Development of Novel Methodologies for the Syntheses of Biologically Relevant Nitrogen-Heterocycles

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Printed with the support of the German Academic Exchange Service (DAAD)

Dedicated to my Family…

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1. Recent Advances of the Povarov Reaction

1.1 Introduction

One of the major challenges in modern organic synthesis is to develop highly selective methodologies affording efficient and rapid access to biologically important molecules or the scaffolds which are found as the privileged structure in natural product and pharmaceutical developments. In this regard, the Povarov reaction, which was developed in 1960s by the Russian Scientist L. S. Povarov, can be considered as one of the most powerful strategies for synthesizing a certain class of ubiquitous nitrogen heterocycles.

Since the pioneering work of Povarov and co-workers,[1–6] significant research interest was attracted and enormous efforts have been implicated in this particular research area to obtain more efficient synthetic routes to directly access tetrahydroquinolines and other interesting heterocyclic scaffolds employing Povarov reaction as the key step. There are a lot of publications coming out each year on this particular topic, providing detail mechanistic insights and discovering novel synthetic applications; therefore, it is justified to summarize the recent advances of the Povarov reaction in a definite time interval. The field was previously reviewed by Kouznetsov,[7] covering the literature up to mid-2008, which mainly focused on the various applications of Povarov reaction, especially, the multi-component coupling strategy allowing a straightforward access to various heterocycles, giving a special attention to environment-friendly methodologies. In 2011, a general review was published on the chemistry of tetrahydroquinoline synthesis, in which some space was also devoted to the Povarov reaction as a tool for synthesizing tetrahydroquinolines and covered the literature up to mid-2010.[8] After this period there have been much more advances carried out concerning especially the mechanistic aspects as well as the asymmetric variations of the Povarov reaction.

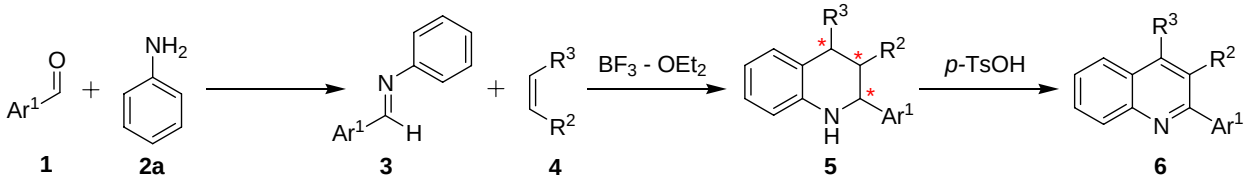
In this present review, we have made an effort to briefly include the critical advances of the Povarov reaction from 2008 to 2012, particularly in light of the detail mechanistic studies, asymmetric variations using various organo-catalysts, giving a special emphasis on the

utilization of Povarov reaction as a key step for creating more complex and diversified molecules by means of choosing appropriate starting materials having multiple functionalities.

1.2 Historical Background of the Povarov reaction

The Povarov reaction was originally reported in 1963 as a one-pot reaction of arylaldimines **3**, derived from condensation of aromatic aldehydes **1** and aniline **2a** with electron-rich olefins, I particular, ethyl vinyl ether **4a** or ethyl vinyl sulfide **4b** in presence of BF_3/OEt_2 as a Lewis acid (LA) catalyst to obtain 2,4-disubstituted tetrahydroquinolines **5a/5b** which were further oxidized to the corresponding quinolines **6a/6b** (Scheme 1.1). The reaction can be considered as a powerful tool for generating three contiguous stereogenic-centers in a single step with an excellent regioselectivity. After almost three decades of Povarov's original work, the reaction was upgraded into a one-pot, multicomponent reaction (MCR), in which the aldimine was generated *in situ*.[9]

Scheme 1.1. Original Protocol of Lewis-Acid Catalyzed One-Pot Povarov Reaction



1 **2a** **3** **4** **5** **6**

R^3 = OR (**4a/ 5a/ 6a**)
= SR (**4b/ 5b/ 6b**)

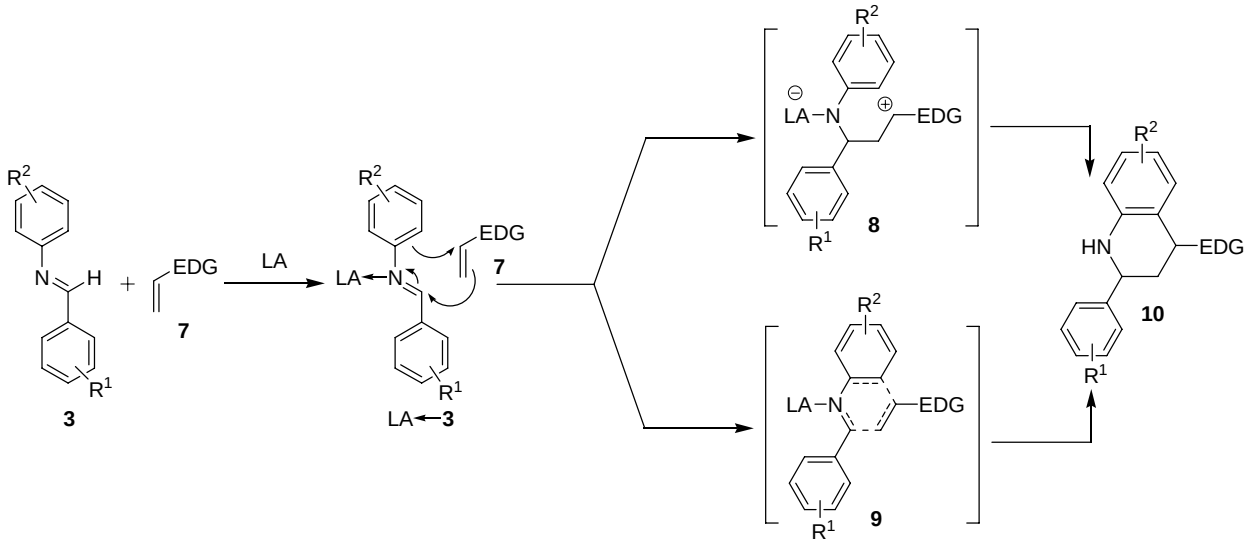
The Povarov reaction can be catalyzed by a variety of reagents, including LAs, Brønsted acids (BAs) and various metal salts. In recent years, catalytic multicomponent version of inter- and intramolecular Povarov reactions have emerged as potential tools in both diversity- and target-oriented syntheses due to the time and step economic aspects. Asymmetric variants of the reaction have also been achieved with a great success, leading to the synthesis of enantiomerically pure tetrahydroquinolines in presence of chiral catalysts. Moreover, the reaction offers a huge variation in substrate selection with respect to the dienes and more importantly, various nucleophilic olefins having multiple functionalities as the dienophilic components. Now-

a-days, syntheses of complex heterocyclic scaffolds, utilizing Povarov reaction as the key step have become an attractive alternative route towards the creation of novel heterocycles.

1.3 Mechanistic Overview

The mechanism of Povarov reaction has been debated for a long time; historically, it was proposed as a concerted, formal [4π+2π]-type inverse electron-demand aza-Diels-Alder reaction. Although, theoretical calculations show that the reaction can proceed through both concerted and stepwise pathways depending on the nature of the solvent[10] and dienophiles used.[11] When, the dienophile is polarized in nature, the reaction is assumed to take place in a stepwise fashion[12] through the initial formation of the imine **3** by condensation of aldehyde and aniline. Once the imine is activated by LA catalyst, it can readily undergo nucleophilic attack by the electron-rich olefin **7** via the well established Mannich-type reaction to give a cationic intermediate **8**. Once the intermediate **8** is formed, it can be trapped by the aromatic ring of the aniline moiety via an intramolecular electrophilic substitution to produce the tetrahydroquinoline derivative **10** (Scheme 1.2)[13,14]

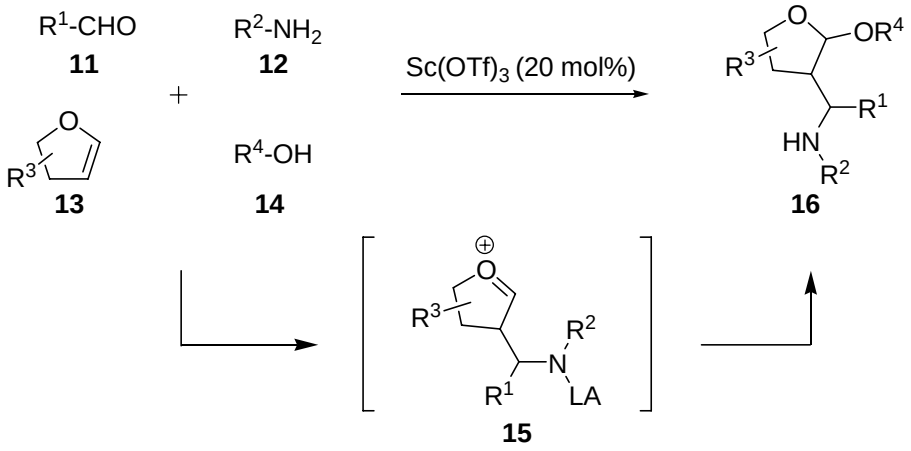
Scheme 1.2. Mechanistic Aspects of the Povarov Reaction: Stepwise Mechanism Leads over the Concerted One



Moreover, this mechanistic assumption could open up the possibility to trap the reactive cationic intermediate **8** by employing an external nucleophile and thus the final ring-closure step could be

terminated affording an acyclic compound rather than the usual cyclic tetrahydroquinoline scaffold. In this context, there are several recent evidences which could well demonstrate the reliability of this stepwise mechanism taking into account the feasible trapping of the ionic intermediate **8**, enabling the possibility of a four component reaction,[12,15a] e.g., Lavilla and co-workers elegantly exploited a LA-catalyzed four-component Povarov reaction of Aldehydes **11**, amines **12**, cyclic enol ethers **13** and alcohols **14**, where the alcohol acts as an external nucleophile or terminator of the Povarov process, trapping the final oxocarbonium intermediate **15**, leading to the formation of a new compound **16** (Scheme 1.3).[15a]

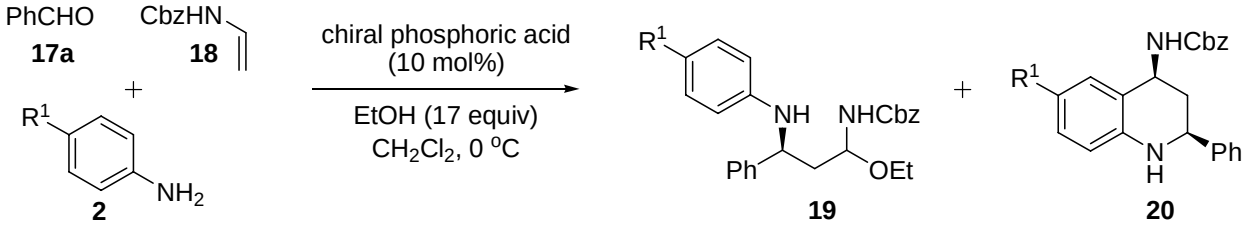
Scheme 1.3. Four-Component Povarov Reaction Using Alcohols 14 as the Terminators



More recently, Masson and Zhu have reported a detailed mechanistic study on three component Povarov reaction, where they have speculated, depending on the polarized nature of the enecarbamate double bond of the dienophile **18**, a stepwise mechanism could be initiated by the Mannich-type reaction. They were able to trap the *N*-acyliminium intermediate generated after the Mannich-type reaction by an alcohol as an external nucleophile. Utilization of benzaldehyde **17a** and 4-methoxyaniline as the aldehyde and amine components respectively in presence of the dienophile **18** and Povarov terminator, EtOH (17 equivalent) afforded the Mannich adduct **19** in 21% yield, together with the tetrahydroquinoline **20** (50%) as the major product. With electron-deficient anilines such as 4-nitroaniline, they could only isolate the Mannich adduct **19** in 72% yield, at the expense of the Povarov product **20** (Scheme 1.4). These results provided direct evidence in support of a stepwise mechanism for catalytic Povarov reaction.[12] In addition, Alves

and co-workers showed that the cycloaddition of glyoxylate imines **21** with *trans*-1,3-dienes produce only a specific diastereomer of the tetrahydroquinoline derivatives **25** with an excellent

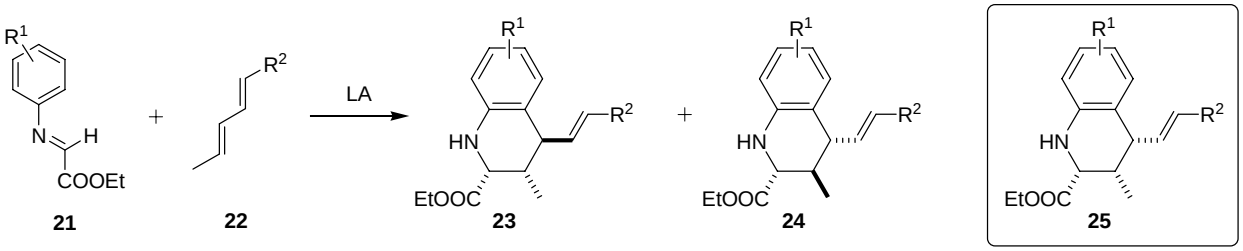
Scheme 1.4. Interrupted Povarov Reaction Leading to Mannich-Type Product 19 as the Major product



$R^1 = NO_2$, **19** = 72%, **20** = 0%
R^1 = OMe, **19** = 21%, **20** = 50%

regio- and stereoselectivity instead of a mixture of **23** and **24** which is also in accord with a stepwise reaction mechanism (Scheme 1.5).[14d]

Scheme 1.5. *Trans*-Dienes in Povarov Reaction Affording a Single Diastereomer 25 Instead of 23 and 24



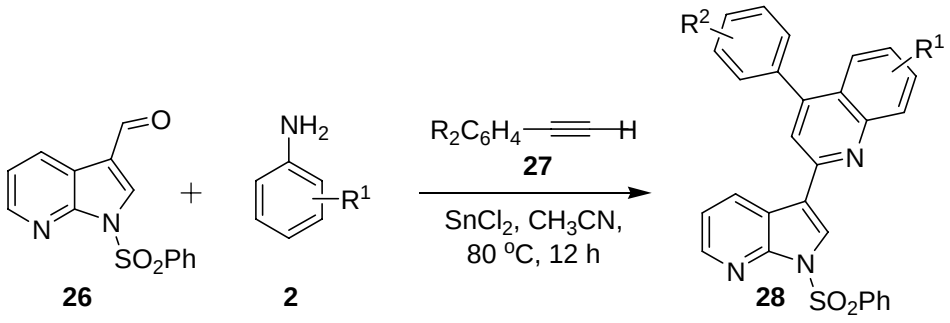
However, there are some experimental evidences indeed, which support the concerted mechanism too,[16] e.g., Lucchini and co-workers showed that depending on the solvent polarity the reaction of tetrahydrofuran and electron-poor imines in presence of BF_3-Et_2O, can proceed either through a concerted or a stepwise mechanism; as in general, an aprotic solvent allows the formation of a transition state and hence allows a concerted mechanism, while a protic solvent stabilizes an ionic intermediate and hence the reaction can proceed through a stepwise pathway.[10] In spite of the presence of a few evidences in support of concerted mechanism, exhaustive recent investigations strongly support only a stepwise mechanism for the Povarov-type reaction.

1.4 Various Catalysts Used for Povarov Reaction

1.4.1 Lewis Acid (LA)-Catalyzed Povarov Reaction

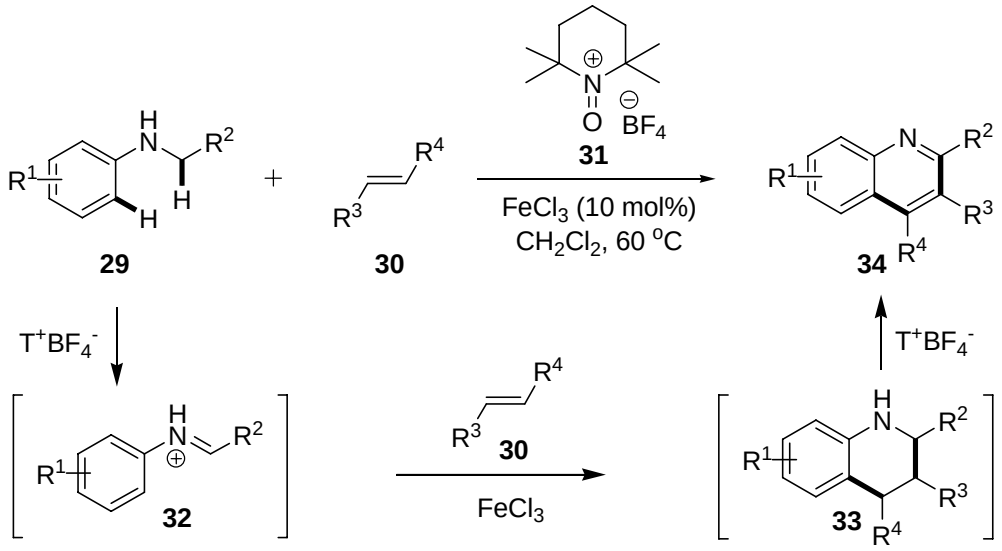
Since the pioneering work of Povarov, who used BF_3/Et_2O as the catalyst, several other LAs have been used for the Povarov reaction till to date. However, many of them are not fully satisfactory with regard to operational simplicity, isolated yields and restricted to mainly specific substrates. In 1967, Hagihara showed that quinoline derivatives could be synthesized utilizing dicobalt octacarbonyl as the catalyst instead of BF_3/Et_2O.[17] Remarkably, Kobayashi and co-workers introduced lanthanide(III) triflates as excellent catalysts for three-component Povarov reaction between *N*-aryl aldimines and alkenes,[18] potentially replacing the stoichiometric use of other LAs. Due to the smaller ionic radii of lanthanide(III) triflates they are more effective towards Lewis bases such as imines. Moreover, the formation of the reactive adduct (LA-imine) between lanthanide(III) and Lewis base becomes more facile due to strong electron withdrawing power of triflate counter anions. However, Xia and Lu recently showed that molecular iodine can also be used as an inexpensive and readily available catalyst for the one-pot Povarov reaction.[19] This might be considered as a pivotal advancement from the point of view of toxic-metal free catalyst developement. Muthusubramanian and co-workers reported an efficient, one-pot synthesis of a range of azaindole substituted quinoline derivatives **28** by Povarov reaction in good yields and diastereoselectivity using inexpensive and readily available $SnCl_2$ as a Lewis acid catalyst (Scheme 1.6).[20] The reaction has been found to be chemo- and regioselective with good atom economy.

Scheme 1.6. $SnCl_2$-Ctalyzed Three-Component Povarov Reaction



Use of TMSCl (20 mol%)[21] and commercially available, inexpensive phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$)[22] as catalysts also provide an access to various furo- or pyranoquinolines with aliphatic, furyl- or thionyl-moieties in excellent yields. Masaki and coworkers developed a polymer-supported π-acid (poly-DCKA-1) catalyst for the two- and three-component imino DA reactions to give pyrano[3,2-c]quinolines at room temperature in water.[23] Thus use of water as a solvent from the point of view of green chemistry shows promising development for certain substrates and further development of solid-supported catalyst brings possibility of easy catalyst handing and reuses. Recently, Menéndez et al. reported CAN-catalyzed reaction of 3,5-disubstituted anilines, vinyl ethers and aromatic aldehydes leading to trans-2-aryl-4-arylaminotetrahydroquinolines.[24] In many cases, Povarov reaction is followed by an oxidation step to form the corresponding quinoline derivatives. This important oxidation step involves a formal removal of four hydrogen atoms from the tetrahydroquinoline intermediate. In general, harsh conditions or large amounts (e.g., MnO_2) of expensive (e.g., Pd-based) or toxic oxidants (e.g., DDQ, nitrobenzene, etc.) are required to successfully furnish this conversion. As a result, introduction of more efficient and environmentally benign oxidants for this transformation is highly desirable. In this context, synthesis of quinolines **34** from *N*-alkyl anilines **29** and olefins **30** via a one-pot Povarov reaction followed by oxidation reaction using a TEMPO salt ($T^+BF_4^-$) (**31**) as a highly efficient, mild and nontoxic oxidant is important (Scheme 1.7).[25]

Scheme 1.7. TEMPO Oxonium Salt (31)-Mediated Povarov Reaction

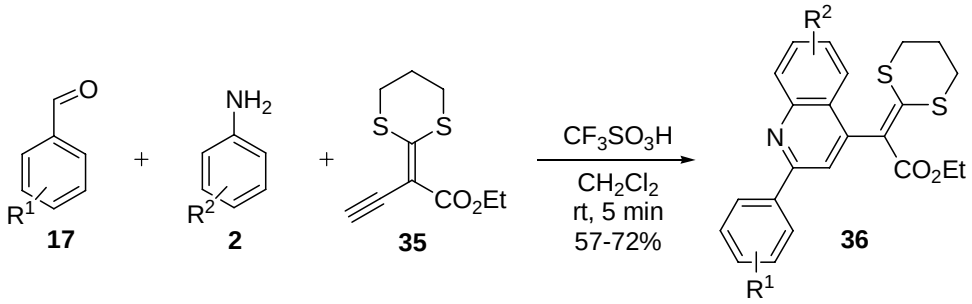


This reaction can also be considered as an alternative method for preparing *N*-aryl iminium cation **32** via TEMPO-mediated dehydrogenative coupling reaction. The main advantage of using this catalytic system is its moisture tolerance and hence the reaction can be performed under aerobic conditions maintaining the same level of efficiency.

1.4.2 Brønsted Acid-Catalyzed Povarov Reaction

In addition to LAs, several Brønsted acids are also known to catalyze the Povarov reactions, e.g.; the three component reaction of aromatic aldehydes **17**, anilines **2** and enynes **35** to synthesize 4-substituted quinolines **36**, reported by Zhao and Liu is noteworthy (Scheme 1.8).[26] Legros et al. reported the use of fluorinated alcohols e.g. trifluoroethanol, TFE or hexafluoroisopropanol (HFIP) as both solvent as well as catalyst for three-component Povarov reaction.[27]

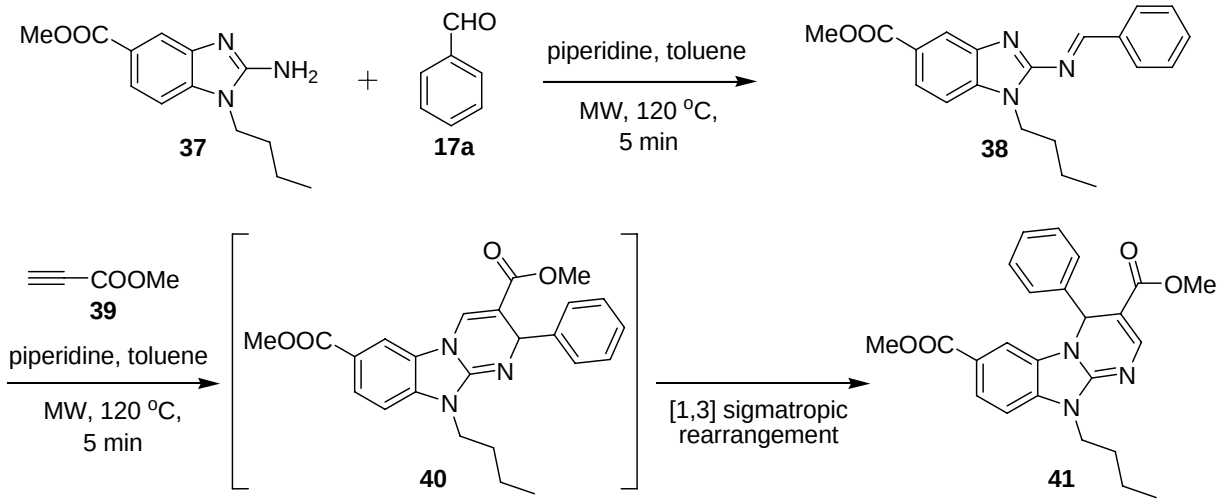
Scheme 1.8. Brønsted Acid-Catalyzed Three Component Povarov Reaction: Application of Ethynyl Ketene-*S*,*S*-Acetals as Highly Electron-Rich Dienophiles



1.4.3 Base-Catalyzed Povarov Reaction

Although, the Povarov cycloaddition reaction is well-established as an acid-catalyzed cycloaddition reaction of electron-rich dienophiles and *N*-arylimines, Sun et al. reported an unprecedented microwave (MW)-assisted base-catalyzed Povarov reaction of electron-deficient alkylpropiolates **39** followed by a [1,3]sigmatropic rearrangement to produce a small library of dihydropyrimido[1,2-a]benzimidazole **41** (Scheme 1.9).[28a]

Scheme 1.9. Syntheses of Dihydropyrimidobenzimidazoles 41 via Base-Catalyzed Povarov Reaction

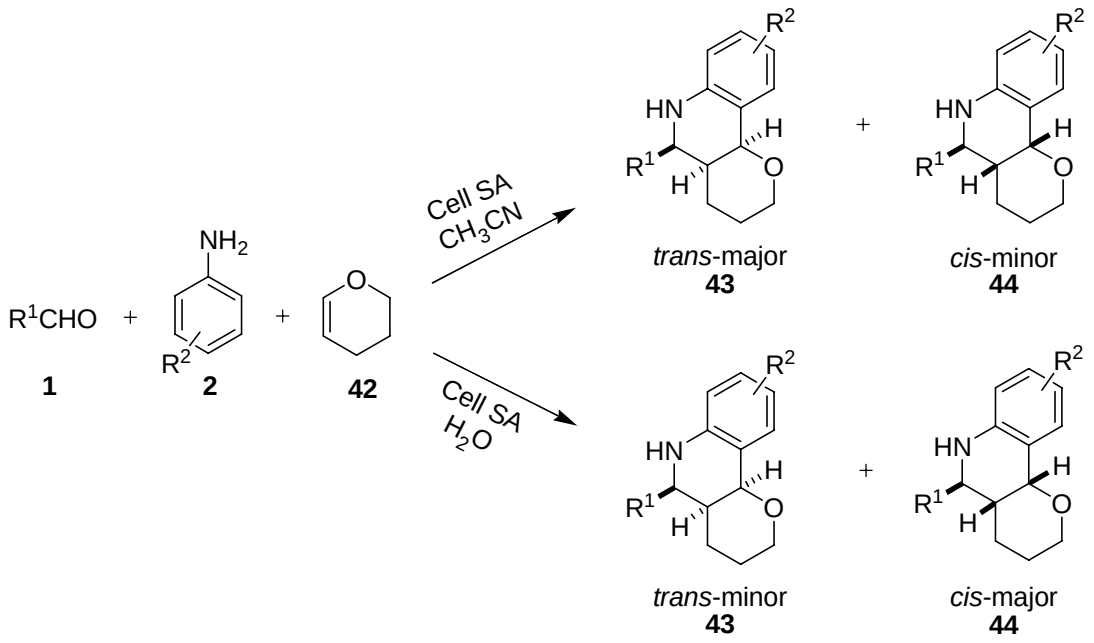


1.4.4 Green Catalysts Used for Povarov Reaction

As we discussed, many of the previous methods utilizes metals or other undesired chemical species into the "environment" during the course of the reaction. Now-a-days, the concept of green chemistry[29] encourages chemists to develop new synthetic method using a safer and non-waste-producing alternative catalyst. Solid acid catalysts are not only environment-friendly but also have many economic advantages.[30] Acidic cation-exchange resins have been used as solid acid catalysts in many fields,[31] including the Povarov reaction, e.g.; in 2003, Li et al. reported an acidic cation-exchange resin (AG® 50W-X2)-catalyzed Povarov reaction of aromatic amines and 3,4-dihydro-2*H*-pyran for the synthesis of tetrahydroquinoline derivatives in water. In all the cases they obtained a mixture of *cis*- and *trans*-diastereomers but, unlike the reactions using LA catalysts, which produce heavy metal or acid pollution, the use of the solid, AG®50W-X2 resin as the catalyst gave rise to a cleaner recyclable procedure.[32] Another interesting approach in this regard is the utilization of natural biopolymers, e.g.; cellulose and starch as solid supported catalysts from renewable resources. The unique biodegradability and cost-effectiveness accomplish these materials as effective catalysts when converted to their sulfonic acid derivatives. In this regard, utilization of cellulose sulphuric acid as an efficient eco-friendly, reusable catalyst for the diversity oriented synthesis of anti-tubercular tetrahydroquinolines via Povarov reaction presents an alternative environment-friendly procedure.[33] The products were obtained as

a mixture of *cis*- and *trans*-isomers with a preference to the *trans*-isomer **43**, but interestingly, when the reaction was carried out in aqueous medium the *cis*-isomer **44** became the major product (Scheme 1.10).

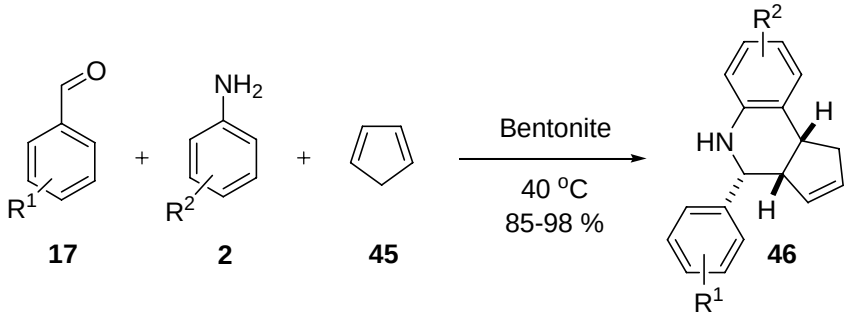
Scheme 1.10. Sulfonated Cellulose-Catalyzed Multi-Component Povarov Reaction



1.4.5 Use of Heterogeneous Catalysis for the Povarov Reaction

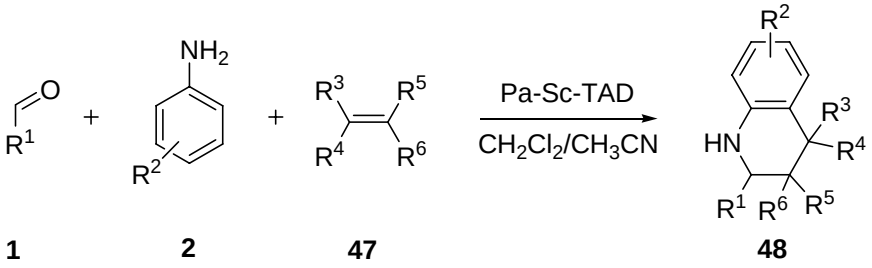
Although, homogeneous catalysts are much more reactive compared to the traditional heterogeneous catalysts, the major drawback of homogeneous catalysis is the difficulty of their recovery from the reaction medium. Recovery of the homogeneous catalyst often needs energy consuming precipitation or distillation of the products which may lead to the deactivation of the catalyst. In this regard, the use of heterogeneous catalysts is always advantageous from both environmental and economical points of view due to its efficient recycling and easy handling. However, there are only a few reports of Povarov MCR using heterogeneous catalysts known till date. For example, Sartori et al. reported a one-pot three component reaction of aromatic aldehydes **17**, aromatic amines **2** and cyclopentadiene **45** in the presence of acid clays as catalysts for the synthesis of cyclopentanetrahydroquinolines **46** in good yields (85–98%) (Scheme 1.11).[34]

Scheme 1.11. Solid Supported Bentonite-Catalyzed Three Component Povarov Reaction



Montmorillonite KSF, acid Bentonite Bieliaca, and Hectorite are efficient catalysts to carry out this one-pot approach, Bentonite Bieliaca being the most efficient catalyst which could be used for five consecutive runs without reducing its efficiency. In all cases the reactions were regio- and stereospecific yielding exclusively the *endo*-product. Kobayashi et al. reported efficient synthesis of various tetrahydroquinoline derivatives **48** in 65-99% yield using a polymer supported scandium catalyst, [(polyallyl)scandium trifylamide ditriflate], (PA-Sc-TAD) (Scheme 1.12).[35]

Scheme 1.12. Solid Supported Sc-Catalyzed Three Component Povarov Reaction



The method is especially useful for the construction of a library of quinoline derivatives due to the high efficiency and simplicity of the process. Recently, it has been reported that Brønsted and solid Lewis acids such as antimony chloride doped on hydroxyapatite ($SbCl_3$-HAP),[36] perchloric acid adsorbed on silica gel ($HClO_4$–SiO_2)[37] Fe^{3+}–K10 Montmorillonite clay and HY zeolite[38] are highly efficient and diastereoselective solid acid catalysts for the one-pot synthesis of pyrano- and furanoquinolines by coupling the three components, benzaldehydes, anilines and 3,4-

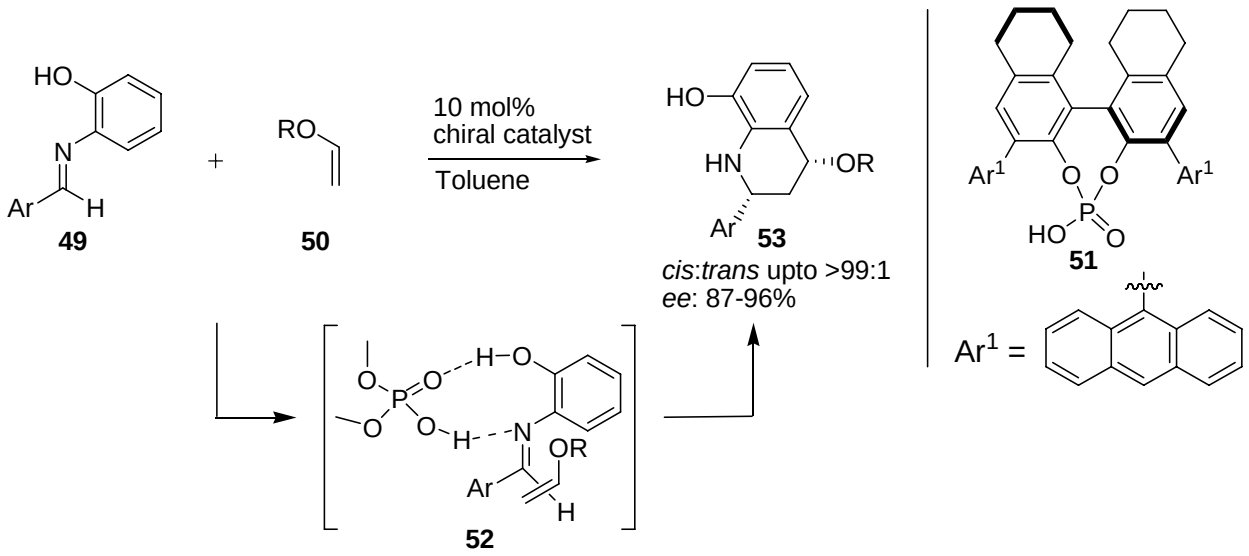
dihydro-2H-pyran or 3,4-dihydro-2H-furan. Although, all of these methods are apparently exciting but often suffer from tedious multi-filtration processes.

1.5 Enantioselective Three-Component Povarov Reactions

Despite of the high potential of constructing functionalized, enantioenriched six-membered cyclic compounds from relatively simple substrates, only a handful of examples describing catalytic asymmetric Povarov reactions have been reported.[39-41] Most of the available methods make use of vinylethers or cyclopentadiene (Grieco cycloaddition) as dienophiles, often in combination with chelating *N*-2-hydroxyphenyl imines activated by chiral Lewis or Brønsted acids.[40a-40c] The limited range of dienophiles, together with the requirement of a specific aryl group at the imine nitrogen in some cases, pose serious limitations to the structural variety of accessible 1,2,3,4-tetrahydroquinolines. Only very recently, the range of dienophilic components was extended to enecarbamates, in a very efficient way. In 1996, the first catalytic asymmetric IEDDA reaction was reported by Kobayashi and Ishitani using chiral binaphthol–ytterbium complexes.[42a] Subsequently, aminodiol–titanium complexes[42b] and chiral phosphoric acids[43,41] have been developed for the stereoselective IEDDA reactions. Although, there are a lot of examples of enantioselective transition metal-catalyzed MC Povarov reactions, metal contamination being highly undesirable for drug synthesis; the application of organocatalysis is highly recommended. Use of chiral phosphoric acids as the efficient catalysts for numerous enantioselective transformation including the Povarov-type reaction was first introduced by the group of Akiyama and Terada,[44] These bifunctional catalysts are generally known to cooperatively activate both the electrophilic imine and the nucleophileic olefin via H-bonding to introduce high enantioselectivities. The first chiral Brønsted acid (**51**)-catalyzed enantioselective Povarov reaction of azabutadiene **49** and electron-rich alkenes **50** was reported by Akiyama et al., leading to tetrahydroquinolines **53** with high enantioselectivity (Scheme 1.13).[43a] They proposed that the reaction proceed through the formation of a nine-membered cyclic transition state **52**, wherein the phosphoryl- oxygen forms a hydrogen bond with the hydrogen of the imine OH moiety, allowing the nucleophilic attack, preferentially from the *re*-face of the imine and

hence a concerted mechanism was proposed in turn. Great breakthroughs in reactivity and enantioselectivity has also been acheived with vinylethers,[41] vinylindoles[45] and enecarbamates[12] as dienophiles.

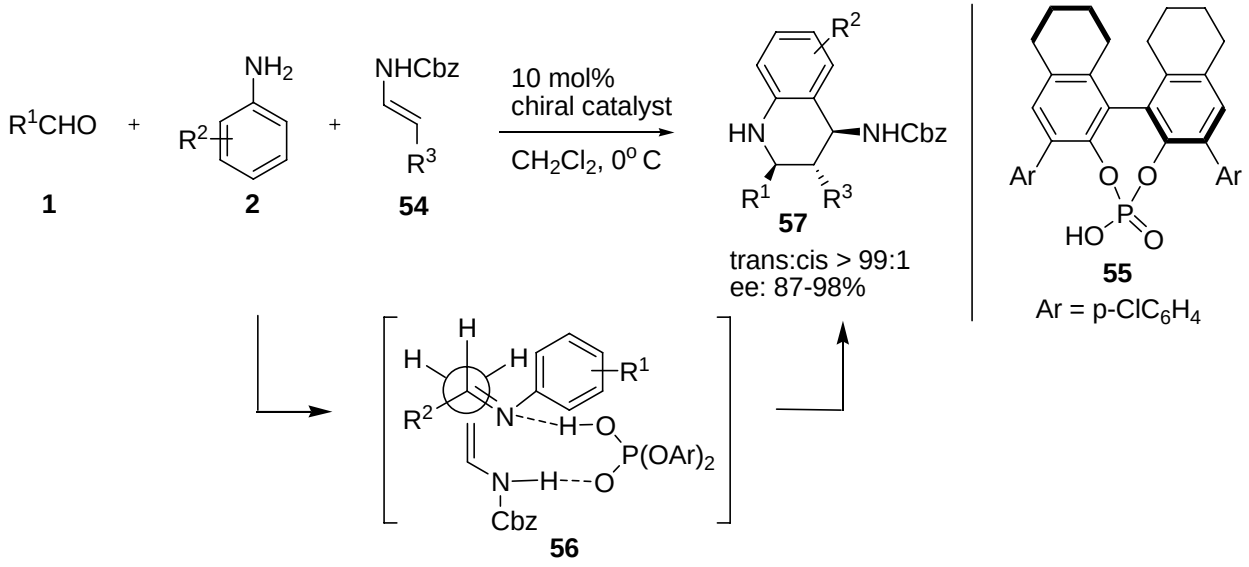
Scheme 1.13. Chiral Phosphoric Acid (51)-Catalyzed Povarov Reaction of Aldimines 6 with Vinyl Ethers 50



In 2011, Masson and Zhu reported chiral phosphoric acid (**55**)-catalyzed, highly enantioselective three-component Povarov reaction with a reversal of enantiofacial selectivity (via the transition state **56**) (Scheme 1.14) relative to Akiyama's catalytic system.[12]

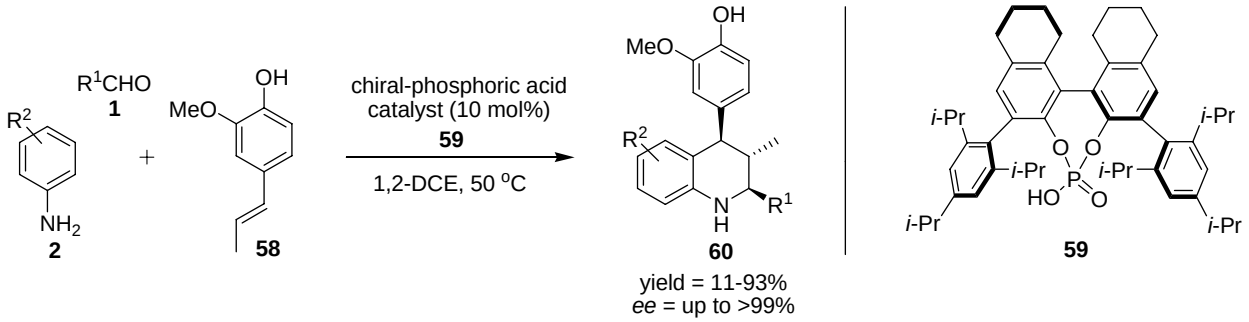
BINOL-phosphoric acid catalysts have been extensively used for Povarov reactions using imines. Because of the generality of this catalyst, it is highly desirable to rationalize the facts behind its mechanism of action. Recently, Simón and Goodmann developed a model, based on DFT calculations for describing the degree and nature of enantioselectivity of BINOL-phosphate catalyzed reactions. Apparently the model works well for a huge number of reactions and requires only the *E*/*Z*- configuration of the transition state and the orientation of the Dienophile.[46] Although, a wide variety of dienophiles such as enol ethers, enecarbamates, and cyclopentadienes have been successfully employed in enantioselective Povarov reactions, the use of simple acyclic alkenes as dienophiles with limited success.

Scheme 1.14. Asymmetric Three-Component Povarov Reaction Using Chiral Phosphoric Acid 55



In this context, Ricci et al.[45] reported the first two-component Povarov reaction using vinylindoles as alkene dienophiles catalyzed by a chiral phosphoric acid. Utilization of unsymmetrical β-substituted alkenes as the dienophile input for the three-component chiral phosphoric acid-catalyzed asymmetric Povarov reaction has been presented for the first time by Masson and co-workers (Scheme 1.15).[47]

Scheme 1.15. Chiral Phosphoric Acid-Catalyzed Povarov Reaction with Unsymmetrical Alkenes 58 as the Dienophile Input

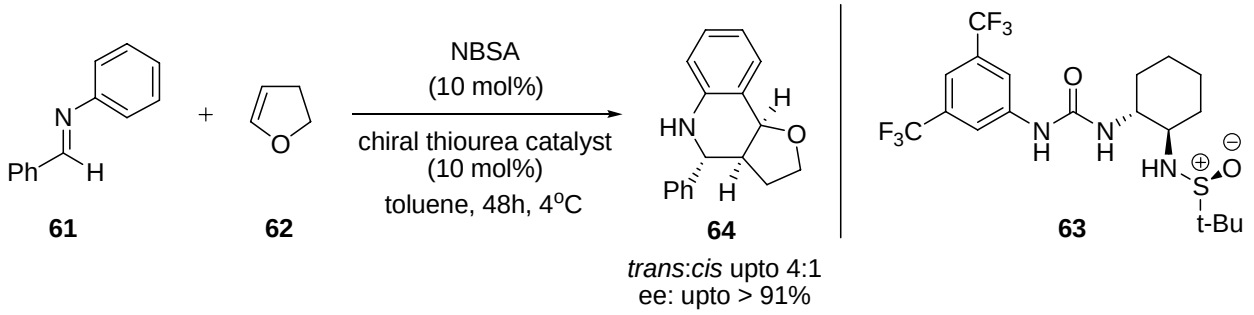


They used isoeugenol derivatives **58** bearing a free phenol functional group as dienophiles. The chiral catalyst **59**, with a bulky 2,4,6-triisopropyl phenyl group in the 3,30-position of (R)-

BINOL, furnished the tetrahydroquinoline **60** with excellent enantioselectivity but with a lower yield which was further improved by using DCE as the solvent.[47]

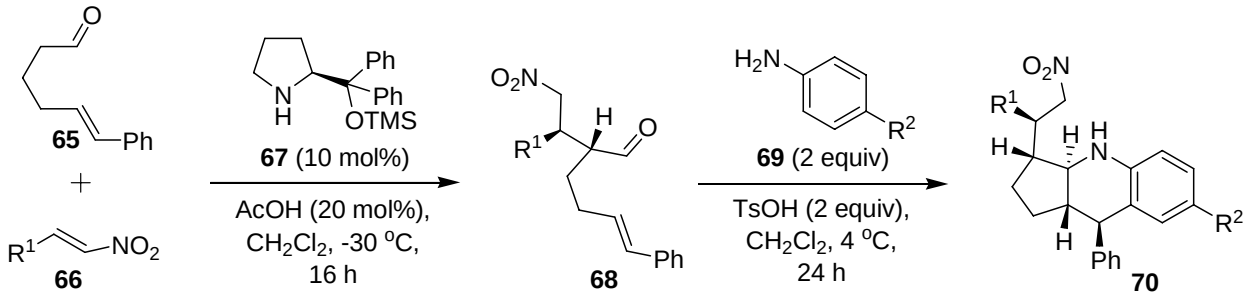
Recently, Jacobsen et al. reported cooperative Brønsted acid catalyzed synthesis of tetrahydroquinolines **64** using chiral thiourea **63** in very good yields and excellent enantioselectivity (Scheme 1.16).[48] The enantioselectivity is achieved in this case via formation of a highly reactive cationic intermediate through specific weak H-bonding interactions.

Scheme 1.16. Chiral Thiourea-Catalyzed Asymmetric Povarov Reaction



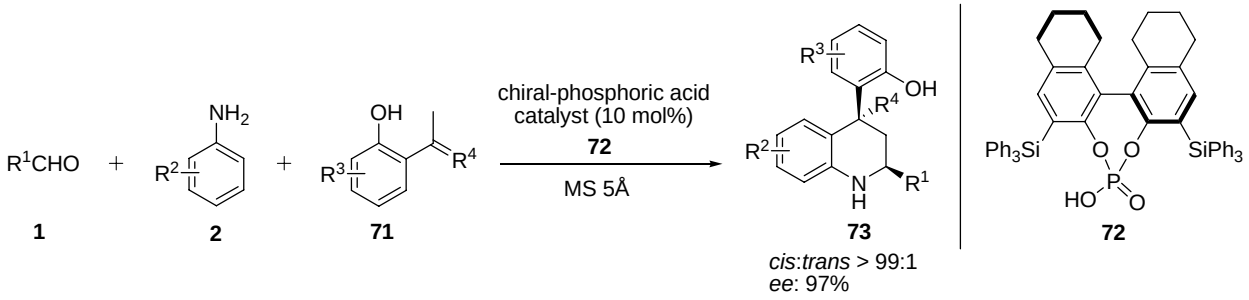
Jørgensen et al. reported an efficient organocatalytic (**67**), one-pot procedure to access enantiomerically pure polycyclic hexahydrocyclopenta[b]quinoline derivatives **70** with five stereogenic centers in high yields. The reaction proceeds through an initial organocatalytic Michael addition of a δ,ε-unsaturated aldehyde **65** and nitroalkene **66**, followed by the subsequent Povarov-type cycloaddition of the Michael adduct **68** to give rise to functionalized-polycyclic compound **70** in presence of a Brønsted acid (TsOH). The system provides great tolerance toward different aldehydes, anilines, and nitroalkenes (Scheme 1.17).[49]

Scheme 1.17. Asymmetric Organocatalytic syntheses of Cyclopenta[b]quinoline Derivatives 6



Recently, Gong et al. established an efficient organocatalytic asymmetric Povarov reaction of 2-hydroxystyrenes **71**. The protocol combines the merits of both organocatalysis and multicomponent reactions, tolerating a wide range of aldehydes, anilines and styrenes to furnish structurally diverse *cis*-tetrahydroquinolines in high stereoselectivities of up to > 99:1 dr and 97% *ee* using 10 mol% of the chiral phosphoric acid **72**. The current protocol not only provides a facile access to tetrahydroquinolines **73** with chiral quaternary stereocenters upon using α-alkyl 2-hydroxystyrenes as substrates, but also furnishes an efficient method to synthesize *cis*-disubstituted tetrahydroquinolines with high enantioselectivity (Scheme 1.18).[50]

Scheme 1.18. Asymmetric Povarov Reaction with 2[8]Hydroxystyrenes 75



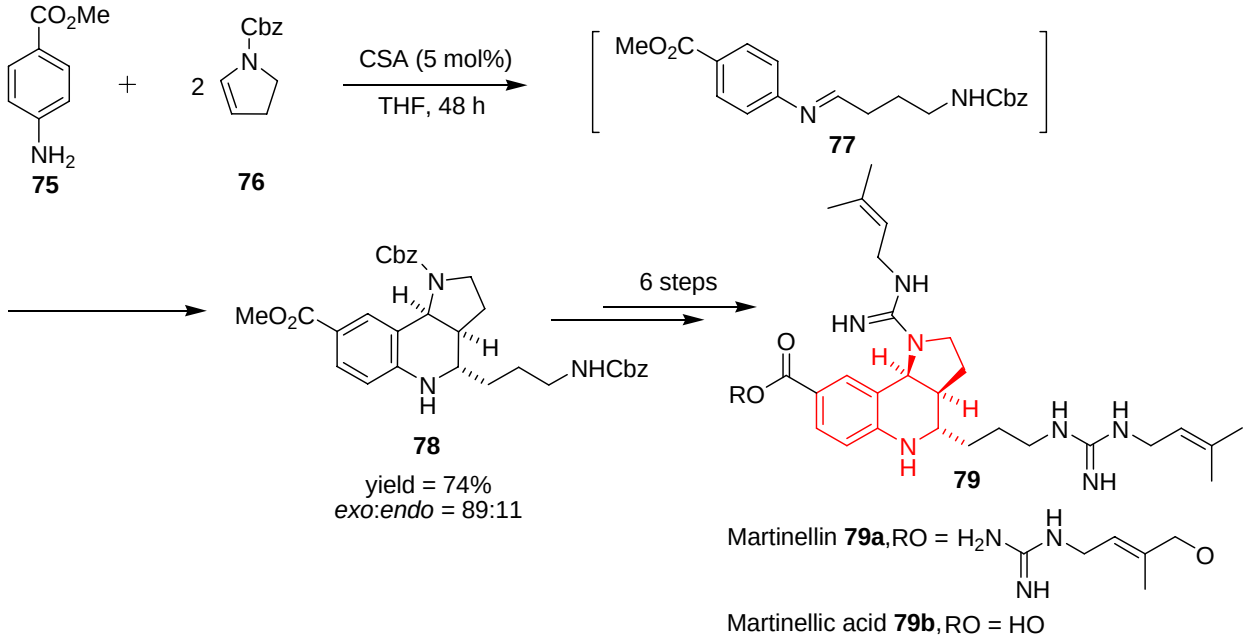
1.6 Applications of Povarov Reaction

1.6.1 Application in Total Synthesis

Natural products have played an important role in the identification of several medicines. Although, many strategies have been invented by chemists in order to facilitate the synthesis of various complex natural products, most of them are time-consuming, impractical and in some cases might also lack structural variability. Following nature's efficiency of multiple bond formation between various substrates, development of novel MCRs in order to achieve diversity oriented molecules in a relatively simpler way is highly desirable. In this context, Povarov reaction can be considered as a potential tool for the total syntheses of several tetrahydroquinoline containing natural products. Among them, the most promising are guanidine-containing alkaloids martinelline **79a** and martinellic acid **79b**. As the first example of biomimetic Povarov reaction, Batey and co-workers synthesized the unprecedented heterocyclic

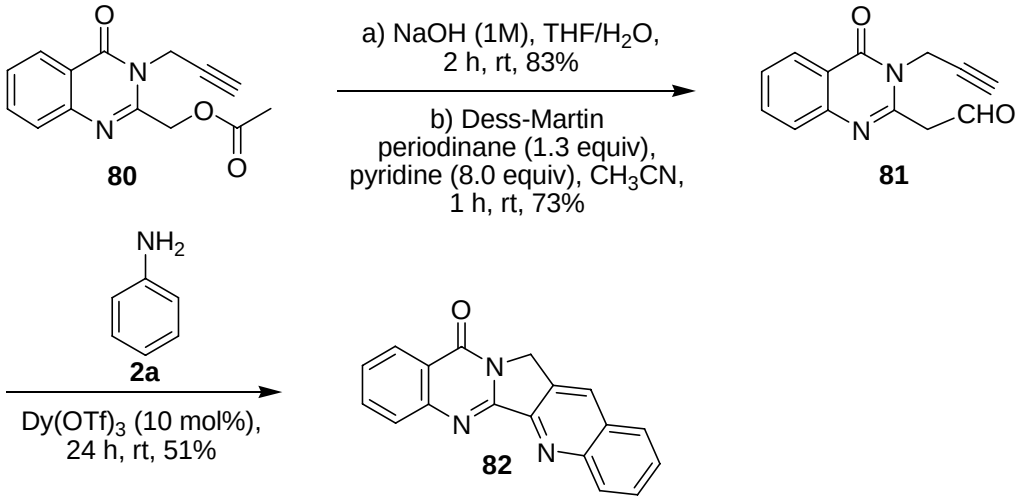
core of these attractive natural products via an intermolecular 2:1 multicomponent coupling of a substituted aniline **75** with two equivalents of an endocyclic enamine **76** (Scheme 1.19).[51]

Scheme 1.19. Total Syntheses of Martinellin and Martinelinc Acid.



The use of lanthanide(III) salts resulted in the formation of the 'wrong' *endo*-product in 92% yield with 85:15 diastereomeric ratio in favor of the *endo*-diastereomer. However, 5 mol% of camphor sulfonic acid (CSA) afforded the desired *exo*-diastereomer **78** in 74% yield after 48 h. Povarov approach (Scheme 1.20).[52] Bodwell and co-workers recently reported an intramolecular Povarov reaction using 3-aminocoumarins and *o*-cinnamylsalicylaldehydes to synthesize a series of pentacyclic heterocycles with high yields and *trans*, *trans* relative stereochemistry.[53]

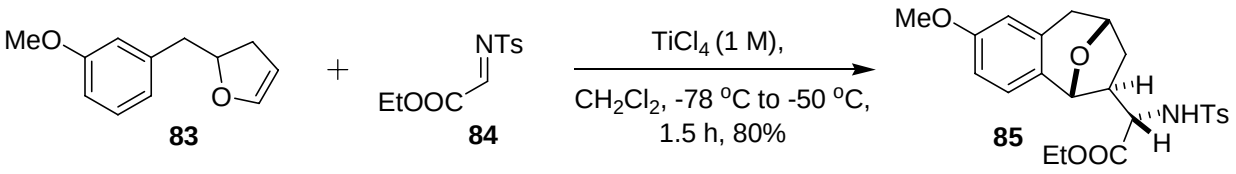
Scheme 1.20. Intramolecular Povarov Reaction for the Synthesis of Luotonin A, 82



1.6.2 Application in the Syntheses of Various Complex Heterocycles

Functionalized benzo-fused oxabicyclooctanes and nonanes are unique heterocyclic scaffolds and their use in molecular design is still restricted. In this context, $TiCl_4$ catalyzed syntheses of substituted benzo-fused 9-oxabicyclo[4.2.1]nonane ring systems **85** in good yields and diastereoselectivity is noteworthy (Scheme 1.21).[54] Due to the high reactivity of $TiCl_4$ the reaction was carried out at low temperature (-78 to -50 °C) to control the selectivity. The reaction proceeds via an initial Povarov-type reaction followed by an intramolecular Friedel-Crafts annulation with electron-rich aromatic system.

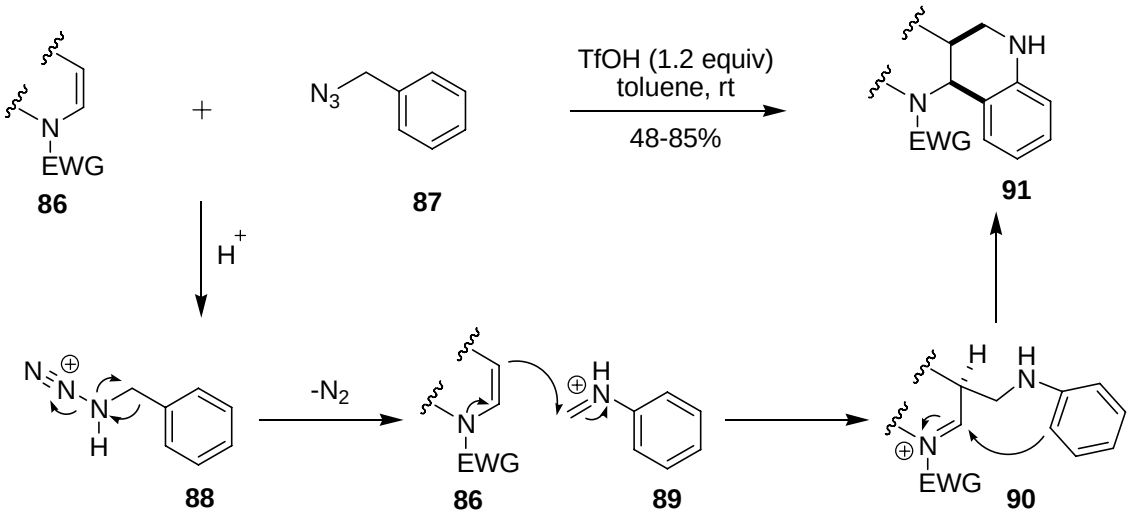
Scheme 1.21. $TiCl_4$-Ctalyzed Syntheses of Benzo-Fused Oxabicyclononanes, 85



Gillaizeau et al. developed a simple triflic acid-catalyzed, one-pot strategy for an efficient diastereoselective synthesis of polyfunctionalized nitrogen-fused tetrahydroquinoline scaffolds **91** via a domino reaction under mild conditions starting from readily available enamides **86** and benzyl azides **87** (Scheme 1.22).[55] The proton catalyzed elimination of N_2 from **87** leads to the

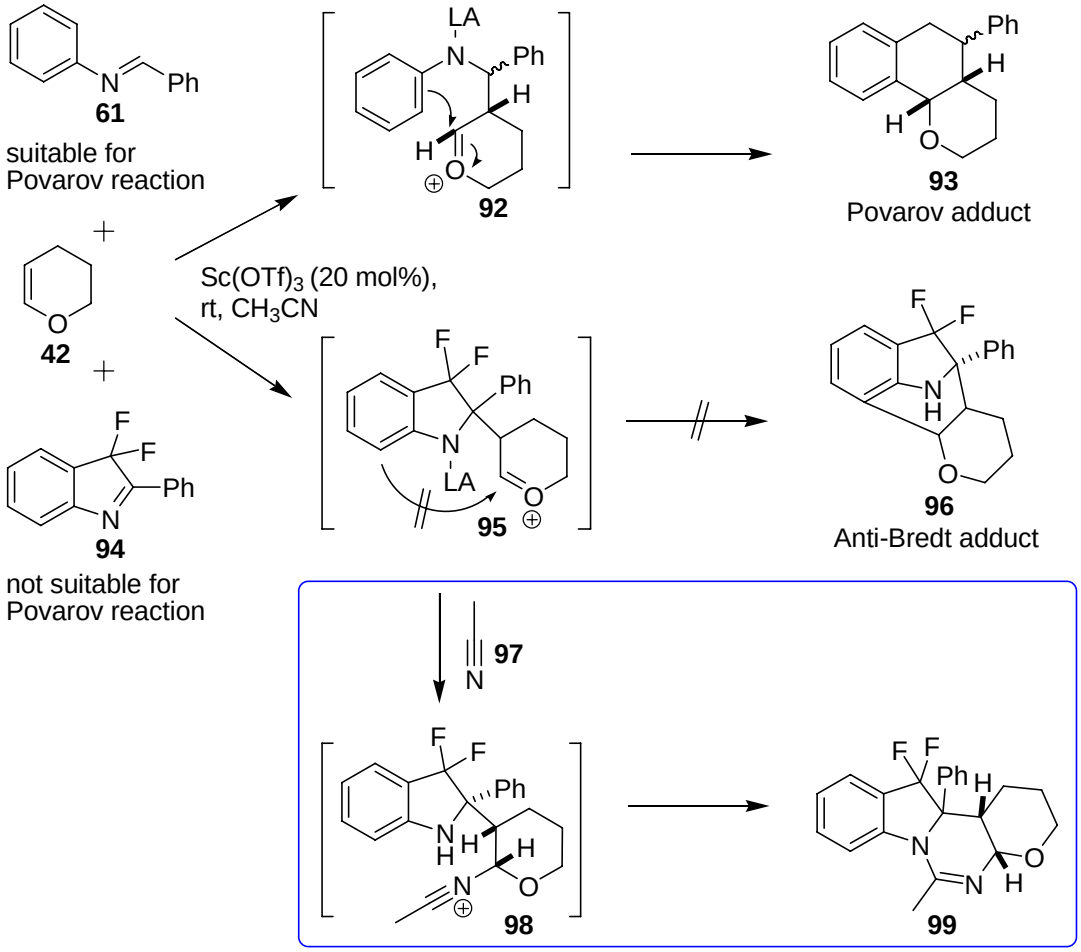
rearranged iminium intermediate **89** which afterwards follows a Povarov type reaction sequence to yield **91** as a desired product.

Scheme 1.22. Syntheses of Nitrogrn-Fused Tetrahydroquinolines 91 via the Reaction of Enamides 86 and Substituted Benzyl Azides 87.



In 2012, Lavilla et al. reported the stereoselective syntheses of cyclic amidines utilizing geometrically or electronically restricted imines in Povarov-type reactions. Normally, in Povarov process, the olefin forms bonds with the imine carbon and one of the un-substituted *ortho*-position of the aniline ring. When one of these positions is blocked, after the Mannich process, instead of formation of the Povarov product, the reaction could follow a sequential Ritter step, provided a third component **97** is introduced as an amphiphilic reactant. The reaction sequence could be completed by amidine formation through intramolecular trapping of the nitrilium ion by the secondary nitrogen centre of **98**, affording the three-component adduct **99** in a highly stereoselective manner (Scheme 1.23).[56]

Scheme 1.23. Forbidden Povarov Process Opens Up the Possibility of New Heterocycle (99) Formation

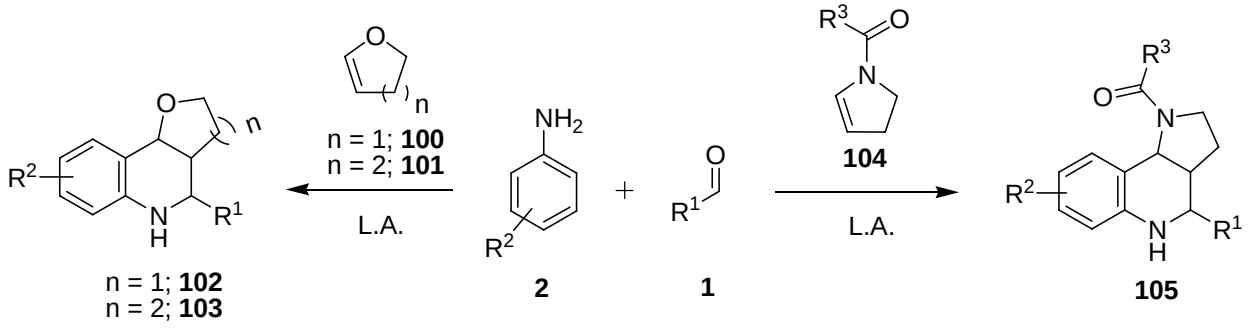


1.7 Scope of Various Electron-Rich Olefins as the Dienophiles

In general, the Povarov reaction is extremely useful with a broad set of anilines and carbonyl derivatives. It is important to state at this point that not only aromatic Schiff bases like *N*-benzylidenaniline, but also *N*-alkyl aldimines can be utilized as the aza-dienes in this type of reactions.[57,58] However, the addition reaction towards these aldimines is difficult to develop, because of their tendency to easy hydrolysis and polymerization under acidic conditions. In 2003, Batey and Menéndez independently showed that aliphatic aldehydes or aldehyde equivalents can be successfully employed under appropriate conditions. They showed that slow

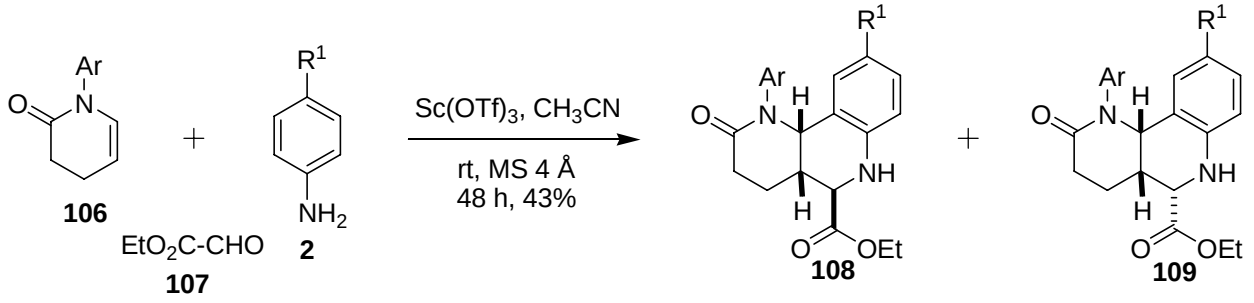
addition of reactants in presence of a mild Lewis acid,[57,58] can minimize the above mentioned trends. It was further smoothened by carrying out the reaction in fluorous solvents.[59] However, further efforts have also been extensively devoted to expand the range of activated olefin input for this reaction. Initially, Cyclic enol ethers, e.g. 2,3-dihydrofuran **100**[60] and 3,4-2H-dihydropyran **101** were used as more popular dienophiles**.** Utilization of these enol ethers afford the corresponding *cis*-fused furo[3,2-c]- and pyrano[3,2-c]quinoline derivatives **102** and **103**. Among the other dienophiles, vinyl enol ethers, vinyl sulfides, silyl enol ethers and their analogues were significantly used in the cycloaddition of *N*-aryl aldimines to obtain 2,4-substituted tetrahydroquinolines. Later on, the introduction of enamine-type functional groups has also been successfully explored.[61] In this context, cyclic enamides (**104**) are specially appealing since they allow access to a new set of functionalized tetrahydropyrroloquinolines **105** (Scheme 1.24).

Scheme 1.24. Multicomponent Povarov Reaction with Different Electron-Rich Dienophiles



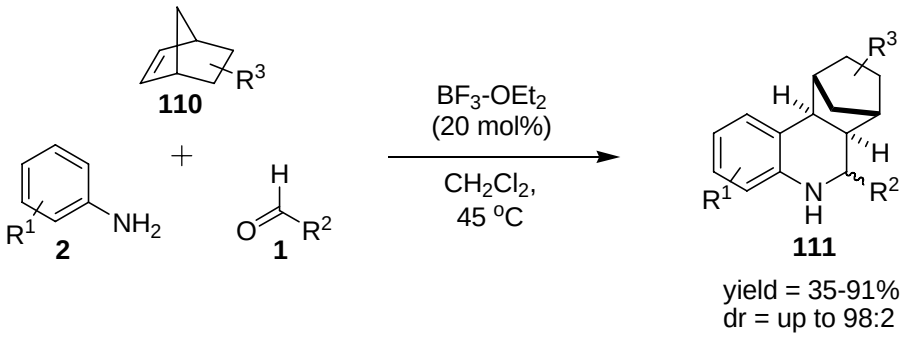
Significantly, the development of this chemistry by Batey and co-workers has allowed a straightforward path for the total synthesis of Martinelline and Martinellic acid.[62a] Lavilla and co-workers reported an excellent example of Povarov-type MCR utilizing dihydropyridines (DHPs) as the dienophiles,[63a,64] which are very good substrates due to their straightforward preparation from commercially available pyridines and the rich chemistry of the enamine products that can be exploited further in different ways. As a continuation of this work, recently they have reported the syntheses of novel tetrahydroquinoline scaffolds with attractive functionalization patterns (**108**, **109**), utilizing unsaturated lactams **106** as synthetically useful substrates for Povarov MCRs (Scheme 1.25).[65]

Scheme 1.25. Unsaturated Lactams as New Olefin Imputs for Povarov MCR



These adducts are readily converted to a variety of quinoline derivatives in a straightforward manner. The introduction of a fourth component to trap the final iminium ion intermediate (Scheme 1.2, intermediate **8)** and the spatial-temporal control of this MCR to functionalize microelectrodes[63] are also noteworthy. Cyclic alkenes like cyclopentadiene and indene are also common dienophiles for the study on catalytic activity of some acids in the imino DA cycloaddition reaction.[66,67] Recently, Liu and co-workers reported a triflic acid catalyzed Povarov-type cycloaddition reaction of alkenyldiazo compounds and aldimines to synthesize diazo-containing cycloadducts in a stereoselective manner. The resulting cycloadducts provide access to various six- and seven-membered azacycles, by either the generation of metal carbenes or the functionalization of the diazo group present.[68] In general, as we discussed previously, the Povarov reaction is limited to electron-rich alkenes. However, Batey and co-workers showed that the introduction of ring strain in the dienophile, as with moderately strained bicyclo[2.2.1]heptenes **110**, enables three-component Povarov reaction with *in situ* formed *N*-arylimines under LA catalyzed conditions (BF_3-OEt_2). The reactions proceed efficiently with a diverse set of commercially available anilines and benzaldehydes, as well as a variety of substituted norbornenes. The corresponding tetrahydroquinolines **111** are formed with high complexity in a multicomponent fashion and are obtained in good yield and high diastereoselectivity (Scheme 1.26).[69]

Scheme 1.26. Utilization of Strained Norbornene-Derived Dienophiles 110 in Three-Component Povarov Reaction



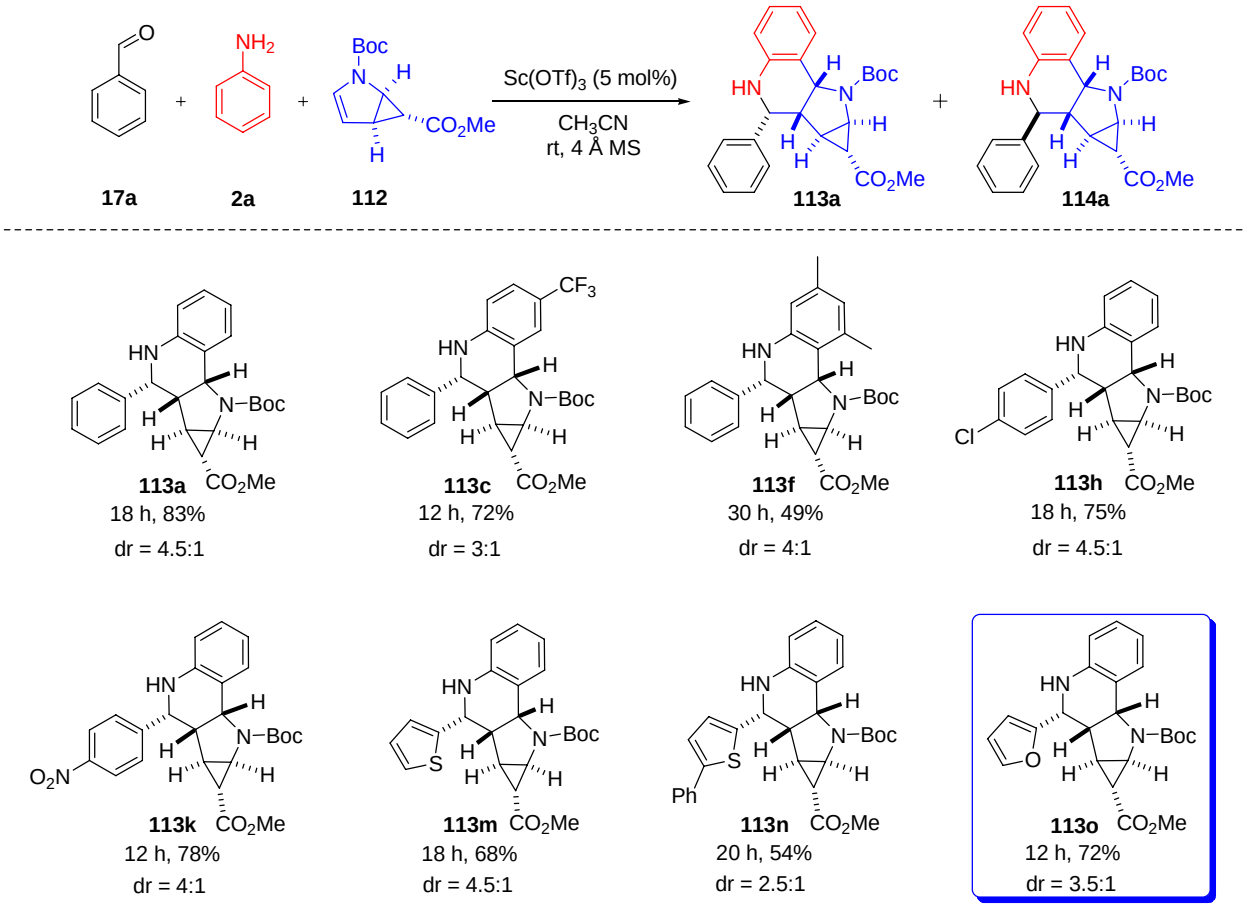
1.8 Cyclic Enamines Bearing Reactive Donor-Acceptor (D-A) Substituted Cyclopropane Moiety as the New Olefin Input for Povarov-Type Reactions

Although, the Povarov reaction has been established to be quite general with respect to its broader substrate scope, the reactivity of the electron-rich olefin in presence of additional functionality, especially in presence of Donor-Acceptor (D-A) substituted cyclopropanes is still to be explored.

D-A substituted cyclopropanes have proven to be of great utility in synthetic organic chemistry[70] and the presence of the cyclopropane group as an additional functionality could give rise to further scopes in terms of further reactivity of the Povarov adducts in diversity oriented synthesis. In this context, recently Reiser et al. reported an efficient Lewis acid catalyzed multicomponent reaction for the stereoselective syntheses of *cis*-4,5-disubstituted pyrrolidinones **116** in high yields, based on monocyclopropanated *N*-Boc-protected pyrrole **112** (Boc = tert-butoxycarbonyl).[71] Initially a set of Povarov products were synthesized by a three component reaction of benzaldehyde **17a**, aniline **2a** and the bicyclic compound **112,** utilizing 5 mol% of $Sc(OTf)_3$ as a catalyst in presence of 4 Å molecular sieves (MS) at room temperature, under N_2 atmosphere; the desired cycloaddition products **113a** and **114a** were obtained with moderate diastereoselectivity in favor of the *endo* isomer **113a** (Scheme 1.27). Application of heterocyclic aldehydes in the three-component reaction under the optimized reaction conditions also proceeded smoothly, giving rise to the desired products in good yields and comparable

diastereoselectivity. Phenyl substitution in 5-position of thiophene and 2-furancarbaldehydes were also tolerated well, although the reaction time was considerably higher.

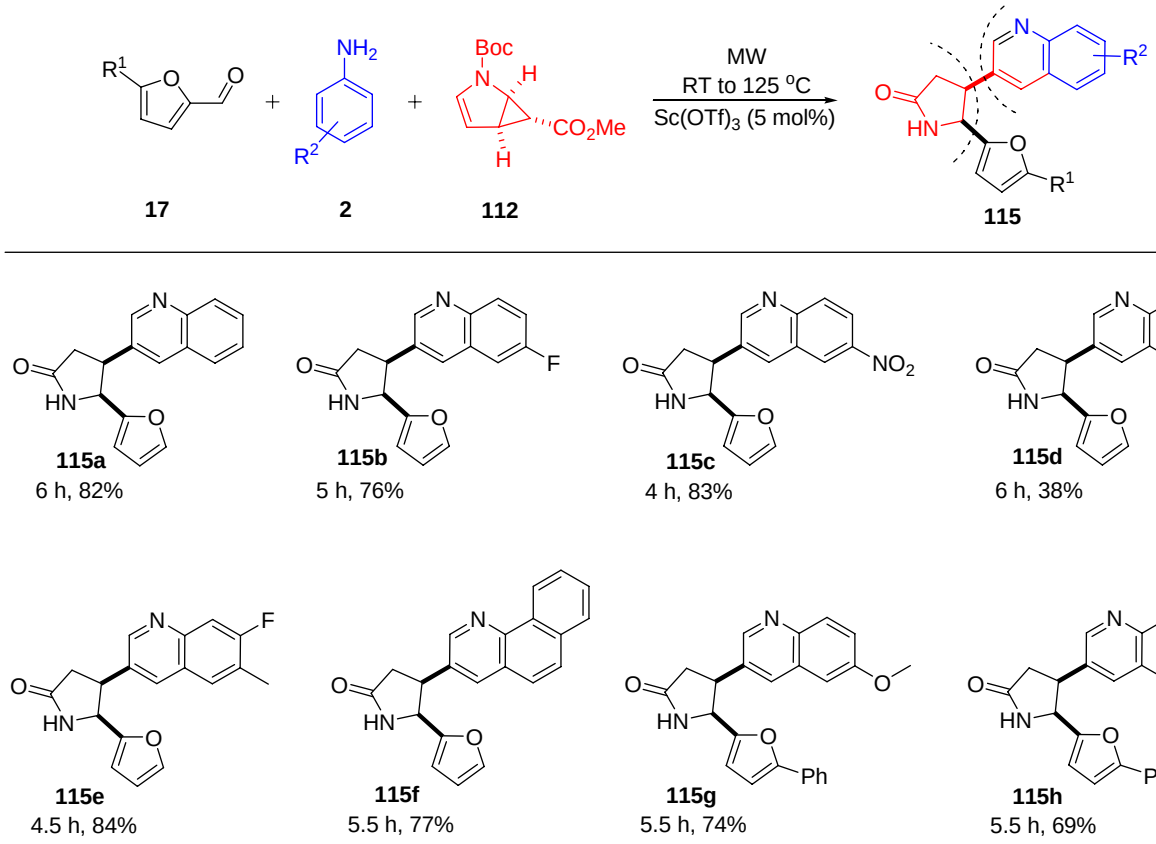
Scheme 1.27. Multicomponent Povarov Reaction Using *Tert*-butyl methyl 2-azabicyclo[3. 1. 0]hex-3-ene-2, 6-dicarboxylate 112



$Sc(OTf)_3$-catalyzed multicomponent assembly of furan-2-carbaldehydes **17l**, aniline **2a** and cyclopropanated *N*-Bocpyrrole **112**, smoothly afforded synthetically challenging *cis*-4,5-disubsti-tuted pyrrolidinone **115a** with an improved yield of 82% and excellent stereoselectivity. Among a large number of Lewis acids screened, 40 mol% of $Sc(OTf)_3$ was emerged as the best catalyst under above mentioned refluxing condition. However, catalyst loading was finally reduced by eight fold (5 mol%) under microwave (MW) irradiation which became best suited for the same goal. Thus, the overall process combined a Povarov reaction, D-A induced cyclopropane ring opening, 1,4-furan ring migration and quinoline formation, involving the formation and breaking of one C-O, four C-N and five C-C bonds. Using readily available furancarbaldehydes **17** and

aromatic amines **2**; a broad range of *cis*-4,5-disubstituted pyrrolidinones **115** could be synthesized with complete chirality transfer from **112** in high yields (Scheme 1.28).

Scheme 1.28. $Sc(OTf)_3$-Catalyzed Synthesis of Substituted Pyrrolidinones 115



1.9 Conclusion

Since the historical development of so-called inverse electron demand aza-DA reaction or the Povarov reaction in 1963, a huge amount of research interest was attracted during the last few decades in order to achieve more detailed mechanistic proofs as well as interesting heterocyclic scaffolds. The major developments in this field mainly constitute, utilization of various catalysts, enantioselective variations, including chiral organocatalysts and more promisingly, construction of diverse heterocycles by manipulating Povarov reaction as the key step, employing multifunctional dienophiles and hence, expansion of substrate scope towards many directions.

Replacement of usual organic solvents by water has also been achieved as a greener approach. Although a lot of efforts have been devoted to gain detail mechanistic insights of the reaction and development of catalytic enantioselective variations, only a few successful reactions have been published till now which implicate the importance of the Povarov reaction in light of synthesizing numerous heterocyclic scaffolds other than the tetrahydroquinolines.

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2. Aim of this Work

It has recently been realized that highly efficient synthetic methods with a strong focus on multiple bond formation in a single step are required which could be obtained through rational designing of novel multicomponent reactions (MCRs). Due to the operational simplicity and high atom economy, MCRs with subsequent transformations, including cyclization and re-functionalization have emerged as the complementary and powerful alternatives to conventional strategies for the synthesis of complex molecules having relevant applications in both combinatorial chemistry and DOS (Figure 2.1).[1,2,3] The aim of this work was to develop efficient and novel multicomponent approaches, based on a bi-functional compound and utilizing the Povarov reaction as the key step for creating complex heterocyclic molecular scaffolds, which could be utilized for various screening processes.

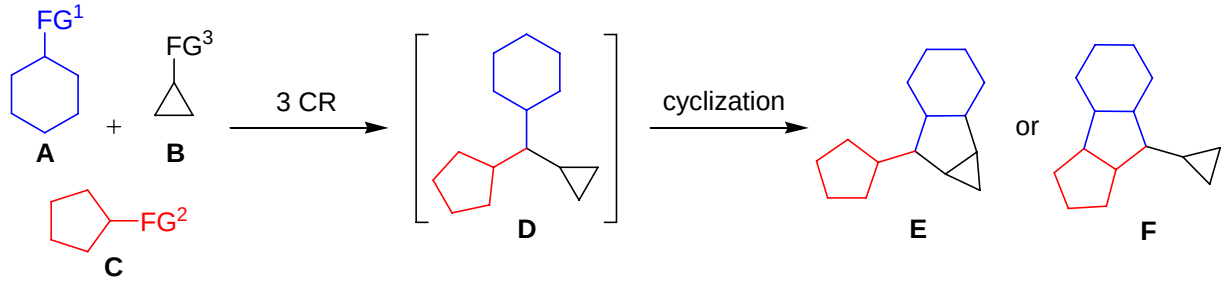

Figure 2.1. Construction of complex heterocycles **E** or **F** via a three component reaction followed by cyclization of **D**.

2.1 Utilization of D-A-Substituted Cyclopropane Ring Containing Electron-Rich Olefin for the Povarov Reaction

The Povarov reaction was vastly exploited for the constructions of tetrahydroquinoline moieties by the reaction of aldimins and a huge range of electron rich olefins. On the contrary, utilization of olefins containing D-A substituted cyclopropane ring as an additional functionality was unprecedented till now. In this context, our aim was to introduce for the first time the bicyclic compound, *tert*-butyl methyl 2-azabicyclo[3.1.0]hex-3-ene-2, 6-dicarboxylate **6** as an electron

rich, bi-functional olefinic component for the Povarov reaction to access tetrahydropyrroloquinolines in a stereoselective manner.

2.2 Utilization of Povarov Reaction as the Key step for Developing Novel Synthetic Strategies to Access Diversified Heterocyclic Scaffolds

It was also intringuing to us whether it is possible to develop synthetic routes to access diversified heteroccyles, e.g., tetrahydropyrroloquinolines (**G**), polycyclic imines (**H**), funtionalized pyrroles (**I**), pyrrolidinones (**J**) and functionalized pyrazolidines (**k**) in stereo-and regioselective manner following multicomponent-one-pot strategy. Most often, multicomponent reaction produces multiple products and suffers from low yield and selectivity. Thus it was challenging for us to develope proper reaction conditions which could give only the desired product in good yield and selectivity (Figure 2.2).

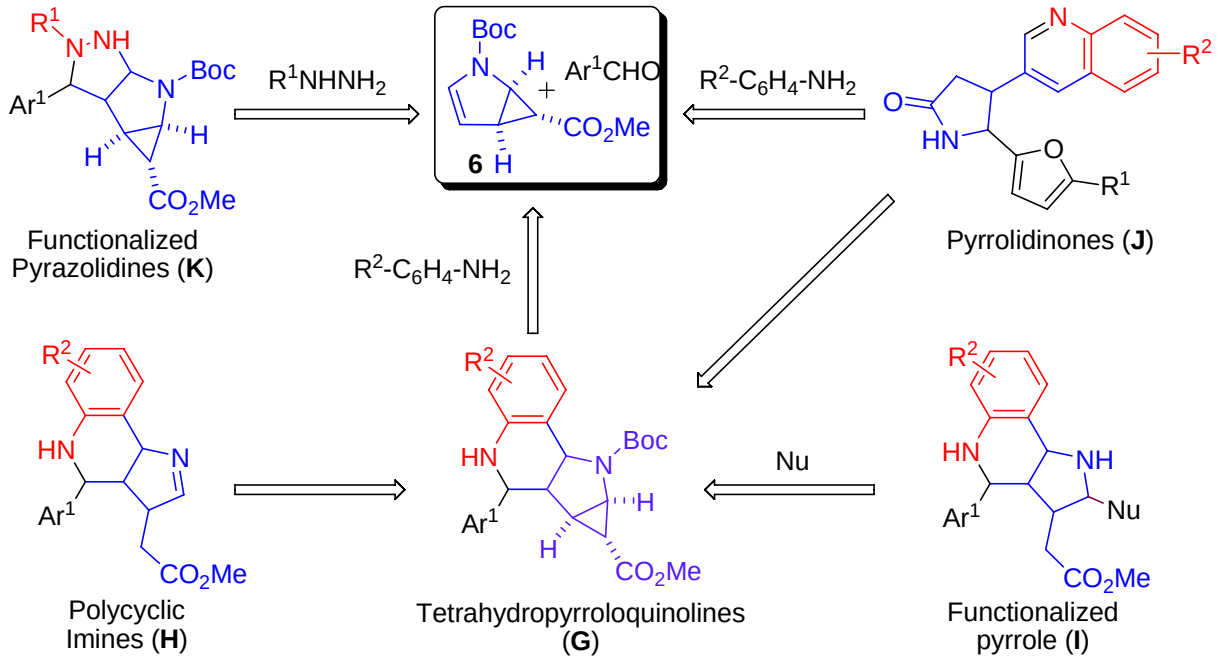

Figure 2.2. Strategy for synthesizing various heterocycles utilizing the Povarov reaction as the key step.

Although, most of the already established MCRs do not require a catalyst, the quest for novel and more efficient MCRs has resulted in an intensified effort to find suitable catalysts in order to obtain diversified products in broader perspective. In this context, we have chosen mainly metal triflates as catalyst due to their inherene afinities towards the non bonding electron pair to form reactive adducts as important intermediates.

2.3 References

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3. A Catalytic Multicomponent Approach for the Syntheses of Biologically Relevant Tetrahydropyrrolo[3,2-*c*]quinoline Derivatives

3.1 Tetrahydropyrroloquinolines as Pharmaceutically Relevant Molecules

Ring-fused tetrahydropyrroloquinolines and relative derivatives constitute the ubiquitous class of nitrogen heterocycles in the nature and have found potential applications as pharmaceuticals and agrochemicals.[1] In 1995, scientists at Merck, first reported the isolation of two novel guanidine alkaloids, martinelline (**1**) and martinellic acid (**2**) from the root extracts of a family of tropical plants, *Martinella iquitosensis* vine, which have long been used by indigenous people for medicinal purposes.[2] Later, these *Martinella* alkaloids were observed to possess not only strong affinity for adrenergic, muscarinic and bradykinin receptors[3] but also moderate antibacterial[4] and potent cytotoxic[5] activities. The unique hexahydropyrrolo[3,2-*c*]quinoline (**3**) moiety (Figure 3.1), present in these molecules is assumed to be responsible for showing such therapeutic applications. Consequently, development of efficient methodologies for the synthesis of such tetrahydropyrroloquinoline framework continues to be an important goal of synthetic organic chemists. One of the most powerful strategies for synthesizing this interesting heterocyclic compound is the Povarov reaction, which has already been thoroughly discussed in the previous chapter in light of the historical background and recent synthetic developments.

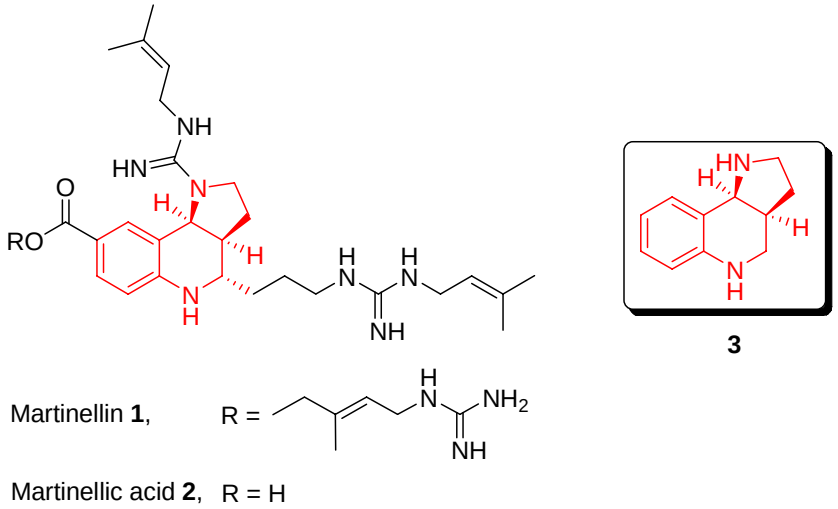


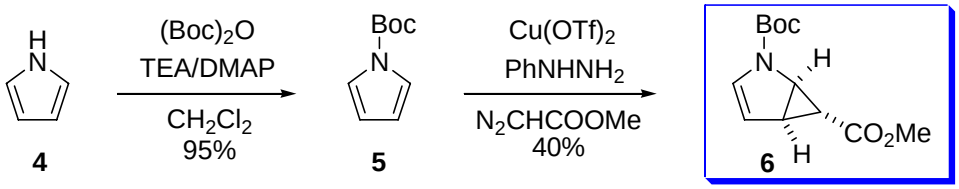
Figure 3.1. *Martinella* alkaloids from *Martinella iquitosensis* vine.

Our contribution to the aforementioned research area will be elaborated in the present and the following chapters with respect to a new olefin input as well as development of novel methodologies, utilizing Povarov reaction as the key step for creation of various heterocycles.

3.2 Cyclic Enamines Bearing Reactive Donor-Acceptor (D-A) Substituted Cyclopropane Moiety as the New Olefin Input for Povarov-Type Reactions

Although, the Povarov reaction has been proved to be quite general with respect to the broader substrate scope, the reactivity of an electron-rich olefin in presence of additional functionality, especially in presence of Donor-Acceptor (D-A) substituted cyclopropanes is still unexplored. The D-A substituted cyclopropanes have proven of great utility in synthetic organic chemistry;[6] our group is focused for long time on the development of new D-A substituted cyclopropane derivatives and exploring their unique reactivity for the syntheses of various pharmaceutically relevant molecules.[7] As a continuation of this work, the diastereoselective syntheses of *tert*-butyl methyl 2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** has already been well established (Scheme 3.1)[8c]

Scheme 3.1. Synthesis of *Tert*-butyl methyl 2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate 6



In quest for constructing novel heterocycles by utilizing Povarov reaction as the key step, we envisioned that the enamine moiety present in **6** could lead to the Povarov-type reaction in presence of *N*-aryl imines, affording functionalized tetrahydropyrroloquinoline derivatives (Figure 3.2). Consequently, we investigated the scope of **6** as a new olefin input for the Povarov reaction.

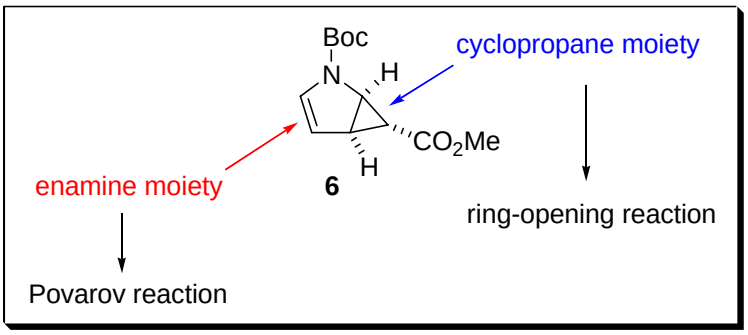
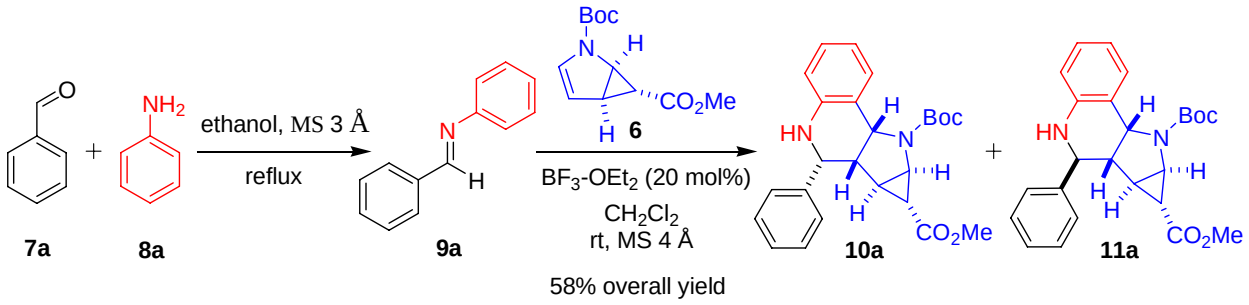


Figure 3.2. Electron-rich enamine **6** bearing additional D-A cyclopropane moiety as a promising olefin input for the Povarov reaction.

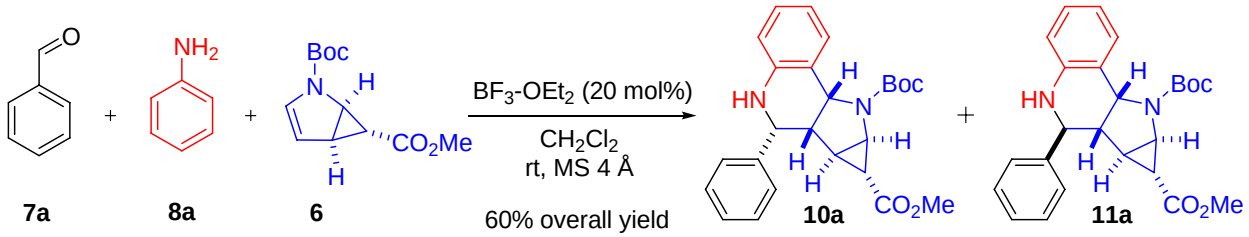
Our initial experiments were performed based on the preformed Schiff's base **9a** (via the condensation of benzaldehyde **7a** and aniline **8a**) and the bicyclic compound **6** utilizing 20 mol% of BF_3/OEt_2 as a catalyst in presence 4 Å molecular sieves (MS) under N_2 atmosphere at 0 °C to room temperature; gratifyingly we obtained the desired cycloaddition products **10a** and **11a** as expected after 48 h with moderate diastereoselectivity of 6:1 in favor of the *endo* isomer **10a** (Scheme 3.2).

Scheme 3.2. One-Pot Povarov Reaction Using *Tert*-butyl methyl 2-azabicyclo[3.1.0]hex-3-ene-2, 6-dicarboxylate 6



The isolated yield of the major diastereomer **10a** was 45%. Next, we focused on carrying out the reaction in a multicomponent one-pot fashion which was highly desirable over the multistep procedure with respect to atom-economic transformation of easily available starting materials into complex organic building blocks. To our delight, we obtained comparable results when we set up a three-component reaction of benzaldehyde **7a**, anilines **8a** and the electron-rich olefin **6** under similar Lewis acid catalysis (Scheme 3.3).

Scheme 3.3. Multicomponent Povarov Reaction Using *Tert*-butyl methyl 2-azabicyclo[3. 1. 0]hex-3-ene-2, 6-dicarboxylate 6

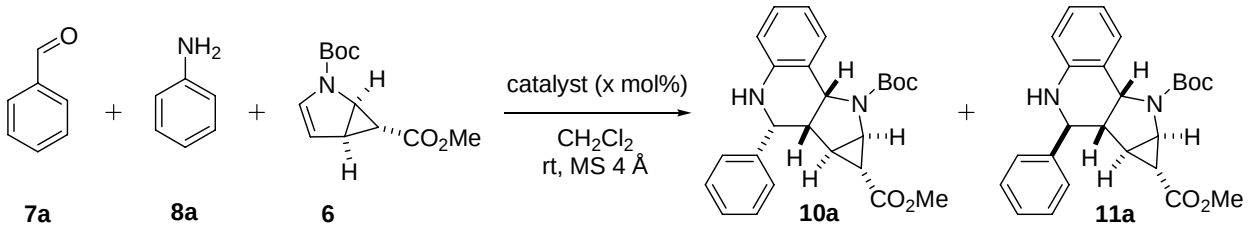


7a **8a** **6**

Next, we turned our attention to optimize the reaction condition in order to decrease the catalyst loading and reaction time. In this regard, several Brønsted and Lewis acid catalysts were screened based on the preliminary reaction of benzaldehyde **7a**, aniline **8a** and olefin **6** and the results are summarized in Table 3.1. When 20 mol% of triflic acid was used as a catalyst, we obtained a completely different diastereoselectivity of 1:6 in favor of the *exo*-isomer **11a** in a much improved isolated yield of 71% after 36 h (Table 3.1, entry 1).

Since, lanthanide metal salts are already proved to be efficient LA catalysts for this type of reaction; we also investigated our system using different lanthanide triflates (Table 3.1, entries 3-6). Although, in all of these cases the time of the reaction decreased significantly but the diastereomeric ratio became much lower. Finally 1 mol% of $Cu(OTf)_2$ was found to be the best catalyst of choice, considering both reaction time as well as diastereoselectivity of the cycloaddition products (Table 3.1, entry 8).

Table 3.1. Catalyst Screening at Room Temperature[a]



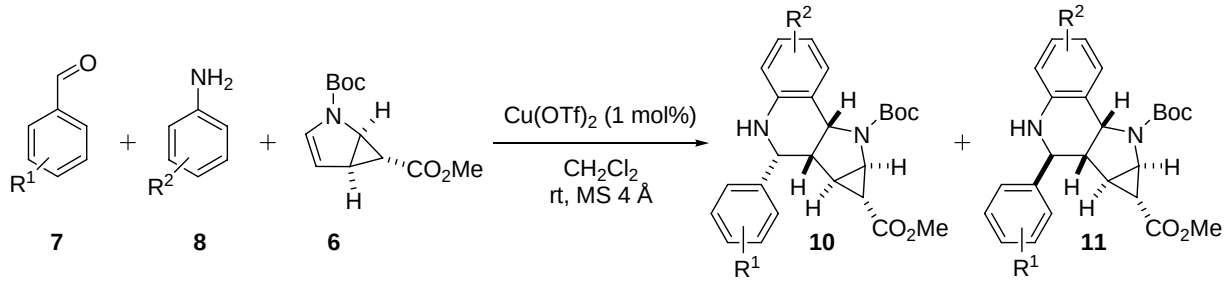
7a **8a** **6** **10a** **11a**

entry	catalyst	x mol%	conversion (%)[b]	time (h)	yield (%)[c]	dr[d]
1	TfOH	20	90	36	71	1:6
2	BF_3-Et_2O	20	60	48	45	6:1
3	$Yb(OTf)_3$	20	100	08	48	1:1
4	$Yb(OTf)_3$	5	100	12	65	2:1
5	$Sc(OTf)_3$	5	100	08	72	2.5:1
6	$Sc(OTf)_3$	1	100	09	72	2.5:1
7	$Cu(OTf)_2$	5	100	12	79	4:1
8	**$Cu(OTf)_2$**	**1**	**100**	**16**	**80**	**4.5:1**

[a] Reaction conditions: 0.835 mmol **7a**, 0.835 mmol **8a**, 0.334 mmol **6**, catalyst (x mol%) and DCM (2 mL). [b] Determined by ^{1}H NMR.[c] Yields of isolated major diastereomer **10a**. [d] Determined by ^{1}H NMR.

With this optimized reaction condition in hand, next we examined the scope of the reaction with respect to different aldehydes and anilines (Table 3.2). The aniline input showed appropriate reactivity, ranging from activated to deactivated systems affording the desired products in good yields and moderate diastereoselectivity (Table 3.2, entries 2-6). When different aldehydes were involved, the more electron-deficient nature of the aldehyde **7** appeared to have a positive effect on the yield of the Povarov products (Table 3.2, entries 8-11). This observation indicates that the electron withdrawing substituent on either aldehyde or aniline part lowers the energy barrier of the reaction and thus resulting in a shorter reaction time and higher yield as expected.

Table 3.2. Scope of Povarov Reaction with Different Aldehydes, Anilines and New Olefin Input[a]



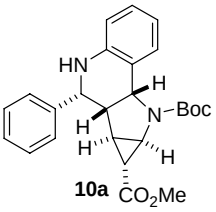
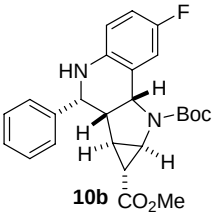
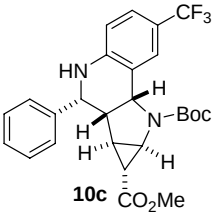
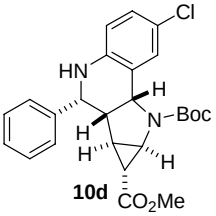
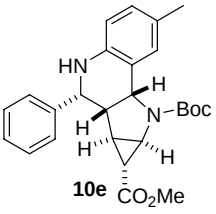
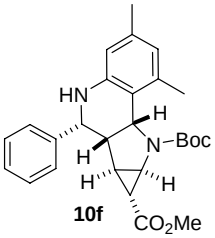
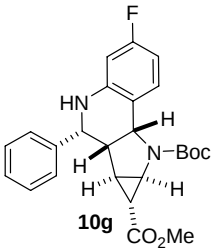
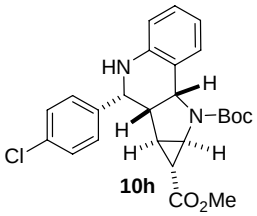
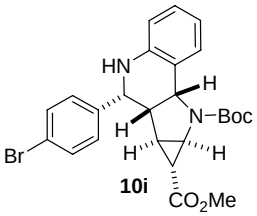
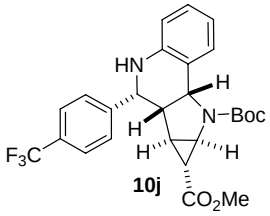
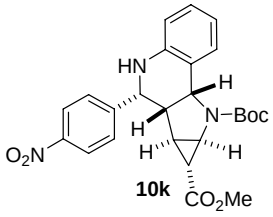
entry	R^1	R^2	major diastereomer	time (h)	isolated yield (%)[b]	endo/exo[c]
1	H	H	 **10a**	18	80	4.5:1
2	H	4-F	 **10b**	16	79	4:1
3	H	4-CF_3	 **10c**	12	72	3:1
4	H	4-Cl	 **10d**	18	70	3:1
5	H	4-Me	 **10e**	22	55	4:1

Table Continued..

entry	R^1	R^2	major diastereomer	time (h)	isolated yield (%)[b]	endo/exo[c]
6	H	3,5-$(Me)_2$	 **10f**	30	49	4:1
7	H	3-F	 **10g**	18	69	4:1
8	4-Cl	H	 **10h**	18	75	4.5:1
9	4-Br	H	 **10i**	18	73	4:1
10	4-CF_3	H	 **10j**	16	77	4:1
11	4-$NO_2C_6H_4$	H	 **10k**	12	78	4:1

[a] Reaction conditions: 0.835 mmol **7**, 0.835 mmol **8**, 0.334 mmol **6**, 0.00334 mmol catalyst (1 mol%) and DCM (2 mL). [b] Yields of isolated major diastereomer **10**. [c] Determined by ^{1}H NMR.

The relative stereochemistry of the products **10a** and **10k** (Table 3.2, entries 1 and 11) were unambiguously established by single crystal X-ray analysis (Figure 3.3).

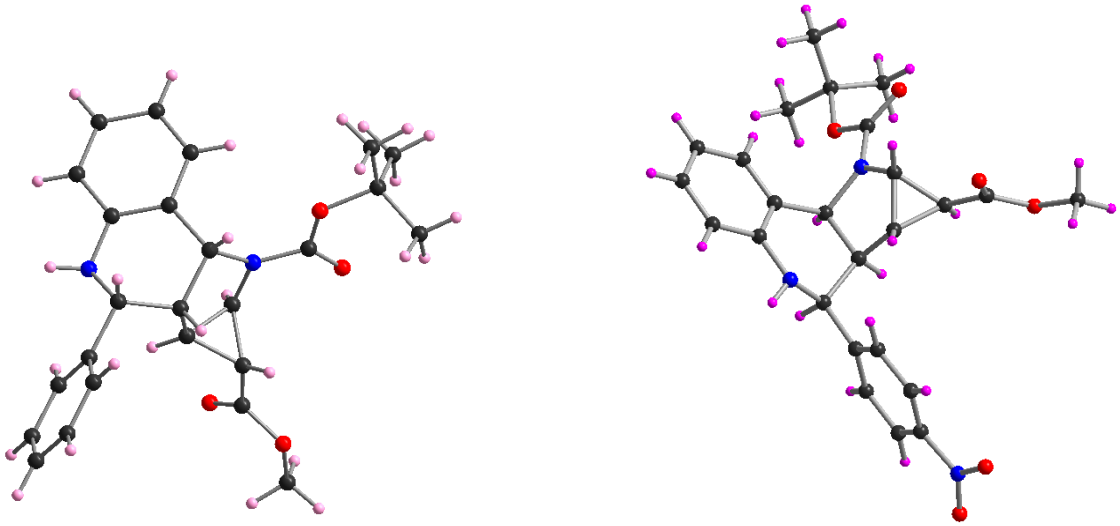
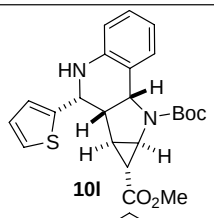
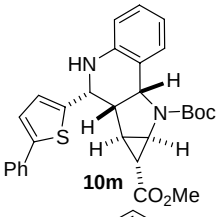
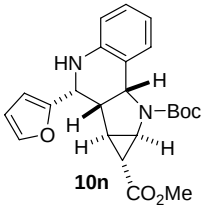
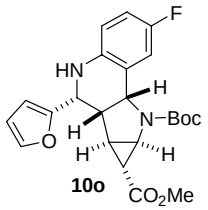
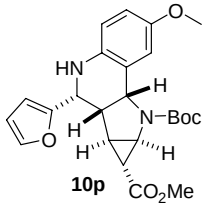
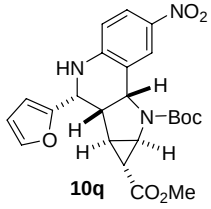
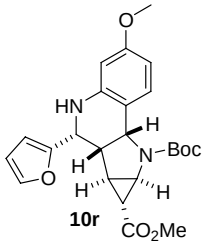
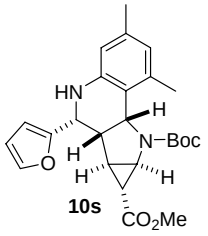
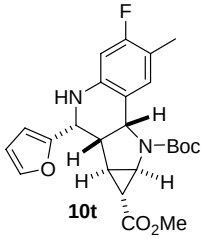
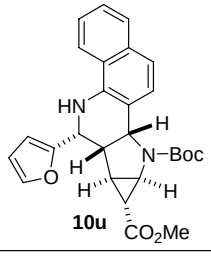


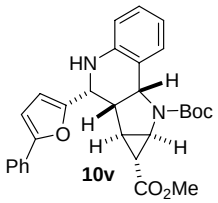
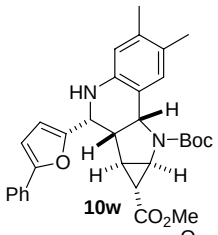
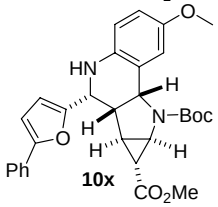
Figure 3.3. X-ray crystal structures of compounds **10a** and **10k**.

Application of heterocyclic aldehydes in the three-component reaction under the optimized reaction conditions also proceeded smoothly, giving rise to the desired products in good yields and comparable diastereoselectivity (Table 3.3).

Table 3.3. Scope of Povarov Reaction with Different Heteroaromatic Aldehydes[a]

entry	R^1	R^2	major diastereomer	time (h)	isolated yield (%)[b]	endo/exo[c]
1	2-thiophenyl	H	 **10l**	18	68	4:1
2	5-Ph-2-thiophenyl	H	 **10m**	20	54	2.5:1
3	2-furayl	H	 **10n**	12	72	3.5:1

entry	R^1	R^2	major diastereomer	time (h)	isolated yield (%)[b]	endo/exo[c]
4	2-furayl	4-F	 **10o**	8	75	3:1
5	2-furayl	4-OMe	 **10p**	14	75	2.5:1
6	2-furayl	4-NO_2	 **10q**	9	78	3:1
7	2-furayl	3-OMe	 **10r**	14	73	2.5:1
8	2-furayl	3,5-$(Me)_2$	 **10s**	13	63	2:1
9	2-furayl	3-F,4-Me	 **10t**	4	70	2.7:1
10	2-furayl	1-napthyl	 **10u**	16	65	2.5:1

entry	R^1	R^2	products	time (h)	isolated yield (%)[b]	endo/exo[c]
11	5-Ph-2-furayl	H	 **10v**	24	66	2.5:1
12	5-Ph-2-furayl	3,4-$(Me)_2$	 **10w**	21	60	2:1
13	5-Ph-2-furayl	4-OMe	 **10x**	22	69	3:1

[a] Reaction conditions: 0.835 mmol **7**, 0.835 mmol **8**, 0.334 mmol **6**, 0.00334 mmol catalyst $Cu(OTf)_2$ (1 mol%) and DCM (2 mL). [b] Yields of isolated major diastereomer **10**. [c] Determined by ^1H NMR.

In this context, furan-2-carbaldehydes were also tolerated well, although the reaction time was considerably increased in those cases (Table 3.3, entries 2, 11, 12, 13). Replacement of anilines with 1-napthylamine resulted in the corresponding tetrahydrobenzo[h]quinoline **10u** in 65% yield (Table 3.3, entry 10). The relative stereochemistry of the product **10n** (Table 3.3, entry 3) was unambiguously established by single crystal X-ray analysis (Figure 3.4).

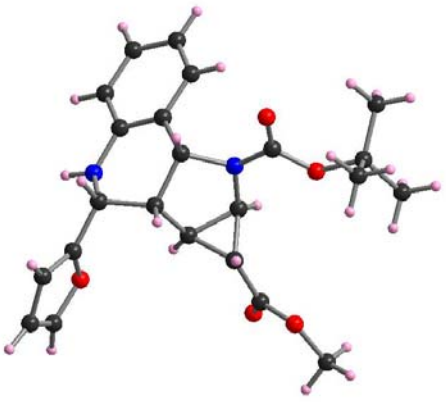
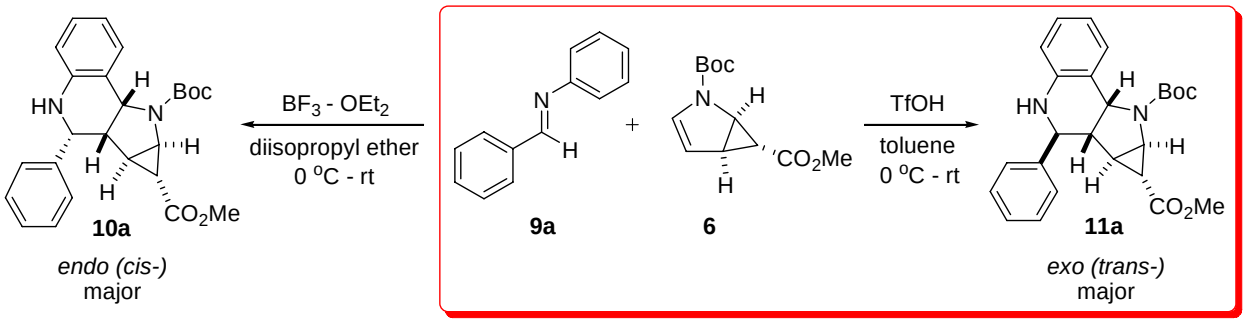


Figure 3.4. X-ray crystal structure of compound **10n**.

