SYNTHESIS OF ALKYNYL-SUBSTITUTED PYRROLE AND 1,4-THIAZEPINE DERIVATIVES

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Approval of the thesis

SYNTHESIS OF ALKYNYL-SUBSTITUTED PYRROLE AND 1,4-THIAZEPINE DERIVATIVES

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I hereby declare that all information in this document has been obtained and presented in accordance with all academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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ABSTRACT

SYNTHESIS OF ALKYNYL-SUBSTITUTED PYRROLE AND 1,4-THIAZEPINE DERIVATIVES

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Heterocyclic compounds have a great importance in medicinal chemistry because of their presence in a number of pharmaceuticals. Among them, pyrroles and 1,4-thiazepines play a vital role in pharmaceutical chemistry because of their presence in a number of bioactive molecules and natural products. For this reason, the development of new synthetic methods for the synthesis of these compounds has attracted much attention. Recently, the cyclization of functionally-substituted alkynes has emerged as a valuable tool in the preparation of various heterocyclic and carbocyclic compounds. In this regard, *N*-propargylic β-enaminones have proven to be useful.

In this study, we have anticipated that the cyclizations of *N*-(2,4-pentadiynyl)-*β*-enaminones would produce biologically important alkynyl-substituted pyrrole and 1,4-thiazepine derivatives.

In the first part of this study, we have shown that conjugate addition of propargylamine to *α,β*-alkynic ketones followed by the coupling of the resulting *N*-propargylic *β*-enaminones with terminal alkynes, yields *N*-(2,4-pentadiynyl)-*β*-enaminones. When treated with a base such as sodium hydride, *N*-(2,4-pentadiynyl)-*β*-enaminones afforded alkynyl-substituted pyrrole derivatives.

In the second part of this study, we have shown that when treated with Lawesson's reagent, *β*-enaminones produced *in situ* *N*-(2,4-pentadiynyl)-*β*-enaminothiones that underwent intramolecular cyclization immediately to afford 2-(2-propyn-1-ylidene)-2,3-dihydro-1,4-thiazepines in good yields in one-pot manner.

In conclusion, 7 novel alkynyl-substituted pyrrole and 12 novel 1,4-thiazepine derivatives were synthesized.

Keywords: Heterocyclic compounds, alkynyl-substituted pyrrole, 1,4-thiazepine, *N*-propargylic *β*-enaminone, *N*-(2,4-pentadiynyl)-*β*-enaminone.

ÖZ

ALKİNİL-SÜBSTİTÜYE PİROL VE 1,4-TİYAZEPİN TÜREVLERİNİN SENTEZİ

Yılmaz, Elif Serel

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Ağustos 2018, 151 sayfa

Heterosiklik bileşikler birçok ilacın yapısında bulunmaları sebebiyle tıbbi kimyada büyük bir yere sahiptir. Bu bileşikler içinde pirol ve 1,4-tiyazepin bileşikleri birçok biyoaktif ve doğal bileşiklerin yapısında yer almasından dolayı ciddi bir öneme sahiptirler. Bu nedenle, bu bileşiklerin sentezi için yeni sentetik metodların geliştirilmesi birçok kimyagerin dikkatini çekmiştir. Son zamanlarda, fonksiyonel grup bağlı alkinlerin halkalaşmaları, çeşitli heterosiklik ve karbosiklik bileşiklerin hazırlanmasında değerli bir araç olarak ortaya çıkmıştır. Bu konuda *N*-proparjilik *β*-enaminonlar elverişlilik sağlamaktadır.

Biz de bu çalışmada *N*-(2,4-pentadiyinil)-*β*-enaminon bileşiklerinin halkalaşma tepkimelerine maruz bırakıldıklarında biyolojik çalışmalar için büyük öneme sahip alkinil-sübstitüye pirol ve 1,4-tiyazepine türevlerini üreteceğini öngördük.

