cell (HA1 is the blue segment and HA2 is the multicolor one.) [68]

Moreover, there are 18 subtypes of HA classified in two groups in a phylogenetic tree (Figure 11).[68] Despite minor structural and functional differences between the various strains of

HA, only specificity to one group versus other has been observed in current inhibitors and no strain specificity.[65]

In collaboration with the laboratories of professors Michael Caffrey and Arnon Lavie at the University of Illinois at Chicago (UIC), we have investigated the development small molecule HA inhibitors, especially fusion inhibitors targeting the HA stem loop region of the influenza virus.

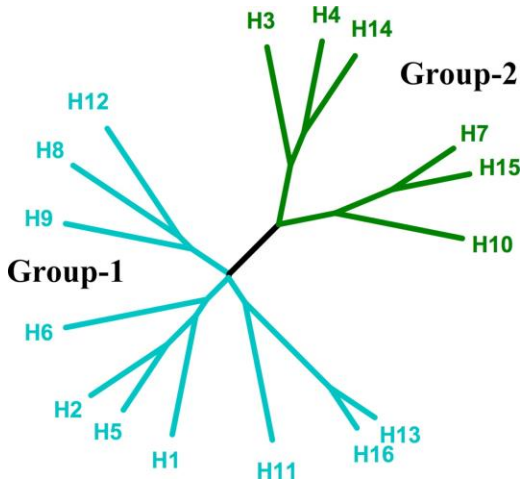
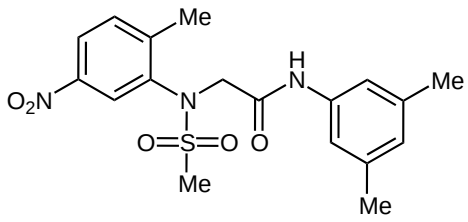



**Figure 11.** Phylogenetic tree of influenza A HA.[68]

### 1.3 Identification of MBX2546 via High Throughput Screening

A high throughput screening (HTS) of thousands of small molecules obtained from various sources was performed to identify inhibitors of HA-mediated viral entry. The avian influenza pseudotype viruses [HIV/HA (H5)] employed in this HTS were prepared to display a H5 HA protein on the envelope and a luciferase reporter gene in its HIV core.[64] Measurement of the luciferase gene activity was used to determine the potency of each small molecule tested.

Moreover, HIV and luciferase enzyme inhibitors, as well as cytotoxic compounds were excluded to conserve only HA inhibitors. Among the thousands of molecules tested, MBX2546 (Figure 12) was identified as a potential fusion inhibitor due to its high potency ($IC_{90}$ < 10 μM), stability and drug-like structure.[64] Microbiotix Inc., a collaborator on this study, provided the initial MBX2546 sample, which could also be purchased from Vitas M.




MBX2546
**98a**

**Figure 12.** Structure of MBX2546 (**98a**)

HTS revealed that MBX2546 inhibits specifically Group 1 influenza viruses demonstrating a high potency against H1 and H5 HA ($IC_{50}$ = 3.6 μM for H5N1 pseudovirus).[64] Subsequent bioassays confirmed that MBX2546 is a fusion inhibitor because it binds a conformational epitope located in the stem region of H5 HA (Figure 13), stabilized the native HA conformation, and inhibited the change of conformation of H5 HA at low pH.[65] Moreover, based on molecular dynamics simulations, the middle of the HA trimer was characterized as the binding site with strong interactions with the hydrophobic amino acids (L98, L99 and M102) of the HA2 segment (Figure 13).[65]

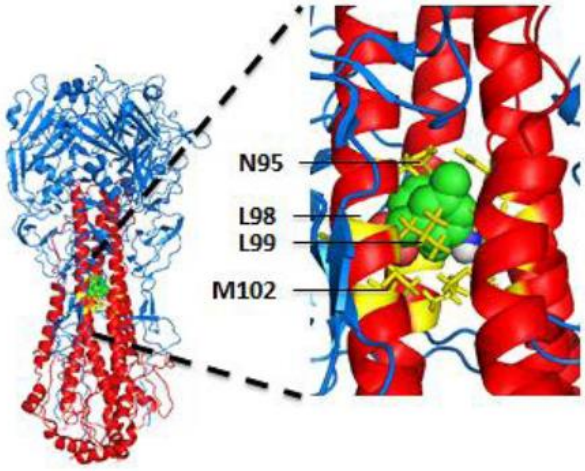



**Figure 13.** MBX2546 Binding Region in HA[65]

Interestingly, in order to accommodate this unusual binding site, MBX2546 adapted a conformation with both aromatic rings facing each other (strong π-stacking effect). However, Saturation transfer difference (STD) NMR revealed that the contact between H5 HA and MBX2546 was not uniform (Figure 14) and in the co-crystallography experiment, the density was not sufficient to fully characterize all structural features of MBX2546.

Therefore, it was decided to design and screen heavy atoms analogs of MBX2546 in order to improve the solubility under the crystallization conditions and to obtain unambiguous X-ray crystallography data of H5 HA in complex with potential fusion inhibitor.

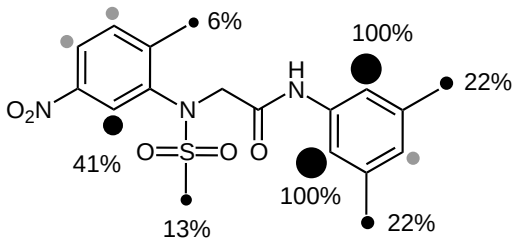



**Figure 14.** Relative STD NMR of MBX2546 Binding H5 HA[64]

# 2 - DESIGN AND SYNTHESIS OF MBX2546 ANALOGS

## 2.1 Design of MBX2546 Analogs

We first focused particularly on the STD NMR results. It was observed a strong electron density on the aniline ring of MBX2546 but poor electron density on the methyl substituents at C3 and C5 positions (Figure 11). It was hypothesized that, (i) a modification of the substituents on the aniline could improve the binding of the fusion inhibitor with H5 HA and, (ii) heavier substituents could provide better co-crystallography data. Consequently, we designed analogs of MBX2546 bearing different substituents on the aniline and the methyl groups at C3 and C5 positions were first substituted with heavy halogens, chloride (**98b**) and iodide (**98c**) (Figure 15). In the second generation of analogs, this scope was expanded and both electron-donating and withdrawing substituents were tested. Analogs bearing methoxy (**98d**), trifluoromethyl (**98e**) groups and fluorine atoms (**98f**) on the aniline were synthesized (Figure 15).

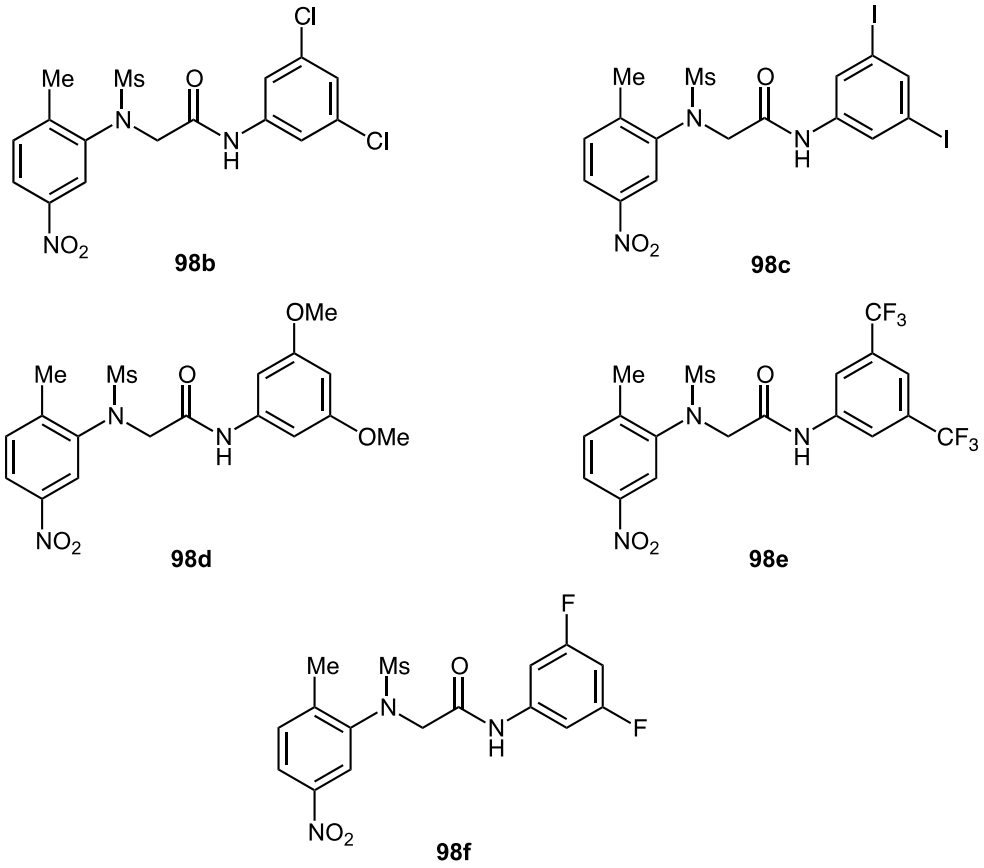
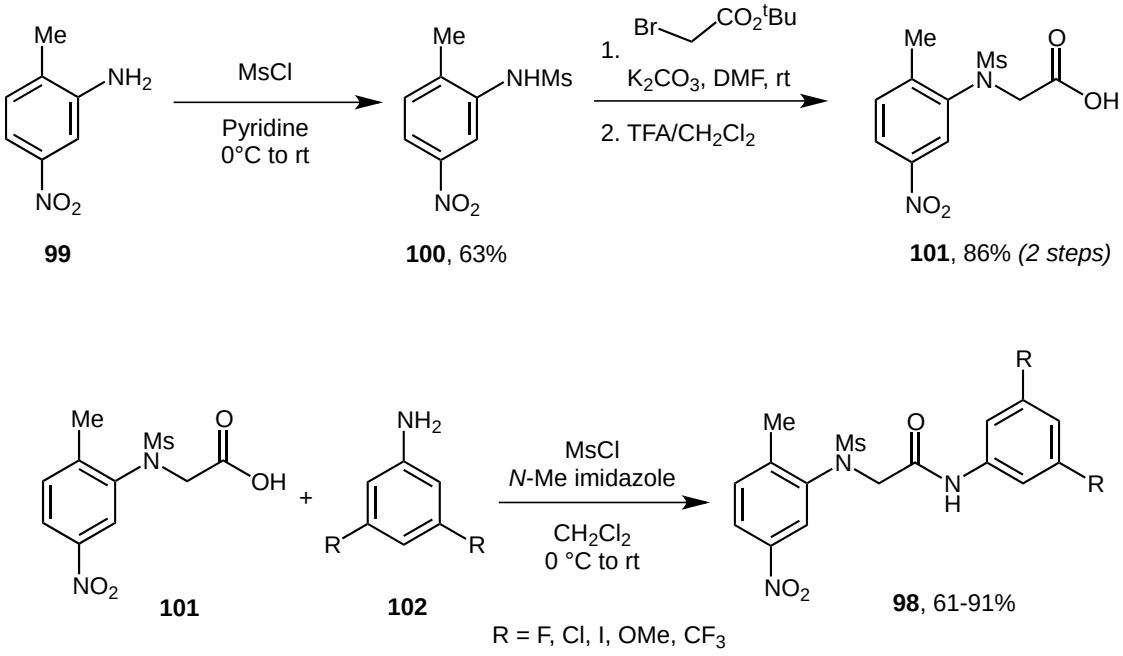



**Figure 15.** Analogs of MBX2546

All analogs of MBX2546 (**98b-c**) were synthesized following a 4-step route from commercially available 2-methyl-5-nitroaniline (**99**) (Scheme 28). After protection with mesyl chloride, the amine was alkylated upon reaction with *tert*-butyl bromoacetate in DMF, using $K_2CO_3$ as a base. The ester was then cleaved in a mixture of trifluoacetic acid and dichloromethane to deliver the desired carboxylic acid **101** in good yield. Due to the weak nucleophilicity of anilines, traditional amide coupling methods employing carbodiimides and hydroxybenzotriazole (HOBt) failed. However, Mao has reported an efficient synthesis of arylamides in presence of methanesulfonyl chloride (MsCl) and *N*-methyl imidazole.[69] We were

pleased to find that under these conditions amides **98** were obtained in good to excellent yields (61-91%).




**Scheme 28.** Synthesis of Analogs of MBX2546

## 2.2 Preliminary Bioassays Results

Due to insolubility issues, compound **98c** was not a good candidate to perform the STD NMR experiments. On the other hand, WaterLOGSY experiments showed that the chlorinated analog **98b** binds to H5 HA at the same site as MBX2546 but with less affinity. Further assays are ongoing to identify the potency of each analog.

## 2.3 Summary

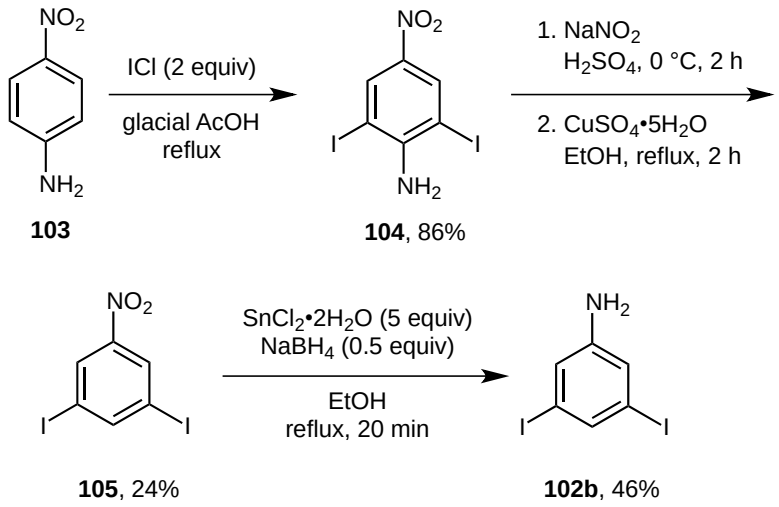
In conclusion, in a collaborative effort with the laboratories of Caffrey and Lavie, a novel family of small molecule inhibitors of H5 HA influenza A viruses have been developed. Based on the encouraging results of MBX2546 as fusion inhibitor, we designed two batches of analogs of this compound and all analogs were synthesized in good yields following a 4-step route. The preliminary WaterLOGSY results showed that **98b** could bind to the H5 HA. Analyses of the second generation of analogs are in progress.

# 3 - EXPERIMENTAL SECTION

## 3.1 General Information

Column chromatography was carried out employing Silicycle Silica-P flash silica gel (40-63 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz) or DPX-400 (400 MHz) instrument. Anhydrous solvents purchased from Sigma-Aldrich were additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system. All anilines used were purchased except 3,5-diiodoaniline, which was prepared according to the methods reported by Nieman[70] and Bérubé.[71]

## 3.2 Synthesis of 3,5-Diiodoaniline (102b)




**103**

**104**, 86%

**105**, 24%

**102b**, 46%

### 2,6-Diiodo-4-nitroaniline (104)

In an oven-dried 3-neck round-bottomed flask connected to a reflux condenser was dissolved 4-nitroaniline (5.04 g, 36.5 mmol, 1 equiv) in glacial acetic acid (13 mL). Then, iodine

monochloride (3.7 ml, 73 mmol, 2 equiv) in glacial acetic acid (7 mL) was added *dropwise* with rapid stirring over 30 min and the reaction mixture was stirred under reflux for 2 h. The solid obtained was filtered and subsequently washed with hot water (200 mL) and a saturated solution of $Na_2S_2O_3$ (40 mL). Recrystallization of the solid in nitrobenzene followed by a wash with ethanol yielded **104** as a yellow solid (12.3 g, 31.5 mmol, 86%). This compound was used in the next step without further purification. The NMR data matched the literature.[70]

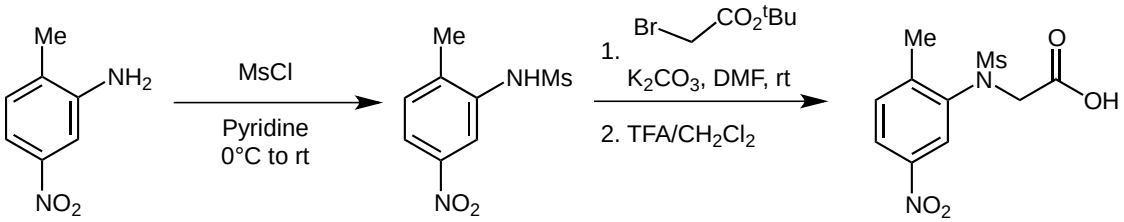
**1,3-Diiodo-5-nitrobenzene (105)**

To an oven-dried 250 mL Erlenmeyer flask containing concentrated sulfuric acid (47 mL) at 0 °C was added 2,6-diiodo-4-nitroaniline (12.3 g, 31.5 mmol, 1 equiv) in small portions. After complete dissolution, $NaNO_2$ (4.78 g, 69.3 mmol, 2.2 equiv) was added and the reaction mixture was stirred for 2 h at 0 °C, then poured over ice and filtered. Then, in an oven-dried 2 L 2-neck round bottomed flask equipped with a condenser was dissolved $CuSO_4 \cdot 5H_2O$ (0.79 g, 3.15 mmol, 0.1 equiv) in ethanol (600 mL). The previously obtained filtrate was added slowly and the reaction mixture was stirred under reflux for 2 h. After cooling to room temperature, the solid formed was filtered, washed with water (100 mL) until neutral pH was observed. Recrystallization in ethanol yielded **105** as brown needles (2.82 g, 7.52 mmol, 24%). This compound was used in the next step without further purification. The NMR data matched the literature.[71]

**3,5-Diiodoaniline (102b)**

In an oven-dried round bottom flask equipped with a condenser were dissolved 1,3-diiodo-5-nitrobenzene (2.82 g, 7.5 mmol, 1 equiv.) and $SnCl_2 \bullet 2H_2O$ (8.47 g, 37.5 mmol, 5 equiv.) in ethanol (30 mL) and the solution was stirred and warmed up under inert atmosphere. $NaBH_4$ in ethanol (0.25 M solution of hydride, 15 mL, 0.5 equiv.) was then added *dropwise* and the reaction mixture was stirred under reflux for 20 min before being cooled down to 0 °C. The reaction was then quenched with water (25 mL) and neutralized with a 2.5 M aqueous NaOH solution (3 mL). The organic phase was extracted with $Et_2O$, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The aniline **102b** was isolated through a short pad of silica gel (20% EtOAc/Hexanes) and a brown-beige solid was obtained (1.2 g, 3.4 mmol, 45%); m.p.: 112-115 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ ppm 7.40 (s, 1H), 6.98 (s, 1H).

## 3.3 General Procedure for the Synthesis of Acid 101




**99** **100**, 63% **101**, 86% *(2 steps)*

***N*-(2-Methyl-5-nitrophenyl)methanesulfonamide (100)**

Sulfonamide **100** was synthesized according to the following procedure:[72]

To a solution of commercially available 2-methyl-5-nitroaniline **99** (1.55 g, 10 mmol) in pyridine (5.25 mL) at 0-5 °C was added *dropwise* methanesulfonyl chloride (0.851 mL, 11

mmol). The reaction mixture was allowed to warm up to room temperature and stirred overnight. Once concentrated, the obtained solid was washed with water (5 mL) then 1 M aqueous solution of HCl (5 mL), dried over reduced pressure and recrystallized with ethanol to yield sulfonamide **100** as a beige solid (1.45 g, 63%); m.p.: 145-148 °C. $^{1}$H NMR (500 MHz, $CDCl_3$): δ ppm 8.32 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 6.60 (s, 1H), 3.14 (s, 3H), 2.43 (s, 3H). $^{13}$C NMR (126 MHz; $(CD_3)_2SO$): δ ppm 146.6, 141.7, 137.1, 132.4, 120.8, 119.6, 40.8, 18.9.

**2-(*N*-(2-Methyl-5-nitrophenyl)methylsulfonamido)acetic acid (101)**

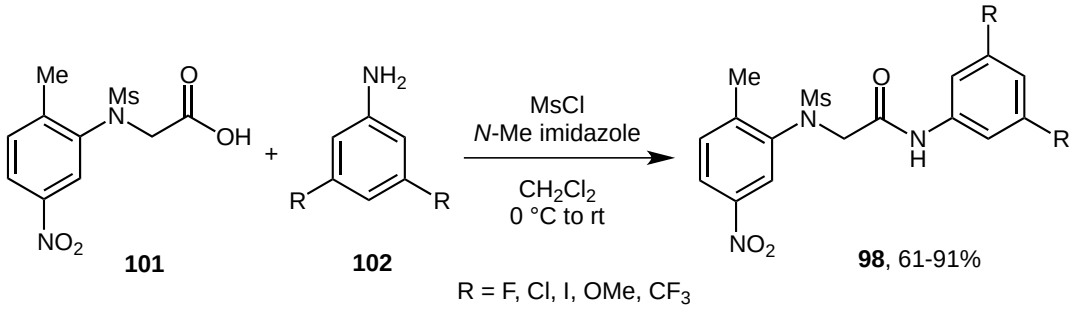
Carboxylic acid **101** was synthesized according to the following procedure:[73]

To a solution of sulfonamide **100** (391 mg, 1.7 mmol) in DMF (10 mL) was added subsequently $K_2CO_3$ (470 mg, 3.4 mmol) and *tert*-butylacetate (0.377 mL, 2.55 mmol). The reaction was stirred at room temperature for 2 h then quenched with water (50 mL). The organic phase was extracted with EtOAc (3 x 25 mL), washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The obtained dark yellow oil was further dried over pump to yield a beige solid (585 mg).

TFA (5.5 mL) was then added to a solution of the ester (585 mg, 1.7 mmol) in dichloromethane (5.5 mL) and stirred at room temperature. After 1 h, the mixture was diluted with water (30 mL) and acidified with 5 M aqueous solution of HCl until pH around 2. The organic phase was extracted with EtOAc (3 x 30 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure to yield **101** as a beige solid (419 mg, 86%); m.p.: 204-206 °C. $^{1}$H NMR (500 MHz, $(CD_3)_2SO$): δ ppm 8.39 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 4.37 (br. s, 2H), 3.32 (s,

1H), 3.18 (s, 3H), 2.48 (s, 3H). $^{13}$C NMR (126 MHz; $(CD_3)_2SO$): δ ppm 170.9, 148.5, 146.5, 140.0, 132.6, 125.1, 123.7, 52.4, 39.6, 19.0.

### 3.4 General Procedure for the Synthesis of Amides 98




Amides **98b-e** were synthesized according to the following procedure:[69]

**General procedure GP-5:** To a solution of **101** (57.7mg, 0.2 mmol) in dry dichloromethane (0.3 mL) at 0-5 °C was added *N*-methyl imidazole (39.9 μL, 0.5 mmol). Then, methanesulfonyl chloride (15 μL, 0.2 mmol) in dry dichloromethane (5 μL) was added and the reaction mixture was stirred at 0-5 °C for 20 min. The corresponding aniline **102** (0.18 mmol) was then added to the mixture, which was stirred at room temperature for about 4h. After, the reaction mixture was quenched with water (20 mL) and the organic phase was extracted with dichloromethane (3x7 mL), washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The desire amide **98** was isolated through silica gel column (5% MeOH/$CH_2Cl_2$).

***N*-(3,5-Dichlorophenyl)-2-(*N*-(2-methyl-5-nitrophenyl)methylsulfonamido) acetamide (98b)**

**98b** was prepared according to GP-5 in 66% yield (57 mg) as a white solid; m.p.: 209-211 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 8.43 (d, *J* = 2.2 Hz, 1H), 8.16 (dd, *J* = 8.5, 2.3 Hz, 1H), 8.12 (s,

1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.46 (s, 2H), 7.12 (s, 1H), 3.27 (s, 3H), 2.52 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$): δ ppm 166.0, 147.5, 146.9, 139.4, 138.8, 135.4, 132.6, 124.91, 124.73, 124.2, 118.1, 55.4, 40.0, 19.0. HRMS (EI) calc'd for $C_{16}H_{15}Cl_2N_3O_5S$ [M]+: 432.0188, found 432.0188.

**_N_-(3,5-Diiodophenyl)-2-(_N_-(2-methyl-5-nitrophenyl)methylsulfonamido)acetamide (98c)**

**98c** was prepared according to GP-5 in 61% yield (76 mg) as a beige solid; m.p.: 220-222 °C. $^1$H NMR (500 MHz, acetone-$d_6$) δ ppm 9.51 (s, 1H), 8.56 (d, *J* = 2.4 Hz, 1H), 8.16 (dd, *J* = 8.5, 2.4 Hz, 1H), 8.07 (d, *J* = 1.0 Hz, 2H), 7.81 (t, *J* = 1.4 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 3.31 (s, 3H), 2.55 (s, 3H). $^{13}$C NMR (126 MHz, solvent) δ ppm 167.6, 148.2, 146.7, 141.3, 140.1, 139.6, 132.3, 127.3, 125.3, 123.5, 94.9, 54.0, 40.0, 18.5. HRMS (EI) calcd for $C_{16}H_{15}I_2N_3O_5S$ [M]+: 615.8900, found 615.8898.

**_N_-(3,5-Dimethoxyphenyl)-2-(_N_-(2-methyl-5-nitrophenyl)methylsulfonamido) acetamide (98d)**

**98d** was prepared according to GP-5 in 91% yield (77mg) as a yellow-brown solid; m.p.: 198-201 °C. $^1$H NMR (500 MHz, acetone-$d_6$): δ ppm 9.26 (s, 1H), 8.58 (d, *J* = 1.5 Hz, 1H), 8.16 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 6.85 (s, 2H), 6.23 (s, 1H), 3.73 (s, 6H), 3.32 (s, 3H), 2.55 (s, 3H). $^{13}$C NMR (126 MHz, acetone-$d_6$): δ ppm 166.8, 161.2, 146.7, 140.2, 132.1, 125.2, 123.4, 97.86, 97.77, 95.7, 54.7, 54.2, 39.8, 18.1. HRMS (EI) calc'd for $C_{18}H_{21}N_3O_7S$ [M]+: 424.1178, found 424.1188.

***N*-(3,5-Bis(trifluoromethyl)phenyl)-2-(*N*-(2-methyl-5-nitrophenyl)methylsulfon-amido)acetamide (98e)**

**98e** was prepared according to GP-5 in 66% yield (66 mg) as a beige solid) m.p.: 201-203 °C. $^{1}$H NMR (500 MHz, acetone-$d_6$) δ ppm 9.88 (s, 1H), 8.57 (d, *J* = 2.3 Hz, 1H), 8.26 (s, 2H), 8.15 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.71 (s, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 3.32 (s, 3H), 2.57 (s, 3H). $^{13}$C NMR (126 MHz, acetone-$d_6$) δ ppm 167.9, 148.0, 146.7, 140.3, 140.0, 131.9 (t, *J* = 34.5 Hz), 125.2, 123.5 (t, *J* = 153.2 Hz), 116.8 (q, *J* = 3.5 Hz), 78.1 (t, *J* = 33.1 Hz), 54.1, 39.8, 18.2. HRMS (EI) calc'd for $C_{18}H_{15}F_6N_3O_5S$ [M]+: 500.0715, found 500.0714.

***N*-(3,5-difluorophenyl)-2-(*N*-(2-methyl-5-nitrophenyl)methylsulfon-amido)acetamide (98f)**

**98f** was prepared according to GP-5 in 84% yield (67 mg) as a beige solid; m.p.: 124-126 ◦C. $^{1}$H NMR (500 MHz, acetone-$d_6$) δ ppm 9.68 (s, 1H), 8.57 (d, *J* = 2.3 Hz, 1H), 8.16 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 2H), 6.72 (t, *J* = 9.2 Hz, 1H), 3.31 (s, 3H), 2.56 (s, 3H). $^{13}$C NMR (126 MHz, acetone-$d_6$): δ ppm 167.5, 163.0 (d, *J* = 244.7 Hz), 148.1, 146.7, 141.0, 140.0, 132.1, 125.3, 123.4, 102.3 (d, $^{2}J$ = 29.7 Hz), 98.6 (d, $^{2}J$ = 26.2 Hz), 54.1, 39.8, 18.1. HRMS (EI) calc'd for $C_{16}H_{15}F_2N_3O_5S$ [M]+: 400.0779, found 400.0789

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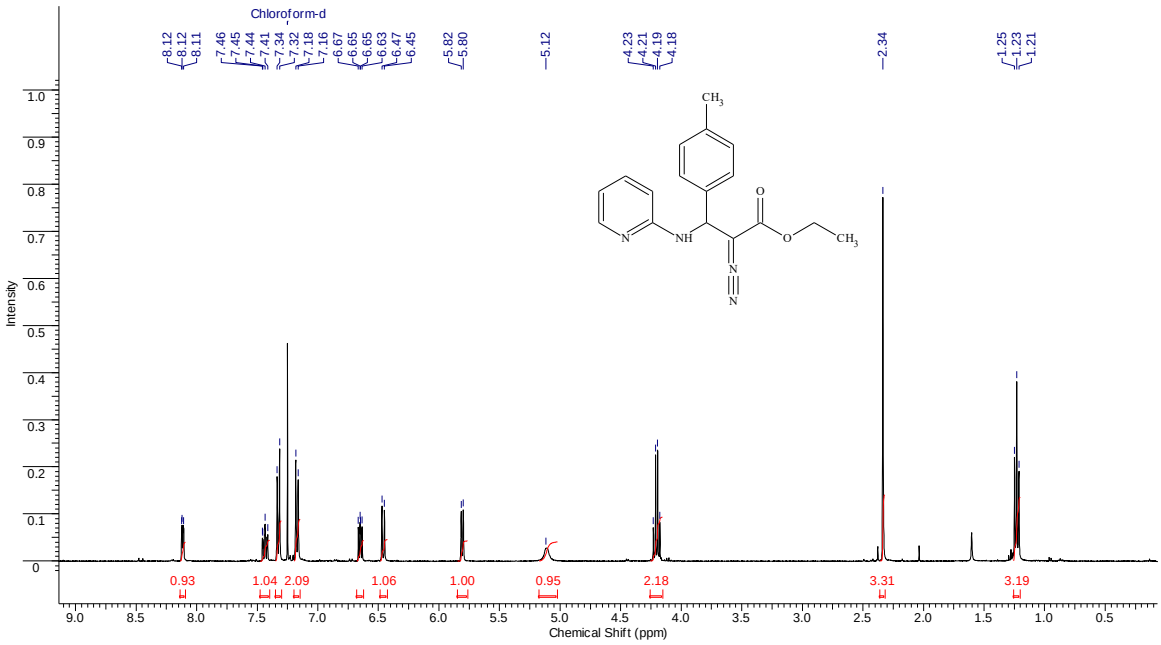
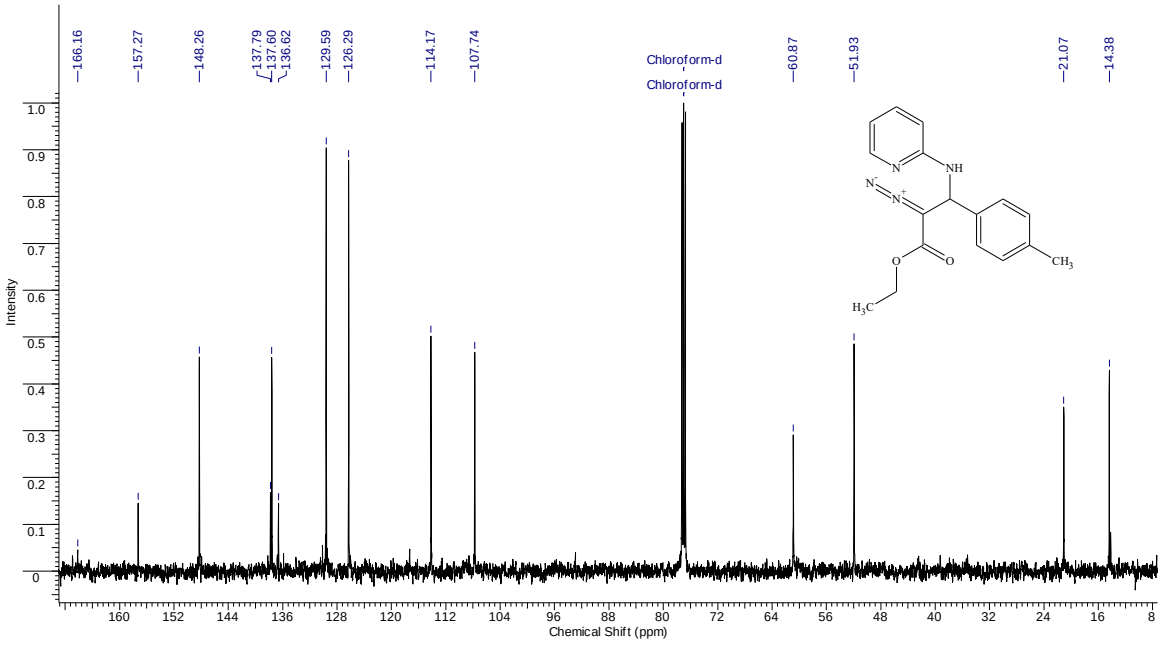
## Appendix B. $^{1}H$ and $^{13}C$ spectra of diazo-compounds 56

