SYNTHESIS OF HIGHLY SUBSTITUTED ALKYNYLPYRIDINES AND DEVELOPMENT OF NEW METHODOLOGIES FOR THE SYNTHESIS OF 1,4-OXAZEPINES, 1,4-THIAZEPINES AND 5-METHYLPYRIDINES

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YILMAZ KELGÖKMEN

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ABSTRACT

SYNTHESIS OF HIGHLY SUBSTITUTED ALKYNYLPYRIDINES AND DEVELOPMENT OF NEW METHODOLOGIES FOR THE SYNTHESIS OF 1,4-OXAZEPINES, 1,4-THIAZEPINES AND 5-METHYLPYRIDINES

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Convenient syntheses of pyridines, 1,4-oxazepines and 1,4-thiazepines have become an important research area among organic chemists since they constitute scaffolds of many medicinal substances. Recently, *N*-propargylic β-enaminones have been widely used for the facile synthesis of potent biologically active heterocycles. Many research groups have focused on the proper synthesis of various heterocycles by using *N*-propargylic β-enaminones. One of the such recent reports using these precursors is the formation of 5-iodopyridines by iodine-mediated electrophilic cyclization reaction. Accordingly, in this thesis work, the first aim is to further functionalize 5-iodopyridines by utilizing Sonogashira cross-coupling reaction. With this way, we have synthesized 28 new 5-alkynylpyridines in 40-99% yields. Secondly, for the synthesis of 1,4-oxazepines, we have reinvestigated $ZnCl_2$-mediated 7-*exo*-*dig* cyclization in refluxing $CHCl_3$ to get higher yields in shorter reaction durations. Thus, we have achieved the smooth synthesis of many 2-methylene-2,3-dihydro-1,4-oxazepine derivatives in good to high yields (66-95%) in 1.5-12.0 h. In some cases, conversion of alkyl-substituted 1,4-oxazepines to the corresponding pyrrole derivatives has been observed to some extent during their isolation on silica gel. In the third part of the thesis work, we

have prepared novel starting *N*-propargylic thio-β-enaminones from the corresponding *N*-propargylic β-enaminone precursors by using Lawesson's reagent (LR). Then, we have examined the cyclization reactions of these thio-β-enaminones by using $ZnCl_2$ in refluxing $CHCl_3$. We have synthesized 20 novel 2-methylene-2,3-dihydro-1,4-thiazepines in 67-90% yields by using this unprecedented synthetic methodology. Finally, base-catalyzed cyclization reactions of *N*-propargylic thio-β-enaminones have been investigated, which afforded methyl-substituted pyridines via sulfur extrusion. Accordingly, in the presence of diisopropylamine (DIPA) at room temperature, many alkylpyridines have been synthesized in moderate to high yields (46-85%), except for one derivative (13%).

Keywords: Pyridines, 1,4-Oxazepines, 1,4-Thiazepines, 7-*Exo-dig* cyclization, *N*-Propargylic thio-β-enaminones

ÖZ

ÇOK GRUPLU ALKİNİLPİRİDİNLERİN SENTEZİ VE 1,4-OKSAZEPİNLER, 1,4-TİYAZEPİNLER VE 5-METİLPİRİDİNLERİN SENTEZİ İÇİN YENİ METODOLOJİLERİN GELİŞTİRİLMESİ

Kelgökmen, Yılmaz
Doktora, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Zora
Nisan 2018, 375 sayfa

Birçok tıbbi maddenin yapı iskelelerini oluşturduklarından dolayı piridinlerin, 1,4-oksazepinlerin ve 1,4-tiyazepinlerin elverişli sentezleri organik kimyacılar arasında önemli bir araştırma alanı olmuştur. Son dönemlerde, biyolojik olarak aktif olabilecek heterohalkaların kolay sentezi için *N*-proparjilik β-enaminonlar yaygın olarak kullanılmaktadır. Birçok araştırma grubu *N*-proparjilik β-enaminonları kullanarak çeşitli heterohalkaların uygun sentezi üzerine odaklanmıştır. Bu öncü maddeler ile son dönemdeki çalışmalardan bir tanesi de iyot aracılığı ile gerçekleşen elektrofilik halkalaşma tepkimesiyle 5-iyotpiridinlerin oluşumudur. Bu doğrultuda bu tez çalışmasındaki ilk amacımız Sonogashira çapraz kenetlenme reaksiyonundan faydalanılarak 5-iyotpiridinleri daha da işlevsel hale getirmektir. Bu şekilde %40-99 verimlerle 28 yeni 5-alkinilpiridin sentezledik. İkinci olarak, 1,4-oksazepinlerin sentezi için, daha kısa sürede daha yüksek verimler elde etmek amacıyla $ZnCl_2$ aracılı 7-*exo-dig* halkalaşmasını kaynayan $CHCl_3$ içinde gerçekleştirmek suretiyle tekrar araştırdık. Böylece birçok 2-metilen-2,3-dihidro-1,4-oksazepin türevinin iyi ve yüksek verimlerle (%66-95) 1.5-12.0 saat arasında değişen zamanlarla sorunsuz sentezini başardık. Bazı durumlarda alkil sübstitüye 1,4-oksazepinlerin silika jel ile izolasyonu esnasında bir dereceye kadar ilgili pirol

türevlerine dönüşümleri gözlemlenmiştir. Tezin üçüncü bölümünde Lawesson reaktifi kullanarak ilgili *N*-proparjilik β-enaminon öncülerinden yeni başlangıç *N*-proparjilik tiyo-β-enaminonları hazırladık. Sonrasında $ZnCl_2$ kullanarak kaynayan $CHCl_3$ içerisinde bu tiyo-β-enaminonların halkalaşma reaksiyonunu inceledik. Bu eşsiz sentetik metodolojiyi kullanarak 20 yeni 2,3-dihidro-1,4-tiyazepin türevini %67-90 verimlerle sentezledik. Son olarak sülfür ekstrüzyonu ile metil sübstitüye piridinleri oluşturan *N*-proparjilik tiyo-β-enaminonların baz katalizörlü halkalaşma reaksiyonları araştırılmıştır. Böylece diisopropilamin (DIPA) varlığında oda sıcaklığında birçok alkilpiridin, biri dışında (%13), orta ve yüksek verimlerle (%46-85) sentezlenmiştir.

Anahtar kelimeler: Piridinler, 1,4-Oksazepinler, 1,4-Tiyazepinler, 7-*Exo-dig* halkalaşması, *N*-Proparjilik tiyo-β-enaminonlar

To My Dear Devoted Family

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SCHEMES

LIST OF ABBREVIATIONS

ACN	acetonitrile
br	broad (spectral)
δ	chemical shift
J	coupling constant
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPA	diisopropylamine
DMF	dimethylformamide
d	doublet (spectral)
dd	doublet of doublets (spectral)
FT	fourier transform
Hz	hertz
LR	Lawesson`s reagent
mL	milliliter(s)
mmol	milimole
m	multiplet (spectral)
ppm	parts per million (in NMR)
q	quartet (spectral)
rt	room temperature
s	singlet (spectral)
THF	tetrahydrofuran
TLC	thin layer chromatography
TEA	triethylamine
td	triplet of doublets(spectral)
t	triplet (spectral)

CHAPTER 1

INTRODUCTION

Organic chemistry as one of the major classes of chemistry mainly deals with synthesis, characterization and description of carbon-containing materials. Carbon-involving compounds have an important role in maintaining continuity of life. Energy production with oxygen from the air, carrying genetic information by DNA and RNA, various types of reactions catalyzed by enzymes are some of the obligatory vital events that include carbon chemistry. In addition, the active roles of organic chemistry have recently become more obvious in other disciplines such as bioengineering, nanotechnology and medicine.[1]

In particular, heterocyclic compounds, having at least one different atom other than carbon, such as nitrogen, oxygen, sulfur in their ring skeletons, constitute a vast majority of organic molecules. They have been found in many natural products, bioactive molecules and vitamins.[2-4] Also, they have become prominent scaffolds of a variety of marketed drugs.[5] For instance, harvoni (a combination of ledipasvir and sofosbuvir), which is used for treatment of the hepatitis C disease,[6] contains certain heterocyclic units in its structure such as tetrahydrofuran, pyrimidinedione, pyrrolidine, imidazole and piperidine (Figure 1). Of the top twenty pharmaceutical products produced worldwide in 2015, it was at the top of the sales list.[7]

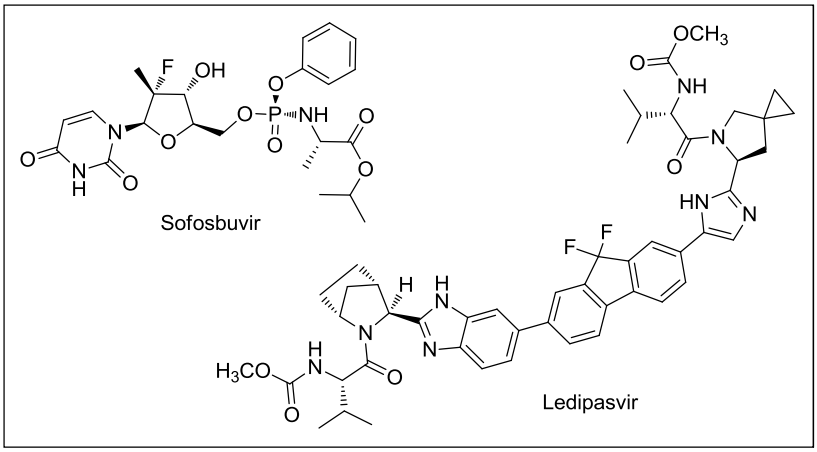
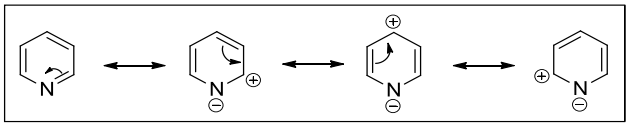


Figure 1. Structure of harvoni (ledipasvir/sofosbuvir).

Among heterocycles, six-membered heterocyclic motifs, especially pyridines, are one of the most permanently studied ones owing to their importance in various areas such as medicine.[8] Also, seven-membered heterocyclic compounds like oxazepines and thiazepines play an important role in the construction of potent biologically active libraries.[9]

1.1 Pyridines

Pyridines are one of the six-membered heterocyclic aromatic compounds having one nitrogen heteroatom in their ring skeletons. In 1849, the first pyridine was discovered in bone oil by Scottish chemist Thomas Anderson. Körner and Dewar independently designated its structure in 1864. It can be considered as resonance hybrid due to having a large dipole of 2.23 D (Scheme 1).[10]

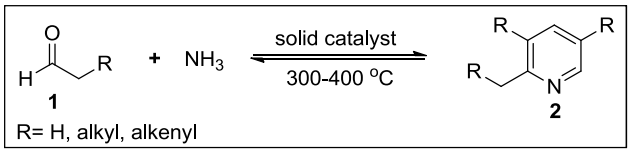


Scheme 1. Resonance forms of pyridine.

1.1.1 Synthesis of Pyridines

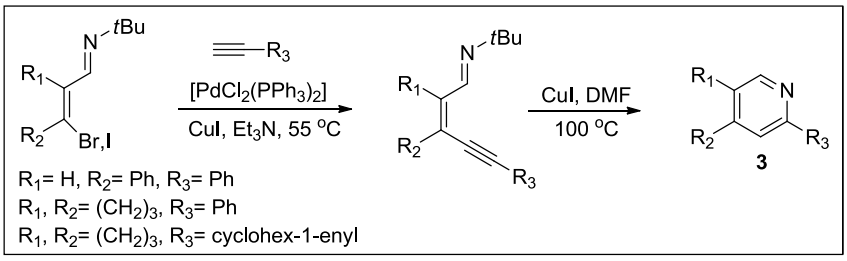
After the exploration of pyridine in bone oil, its early synthesis gained great importance among organic chemists. In 1876, Ramsay achieved its first synthesis via the reaction of acetylene with hydrogen cyanide in a hot tube.[11] After that pyridine synthesis was continued by various types of methods such as Hantzsch reaction,[12] Ciamician-Dennstedt rearrangement,[13] and Guareschi-Thorpe reaction.[13,14]

In 1924, Chichibabin found a new methodology for the synthesis of substituted pyridines **2**, which was heavily used in the mass production of pyridine derivatives.[15] In this reaction, at elevated temperatures (300-400 ^{o}C), aldehyde derivatives **1** were condensed with ammonia in the presence of solid catalysts such as alumina (Scheme 2).



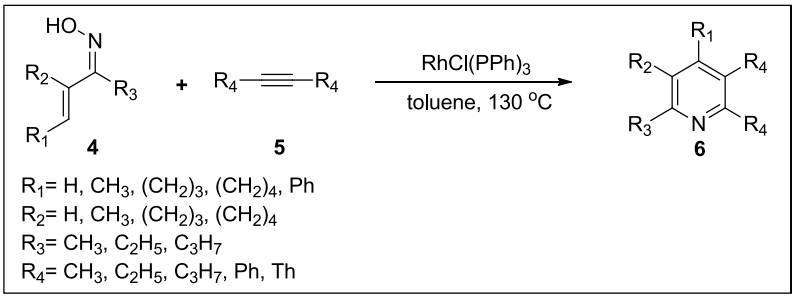
Scheme 2. Chichibabin pyridine synthesis.

Recently, efficient and facile synthesis of pyridines has been in progress and appeared as an important topic by synthetic chemists. Larock research group developed a new method for the synthesis of pyridines, including transition metal-catalyzed route to afford 2,4-di- and 2,4,5-trisubstituted pyridines **3** (Scheme 3).[16]



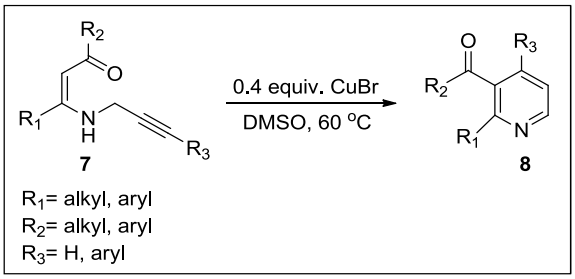
Scheme 3. Pd- and Cu-catalyzed synthesis of pyridines **3**.

Also, Cheng and co-workers synthesized highly substituted pyridine derivatives via C-H activation (Scheme 4).[17] α,β-Unsaturated ketoximes **4** were activated by rhodium complex and reacted with alkynes **5** to give polysubstituted pyridine derivatives **6**.



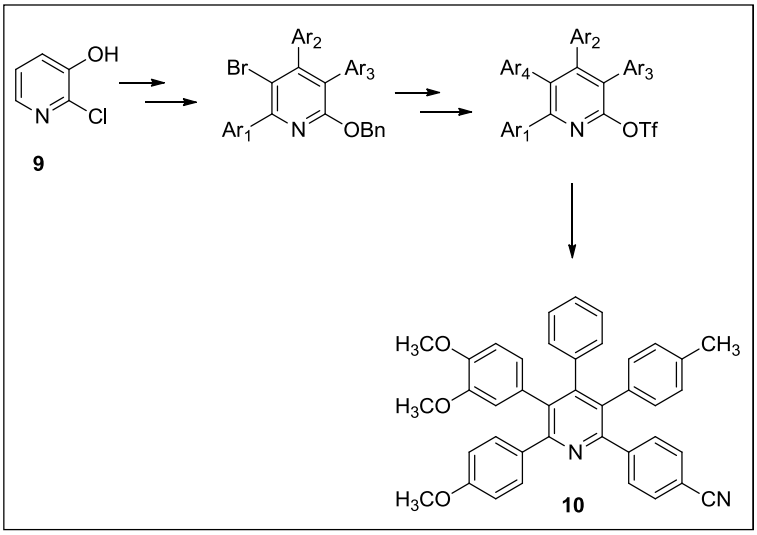
Scheme 4. Synthesis of highly substituted pyridines **6**.

Cacchi research group performed a remarkable study in 2008.[18] They used *N*-propargylic β-enaminones **7** as beneficial intermediates for the synthesis of various pyridine derivatives **8** (Scheme 5). Catalytic usage of CuBr enabled 6-*endo*-*dig* cyclization of β-enaminones **7** and formed target pyridines **8**.



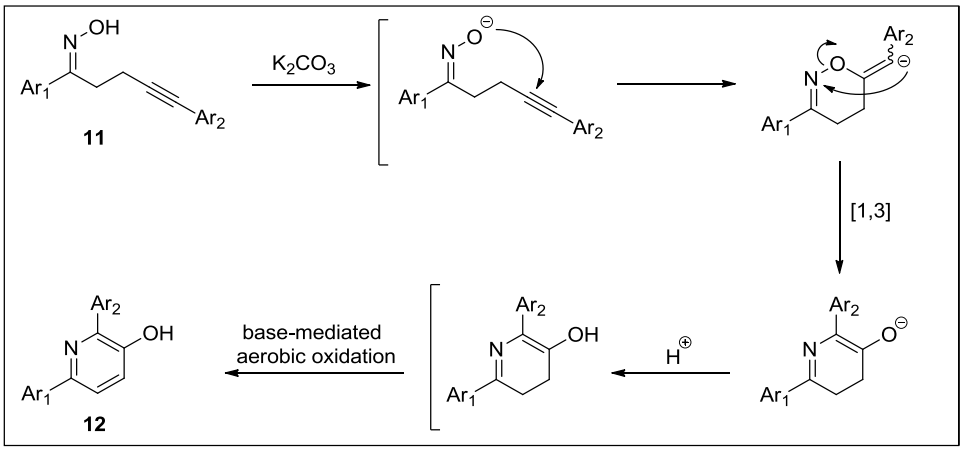
Scheme 5. CuBr-catalyzed synthesis of pyridines.

In 2014, Schmitt *et al.* have achieved the synthesis of the first prototypical pentaaryl-substituted pyridine derivative **10**, bearing five different aryl groups, starting from commercially available 2-chloro-3-hydroxypyridine (**9**) (Scheme 6).[19] Their strategy involves regioselective halogenations, protection and activation of phenol groups and five successive Suzuki-Miyaura cross-coupling reactions using five different aryl boronic acids.



Scheme 6. Synthesis of differently substituted pentaarylpyridine derivative **10**.

Most recently, Guan research group has developed an approach towards the synthesis of hydroxyl-substituted pyridine derivatives **12**, called pyridols (Scheme 7).[20] They have proposed the formation of corresponding pyridols **12** via K_2CO_3-mediated nucleophilic cyclization of γ,δ-alkynyl oximes **11**, followed by an unusual [1,3]-rearrangement of the resulting *O*-vinyl oximes.



Scheme 7. Proposed reaction mechanism for the synthesis of hydroxyl-substituted pyridines **12**.

1.1.2 Importance of Pyridines

One of the most important reasons to develop facile methodologies for the synthesis of pyridines is that they have distinct place in the structures of many biologically active natural products. For example, skin extracts of dendrobatid frogs contain many pyridine-bearing alkaloids, as depicted in Figure 2.[21] Among them, epibatidine has been shown to display more potent analgesic activity than morphine.[21,22] In addition, nicotine, also found in many plants, has an active role in oxidative stress, apoptosis and dopamine reward systems.[23]

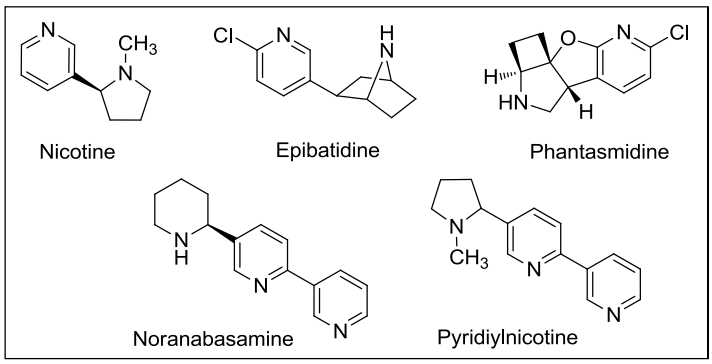


Figure 2. Structures of pyridine-containing natural products in frogs.

In 2009, two new pyridine-containing natural products, fuzanin C and fuzanin D, were recognized in culture supernatant of *Kitasatospora* sp. IFM10917, isolated from a soil sample collected in Japan (Figure 3). Fuzanin D was proved to demonstrate cytotoxic property against DLD-1 cells.[24] Their recently synthesized analogues have also been potentially active against HT29 colon cancer lines.[25]

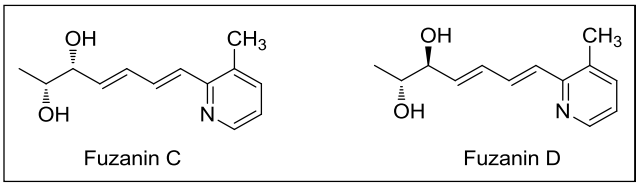


Figure 3. Structures of fuzanin C and fuzanin D.

Furthermore, water-soluble B_3 and B_6 vitamins include variable pyridine derivatives as illustrated in Figure 4. Deficiency of vitamin B_3 may cause pellagra disease in humans. Vitamin B_6 plays an active role in amino acid metabolism.[2]

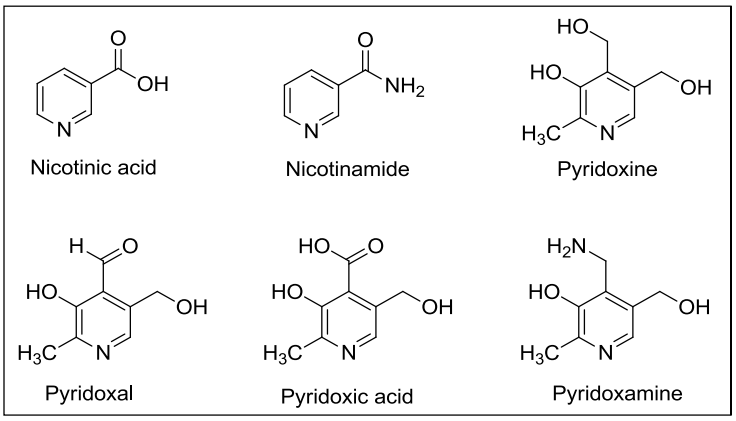


Figure 4. Structures of vitamin B_3 (nicotinic acid and nicotinamide) and vitamin B_6 (pyridoxine, pyridoxal, pyridoxic acid and pyridoxamine).

In addition to occurrence in natural bioactive molecules, pyridines have prominently gained importance in pharmaceutical industry. In 2014, according to the analysis of the structural diversity of nitrogen heterocycles, among all U.S. FDA approved pharmaceuticals, pyridine moiety became the second most prevalently used nitrogen-bearing heterocycle.[26] Moreover, in 2015, nexium (esomeprazole) including tetrasubstituted pyridine derivative placed in the top twenty pharmaceutical products by sales worldwide (Figure 5).[7] It functions as proton-pump inhibitor and used in the treatment of gastric ulcer disease and functional dyspepsia.[27]

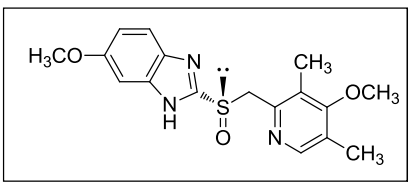


Figure 5. Structure of nexium (esomeprazole).

There are also type-2 diabetes drugs containing pyridine scaffolds in their structures. To illustrate, rosiglitazone and pioglitazone act as significant agents in controlling the metabolism of carbohydrates and fatty acids (Figure 6).[28]

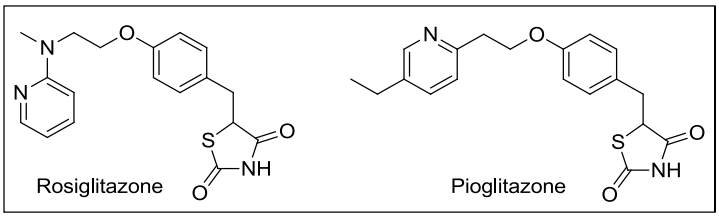


Figure 6. Structures of rosiglitazone and pioglitazone.

Moreover, pyridines have been employed to construct bioactive molecules used in treatment of different types of cancer diseases. For example, vismodegib is used in the cure of metastatic or locally advanced basal cell carcinoma (BCC).[29] Sorafenib[30] and crizotinib[31] are also used in treatment of advanced primary liver cancer and non-small cell lung cancer (NSCLC), respectively (Figure 7).

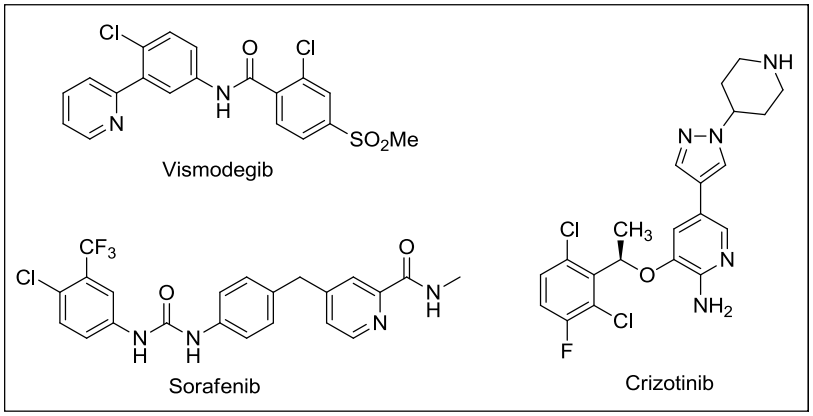


Figure 7. Structures of vismodegib, sorafenib and crizotinib.

Furthermore, pirfenidone, a pyridinone derivative, has appeared to exert antifibrotic, anti-inflammatory and antioxidant activities.[32] Rupatadine has been stated to show anti-allergic and antihistaminic properties (Figure 8).[33]

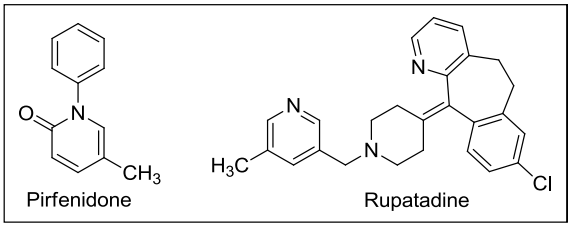


Figure 8. Structures of pirfenidone and rupatadine.

1.1.3 Alkynylpyridines

In particular, alkynylpyridines have a unique place in medicinal chemistry. Recently, the trends of their useful performance on biological processes have been increasing remarkably. In 2004, Ahn and co-workers synthesized symmetrical bis-alkynylpyridine derivatives **13** and **14** by Sonogashira reaction, the structures of which are shown in Figure 9. They have verified their strong anti-angiogenic activities on the human umbilical vein endothelial cells (HUVEC).[34]

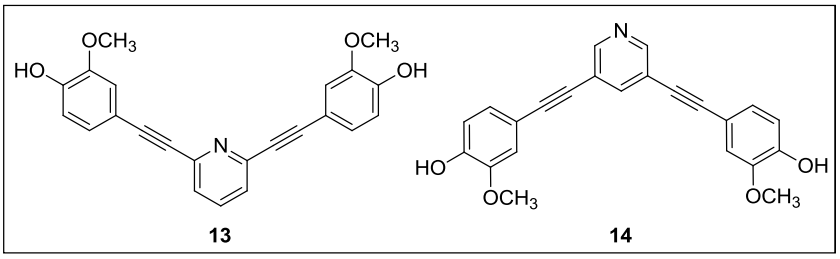


Figure 9. Structures of symmetrical bis-alkynylpyridine derivatives **13** and **14**.

One year later, Chua *et al.* discovered novel alkynylpyridines **15**, **16** and **17** (Figure 10) having potent metabotropic glutamate receptor (mGlu5) antagonists based on structure-activity relationship studies.[35] Various cyclohexenyl and dehydropiperidinyl groups have been involved in the corresponding potent antagonist pyridine moieties.

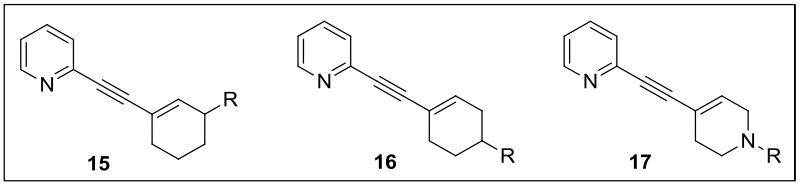


Figure 10. General structures of alkynylpyridines **15**, **16**, and **17**.

Additionally, many 5-alkynylpyridine derivatives have been patented in 2013 since they show inhibiting activity of PI3K alpha and can be used as SMAC mimetics for the treatment of diseases such as cancer.[36] A most recent discovery of 3-alkynylpyridines **18** (Figure 11) has emerged in 2017 for their use in treatment or prevention of anemia such as anemia secondary to chronic kidney disease and other similar diseases.[37]

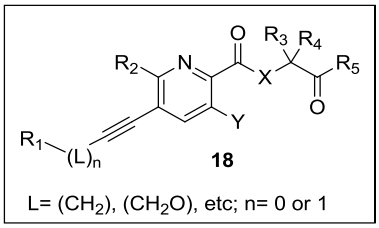


Figure 11. General structure of 3-alkynylpyridines **18**.

Alkynylpyridines possess not only beneficial effects on certain types of diseases but also exhibit good opto-electronic properties for the preparation of conjugated oligomers and complexes. In 2004, Takayama research group has prepared highly fluorescent π-conjugated oligomers **19** having sequential 2-vinyl-5-alkynylpyridine units in their structures (Figure 12).[38]

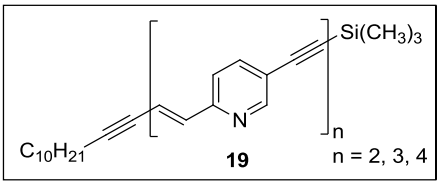


Figure 12. Structures of highly fluorescent $\boldsymbol{\pi}$-conjugated oligomers **19**.

In 2016, Starck, Pal and Parker described four anionic europium(III) complexes, each of which bears three aryl-alkynyl pyridine groups permitting different microscopy applications, such as time-gated FRET microscopy. These probes can be used to treat the disease by time-dependent measurements of lysosomal pH in the presence or absence of novel potential drugs.[39]

Alkynylpyridines can also be further diversified and derivatized due to nucleophilic, electrophilic, radicalic and cycloaddition reactivity of their triple bonds. Accordingly, by utilizing their chemical reactivity properties, new potentially biologically active and well behaved opto-electronic substances can be synthesized by organic chemists.

1.2 Seven-membered Heterocyclic Compounds

Seven-membered heterocyclic compounds constitute significant class of heterocycles in organic chemistry. They vary with the number and kind of heteroatoms in their ring structures (Figure 13).[40]

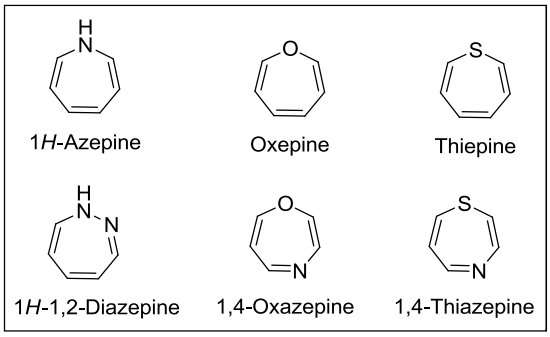


Figure 13. Some examples of seven-membered heterocycles.

Researchers made many efforts for the initial syntheses of seven-membered heterocylic compounds in the past. In 1964, the first thermally very unstable 1*H*-azepine was obtained as a result of alkaline hydrolysis of *N*-ethoxycarbonylazepine.[41] Although the synthesis of first representative monocyclic oxepine derivative was achieved in the same year by Vogel research group,[42] the

existence of unsubstituted oxepine with it valence tautomeric form was reported in 1967.[43] The same strategy did not give the corresponding thiepine because of readily occured sulfur extrusion.[44] Many attempts were made for the synthesis of simple and stable thiepine derivatives until 1979.[45] In 1979, Murata *et al*. synthesized the first stable and simple monocyclic thiepine bearing bulky groups.[46] On the other hand, the first seven-membered monocylic 1*H*-1,2-diazepine derivative was produced by photolysis of *N*-acyliminopyridinium ylide and its only isolation as iron tricarbonyl complex was succeeded.[47] In contrast to these monocyclic seven-membered heterocycles, their first benzo-fused analogues were much easily synthesized and isolated more efficiently due to aromaticity of benzene ring.[43b,48]

First descriptions of seven-membered heterocyclic compounds have led to an increasing rate in the convenient syntheses of these heterocycles by several methods.[9,49-51] Another important effect for the synthetic improvements of these molecules is that they exist in a number of biologically active natural products.[5,51,52] Two oxepine-containing aranotin extracted from *Arachniotus aureus* has showed antiviral activity.[52,53] Also, the roots of *Stemona* plants, having many pyrrolo[1,2-a]azepine-bearing alkaloids, such as croomine, have been used for years in treatment of some diseases like bronchitis and tuberculosis (Figure 14).[52,54]

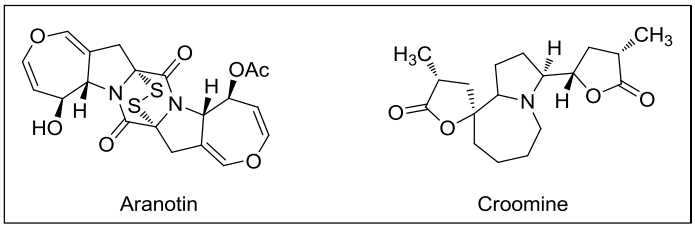


Figure 14. Structures of natural products having seven-membered heterocycles.

Besides that, seven-membered heterocyclic scaffolds have concretely been involved in medicinal chemistry. For example, oxetorone, zotepine and nimetazepam have been used as analgesic, antipsychotic and hypnotic, respectively (Figure 15).[5,55]

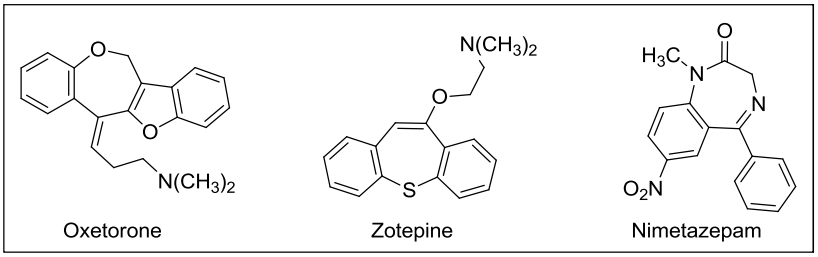
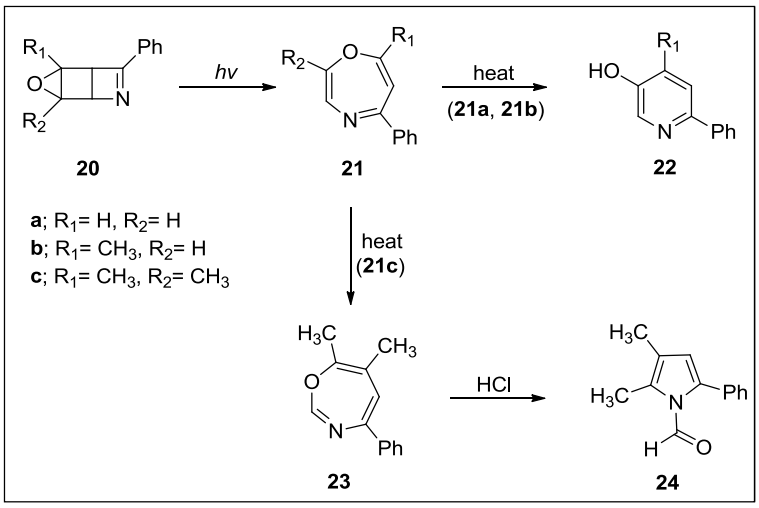


Figure 15. Structures of drugs having seven-membered heterocycles.

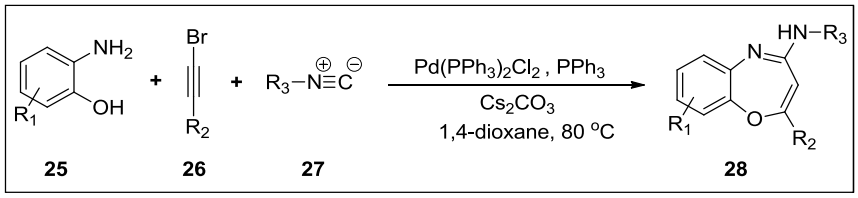
1.2.1 Synthesis of Oxazepines

Synthesis of aryl-fused benzoxapine derivatives dates from 1957.[56] In the beginning of 1980's the first synthesis of monocyclic 1,2-oxazepinum perchlorate derivative and a tentatively assigned trisubstituted 1,2-oxazepine were reported by different research groups.[57] Tsuchiya *et al.* pioneered the synthesis of monocyclic 1,4-oxazepines after the discovery of corresponding synthesis of 1,3-isomer.[58] In 1986, the same research group accomplished the first synthesis of fully unsaturated 1,4-oxazepine derivatives **21** in 90-95% yields by irradiation of tricycloheptenes **20** in acetonitrile (ACN) (Scheme 8).[59] Thermal rearrangements of compounds **21a** and **21b** at 100-120 ^{o}C afforded corresponding 5-hydroxypyridines **22** in 65-75% yields. Interestingly, 6,7-dimethyl-5-phenyl-1,3-oxazepine (**23**) was formed in 90% yield upon heating of dimethyl substituted oxazepine derivative **21c** at 80 ^{o}C. The formation of these products could be explained over oxanocaradiene intermediate which may appear during the isomerization of compounds **20** to give **21**. *N*-formylpyrrole derivative **24** was also obtained quantitatively by treatment of 1,3-oxazepine derivative **23** with HCl in THF.



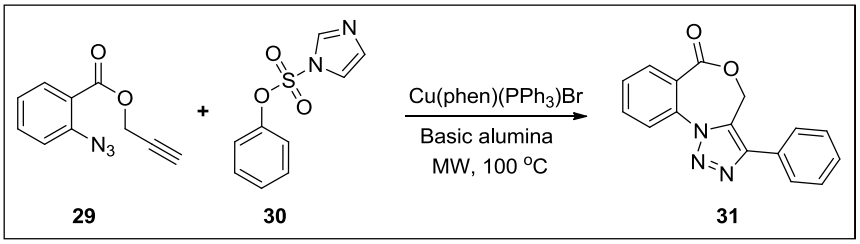
Scheme 8. Synthesis of fully unsaturated 1,4-oxazepines and formation of corresponding pyridine and pyrrole derivatives.

Many other different methodologies have emerged for the proper synthesis of 1,4-oxazepine derivatives.[9,56] Development of useful methods has also been recently one of the hot topics among organic chemists. In 2012, Jiang research group has synthesized various benzo[1,4]oxazepine derivatives **28** by tandem reaction of *o*-aminophenols **25** with bromoalkynes **26** and isocyanides **27** (Scheme 9).[60]



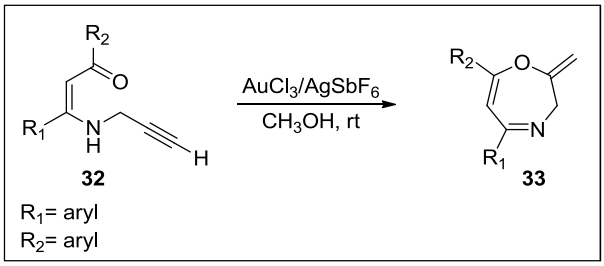
Scheme 9. Synthesis of 1,4-benzoxapine derivatives **28**.

Two years later, single-step construction of triazole-fused benzoxazepine derivative **31** from the reaction of *o*-propargylic azidobenzoate **29** and phenyl sulfonate **30** under MW irradiation was accomplished by Sen research group (Scheme 10).[61] In this method, Cu(phen)(PPh_3)Br was used as a catalyst and basic alumina acted as a support material and base.



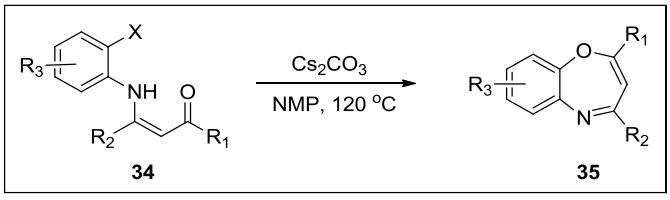
Scheme 10. Synthesis of triazole-fused benzoxazepine derivative **31**.

In 2015, Karunakar and co-workers reported the another synthesis of 1,4-oxazepine derivatives by using gold and silver catalysts. Intramolecular electrophilic cyclization of terminal *N*-propargylic β-enaminones **32** resulted in formation of corresponding oxazepine compounds **33** (Scheme 11).[62]



Scheme 11. Synthesis of monocyclic 1,4-oxazepine derivatives **33**.

In addition, Shen *et al*. have developed a new methodology for the synthesis of substituted benzo[b][1,4]-oxazepines. The base-promoted cyclization of *N*-(2-haloaryl)enaminones **34** at 120 °C yielded desired target molecules **35** (Scheme 12).[63]



Scheme 12. Synthesis of benzo[b][1,4]-oxazepine derivatives **35**.

1.2.2 Importance of Oxazepines

Oxazepine scaffolds are valuable building blocks in medicinal chemistry since they exist in a variety of biologically active compounds used as, such as antihistaminic, antipyretic, anti-inflammatory, antidepressant agents.[51,56,64] Some dibenzoxazepine and triazolobenzoxazepine derivatives exhibited high analgesic[65] and anticonvulsant[9,66] activities, respectively (Figure 16).

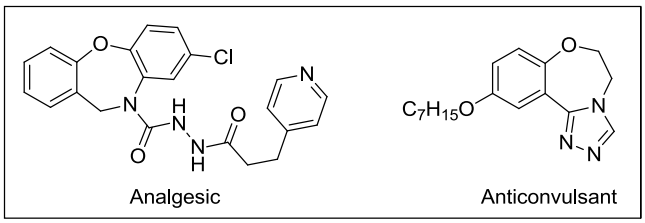


Figure 16. Biologically active benzoxazepine derivatives.

Recently, Takeuchi *et al*. have discovered a novel dihydrobenzoxazepine derivative acting as highly potent and selective mammalian target of rapamycin (mTOR) inhibitor with low nanomolar concentration (Figure 17).[67]

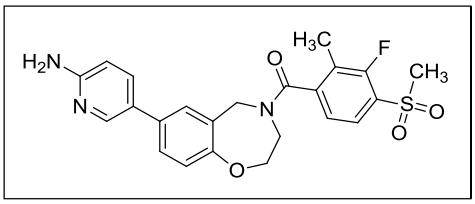


Figure 17. Structure of a novel dihydrobenzoxazepine derivative.

Moreover, there are pharmaceutical products bearing the 1,4-oxazepine cores in their structures used in treatment of chronic disorders (Figure 18). For example, loxapine[68] has widely been used in the treatment of schizophrenia. For the curation of depressive disorders, amoxapine[69] and sintamil[70] have been utilized.

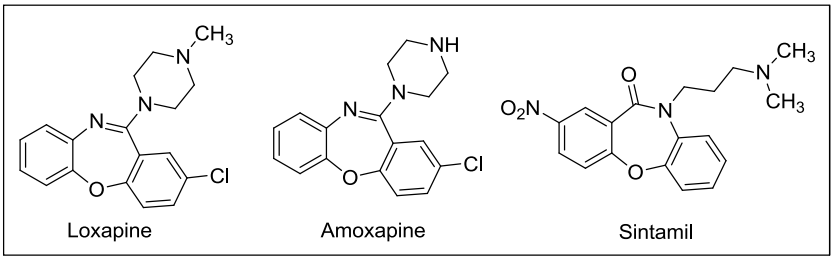
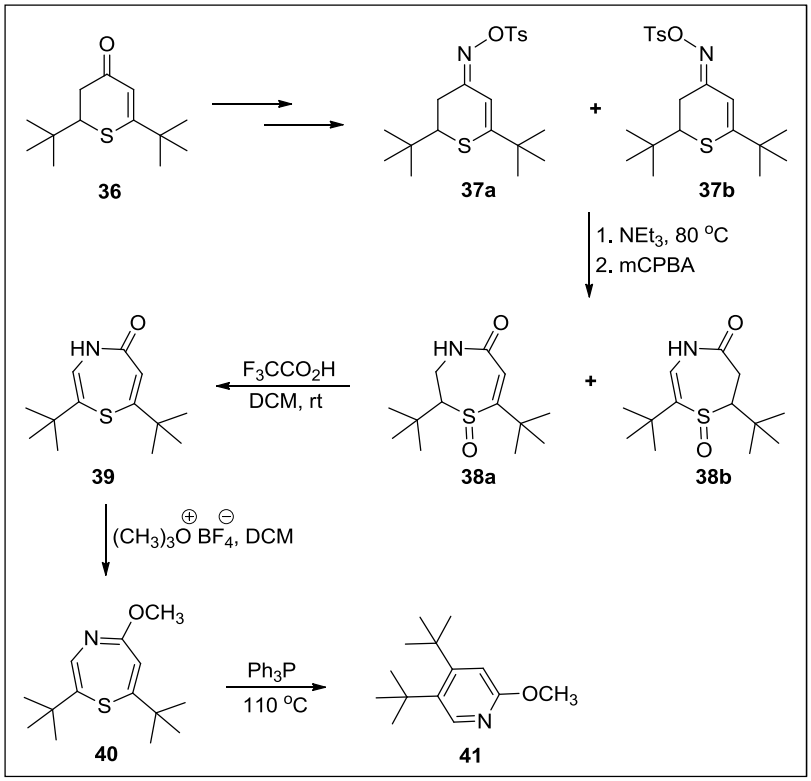


Figure 18. Structures of some drugs bearing 1,4-oxazepine cores.

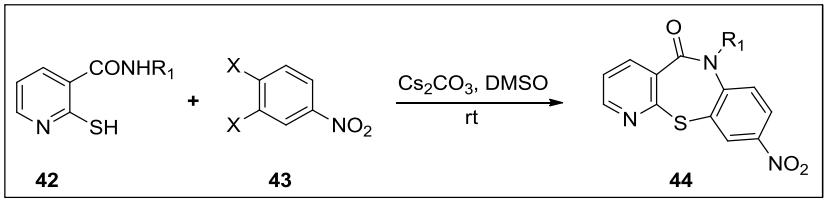
1.2.3 Synthesis of Thiazepines

To the best of our knowledge, synthesis of monocyclic fully unsaturated 1,2-thiazepines has not been reported yet, whereas first stable examples of 1,2-benzothiazepines were demonstrated in 1976 by the ring expansion of corresponding 1,2-benzoisothiazoles.[71] Bradsher *et al.* explored earlier synthesis of pyridobenzo-1,3-thiazepinium salts from suitable 2-phenylthiopyridines.[72] There are many studies describing the synthesis of tetra- and perhydro-1,4-thiazepine derivatives especially through penicilin chemistry.[73] Notably, first synthesis of monocyclic dihydro-1,4-thiazepine was achieved by Tsuchiya research group in 1983 as in the case of 1,4-oxazepines.[58b] In 1986, Murata and co-workers developed a first multi-step synthesis of fully unsaturated stable monocyclic 1,4-thiazepine derivative (Scheme 13).[74] They initially prepared the precursor dihydrothiopyranone **36** from 2-*tert*-butyl-5-pivaloylthiophene in seven steps. Tosylation reaction after treating it with hydroxylamine gave a mixture of oximes, *syn*-**37a** and *anti*-**37b**. Then, Beckmann rearrangement in basic medium and oxidation with mCPBA were employed subsequently to yield corresponding sulfoxide derivatives **38a** and **38b**. As a result of Pummerer reaction of sulfoxide **38a**, desired 1,4-thiazepinone derivative **39** was obtained in 79% yield. Lastly, 2,7-di-*tert*-butyl-5-methoxy-1,4-thiazepine (**40**) was formed after reacting compound **39** with a methylating agent. The generated thiazepine **40** was stable up to 130 ^{o}C but in the presence of Ph_3P at 110 ^{o}C it was converted to 2-methoxypyridine derivative **41** (Scheme 13).



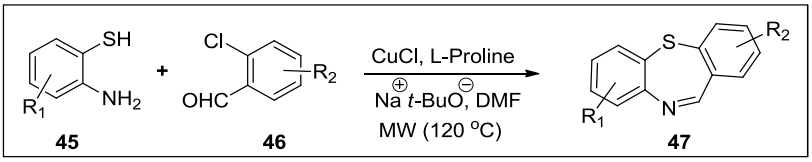
Scheme 13. Synthesis of fully unsaturated stable monocyclic 1,4-thiazepine **40**.

Recently, many researchers have concentrated on investigating various new techniques in order to develop thiazepine ring systems.[9,75] In 2014, Yang *et al*. reported transition metal-free synthesis of fused 1,4-thiazepines in one-pot manner.[76] 2-Mercaptonicotinamide derivative **42** was reacted with 1,2-dihalo-4-nitrobenzene **43** via Smiles rearrangement process in basic medium to afford 1,4-thiazepin-5(4*H*)-ones **44** (Scheme 14).



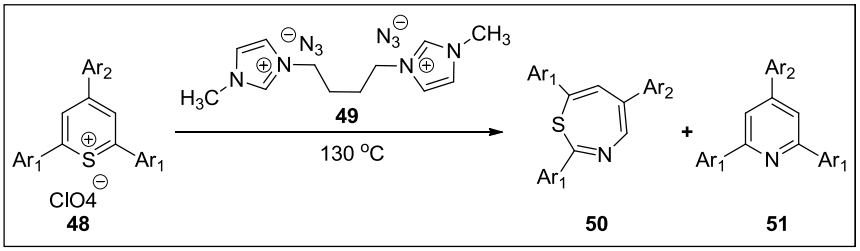
Scheme 14. Synthesis of 1,4-thiazepin-5(4*H*)-ones **44**.

Shortly after, Sharma research group has performed base-catalyzed condensation of 2-aminothiophenols **45** with 2-chlorobenzaldehydes **46** followed by copper-assisted intramolecular *S*-arylation to form dibenzo-fused 1,4-thiazepine derivatives **47** (Scheme 15).[77]



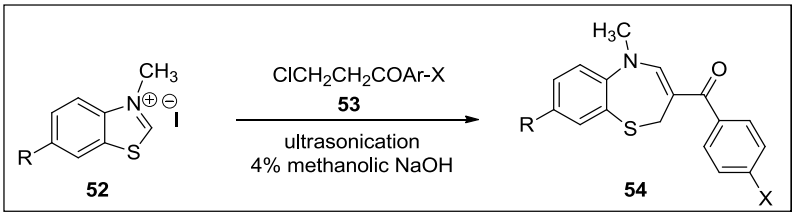
Scheme 15. Synthesis of dibenzo-fused 1,4-thiazepines **47**.

An efficient synthesis of novel triaryl-1,3-thiazepine derivatives **50** via ring expansion of triarylthiopyrylium salts **48** using a specific ionic liquid bearing azide anions **49** has been succeeded by Mouradzadegun and co-workers. However, mechanistic formation of triarylpyridine derivatives **51** as side products by sulfur extrusion was a drawback for the chemoselectivity of this methodology (Scheme 16).[78]



Scheme 16. Synthesis of triaryl-1,3-thiazepine derivatives **50**.

In 2017, Preet and Cannoo have established a ring expansion strategy to synthesize dihydro-1,4-thiazepines **54** in high yields. Thiazolium salts **52** were reacted with 3-chloro-1-(aryl)-propan-1-one **53** in the presence of base via ultrasonication (Scheme 17).[79]



Scheme 17. Synthesis of dihydro-1,4-thiazepines **54**.

1.2.4 Importance of Thiazepines

Many thiazepine-embedded compounds, especially 1,4-thiazepine bearing ones, have been introduced to exhibit diverse biological activities, such as anticonvulsant,[66a] antifungal, antimicrobial,[75,80] antioxidant and cytotoxic properties (Figure 19).[81]

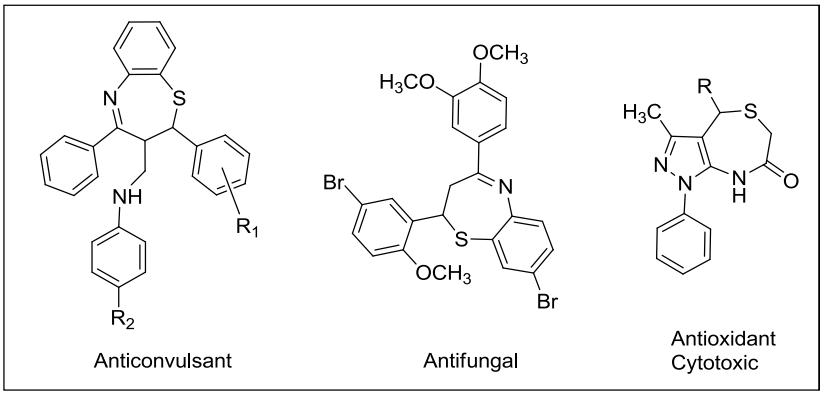


Figure 19. Biologically active thiazepine derivatives.

Notably, compounds including thiazepine moieties have played an active role in treatment of mental health problems and cardiovascular disorders. Accordingly, quetiapine[82] and diltiazem,[83] are used as antipsychotics and chalcium channel blockers, respectively (Figure 20).

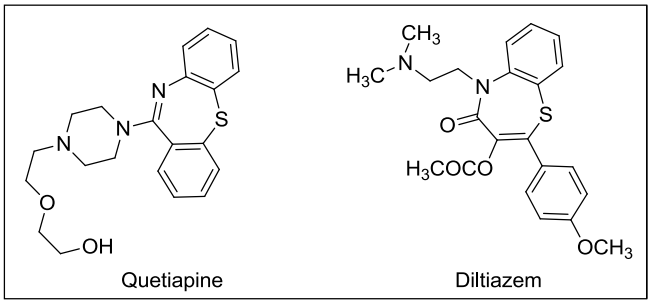


Figure 20. Structures of quetiapine and diltiazem.

In addition to synthetically bioactive derivatives, thiazepine units are found in the structures of natural products. Very recently, Mohammed and Mohamed have brought about the existence of three promising bioactive 1,3-thiazepine-containing alkaloids in the extract of *Ixora undulata* Roxb. leaves (Figure 21).[84]

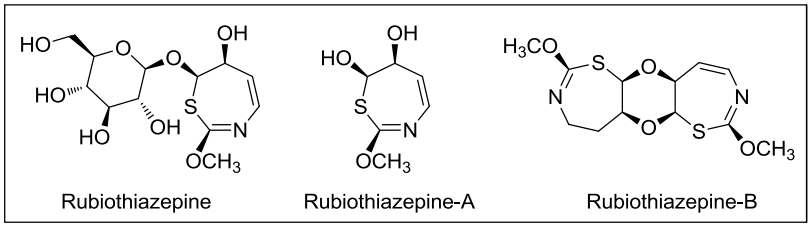
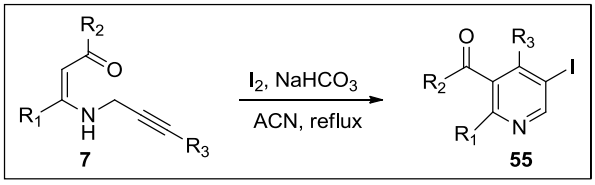


Figure 21. Structures of 1,3-thiazepine-containing alkaloids.

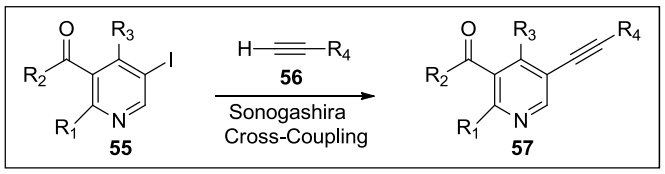
1.3 Aim of Thesis

N-Propargylic β-enaminones have commonly been used as useful substrates among organic chemists to generate *N*-heterocycles since they are multifaceted and derivatizable building blocks as well as easily handed in low-cost.[85] Not only pyridine derivatives,[18,86] but also many different pyrroles,[85,87] azaanthraquinones,[88] azabicycloheptadienes[89] and pyridoacridinones[90] have been produced from variable *N*-propargylic β-enaminone precursors. In this regard, our research group have recently shown the formation of 5-iodopyridines **55** via iodine-mediated electrophilic cyclization of *N*-propargylic β-enaminones **7** in the presence of sodium bicarbonate (Scheme 18).[91]



Scheme 18. Synthesis of 5-iodopyridines **55**.

Derivatization of 5-iodopyridines **55** by substitution of iodine with alkynyl groups may result in formation of potentially bioactive alkynylpyridine derivatives.[34-37] Thus, our first aim was to synthesize polysubstituted novel 5-alkynylpyridines **57** via Pd-catalyzed Sonogashira cross-coupling reaction between 5-iodopyridines **55** and terminal alkynes **56** (Scheme 19).

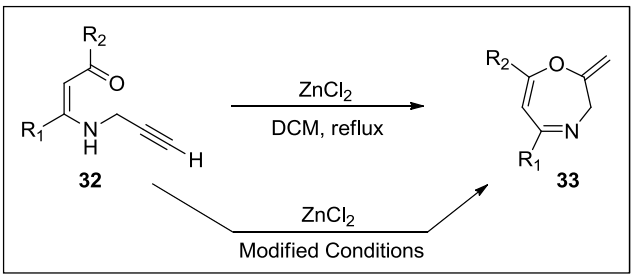


Scheme 19. Synthesis of 5-alkynylpyridines **57**.

As mentioned above, there have been many successful reactions with *N*-propargylic β-enaminones to synthesize five and six-membered heterocyles as well as aryl-fused ones. However, there is only one study involving directly synthesis of monocyclic seven-membered oxazepines from *N*-propargylic β-enaminones. In that method, as stated before, Au- and Ag-catalyed intramolecular cyclization of β-enaminones afforded monocyclic 1,4-oxazepine derivatives.[62] In one case, fully unsaturated monocyclic 1,4-oxazepines have been observed as the reaction intermediates during synthesis of 2-(1*H*-pyrrolyl)pyridines.[86b]

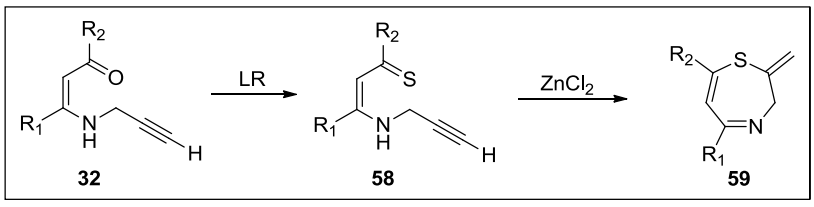
Lack of methodologies have prompted us to develop new strategies for the synthesis of monocyclic 1,4-oxazepines. In this respect, our research group has recently found a new method for the synthesis of monocyclic 1,4-oxazepines **33** from corresponding *N*-propargylic β-enaminones **32**. $ZnCl_2$-mediated 7-*exo*-*dig* intramolecular cyclization in refluxing DCM has yielded 1,4-oxazepine derivatives

33 (Scheme 20). This new process has provided an economically better alternative with the usage of low-cost $ZnCl_2$ for the synthesis of 1,4-oxazepine derivatives. However, in some cases, the yields were not so good and reactions were accomplished in longer reaction times (9-24 h.). Therefore, as a second aim of the project, we decided to modify the reaction conditions to obtain better yields of 1,4-oxazepine derivatives from related *N*-propargylic β-enaminones in shorter reaction times (Scheme 20).



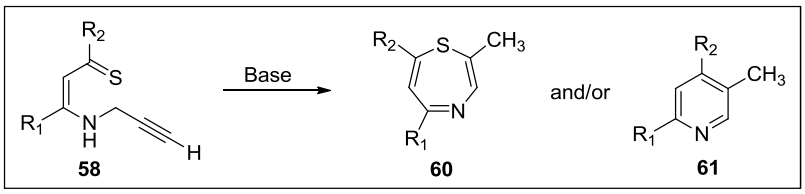
Scheme 20. $ZnCl_2$-mediated synthesis of monocyclic 1,4-oxazepines **33**.

In the same manner, there is room for improvement of synthesis of monocyclic 1,4-thiazepines. According to our knowledge, there is no any example reporting formation of them from thionated *N*-propargylic β-enaminones. In the light of our experience in the synthesis of monocyclic 1,4-oxazepines **33**, as a third aim, we will investigate $ZnCl_2$-mediated intramolecular cyclization reactions of thionated *N*-propargylic β-enaminones **58** to obtain monocyclic 2,3-dihydro-1,4-thiazepines **59**. For this reason, we will first prepare thionated *N*-propargylic β-enaminones **58** from *N*-propargylic β-enaminones **32** by Lawesson's reagent (LR) (Scheme 21).



Scheme 21. $ZnCl_2$-mediated synthesis of monocyclic 1,4-thiazepines **59**.

Moreover, we will also examine the reaction of thionated *N*-propargylic β-enaminones **58** under basic conditions to isolate fully unsaturated 1,4-thiazepines **60** and/or 5-methylpyridine derivatives **61** due to sulfur extrusion[44] (Scheme 22).



Scheme 22. Base-mediated synthesis of fully unsaturated monocyclic 1,4-thiazepines **60** and/or 5-methylpyridines **61**.

Briefly, the scope, limitations and proposed mechanisms for the syntheses of 5-alkynylpyridines **57**, monocyclic 1,4-oxazepines **33** under modified conditions**,** monocyclic 2,3-dihydro-1,4-thiazepines **59**, fully unsaturated monocyclic 1,4-thiazepines **60** and/or 5-methylpyidines **61** will be discussed in detail.

CHAPTER 2

RESULTS AND DISCUSSIONS

2.1 Synthesis of Starting Materials

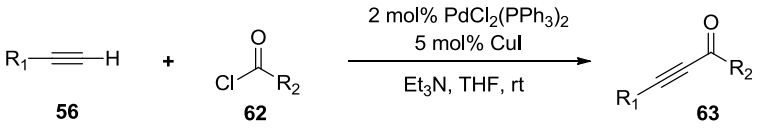
2.1.1 Synthesis of α,β-Alkynic Ketones 63

At the initial stage of the project, we have readily synthesized α,β-alkynic ketones **63** via Sonogashira cross-coupling of aryl chlorides **62** with terminal alkynes **56**. We employed a Pd- and Cu-catalyzed reaction by taking 1.0 equiv. of terminal alkyne **56** and 1.2 equiv. of aryl chloride **62** in the presence of Et_3N under argon atmosphere (Scheme 23).

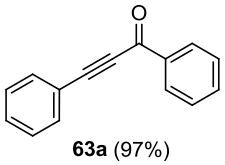
Scheme 23. Synthesis of α,β-alkynic ketones **63**.

26 alkynic ketone derivatives **63** were synthesized in 50-99% yields in addition to commercially obtained acetyl-bearing alkynic ketone, 4-phenylbut-3-yn-2-one (**63aa**), as shown in Table 1.

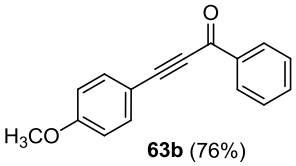
Table 1. Synthesized α,β-alkynic ketone derivatives **63**.[a]



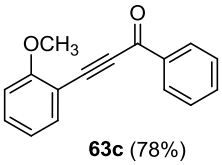
56 **62** **63**



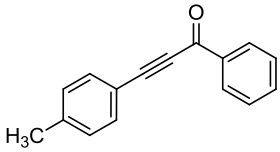
63a (97%)



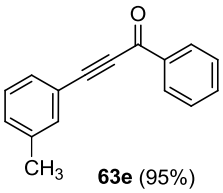
63b (76%)



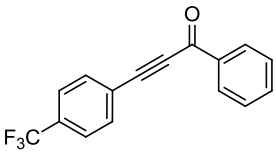
63c (78%)



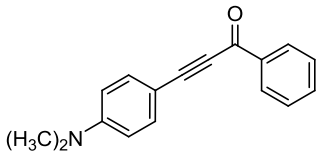
63d (81%)



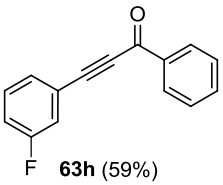
63e (95%)



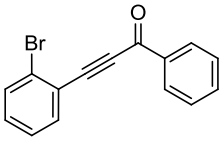
63f (60%)



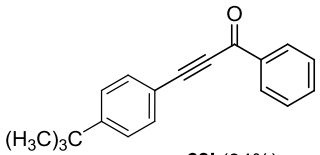
63g (95%)



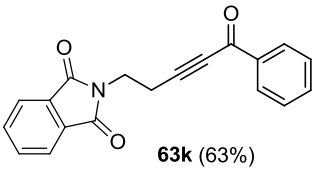
63h (59%)



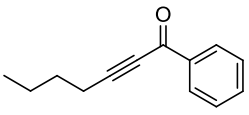
63i (85%)



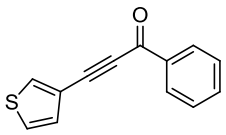
63j (94%)



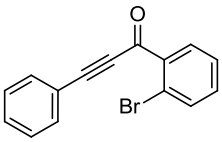
63k (63%)



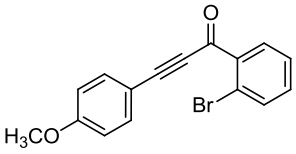
63l (94%)



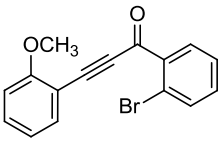
63m (87%)



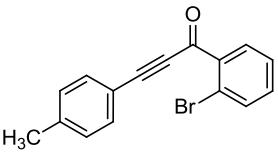
63n (50%)



63o (67%)

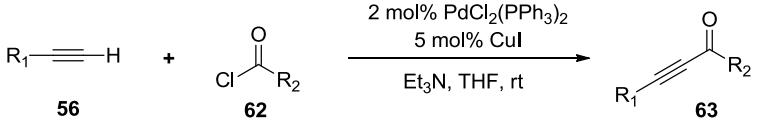


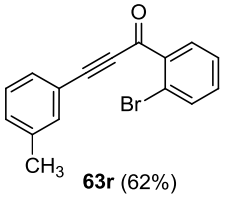
63p (78%)



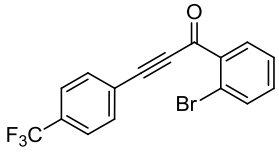
63q (61%)

Table1. Continued.

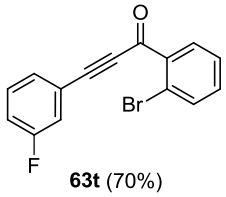




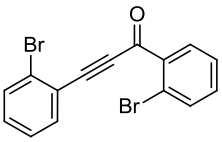
63r (62%)



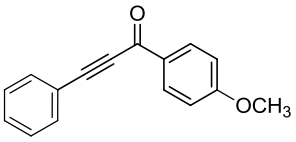
63s (77%)



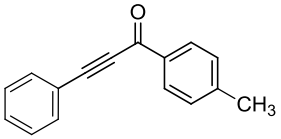
63t (70%)



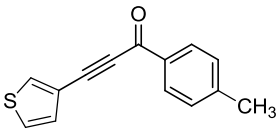
63u (64%)



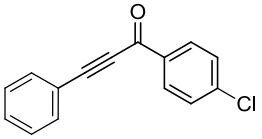
63v (99%)



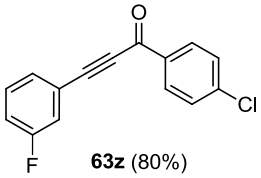
63w (95%)



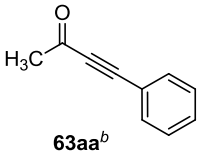
63x (74%)



63y (99%)



63z (80%)

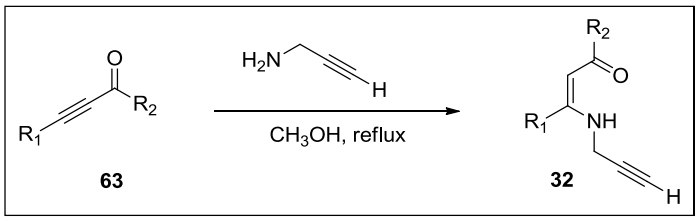


63aa[b]

[a]Isolated yields. [b]Commercially obtained.

2.1.2 Synthesis of *N*-Propargylic β-Enaminones 32

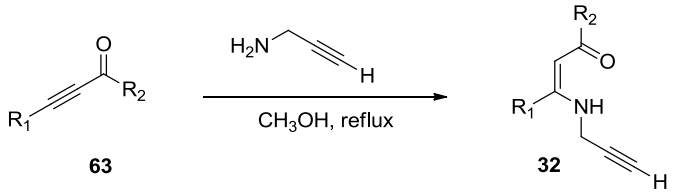
After obtaining α,β-alkynic ketones **63**, we have synthesized *N*-propargylic β-enaminones **32** by conjugate addition of propargyl amine to corresponding alkynic ketones **63** (Scheme 24). It is noteworthy to mention that we have isolated only *Z* isomer of *N*-propargylic β-enaminones **32**. Interestingly *E* izomers were not formed in these reactions. Cacchi research group[18] and we have elucidated single *Z* isomer formation by NOESY experiments. We have clearly showed the NOE interaction between vinylic hydrogen and allylic hydrogens of compound **32l**, whose structure is given in Table 2 (for the correlation of related atoms see Figure 113 in Appendices). In addition to NOE interaction, existence of intramolecular H-bonding also (N−H····O) acts as an active role in the stability of *Z* isomer of *N*-propargylic β-enaminones **32**.



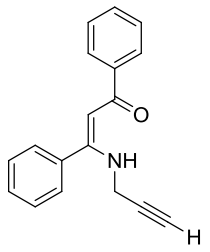
Scheme 24. Synthesis of *N*-propargylic β-enaminones **32**.

We have totally synthesized 27 *N*-propargylic β-enaminone derivatives **32** as depicted in Table 2. Except for compound **32k**, whose yield was 61%, the obtained yields were good and high (73-98%). Their structural analyses were performed mainly by ^{1}H and ^{13}C NMR spectra.

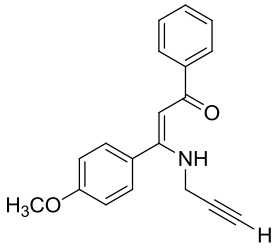
Table 2. Synthesized *N*-propargylic β-enaminone derivatives **32**.[a]



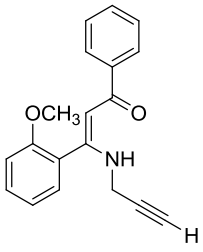
63 **32**



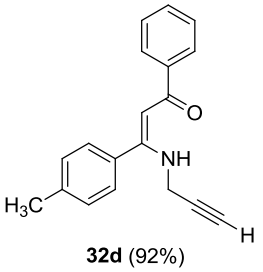
32a (97%)



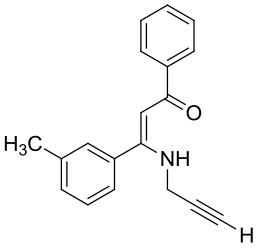
32b (98%)



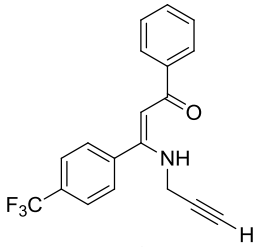
32c (86%)



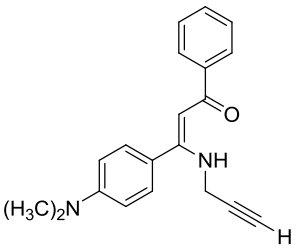
32d (92%)



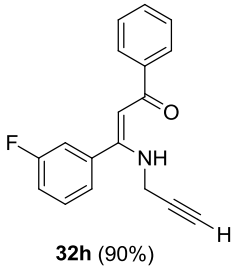
32e (95%)



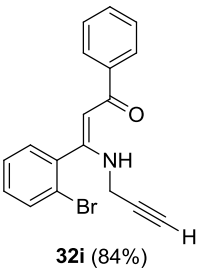
32f (81%)



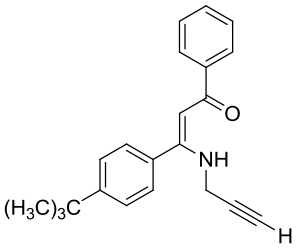
32g (84%)



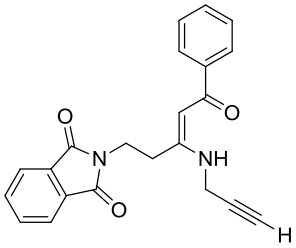
32h (90%)



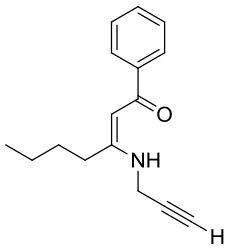
32i (84%)



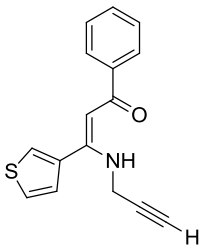
32j (91%)



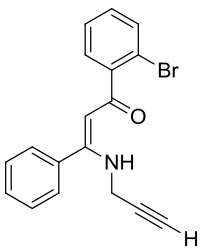
32k (61%)



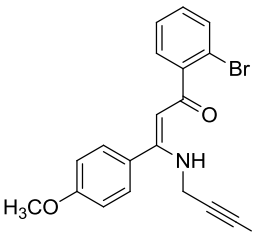
32l (95%)



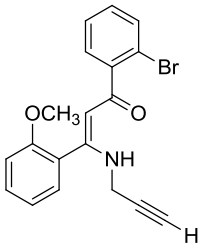
32m (92%)



32n (87%)

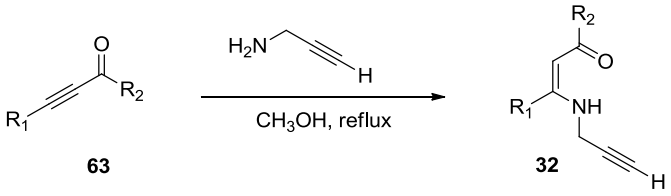


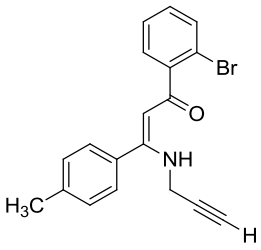
32o (76%)



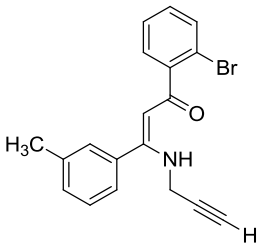
32p (76%)

Table 2. Continued.

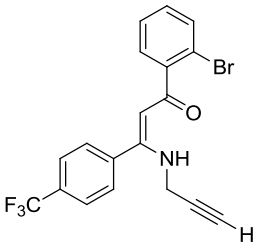




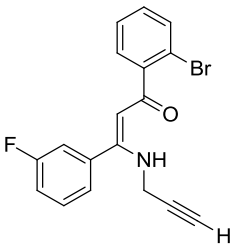
32q (85%)



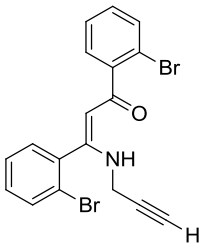
32r (87%)



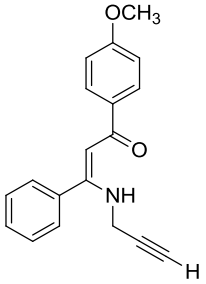
32s (88%)



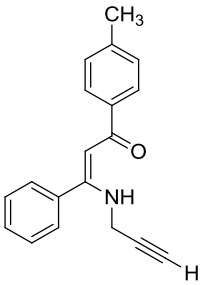
32t (95%)



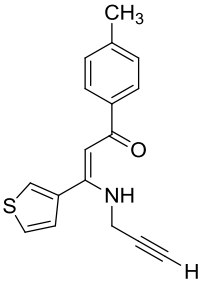
32u (86%)



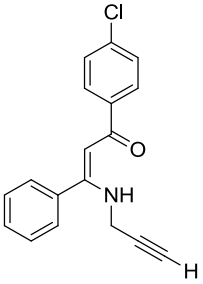
32v (98%)



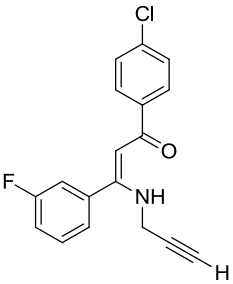
32w (93%)



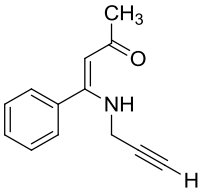
32x (75%)



32y (95%)



32z (91%)



32aa (73%)

[a]Isolated yields.

As a representative example, ^{1}H and ^{13}C NMR spectra of compound **32a** are given in Figures 22 and 23, respectively. As seen in the ^{1}H NMR spectrum, due to H-bonding (N−H····O) N-H proton resonates at lower field (11.33 ppm) as a broad singlet. Phenyl protons appear between 7.37 and 7.95 ppm as multiplet. Vinylic proton gives a singlet at 5.85 ppm. In the higher field of spectrum, the signals of methylenic proton and alkynyl proton appear at 3.95 and 2.31 ppm, as doublet of doublets (J = 6.3, 2.5 Hz) and triplet (J = 2.5 Hz), respectively. In the case of ^{13}C NMR, there are 14 different carbon signals. One belongs to carbonyl carbon peak resonating at 189.3 ppm. At 166.0 ppm, β ipso carbon peak signal (N-C) is observed. The resonance signals resonating between 127.3 and 140.1 ppm belong to aromatic carbons. The signal of α CH carbon appears at 94.8 ppm. The remaining three signals, appearing at 79.9, 72.6, 34.3 ppm, relate to peaks of alkynyl carbons and methylenic CH_2 carbon, respectively.

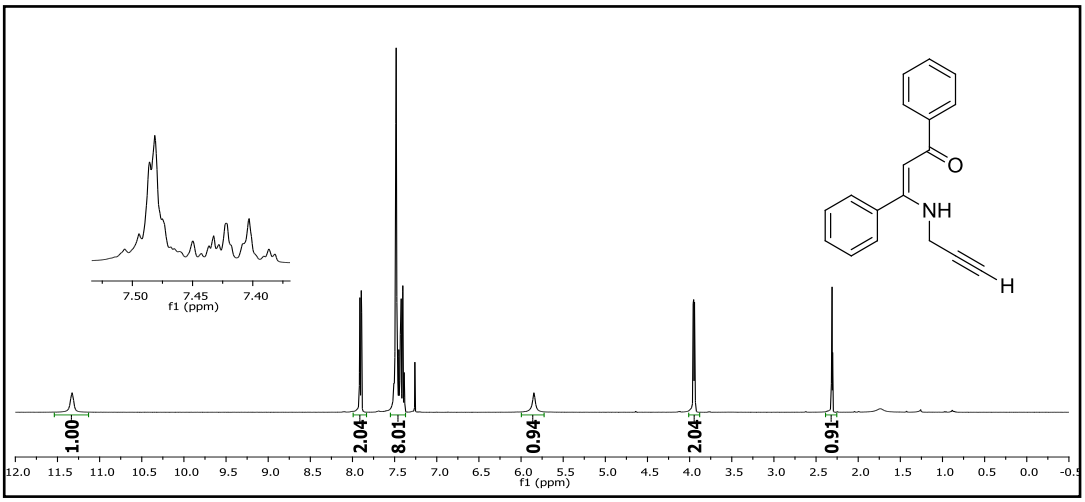


Figure 22. ^{1}H NMR spectrum of compound **32a**.

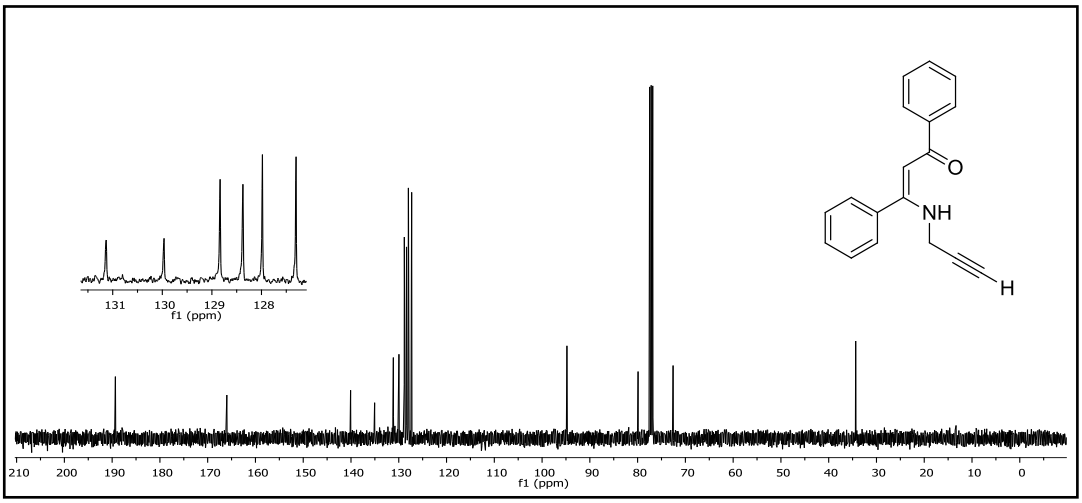
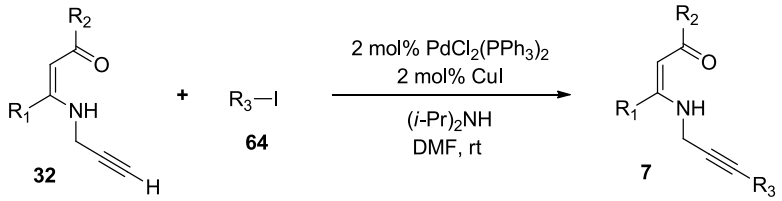


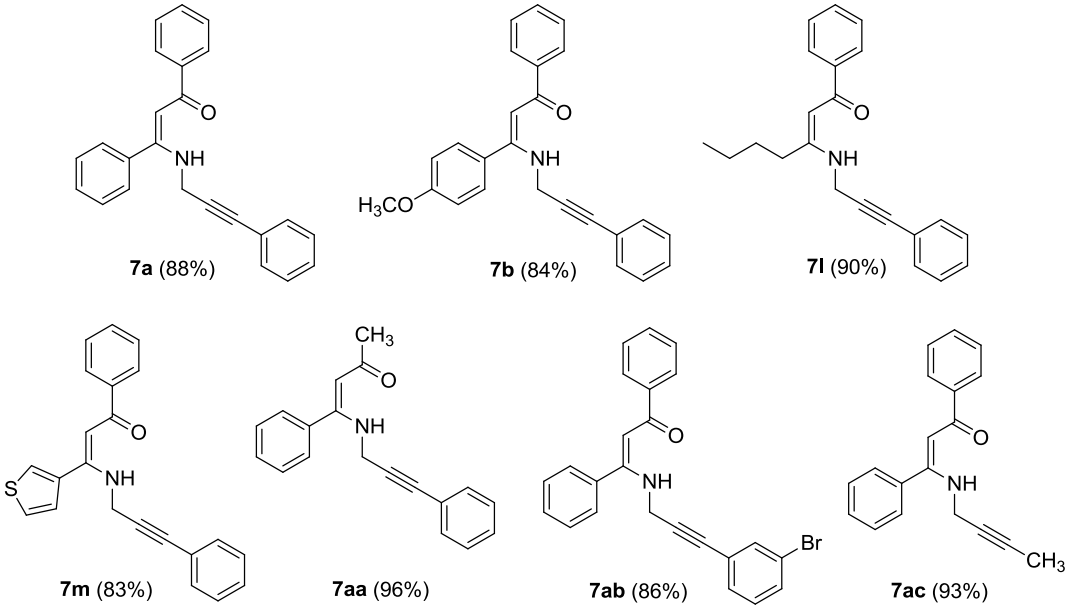
Figure 23. ^{13}C NMR spectrum of compound **32a**.

2.1.3 Synthesis of *N*-Propargylic β-Enaminones 7

Some of the β-enaminones **32** having terminal alkyne units in their structures were subjected to Sonogashira cross-coupling reaction with aryl iodides **64**. This Pd-catalyzed reaction under basic conditions at room temperature afforded functionalized aryl-substituted *N*-propargylic β-enaminones **7** in 83-96% yields (Table 3). Since the Sonogashira conditions were not applicable for the alkyl halides, in one case, 2-butynylamine was directly reacted with 1,3-diphenylprop-2-yn-1-one (**63a**) to generate butynyl-substituted β-enaminone **7ac**. By this way, the synthesis of compound **7ac** was achieved in high yield (93%). Hence, totally seven different *N*-propargylic β-enaminones were ready for the iodine-mediated electrophilic cyclization.

Table 3. Synthesized *N*-propargylic β-enaminone derivatives **7**.[a]



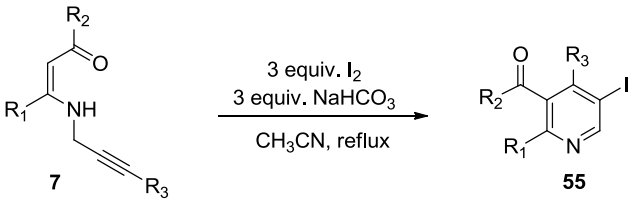


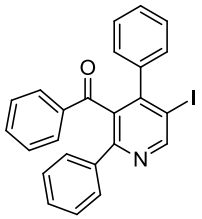
[a]Isolated yields.

2.1.4 Synthesis of 5-Iodopyridines 55

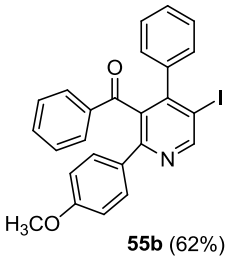
Electrophilic cyclization of *N*-propargylic β-enaminones **7** with I_2 under basic conditions were investigated by our research group.[91] The best optimized conditions were applied for the synthesis of 5-iodopyridines **55.** By taking 3.0 equiv. of both I_2 and $NaHCO_3$ in refluxing ACN under open atmosphere, seven iodo-substituted pyridine derivatives **55** were synthesized from the corresponding *N*-propargylic β-enaminones **7** in 47-80% yields.

Table 4. Synthesized 5-iodopyridine derivatives **55**.[a]

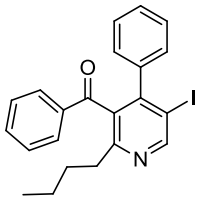




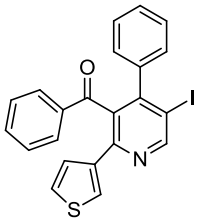
55a (80%)



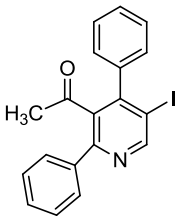
55b (62%)



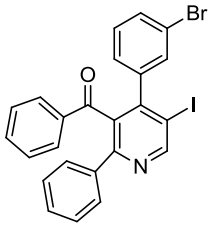
55l (65%)



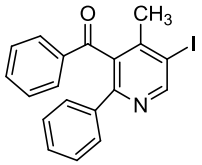
55m (75%)



55aa (47%)



55ab (57%)



55ac (51%)

[a]Isolated yields.

Formation of these target compounds were deduced from especially their ^{1}H and ^{13}C NMR spectra. Characteristic α-proton peaks of pyridines observed at about 9.10 ppm as singlet and their bonded carbons resonate in between 157.0 and 157.7 ppm. As expected, iodine-attached carbon atoms resonate at high field due to heavy-atom effect. Their signals appear between 98.0 and 100.4 ppm. Representative ^{1}H and ^{13}C NMR spectra of compound **55a** were given in Figure 24 and 25, respectively.

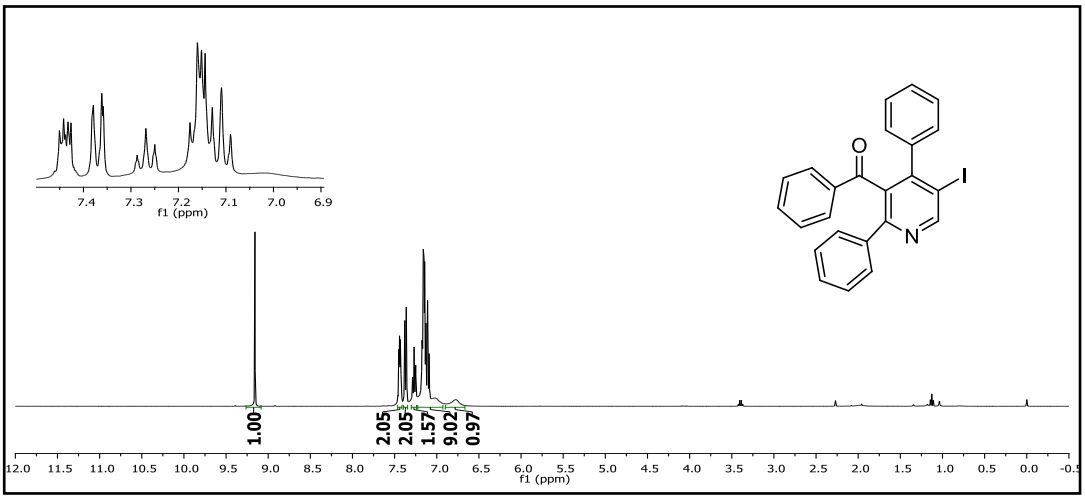


Figure 24. ^{1}H NMR spectrum of compound **55a**.

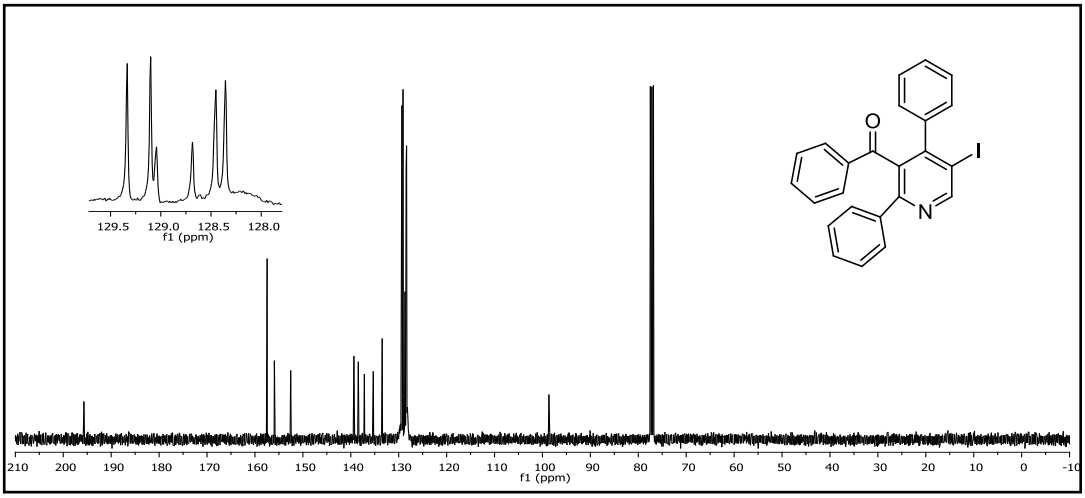
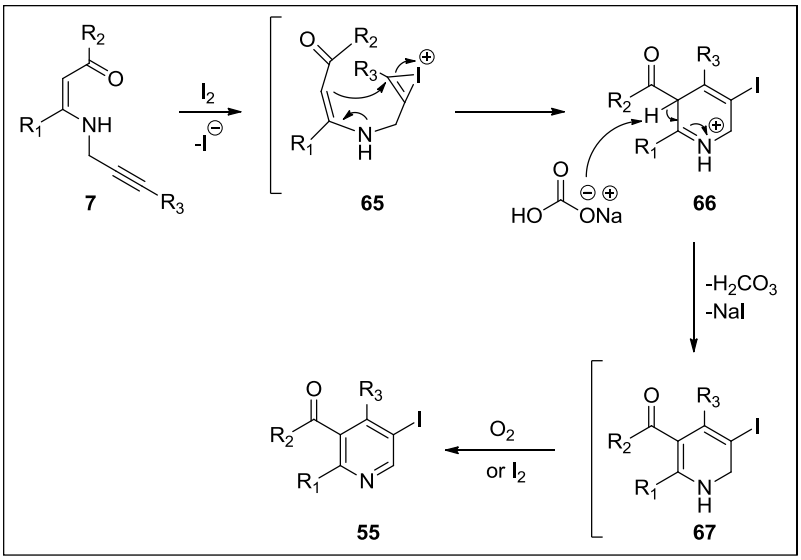


Figure 25. ^{13}C NMR spectrum of compound **55a**.

The proposed mechanism for the synthesis of 5-iodopyridines **55** is described in Scheme 25.[91] Firstly, iodine interacts with alkyne group of *N*-propargylic β-enaminone and forms iodonium ion **65**. Subsequently, 6-*endo*-*dig* electrophilic cyclization occurs by α-carbon and generates intermediate **66**. Then, deprotonation with base gives 1,2-dihydropyridine **67**. Lastly, aerobic and/or iodine-assisted oxidation produces the target iodopyridine compounds **55** (Scheme 25).



Scheme 25. Proposed mechanism for the formation of 5-iodopyridines **55**.

2.1.5 Synthesis of *N*-Propargylic Thio-β-enaminones 58

According to recent studies about thionation reactions, 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide known as Lawesson's reagent (LR), whose structure is given in Figure 26, has recently been preferred to be used as the thionating reagent in synthetic organic chemistry.[92]

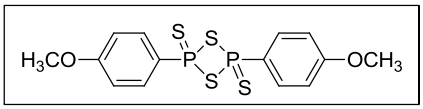
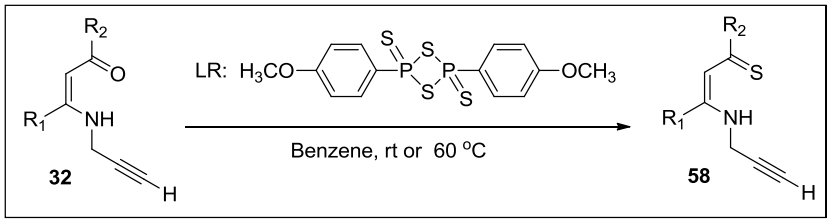


Figure 26. Chemical structure of Lawesson's reagent (LR).

In this part of thesis work, thionation reaction of *N*-propargylic β-enaminones **32** with LR has been investigated to obtain the corresponding thionated *N*-propargylic β-enaminone derivatives **58** (Scheme 26).

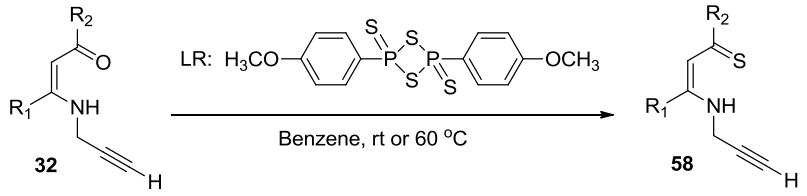


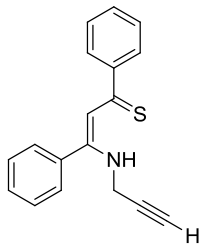
Scheme 26. Synthesis of *N*-propargylic thio-β-enaminones **58**.

We initially performed the reaction of *N*-propargylic β-enaminone derivative **32a** ($R_1 = R_2 = Ph$) by using 0.5 equiv. of LR in refluxing benzene (80 ^oC) under argon atmosphere. As a result of this reaction, we isolated *N*-propargylic thio-β-enaminone **58a** in 85% yield in 0.5 h with some decomposition (Table 5). In order to prevent the decomposition and to get higher yield, we decreased the reaction temperature. When the temperature was lowered to 60 ^oC, the same reaction afforded compound **58a** in 94% yield. On the other hand, lowering the temperature to room temperature decreased the yield of **58a** to 50% in 24 h. Therefore, thionation reactions of *N*-propargylic β-enaminones were conducted with 0.5 equiv. of LR in benzene at 60 ^oC under argon atmosphere.

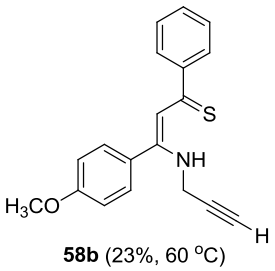
By using this reaction conditions, we synthesized various *N*-propargylic thio-β-enaminone derivatives **58** from the corresponding β-enaminone derivatives **32** as summarized in Table 5. For 14 derivatives, thionation reactions proceeded efficiently and afforded the corresponding thionated *N*-propargylic β-enaminones **58** in good to high yields (60-94%). However, in two cases, we isolated the target compounds **58b** and **58r** in 23% and 25% yields, respectively, which were the lowest ones among the synthesized derivatives. For this reason, we performed the same reactions at room temperature to get higher yields by preventing possible decomposition. We obtained the same products in relatively higher yields (55% and 50%) at room temperature. In the same manner, the reactions of *o*-methoxyphenyl and other 2-bromo-substituted *N*-propargylic β-enaminones (**58c**, **58n**, **58s**, **58t**) with LR were directly carried out at room temperature. These reactions afforded the corresponding thionated enaminones in 79%, 31%, 48% and 41% yields, respectively, in longer reaction times.

Table 5. Synthesized *N*-propargylic thio-β-enaminone derivatives **58**.[a]

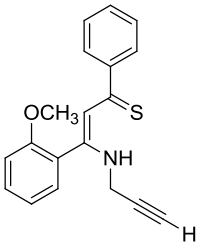




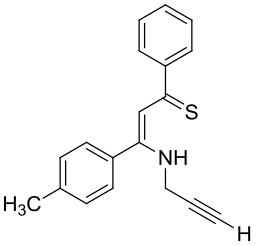
58a[b] (94%, 60 °C)



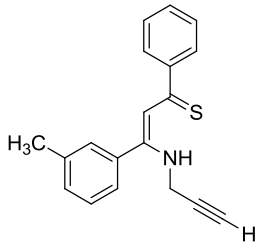
58b (23%, 60 °C)
(55%, rt)



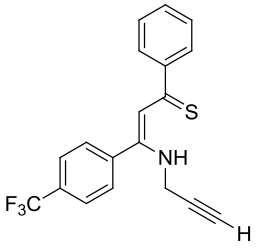
58c (79%, rt)



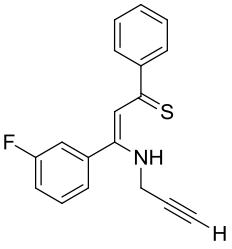
58d (67%, 60 °C)



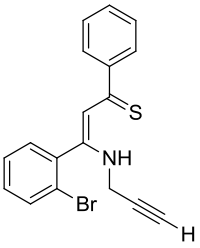
58e (60%, 60 °C)



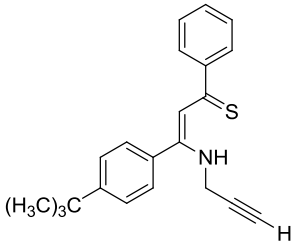
58f (75%, 60 °C)



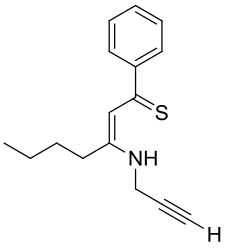
58h (73%, 60 °C)



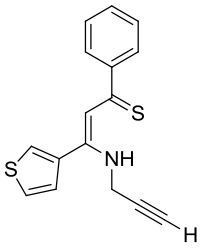
58i (71%, 60 °C)



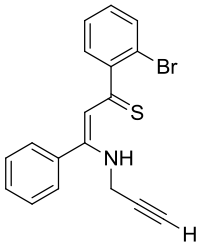
58j (77%, 60 °C)



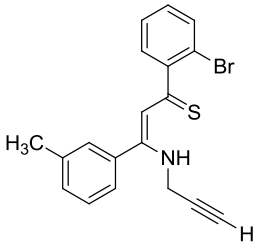
58l (87%, 60 °C)



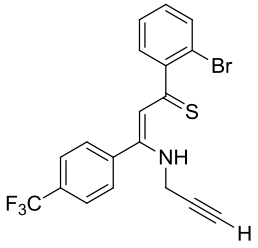
58m (82%, 60 °C)



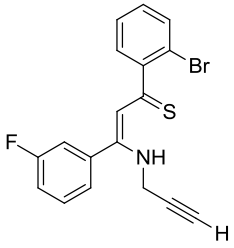
58n (31%, rt)



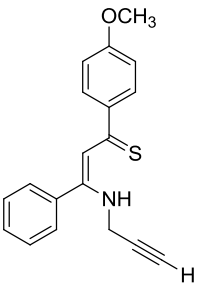
58r (25%, 60 °C)
(50%, rt)



58s (48%, rt)

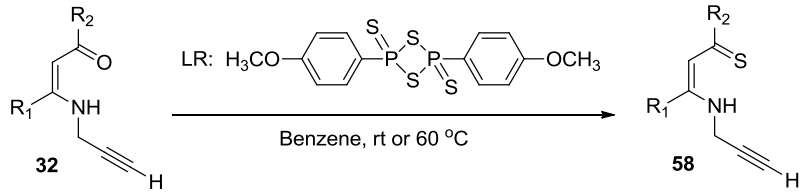


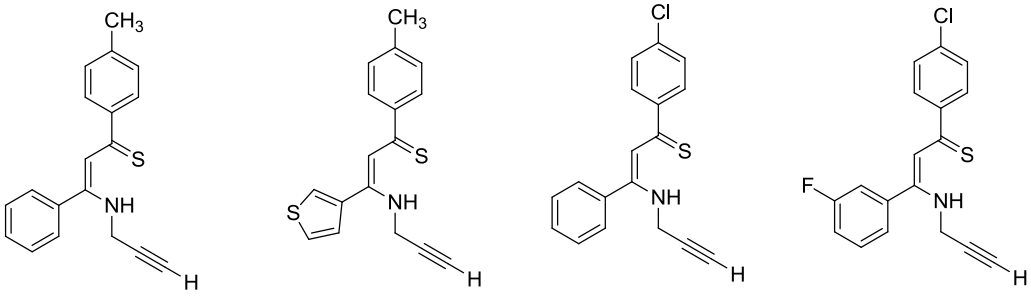
58t (41%, rt)



58v (70%, 60 °C)

Table 5. Continued.



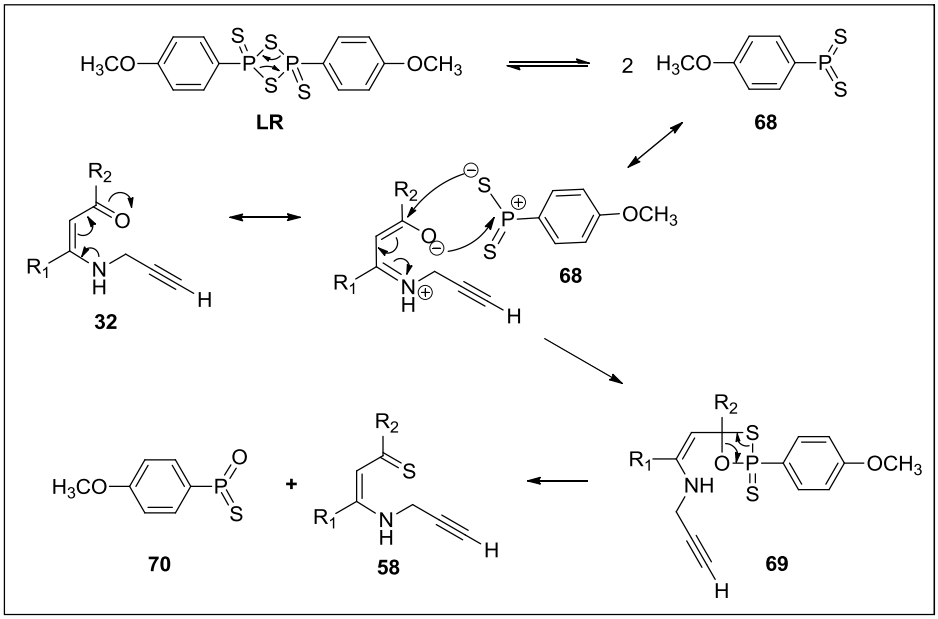


[a]All the reactions were performed with 1.0 equiv. of compound **32** and 0.5 equiv. of LR under argon and the yields are of isolated yields. [b]When the same reaction was performed at rt and reflux conditions, it afforded the *N*-propargylic thio-β-enaminone **58a** in 50% and 85% yields, respectively.

It can be deduced from these results that strong electron donating groups such as methoxy group on phenyl rings of *N*-propargylic β-enaminones (**32b** and **32c**) rapidly activates the thionation reaction at room temperature. Due to this reason, elevating the temperature to 60 °C may promote decompositions of generated thionated *N*-propargylic β-enaminones (**58b** and **58c**) and can lead their isolations in lower yields. For the 2-bromo-substituted ones (**32n**, **32r**, **32s**, **32t**), high temperature may also cause coordination of in-situ generated ylides with bromo group while interaction with carbonyl group occurs during the reaction. This may lower the formation yields of compounds **58n**, **58s**, **58t** at 60 °C as in the case of compound **58r** formation.

The proposed mechanism for this transformation is shown in Scheme 27. It starts with the in-situ dissociation of one equiv. of LR to two equiv. of phenylphsophine disulfide compounds **68**. Then, carbonyl functional group of *N*-propargylic β-enaminone **32** reacts with this ylide **68** by the resonance effect and generating four-

membered ring **69**. Lastly, ring opening of this intermediate **69** affords the desired thionated ketone **58** and thioxo phosphineoxide **70** as a byproduct.

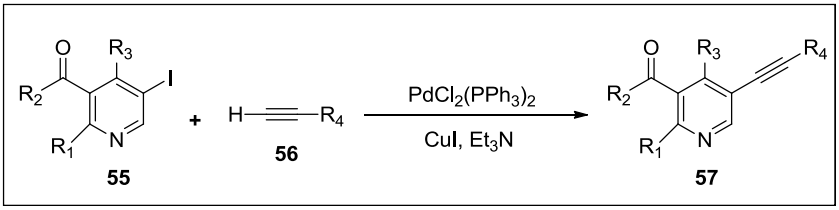


Scheme 27. Proposed mechanism for the formation of *N*-propargylic thio-β-enaminone derivatives **58**.

2.2 Synthesis of Target Compounds

2.2.1 Synthesis of 5-Alkynylpyridines 57

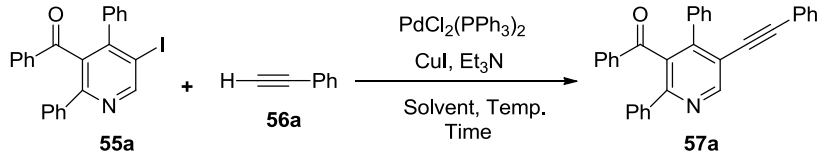
Synthesis of 5-alkynylpyridines **57** from 5-iodopyridines **55** by using Sonogashira cross-coupling reaction establishes the goal of this part of thesis work (Scheme 28).



Scheme 28. Synthesis of 5-alkynylpyridines **57**.

First of all, optimization studies were run to get higher yields of 5-alkynylpyridine derivatives **57**. For this purpose, cross-coupling reaction of diphenyl-substituted iodopyridine derivative **55a** with phenyl acetylene (**56a**) at different reaction conditions has been investigated (Table 6). Initially, 5-iodopyridine compound **55a** has been reacted with 1.5 equiv. of phenyl acetylene (**56a**) by using 5 mol% of both $PdCl_2(PPh_3)_2$ and CuI in various solvents, in turn with DCM, THF, ACN, dioxane, DMF and DMSO (Table 6, entries 1-6). Except for those in DMF and DMSO, other overnight reactions, affording alkynyl product **57a** in 40-79% yields, did not go to fully completion and starting material **55a** was recovered with some decomposition. Although the yield obtained in DMF (83%) was very close to the one obtained in DMSO (82%), we continued reactions with DMF because of easier removal of it than DMSO. Raising the temperature to 65 ^oC increased the yield from 83% to 91% (Table 6, entry 7). However, performing the reaction at 100 ^oC gave the desired product in 76% yield (Table 6, entry 8). Apparently, higher temperature than 65 ^oC might cause decompositon of the reaction product **57a** and lowered the yield. After determining the reaction temperature as 65 ^oC, effective number of equivalents of terminal alkyne **56a** was determined. Reaction with 1.0 equiv. of phenyl acetylene (**56a**) decreased the yield (68%) while higher number of equivalents did not change the yield (91%) (Table 6, entries 9-10). In the absence of the Pd catalyst, 5-alkynylpyridine **57a** was not formed and starting material was recovered in 89% yield (Table 6, entry 11). By using 2 mol% of Pd catalyst, the same reaction afforded the target compound **57a** in 78% yield (Table 6, entry 12). Lastly, the reaction was carried out in the absence of Cu catalyst. In this reaction, the yield of obtained product was slightly lower (89%) (Table 6, entry 13). As a result of these reactions, the highest yield (91%) was obtained by using 1.5 equiv. of terminal alkyne **56a**, 5 mol% of $PdCl_2(PPh_3)_2$ and 5 mol% of CuI in DMF at 65 ^oC (Table 6, entry 7). These optimized reaction conditions were applied for Sonogashira reaction of 5-iodopyridines **55** with terminal alkynes **56** to synthesize a diverse range of 5-alkynylpyridine derivatives **57**.

Table 6. Optimization studies for Sonogashira cross-coupling reaction of 5-iodopyridine **55a** with phenylacetylene (**56a**)[a]

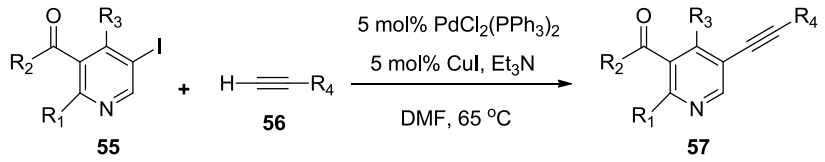


Entry	Alkyne (equiv.)	$PdCl_2(PPh_3)_2$ (mol %)	CuI (mol %)	Solvent	Temp. (^oC)	Time (h)	Yield[b] (%)
1	1.5	5	5	DCM	rt	24	40[c]
2	1.5	5	5	THF	rt	24	79[d]
3	1.5	5	5	ACN	rt	24	78[e]
4	1.5	5	5	Dioxane	rt	24	74[f]
5	1.5	5	5	DMF	rt	24	83
6	1.5	5	5	DMSO	rt	24	82
7	1.5	5	5	DMF	65	1.5	91
8	1.5	5	5	DMF	100	1.5	76
9	1.0	5	5	DMF	65	1.5	68
10	2.0	5	5	DMF	65	1.5	91
11	1.5	-	5	DMF	65	1.5	-[g]
12	1.5	2	5	DMF	65	4.0	78
13	1.5	5	-	DMF	65	1.5	89

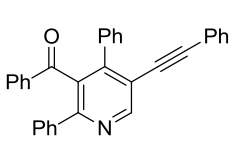
[a]Reactions were performed on a scale of 0.15 mmol of 5-iodopyridine **55a** in 2.25 mL of solvent by using 2.25 mL of Et_3N under argon with the indicated conditions. [b]Isolated yields. [c]The starting 5-iodopyridine **55a** was recovered in 45% yield as well. [d]The starting 5-iodopyridine **55a** was recovered in 13% yield as well. [e]The starting 5-iodopyridine **55a** was recovered in 10% yield as well. [f]The starting 5-iodopyridine **55a** was recovered in 8% yield as well. [g]Product formation was not observed and the starting 5-iodopyridine **55a** was recovered in 89% yield.

As shown in Table 7, we synthesized totally 28 new 5-alkynylpyridine derivatives **57** from the corresponding iodopyridines **55** and terminal alkynes **56**. In the majority of them, the coupling reactions were carried out efficiently and afforded target alkynylpyridines **57** in good to high yields. The isolated yields of all derivatives were in a range of 40% and 99%. Two fluorine-containing alkynyl pyridines, **57f** and **57h** were synthesized in 92% and 95% yields, respectively. Also, six thiophen-3-yl- and thiophen-3-ylethynyl-substituted pyridine derivatives, **57m**, **57bm**, **57ma**, **57md**, **57mm** and **57mr**, were synthesized in 73-98% yields. It should be mentioned that in the structure of compound **57mr**, there is a ferrocenyl unit as well. Other than this derivative, two ferrocenylethynyl-substituted pyridines, **57r** and **57br**, were synthesized in excellent yields (99% and 92%, respectively). On the other hand, one pyridin-2-ylethynyl-substituted pyridine derivative, **57q**, was synthesized in an acceptable yield (40%). Moreover, different alkyl groups, such as butyl, pentyl, cyclopentylmethyl, hydroxycyclohexyl and *N*-phthalimidylethyl were included in the structures of alkynylpyridine compounds, **57l, 57n, 57o, 57p** and **57k**, which were synthesized in 66-87% yields.

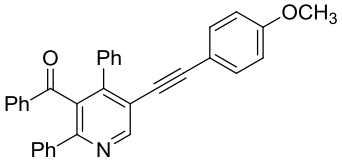
Table 7. Synthesized 5-alkynylpyridine derivatives **57**.[a]



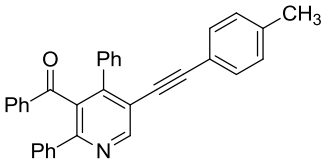
55 + **56** → **57**



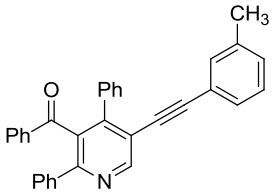
57a (91%)



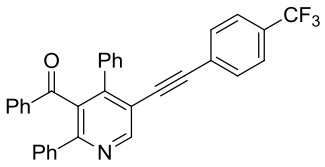
57b (57%)



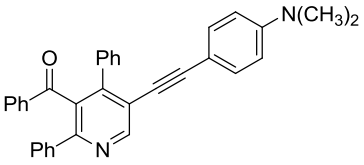
57d (98%)



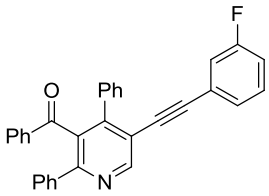
57e (95%)



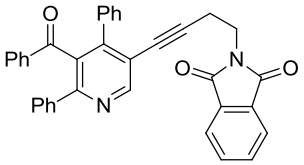
57f (92%)



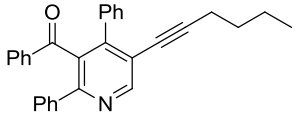
57g (72%)



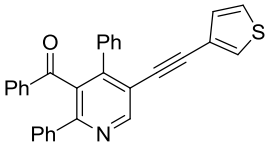
57h (95%)



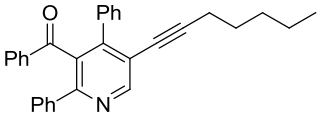
57k (66%)



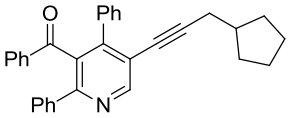
57l (80%)



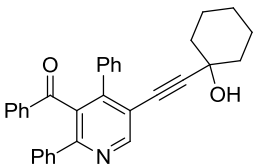
57m (98%)



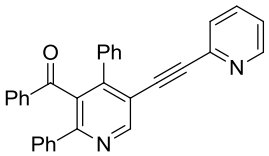
57n (80%)



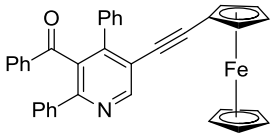
57o (87%)



57p (66%)

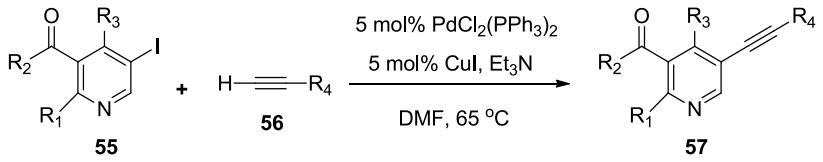


57q (40%)

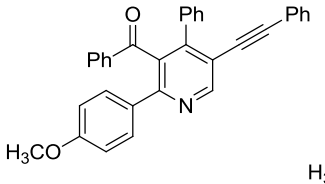


57r (99%)

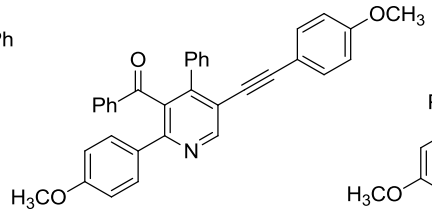
Table 7. Continued.



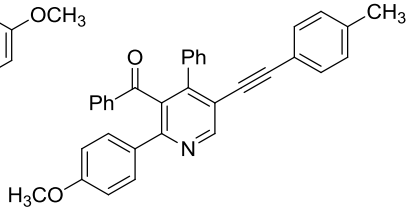
55 + **56** → **57**



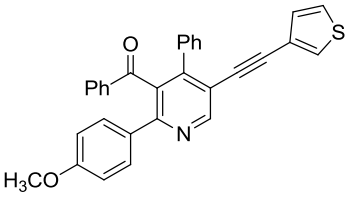
57ba (78%)



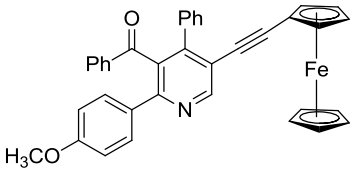
57bb (87%)



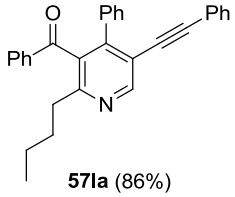
57bd (99%)



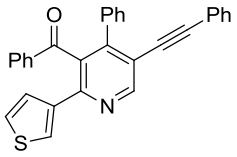
57bm (98%)



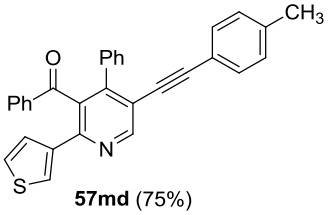
57br (92%)



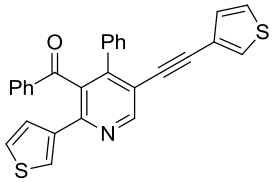
57la (86%)



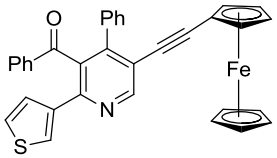
57ma (90%)



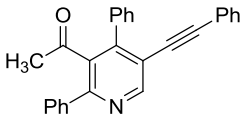
57md (75%)



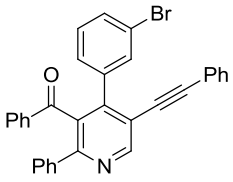
57mm (73%)



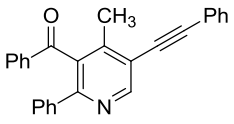
57mr (80%)



57aaa (91%)



57aba (84%)



57aca (85%)

[a]Isolated yields.

All the structures of synthesized 5-alkynylpyridines **57** were supported by ^{1}H and ^{13}C NMR analyses. In their corresponding ^{13}C NMR data, there were characteristic peaks verifying the formation of target compounds **57**. For instance, ^{1}H and ^{13}C NMR spectra of compound **57a** are depicted in Figures 27 and 28, respectively. In the ^{1}H NMR spectrum, it can be clearly seen that the pyridine hydrogen peak resonates at 9.06 ppm as a singlet while it appears at 9.16 ppm in the ^{1}H NMR of starting compound **55a** (see Figure 24). In the ^{13}C NMR spectrum, the signal at 98.7 ppm corresponding to carbon attached to iodine in starting material **55a** (see Figure 25) is disappeared. Instead, in this region, there are characteristic alkynyl carbon peaks appearing at 85.5 and 96.6 ppm. These peaks strongly indicate that an acetylene unit is incorporated in the molecule. Also, the carbon having a hydrogen (C-H) in pyridine unit resonates in relatively higher field (152.5 ppm) as compared to that of signal (157.5 ppm) in ^{13}C NMR spectrum of starting compound **55a**.

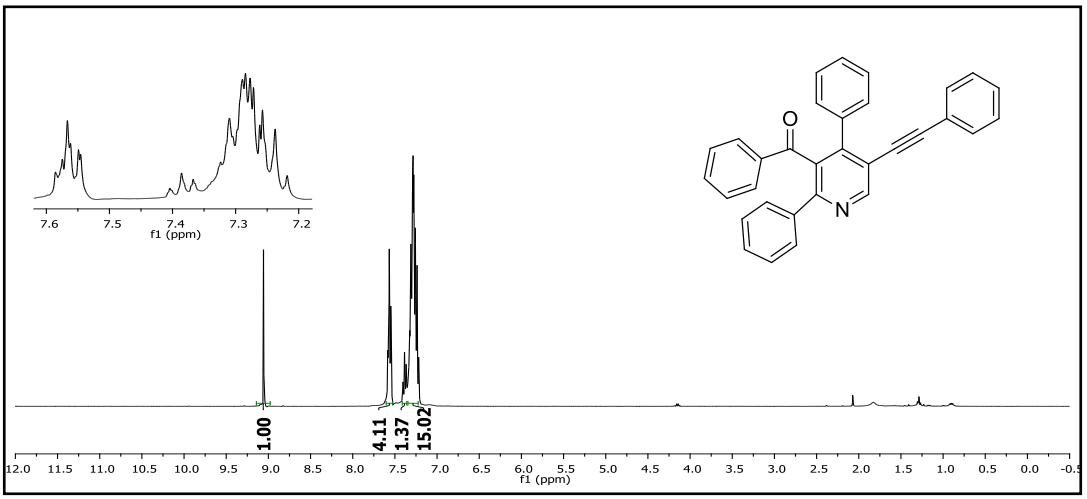


Figure 27. ^{1}H NMR spectrum of compound **57a**.

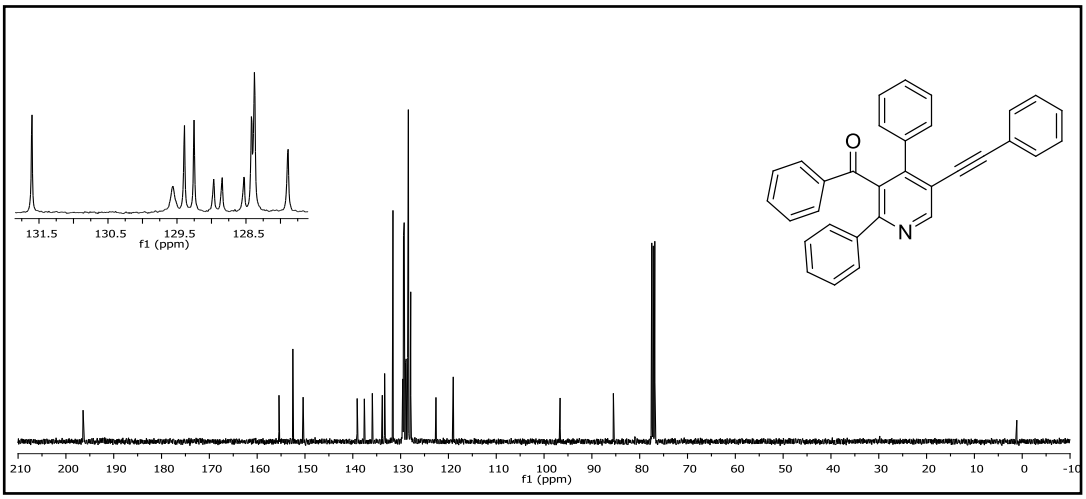
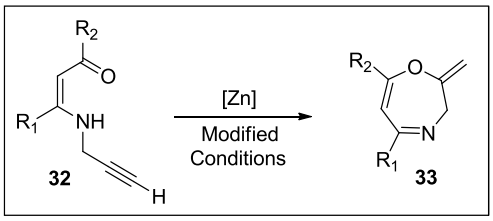


Figure 28. ^{13}C NMR spectrum of compound **57a**.

2.2.2 Synthesis of 2,3-Dihydro-1,4-oxazepines 33

Zinc-mediated cyclization of *N*-propargylic β-enaminones **32** in refluxing DCM for the synthesis of 2,3-dihydro-1,4-oxazepines **33** has recently been achieved by Zora research group.[93] Alternatively, the modification of the reaction conditions to obtain monocyclic 1,4-oxazepine derivative **33** in shorter reaction time and higher yield constitutes the goal of this chapter of thesis work (Scheme 29).

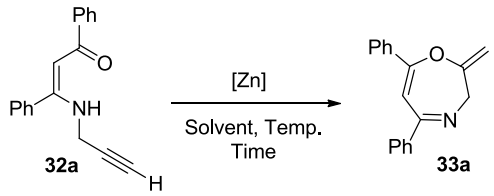


Scheme 29. Synthesis of 2,3-dihydro-1,4-oxazepines **33** in modified conditions.

For this reason, we have made a quick optimization as depicted in Table 8. We have carried out several reactions in order to get shorter reaction time as compared to previously found one (Table 8, entry 1). With *N*-propargylic β-enaminone **32a** in hand, firstly, metallic Zn dust was tried to produce the reaction product, 2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**33a**), which was carried out in

DCM for 9.0 h (Table 8, entry 2). However, there was no reaction with Zn dust, showing that the reaction mainly proceeds with Zn^{2+} cation, instead of metallic Zn. Thus, the optimization reactions were continued with $ZnCl_2$. In order to decrease the reaction time, the amount of $ZnCl_2$ was increased from 1.0 equiv. to 1.5 equiv. (Table 8, entry 3). In this case, the reaction proceeded in 8.0 h, which was only 1.0 h shorter than previous reaction time (9.0 h). In other words, increasing $ZnCl_2$ amount did not affect the reaction time substantially. After that, the type of solvent was changed in order to proceed the cyclization reaction at higher temperature than 40 ^{o}C. By refluxing in $CHCl_3$ for 5.0 h, the reaction afforded the target compound **33a** in 95% yield (Table 8, entry 4). Reducing the reaction time from 5.0 h to 1.5 h did not affect the yield so the same yield was obtained (Table 8, entry 5). Notably, the reaction at higher temperature such as in refluxing DCE did not improve the yield (Table 8, entry 6). The reason might be the possible decomposition of reaction product **33a** at higher temperature. As a result of these optimization studies, new optimal reaction conditions (i.e., in refluxing $CHCl_3$) to generate 1,4-oxazepine derivative **33a** in high yield (95%) in shorter reaction time (1.5 h) was established (Table 8, entry 5).

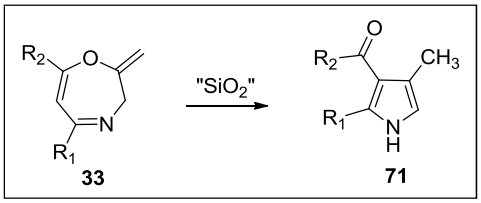
Table 8. Optimization studies for Zn-mediated cyclization reaction of *N*-propargylic β-enaminone **32**[a]



Entry	[Zn] (equiv.)	Solvent	Temp. (^oC)	Time (h)	Yield[b] (%)
1	$ZnCl_2$ (1.0)	DCM	reflux	9.0	95[c]
2	Zn dust (1.0)	DCM	reflux	9.0	-[d]
3	$ZnCl_2$ (1.5)	DCM	reflux	8.0	95
4	$ZnCl_2$ (1.0)	$CHCl_3$	reflux	5.0	95
5	$ZnCl_2$ (1.0)	$CHCl_3$	reflux	1.5	95
6	$ZnCl_2$ (1.0)	DCE	reflux	3.0	76

[a] Reaction were performed on a scale of 0.3 mmol of *N*-propargylic β-enaminone **32a** in 5.0 mL of solvent under argon with the indicated conditions. [b]Isolated yields. [c]The best yield which was obtained from afore studies by Zora research group. [d]Product formation was not observed and the starting *N*-propargylic β-enaminone **32** was recovered with some decomposition.

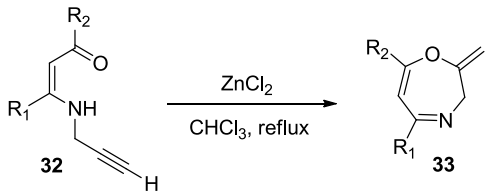
We have synthesized 21 different 2,3-dihydro-1,4-oxazepine derivatives **33** by applying the optimized reaction conditions. The structures and yields of the synthesized 1,4-oxazepine derivatives **33** are given in Table 9. The isolated yields were good and high (72% - 95%) in the case of 17 derivatives. For compound **33c** and **33u**, the obtained yields (66% and 68%, respectively) were fair. Only in two cases, the cyclization reaction afforded target compounds **33g** and **33k** both in 40% yields. On the other hand, the reaction durations for the formations of 19 1,4-oxazepine derivatives **33** were maximum 6.0 h. However, the reactions for the formation of compound **33i** and **33k** were completed barely in 12.0 h and 9.0 h, respectively. Interestingly, in some cases, pyrrole formations were observed during isolation step by column chromatography on SiO_2 (Scheme 30).

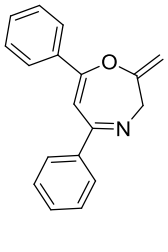


Scheme 30. General reaction for the pyrrole formations.

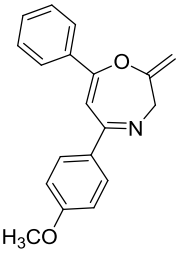
Two pyrrole derivatives, **71k** and **71l**, were isolated together with corresponding 1,4-oxazepine derivatives, **33k** and **33l**, from flash-column chromatography in 12% and 9% yields, respectively. However, they had not been formed during the cyclization reaction since there had been no characteristic peaks in their crude NMR spectra. To figure out the effect of SiO_2, firstly pure 1,4-oxazepine derivative **33l** was directly subjected to flash-column chromatography on silica gel. From this rechromatography, 9% yield of pyrrole derivative **71l** was obtained while 72% yield of 1,4-oxazepine **33l** was recovered. There was a 19% of loss due to probable decomposition during isolation. It means that SiO_2 played an active role for the pyrrole (**71k** and **71l**) formations. Also, 80% yield of conversion of compound **33l** to pyrrole **72l** was obtained in the presence of SiO_2 in refluxing EtOAc. The same reaction was carried out with phenyl-substituted 1,4-oxazepine derivative **33a** but it did not produce any corresponding pyrrole derivative **71a**. Only in elevated temperatures (in refluxing dioxane) it produced pyrrole **71a** in 26% yield as well as recovery of starting compound **33a** in 11% yield. The remaining 63% of **33a** was possibly decomposed. SiO_2-catalyzed mechanism for the formation of pyrroles **71** will later be proposed. It can be inferred from these results that alkyl-substituted 1,4-oxazepines (**33k** and **33l**) were not so stable as phenyl-substituted ones **33**.

Table 9. Synthesized 2,3-dihydro-1,4-oxazepine derivatives **33**.[a]

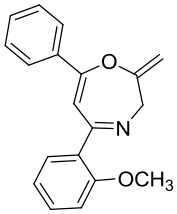




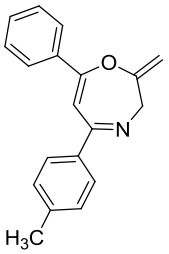
33a (95%, 1.5 h)



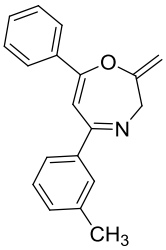
33b (73%, 3.0 h)



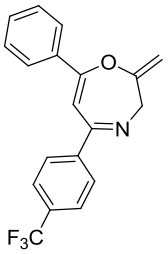
33c (66%, 6.0 h)



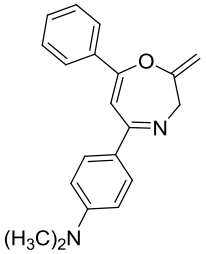
33d (74%, 2.0 h)



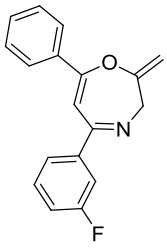
33e (74%, 1.5 h)



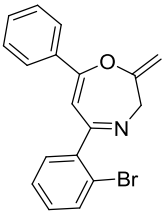
33f (82%, 2.0 h)



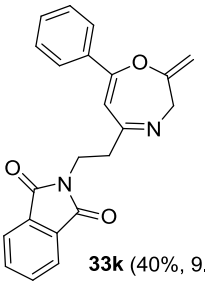
33g (40%, 1.5 h)



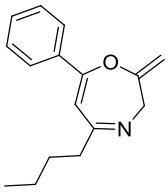
33h (90%, 2.0 h)



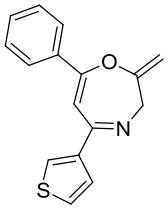
33i (73%, 12.0 h)



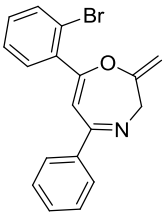
33k (40%, 9.0 h)[b]



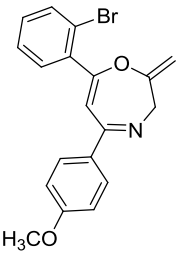
33l (72%, 5.0 h)[c]



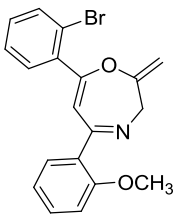
33m (84%, 2.0 h)



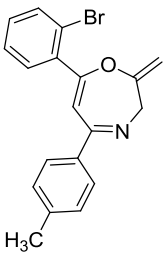
33n (81%, 1.5 h)



33o (90%, 2.5 h)

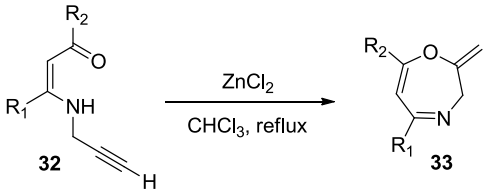


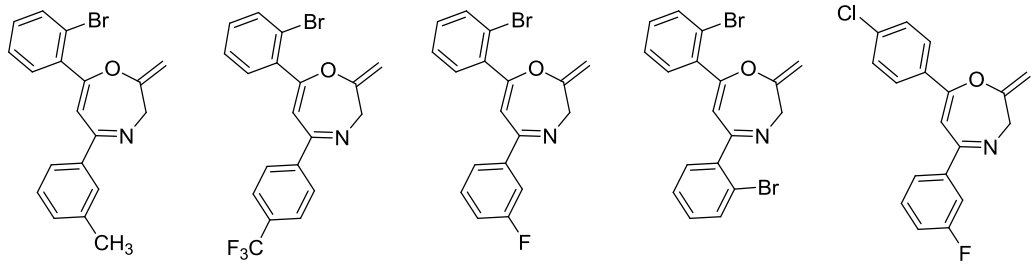
33p (88%, 6.0 h)



33q (90%, 2.0 h)

Table 9. Continued.





[a]Isolated yields. [b]Along with **33k**, pyrrole isomer **71k** was also isolated in 12% yield (see Figure 29 for its structure). [c]Along with **33l**, pyrrole isomer **71l** was also isolated in 9% yield (see Figure 29 for its structure).

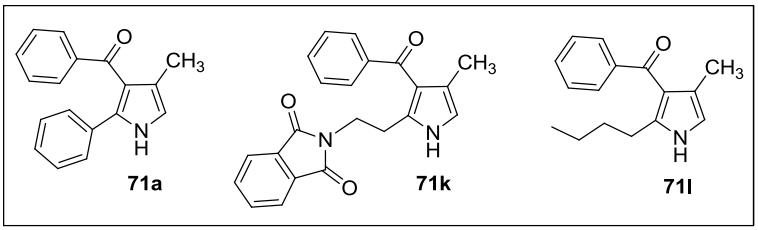


Figure 29. Structures of pyrrole derivatives isolated along with 1,4-oxazepines.

Formation of 1,4-oxazepine derivatives **33** were mainly confirmed by analysis of their ^{1}H and ^{13}C NMR data. For instance, ^{1}H and ^{13}C NMR spectra of compound **33a** were demonstrated in Figures 30 and 31, respectively. In the ^{1}H NMR spectrum, the protons of *exo*-methylenic carbon give distinct high-field signals at 4.40 ppm and 4.76 ppm as doublets with small coupling constants (J = 1.4-1.5 Hz). A singlet appearing at 4.57 ppm belongs to protons of the methylenic carbon in the seven-membered ring. The other olefinic proton resonates as singlet at 6.41 ppm. Remaining 10 phenyl hydrogens appear as multiplet between 7.38 and 7.87 ppm.

In the ^{13}C NMR spectrum, there are three ipso carbon peaks belonging to the seven-membered ring carbons coming at 167.1, 159.0 and 158.2 ppm. Eight different phenyl carbon peaks appear in between 126.4 ppm and 139.8 ppm. The signals rising at 99.8 and 55.6 ppm belong to the olefinic and methylenic carbons of the ring, respectively. The remaining *exo*-methylenic carbon signal is observed at 94.0 ppm.

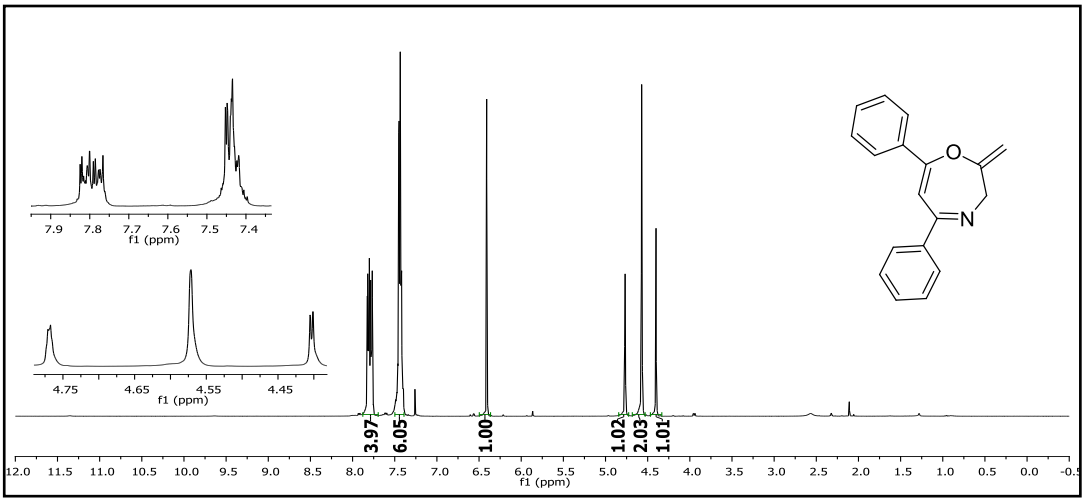


Figure 30. ^{1}H NMR spectrum of compound **33a**.

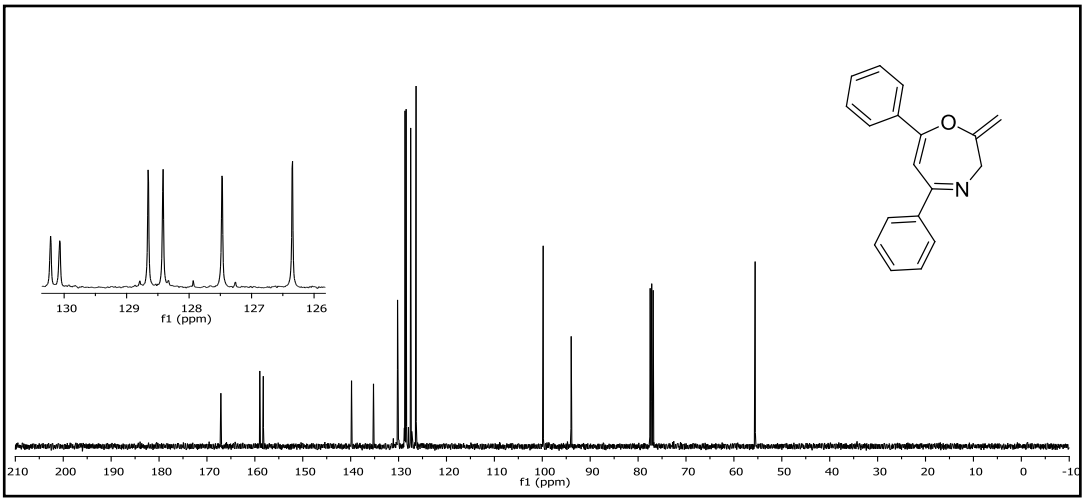
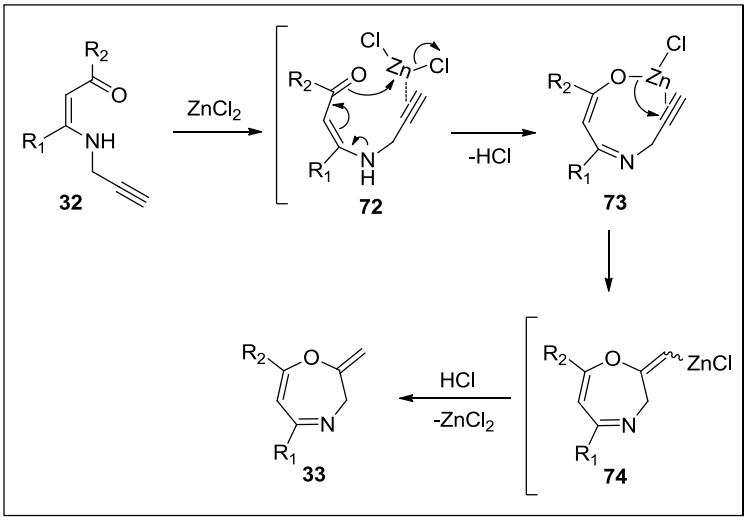


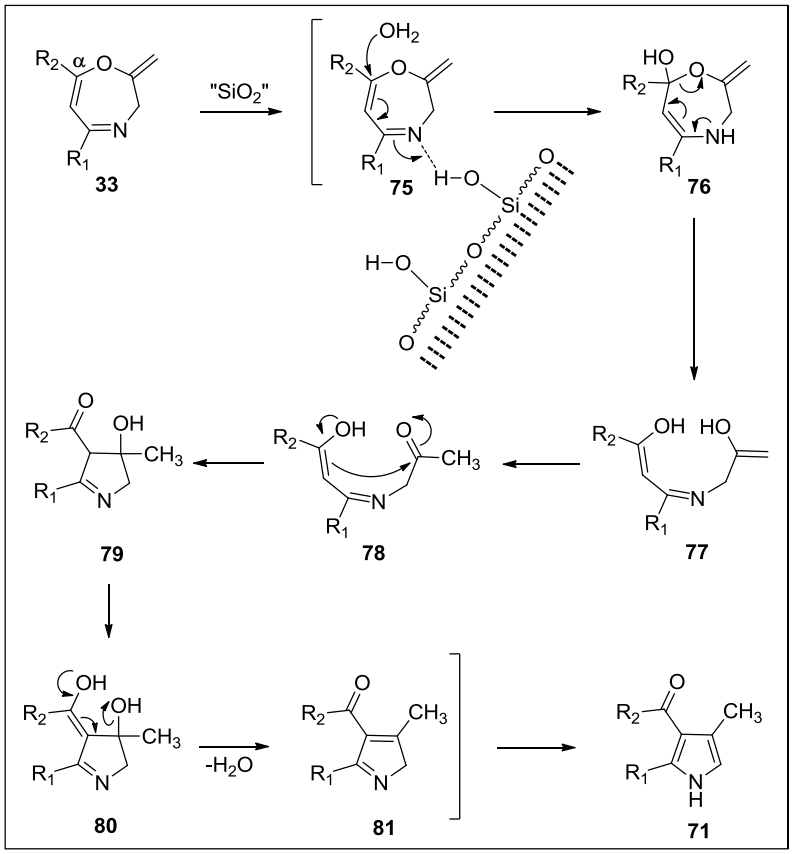
Figure 31. ^{13}C NMR spectrum of compound **33a**.

The suggested mechanism for the generation of 1,4-oxazepine derivatives is described in Scheme 31. Initially, zinc chloride coordinates through the triple bond of the alkyne unit **32** and forms intermediate **72**. After that, carbonyl oxygen is coordinated with zinc by amido-imido tautomerization and generates intermediate **73**, providing closeness of carbonyl oxygen and alkynyl group to each other. Then, vinyl zinc intermediate **74** is constituted via intramolecular 7-*exo-dig* cyclization. Lastly, in-situ hydolysis with HCl gives target 2,3-dihydro-1,4-oxazepine derivatives **33**.



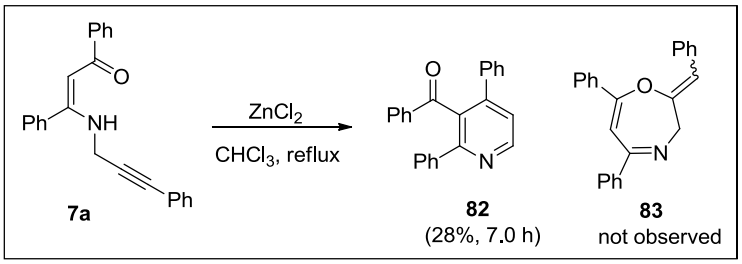
Scheme 31. Proposed mechanism for the formation of 2,3-dihydro-1,4-oxazepine derivatives **33**.

A possible SiO_2-catalyzed mechanism for the formation of pyrroles **71** from 1,4-oxazepines **33** is introduced in Scheme 32. Enhancement of electrophilicity of α carbon by coordination of silica gel through nitrogen facilitates nucleophilic attack of water to intermediate **75** so that it can produce hemiketal **76**. Afterwards, ring is opened to give dienol intermediate **77**, which rearranges to isomer **78** via keto-enol tautomerization. Subsequently, intramolecular aldol condensation takes place to afford compound **79**. Dehydration of compound **80** gives 2*H*-pyrrole **81**. Lastly, valence isomerization affords pyrrole derivatives **71**.



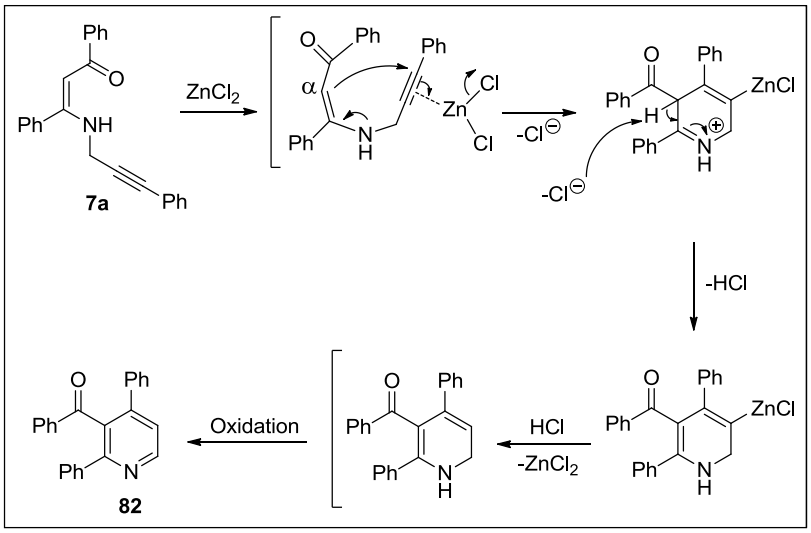
Scheme 32. Proposed mechanism for the formation of pyrroles **71**.

Additionally, we studied the reaction of phenyl-substituted *N*-propargylic β-enaminone **7a** with $ZnCl_2$ in refluxing $CHCl_3$. Surprisingly, pyridine derivative **82** was formed in 28% yield instead of expected 2,3-dihydro-1,4-oxazepine derivative **83** (Scheme 33).



Scheme 33. Formation of pyridine **82** from phenyl-substituted *N*-propargylic β-enaminone **7a**.

In this reaction pathway, most probably, coordination of carbonyl oxygen with zinc moiety could not occur. Only, alkynyl group is activated so that nucleophilic α carbon of starting compound **7a** attacks to the alkyne functionality and affords pyridine derivative **82** via 6-*endo-dig* cyclization (Scheme 34).



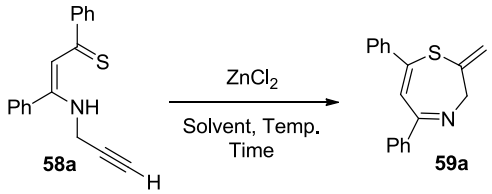
Scheme 34. Proposed mechanism for the formation of pyridine **82**.

2.2.3 Synthesis of 2,3-Dihydro-1,4-thiazepines 59

Investigation of cyclization of *N*-propargylic thio-β-enaminones **58** by using $ZnCl_2$ comprises the basis of this section of the thesis work. They were prepared from *N*-propargylic β-enaminones **32** by employing thionation reaction with LR. The representative phenyl-substituted thionated-*N*-propargylic β-enaminone **58a** was used for its cyclization reaction to find optimized reaction conditions with the best yield. In the light of the experience from the cyclization of *N*-propargylic β-enaminones **32** into 2,3-dihydro-1,4-oxazepines **33**, studies have been carried out by using 1.0 equiv. of $ZnCl_2$ as a mediator in chlorinated solvents, such as DCM, $CHCl_3$ and DCE, under reflux conditions (Table 10). All these reactions have afforded the expected 2,3-dihydro-1,4-thiazepine compound **59a** in high yields (88-90%) (Table 10, entries 1-3). When the reactions have been performed in the absence of $ZnCl_2$ in $CHCl_3$ and DCE, the expected compound **59a** was obtained

but in low yields as 16% and 22%, respectively (Table 1, entries 4 and 5). Although the starting material **58a** was recovered to some extent in those cases, it is important to note that the decomposition have mainly occurred in refluxing DCE. As a result of these reactions, we have adopted the condition of the reaction given in Entry 2 as the optimized reaction conditions since it gave the highest yield of the product (90%) in a shorter reaction time (1.5 h).

Table 10. Optimization studies for $ZnCl_2$-mediated cyclization reaction of *N*-propargylic thio-β-enaminone **58**[a]



Entry	$ZnCl_2$ (equiv.)	Solvent	Temp. (^oC)	Time (h)	Yield[b] (%)
1	1.0	DCM	reflux	9.0	90
2	1.0	$CHCl_3$	reflux	1.5	90
3	1.0	DCE	reflux	1.0	88
4	-	$CHCl_3$	reflux	15.0	16[c]
5	-	DCE	reflux	15.0	22[d]

[a]Reactions were performed on a scale of 0.3 mmol of *N*-propargylic thio-β-enaminone **58a** in 5.0 mL of solvent under argon with the indicated conditions. [b]Isolated yields. [c]The starting *N*-propargylic thio-β-enaminone **58a** was also recovered in 63% yield. [d]The starting *N*-propargylic thio-β-enaminone **58a** was also recovered in 28% yield.

Formation of 2,3-dihydro-1,4-thiazepine **59a** was principally confirmed by its ^1H and ^{13}C NMR spectra, which are given in Figures 32 and 33, respectively. According to the ^1H NMR spectrum, protons of *exo*-methylenic carbon resonate very close to each other appearing as high-field signals at 5.21 ppm and 5.18 ppm as doublet with small coupling constant (J = 0.7 Hz) and broad singlet. Around 0.30 ppm higher-field, there is a singlet peak at 4.81 ppm corresponding to the protons of methylenic carbon in the seven-membered ring, where other olefinic

proton resonates as singlet at 6.81 ppm. Other 10 aromatic hydrogens rise as multiplets between 7.39 and 7.83 ppm as expected. In the ^{13}C NMR spectrum, *exo*-methylenic carbon signal is observed at 110.4 ppm. The signals occuring at 59.3 and 123.2 ppm belong to the peaks of methylenic and olefinic carbons on the ring, respectively. Eight distinct phenyl carbon peaks emerge in between 127.6 ppm and 140.1 ppm. Remaining three ipso-carbon peaks belonging to the ring appear at 145.2, 150.0 and 167.4 ppm.

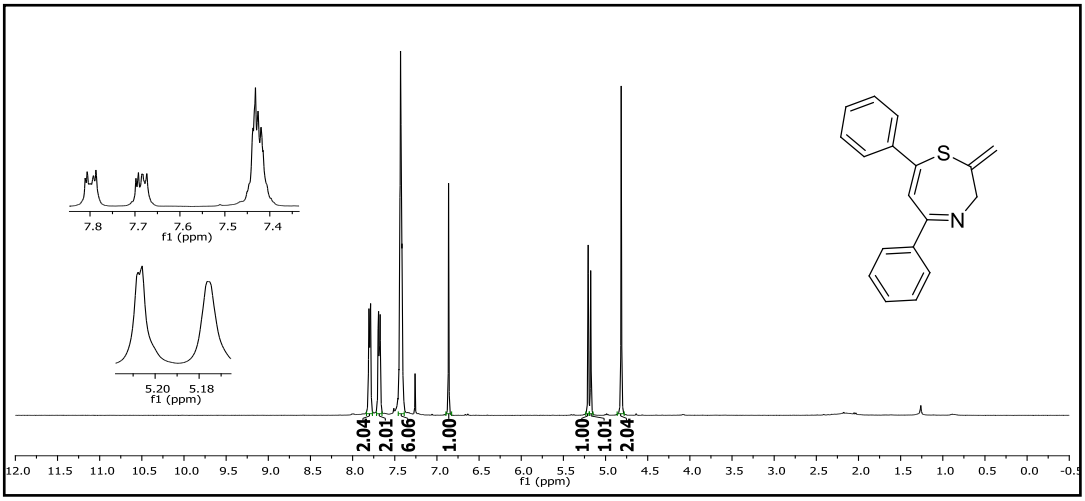


Figure 32. ^{1}H NMR spectrum of compound **59a**.

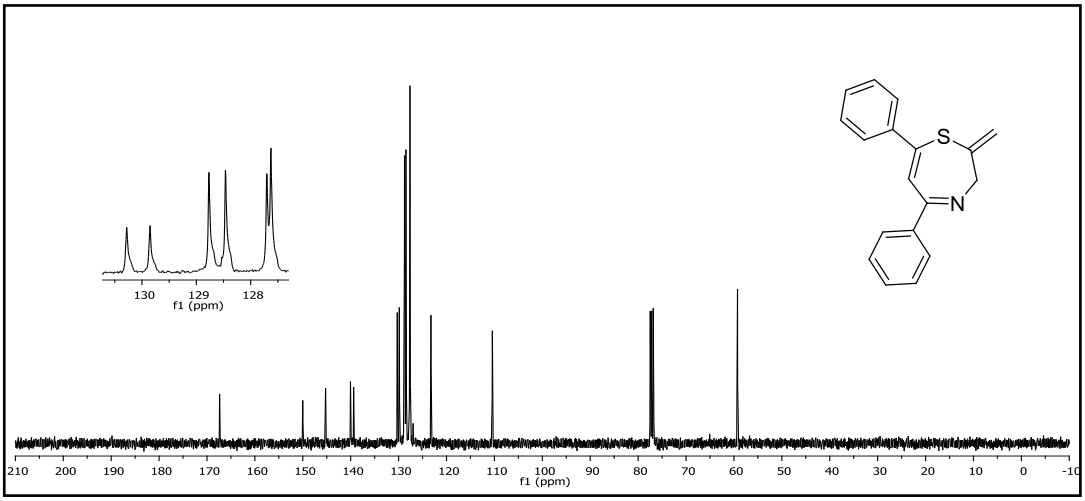
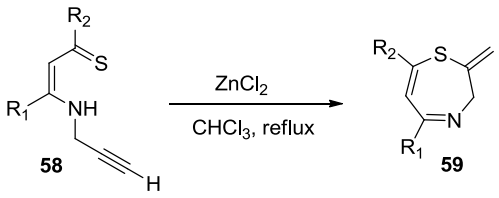
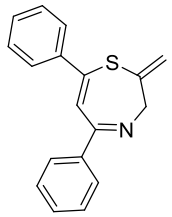


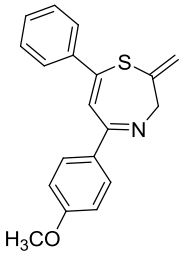
Figure 33. ^{13}C NMR spectrum of compound **59a**.