3.3 Asymmetric Povarov Reaction Using Chiral Thiourea Catalyst

As already discussed in Chapter 1, Section 2.5, the catalytic enantioselective Povarov reaction of electron-rich olefins with aldimines is an extremely powerful strategy for the construction of tetrahydroquinolines with high enantiopurity. Inspired by the recent work of Jacobsen et al.[9] we decided to investigate the effect of chiral thiourea mediated Brønsted acid (BA) catalysis on our reaction system. Initial optimization studies with triflic acid showed a reversal in the trend of general diastereoselectivity of the products and the *exo*-diastereomers were found to be the major product (Scheme 3.4).

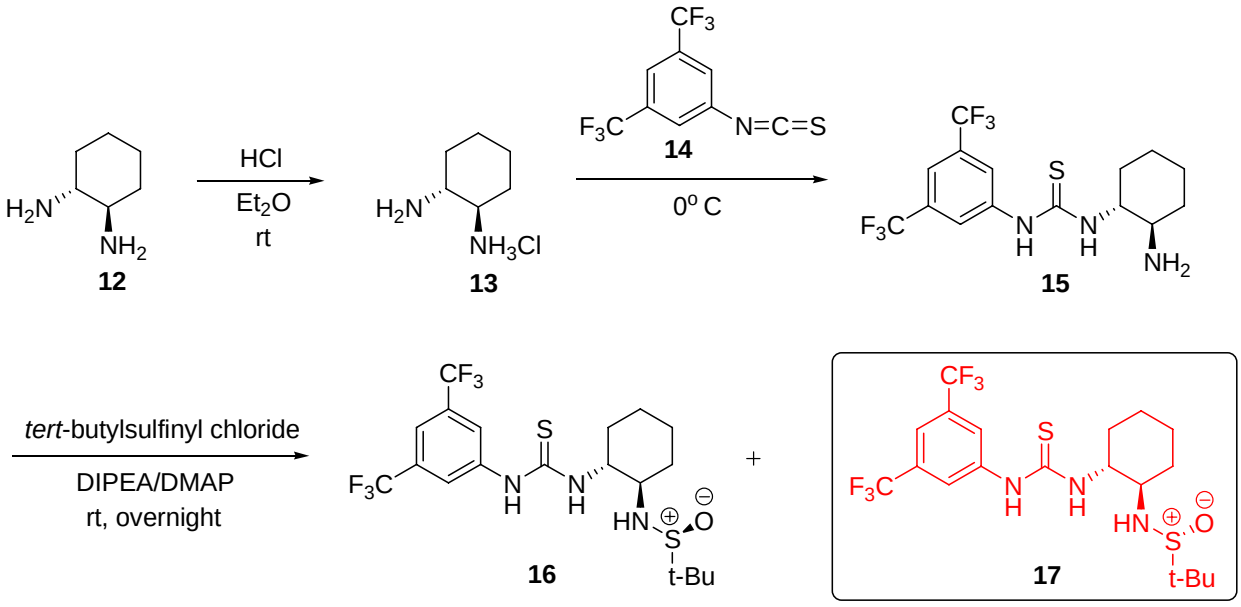
Scheme 3.4. LA- and BA-Catalyzed Povarov Reaction: Effect on Diastereoselectivity



Next, we turned our attention towards combining the BA with the bifunctional sulfinamido thiourea derivative **17** in order to obtain enantiomerically pure tetrahydropyrroloquinoline **11**. The thiourea catalyst **17** was prepared by literature known procedure and after purification on silica, employed for the subsequent optimization studies (Scheme 3.5).[10]

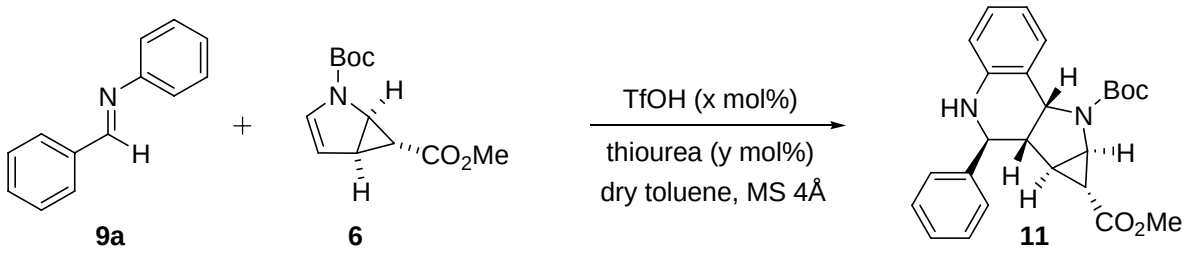
Initial experiments were performed with the benzylidine aniline **9a** and the racemic-bicyclic cyclopropanated compound **6** in presence of 10 mol% of each of TfOH and the thiourea catalyst **17**. When the reaction was carried out at room temperature, the desired product was formed as a recemic mixture after 48 h in 75% of isolated yield with a diastereoselectivity of 8:1 in favor of the *exo*-isomer (Table 3.4, entry 1). In order to achieve enantioselectivity, the temperature was then reduced to -55 ^{o}C as reported by Jacobsen et al. But unfortunately, we obtained only a trace amount of the product (<10%) (Table 3.3, entry 4).

Scheme 3.5. Synthesis of Jacobsen's Thiourea Catalyst



In order to have a better conversion, we then slightly increased the temperature to -45 °C, but after 48 h we could get only 12% of the product **11** with excellent diastereoselectivity of 99:1 in favor of the *exo*-isomer **11** in very good enantiomeric excess; *ee* = 96% (Table 3.4, entry 6). Encouraged by this result, next we decided to increase the BA loading to 12 mol% in order to have better conversion. Several conditions were screened, altering also the BA-thiourea ratio and finally, we obtained the desired product **11** with excellent diastereo- and enantioselectivity (Table 3.4, entry 10) but only with a moderate yield of 25%. It is important to mention at this point that since, we initiated our studies with a racemic mixture of **6**, the maximum yield of the enantiomerically pure product **11** could be as high as 50% only. Considering the above observations, we concluded that our effort towards the efficient enantioselective syntheses of tetrahydropyrroloquinolines via chiral thiourea mediated BA-catalysis might not be a suitable route to achieve our goal. Therefore, we decided to plan for an alternative methodology utilizing organocatalysis and the process is still under investigation.

Table 3.4. Brønsted Acid/Thiourea-Catalyzed Asymmetric Povarov Reaction



9a **6** **11**

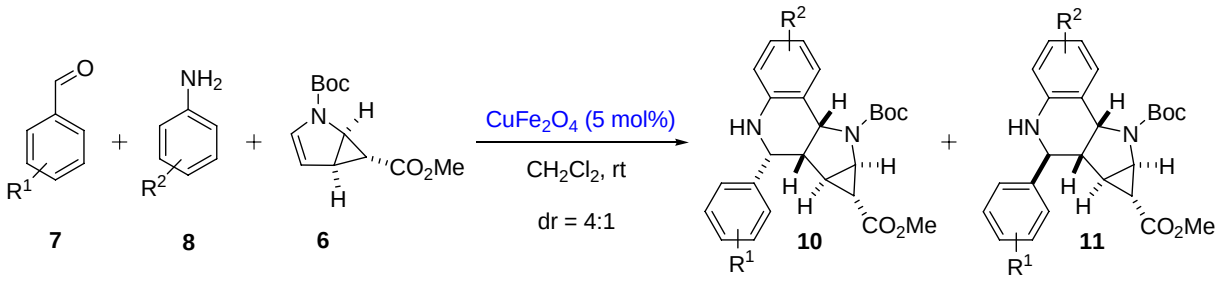
entry	TfOH (mol %)	thiourea (mol %)	temp (^{o} C)	yield (%)[a]	dr (*exo*:*endo*)[b]	*ee* (%) *exo* isomer[c]
1	10	10	RT	75	8:1	rac.
2	15	10	RT	86	6:1	rac.
3	5	10	-55	no reaction	-	-
4	10	10	-55	very little product	-	-
5	10	10	-50	10	99:1	52
6	10	10	-45	12	99:1	96
7	10	5	-45	12	1:1	rac.
8	12	10	-40	16	99:1	98
9	15	10	-40	21	99:1	26
10	**12**	**10**	**-30**	**25**	**49:1**	**>99**

[a] Major diastereomer, separated by column chromatography. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis after 48 h.

3.4. $CuFe_2O_4$ Nanoparticles as an Efficient Magnetically Recoverable Catalyst for the Povarov MCR

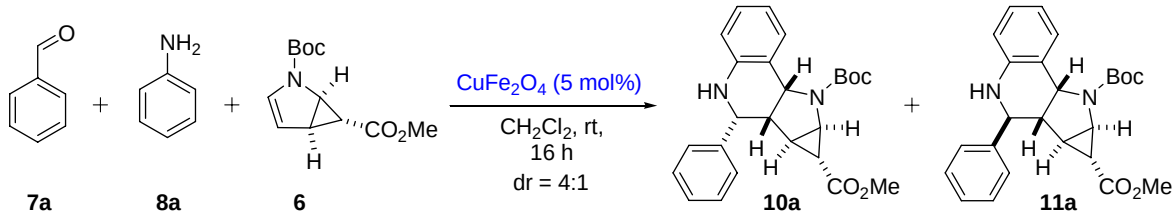
In recent years, the use of magnetic nanoparticles has become more and more attractive due to their numerous applications in synthesis and catalysis.[11] Catalyst recycling via magnetic separation is a promising alternative to filtration or centrifugation as it potentially prevents loss of catalyst and hence much more suitable for industrial applications. Although, various catalysts have been used for the Povarov-type reaction till date but only a few of them were recyclable. In this context, the use of heterogeneous catalysis, especially the use of magnetic Cu–Fe spinel catalyst ($CuFe_2O_4$) for this type of reaction is highly fascinating. Our aim was to exploit magnetically separable $CuFe_2O_4$ nanoparticles as a reusable catalyst for the synthesis of tetrahydropyrroloquinolines (**10** and **11**) from easily available starting materials (Scheme 3.6).

Scheme 3.6. Magnetically Recoverable $CuFe_2O_4$-Nanoparticle Catalyzed Povarov Reaction



To test the catalytic property with respect to the Povarov reaction, $CuFe_2O_4$ nanoparticles were prepared by literature known procedure.[12] Initial studies were performed using benzaldehyde **7a**, aniline **8a** and the electron rich olefin **6** in presence of different mol% of the catalyst and finally 5 mol% of $CuFe_2O_4$ was found to be the best considering both time as well as diastereoselectivity of the products (Table 3.5).

Table 3.5. Optimization of Reaction Condition with $CuFe_2O_4$ Nanoparticles as Catalyst[a]



7a **8a** **6** **10a** **11a**

entry	x mol%	conversion (%)[b]	time (h)	yield (%)[c]	dr[d]
1	20	100	12	72	3:1
2	15	100	12	72	3:1
3	10	100	15	70	3:1
4	5	100	16	75	4:1
5	2	85	24	61	4:1
6	1	80	24	58	4:1

[a] Reaction conditions: 0.835 mmol **7a**, 0.835 mmol **8a**, 0.334 mmol **6**, Catalyst (x mol%) and DCM (2 mL). [b] Determined by ^{1}H NMR. [c] Yields of isolated major diastereomer **10a**. [d] Determined by ^{1}H NMR.

To check the recyclability of the catalyst, after the reaction was complete, the catalyst was separated from the reaction mixture by magnetic decantation, washed with methanol and CH_2Cl_2, dried under vacuum and reused for the next cycle. The catalyst was found to be highly active up to 3 runs after which the reaction time was significantly increased for quantitative conversion of the olefin **6** (Table 3.6).

Table 3.6. Povarov Reaction Using $CuFe_2O_4$ Nanoparticles as Catalyst: Recycling Experiment[a]

entry	run	time (h)	yield (%)[b]	dr[c]
1	1	16	75	4:1
2	2	16	73	4:1
3	3	16	74	4:1
4	4	24	66	4:1

[a] Reaction conditions: 0.835 mmol **7a**, 0.835 mmol **8a**, 0.334 mmol **6**, 0.0167 mmol Catalyst (5 mol%) and DCM (2 mL). [b] Yields of isolated major diastereomer **10a**. [c] Determined by ^{1}H NMR.

3.5 Conclusion

In summary, we have successfully introduced a cyclopropanated enamine as a new olefin input for $Cu(OTf)_2$ catalyzed three component Povarov reaction affording a convenient way to synthesize pharmaceutically relevant tetrahydropyrroloquinoline scaffolds with novel connectivity and functionalization in very good yields and moderate diastereoselectivity. We have also focused to develop an efficient route to synthesize enantiomarically pure tetrahydropyrroloquinoline using a previously reported chiral thiourea catalyst and the process is still under investigation. Utilization of magnetically separable $CuFe_2O_4$-nanoparticles as the catalyst under mild reaction conditions is an additional sustainable contribution to this method. The catalyst was successfully recovered after completion of the reaction and reused for up to three consecutive cycles with high efficiency. Further extension of this work in light of the utilization of magnetic nanoparticles as the reusable catalyst and screening of some of the Povarov products for biological activities is ongoing.

3.6 References

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4. A Catalytic Multicomponent Approach for the Stereoselective Syntheses of *Cis*-4,5-Disubstituted Pyrrolidinones

4.1 *Cis*-4,5-Disubstituted Pyrrolidinones as Pharmaceutically Relevant Molecules

Pyrrolidinones are more commonly known as γ-lactams **19**, which represent the widespread structural features of many natural and designed biologically active molecules. A careful look at the structure of these five-membered heterocycles reveals that they are closely related to the folded conformation of γ-Amino-Butyric Acid (GABA) **18** (Figure 1), which is the dominant inhibitory neurotransmitter present in the mammalian central nervous system and seems to play a key role in the transportation of GABA across the membranes into different nerve tissues.[1]

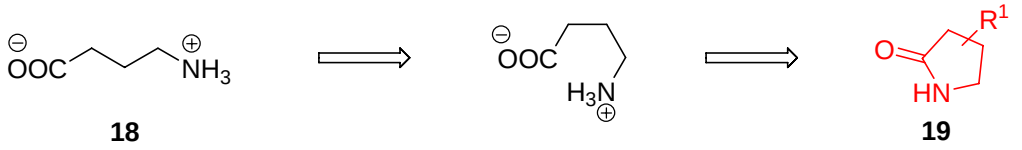


Figure 1. Structural resemblance of pyrrolidinones **19** with γ-amino-butyric acid **18**.

Consequently, pyrrolidinones have found profound applications in pharmaceutical development.[2] They are the core structures of nootropics or the so-called 'smart drugs' which are reported to improve several mental functions such as cognition, memory, concentration etc. Rolipram (**20**) is one of the examples of the nootropics which is a potent PDE4-inhibitor and hence, acts as an anti-inflammatory drug (Figure 2).[3]

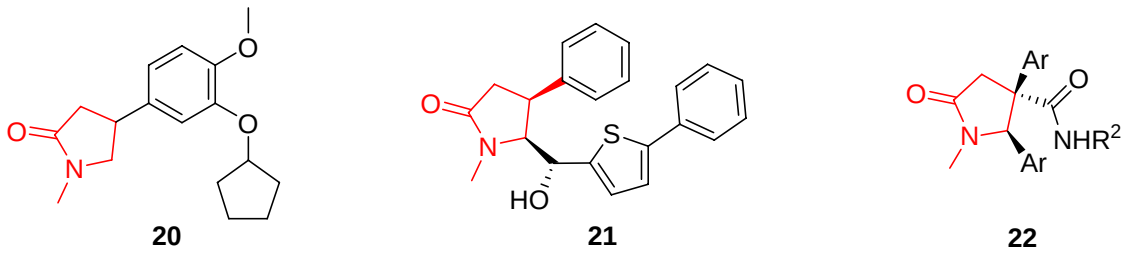


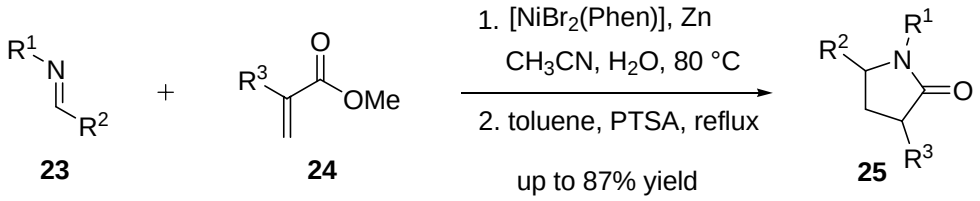
Figure 2. Pharmaceutically important pyrrolidinones.

Especially relevant for our study, Bayer Healthcare has identified *cis*-4,5-disubstituted pyrrolidinones containing aromatic and heteroaromatic groups (**21**) as lead structures for inhibition of type II 17β-hydroxysteroid dehydrogenase; being implicated in the treatment of osteoporosis.[2a] Likewise, *cis*-4,5-diarylated pyrrolidinones (**22**) have been reported to inhibit transcription factor HOXA13, a regulator of mammalian development of certain cancer types (Figure 2).[2c]

4.2 Syntheses of *Cis*-4,5-Disubstituted Pyrrolidinones

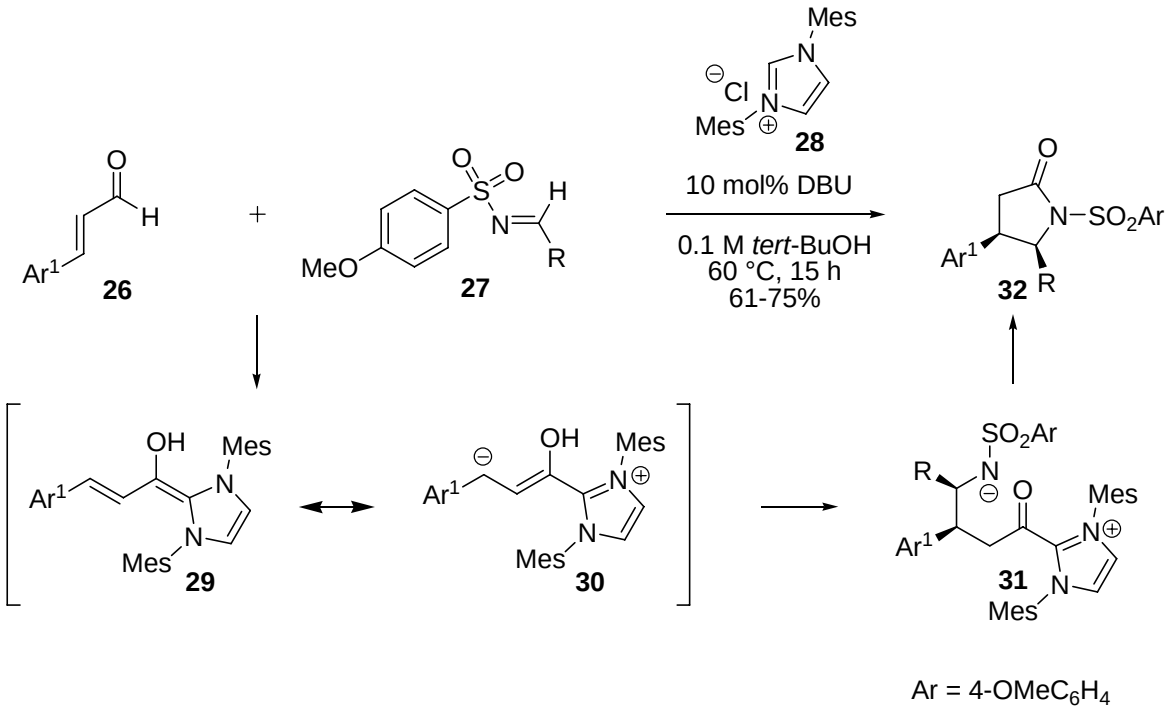
Because of the prevalence in pharmaceutical development and natural products, methods for the efficient stereoselective synthesis of substituted pyrrolidinones are on great demand.[4] Although, considerable efforts have been directed to a great number of synthetic approaches to these biologically important nitrogen-heterocycles, mainly based on Pd-catalyzed cyclization,[5] Ni-catalyzed reductive coupling of aldimines and activated alkenes (Scheme 4.1),[6] Rh-catalyzed intramolecular C-H insertion of diazo derivatives,[7] addition of homoenolates to imines,[8] *N*-heterocyclic carbene catalyzed addition of enals to imines,[9] ring expansion of β-lactams[10] and several cycloaddition strategies[10]; surprisingly, only a few methods exist related to *cis*-4,5-disubstituted pyrrolidinones,[5a,9a-b,10,13a-c] moreover, methods employing multicomponent reactions (MCR) are scarce in general.[11a,d]

Scheme 4.1. Regioselective Synthesis of Pyrrolidinones 25 by Nickel-Catalyzed Reductive Coupling of Aldimines 23 and Activated Alkenes 24



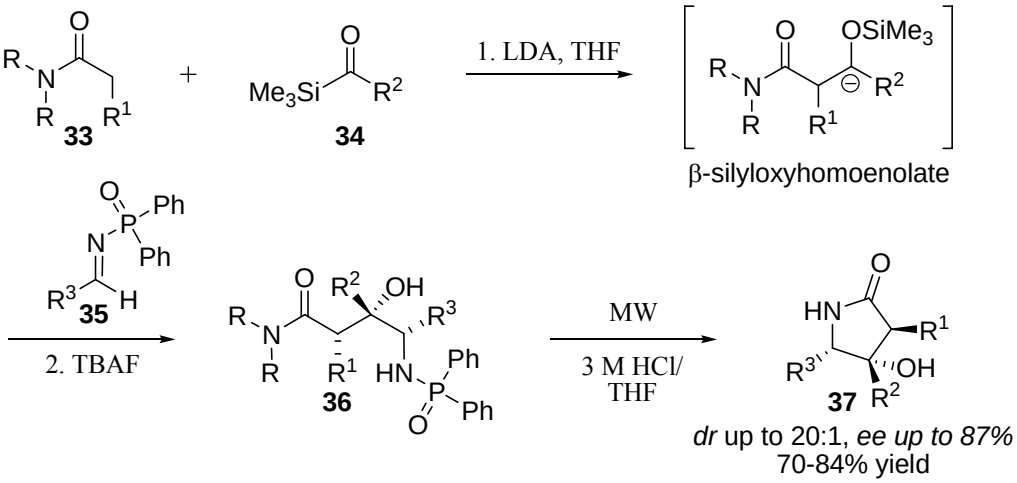
In this context, Bode et al. described the efficient synthesis of pyrrolidinones **32** via direct annulations of enals **26** and *N*-sulfonylimines **27** using *in situ*-generated, protonated *N*-heterocyclic carbene salt **28** as catalyst (Scheme 4.2).[9]

Scheme 4.2. Synthesis of Pyrrolidinones via Direct Annulation of Enals and *N*-Sulfonylimines



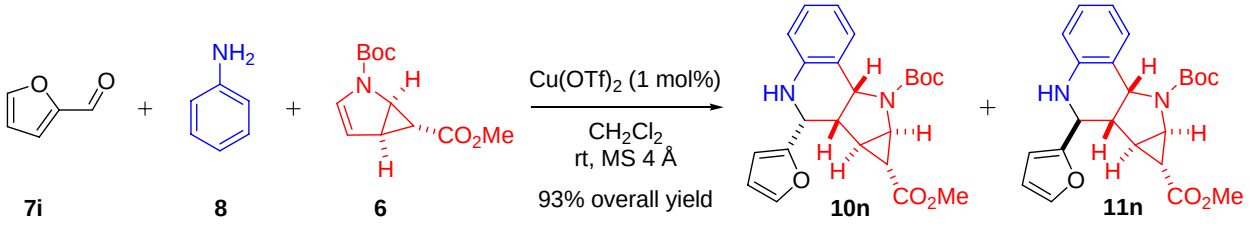
More recently, Scheidt et al. reported the stereoselective synthesis of substituted pyrrolidinones **37** from amideenolate **33**, acylsilane **34** and *N*-phosphenyl imine **35** in presence of LDA. Mechanistically, the reaction proceeds via the intermediate formation of a β-silyloxyhomoenolate equivalent (Scheme 4.3).[8]

Scheme 4.3. Stereoselective Synthesis of Substituted Pyrrolidinones 37 from Acylsilanes 34



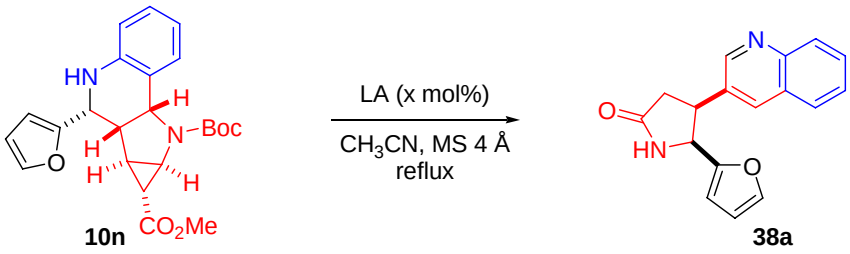
However, all of these processes suffer from lack of operational simplicity; hence development of alternative methodologies to access these valuable heterocycles by exploring new chemical building blocks is of great significance. In this context, utilization of multicomponent approaches, involving highly strained, functionalized D-A cyclopropane, bearing both electrophilic and nucleophilic centers to access pyrrolidinones is novel. As a continuation of our ongoing research, investigations into the unique chemistry of Lewis acid (LA) promoted cyclopropane ring-opening of the Povarov products revealed novel reactivity; especially, with a typical furyl substitution on the aldehyde part (**10n** and **11n**). As discussed in the previous chapter, a three-component reaction of furan-2-carbaldehyde **7i**, anilines **8a** and the cyclopropanated olefin **6** smoothly afforded the Povarov products **10n** and **11n** as a 3.5:1 diastereomeric mixture in favor of the *endo*-isomer **10n**, in presence of 1 mol% of $Cu(OTf)_2$ as a catalyst (Scheme 4.4). The two diastereomers obtained, can easily be separated on silica.

Scheme 4.4. Multicomponent Povarov Reaction Using $Cu(OTf)_2$ as Catalyst



Upon addition of one equivalent of $Yb(OTf)_3$ to **10n** (major diastereomer) in CH_3CN under reflux condition, surprisingly afforded the *cis*-4,5-disubstituted pyrrolidinone **38a**; an unusual, rearranged product as a single diastereomer in 79% of isolated yield (Table 4.1, entry 4). Lowering in the catalyst loading reduced the conversion as well as the yield of the product **38a** with an increased reaction time (Table 4.1, entry 3), a lowered catalyst loading of 50 mol% of $Yb(OTf)_3$ gave only a little conversion, indicating very weak substrate-metal binding (Table 4.1, entries 1 and 2). No reaction was observed in absence of the catalyst, revealing the necessity of the catalyst for the generation of the 1,3-dipole (Table 4.1, entry 14). In order to avoid stoichiometric catalyst loading, a variety of other LAs were screened and finally 40 mol% of $Sc(OTf)_3$ was emerged as the catalyst of choice, ensuing a clean reaction, giving the same rearranged product **38a** after 12 h as a single diastereomer in 80% of isolated yield (Table 4.1, entry 7).

Table 4.1. Optimization of Metal-Triflate Catalyzed Rearrangement of the Povarov Product 10n[a]



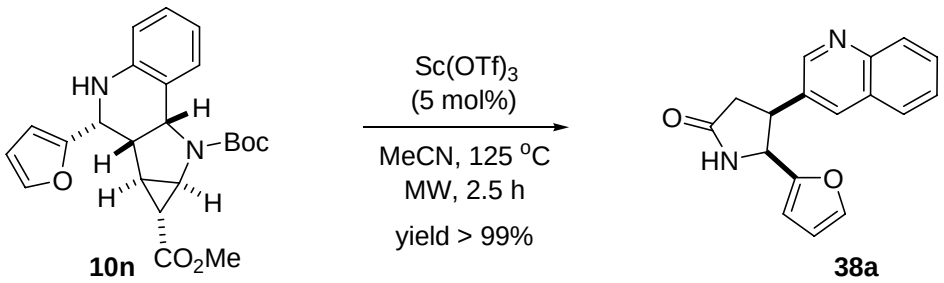
10n **38a**

entry	catalyst	x mol%	conversion[b] (%)	isolated yield (%)	time (h)
1	$Yb(OTf)_3$	40	0	--	--
2	$Yb(OTf)_3$	50	0	--	--
3	$Yb(OTf)_3$	75	80	55	36
4	$Yb(OTf)_3$	100	100	79	24
5	$Sc(OTf)_3$	20	80	50	36
6	$Sc(OTf)_3$	30	91	69	36
7	$Sc(OTf)_3$	40	100	80	12
8	$Y(OTf)_3$	20	50	45	48
9	$Y(OTf)_3$	30	50	45	40
10	$Y(OTf)_3$	40	65	60	36
11	$Gd(OTf)_3$	20	40	21	36
12	$Gd(OTf)_3$	40	50	35	48
13	$Cu(OTf)_2$	40	no reaction	--	--
14	Blank	--	no reaction	--	--

[a] Reaction conditions: 0.5 mmol **10n**, Catalyst (x mol%) and MeCN (2 mL), [b] Determined by ^1H NMR.

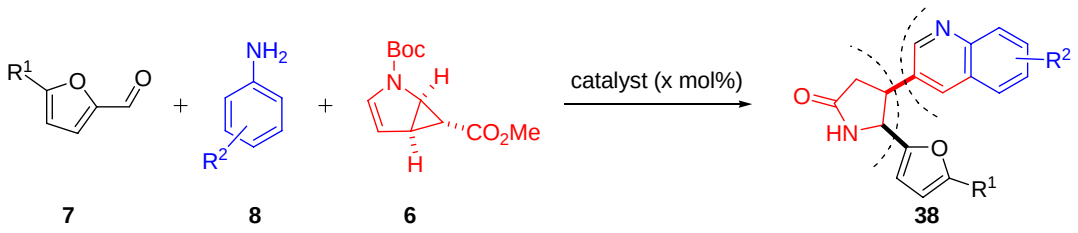
The higher oxophilicity and smaller ionic radius of $Sc(OTf)_3$, compared to the other lanthanide triflates presumably helps in its more effective binding to the substrate and hence, $Sc(OTf)_3$ behaves as a more active catalyst in this case. When the catalyst loading was decreased to 20 mol%, the desired product **38a** was obtained with only 50% yield and increased reaction time of 36 h (Table 4.1, entry 5). The relatively higher catalyst loading prompted us to look for better alternatives. In this context, microwave (MW)-assisted organic synthesis has demonstrated itself to be superior in many instances when compared to reactions carried out using conventional thermal conditions.[12] The use of MW irradiation often helps to reduce reaction time, minimize side products and also to improve yields. Based on these facts, we examined the effect of microwave heating on our reaction system. Gratifyingly, a much lower (eight times) loading of only 5 mol% $Sc(OTf)_3$ afforded the same desired product **38a** in 99% of isolated yield, when the reaction mixture was irradiated in a microwave at 125 °C for 2.5 h (Scheme 4.5) in absence of molecular sieves. Next, we turned our attention to synthesize the *cis*-pyrrolidinones **38** in a multicomponent (MCR) one-pot fashion to overcome the time consuming as well as expensive purification methods of the stepwise procedure.[13-16]

Scheme 4.5. Microwave-Assisted Rearrangement of 10n.



To our delight, $Sc(OTf)_3$-catalyzed multicomponent assembly of furan-2-carbaldehydes **7i**, aniline **8a** and cyclopropanated *N*-Bocpyrrole **6**, smoothly afforded synthetically challenging *cis*-4,5-disubstituted pyrrolidinone **38a** in high yield (82%) with excellent stereoselectivity (Table 4.2, entry 15). Among a number of Lewis acids which were screened, we found that 5 mol% of $Sc(OTf)_3$) under microwave (MW) irradiation is best suited for this process which combines a Povarov reaction,[17] donor-acceptor induced cyclopropane ring opening, a 1,4-furan ring migration and quinoline formation, involving the formation and breaking of one C-O, four C-N and five C-C bonds.

Table 4.2. Optimization of Metal-Triflate Catalyzed Multicomponent Reaction of 7, 8 and 6[a]



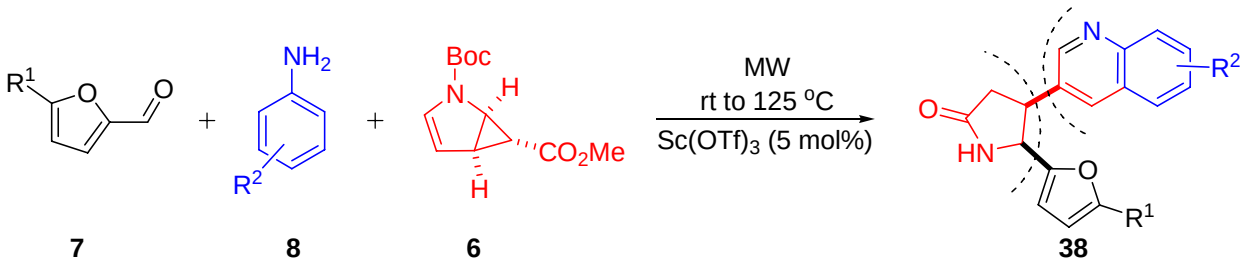
7 **8** **6** **38**

entry	catalyst	x mol%	conversion %[b]	yield of **38** (%)[c]	condition	time (h)
1	$Cu(OTf)_2$	20	only **10n** was obtained	--	reflux	--
2	$Yb(OTf)_3$	40	only **10n** was obtained	--	reflux	--
3	$Yb(OTf)_3$	50	only **10n** was obtained	--	reflux	--
4	$Yb(OTf)_3$	75	80	55	reflux	36
5	$Yb(OTf)_3$	100	100	79	reflux	24
6	$Y(OTf)_3$	20	50	45	reflux	48
7	$Y(OTf)_3$	30	50	45	reflux	40
8	$Gd(OTf)_3$	40	50	35	reflux	48
9	$Y(NO_3)_3$	40	40	36	reflux	72
10	$Sc(OTf)_3$	40	100	85	reflux MW	12 2
11	$Sc(OTf)_3$	30	90	79	reflux	36
12	$Sc(OTf)_3$	20	100	82	reflux MW	36 2.5
13	**$Sc(OTf)_3$**	**5**	**100**	**82**	**MW**	**6**

[a] Reaction conditions: 0.4 mmol **7**, 0.4 mmol **8**, 0.334 mmol **6**, Catalyst (x mol%) and MeCN (2 mL), [b] Determined by ^1H NMR.[c] Yields of isolated product **38**.

Using readily available furancarbaldehydes **7** and aromatic amines **8**; a broad range of *cis*-4,5-disubstituted pyrrolidinones could be synthesized with complete chirality transfer from **6** in high yields. For the majority of transformations investigated (*rac*)-**6** was employed, nevertheless, employing enantiopure (+)-**6** (Table 4.3, entry 1) gives rise to **38a** with no erosion of stereochemistry.

Table 4.3. $Sc(OTf)_3$ catalyzed one-pot reaction of 7, 8 and 6[a]



7 **8** **6** **38**

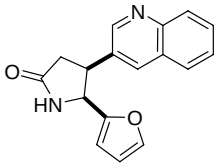
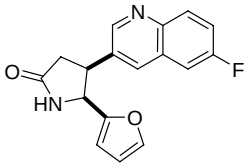
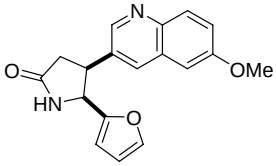
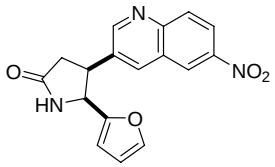
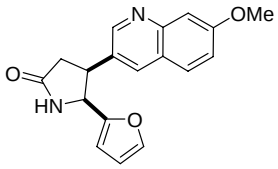
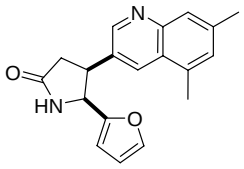
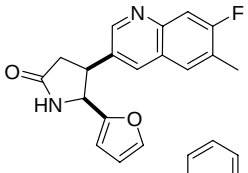
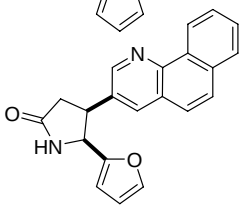
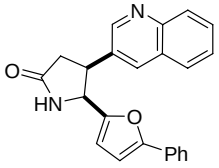
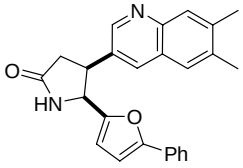
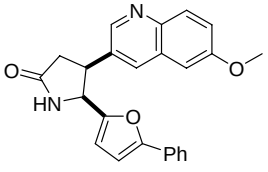
entry	R^1	R^2	product	**35**	time (h)	yield (%)[b]
1	H	H		**38a**	6.0	82
2	H	F		**38b**	5.0	76
3	H	4-OMe		**38c**	5.5	75

Table continued..

entry	R^1	R^2	product	**38**	time (h)	yield (%)[b]
4	H	4-NO_2		**38d**	4.0	83
5	H	3-OMe		**38e**	5.5	65
6	H	3,5-$(Me)_2$		**38f**	6.0	38
7	H	3-F,4-Me		**38g**	4.5	84
8	H	1-napthyl		**38h**	5.5	77
9	Ph	H		**38i**	5.5	71
10	Ph	3,4-$(Me)_2$		**38j**	5.5	69
11	Ph	4-OMe		**38k**	5.5	74

[a] Reaction conditions: 0.4 mmol **7**, 0.4 mmol **8**, 0.334 mmol **6**, $Sc(OTf)_3$ (5 mol%), 1.5 h room temp., 3-4.5 h 125 ^oC, MW. [b] Yield of isolated product.

Both electron withdrawing and donating substituents on aniline are tolerated well, allowing the generation of a variety of quinoline moieties in 4-position of the pyrrolidinone (Table 4.3, entries 2-7, 10-11). Out of the two regioisomers possible when 3-substituted anilines are employed (Table 4.3, entries 5-7), only the sterically less hindered quinoline placing that group in 7- rather than 5-position is formed. When the sterically more crowded 5-position cannot be avoided, yield of the product significantly decreases as 1-napthylamine resulted in the corresponding benzo[h]quinoline moiety instead of a quinoline (Table 4.3, entry 8). Also, phenyl substitution in 5-position of furans is tolerated well (Table 4.3, entries 9-11).

The structural assignment of pyrrolidinones **38** (Table 4.3, entries 1 and 10) was confirmed unambiguously by single-crystal X-ray analysis of **38a** and **38j** (Figure 4.3).

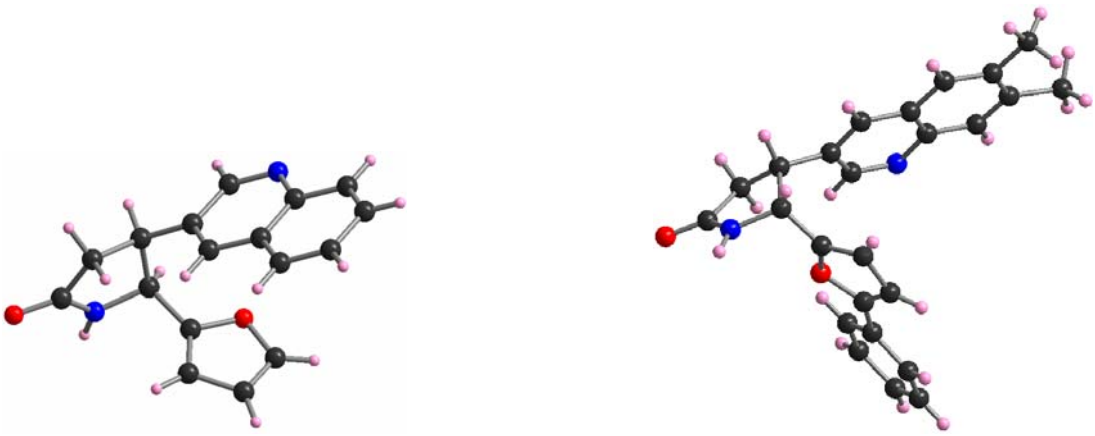


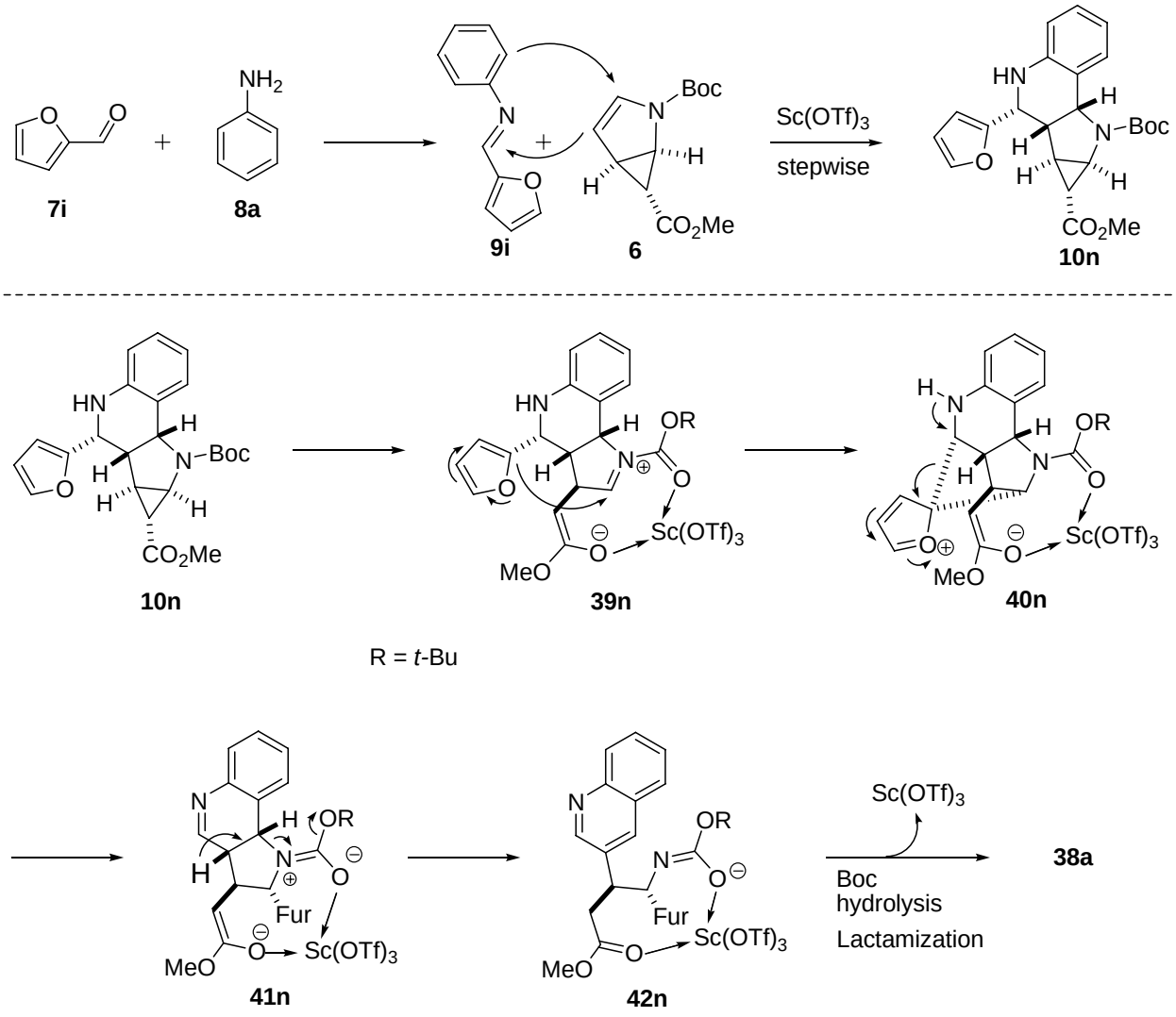
Figure 4.3. X-ray crystal structures of **38a** and **38j** in Table 4.3.

4.3 Proposed Mechanism

A plausible mechanism for the synthesis of **38** (Scheme 4.6) involves the initial Povarov reaction (sequence of Mannich reaction and intramolecular electrophilic substitution)[18] of aldimine **9i** onto enamide **6** at its *exo*-face. Interestingly, the bicyclic structure of **6** must also control the stereochemistry of the furan group, which is found on the *endo*-face of the bicyclo[4.3.0] ring system, being opposite as found in Povarov reactions with simple 2,3-dihydrofuran or 2,3-

dihydro-1*H*-pyrroles.[18a] As a consequence of this stereochemical outcome, the *cis*-configured aldimine **9i** rather than the *trans*-isomer must undergo the cycloaddition.

Scheme 6. Plausible Mechanism for the Synthesis of Substituted Pyrrolidinones 38

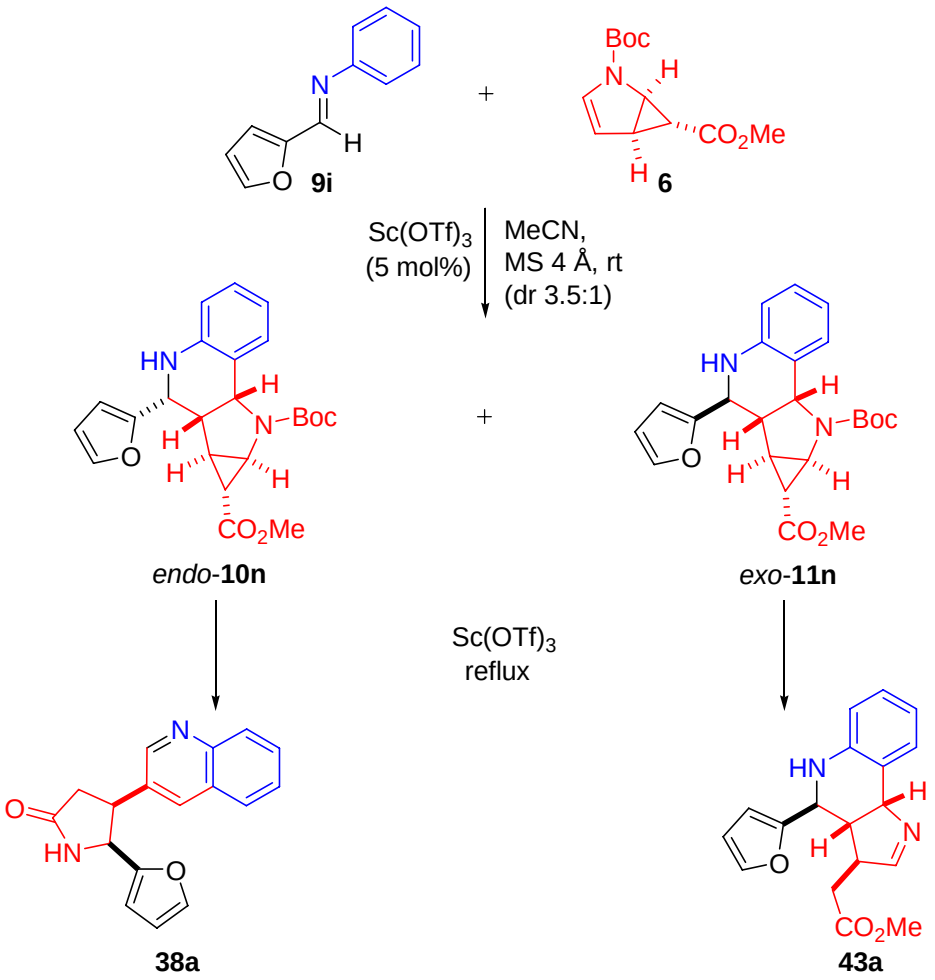


Subsequent formation of iminium ion **39n** by $Sc(OTf)_3$-mediated cyclopropane ring opening followed by furan migration via a spiroannulated intermediate[19] **40n** could lead to **41n**, which undergoes rearomatization that requires an unusual C-N-bond cleavage to give rise to **42n** that finally collapses to the pyrrolidinone **38a** upon *N*-Boc hydrolysis and lactamization. Indeed, as we discussed earlier, the Povarov products **10n** and **11n** could be obtained by carrying out the reaction at ambient temperature rather than at reflux condition. Notable, both *endo*- and *exo*-

diastereomers with respect to the stereochemistry of the furan substituent, being readily separated on silica, could be obtained. While *endo*-**10n** was still the major stereoisomer formed, under these reaction conditions more of *exo*-**11n** must have formed compared to the reaction conditions for the one-step process to pyrrolidinones **38** described above.

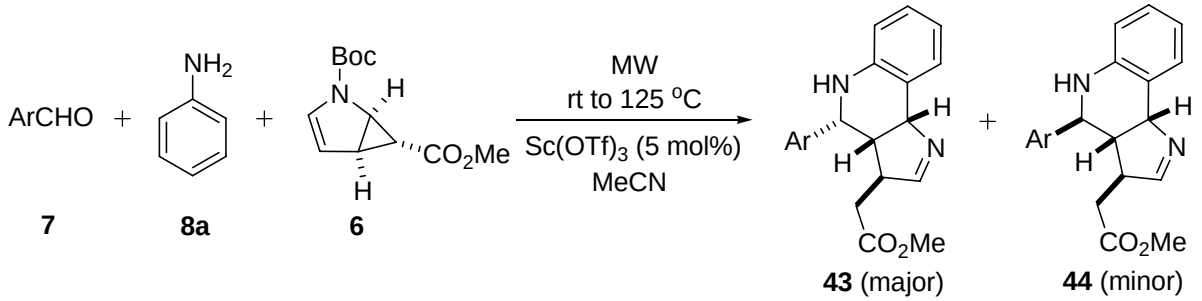
Subjecting *endo*-**10n** and *exo*-**11n** individually to those conditions, *endo*-**10n** cleanly rearranged to the previously obtained pyrrolidinone **38a**, while *exo*-**11n** yielded the ring-opened polycyclic imine **43a** indicating that the specific conformational arrangement of the *endo*-**10n** is optimal for the rearrangement to proceed. In the case of *exo*-**11n**, the migration of the furan moiety to the iminium-centre through the formation of crucial spiro-intermediate is presumably blocked by the H-atom on the ring C-atom next to the furan (Scheme 4.7).

Scheme 4.7. Cycloaddition of 9i, 6 and Subsequent Rearrangement.



When other aromatic aldehydes but furans were employed, stable polycyclic imines **43** and **44** were obtained as a diastereomeric mixture in very good overall yields (Table 4.4), suggesting that the furan moiety is unique for the observed 1,4-migration.

Table 4.4. Synthesis of Policyclic Imine Derivatives 43[a]



7 **8a** **6** **43** (major) **44** (minor)

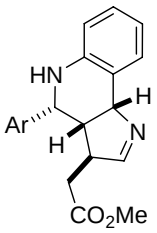
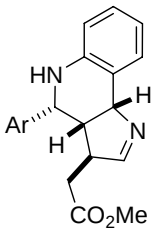
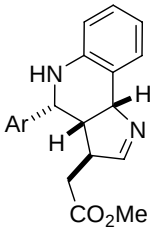
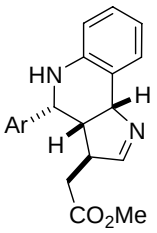
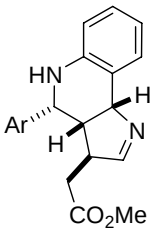
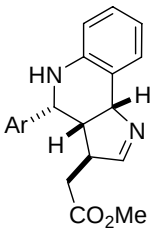
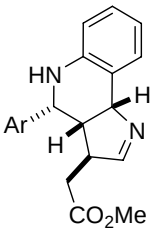
entry	Ar	product[b,c]	**43**	time (h)	yield (%)[d]	dr[e]
1	Ph		**43a**	3.5	64	2:1
2	4-ClC_6H_4		**43b**	3.0	69	2.5:1
3	4-MeC_6H_4		**43c**	3.0	61	2:1

Table continued..

entry	Ar	product[b,c]	**43**	time (h)	yield (%)[d]	dr[e]
4	4-$OMeC_6H_4$		**43d**	3.0	60	2:1
5	4-$NO_2C_6H_4$		**43e**	2.5	65	2:1
6	1-napthyl		**43f**	2.0	70	2.6:1
7	2-thionyl		**43g**	1.0	53	1.5:1

[a] Reaction conditions: Aromatic aldehyde **7** (0.40 mmol), aniline **8** (0.40 mmol) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (0.334 mmol) in 4 mL, 5 mol% $Sc(OTf)_3$ (0.016 mmol) acetonitrile, 1.5 h at room temp., 1-3.5 h at 125 ^oC, MW. [b] Major diastereomer, separated by column chromatography. [c] Stereochemistry determined by analogy to entry 1, Table 2. [d] Isolated yield of major isomers. [e] Determined by ^1H NMR.

The structure of **43a** (Table 4.4, entry 1) was unequivocally established by single-crystal X-ray analysis (Figure 4.4).

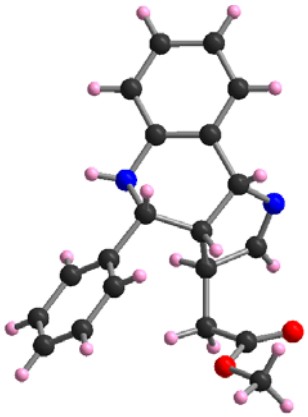
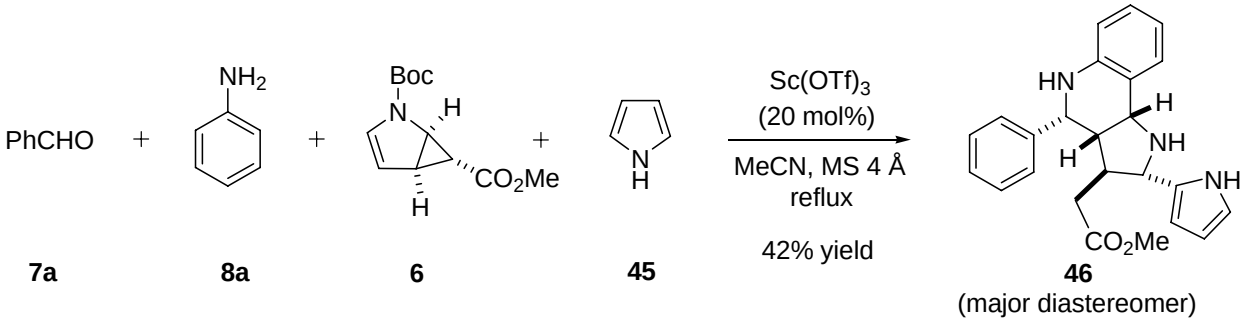


Figure 4.4. X-ray crystal structures of **43a** in Table 4.4.

This observation opens up the opportunity for a four component reaction by introducing suitable external nucleophile that could add to the imine functionality in **43**. Indeed, $Sc(OTf)_3$ catalyzed MCR between benzaldehyde **7a**, aniline **8a**, enamide **6** and pyrrole **45** resulted in the formation of a polycyclic compound **46** as a mixture of four diastereomers (4.5:2.5:2:1) with 42% of isolated yield of the major diastereomer (Scheme 4.8).

Scheme 4.8. Functionalization of 43 via Intermolecular Trapping of Iminium Ion



4.4 Properties of the *Cis*-Pyrrolidinones

As an initial effort towards studying biological activities, we measured the fluorescence spectra of some of the *cis*-pyrrolidinones and interestingly compounds **38a** and **38h** showed a strong fluorescent property, which could make them potentially useful as biomarkers (Figures 4.5 and 4.6). Some more studies are still under investigation.

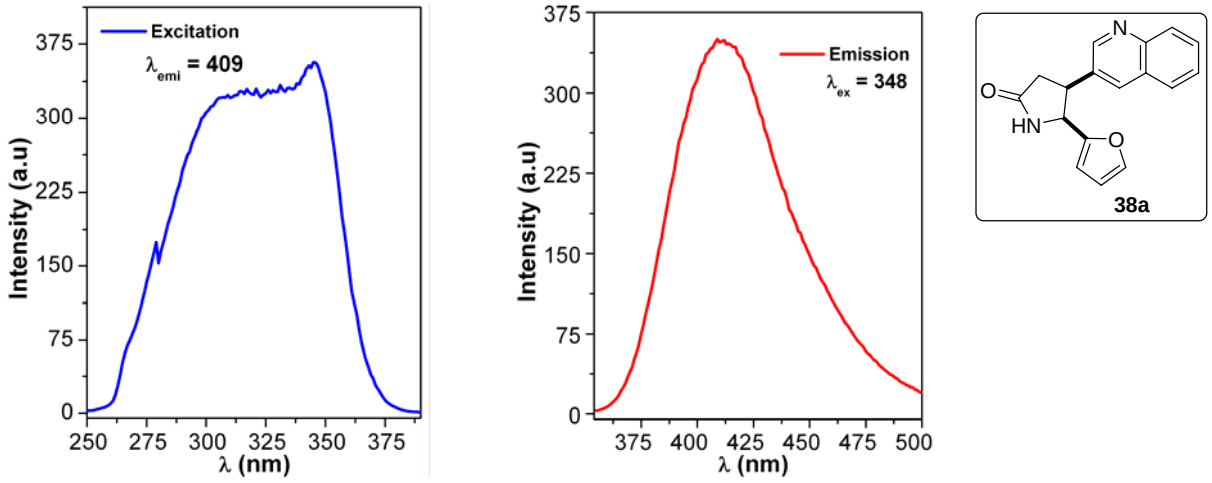


Figure 4.5. Excitation (left) and Emission (right) spectra of compound **38a** (0.2 μM solution in acetonitrile) with their indicated maxima.

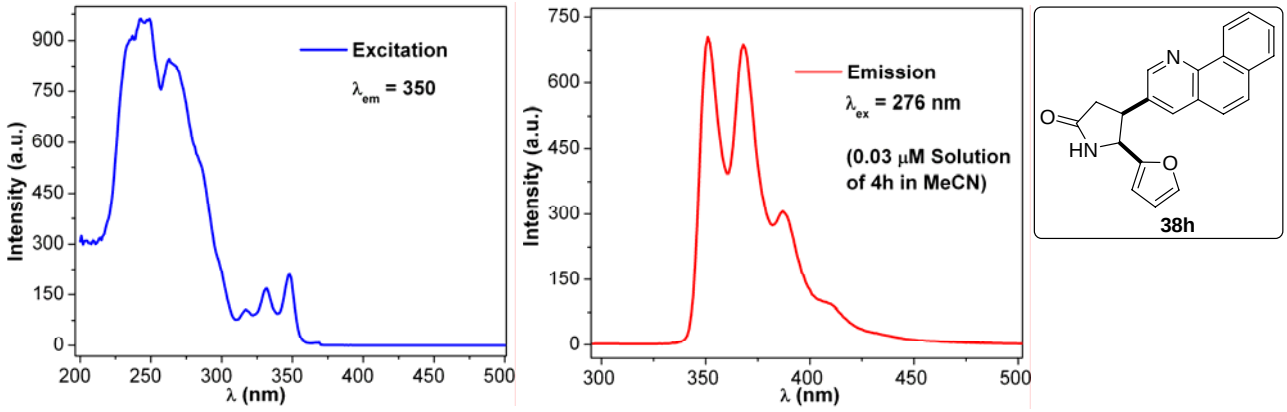


Figure 4.6. Excitation (left) and Emission (right) spectra of compound **38h** (0.2 μM solution in acetonitrile) with their indicated maxima.

4.5 Conclusion

In conclusion, we have developed an unprecedented, catalytic three component reaction, based on the readily available donor-acceptor substituted cyclopropane adduct of *N*-Boc-pyrrole **6** to access a range of functionalized *cis*-4,5-disubstituted pyrrolidinones **38** in a stereoselective manner with high yield. The use of chiral cyclopropane derivative in the initial step affords the

pyrrolidinones in high enantiomeric excess. Finally, systematic multi-step syntheses were performed to establish the plausible mechanism for the stero-specific nature of this MCR which shows that $Sc(OTf)_3$ catalyzed opening of cyclopropane ring leads to the formation of iminium cation as a common and key intermediate which was further trapped employing external nucleophile. Furan containing *endo*-Povarov product can undergo a facile 1,4 furan migration through a spiro-intermediate leading to stereo-selective synthesis of *cis*-lactam, while its *exo*-analogue cannot afford such migration due to the steric hindrance by it neighboring H-atom and thus results in the formation of the polycyclic imine. Moreover, other non-furan aromatic analogues give rise to similar polycyclic imines as they presumably lack the formation of important spiro-intermediate for such long distance 1,4 migration. Since, *cis*-pyrrolidinones are ubiquitous structural constituents in pharmacologically important molecules with many interesting applications; the operational simplicity and excellent yields, combined with lower amount of catalyst loading, time and step economic aspects should make this new heterocycle synthetic strategy highly attractive and promising in the development of new functionalized molecules.

4.6 References

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5. A Catalytic Multicomponent Approach for the Efficient Syntheses of Tetrahydro-, Dihydro- and 1*H*-Pyrazoles

5.1 Biological Importance

Five-membered aza-heterocycles containing two ring nitrogen atoms, e.g., tetrahydro-, dihydro- and 1*H*-pyrazoles are found as core structural components of a few complex natural products and numerous synthetically designed bioactive molecules including agrochemicals[1] and important drugs such as Celebrex[2] and Viagra.[3] Most of these heterocyclic compounds not only demonstrate high potential as antidepressants,[4] analgesics,[5] anticonvulsants,[6] but also possess many other therapeutic applications (Figure 5.1).[7-9] As a consequence, these aza-heterocycles have become attractive synthetic targets, demanding the development of new/alternative chemical reactions for their easy access from readily available starting materials.

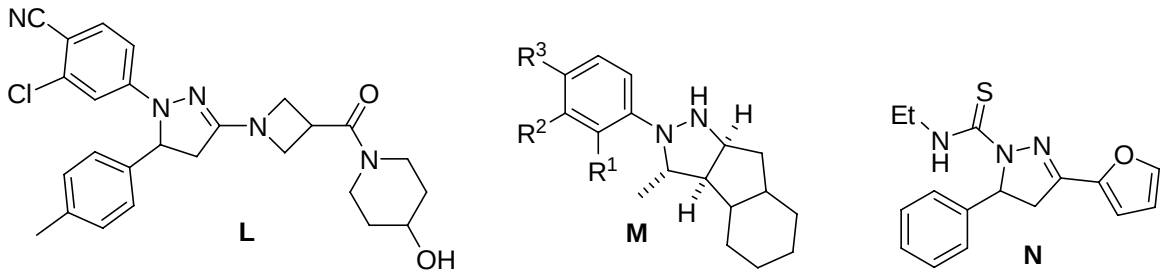


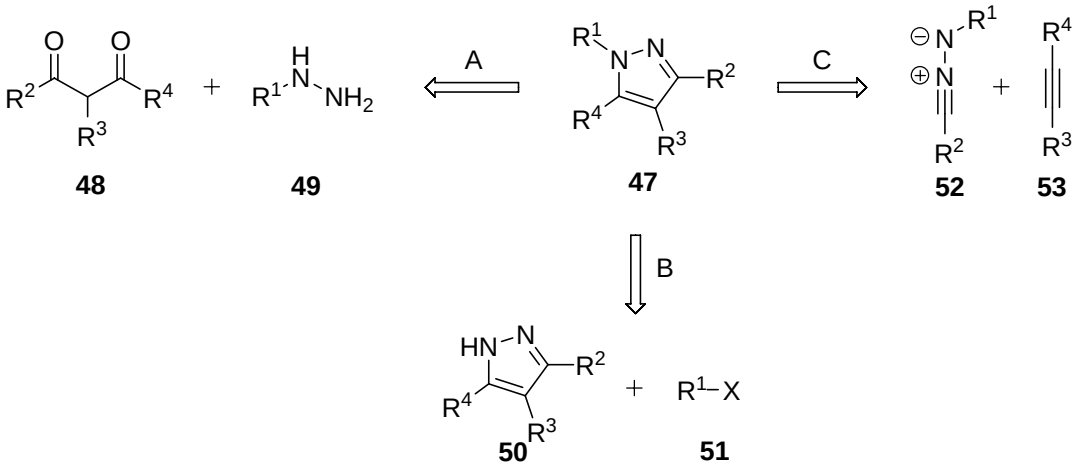
Figure 5.1. Compound **L** is used for treating and/or preventing renal injury, cardiovascular diseases, especially hypertension, and/or endocrine diseases; Compound **M** is a potent anti-proliferative agent;[10] Compound **N** shows antidepressant activity.

5.2 Literature Precedence on the Syntheses of Tetrahydro-, Dihydro- and 1*H*-Pyrazoles

Cyclocondensation of 1,3-dicarbonyl compounds **48** with hydrazine derivatives **49** represents one of the simplest and most general approaches for the construction of pyrazole derivatives (Scheme 5.1, route A).[11] A serious drawback of this cycloaddition method is the lack of

selectivity; products are obtained as a mixture of different regioisomers, if the reactivity of the two carbonyl groups is not profoundly different. Replacement of 1,3-dicarbonyl compounds with α,β-ethynyl ketones or esters could afford regioselectivity, depending on specific substrates.[12] However, if a diversity-oriented synthesis of pyrazoles is desired, these methods become cumbersome as each 1,3-diketone must be purified prior to use, since they are often obtained as a mixture of condensation products. Furthermore, the presence of electron-withdrawing functional groups on **48**, such as aldehydes, nitriles, esters and alkyl halides, prevent the required transformation to access the desired pyrazole **47**. Another increasingly utilized approach is the functionalization at N-1 of the preformed tri-substituted pyrazole **50** by either nucleophilic substitution or transition metal catalyzed C-N bond formation reaction (Scheme 5.1, route B).[13]

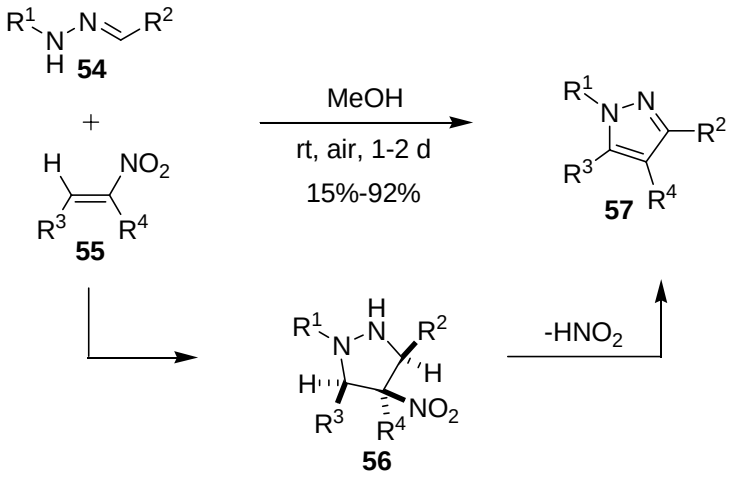
Scheme 5.1. General Approaches for the Syntheses of Substituted Pyrazoles



Arguably, the most popular and potential approach for the synthesis of substituted pyrazoles is the 1,3-dipolar cycloaddition of azomethine imines **52** with multiple-bond containing systems **53** under thermal or strongly acidic conditions (Scheme 5.1, route C).[14-16]

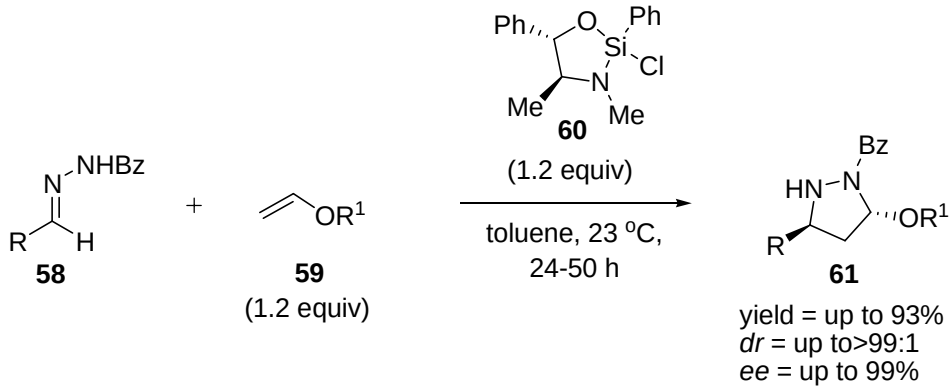
Reaction of *N*-monosubstituted hydrazones **54** with electron-deficient nitroolefins **55** to afford substituted pyrazoles **57** in a regioselective manner under catalyst free condition, can be considered as a significant alternative to the previously mentioned harsh reaction conditions (Scheme 5.2).[17]

Scheme 5.2. Reaction of *N*-Monosubstituted Hydrazones 54 with Nitro-Olefins 55



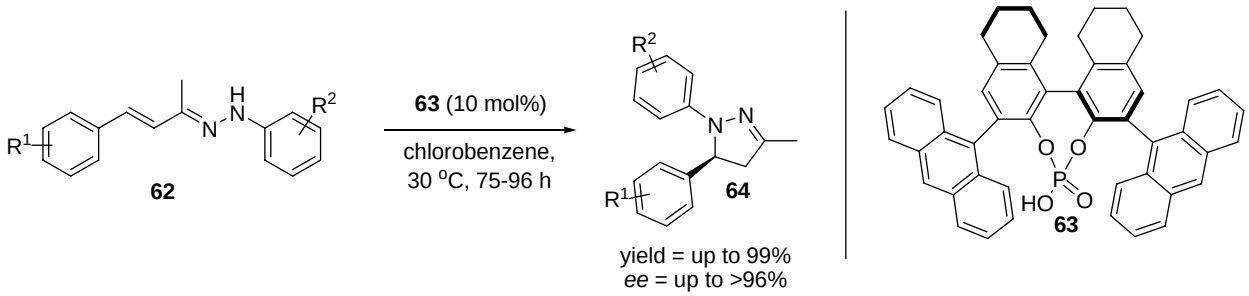
Methods have also been developed for the enantioselective synthesis of these valuable heterocycles. In this regard, Leighton and co-workers reported an asymmetric intermolecular [3+2] cycloaddition of benzoylhydrazone **58** and acyclic enol ether **59** using 1.2 equivalents of a chiral pseudoephedrine-derived silane Lewis acid **60** to afford the corresponding enantiopure tetrahydropyrazoles **61** in good yields and diastereoselectivity (Scheme 5.3).[18]

Scheme 5.3. Chiral Silicon Lewis Acid Catalyzed [3+2] Cycloaddition of Acylhydrazone 58 and Enol Ether 59



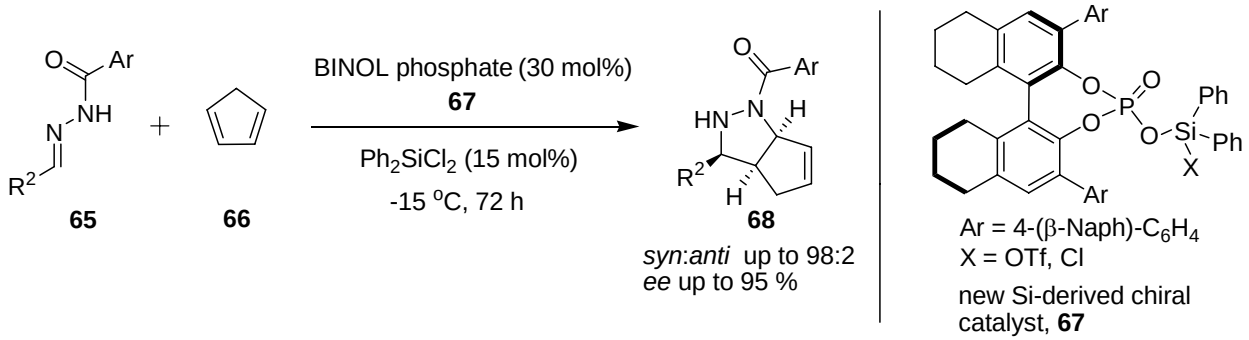
In 2009 Müller and List showed that chiral Brønsted acids (**63**) can efficiently catalyze the cycloisomerization of α,β-unsaturated hydrazones **62** to produce pyrazolines or dihydropyrazoles **64** in high yields and enantiomeric excess (Scheme 5.4).[19]

Scheme 5.4. Chiral Phosphoric Acid-Catalyzed Intramolecular 6π-Electrocyclization of α-β-Unsaturated Arylhydrazones 62



Recently, Tsogoeva et al. reported an *in situ*-generated silicon Lewis acid-derived chiral Brønsted acid (**67**) catalyzed [3+2] cycloaddition of preformed acylhydrazone **65** and cyclopentadiene **66** for the enantioselective synthesis of pyrazolidines or the so called tetrahydropyrazoles **68** (Scheme 5.5).[20]

Scheme 5.5. [3+2] Cycloaddition of Acylhydrazone 65 and Cyclopentadiene 66 Using BINOL Phosphate/Ph_2SiCl_2 67 as a Catalytic System.

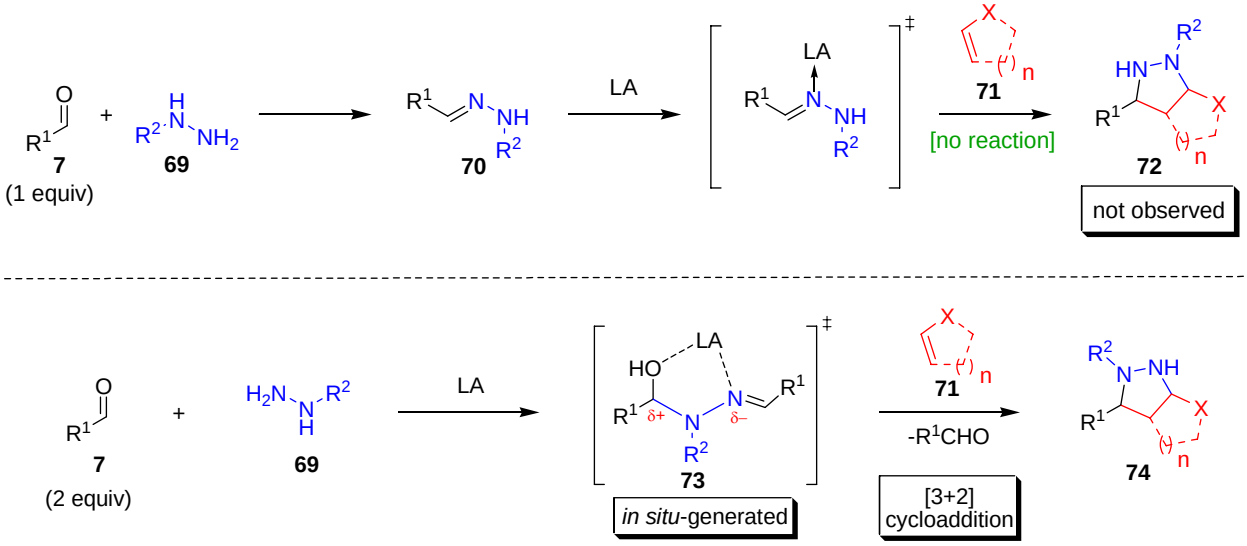


5.3 $Cu(OTf)_2$-Ctalyzed Multicomponent (AAB-Type) Approach for the Syntheses of Tetrahydro-, Dihydro- and 1*H*-Pyrazoles

Although, the use of various Lewis acids allows the cycloaddition to proceed under milder condition with improved diastereoselectivity compared to the conventional methods,[21-23] many available methods for synthesizing aza-heterocycles are limited to intramolecular versions[24a,b] and/or the substrates are mainly restricted to preformed acylhydrazones[25] and acyclic enol ethers[24c] or silyl enol ethers, confined by several drawbacks such as unsatisfactory yields, poor chemo- and/or stereoselectivity, etc. Electron-deficient olefins, such as nitroolefins are usually

known to undergo this type of cycloaddition, mainly with *N*-monosubstituted hydrazones[17] or diazo compounds[26]. Therefore, the development of more general strategies for the syntheses of these structurally diverse heterocyclic compounds with multiple functionalities is highly desirable. Till to date, there are no such reports where enamides and cyclic enol ethers are employed as electron-rich olefins for synthesizing pyrazoles and related five-membered heterocycles. Moreover, utilization of *in situ*-derived *N*-hydroxymethyl hydrazones **73** from readily available aldehydes and *N*-monosubstituted hydrazines in a one-pot multicomponent fashion (AAB-type), instead of using preformed hydrazones **70** is novel. As a continuation of our ongoing interest in exploring the scope of LA-catalyzed cycloaddition reactions,[27] we envisioned the possibility of generating a 1,3-dipol on the *in situ*-generated α-hydroxy-*N*-aminomethylphenylhydrazone **73** by the condensation of two equivalents of aldehyde and one equivalent of *N*-methyl hydrazine, which could then undergo a cycloaddition reaction with various electron-rich olefins **71** affording functionalized five-membered aza-heterocycles **74** (Scheme 5.6).

Scheme 5.6. Strategy for the Syntheses of Five-Membered Aza-Heterocycles 74[a,b]



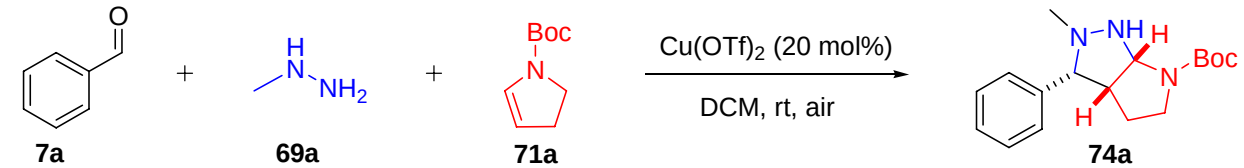
[a] X = N-Boc, O; n = 1, 2. [b] When one equiv of aldehyde **7** was used, the corresponding hydrazone **70** was obtained, but the desired cycloaddition product **72** was not observed upon addition of the olefin **71**.

In this scenario, a few challenges had to be encountered: (1) the hydrazine **69** should not deactivate the LA catalyst; (2) the catalyst should preferentially coordinate to the active

intermediate **73** to introduce regioselectivity but not with the azomethine imine **70** which might form first during the course of the reaction; (3) the reaction should proceed through a concerted pathway in order to achieve diastereoselectivity.

We initiated our studies by investigating a one-pot, three component (AAB-type) reaction of two equivalents of benzaldehyde **7a**, one equivalent of *N*-methyl hydrazine **69a** and *tert*-butyl 2,3-dihydropyrrole-1-carboxylate **71a** in presence of various LA catalysts and the results are summarized in Table 5.1.

Table 5.1. Optimization of Lewis Acid Catalyzed [3+2] Cycloaddition Reaction[a]



7a (2 equiv) **69a** **71a** **74a**

entry	catalyst	x mol%	yield[b] (%)	condition	time (h)
1	Blank	--	--	rt	24
2	Blank	--	--	reflux	24
3	Blank	--	--	MW, 125 °C	2
4	CuI	20	--	rt	24
5	$Cu(OTf)_2$	10	45	rt	12
6	$Cu(OTf)_2$	15	56	rt	12
7	**$Cu(OTf)_2$**	**20**	**65**	**rt**	**6**
8	$Yb(OTf)_3$	10	>10	rt	12
9	$Yb(OTf)_3$	20	25	rt	12

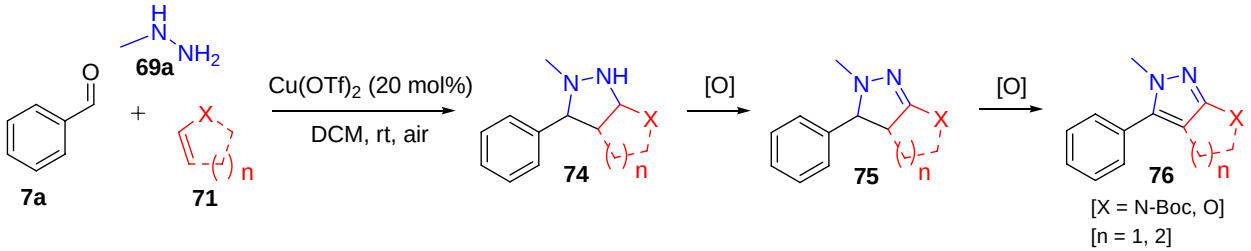
Table continued..

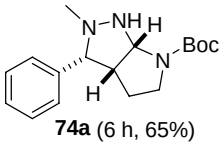
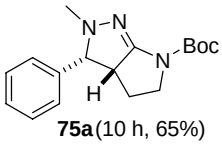
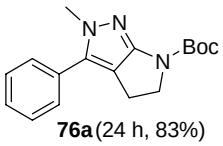
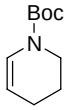
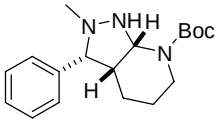
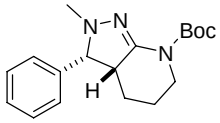
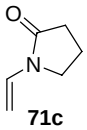
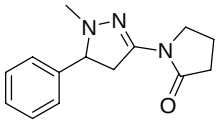
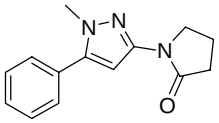
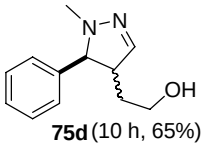
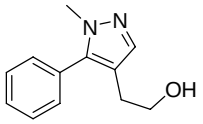
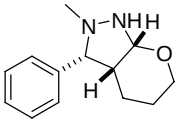
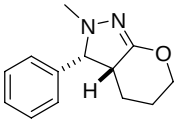
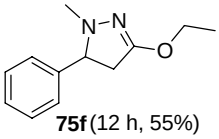
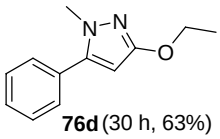
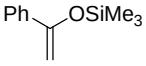
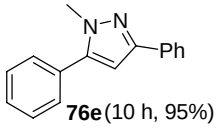
entry	catalyst	x mol%	yield[b] (%)	condition	time (h)
10	$Sc(OTf)_3$	15	55	rt	14
11	$Sc(OTf)_3$	20	64[c]	rt	9

[a]Reaction conditions: 0.94 mmol **7a** (2.0 equiv), 0.47 mmol **69a** (1.0 equiv), 0.47 mmol **71a** (1.0 equiv), Catalyst (x mol%) and DCM (2 mL). [b]Yields of isolated product **74a**. [c]1:1 mixture of two diastereomers.

To our delight, the desired cycloaddition occurred at room temperature affording tetrahydropyrrolo[2,3-c]pyrazole **74a** after 6 h in 65% yield as a single diastereomer in presence of 20 mol% of $Cu(OTf)_2$ as the best suited catalyst (Table 5.1, entry 7). Lowering in the catalyst loading resulted in decreased yield of **74a** in parallel with an increased reaction time (Table 5.1, entries 5 and 6). Among the other Lewis acids, 20 mol% of $Sc(OTf)_3$ was also found to produce comparable result with a significant loss of diastereoselectivity of the products (*dr* 1:1). Further optimization studies revealed that the aforementioned reaction does not occur under N_2 atmosphere; initial exposure of the reaction vessel to air for 15-30 minutes is necessary to have a specific control over formation of the desired products. To investigate the role of areal oxygen, we carried out a reaction in O_2 atmosphere, which failed to produce the desired products. A complex mixture of products was formed in this case which could not be characterized. This observation led us to conclude that the role of moderate amount of aerial O_2 was presumably crucial to regenerate Cu(II), the active catalyst; since, Cu(II) ions of $Cu(OTf)_2$ are known to be reduced to Cu(I) ions by hydrazine[28]. No product formation was observed, when the reaction was carried out in presence of cupper iodide, proving that Cu(I) ion was unable to catalyze this reaction. When the reaction was continued for longer time in air, the corresponding dihydropyrazole **75a** was isolated instead of **74a** after 10 h in 65% yield. A prolonged reaction time of 24 h resulted in the corresponding 1*H*-pyrazole **76a** as a single regioisomer in 83% yield (Table 5.2, entry 1). With these optimized reaction conditions in hand, we next investigated the scope of cycloaddition using a variety of other electron-rich olefins **71** (Table 5.2). The reaction was well tolerated with various cyclic and acyclic enamines and enol ethers to afford **74-76** depending upon the time of reaction in moderate to good yields with excellent regio- and stereoselectivity.

Table 5.2. Substrate Scope with Different Olefins[a]



entry	olefin **71**	tetrahydropyrazole **74**	dihdropyrazole[b,c] **75**	1H-pyrazole[b,c] **76**
1	 **71a**	 **74a** (6 h, 65%)	 **75a** (10 h, 65%)	 **76a** (24 h, 83%)
2	 **71b**	 **74b** (12 h, 75%)	 **75b** (30 h, 77%)	--
3	 **71c**	--	 **75c** (6 h, 85%)	 **76b** (24 h, 88%)
4	 **71d**	--	 **75d** (10 h, 65%)	 **76c** (28 h, 67%)
5	 **71e**	 **74c** (16 h, 60%)	 **75e** (30 h, 61%)	--
6	 **71f**	--	 **75f** (12 h, 55%)	 **76d** (30 h, 63%)
7	 **71g**	--	--	 **76e** (10 h, 95%)

[a]Reaction conditions: 0.94 mmol **7** (2.0 equiv), 0.47 mmol **69** (1.0 equiv), 0.47 mmol **71** (1.0 equiv), $Cu(OTf)_2$ (20 mol%) and DCM (2 mL) in air at room temperature. [b]Time of reaction and yield of isolated products are in the parenthesis. [c]Reactons were performed in separate vessels for longer time.

The formation of a mixture of compounds **74**, **75** and **76** was never encountered due to well resolved reaction time under the provided reaction conditions (see experimental part and Table 5.3). Six-membered cyclic enamine **71b** afforded **74b** as a single diastereomer in 75% yield after 12 h. When the reaction was carried out for 30 h, **75b** was obtained in 77% as a single diastereomer (Table 5.2, entry 3). In this case, we could not obtain the corresponding 1*H*-pyrazole even after carrying out the reaction for 2 days in air. Moreover, no pyrazole formation was observed even after treating the dihydropyrazole **75b** with Pd/C in air or with the oxidizing reagent DDQ, which caused presumably due to the resistance towards the generation of two adjacent exo-cyclic double bonds to the six membered hydrocarbon back bone. The acyclic enamide **71c** afforded the desired products **75c** and **76b** in excellent yields and selectivity in a much shorter reaction time (Table 5.2, entry 3). In this case we could not isolate the corresponding tetrahydropyrazole, presumably due to faster conversion of tetrahydro-analogue to dihydro-analogue **75c**. However, when enamines were replaced by enol ethers, the latter were found to be less reactive as expected and increased reaction time was required to produce the desired products (Table 5.2, entries 4, 5 and 6). In case of five-membered cyclic enol ether **71d** the cycloaddition resulted in the formation of ring-opened product **75d** as a mixture of two inseparable diastereomers (*dr* 1:1). The structural assignment of **75c** and **75d** (Table 5.1, entry 3 and 4) were confirmed unambiguously by single-crystal X-ray analysis (Figure 5.2).

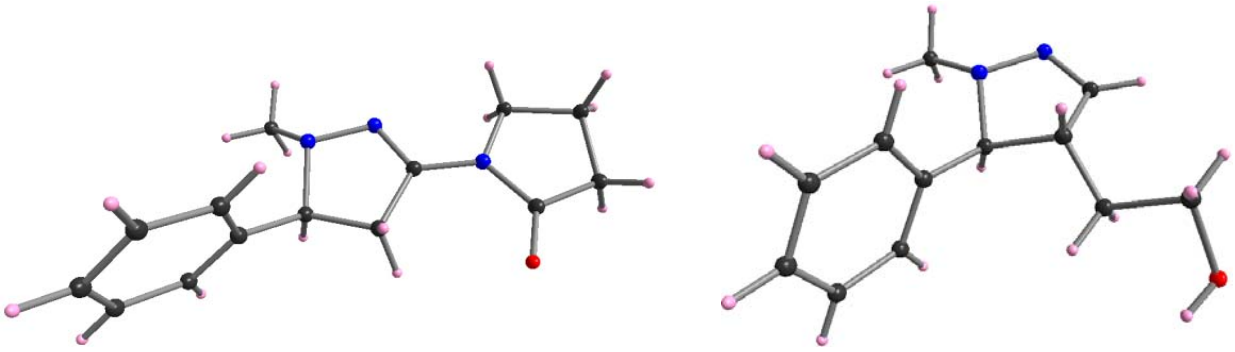
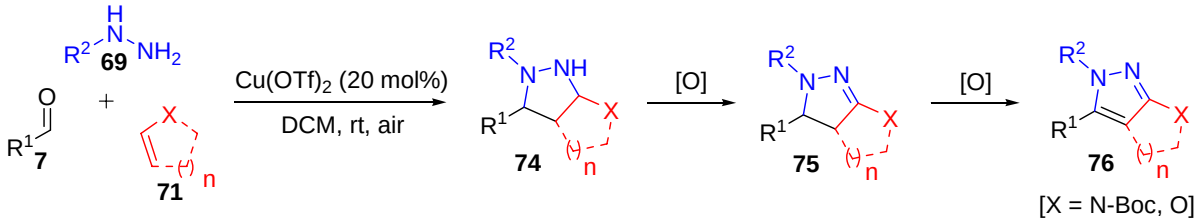


Figure 5.2. X-ray crystal structure of compounds **75c** and **75d** in Table 5.2.

Six-membered enol ether, 3,4-dihydro-2*H*-pyran **71e** afforded the corresponding tetrahydro- and dihydro pyrazoles (**74c** and **75e**) in moderate yields, however, corresponding pyrazole was not obtained even after 2 days, similar to the case of **71b**. Next, we examined the substrate generality with respect to aldehydes **7** and *N*-monosubstituted hydrazines **69** and the results are summarized

in Table 5.3. In this context, it is important to mention that in all the cases, three different types of products were isolated separately from different reaction vessels based on the controlled reaction times provided before quenching the catalyst. Both electron withdrawing and donating substituents on aldehyde are tolerated well.

Table 5.3. Scope of the Aldehydes and *N*-Mono-substituted Hydrazines[a]



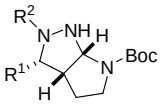
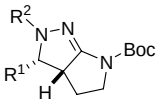
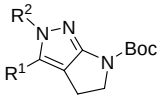
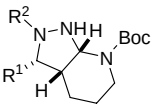
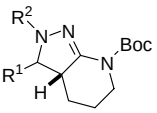
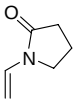
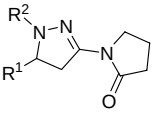
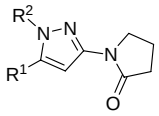
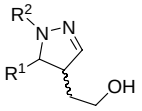
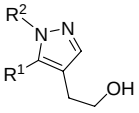
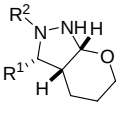
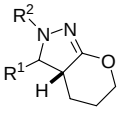
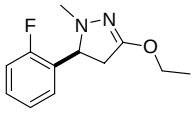
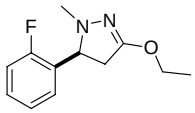
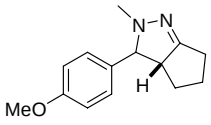
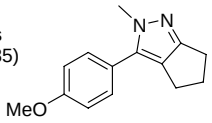
entry	R^1	R^2	olefin **71**	**74**	time (h), yield(%)[b]	**75**[c]	time (h), yield(%)[b]	**76**[c]	time (h), yield(%)[b]
1	4-$NO_2C_6H_4$	Me	 **71a**		**74d** (8, 76)		**75g** (8, 85)		**76f** (10, 87)
2	4-MeC_6H_4	Me			**74e** (10, 75)		--		**76g** (15, 79)
3	2-$OMeC_6H_4$	Ph			--		--		**76h** (18, 70)
4	*i*-Bu	Me	 **71b**		**74f** (15, 51)		**75h** (30, 55)	--	--
5	4-BrC_6H_4	Ph			**74g** (10, 75)		**75i** (26, 71)		--
6	2-$OMeC_6H_4$	Me			**74h** (16, 64)		**75j** (32, 60)		--
7	4-ClC_6H_4	Me	 **71c**	--	--		**75k** (6, 86)		**76i** (15, 88)
8	*i*-Bu	Me			--		**75l** (12, 55)		**76j** (18, 59)
9	2-F	Me			--		--		**76k** (15, 89)
10	4-OMe	Me			--		--		**76l** (24, 80)
11	2-FC_6H_4	Me	 **71d**	--	--		**75m** (10, 65)		**76m** (24, 69)
12	*i*-Pr	Me			--		**75n** (15, 45)		**76n** (30, 47)
13	4-ClC_6H_4	Me	 **71e**		**74i** (14, 69)		**75o** (30, 71)		--
14	2-FC_6H_4	Ph			**74j** (12, 70		**75p** (24, 73)	--	--
15	4-$NO_2C_6H_4$	Me			**74k** (12, 70)		**75q** (20, 70)		--

Table continued..

entry	R^1	R^2	olefin **71**	**74**	time (h), yield(%)[b]	**75**[c]	time (h), yield(%)[b]	**76**[c]	time (h), yield(%)[b]
16	2-FC_6H_4	Me	 **71f**		--		**75r** (10, 64)	--	**76o** (18, 65)
17	4-$OMeC_6H_4$	Me	 **71h**	--	--		**75s** (16, 85)		**76p** (24, 88)

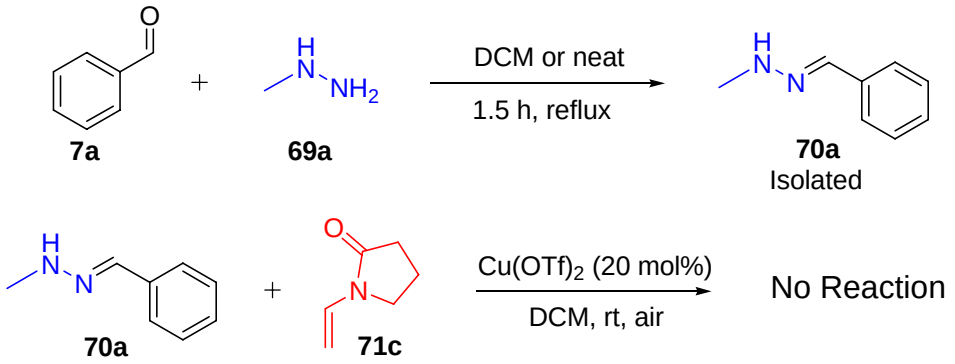
[a] Reaction conditions: 0.94 mmol **7** (2.0 equiv), 0.47 mmol **69** (1.0 equiv), 0.47 mmol **71** (1.0 equiv), $Cu(OTf)_2$ (20 mol%) and DCM (2 mL) in air at room temperature. [b] Time of reaction and yield of isolated products are in the parenthesis. [c] Reactions were performed in separate vessels for longer time.

Electron withdrawing groups on *ortho*- or *para*- positions of aldehyde increased the yield of the products with a shortened reaction time (Table 5.3, entries 1, 5, 7, 11, 13, 14, 15 and 16). Six membered cyclic enamide, *tert*-butyl 3,4-dihydropyridine-1(2*H*)-carboxylate (**71b**) and enol ether, 3,4-dihydro-2*H*-pyran (**71e**) did not afford any pyrazole, but only the corresponding tetrahydro- and dihydro pyrazoles were obtained due to the lack of an appropriate orientation for the final dehydrogenation step. The silyl enol ethers were also suitable substrates (Table 5.2, entry 7 and Table 5.3, entry 17), resulting in **76e** and **76p** in 95% and 88% yields respectively.[29]

5.4 Mechanistic Investigation

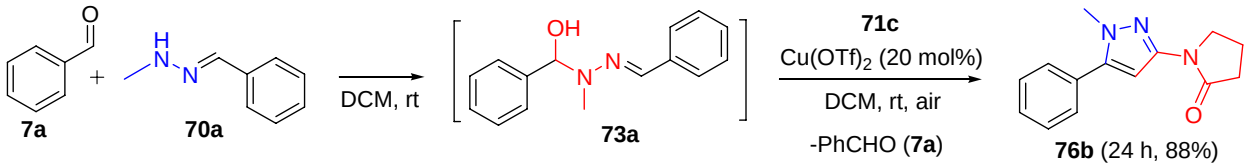
To clarify the reaction mechanism (Schemes 5.7-5.9), we performed a step wise reaction sequence, initially with one equivalent of aldehyde **7**. Addition of olefin **71c** to hydrazone **70a**, formed by the condensation of one equivalent of benzaldehyde **7a** and methylhydrazine **69a** in presence of 20 mol% of $Cu(OTf)_2$ failed to produce the desired product **76b** (Scheme 5.7). All the starting materials were recovered after 24 h. This experiment proved that for this particular system, addition of electron-rich olefins to normal *N*-methylhydrazone does not take place in a normal [3+2] cycloaddition mode.

Scheme 5.7. Stepwise Reaction Sequence Using One Equivalent of Benzaldehyde 7a.



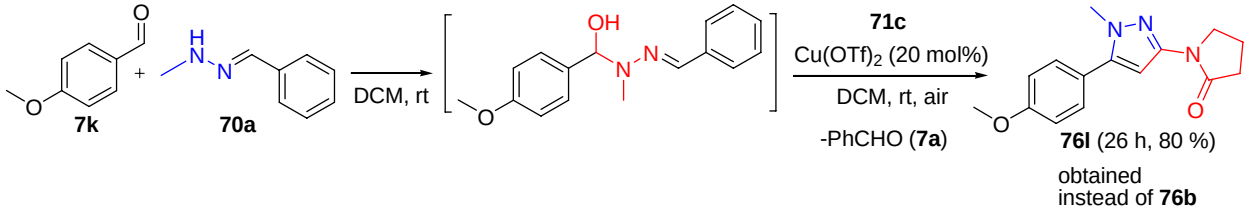
Next, we introduced two equivalents of aldehyde in a sequential manner. The preformed hydrazone **70a** was added to a pre-stirred (30 minutes) solution of 20 mol% of $Cu(OTf)_2$ and one equivalent of benzaldehyde **7a**, stirred for another 15 minutes to form the aminoalcohol intermediate **73a** which was isolated and characterized by NMR spectroscopy. The addition of olefin **71c** to the α-hydroxymethyl hydrazone **73a** resulted in the formation of the desired product **76b** after 24 h in 88% of isolated yield (Scheme 5.8).

Scheme 5.8. $Cu(OTf)_2$-Catalyzed Syntheses of Pyrazoles 76 in a Sequential Manner with Two Equivalents of Aldehyde 7a.



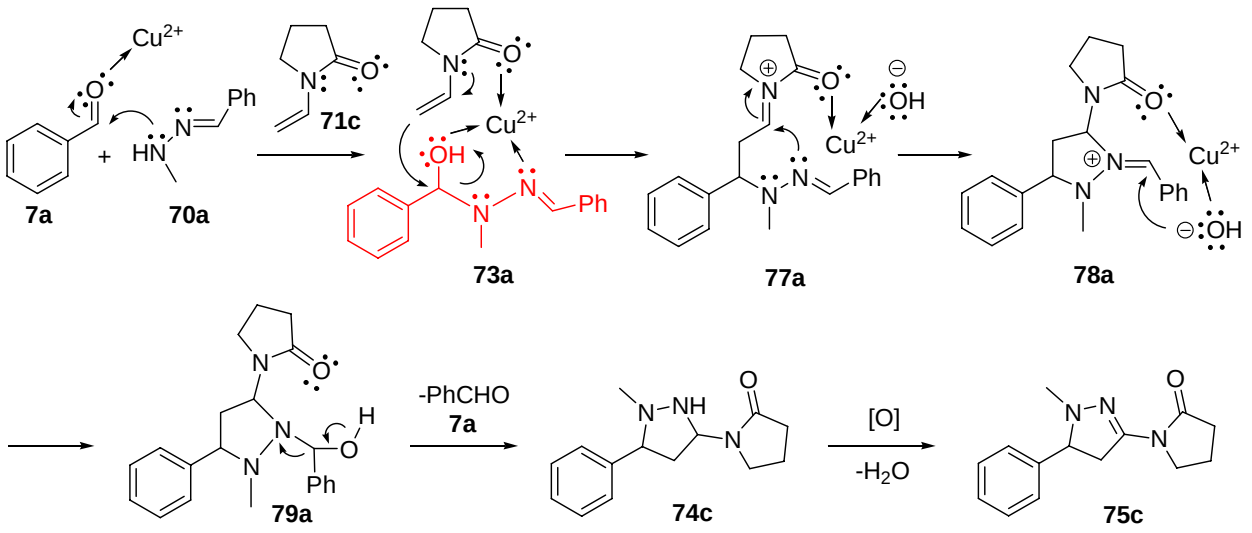
Introduction of a different aldehyde **7k** instead of **7a** at the second step of the previously mentioned reaction sequence afforded the pyrazole **76l** having *para*-methoxyphenyl substitution at the five position which corresponds to the aldehyde **7k** (Scheme 5.9).

Scheme 5.9. $Cu(OTf)_2$-Catalyzed Syntheses of Pyrazoles 76 in a Sequential Manner with Two Equivalents of Different Aldehydes 7a and 7k.



Based on these observations, a plausible mechanism is proposed for the current multicomponent reaction (Scheme 5.10), involving the initial formation of mono-phenyl substituted-*N*-methylhydrazone (azomethine imine, **70a**), which consequently undergoes nucleophilic attack at the carbonyl-C of aldehyde by the *sec*-amine center of **70a** to form the active intermediate, α-phenyl-*N*-hydroxymethyl-*N*-methylhydrazone **73a**, which could also be formed even in the absence of Cu(II) ions but could not afford the desired products upon addition of electron rich olefins. However, utilization of 20 mol% of $Cu(OTf)_2$ smoothly afforded **77a** through the chelation of **73a** to Cu(II) ion, utilizing the α-hydroxy and imine N-atom of Ph-CH(OH)-NMe-N=CH-Ph (**73a**) as chelating arms. The Cu(II) ions also promote the assembling process through further binding to the hetero-atom of electron rich olefin which subsequently undergoes nucleophilic substitution at the carbon center bearing the hydroxyl group in a concerted fashion and a much shortened reaction time was required in this case. In some cases (mainly for five membered cyclic enol-ether, Table 5.3, entry 11) presumably, the cationic intermediate Ph-HC=N^+(Me)-N=CH-Ph (**78a**) is formed first as a consequence the OH^- group being transferred to Cu(II) ion from the intermediate **73a**, resulting in the formation of 1:1 diastereomeric mixture of the products. Thus Cu(II) ion promotes C-OH bond activation as an important step.

Scheme 5.10. Plausible Mechanism for the Syntheses of Aza-Heterocycles and Model for Stereoselection

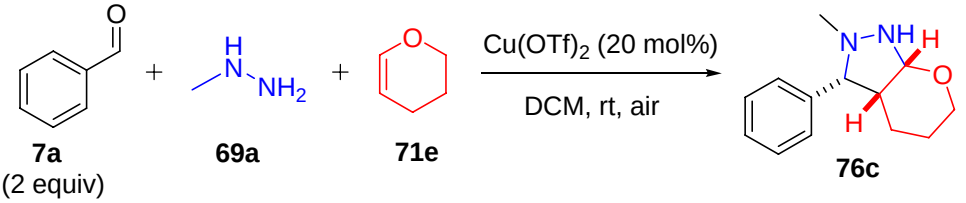


The corresponding cationic species (iminum or olefinium ion **77a**) undergoes ring closer to form the desired cationic five-membered aza-heterocycle (**78a**) which then undergoes hydrolysis

producing tetrahydropyrazole (**74c**) with the removal of a molecule of benzaldehyde. In most of the cases, the tetrahydropyrazoles **74c** undergo subsequent aerial oxidation to their corresponding dihydro- and/or 1*H*-pyrazole analogues. In terms of regio- and stereoselectivity, the formation of **70a** through the protection of -NH_2 group of hydrazine and substitution of OH^- group of **73a** in a concerted pathway are the crucial steps. The mechanism is also supported by the complete consumption of aldehyde at the beginning and then regeneration of aldehyde at the completion of the reaction, observed on the TLC and monitored by IR studies (Scheme 5.11).

The IR spectra revealed initial decrease in the relative intensity of the previous carbonyl stretching at 1699 cm^{-1} (Figure 5.3, B), after 1 h of addition of **69a** the sharp band at 1699 cm^{-1} had almost disappeared (Figure 5.3, C). The IR spectra, recorded after addition of olefin **71c** showed the reappearance of the sharp peak at 1699 cm^{-1} (Figure 5.3, D). After 6 h, the relative intensity of the aldehyde peak was significantly increased (Figure 5.3, E) supporting the removal of a molecule of aldehyde **7a**.

Scheme 5.11. Mechanistic Proof: IR Studies Showing the Consumption and Regeneration of Benzaldehyde[a]



[a] Reaction conditions: 0.4 mmol benzaldehyde **7a** (2.0 equiv), 0.235 mmol methylhydrazine **69a** (1.2 equiv), 0.4 mmol 3,4-dihydro-2H-pyran **71e** (1.0 equiv), $Cu(OTf)_2$ (20 mol%) and DCM (2 mL);

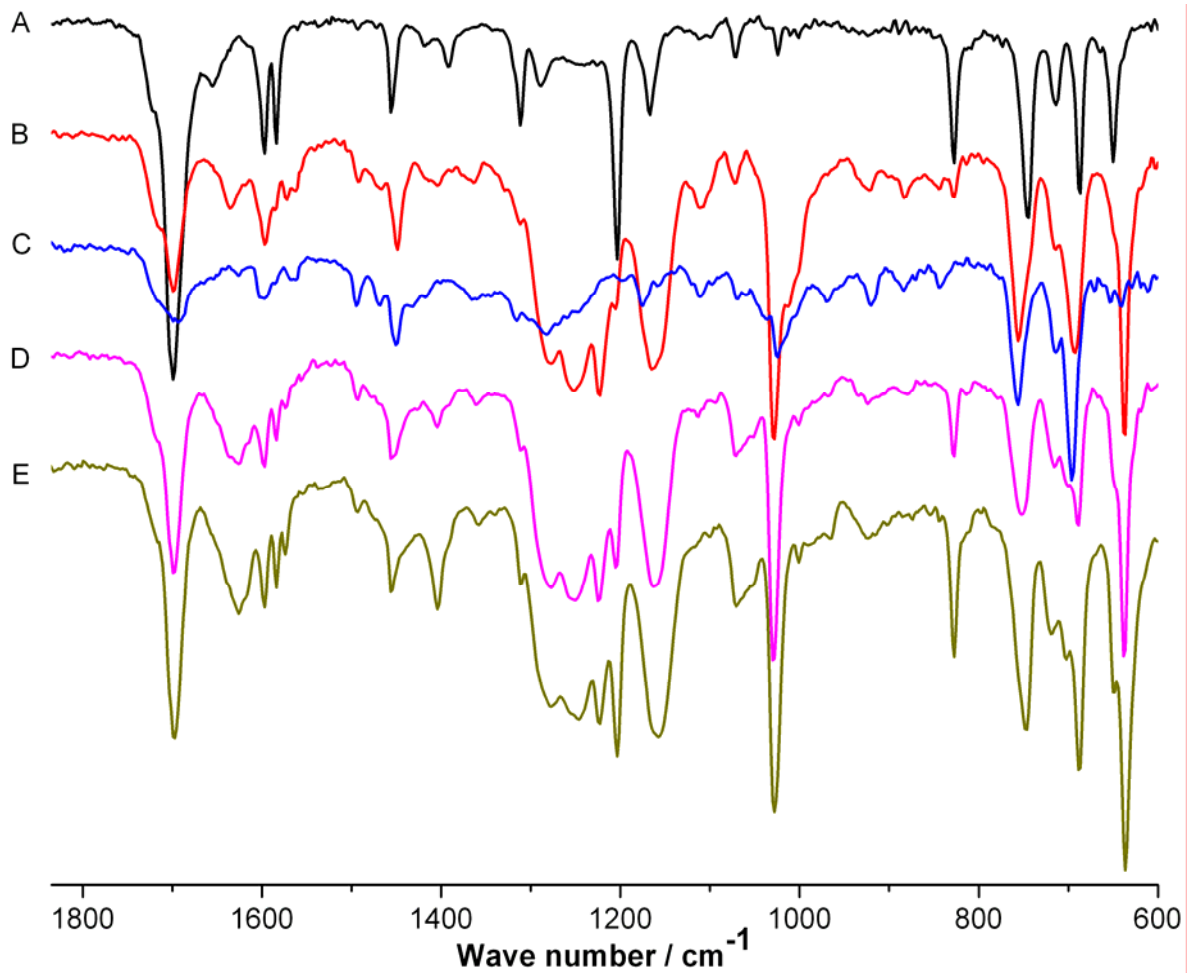
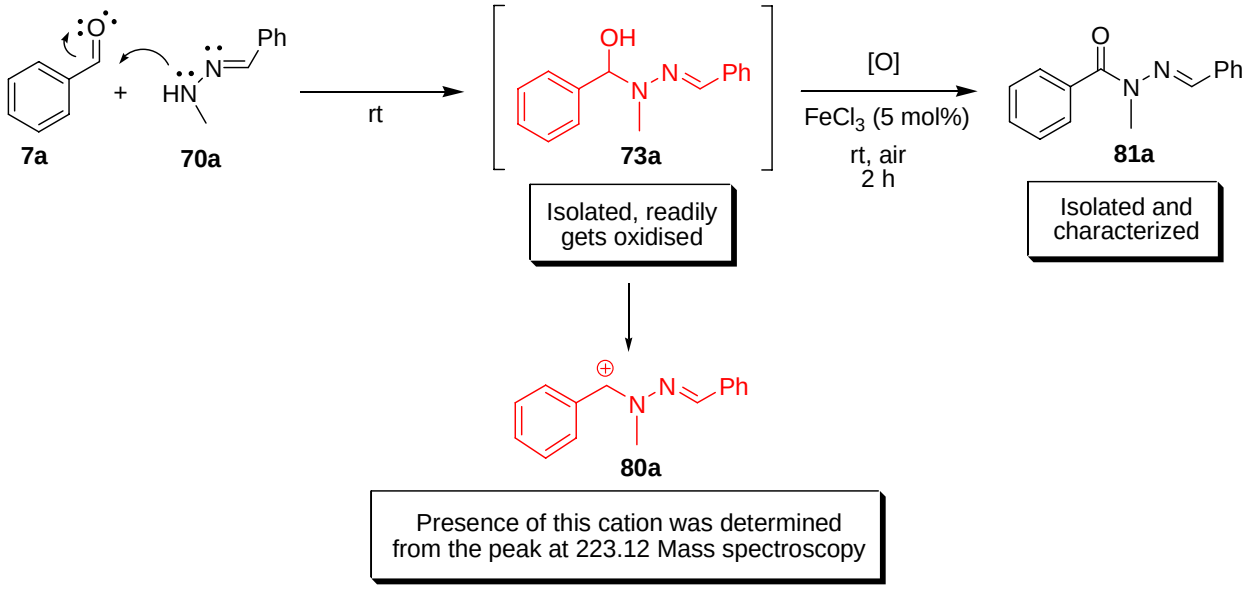


Figure 5.3. (A) Benzaldehyde + $Cu(OTf)_2$ in DCM (0.5 mL); (B) After addition of methylhydrazine; (C) After 1 h of addition of methylhydrazine; (D) After 2 h of addition of olefin; (E) After 6 h of addition of olefin.

Moreover, the active intermediate α-phenyl-*N*-hydroxymethyl-N-methylhydrazone **73a** was isolated and characterized by NMR and Mass spectrometric methods. The mass spectrum of **73a** shows M^+/z value of 223.12 of the corresponding cation Ph-HC=N^+(Me)-N=CH-Ph (**80a**) upon loss of OH^- anion. In absence of any olefin, **73a** undergoes aerial oxidation into the corresponding amidohydrazone **81a** which was isolated and well characterized by NMR[30] and Mass-spectroscopic methods after 24 h. The similar oxidized product can also be quantitatively obtained using 5 mol% of anhydrous $FeCl_3$ instead of 20 mol% of $Cu(OTf)_2$, after 3 h in presence of air (Scheme 5.12).

Scheme 5.12. $FeCl_3$ Catalyzed Oxidation of Intermediate 73a to the Corresponding Amide 81a



5.5 Conclusion

In summary, we have developed a Cu(II)-catalyzed multicomponent, regio- and stereoselective syntheses of pharmaceutically relevant aza-heterocycles via a [3+2]-type cycloaddition based on the *in situ*-derived α-hydroxy-aminomethyl-phenylhydrazone (**73**) in good to excellent yields. The regio- and stereoselectivity come into play through the protection of $–NH_2$ group of mono substituted hydrazine and Cu(II) catalyzed substitution of OH^- group of **73** in a concerted pathway. Functionalized pyrazoles were thus synthesized from readily available aldehydes, hydrazines and olefins. The broad chemistry and good substrates scope are further attractive aspects of this novel methodology.

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6.1 Summary

This Ph.D thesis describes the development of a number of novel multicomponent synthetic methodologies for making various biologically and pharmaceutically relevant heterocyclic compounds in good yields and excellent selectivity under appropriate conditions, which are briefly summarized in Figure 6.1.