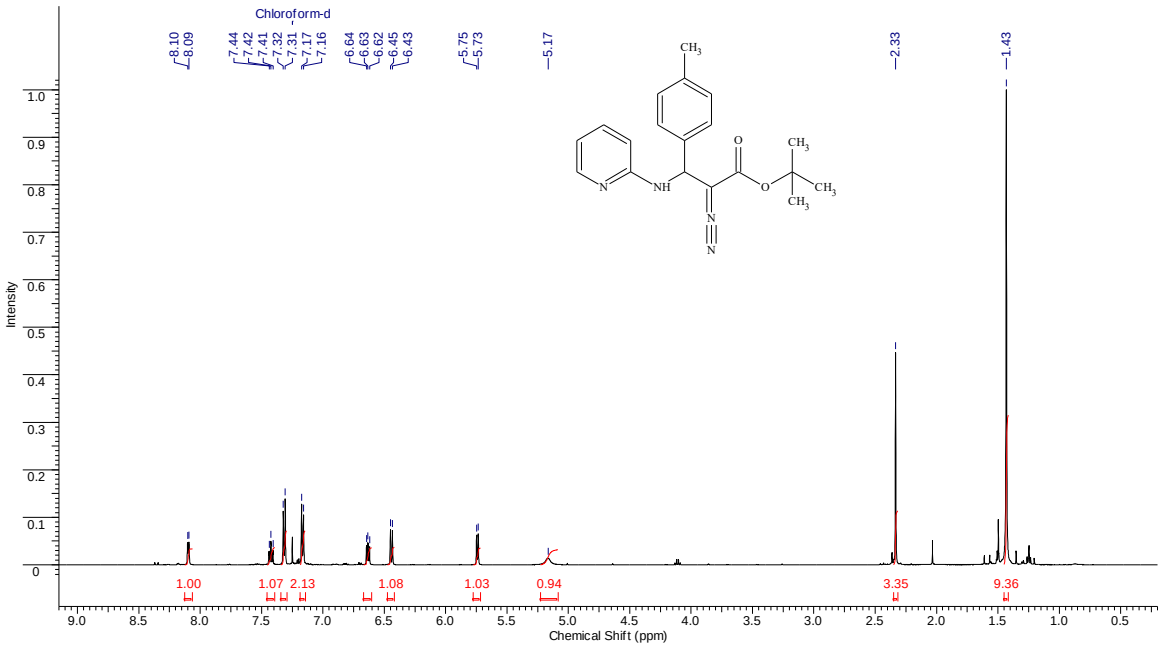
$^{1}H$ NMR spectrum of **56a**



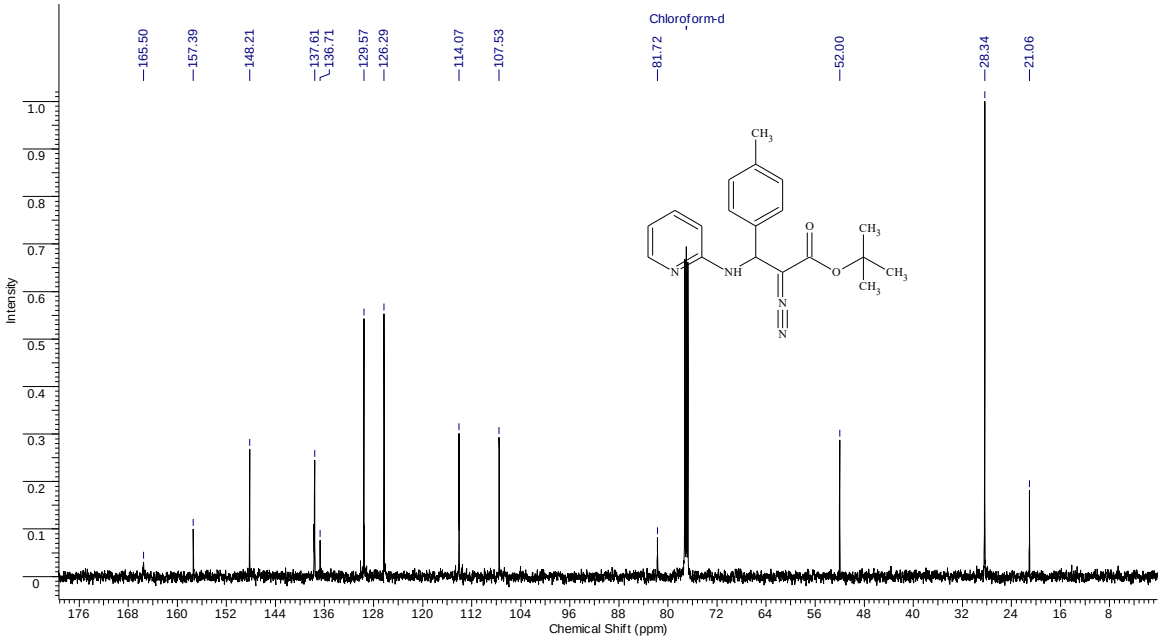

$^{13}C$ NMR spectrum of **56a**



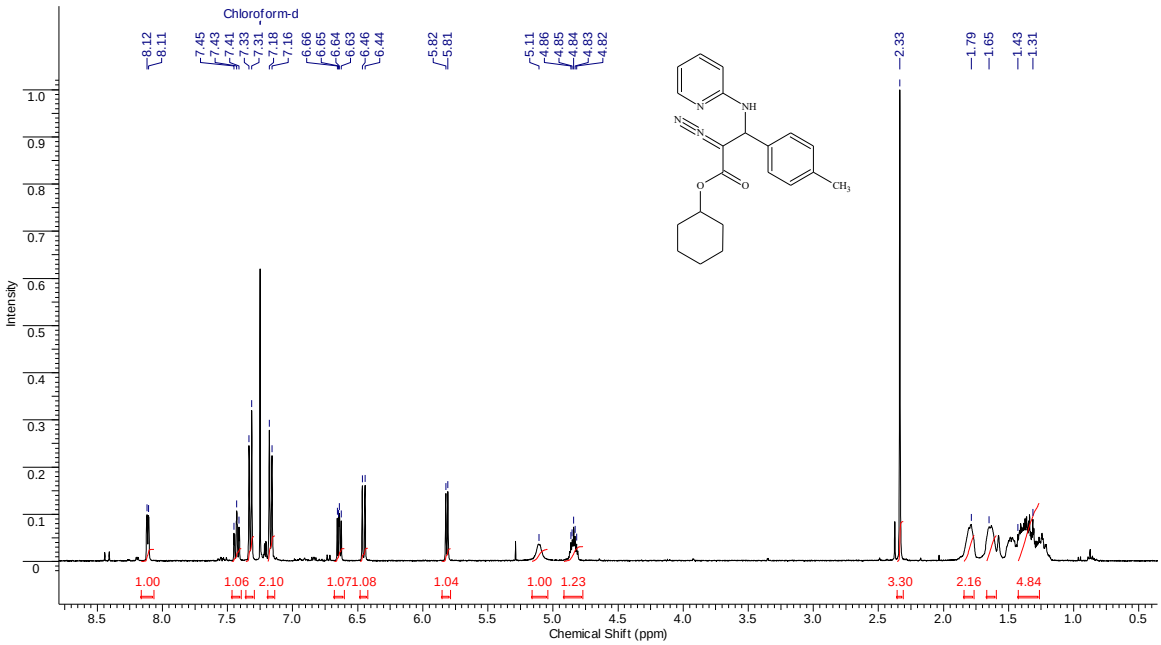

$^{1}H$ NMR spectrum of **56b**



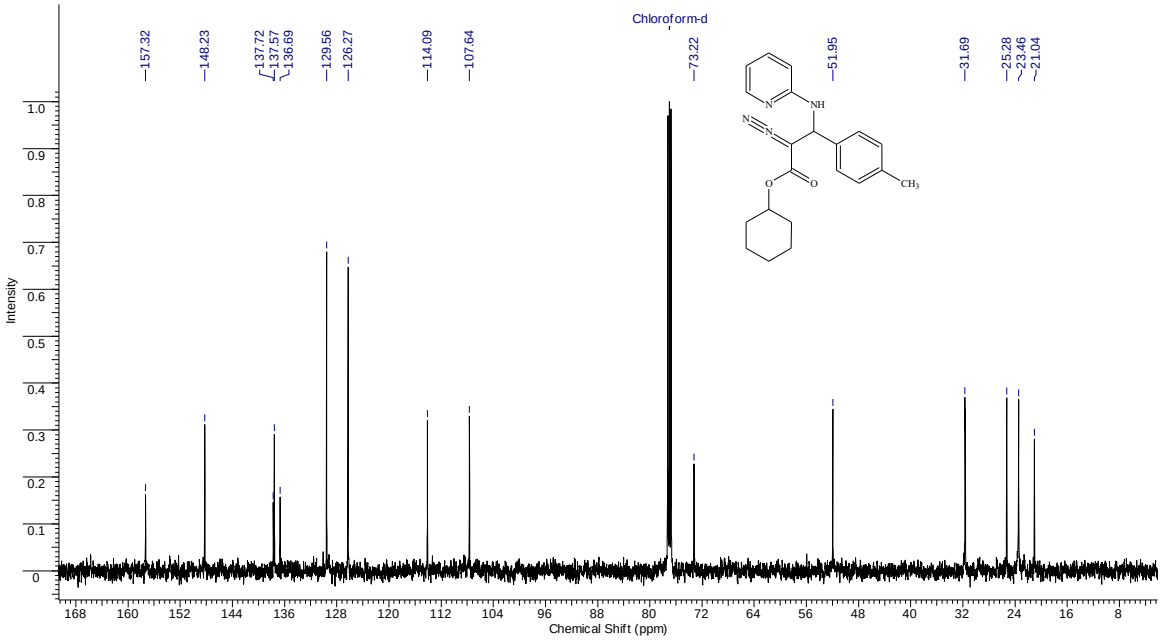

$^{13}$C NMR spectrum of **56b**



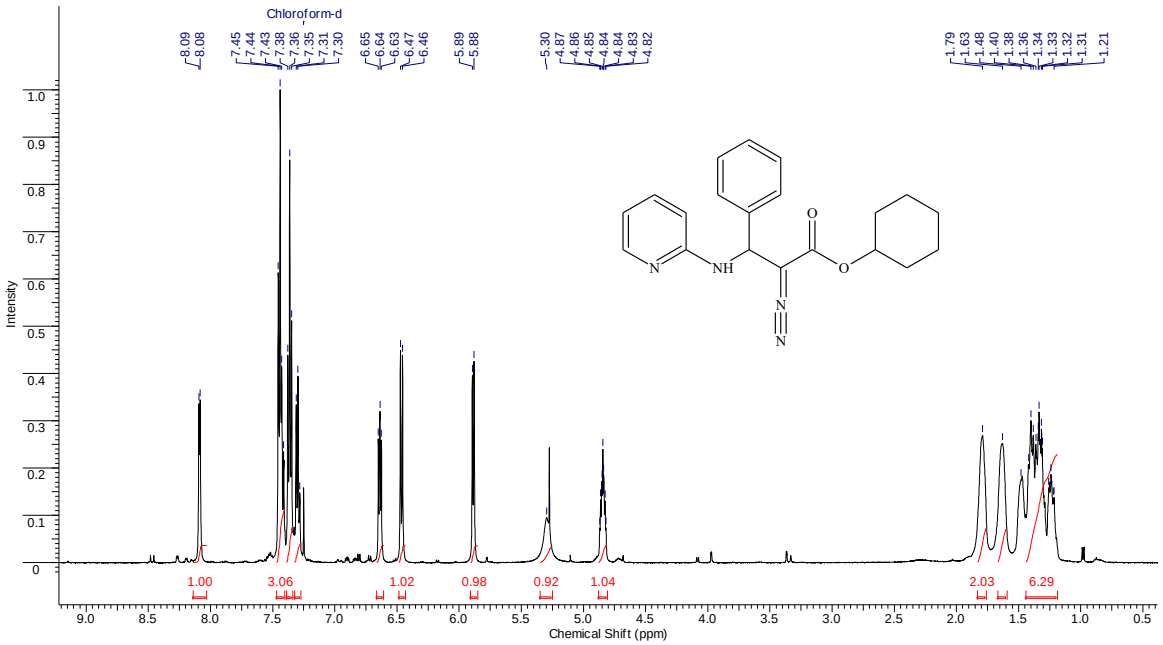

$^{1}$H NMR spectrum of **56c**



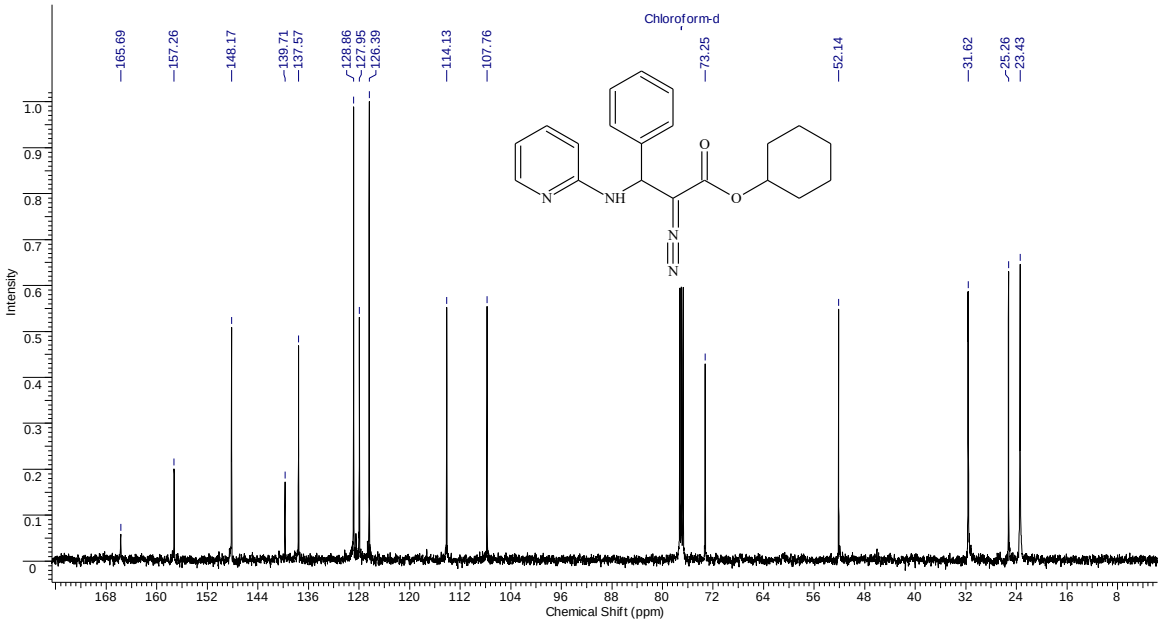

$^{13}$C NMR spectrum of **56c**



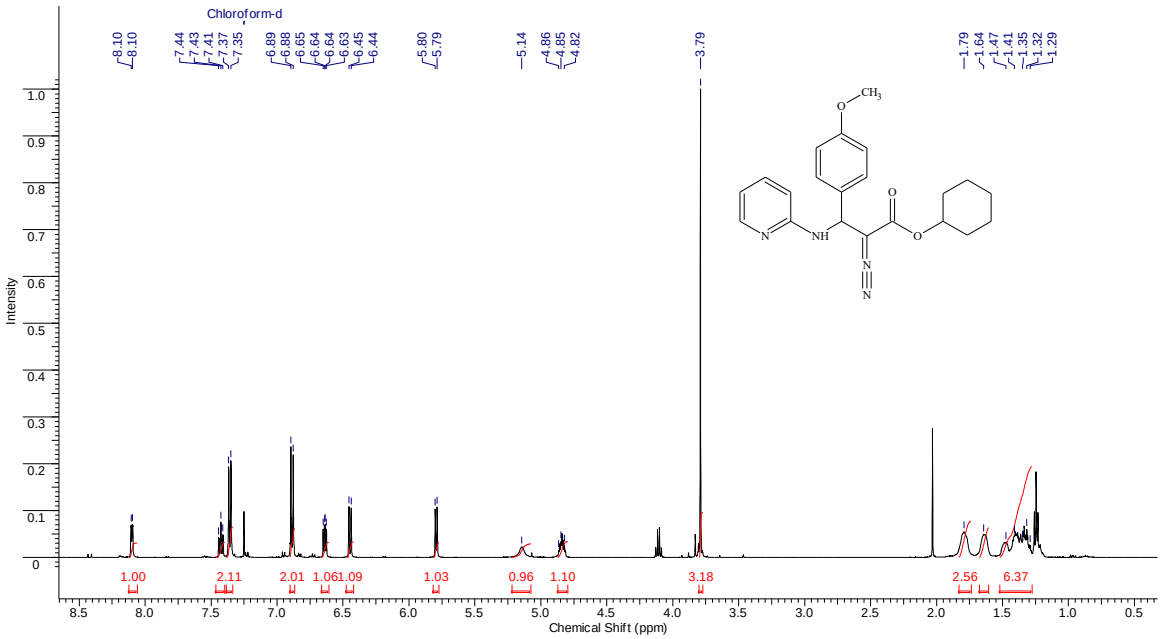

$^{1}$H NMR spectrum of **56d**



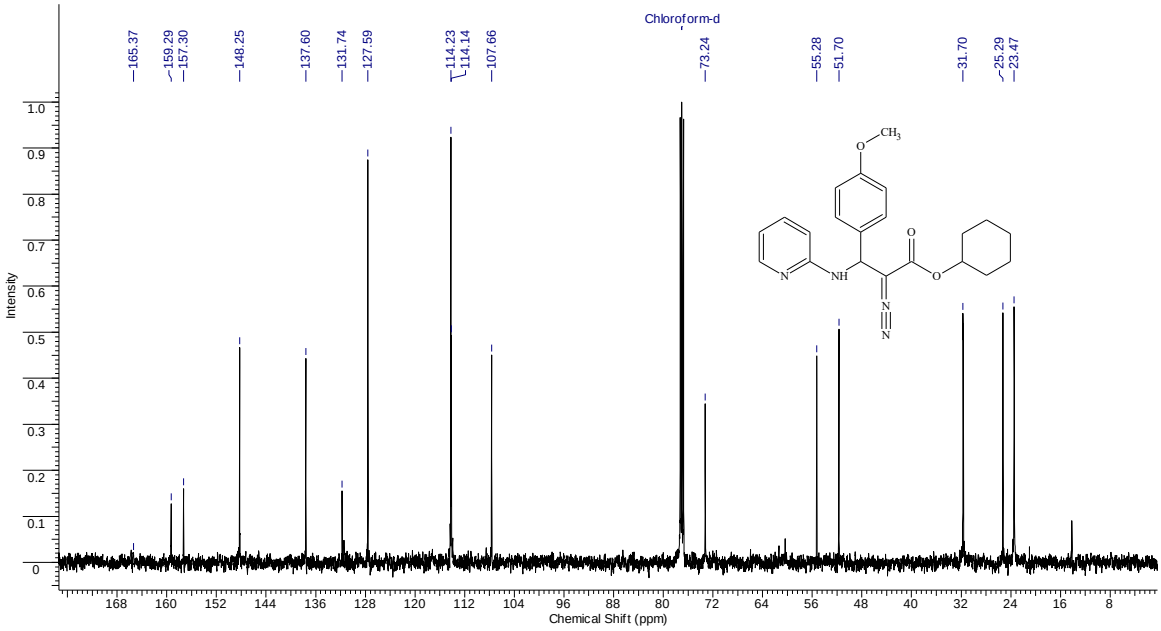

$^{13}$C NMR spectrum of **56d**



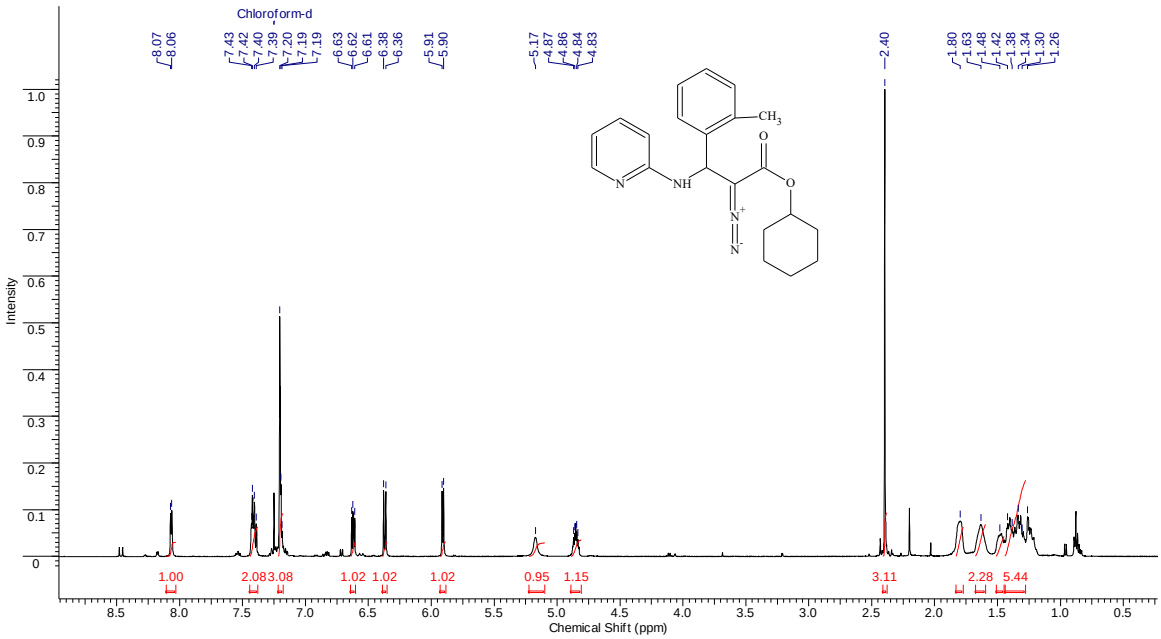

$^{1}$H NMR spectrum of **56e**



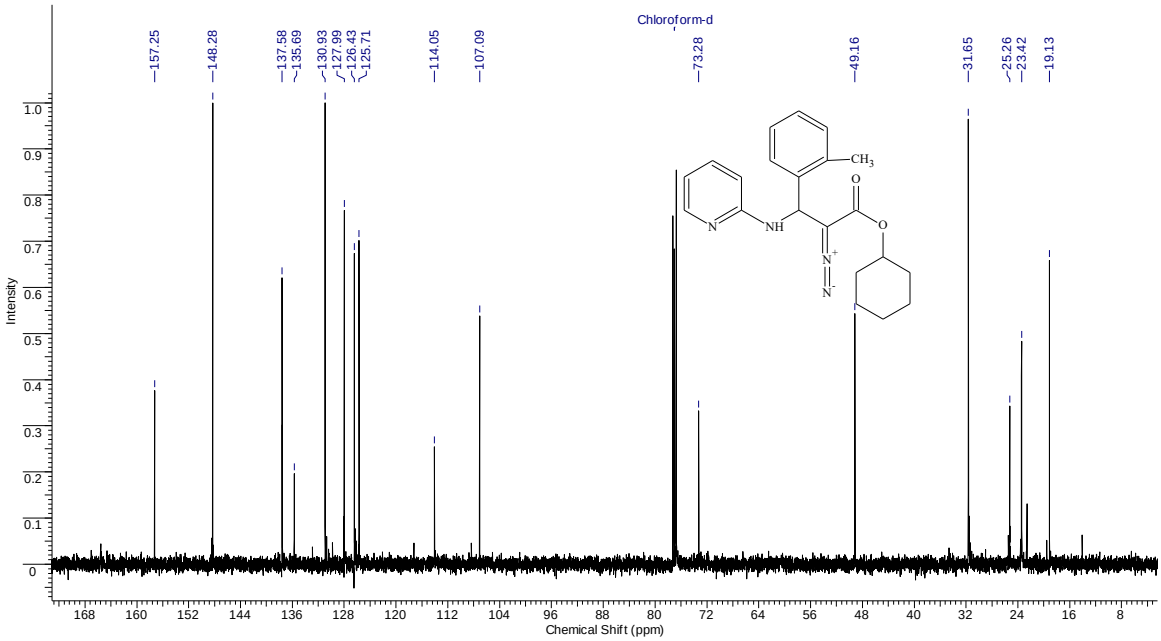

$^{13}$C NMR spectrum of **56e**



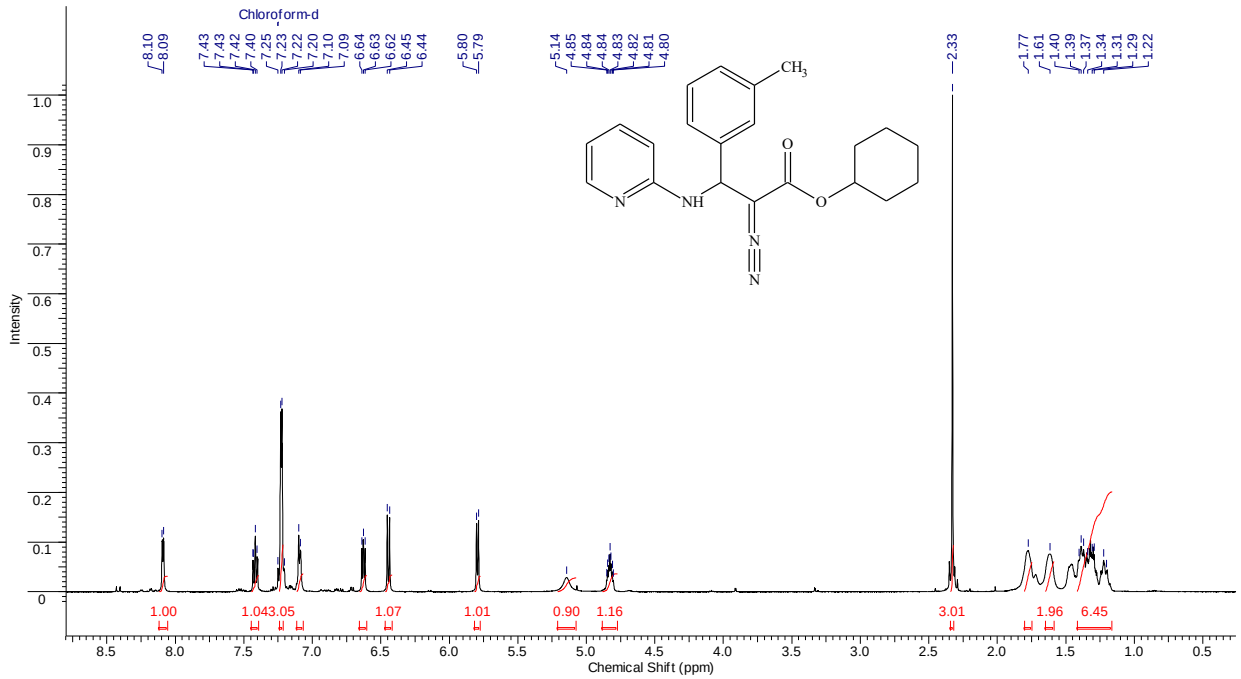

$^{1}$H NMR spectrum of **56f**



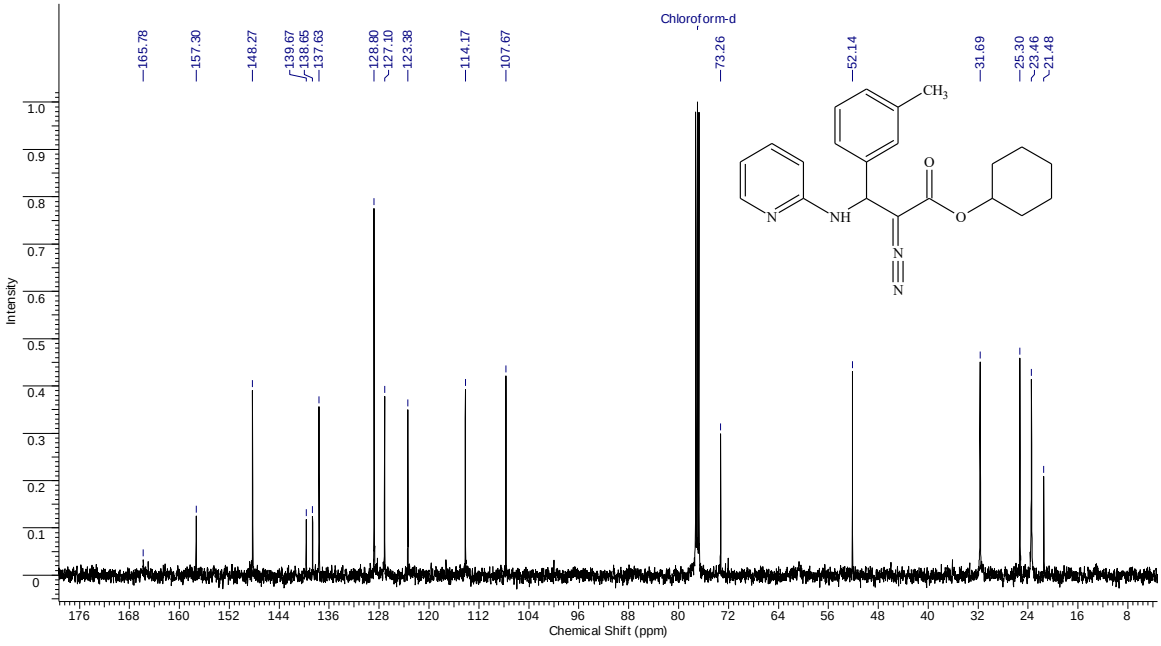

$^{13}$C NMR spectrum of **56f**



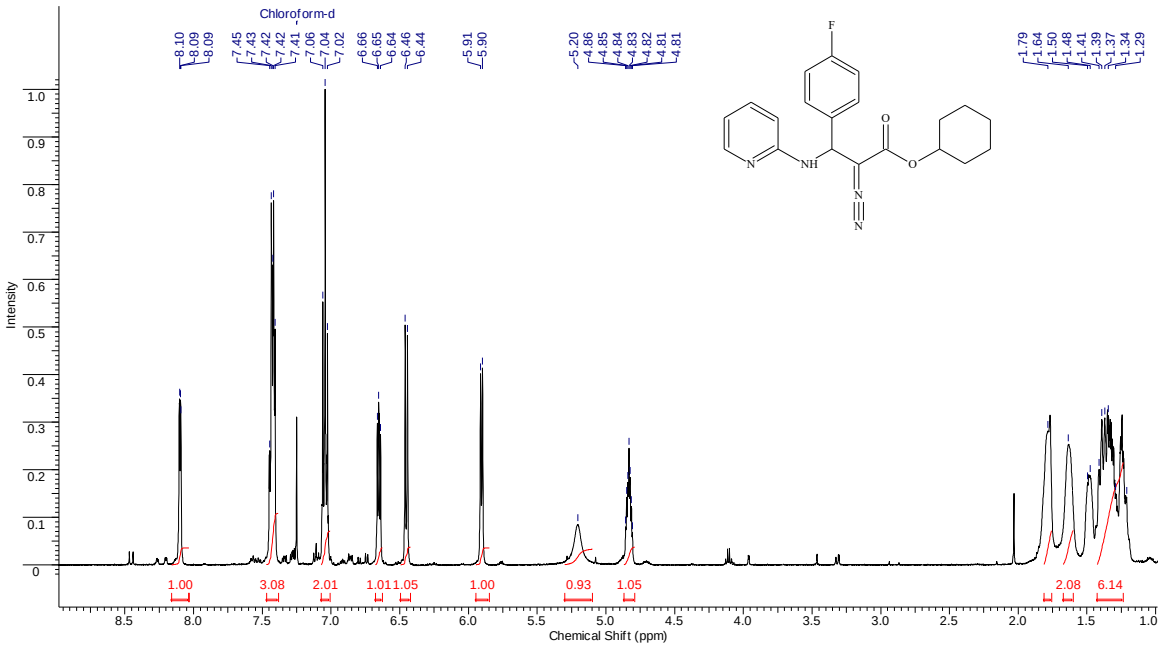

$^{1}$H NMR spectrum of **56g**



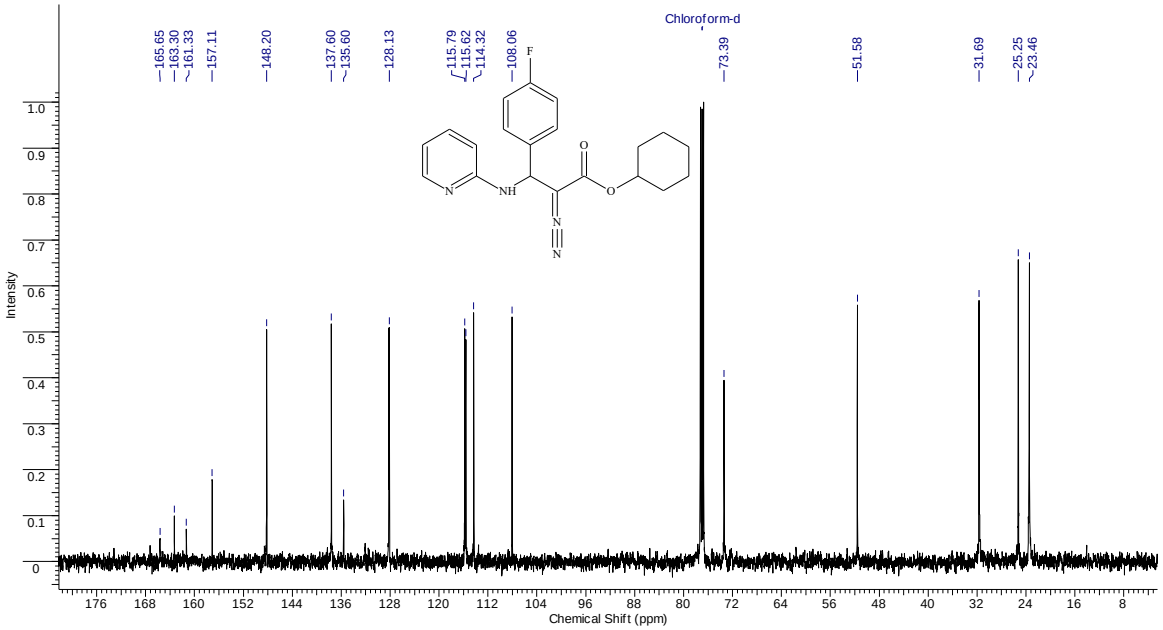

$^{13}$C NMR spectrum of **56g**



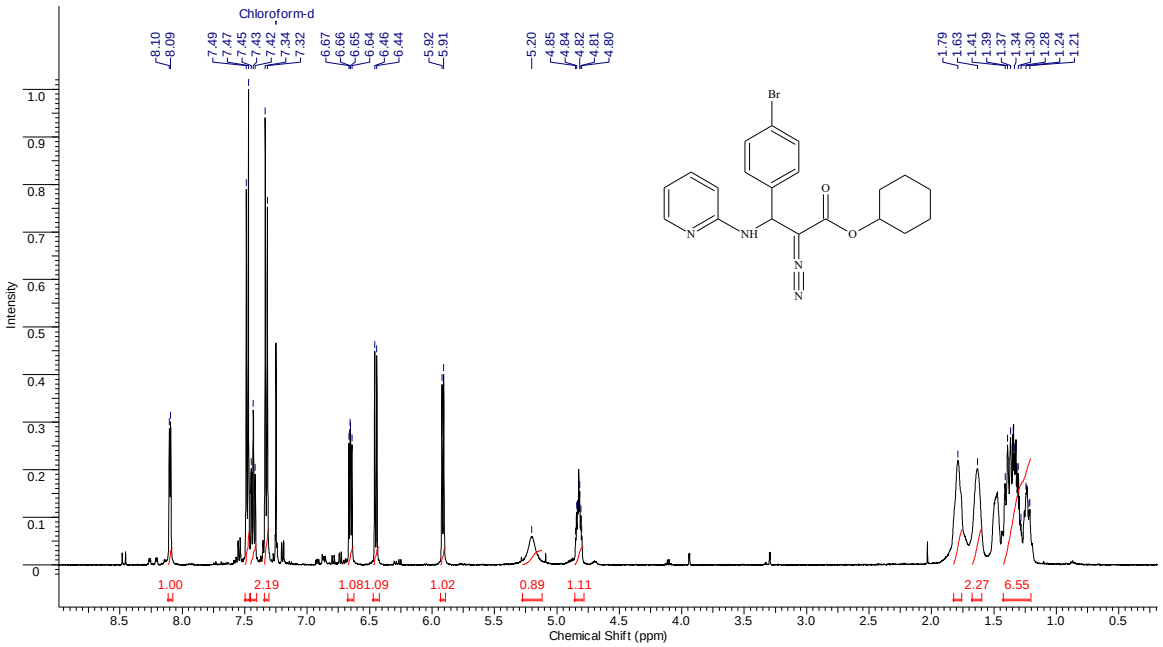

$^{1}$H NMR spectrum of **56h**



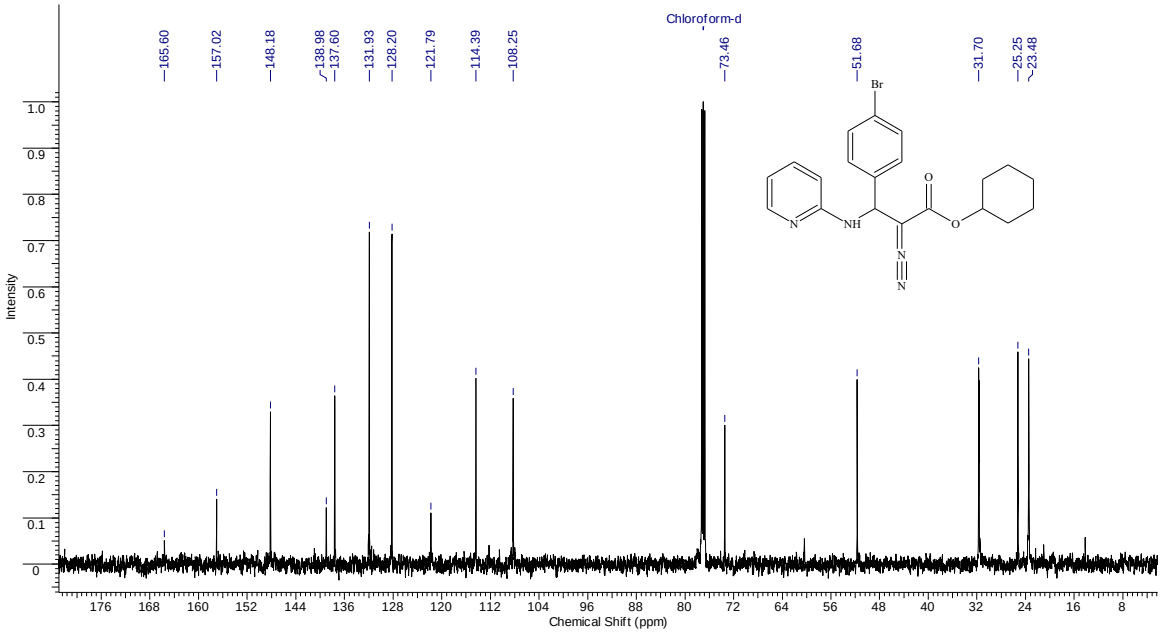

$^{13}$C NMR spectrum of **56h**



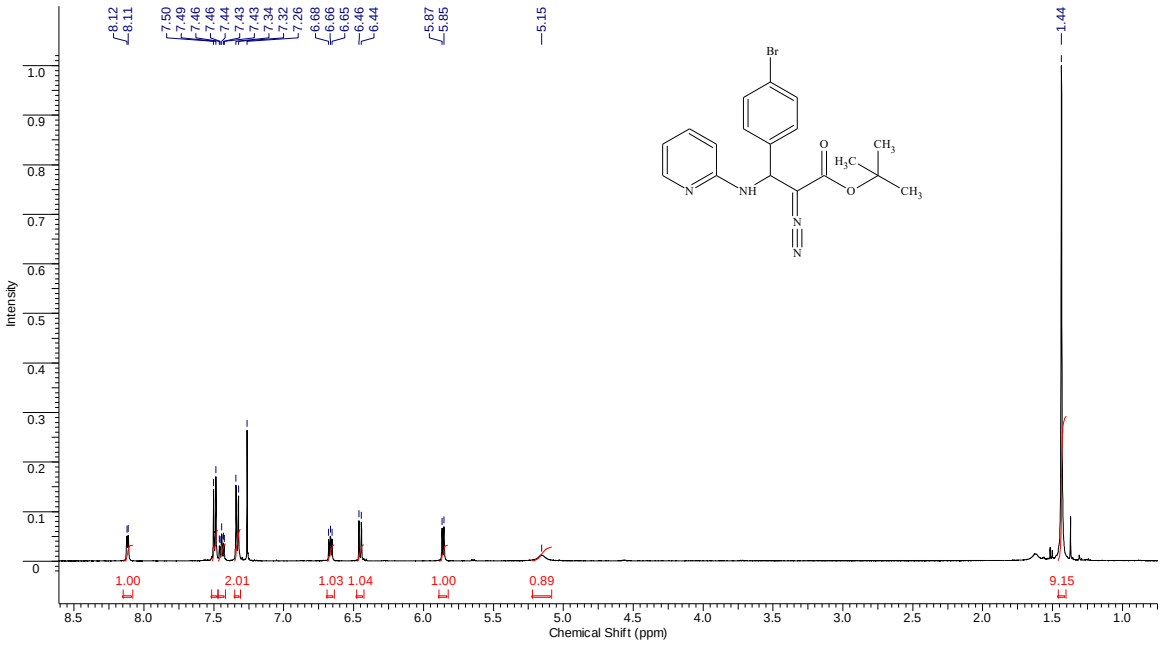

$^{1}$H NMR spectrum **56i**



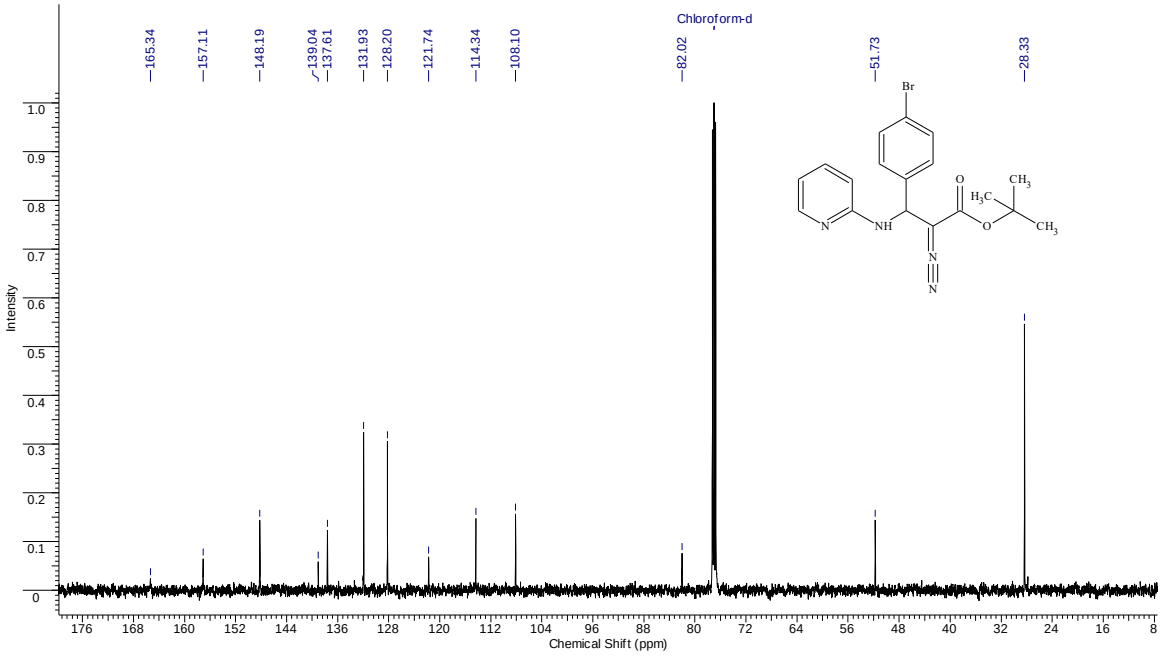

$^{13}$C NMR spectrum of **56i**



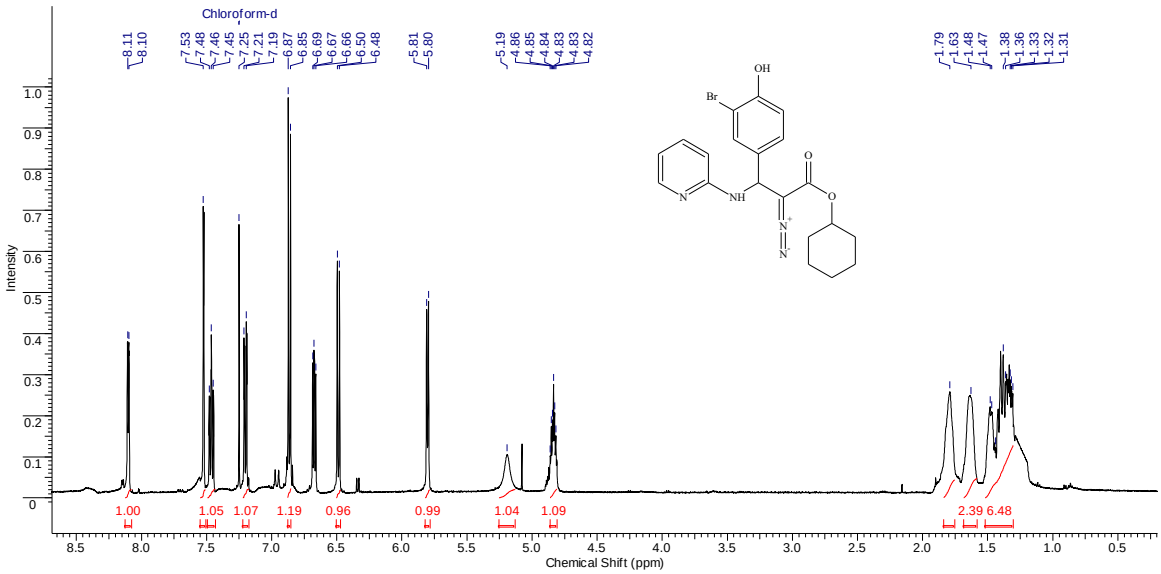

$^{1}$H NMR spectrum **of 56j**



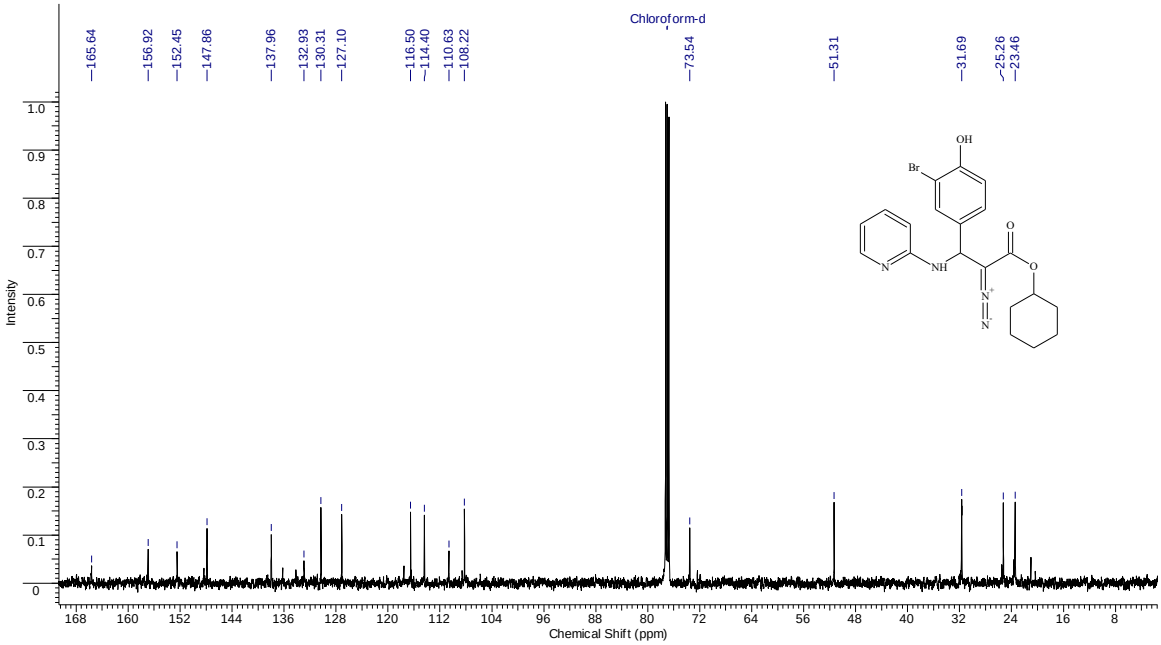

$^{13}$C NMR spectrum of **56j**



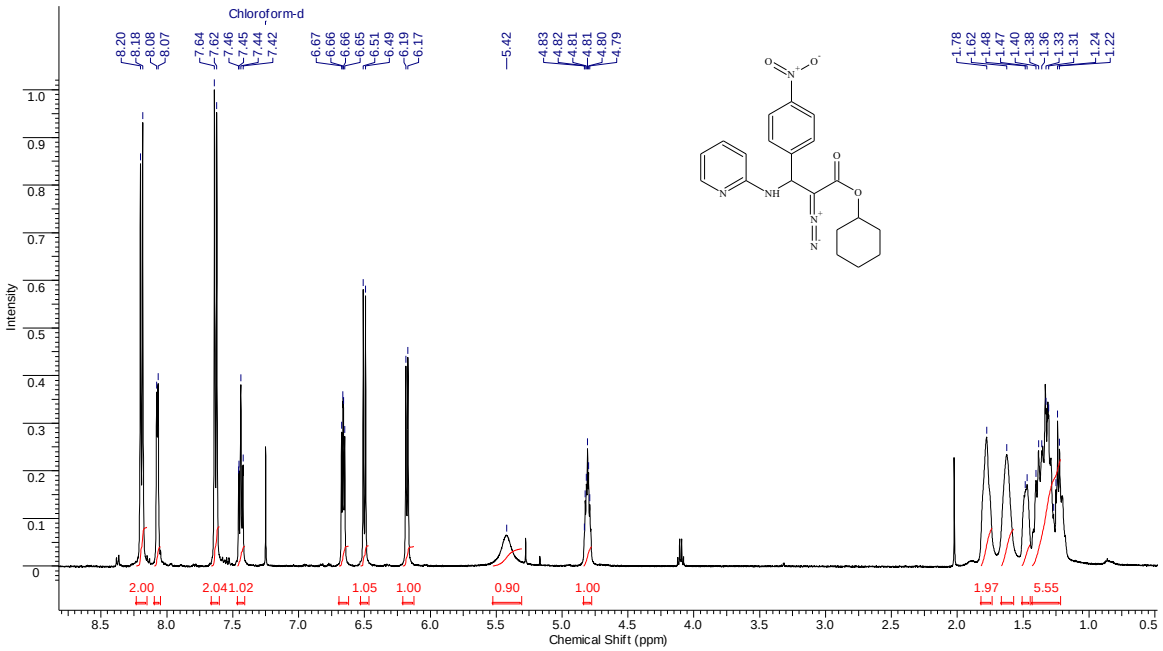

$^{1}$H NMR spectrum of **56k**



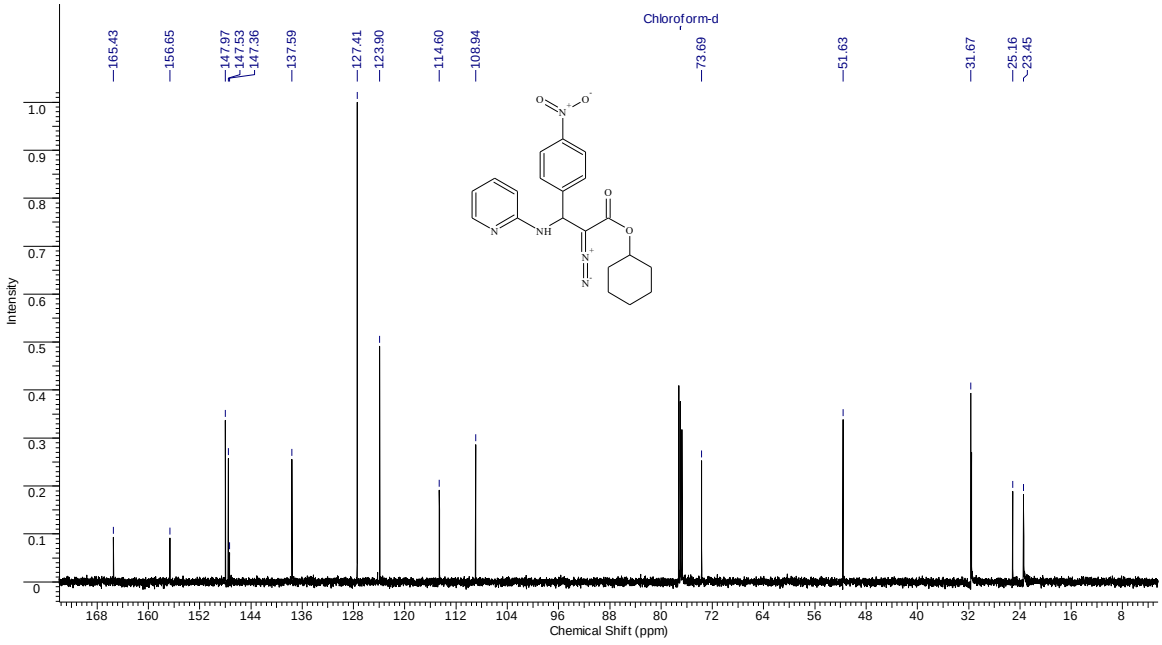

$^{13}$C NMR spectrum of **56k**



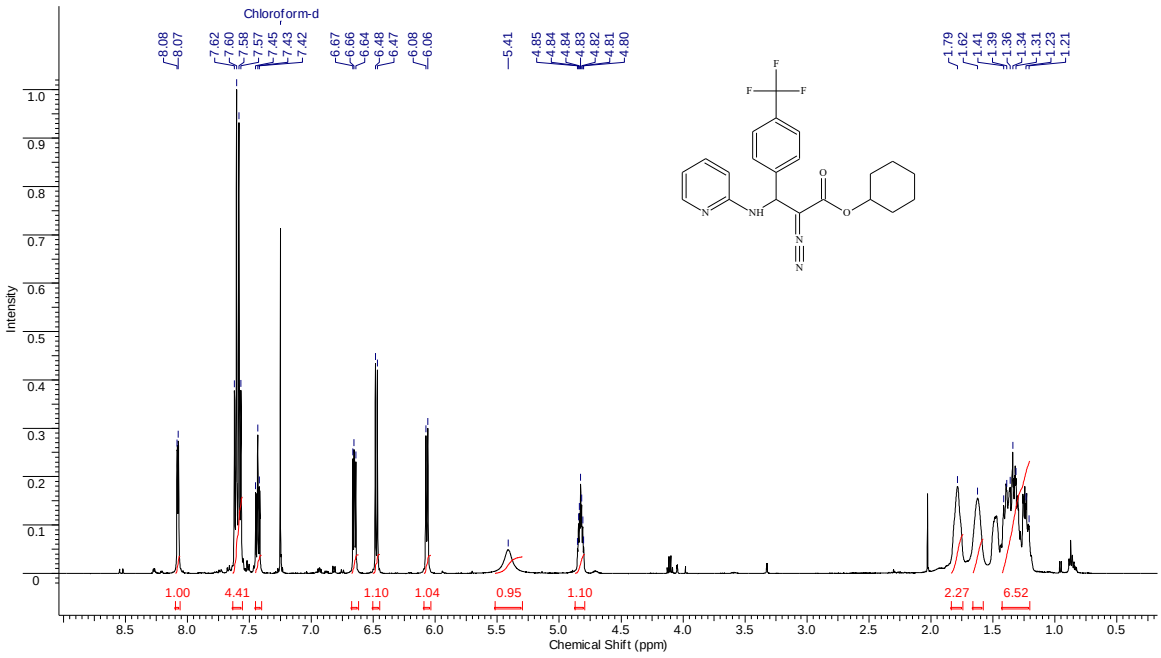

$^{1}$H NMR spectrum of **56l**



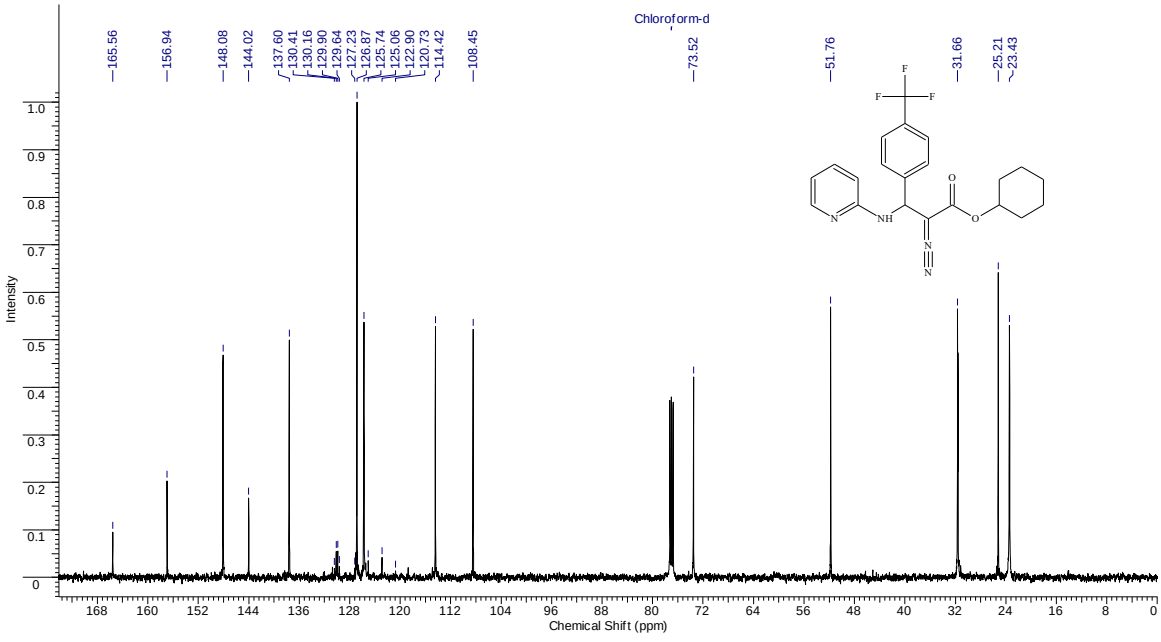

$^{13}$C NMR spectrum of **56l**



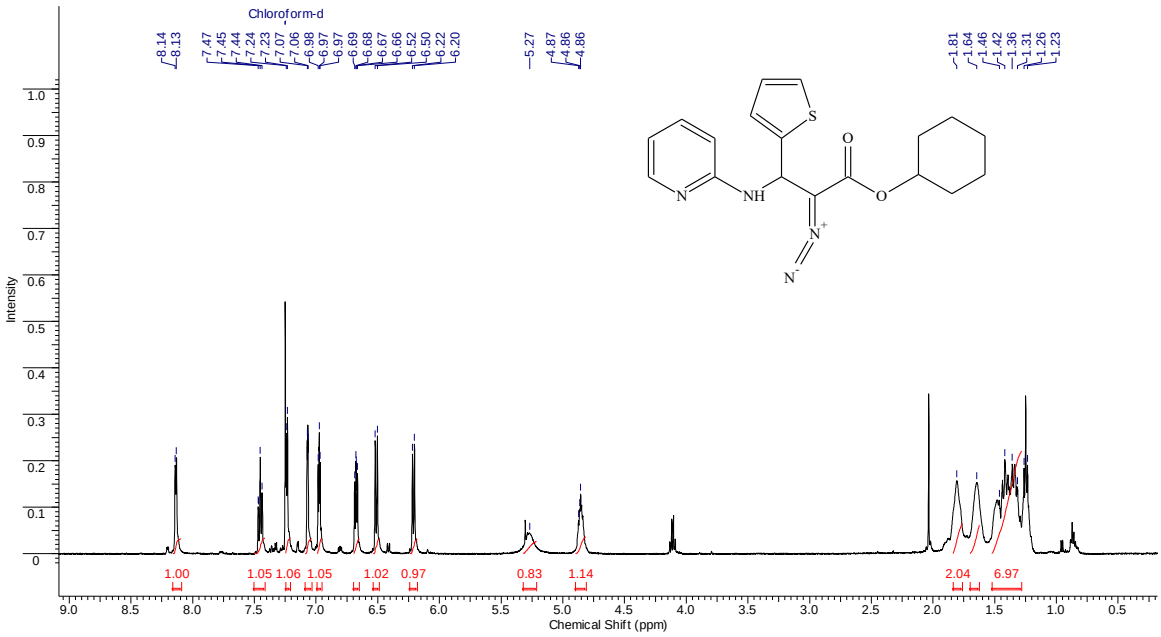

$^{1}$H NMR spectrum of **56m**



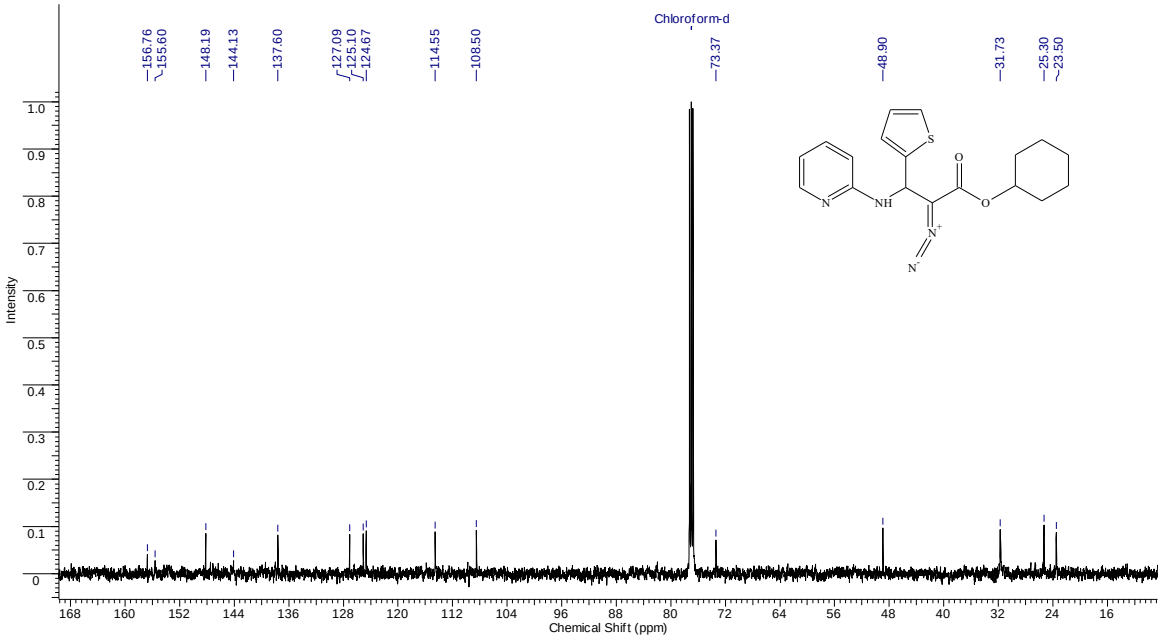