Bu çalışmanın ilk basamağında proparjilamin bileşiğinin *α,β*-alkinik ketonlara konjuge katılması ve ardından terminal alkinlerle kenetlenme tepkimesi sonucu *N*-(2,4-pentadiyinil)-*β*-enaminon bileşiklerini sentezledik. Daha sonra bu bileşiklerin sodyum hidrür gibi bir bazla tepkimeye sokulduklarında alkinil-sübstitüye pirol türevlerini oluşturduğunu bulduk.

Çalışmanın ikinci basamağında *N*-(2,4-pentadiyinil)-*β*-enaminon bileşiklerinin Lawesson reaktifi ile tepkimeye girmesi sonucunda oluşan sulfurlenmiş-*β*-enaminon bileşikleri reaksiyon ortamında oluşur oluşmaz intramoleküler halkalaşma tepkimesine girmekte ve bunun sonucunda da 1,4-tiyazepin bileşiklerini tek kap metodu ile iyi verimlerle oluşturmuştur.

Sonuç olarak, 7 yeni alkinil-sübtitüye pirol ve 12 yeni 1,4-tiyazepin bileşiği sentezlenmiştir.

Anahtar Kelimeler: Heterosiklik bileşikler, alkinil-sübstütiye pirol, 1,4-tiyazepin, *N*-proparjilik *β*-enaminon, *N*-(2,4-pentadiyinil)-*β*-enaminon.

To My Dear Devoted Family

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LIST OF ABBREVIATIONS

ACN	acetonitrile
br	broad (spectral)
d	doublet (spectral)
DCM	dichloromethane
DCE	dichloroethane
dd	doublet of doublet (spectral)
DMF	dimetylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets (spectral)
FT	fourier transform
Hz	Hertz
J	coupling constant
LR	Lawesson’s reagent
m	multiplet (spectral)
mCPBA	meta-Chloroperoxybenzoic acid
min	minute(s)
NOESY	Nuclear overhauser effect spectroscopy
ppm	parts per million (in NMR)
q	quartet (spectral)
r.t.	room temperature
s	singlet (spectral)
t	triplet (spectral)
THF	tetrahydrofuran
TLC	thin layer chromatography
td	triplet of doublets (spectral)
tdd	triplet of doublet of doublets (spectral)
TMEDA	tetrametyletylenediamine

TMS	trimethylsilane
tt	triplet of triplets (spectral)
δ	chemical shift in parts per million downfield from tetramethylenesilane (TMS)

CHAPTER 1

INTRODUCTION

Organic chemistry is the study of carbon compounds in every manner, which mainly includes the synthesis of organic compounds and organic materials that contain carbon atoms. In fact, organic compounds build the basis of life on Earth and make up an important part of human strive in chemistry because all living organisms are organic. For example, proteins that construct our muscles and skins, DNA that carries our genetic information, the drugs that treat our diseases are all organic compounds.[1,2]

During the early nineteenth century, scientists have explored that organic compounds can be synthesized and studied. At that time, French chemist Michele Eugene Chevreul made an important contribution to organic chemistry by finding the true nature of soap that could be separated into pure organic compounds which he named as fatty acids.[1] He isolated stearic and oleic acids as well.

In 1828, Friedrich Wöhler synthesized urea (carbamide) from ammonium cyanate salt, which is the major organic component of human urine. In 1856, synthetic organic dye, mauveine, was produced by British chemist William Henry Perkin accidentally. This discovery led to increase of interest in the field of organic chemistry.[1]

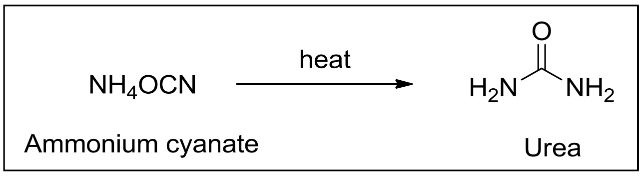


Figure 1. Synthesis of urea (carbamide).