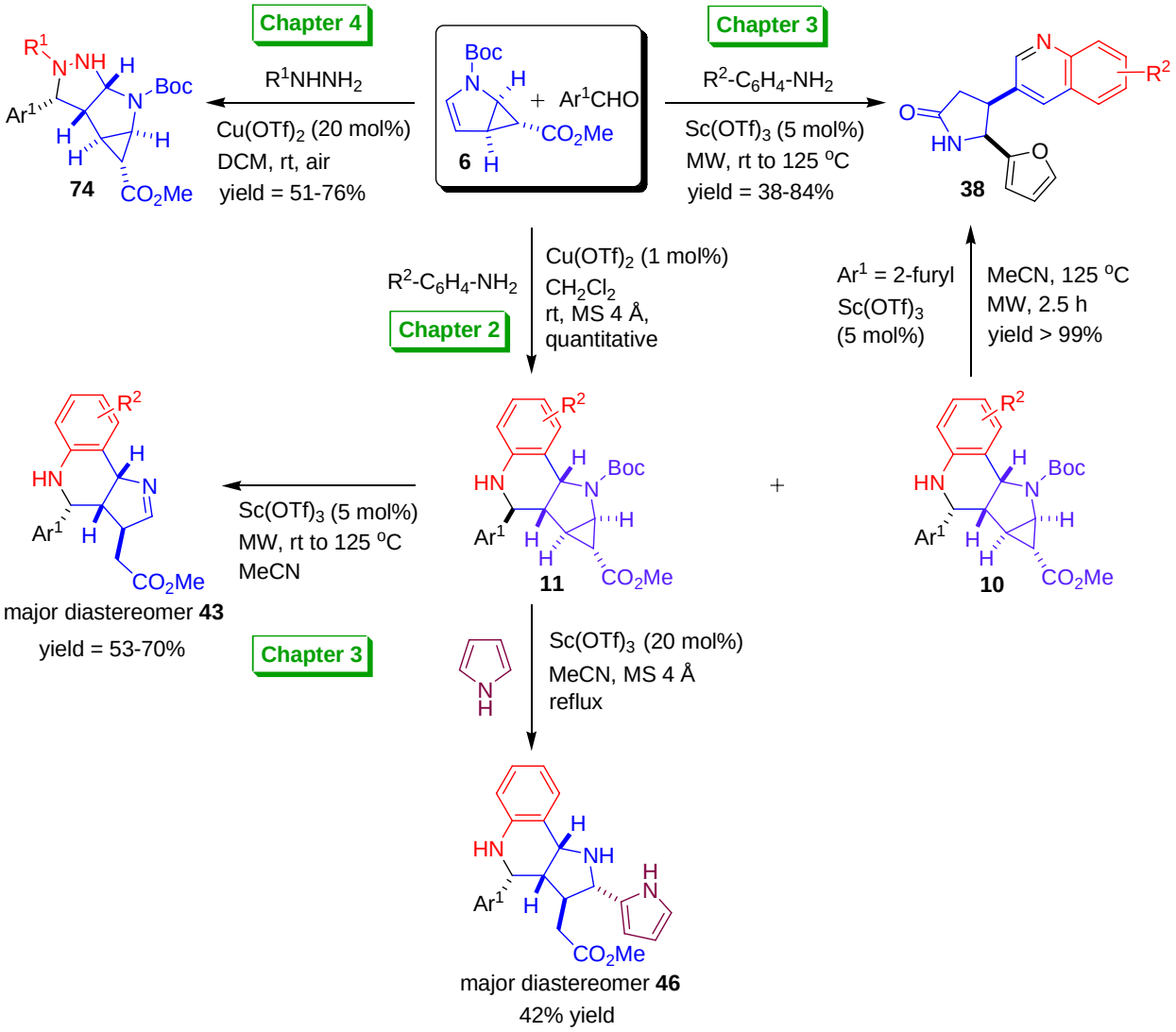


Figure 6.1. Syntheses of various nitrogen-heterocycles, utilizing the Povarov-type reaction as the key step.

In Chapter 1, we have given a brief overview on the recent advancements of the Povarov reaction. Several trends have been shown, how important heterocyclic scaffolds other than tetrahydroquinolines could be synthesized utilizing the Povarov reaction as a key step.

In Chapter 2, we have introduced the monocyclopropanated *N*-Boc-protected pyrrole **6** (Boc = *tert*-butoxycarbonyl) as an electron-rich olefinic component, keeping in mind the plethora of chemistry of the D-A substituted cyclopropane derivatives. We have successfully synthesized a range of functionalized tetrahydropyrroloquinolines **10** and **11**. Both *endo*- and *exo*-diastereomers (**10** and **11** respectively) have been isolated in good yields, following a LA-catalyzed MC Povarov reaction. Several substituted aromatic aldehydes and anilines have been well tolerated for the reaction. The presence of electron withdrawing groups on either aldehyde or aniline part has shown positive impacts on both yield and reaction time. We have found $Cu(OTf)_2$ as the best catalyst among all other metal-triflates examined, presumably due to its strongest binding to N-atom of *in situ*-generated *N*-arylaldimines. Lewis acids have predominantly produced the *endo*-product **10**, while, the trend have been found to be reversed when the system is tuned by replacing Lewis Acids [$M(OTf)_x$] by Brønsted acids (TfOH). Moreover, we have demonstrated the utilization of magnetically separable $CuFe_2O_4$-nanoparticles as a reusable heterogeneous catalyst for the Povarov reaction with the efficient recycling of the catalyst up to three consecutive cycles. The syntheses of enantiopure pyrroloquinolines have also been carried out utilizing Jacobsen´s chiral thiourea catalyst which has been previously examined by the group of Jacobsen for the Povarov reaction with different substrates.

In Chapter 3, we have shown that furyl substituted *endo*-tetrahydropyrroloquonolines (**10n** to **10x**) (Ar^1 = 2-furyl or 2-C_6H_5-furyl) can further undergo an unprecedented rearrangement to produce *cis*-4,5-disubstituted pyrrolidinones (**38**) in very good yields with excellent stereoselectivity, when refluxed for 12 hours in the presence of 40 mol% of $Sc(OTf)_3$. The catalyst loading has been successfully reduced by eight times (5 mol%) with an increased yield of 99%, when irradiated under microwave at 125 °C. A plausible mechanism has been proposed for the aforementioned rearrangement, initiated by the generation of $Sc(OTf)_3$-mediated iminium ion as a key intermediate through the cyclopropane ring-opening, followed by a 1,4-furan

migration via a spiroannulated intermediate. The formation of the spiroannular intermediate has been proposed as the critical step for the rearrangement to occur, which once formed; undergo a 1,4-furan migration followed by rearomatization at the expense of an unusual C-N-bond cleavage giving rise to the *cis*-pyrrolidinone (**38**) upon *N*-Boc hydrolysis and lactamization. On the contrary, the *exo*-diastereomers **11n** (Ar^1 = 2-furyl or 2-C_6H_5-furyl) has been found to undergo a simple cyclopropane ring-opening reaction to form the polycyclic imines (**43**), failing to undergo 1,4-furane migration due to the steric hindrance, created by the H-atom, connected to the next C-atom of –CH(NHR)-2-furyl centre. For non-furan aromatic aldehydes, both the *exo*- and *endo*-diastereomers (**10** and **11** with Ar^1 = other than furan or substituted furan) have resulted in similar polycyclic imines (**43**), due to lack of long distance 1,4-migration of non furan aromatic rings. As a partial proof of the proposed reaction mechanism, the iminium intermediate has been trapped (as functionalized pyrrole **46**) by introducing an external nucleophile, e.g., pyrrole. Finally, we have optimized the reaction condition for synthesizing the *cis*-pyrrolidinones (**38**) as a one-pot, multicomponent reaction under MW irradiation. When a mixture of furan-2-aldehydes **7i**, anilines **8** and **6** has been irradiated under MW, in the presence of 5 mol% of $Sc(OTf)_3$, initially at room temperature (to minimize the formation of the *exo*-isomer) and then at a higher temperature of 125 °C for 4.5-6 h, similar pyrrolidinones (**38**) are obtained in good yields.

In Chapter 4, we have described a $Cu(OTf)_2$ catalyzed MCR (AAB-type) of aldehydes, electron rich olefins and *N*-monosubstituted hydrazines. The chemistry has followed its own way and produced functionalized tetrahydropyrazoles (**74**). The preformed hydrazone did not react with electron rich olefins in the presence of LA [$Cu(OTf)_2$]. The systematic investigations showed that the first equivalent of aldehyde was utilized for the *in situ*-generation of the hydrozone, which further reacted with the second equivalent of the aldehyde to give an α-hydroxyaminomethylhydrazone as the key intermediate, followed by the Cu(II) catalyzed nucleophilic -OH substitution by olefin in a concerted way in order to produce functionalized tetrahydropyrazoles in regio- and stereoselective manner. The tetrahydropyrazole can be further oxidized to the corresponding dihydro- (**75**) and 1*H*-pyrazoles (**76**) depending upon the substrate as well as the reaction time. The reaction sequence was monitored by IR studies and cross-

aldehyde experiments. Moreover, the critical α-hydroxyaminomethylhydrazone intermediated was isolated as the corresponding amide and well-characterized by spectroscopic methods.

6.2 Future Prospective

We have made a plenty of functionally diverse heterocyclic compounds by utilizing novel synthetic approaches. Some of these compounds had been sent to the Kansas University, USA, which will be finally sent to NIH, USA for screening after a thorough purification tests. At the moment, eighteen compounds have successfully passed through the purity-test and their screening processes are still under investigation.

7. Experimental Part

7.1 General Information

^{1}H NMR-Spectra were recorded on Bruker Avance 300, Bruker Avance 400, Bruker Avance 600, Varian Inova 600, Bruker DRX-400 with a H/C/P/F QNP gradient probe and Bruker Avance 500 with a dual carbon/proton CPDUL cryoprobe. The chemical shift δ is given in [ppm], calibration was set on chloroform-d_1 (7.26 ppm) or tetramethylsilane (0.00 ppm) as internal standard. The spectra were evaluated in 1st order and the coupling constants are given in Hertz [Hz]. The following abbreviations for the spin multiplicity were used: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, m = multiplet, dt = doublet of a triplet, dd = double doublet, ddd = doublet of a double doublet, sept = septet. The used deuterated solvents are given separately.

^{13}C NMR-Spectra were recorded on Bruker Avance 300, Bruker Avance 400, Bruker Avance 600, Varian Inova, Bruker DRX-400 with a H/C/P/F QNP gradient probe and Bruker Avance 500 with a dual carbon/proton CPDUL cryoprobe. The chemical shift δ is given in [ppm], calibration was set on chloroform-d_1 (77.16 ppm), or tetramethylsilane (0.00 ppm) as internal standard. The multiplicity of the signals were detected by DEPT 135 and 90 (DEPT = distortionless enhancement by polarization transfer)

Masspectrometry was performed on Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000, Nermag quadrupoles, VG ZAB high-resolution double-focusing and VG Autospec-Q tandem hybrid with EBEqQ configuration. The percentage set in brackets gives the peak intensity related to the basic peak (I = 100%). High resolution mass spectrometry (HRMS): The molecular formula was proven by the calculated precise mass.

Thin layer chromatography (TLC) was prepared on TLC-aluminium sheets (Merck, silica gel 60 F_{254}, 0.2 mm). Detection in UV-light l = 254 nm, staining with I_2, Mostain, molybdatophosphoric-acid (5% in ethanol), $KMnO_4$ solution or vanillin-sulfuric acid.

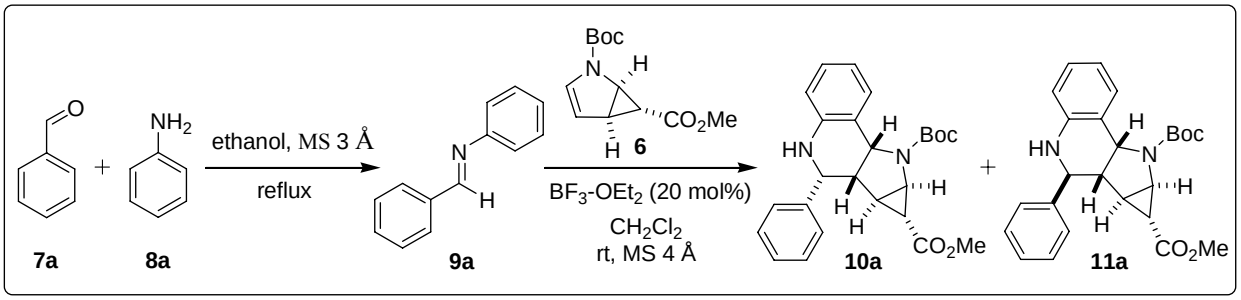
Column chromatography was performed in glass columns (G2 or G3). As a stationary phase silica gel Merck-Geduran 60 (0.063-0.200 mm) or flash silica gel Merck 60 (0.040-0.063 mm) was used.

Solvents: Abs. solvents were prepared according to usual lab procedures or taken from the MB-SPS solvent purification system. Ethylacetate, hexanes (40-60 °C) and dichloromethane were purified by distillation before use. Further solvents and reagents were of p.a. quality.

Reactions with oxygen- and moisture sensitive reactants were performed in oven dried and in vacuo heated reaction flasks under a pre-dried inert gas (nitrogen or argon) atmosphere. For cooling to temperatures < -40 °C a cryostat Haake EK 90 or dry ice/*iso*-propanol mixture was used.

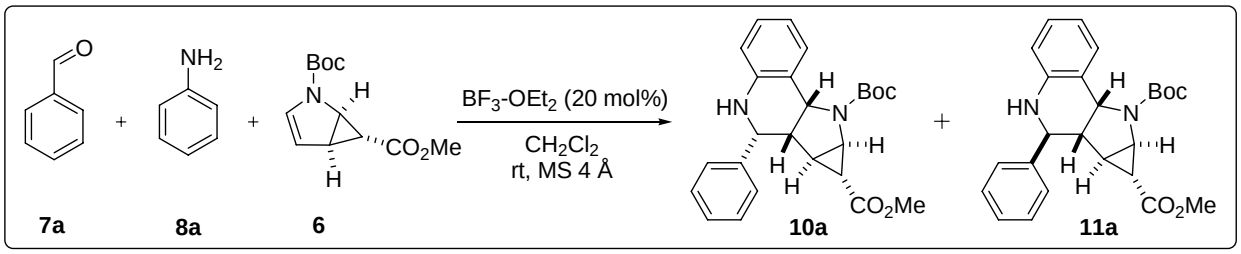
7.2 General Procedure for BF_3-OEt_2-Catalyzed Syntheses of Povarov-Type Products 10a and 11a.

7.2a General Procedure A[1]



Aldimine **6a** was prepared by condensation of benzaldehyde **7a** (0.833 mmol) and aniline **8a** (0.833 mol) in ethanol under refluxing condition, re-crystallized from hexane, dried under vacuum and used for the next step. A mixture of aldimine **9a** (0.833 mmol) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (0.334 mmol) in 4 mL dichloromethane was placed in a dry Schlenck tube and the mixture was degassed by sparging with nitrogen. The reaction mixture was then cooled to 0 ^{o}C. A solution of BF_3-OEt_2 (20 mol%) in dry dichloromethane (0.5 mL) was then added dropwise under N_2 and the tube was sealed with a teflon lined cap at once. This mixture was then allowed to warm to room temperature and stirred for 48 hours or until complete consumption of the starting material as indicated by TLC or by ^{1}H NMR. The reaction mixture was then quenched with Et_3N, concentrated *in vacuo*, extracted with chloroform and washed with distilled water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using column chromatography (2-15% ethylacetate in hexane) to yield the desired products **10a** and **11a**.

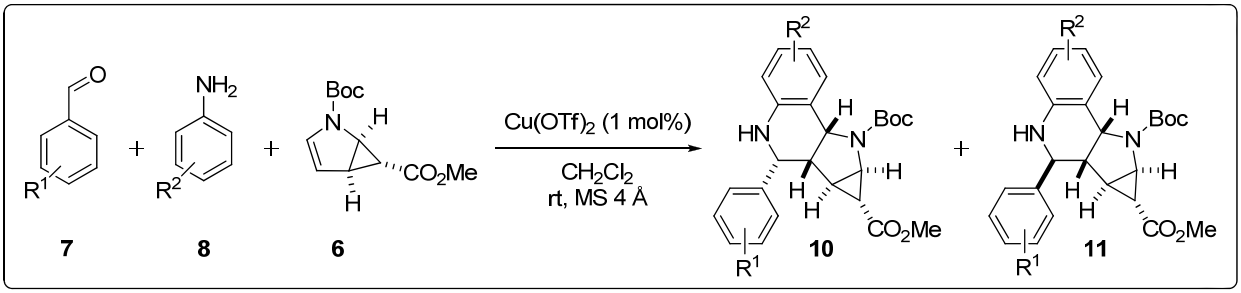
7.2b General Procedure A[2]



To a 25 mL dry round bottom flask was added a solution of aromatic benzaldehyde **7a** (0.833 mmol), aniline **8a** (0.833 mmol) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (0.334 mmol) in 4 mL DCM under N_2 atmosphere, $Cu(OTf)_2$ (20 mol%). This mixture was then allowed to warm to room temperature and stirred for 48 hours or until complete consumption of the starting material as indicated by TLC or by ^1H NMR. The reaction mixture was then concentrated *in vacuo*, extracted with ethylacetate and washed with distilled water. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified on silica to afford the desired tetrahydropyrroloquinolines **10a** and **11a**.

7.3 General Procedure for $Cu(OTf)_2$-Catalyzed Three-Component Syntheses of Povarov-Type Products 10a and 11a.

7.3a General Procedure A[3]

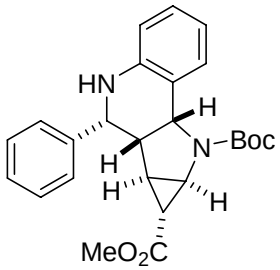


To a 25 mL dry round bottom flask was added a solution of aromatic aldehyde **7** (0.833 mmol), substituted aniline **8** (0.833 mmol) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-

dicarboxylate **6** (0.334 mmol) in 4 mL DCM under N_2 atmosphere, $Cu(OTf)_2$ (20 mol%). This mixture was then allowed to warm to room temperature and stirred for 48 hours or until complete consumption of the starting material as indicated by TLC or by ^{1}H NMR. The reaction mixture was then concentrated *in vacuo*, extracted with ethylacetate and washed with distilled water. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified on silica to afford the desired tetrahydropyrroloquinolines **10** and **11**.

7.4 Characterization Data of Compounds 10 and 11.

Compound 10a: Synthesized according to General Procedure A[3] using benzaldehyde **7a** (85



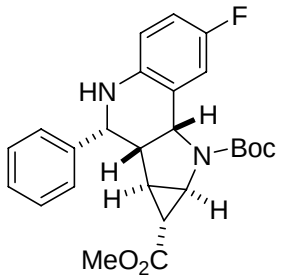
μL), aniline **8a** (76 μL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-15% ethylacetate in hexane) to afford 112 mg (Yield: 80%) of a white solid **10a**, mp = 68-71 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.51 – 7.46 (m, 2H), 7.44 – 7.38 (m, 2H), 7.37 – 7.32 (m, 2H), 7.15 – 7.07 (m, 1H), 6.84 (t, J = 5.3 Hz, 1H), 6.68 – 6.64 (m, 1H), 5.44 (t, J = 16.7 Hz, 1H), 4.50 (d, J = 2.6 Hz, 1H), 3.91 (s, 1H), 3.65 (s, 1H), 3.60 – 3.52 (m, 3H), 3.34 (t, J = 15.5 Hz, 1H), 2.75 (dt, J = 7.1, 2.4 Hz, 1H), 2.46 – 2.38 (m, 1H), 1.52 – 1.41 (m, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 170.62, 156.33, 145.74, 142.39, 140.39, 129.04, 128.89, 128.26, 127.92, 126.93, 126.52, 122.05, 119.20, 114.26, 80.48, 77.48, 77.05, 76.63, 59.17, 51.80, 51.67, 48.61, 44.65, 28.44, 27.02, 23.25.

HR-EIMS ($C_{25}H_{28}N_2O_4$): calculated: 420.2, found: 420.2049.

Compound 10b: Synthesized according to General Procedure A[3] using benzaldehyde **7a**



(85 μL), 4-fluoroaniline **8b** (80 μL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-15% ethylacetate in hexane) to afford 115 mg (Yield: 79%) of a white solid **10b**, mp = 83-85 ^{o}C.

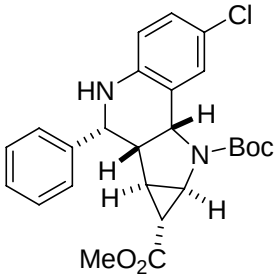
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.51 – 7.37 (m, 4H), 7.37 – 7.33 (m, 1H), 7.34 – 7.29 (m, 1H), 6.83 (td, J = 8.4, 2.6 Hz, 1H), 6.60 (dd, J = 8.8, 4.7 Hz, 1H), 5.37 (t, J = 18.8 Hz, 1H), 4.45 (d, J = 2.2 Hz, 1H), 3.82 (s, 1H), 3.57 (s, 3H), 3.33 (t, J = 11.1 Hz, 1H), 2.74 (d, J = 7.4 Hz, 1H), 2.44 – 2.36 (m, 1H), 1.58 (s, 3H), 1.54 (d, 1H), 1.47 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.13, 150.59, 141.97, 140.78, 128.98, 128.89, 127.99, 127.06, 126.15, 116.37, 115.07, 80.47, 59.58, 51.40, 44.77, 44.49, 44.23, 28.23, 26.62.

^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ: -124.56.

HR-EIMS ($C_{25}H_{27}FN_2O_4$): calculated: 438.20, found: 438.1960.

Compound 10d: Synthesized according to General Procedure A[3] using benzaldehyde **7a**



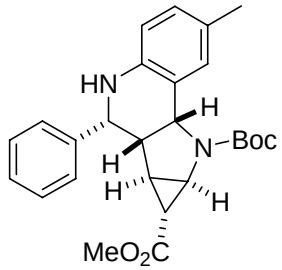
(85 μL), 4-chloroaniline **8d** (74 μL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-15% ethylacetate in hexane) to afford 106 mg (Yield: 70%) of a dirty-white solid **10d**, mp = 80-82 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.57 (d, J = 2.3 Hz, 1H), 7.44 (dd, J = 4.8, 0.9 Hz, 2H), 7.40 (d, J = 7.6 Hz, 2H), 7.35 (dt, J = 6.1, 2.4 Hz, 1H), 7.05 (dd, J = 8.5, 2.4 Hz, 1H), 6.59 (d, J = 8.6 Hz, 1H), 5.35 (d, J = 28.6 Hz, 1H), 4.46 (d, J = 2.0 Hz, 1H), 3.92 (s, 1H), 3.57 (s, 3H), 3.38 (dd, J = 17.0, 14.2 Hz, 1H), 2.74 (s, 1H), 2.43 – 2.34 (m, 1H), 1.57 (d, J = 4.8 Hz, 1H), 1.51 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 170.15, 155.52, 144.29, 144.29, 139.99, 129.09, 128.29, 128.29, 128.06, 126.44, 126.44, 116.76, 80.10, 57.74, 51.69, 46.19, 44.56, 28.41, 27.00.

HR-EIMS ($C_{25}H_{27}ClN_2O_4$): calculated: 454.17, found: 454.1660.

Compound 10e: Synthesized according General Procedure A[3] using benzaldehyde **7a** (85 µL),



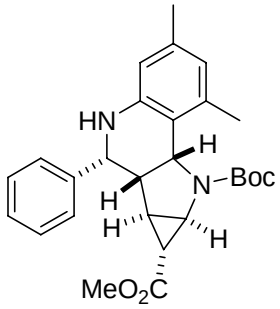
4-methylaniline **8e** (89 mg) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-10% ethylacetate in hexane) to afford 79 mg (Yield: 55%) of a white solid **10e**, mp = 63-65 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.48 (d, J = 7.4 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.34 (t, J = 4.8 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 5.38 (dd, J = 36.9, 8.4 Hz, 1H), 4.45 (d, J = 2.0 Hz, 1H), 3.77 (s, 1H), 3.53 (s, 3H), 3.31 (d, J = 6.0 Hz, 1H), 2.73 (d, J = 5.9 Hz, 1H), 2.42 (s, 1H), 2.24 (s, 3H), 1.74 (dd, J = 14.9, 11.2 Hz, 1H), 1.51 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ: 170.07, 150.77, 147.03, 139.23, 129.32, 129.00, 128.49, 127.44, 126.30, 124.56, 122.57, 114.98, 81.07, 60.38, 57.05, 53.40, 51.78, 44.20, 28.38, 26.85, 25.39, 21.03.

HR-EIMS ($C_{26}H_{30}N_2O_4$): calculated: 434.22, found: 434.2205.

Compound 10f: Synthesized according to General Procedure A[3] using benzaldehyde **7a** (85



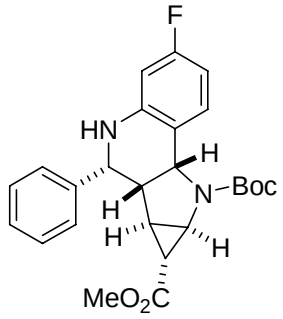
µL), 3,5-dimethylaniline **8f** (104 µL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-10% ethylacetate in hexane) to afford 73 mg (Yield: 49%) of a white sticky solid **10f**.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.47 (d, J = 7.3 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.33 (dd, J = 6.2, 3.6 Hz, 1H), 6.51 (s, 1H), 6.37 (s, 1H), 5.50 (d, J = 5.8 Hz, 1H), 4.46 (d, J = 1.3 Hz, 1H), 3.84 (s, 1H), 3.58 (s, 3H), 3.21 (d, J = 6.6 Hz, 1H), 2.66 – 2.57 (m, 2H), 2.29 (s, 3H), 2.23 (s, 3H), 1.55 (s, 1H), 1.46 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ: 170.40, 156.15, 146.77, 141.21, 140.34, 137.83, 129.11, 128.94, 128.54, 127.77, 126.36, 123.32, 117.36, 114.17, 80.09, 64.35, 56.87, 52.09, 51.60, 49.74, 44.84, 37.20, 29.68, 29.08, 28.30, 28.17, 21.85, 20.86, 20.39, 18.53.

HR-EIMS ($C_{27}H_{32}N_2O_4$): calculated: 448.24, found: 448.2361.

Compound 10g: Synthesized according to General Procedure A[3] using benzaldehyde **7a** (85



μL), 3-fluoroaniline **8g** (80 μL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-10% ethylacetate in hexane) to afford 101 mg (Yield: 69%) of a white solid **10g**.

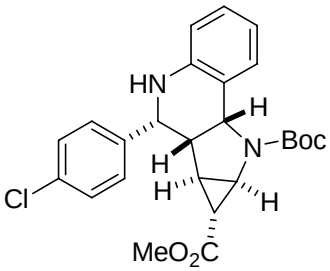
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.47 (d, J = 8.2 Hz, 1H), 7.44 – 7.35 (m, 1H), 7.35 – 7.27 (m, 4H), 6.48 (td, J = 8.6, 2.5 Hz, 1H), 6.32 (dd, J = 10.2, 2.4 Hz, 1H), 4.75 (d, J = 7.4 Hz, 1H), 4.29 – 4.19 (m, 2H), 3.65 (s, 3H), 3.52 (dd, J = 6.8, 1.4 Hz, 1H), 2.78 (dd, J = 12.4, 4.8 Hz, 1H), 2.24 (ddd, J = 6.6, 3.7, 1.9 Hz, 1H), 1.79 (dd, J = 3.6, 1.4 Hz, 1H), 1.50 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 170.65, 156.34, 142.00, 128.95, 127.78, 126.77, 126.15, 117.21, 105.69, 100.46, 80.48, 58.37, 51.85, 46.15, 45.77, 44.15, 28.42, 27.01, 21.27.

^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ: -114.64.

HR-EIMS ($C_{25}H_{27}FN_2O_4$): calculated: 438.2, found: 438.1957.

Compound 10h: Synthesized according to General Procedure A[3] using 4-chlorobenzaldehyde



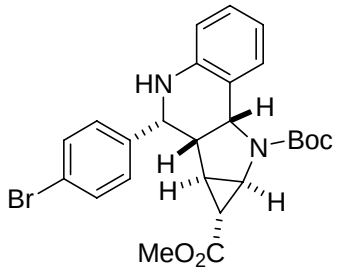
7b (117 mg), aniline **8a** (76 μL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-10% ethylacetate in hexane) to afford 113 mg (Yield: 75%) of a white solid **10h**.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.57 (s, 1H), 7.40 (td, J = 8.6, 4.3 Hz, 4H), 7.15 – 7.07 (m, 1H), 6.84 (dd, J = 10.9, 4.1 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 5.44 (s, 1H), 4.48 (d, J = 2.6 Hz, 1H), 3.84 (s, 1H), 3.58 (s, 3H), 3.31 (s, 1H), 2.73 – 2.65 (m, 1H), 2.39 – 2.30 (m, 1H), 1.72 – 1.61 (m, 1H), 1.55 (s, 3H), 1.47 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 170.13, 153.11, 145.37, 139.41, 133.66, 129.22, 128.32, 127.82, 123.22, 119.98, 115.49, 80.08, 57.16, 56.76, 51.71, 46.16, 44.17, 35.99, 28.44.

HR-EIMS ($C_{25}H_{27}ClN_2O_4$): calculated: 454.17, found: 454.1654.

Compound 10i: Synthesized according to General Procedure A[3] using 4-bromobenzaldehyde **7c**



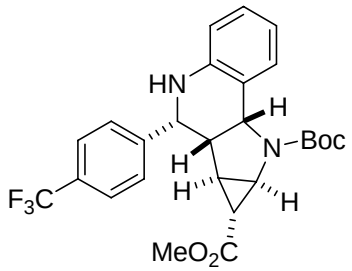
(154 mg), aniline **8a** (76 μL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-10% ethylacetate in hexane) to afford 121 mg (Yield: 73%) of a white solid **10i**, mp = 85-89 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.62 – 7.50 (m, 3H), 7.37 (d, J = 8.4 Hz, 2H), 7.10 (dd, J = 11.0, 4.2 Hz, 1H), 6.84 (t, J = 7.5 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 5.37 (d, J = 42.4 Hz, 1H), 4.46 (d, J = 2.5 Hz, 1H), 3.83 (s, 1H), 3.58 (s, 3H), 3.31 (d, J = 3.2 Hz, 1H), 2.73 – 2.65 (m, 1H), 2.37 – 2.30 (m, 1H), 1.58 (s, 3H), 1.47 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 174.28, 145.32, 139.58, 137.58, 131.83, 130.59, 127.80, 121.63, 119.99, 81.27, 57.16, 52.71, 51.90, 40.82, 28.22, 27.01, 21.65.

HR-EIMS ($C_{25}H_{27}BrN_2O_4$): calculated: 498.11, found: 498.1153.

Compound 10j: Synthesized according to General Procedure A[3] using 4-trifluoromethylbenzal



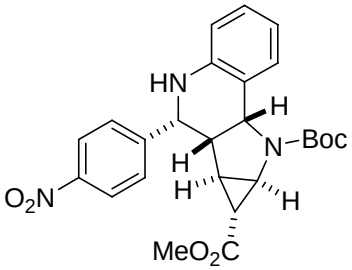
-dehyde **7d** (114 μL), aniline **8a** (76 μL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-10% ethylacetate in hexane) to afford 115 mg (Yield: 77%) of a white solid **10j**, mp = 93-95 ^{o}C.

^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ: 7.68 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 6.86 (t, J = 7.4 Hz, 1H), 6.68 (d, J = 7.9 Hz, 1H), 5.43 (d, J = 64.0 Hz, 1H), 4.57 (d, J = 2.1 Hz, 1H), 3.88 (s, 1H), 3.58 (s, 3H), 3.41 – 3.27 (m, 1H), 2.74 (dt, J = 7.2, 2.7 Hz, 1H), 2.36 – 2.32 (m, 1H), 1.77 – 1.64 (m, 2H), 1.56 (s, 3H), 1.47 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ: 170.16, 155.36, 145.06, 144.78, 130.58, 128.14, 126.77, 124.85, 123.49, 123.00, 120.21, 115.44, 79.94, 57.23, 51.73, 48.29, 45.23, 44.12, 29.72, 28.40, 26.92, 21.49.

HR-EIMS ($C_{26}H_{27}FN_3O_4$): calculated: 488.19, found: 488.1918.

Compound 10k: Synthesized according to General Procedure A[3] using 4-nitrobenzaldehyde **7e**



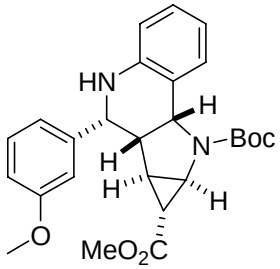
(126 mg), aniline **8a** (76 μL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-15% ethylacetate in hexane) to afford 121 mg (Yield: 78%) of a white solid **10k**.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.25 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 6.0 Hz, 1H), 7.17 – 7.09 (m, 1H), 6.93 – 6.84 (m, 1H), 6.73 – 6.65 (m, 1H), 5.48 (s, 1H), 4.62 (d, J = 2.6 Hz, 1H), 4.02 – 3.90 (m, 1H), 3.54 (d, J = 15.7 Hz, 3H), 3.29 (s, 1H), 2.74 (dd, J = 5.0, 2.1 Hz, 1H), 2.34 – 2.27 (m, 1H), 1.65 (d, J = 12.0 Hz, 1H), 1.56 (s, 3H), 1.47 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 170.16, 152.19, 148.18, 147.67, 144.80, 128.49, 127.40, 124.32, 120.40, 115.47, 82.89, 77.46, 77.04, 76.61, 57.16, 51.81, 48.20, 45.75, 44.17, 35.59, 28.43, 26.60, 25.39.

HR-EIMS ($C_{25}H_{27}N_3O_6$): calculated: 465.19, found: 465.1900.

Compound 10k′: Synthesized according to General Procedure A[3] using 3-methoxybenzaldehy



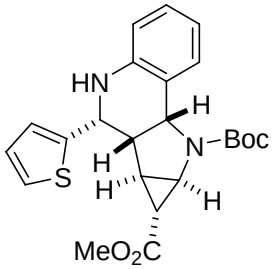
-de **7f** (101 µL), aniline **8a** (76 µL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-15% ethylacetate in hexane) to afford 88 mg (Yield: 59%) of a white solid **10k′**.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.33 (t, J = 7.9 Hz, 1H), 7.08 (t, J = 6.8 Hz, 2H), 7.02 (s, 1H), 6.92 – 6.78 (m, 3H), 6.66 (d, J = 7.8 Hz, 1H), 5.39 (dd, J = 37.9, 13.2 Hz, 1H), 4.47 (d, J = 2.5 Hz, 1H), 3.88 (s, 1H), 3.84 (s, 3H), 3.56 (d, J = 7.8 Hz, 3H), 3.31 (d, J = 6.2 Hz, 1H), 2.78 – 2.71 (m, 1H), 2.58 (q, J = 7.2 Hz, 1H), 2.45 – 2.38 (m, 1H), 1.49 (s, 3H), 1.47 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 170.15, 160.06, 154.31, 145.72, 132.61, 130.08, 128.18, 118.69, 115.46, 113.20, 112.21, 81.27, 57.58, 55.33, 51.66, 45.78, 44.56, 28.44, 27.00, 24.18.

HR-EIMS ($C_{26}H_{30}N_2O_5$): calculated: 450.22, found: 450.2155.

Compound 10l: Synthesized according to General Procedure A[3] using thiophene-2-carboxal-



dehyde **7g** (77 µL), aniline **8a** (76 µL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-20% ethylacetate in hexane) to afford 96 mg (Yield: 68%) of a white solid **10l**.

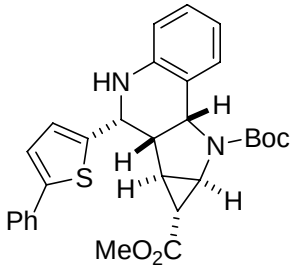
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.61 – 7.48 (m, 1H), 7.29 (dd, J = 5.1, 1.2 Hz, 1H), 7.14 (d, J = 3.4 Hz, 1H), 7.12 – 7.07 (m, 1H), 7.04 (dd, J = 5.1, 3.5 Hz, 1H), 6.85 (t, J = 7.1 Hz, 1H),

6.68 – 6.62 (m, 1H), 5.41 (t, *J* = 16.9 Hz, 1H), 4.76 (d, *J* = 2.6 Hz, 1H), 3.99 (s, 1H), 3.62 (s, 3H), 3.32 (d, *J* = 6.7 Hz, 1H), 2.76 (dt, *J* = 7.2, 2.7 Hz, 1H), 2.65 – 2.54 (m, 1H), 1.67 (d, *J* = 21.7 Hz, 1H), 1.57 (s, 3H), 1.49 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 170.66, 145.07, 143.91, 130.64, 127.01, 124.76, 124.49, 120.01, 115.06, 80.06, 53.99, 51.74, 49.01, 44.17, 28.43, 27.81, 26.59.

HR-EIMS ($C_{23}H_{26}N_2O_4S$): calculated: 426.16, found: 426.1603.

Compound 10m: Synthesized according to General Procedure A[3] using 5-phenylthiophene-2-carbaldehyde **7h** (157 mg), aniline **8a** (76 µL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2-20% ethylacetate in hexane) to afford 90 mg (Yield: 54%) of a white solid **10m**.

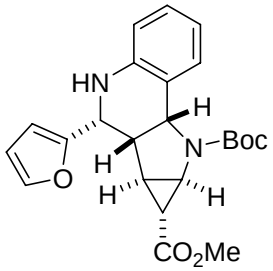


^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.65 – 7.50 (m, 3H), 7.43 – 7.35 (m, 2H), 7.33 – 7.28 (m, 1H), 7.23 (d, *J* = 3.7 Hz, 1H), 7.16 – 7.11 (m, 1H), 7.10 – 7.08 (m, 1H), 6.85 (dd, *J* = 10.9, 4.0 Hz, 1H), 6.67 (d, *J* = 7.7 Hz, 1H), 5.42 (t, *J* = 16.0 Hz, 1H), 4.73 (d, *J* = 2.5 Hz, 1H), 4.03 (s, 1H), 3.61 (s, 3H), 3.33 (d, *J* = 6.6 Hz, 1H), 2.82 – 2.74 (m, 1H), 2.63 (d, *J* = 2.9 Hz, 1H), 1.78 – 1.62 (m, 1H), 1.56 (d, *J* = 2.3 Hz, 3H), 1.51 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 170.44, 155.60, 145.05, 143.66, 143.22, 134.08, 130.66, 128.98, 128.30, 127.70, 125.75, 125.38, 123.57, 122.87, 120.38, 115.53, 80.27, 54.20, 51.76, 49.07, 44.46, 28.45, 27.93, 23.68.

HR-EIMS ($C_{29}H_{30}N_2O_4S$): calculated: 502.19, found: 502.1919.

Compound 10n: Synthesized according to General Procedure A[3] using furan-2-carbaldehyde **7i**



(69 μL), aniline **8a** (76 μL) and tert-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2% to 10% EtOAc/hexanes) to afford 98 mg (Yield: 72%) of a white solid **10n**, mp = 73-75 °C.

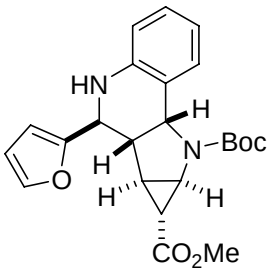
^{1}H NMR (600 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 7.59 (dd, J = 6.2, 3.2 Hz, 1H), 7.42 (d, J = 1.0 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.83 (t, J = 7.4 Hz, 1H), 6.65 (d, J = 7.9 Hz, 1H), 6.36 (dd, J = 1.7, 3.1 Hz, 2H), 5.42 (d, J = 6.2 Hz) and 5.30 (s)[1H], 4.50 (d, J = 2.3 Hz, 1H), 4.02 (br s, 1H), 3.38 (s) and 3.33 (d, J = 5.4 Hz)[1H], 2.88 (dd, J = 2.4, 4.8 Hz, 1H), 2.50 (s, 1H), 1.69 (d, J = 14.5, 1H), 1.57 and 1.48 (s, 9H), 1.28 (d, J = 17.3 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 170.4 and 170.3, 155.5, 153.6, 144.8, 142.1, 130.6, 128.3 and 128.3, 128.2, 123.5, 120.1, 115.3, 110.4, 106.2, 80.1, 62.8, 51.9 and 51.6, 45.4, 44.4, 35.7, 31.3, 30.2 and 30.1, 28.3.

FT-IR (neat): 3367, 3116, 3059, 2975, 2927, 2852, 1726, 1695, 1605, 1480, 1441, 1390, 1366, 1335, 1289, 1250, 1167, 1121, 1068, 1009, 978, 945, 880, 851, 750, 595 cm^{-1}.

HR-EIMS ($C_{23}H_{26}N_2O_5$): calculated: 410.1842, found: 410.1835.

Compound 11n: Synthesized according to General Procedure A[3] Yield: 27%; Yellow solid, 70-71 °C.



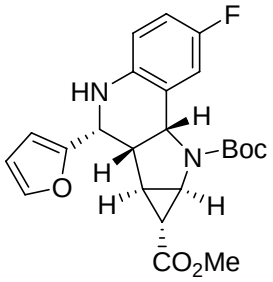
^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ: 7.45 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 1.0 Hz, 1H), 7.07 (J = 8.0 Hz, 1H), 6.76 (t, J = 7.8 Hz, 1H), 6.60 (d, J = 7.8 Hz, 1H), 6.22 (dd, J= 1.8, 3.1 Hz, 1H), 6.05 (d, J = 3.2 Hz, 1H), 5.05 (d, J = 7.5 Hz, 1H), 4.48 (d, J = 3.8 Hz, 1H), 4.15 (s, 1H), 3.67 (s, 3H), 3.46 (dd, J = 1.3, 6.9 Hz, 1H), 3.00-2.97 (m, 1H), 2.40-2.38 (m, 1H), 1.81 (dd, J = 1.3, 3.4 Hz, 1H), 1.50 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ: 170.4, 155.0, 143.1, 141.9, 129.9, 128.2, 122.7, 119.4, 114.9, 110.2, 106.4, 80.4, 60.2, 52.0, 51.7, 44.6, 44.2, 35.1, 31.4, 31.0, 30.1, 29.6, 28.4,22.6.

FT-IR (neat): 3377, 2963, 2926, 1727, 1696, 1606, 1494, 1441, 1393, 1317, 1254, 1165, 1125, 1009, 750, 596 cm^{-1}.

HR-ESI-MS exact mass calculated for $C_{23}H_{26}N_2O_5$: *m/z* 411.1914 $[M+H]^+$, found: *m/z* 411.1922 $[M+H]^+$.

Compound 10o: Synthesized according to General Procedure A[3] using furan-2-carbaldehyde **7i**



(69 μL), 4-fluoroaniline **8b** (80 μL) and tert-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2% to 12% EtOAc/hexanes) to afford 107 mg (Yield: 75%) of a pale yellow solid **10o**, mp = 90-93 ^{o}C.

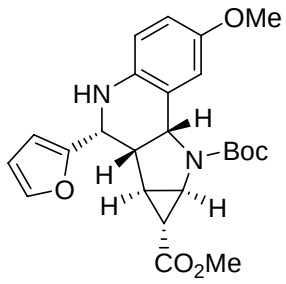
^{1}H NMR (300 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 7.40 (d, J = 1.2 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 6.81 (td, J = 2.8, 11.1 Hz, 1H), 6.59 (dd, J = 4.7, 8.7 Hz, 1H), 6.37 (dd, J = 1.8, 3.2 Hz, 1H), 6.34 (d, 3.2 Hz, 1H), 5.33 (d, 25.5 Hz, 1H), 4.44 (d, J = 2.4 Hz, 1H), 3.98 (s, 1H), 3.62 (s, 3H), 3.32 (d, J = 16.0 Hz, 1H), 2.87 (d, J = 6.9 Hz, 1H), 2.47 (d. J = 2.6 Hz, 1H), 1.68 (d, J = 20.4 Hz, 1H), 1.56 and 1.47 (s, 9H).

^{13}C NMR (300 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 170.3, 158.5, 158.5, 155.5, 153.4, 142.2, 141.1, 124.7 and 124.7, 124.0, 116.6, 116.4, 116.3, 116.3, 115.6, 115.3, 110.4, 106.3, 80.4, 62.8, 52.2 and 51.7, 45.9, 45.2, 44.3 and 44.1, 44.1, 35.7 and 35.4, 28.4 .

FT-IR (neat): 3416, 2978, 2933, 2865, 1726, 1698, 1505, 1477, 1440, 1389, 1338, 1299, 1272, 1251, 1233, 1168, 1121, 1011, 930, 884, 816, 735, 599, 547, 463 cm^{-1}.

HR-ESMS exact mass calculated for $C_{23}H_{25}FN_2O_5$: *m/z* 429.1820 $[M+H]^+$, found: *m/z* 429.1821 $[M+H]^+$.

Compound 10p: Synthesized according to General Procedure A[3] using furan-2-carbaldehyde **7i**



(69 μL), 4-methoxyaniline **8h** (103 mg) and tert-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2% to 15% EtOAc/hexanes) to afford 110 mg (Yield: 75%) of a white sticky solid **10p**.

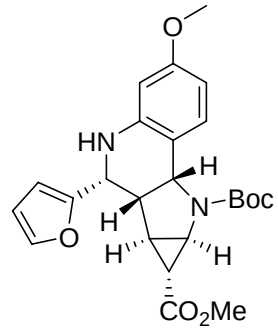
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.41 (s, 1H), 7.22 (d, J = 35.5 Hz, 1H), 6.71 (dd, J = 2.5, 8.6 Hz, 1H), 6.62 (d, J = 8.7 Hz, 1H), 6.35 (d, J = 8.6 Hz, 2H), 5.37 (dd, J = 7.1, 33.5 Hz, 1H), 4.44 (s, 1H), 3.82 (br s, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 3.41-3.33 (m, 1H), 2.91-2.86 (m, 1H), 2.49 (s, 1H), 1.75-1.69 (m, 1H), 1.57 (d, J = 6.3 Hz, 3H), 1.47 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ: 170.45, 155.5, 153.8, 153.7, 142.1, 138.7, 124.3, 116.5, 115.9, 113.7, 110.4, 106.1, 80.2, 63.0, 55.5, 51.7, 45.4, 44.4, 35.6, 28.4, 28.3, 28.1.

FT-IR (neat): 3432, 2962, 2931, 2848, 1728, 1695, 1620, 1509, 1441, 1392, 1335, 1239, 1164, 1112, 1044, 952, 882, 809, 467 cm^{-1}.

HR-ESMS exact mass calculated for $C_{24}H_{28}N_2O_6$: *m/z* 441.2020 $[M+H]^+$, found: *m/z* 441.2026 $[M+H]^+$.

Compound 10r: Synthesized according to General Procedure A[3] using furan-2-carbaldehyde **7i**



(69 μL), 3-methoxyaniline **8j** (94 μL) and tert-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (4% to 16% EtOAc/hexanes) to afford 107 mg (Yield: 73%) of a white sticky solid **10r**.

^{1}H NMR (300 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 7.40 (d, J = 1.9 Hz, 1H), 7.07-6.98 (m, 1H), 6.44-6.19 (m, 5H), 5.45 (dd, J = 6.7, 29.6 Hz, 1H), 4.47 (s, 1H), 4.05 (s,

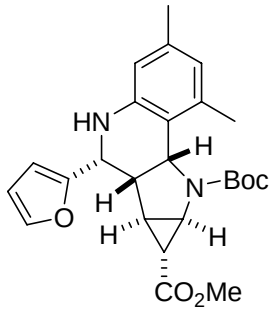
1H), 3.76 and 3.75 (s, 3H), 3.62 (s, 3H), 2.86-2.72 (m, 1H), 2.59-2.54 (m, 1H), 1.69 (dd, J = 1.3, 3.6 Hz, 1H), 1.48 and 1.42 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 170.8 and 170.5, 160.1, 154.9, 153.9, 146.6, 146.0, 144.4, 142.2 and 142.1, 141.9, 128.9 and 128.8, 110.4, 108.2, 107.6, 106.3, 101.5, 100.6, 79.4, 55.1, 51.7 and 51.2, 44.7, 43.9 and 42.9, 36.7, 29.6, 28.3 .

FT-IR (neat): 3007, 2978, 2934, 1695, 1604, 1495, 1478, 1438, 1365, 1268, 1248, 1163, 1268, 1248, 1163, 1113, 1007, 944, 896, 696, 667, 598 cm^{-1}.

HR-ESMS exact mass calculated for $C_{24}H_{28}N_2O_6$: *m/z* 441.2020 $[M+H]^+$, found: *m/z* 441.2021 $[M+H]^+$.

Compound 10s: Synthesized according to General Procedure A[3] using furan-2-carbaldehyde **7i**



(69 μL), 3,5-dimethylaniline **8f** (104 μL) and tert-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2% to 14% EtOAc/hexanes) to afford 92 mg (Yield: 63%) of a white solid **10s**, mp = 88-90 ^{o}C.

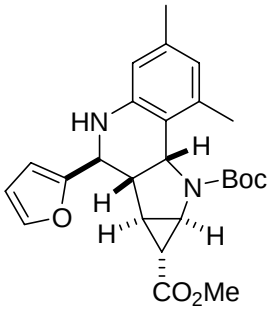
^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ: 7.40 (d, J = 1.6 Hz, 1H), 6.50 (s, 1H), 6.38 (d, J = 1.8, 3.2 Hz, 1H), 6.42 (s, 1H), 6.33 (d, J = 3.2 Hz, 1H), 5.45 (br s, 1H), 4.46 (s, 1H), 3.97 (br s, 1H), 3.64 (s, 3H), 3.23 (d, J = 5.6 Hz, 1H), 2.76 (d, J = 2.6 Hz, 1H), 2.86-2.66 (m, 1H), 2.28 (s, 3H); 2.22 (s, 3H), 1.70 (br s, 1H), 1.54(s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 170.2, 156.0, 153.9, 145.8, 142.0, 140.2, 137.7, 123.3, 114.0, 110.3, 105.9, 80.0, 63.4 and 63.4, 51.6 and 51.6, 46.2 and 46.1, 44.7 and 44.7, 37.1 and 37.1, 30.2, 28.2, 21.2, 20.7, 20.3

FT-IR (neat): 3000, 2977, 2919, 1690, 1616, 1582, 1469, 1439, 1356, 1333, 1295, 1266, 1164, 1113, 1013, 947, 834, 679, 667, 597 cm^{-1}.

HR-ESMS exact mass calculated for $C_{25}H_{30}N_2O_5$: *m/z* 439.2227 $[M+H]^+$, found: *m/z* 439.2227 $[M+H]^+$.

Compound 11s: Synthesized according to General Procedure A[3]; Yield: 18%; White solid.



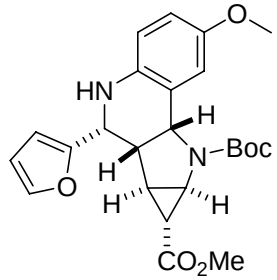
^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ: 7.28 (d, J = 1.1 Hz, 1H), 6.40 (s, 1H), 6.26 (s, 1H), 6.21 (dd, J = 1.8, 3.1 Hz, 1H), 6.04 (d, J = 3.1 Hz, 1H), 4.99 (d, J = 5.8 Hz, 1H), 4.46 (d, J = 3.9 Hz, 1H), 4.09 (br s, 1H), 3.67 (s, 3H), 3.46 (d, J = 6.4 Hz, 1H), 2.75-2.73 (m, 1H), 2.49-2.47 (m, 1H), 2.20 (s, 3H), 2.18 (s, 3H), 1.90 (d, J = 2.2 Hz, 1H), 1.43 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ: 170.5, 155.7, 155.2, 143.6, 141.8, 140.0, 137.8, 122.6, 113.4, 110.1, 106.2, 80.1, 64.2, 59.3, 51.7, 50.6, 44.1, 44.0, 28.2, 20.9, 20.2.

FT-IR (neat): 3000, 2977, 2919, 1690, 1616, 1582, 1469, 1439, 1356, 1333, 1295, 1266, 1164, 1113, 1013, 947, 834, 679, 667, 597 cm^{-1}.

HR-ESMS exact mass calculated for $C_{25}H_{30}N_2O_5$: *m/z* 439.2227 $[M+H]^+$, found: *m/z* 439.2225 $[M+H]^+$.

Compound 10s′: Synthesized according to General Procedure A[3] using furan-2-carbaldehyde **7i**



(69 μL), 4-methoxyaniline **8h** (103 mg) and tert-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (4% to 16% EtOAc/hexanes) to afford 103 mg (Yield: 70%) of a white sticky solid **10s′**.

^{1}H NMR (600 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 7.41 (d, J = 1.1 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 6.38 (dd, J = 1.8, 3.2 Hz, 1H), 6.34 (d, J = 3.2 Hz, 1H), 6.32 (d, J = 10.7 Hz, 1H), 5.33 (d, J = 5.8 Hz) and 5.22 (s)[1H], 4.45 (d, J = 2.3 Hz, 1H), 3.96 (s, 1H), 3.63 (s, 3H), 3.38 (s) and 3.32 (d, J = 4.9 Hz) [1H], 2.85 (br s, 1H), 2.47 (d, J = 2.6 Hz, 1H), 2.15 (s, 3H), 1.75 and 1.67 (s, 1H), 1.57 and 1.48 (s, 9H).

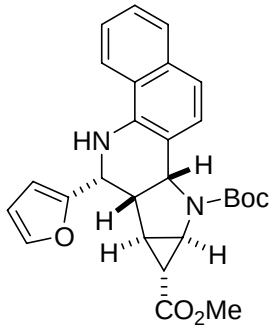
^{13}C NMR (600 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 170.3, 161.7, 160.0, 155.5, 155.5, 153.3, 144.1, 144.1, 142.2, 133.1, 133.1, 119.1, 110.4, 106.3, 101.6, 101.5, 80.3, 62.5, 51.7, 45.3, 44.2, 35.7, 28.3, 13.8 and 13.8 .

^{19}F NMR (300 MHz, $CDCl_3$, ppm) δ: -118.5 and 118.5.

FT-IR (neat): 3392, 2968, 2956, 2926, 1721, 1688, 1632, 1507, 1439, 1389, 1303, 1261, 1243, 1169, 1121, 1009, 945, 877, 834, 747, 541 cm^{-1}.

HR-ESMS exact mass calculated for $C_{24}H_{27}FN_2O_5$: *m/z* 443.1977 $[M+H]^+$, found: *m/z* 443.1976 $[M+H]^+$.

Compound 10u: Synthesized according to General Procedure A[3] using furan-2-carbaldehyde **7i**



(69 µL), 1-napthylaniline **8l** (183 mg) and tert-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (4% to 16% EtOAc/hexanes) to afford 99 mg (Yield: 65%) of a white solid **10u**, mp = 195-196 ^{o}C.

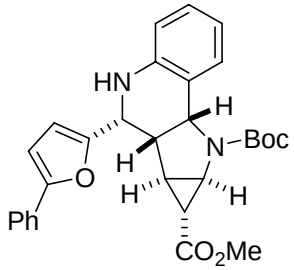
^{1}H NMR (300 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 7.82-7.77 (m, 2H), 7.66 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 7.2 Hz, 3H), 7.36 (d, J = 8.5 Hz, 1H), 6.47 (d, J = 3.2 Hz, 1H), 6.45 (dd, J = 1.8, 3.1 Hz, 1H), 5.59 (dd, J = 7.2, 36.0 Hz, 1H), 4.75 (s, 1H), 4.60 (d, J = 2.4 Hz, 1H), 3.64 (s, 3H), 3.31- 3.25 (m, 1H), 2.97-2.93 (m, 1H), 2.59 (d, J = 3.3 Hz, 1H), 1.82-1.75 (m, 1H), 1.61 and 1.50 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 170.4, 155.7, 153.7, 142.4, 139.7, 133.3, 128.5, 127.8, 126.1, 125.4, 122.9, 119.8, 117.5, 110.5, 106.5, 80.2, 63.6, 51.7, 45.1, 44.3, 35.0, 28.4.

FT-IR (neat): 3120, 3050, 2975, 2826, 1789, 1686, 1574, 1515, 1454, 1436, 1388, 1296, 1259, 1191, 1164, 1116, 1020, 1032, 877, 858, 794, 748, 663, 616, 5075, 507 cm^{-1}.

HR-EIMS ($C_{27}H_{28}N_2O_5$): calculated: 460.2, found: 460.1996.

Compound 10v: Synthesized according to General Procedure A[3] using 5-phenylfuran-2-carbal-



dehyde **7j** (143 mg), aniline **8a** (76 μL) and tert-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (4% to 16% EtOAc/hexanes) to afford 107 mg (Yield: 66%) of a white solid **10v**, mp = 94 ^{o}C.

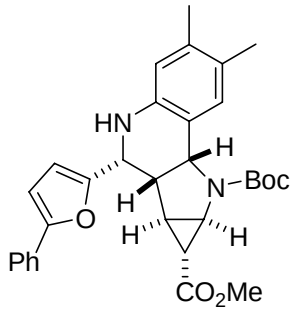
^{1}H NMR (600 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 7.65 (d, J = 7.6 Hz, 2H), 7.60 and 7.53 (d, J = 5.5 Hz, and d, J = 6.7 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.27 (d, J = 7.3 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 6.85 (t, J = 7.4 Hz, 1H), 6.68 (d, J = 7.9 Hz, 1H), 6.64 (d, J = 3.2 Hz, 1H), 6.45 (d, J = 3.1 Hz, 1H), 5.45-5.34 (m, 1H), 4.57 (d, J = 2.0 Hz, 1H), 4.04 (br s, 1H), 3.63 (s, 3H), 3.42-3.36 (m, 1H), 2.92 (d, J = 7.1 Hz, 1H), 2.65 (s, 1H), 1.80 and 1.72 (br s, 1H), 1.58 and 1.49 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ: 170.3, 155.5, 153.6, 144.8, 130.4, 128.6, 127.5, 123.6, 120.1, 115.3, 108.6, 105.6, 80.1, 62.9, 51.6, 45.6, 44.3, 35.8, 28.4 and 28.3.

FT-IR (neat): 3012, 2978, 1721, 1691, 1609, 1480, 1439, 1391, 1367, 1248, 1166, 1121, 1021, 789, 754, 692, 667 cm^{-1}.

HR-ESMS exact mass calculated for $C_{29}H_{30}N_2O_5$: *m/z* 487.2227 $[M+H]^+$, found: *m/z* 487.2232 $[M+H]^+$.

Compound 10w: Synthesized according to General Procedure A[3] using 5-phenylfuran-2-carbal-



dehyde **7j** (143 mg), 3,4-dimethylaniline **8m** (94 μL) and tert-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2% to 15% EtOAc/hexanes) to afford 102 mg (Yield: 60%) of a white solid **10w**, mp = 92-94 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.66-7.65 (m, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.30-7.25 (m, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.63 (d, J = 3.3 Hz, 1H), 6.50 (d, J = 8.1 Hz, 1H), 6.43 (d, J = 3.75

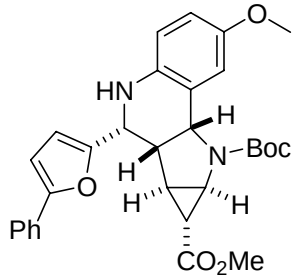
Hz, 1H), 5.56 (d, *J* = 5.7 Hz, 1H), 4.51 (s, 1H), 3.94 (br s, 1H), 3.65 (s, 3H), 3.27 (d, *J* = 6.6 Hz, 1H), 2.87-2.83 (m, 2H), 2.26 (s, 3H), 2.22 (s, 3H), 1.74 (d, *J* = 1.6 Hz, 1H), 1.51 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 170.4, 156.3, 153.6, 144.2, 138.6, 130.5, 130.3, 129.8, 128.7, 128.2, 127.5, 123.7, 120.5, 116.9, 113.1, 112.6, 108.4, 105.6, 80.2, 51.7, 46.6, 44.8, 28.3, 20.1, 16.3

FT-IR (neat): 3014, 2973, 1722, 1690, 1604, 1485, 1439, 1356, 1257, 1162, 1115, 1065, 1023, 896, 812, 760, 692, 667 cm^{-1}.

HR-ESI-MS exact mass calculated for $C_{31}H_{34}N_2O_5$: *m/z* 515.2540 $[M+H]^+$, found: *m/z* 515.2551 $[M+H]^+$.

Compound 10x: Synthesized according to General Procedure A[3] using 5-phenylfuran-2-carbal-



dehyde **7j** (143 mg), 4-methoxyaniline **8h** (103 mg) and tert-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (5% to 20% EtOAc/hexanes) to afford 118 mg (Yield: 69%) of a white sticky solid **10x**.

^{1}H NMR (300 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 7.66 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.29-7.24 (m, 2H), 6.73 (dd, *J* = 2.7, 8.7 Hz, 1H), 6.64 (s, 1H), 6.63 (d, *J* = 5.9 Hz, 1H), 6.44 (d, *J* = 3.2 Hz, 1H), 5.40 (dd, *J* = 7.3, 32.1 Hz, 1H), 4.50 (d, *J* = 2.4 Hz, 1H), 3.84 (s, 1H), 3.74 (s, 3H), 3.62 (s, 3H), 3.41-3.35 (m, 1H), 2.93-2.9 (m, 1H), 2.64-2.62 (m, 1H), 1.79-1.72 (m, 1H), 1.58 and 1.48 (s, 9H).

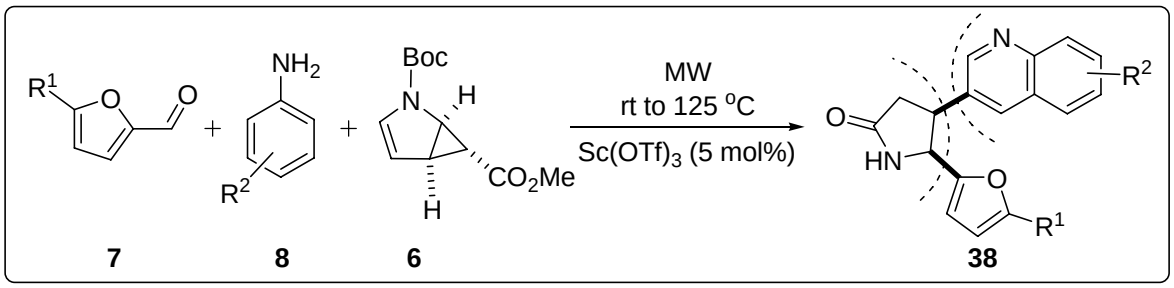
^{13}C NMR (300 MHz, $CDCl_3$, ppm) δ: 170.4, 155.5, 153.6, 138.7, 130.5, 128.7,127.5, 124.3, 123.7, 116.8, 116.6, 115.9, 115.8, 113.7, 108.6, 105.7, 80.2, 63.2, 55.6, 52.5, 51.7, 45.6, 44.3, 35.7, 28.4

FT-IR (neat): 3358, 2949, 2835, 1721, 1693, 1616, 1504, 1473, 1441, 1390, 1331, 1243, 1664, 1116, 1037, 1022, 969, 921, 866, 759 cm^{-1}.

HR-ESI-MS exact mass calculated for $C_{30}H_{32}N_2O_6$: *m/z* 517.2333 $[M+H]^+$, found: *m/z* 517.2336 $[M+H]^+$.

7.5 General Procedure for Stereoselective Synthesis of *Cis*-4,5-Disubstituted Pyrrolidinones 38.

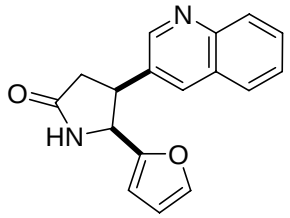
7.5a General Procedure A[4]



A solution of furan-2-carbaldehyde **7i** (0.40 mmol), aniline **8a** (0.40 mmol) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (0.334 mmol) in 4 mL acetonitrile was placed in a microwave vial, the solution was degassed by sparging with nitrogen. $Sc(OTf)_3$ (0.016 mmol, 5 mol%) was added to the solution and the capped vial containing the reaction mixture was stirred at room temperature for 1.5 h and then at 125 ^oC under microwave irradiation for 3-5 h until **6** disappeared. The reaction mixture was concentrated; the residue was dissolved in ethylacetate and extracted. The organic layer was dried, concentrated and purified on silica to afford the desired pyrrolidinone **38**.

7.6 Characterization Data of Compound 38.

(4S,5S)-5-(furan-2-yl)-4-(quinoline-3-yl)pyrrolidine-2-one (38a). Synthesized according to the



General Procedure A[4] using furan-2-carbaldehyde **7i** (33 μL), aniline **8a** (36 μL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (50% to 100% EtOAc/hexanes) to afford 76 mg of a pale yellow solid **38a** (Yield: 82%). Mp = 186-187 ^{o}C.

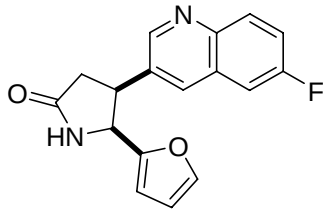
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.54 (d, J = 2.08, 1H), 8.01 (d, J = 8.30 Hz, 1H), 7.67 (d, J = 8.71 Hz, 3H), 7.50 (td, J = 0.9, 8.2 Hz, 1H), 7.5 (d, J = 1.1 Hz, 1H), 6.83 (s, 1H), 6.09 (dd, J = 1.8, 3.1 Hz, 1H), 6.05 (d, J = 3.2 Hz, 1H), 5.15 (d, J = 7.6 Hz, 1H), 4.22 (dt, J = 10.5, 8.1 Hz, 1H), 3.05 (dd, J = 10.6, 16.6 Hz, 1H), 2.75 (dd, J = 8.4, 16.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 177.0, 151.0, 150.6, 147.2, 142.7, 134.1, 130.5, 129.4, 129.0, 127.6, 127.5, 126.8, 110.4, 108.6, 56.5, 43.5, 34.5.

FT-IR (neat): 2984, 1737, 1440, 1373, 1233, 1043, 938, 847, 608 cm^{-1}.

HR-EI-MS ($C_{17}H_{14}N_2O_2$): calculated: 278.1055, found: 278.1056.

(4S,5S)-4-(6-fluoroquinoline-3-yl)-5-(furan-2-yl)pyrrolidine-2-one (38b). Synthesized



according to the General Procedure A[4] using furan-2-carbaldehyde **7i** (33 μL), 4-fluouroaniline **8b** (38 μL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (50% to 100% EtOAc/hexanes) to afford 75 mg (Yield: 76%) of a pale yellow sticky solid **38b**.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.52 (bs, 1H), 8.01 (dd, J = 5.3, 9.1 Hz, 1H), 7.64 (s, 1H), 7.42 (td, J = 2.7, 11.3 Hz, 1H), 7.29 (dd, J = 2.5, 8.8 Hz, 1H), 7.12 (d, J = 1.2, 1H), 6.25 (bs,

1H), 6.11 (dd, *J* = 1.8, 3.1 Hz, 1H), 6.06 (d, *J* = 3.2 Hz, 1H), 4.27-4.18 (m, 1H), 3.04 (dd, *J* = 10.5, 16.6 Hz, 1H), 2.81 (dd, *J* = 8.4, 16.6 Hz, 1H).

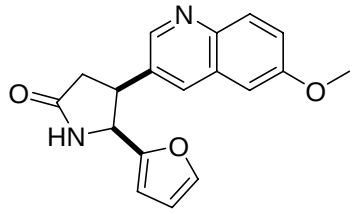
^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 176.5, 162.2, 150.9, 142.8, 133.4, 133.3, 131.7, 131.6, 131.3, 130.4, 119.8, 119.5, 110.4, 108.6, 56.4, 43.4, 34.3.

^{19}F NMR (282 MHz, $CDCl_3$, ppm) δ: -113.2 to -113.3 (m, 1F).

FT-IR (neat): 2925, 2853, 1698, 1629, 1502, 1445, 1422, 1220, 1146, 1011, 912, 832, 751, 598 cm^{-1}.

HR-EI-MS ($C_{17}H_{13}FN_2O_2$): calculated: 296.0961, found: 296.0962.

(4S,5S)-5-(furan-2-yl)-4-(6-methoxyquinoline-3-yl)pyrrolidine-2-one (38c). Synthesized



according to the General Procedure A[4] using furan-2-carbaldehyde **7i** (33 μL), 4-methoxyaniline **8h** (50 mg) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (60% to 100% EtOAc/hexanes) to afford 77 mg (Yield: 75%) of a pale yellow sticky solid **38c**.

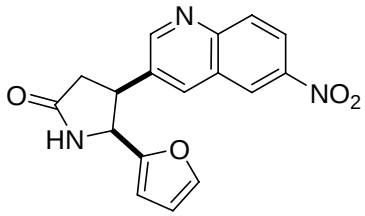
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.38 (d, *J* = 2.1 Hz, 1H), 7.87 (d, *J* = 9.1 Hz, 1H), 7.60 (d, *J* = 1.9 Hz, 1H), 7.30 (dd, *J* = 2.7, 9.1 Hz, 1H), 7.12 (d, *J* = 1.2 Hz, 1H), 6.93 (d, *J* = 2.7 Hz, 1H), 6.52 (s, 1H), 6.09 (dd, *J* = 1.8, 3.2 Hz, 1H), 6.04 (d, *J* = 3.2 Hz, 1H), 5.12 (d. *J* = 7.6 Hz, 1H), 4.23-4.14 (m, 1H), 3.89 (s, 3H), 3.04 (dd, *J* = 10.5, 16.6 Hz, 1H), 2.75 (dd, *J* = 8.3, 16.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 177.0, 157.9, 151.0, 148.0, 143.3, 142.6, 132.8, 130.8, 130.4, 128.6, 122.1, 110.3, 108.5, 104.9, 56.5, 55.5, 43.4, 34.5.

FT-IR (neat): 2927, 2857, 1695, 1604, 1578, 1498, 1472, 1331, 1268, 1208, 1093, 1010, 815, 746 cm^{-1}.

HR-ESI-MS exact mass calculated for $C_{18}H_{16}N_2O_3$: *m/z* 309.1234 $[M+H]^+$, found: *m/z* 309.1236 $[M+H]^+$.

(4S,5S)-5-(furan-2-yl)-4-(6-nitroquinoline-3-yl)pyrrolidine-2-one (38d). Synthesized



according to the General Procedure A[4] using furan-2-carbaldehyde **7i** (33 μL), 4-nitroaniline **8i** (55 mg) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (70% to 100% EtOAc/ hexanes) to afford 89 mg (Yield: 83%) of a red-yellow solid **38d**. Mp = 94-96 ^{o}C.

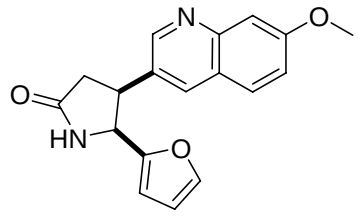
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.73 (d, J = 2.2 Hz, 1H), 8.64 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 2.4, 6.7 Hz, 1H), 8.16 (d, J = 9.2 Hz, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.11 (s, 1H), 6.70 (bs, 1H), 6.12-6.09 (m, 2H), 5.17 (d, J = 7.6 Hz, 1H), 4.33-4.24 (m, 1H), 3.05 (dd, J = 7.6, 10.3 Hz, 1H), 2.83 (dd, J = 8.4, 16.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 176.4, 154.1, 150.6, 149.1, 145.7, 142.9, 135.6, 132.9, 131.0, 126.4, 124.3, 122.8, 110.5, 108.8, 56.3, 43.3, 34.4.

FT-IR (neat): 2923, 2857, 1688, 1623, 1526, 1491, 1434, 1349, 1259, 1169, 1031, 1011, 928, 840, 735, 641, 592, 573, 520, 476.

HR-ESI-MS exact mass calculated for $C_{17}H_{13}N_3O_4$: *m/z* 324.0979 $[M+H]^+$, found: *m/z* 324.0982 $[M+H]^+$.

(4S,5S)-5-(furan-2-yl)-4-(7-methoxyquinoline-3-yl)pyrrolidine-2-one (38e). Synthesized



according to the General Procedure A[4] using furan-2-carbaldehyde **7i** (33 μL), 3-methoxyaniline **8j** (50 mg) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (50% to 100% EtOAc/hexanes) as a mixture of two diastereomers to afford 66 mg of a sticky yellow solid **38e**.

^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ: 8.50 (d. J = 2.2 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.60-7.59 (m, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.13 (s, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.09-6.08 (m, 1H), 6.04

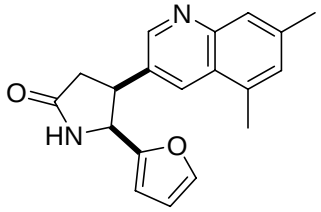
(d, *J* = 3.3 Hz, 1H), 5.1 (d, *J* = 7.7 Hz, 1H), 4.25-4.19 (m, 1H), 3.97 (s, 3H), 3.11 (dd, *J* = 10.8, 16.6 Hz, 1H), 2.76 (dd, *J* = 8.3, 16.6 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ: 176.7, 160.6, 154.9, 150.6, 147.9, 142.7, 133.8, 129.2, 129.0, 121.1, 120.0, 119.9, 110.2, 108.6, 104.4, 56.4, 55.7, 43.6, 34.3.

FT-IR (neat): 2929, 2856, 1698, 1604, 1578, 1498, 1472, 1331, 1268, 1208, 1096, 1012, 815, 747 cm^{-1}.

HR-ESI-MS exact mass calculated for $C_{18}H_{16}N_2O_3$: *m/z* 309.1234 $[M+H]^+$, found: *m/z* 309.1236 $[M+H]^+$.

(4S,5S)-5-(furan-2-yl)-4-(5,7-dimethylquinoline-3-yl)pyrrolidine-2-one (38f). Synthesized



according to the General Procedure A[4] using furan-2-carbaldehyde **7i** (33 µL), 3,5-dimetahylaniline **8f** (50 µL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (40% to 90% EtOAc/hexanes) to afford 38 mg (Yield: 38%) of a dark yellow sticky solid **38f**.

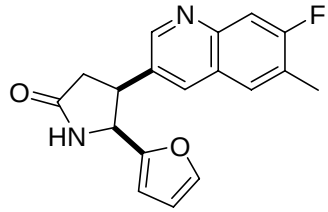
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.54 (d, *J* = 2.0 Hz, 1H), 7.79 (d, *J* = 1.9 Hz,1H), 7.67 (s,1H), 7.19 (s, 1H), 7.15 (dd, *J* = 0.7, 1.7 Hz, 1H), 6.13 (dd, *J* = 1.8, 3.2 Hz, 1H), 6.11 (s, 1H), 6.07 (d, *J* = 3.3 Hz, 1H), 5.07 (d, *J* = 7.7 Hz, 1H), 4.26-4.21 (m, 1H), 3.06 (dd, 11.1, 16.6 Hz, 1H), 2.77 (dd, 8.4, 16.6 Hz, 1H), 2.53 (s, 3H), 2.49 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 176.6, 151.1, 149.5, 147.2, 142.7, 139.9, 133.9, 131.1, 129.9, 129.1, 125.7, 125.0, 110.4, 108.7, 56.5, 43.6, 34.7, 21.8, 18.4.

FT-IR (neat): 2887, 1688, 1680, 1651, 1618, 1576, 1482, 1473, 1458, 1379, 1252, 1153, 1070, 950.

HR-ESI-MS exact mass calculated for $C_{19}H_{18}N_2O_2$: *m/z* 307.1441 $[M+H]^+$, found: *m/z* 307.1442 $[M+H]^+$.

(4S,5S)-4-(7-fluoro-6-methylquinoline-3-yl)-5-(furan-2-yl)pyrrolidine-2-one (38g).



Synthesized according to the General Procedure A[4] using furan-2-carbaldehyde **7i** (33 µL), 3-fluoro-4-metahylaniline **8k** (50 mg) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (86 mg). The product was purified by column chromatography (50% to 100% EtOAc/hexanes) to afford 86 mg (Yield: 84%) of a dirty white solid **38g**. Mp = 214-215 ^{o}C.

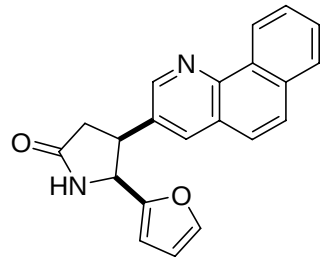
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.48 (s, 1H), 7.59 (d, J = 10.1 Hz, 2H), 7.46 (d, J = 7.6 Hz, 1H), 7.11 (s, 1H), 6.62 (s, 1H), 6.06 (d, J = 34.3, 2H), 5.1 (d, J = 6.5 Hz, 1H), 4.19 (d, J = 7.9, 1H), 3.01 (dd, J = 10.7, 16.1 Hz, 1H), 2.76 (dd J = 7.8, 16.2 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 176.8, 163.1, 161.4, 151.0 (d), 146.9 (d), 142.6, 133.1, 129.7 (d), 128.9 (d), 127.4 (d), 124.6, 112.1 (d), 110.3, 108.5, 56.5, 43.3, 34.5, 15.2 (d).

FT-IR (neat): 2931, 2859, 1698, 1575, 1500, 1431, 1349, 1248, 1149, 1112, 1011, 919, 746, 666, 597 cm^{-1}.

HR-ESI-MS exact mass calculated for $C_{18}H_{15}FN_2O_2$: *m/z* 311.1190 $[M+H]^+$, found: *m/z* 311.1195 $[M+H]^+$.

(4S,5S)-4-(benzo[h]quinolin-3-yl)-5-(furan-2-yl)pyrrolidine-2-one (38h). Synthesized according to the General Procedure A[4] using furan-2-carbaldehyde **7i** (33 µL), 1-napthyl amine **8l** (57 mg) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (40% to 90% EtOAc/ hexanes) to afford 84 mg (Yield: 77%) of a pale yellow solid **38h**. Mp = 97-98 ^{o}C.



^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.68 (d, J = 2.2 Hz, 1H), 7.87 (d, J = 7.1 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.71-7.67 (m, 3H), 7.54 (d, J = 8.8 Hz, 1H), 7.10 (s, 1H), 6.73 (s, 1H), 6.08-6.04

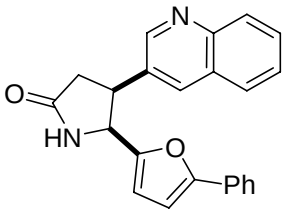
(m, 1H), 5.12 (d, *J* = 7.7 Hz, 1H), 4.31-4.22 (m, 1H), 3.11 (dd, *J* = 10.6, 16.6 Hz, 1H), 2.79 (dd, *J* = 8.4, 16.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 177.1, 151.1, 148.9, 145.6, 142.6, 134.0, 133.5, 131.2, 131.2, 128.2, 128.0, 127.8, 127.1, 125.7, 125.1, 124.2, 110.4, 108.5, 56.7, 43.4, 34.6.

FT-IR (neat): 2918, 1699, 1623, 1504, 1452, 1406, 1331, 1230, 1186, 1145, 1072, 1011, 912, 803, 746, 720 cm^{-1}.

HR-EI-MS ($C_{21}H_{16}N_2O_2$): calculated: 328.1212, found: 328.1210.

(4S,5S)-5-(5-phenylfuran-2-yl)-4-(quinoline-3-yl)pyrrolidine-2-one (38i). Synthesized



according to the General Procedure A[4] using 5-phenylfuran-2-carbaldehyde **7j** (69 mg),aniline **8a** (36 µL) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (40% to 90% EtOAc/ hexanes) to afford 83 mg (Yield: 71%) of a yellow sticky solid **38i**.

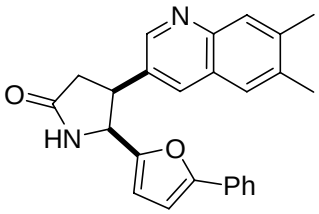
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.66 (d, *J* = 1.9 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 1.5 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 6.9 Hz, 1H), 7.23-7.18 (m, 5H), 6.30 (d, *J* = 3.2 Hz, 1H), 6.18 (s, 1H), 6.12 (d, *J* = 3.3 Hz, 1H), 5.16 (d, *J* = 7.5 Hz, 1H), 4.33-4.24 (m, 1H), 3.14 (dd, *J* = 10.5, 16.6 Hz, 1H), 2.82, (dd, *J* = 8.2, 16.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 175.7, 154.6, 151.3, 150.2, 147.6, 133.5, 133.3, 130.2, 129.6, 129.2, 128.8, 127.8, 127.8, 127.6, 127.2, 123.8, 110.0, 105.6, 59.0, 44.3, 37.3.

FT-IR (neat): 2929, 2856, 1699, 1573, 1496, 1430, 1276, 1021, 911, 789, 758, 693 cm^{-1}.

HR-ESI-MS exact mass calculated for $C_{23}H_{18}N_2O_2$: *m/z* 355.1441 $[M+H]^+$, found: *m/z* 355.1443 $[M+H]^+$.

(4S,5S)-4-(6,7-dimethylquinoline-3-yl)-5-(5-phenylfuran-2-yl)pyrrolidine-2-one (38j).



Synthesized according to the General Procedure A[4] using 5-phenylfuran-2-carbaldehyde **7j** (69 mg), 3,4-dimethylaniline **8m** (48 mg) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **3** (80 mg). The product was purified by column chromatography (40% to 90% EtOAc/hexanes) to afford 88 mg (Yield: 69%) of a yellow sticky solid **38j**.

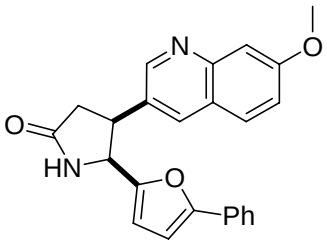
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.54 (d, J = 2.2 Hz, 1H), 7.7 (s, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.30-7.19 (m, 5H), 6.28 (d, J = 3.3 Hz, 1H), 6.08 (d, J = 3.3 Hz, 1H), 5.12 (d, J = 7.5 Hz, 1H), 4.28-4.20 (m, 1H), 3.12 (dd, J = 10.6, 16.5 Hz, 1H), 2.79 (dd, J = 8.3, 16.6 Hz, 1H), 2.38 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (300 MHz, $CDCl_3$, ppm) δ: 176.9, 154.2, 150.3, 149.7, 146.5, 139.6, 136.7, 132.9, 129.9, 129.4, 128.5, 128.3, 127.4, 126.7, 126.1, 123.5, 110.6, 105.4, 56.7, 43.5, 34.1, 20.3, 19.9.

FT-IR (neat): 2918, 2849, 1698, 1491, 1448, 1215, 1023, 920, 757, 667 cm^{-1}.

HR-EI-MS ($C_{25}H_{22}N_2O_2$): calculated: 382.1681, found: 382.1678.

(4S,5S)-4-(7-methoxyquinoline-3-yl)-5-(5-phenylfuran-2-yl)pyrrolidine-2-one (38k).



Synthesized according to the General Procedure A[4] using 5-phenylfuran-2-carbaldehyde **7j** (69 mg), 3-methoxyaniline **8j** (49 mg) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **3** (80 mg). The product was purified by column chromatography (50% to 100% EtOAc/hexanes) to afford 94 mg (Yield: 74%) of a pale yellow sticky solid **38k**.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.49 (d, J = 2.2 Hz, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.27-7.16 (m, 6H), 6.81 (d, J = 2.7 Hz, 1H), 6.32 (s, 1H), 6.30 (d, J = 3.34 Hz, 1H), 6.10 (d, J = 3.34 Hz,

1H), 5.14 (d, *J* = 7.5 Hz, 1H), 4.29-4.20 (m, 1H), 3.79 (s, 3H), 3.12 (dd, *J* = 10.4, 16.6, Hz, 1H), 2.80 (dd, *J* = 8.3, 16.6 Hz, 1H).

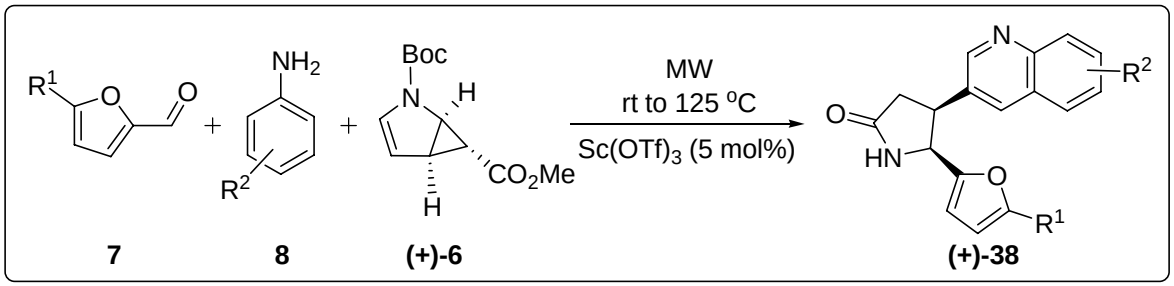
^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 176.8, 157.9, 154.2, 150.3, 132.8, 130.3, 129.9, 128.5, 127.5, 123.5, 122.2, 110.6, 105.4, 104.8, 56.7, 55.4, 43.4, 34.2.

FT-IR (neat): 2949, 2835, 1721, 1693, 1616, 1504, 1473, 1441, 1390, 1331, 1243, 1664, 1116, 1037, 1022, 969, 921, 866, 759.

HR-EIMS ($C_{24}H_{20}N_2O_3$): calculated: 384.1474, found: 384.1468.

7.7 General Procedure for Synthesis of Chiral *Cis*-4,5-Disubstituted Pyrrolidinones (+)-38.

7.7a General Procedure A[5]



A mixture of furan-2-carbaldehyde **7i** (0.40 mmol), aniline **8a** (0.40 mmol) and (+)-(1*R*,5*R*,6*R*)-*tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **(+)-6** (0.334 mmol) in 4 mL acetonitrile was placed in a microwave vial and the solution was degassed by sparging with nitrogen. $Sc(OTf)_3$ (0.016 mmol) was added, the vial capped the reaction mixture was microwaved initially at room temperature for 1.5 h and then at 125 ^{o}C for 3-5 h until the starting materials disappear. The reaction mixture was concentrated *in vacuo*, extracted with ethylacetate and washed with distilled water. The organic layer was dried over anhydrous sodiumsulphate, concentrated *in vacuo* and purified using column chromatography (50-90% ethylacetate in hexane) to yield the desired chiral pyrrolidinones **(+)-38**.

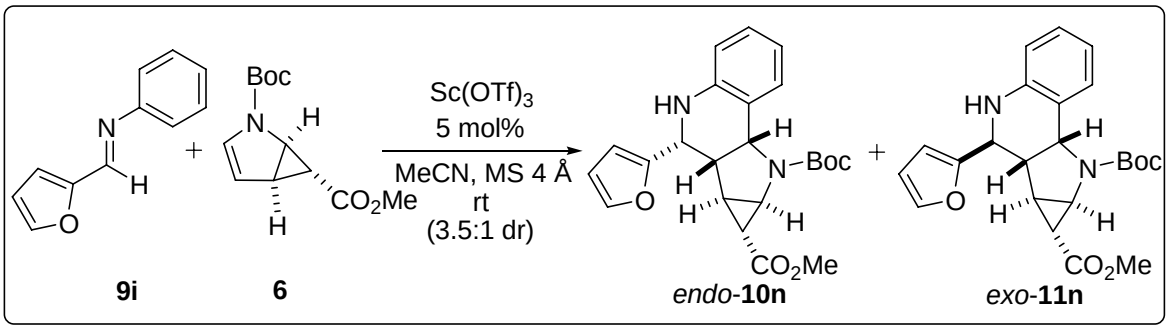
(4S,5S)-5-(furan-2-yl)-4-(quinoline-3-yl)pyrrolidine-2-one (38a). 97% *ee*. HPLC Phenomenex Lux Cellulose-1, 4.6×250 nm, 5µm, *n*-heptane/2-propanol = 70/30, flow rate = 0.5 mL/min, λ = 215 nm, retention time: 29.41 min and 36.68 min.

(4S,5S)-5-(furan-2-yl)-4-(6-nitroquinoline-3-yl)pyrrolidine-2-one (38d). 97% *ee*. HPLC Phenomenex Lux Cellulose-1, 4.6×250 nm, 5µm, *n*-heptane/2-propanol = 50/50, flow rate = 0.5 mL/min, λ = 215 nm, retention time: 27.45 min and 32.70 min.

(4S,5S)-4-(benzo[h]quinolin-3-yl)-5-(furan-2-yl)pyrrolidine-2-one (38h). 95% *ee*. HPLC Phenomenex Lux Cellulose-1, 4.6×250 nm, 5µm, *n*-heptane/2-propanol = 50/50, flow rate = 0.5 mL/min, λ = 215 nm, retention time: 23.76 min and 33.75 min.

7.8 Experimental Procedure for the $Sc(OTf)_3$-Catalyzed Synthesis of *endo*-10n and *exo*-11n.

7.8a General Procedure A[6]

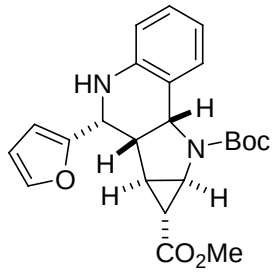


9i **6** *endo*-**10n** *exo*-**11n**

A mixture of aldimine[3] **9i** (0.833 mmol) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (0.334 mmol) in 4 mL acetonitrile was placed in a dry Schlenck tube and the mixture was degassed by sparging with nitrogen. $Sc(OTf)_3$ (0.016 mmol) was added at room temperature under N_2 and the tube was sealed with a Teflon lined cap at once and the reaction

mixture was allowed to stir for 8-24 h until the starting materials disappear. The reaction mixture was concentrated *in vacuo*, extracted with chloroform and washed with distilled water. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude product was purified using column chromatography (2 -15% ethylacetate in hexane) to yield the desired products *endo*-**10n** and *exo*-**11n**.

Compound *endo*-10n: Synthesized according to the General Procedure A[6] using aldimine **9i**



(143 mg) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (80 mg). The product was purified by column chromatography (2% to 10% EtOAc/hexane; R_f = 0.4) to afford 98 mg (Yield: 77%) of a white solid **10n**. Mp = 73-75 ^oC.

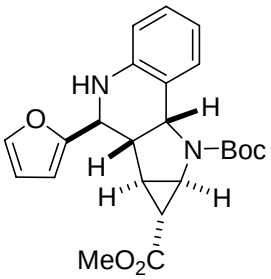
^1H NMR (600 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 7.59 (dd, J = 6.2, 3.2 Hz, 1H), 7.42 (d, J = 1.0 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.83 (t, J = 7.4 Hz, 1H), 6.65 (d, J = 7.9 Hz, 1H), 6.36 (dd, J = 1.7, 3.1 Hz, 2H), 5.42 (d, J = 6.2 Hz) and 5.30 (s)[1H], 4.50 (d, J = 2.3 Hz, 1H), 4.02 (br s, 1H), 3.38 (s) and 3.33 (d, J = 5.4 Hz)[1H], 2.88 (dd, J = 2.4, 4.8 Hz, 1H), 2.50 (s, 1H), 1.69 (d, J = 14.5, 1H), 1.57 and 1.48 (s, 9H), 1.28 (d, J = 17.3 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$, ppm, signal doubling because of rotamers) δ: 170.4 and 170.3, 155.5, 153.6, 144.8, 142.1, 130.6, 128.3 and 128.3, 128.2, 123.5, 120.1, 115.3, 110.4, 106.2, 80.1, 62.8, 51.9 and 51.6, 45.4, 44.4, 35.7, 31.3, 30.2 and 30.1, 28.3.

FT-IR (neat): 3367, 3116, 3059, 2975, 2927, 2852, 1726, 1695, 1605, 1480, 1441, 1390, 1366, 1335, 1289, 1250, 1167, 1121, 1068, 1009, 978, 945, 880, 851, 750, 595 cm^{-1}.

HR-EIMS ($C_{23}H_{26}N_2O_5$): calculated: 410.1842, found: 410.1835.

Compound *exo*-10n: Synthesized according to the General Procedure A[6]; Yield: 22%; Yellow sticky solid; $R_f = 0.33$



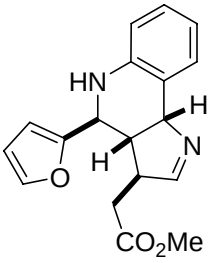
^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ: 7.45 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 1.0 Hz, 1H), 7.07 (J = 8.0 Hz, 1H), 6.76 (t, J = 7.8 Hz, 1H), 6.60 (d, J = 7.8 Hz, 1H), 6.22 (dd, J= 1.8, 3.1 Hz, 1H), 6.05 (d, J = 3.2 Hz, 1H), 5.05 (d, J = 7.5 Hz, 1H), 4.48 (d, J = 3.8 Hz, 1H), 4.15 (s, 1H), 3.67 (s, 3H), 3.46 (dd, J = 1.3, 6.9 Hz, 1H), 3.00-2.97 (m, 1H), 2.40-2.38 (m, 1H), 1.81 (dd, J = 1.3, 3.4 Hz, 1H), 1.50 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ: 170.4, 155.0, 143.1, 141.9, 129.9, 128.2, 122.7, 119.4, 114.9, 110.2, 106.4, 80.4, 60.2, 52.0, 51.7, 44.6, 44.2, 35.1, 31.4, 31.0, 30.1, 29.6, 28.4,22.6.

FT-IR (neat): 3377, 2963, 2926, 1727, 1696, 1606, 1494, 1441, 1393, 1317, 1254, 1165, 1125, 1009, 750, 596 cm^{-1}.

HR-ESI-MS exact mass calculated for $C_{23}H_{26}N_2O_5$: *m/z* 411.1914 $[M+H]^+$, found: *m/z* 411.1922 $[M+H]^+$.

Compound **38n′:** Synthesized by heating a solution of *exo*-**11n** (0.089 mmol) in 3ml acetonitrile



and $Sc(OTf)_3$ (5 mol%) under reflux condition for 2h. The reaction mixture was concentrated *in vacuo*, extracted with chloroform and washed with distilled water. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude product was purified using column chromatography (2-5% methanol in chloroform) to give a pale-yellow sticky solid of **38n′** in 72% yield.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.61 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 1.1 Hz, 1H), 7.07 (t, J = 15.2, 1H), 6.85 (t, J = 14.8 Hz, 1H), 6.62 (d, J = 7.9 Hz, 1H), 6.36 (dd, J = 1.8, 3.2 Hz, 1H), 6.29 (d, J = 3.2 Hz, 1H), 5.13 (d, J = 7.2 Hz, 1H), 3.9 (br s, 1H), 3.83 (d, J = 9.6 Hz, 1H), 3.64 (s, 3H), 3.20 (t, J = 15.2 Hz, 1H), 2.70-2.63 (m, 1H), 2.56-2.41 (m, 2H).

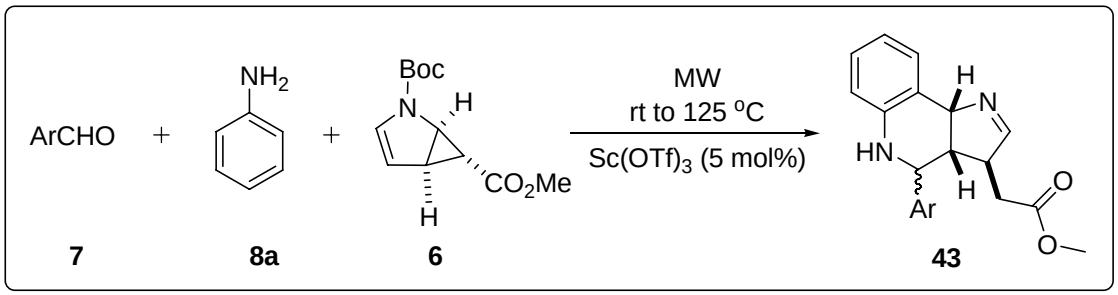
^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 171.5, 167.0, 154.3, 144.4, 142.5, 130.7, 127.8, 121.8, 119.5, 115.3, 110.3, 107.7, 69.7, 52.0, 51.2, 50.3, 45.5, 35.0.

FT-IR (neat): 3367, 3261, 3107, 2949, 2923, 2857, 1732, 1612, 1592, 1489, 1434, 1366, 1331, 1305, 1256, 1195, 1167, 1125, 1070, 1011, 926, 884, 752, 669 cm^{-1}.

HR-ESI-MS exact mass calculated for $C_{18}H_{18}N_2O_3$: *m/z* 311.139 $[M+H]^+$, found: *m/z* 311.1389 $[M+H]^+$.

7.9 General Procedure for the $Sc(OTf)_3$-Catalyzed Synthesis of Substituted Polycyclic Imines 43.

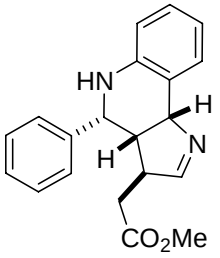
7.9a General Procedure A[7]



A mixture of aromatic aldehyde **7** (0.40 mmol), aniline **8a** (0.40 mmol) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (0.334 mmol) in 4 mL acetonitrile was placed in a microwave vial and the solution was degassed by sparging with nitrogen. $Sc(OTf)_3$ (0.016 mmol) was added, the vial capped the reaction mixture was microwaved initially at room temperature for 1.5 h and then at 125 ^oC for 2-4 h until the starting materials disappear. The reaction mixture was concentrated *in vacuo*, extracted with ethylacetate and washed with distilled water. The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified using column chromatography (20-60% ethylacetate in hexane) to yield the polycyclic imine **43**.

7.10 Characterization Data of the Polycyclic Imines 43.

Compound **43a** (major diastereomer): Synthesized according to the General Procedure A[7]; Yield: 64%, White sticky solid; R_f = 0.2.



^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.44 (d, J = 7.2 Hz, 2H), 7.41-7.36 (m, 4H), 7.31-7.28 (m, 2H), 7.00 (t, J = 7.1 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 5.50 (d, J = 9.1 Hz, 1H), 4.67 (d, J = 3.1 Hz, 1H), 3.52 (s, 3H), 3.46-3.43 (m, 1H), 2.68 (td, J = 3.4, 12.5 Hz, 1H), 2.48-2.39 (m, 1H), 2.30 (dd, J = 8.2, 15.2 Hz, 1H):

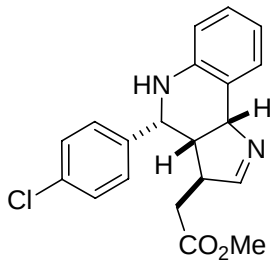
^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 171.9, 170.0, 148.0, 143.0, 131.1, 129.9, 129.7, 129.6, 128.8, 128.7, 127.4, 123.8, 120.1, 117.3, 73.4, 58.6, 52.1, 49.8, 46.2, 35.9.

FT-IR (neat): 3362, 3255, 3029, 2948, 2848, 1734, 1612, 1483, 1455, 1436, 1352, 1307, 1256, 1198, 1164, 1109, 1067, 1020, 982, 878, 850, 755, 703, 631, 540 cm^{-1}.

HR-EIMS ($C_{20}H_{20}N_2O_2$): calculated: 320.1525, found: 320.1521.

Compound 43b (major diastereomer): Synthesized according to the General Procedure A[7]; Yield: 69%, Pale yellow solid; R_f = 0.22; Mp = 190-193 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.44 (d, J = 7.0 Hz, 1H), 7.38 (d, J = 1.2 Hz, 4H), 7.08-7.04 (m, 1H), 6.86-6.82 (m, 1H), 6.64 (d, J = 8.6 Hz, 1H), 5.60 (d, J = 8.9 Hz, 1H),



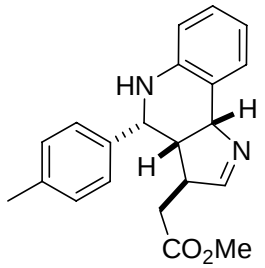
4.73 (d, J = 3.0 Hz, 1H), 3.72 (br s, 1H), 3.59 (s, 3H), 3.54-3.48 (m, 1H), 2.63-2.58 (m, 1H), 1.76 (dd, J = 9.4, 16.3 Hz, 1H), 1.65 (dd, J = 4.1, 16.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 171.7, 168.9, 145.0, 139.9, 133.6, 130.4, 129.2, 127.8, 127.4, 120.1, 115.9, 72.3, 57.1, 51.6, 49.0, 44.7, 35.7.

FT-IR (neat): 3165, 3059, 2993, 2918, 2848, 1732, 1693, 1629, 1605, 1592, 1487, 1434, 1408, 1370, 1307, 1265, 1228, 1195, 1169, 1088, 1013, 985, 941, 820, 757, 684, 508 cm^{-1}.

HR-EIMS ($C_{20}H_{19}ClN_2O_2$): calculated: 354.1125, found: 354.1132.

Compound **43c** (major diastereomer): Synthesized according to the General Procedure A[7]; Yield: 61%, White sticky solid; R_f = 0.2.



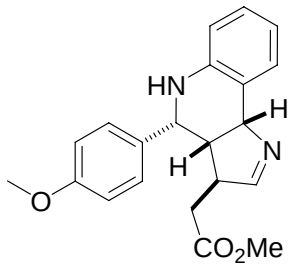
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.45 (d, J = 6.3 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 7.05 (t, J = 7.6 Hz, 1H), 6.82 (t, J = 7.4 Hz, 1H), 6.64 (d, J = 7.9 Hz, 1H), 5.59 (d, J = 8.9 Hz, 1H), 4.73 (d, J = 2.9 Hz, 1H), 3.75 (s, 1H), 3.58 (s, 3H), 3.57-3.50 (m, 1H), 2.63-2.56 (m, 1H), 2.36 (s, 3H), 1.73 (dd, J = 10.0, 16.4 Hz, 1H), 1.63 (dd, J = 4.3, 11.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 172.0, 169.2, 145.5, 138.3, 137.6, 130.4, 129.6, 127.7, 125.8, 123.1, 119.7, 116.5, 115.8, 72.4, 57.3, 51.6, 49.2, 44.8, 35.8, 21.1.

FT-IR (neat): 3151, 2953, 2923, 2870, 2839, 2725, 1632, 1682, 1607, 1480, 1458, 1375, 1272, 1217, 1164, 1123, 1070, 1040, 996, 974, 840, 807, 755, 505 cm^{-1}.

HR-EIMS ($C_{21}H_{22}N_2O_2$): calcd: 334.1681, found: 334.1680.

Compound **43d** (major diastereomer): Synthesized according to the General Procedure A[7]; Yield: 60%, Pale yellow sticky solid; R_f = 0.15



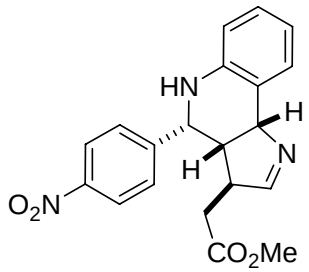
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.67 (d, J = 5.1 Hz, 1H), 7.12 (d, J = 7.4 Hz, 1H), 7.03-7.00 (m, 1H), 6.67-6.64 (m, 1H), 6.50 (d, J = 4.9 Hz, 1H), 4.57 (dd, J = 12.57, 18.14 Hz, 2H), 4.20 (s, 1H), 3.75-3.71 (m, 1H), 3.50-3.46 (m, 1H), 3.36 (s, 3H), 3.33 (s, 3H), 2.87-2.80 (m, 1H), 2.33-2.27 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 157.09, 143.30, 126.75, 125.36, 121.92, 120.93, 118.87, 88.40, 71.70, 71.68, 58.70, 56.20, 49.14, 49.11.

FT-IR (neat): 3447, 3261, 3110, 3076, 3011, 2953, 2921, 2851, 2817, 1734, 1631, 1608, 1522, 1487, 1436, 1350, 1320, 1261, 1198, 1169, 1110, 1018, 981, 860, 758, 705, 523 cm^{-1}.

HR-ESI-MS ($C_{14}H_{18}N_2O_2$): calculated: 246.14, found: 246.1416.

Compound **43e** (major diastereomer): Synthesized according to the General Procedure A[7]; Yield: 65%, Pale yellow sticky solid; R_f = 0.1.



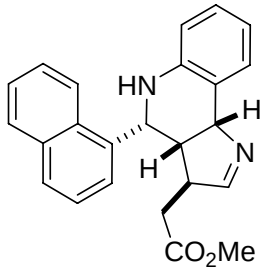
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.30 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 11.1 Hz, 2H), 7.12-7.06 (m, 1H), 6.91-6.86 (m, 1H), 6.69 (d, J = 7.3 Hz, 1H), 5.65 (d, J = 8.9 Hz, 1H), 4.88 (d, J = 3.1 Hz, 1H), 3.79 (s, 1H), 3.58 (s, 3H), 3.55-3.47 (m, 1H), 2.71-2.64 (m, 1H), 1.74 (dd, J = 9.8, 16.3 Hz, 1H), 1.57 (dd. J = 4.1, 16.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 171.4, 168.6, 148.8, 147.5, 144.¸130.4, 127.9, 127.0, 124.3, 122.9, 120.5, 116.1, 72.4, 57.4, 51.8, 48.7, 44.6, 35.7.

FT-IR (neat): 3447, 3261, 3110, 3076, 3011, 2953, 2921, 2851, 2817, 1734, 1631, 1608, 1522, 1487, 1436, 1350, 1320, 1261, 1198, 1169, 1110, 1018, 981, 860, 758, 705, 523 cm^{-1}.

HR-ESI-MS ($C_{20}H_{19}N_3O_4$): calculated: 366.1448, found: 366.1456.

Compound **43f** (major diastereomer): Synthesized according to the General Procedure A[7]; Yield: 70%, White sticky solid; R_f = 0.3.



^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 8.04 (d, J = 9.2 Hz, 1H), 7.94-7.90 (m, 1H), 7.86 (t, J = 6.5 Hz, 1H), 7.57-7.50 (m, 4H), 7.45 (br s, 1H), 7.10 (td, J = 1.4, 8.8 Hz, 1H), 6.88 (td, J = 1.0, 8.4 Hz, 1H), 6.72 (d, J =

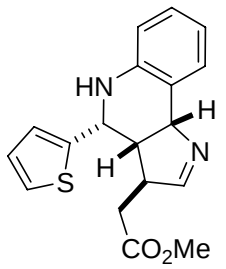
7.8 Hz, 1H), 5.72 (d, *J* = 9.0 Hz, 1H), 5.54 (d, *J* = 2.4 Hz, 1H), 3.78 (br s, 1H), 3.62-3.55 (m, 1H), 3.43 (s, 3H), 2.96-2.89 (m, 1H), 1.46 (dd, *J* = 10.3, 16.4 Hz, 1H), 1.24 (t, *J* = 4.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 171.7, 169.2, 145.9, 136.9, 133.7, 130.5, 130.0, 129.3, 128.4, 127.8, 126.6, 126.0, 125.6, 123.3, 122.3, 122.0, 120.0, 116.1, 72.3, 53.5, 51.5, 46.8, 45.3, 35.4.

FT-IR (neat): 3050, 3010, 2945, 2918, 2848, 1730, 1623, 1592, 1605, 1592, 1480, 1434, 1377, 1351, 1324, 1289, 1254, 1224, 1197, 1169, 1083, 1033, 993, 904, 884, 860, 779, 750, 660, 634, 461 cm^{-1}.

HR-EIMS ($C_{24}H_{22}N_2O_2$): calculated: 370.1681, found: 370.1684.

Compound **43g** (major diastereomer): Synthesized according to the General Procedure A[7]; Yield: 53%, White sticky solid; R_f = 0.15



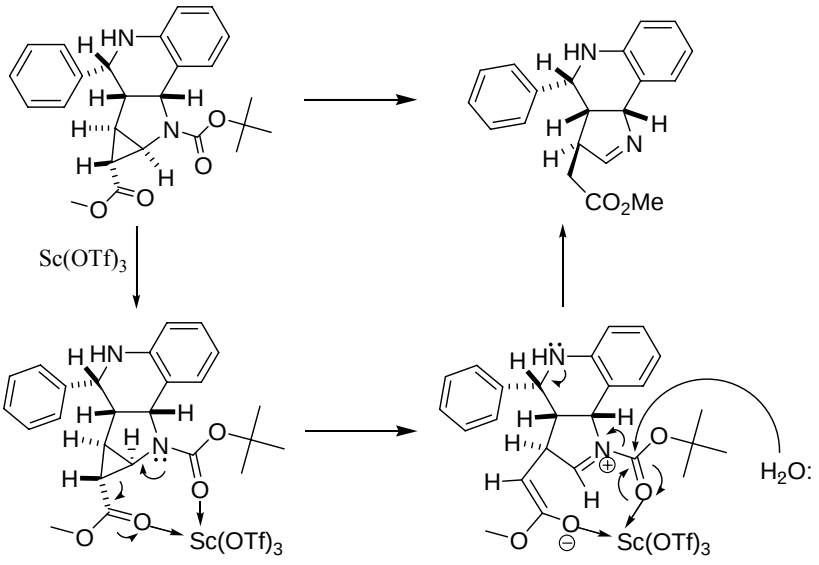
^{1}H NMR (300 MHz, CD_3OD, ppm) δ: 7.47 (s, 1H), 7.31 (dd, *J* = 1.1, 5.0 Hz, 1H), 7.29 (s, 1H), 7.12 (d, *J* = 3.4 Hz, 1H), 7.04-7.01 (m, 1H), 7.00 (dd, *J* = 1.2, 7.6 Hz, 1H), 6.75 (t, *J* = 7.2 Hz, 1H), 5.49 (d, *J* = 9.1 Hz, 1H), 4.93 (d. *J* = 3.5 Hz, 1H), 3.58 (s, 3H), 3.48 (d, *J* = 8.3 Hz, 1H), 2.74-2.67 (m, 1H), 1.84 (d, 1H), 1.81 (s, 1H).

^{13}C NMR (75 MHz, CD_3OD, ppm) δ: 173.7, 172.2, 147.3, 146.5, 131.1, 128.8, 128.0, 125.0, 124.7, 123.7, 120.5, 117.4, 72.8, 55.0, 52.1, 50.0, 46.8, 35.9.

FT-IR (neat): 3313, 3061, 2935, 2847, 1716, 1623, 1588, 1559, 1532, 1500, 1432, 1406, 1374, 1352, 1273, 1202, 1147, 1103, 1039, 995, 952, 911, 846, 829, 768, 738, 706, 659, 610, 573, 472 cm^{-1}.

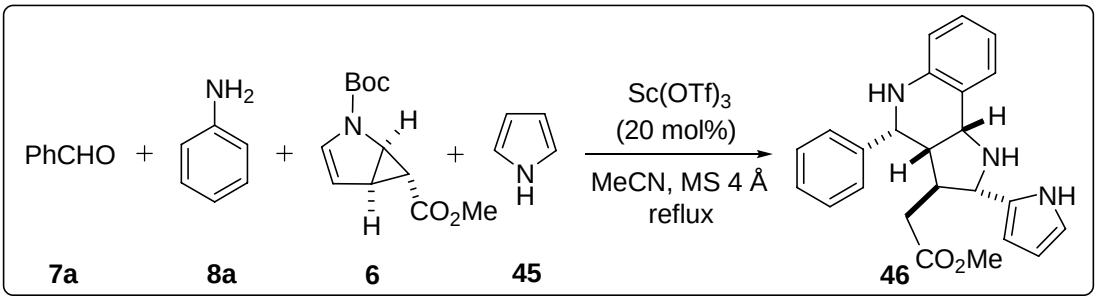
HR-EIMS ($C_{18}H_{18}SN_2O_2$): calculated: 326.1089, found: 326.1092.

7.11 Plausible Mechanism for the Synthesis of Imine Derivatives.



7.12 Experimental Procedure for the $Sc(OTf)_3$-Catalyzed Functionalization of 43 via Intermolecular Trapping of Iminium Ion.

7.12a General Procedure A[8]

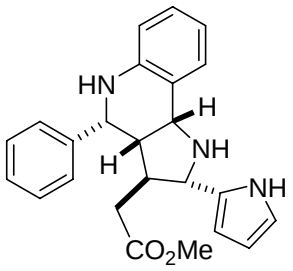


A mixture of benzaldehyde **7a** (0.40 mmol), aniline **8a** (0.40 mmol) and *tert*-butyl methyl 2-aza-bicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate **6** (0.334 mmol) in pyrrole **45** (excess or as solvent) was placed in a microwave vial and the solution was degassed by sparging with nitrogen. $Sc(OTf)_3$ (0.032 mmol) was added, the vial capped the reaction mixture was microwaved initially at room temperature for 1.5 h and then at 125 ^oC for 2 h until the starting materials disappear. The reaction can also be done under reflux condition using molecular sieves and 20 mol%

$Sc(OTf)_3$ to produce similar product. The reaction mixture was concentrated *in vacuo*, extracted with ethylacetate and washed with distilled water. The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the major diastereomer was separated using column chromatography (30-70% ethylacetate in hexane) to yield **46**.