$^{13}$C NMR spectrum of **56m**



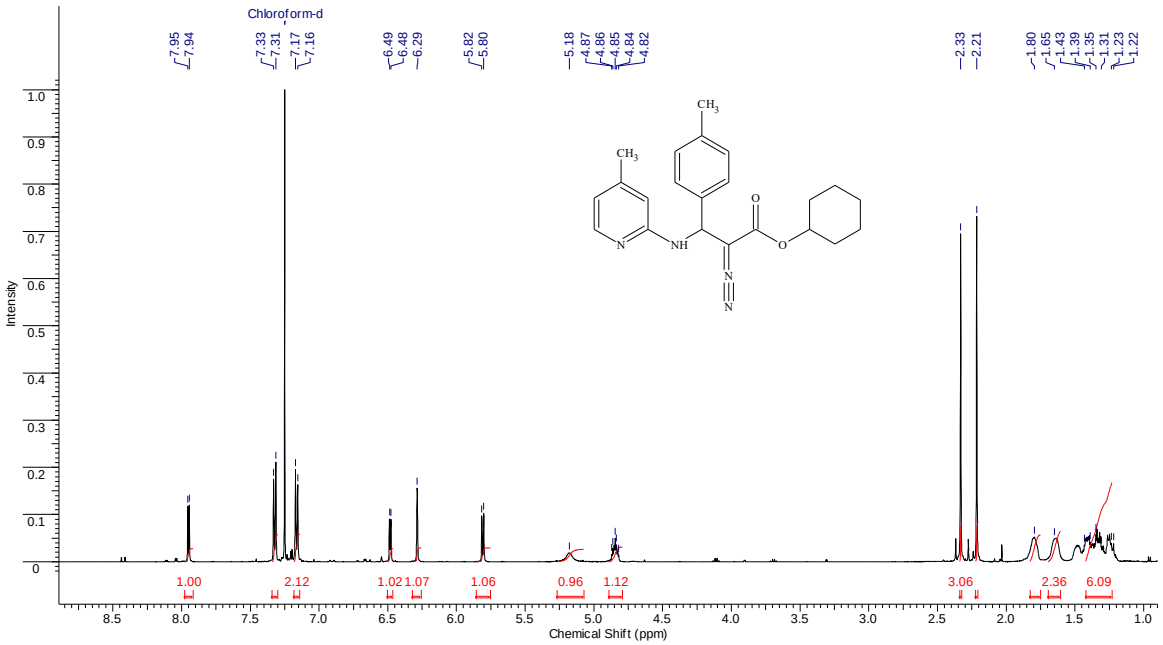

$^{1}$H NMR spectrum of **56n**



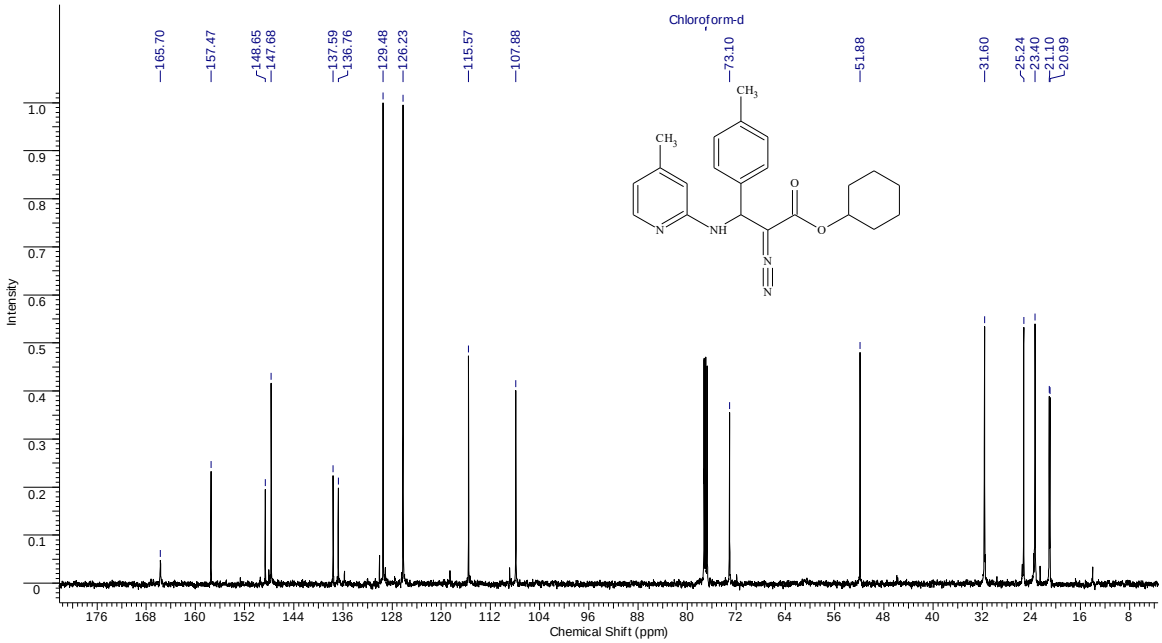

$^{13}$C NMR spectrum of **56n**



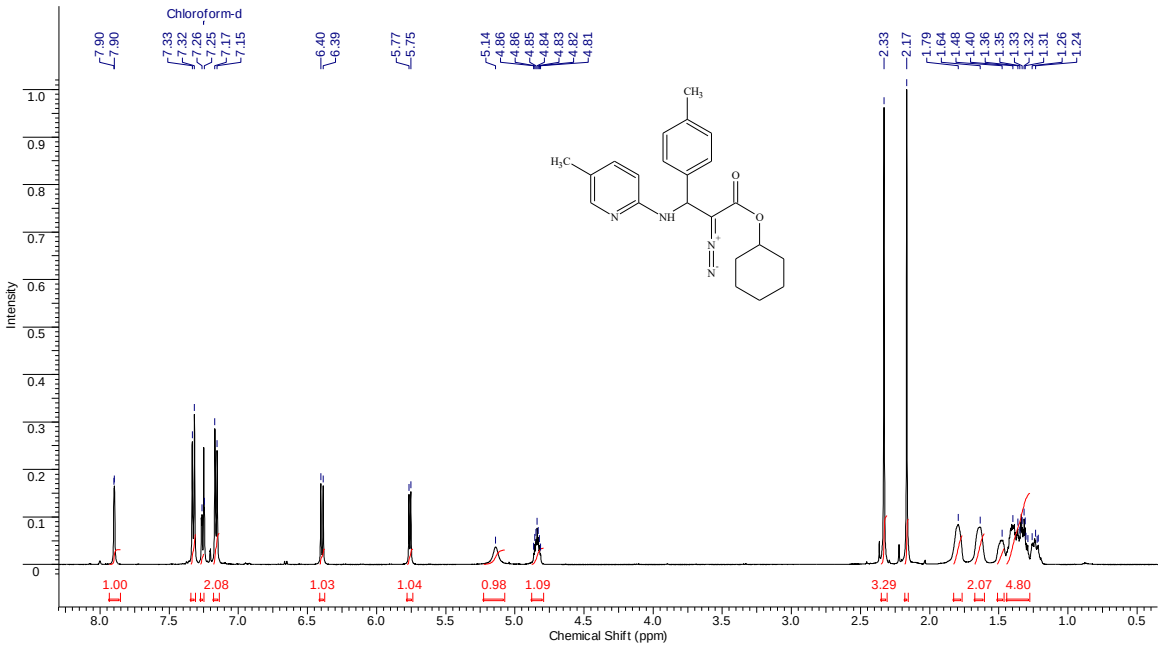

$^{1}$H NMR spectrum of **56o**



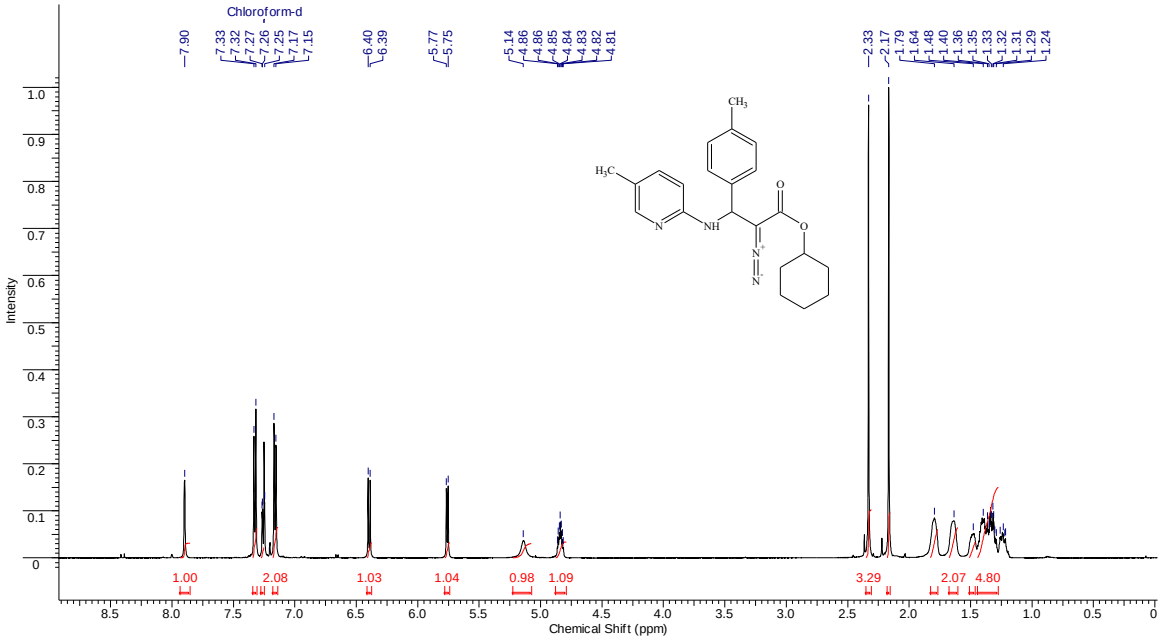

$^{13}$C NMR spectrum of **56o**



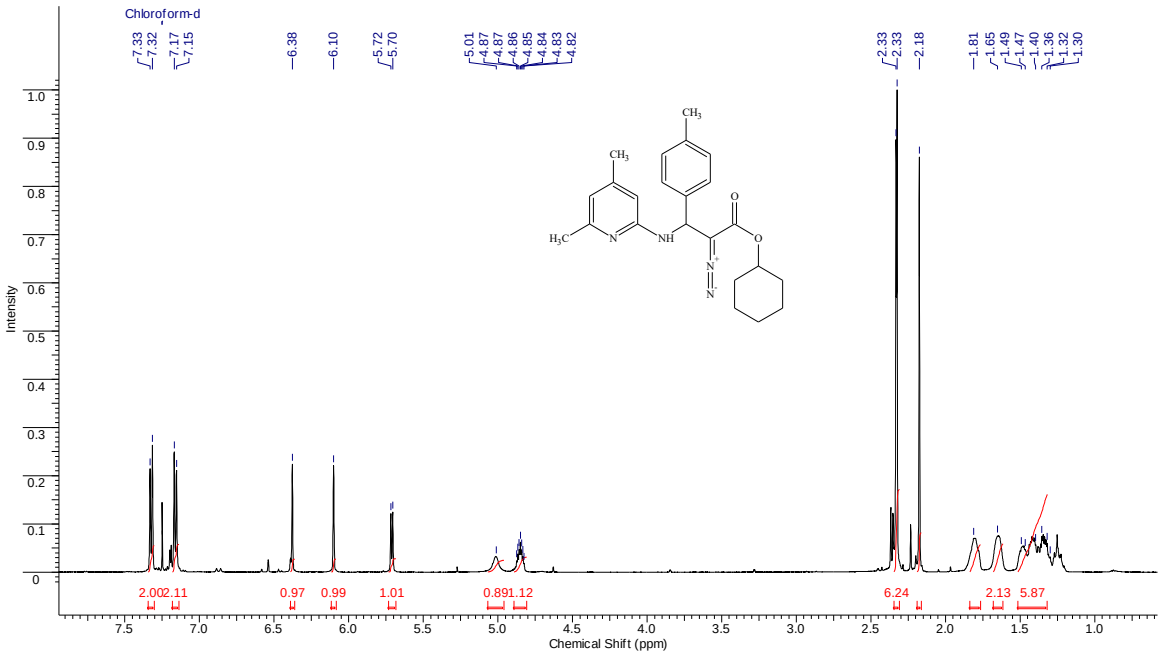

$^{1}$H NMR spectrum of **56p**



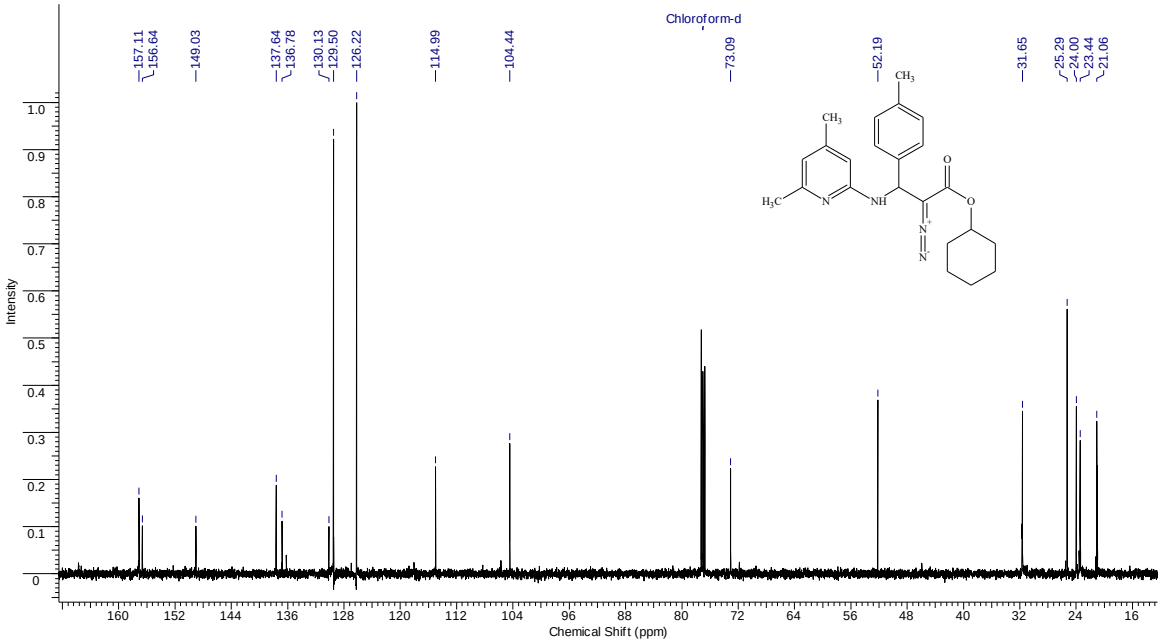

$^{13}$C NMR spectrum of **56p**



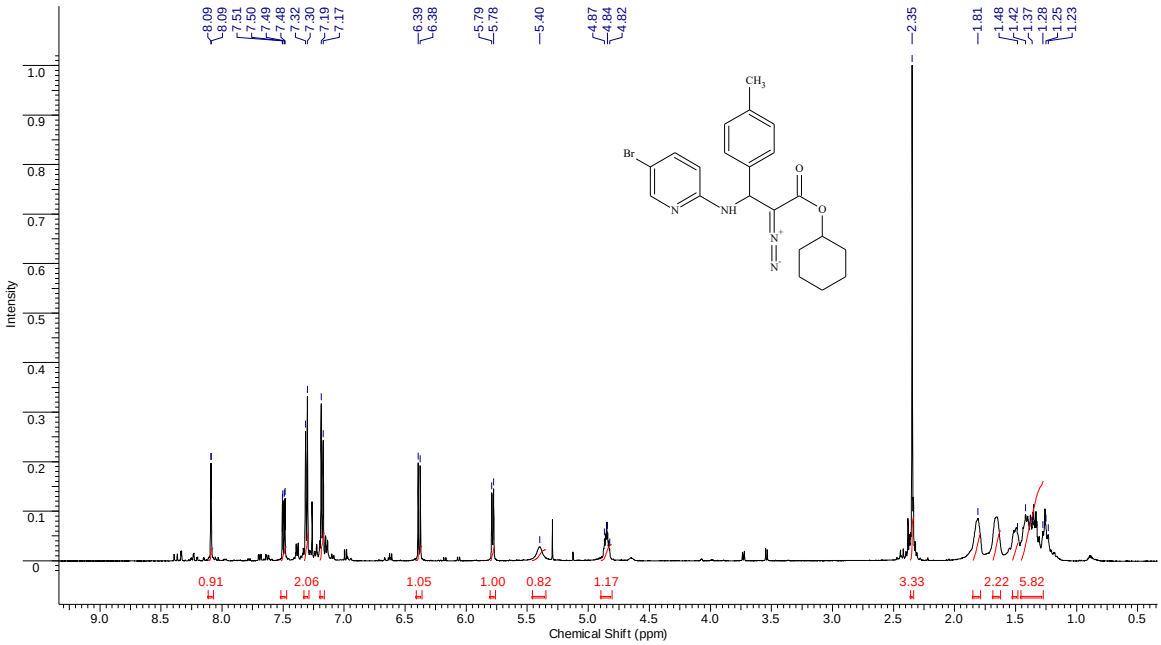

$^{1}$H NMR spectrum of **56q**



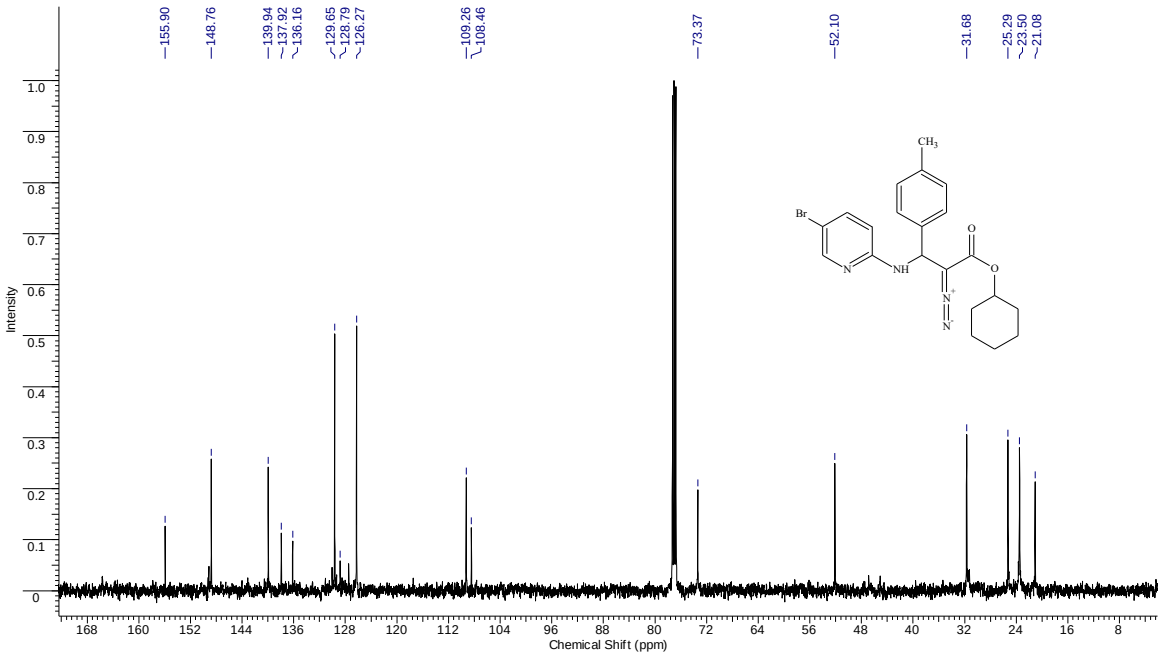

$^{13}$C NMR spectrum of **56q**



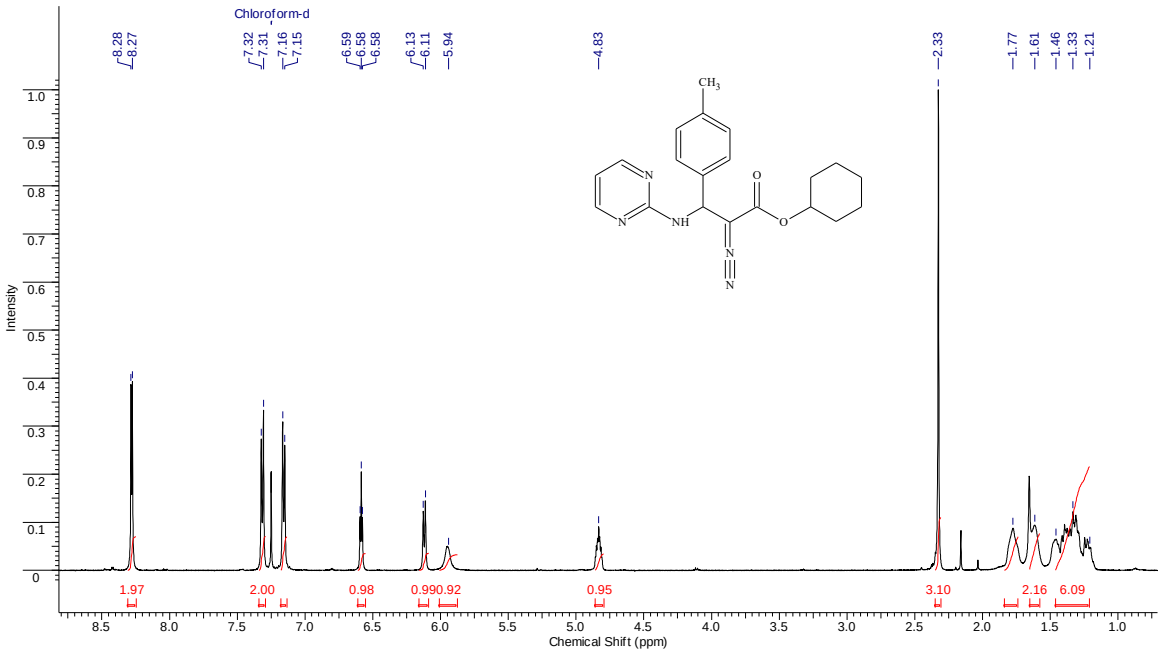

$^{1}$H NMR spectrum of **56r**



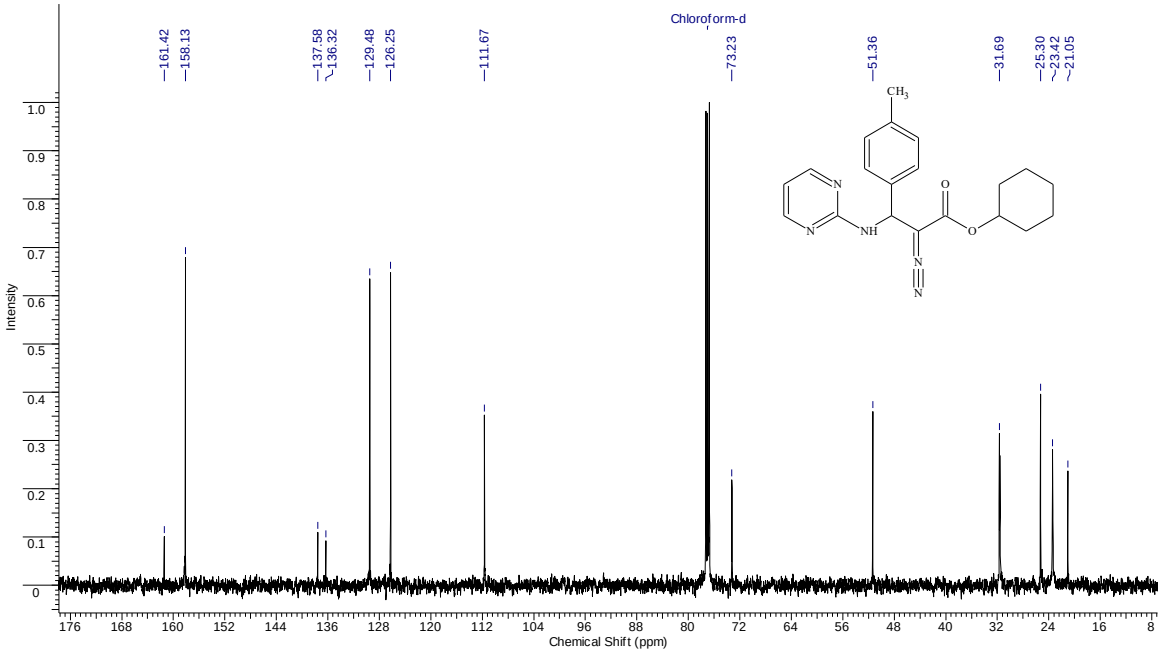

$^{13}$C NMR spectrum **of 56r**



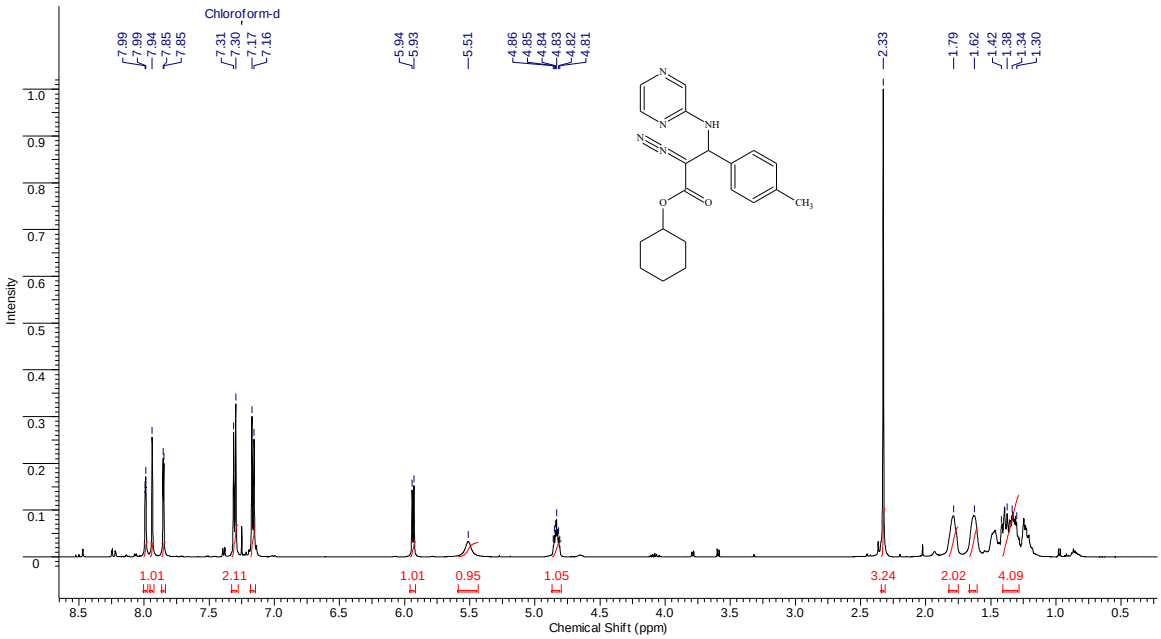

$^{1}$H NMR spectrum of **56s**



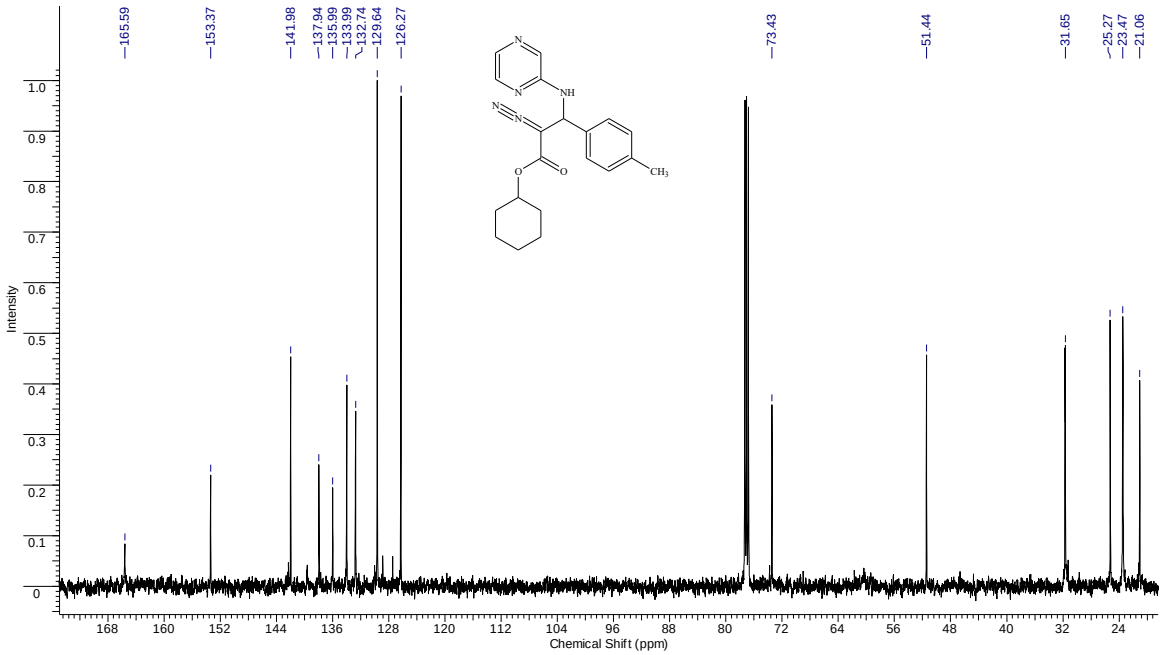

$^{13}$C NMR spectrum of **56s**



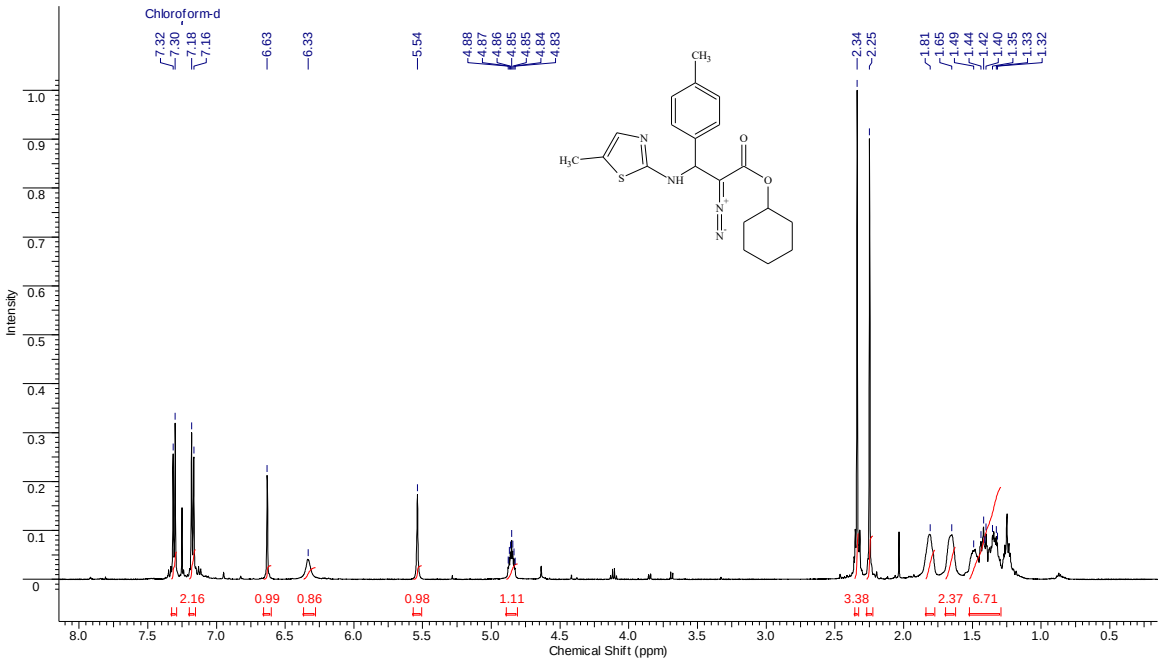

$^{1}$H NMR spectrum of **56t**



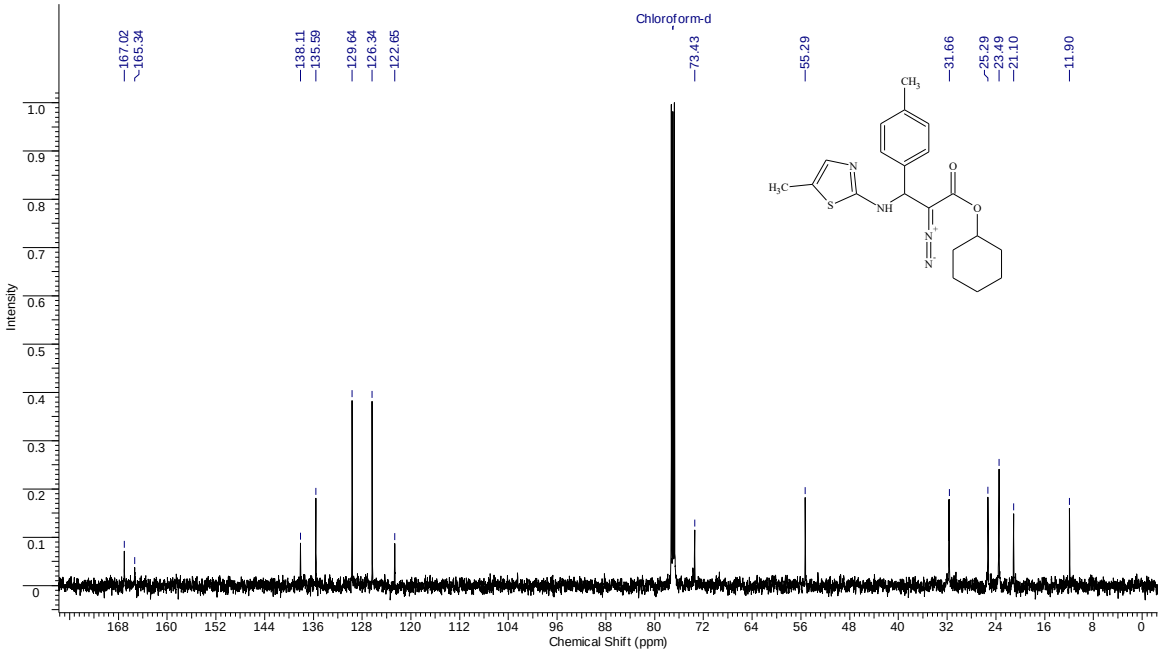

$^{13}$C NMR spectrum of **56t**



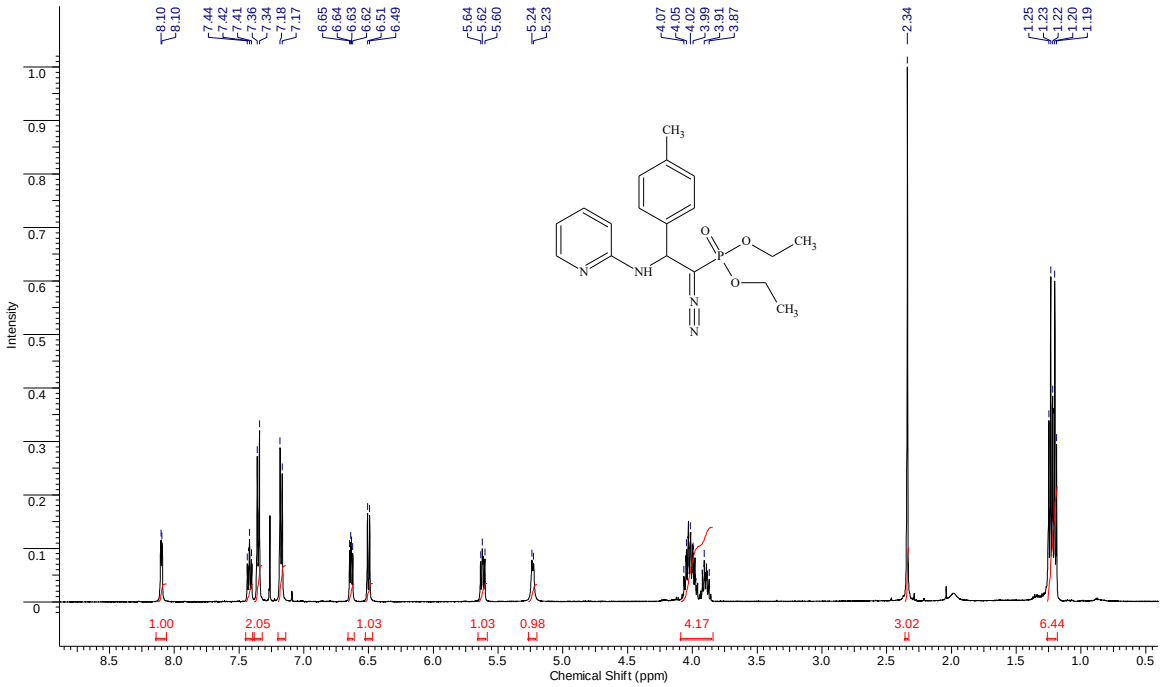

$^{1}$H NMR spectrum of **56u**



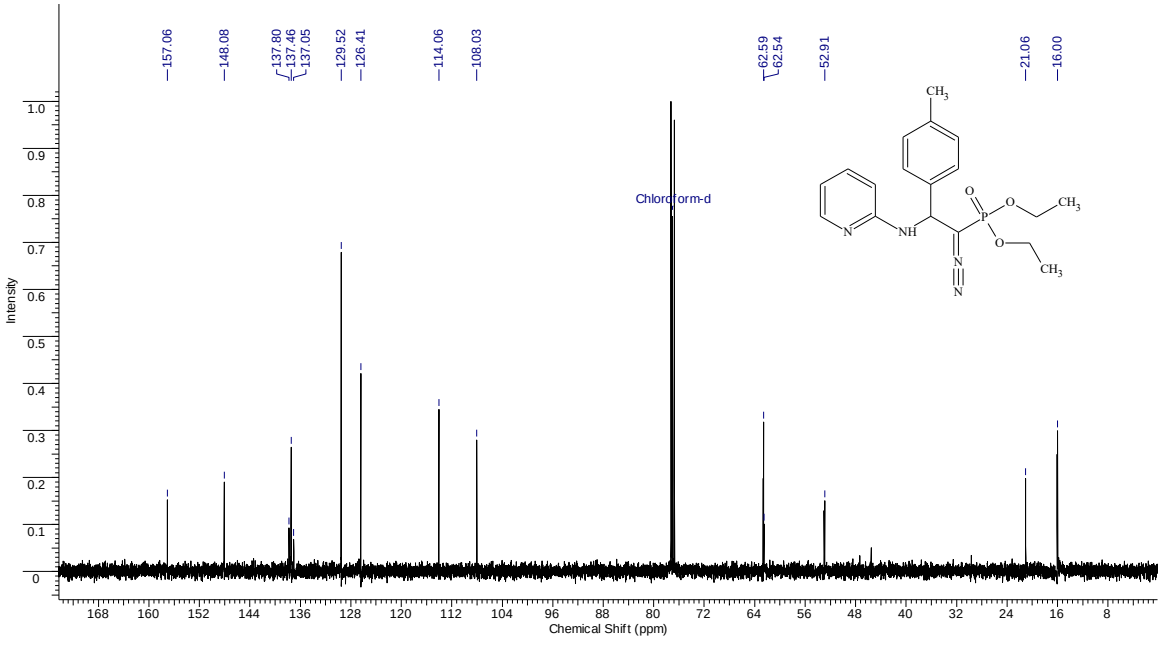

$^{13}$C NMR spectrum of **56u**



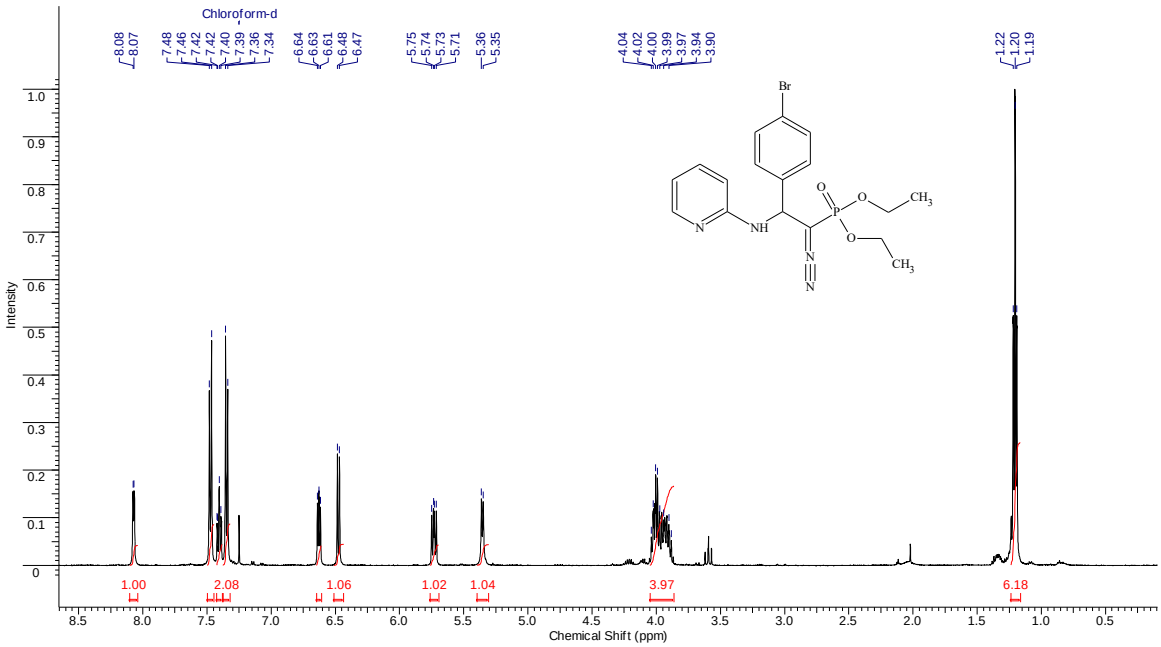

$^{1}$H NMR spectrum of **56v**



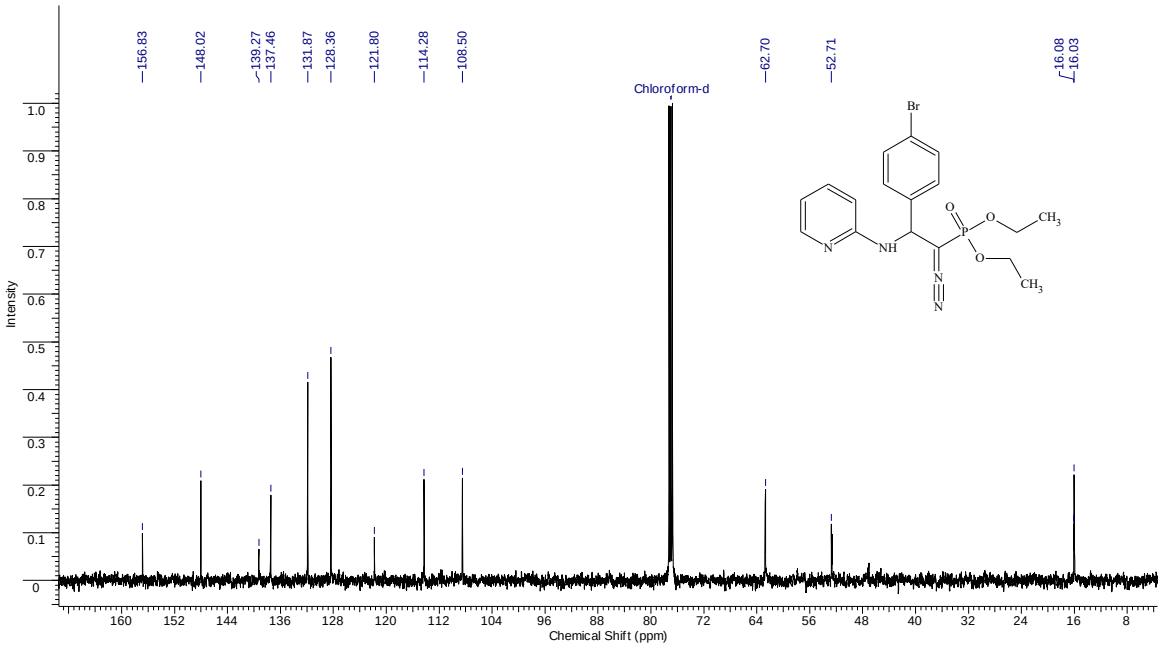

$^{13}$C NMR spectrum of **56v**




$^{1}$H NMR spectrum of **56w**

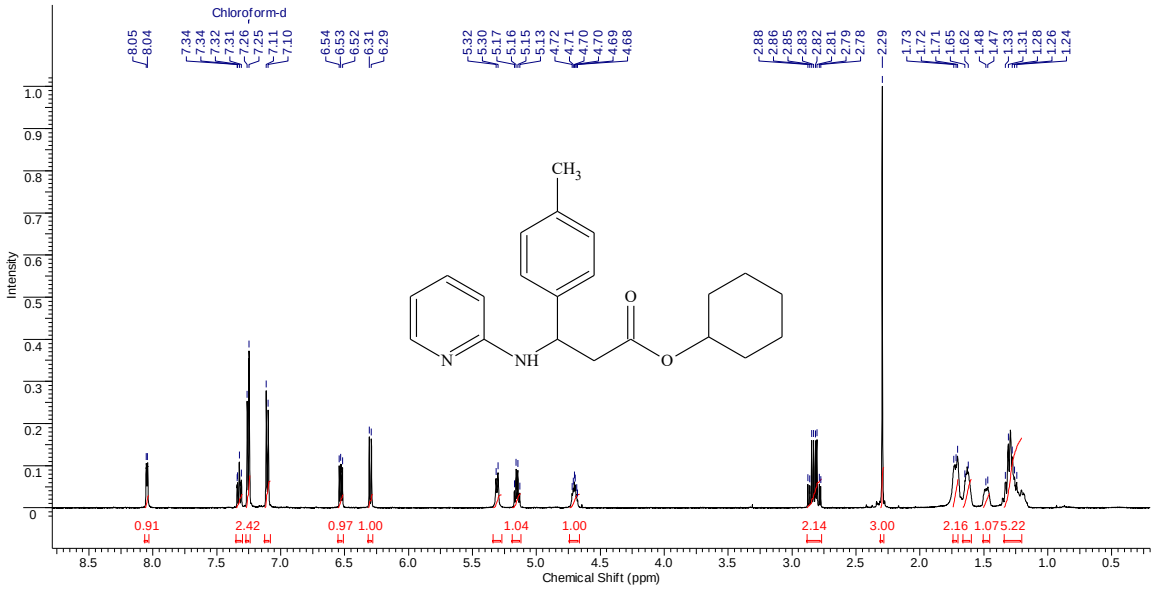



$^{13}$C NMR spectrum of **56w**

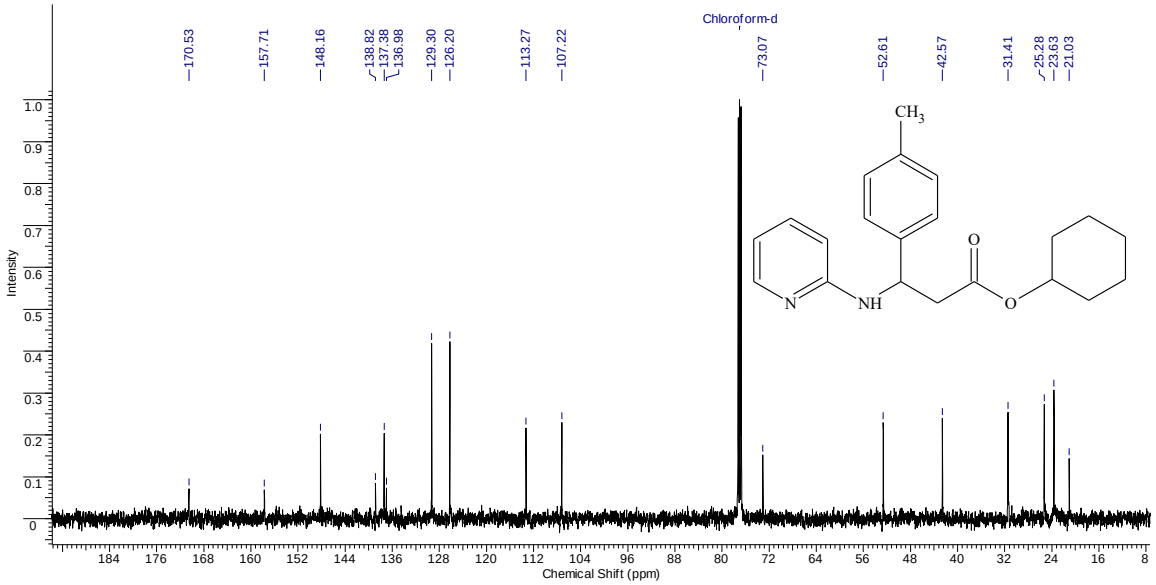



**Appendix C**. **$^{1}$H and $^{13}$C spectra of compounds 61, 57a, 58b, 57e**

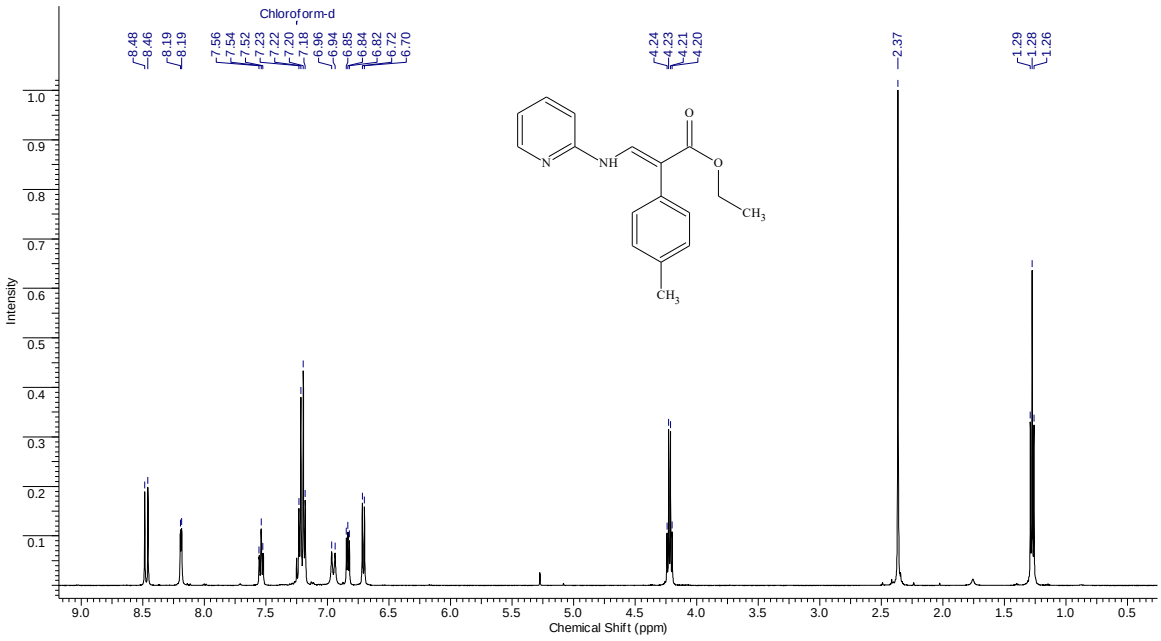
$^{1}$H NMR spectrum of **61**



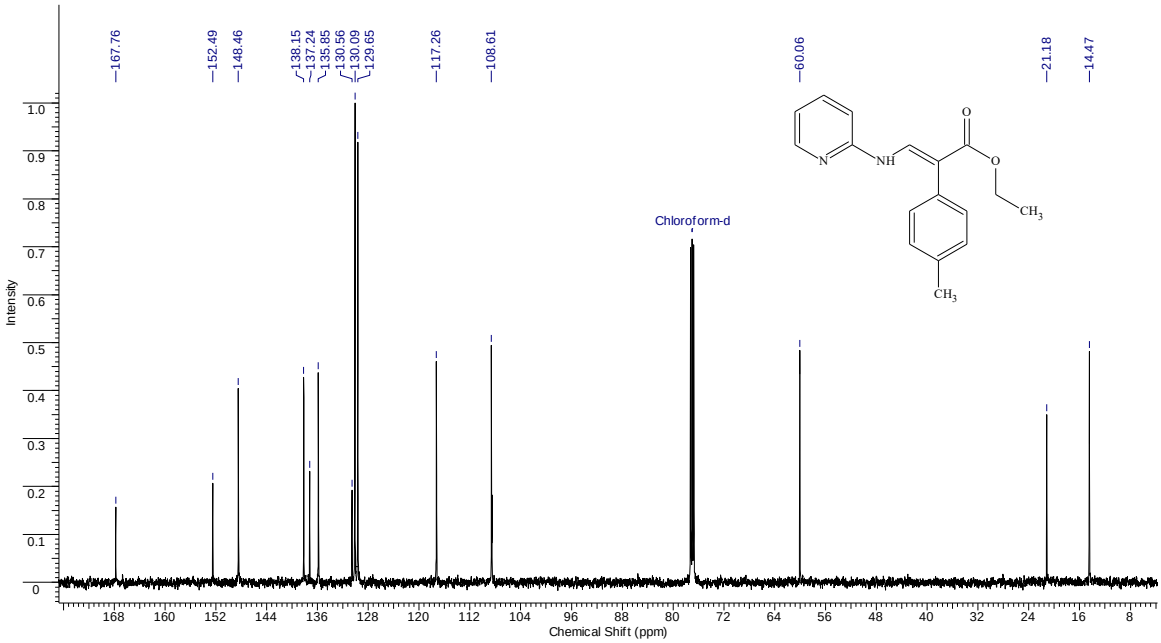

$^{13}$C NMR spectrum of **61**



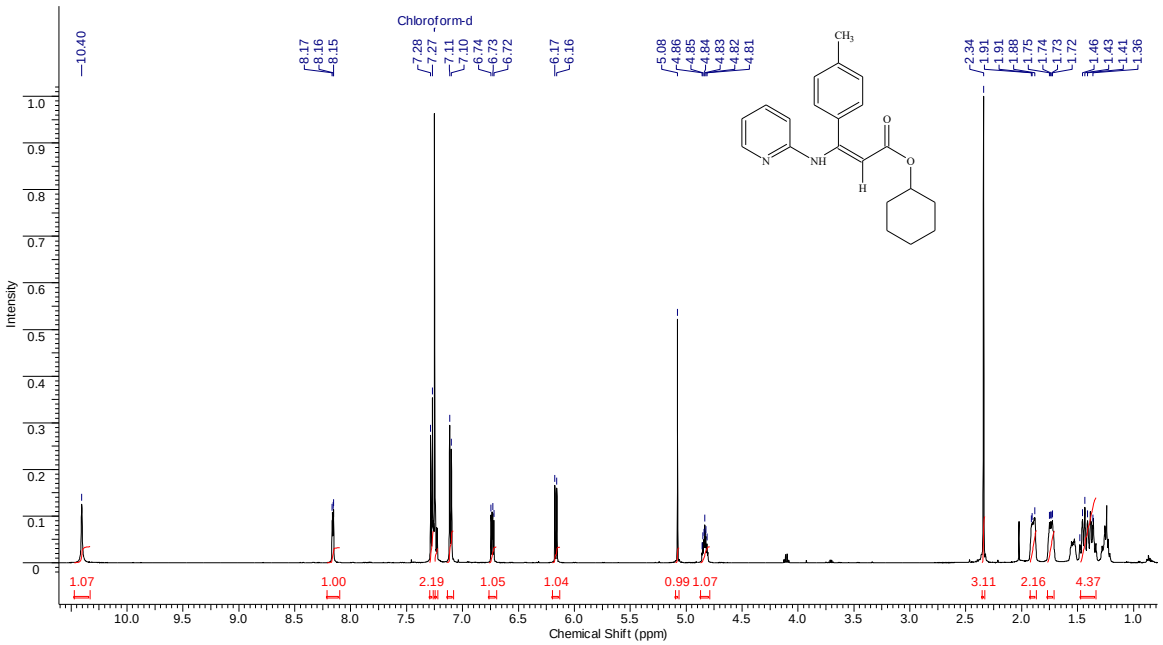

$^{1}$H NMR spectrum of **57a**



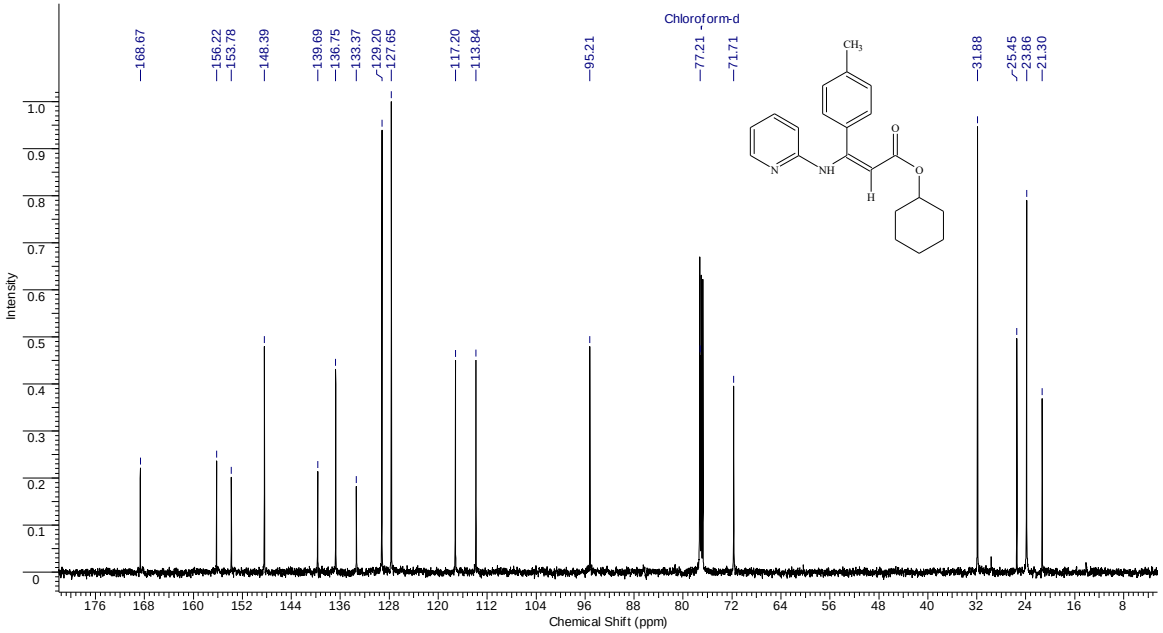

$^{13}$C NMR spectrum of **57a**



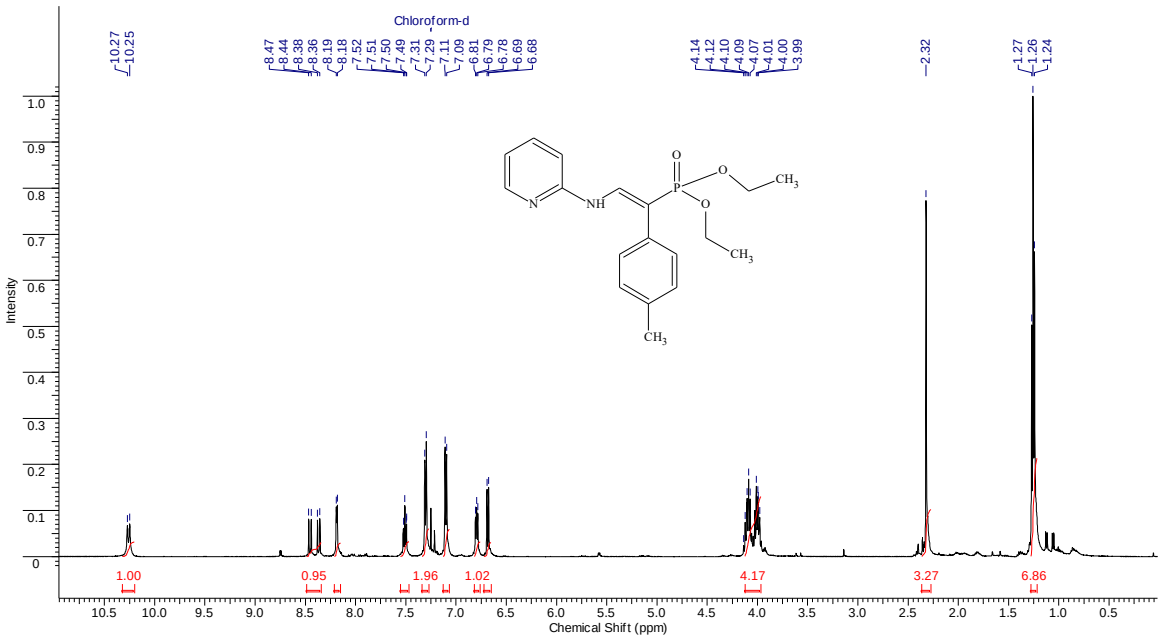