Nowadays, synthetic organic chemistry is an ever-developing research field in chemistry. In particular, heterocyclic compounds play an extensive part of synthetic organic chemistry due to their ease of preparation and bioactivity.[3]

1.1 Heterocyclic Compounds

Heterocyclic compounds are one of the most important classes of organic compounds because of their roles in organic synthesis and medicinal chemistry. Heterocyclic compounds are composed of cyclic structures that contain heteroatoms such as oxygen, nitrogen and sulphur, which are the most found heteroatoms in heterocyclic compounds (Figure 2). The application fields of heterocyclic compounds are very broad.[4] Many heterocyclic compounds are found in electronics, biology, optics, pharmacology and material science.[3]

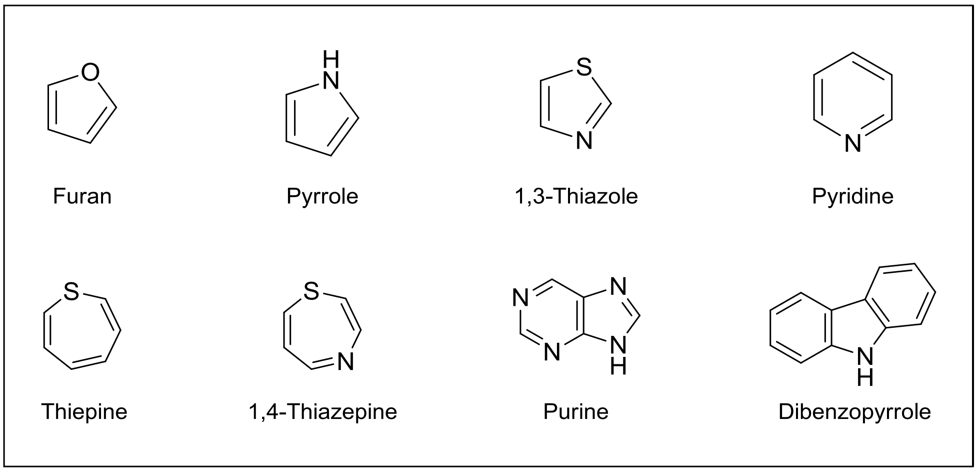
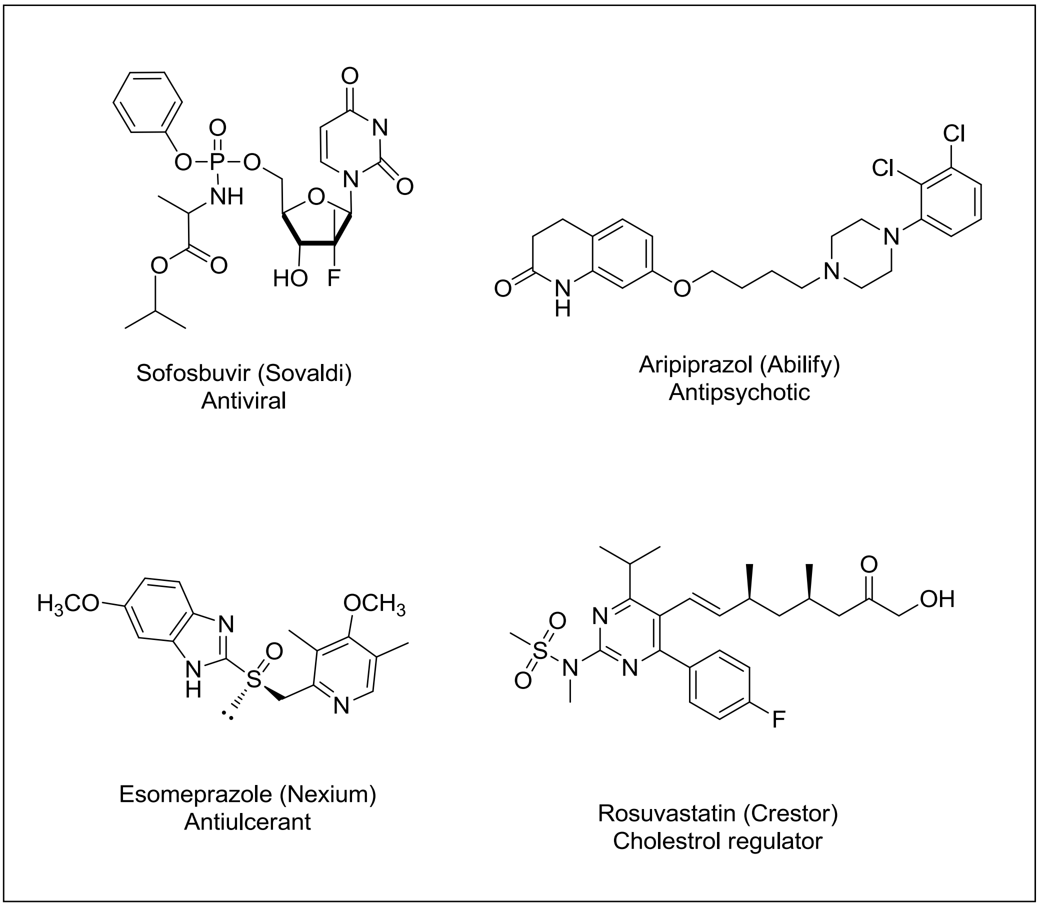