By employing the optimized reaction conditions, we have synthesized many 2,3-dihydro-1,4-thiazepine derivatives **59** from their corresponding thionated *N*-propargylic β-enaminones **58** as given in Table 11. Cyclization reactions proceeded efficiently and afforded the corresponding 2,3-dihydro-1,4-thiazepine derivatives in good to high yields (67-90%). Due to potential biological activity of fluorine-bearing substituents in new organic compounds,[94] three derivatives containing fluorine (**59h**, **59t**, **59z**) and two derivatives containing trifluoromethyl groups (**59f**, **59s**) have been synthesized in good yields (69-85%). We have also produced compound **59m** and **59x** both including thiophenyl group in their structures in 76% and 83% yields, respectively. Moreover, many derivatives containing methyl, *tert*-butyl, methoxy, bromo and chloro groups on different positions of the phenyl substituents of target compounds have been synthesized in a range of 67-87% yields. Furthermore, butyl-substituted 1,4-thiazepine **59l** was synthesized in 78% yield. Importantly, there was no observable conversion to any other heterocycles during its isolation by flash-column chromatography in contrast to its 1,4-oxazepine analog **33l** which produced pyrrole derivative **71l** during its isolation. It might be due to higher stability of compound **59l**, as compared to **33l**.

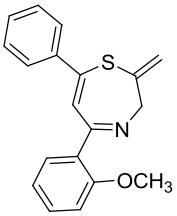
Table 11. Synthesized 2,3-dihydro-1,4-thiazepine derivatives **59**.[a]



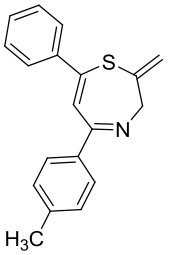

59a (90%, 1.5 h)



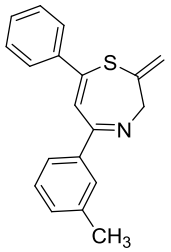
59b (80%, 4.0 h)



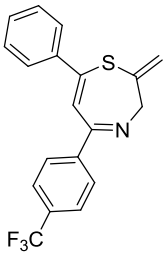
59c (70%, 3.0 h)



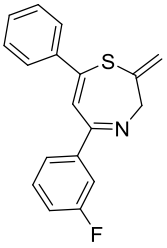
59d (85%, 2.0 h)



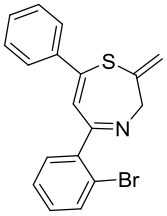
59e (81%, 2.0 h)



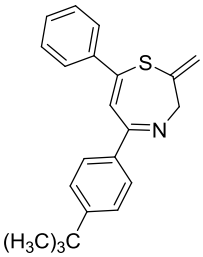
59f (70%, 2.0 h)



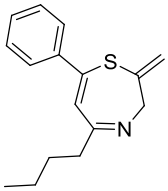
59h (69%, 2.5 h)

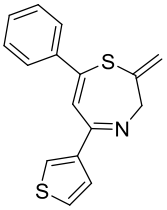


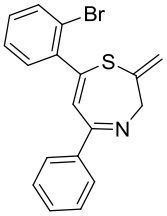
59i (67%, 3.0 h)



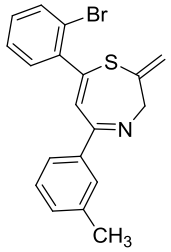
59j (87%, 1.5 h)


59l (78%, 2.5 h)

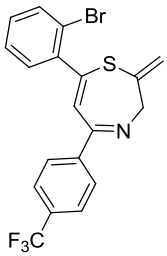

59m (76%, 2.0 h)



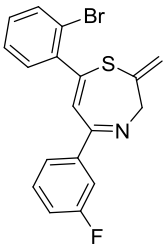
59n (84%, 3.0 h)



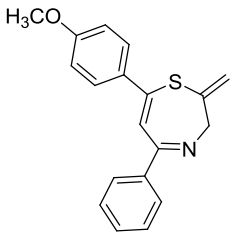
59r (84%, 1.5 h)



59s (77%, 2.0 h)

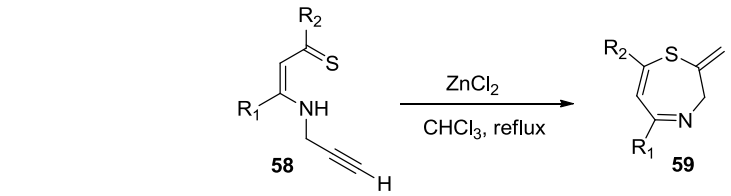


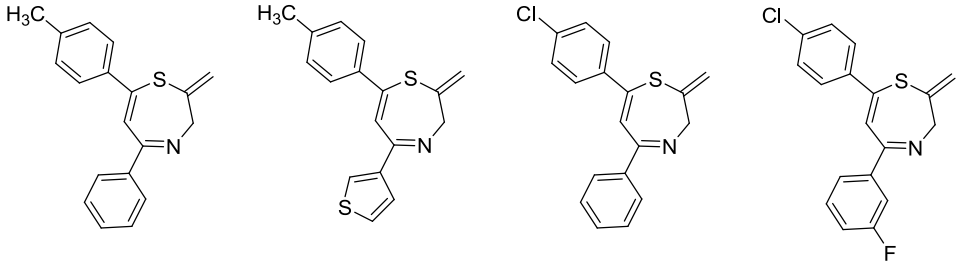
59t (81%, 2.0 h)



59v (82%, 2.0 h)

Table 11. Continued.

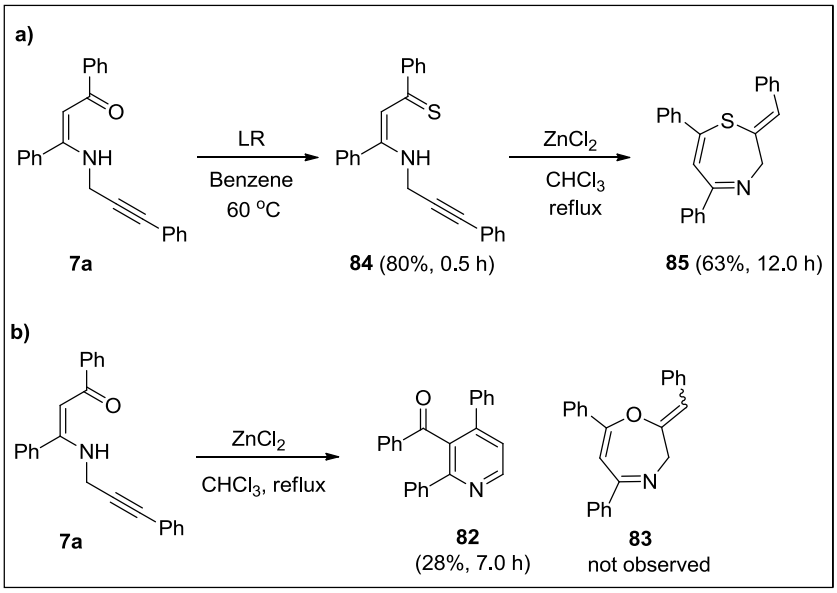




59w (82%, 2.0 h) **59x** (83%, 1.5 h) **59y** (86%, 2.0 h) **59z** (85%, 2.0 h)

[a]Isolated yields.

In order to expand the scope of the seven-*exo-dig* cyclization reaction, we have also elaborated on $ZnCl_2$-mediated reactivity of phenyl-substituted *N*-propargylic thio-β-enaminone **84**, which was prepared from its carbonyl analogue **7a** via thionation with LR (Scheme 35a). Interestingly, it produced 1,4-thiazepine derivative **85** in 63% yield although its carbonyl analogue had formed trisubstituted pyridine derivative **82** instead of the corresponding 1,4-oxazepine compound **83** (Scheme 35b). Presumably, greater nucleophilicity of sulfur atom in thicarbonyl group has played an active role in the formation of 1,4-thiazepine compound **85** rather than corresponding pyridine occurrence.



Scheme 35. $ZnCl_2$-mediated reactions of alkyne-tethered *N*-propargylic thio-β-enaminone **84** (**a**) and alkyne-tethered *N*-propargylic β-enaminone **7a** (**b**) in refluxing $CHCl_3$.

It should be mentioned that geometry of double bond in compound **85** was determined to be *Z* by the NOESY experiment (Figure 34). An NOE interaction between methylenic hydrogens (*C*<u>*H*</u>$_2$) on the ring and exo double bond hydrogen (=*C*<u>*H*</u>*Ph*) was observed, approving the Z configuration of exo double bond.

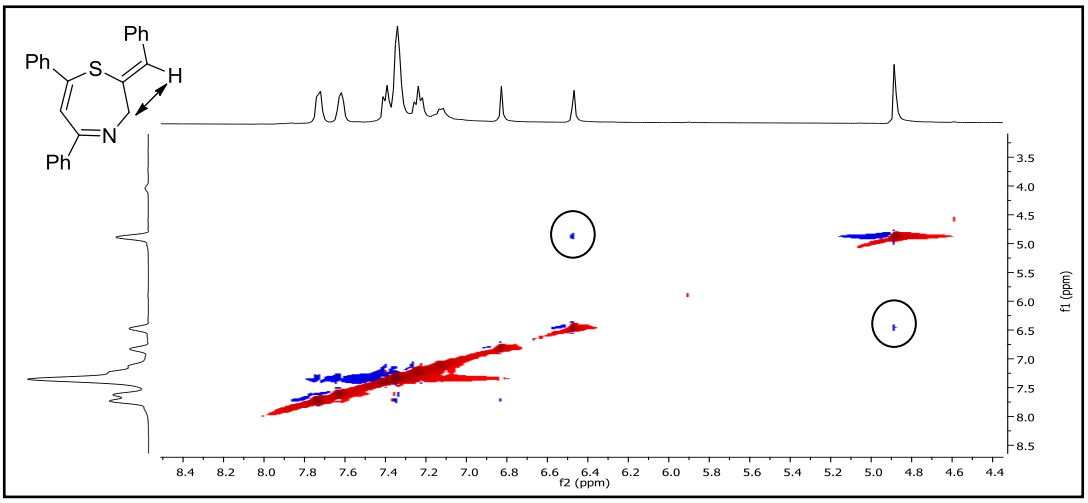
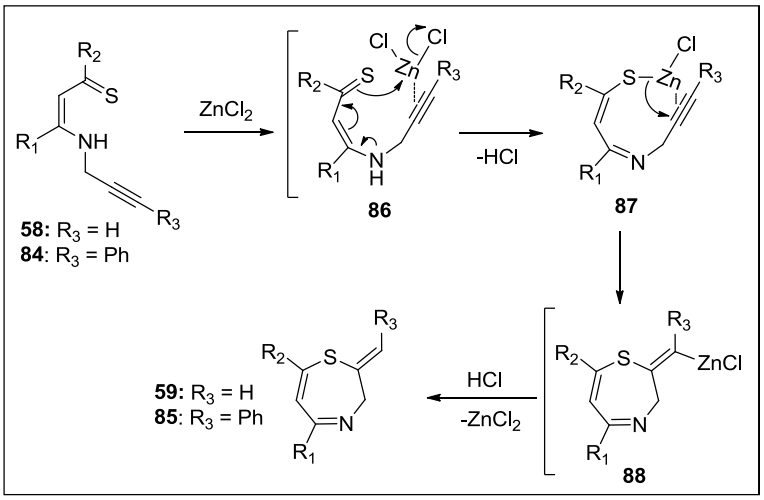


Figure 34. NOESY NMR spectrum of compound **85.**
(Cross peaks in circles represent the NOE interactions shown on the structure).

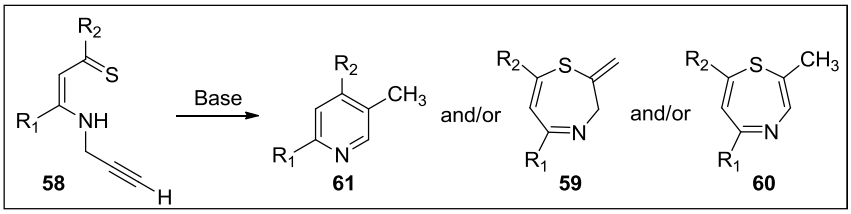
A plausible mechanism for the formation of 2-methylene-2,3-dihydro-1,4-thiazepines **59** and phenyl-substituted 1,4-thiazepine **85** is described in Scheme 29. Initially, electrophilicity of alkyne moiety increases via coordination of zinc chloride to triple bond of alkyne unit and forming intermediate **86**. After that, thiocarbonyl sulfur is coordinated with zinc by amido-imido tautomerization and generates intermediate **87**, providing a close proximity of sulfur and alkynyl groups. Then, vinyl zinc intermediate **88** is established via intramolecular cyclization. Lastly, in-situ hydolysis with HCl gives target 2,3-dihydro-1,4-thiazepine derivatives **59** and phenyl-substituted 1,4-thiazepine derivative **85**.



Scheme 36. Plausible mechanism for the formation of 1,4-thiazepines (**59**, **85**).

2.2.4 Synthesis of 5-Methylpyridines 61

In the last stage of the thesis work, we focused on examination of reactivity of *N*-propargylic thio-β-enaminones **58** under basic conditions (Scheme 37).

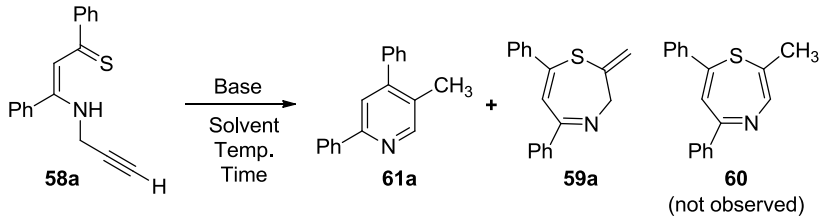


Scheme 37. Reaction of *N*-propargylic thio-β-enaminones **58** in basic conditions.

For this purpose, phenyl-substituted *N*-propargylic thio-β-enaminone **58a** was initially used as a representative starting material in the cyclization reactions. Many reactions of compound **58a** in different basic conditions were carried out. The results were given in Table 12. In many cases, both trisusbtituted pyridine derivative **61a** and 2,3-dihydro-1,4-thiazepine derivative **59a** were formed as a main product and a side product, respectively. At first, diisopropylamine (DIPA) was used as a base and under neat conditions no reaction was observed (Table 12, entry 1). Then, DMF was chosen as a reaction solvent. In DMF, at room temperature and 50 ^{o}C, *N*-propargylic thio-β-enaminone **58a** underwent cyclization reactions by using 0.1 mL of DIPA to afford 5-methylpyridine **61a** in 75% and 67% yields, respectively (Table 12, entries 2 and 3). Thus, we continued the optimization studies at room temprature. Using higher amount of DIPA (0.2 mL) did not complete the reaction in 4.5 h (Table 12, entry 4). When the reaction time was increased from 4.5 to 16.0 h, the corresponding pyridine compound **61a** was isolated in 79% yield (Table 12, entry 5). Although using 0.3 mL of DIPA lead to rise of yield only by 1% (Table 12, entry 6), with 0.5 mL of DIPA, highest yield of pyridine **61a** (85%) formation was achieved only in 2.0 h (Table 12, entry 7). Two times increase of base did not change the yield of products (Table 12, entry 8). We also tried the cyclization reaction in ACN and DMSO but the obtained yields were lower and/or same and the reaction durations were longer compared with those in DMF using the same amount of base (Table 12, entries 9 and 10). In the same way, employing the reactions with triethylamine (TEA) instead of DIPA, did not enhance the yield of main product **61a** (Table 12, entries 11 and 12). Moreover, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) was used as a base in a series of reactions in variable conditions, none of which has improved the yield of target compound **61a**

(Table 12, entries 13-18). Furthermore, NaH-mediated reactions lowered the yield of **61a** by using either 1.0 equiv. or 2.0 equiv. (Table 12, entries 19 and 20). Lastly, Cs_2CO_3 was tried but lowest yield (27%) of main product **61a** and comparable yield (10%) of side product **59a** were obtained (Table 12, entry 21). It should also be mentioned that in many cases, 1,4-thiazepine derivative **59a** was generated in a range of 4% to 9% yields as a side product (Table 12, entries 2-13). Also, no reaction conditions were found for the formation of fully-unsaturated 1,4-thiazepine derivative **60**. As a result of these optimization reactions, using 0.5 mL of DIPA for 0.3 mmol of starting material **58a** in DMF at room temperature was determined as the best reaction conditions since the highest yield (85%) of target compound **61a** was obtained in these conditions although it produced 2,3-dihydro-1,4-thiazepine compound **59a** as well (Table 12, entry 7).

Table 12. Optimization studies for cyclization reaction of *N*-propargylic thio-β-enaminone **58** in basic conditions[a]

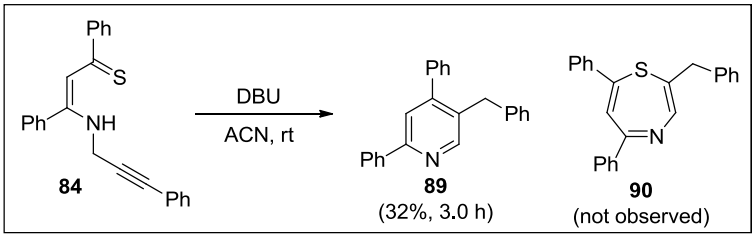


Entry	Amount of Base	Solvent	Temp. (^oC)	Time (h)	Yield: (61a + 59a)[b] (%)
1	DIPA (1.0 mL)	-	rt	3.0	NR[c]
2	DIPA (0.1 mL)	DMF	rt	40.0	(75 + 4)
3	DIPA (0.1 mL)	DMF	50	1.0	(67 + 5)
4	DIPA (0.2 mL)	DMF	rt	4.5	(61 + 5)[d]
5	DIPA (0.2 mL)	DMF	rt	16.0	(79 + 5)
6	DIPA (0.3 mL)	DMF	rt	5.0	(80 + 5)
7	DIPA (0.5 mL)	DMF	rt	2.0	(85 + 5)
8	DIPA (1.0 mL)	DMF	rt	2.0	(85 + 5)
9	DIPA (0.2 mL)	ACN	rt	20.0	(79 + 5)
10	DIPA (0.2 mL)	DMSO	rt	20.0	(69 + 5)
11	TEA (0.2 mL)	DMF	rt	20.0	(62 + 8)[e]
12	TEA (0.2 mL)	DMF	rt	48.0	(77 + 9)
13	DBU (0.2 equiv.)	DMF	rt	20.0	(51 + 5)[f]
14	DBU (0.4 equiv.)	DMF	rt	3.0	(69 + 0)
15	DBU (1.0 equiv.)	DMF	rt	3.0	(72 + 0)
16	DBU (2.0 equiv.)	DMF	rt	3.0	(59 + 0)
17	DBU (2.0 equiv.)	DMF	0 to rt	3.0	(63 + 0)
18	DBU (2.0 equiv.)	ACN	rt	3.0	(68 + 0)
19	NaH (1.0 equiv.)	DMF	rt	3.0	(45 + 0)
20	NaH (2.0 equiv.)	DMF	rt	3.0	(45 + 0)
21	Cs_2CO_3 (1.0 equiv.)	DMF	rt	3.0	(27 + 10)

[a]The reactions were carried out on a 0.30 mmol scale of *N*-propargylic-thio-β-enaminone **58a** in given amount of solvent under indicated conditions in entries. [b]Isolated yield. [c]NR: No Reaction. The starting thio-β-enaminone **58a** was recovered in 97% yield. [d]The starting thio-β-enaminone **58a** was recovered in 18% yield as well. [e]The starting thio-β-enaminone **58a** was recovered in 16% yield as well. [f]The starting thio-β-enaminone **58a** was recovered in 10% yield as well.

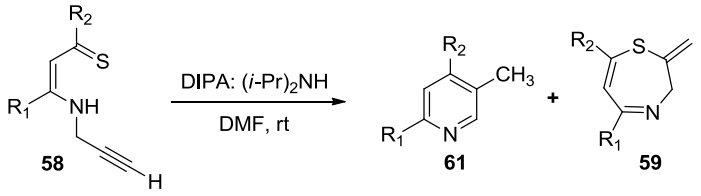
By using the optimized reaction conditions (Table 12, entry 7), we synthesized a diverse range of trisubstituted pyridine derivatives **61** in moderate to high yields (46-85%), which are depicted in Table 13. Only one derivative **61l** bearing a butyl group was synthesized in low yield (13%). In all cases, formation of 2,3-dihydro-1,4-thiazepine derivatives **59** were also observed as side products and they were isolated in 2-13% yields. Many compounds having electron donating and electron withdrawing groups on phenyl susbstituents were tolerated under the determined reaction conditions. For instance, nine pyridines, **61b-61e**, **61j**, **61r**, **61v-61x** containing one of the methyl, methoxy, and *tert*-butyl groups, which are attached to the corresponding phenyl rings, were synthesized in 46-83% yields. Since fluorine-containing compounds may show effective biological activity,[94] three pyridines, **61h**, **61t** and **61z**, having one fluoro group and two ones, **61f** and **61s**, having trifluoromethyl group on the related phenyl rings were produced in 51-71% yields. The optimized reaction conditions were also efficient in the synthesis of other halo-containing ones. Bromine and chlorine-bearing pyridines **61i**, **61n**, **61r-61t**, **61y-61z**, were isolated in a range of 49-71% yields. It should be noted that methyl, trifluoromethyl, fluorine substituents were also involved in the structures of **61r-61t** and **61z**. It is important to state that we have introduced another heterocycle, thiophenyl group, to the corresponding pyridine compounds, **61m** and **61x**, which were synthesized in 69% and 77% yields, respectively.

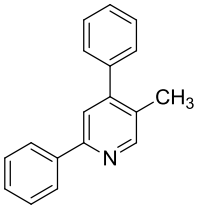
In addition, reactivity of phenyl-substituted *N*-propargylic thio-β-enaminone **84** with a base was explored. Taking 1.0 equiv. of DBU as a base, only 5-benzyl-2,4-diphenylpyridine (**89**) was isolated in 32% yield (Scheme 38). Notably, no formation of 2-benzyl-1,4-thiazepine derivative **90** was observed in this reaction.



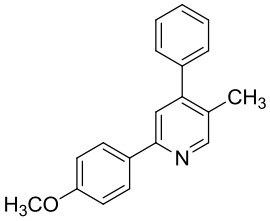
Scheme 38. Base-mediated reaction of alkyne-tethered thio-β-enaminone **84**.

Table 13. Synthesized 5-methylpyridine derivatives **61**.[a]

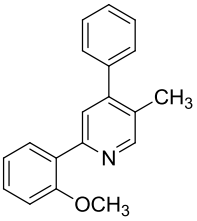




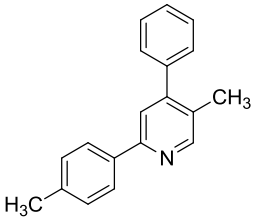
61a (85%)
[**59a** 5%]



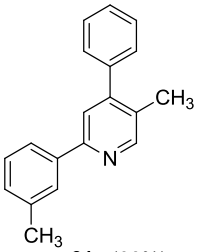
61b (76%)
[**59b** 9%]



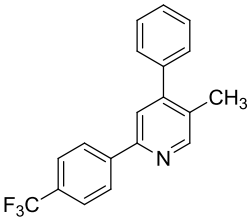
61c (46%)
[**59c** 8%]



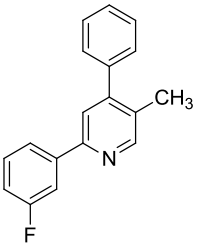
61d (74%)
[**59d** 8%]



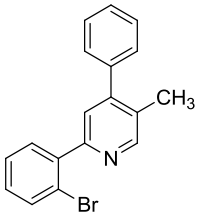
61e (66%)
[**59e** 5%]



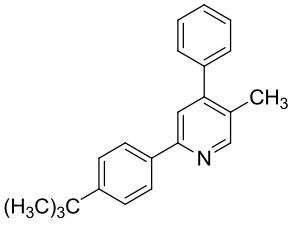
61f (56%)
[**59f** 5%]



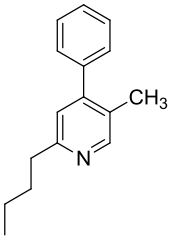
61h (67%)
[**59h** 5%]



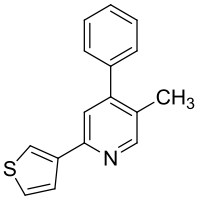
61i (60%)
[**59i** 13%]



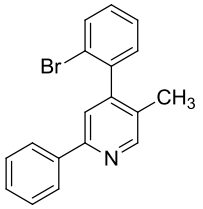
61j (68%)
[**59j** 5%]



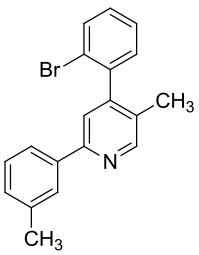
61l (13%)
[**59l** 2%]



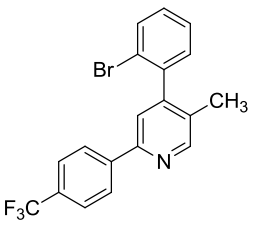
61m (69%)
[**59m** 6%]



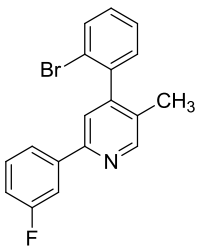
61n (53%)
[**59n** 10%]



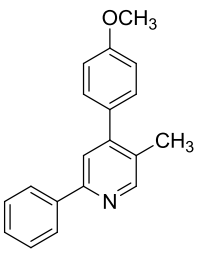
61r (49%)
[**59r** 7%]



61s (54%)
[**59s** 10%]

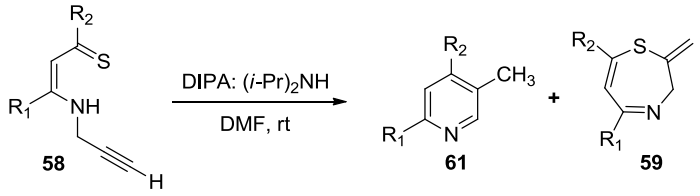


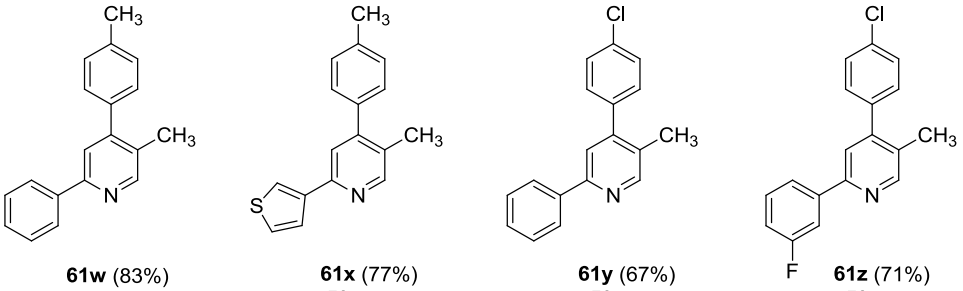
61t (51%)
[**59t** 9%]



61v (53%)
[**59v** 7%]

Table 13. Continued.





[a]Isolated yields.

All the structures of synthesized trisubstituted pyridines **61** and **89** were proved especially by the analysis of their corresponding ^{1}H and ^{13}C NMR spectra. Their HRMS data also helped us to figure out non-existence of sulfur atom in the target molecule. Thus, possible formation of fully-unsaturated 1,4-thiazepine derivatives **60** was eliminated. On the other hand, ^{1}H and ^{13}C NMR spectra of representative 2,4-diphenyl-5-methylpyridine (**61a**) compound shown in Figures 35 and 36, respectively, are compatible with those given in literature.[95] In the ^{1}H NMR spectrum, two separate signals belong to pyridine protons appear as singlets at 8.61 and 7.63 ppm. Two of 10 phenyl protons resonate at 8.03 ppm as doublet. Other eight protons give multiplet between 7.53 and 7.37 ppm. Also, at higher field region, the singlet of methyl protons can easily be seen at 2.32 ppm. In the ^{13}C NMR spectrum, there are 14 different signals as expected. Characteristically, C-H signals of pyridine ring resonate at 151.3 and 121.0 ppm. Remaining aromatic C-H signals appear between 128.8 and 126.8 ppm. In addition, quatenary carbon peaks rise in lower field region (155.4 - 129.2 ppm). The last high-field signal at 17.0 ppm belongs to CH_3 group.

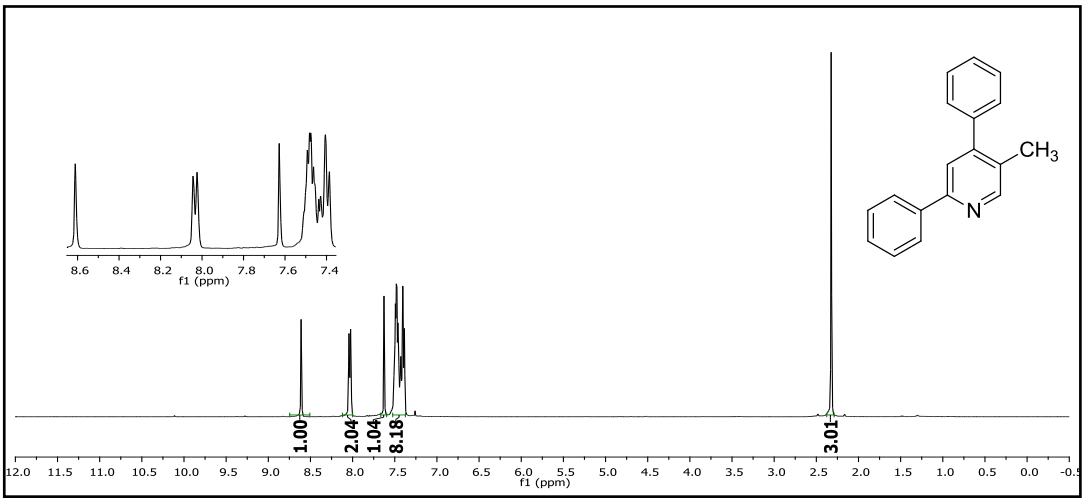


Figure 35. ^{1}H NMR spectrum of compound **61a**.

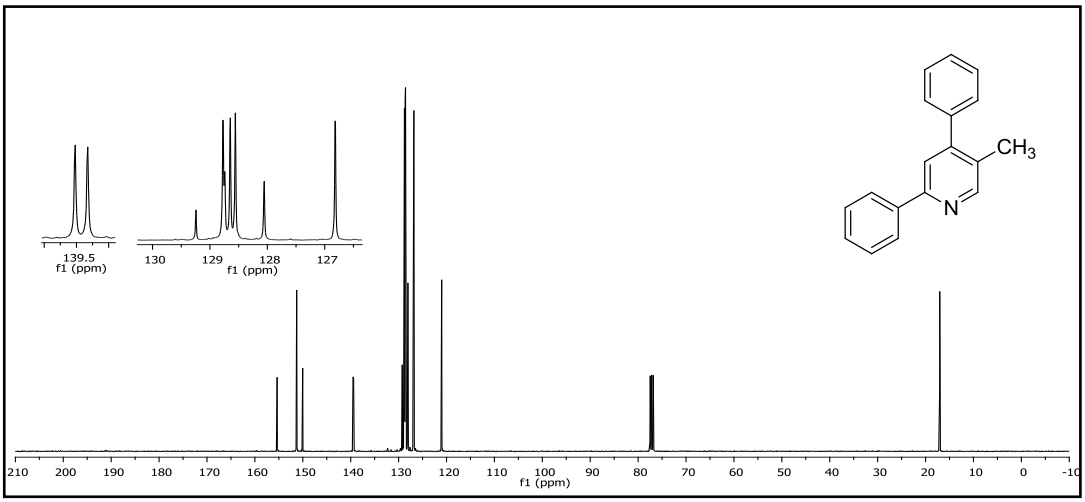
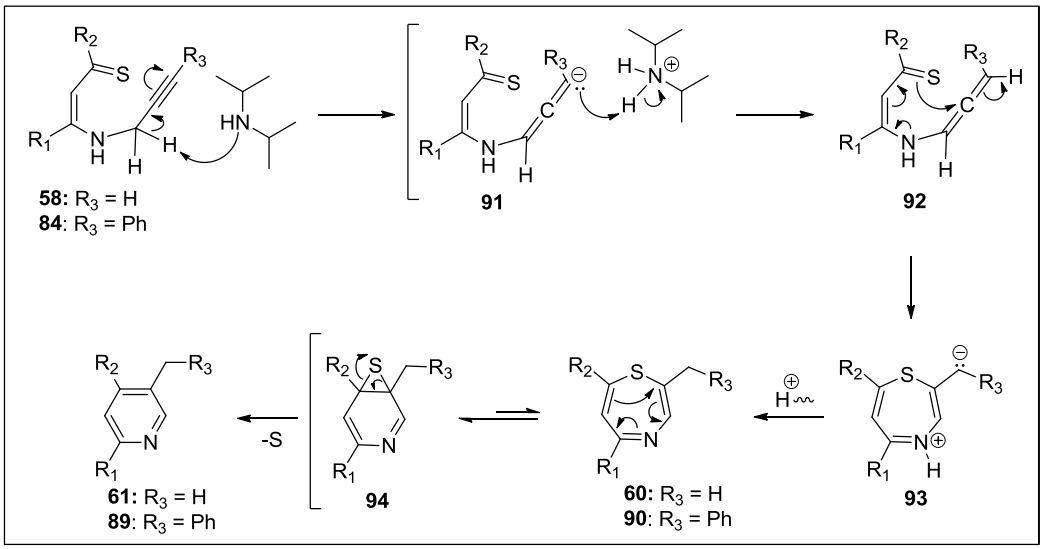


Figure 36. ^{13}C NMR spectrum of compound **61a**.

The proposed mechanism for the formation of 5-methylpyridines **61** and 5-benzylpyridine **89** is outlined in Scheme 39, which proceeds through propargyl-allene isomerization.[96] First, DIPA abstracts a proton from methylene group of thionated *N*-propargylic β-enaminone **58** and **84** to form allenyl carbanion **91**. Delivering a proton from diisopropylamonium ion forms allene intermediate **92**. Then cyclization reaction takes place by attacking of thicarbonyl sulfur to central electrophilic carbon of allene through resonance interaction. By this way, seven-

membered 1,4-thiazepinium ion **93** is generated. It readily rearranges by proton shifting to afford the corresponding 1,4-thiazepine intermediates **60** and **90**, the isolations of which could not be achieved. Next, valence isomerization gives 7-thionorcaradiene derivative **94**. Then, sulfur extrusion rapidly occurs and affords final pyridine products **61** and **89**.

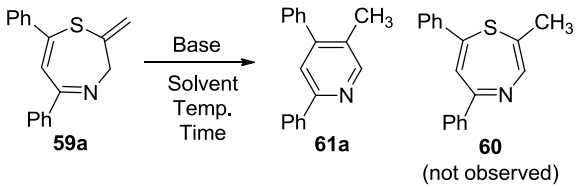


Scheme 39. Proposed mechanism for the formation of trisubstituted pyridines **61** and **89** from corresponding *N*-propargylic thio-β-enaminones **58** and **84**.

We have also interested in conversion of 2,3-dihydro-1,4-thiazepine compounds **59** to 5-methylpyridines **61** and/or 2-methyl-1,4-thiazepines **60**. For this purpose, compound **59a** was selected as a representative dihydro-1,4-thiazepine compound. We have carried out some reactions with this molecule in basic conditions, which are shown in Table 14. Firstly, reactions were run with DIPA in DMF at room temperature and 60 ^{o}C. However, the maximum yield of 5-methylpyridine **61a** was only 11% in both conditions (Table 14, entries 1-2). In the same way, using 1.0 equiv. of NaH at room temperature did not improve the conversion yield (10%) (Table 14, entry 3). When the same reaction was conducted at 60 ^{o}C, the yield of conversion to 5-methylpyridine **61a** was increased to 37% (Table 14, entry 4). Additionally, 2.0 equiv. of NaH enhanced the yield of 5-methylpyridine **61a** 4% more (Table 14, entry 5). One can infer from these results that stronger base (NaH)

and higher temperature (60 ^{o}C) are required to achieve conversion reaction in an acceptable yield. It is important to state that we have never isolated 2-methyl-1,4-thiazepine compound **60** from these reactions. The reason is that, [1,3]-H shift in compound **59a** in basic conditions most probably forms unstable 2-methyl-1,4-thiazepine **60** as an intermediate during the reaction. Then, as depicted in Scheme 39, it immediately undergoes valence isomerization and sulfur extrusion occurs, affording final pyridine product **61a**.

Table 14. Optimization studies for conversion of 2,3-dihydro-1,4-thiazepine **59a** to 5-methylpyridine **61a**.[a]



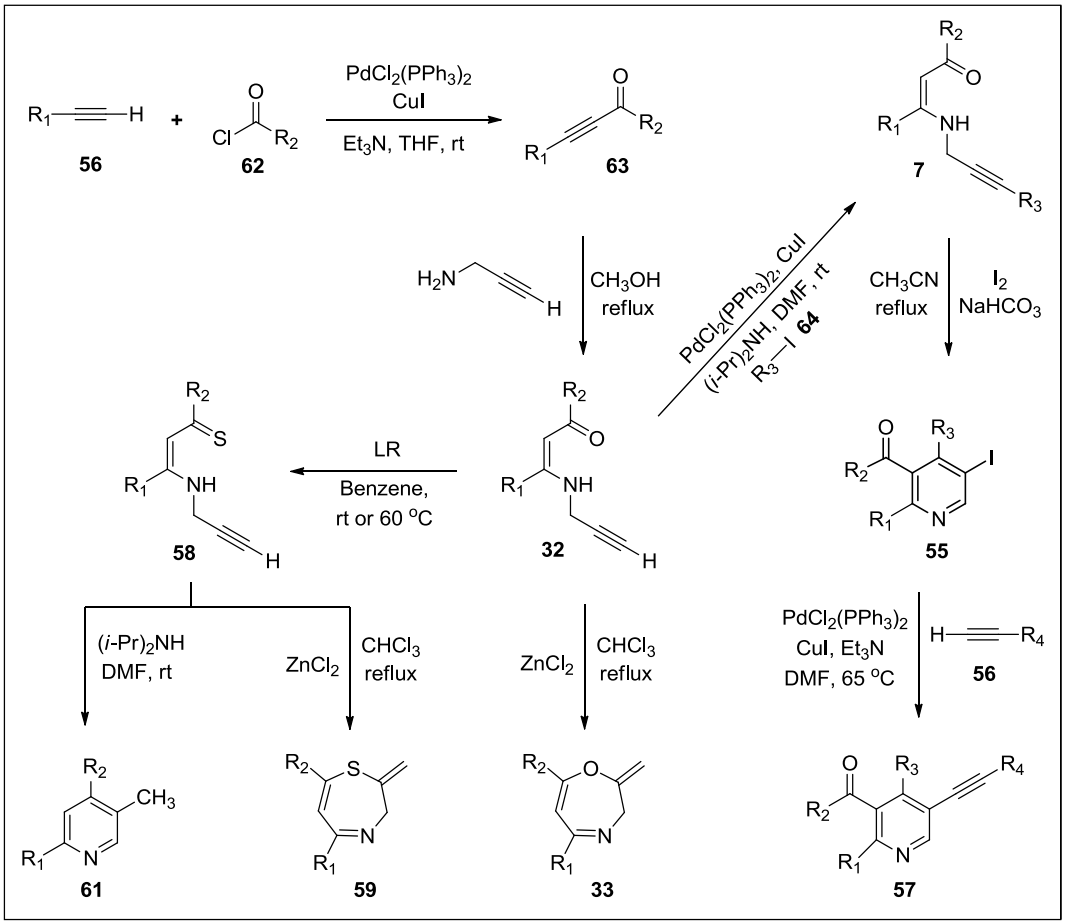
Entry	Amount of Base	Solvent	Temp. (^{o}C)	Time (h)	Yield (61a) (%)[b]
1	DIPA (0.2 mL)	DMF	rt	96.0	7[c]
2	DIPA (0.2 mL)	DMF	60	9.0	11[d]
3	NaH (1.0 equiv.)	DMF	rt	96.0	10[e]
4	NaH (1.0 equiv.)	DMF	60	5.0	37
5	NaH (2.0 equiv.)	DMF	60	0.5	41

[a]Reactions were performed on a scale of 0.30 mmol of 1,4-thiazepine **59a** in 0.5 mL of solvent with the indicated conditions. [b]Isolated yields. [c]The starting 1,4-thiazepine **59a** was recovered in 59% yield as well. [d]The starting 1,4-thiazepine **59a** was recovered in 58% yield as well. [e]The starting 1,4-thiazepine **59a** was recovered in 21% yield as well.

CHAPTER 3

CONCLUSION

In brief, many novel and potentially bioactive 5-alkynylpyridines, 2,3-dihydro-1,4-oxazepines, 2,3-dihydro-1,4-thiazepines and trisubstituted pyridines have been synthesized in good to high yields (Scheme 40).



Scheme 40. General synthetic pathways for the synthesis of target compounds.

Facile methodologies with optimized reaction conditions for the proper synthesis of each heterocyclic unit have been determined successfully.

In the first chapter, important strategies for the synthetic improvement of such kind of pyridines, oxazepines and thiazepines were mainly stated from a detailed literature survey. Additionally, their natural and pharmaceutical importance were explored and supported with several examples.

Then, firstly, preparation of starting materials was described in a detail (Scheme 40). In the synthesis of α,β-alkynic ketones, Pd- and Cu-catalyzed Sonogashira cross-coupling reactions of aryl chlorides with terminal alkynes were used and many alkynic ketone derivatives were synthesized in 50-99% yields. Conjugate addition of propargyl amine to alkynic ketones gave the corresponding *N*-propargylic β-enaminones in 61-98% yields. Isolation of only *Z* isomers of β-enaminones from these reactions was confirmed by the NOESY experiments. They were also further functionalized with aryl iodides by Sonogashira reaction to obtain phenyl-substituted *N*-propargylic β-enaminones in 83-96% yields. Then, they were subjected to electrophilic cyclization by using 3.0 equiv. of both I_2 and $NaHCO_3$ in refluxing ACN under open atmosphere. Thus, seven 5-iodopyridine derivatives were synthesized in 47-80% yields. For the synthesis of *N*-propargylic thio-β-enaminones, Lawesson's reagent (LR) was selected to be used due to their recent applications in the conversion of carbonyl groups to thiocarbonyl functiones. 20 derivatives of *N*-propargylic thio-β-enaminones were synthesized from their corresponding β-enaminone precursors by using 0.5 equiv. of LR at room temperature and/or 60 ^{o}C in 23-94% yields.

After preparation of those starting materials, proper reaction conditions for the facile synthesis of target compounds were investigated. A series of optimization reactions were carried out to synthesize 5-alkynylpyridines by using representative phenyl-substituted 5-iodopyridine derivative. As a result of these reactions, the best yield (91%) was achieved by using 1.5 equiv. of terminal alkyne, 5 mol% of $PdCl_2(PPh_3)_2$ and 5 mol% of CuI in DMF at 65 ^{o}C. These optimized reaction conditions were employed for Sonogashira reaction of 5-iodopyridines with termi-

nal alkynes and 28 novel 5-alkynylpyridine derivatives were synthesized in 40-99% yields. These results were published in *RSC Advances* in 2016.[97]

In addition, an alternative reaction conditions (i.e., in $CHCl_3$ at reflux conditions) was found for the $ZnCl_2$-mediated generation of monocyclic 1,4-oxazepines. This modified condition provided 19 derivatives of 1,4-oxazepines in good to high yields (66-95%) with short reaction times (1.5-12.0 h) in most cases. Only in two cases, target 1,4-oxazepine compounds were isolated in 40% yields. On the other hand, $ZnCl_2$-mediated cyclization of phenyl-substituted *N*-propargylic β-enaminone afforded a corresponding pyridine derivative in 28% yield, instead of the related 1,4-oxazepine compounds. Also, conversion of alkyl-substituted 1,4-oxazepines to corresponding pyrrole derivatives during flash-column chromatography were observed to some extent and studied thoroughly in the presence of silica-gel (SiO_2). These new results were published together with early results in *European Journal of Organic Chemistry* in 2017.[93]

Moreover, the modified reaction conditions for the synthesis of 2,3-dihydro-1,4-oxazepines were also imparted to the synthesis of thiazepines. By using 1.0 equiv. of $ZnCl_2$ in refluxing $CHCl_3$, 20 new 2,3-dihydro-1,4-thiazepines were synthesized from thionated *N*-propargylic β-enaminones in 67-90% yields. In these conditions, interestingly, phenyl-substituted *N*-propargylic thio-β-enaminone afforded the corresponding 1,4-thiazepine derivative in 63% yield in contrast to the case of its β-enaminone anlaogue.

Lastly, *N*-propargylic thio-β-enaminones were subjected to cyclization reaction to afford monocyclic 1,4-thiazepines and/or 5-methylpyridines under basic conditions. Many reactions regarding the optimization of the conditions were performed with phenyl-substituted *N*-propargylic thio-β-enaminone. In all cases, except for neat conditions, 5-methylpyridine compound was formed as the major product through the sulfur extrusion of the fully-unsaturated 1,4-thiazepine intermediate, which could not be isolated in any case. Running the reaction with 0.5 mL of DIPA for 0.3 mmol of starting material in DMF at room temperature was found the best reaction conditions. By using the optimized reaction conditions,

many methyl-substituted pyridine derivatives were synthesized in moderate to high yields (46-85%), except for butyl-substituted one (13%).

CHAPTER 4

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) relative to $CDCl_3$ (7.26 and 77.16 ppm in ^{1}H and ^{13}C NMR, respectively). Coupling constants (*J*) are reported in Hertz (Hz), and spin multiplicities are presented by the following symbols: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C NMR information is given in parentheses as C, CH, CH_2 and CH_3. Infrared spectra (IR) were recorded by using attenuated total reflection (ATR). Band positions are reported in reciprocal centimeters (cm^{-1}). Mass spectra (MS) and high resolution mass spectra (HRMS) were obtained by using Electrospray Ionization (ESI) with Micro-Tof; *m/z* values are reported (For each measurement, the mass scale was recalibrated with sodium formate clusters, and samples were dissolved and measured in MeOH or CH_3CN). Flash chromatography was performed using thick-walled glass columns and "flash grade" silica gel (230-400 mesh) or aluminium oxide (neutral, 70-230 mesh). Thin layer chromatography (TLC) was performed by using commercially prepared 0.25 mm silica gel or aluminium oxide (neutral) plates and visualization was effected with short wavelength UV lamp (254 nm). The relative proportions of solvents in chromatography solvent mixtures refer to the volume:volume ratio. All commercially available reagents were used directly without purification unless otherwise stated. All solvents used in reactions and chromatography were distilled and/or dried properly for purity. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon. All glassware was dried in oven prior to use.

4.1 General Procedure for the Synthesis of α,β-Alkynic Ketones 63

A mixture of the corresponding aryl chloride **62** (3.0 mmol), $PdCl_2(PPh_3)_2$ (0.05 mmol) and Et_3N (3.0 mmol) in anhydrous THF (7.5 mL) were stirred for 10 min at room temperature under argon. CuI (0.1 mmol) was then added and the reaction mixture was stirred for another 10 min. After the addition of the appropriate terminal alkyne **56** (2.5 mmol) over 15 min, the resulting mixture was stirred at room temperature for approximately 6 h (Note that the progress of the reaction was monitored by routine TLC for the disappearance of alkyne). After the reaction was completed, ethyl acetate (50 mL) was added, and the resulting solution was washed with 0.1 N HCl (10 mL) and subsequently with a saturated NH_4Cl solution (10 mL) in a separatory funnel. Then combined water phases were extracted with ethyl acetate (50 mL) again. After the layers were separated, organic phase was dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (19:1) as the eluent to afford the corresponding α,β-alkynic ketone **63**.

4.1.1 1,3-Diphenylprop-2-yn-1-one (63a)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and phenylacetylene (**56a**) (255.4 mg, 2.5 mmol) were employed to afford 500.2 mg (97%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29-8.20 (m, 2H), 7.74-7.67 (m, 2H), 7.67-7.61 (m, 1H), 7.57-7.46 (m, 3H), 7.47-7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2 (C=O), 137.1 (C), 134.3 (CH), 133.2 (CH), 130.9 (CH), 129.7 (CH), 128.83 (CH), 128.77 (CH), 120.3 (C), 93.2 (C), 87.0 (C). The spectral data were in agreement with those reported previously for this compound.[98-102]

4.1.2 3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (63b)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol),

Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 4-ethynylanisole (**56b**) (330.4 mg, 2.5 mmol) were employed to afford 448.9 mg (76%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23-8.15 (m, 2H), 7.64-7.55 (m, 3H), 7.51-7.43 (m, 2H), 6.94-6.85 (m, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (C=O), 161.7 (C), 137.0 (C), 135.1 (CH), 133.9 (CH), 129.4 (CH), 128.5 (CH), 114.4 (CH), 111.8 (C), 94.3 (C), 86.9 (C), 55.3 (OCH_3). The spectral data were in agreement with those reported previously for this compound.[98,100,102,103]

4.1.3 3-(2-Methoxyphenyl)-1-phenylprop-2-yn-1-one (63c)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 2-ethynylanisole (**56c**) (330.4 mg, 2.5 mmol) were employed to afford 460.7 mg (78%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34-8.28 (m, 2H), 7.61-7.54 (m, 2H), 7.52-7.45 (m, 2H), 7.40 (ddd, J = 8.5, 7.6, 1.7 Hz, 1H), 6.98-6.87 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C=O), 161.9 (C), 137.1 (C), 134.9 (CH), 133.9 (CH), 132.7 (CH), 129.7 (CH), 128.5 (CH), 120.7 (CH), 110.9 (CH), 109.3 (C), 91.2 (C), 90.6 (C), 55.9 (OCH_3). The spectral data were in agreement with those reported previously for this compound.[100]

4.1.4 1-Phenyl-3-(*p*-tolyl)prop-2-yn-1-one (63d)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 4-ethynyltoluene (**56d**) (290.4 mg, 2.5 mmol) were employed to afford 446.1 mg (81%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.19 (m, 2H), 7.66-7.54 (m, 3H), 7.50 (t, J = 7.6 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0 (C=O), 141.6 (C), 136.9 (C), 134.0 (CH), 133.1 (CH), 129.5 (CH), 128.6 (CH), 117.0 (C), 93.9 (C), 86.8 (C), 21.8 (CH_3) (Note that two CH peaks overlap on each other). The spectral data were in agreement with those reported previously for this compound.[98,100,101,103,104]

4.1.5 1-Phenyl-3-(*m*-tolyl)prop-2-yn-1-one (63e)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 3-ethynyltoluene (**56e**) (290.4 mg, 2.5 mmol) were employed to afford 523.1 mg (95%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.22 (m, 2H), 7.66-7.60 (m, 1H), 7.56-7.46 (m, 4H), 7.34-7.26 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (C=O), 138.5 (C), 136.9 (C), 134.0 (CH), 133.5 (CH), 131.7 (CH), 130.2 (CH), 129.5 (CH), 128.59 (CH), 128.57 (CH), 119.9 (C), 93.5 (C), 86.7 (C), 21.1 (CH_3). The spectral data were in agreement with those reported previously for this compound.[101,103,104]

4.1.6 1-Phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (63f)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 4-ethynyl-α,α,α-trifluorotoluene (**56f**) (425.3 mg, 2.5 mmol) were employed to afford 411.4 mg (60%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20-8.10 (m, 2H), 7.72 (d, J = 8.1 Hz, 2H), 7.65-7.55 (m, 3H), 7.51-7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (C=O), 136.7 (C), 134.6 (CH), 133.3 (CH), 132.4 (q, ^2J = 32.5 Hz, C), 129.8 (CH), 128.9 (CH), 125.8 (q, ^3J = 3.7 Hz, CH), 124.1 (C), 123.2 (q, ^1J = 272.7 Hz, CF_3), 90.6 (C), 88.2 (C). The spectral data were in agreement with those reported previously for this compound.[103,105]

4.1.7 3-(4-(Dimethylamino)phenyl)-1-phenylprop-2-yn-1-one (63g)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 4-ethynyl-*N*,*N*-dimethylaniline (**56g**) (363.0 mg, 2.5 mmol) were employed to afford 592.1 mg (95%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29-8.20 (m, 2H), 7.65-7.55 (m, 3H), 7.52 (t, J = 7.4 Hz, 2H), 6.69-6.61 (m, 2H), 3.0 (s, 6H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 177.9 (C=O), 151.8 (C), 137.4 (C), 135.2 (CH), 133.5 (CH), 129.3 (CH), 128.5 (CH), 111.6 (CH), 105.4 (C), 97.8 (C), 87.9 (C), 39.9 ($N(CH_3)_2$). The spectral data were in agreement with those reported previously for this compound.[106]

4.1.8 3-(3-Fluorophenyl)-1-phenylprop-2-yn-1-one (63h)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 1-ethynyl-3-fluorobenzene (**56h**) (300.3 mg, 2.5 mmol) were employed to afford 330.7 mg (59%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-7.98 (m, 2H), 7.50-7.41 (m, 1H), 7.33 (t, J = 7.7 Hz, 2H), 7.26 (dt, J = 7.7, 1.2 Hz, 1H), 7.23-7.18 (m, 1H), 7.17-7.12 (m, 1H), 6.99 (tdd, J = 8.4, 2.6, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C=O), 162.1 (d, ^1J = 248.2 Hz, CF), 136.6 (C), 134.2 (CH), 130.4 (d, ^3J = 8.4 Hz, CH), 129.4 (CH), 128.8 (d, ^4J = 3.1 Hz, CH), 128.6 (CH), 121.8 (d, ^3J = 9.1 Hz, C), 119.5 (d, ^2J = 23.3 Hz, CH), 118.1 (d, ^2J = 21.2 Hz, CH), 90.9 (d, ^4J = 3.4 Hz, C), 87.1 (C). The spectral data were in agreement with those reported previously for this compound.[102]

4.1.9 3-(2-Bromophenyl)-1-phenylprop-2-yn-1-one (63i)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 1-bromo-2-ethynylbenzene (**56i**) (452.6 mg, 2.5 mmol) were employed to afford 605.9 mg (85%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 5.2, 3.3 Hz, 2H), 7.47 (dd, J = 7.5, 1.9 Hz, 1H), 7.45-7.38 (m, 2H), 7.30 (t, J = 7.5, 2H), 7.18-7.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (C=O), 136.8 (C), 135.3 (CH), 134.3 (CH), 132.8 (CH), 131.9 (CH), 129.8 (CH), 128.7 (CH), 127.4 (CH), 126.8 (C), 122.7 (C), 90.6 (C), 90.4 (C). The spectral data were in agreement with those reported previously for this compound.[107]

4.1.10 3-(4-(*tert*-Butyl)phenyl)-1-phenylprop-2-yn-1-one (63j)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 1-(*tert*-butyl)-4-ethynylbenzene (**56j**) (452.6 mg, 2.5 mmol) were employed to afford 605.9 mg (94%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.22 (m, 2H), 7.65-7.57 (m, 3H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.44-7.40 (m, 2H), 1.32 (s, 9H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (C=O), 154.4 (C), 136.9 (C), 133.9 (CH), 132.9 (CH), 129.4 (CH), 128.5 (CH), 125.7 (CH), 116.9 (C), 93.7 (C), 86.7 (C), 34.9 (C), 30.9 (CH_3). The spectral data were in agreement with those reported previously for this compound.[106,108]

4.1.11 2-(5-Oxo-5-phenylpent-3-yn-1-yl)isoindoline-1,3-dione (63k)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and *N*-(3-butynyl)phthalimide (**56k**) (498.0 mg, 2.5 mmol) were employed to afford 477.7 mg (63%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.03 (m, 2H), 7.89-7.81 (m, 2H), 7.76-7.68 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44-7.32 (m, 2H), 4.01 (t, J = 6.9 Hz, 2H), 2.94 (t, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (C=O), 167.9 (C=O), 136.6 (C), 134.3 (CH), 134.1 (CH), 132.0 (C), 129.7 (CH), 128.6 (CH), 123.6 (CH), 91.5 (C), 80.9 (C), 35.8 (CH_2), 19.2 (CH_2); IR (neat): 3069, 2670, 2234, 1769, 1706, 1686, 1638, 1594, 1578, 1451, 1425, 1391, 1362, 1310, 1281, 1256, 1177, 1111, 1071, 993, 866, 797, 702 cm^{-1}; MS (ESI, m/z): 304.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{14}NO_3$: 304.0968 $[M+H]^+$, found: 304.0975.

4.1.12 1-Phenylhept-2-yn-1-one (63l)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 1-hexyne (**56l**) (205.4

mg, 2.5 mmol) were employed to afford 437.7 mg (94%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-8.10 (m, 2H), 7.62-7.56 (m, 1H), 7.50-7.44 (m, 2H), 2.50 (t, *J* = 7.1 Hz, 2H), 1.66 (p, *J* = 7.3 Hz, 2H), 1.51 (sextet, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C=O), 136.9 (C), 133.8 (CH), 129.4 (CH), 128.4 (CH), 96.7 (C), 79.6 (C), 29.8 (CH_2), 22.0 (CH_2), 18.8 (CH_2), 13.4 (CH_3). The spectral data were in agreement with those reported previously for this compound.[99,100]

4.1.13 1-Phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (63m)

Benzoyl chloride (**62a**) (421.7 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 3-ethynylthiophene (**56m**) (270.4 mg, 2.5 mmol) were employed to afford 461.7 mg (87%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26-8.17 (m, 2H), 7.85 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.66-7.59 (m, 1H), 7.55-7.48 (m, 2H), 7.37 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.32 (dd, *J* = 5.0, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C=O), 137.0 (C), 134.2 (CH), 134.0 (CH), 130.4 (CH), 129.6 (CH), 128.7 (CH), 126.4 (CH), 119.5 (C), 88.6 (C), 87.3 (C). IR (neat): 3105, 3063, 2184, 1631, 1266, 1217, 1167, 1032, 1014, 784, 695, 652, 625 cm^{-1}; MS (ESI, m/z): 213.04 $[M+H]^+$; HRMS (ESI): calcd. for $C_{13}H_9OS$: 213.0369 $[M+H]^+$, found: 213.0392.

4.1.14 1-(2-Bromophenyl)-3-phenylprop-2-yn-1-one (63n)

2-Bromobenzoyl chloride (**62b**) (658.4 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and phenylacetylene (**56a**) (255.4 mg, 2.5 mmol) were employed to afford 356.5 mg (50%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.05 (m, 1H), 7.72-7.68 (m, 1H), 7.66-7.61 (m, 2H), 7.51-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6 (C=O), 137.6 (C), 135.0 (CH), 133.5 (CH), 133.2 (CH), 132.8 (CH), 131.1 (CH), 128.8 (CH), 127.5 (CH), 121.3 (C), 120.1 (C), 94.3 (C), 88.1 (C). The spectral data were in agreement with those reported previously for this compound.[109]

4.1.15 1-(2-Bromophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-one (63o)

2-Bromobenzoyl chloride (**62b**) (658.4 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 4-ethynylanisole (**56b**) (330.4 mg, 2.5 mmol) were employed to afford 527.9 mg (67%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.63-7.57 (m, 2H), 7.44 (td, *J* = 7.5, 1.2 Hz, 1H), 7.37 (td, *J* = 7.7, 1.8 Hz, 1H), 6.95-6.89 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (C=O), 162.1 (C), 138.1 (C), 135.4 (CH), 135.0 (CH), 133.2 (CH), 132.6 (CH), 127.5 (CH), 121.2 (C), 114.6 (CH), 111.9 (C), 95.8 (C), 88.3 (C), 55.6 (OCH_3). The spectral data were in agreement with those reported previously for this compound.[110]

4.1.16 1-(2-Bromophenyl)-3-(2-methoxyphenyl)prop-2-yn-1-one (63p)

2-Bromobenzoyl chloride (**62b**) (658.4 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 2-ethynylanisole (**56c**) (330.4 mg, 2.5 mmol) were employed to afford 614.6 mg (78%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.66 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.54 (dd, J = 7.6, 1.7 Hz, 1H), 7.46-7.38 (m, 2H), 7.34 (td, *J* = 7.7, 1.8 Hz, 1H), 6.93 (td, *J* = 7.6, 0.8 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (C=O), 161.9 (C), 137.2 (C), 134.96 (CH), 134.92 (CH), 133.6 (CH), 133.3 (CH), 132.9 (CH), 127.3 (CH), 121.2 (C), 120.7 (CH), 110.9 (CH), 109.1 (C), 92.1(C), 91.4 (C), 55.9 (OCH_3). The spectral data were in agreement with those reported previously for this compound.[110]

4.1.17 1-(2-Bromophenyl)-3-(*p*-tolyl)prop-2-yn-1-one (63q)

2-Bromobenzoyl chloride (**62b**) (658.4 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 4-ethynyltoluene

(**56d**) (290.4 mg, 2.5 mmol) were employed to afford 456.2 mg (61%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.70 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.45 (td, *J* = 7.5, 1.2 Hz, 1H), 7.37 (td, *J* = 7.6, 1.8 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (C=O), 141.9 (C), 137.9 (C), 135.0 (CH), 133.33 (CH), 133.29 (CH), 132.8 (CH), 129.6 (CH), 127.5 (CH), 121.3 (C), 117.0 (C), 95.1 (C), 88.1 (C), 21.9 (CH_3). The spectral data were in agreement with those reported previously for this compound.[110]

4.1.18 1-(2-Bromophenyl)-3-(*m*-tolyl)prop-2-yn-1-one (63r)

2-Bromobenzoyl chloride (**62b**) (658.4 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 3-ethynyltoluene (**56e**) (290.4 mg, 2.5 mmol) were employed to afford 463.7 mg (62%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.36 (dd, *J* = 10.7, 4.1 Hz, 3H), 7.28 (td, *J* = 7.7, 1.6 Hz, 1H), 7.23-7.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6 (C=O), 138.6 (C), 137.7 (C), 135.0 (CH), 133.6 (CH), 133.4 (CH), 132.8 (CH), 132.0 (CH), 130.4 (CH), 128.7 (CH), 127.5 (CH), 121.3 (C), 119.9 (C), 94.7 (C), 87.8 (C), 21.3 (CH_3); IR (neat): 2918, 2185, 1646, 1584, 1562, 1482, 1463, 1430, 1300, 1262, 1221, 1127, 1063, 1017, 901, 783, 737 cm^{-1}; MS (ESI, m/z): 299.01 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{12}{}^{79}BrO$: 299.0066 $[M+H]^+$, found: 299.0070.

4.1.19 1-(2-Bromophenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (63s)

2-Bromobenzoyl chloride (**62b**) (658.4 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 4-ethynyl-α,α,α-trifluorotoluene (**56f**) (425.3 mg, 2.5 mmol) were employed to afford 679.8 mg (77%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.71 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.67 (d, *J* =

8.2 Hz, 2H), 7.47 (td, *J* = 7.5, 1.2 Hz, 1H), 7.40 (td, *J* = 7.6, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (C=O), 137.2 (C), 135.2 (CH), 133.8 (CH), 133.3 (CH), 133.0 (CH), 132.5 (q, ^2J = 32.9 Hz, C), 127.6 (CH), 125.7 (q, ^3J = 3.8 Hz, CH), 123.9 (C), 123.6 (q, ^1J = 272.8 Hz, CF_3), 121.5 (C), 91.6 (C), 89.1 (C); IR (neat): 3058, 2200, 1648, 1611, 1583, 1562, 1462, 1432, 1402, 1318, 1296, 1275, 1203, 1172, 1119, 1105, 1067, 1055, 1014, 999, 849, 780 cm^{-1}.

4.1.20 1-(2-Bromophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (63t)

2-Bromobenzoyl chloride (**62b**) (658.4 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 1-ethynyl-3-fluorobenzene (**56h**) (300.3 mg, 2.5 mmol) were employed to afford 530.5 mg (70%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.50-7.35 (m, 4H), 7.33-7.27 (m, 1H), 7.18 (tdd, *J* = 8.3, 2.6, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (C=O), 162.2 (d, ^1J = 248.4 Hz, CF), 137.1 (C), 135.0 (CH), 133.6 (CH), 132.8 (CH), 130.5 (d, ^3J = 8.6 Hz, CH), 129.0 (d, ^4J = 3.0 Hz, CH), 127.5 (CH), 121.8 (d, ^3J = 9.4 Hz, C), 121.3 (C), 119.6 (d, ^2J = 23.1 Hz, CH), 118.4 (d, ^2J = 21.2 Hz, CH), 92.1 (d, ^4J = 3.2 Hz, C), 88.1 (C); IR (neat): 3071, 2191, 1648, 1575, 1482, 1463, 1426, 1297, 1264, 1219, 1148, 1129, 1078, 1059, 1010, 999, 958, 864, 790, 778 cm^{-1}; MS (ESI, m/z): 302.98 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_9{}^{79}BrFO$: 302.9815$[M+H]^+$, found: 302.9823.

4.1.21 1,3-Bis(2-bromophenyl)prop-2-yn-1-one (63u)

2-Bromobenzoyl chloride (**62b**) (658.4 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 1-bromo-2-ethynylbenzene (**56i**) (452.6 mg, 2.5 mmol) were employed to afford 582.5 mg (64%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.57-7.51 (m, 2H), 7.37 (td, *J* = 7.6, 1.0 Hz, 1H), 7.32-7.16 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9 (C=O), 136.7 (C),

135.22 (CH), 135.15 (CH), 133.8 (CH), 133.7 (CH), 132.9 (CH), 132.1 (CH), 127.5 (CH), 126.9 (C), 122.5 (C), 121.4 (C), 91.4 (C), 91.0 (C) (Note that two CH peaks overlap on each other); IR (neat): 3051, 2188, 1647, 1581, 1562, 1463, 1431, 1293, 1272, 1244, 1202, 1131, 1059, 1044, 1027, 997, 946, 820, 754 cm^{-1}; MS (ESI, m/z): 362.90 and 364.90 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_9{}^{79}Br_2O$: 362.9015 $[M+H]^+$, found: 362.9018; calcd. for $C_{15}H_9{}^{79}Br^{81}BrO$: 364.8895 $[M+H]^+$, found: 364.9001.

4.1.22 1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-one (63v)

4-Methoxybenzoyl chloride (**62c**) (511.8 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and phenylacetylene (**56a**) (255.4 mg, 2.5 mmol) were employed to afford 584.8 mg (99%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22-8.17 (m, 2H), 7.70-7.64 (m, 2H), 7.50-7.44 (m, 1H), 7.41 (tt, *J* = 6.8, 1.7 Hz, 2H), 7.04-6.95 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (C=O), 164.6 (C), 133.1 (CH), 132.1 (CH), 130.7 (CH), 130.5 (C), 128.8 (CH), 120.5 (C), 114.0 (CH), 92.4 (C), 87.1 (C), 55.7 (CH_3). The spectral data were in agreement with those reported previously for this compound.[98,100]

4.1.23 3-Phenyl-1-(*p*-tolyl)prop-2-yn-1-one (63w)

4-Methylbenzoyl chloride (**62d**) (463.8 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and phenylacetylene (**56a**) (255.4 mg, 2.5 mmol) were employed to afford 523.2 mg (95%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13-8.10 (m, 2H), 7.70-7.66 (m, 2H), 7.51-7.45 (m, 1H), 7.44-7.38 (m, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (C=O), 145.3 (C), 134.7 (C), 133.1 (CH), 130.8 (CH), 129.8 (CH), 129.5 (CH), 128.8 (CH), 120.4 (C), 92.7 (C), 87.1 (C), 21.9 (CH_3). The spectral data were in agreement with those reported previously for this compound.[98,100]

4.1.24 3-(Thiophen-3-yl)-1-(*p*-tolyl)prop-2-yn-1-one (63x)

4-Methylbenzoyl chloride (**62d**) (463.8 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 3-ethynylthiophene (**56m**) (270.4 mg, 2.5 mmol) were employed to afford 418.8 mg (74%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.2 Hz, 2H), 7.83 (dd, J = 2.9, 1.1 Hz, 1H), 7.36 (dd, J = 5.0, 3.0 Hz, 1H), 7.32-7.28 (m, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (C=O), 145.3 (C), 134.7 (C), 133.8 (CH), 130.4 (CH), 129.8 (CH), 129.4 (CH), 126.3 (CH), 119.6 (C), 88.1 (C), 87.3 (C), 21.9 (CH_3).

4.1.25 1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one (63y)

4-Chlorobenzoyl chloride (**62e**) (525.1 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and phenylacetylene (**56a**) (255.4 mg, 2.5 mmol) were employed to afford 595.7 mg (99%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.13 (m, 2H), 7.71-7.65 (m, 2H), 7.54-7.46 (m, 3H), 7.46-7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (C=O), 140.8 (C), 135.5 (C), 133.2 (CH), 131.1 (CH), 131.0 (CH), 129.1 (CH), 128.9 (CH), 120.0 (C), 93.8 (C), 86.7 (C). The spectral data were in agreement with those reported previously for this compound.[100,111]

4.1.26 1-(4-Chlorophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (63z)

4-Chlorobenzoyl chloride (**62e**) (525.0 mg, 3.0 mmol), $PdCl_2(PPh_3)_2$ (36.0 mg, 0.05 mmol), Et_3N (303.6 mg, 3.0 mmol), CuI (19.1 mg, 0.1 mmol) and 1-ethynyl-3-fluorobenzene (**56h**) (300.3 mg, 2.5 mmol) were employed to afford 517.3 mg (80%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-8.10 (m, 2H), 7.53-7.44 (m, 3H), 7.44-7.39 (m, 1H), 7.36 (ddd, J = 8.9, 2.4, 1.3 Hz, 1H), 7.21 (tdd, J = 8.4, 2.6, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (C=O), 162.4 (d, ^1J = 248.7 Hz, CF), 141.0 (C), 135.2 (C), 131.0 (CH), 130.6 (d, ^3J = 8.4 Hz,

CH), 129.2 (CH), 129.1 (d, ^4J = 3.1 Hz, CH), 121.8 (d, ^3J = 9.3 Hz, C), 119.8 (d, ^2J = 23.3 Hz, CH), 118.5 (d, ^2J = 20.9 Hz, CH), 91.7 (d, ^4J = 3.2 Hz, C), 86.9 (C); IR (neat): 3059, 2203, 1634, 1582, 1481, 1428, 1399, 1360, 1305, 1248, 1168, 1154, 1108, 1088, 1031, 1009, 954, 890, 784 cm^{-1}.

4.2 General Procedure for the Synthesis of *N*-Propargylic β-Enaminones 32

To a stirred solution of the corresponding α,β-alkynic ketone **63** (2.5 mmol) in absolute MeOH (10 mL) was added propargylamine (3.0 mmol) and the resulting mixture was heated at reflux conditions (65 ^oC) for approximately 6 h (Note that the progress of the reaction was monitored by routine TLC for the disappearance of alkynic ketone). After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (50 mL) and a saturated NaCl solution (50 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding β-enaminone **32**.

4.2.1 1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32a)

1,3-Diphenylprop-2-yn-1-one (**63a**) (515.6 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 633.8 mg (97%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 11.33 (br s, 1H), 7.95-7.87 (m, 2H), 7.55-7.37 (m, 8H), 5.85 (br s, 1H), 3.95 (dd, J = 6.3, 2.5 Hz, 2H), 2.31 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3 (C=O), 166.0 (C), 140.1 (C), 135.1 (C), 131.1 (CH), 130.0 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 127.3 (CH), 94.8 (CH), 79.9 (C), 72.6 (CH), 34.3 (CH_2). The spectral data were in agreement with those reported previously for this compound.[18]

4.2.2 3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32b)

3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (**63b**) (590.7 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 713.8 mg (98%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.35 (br s, 1H), 7.94-7.87 (m, 2H), 7.48-7.37 (m, 5H), 7.02-6.96 (m, 2H), 5.84 (s, 1H), 3.98 (dd, *J* = 6.3 and 2.5 Hz, 2H), 3.86 (s, 3H), 2.32 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C=O), 166.0 (C), 161.0 (C), 140.2 (C), 131.0 (CH), 129.6 (CH), 128.3 (CH), 127.3 (CH), 114.2 (CH), 94.7 (CH), 80.1 (C), 72.5 (CH), 55.5 (OCH_3), 34.4 (CH_2) (Note that two C peaks overlap on each other). IR (neat): 3285, 3056, 2931, 2837, 1593, 1559, 1497, 1247, 1173, 1142, 1023, 836, 757, 689 cm^{-1}; MS (ESI, m/z): 292.13 $[M+H]^+$; HRMS (ESI): calcd. for $C_{19}H_{18}NO_2$: 292.1332 $[M+H]^+$, found: 292.1337.

4.2.3 3-(2-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32c)

3-(2-Methoxyphenyl)-1-phenylprop-2-yn-1-one (**63c**) (590.7 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 626.4mg (86%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.51 (br s, 1H), 7.96-7.86 (m, 2H), 7.48-7.35 (m, 4H), 7.31 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.79 (s, 1H), 4.00-3.70 (m, 5H), 2.27 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (C=O), 163.3 (C), 156.0 (C), 140.1 (C), 131.2 (CH), 130.7 (CH), 129.8 (CH), 128.1 (CH), 127.1 (CH), 123.6 (C), 120.9 (CH), 110.8 (CH), 94.0 (CH), 79.4 (C), 72.1 (CH), 55.5 (OCH_3), 33.8 (CH_2); IR (neat): 3285, 2935, 1732, 1594, 1567, 1482, 1455, 1326, 1241, 1145, 1114, 1056, 1023, 808, 753, 692 cm^{-1}; MS (ESI, m/z): 292.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO_2$: 292.1332 $[M+H]^+$, found: 292.1341.

4.2.4 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-en-1-one (32d)

1-Phenyl-3-*p*-tolylprop-2-yn-1-one (**63d**) (550.7 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 633.3 mg (92%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (br t, *J* = 5.6 Hz, 1H), 7.97-7.89 (m, 2H), 7.49-7.37 (m, 5H), 7.28 (d, *J* = 7.9 Hz, 2H), 5.87 (s, 1H), 3.96 (dd, *J* = 6.3, 2.5 Hz, 2H), 2.42 (s, 3H), 2.35 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (C=O), 166.1 (C), 140.0 (C), 131.9 (C), 130.9 (C), 129.3 (CH), 128.2 (CH), 127.7 (CH), 127.1 (CH), 94.5 (CH), 79.9 (C), 72.4 (CH), 34.1 (CH_2), 21.3 (CH_3) (Note that two CH peaks overlap on each other); IR (neat): 3288, 3056, 3025, 2919, 1579, 1554, 1498, 1326, 1295, 1141, 1055, 1023, 825, 754, 690 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI): calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1390.

4.2.5 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-en-1-one (32e)

1-Phenyl-3-*m*-tolylprop-2-yn-1-one (**63e**) (550.7 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 653.9 mg (95%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (br t, *J* = 6.0 Hz, 1H), 7.97-7.89 (m, 2H), 7.48-7.24 (m, 7H), 5.86 (s, 1H), 3.93 (dd, *J* = 6.3, 2.5 Hz, 2H), 2.41 (s, 3H), 2.35 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (C=O), 165.9 (C), 139.8 (C), 138.4 (C), 134.6 (C), 130.8 (CH), 130.4 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 124.7 (CH), 94.3 (CH), 79.8 (C), 72.4 (CH), 34.0 (CH_2), 21.2 (CH_3); IR (neat): 3224, 3055, 2113, 1667, 1594, 1550, 1476, 1324, 1270, 1226, 1173, 1134, 1054, 1024, 789, 733 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1380.

4.2.6 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (32f)

1-Phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (**63f**) (685.6 mg, 2.5 mmol

) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 666.9 mg (81%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (br t, *J* = 5.6 Hz, 1H), 7.90 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.49-7.36 (m, 3H), 5.83 (s, 1H), 3.87 (dd, *J* = 6.4, 2.4 Hz, 2H), 2.33 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4 (C=O), 164.0 (C), 139.6 (C), 138.4 (C), 131.8 (q, ^{2}J = 32.7 Hz, C), 131.3 (CH), 128.4 (CH), 128.3 (CH), 127.2 (CH), 125.7 (q, ^{3}J = 3.7 Hz, CH), 123.8 (q, ^{1}J = 272.4 Hz, CF_3), 94.9 (CH), 79.5 (C), 72.8 (CH), 34.2 (CH_2); IR (neat): 3055, 2116, 1600, 1583, 1548, 1502, 1430, 1321, 1294, 1240, 1225, 1163, 1104, 1072, 1050, 1015, 925, 849, 737 cm^{-1}; MS (ESI, m/z): 330.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}F_3NO$: 330.1100 $[M+H]^+$, found: 330.1100.

4.2.7 3-(4-(Dimethylamino)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32g)

3-(4-(Dimethylamino)phenyl)-1-phenylprop-2-yn-1-one (**63g**) (623.3 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 639.2 mg (84%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (br t, *J* = 5.5 Hz, 1H), 7.93 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.48-7.35 (m, 5H), 6.72 (d, *J* = 8.8 Hz, 2H), 5.88 (s, 1H), 4.05 (dd, *J* = 6.2, 2.4 Hz, 2H), 2.99 (s, 6H), 2.34 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2 (C=O), 166.9 (C), 151.4 (C), 140.4 (C), 130.6 (CH), 129.2 (CH), 128.1 (CH), 127.0 (CH), 121.7 (C), 111.5 (CH), 94.0 (CH), 80.3 (C), 72.3 (CH), 40.1 ($N(CH_3)_2$), 34.4 (CH_2); IR (neat): 3208, 2884, 2805, 2111, 1614, 1579, 1502, 1481, 1446, 1328, 1264, 1233, 1194, 1141, 1054, 928, 815, 797, 743, 729 cm^{-1}; MS (ESI, m/z): 305.17 $[M+H]^+$; HRMS (ESI) calcd. for $C_{20}H_{21}N_2O$: 305.1648 $[M+H]^+$, found: 305.1653.

4.2.8 3-(3-Fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32h)

3-(3-Fluorophenyl)-1-phenylprop-2-yn-1-one (**63h**) (560.6 mg, 2.5 mmol) and

propargylamine (165.3 mg, 3.0 mmol) were employed to afford 628.4 mg (90%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (br s, 1H), 7.98-7.88 (m, 2H), 7.55-7.39 (m, 4H), 7.33-7.14 (m, 3H), 5.86 (s, 1H), 3.95 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.35 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5 (C=O), 164.2 (C), 162.7 (d, ^{1}J = 248.4 Hz, CF), 139.8 (C), 137.0 (d, ^{3}J = 7.6 Hz, C), 131.3 (CH), 130.6 (d, ^{3}J = 8.2 Hz, CH), 128.4 (CH), 127.3 (CH), 123.8 (d, ^{4}J = 3.1 Hz, CH), 116.9 (d, ^{2}J = 21.0 Hz, CH), 115.2 (d, ^{2}J = 22.7 Hz, CH), 94.8 (CH), 79.7 (C), 72.8 (CH), 34.3 (CH_2); IR (neat): 3222, 1600, 1570, 1549, 1520, 1474, 1431, 1323, 1299, 1284, 1265, 1250, 1226, 1203, 1025, 1000, 965, 876, 788 cm^{-1}; MS (ESI, m/z): 280.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}FNO$: 280.1132 $[M+H]^+$, found: 280.1134.

4.2.9 3-(2-Bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32i)

3-(2-Bromophenyl)-1-phenylprop-2-yn-1-one (**63i**) (712.8 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 714.4 mg (84%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (br s, 1H), 7.82-7.69 (m, 2H), 7.52-7.46 (m, 1H), 7.34-7.20 (m, 5H), 7.18-7.12 (m, 1H), 5.62 (s, 1H), 3.78 (ddd, *J* = 17.7, 4.9, 2.5 Hz, 1H), 3.58 (ddd, *J* = 17.6, 7.1, 2.4 Hz, 1H), 2.14 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2 (C=O), 163.2 (C), 139.6 (C), 135.5 (C), 132.9 (CH), 131.0 (CH), 130.8 (CH), 129.8 (CH), 128.2 (CH), 127.6 (CH), 127.1 (CH), 121.4 (CBr), 93.9 (CH), 79.0 (C), 72.6 (CH), 33.6 (CH_2); IR (neat): 3291, 1732, 1595, 1572, 1549, 1462, 1322, 1306, 1254, 1145, 1054, 1024, 944, 853, 749 cm^{-1}; MS (ESI, m/z): 340.03 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}{}^{79}BrNO$: 340.0332 $[M+H]^+$, found: 340.0329.

4.2.10 3-(4-(*tert*-Butyl)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32j)

3-(4-(*tert*-Butyl)phenyl)-1-phenylprop-2-yn-1-one (**63j**) (655.9 mg, 2.5 mmol) and

propargylamine (165.3 mg, 3.0 mmol) were employed to afford 722.1 mg (91%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (br s, 1H), 7.91 (d, *J* = 6.9 Hz, 2H), 7.59-7.34 (m, 7H), 5.86 (s, 1H), 3.98 (d, *J* = 4.1 Hz, 2H), 2.33 (br s, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C=O), 166.1 (C), 153.2 (C), 140.1 (C), 132.0 (C), 131.0 (CH), 128.3 (CH), 127.7 (CH), 127.2 (CH), 125.7 (CH), 94.6 (CH), 80.0 (C), 72.5 (CH), 34.9 (C), 34.4 (CH_2), 31.3 (CH_3).

4.2.11 2-(5-Oxo-5-phenyl-3-(prop-2-yn-1-ylamino)pent-3-en-1-yl)isoindoline-1,3-dione (32k)

2-(5-Oxo-5-phenylpent-3-yn-1-yl)isoindoline-1,3-dione (**63k**) (758.3 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 546.5 mg (61%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.30 (br t, *J* = 5.8 Hz, 1H), 7.86-7.72 (m, 4H), 7.70-7.61 (m, 2H), 7.43-7.29 (m, 3H), 5.76 (s, 1H), 4.21 (dd, *J* = 6.2, 2.4 Hz, 2H), 4.03-3.87 (m, 2H), 2.85-2.70 (m, 2H), 2.35 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C=O), 167.9 (C), 162.8 (C=O), 139.7 (C), 134.1 (CH), 131.9 (CH), 130.9 (C), 128.2 (CH), 127.0 (CH), 123.4 (CH), 93.0 (CH), 79.2 (C), 72.8 (CH), 36.0 (CH_2), 32.4 (CH_2), 30.8 (CH_2); IR (neat): 3260, 1775, 1713, 1594, 1580, 1392, 1337, 1247, 1188, 1098, 970, 753 cm^{-1}; MS (ESI, m/z): 359.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{19}N_2O_3$: 359.1390 $[M+H]^+$, found: 359.1399.

4.2.12 1-Phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (32l)

1-Phenylhept-2-yn-1-one (**63l**) (465.7 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 573.2 mg (95%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.48 (br s, 1H), 7.89-7.83 (m, 2H), 7.46-7.36 (m, 3H), 5.75 (s, 1H), 4.08 (dd, *J* = 6.2, 2.5 Hz, 2H), 2.42-2.35 (m, 2H), 2.32 (t, *J* = 2.5 Hz, 1H), 1.67-1.57 (m, 2H), 1.44 (sextet, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (C=O), 168.2 (C), 140.4 (C), 130.7 (CH), 128.2 (CH), 127.1 (CH), 92.2 (CH), 79.2 (C), 72.5 (CH), 32.3 (CH_2), 31.9 (CH_2),

30.2 (CH_2), 22.7 (CH_2), 13.9 (CH_3); IR (neat): 3296, 3064, 2953, 2866, 1578, 1558, 1544, 1280, 1244, 1107, 1025, 784, 663, 628 cm^{-1}; MS (ESI, m/z): 242.15 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{20}NO$: 242.1545 $[M+H]^+$, found: 242.1524.

4.2.13 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (32m)

1-Phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (**63m**) (530.7 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 614.9 mg (92%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 11.44 (br t, *J* = 6.1 Hz, 1H), 7.95-7.86 (m, 2H), 7.59 (dd, *J* = 2.9, 1.1 Hz, 1H), 7.46-7.32 (m, 4H), 7.24 (dd, *J* = 5.0, 1.0 Hz, 1H), 5.92 (s, 1H), 3.97 (dd, *J* = 6.4, 2.4 Hz, 2H), 2.38 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5 (C=O), 160.3 (C), 139.6 (C), 135.1 (C), 130.7 (CH), 128.0 (CH), 127.0 (CH), 126.9 (CH), 126.5 (CH), 126.1 (CH), 93.9 (CH), 79.9 (C), 72.6 (CH), 33.9 (CH_2); IR (neat): 3249, 3214, 1653, 1593, 1577, 1290, 1247, 1227, 1079, 1057, 799, 754, 720 cm^{-1}; MS (ESI, m/z): 268.08 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{14}NOS$: 268.0796 $[M+H]^+$, found: 268.0775.

4.2.14 1-(2-Bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32n)

1-(2-Bromophenyl)-3-phenylprop-2-yn-1-one (**63n**) (712.8 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 740.0 mg (87%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 11.10 (br s, 1H), 7.56 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.52-7.40 (m, 6H), 7.30 (td, *J* = 7.5, 1.1 Hz, 1H), 7.21-7.15 (m, 1H), 5.47 (s, 1H), 3.96 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.33 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1 (C=O), 165.8 (C), 143.1 (C), 134.4 (C), 133.4 (CH), 130.3 (CH), 130.1 (CH), 129.2 (CH), 128.8 (CH), 127.9 (CH), 127.2 (CH), 119.5 (CBr), 98.4 (CH), 79.6 (C), 72.8 (CH), 34.4 (CH_2); IR (neat): 3290, 1731, 1588, 1560, 1483, 1461, 1427, 1317, 1244, 1145, 1082, 1023, 949, 751 cm^{-1}; MS (ESI, m/z): 340.03 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}{}^{79}BrNO$: 340.0332 $[M+H]^+$, found: 340.0333.

4.2.15 1-(2-Bromophenyl)-3-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32o)

1-(2-Bromophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-one (**63o**) (787.9 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 703.5 mg (76%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (br s, 1H), 7.56 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.50-7.41 (m, 3H), 7.30 (td, *J* = 7.5, 1.1 Hz, 1H), 7.21-7.15 (m, 1H), 6.98-6.92 (m, 2H), 5.45 (br s, 1H), 4.00 (dd, *J* = 6.4, 2.5 Hz, 2H), 3.83 (s, 3H), 2.34 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8 (C=O), 165.9 (C), 161.1 (C), 143.3 (C), 133.4 (CH), 130.3 (CH), 129.6 (CH), 129.3 (CH), 127.2 (CH), 126.7 (C), 119.5 (CBr), 114.2 (CH), 98.3 (CH), 79.9 (C), 72.7 (CH), 55.5 (OCH_3), 34.50 (CH_2); IR (neat): 3286, 1587, 1558, 1490, 1323, 1296, 1247, 1174, 1083, 1021, 873, 759 cm^{-1}; MS (ESI, m/z): 370.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}{}^{79}BrNO_2$: 370.0437 $[M+H]^+$, found: 370.0440.

4.2.16 1-(2-Bromophenyl)-3-(2-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32p)

1-(2-Bromophenyl)-3-(2-methoxyphenyl)prop-2-yn-1-one (**63p**) (787.9 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 703.5 mg (76%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (br s, 1H), 7.57 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.46-7.40 (m, 1H), 7.35-7.27 (m, 2H), 7.19 (td, *J* = 7.7, 1.7 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 5.40 (br s, 1H), 4.02-3.77 (m, 2H), 3.88 (s, 3H), 2.28 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8 (C=O), 163.4 (C), 156.1 (C), 143.2 (C), 133.4 (CH), 131.5 (CH), 130.2 (CH), 130.0 (CH), 129.4 (CH), 127.1 (CH), 123.4 (C), 121.0 (CH), 119.6 (CBr), 111.0 (CH), 98.0 (CH), 79.3 (C), 72.3 (CH), 55.7 (OCH_3), 34.1 (CH_2); IR (neat): 3247, 2190, 1587, 1536, 1485, 1461, 1328, 1237, 1163, 1084, 1065, 1023, 796, 753 cm^{-1}; MS (ESI, m/z): 370.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}{}^{79}BrNO_2$: 370.0437 $[M+H]^+$, found: 370.0440.

4.2.17 1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-en-1-one (32q)

1-(2-Bromophenyl)-3-(*p*-tolyl)prop-2-yn-1-one (**63q**) (747.9 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 752.8 mg (85%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (br s, 1H), 7.58 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.48 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.32 (td, *J* = 7.5, 1.1 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 2H), 7.20 (td, *J* = 7.7, 1.7 Hz, 1H), 5.48 (s, 1H), 4.00 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.41 (s, 3H), 2.36 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9 (C=O), 166.1 (C), 143.2 (C), 140.3 (C), 133.4 (CH), 131.5 (C), 130.3 (CH), 129.4 (CH), 129.3 (CH), 127.9 (CH), 127.2 (CH), 119.5 (CBr), 98.3 (CH), 79.8 (C), 72.7 (CH), 34.4 (CH_2), 21.4 (CH_3); IR (neat): 3280, 1586, 1571, 1492, 1310, 1256, 1046, 1080, 1021, 827, 791, 757 cm^{-1}; MS (ESI, m/z): 354.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}{}^{79}BrNO$: 354.0488 $[M+H]^+$, found: 354.0489.

4.2.18 1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-en-1-one (32r)

1-(2-Bromophenyl)-3-(*m*-tolyl)prop-2-yn-1-one (**63r**) (747.9 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 770.5 mg (87%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (br s, 1H), 7.57 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.50-7.44 (m, 1H), 7.38-7.24 (m, 5H), 7.22-7.16 (m, 1H), 5.47 (s, 1H), 3.98 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.40 (s, 3H), 2.36 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9 (C=O), 166.1 (C), 143.0 (C), 138.5 (C), 134.2 (C), 133.3 (CH), 130.8 (CH), 130.2 (CH), 129.1 (CH), 128.5 (CH), 128.3 (CH), 127.1 (CH), 124.8 (CH), 119.4 (CBr), 98.1 (CH), 79.6 (C), 72.7 (CH), 34.3 (CH_2), 21.4 (CH_3); IR (neat): 3289, 1731, 1561, 1479, 1359, 1256, 1082, 1023, 758 cm^{-1}; MS (ESI, m/z): 354.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}{}^{79}BrNO$: 354.0488 $[M+H]^+$, found: 354.0490.

4.2.19 1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (32s)

1-(2-Bromophenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (**63s**) (882.8 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 898.1 mg (88%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (br t, *J* = 5.8 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.55 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.45 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.30 (td, *J* = 7.5, 1.0 Hz, 1H), 7.18 (td, *J* = 7.7, 1.7 Hz, 1H), 5.46 (s, 1H), 3.91 (dd, *J* = 6.5, 2.5 Hz, 2H), 2.35 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3 (C=O), 163.8 (C), 142.6 (C), 137.9 (C), 133.4 (CH), 131.9 (q, ^{2}J = 32.8 Hz, C), 130.5 (CH), 129.2 (CH), 128.4 (CH), 127.2 (CH), 125.7 (q, ^{3}J = 3.7 Hz, CH), 123.7 (q, ^{1}J = 272.4 Hz, CF_3), 119.3 (CBr), 98.6 (CH), 79.3 (C), 73.0 (CH), 34.3 (CH_2); IR (neat): 3297, 1587, 1561, 1319, 1167, 1125, 1063, 1018, 849, 740 cm^{-1}; MS (ESI, m/z): 408.02 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{14}{}^{79}BrF_3NO$: 408.0205 $[M+H]^+$, found: 408.0206.

4.2.20 1-(2-Bromophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32t)

1-(2-Bromophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (**63t**) (787.9 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 850.7 mg (95%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.01 (br s, 1H), 7.57 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.48-7.39 (m, 2H), 7.35-7.26 (m, 2H), 7.25-7.12 (m, 3H), 5.47 (s, 1H), 3.95 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.35 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4 (C=O), 164.2 (C), 162.6 (d, ^{1}J = 248.4 Hz, CF), 142.9 (C), 136.4 (d, ^{3}J = 7.6 Hz, C), 133.5 (CH), 130.6 (d, ^{3}J = 8.2 Hz, CH), 130.5 (CH), 129.3 (CH), 127.3 (CH), 123.8 (d, ^{4}J = 3.1 Hz, CH), 119.5 (CBr), 117.1 (d, ^{2}J = 21.0 Hz, CH), 115.3 (d, ^{2}J = 22.9 Hz, CH), 98.5 (CH), 79.5 (C), 73.0 (CH), 34.4 (CH_2); IR (neat): 3294, 1562, 1477, 1321, 1224, 1197, 1079, 1023, 872, 790, 758 cm^{-1}; MS (ESI, m/z): 358.02 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{79}BrFNO$: 358.0237 $[M+H]^+$, found: 358.0239.

4.2.21 1,3-Bis(2-bromophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32u)

1,3-Bis(2-bromophenyl)prop-2-yn-1-one (**63u**) (910.1 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 901.1 mg (86%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (br t, *J* = 5.5 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.39-7.31 (m, 2H), 7.30-7.23 (m, 2H), 7.15 (td, *J* = 8.0, 1.6 Hz, 1H), 5.34 (s, 1H), 3.92 (ddd, *J* = 17.7, 5.0, 2.5 Hz, 1H), 3.72 (ddd, *J* = 17.7, 7.0, 2.4 Hz, 1H), 2.28 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2 (C=O), 163.2 (C), 142.6 (C), 135.0 (C), 133.2 (CH), 132.8 (CH), 130.9 (CH), 130.3 (CH), 129.6 (CH), 129.0 (CH), 127.6 (CH), 127.0 (CH), 121.2 (CBr), 119.3 (CBr), 97.7 (CH), 78.6 (C), 72.8 (CH), 33.7 (CH_2); IR (neat): 3291, 1704, 1586, 1548, 1457, 1426, 1355, 1255, 1074, 1023, 750 cm^{-1}; MS (ESI, m/z): 417.94 and 419.94 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{79}Br_2NO$: 417.9437 $[M+H]^+$, found: 417.9442; calcd. for $C_{18}H_{14}{}^{79}Br^{81}Br$ NO: 419.9417 $[M+H]^+$, found: 419.9420.

4.2.22 1-(4-Methoxyphenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32v)

1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-one (**63v**) (590.7 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 713.9 mg (98%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (br t, *J* = 5.6 Hz, 1H), 7.92-7.86 (m, 2H), 7.52-7.42 (m, 5H), 6.93-6.86 (m, 2H), 5.81 (s, 1H), 3.91 (dd, *J* = 6.4, 2.5 Hz, 2H), 3.82 (s, 3H), 2.29 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3 (C=O), 165.3 (C), 162.1 (C), 135.2 (C), 132.7 (C), 129.8 (CH), 129.2 (CH), 128.7 (CH), 127.9 (CH), 113.5 (CH), 94.4 (CH), 80.0 (C), 72.4 (CH), 55.4 (CH_3), 34.2 (CH_2). The spectral data were in agreement with those reported previously for this compound.[18]

4.2.23 3-Phenyl-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (32w)

3-Phenyl-1-(*p*-tolyl)prop-2-yn-1-one (**63w**) (550.7 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 640.3 mg (93%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (br t, *J* = 5.4 Hz, 1H), 7.86-7.81 (m, 2H), 7.54-7.44 (m, 5H), 7.22 (d, *J* = 7.9 Hz, 2H), 5.85 (s, 1H), 3.94 (dd, *J* = 6.3 and 2.5 Hz, 2H), 2.39 (s, 3H), 2.32 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1 (C=O), 165.6 (C), 141.5 (C), 137.4 (C), 135.1 (C), 129.9 (CH), 129.1 (CH), 128.8 (CH), 128.0 (CH), 127.3 (CH), 94.7 (CH), 80.0 (C), 72.5 (CH), 34.3 (CH_2), 21.6 (CH_3); IR (neat): 3290, 3052, 2920, 1559, 1542, 1480, 1321, 1289, 1270, 1177, 1142, 756, 696 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI): calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1390.

4.2.24 3-(Prop-2-yn-1-ylamino)-3-(thiophen-3-yl)-1-(*p*-tolyl)prop-2-en-1-one (32x)

3-(Thiophen-3-yl)-1-(*p*-tolyl)prop-2-yn-1-one (**63x**) (565.7 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 527.6 mg (75%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (br s, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.66 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.43 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.31 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 5.94 (s, 1H), 4.05 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.40 (s, 3H), 2.38 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (C=O), 160.4 (C), 141.5 (C), 137.2 (C), 135.6 (C), 129.0 (CH), 127.4 (CH), 127.2 (CH), 126.6 (CH), 126.3 (CH), 94.2 (CH), 80.2 (C), 72.6 (CH), 34.3 (CH_2), 21.5 (CH_3).

4.2.25 1-(4-Chlorophenyl)-3-phenyl-3-(prop-2-ynylamino)prop-2-en-1-one (32y)

1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one (**63y**) (601.8 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 702.5 mg (95%) of

the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.34 (br s, 1H), 7.90-7.77 (m, 2H), 7.47 (br s, 5H), 7.40-7.32 (m, 2H), 5.78 (br s, 1H), 3.94 (dd, *J* = 6.3 and 2.5 Hz, 2H), 2.32 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 187.7 (C=O), 166.3 (C), 138.4 (C), 137.2 (C), 134.8 (C), 130.1 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 127.9 (CH), 94.4 (CH), 79.7 (C), 72.7 (CH), 34.4 (CH_2). The spectral data were in agreement with those reported previously for this compound.[18]

4.2.26 1-(4-Chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (32z)

1-(4-Chlorophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (**63z**) (646.7 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 713.8 mg (91%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (br s, 1H), 7.90-7.80 (m, 2H), 7.51-7.42 (m, 1H), 7.41-7.34 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.26-7.15 (m, 2H), 5.79 (s, 1H), 3.94 (dd, *J* = 6.2, 2.2 Hz, 2H), 2.35 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9 (C=O), 164.6 (C), 162.7 (d, ^{1}J = 248.5 Hz, CF), 138.1 (C), 137.4 (C), 136.8 (d, ^{3}J = 7.8 Hz, C), 130.6 (d, ^{3}J = 8.3 Hz, CH), 128.7 (CH), 128.6 (CH), 123.7 (d, ^{4}J = 3.0 Hz, CH), 117.0 (d, ^{2}J = 21.1 Hz, CH), 115.2 (d, ^{2}J = 22.9 Hz, CH), 94.4 (CH), 79.5 (C), 72.9 (CH), 34.3 (CH_2); IR (neat): 3232, 1570, 1545, 1473, 1325, 1282, 1265, 1231, 1092, 1065, 878, 764 cm^{-1}; MS (ESI, m/z): 314.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClFNO$: 314.0743 $[M+H]^+$, found: 314.0746.

4.2.27 4-Phenyl-4-(prop-2-ynylamino)but-3-en-2-one (32aa)

4-Phenylbut-3-yn-2-one (**63aa**) (360.5 mg, 2.5 mmol) and propargylamine (165.3 mg, 3.0 mmol) were employed to afford 363.6 mg (73%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (br s, 1H), 7.48-7.36 (m, 5H), 5.13 (s, 1H), 3.84 (dd, *J* = 6.4 and 2.5 Hz, 2H), 2.26 (t, *J* = 2.5 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8 (C=O), 164.2 (C), 134.7 (C), 129.8 (CH), 128.7 (CH), 127.9 (CH), 98.2 (CH), 80.0 (C), 72.3 (CH), 34.1 (CH_2), 29.5 (CH_3). The spectral

data were in agreement with those reported previously for this compound.[18]

4.3 General Procedure for the Synthesis of *N*-Propargylic β-Enaminones 7

To a stirred solution of the corresponding β-enaminone **32** (1.8 mmol) in DMF (0.45 mL) at room temperature under argon was added (*i*-Pr)$_2$NH (3.6 mL), $PdCl_2(PPh_3)_2$ (0.036 mmol) and CuI (0.036 mmol) in turn and the reaction mixture was stirred for 10 min. The appropriate aryl iodide **64** (2.8 mmol) was then added and the resulting mixture was stirred at room temperature for approximately 3-5 h (Note that stirring was continued until β-enaminone **32** was completely consumed as monitored by routine TLC). After the reaction was over, ethyl acetate (50 mL) was added, and the resulting solution was washed with 0.1 N HCl (10 mL) and subsequently with a saturated NH_4Cl solution (10 mL) in a separatory funnel. After the layers were separated, organic phase was dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding β-enaminone **7**.

4.3.1 1,3-Diphenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-en-1-one (7a)

1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32a**) (470.8 mg, 1.8 mmol), (*i*-Pr)$_2$NH (3.6 mL), $PdCl_2(PPh_3)_2$ (25.8 mg, 0.036 mmol), CuI (6.9 mg, 0.036 mmol) and iodobenzene (**64a**) (571.3 mg, 2.8 mmol) were employed to afford 534.5 mg (88%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (br s, 1H), 7.95-7.89 (m, 2H), 7.57-7.52 (m, 2H), 7.51-7.47 (m, 3H), 7.46-7.39 (m, 5H), 7.34-7.28 (m, 3H), 5.87 (s, 1H), 4.18 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C=O), 165.9 (C), 140.0 (C), 135.1 (C), 131.7 (CH), 130.9 (CH), 129.8 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.2 (CH), 122.6 (C), 94.5 (CH), 85.2 (C), 84.2 (C), 35.0 (CH_2); IR (neat): 3056, 3031, 2922, 2853, 1594, 1582, 1559, 1476, 1293, 1224, 1139, 1054, 1023, 747, 688 cm^{-1}; MS (ESI, m/z): 338.15 $[M+H]^+$; HRMS (ESI): calcd. for $C_{24}H_{20}NO$: 338.1545 $[M+H]^+$, found: 338.1548.

4.3.2 3-(4-Methoxyphenyl)-1-phenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-en-1-one (7b)

3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32b**) (524.5 mg, 1.8 mmol), (*i*-Pr)$_2$NH (3.6 mL), $PdCl_2(PPh_3)_2$ (25.8 mg, 0.036 mmol), CuI (6.9 mg, 0.036 mmol) and iodobenzene (**64a**) (571.3 mg, 2.8 mmol) were employed to afford 555.6 mg (84%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.48 (br t, *J* = 6.0 Hz, 1H), 7.95-7.91 (m, 2H), 7.54-7.48 (m, 2H), 7.46-7.39 (m, 5H), 7.35-7.28 (m, 3H), 7.04-6.97 (m, 2H), 5.87 (s, 1H), 4.21 (d, *J* = 6.3 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (C=O), 166.1 (C), 160.9 (C), 140.3 (C), 131.8 (CH), 130.9 (CH), 129.5 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.4 (C), 127.2 (CH), 122.7 (C), 114.2 (CH), 94.5 (CH), 85.4 (C), 84.2 (C), 55.5 (CH_3), 35.2 (CH_2); IR (neat): 3057, 3003, 2934, 2838, 1667, 1594, 1582, 1560, 1498, 1295, 1250, 1176, 837, 760, 699 cm^{-1}; MS (ESI, m/z): 368.16 $[M+H]^+$; HRMS (ESI): calcd. for $C_{25}H_{22}NO_2$: 368.1651 $[M+H]^+$, found: 368.1644.

4.3.3 1-Phenyl-3-((3-phenylprop-2-yn-1-yl)amino)hept-2-en-1-one (7l)

1-Phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (**32l**) (434.4 mg, 1.8 mmol), (*i*-Pr)$_2$NH (3.6 mL), $PdCl_2(PPh_3)_2$ (25.8 mg, 0.036 mmol), CuI (6.9 mg, 0.036 mmol) and iodobenzene (**64a**) (571.3 mg, 2.8 mmol) were employed to afford 514.3 mg (90%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (br t, *J* = 5.2 Hz, 1H), 7.81-7.76 (m, 2H), 7.36-7.28 (m, 5H), 7.23-7.15 (m, 3H), 5.67 (s, 1H), 4.19 (d, *J* = 6.1 Hz, 2H), 2.37-2.29 (m, 2H), 1.61-1.52 (m, 2H), 1.36 (hextet, *J* = 7.4 Hz, 2H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6 (C=O), 168.3 (C), 140.5 (C), 131.8 (CH), 130.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.0 (CH), 122.5 (C), 92.2 (CH), 84.5 (C), 84.1 (C), 33.1 (CH_2), 32.0 (CH_2), 30.3 (CH_2), 22.7 (CH_2), 13.9 (CH_3); IR (neat): 3059, 2956, 2928, 2870, 1718, 1594, 1579, 1559, 1314, 1267, 755, 690 cm^{-1}; MS (ESI, m/z): 318.19 $[M+H]^+$; HRMS (ESI): calcd. for $C_{22}H_{24}NO$: 318.1858 $[M+H]^+$, found: 318.1856.

4.3.4 1-Phenyl-3-((3-phenylprop-2-yn-1-yl)amino)-3-(thiophen-3-yl)prop-2-en-1-one (7m)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**32m**) (481.3 mg, 1.8 mmol), (*i*-Pr)$_2$NH (3.6 mL), $PdCl_2(PPh_3)_2$ (25.3 mg, 0.036 mmol), CuI (6.9 mg, 0.036 mmol) and iodobenzene (**64a**) (571.3 mg, 2.8 mmol) were employed to afford 513.1 mg (83%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.62 (br s, 1H), 8.00 (d, *J* = 7.5 Hz, 2H), 7.68 (br s, 1H), 7.53-7.38 (m, 6H), 7.37-7.27 (m, 4H), 6.01 (s, 1H), 4.26 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7 (C=O), 160.4 (C), 139.9 (C), 135.5 (C), 131.6 (CH), 130.88 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.2 (CH), 127.0 (CH), 126.5 (CH), 126.2 (CH), 122.3 (C), 94.0 (CH), 85.2 (C), 84.2 (C), 34.9 (CH_2); IR (neat): 3095, 3063, 2922, 1559, 1507, 1273, 1226, 1174, 1068, 1022, 754, 688 cm^{-1}; MS (ESI, m/z): 344.11 $[M+H]^+$; HRMS (ESI): calcd. for $C_{22}H_{18}NOS$: 344.1109 $[M+H]^+$, found: 344.1107.

4.3.5 4-Phenyl-4-((3-phenylprop-2-yn-1-yl)amino)but-3-en-2-one (7aa)

4-Phenyl-4-(prop-2-yn-1-ylamino)but-3-en-2-one (**32aa**) (358.7 mg, 1.8 mmol), (*i*-Pr)$_2$NH (3.6 mL), $PdCl_2(PPh_3)_2$ (25.8 mg, 0.036 mmol), CuI (6.9 mg, 0.036 mmol) and iodobenzene (**64a**) (571.3 mg, 2.8 mmol) were employed to afford 475.8 mg (96%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.85 (br s, 1H), 7.50-7.43 (m, 5H), 7.43-7.38 (m, 2H), 7.34-7.27 (m, 3H), 5.18 (s, 1H), 4.08 (d, *J* = 5.9 Hz, 2H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6 (C=O), 164.1 (C), 134.8 (C), 131.6 (CH), 129.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 122.6 (C), 98.0 (CH), 85.4 (C), 83.9 (C), 34.8 (CH_2), 29.4 (CH_3). The spectral data were in agreement with those reported previously for this compound.[18]

4.3.6 3-((3-(3-Bromophenyl)prop-2-yn-1-yl)amino)-1,3-diphenylprop-2-en-1-one (7ab)

1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32a**) (470.4 mg, 1.8 mmol), (*i*-Pr)$_2$NH (3.6 mL), $PdCl_2(PPh_3)_2$ (25.3 mg, 0.036 mmol), CuI (6.9 mg, 0.036 mmol) and 3-bromoiodobenzene (**64b**) (792.2 mg, 2.8 mmol) were employed to afford 644.5 mg (86%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (br t, *J* = 5.7 Hz, 1H), 7.95-7.89 (m, 2H), 7.57-7.48 (m, 6H), 7.47-7.39 (m, 4H), 7.34 (dt, *J* = 7.8 and 1.0 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 5.88 (s, 1H), 4.17 (d, *J* = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3 (C=O), 165.9 (C), 140.1 (C), 135.1 (C), 134.6 (CH), 131.7 (CH), 131.1 (CH), 130.4 (CH), 129.9 (CH), 129.8 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 127.3 (CH), 124.6 (C), 122.2 (C), 94.8 (CH), 86.6 (C), 82.7 (C), 35.0 (CH_2); IR (neat): 3061, 2981, 1773, 1667, 1593, 1560, 1474, 1325, 1243, 1044, 1023, 784, 757, 695 cm^{-1}; MS (ESI, m/z): 416.06 and 418.06 $[M+H]^+$; HRMS (ESI): calcd. for $C_{24}H_{19}{}^{79}BrNO$: 416.0650 $[M+H]^+$, found: 416.0628; calcd. for $C_{24}H_{19}{}^{81}BrNO$: 418.0630 $[M+H]^+$, found: 418.0616.

4.3.7 3-(But-2-yn-1-ylamino)-1,3-diphenylprop-2-en-1-one (7ac)

1,3-Diphenylprop-2-yn-1-one (**63a**) (515.6 mg, 2.5 mmol) and 2-butynylamine (but-2-yn-1-amine) (207.3 mg, 3.0 mmol) were employed to afford 640.2 mg (93%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.34 (br s, 1H), 7.93-7.87 (m, 2H), 7.54-7.35 (m, 8H), 5.80 (s, 1H), 3.88 (dq, *J* = 6.1 and 2.4 Hz, 2H), 1.80 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (C=O), 165.9 (C), 140.1 (C), 135.1 (C), 130.9 (CH), 129.7 (CH), 128.6 (CH), 128.2 (CH), 127.8 (CH), 127.1 (CH), 94.1 (CH), 80.4 (C), 75.0 (C), 34.7 (CH_2), 3.6 (CH_3); IR (neat): 3055, 2952, 2929, 1735, 1586, 1544, 1522, 1482, 1439, 1361, 1330, 1272, 1249, 1226, 1181, 1148, 1130, 1056, 1023, 924, 873, 768, 751, 691 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI): calcd. for $C_{19}H_{18}NO$: 276.1388 $[M+H]^+$, found: 276.1386.

4.4 General Procedure for the Synthesis of 5-Iodopyridines 55

To a stirred solution of the corresponding *N*-propargylic β-enaminone **7** (0.25 mmol) in acetonitrile (10 mL) were added iodine (0.75 mmol) and $NaHCO_3$ (0.75 mmol). The resulting mixture was then refluxed under air for nearly 8-10 h (Note that stirring was continued until β-enaminone **7** was completely consumed as monitored by routine TLC). After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (30 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (30 mL) were added (Note that the treatment of the reaction mixture with a saturated $Na_2S_2O_3$ solution removes the unreacted/excess I_2). After the layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding iodopyridine **55**.

4.4.1 (5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (55a)

1,3-Diphenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-en-1-one (**7a**) (84.4 mg, 0.25 mmol), I_2 (190.4 mg, 0.75 mmol) and $NaHCO_3$ (63.0 mg, 0.75 mmol) were employed to afford 92.3 mg (80%) of the indicated product as an off-white solid: mp 166.9-167.8 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.47-7.41 (m, 2H), 7.40-7.35 (m, 2H), 7.27 (tt, *J* = 7.4 and 1.1 Hz, 2H), 7.22-6.92 (m, 8H), 6.78 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7 (C=O), 157.5 (CH), 155.9 (C), 152.5 (C), 139.4 (C), 138.4 (C), 137.2 (C), 135.3 (C), 133.4 (CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.0 (CH), 128.0 (CH), 98.6 (C); IR (neat): 3066, 1667, 1503, 1443, 1421, 1311, 1279, 1225, 945, 762, 698, 683, 653, 570; MS (ESI, m/z): 462.03 $[M+H]^+$; HRMS (ESI): calcd. for $C_{24}H_{17}INO$: 462.0349 $[M+H]^+$, found: 462.0345.

4.4.2 (5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (55b)

3-(4-Methoxyphenyl)-1-phenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-en-1-one (**7b**) (91.9 mg, 0.25 mmol), I_2 (190.4 mg, 0.75 mmol) and $NaHCO_3$ (63.0 mg, 0.75 mmol) were employed to afford 76.2 mg (62%) of the indicated product as a yellow solid: mp 175.2-176.4 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.44-7.34 (m, 4H), 7.27 (tt, *J* = 7.4 and 1.1 Hz, 2H), 7.19-7.07 (m, 4H), 6.99 (br s, 1H), 6.74 (br s, 1H), 6.70-6.64 (m, 2H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0 (C=O), 160.3 (C), 157.3 (CH), 155.5 (C), 152.4 (C), 139.4 (C), 137.2 (C), 134.9 (C), 133.4 (CH), 131.0 (C), 130.5 (CH), 129.3 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 113.9 (CH), 97.9 (C), 55.3 (CH_3); IR (neat): 2963, 2839, 1658, 1535, 1471, 1411, 1327, 1228, 1160, 1012, 837, 777, 633, 614, 582; MS (ESI, m/z): 492.05 $[M+H]^+$; HRMS (ESI): calcd. for $C_{25}H_{19}INO_2$: 492.0460 $[M+H]^+$, found: 492.0454.

4.4.3 (2-Butyl-5-iodo-4-phenylpyridin-3-yl)(phenyl)methanone (55l)

1-Phenyl-3-((3-phenylprop-2-yn-1-yl)amino)hept-2-en-1-one (**7l**) (79.5 mg, 0.25 mmol), I_2 (190.4 mg, 0.75 mmol) and $NaHCO_3$ (63.0 mg, 0.75 mmol) were employed to afford 71.8 mg (65%) of the indicated product as a light yellowish orange solid: mp 99.5-101.2 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.47-7.42 (m, 2H), 7.39 (tt, *J* = 7.4 and 1.2 Hz, 1H), 7.29-7.18 (m, 3H), 7.11 (t, *J* = 6.6 Hz, 2H), 6.93 (br s, 2H), 2.53 (t, *J* = 7.7 Hz, 2H), 1.60 (br s, 2H), 1.20 (hextet, *J* = 7.4 Hz, 2H), 0.74 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2 (C=O), 158.5 (C), 157.2 (CH), 151.1 (C), 139.2 (C), 137.0 (C), 135.6 (C), 133.8 (CH), 129.3 (CH), 128.59 (CH), 128.55 (CH), 128.2 (CH), 128.1 (CH), 96.4 (C), 35.7 (CH_2), 31.7 (CH_2), 22.7 (CH_2), 13.9 (CH_3); IR (neat): 2959, 2924, 2855, 1657, 1592, 1577, 1543, 145, 1312, 1275, 1226, 943, 759, 696, 682; MS (ESI, m/z): 442.07 $[M+H]^+$; HRMS (ESI): calcd. for $C_{22}H_{21}INO$: 442.0668 $[M+H]^+$, found: 442.0654.

4.4.4 (5-Iodo-4-phenyl-2-(thiophen-3-yl)pyridin-3-yl)(phenyl)methanone (55m)

1-Phenyl-3-((3-phenylprop-2-yn-1-yl)amino)-3-(thiophen-3-yl)prop-2-en-1-one (**7m**) (85.9 mg, 0.25 mmol), I_2 (190.4 mg, 0.75 mmol) and $NaHCO_3$ (63.0 mg, 0.75 mmol) were employed to afford 87.3 mg (75%) of the indicated product as a light yellow solid: mp 154.8-155.7 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.57-7.51 (m, 3H), 7.46-7.34 (m, 3H), 7.30-7.22 (m, 4H), 7.19 (dd, *J* = 5.0 and 3.0 Hz, 1H), 7.09 (br s, 1H), 6.85 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1 (C=O), 157.3 (CH), 152.2 (C), 150.4 (C), 139.5 (C), 139.1 (C), 136.9 (C), 134.4 (C), 133.7 (CH), 129.2 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 126.8 (CH), 125.9 (CH), 97.9 (C); IR (neat): 2963, 1652, 1590, 1540, 1514, 1493, 1431, 1310, 1285, 1229, 940, 782, 759, 695, 666; MS (ESI, m/z): 467.99 $[M+H]^+$; HRMS (ESI): calcd. for $C_{22}H_{15}INOS$: 467.9919 $[M+H]^+$, found: 467.9913.

4.4.5 1-(5-Iodo-2,4-diphenylpyridin-3-yl)ethanone (55aa)

4-Phenyl-4-((3-phenylprop-2-yn-1-yl)amino)but-3-en-2-one (**7aa**) (68.9 mg, 0.25 mmol), I_2 (190.4 mg, 0.75 mmol) and $NaHCO_3$ (63.0 mg, 0.75 mmol) were employed to afford 45.0 mg (47%) of the indicated product as a brownish yellow solid: mp 108.3-110.8 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.59-7.55 (m, 2H), 7.49-7.41 (m, 6H), 7.22-7.18 (m, 2H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1 (C=O), 157.0 (CH), 154.6 (C), 151.0 (C), 139.6 (C), 138.5 (C), 137.9 (C), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.9 (2 x CH), 128.6 (CH), 98.6 (C), 32.4 (CH_3); IR (neat): 3058, 2935, 1698, 1627, 1531, 1407, 1347, 1300, 1196, 1068, 765, 690, 637; MS (ESI, m/z): 400.02 $[M+H]^+$; HRMS (ESI): calcd. for $C_{19}H_{15}INO$: 400.0198 $[M+H]^+$, found: 400.0192.

4.4.6 (4-(3-Bromophenyl)-5-iodo-2-phenylpyridin-3-yl)(phenyl)methanone (55ab)

3-((3-(3-Bromophenyl)prop-2-yn-1-yl)amino)-1,3-diphenylprop-2-en-1-one (**7ab**) (104.1 mg, 0.25 mmol), I_2 (190.4 mg, 0.75 mmol) and $NaHCO_3$ (63.0 mg, 0.75 mmol) were employed to afford 77.0 mg (57%) of the indicated product as an orangish yellow solid: mp 133.5-134.9 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.47-7.42 (m, 2H), 7.39-7.27 (m, 5H), 7.20-6.87 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5 (C=O), 157.6 (CH), 156.1 (C), 150.9 (C), 141.1 (C), 138.3 (C), 137.1 (C), 135.2 (C), 133.7 (CH), 131.8 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 127.4 (CH), 122.3 (C), 98.0 (C); IR (neat): 3054, 2161, 1655, 1591, 1531, 1455, 1419, 1307, 1224, 1072, 1020, 936, 761, 689, 653; MS (ESI, m/z): 539.95 and 541.94 $[M+H]^+$; HRMS (ESI): calcd. for $C_{24}H_{16}{}^{79}BrINO$: 539.9460 $[M+H]^+$, found: 539.9452; calcd. for $C_{24}H_{16}{}^{81}BrINO$: 541.9439 $[M+H]^+$, found: 541.9434.

4.4.7 (5-Iodo-4-methyl-2-phenylpyridin-3-yl)(phenyl)methanone (55ac)

3-(But-2-yn-1-ylamino)-1,3-diphenylprop-2-en-1-one (**7ac**) (68.9 mg, 0.25 mmol), I_2 (190.4 mg, 0.75 mmol) and $NaHCO_3$ (63.0 mg, 0.75 mmol) were employed to afford 50.9 mg (51%) of the indicated product as a yellow solid: mp 137.2-140.0 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.63-7.58 (m, 2H), 7.49-7.41 (m, 3H), 7.31 (t, J = 7.8 Hz, 2H), 7.23-7.17 (m, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1 (C=O), 157.3 (CH), 155.7 (C), 147.9 (C), 138.6 (C), 136.6 (C), 135.4 (C), 134.0 (CH), 129.5 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 100.3 (C), 25.4 (CH_3); IR (neat): 3057, 3025, 1735, 1663, 1594, 1580, 1542, 1448, 1425, 1369, 1312, 1285, 1252, 1228, 1174, 1119, 1073, 934, 885, 796, 770, 749, 652, 607 cm^{-1}; MS (ESI, m/z): 400.02 $[M+H]^+$; HRMS (ESI): calcd. for $C_{19}H_{15}INO$: 400.0198 $[M+H]^+$, found: 400.0203.

4.5 General Procedure for the Synthesis of of *N*-Propargylic Thio-β-enaminones 58

To a stirred solution of the corresponding *N*-propargylic β-enaminone **32** or **7** (1.0 mmol) in absolute benzene (10.0 mL) was added Lawesson`s Reagent (LR) (0.5 mmol) and the resulting mixture was heated at 60 ^{o}C for approximately 0.5 h or stirred at room temperature (Note that the progress of the reaction was monitored by routine TLC for the disappearance of *N*-propargylic β-enaminone **32** or **7**). After the reaction was over, the solvent was removed on a rotary evaporator, and resulted mixture was directly purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding thionated β-enaminone **58** or **84**.

4.5.1 1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (58a)

1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32a**) (261.3 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (260.7 mg (94%) at 60 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.48 (br s, 1H), 7.74 (dd, *J* = 7.6, 1.7 Hz, 2H), 7.51 (s, 5H), 7.38-7.30 (m, 3H), 6.63 (s, 1H), 4.08 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.41 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2 (C=S), 167.2 (C), 148.8 (C), 135.0 (C), 130.5 (CH), 129.6 (CH), 129.1 (CH), 128.1 (CH), 127.7 (CH), 127.0 (CH), 113.4 (CH), 78.5 (C), 73.8 (CH), 34.6 (CH_2); IR (neat): 3275, 1581, 1556, 1528, 1481, 1444, 1373, 1340, 1320, 1263, 1201, 1125, 1063, 1025, 998, 962, 932, 827, 779, 758, 719, 702, 677, 648, 589, 538, 489 cm^{-1}; MS (ESI, m/z): 278.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{16}NS$: 278.0998 $[M+H]^+$, found: 278.1003.

4.5.2 3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (58b)

3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32b**)

(291.3 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (70.7 mg (23%) at 60 ^{o}C; 169.1 mg (55%) at rt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.47 (br s, 1H), 7.75 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.40-7.29 (m, 3H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.65 (s, 1H), 4.12 (dd, *J* = 6.0, 2.5 Hz, 2H), 3.86 (s, 3H), 2.42 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7 (C=S), 167.1 (C), 161.4 (C), 148.9 (C), 129.4 (CH), 128.0 (CH), 127.0 (C), 126.9 (CH), 114.4 (CH), 113.6 (CH), 78.6 (C), 73.6 (CH), 55.5 (OCH_3), 34.6 (CH_2). (Note that two CH peaks overlap on each other); IR (neat): 3277, 2837, 1604, 1584, 1558, 1495, 1459, 1373, 1334, 1307, 1291, 1245, 1175, 1128, 1074, 1021, 942, 810, 787, 760, 713, 692, 642, 549 cm^{-1}; MS (ESI, m/z): 308.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NOS$: 308.1104 $[M+H]^+$, found: 308.1093.

4.5.3 3-(2-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (58c)

3-(2-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32c**) (291.3 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (242.9 mg (79%) at rt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.67 (br s, 1H), 7.84-7.74 (m, 2H), 7.54-7.45 (m, 1H), 7.41-7.29 (m, 4H), 7.09 (td, *J* = 7.5, 0.7 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.61 (s, 1H), 4.19-3.91 (m, 2H), 3.88 (s, 3H), 2.37 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3 (C=S), 164.7 (C), 155.7 (C), 148.6 (C), 131.8 (CH), 129.2 (CH), 129.1 (CH), 127.8 (CH), 126.8 (CH), 123.5 (C), 121.0 (CH), 113.2 (CH), 111.0 (CH), 77.9 (C), 73.2 (CH), 55.5 (OCH_3), 34.1 (CH_2); IR (neat): 3277, 2909, 2126, 1586, 1566, 1525, 1485, 1447, 1433, 1373, 1333, 1318, 1250, 1205, 1164, 1140, 1105, 1059, 1022, 931, 916, 811, 757, 711, 684, 665, 648, 549, 493 cm^{-1}; MS (ESI, m/z): 308.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NOS$: 308.1104 $[M+H]^+$, found: 308.1111.

4.5.4 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-ene-1-thione (58d)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-en-1-one (**32d**) (275.3 mg,

1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (195.2 mg (67%) at 60 ^{o}C).^{1}H NMR (400 MHz, $CDCl_3$) δ 14.50 (br s, 1H), 7.79-7.74 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.28 (m, 5H), 6.65 (s, 1H), 4.10 (dd, *J* = 6.0, 2.5 Hz, 2H), 2.43 (s, 3H), 2.42 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2 (C=S), 167.3 (C), 148.7 (C), 140.8 (C), 131.9 (C), 129.6 (CH), 129.4 (CH), 127.9 (CH), 127.5 (CH), 126.8 (CH), 113.3 (CH), 78.5 (C), 73.6 (CH), 34.5 (CH_2), 21.4 (CH_3); IR (neat): 3285, 2916, 1580, 1555, 1485, 1444, 1373, 1333, 1259, 1179, 1124, 1019, 814, 759, 690, 496 cm^{-1}; MS (ESI, m/z): 292.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NS$: 292.1155 $[M+H]^+$, found: 292.1145.

4.5.5 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-ene-1-thione (58e)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-en-1-one (**32e**) (275.3 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (174.8 mg (60%) at 60 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.36 (br s, 1H), 7.69-7.59 (m, 2H), 7.35-7.14 (m, 7H), 6.51 (s, 1H), 3.95 (dd, *J* = 6.0, 2.5 Hz, 2H), 2.30 (s, 3H), 2.29 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5 (C=S), 167.3 (C), 148.7 (C), 138.9 (C), 134.8 (C), 131.1 (CH), 129.4 (CH), 128.8 (CH), 128.0 (CH), 127.9 (CH), 126.8 (CH), 124.5 (CH), 113.2 (CH), 78.5 (C), 73.6 (CH), 34.5 (CH_2), 21.4 (CH_3); IR (neat): 3285, 2922, 2169, 2113, 1935, 1591, 1562, 1523, 1478, 1444, 1375, 1333, 1261, 1166, 1066, 1029, 916, 790, 790, 759, 692 cm^{-1}; MS (ESI, m/z): 292.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NS$: 292.1155 $[M+H]^+$, found: 292.1145.

4.5.6 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-ene-1-thione (58f)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**32f**) (329.3 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (259.0 mg (75%) at 60 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.42 (br s, 1H), 7.84-7.72 (m, 4H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.41-7.31

(m, 3H), 6.59 (s, 1H), 4.02 (dd, J = 6.1, 2.5 Hz, 2H), 2.43 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1 (C=S), 165.1 (C), 148.5 (C), 138.4 (C), 132.3 (q, ^2J = 32.9 Hz, C) 129.9 (CH), 128.2 (CH), 128.1 (CH), 126.8 (CH), 126.0 (q, ^3J = 3.7 Hz, CH), 123.7 (q, ^1J = 272.6 Hz, CF_3), 112.7 (CH), 78.2 (C), 74.0 (CH), 34.5 (CH_2); IR (neat): 3289, 3057, 1584, 1561, 1534, 1502, 1487, 1446, 1408, 1319, 1263, 1164, 1109, 1065, 1015, 846, 762, 717, 690, 612 cm^{-1}; MS (ESI, m/z): 346.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}F_3NS$: 346.0872 $[M+H]^+$, found: 346.0861.

4.5.7 3-(3-Fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (58h)

3-(3-Fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32h**) (279.3 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (215.6 mg (73%) at 60 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.46 (br s, 1H), 7.85-7.74 (m, 2H), 7.55-7.48 (m, 1H), 7.42-7.30 (m, 4H), 7.29-7.21 (m, 2H), 6.63 (s, 1H), 4.08 (dd, J = 6.1, 2.5 Hz, 2H), 2.46 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2 (C=S), 165.2 (C), 162.5 (d, ^1J = 249.1 Hz, CF), 148.5 (C), 136.7 (d, ^3J = 7.6 Hz, C), 130.8 (d, ^3J = 8.2 Hz, CH), 129.7 (CH), 128.0 (CH), 126.8 (CH), 123.4 (d, ^4J = 3.2 Hz, CH), 117.4 (d, ^2J = 20.8 Hz, CH), 114.8 (d, ^2J = 23.1 Hz, CH), 112.7 (CH), 78.2 (C), 73.8 (CH), 34.4 (CH_2); IR (neat): 3289, 3057, 1563, 1525, 1475, 1442, 1374, 1334, 1261, 1183, 1113, 1073, 1000, 878, 789, 759, 728, 688, 521 cm^{-1}; MS (ESI, m/z): 296.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}FNS$: 296.0904 $[M+H]^+$, found: 296.0898.

4.5.8 3-(2-Bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (58i)

3-(2-Bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32i**) (340.2 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (253.0 mg (71%) at 60 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ

14.50 (br s, 1H), 7.79-7.74 (m, 2H), 7.71-7.66 (m, 1H), 7.47-7.41 (m, 1H), 7.40-7.29 (m, 5H), 6.52 (s, 1H), 4.06 (ddd, *J* = 17.8, 4.9, 2.6 Hz, 1H), 3.86 (ddd, *J* = 17.8, 6.6, 2.6 Hz, 1H), 2.36 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2 (C=S), 164.7 (C), 148.3 (C), 135.7 (C), 133.2 (CH), 131.3 (CH), 129.6 (CH), 129.2 (CH), 127.92 (CH), 127.88 (CH), 126.8 (CH), 121.0 (CBr), 112.3 (CH), 77.6 (C), 73.7 (CH), 34.0 (CH_2); IR (neat): 3286, 1556, 1524, 1461, 1428, 1373, 1332, 1258, 1201, 1131, 1068, 1023, 924, 820, 759, 713, 682, 644, 546 cm^{-1}; MS (ESI, m/z): 356.01 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}{}^{79}BrNS$: 356.0103 $[M+H]^+$, found: 356.0058.

4.5.9 3-(4-(*tert*-Butyl)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (58j)

3-(4-(*tert*-Butyl)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32j**) (317.4 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (256.8 mg (77%) at 60 ^oC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.48 (br s, 1H), 7.74 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.37-7.28 (m, 3H), 6.65 (s, 1H), 4.12 (dd, *J* = 6.0, 2.5 Hz, 2H), 2.42 (t, *J* = 2.5 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5 (C=S), 167.4 (C), 154.1 (C), 149.0 (C), 132.1 (C), 129.5 (CH), 128.1 (CH), 127.6 (CH), 127.0 (CH), 126.0 (CH), 113.6 (CH), 78.7 (C), 73.7 (CH), 35.1 (C), 34.7 (CH_2), 31.3 (CH_3); IR (neat): 3285, 2959, 1733, 1578, 1548, 1496, 1444, 1364, 1334, 1264, 1203, 1133, 1103, 1073, 1016, 940, 841, 763, 731, 692, 601, 555 cm^{-1}; MS (ESI, m/z): 334.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{24}NS$: 334.1624 $[M+H]^+$, found: 334.1635.

4.5.10 1-Phenyl-3-(prop-2-yn-1-ylamino)hept-2-ene-1-thione (58l)

1-Phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (**32l**) (241.3 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (223.9 mg (87%) at 60 ^oC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.49 (br s, 1H), 7.81-

7.69 (m, 2H), 7.44-7.28 (m, 3H), 6.60 (s, 1H), 4.19 (dd, *J* = 5.7, 2.5 Hz, 2H), 2.55-2.36 (m, 2H), 2.44 (t, *J* = 2.5 Hz, 1H), 1.72-1.58 (m, 2H), 1.46 (sextet, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6 (C=S), 170.3 (C), 148.5 (C), 129.0 (CH), 127.7 (CH), 126.6 (CH), 111.8 (CH), 77.4 (C), 73.5 (CH), 33.1 (CH_2), 32.3 (CH_2), 29.8 (CH_2), 22.4 (CH_2), 13.6 (CH_3); IR (neat): 3204, 2951, 2866, 2123, 1580, 1528, 1459, 1386, 1338, 1317, 1299, 1249, 1194, 1090, 1030, 994, 969, 944, 918, 866, 823, 786, 759, 726, 684, 624, 555, 515 cm^{-1}; MS (ESI, m/z): 258.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{20}NS$: 258.1311 $[M+H]^+$, found: 258.1314.

4.5.11 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-ene-1-thione (58m)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**32m**) (267.3 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (232.4 mg (82%) at 60 ^oC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.49 (br s, 1H), 7.82-7.70 (m, 3H), 7.47 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.40-7.29 (m, 4H), 6.73 (s, 1H), 4.18 (dd, *J* = 6.2, 2.5 Hz, 2H), 2.45 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6 (C=S), 161.9 (C), 148.9 (C), 135.7 (C), 129.6 (CH), 128.1 (CH), 127.32 (CH), 127.30 (CH) 127.2 (CH), 126.9 (CH), 113.1 (CH), 78.8 (C), 73.9 (CH), 34.6 (CH_2); IR (neat): 3285, 3080, 2916, 1730, 1591, 1567, 1488, 1444, 1410, 1371, 1310, 1238, 1176, 1073, 1044, 865, 792, 758, 691 cm^{-1}; MS (ESI, m/z): 284.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{14}NS_2$: 284.0562 $[M+H]^+$, found: 284.0570.

4.5.12 1-(2-Bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (58n)

1-(2-Bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32n**) (340.2 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (110.4 mg (31%) at rt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.31

(br s, 1H), 7.59-7.47 (m, 6H), 7.41 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.33-7.27 (m, 1H), 7.12 (td, *J* = 7.7, 1.7 Hz, 1H), 6.39 (s, 1H), 4.14 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.46 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6 (C=S), 166.7 (C), 150.5 (C), 134.4 (C), 132.8 (CH), 130.7 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 127.7 (CH), 127.2 (CH), 118.1 (CBr), 116.5 (CH), 78.2 (C), 74.0 (CH), 34.7 (CH_2); IR (neat): 3285, 3056, 1585, 1560, 1526, 1484, 1462, 1429, 1377, 1334, 1249, 1205, 1128, 1062, 1023, 940, 753, 732, 696 cm^{-1}; MS (ESI, m/z): 356.01 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}{}^{79}BrNS$: 356.0103 $[M+H]^+$, found: 356.0099.

4.5.13 1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-ene-1-thione (58r)

1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-en-1-one (**32r**) (354.2 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (92.6 mg (25%) at 60 ^{o}C; 185.2 mg (50%) at rt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.30 (br s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.43-7.37 (m, 2H), 7.36-7.27 (m, 4H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.39 (s, 1H), 4.20-4.07 (m, 2H), 2.49-2.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2 (C=S), 167.1 (C), 150.5 (C), 139.0 (C), 134.3 (C), 132.8 (CH), 131.5 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.2 (CH), 127.3 (CH), 124.8 (CH), 118.1 (CBr), 116.5 (CH), 78.3 (C), 73.9 (CH), 34.8 (CH_2), 21.5 (CH_3); IR (neat): 3278, 2920, 2165, 2044, 1563, 1527, 1481, 1462, 1428, 1377, 1333, 1262, 1173, 1116, 1067, 1049, 1025, 790, 757, 702 cm^{-1}; MS (ESI, m/z): 370.02 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}{}^{79}BrNS$: 370.0260 $[M+H]^+$, found: 370.0243.

4.5.14 1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-ene-1-thione (58s)

1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**32s**) (408.2 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (203.7 mg (48%) at rt). ^{1}H NMR (400

MHz, $CDCl_3$) δ 14.13 (br s, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.43 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.28 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.22-7.15 (m, 1H), 7.05-6.99 (m, 1H), 6.23 (s, 1H), 3.96 (dd, *J* = 6.2, 2.5 Hz, 2H), 2.36 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9 (C=S), 164.6 (C), 150.3 (C), 137.9 (C), 132.9 (CH), 132.5 (q, ^2J = 33.0 Hz, C), 129.1 (CH), 128.2 (CH), 127.3 (CH), 126.1 (q, ^3J = 3.7 Hz, CH), 123.6 (q, ^1J = 272.5 Hz, CF_3), 117.9 (CBr), 116.1 (CH), 78.0 (C), 74.3 (CH), 34.7 (CH_2). (Note that two CH peaks overlap on each other); IR (neat): 3298, 2919, 1733, 1616, 1563, 1536, 1464, 1431, 1409, 1320, 1240, 1164, 1110, 1065, 1014, 943, 835, 759, 727, 597 cm^{-1}; MS (ESI, m/z): 424.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{14}{}^{79}BrF_3NS$: 423.9977 $[M+H]^+$, found: 423.9981.

4.5.15 1-(2-Bromophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (58t)

1-(2-Bromophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32t**) (358.2 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (153.5 mg (41%) at rt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.25 (br s, 1H), 7.55 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.49 (td, *J* = 8.0, 5.7 Hz, 1H), 7.39 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.36-7.30 (m, 2H), 7.29-7.19 (m, 2H), 7.13 (ddd, *J* = 9.2, 7.7, 1.7 Hz, 1H), 6.36 (s, 1H), 4.12 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.48 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0 (C=S), 164.8 (C), 162.6 (d, ^1J = 249.2 Hz, CF), 150.3 (C), 136.2 (d, ^3J = 7.9 Hz, C), 132.8 (CH), 130.9 (d, ^3J = 8.2 Hz, CH), 129.01 (CH), 128.95 (CH), 127.3 (CH), 123.5 (d, ^4J = 3.0 Hz, CH), 117.9 (CBr), 117.7 (d, ^2J = 20.8 Hz, CH), 116.0 (CH), 114.9 (d, ^2J = 23.2 Hz, CH), 78.0 (C), 74.2 (CH), 34.7 (CH_2); IR (neat): 3285, 2349, 2164, 1563, 1526, 1477, 1462, 1431, 1376, 1334, 1252, 1186, 1111, 1024, 877, 789, 756, 671, 521 cm^{-1}; MS (ESI, m/z): 374.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{79}BrFNS$: 374.0009 $[M+H]^+$, found: 373.9991.

4.5.16 1-(4-Methoxyphenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (58v)

1-(4-Methoxyphenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32v**) (291.3 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (215.2 mg (70%) at 60 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.39 (br t, *J* = 5.3 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.49 (s, 5H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.60 (s, 1H), 4.05 (dd, *J* = 6.0, 2.5 Hz, 2H), 3.80 (s, 3H), 2.40 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5 (C=S), 166.7 (C), 161.2 (C), 141.1 (C), 135.0 (C), 130.3 (CH), 128.9 (CH), 128.6 (CH), 127.5 (CH), 113.1 (CH), 112.0 (CH), 78.5 (C), 73.5 (CH), 55.3 (OCH_3), 34.4 (CH_2); IR (neat): 3283, 2930, 2835, 1732, 1599, 1560, 1503, 1460, 1441, 1373, 1333, 1300, 1245, 1170, 1125, 1109, 1062, 1026, 827, 766, 694, 510 cm^{-1}; MS (ESI, m/z): 308.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NOS$: 308.1104 $[M+H]^+$, found: 308.1118.

4.5.17 3-Phenyl-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-ene-1-thione (58w)

3-Phenyl-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (**32w**) (275.3 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (247.7 mg (85%) at 60 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.47 (br s, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.51 (s, 5H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.64 (s, 1H), 4.07 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.41 (t, *J* = 2.5 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8 (C=S), 166.9 (C), 146.0 (C), 139.9 (C), 135.0 (C), 130.3 (CH), 129.0 (CH), 128.7 (CH), 127.6 (CH), 126.9 (CH), 112.8 (CH), 78.5 (C), 73.6 (CH), 34.5 (CH_2), 21.3 (CH_3); IR (neat): 3284, 3024, 2917, 1732, 1585, 1560, 1526, 1504, 1483, 1444, 1372, 1334, 1259, 1216, 1179, 1125, 1110, 1043, 1001, 940, 810, 766, 694, 639, 491 cm^{-1}; MS (ESI, m/z): 292.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NS$: 292.1155 $[M+H]^+$, found: 292.1168.

4.5.18 3-(Prop-2-yn-1-ylamino)-3-(thiophen-3-yl)-1-(*p*-tolyl)prop-2-ene-1-thione (58x)

3-(Prop-2-yn-1-ylamino)-3-(thiophen-3-yl)-1-(*p*-tolyl)prop-2-en-1-one (**32x**) (281.4 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (178.5 mg (60%) at 60 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.47 (br s, 1H), 7.73 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.70-7.65 (m, 2H), 7.47 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.32 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.73 (s, 1H), 4.16 (dd, *J* = 6.2, 2.5 Hz, 2H), 2.45 (t, *J* = 2.5 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2 (C=S), 161.7 (C), 146.0 (C), 139.9 (C), 135.7 (C), 128.7 (CH), 127.22 (CH), 127.17 (CH), 127.14 (CH), 126.9 (CH), 112.6 (CH), 78.8 (C), 73.8 (CH), 34.5 (CH_2), 21.3 (CH_3); IR (neat): 3282, 2915, 1730, 1569, 1537, 1493, 1405, 1370, 1332, 1257, 1216, 1178, 1110, 1082, 1062, 1018, 945, 921, 868, 786, 639 cm^{-1}; MS (ESI, m/z): 298.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{16}NS_2$: 298.0719 $[M+H]^+$, found: 298.0718.

4.5.19 1-(4-Chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (58y)

1-(4-Chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-e-1-one (**32y**) (295.8 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (230.8 mg (74%) at 60 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.50 (br s, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.60-7.48 (m, 5H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.61 (s, 1H), 4.11 (dd, *J* = 6.0, 2.4 Hz, 2H), 2.45 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5 (C=S), 167.3 (C), 146.8 (C), 135.6 (C), 134.6 (C), 130.6 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 127.5 (CH), 113.0 (CH), 78.2 (C), 73.8 (CH), 34.6 (CH_2); IR (neat): 3260, 1587, 1561, 1523, 1478, 1441, 1396, 1368, 1327, 1259, 1198, 1129, 1090, 1010, 937, 830, 804, 768, 736, 702, 658, 545, 510 cm^{-1}; MS (ESI, m/z): 312.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}ClNS$: 312.0608 $[M+H]^+$, found: 312.0607.

4.5.20 1-(4-Chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (58z)

1-(4-Chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32z**) (313.8 mg, 1.00 mmol) and LR (202.2 mg, 0.50 mmol) were employed to afford the indicated product (267.2 mg (81%) at 60 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.43 (br s, 1H), 7.72-7.68 (m, 2H), 7.56-7.46 (m, 1H), 7.35-7.29 (m, 3H), 7.28-7.22 (m, 2H), 6.57 (s, 1H), 4.08 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.46 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9 (C=S), 165.6 (C), 162.6 (d, ^{1}J = 249.3 Hz, CF), 146.7 (C), 136.6 (d, ^{3}J = 7.6 Hz, C), 135.8 (C), 131.0 (d, ^{3}J = 8.3 Hz, CH), 128.2 (CH), 128.1 (CH), 123.4 (d, ^{4}J = 3.1 Hz, CH), 117.6 (d, ^{2}J = 21.0 Hz, CH), 114.9 (d, ^{2}J = 23.0 Hz, CH), 112.5 (CH), 78.1 (C), 74.0 (CH), 34.5 (CH_2); IR (neat): 3247, 3065, 2923, 1566, 1525, 1476, 1434, 1398, 1372, 1330, 1257, 1183, 1156, 1090, 1011, 881, 784, 743, 668, 521 cm^{-1}; MS (ESI, m/z): 330.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClFNS$: 330.0514 $[M+H]^+$, found: 330.0518.

4.5.21 1,3-Diphenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-ene-1-thione (84)

N-Propargylic β-enaminone **7a** (500.0 mg, 1.48 mmol) and Lawesson`s Reagent (LR) (299.3 mg, 0.74 mmol) were employed to afford the indicated product (418.5 mg (80%) at 60 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.63 (br s, 1H), 7.87-7.77 (m, 2H), 7.60-7.52 (m, 5H), 7.50-7.44 (m, 2H), 7.44-7.30 (m, 6H), 6.70 (s, 1H), 4.32 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3 (C=S), 167.0 (C), 148.7 (C), 134.9 (C), 131.7 (CH), 130.3 (CH), 129.4 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 127.9 (CH), 127.5 (CH), 126.8 (CH), 122.1 (C), 113.3 (CH), 85.1 (C), 83.7 (C), 35.4 (CH_2); IR (neat): 3054, 1583, 1557, 1524, 1480, 1442, 1375, 1334, 1261, 1204, 1123, 1061, 999, 937, 842, 753, 721, 688 cm^{-1}; MS (ESI, m/z): 354.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{20}NS$: 354.1311 $[M+H]^+$, found: 354.1370.

4.6 General Procedure for the Synthesis of 5-Alkynylpyridines 57

In a two-neck round-bottom flask equipped with a reflux condenser, 5-iodopyridine derivative **55** (0.20 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol) and CuI (0.01 mmol) were dissolved in a mixture of triethylamine (3.0 mL) and DMF (1.5 mL) by vigorous stirring under argon. Meanwhile, separately in a flask under argon, the corresponding terminal alkyne **56** (0.30 mmol) was dissolved in DMF (1.5 mL) and added slowly to the first reaction flask over 20 min. Then the resulting reaction mixture was heated at 65 ^oC with stirring under argon. After the reaction was over, as indicated by the routine TLC analysis, the reaction mixture was transferred into a separatory funnel, and ethyl acetate (30 mL) and a saturated aqueous solution of NH_4Cl (20 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator. The resulting crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as eluent to afford the corresponding 5-alkynylpyridine **57**.

4.6.1 (2,4-Diphenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl)methanone (57a)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and phenylacetylene (**56a**) (30.6 mg, 0.30 mmol) were employed to afford 79.3 mg (91%) of the indicated product as a yellow solid (R_f = 0.53 in 4:1 hexane/ethyl acetate): mp 151.8–153.5 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.60-7.52 (m, 4H), 7.41-7.36 (m, 1H), 7.35-7.21 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4 (C=O), 155.4 (C), 152.5 (CH), 150.4 (C), 139.1 (C), 137.6 (C), 135.9 (C), 133.8 (C), 133.3 (CH), 131.6 (CH), 129.6 (CH), 129.4 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.5 (CH), 128.42 (CH), 128.38 (2 x CH), 127.9 (CH), 122.6 (C), 119.0 (C), 96.6 (C), 85.5 (C); IR (neat): 3056, 3025, 2960, 2922, 2214, 1669, 1593, 1578, 1553, 1516, 1489, 1434, 1377, 1323, 1286, 1259, 1221, 1176, 1095, 1071, 1016, 1003, 921, 873, 801, 770, 701, 686, 670, 640, 529, 514 cm^{-1}; MS (ESI, m/z):

436.17 $[M+H]^+$; HRMS (ESI): calcd. for $C_{32}H_{22}NO$: 436.1695 $[M+H]^+$, found: 436.1692.

4.6.2 (5-((4-Methoxyphenyl)ethynyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (57b)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 4-ethynylanisole (**56b**) (39.6 mg, 0.30 mmol) were employed to afford 53.1 mg (57%) of the indicated product as a yellow solid (R_f = 0.37 in 4:1 hexane/ethyl acetate): mp 181.5–184.3 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.49-7.41 (m, 4H), 7.27 (tt, J = 7.4 and 1.2 Hz, 1H), 7.23-7.09 (m, 10H), 7.10-7.05 (m, 2H), 6.74-6.69 (m, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5 (C=O), 160.2 (CO), 155.1 (C), 152.3 (CH), 150.1 (C), 139.2 (C), 137.6 (C), 136.1 (C), 133.8 (C), 133.3 (CH), 133.2 (CH), 129.6 (CH), 129.4 (CH), 129.3 (CH), 128.9 (CH), 128.5 (CH), 128.4 (2 x CH), 127.9 (CH), 119.4 (C), 114.7 (C), 114.1 (CH), 96.9 (C), 84.4 (C), 55.4 (CH_3); IR (neat): 3054, 3025, 2962, 2936, 2217, 1671, 1602, 1509, 1441, 1292, 1254, 1227, 1174, 1162, 1030, 992, 877, 833, 807, 768, 757, 697, 672, 534, 509 cm^{-1}; MS (ESI, m/z): 466.18 $[M+H]^+$; HRMS (ESI): calcd. for $C_{33}H_{24}NO_2$: 466.1802 $[M+H]^+$, found: 466.1802.

4.6.3 (2,4-Diphenyl-5-(*p*-tolylethynyl)pyridin-3-yl)(phenyl)methanone (57d)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 4-ethynyltoluene (**56d**) (34.8 mg, 0.30 mmol) were employed to afford 88.1 mg (98%) of the indicated product as a yellow solid (R_f = 0.57 in 4:1 hexane/ethyl acetate): mp 170.3–174.5 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.48-7.41 (m, 4H), 7.27 (t, J = 7.4 Hz, 1H), 7.22-7.09 (m, 10H), 7.05 (d, 8.4 Hz, 2H), 6.99 (d, 8.0 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5 (C=O), 155.3 (C), 152.5 (CH), 150.2 (C), 139.2 (C), 139.1 (C), 137.6 (C), 136.0 (C), 133.8 (C), 133.3 (CH),

131.5 (CH), 129.6 (CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.9 (CH), 128.5 (CH), 128.4 (2 x CH), 127.9 (CH), 119.6 (C), 119.2 (C), 96.9 (C), 84.9 (C), 21.6 (CH_3); IR (neat): 3053, 3025, 2215, 2197, 1671, 1597, 1579, 1553, 1508, 1438, 1315, 1262, 1226, 1175, 1161, 1074, 993, 875, 813, 767, 756, 696, 671, 655, 638, 577, 529, 507 cm^{-1}; MS (ESI, m/z): 450.18 $[M+H]^+$; HRMS (ESI): calcd. for $C_{33}H_{24}NO$: 450.1852 $[M+H]^+$, found: 450.1847.

4.6.4 (2,4-Diphenyl-5-(*m*-tolylethynyl)pyridin-3-yl)(phenyl)methanone (57e)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 3-ethynyltoluene (**56e**) (34.8 mg, 0.30 mmol) were employed to afford 85.4 mg (95%) of the indicated product as an orange solid (R_f = 0.47 in 4:1 hexane/ethyl acetate): mp 126.4–129.5 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.59-7.54 (m, 4H), 7.39 (tt, *J* = 7.4 and 1.2 Hz, 1H), 7.34-7.20 (m, 10H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 7.05 (d, *J* = 7.2 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5 (C=O), 155.4 (C), 152.6 (CH), 150.3 (C), 139.1 (C), 138.1 (C), 137.6 (C), 135.9 (C), 133.8 (C), 133.4 (CH), 132.2 (CH), 129.8 (CH), 129.6 (CH), 129.5 (CH), 129.4 (CH), 129.2 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 122.4 (C), 119.1 (C), 96.9 (C), 85.2 (C), 21.3 (CH_3); IR (neat): 3058, 3024, 2208, 1734, 1669, 1593, 1578, 1552, 1515, 1483, 1447, 1438, 1375, 1324, 1314, 1284, 1260, 1232, 1205, 1175, 1000, 910, 849, 784, 770, 758, 699, 670, 640, 593, 517 cm^{-1}; MS (ESI, m/z): 450.19 $[M+H]^+$; HRMS (ESI): calcd. for $C_{33}H_{24}NO$: 450.1852 $[M+H]^+$, found: 450.1862.

4.6.5 (2,4-Diphenyl-5-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (57f)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 4-ethynyl-α,α,α-trifluorotoluene (**56f**) (51.0 mg, 0.30 mmol) were employed to afford 92.6 mg (92

%) of the indicated product as a red solid (R_f = 0.43 in 4:1 hexane/ethyl acetate): mp 158.1–159.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.61-7.52 (m, 6H), 7.39 (tt, J = 7.4 and 1.2 Hz, 1H), 7.35-7.27 (m, 10H), 7.24 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3 (C=O), 156.0 (C), 152.6 (CH), 150.9 (C), 139.0 (C), 137.5 (C), 135.8 (C), 133.9 (C), 133.5 (CH), 131.8 (CH), 130.5 (q, ^2J = 32.0 Hz, C), 129.5 (CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.7 (CH), 128.47 (CH), 128.45 (CH), 128.0 (CH), 126.4 (C), 125.4 (q, ^3J = 3.8 Hz, CH), 123.9 (q, ^1J = 271.2 Hz, CF_3), 118.4 (C), 95.0 (C), 87.8 (C); IR (neat): 3056, 3027, 2325, 1668, 1613, 1596, 1579, 1515, 1495, 1437, 1404, 1377, 1329, 1287, 1223, 1165, 1121, 1105, 1064, 1015, 1002, 921, 875, 840, 767, 755, 715, 696, 672, 596, 576, 523 cm^{-1}; MS (ESI, m/z): 504.16 $[M+H]^+$; HRMS (ESI): calcd. for $C_{33}H_{21}F_3NO$: 504.1570 $[M+H]^+$, found: 504.1564.

4.6.6 (5-((4-(Dimethylamino)phenyl)ethynyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (57g)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 4-ethynyl-*N*,*N*-dimethylaniline (**56g**) (43.6 mg, 0.30 mmol) were employed to afford 68.9 mg (72%) of the indicated product as a yellow solid (R_f = 0.33 in 4:1 hexane/ethyl acetate): mp 178.5–181.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.48-7.42 (m, 4H), 7.26 (t, J = 7.4 Hz, 1H), 7.22-7.09 (m, 10H), 7.00 (d, J = 9.2 Hz, 2H), 6.47 (d, J = 8.9 Hz, 2H), 2.86 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7 (C=O), 154.5 (C), 152.1 (CH), 150.5 (C), 149.5 (C), 139.3 (C), 137.7 (C), 136.2 (C), 133.7 (C), 133.2 (CH), 132.8 (2 x CH), 129.7 (CH), 129.4 (CH), 129.2 (CH), 128.8 (CH), 128.3 (2 x CH), 127.8 (CH), 119.9 (C), 111.8 (CH), 109.2 (C), 98.5 (C), 83.8 (C), 40.2 (CH_3); IR (neat): 2914, 2853, 2802, 2187, 1669, 1579, 1549, 1522, 1491, 1442, 1370, 1332, 1315, 1287, 1262, 1228, 1200, 1155, 1129, 1072, 1030, 1011, 991, 945, 873, 810, 766, 755, 694, 649, 636, 578, 525, 514 cm^{-1}; MS (ESI, m/z): 479.21 $[M+H]^+$; HRMS (ESI): calcd. for $C_{34}H_{27}N_2O$: 479.2118 $[M+H]^+$, found: 479.2133.

4.6.7 (5-((3-Fluorophenyl)ethynyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (57h)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 1-ethynyl-3-fluorobenzene (**56h**) (36.0 mg, 0.30 mmol) were employed to afford 86.2 mg (95%) of the indicated product as a yellow solid (R_f = 0.43 in 4:1 hexane/ethyl acetate): mp 132.1–135.6 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.62-7.53 (m, 4H), 7.39 (tt, J = 7.4 and 1.2 Hz, 1H), 7.34-7.21 (m, 11H), 7.06-6.99 (m, 2H), 6.92 (ddd, J = 9.3, 2.4 and 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3 (C=O), 162.4 (d, ^1J = 245.6 Hz, CF), 155.8 (C), 152.6 (CH), 150.6 (C), 139.0 (C), 137.5 (C), 135.8 (C), 133.9 (C), 133.4 (CH), 130.0 (d, ^3J = 8.4 Hz, CH), 129.5 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 128.4 (2 x CH), 128.0 (CH), 127.5 (d, ^4J = 2.9 Hz, CH), 124.4 (d, ^3J = 9.4 Hz, C), 118.5 (C), 118.3 (d, ^2J = 22.7 Hz, CH), 116.2 (d, ^2J = 21.4 Hz, CH), 95.2 (d, ^4J = 3.5 Hz, C), 86.4 (C); IR (neat): 3061, 3027, 2213, 1670, 1605, 1593, 1577, 1553, 1486, 1448, 1427, 1315, 1260, 1232, 1206, 1176, 1134, 1005, 932, 873, 854, 786, 770, 757, 741, 699, 680, 661, 592, 517 cm^{-1}. MS (ESI, m/z): 454.16 $[M+H]^+$; HRMS (ESI): calcd. for $C_{32}H_{21}FNO$: 454.1602 $[M+H]^+$, found: 454.1619.