7.13 Characterization Data of Compound 46.

Compound **46** (major diastereomer): Synthesized according to the General Procedure A[8];



Yield: 42%, Yellow sticky solid; $R_f = 0.45$.

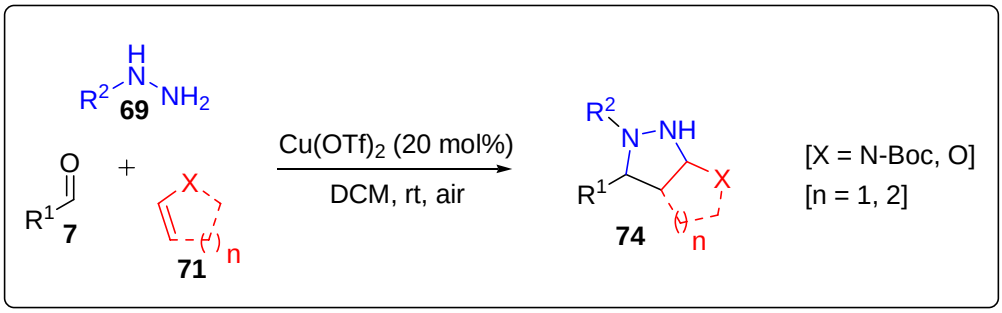
^{1}H NMR (600 MHz, CD_3OD, ppm) δ: 7.51 (d, J = 7.4 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.3 Hz, 1H), 7.22(dd, J = 1.2, 7.5 Hz, 1H), 7.09 (td, J = 1.4, 7.9 Hz, 1H), 6.89 (dd, J = 0.8, 8.0 Hz, 1H), 6.78 (td, J = 1.1, 7.4 Hz, 1H), 5.88 (t, J = 3.1 Hz, 1H), 5.79 (dd, J = 1.4, 3.3 Hz, 1H), 4.51 (d, J = 3.7 Hz, 1H), 4.50 (br s, 1H), 3.87 (d, J = 10.1 Hz, 1H), 3.33 (s, 1H), 3.24 (s, 3H), 2.82-2.78 (m, 1H), 2.72-2.66 (m, 1H), 1.50 (dd, J = 8.3, 15.5 Hz, 1H), 1.41 (dd, J = 3.2, 15.5 Hz, 1H), 1.28 (br s, 1H).

^{13}C NMR (150 MHz, CD_3OD, ppm) δ: 172.9, 148.0, 141.0, 129.6, 129.0, 128.7, 128.2, 127.5, 127.0, 124.8, 119.7, 117.7, 116.3, 107.4, 106.6, 62.1, 58.1, 50.9, 50.7, 42.7, 35.5.

HR-EIMS ($C_{24}H_{25}N_3O_2$): calculated: 387.19, found: 387.1000.

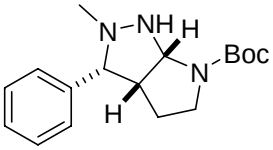
7.14 General Procedure and Characterization Data for $Cu(OTf)_2$-Catalyzed, Multicomponent Syntheses of Substituted Tetrahydro Pyrazoles 74.

7.14a General Procedure A[9]



To a 20 mL glass vial equipped with a magnetic stir bar, was sequentially added aldehyde **7** (0.90 mmol), CH_2Cl_2 (5 mL) and $Cu(OTf)_2$ (0.09 mmol, 20 mol%). The resulting mixture was stirred for 15 minutes and then hydrazine **69** (0.45 mmol) and olefin **71** (0.45 mmol) were added drop wise in a sequential manner. The reaction mixture was stirred at room temperature initially under aerial atmosphere for 1.0 h and then the vial was capped, fitted with small needles, kept for stirring and monitored periodically by TLC. Upon consumption of the olefin **71** (6 – 12 h), the reaction mixture was concentrated; the residue was dissolved in ethylacetate, washed with distilled water and extracted in ethylacetate. The organic layer was dried, concentrated and subjected to silica gel chromatography (hexanes/ethylacetate) to give the desired products **74**.

(3R,3aR,6aS)-*Tert*-butyl hexahydro-2-methyl-3-phenylpyrrolo[2,3-c]pyrazole-6(6aH)-carboxylate (74a). Synthesized according to the Synthesized according to the General Procedure



A[9] using benzaldehyde **7a** (92 µL), methylhydrazine **69a** (24 µL) and *tert*-butyl 2,3-dihydropyrrole-1-carboxylate **71a** (73 µL). The product was purified by column chromatography (0 to 25% EtOAc/hexanes) to afford 88 mg (Yield: 65%) of a white gummy solid **74a**. R_f = 0.4 (30% EtOAc/hexanes), mp = 105-108 ^oC.

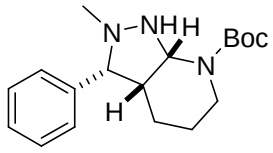
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.52 (d, J = 28.1 Hz, 2H), 7.27 (d, J = 8.4 Hz, 3H), 4.93 (s, 1H), 3.62 (d, J = 6.6 Hz, 1H), 3.12 (dd, J = 15.7, 10.8 Hz, 1H), 3.04 (dd, J = 11.9, 3.6 Hz, 1H), 2.96 (s, 3H), 2.74 (d, J = 8.8 Hz, 1H), 2.09 – 1.99 (m, 2H), 1.42 (dd, J = 8.9, 5.7 Hz, 1H), 1.30 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 163.27, 141.20, 127.81, 127.60, 127.10, 79.66, 71.15, 46.42, 44.84, 28.18, 27.38.

FT-IR (neat) cm^{-1}: 3370, 3322, 3276, 2976, 2931, 2866, 1706, 1517, 1457, 1388, 1364, 1273, 1253, 1169, 995, 910, 785, 760, 726, 701, 472, 442, 417.

HR-ESI-MS exact mass calculated for $C_{17}H_{25}N_3O_2$: *m/z* 303.19, found: *m/z* 304.2010 $[M+H]^+$.

(3R,3aR,6aS)-*Tert*-butyl hexahydro-2-methyl-3-phenyl-1H-pyrazolo[3,4-c]pyridine-6(7aH)-carboxylate (74b). Synthesized according to the General Procedure A[9] using benzalde-



hyde **7a** (92 µL), methylhydrazine **69a** (24 µL) and *tert*-butyl 3,4-dihydropyridine-1(2H)-carboxylate **71b** (80 µL). The product was purified by column chromatography (0 to 15% EtOAc/hexanes) to afford 115 mg (Yield: 81%) of a pale yellow gummy solid **74b**. R_f = 0.5 (20% EtOAc/hexanes)

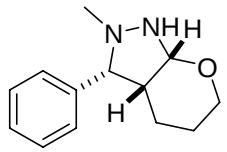
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.45 (d, J = 6.8 Hz, 2H), 7.37 – 7.33 (m, 2H), 7.13 (d, J = 3.8 Hz, 1H), 4.14 – 4.04 (m, 1H), 3.38 (d, J = 13.5 Hz, 1H), 3.11 (td, J = 12.4, 3.1 Hz, 1H), 2.96 – 2.80 (m, 1H), 2.68 (s, 3H), 1.98 (dd, J = 13.9, 7.7 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.52 (s, 9H), 1.40 (dt, J = 10.1, 5.0 Hz, 4H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 151.77, 128.66, 128.00, 127.72, 81.27, 79.67, 77.46, 77.03, 76.61, 51.92, 45.55, 42.56, 28.26, 27.11, 23.17.

FT-IR (neat) cm^{-1}: 3026, 2980, 2951, 2936, 2866, 2781, 1702, 1602, 1507, 1452, 1408, 1363, 1343, 1293, 1253, 1213, 1159, 905, 751, 726, 701, 671, 432.

HR-ESI-MS exact mass calculated for $C_{18}H_{27}N_3O_2$: *m/z* 317.21, found: *m/z* 318.2186 $[M+H]^+$.

(3R,3aR,7aR)-Octahydro-2-methyl-3-phenylpyrano[2,3-c]pyrazole (74c). Synthesized according to the General Procedure A[9] using 2-methoxy benzaldehyde **7n** (123 mg),



methylhydrazine **69a** (24 µL) and 3,4-dihydro-2H-pyran **71e** (41 µL). The product was purified by column chromatography (0 to 40% EtOAc/hexanes) to afford 60 mg (Yield: 62%) of a pale yellow gummy solid **74c**. R_f = 0.25 (40% EtOAc/hexanes)

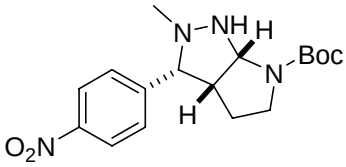
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.48 – 7.43 (m, 1H), 7.40 (dd, J = 5.0, 2.0 Hz, 1H), 7.35 (dd, J = 5.3, 3.0 Hz, 2H), 4.25 (t, 2H) (two doublets immerging with each other), 3.70 (s, 3H), 2.58 (s, 1H), 2.54 (t, J = 6.3 Hz, 2H), 1.92 (dt, J = 10.5, 6.3 Hz, 2H), 1.82 – 1.73 (m, 1H), 1.73 – 1.63 (m, 1H), 1.59 – 1.42 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 139.99, 130.29, 128.93, 128.69, 128.29, 98.32, 69.85, 68.01, 48.58, 36.86, 22.97, 18.51.

FT-IR (neat) cm^{-1}: 2980, 2946, 2926, 2851, 2781, 1716, 1677, 1637, 1507, 1492, 1463, 1402, 1353, 1333, 1288, 1213, 1089, 1064, 1014, 995, 930, 905, 840, 825, 666, 481, 422.

HR-ESI-MS exact mass calculated for $C_{13}H_{18}N_2O$: *m/z* 218.14, found: *m/z* 219.1491 $[M+H]^+$.

(3R,3aR,6aS)-*tert*-butyl hexahydro-2-methyl-3-(4-nitrophenyl)pyrrolo[2,3-c]pyrazole-6(6aH)-carboxylate (74d): Synthesized according to the General Procedure A[9] using 4-nitro



benzaldehyde **7e** (136 mg), methylhydrazine **69a** (24 µL) and *tert*-butyl 2,3-dihydropyrrole-1-carboxylate **71a** (73 µL). The product was purified by column chromatography (0 to 50% EtOAc/ hexanes) to afford 119 mg (Yield: 76%) of a white gummy solid **74d**. R_f = 0.1 (40% EtOAc/hexane)

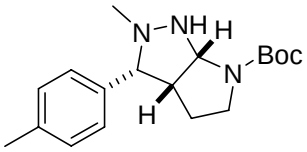
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.22 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 4.78 (d, J = 9.1 Hz, 1H), 4.27 (dt, J = 18.8, 9.4 Hz, 1H), 4.01 (dd, J = 10.8, 8.8 Hz, 1H), 3.92 – 3.84 (m, 1H), 2.86 (s, 3H), 1.84 – 1.74 (m, 2H), 1.57 (d, J = 11.1 Hz, 1H), 1.53 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 161.19, 149.51, 147.75, 129.47, 123.93, 82.76, 70.25, 53.60, 40.62, 29.21, 27.97, 21.99.

FT-IR (neat) cm^{-1}: 3021, 2981, 2926, 2892, 2845, 1731, 1704, 1514, 1405, 1344, 1188, 855, 556, 474.

HR-ESI-MS exact mass calculated for $C_{17}H_{14}N_2O_4$: *m/z* 348.18, found: *m/z* 348.1911 $[M+H]^+$.

(3R,3aR,6aS)-*tert*-butyl hexahydro-2-methyl-3-p-tolylpyrrolo[2,3-c]pyrazole-6(6aH)-carboxylate (74e): Synthesized according to the General Procedure A[9] using 4-methyl



benzaldehyde **7k** (106 μL), methylhydrazine **69a** (24 μL) and *tert*-butyl 2,3-dihydropyrrole-1-carboxylate **71a** (73 μL). The product was purified by column chromatography (0 to 20% EtOAc/ hexanes) to afford 107 mg (Yield: 75%) of a white gummy solid **74e**. R_f = 0.45 (30% EtOAc/ hexanes)

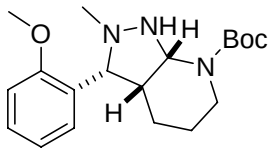
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.66 – 7.33 (m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 4.90 (d, 1H), 3.62 (d, J = 6.7 Hz, 1H), 3.12 (dd, J = 9.7, 5.0 Hz, 1H), 3.03 (dd, J = 11.8, 3.4 Hz, 1H), 2.95 (s, 3H), 2.72 (s, 1H), 2.31 (s, 3H), 2.10 – 1.93 (m, 2H), 1.41 (t, J = 7.3 Hz, 1H), 1.32 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 159.15, 128.50, 126.98, 80.06, 70.69, 46.45, 44.96, 28.19, 21.20.

FT-IR (neat) cm^{-1}: 3359, 3021, 2976, 2951, 2926, 2856, 1711, 1512, 1448, 1388, 1363, 1248, 1174, 1034, 980, 905, 815, 751, 527, 462, 427.

HR-ESI-MS exact mass calculated for $C_{18}H_{27}N_3O_2$: *m/z* 317.21, found: *m/z* 317.2208 $[M+H]^+$.

(3R,3aR,7aS)-*Tert*-butyl hexahydro-3-(2-methoxyphenyl) -2-methyl-1H-pyrazolo[3,4-b]pyridine-7(7aH)-carboxylate (74h). Synthesized according to the General Procedure A[9]



using 2-methoxybenzaldehyde **7n** (123 mg), methylhydrazine **69a** (24 μL) and *tert*-butyl 3,4-dihydropyridine-1(2H)-carboxylate **71b** (80 μL). The product was purified by column chromatography (0 to 30% EtOAc/hexanes) to afford 100 mg (Yield: 64%) of a pale yellow gummy solid **74h**. R_f = 0.3 (40% EtOAc/hexanes)

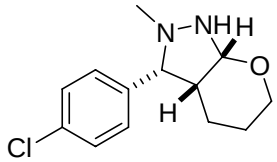
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.22 (t, J = 7.8 Hz, 2H), 6.88 (td, J = 7.4, 0.7 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.53 (d, J = 5.8 Hz, 1H), 3.77 (s, 3H), 3.59 (d, J = 13.7 Hz, 1H), 3.19 (dd, J = 12.0, 2.3 Hz, 1H), 2.96 (s, 3H), 2.31 (t, J = 13.2 Hz, 1H), 2.03 (s, 2H), 1.78 (dd, J = 10.0, 3.4 Hz, 2H), 1.59 – 1.50 (m, 2H), 1.39 (s, 3H), 1.31 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 157.52, 130.99, 129.40, 128.99, 120.01, 109.82, 79.26, 75.53, 55.14, 49.40, 45.79, 41.23, 40.02, 29.83, 28.22, 25.81, 25.00.

FT-IR (neat) cm^{-1}: 3384, 3364, 3319, 2961, 2936, 2926, 2856, 2836, 2787, 1711, 1602, 1522, 1492, 1463, 1283, 1243, 1174, 1104, 1049, 1029, 905, 756, 731, 651, 512, 407.

HR-ESI-MS exact mass calculated for $C_{19}H_{29}N_3O_3$: *m/z* 347.22, found: *m/z* 348.2306 $[M+H]^+$.

(3R,3aR,7aR)-3-(4-chlorophenyl)-Octahydro-2-methylpyrano[2,3-c]pyrazole (74i). Synthesized according to the General Procedure A[9] using 4-chlorobenzaldehyde **7b** (126 mg),



methylhydrazine **69a** (24 μL) and 3,4-dihydro-2H-pyran **71e** (41 μL). The product was purified by column chromatography (0 to 40% EtOAc/hexanes) to afford 78 mg (Yield: 69%) of a pale white gummy solid **74i**. R_f = 0.28 (40% EtOAc/hexanes)

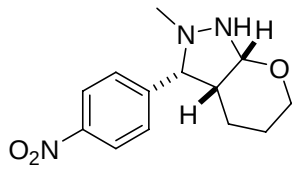
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.43 – 7.30 (m, 4H), 4.35 (d, J = 9.7 Hz, 1H), 3.99 – 3.89 (m, 1H), 3.42 (d, J = 13.4 Hz, 1H), 2.79 (dt, J = 16.6, 11.1 Hz, 1H), 2.58 (s, 3H), 2.04 (dd, J = 6.3, 4.4 Hz, 1H), 1.79 (dd, J = 11.0, 7.3 Hz, 2H), 1.56 (ddd, J = 20.3, 15.4, 9.0 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 146.13, 133.84, 128.95, 127.78, 125.77, 80.38, 77.46, 77.04, 76.62, 70.07, 62.11, 48.46, 43.03, 25.60, 23.07.

FT-IR (neat) cm^{-1}: 3397, 3063, 2987, 2946, 2857, 2782, 1691, 1636, 1596, 1493, 1452, 1404, 1350, 1336, 1288, 1179, 1090, 1064, 1016, 981, 927, 824, 722, 668, 524, 476, 415.

HR-ESI-MS exact mass calculated for $C_{13}H_{17}ClN_2O$: *m/z* 252.10, found: *m/z* 252.1099 $[M+H]^+$.

(3R,3aR,7aR)-Octahydro-2-methyl-3-(4-nitrophenyl)pyrano[2,3-c]pyrazole (74k): Synthesized according to the General Procedure A[9] using 4-nitrobenzaldehyde **7e** (136 mg),



methylhydrazine **69a** (24 μL) and 3,4-dihydro-2H-pyran **71e** (41 μL). The product was purified by column chromatography (0 to 50% EtOAc/hexanes) to afford 82 mg (Yield: 70%) of a pale white gummy solid **74k**. R_f = 0.10 (50% EtOAc/hexanes)

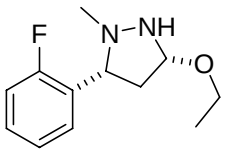
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 4.37 (d, J = 10.9 Hz, 1H), 3.96 (td, J = 11.0, 4.7 Hz, 1H), 3.74 – 3.64 (m, 1H), 3.56 (d, J = 13.5 Hz, 1H), 2.90 – 2.72 (m, 1H), 2.59 (s, 3H), 2.04 (s, 1H), 1.84 – 1.77 (m, 2H), 1.66 – 1.58 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.77, 147.75, 145.74, 128.56, 124.04, 80.08, 70.27, 62.52, 49.00, 43.35, 25.39, 22.86.

FT-IR (neat) cm^{-1}: 3020, 2926, 2901, 2856, 1512, 1348, 1213, 905, 751, 731, 666, 651, 502, 437.

HR-ESI-MS exact mass calculated for $C_{13}H_{17}N_3O_3$: *m/z* 263.12, found: *m/z* 264.1339 $[M+H]^+$.

(3R,5R)-3-ethoxy-5-(2-fluorophenyl)-1-methylpyrazolidine (74l): Synthesized according to



the General Procedure A[9] using 2-fluorobenzaldehyde **7q** (0.90 mmol), methylhydrazine **66a** (0.45 mmol) and ethyl-vinyl ether **71f** (0.45 mmol). The product was purified by column chromatography (0 to 30% EtOAc/ hexanes) to afford 59 mg (Yield: 59%) of a pale white gummy solid **74l**. R_f = 0.32 (35% EtOAc/hexane)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69 – 7.61 (m, 1H), 7.17 (d, J = 6.7 Hz, 1H), 7.12 (d, J = 10.3 Hz, 1H), 7.04 (t, 1H), 4.21 (t, J = 5.9 Hz, 1H), 4.19 – 4.13 (m, 1H), 3.73 – 3.50 (m, 2H), 3.08 (s, 1H), 3.01 – 2.95 (m, 1H), 2.81 – 2.74 (m, 1H), 2.62 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 158.33, 128.59, 128.18, 124.43, 115.47, 103.67, 88.24, 77.45, 77.03, 76.60, 66.53, 64.53, 44.15, 39.60, 14.28.

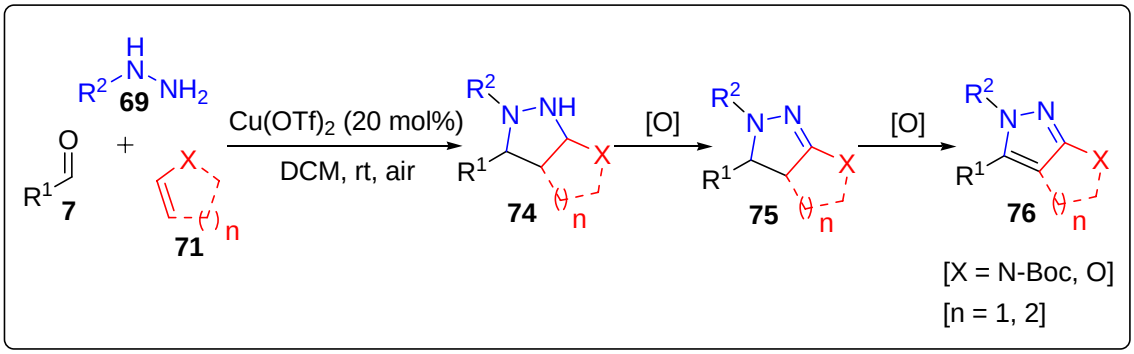
^{19}F NMR (282 MHz, $CDCl_3$) δ: -119.62.

FT-IR (neat) cm^{-1}: 2926, 2856, 2801, 1731, 1622, 1592, 1567, 1487, 1457, 1363, 1278, 1250, 1164, 1114, 1089, 1059, 984, 756, 577, 502, 442.

HR-ESI-MS exact mass calculated for $C_{12}H_{17}FN_2O$: *m/z* 224.13, found: *m/z* 224.1411 $[M+H]^+$.

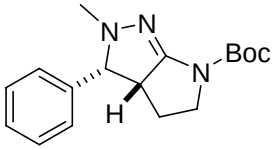
7.15 General Procedure and Characterization Data for $Cu(OTf)_2$-Catalyzed, Multicomponent Syntheses of Dihydro- and 1*H*-Pyrazoles 74-76.

7.15a General Procedure A[10]



To a 20 ml glass vial equipped with a magnetic stir bar, was sequentially added aldehyde **7** (0.90 mmol), CH_2Cl_2 (5 mL) and $Cu(OTf)_2$ (0.09 mmol, 20 mol%). The resulting mixture was stirred for 15 minutes and then hydrazine **69** (0.45 mmol) and olefin **71** (0.45 mmol) were added drop wise in a sequential manner. The reaction mixture was stirred at room temperature initially under air for 1.0 h and then the vial was capped, fitted with small needles, kept for stirring and monitored periodically by TLC. After consumption of the olefin **71** (6 – 12 h), the reaction mixture was kept for stirring for longer time (12 – 24 h) under air until the preformed **74** disappear and a new spot of **75** and **76** form successively in different reaction vials depending on the reaction time. The reaction mixture was then concentrated; the residue was dissolved in ethylacetate, washed with distilled water and extracted in ethylacetate. The organic layer was dried, concentrated and subjected to silica gel chromatography (hexanes/ethylacetate) to give the desired products **75** and **76** in separate reactions.

***tert*-butyl 3,3a,4,5-tetrahydro-2-methyl-3-phenylpyrrolo[2,3-c]pyrazole-6(2H)-carboxylate (75a):** Synthesized according to the General Procedure A[10] using benzaldehyde **7a** (92 μL),



methylhydrazine **69a** (24 μL) and *tert*-butyl 2,3-dihydropyrrole-1-carboxylate **71a** (73 μL). The product was purified by column chromatography (0 to 25% EtOAc/hexanes) to afford 83 mg (Yield: 65%) of a pale yellow gummy solid **75a**. R_f = 0.45 (30% EtOAc/hexanes)

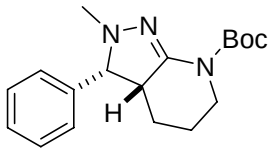
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 – 7.42 (m, 2H), 7.40 – 7.39 (m, 1H), 7.38 – 7.35 (m, 2H), 4.24 (t, J = 7.9 Hz, 2H), 3.79 (s, 3H), 2.92 (t, J = 2.9 Hz, 2H), 1.56 (s, 9H), 1.42 (dd, J = 9.1, 5.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.82, 156.28, 138.01, 130.23, 128.75, 128.42, 128.29, 127.53, 80.38, 53.17, 45.81, 37.84, 29.68, 28.35, 28.12, 28.00.

FT-IR (neat) cm^{-1}: 3076, 3056, 2966, 2921, 2851, 2831, 1696, 1531, 1506, 1476, 1446, 1371, 1337, 1247, 1148, 1048, 764, 739, 699, 539, 520, 460.

HR-ESI-MS exact mass calculated for $C_{16}H_{20}N_3O_2$: *m/z* 286.16, found: *m/z* 286.1723 $[M+H]^+$.

(3R,3aR)-*tert*-butyl 2,3,3a,4,5,6-hexahydro-2-methyl-3-phenylpyrazolo[3,4-b]pyridine-7-carboxylate (75b): Synthesized according to the General Procedure A[10] using benzaldehyde **7a**



(92 µL), methylhydrazine **69a** (24 µL) and *tert*-butyl 3,4-dihydropyridine-1(2H)-carboxylate **71b** (80 µL). The product was purified by column chromatography (0 to 15% EtOAc/hexanes) to afford 113 mg (Yield: 80%) of a pale yellow gummy solid **75b**. R_f = 0.48 (20% EtOAc/hexanes)

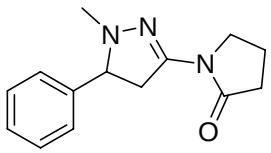
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.54 – 7.42 (m, 2H), 7.30 – 7.24 (m, 2H), 7.20 (dd, J = 6.5, 1.4 Hz, 1H), 5.52 – 5.20 (m, 1H), 3.70 (dd, 1H), 3.14 (dd, J = 11.8, 2.1 Hz, 1H), 2.99 (s, 4H), 2.20 – 2.02 (m, 2H), 1.85 – 1.67 (m, 2H), 1.54 (s, 3H), 1.41 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 155.05, 143.00, 137.28, 127.79, 127.32, 126.36, 79.76, 55.14, 47.74, 46.02, 40.57, 29.98, 28.59, 28.40, 26.09, 24.59.

FT-IR (neat) cm^{-1}: 3026, 2980, 2951, 2936, 2866, 2781, 1702, 1602, 1507, 1452, 1408, 1363, 1343, 1293, 1253, 1213, 1159, 905, 751, 726, 701, 671, 432.

HR-ESI-MS exact mass calculated for $C_{18}H_{25}N_3O_2$: *m/z* 315.19, found: *m/z* 316.2018 $[M+H]^+$.

1-(4,5-dihydro-1-methyl-5-phenyl-1H-pyrazol-3-yl)pyrrolidin-2-one (75c): Synthesized



according to the General Procedure A[10] using benzaldehyde **7a** (92 µL), methylhydrazine **69a** (24 µL) and vinylpyrrolidin-2-one **71c** (48 µL). The product was purified by column chromatography (0 to 45% EtOAc/ hexanes) to afford 93 mg (Yield: 85%) of a pale yellow gummy solid **75c**. R_f = 0.3 (50% EtOAc/hexane)

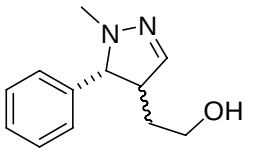
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.57 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.24 (d, J = 7.2 Hz, 1H), 3.97 (t, J = 3.9 Hz, 1H), 3.43 (t, J = 3.4 Hz, 2H), 2.90 (s, 3H), 2.62 – 2.47 (m, 1H), 2.39 (t, J = 8.1 Hz, 2H), 2.16 (td, J = 14.6, 7.0 Hz, 1H), 2.02 – 1.90 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.91, 147.35, 133.08, 128.56, 127.71, 125.73, 77.46, 77.04, 76.61, 65.16, 47.20, 37.17, 35.54, 30.98, 18.07.

FT-IR (neat) cm^{-1}: 2894, 2831, 2782, 1702, 1604, 1492, 1407, 1372, 1260, 1197, 1127, 1092, 1036, 994, 917, 861, 749, 735, 700, 643, 601, 581, 525, 554, 421

HR-ESI-MS exact mass calculated for $C_{14}H_{17}N_3O$: *m/z* 243.14, found: *m/z* 244.1446 $[M+H]^+$.

2-(4,5-dihydro-1-methyl-5-phenyl-1H-pyrazol-4-yl)ethanol (75d): Synthesized according to the General Procedure A[10] using benzaldehyde **7a** (92 μL), methylhydrazine **69a** (24 μL) and



2,3-dihydrofuran **71d** (34 μL). The product was purified by column chromatography (0 to 50% EtOAc/hexanes) to afford 61 mg (Yield: 67%) of a white gummy solid **75d**. R_f = 0.1 (50% EtOAc/hexanes)

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ (Diastereomer 1): 7.44 – 7.39 (m, 2H), 7.34 – 7.28 (m, 3H), 6.94 (s, 1H), 4.01 (d, *J* = 9.8 Hz, 1H), 3.73 – 3.60 (m, 2H), 3.43 (dd, *J* = 7.2, 2.9 Hz, 1H), 3.19 (dd, *J* = 9.6, 5.5 Hz, 1H), 2.74 (s, 3H), 1.86 (dd, *J* = 13.8, 6.9 Hz, 1H), 1.41 (ddt, *J* = 13.9, 9.9, 6.2 Hz, 1H).

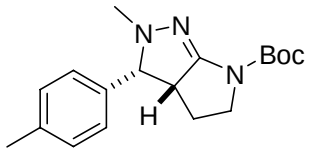
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ (Diastereomer 2): 7.35 (d, *J* = 4.4 Hz, 5H), 6.80 (s, 1H), 4.01 (d, *J* = 9.8 Hz, 1H), 3.73 – 3.60 (m, 2H), 3.38 (dd, *J* = 7.3, 3.4 Hz, 1H), 3.10 (dd, *J* = 13.2, 6.5 Hz, 1H), 2.67 (s, 3H), 1.81 – 1.73 (m, 1H), 1.27 – 1.12 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 146.15, 145.34, 139.71, 136.33, 128.73, 128.50, 128.04, 127.92, 127.64, 60.76, 60.71, 54.43, 48.67, 41.67, 41.21, 33.40, 31.05.

FT-IR (neat) cm^{-1}: 3365, 2921, 2862, 2787, 1585, 1448, 1046, 744, 703, 636, 535, 443.

HR-ESI-MS exact mass calculated for $C_{12}H_{16}N_2O$: *m/z* 204.13, found: *m/z* 205.1335 $[M+H]^+$.

***Tert*-butyl 3,3a,4,5-tetrahydro-2-methyl-3-p-tolylpyrrolo[2,3-c]pyrazole-6(2H)-carboxylate (75h):** Synthesized according to the General Procedure A[10] using 4-methylbenzaldehyde **7k**



(106 µL), methylhydrazine **69a** (24 µL) and *tert*-butyl 2,3-dihydropyrrole-1-carboxylate **71a** (73 µL). The product was purified by column chromatography (0 to 30% EtOAc/hexanes) to afford 106 mg (Yield: 75%) of a pale yellow gummy solid **75h**. R_f = 0.48 (40% EtOAc/hexanes))

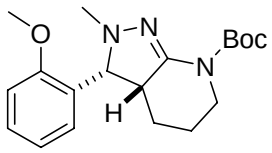
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.21 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.0 Hz, 2H), 4.33 (d, J = 14.9 Hz, 1H), 4.08 (d, J = 14.9 Hz, 1H), 2.72 (s, 3H), 2.42 (dd, J = 8.4, 5.1 Hz, 1H), 2.34 (s, 3H), 1.57 – 1.48 (m, 1H), 1.43 (d, J = 6.8 Hz, 2H), 1.37 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 155.50, 138.75, 137.55, 129.30, 129.25, 127.93, 80.06, 57.57, 48.60, 41.23, 38.43, 28.35, 21.31, 21.15.

FT-IR (neat) cm^{-1}: 3349, 2976, 2926, 2851, 1706, 1691, 1527, 1512, 1393, 1363, 1253, 1213, 1169, 905, 751, 726, 671, 421.

HR-ESI-MS exact mass calculated for $C_{18}H_{25}N_3O_2$: *m/z* 315.19, found: *m/z* 316.2020 $[M+H]^+$.

(3R,3aR)-tert-butyl 2,3,3a,4,5,6-hexahydro-3-(2-methoxyphenyl)-2-methylpyrazolo[3,4-b]pyridine-7-carboxylate (75i): Synthesized according to the General Procedure A[10] using 2-



methoxybenzaldehyde **7n** (123 mg), methylhydrazine **69a** (24 µL) and *tert*-butyl 3,4-dihydropyridine-1(2H)-carboxylate **71b** (80 µL). The product was purified by column chromatography (0 to 40% EtOAc/ hexanes) to afford 93 mg (Yield: 60%) of a pale yellow gummy solid **75i**. R_f = 0.3 (40% EtOAc/hexane)

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.31 (d, J = 7.4 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 6.88 (td, J = 7.4, 0.7 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 3.78 (d, J = 9.8 Hz, 3H), 3.59 (d, J = 13.7 Hz, 1H),

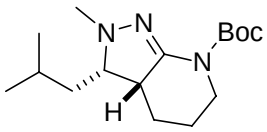
3.19 (dd, *J* = 12.0, 2.3 Hz, 1H), 2.96 (s, 3H), 2.31 (t, *J* = 13.2 Hz, 1H), 2.03 (s, 1H), 1.77 (dd, *J* = 10.2, 3.6 Hz, 2H), 1.59 – 1.49 (m, 1H), 1.39 (s, 3H), 1.31 (s, 6H), 0.94 – 0.76 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 157.52, 154.72, 130.99, 129.40, 128.56, 120.01, 110.22, 78.74, 77.46, 77.03, 76.61, 55.14, 49.40, 45.79, 41.23, 29.83, 28.27, 26.20, 24.59.

FT-IR (neat) cm^{-1}: 3085, 2976, 2936, 2931, 2856, 1716, 1691, 1688, 1602, 1502, 1463, 1368, 1333, 1288, 1253, 1159, 1119, 1054, 1020, 760, 666, 527, 477.

HR-ESI-MS exact mass calculated for $C_{19}H_{27}N_3O_3$: *m/z* 345.21, found: *m/z* 345.2199 $[M+H]^+$.

(3S,3aR)-tert-butyl 2,3,3a,4,5,6-hexahydro-3-isobutyl-2-methylpyrazolo[3,4-b]pyridine-7-carboxylate (75j): Synthesized according to the General Procedure A[10] using 3-methylbutanal



7o (94 µL), methylhydrazine **69a** (24 µL) and *tert*-butyl 3,4-dihydropyridine-1(2H)-carboxylate **71b** (80 µL). The product was purified by column chromatography (0 to 12% EtOAc/hexanes) to afford 73 mg (Yield: 55%) of a pale yellow gummy solid **75j**. R_f = 0.55 (20% EtOAc/hexanes)

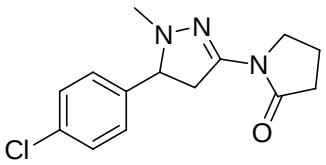
^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.01 (dt, *J* = 7.0, 5.9 Hz, 1H), 3.03 (t, *J* = 10.7 Hz, 1H), 2.71 (s, 3H), 2.39 – 2.29 (m, 1H), 2.16 – 2.02 (m, 1H), 1.82 – 1.72 (m, 1H), 1.67 (dd, *J* = 10.7, 4.8 Hz, 1H), 1.65 – 1.57 (m, 2H), 1.49 (d, *J* = 4.7 Hz, 2H), 1.42 (s, 9H), 1.21 (t, 1H), 0.88 (dd, *J* = 12.3, 6.2 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.18, 150.17, 81.67, 49.36, 45.20, 42.96, 41.21, 28.41, 28.20, 25.39, 23.82, 23.08, 22.19.

FT-IR (neat, cm^{-1}): 3095, 2951, 2926, 2866, 1702, 1627, 1507, 1457, 1406, 1388, 1368, 1343, 1293, 1268, 1253, 1213, 1154, 905, 850, 751, 731, 666, 567, 457.

HR-ESI-MS exact mass calculated for $C_{16}H_{29}N_3O_2$: *m/z* 295.23, found: *m/z* 296.2337 $[M+H]^+$.

1-(5-(4-chlorophenyl)-4,5-dihydro-1-methyl-1*H*-pyrazol-3yl)pyrrolidin-2-one (75m): Synthesized according to the General Procedure A[10] 4-chlorobenzaldehyde **7b** (126 mg),



methylhydrazine **69a** (24 µL) and vinylpyrrolidin-2-one **71c** (48 µL). The product was purified by column chromatography (0 to 46% EtOAc/hexanes) to afford 107 mg (Yield: 86%) of a dirty white gummy solid **75m**. R_f = 0.32 (50% EtOAc/hexanes)

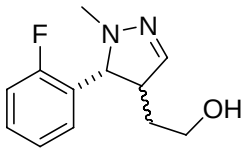
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.39 – 7.29 (m, 4H), 3.88 (d, 2H), 3.81 (dt, 2H), 3.03 (dd, *J* = 19.5, 17.4 Hz, 1H), 2.61 (s, 3H), 2.50 (t, *J* = 8.1 Hz, 2H), 2.11 (dt, *J* = 15.6, 8.0 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 174.26, 174.14, 148.09, 138.20, 137.99, 133.56, 133.31, 130.02, 128.97, 128.90, 128.78, 46.89, 46.82, 42.66, 42.15, 32.14, 18.25, 17.97.

FT-IR (neat) cm^{-1}: 3069, 3027, 2985, 2956, 2894, 2831, 2782, 1702, 1604, 1492, 1407, 1372, 1260, 1197, 1127, 1092, 1036, 994, 917, 861, 749, 735, 700, 643, 601, 581, 525, 554, 421.

HR-ESI-MS exact mass calculated for $C_{14}H_{16}ClN_3O$: *m/z* 277.1, found: *m/z* 278.1099 $[M+H]^+$.

2-((R)-5-(2-fluorophenyl)-4,5-dihydro-1-methyl-1H-pyrazol-4-yl)ethanol (75o): Synthesized according to the General Procedure A[10] using 2-fluorobenzaldehyde **7q** (95 µL), methylhydrazine **69a** (24 µL) and 2,3-dihydrofuran **71d** (34 µL). The product was purified by column chromatography (0 to 50% EtOAc/hexanes) to afford 65 mg (Yield: 65%) of a white gummy solid **75o**. R_f = 0.15 (50% EtOAc/hexane)



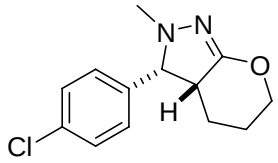
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (td, *J* = 7.5, 1.8 Hz, 1H), 7.16 – 7.08 (m, 2H), 7.06 – 6.97 (m, 2H), 6.75 (s, 1H), 3.90 (d, *J* = 13.4 Hz, 1H), 3.74 – 3.57 (m, 3H), 3.20 – 3.08 (m, 1H), 2.67 (s, 3H), 1.88 – 1.80 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.13, 136.75, 128.99, 128.59, 124.45, 115.96, 115.46, 100.85, 70.28, 60.89, 53.53, 41.64, 33.54, 29.84.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -119.58.

HR-ESI-MS exact mass calculated for $C_{12}H_{15}FN_2O$: *m/z* 222.12, found: *m/z* 223.1241 $[M+H]^+$.

(3R,3aR)-3-(4-chlorophenyl)-2,3,3a,4,5,6-hexahydro-2-methylpyrano[2,3-c]pyrazole (75q): Synthesized according to the General Procedure A[10] 4-chlorobenzaldehyde **7b** (126 mg),



methylhydrazine **69a** (24 μL) and 3,4-dihydro-2H-pyran **71e** (41 μL). The product was purified by column chromatography (0 to 44% EtOAc/hexanes) to afford 80 mg (Yield: 71%) of a white gummy solid **75q**. R_f = 0.25 (50% EtOAc/hexanes)

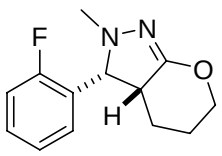
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.41 – 7.30 (m, 4H), 4.35 (d, *J* = 10.7 Hz, 1H), 4.00 – 3.88 (m, 1H), 3.41 (d, *J* = 13.5 Hz, 1H), 2.79 (dt, *J* = 12.0, 6.6 Hz, 1H), 2.57 (s, 3H), 2.08 – 1.96 (m, 1H), 1.86 – 1.70 (m, 2H), 1.61 – 1.47 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 161.15, 146.13, 133.84, 128.95, 127.78, 126.16, 70.07, 54.73, 48.46, 43.03, 25.60, 23.07.

FT-IR (neat) cm^{-1}: 2851, 2781, 1716, 1677, 1637, 1507, 1492, 1463, 1402, 1353, 1333, 1288, 1213, 1089, 1064, 1014, 995, 930, 905, 840, 825, 751, 721, 666, 481, 422.

HR-ESI-MS exact mass calculated for $C_{13}H_{15}ClN_2O$: *m/z* 250.09, found: *m/z* 251.0946 $[M+H]^+$.

(3R,3aR)-3-(2-fluorophenyl)-2,3,3a,4,5,6-hexahydro-2-methylpyrano[2,3-c]pyrazole (75r): Synthesized according to the General Procedure A[10] using 2-fluorobenzaldehyde **7q** (95 μL),



methylhydrazine **69a** (24 μL) and 3,4-dihydro-2H-pyran **71e** (41 μL). The product was purified by column chromatography (0 to 40% EtOAc/hexanes) to afford 76 mg (Yield: 73%) of a white gummy solid **75r**. R_f = 0.30 (50% EtOAc/hexanes)

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.55 (td, J = 7.5, 1.7 Hz, 1H), 7.16 (td, J = 7.5, 1.0 Hz, 1H), 7.09 – 7.02 (m, 1H), 6.91 (s, 1H), 4.22 (d, J = 7.5 Hz, 1H), 3.44 (t, J = 6.4 Hz, 2H), 3.26 – 3.17 (m, 1H), 2.78 (s, 3H), 1.54 – 1.39 (m, 2H), 1.39 – 1.27 (m, 2H).

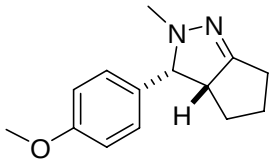
^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 159.44, 146.11, 129.02, 128.96, 128.91, 124.24, 124.19, 123.92, 115.20, 114.92, 68.05, 62.54, 49.76, 41.54, 30.31, 24.44.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -118.62.

FT-IR (neat) cm^{-1}: 3419, 2951, 2926, 2856, 2801, 1731, 1622, 1592, 1567, 1487, 1457, 1363, 1278, 1224, 1114, 1089, 1059, 984, 756, 577, 502, 442.

HR-ESI-MS exact mass calculated for $C_{13}H_{15}FN_2O$: *m/z* 234.12, found: *m/z* 235.1244 $[M+H]^+$.

(3R,3aR)-2,3,3a,4,5,6-hexahydro-3-(4-methoxyphenyl)-2-methylcyclopenta[c]pyrazole (75u): Synthesized according to the General Procedure A[10] using 4-methoxy benzaldehyde **7l**



(103 μL), methylhydrazine **69a** (24 μL) and (cyclopentenyloxy)trimethylsilane **71g** (160 μL). The product was purified by column chromatography (0 to 15% EtOAc/hexanes) to afford 86 mg (Yield: 83%) of a yellow gummy solid **75u**. R_f = 0.60 (20% EtOAc/hexanes)

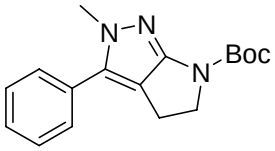
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38 – 7.32 (m, 2H), 6.90 – 6.86 (m, 2H), 3.80 (s, 3H), 3.55 (d, J = 12.5 Hz, 1H), 2.83 (dd, J = 9.0, 4.3 Hz, 1H), 2.64 (s, 3H), 2.45 – 2.32 (m, 2H), 2.22 – 2.11 (m, 1H), 2.05 – 1.91 (m, 2H), 1.48 (tdd, J = 11.7, 11.2, 7.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.13, 157.72, 130.37, 127.54, 125.53, 112.91, 59.85, 54.14, 41.49, 36.17, 27.57, 25.96.

FT-IR (neat) cm^{-1}: 3064, 3064, 2953, 2863, 2835, 2773, 1733, 1643, 1616, 1511, 1456, 1435, 1366, 1290, 1242, 1172, 1109, 1026, 832, 735, 686, 604, 575, 542, 527, 458, 437, 417.

HR-ESI-MS exact mass calcd for $C_{14}H_{18}N_2O$: *m/z* 230.14, found: *m/z* 231.1492 $[M+H]^+$.

***Tert*-butyl 4,5-dihydro-2-methyl-3-phenylpyrrolo[2,3-c]pyrazole-6(2H)-carboxylate (76a).** Synthesized according to the General Procedure A[10] using benzaldehyde **7a** (92 μL), methyl



hydrazine **69a** (24 μL) and *tert*-butyl 2,3-dihydropyrrole-1-carboxylate **71a** (73 μL). The product was purified by column chromatography (0 to 30% EtOAc/hexanes) to afford 111 mg (Yield: 83%) of a yellow gummy solid **76a**. R_f = 0.40 (40% EtOAc/hexanes), mp = 187-190 ^oC.

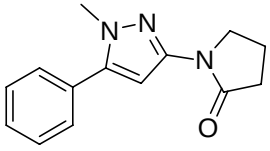
^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.53 – 7.47 (m, 3H), 7.33 – 7.30 (m, 1H), 7.29 (d, J = 1.8 Hz, 1H), 3.84 (s, 3H), 3.22 (t, J = 6.3 Hz, 2H), 2.59 (t, J = 6.8 Hz, 2H), 1.41 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 155.77, 153.50, 141.20, 138.20, 130.09, 129.75, 128.80, 128.69, 116.51, 79.12, 41.23, 37.25, 28.39, 24.57.

FT-IR (neat) cm^{-1}: 2851, 2831, 1696, 1531, 1506, 1476, 1446, 1371, 1337, 1247, 1148, 1048, 764, 739, 699, 539, 520, 460.

HR-ESI-MS exact mass calculated for $C_{17}H_{21}N_3O_2$: *m/z* 299.16, found: *m/z* 300.1707 $[M+H]^+$.

1-(1-methyl-5-phenyl-1H-pyrazol-3-yl)pyrrolidin-2-one (76b): Synthesized according to the General Procedure A[10] using benzaldehyde **7a** (92 μL), methylhydrazine **69a** (24 μL) and 1-



vinylpyrrolidin-2-one **71c** (48 μL). The product was purified by column chromatography (0 to 40% EtOAc/hexanes) to afford 81 mg (Yield: 88%) of a white gummy solid **76b**. R_f = 0.20 (50% EtOAc/hexanes)

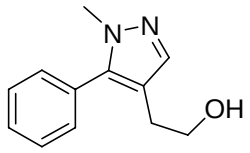
^1H NMR (300 MHz, $CDCl_3$) δ: 7.44 – 7.34 (m, 5H), 6.89 (s, 1H), 3.96 – 3.89 (m, 2H), 3.77 (s, 3H), 2.54 (dd, J = 10.1, 6.1 Hz, 2H), 2.18 – 2.06 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.49, 146.98, 144.63, 135.95, 130.45, 128.78, 128.67, 128.61, 127.38, 125.75, 96.77, 77.50, 77.08, 76.65, 46.86, 37.17, 32.10, 18.27.

FT-IR (neat) cm^{-1}: 2950, 2891, 1698, 1547, 1512, 1477, 1458, 1438, 1370, 1286, 1266, 1105, 1021, 795, 765, 697, 589.

HR-ESI-MS exact mass calculated for $C_{14}H_{15}N_3O$: *m/z* 241.12, found: *m/z* 242.1292 $[M+H]^+$.

2-(1-methyl-5-phenyl-1H-pyrazol-4-yl)ethanol (76c): Synthesized according to the General Procedure A[10] using benzaldehyde **7a** (92 μL), methylhydrazine **69a** (24 μL) and 2,3-dihydro-



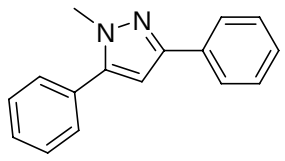
furan **71d** (34 μL). The product was purified by column chromatography (0 to 46% EtOAc/hexanes) to afford 58 mg (Yield: 67%) of a white gummy solid **76c**. R_f = 0.2 (50% EtOAc/hexanes)

^{1}H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 7.47 (d, *J* = 7.7 Hz, 3H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 4.2 Hz, 1H), 7.34 – 7.29 (m, 2H), 3.75 (s, 3H), 3.69 (t, *J* = 6.7 Hz, 2H), 2.65 (t, *J* = 6.6 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) *δ*: 138.31, 137.21, 133.50, 129.83, 128.80, 128.75, 128.38, 127.84, 117.33, 63.12, 37.27, 27.47.

FT-IR (neat) cm^{-1}: 3382, 3058, 2955, 2920, 2865, 2790, 1586, 1496, 1454, 1262, 1166, 1048, 973, 732, 704, 415.

HR-ESI-MS exact mass calculated for $C_{12}H_{14}N_2O$: *m/z* 202.11, found: *m/z* 203.1183 $[M+H]^+$.



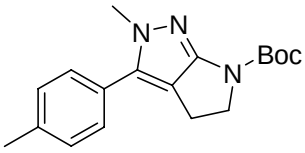
1-methyl-3,5-diphenyl-1H-pyrazole (76e): Synthesized according to the General Procedure A[10] **7a** (92 μL), methylhydrazine **69a** (24 μL) and (1-phenylvinyloxy)trimethylsilane **71h** (173 mg). The product was purified by column chromatography (0 to 15% EtOAc/hexanes) to afford 94 mg (Yield: 90%) of a white gummy solid **76e**. R_f = 0.4 (20% EtOAc/hexanes)

^{1}H NMR (300 MHz, $CDCl_3$, ppm) *δ*: 7.80 (dt, *J* = 3.1, 1.8 Hz, 2H), 7.45 – 7.40 (m, 5H), 7.39 (t, *J* = 1.6 Hz, 1H), 7.36 (dd, *J* = 6.3, 1.3 Hz, 2H), 6.58 (s, 1H), 3.91 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) *δ*: 150.16, 144.92, 133.02, 130.61, 128.78, 128.69, 128.16, 127.80, 125.62, 103.29, 77.46, 77.04, 76.62, 37.58.

FT-IR (neat) cm^{-1}: 3059, 3025, 2963, 2929, 2860, 1683, 1600, 1572, 1469, 1448, 1393, 1338, 1304, 1263, 1173, 1097, 1077, 1042, 1022, 801, 760, 726, 691, 601, 512, 430.

***Tert*-butyl 4,5-dihydro-2-methyl-3-*p*-tolylpyrrolo[2,3-c]pyrazole-6(2H)-carboxylate (76f):** Synthesized according to the General Procedure A[10] 4-methylbenzaldehyde **7k** (106 µL), methyl



hydrazine **69a** (24 µL) and *tert*-butyl 2,3-dihydropyrrole-1-carboxylate **71a** (73 µL). The product was purified by column chromatography (0 to 30% EtOAc/hexanes) to afford 111 mg (Yield: 79%) of a yellow gummy solid **76f**. R_f = 0.42 (40% EtOAc/hexanes)

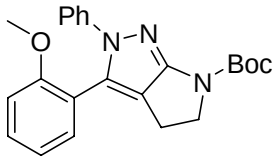
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.43 (s, 1H), 7.29 (s, 1H), 7.17 (d, J = 8.0 Hz, 2H), 3.74 (s, 3H), 3.20 (dd, J = 6.2 Hz, 2H), 2.55 (t, J = 6.8 Hz, 2H), 2.42 (s, 3H), 1.40 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 156.72, 155.52, 141.59, 138.78, 137.56, 129.39, 128.17, 126.57, 116.38, 80.05, 57.57, 37.18, 28.19, 24.19, 21.25.

FT-IR (neat) cm^{-1}: 3349, 2976, 2926, 2851, 1706, 1691, 1527, 1512, 1393, 1363, 1253, 1213, 1169, 905, 751, 726, 671, 421.

HR-ESI-MS exact mass calculated for $C_{18}H_{23}N_3O_2$: *m/z* 313.18, found: *m/z* 314.1873 $[M+H]^+$.

***Tert*-butyl 4,5-dihydro-3-(2-methocyphenyl)-2- phenylpyrrolo[2,3-c]pyrazole-6(2H)-carboxylate (76g):** Synthesized according to the General Procedure A[10] using 2-methoxy



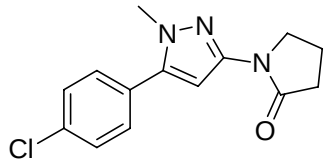
benzaldehyde **7n** (123 µL), phenylhydrazine **69b** (24 µL) and *tert*-butyl 2,3-dihydropyrrole-1-carboxylate **71a** (73 µL). The product was purified by column chromatography (0 to 35% EtOAc/hexanes) to afford 123 mg (Yield: 70%) of a yellow gummy solid **76g**. R_f = 0.3 (40% EtOAc/hexanes)

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.73 (d, 2H), 7.43 (t, J = 5.9 Hz, 3H), 7.38 (dd, J = 9.7, 1.8 Hz, 1H), 7.23 (d, J = 7.4 Hz, 1H), 7.05 (d, J = 7.4 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H), 3.31 (d, J = 7.8 Hz, 2H), 2.65 (t, J = 6.8 Hz, 2H), 1.41 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 157.21, 140.08, 131.82, 129.94, 129.32, 126.02, 125.64, 122.42, 120.88, 118.75, 110.95, 79.24, 77.46, 77.04, 76.61, 55.49, 40.82, 28.41, 24.58.

HR-ESI-MS exact mass calculated for $C_{23}H_{25}N_3O_3$: *m/z* 391.19, found: *m/z* 392.2001 $[M+H]^+$.

1-(5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl)pyrrolidin-2-one (76h): Synthesized according to the General Procedure A[10] 4-chlorobenzaldehyde **7b** (126 µL), methylhydrazine



69a (24 µL) and 1-vinylpyrrolidin-2-one **68c** (48 µL). The product was purified by column chromatography (0 to 40% EtOAc/hexanes) to afford 68 mg (Yield: 85%) of a brown-yellow gummy solid **76h**. R_f = 0.40 (50% EtOAc/hexanes)

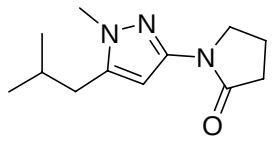
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.30 (m, 4H), 6.92 (s, 1H), 4.00 – 3.90 (m, 2H), 3.78 (s, 3H), 2.57 (t, J = 8.1 Hz, 2H), 2.24 – 2.10 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.54, 147.02, 143.43, 134.80, 130.02, 128.98, 128.85, 96.95, 46.83, 37.17, 32.07, 18.26.

FT-IR (neat) cm^{-1}: 2950, 2920, 2895, 1701, 1545, 1510, 1479, 1454, 1389, 1363, 1288, 1262, 1096, 1016, 996, 834, 789, 588.

HR-ESI-MS exact mass calculated for $C_{14}H_{14}ClN_3O$: *m/z* 275.08, found: *m/z* 276.0891 $[M+H]^+$.

1-(5-isobutyl-1-methyl-1*H*-pyrazol-3-yl)pyrrolidin-2-one (76i): Synthesized according to the



General Procedure A[10] using 3-methylbutanal **7o** (94 µL), methyl hydrazine **69a** (24 µL) and 1-vinylpyrrolidin-2-one **71c** (48 µL). The product was purified by column chromatography (0 to 25% EtOAc/

hexanes) to afford 58 mg (Yield: 59%) of a brown-yellow gummy solid **76i**. R_f = 0.50 (50% EtOAc/hexanes)

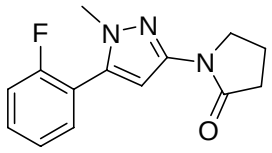
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 6.62 (s, 1H), 3.90 (t, J = 7.1 Hz, 2H), 3.70 (s, 3H), 2.54 (t, J = 8.1 Hz, 2H), 2.44 (d, J = 7.2 Hz, 2H), 2.21 – 2.06 (m, 2H), 1.92 (dt, J = 13.5, 6.8 Hz, 1H), 0.95 (d, J = 6.6 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 173.08, 146.54, 143.31, 96.01, 46.82, 35.86, 34.92, 32.16, 28.38, 22.48, 18.24.

FT-IR (neat) cm^{-1}: 2956, 2926, 2971, 1702, 1542, 1492, 1463, 1373, 1288, 1268, 1009, 905, 756, 732.

HR-ESI-MS exact mass calculated for $C_{12}H_{19}N_3O$: *m/z* 221.15, found: *m/z* 222.1606 $[M+H]^+$.

1-(5-(2-fluorophenyl)-1-methyl-1H-pyrazol-3-yl)pyrrolidin-2-one (76j): Synthesized according to the General Procedure A[10] using 2-fluorobenzaldehyde **7q** (95 µL), methyl



hydrazine **69a** (24 µL) and 1-vinylpyrrolidin-2-one **71c** (48 µL). The product was purified by column chromatography (0 to 40% EtOAc/hexanes) to afford 103 mg (Yield: 89%) of a white gummy solid **76j**. R_f = 0.32 (50% EtOAc/hexanes)

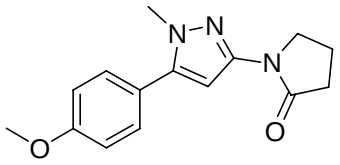
^{1}H NMR (300 MHz, $CDCl_3$) δ (Two rotamars are present): 7.48 – 7.34 (m, 4H), 6.94 (d, J = 2.6 Hz, 1H), 3.97 (dd, J = 8.4, 5.9 Hz, 2H), 3.82 (s, 1H), 3.73 (dd, J = 4.2, 1.5 Hz, 2H), 2.58 (t, J = 8.1 Hz, 2H), 2.25 – 2.11 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.47, 146.94, 131.41, 131.04, 128.79, 128.70, 124.42, 115.95, 97.99, 96.31, 46.86, 36.81, 32.08, 18.28.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -113.49.

HR-ESI-MS exact mass calculated for $C_{14}H_{14}FN_3O$: *m/z* 259.11, found: *m/z* 260.1195 $[M+H]^+$.

1-(5-(4-methoxyphenyl)-1-methyl-1H-pyrazol-3-yl)pyrrolidin-2-one (76k): Synthesized according to the General Procedure A[10] using 4-methoxybenzaldehyde **7l** (110 μL), methyl



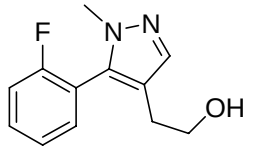
hydrazine **69a** (24 μL) and 1-vinylpyrrolidin-2-one **71c** (48 μL). The product was purified by column chromatography (0 to 45% EtOAc/hexanes) to afford 97 mg (Yield: 80%) of a pale-yellow gummy solid **76k**. R_f = 0.20 (50% EtOAc/hexanes)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 – 7.32 (m, 2H), 7.01 – 6.94 (m, 2H), 6.89 (s, 1H), 4.03 – 3.93 (t, J = 7.0 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 2.62 – 2.54 (m, 2H), 2.18 (dt, J = 15.5, 7.7 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.48, 160.35, 159.95, 129.79, 119.60, 114.27, 96.30, 55.14, 46.97, 36.76, 31.85, 18.03.

HR-ESI-MS exact mass calculated for $C_{15}H_{17}N_3O_2$: *m/z* 271.13, found: *m/z* 272.1393 $[M+H]^+$.

2-(5-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)ethanol (76l): Synthesized according to the General Procedure A[10] using 2-fluorobenzaldehyde **7q** (95 μL), methylhydrazine **69a** (24 μL)



and 2,3-dihydrofuran **71d** (34 μL). The product was purified by column chromatography (0 to 44% EtOAc/hexanes) to afford 76 mg (Yield: 69%) of a pale yellow gummy solid **76l**. R_f = 0.3 (50% EtOAc/hexanes)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 – 7.39 (m, 2H), 7.26 (dd, J = 6.2, 2.8 Hz, 1H), 7.19 (t, J = 11.7 Hz, 1H), 3.70 (s, 3H), 3.66 (d, J = 6.7 Hz, 2H), 2.60 (t, J = 6.7 Hz, 2H), 2.02 – 1.80 (m, 1H).

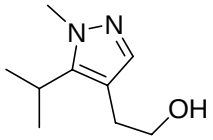
^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.66, 158.34, 138.43, 135.13, 132.13, 131.02, 124.48, 116.36, 115.44, 62.91, 37.16, 27.39.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -113.19.

FT-IR (neat) cm^{-1}: 3423, 3337, 2950, 2867, 2791, 1616, 1581, 1491, 1450, 1353, 1256, 1227, 1172, 1095, 1061, 970, 922, 811, 755, 533, 470, 429.

HR-ESI-MS exact mass calculated for $C_{12}H_{13}FN_2O$: *m/z* 220.1, found: *m/z* 221.1084 $[M+H]^+$.

2-(5-isopropyl-1-methyl-1H-pyrazol-4-yl)ethanol (76m): Synthesized according to the General Procedure A[10] using isobutyraldehyde **7r** (82 μL), methylhydrazine **69a** (24 μL) and 2,3-



dihydrofuran **71d** (34 μL). The product was purified by column chromatography (0 to 30% EtOAc/hexanes) to afford 58 mg (Yield: 47%) of a pale yellow gummy solid **76m**. R_f = 0.4 (40)

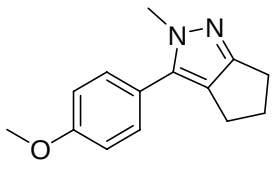
^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.51 (s, 1H), 5.05 (s, 3H), 3.77 (t, J = 8.5, 4.4 Hz, 2H), 2.69 (t, J = 6.5 Hz, 2H), 2.57 (d, J = 7.3 Hz, 1H), 1.98 (dt, J = 13.5, 6.8 Hz, 1H), 0.95 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 152.69, 138.36, 136.34, 121.62, 62.52, 41.23, 28.62, 22.06.

FT-IR (neat) cm^{-1}: 3423, 3020, 2955, 2916, 2871, 2791, 1448, 1213, 1039, 905, 756, 726, 666, 651, 422.

HR-ESI-MS exact mass calculated for $C_9H_{16}N_2O$: *m/z* 168.13, found: *m/z* 169.1335 $[M+H]^+$.

2,4,5,6-tetrahydro-3-(4-methoxyphenyl)-2-methylcyclopenta[c]pyrazole (76n): Synthesized according to the General Procedure A[10] using 4-methoxybenzaldehyde **7l** (110 μL), methyl



hydrazine **69a** (24 μL) and (cyclopentenyloxy)trimethylsilane **71h** (141 mg). The product was purified by column chromatography (0 to 20% EtOAc/hexanes) to afford 90 mg (Yield: 88%) of a white gummy solid **76n**. R_f = 0.3 (25% EtOAc/hexanes)

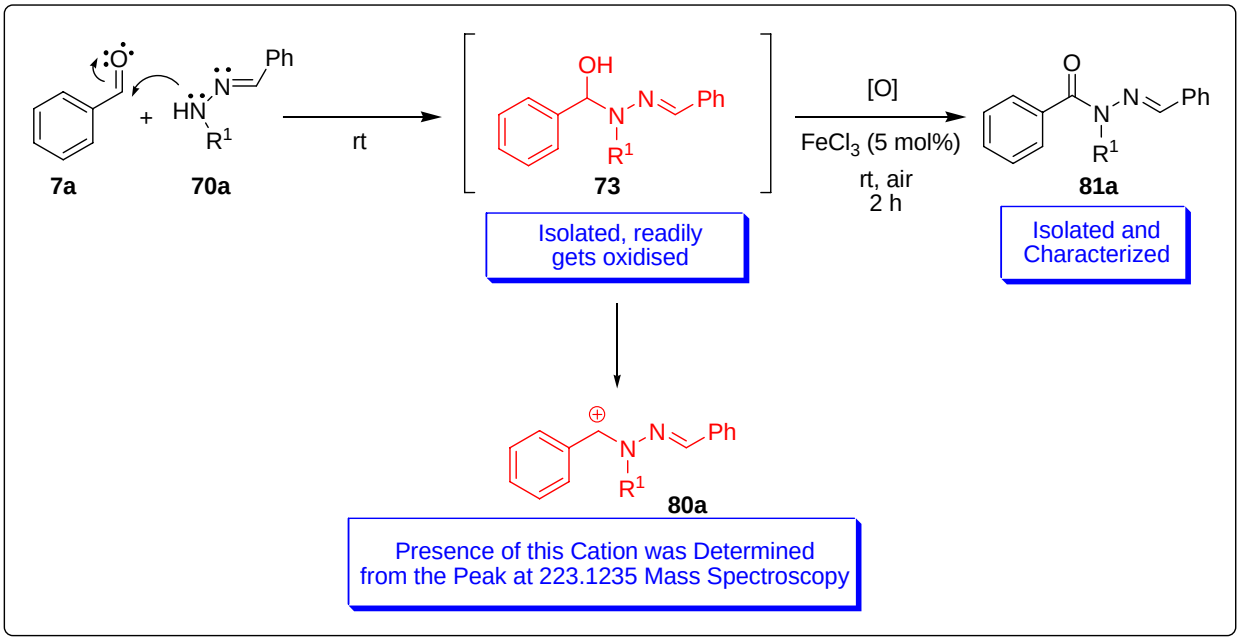
^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.76 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 2.87 (d, J = 7.0 Hz, 2H), 2.75 (t, 2H), 2.66 (d, J = 7.3 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 144.53, 139.18, 129.38, 126.98, 126.57, 114.22, 55.15, 52.72, 45.35, 39.62, 29.42, 24.97, 23.27.

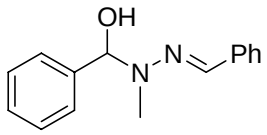
FT-IR (neat) cm^{-1}: 2773, 1733, 1643, 1616, 1511, 1456, 1435, 1366, 1290, 1242, 1172, 1109, 1026, 832, 735, 686, 604, 575, 542, 527, 458, 437, 417.

HR-ESI-MS exact mass calculated for $C_{14}H_{16}N_2O$: *m/z* 228.13, found: *m/z* 229.1337 $[M+H]^+$.

7.16 Characterization Data of the Reactive Intermediate 73a and Corresponding Amide 81a.



Compound **73a**:

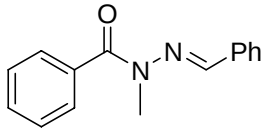


^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.68 (s, 1H), 7.88 – 7.83 (m, 1H), 7.58 (d, J = 7.4 Hz, 2H), 7.46 (dd, J = 5.1, 1.8 Hz, 2H), 7.35 (d, J = 7.1 Hz, 3H), 7.30 (d, J = 8.7 Hz, 2H), 5.30 (s, 1H), 4.98 (s, 1H), 2.96 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.53, 134.42, 128.74, 128.53, 128.19, 127.42, 127.09, 126.42, 125.70, 125.52, 99.19, 35.51.

HR-ESI-MS exact mass calcd for $C_{15}H_{16}N_2O$: *m/z* 223.123, found as $C_{15}H_{15}N_2$ (-H_2O): *m/z* 223.1235 $[M]^+$.

(E)-*N*'-benzylidene-*N*-methylbenzohydrazide (81a):



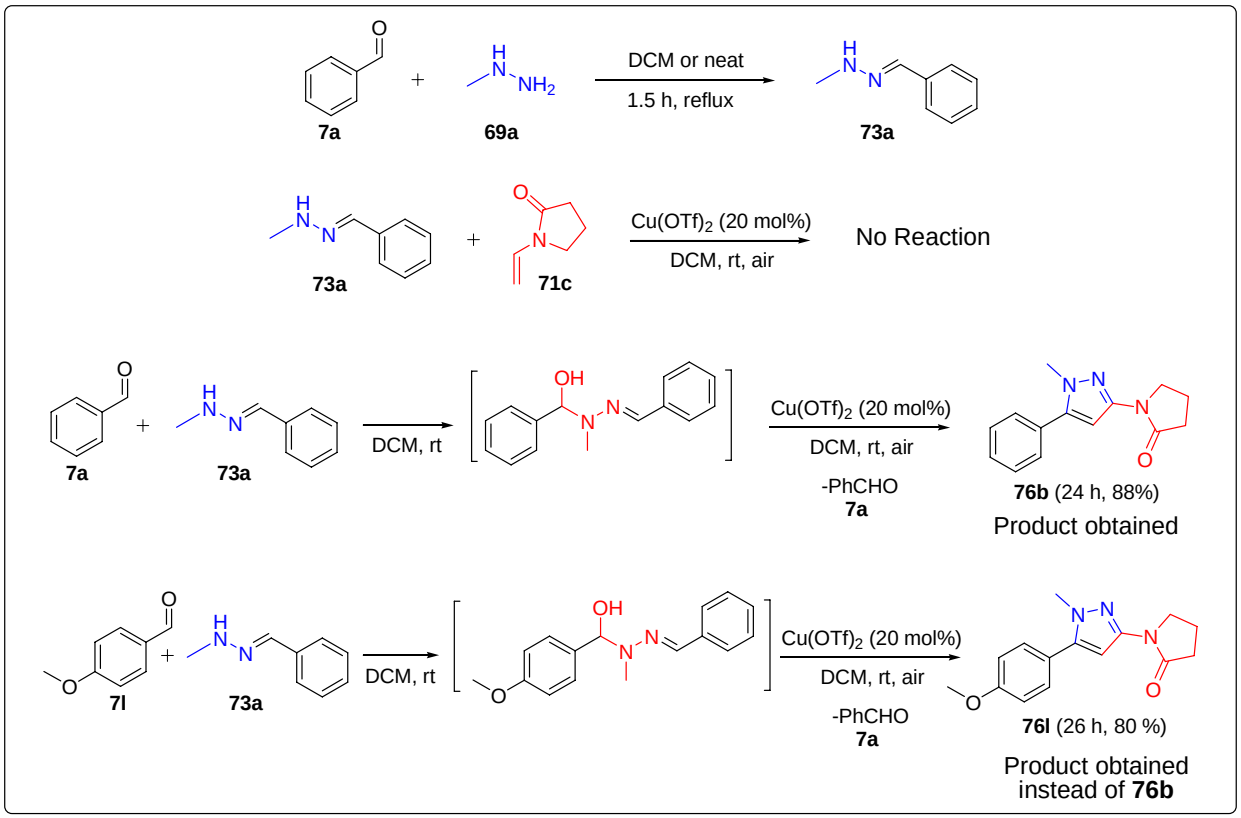
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.76 (s, 1H), 7.75 – 7.71 (m, 2H), 7.52 – 7.48 (m, 2H), 7.46 – 7.40 (m, 3H), 7.36 – 7.30 (m, 3H), 3.57 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 171.03, 140.78, 138.78, 135.15, 134.33, 129.79, 128.59, 126.97, 28.62.

FT-IR (neat) cm^{-1}: 1685, 1653, 1605, 1573, 1489, 1471, 1444, 1395, 1337, 1306, 1388, 1252, 1177, 1048, 1025, 938, 879, 789, 754, 714, 696, 665, 603, 567, 513, 420, 402.

HR-ESI-MS exact mass calcd for $C_{15}H_{14}N_2O$: *m/z* 238.11, found: *m/z* 239.1185 $[M+H]^+$.

7.17 Mechanistic Proof: Search for Plausible Mechanism-Stepwise Reaction Sequences with Two Equivalents of Same and Different Aldehydes.



7.17a Procedure for $Cu(OTf)_2$-Catalyzed Syntheses of Pyrazoles 76 in a Sequential Manner with Two Equivalents of Same Aldehyde.

7.17a General Procedure A[11]

To a 10 mL round bottom flask equipped with a magnetic stir bar, was sequentially added benzaldehyde **7a** (0.45 mmol), CH_2Cl_2 (0.5 mL) and methylhydrazine **69a** (0.45 mmol). The resulting mixture was stirred for 1.5 h under refluxing condition. To this, a pre-stirred (30 mints) solution of another equivalent of benzaldehyde **7a** (0.45 mmol) and $Cu(OTf)_2$ (0.09 mmol, 20 mol%) in CH_2Cl_2 (1.5 mL) and a solution of the olefin **71c** (0.45 mmol) in CH_2Cl_2 (0.5 mL) were added drop wise in a sequential manner. The resulting reaction mixture was stirred at room

temperature in air and monitored periodically by TLC. Upon consumption of the olefin **71c** (24 h), the reaction mixture was concentrated; the residue was dissolved in ethylacetate, washed with distilled water and extracted in ethylacetate. The organic layer was dried, concentrated and subjected to silica gel chromatography (hexanes/ethylacetate) to give the desired products **76b** as a single diastereomer in 88 % yield.

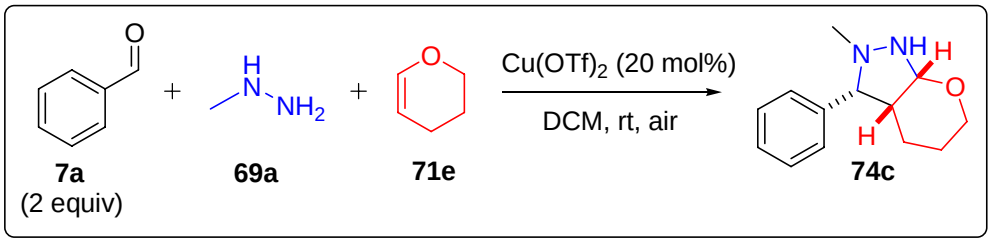
7.17b Procedure for $Cu(OTf)_2$-Catalyzed Syntheses of Pyrazoles 76 in a Sequential Manner with Two Equivalents of Different Aldehydes.

7.17b General Procedure A[12]

To a 10 mL round bottom flask equipped with a magnetic stir bar, was sequentially added benzaldehyde **7a** (0.45 mmol), CH_2Cl_2 (0.5 mL) and methylhydrazine **69a** (0.45 mmol). The resulting mixture was stirred for 1.5 h under refluxing condition. To this, a pre-stirred (30 mints) solution of 4-methoxybenzaldehyde **7l** (0.45 mmol) and $Cu(OTf)_2$ (0.09 mmol, 20 mol%) in CH_2Cl_2 (1.5 mL) and a solution of the olefin **71c** (0.45 mmol) in CH_2Cl_2 (0.5 mL) were added drop wise in a sequential manner. The resulting reaction mixture was stirred at room temperature in air and monitored periodically by TLC. Upon consumption of the olefin **71c** (22 h), the reaction mixture was concentrated; the residue was dissolved in ethylacetate, washed thoroughly with distilled water to remove the catalyst and extracted in ethylacetate. The organic layer was dried, concentrated and purified on silica to afford a pale yellow gummy solid product as a single diastereomer in 80% yield (using hexanes/ethylacetate as the eluants). Characterization of the product via NMR and Mass spectroscopy confirmed it as the desired cross-aldehyde product **76l**. Absence of the product **76b** indicated that only the second molecule of the aldehyde (**7l** here), used during the reaction course gave rise to the product. Initial one equivalent of aldehyde (**7a** here) was involved only to produce the active intermediate and at the end of the reaction it gets removed from the reaction system.

7.17c Mechanistic Proof: IR Studies Showing the Consumption and Regeneration of Benzaldehyde[a]

7.17c General Procedure A[13]



To a 5 mL glass vial equipped with a magnetic stir bar, was sequentially added benzaldehyde **7a** (0.40 mmol), CH_2Cl_2 (0.5 mL) and $Cu(OTf)_2$ (0.04 mmol, 20 mol%). The resulting mixture was stirred for 15 minutes and the IR spectrum was recorded, showing a sharp band at 1699 cm^{-1} corresponding to the carbonyl stretching of the aldehyde (Chapter 4, Figure 3, A). Methylhydrazine **69a** (0.235 mmol) was then added to the reaction mixture and the IR spectrum was recorded, showing a decrease in the relative intensity of the previous carbonyl stretching (Chapter 4, Figure 3, B), after 1 h of addition of **69a** the sharp band at 1699 cm^{-1} was found to be almost disappeared (Chapter 4, Figure 3, C). Olefin **71e** (0.40 mmol) was then added drop wise to the reaction mixture and stirred at room temperature in air for 2.0 h and IR spectrum was recorded again, showing the reappearance of the peak at 1699 cm^{-1} (Chapter 4, Figure 3, D). After 6 h, again the IS spectrum of the reaction mixture was recorded showing the large increase in the relative intensity of the aldehyde peak (Chapter 4, Figure 3, E) and hence supporting the removal of aldehyde.

8. Appendix

8.1 X-Ray Diffraction Structures

The data were collected at 123 K using an Oxford Diffraction Cryojet Cooler. The structure was solved by direct methods (*SIR97*) and refined by full-matrix anisotropic least squares (*SHELXL97*). Most of the H-atoms were calculated geometrically and a riding model was used during refinement process; the remaining ones were located by difference Fourier syntheses and refined isotropically.

Refinement: Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit S are based on F^2, conventional *R*-factors *R* are based on *F*, with F set to zero for negative F^2. The threshold expression of $F^2 > 2$ sigma (F^2) is used only for calculating *R*-factors (gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*– factors based on ALL data will be even larger.

8.1A Crystal Structure of Compound 10a.

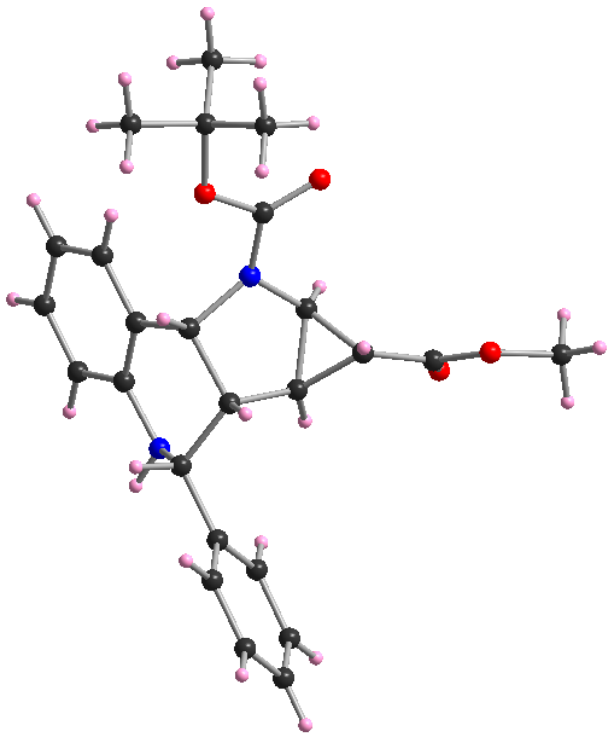


Table S1. Crystallographic data and structure refinement parameters for compound **10a**.

Compound	**10a**	***V* [Å^3]**	1351.97 (11)
Formula	$C_{25}H_{28}N_2O_4 \cdot CHCl_3$	**Z**	2
Mr	540.19	**ρ_{calcd} [g cm^{-3}]**	1.327
Cryst size[mm]	0.32 × 0.22 × 0.05	***μ*(Cu Kα) [mm^{-1}]**	3.36
Cryst colour	Colourless	***F*(000)**	564
Cryst description	Plate	**reflns collected**	9102
Cryst System	Triclinic	**unique reflns**	5060
Space group	*P*-1	**R_{int}**	0.015
T[K]	123	**reflns with *I* > 2σ(I)**	4664
***a* [Å]**	9.2264 (4)	**parameters/restraints**	339/0
***b* [Å]**	10.1560 (5)	**GOF on F^2**	1.07
***c* [Å]**	14.9764 (7)	**R1 [*I* > 2σ(I)]**	0.049
***α* [deg]**	82.805 (4)	**wR2 (all data)**	0.133
***β* [deg]**	76.505 (4)	**Largest difference peak/hole [e Å^{-3}]**	+0.93/-0.69
***γ* [deg]**	85.408 (4)	**CCDC number**	

8.1B Crystal Structure of Compound 10b.

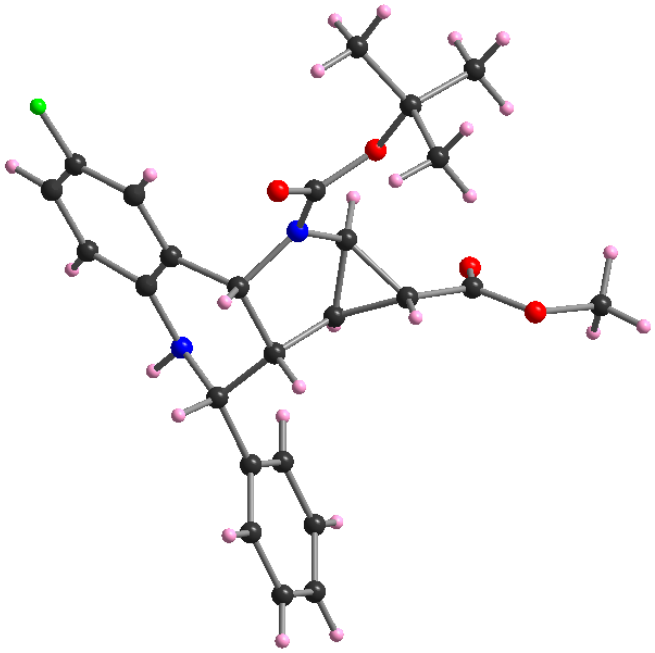


Table S2. Crystallographic data and structure refinement parameters for compound **10b**

Compound	**10b**	***V* [Å^3]**	1264.82 (11)
Formula	$C_{25}H_{27}FN_2O_4$	**Z**	2
Mr	438.49	**ρ_{calcd} [g cm^{-3}]**	1.279
Cryst size[mm]	0.19 × 0.15 × 0.04	***μ*(Cu Kα) [mm^{-1}]**	0.79
Cryst colour	Colourless	***F*(000)**	513
Cryst description	Flat prism	**reflns collected**	24718
Cryst System	Triclinic	**unique reflns**	4806
Space group	*P*-1	**R_{int}**	0.019
T[K]	123	**reflns with *I* > 2σ(I)**	4401

***a* [Å]**	10.2350 (4)	**parameters/restraints**	299/2
***b* [Å]**	11.4890 (6)	**GOF on F^2**	1.09
***c* [Å]**	12.0711 (5)	**R1 [$I > 2\sigma(I)$]**	0.037
***α* [deg]**	102.210 (4)	**wR2 (all data)**	0.099
***β* [deg]**	112.650 (4)	**Largest difference peak/hole [e Å^{-3}]**	+0.21/-0.18
***γ* [deg]**	93.355 (4)	**CCDC number**	

8.1C Crystal Structure of Compound 10k.

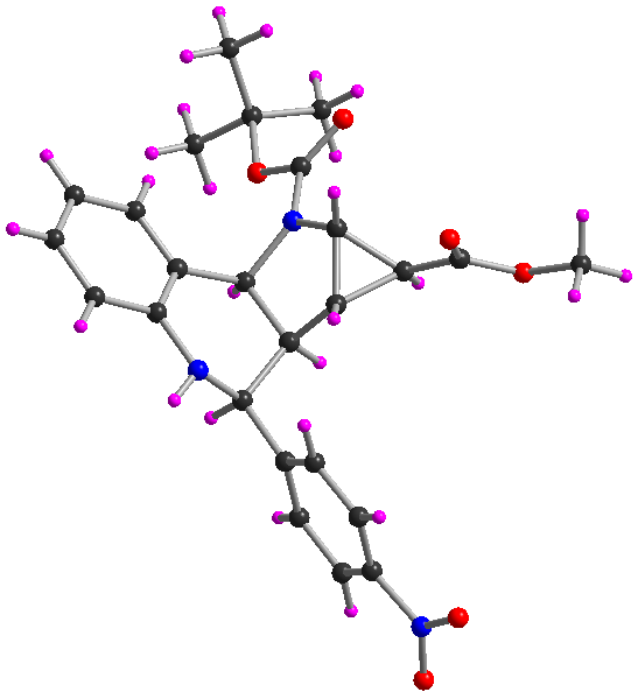


Table S3. Crystallographic data and structure refinement parameters for compound **10k**.

Compound	**10k**	***V* [Å^3]**	3148.93 (10)
Formula	$C_{25}H_{27}N_3O_6 \cdot 2(CHCl_3)$	**Z**	4
Mr	704.23	**ρ_{calcd} [g cm^{-3}]**	1.485
Cryst size[mm]	0.32 × 0.08 × 0.06	***μ*(Cu K*α*) [mm^{-1}]**	5.36
Cryst colour	Colourless	***F*(000)**	1448
Cryst description	Stick	**reflns collected**	45266
Cryst System	Monoclinic	**unique reflns**	6024
Space group	$P2_1/c$	**R_{int}**	0.063
T[K]	123	**reflns with *I* > 2σ(I)**	5408
***a* [Å]**	12.1149 (2)	**parameters/restraints**	388/0
***b* [Å]**	14.3143 (3)	**GOF on *F*^{2}**	1.04
***c* [Å]**	18.2524 (3)	**R1 [*I* > 2σ(I)]**	0.040
***α* [deg]**	90.00	**wR2 (all data)**	0.107
***β* [deg]**	95.8232 (17)	**Largest difference peak/hole [e Å^{-3}]**	+0.70/-0.77
***γ* [deg]**	90.00	**CCDC number**	

8.1D Crystal Structure of Compound 10n.

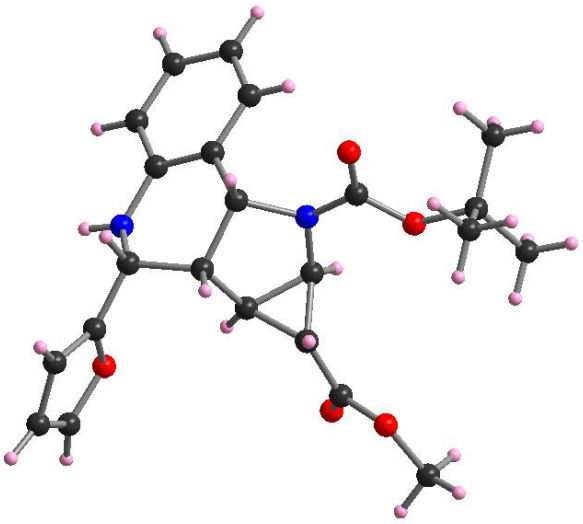


Table S4. Crystallographic data and structure refinement parameters for compound **10n**.

Compound	**10n**	***V* [Å^3]**	1150.94 (11)
Formula	$C_{23}H_{26}N_2O_5 \cdot C_2H_3N$	**Z**	2
M_r	451.51	**ρ_{calcd} [g cm^{-3}]**	1.303
Cryst size[mm]	0.62 × 0.12 × 0.09	***μ*(Cu Kα) [mm^{-1}]**	0.75
Cryst colour	Colourless	***F*(000)**	480
Cr st description	Stick	**reflns collected**	7492
Cryst System	Triclinic	**unique reflns**	4107
Space group	*P*-1	**R_{int}**	0.023
T[K]	123	**reflns with $I > 2\sigma(I)$**	3714
***a* [Å]**	9.7271 (6)	**parameters/restraints**	302/0
***b* [Å]**	11.1563 (6)	**GOF on F^2**	1.06

***c* [Å]**	11.4379 (5)	**R1 [$I > 2\sigma(I)$]**	0.045
***α* [deg]**	101.815 (4)	**wR2 (all data)**	0.127
***β* [deg]**	103.484 (4)	**Largest difference peak/hole [e Å^{-3}]**	+0.52/-0.56
***γ* [deg]**	99.621 (5)	**CCDC number**	

8.1E Crystal Structure of Compound 38a.

Table S5. Crystallographic data and structure refinement parameters for compounds **38a**.

Compound	**38a**	***V* [Å^3]**	1376.21 (5)
Formula	$C_{17}H_{14}N_2O_2$	**Z**	4
Mr	278.30	**ρ_{calcd} [g cm^{-3}]**	1.343
Cryst size[mm]	0.17 × 0.15 × 0.03	***μ*(Cu Kα) [mm^{-1}]**	0.72
Cryst colour	Colourless	***F*(000)**	584
Cryst description	Prism	**reflns collected**	10062
Cryst System	Orthorhombic	**unique reflns**	2673
Space group	$P2_12_12_1$	**R_{int}**	0.019
T[K]	123	**reflns with $I > 2\sigma(I)$**	2655

***a* [Å]**	5.67652 (13)	**parameters/restraints**	193/0
***b* [Å]**	7.84185 (14)	**GOF on F^2**	1.11
***c* [Å]**	30.9161 (5)	**R1 [$I > 2\sigma(I)$]**	0.028
***α* [deg]**	90	**wR2 (all data)**	0.071
***β* [deg]**	90	**Largest difference peak/hole [e Å^{-3}]**	+0.16/-0.23
***γ* [deg]**	90	**CCDC number**	

8.1F Crystal Structure of Compound 38j.

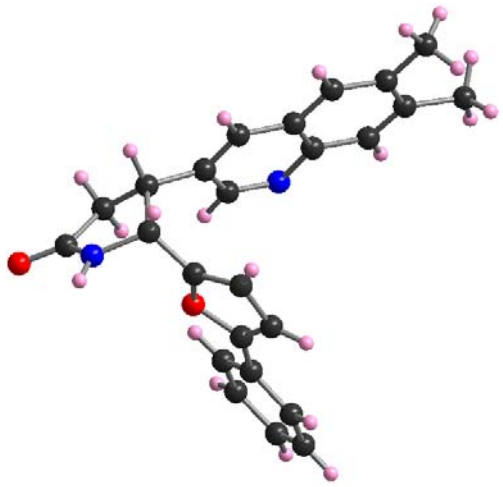


Table S6. Crystallographic data and structure refinement parameters for compounds **38j**.

Compound	**38j**	***V* [Å^3]**	1006.78 (4)
Formula	$C_{25}H_{22}N_2O_2$	**Z**	2
Mr	382.45	**ρ_{calcd} [g cm^{-3}]**	1.262
Cryst size[mm]	0.7676 x 0.1181 x 0.0883 mm	***μ*(Cu Kα) [mm^{-1}]**	0.64
Cryst colour	faint yellow	***F*(000)**	404
Cryst description	stick	**Reflns collected**	4069

Cryst System	Monoclinic	**Unique reflns**	2758
Space group	$P2_1$	R_{int}	0.018
T[K]	123	**Reflns with $I > 2\sigma(I)$**	2640
***a* [Å]**	12.3990 (3)	**Parameters/restraints**	268/1
***b* [Å]**	6.6618 (1)	**GOF on F^2**	0.90
***c* [Å]**	13.1194 (3)	**R1 [$I > 2\sigma(I)$]**	0.031
***α* [deg]**	90	**wR2 (all data)**	0.088
***β* [deg]**	111.712 (3)	**Largest difference peak/hole [e Å^{-3}]**	+0.16/−0.15
***γ* [deg]**	90	**CCDC number**	

8.1G Crystal Structure of Compound 75c.

Table S7. Crystallographic data and structure refinement parameters for compounds **75c**.

Compound	**75c**	***V* [Å^3]**	1245.75 (4)
Formula	$C_{14}H_{17}N_3O$	**Z**	4
Mr	243.31	**ρ_{calcd} [g cm^{-3}]**	1.297
Cryst size[mm]	0.32 × 0.24 × 0.12	***μ*(Cu Kα) [mm^{-1}]**	0.67
Cryst colour	Colourless	***F*(000)**	520
Cryst description	Block	**reflns collected**	6795
Cryst System	Monoclinic	**unique reflns**	2452
Space group	$P2_1/n$	**R_{int}**	0.063
T[K]	123	**reflns with *I* > 2σ(I)**	2149
***a* [Å]**	11.1353 (2)	**parameters/restraints**	164/0
***b* [Å]**	7.3686 (1)	**GOF on *F*^{2}**	1.11
***c* [Å]**	15.4910 (3)	**R1 [*I* > 2σ(I)]**	0.039
***α* [deg]**	90.00	**wR2 (all data)**	0.116
***β* [deg]**	101.454 (2)	**Largest difference peak/hole [e Å^{-3}]**	+0.26/-0.19
***γ* [deg]**	90.00	**CCDC number**	

8.1H Crystal structure of compound 75d.

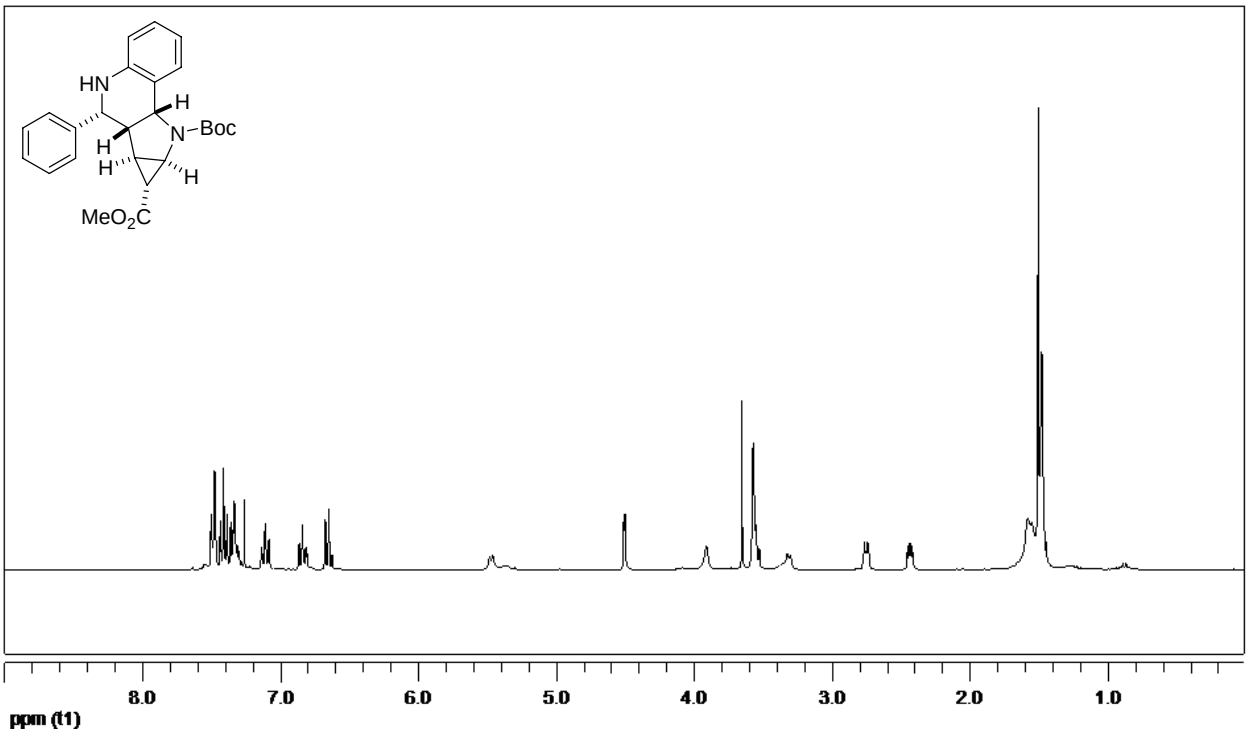
Table S8. Crystallographic data and structure refinement parameters for compounds **75d**.

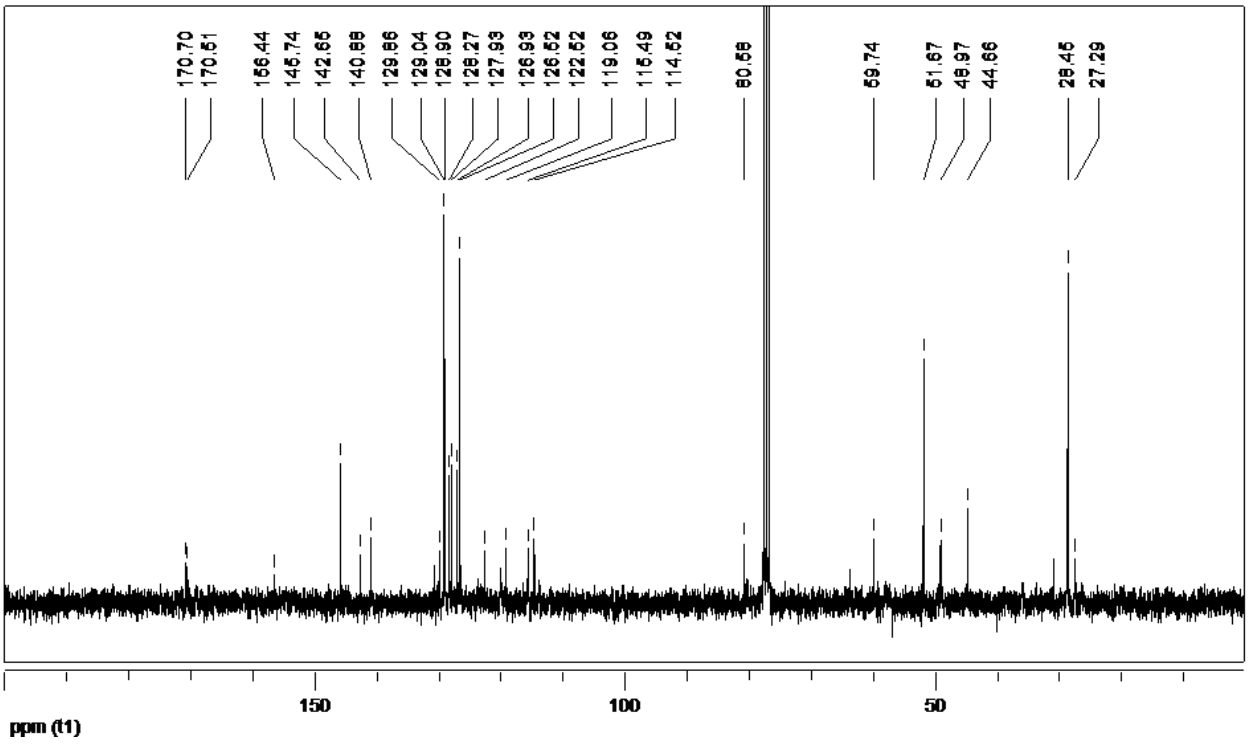
Compound	**75d**	***V* [Å^3]**	1106.4 (2)
Formula	$C_{12}H_{16}N_2O$	**Z**	4
Mr	204.27	**ρ_{calcd} [g cm^{-3}]**	1.226
Cryst size[mm]	0.24 × 0.19 × 0.15	***μ*(Cu Kα) [mm^{-1}]**	0.63
Cryst colour	Colourless	***F*(000)**	440
Cryst description	Prism	**reflns collected**	4748
Cryst System	Monoclinic	**unique reflns**	2098
Space group	$P2_1/c$	**R_{int}**	0.023
T[K]	123	**reflns with *I* > 2σ(I)**	1756
***a* [Å]**	10.7781 (13)	**parameters/restraints**	188/2

***b* [Å]**	7.3422 (8)	**GOF on F^2**	1.07
***c* [Å]**	14.0343 (15)	**R1 [$I > 2\sigma(I)$]**	0.075
***α* [deg]**	90.00	**wR2 (all data)**	0.185
***β* [deg]**	94.988 (11)	**Largest difference peak/hole [e Å^{-3}]**	+0.29/-0.25
***γ* [deg]**	90.00	**CCDC number**	

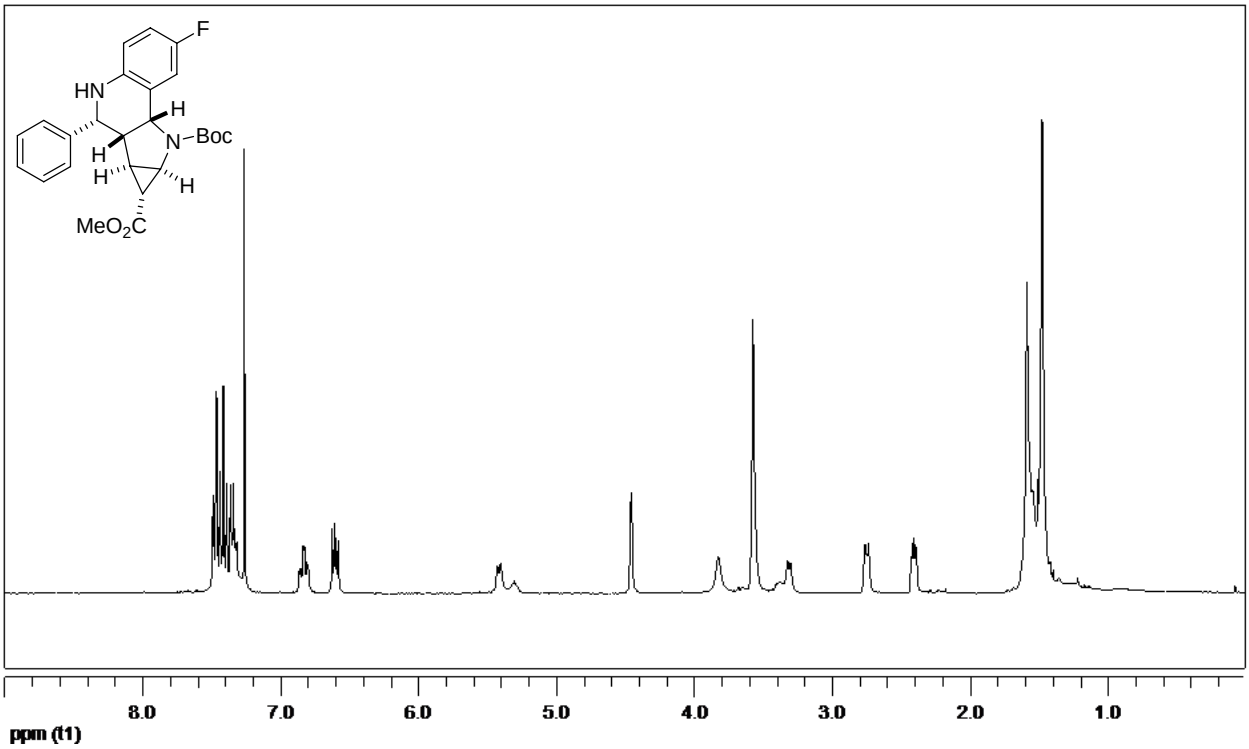
8.2 Copies of ^{1}H and ^{13}C NMR spectra

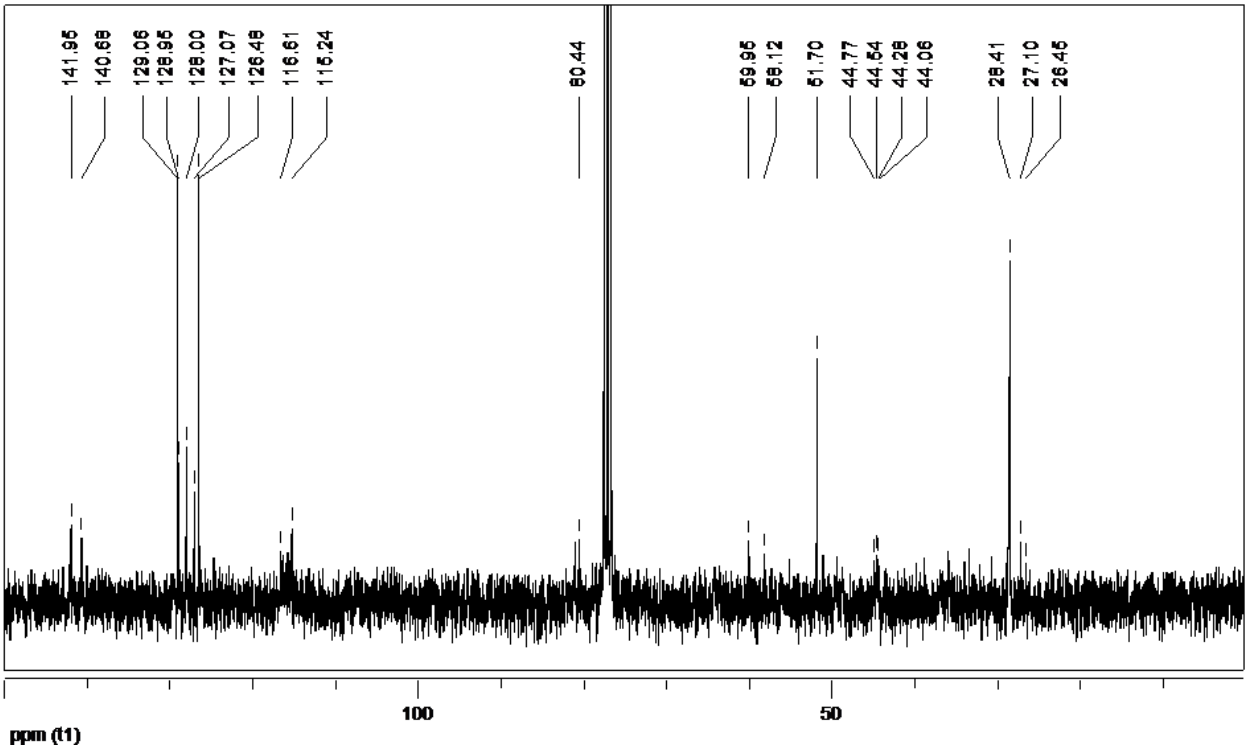
Compound **10a**

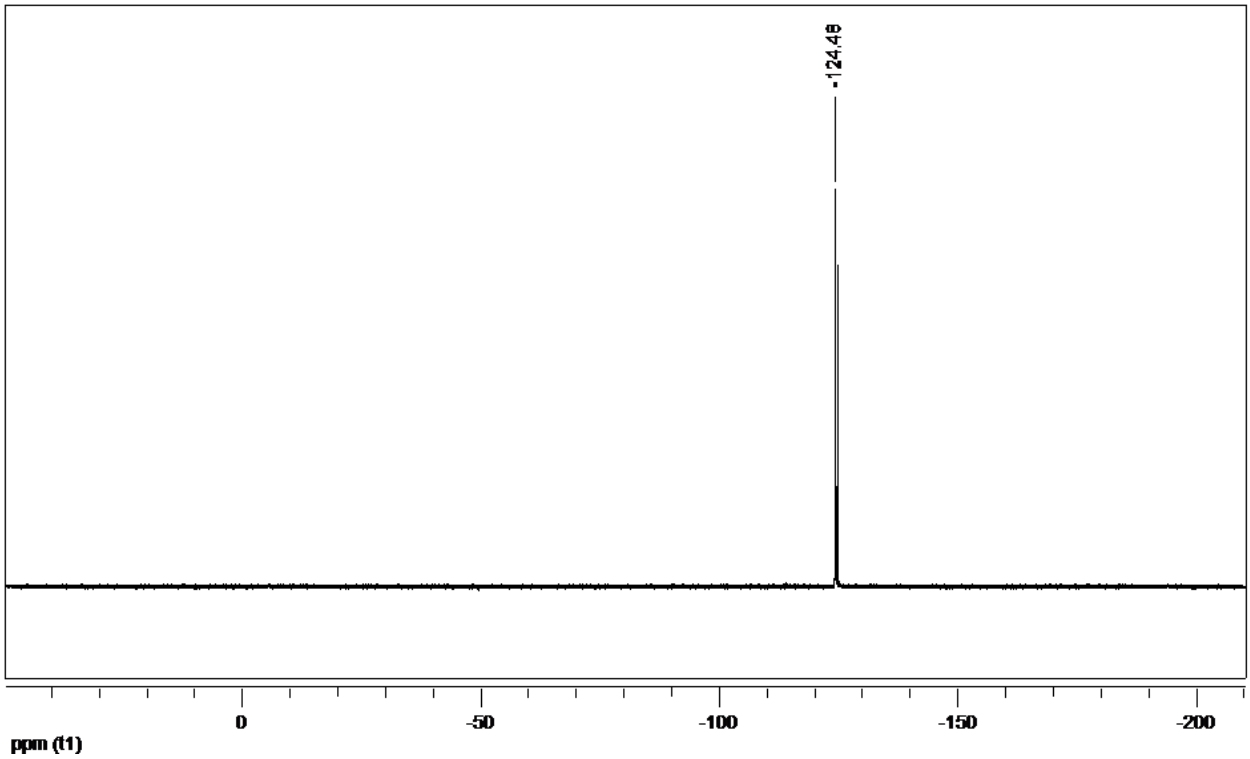




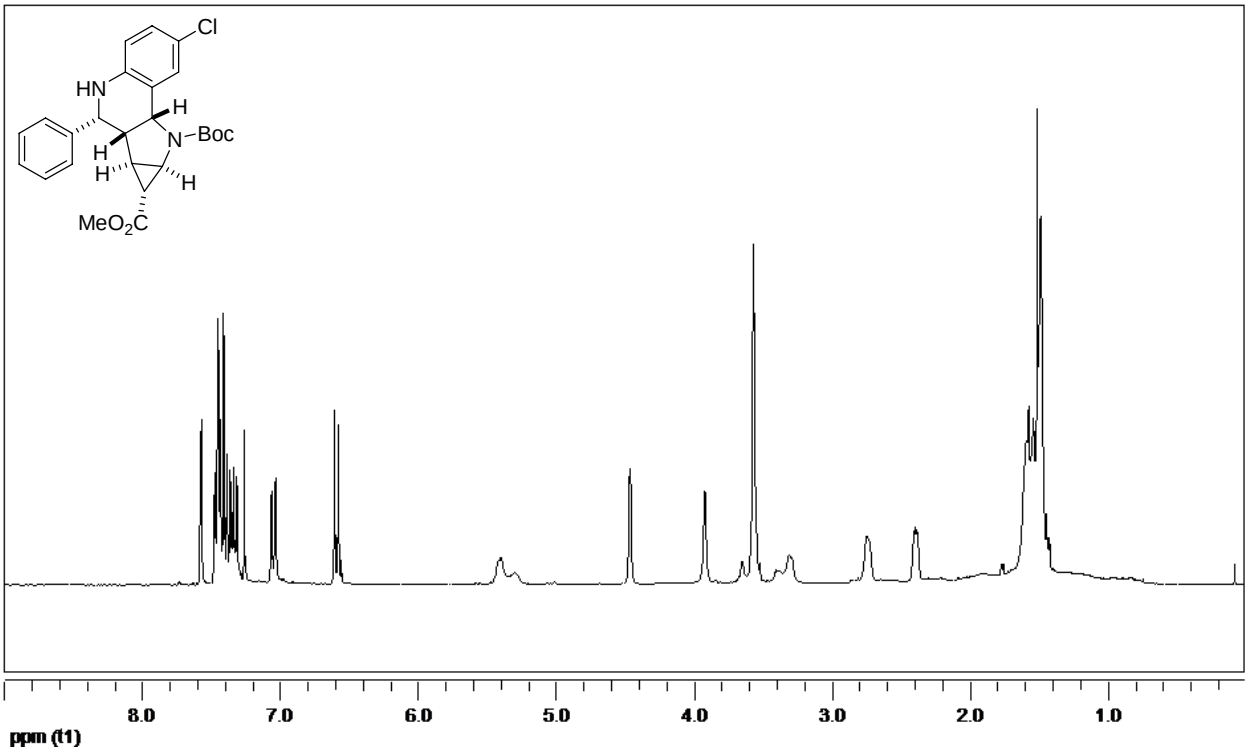
Compound **10b**

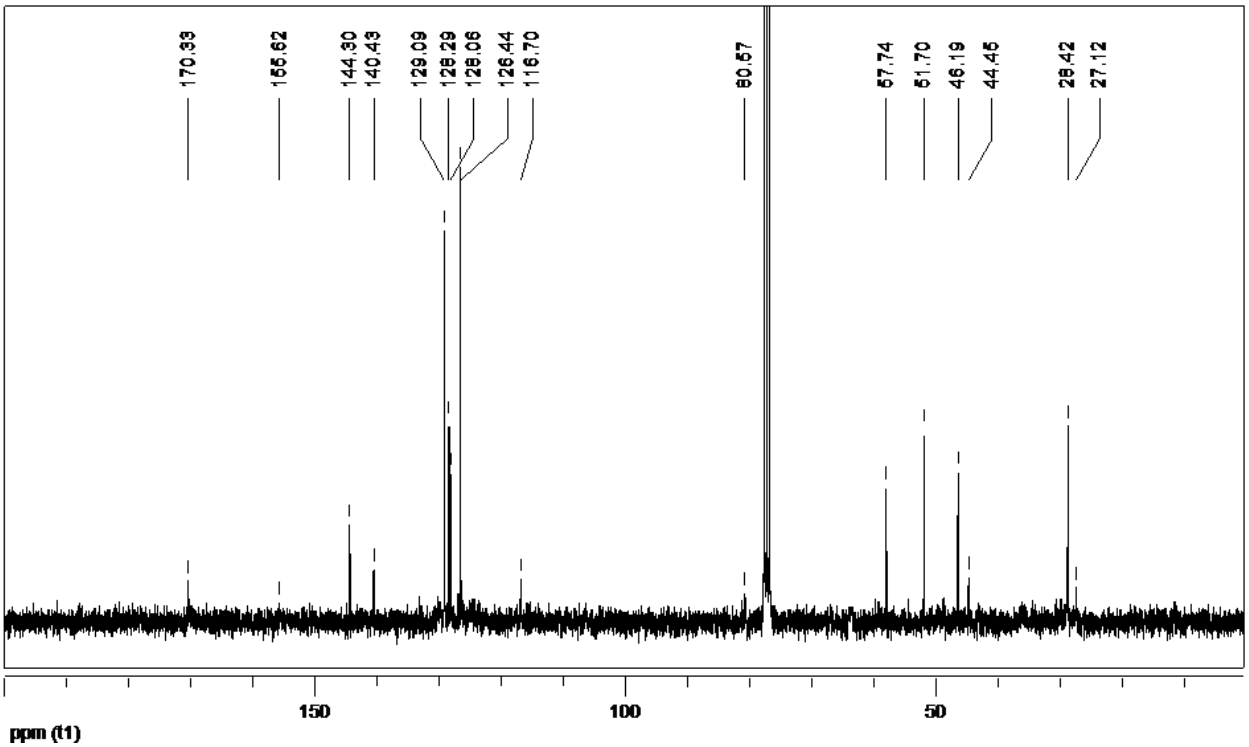




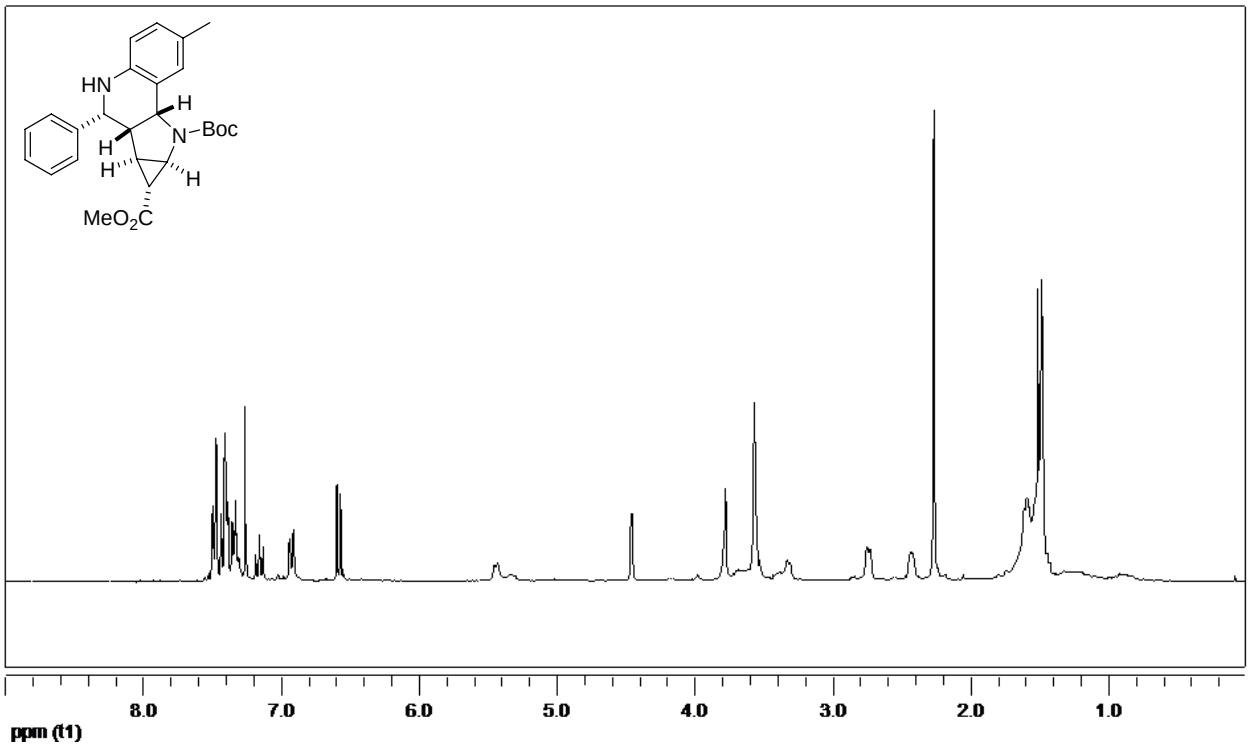

-124.49
0
-50
-100
-150
-200
ppm (t1)