Figure 2. Some examples of heterocyclic compounds.

Considerable biological activities of heterocyclic compounds make these molecules more vital. For example, they are used as antifungal, antiinflammatory, antibacterial, anticonvulsant, antiallergic and anticancer agents.[5] A large number of heterocyclic compounds form the content of many important pharmaceuticals. For instance, diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine, barbiturates, antipyrine, captopril and methotrexate are known as the synthetic heterocyclic drugs. On the other hand, papaverine, theobromine, quinine, emetine, theophylline, atropine, procaine, codeine, reserpine and morphine are the examples of natural heterocyclic drugs.[6] Examples of some commercial drugs are given in Figure 3.[4] In short, heterocylic compounds contribute and assist to healing the human health.[3]



Sofosbuvir (Sovaldi)
Antiviral

Aripiprazol (Abilify)
Antipsychotic

Esomeprazole (Nexium)
Antiulcerant

Rosuvastatin (Crestor)
Cholestrol regulator

Figure 3. Examples of some commercial drugs including heterocyclic units.

1.2 Pyrroles

Pyrrole is defined as a five-membered unsaturated aromatic heterocyclic compound with the formula C_4H_5N.[7] It was first recognized by Runge in 1834 and then isolated in 1857 by Anderson from the pyrolysate of bone.[8] It was found as the structural fragment of heme and chlorophyll. Notably, a broad range of medicines and natural products include pyrrole skeleton in their structures. Some representative examples of pyrrole containing natural products and drugs are summarized in Figure 4.[9]