4.6.8 2-(4-(5-Benzoyl-4,6-diphenylpyridin-3-yl)but-3-yn-1-yl)isoindoline-1,3-dione (57k)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and *N*-(3-butynyl)phthalimide (**56k**) (59.8 mg, 0.30 mmol) were employed to afford 70.3 mg (66%) of the indicated product as a yellowish brown solid (R_f = 0.10 in 4:1 hexane/ethyl acetate): mp 340.0 ^oC (decomp.). ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.83-7.74 (m, 2H), 7.70-7.63 (m, 2H), 7.45-7.35 (m, 4H), 7.27 (t, J = 7.4 Hz, 1H), 7.20-7.00 (m, 10H), 3.70 (t, J = 7.0 Hz, 2H), 2.60 (t, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5 (C=O), 168.0 (C=O), 155.2 (C), 153.2 (CH),

150.3 (C), 139.1 (C), 137.6 (C), 135.8 (C), 134.2 (CH), 133.7 (C), 133.3 (C), 132.1 (CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.9 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 127.8 (CH), 123.5 (CH), 118.8 (C), 93.3 (C), 78.2 (C), 36.5 (CH_2), 19.6 (CH_2); IR (neat): 3057, 2924, 2853, 2232, 1772, 1708, 1668, 1595, 1580, 1555, 1521, 1495, 1436, 1393, 1361, 1303, 1241, 1214, 1188, 1158, 1112, 1074, 1044, 998, 961, 939, 892, 867, 735, 717, 695, 625, 582, 529 cm^{-1}; MS (ESI, m/z): 533.19 $[M+H]^+$; HRMS (ESI): calcd. for $C_{36}H_{25}N_2O_3$: 533.1860 $[M+H]^+$, found: 533.1856.

4.6.9 (5-(Hex-1-yn-1-yl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (57l)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 1-hexyne (**56l**) (24.6 mg, 0.30 mmol) were employed to afford 66.5 mg (80%) of the indicated product as a light yellow solid (R_f = 0.52 in 4:1 hexane/ethyl acetate): mp 107.5–109.1 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.55-7.49 (m, 4H), 7.39-7.34 (m, 1H), 7.27-7.18 (m, 10H), 2.28 (t, J = 6.9 Hz, 2H), 1.37 (quintet, J = 7.2 Hz, 2H), 1.21 (sextet, J = 7.2 Hz, 2H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6 (C=O), 154.7 (C), 152.9 (CH), 150.2 (C), 139.2 (C), 137.7 (C), 136.1 (C), 133.7 (C), 133.3 (CH), 129.4 (2 x CH), 129.2 (CH), 128.8 (CH), 128.3 (CH), 128.3 (CH), 128.3 (CH), 127.8 (CH), 119.6 (C), 98.2 (C), 76.5 (C), 30.3 (CH_2), 21.7 (CH_2), 19.3 (CH_2), 13.7 (CH_3); IR (neat): 3053, 2955, 2926, 2855, 2224, 1668, 1635, 1593, 1579, 1555, 1519, 1495, 1449, 1435, 1378, 1318, 1291, 1260, 1214, 1175, 1077, 1025, 1000, 934, 926, 846, 799, 768, 754, 701, 689, 664, 587, 517 cm^{-1}; MS (ESI, m/z): 416.20 $[M+H]^+$; HRMS (ESI): calcd. for $C_{30}H_{26}NO$: 416.2009 $[M+H]^+$, found: 416.202.

4.6.10 (2,4-Diphenyl-5-(thiophen-3-ylethynyl)pyridin-3-yl)(phenyl)methanone (57m)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol),

$PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 3-ethynylthiophene (**56m**) (32.4 mg, 0.30 mmol) were employed to afford 86.5 mg (98%) of the indicated product as a light yellow solid (R_f = 0.50 in 4:1 hexane/ethyl acetate): mp 147.5–149.2 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.48-7.42 (m, 4H), 7.31-7.25 (m, 1H), 7.22-7.11 (m, 12H), 6.83 (dd, J = 5.0 and 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4 (C=O), 155.3 (C), 152.4 (CH), 150.2 (C), 139.1 (C), 137.5 (C), 135.9 (C), 133.8 (C), 133.3 (CH), 129.6 (CH), 129.5 (CH), 129.4 (CH), 129.4 (CH), 129.2 (CH), 128.9 (CH), 128.5 (CH), 128.4 (2 x CH), 127.9 (CH), 125.6 (CH), 121.7 (C), 119.0 (C), 91.9 (C), 85.1 (C); IR (neat): 3093, 3061, 2209, 1668, 1593, 1578, 1555, 1514, 1493, 1448, 1437, 1375, 1361, 1316, 1285, 1259, 1224, 1210, 1176, 1080, 1004, 931, 856, 796, 769, 757, 694, 684, 630, 594, 511 cm^{-1}. MS (ESI, m/z): 442.13 $[M+H]^+$; HRMS (ESI): calcd. for $C_{30}H_{20}NOS$: 442.1260 $[M+H]^+$, found: 442.1262.

4.6.11 (5-(Hept-1-yn-1-yl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (57n)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 1-heptyne (**56n**) (28.9 mg, 0.30 mmol) were employed to afford 68.7 mg (80%) of the indicated product as a yellow solid (R_f = 0.63 in 4:1 hexane/ethyl acetate): mp 117.1–120.4 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.46-7.39 (m, 4H), 7.27 (t, J = 7.4 Hz, 1H), 7.18-7.08 (m, 10H), 2.17 (t, J = 6.9 Hz, 2H), 1.30 (quintet, J = 7.2 Hz, 2H), 1.20-1.06 (m, 4H), 0.76 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6 (C=O), 154.8 (C), 153.0 (CH), 150.2 (C), 139.2 (C), 137.7 (C), 136.1 (C), 133.7 (C), 133.3 (CH), 129.4 (2 x CH), 129.2 (CH), 128.8 (CH), 128.4 (CH), 128.3 (2 x CH), 127.8 (CH), 119.7 (C), 98.3 (C), 76.6 (C), 30.9 (CH_2), 28.0 (CH_2), 22.3 (CH_2), 19.6 (CH_2), 14.0 (CH_3); IR (neat): 2952, 2923, 2855, 2223, 1667, 1593, 1578, 1554, 1519, 1495, 1448, 1434, 1377, 1317, 1290, 1260, 1213, 1175, 1076, 1042, 1024, 1000, 934, 799, 769, 753, 716, 688, 664, 612, 586, 511 cm^{-1}; MS

(ESI, m/z): 430.22 $[M+H]^+$; HRMS (ESI): calcd. for $C_{31}H_{28}NO$: 430.2165 $[M+H]^+$, found: 430.2163.

4.6.12 (5-(3-Cyclopentylprop-1-yn-1-yl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (57o)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 3-cyclopentyl-1-propyne (**56o**) (32.5 mg, 0.30 mmol) were employed to afford 76.8 mg (87%) of the indicated product as an orange solid (R_f = 0.63 in 4:1 hexane/ethyl acetate): mp 132.8–135.3 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.46-7.38 (m, 4H), 7.28-7.23 (m, 1H), 7.19-7.07 (m, 10H), 2.19 (d, J = 6.6 Hz, 2H), 1.86-1.74 (m, 1H), 1.54-1.34 (m, 6H), 1.03-0.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6 (C=O), 154.7 (C), 153.0 (CH), 150.2 (C), 139.2 (C), 137.6 (C), 136.1 (C), 133.7 (C), 133.2 (CH), 129.4 (CH), 129.4 (CH), 129.2 (CH), 128.8 (CH), 128.32 (CH), 128.30 (CH), 128.2 (CH), 127.8 (CH), 119.7 (C), 97.7 (C), 76.6 (C), 38.8 (CH), 31.8 (CH_2), 25.3 (CH_2), 25.2 (CH_2); IR (neat): 3063, 3026, 2947, 2861, 2218, 1668, 1593, 1578, 1550, 1518, 1493, 1448, 1432, 1375, 1317, 1292, 1259, 1212, 1176, 1095, 1077, 1040, 1024, 1000, 928, 843, 800, 769, 755, 718, 688, 642, 584, 515 cm^{-1}; MS (ESI, m/z): 442.22 $[M+H]^+$; HRMS (ESI): calcd. for $C_{32}H_{28}NO$: 442.2165 $[M+H]^+$, found: 442.2179.

4.6.13 (5-((1-Hydroxycyclohexyl)ethynyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (57p)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 1-ethynyl-1-cyclohexanol (**56p**) (37.3 mg, 0.30 mmol) were employed to afford 60.4 mg (66%) of the indicated product as a yellow solid (R_f = 0.07 in 4:1 hexane/ethyl acetate): mp 181.9–185.0 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.46-7.37 (m, 4H), 7.27 (t, J = 7.4 Hz, 1H), 7.20-7.08 (m, 10H), 2.96 (br s, 1H), 1.65 (d, J = 10.7 Hz,

2H), 1.46-1.16 (m, 6H), 0.99 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3 (C=O), 155.3 (C), 152.6 (CH), 150.8 (C), 138.8 (C), 137.5 (C), 135.9 (C), 133.9 (C), 133.4 (CH), 129.4 (CH), 129.3 (2 x CH), 129.0 (CH), 128.4 (CH), 128.4 (2 x CH), 127.9 (CH), 118.8 (C), 100.8 (C), 80.1 (C), 69.1 (C), 39.7 (CH_2), 25.1 (CH_2), 23.1 (CH_2); IR (neat): 3270, 2956, 2857, 2199, 1664, 1591, 1579, 1557, 1523, 1438, 1408, 1314, 1297, 1259, 1210, 1083, 1057, 1029, 1015, 968, 934, 871, 802, 766, 692, 648, 638, 580 cm^{-1}; MS (ESI, m/z): 458.21 $[M+H]^+$; HRMS (ESI): calcd. for $C_{32}H_{28}NO_2$: 458.2115 $[M+H]^+$, found: 458.2127.

4.6.14 (2,4-Diphenyl-5-(pyridin-2-ylethynyl)pyridin-3-yl)(phenyl)methanone (57q)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 2-ethynylpyridine (**56q**) (30.9 mg, 0.30 mmol) were employed to afford 34.9 mg (40%) of the indicated product as a brown solid (R_f = 0.03 in 4:1 hexane/ethyl acetate): mp 160.9–163.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.50 (d, J = 4.3 Hz, 1H), 7.53-7.41 (m, 5H), 7.29 (t, J = 7.4 Hz, 1H), 7.25-7.11 (m, 11H), 6.96 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3 (C=O), 156.2 (C), 153.2 (CH), 150.9 (C), 150.1 (CH), 142.9 (C), 139.0 (C), 137.5 (C), 136.3 (CH), 135.7 (C), 133.9 (CH), 133.4 (CH), 129.6 (CH), 129.5 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 128.4 (2 x CH), 128.0 (CH), 127.6 (CH), 123.2 (C), 118.0 (C), 95.2 (C), 85.3 (C); IR (neat): 3066, 2958, 2920, 2850, 1670, 1593, 1577, 1560, 1553, 1517, 1492, 1462, 1436, 1423, 1377, 1329, 1314, 1286, 1260, 1224, 1173, 1079, 1026, 1005, 985, 931, 876, 802, 776, 756, 698, 629, 511 cm^{-1}; MS (ESI, m/z): 437.17 $[M+H]^+$; HRMS (ESI): calcd. for $C_{31}H_{21}N_2O$: 437.1648 $[M+H]^+$, found: 437.1658.

4.6.15 5-(Ferrocenylethynyl)-(2,4-diphenylpyridin-3-yl)(phenyl)methanone (57r)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**55a**) (92.3 mg, 0.20 mmol),

$PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and ethynylferrocene (**56r**) (63.0 mg, 0.30 mmol) were employed to afford 107.6 mg (99%) of the indicated product as a red solid (R_f = 0.55 in 4:1 hexane/ethyl acetate): mp 190.9–194.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.50-7.40 (m, 4H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.23-7.09 (m, 10H), 4.19 (t, *J* = 1.8 Hz, 2H), 4.11-4.07 (m, 2H), 3.93 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5 (C=O), 154.7 (C), 152.3 (CH), 149.9 (C), 139.2 (C), 137.6 (C), 136.3 (C), 133.8 (C), 133.3 (CH), 129.44 (CH), 129.38 (CH), 129.2 (CH), 128.8 (CH), 128.4 (CH), 128.3 (2 x CH), 127.9 (CH), 119.6 (C), 96.4 (C), 81.6 (C), 71.4 (CH), 70.1 (CH), 69.2 (CH), 64.1 (C); IR (neat): 3026, 2961, 2214, 1655, 1596, 1580, 1555, 1515, 1495, 1469, 1430, 1413, 1318, 1262, 1228, 1174, 1106, 1044, 1028, 1000, 971, 916, 823, 814, 772, 756, 729, 710, 695, 643, 602, 574, 523, 497, 484, 460 cm^{-1}; MS (ESI, m/z): 542.15 $[M+H]^+$; HRMS (ESI): calcd. For $C_{36}H_{26}{}^{54}FeNO$: 542.1405 $[M+H]^+$, found: 542.1466.

4.6.16 (2-(4-Methoxyphenyl)-4-phenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl)methanone (57ba)

(5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (**55b**) (98.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and phenylacetylene (**56a**) (30.6 mg, 0.30 mmol) were employed to afford 72.6 mg (78%) of the indicated product as a yellow solid (R_f = 0.33 in 4:1 hexane/ethyl acetate): mp 154.1–155.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.48-7.41 (m, 4H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.22-7.10 (m, 12H), 6.72-6.68 (m, 2H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8 (C=O), 160.3 (CO), 155.0 (C), 152.5 (CH), 150.4 (C), 137.6 (C), 136.0 (C), 133.4 (CH), 131.7 (C), 131.6 (CH), 130.7 (CH), 129.6 (C), 129.5 (CH), 129.4 (CH), 128.8 (CH), 128.5 (CH), 128.4 (2 x CH), 127.9 (CH), 122.7 (C), 118.4 (C), 113.9 (CH), 96.4 (C), 85.6 (C), 55.3 (CH_3); IR (neat): 3019, 2965, 2933, 2839, 2219, 1665, 1609, 1595, 1578, 1515, 1489, 1437, 1416, 1378, 1320, 1248, 1225, 1175, 1110, 1072, 1022, 1002, 929, 874, 841, 812, 760, 732, 699, 679, 639, 584, 522 cm^{-1}; MS (ESI, m/z): 466.18 $[M+H]^+$; HRMS

(ESI): calcd. for $C_{33}H_{24}NO_2$: 466.1802 $[M+H]^+$, found: 466.1820.

4.6.17 (2-(4-Methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-4-phenylpyridin-3-yl)(phenyl)methanone (57bb)

(5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (**55b**) (98.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 4-ethynylanisole (**56b**) (39.6 mg, 0.30 mmol) were employed to afford 86.2 mg (87%) of the indicated product as a yellow solid (R_f = 0.20 in 4:1 hexane/ethyl acetate): mp 179.0–180.0 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.57-7.50 (m, 4H), 7.39 (t, J = 7.4 Hz, 1H), 7.29-7.22 (m, 7H), 7.19-7.14 (m, 2H), 6.84-6.77 (m, 4H), 3.81 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8 (C=O), 160.2 (CO), 160.1 (CO), 154.6 (C), 152.2 (CH), 150.0 (C), 137.63 (C), 137.61 (C), 136.1 (C), 133.3 (CH), 133.1 (CH), 131.7 (C), 130.7 (CH), 129.6 (CH), 129.4 (CH), 128.4 (2 x CH), 127.8 (CH), 118.8 (C), 114.8 (C), 114.1 (CH), 113.9 (CH), 96.7 (C), 84.5 (C), 55.4 (CH_3), 55.3 (CH_3); IR (neat): 2957, 2933, 2835, 2200, 1666, 1603, 1578, 1508, 1437, 1416, 1377, 1289, 1246, 1224, 1173, 1129, 1108, 1028, 1001, 931, 876, 831, 808, 790, 761, 698, 677, 579, 535 cm^{-1}; MS (ESI, m/z): 496.19 $[M+H]^+$; HRMS (ESI): calcd. for $C_{34}H_{26}NO_3$: 496.1907 $[M+H]^+$, found: 496.1921.

4.6.18 (2-(4-Methoxyphenyl)-4-phenyl-5-(*p*-tolylethynyl)pyridin-3-yl)(phenyl)methanone (57bd)

(5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (**55b**) (98.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 4-ethynyltoluene (**56d**) (34.8 mg, 0.30 mmol) were employed to afford 95.0 mg (99%) of the indicated product as a yellow solid (R_f = 0.33 in 4:1 hexane/ethyl acetate): mp 167.2–169.4 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.54 (dt, J = 5.8 and 5.3 Hz, 4H), 7.42-7.36 (m, 1H), 7.32-7.21 (m, 7H), 7.16-7.07 (m, 4H), 6.84-6.78 (m, 2H), 3.75 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8

(C=O), 160.2 (CO), 154.8 (C), 152.4 (CH), 150.2 (C), 139.0 (C), 137.6 (C), 136.0 (C), 133.4 (CH), 133.3 (C), 131.7 (C), 131.5 (CH), 130.7 (CH), 129.6 (CH), 129.4 (CH), 129.2 (CH), 128.4 (2 x CH), 127.8 (CH), 119.6 (C), 118.6 (C), 113.9 (CH), 96.7 (C), 85.0 (C), 55.3 (CH_3), 21.6 (CH_3); IR (neat): 3031, 3004, 2933, 2810, 2219, 1614, 1594, 1577, 1509, 1492, 1438, 1379, 1318, 1291, 1247, 1225, 1177, 1044, 1028, 992, 875, 842, 819, 764, 698, 623,583, 532, 515 cm^{-1}; MS (ESI, m/z): 480.20 $[M+H]^+$; HRMS (ESI): calcd. for $C_{34}H_{26}NO_2$: 480.1958 $[M+H]^+$, found: 480.1975.

4.6.19 (2-(4-Methoxyphenyl)-4-phenyl-5-(thiophen-3-ylethynyl)pyridin-3-yl)(phenyl)methanone (57bm)

(5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (**55b**) (98.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 3-ethynylthiophene (**56m**) (32.4 mg, 0.30 mmol) were employed to afford 92.4 mg (98%) of the indicated product as an orange solid (R_f = 0.30 in 4:1 hexane/ethyl acetate): mp 139.5–140.5 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.58-7.51 (m, 4H), 7.42-7.36 (m, 1H), 7.31-7.21 (m, 9H), 6.92 (dd, J = 5.0 and 1.1 Hz, 1H), 6.82-6.78 (m, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8 (C=O), 160.3 (CO), 154.9 (C), 152.3 (CH), 150.3 (C), 137.6 (C), 136.0 (C), 133.38 (CH), 133.35 (C), 131.7 (C), 130.7 (CH), 129.7 (CH), 129.5 (CH), 129.4 (CH), 129.3 (CH), 128.4 (2 x CH), 127.9 (CH), 125.6 (CH), 121.8 (C), 118.4 (C), 113.9 (CH), 91.7 (C), 85.2 (C), 55.3 (CH_3); IR (neat): 3106, 2951, 2926, 2834, 2228, 1658, 1596, 1575, 1510, 1491, 1438, 1409, 1304, 1294, 1247, 1223, 1206, 1172, 1110, 1029, 1018, 929, 834, 820, 785, 767, 715, 697, 677, 624, 534 cm^{-1}; MS (ESI, m/z): 472.14 $[M+H]^+$; HRMS (ESI): calcd. for $C_{31}H_{22}NO_2S$: 472.1366 $[M+H]^+$, found: 472.1386.

4.6.20 (5-(Ferrocenylethynyl)-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (57br)

(5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (**55b**) (98.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and ethynylferrocene (**56r**) (63.0 mg, 0.30 mmol) were employed to afford 105.5 mg (92%) of the indicated product as a red solid (R_f = 0.33 in 4:1 hexane/ethyl acetate): mp 175.1–178.8 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.44 (t, J = 8.6 Hz, 4H), 7.29 (t, J = 7.4 Hz, 1H), 7.24-7.16 (m, 5H), 7.14 (t, J = 7.7 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 4.21-4.17 (m, 2H), 4.11-4.08 (m, 2H), 3.93 (s, 5H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8 (C=O), 160.2 (C), 154.3 (C), 152.3 (CH), 150.0 (C), 137.6 (C), 136.4 (C), 133.4 (CH), 133.3 (C) 131.8 (C), 130.7 (CH), 129.4 (2 x CH), 128.4 (2 x CH), 127.9 (CH), 119.1 (C), 113.4 (CH), 96.1 (C), 81.7 (C), 71.4 (CH), 70.1 (CH), 69.2 (CH), 64.2 (C), 55.3 (CH_3); IR (neat): 2958, 2931, 2836, 2211, 1664, 1607, 1578, 1555, 1512, 1466, 1449, 1429, 1416, 1374, 1320, 1307, 1245, 1228, 1175, 1107, 1041, 1027, 999, 917, 822, 792, 695, 676, 647, 585, 569, 536, 486 cm^{-1}; MS (ESI, m/z): 572.16 $[M+H]^+$; HRMS (ESI): calcd. for $C_{37}H_{28}{}^{54}FeNO_2$: 572.1511 $[M+H]^+$, found: 572.1584.

4.6.21 (2-Butyl-4-phenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl)methanone (57la)

(2-Butyl-5-iodo-4-phenylpyridin-3-yl)(phenyl)methanone (**55l**) (88.3 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and phenylacetylene (**56a**) (30.6 mg, 0.30 mmol) were employed to afford 71.5 mg (86%) of the indicated product as an orangish yellow solid (R_f = 0.57 in 4:1 hexane/ethyl acetate): mp 86.2–89.1 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.49 (dd, J = 5.2 and 3.3 Hz, 2H), 7.36 (tt, J = 7.1 and 1.2 Hz, 1H), 7.24-7.10 (m, 12H), 2.61 (t, J = 7.8 Hz, 2H), 1.61 (br s, 2H), 1.22 (sextet, J = 7.2 Hz, 2H), 0.75 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0 (C=O), 158.4 (C), 152.5 (CH), 149.0 (C), 137.3 (C), 135.9 (C), 133.9 (C), 133.7 (CH), 131.5 (CH),

129.7 (CH), 129.4 (CH), 128.7 (CH), 128.5 (2 x CH), 128.4 (CH), 127.8 (CH), 122.8 (C), 117.5 (C), 95.5 (C), 85.6 (C), 36.2 (CH_2), 31.9 (CH_2), 22.8 (CH_2), 13.9 (CH_3); IR (neat): 3052, 2954, 2928, 2865, 1735, 1665, 1596, 1579, 1560, 1525, 1490, 1447, 1421, 1326, 1281, 1266, 1223, 1154, 1071, 1002, 992, 916, 882, 754, 717, 701, 688, 669, 522 cm^{-1}; MS (ESI, m/z): 416.20 $[M]^+$; HRMS (ESI): calcd. for $C_{30}H_{26}NO$: 416.2009 $[M+H]^+$, found: 416.2032.

4.6.22 Phenyl(4-phenyl-5-(phenylethynyl)-2-(thiophen-3-yl)pyridin-3-yl)methanone (57ma)

(5-Iodo-4-phenyl-2-(thiophen-3-yl)pyridin-3-yl)(phenyl)methanone (**55m**) (93.5 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and phenylacetylene (**56a**) (30.6 mg, 0.30 mmol) were employed to afford 79.5 mg (90%) of the indicated product as a yellow solid (R_f = 0.50 in 4:1 hexane/ethyl acetate): mp 177.1–181.2 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.51-7.47 (m, 2H), 7.46 (dd, J = 2.9 and 1.3 Hz, 1H), 7.35-7.29 (m, 2H), 7.24-7.14 (m, 10H), 7.12 (ddd, J = 5.1, 3.0 and 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9 (C=O), 152.5 (CH), 150.2 (C), 149.9 (C), 140.3 (C), 137.4 (C), 135.8 (C), 133.6 (CH), 133.0 (C), 131.6 (CH), 129.6 (CH), 129.4 (CH), 128.8 (CH), 128.6 (CH), 128.54 (CH), 128.48 (CH), 128.4 (CH), 127.9 (CH), 127.0 (CH), 125.8 (CH), 122.7 (C), 118.7 (C), 96.6 (C), 85.6 (C); IR (neat): 3057, 3027, 2211, 1734, 1669, 1594, 1578, 1555, 1526, 1490, 1440, 1346, 1324, 1285, 1257, 1223, 1174, 1158, 1078, 1002, 908, 878, 867, 783, 765, 703, 686, 674, 641, 622, 522 cm^{-1}; MS (ESI, m/z): 442.13 $[M+H]^+$; HRMS (ESI): calcd. for $C_{30}H_{20}NOS$: 442.1260 $[M+H]^+$, found: 442.1283.

4.6.23 Phenyl(4-phenyl-2-(thiophen-3-yl)-5-(*p*-tolylethynyl)pyridin-3-yl)methanone (57md)

(5-Iodo-4-phenyl-2-(thiophen-3-yl)pyridin-3-yl)(phenyl)methanone (**55m**) (93.5 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and

4-ethynyltoluene (**56d**) (34.8 mg, 0.30 mmol) were employed to afford 68.3 mg (75%) of the indicated product as a yellow solid (R_f = 0.48 in 4:1 hexane/ethyl acetate): mp 184.4–187.0 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.51-7.47 (m, 2H), 7.45 (dd, *J* = 3.0 and 1.3 Hz, 1H), 7.32 (m, 2H), 7.22-7.14 (m, 7H), 7.12 (dd, *J* = 5.1 and 3.0 Hz, 1H), 7.05-6.94 (m, 4H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0 (C=O), 152.4 (CH), 150.0 (C), 149.7 (C), 140.2 (C), 139.1 (C), 137.4 (C), 135.8 (C), 133.6 (CH), 133.0 (C), 131.5 (CH), 129.6 (CH), 129.4 (CH), 129.2 (CH), 128.6 (CH), 128.49 (CH), 128.45 (CH), 127.9 (CH), 126.9 (CH), 125.8 (CH), 119.6 (C), 118.8 (C), 96.9 (C), 85.0 (C), 21.7 (CH_3); IR (neat): 3055, 3024, 2213, 1670, 1594, 1556, 1524, 1507, 1495, 1441, 1327, 1286, 1260, 1224, 1174, 1155, 1121, 1103, 1077, 1001, 1077, 1001, 908, 868, 816, 791, 764, 702, 686, 670, 617, 579, 530 cm^{-1}; MS (ESI, m/z): 456.14 $[M+H]^+$; HRMS (ESI): calcd. for $C_{31}H_{22}NOS$: 456.1417 $[M+H]^+$, found: 456.1438.

4.6.24 Phenyl(4-phenyl-2-(thiophen-3-yl)-5-(thiophen-3-ylethynyl)pyridin-3-yl)methanone (57mm)

(5-Iodo-4-phenyl-2-(thiophen-3-yl)pyridin-3-yl)(phenyl)methanone (**55m**) (93.5 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and 3-ethynylthiophene (**56m**) (32.4 mg, 0.30 mmol) were employed to afford 65.3 mg (73%) of the indicated product as a brown solid (R_f = 0.35 in 4:1 hexane/ethyl acetate): mp 189.0–192.2 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.51-7.46 (m, 2H), 7.45 (dd, *J* = 2.9, 1.2 Hz, 1H), 7.35-7.28 (m, 2H), 7.22-7.10 (m, 10H), 6.81 (dd, *J* = 5.0 and 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9 (C=O), 152.3 (CH), 150.1 (C), 149.8 (C), 140.2 (C), 137.4 (C), 135.8 (C), 133.6 (CH), 133.0 (C), 129.7 (CH), 129.6 (CH), 129.4 (2 x CH), 128.6 (CH), 128.51 (CH), 128.45 (CH), 127.9 (CH), 127.0 (CH), 125.8 (CH), 125.6 (CH), 121.8 (C), 118.7 (C), 91.9 (C), 85.2 (C); IR (neat): 3093, 3080, 2209, 1732, 1666, 1593, 1558, 1517, 1493, 1443, 1342, 1313, 1299, 1226, 1207, 1174, 1078, 1007, 930, 881, 850, 791, 778, 761, 717, 702, 676, 641, 612, 566 cm^{-1}; MS (ESI, m/z): 448.08 $[M+H]^+$; HRMS (ESI): calcd. for $C_{28}H_{18}NOS_2$: 448.0824 $[M+H]^+$, found: 448.0848.

4.6.25 Phenyl(4-phenyl-5-(ferrocenylethynyl)-2-(thiophen-3-yl)pyridin-3-yl)methanone (57mr)

(5-Iodo-4-phenyl-2-(thiophen-3-yl)pyridin-3-yl)(phenyl)methanone (**55m**) (93.5 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and ethynylferrocene (**56r**) (63.0 mg, 0.30 mmol) were employed to afford 87.9 mg (80%) of the indicated product as a red solid (R_f = 0.50 in 4:1 hexane/ethyl acetate): mp 176.8–178.5 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.53 (dd, *J* = 8.3 and 1.1 Hz, 2H), 7.50 (dd, *J* = 2.9 and 1.3 Hz, 1H), 7.41-7.35 (m, 2H), 7.29-7.20 (m, 7H), 7.16 (dd, *J* = 5.1 and 3.0 Hz, 1H), 4.21 (t, *J* = 1.8 Hz, 2H), 4.12 (t, *J* = 1.8 Hz, 2H), 3.95 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6 (C=O), 152.3 (CH), 149.7 (C), 149.2 (C), 140.5 (C), 137.6 (C), 136.3 (C), 133.5 (CH), 133.0 (C), 129.7 (CH), 129.4 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.0 (CH), 126.8 (CH), 125.6 (CH), 119.3 (C), 96.4 (C) 81.9 (C), 71.5 (CH), 70.2 (CH), 69.2 (CH), 64.4 (C); IR (neat): 3107, 3089, 2212, 1734, 1667, 1594, 1578, 1559, 1524, 1474, 1447, 1435, 1412, 1344, 1315, 1218, 1175, 1160, 1104, 1043, 1024, 1001, 911, 881, 850, 831, 808, 780, 721, 699, 679, 610, 576, 534, 494, 483, 466 cm^{-1}; MS (ESI, m/z): 548.10 $[M+H]^+$; HRMS (ESI): calcd. for $C_{34}H_{24}{}^{54}FeNOS$: 548.0969 $[M+H]^+$, found: 548.1042.

4.6.26 1-(2,4-Diphenyl-5-(phenylethynyl)pyridin-3-yl)ethanone (57aaa)

1-(5-Iodo-2,4-diphenylpyridin-3-yl)ethanone (**55aa**) (79.8 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and phenylacetylene (**56a**) (30.6 mg, 0.30 mmol) were employed to afford 68.0 mg (91%) of the indicated product as a yellow solid (R_f = 0.53 in 4:1 hexane/ethyl acetate): mp 129.8–132.5 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.54-7.50 (m, 2H), 7.41-7.34 (m, 6H), 7.34-7.30 (m, 2H), 7.22-7.15 (m, 3H), 7.13 (dt, *J* = 8.0 and 2.1 Hz, 2H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9 (C=O), 154.0 (C), 152.0 (CH), 148.8 (C), 139.1 (C), 136.6 (C), 136.1 (C), 131.6 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 128.88 (CH), 128.75 (CH), 128.4 (CH), 128.3 (2 x CH),

122.6 (C), 119.1 (C), 96.7 (C), 85.4 (C), 32.7 (CH_3); IR (neat): 3054, 2208, 1960, 1897, 1703, 1554, 1518, 1487, 1440, 1411, 1375, 1348, 1325, 1309, 1196, 1178, 1101, 1073, 1025, 974, 919, 910, 754, 701, 690, 668, 651, 511 cm^{-1}; MS (ESI, m/z): 374.15 $[M]^+$; HRMS (ESI): calcd. for $C_{27}H_{20}NO$: 374.1539 $[M+H]^+$, found: 374.1543.

4.6.27 (4-(3-Bromophenyl)-2-phenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl)methanone (57aba)

(4-(3-Bromophenyl)-5-iodo-2-phenylpyridin-3-yl)(phenyl)methanone (**55ab**) (108.0 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and phenylacetylene (**56a**) (30.6 mg, 0.30 mmol) were employed to afford 82.3 mg (84%) of the indicated product as an orangish yellow solid (R_f = 0.45 in 4:1 hexane/ethyl acetate): mp 168.0–171.0 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.60-7.51 (m, 5H), 7.42 (ddd, J = 5.3, 3.3 and 1.3 Hz, 2H), 7.36-7.30 (m, 5H), 7.28 (dt, J = 10.9 and 4.7 Hz, 5H), 7.20 (br s, 1H), 7.17-7.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2 (C=O), 155.6 (C), 152.7 (CH), 148.6 (C), 139.0 (C), 137.9 (C), 137.5 (C), 133.7 (CH), 133.6 (CH), 132.7 (C), 131.8 (CH), 131.7 (CH), 129.6 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 129.1 (CH), 128.6 (CH), 128.54 (2 x CH), 128.48 (CH), 122.4 (C), 121.9 (C), 118.8 (C), 97.3 (C), 85.0 (C); IR (neat): 3057, 3027, 2217, 2201, 1731, 1665, 1595, 1552, 1490, 1477, 1437, 1324, 1285, 1257, 1222, 1176, 1072, 1004, 994, 875, 785, 754, 726, 689, 526 cm^{-1}; MS (ESI, m/z): 514.08 $[M]^+$; HRMS (ESI): calcd. for $C_{32}H_{21}{}^{79}BrNO$: 514.0801 $[M+H]^+$, found: 514.0817.

4.6.28 (4-Methyl-2-phenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl)methanone (57aca)

(5-Iodo-4-methyl-2-phenylpyridin-3-yl)(phenyl)methanone (**55ac**) (79.8 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol) and phenylacetylene (**56a**) (30.6 mg, 0.30 mmol) were employed to afford 63.5 mg (85%) of the indicated product as an light yellow solid (R_f = 0.50 in 4:1

hexane/ethyl acetate): mp 104.0–107.1 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.55 (dd, *J* = 5.2 and 3.3 Hz, 2H), 7.50 (dt, *J* = 5.0 and 3.0 Hz, 2H), 7.44-7.35 (m, 3H), 7.31 (dd, *J* = 5.9 and 2.6 Hz, 3H), 7.23 (t, *J* = 7.8 Hz, 2H), 7.18-7.11 (m, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5 (C=O), 154.8 (C), 152.3 (CH), 146.9 (C), 139.2 (C), 136.9 (C), 134.2 (C), 133.9 (CH), 131.8 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 122.7 (C), 119.9 (C), 97.5 (C), 84.8 (C), 18.1 (CH_3); IR (neat): 3049, 2923, 2851, 1993, 1595, 1529, 1487, 1438, 1375, 1319, 1285, 1247, 1207, 1175, 1148, 1068, 1026, 999, 963, 938, 889, 844, 754, 712, 699, 687, 531 cm^{-1}; MS (ESI, m/z): 374.16 $[M+H]^+$; HRMS (ESI): calcd. for $C_{27}H_{20}NO$: 374.1539 $[M+H]^+$, found: 374.1604.

4.7 General Procedure for the Synthesis of 2,3-Dihydro-1,4-oxazepines 33

To a stirred solution of the corresponding *N*-propargylic β-enaminone **32** (0.30 mmol) in $CHCl_3$ (5.0 mL) at room temperature under argon were added $ZnCl_2$ (0.30 mmol). The resulting mixture was then refluxed (Note that reaction was continued until *N*-propargylic β-enaminone **32** was completely consumed as monitored by routine TLC). After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (40 mL) and a saturated aqueous solution of NH_4Cl (15 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding 1,4-oxazepine derivative **33.**

4.7.1 2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (33a)

1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**1a**) (78.4 mg, 0.30 mmol) and $ZnCl_2$ (40.9 mg, 0.30 mmol) were employed to afford the indicated product (74.5 mg (95%) in refluxing $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.72 (m,

4H), 7.51-7.38 (m, 6H), 6.41 (s, 1H), 4.76 (d, J = 1.4 Hz 1H), 4.57 (s, 2H), 4.40 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C), 159.0 (C), 158.2 (C), 139.8 (C), 135.2 (C), 130.2 (CH), 130.1 (CH), 128.7 (CH), 128.4 (CH), 127.5 (CH), 126.4 (CH), 99.8 (CH), 94.0 (CH_2), 55.6 (CH_2); IR (neat): 3104, 3059, 2994, 2955, 2837, 1656, 1627, 1587, 1570, 1491, 1446, 1361, 1313, 1290, 1260, 1230, 1191, 1176, 1110, 1076, 1055, 1027, 999, 946, 926, 882, 832, 804, 762 cm^{-1}; MS (ESI, m/z): 262.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{16}NO$: 262.1226 $[M+H]^+$, found: 262.1236. The spectral data were in agreement with those reported previously for this compound.[62]

4.7.2 5-(4-Methoxyphenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (33b)

3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32b**) (131.1 mg, 0.45 mmol) and $ZnCl_2$ (61.3 mg, 0.45 mmol) were employed to afford the indicated product (95.7 mg (73%) in refluxing $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.74 (m, 4H), 7.46-7.41 (m, 3H), 6.95-6.89 (m, 2H), 6.39 (s, 1H), 4.73 (d, J = 1.1 Hz, 1H), 4.53 (s, 2H), 4.38 (d, J = 1.5 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C), 161.4 (C), 158.9 (C), 158.6 (C), 135.4 (C), 132.4 (C), 130.2 (CH), 129.1 (CH), 128.7 (CH), 126.4 (CH), 113.8 (CH), 99.9 (CH), 93.7 (CH_2), 55.5 (OCH_3), 55.3 (CH_2); IR (neat): 3081, 3052, 2996, 2953, 2835, 1656, 1630, 1604, 1586, 1562, 1510, 1492, 1462, 1432, 1367, 1315, 1299, 1254, 1199, 1172, 1109, 1063, 1029, 999, 869, 856, 820, 762 cm^{-1}; MS (ESI, m/z): 292.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO_2$: 292.1332 $[M+H]^+$, found: 292.1346.

4.7.3 5-(2-Methoxyphenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (33c)

3-(2-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32c**) (110.7 mg, 0.38 mmol) and $ZnCl_2$ (51.8 mg, 0.38 mmol) were employed to afford

the indicated product (73.1 mg (66%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.69 (m, 2H), 7.51 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.43-7.34 (m, 4H), 7.03-6.97 (m, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.37 (s, 1H), 4.77 (d, *J* = 0.9 Hz, 1H), 4.56 (s, 2H), 4.40 (d, *J* = 1.3 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7 (C), 157.8 (C), 157.3 (C), 156.8 (C), 135.5 (C), 130.8 (CH), 130.3 (CH), 130.0 (CH), 128.6 (CH), 126.4 (CH), 120.9 (CH), 111.6 (CH), 102.6 (CH), 94.2 (CH_2), 55.9 (OCH_3), 55.7 (CH_2) (Note that one C and one CH peak overlap on each other); IR (neat): 3059, 2937, 2836, 1731, 1710, 1657, 1623, 1597, 1567, 1487, 1461, 1434, 1365, 1321, 1241, 1179, 1161, 1120, 1063, 1046, 1020, 904, 813, 751 cm^{-1}; MS (ESI, m/z): 292.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO_2$: 292.1332 $[M+H]^+$, found: 292.1345.

4.7.4 2-Methylene-7-phenyl-5-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (33d)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-en-1-one (**32d**) (88.1 mg, 0.32 mmol) and $ZnCl_2$ (43.6 mg, 0.32 mmol) were employed to afford the indicated product (65.2 mg (74%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.74 (m, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.48-7.41 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.40 (s, 1H), 4.75 (s, 1H), 4.55 (s, 2H), 4.39 (d, *J* = 1.5 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (C), 158.8 (C), 158.4 (C), 140.2 (C), 137.1 (C), 135.3 (C), 130.1 (CH), 129.1 (CH), 128.6 (CH), 127.4 (CH), 126.3 (CH), 100.0 (CH), 93.7 (CH_2), 55.4 (CH_2), 21.4 (CH_3); IR (neat): 3112, 3055, 3025, 3000, 2962, 2836, 1659, 1624, 1584, 1561, 1508, 1492, 1446, 1362, 1316, 1292, 1264, 1229, 1198, 1179, 1109, 1063, 1028, 950, 882, 854, 812, 758 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1386.

4.7.5 2-Methylene-7-phenyl-5-(*m*-tolyl)-2,3-dihydro-1,4-oxazepine (33e)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-en-1-one (**32e**) (90.9 mg, 0.33 mmol) and $ZnCl_2$ (45.0 mg, 0.33 mmol) were employed to afford the indicated product (67.3 mg (74%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.84-

7.77 (m, 2H), 7.67 (s, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.51-7.42 (m, 3H), 7.37-7.24 (m, 2H), 6.43 (s, 1H), 4.79 (d, J = 0.9 Hz, 1H), 4.59 (s, 2H), 4.42 (d, J = 1.5 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C), 158.9 (C), 158.2 (C), 139.7 (C), 138.1 (C), 135.3 (C), 130.9 (CH), 130.2 (CH), 128.7 (CH), 128.3 (CH), 128.0 (CH), 126.4 (CH), 124.7 (CH), 99.9 (CH), 93.9 (CH_2), 55.5 (CH_2), 21.5 (CH_3); IR (neat): 3056, 3026, 2920, 1707, 1657, 1622, 1596, 1546, 1491, 1447, 1373, 1315, 1260, 1198, 1067, 1044, 1024, 999, 907, 831, 787, 764 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1394.

4.7.6 2-Methylene-7-phenyl-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1,4-oxazepine (33f)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**32f**) (98.8 mg, 0.30 mmol) and $ZnCl_2$ (40.9 mg, 0.30 mmol) were employed to afford the indicated product (81.0 mg (82%) in refluxing $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 2H), 7.80-7.74 (m, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.50-7.41 (m, 3H), 6.36 (s, 1H), 4.80 (d, J = 1.1 Hz, 1H), 4.59 (s, 2H), 4.42 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0 (C), 159.8 (C), 157.8 (C), 143.1 (C), 135.0 (C), 131.9 (q, ^2J = 32.4 Hz, C), 130.5 (CH), 128.8 (CH), 127.9 (CH), 126.5 (CH), 125.4 (q, ^3J = 3.7 Hz, CH), 124.2 (q, ^1J = 272.2 Hz, CF_3), 99.0 (CH), 94.7 (CH_2), 55.8 (CH_2); IR (neat): 3109, 3085, 3054, 3039, 1660, 1623, 1586, 1565, 1491, 1446, 1408, 1365, 1326, 1315, 1264, 1201, 1183, 1153, 1105, 1067, 1014, 947, 884, 861, 819, 759 cm^{-1}; MS (ESI, m/z): 330.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}F_3NO$: 330.1100 $[M+H]^+$, found: 330.1101.

4.7.7 *N,N*-Dimethyl-4-(2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepin-5-yl)aniline (33g)

3-(4-(Dimethylamino)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32g**) (91.3 mg, 0.30 mmol) and $ZnCl_2$ (40.9 mg, 0.30 mmol) were employed to

afford the indicated product (36.5 mg (40%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79-7.75 (m, 2H), 7.74-7.70 (m, 2H), 7.46-7.40 (m, 3H), 6.75-6.65 (m, 2H), 6.43 (s, 1H), 4.70 (d, *J* = 1.0 Hz, 1H), 4.51 (s, 2H), 4.37 (d, *J* = 1.4 Hz, 1H), 3.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C), 159.0 (C), 158.5 (C), 151.8 (C), 135.5 (C), 130.0 (CH), 128.7 (CH), 128.6 (CH), 127.2 (C), 126.3 (CH), 111.5 (CH), 100.3 (CH), 93.2 (CH_2), 54.9 (CH_2), 40.4 ($N(CH_3)_2$); IR (neat): 2891, 2828, 1737, 1646, 1629, 1606, 1578, 1548, 1523, 1490, 1447, 1357, 1317, 1267, 1189, 1107, 1059, 811, 758, 683 cm^{-1}; MS (ESI, m/z): 305.17 $[M+H]^+$; HRMS (ESI) calcd. for $C_{20}H_{21}N_2O$: 305.1648 $[M+H]^+$, found: 305.1662.

4.7.8 5-(3-Fluorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (33h)

3-(3-Fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32h**) (89.4 mg, 0.32 mmol) and $ZnCl_2$ (43.6 mg, 0.32 mmol) were employed to afford the indicated product (80.5 mg (90%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79-7.74 (m, 2H), 7.59-7.56 (m, 1H), 7.55-7.51 (m, 1H), 7.48-7.41 (m, 3H), 7.37 (td, *J* = 8.0, 5.8 Hz, 1H), 7.13 (tdd, *J* = 8.3, 2.6, 0.8 Hz, 1H), 6.35 (s, 1H), 4.78 (d, *J* = 0.4 Hz, 1H), 4.56 (s, 2H), 4.41 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)
δ 166.0 (C), 162.9 (d, ^1J = 246.2 Hz, CF), 159.5 (C), 158.0 (C), 142.1 (d, ^3J = 7.1 Hz, C), 135.1 (C), 130.4 (CH), 130.0 (d, ^3J = 8.0 Hz, CH), 128.7 (CH), 126.4 (CH), 123.2 (d, ^4J = 2.5 Hz, CH), 116.7 (d, ^2J = 21.6 Hz, CH), 114.5 (d, ^2J = 22.7 Hz, CH), 99.2 (CH), 94.4 (CH_2), 55.6 (CH_2). IR (neat): 3102, 2993, 2951, 2837, 1731, 1704, 1656, 1624, 1569, 1483, 1447, 1431, 1361, 1313, 1296, 1261, 1248, 1196, 1174, 1104, 1077, 1055, 874, 825, 790, 762 cm^{-1}; MS (ESI, m/z): 280.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}FNO$: 280.1132 $[M+H]^+$, found: 280.1137.

4.7.9 5-(2-Bromophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (33i)

3-(2-Bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32i**) (112.3 mg, 0.33 mmol) and $ZnCl_2$ (45.0 mg, 0.33 mmol) were employed to afford the indicated product (82.0 mg (73%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.67 (m, 2H), 7.60 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.48-7.32 (m, 5H), 7.27-7.20 (m, 1H), 6.13 (s, 1H), 4.84 (d, *J* = 1.0 Hz, 1H), 4.58 (s, 2H), 4.44 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6 (C), 157.9 (C), 157.2 (C), 142.0 (C), 135.0 (C), 133.2 (CH), 130.2 (CH), 130.2 (CH), 130.1 (CH), 128.6 (CH), 127.5 (CH), 126.4 (CH), 121.3 (CBr), 101.4 (CH), 95.2 (CH_2), 56.1 (CH_2); IR (neat): 3058, 1657, 1623, 1597, 1571, 1464, 1365, 1318, 1294, 1257, 1193, 1153, 1119, 1066, 1045, 1024, 848, 826, 757 cm^{-1}; MS (ESI, m/z): 340.03 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}{}^{79}BrNO$: 340.0332 $[M+H]^+$, found: 340.0330.

4.7.10 2-(2-Methylene-7-phenyl-2,3-dihydro-1,4-oxazepin-5-yl)isoindoline-1,3-dione (33k) and 2-(2-(3-benzoyl-4-methyl-1*H*-pyrrol-2-yl)ethyl)isoindoline-1,3-dione (71k)

2-(5-Oxo-5-phenyl-3-(prop-2-yn-1-ylamino)pent-3-en-1-yl)isoindoline-1,3-dione (**32k**) (75.1 mg, 0.21 mmol) and $ZnCl_2$ (28.6 mg, 0.21 mmol) were employed. Chromatographic purification of crude product on silica gel produced a mixture of two compounds. The mixture was then rechromatographed on aluminium oxide (neutral), which afforded two fractions. The product in the first fraction was identified as 2-(2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepin-5-yl)isoindoline-1,3-dione (**33k**) (30.0 mg (40%) in refluxing $CHCl_3$). Second fraction produced a mixture of 1,4-oxazepine **33k** and pyrrole **71k**. Spectroscopic identification of pyrrole **71k** was made by peak picking of ^1H NMR spectrum of the mixture. Yield of pyrrole **71k** was calculated by the integration of the related ^1H NMR peaks of the mixture, which was found to be 12% (equivalent to 9.0 mg) in refluxing $CHCl_3$.

33k: ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, CDCl3) δ 7.83-7.79

(m, 2H), 7.69-7.65 (m, 2H), 7.65-7.62 (m, 2H), 7.41-7.34 (m, 3H), 5.87 (s, 1H), 4.67 (d, *J* = 1.0 Hz, 1H), 4.27 (s, 2H), 4.24 (d, *J* = 1.4 Hz, 1H), 4.02 (t, *J* = 7.3 Hz, 2H), 2.77 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2 (C=O), 158.1 (C), 157.0 (C), 134.9 (C), 133.9 (CH), 132.6 (CH), 132.3 (C), 130.2 (C), 128.6 (CH), 126.4 (CH), 123.3 (CH), 100.4 (CH), 94.6 (CH_2), 55.2 (CH_2), 38.4 (CH_2), 36.0 (CH_2); IR (neat): 3393, 3180, 2917, 2848, 1764, 1698, 1644, 1596, 1468, 1419, 1400, 1362, 1319, 1258, 1091, 992, 829, 760, 718 cm^{-1}; MS (ESI, m/z): 359.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{19}N_2O_3$: 359.1390 $[M+H]^+$, found: 359.1400.

71k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (br s, 1H), in 7.84-7.75 (m, 2H), in 7.69-7.65 (m, 2H), in 7.41-7.34 (m, 5H), 6.55 (dd, *J* = 2.2, 1.0 Hz, 1H), 3.92 (t, *J* = 7.5 Hz, 2H), in 2.84-2.74 (m, 2H), 2.26 (d, *J* = 0.9 Hz, 3H). As mentioned above, pyrrole **71k** could not be isolated in pure state from flash column chromatography. That's why; further characterization of this compound could not be achieved.

4.7.11 5-Butyl-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (33l) and (2-butyl-4-methyl-1*H*-pyrrol-3-yl)(phenyl)methanone (71l)

1-Phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (**32l**) (72.4 mg, 0.30 mmol) and $ZnCl_2$ (40.9 mg, 0.30 mmol) were employed. Chromatographic purification of crude product on silica gel produced a mixture of two compounds. The mixture was then rechromatographed on aluminium oxide (neutral), which afforded two fractions. The product in the first fraction was identified as 5-butyl-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**33l**) (52.1 mg (72%) in refluxing $CHCl_3$). The product in the second fraction was assigned as (2-butyl-4-methyl-1*H*-pyrrol-3-yl)(phenyl)methanone (**71l**) (6.5 mg (9%) in refluxing $CHCl_3$).

33l: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.63 (m, 2H), 7.44-7.35 (m, 3H), 5.88 (s, 1H), 4.68 (d, *J* = 1.1 Hz, 1H), 4.31 (s, 3H), 2.43-2.34 (m, 2H), 1.60 (tt, *J* = 7.8, 6.5 Hz, 2H), 1.37 (sextet, *J* = 7.3 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (C), 157.8 (C), 157.1 (C), 135.2 (C), 130.0 (CH), 128.6

(CH), 126.3 (CH), 100.9 (CH), 93.8 (CH_2), 55.2 (CH_2), 40.3 (CH_2), 29.9 (CH_2), 22.5 (CH_2), 14.1 (CH_3); IR (neat): 3268, 2957, 2928, 2870, 1703, 1623, 1596, 1450, 1428, 1378, 1266, 1175, 1107, 1072, 1025, 767, 699 cm^{-1}; MS (ESI, m/z): 242.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{20}NO$: 242.1539 $[M+H]^+$, found: 242.1541.

71l: ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.47-7.31 (m, 5H), 6.56 (dd, *J* = 2.2, 1.0 Hz, 1H), 2.39-2.31 (m, 2H), 2.26 (d, *J* = 0.8 Hz, 3H), 1.51-1.42 (m, 2H), 1.10 (sextet, *J* = 7.4 Hz, 2H), 0.73 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8 (C=O), 136.6 (C), 133.7 (C), 129.2 (CH), 128.6 (CH), 128.5 (CH), 122.2 (C), 121.8 (C), 117.0 (CH), 42.2 (CH_2), 27.2 (CH_2), 22.4 (CH_2), 13.9 (CH_3), 12.6 (CH_3); IR (neat): 3467, 3194, 3056, 2954, 2928, 1708, 1679, 1622, 1450, 1421, 1402, 1340, 1281, 1060, 768, 696 cm^{-1}; MS (ESI, m/z): 242.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{20}NO$: 242.1539 $[M+H]^+$, found: 242.1551.

4.7.12 2-Methylene-7-phenyl-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (33m)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**32m**) (82.9 mg, 0.31 mmol) and $ZnCl_2$ (42.3 mg, 0.31 mmol) were employed to afford the indicated product (69.6 mg (84%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81-7.72 (m, 2H), 7.68 (dd, *J* = 2.9, 1.2 Hz, 1H), 7.56 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.48-7.40 (m, 3H), 7.31 (dd, *J* = 5.1, 3.0 Hz, 1H), 6.41 (s, 1H), 4.75 (br s, 1H), 4.53 (s, 2H), 4.40 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (C), 158.6 (C), 158.1 (C), 142.9 (C), 135.2 (C), 130.2 (CH), 128.7 (CH), 126.9 (CH), 126.4 (CH), 126.0 (CH), 125.7 (CH), 99.5 (CH), 94.1 (CH_2), 55.4 (CH_2); IR (neat): 3098, 2989, 2954, 2832, 1656, 1626, 1577, 1492, 1448, 1352, 1312, 1283, 1261, 1194, 1110, 1057, 1028, 872, 764, 689 cm^{-1}; MS (ESI, m/z): 268.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{14}NOS$: 268.0791 $[M+H]^+$, found: 268.0791.

4.7.13 7-(2-Bromophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (33n)

1-(2-Bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32n**) (88.5 mg, 0.26 mmol) and $ZnCl_2$ (35.4 mg, 0.26 mmol) were employed to afford the indicated product (71.7 mg (81%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.76-7.70 (m, 2H), 7.57 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.38-7.27 (m, 4H), 7.23-7.16 (m, 1H), 5.95 (s, 1H), 4.60 (s, 3H), 4.29 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C), 159.7 (C), 158.9 (C), 139.2 (C), 137.9 (C), 133.5 (CH), 130.9 (CH), 130.8 (CH), 130.3 (CH), 128.5 (CH), 127.54 (CH), 127.47 (CH), 122.1 (CBr), 104.7 (CH), 94.2 (CH_2), 55.6 (CH_2); IR (neat): 3246, 3055, 2966, 2841, 1655, 1629, 1587, 1563, 1485, 1464, 1434, 1360, 1313, 1253, 1189, 1180, 1114, 1077, 1064, 1025, 953, 857, 831, 755 cm^{-1}; MS (ESI, m/z): 340.03 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}{}^{79}BrNO$: 340.0332 $[M+H]^+$, found: 340.0332.

4.7.14 7-(2-Bromophenyl)-5-(4-methoxyphenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (33o)

1-(2-Bromophenyl)-3-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32o**) (74.0 mg, 0.20 mmol) and $ZnCl_2$ (27.3 mg, 0.20 mmol) were employed to afford the indicated product (66.6 mg (90%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.84-7.77 (m, 2H), 7.67 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.56 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.40 (td, *J* = 7.5, 1.0 Hz, 1H), 7.33-7.27 (m, 1H), 6.97-6.90 (m, 2H), 6.05 (s, 1H), 4.68 (s, 3H), 4.38 (d, *J* = 0.8 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (C), 161.4 (C), 159.33 (C), 159.30 (C), 137.9 (C), 133.4 (CH), 131.9 (C), 130.87 (CH), 130.83 (CH), 129.0 (CH), 127.5 (CH), 122.1 (CBr), 113.7 (CH), 104.8 (CH), 93.7 (CH_2), 55.4 (OCH_3), 55.3 (CH_2); IR (neat): 2993, 2952, 2835, 1656, 1627, 1603, 1587, 1569, 1510, 1492, 1461, 1361, 1312, 1192, 1168, 1107, 1072, 1028, 1000, 945, 855, 821, 759 cm^{-1}; MS (ESI, m/z): 370.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}{}^{79}BrNO_2$: 370.0437 $[M+H]^+$, found: 370.0442.

4.7.15 7-(2-Bromophenyl)-5-(2-methoxyphenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (33p)

1-(2-Bromophenyl)-3-(2-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32p**) (74.0 mg, 0.20 mmol) and $ZnCl_2$ (27.3 mg, 0.20 mmol) were employed to afford the indicated product (65.1 mg (88%) in refluxing $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.41-7.33 (m, 2H), 7.30-7.25 (m, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.02 (s, 1H), 4.71 (s, 2H), 4.70 (s, 1H), 4.38 (d, *J* = 1.3 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5 (C), 158.9 (C), 157.2 (C), 157.1 (C), 138.1 (C), 133.3 (CH), 130.83 (CH), 130.77 (CH), 130.7 (CH), 130.3 (CH), 129.6 (C) 127.4 (CH), 122.2 (CBr), 120.9 (CH), 111.4 (CH), 107.7 (CH), 93.8 (CH_2), 55.9 (OCH_3), 55.8 (CH_2); IR (neat): 2962, 2831, 1656, 1630, 1591, 1569, 1486, 1465, 1433, 1360, 1313, 1300, 1253, 1189, 1162, 1113, 1076, 1027, 943, 872, 851, 832, 751 cm^{-1}; MS (ESI, m/z): 370.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}{}^{79}BrNO_2$: 370.0437 $[M+H]^+$, found: 370.0440.

4.7.16 7-(2-Bromophenyl)-2-methylene-5-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (33q)

1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-en-1-one (**32q**) (102.7 mg, 0.29 mmol) and $ZnCl_2$ (39.5 mg, 0.29 mmol) were employed to afford the indicated product (92.4 mg (90%) in refluxing $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.44-7.37 (m, 1H), 7.33-7.27 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.06 (s, 1H), 4.70 (s, 3H), 4.40 (br s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6 (C), 159.5 (C), 159.0 (C), 140.5 (C), 137.8 (C), 136.3 (C), 133.4 (CH), 130.9 (CH), 130.8 (CH), 129.2 (CH), 127.5 (CH), 127.4 (CH), 122.1 (CBr), 104.8 (CH), 94.0 (CH_2), 55.4 (CH_2), 21.5 (CH_3); IR (neat): 2951, 2920, 2839, 1656, 1626, 1610, 1589, 1562, 1509, 1467, 1434, 1353, 1310, 1277, 1252, 1181, 1107, 1071, 1040, 1030, 861, 812, 754 cm^{-1}; MS (ESI, m/z): 354.05 $[M+H]^+$; HRMS (ESI)

calcd. for $C_{19}H_{17}{}^{79}BrNO$: 354.0488 $[M+H]^+$, found: 354.0489.

4.7.17 7-(2-Bromophenyl)-2-methylene-5-(*m*-tolyl)-2,3-dihydro-1,4-oxazepine (33r)

1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-en-1-one (**32r**) (77.9 mg, 0.22 mmol) and $ZnCl_2$ (30.0 mg, 0.22 mmol) were employed to afford the indicated product (74.0 mg (95%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.50 (m, 4H), 7.47-7.17 (m, 4H), 6.06 (s, 1H), 4.71 (s, 3H), 4.40 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (C), 159.5 (C), 158.9 (C), 139.1 (C), 138.2 (C), 137.8 (C), 133.5 (CH), 131.0 (CH), 130.9 (CH), 130.8 (CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 124.6 (CH), 122.1 (CBr), 104.8 (CH), 94.1 (CH_2), 55.5 (CH_2), 21.5 (CH_3); IR (neat): 3021, 2921, 2855, 1653, 1632, 1592, 1572, 1466, 1355, 1310, 1255, 1184, 1106, 1066, 1039, 1021, 951, 862, 831, 796, 757 cm^{-1}; MS (ESI, m/z): 354.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}{}^{79}BrNO$: 354.0488 $[M+H]^+$, found: 354.0495.

4.7.18 7-(2-Bromophenyl)-2-methylene-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1,4-oxazepine (33s)

1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**32s**) (93.9 mg, 0.23 mmol) and $ZnCl_2$ (31.4 mg, 0.23 mmol) were employed to afford the indicated product (85.4 mg (91%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.1 Hz, 3H), 7.57 (dd, J = 7.6, 1.7 Hz, 1H), 7.41 (td, J = 7.5, 1.1 Hz, 1H), 7.32 (td, J = 7.7, 1.7 Hz, 1H), 6.03 (s, 1H), 4.75 (s, 1H), 4.74 (s, 2H), 4.43 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 (C), 160.2 (C), 158.5 (C), 142.5 (C), 137.6 (C), 133.5 (CH), 131.9 (q, ^2J = 32.5 Hz, C), 131.1 (CH), 130.7 (CH), 127.8 (CH), 127.6 (CH), 125.4 (q, ^3J = 3.7 Hz, CH), 124.1 (q, ^1J = 272.3 Hz, CF_3), 122.0 (CBr), 104.0 (CH), 94.8 (CH_2), 55.8 (CH_2); IR (neat): 3054, 2985, 1650, 1632, 1595, 1571, 1467, 1443, 1408, 1359, 1320, 1256, 1185, 1173, 1119, 1105, 1071, 1062, 1029, 1013,

954, 853, 767 cm^{-1}; MS (ESI, m/z): 408.02 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{14}{}^{79}BrF_3NO$: 408.0205 $[M+H]^+$, found: 408.0213.

4.7.19 7-(2-Bromophenyl)-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (33t)

1-(2-Bromophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32t**) (96.7 mg, 0.27 mmol) and $ZnCl_2$ (36.8 mg, 0.27 mmol) were employed to afford the indicated product (83.2 mg (86%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.53-7.48 (m, 1H), 7.48-7.42 (m, 2H), 7.34-7.25 (m, 2H), 7.24-7.17 (m, 1H), 7.07-7.01 (m, 1H), 5.90 (s, 1H), 4.62 (d, *J* = 1.4 Hz, 1H), 4.60 (s, 2H), 4.31 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (C), 162.9 (d, ^1J = 246.2 Hz, CF), 160.2 (C), 158.5 (C), 141.3 (d, ^3J = 7.7 Hz, C), 137.6 (C), 133.5 (CH), 131.1 (CH), 130.8 (CH), 130.0 (d, ^3J = 8.1 Hz, CH), 127.6 (CH), 123.2 (d, ^4J = 2.5 Hz, CH), 122.0 (CBr), 117.21 (d, ^2J = 21.4 Hz, CH), 114.4 (d, ^2J = 22.8 Hz, CH), 104.1 (CH), 94.7 (CH_2), 55.5 (CH_2); IR (neat): 3063, 2959, 1657, 1625, 1571, 1484, 1468, 1439, 1359, 1309, 1297, 1277, 1258, 1241, 1194, 1161, 1110, 1072, 1042, 1027, 1010, 981, 945, 897, 857, 786, 756 cm^{-1}; MS (ESI, m/z): 358.02 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{79}BrFNO$: 358.0237 $[M+H]^+$, found: 358.0242.

4.7.20 5,7-Bis(2-bromophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (33u)

1,3-Bis(2-bromophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32u**) (83.8 mg, 0.20 mmol) and $ZnCl_2$ (27.3 mg, 0.20 mmol) were employed to afford the indicated product (57.0 mg (68%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.60 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.54 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.45 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.36 (td, *J* = 7.5, 1.2 Hz, 2H), 7.31-7.21 (m, 2H), 5.78 (s, 1H), 4.79 (s, 1H), 4.72 (s, 2H), 4.43 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6 (C), 158.7 (C), 158.1 (C), 141.4 (C), 137.6 (C), 133.4 (CH), 133.2 (CH), 130.9 (CH), 130.6 (CH), 130.4 (CH), 130.2 (CH), 127.6 (CH),

127.5 (CH), 122.1 (CBr), 121.3 (CBr), 106.3 (CH), 95.1 (CH_2), 56.1 (CH_2); IR (neat): 3055, 2973, 1656, 1629, 1589, 1577, 1562, 1466, 1428, 1360, 1316, 1300, 1247, 1190, 1117, 1075, 1024, 943, 854, 828, 753 cm^{-1}; MS (ESI, m/z): 417.94 and 419.94 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{79}Br_2NO$: 417.9437 $[M+H]^+$, found: 417.9432; calcd. for $C_{18}H_{14}{}^{79}Br^{81}Br$ NO: 419.9417 $[M+H]^+$, found: 419.9417.

4.7.21 7-(4-Chlorophenyl)-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (33z)

1-(4-Chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**32z**) (72.2 mg, 0.23 mmol) and $ZnCl_2$ (31.4 mg, 0.23 mmol) were employed to afford the indicated product (55.6 mg (77%) in refluxing $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73-7.66 (m, 2H), 7.55 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.53-7.48 (m, 1H), 7.44-7.33 (m, 3H), 7.17-7.09 (m, 1H), 6.31 (s, 1H), 4.77 (d, *J* = 1.2 Hz, 1H), 4.55 (s, 2H), 4.41 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (C), 162.9 (d, ^1J = 246.3 Hz, CF), 158.4 (C), 157.8 (C), 141.9 (d, ^3J = 7.1 Hz, C), 136.5 (C), 133.5 (C), 130.0 (d, ^3J = 8.1 Hz, CH), 128.9 (CH), 127.7 (CH), 123.2 (d, ^4J = 2.6 Hz, CH), 117.10 (d, ^2J = 21.5 Hz, CH), 114.5 (d, ^2J = 22.7 Hz, CH), 99.3 (CH), 94.7 (CH_2), 55.5 (CH_2); IR (neat): 3297, 2997, 1657, 1623, 1591, 1573, 1484, 1439, 1402, 1362, 1314, 1259, 1178, 1090, 1055, 1010, 984, 881, 819, 783 cm^{-1}; MS (ESI, m/z): 314.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClFNO$: 314.0743 $[M+H]^+$, found: 314.0750.

4.8 Reaction of *N*-Propargylic β-Enaminone 7a with $ZnCl_2$

To a stirred solution of 1,3-diphenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-en-1-one (**7a**) (57.4 mg, 0.17 mmol) in $CHCl_3$ (3 mL) at room temperature under argon were added $ZnCl_2$ (23.2 mg, 0.17 mmol). The resulting mixture was then refluxed (Note that reaction was continued until *N*-propargylic β-enaminone **7a** was completely consumed as monitored by routine TLC). After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (25 mL)

and a saturated aqueous solution of NH_4Cl (10 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to 16.0 mg (28%) in refluxing $CHCl_3$ of (2,4-diphenylpyridin-3-yl)(phenyl)methanone (**82**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 5.1 Hz, 1H), 7.59-7.54 (m, 2H), 7.54-7.49 (m, 2H), 7.39 (d, *J* = 5.0 Hz, 1H), 7.39-7.34 (m, 1H), 7.30-7.19 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3 (C=O), 157.2 (C), 149.9 (CH), 149.3 (C), 139.6 (C), 137.9 (C), 137.7 (C), 133.7 (C), 133.3 (CH), 129.4 (CH), 129.3 (CH), 128.8 (CH), 128.7 (CH), 128.5 (2 x CH), 128.4 (CH), 128.3 (CH), 123.2 (CH); IR (neat): 3054, 1663, 1595, 1538, 1492, 1441, 1384, 1293, 1248, 1178, 1155, 1026, 921, 858, 753, 695 cm^{-1}; MS (ESI, m/z): 336.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{18}NO$: 336.1383 $[M+H]^+$, found: 336.1398. The spectral data were in agreement with those reported previously for this compound.[112]

4.9 Reaction of 2,3-Dihydro-1,4-oxazepine 33a with SiO_2

To a stirred solution of 2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**33a**) (55.0 mg, 0.21 mmol) in EtOAc (5.0 mL) at room temperature were added excess SiO_2. The resulting mixture was then refluxed (Note that reaction was continued for 5 h and monitored by routine TLC). Due to no change in TLC in 5 h, EtOAc was evaporated and the mixture was again refluxed with 5.0 mL of 1,4-dioxane (Note that reaction was continued for 15 h and monitored by routine TLC). After 15 h, 1,4-dioxane was evaporated on a rotary evaporator and chromatographic purification with silica gel using hexane/ethyl acetate (15:1 followed by 9:1) as the eluent afforded two products. The mixture was then rechromatographed on aluminium oxide (neutral), which afforded two fractions. The product in the first fraction was identified as starting material, 2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**33a**) (6.1 mg, 11%). The product in the second fraction was assigned as (4-methyl-2-phenyl-1*H*-pyrrol-3-yl)(phenyl)methanone (**71a**) (14.3 mg, 26%).

71a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.67-7.63 (m, 2H), 7.33-7.27 (m, 1H), 7.20-7.08 (m, 7H), 6.68-6.64 (m, 1H), 2.18 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0 (C=O), 139.6 (C), 136.4 (C), 132.4 (C), 131.9 (CH), 129.9 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.4 (CH), 122.4 (C), 120.5 (C), 117.4 (CH), 11.7 (CH_3); IR (neat): 3259, 3057, 2922, 1721, 1614, 1595, 1574, 1449, 1424, 1282, 1241, 1072, 901, 767, 732, 692 cm^{-1}; MS (ESI, m/z): 262.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{16}NO$: 262.1226 $[M+H]^+$, found: 262.1239.

4.10 General Procedure for the Synthesis of 1,4-Thiazepines 59 and 85

To a stirred solution of the corresponding thionated *N*-propargylic β-enaminone **58** or **84** (0.30 mmol) in $CHCl_3$ (5 mL) at room temperature under argon were added $ZnCl_2$ (0.30 mmol). The resulting mixture was then refluxed (Note that reaction was continued until thionated *N*-propargylic β-enaminone **58** or **84** was completely consumed as monitored by routine TLC). After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (40 mL) and a saturated aqueous solution of NH_4Cl (15 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding 1,4-thiazepine **59** or **85**.

4.10.1 2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-thiazepine (59a)

1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58a**) (83.2 mg, 0.30 mmol) and $ZnCl_2$ (40.9 mg, 0.30 mmol) were employed to afford 74.9 mg (90%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.77 (m, 2H), 7.72-7.65 (m, 2H), 7.46-7.39 (m, 6H), 6.86 (s, 1H), 5.21 (d, *J* = 0.7 Hz, 1H), 5.18 (s, 1H), 4.81 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4 (C), 150.0 (C), 145.2 (C), 140.1

(C), 139.4 (C), 130.3 (CH), 129.9 (CH), 128.8 (CH), 128.5 (CH), 127.7 (CH), 127.6 (CH), 123.2 (CH), 110.4 (CH_2), 59.3 (CH_2); IR (neat): 2945, 2846, 1613, 1569, 1488, 1443, 1328, 1308, 1262, 1236, 1164, 1067, 1027, 999, 943, 921, 901, 875, 856, 779, 755, 686, 567, 548 cm^{-1}; MS (ESI, m/z): 278.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{16}NS$: 278.0998 $[M+H]^+$, found: 278.0992.

4.10.2 5-(4-Methoxyphenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-thiazepine (59b)

3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58b**) (86.1 mg, 0.28 mmol) and $ZnCl_2$ (38.2 mg, 0.28 mmol) were employed to afford 68.9 mg (80%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.74 (m, 2H), 7.72-7.65 (m, 2H), 7.45-7.38 (m, 3H), 6.96-6.90 (m, 2H), 6.86 (s, 1H), 5.17 (d, *J* = 0.8 Hz, 1H), 5.16 (d, *J* = 0.5 Hz, 1H), 4.76 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (C), 161.4 (C), 149.3 (C), 145.9 (C), 140.2 (C), 132.1 (C), 129.8 (CH), 129.2 (CH), 128.8 (CH), 127.6 (CH), 123.6 (CH), 113.8 (CH), 109.8 (CH_2), 59.1 (CH_2), 55.4 (OCH_3); IR (neat): 2938, 2851, 1602, 1564, 1506, 1447, 1413, 1324, 1307, 1233, 1167, 1111, 1081, 1026, 940, 863, 834, 763, 734, 695, 660, 620, 565, 548, 515 cm^{-1}; MS (ESI, m/z): 308.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NOS$: 308.1104 $[M+H]^+$, found: 308.1107.

4.10.3 5-(2-Methoxyphenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-thiazepine (59c)

3-(2-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58c**) (110.7 mg, 0.36 mmol) and $ZnCl_2$ (49.0 mg, 0.36 mmol) were employed to afford 77.5 mg (70%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67-7.60 (m, 2H), 7.54 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.40-7.34 (m, 4H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.84 (s, 1H), 5.22 (s, 1H), 5.16 (s, 1H), 4.83 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2 (C), 157.4 (C), 146.5 (C), 145.1 (C), 140.3 (C), 130.9 (CH), 130.3 (CH), 129.9 (C), 129.5 (CH), 128.6 (CH), 127.7

(CH), 125.9 (CH), 121.1 (CH), 111.7 (CH), 110.2 (CH_2), 59.5 (CH_2), 56.0 (OCH_3); IR (neat): 2942, 2837, 1612, 1595, 1578, 1561, 1486, 1433, 1332, 1287, 1242, 1162, 1116, 1093, 1048, 1023, 944, 903, 845, 772, 749, 696, 672, 651, 567, 541 cm^{-1}; MS (ESI, m/z): 308.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NOS$: 308.1104 $[M+H]^+$, found: 308.1104.

4.10.4 2-Methylene-7-phenyl-5-(*p*-tolyl)-2,3-dihydro-1,4-thiazepine (59d)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-ene-1-thione (**58d**) (96.2 mg, 0.33 mmol) and $ZnCl_2$ (45.0 mg, 0.33 mmol) were employed to afford 81.7 mg (85%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76-7.65 (m, 4H), 7.47-7.39 (m, 3H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.87 (s, 1H), 5.20 (d, *J* = 0.7 Hz, 1H), 5.18 (d, *J* = 0.5 Hz, 1H), 4.80 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C), 149.5 (C), 145.6 (C), 140.4 (C), 140.1 (C), 136.7 (C), 129.8 (CH), 129.2 (CH), 128.7 (CH), 127.64 (CH), 127.62 (CH), 123.6 (CH), 110.1 (CH_2), 59.2 (CH_2), 21.5 (CH_3); IR (neat): 2940, 2847, 1607, 1572, 1561, 1487, 1444, 1332, 1308, 1263, 1236, 1179, 1164, 1113, 1081, 1017, 942, 916, 884, 861, 841, 820, 763, 696, 658, 567, 531, 497cm^{-1}; MS (ESI, m/z): 292.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NS$: 292.1155 $[M+H]^+$, found: 292.1161.

4.10.5 2-Methylene-7-phenyl-5-(*m*-tolyl)-2,3-dihydro-1,4-thiazepine (59e)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-ene-1-thione (**58e**) (72.9 mg, 0.25 mmol) and $ZnCl_2$ (34.1 mg, 0.25 mmol) were employed to afford 59.0 mg (81%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.56 (m, 2H), 7.54 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.35-7.30 (m, 3H), 7.24-7.18 (m, 1H), 7.17-7.14 (m, 1H), 6.76 (s, 1H), 5.10 (d, *J* = 0.5 Hz, 1H), 5.08 (s, 1H), 4.70 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5 (C), 149.8 (C), 145.4 (C), 140.1 (C), 139.4 (C), 138.2 (C), 131.1 (CH), 129.8 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 125.0 (CH), 123.5 (CH), 110.4 (CH_2), 59.2 (CH_2), 21.5 (CH_3); IR (neat): 2959, 2915, 2857, 1605, 1569, 1486, 1443, 1380, 1323, 1305, 1267,

1220, 1175, 1155, 1088, 996, 946, 922, 882, 869, 844, 791, 758, 712, 692, 561, 531 cm^{-1}; MS (ESI, m/z): 292.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NS$: 292.1155 $[M+H]^+$, found: 292.1160.

4.10.6 2-Methylene-7-phenyl-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1,4-thiazepine (59f)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-ene-1-thione (**58f**) (89.8 mg, 0.26 mmol) and $ZnCl_2$ (35.4 mg, 0.26 mmol) were employed to afford 62.9 mg (70%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 2H), 7.72-7.64 (m, 4H), 7.49-7.39 (m, 3H), 6.81 (s, 1H), 5.25 (d, J = 0.9 Hz, 1H), 5.19 (d, J = 0.6 Hz, 1H), 4.85 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 (C), 151.2 (C), 144.7 (C), 142.9 (C), 139.9 (C), 132.0 (q, ^2J = 32.4 Hz, C), 130.1 (CH), 128.9 (CH), 128.1 (CH), 127.6 (CH), 125.5 (q, ^3J = 3.7 Hz, CH), 124.2 (q, ^1J = 272.2 Hz, CF_3), 122.2 (CH), 111.2 (CH_2), 59.7 (CH_2); IR (neat): 3035, 2951, 2849, 1613, 1556, 1491, 1445, 1410, 1322, 1260, 1237, 1158, 1116, 1084, 1064, 1016, 945, 917, 890, 867, 835, 770, 751, 722, 696, 666, 599, 572, 514 cm^{-1}; MS (ESI, m/z): 346.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}F_3NS$: 346.0872 $[M+H]^+$, found: 346.0884.

4.10.7 5-(3-Fluorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-thiazepine (59h)

3-(3-Fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58h**) (94.5 mg, 0.32 mmol) and $ZnCl_2$ (43.6 mg, 0.32 mmol) were employed to afford 65.2 mg (69%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.63 (m, 2H), 7.60-7.51 (m, 2H), 7.47-7.35 (m, 4H), 7.13 (tdd, J = 8.3, 2.6, 0.9 Hz, 1H), 6.81 (s, 1H), 5.23 (d, J = 0.9 Hz, 1H), 5.18 (d, J = 0.5 Hz, 1H), 4.82 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 (C), 162.9 (d, ^1J = 246.1 Hz, CF), 150.7 (C), 144.9 (C), 141.8 (d, ^3J = 7.1 Hz, C), 140.0 (C), 130.0 (CH), 129.9 (CH), 128.8 (CH), 127.6 (CH), 123.5 (d, ^4J = 2.5 Hz, CH), 122.5 (CH), 117.2 (d, ^2J = 21.3 Hz,

CH), 114.6 (d, ^2J = 22.7 Hz, CH), 110.8 (CH_2), 59.4 (CH_2); IR (neat): 3053, 2949, 1616, 1567, 1481, 1436, 1309, 1261, 1243, 1168, 1149, 1075, 1061, 988, 949, 926, 874, 826, 790, 755, 685, 657, 566, 524 cm^{-1}; MS (ESI, m/z): 296.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}FNS$: 296.0904 $[M+H]^+$, found: 296.0907.

4.10.8 5-(2-Bromophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-thiazepine (59i)

3-(2-Bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58i**) (85.5 mg, 0.24 mmol) and $ZnCl_2$ (32.7 mg, 0.24 mmol) were employed to afford 57.3 mg (67%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.57 (m, 3H), 7.50-7.33 (m, 5H), 7.30-7.22 (m, 1H), 6.58 (s, 1H), 5.33 (s, 1H), 5.18 (s, 1H), 4.88 (s, 2H); ^{13}C NMR (100 MHz, CDCl3) δ 169.2 (C), 150.0 (C), 143.7 (C), 141.8 (C), 139.9 (C), 133.2 (CH), 130.4 (CH), 130.2 (CH), 129.8 (CH), 128.7 (CH), 127.6 (2xCH), 123.4 (CH), 121.6 (CBr), 111.7 (CH_2), 59.8 (CH_2); IR (neat): 3055, 2850, 1731, 1612, 1559, 1489, 1465, 1426, 1268, 1235, 1211, 1160, 1090, 1024, 944, 913, 868, 837, 754, 730, 693, 641, 552 cm^{-1}; MS (ESI, m/z): 356.01 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}{}^{79}BrNS$: 356.0103 $[M+H]^+$, found: 356.0105.

4.10.9 5-(4-(*tert*-Butyl)phenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-thiazepine (59j)

3-(4-(*tert*-Butyl)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58j**) (110.1 mg, 0.33 mmol) and $ZnCl_2$ (45.0 mg, 0.33 mmol) were employed to afford 95.7 mg (87%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.73-7.68 (m, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.44-7.41 (m, 3H), 6.90 (s, 1H), 5.20 (s, 1H), 5.18 (s, 1H), 4.81 (s, 2H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C), 153.6 (C), 149.4 (C), 145.6 (C), 140.2 (C), 136.7 (C), 129.8 (CH), 128.7 (CH), 127.7 (CH), 127.4 (CH), 125.4 (CH), 123.6 (CH), 110.0 (CH_2), 59.2 (CH_2), 34.9 (C), 31.3 (CH_3); IR (neat): 2959, 2903, 2865, 1607, 1566,

1489, 1460, 1445, 1405, 1362, 1325, 1305, 1268, 1236, 1189, 1110, 1081, 1017, 943, 832, 764, 747, 693, 662, 552 cm^{-1}; MS (ESI, m/z): 334.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{24}NS$: 334.1624 $[M+H]^+$, found: 334.1636.

4.10.10 5-Butyl-2-methylene-7-phenyl-2,3-dihydro-1,4-thiazepine (59l)

1-Phenyl-3-(prop-2-yn-1-ylamino)hept-2-ene-1-thione (**58l**) (77.2 mg, 0.30 mmol) and $ZnCl_2$ (40.9 mg, 0.30 mmol) were employed to afford 60.2 mg (78%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.52 (m, 2H), 7.43-7.35 (m, 3H), 6.40 (s, 1H), 5.16 (s, 1H), 5.08 (s, 1H), 4.58 (s, 2H), 2.43-2.36 (m, 2H), 1.66-1.55 (m, 2H), 1.39 (sextet, J = 7.4 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1 (C), 147.9 (C), 144.7 (C), 140.1 (C), 129.7 (CH), 128.7 (CH), 127.6 (CH), 124.2 (CH), 110.2 (CH_2), 59.0 (CH_2), 40.3 (CH_2), 29.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3); IR (neat): 3234, 2956, 2927, 2869, 1600, 1561, 1489, 1444, 1377, 1314, 1273, 1204, 1175, 1073, 1028, 999, 912, 759, 694, 616 cm^{-1}; MS (ESI, m/z): 258.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{20}NS$: 258.1311 $[M+H]^+$, found: 258.1312.

4.10.11 2-Methylene-7-phenyl-5-(thiophen-3-yl)-2,3-dihydro-1,4-thiazepine (59m)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-ene-1-thione (**58m**) (90.7 mg, 0.32 mmol) and $ZnCl_2$ (43.6 mg, 0.32 mmol) were employed to afford 68.9 mg (76%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.62 (m, 3H), 7.56 (dd, J = 5.1, 1.2 Hz, 1H), 7.46-7.38 (m, 3H), 7.32 (dd, J = 5.1, 2.9 Hz, 1H), 6.88 (s, 1H), 5.20 (d, J = 0.6 Hz, 1H), 5.17 (s, 1H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (C), 149.6 (C), 145.0 (C), 142.6 (C), 140.0 (C), 129.9 (CH), 128.8 (CH), 127.6 (CH), 126.9 (CH), 126.3 (CH), 126.0 (CH), 122.7 (CH), 110.5 (CH_2), 59.1 (CH_2); IR (neat): 3046, 2929, 2851, 1605, 1567, 1517, 1489, 1442, 1410, 1389, 1299, 1252, 1231, 1219, 1192, 1157, 1084, 988, 946, 922, 865, 832, 761, 722, 689, 664, 627, 597, 564, 547 cm^{-1}; MS (ESI, m/z): 284.06 $[M+H]^+$;

HRMS (ESI) calcd. for $C_{16}H_{14}NS_2$: 284.0562 $[M+H]^+$, found: 284.0563.

4.10.12 7-(2-Bromophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-thiazepine (59n)

1-(2-Bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58n**) (74.8 mg, 0.21 mmol) and $ZnCl_2$ (28.6 mg, 0.21 mmol) were employed to afford 62.8 mg (84%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.79 (m, 2H), 7.67 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.50-7.35 (m, 5H), 7.30-7.24 (m, 1H), 6.67 (s, 1H), 5.20 (s, 2H), 4.95 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (C), 149.3 (C), 145.8 (C), 140.9 (C), 139.3 (C), 133.4 (CH), 130.8 (CH), 130.33 (CH), 130.29 (CH), 128.5 (CH), 127.7 (CH), 127.6 (CH), 126.4 (CH), 122.5 (CBr), 110.5 (CH_2), 59.4 (CH_2); IR (neat): 3055, 2942, 2848, 1725, 1613, 1572, 1462, 1431, 1324, 1260, 1232, 1160, 1087, 1067, 1050, 1025, 941, 920, 865, 752, 689, 646, 579, 556, 519 cm^{-1}; MS (ESI, m/z): 356.01 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}{}^{79}BrNS$: 356.0103 $[M+H]^+$, found: 356.0105.

4.10.13 7-(2-Bromophenyl)-2-methylene-5-(*m*-tolyl)-2,3-dihydro-1,4-thiazepine (59r)

1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-ene-1-thione (**58r**) (66.7 mg, 0.18 mmol) and $ZnCl_2$ (24.5 mg, 0.18 mmol) were employed to afford 56.0 mg (84%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.65 (m, 2H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.34-7.25 (m, 3H), 6.66 (s, 1H), 5.23 (s, 1H), 5.22 (s, 1H), 4.94 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C), 150.0 (C), 145.5 (C), 140.9 (C), 138.9 (C), 138.3 (C), 133.4 (CH), 131.4 (CH), 130.8 (CH), 130.4 (CH), 128.40 (CH), 128.35 (CH), 127.6 (CH), 126.3 (CH), 125.1 (CH), 122.5 (CBr), 111.0 (CH_2), 59.1 (CH_2), 21.5 (CH_3); IR (neat): 3051, 2918, 2850, 1712, 1613, 1579, 1536, 1462, 1427, 1307, 1267, 1160, 1071, 1049, 1025, 942, 918, 864, 846, 790, 755, 728, 687, 646, 580, 561, 508 cm^{-1}; MS (ESI, m/z): 370.03 $[M+H]^+$; HRMS

(ESI) calcd. for $C_{19}H_{17}{}^{79}BrNS$: 370.0260 $[M+H]^+$, found: 370.0266.

4.10.14 7-(2-Bromophenyl)-2-methylene-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1,4-thiazepine (59s)

1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-ene-1-thione (**58s**) (110.3 mg, 0.26 mmol) and $ZnCl_2$ (35.4 mg, 0.26 mmol) were employed to afford 84.9 mg (77%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 3H), 7.34 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.27 (td, *J* = 7.5, 1.1 Hz, 1H), 7.16 (td, *J* = 7.6, 1.8 Hz, 1H), 6.50 (s, 1H), 5.12 (d, *J* = 0.9 Hz, 1H), 5.10 (s, 1H), 4.86 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C), 150.5 (C), 145.0 (C), 142.6 (C), 140.6 (C), 133.4 (CH), 132.0 (q, ^2J = 32.4 Hz, C), 130.7 (CH), 130.5 (CH), 128.1 (CH), 127.7 (CH), 125.4 (q, ^3J = 3.8 Hz, CH), 125.3 (CH), 124.2 (q, ^1J = 272.2 Hz, CF_3), 122.4 (CBr), 111.3 (CH_2), 59.7 (CH_2); IR (neat): 3058, 2947, 2852, 1734, 1616, 1571, 1464, 1431, 1408, 1319, 1234, 1163, 1121, 1081, 1065, 1015, 941, 834, 760, 748, 725, 688, 648, 595 cm^{-1}; MS (ESI, m/z): 424.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{14}{}^{79}BrF_3NS$: 423.9977 $[M+H]^+$, found: 423.9983.

4.10.15 7-(2-Bromophenyl)-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-thiazepine (59t)

1-(2-Bromophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58t**) (74.9 mg, 0.20 mmol) and $ZnCl_2$ (27.3 mg, 0.20 mmol) were employed to afford 60.6 mg (81%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.62-7.53 (m, 2H), 7.47-7.35 (m, 3H), 7.30-7.25 (m, 1H), 7.14 (tdd, *J* = 8.3, 2.6, 0.8 Hz, 1H), 6.61 (s, 1H), 5.22 (d, *J* = 0.8 Hz, 1H), 5.21 (s, 1H), 4.95 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (d, ^4J = 3.0 Hz, C), 162.9 (d, ^1J = 246.3 Hz, CF), 150.1 (C), 145.2 (C), 141.5 (d, ^3J = 6.9 Hz, C), 140.7 (C), 133.4 (CH), 130.7 (CH), 130.5 (CH), 130.0 (d, ^3J = 8.1 Hz, CH), 127.6 (CH), 125.6 (CH), 123.5 (d, ^4J = 2.8 Hz, CH), 122.5 (CBr), 117.2 (d, ^2J = 21.2 Hz, CH),

114.6 (d, ^{2}J = 22.7 Hz, CH), 111.0 (CH_2), 59.5 (CH_2); IR (neat): 3067, 2945, 2850, 1731, 1613, 1575, 1484, 1463, 1433, 1308, 1263, 1237, 1176, 1152, 1050, 1025, 985, 943, 920, 874, 846, 787, 756, 730, 705, 686, 647, 578 cm^{-1}; MS (ESI, m/z): 374.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{79}BrFNS$: 374.0009 $[M+H]^+$, found: 374.0013.

4.10.16 7-(4-Methoxyphenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-thiazepine (59v)

1-(4-Methoxyphenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58v**) (86.1 mg, 0.28 mmol) and $ZnCl_2$ (27.3 mg, 0.28 mmol) were employed to afford 70.6 mg (82%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.3, 2.1 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.47-7.39 (m, 3H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.80 (s, 1H), 5.18 (s, 1H), 5.16 (s, 1H), 4.79 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5 (C), 161.0 (C), 149.3 (C), 145.4 (C), 139.6 (C), 132.3 (C), 130.2 (CH), 129.0 (CH), 128.4 (CH), 127.7 (CH), 122.0 (CH), 114.1 (CH), 110.0 (CH_2), 59.3 (CH_2), 55.5 (OCH_3); IR (neat): 2940, 2846, 1602, 1564, 1503, 1446, 1435, 1328, 1306, 1288, 1252, 1238, 1177, 1161, 1113, 1087, 1068, 1028, 944, 921, 879, 846, 826, 772, 721, 700, 688, 634, 562, 544, 505 cm^{-1}; MS (ESI, m/z): 308.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NOS$: 308.1104 $[M+H]^+$, found: 308.1113.

4.10.17 2-Methylene-5-phenyl-7-(*p*-tolyl)-2,3-dihydro-1,4-thiazepine (59w)

3-Phenyl-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-ene-1-thione (**58w**) (90.3 mg, 0.31 mmol) and $ZnCl_2$ (42.3 mg, 0.31 mmol) were employed to afford 74.1 mg (82%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.79 (m, 2H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.47-7.40 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.84 (s, 1H), 5.20 (s, 1H), 5.17 (s, 1H), 4.81 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4 (C), 149.8 (C), 145.4 (C), 140.1 (C), 139.5 (C), 137.2 (C), 130.2 (CH), 129.4 (CH), 128.4 (CH), 127.7 (CH), 127.5 (CH), 122.6 (CH), 110.1 (CH_2), 59.3

(CH_2), 21.4 (CH_3); IR (neat): 3025, 2943, 2851, 1611, 1568, 1504, 1492, 1444, 1326, 1307, 1259, 1235, 1178, 1160, 1088, 1066, 1031, 1001, 940, 919, 881, 866, 848, 815, 770, 688, 651, 636, 563, 529, 503 cm^{-1}; MS (ESI, m/z): 292.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NS$: 292.1155 $[M+H]^+$, found: 292.1157.

4.10.18 2-Methylene-5-(thiophen-3-yl)-7-(*p*-tolyl)-2,3-dihydro-1,4-thiazepine (59x)

3-(Prop-2-yn-1-ylamino)-3-(thiophen-3-yl)-1-(*p*-tolyl)prop-2-ene-1-thione (**58x**) (65.4 mg, 0.22 mmol) and $ZnCl_2$ (30.0 mg, 0.22 mmol) were employed to afford 54.3 mg (83%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 2.9, 1.2 Hz, 1H), 7.60-7.52 (m, 3H), 7.32 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.86 (s, 1H), 5.18 (d, *J* = 0.7 Hz, 1H), 5.16 (s, 1H), 4.76 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (C), 149.5 (C), 145.2 (C), 142.7 (C), 140.1 (C), 137.2 (C), 129.5 (CH), 127.5 (CH), 127.0 (CH), 126.2 (CH), 125.9 (CH), 122.1 (CH), 110.2 (CH_2), 59.1 (CH_2), 21.4 (CH_3); IR (neat): 2929, 2843, 1606, 1574, 1504, 1450, 1408, 1373, 1310, 1235, 1185, 1168, 1082, 1018, 950, 922, 897, 867, 835, 812, 777, 726, 682, 655, 639, 591, 562, 521 cm^{-1}; MS (ESI, m/z): 298.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{16}NS_2$: 298.0719 $[M+H]^+$, found: 298.0723.

4.10.19 7-(4-Chlorophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-thiazepine (59y)

1-(4-Chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58y**) (99.8 mg, 0.32 mmol) and $ZnCl_2$ (43.6 mg, 0.32 mmol) were employed to afford 85.8 mg (86%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82-7.75 (m, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.48-7.35 (m, 5H), 6.82 (s, 1H), 5.20 (s, 1H), 5.18 (s, 1H), 4.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C), 148.5 (C), 145.1 (C), 139.3 (C), 138.5 (C), 135.8 (C), 130.3 (CH), 129.0 (CH), 128.9 (CH), 128.5 (CH), 127.6 (CH), 123.7 (CH), 110.6 (CH_2), 59.2 (CH_2); IR (neat): 3020,

2954, 1613, 1590, 1574, 1483, 1443, 1396, 1323, 1310, 1293, 1234, 1168, 1088, 1067, 1027, 1011, 944, 882, 850, 823, 765, 722, 708, 685, 658, 614, 570, 560 cm^{-1}; MS (ESI, m/z): 312.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}ClNS$: 312.0608 $[M+H]^+$, found: 312.0603.

4.10.20 7-(4-Chlorophenyl)-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-thiazepine (59z)

1-(4-Chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58z**) (75.9 mg, 0.23 mmol) and $ZnCl_2$ (31.4 mg, 0.23 mmol) were employed to afford 64.5 mg (85%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.5 Hz, 2H), 7.57-7.47 (m, 2H), 7.43-7.35 (m, 3H), 7.13 (td, J = 8.3, 2.4 Hz, 1H), 6.77 (s, 1H), 5.22 (s, 1H), 5.18 (s, 1H), 4.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (d, ^4J = 2.4 Hz, C), 162.9 (d, ^1J = 246.4 Hz, CF), 149.4 (C), 144.6 (C), 141.6 (d, ^3J = 7.1 Hz, C), 138.3 (C), 136.1 (C), 130.0 (d, ^3J = 8.1 Hz, CH), 129.05 (CH), 128.95 (CH), 123.4 (d, ^4J = 2.6 Hz, CH), 122.9 (CH), 117.3 (d, ^2J = 21.4 Hz, CH), 114.6 (d, ^2J = 22.7 Hz, CH), 111.1 (CH_2), 59.4 (CH_2); IR (neat): 2962, 1615, 1598, 1572, 1483, 1431, 1397, 1326, 1269, 1239, 1163, 1145, 1089, 1062, 1012, 988, 949, 920, 884, 862, 827, 816, 786, 726, 700, 676, 654, 624, 577, 563, 544, 523 cm^{-1}; MS (ESI, m/z): 330.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClFNS$: 330.0514 $[M+H]^+$, found: 330.0516.

4.10.21 (*Z*)-2-Benzylidene-5,7-diphenyl-2,3-dihydro-1,4-thiazepine (85)

1,3-Diphenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-ene-1-thione (**84**) (78.6 mg, 0.22 mmol) and $ZnCl_2$ (30 mg, 0.22 mmol) were employed to afford 49.5 mg, (63%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88-7.80 (m, 2H), 7.76-7.69 (m, 2H), 7.50 (d, J = 7.5 Hz, 2H), 7.48-7.40 (m, 6H), 7.34 (t, J = 7.7 Hz, 2H), 7.22 (t, J = 7.4 Hz, 1H), 6.93 (s, 1H), 6.57 (s, 1H), 4.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C), 150.1 (C), 140.3 (C), 139.2 (C), 137.6 (C), 136.1 (C), 130.4 (CH), 129.9 (CH), 128.81 (CH), 128.75 (CH), 128.5 (CH), 128.4 (CH),

127.9 (CH), 127.8 (CH), 127.2 (CH), 125.4 (CH), 123.8 (CH), 61.3 (CH_2); IR (neat): 3050, 3021, 2921, 2854, 1611, 1596, 1567, 1488, 1443, 1309, 1259, 1213, 1183, 1089, 1069, 1026, 990, 941, 910, 864, 848, 780, 753, 686, 647 cm^{-1}; MS (ESI, m/z): 354.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{20}NS$: 354.1311 $[M+H]^+$, found: 354.1320.

4.11 General Procedure for the Synthesis of 5-Methylpyridines 61

To a stirred solution of the corresponding thio-β-enaminone **58** (0.3 mmol) in DMF (0.5 mL) at room temperature under argon was added (*i*-Pr)$_2$NH (0.5 mL), and the resulting mixture was stirred at room temperature. (Note that stirring was continued until thio-β-enaminone **58** was completely consumed as monitored by routine TLC). After the reaction was over, ethyl acetate (40 mL) was added, and the resulting solution was washed with a saturated NH_4Cl solution (15 mL) in a separatory funnel. After the layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 30 mL). Then, organic phase was dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (15:1 followed by 9:1) as the eluent to afford the 5-methylpyridine **61**.

4.11.1 5-Methyl-2,4-diphenylpyridine (61a)

1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58a**) (83.2 mg, 0.30 mmol) and (*i*-Pr)$_2$NH (0.50 mL, 3.56 mmol) were employed to afford 62.4 mg (85%) of the indicated product and 4.2 mg (5%) of 2-methylene-5,7-diphenyl-2,3-dihydro-1,4-thiazepine (**59a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.03 (d, *J* = 7.5 Hz, 2H), 7.63 (s, 1H), 7.53-7.37 (m, 8H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4 (C), 151.3 (CH), 150.0 (C), 139.5 (C), 139.4 (C), 129.2 (C), 128.8 (CH), 128.74 (CH), 128.65 (CH), 128.6 (CH), 128.1 (CH), 126.8 (CH), 121.0 (CH), 17.0 (CH_3); IR (neat): 3056, 2999, 2921, 1735, 1591, 1574, 1541, 1495, 1474, 1442, 1370, 1241, 1229, 1075, 1025, 1000, 918, 892, 850, 775, 746,

715, 696, 632, 597, 536 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[113]

4.11.2 2-(4-Methoxyphenyl)-5-methyl-4-phenylpyridine (61b)

3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58b**) (104.5 mg, 0.34 mmol) and (*i*-Pr)$_2$NH (0.57 mL, 4.03 mmol) were employed to afford 71.1 mg (76%) of the indicated product and 9.4 mg (9%) of 5-(4-methoxyphenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-thiazepine (**59b**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.99-7.94 (m, 2H), 7.55 (s, 1H), 7.50-7.36 (m, 5H), 7.03-6.95 (m, 2H), 3.85 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3 (C), 155.0 (C), 151.1 (CH), 150.0 (C), 139.6 (C), 132.0 (C), 128.7 (CH), 128.54 (CH), 128.49 (C), 128.04 (CH), 128.01 (CH), 120.3 (CH), 114.2 (CH), 55.4 (OCH_3), 17.0 (CH_3); IR (neat): 2991, 2956, 2931, 2835, 1606, 1592, 1542, 1513, 1494, 1472, 1441, 1416, 1369, 1305, 1239, 1171, 1110, 1028, 896, 854, 826, 786, 775, 757, 742, 712, 704, 679, 657, 626, 568 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1393.

4.11.3 2-(2-Methoxyphenyl)-5-methyl-4-phenylpyridine (61c)

3-(2-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58c**) (110.7 mg, 0.36 mmol) and (*i*-Pr)$_2$NH (0.60 mL, 4.27 mmol) were employed to afford 45.4 mg (46%) of the indicated product and 8.9 mg (8%) of 5-(2-methoxyphenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-thiazepine (**59c**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.79 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.71 (s, 1H), 7.51-7.34 (m, 6H), 7.09 (td, *J* = 7.5, 1.0 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 3.84 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0 (C), 154.0 (C), 150.9 (CH), 149.0 (C), 139.7 (C), 131.2 (CH), 129.8 (CH), 129.1 (C), 128.82 (CH), 128.78 (C), 128.5 (CH), 127.9 (CH), 125.4 (CH), 121.1 (CH), 111.4 (CH), 55.7 (OCH_3), 17.2 (CH_3); IR (neat): 2995, 2954, 2930, 2834, 1593, 1578, 1540, 1495, 1465, 1435, 1367, 1277, 1240, 1177, 1121, 1058, 1024, 897, 852, 795, 772, 752,

703, 633, 601 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1390.

4.11.4 5-Methyl-4-phenyl-2-(*p*-tolyl)pyridine (61d)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-ene-1-thione (**58d**) (99.1 mg, 0.34 mmol) and $(i\text{-Pr})_2NH$ (0.57 mL, 4.03 mmol) were employed to afford 65.4 mg (74%) of the indicated product and 7.9 mg (8%) of 2-methylene-7-phenyl-5-(*p*-tolyl)-2,3-dihydro-1,4-thiazepine (**59d**). ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.62 (s, 1H), 7.54-7.39 (m, 5H), 7.31 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4 (C), 151.2 (CH), 150.0 (C), 139.6 (C), 138.7 (C), 136.6 (C), 129.5 (CH), 128.9 (C), 128.7 (CH), 128.6 (CH), 128.0 (CH), 126.7 (CH), 120.7 (CH), 21.3 (CH_3), 17.1 (CH_3); IR (neat): 3024, 2919, 1592, 1574, 1542, 1494, 1473, 1442, 1369, 1179, 1111, 1042, 1018, 889, 822, 772, 754, 738, 702, 627, 564 cm^{-1}; MS (ESI, m/z): 260.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}N$: 260.1434 $[M+H]^+$, found: 260.1442.

4.11.5 5-Methyl-4-phenyl-2-(*m*-tolyl)pyridine (61e)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-ene-1-thione (**58e**) (99.1 mg, 0.34 mmol) and $(i\text{-Pr})_2NH$ (0.57 mL, 4.03 mmol) were employed to afford 58.5 mg (66%) of the indicated product and 5.0 mg (5%) of 2-methylene-7-phenyl-5-(*m*-tolyl)-2,3-dihydro-1,4-thiazepine (**59e**). ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.91-7.74 (m, 2H), 7.64 (s, 1H), 7.54-7.35 (m, 6H), 7.25 (d, J = 7.3 Hz, 1H), 2.47 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5 (C), 151.2 (CH), 150.0 (C), 139.6 (C), 139.4 (C), 138.4 (C), 129.5 (CH), 129.2 (C), 128.7 (2xCH), 128.6 (CH), 128.1 (CH), 127.6 (CH), 123.9 (CH), 121.1 (CH), 21.6 (CH_3), 17.1 (CH_3); IR (neat): 3060, 2989, 2918, 1590, 1542, 1495, 1471, 1451, 1440, 1383, 1358, 1229, 1061, 1040, 888, 816, 799, 770, 757, 740, 632, 601, 553 cm^{-1}; MS (ESI, m/z): 260.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}N$: 260.1434 $[M+H]^+$, found: 260.1446.

4.11.6 5-Methyl-4-phenyl-2-(4-(trifluoromethyl)phenyl)pyridine (61f)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-ene-1-thione (**58f**) (86.3 mg, 0.25 mmol) and (*i*-Pr)$_2$NH (0.42 mL, 2.96 mmol) were employed to afford 44.0 mg (56%) of the indicated product and 4.3 mg (5%) of 2-methylene-7-phenyl-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1,4-thiazepine (**59f**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.13 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.64 (s, 1H), 7.53-7.43 (m, 3H), 7.41-7.36 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8 (C), 151.6 (CH), 150.4 (C), 142.8 (C), 139.3 (C), 130.7 (q, ^2J = 32.4 Hz, C), 130.4 (C), 128.73 (CH), 128.67 (CH), 128.3 (CH), 127.1 (CH) 125.8 (q, ^3J = 3.7 Hz, CH), 124.2 (q, ^1J = 272.2 Hz, CF_3), 121.4 (CH), 17.2 (CH_3); IR (neat): 2994, 1617, 1594, 1577, 1542, 1493, 1475, 1411, 1326, 1153, 1117, 1102, 1069, 1013, 999, 893, 847, 775, 758, 734, 703, 653, 640, 618, 590 cm^{-1}; MS (ESI, m/z): 314.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}F_3N$: 314.1151 $[M+H]^+$, found: 314.1163.

4.11.7 2-(3-Fluorophenyl)-5-methyl-4-phenylpyridine (61h)

3-(3-Fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58h**) (97.5 mg, 0.33 mmol) and (*i*-Pr)$_2$NH (0.55 mL, 3.91 mmol) were employed to afford 58.5 mg (67%) of the indicated product and 4.9 mg (5%) of 5-(3-fluorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-thiazepine (**59h**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.81-7.73 (m, 2H), 7.59 (s, 1H), 7.52-7.36 (m, 6H), 7.08 (td, J = 8.2, 2.5 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (d, ^1J = 245.3 Hz, CF), 154.0 (d, ^4J = 2.5 Hz, C), 151.4 (CH), 150.2 (C), 141.7 (d, ^3J = 7.5 Hz, C), 139.3 (C), 130.3 (d, ^3J = 8.3 Hz, CH), 130.0 (C), 128.7 (CH), 128.2 (CH), 122.3 (d, ^4J = 2.5 Hz, CH), 121.1 (CH), 115.6 (d, ^2J = 21.2 Hz, CH), 113.8 (d, ^2J = 22.8 Hz, CH), 17.1 (CH_3) (Note that two CH peaks overlap on each other); IR (neat): 3063, 3026, 1612, 1582, 1545, 1494, 1465, 1440, 1359, 1253, 1198, 1170, 1150, 1072, 1051, 991, 900, 880, 822, 787, 771, 755, 737, 690, 632, 597 cm^{-1}; MS (ESI, m/z): 264.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}FN$: 264.1183 $[M+H]^+$, found: 264.1195.

4.11.8 2-(2-Bromophenyl)-5-methyl-4-phenylpyridine (61i)

3-(2-Bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58i**) (89.1 mg, 0.25 mmol) and (*i*-Pr)$_2$NH (0.42 mL, 2.96 mmol) were employed to afford 49.0 mg (60%) of the indicated product and 11.6 mg (13%) of 5-(2-bromophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-thiazepine (**59i**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.70 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.61 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.53 (s, 1H), 7.52-7.40 (m, 6H), 7.29-7.23 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.10 (C), 151.1 (CH), 149.1 (C), 141.2 (C), 139.2 (C), 133.4 (CH), 131.6 (CH), 129.7 (CH), 129.6 (C), 128.8 (CH), 128.6 (CH), 128.2 (CH), 127.6 (CH), 125.2 (CH), 122.1 (CBr), 17.2 (CH_3); IR (neat): 3055, 3024, 2997, 2956, 2923, 1594, 1562, 1538, 1493, 1461, 1440, 1427, 1368, 1256, 1075, 1046, 1024, 1001, 896, 852, 772, 751, 701, 655, 631 cm^{-1}; MS (ESI, m/z): 324.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}{}^{79}BrN$: 324.0382 $[M+H]^+$, found: 324.0392.

4.11.9 2-(4-(*tert*-Butyl)phenyl)-5-methyl-4-phenylpyridine (61j)

3-(4-(*tert*-Butyl)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58j**) (116.7 mg, 0.35 mmol) and (*i*-Pr)$_2$NH (0.58 mL, 4.15 mmol) were employed to afford 71.2 mg (68%) of the indicated product and 5.8 mg (5%) of 5-(4-(*tert*-butyl)phenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-thiazepine (**59j**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.98-7.94 (m, 2H), 7.61 (s, 1H), 7.50 (ddd, *J* = 8.2, 5.1, 1.6 Hz, 4H), 7.46-7.43 (m, 1H), 7.41-7.37 (m, 2H), 2.32 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4 (C), 151.9 (C), 151.3 (CH), 149.9 (C), 139.6 (C), 136.6 (C), 128.9 (C), 128.7 (CH), 128.6 (CH), 128.0 (CH), 126.5 (CH), 125.8 (CH), 120.8 (CH), 34.8 (C), 31.4 (CH_3), 17.1 (CH_3); IR (neat): 2960, 2903, 2865, 1592, 1541, 1494, 1474, 1369, 1268, 1112, 1022, 1013, 889, 839, 772, 734, 701, 657, 625 cm^{-1}; MS (ESI, m/z): 302.19 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{24}N$: 302.1916 $[M+H]^+$, found: 302.1903.

4.11.10 2-Butyl-5-methyl-4-phenylpyridine (61l)

1-Phenyl-3-(prop-2-yn-1-ylamino)hept-2-ene-1-thione (**58l**) (87.5 mg, 0.34 mmol) and (*i*-Pr)$_2$NH (0.57 mL, 4.03 mmol) were employed to afford 9.6 mg (13%) of the indicated product and 1.8 mg (2%) of 5-butyl-2-methylene-7-phenyl-2,3-dihydro-1,4-thiazepine (**59l**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.48-7.37 (m, 3H), 7.35-7.30 (m, 2H), 7.03 (s, 1H), 2.84-2.77 (m, 2H), 2.24 (s, 3H), 1.72 (tt, *J* = 7.8, 6.7 Hz, 2H), 1.40 (sextet, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); IR (neat): 2954, 2926, 2857, 1618, 1595, 1543, 1480, 1407, 1385, 1274, 1196, 1074, 1046, 881, 774, 736, 701, 630 cm^{-1}; MS (ESI, m/z): 226.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{20}N$: 226.1590 $[M+H]^+$, found: 226.1596.

4.11.11 5-Methyl-4-phenyl-2-(thiophen-3-yl)pyridine (61m)

1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-ene-1-thione (**58m**) (90.7 mg, 0.32 mmol) and (*i*-Pr)$_2$NH (0.53 mL, 3.79 mmol) were employed to afford 55.3 mg (69%) of the indicated product and 5.4 mg (6%) of 2-methylene-7-phenyl-5-(thiophen-3-yl)-2,3-dihydro-1,4-thiazepine (**59m**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.88 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.66 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.53-7.35 (m, 7H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6 (C), 151.2 (CH), 150.0 (C), 142.2 (C), 139.4 (C), 129.0 (C), 128.63 (CH), 128.59 (CH), 128.1 (CH), 126.3 (CH), 123.0 (CH), 120.8 (CH), 17.1 (CH_3). (Note that two CH peaks overlap on each other); IR (neat): 3089, 3059, 2918, 1592, 1535, 1495, 1473, 1441, 1377, 1334, 1272, 1226, 1200, 1074, 1043, 1022, 1000, 916, 891, 863, 838, 798, 771, 751, 738, 703, 677, 628, 595 cm^{-1}; MS (ESI, m/z): 252.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{14}NS$: 252.0842 $[M+H]^+$, found: 252.0839.

4.11.12 4-(2-Bromophenyl)-5-methyl-2-phenylpyridine (61n)

1-(2-Bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58n**) (60.6 mg, 0.17 mmol) and (*i*-Pr)$_2$NH (0.28 mL, 2.02 mmol) were employed to

afford 29.1 mg (53%) of the indicated product and 6.1 mg (10%) of 7-(2-bromophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-thiazepine (**59n**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 1H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.34-7.27 (m, 2H), 7.21 (td, *J* = 7.9, 1.6 Hz, 1H), 7.14 (dd, *J* = 7.5, 1.5 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1 (C), 150.8 (CH), 149.6 (C), 140.3 (C), 139.1 (C), 133.0 (CH), 130.1 (C), 130.1 (CH), 129.7 (CH), 128.91 (CH), 128.85 (CH), 127.6 (CH), 126.9 (CH), 122.6 (CBr), 120.9 (CH), 16.6 (CH_3); IR (neat): 3051, 2919, 1600, 1561, 1544, 1483, 1464, 1431, 1381, 1368, 1257, 1225, 1065, 1016, 996, 887, 850, 777, 765, 745, 732, 693, 666 cm^{-1}; MS (ESI, m/z): 324.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}{}^{79}BrN$: 324.0382 $[M+H]^+$, found: 324.0399.

4.11.13 4-(2-Bromophenyl)-5-methyl-2-(*m*-tolyl)pyridine (61r)

1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-ene-1-thione (**58r**) (66.7 mg, 0.18 mmol) and $(i\text{-Pr})_2NH$ (0.30 mL, 2.13 mmol) were employed to afford 30.0 mg (49%) of the indicated product and 4.7 mg (7%) of 7-(2-bromophenyl)-2-methylene-5-(*m*-tolyl)-2,3-dihydro-1,4-thiazepine (**59r**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.85 (s, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.29 (td, *J* = 7.7, 1.5 Hz, 1H), 7.25-7.20 (m, 2H), 2.43 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2 (C), 150.7 (CH), 149.6 (C), 140.3 (C), 139.0 (C), 138.5 (C), 133.0 (CH), 130.2 (CH), 130.1 (C), 129.7 (CH), 128.8 (CH), 127.63 (CH), 127.62 (CH), 124.0 (CH), 122.6 (CBr), 121.0 (CH), 21.7 (CH_3), 16.6 (CH_3). (Note that two CH peaks overlap on each other); IR (neat): 3049, 2950, 2918, 1599, 1584, 1561, 1543, 1463, 1431, 1380, 1358, 1260, 1226, 1092, 1063, 1020, 995, 882, 817, 791, 748, 729, 700, 666, 629 cm^{-1}; MS (ESI, m/z): 338.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}{}^{79}BrN$: 338.0539 $[M+H]^+$, found: 338.0554.

4.11.14 4-(2-Bromophenyl)-5-methyl-2-(4-(trifluoromethyl)phenyl)pyridine (61s)

1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-ene-1-thione (**58s**) (110.3 mg, 0.26 mmol) and (*i*-Pr)$_2$NH (0.43 mL, 3.08 mmol) were employed to afford 55.2 mg (54%) of the indicated product and 11.0 mg (10%) of 7-(2-bromophenyl)-2-methylene-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1,4-thiazepine (**59s**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 2H), 7.65-7.59 (m, 3H), 7.47 (s, 1H), 7.34 (td, *J* = 7.5, 1.2 Hz, 1H), 7.22 (td, *J* = 7.8, 1.7 Hz, 1H), 7.14 (dd, *J* = 7.5, 1.7 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6 (C), 151.3 (CH), 149.7 (C), 142.6 (C), 140.0 (C), 133.1 (CH), 131.2 (C), 130.7 (q, ^2J = 32.4 Hz, C), 130.2 (CH), 129.9 (CH), 127.7 (CH), 127.1 (CH), 125.8 (q, ^3J = 3.7 Hz, CH), 124.4 (q, ^1J = 274.0 Hz, CF_3), 122.5 (CBr), 121.2 (CH), 16.6 (CH_3); IR (neat): 2926, 1616, 1603, 1562, 1485, 1466, 1433, 1412, 1385, 1321, 1257, 1158, 1117, 1068, 1013, 891, 847, 835, 767, 746, 727, 706, 658, 629, 618 cm^{-1}; MS (ESI, m/z): 392.03 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{14}{}^{79}BrF_3N$: 392.0256 $[M+H]^+$, found: 392.0271.

4.11.15 4-(2-Bromophenyl)-2-(3-fluorophenyl)-5-methylpyridine (61t)

1-(2-Bromophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58t**) (116.0 mg, 0.31 mmol) and (*i*-Pr)$_2$NH (0.52 mL, 3.68 mmol) were employed to afford 54.5 mg (51%) of the indicated product and 10.4 mg (9%) of 7-(2-bromophenyl)-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-thiazepine (**59t**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.72-7.60 (m, 3H), 7.43 (s, 1H), 7.33 (td, *J* = 7.8, 6.6 Hz, 2H), 7.22 (td, *J* = 7.8, 1.7 Hz, 1H), 7.15 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.01 (tdd, *J* = 8.3, 2.5, 0.8 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (d, ^1J = 245.4 Hz, CF), 155.8 (d, ^4J = 2.4 Hz, C), 151.1 (CH), 149.6 (C), 141.7 (d, ^3J = 7.6 Hz, C), 140.1 (C), 133.1 (CH), 130.8 (C), 130.3 (d, ^3J = 8.2 Hz, CH), 130.2 (CH), 129.8 (CH), 127.7 (CH), 122.6 (CBr), 122.4 (d, ^4J = 2.8 Hz, CH), 120.9 (CH), 115.7 (d, ^2J = 21.3 Hz, CH), 113.9 (d, ^2J = 22.7 Hz, CH), 16.6 (CH_3);

IR (neat): 2977, 1735, 1601, 1585, 1561, 1544, 1486, 1461, 1371, 1243, 1201, 1175, 1155, 1046, 1020, 905, 878, 825, 788, 763, 730, 695, 666, 629 cm^{-1}; MS (ESI, m/z): 342.03 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{79}BrFN$: 342.0288 $[M+H]^+$, found: 342.0302.

4.11.16 4-(4-Methoxyphenyl)-5-methyl-2-phenylpyridine (61v)

1-(4-Methoxyphenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58v**) (86.1 mg, 0.28 mmol) and $(i\text{-Pr})_2NH$ (0.47 mL, 3.32 mmol) were employed to afford 40.5 mg (53%) of the indicated product and 6.0 mg (7%) of **7-**(4-methoxyphenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-thiazepine (**59v**). ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.00 (d, *J* = 7.2 Hz, 2H), 7.60 (s, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6 (C), 155.4 (C), 151.3 (CH), 149.8 (C), 139.5 (C), 131.8 (C), 130.0 (CH), 129.4 (C), 128.83 (CH), 128.78 (CH), 126.9 (CH), 121.2 (CH), 114.1 (CH), 55.5 (OCH_3), 17.3 (CH_3); IR (neat): 2928, 2834, 1608, 1594, 1576, 1511, 1474, 1442, 1369, 1295, 1246, 1176, 1109, 1043, 1029, 889, 833, 778, 750, 695, 606 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1396.[114]

4.11.17 5-Methyl-2-phenyl-4-(*p*-tolyl)pyridine (61w)

3-Phenyl-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-ene-1-thione (**58w**) (93.3 mg, 0.32 mmol) and $(i\text{-Pr})_2NH$ (0.53 mL, 3.79 mmol) were employed to afford 69.0 mg (83%) of the indicated product and 6.5 mg (7%) of 2-methylene-5-phenyl-7-(*p*-tolyl)-2,3-dihydro-1,4-thiazepine (**59w**). ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.09-8.00 (m, 2H), 7.64 (s, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.32 (s, 4H), 2.47 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3 (C), 151.2 (CH), 150.1 (C), 139.4 (C), 137.9 (C), 136.5 (C), 129.33 (C), 129.26 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 126.8 (CH), 121.1 (CH), 21.3 (CH_3),

17.2 (CH_3); IR (neat): 3025, 2919, 1594, 1542, 1511, 1474, 1444, 1381, 1369, 1183, 1111, 1074, 1038, 1024, 889, 853, 821, 777, 747, 707, 694, 605 cm^{-1}; MS (ESI, m/z): 260.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}N$: 260.1434 $[M+H]^+$, found: 260.1446.

4.11.18 5-Methyl-2-(thiophen-3-yl)-4-(*p*-tolyl)pyridine (61x)

3-(Prop-2-yn-1-ylamino)-3-(thiophen-3-yl)-1-(*p*-tolyl)prop-2-ene-1-thione (**58x**) (86.3 mg, 0.29 mmol) and (*i*-Pr)$_2$NH (0.48 mL, 3.44 mmol) were employed to afford 59.5 mg (77%) of the indicated product and 8.6 mg (10%) of 2-methylene-5-(thiophen-3-yl)-7-(*p*-tolyl)-2,3-dihydro-1,4-thiazepine (**59x**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.77 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.55 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.39 (s, 1H), 7.28 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.22-7.16 (m, 4H), 2.34 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5 (C), 151.1 (CH), 150.0 (C), 142.2 (C), 138.0 (C), 136.5 (C), 129.3 (CH), 129.0 (C), 128.6 (CH), 126.3 (CH), 122.9 (CH), 120.9 (CH), 21.4 (CH_3), 17.2 (CH_3). (Note that two CH peaks overlap on each other); IR (neat): 2919, 1594, 1540, 1511, 1474, 1444, 1419, 1380, 1335, 1184, 1112, 1051, 1037, 868, 843, 821, 794, 751, 727, 713, 677, 605 cm^{-1}; MS (ESI, m/z): 266.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{16}NS$: 266.0998 $[M+H]^+$, found: 266.1010.

4.11.19 4-(4-Chlorophenyl)-5-methyl-2-phenylpyridine (61y)

1-(4-Chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58y**) (109.1 mg, 0.35 mmol) and (*i*-Pr)$_2$NH (0.58 mL, 4.15 mmol) were employed to afford 65.5 mg (67%) of the indicated product and 4.4 mg (4%) of 7-(4-chlorophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-thiazepine (**59y**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.47 (s, 1H), 7.40-7.28 (m, 5H), 7.22 (d, *J* = 8.4 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5 (C), 151.4 (CH), 148.8 (C), 139.2 (C), 137.9 (C), 134.3 (C), 130.1 (CH), 129.1 (C), 128.90 (CH), 128.85 (CH), 126.8 (CH), 120.8 (CH), 17.0 (CH_3). (Note

that two CH peaks overlap on each other); IR (neat): 3059, 2999, 2961, 1602, 1588, 1540, 1491, 1473, 1442, 1384, 1370, 1243, 1228, 1178, 1087, 1051, 1036, 1015, 997, 894, 843, 830, 780, 749, 710, 694, 665, 599 cm^{-1}; MS (ESI, m/z): 280.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}ClN$: 280.0888 $[M+H]^+$, found: 280.0901.

4.11.20 4-(4-Chlorophenyl)-2-(3-fluorophenyl)-5-methylpyridine (61z)

1-(4-Chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-ene-1-thione (**58z**) (89.1 mg, 0.27 mmol) and $(i\text{-Pr})_2NH$ (0.45 mL, 3.20 mmol) were employed to afford 57.0 mg (71%) of the indicated product and 6.2 mg (7%) of 7-(4-chlorophenyl)-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-thiazepine (**59z**). ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.77-7.71 (m, 2H), 7.54 (s, 1H), 7.48-7.44 (m, 2H), 7.41 (dd, J = 10.9, 5.0 Hz, 1H), 7.34-7.28 (m, 2H), 7.12-7.05 (m, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (d, ^1J = 245.5 Hz, CF), 154.1 (d, ^4J = 2.5 Hz, C), 151.5 (CH), 149.0 (C), 141.5 (d, ^3J = 7.3 Hz, C), 137.7 (C), 134.4 (C), 130.3 (d, ^3J = 8.2 Hz, CH), 130.0 (CH), 129.8 (C), 128.9 (CH), 122.3 (d, ^4J = 2.8 Hz, CH), 120.9 (CH), 115.7 (d, ^2J = 21.4 Hz, CH), 113.8 (d, ^2J = 22.8 Hz, CH), 17.1 (CH_3); IR (neat): 3040, 1614, 1584, 1570, 1541, 1496, 1469, 1437, 1377, 1358, 1254, 1197, 1172, 1152, 1092, 1054, 1033, 1010, 992, 906, 877, 845, 817, 776, 750, 724, 697, 682, 655, 627 cm^{-1}; MS (ESI, m/z): 298.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClFN$: 298.0793 $[M+H]^+$, found: 298.0793.

4.12 Reaction of *N*-Propargylic Thio-β-enaminone 84 with DBU

1,3-Diphenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-ene-1-thione (**84**) (106.0 mg, 0.30 mmol) and DBU (45.7 mg, 0.30 mmol) in 0.5 mL of ACN were employed to afford 30.9 mg (32%) 5-benzyl-2,4-diphenylpyridine (**89**). ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.09-8.03 (m, 2H), 7.67 (s, 1H), 7.53-7.47 (m, 2H), 7.47-7.41 (m, 4H), 7.33-7.28 (m, 2H), 7.27-7.17 (m, 3H), 7.01 (d, J = 7.2 Hz, 2H), 4.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5 (C), 151.6 (CH), 150.6 (C), 140.4 (C), 139.2 (C), 139.1 (C), 132.3 (C), 129.0 (CH), 128.9 (CH), 128.8

(CH), 128.7 (CH), 128.6 (2 x CH), 128.2 (CH), 126.9 (CH), 126.3 (CH), 121.5 (CH), 36.3 (CH_2); IR (neat): 3057, 3025, 1590, 1538, 1493, 1473, 1444, 1373, 1178, 1156, 1074, 1027, 888, 759, 716, 695, 670 cm^{-1}; MS (ESI, m/z): 322.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{20}N$: 322.1590 $[M+H]^+$, found: 322.1599.[115]

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APPENDIX A

NMR SPECTRA

Bruker Spectrospin Avance DPX400 Ultrashield spectromer was used for the records of ^{1}H, ^{13}C, DEPT-90, DEPT-135, COSY, HETCOR, NOESY and HMBC NMR spectra. Chemical shifts are reported in parts per million (ppm) relative to $CDCl_3$ (7.26 and 77.16 ppm in ^{1}H and ^{13}C NMR, respectively).

NMR spectra of synthesized starting materials and products are given below.

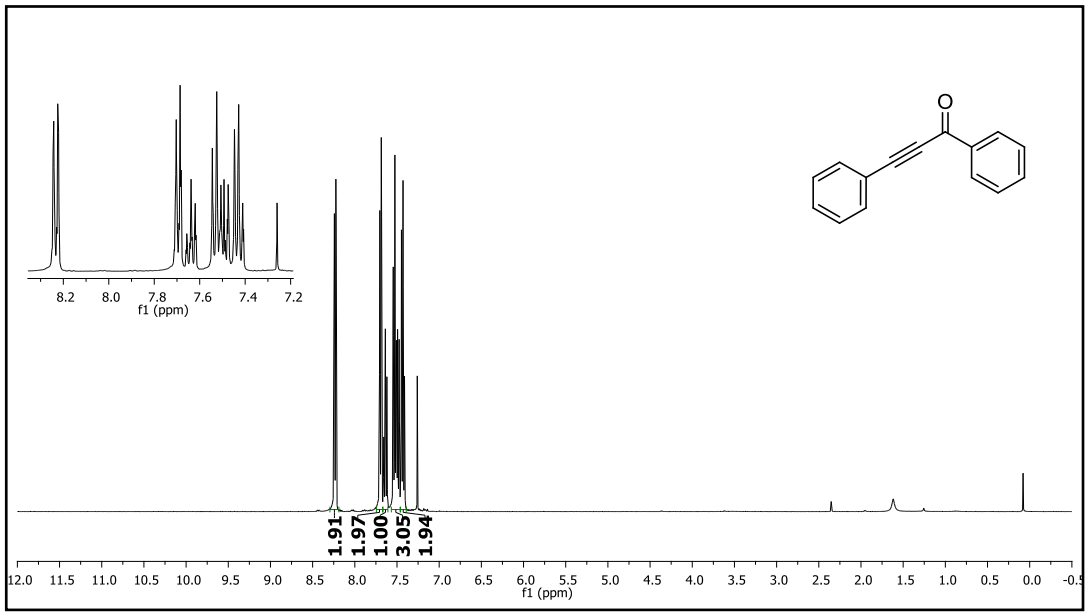

Figure 37. ^{1}H NMR spectrum of compound **63a**.

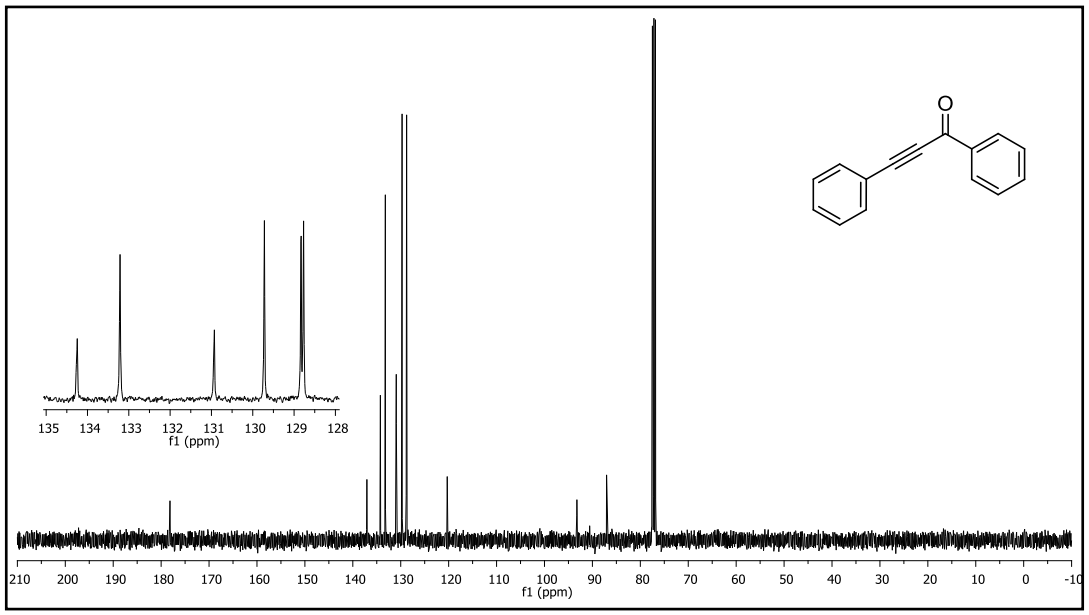

Figure 38. ^{13}C NMR spectrum of compound **63a**.

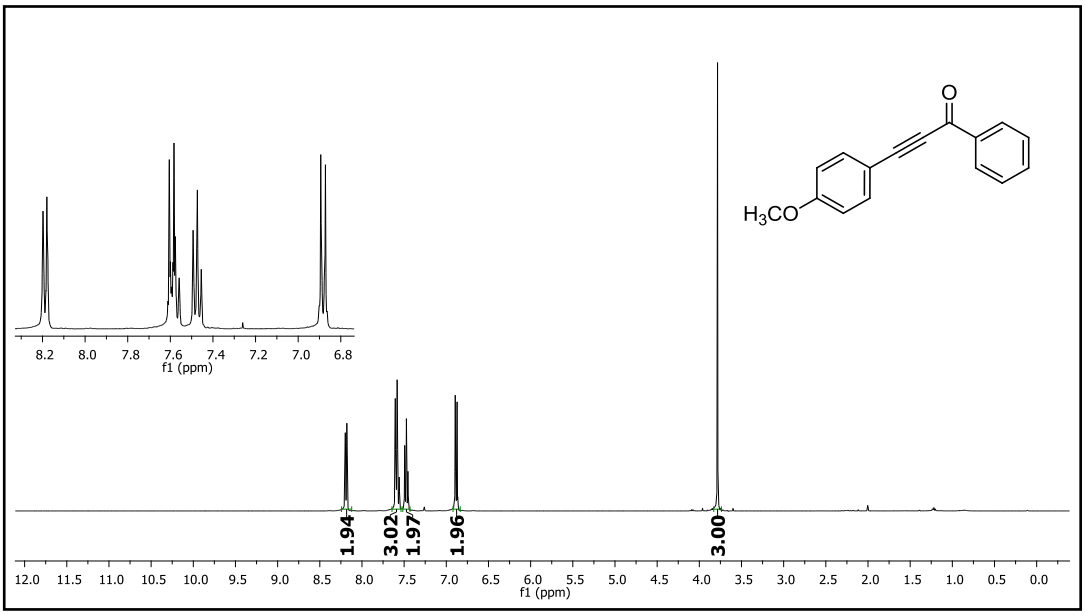

Figure 39. ^{1}H NMR spectrum of compound **63b**.

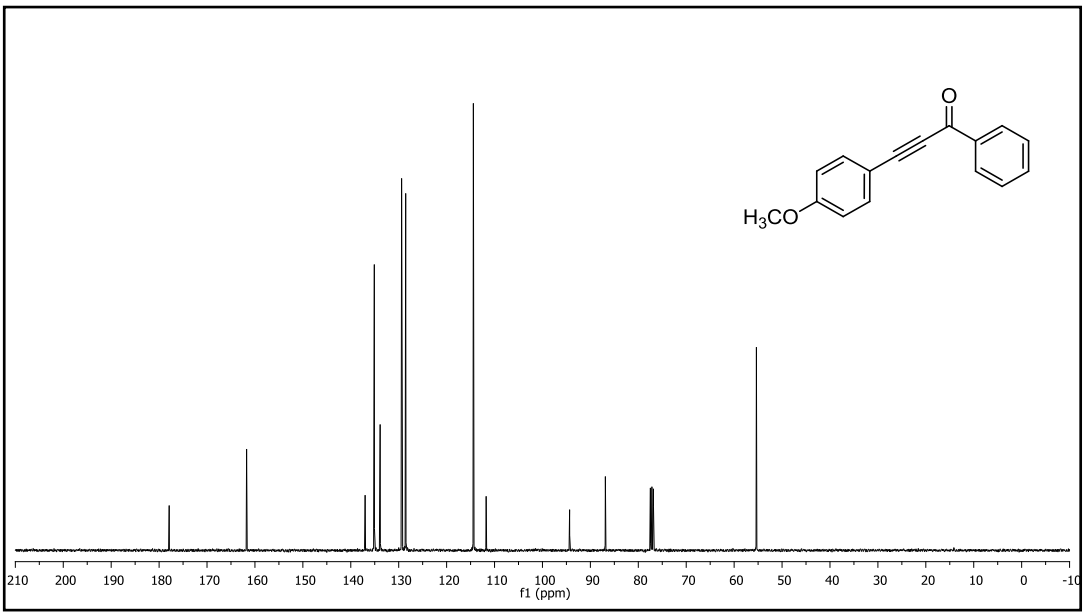

Figure 40. ^{13}C NMR spectrum of compound **63b**.

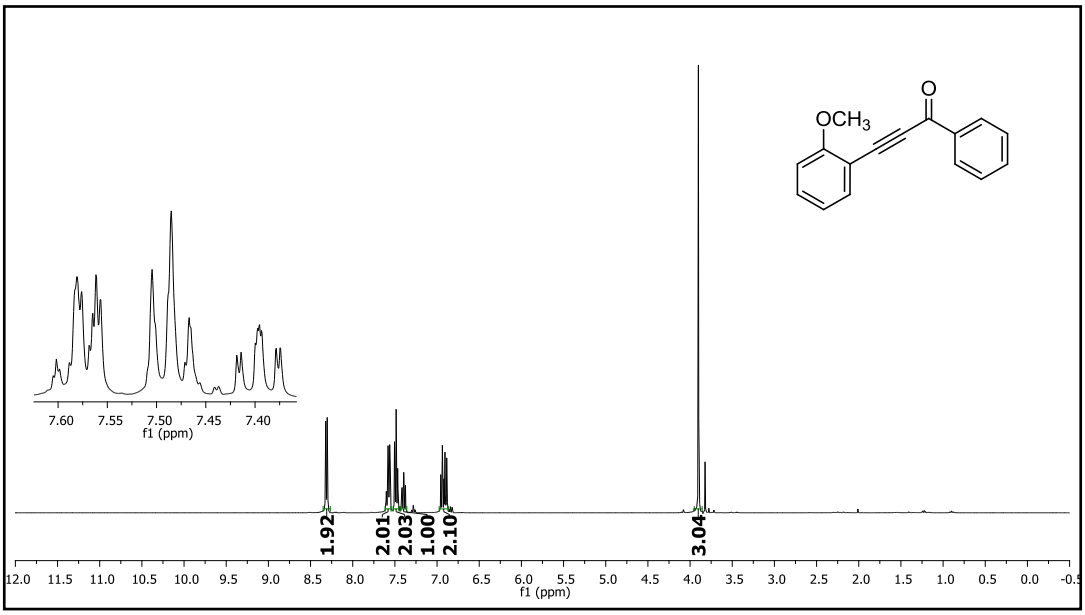

Figure 41. ^{1}H NMR spectrum of compound **63c**.

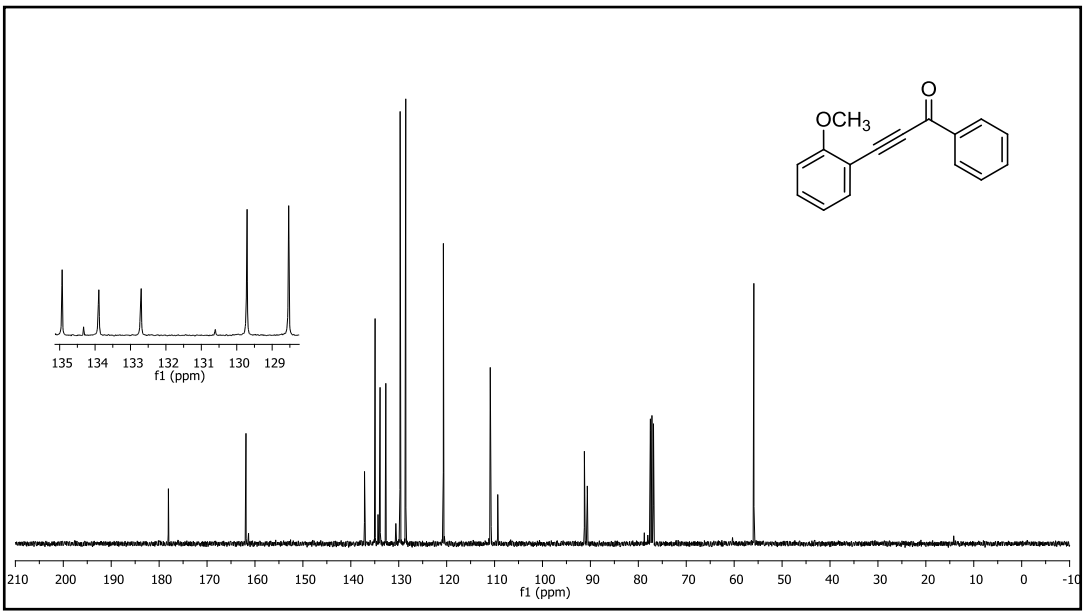

Figure 42. ^{13}C NMR spectrum of compound **63c**.

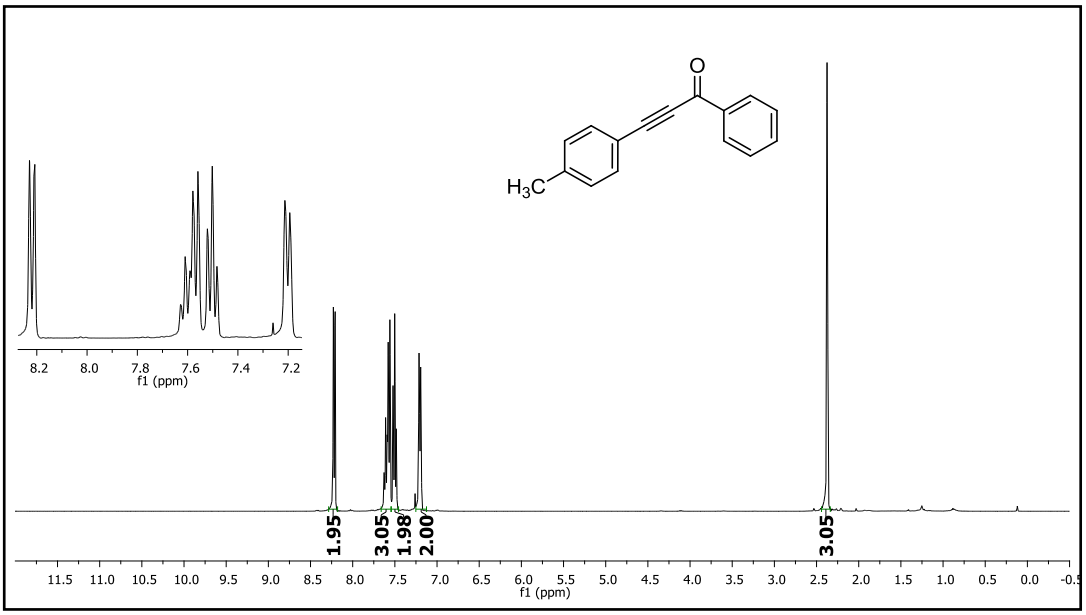

Figure 43. ^{1}H NMR spectrum of compound **63d**.

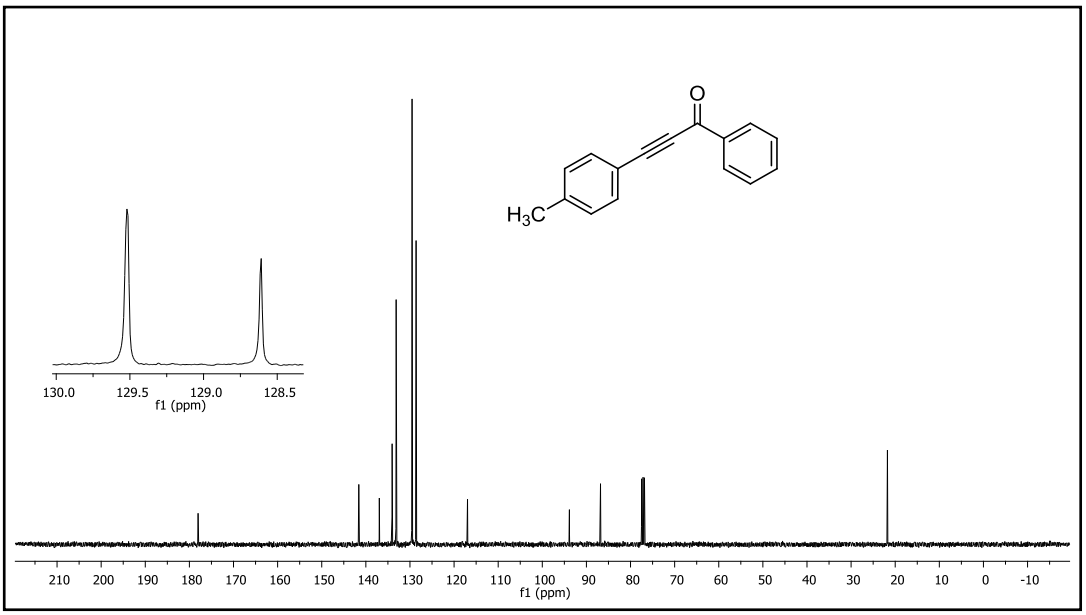

Figure 44. ^{13}C NMR spectrum of compound **63d**.

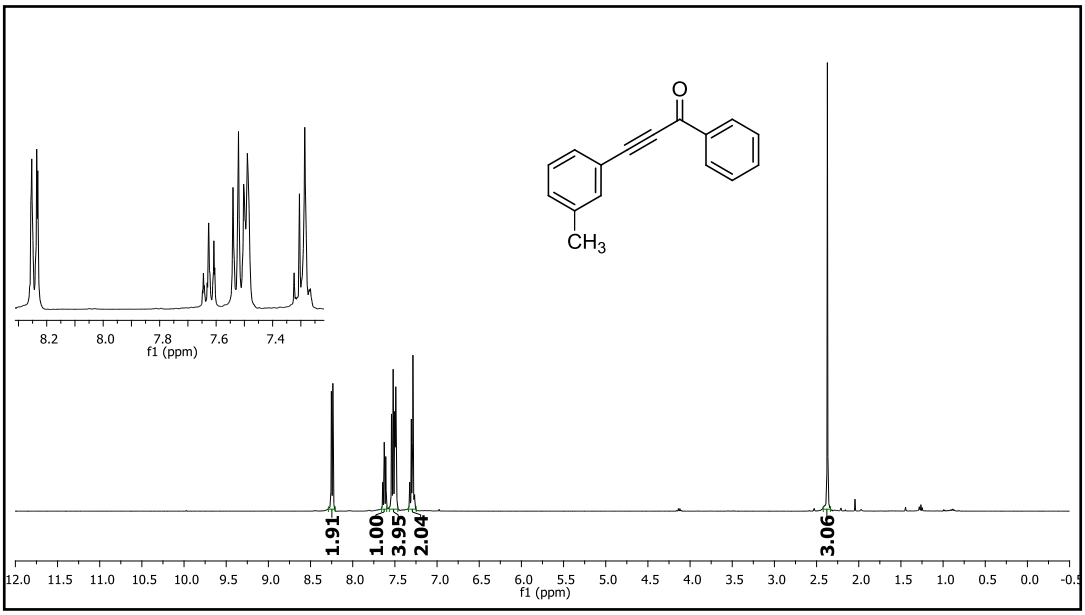

Figure 45. ^{1}H NMR spectrum of compound **63e**.

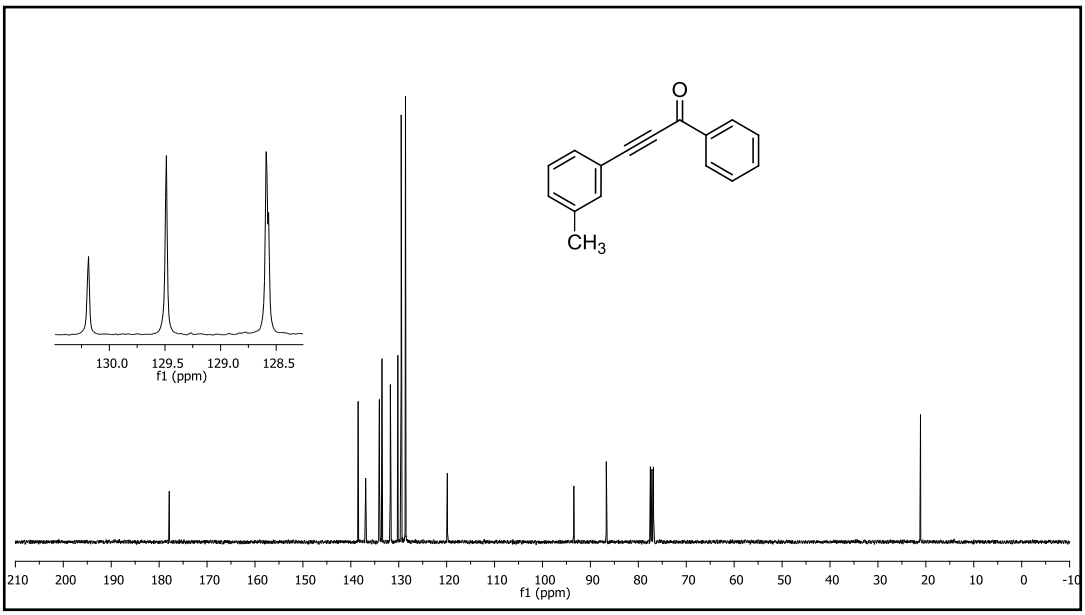

Figure 46. ^{13}C NMR spectrum of compound **63e**.

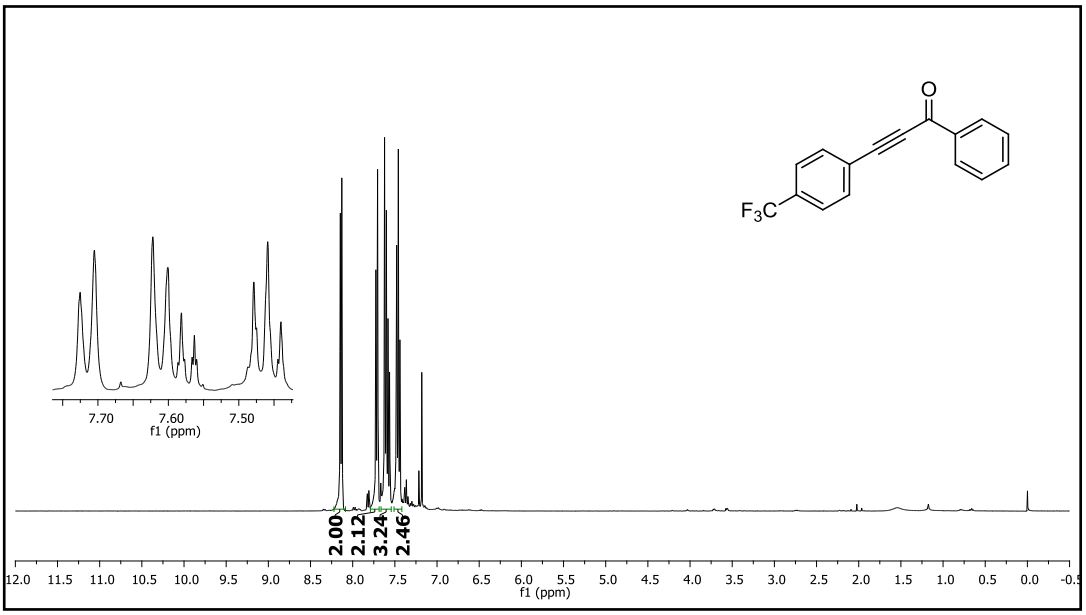

Figure 47. ^{1}H NMR spectrum of compound **63f**.

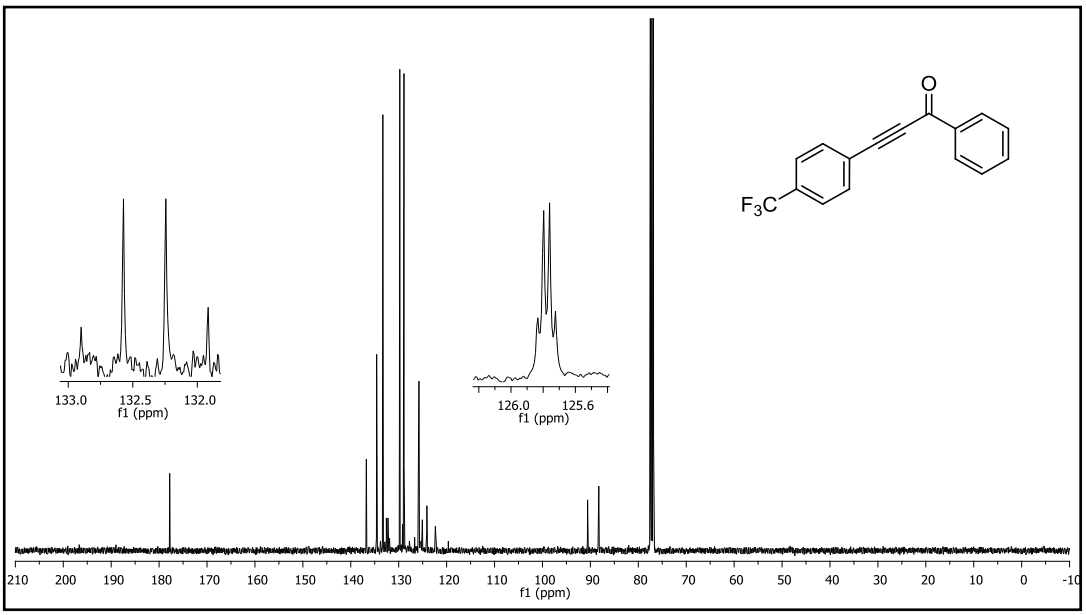

Figure 48. ^{13}C NMR spectrum of compound **63f**.

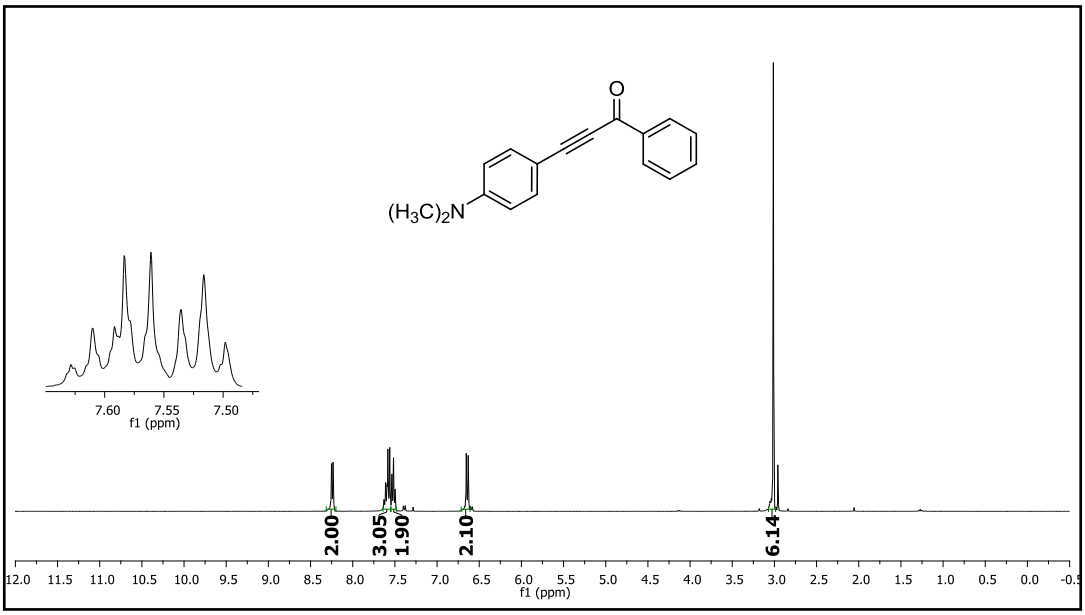

Figure 49. ^{1}H NMR spectrum of compound **63g**.

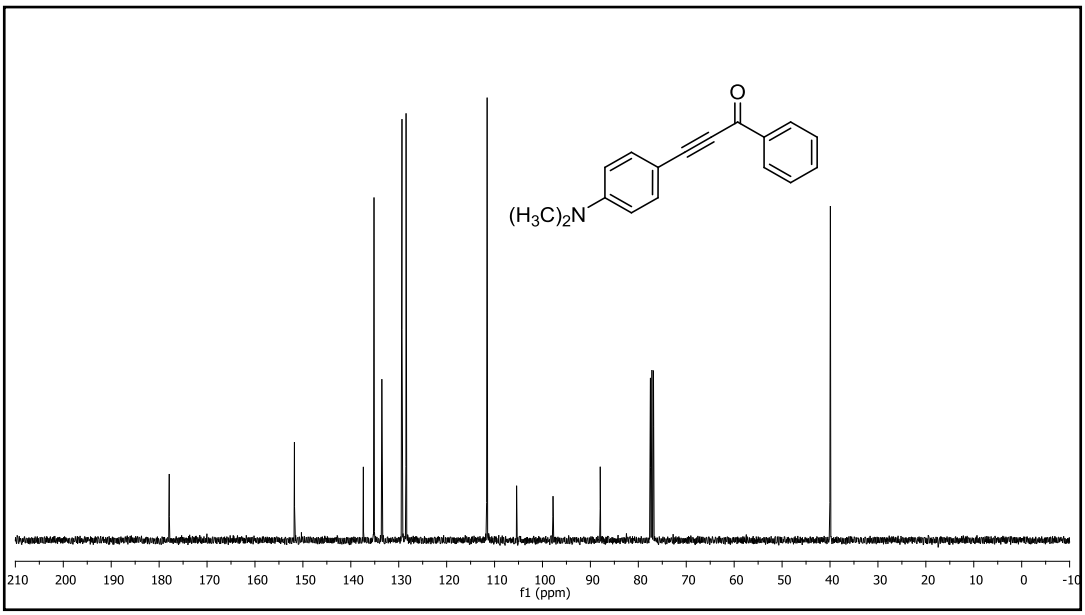

Figure 50. ^{13}C NMR spectrum of compound **63g**.