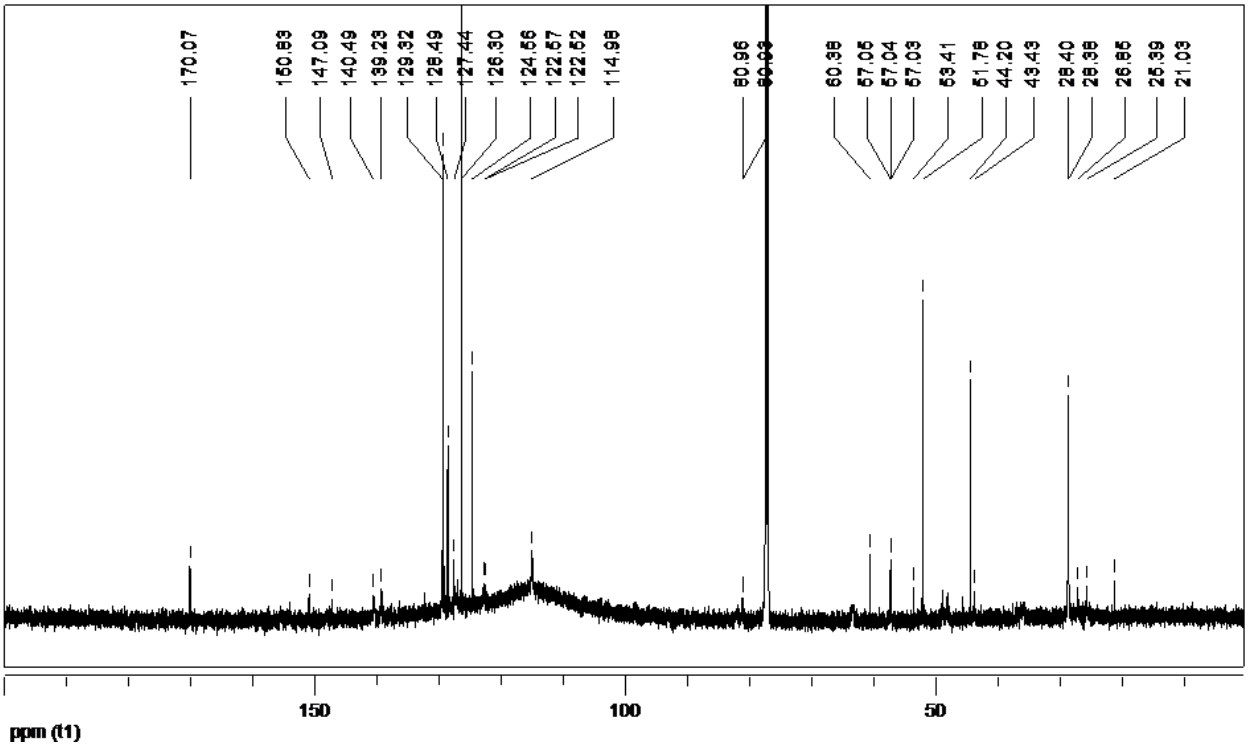
Compound **10d**



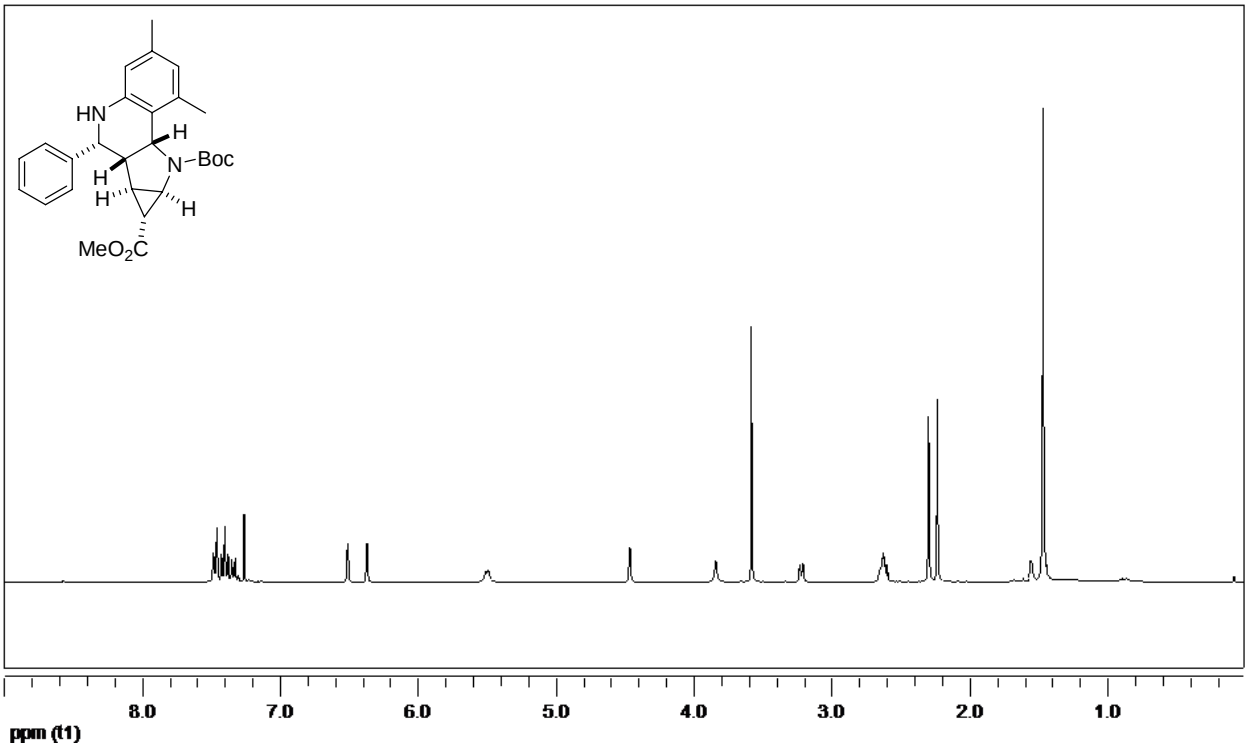


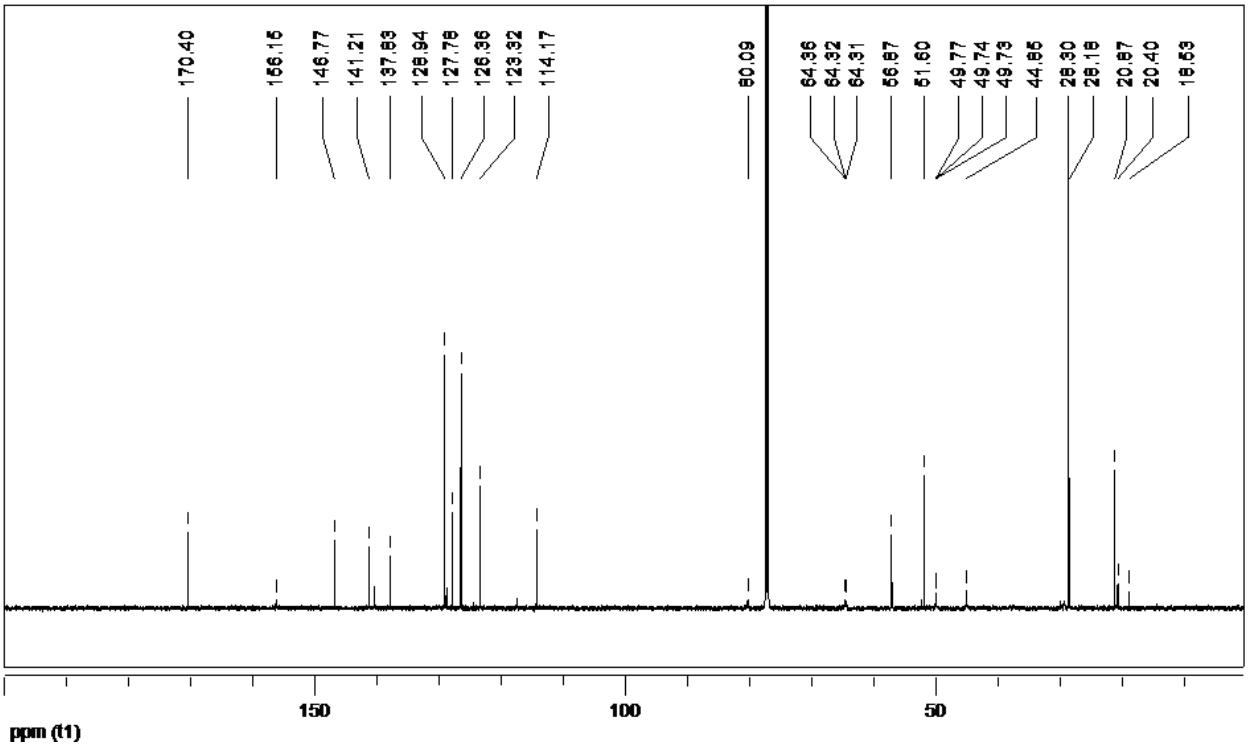
Compound **10e**



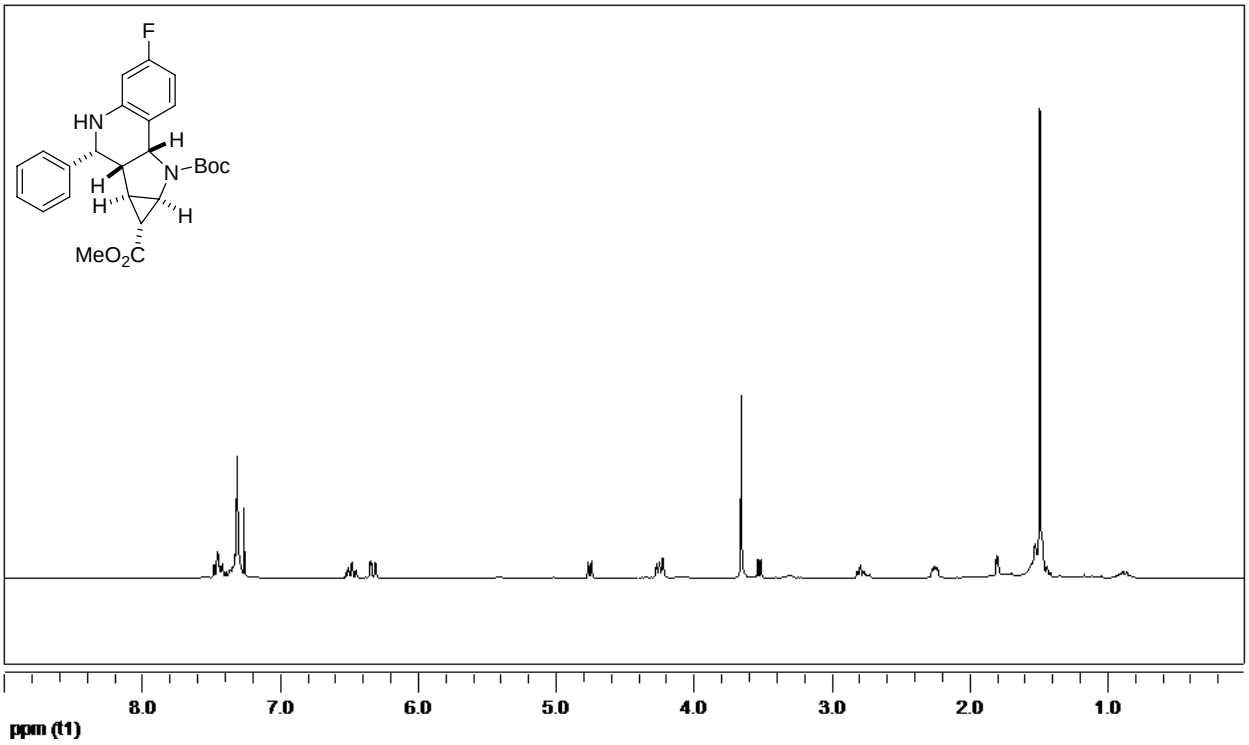


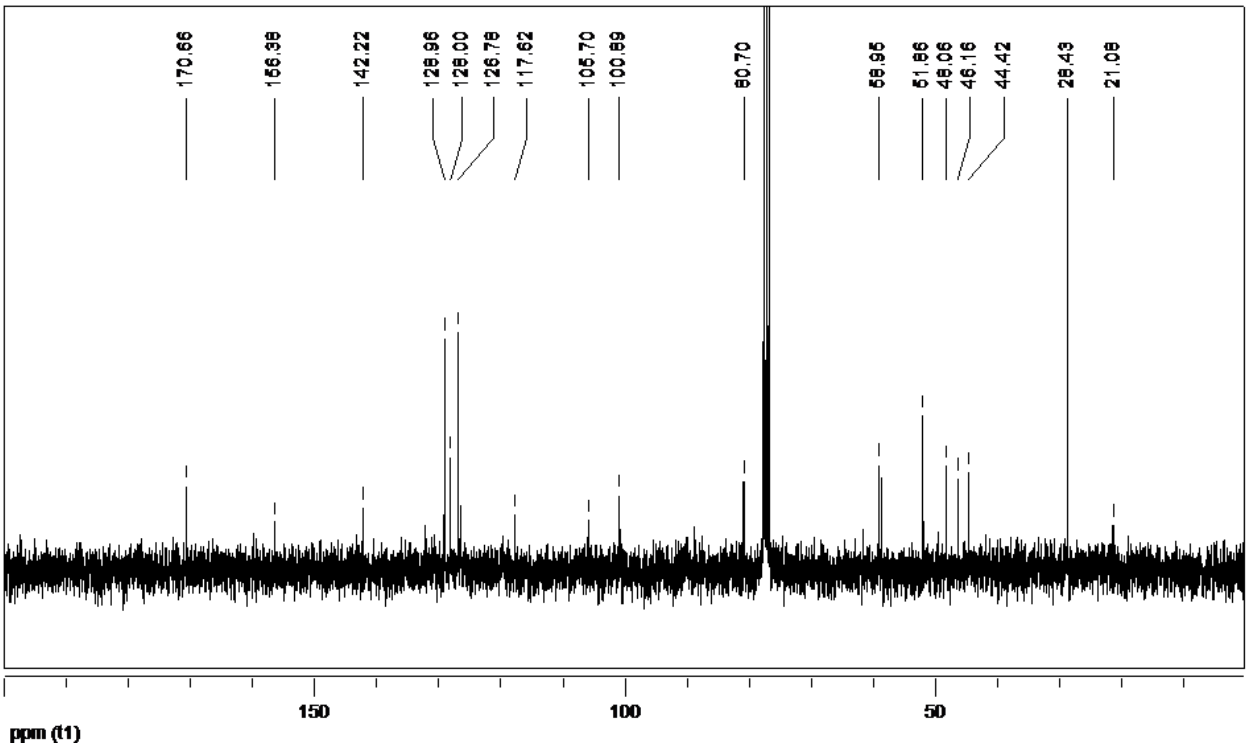
Compound **10f**

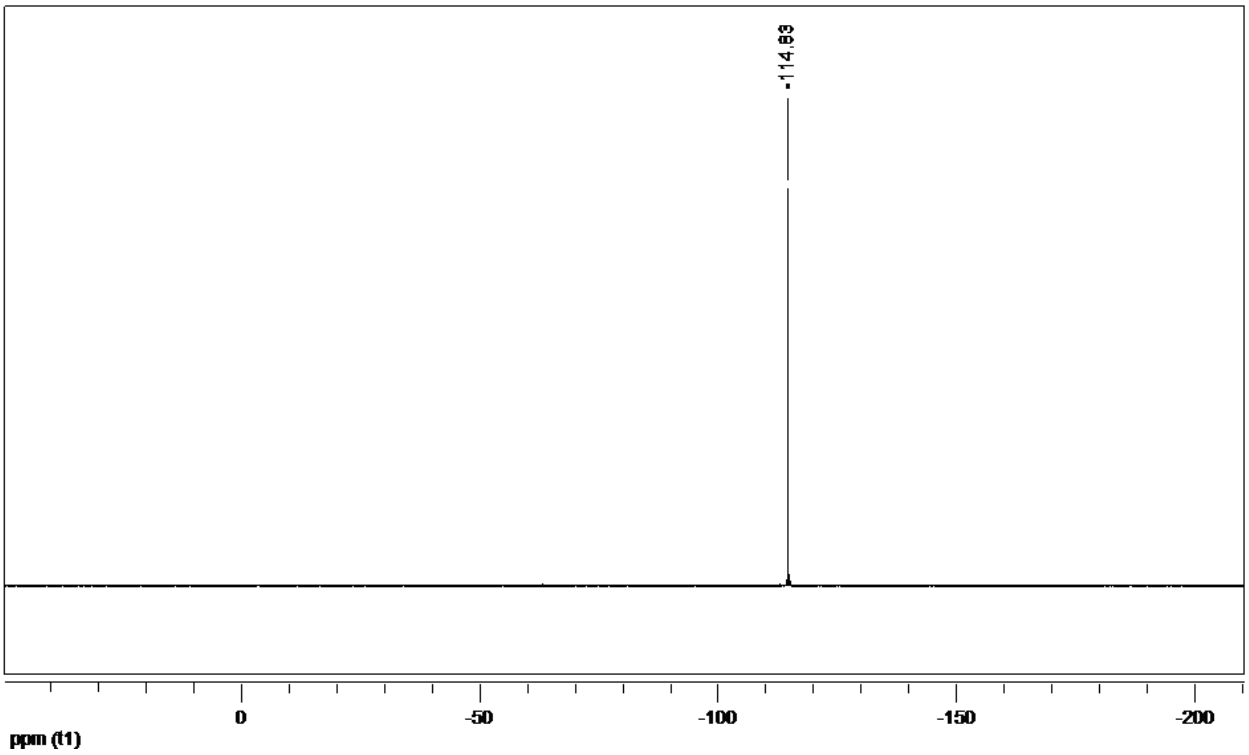




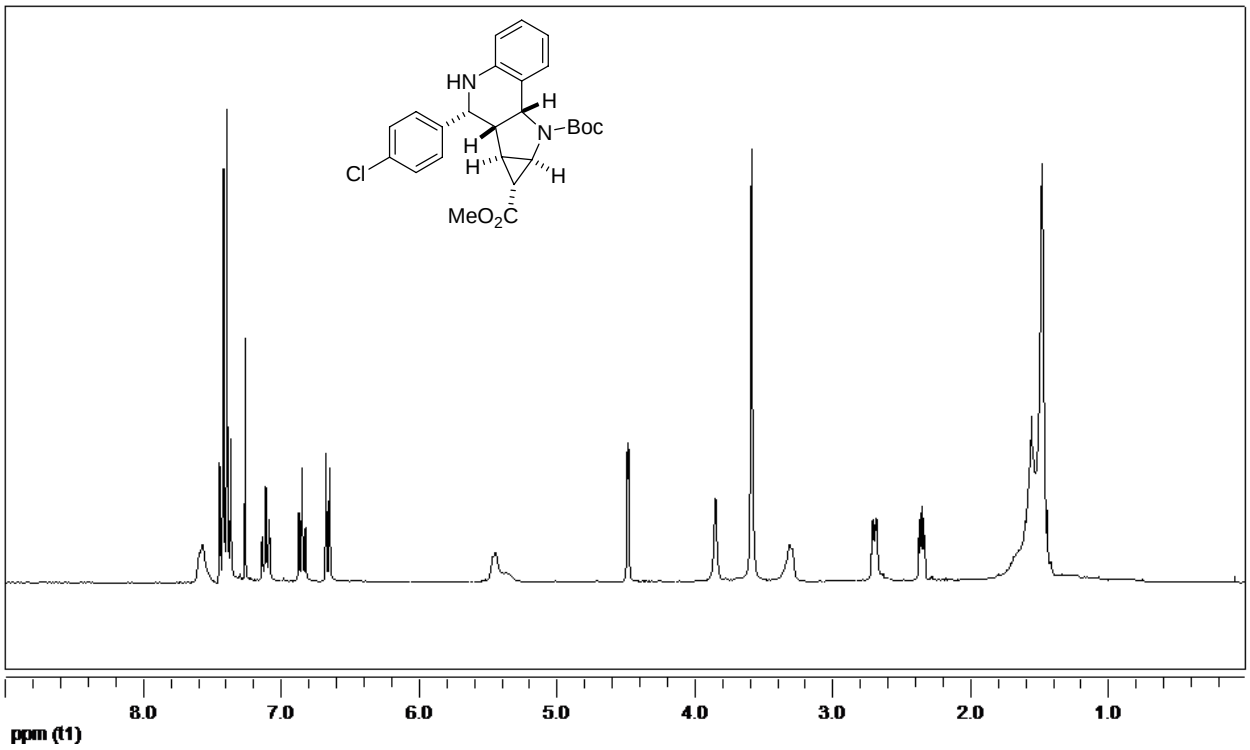
Compound **10g**

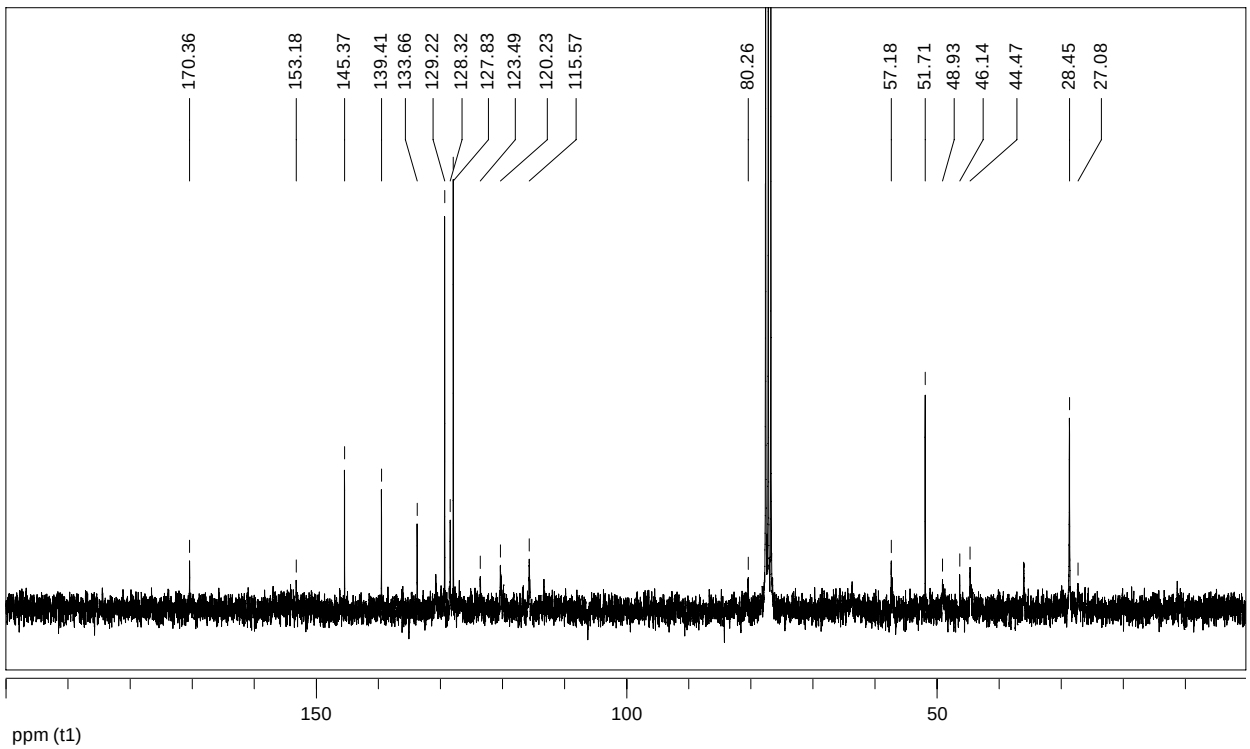




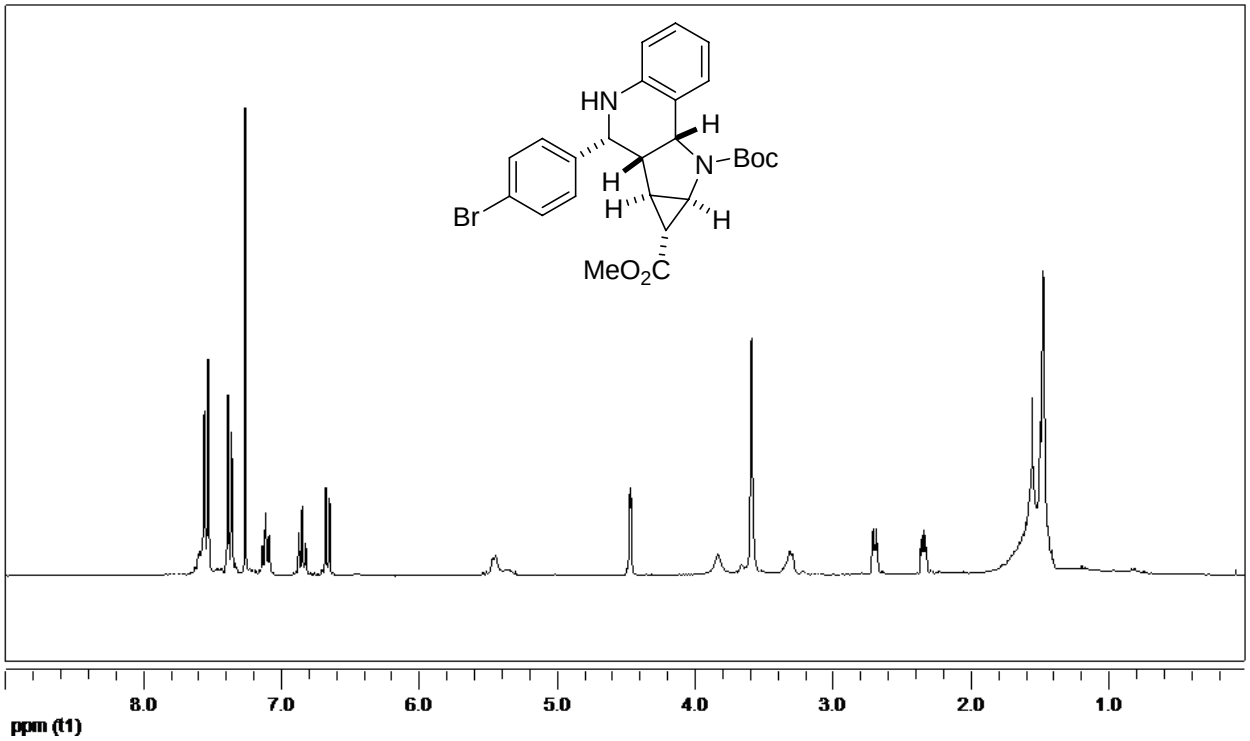

-114.83
0
-50
-100
-150
-200
ppm (t1)

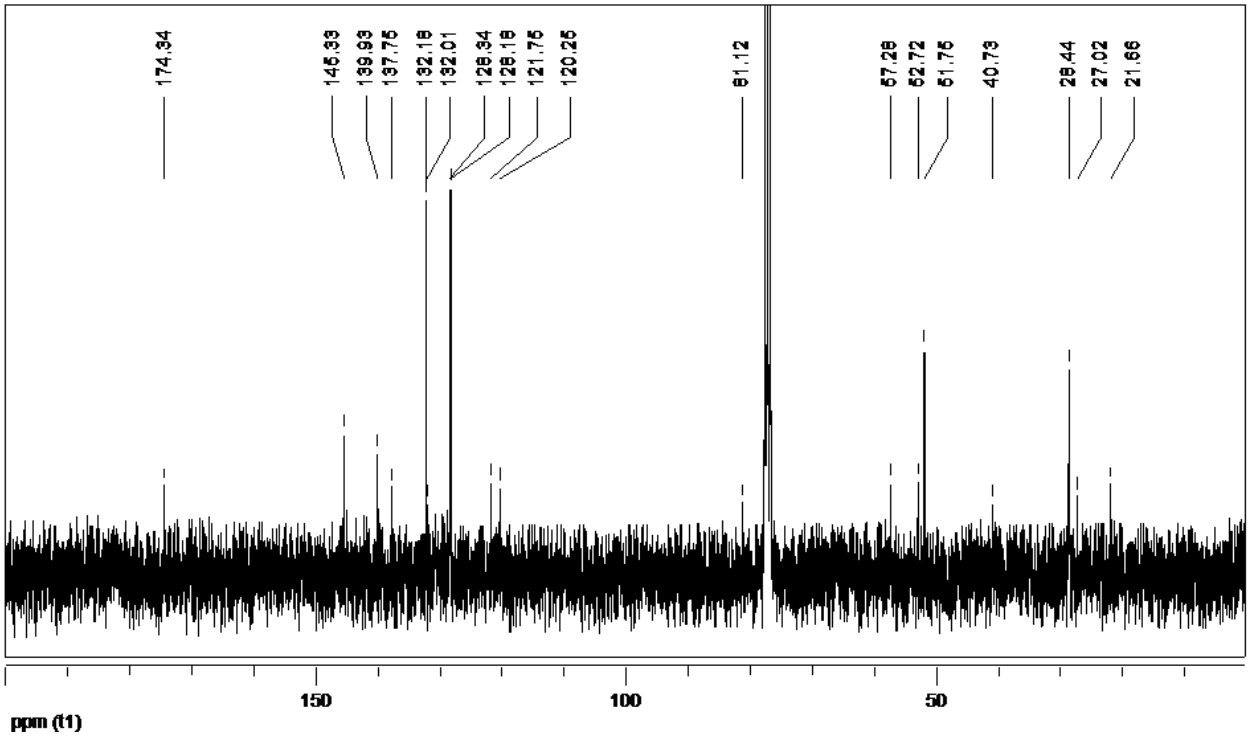
Compound **10h**



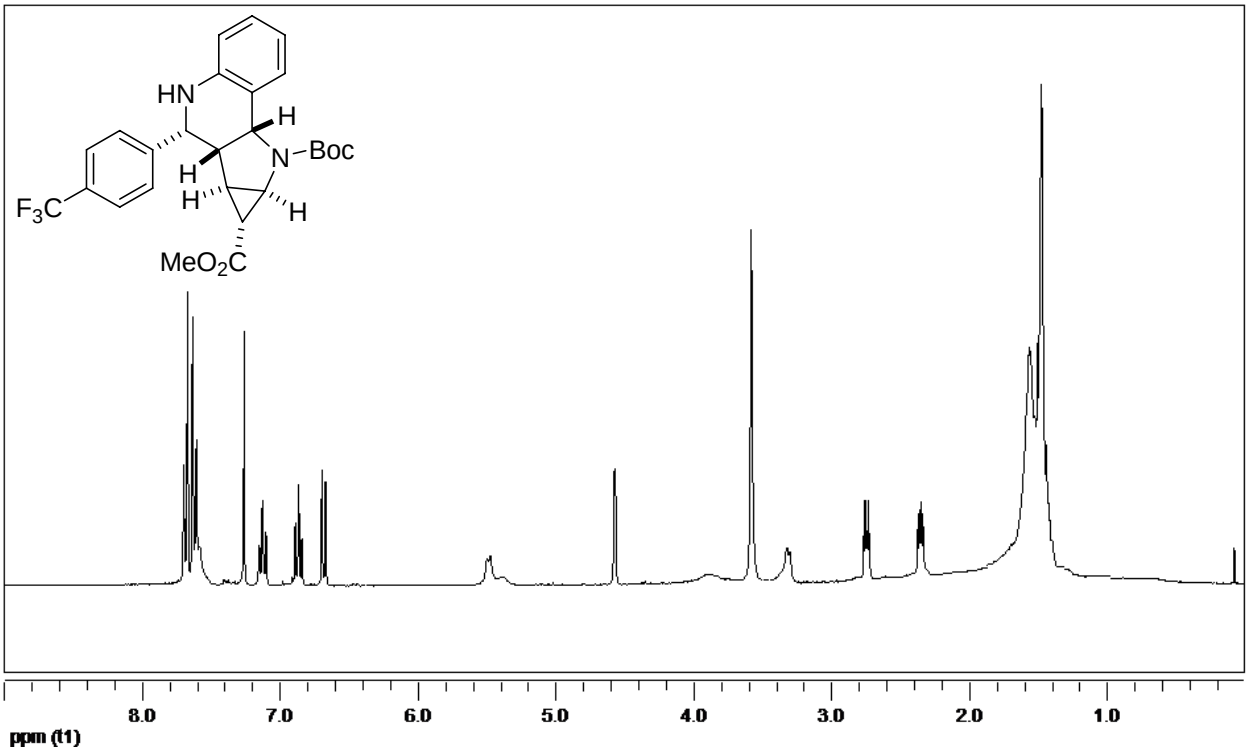


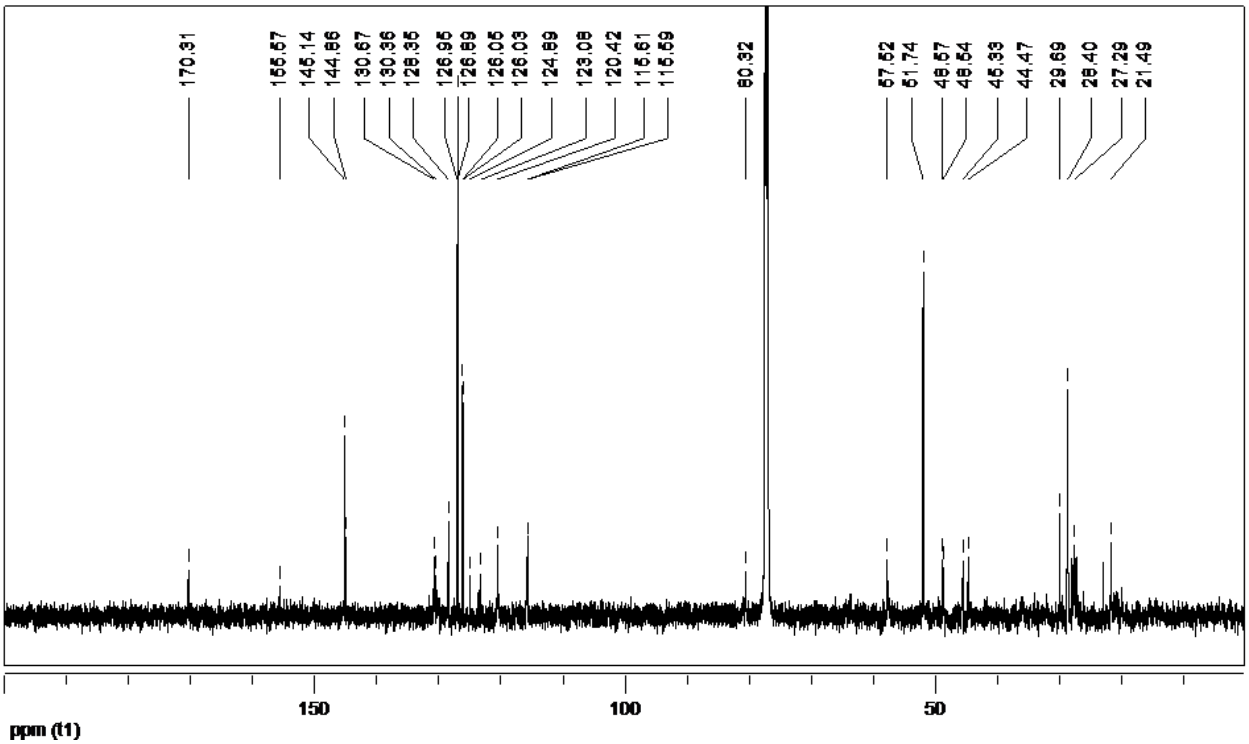
Compound **10i**



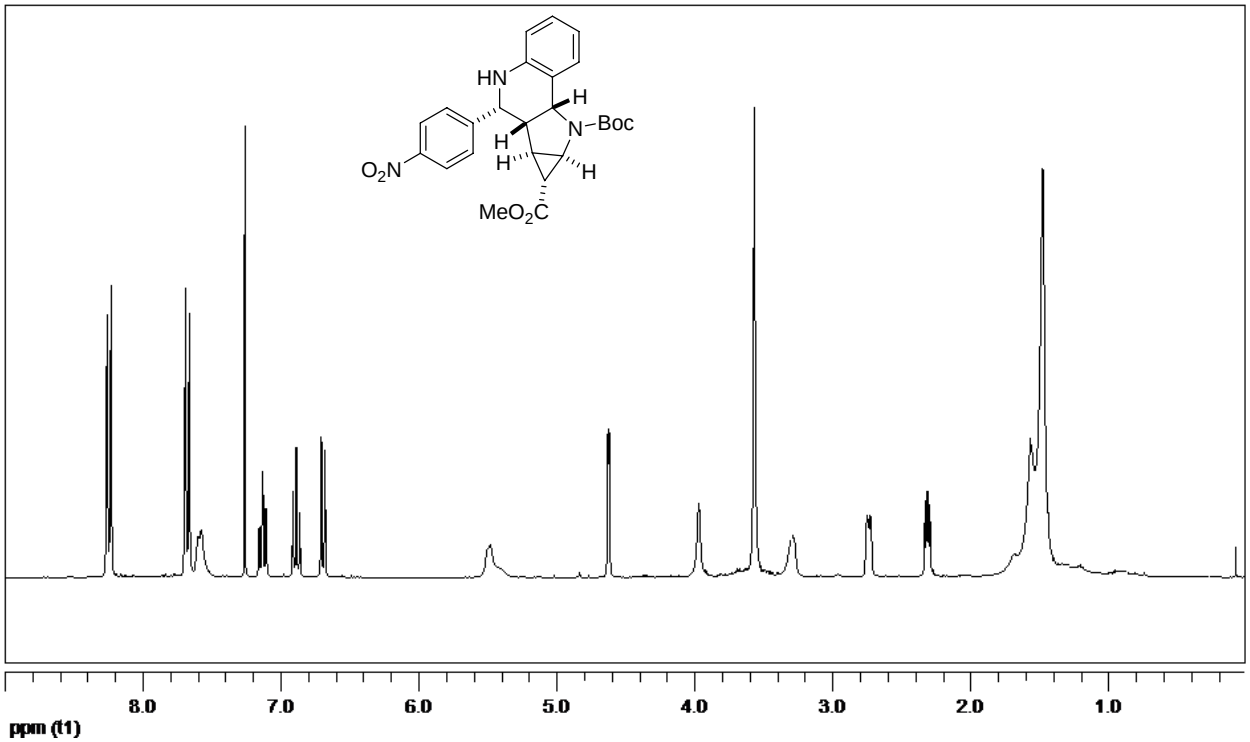


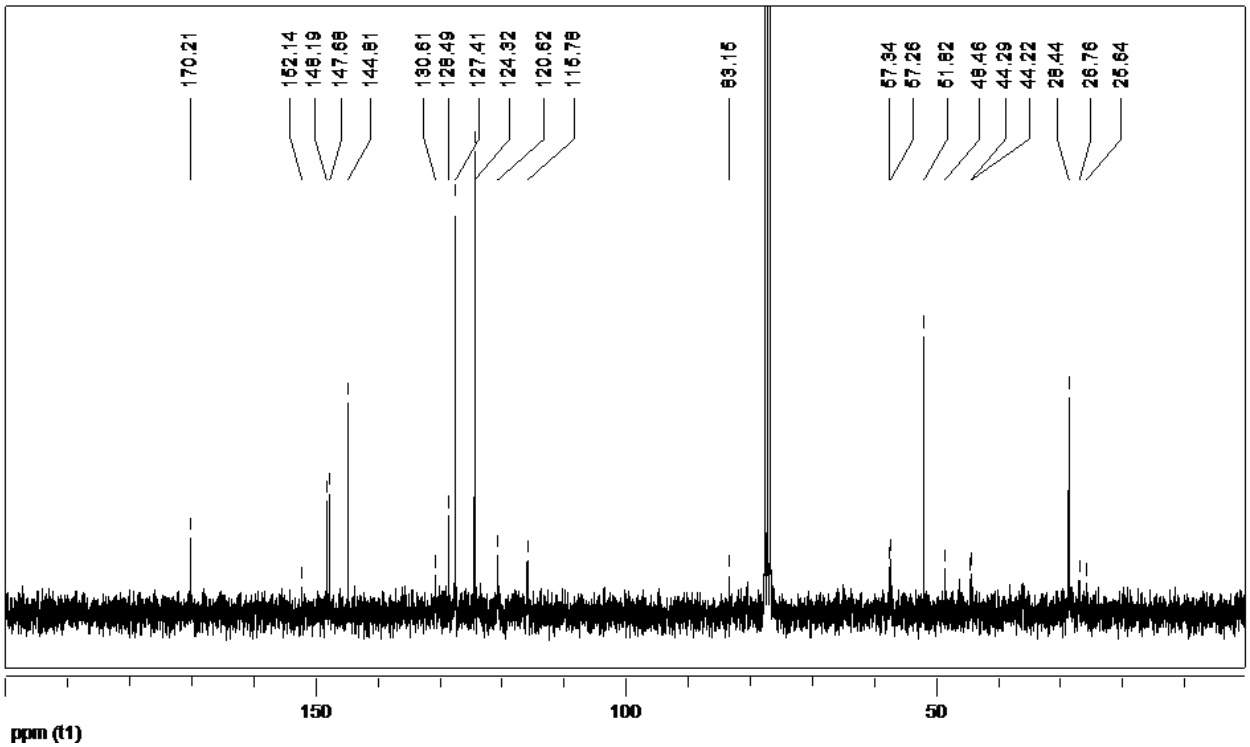
Compound **10j**



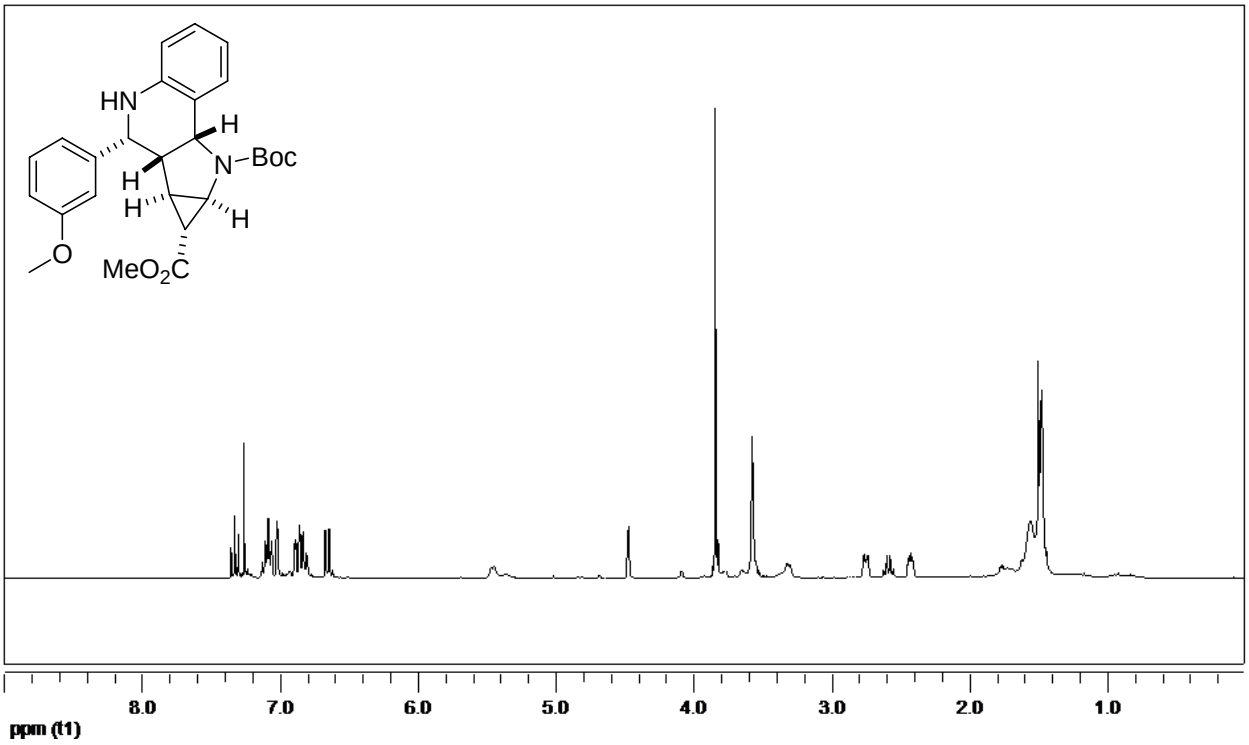


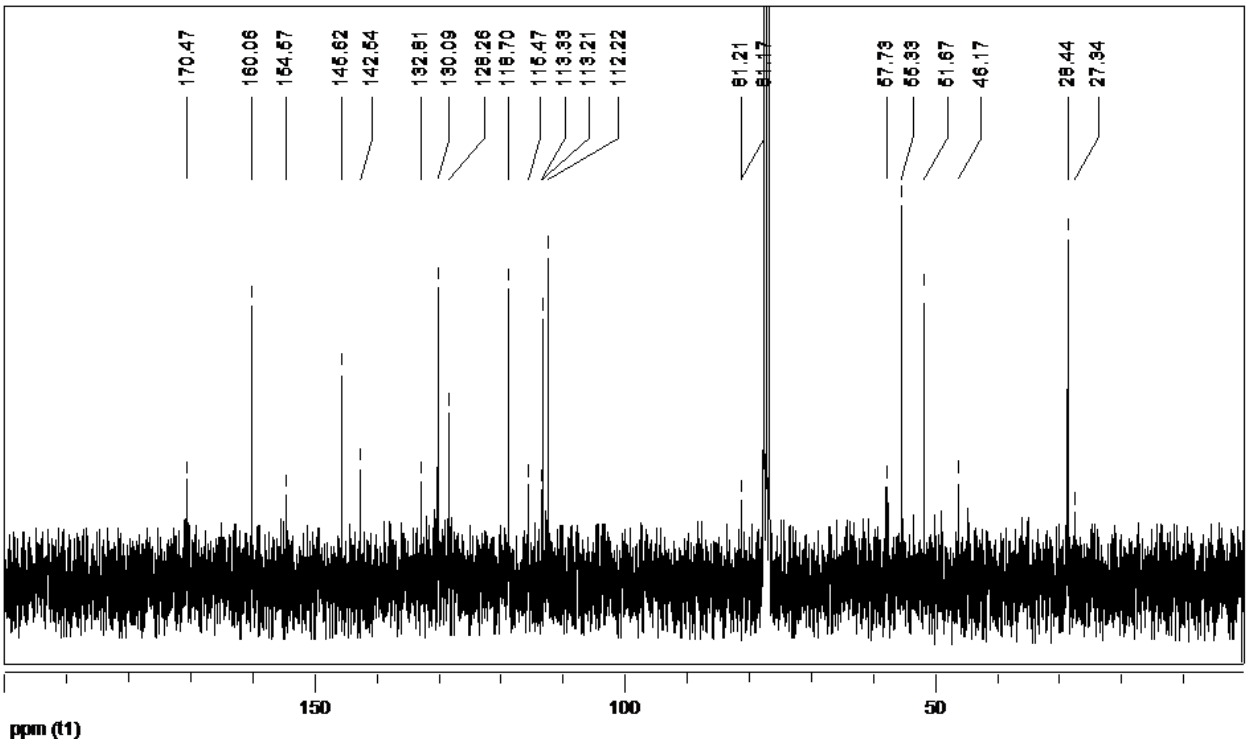
Compound **10k**



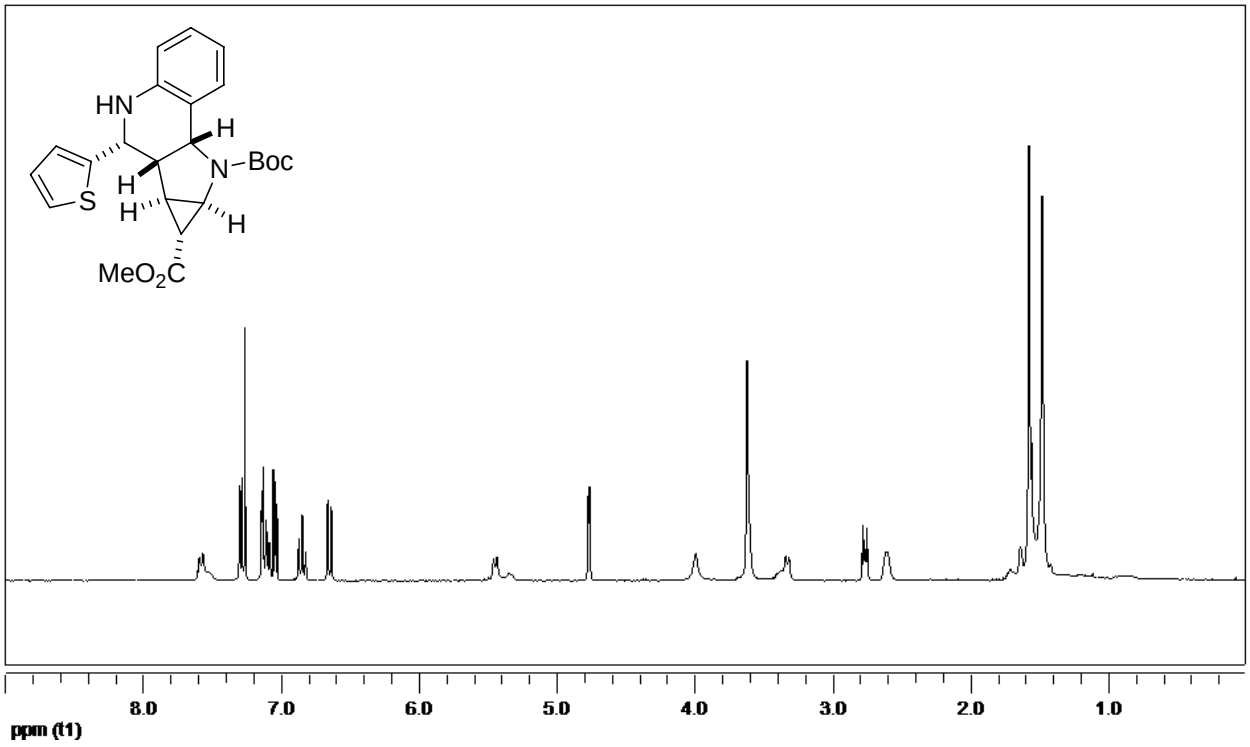


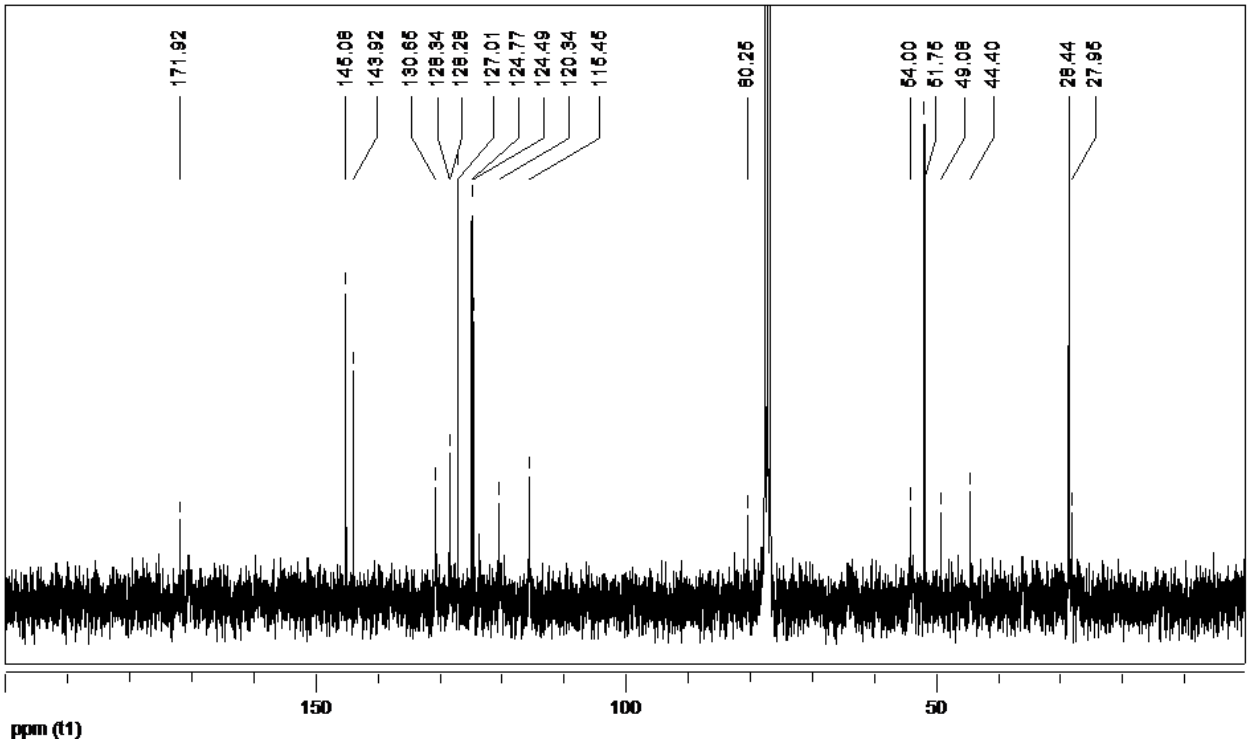
Compound **10k′**



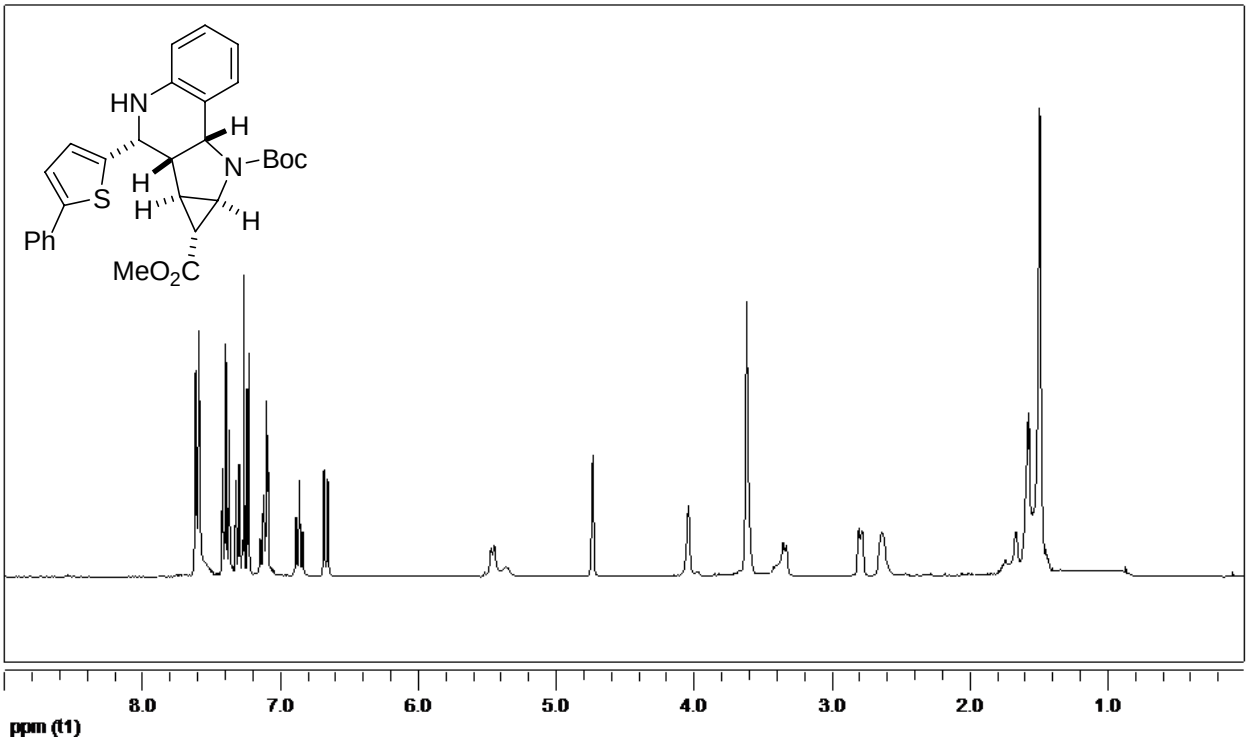


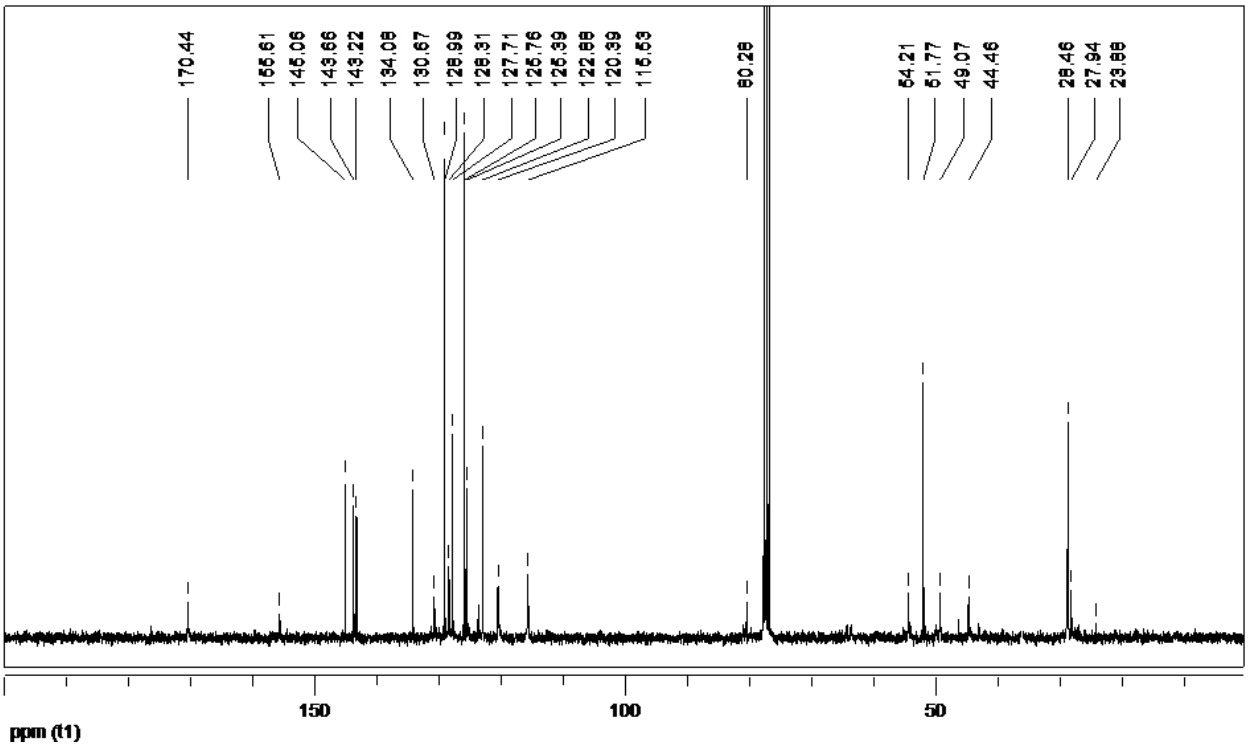
Compound **10l**



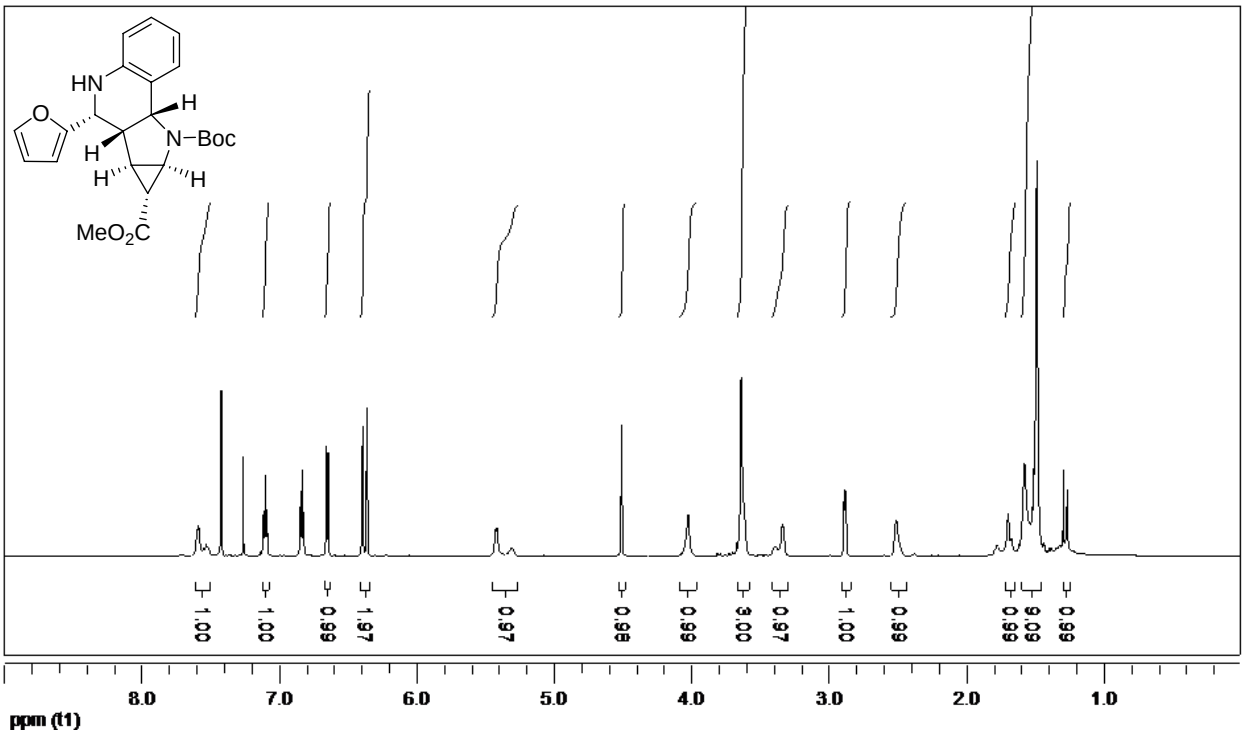


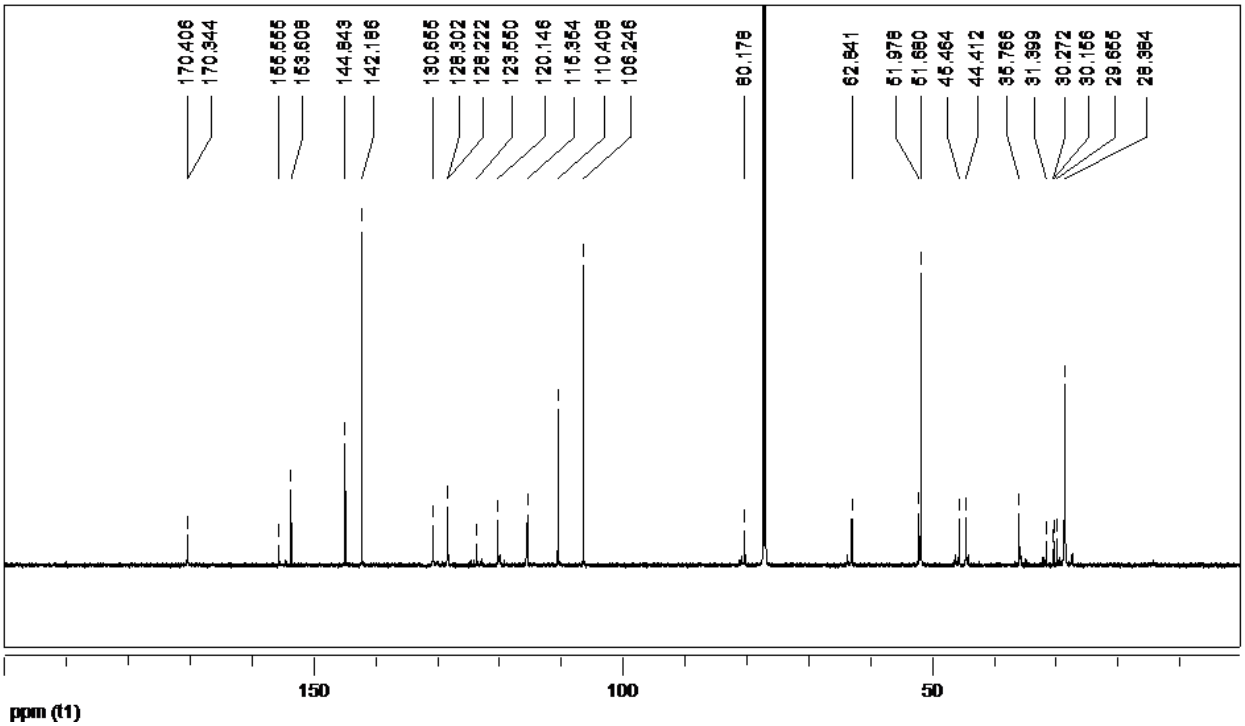
Compound **10m**



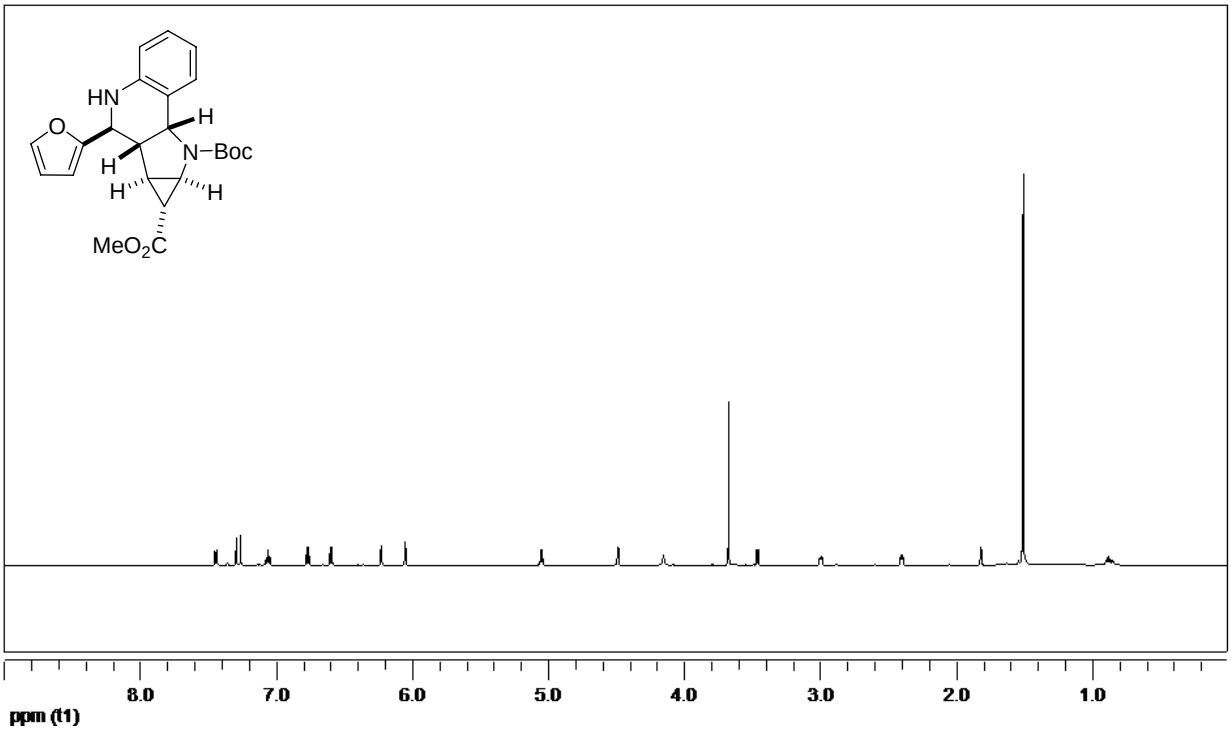


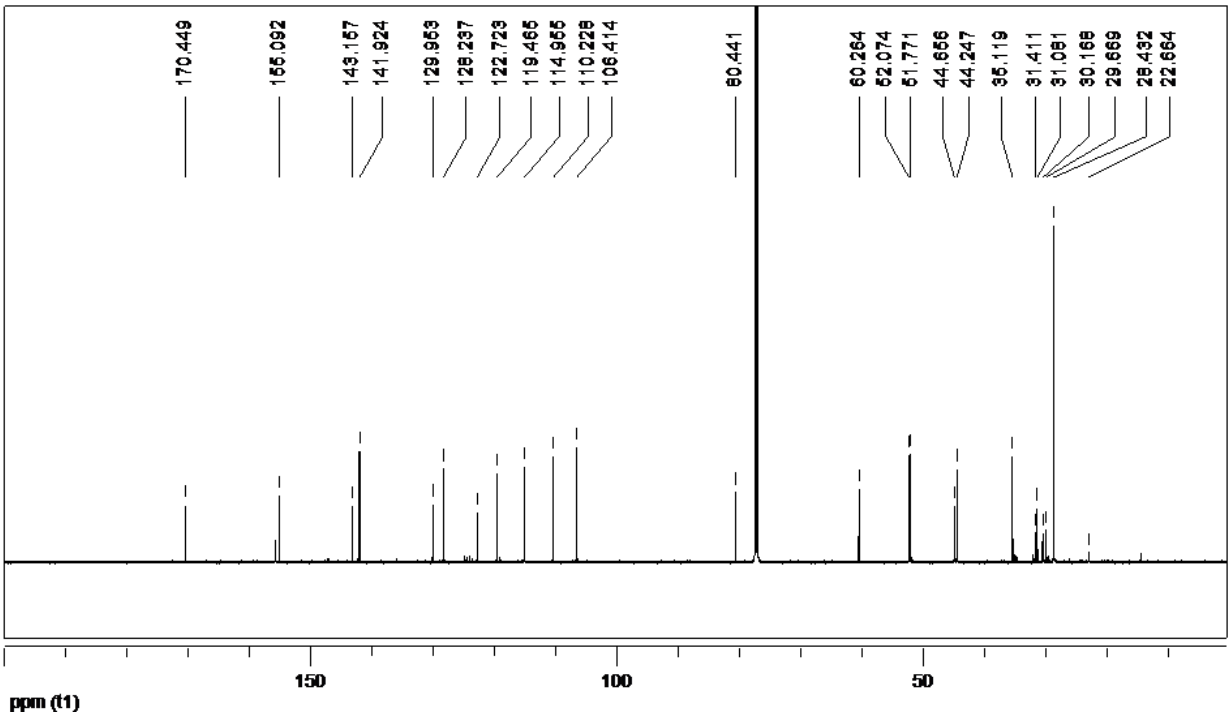
Compound **10n**



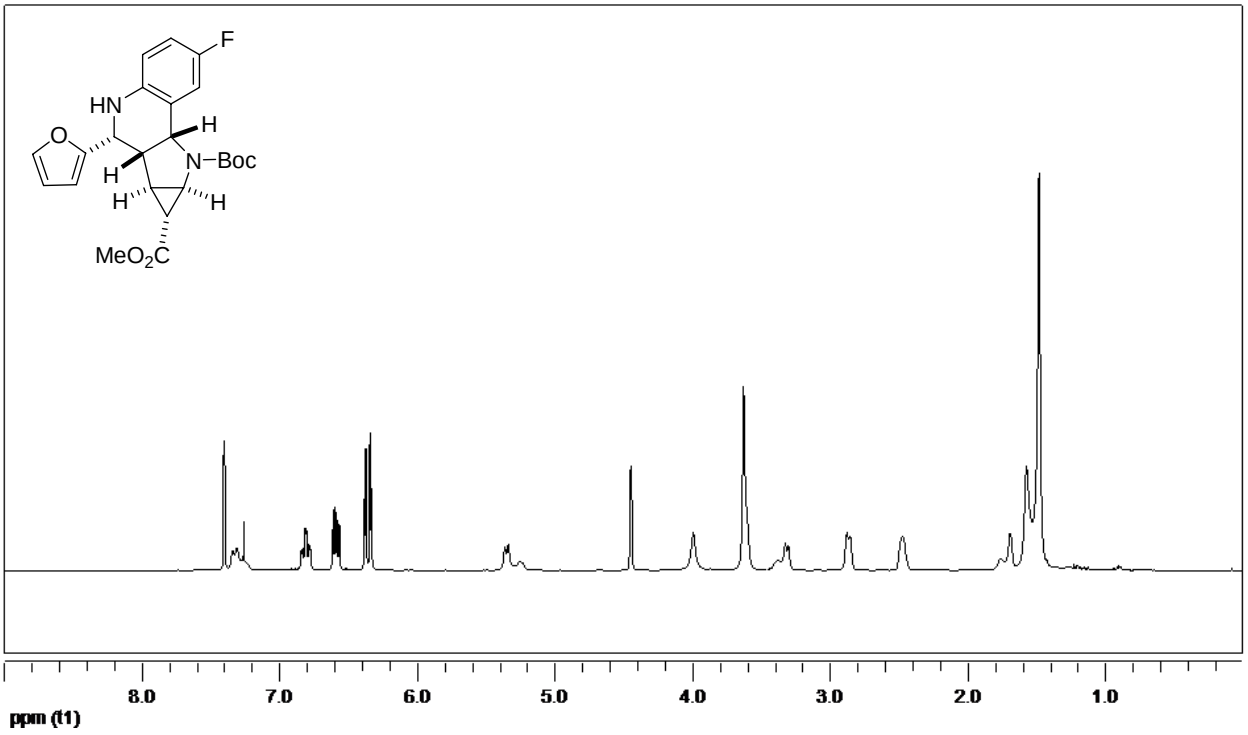


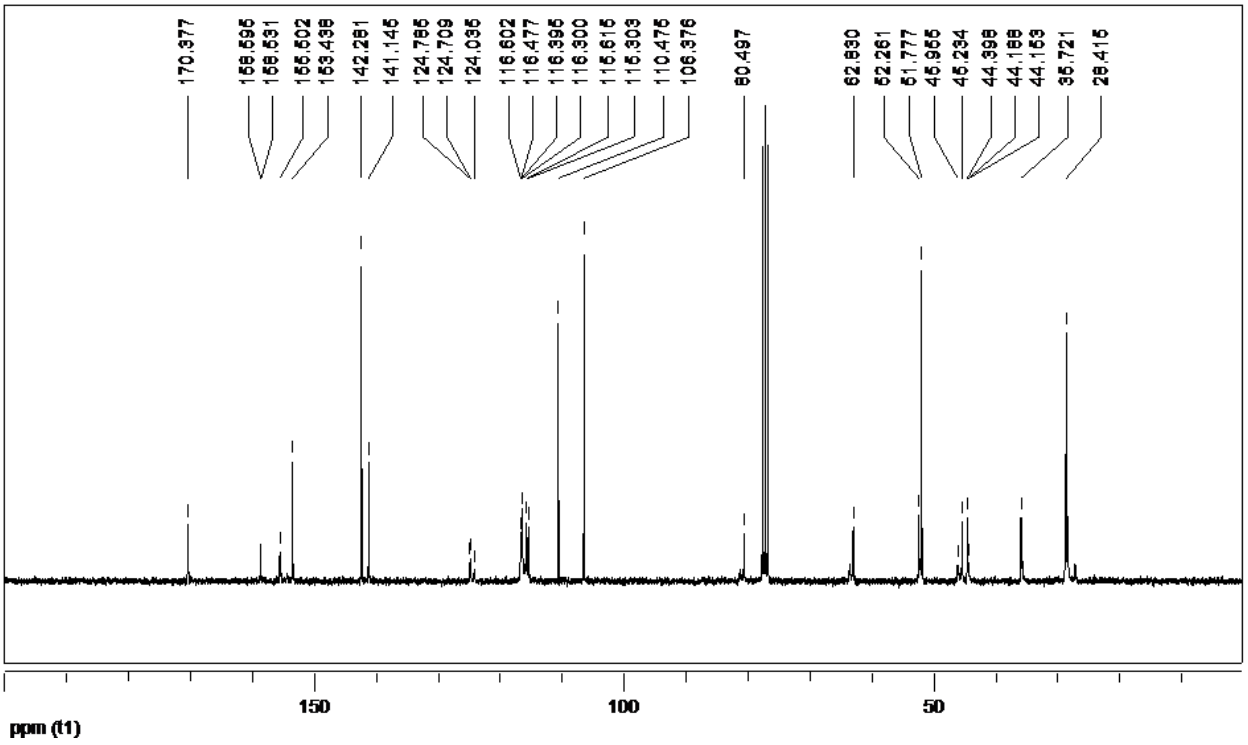
Compound **11n**



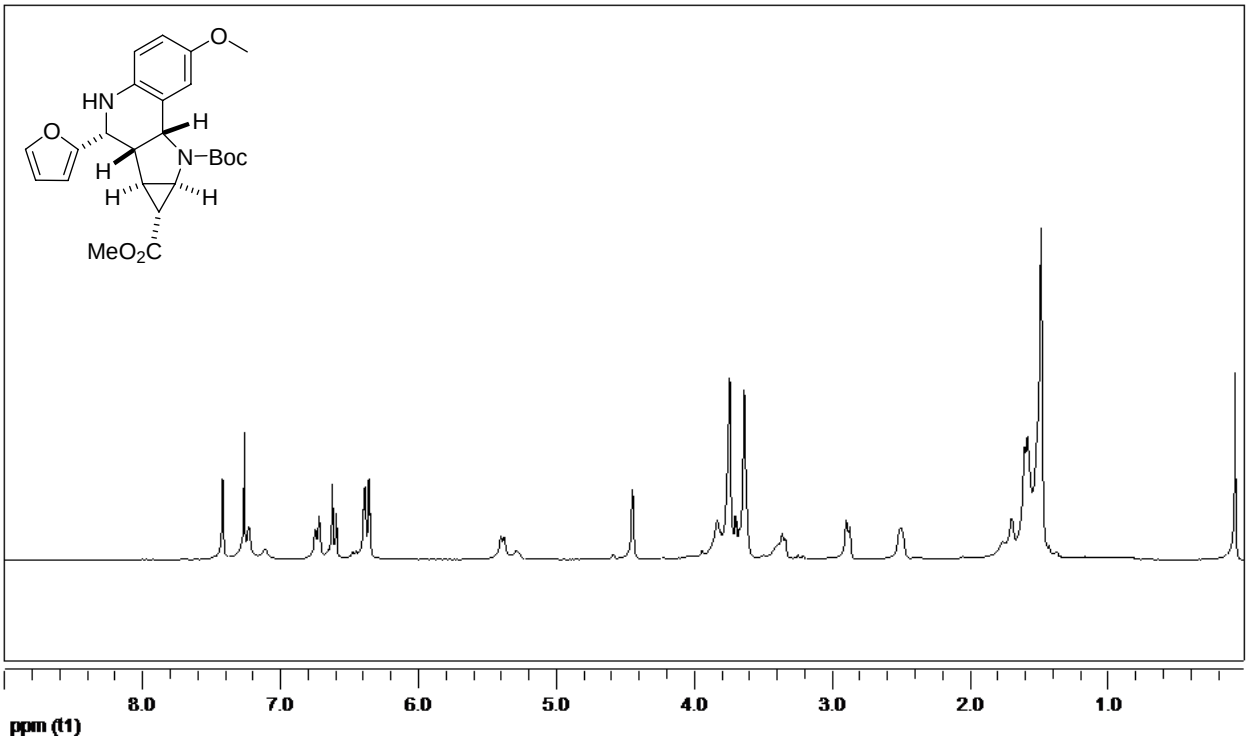


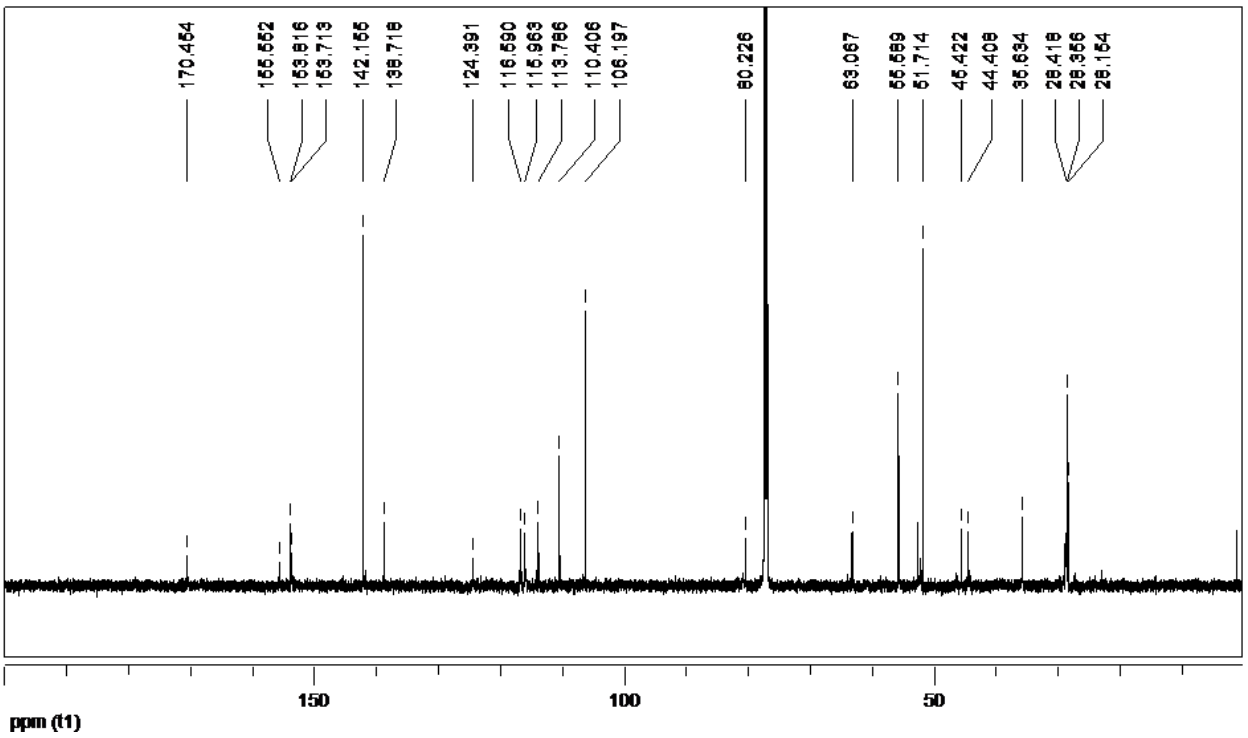
Compound **10o**



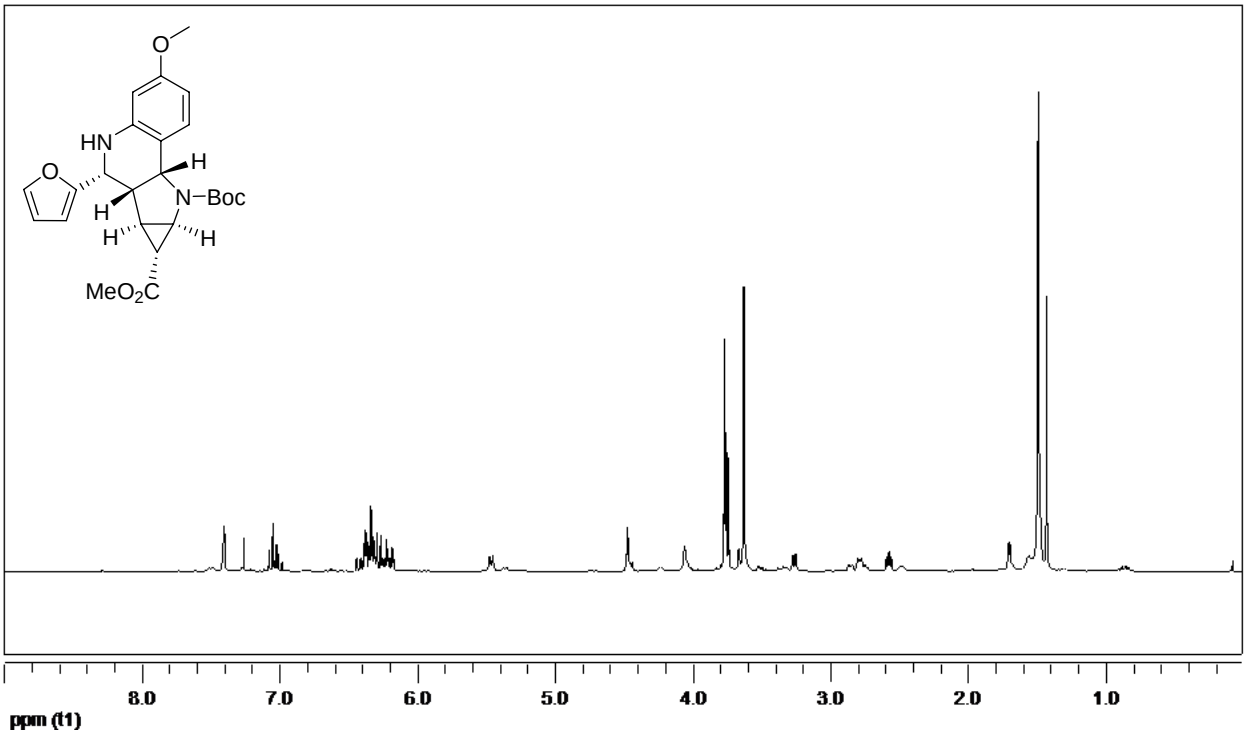


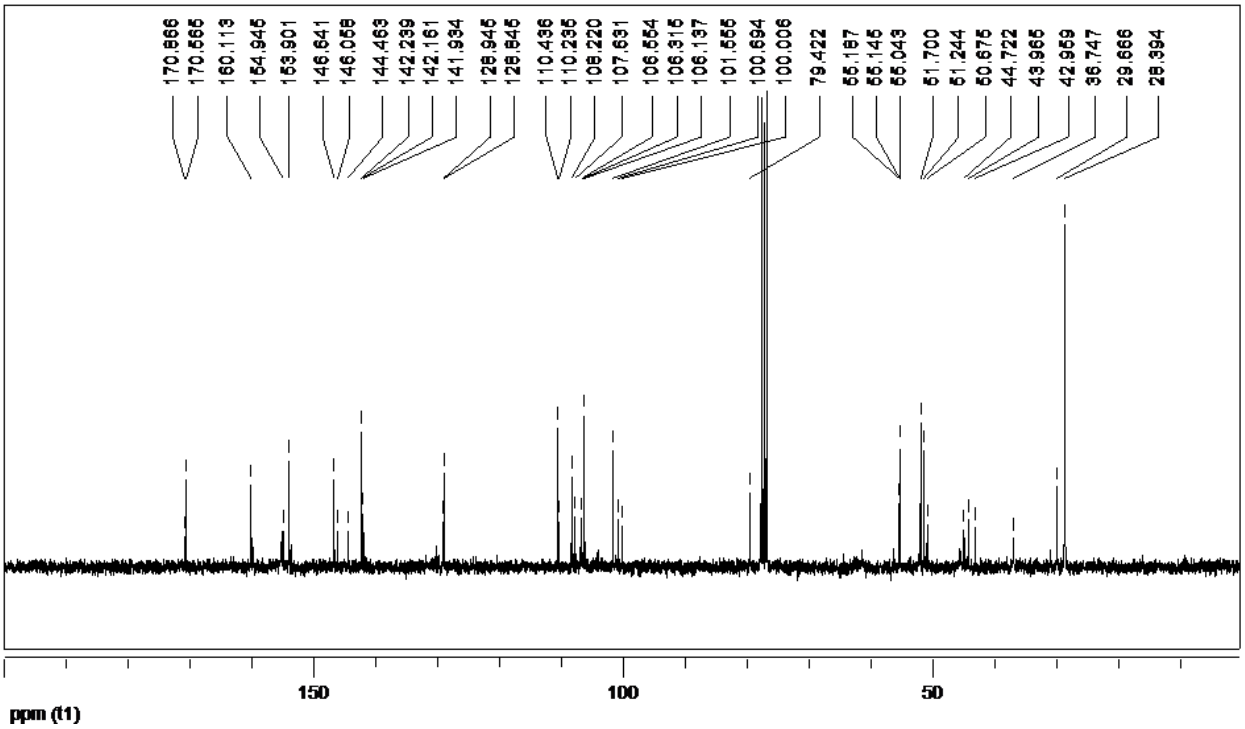
Compound **10p**



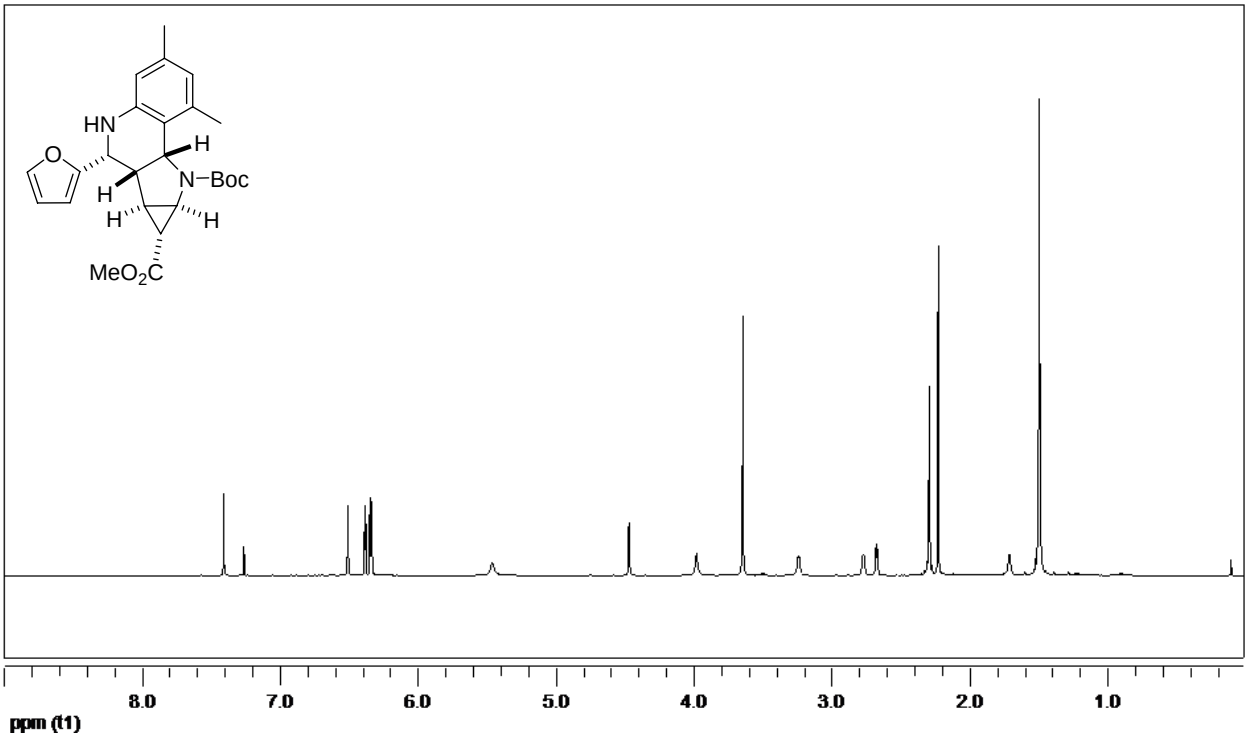


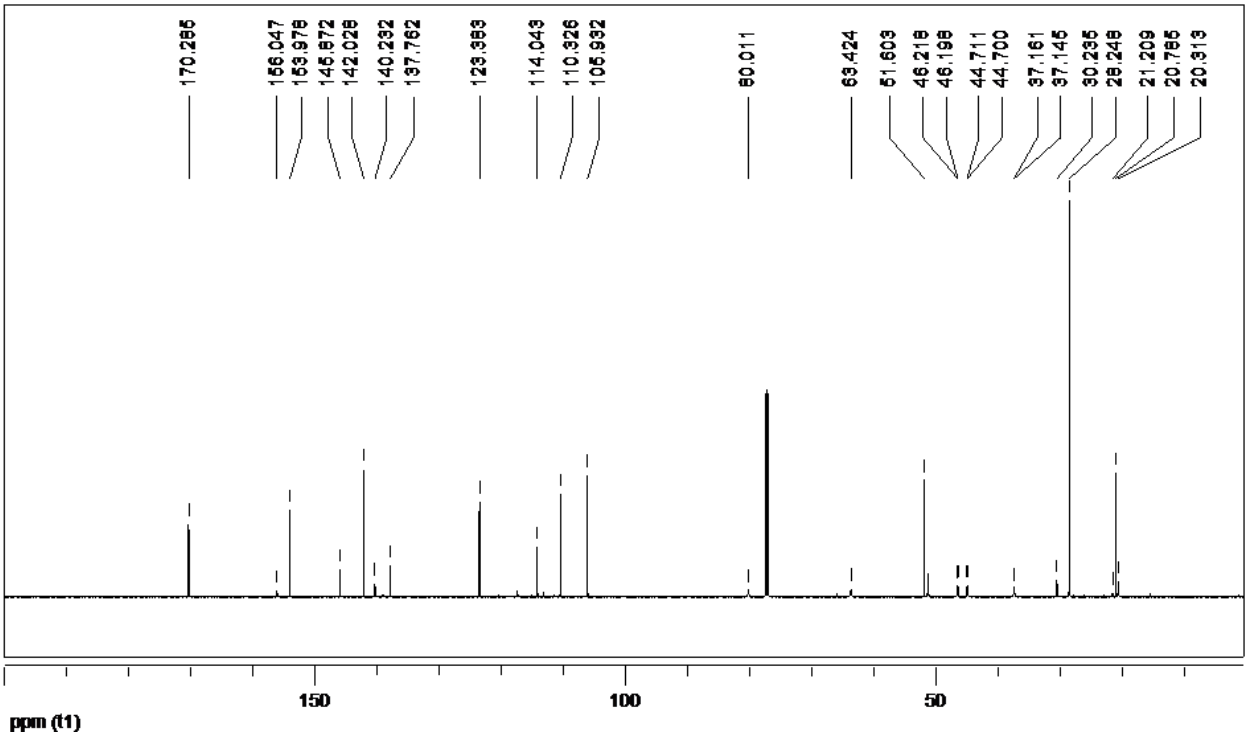
Compound **10r**



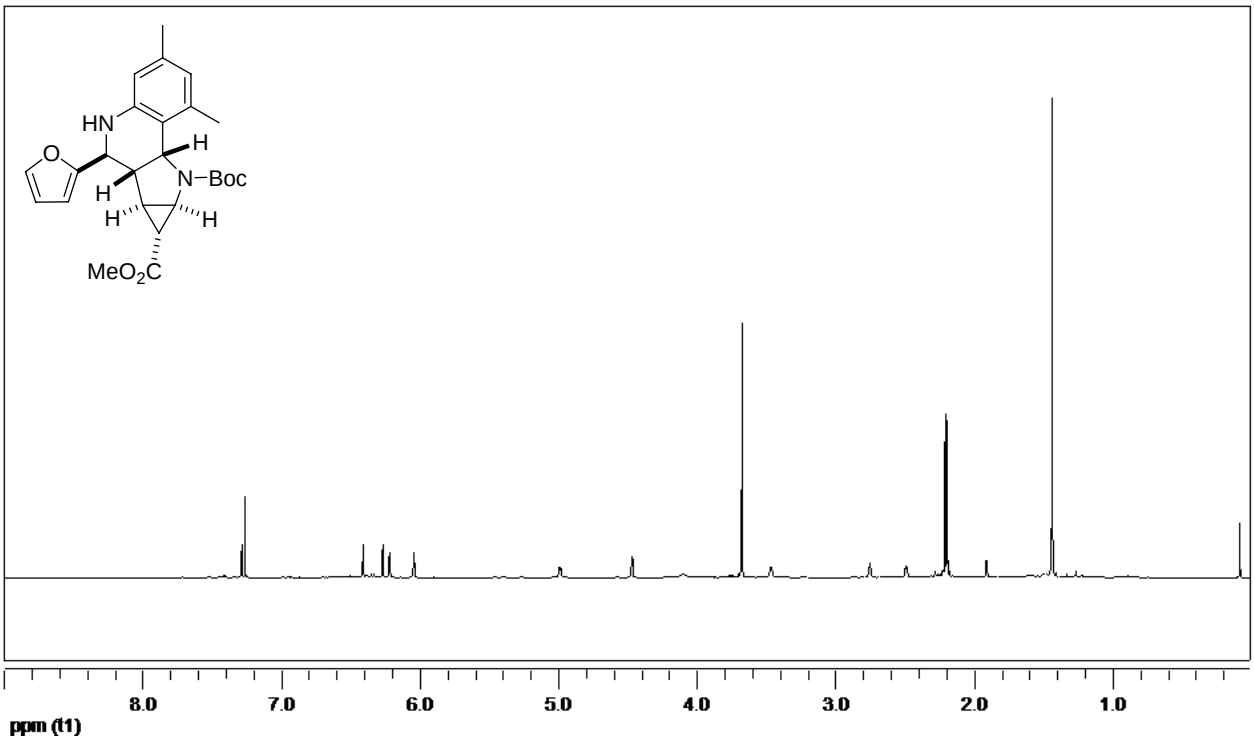


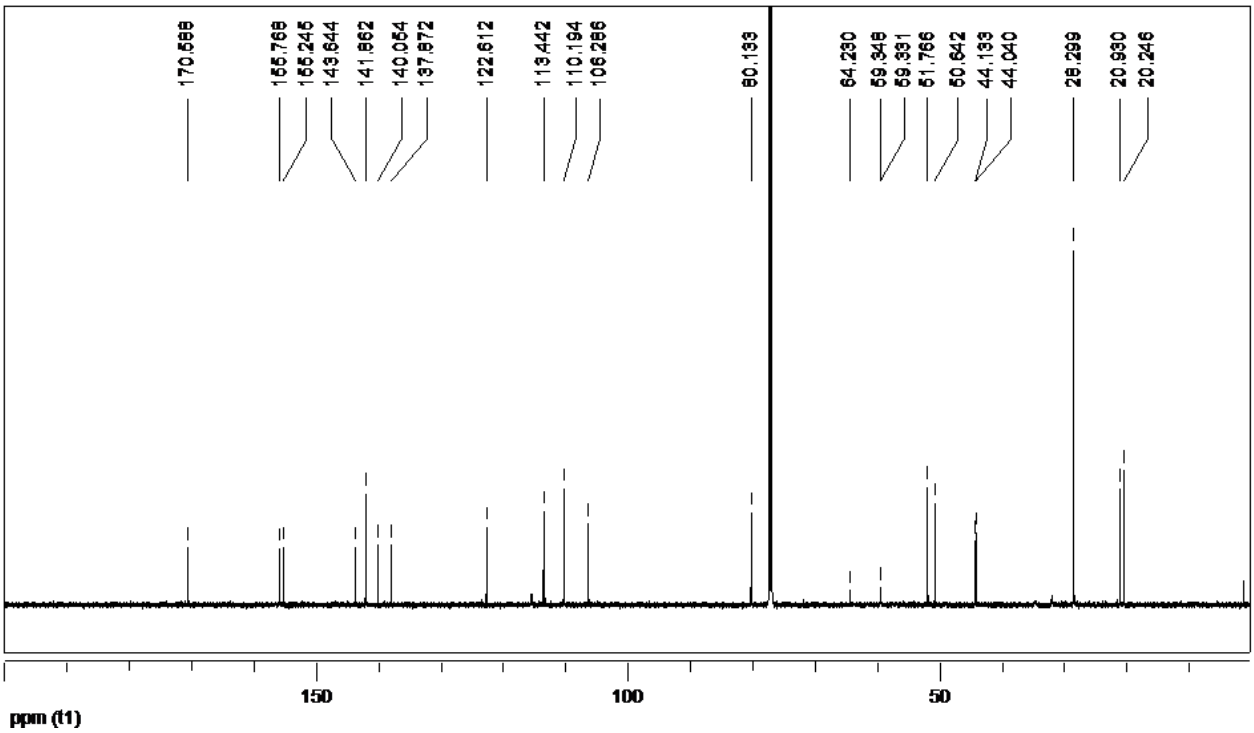
Compound **10s**



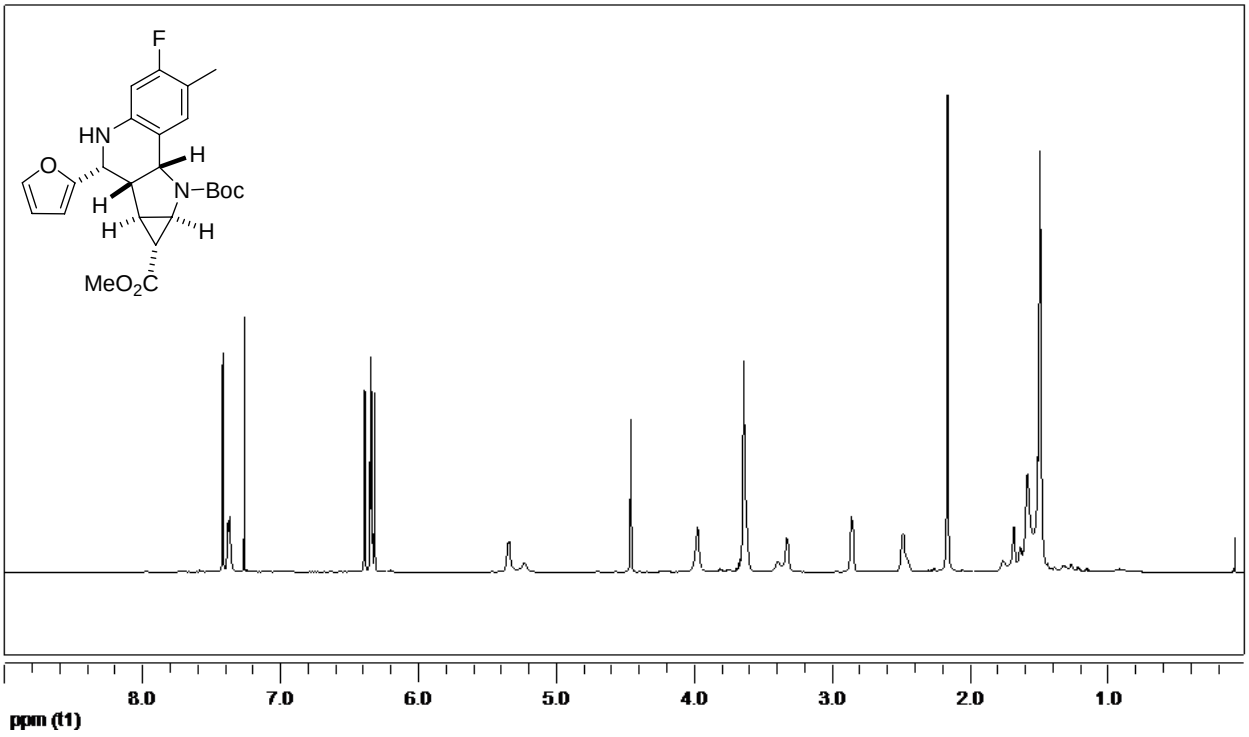


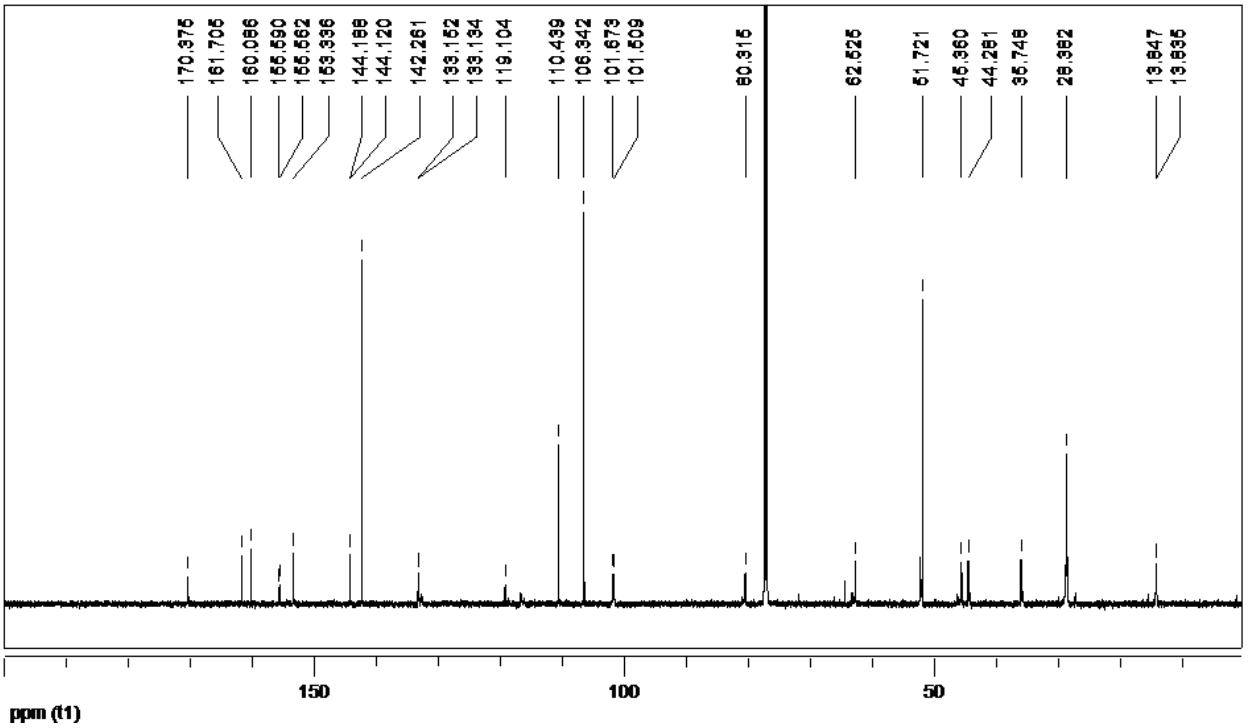
Compound **11s**

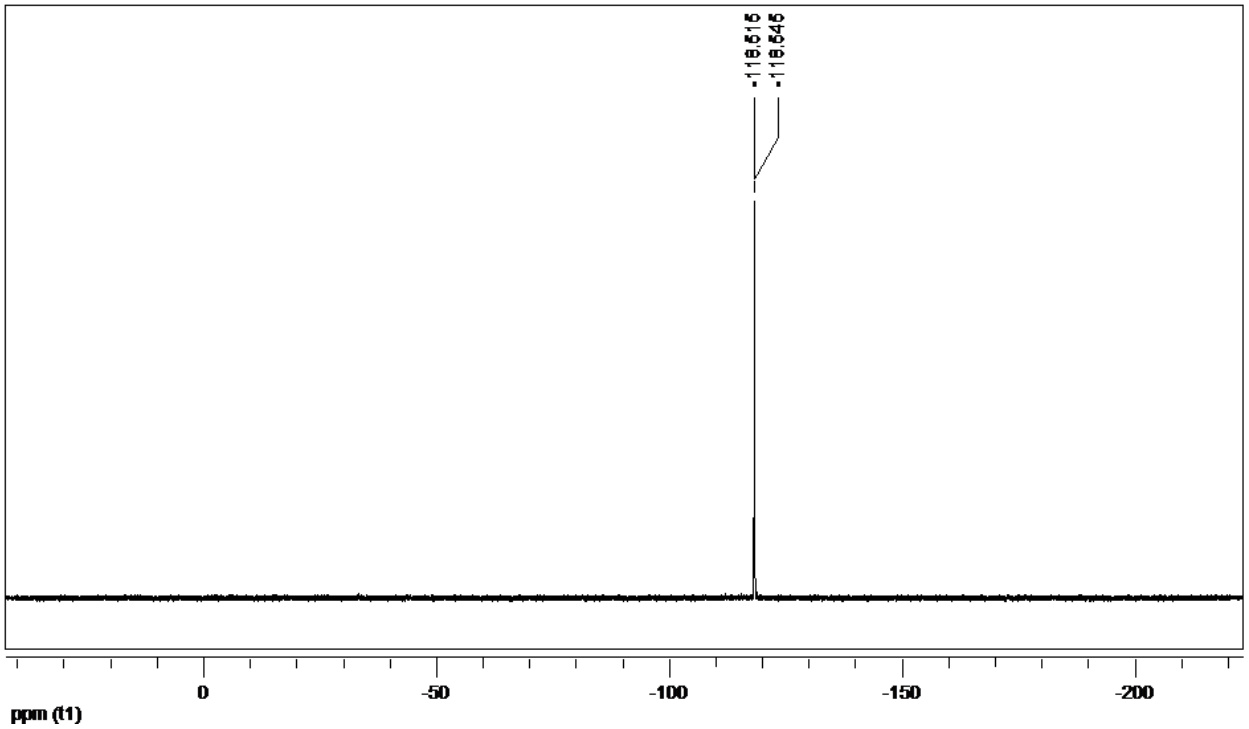




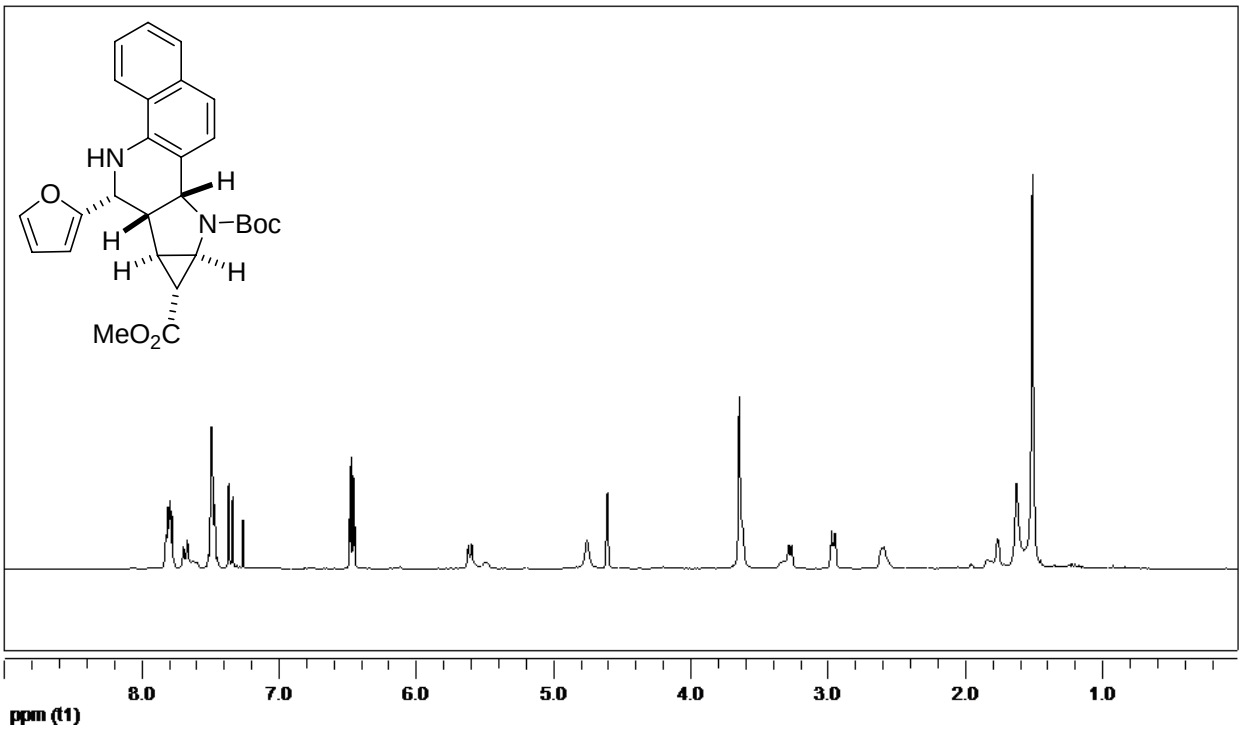
Compound **10t**

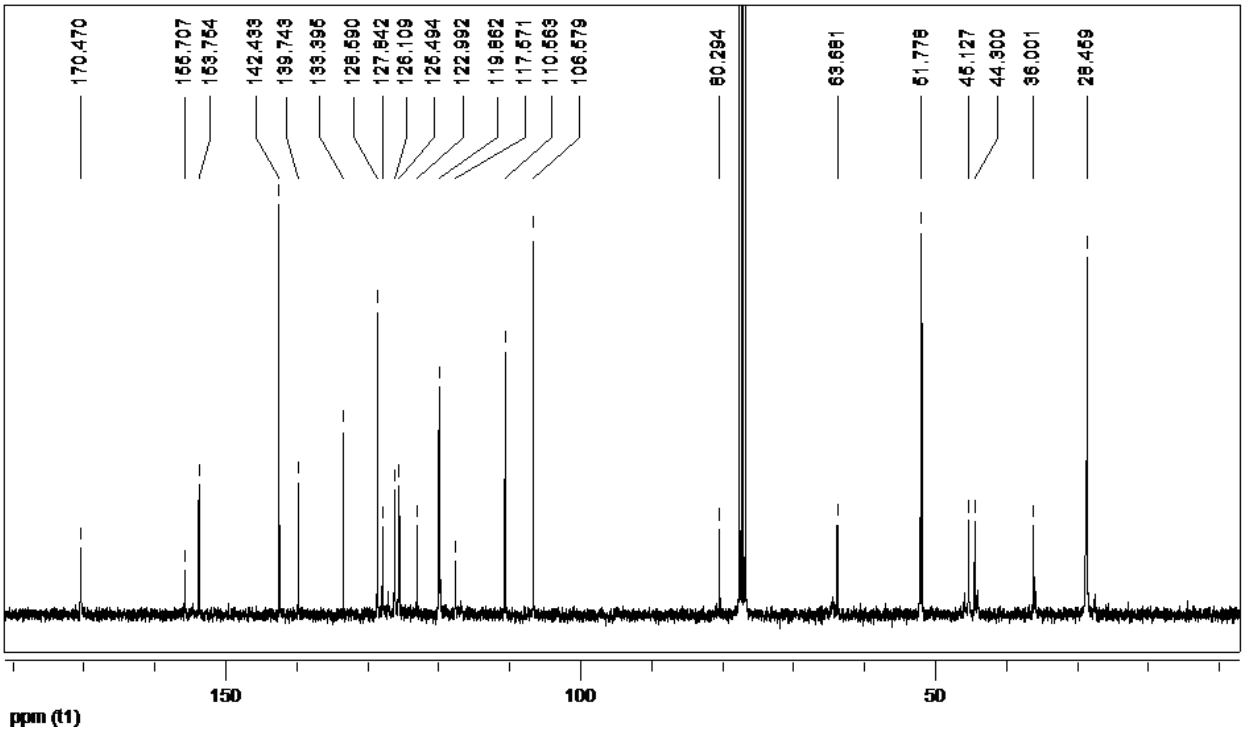




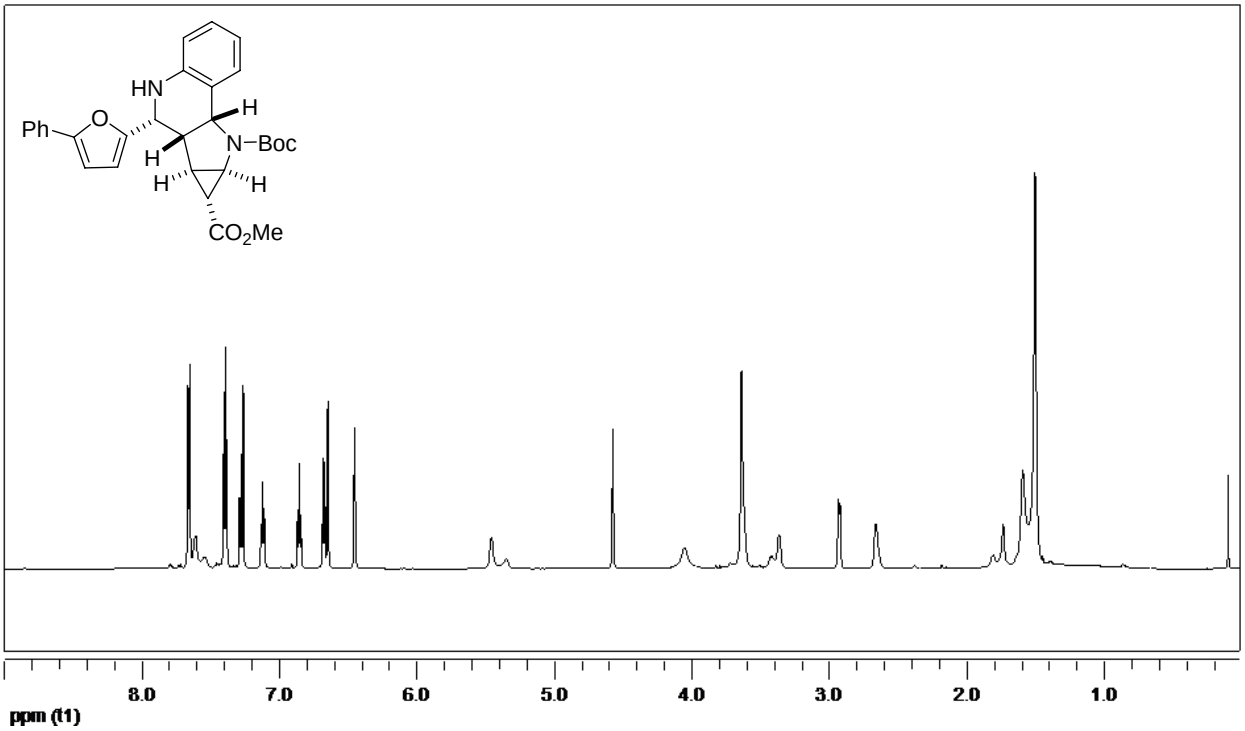

-118.615
-118.645
0
-50
-100
-150
-200
ppm (t1)