$^{1}$H NMR spectrum of **58b**



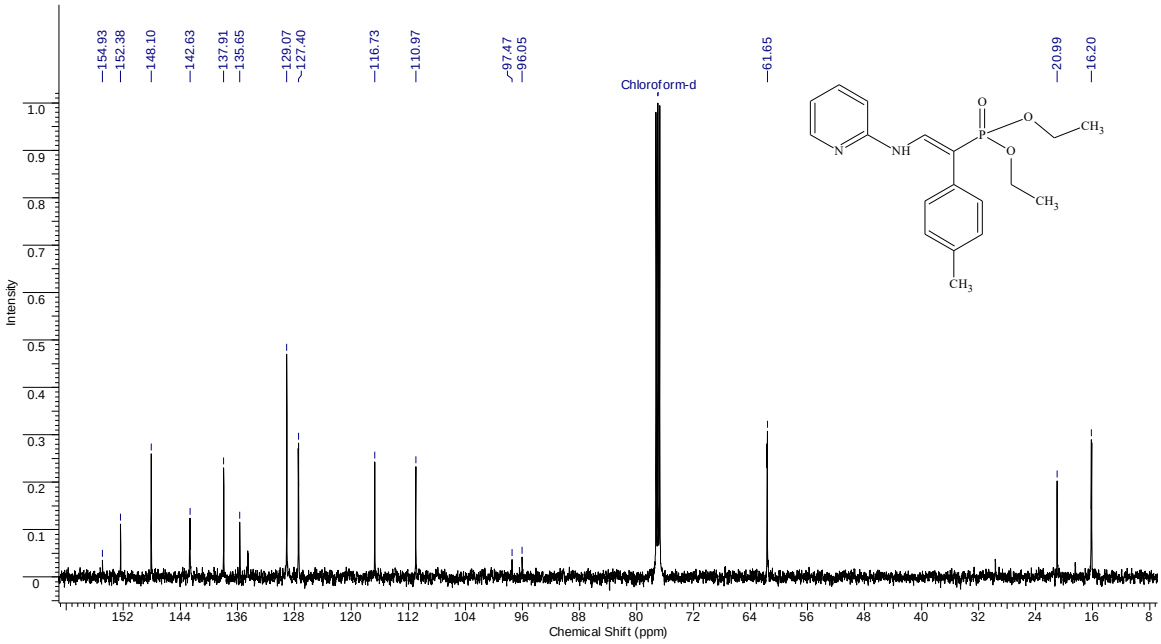

$^{13}$C NMR spectrum of **58b**



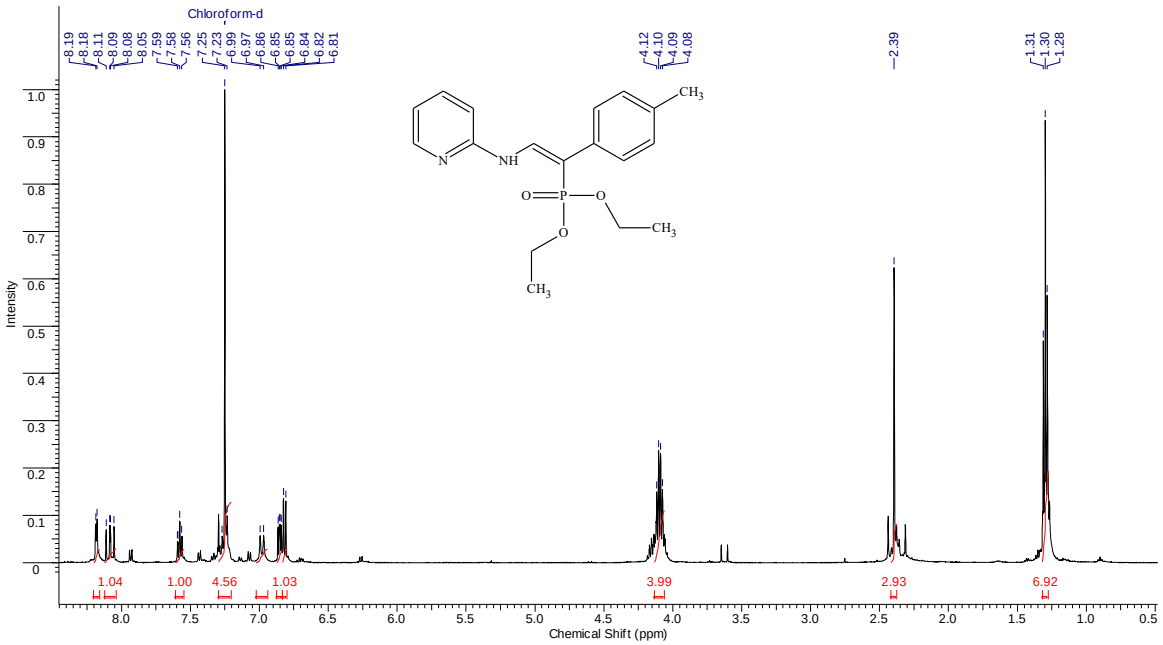

$^{1}$H NMR spectrum of **(*E*)-57e**



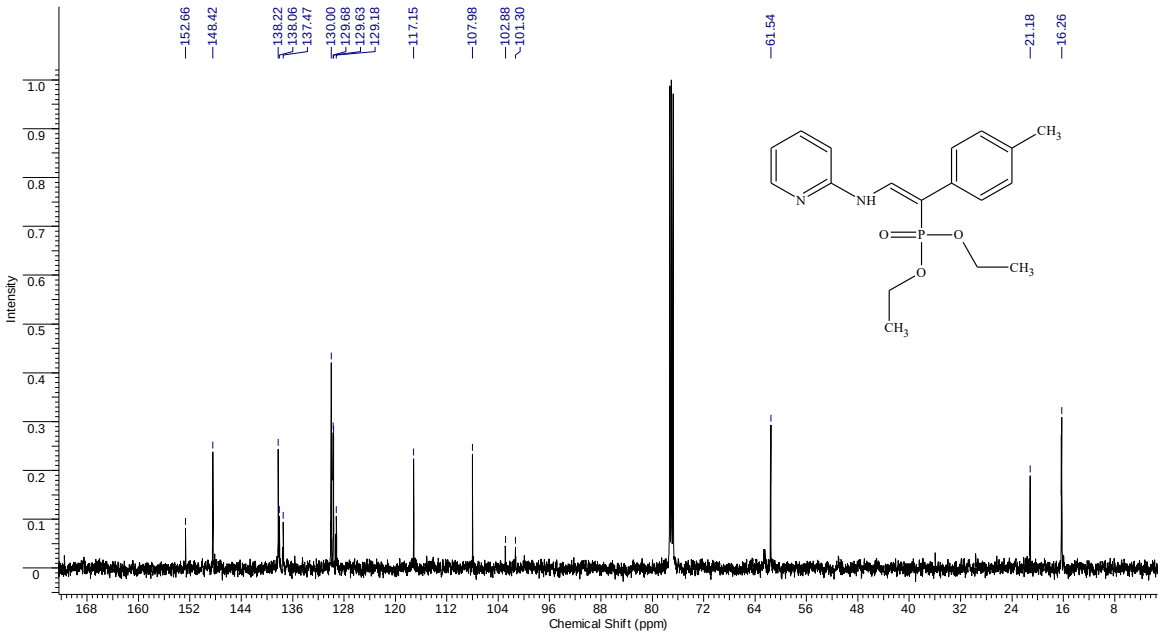

$^{13}$C NMR spectrum of **(*E*)-57e**



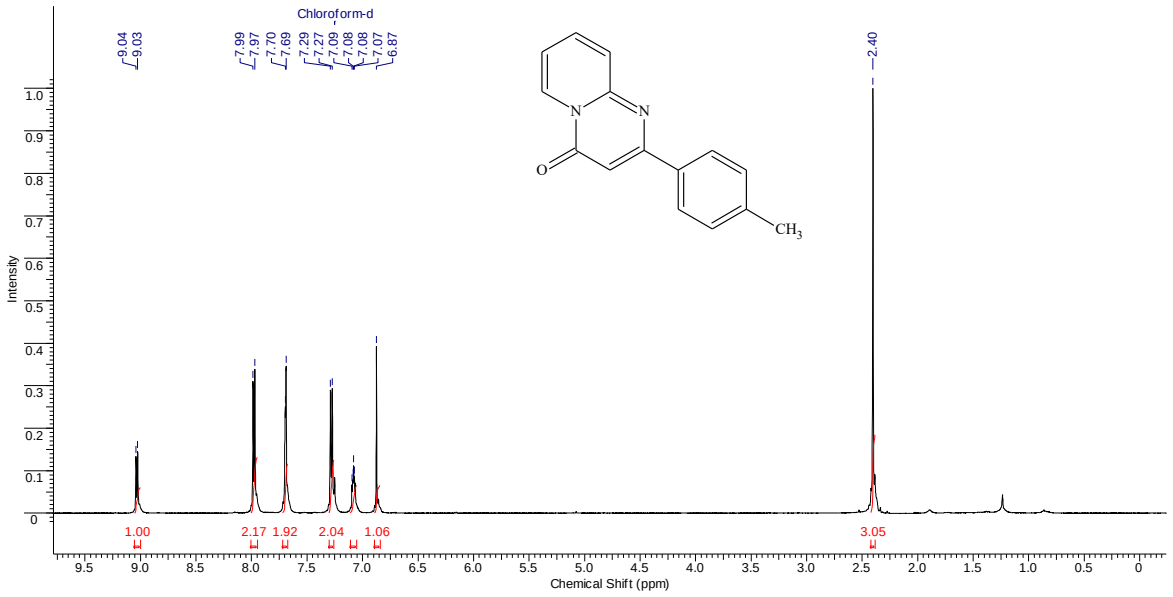

$^{1}$H NMR spectrum of **(*Z*)-57e**



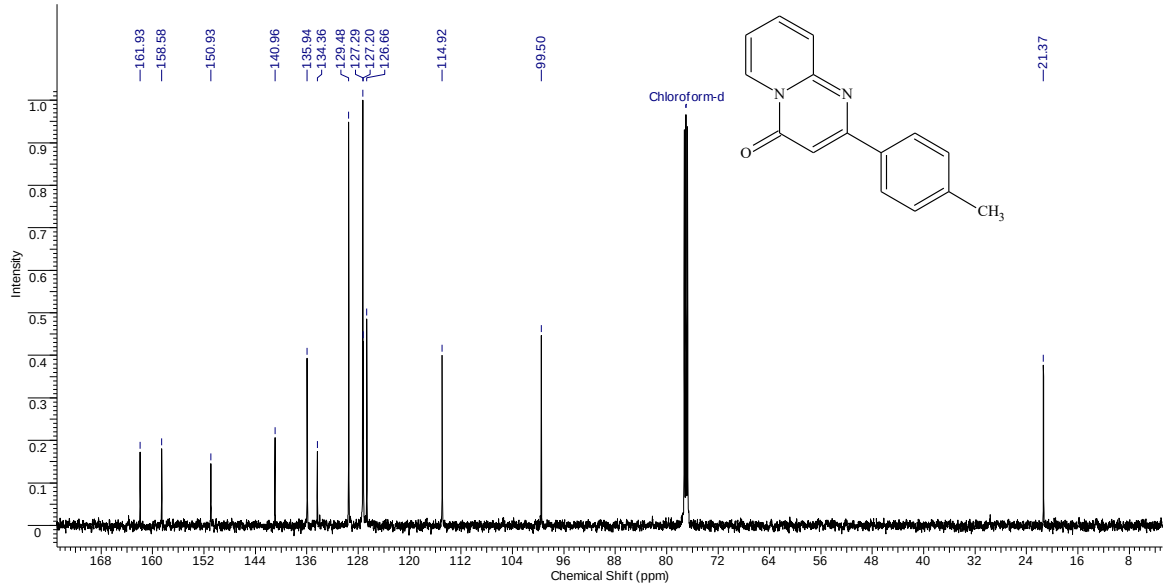

$^{13}$C NMR spectrum of **(*Z*)-57e**




$^{1}$H NMR spectrum of **62**

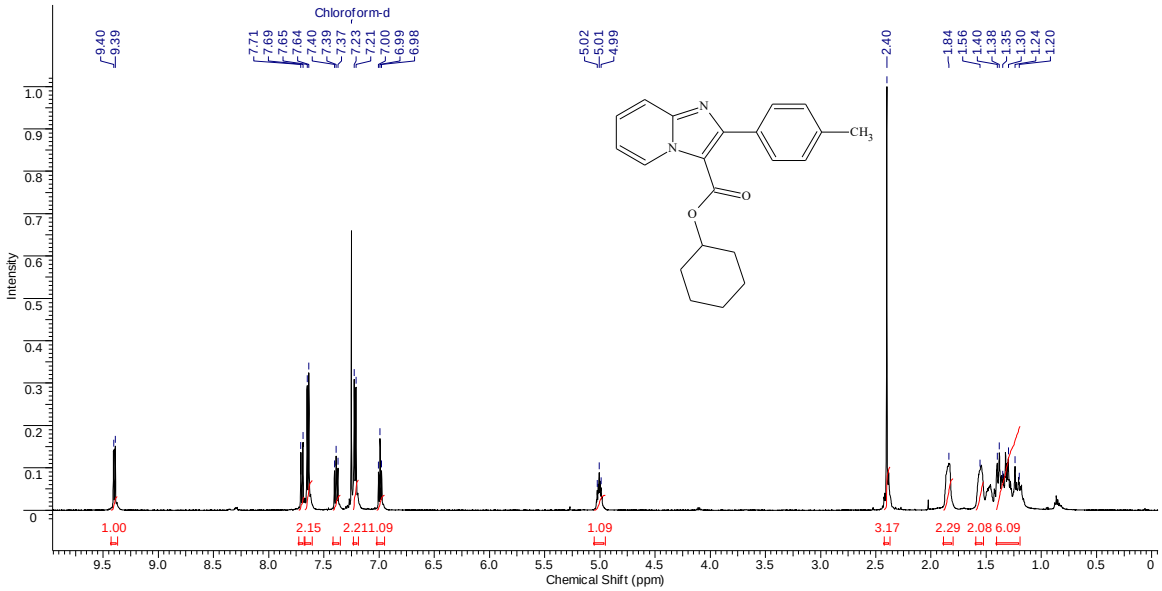



$^{13}$C NMR spectrum of **62**

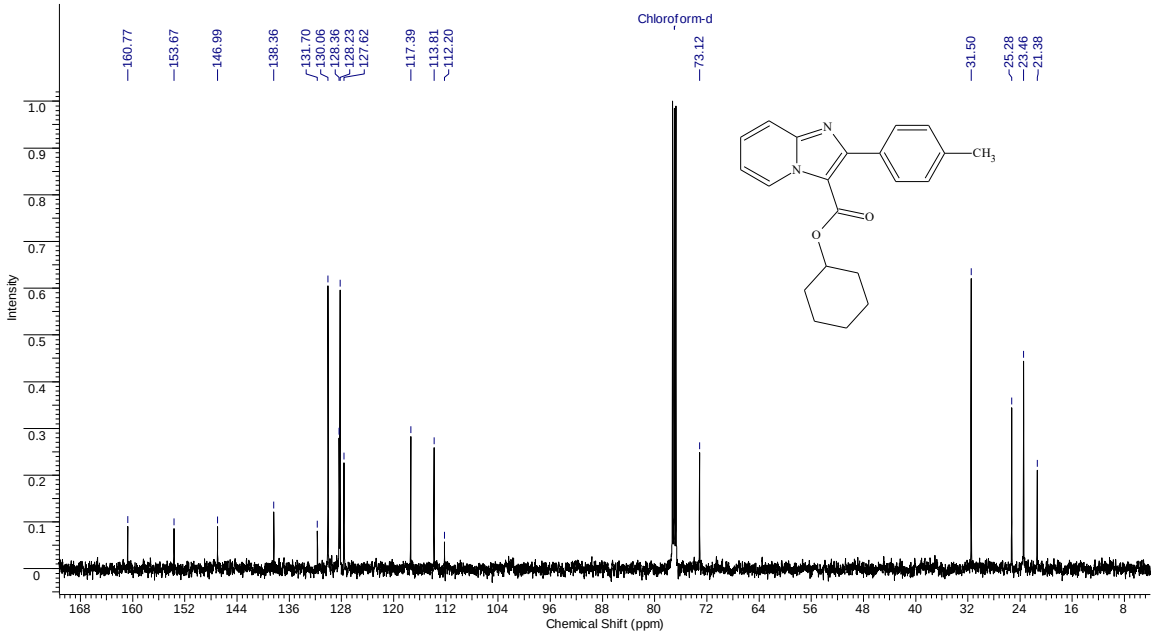



## Appendix D. $^{1}$H and $^{13}$C spectra of imidazopyridines 63

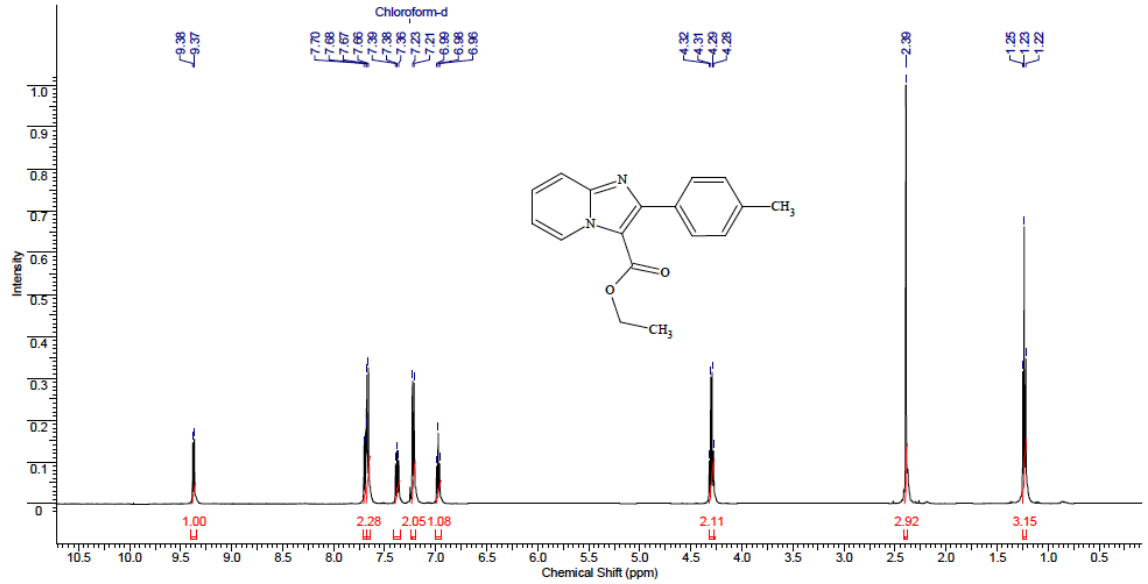
$^{1}$H NMR spectrum of **63a**



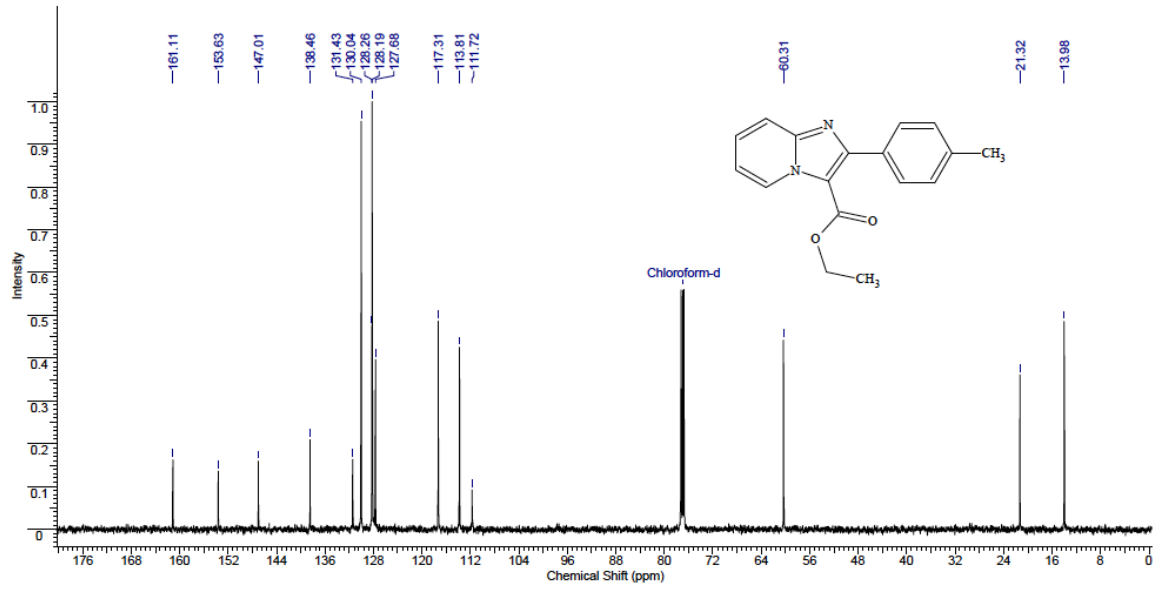

$^{13}$C NMR spectrum of **63a**



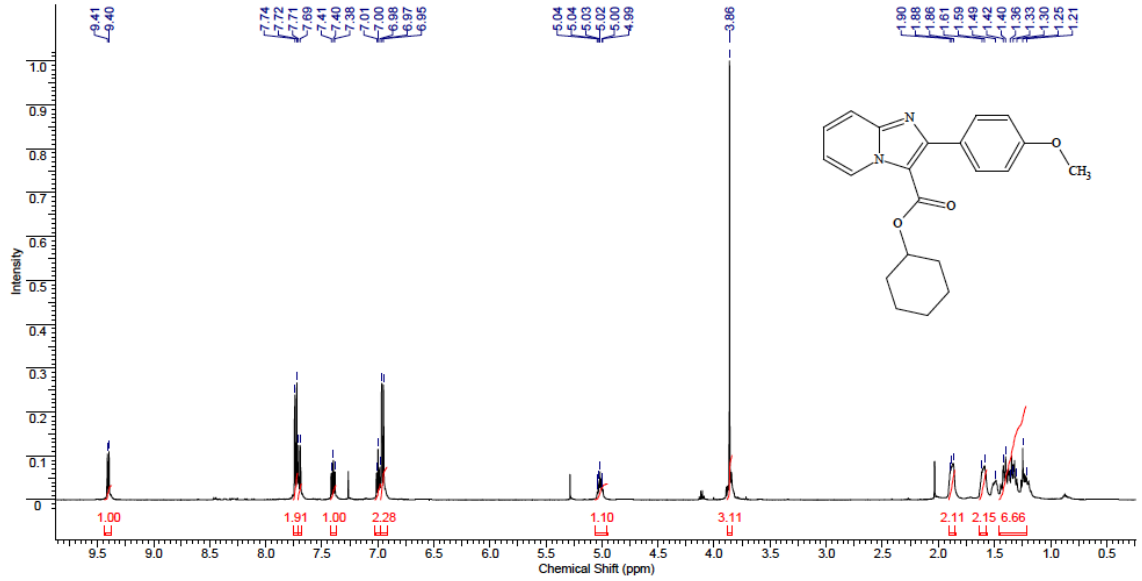

$^{1}$H NMR spectrum of **63b**



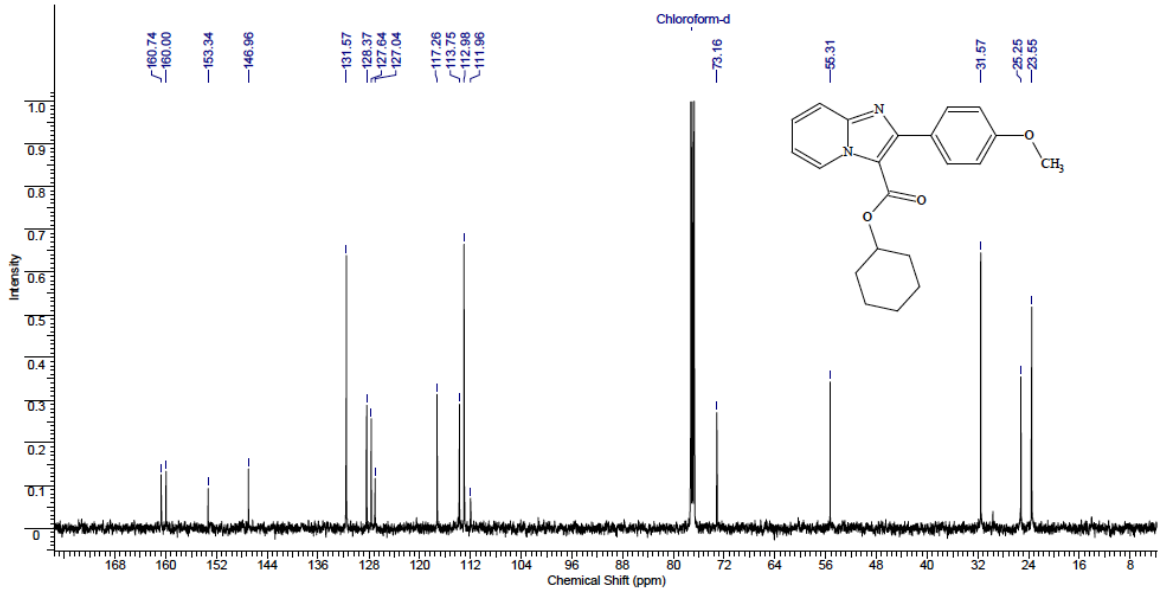

$^{13}$C NMR spectrum of **63b**



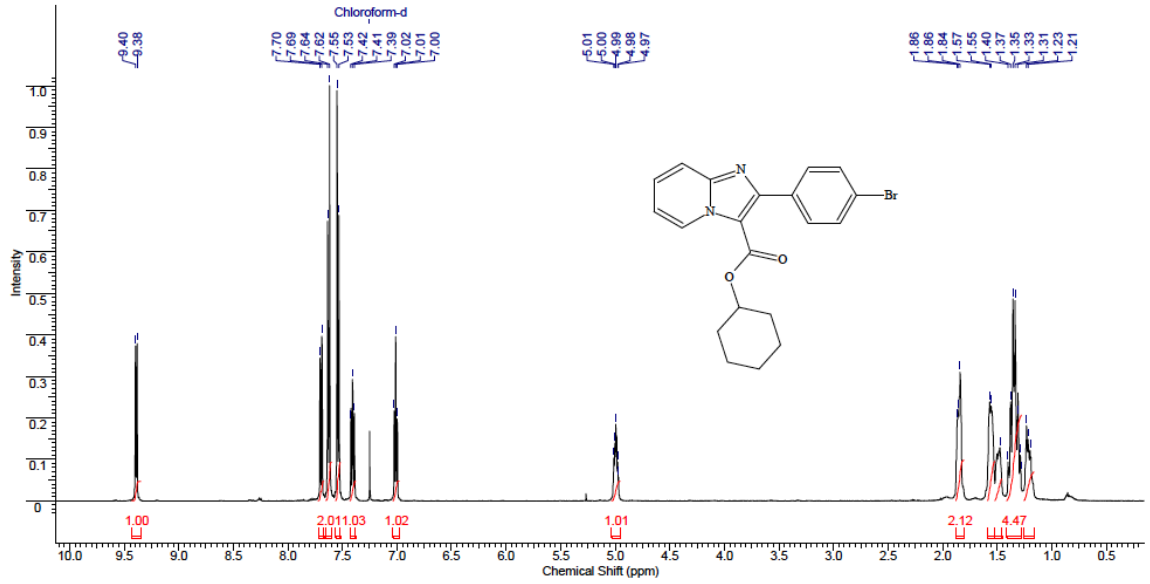

$^{1}$H NMR spectrum of **63d**



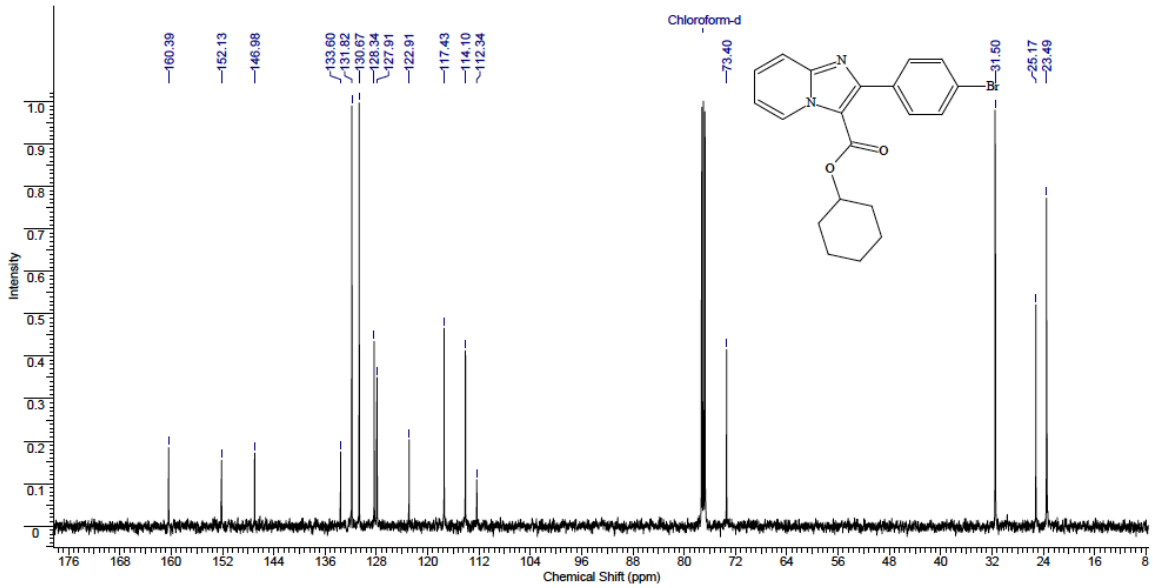

$^{13}$C NMR spectrum of **63c**



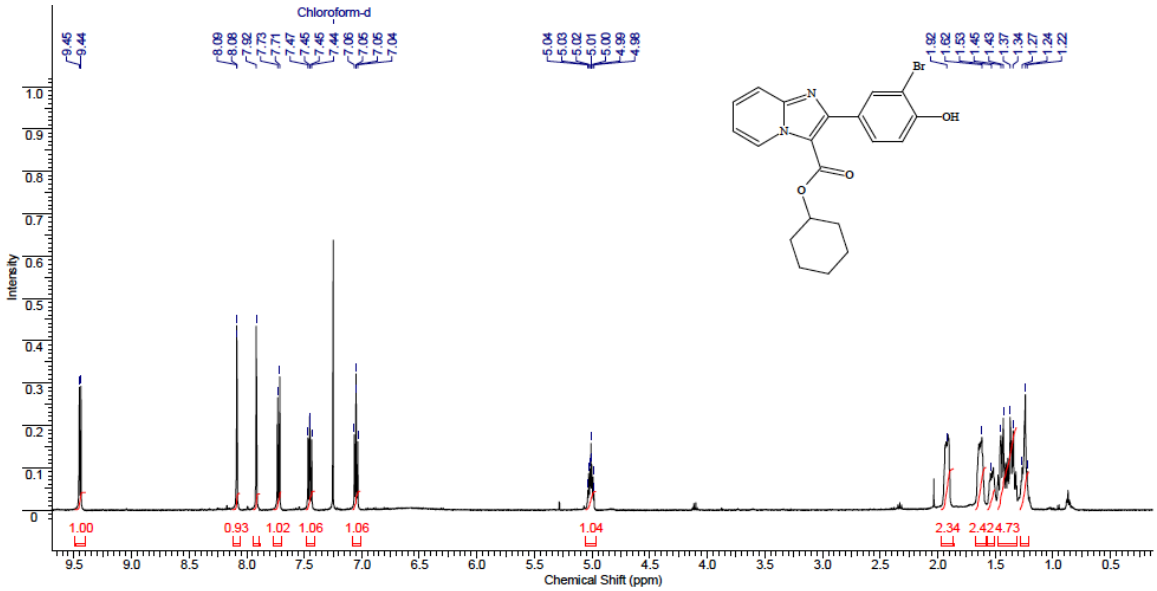

$^{1}$H NMR spectrum of **63d**



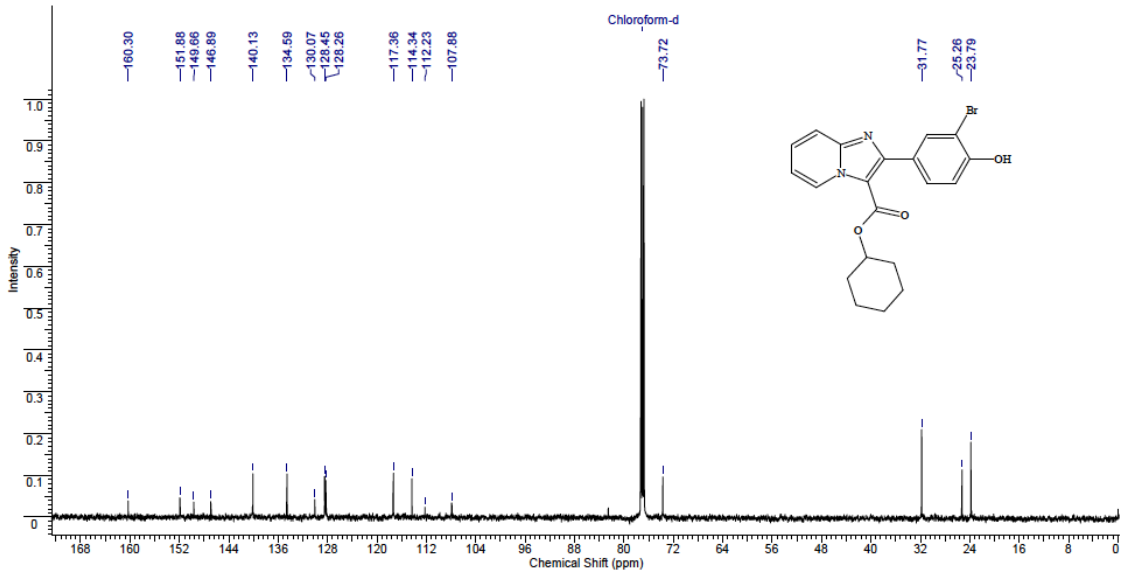

$^{13}$C NMR spectrum of **63d**



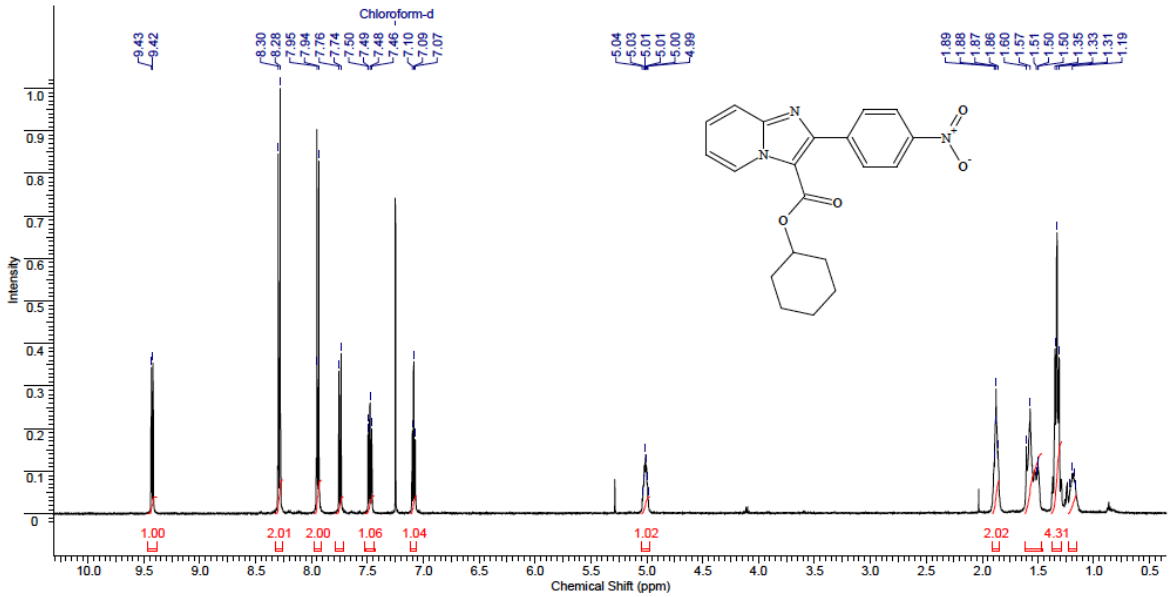

$^{1}$H NMR spectrum of **63e**



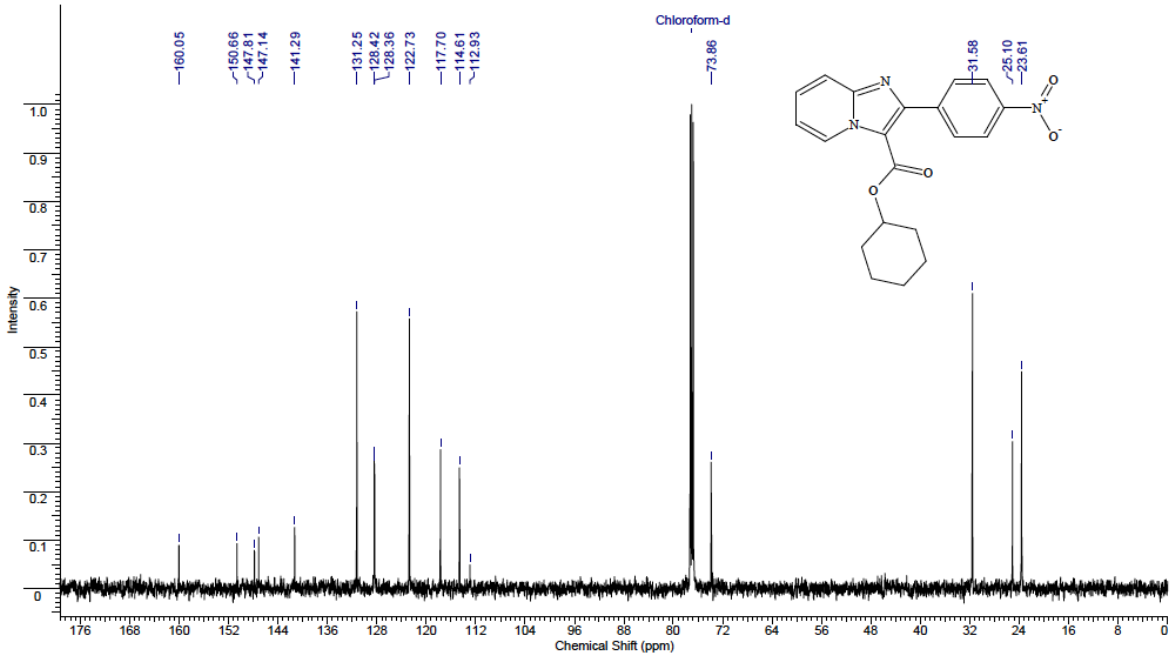

$^{13}$C NMR spectrum of **63e**



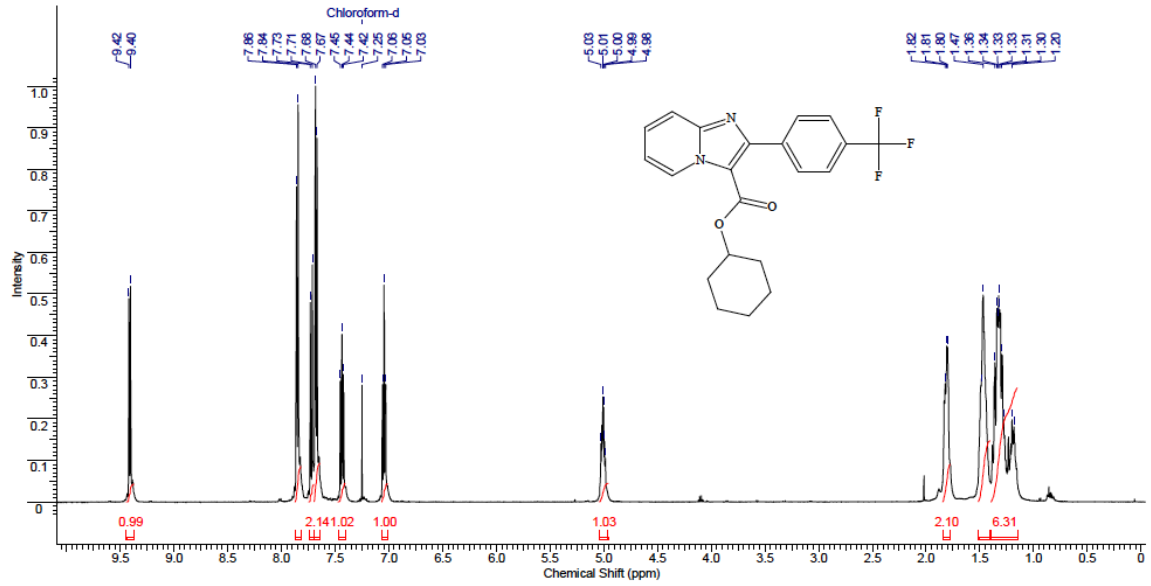

$^{1}$H NMR spectrum of **63f**



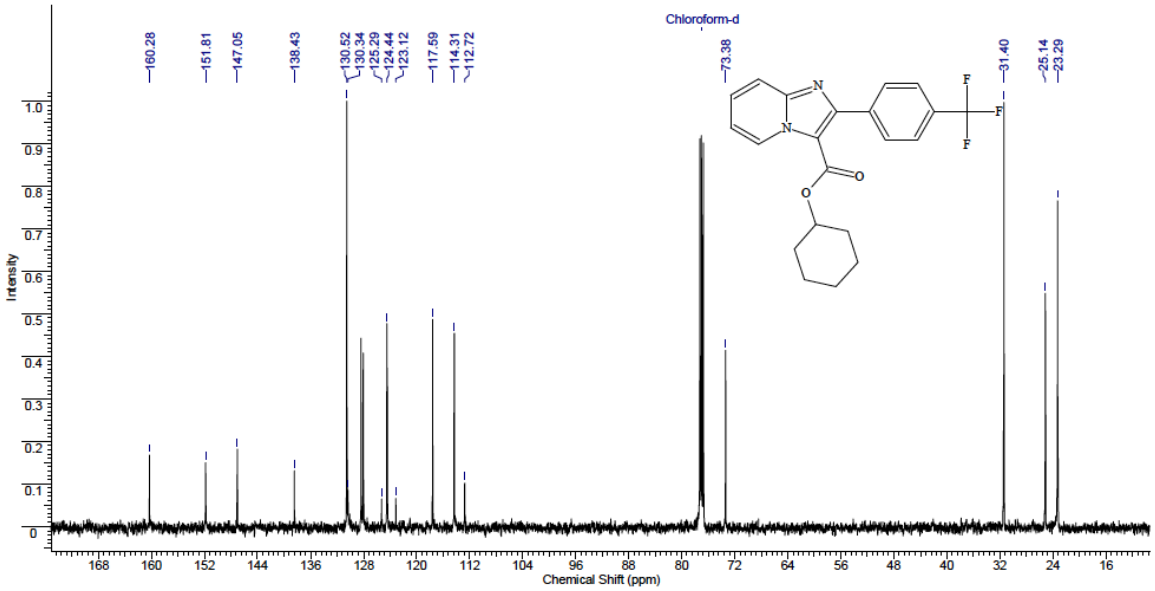

$^{13}$C NMR spectrum of **63f**



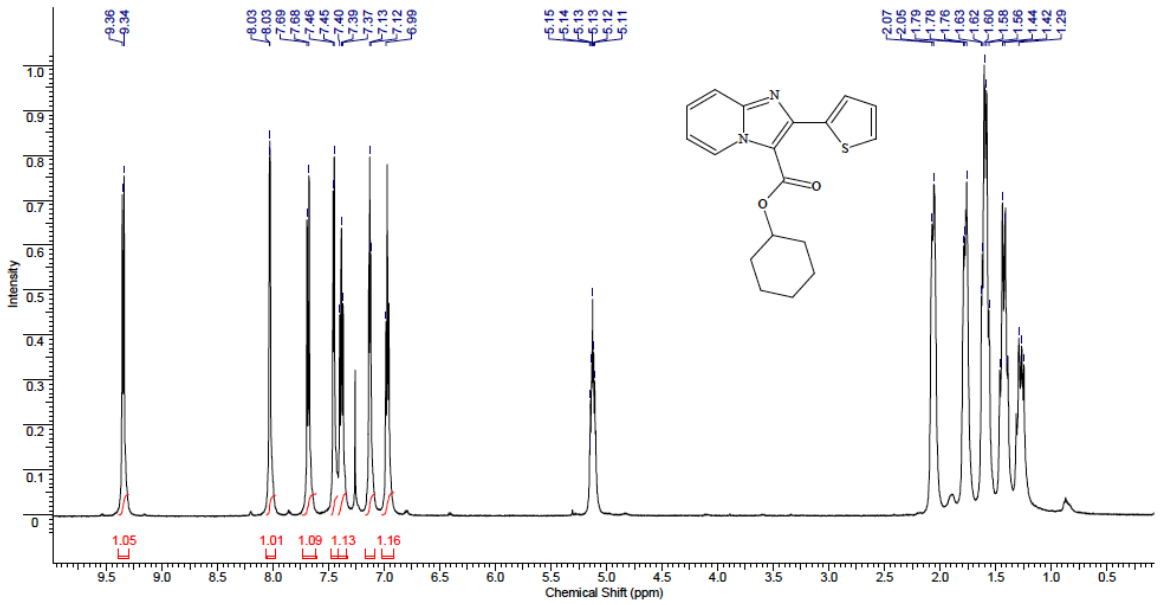

$^{1}$H NMR spectrum of **63g**



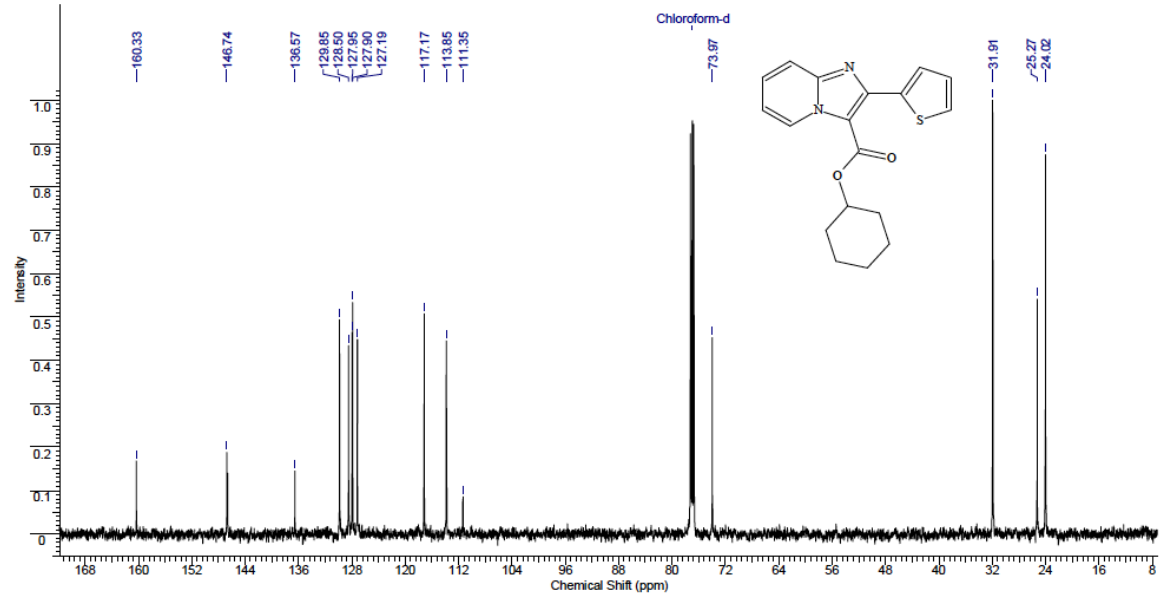

$^{13}$C NMR spectrum of **63g**



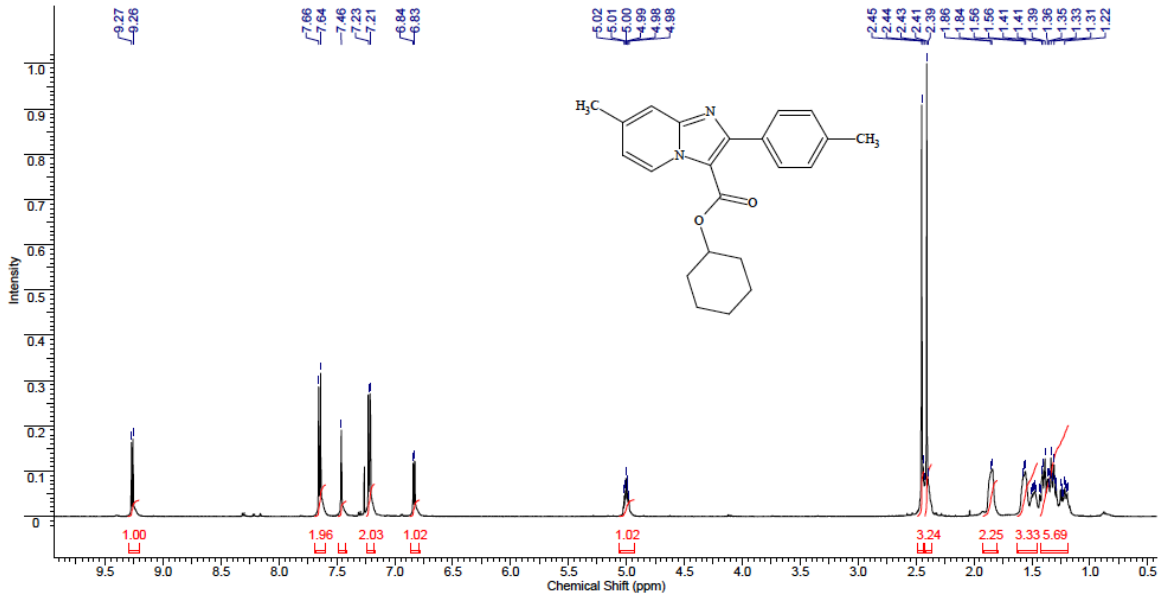

$^{1}$H NMR spectrum of **63h**



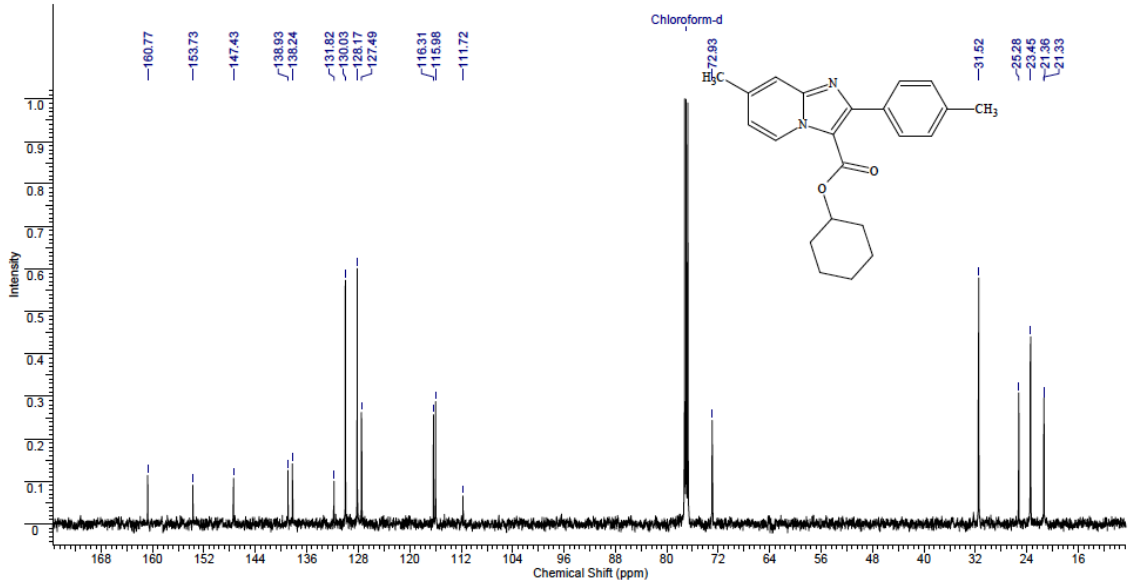

$^{13}$C NMR spectrum of **63h**



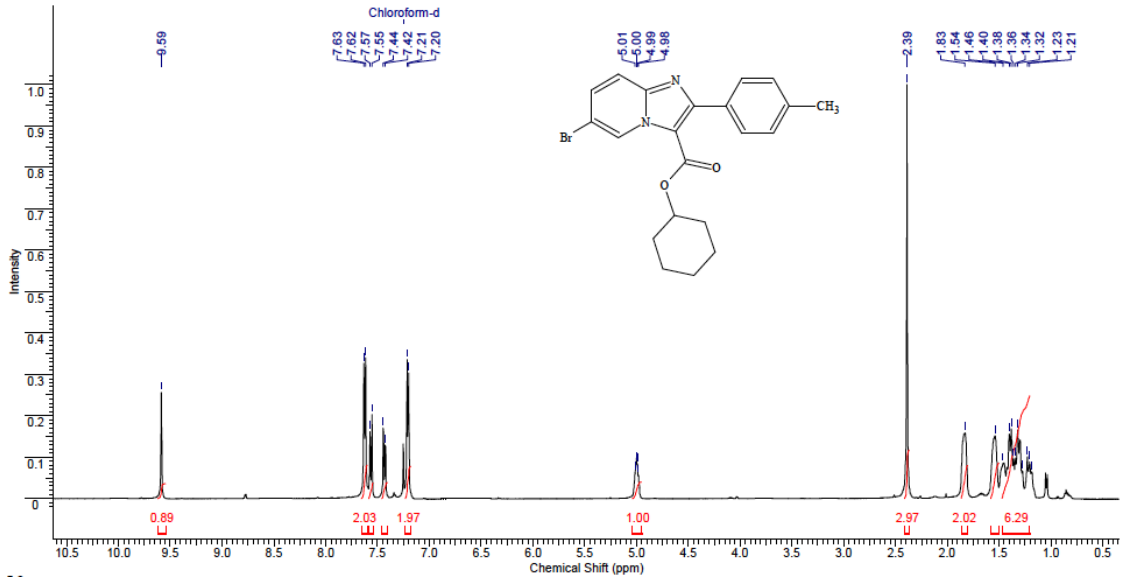

$^{1}$H NMR spectrum of **63i**