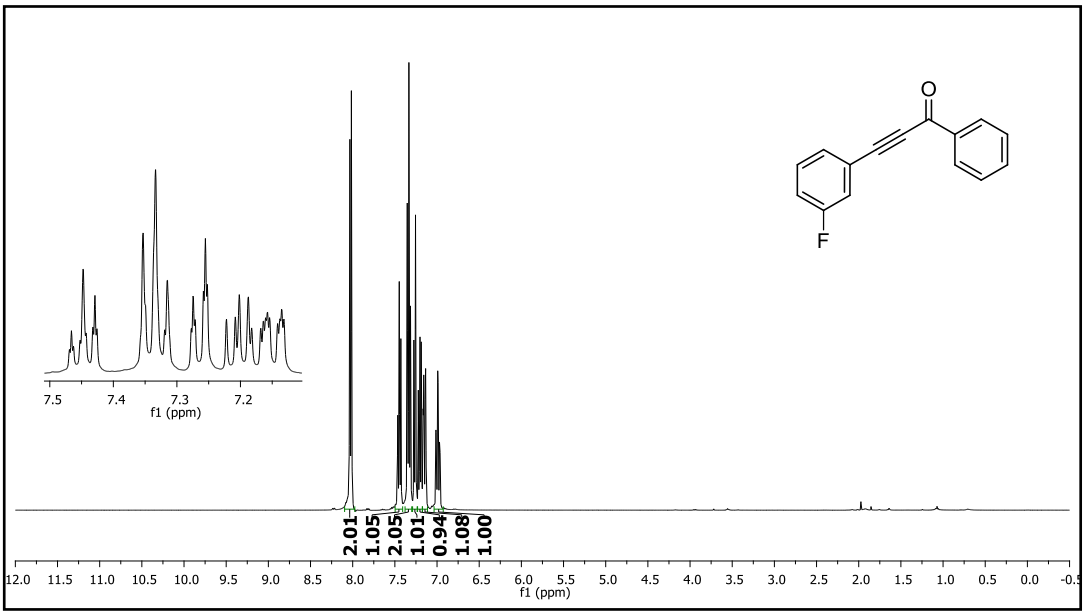

Figure 51. ^{1}H NMR spectrum of compound **63h**.

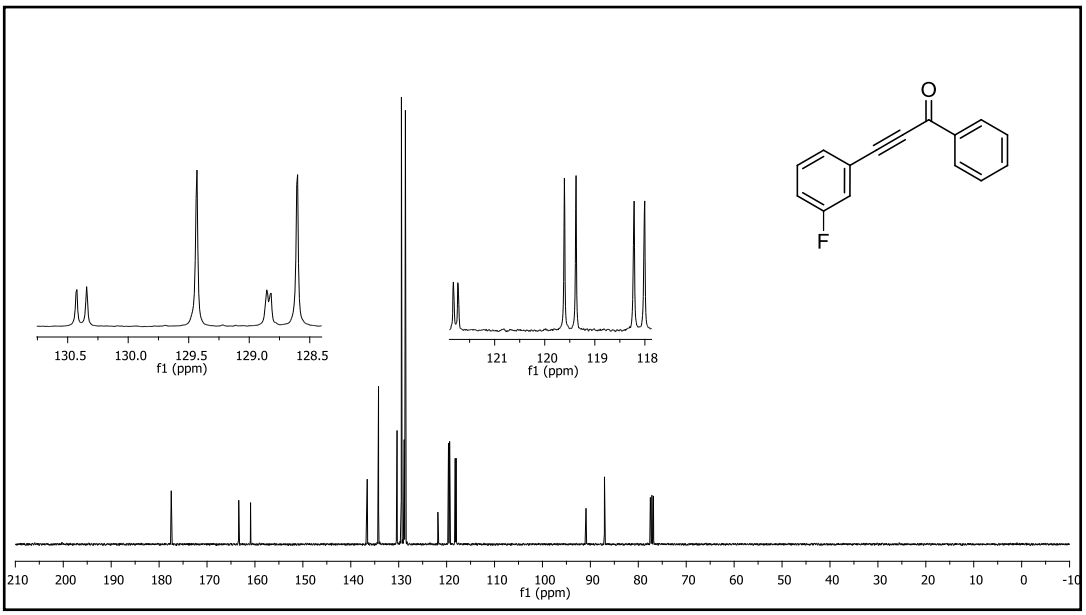

Figure 52. ^{13}C NMR spectrum of compound **63h**.

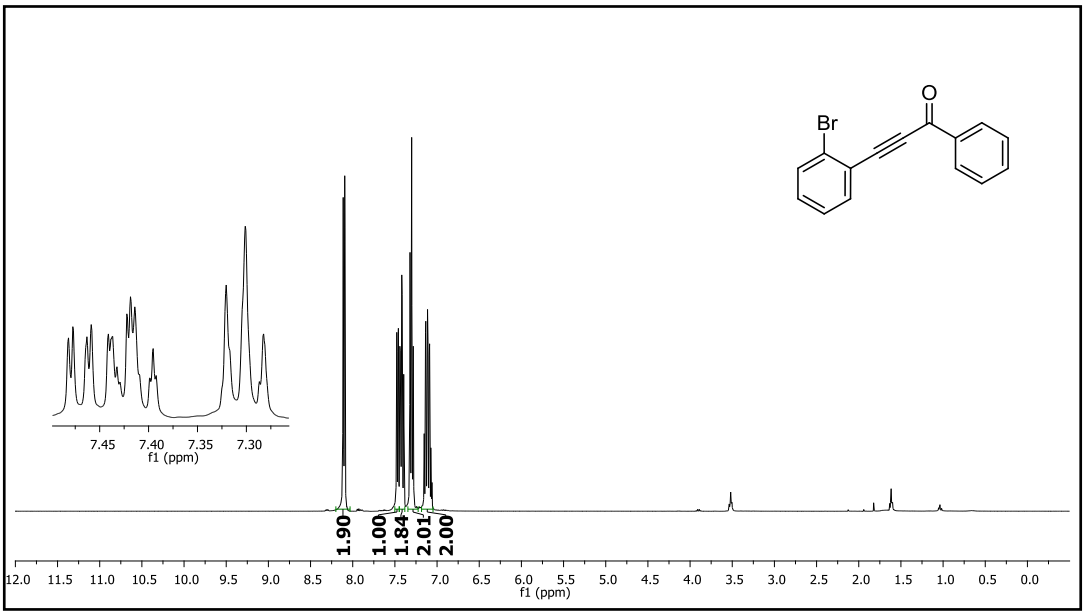

Figure 53. ^{1}H NMR spectrum of compound **63i**.

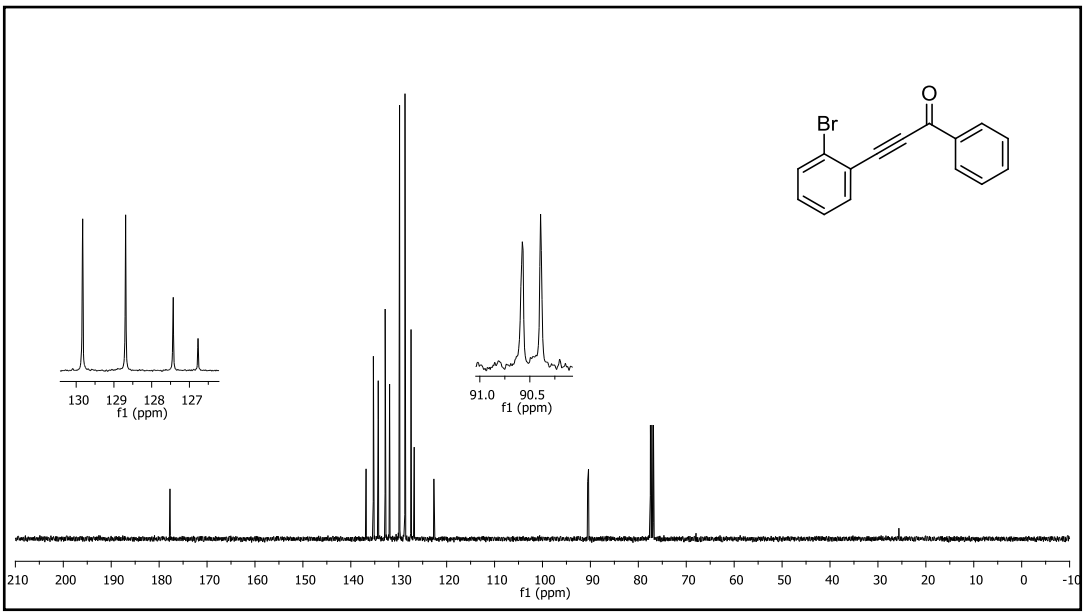

Figure 54. ^{13}C NMR spectrum of compound **63i**.

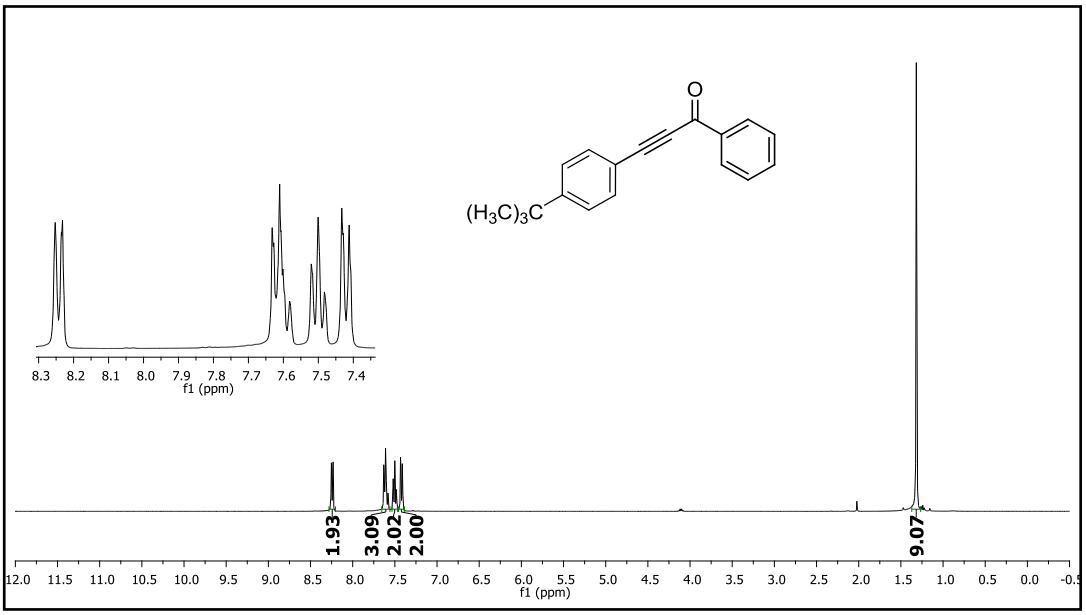

Figure 55. ^{1}H NMR spectrum of compound **63j**.

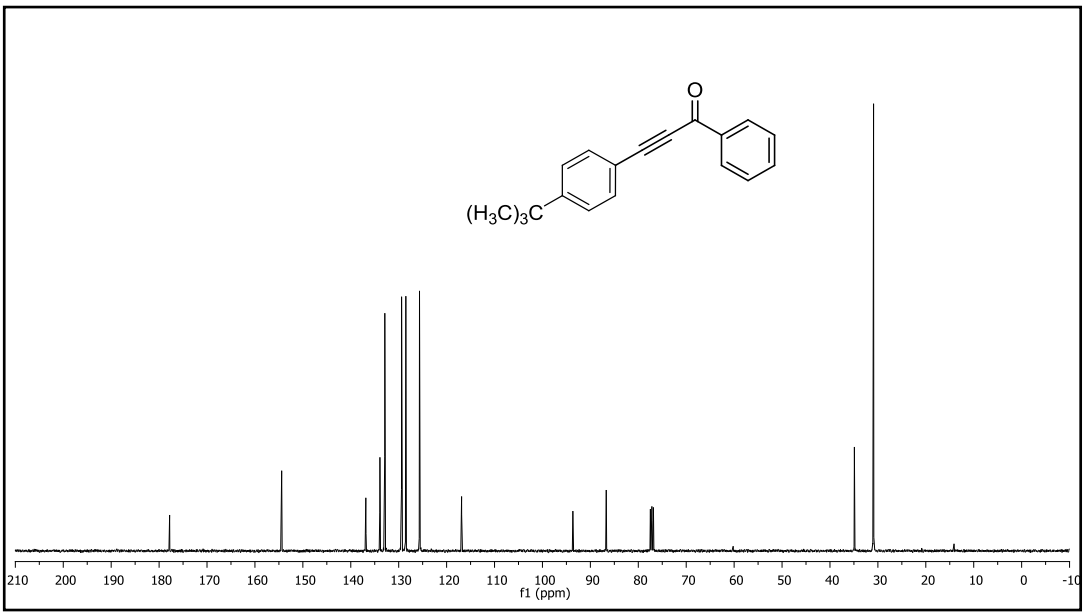

Figure 56. ^{13}C NMR spectrum of compound **63j**.

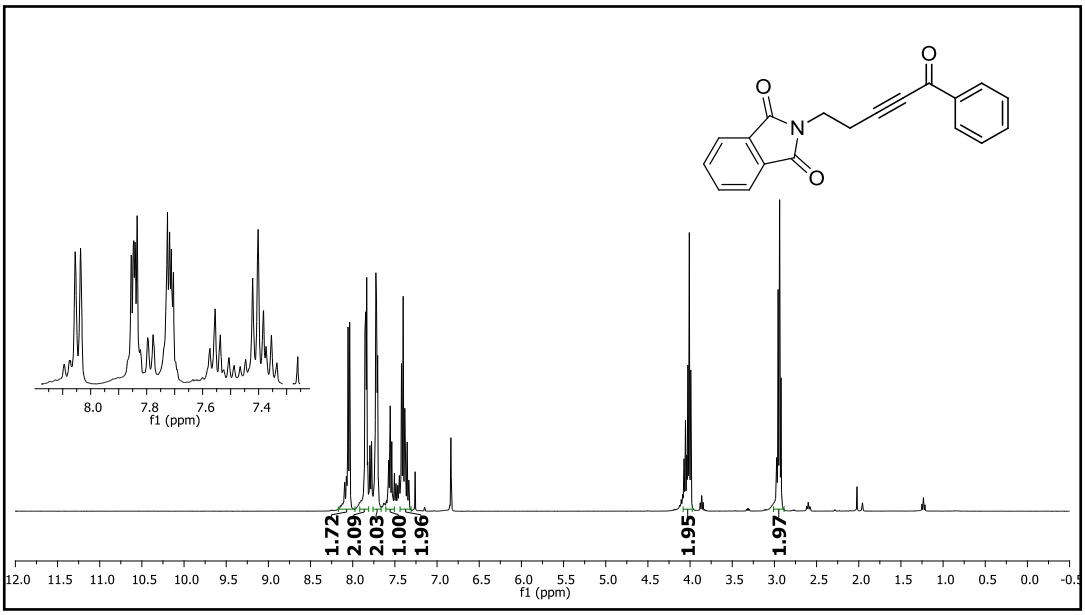

Figure 57. ^{1}H NMR spectrum of compound **63k**.

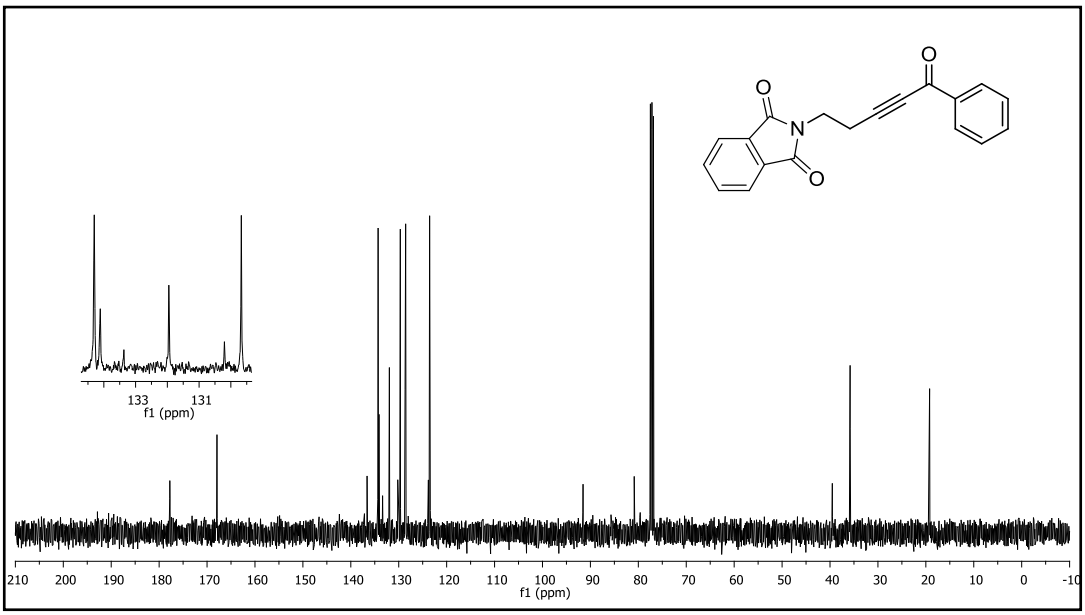

Figure 58. ^{13}C NMR spectrum of compound **63k**.

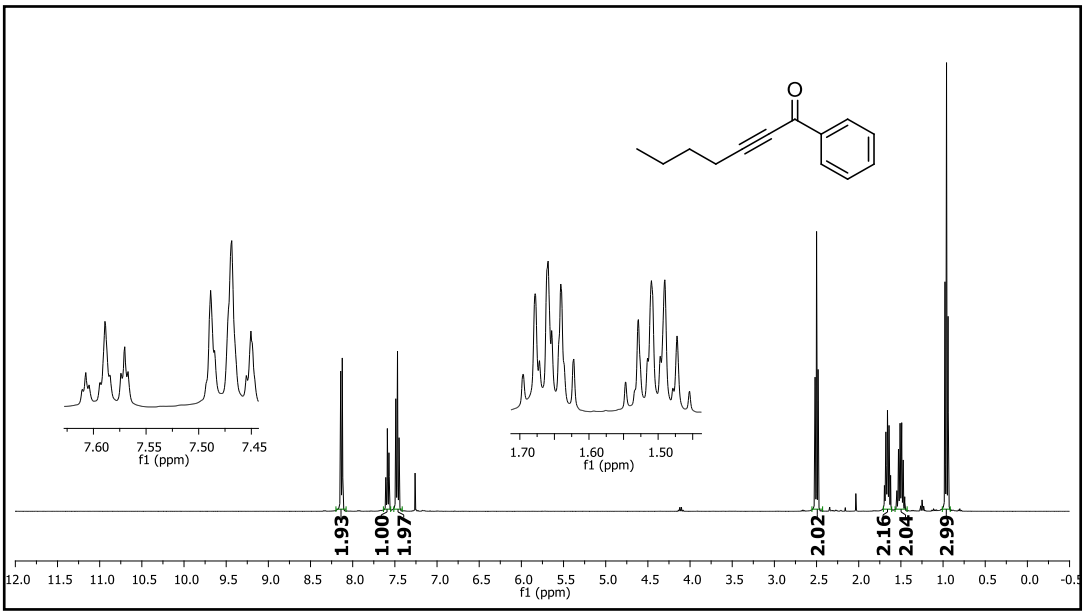

Figure 59. ^{1}H NMR spectrum of compound **63l**.

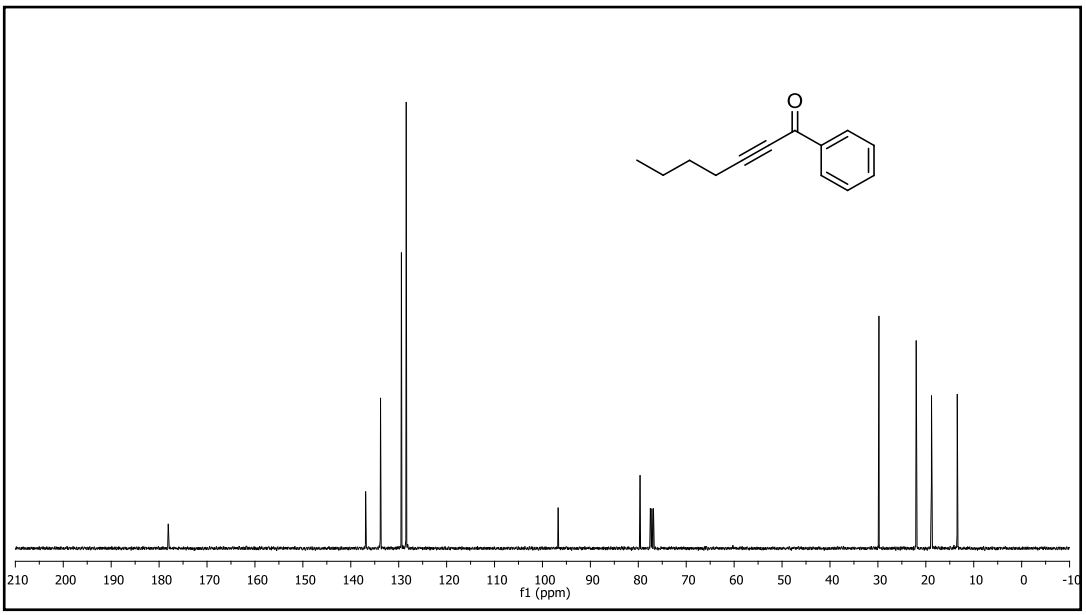

Figure 60. ^{13}C NMR spectrum of compound **63l**.

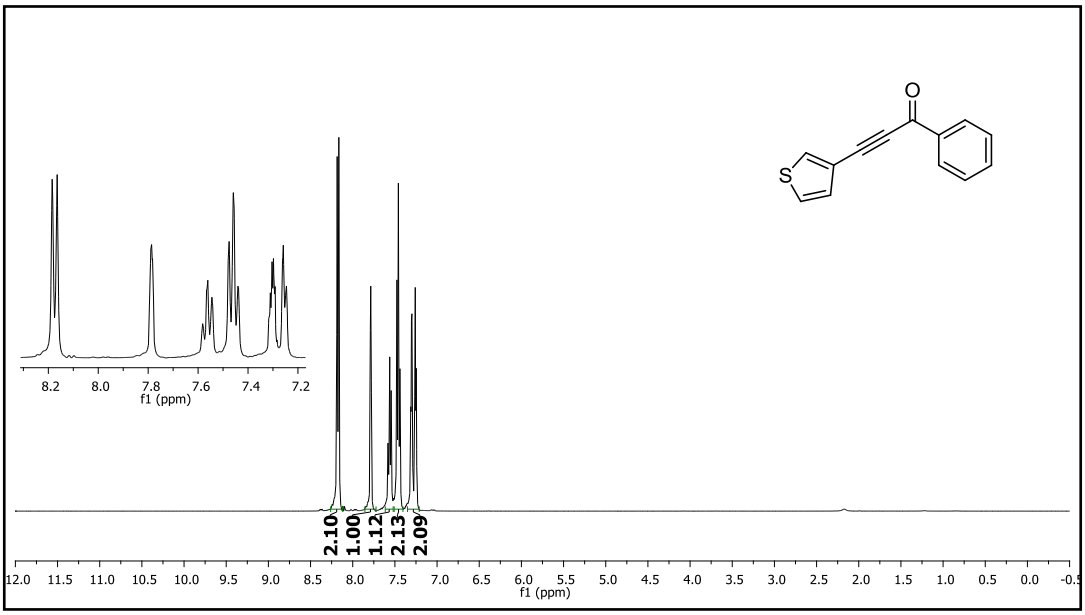

Figure 61. ^{1}H NMR spectrum of compound **63m**.

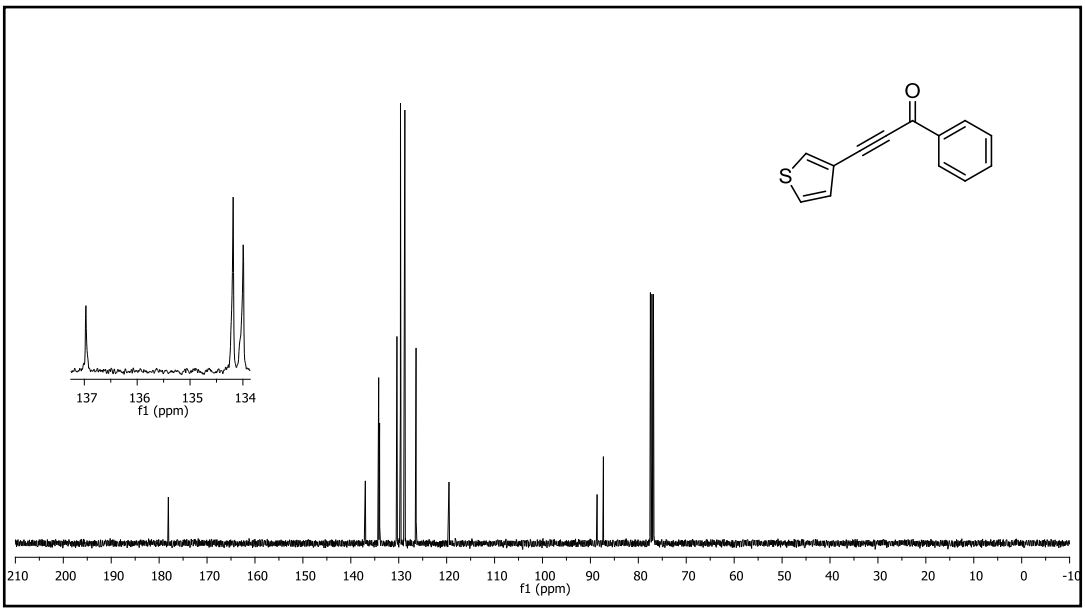

Figure 62. ^{13}C NMR spectrum of compound **63m**.

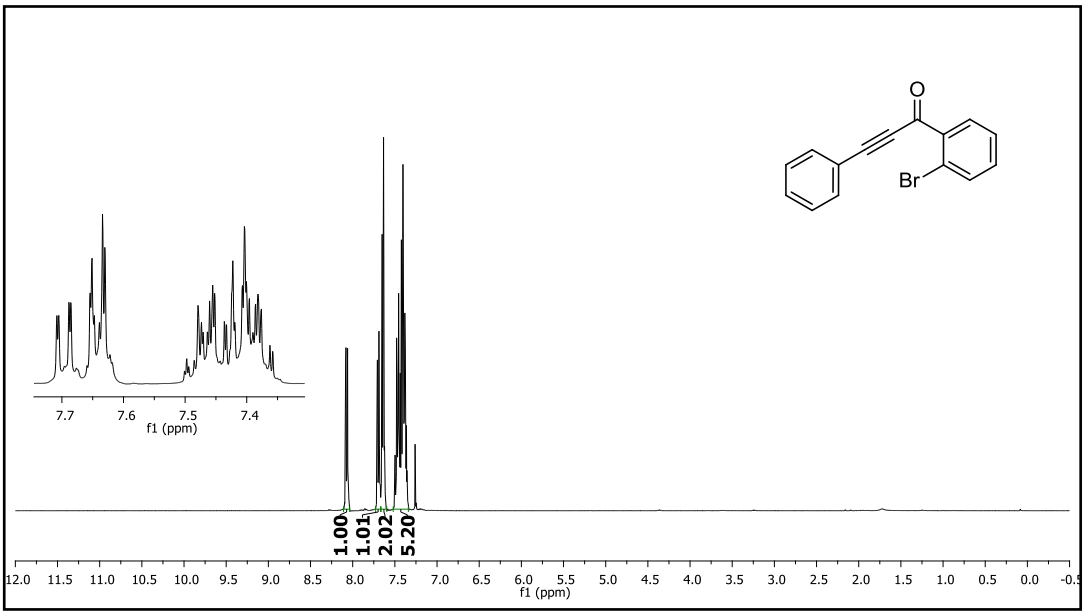

Figure 63. ^{1}H NMR spectrum of compound **63n**.

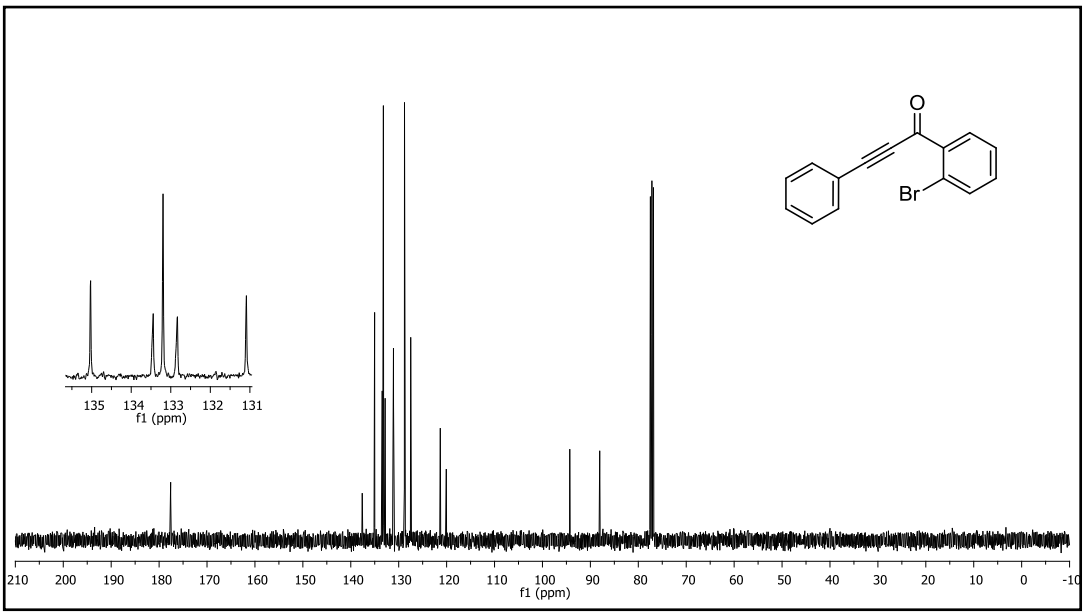

Figure 64. ^{13}C NMR spectrum of compound **63n**.

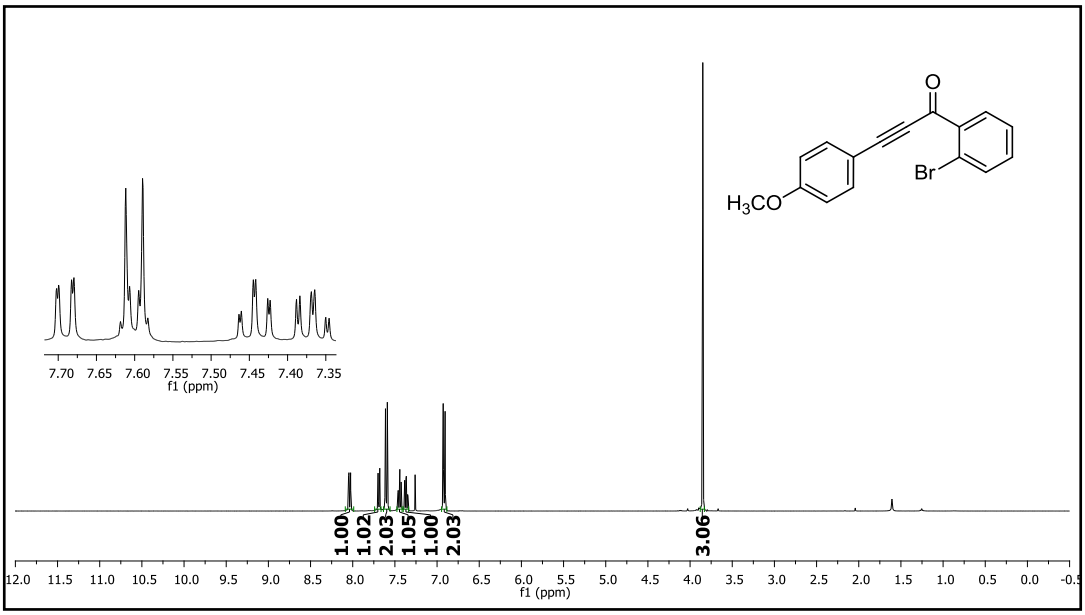

Figure 65. ^{1}H NMR spectrum of compound **63o**.

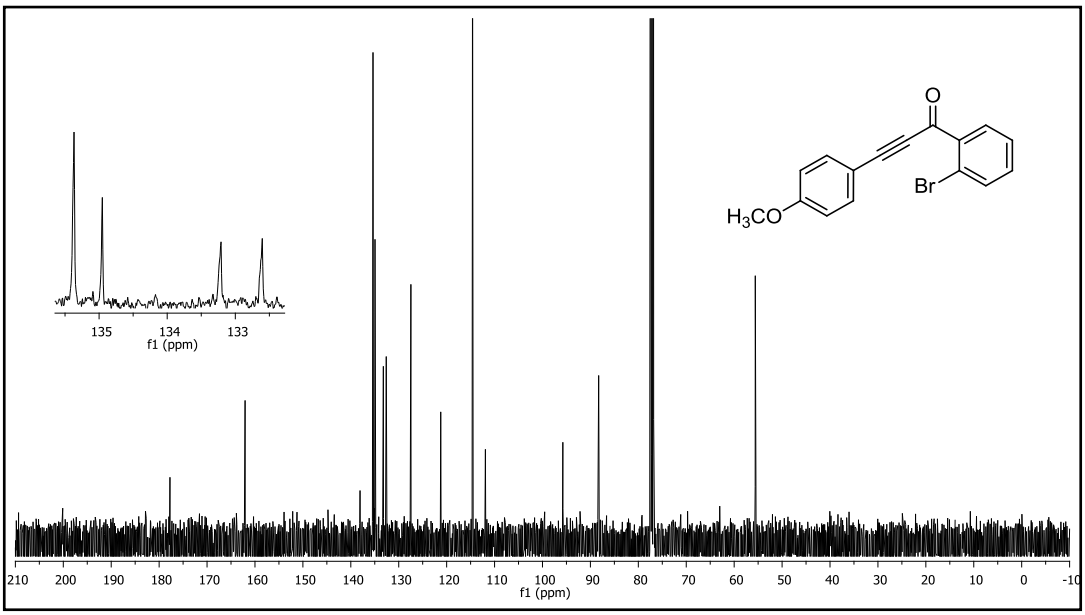

Figure 66. ^{13}C NMR spectrum of compound **63o**.

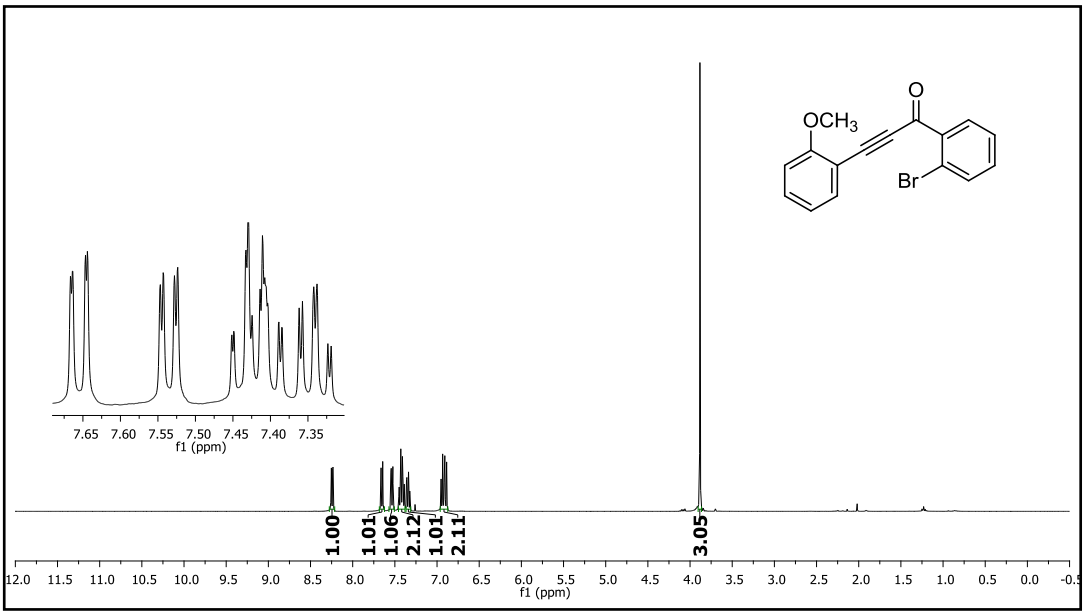

Figure 67. ^{1}H NMR spectrum of compound **63p**.

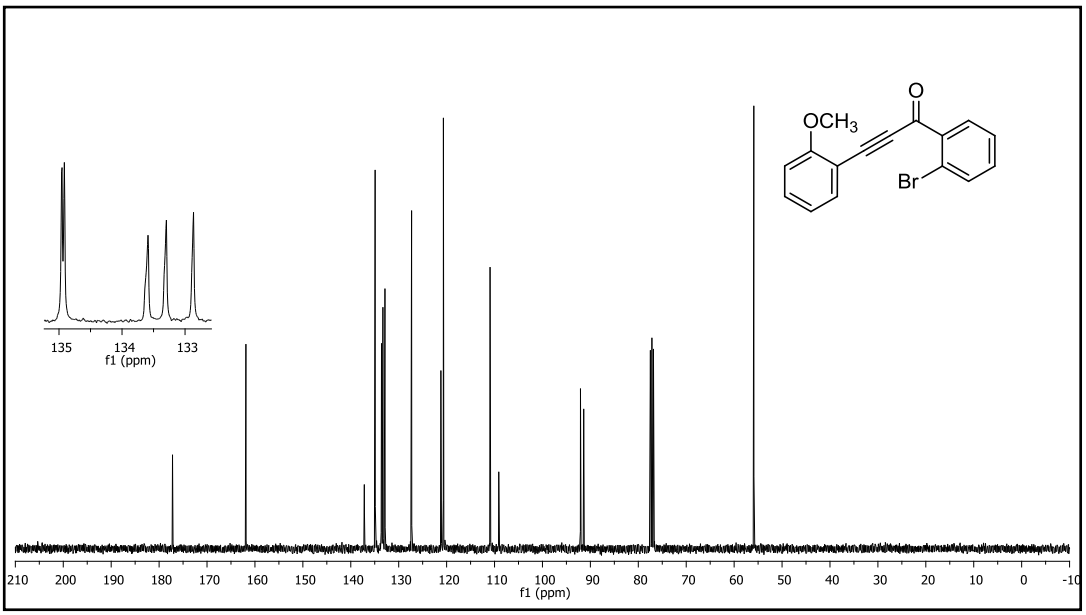

Figure 68. ^{13}C NMR spectrum of compound **63p**.

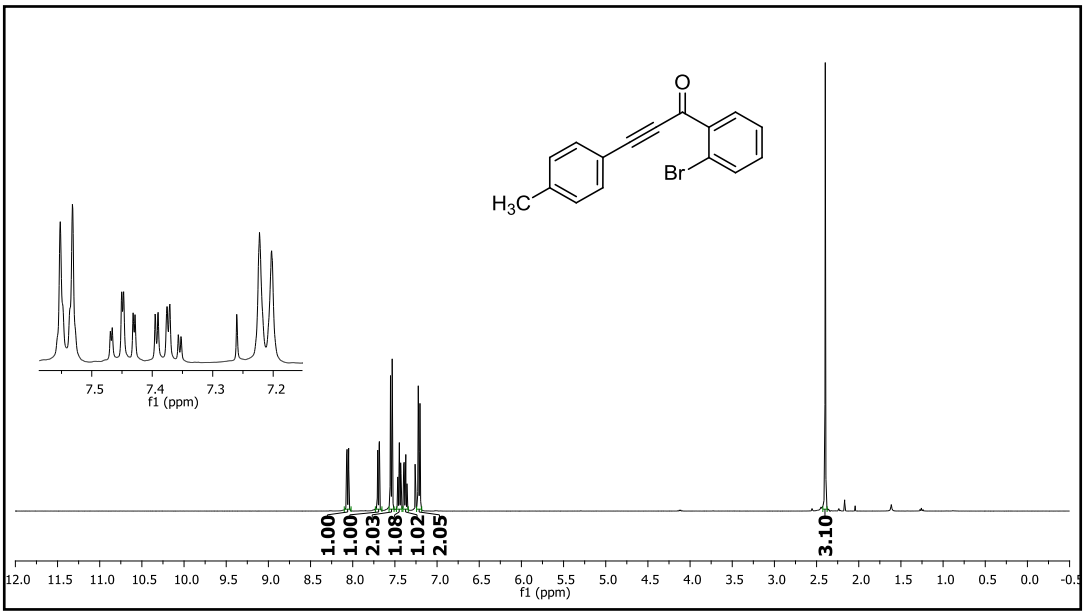

Figure 69. ^{1}H NMR spectrum of compound **63q**.

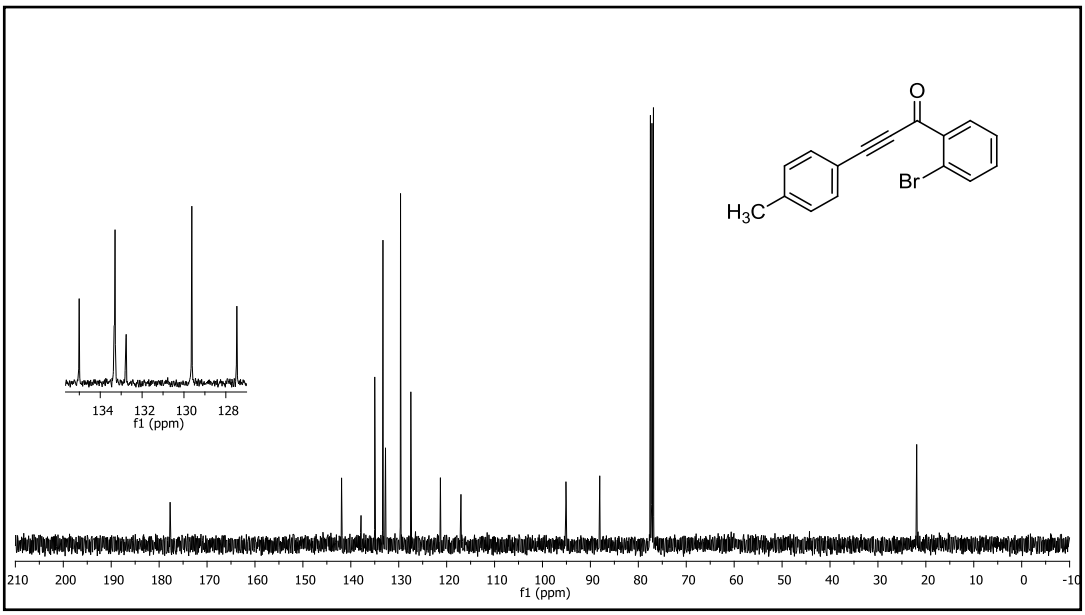

Figure 70. ^{13}C NMR spectrum of compound **63q**.

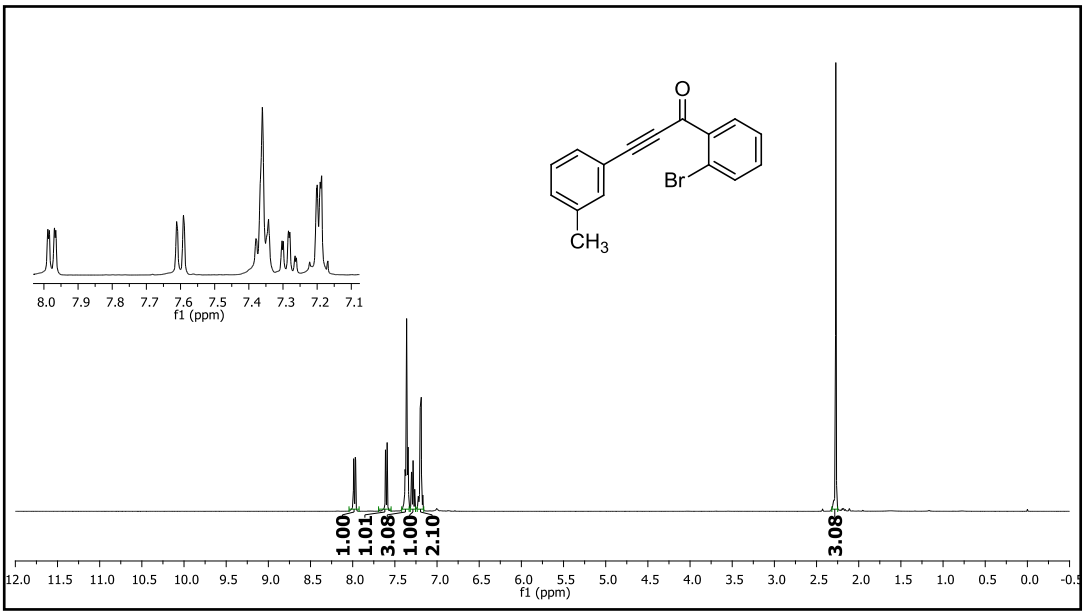

Figure 71. ^{1}H NMR spectrum of compound **63r**.

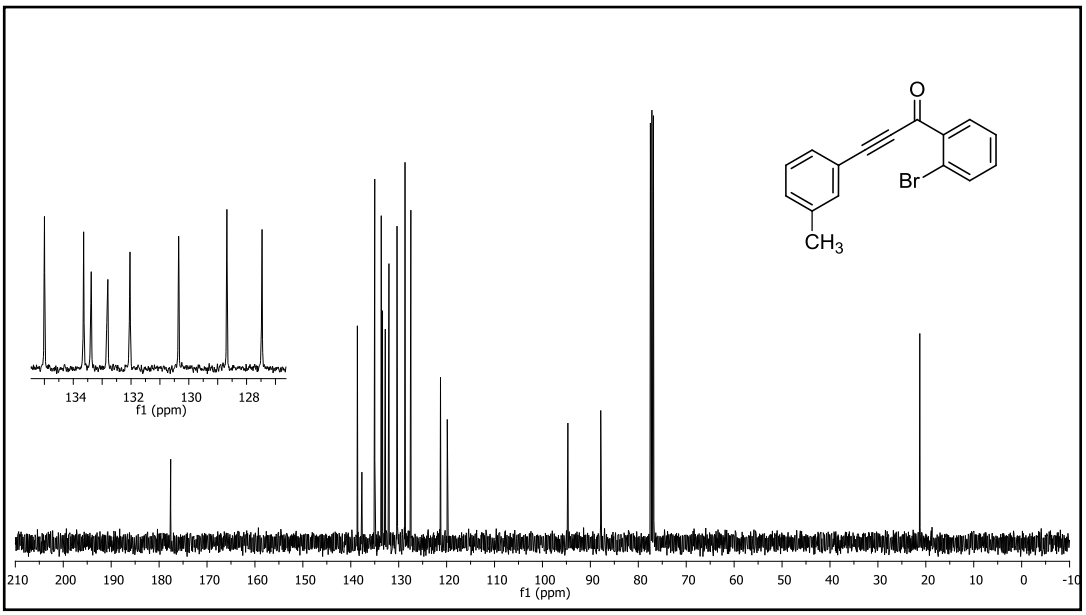

Figure 72. ^{13}C NMR spectrum of compound **63r**.

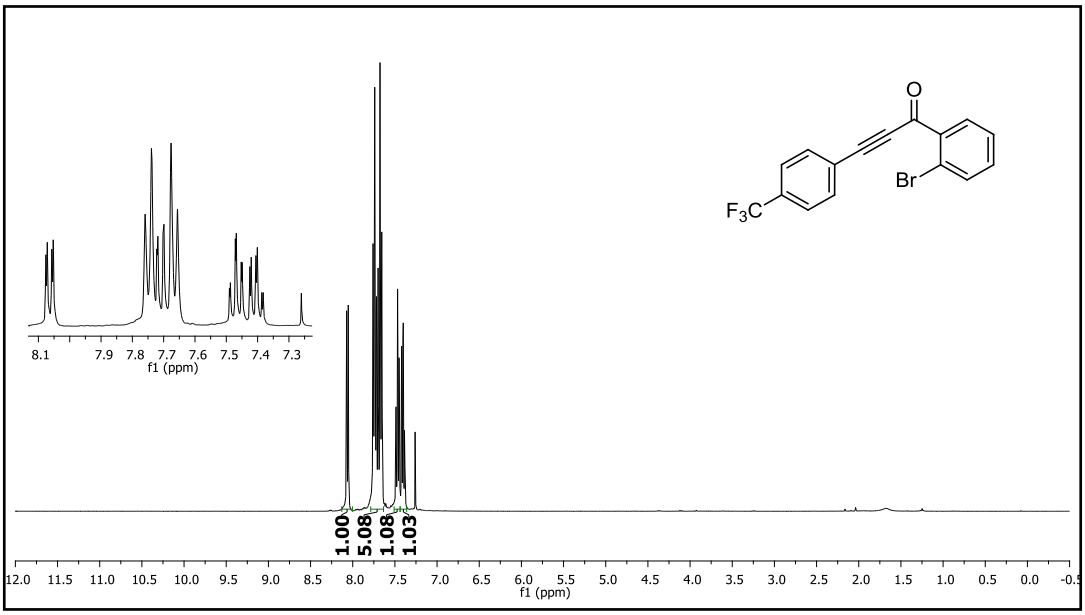

Figure 73. ^{1}H NMR spectrum of compound **63s**.

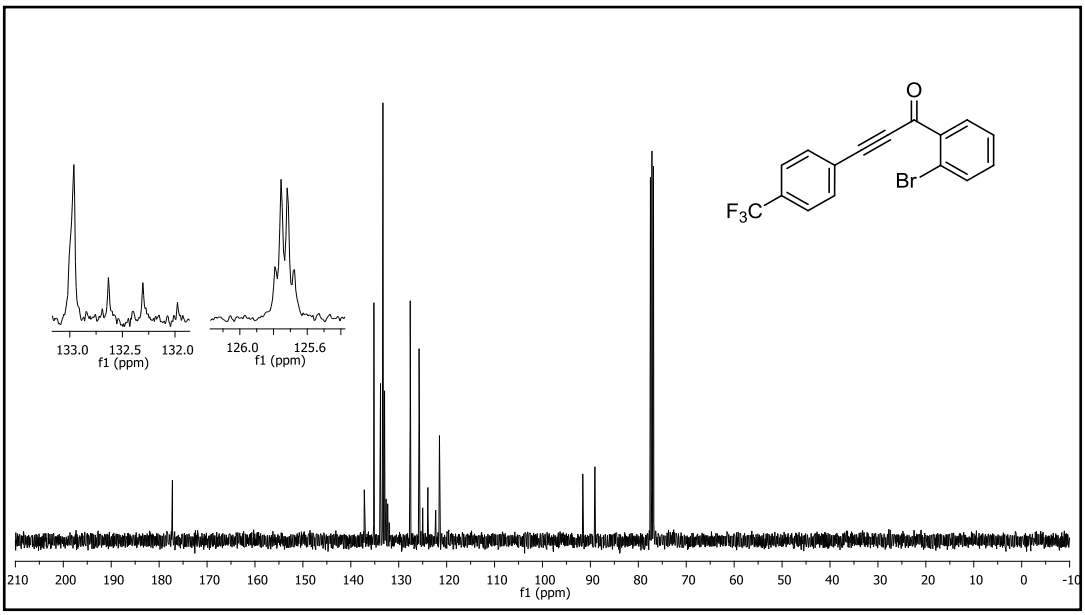

Figure 74. ^{13}C NMR spectrum of compound **63s**.

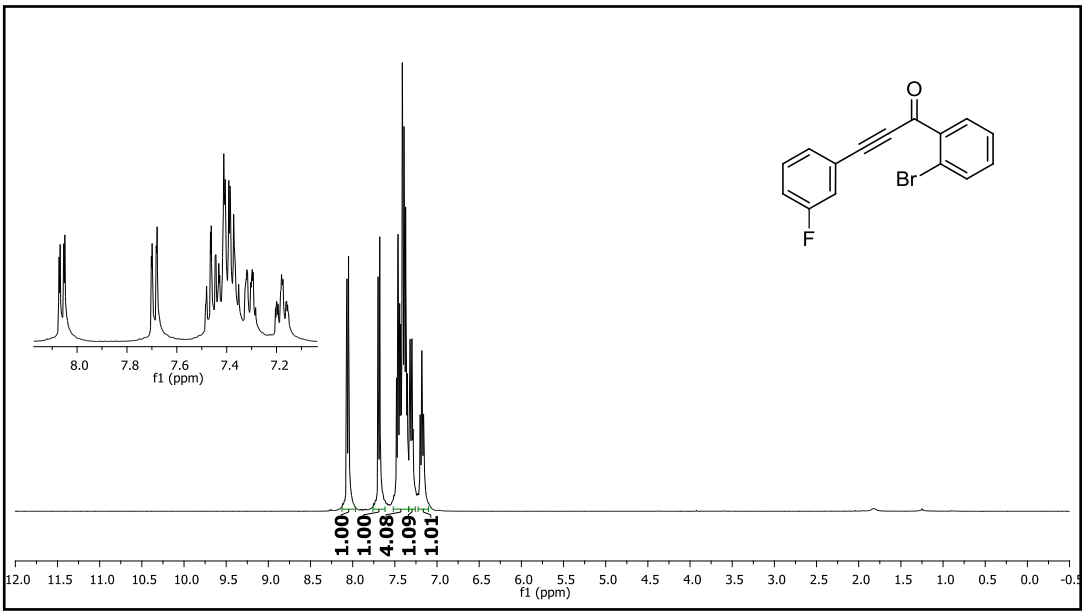

Figure 75. ^{1}H NMR spectrum of compound **63t**.

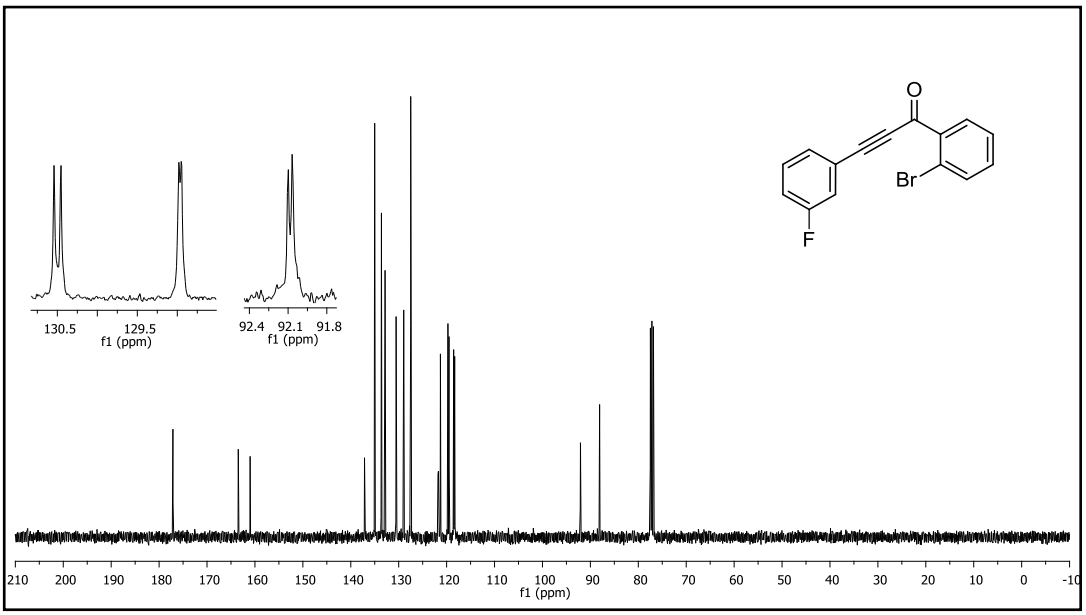

Figure 76. ^{13}C NMR spectrum of compound **63t**.

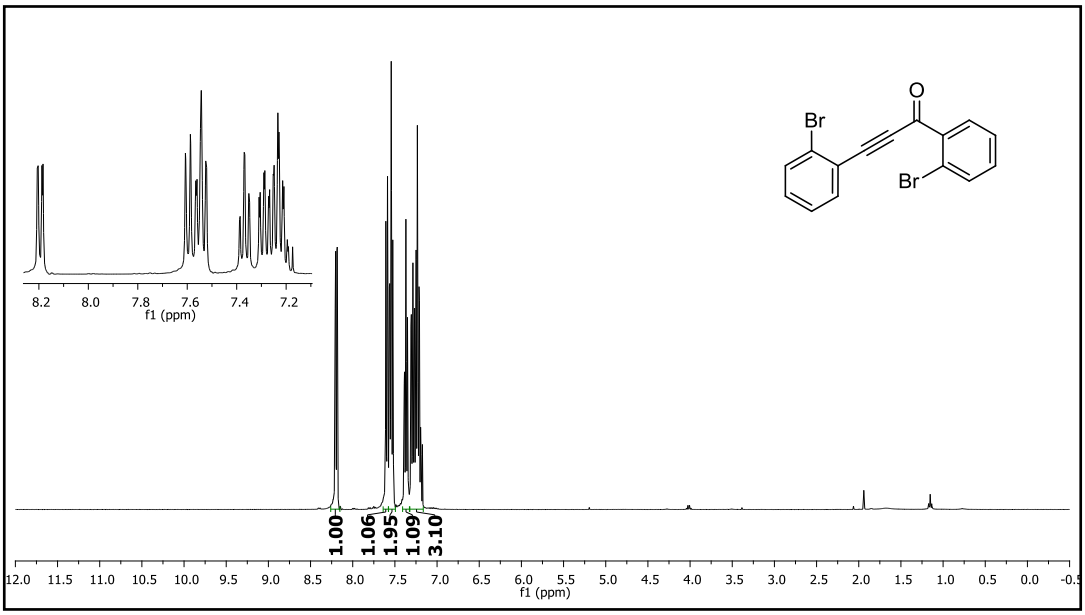

Figure 77. ^{1}H NMR spectrum of compound **63u**.

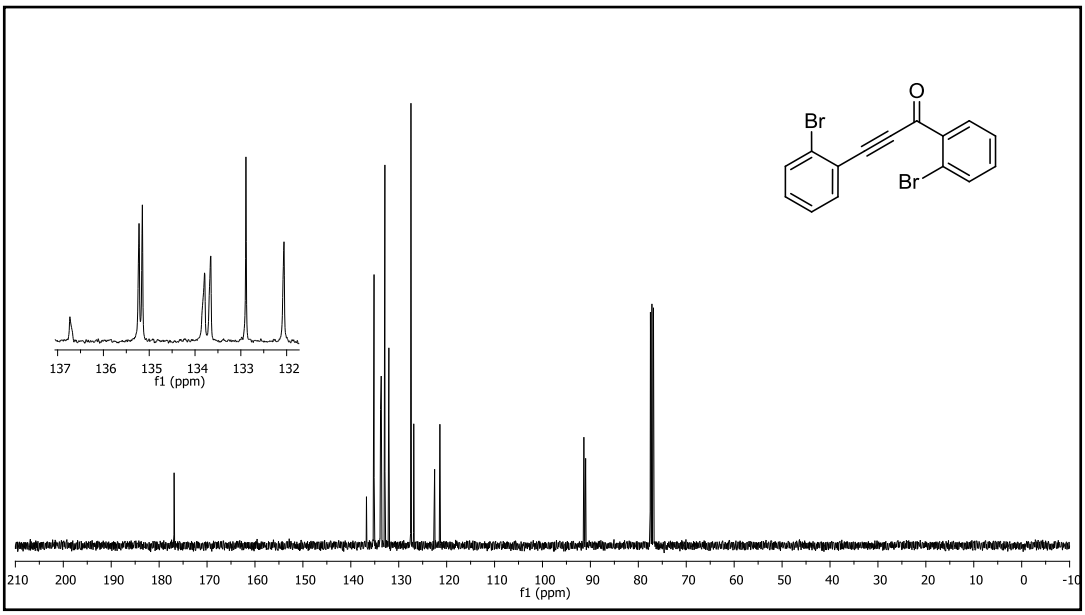

Figure 78. ^{13}C NMR spectrum of compound **63u**.

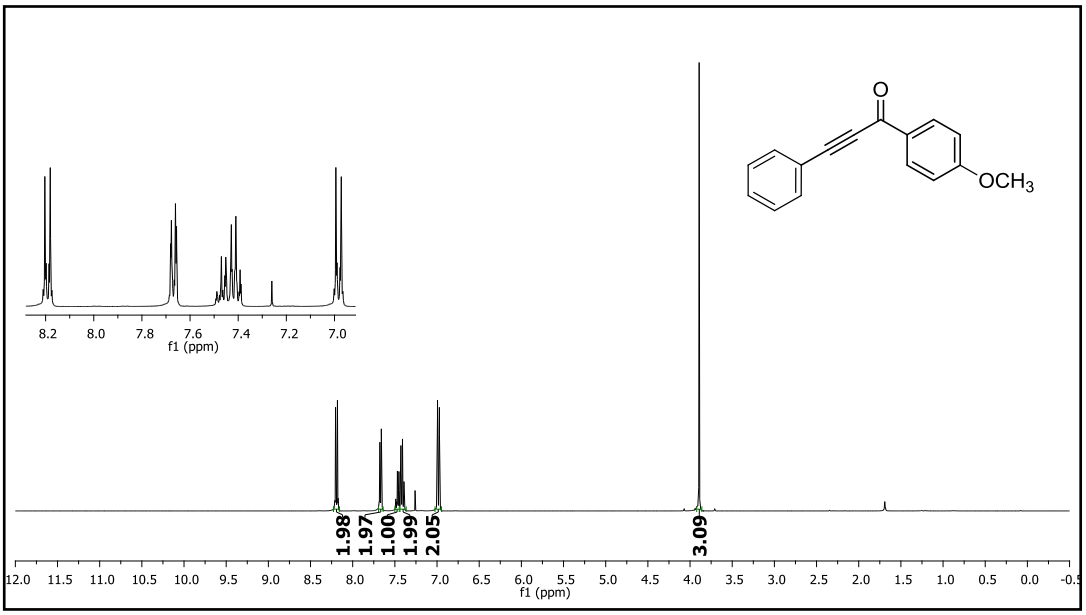

Figure 79. ^{1}H NMR spectrum of compound **63v**.

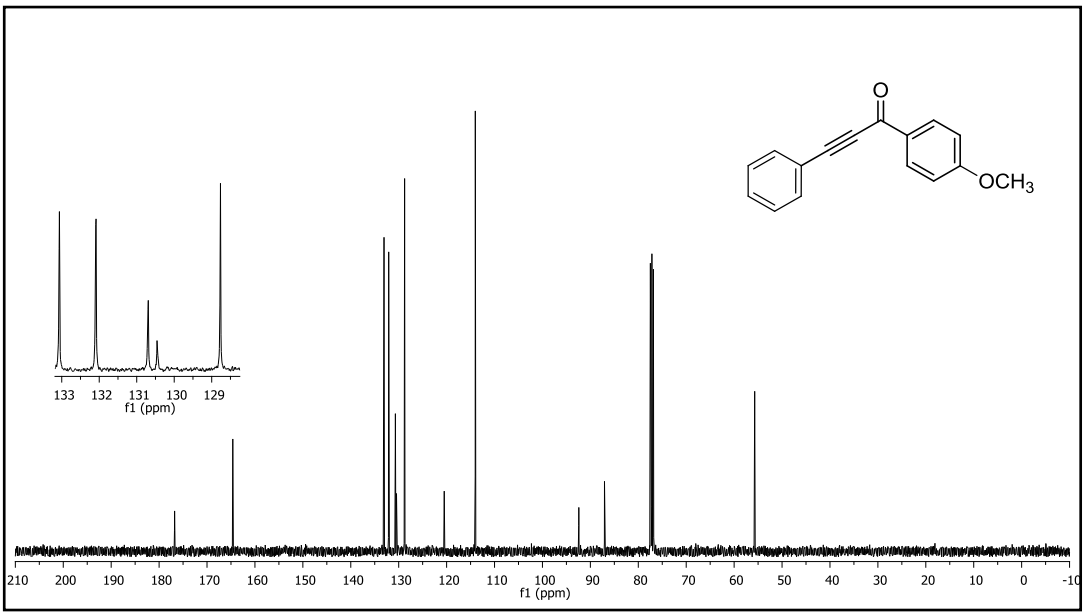

Figure 80. ^{13}C NMR spectrum of compound **63v**.

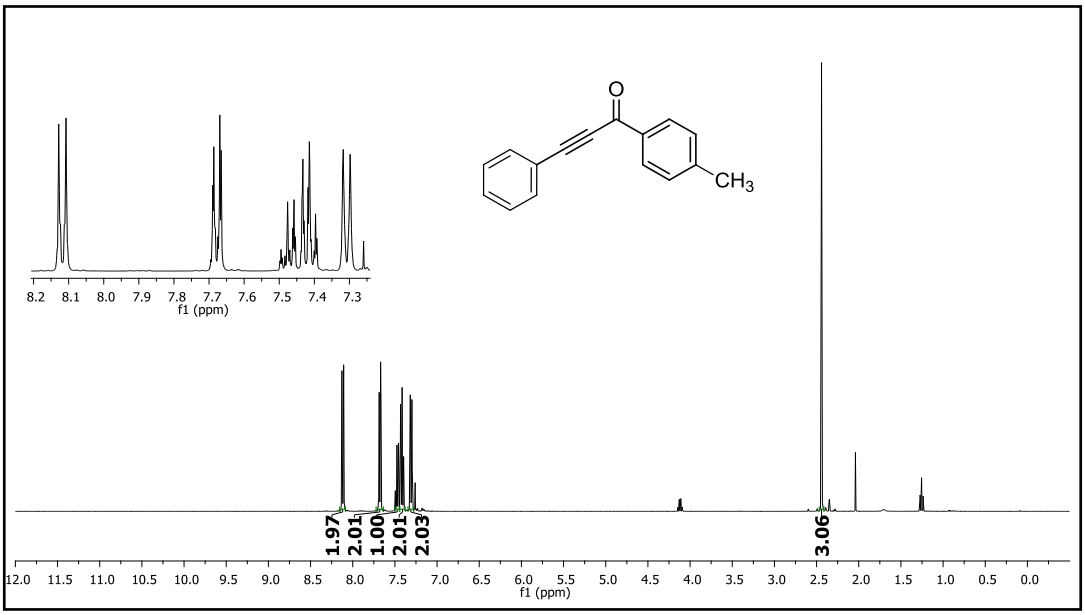

Figure 81. ^{1}H NMR spectrum of compound **63w**.

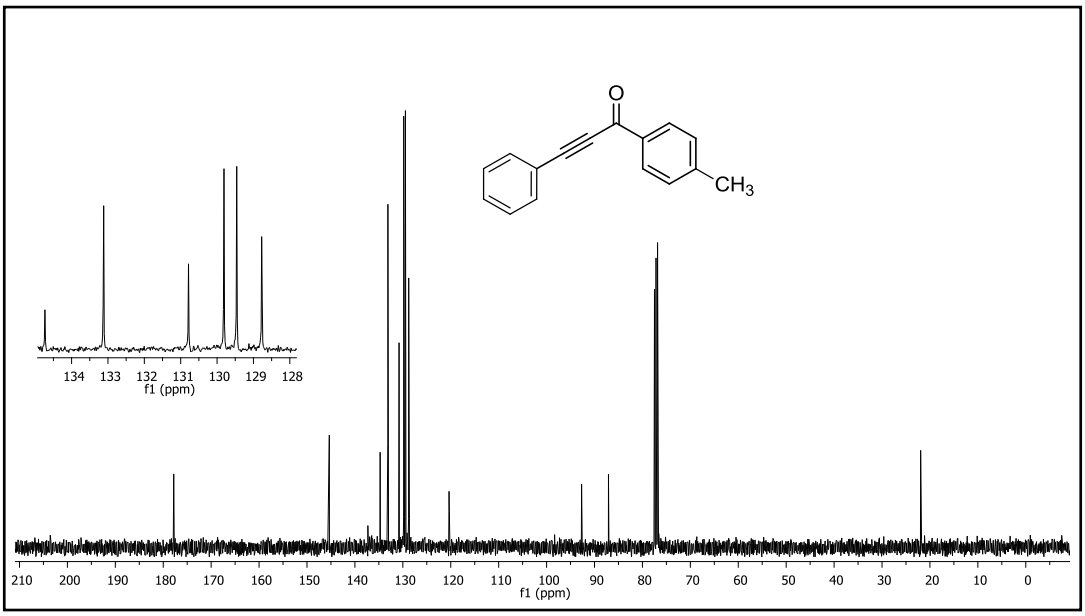

Figure 82. ^{13}C NMR spectrum of compound **63w**.

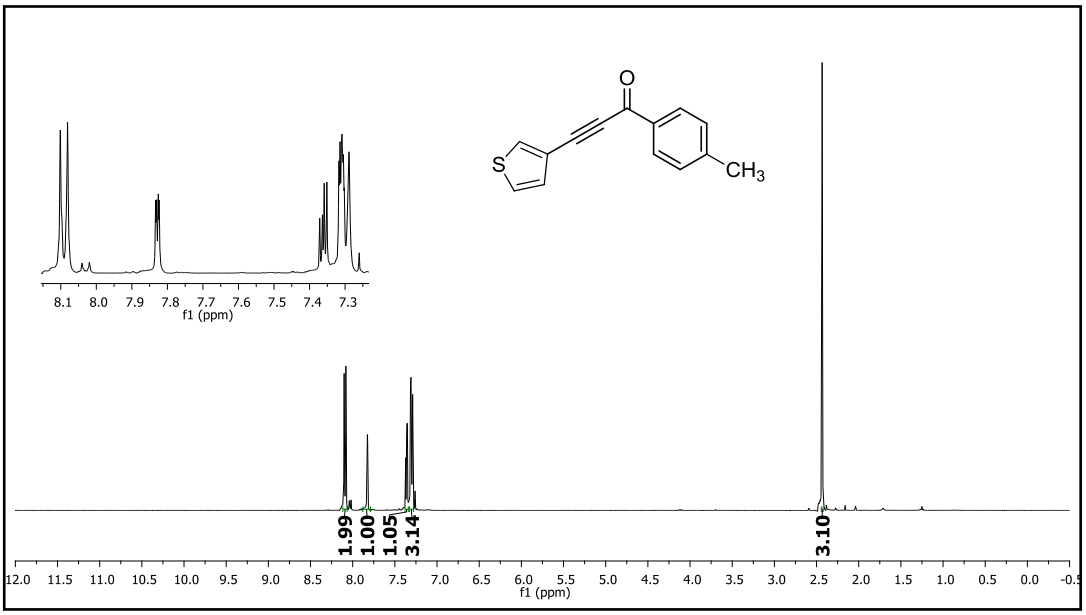

Figure 83. ^{1}H NMR spectrum of compound **63x**.

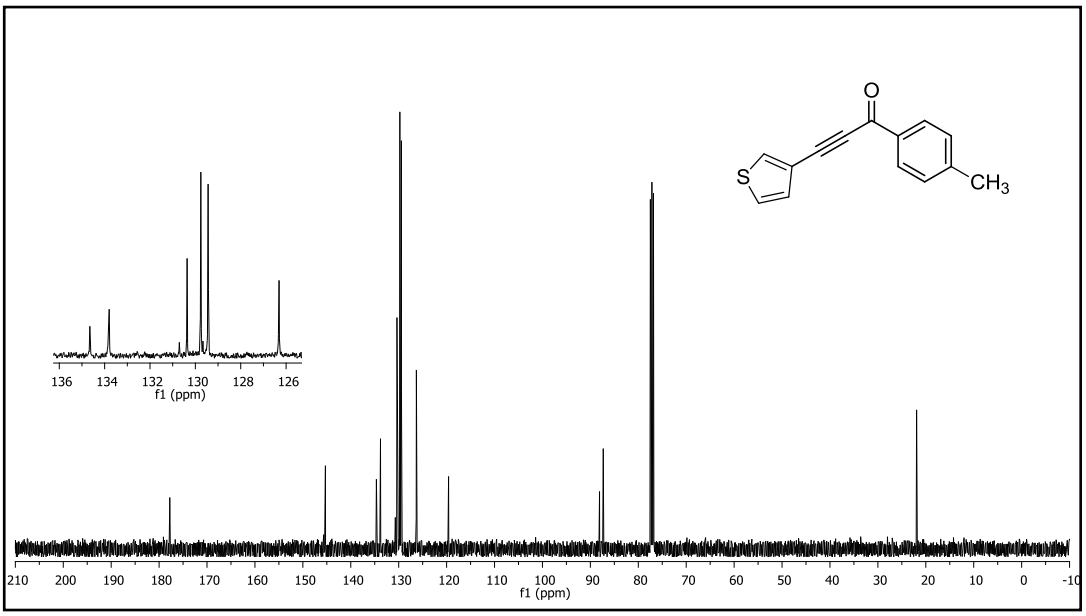

Figure 84. ^{13}C NMR spectrum of compound **63x**.

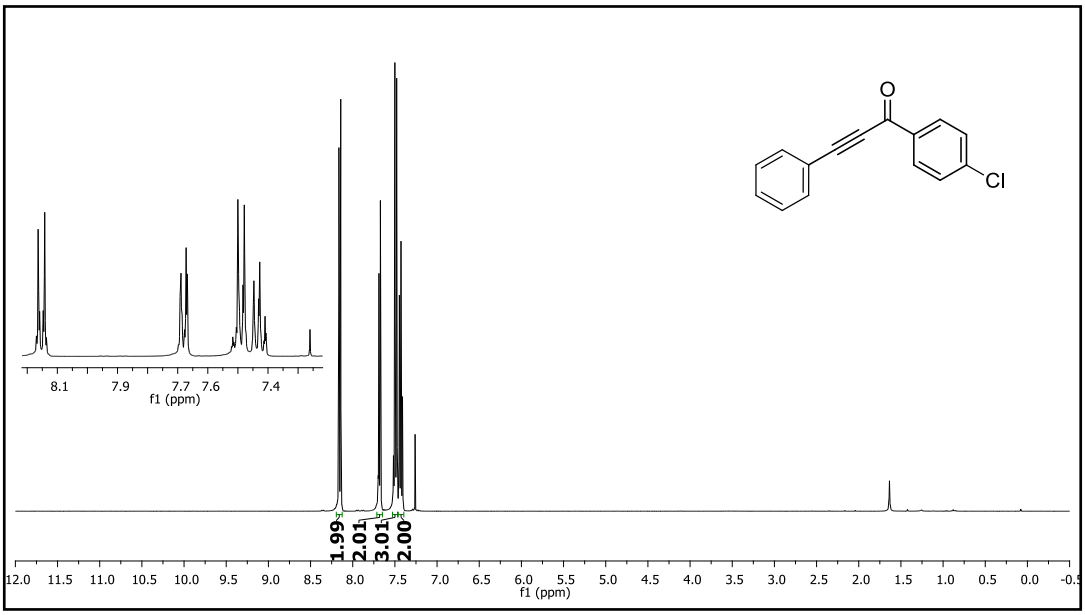

Figure 85. ^{1}H NMR spectrum of compound **63y**.

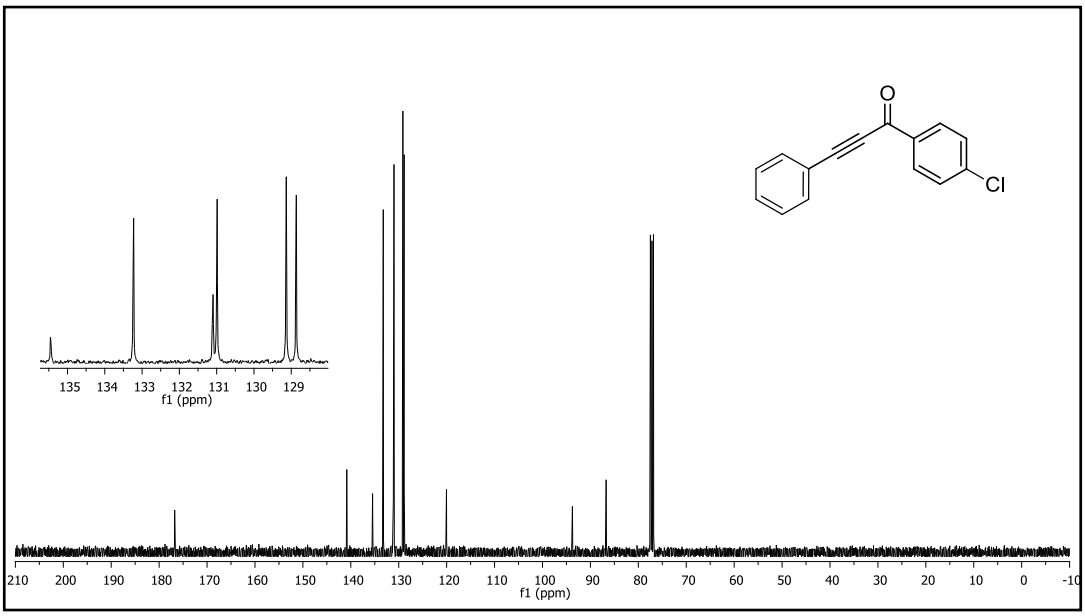

Figure 86. ^{13}C NMR spectrum of compound **63y**.

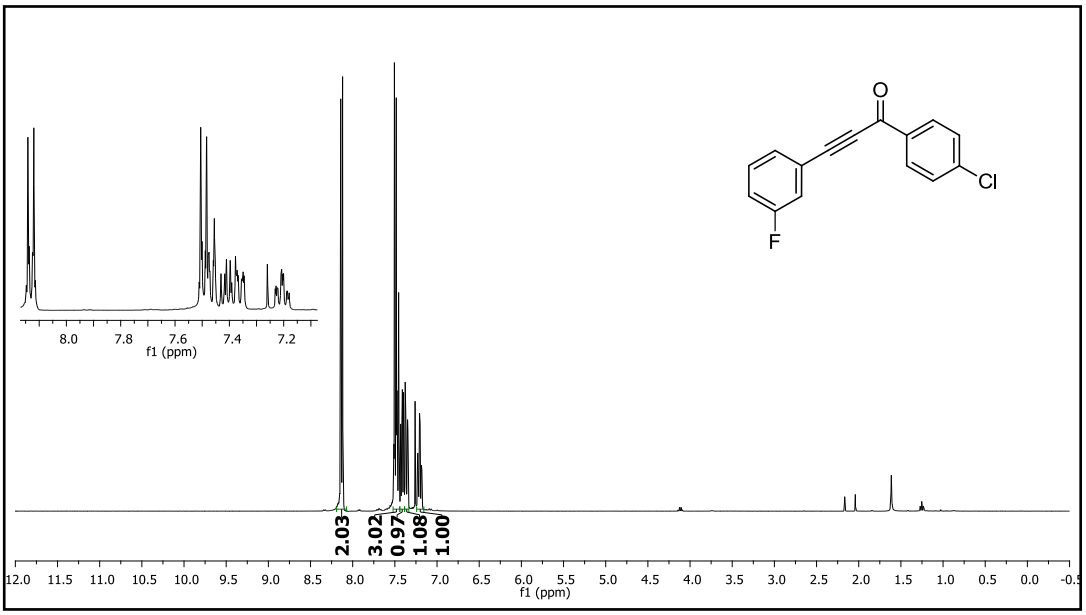

Figure 87. ^{1}H NMR spectrum of compound **63z**.

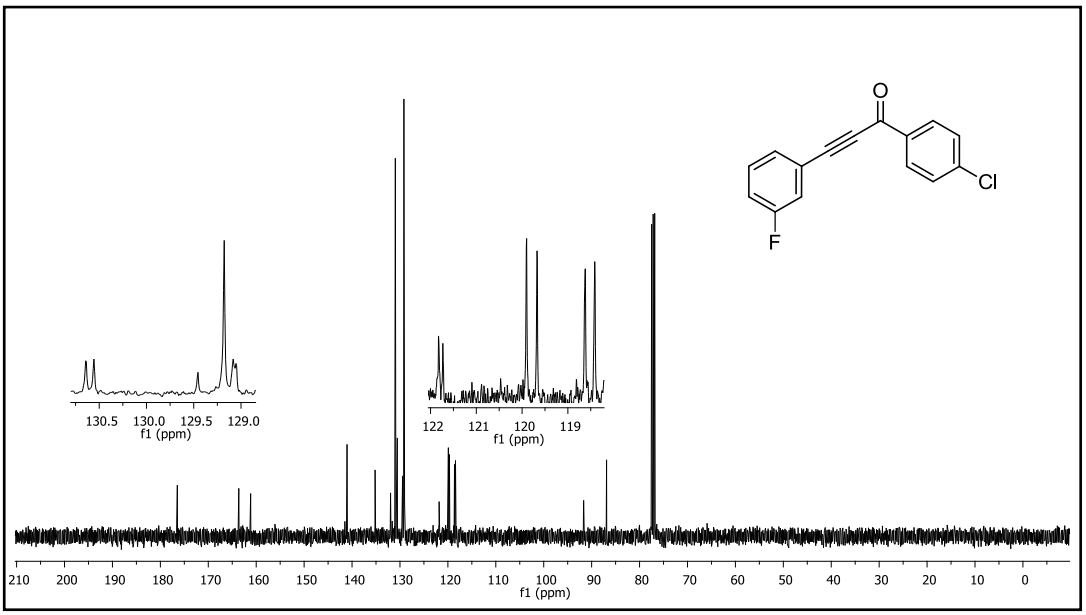

Figure 88. ^{13}C NMR spectrum of compound **63z**.

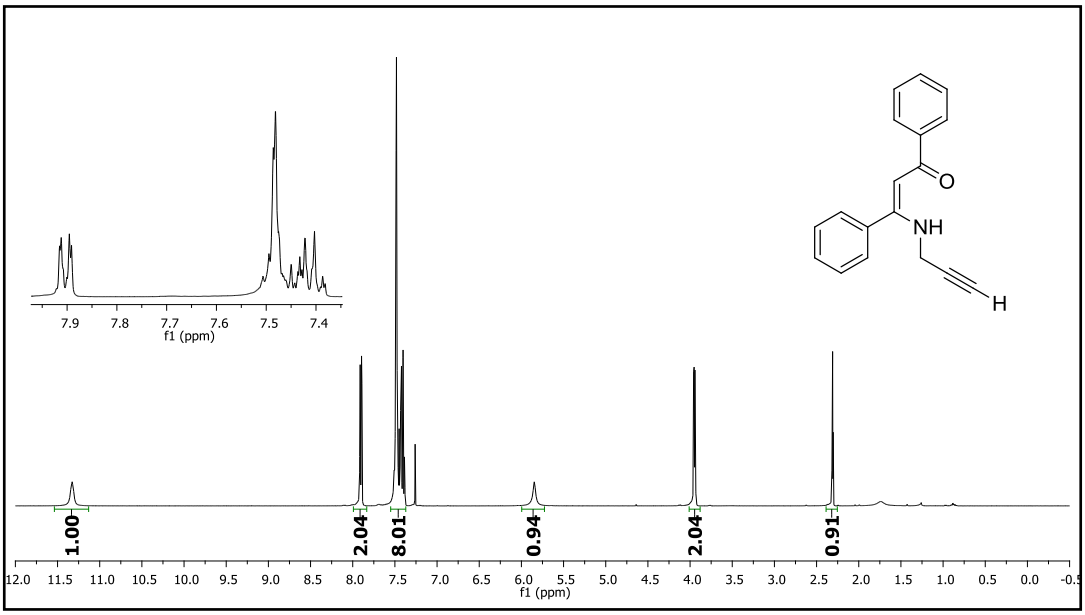

Figure 89. ^{1}H NMR spectrum of compound **32a**.

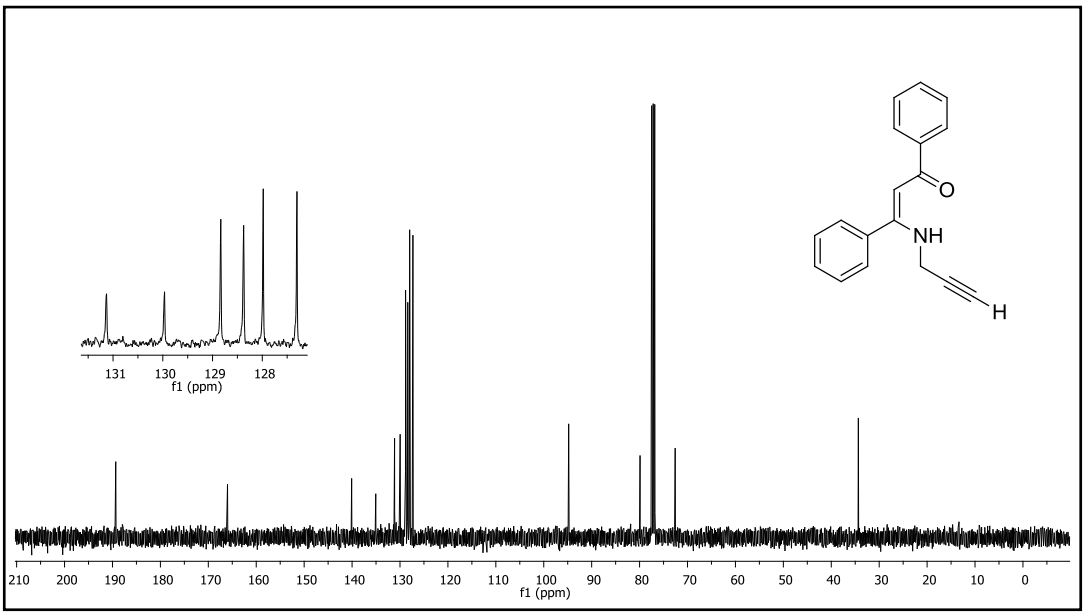

Figure 90. ^{13}C NMR spectrum of compound **32a**.

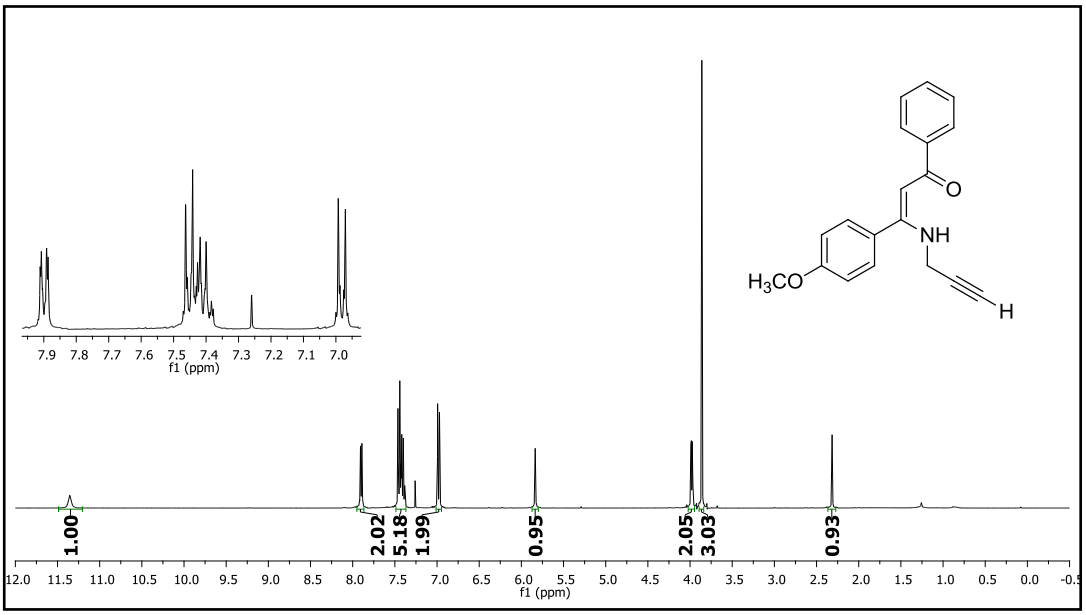

Figure 91. ^{1}H NMR spectrum of compound **32b**.

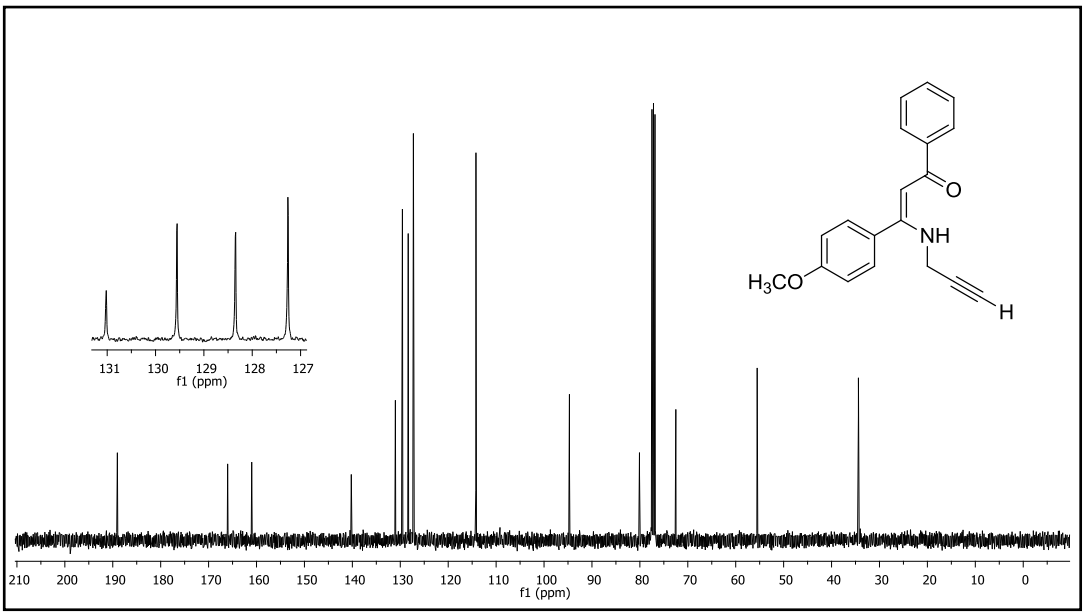

Figure 92. ^{13}C NMR spectrum of compound **32b**.

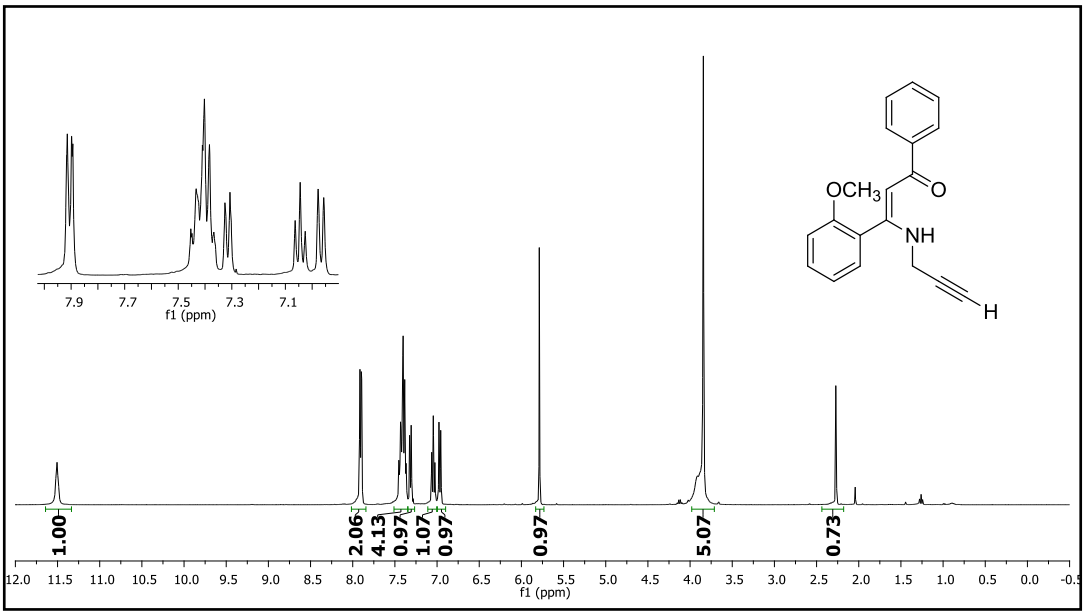

Figure 93. ^{1}H NMR spectrum of compound **32c**.

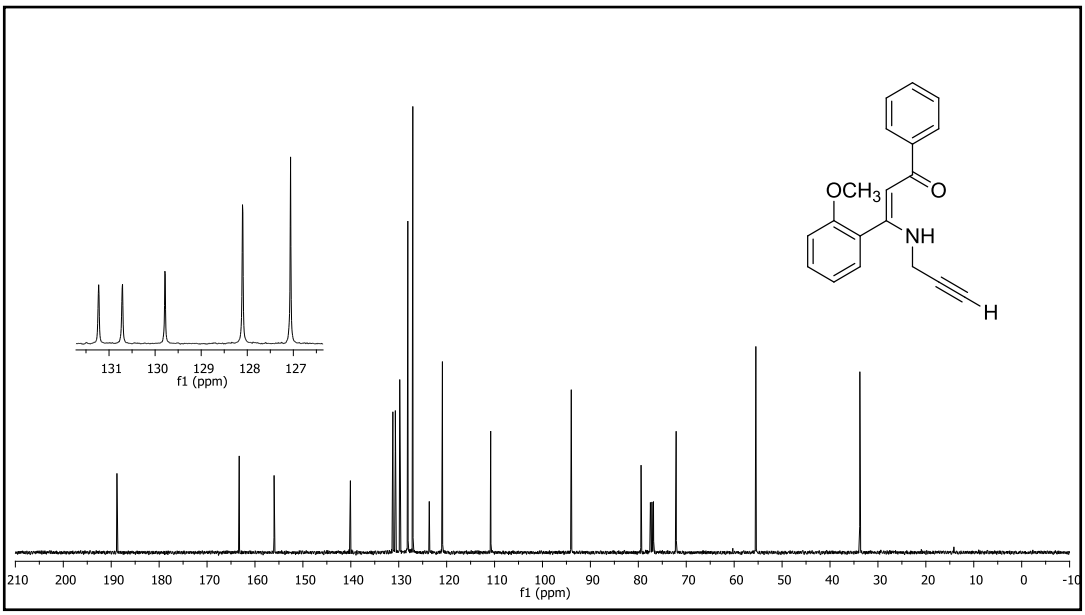

Figure 94. ^{13}C NMR spectrum of compound **32c**.

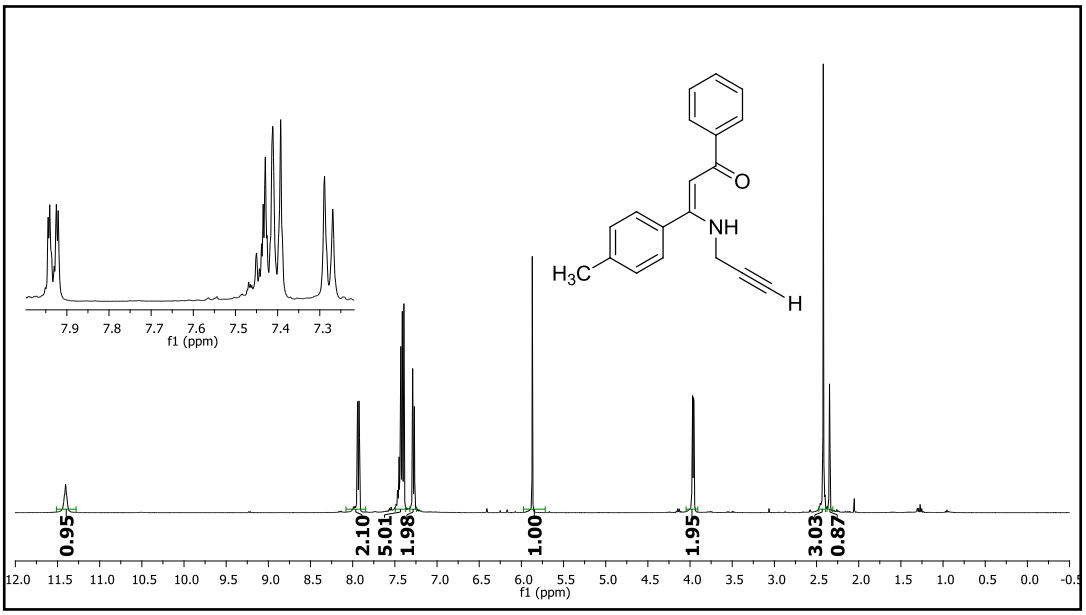

Figure 95. ^{1}H NMR spectrum of compound **32d**.

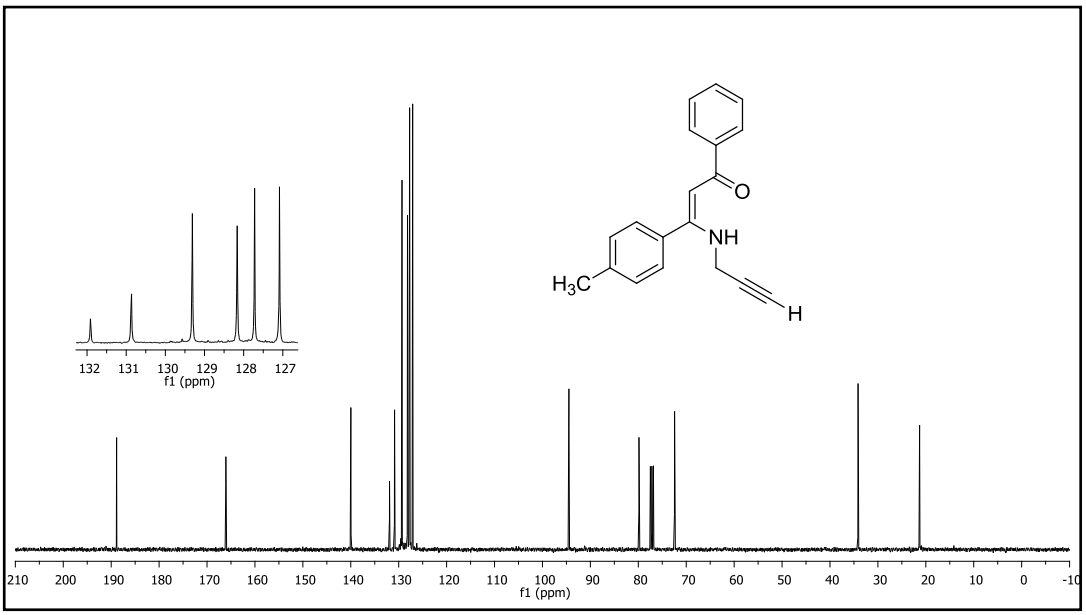

Figure 96. ^{13}C NMR spectrum of compound **32d**.

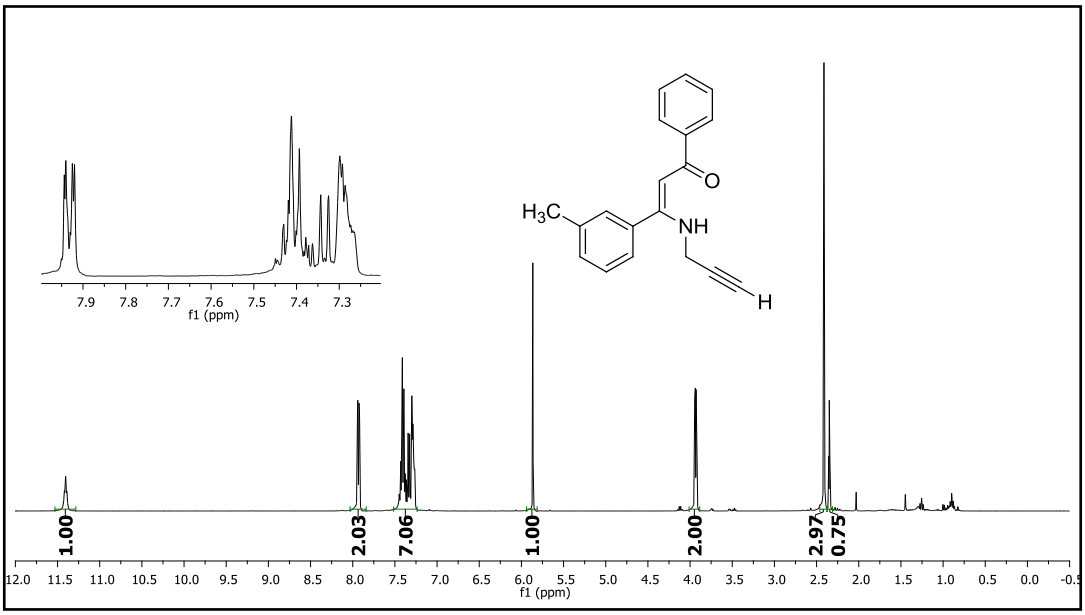

Figure 97. ^{1}H NMR spectrum of compound **32e**.

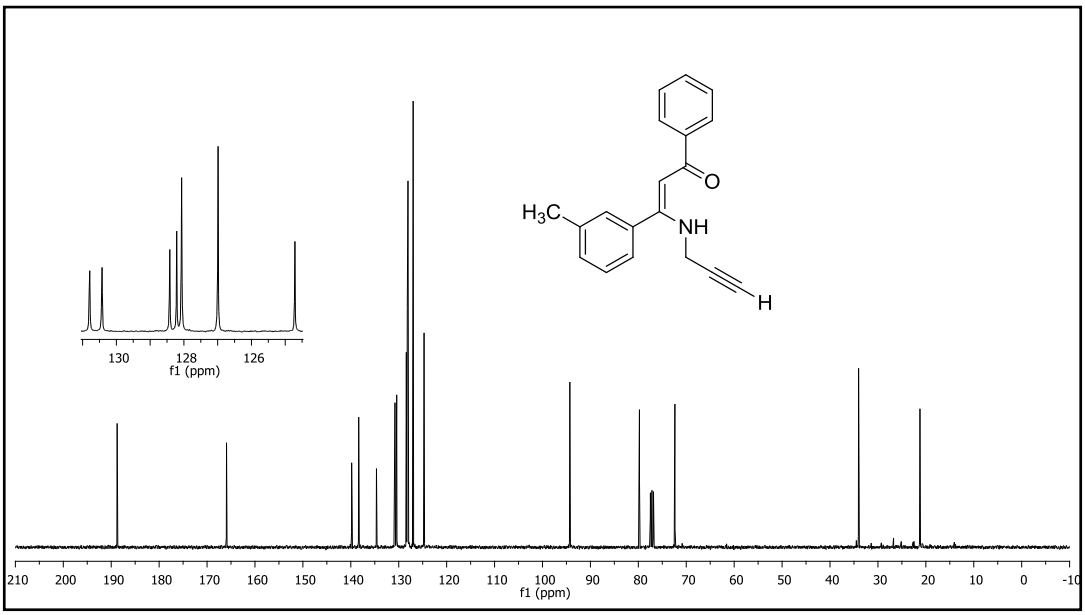

Figure 98. ^{13}C NMR spectrum of compound **32e**.

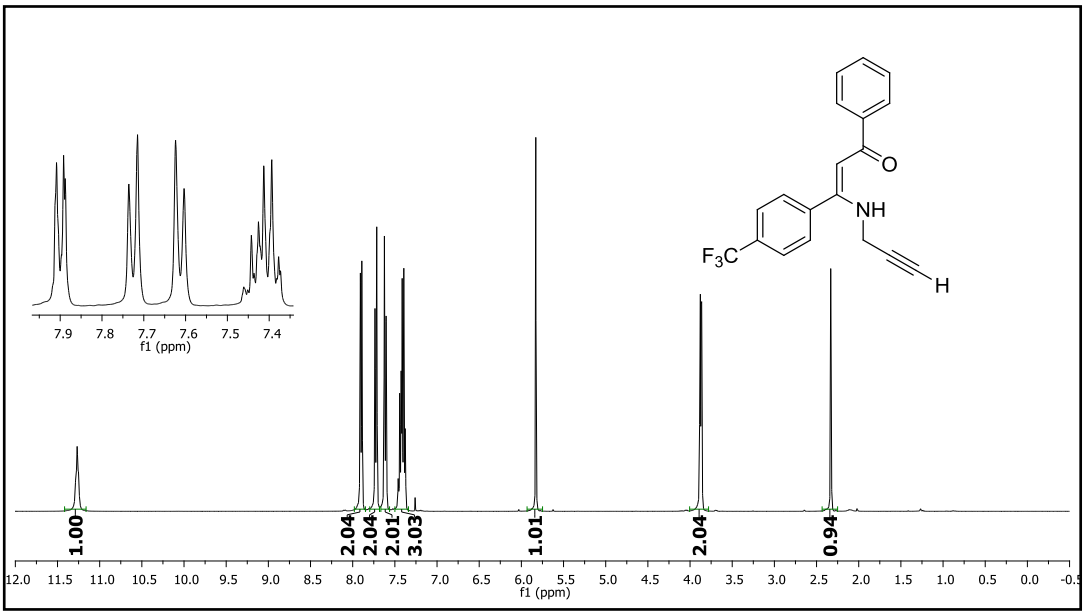

Figure 99. ^{1}H NMR spectrum of compound **32f**.

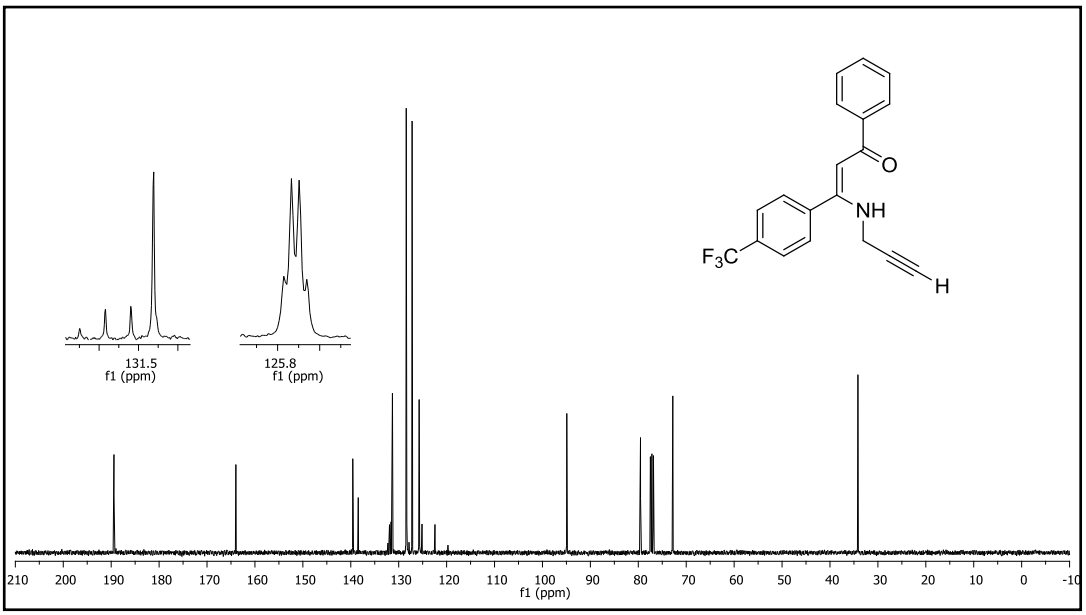

Figure 100. ^{13}C NMR spectrum of compound **32f**.

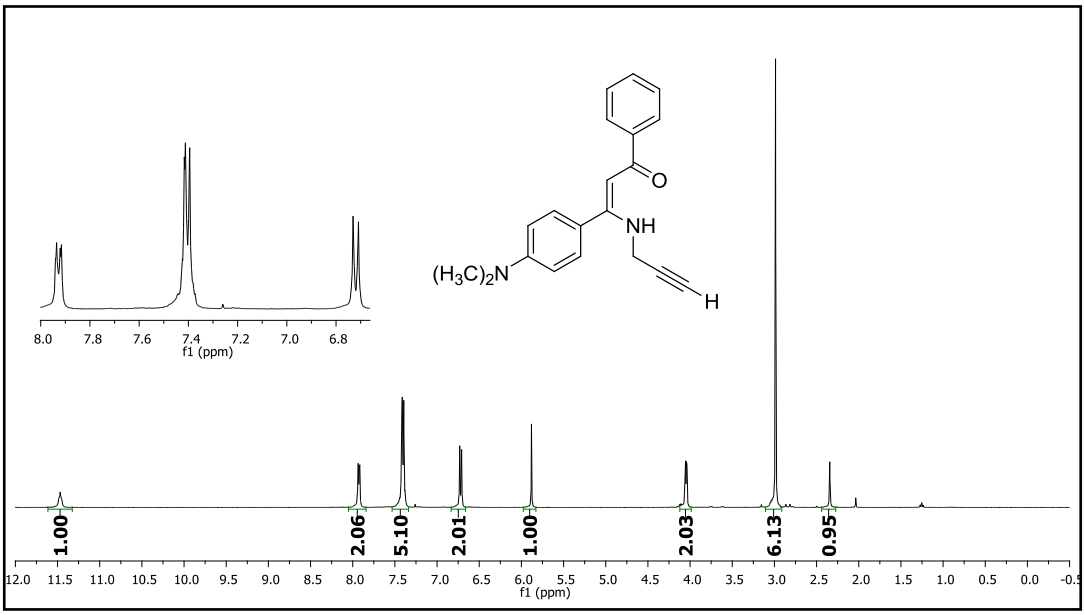

Figure 101. ^{1}H NMR spectrum of compound **32g**.

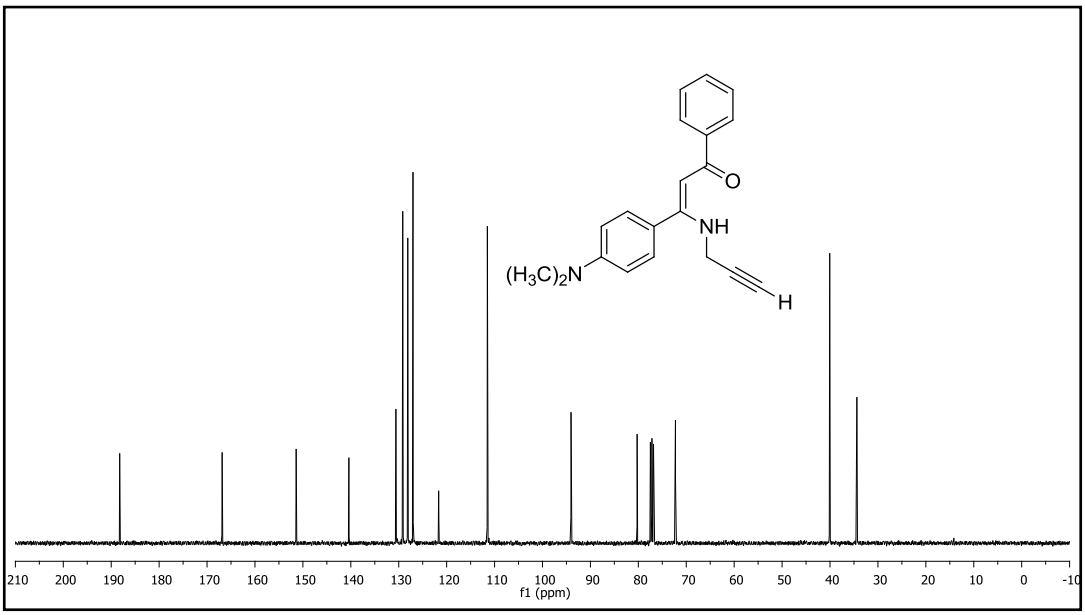

Figure 102. ^{13}C NMR spectrum of compound **32g**.

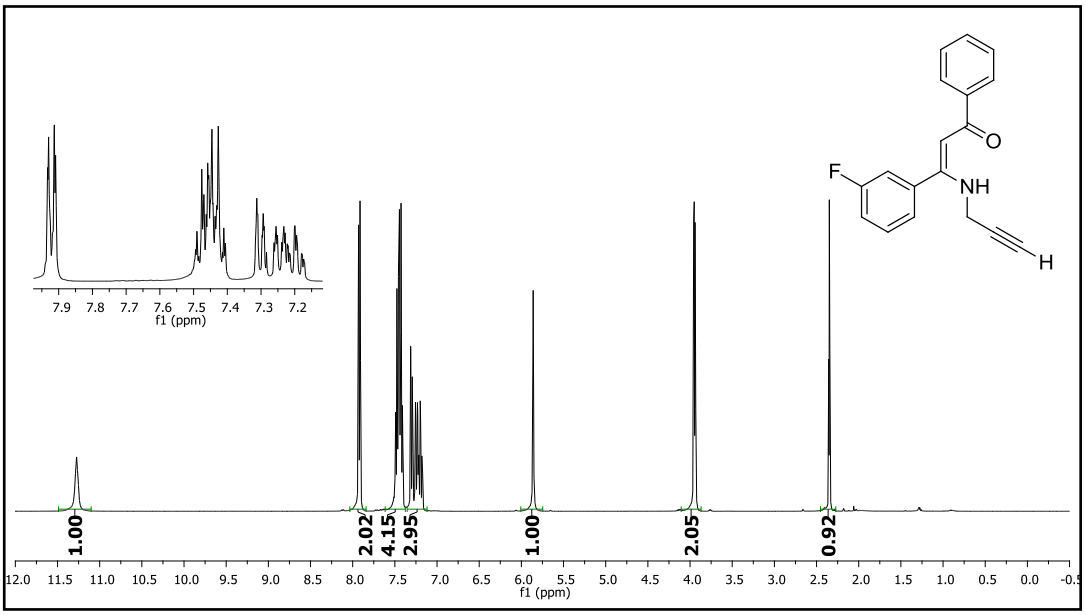

Figure 103. ^{1}H NMR spectrum of compound **32h**.

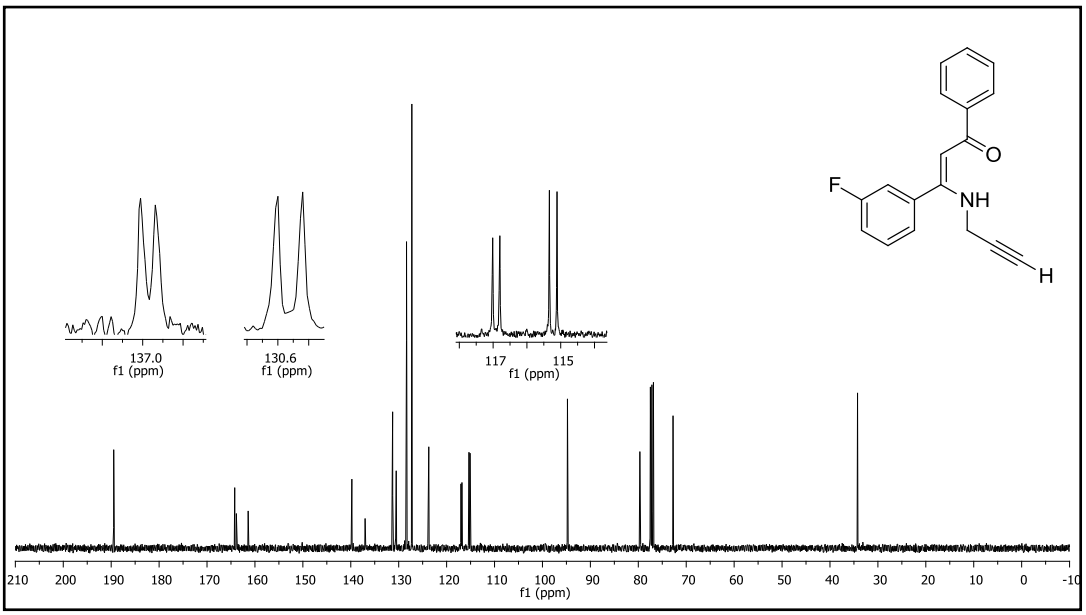

Figure 104. ^{13}C NMR spectrum of compound **32h**.

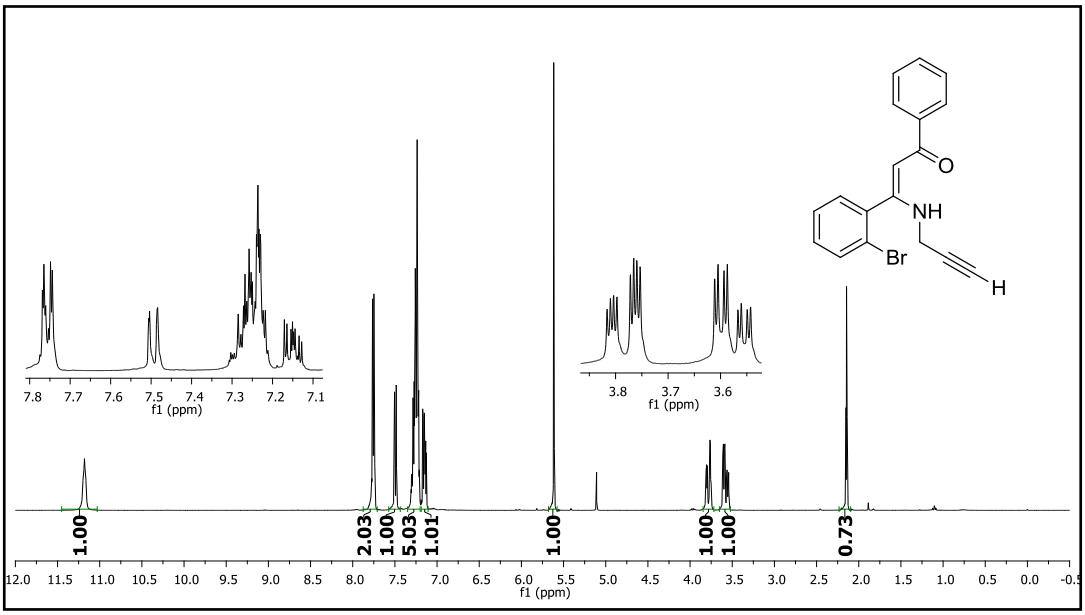

Figure 105. ^{1}H NMR spectrum of compound **32i**.

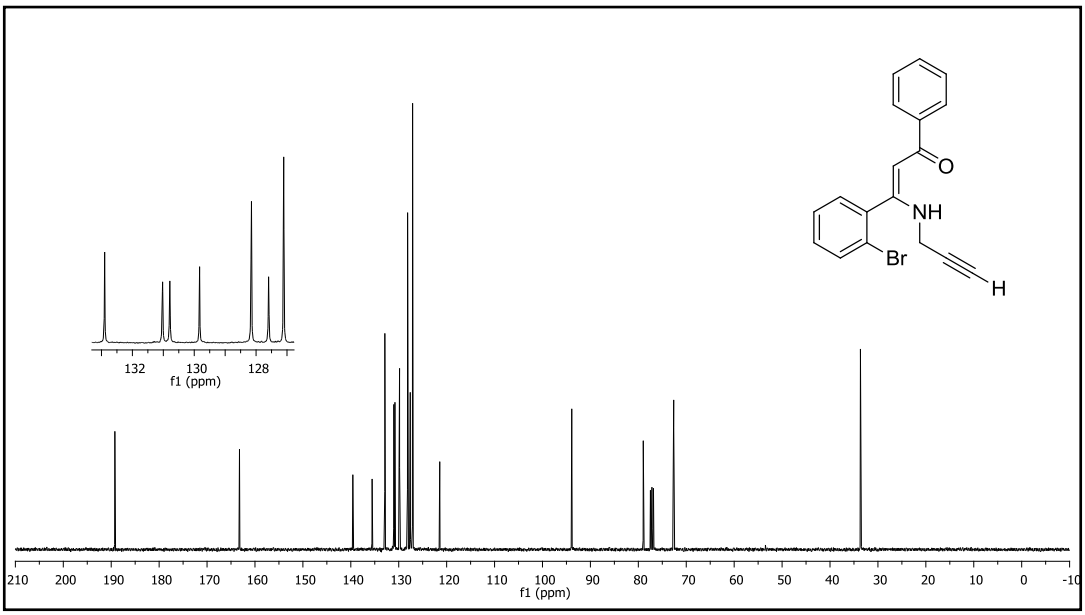

Figure 106. ^{13}C NMR spectrum of compound **32i**.

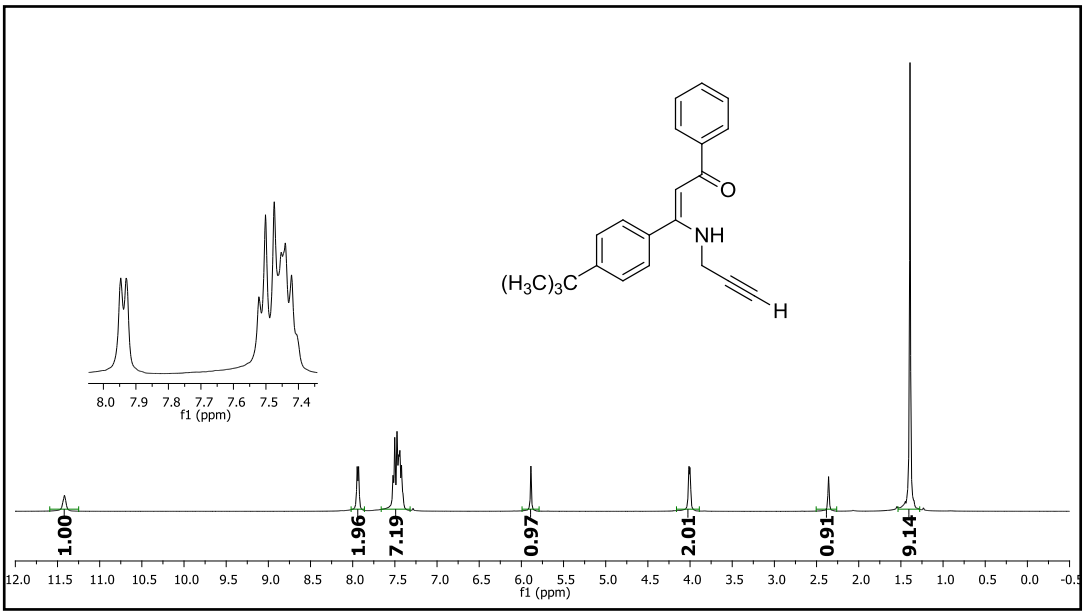

Figure 107. ^{1}H NMR spectrum of compound **32j**.

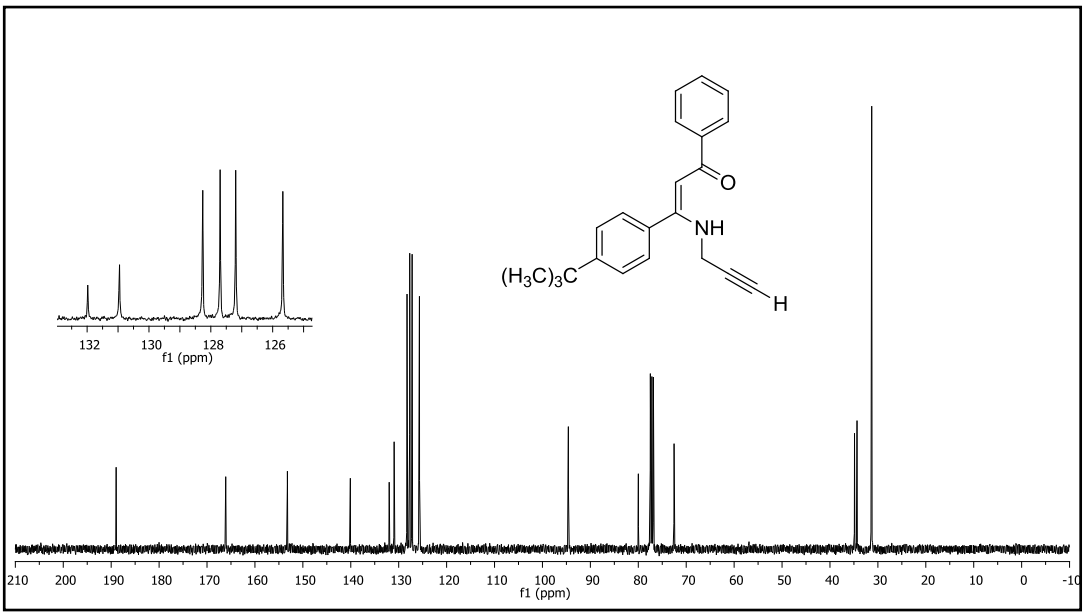

Figure 108. ^{13}C NMR spectrum of compound **32j**.

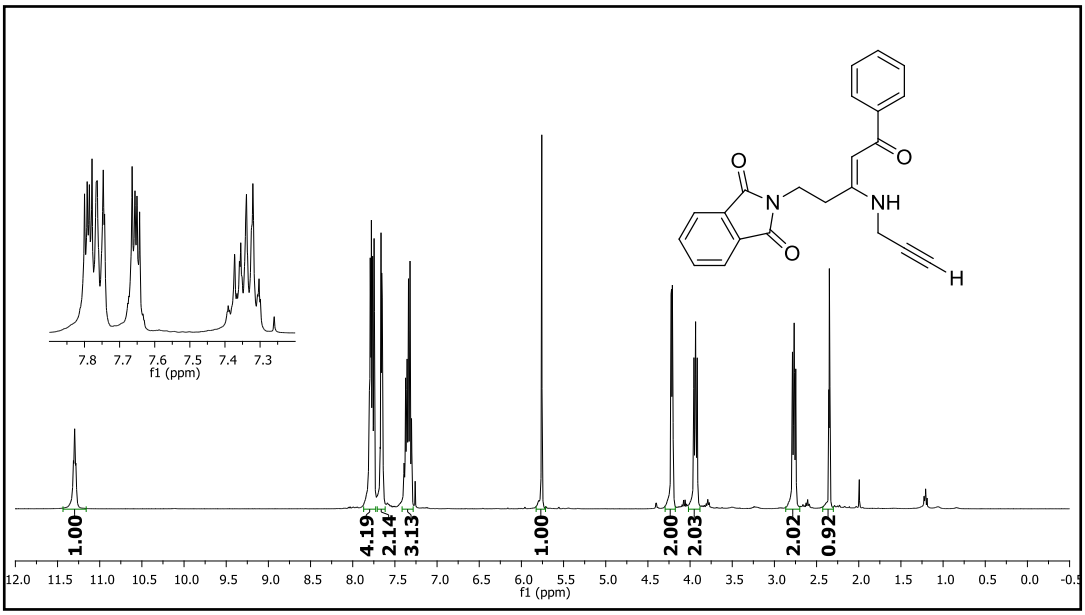

Figure 109. ^{1}H NMR spectrum of compound **32k**.

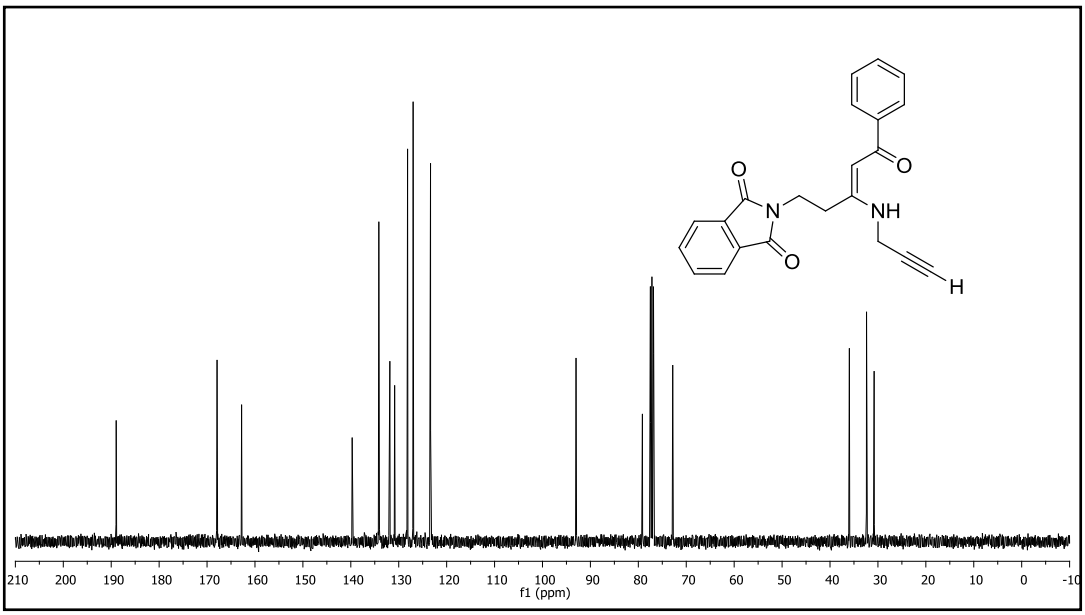

Figure 110. ^{13}C NMR spectrum of compound **32k**.

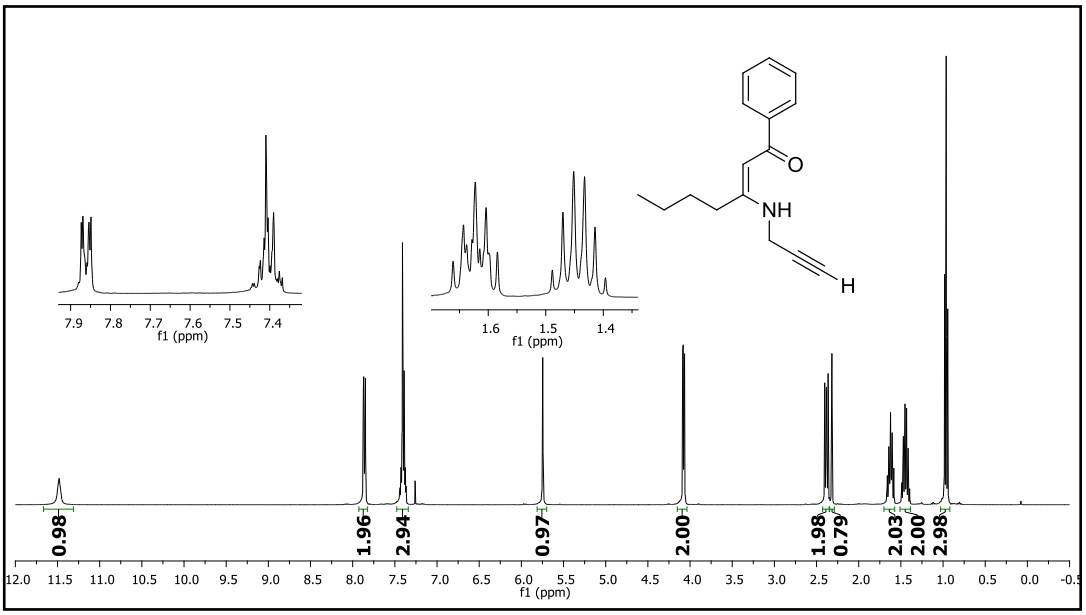

Figure 111. ^{1}H NMR spectrum of compound **32l**.

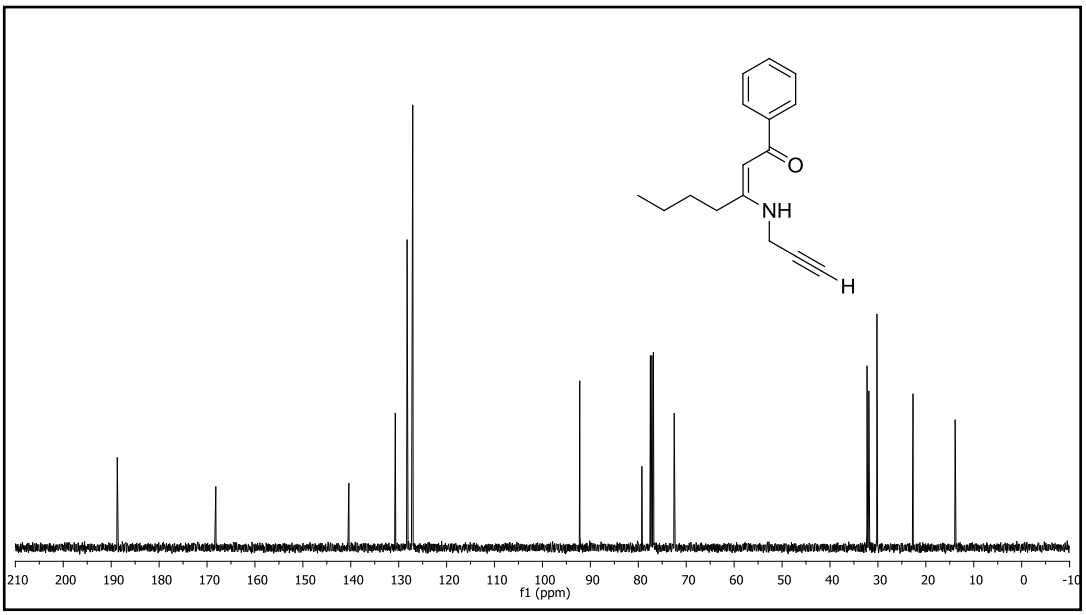

Figure 112. ^{13}C NMR spectrum of compound **32l**.

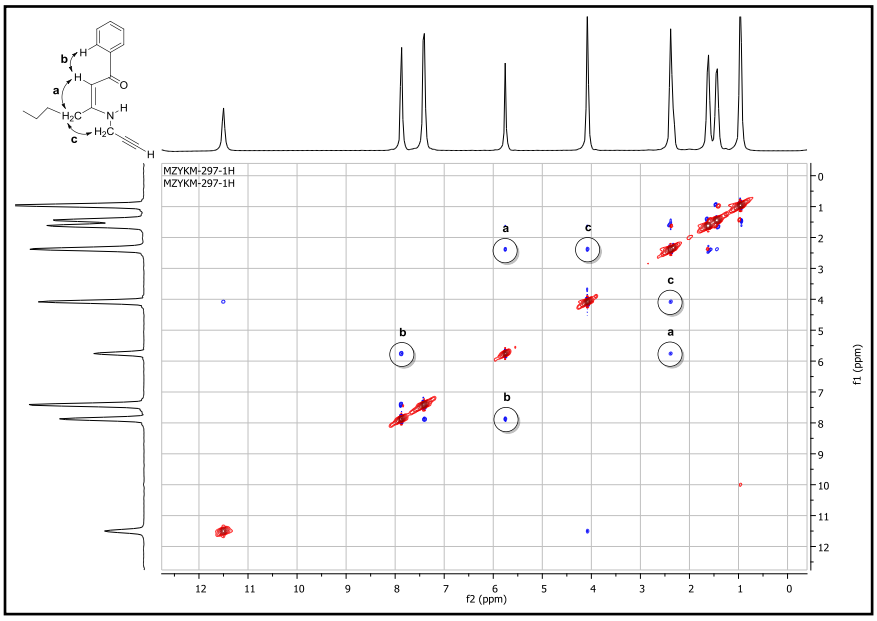

Figure 113. NOESY NMR spectrum of compound **32l**.
(Cross peaks in circles represent the NOE interactions **a, b** and **c** on the structure)

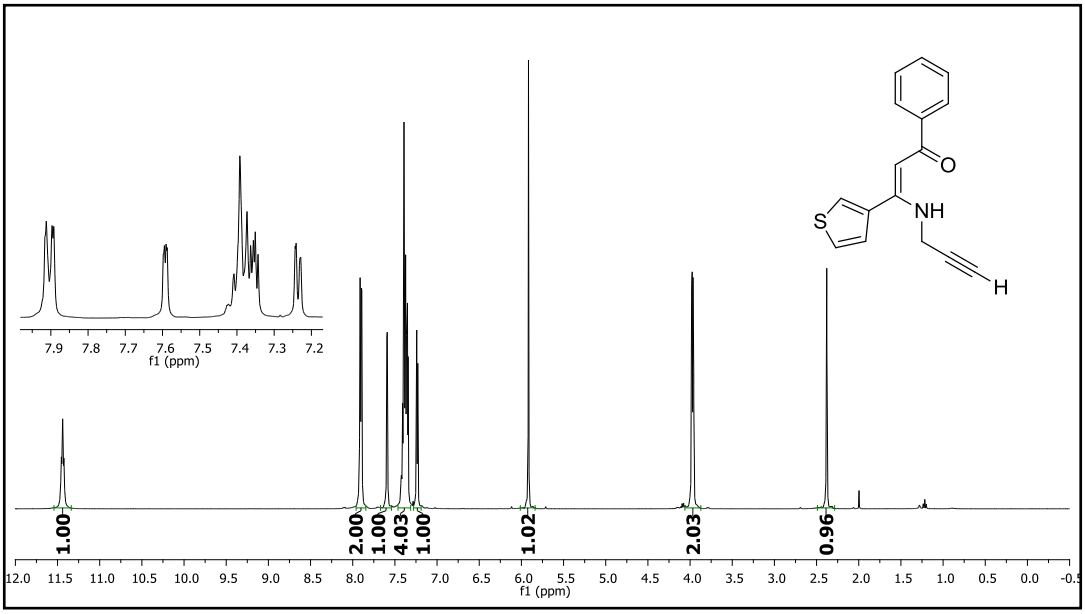

Figure 114. ^{1}H NMR spectrum of compound **32m**.

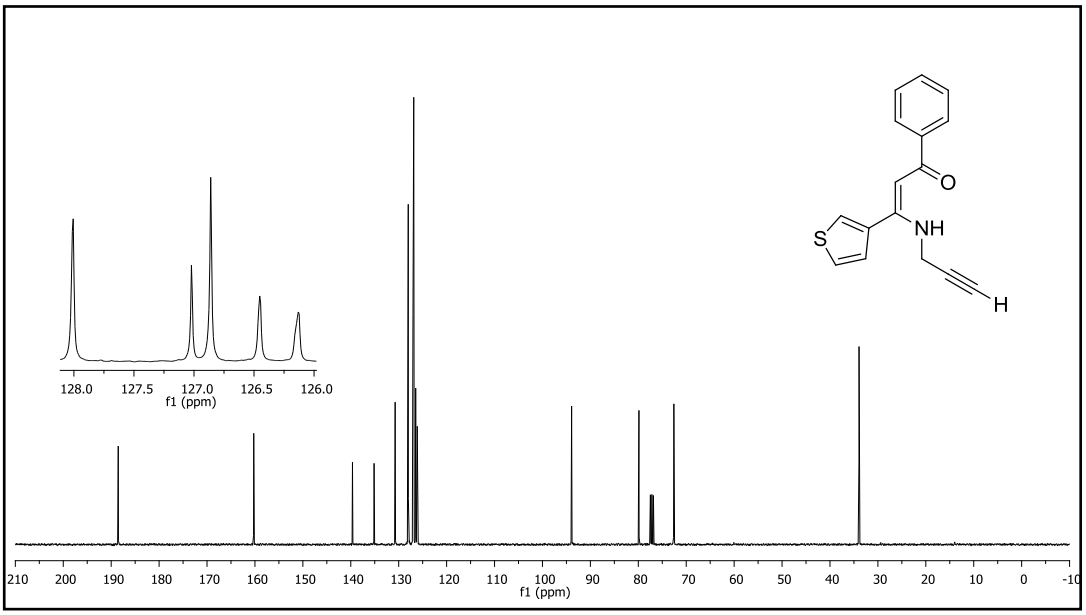

Figure 115. ^{13}C NMR spectrum of compound **32m**.

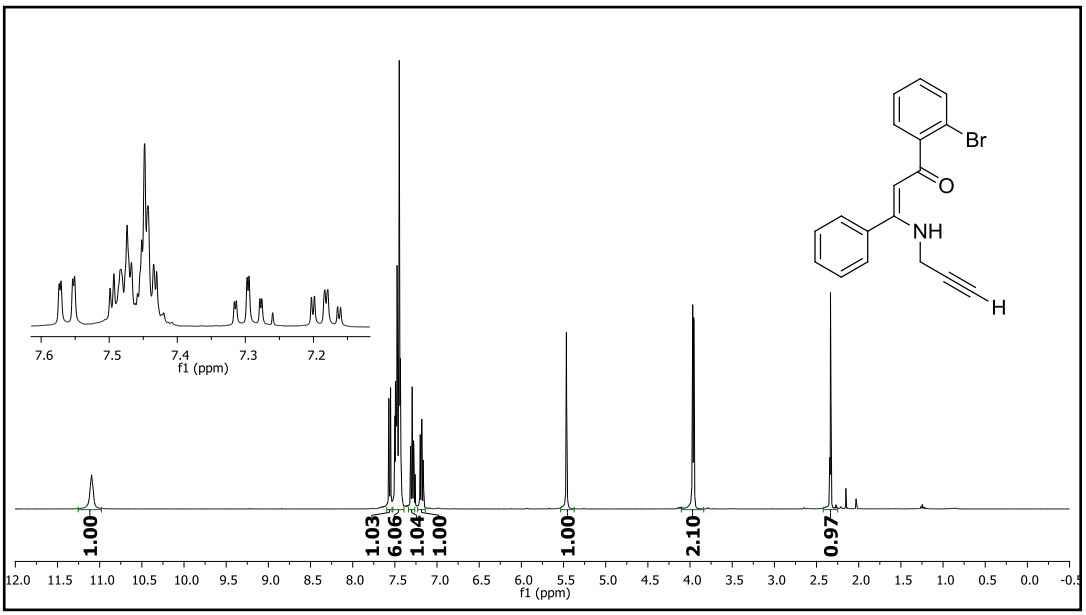

Figure 116. ^{1}H NMR spectrum of compound **32n**.

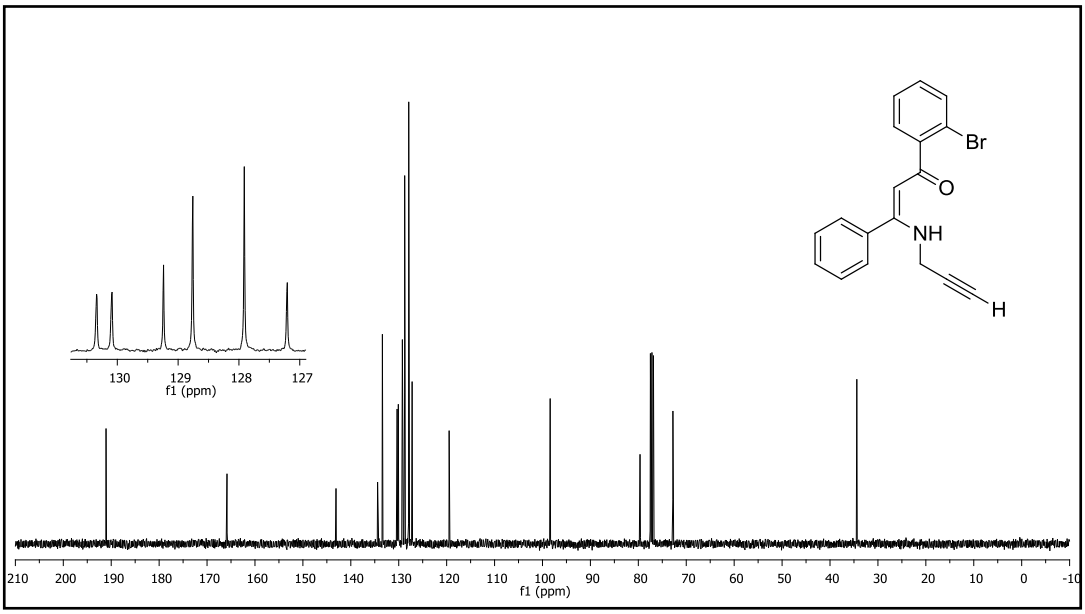

Figure 117. ^{13}C NMR spectrum of compound **32n**.

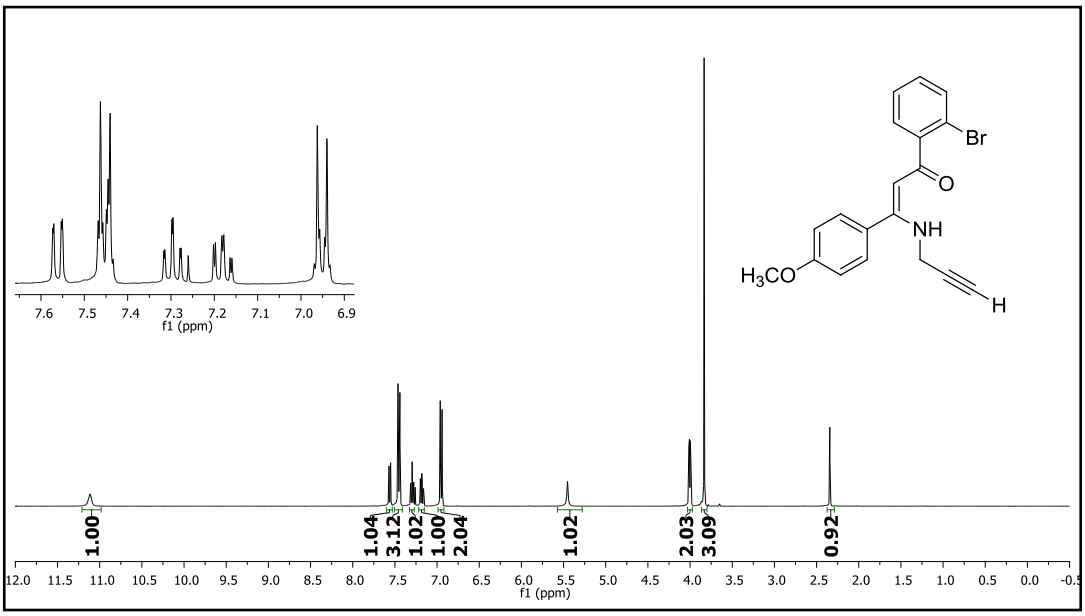

Figure 118. ^{1}H NMR spectrum of compound **32o**.

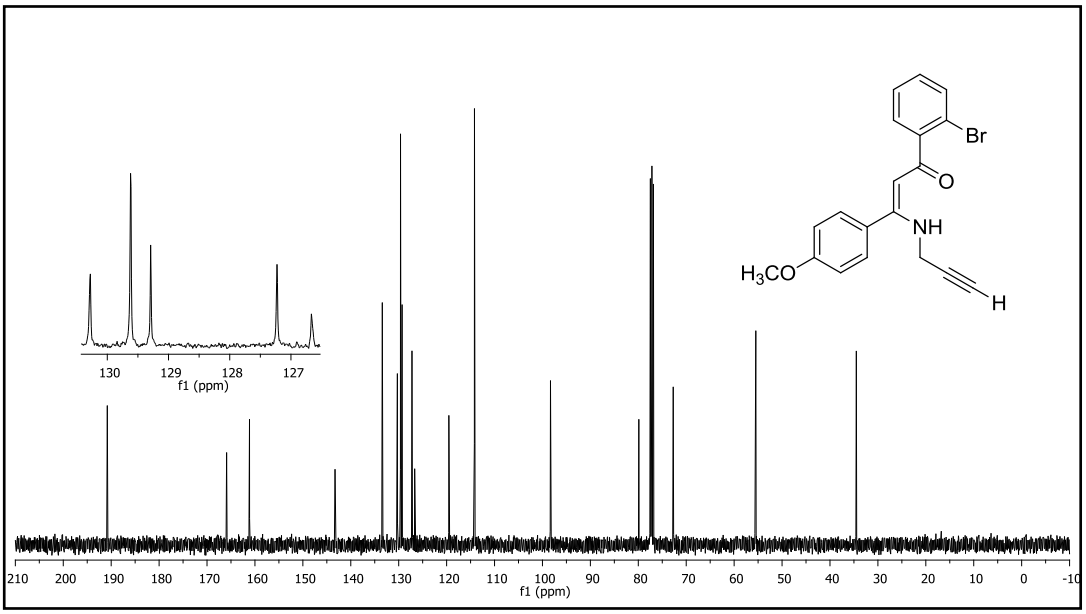

Figure 119. ^{13}C NMR spectrum of compound **32o**.

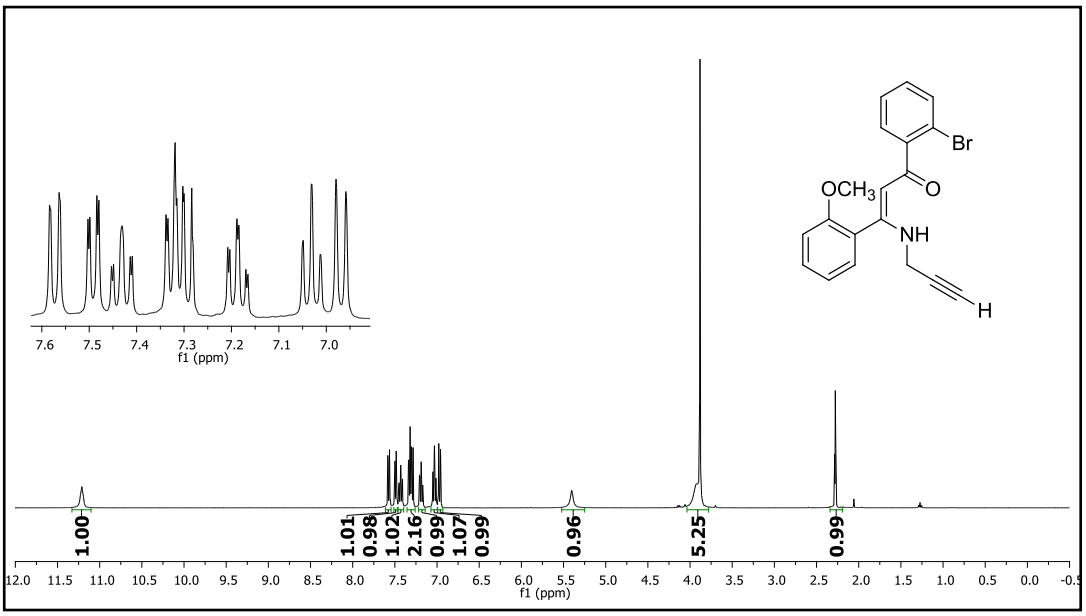

Figure 120. ^{1}H NMR spectrum of compound **32p**.

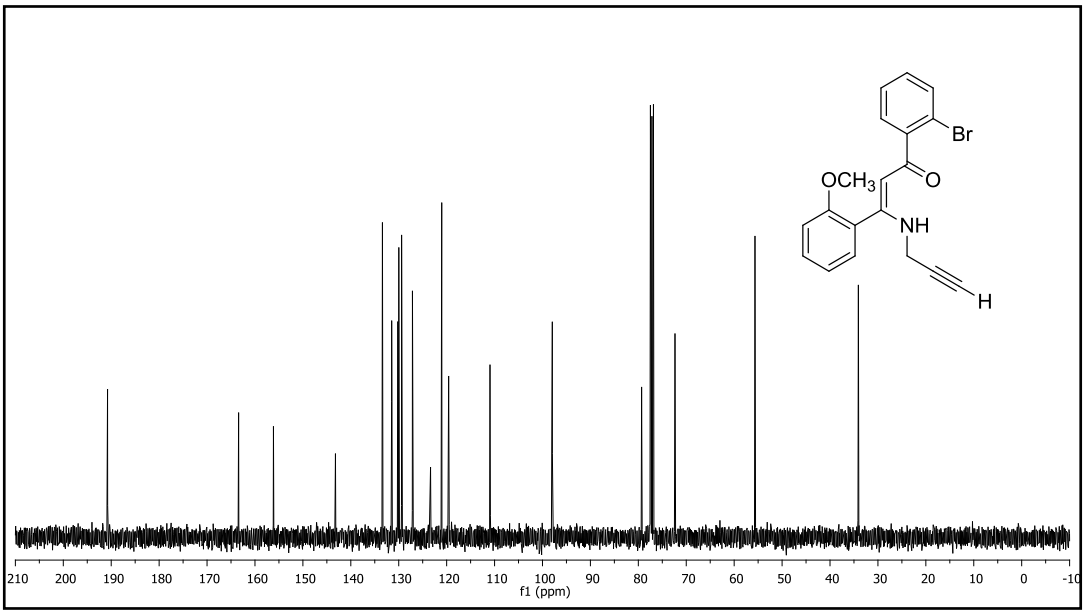

Figure 121. ^{13}C NMR spectrum of compound **32p**.

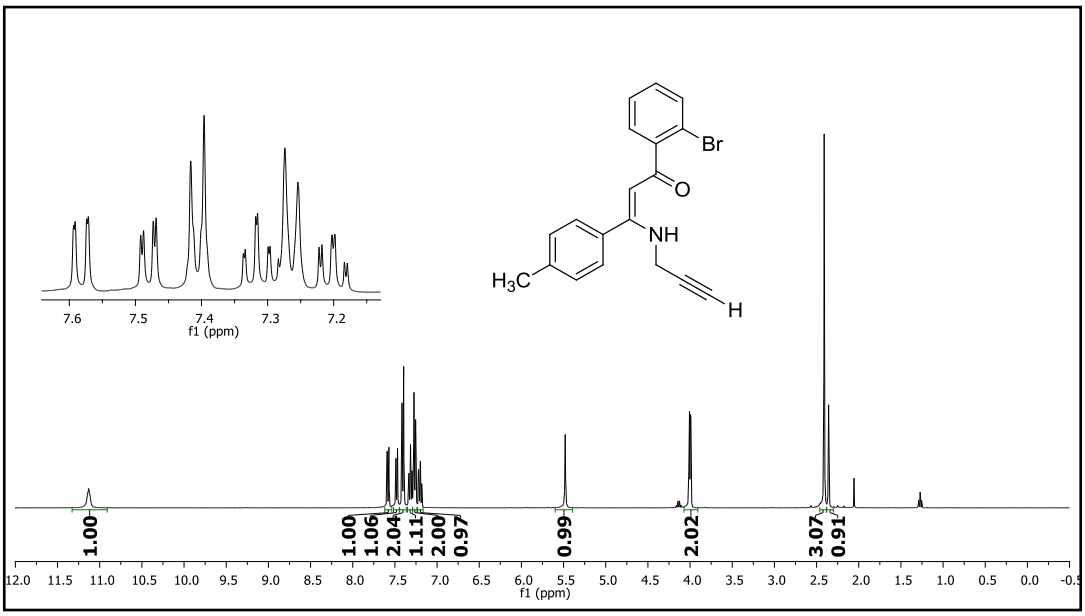

Figure 122. ^{1}H NMR spectrum of compound **32q**.

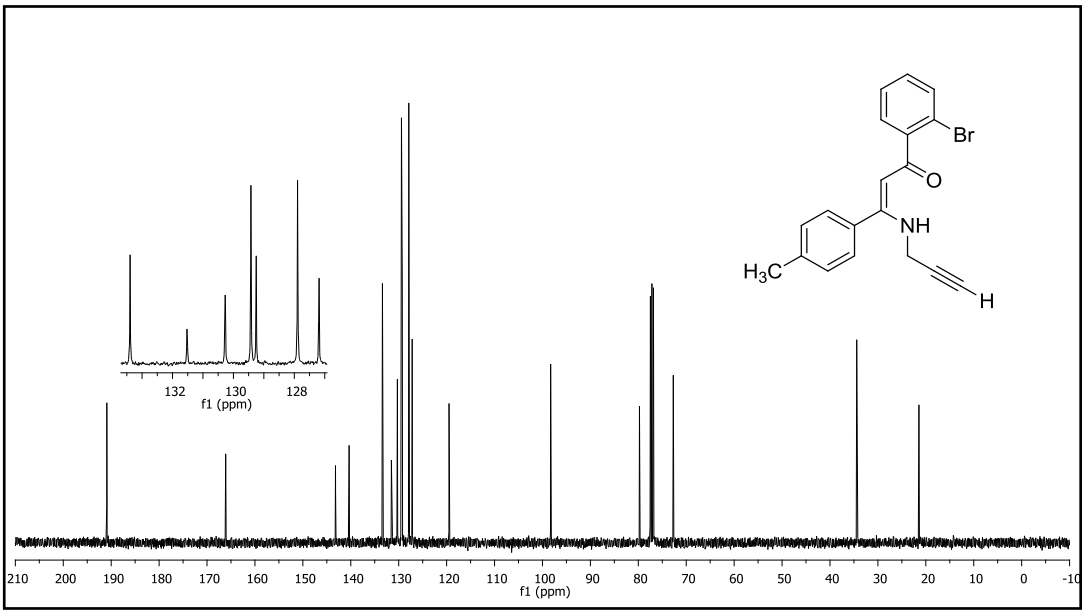

Figure 123. ^{13}C NMR spectrum of compound **32q**.