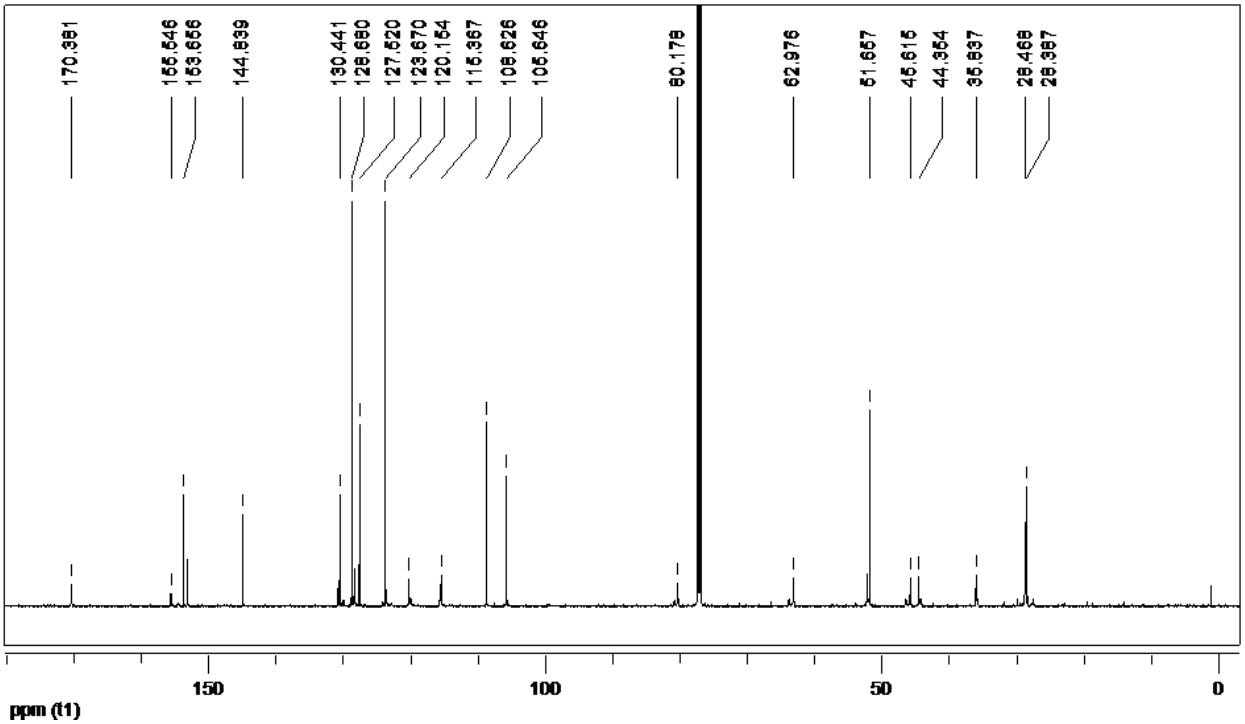
Compound **10u**



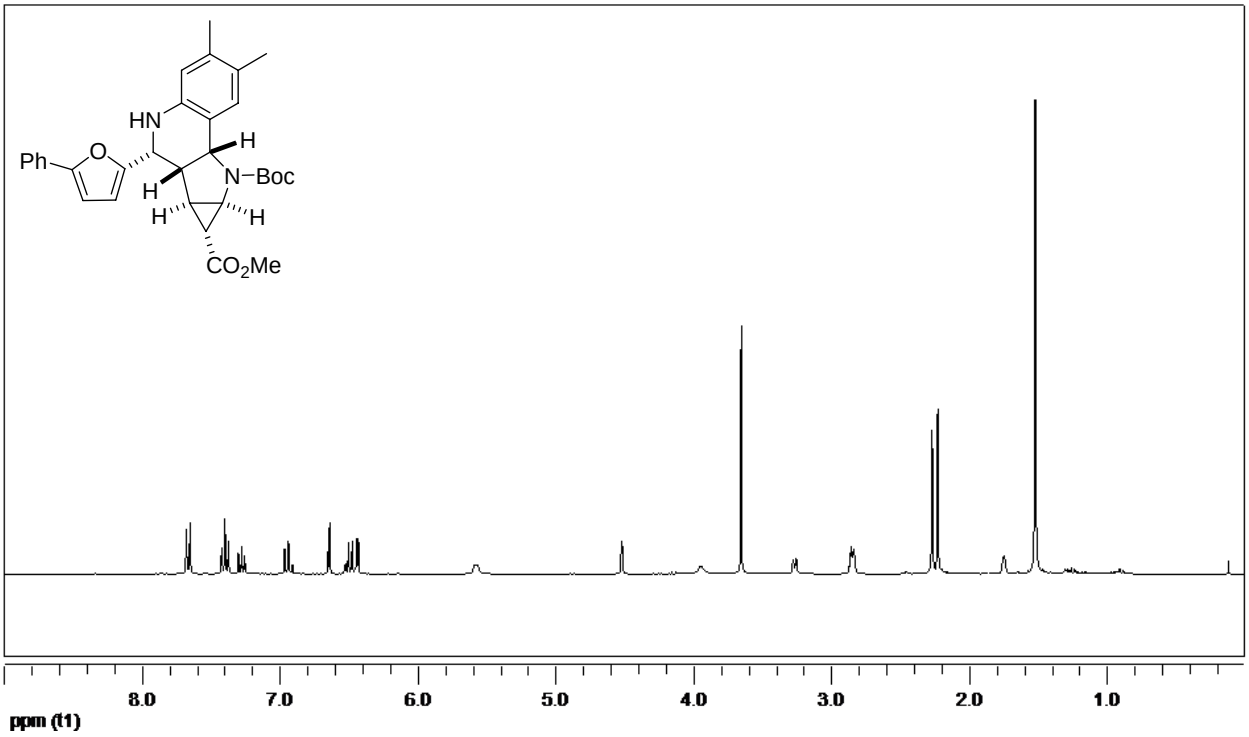


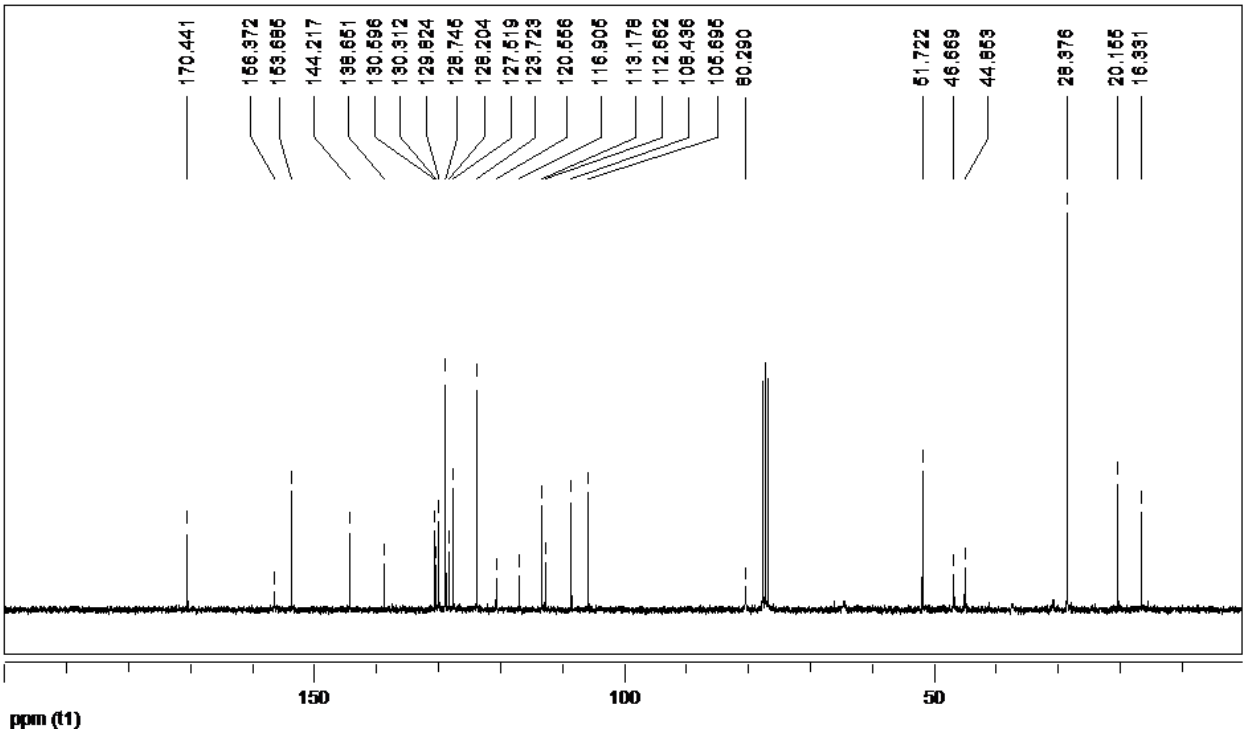
Compound **10v**



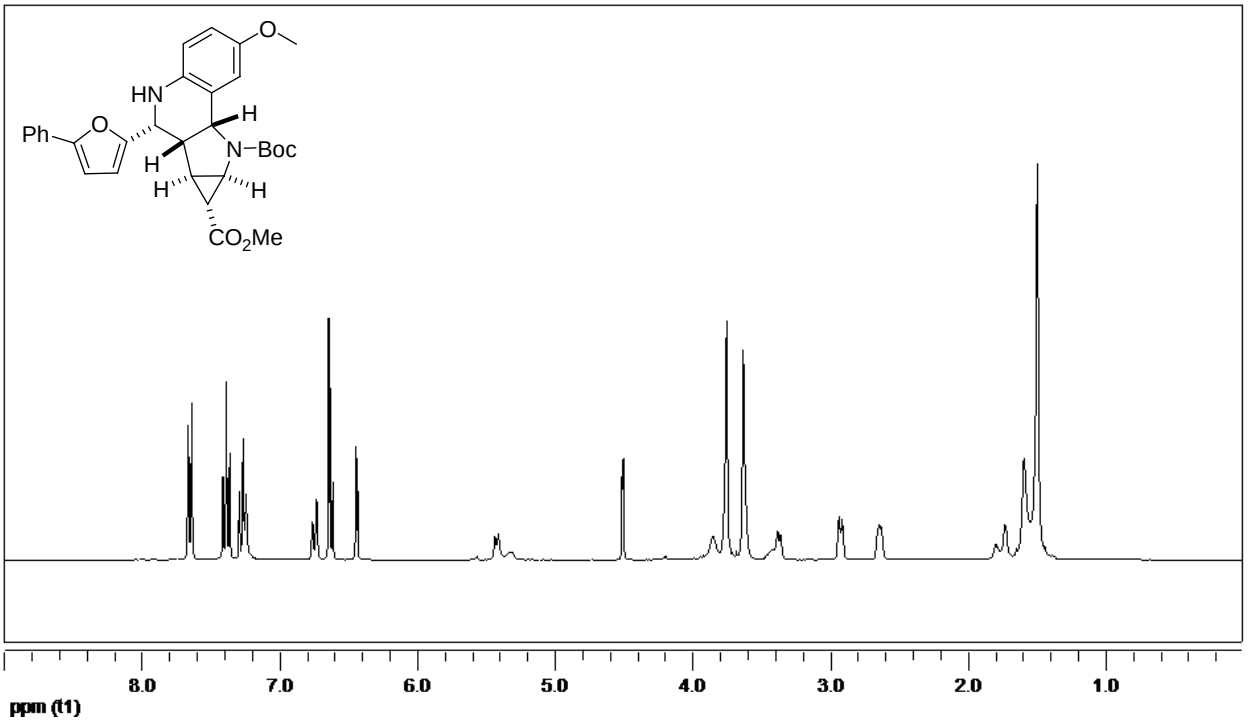


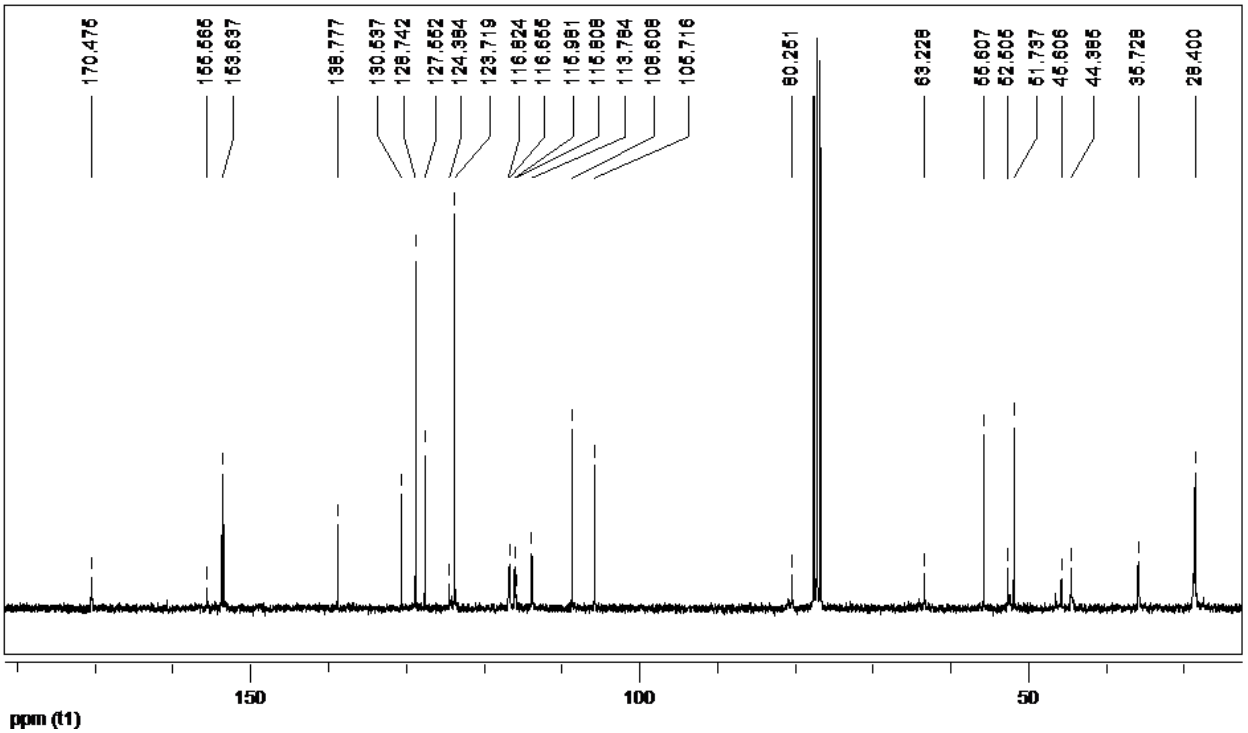
Compound **10w**



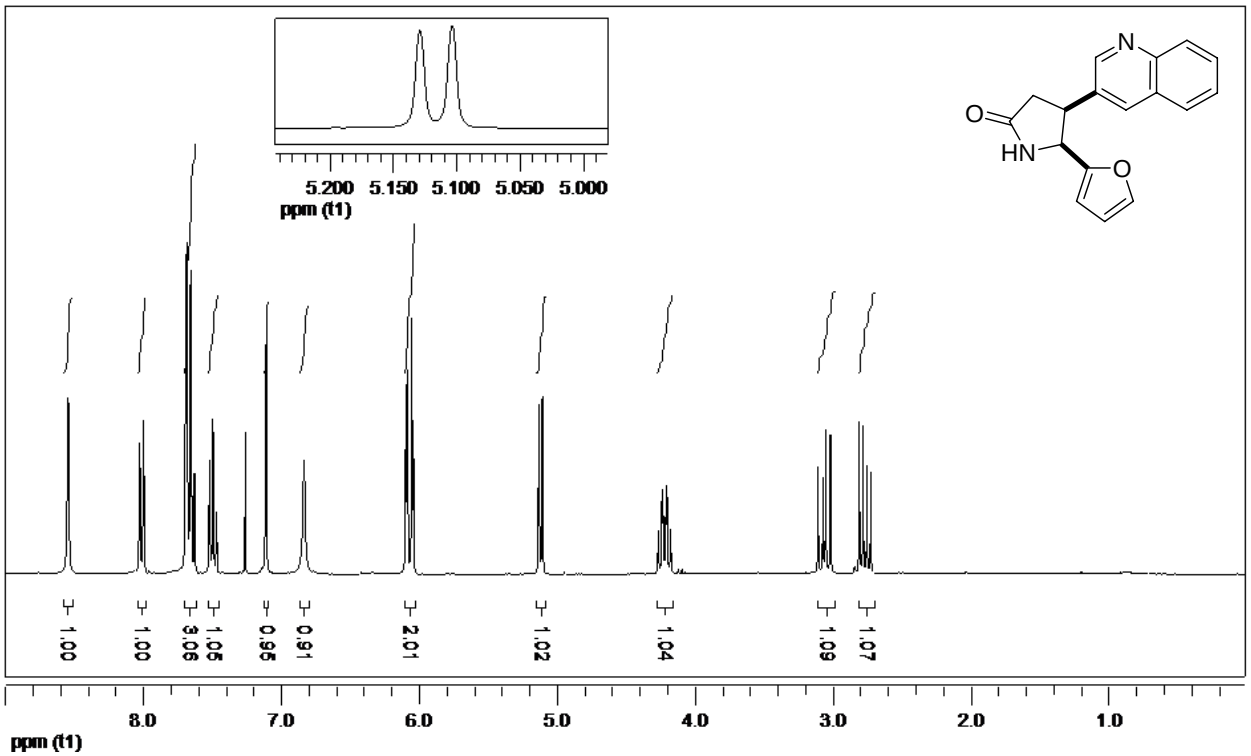


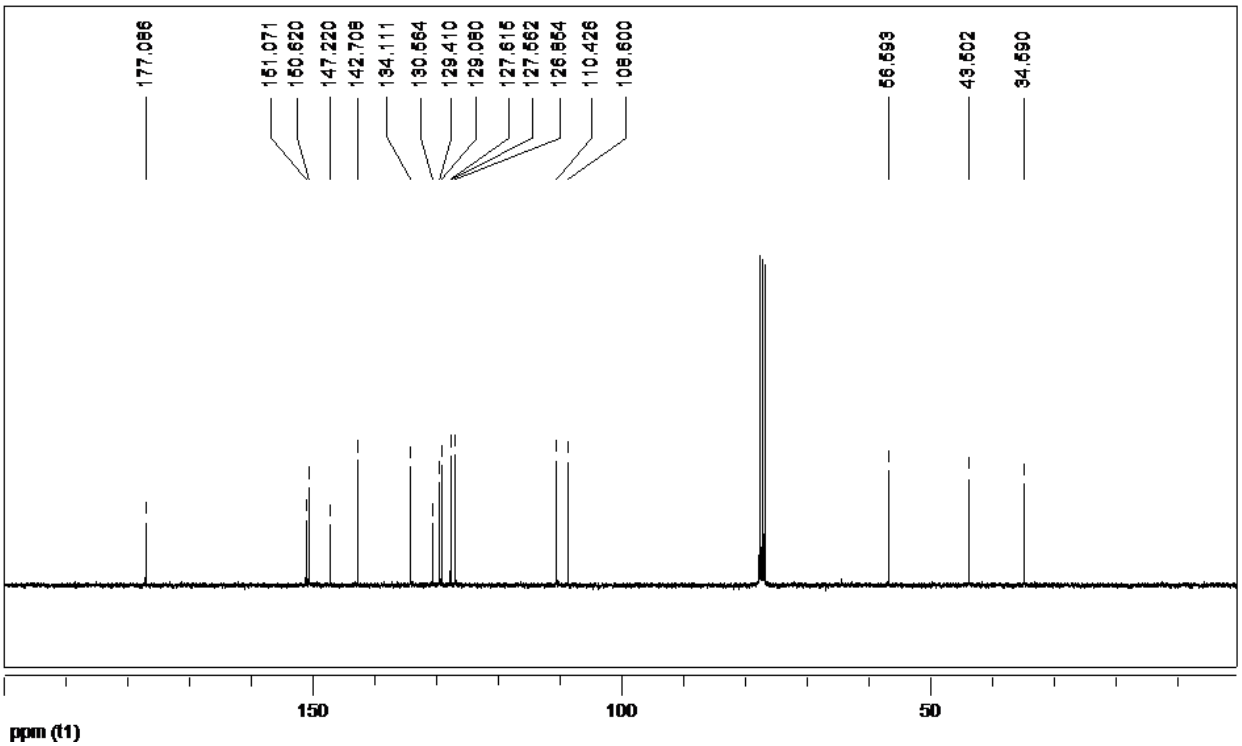
Compound **10x**



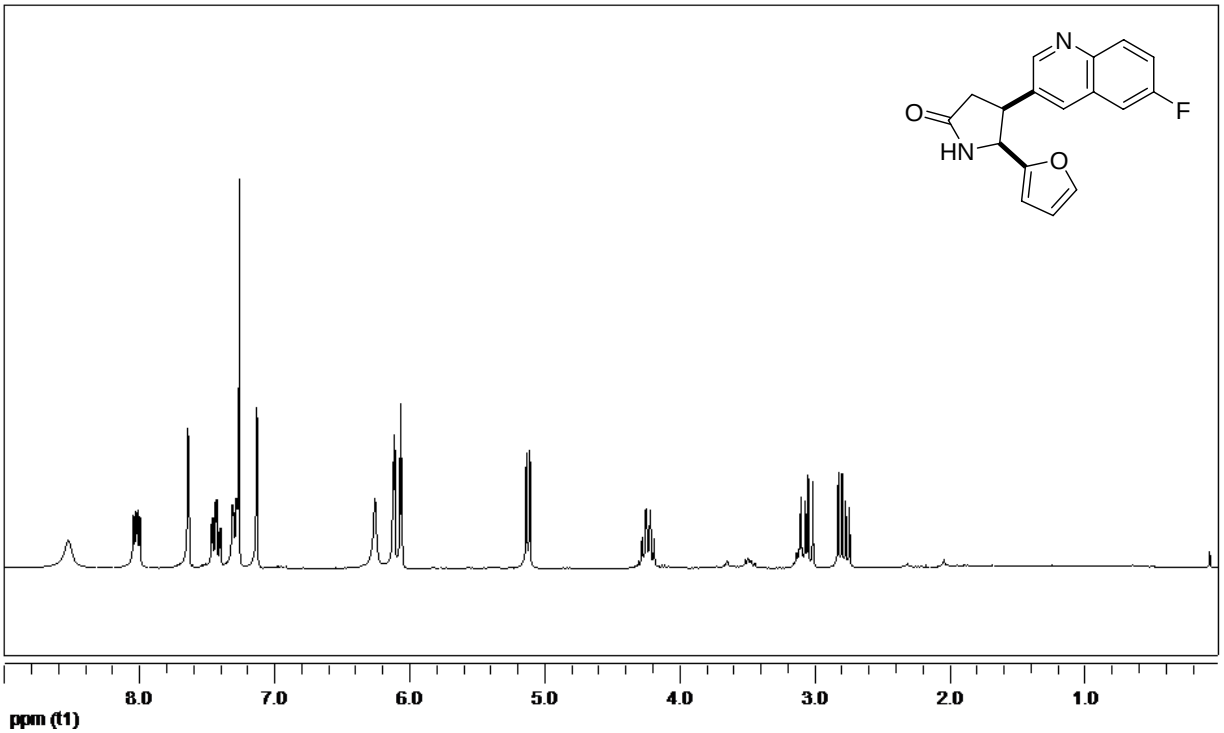


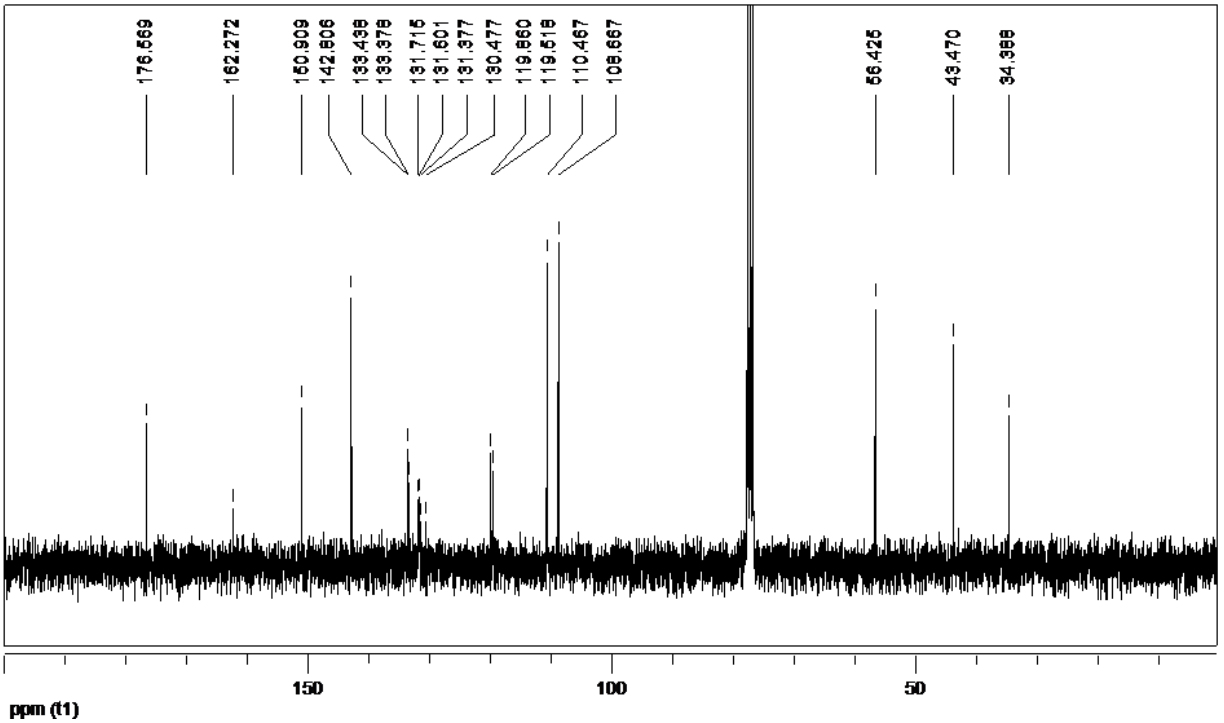
Compound **38a**

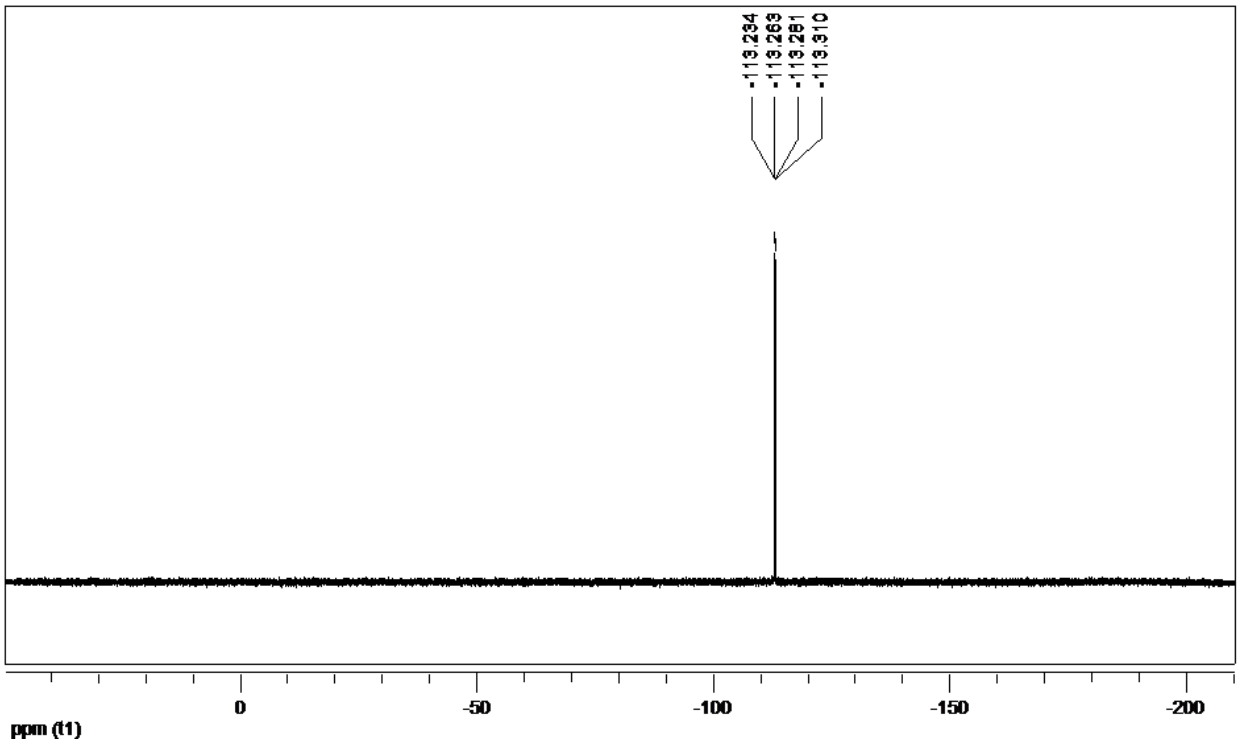




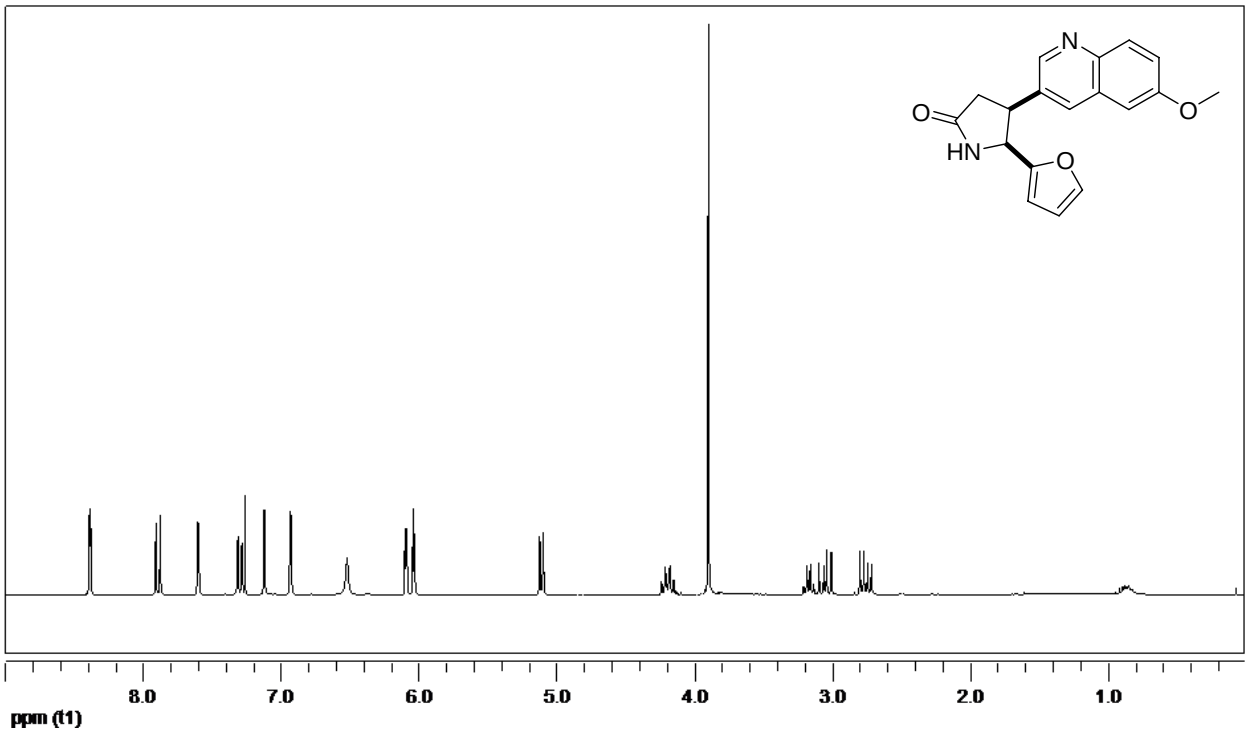
Compound **38b**

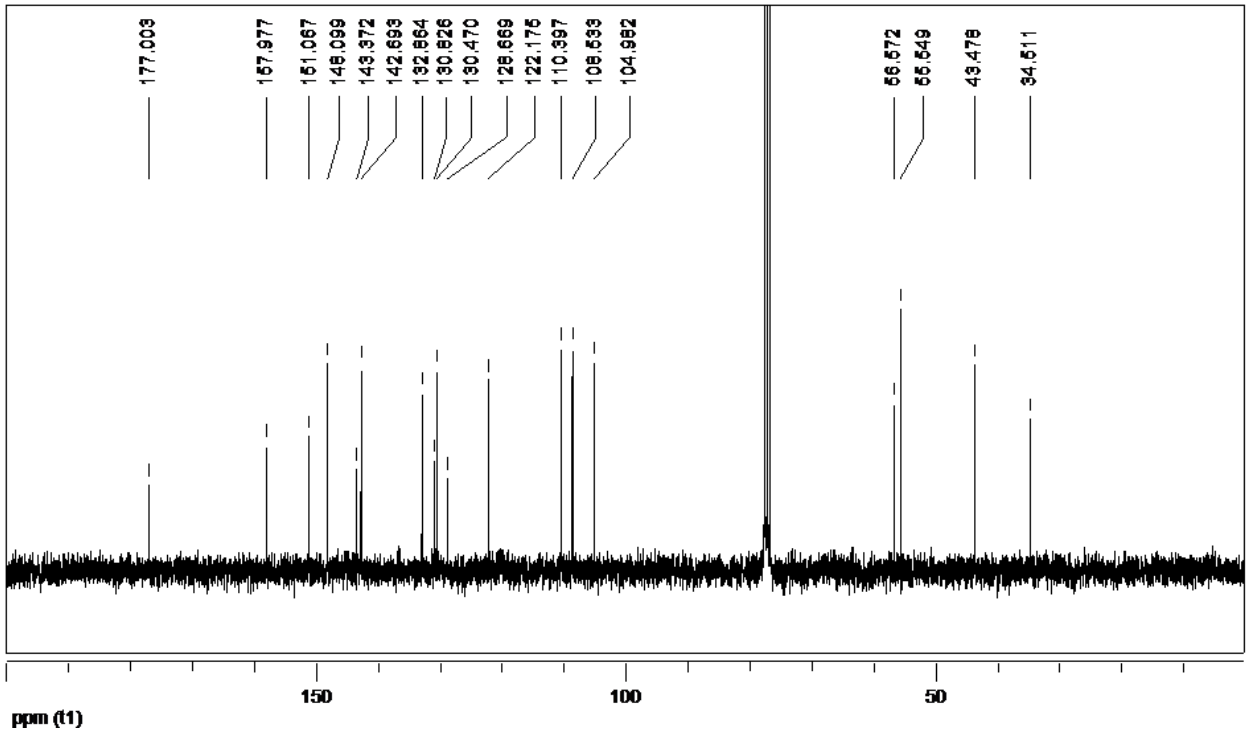




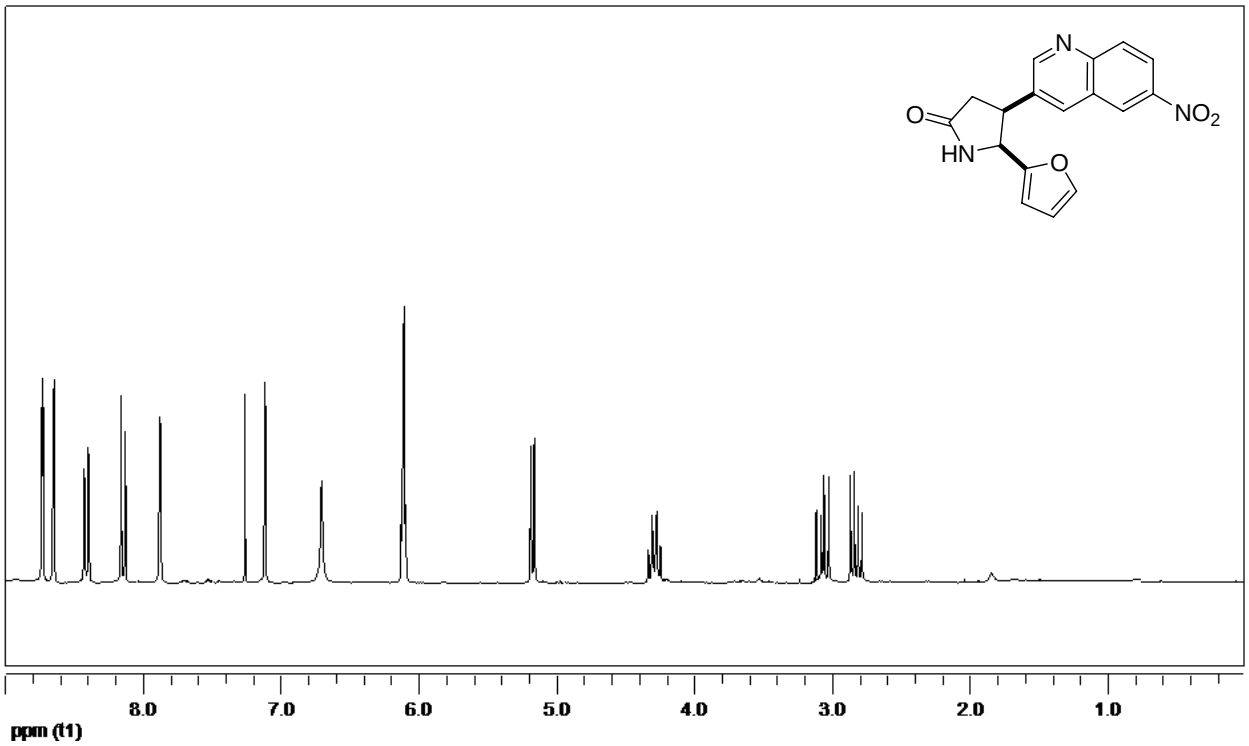

-113.294
-113.269
-113.261
-113.310
0
-50
-100
-150
-200
ppm (t1)

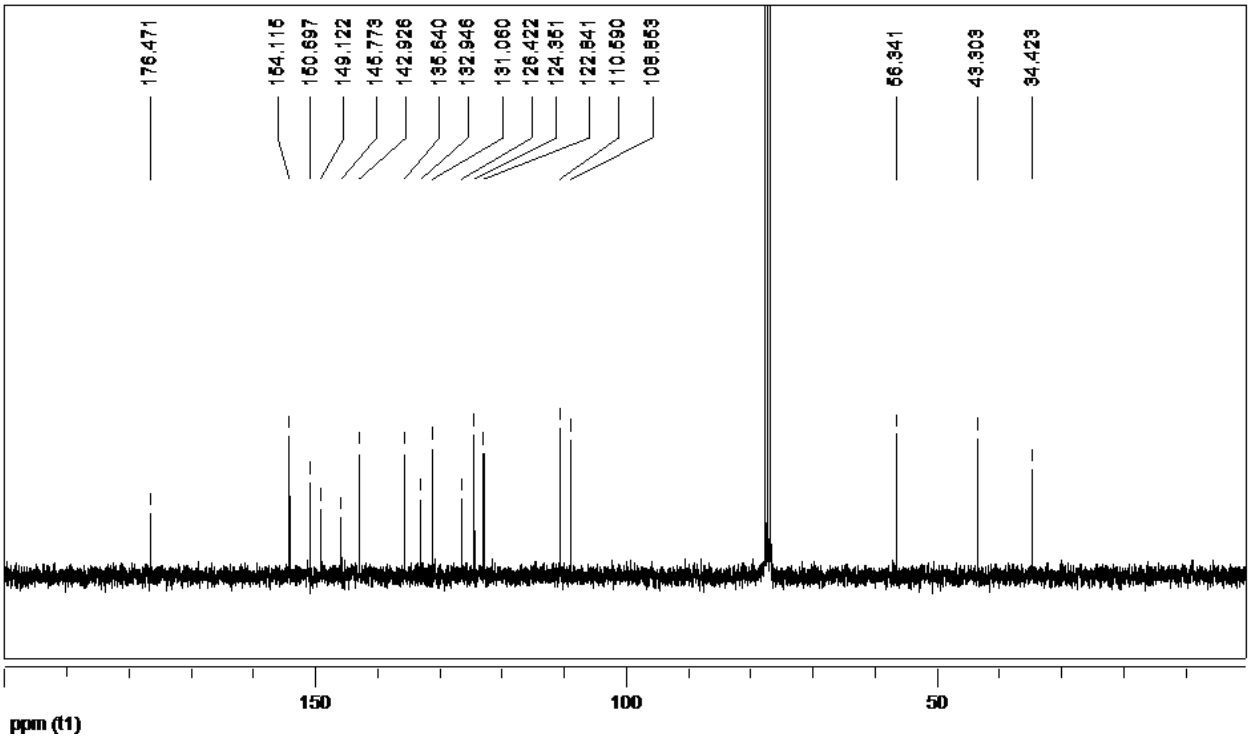
Compound **38c**



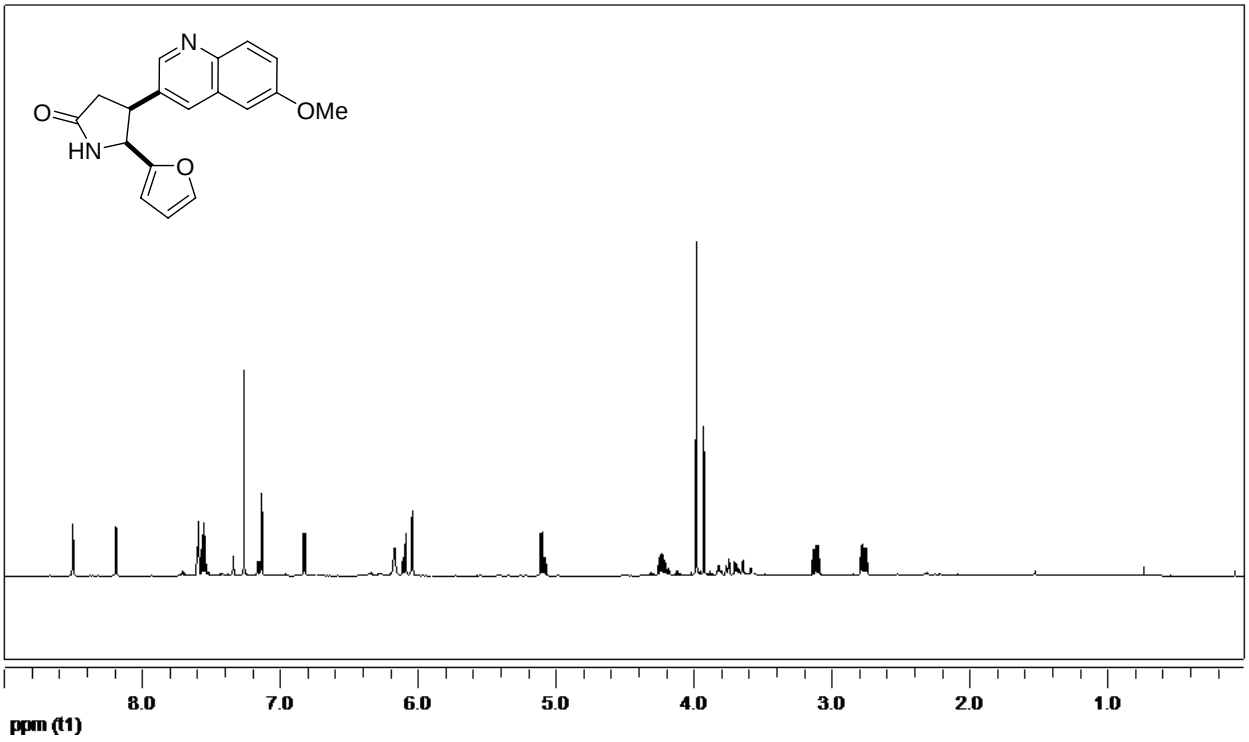


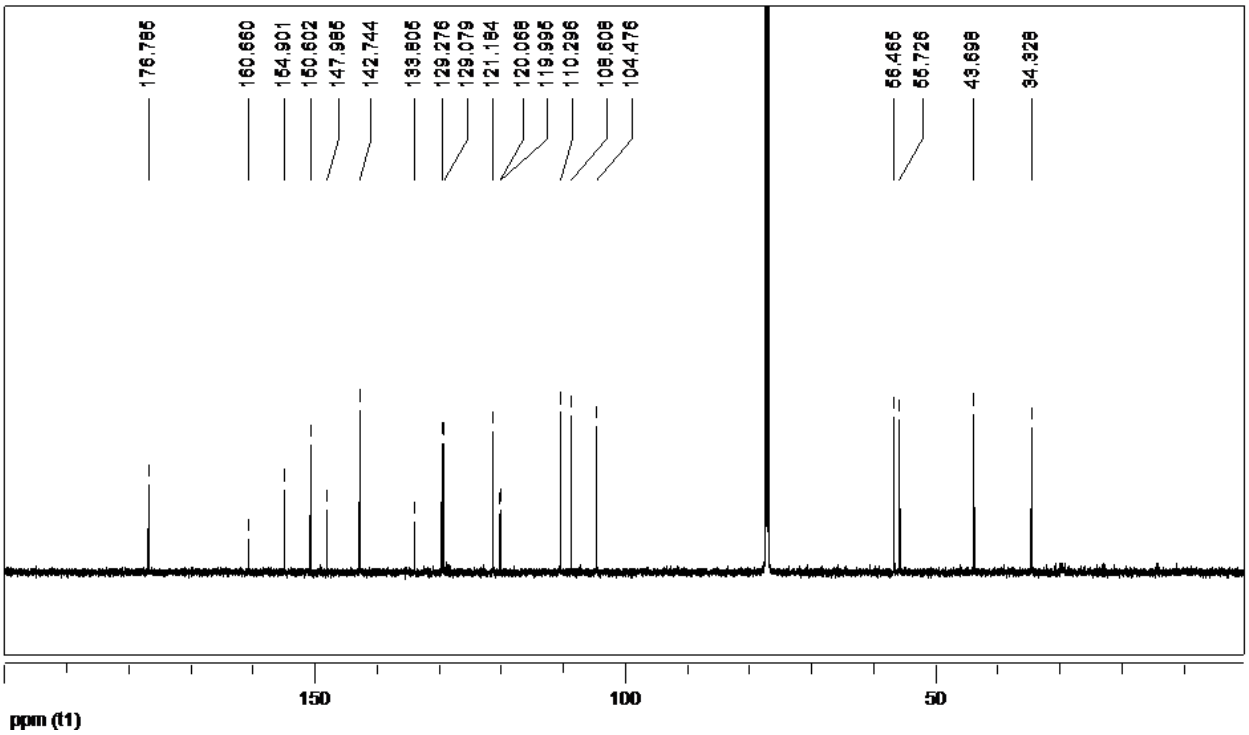
Compound **38d**



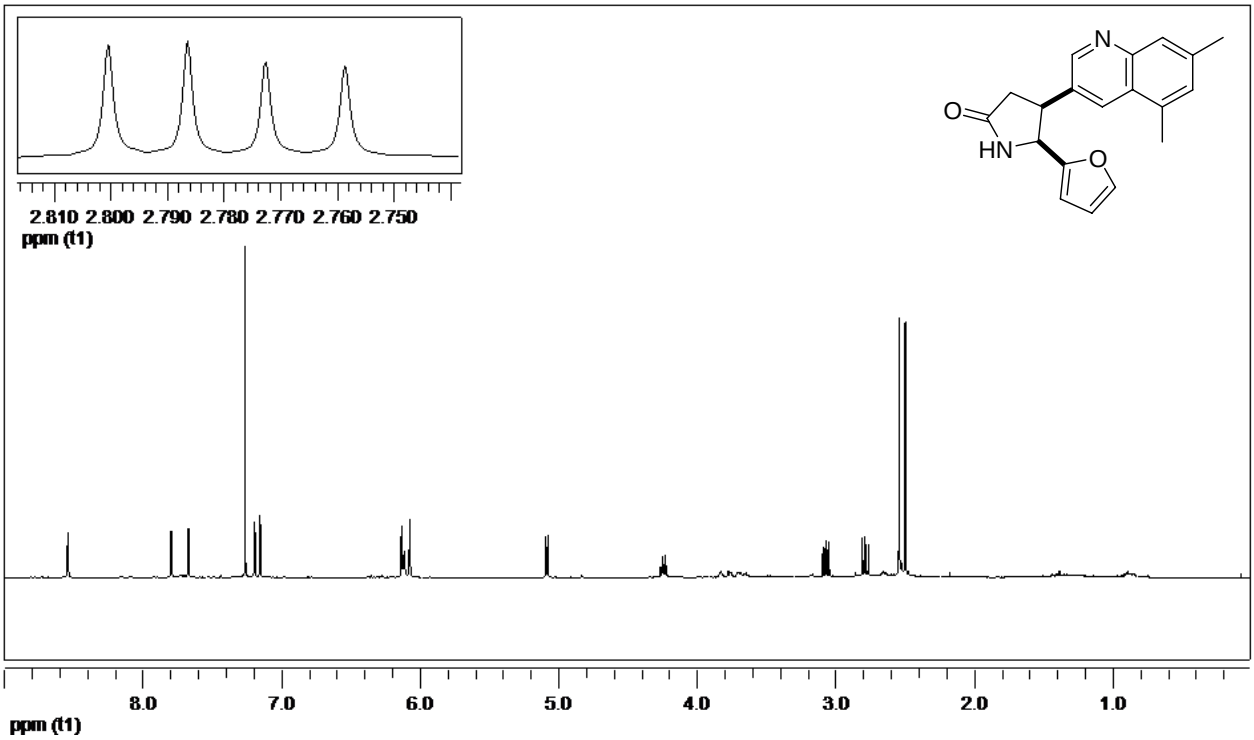


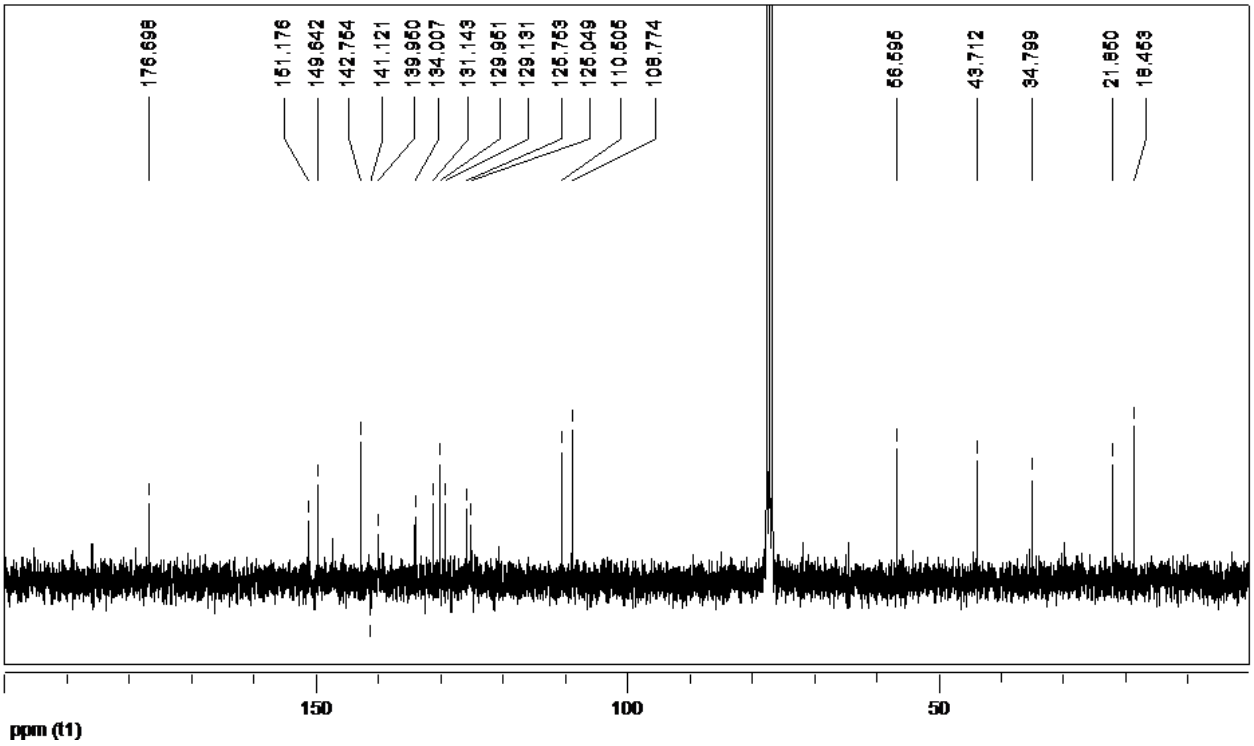
Compound **38e**



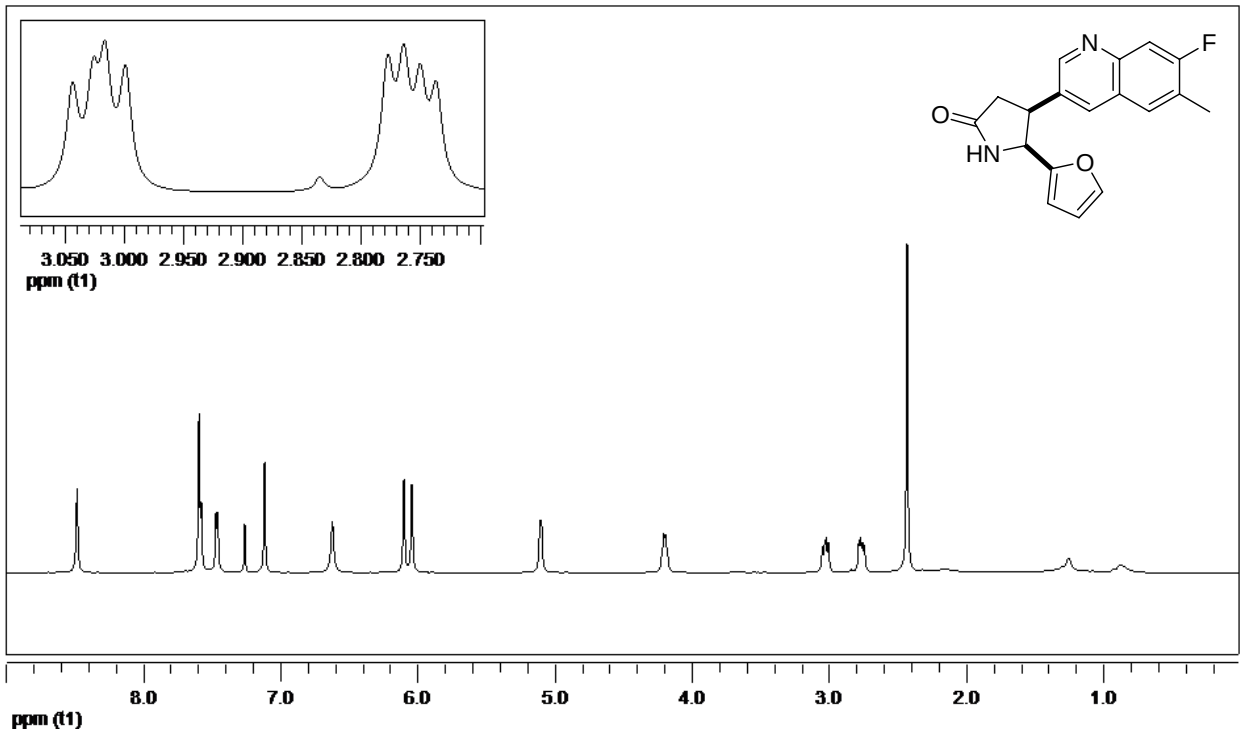


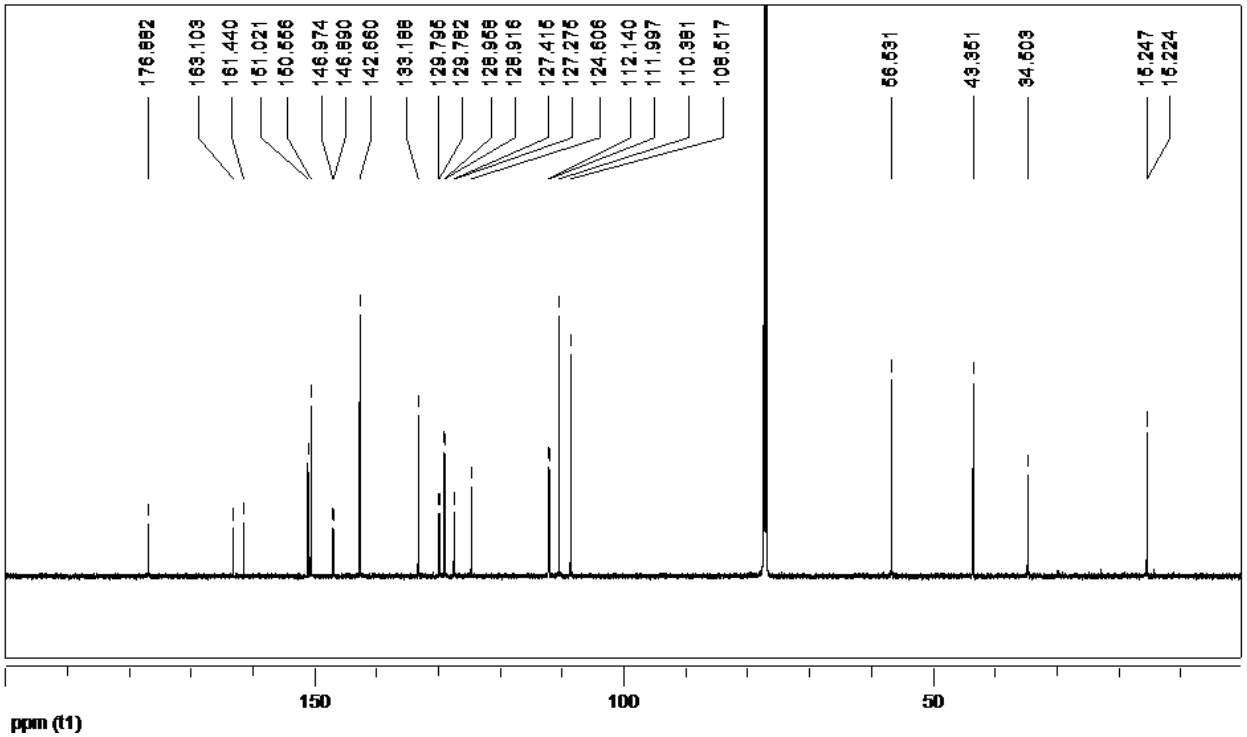
Compound **38f**



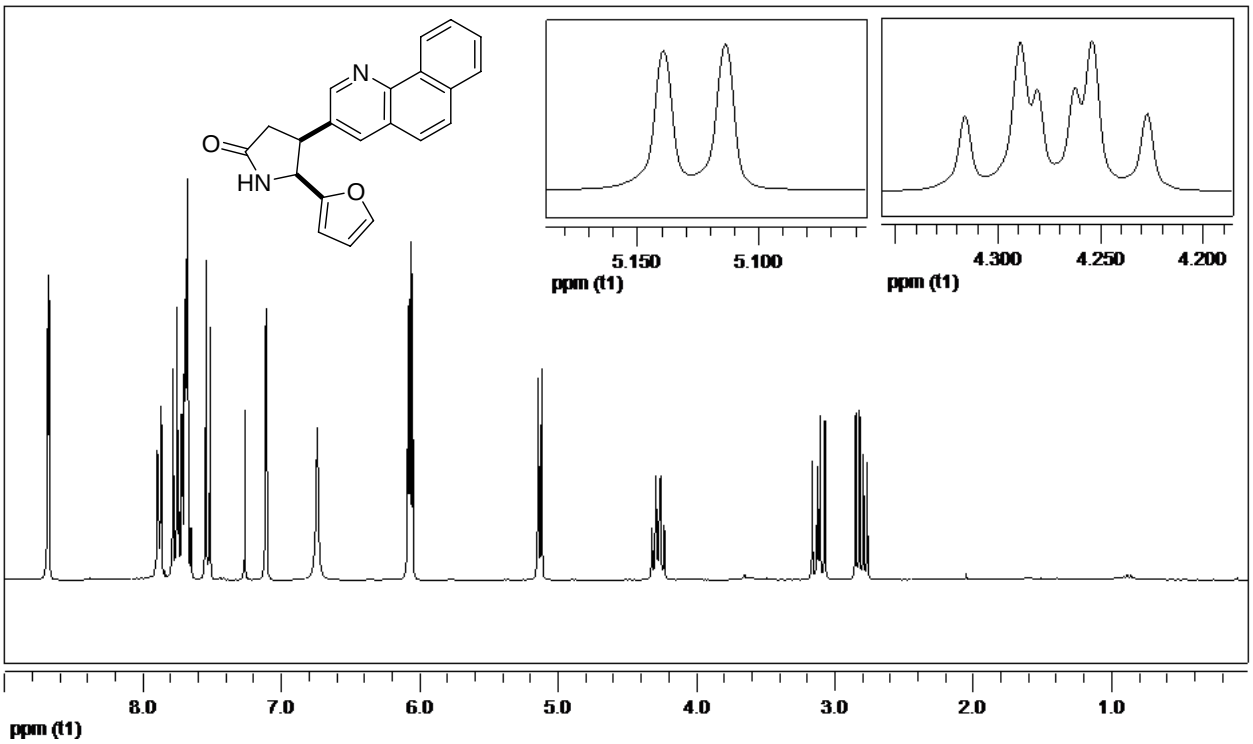


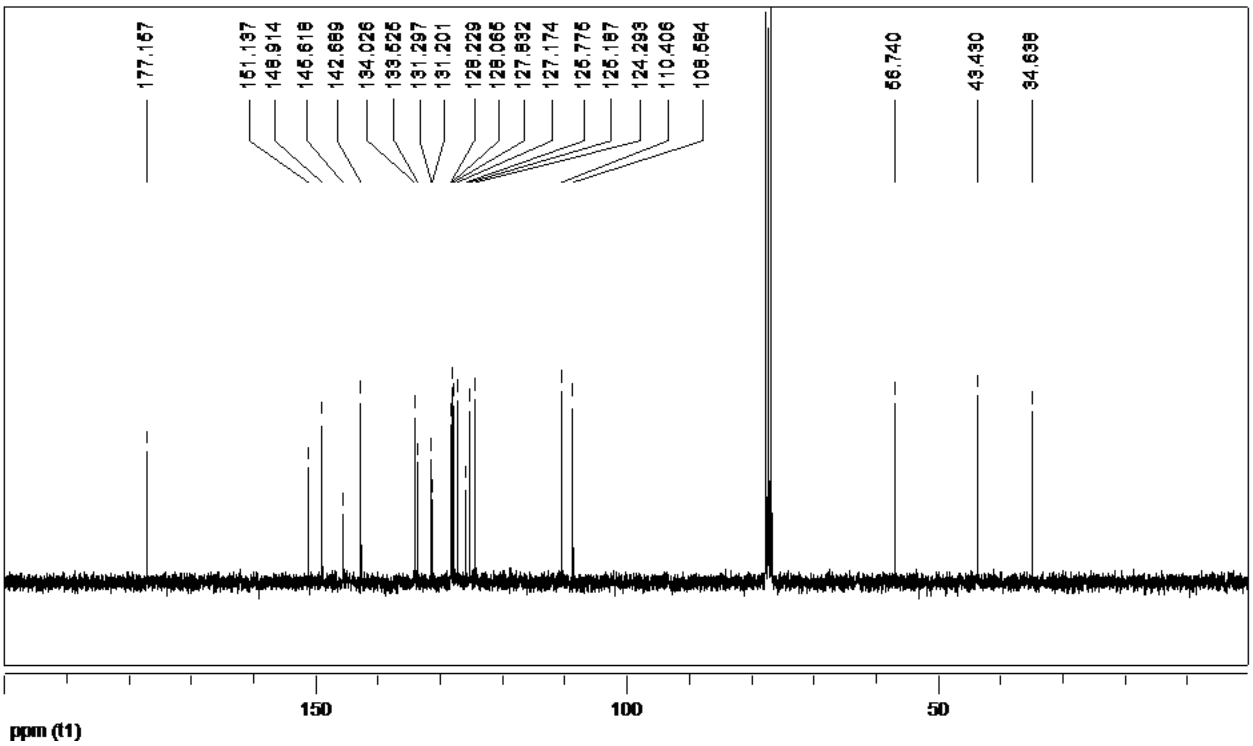
Compound **38g**



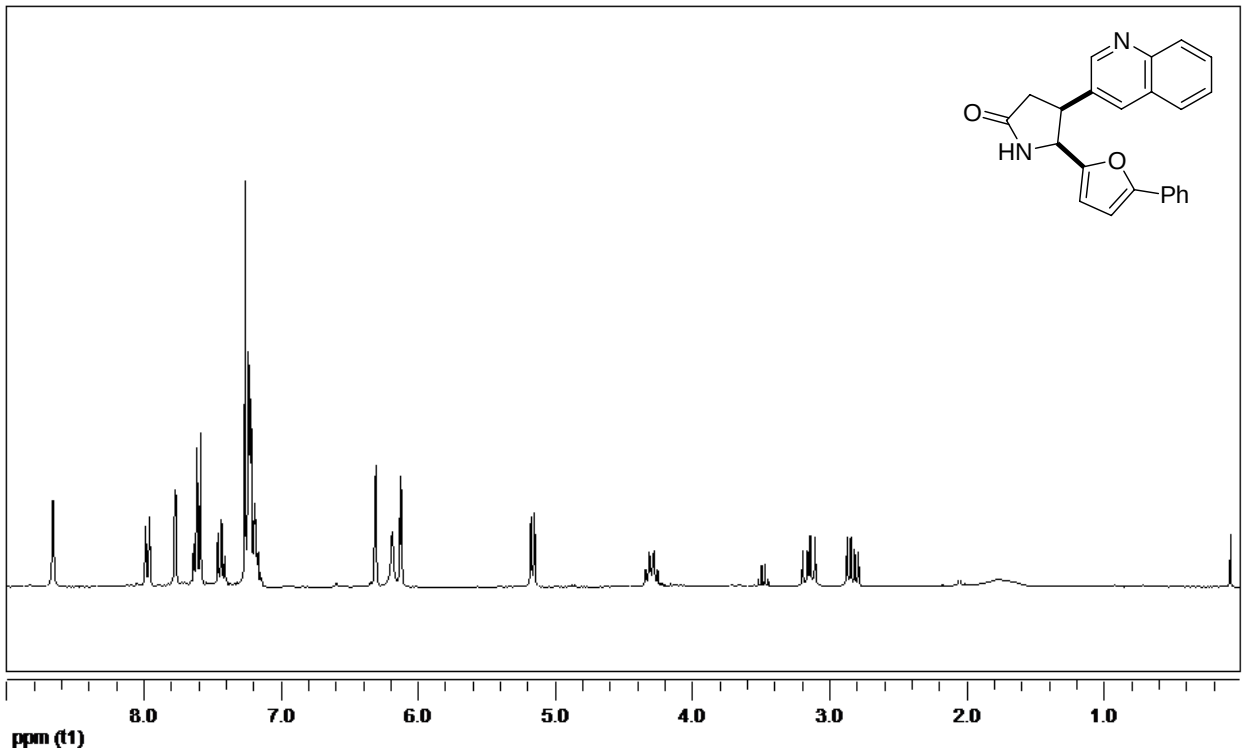


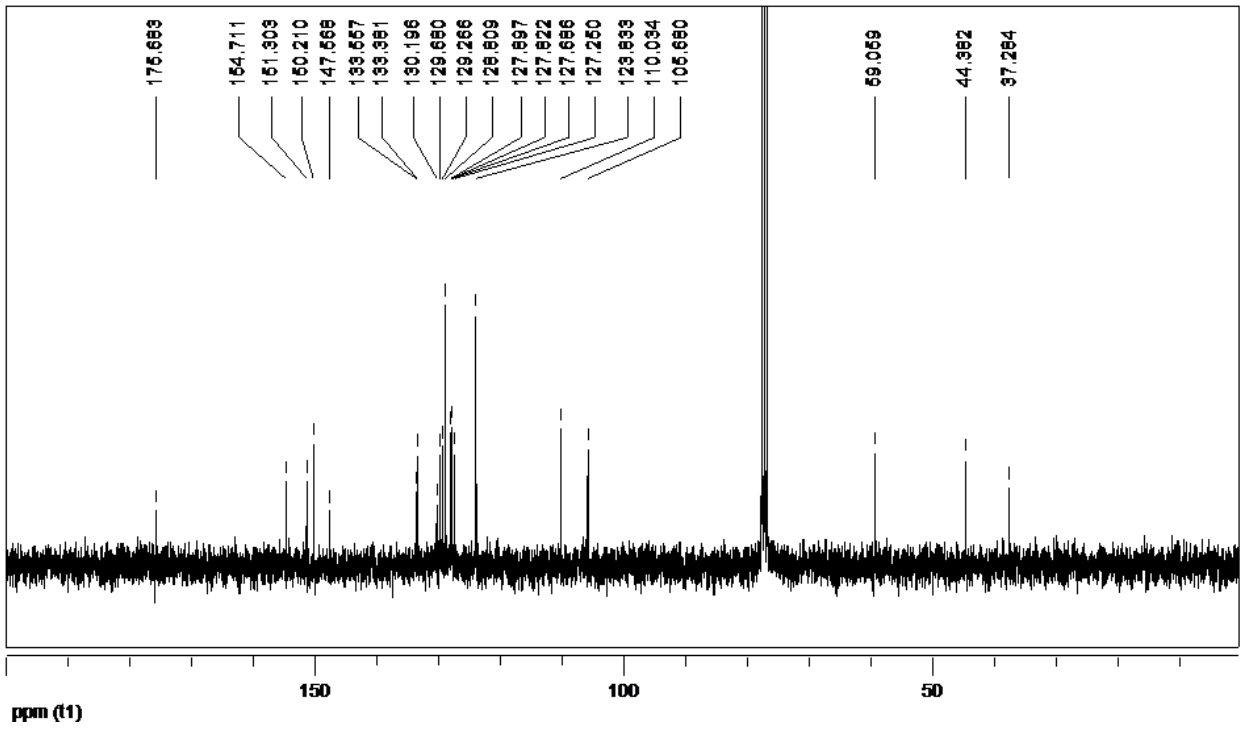
Compound **38h**



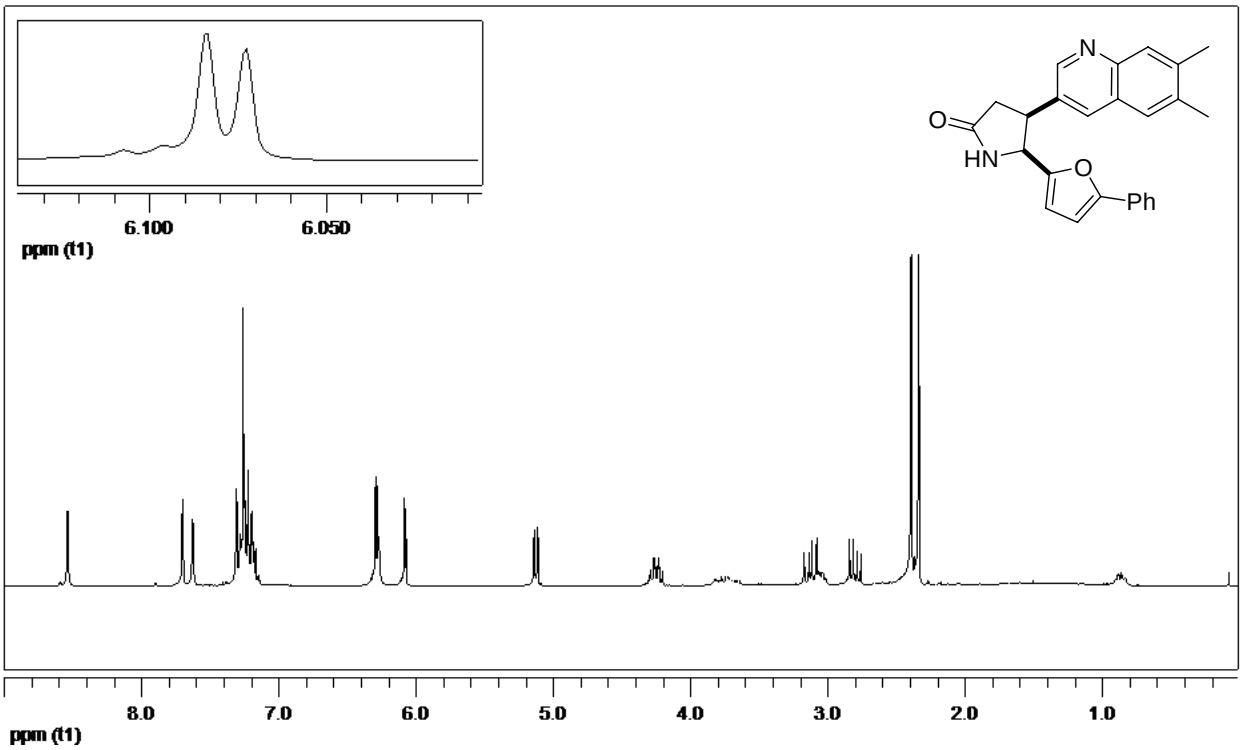


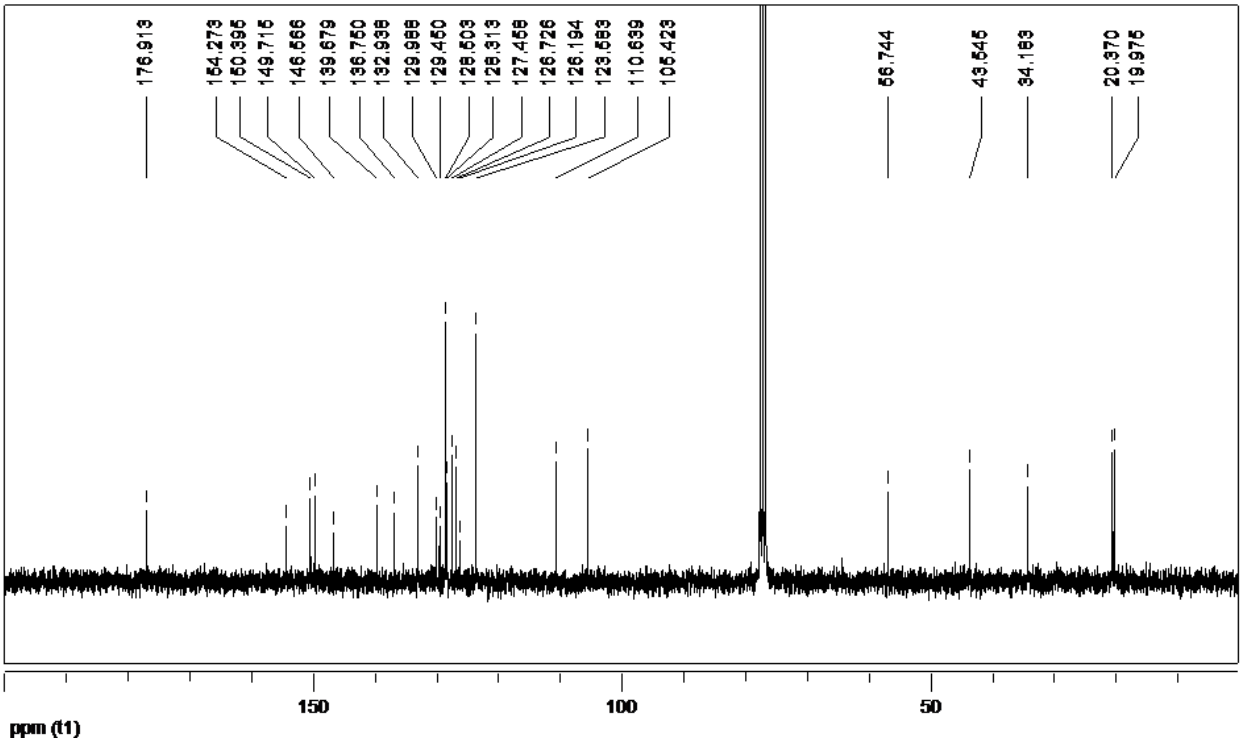
Compound **38i**



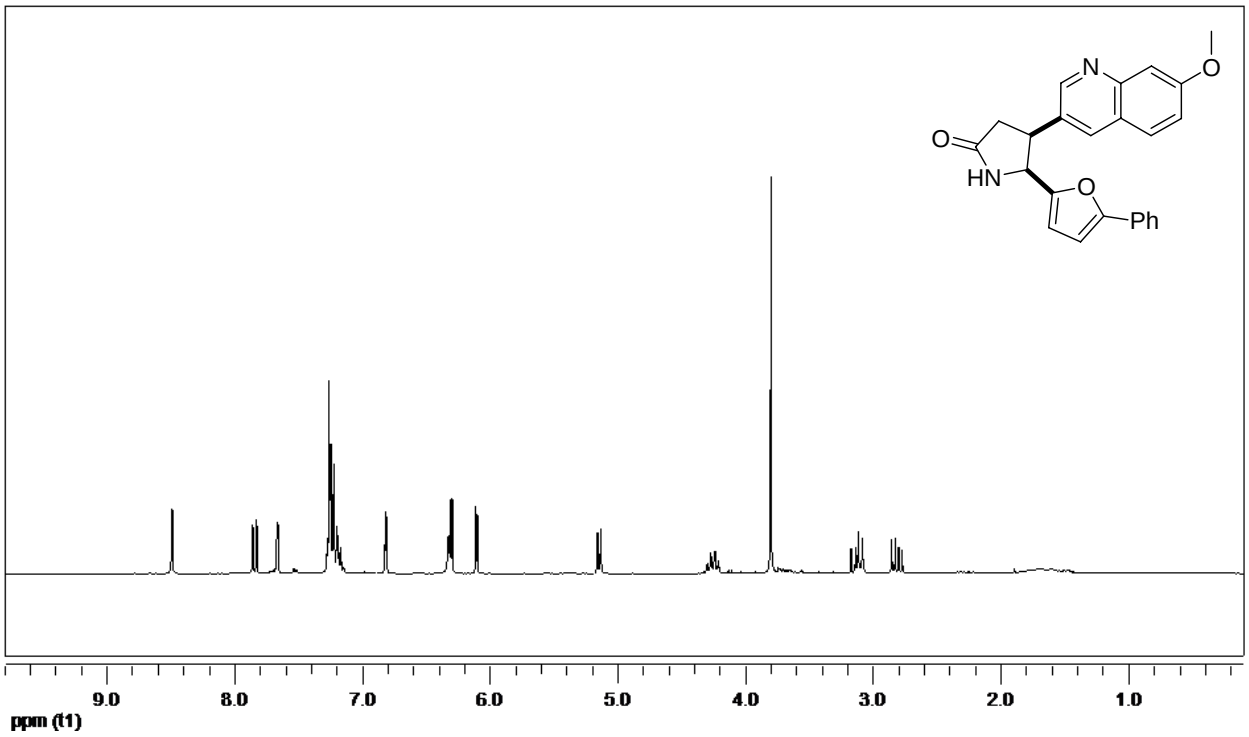


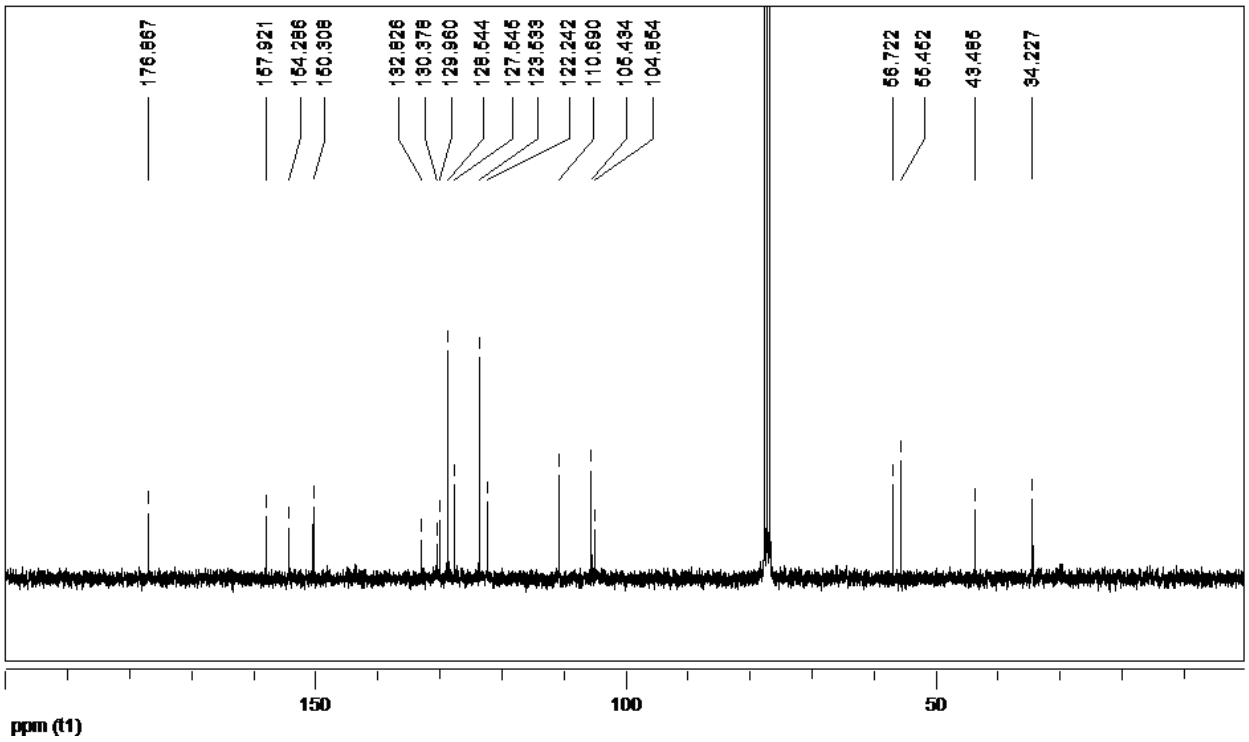
Compound **38j**



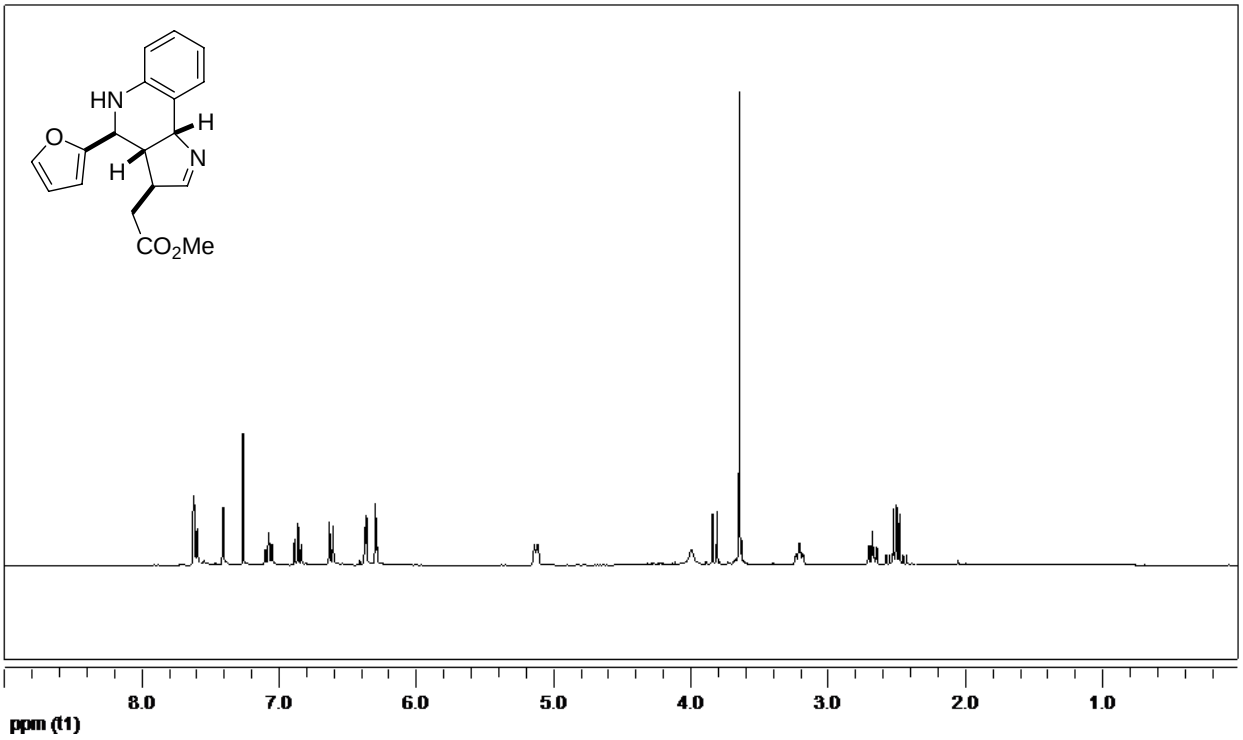


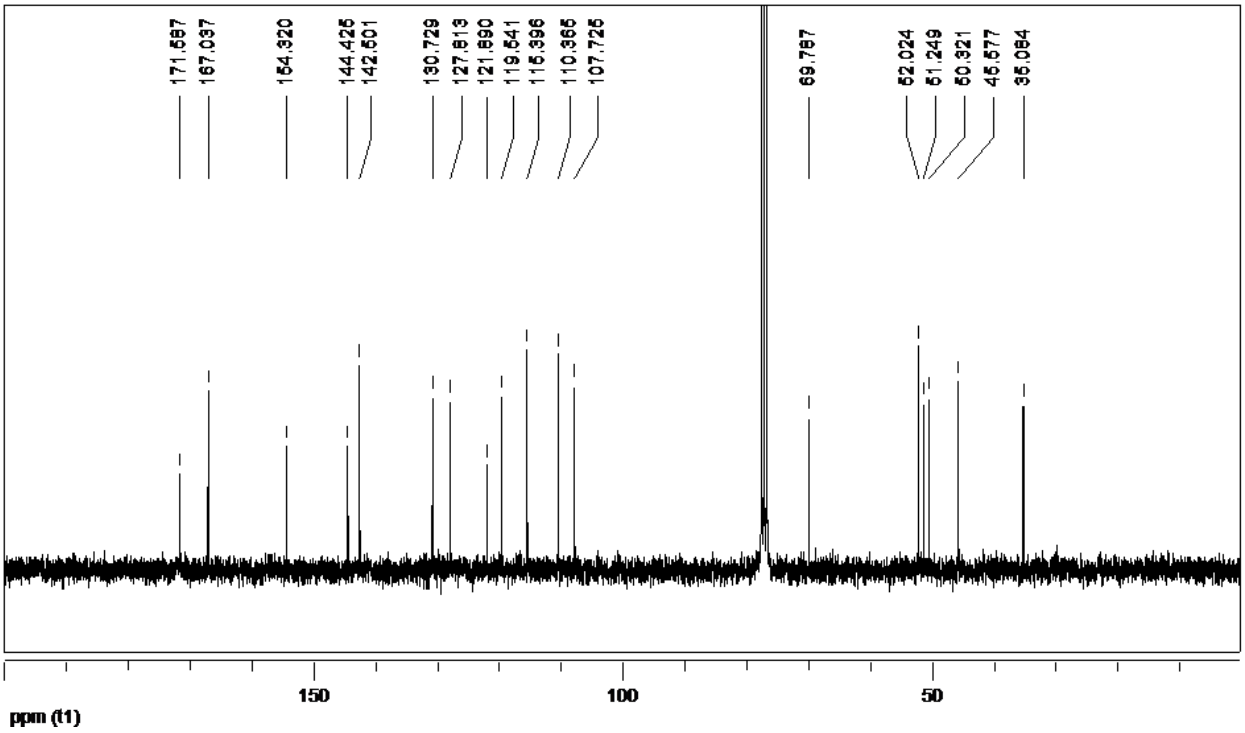
Compound **38k**



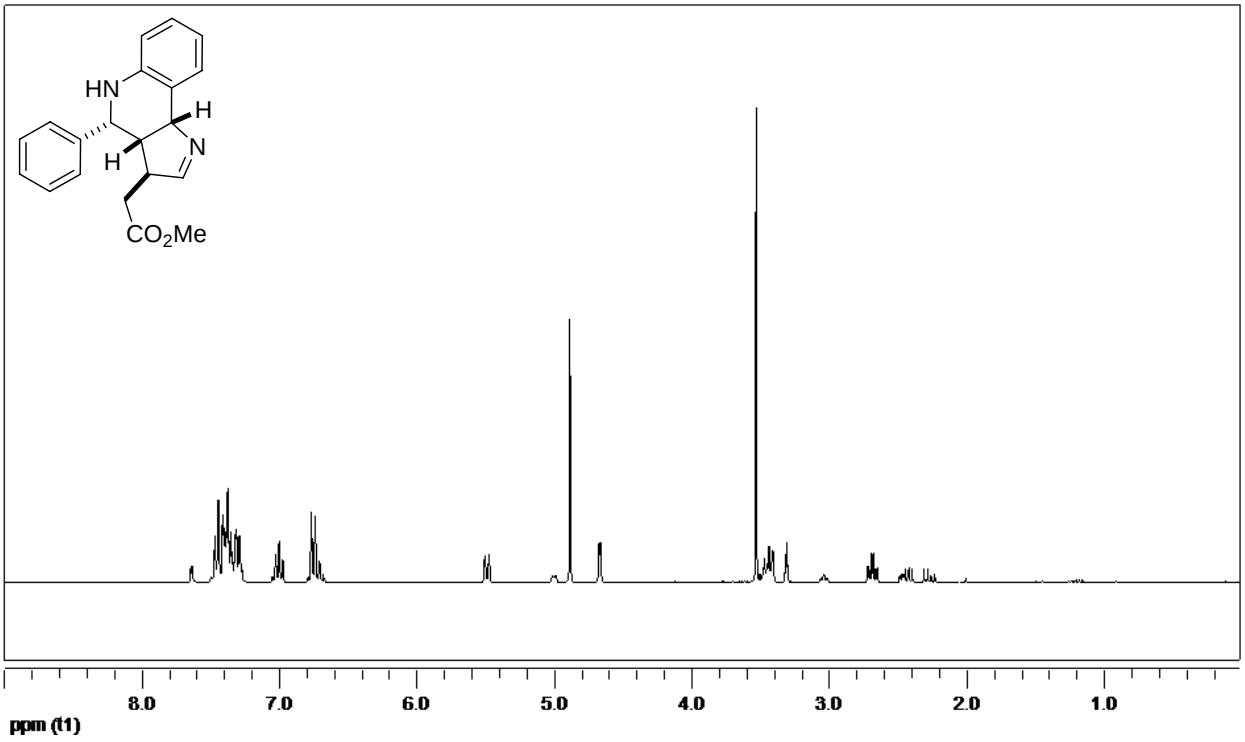


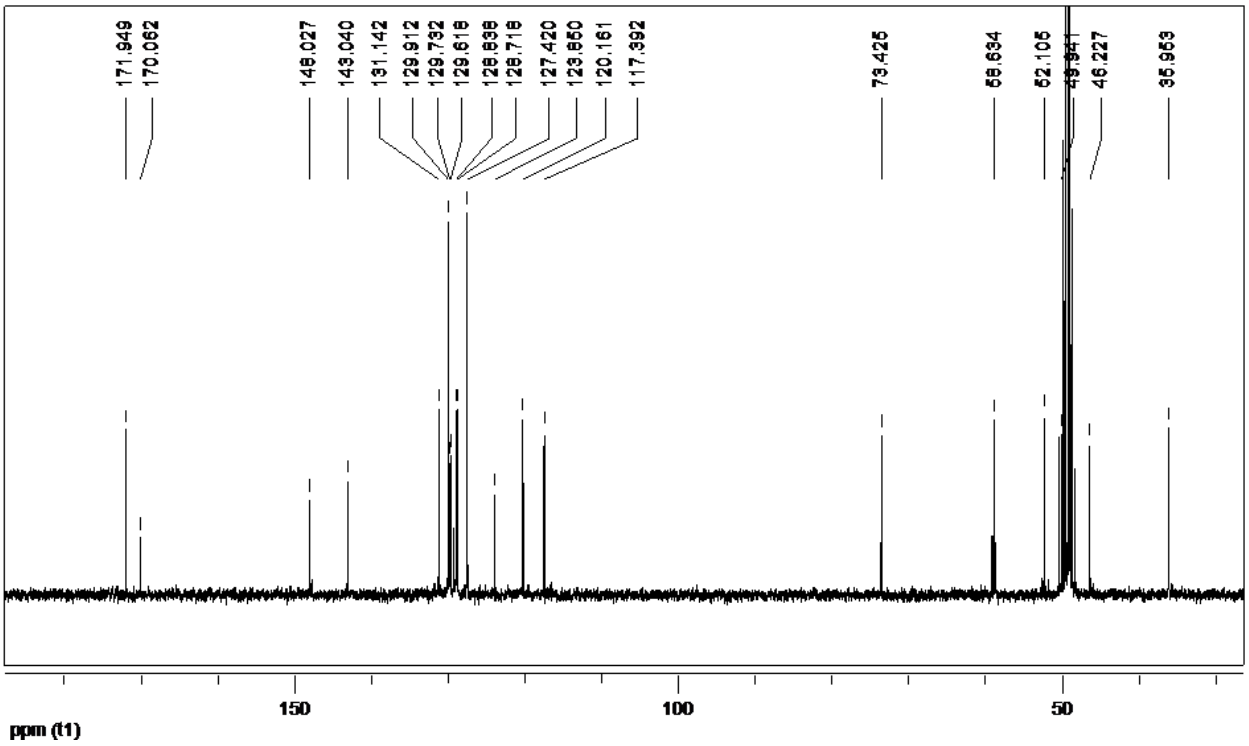
Compound **11n**



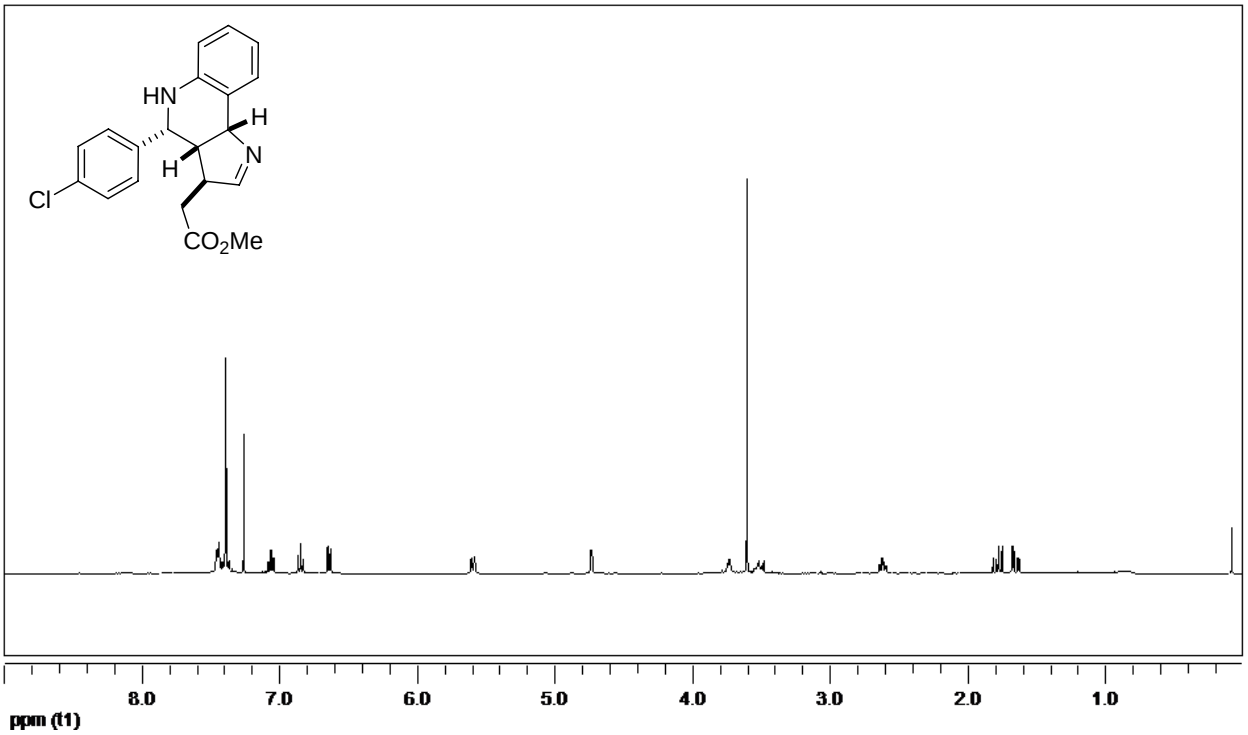


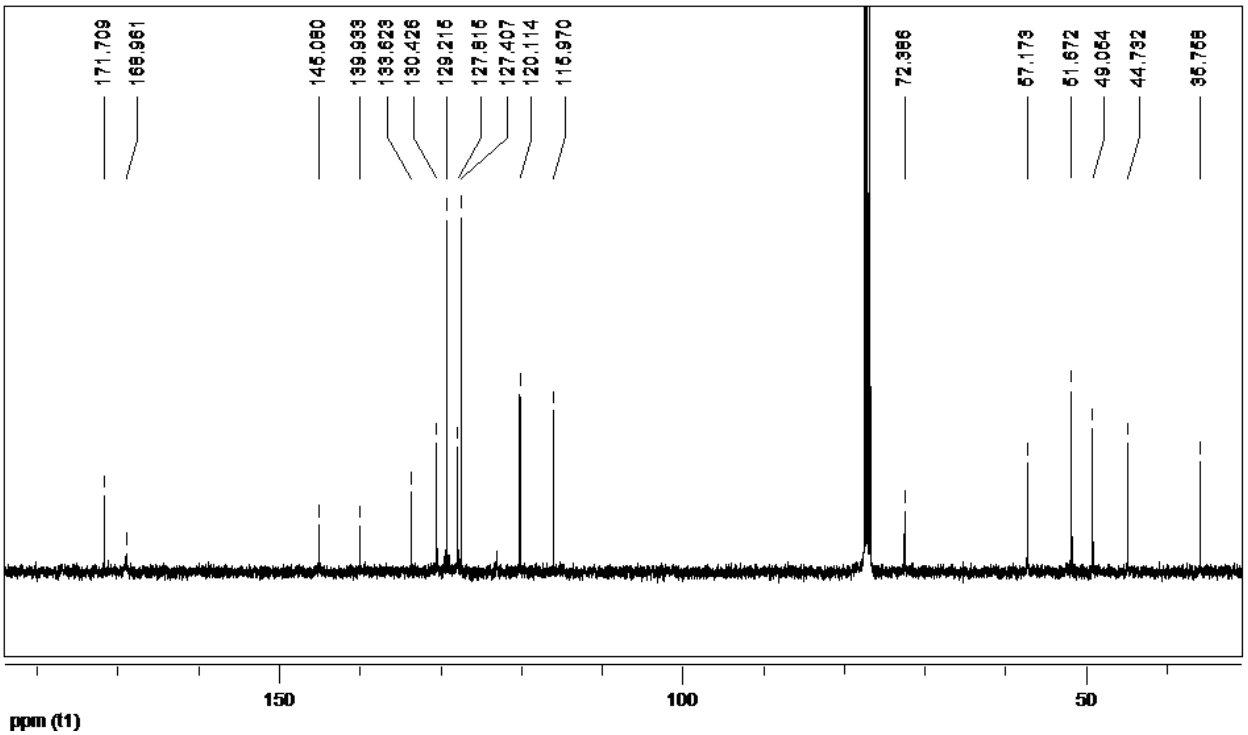
Compound **43a** (major diastereomer)



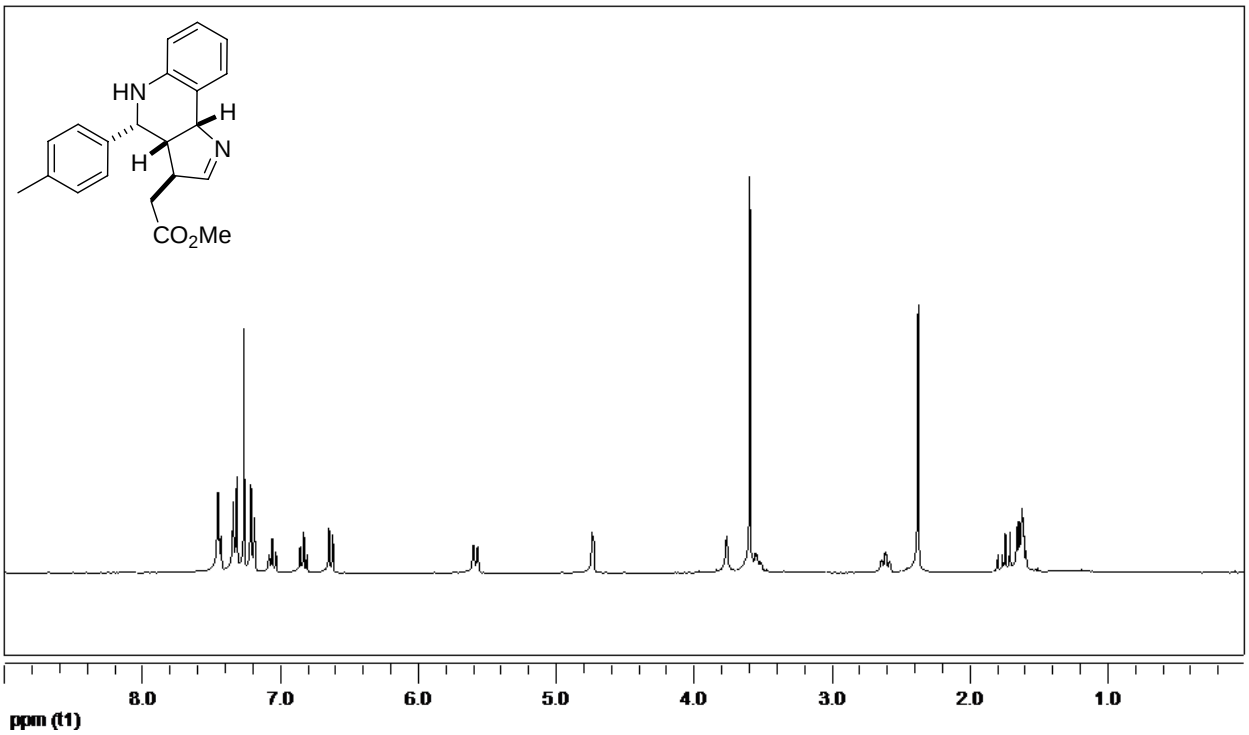


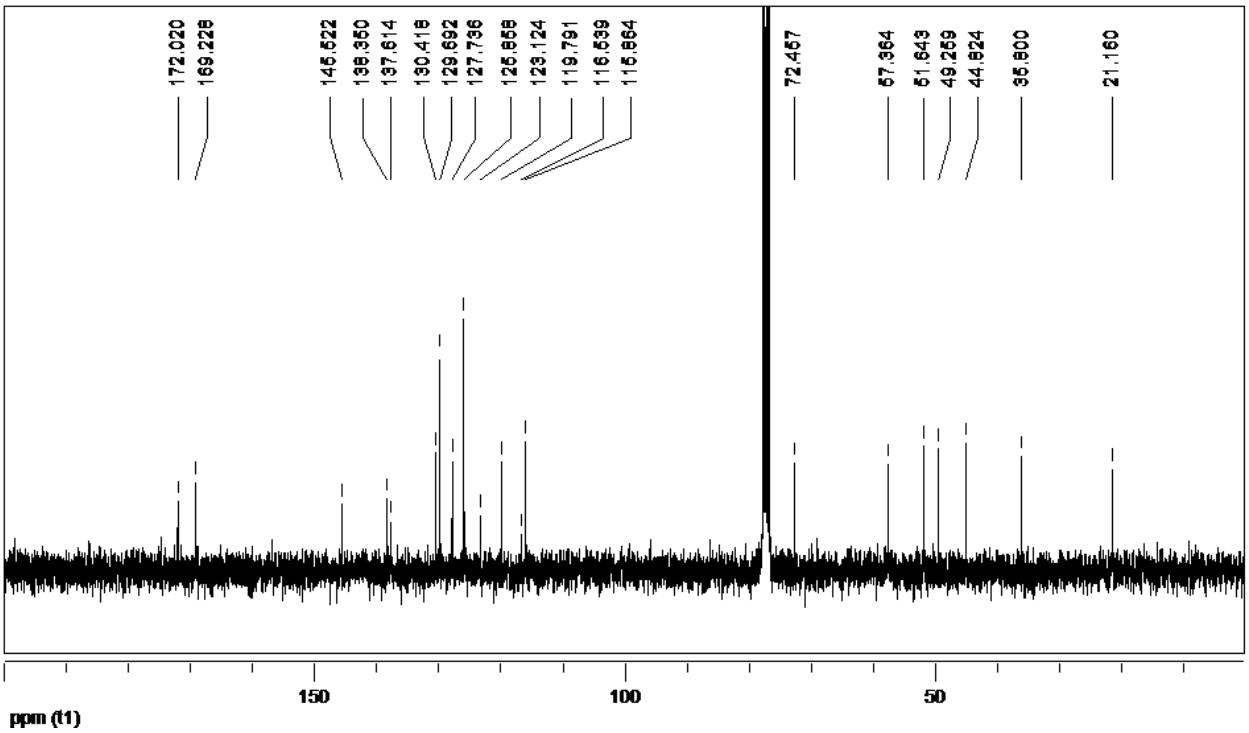
Compound **43b** (major diastereomer)