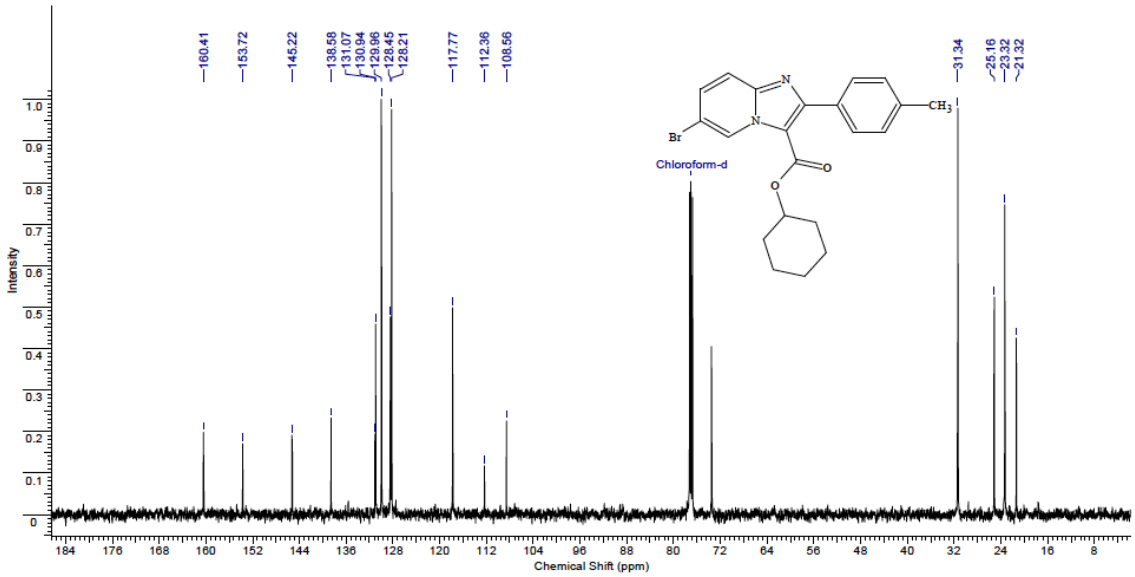

$^{13}$C NMR spectrum of **63i**



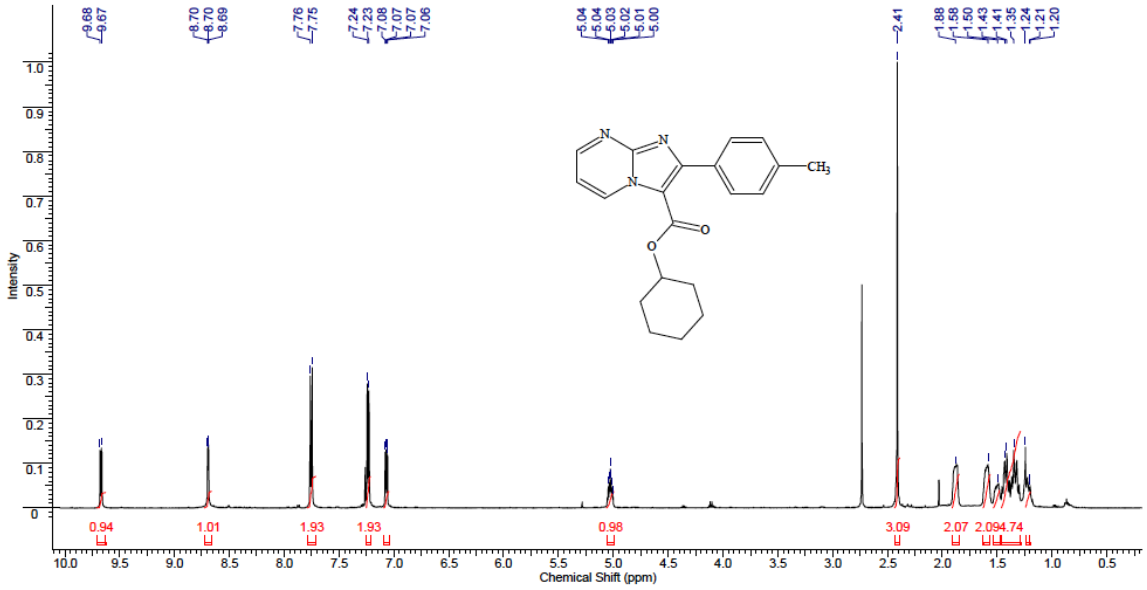

$^{1}$H NMR spectrum of **63j**



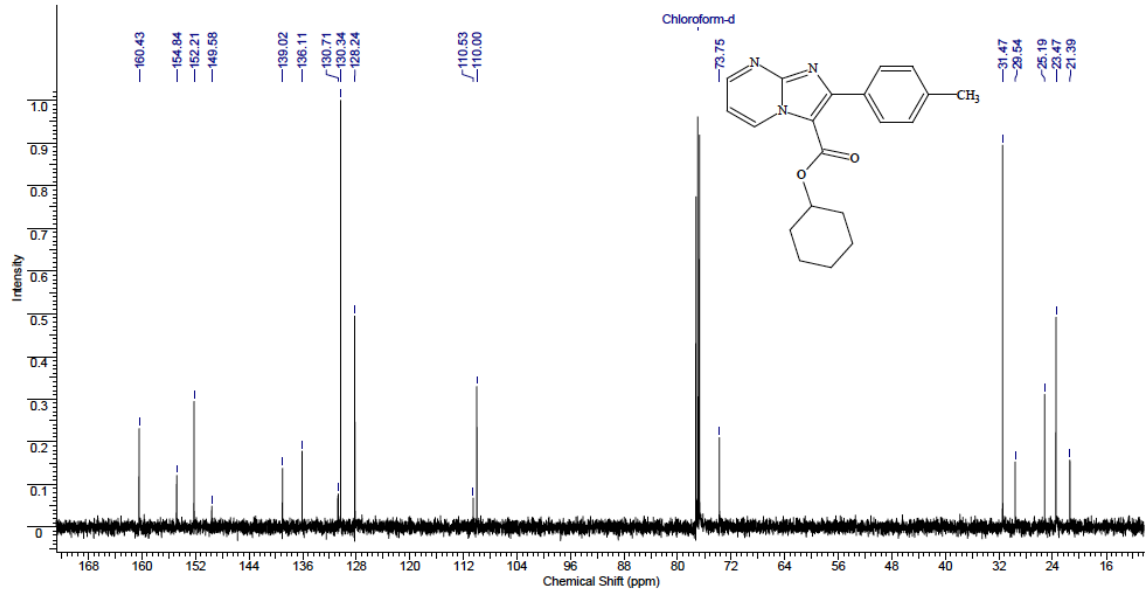

$^{13}$C NMR spectrum of **63j**



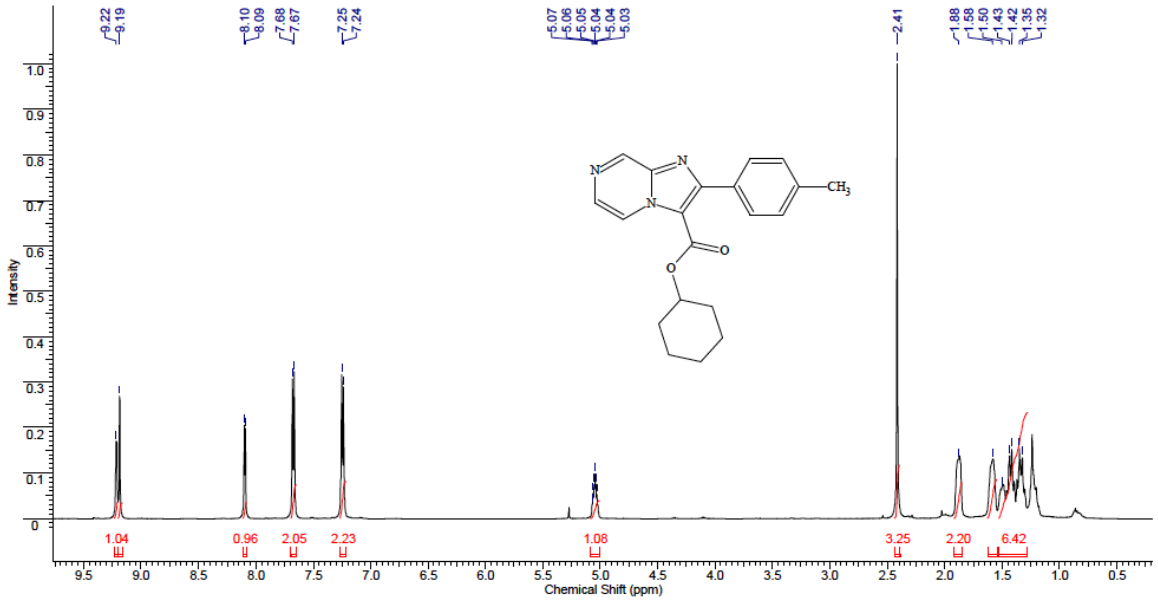

$^{1}$H NMR spectrum of **63k**



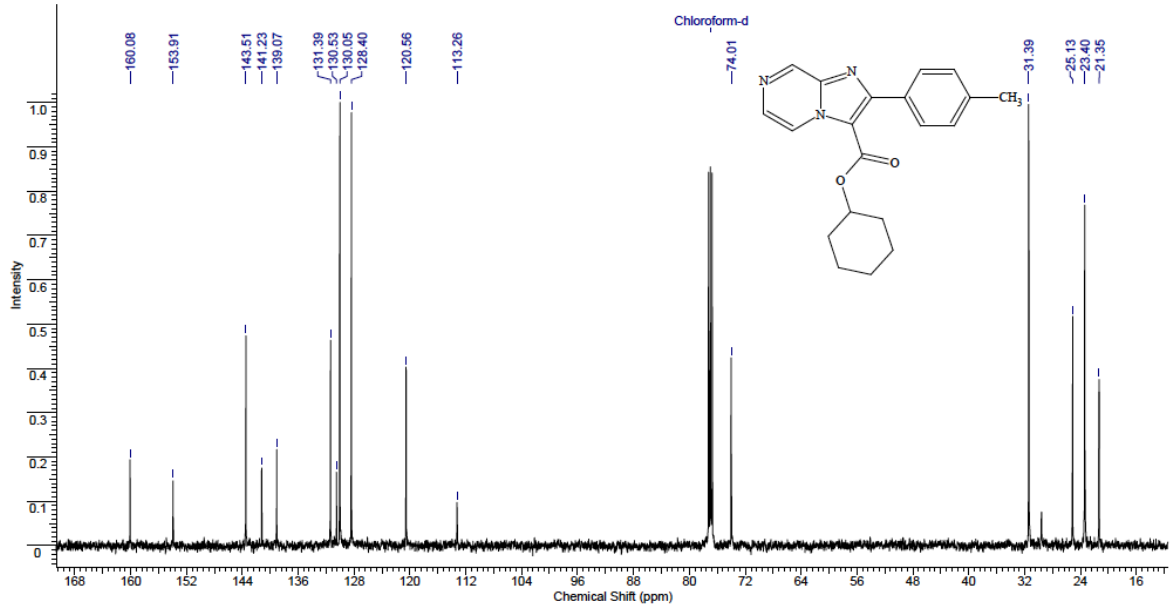

$^{13}$C NMR spectrum of **63**k




$^{1}$H NMR spectrum of **63l**

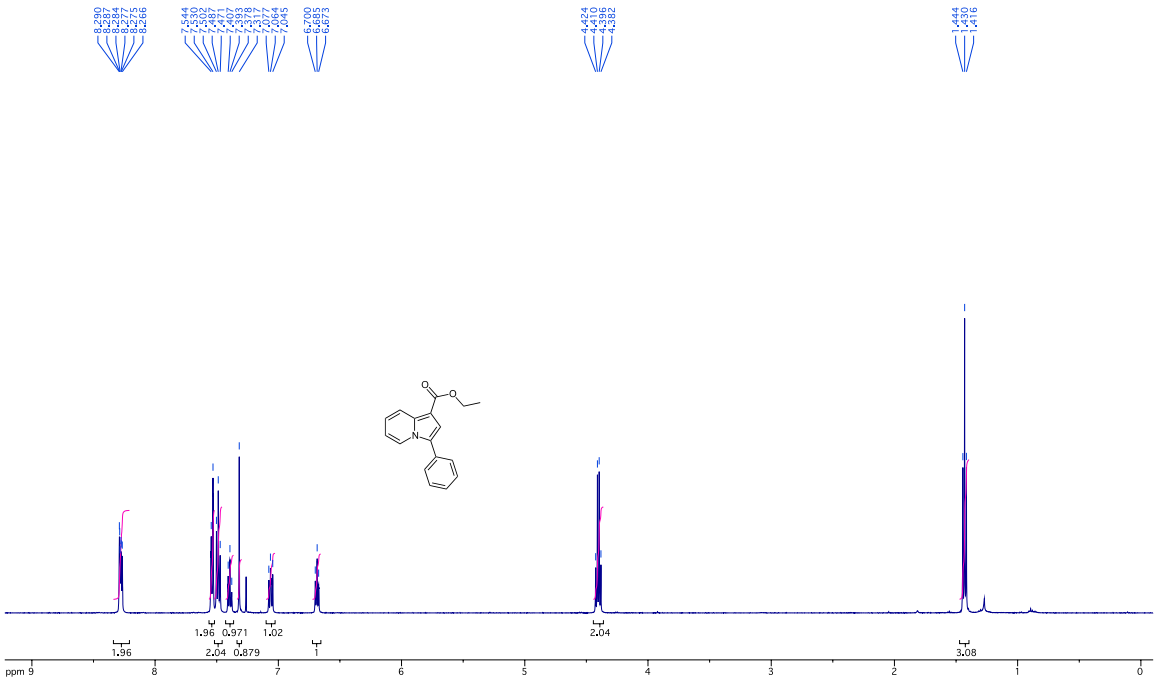



$^{13}$C NMR spectrum of **63**l

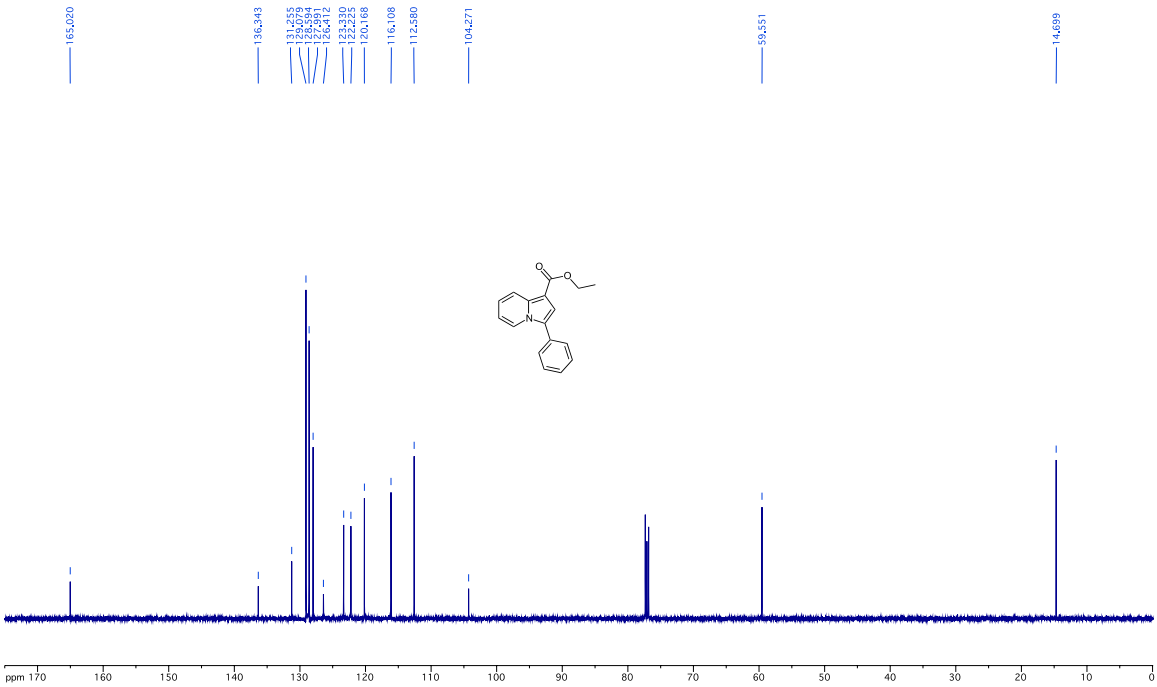



## Appendix E. $^{1}$H and $^{13}$C spectra of indolizines 85

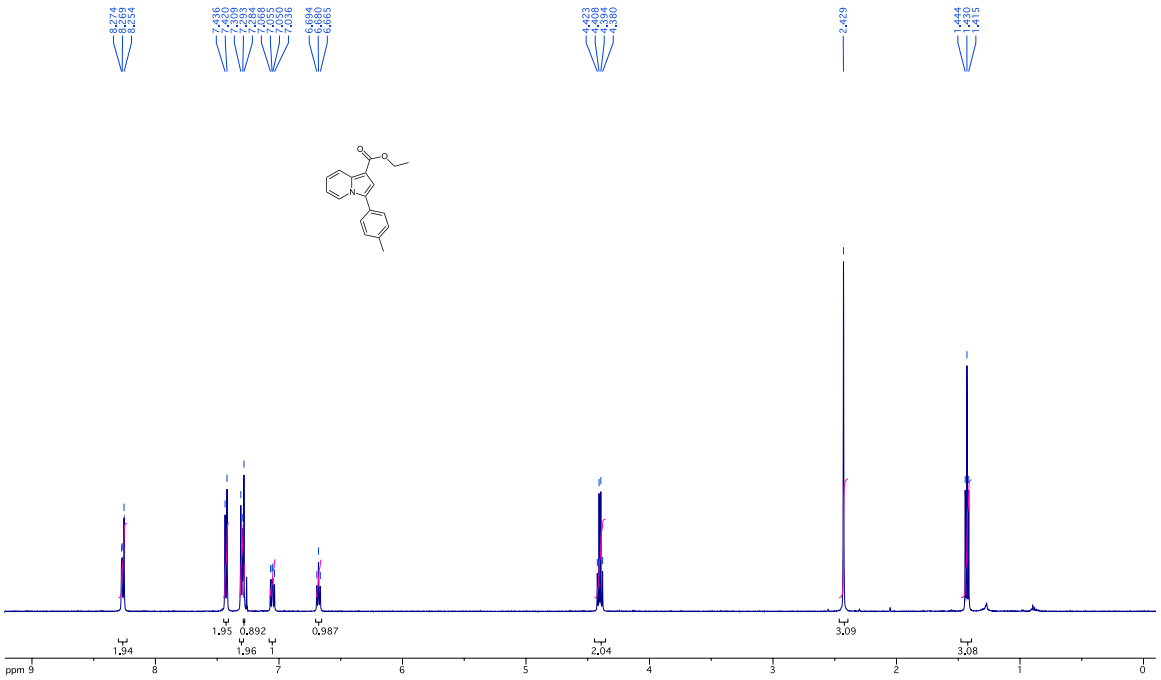
$^{1}$H NMR spectrum of **85a**



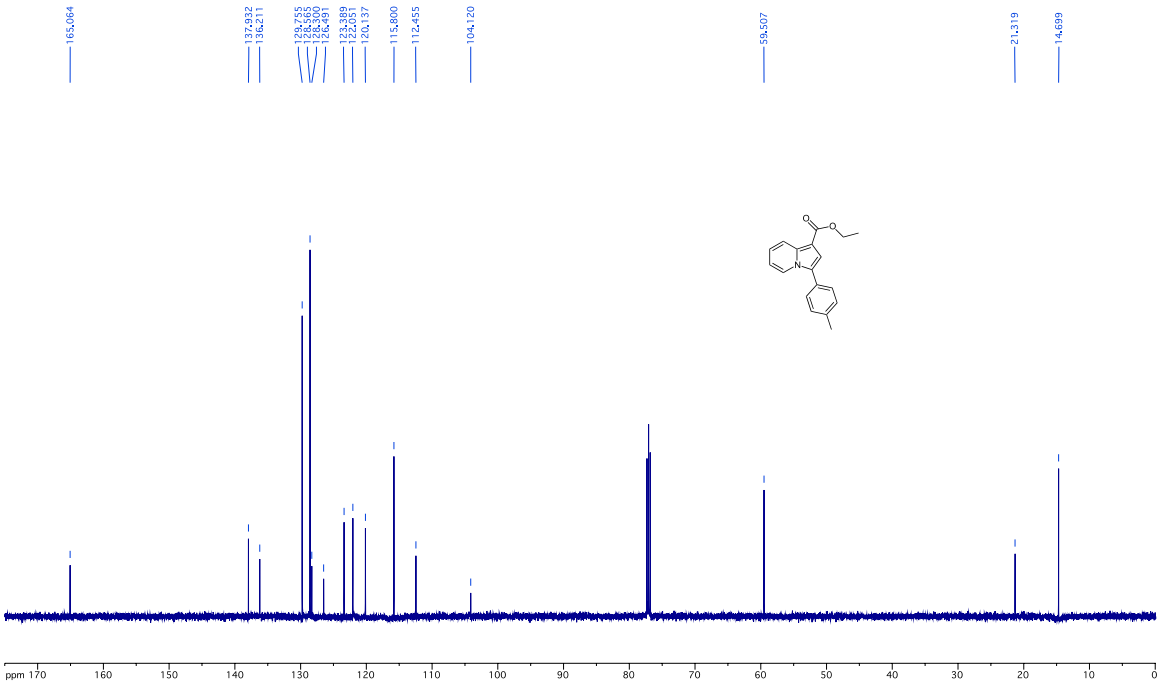

$^{13}$C NMR spectrum of **85a**



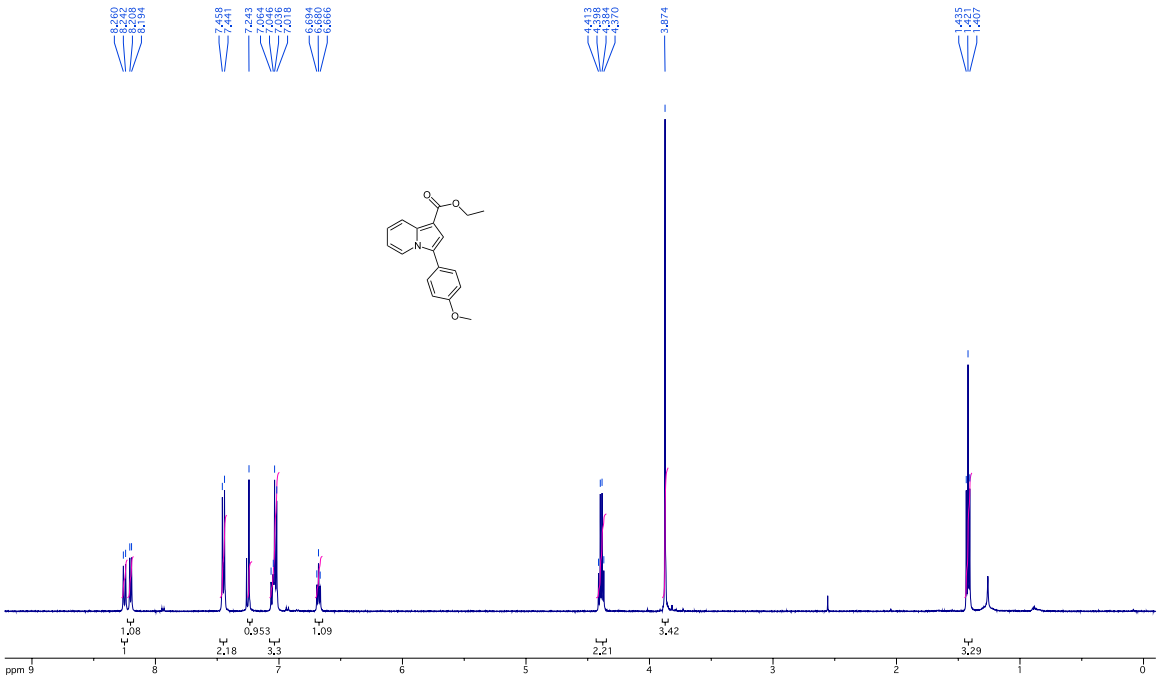

$^{1}$H NMR spectrum of **85b**



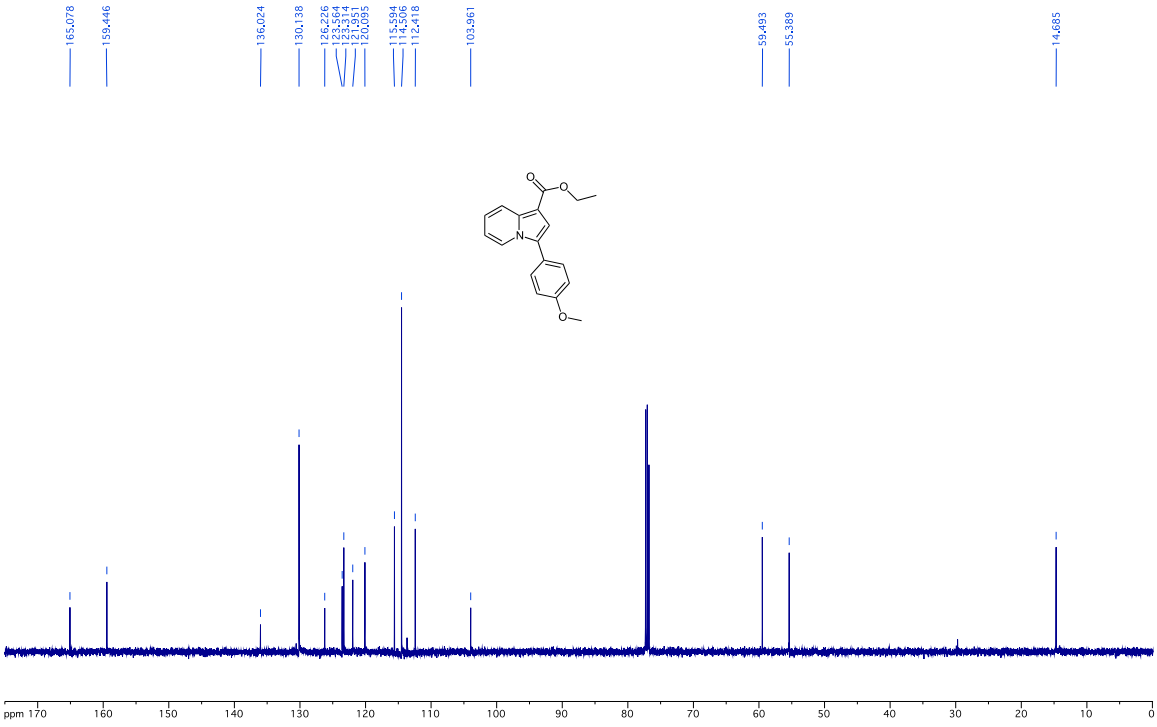

$^{13}$C NMR spectrum of **85b**



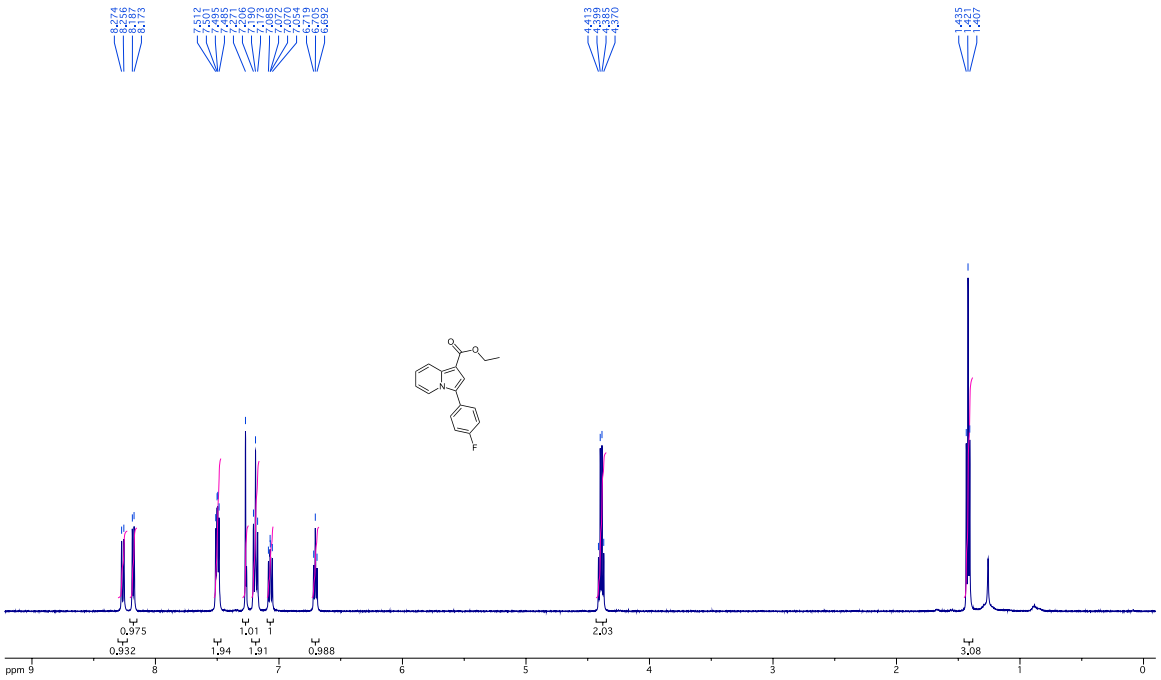

$^{1}$H NMR spectrum of **85c**



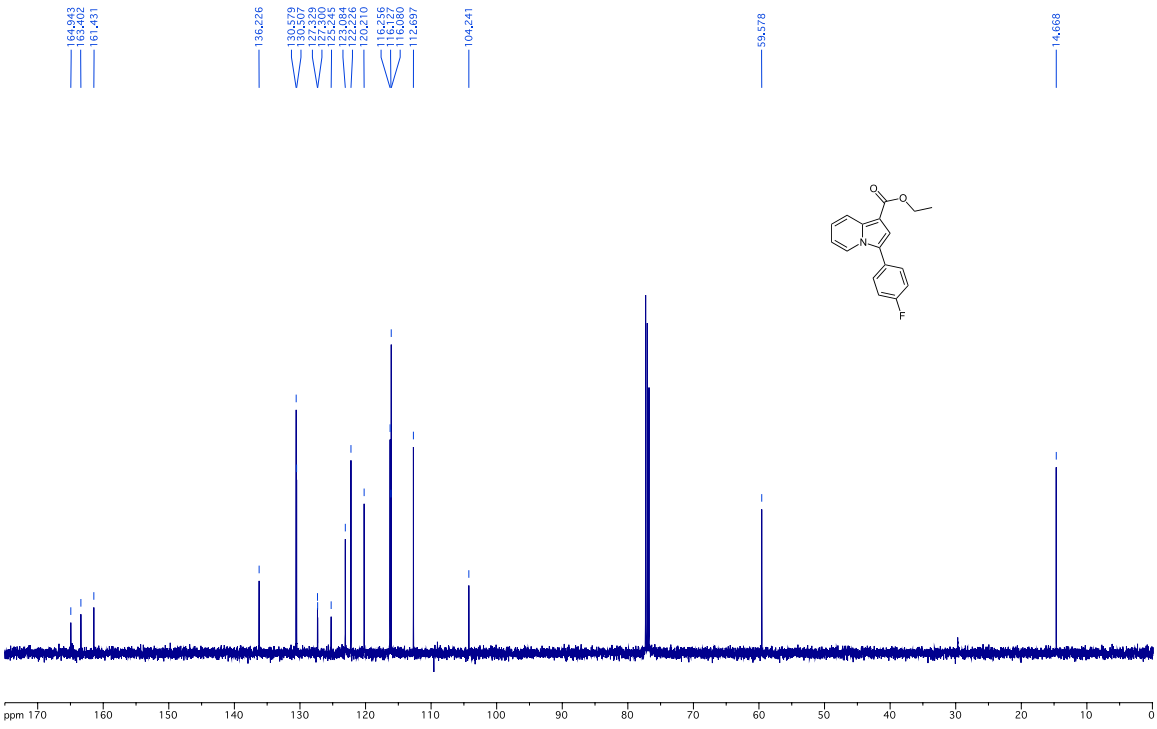

$^{13}$C NMR spectrum of **85c**



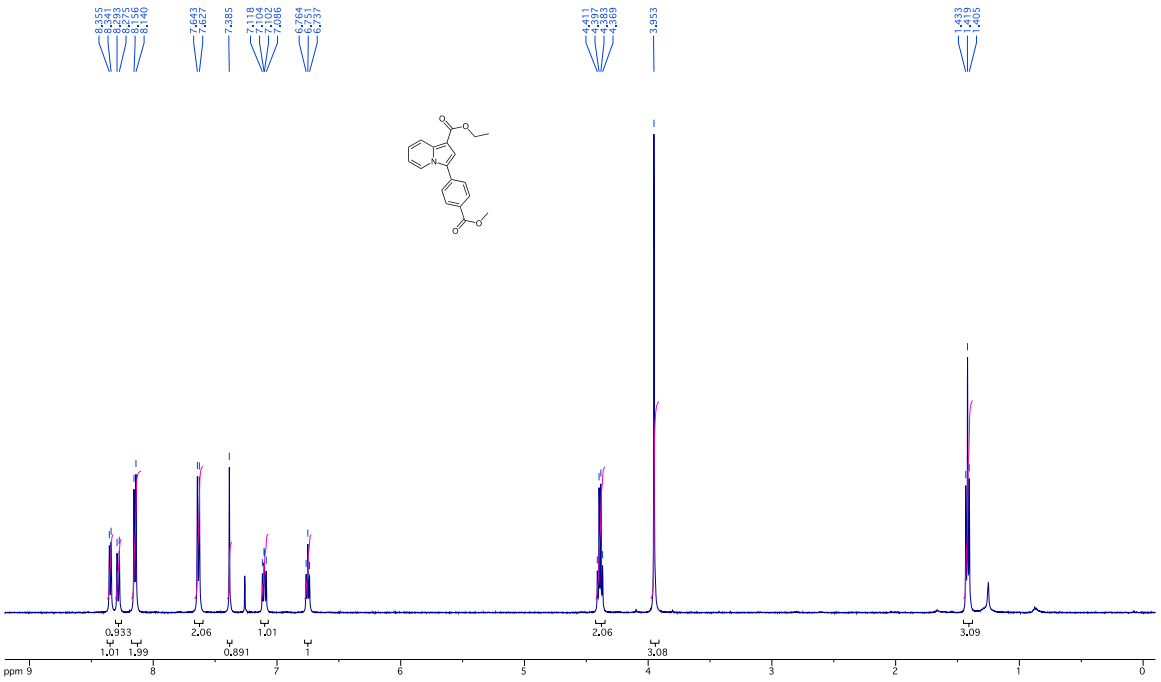

$^{1}$H NMR spectrum of **85d**



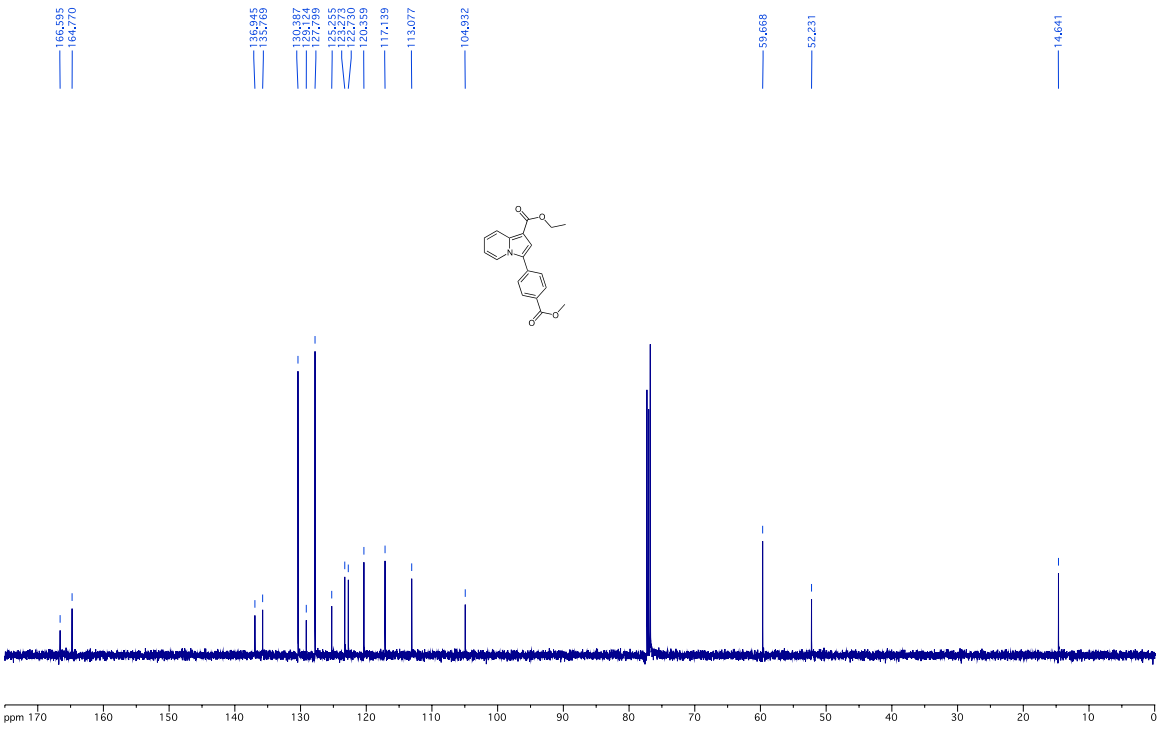

$^{13}$C NMR spectrum of **85d**



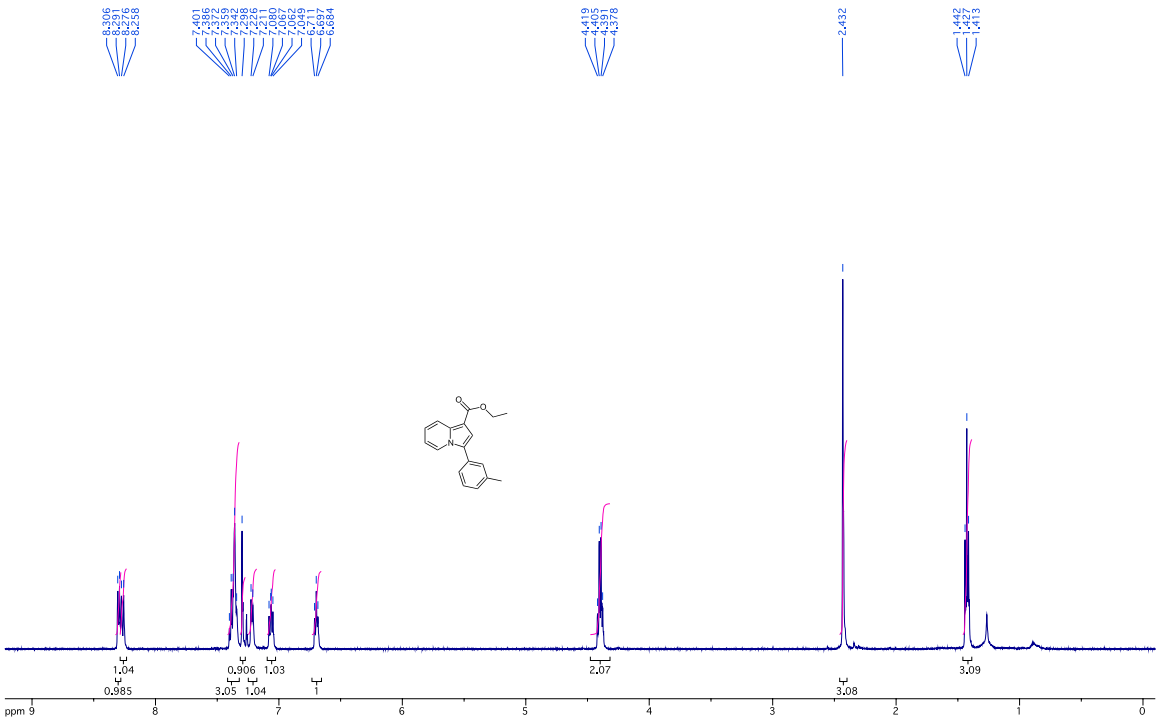

$^{1}$H NMR spectrum of **85e**



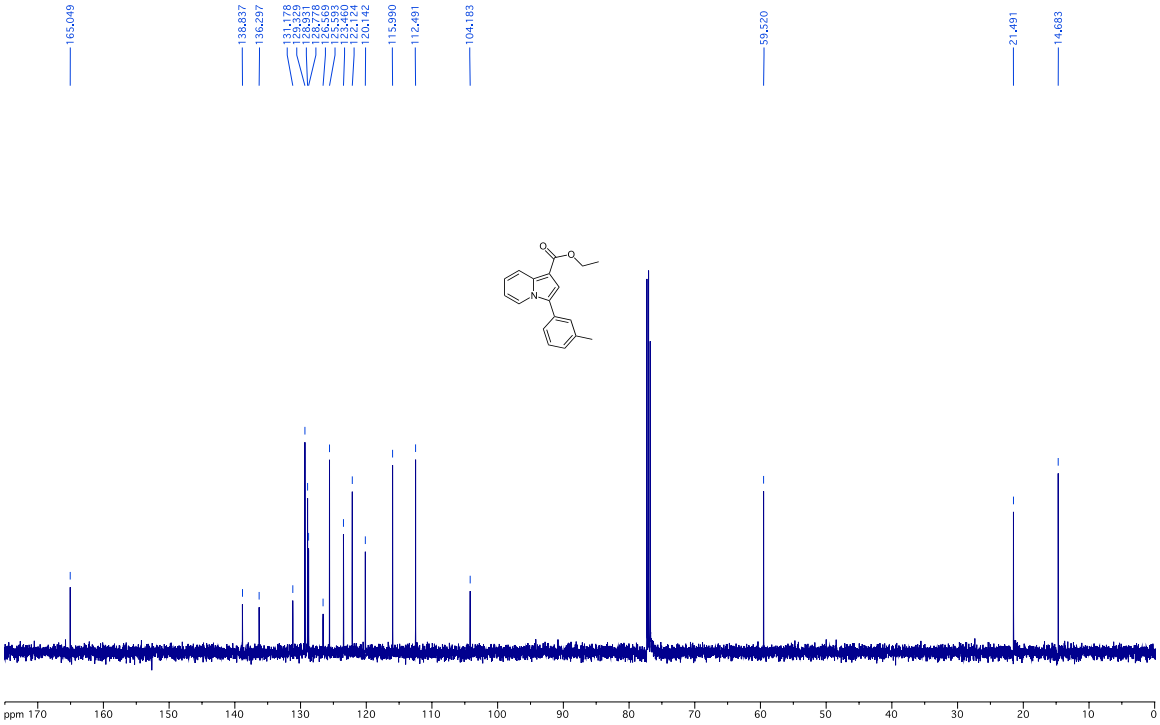

$^{13}$C NMR spectrum of **85e**



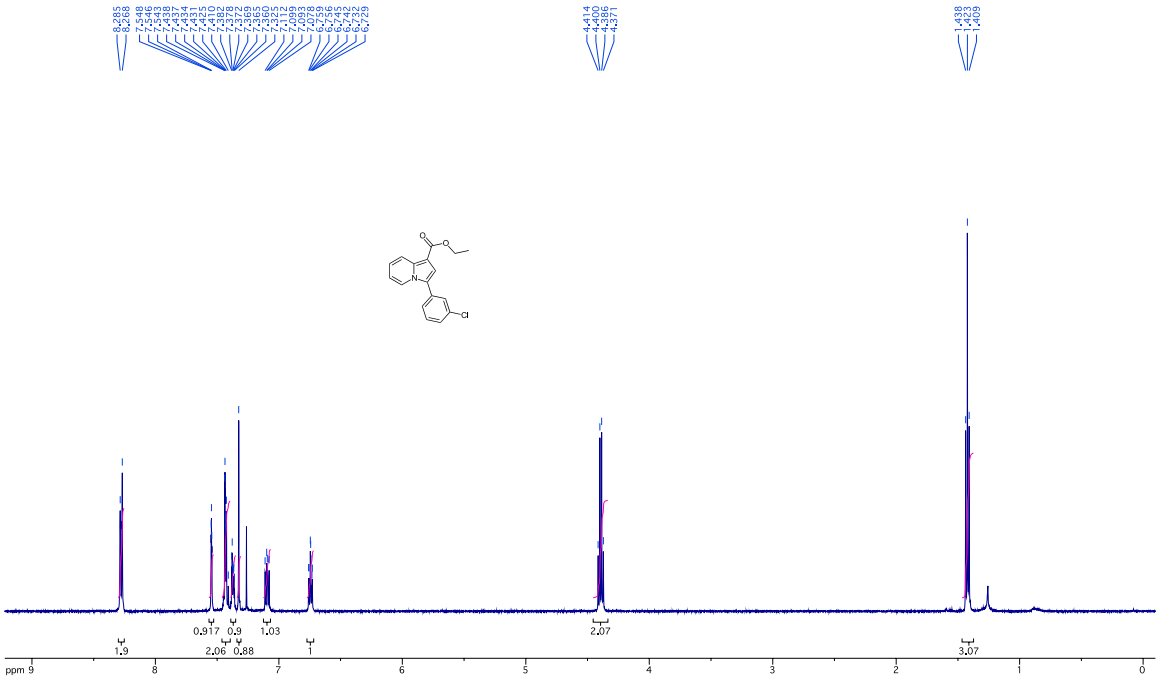

$^{1}$H NMR spectrum of **85f**



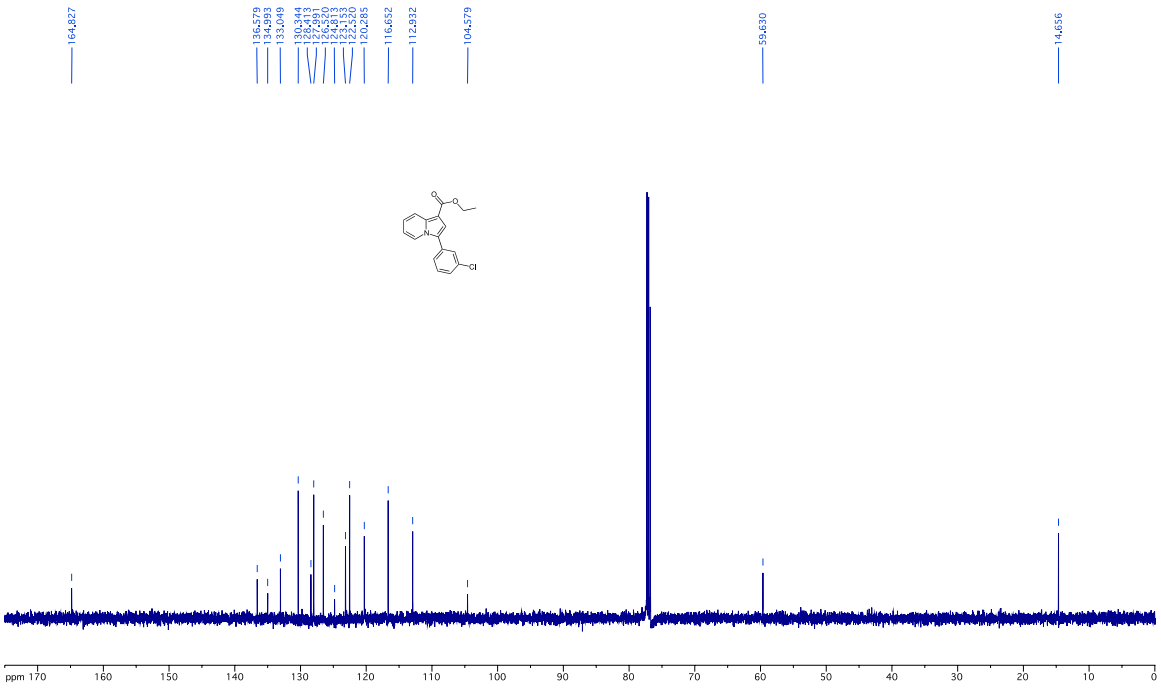

$^{13}$C NMR spectrum of **85f**



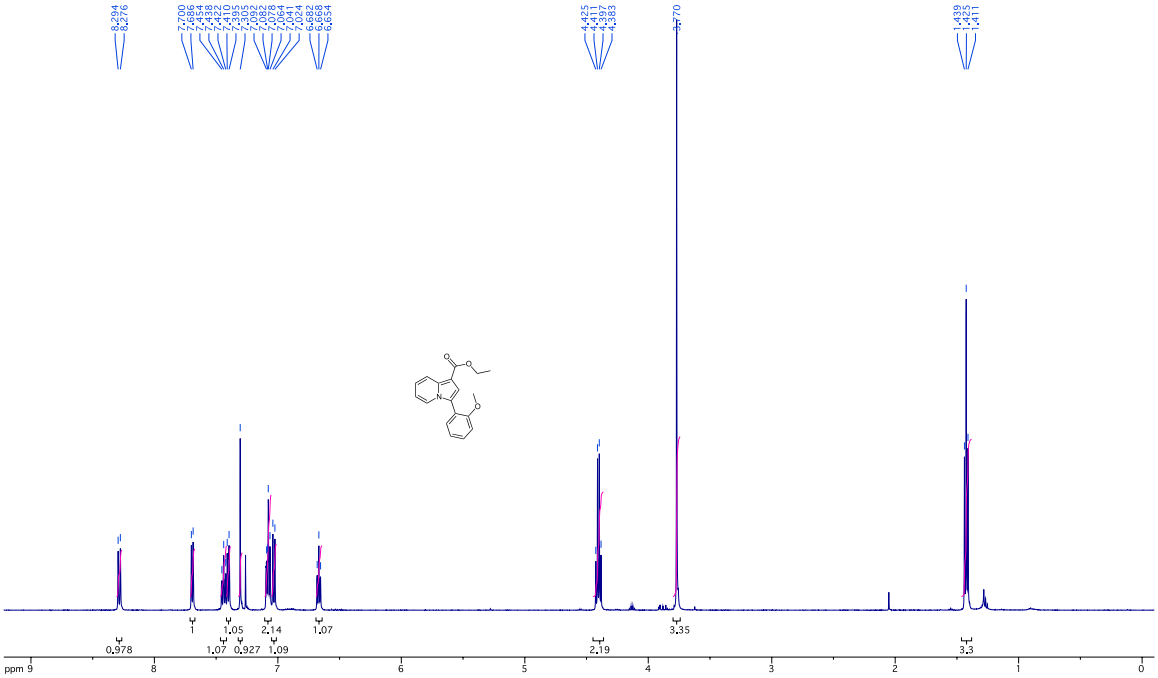

$^{1}$H NMR spectrum of **85g**



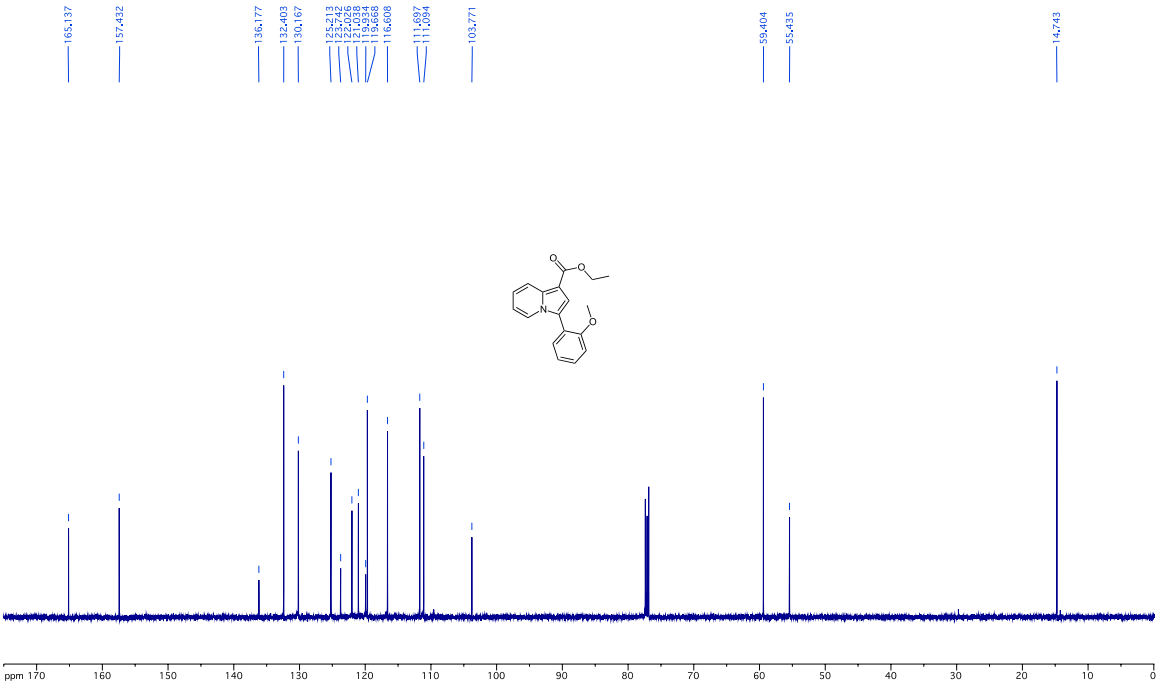

$^{13}$C NMR spectrum of **85g**



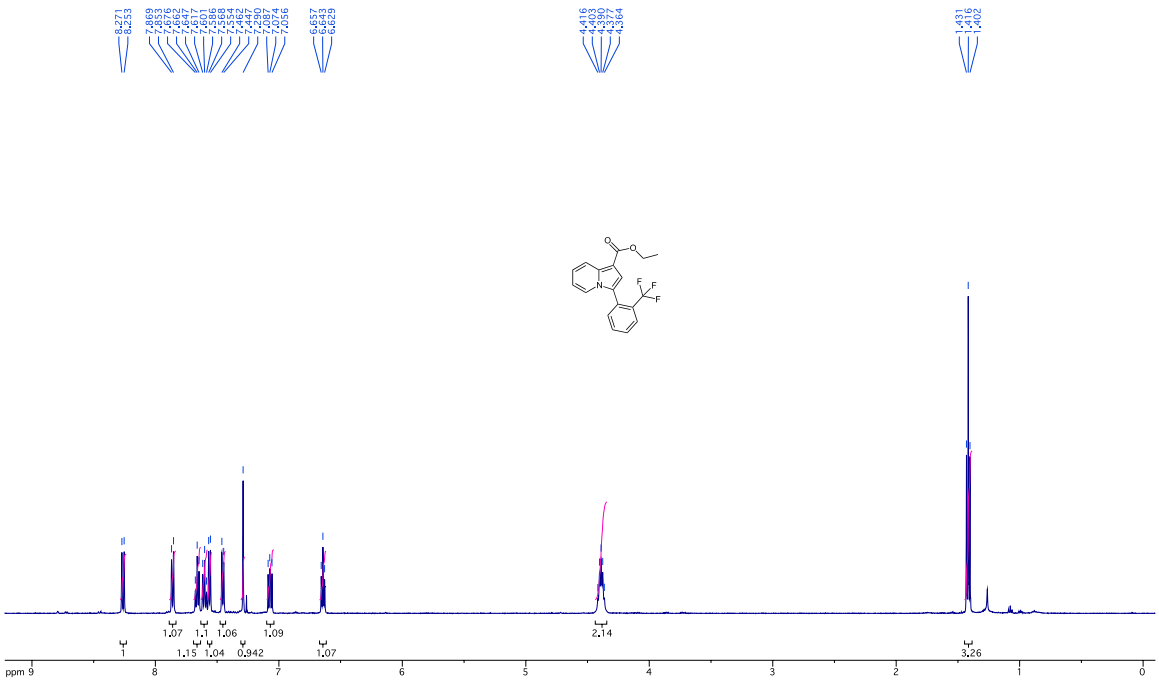

$^{1}$H NMR spectrum of **85h**



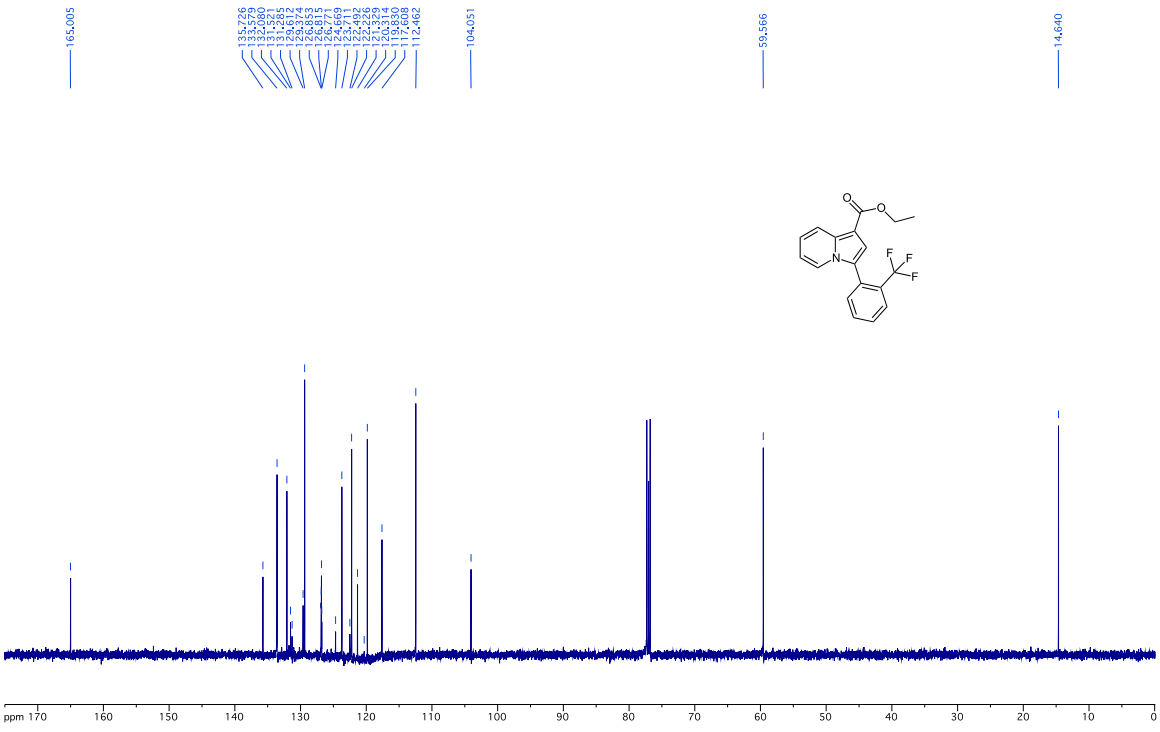

$^{13}$C NMR spectrum of **85h**



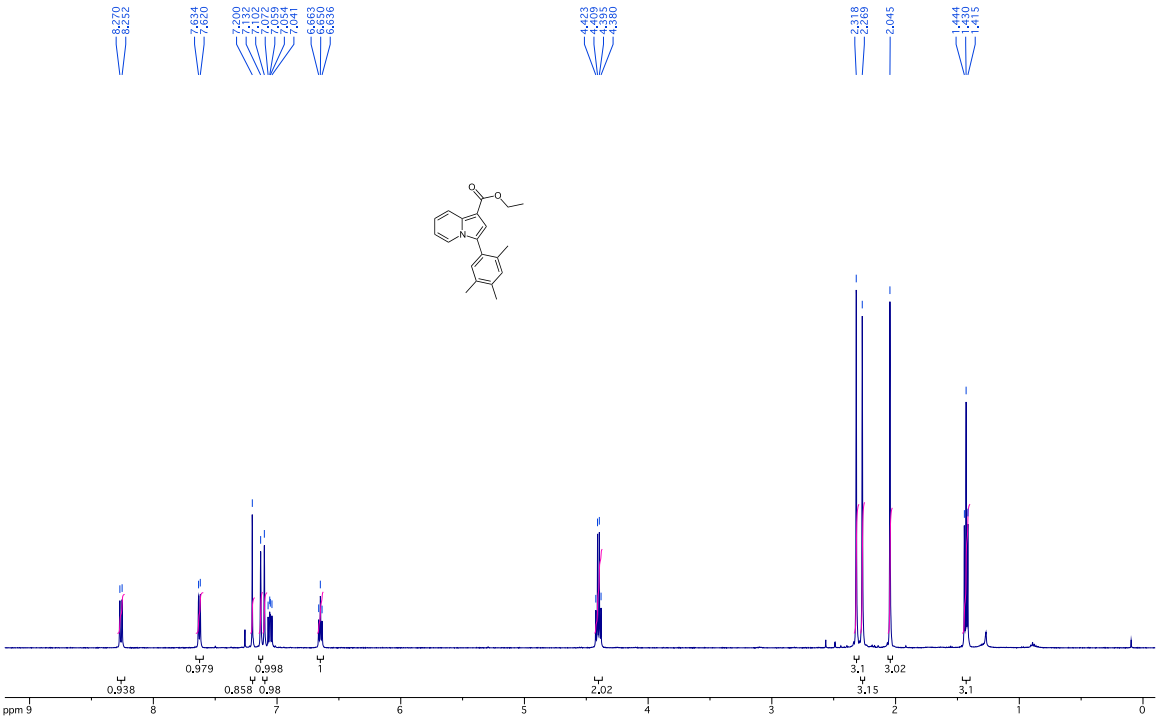

$^{1}$H NMR spectrum of **85i**



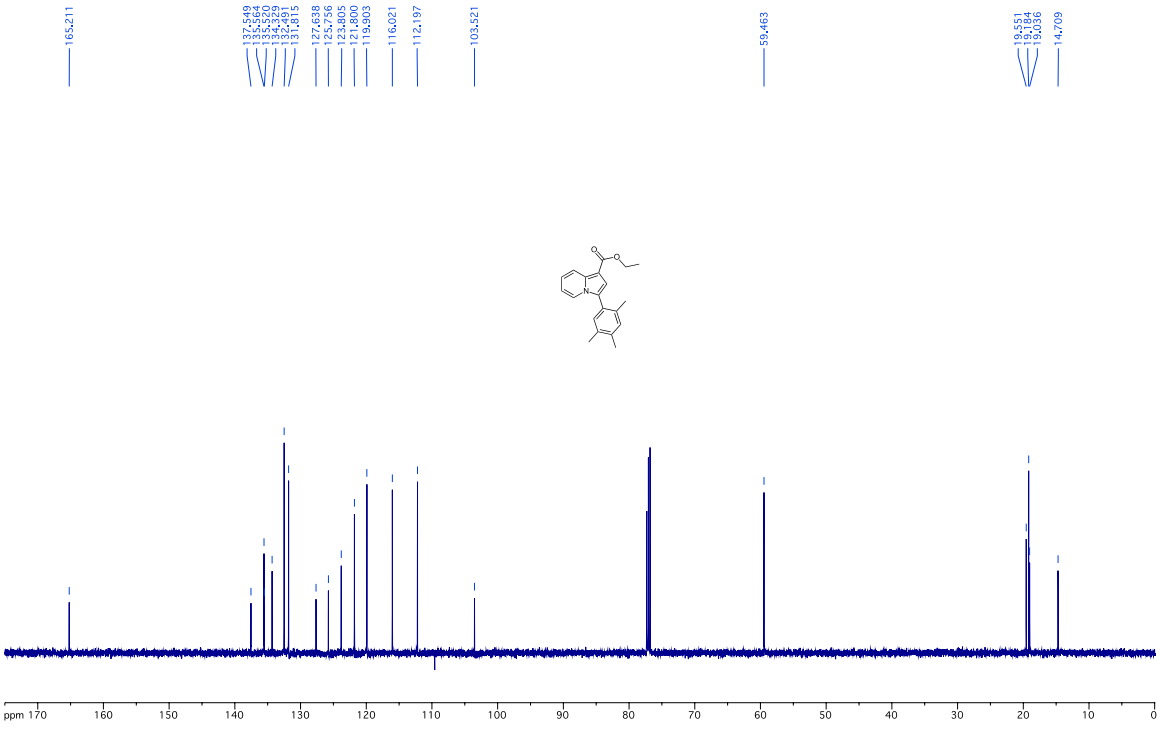