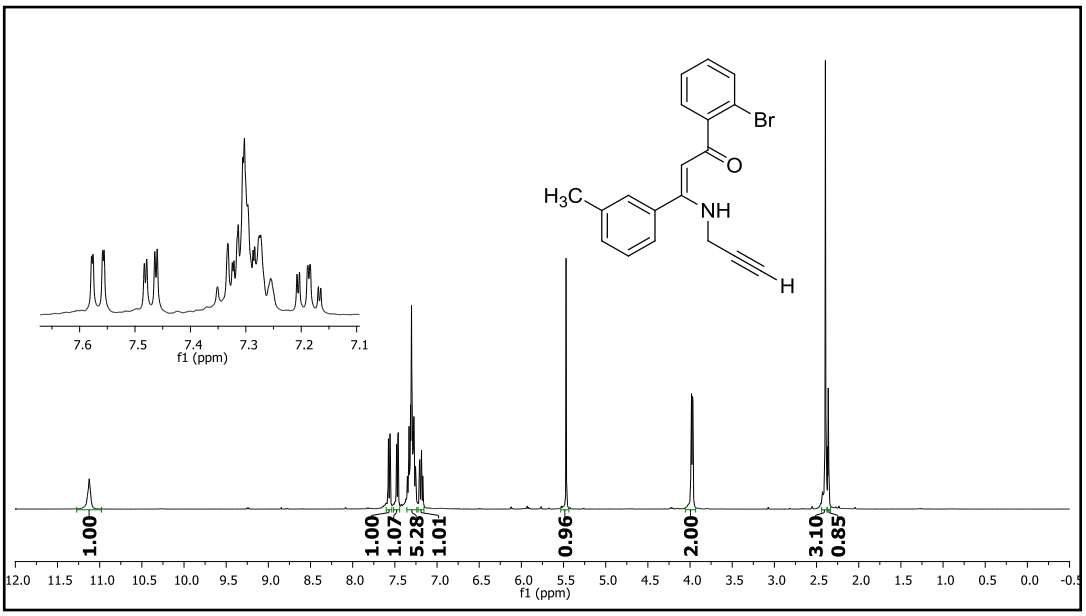

Figure 124. ^{1}H NMR spectrum of compound **32r**.

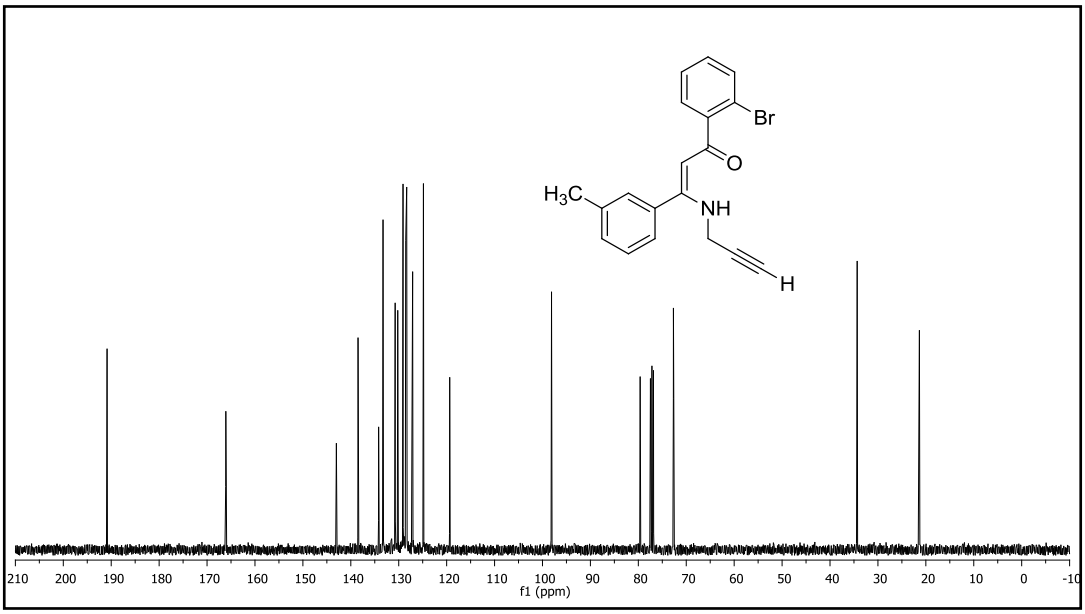

Figure 125. ^{13}C NMR spectrum of compound **32r**.

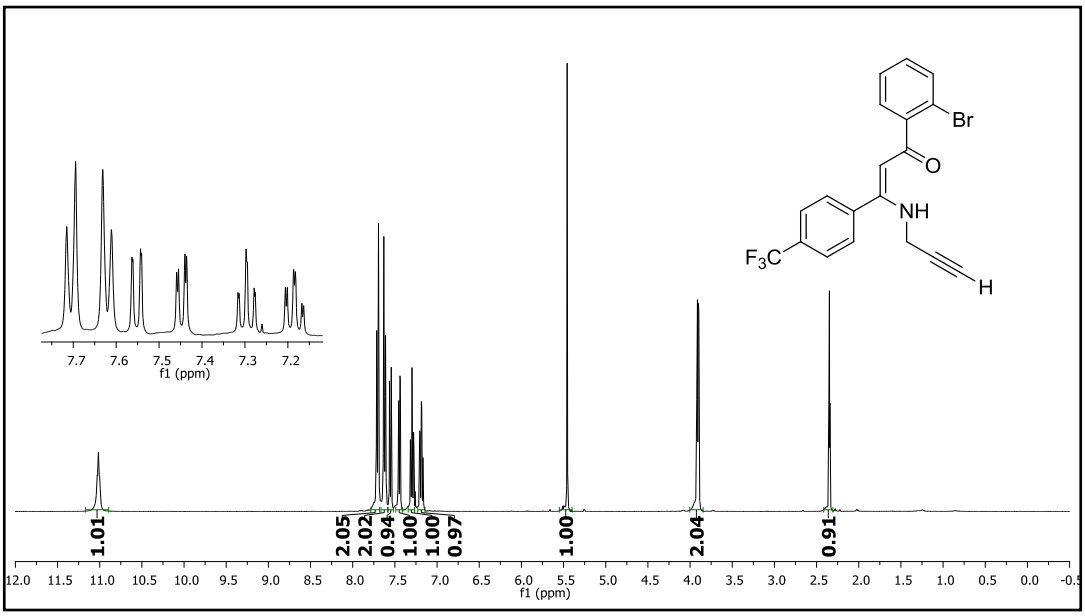

Figure 126. ^{1}H NMR spectrum of compound **32s**.

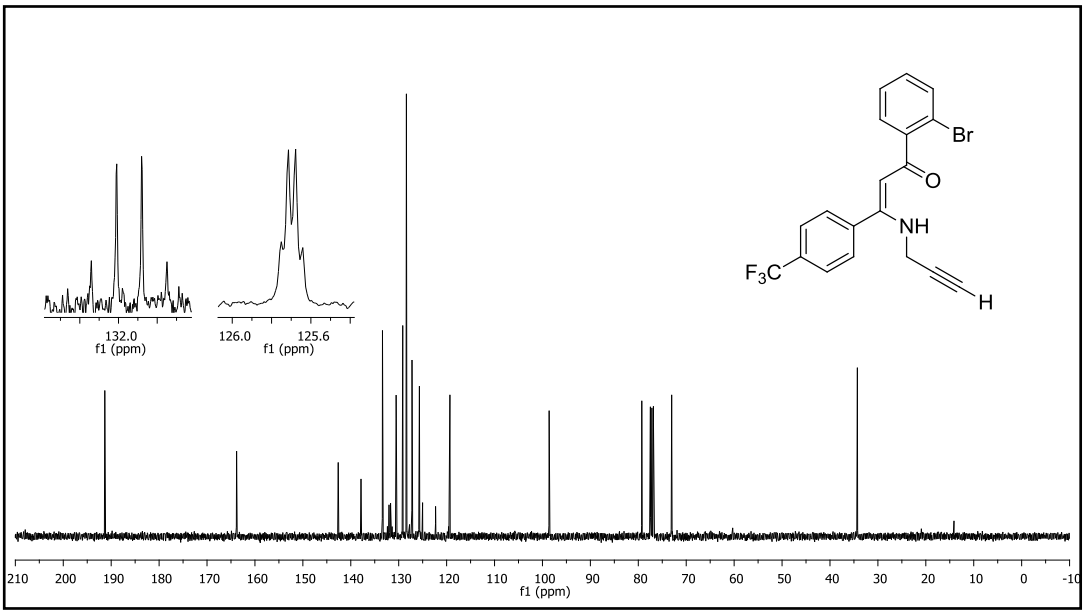

Figure 127. ^{13}C NMR spectrum of compound **32s**.

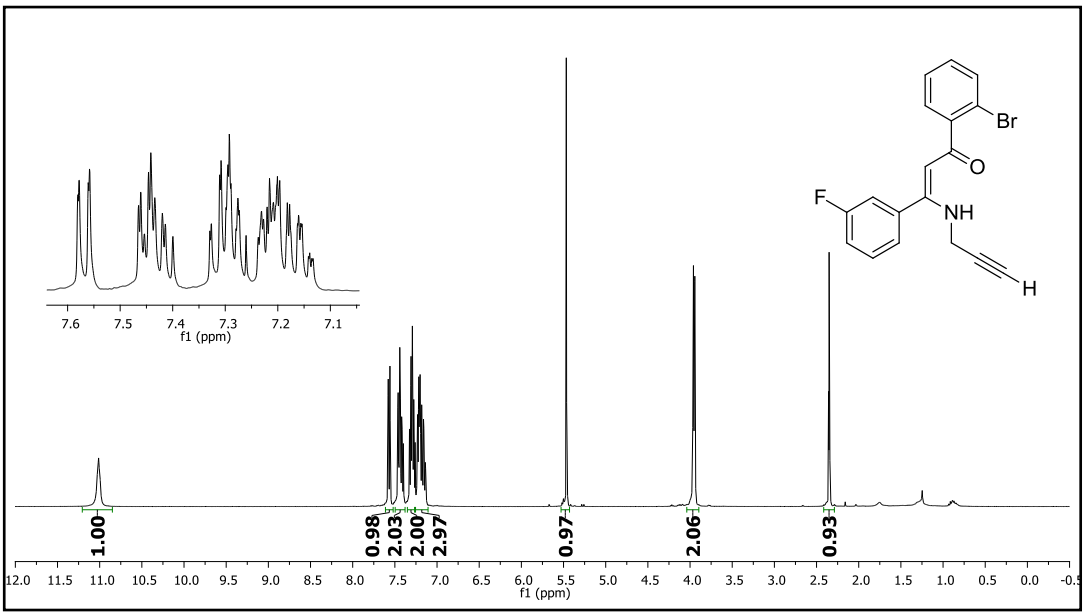

Figure 128. ^{1}H NMR spectrum of compound **32t**.

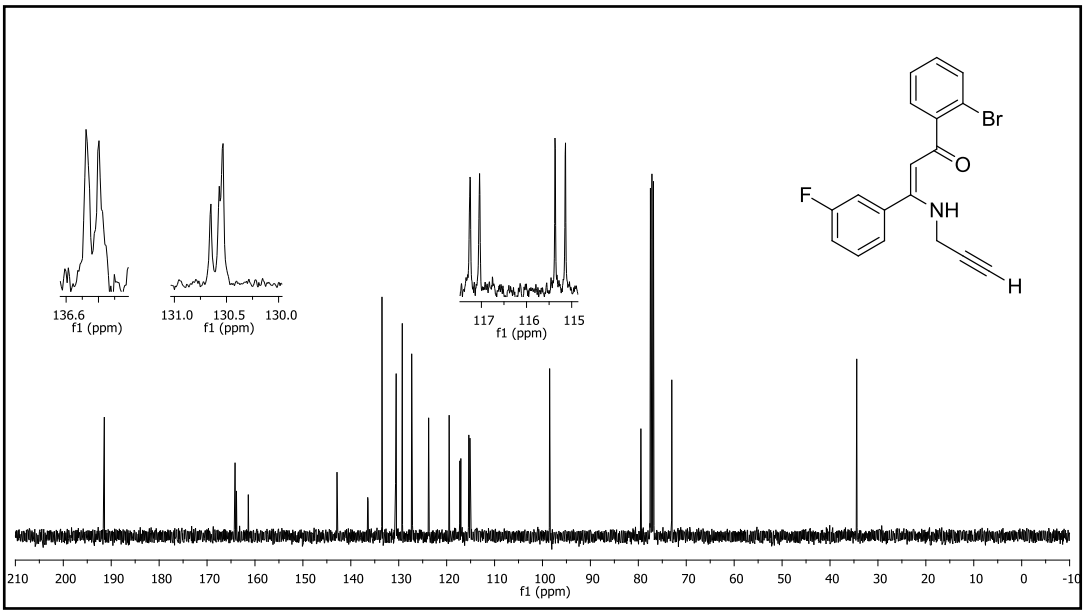

Figure 129. ^{13}C NMR spectrum of compound **32t**.

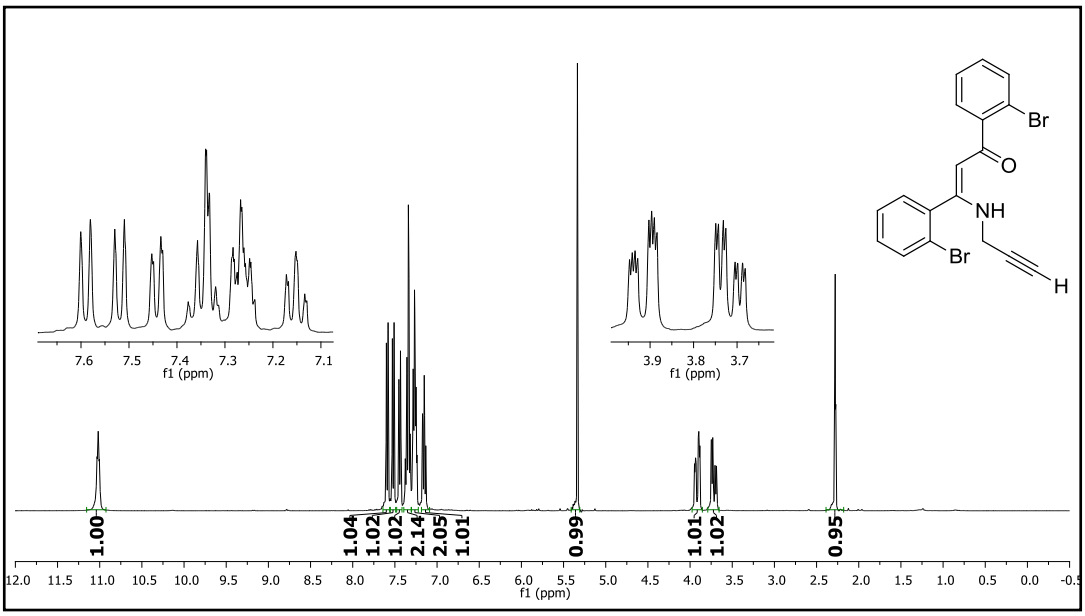

Figure 130. ^{1}H NMR spectrum of compound **32u**.

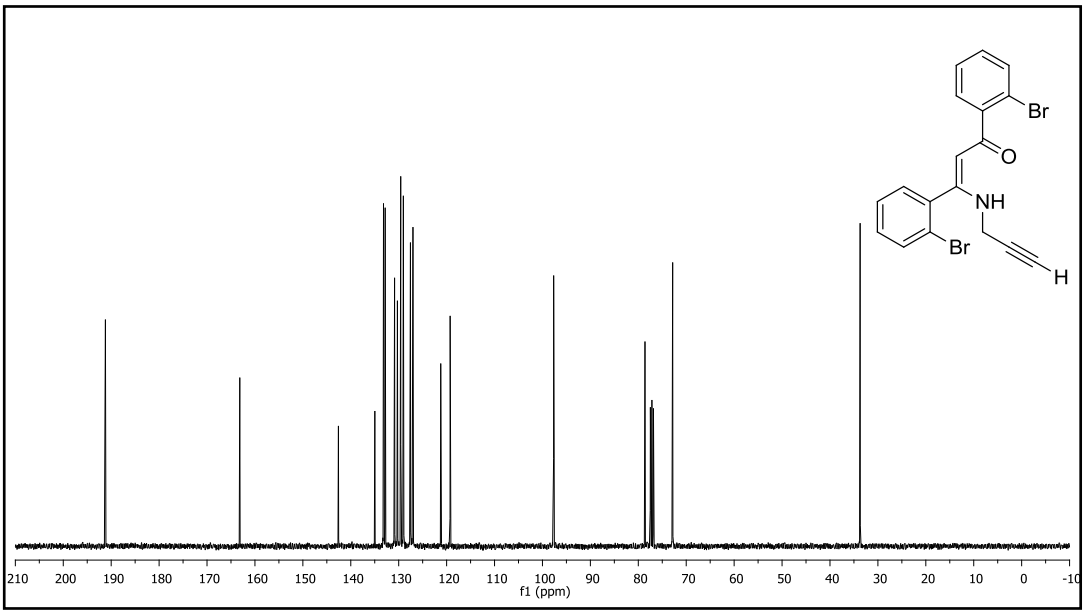

Figure 131. ^{13}C NMR spectrum of compound **32u**.

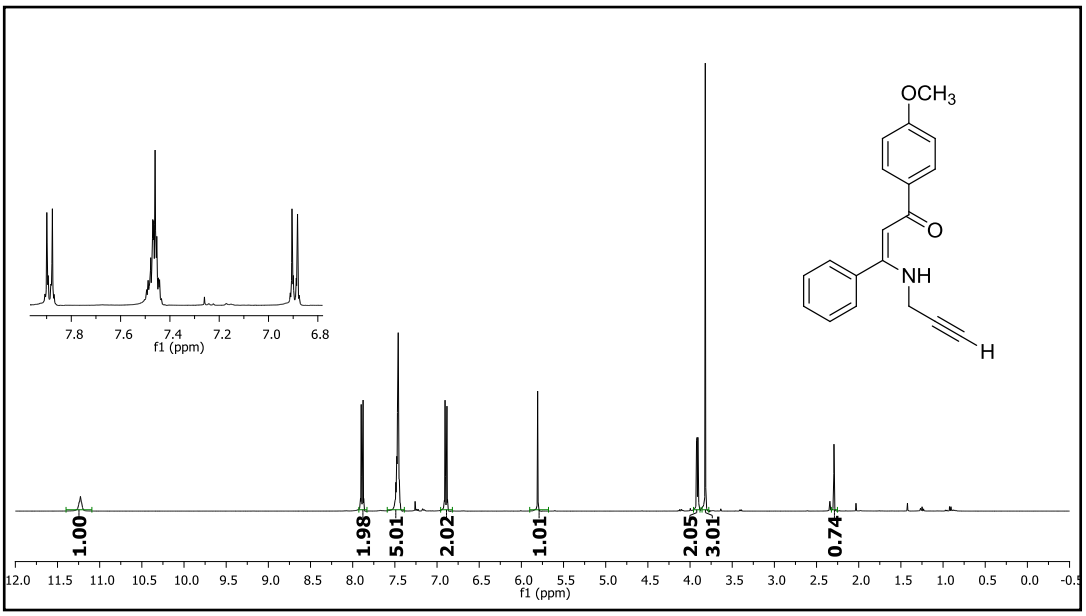

Figure 132. ^{1}H NMR spectrum of compound **32v**.

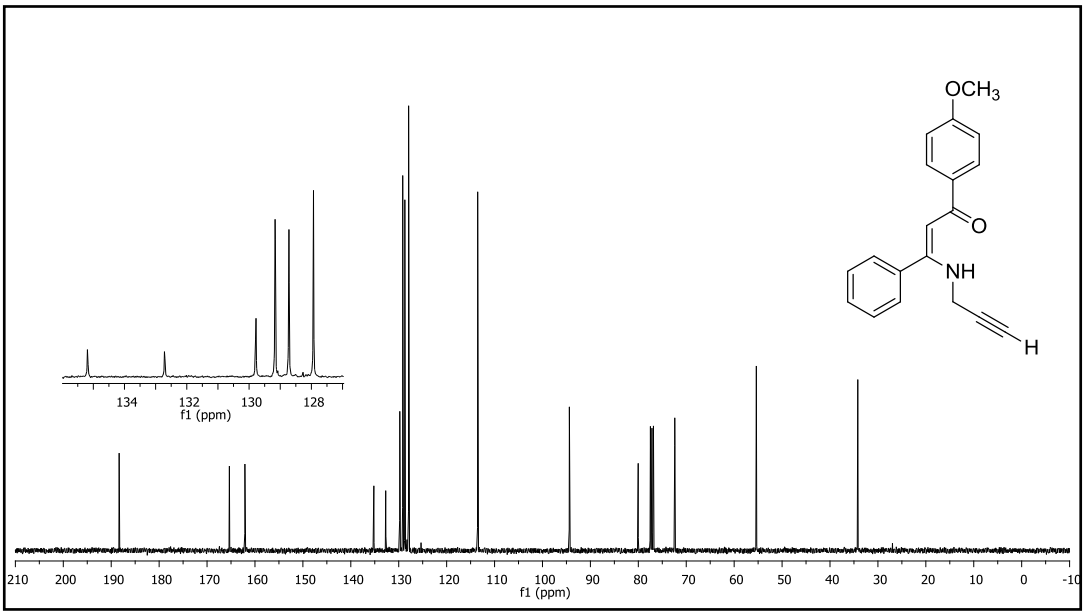

Figure 133. ^{13}C NMR spectrum of compound **32v**.

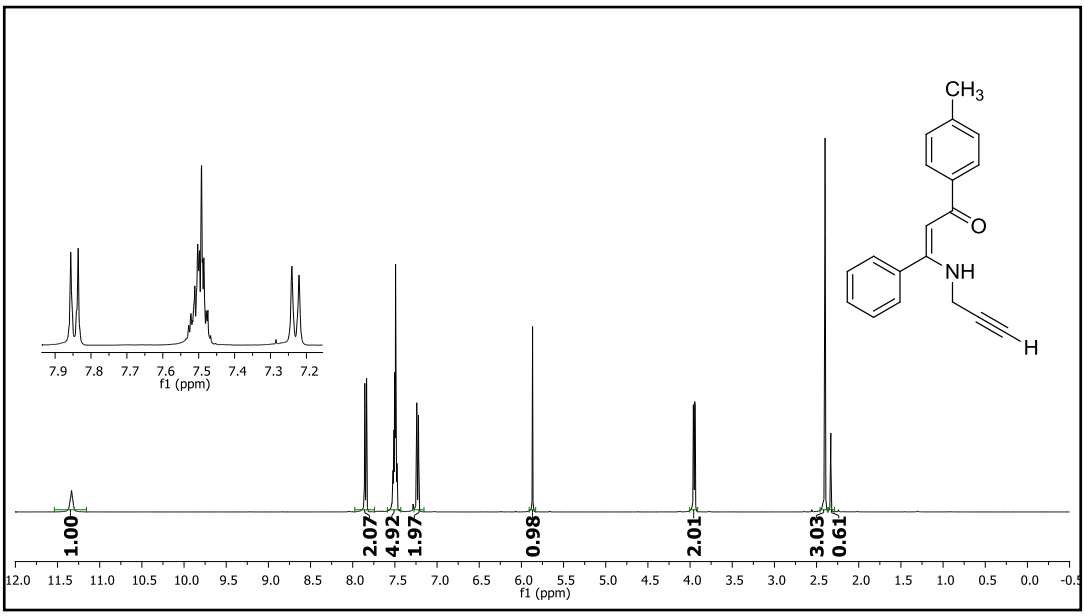

Figure 134. ^{1}H NMR spectrum of compound **32w**.

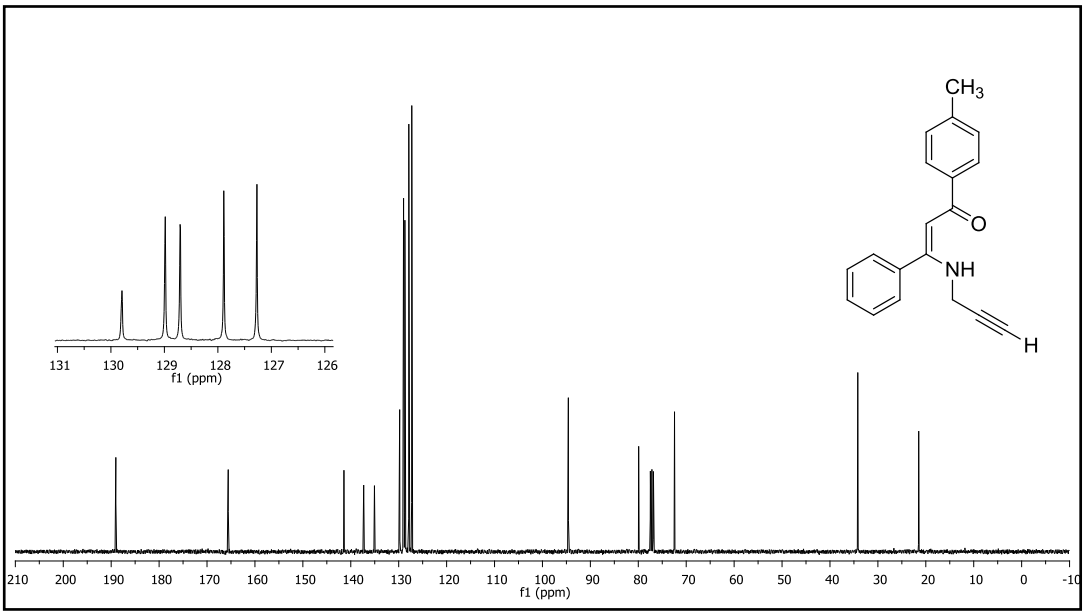

Figure 135. ^{13}C NMR spectrum of compound **32w**.

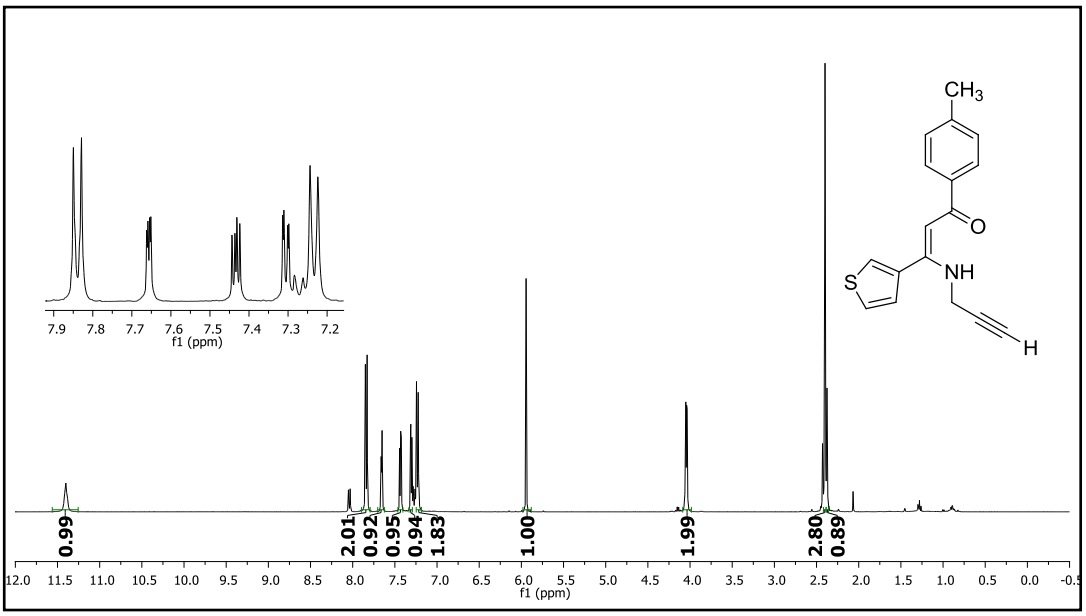

Figure 136. ^{1}H NMR spectrum of compound **32x**.

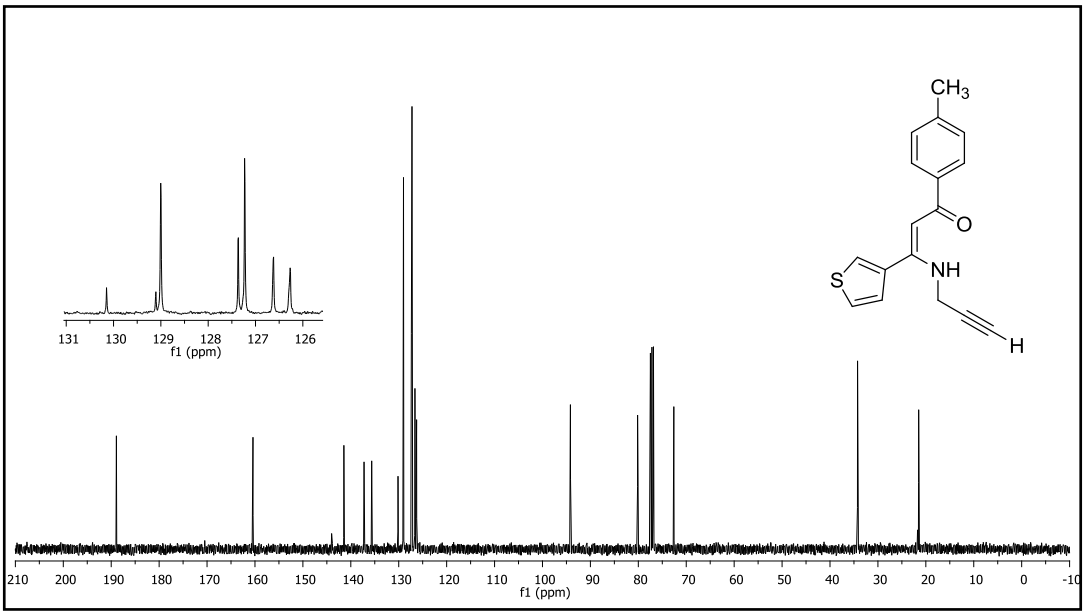

Figure 137. ^{13}C NMR spectrum of compound **32x**.

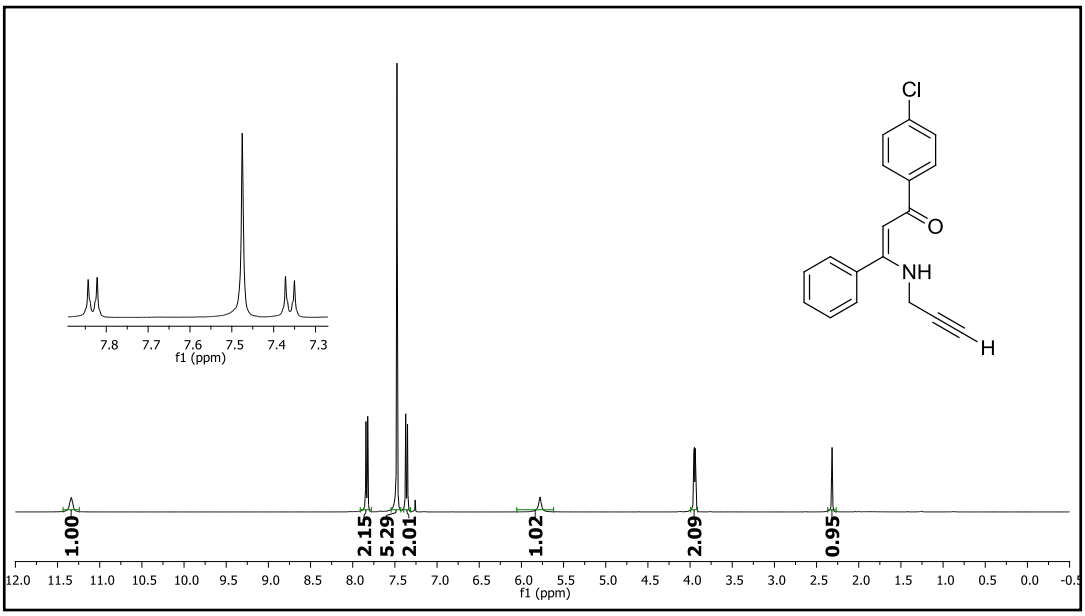

Figure 138. ^{1}H NMR spectrum of compound **32y**.

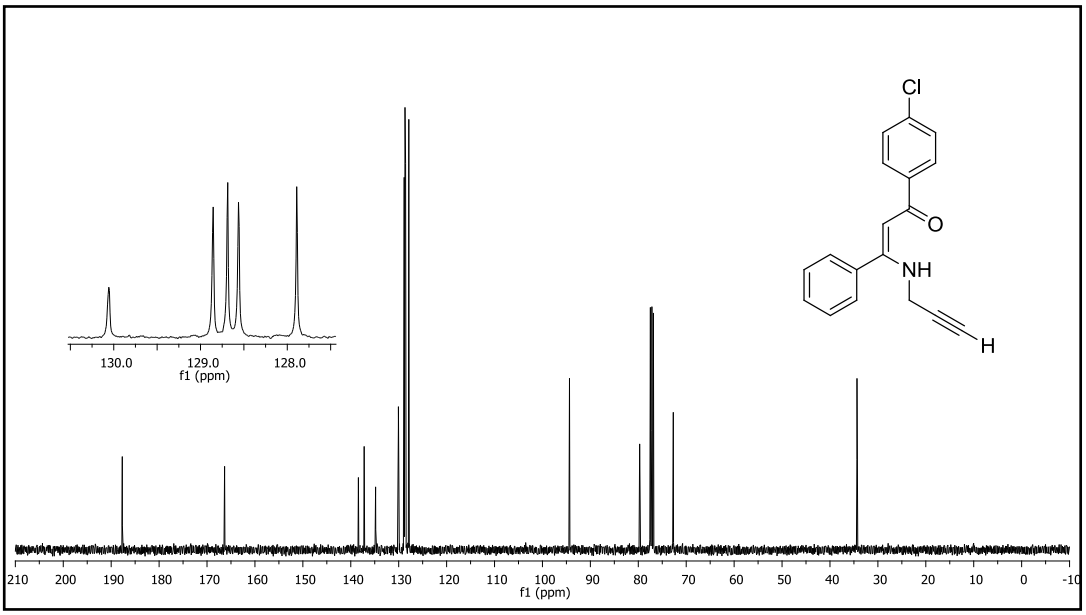

Figure 139. ^{13}C NMR spectrum of compound **32y**.

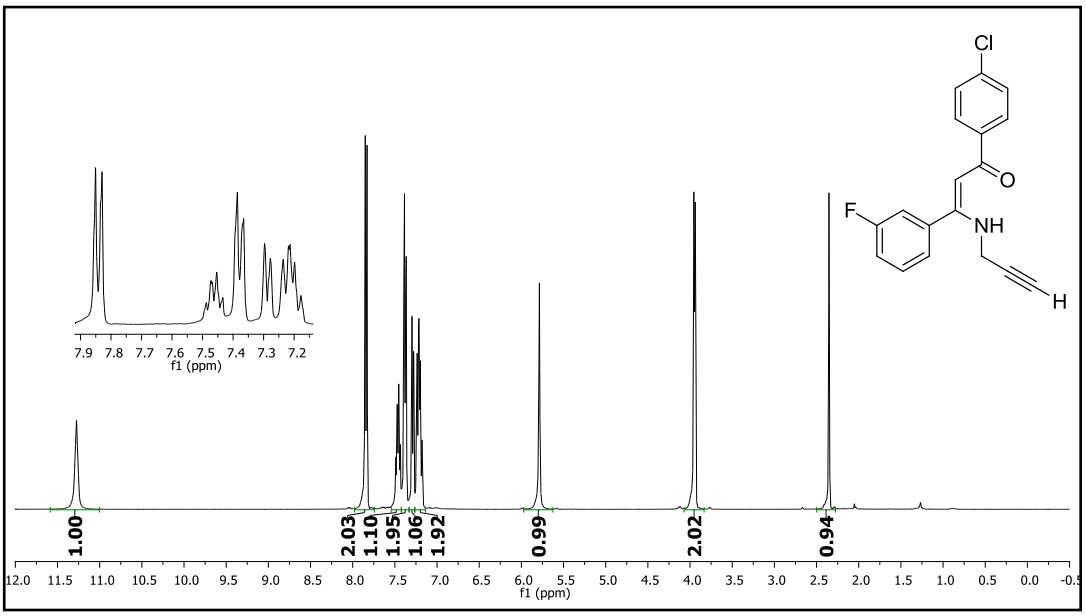

Figure 140. ^{1}H NMR spectrum of compound **32z**.

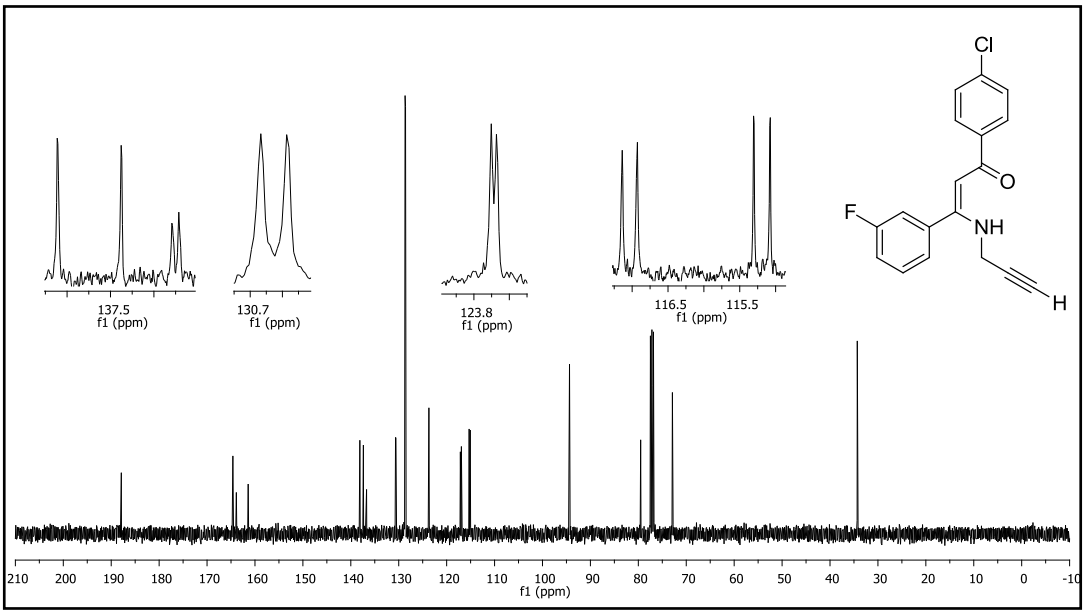

Figure 141. ^{13}C NMR spectrum of compound **32z**.

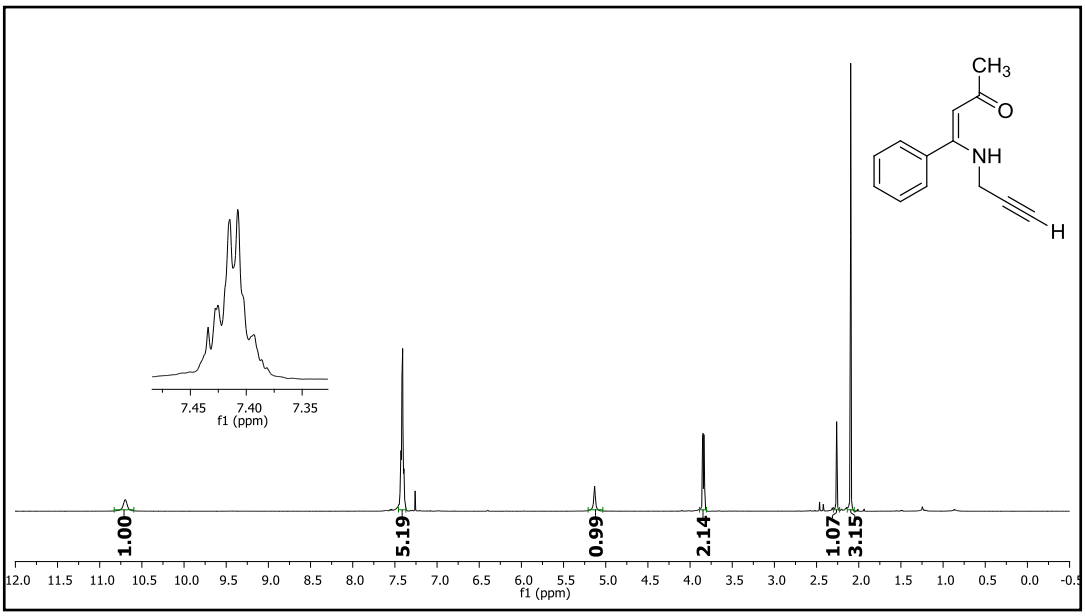

Figure 142. ^{1}H NMR spectrum of compound **32aa**.

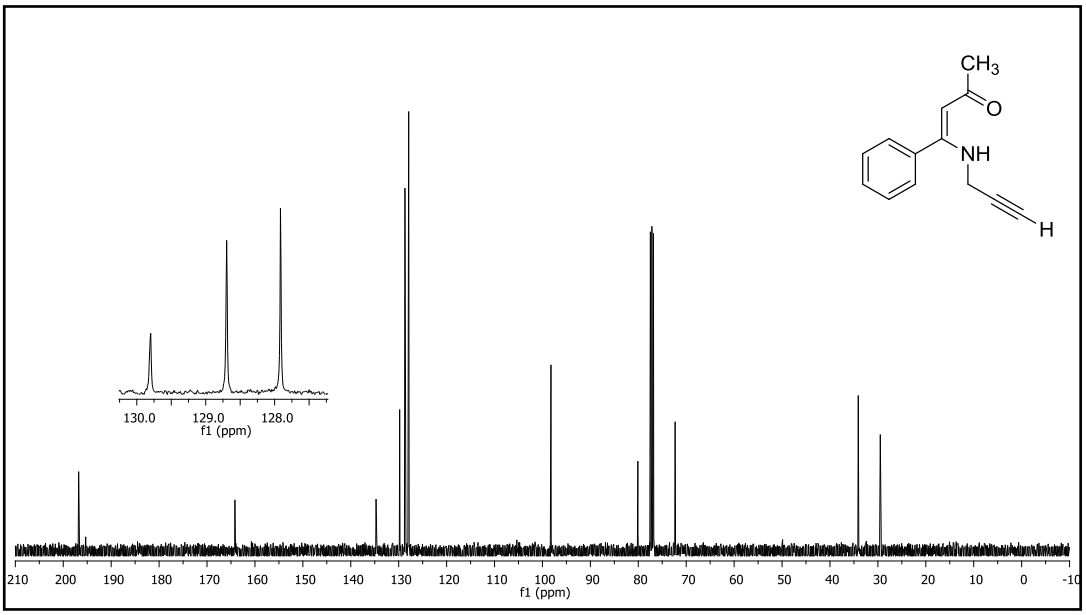

Figure 143. ^{13}C NMR spectrum of compound **32aa**.

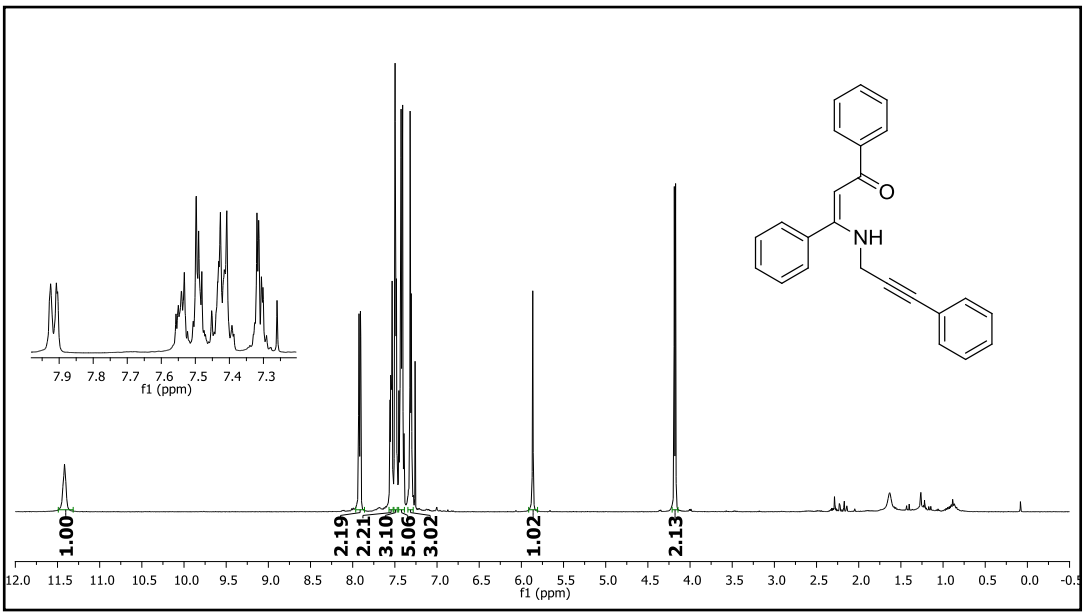

Figure 144. ^{1}H NMR spectrum of compound **7a**.

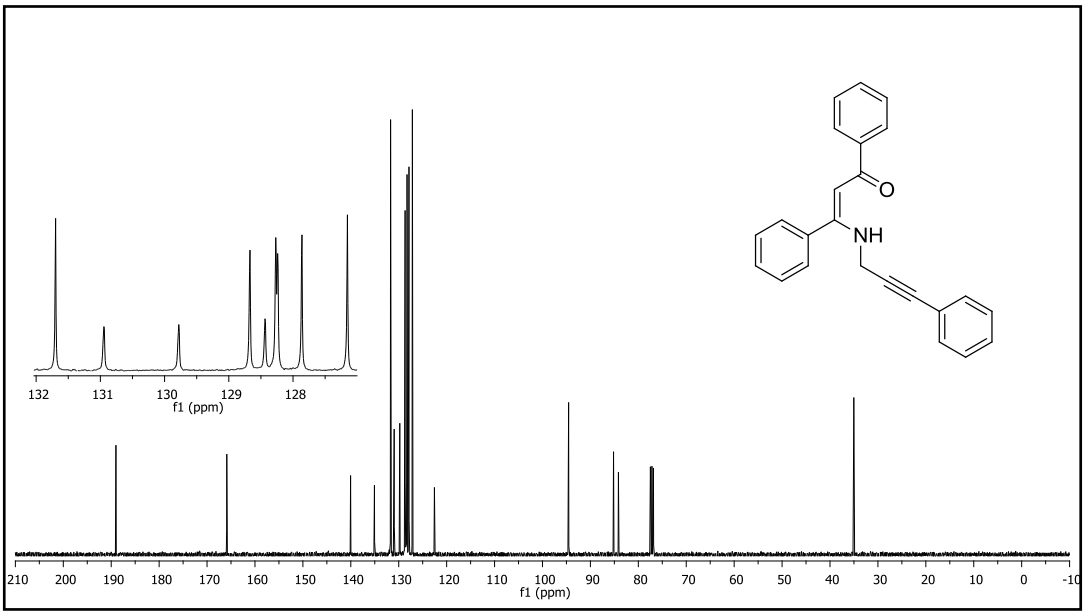

Figure 145. ^{13}C NMR spectrum of compound **7a**.

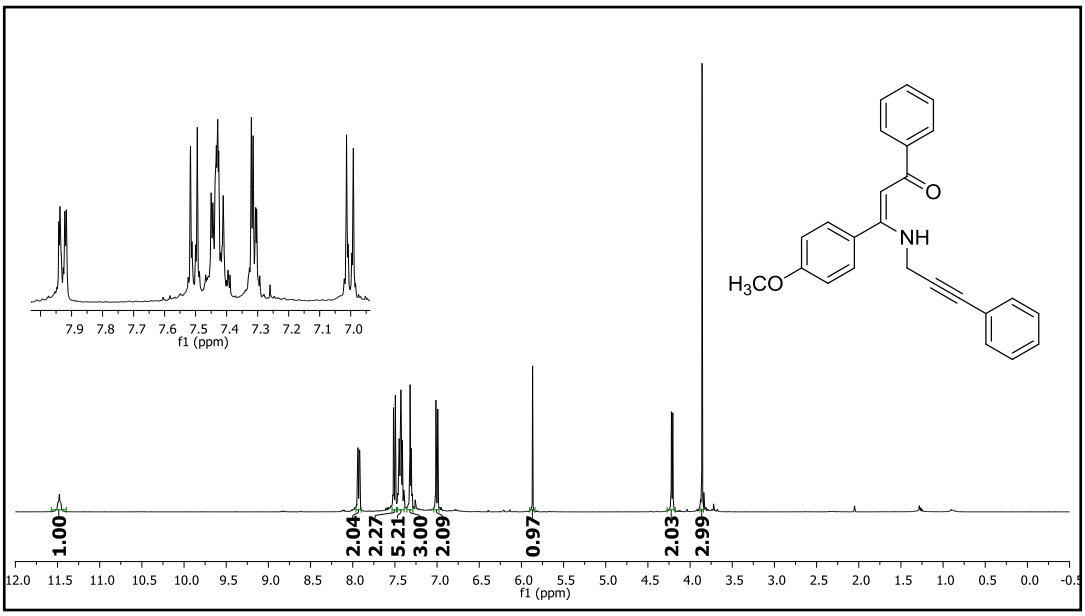

Figure 146. ^{1}H NMR spectrum of compound **7b**.

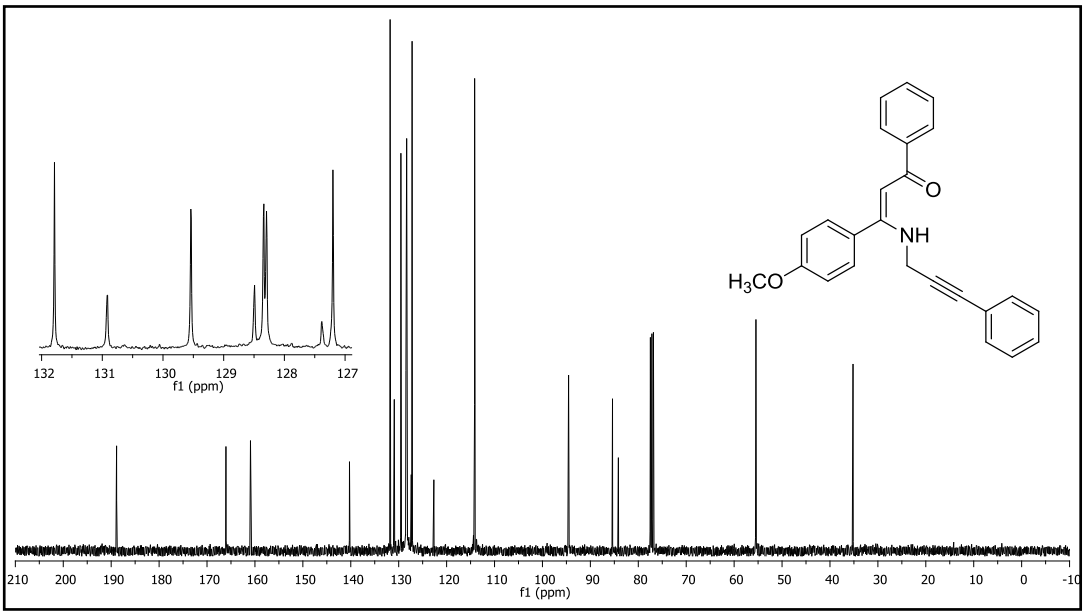

Figure 147. ^{13}C NMR spectrum of compound **7b**.

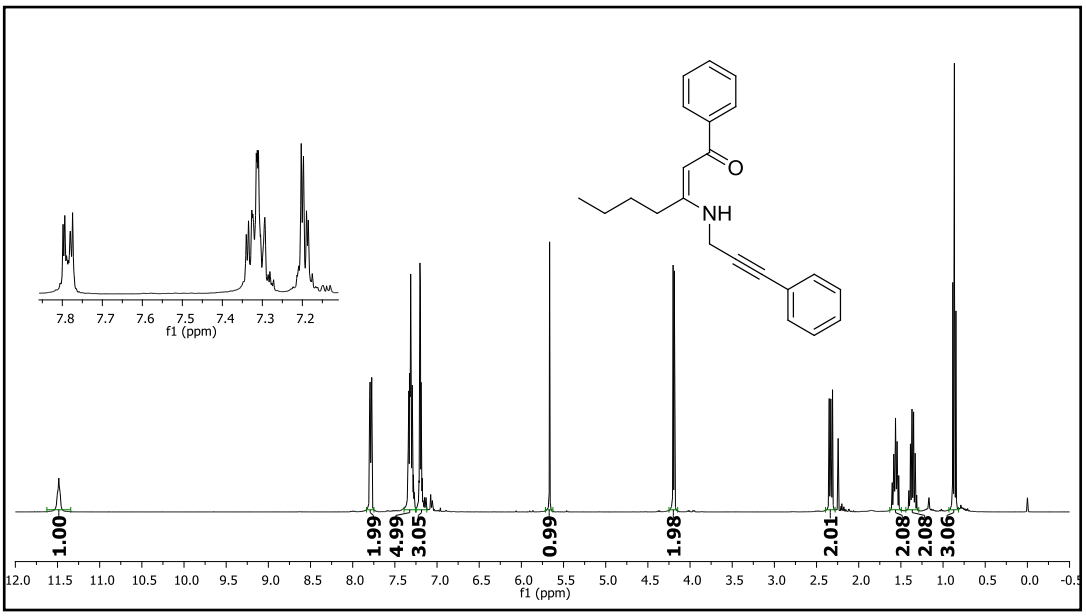

Figure 148. ^{1}H NMR spectrum of compound **7l**.

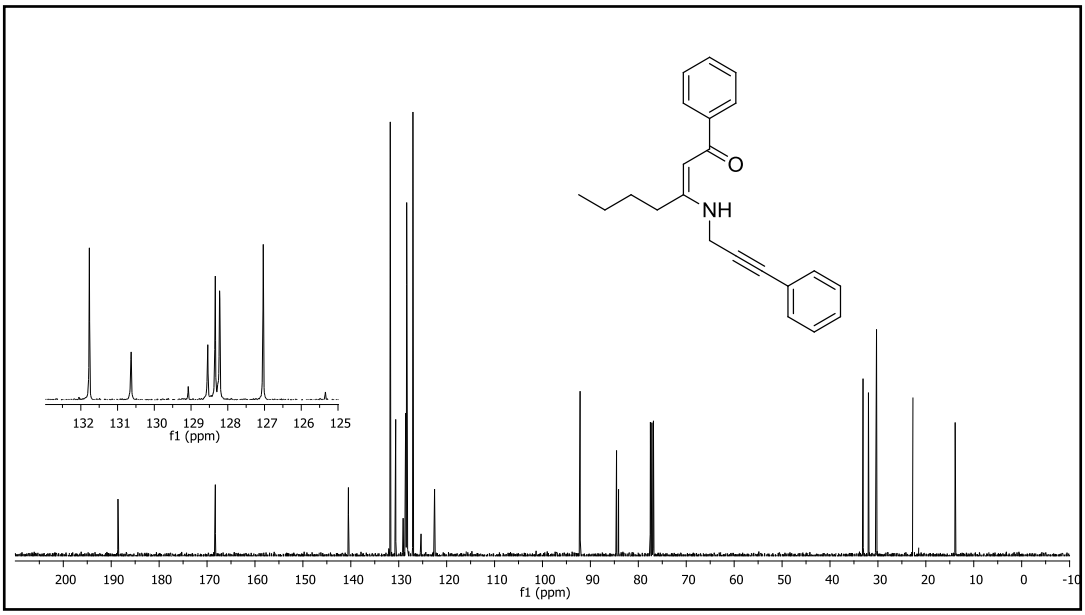

Figure 149. ^{13}C NMR spectrum of compound **7l**.

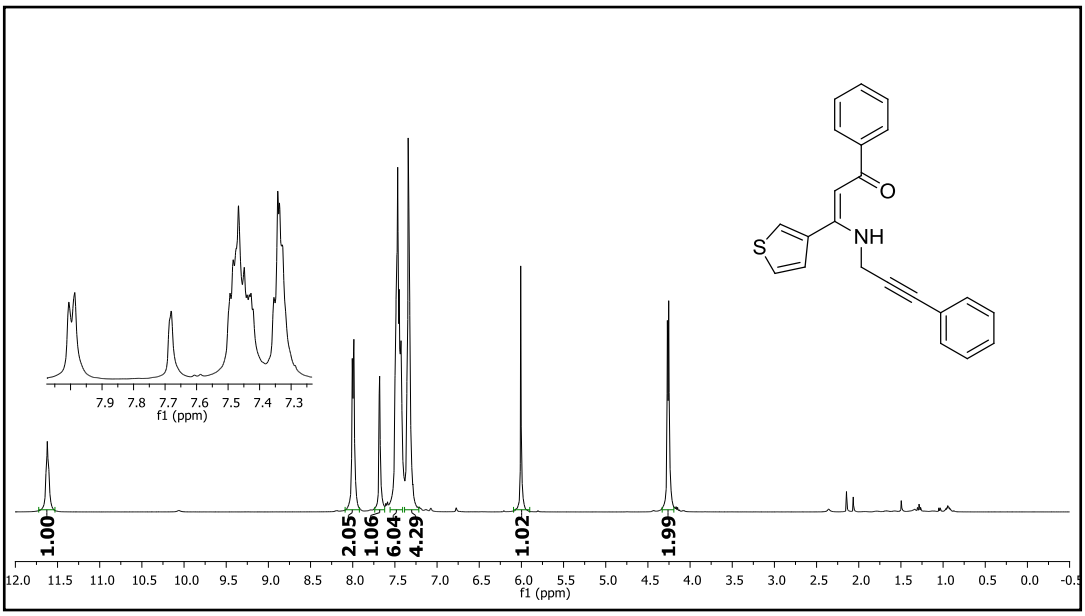

Figure 150. ^{1}H NMR spectrum of compound **7m**.

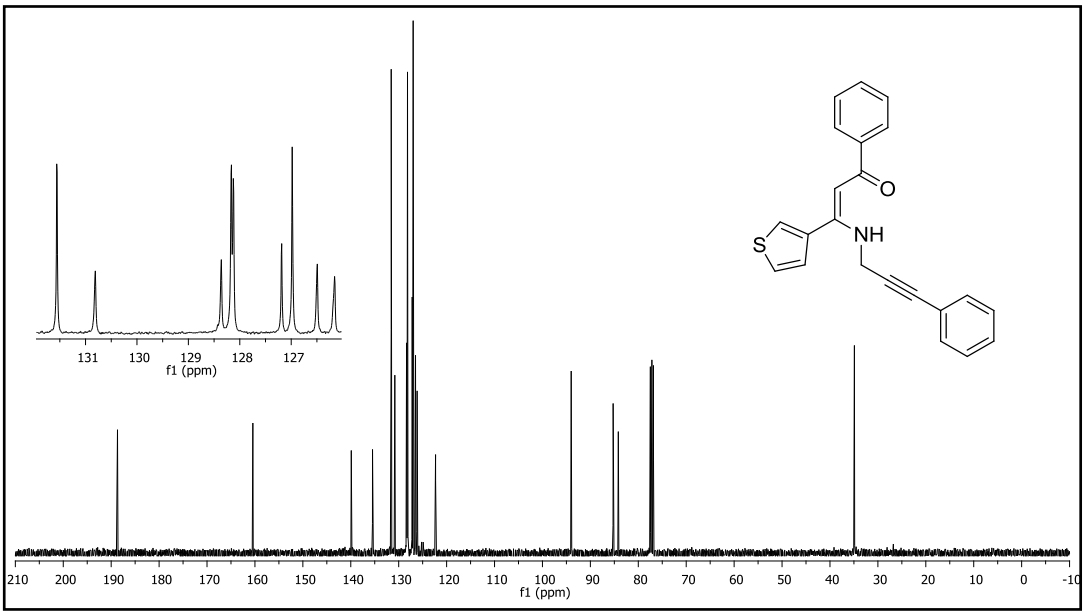

Figure 151. ^{13}C NMR spectrum of compound **7m**.

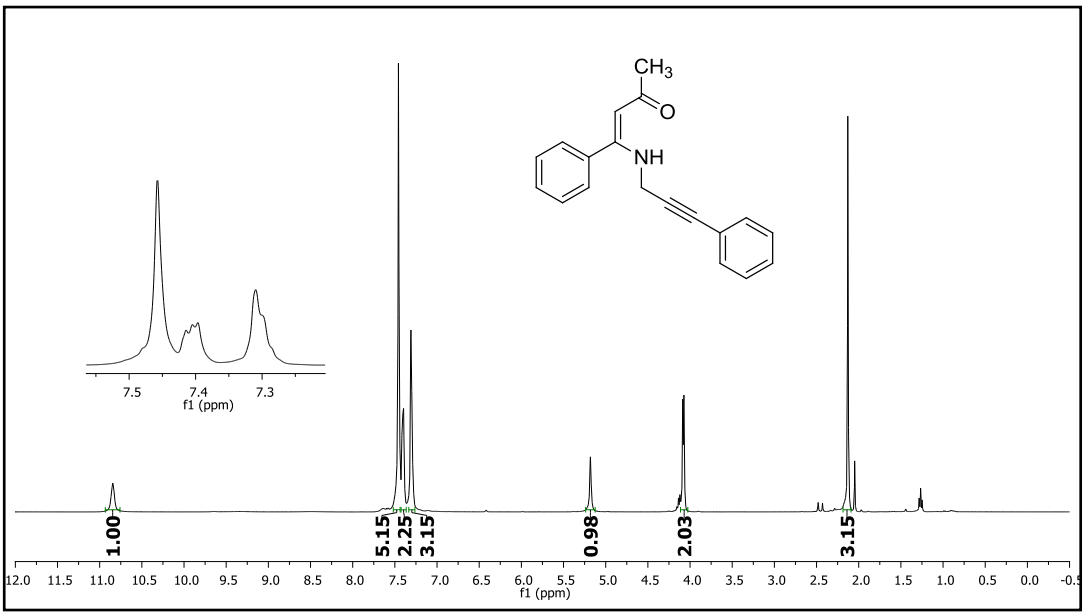

Figure 152. ^{1}H NMR spectrum of compound **7aa**.

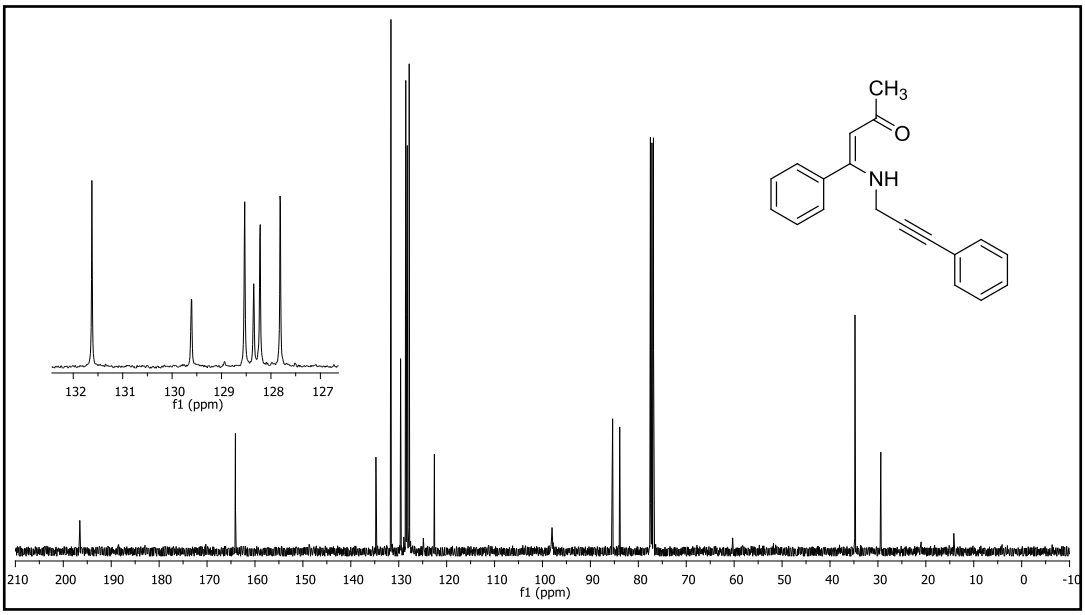

Figure 153. ^{13}C NMR spectrum of compound **7aa**.

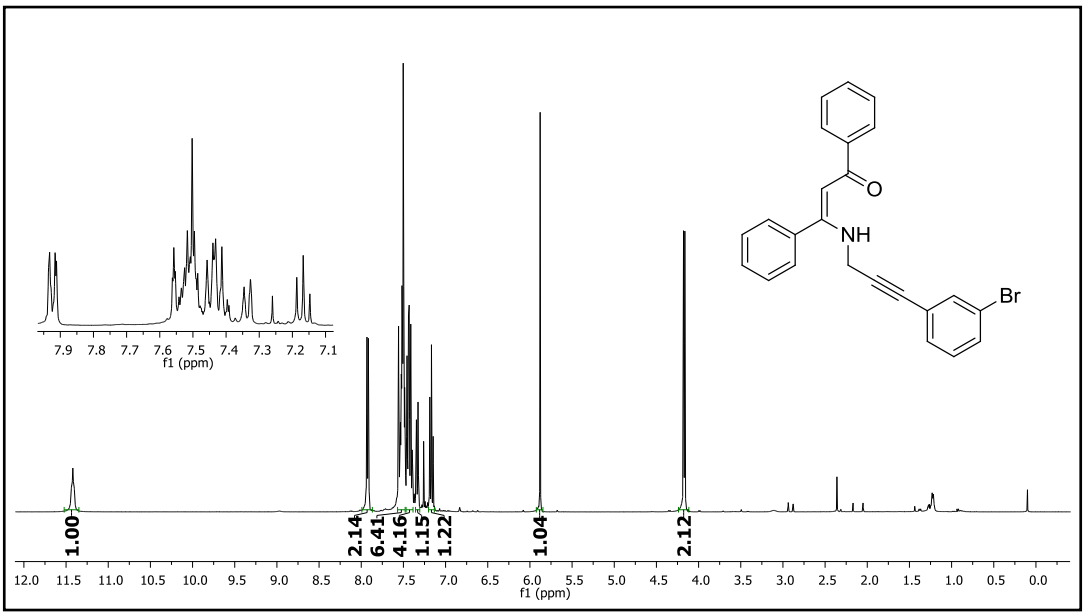

Figure 154. ^{1}H NMR spectrum of compound **7ab**.

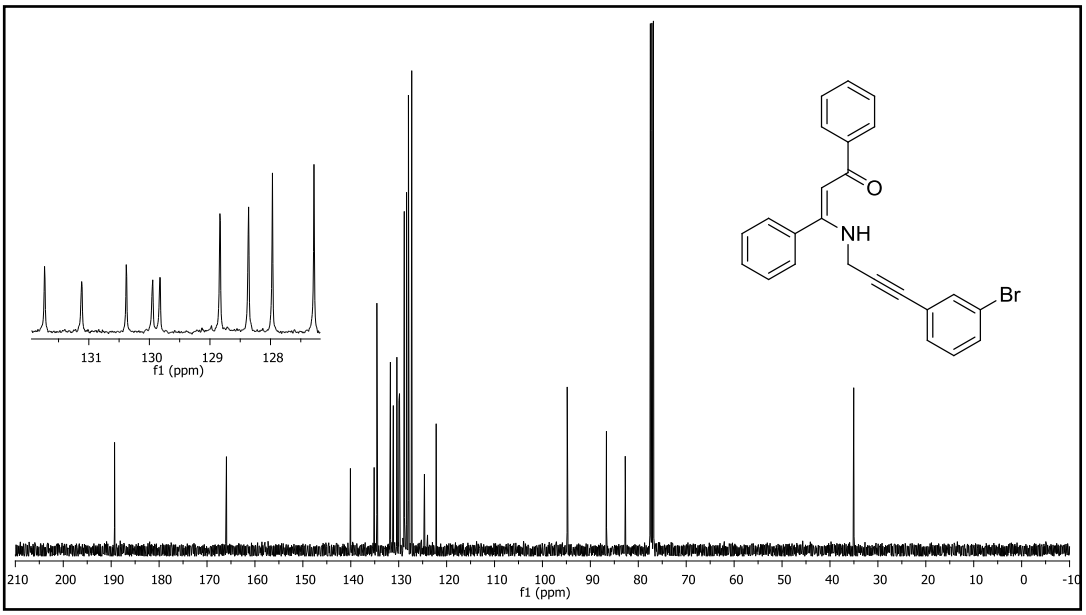

Figure 155. ^{13}C NMR spectrum of compound **7ab**.

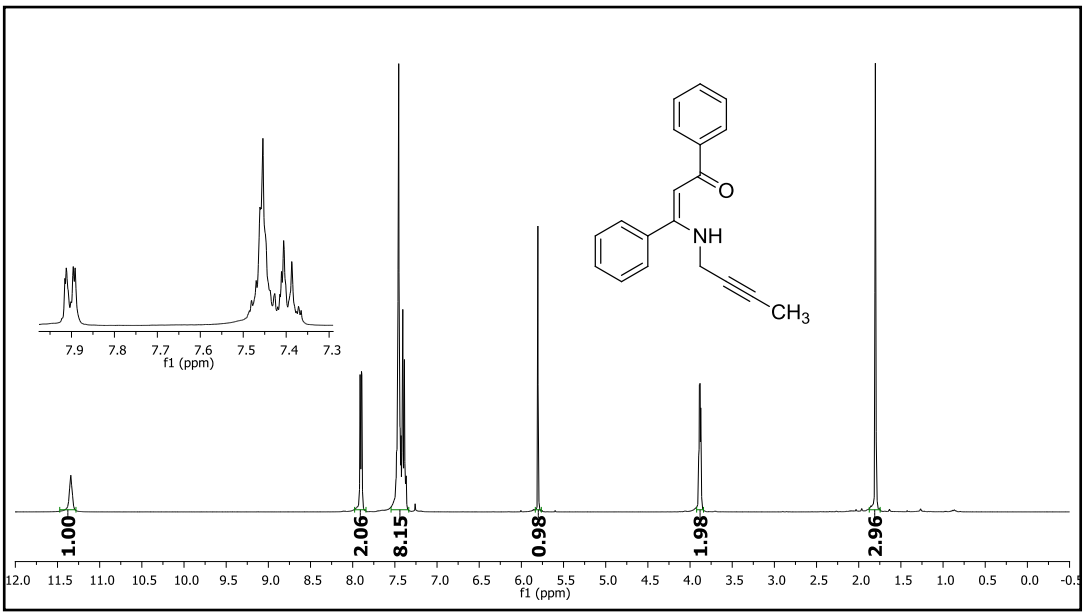

Figure 156. ^{1}H NMR spectrum of compound **7ac**.

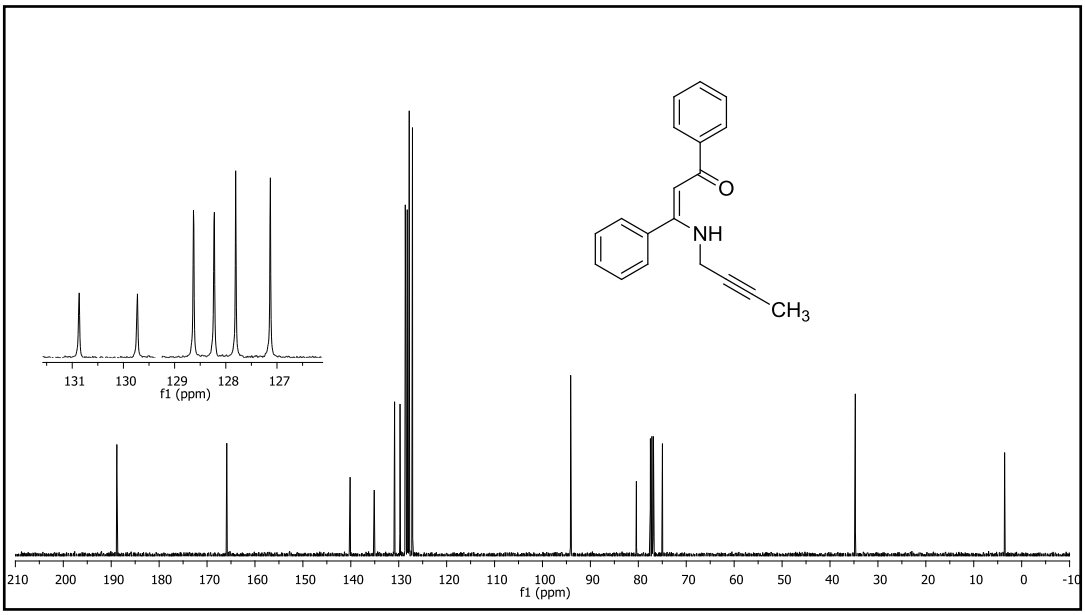

Figure 157. ^{13}C NMR spectrum of compound **7ac**.

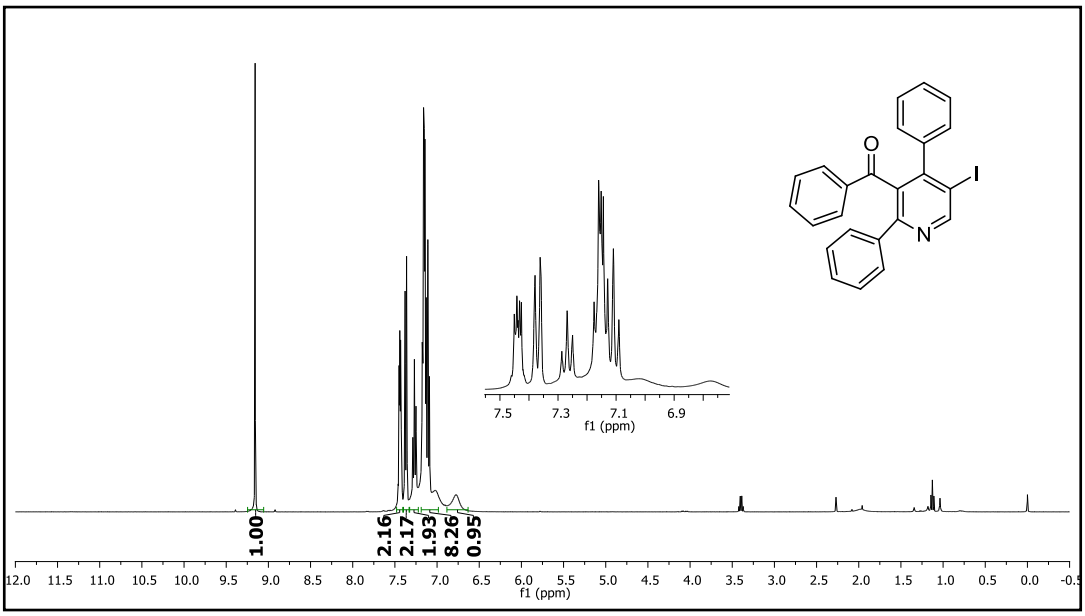

Figure 158. ^{1}H NMR spectrum of compound **55a**.

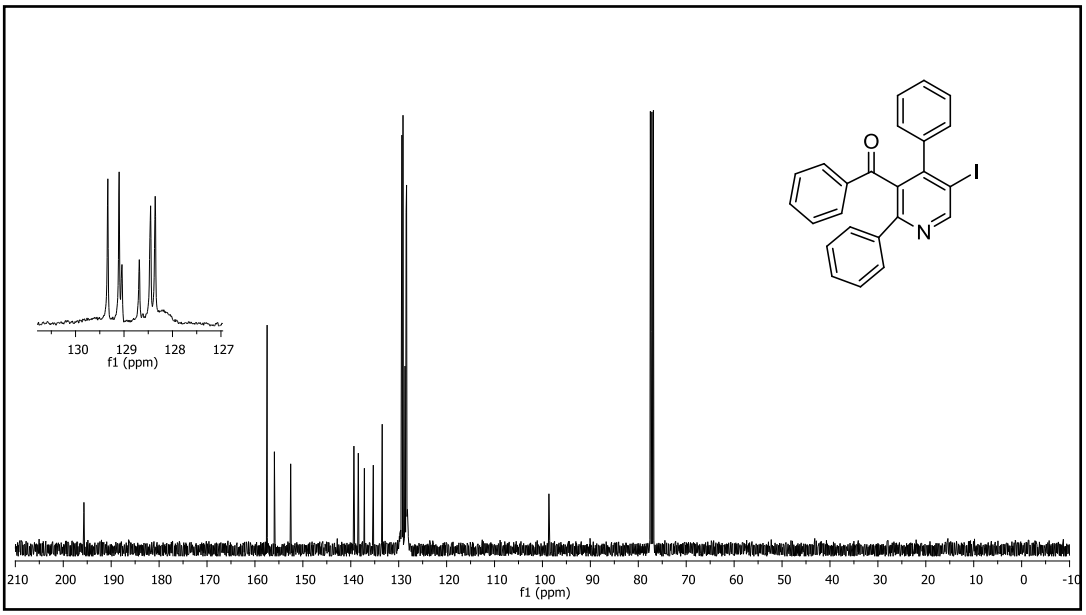

Figure 159. ^{13}C NMR spectrum of compound **55a**.

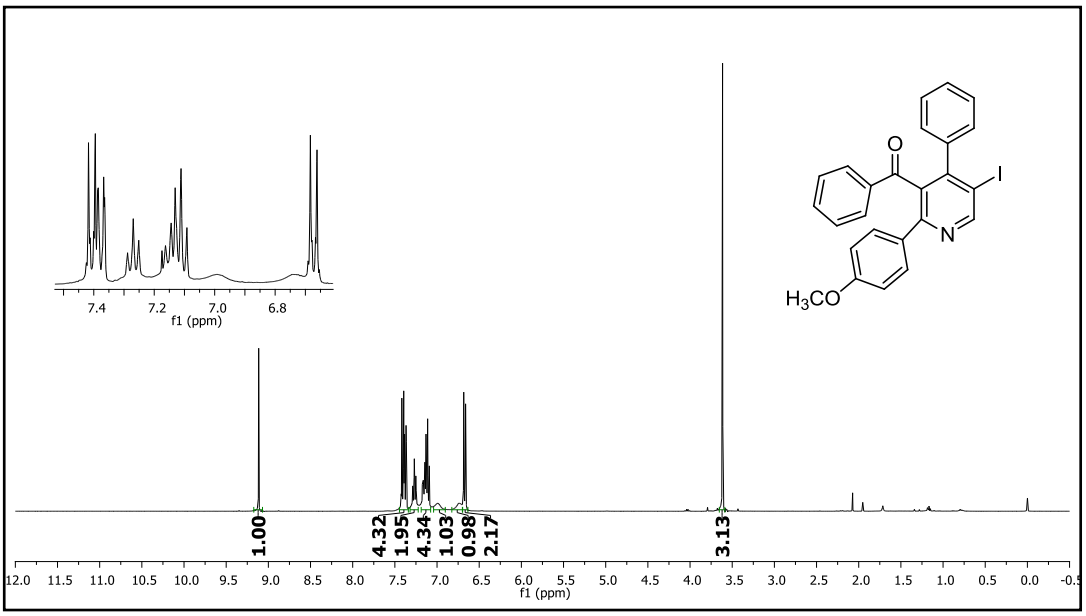

Figure 160. ^{1}H NMR spectrum of compound **55b**.

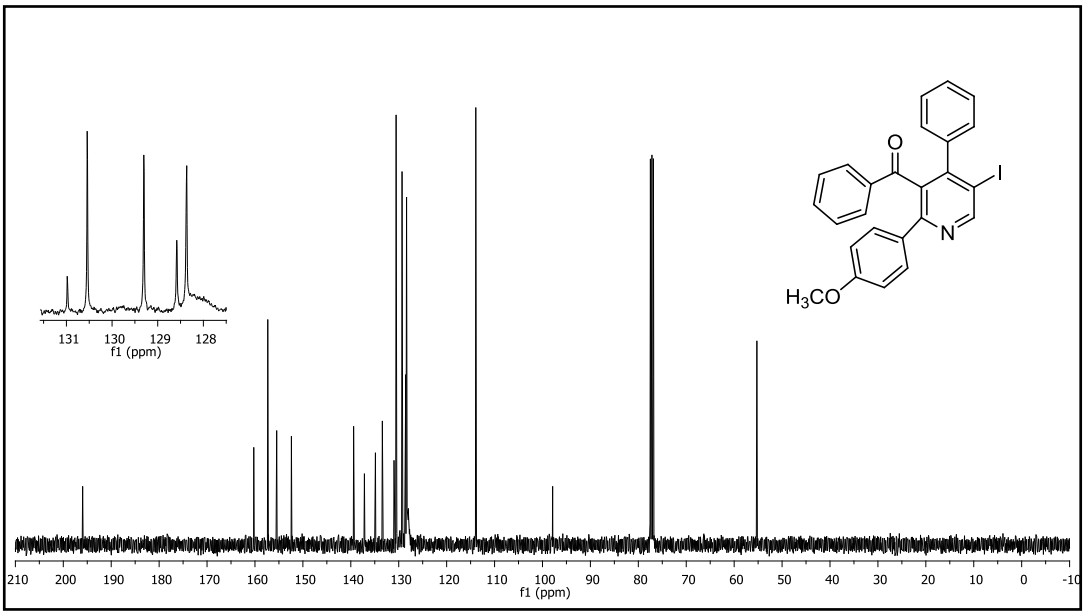

Figure 161. ^{13}C NMR spectrum of compound **55b**.

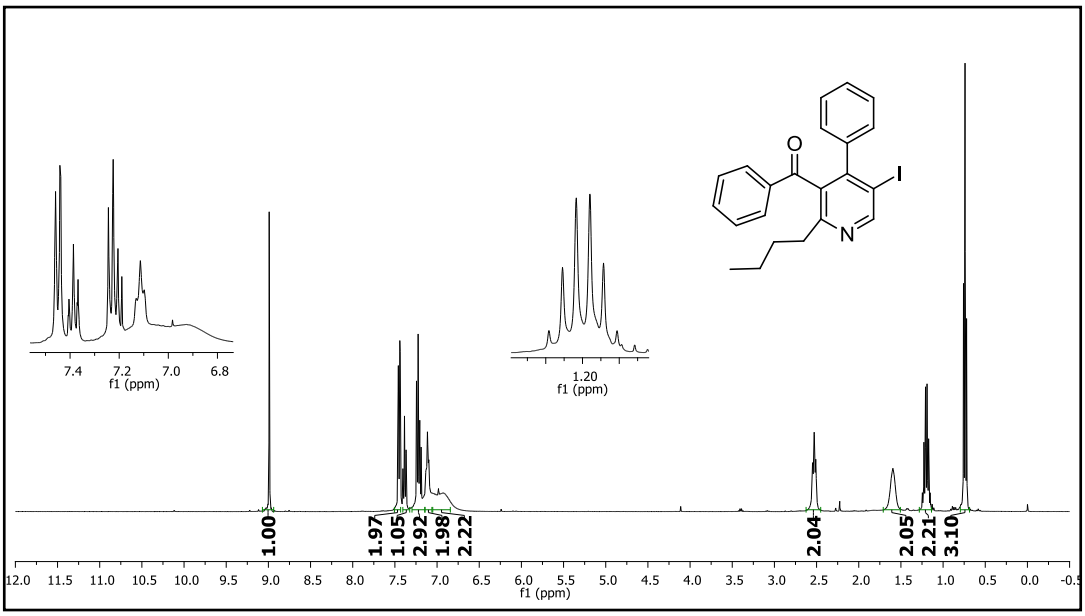

Figure 162. ^{1}H NMR spectrum of compound **55l**.

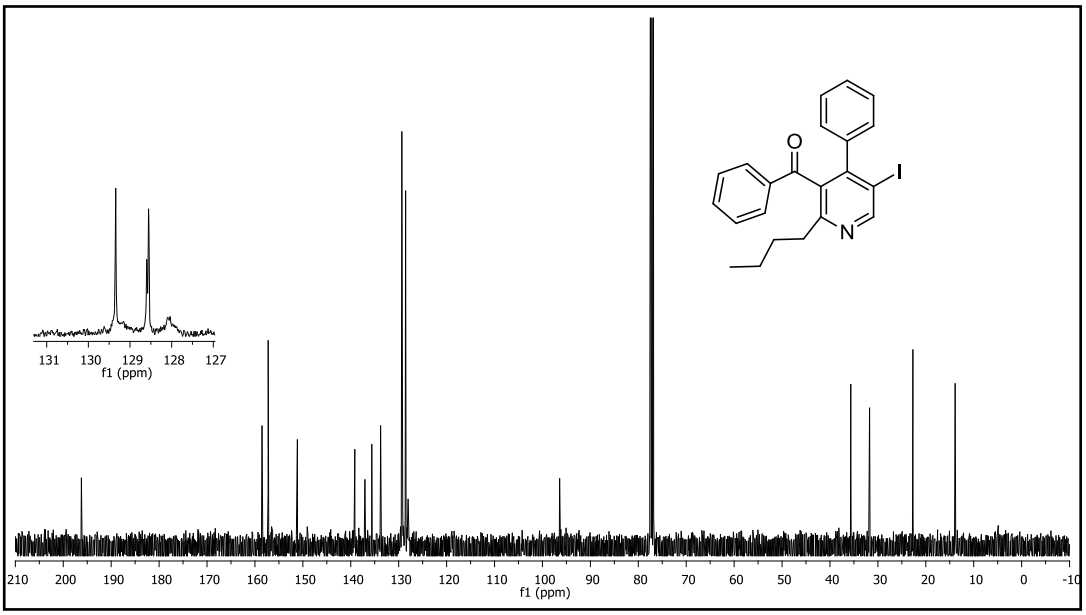

Figure 163. ^{13}C NMR spectrum of compound **55l**.

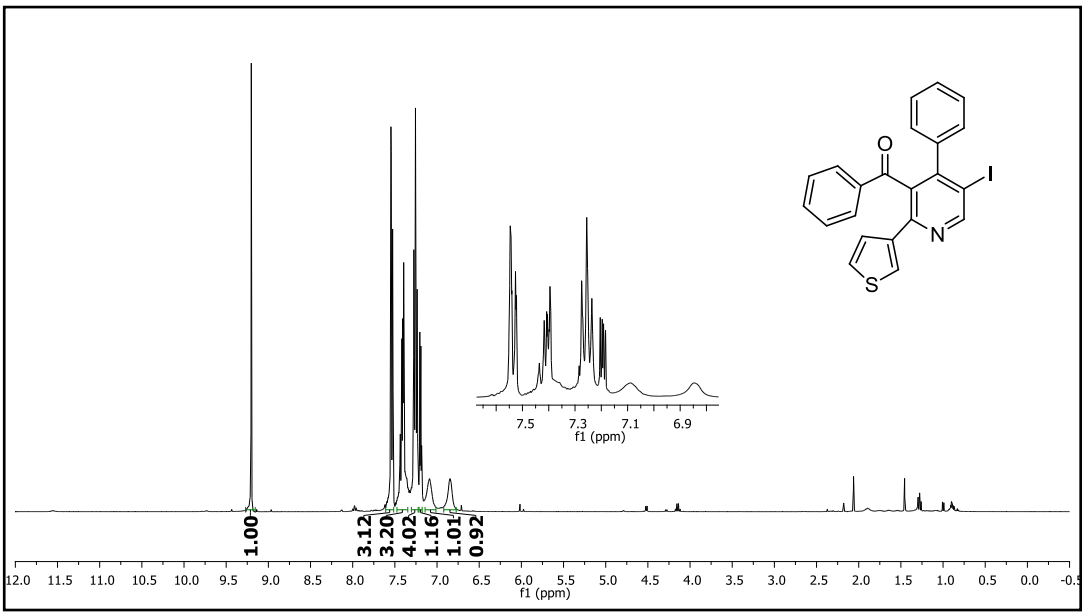

Figure 164. ^{1}H NMR spectrum of compound **55m**.

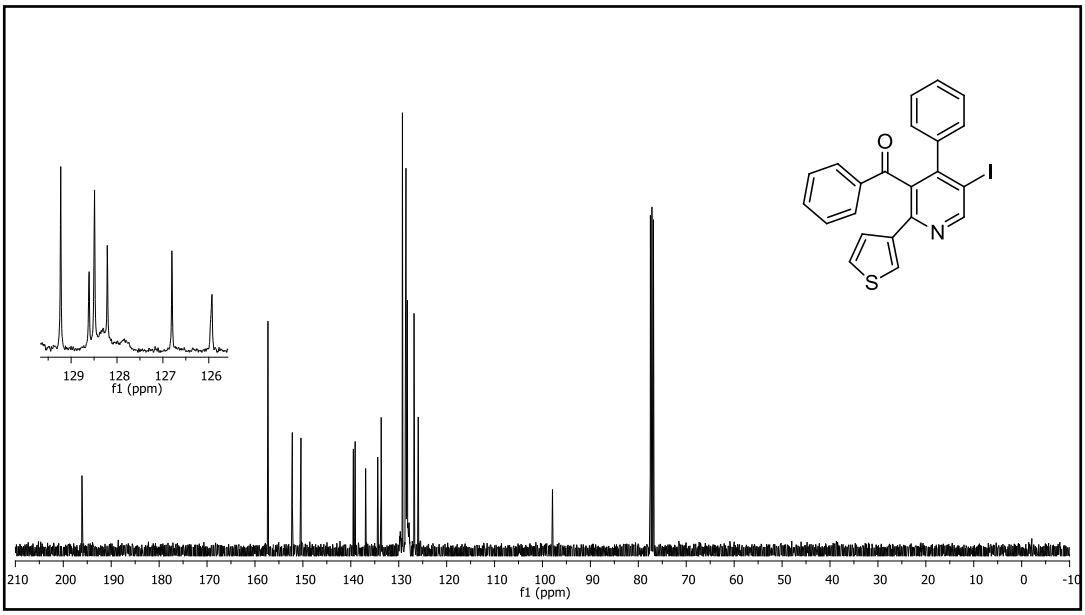

Figure 165. ^{13}C NMR spectrum of compound **55m**.

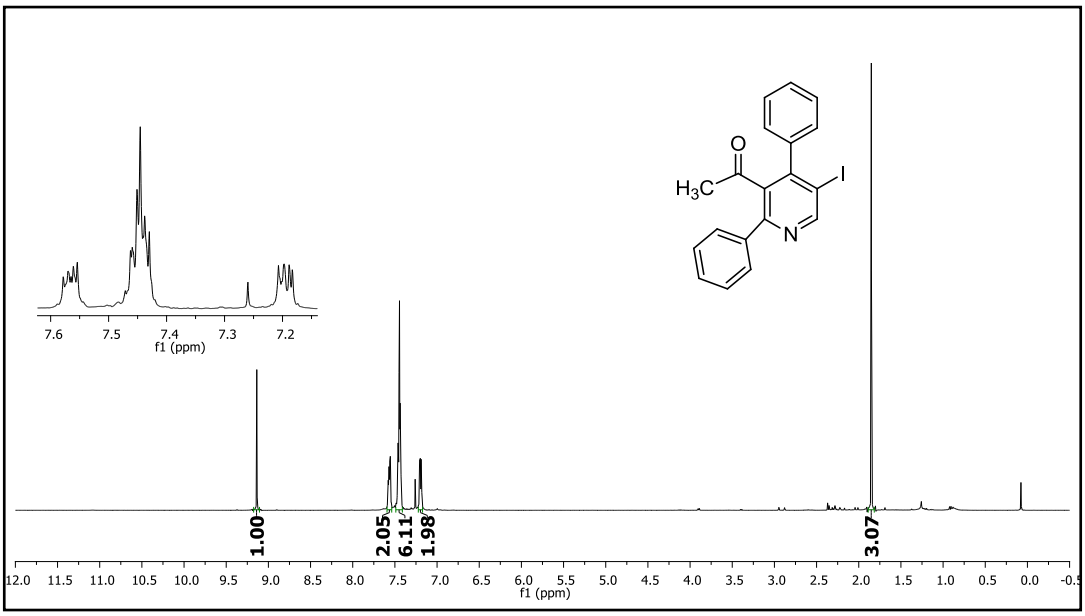

Figure 166. ^{1}H NMR spectrum of compound **55aa**.

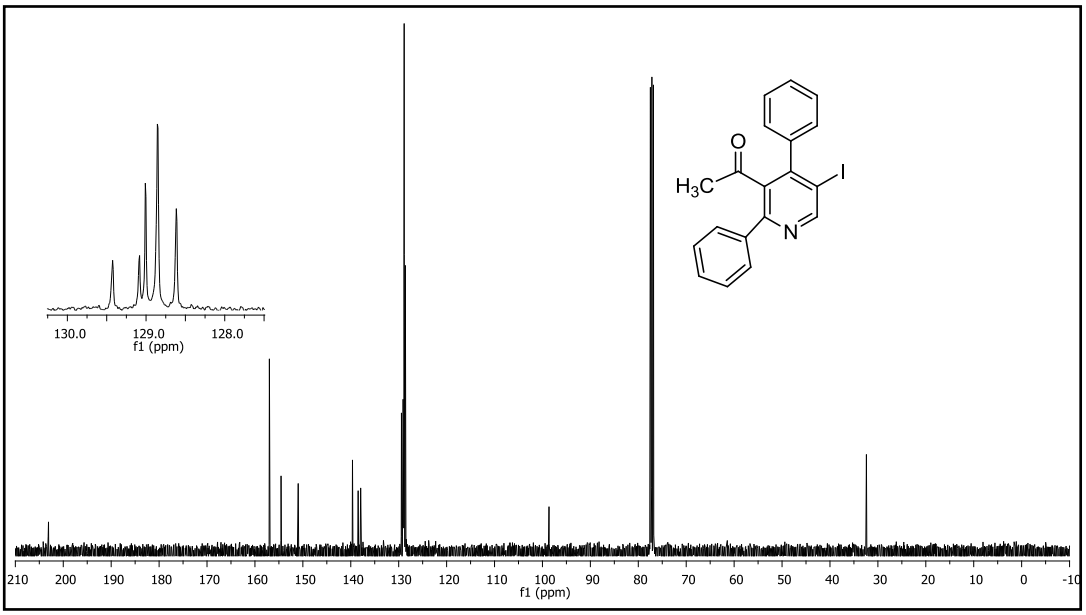

Figure 167. ^{13}C NMR spectrum of compound **55aa**.

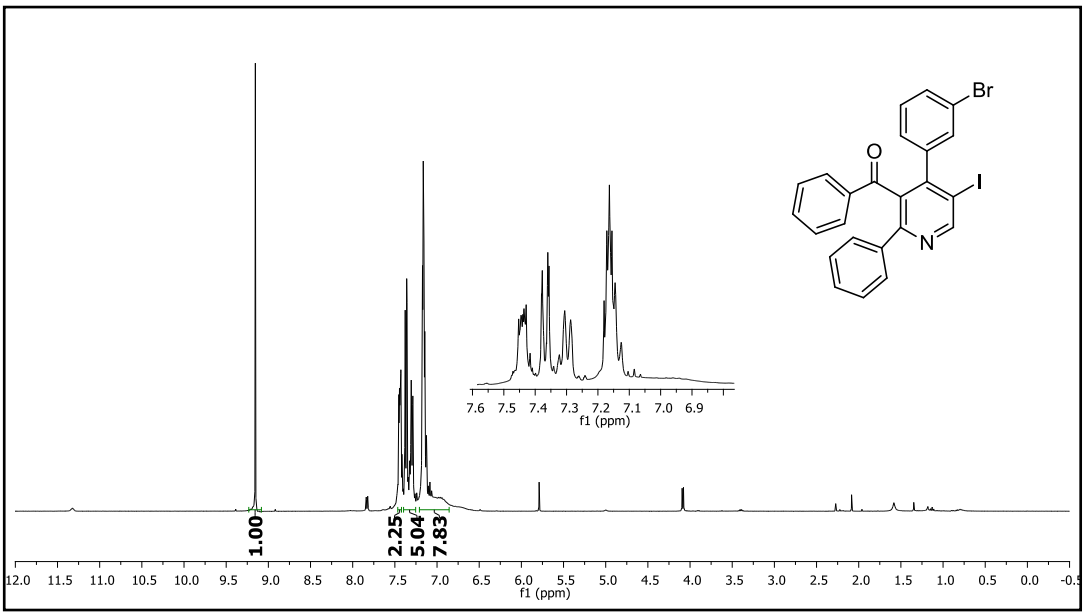

Figure 168. ^{1}H NMR spectrum of compound **55ab**.

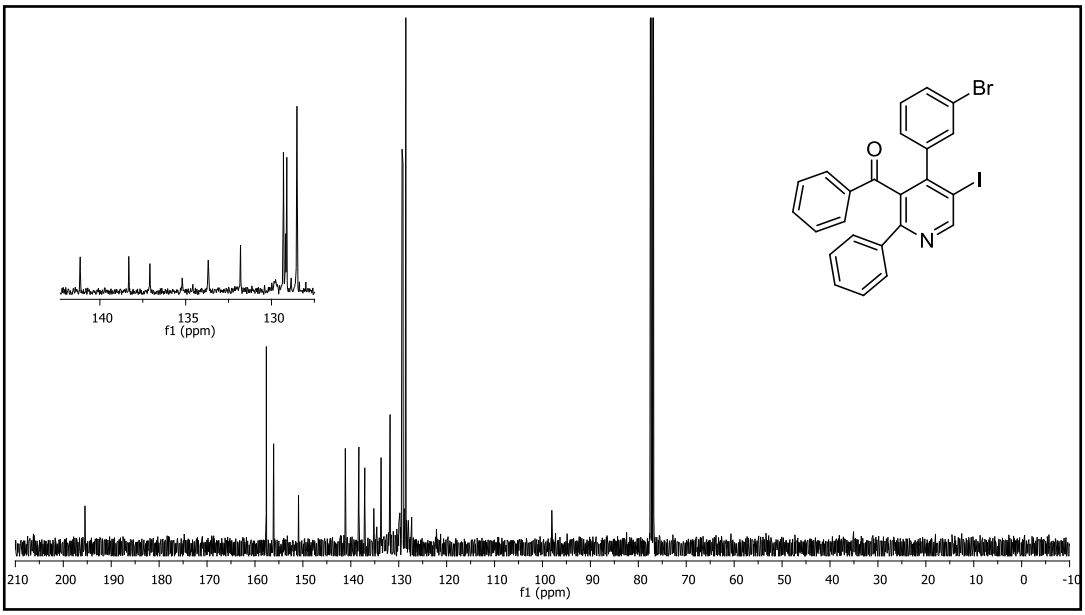

Figure 169. ^{13}C NMR spectrum of compound **55ab**.

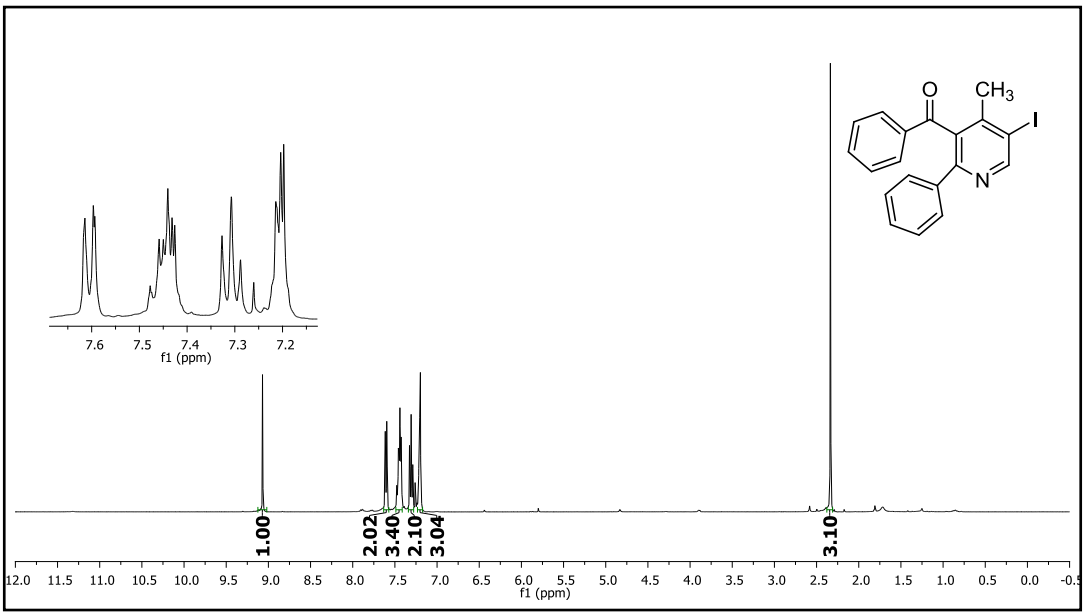

Figure 170. ^{1}H NMR spectrum of compound **55ac**.

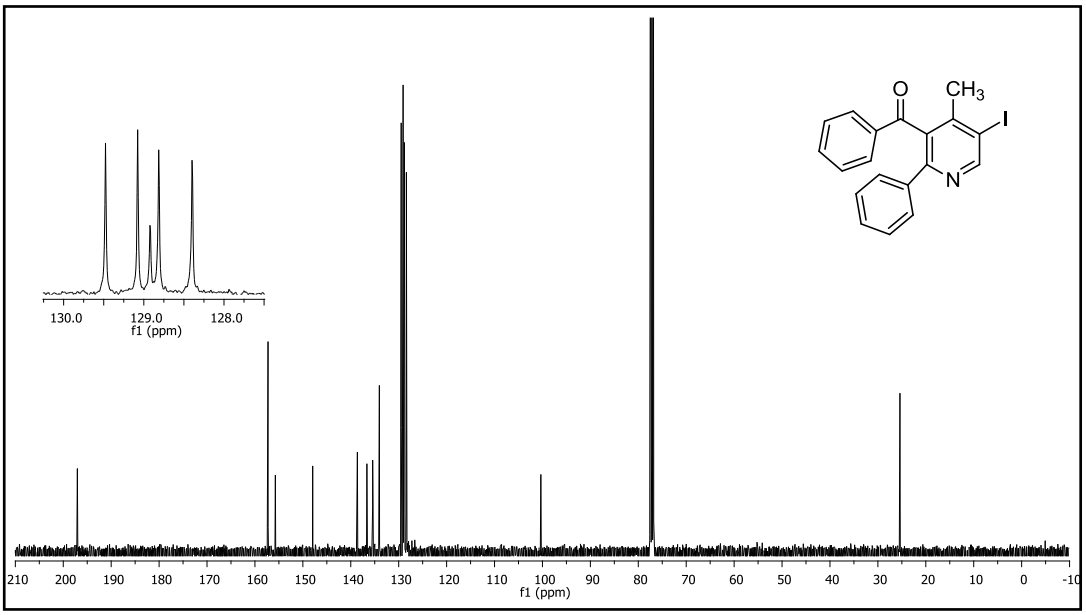

Figure 171. ^{13}C NMR spectrum of compound **55ac**.

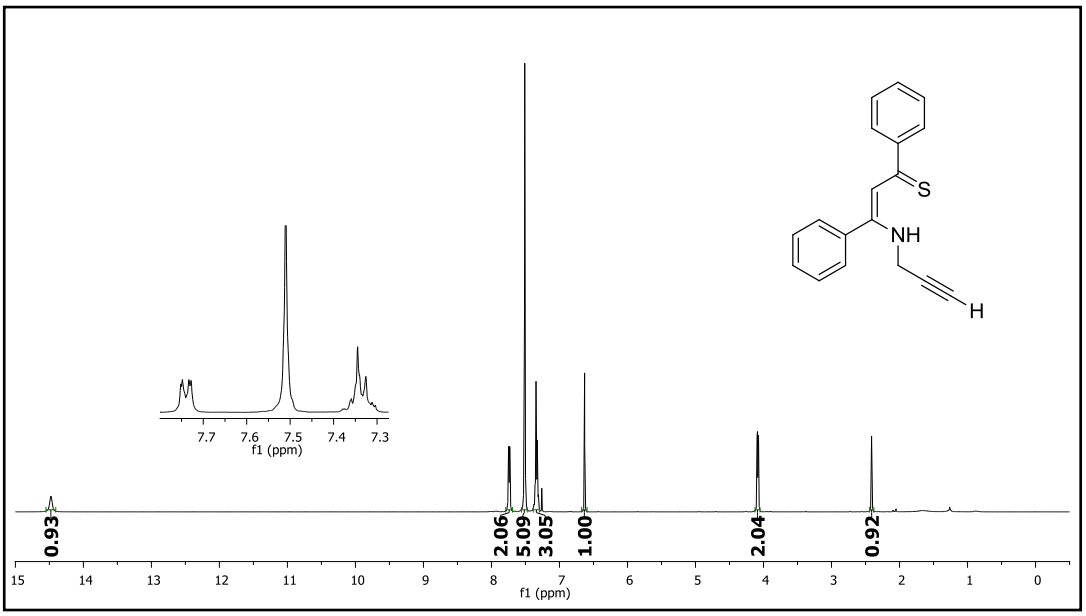

Figure 172. ^{1}H NMR spectrum of compound **58a**.

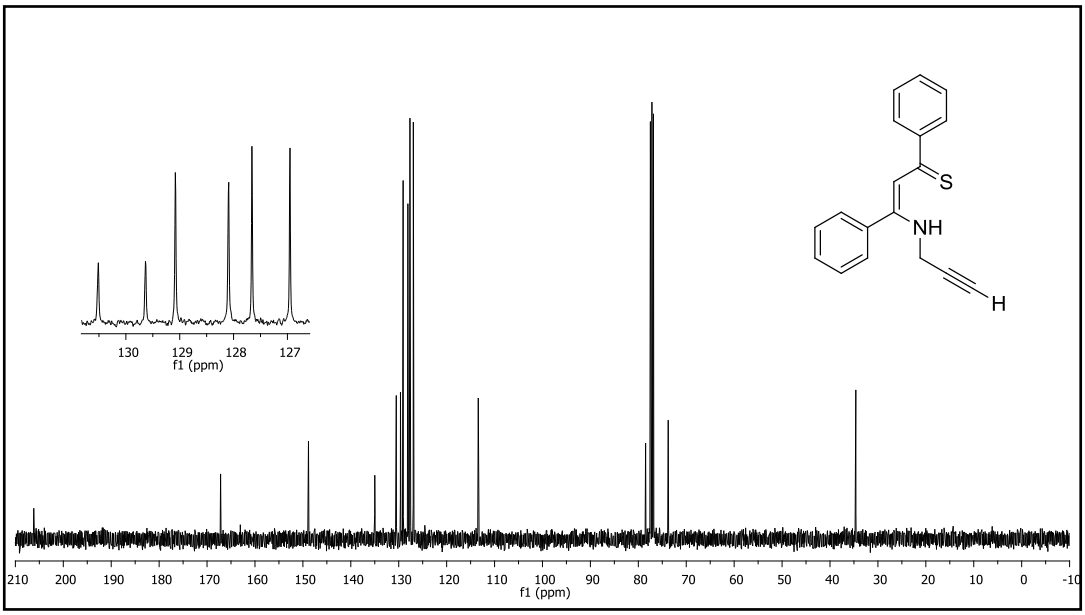

Figure 173. ^{13}C NMR spectrum of compound **58a**.

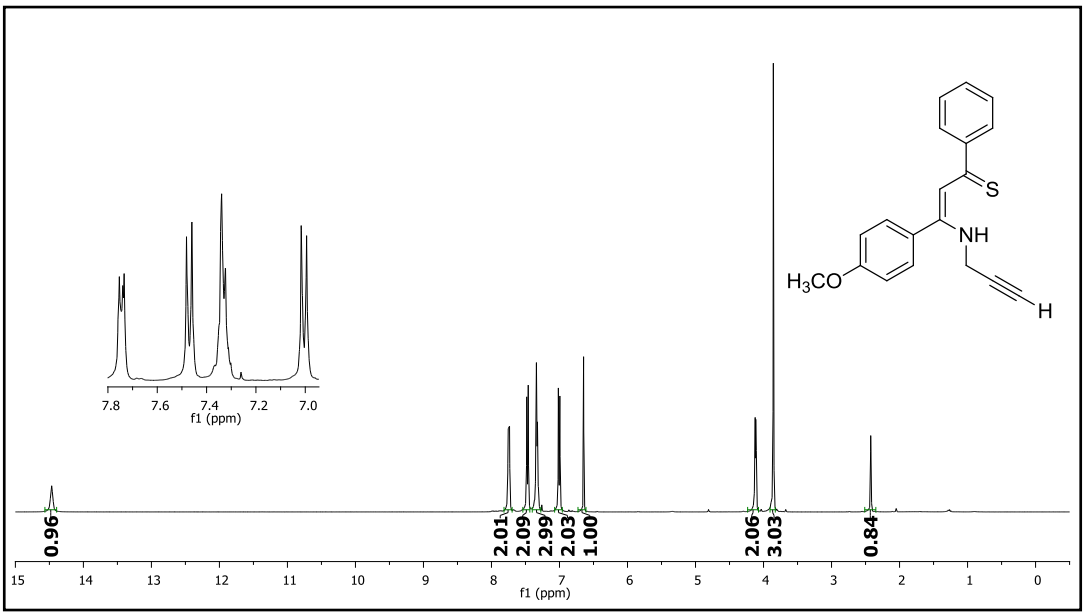

Figure 174. ^{1}H NMR spectrum of compound **58b**.

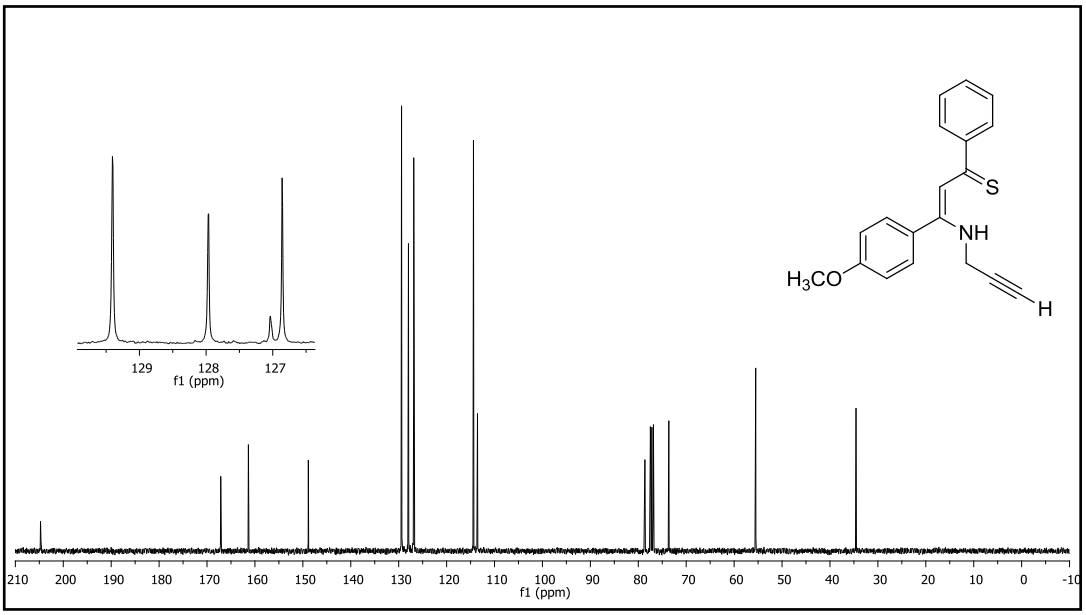

Figure 175. ^{13}C NMR spectrum of compound **58b**.

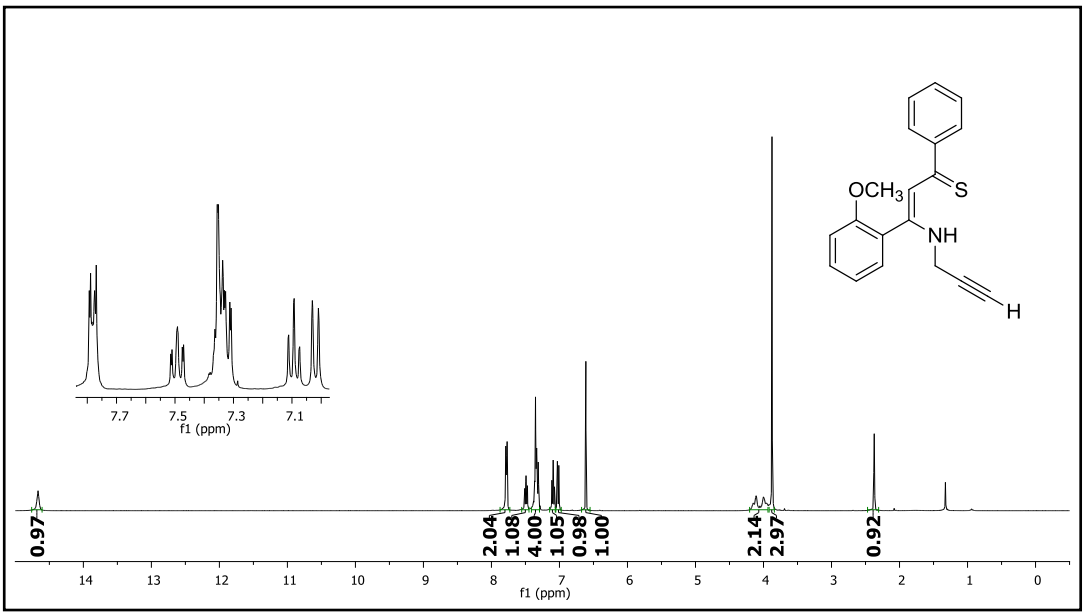

Figure 176. ^{1}H NMR spectrum of compound **58c**.

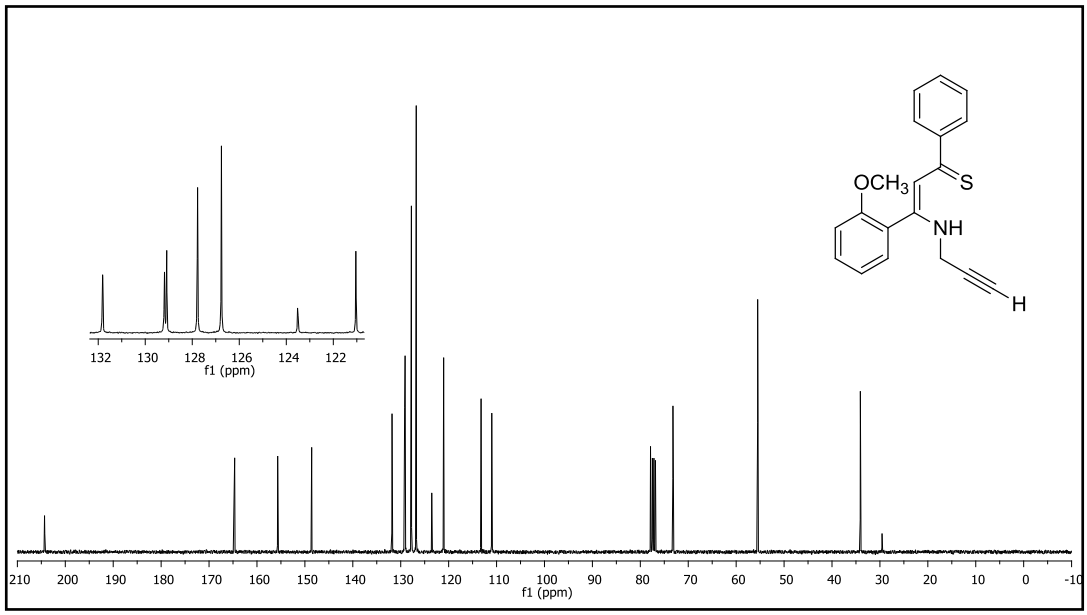

Figure 177. ^{13}C NMR spectrum of compound **58c**.

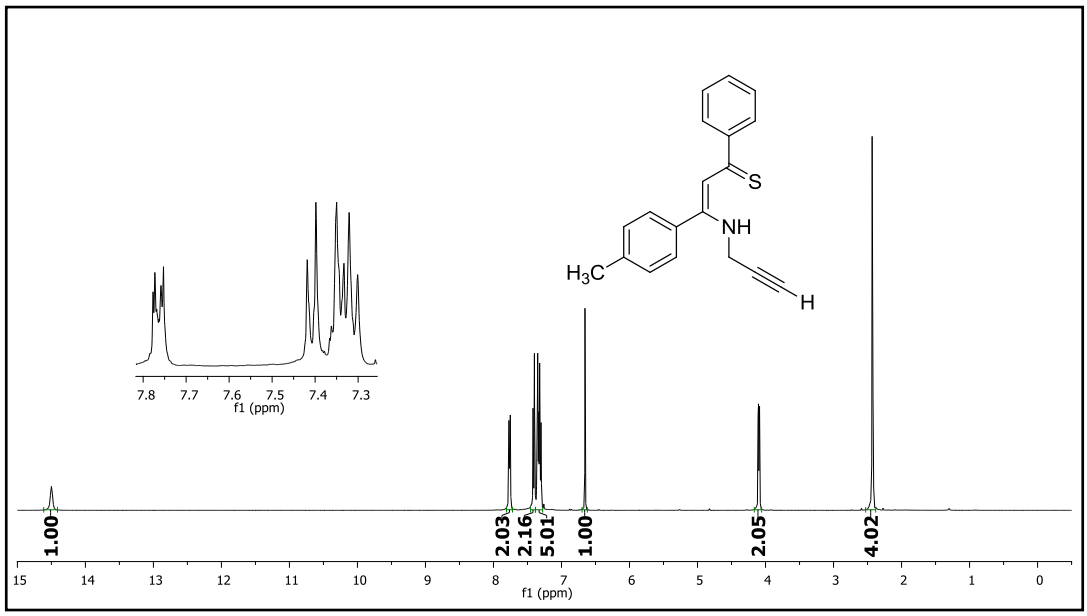

Figure 178. ^{1}H NMR spectrum of compound **58d**.

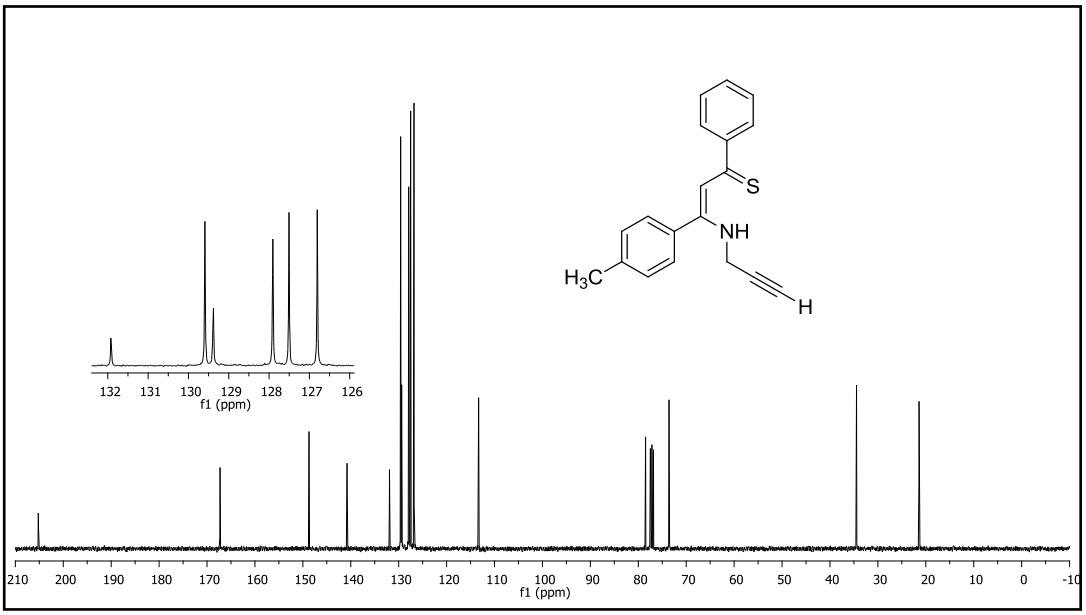

Figure 179. ^{13}C NMR spectrum of compound **58d**.

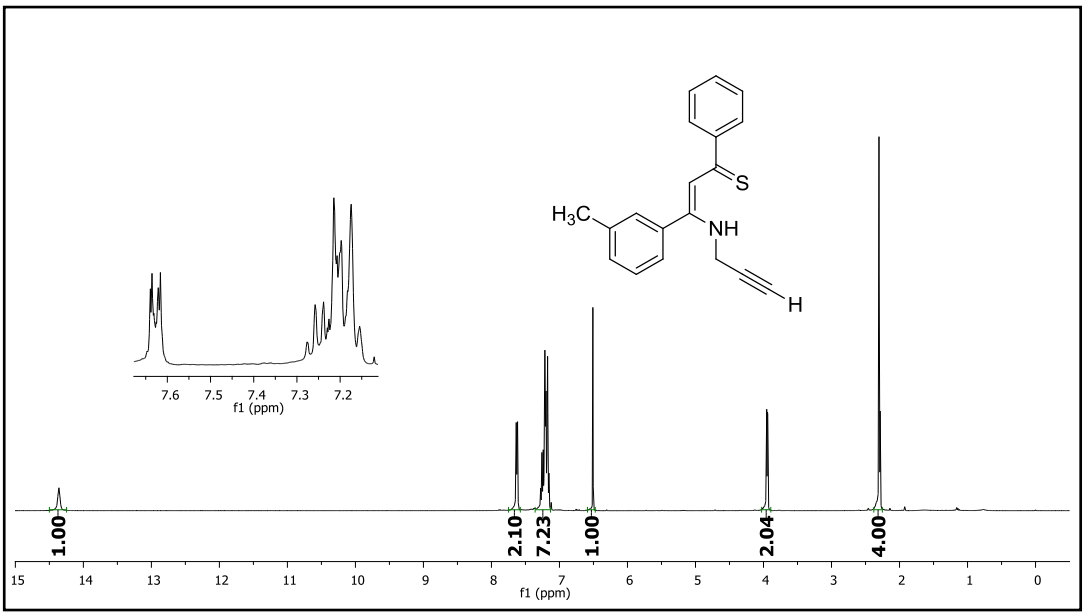

Figure 180. ^{1}H NMR spectrum of compound **58e**.

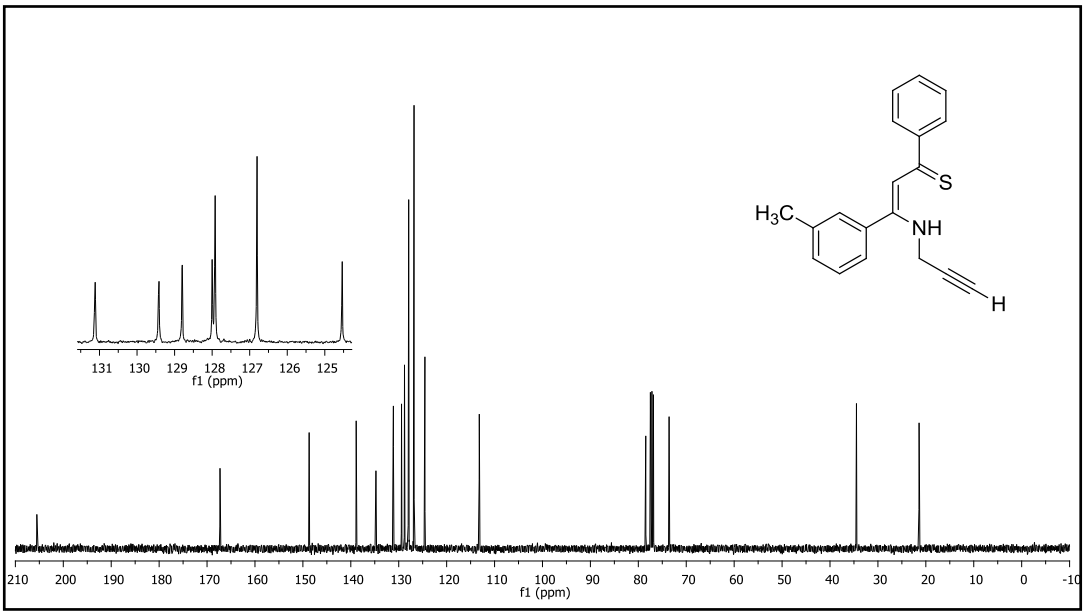

Figure 181. ^{13}C NMR spectrum of compound **58e**.

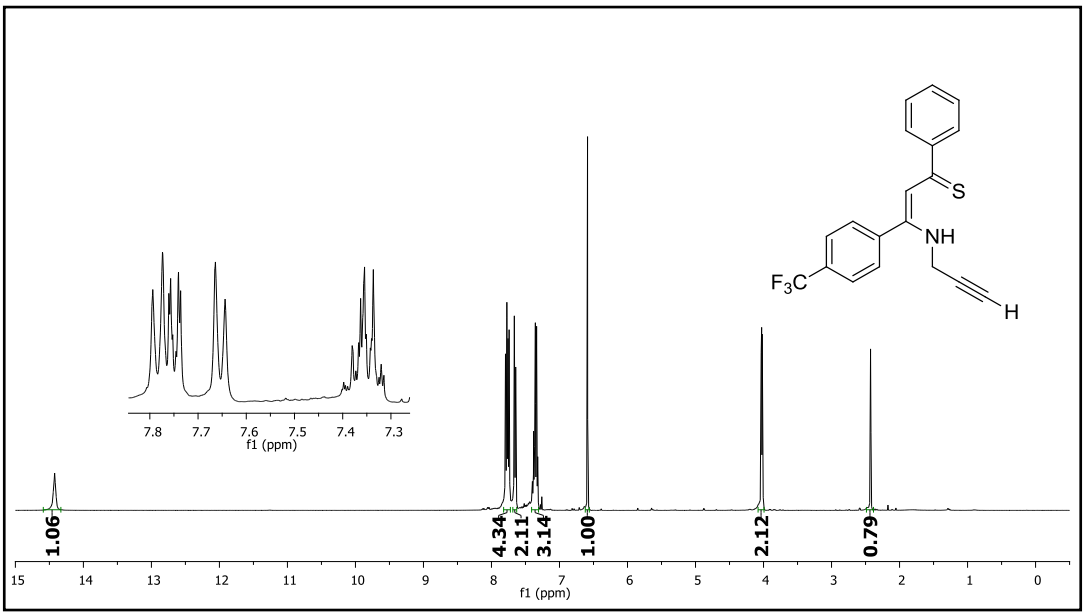

Figure 182. ^{1}H NMR spectrum of compound **58f**.

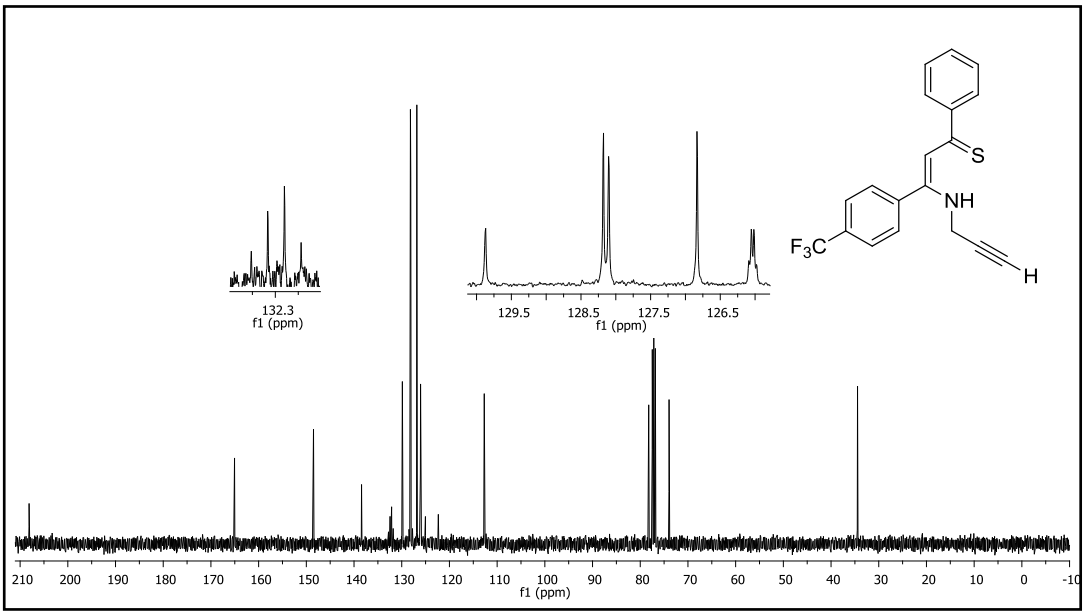

Figure 183. ^{13}C NMR spectrum of compound **58f**.

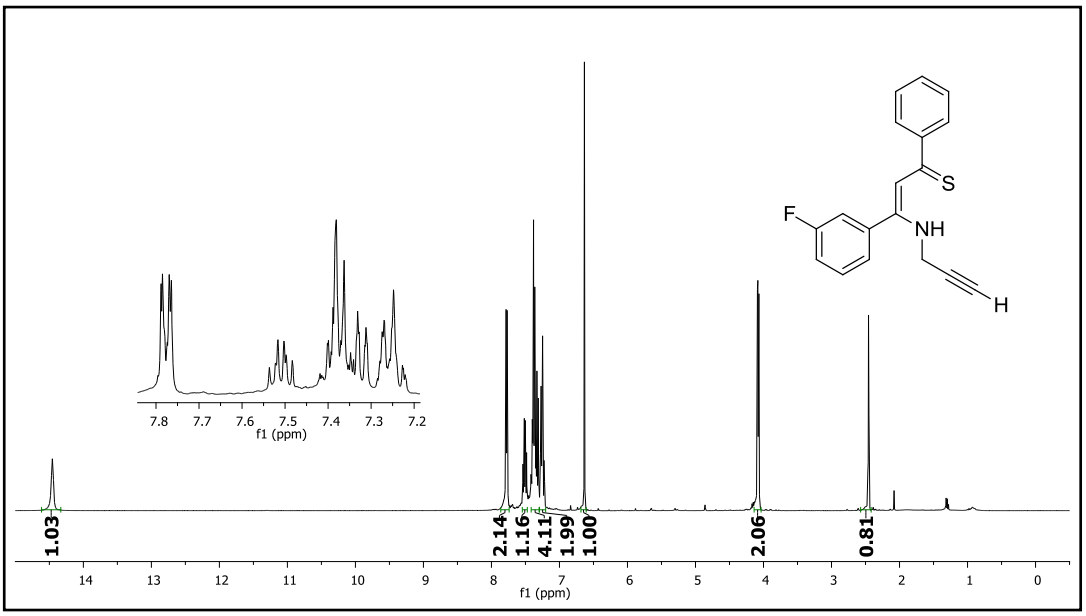

Figure 184. ^{1}H NMR spectrum of compound **58h**.

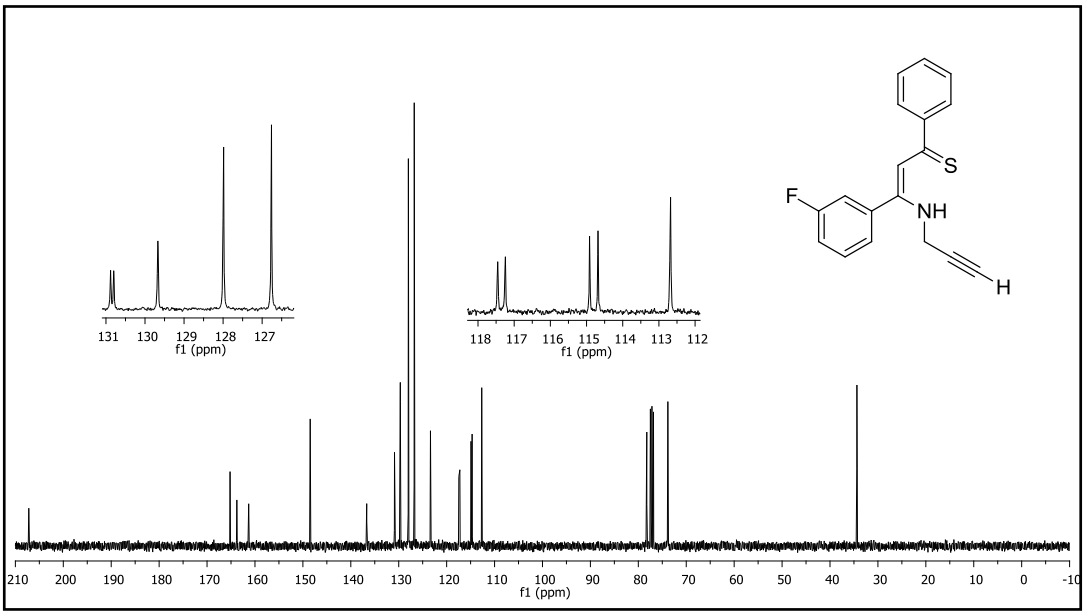

Figure 185. ^{13}C NMR spectrum of compound **58h**.

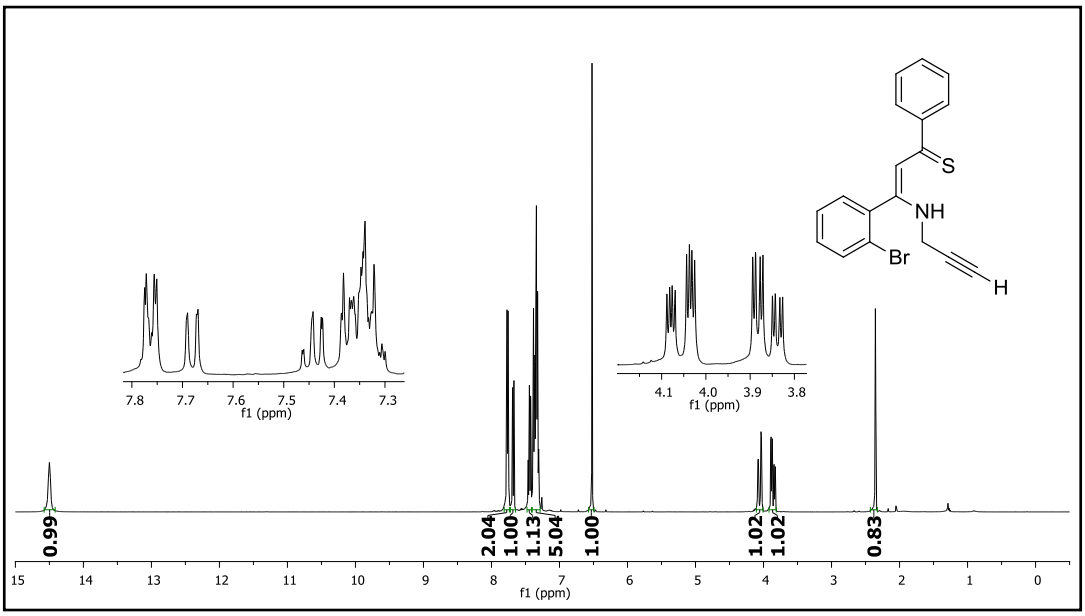

Figure 186. ^{1}H NMR spectrum of compound **58i**.

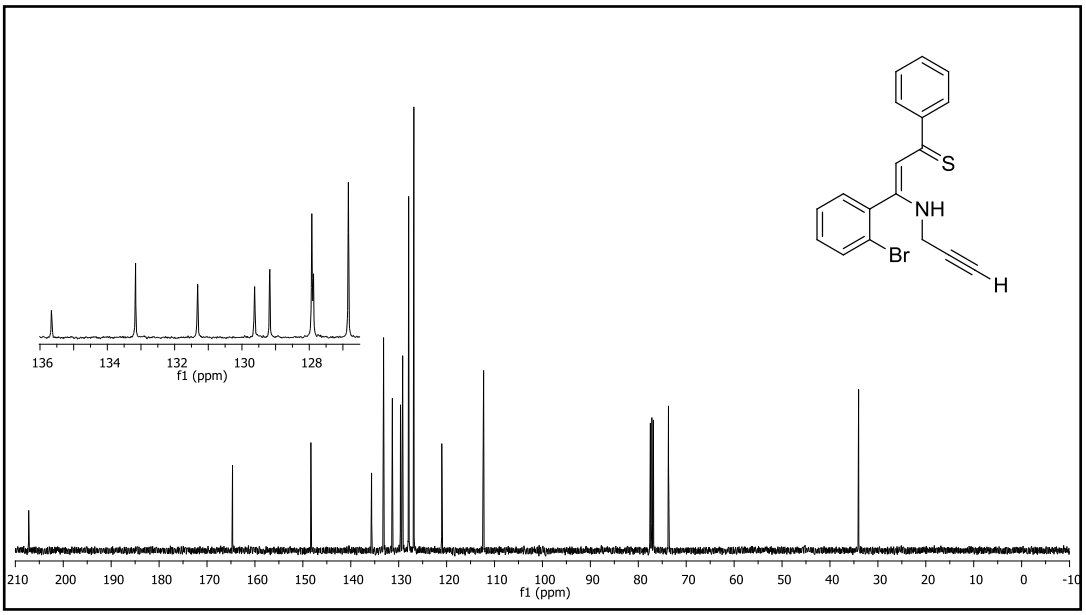

Figure 187. ^{13}C NMR spectrum of compound **58i**.

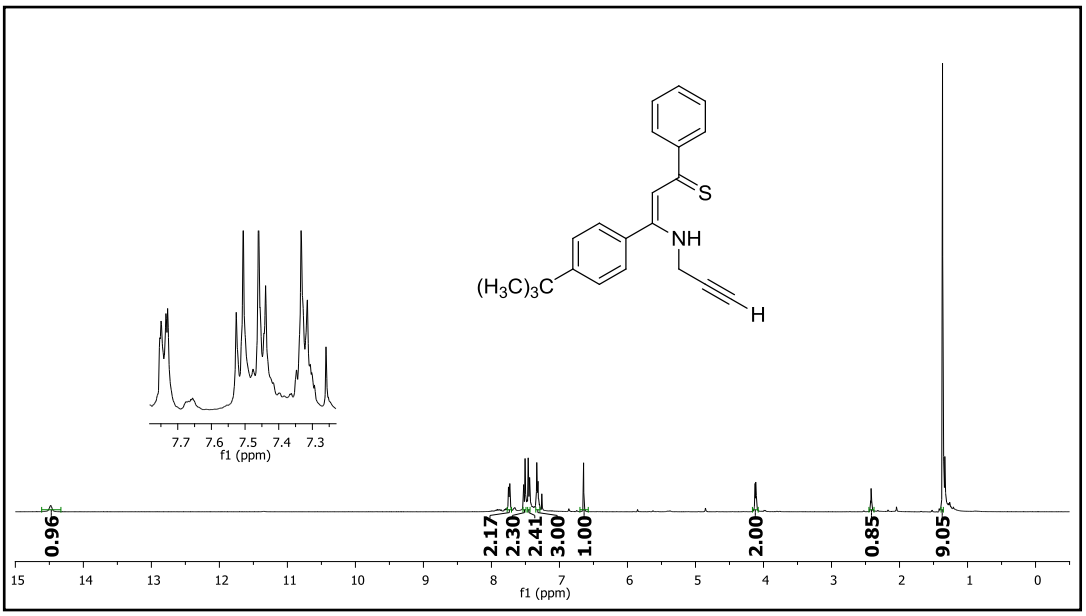

Figure 188. ^{1}H NMR spectrum of compound **58j**.

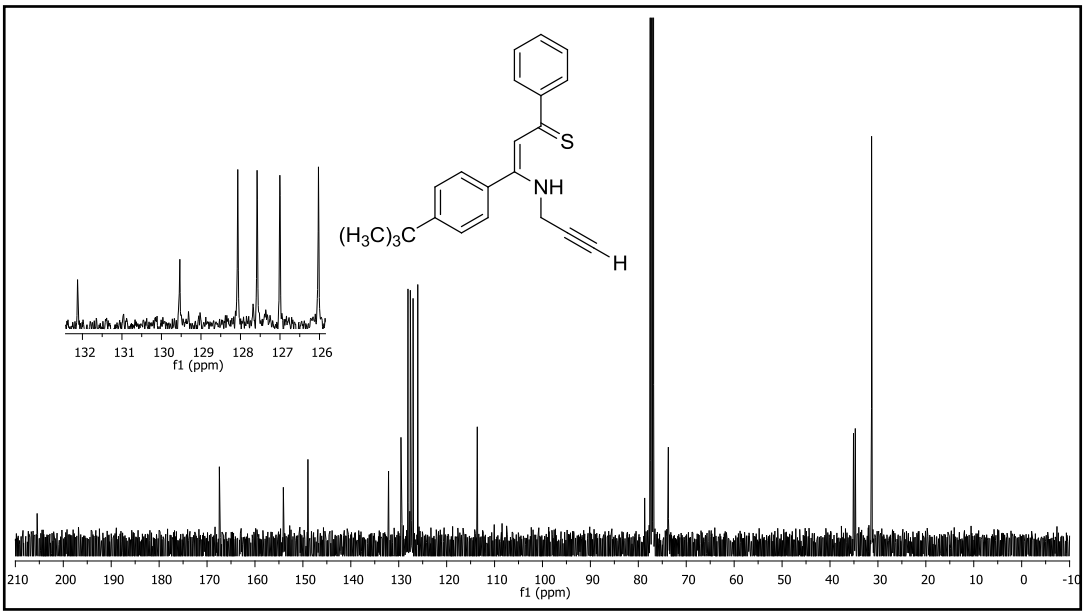

Figure 189. ^{13}C NMR spectrum of compound **58j**.

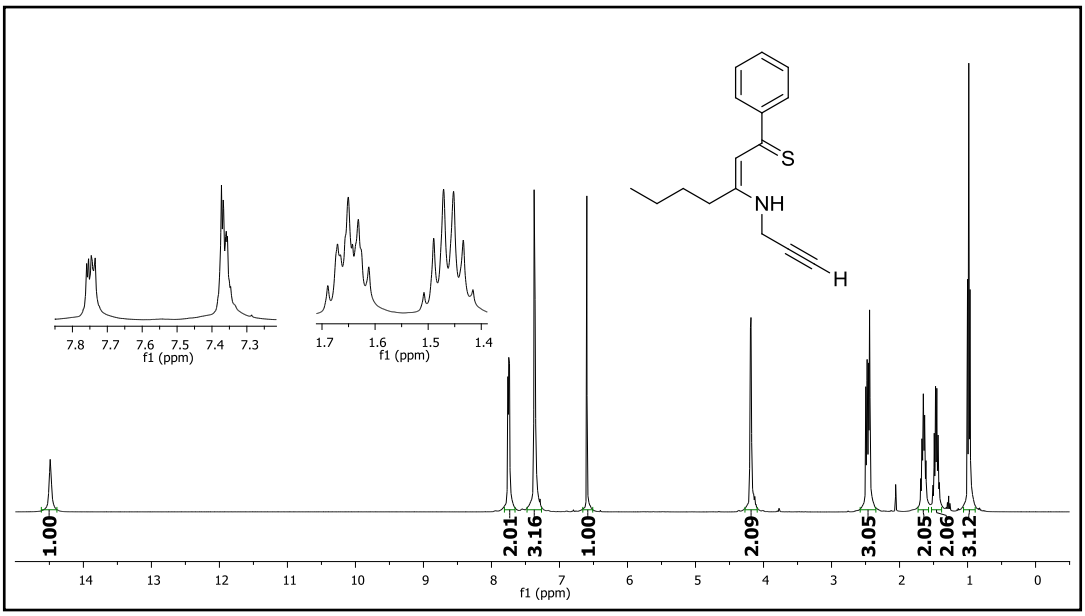

Figure 190. ^{1}H NMR spectrum of compound **58l**.

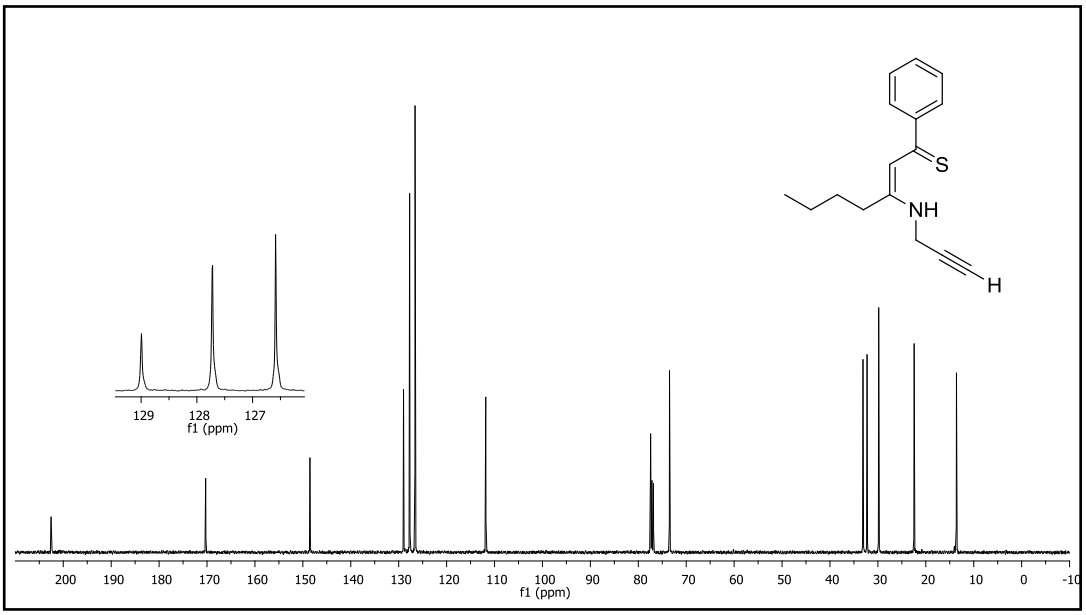

Figure 191. ^{13}C NMR spectrum of compound **58l**.

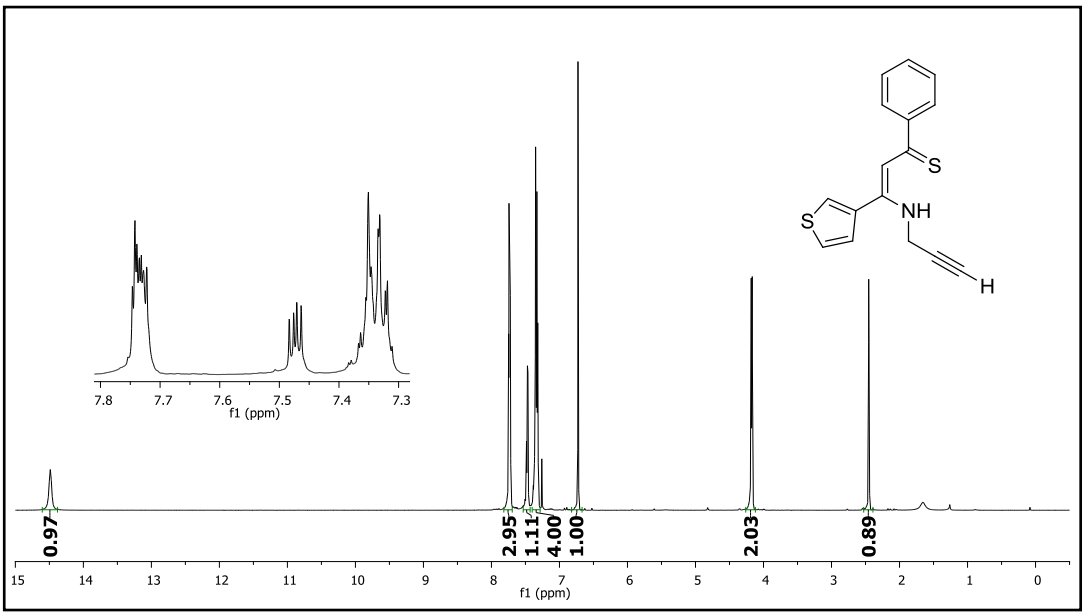

Figure 192. ^{1}H NMR spectrum of compound **58m**.

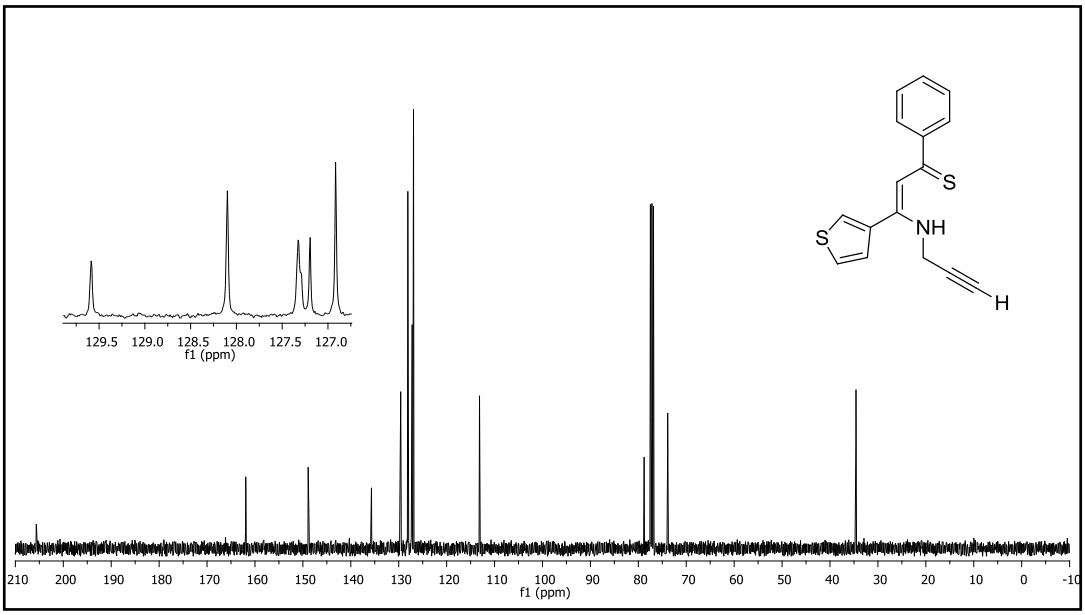

Figure 193. ^{13}C NMR spectrum of compound **58m**.

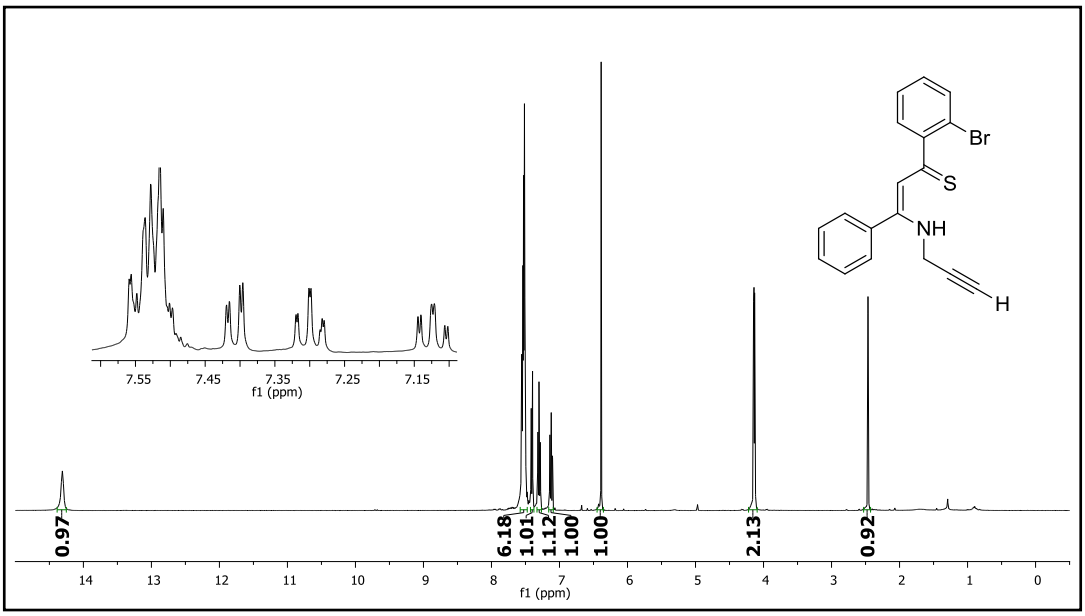

Figure 194. ^{1}H NMR spectrum of compound **58n**.

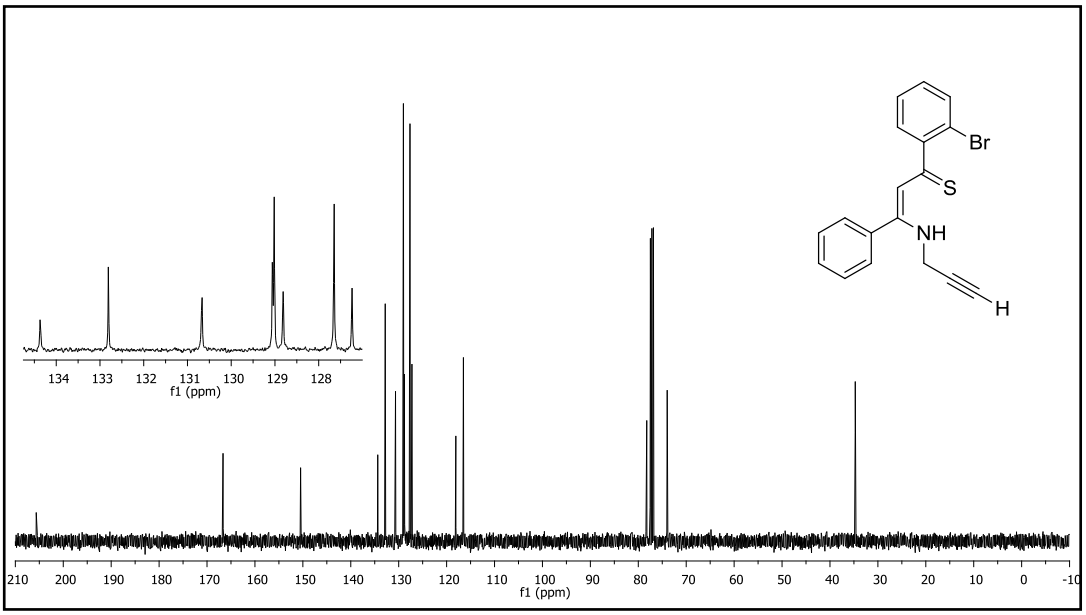

Figure 195. ^{13}C NMR spectrum of compound **58n**.