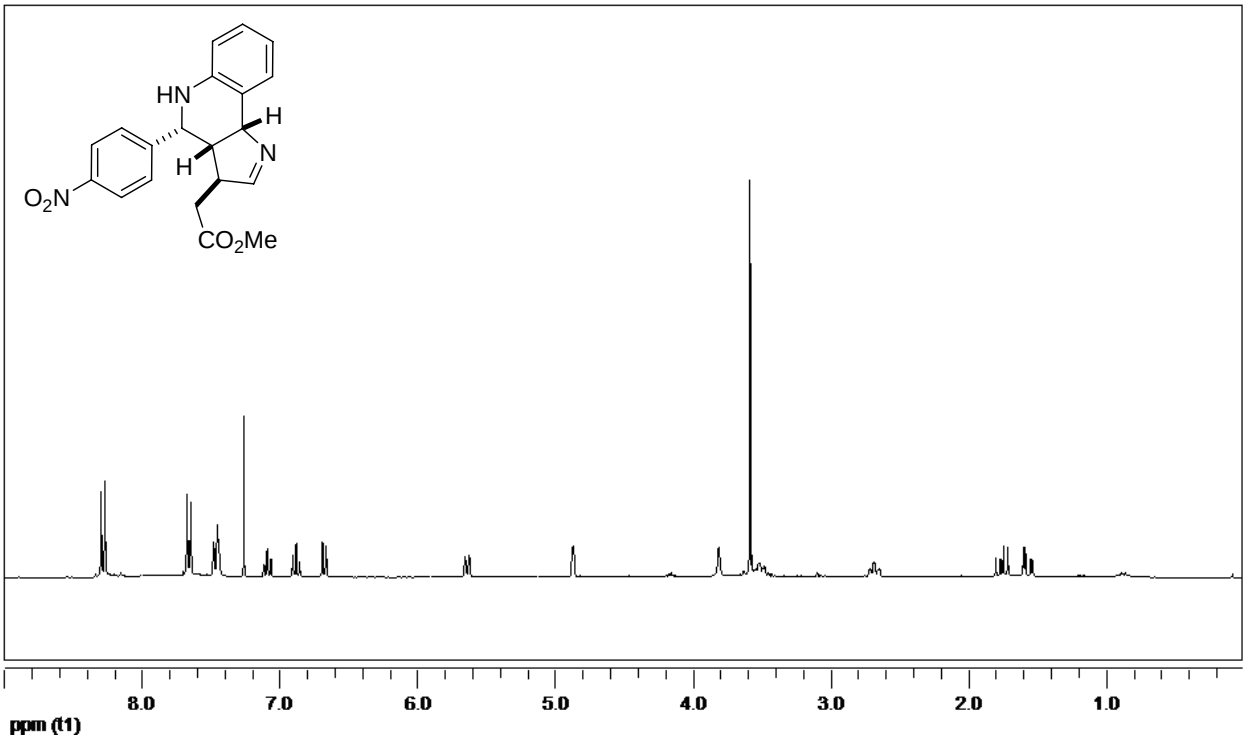


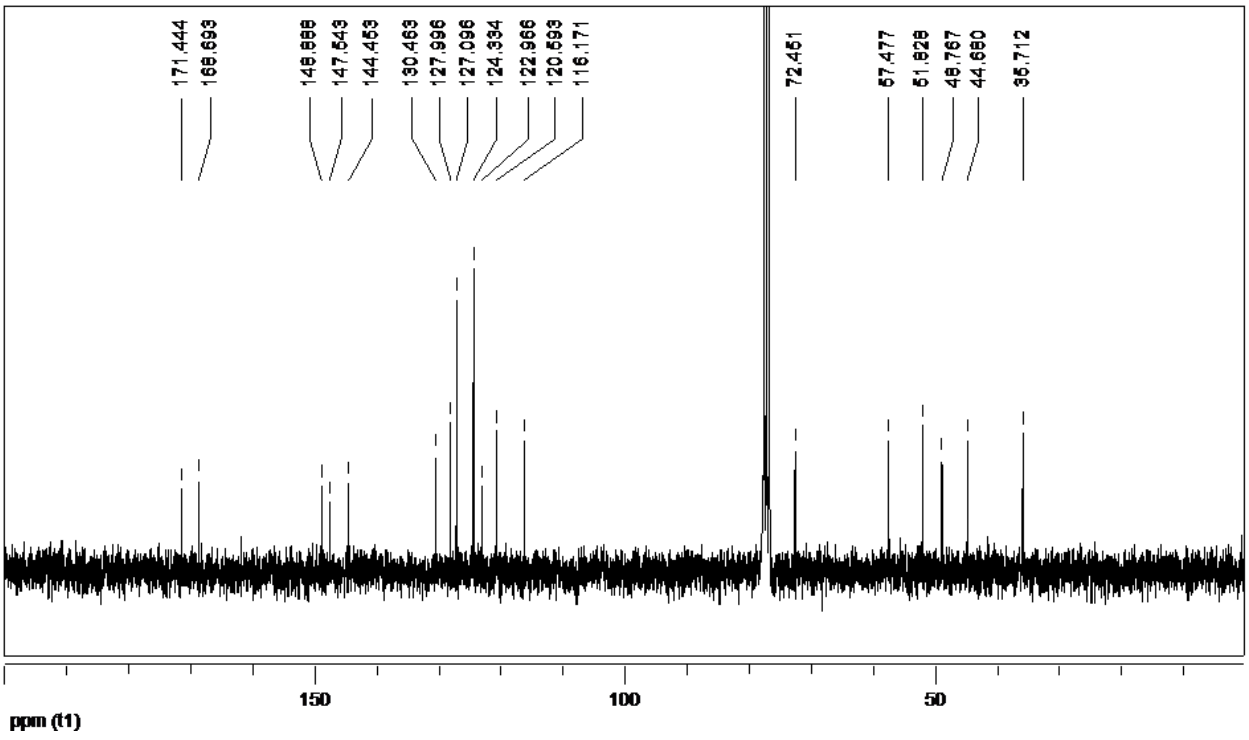
Compound **43c** (major diastereomer)



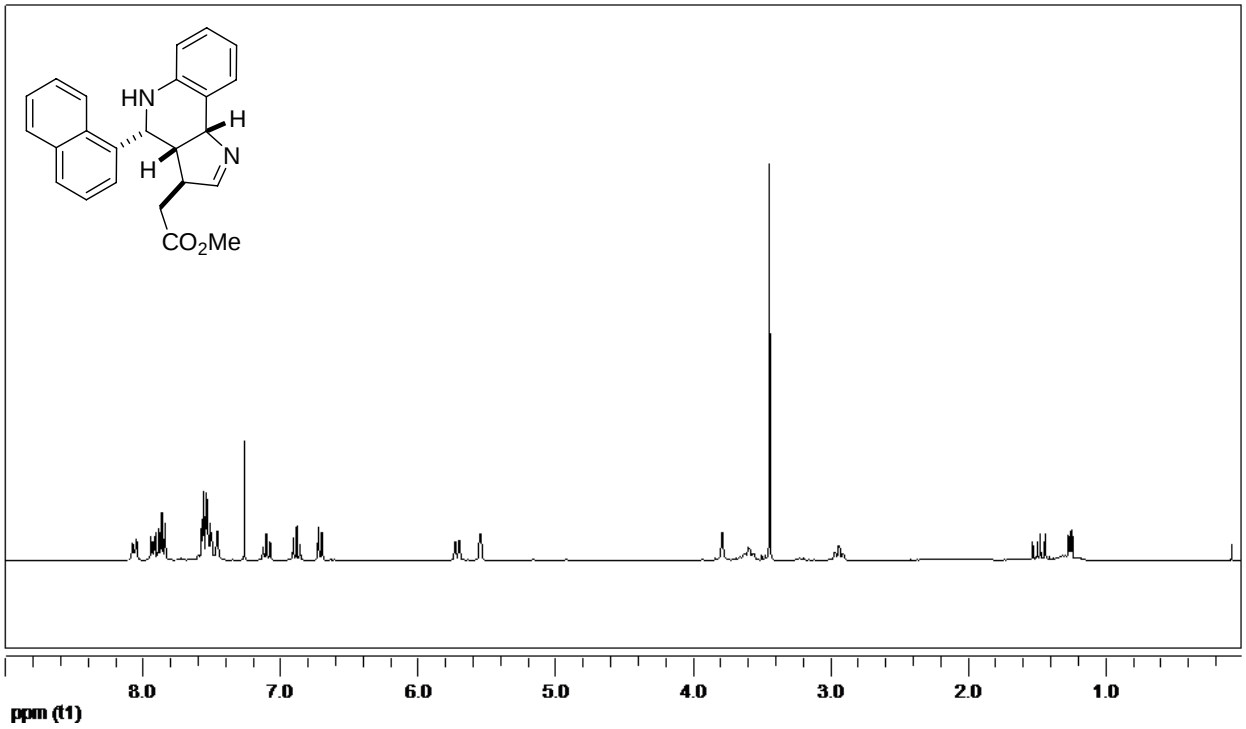


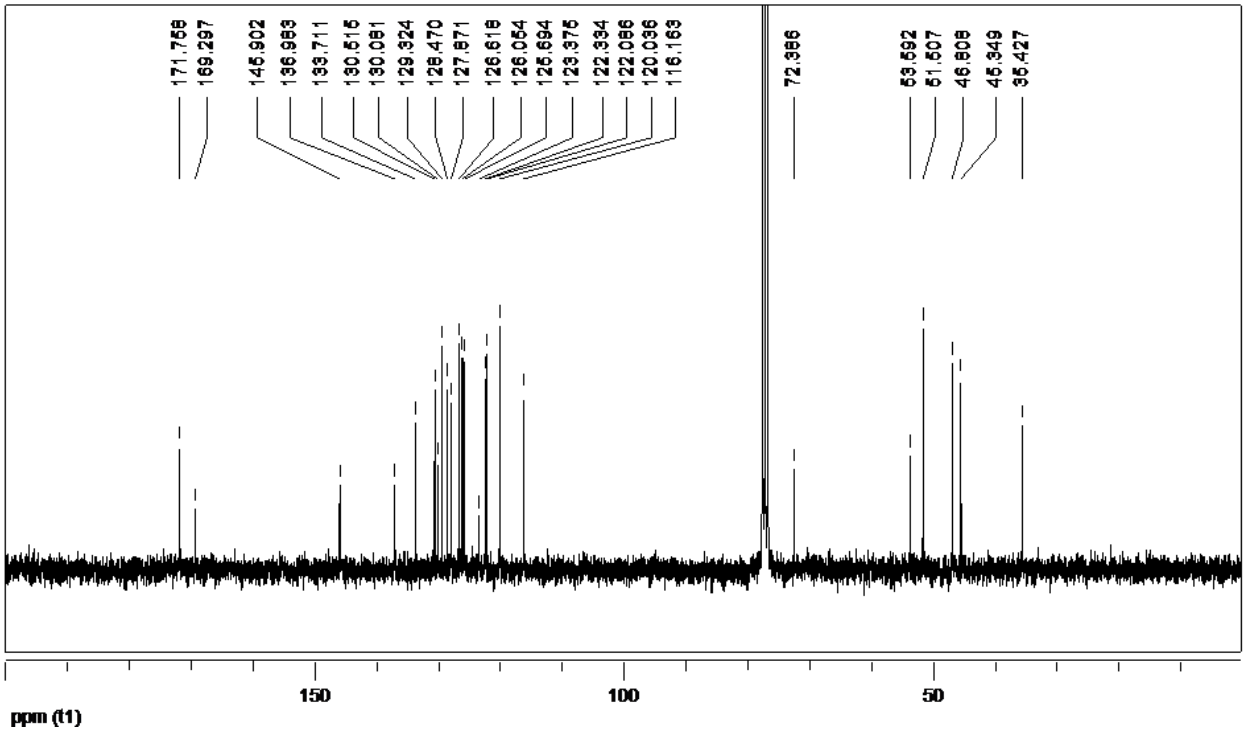
Compound **43e** (major diastereomer)



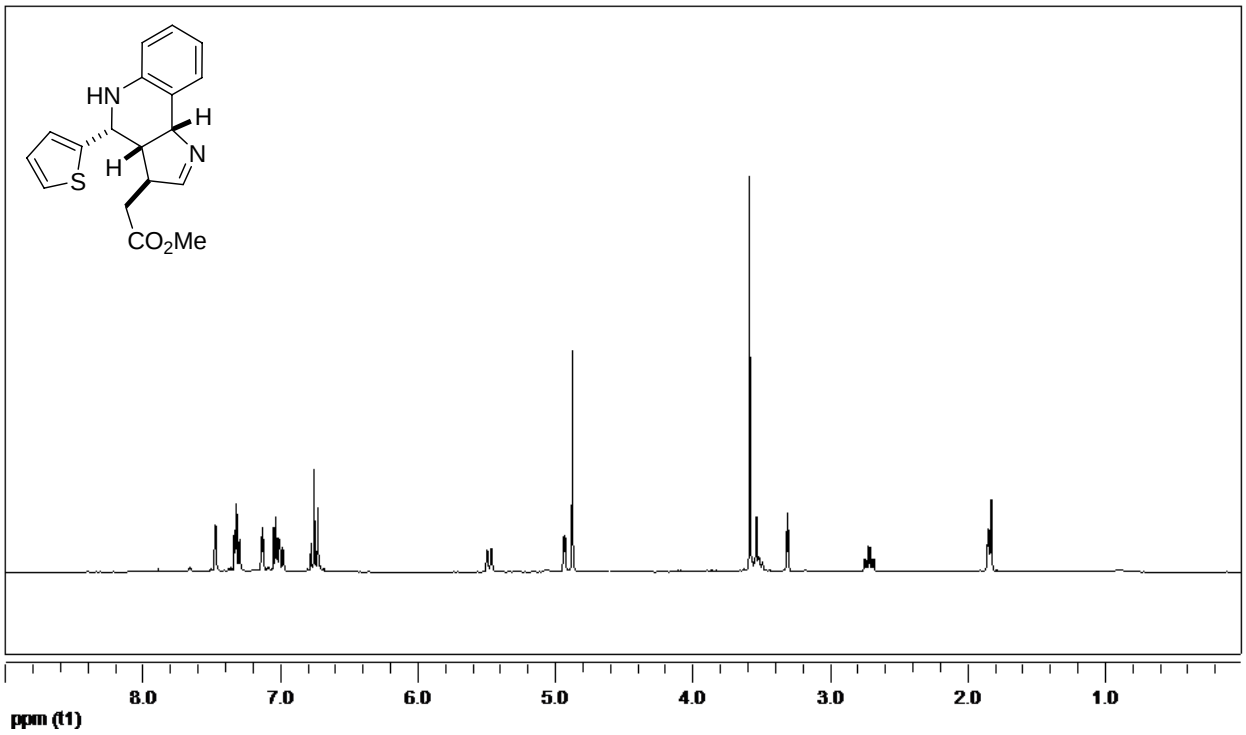


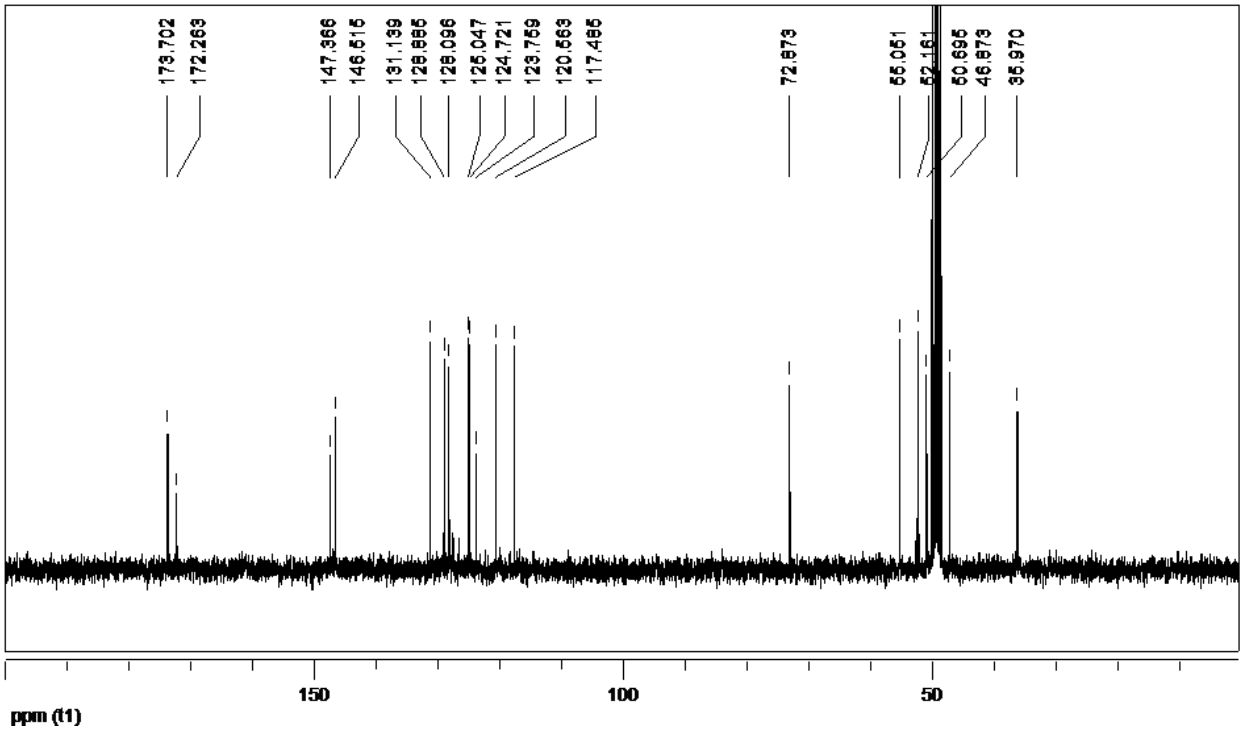
Compound **43f** (major diastereomer)



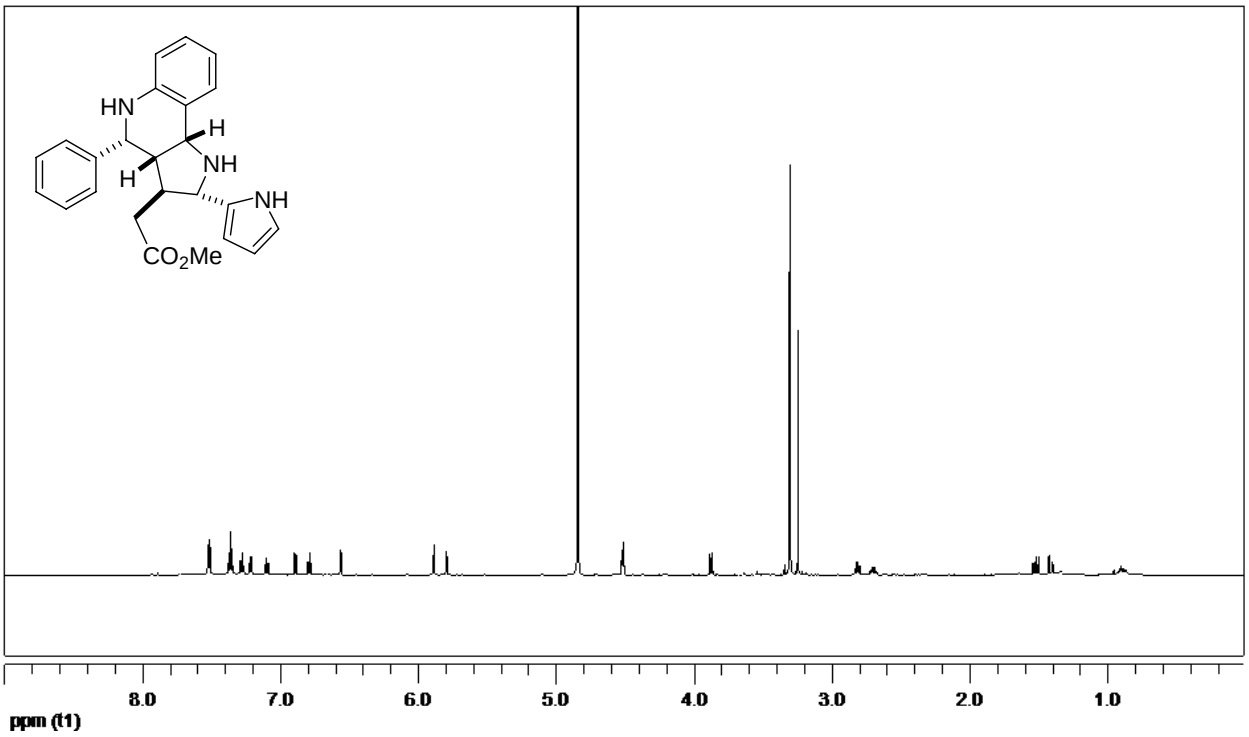


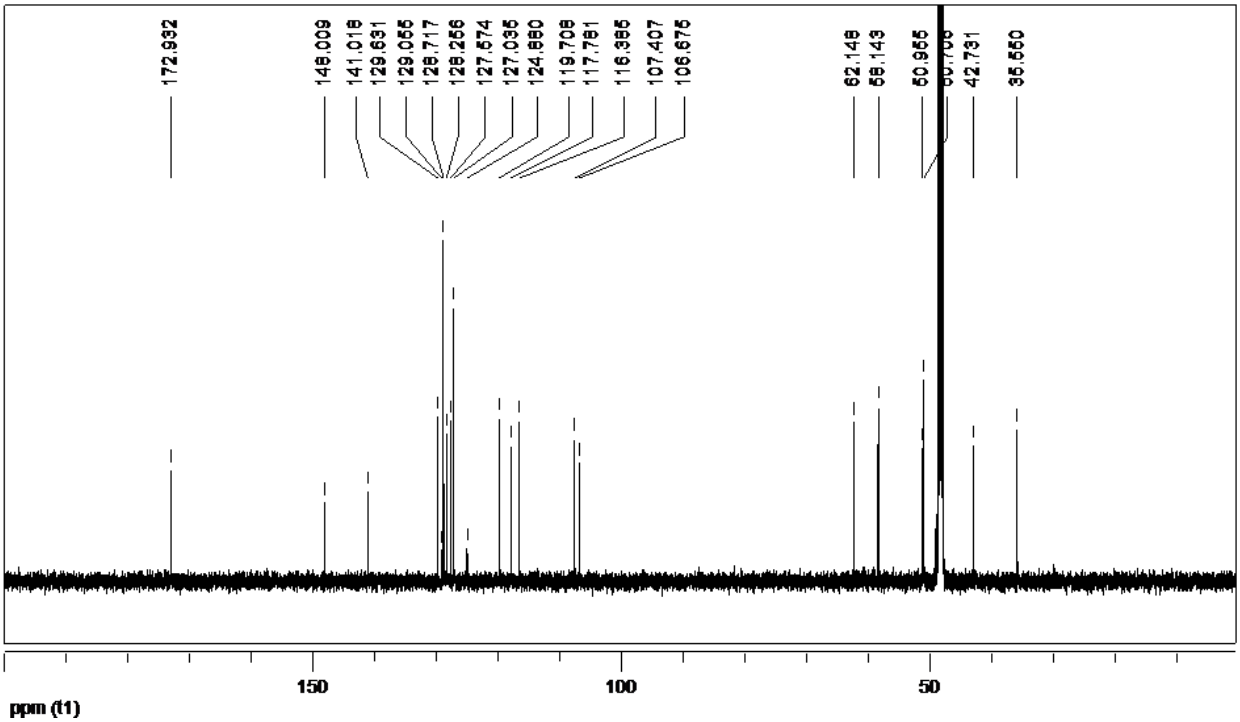
Compound **43g** (major diastereomer)



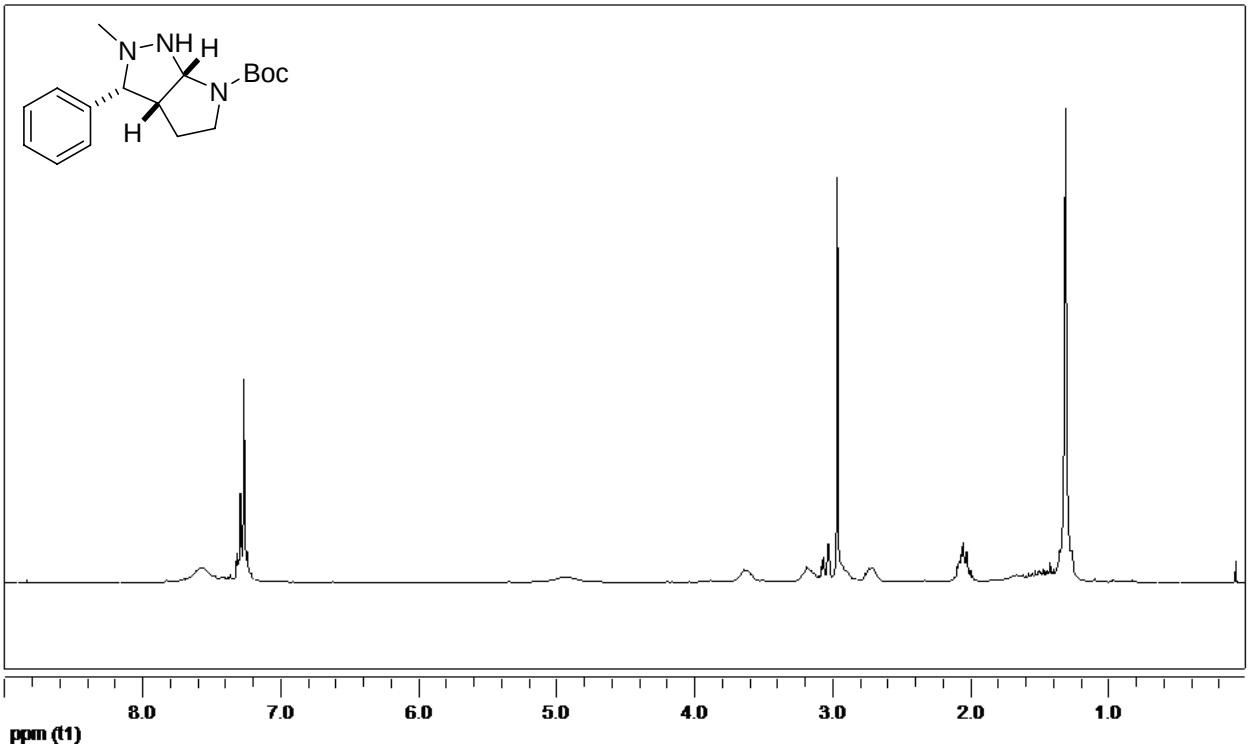


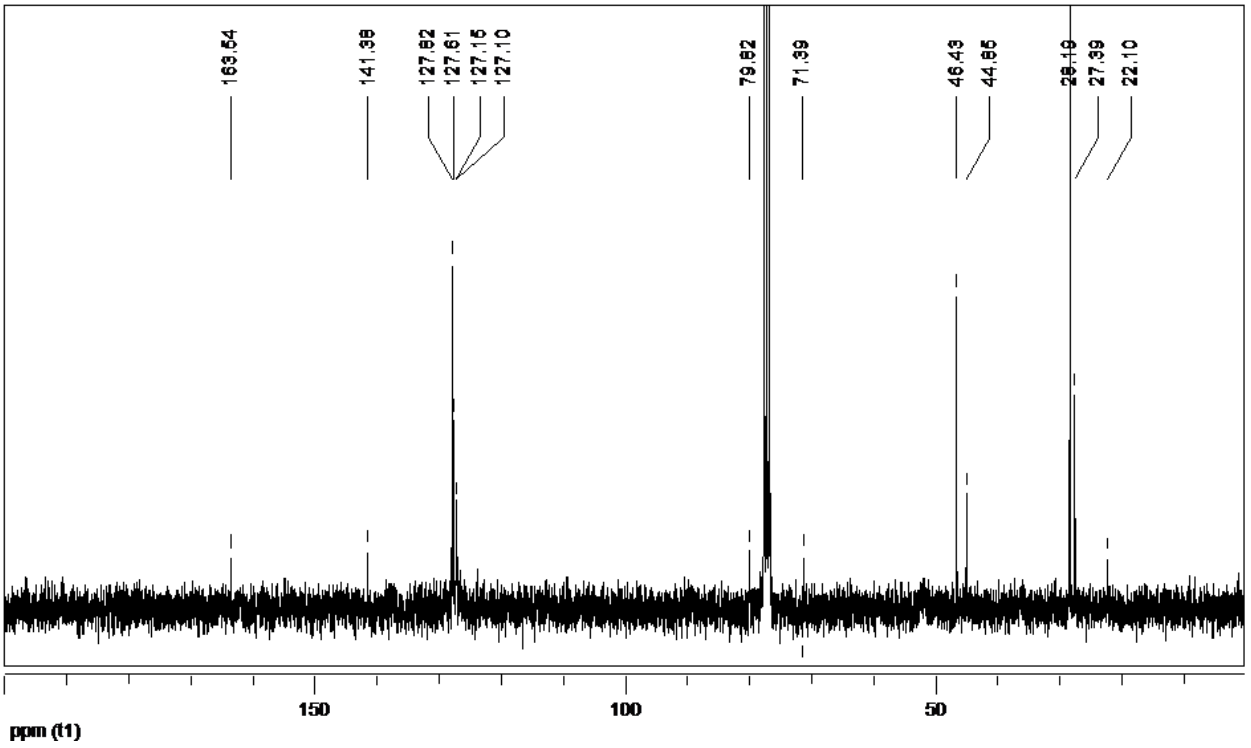
Compound **46** (major diastereomer)



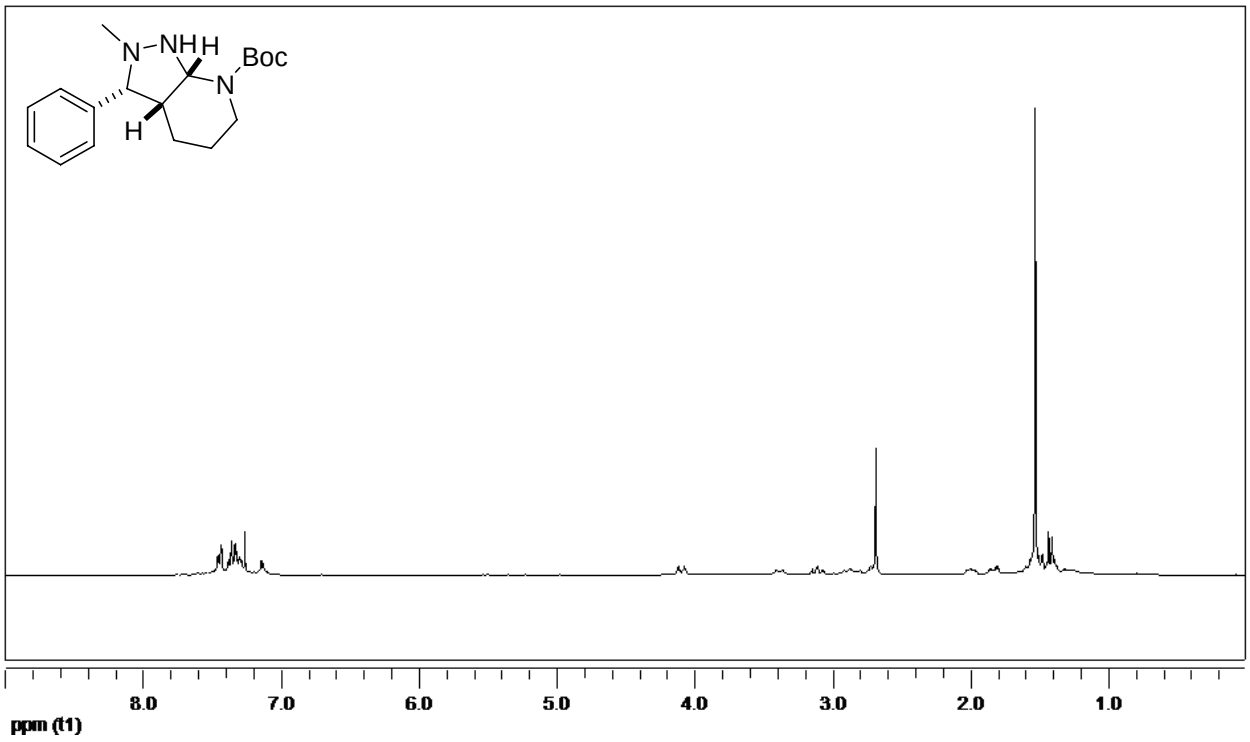


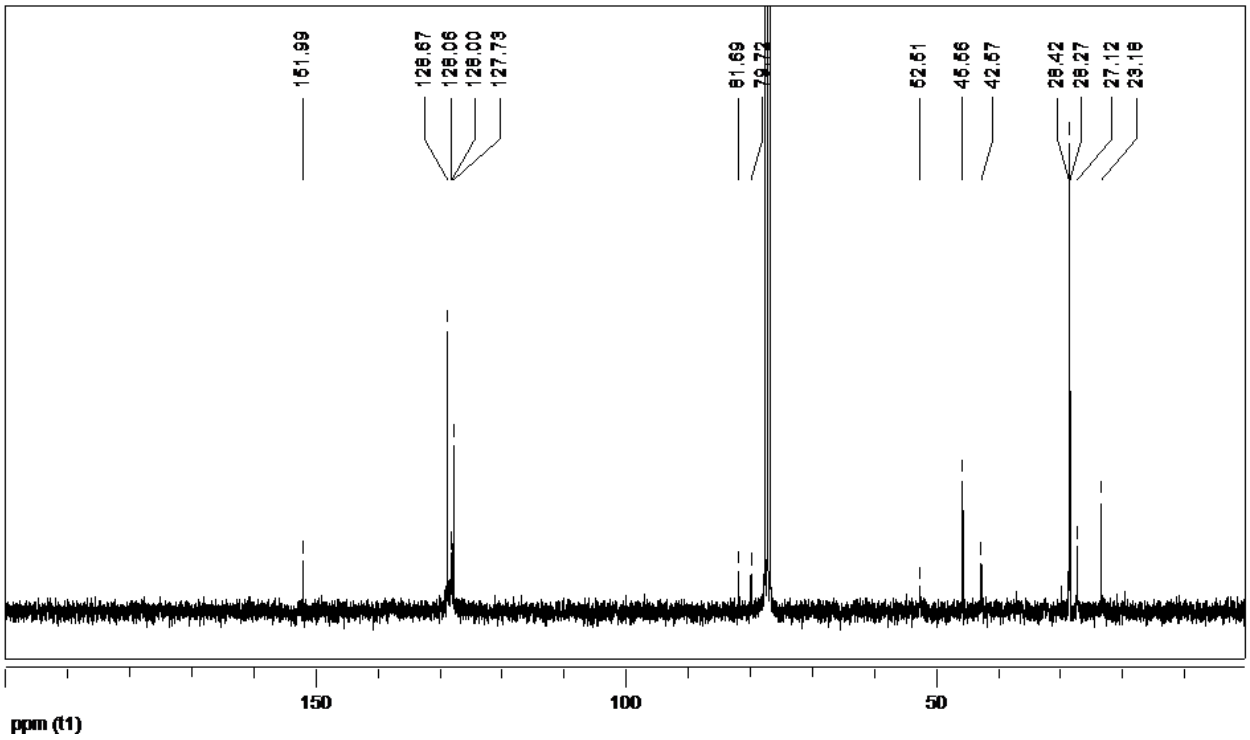
Compound **74a**



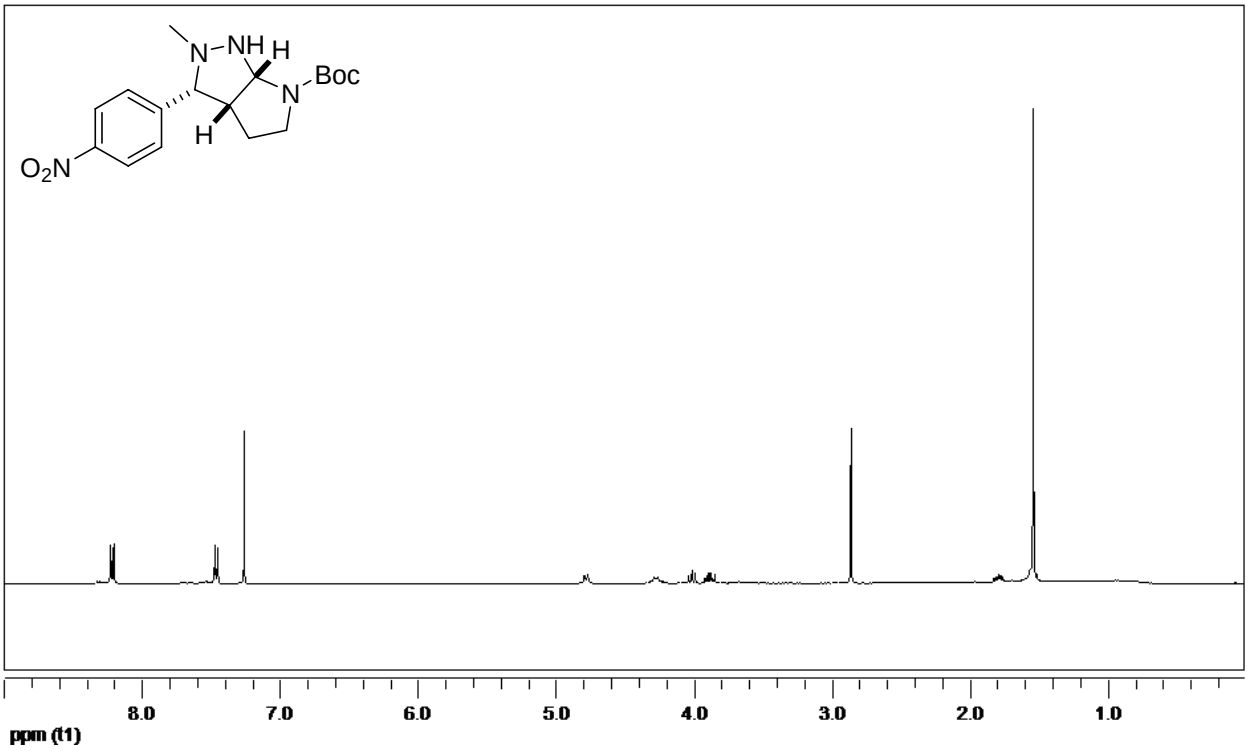


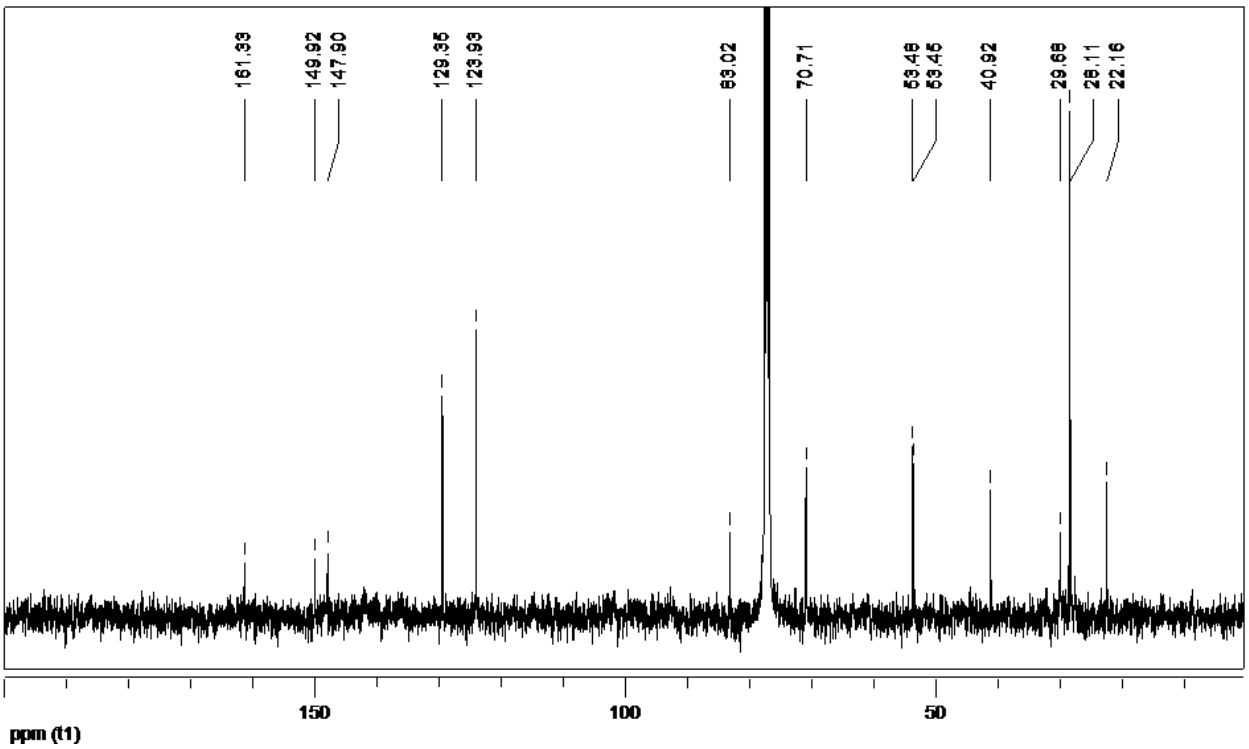
Compound **74b**



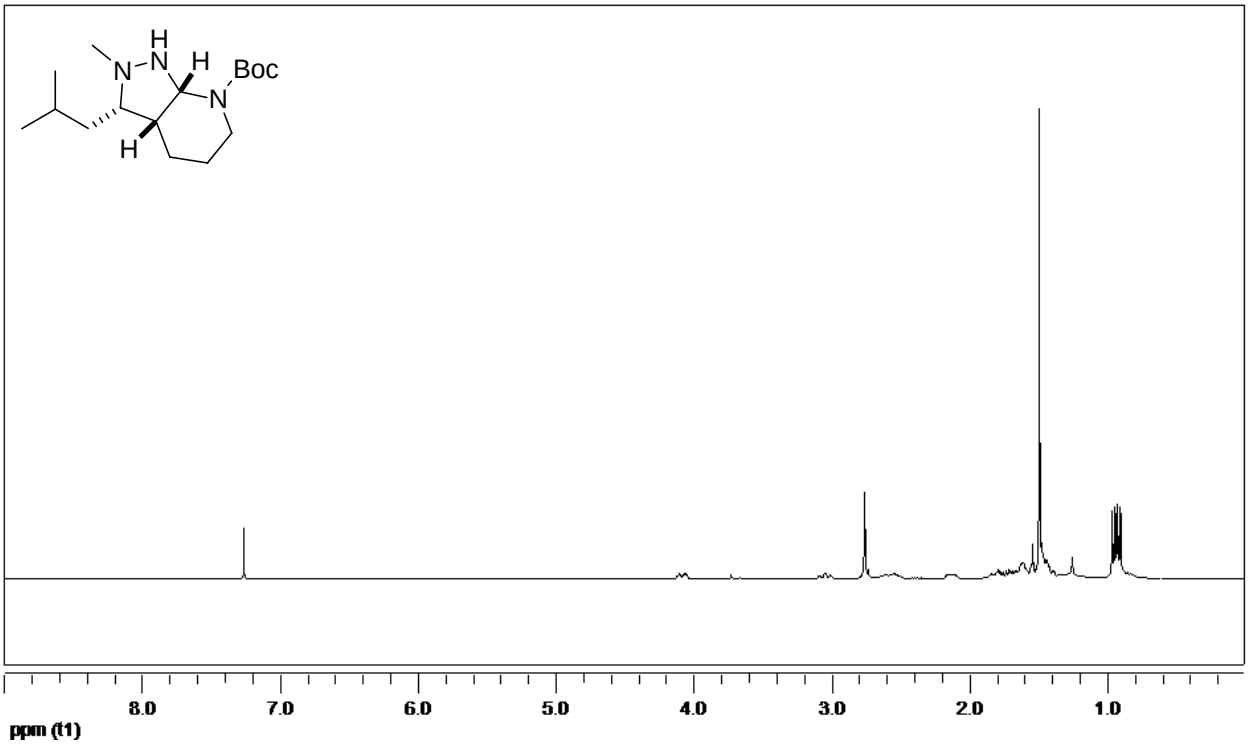


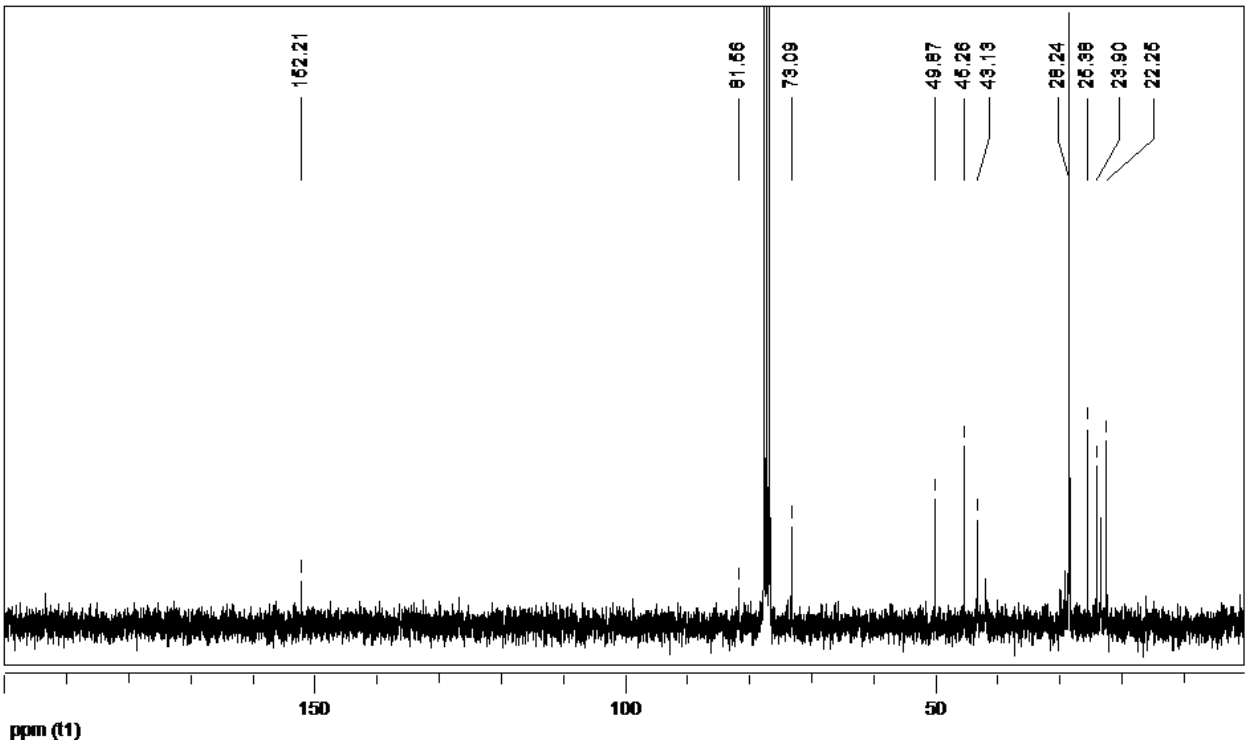
Compound **74d**



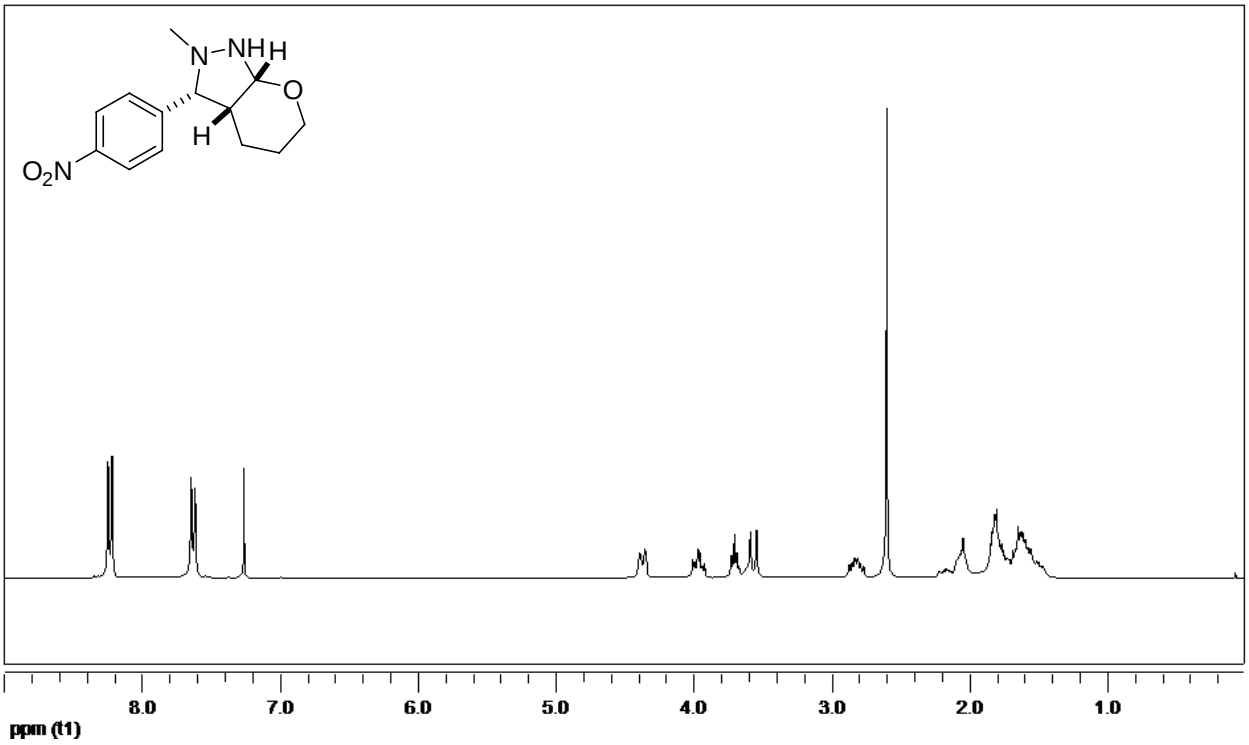


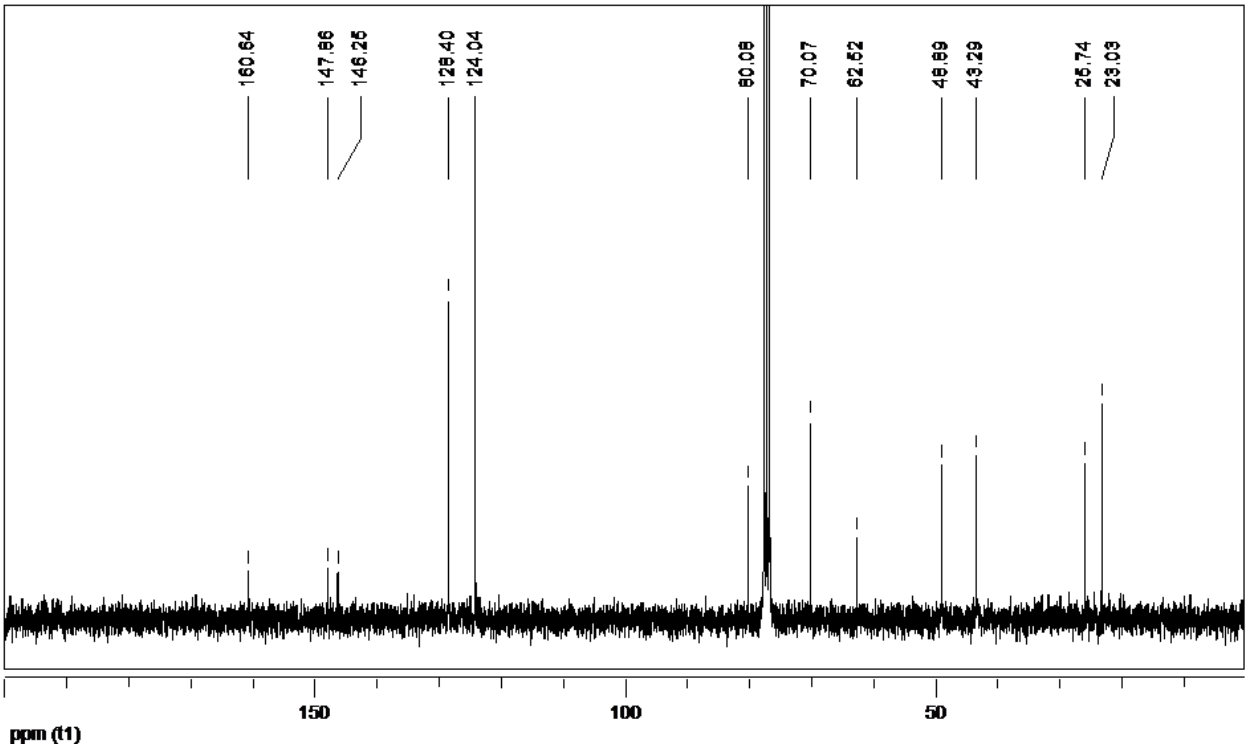
Compound **74f**



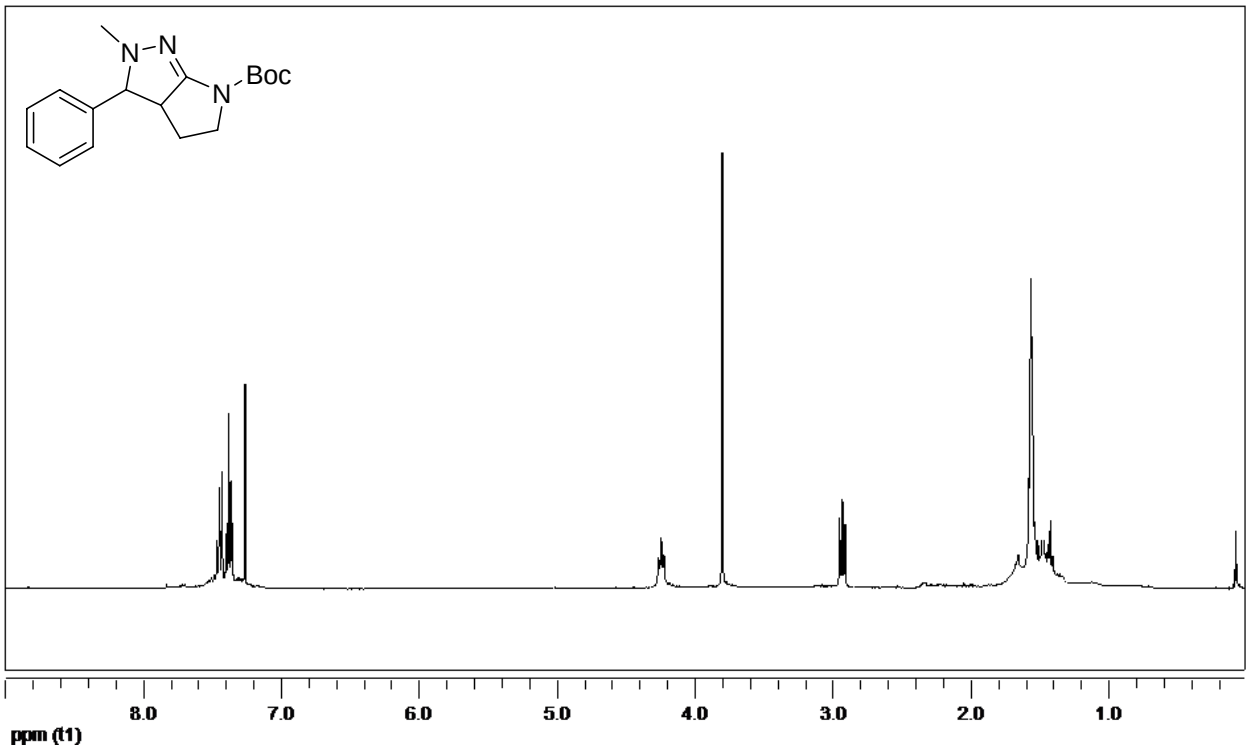


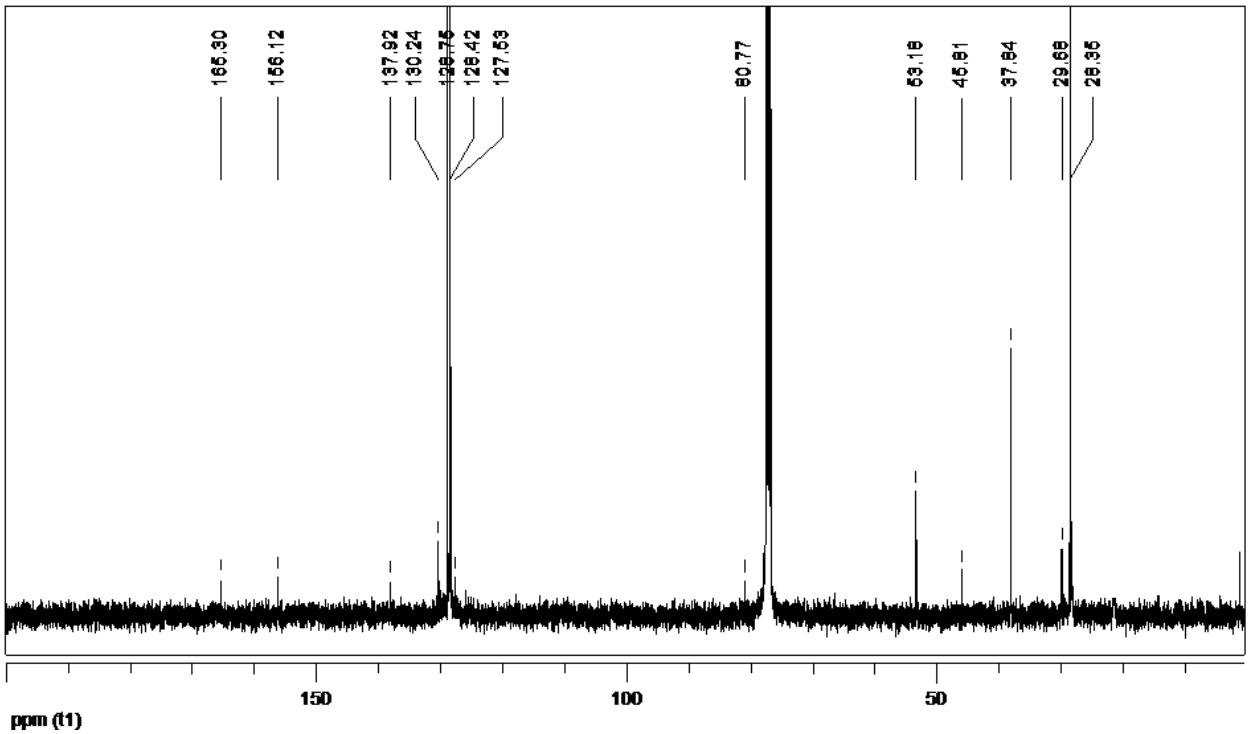
Compound **74k**



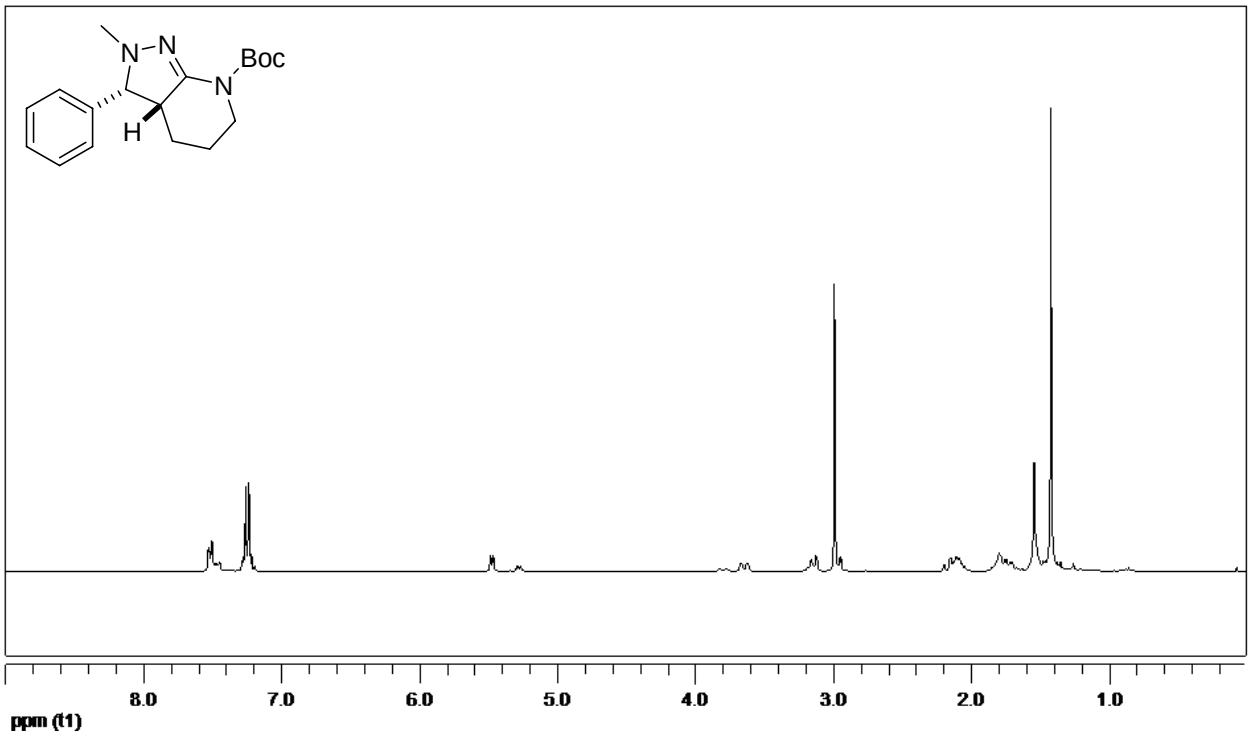


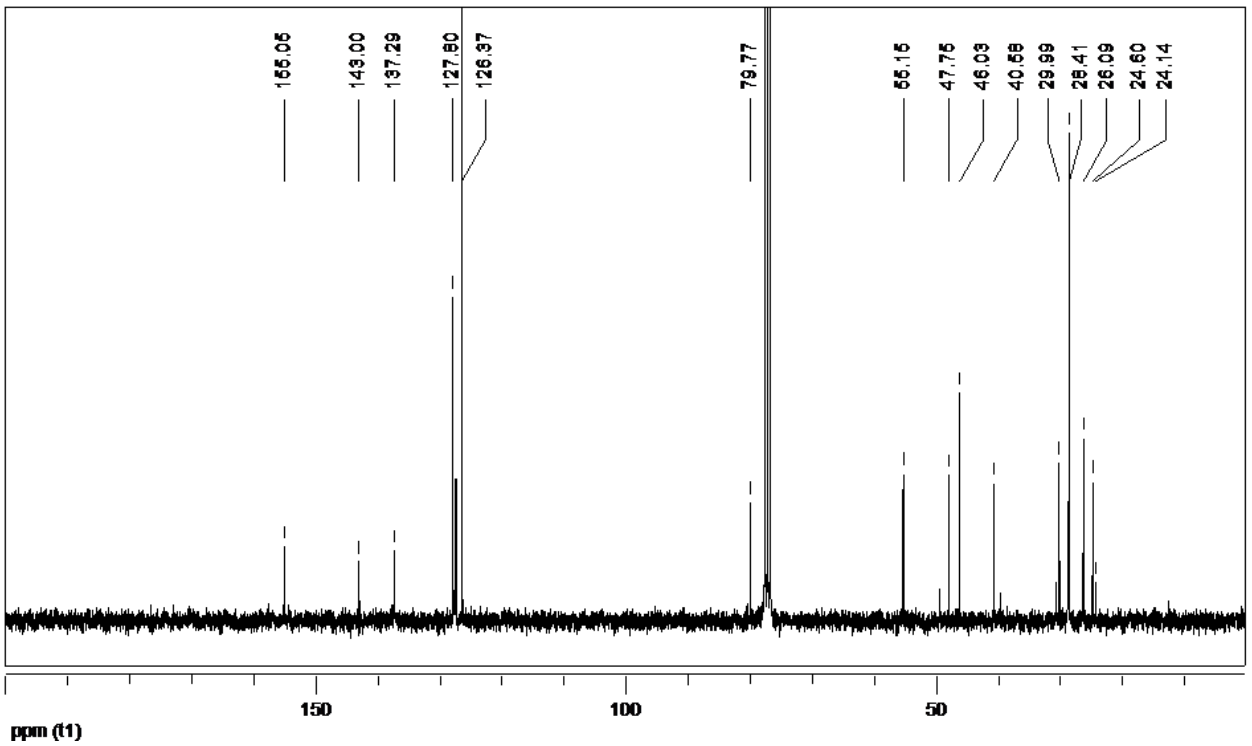
Compound **75a**



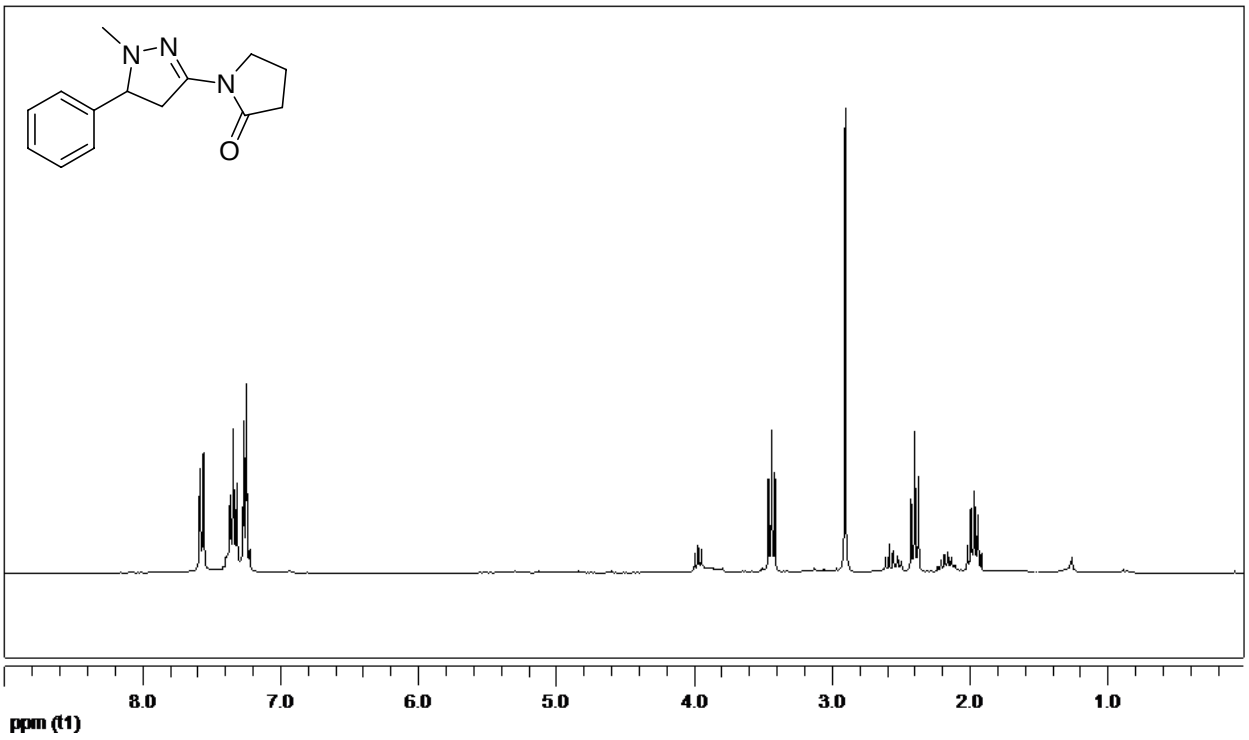


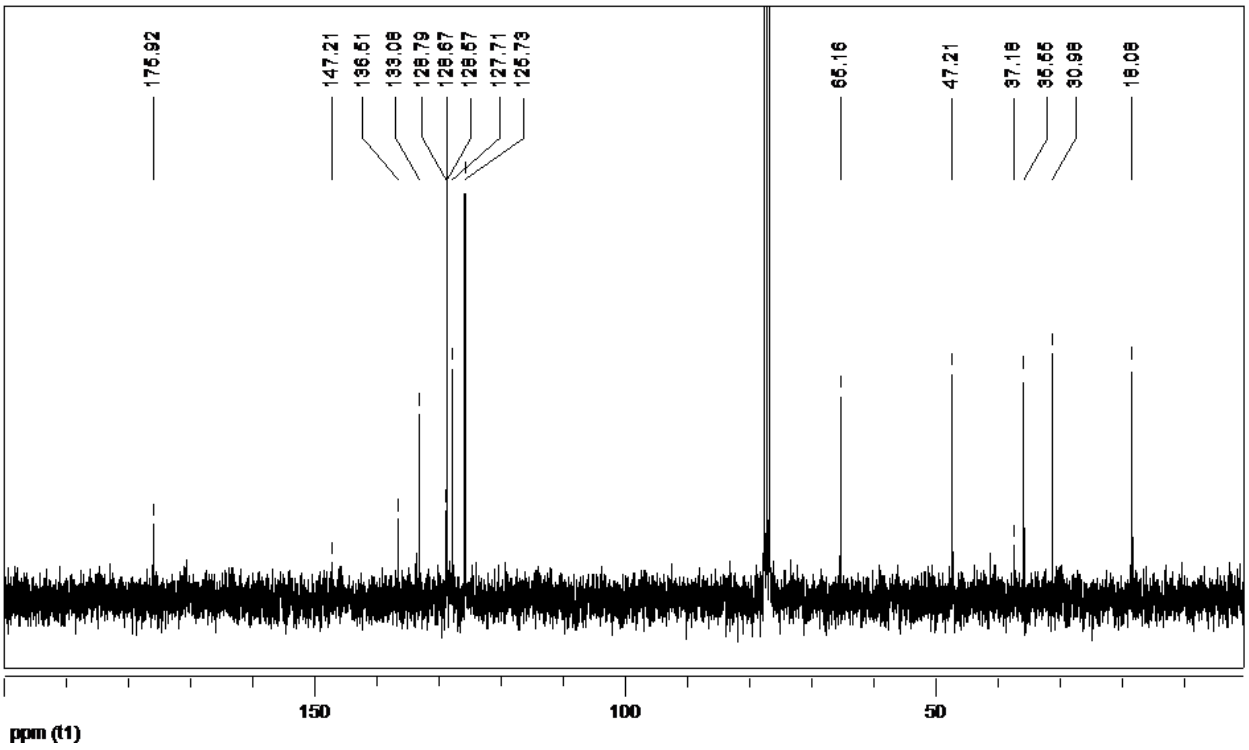
Compound **75b**



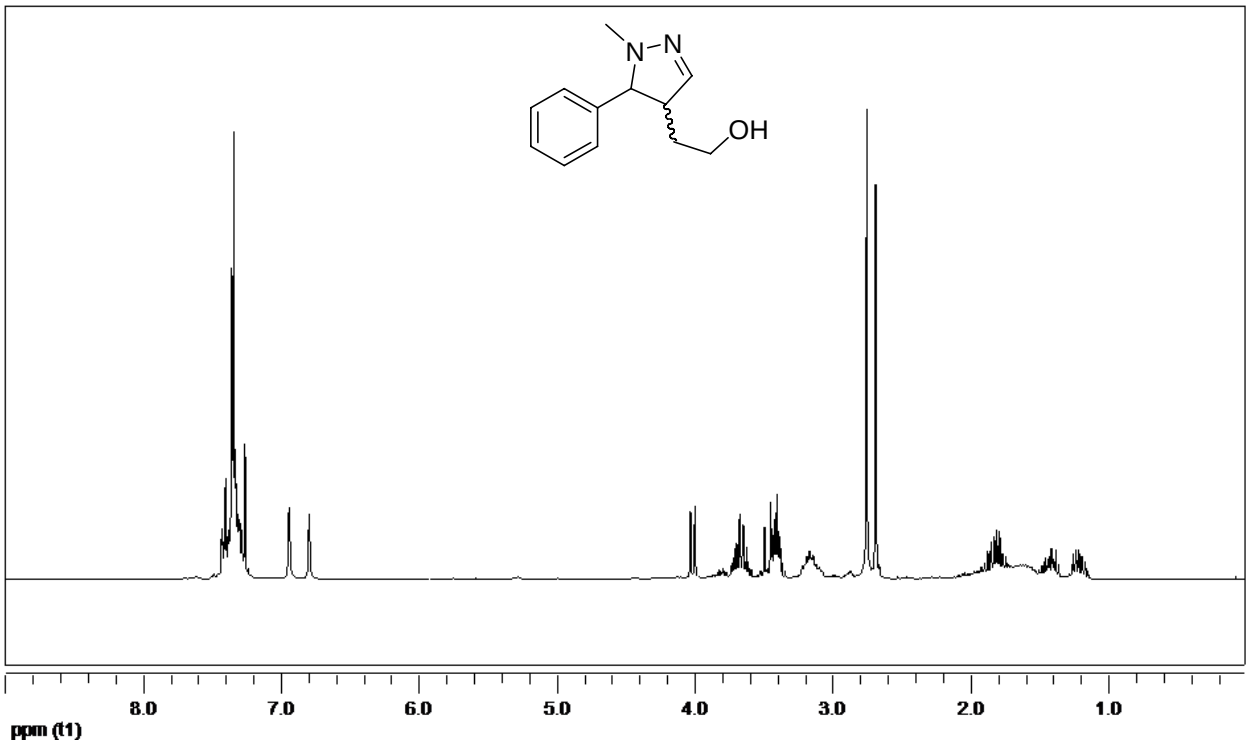


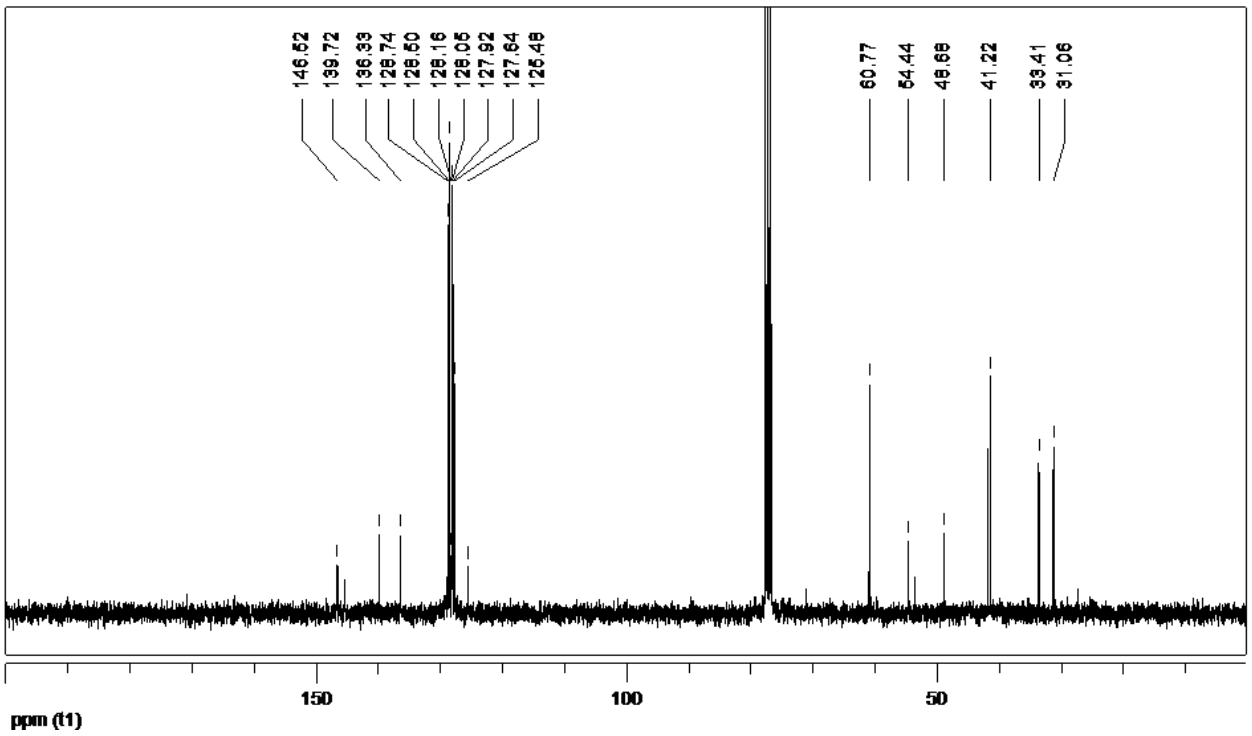
Compound **75c**



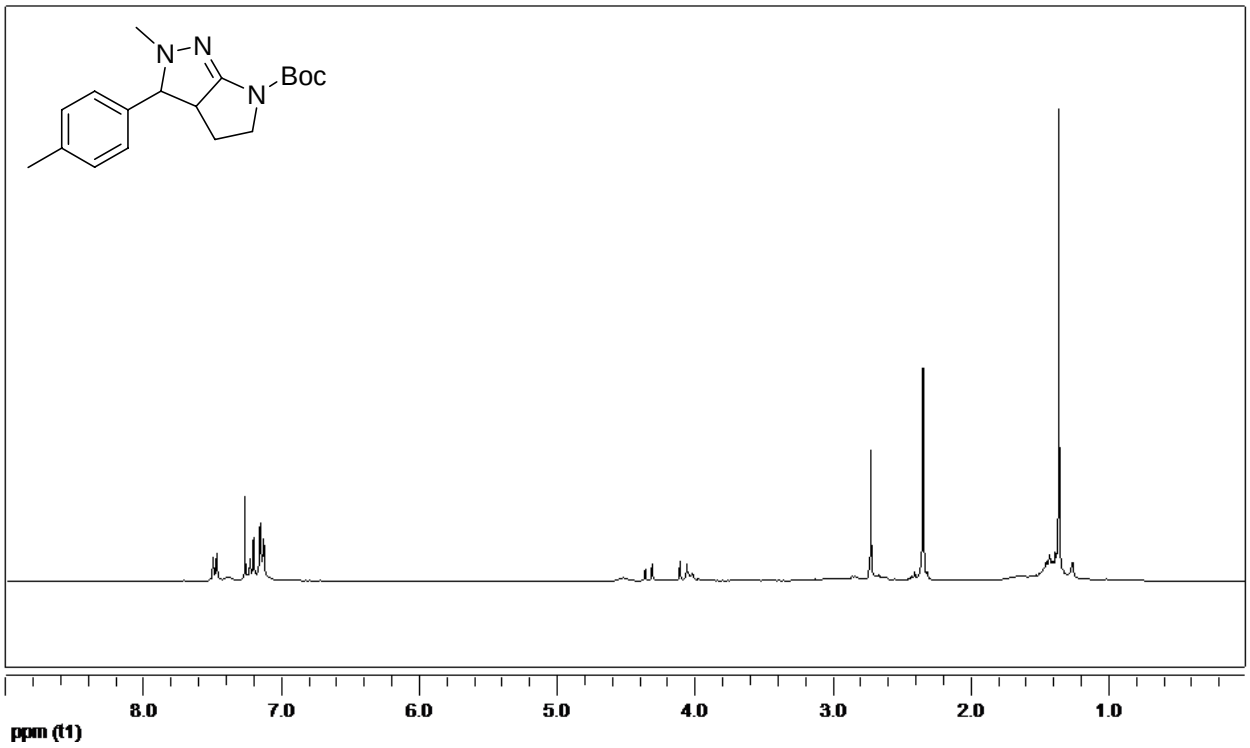


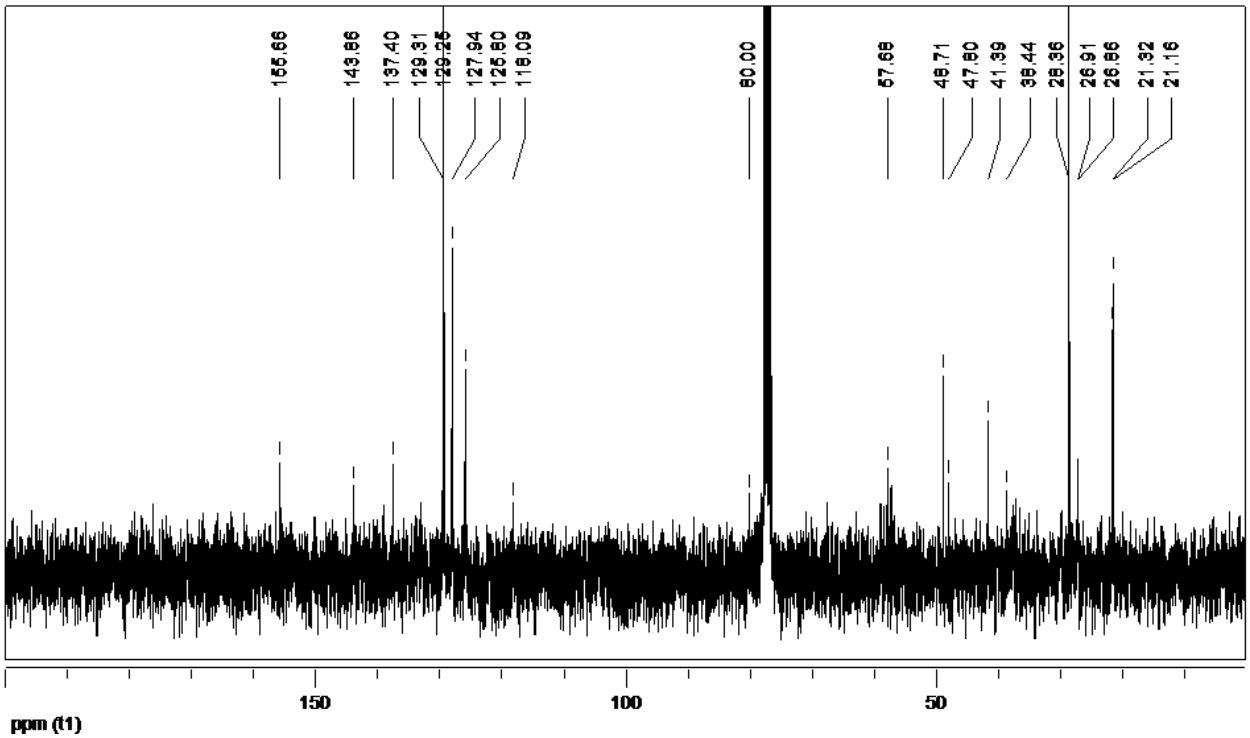
Compound **75d**



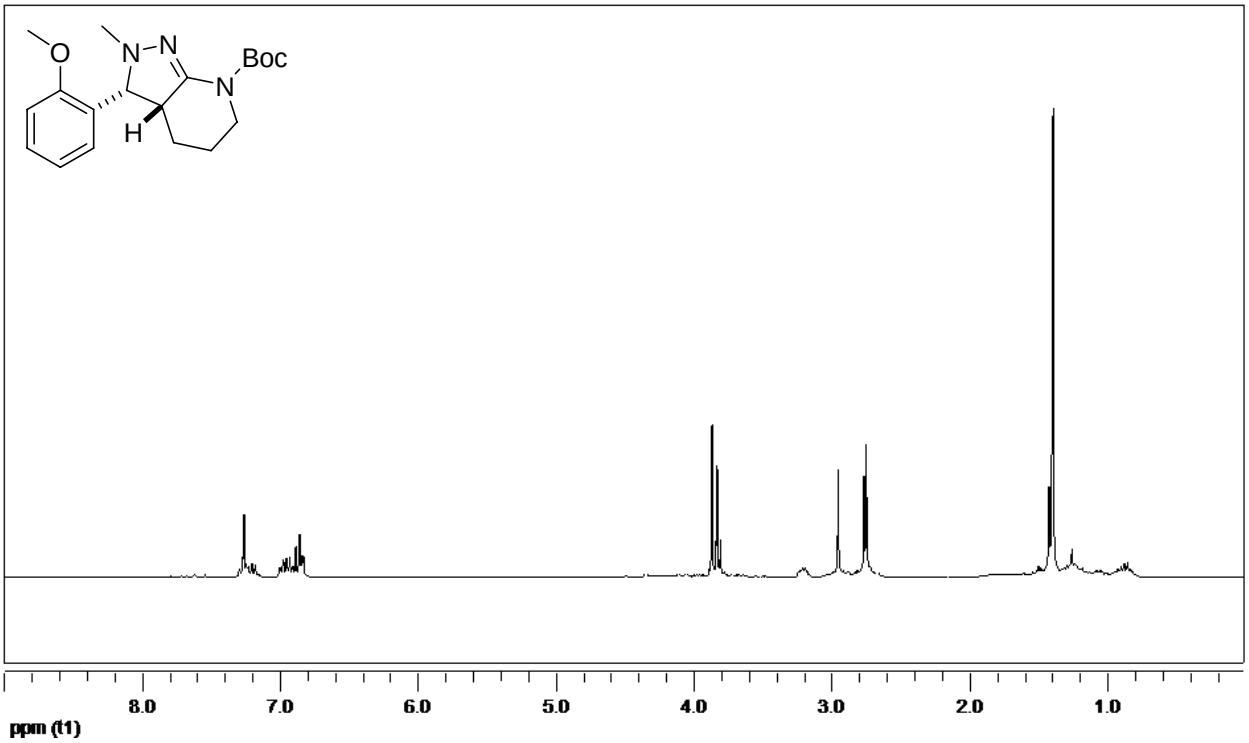


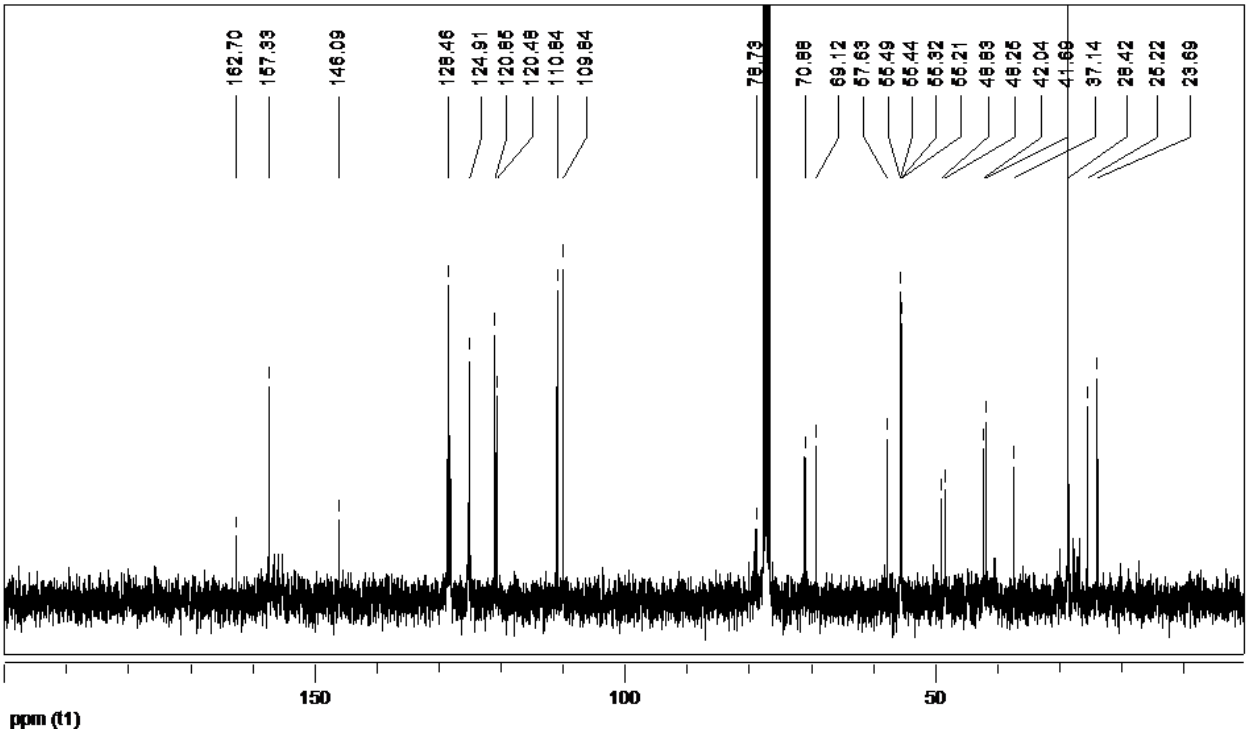
Compound **75h**



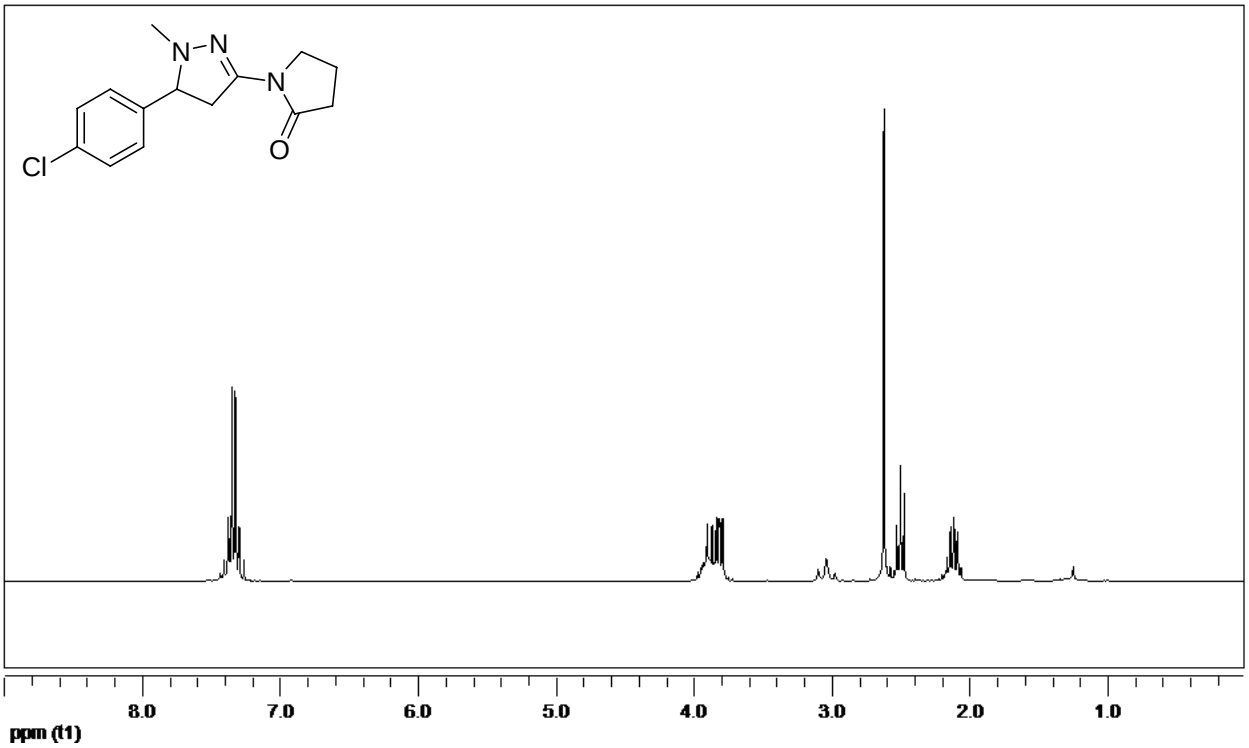


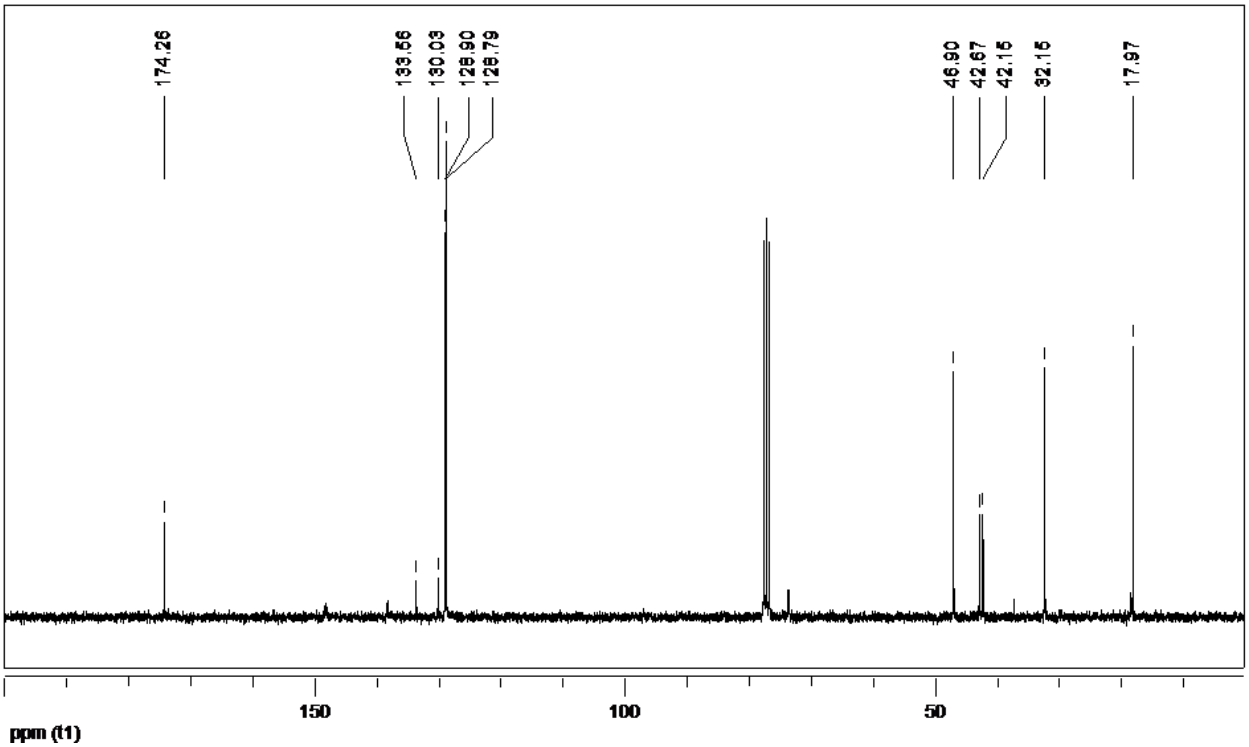
Compound **75l**



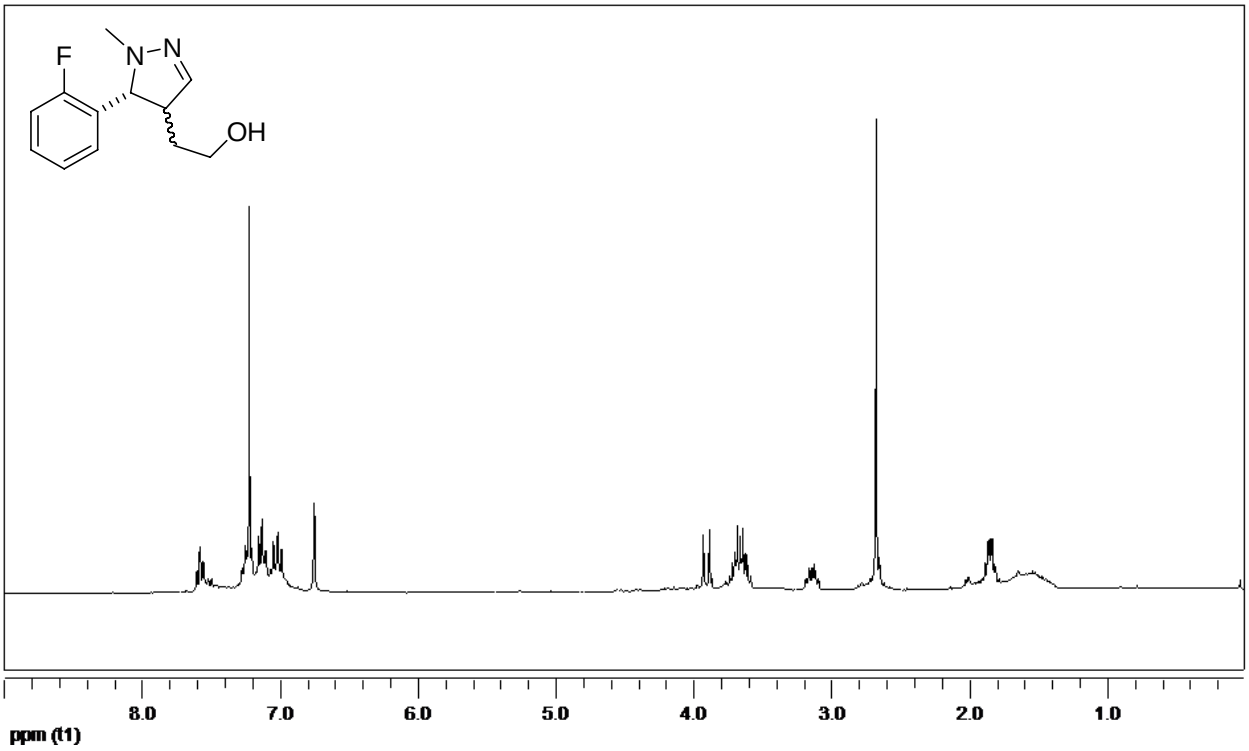


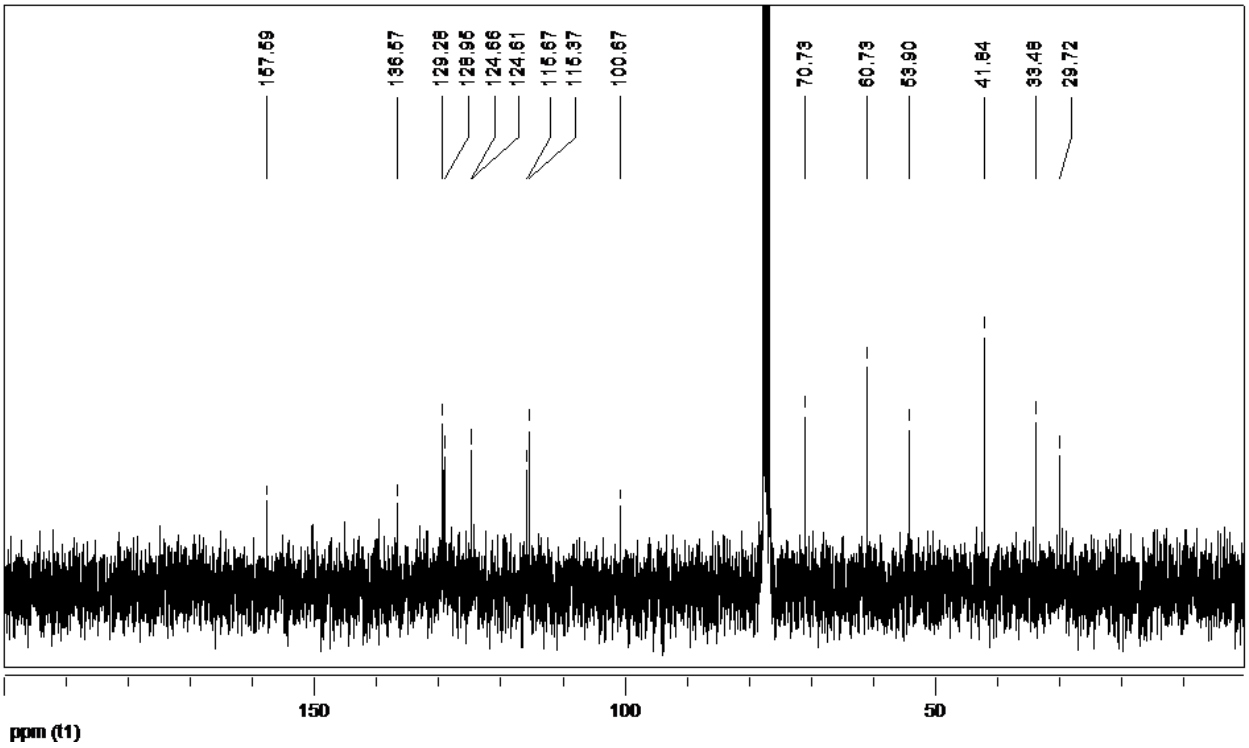
Compound **75m**

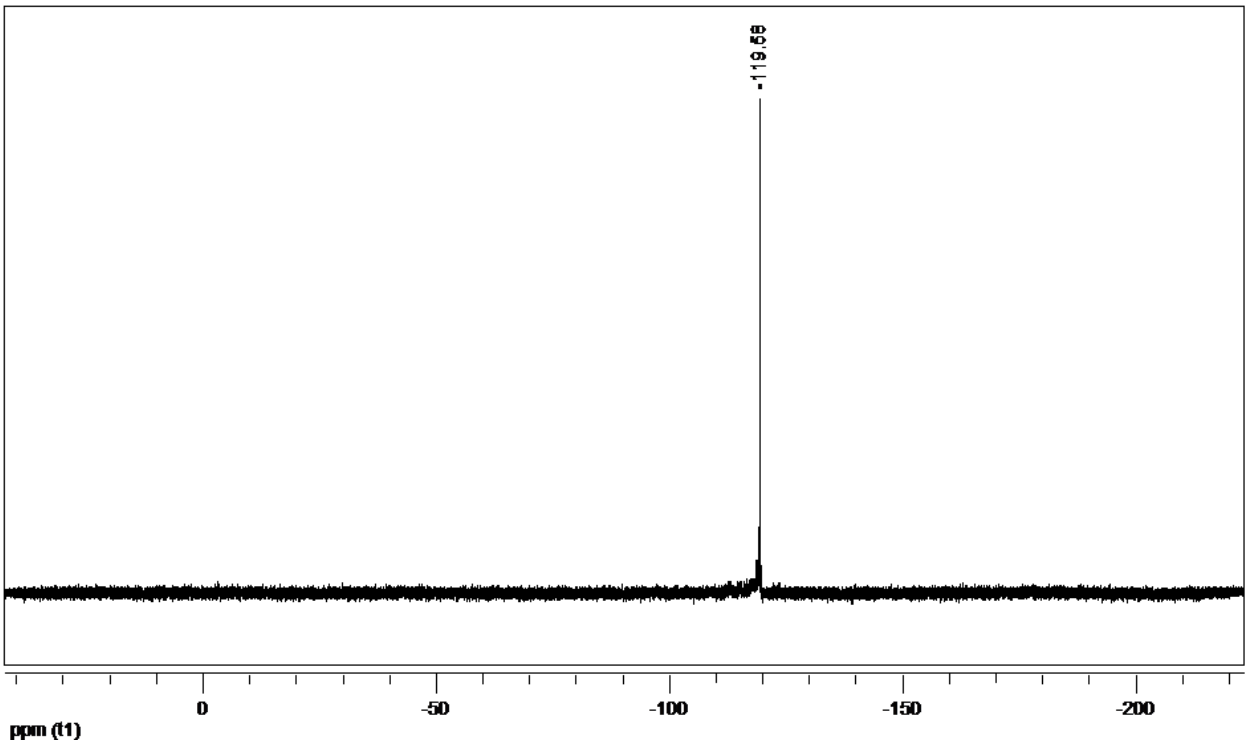




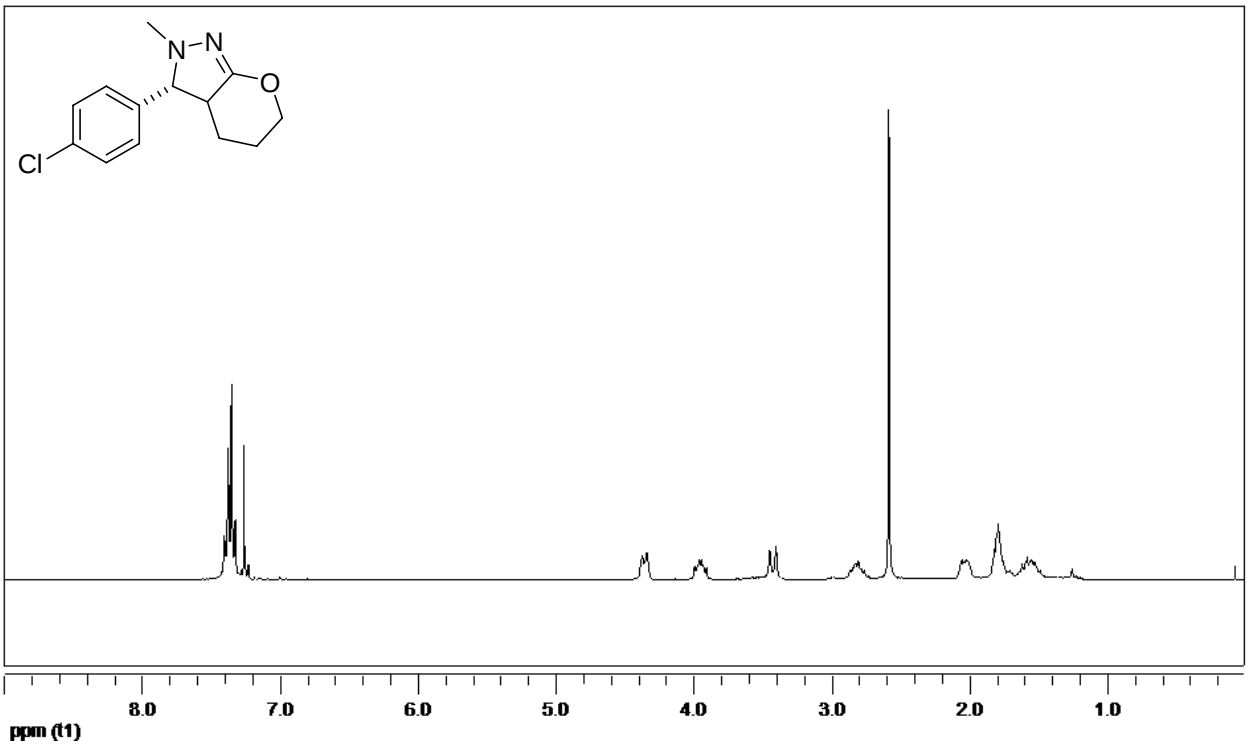
Compound **75o**

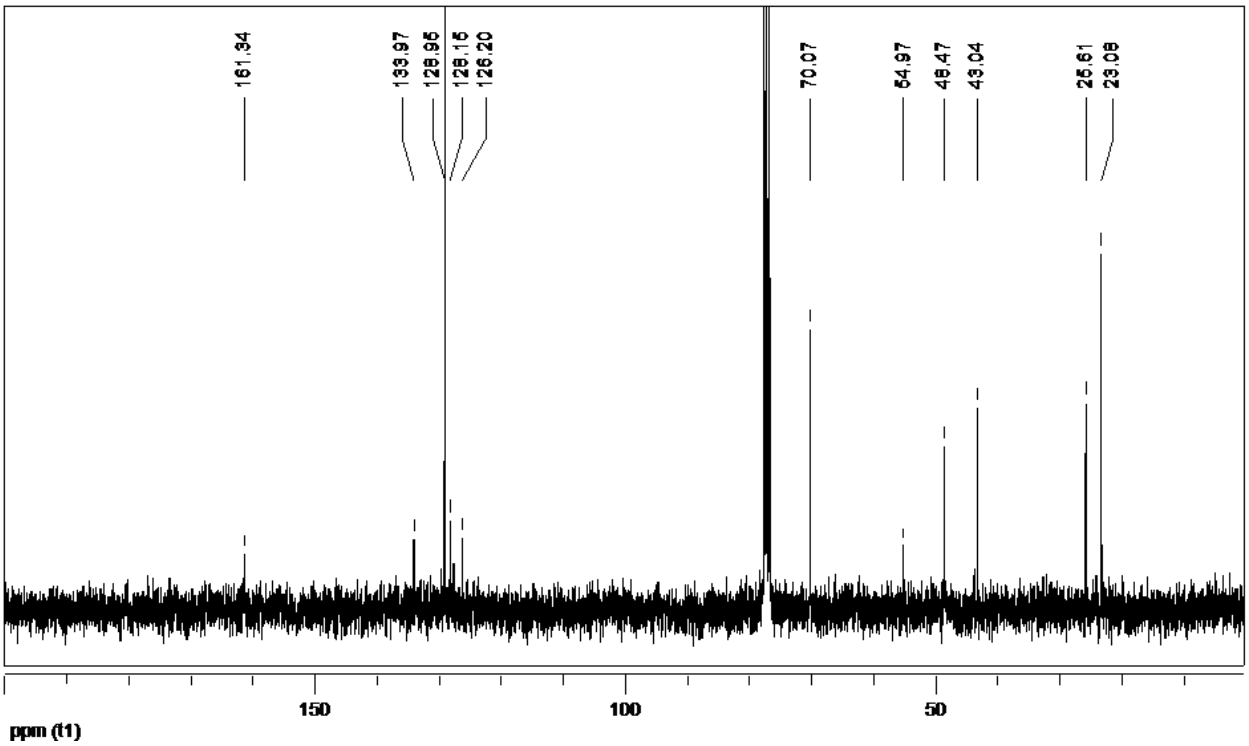




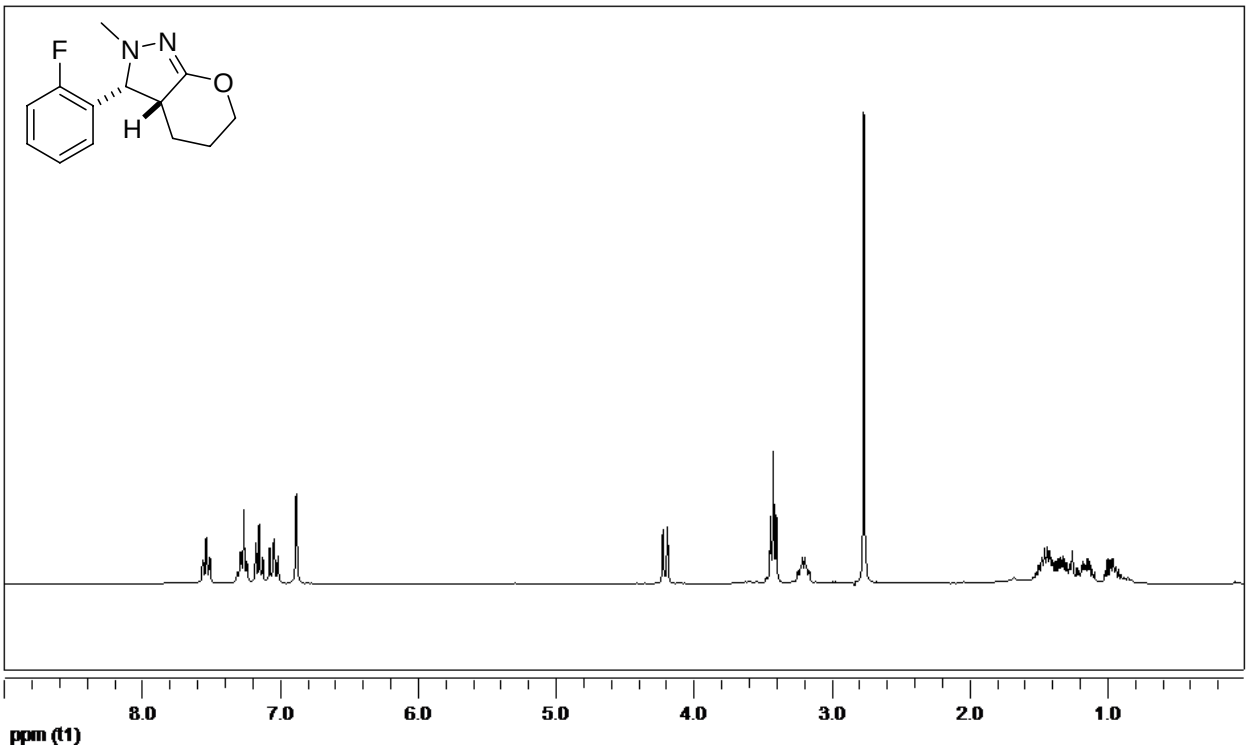

-119.56
0
-50
-100
-150
-200
ppm (t1)