$^{13}$C NMR spectrum of **85i**



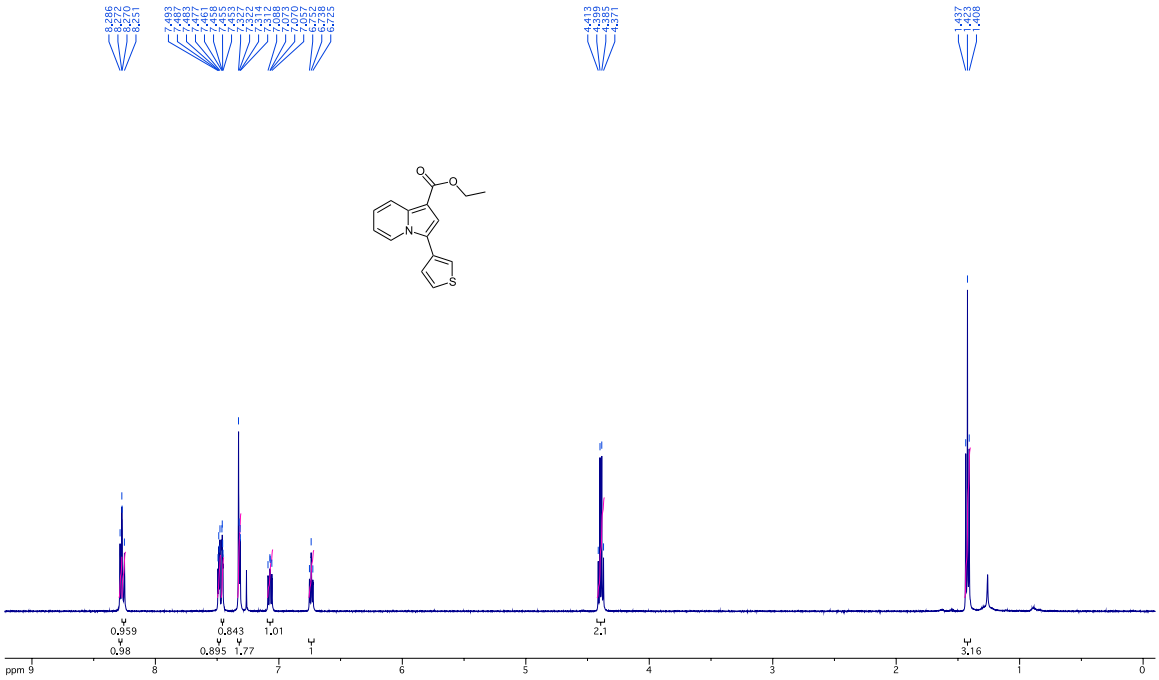
$^{1}$H NMR spectrum of **85j**



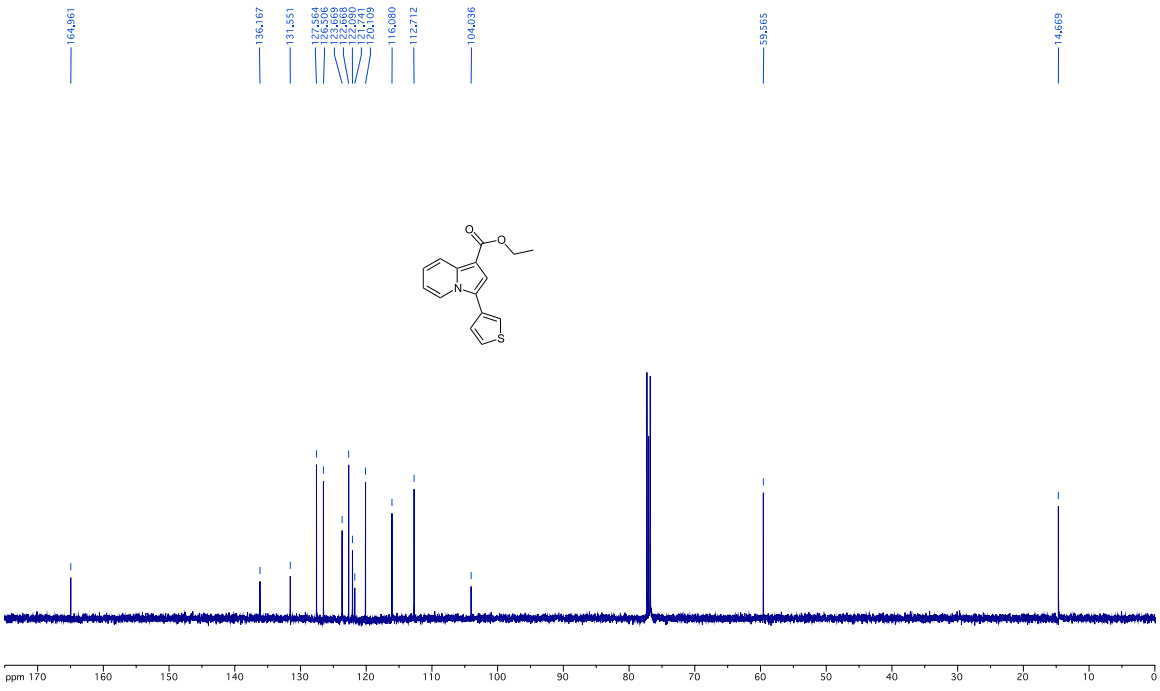

$^{13}$C NMR spectrum of **85j**



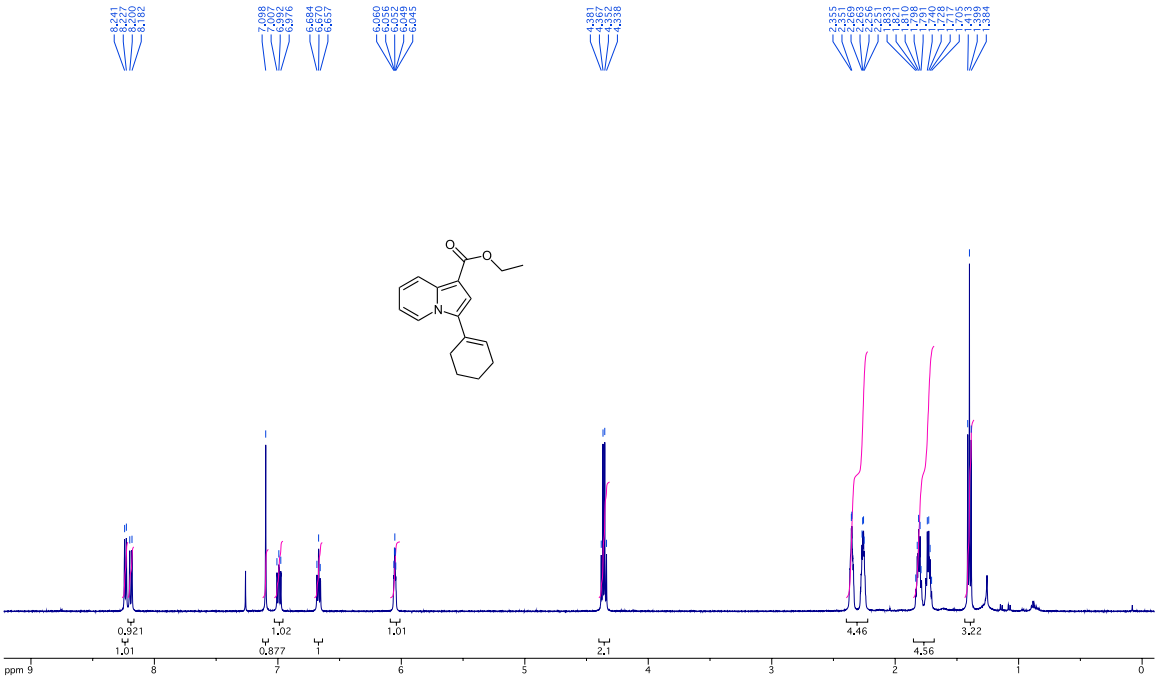

$^{1}$H NMR spectrum of **85k**



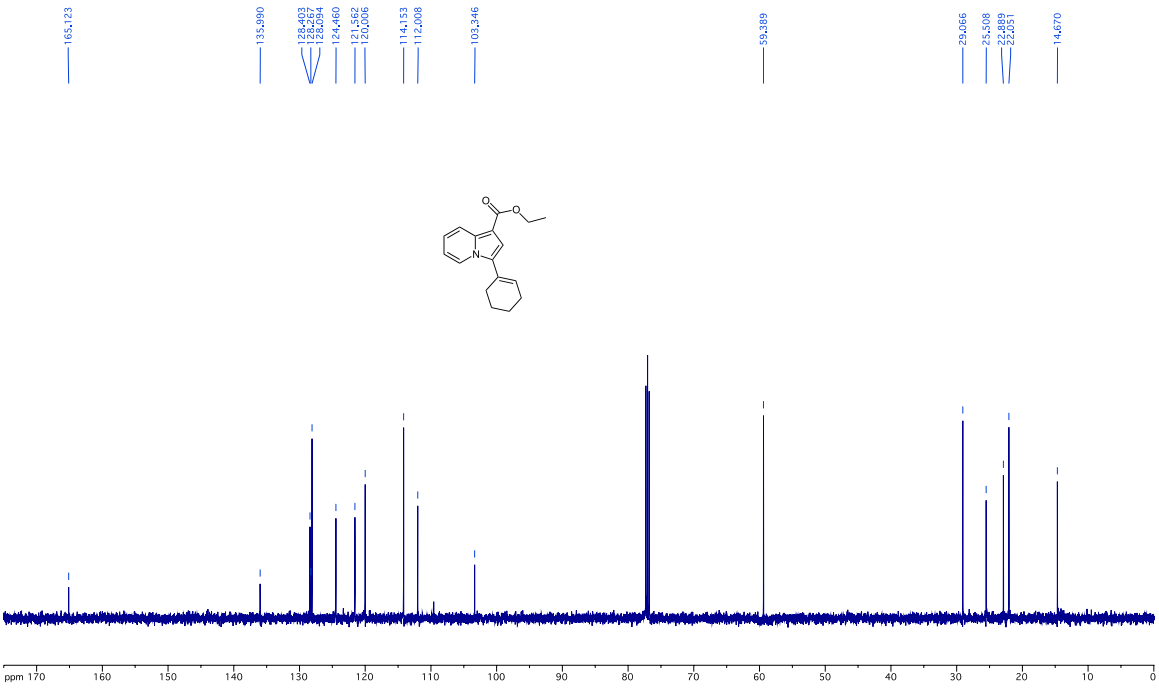
$^{13}$C NMR spectrum of **85k**



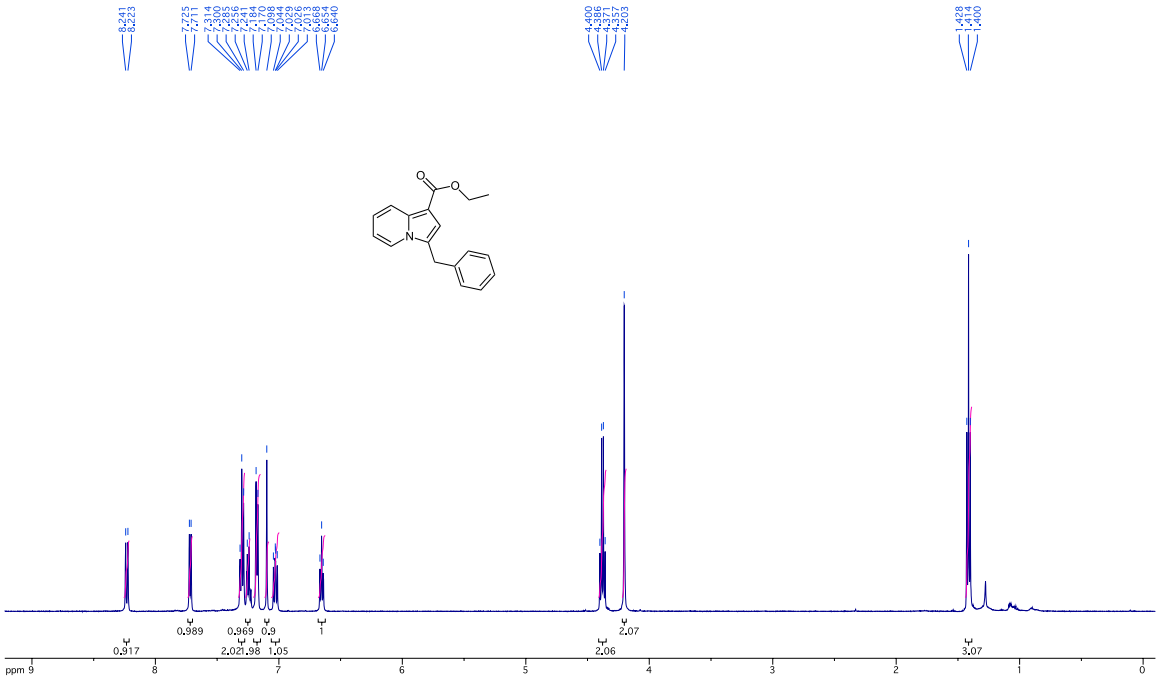
$^{1}$H NMR spectrum of **85l**



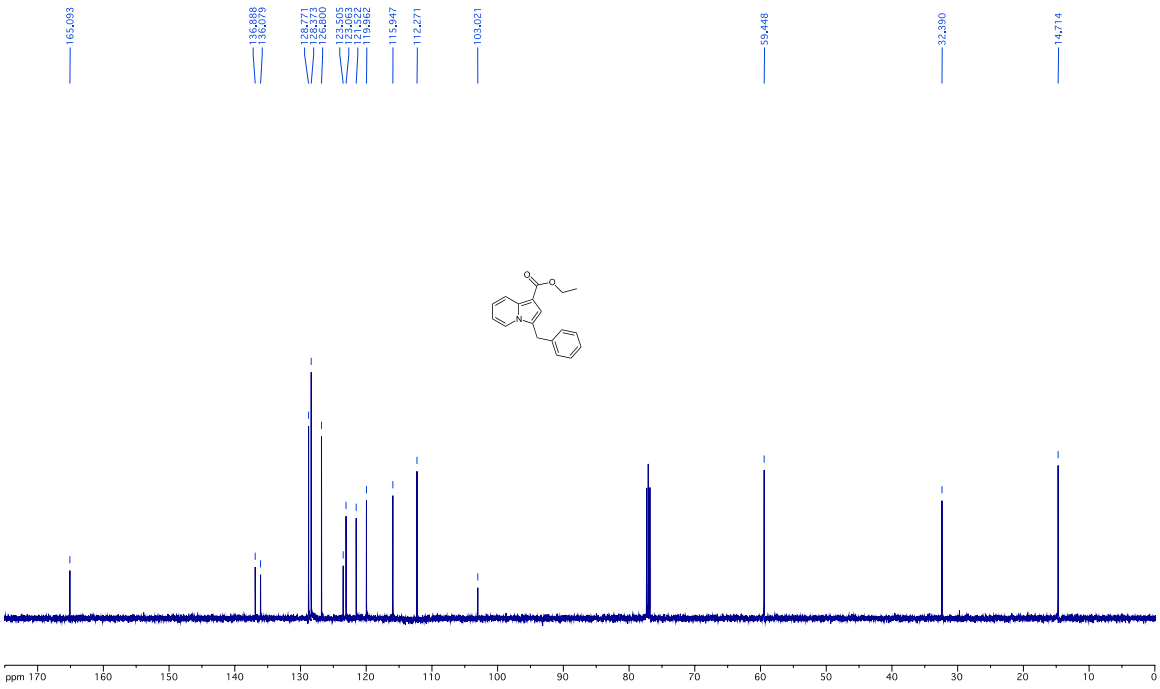
$^{13}$C NMR spectrum of **85l**



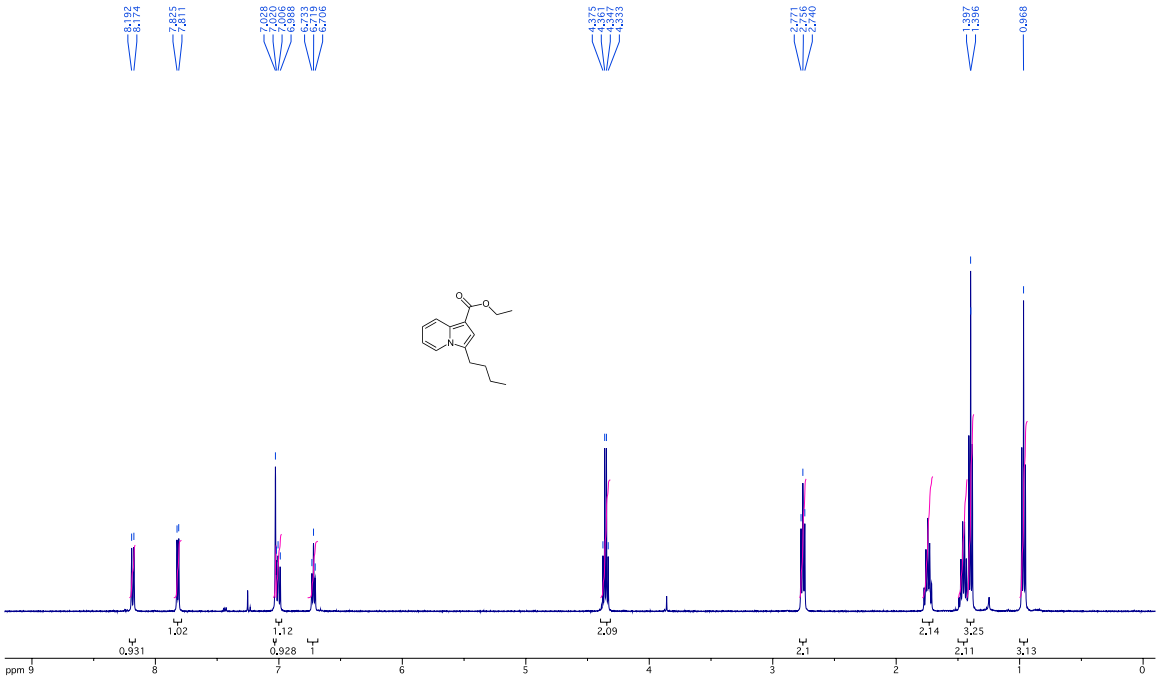
$^{1}$H NMR spectrum of **85m**



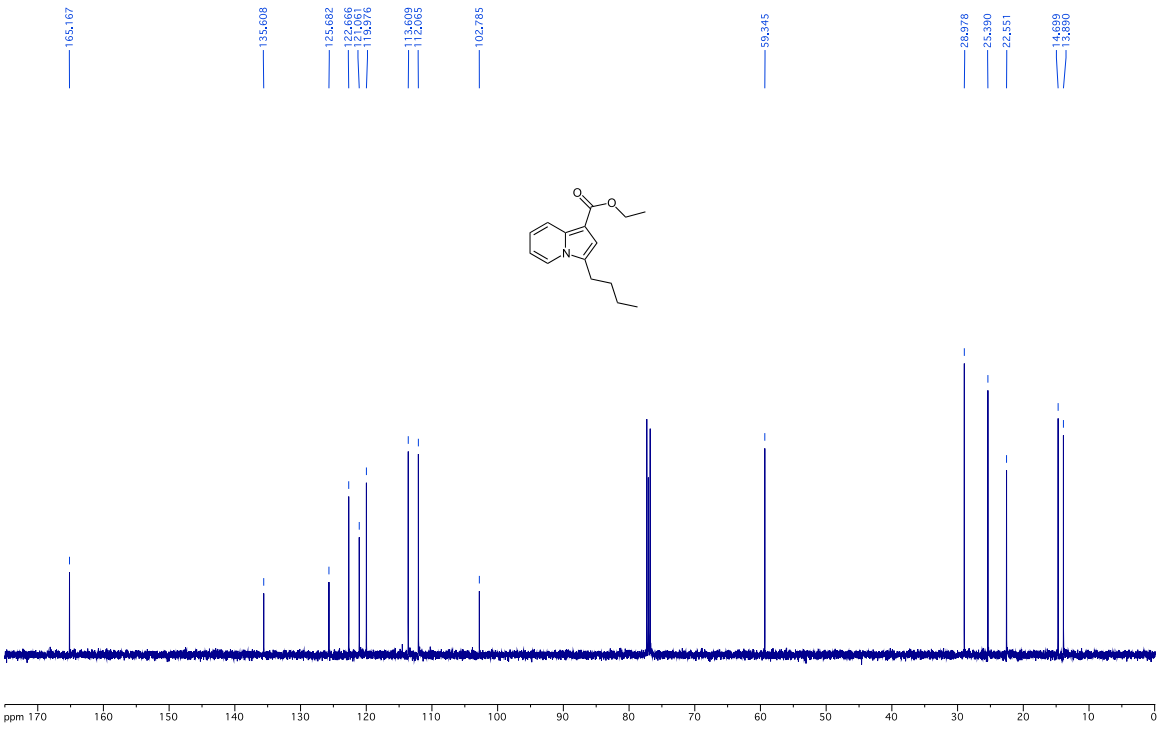
$^{13}$C NMR spectrum of **85m**



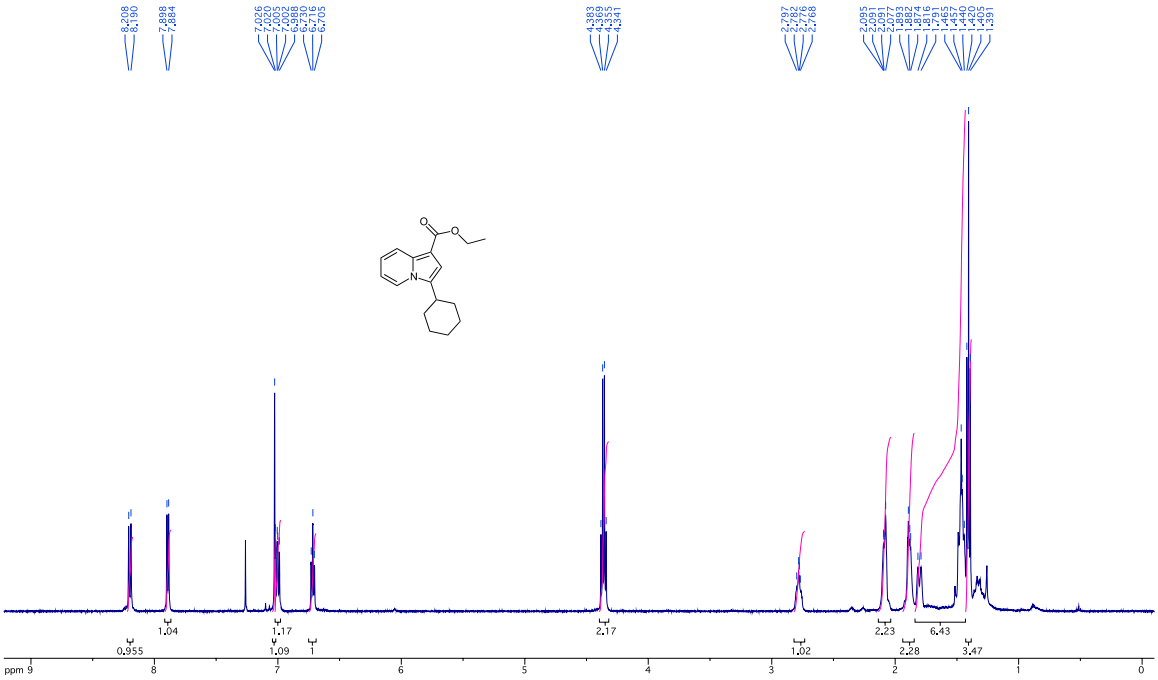
$^{1}$H NMR spectrum of **85n**



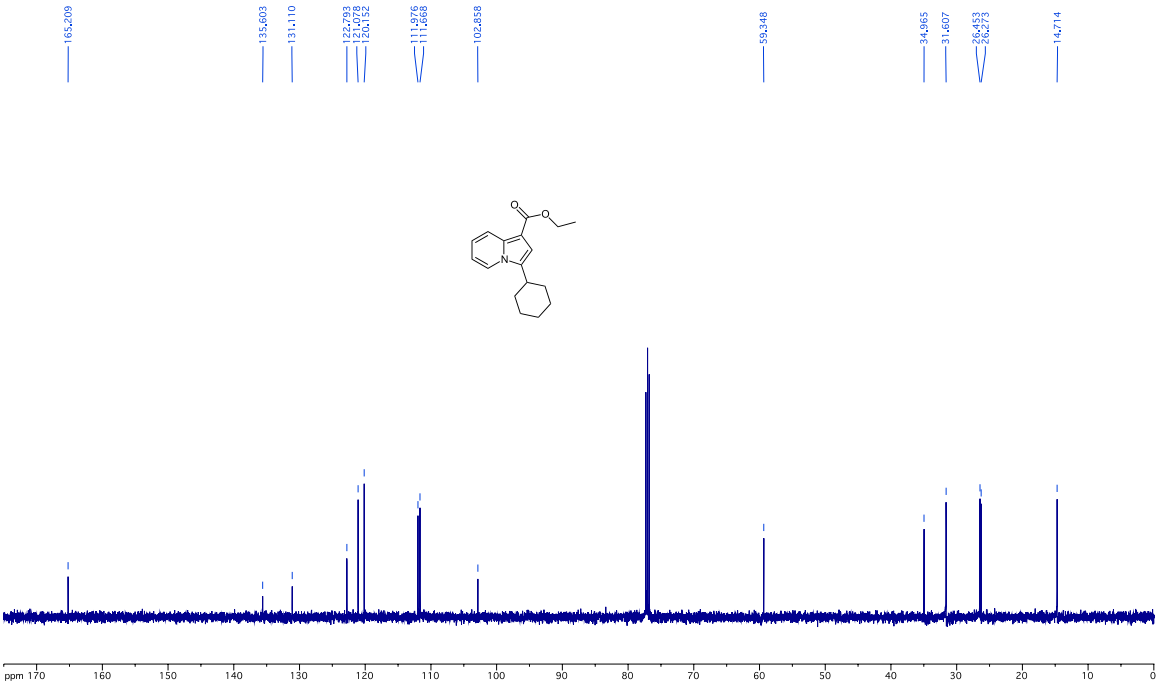

$^{13}$C NMR spectrum of **85n**



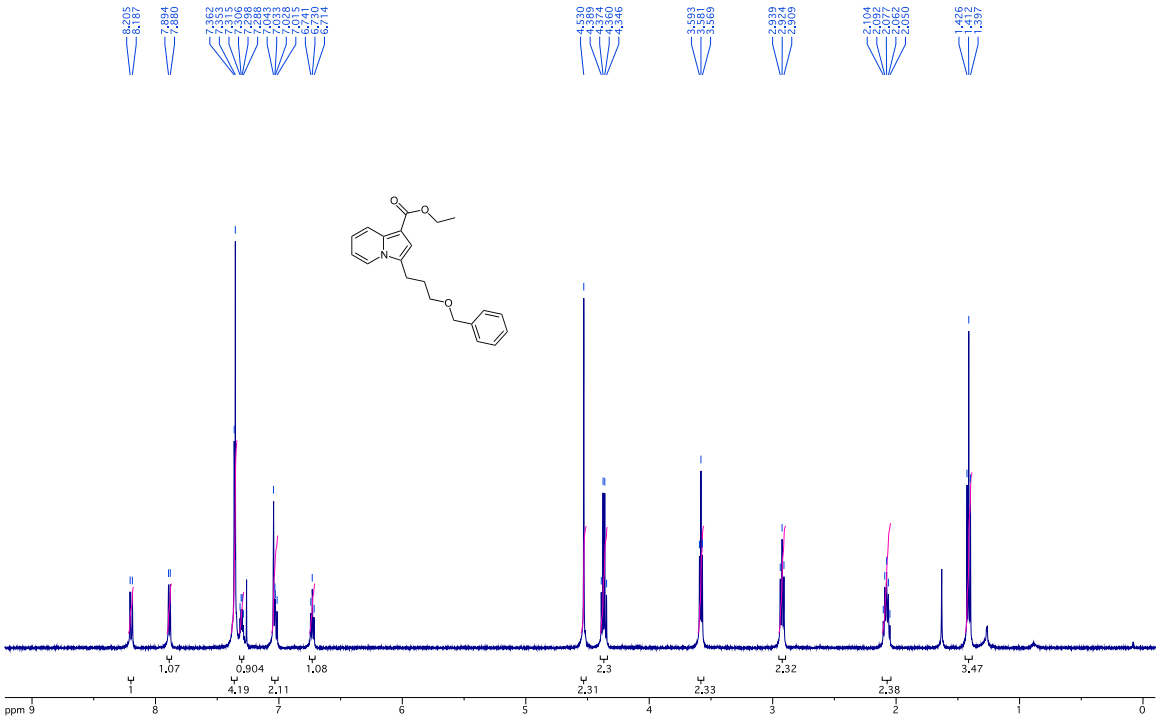

$^{1}$H NMR spectrum of **85o**



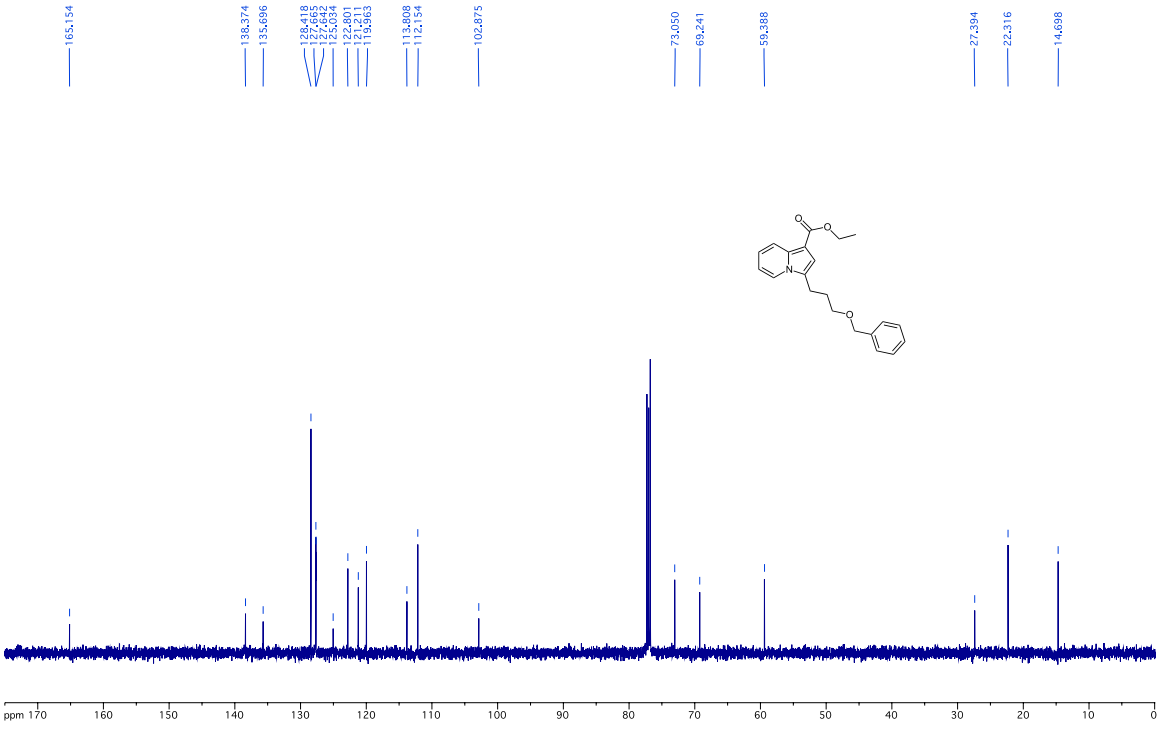
$^{13}$C NMR spectrum of **85o**



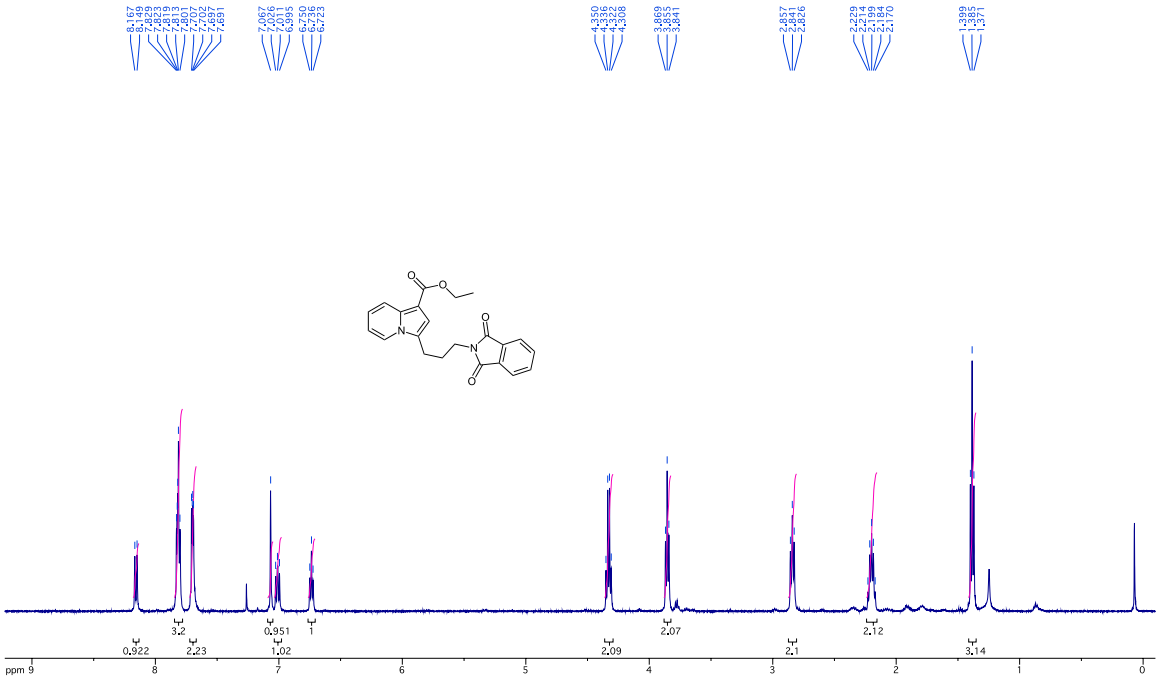
$^{1}$H NMR spectrum of **85p**



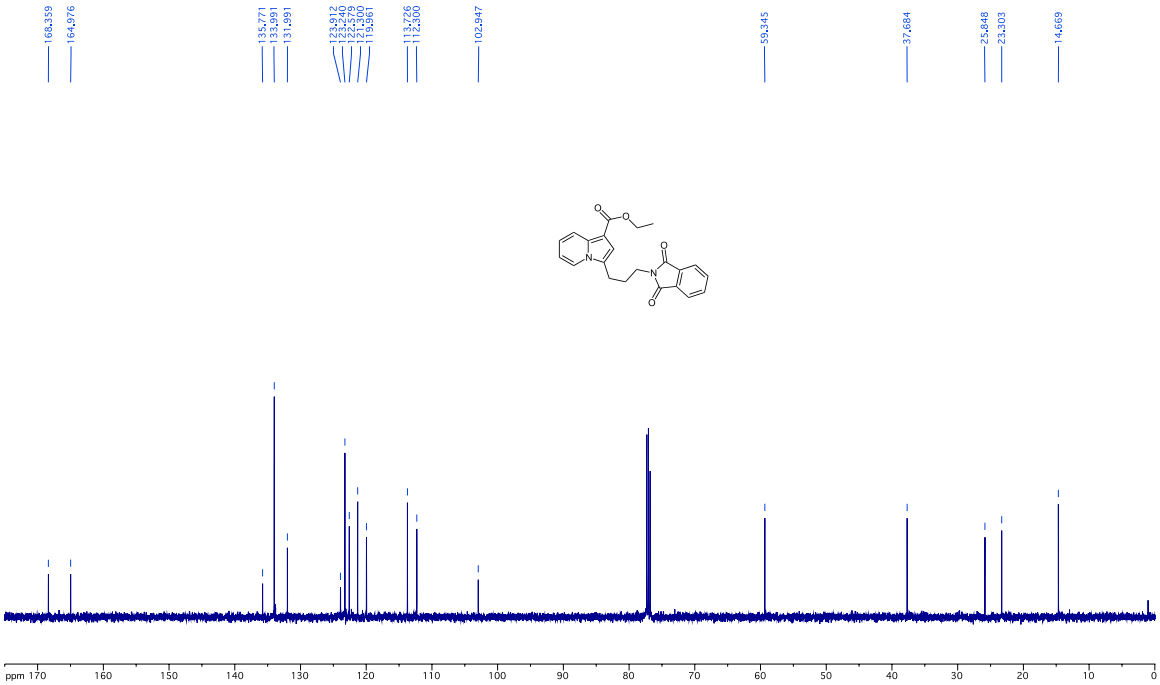

$^{13}$C NMR spectrum of **85p**



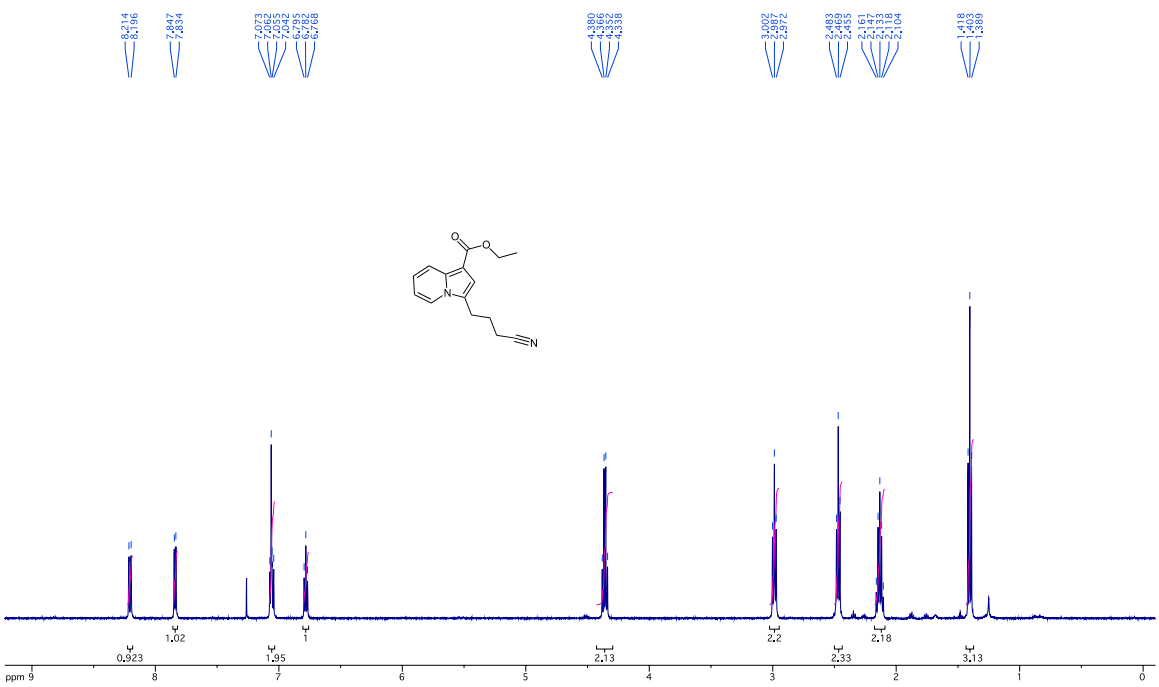

$^{1}$H NMR spectrum of **85q**



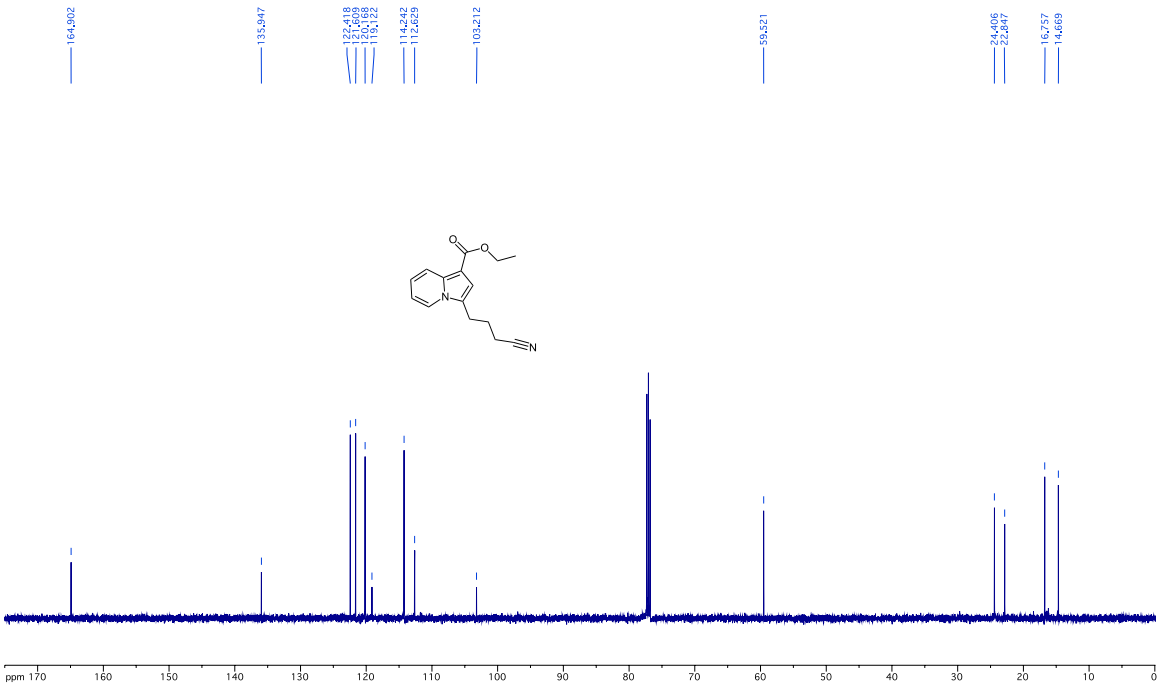
$^{13}$C NMR spectrum of **85q**



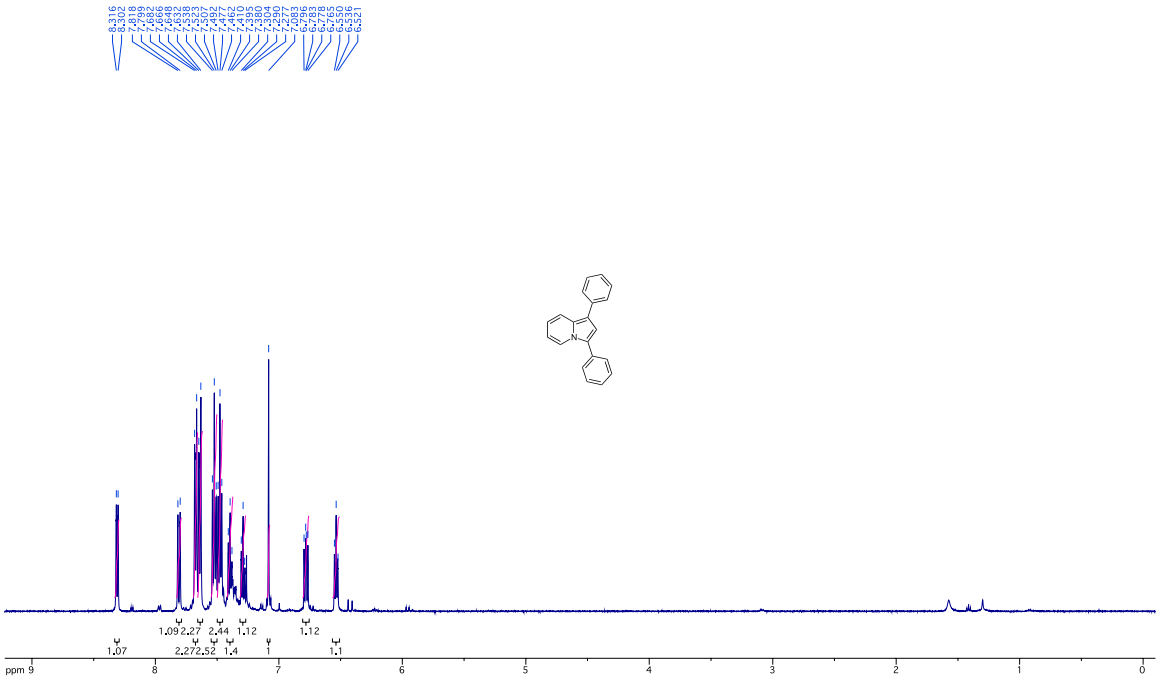
$^{1}$H NMR spectrum of **85r**



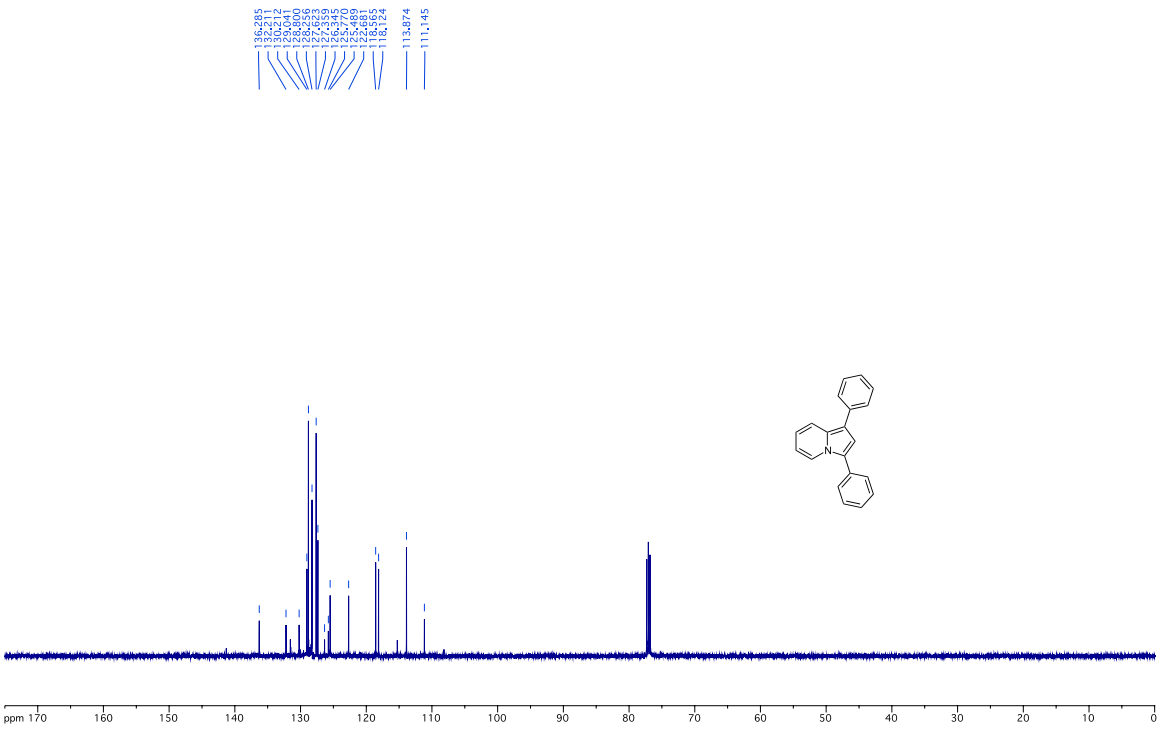

$^{13}$C NMR spectrum of **85r**



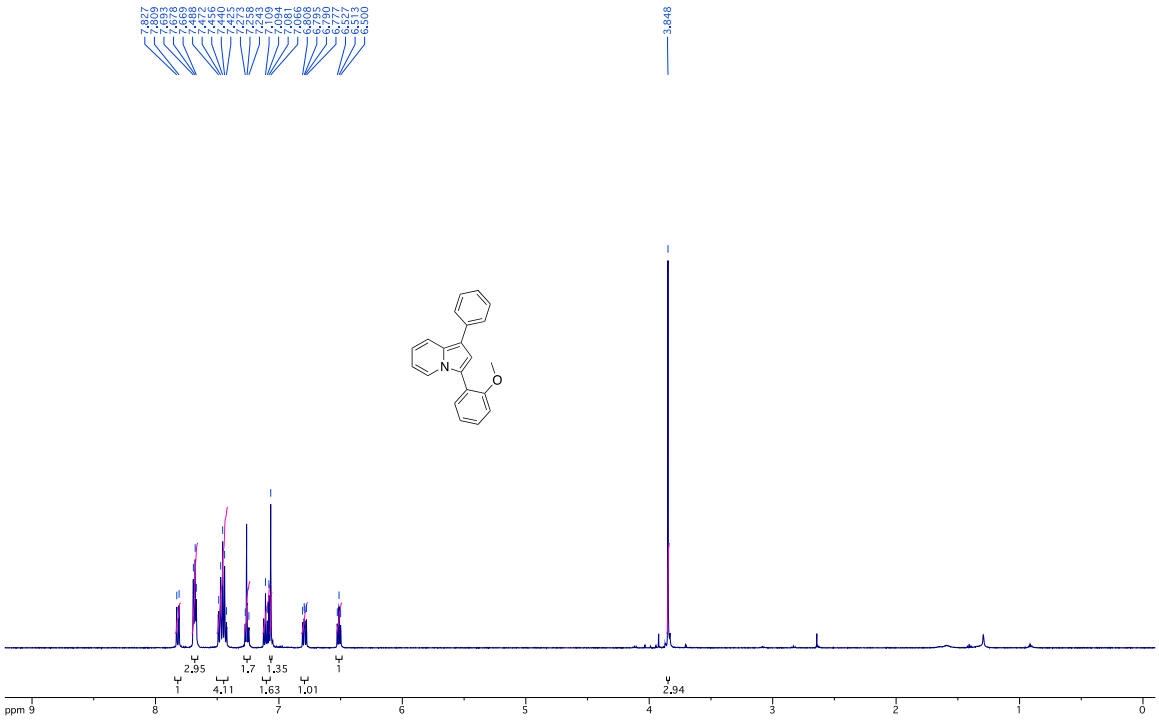

$^{1}$H NMR spectrum of **85s**



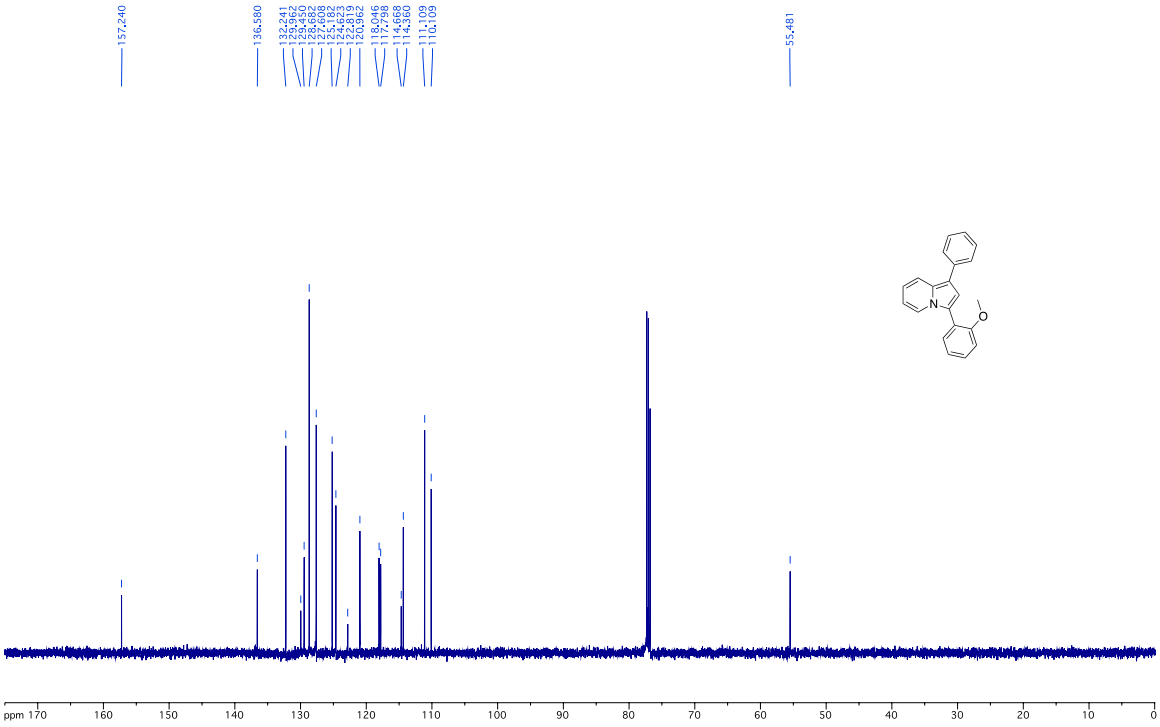
$^{13}$C NMR spectrum of **85s**



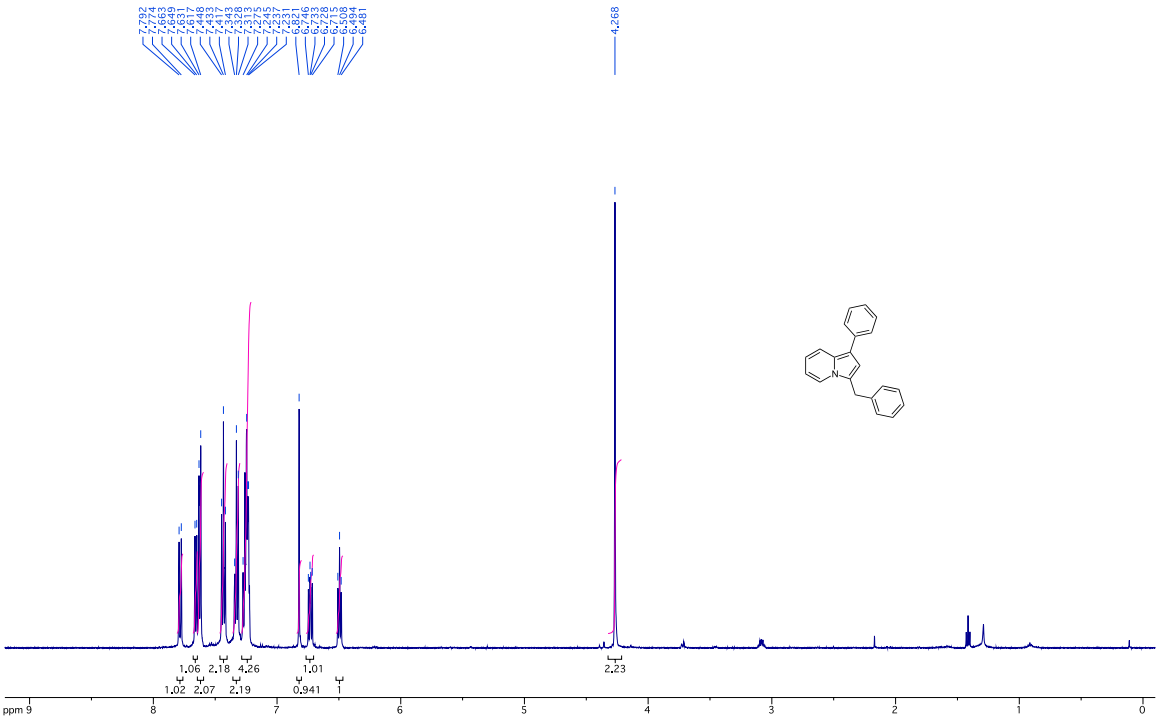
$^{1}$H NMR spectrum of **85t**



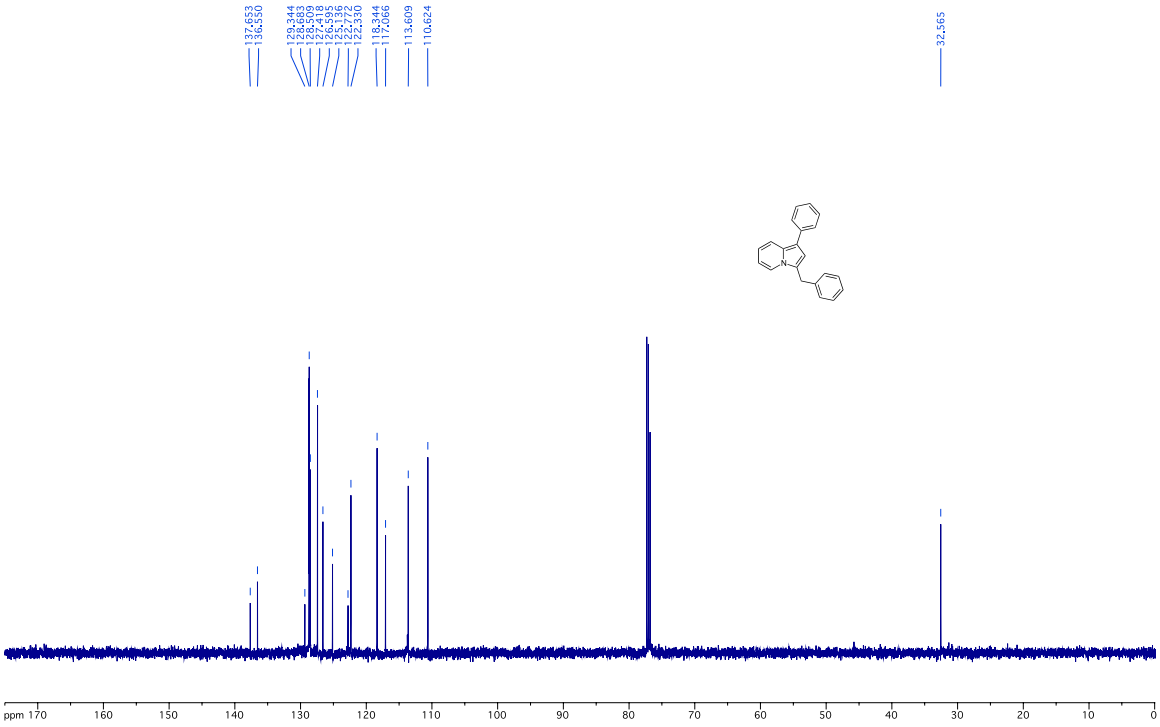

$^{13}$C NMR spectrum of **85t**



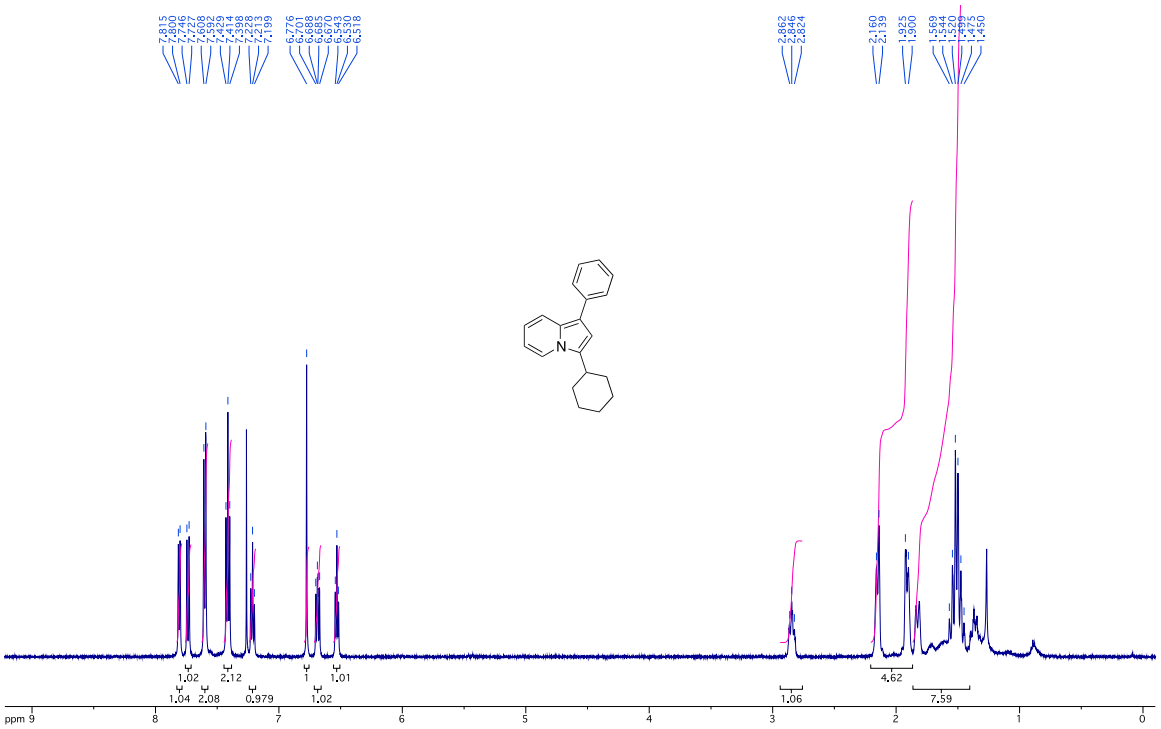

$^{1}$H NMR spectrum of **85u**



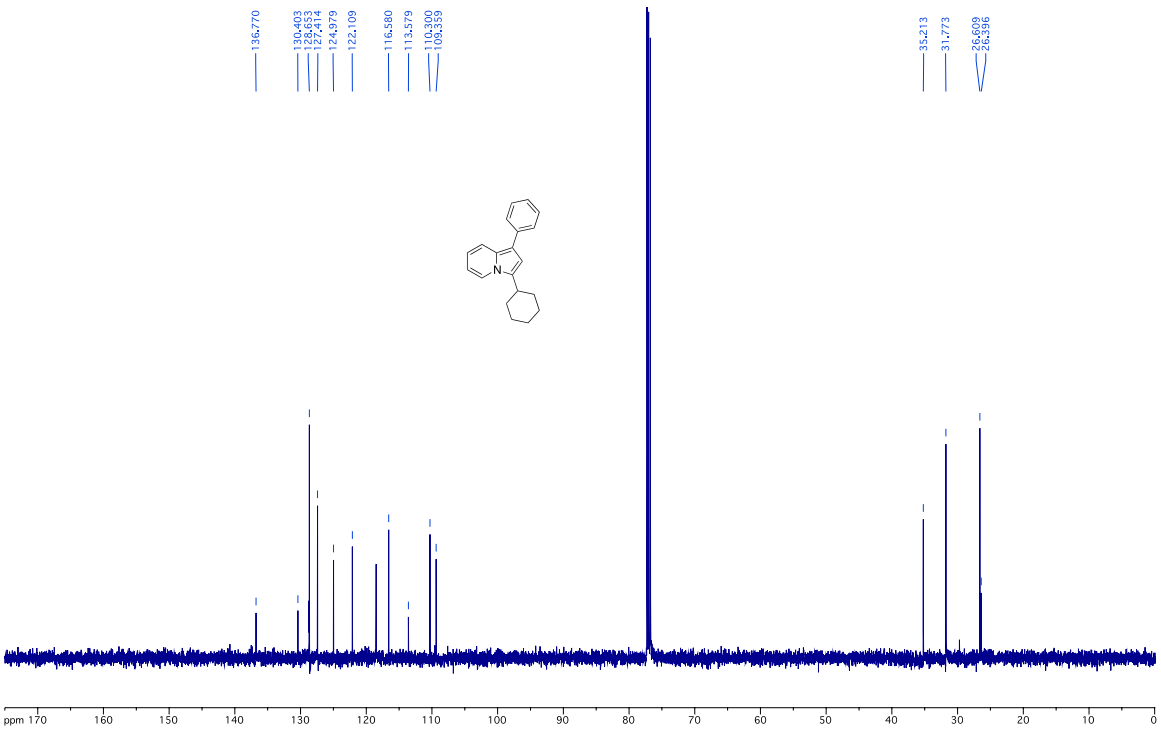

$^{13}$C NMR spectrum of **85u**



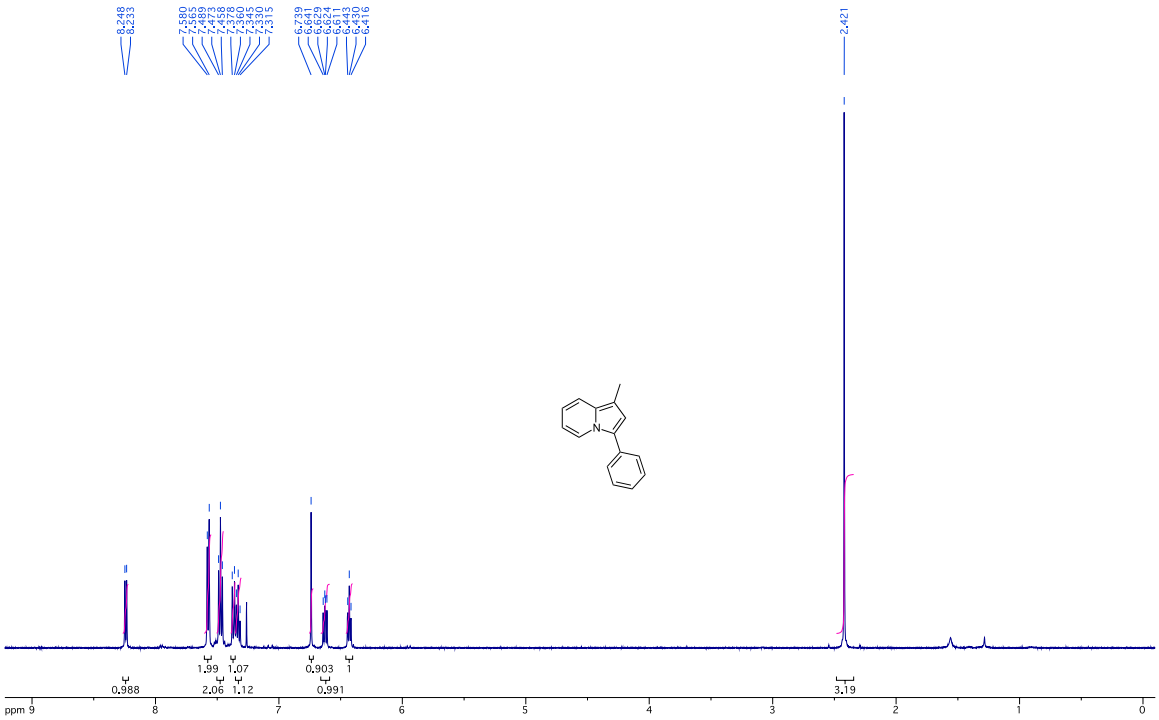

$^{1}$H NMR spectrum of **85v**



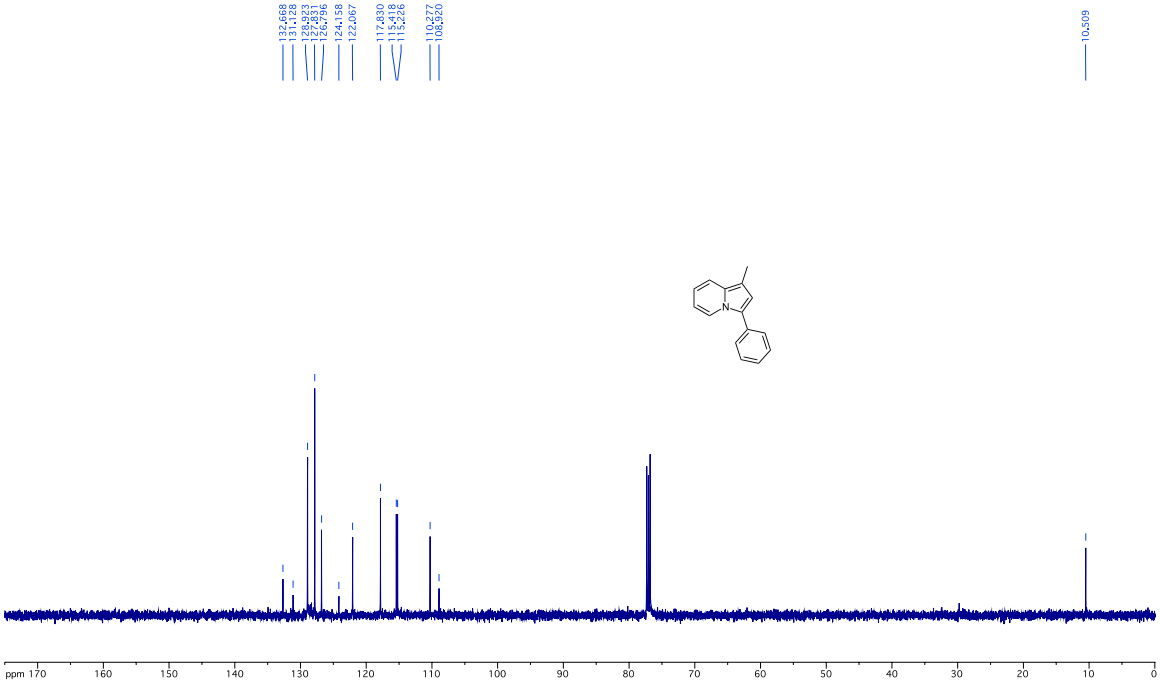