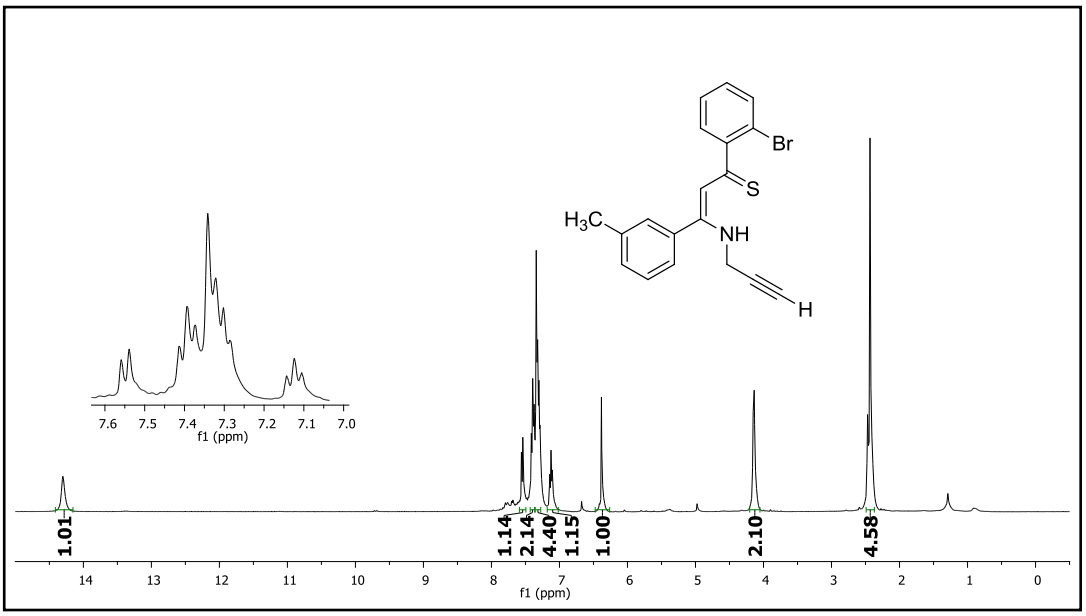

Figure 196. ^{1}H NMR spectrum of compound **58r**.

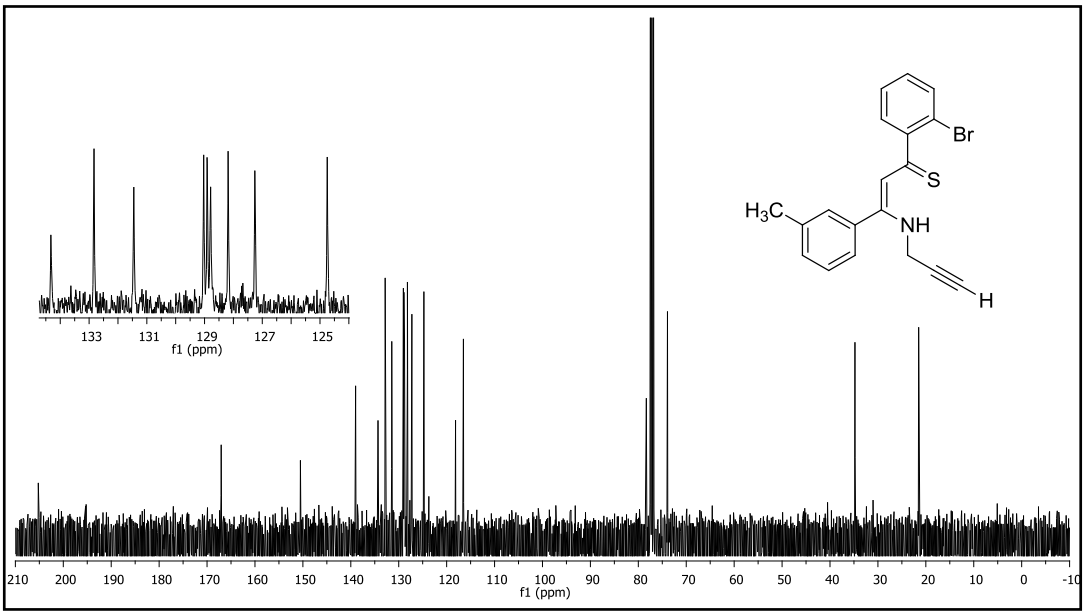

Figure 197. ^{13}C NMR spectrum of compound **58r**.

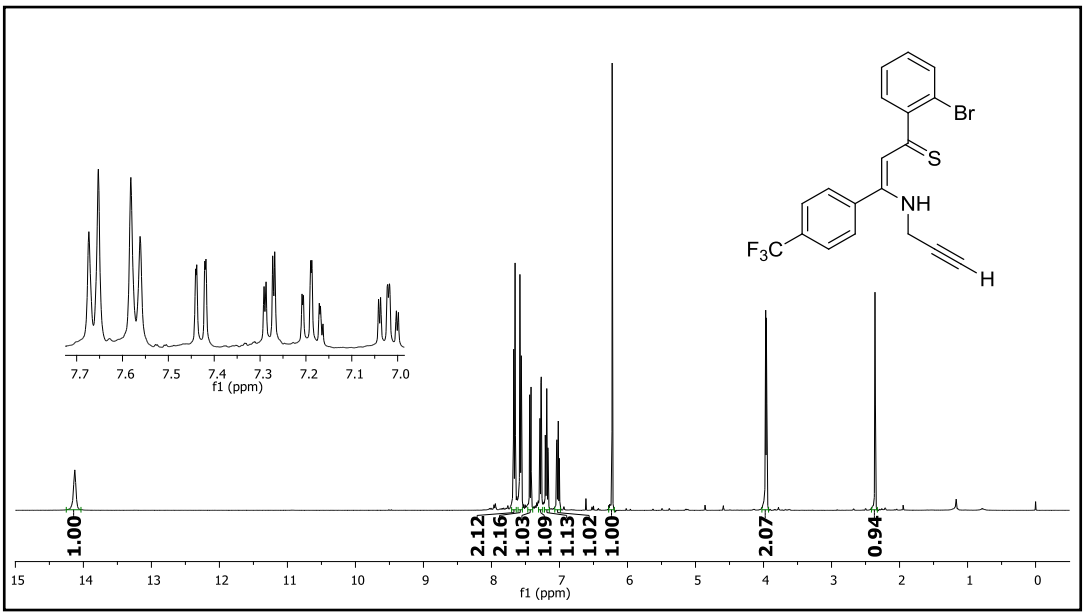

Figure 198. ^{1}H NMR spectrum of compound **58s**.

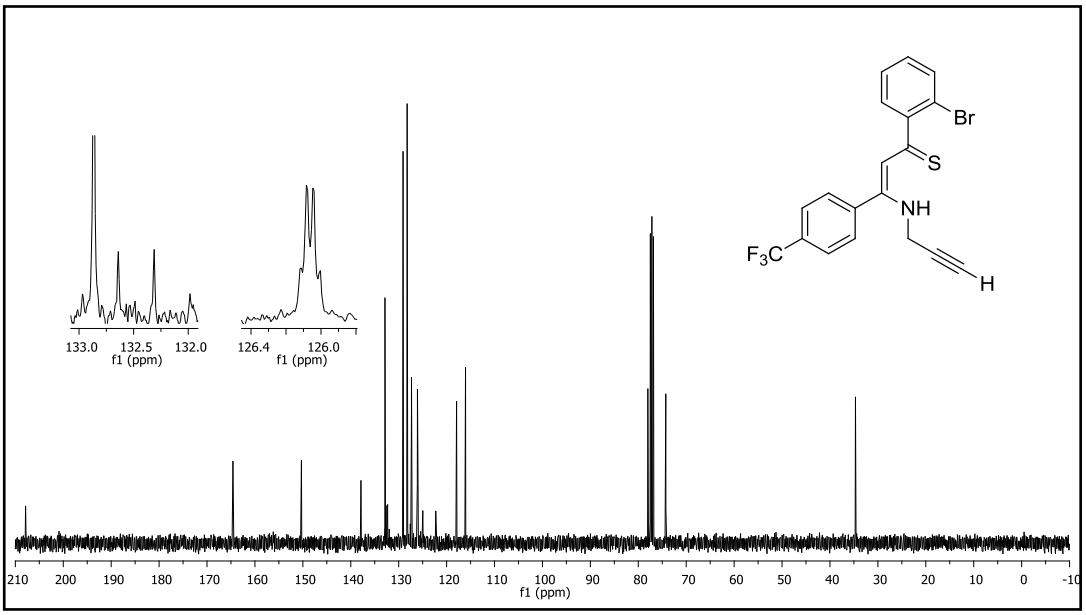

Figure 199. ^{13}C NMR spectrum of compound **58s**.

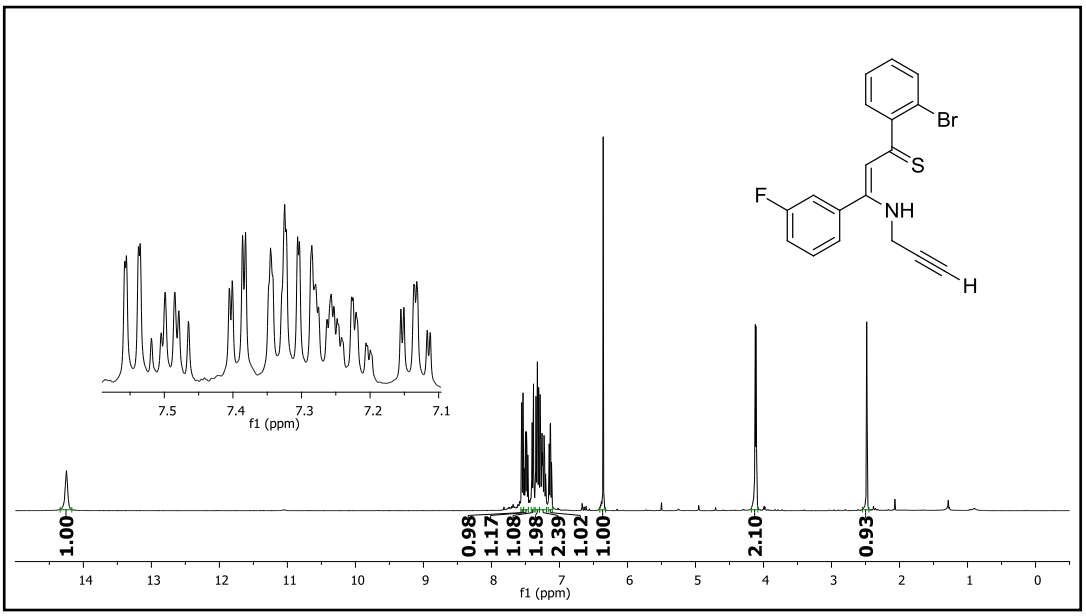

Figure 200. ^{1}H NMR spectrum of compound **58t**.

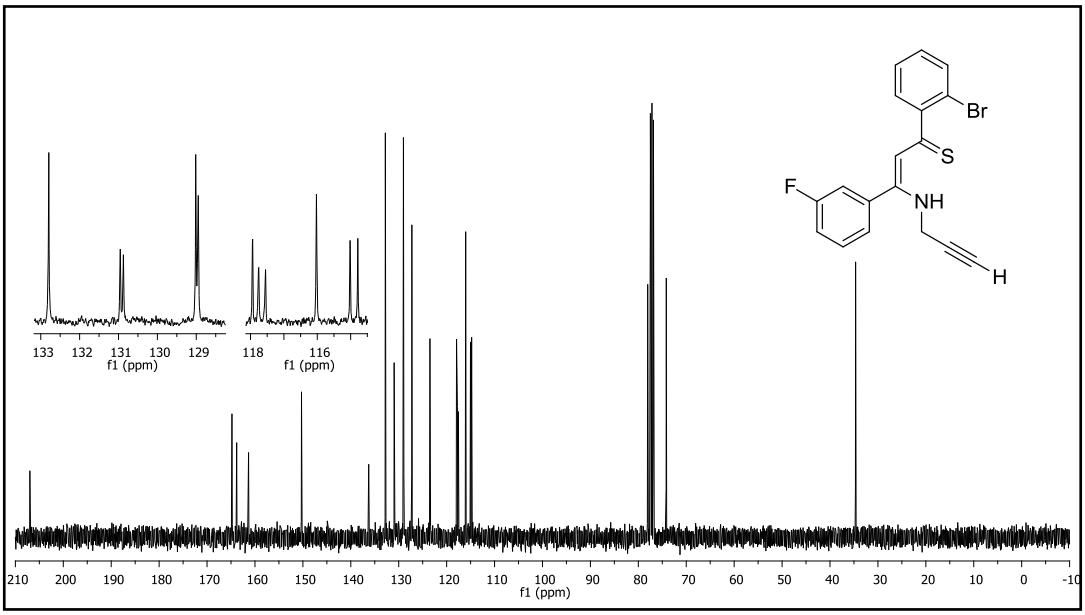

Figure 201. ^{13}C NMR spectrum of compound **58t**.

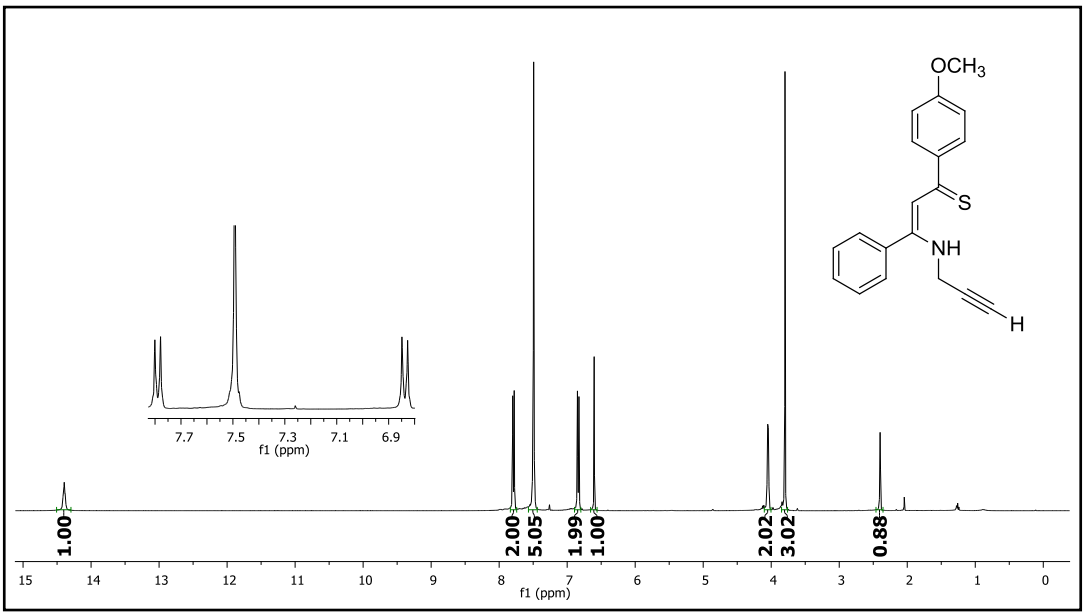

Figure 202. ^{1}H NMR spectrum of compound **58v**.

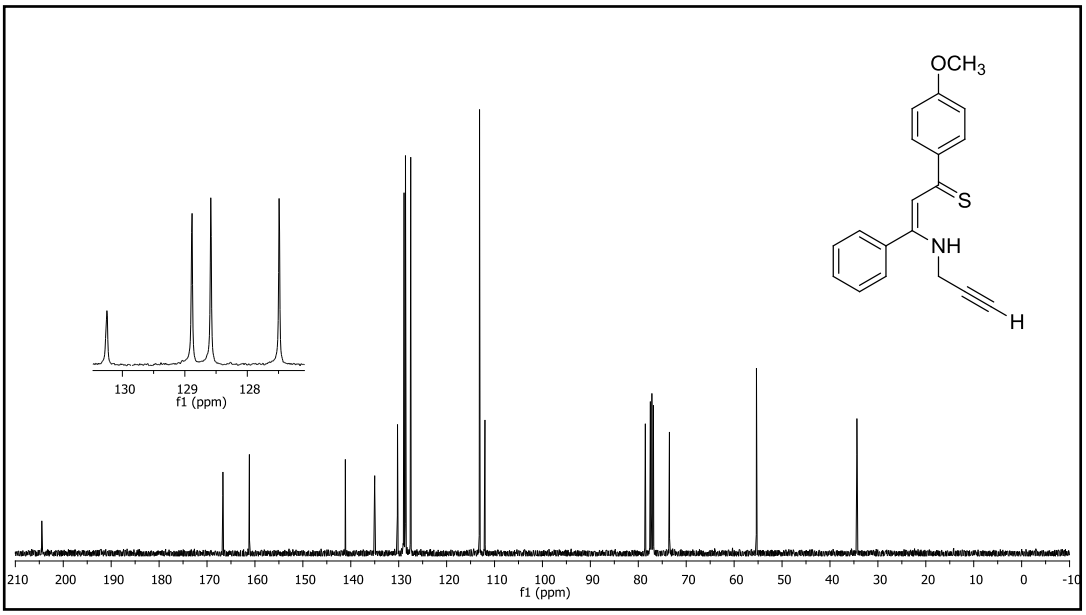

Figure 203. ^{13}C NMR spectrum of compound **58v**.

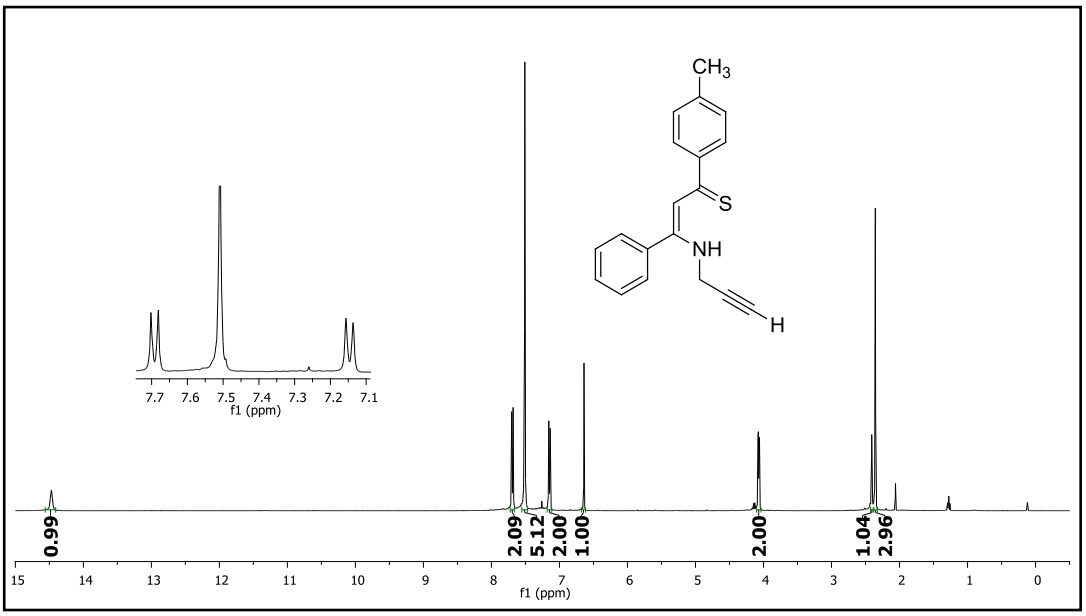

Figure 204. ^{1}H NMR spectrum of compound **58w**.

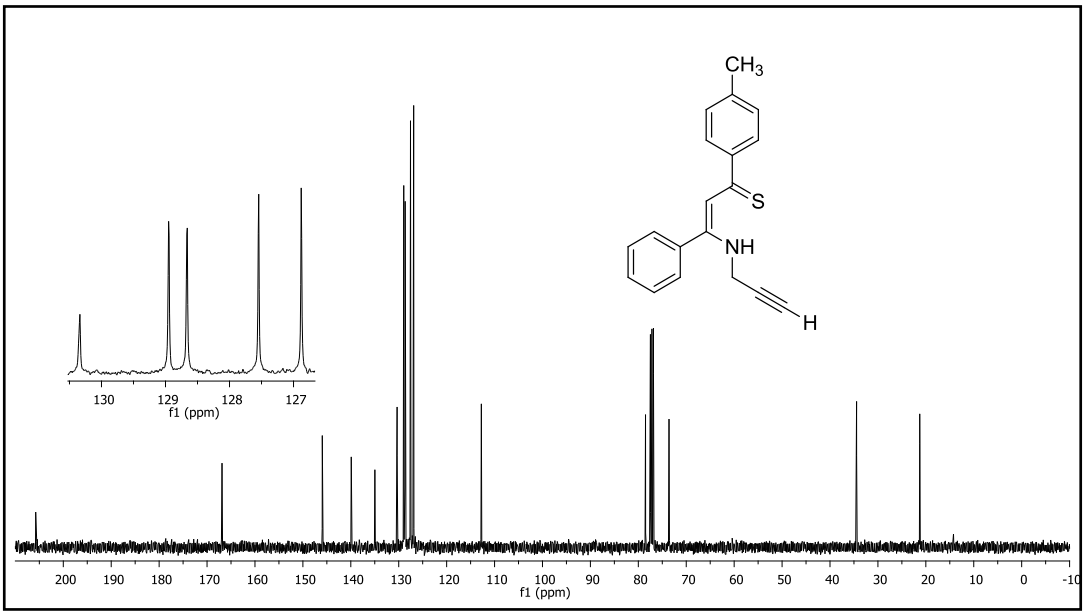

Figure 205. ^{13}C NMR spectrum of compound **58w**.

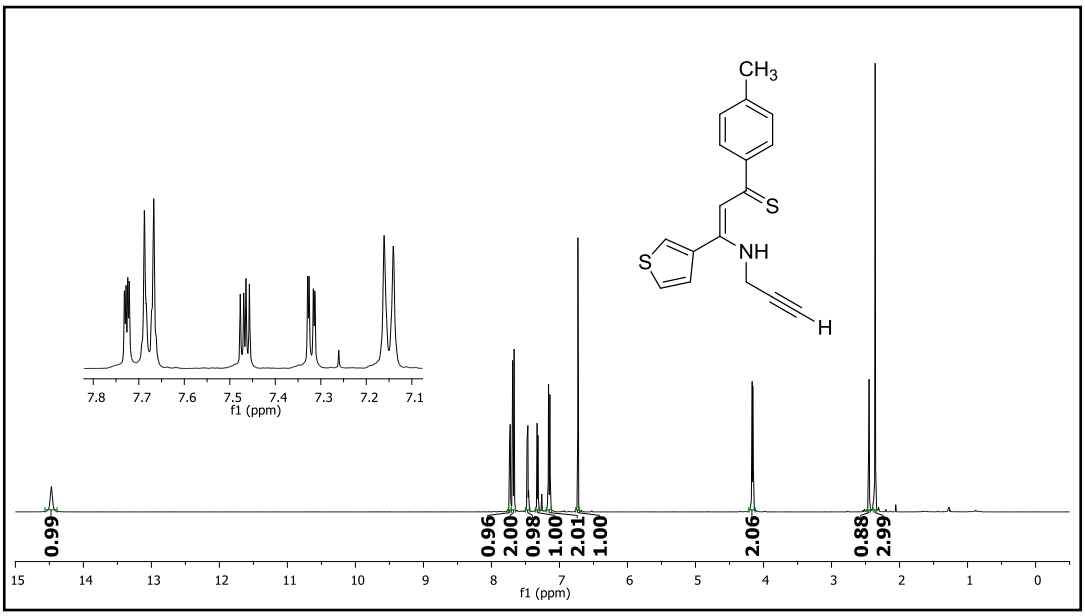

Figure 206. ^{1}H NMR spectrum of compound **58x**.

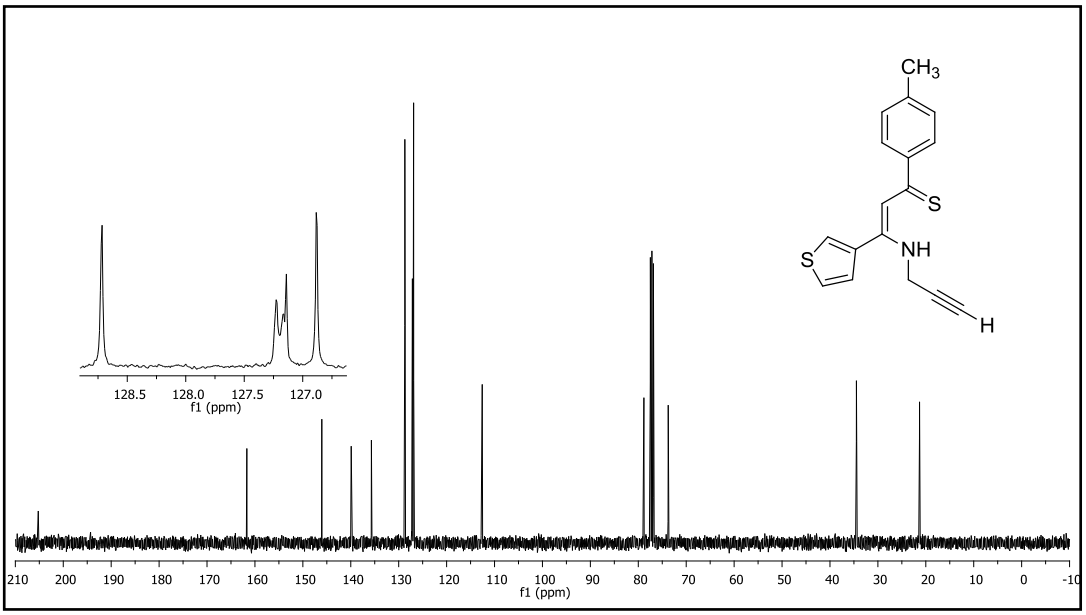

Figure 207. ^{13}C NMR spectrum of compound **58x**.

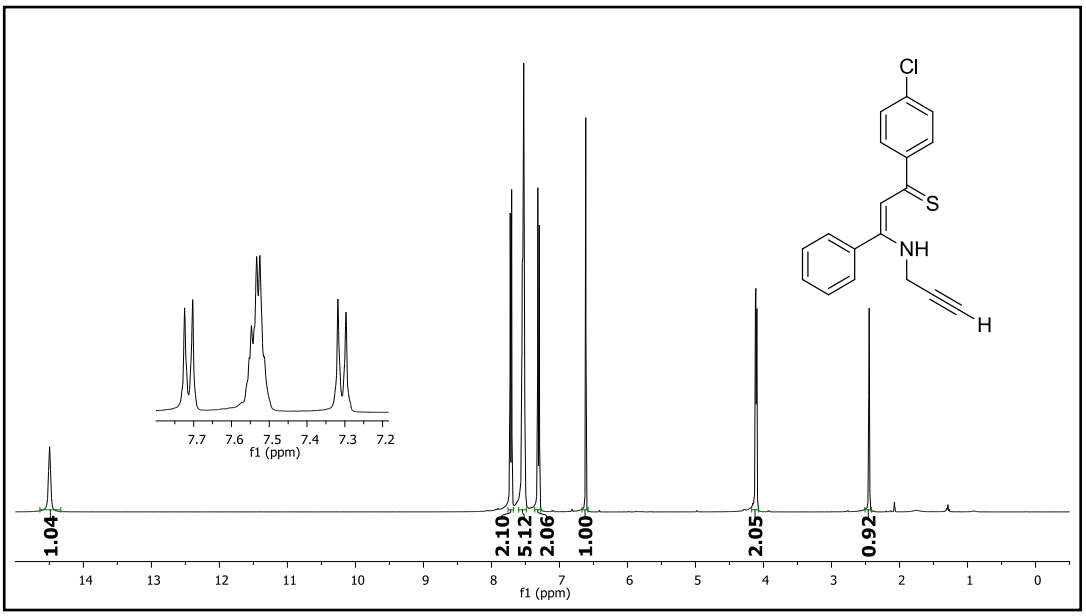

Figure 208. ^{1}H NMR spectrum of compound **58y**.

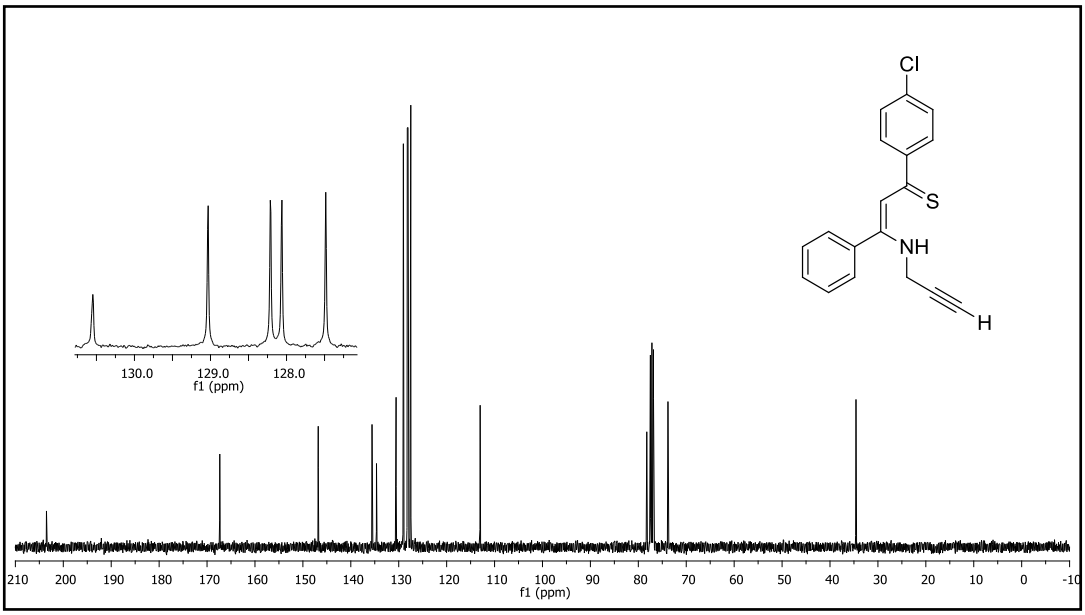

Figure 209. ^{13}C NMR spectrum of compound **58y**.

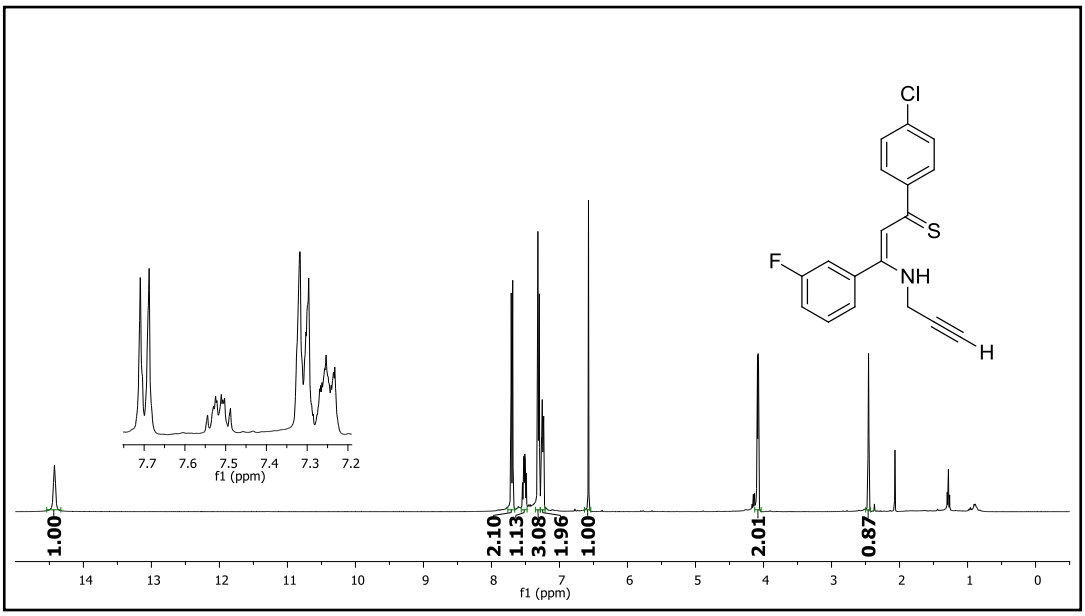

Figure 210. ^{1}H NMR spectrum of compound **58z**.

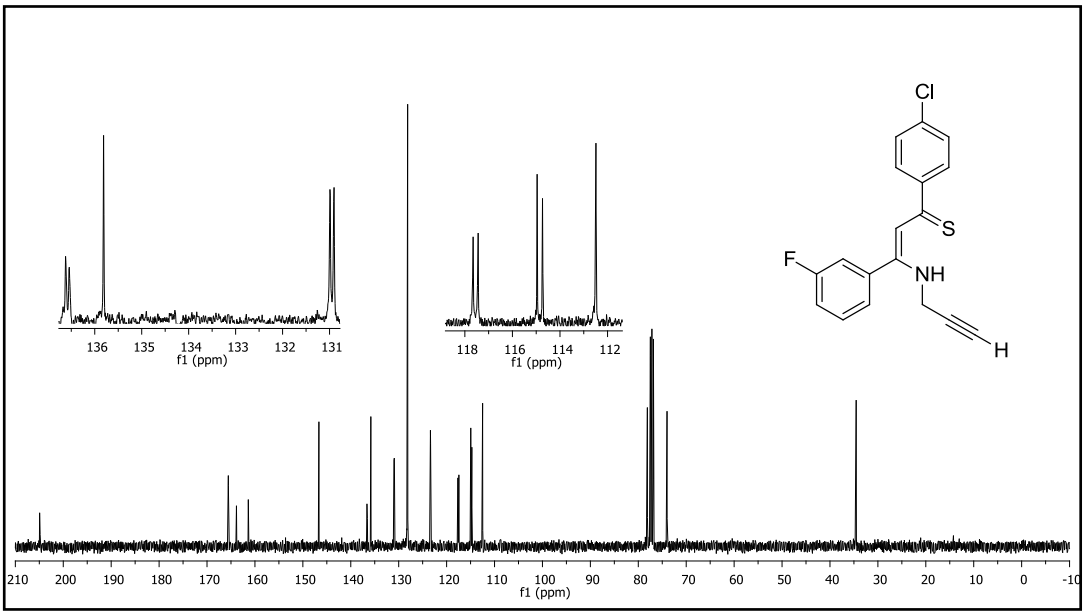

Figure 211. ^{13}C NMR spectrum of compound **58z**.

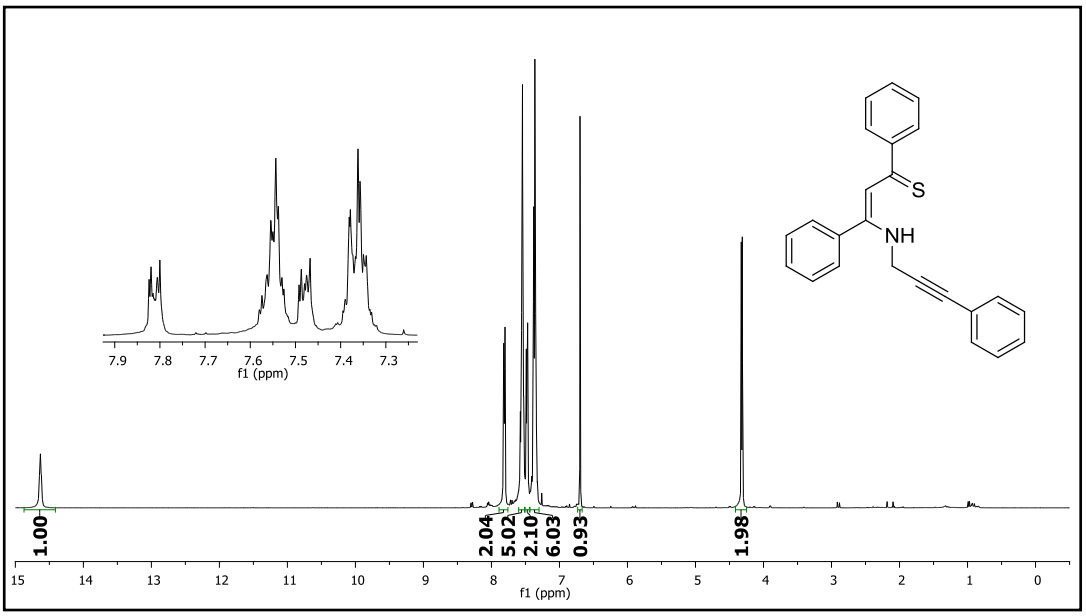

Figure 212. ^{1}H NMR spectrum of compound **84**.

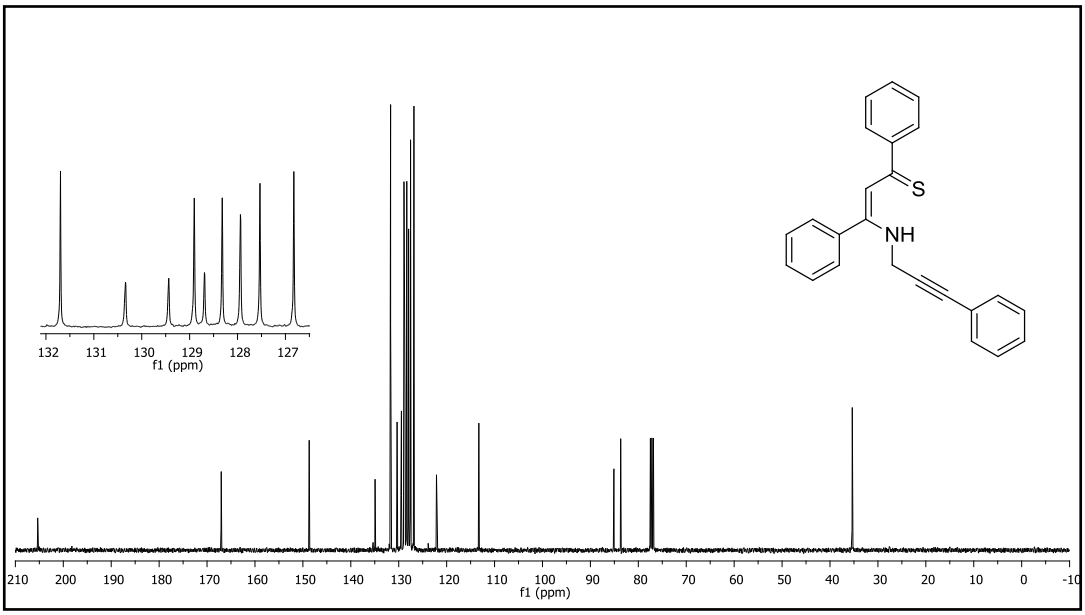

Figure 213. ^{13}C NMR spectrum of compound **84**.

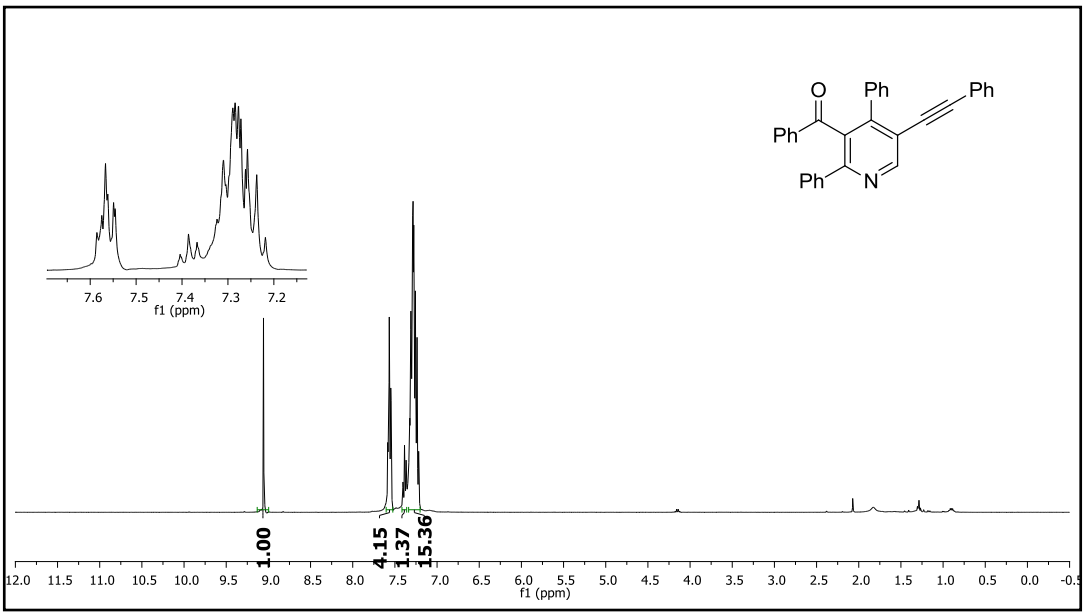

Figure 214. ^{1}H NMR spectrum of compound **57a**.

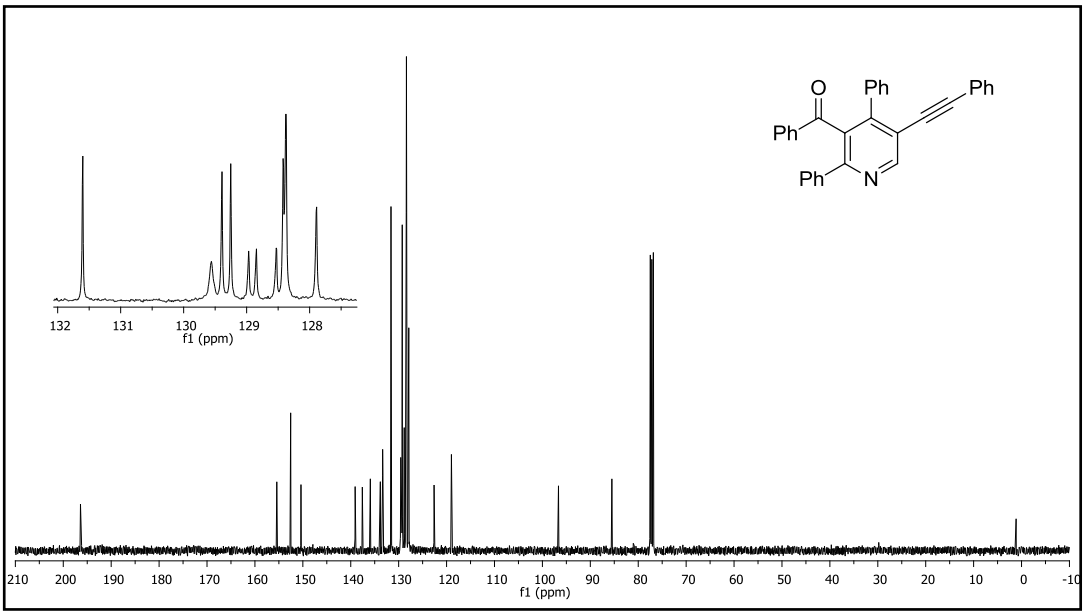

Figure 215. ^{13}C NMR spectrum of compound **57a**.

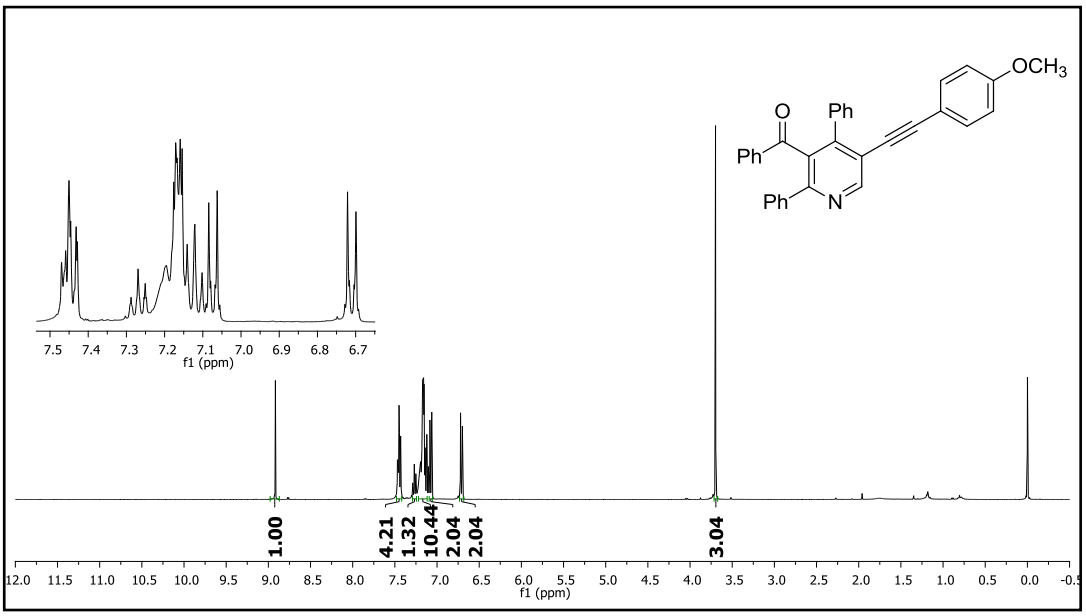

Figure 216. ^{1}H NMR spectrum of compound **57b**.

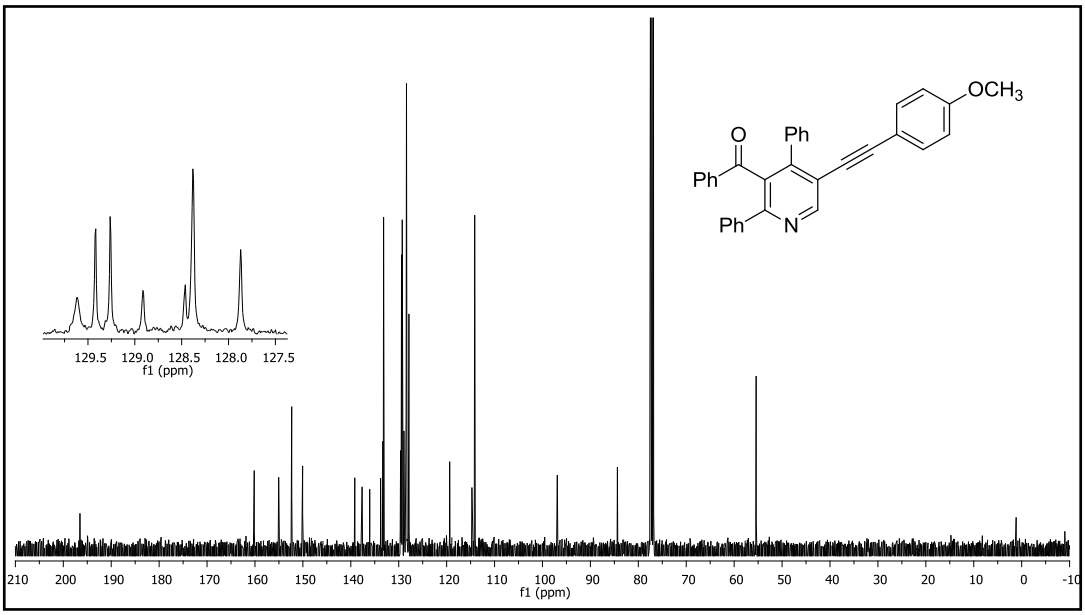

Figure 217. ^{13}C NMR spectrum of compound **57b**.

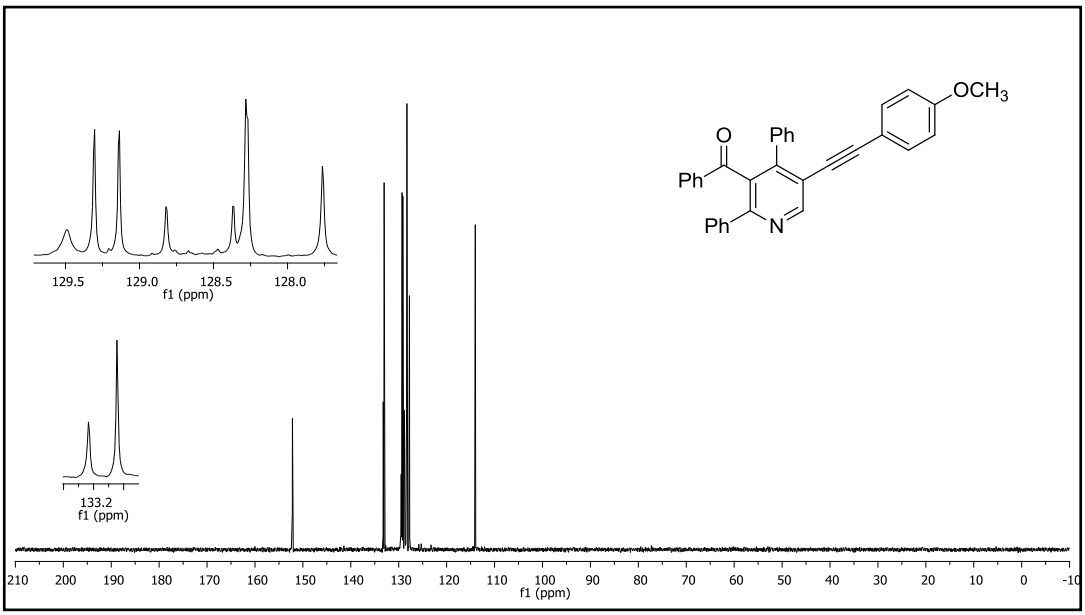

Figure 218. DEPT-90 NMR spectrum of compound **57b**.

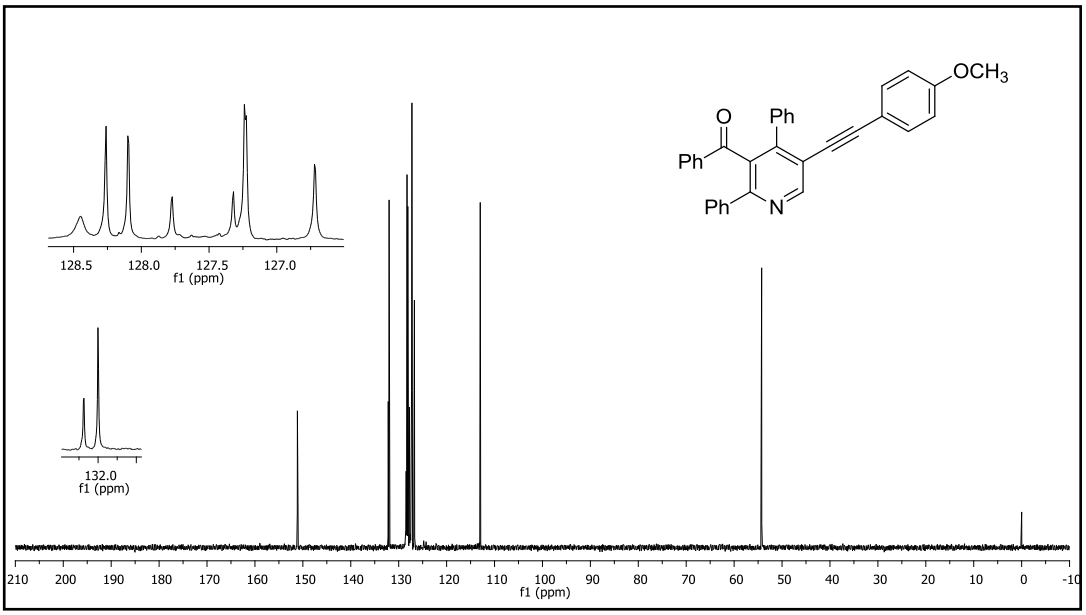

Figure 219. DEPT-135 NMR spectrum of compound **57b**.

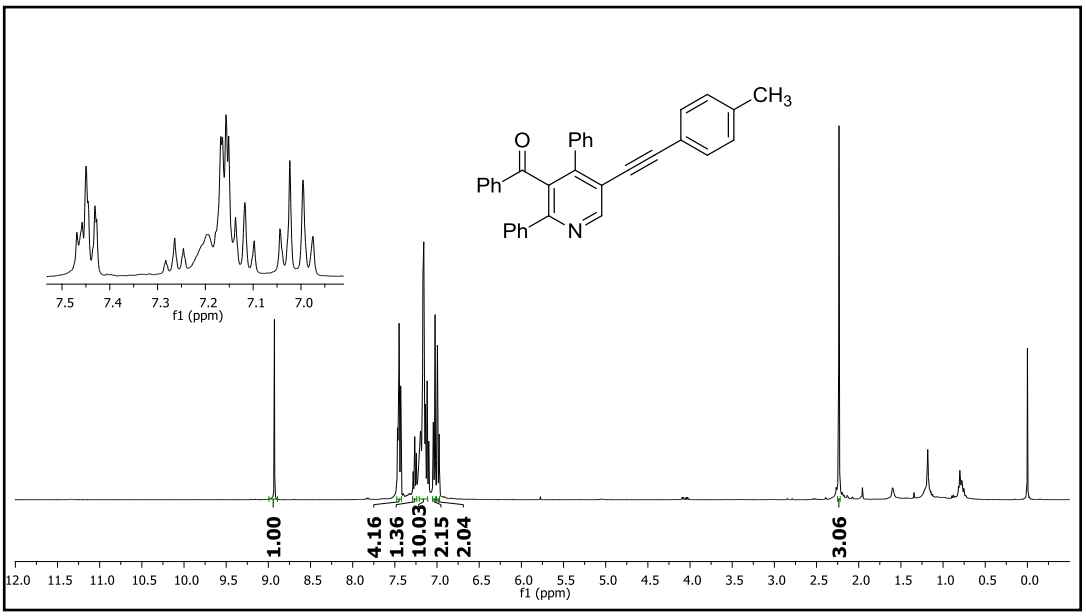

Figure 220. ^{1}H NMR spectrum of compound **57d**.

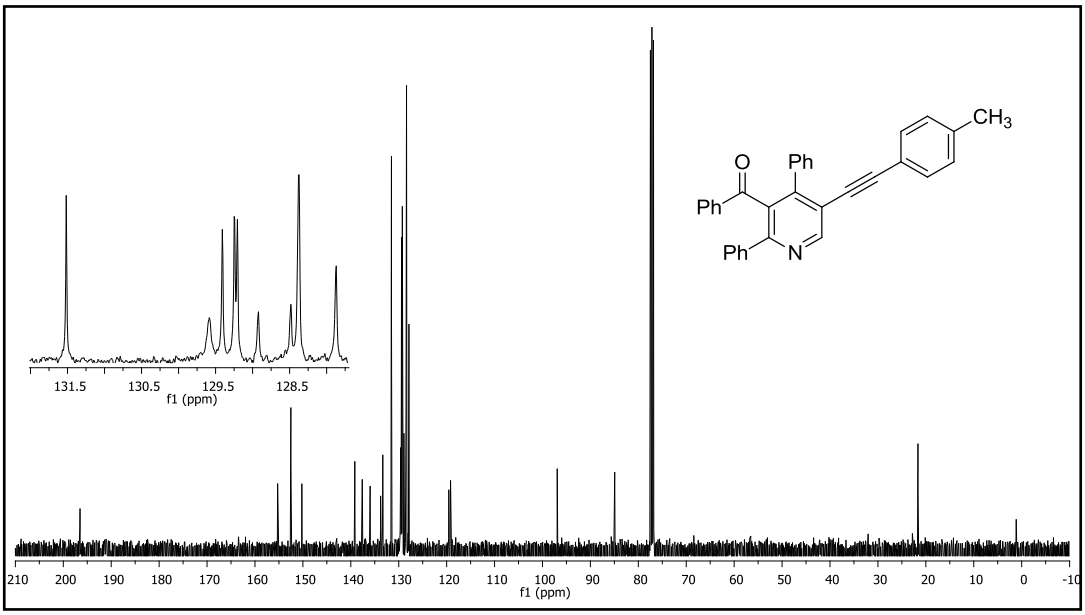

Figure 221. ^{13}C NMR spectrum of compound **57d**.

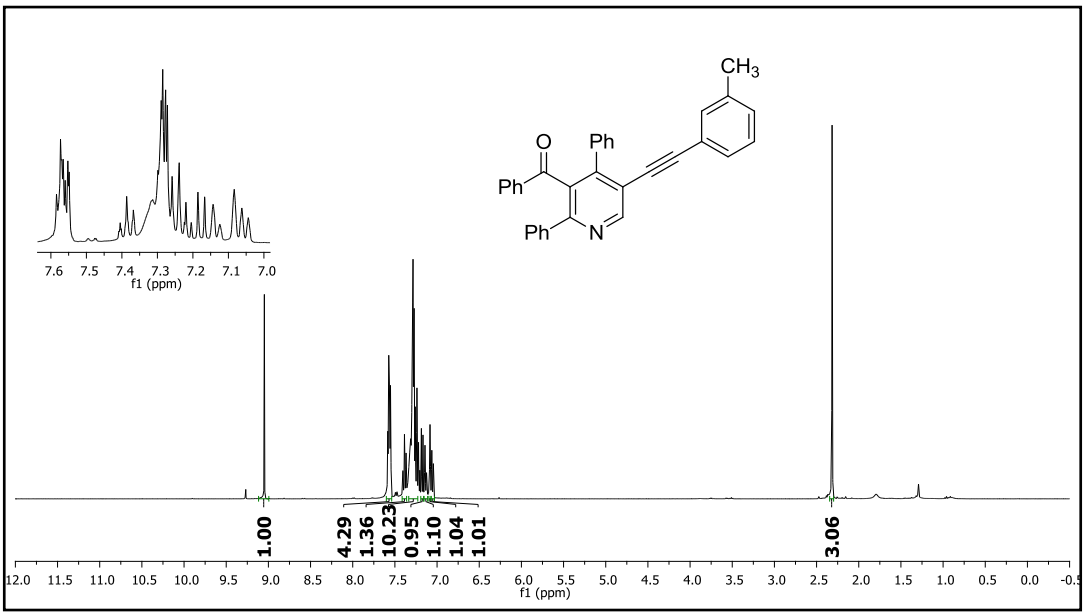

Figure 222. ^{1}H NMR spectrum of compound **57e**.

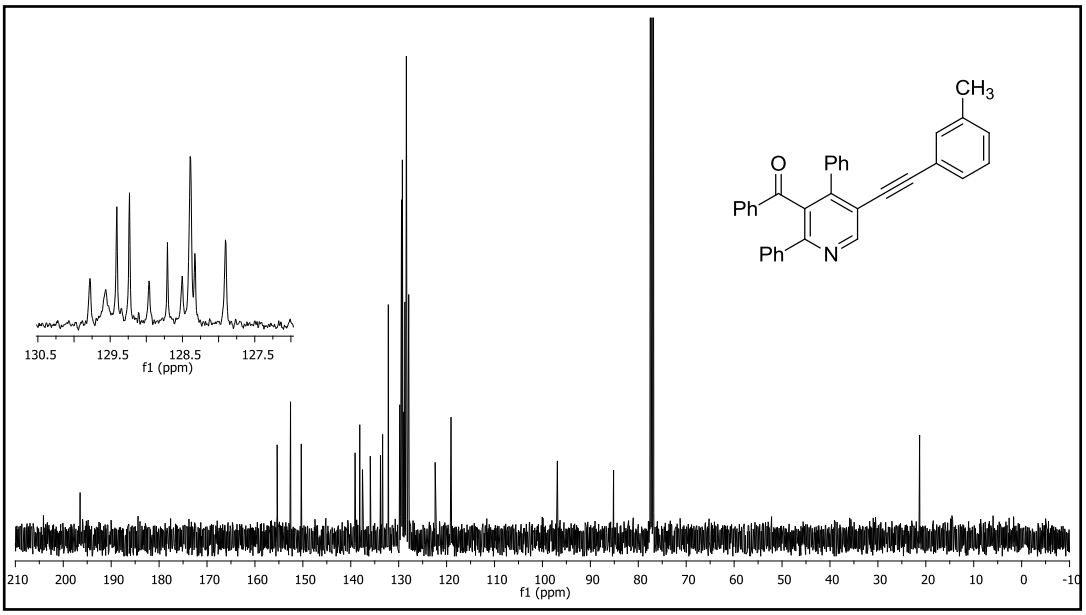

Figure 223. ^{13}C NMR spectrum of compound **57e**.

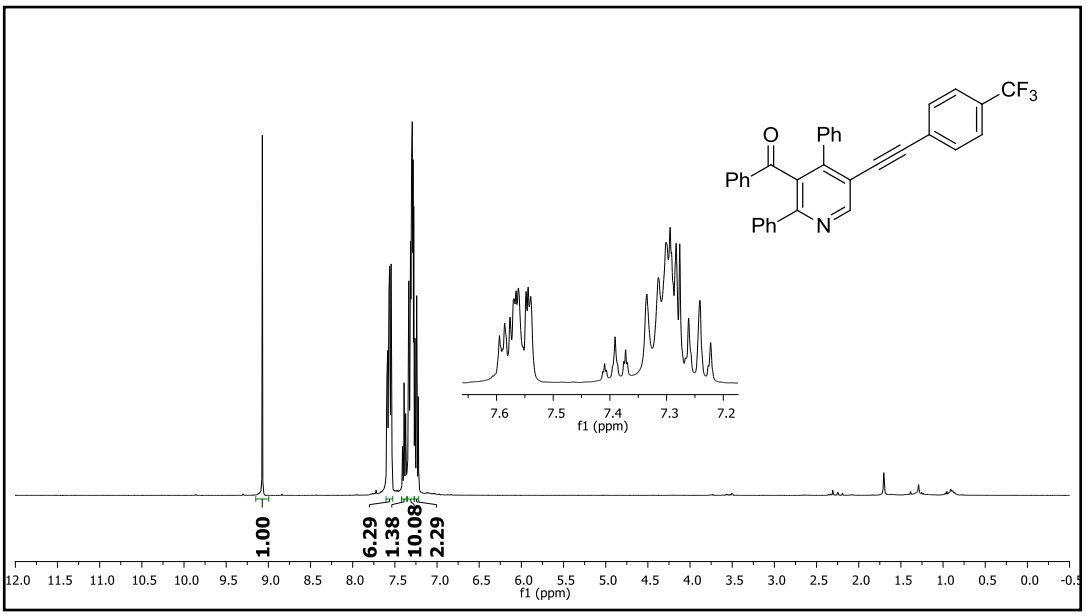

Figure 224. ^{1}H NMR spectrum of compound **57f**.

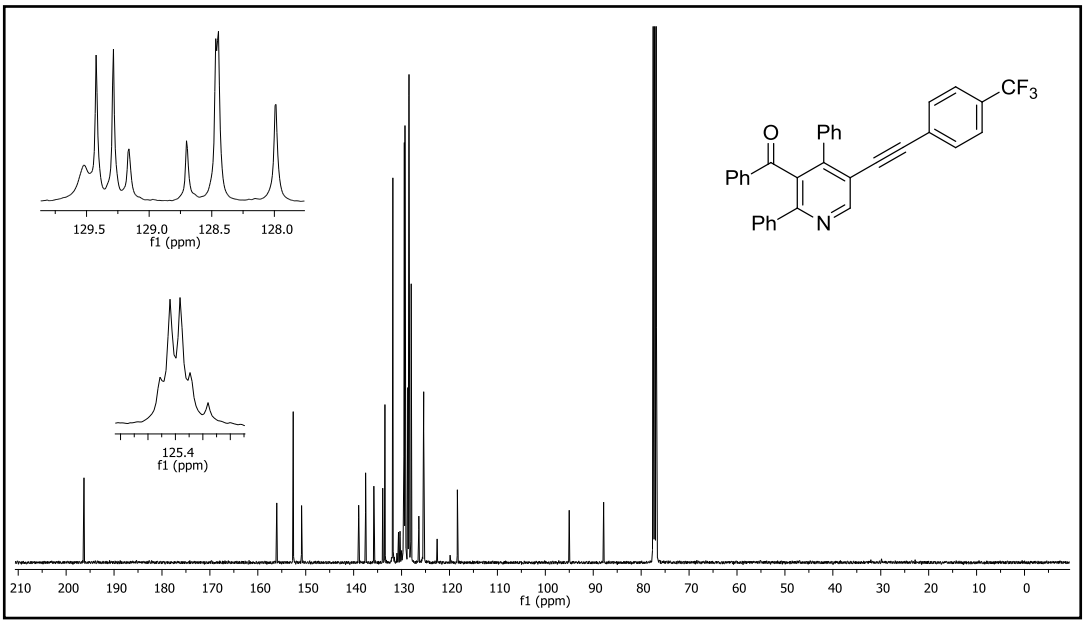

Figure 225. ^{13}C NMR spectrum of compound **57f**.

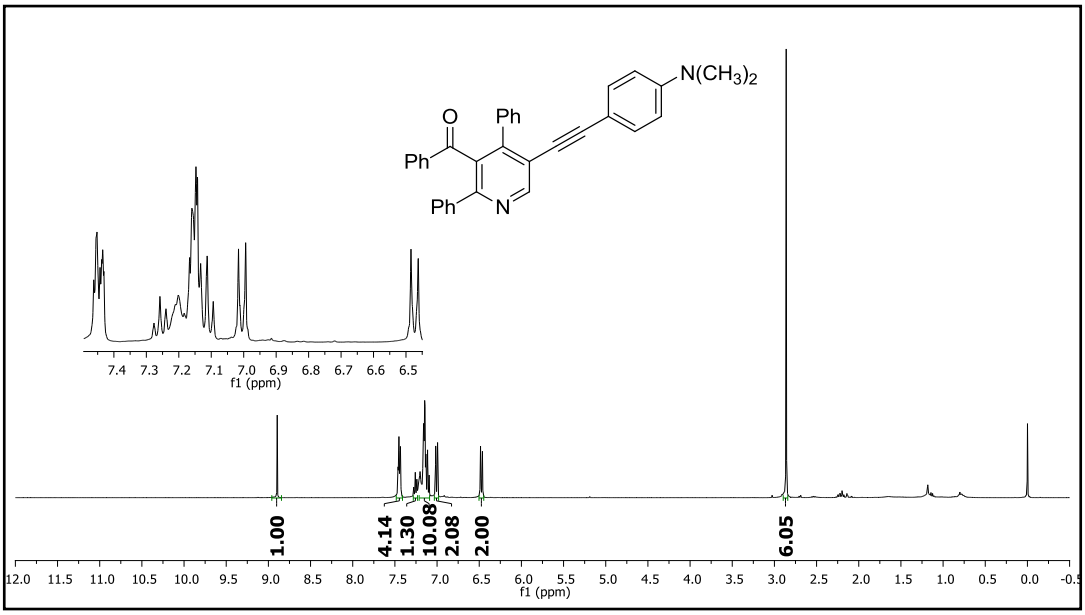

Figure 226. ^{1}H NMR spectrum of compound **57g**.

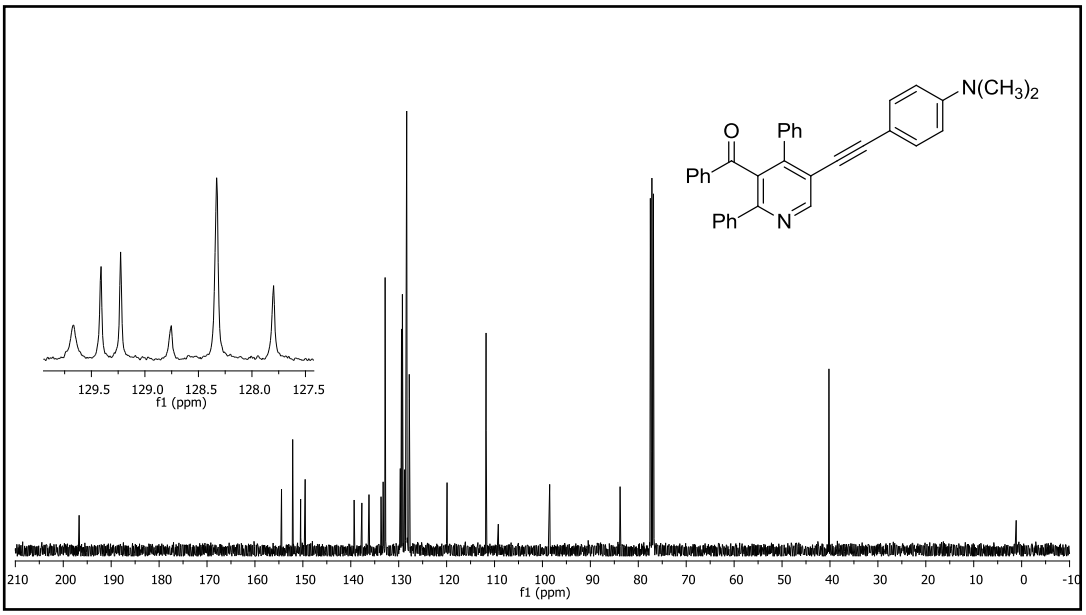

Figure 227. ^{13}C NMR spectrum of compound **57g**.

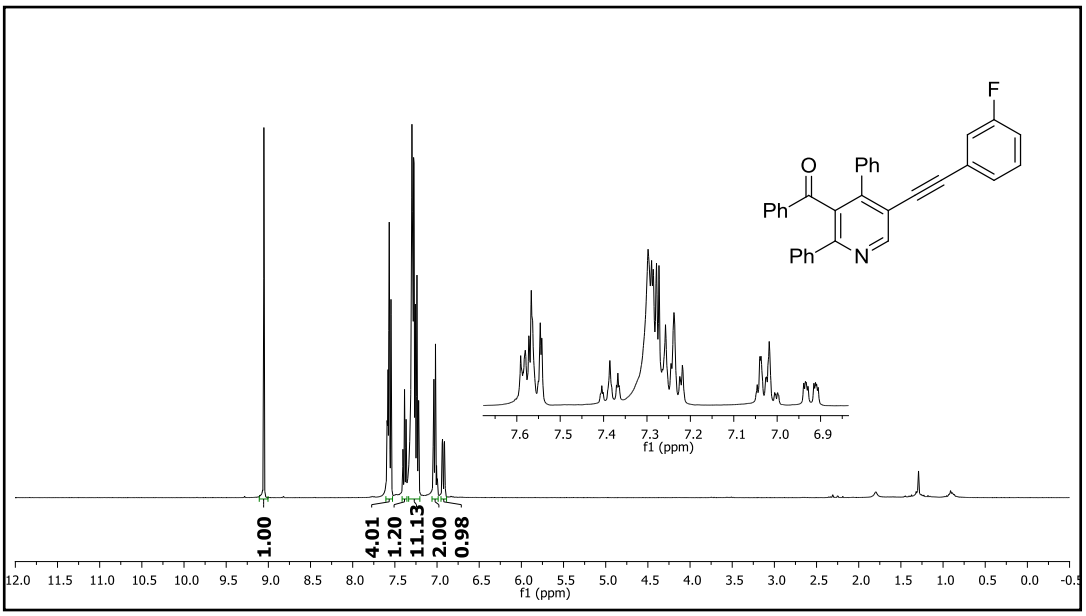

Figure 228. ^{1}H NMR spectrum of compound **57h**.

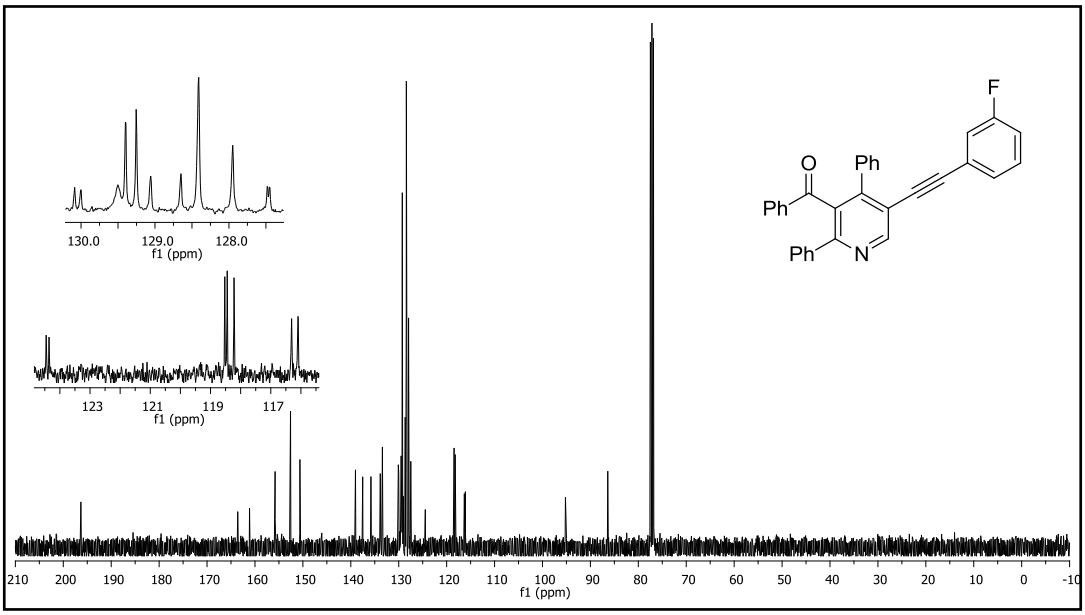

Figure 229. ^{13}C NMR spectrum of compound **57h**.

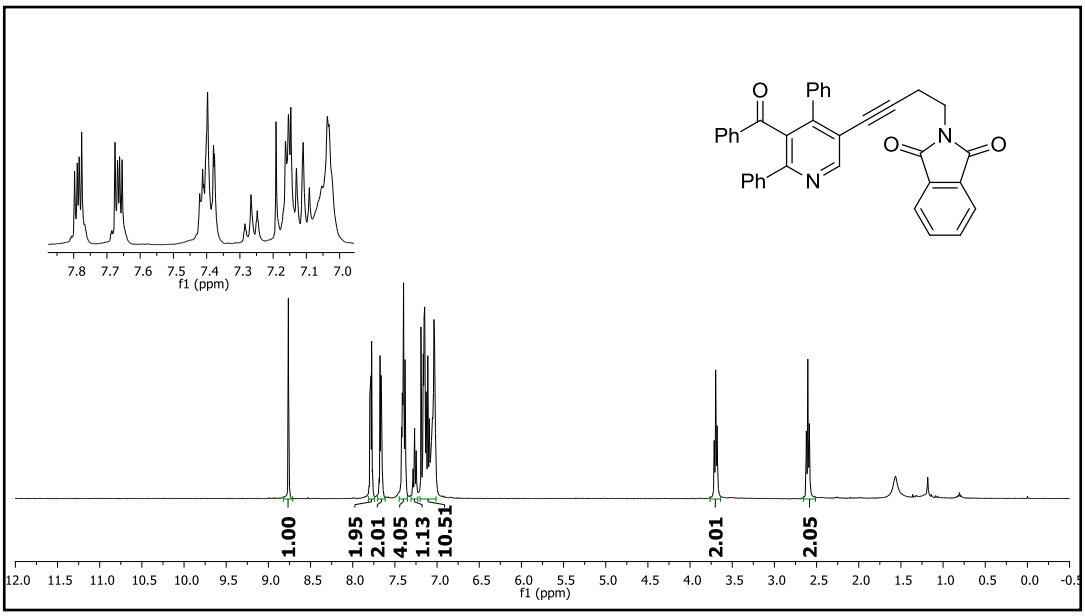

Figure 230. ^{1}H NMR spectrum of compound **57k**.

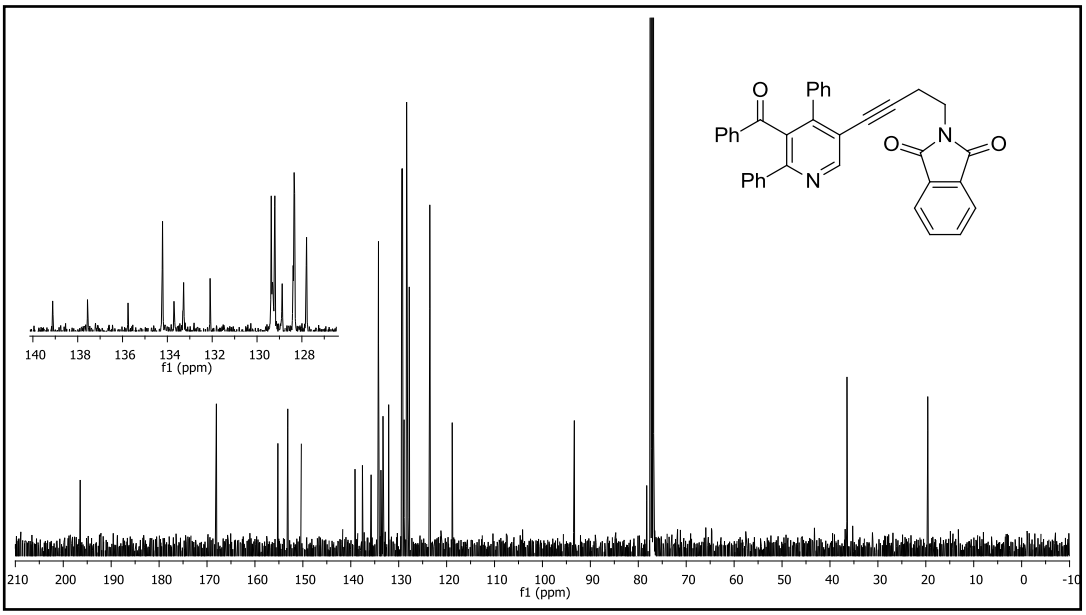

Figure 231. ^{13}C NMR spectrum of compound **57k**.

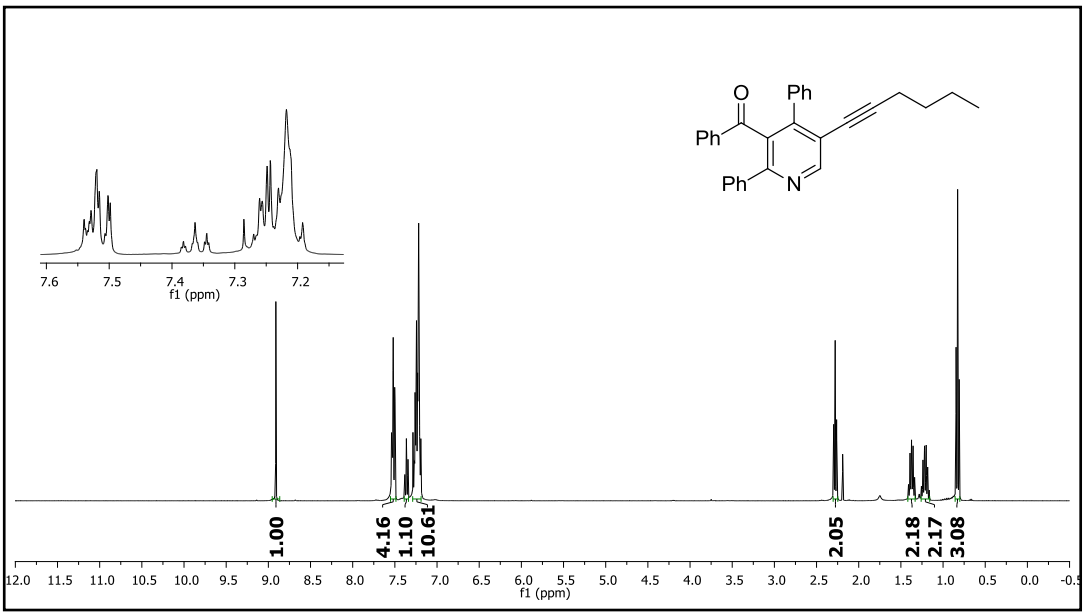

Figure 232. ^{1}H NMR spectrum of compound **57l**.

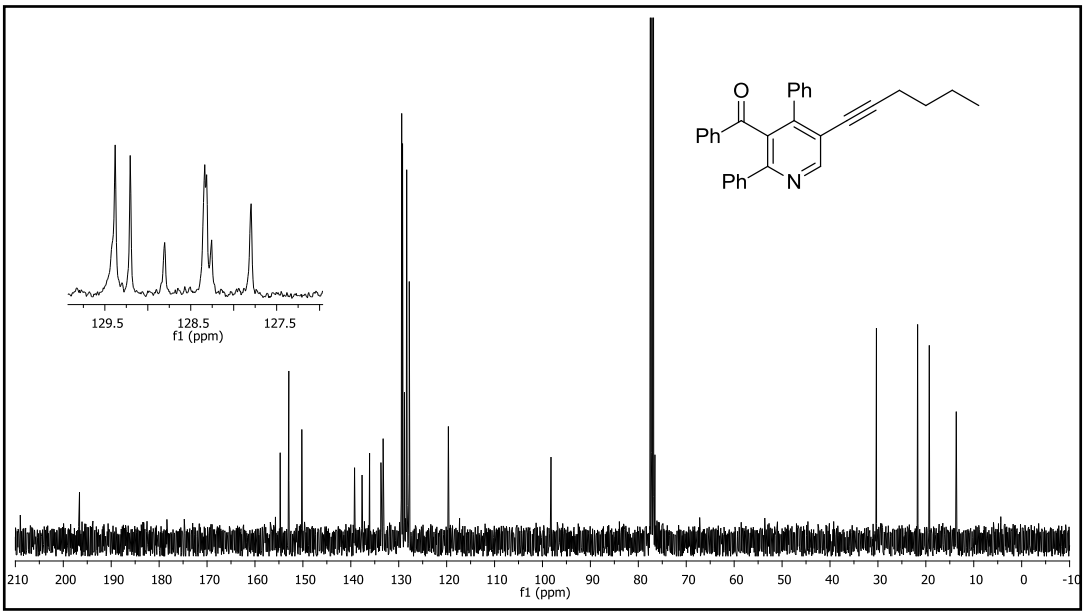

Figure 233. ^{13}C NMR spectrum of compound **57l**.

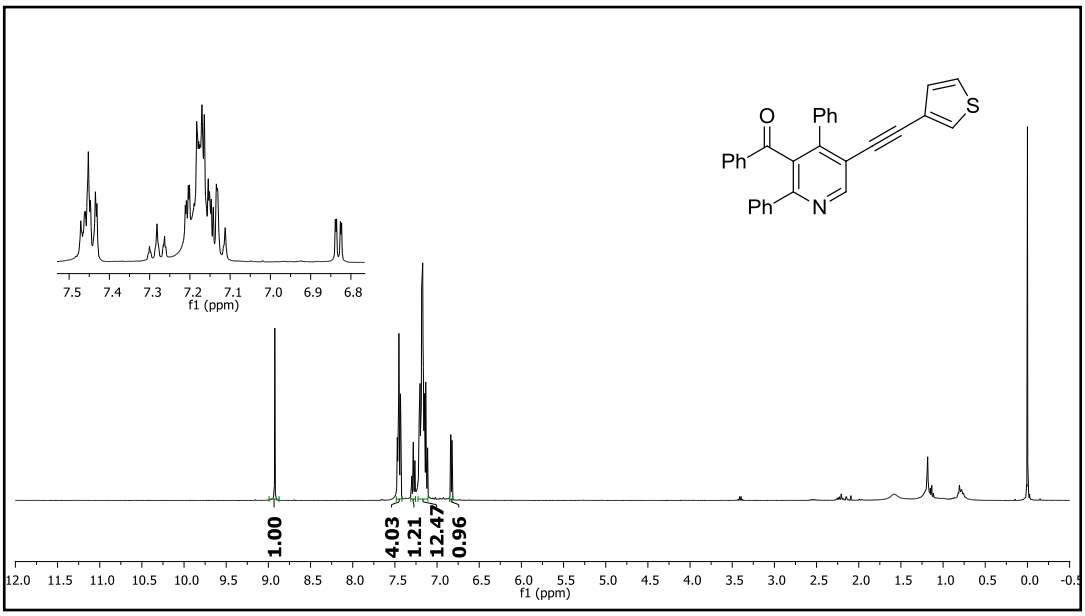

Figure 234. ^{1}H NMR spectrum of compound **57m**.

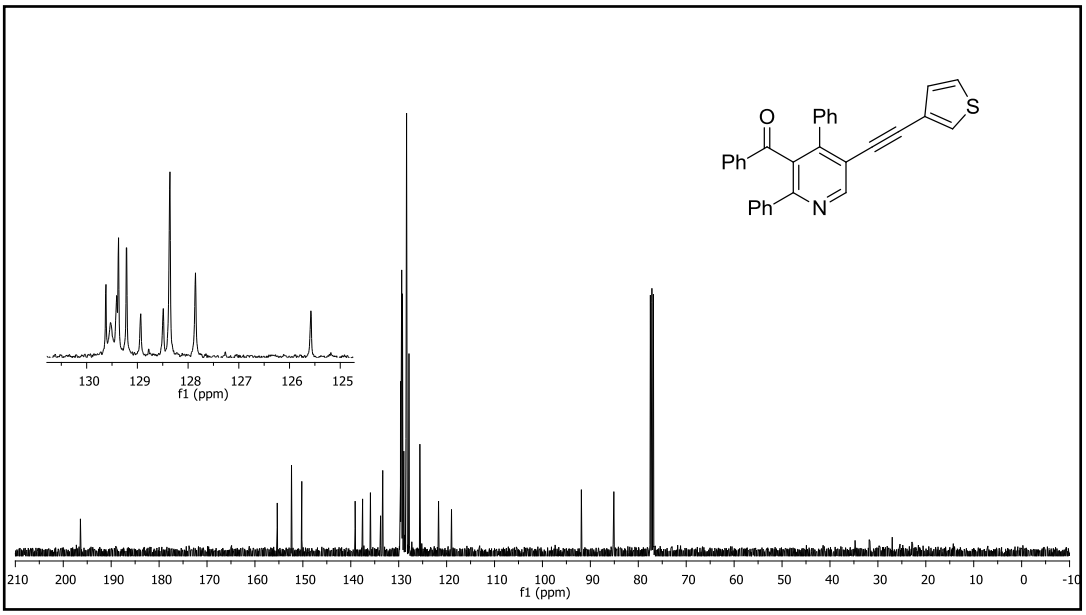

Figure 235. ^{13}C NMR spectrum of compound **57m**.

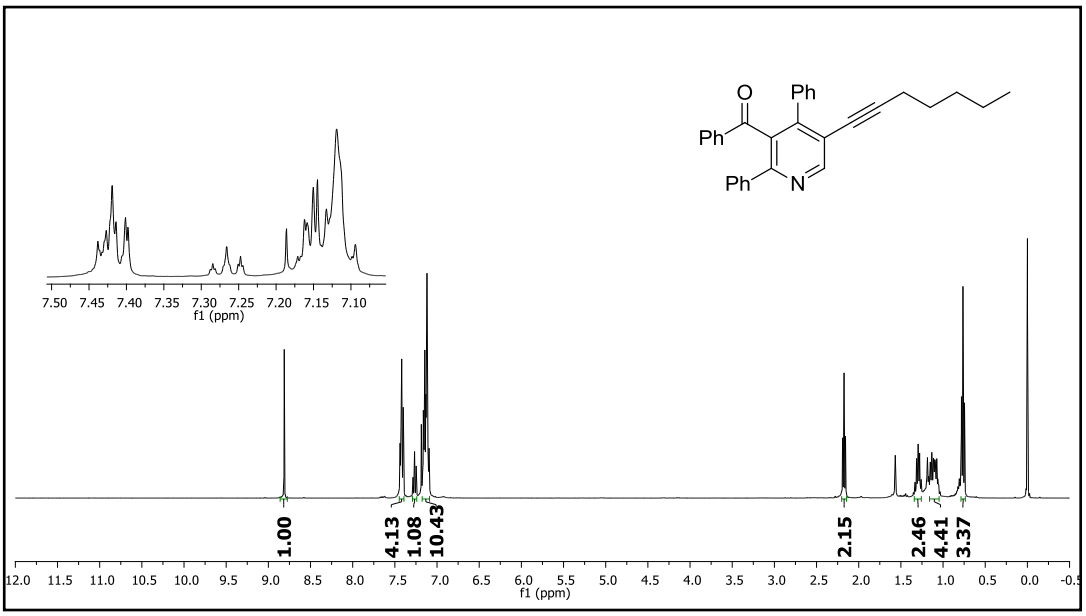

Figure 236. ^{1}H NMR spectrum of compound **57n**.

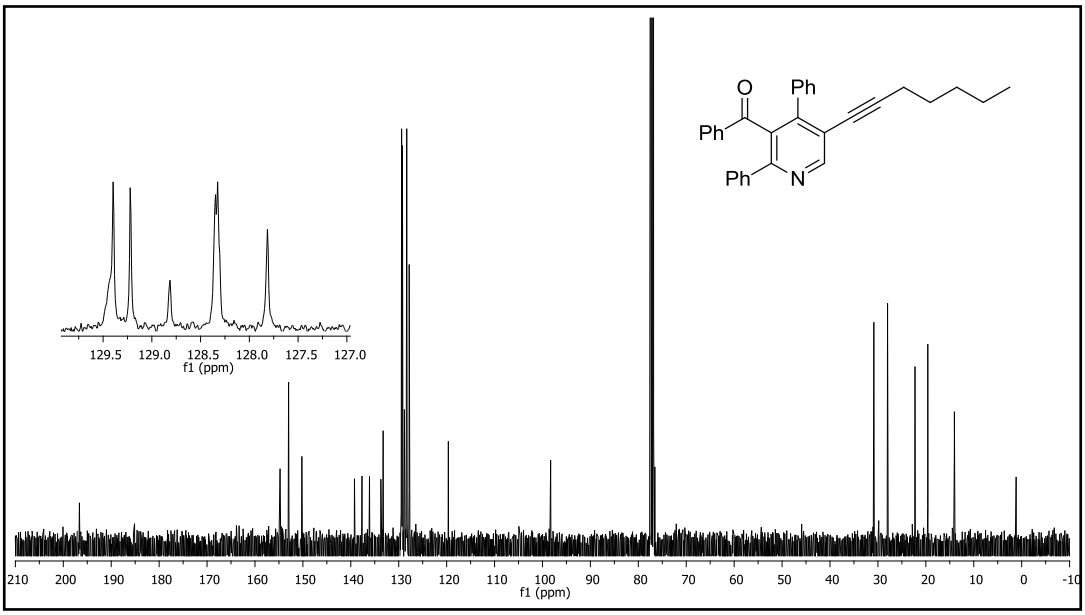

Figure 237. ^{13}C NMR spectrum of compound **57n**.

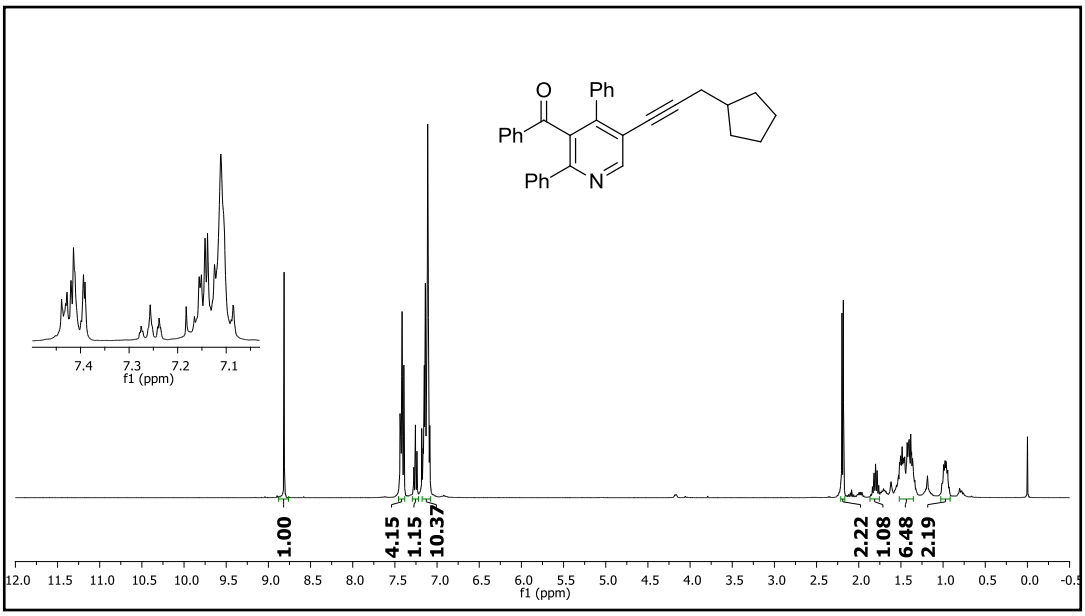

Figure 238. ^{1}H NMR spectrum of compound **57o**.

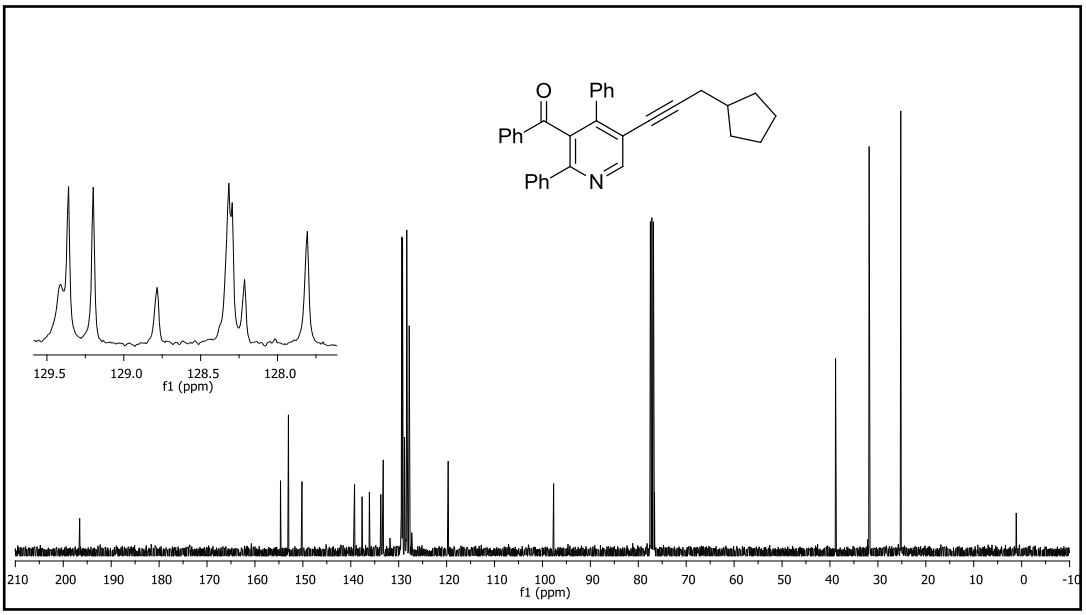

Figure 239. ^{13}C NMR spectrum of compound **57o**.

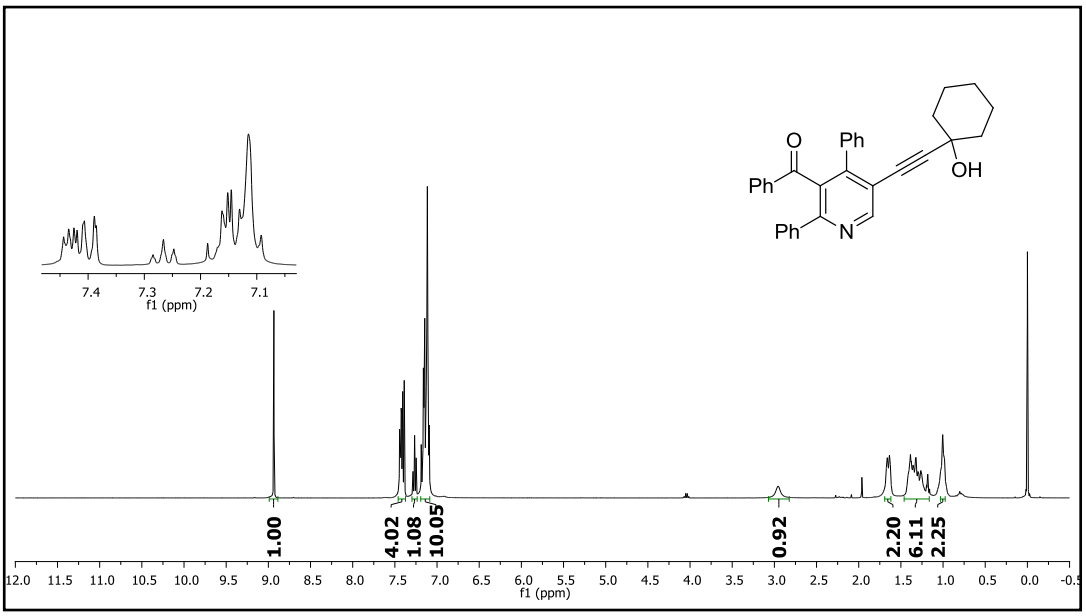

Figure 240. ^{1}H NMR spectrum of compound **57p**.

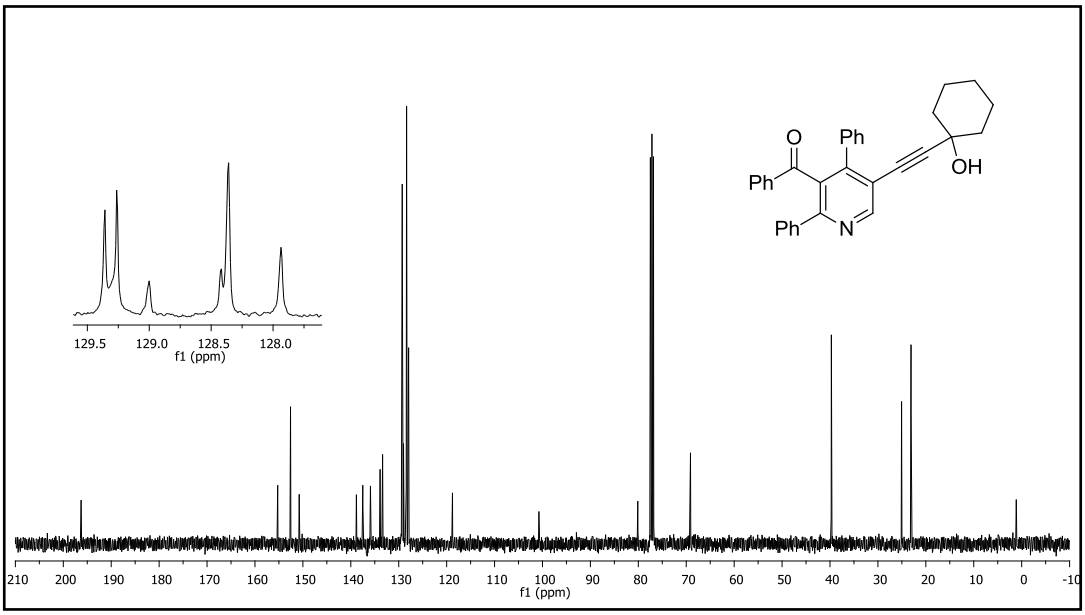

Figure 241. ^{13}C NMR spectrum of compound **57p**.

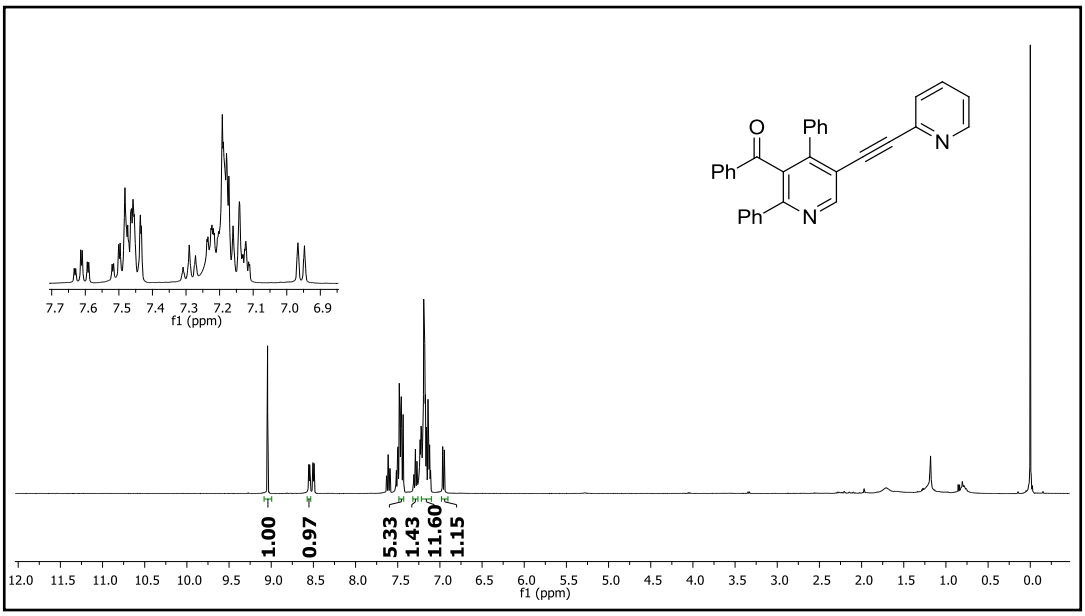

Figure 242. ^{1}H NMR spectrum of compound **57q**.

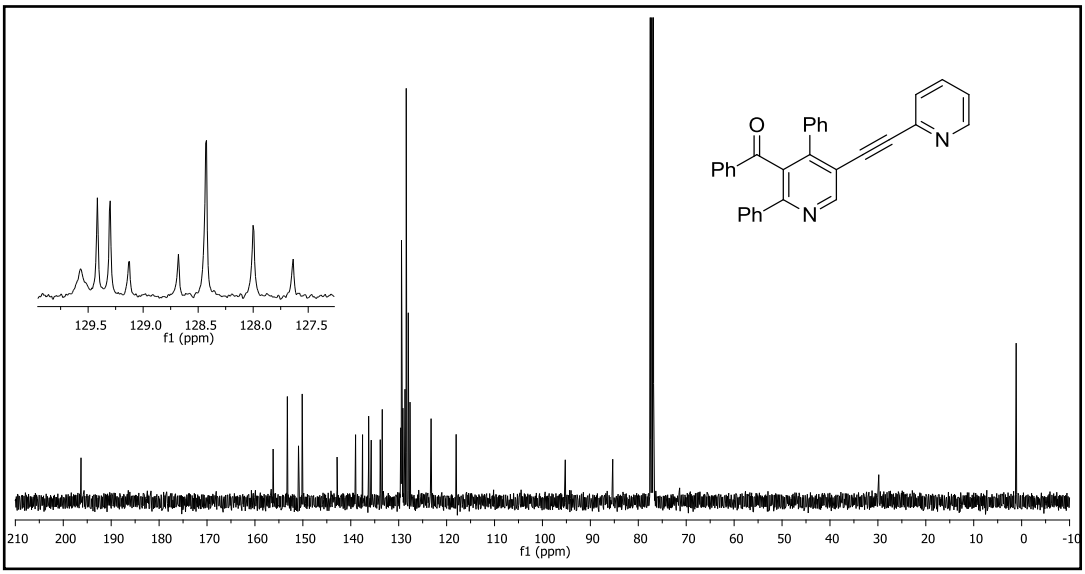

Figure 243. ^{13}C NMR spectrum of compound **57q**.

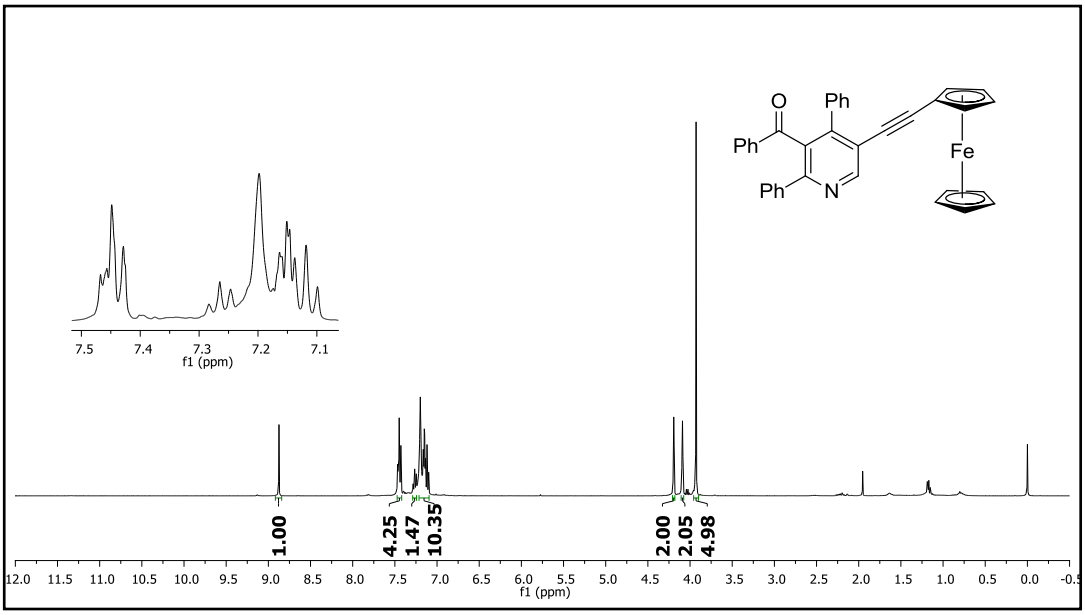

Figure 244. ^{1}H NMR spectrum of compound **57r**.

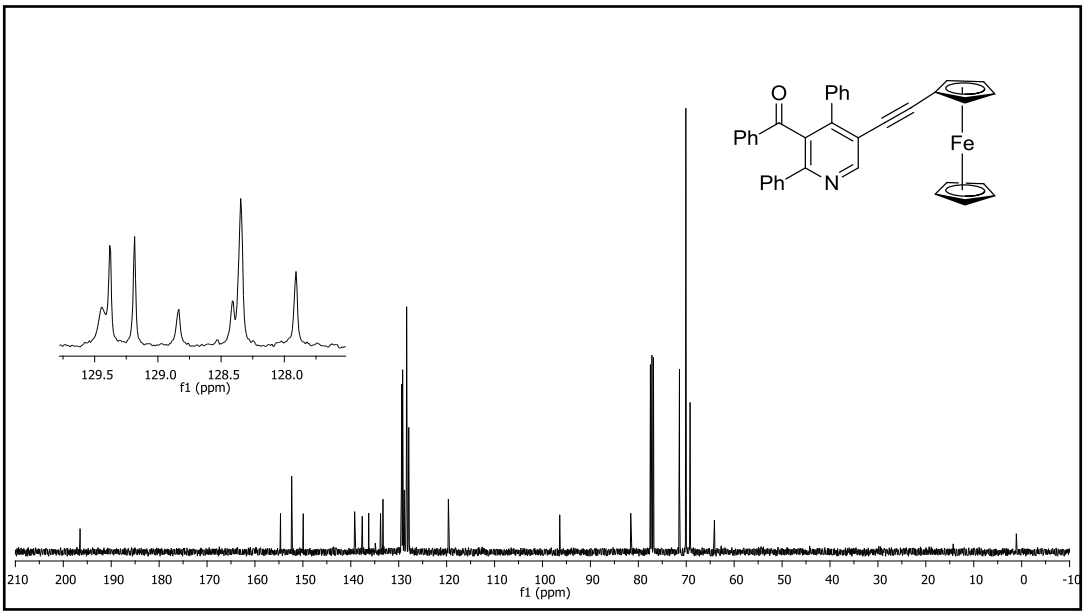

Figure 245. ^{13}C NMR spectrum of compound **57r**.

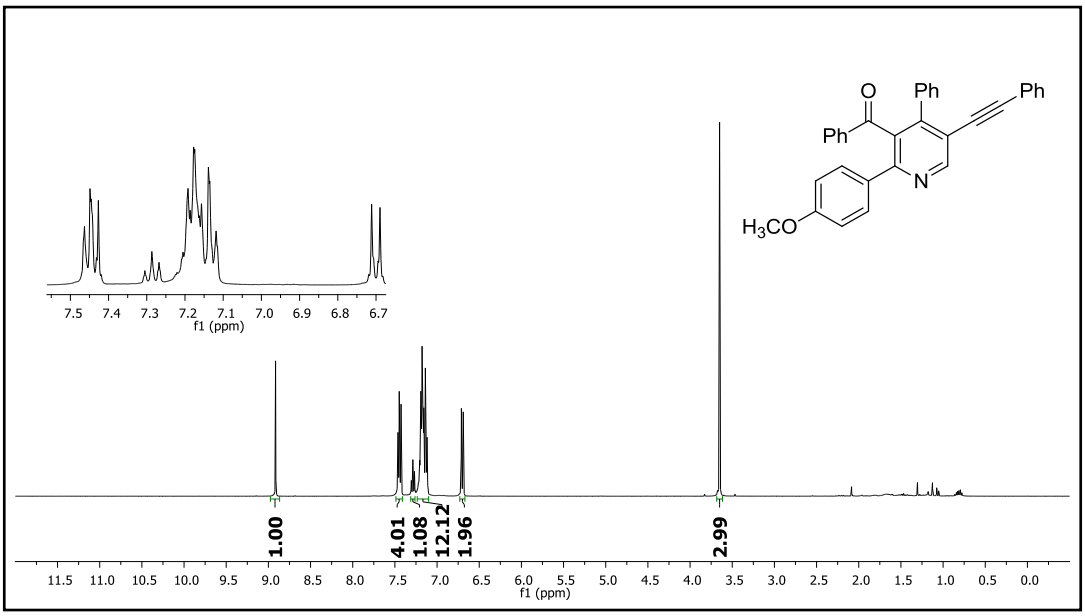

Figure 246. ^{1}H NMR spectrum of compound **57ba**.

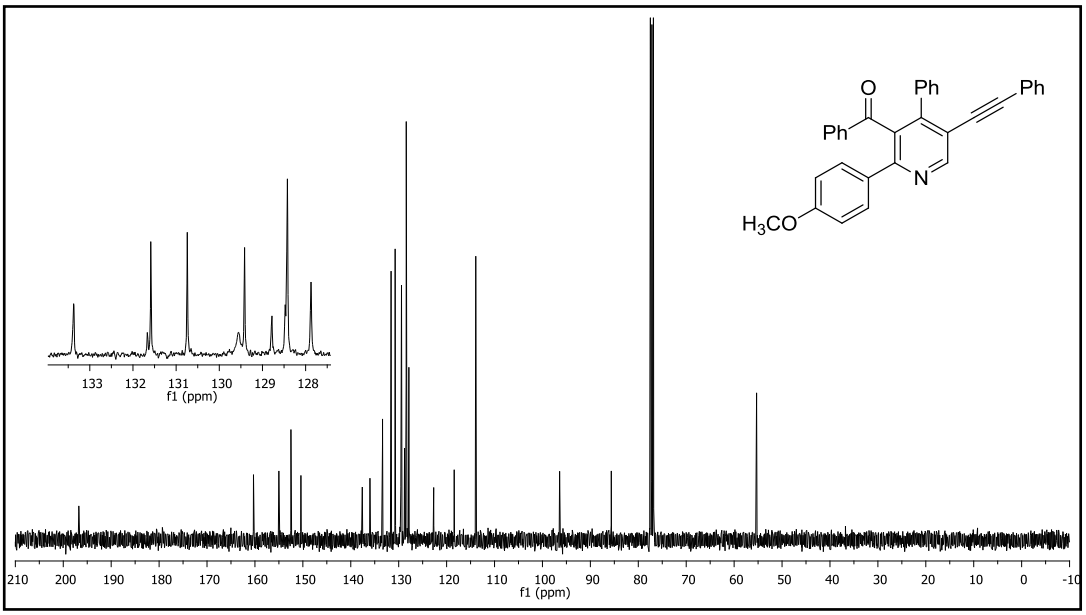

Figure 247. ^{13}C NMR spectrum of compound **57ba**.

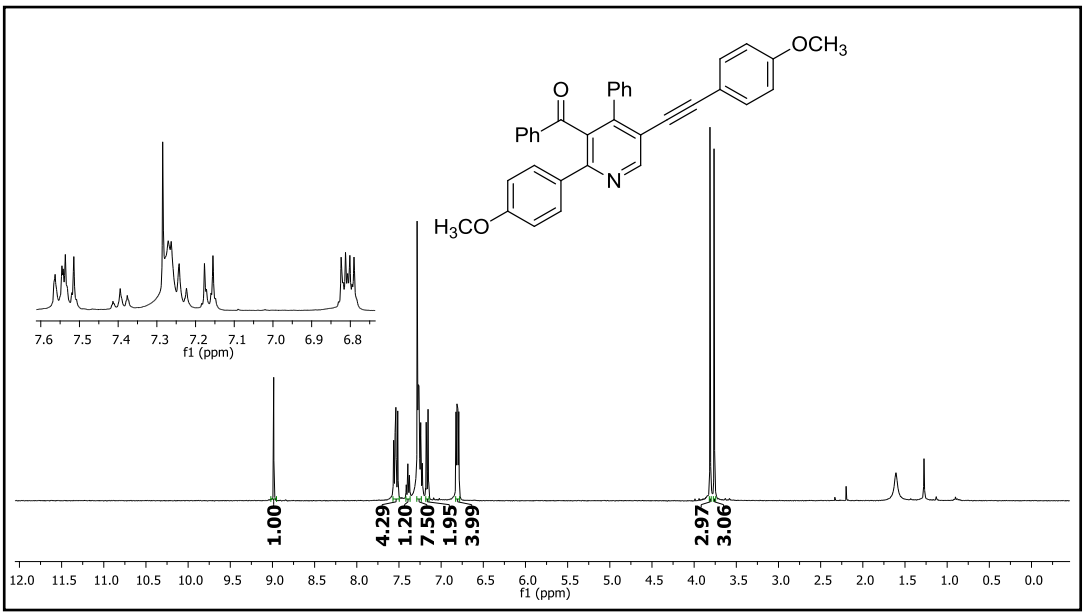

Figure 248. ^{1}H NMR spectrum of compound **57bb**.

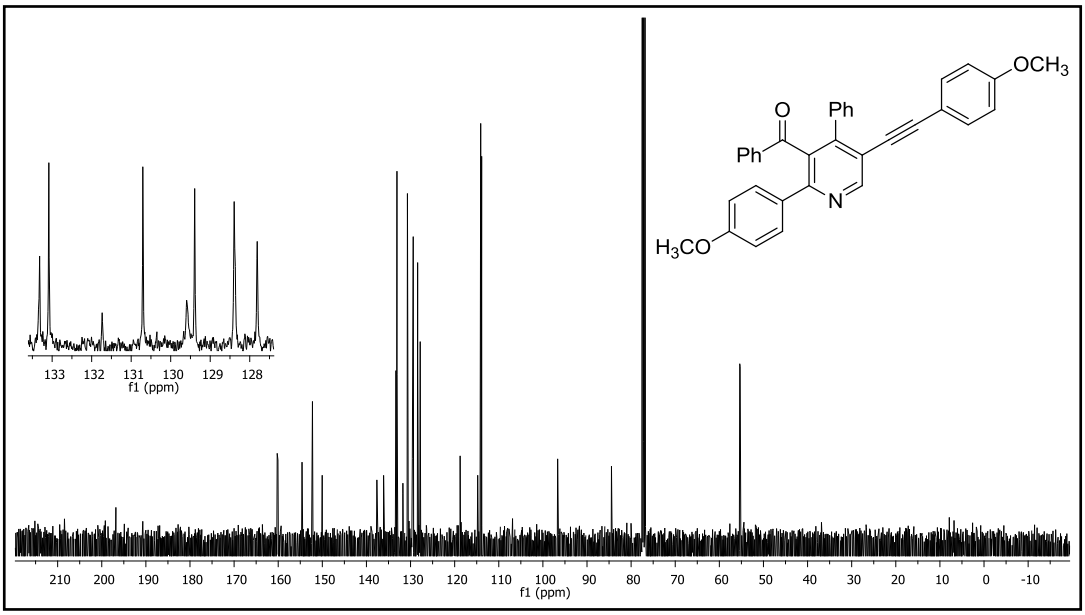

Figure 249. ^{13}C NMR spectrum of compound **57bb**.

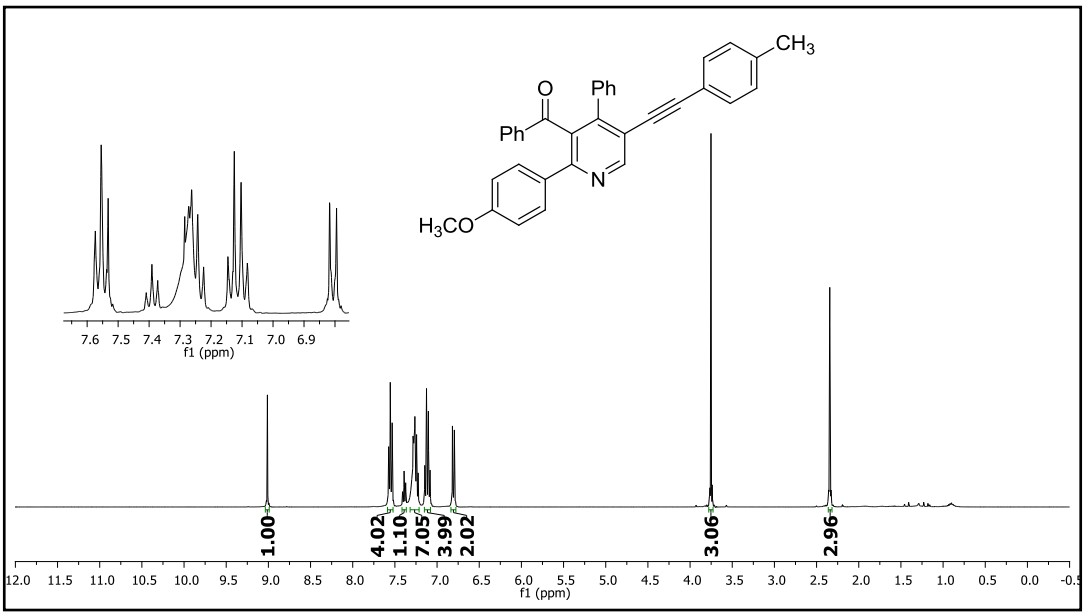

Figure 250. ^{1}H NMR spectrum of compound **57bd**.

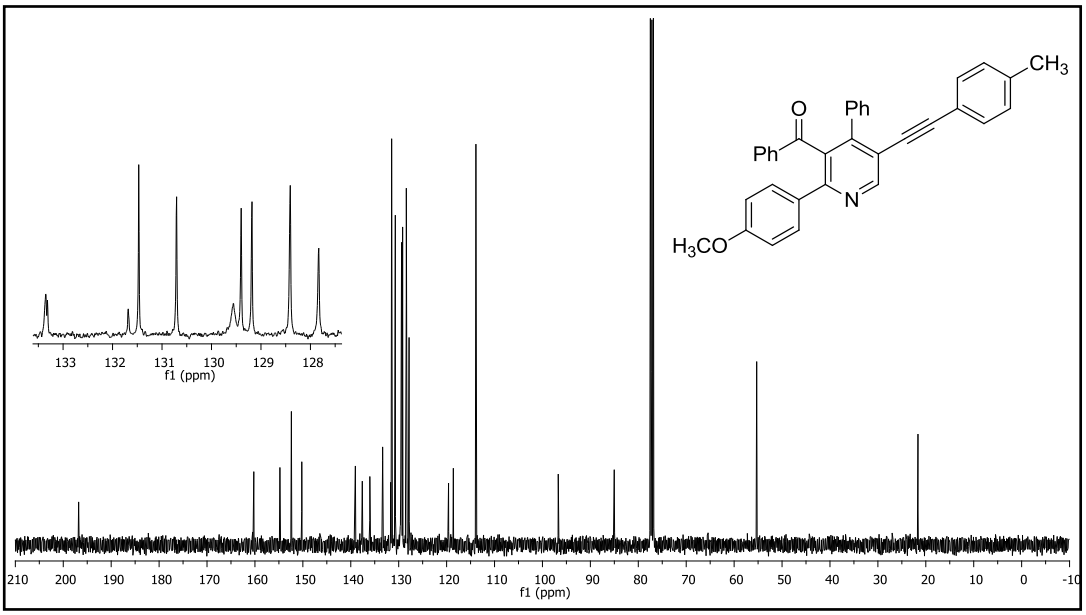

Figure 251. ^{13}C NMR spectrum of compound **57bd**.

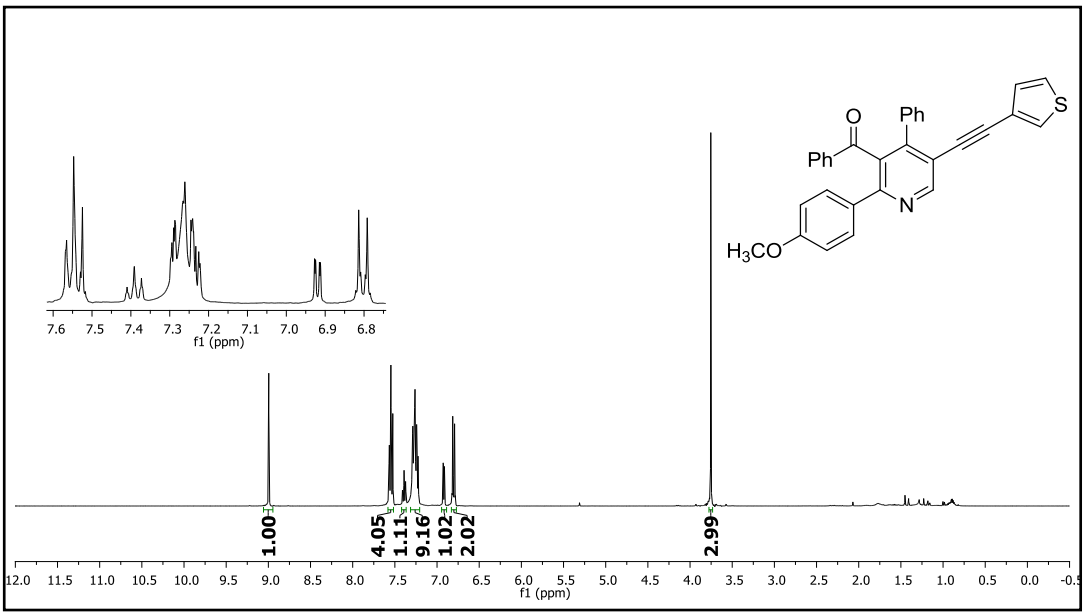

Figure 252. ^{1}H NMR spectrum of compound **57bm**.

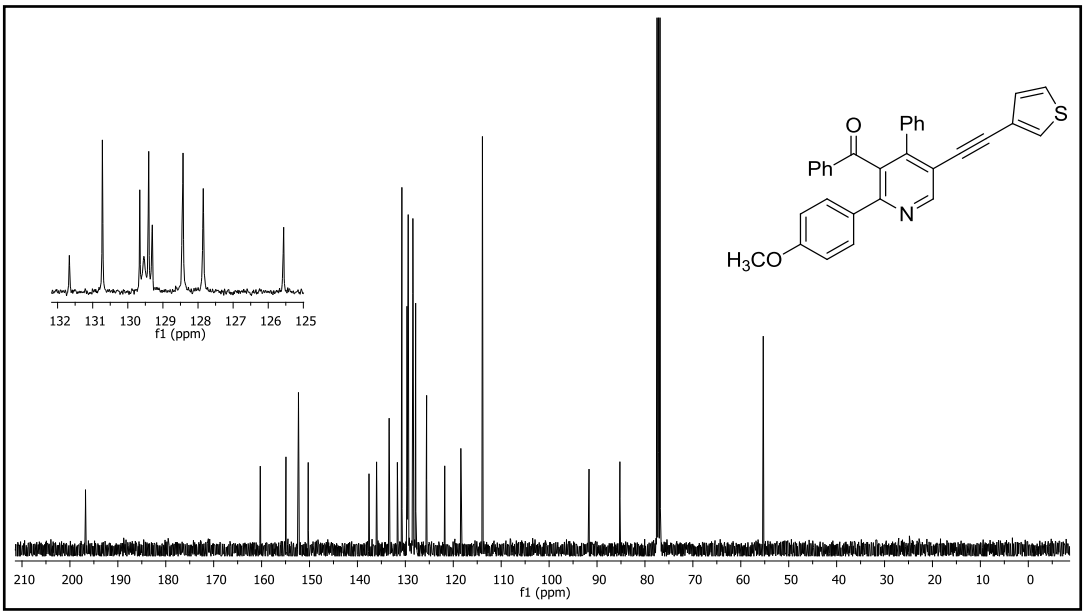

Figure 253. ^{13}C NMR spectrum of compound **57bm**.

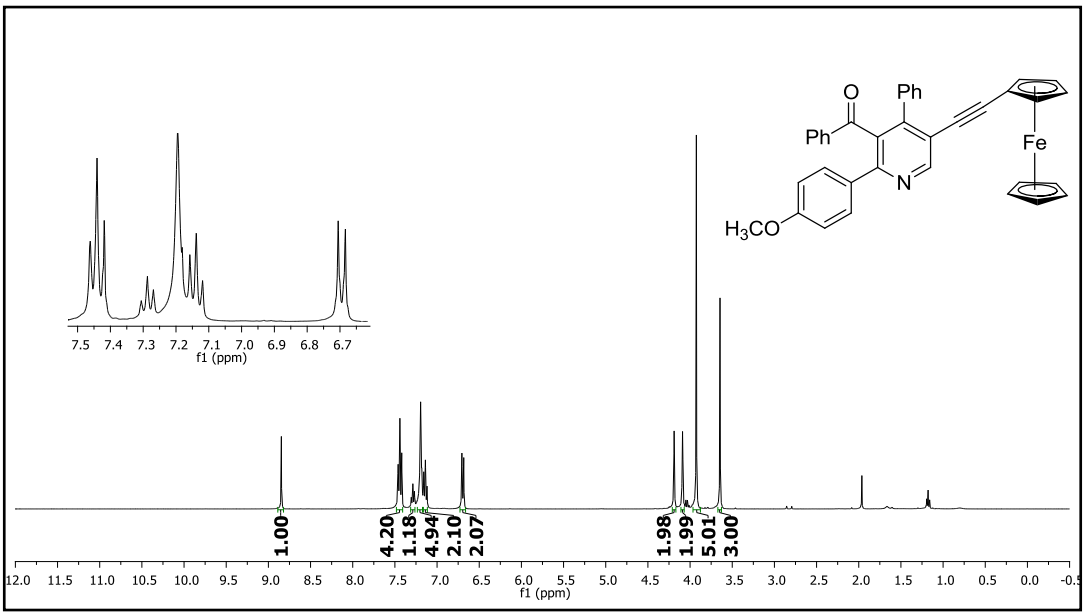

Figure 254. ^{1}H NMR spectrum of compound **57br**.

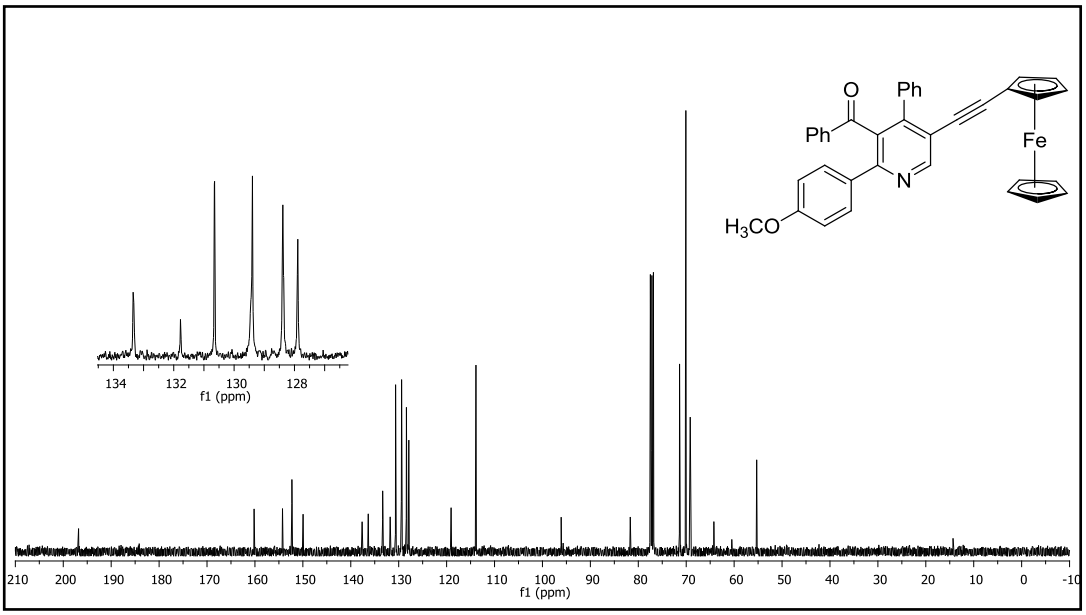

Figure 255. ^{13}C NMR spectrum of compound **57br**.

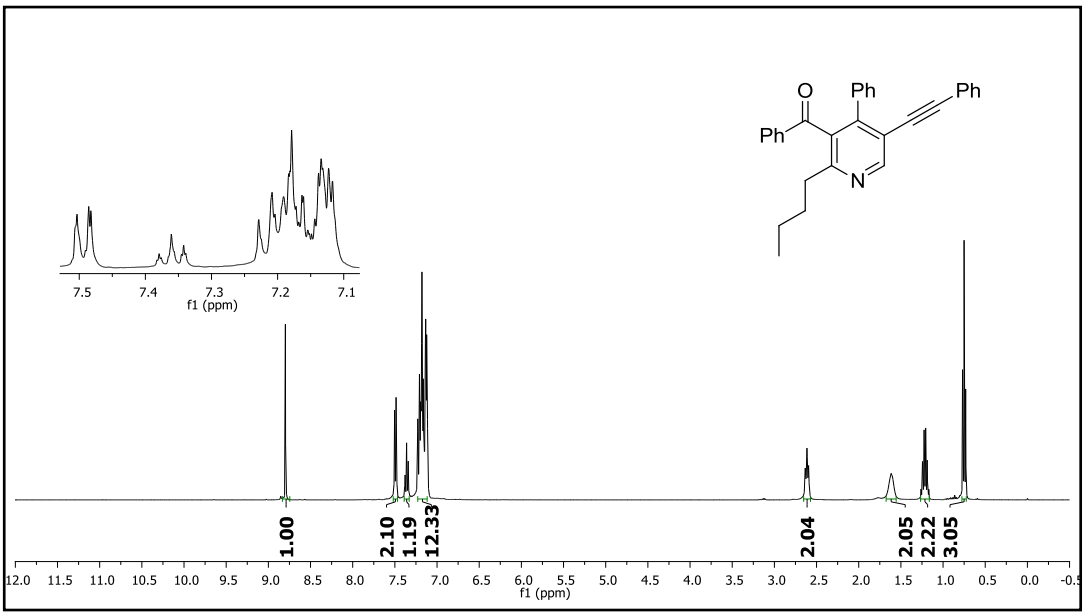

Figure 256. ^{1}H NMR spectrum of compound **57la**.

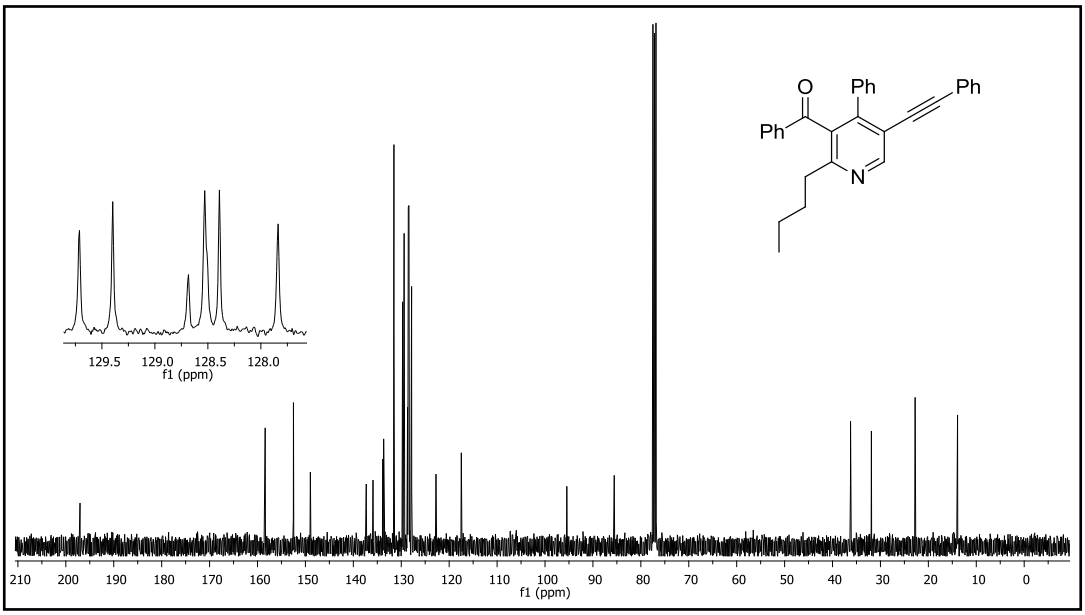

Figure 257. ^{13}C NMR spectrum of compound **57la**.

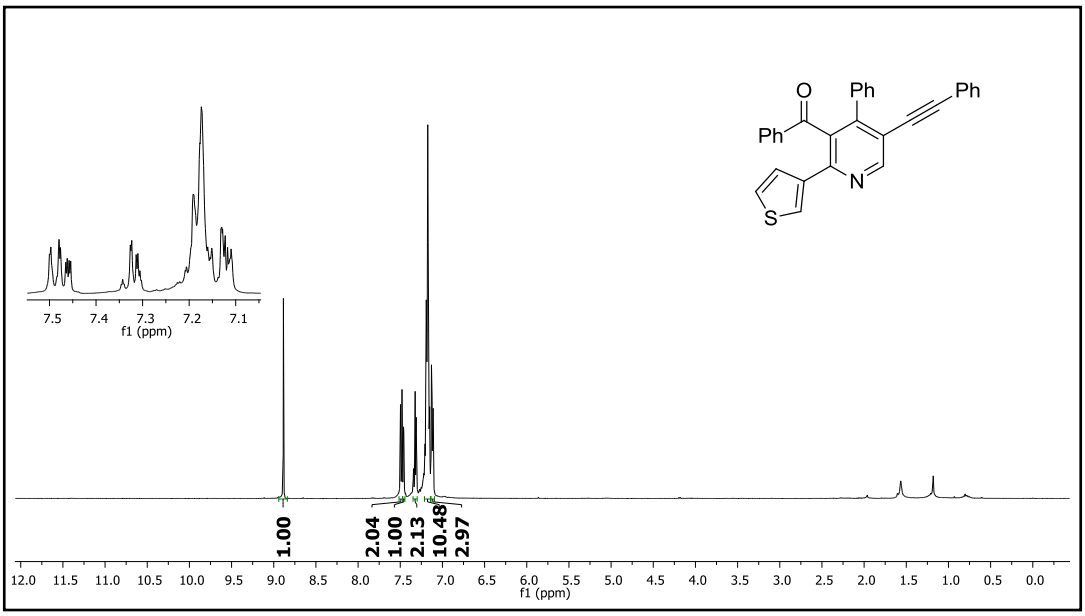

Figure 258. ^{1}H NMR spectrum of compound **57ma**.

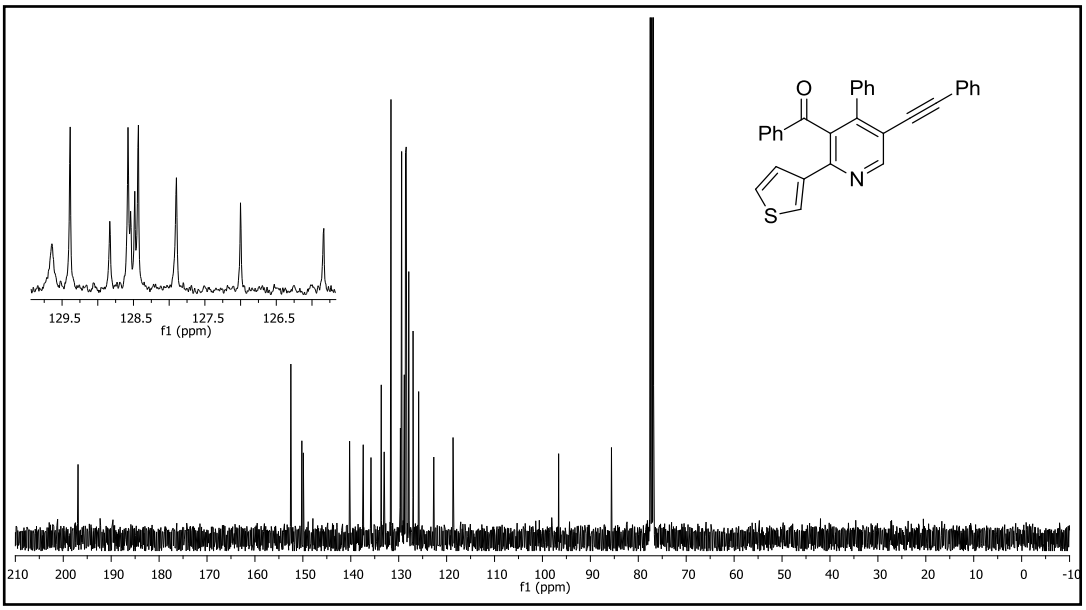

Figure 259. ^{13}C NMR spectrum of compound **57ma**.

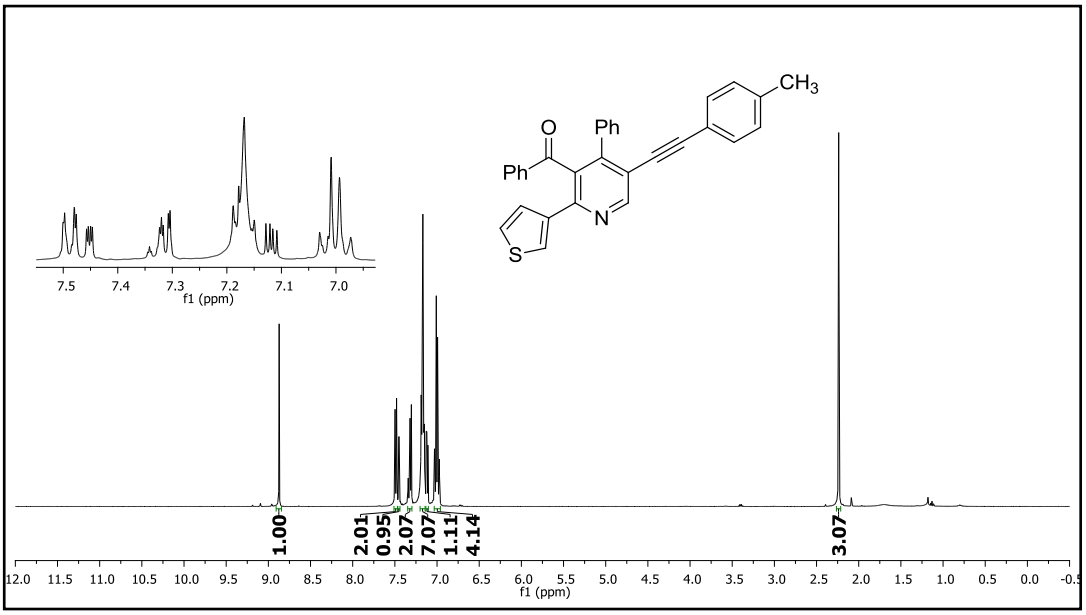

Figure 260. ^{1}H NMR spectrum of compound **57md**.

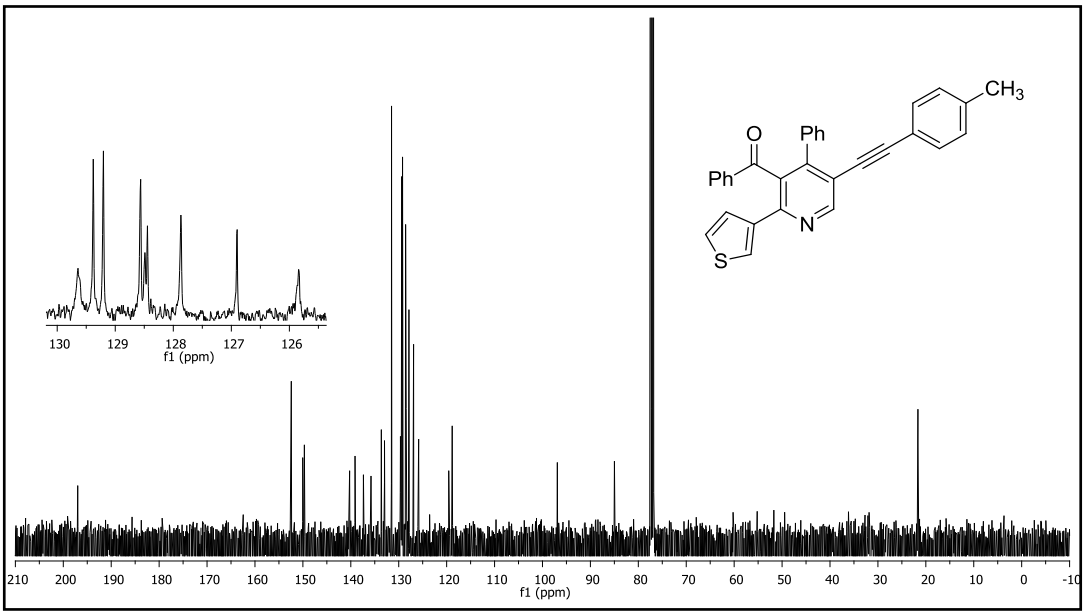

Figure 261. ^{13}C NMR spectrum of compound **57md**.

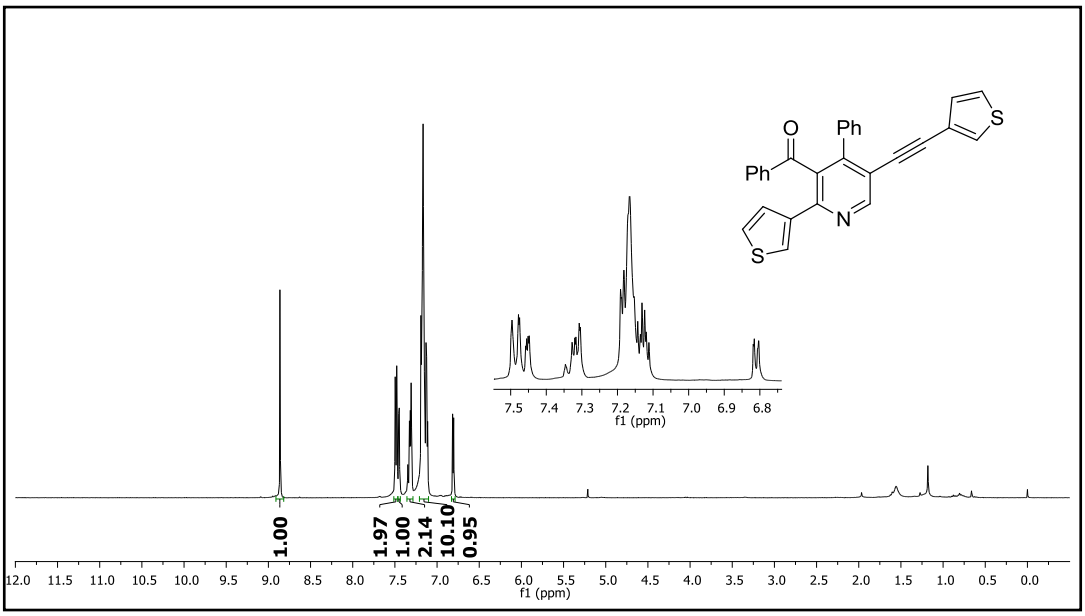

Figure 262. ^{1}H NMR spectrum of compound **57mm**.

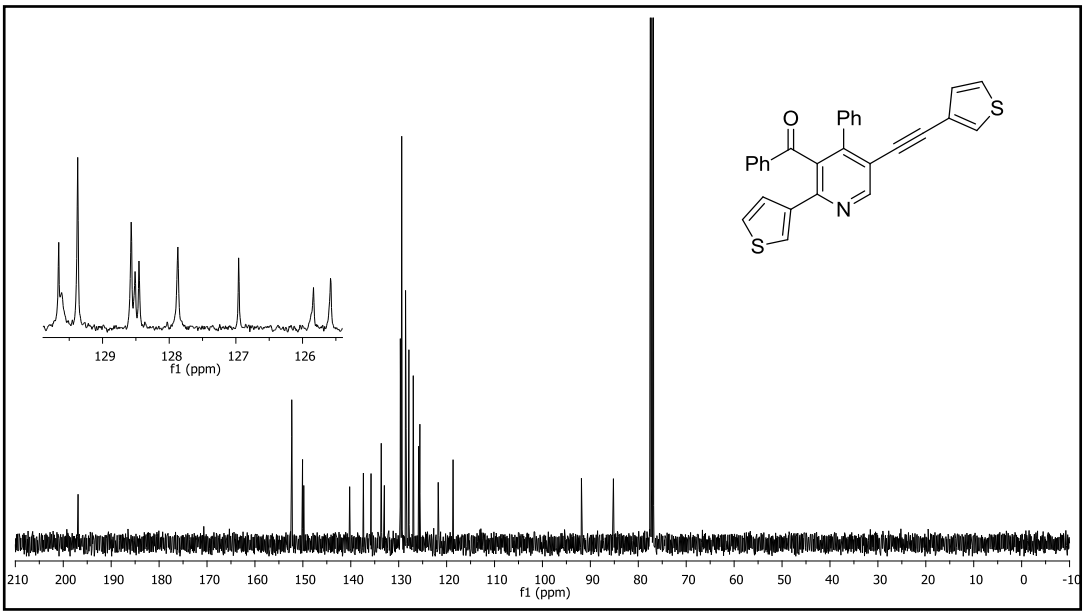

Figure 263. ^{13}C NMR spectrum of compound **57mm**.

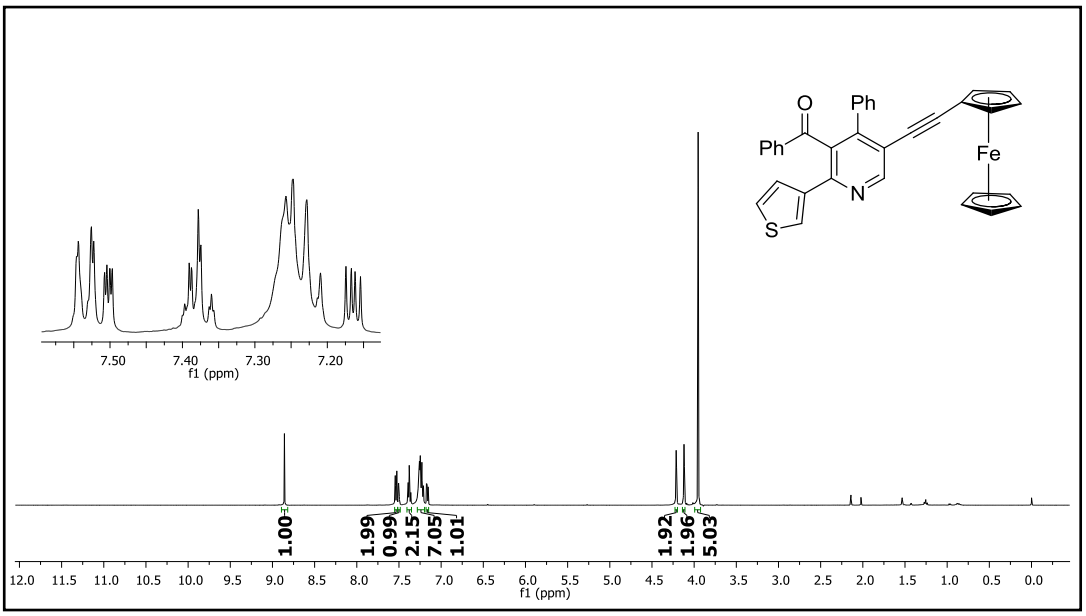

Figure 264. ^{1}H NMR spectrum of compound **57mr**.

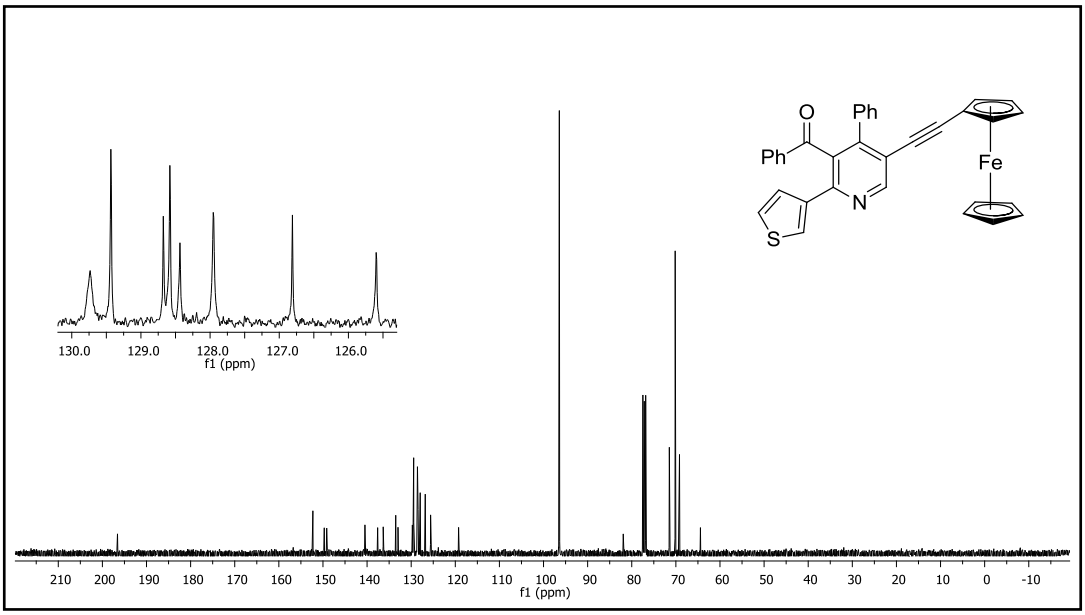

Figure 265. ^{13}C NMR spectrum of compound **57mr**.

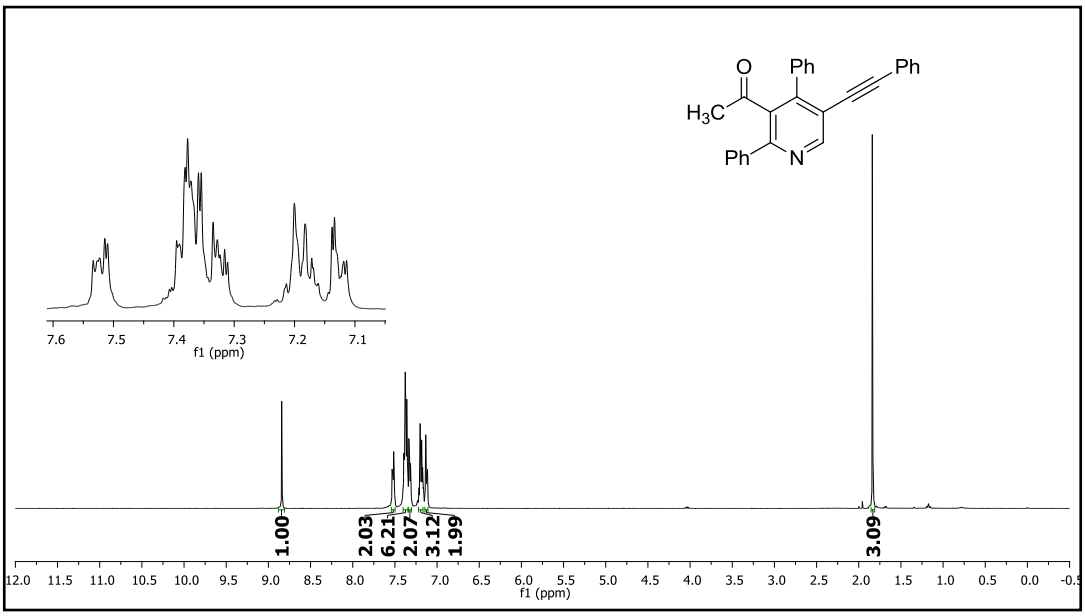

Figure 266. ^{1}H NMR spectrum of compound **57aaa**.

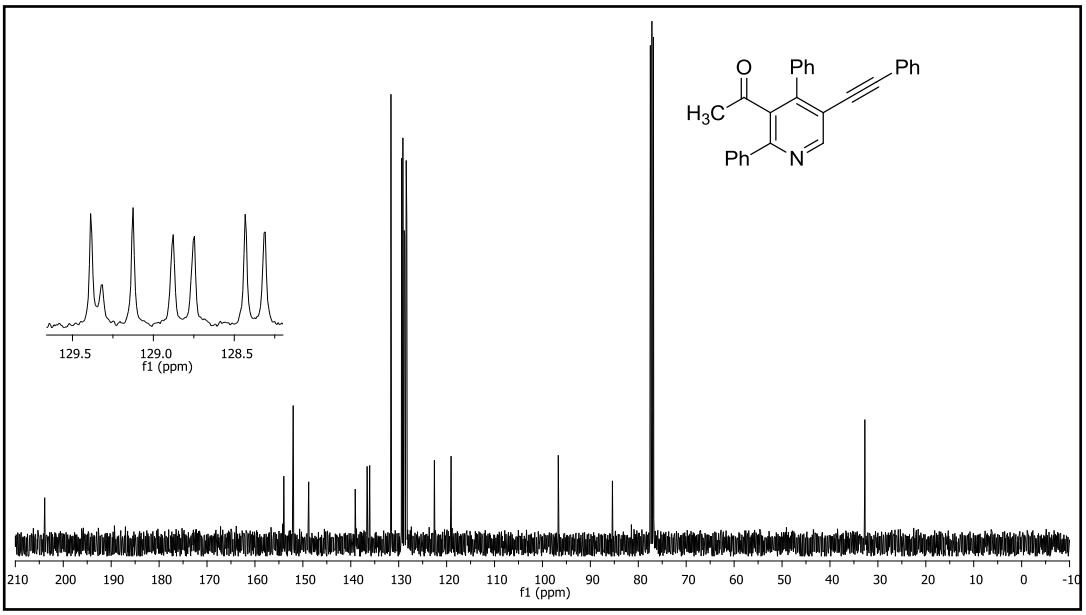

Figure 267. ^{13}C NMR spectrum of compound **57aaa**.

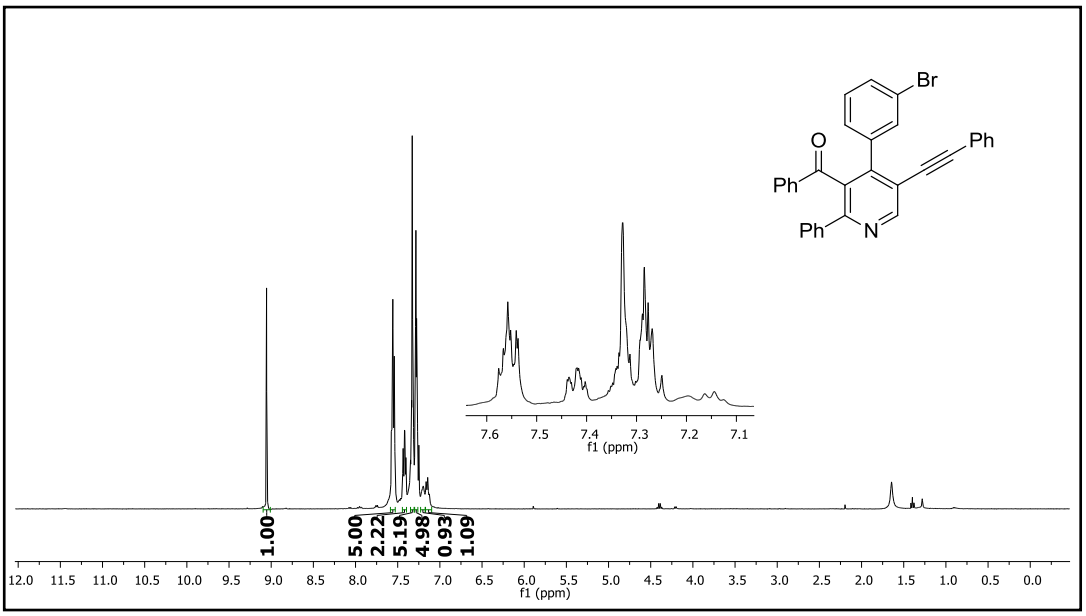

Figure 268. ^{1}H NMR spectrum of compound **57aba**.