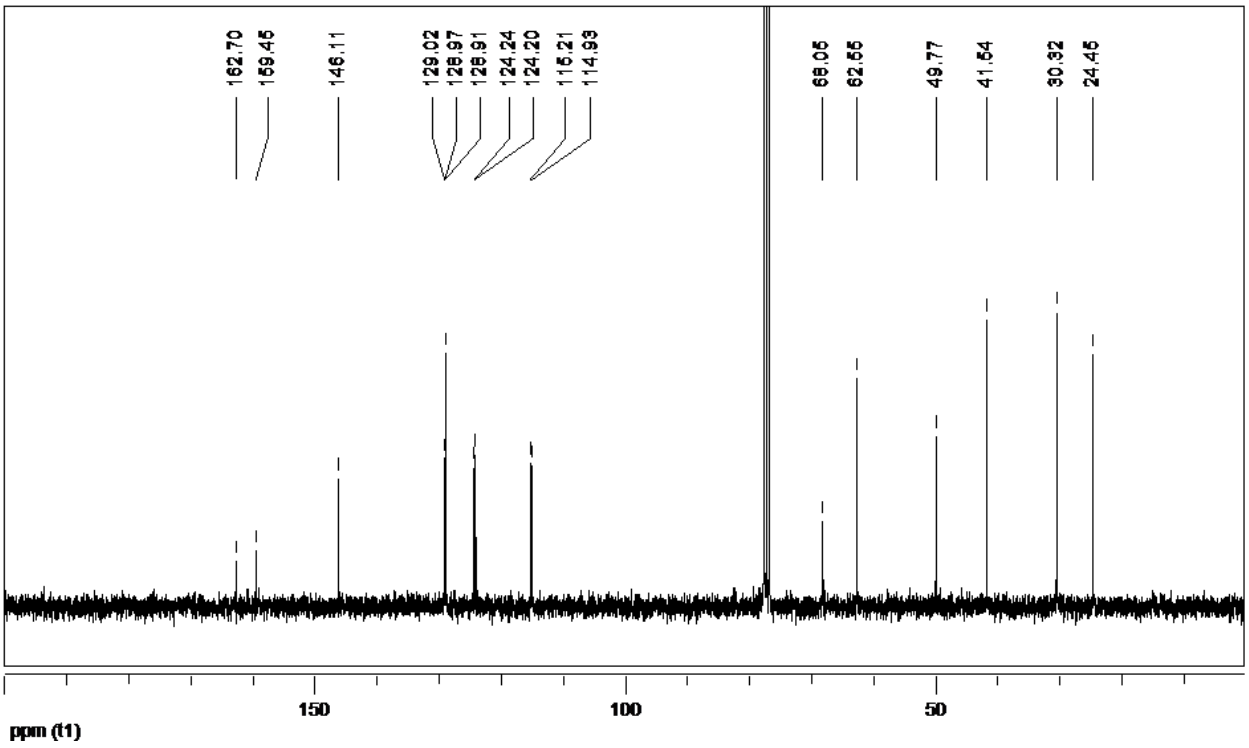
Compound **75q**

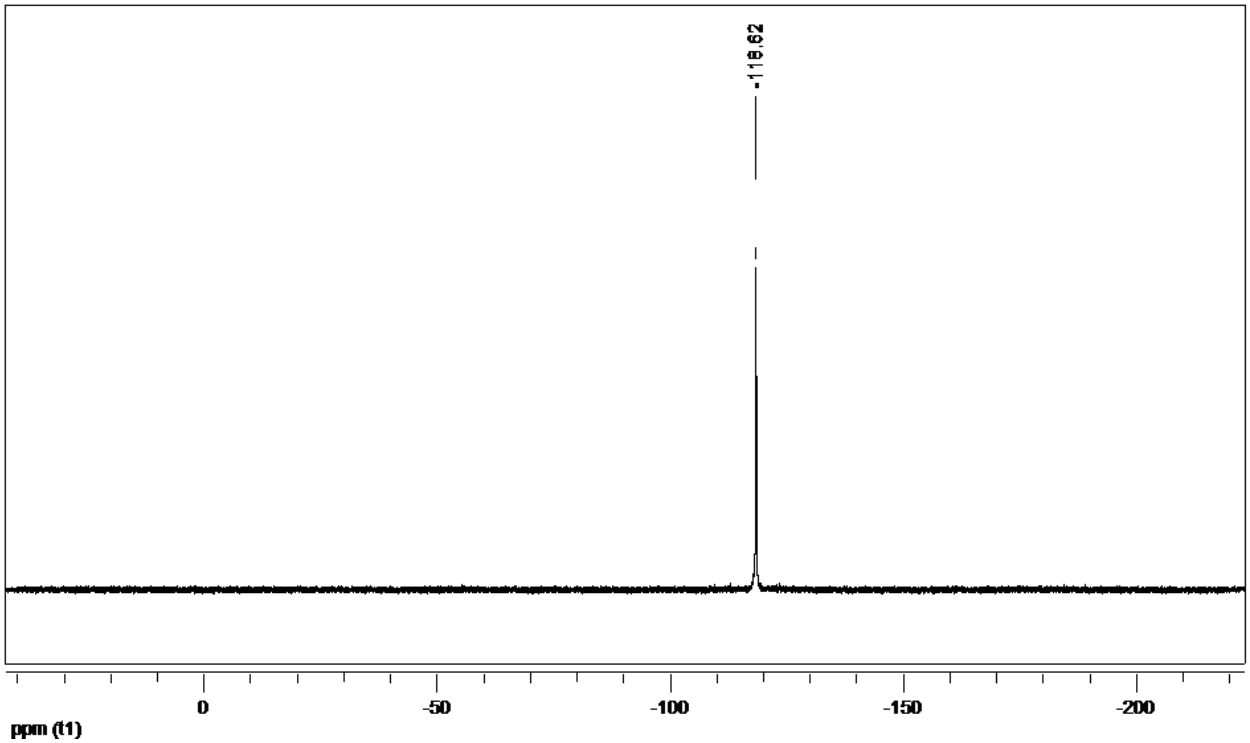




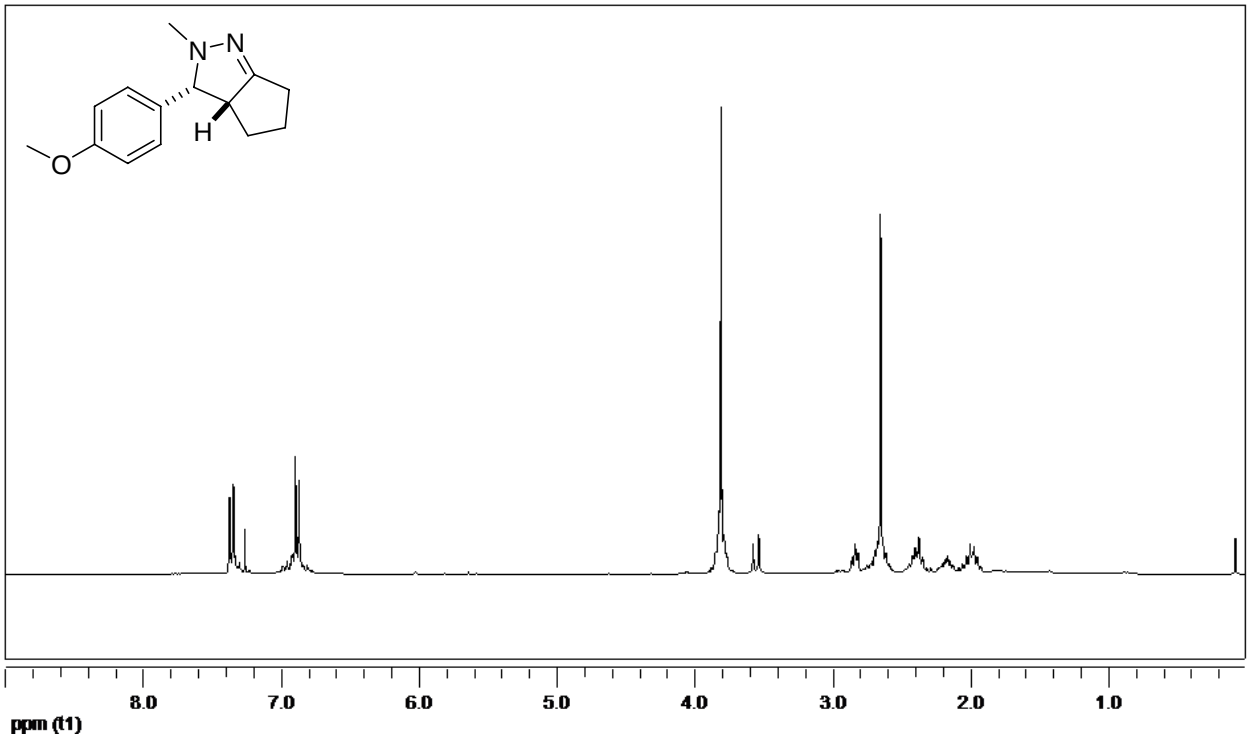
Compound **75r**

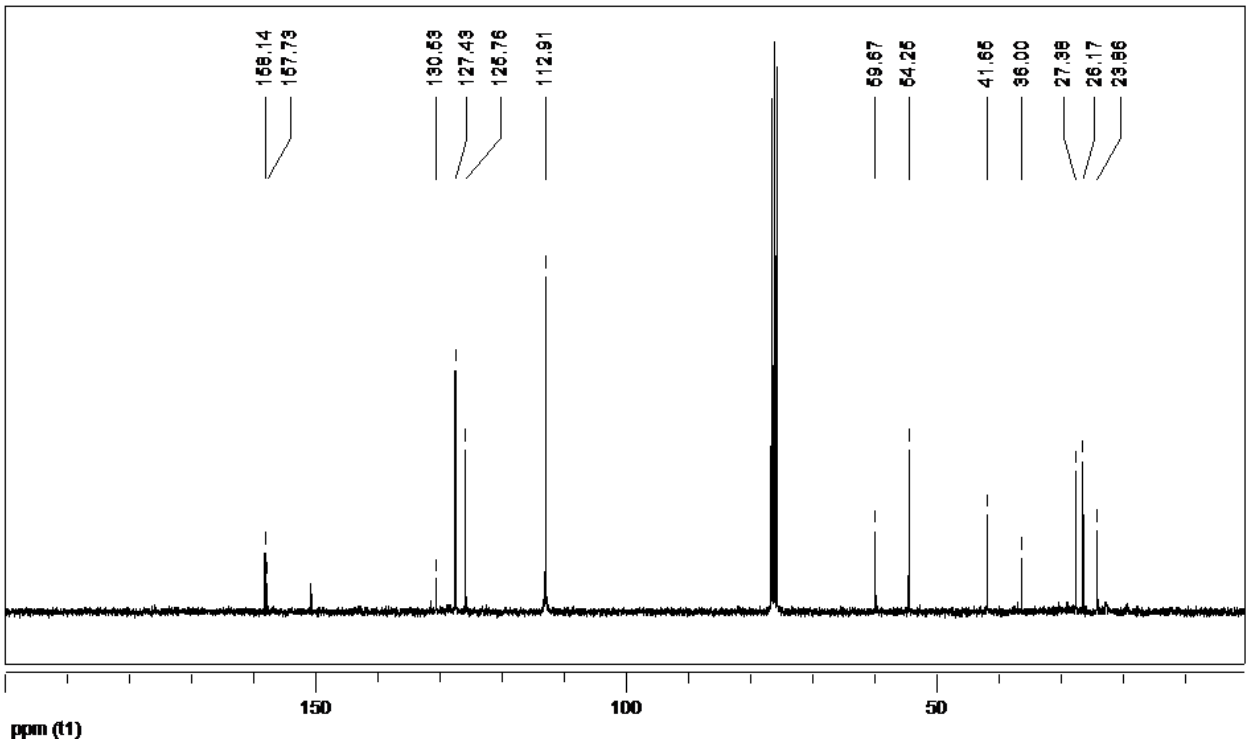





-116.62
0
-50
-100
-150
-200
ppm (t1)

Compound **75u**





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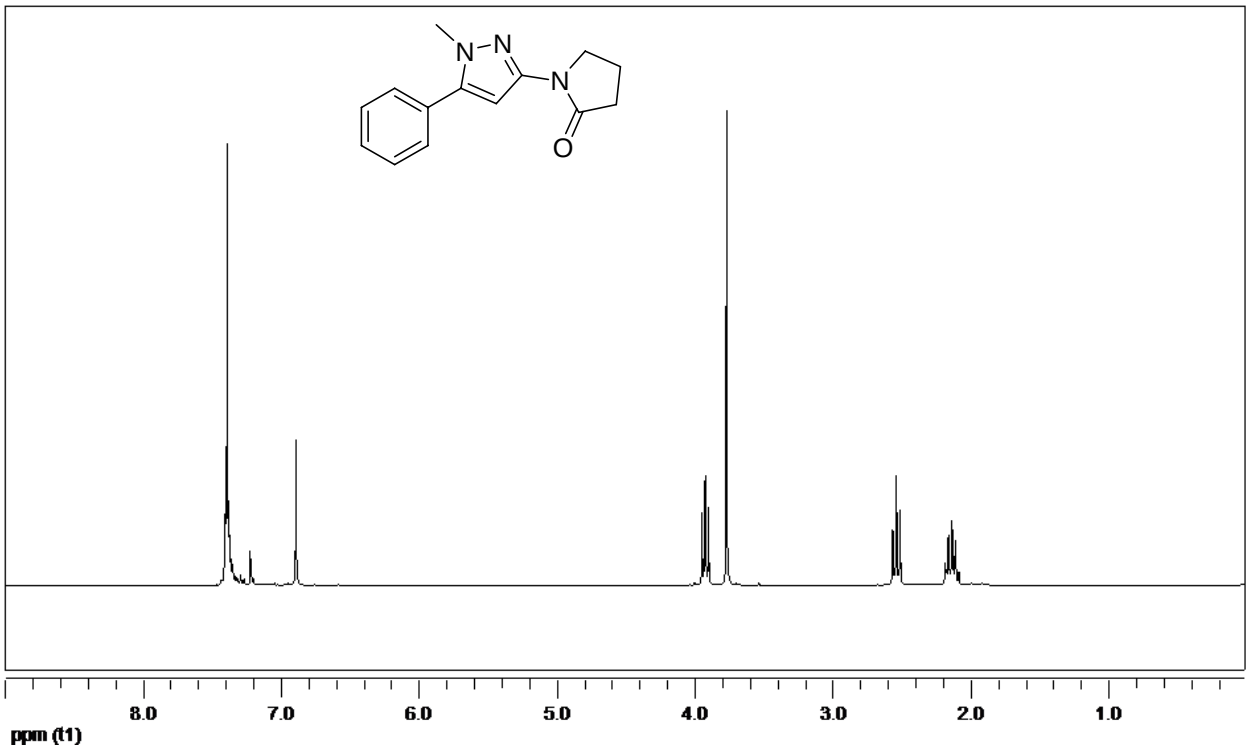

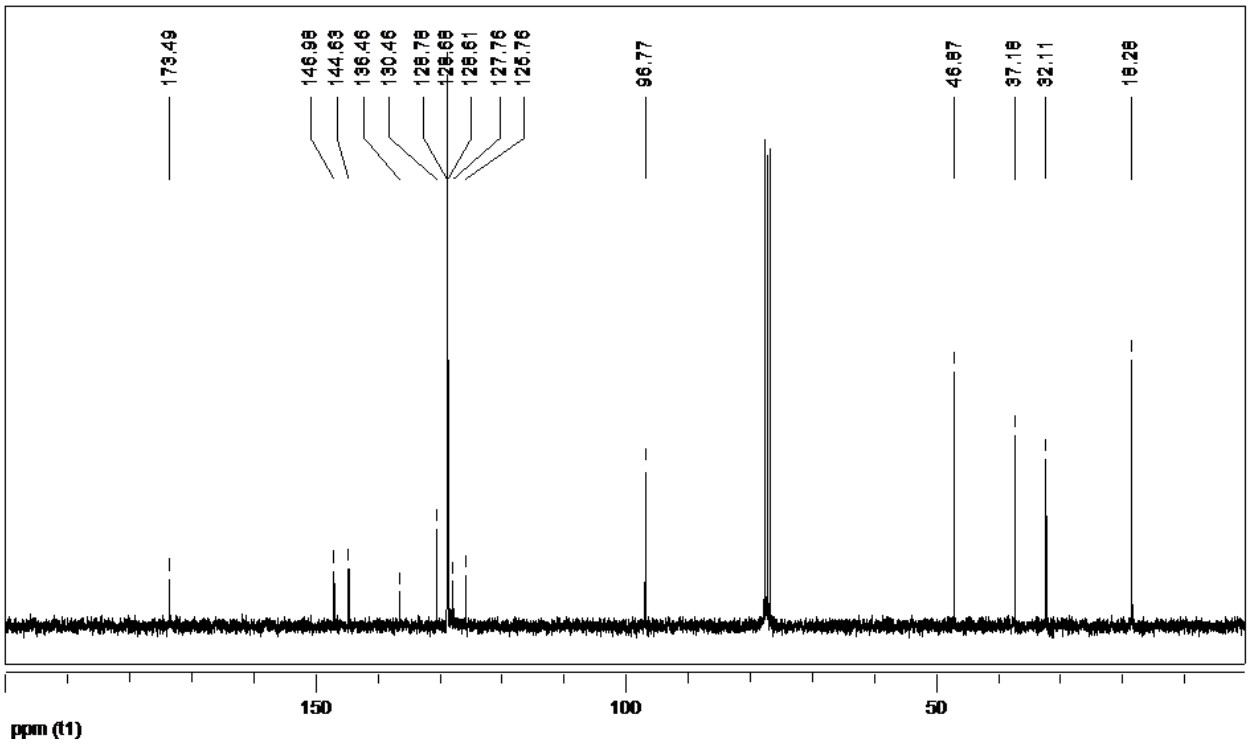

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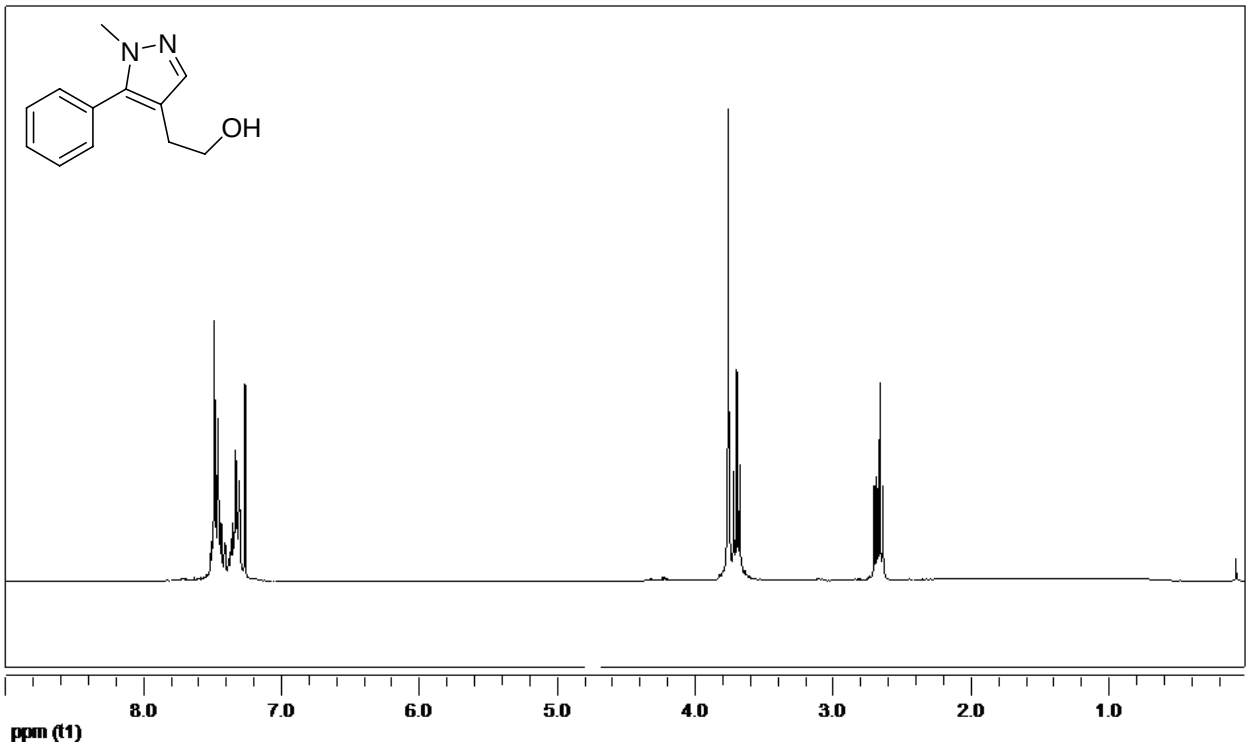
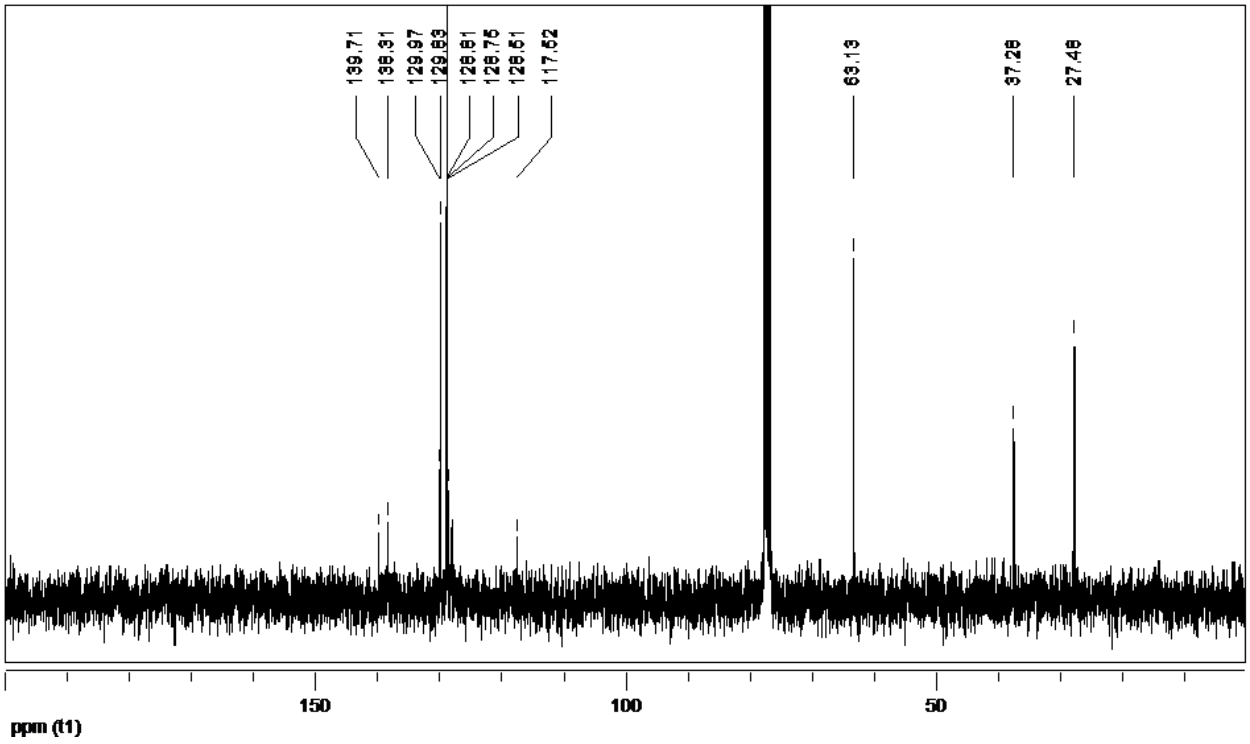
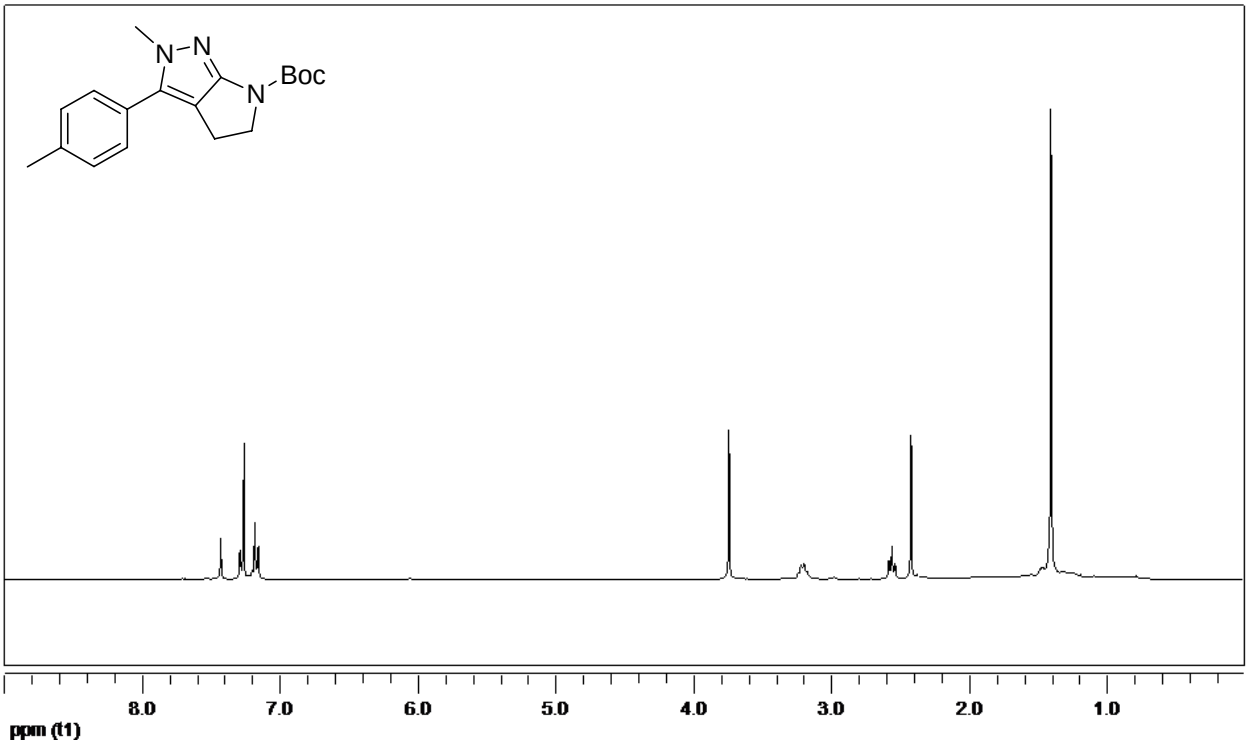
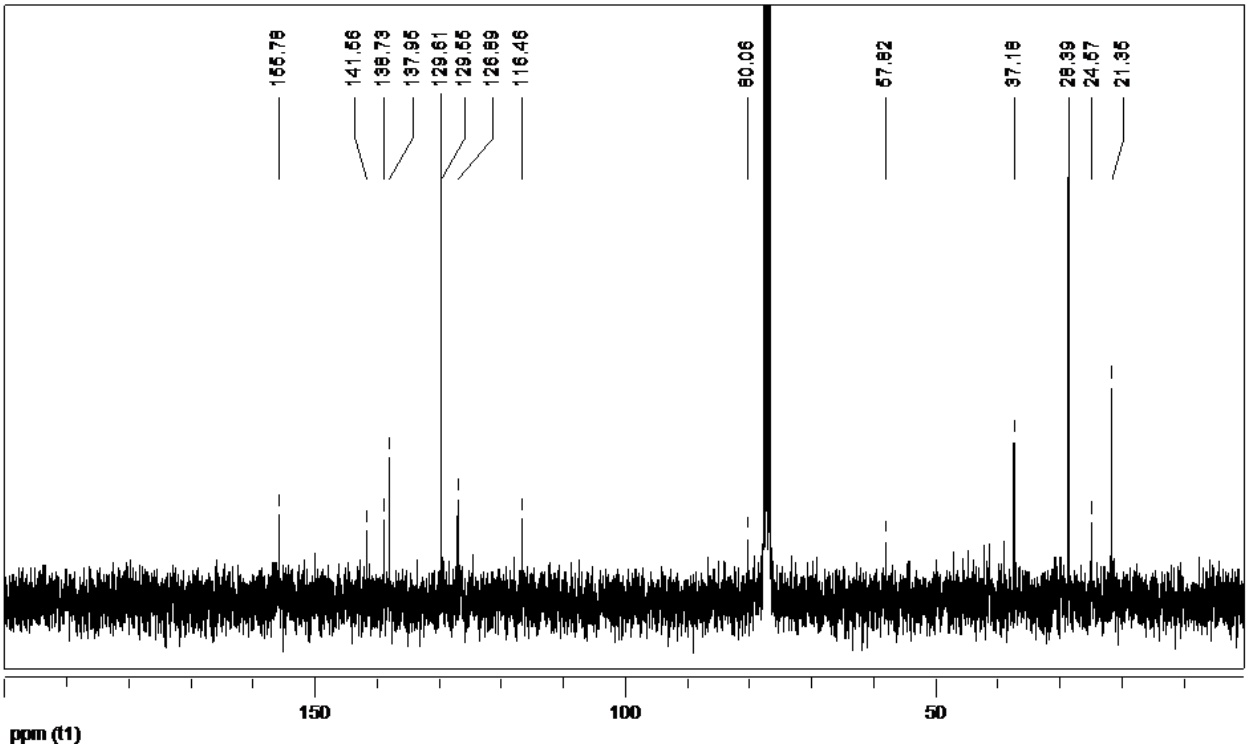


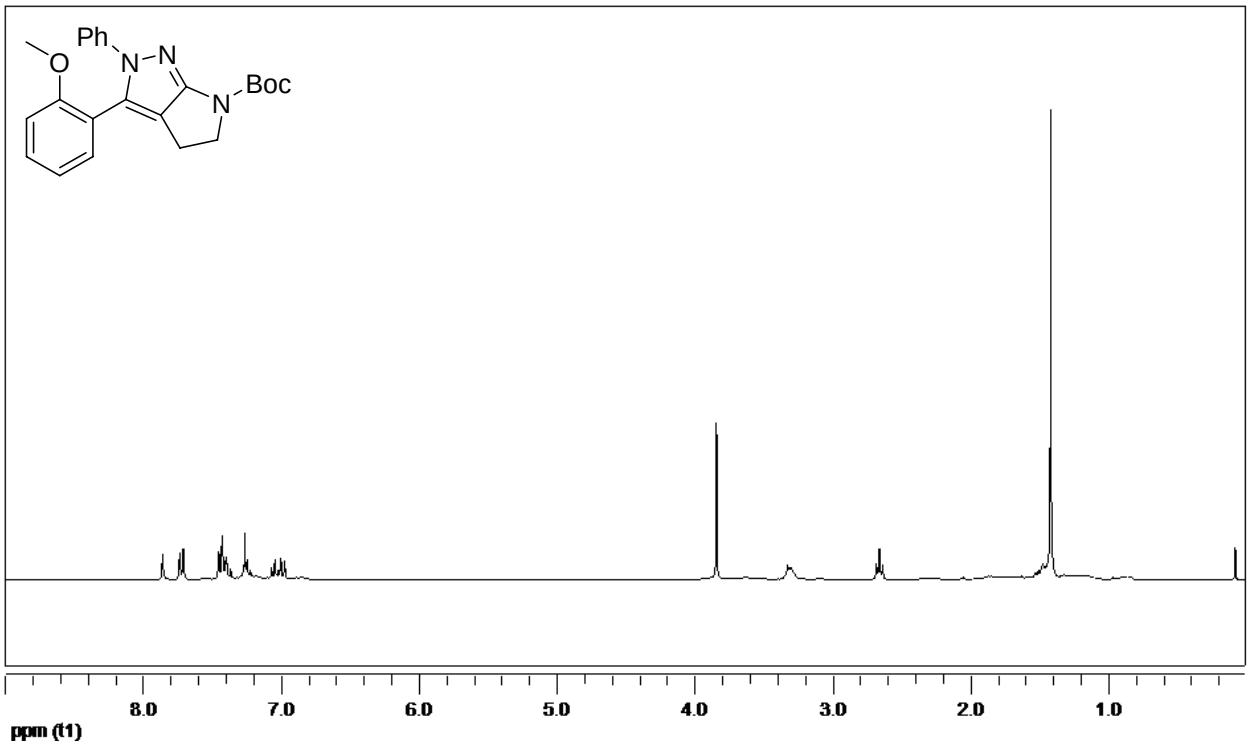


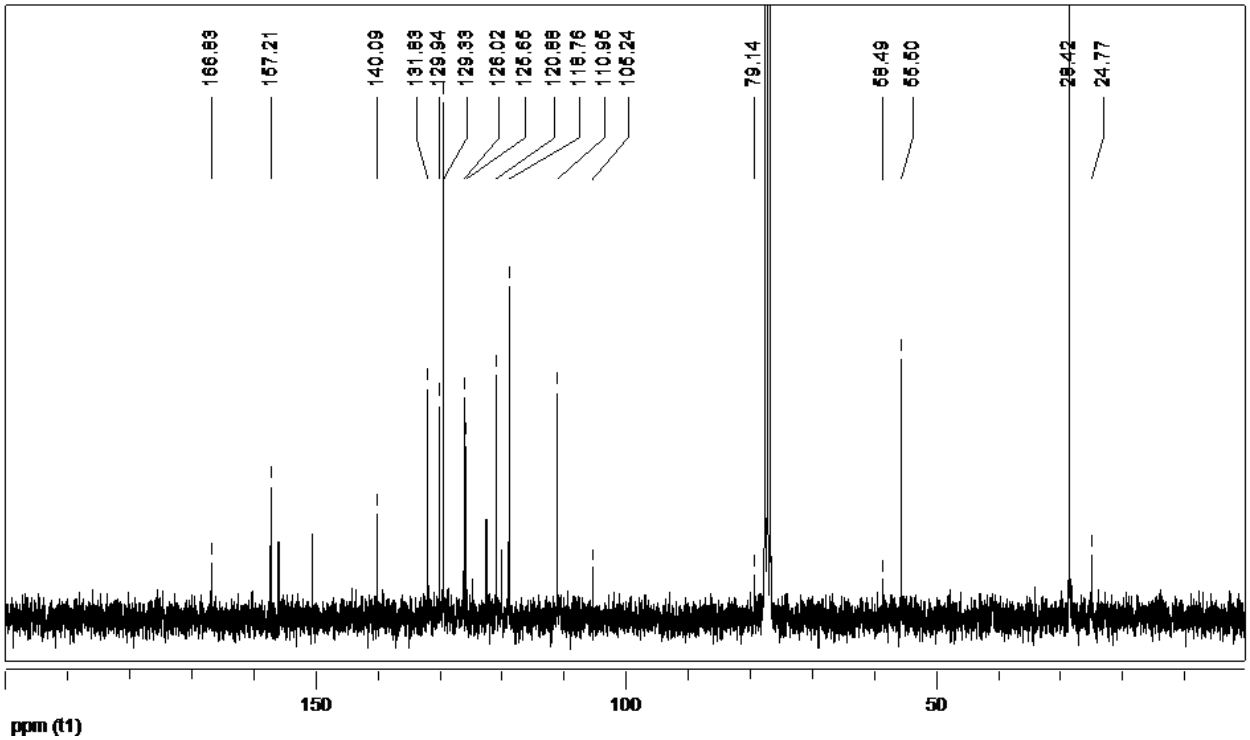
Compound **76f**



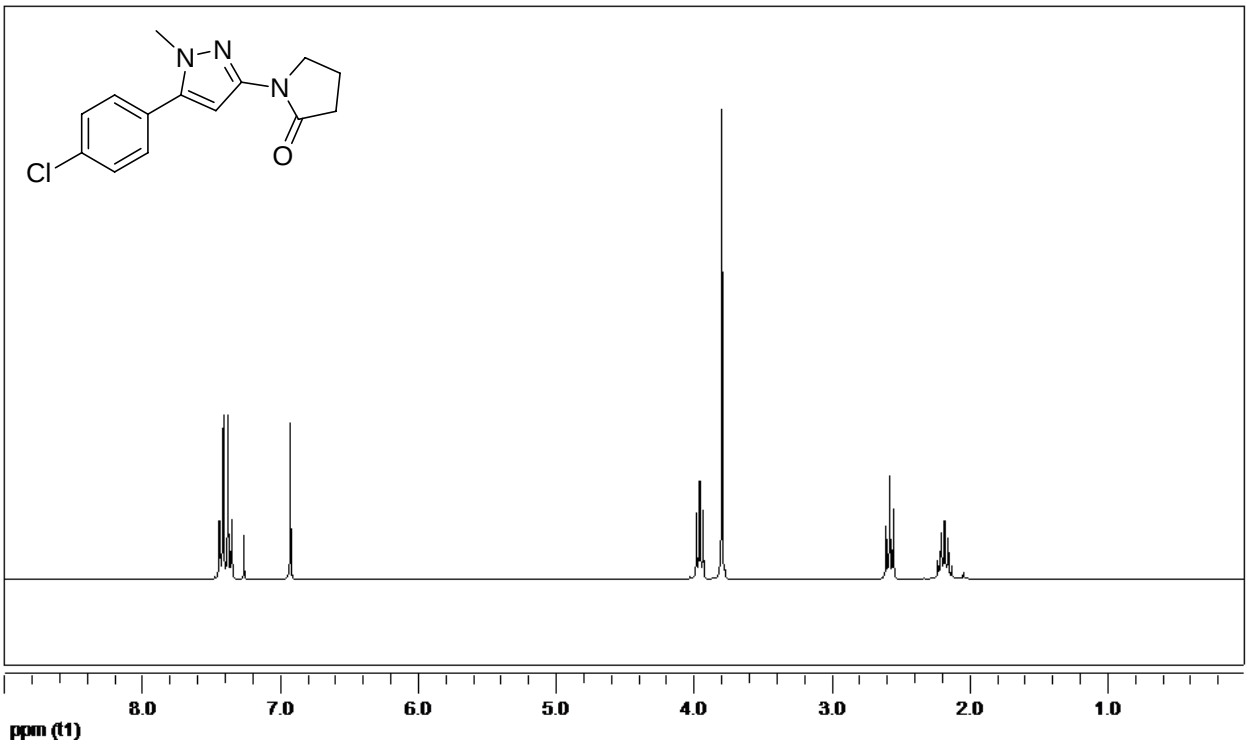


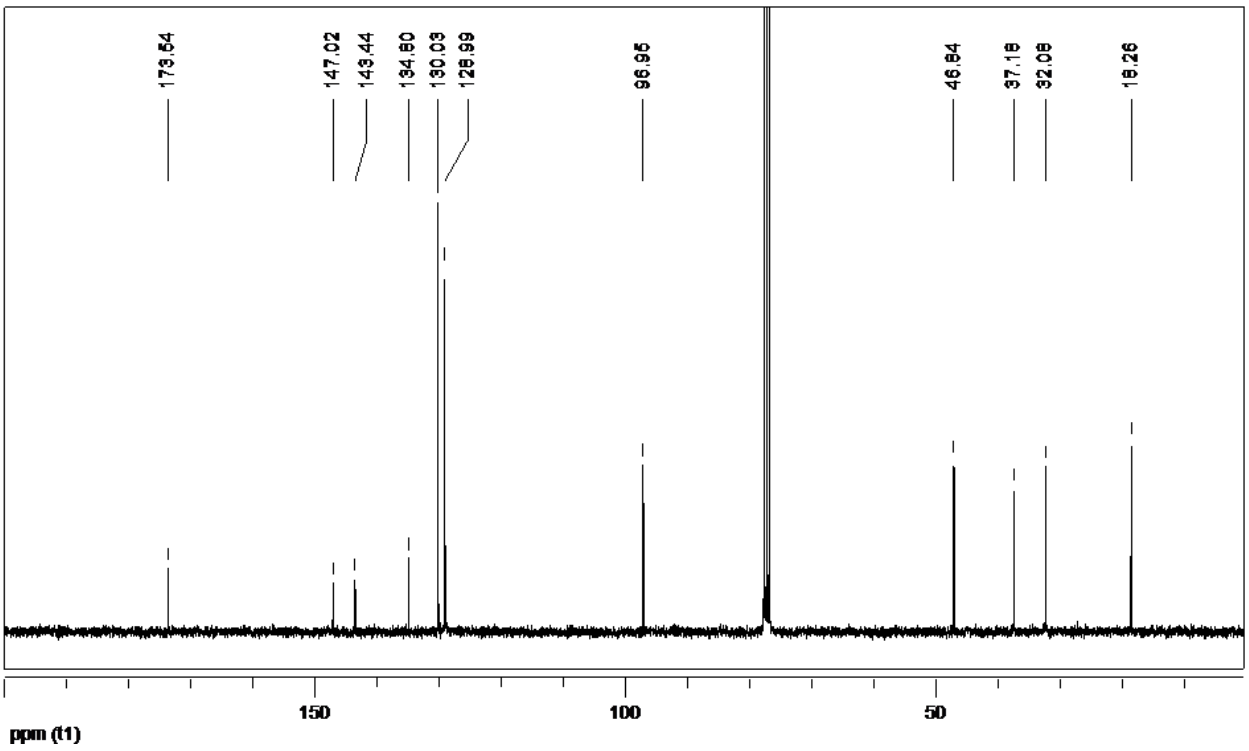
Compound **76g**



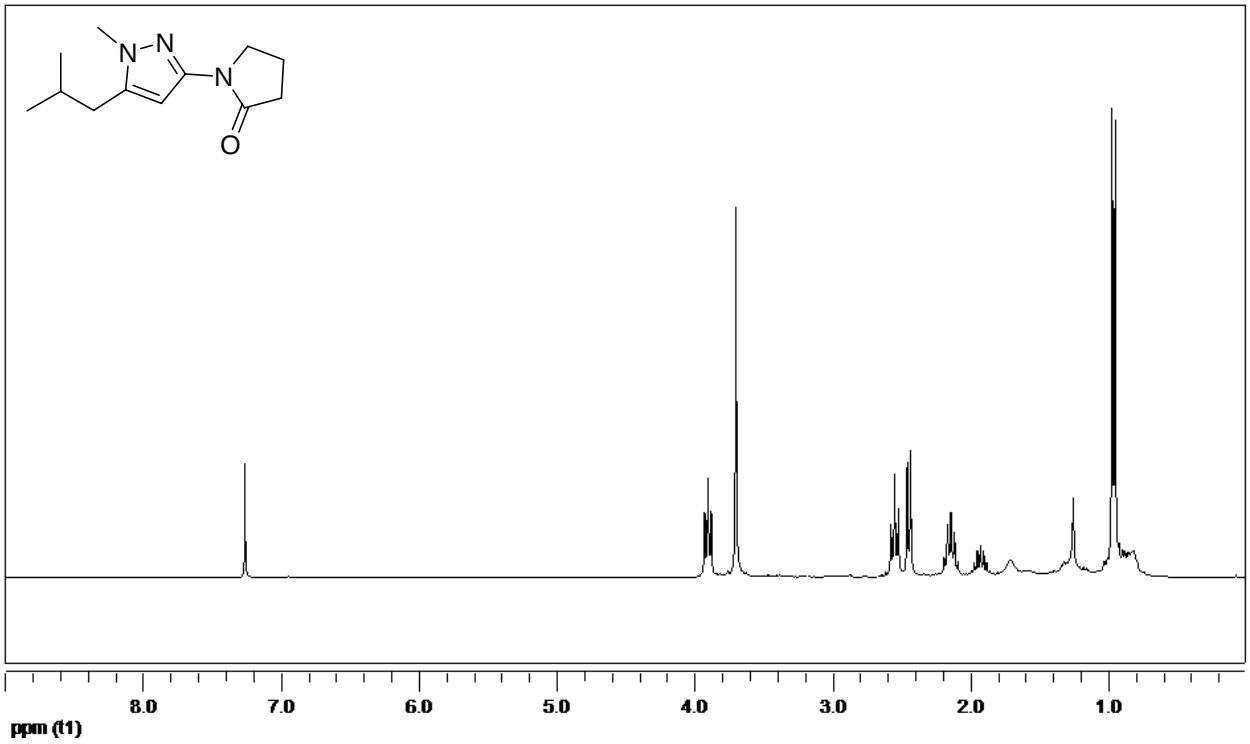


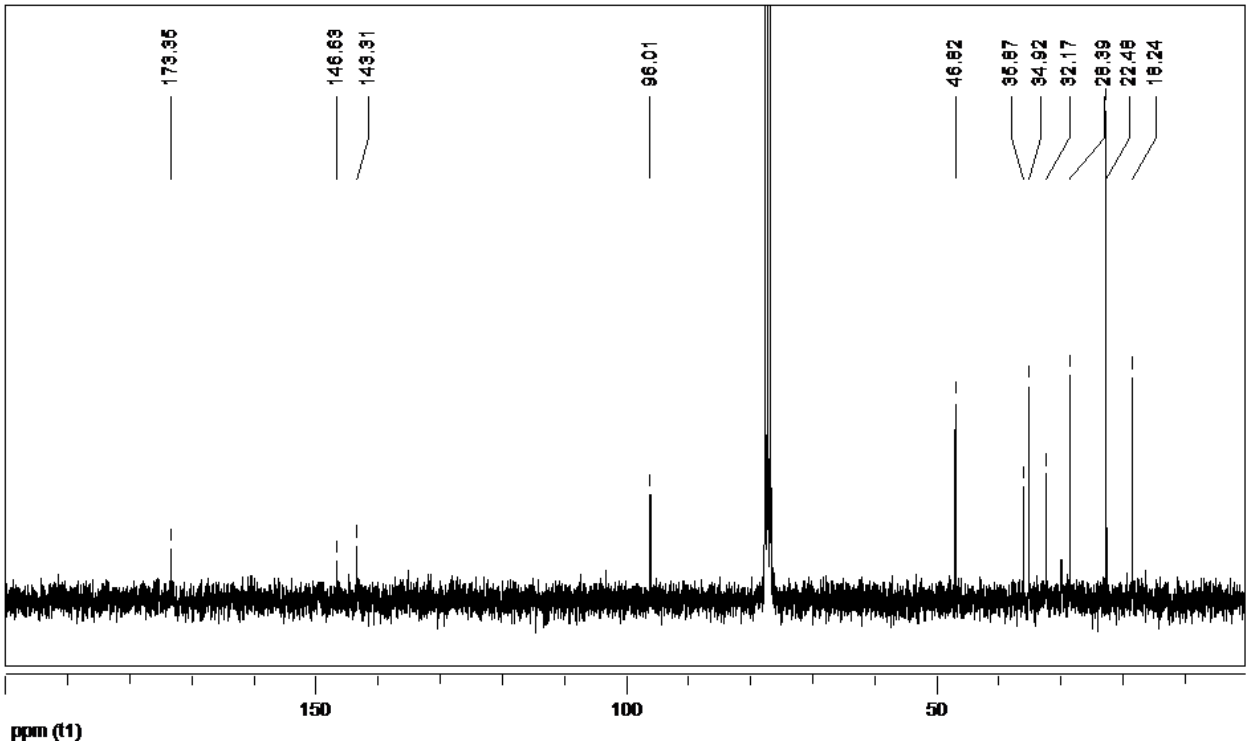
Compound **76h**



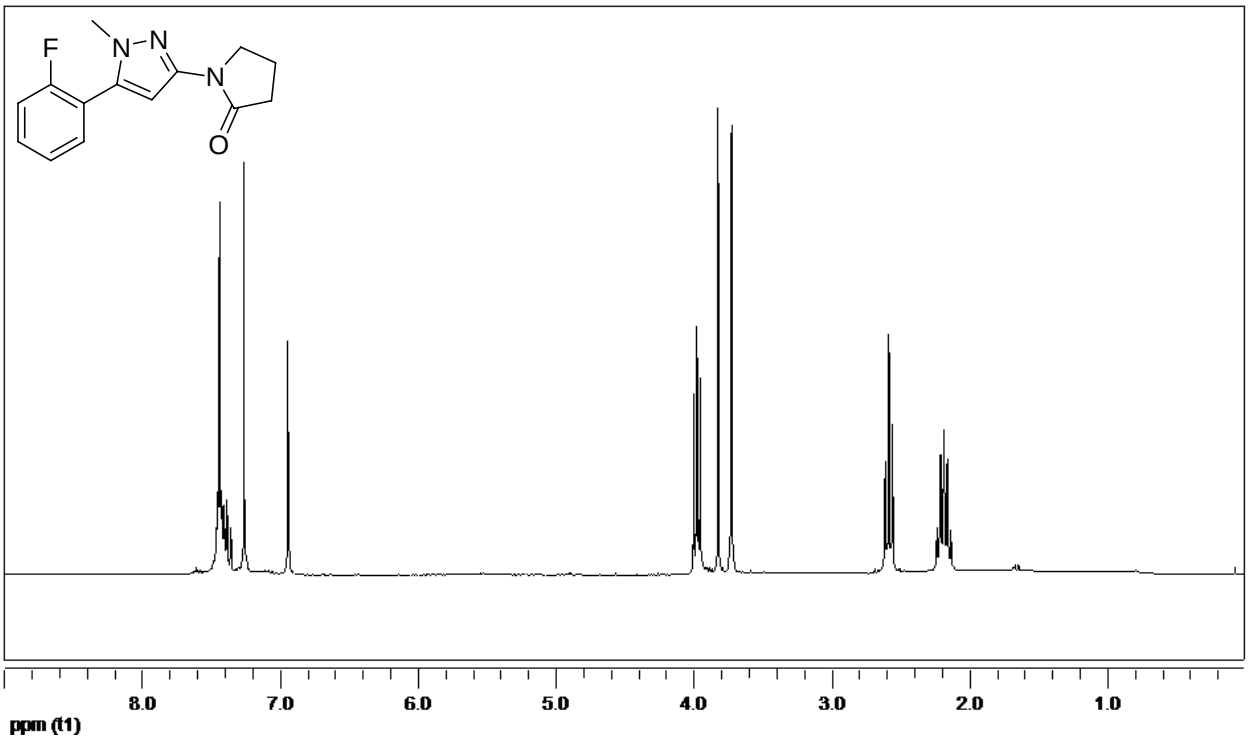


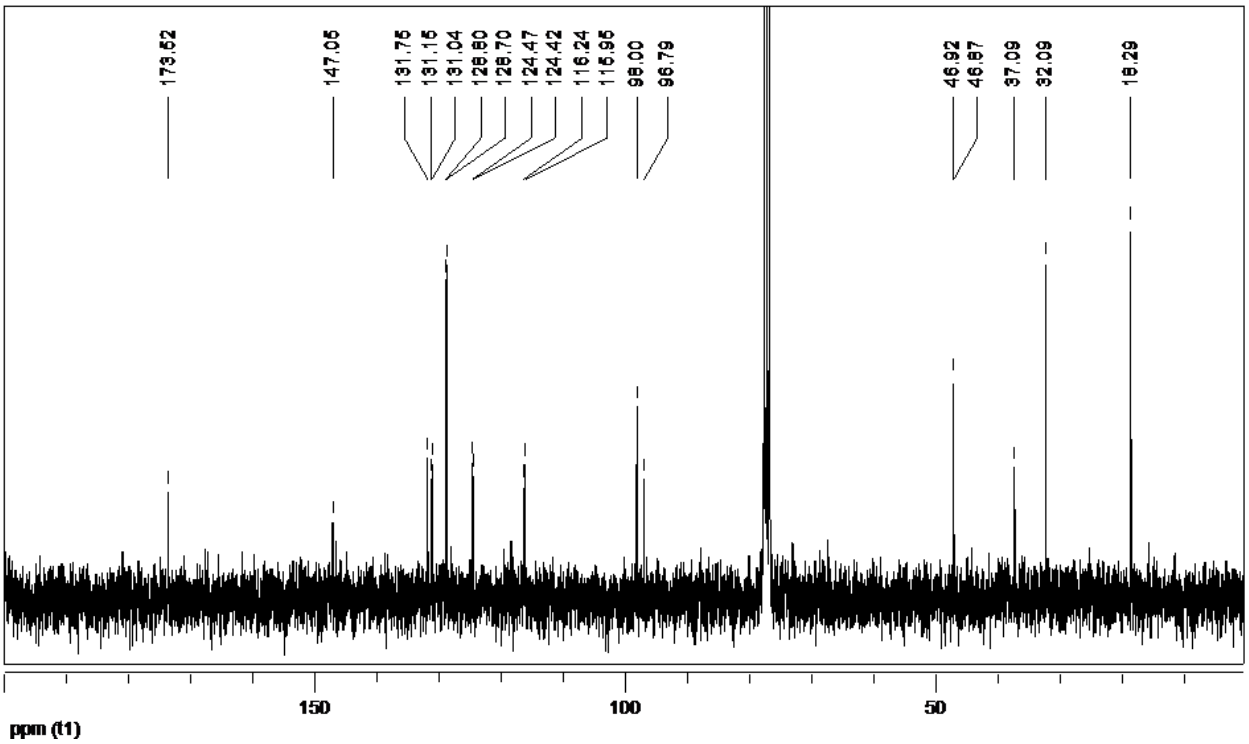
Compound **76i**

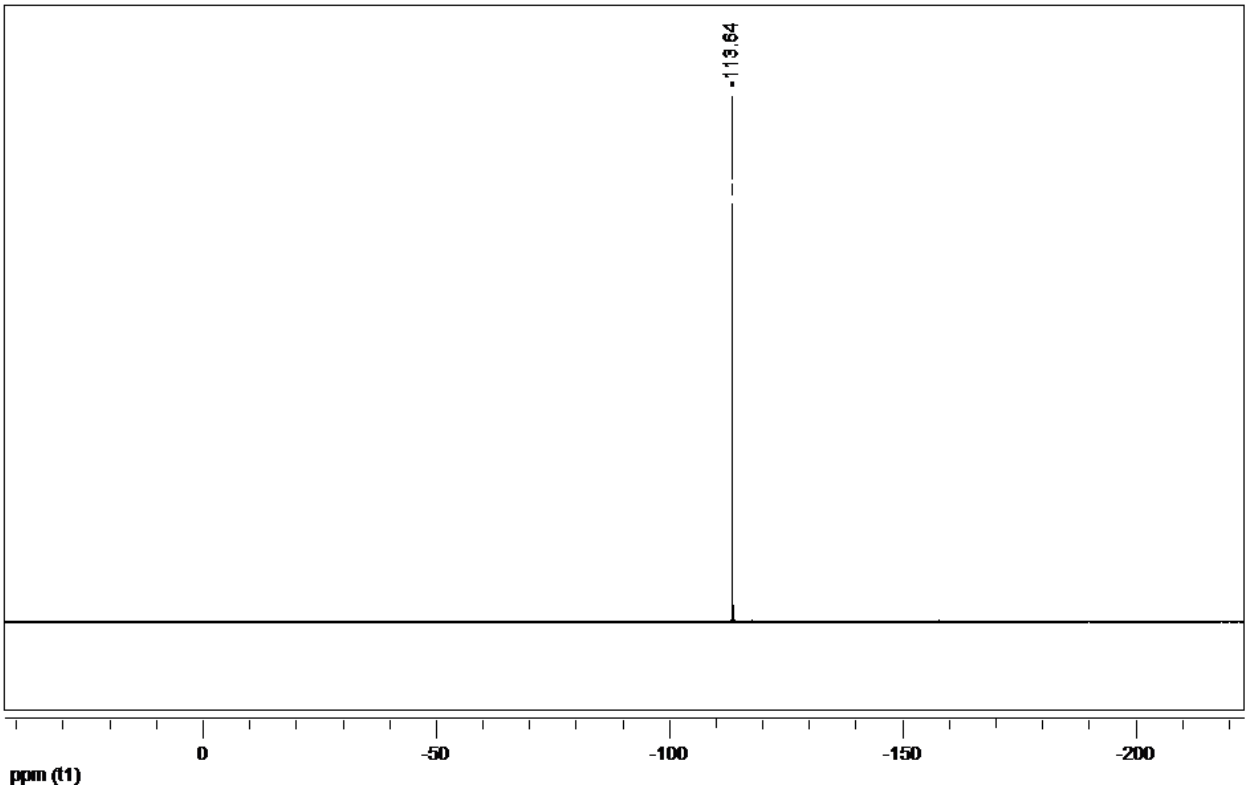




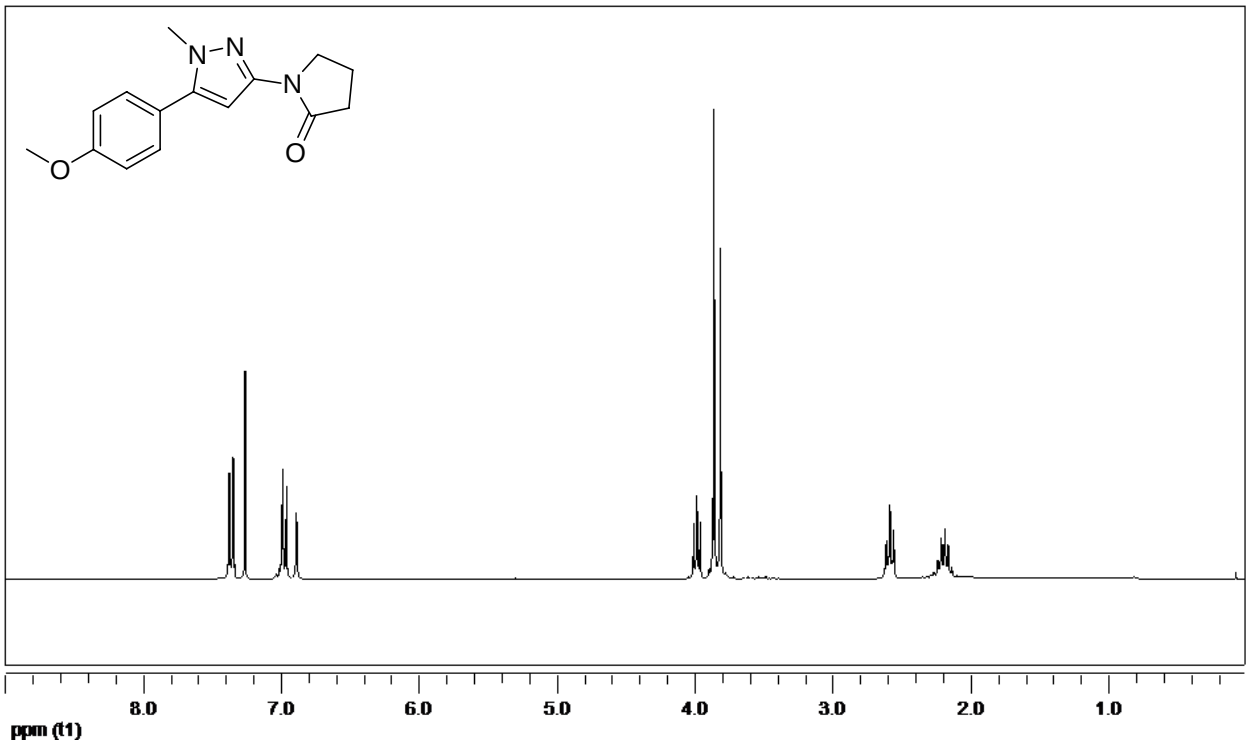
Compound **76j**

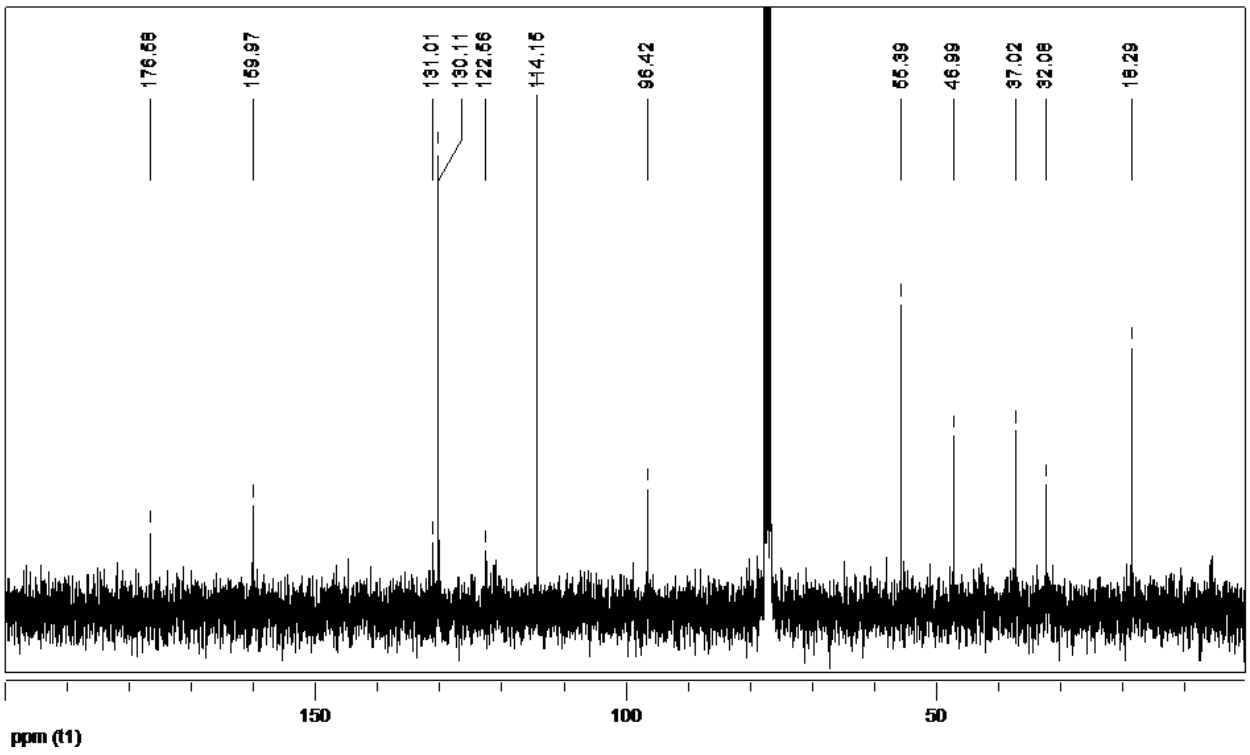




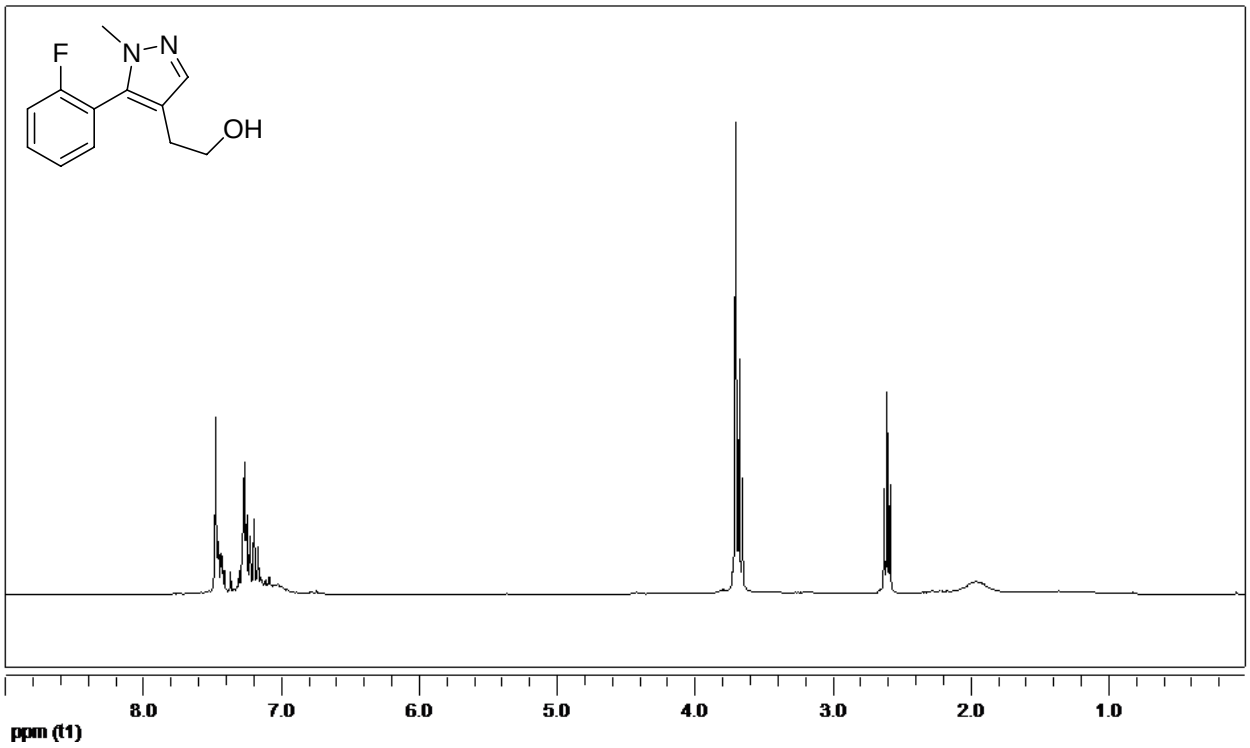

-113.64
0
-50
-100
-150
-200
ppm (t1)

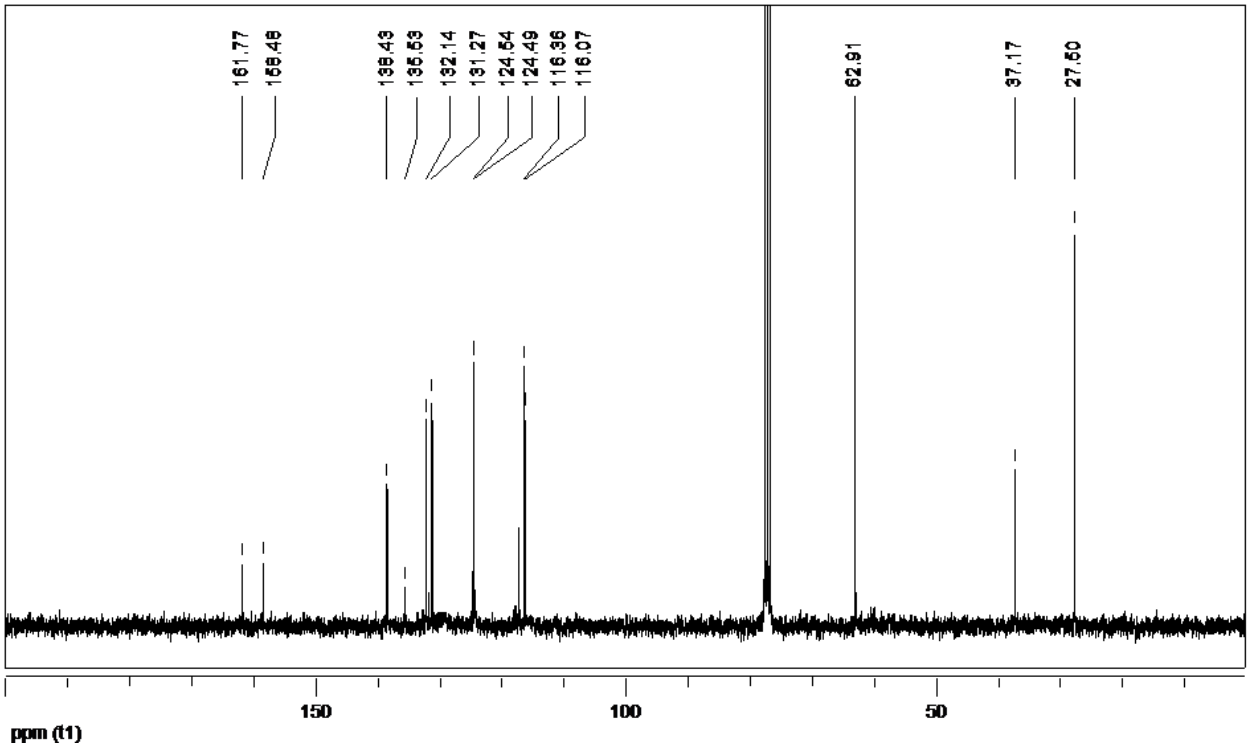
Compound **76k**

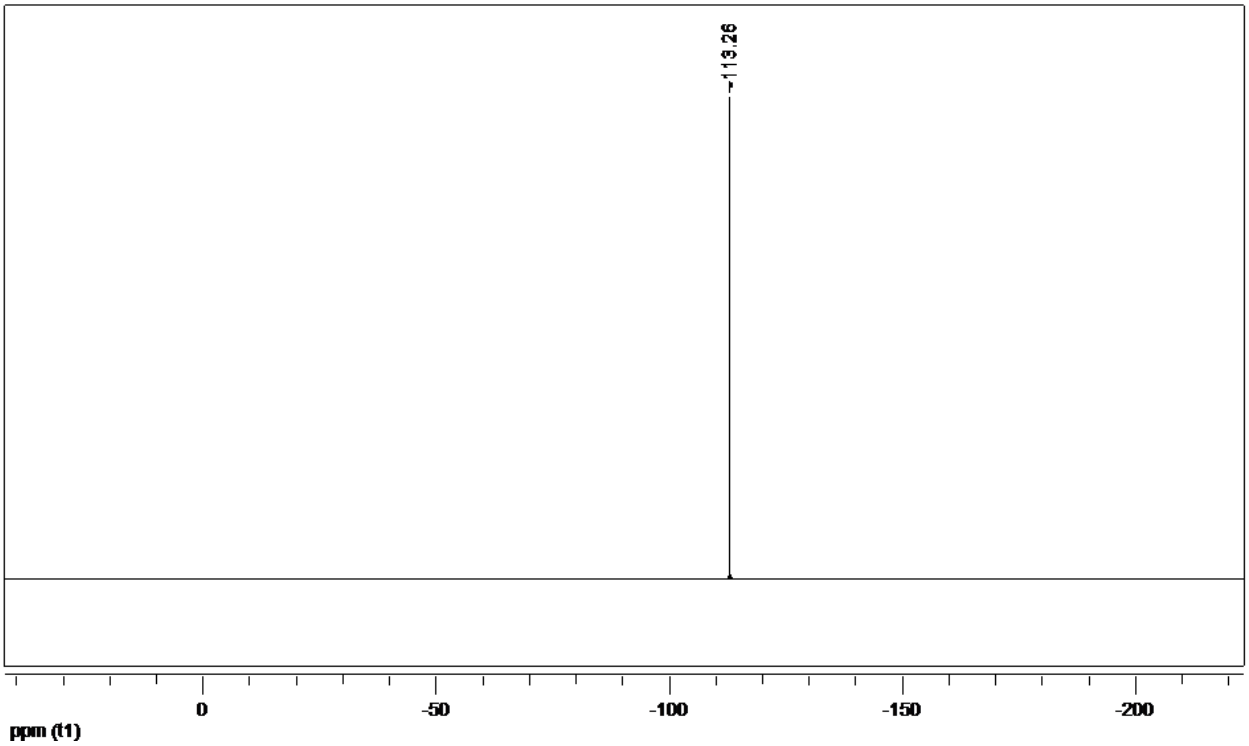




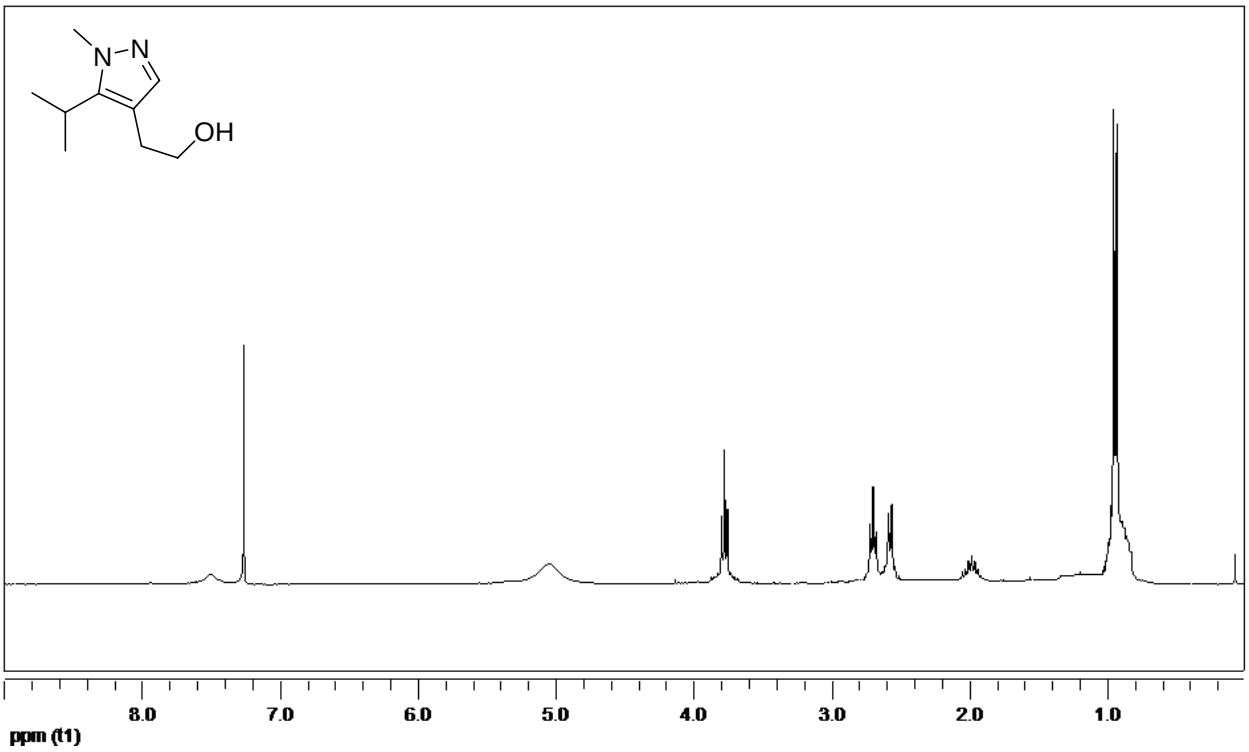
Compound **76l**

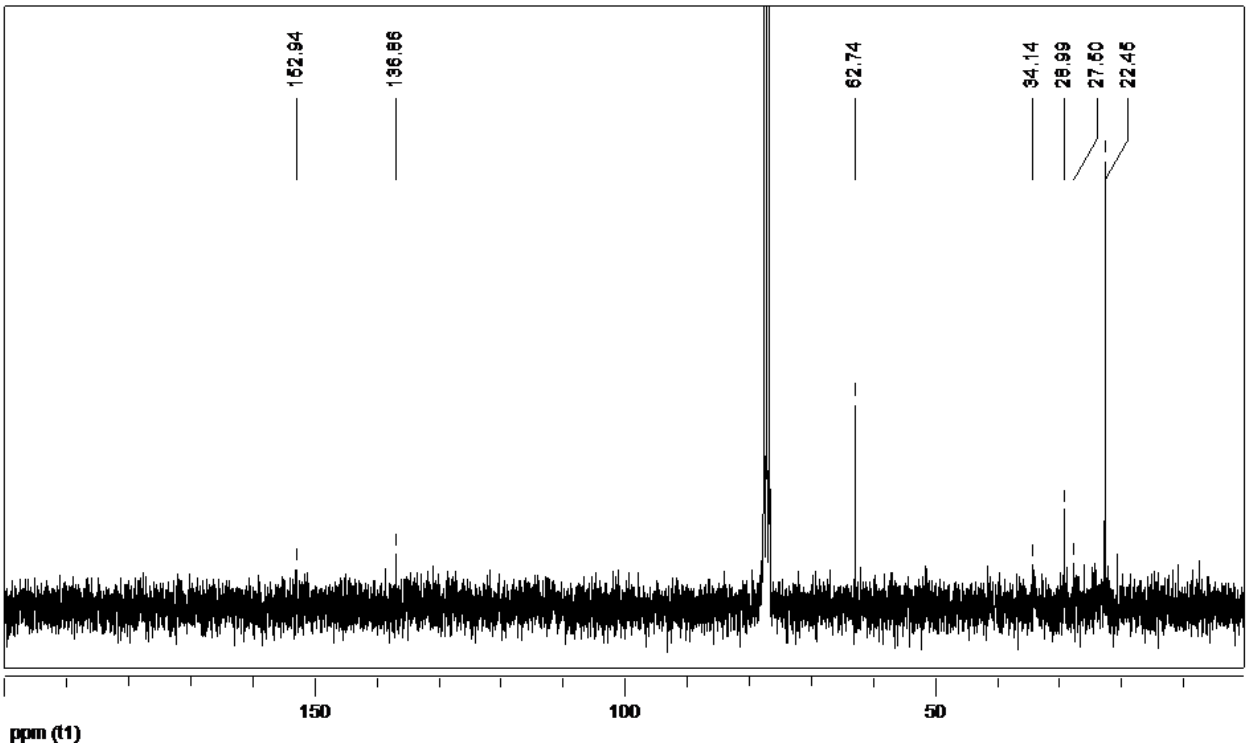





-113.26
0
-50
-100
-150
-200
ppm (t1)

Compound **76m**





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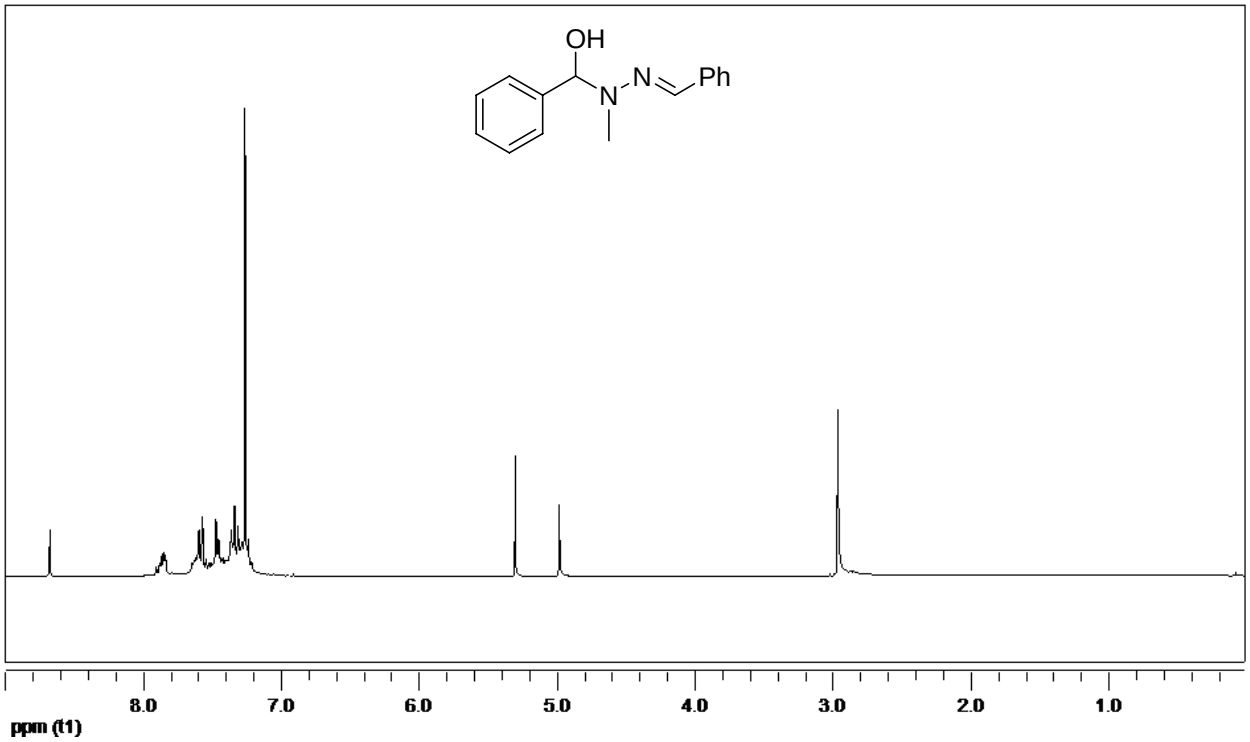
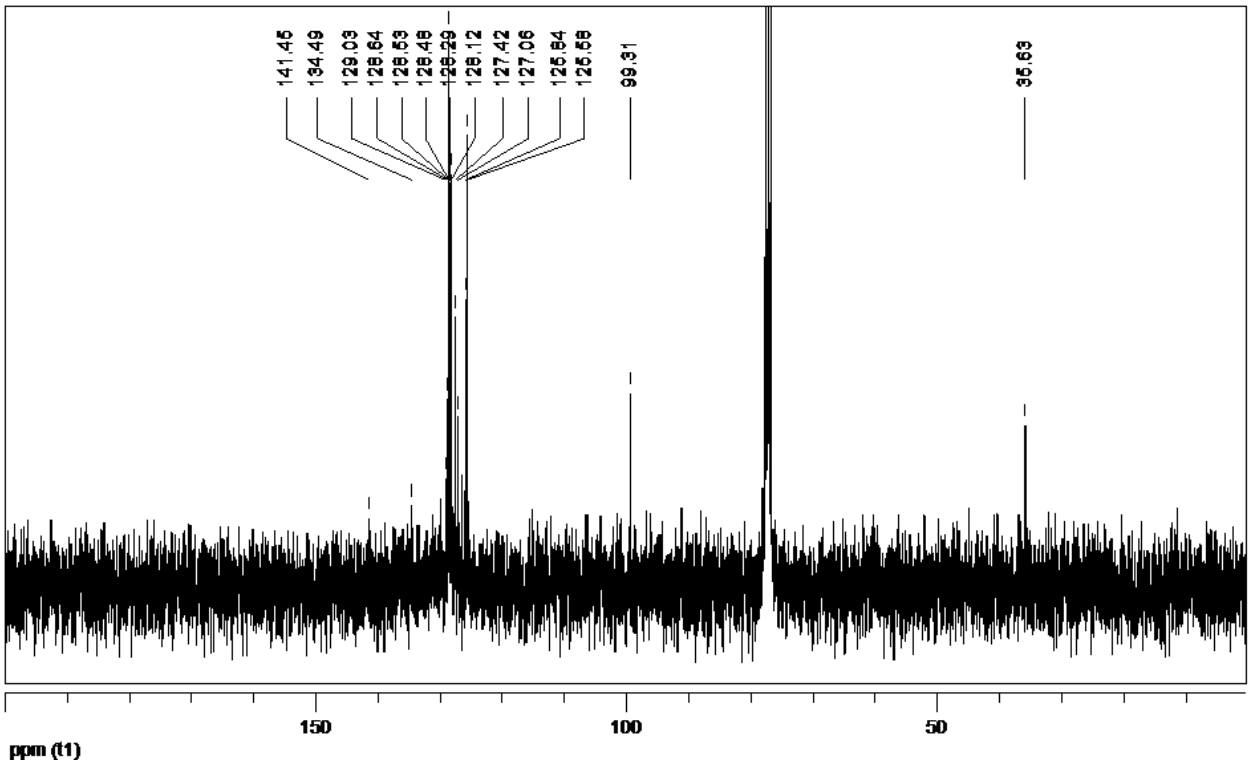
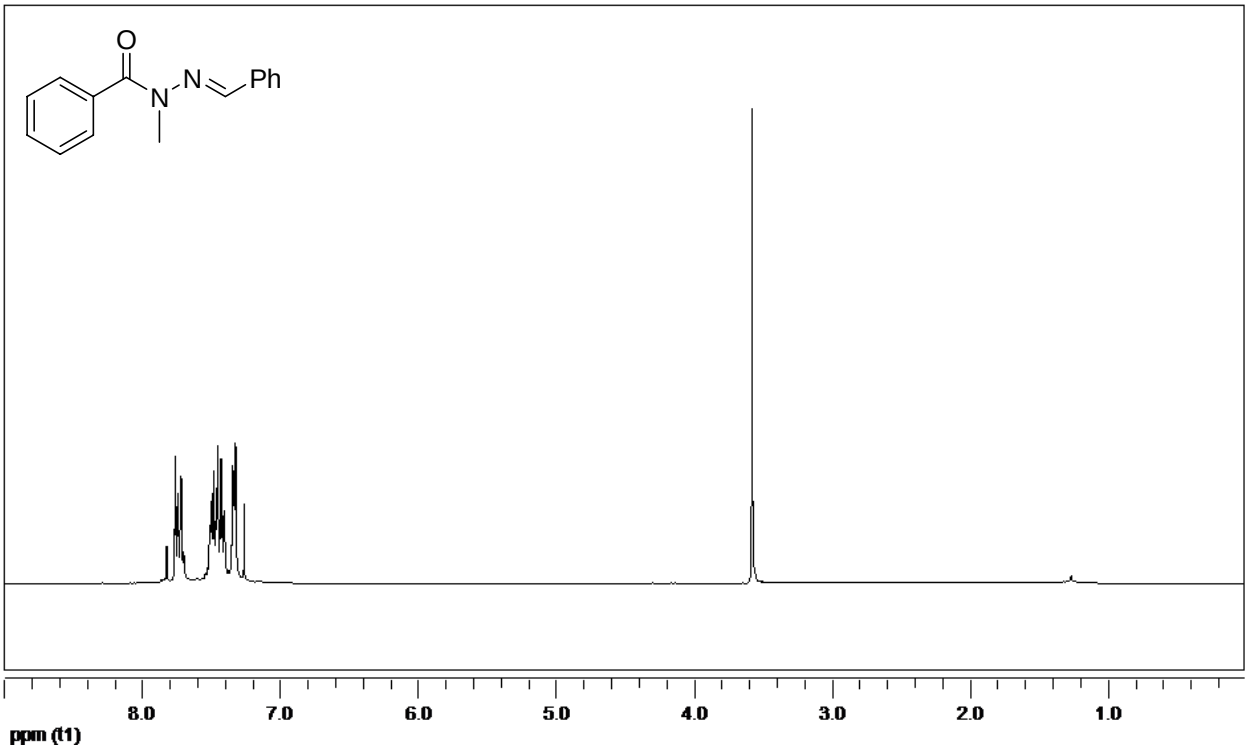
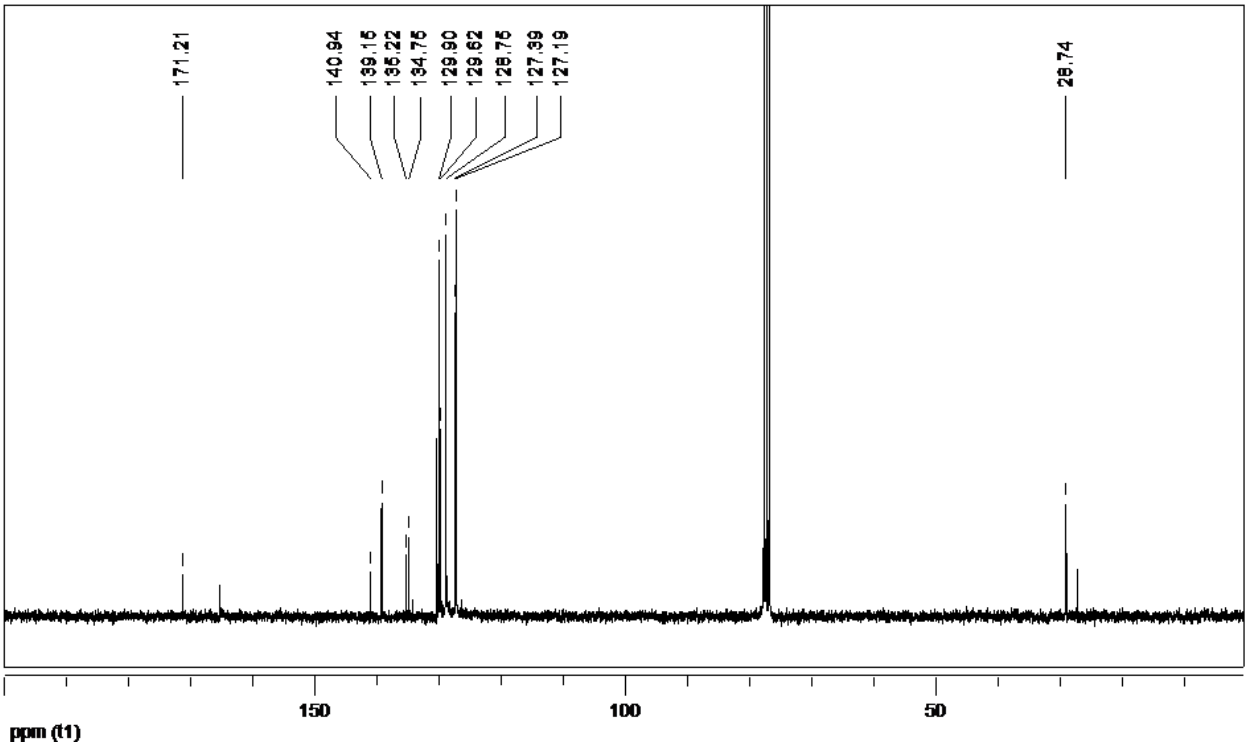




Compound **81a**





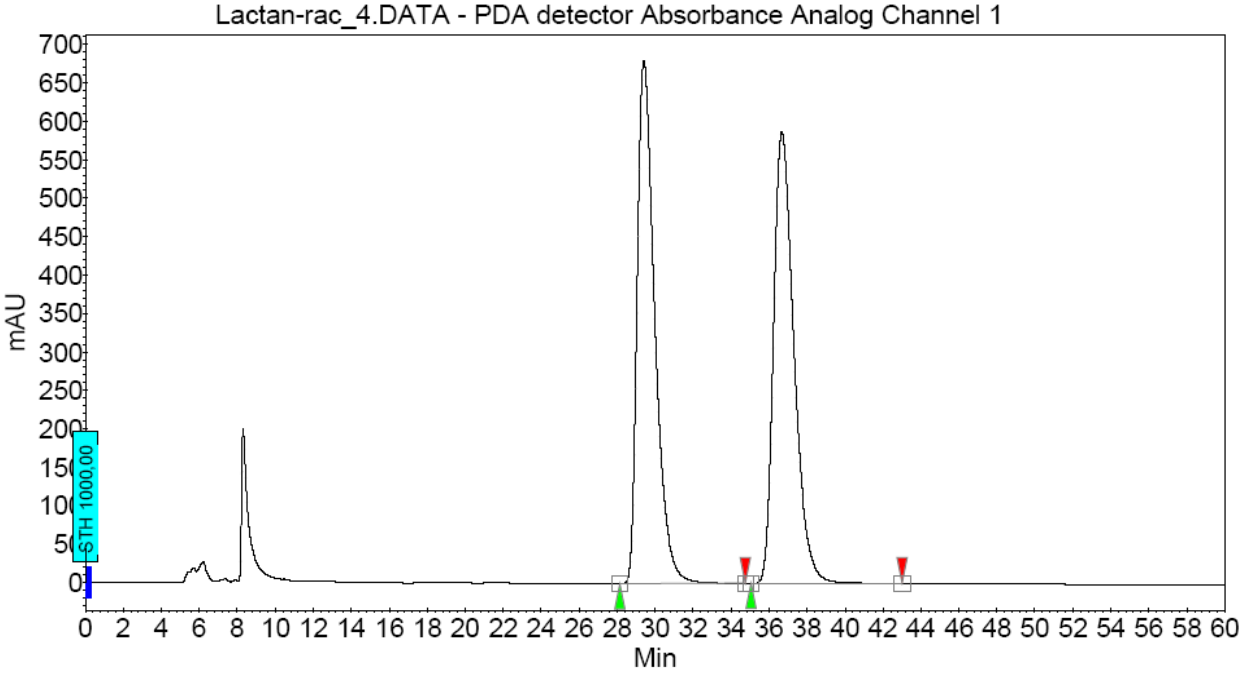
8.3 HPLC data

8.3A HPLC data for racemic and (+)-38a.

Vail : 35
Method : Phex-Cel1_70-30_0.5
Run time : 60,00 min
Inj. vol. : 10,000 µl

λ : _____ nm

Column : Phenomenex Lux Cellulose-1,
4.6 x 250 mm, 5 µm
Eluents : A = n-Heptane
B = i-Propanol
Flow : 0.5 ml/min



Peak Results :

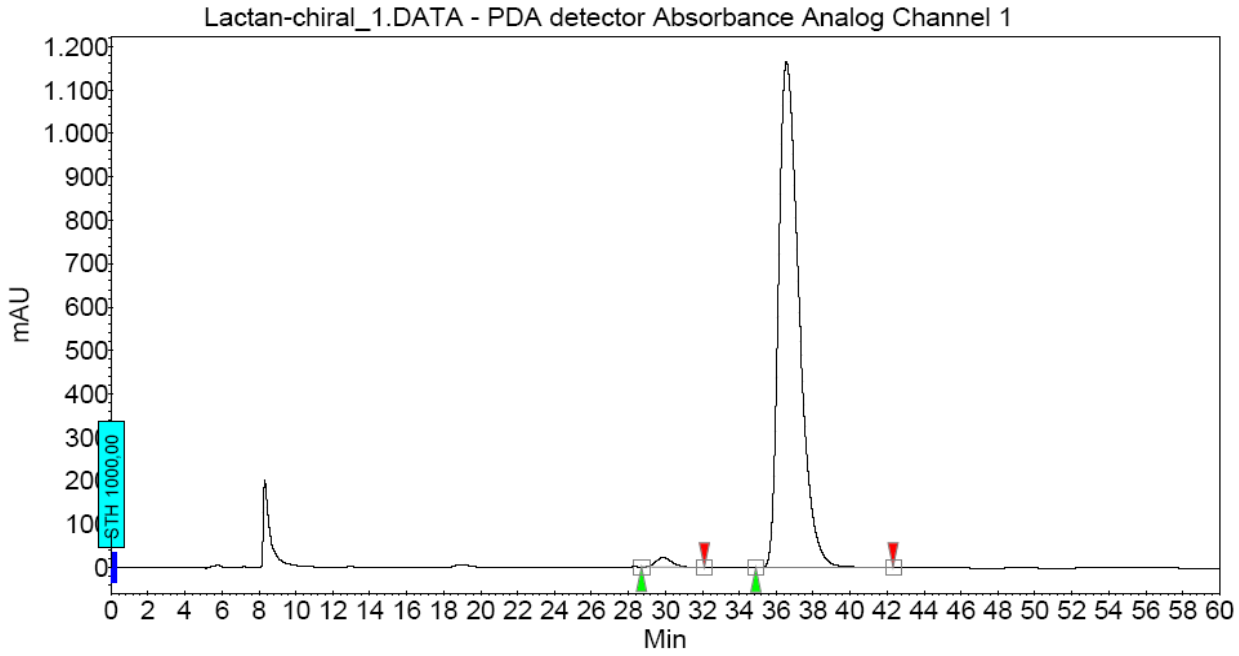
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	29,41	49,90	680,0	721,7	49,895
2	UNKNOWN	36,68	50,10	587,8	724,8	50,105
Total			100,00	1267,8	1446,5	100,000

Lactan-chiral_1

Vail : 36
Method : Phex-Cel1_70-30_0.5
Run time : 60,00 min
Inj. vol. : 10,000 µl

λ : _____ nm

Column : Phenomenex Lux Cellulose-1,
4.6 x 250 mm, 5 µm
Eluents : A = n-Heptane
B = i-Propanol
Flow : 0.5 ml/min



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	29,87	1,52	21,8	23,0	1,521
2	UNKNOWN	36,55	98,48	1164,5	1490,7	98,479
Total			100,00	1186,3	1513,7	100,000

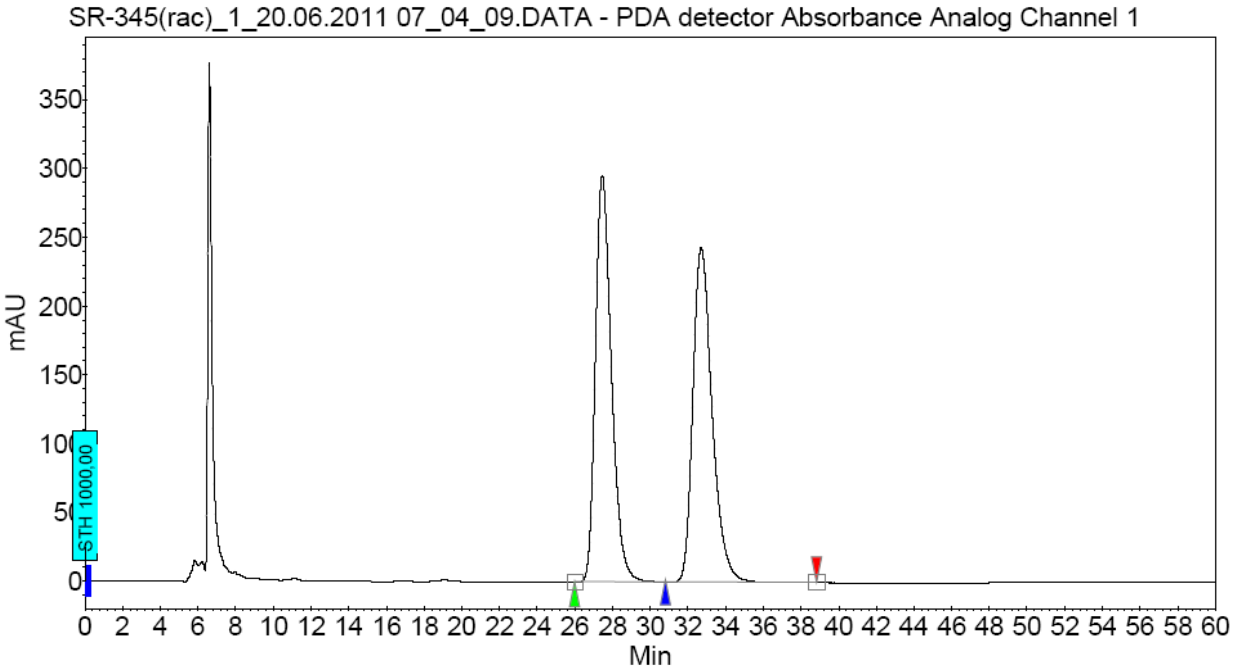
8.3B HPLC data for racemic and (+)-38d.

SR-345(rac)_1_20.06.2011 07_04_09

Vail : 142
Method : Phex-Cel1_50-50_0.5
Run time : 60,00 min
Inj. vol. : 10,000 µl

λ : _____ nm

Column : Phenomenex Lux Cellulose-1,
4.6 x 250 mm, 5 µm
Eluents : A = n-Heptane
B = i-Propanol
Flow : 0.5 ml/min



Peak Results :

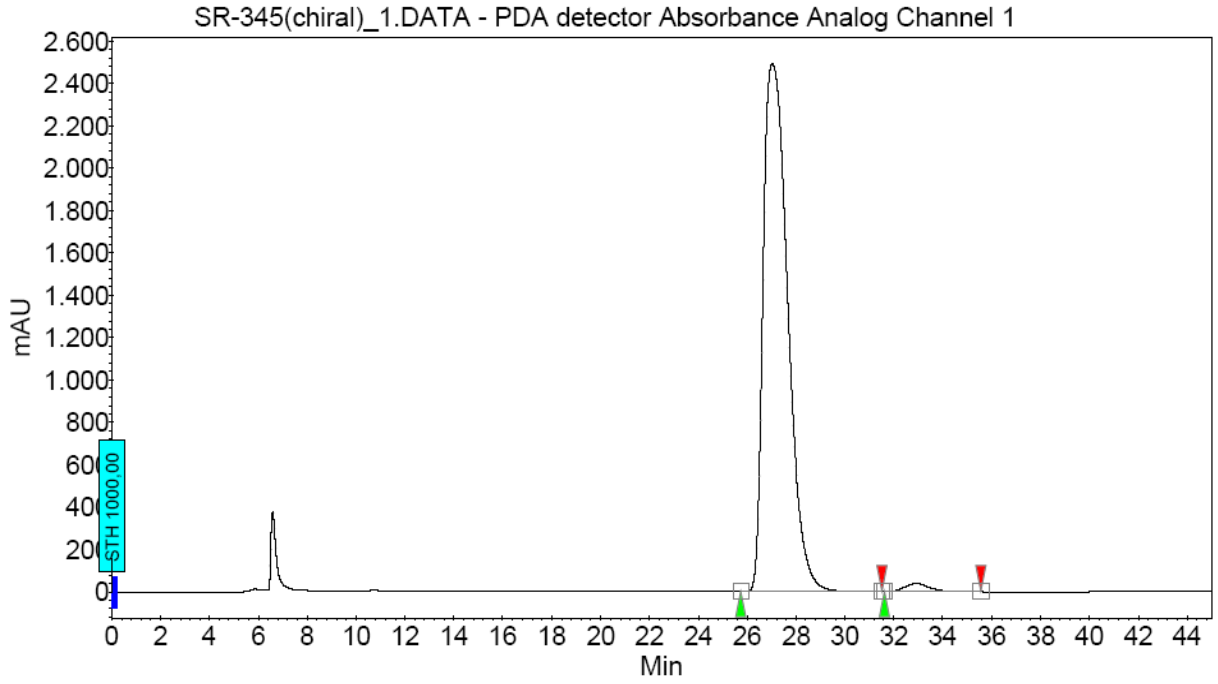
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	27,45	49,92	295,9	289,3	49,919
2	UNKNOWN	32,70	50,08	243,0	290,2	50,081
Total			100,00	538,9	579,5	100,000

SR-345(chiral)_1

Vail : 143
Method : Phex-Cel1_50-50_0.5
Run time : 45,00 min
Inj. vol. : 10,000 µl

λ : _____ nm

Column : Phenomenex Lux Cellulose-1,
4.6 x 250 mm, 5 µm
Eluents : A = n-Heptane
B = i-Propanol
Flow : 0.5 ml/min



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	27,04	98,46	2494,0	2872,3	98,456
2	UNKNOWN	32,90	1,54	37,8	45,0	1,544
Total			100,00	2531,8	2917,3	100,000

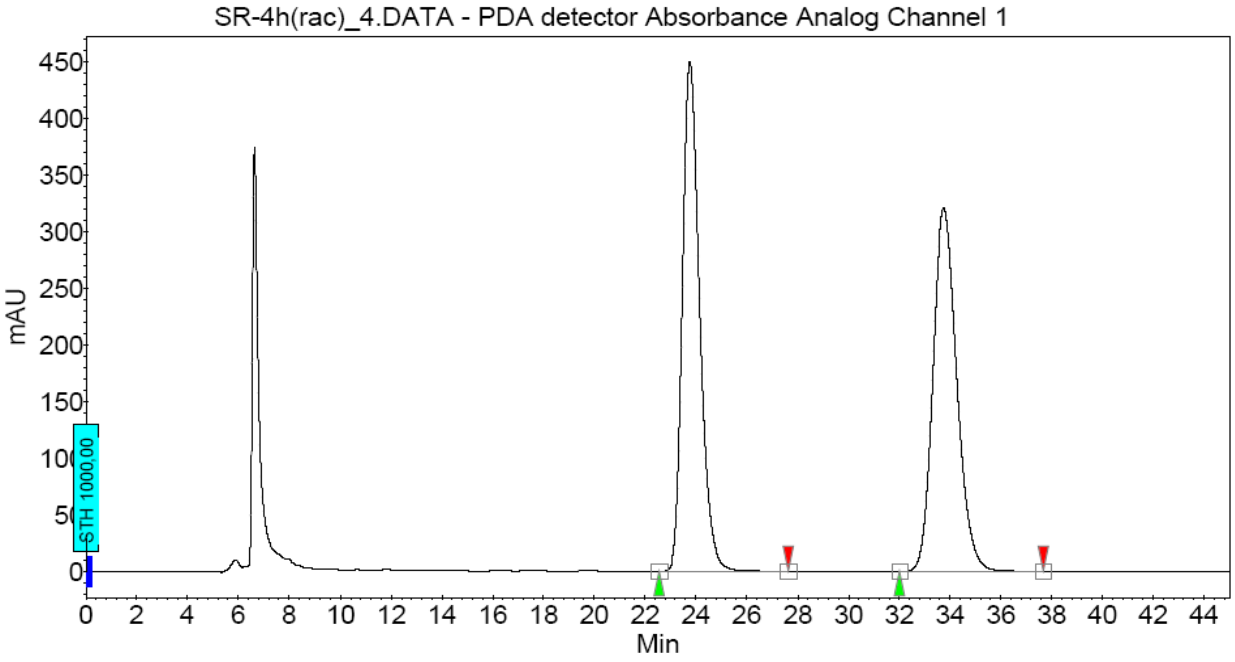
8.3C HPLC data for racemic and (+)-38h.

SR-4h(rac)_4

Vail : 174
Method : Phex-Cel1_50-50_0.5
Run time : 45,00 min
Inj. vol. : 10,000 µl

λ : _____ nm

Column : Phenomenex Lux Cellulose-1,
4.6 x 250 mm, 5 µm
Eluents : A = n-Heptane
B = i-Propanol
Flow : 0.5 ml/min



Peak Results :

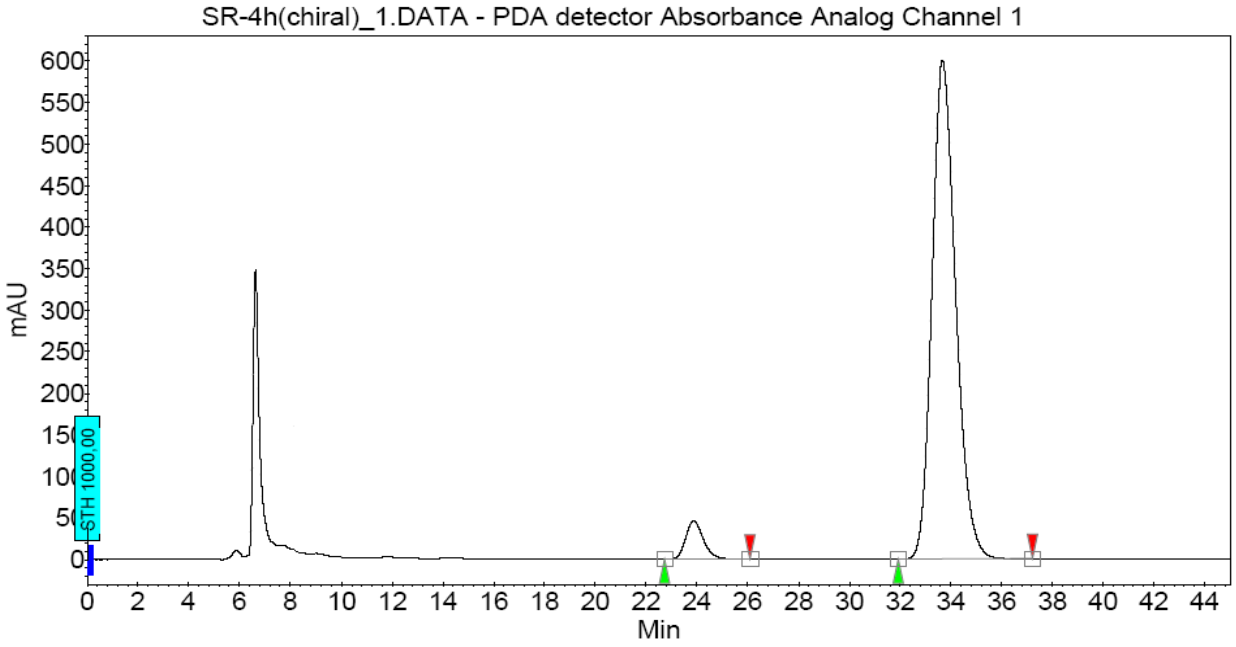
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23,76	50,02	449,4	349,1	50,017
2	UNKNOWN	33,75	49,98	320,6	348,8	49,983
Total			100,00	770,0	697,9	100,000

SR-4h(chiral)_1

Vail : 173
Method : Phex-Cel1_50-50_0.5
Run time : 45,00 min
Inj. vol. : 10,000 µl

λ : _____ nm

Column : Phenomenex Lux Cellulose-1,
4.6 x 250 mm, 5 µm
Eluents : A = n-Heptane
B = i-Propanol
Flow : 0.5 ml/min



Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23,87	5,30	45,7	36,5	5,298
2	UNKNOWN	33,68	94,70	600,2	653,2	94,702
Total			100,00	646,0	689,8	100,000

Abbreviations

abs	absolute
Ar	aryl
atm.	atmosphere
BA	Brønsted acid
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bz	benzoyl
Cbz	carboxybenzyloxy
dr	diastereomeric ratio
D-A	donor-acceptor
DBU	1,8-diazabicyclo[4.4.0] undec-7-ene
DCM	dichloromethane
DMF	dimethyl formamide
DOS	diversity-oriented synthesis
ee	enantiomeric excess
EE	ethylacetate
EI	electron impact (MS)
equiv	equivalents
ESI	electronspray ionization (MS)
EtOH	ethanol
Et	ethyl
etc.	etcetera
H	hour (s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
LA	Lewis acid
^{i}Pr	*iso*-propyl
IR	infrared spectroscopy
M	metal
MCR	multicomponent reaction
Me	methyl
MeCN	acetonitril
min	minutes
MS	molecular sieves
^{n}Bu	*n*-butyl
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	nucleophile
^{n}Pr	*n*-propyl
o-	*ortho*-
OAc	acetate
OTf	triflate
p-	*para*
Ph	phenyl
quant.	quantitative
rac	racemic
rt	room temperature
^{t}Bu	*tert-butyl*
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	trifluormethanesulfonate
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
UV	ultraviolet
x	arbitrary number
X	arbitrary anion

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10/2009 – 12/2012: Ph.D under supervision of
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06/2009 – 09/2009: German courses at the Goethe-Institut Mannheim
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11/2007 - 03/2009: Research project under supervision of
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08/2007 – 10/2007: Research project under supervision of
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Academic Achievements:

- PhD fellowship from **DAAD 2009** (Deutscher Akademischer Austausch Dienst).
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Scientific Publications:

1. **Sudipta Roy** and Oliver Reiser*, A Catalytic Multicomponent Approach for the Stereoselective Synthesis of *Cis*-4,5-Disubstituted Pyrrolidinones and Tetrahydro-3*H*-pyrrolo[3,2-*c*]quinolines, *Angew. Chem., Int. Ed.* **2012**, *51*, 4722.
DOI: 10.1002/anie.201107831

2. **Sudipta Roy** and Oliver Reiser*, Highly Regioselective Synthesis of *Cis*-4,5-Disubstituted Pyrrolidinones via a Microwave-Assisted Povarov-Cyclopropane Ring-Opening-Intramolecular Furan Ring Migration Reaction,

Abstracts of Papers, 242nd ACS National Meeting, Denver, Colorado, United States, August 28 to September 1st, **2011**.

3. Shrutisagar Dattatraya Haveli, **Sudipta Roy** and Srinivasan Chandrasekaran*, Synthesis of Unnatural C-2 Amino Acid Nucleosides Using NIS-Mediated Ring Opening of 1,2-Cyclopropane Carboxylated Sugar Derivatives, *Synlett*, **2009**, 451.
DOI: 10.1055/s-0028-1087545

4. **Sudipta Roy** and Oliver Reiser*, A Regio- and Stereoselective Catalytic Multicomponent Approach for Syntheses of Functionalized Tetrahydro-, Dihydro- and 1*H*-Pyrazoles (*Manuscript under process*).

5. **Sudipta Roy** and Oliver Reiser*, Recent Developments of Povarov Reaction (*Review article under process*).

Presentations:

1. A Catalytic Multicomponent Approach for the Efficient Synthesis of Pyrrolidinones and Pyrazolidines (**Short Lecture & Poster Presentation**) - ORCHEM **2012**, Weimar, Germany.

2. Catalytic Multicomponent Approaches for the Efficient Syntheses of Pyrrolidinones and Pyrazolidines (**Poster Presentation**) – A thematic mini-symposium, June 4-6, **2012**, University of Regensburg, Germany.

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