$^{13}$C NMR spectrum of **85v**



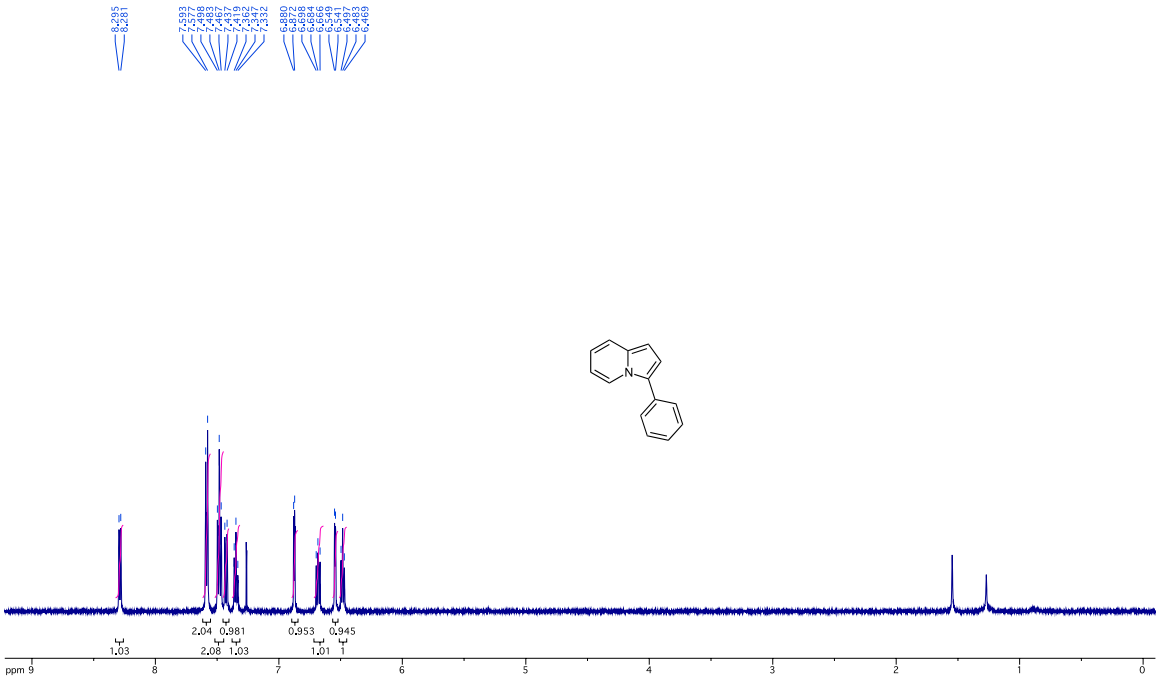

$^{1}$H NMR spectrum of **85w**



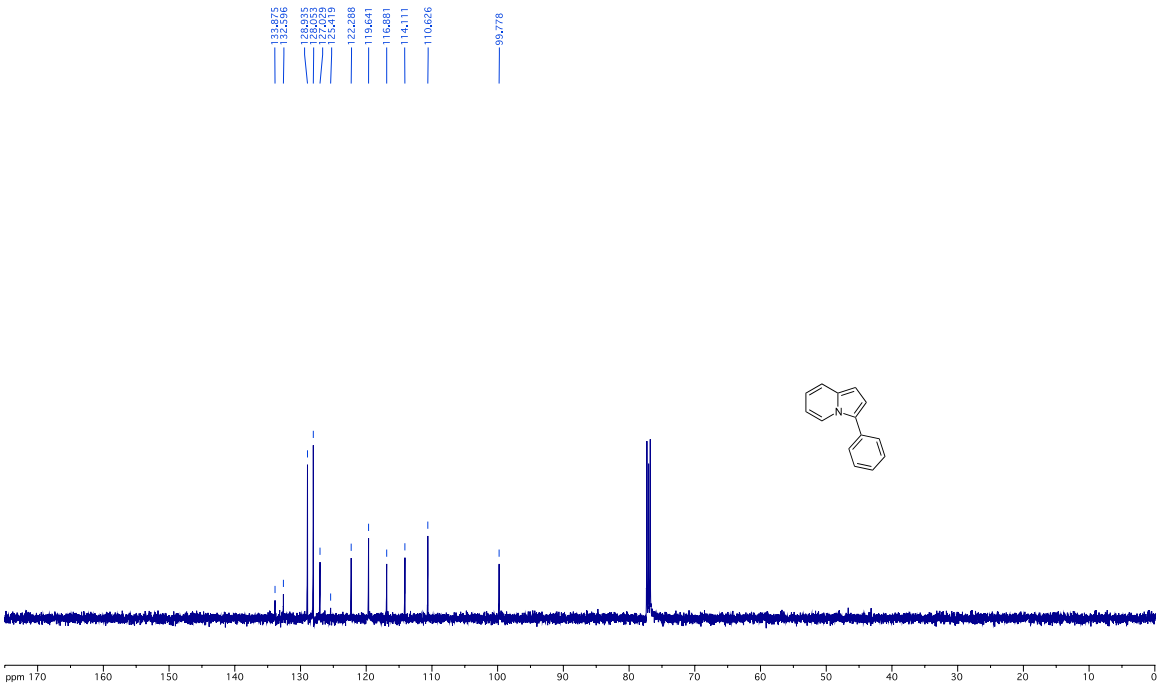

$^{13}$C NMR spectrum of **85w**




$^{1}$H NMR spectrum of **85x**

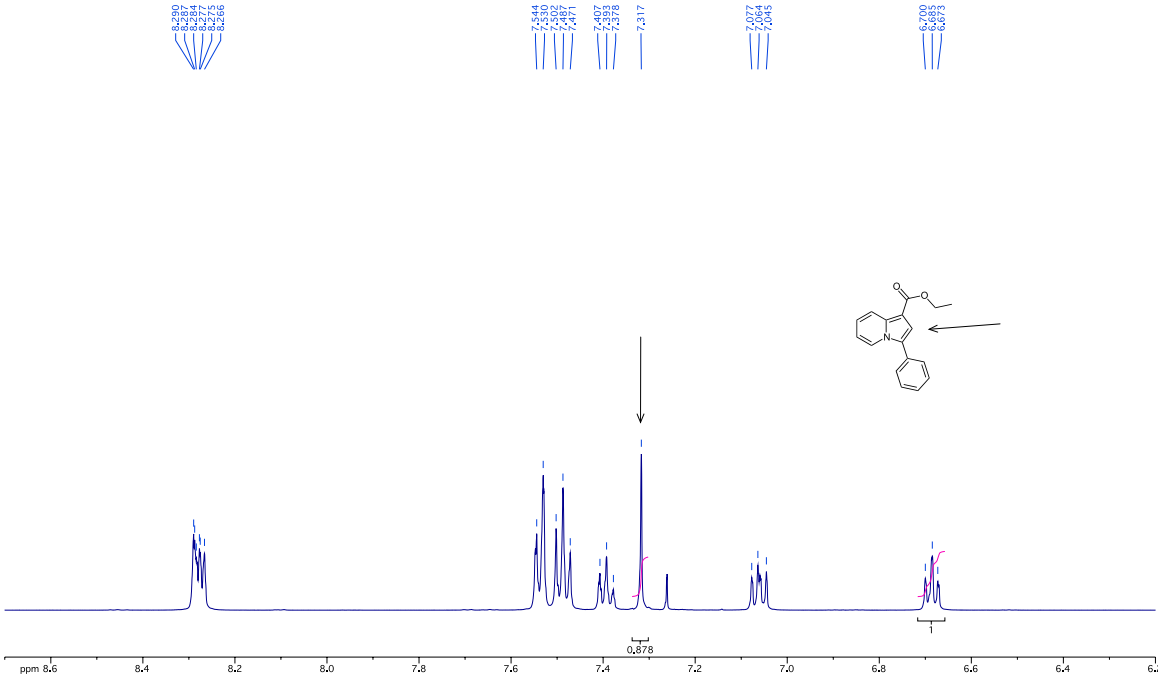


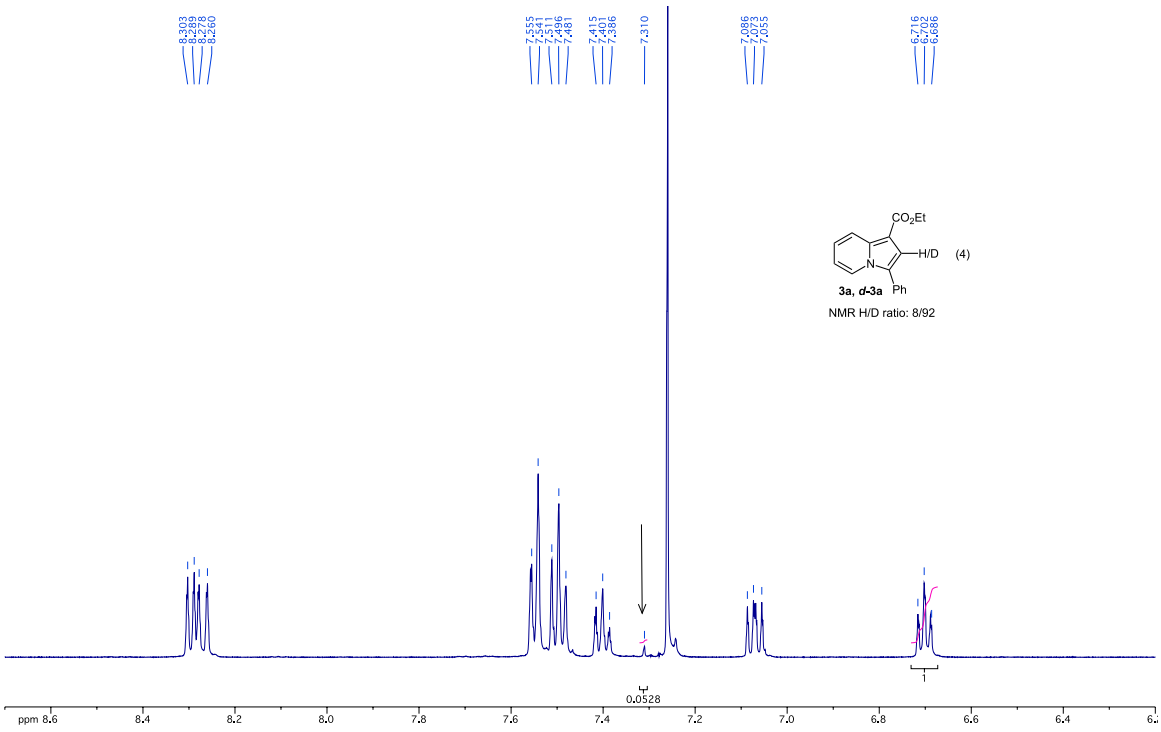

$^{13}$C NMR spectrum of **85x**

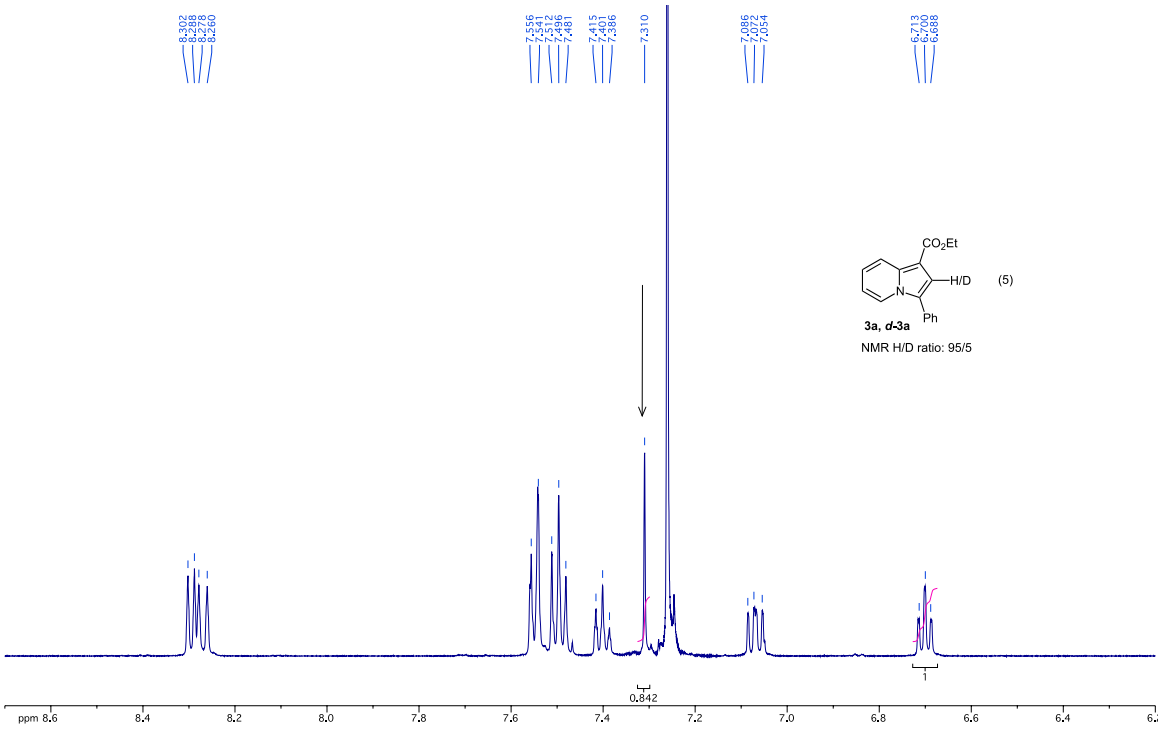


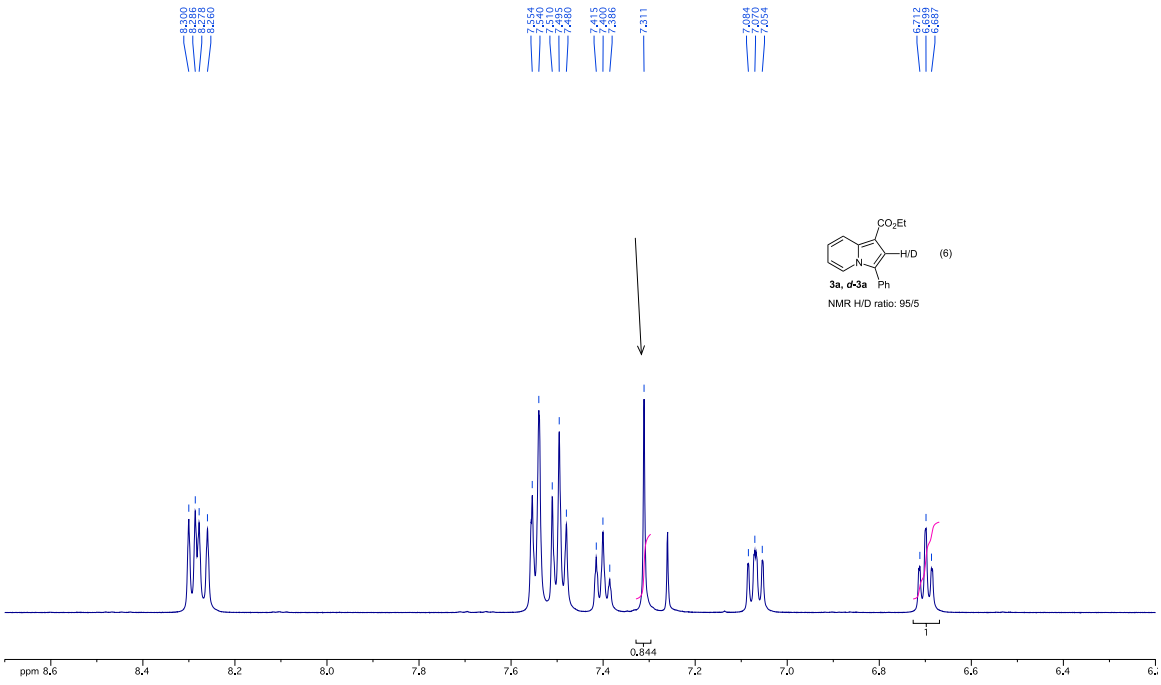

**$^{1}$H NMR Spectra for Deuterium-Labeling Studies of 85a**

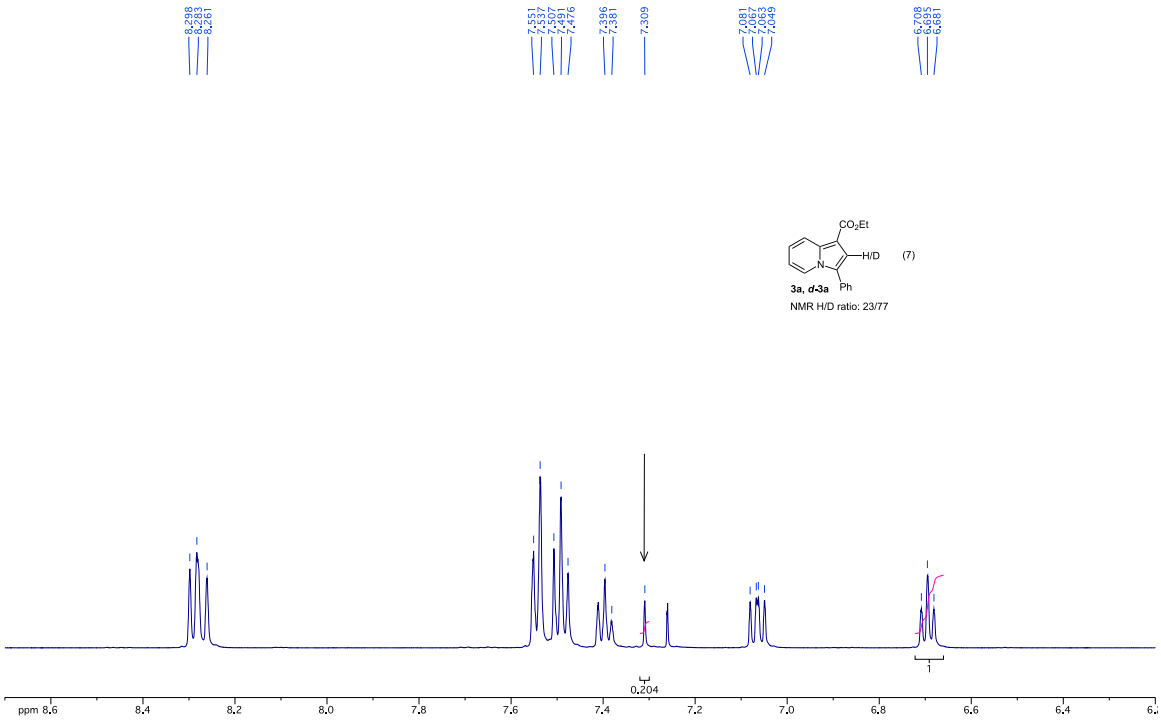
The spectra presented were zoomed in to the area containing the proton of interest.



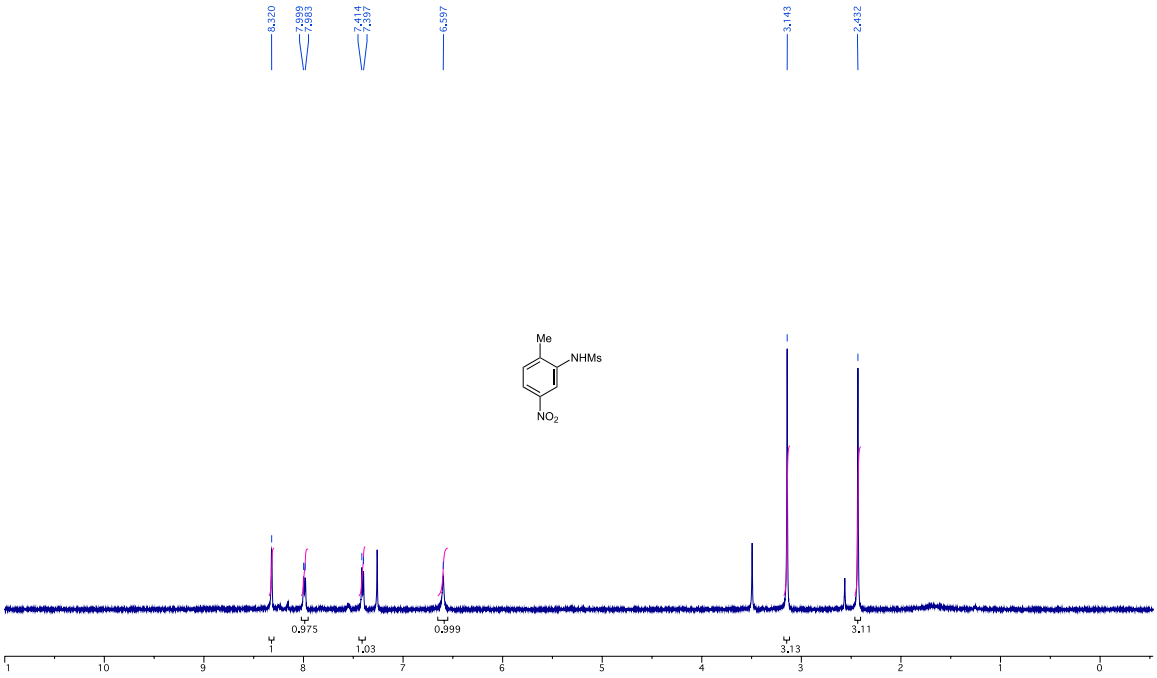

8.302
8.288
8.278
8.260
7.556
7.541
7.512
7.496
7.481
7.415
7.401
7.386
7.310
7.086
7.072
7.054
6.713
6.700
6.688
CO2Et
H/D
(5)
N
Ph
3a, d-3a
NMR H/D ratio: 95/5
0.842
1
ppm 8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4


8.300
8.286
8.270
8.260
7.554
7.540
7.510
7.495
7.480
7.415
7.400
7.386
7.311
7.084
7.070
7.054
6.712
6.699
6.687
CO2Et
H/D
(6)
N
Ph
3a, d-3a
NMR H/D ratio: 95/5
0.844
1
ppm 8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4

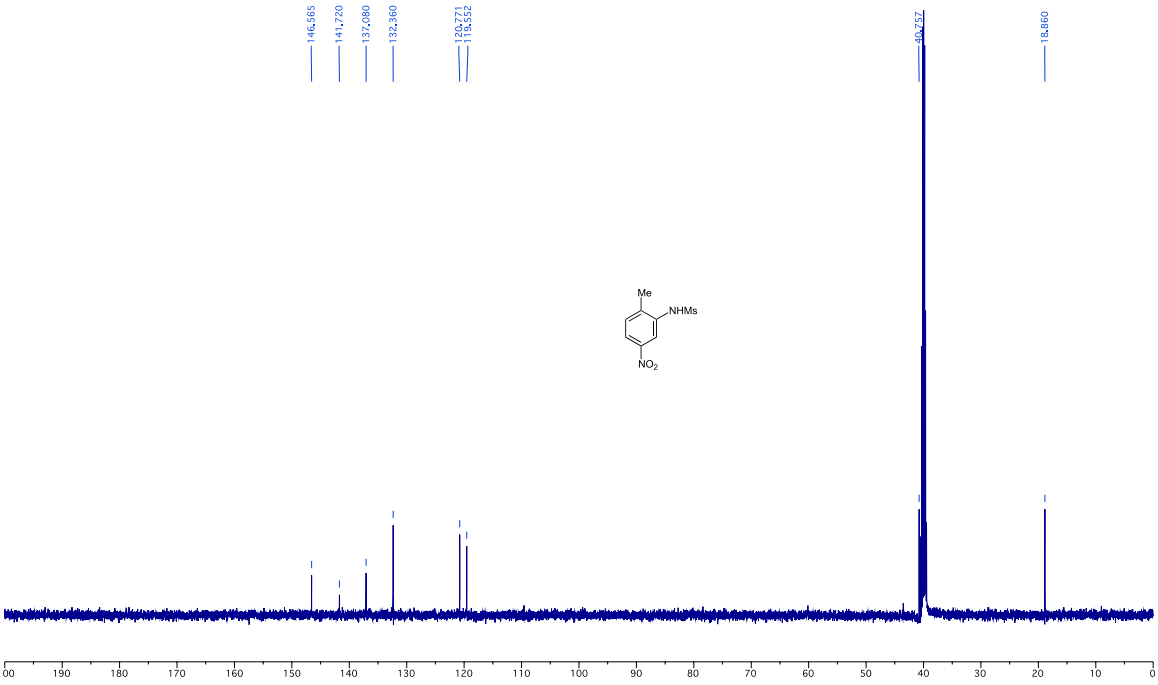

8.298
8.283
8.261
7.551
7.537
7.527
7.491
7.476
7.396
7.381
7.309
7.081
7.067
7.063
7.049
6.708
6.695
6.681
CO2Et
H/D
(7)
N
Ph
3a, d-3a
NMR H/D ratio: 23/77
0.204
1
ppm 8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4

## Appendix F. $^{1}H$ and $^{13}C$ spectra of compounds 100, 101 and amides 98b-f

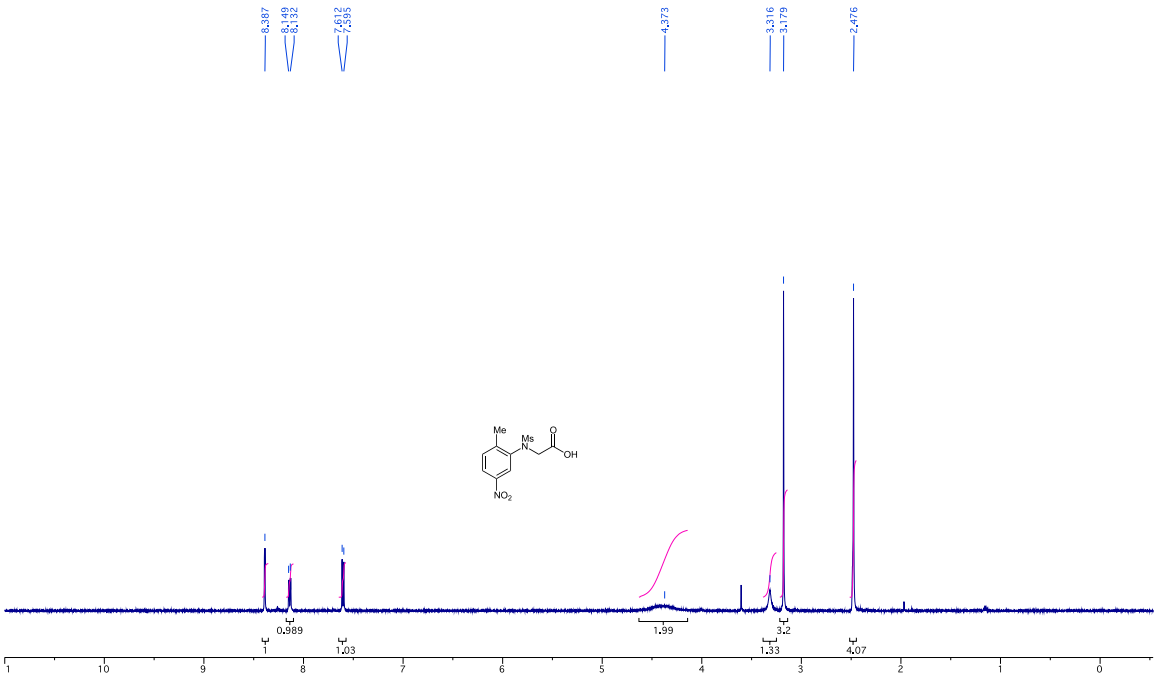
$^{1}H$ NMR spectrum of **100**



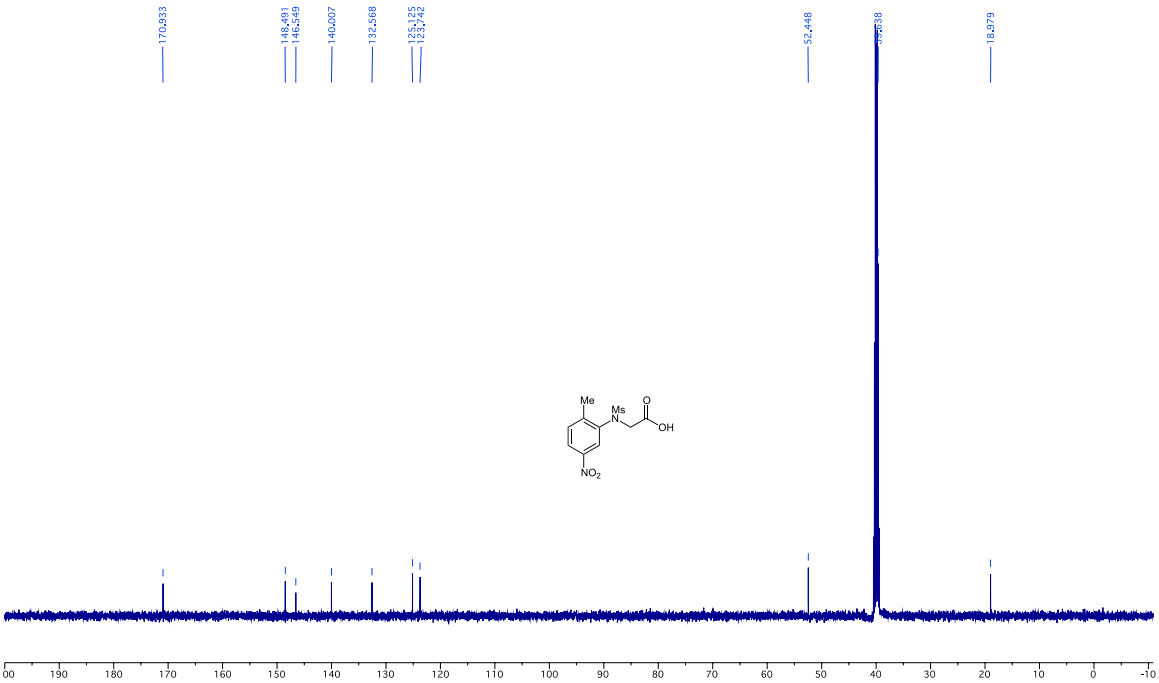

$^{13}C$ NMR spectrum of **100**



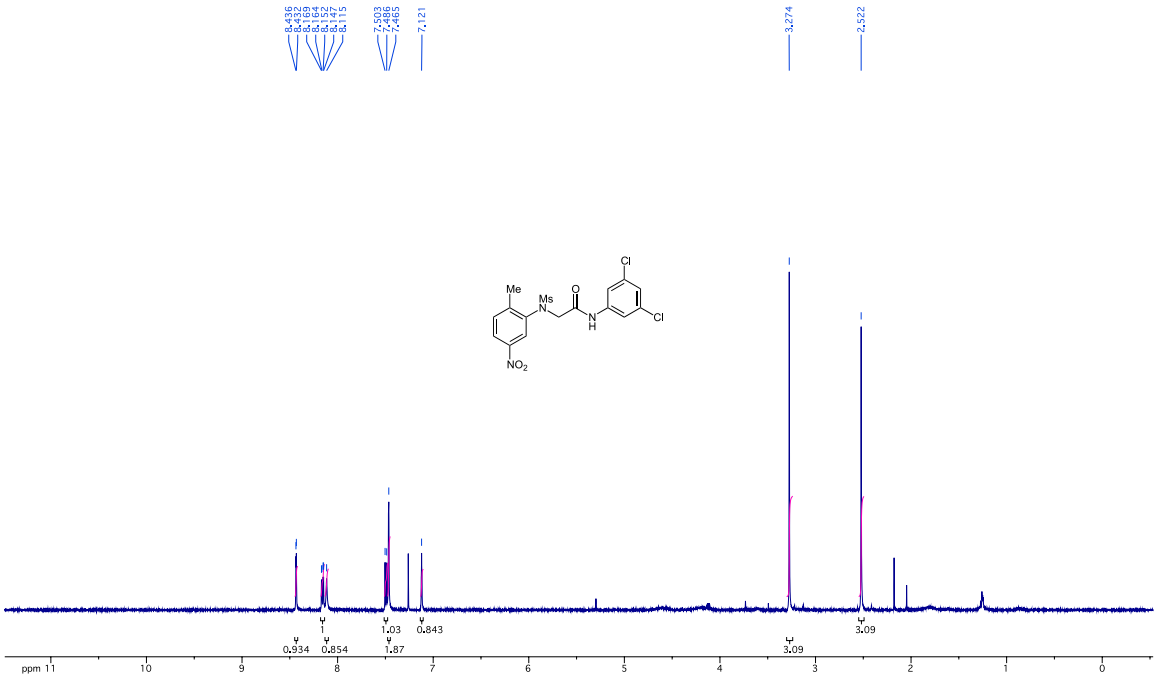
$^{1}$H NMR spectrum of **101**



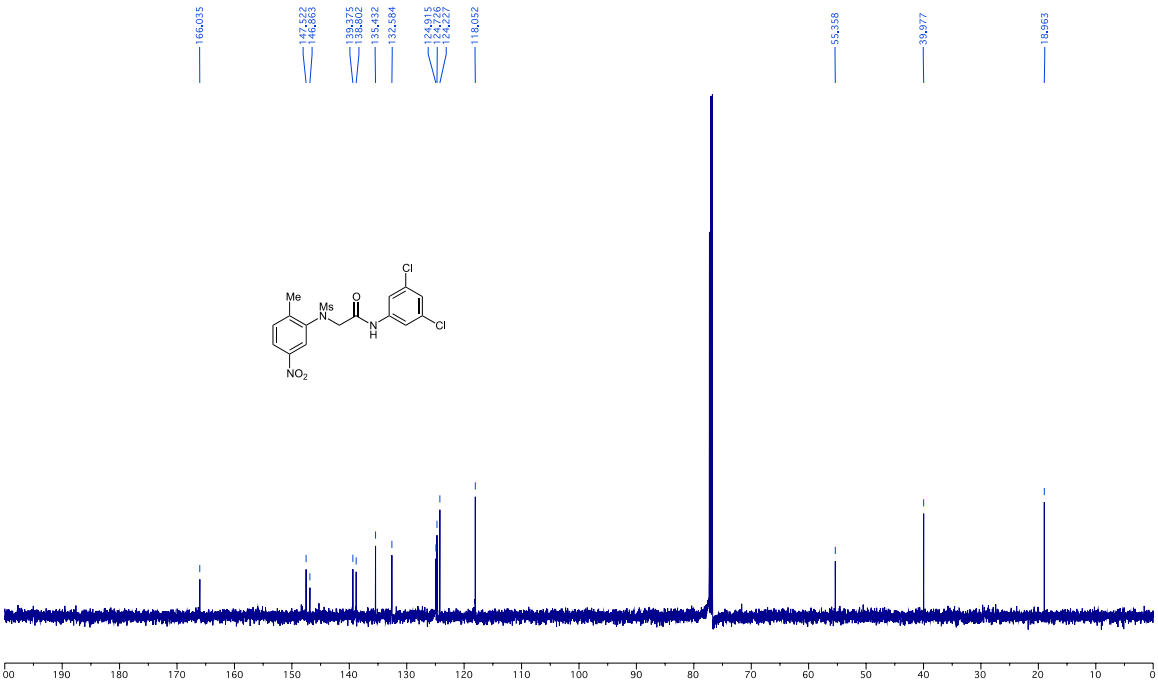

$^{13}$C NMR spectrum of **101**



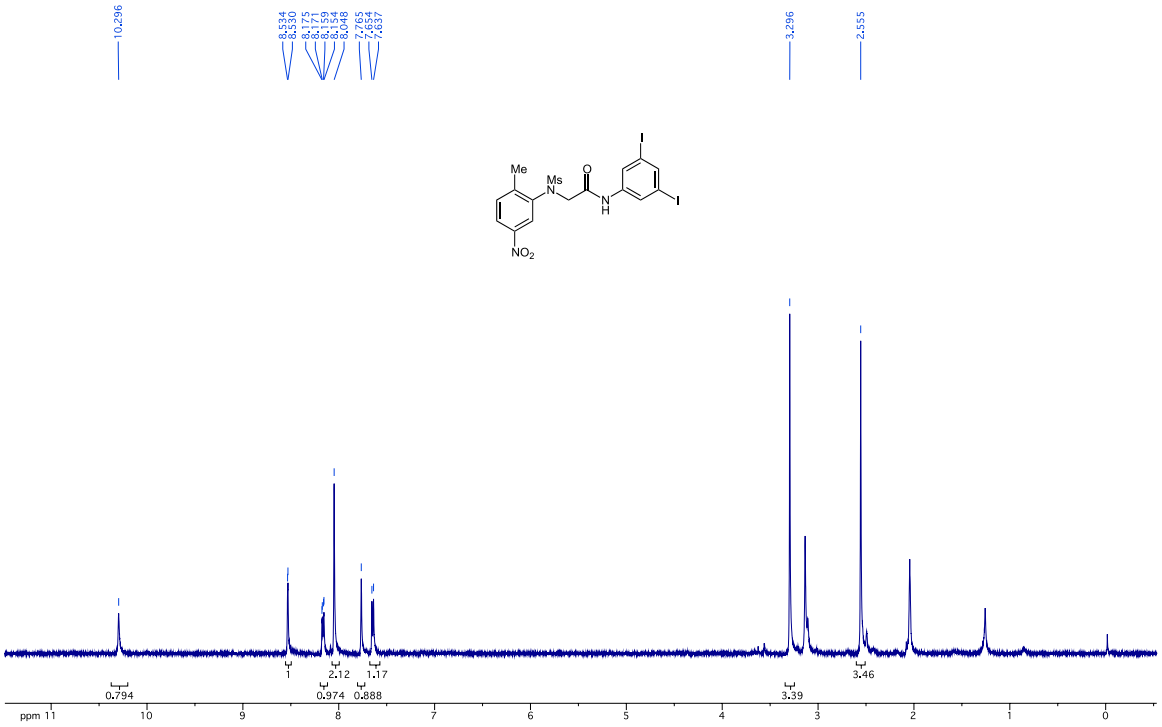
$^{1}$H NMR spectrum of **98b**



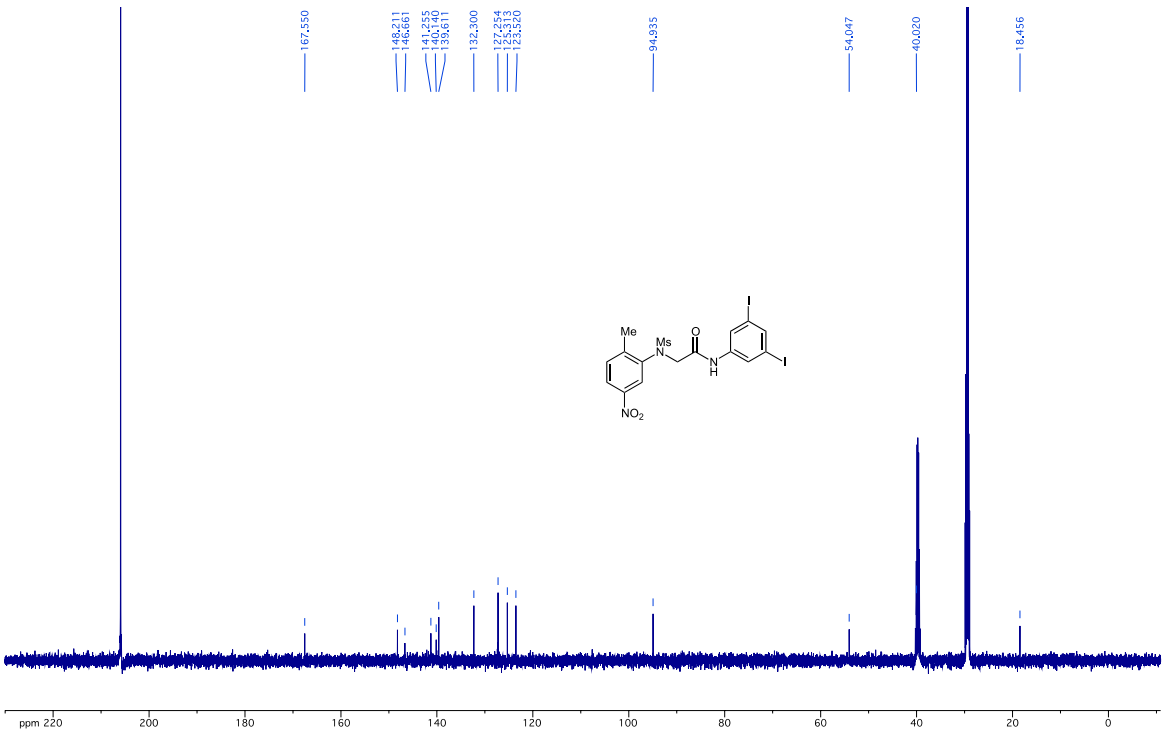

$^{13}$C NMR spectrum of **98b**



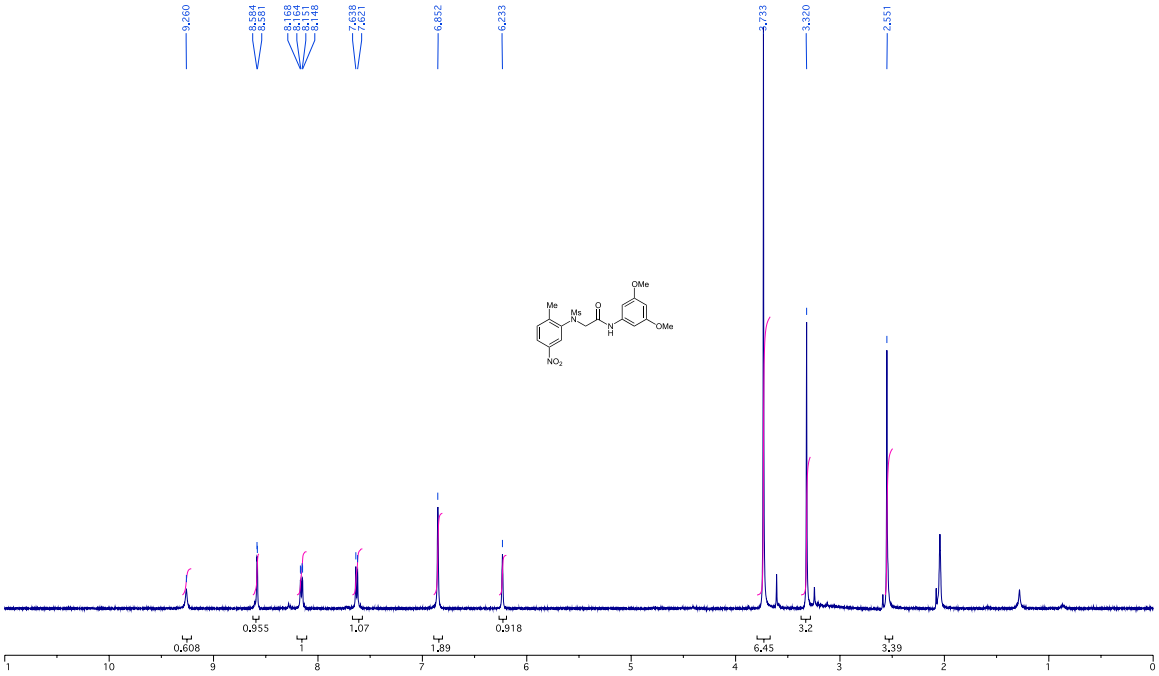