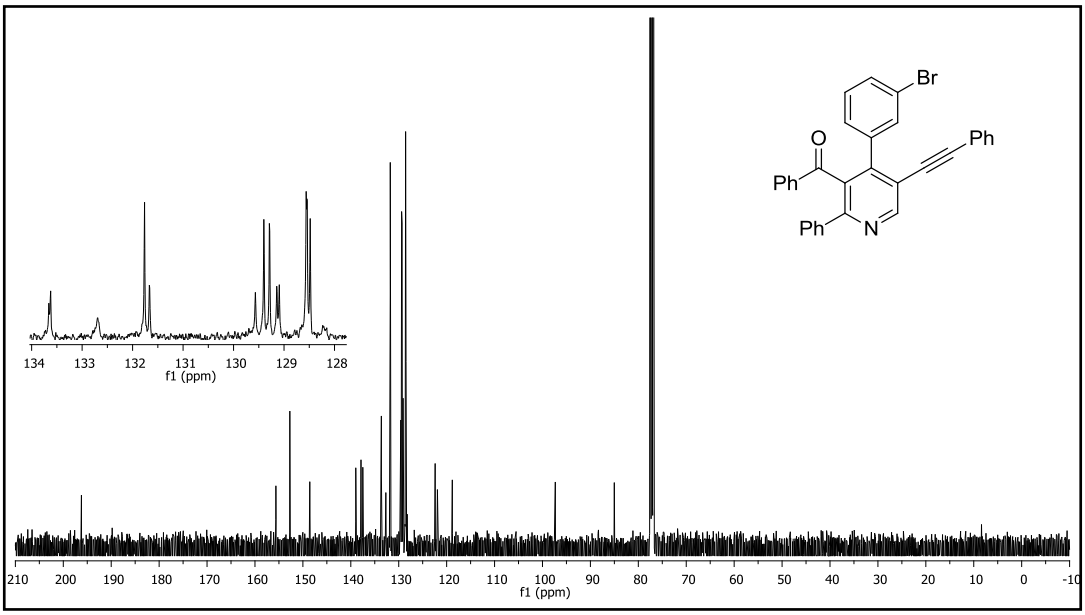

Figure 269. ^{13}C NMR spectrum of compound **57aba**.

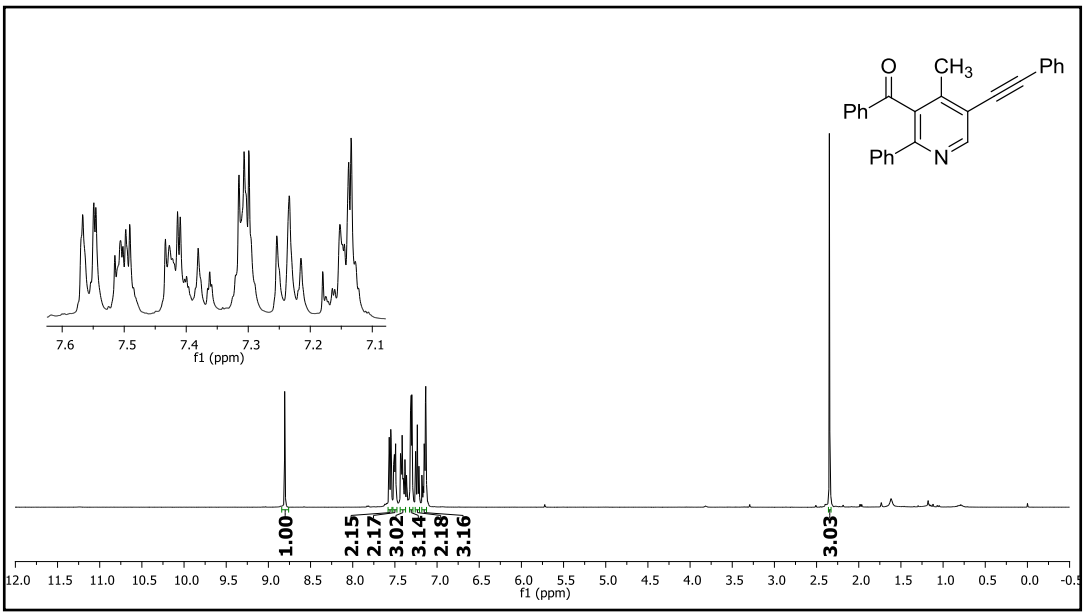

Figure 270. ^{1}H NMR spectrum of compound **57aca**.

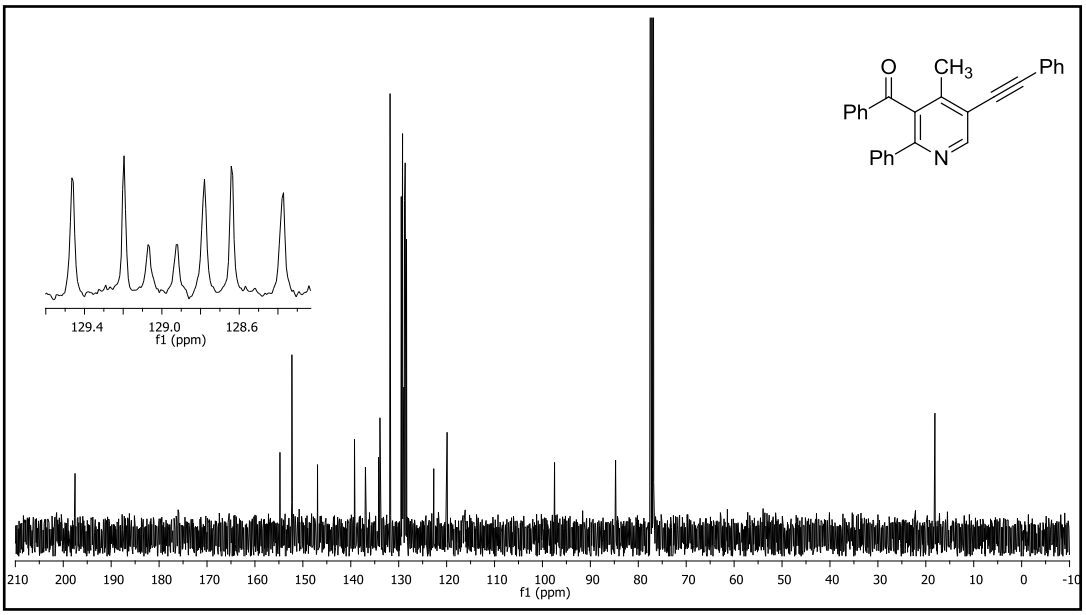

Figure 271. ^{13}C NMR spectrum of compound **57aca**.

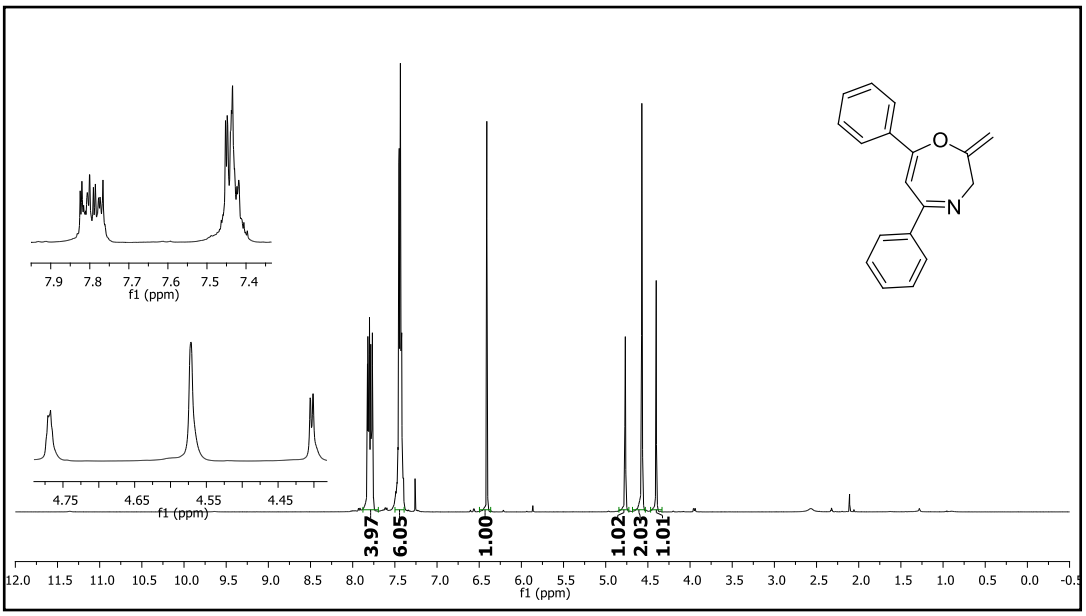

Figure 272. ^{1}H NMR spectrum of compound **33a**.

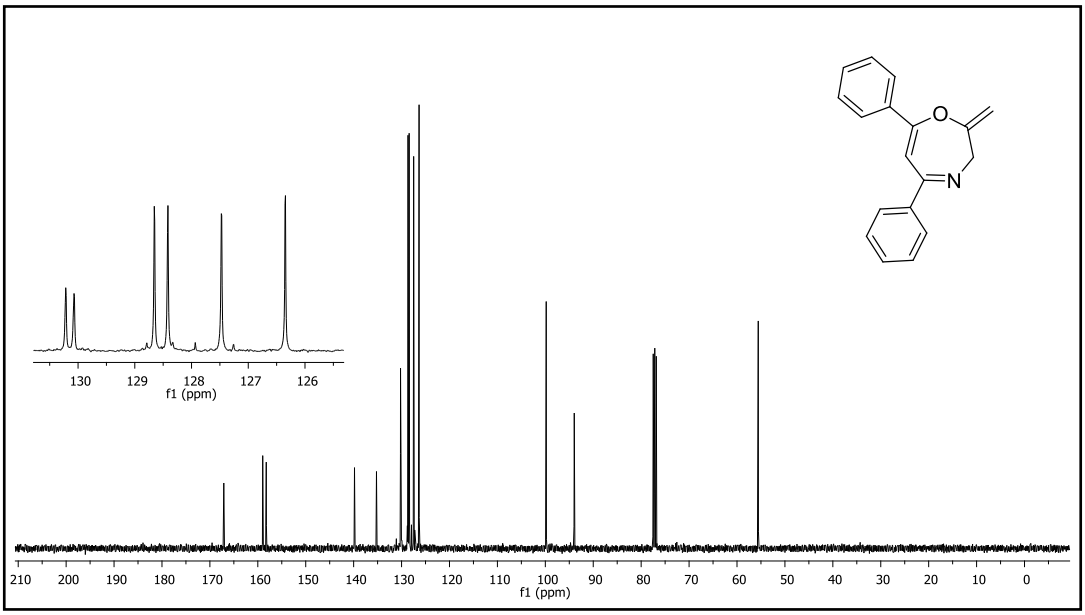

Figure 273. ^{13}C NMR spectrum of compound **33a**.

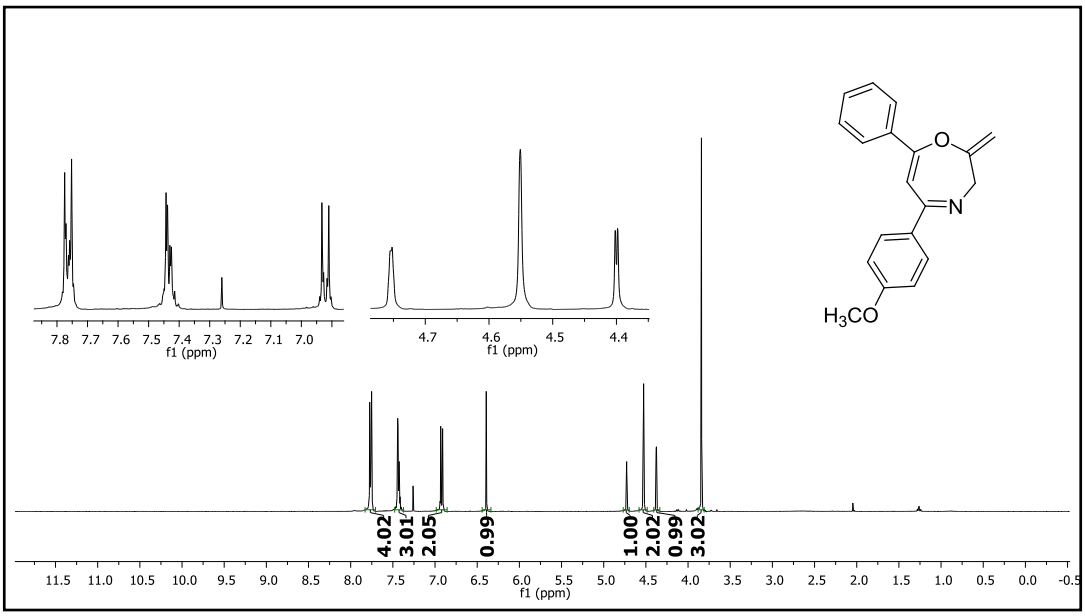

Figure 274. ^{1}H NMR spectrum of compound **33b**.

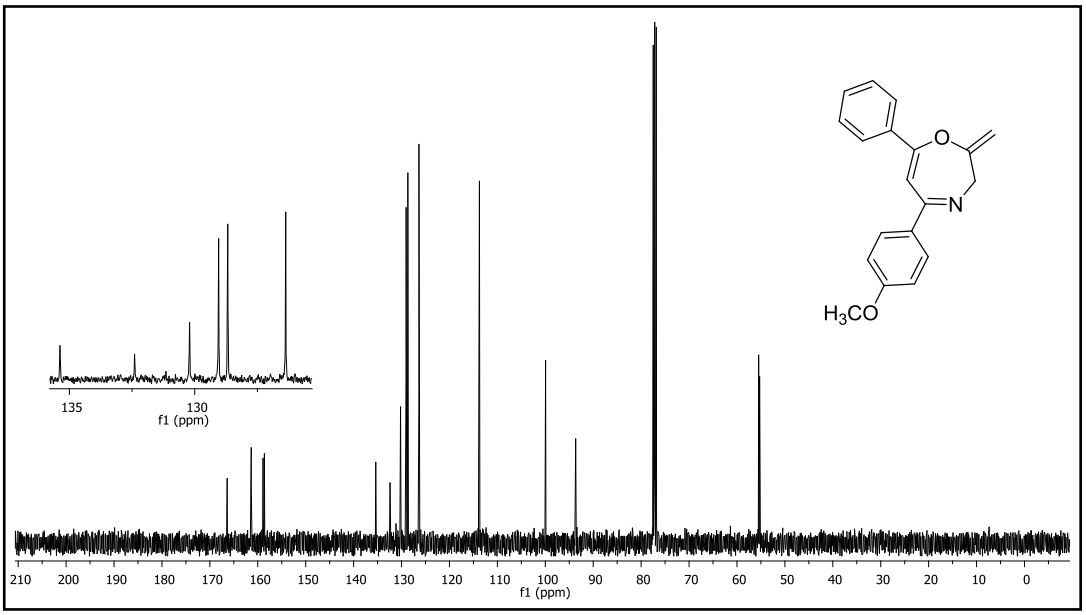

Figure 275. ^{13}C NMR spectrum of compound **33b**.

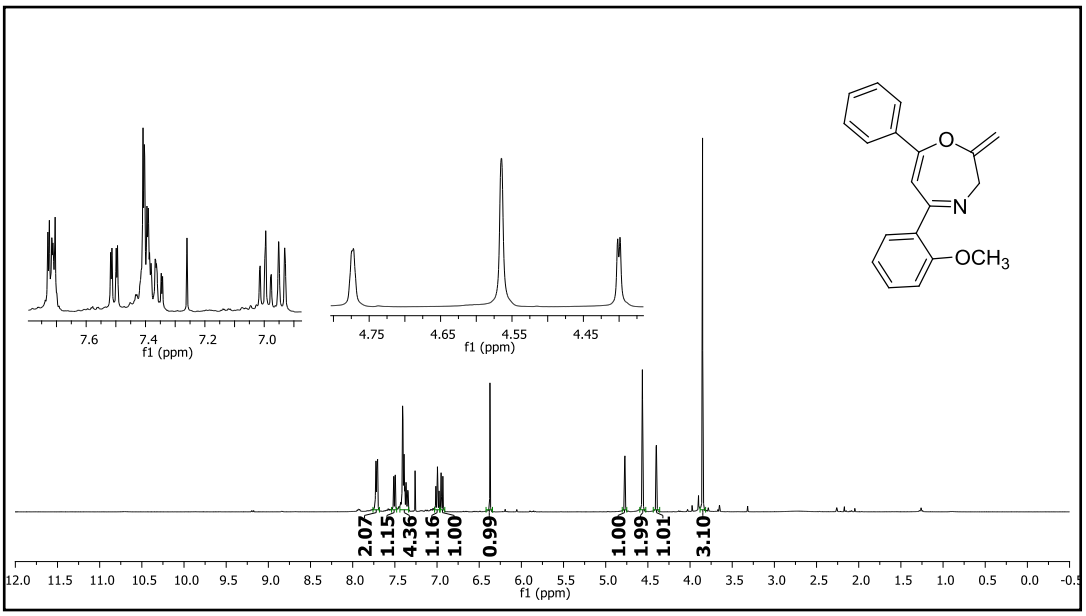

Figure 276. ^{13}C NMR spectrum of compound **33c**.

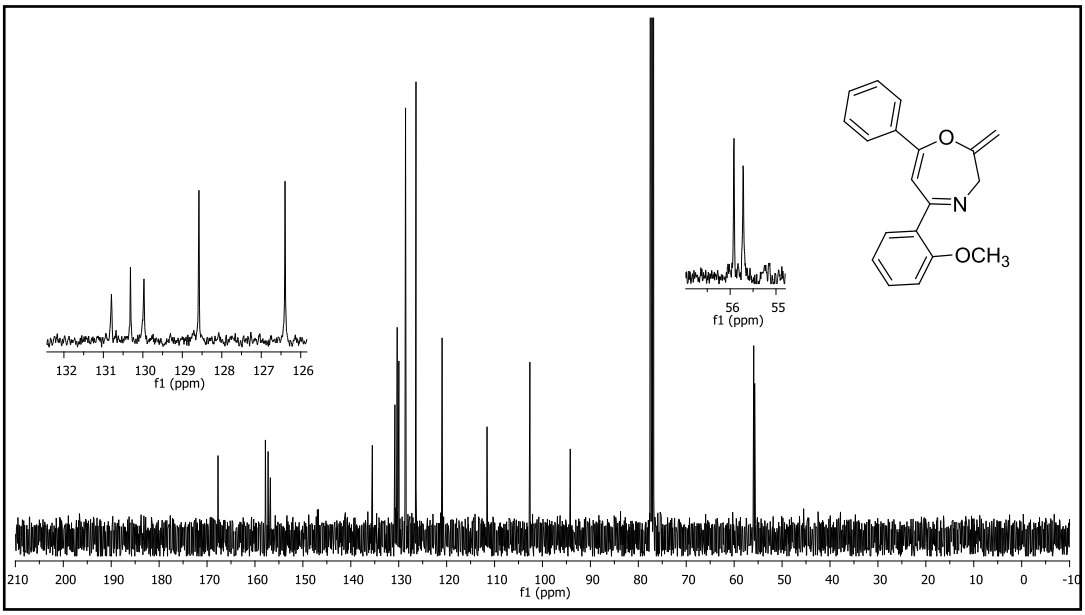

Figure 277. ^{13}C NMR spectrum of compound **33c**.

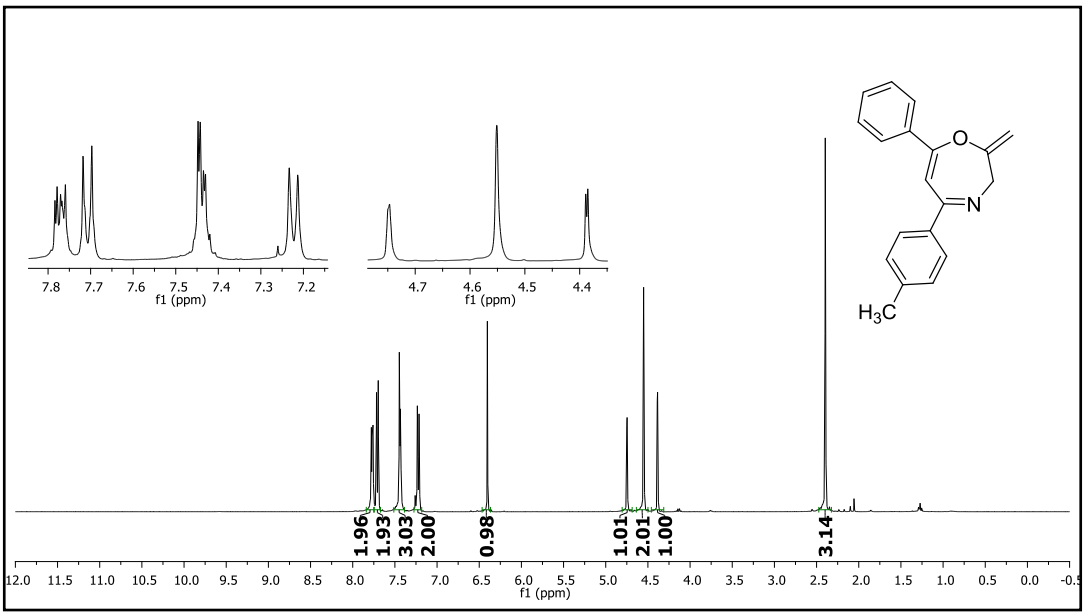

Figure 278. ^{1}H NMR spectrum of compound **33d**.

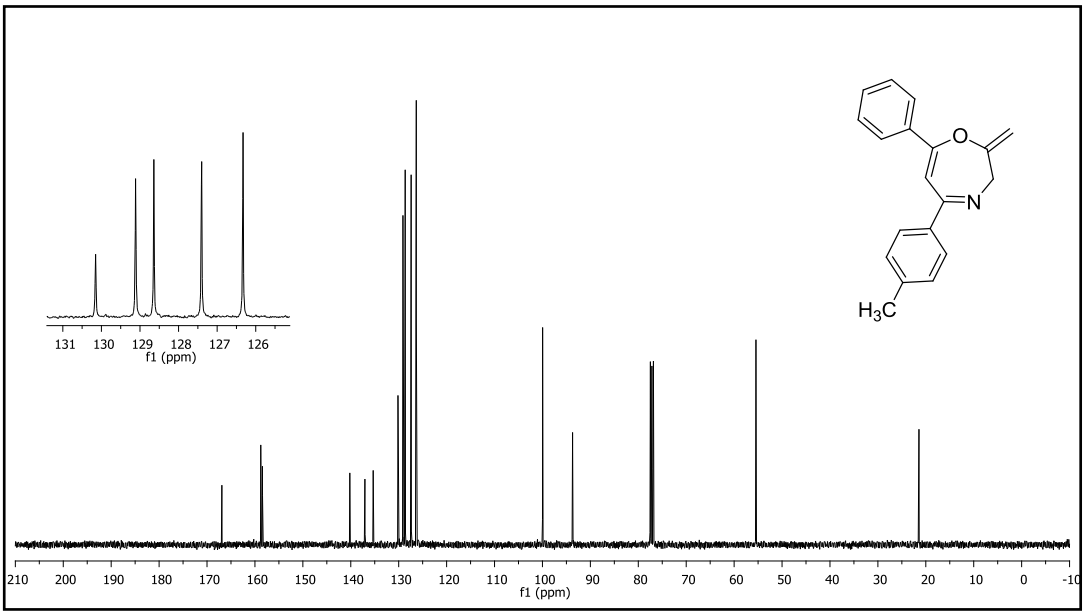

Figure 279. ^{13}C NMR spectrum of compound **33d**.

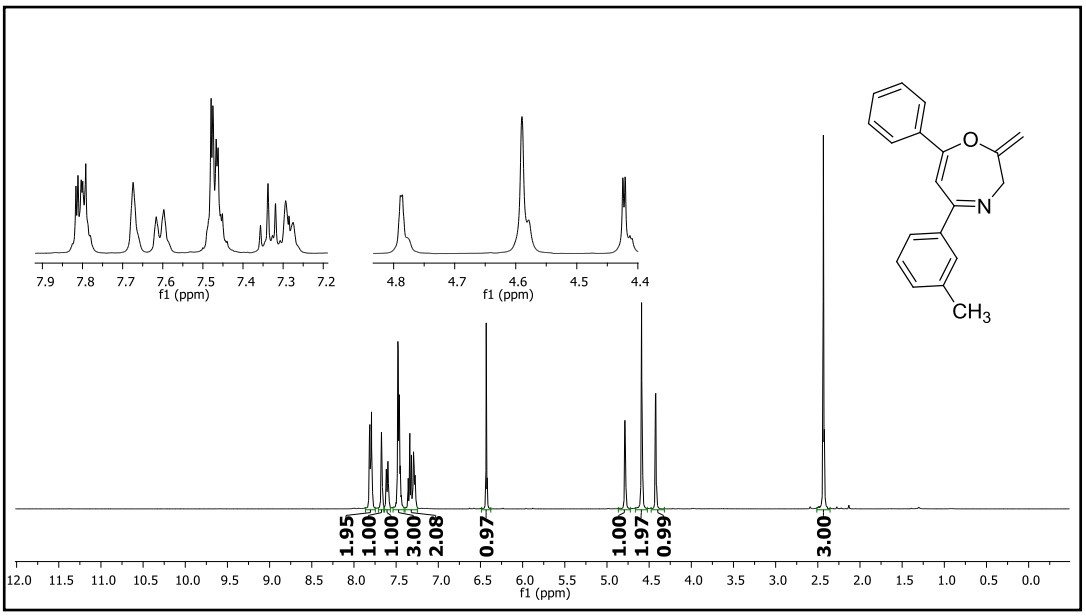

Figure 280. ^{1}H NMR spectrum of compound **33e**.

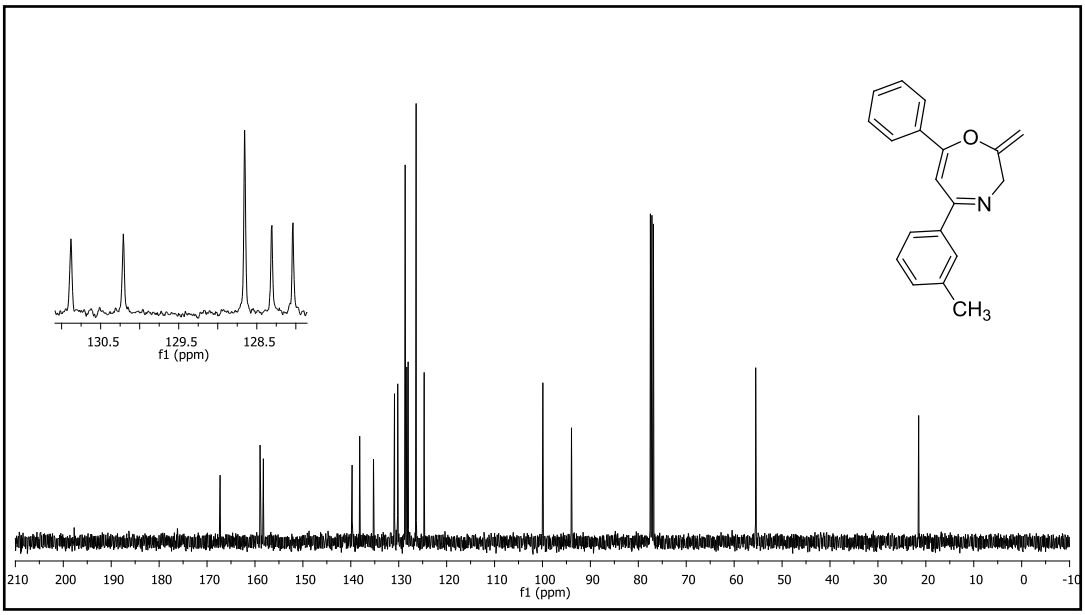

Figure 281. ^{13}C NMR spectrum of compound **33e**.

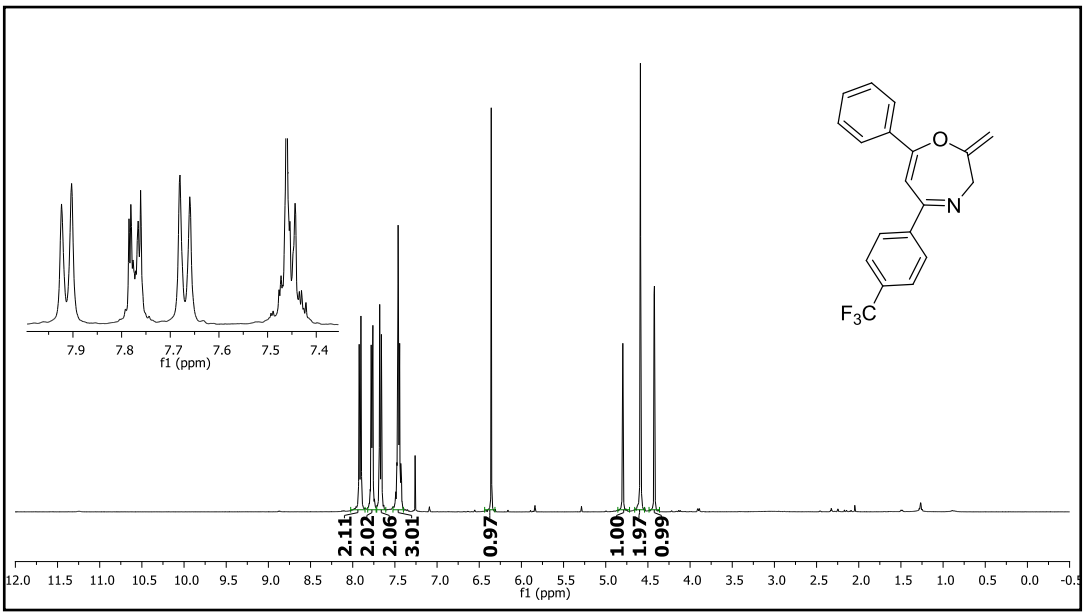

Figure 282. ^{1}H NMR spectrum of compound **33f**.

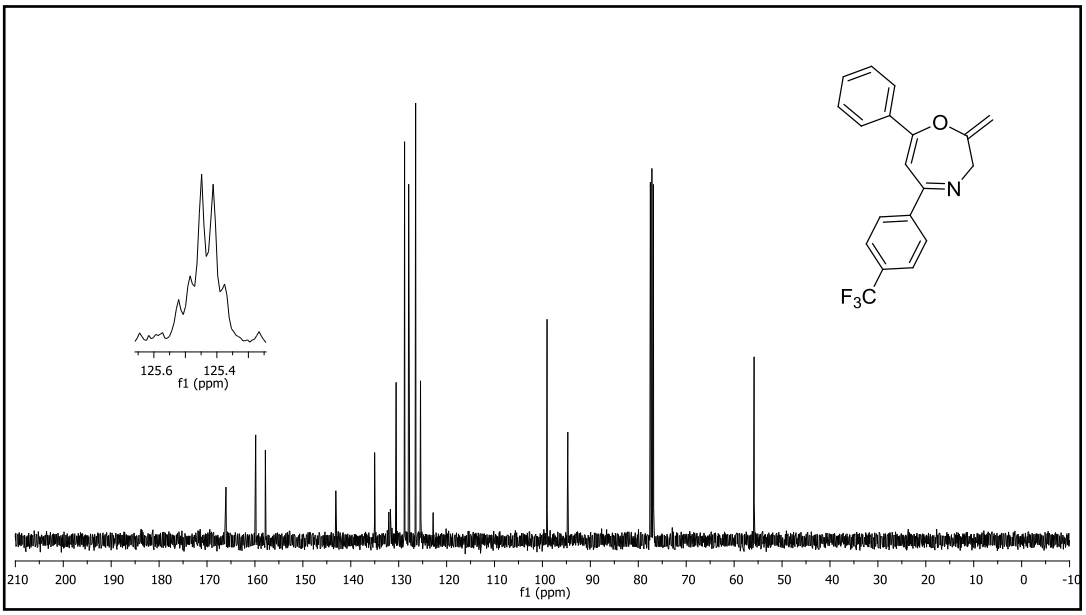

Figure 283. ^{13}C NMR spectrum of compound **33f**.

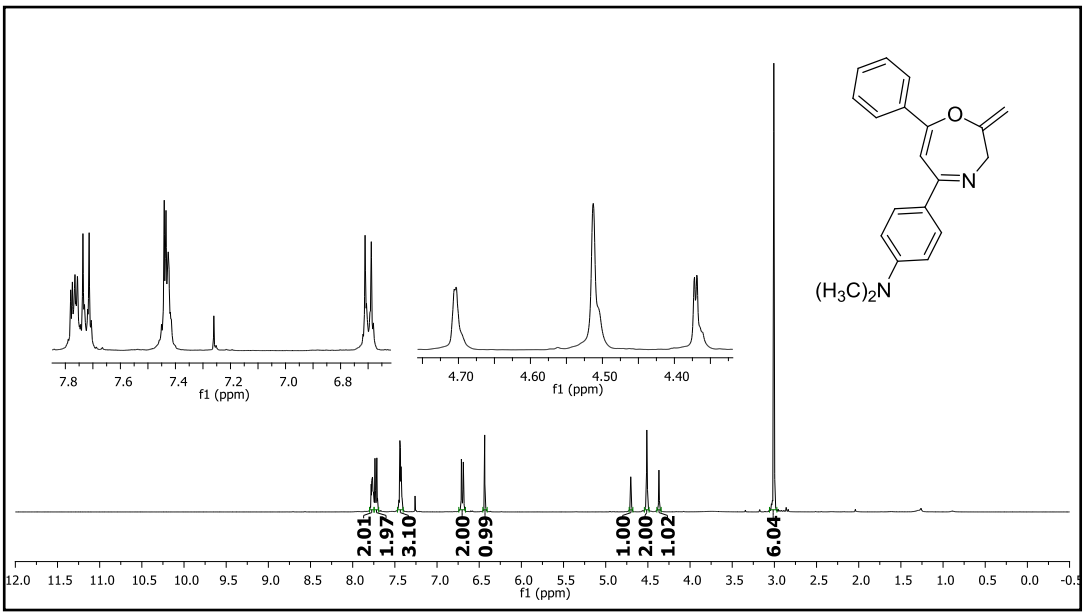

Figure 284. ^{1}H NMR spectrum of compound **33g**.

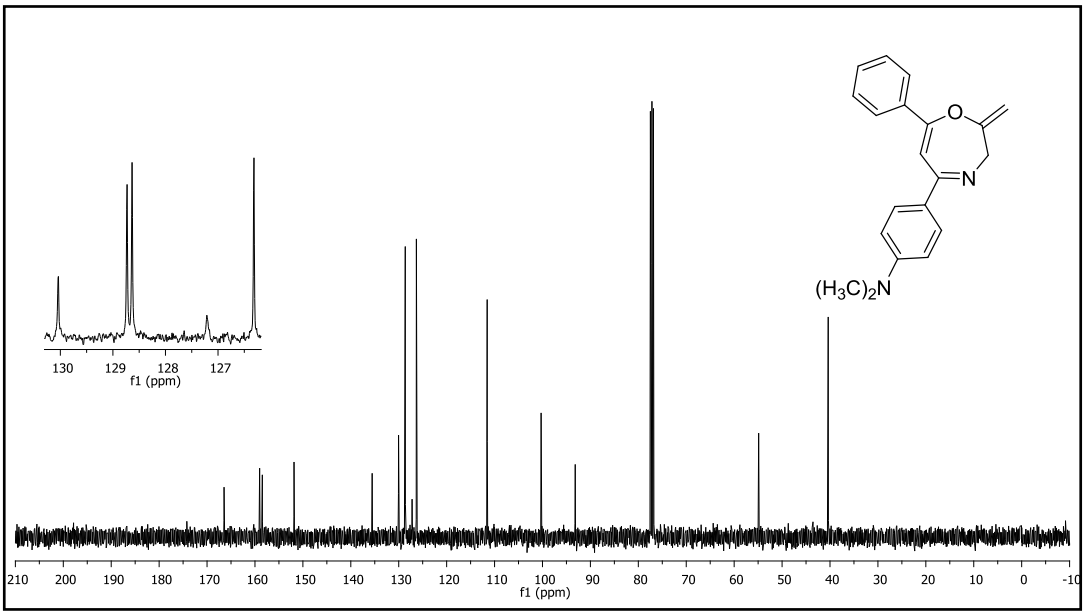

Figure 285. ^{13}C NMR spectrum of compound **33g**.

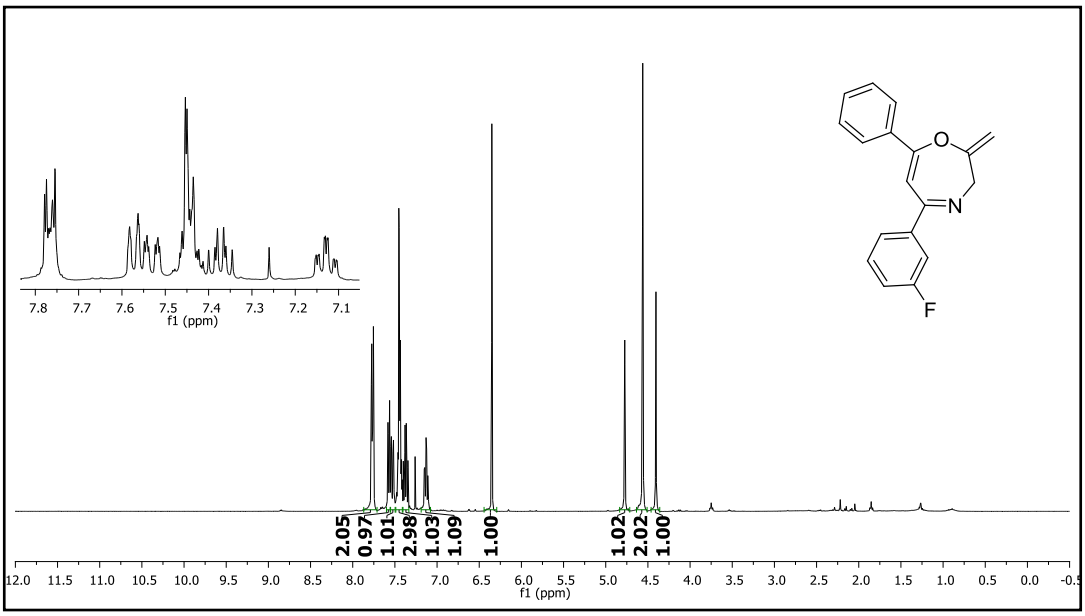

Figure 286. ^{1}H NMR spectrum of compound **33h**.

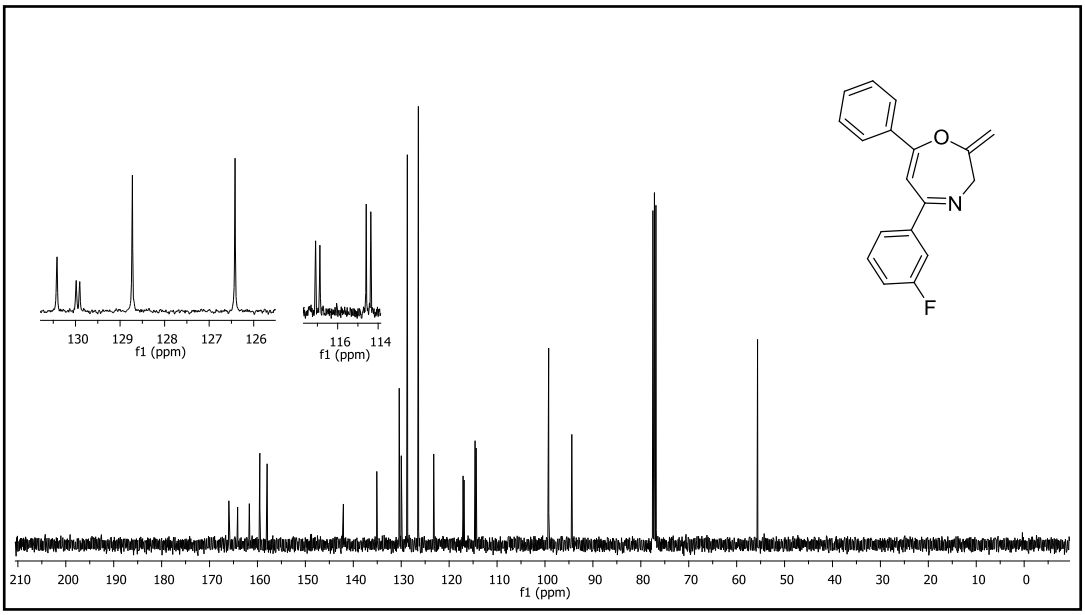

Figure 287. ^{13}C NMR spectrum of compound **33h**.

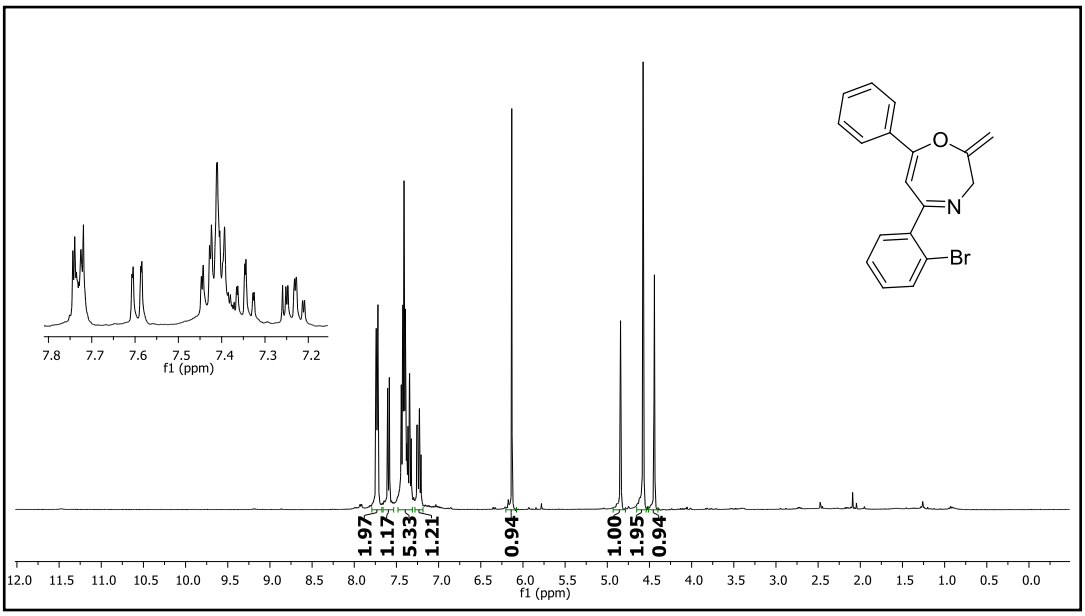

Figure 288. ^{1}H NMR spectrum of compound **33i**.

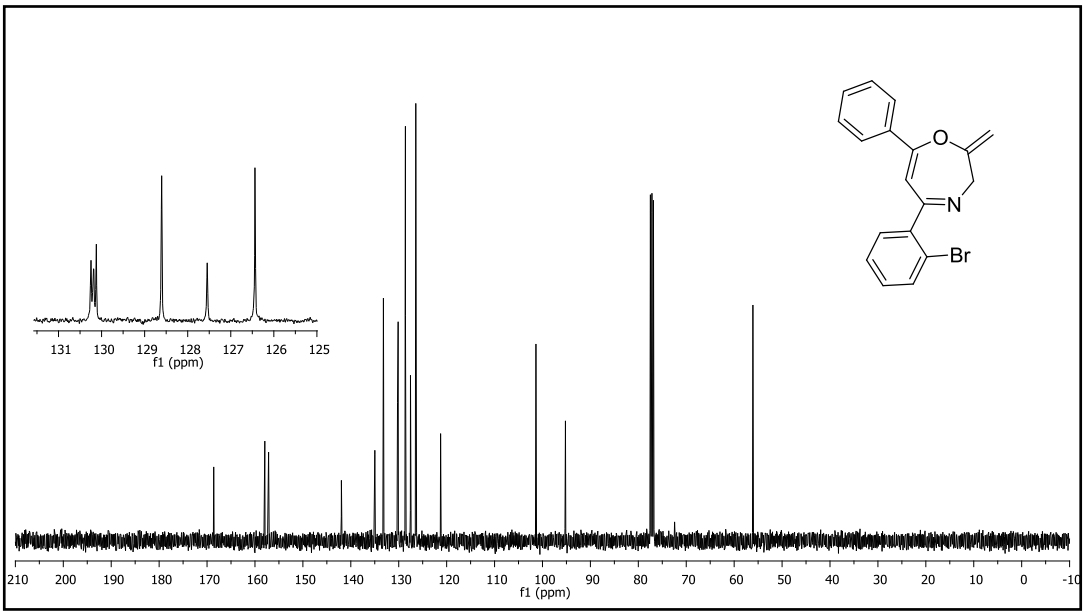

Figure 289. ^{13}C NMR spectrum of compound **33i**.

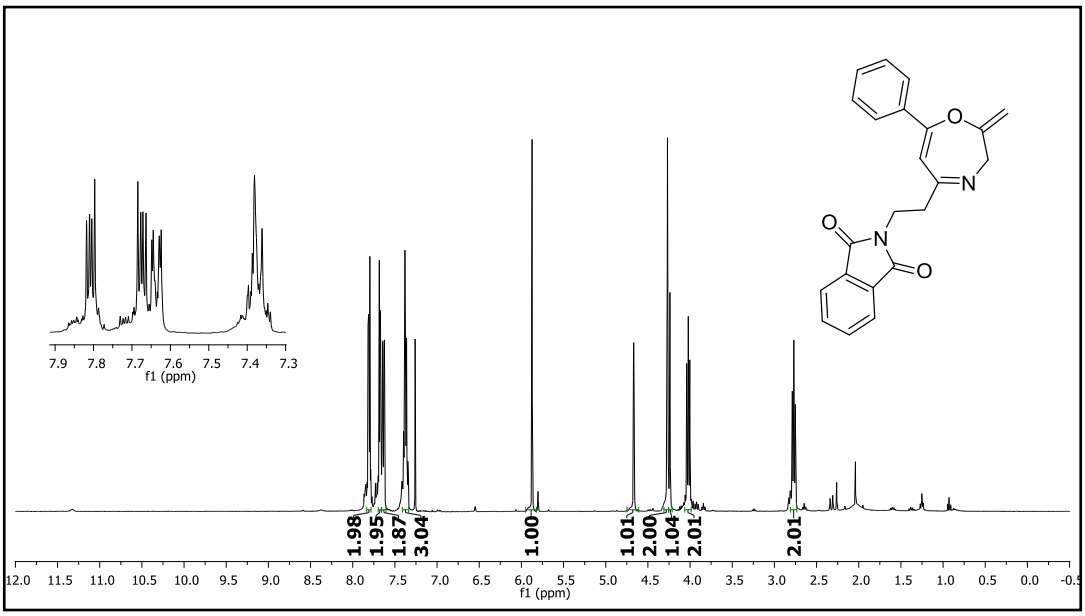

Figure 290. ^{1}H NMR spectrum of compound **33k**.

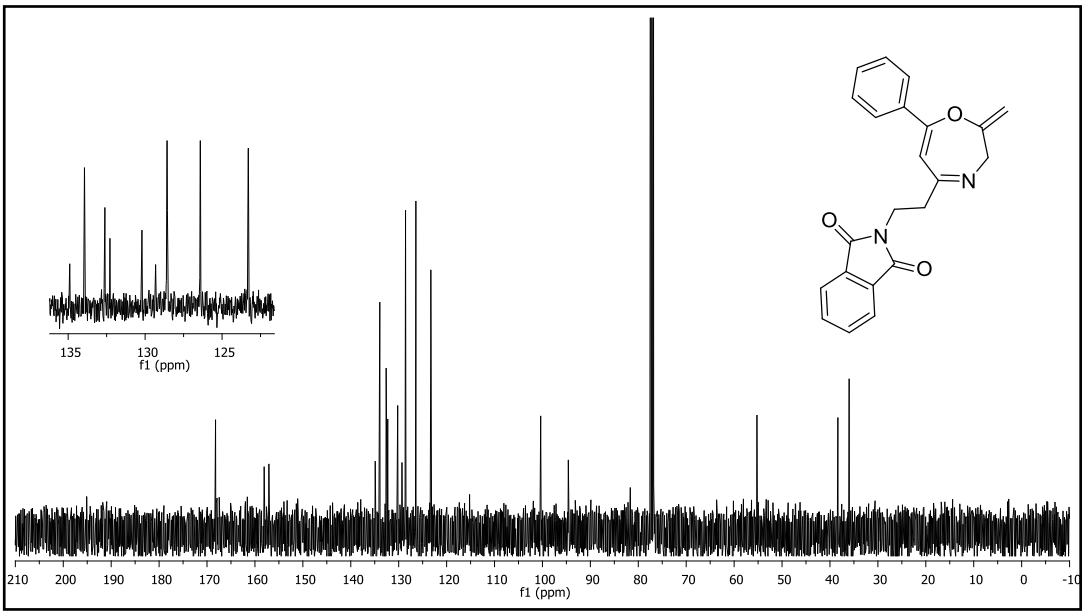

Figure 291. ^{13}C NMR spectrum of compound **33k**.

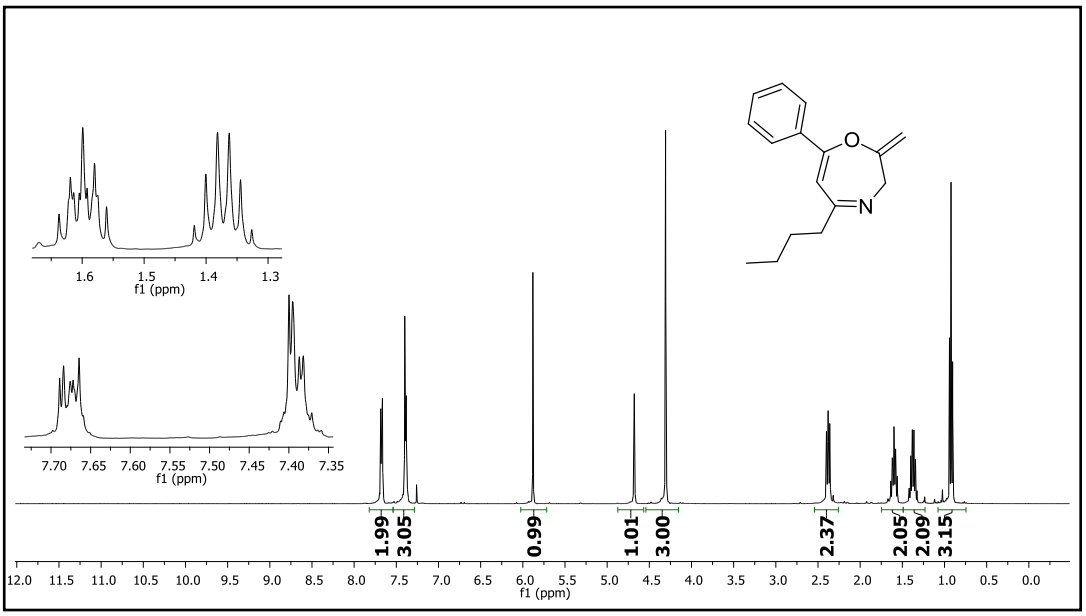

Figure 292. ^{1}H NMR spectrum of compound **33l**.

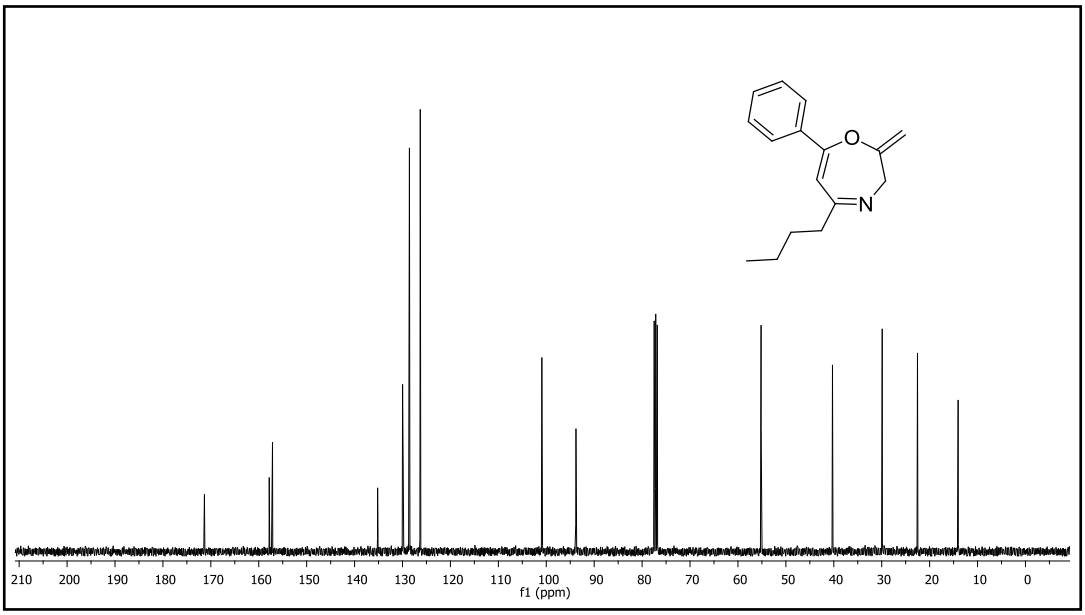

Figure 293. ^{13}C NMR spectrum of compound **33l**.

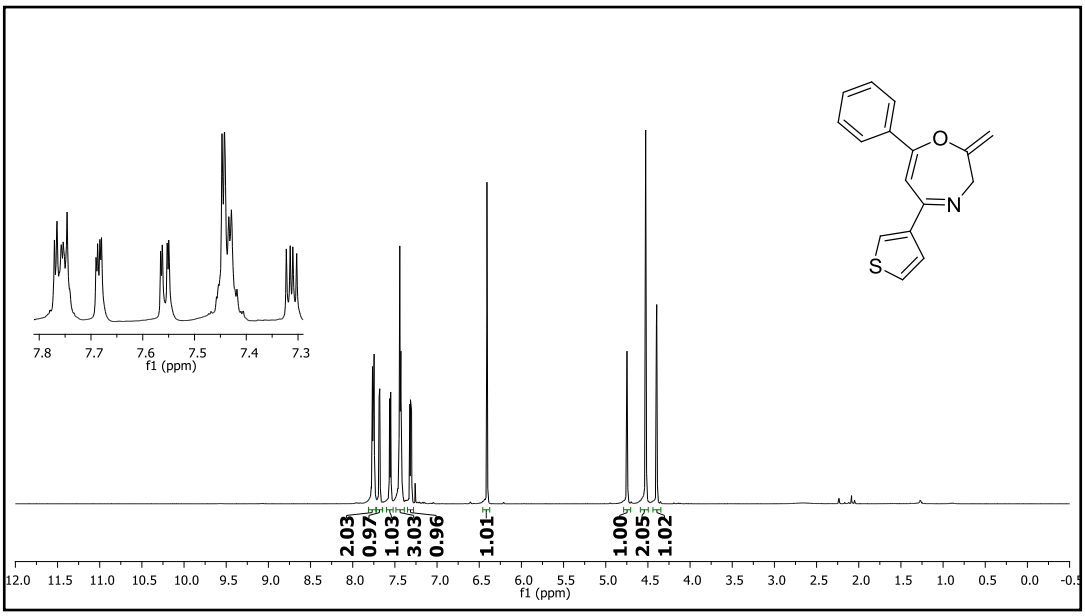

Figure 294. ^{1}H NMR spectrum of compound **33m**.

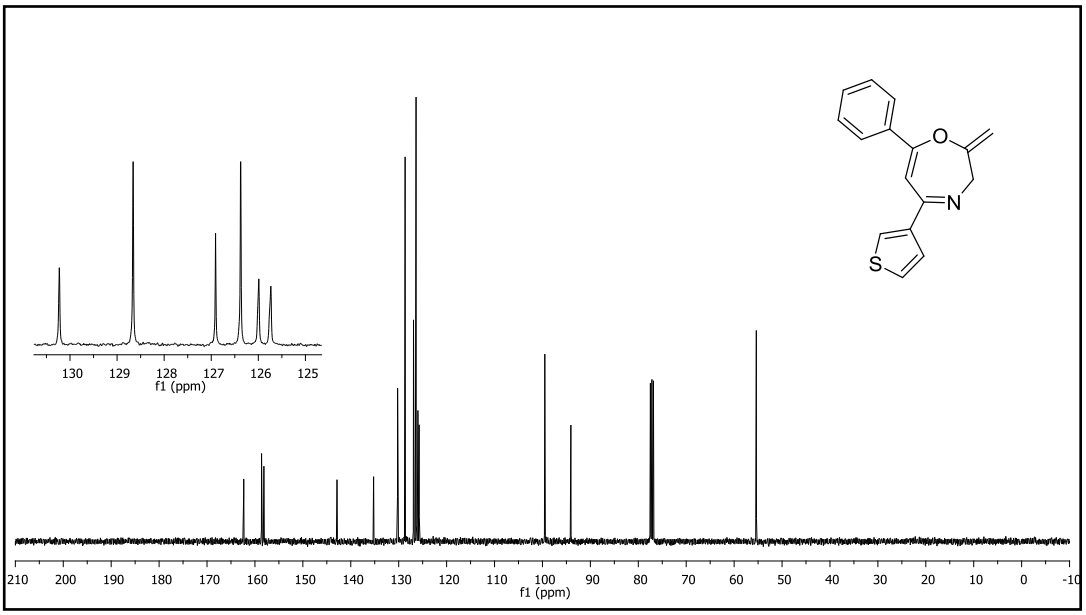

Figure 295. ^{13}C NMR spectrum of compound **33m**.

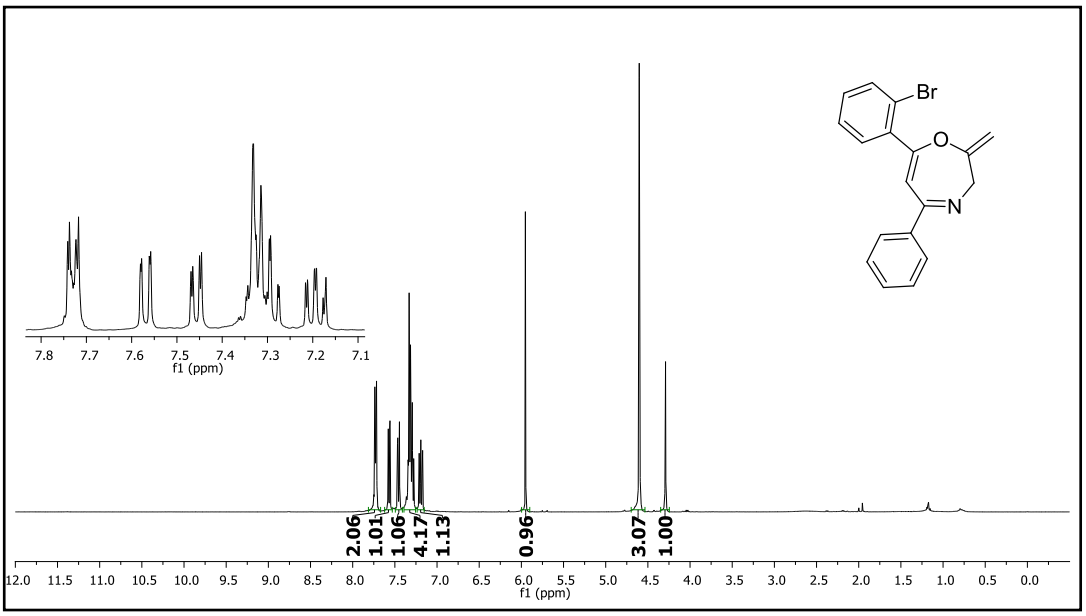

Figure 296. ^{1}H NMR spectrum of compound **33n**.

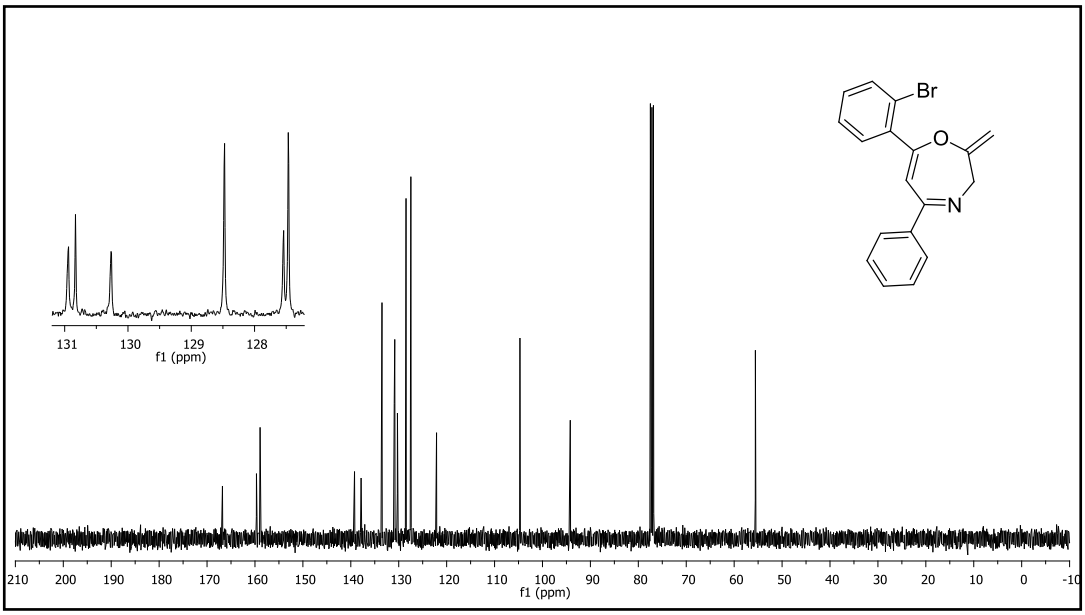

Figure 297. ^{13}C NMR spectrum of compound **33n**.

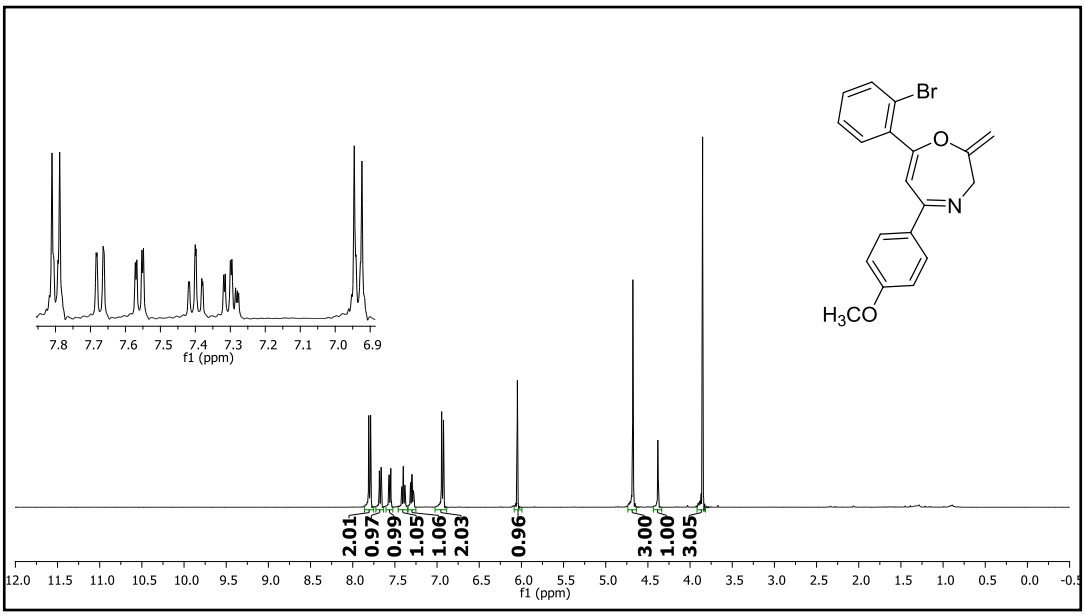

Figure 298. ^{1}H NMR spectrum of compound **33o**.

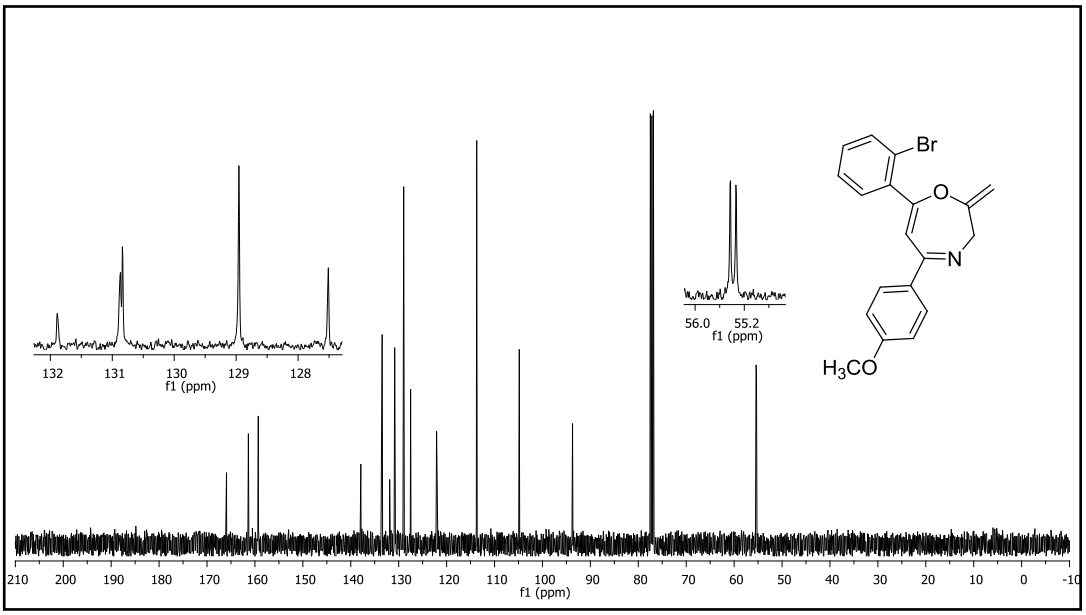

Figure 299. ^{13}C NMR spectrum of compound **33o**.

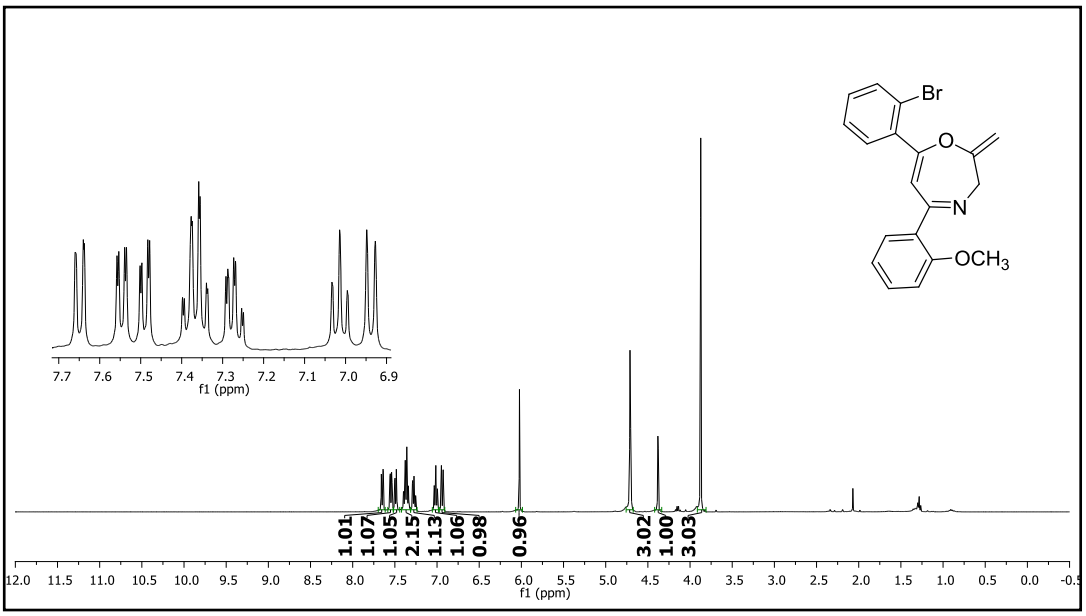

Figure 300. ^{1}H NMR spectrum of compound **33p**.

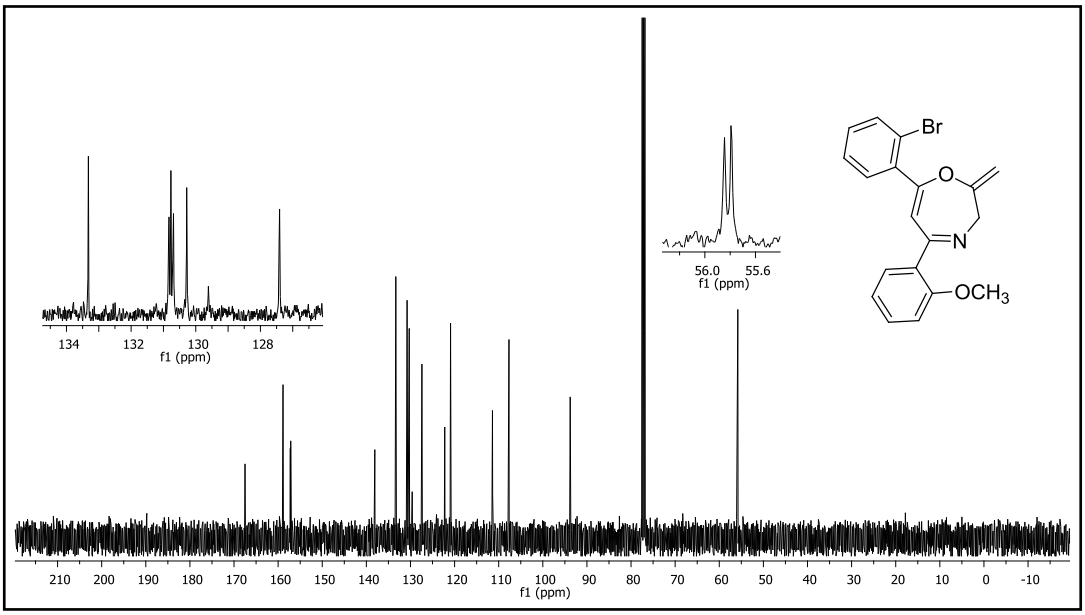

Figure 301. ^{13}C NMR spectrum of compound **33p**.

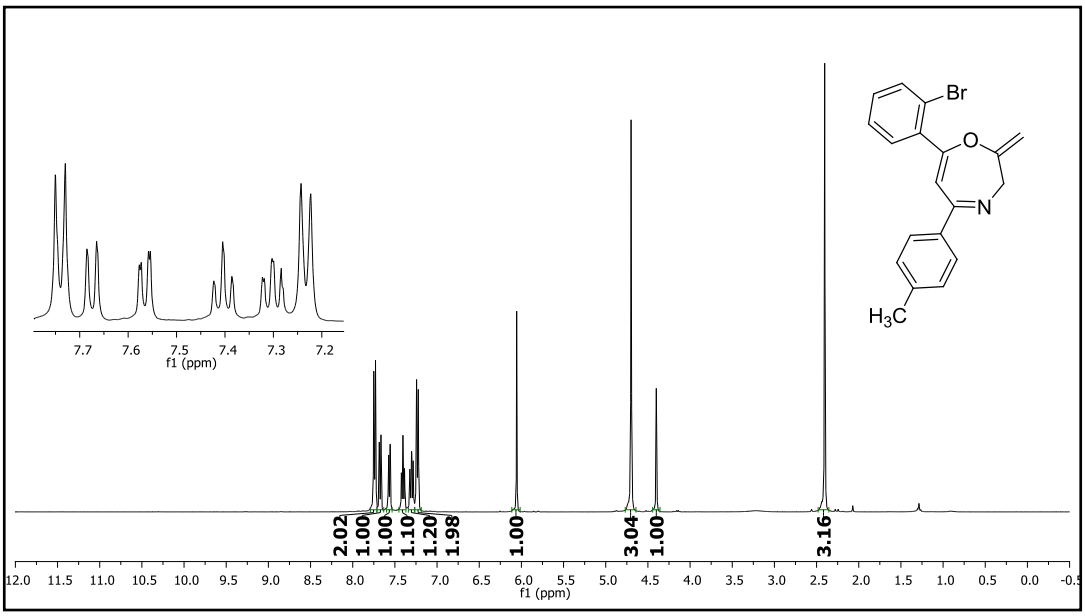

Figure 302. ^{1}H NMR spectrum of compound **33q**.

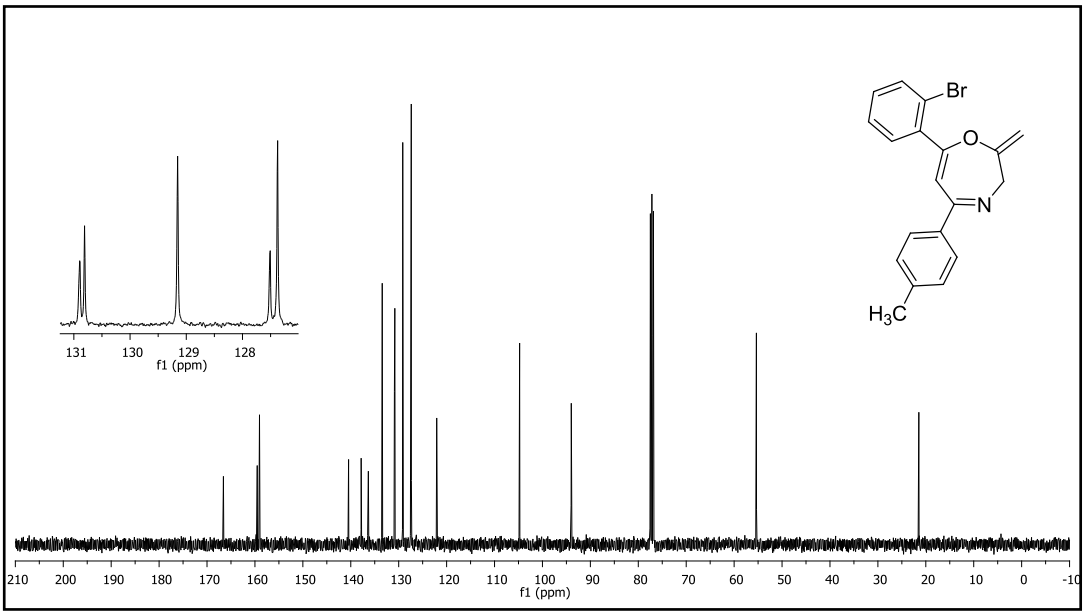

Figure 303. ^{13}C NMR spectrum of compound **33q**.

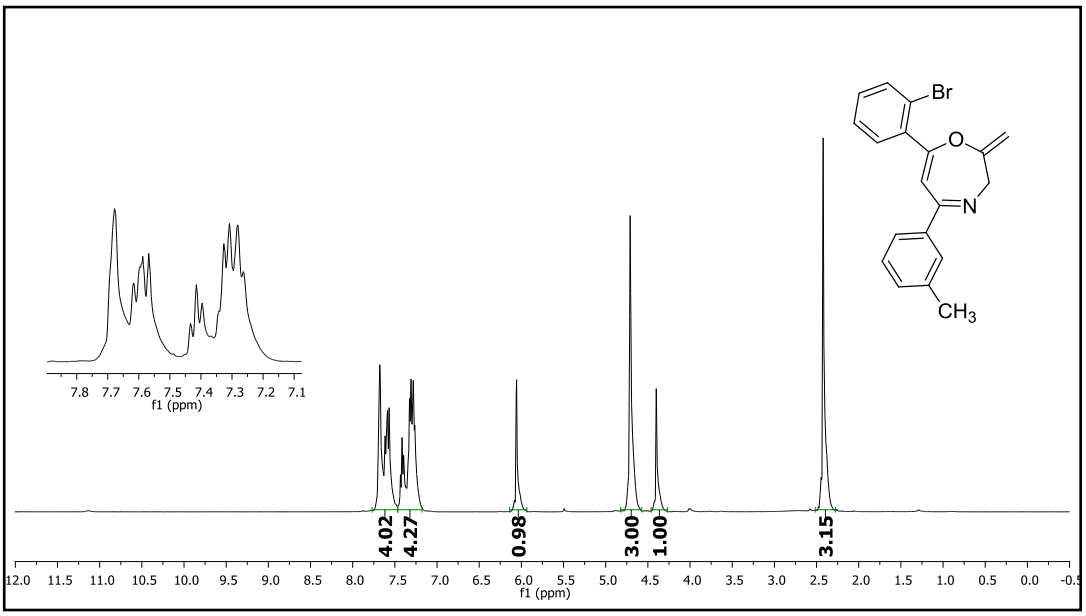

Figure 304. ^{1}H NMR spectrum of compound **33r**.

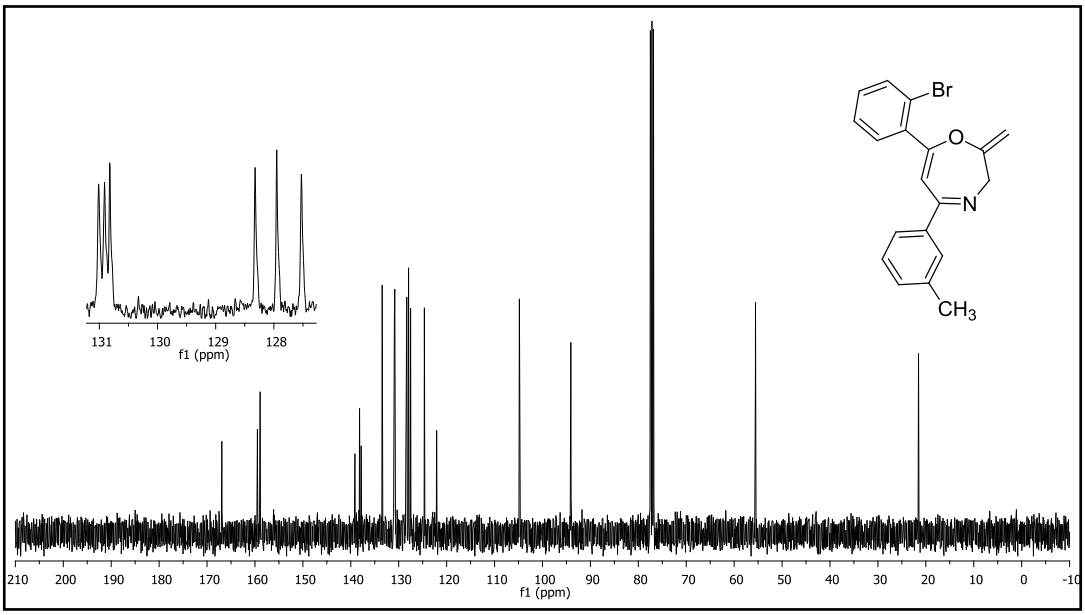

Figure 305. ^{13}C NMR spectrum of compound **33r**.

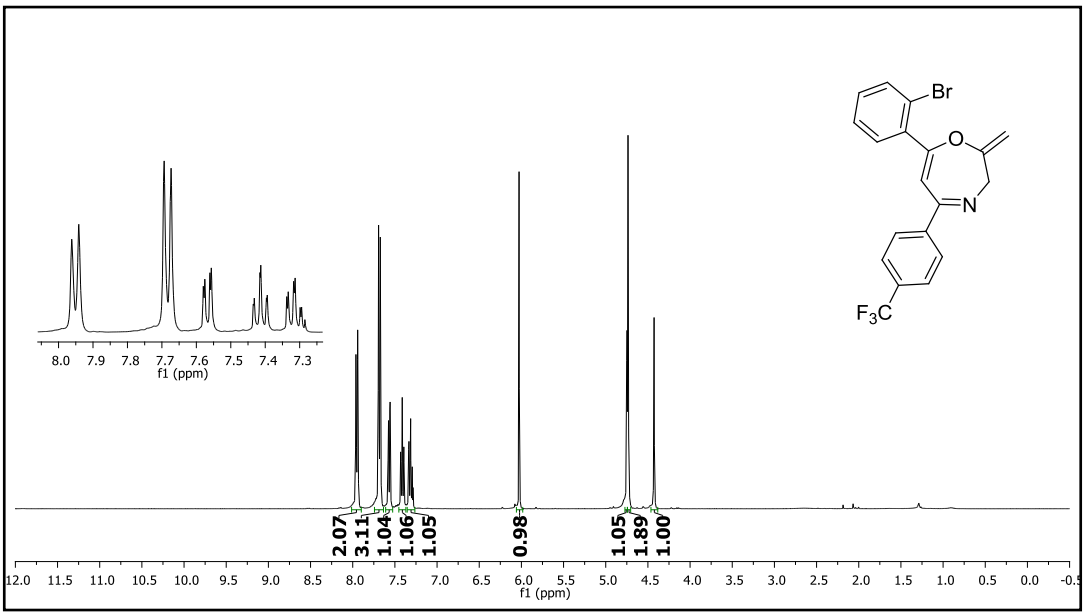

Figure 306. ^{1}H NMR spectrum of compound **33s**.

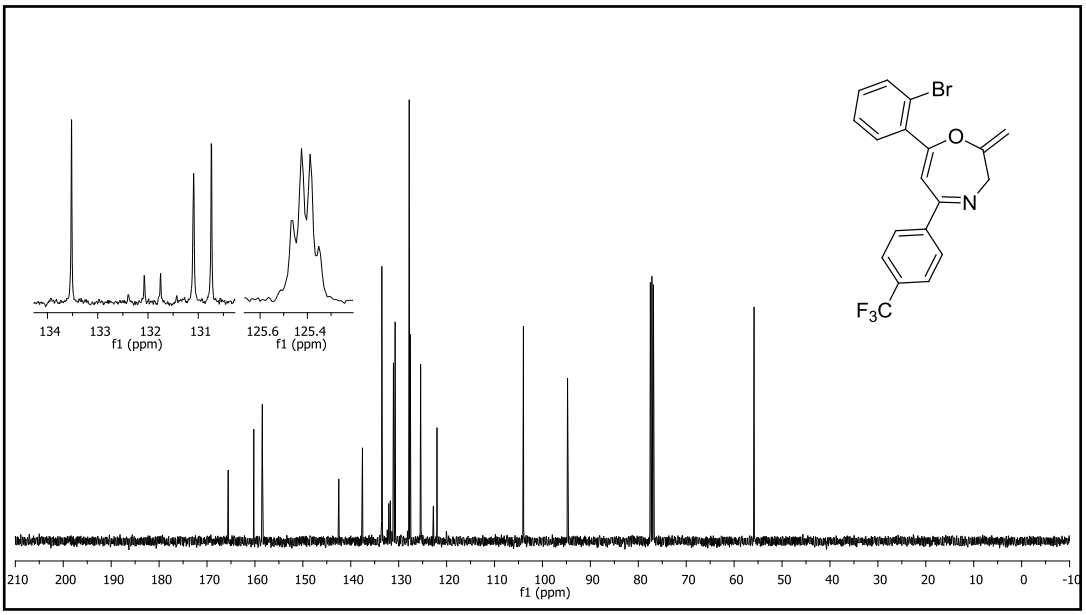

Figure 307. ^{13}C NMR spectrum of compound **33s**.

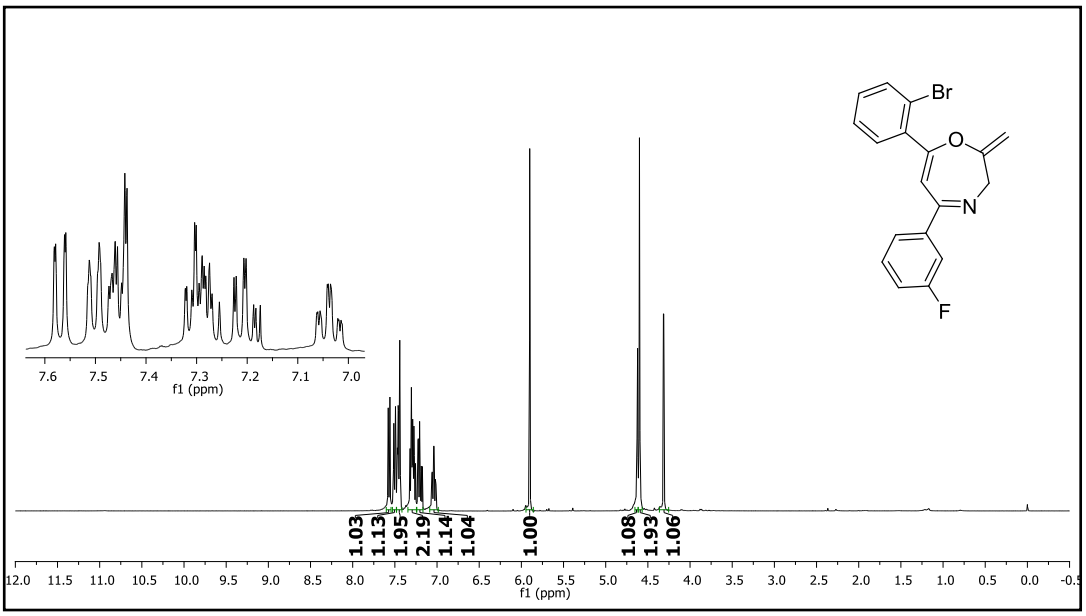

Figure 308. ^{1}H NMR spectrum of compound **33t**.

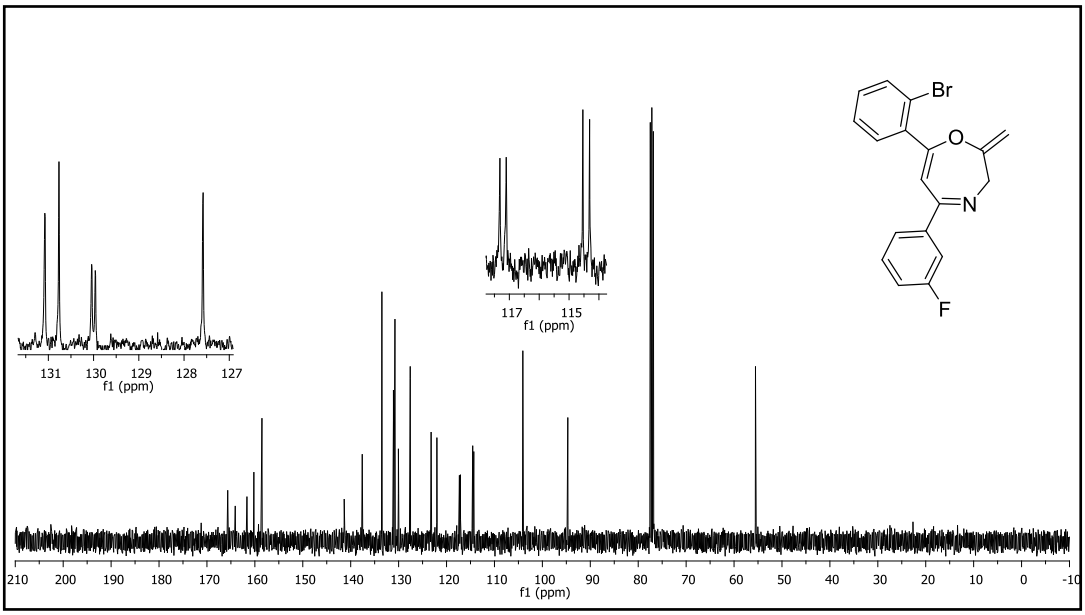

Figure 309. ^{13}C NMR spectrum of compound **33t**.

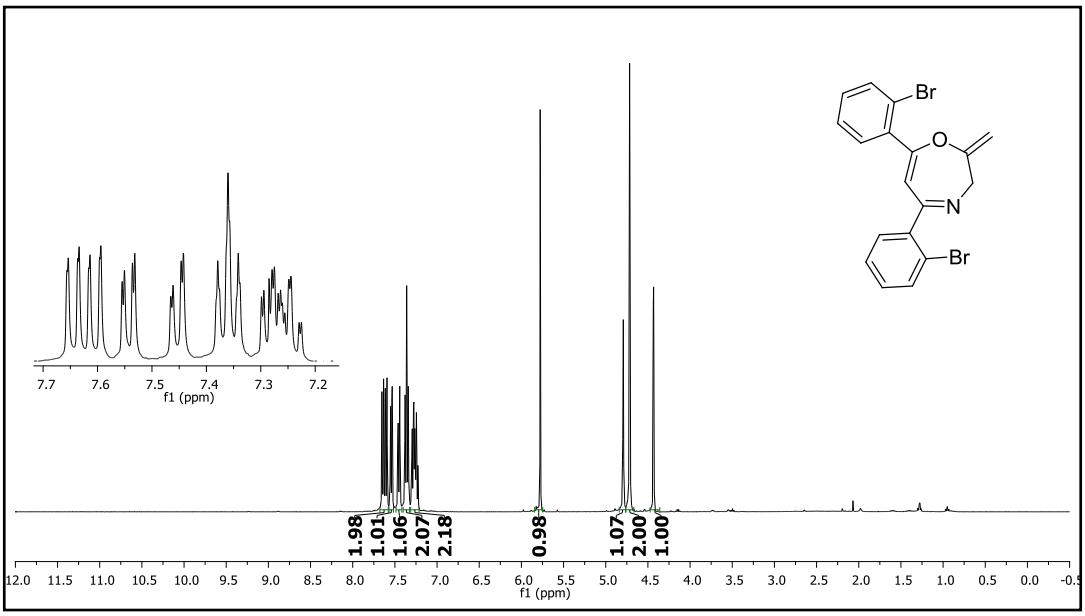

Figure 310. ^{1}H NMR spectrum of compound **33u**.

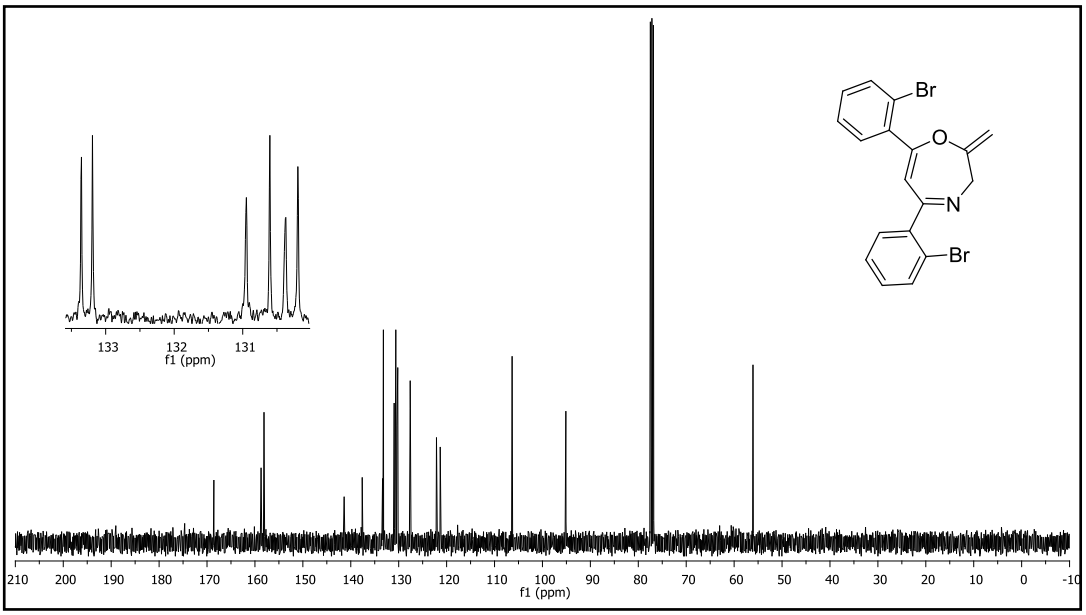

Figure 311. ^{13}C NMR spectrum of compound **33u**.

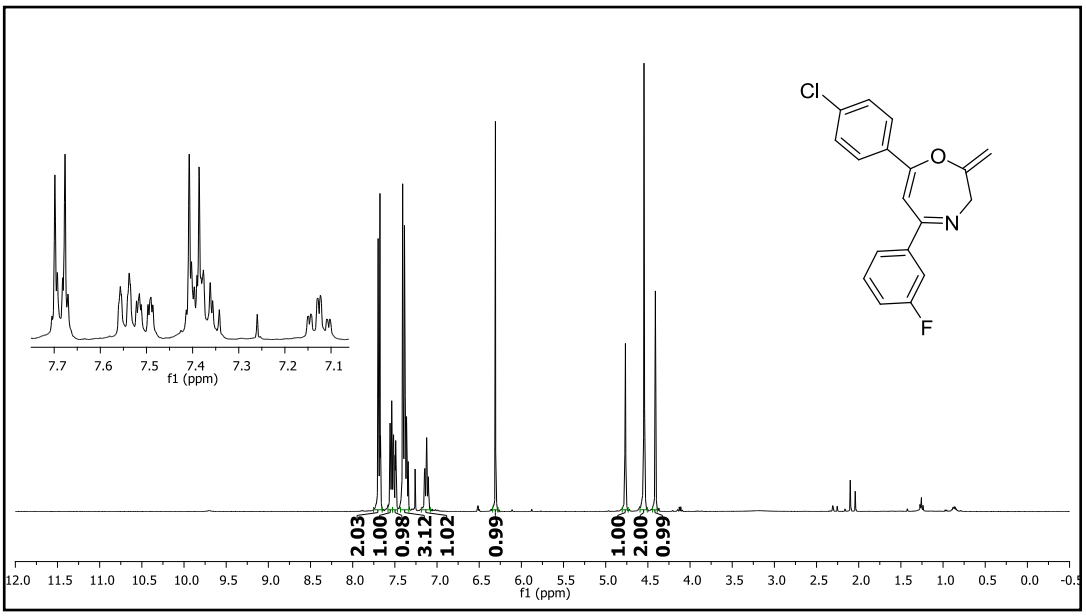

Figure 312. ^{1}H NMR spectrum of compound **33z**.

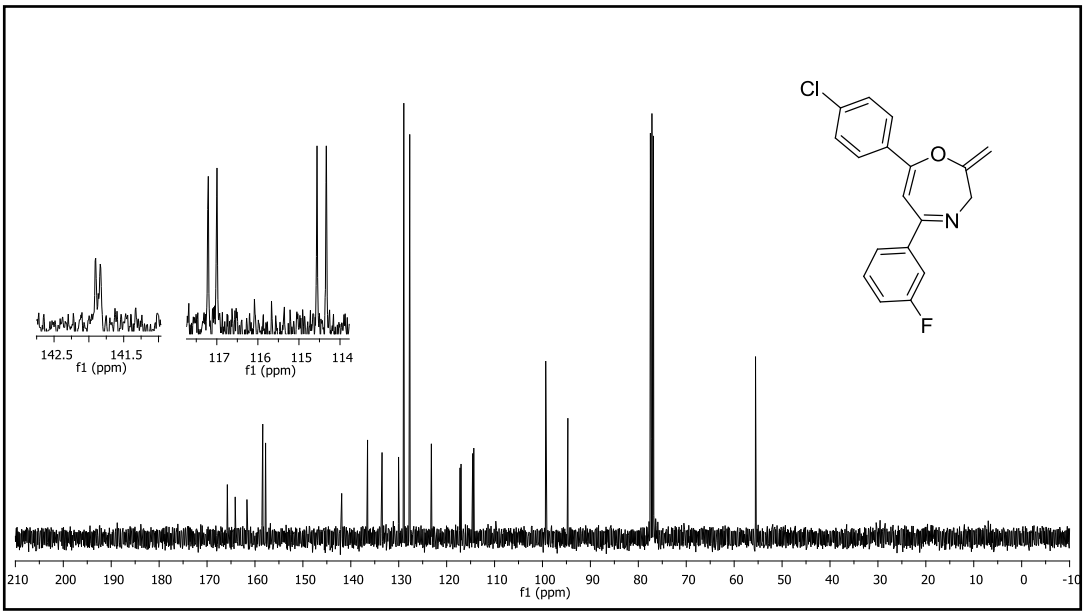

Figure 313. ^{13}C NMR spectrum of compound **33z**.

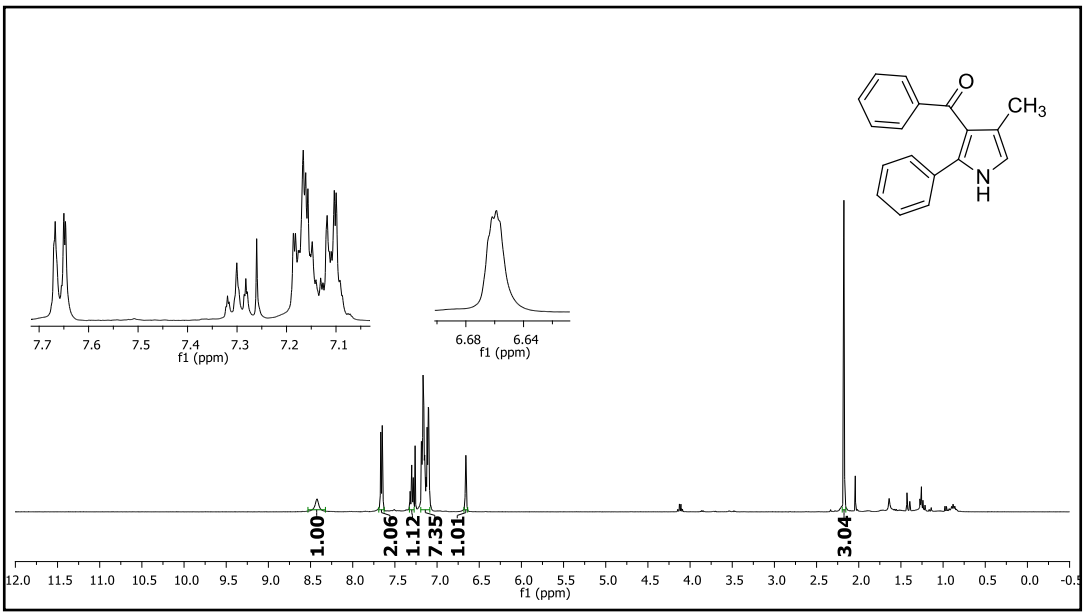

Figure 314. ^{1}H NMR spectrum of compound **71a**.

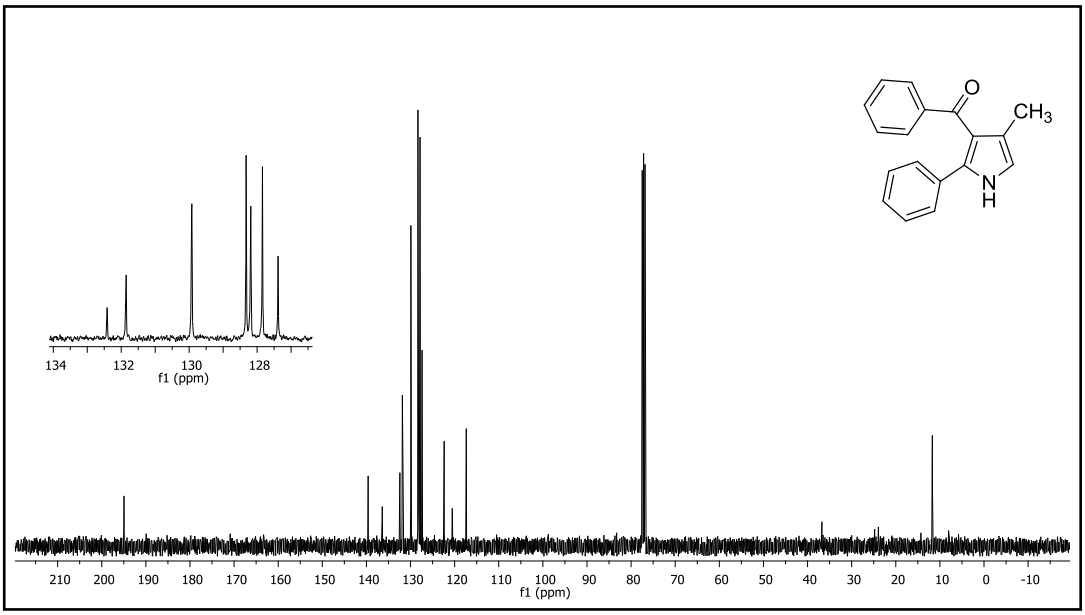

Figure 315. ^{13}C NMR spectrum of compound **71a**.

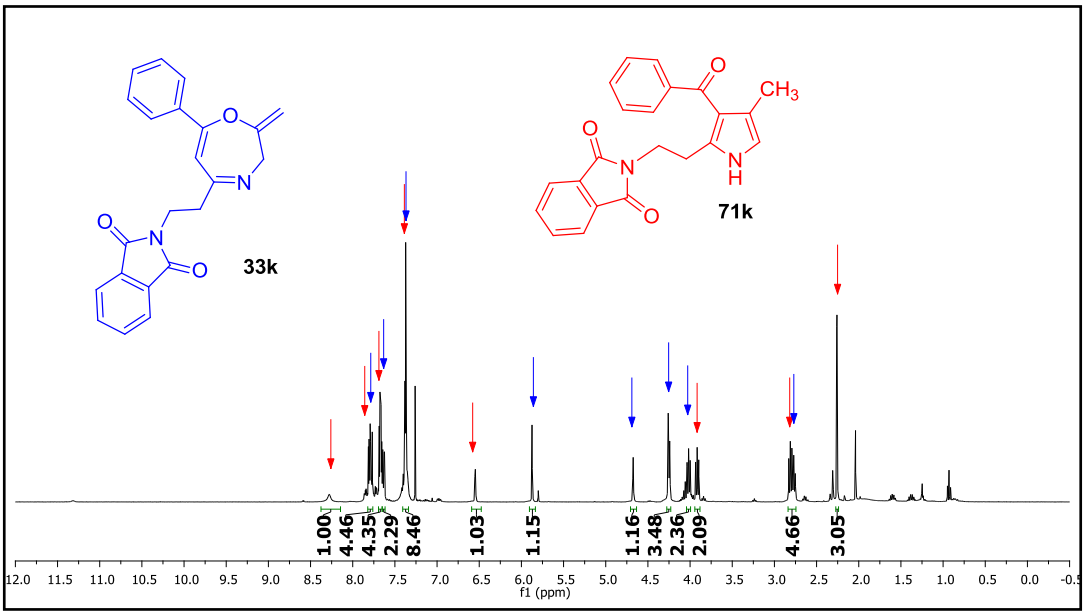

Figure 316. ^{1}H NMR spectrum of a mixture of compounds **33k** and **71k** with a ratio of 1.15:1.00, respectively.

Note that pyrrole **71k** could not be obtained in pure state from flash column chromatography since it came together with 1,4-oxazepine **33k** in the last fractions of column chromatography. Peak assignments were made by peak picking. In the spectrum (Figure 316), peaks belong to 1,4-oxazepine **33k** are shown by blue arrows while those belong to pyrrole **71k** are depicted by red arrows. For ^{1}H NMR data of pyrrole **71k**, see experimental part.

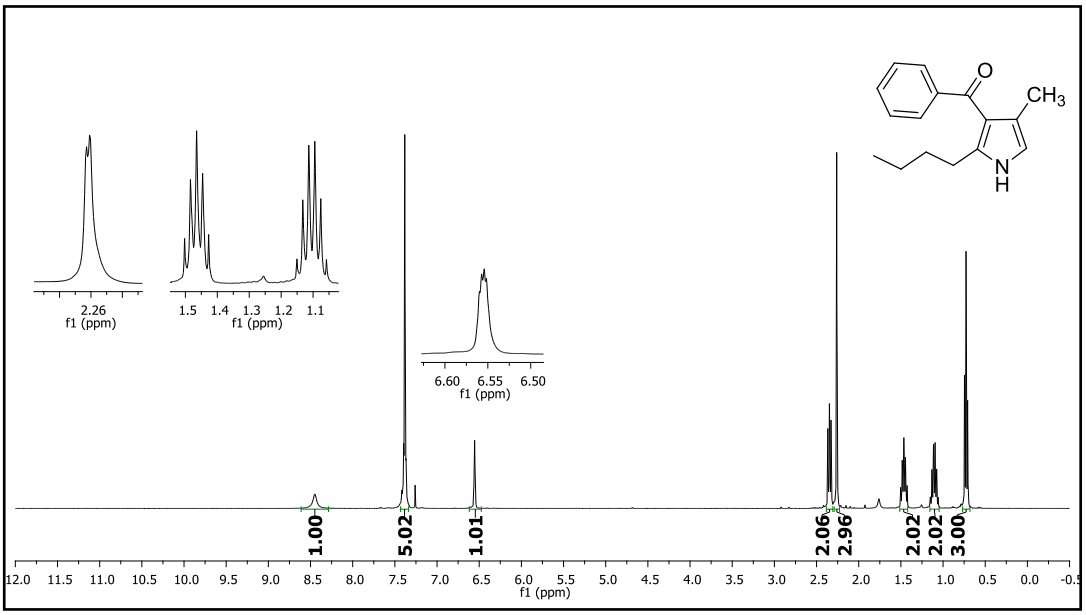

Figure 317. ^{1}H NMR spectrum of compound **71l**.

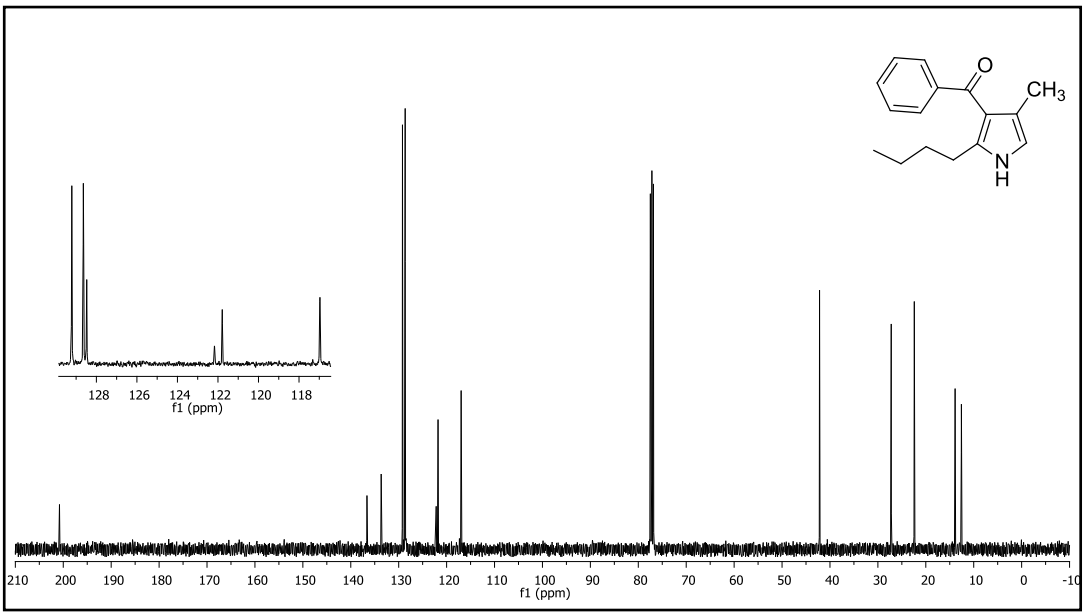

Figure 318. ^{13}C NMR spectrum of compound **71l**.

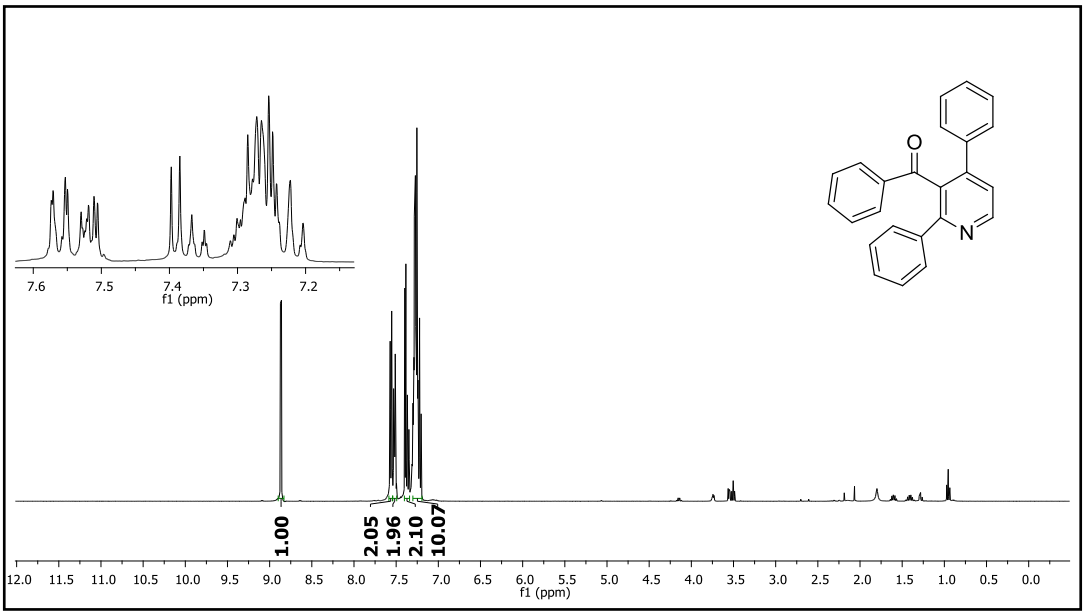

Figure 319. ^{1}H NMR spectrum of compound **82**.

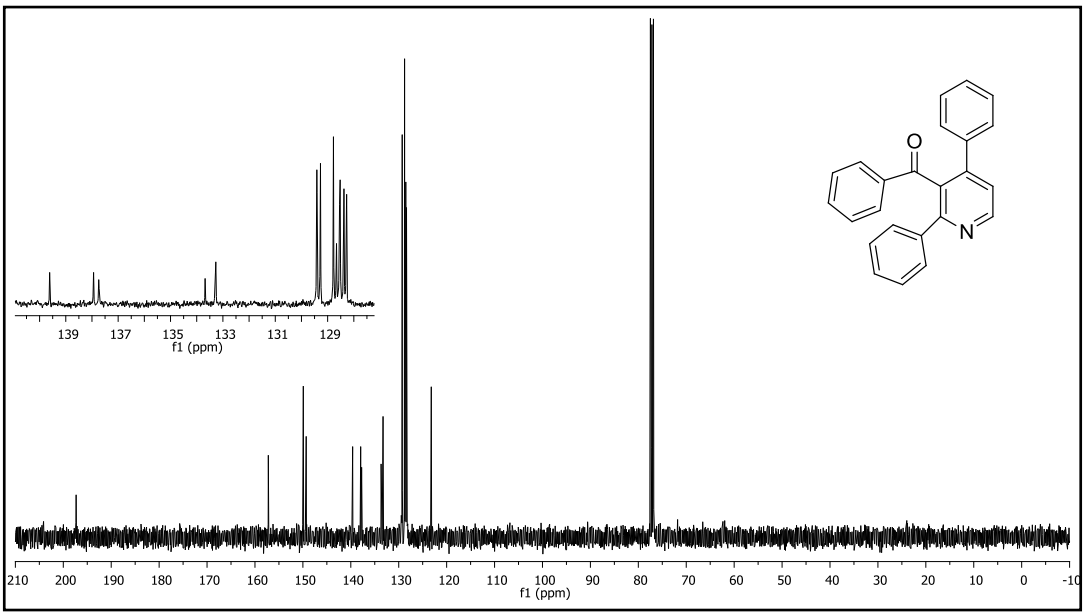

Figure 320. ^{13}C NMR spectrum of compound **82**.

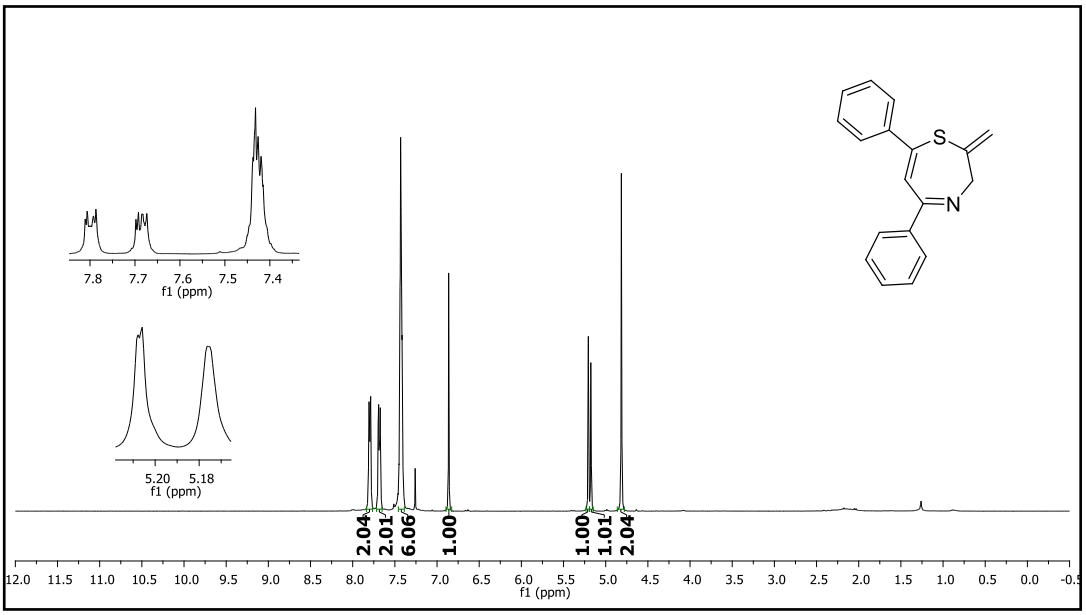

Figure 321. ^{1}H NMR spectrum of compound **59a**.

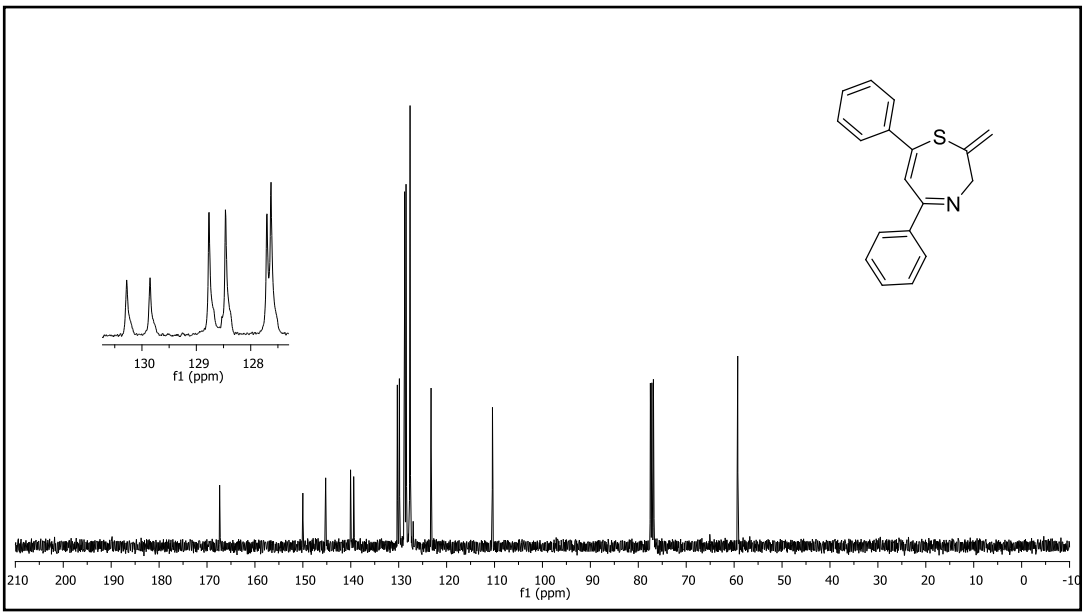

Figure 322. ^{13}C NMR spectrum of compound **59a**.

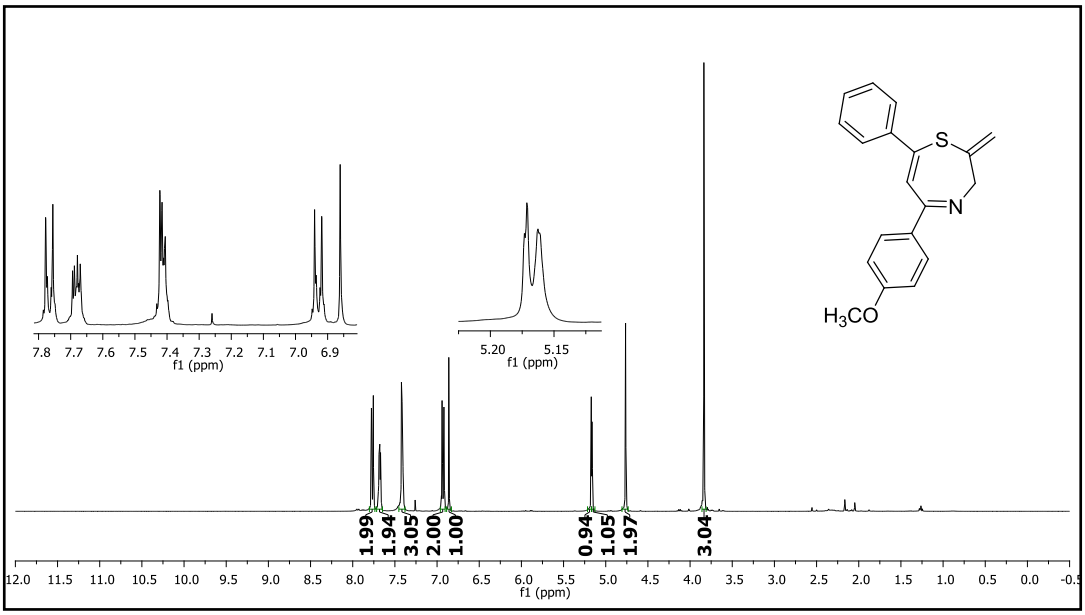

Figure 323. ^{1}H NMR spectrum of compound **59b**.

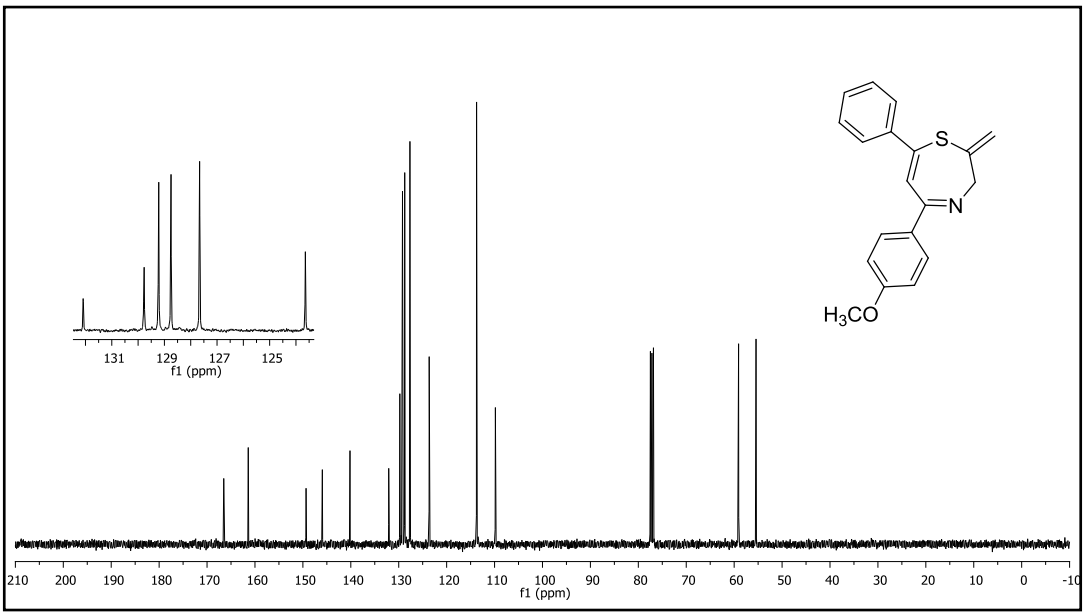

Figure 324. ^{13}C NMR spectrum of compound **59b**.

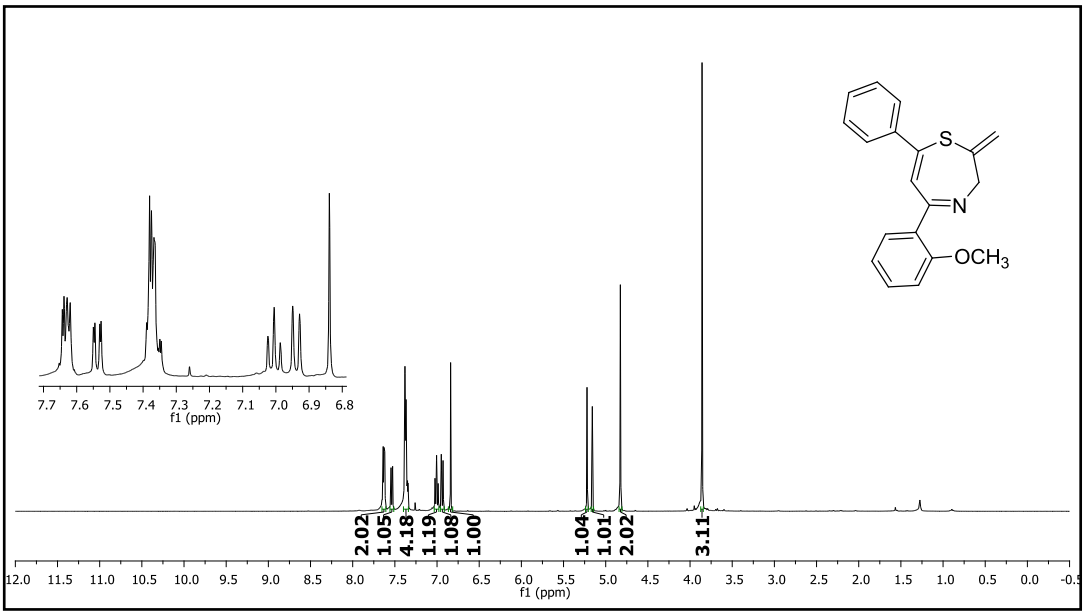

Figure 325. ^{1}H NMR spectrum of compound **59c**.

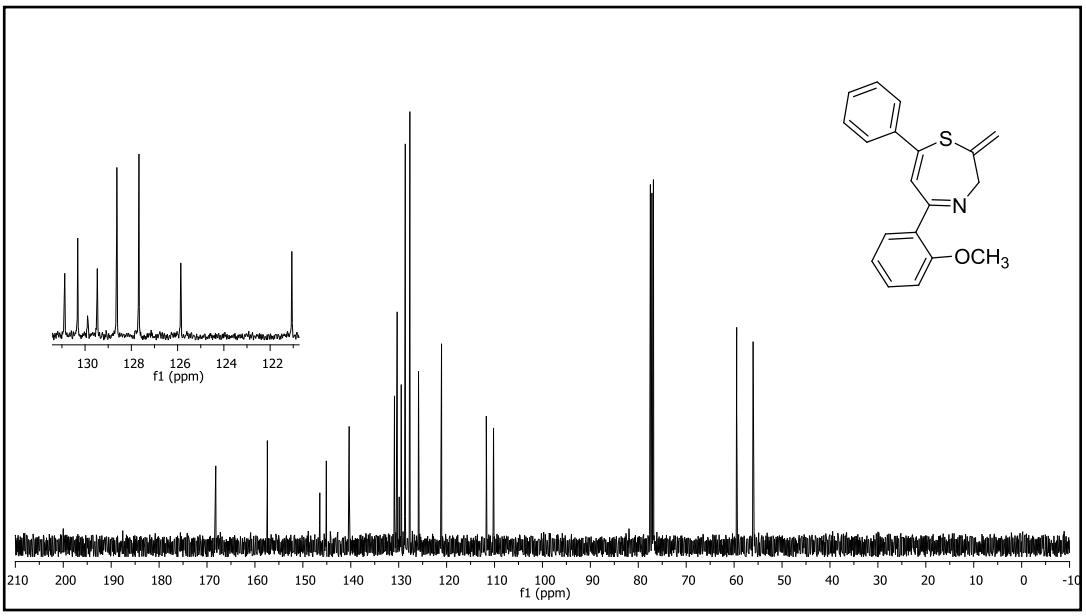

Figure 326. ^{13}C NMR spectrum of compound **59c**.

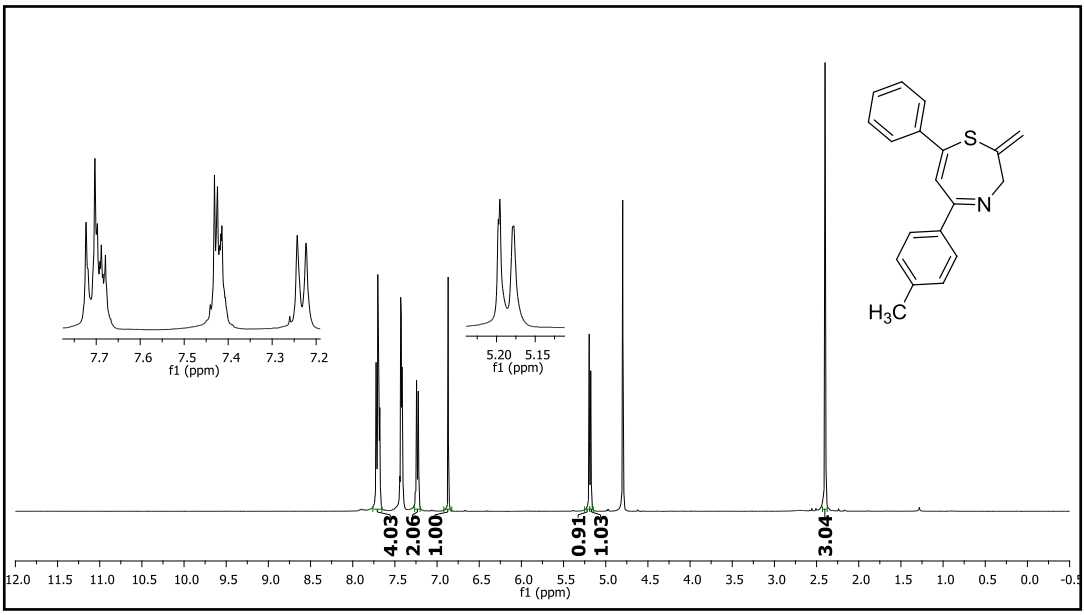

Figure 327. ^{1}H NMR spectrum of compound **59d**.

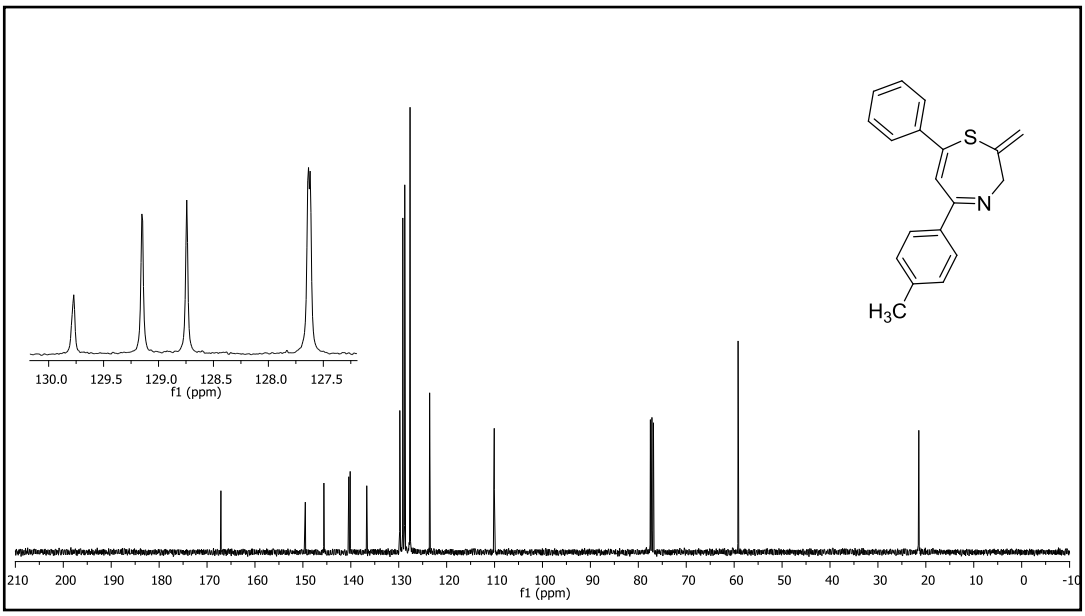

Figure 328. ^{13}C NMR spectrum of compound **59d**.

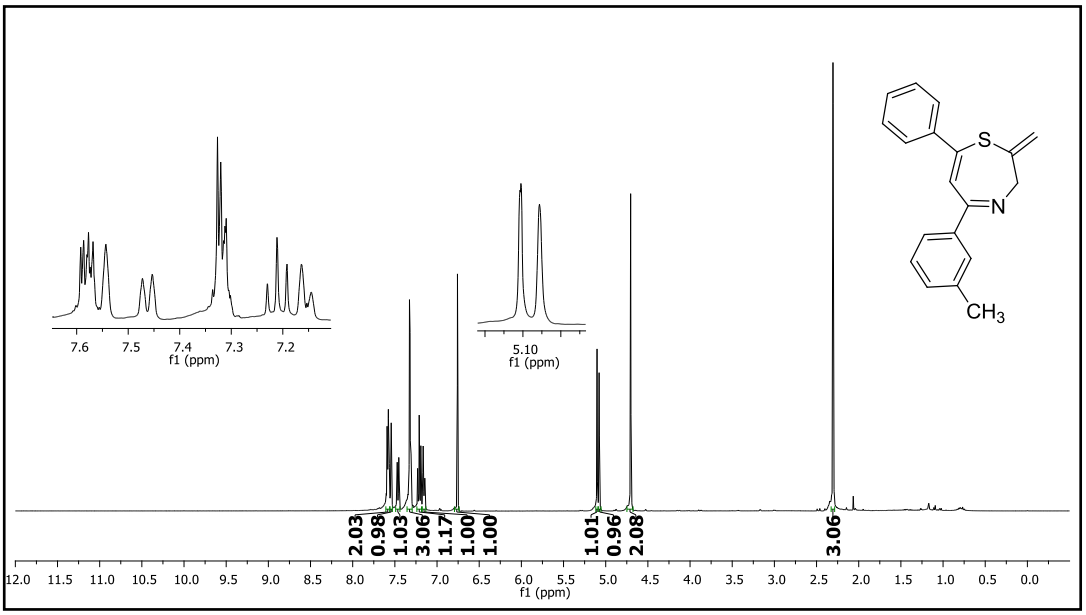

Figure 329. ^{1}H NMR spectrum of compound **59e**.

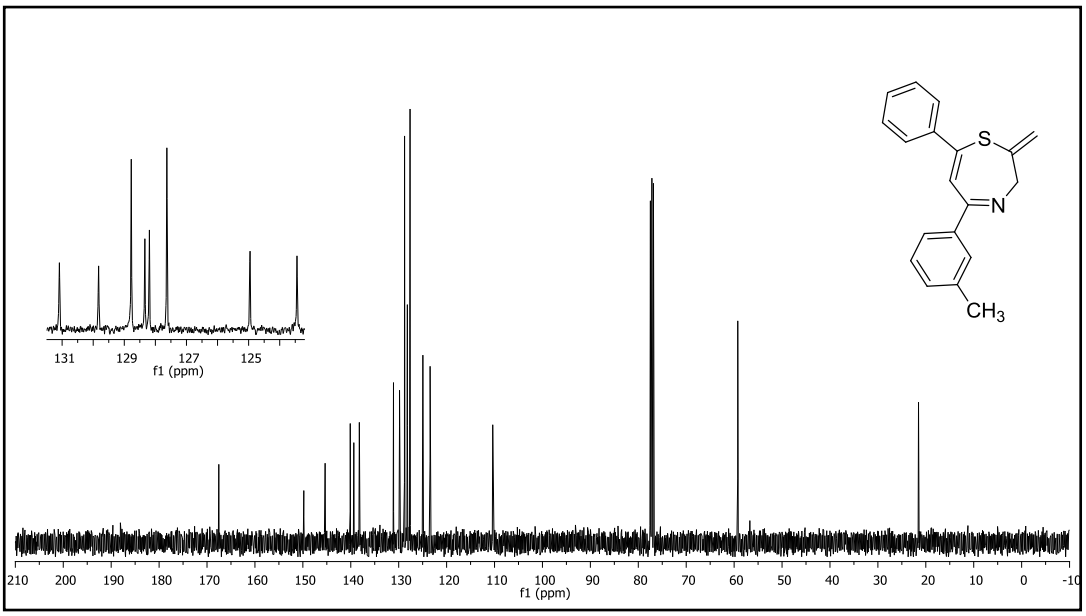

Figure 330. ^{13}C NMR spectrum of compound **59e**.

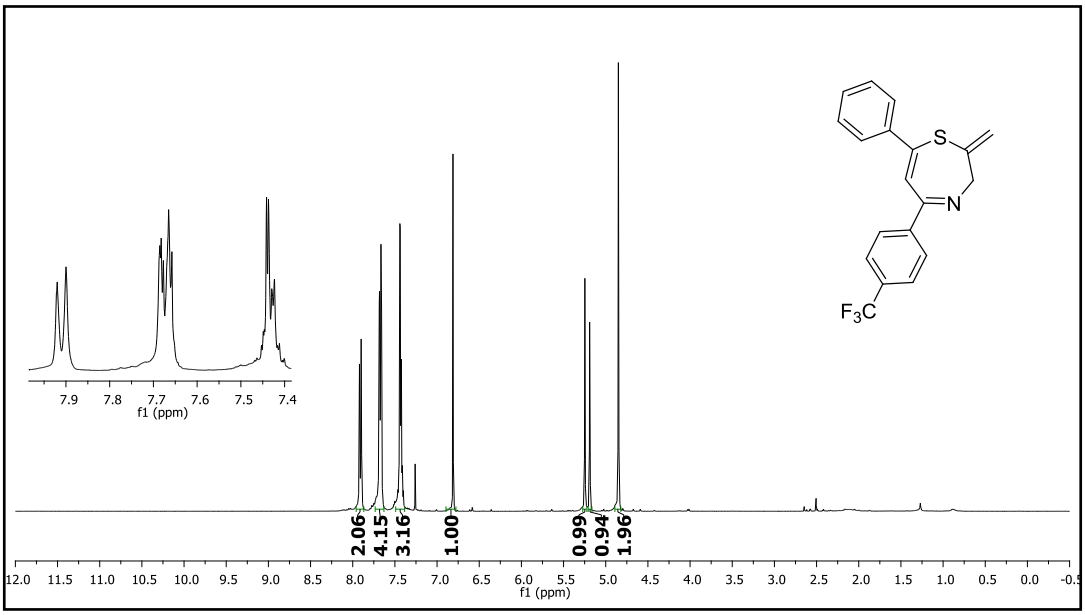

Figure 331. ^{1}H NMR spectrum of compound **59f**.

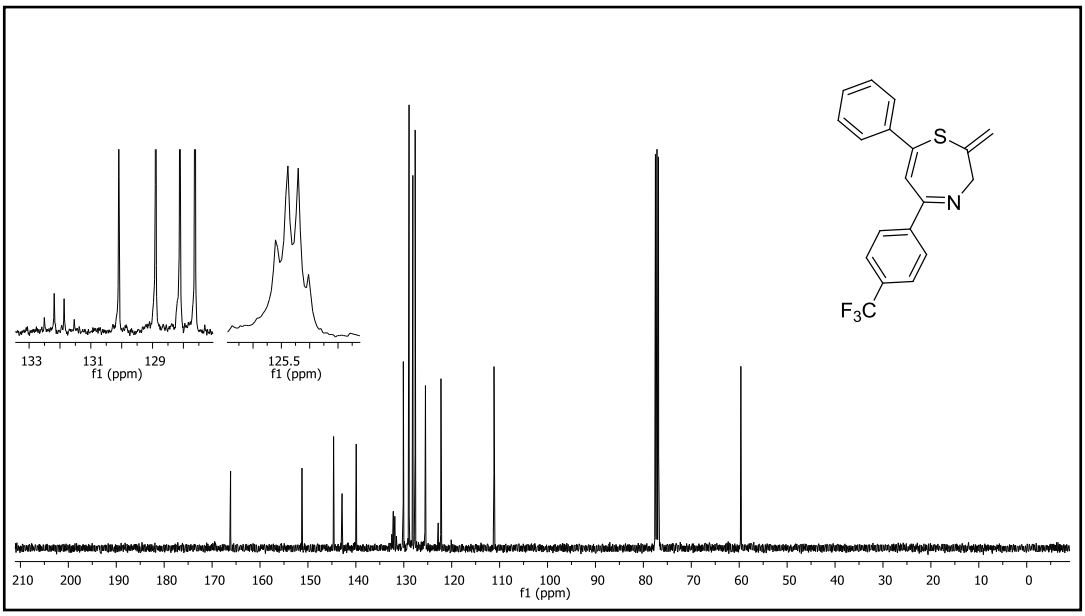

Figure 332. ^{13}C NMR spectrum of compound **59f**.

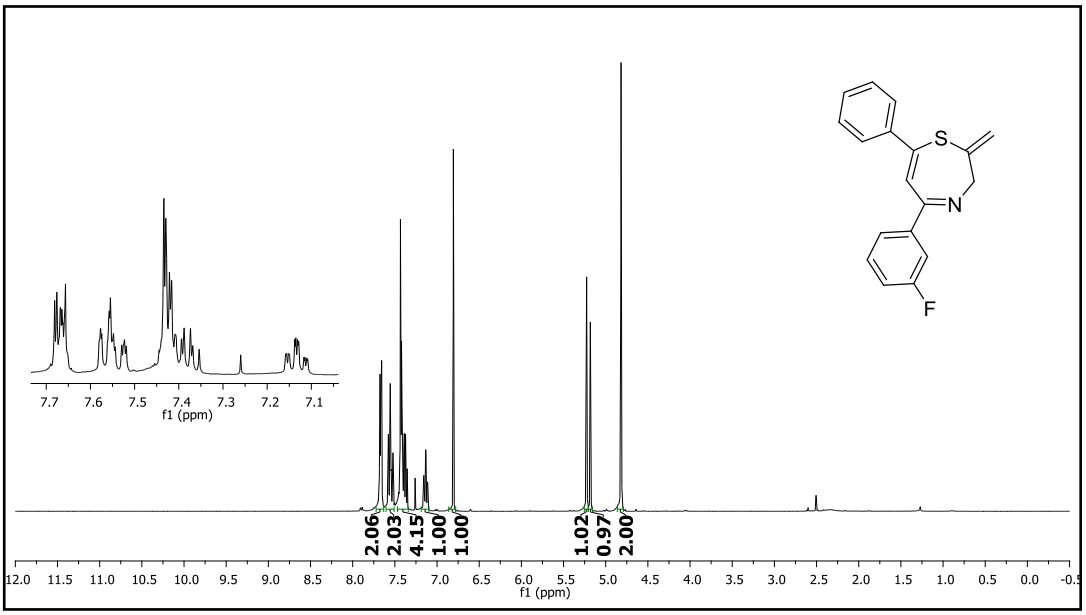

Figure 333. ^{1}H NMR spectrum of compound **59h**.

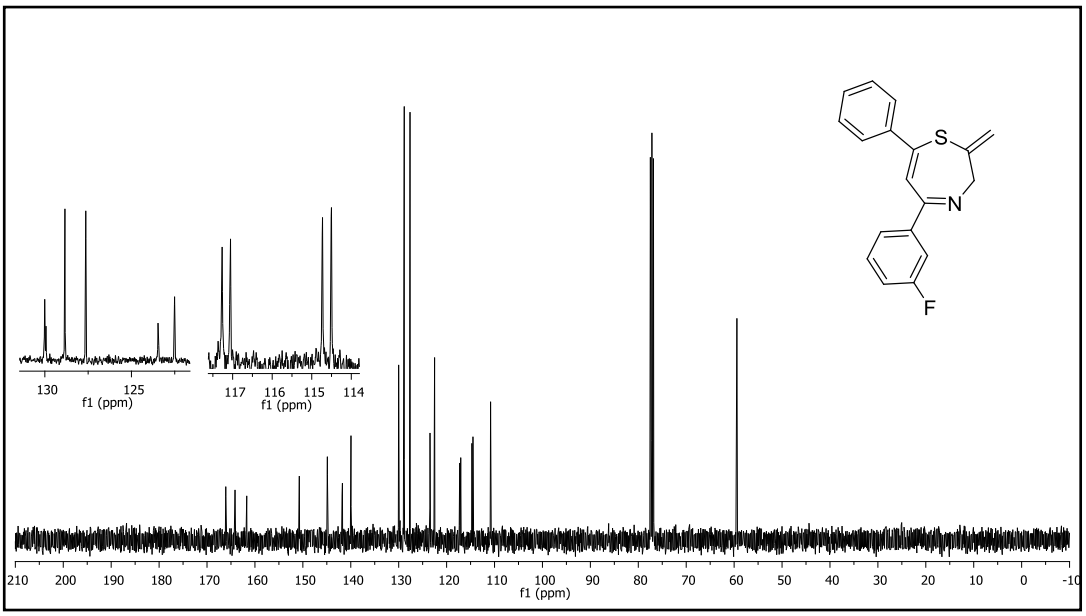

Figure 334. ^{13}C NMR spectrum of compound **59h**.

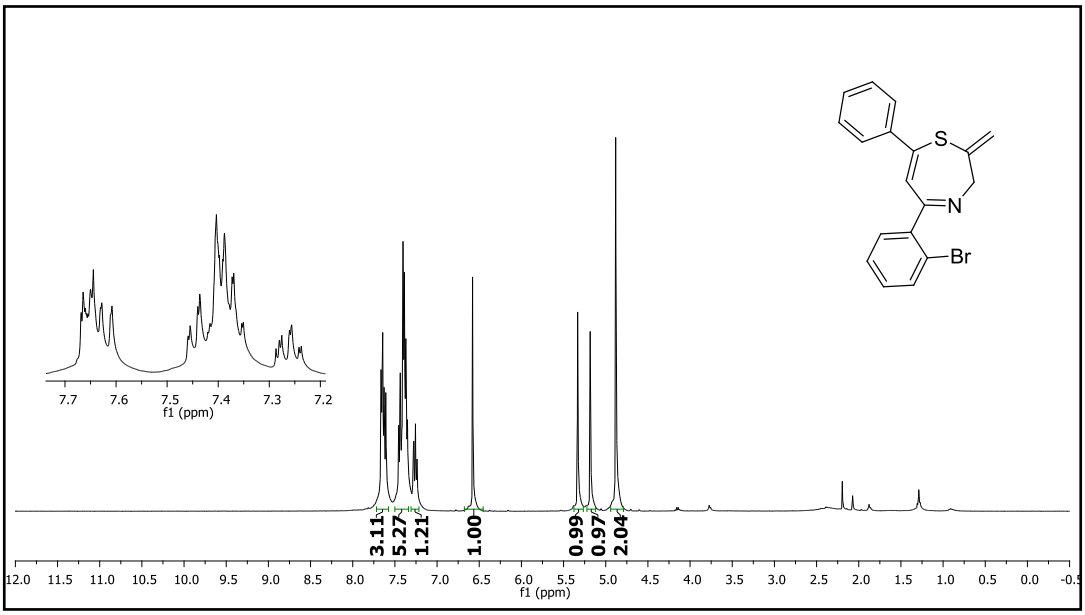

Figure 335. ^{1}H NMR spectrum of compound **59i**.

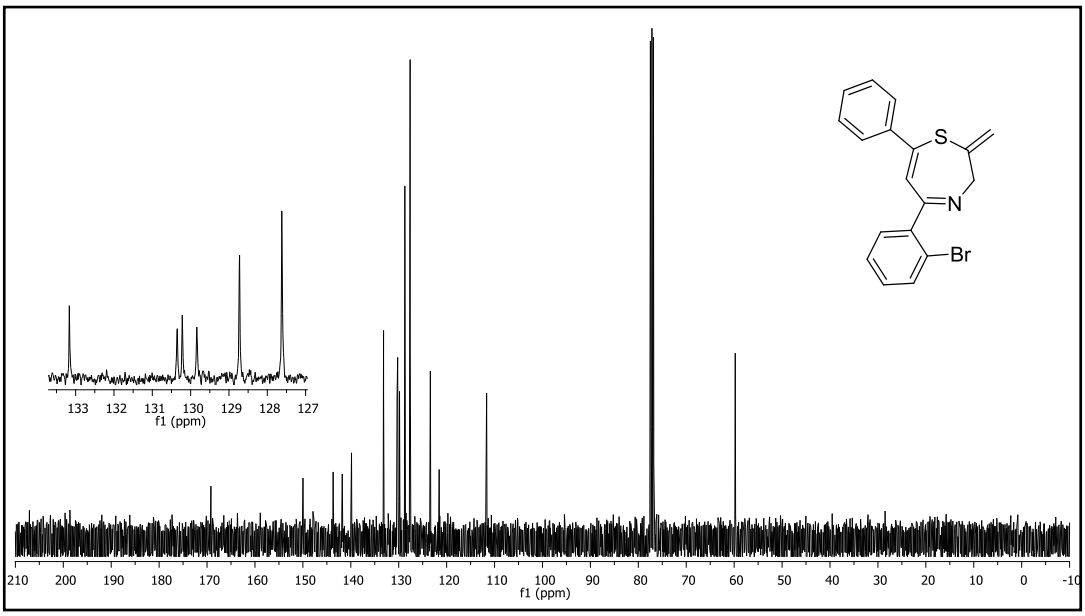

Figure 336. ^{13}C NMR spectrum of compound **59i**.

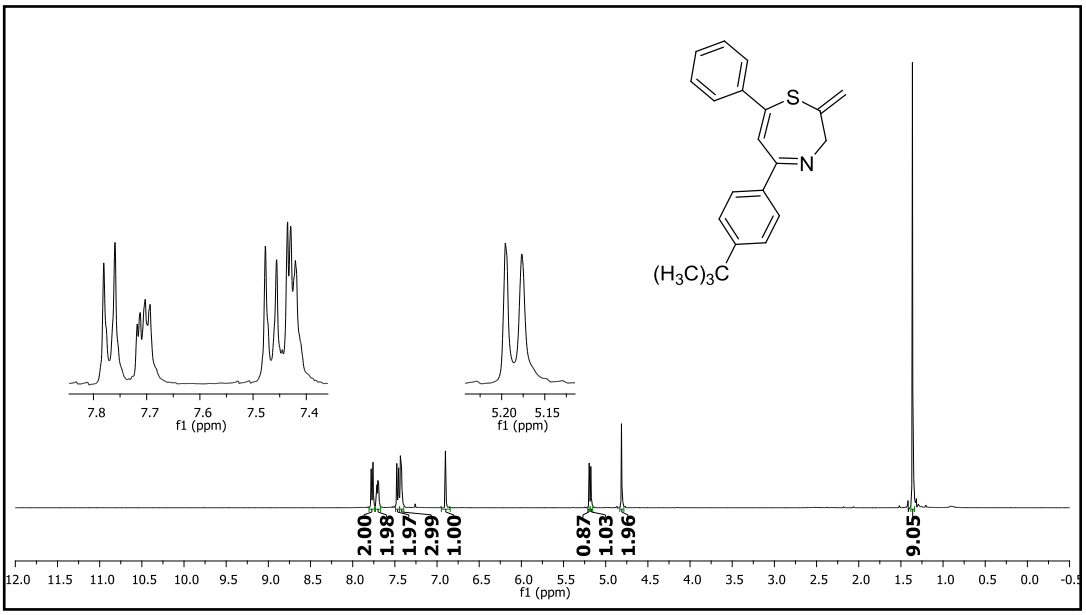

Figure 337. ^{1}H NMR spectrum of compound **59j**.

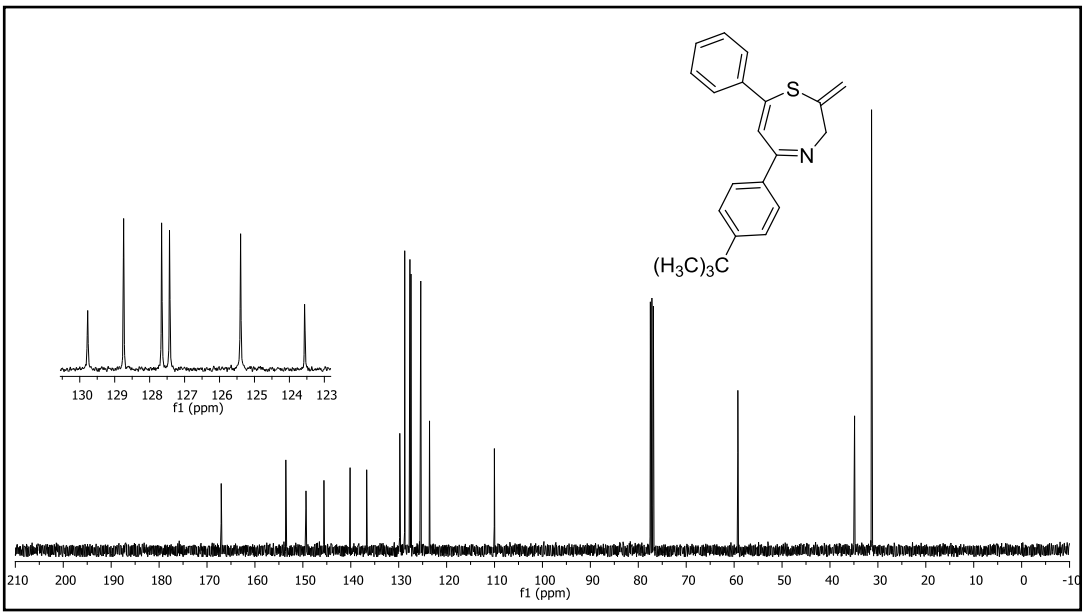

Figure 338. ^{13}C NMR spectrum of compound **59j**.

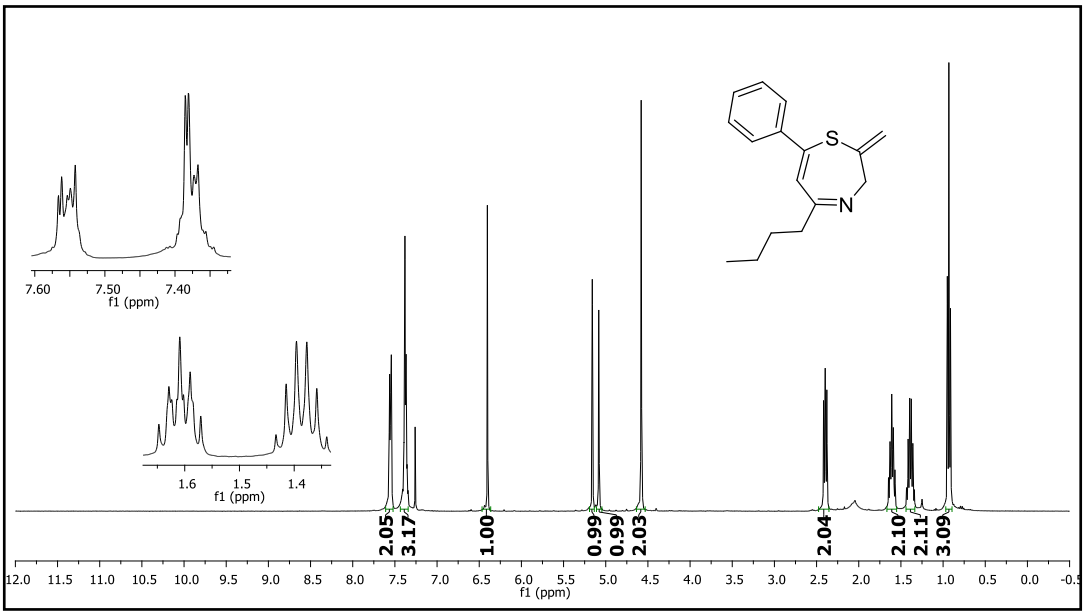

Figure 339. ^{1}H NMR spectrum of compound **59l**.

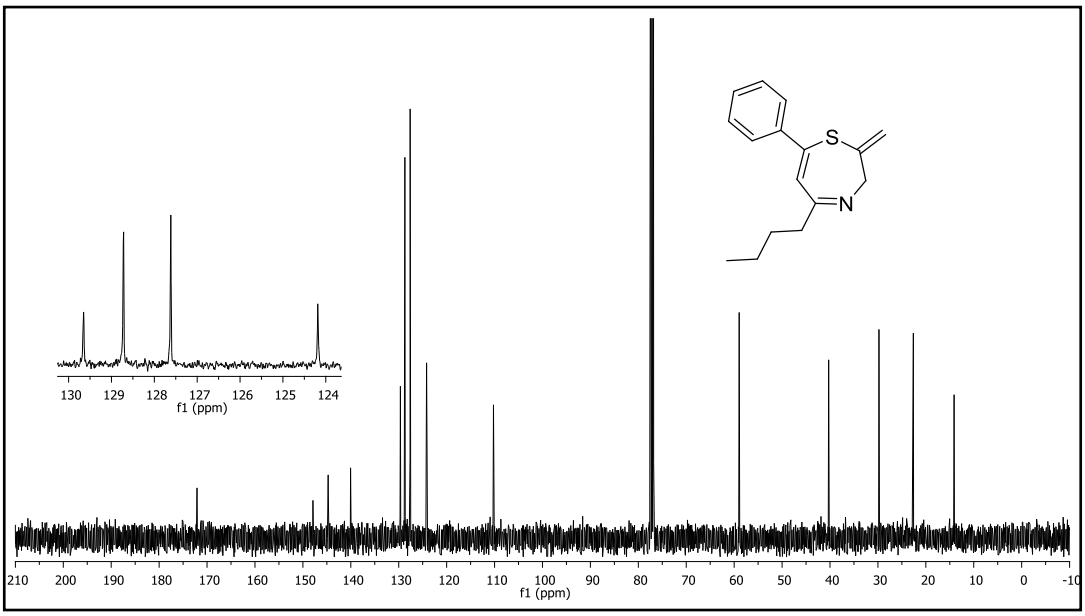

Figure 340. ^{13}C NMR spectrum of compound **59l**.