$^{1}$H NMR spectrum of **98c**



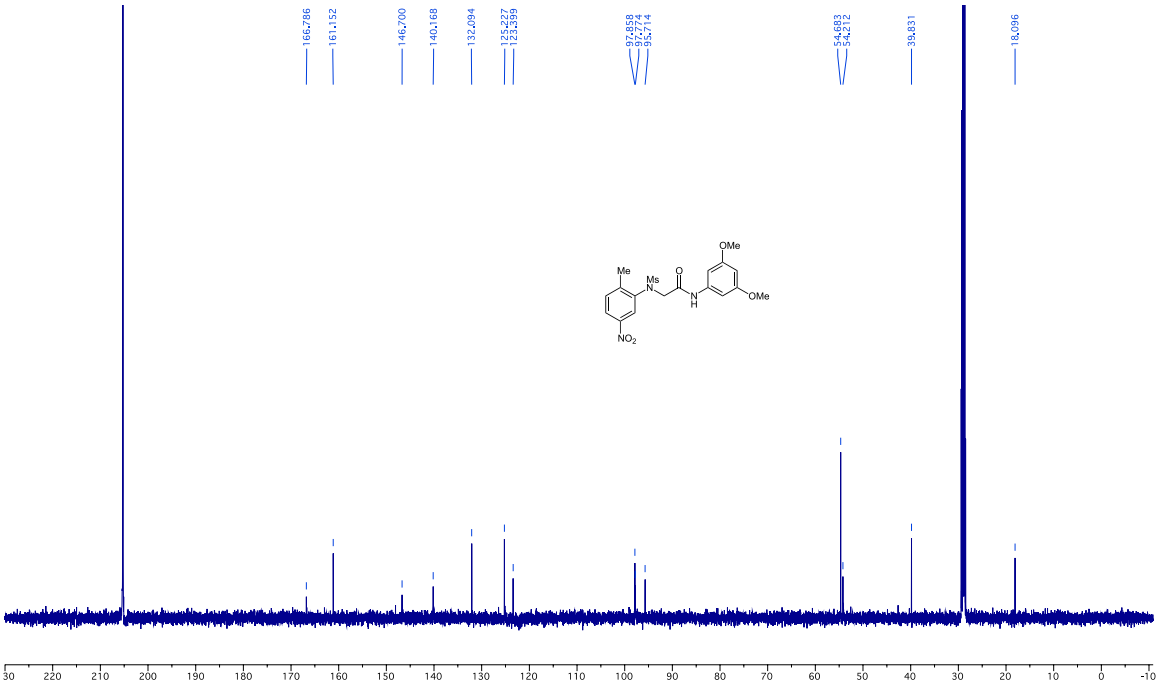

$^{13}$C NMR spectrum of **98c**



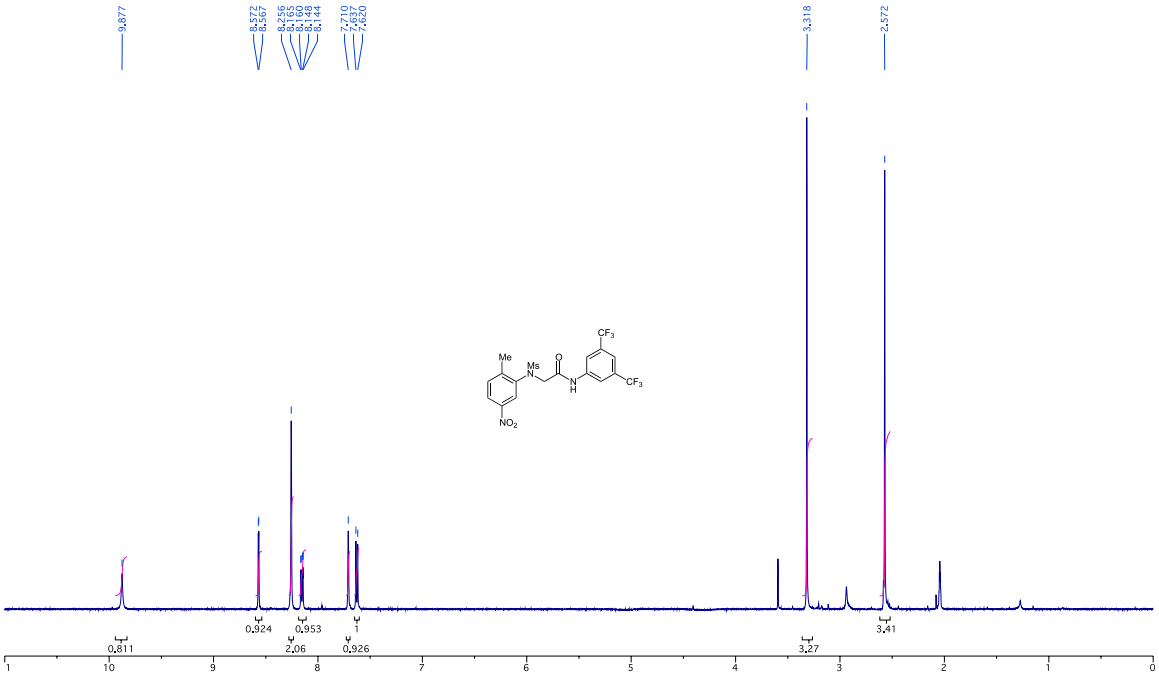
$^{1}$H NMR spectrum of **98d**



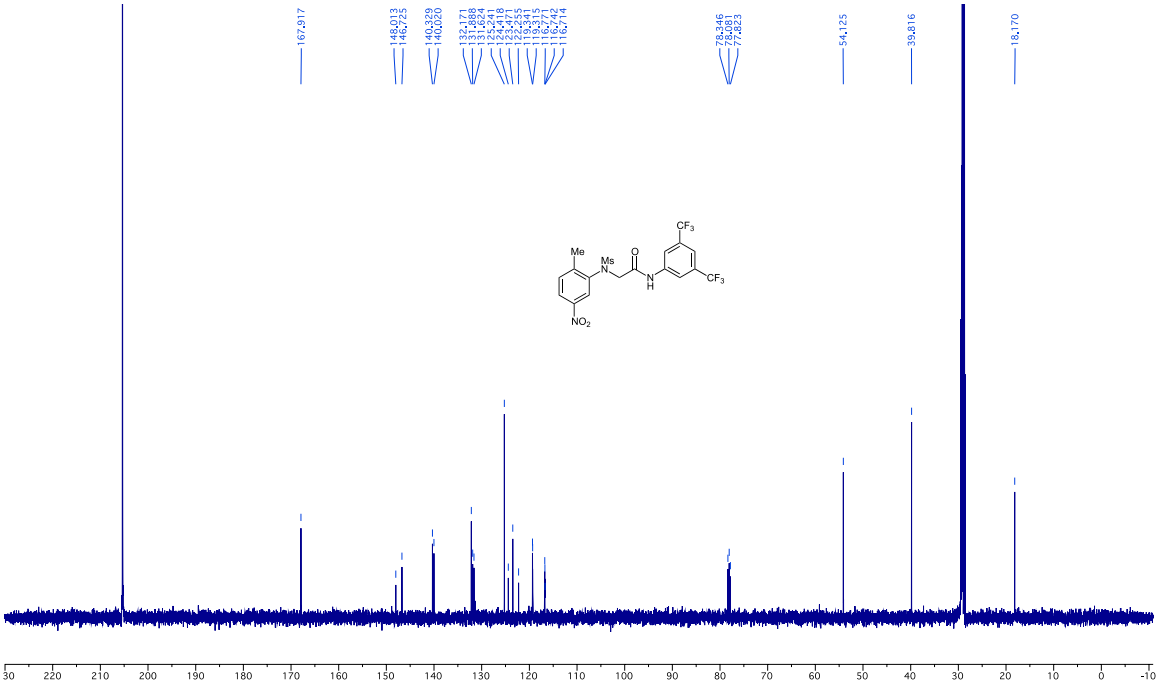

$^{13}$C NMR spectrum of **98d**



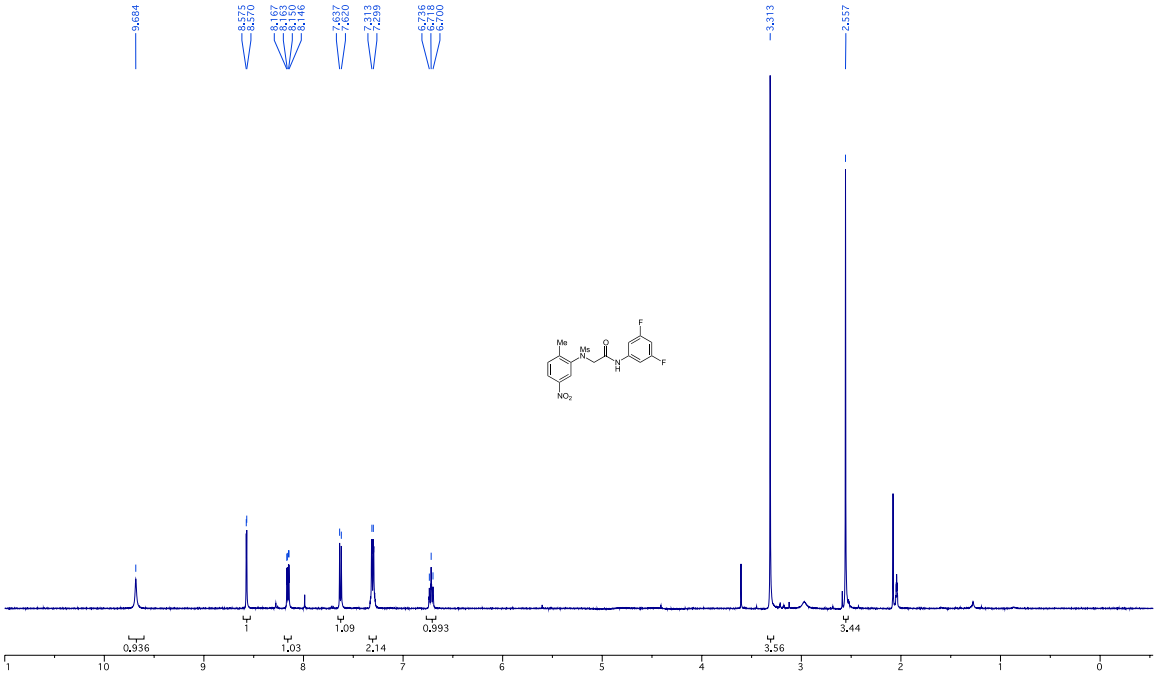
$^{1}$H NMR spectrum of **98e**



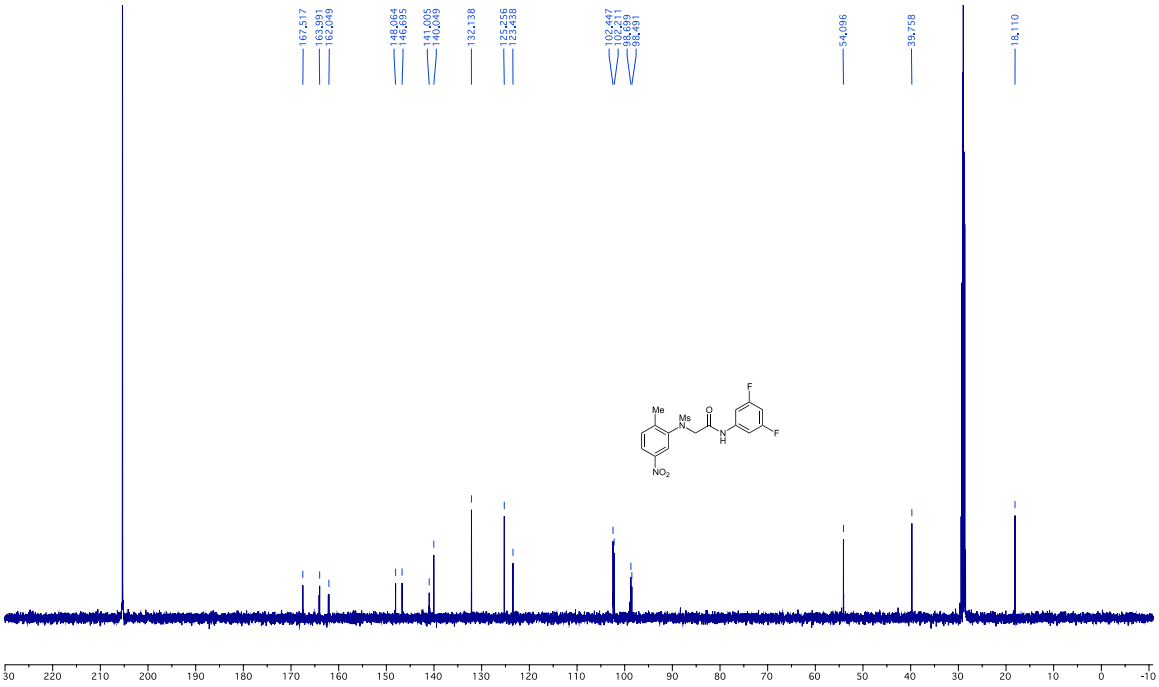

$^{13}$C NMR spectrum of **98e**



$^{1}$H NMR spectrum of **98f**




$^{13}$C NMR spectrum of **98f**



# VITA

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PUBLICATIONS: "Cu-Catalyzed Transannulation Reaction of Pyridotriazoles with Terminal Alkynes Under Aerobic Conditions: Efficient Synthesis of Indolizines" Helan, V.; Gulevich, A.V.; Gevorgyan, V. *Chem. Sci.* **2015**, *6*, 1928

"Pyridine Group Assisted Addition of Diazo-Compounds to Imines in the 3-CC Reaction of 2-Aminopyridines, Aldehydes, and Diazo-Compounds" Gulevich, A. V.; Helan, V; Wink, D. J.; Gevorgyan, V. *Org. Lett.* **2013**, *15*, 956

"A Rapid Three-Component $MgI_2$ Mediated Synthesis of 3,3-Pyrollidinyl-spirooxindoles" Helan,V.; Mills, A.; Drewry, D.; Grant, D. *J. Org. Chem.* **2010**, *75*, 6693

PRESENTATIONS: "Design of a Green Methodology: Efficient Synthesis of Indolizines" at GWIS-Chicago Chapter 2nd Science Talks (September **2016**, Chicago, IL) Helan, V. (talk)

"Cu-Catalyzed Transannulation Reaction of Pyridotriazoles with Terminal Alkynes Under Aerobic Conditions: Efficient Synthesis of Indolizines" at 252nd ACS National Meeting (August **2016**, Philadelphia, PA) and at 7th Negishi-Bown lectures (October **2014**, Purdue University, West Lafayette, IN). Helan, V.; Gulevich, A. V.; Gevorgyan, V. (poster)

"Pyridine Group Assisted Addition of Diazo-Compounds to Imines in the 3-CC Reactionof 2-Aminopyridines, Aldehydes, and Diazo-Compounds" 6th Negishi-Brown lectures (October **2013**, Purdue University, West Lafayette, IN). Gulevich, A. V.; Helan, V.; Wink, D. J.; Gevorgyan, V. (poster)