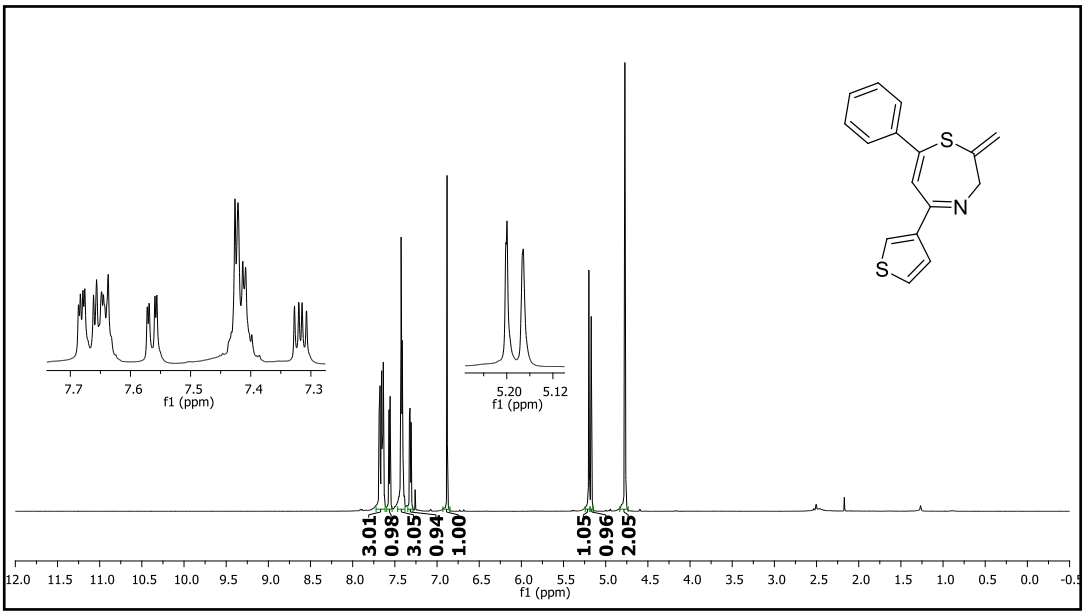

Figure 341. ^{1}H NMR spectrum of compound **59m**.

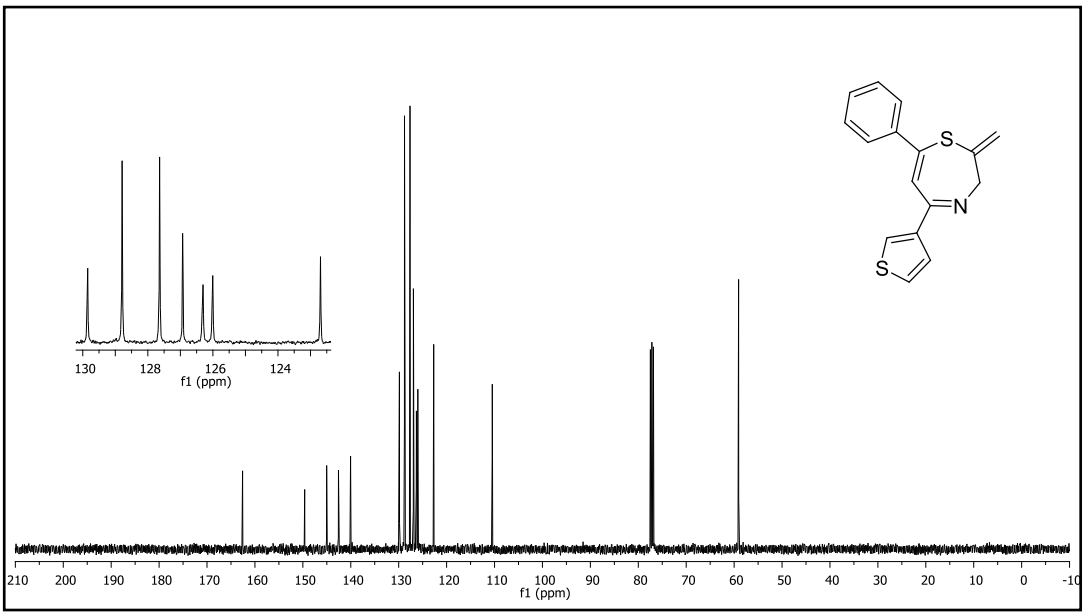

Figure 342. ^{13}C NMR spectrum of compound **59m**.

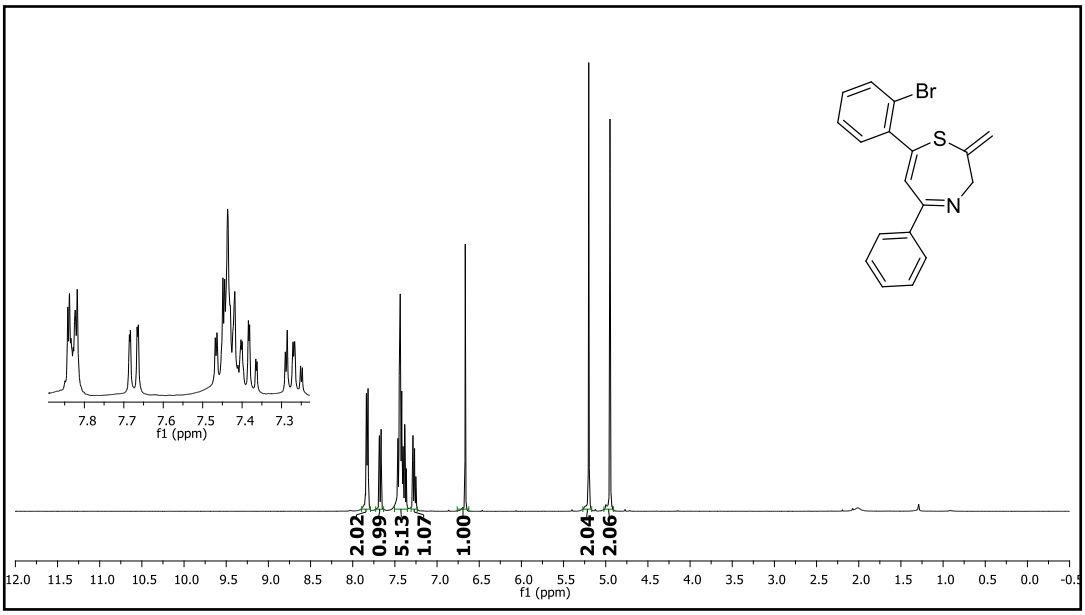

Figure 343. ^{1}H NMR spectrum of compound **59n**.

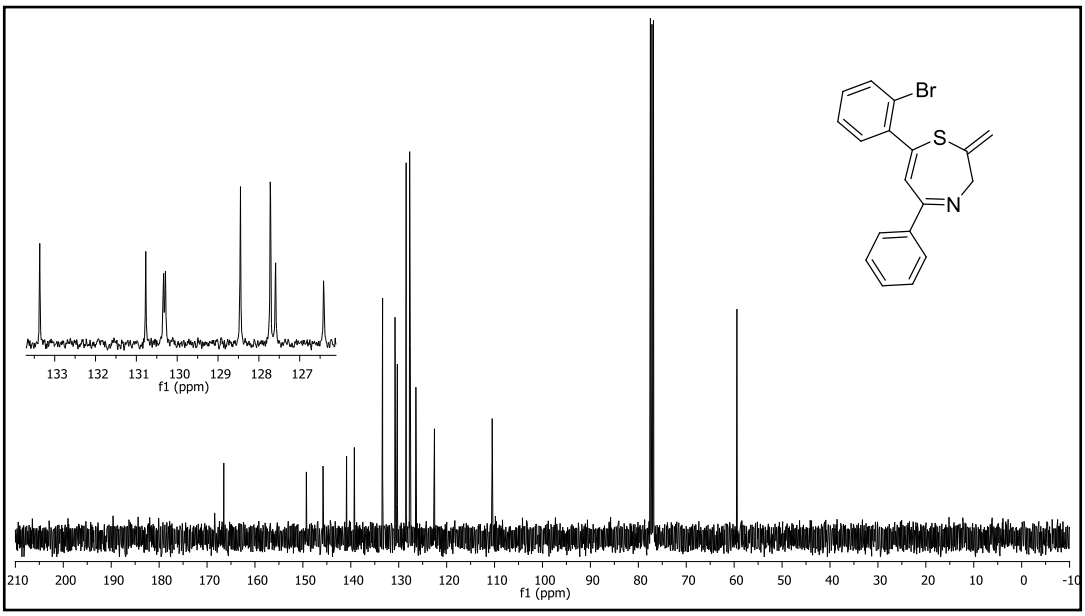

Figure 344. ^{13}C NMR spectrum of compound **59n**.

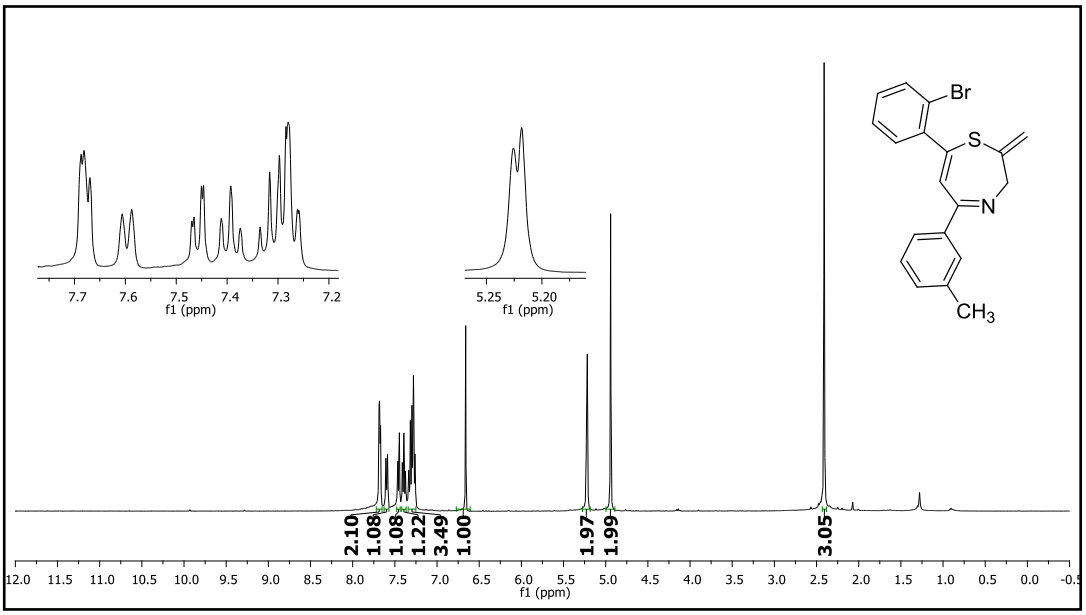

Figure 345. ^{1}H NMR spectrum of compound **59r**.

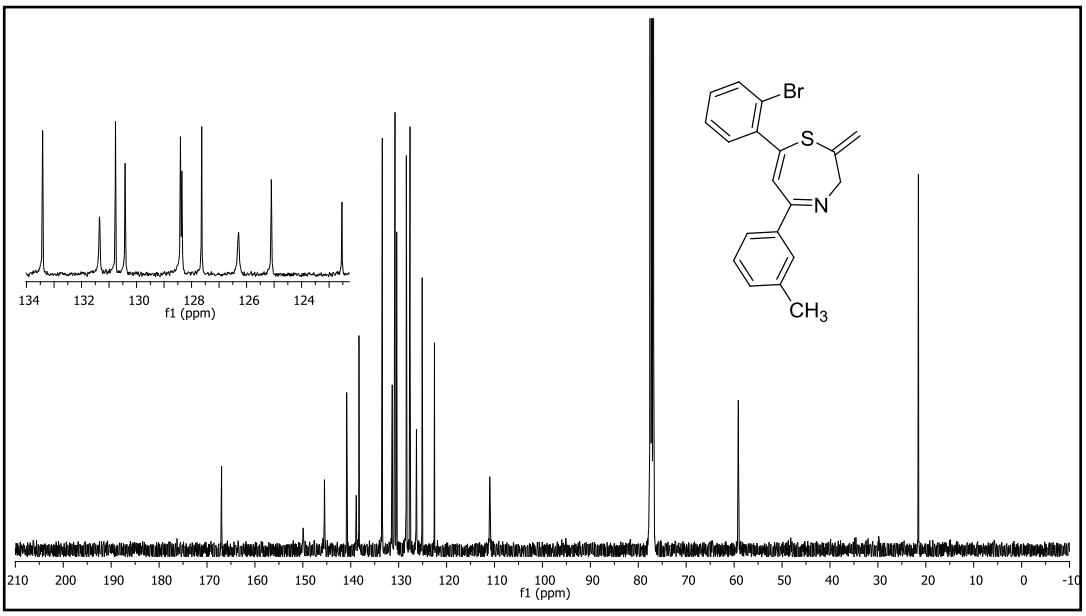

Figure 346. ^{13}C NMR spectrum of compound **59r**.

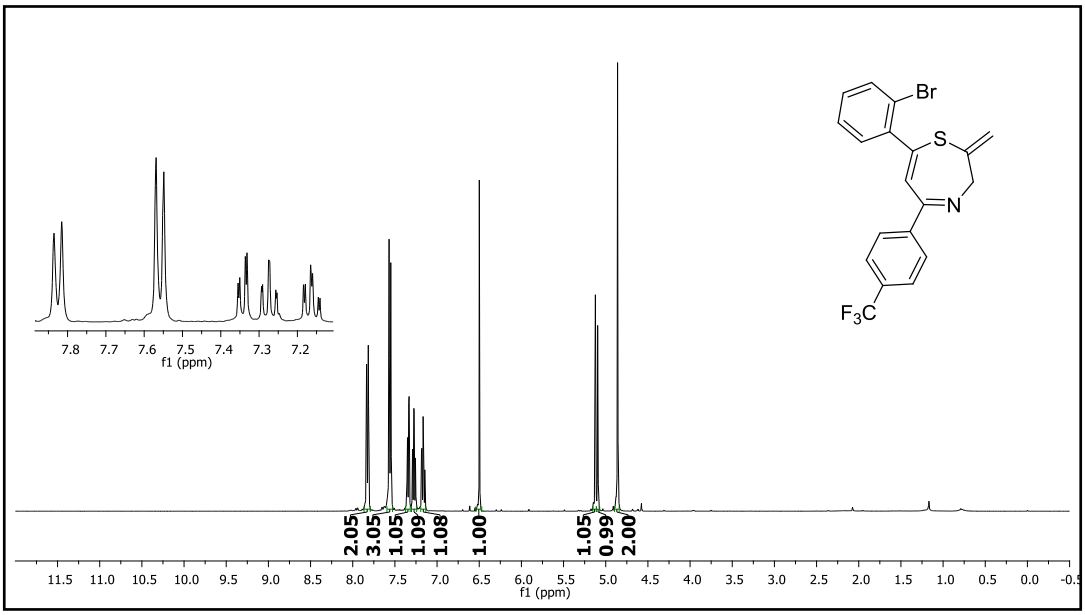

Figure 347. ^{1}H NMR spectrum of compound **59s**.

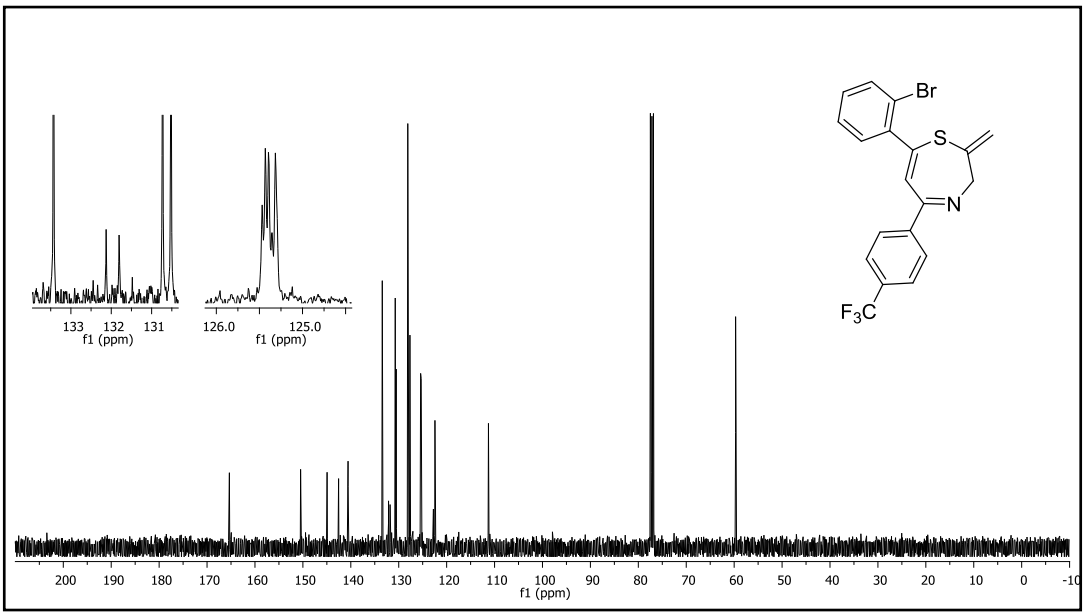

Figure 348. ^{13}C NMR spectrum of compound **59s**.

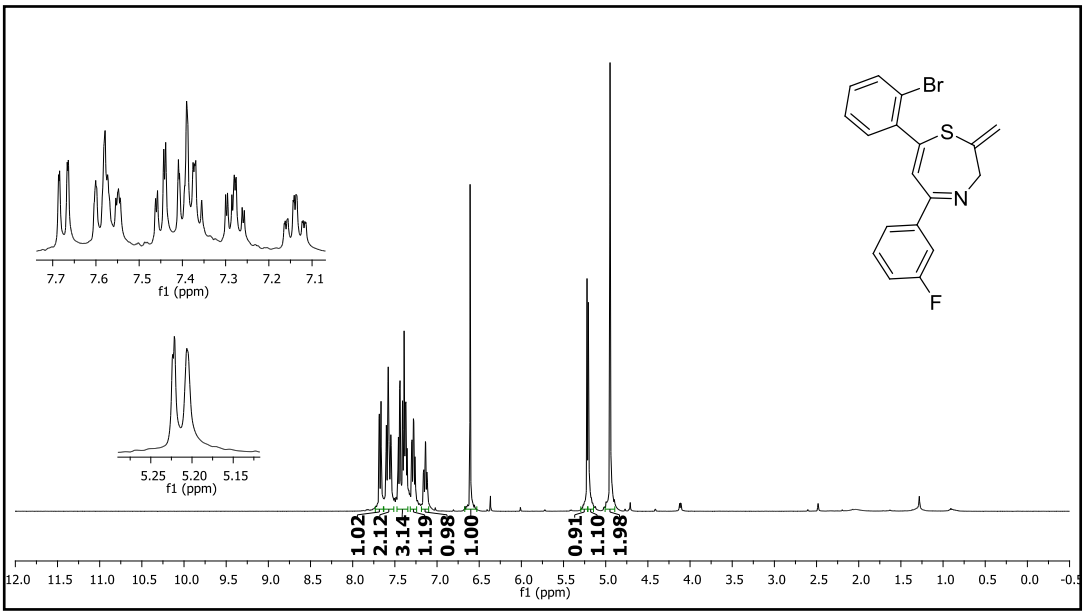

Figure 349. ^{1}H NMR spectrum of compound **59t**.

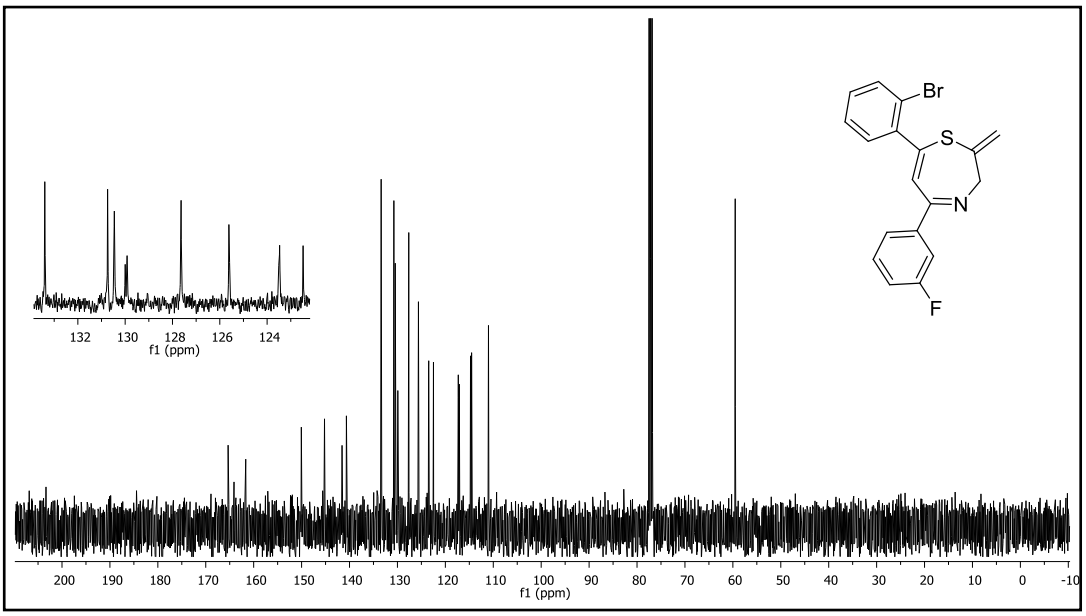

Figure 350. ^{13}C NMR spectrum of compound **59t**.

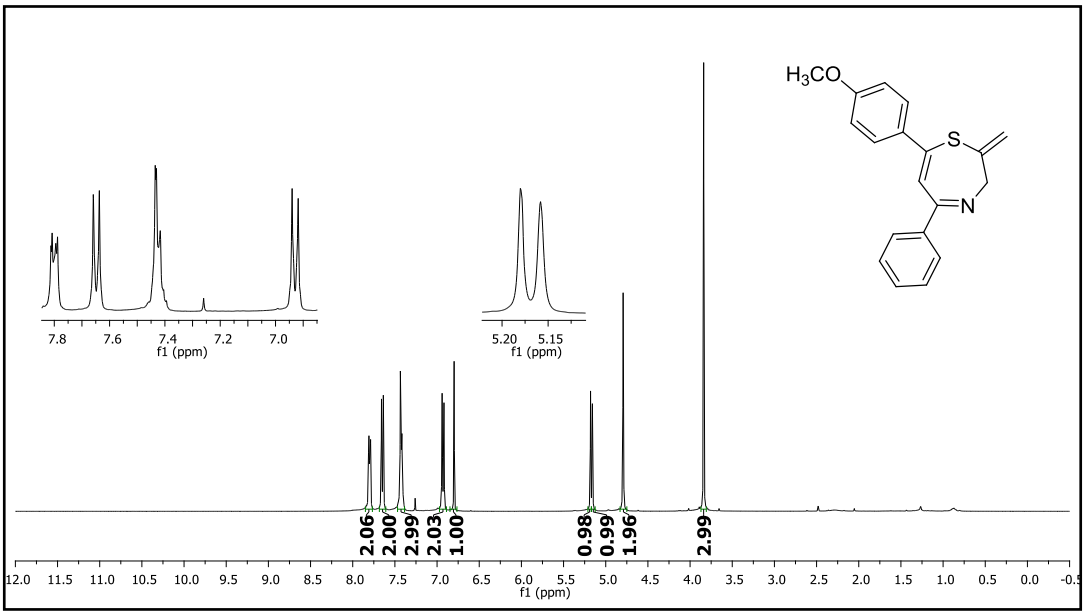

Figure 351. ^{1}H NMR spectrum of compound **59v**.

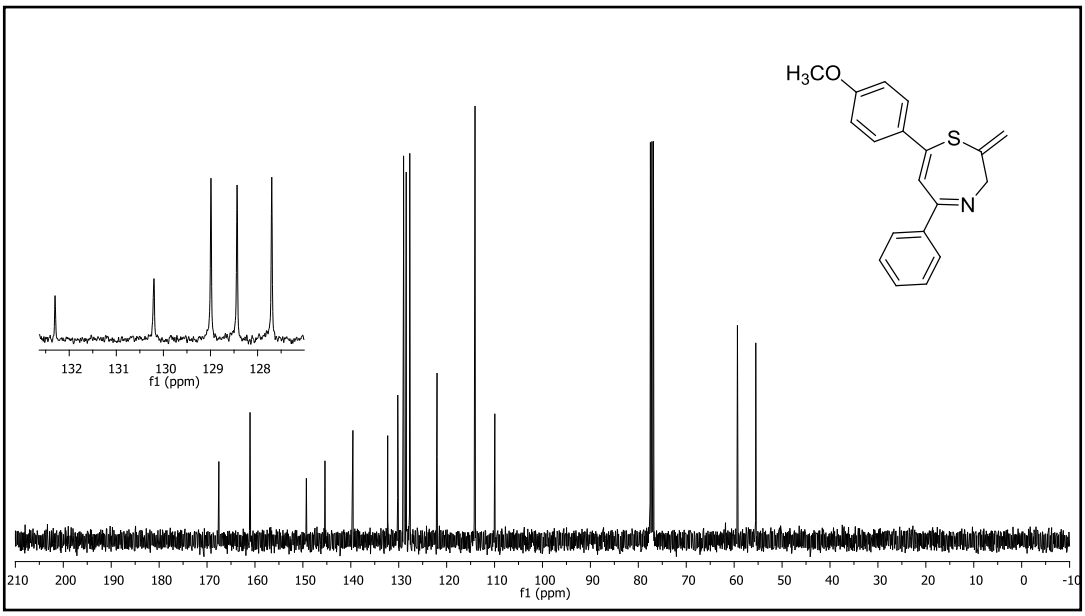

Figure 352. ^{13}C NMR spectrum of compound **59v**.

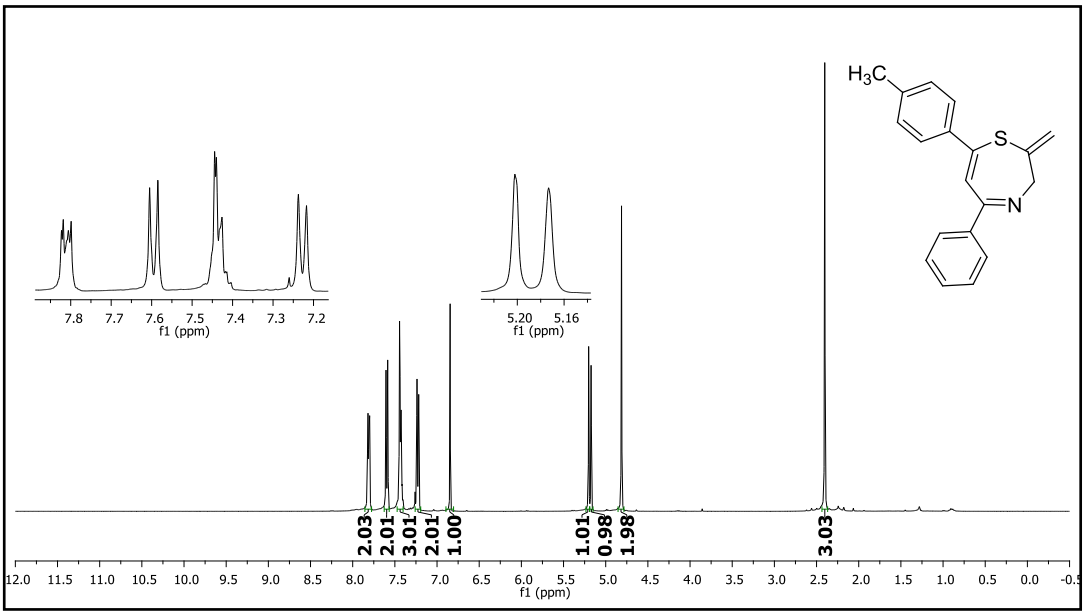

Figure 353. ^{1}H NMR spectrum of compound **59w**.

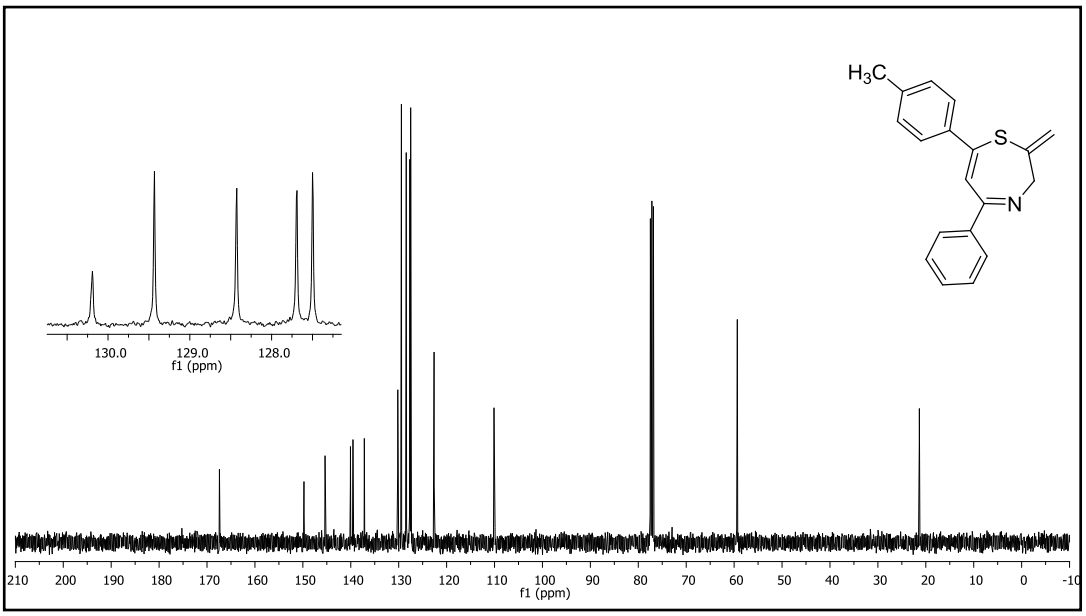

Figure 354. ^{13}C NMR spectrum of compound **59w**.

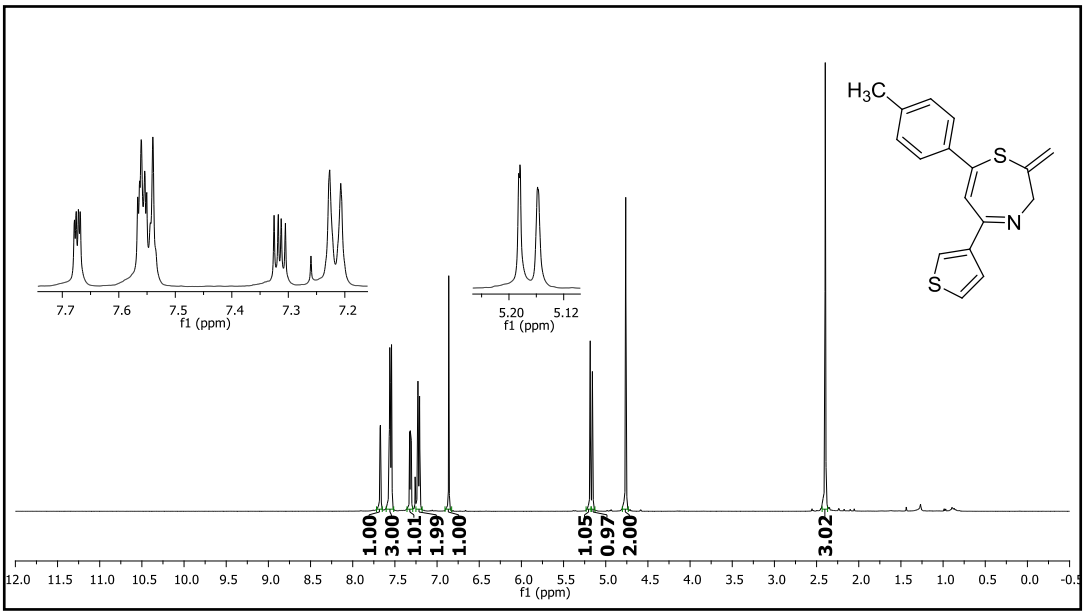

Figure 355. ^{1}H NMR spectrum of compound **59x**.

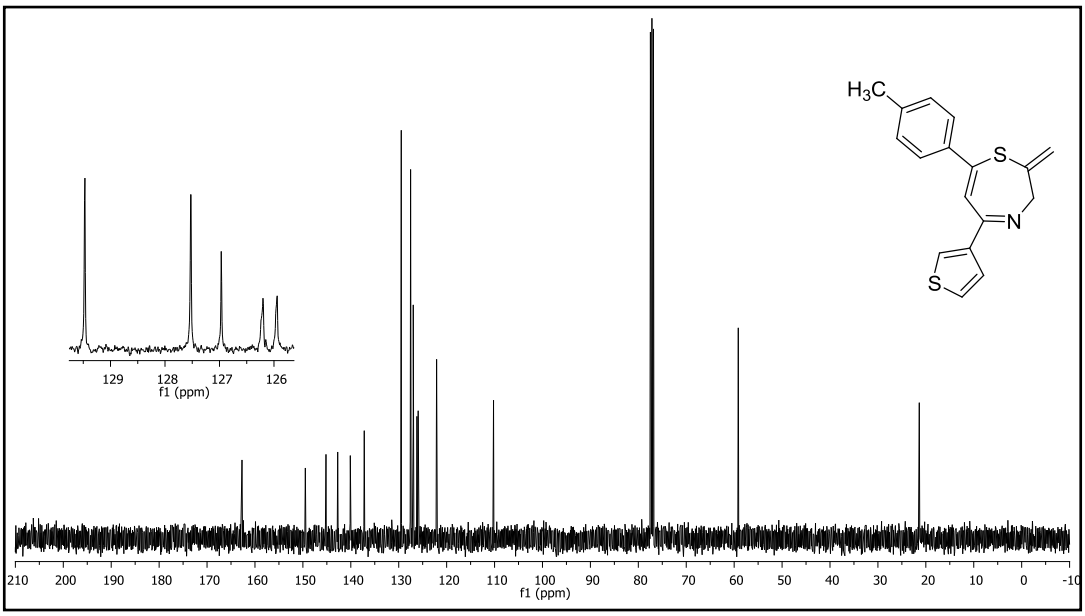

Figure 356. ^{13}C NMR spectrum of compound **59x**.

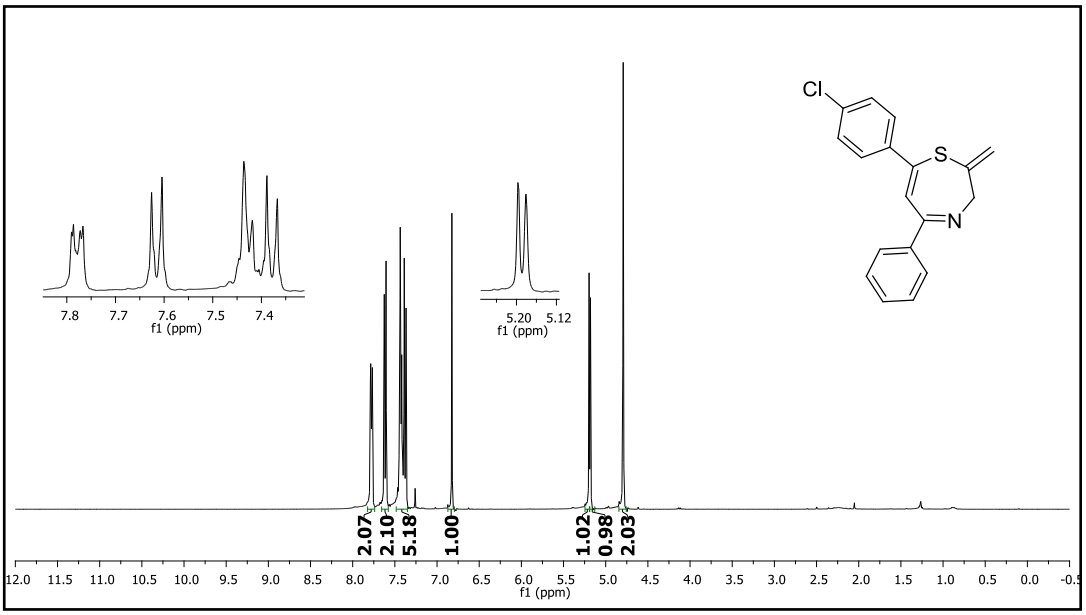

Figure 357. ^{1}H NMR spectrum of compound **59y**.

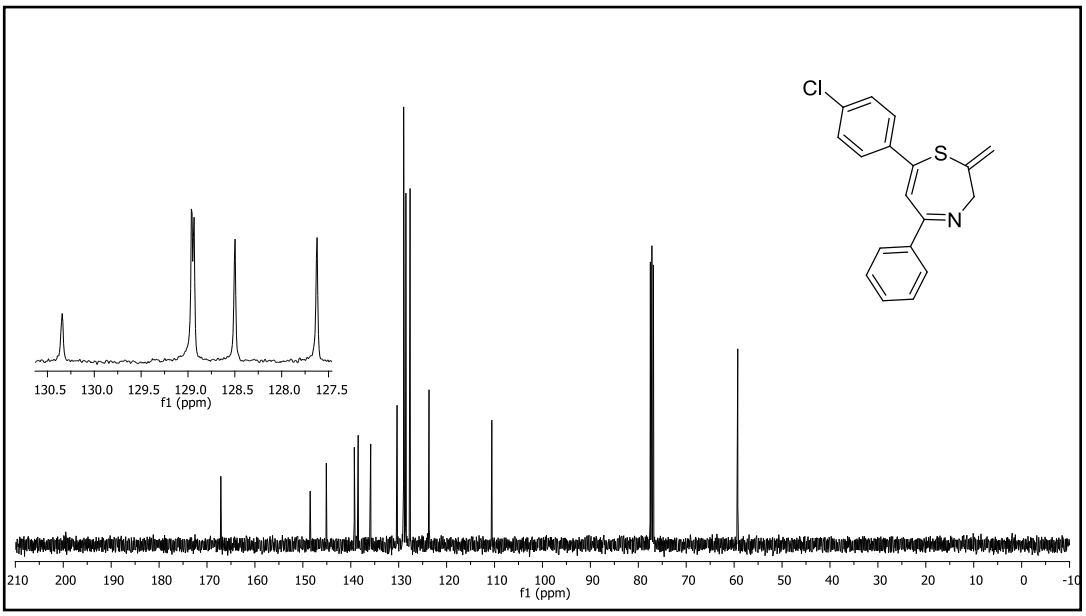

Figure 358. ^{13}C NMR spectrum of compound **59y**.

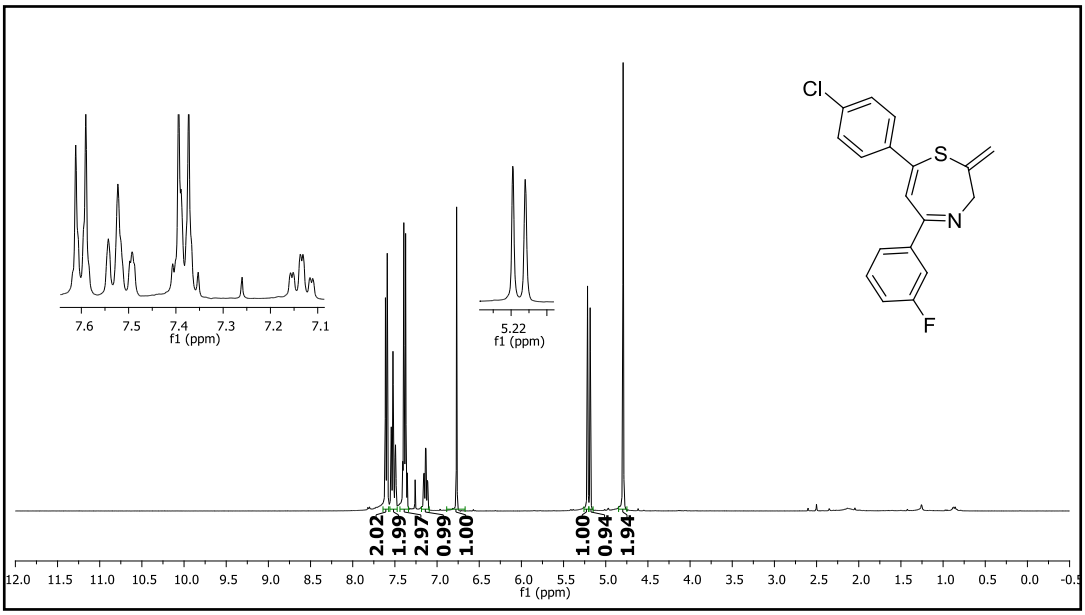

Figure 359. ^{1}H NMR spectrum of compound **59z**.

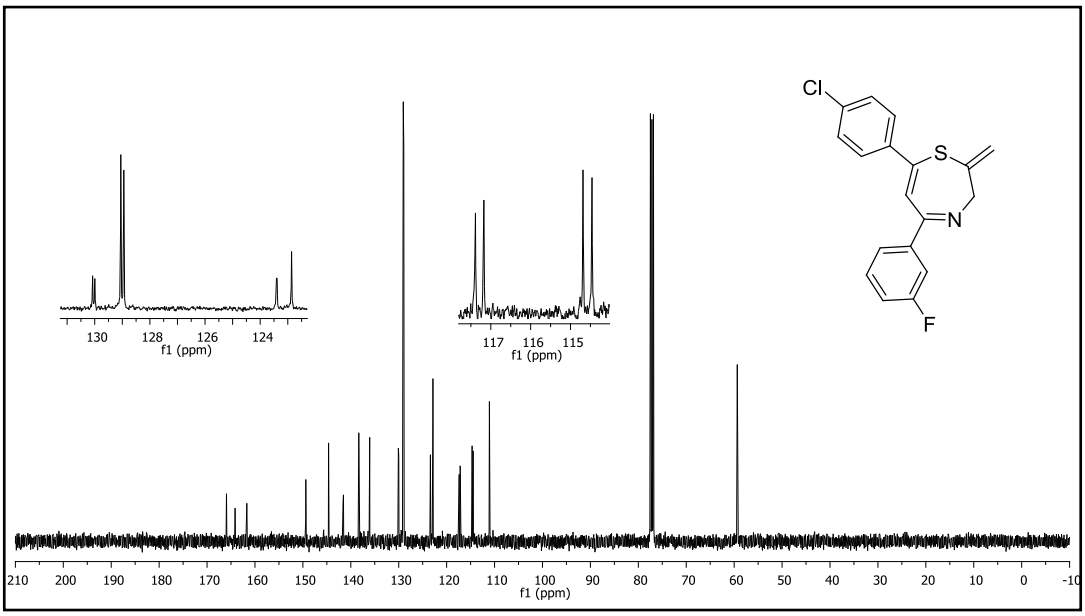

Figure 360. ^{13}C NMR spectrum of compound **59z**.

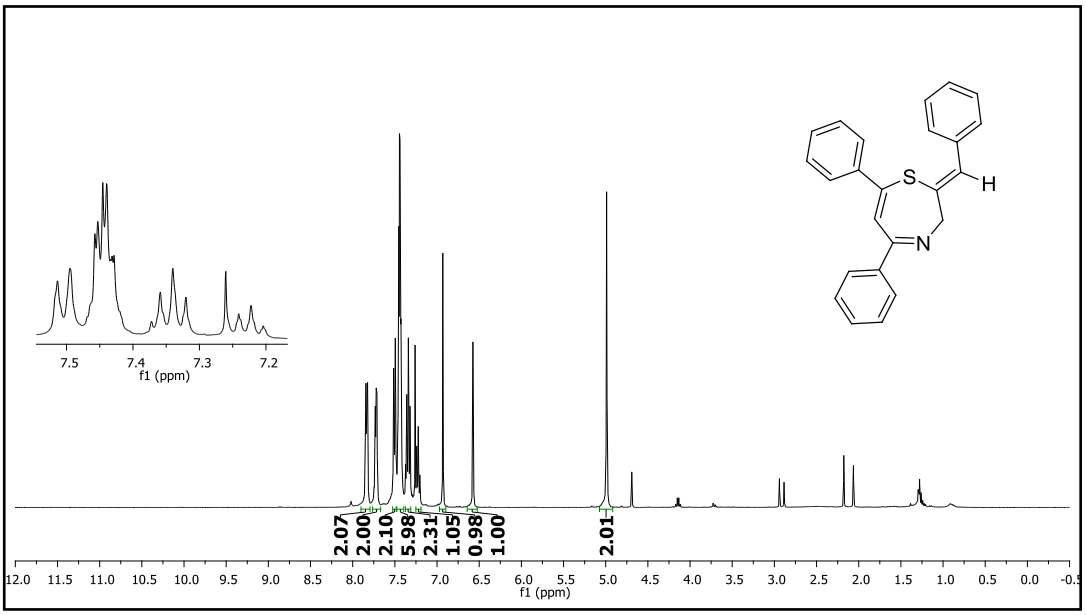

Figure 361. ^{1}H NMR spectrum of compound **85**.

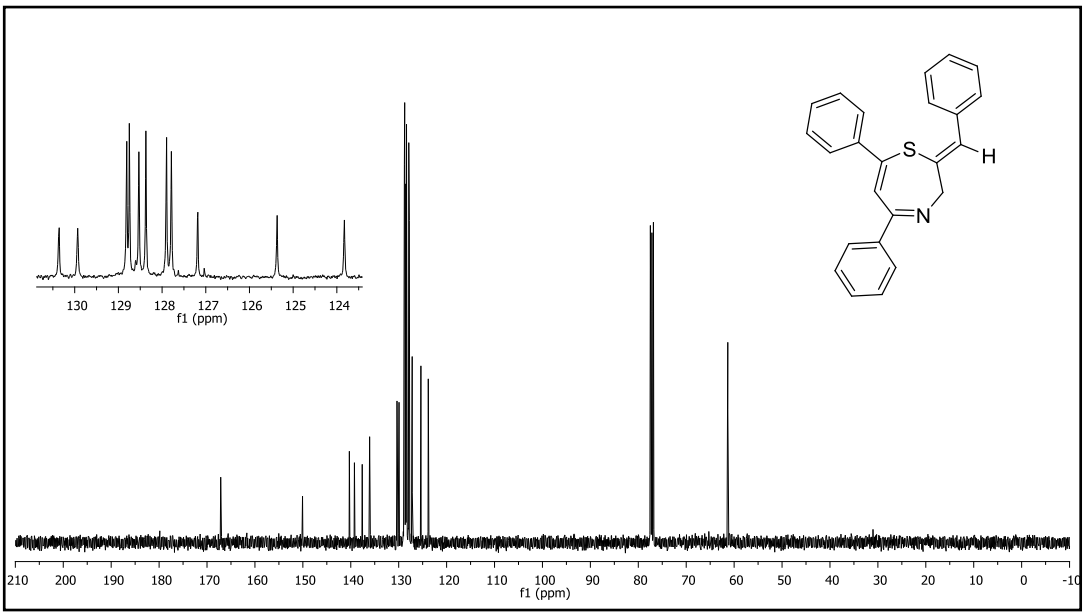

Figure 362. ^{13}C NMR spectrum of compound **85**.

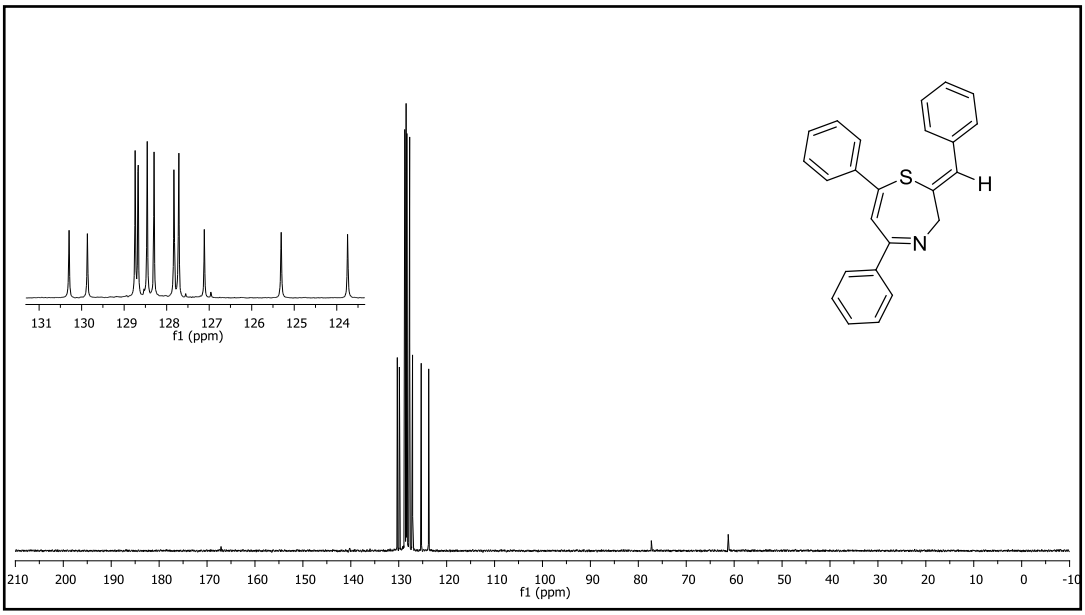

Figure 363. DEPT-90 NMR spectrum of compound **85**.

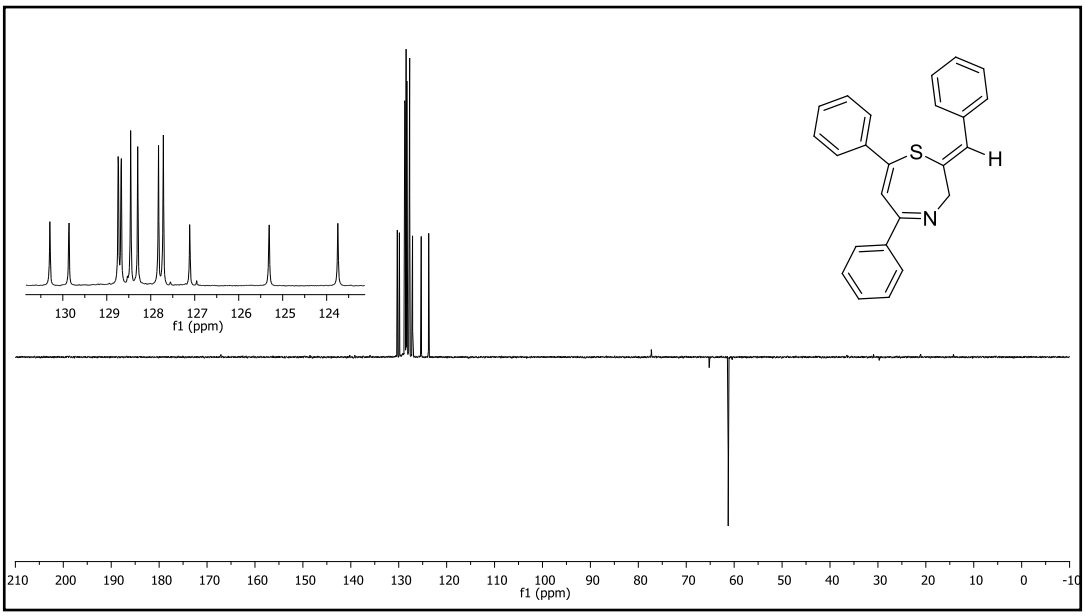

Figure 364. DEPT-135 NMR spectrum of compound **85**.

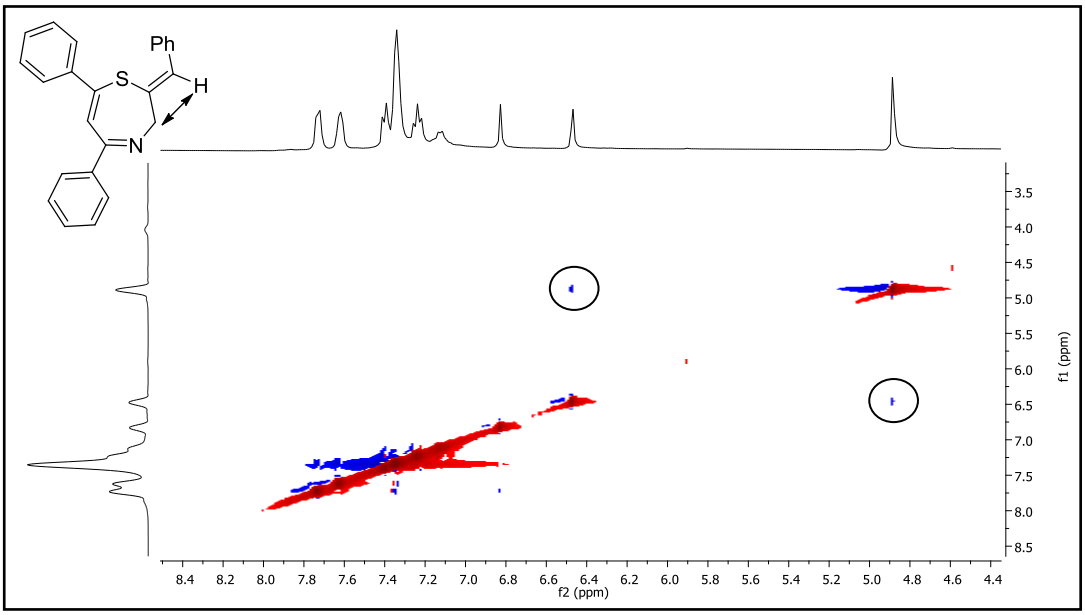

Figure 365. NOESY NMR spectrum of compound **85**.
(Cross peaks in circles represent the NOE interactions shown on the structure)

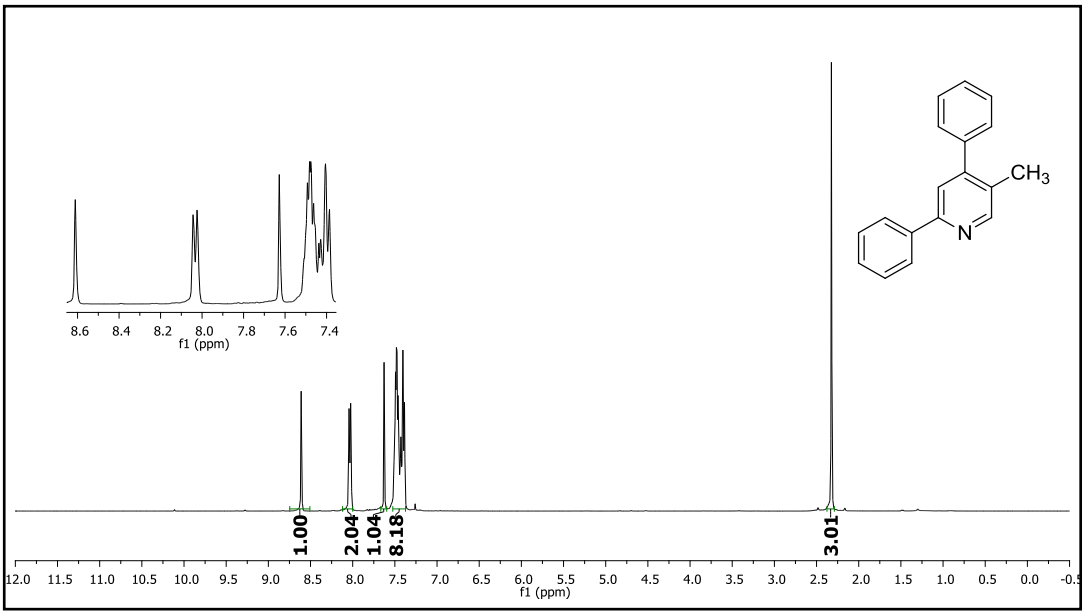

Figure 366. ^{1}H NMR spectrum of compound **61a**.

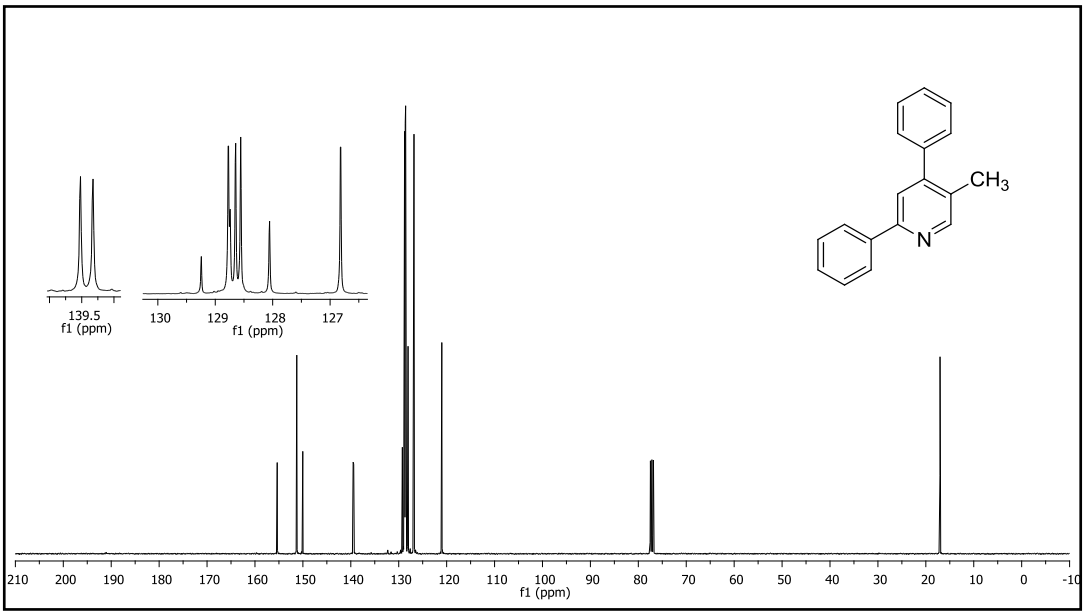

Figure 367. ^{13}C NMR spectrum of compound **61a**.

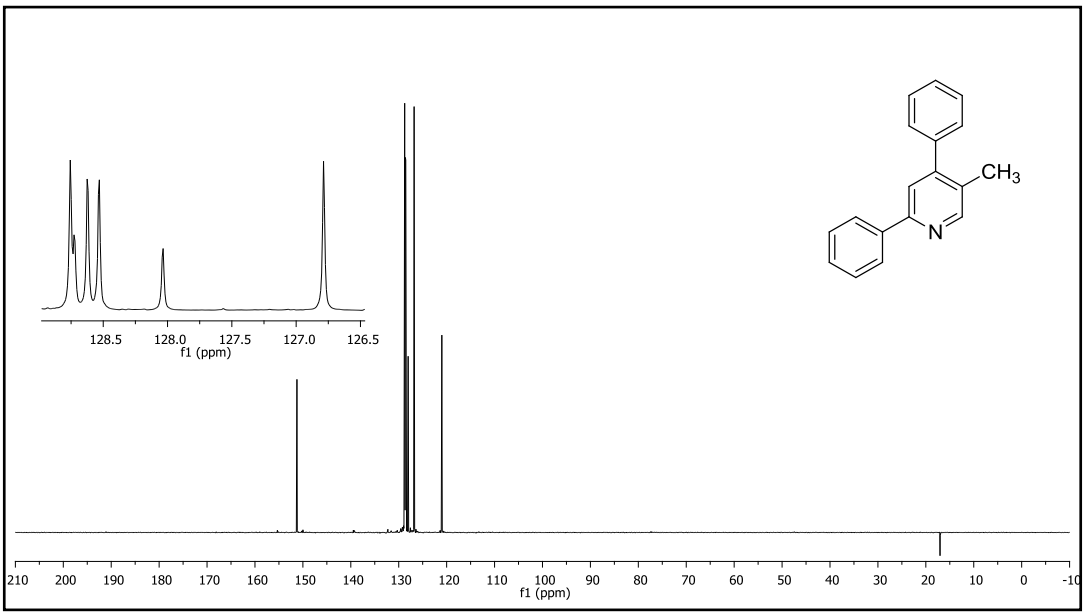

Figure 368. DEPT-90 NMR spectrum of compound **61a**.

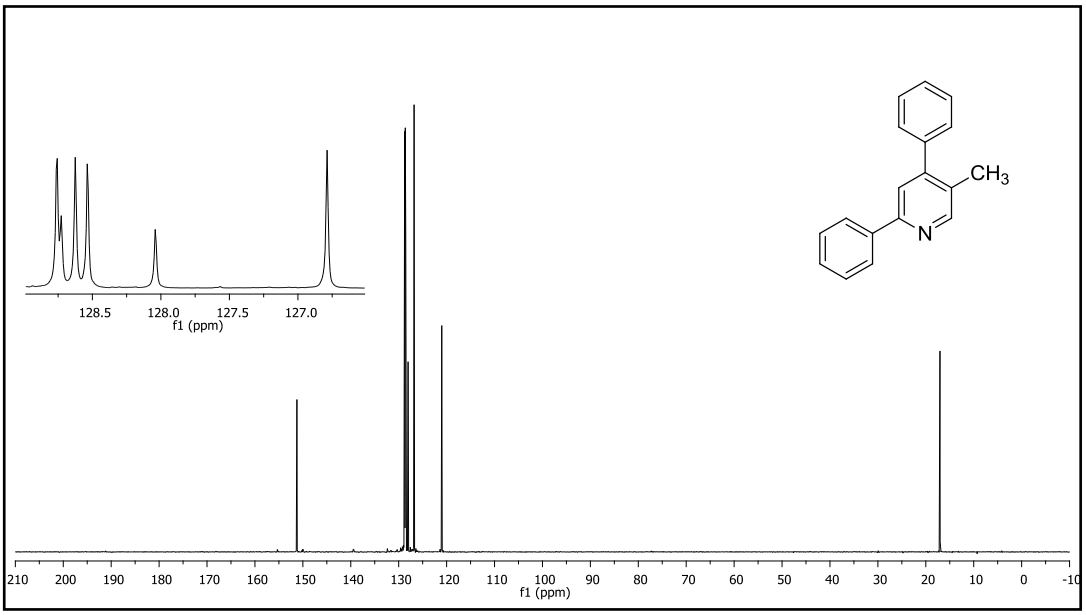

Figure 369. DEPT-135 NMR spectrum of compound **61a**.

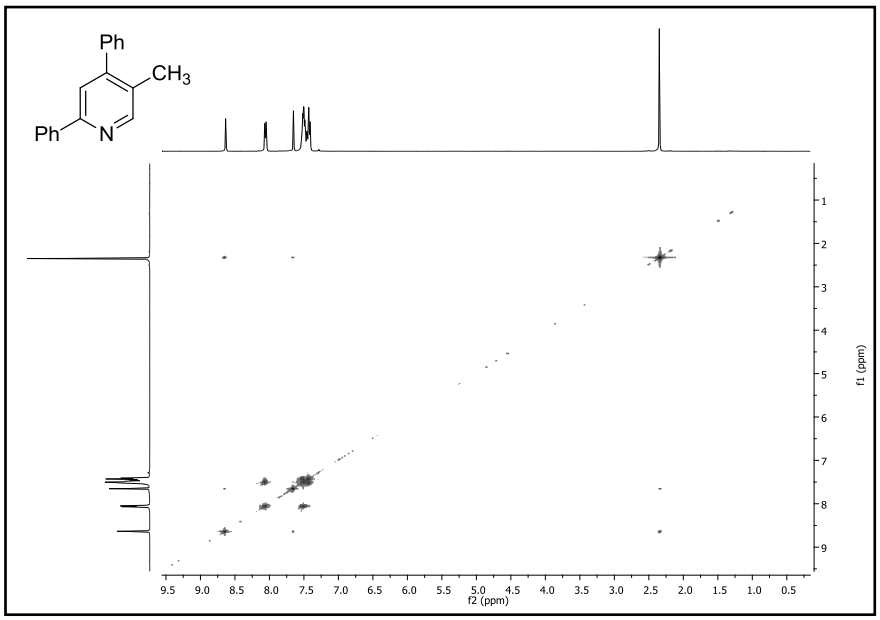

Figure 370. COSY NMR spectrum of compound **61a**.

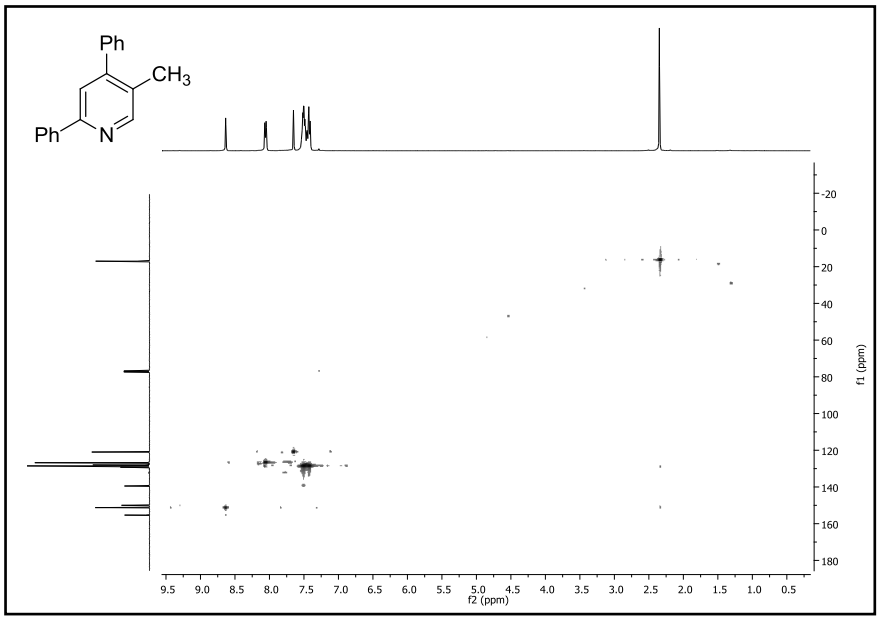

Figure 371. HSQC NMR spectrum of compound **61a**.

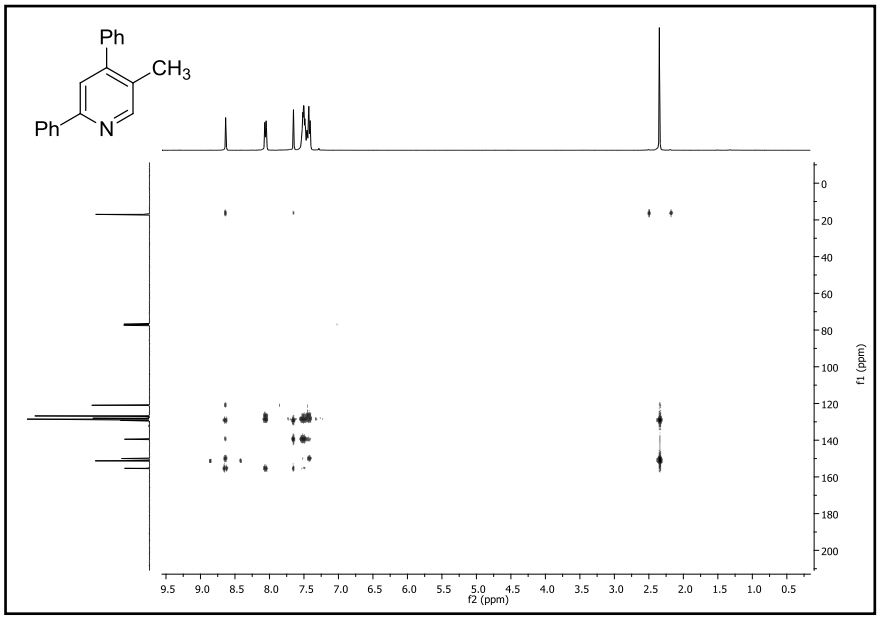

Figure 372. HMBC NMR spectrum of compound **61a**.

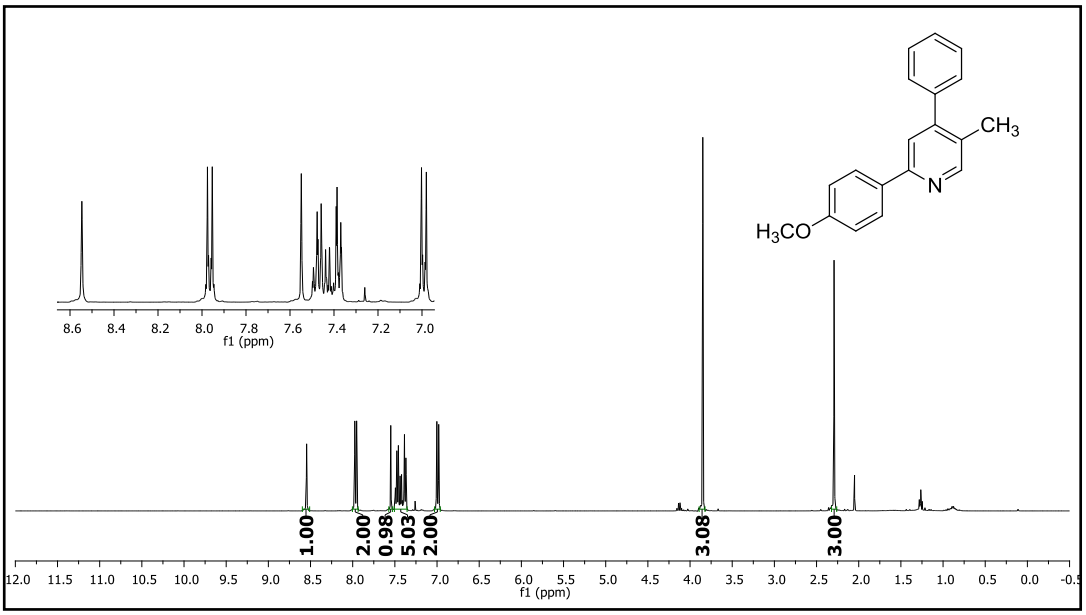

Figure 373. ^{1}H NMR spectrum of compound **61b**.

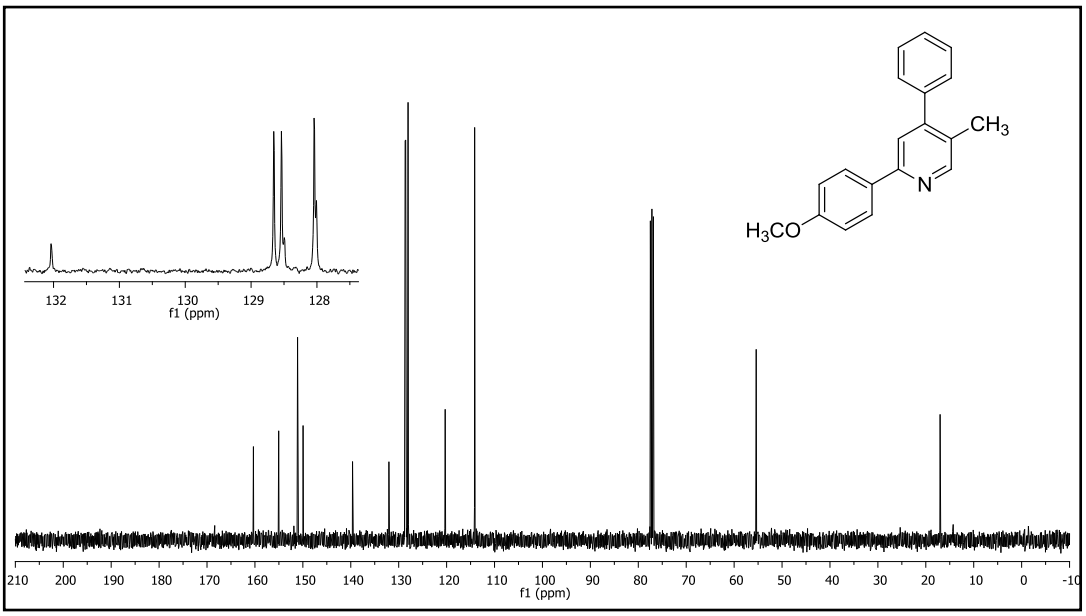

Figure 374. ^{13}C NMR spectrum of compound **61b**.

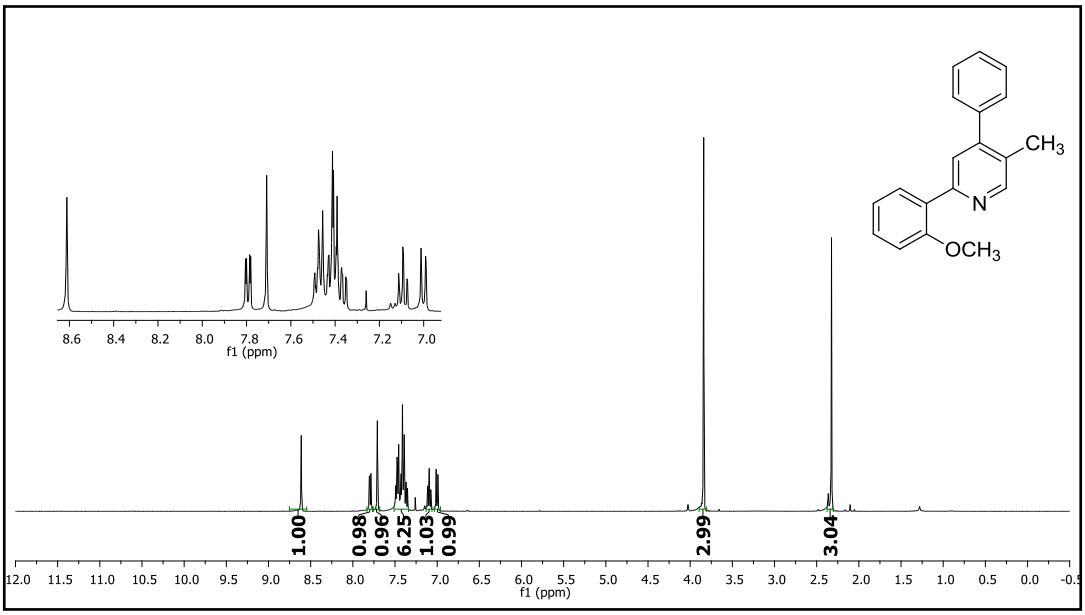

Figure 375. ^{1}H NMR spectrum of compound **61c**.

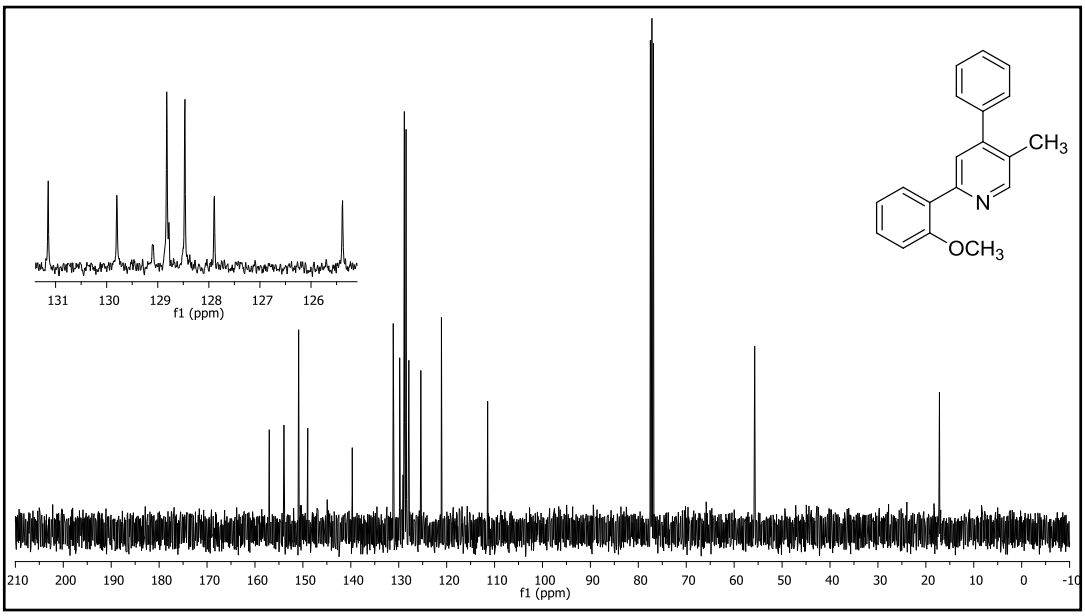

Figure 376. ^{13}C NMR spectrum of compound **61c**.

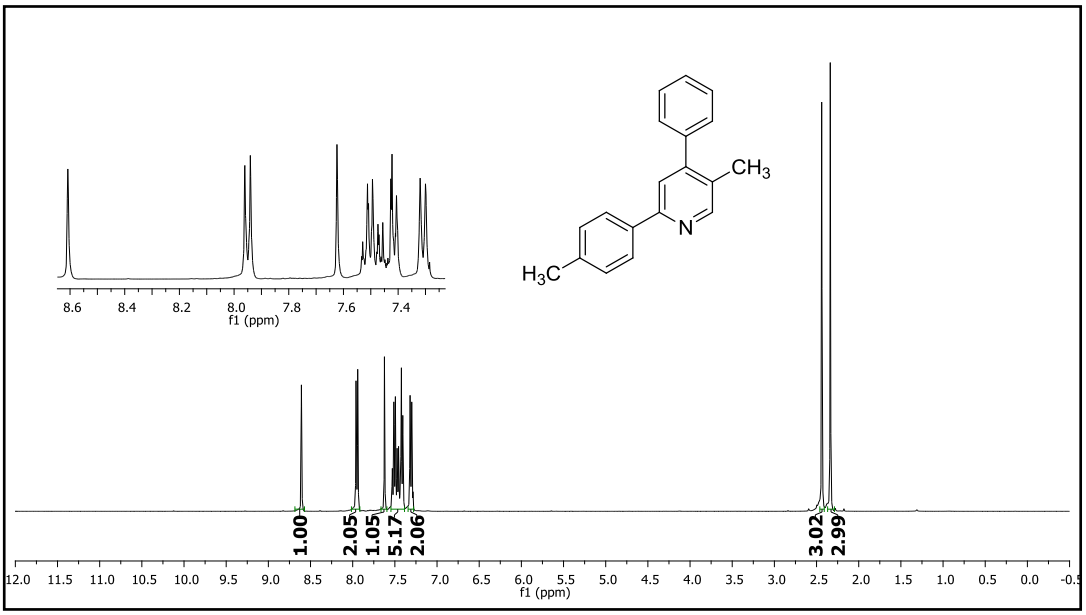

Figure 377. ^{1}H NMR spectrum of compound **61d**.

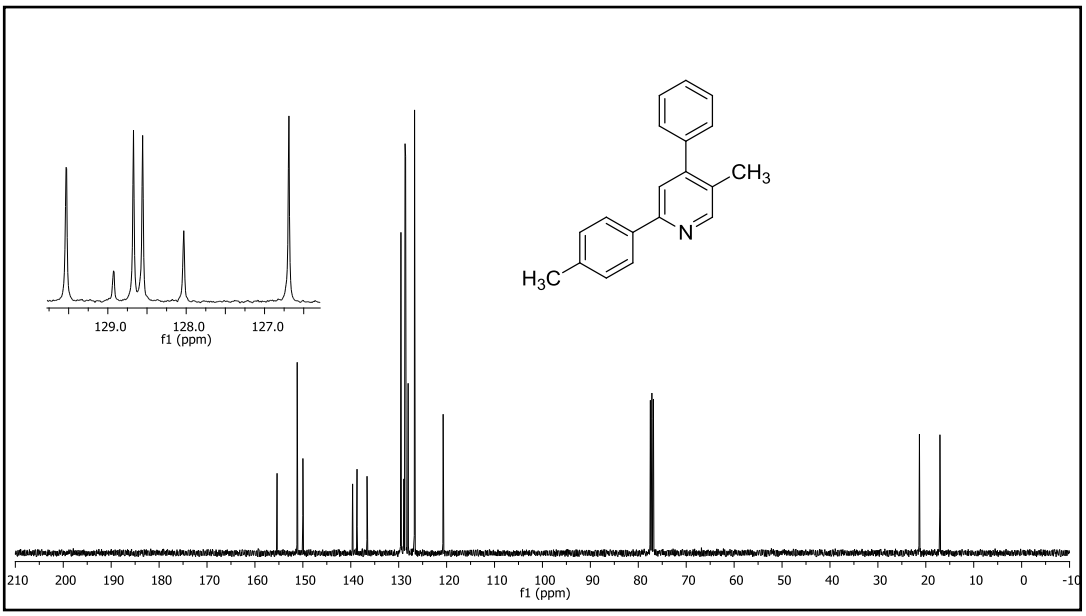

Figure 378. ^{13}C NMR spectrum of compound **61d**.

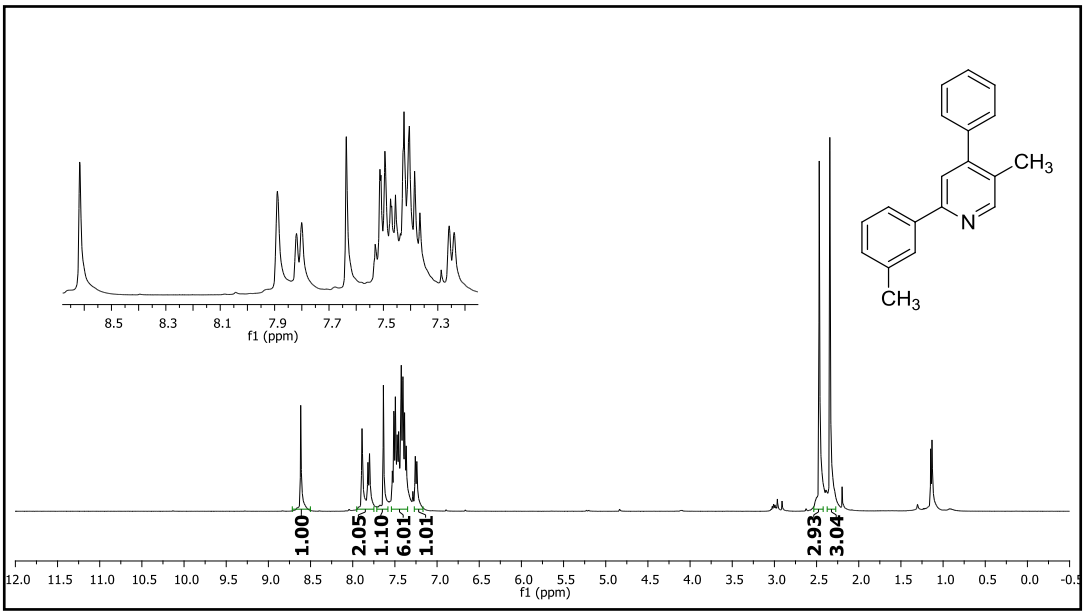

Figure 379. ^{1}H NMR spectrum of compound **61e**.

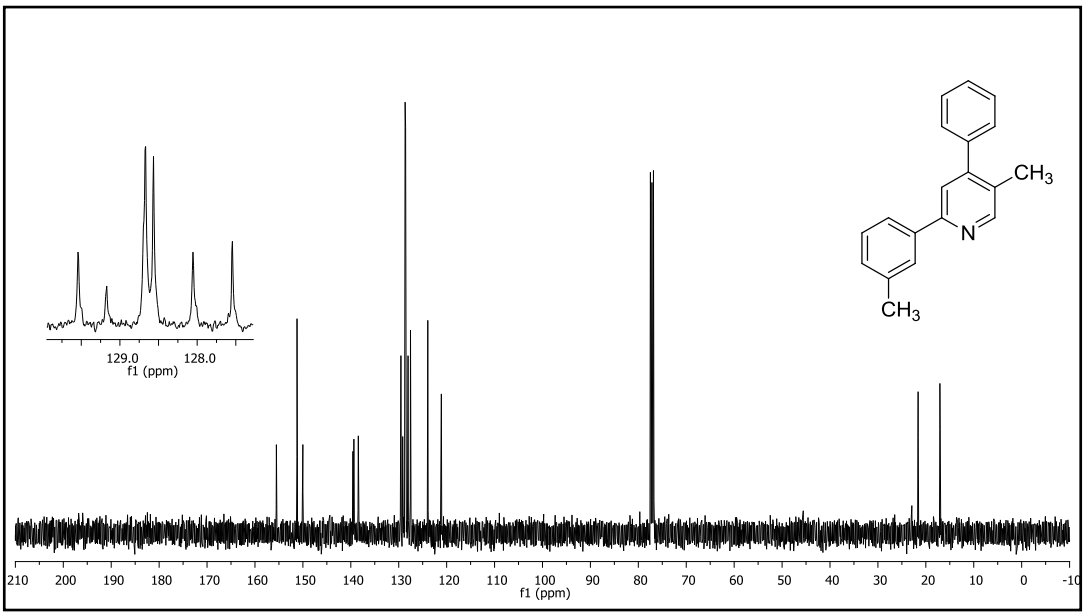

Figure 380. ^{13}C NMR spectrum of compound **61e**.

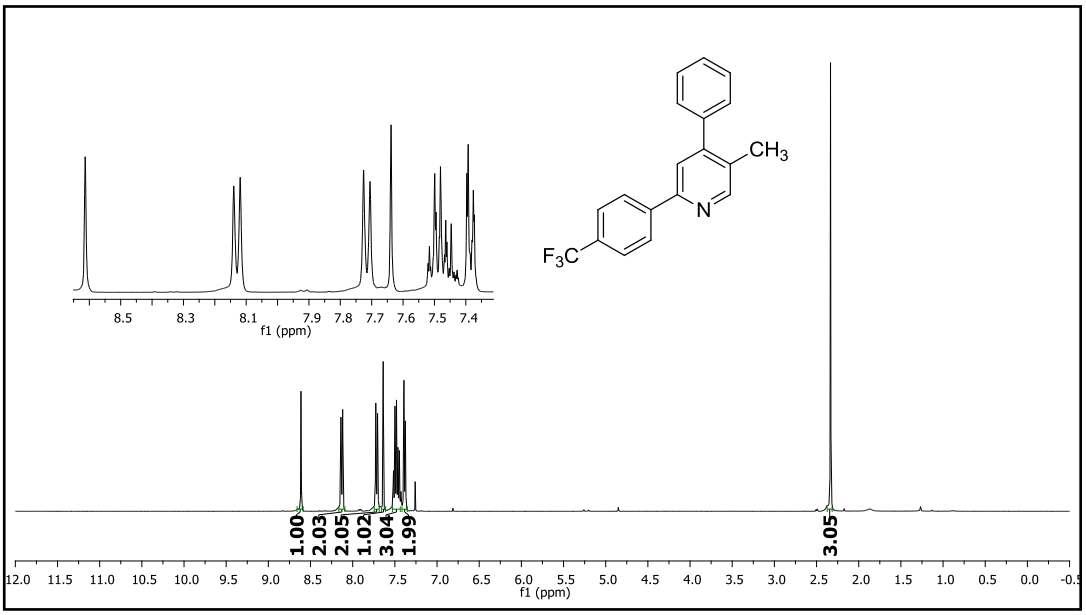

Figure 381. ^{1}H NMR spectrum of compound **61f**.

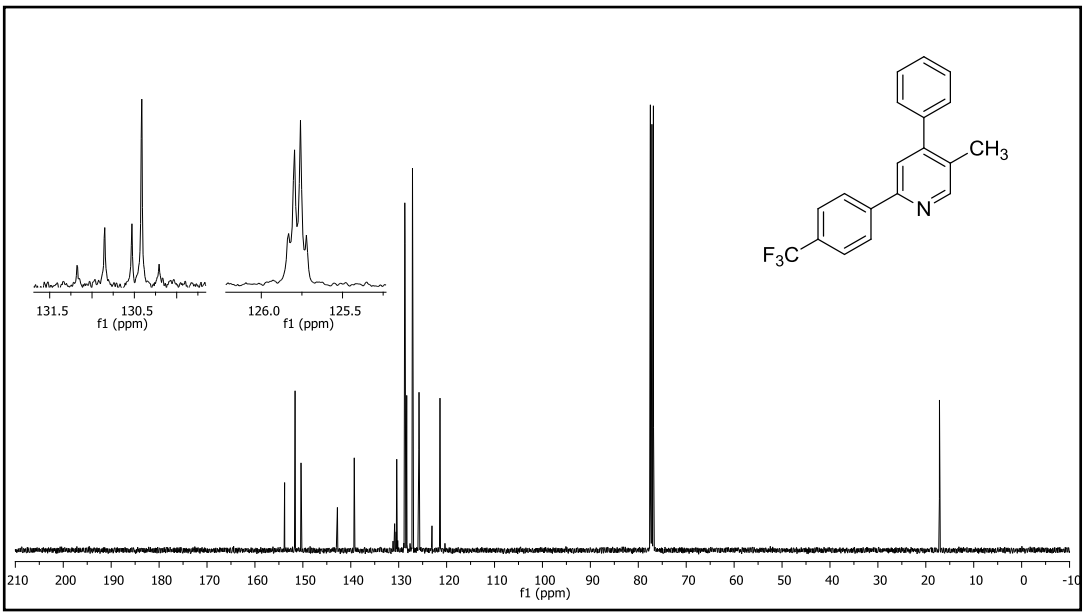

Figure 382. ^{13}C NMR spectrum of compound **61f**.

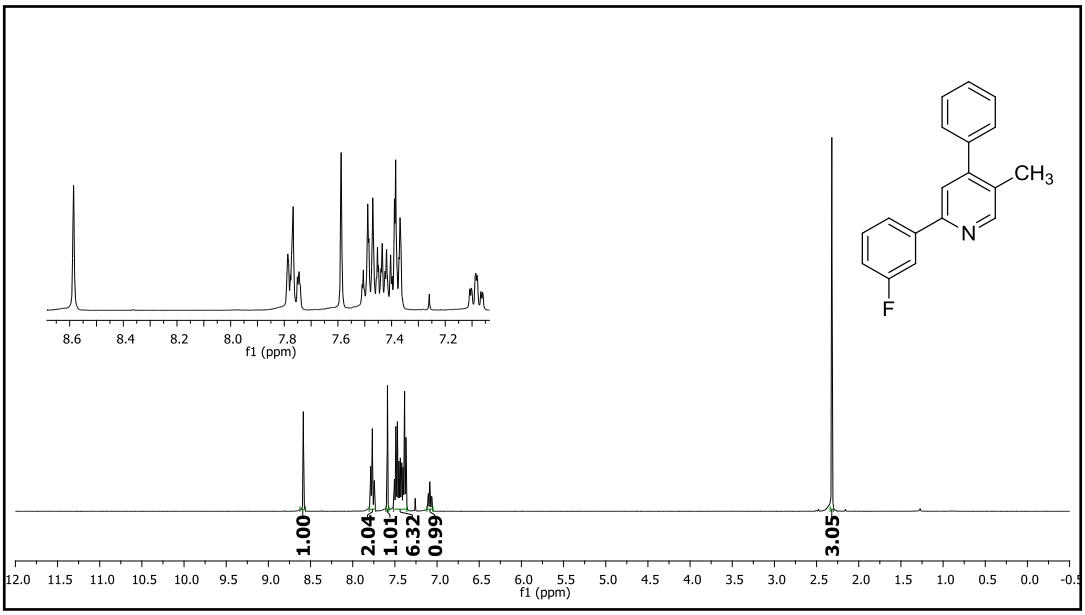

Figure 383. ^{1}H NMR spectrum of compound **61h**.

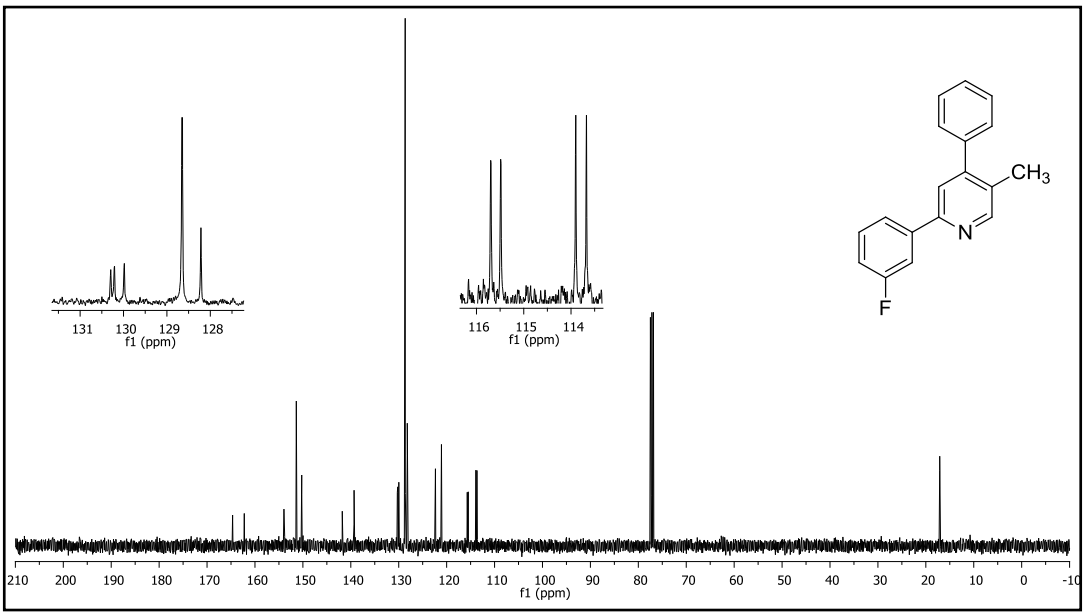

Figure 384. ^{13}C NMR spectrum of compound **61h**.

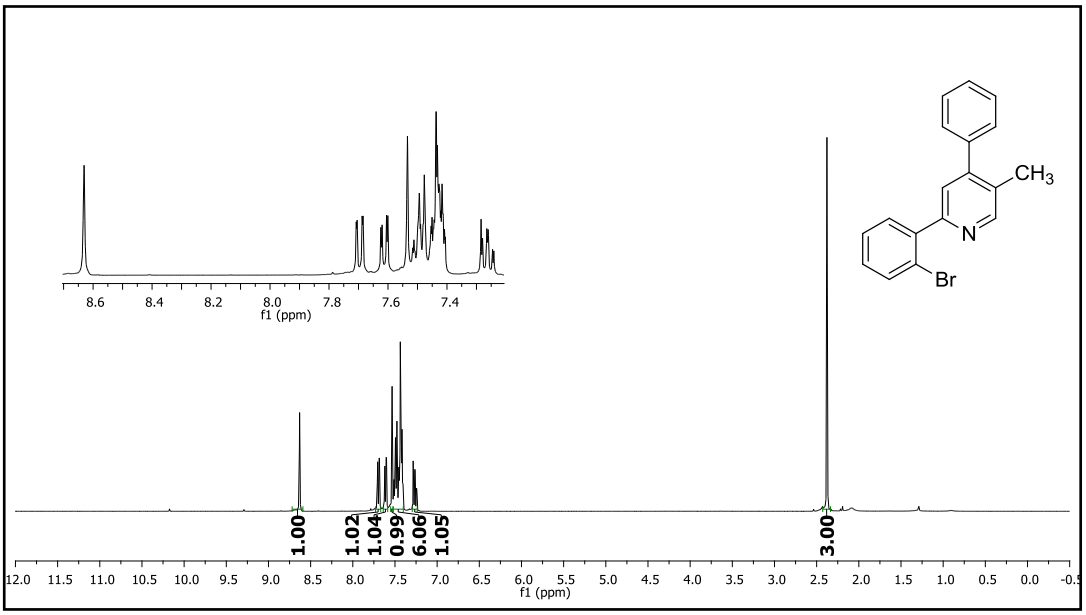

Figure 385. ^{1}H NMR spectrum of compound **61i**.

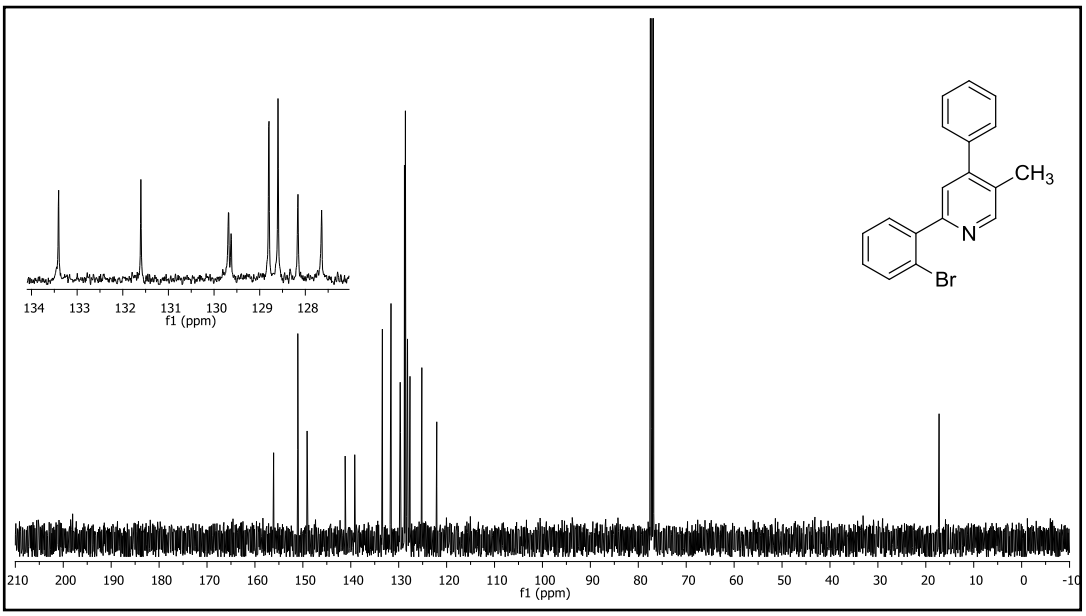

Figure 386. ^{13}C NMR spectrum of compound **61i**.

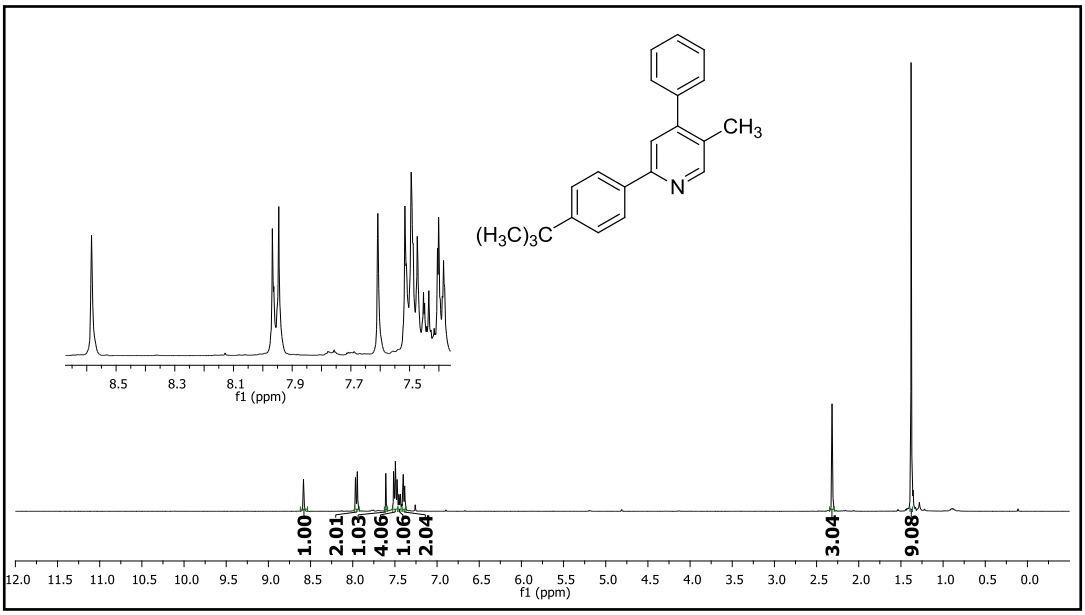

Figure 387. ^{1}H NMR spectrum of compound **61j**.

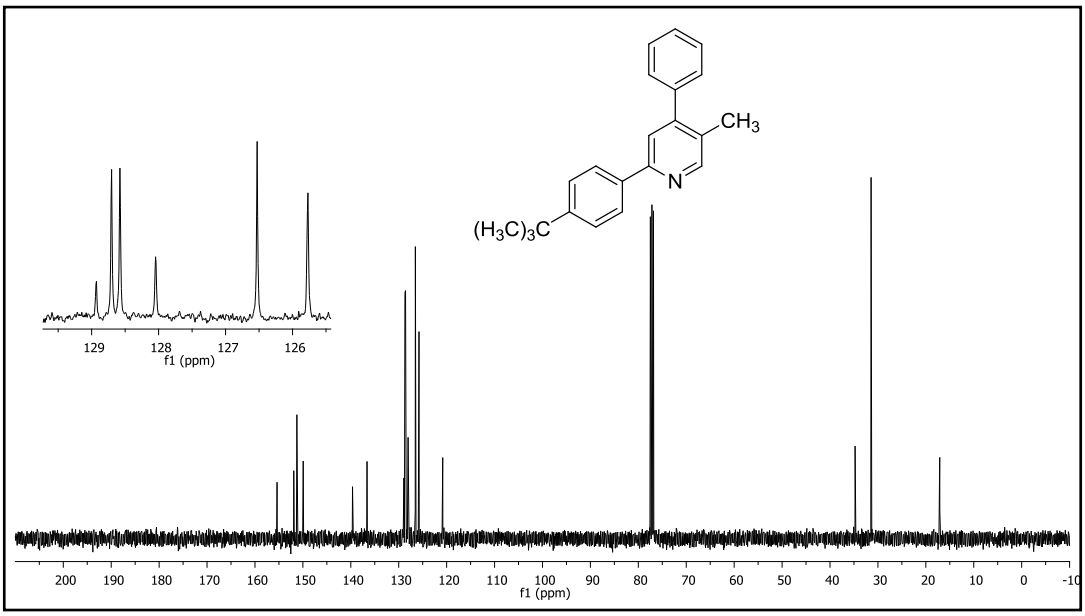

Figure 388. ^{13}C NMR spectrum of compound **61j**.

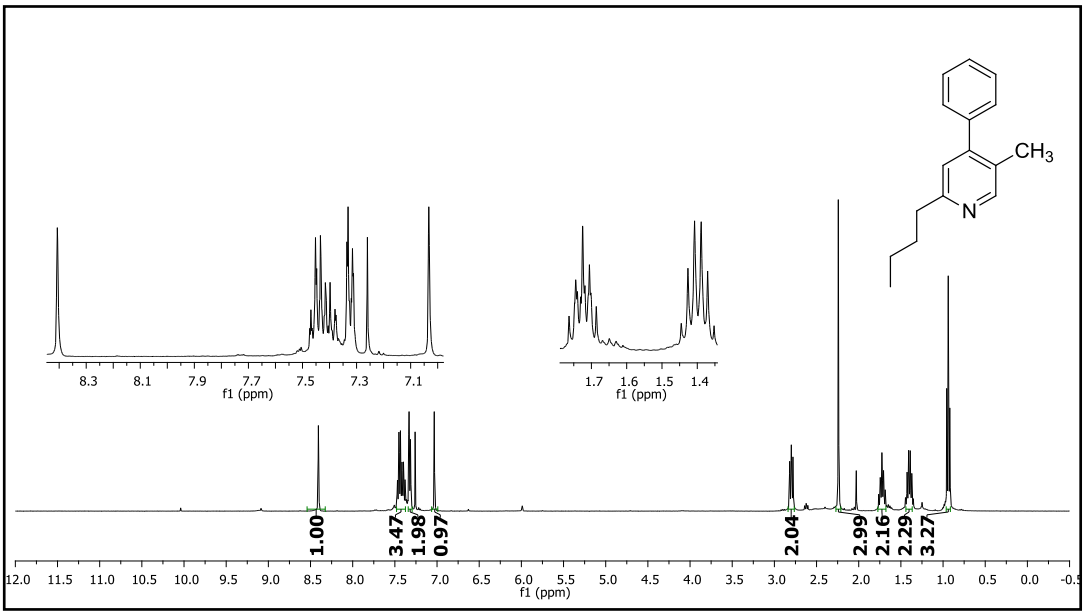

Figure 389. ^{1}H NMR spectrum of compound **61l**.

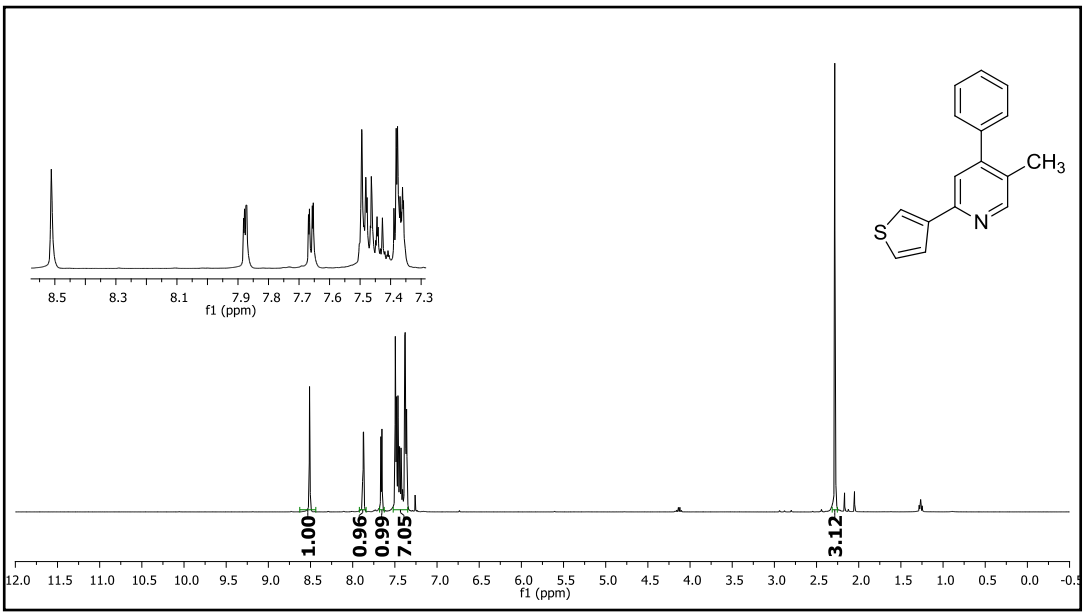

Figure 390. ^{1}H NMR spectrum of compound **61m**.

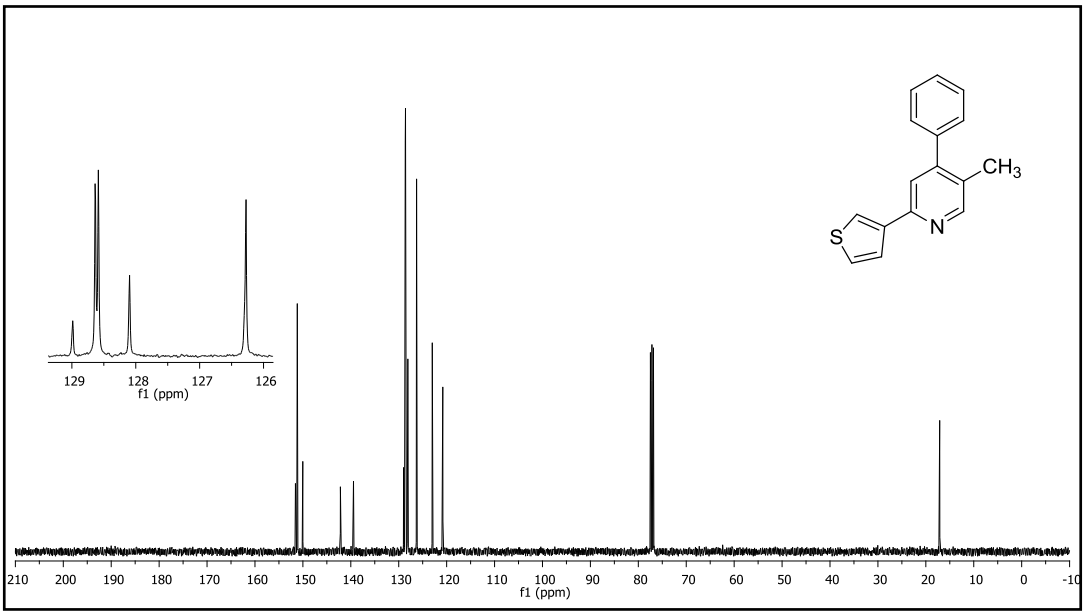

Figure 391. ^{13}C NMR spectrum of compound **61m**.

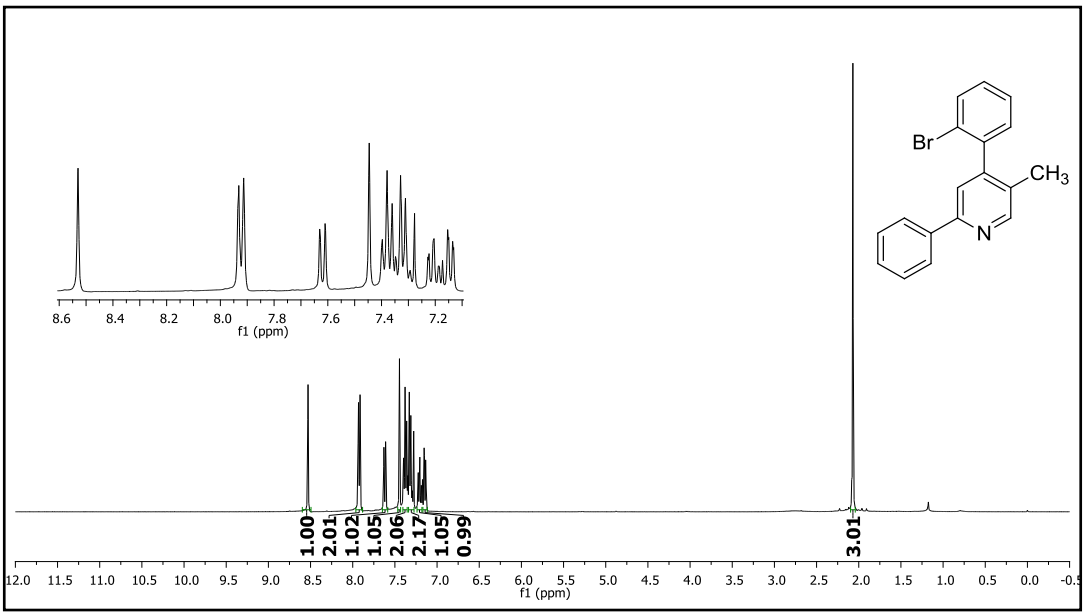

Figure 392. ^{1}H NMR spectrum of compound **61n**.

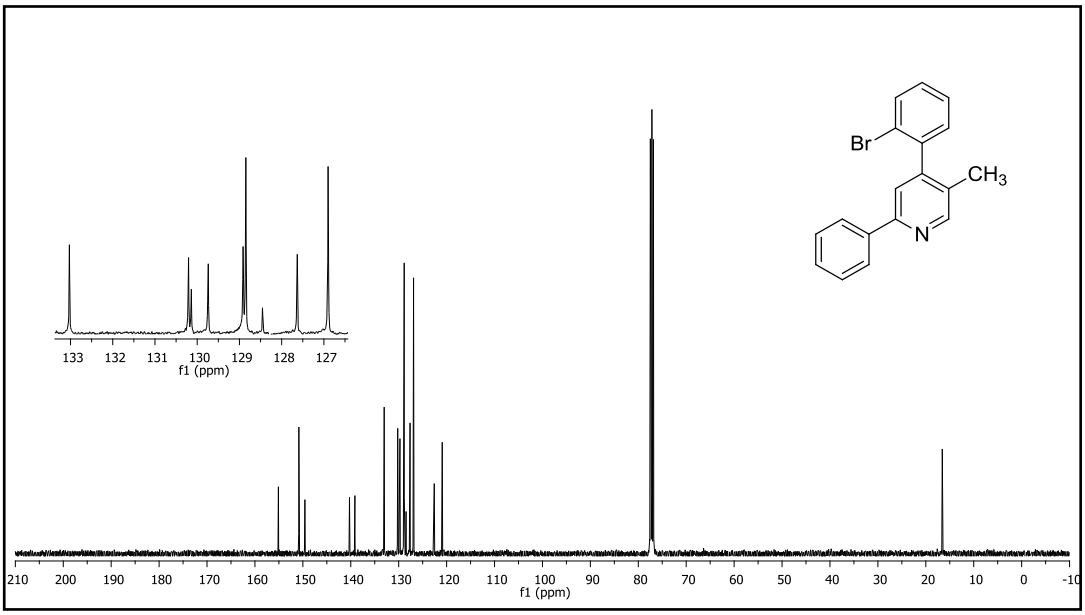

Figure 393. ^{13}C NMR spectrum of compound **61n**.

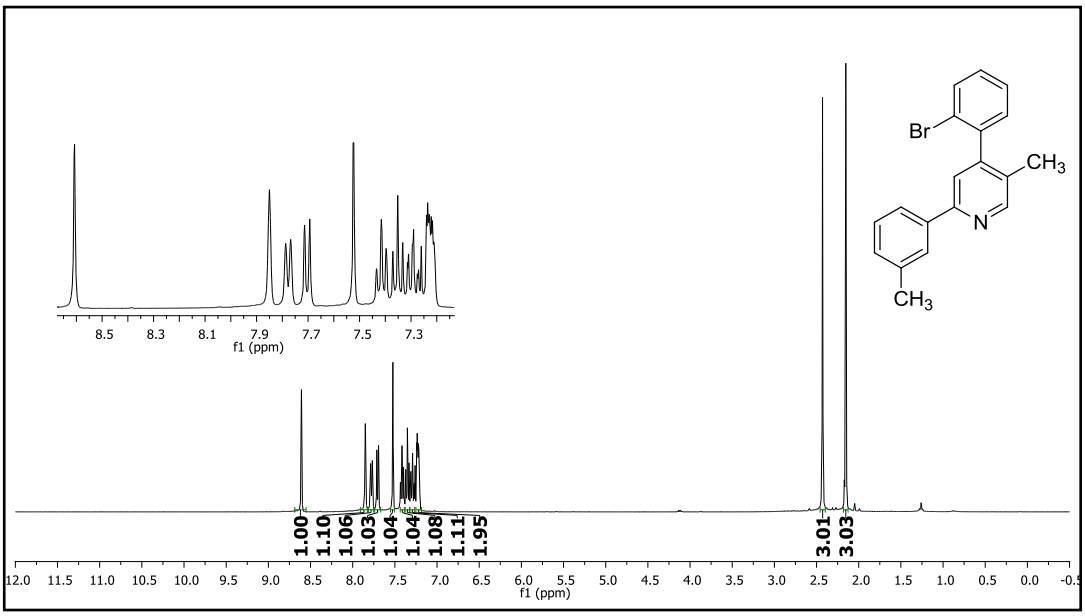

Figure 394. ^{1}H NMR spectrum of compound **61r**.

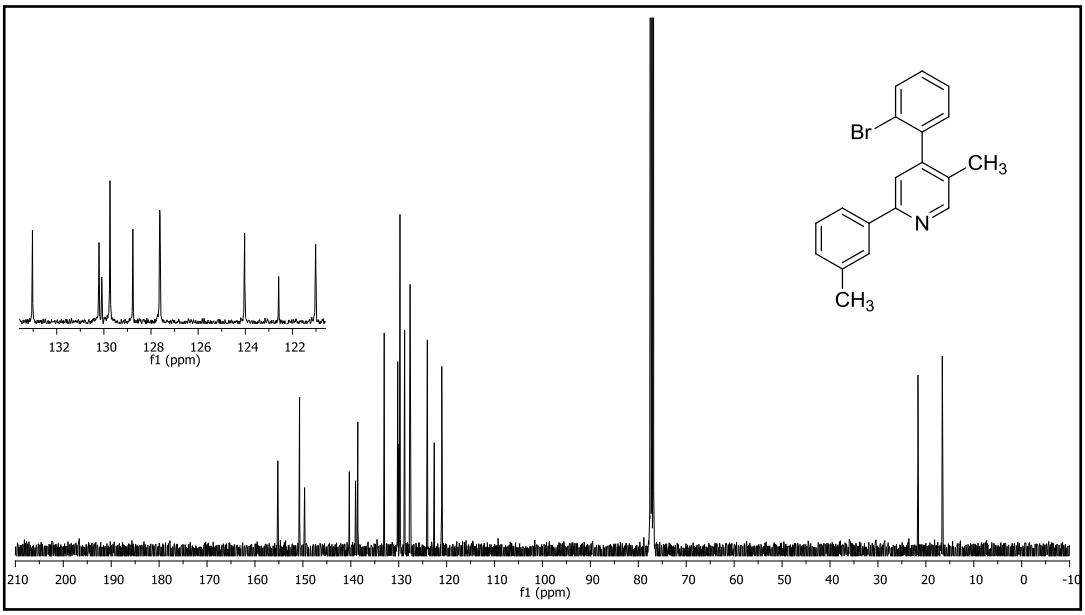

Figure 395. ^{13}C NMR spectrum of compound **61r**.

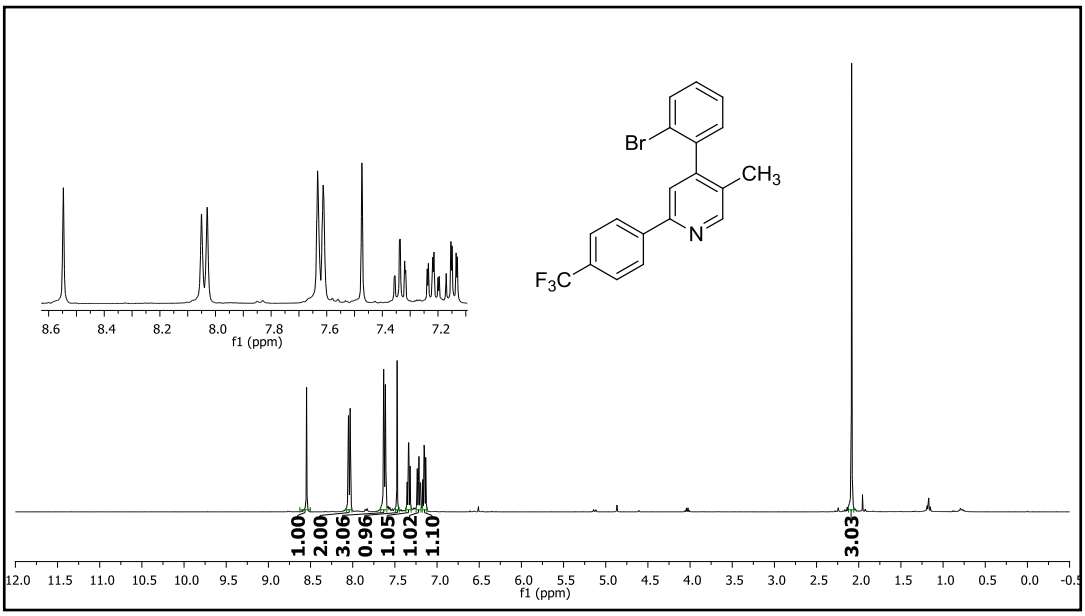

Figure 396. ^{1}H NMR spectrum of compound **61s**.

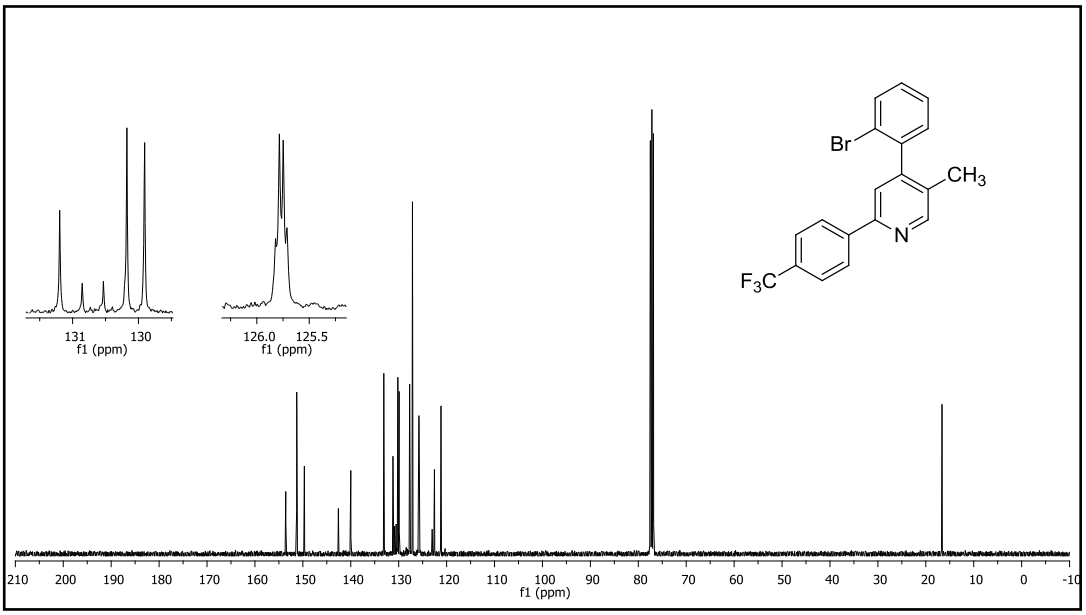

Figure 397. ^{13}C NMR spectrum of compound **61s**.

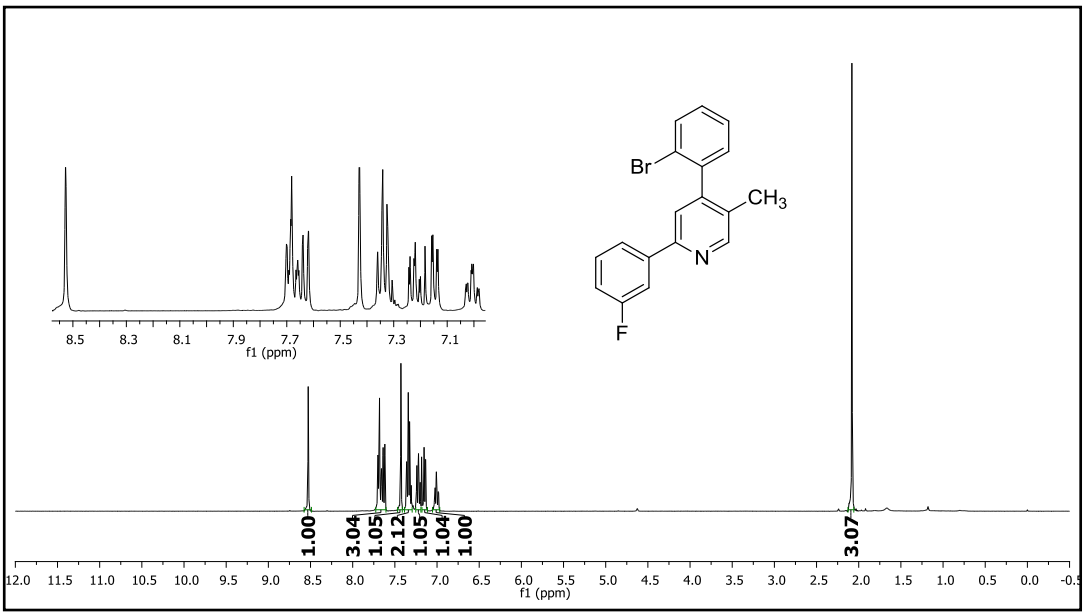

Figure 398. ^{1}H NMR spectrum of compound **61t**.

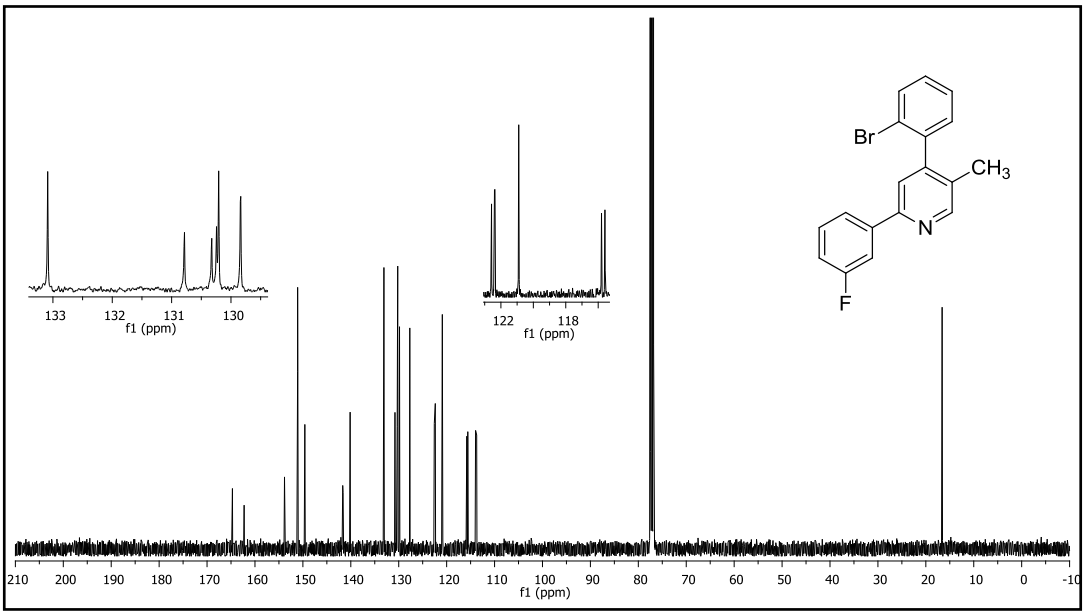

Figure 399. ^{13}C NMR spectrum of compound **61t**.

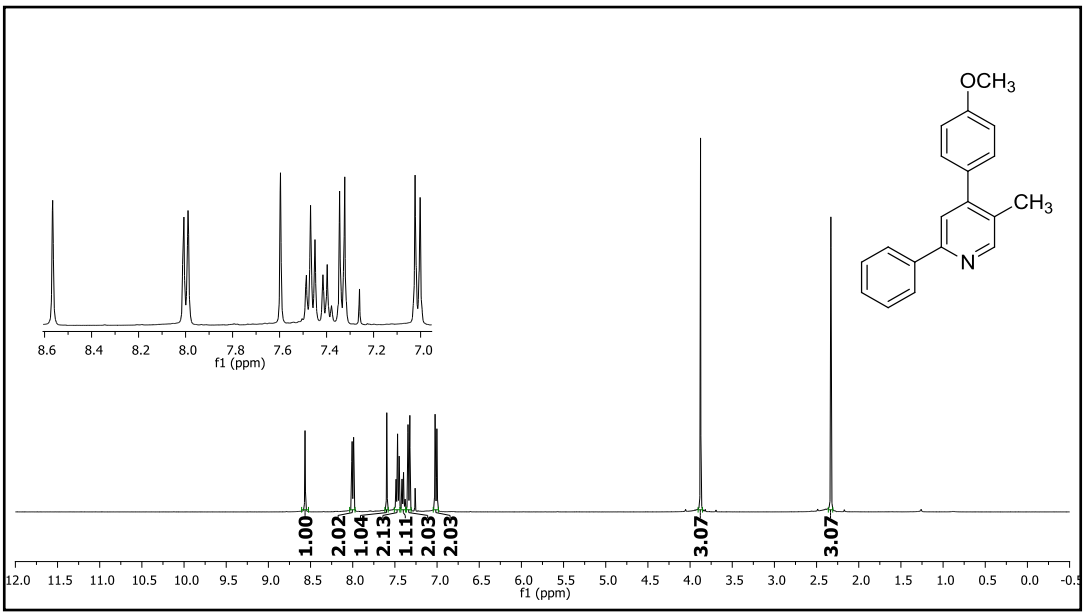

Figure 400. ^{1}H NMR spectrum of compound **61v**.

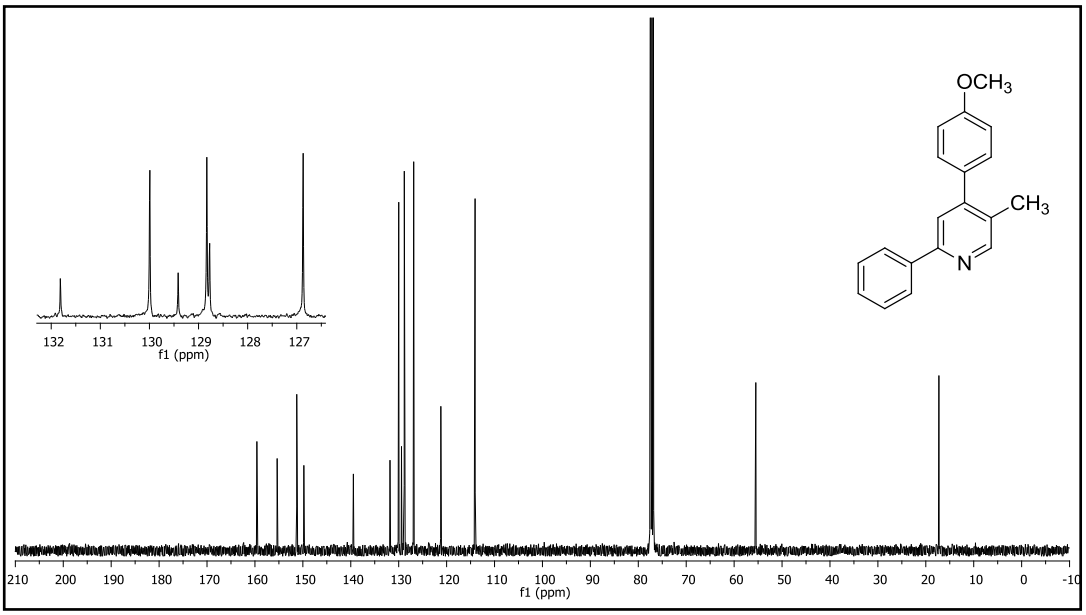

Figure 401. ^{13}C NMR spectrum of compound **61v**.

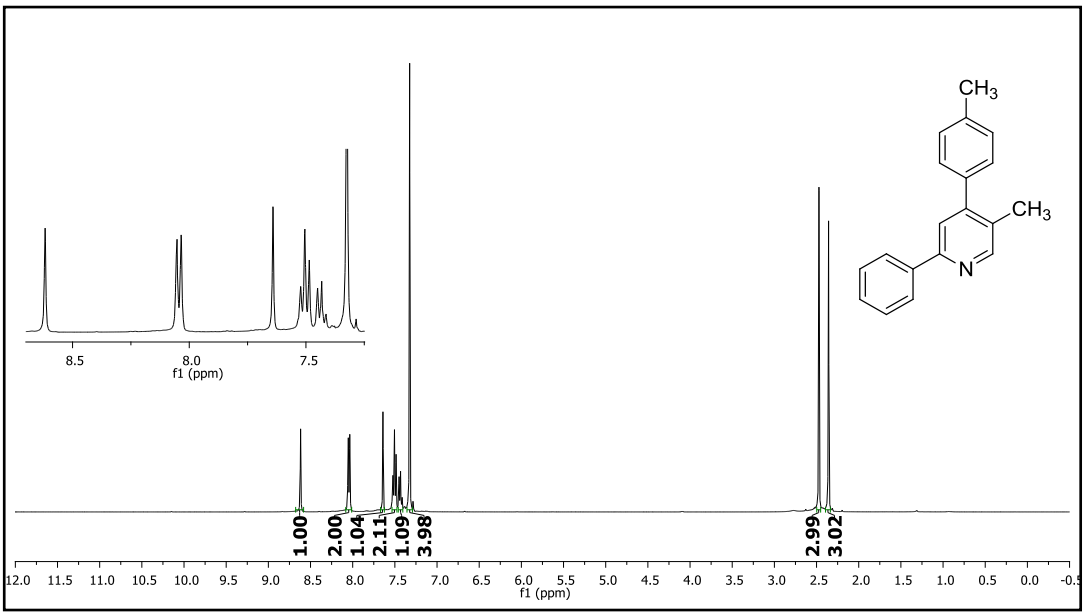

Figure 402. ^{1}H NMR spectrum of compound **61w**.

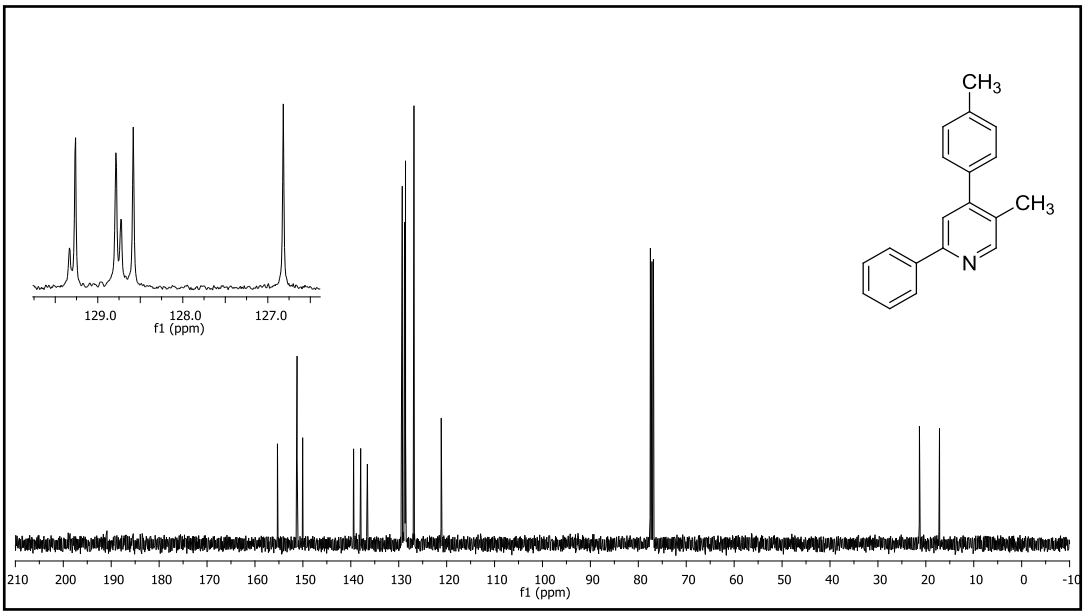

Figure 403. ^{13}C NMR spectrum of compound **61w**.

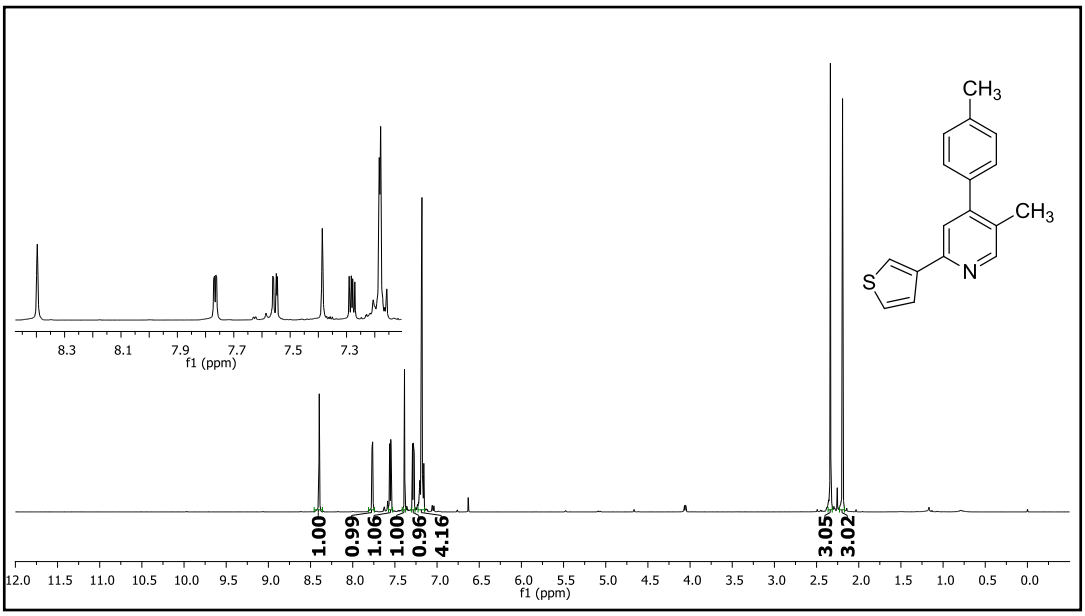

Figure 404. ^{1}H NMR spectrum of compound **61x**.

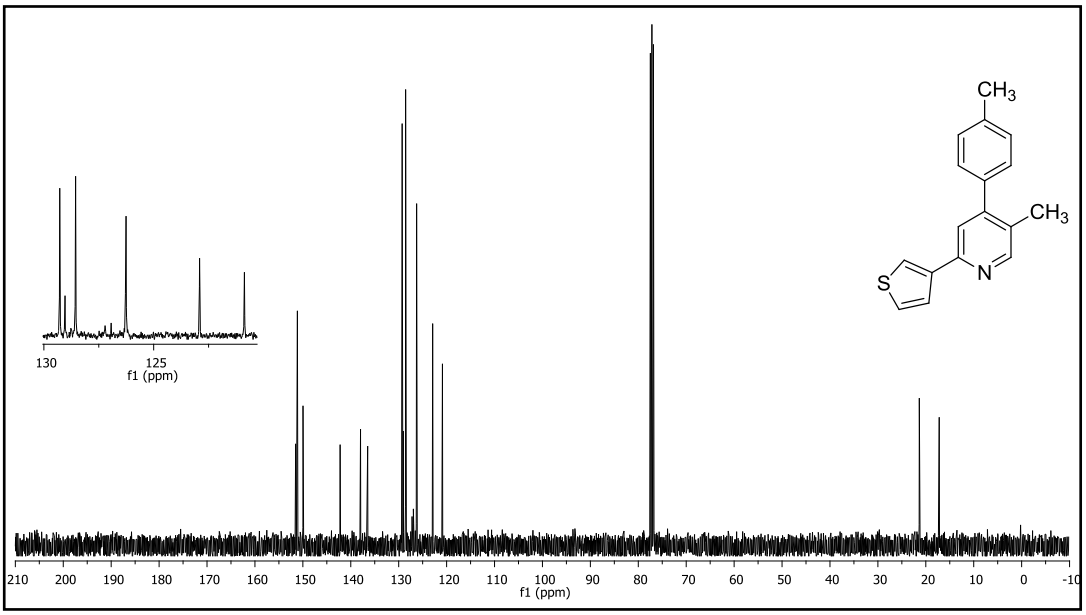

Figure 405. ^{13}C NMR spectrum of compound **61x**.

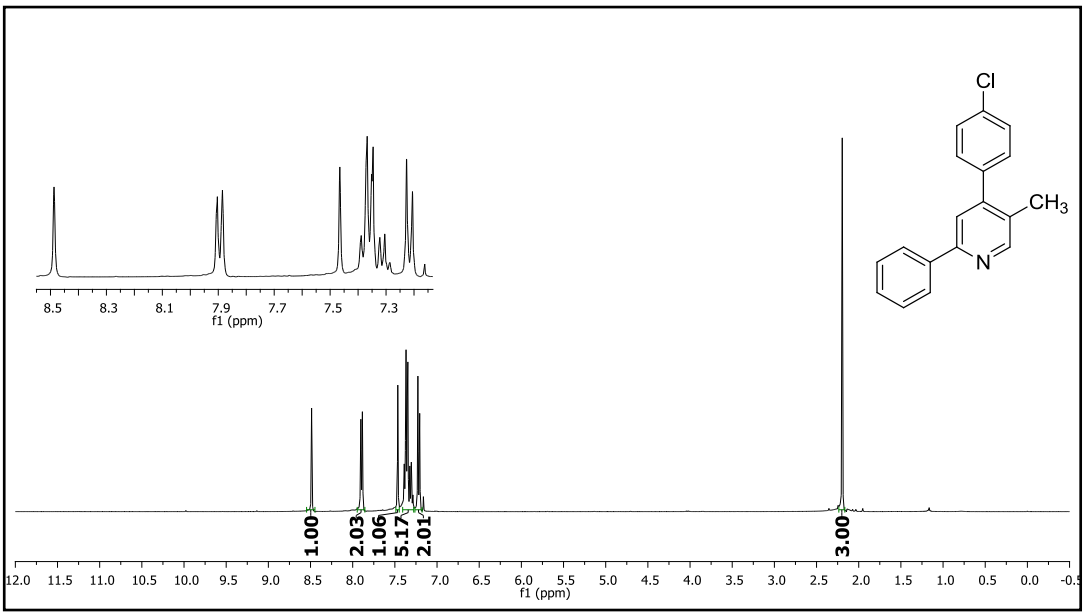

Figure 406. ^{1}H NMR spectrum of compound **61y**.

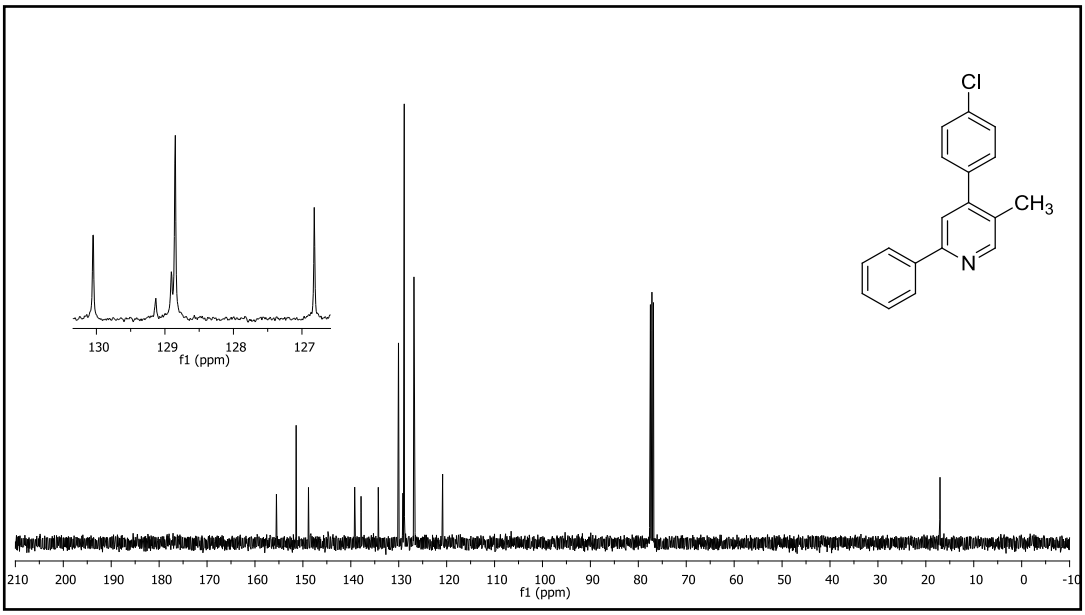

Figure 407. ^{13}C NMR spectrum of compound **61y**.

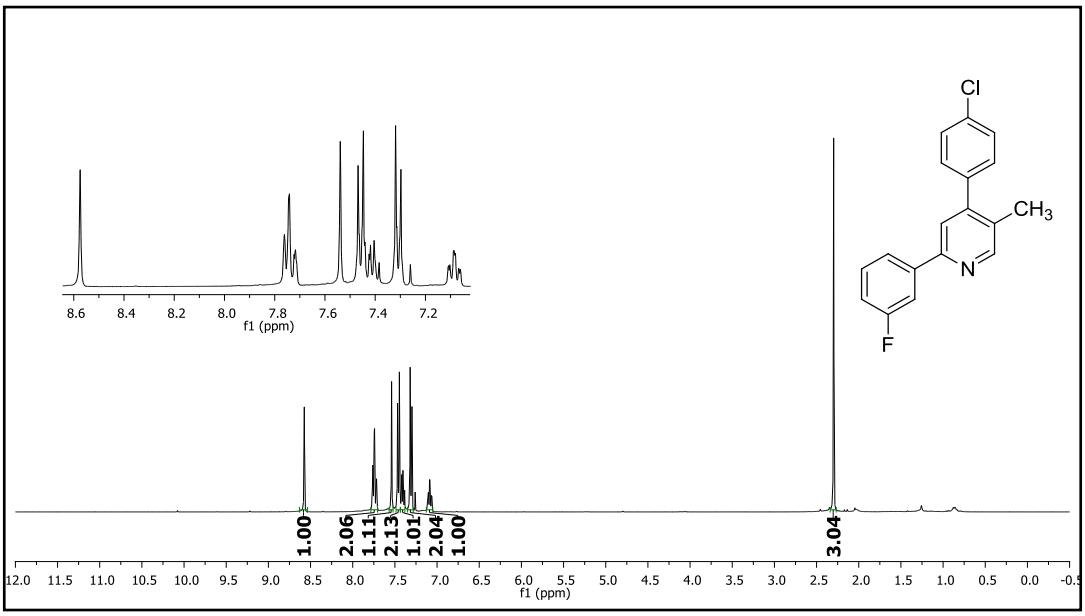

Figure 408. ^{1}H NMR spectrum of compound **61z**.

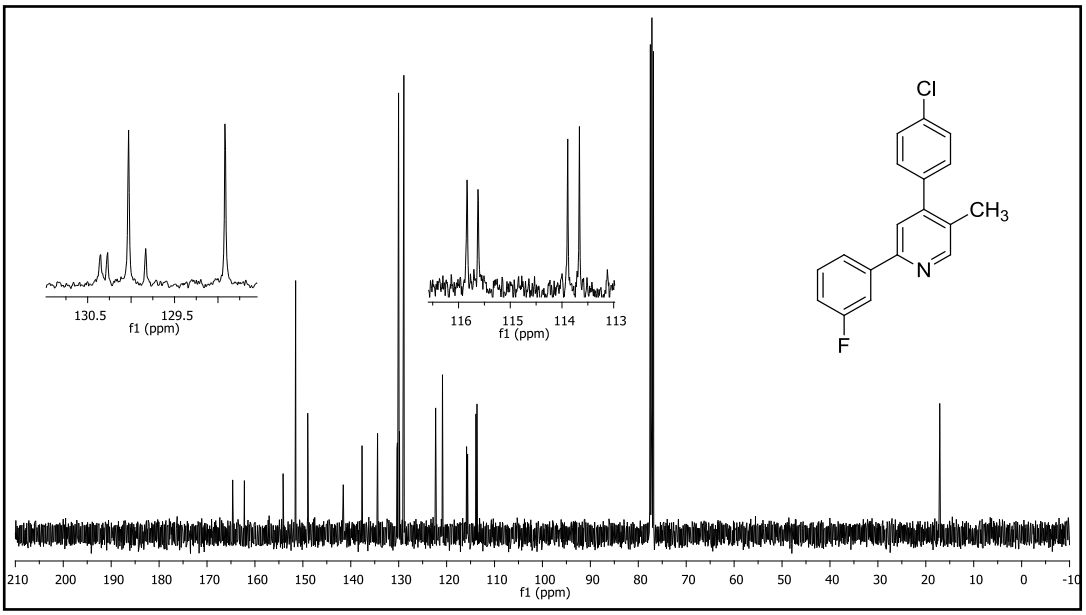

Figure 409. ^{13}C NMR spectrum of compound **61z**.

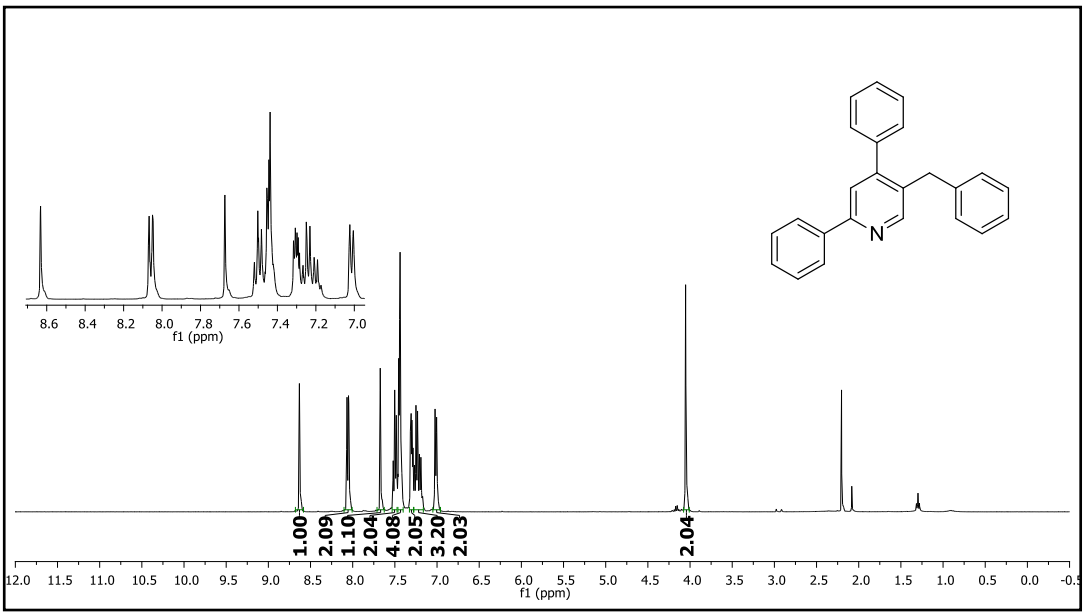

Figure 410. ^{1}H NMR spectrum of compound **89**.

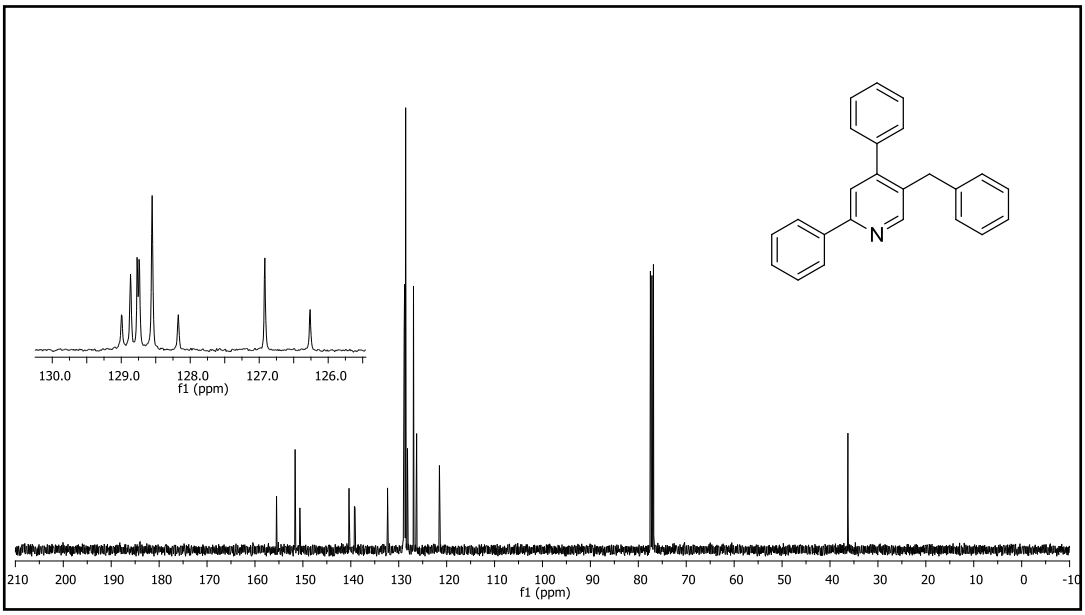

Figure 411. ^{13}C NMR spectrum of compound **89**.

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WORK EXPERIENCE

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PUBLICATIONS

1. Metin ZORA, Ezel DİKMEN, **Yılmaz KELGÖKMEN**. (One-pot synthesis of iodine-substituted 1,4-oxazepines). *Tetrahedron Lett.* **2018**, *59*, 823 (DOI: 10.1016/j.tetlet.2018.01.048).

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5. Sedef KARABIYIKOĞLU, **Yılmaz KELGÖKMEN**, Metin ZORA. (Facile synthesis of iodopyridines from *N*-propargylic β-enaminones via iodine-mediated electrophilic cyclization). *Tetrahedron* **2015**, *71*, 4324 (DOI: 10.1016/j.tet.2015.04.070).

6. Metin ZORA, Arif KIVRAK, **Yılmaz KELGÖKMEN**. (A novel one-pot synthesis of ferrocenylsubstituted1,2,4-oxadiazoles). *J. Organomet. Chem*. **2014**, *759*, 67 (DOI: 10.1016/j.jorganchem.2014.02.018).

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1. Metin ZORA, **Yılmaz KELGÖKMEN**, Yasemin ÇAYAN. (Development of a new methodology for synthesis of 1,4-oxazepines). *254. American-Chemical-Society Meeting*, Washington, **20 August-24 August 2017** (Oral Presentation).

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3. **Yılmaz KELGÖKMEN**, Yasemin ÇAYAN, Metin ZORA. (2,3-Dihidro-1,4-oksazepin Türevlerinin *N*-Proparjilik β-Enaminon Bileşiklerinden Sentezi). *Uluslararası Katılımlı 5. İlaç Kimyası Kongresi*, Antalya, **30 March-2 April 2017** (Oral Presentation).

4. Ezel DİKMEN, **Yılmaz KELGÖKMEN**, Metin ZORA. (2-(İyodometilen)-2,3-dihidro-1,4-oksazepin Türevlerinin *N*-Proparjilik β-Enaminon Bileşiklerinden Sentezi). *Uluslararası Katılımlı 5. İlaç Kimyası Kongresi*, Antalya, **30 March -2 April 2017** (Poster Presentation).

5. Elif Serel YILMAZ, **Yılmaz KELGÖKMEN**, Metin ZORA. (Synthesis of alkynyl-substituted pyrroles). *Anatolian Conference on Synthetic Organic Chemistry* (*ACSOC II*), Aydın, **21 March-24 March 2016** (Poster Presentation).

6. Metin ZORA, Deniz DEMİRCİ, Arif KIVRAK, **Yılmaz KELGÖKMEN**. (Efficient one-pot synthesis of 4-(phenylselanyl)-substituted pyrazoles). *Anatolian Conference on Synthetic Organic Chemistry* (*ACSOC II*), Aydın, **21 March-24 March 2016** (Poster Presentation).

7. Metin ZORA, Sedef KARABIYIKOĞLU, **Yılmaz KELGÖKMEN**, Özge İBİŞ. (Development of new methodologies for the synthesis of pyridine derivatives). *Anatolian Conference on Synthetic Organic Chemistry* (*ACSOC II*), Aydın, **21 March-24 March 2016** (Poster Presentation).

8. **Yılmaz KELGÖKMEN**, Metin ZORA. (Facile Synthesis of Alkenyl-Substituted Pyridines). *Trans Mediterranean Colloquium on Heterocyclic Chemistry TRAMECH VIII*, Antalya, **11 November-15 November 2015** (Poster Presentation).

9. Metin ZORA, **Yılmaz KELGÖKMEN**, Nihan Zulay KILIÇASLAN. (Synthesis of highly substituted pyridines by Pd-catalyzed Sonogashira and Suzuki-Miyaura couplings of 4-iodopyridines. *243. American-Chemical-Society Meeting*, SanDiego, **25 March-29 March 2012** (Poster Presentation).

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1. **Yılmaz KELGÖKMEN**, Yasemin ÇAYAN, Metin ZORA. (*N*-Proparjilik β-Enaminon Bileşiklerinden 2,3-Dihidro-1,4-oksazepin Türevlerinin Sentezi). *29. Ulusal Kimya Kongresi*, Ankara, **10 September-14 September 2017** (Oral Presentation).

2. Ezel DİKMEN, **Yılmaz KELGÖKMEN**, Metin ZORA. (*N*-Proparjilik β-Enaminon Bileşiklerinden 2-(İyodometilen)-2,3-dihidro-1,4-oksazepin Türevlerinin Sentezi). *29. Ulusal Kimya Kongresi*, Ankara, **10 September -14 September 2017** (Poster Presentation).

3. **Yılmaz KELGÖKMEN**, Metin ZORA. (cis-2,3-Divinil-1-heterosiklopropan Bilesiklerinin Cope Düzenlenmelerinin Yogunluk Fonksiyonu Teorisi (DFT) ile Incelenmesi). *1. Ulusal Hesaplamalı Kimya Çalıstayı*, Van, **29 May-31 May 2014** (Poster Presentation).

4. Yılmaz KELGÖKMEN, Ezel DİKMEN, Yasemin ÇAYAN, Metin ZORA. (5-Alkinilpiridin Türevlerinin Pd-katalizli Sonogashira Kenetlenme Tepkimesi ile 5-İyotpiridin Bileşiklerinden Sentezi). *26.Ulusal Kimya Kongresi*, Muğla, **1 October-6 October 2012** (Poster Presentation).