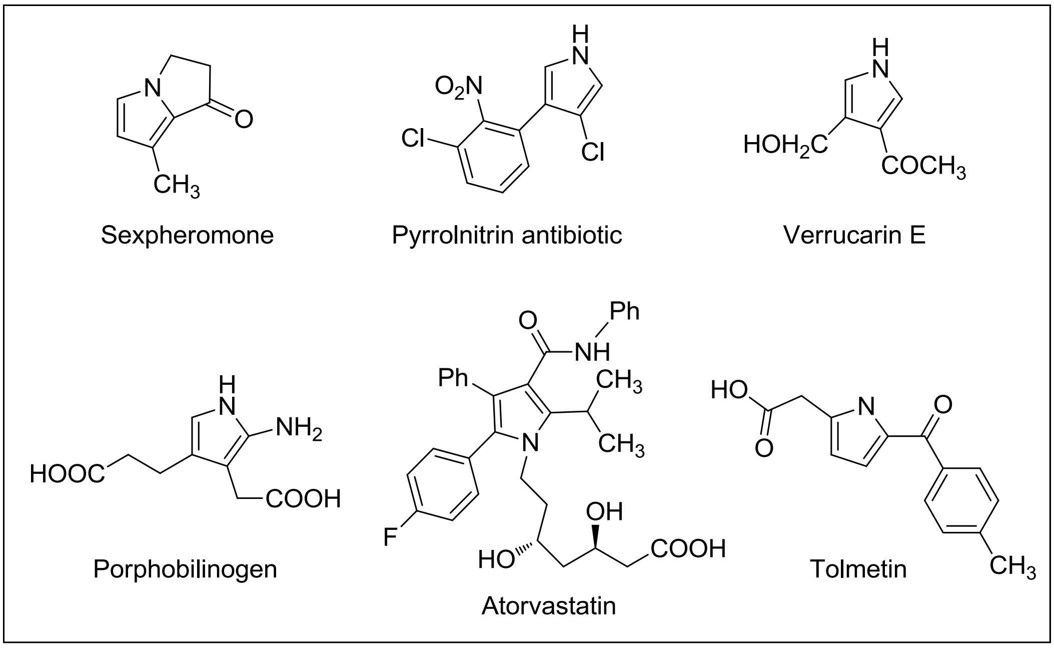
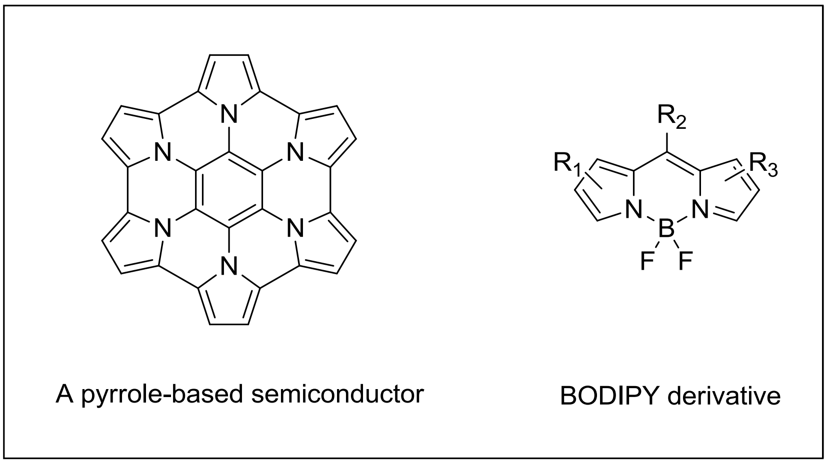


Figure 4. Some examples of pyrrole containing natural products and drugs.

Pyrroles became one of the most significant class of heterocyclic compounds since they have various biological and pharmacological activities. They possess diverse nature of biological activities, including antiinflammatory, anticancer, antimalarial, antiviral and antimicrobial activities.[10] Many substituted pyrrole derivatives have also been used as HIV fusion inhibitors and antitubercular drugs.[10] As examples of pyrrole derived medicines, Atorvastatin which is the top selling cholesterol lowering drug in pharmaceutical history and Tolmetin which is known as antiinflammatory drug could be given (Figure 4).[10]

In addition, pyrrole compounds have various applications in material science. Semiconducting materials and glucose sensors based on polypyrrole latex materials contain pyrrole units (Figure 5).[10]



A pyrrole-based semiconductor

BODIPY derivative

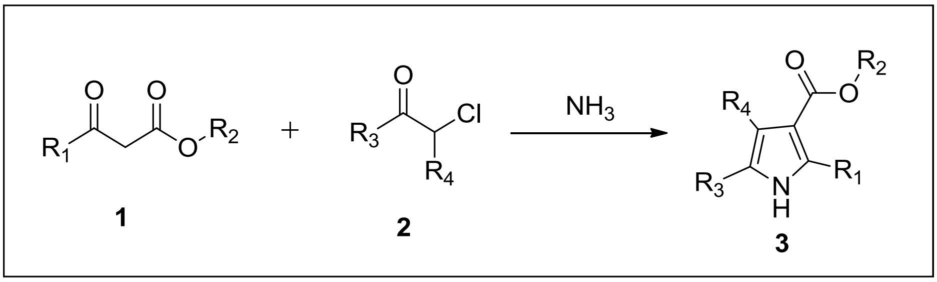
Figure 5. Representative examples of pyrrole containing semiconductors and dyes.

Because of their importance in medicinal chemistry, material science and organic synthesis, pyrroles became popular targets for synthetic chemists. For the synthesis of pyrrole derivatives, many synthetic methods have been developed and new approaches continue to appear stimulated by the broad spectrum of medicinal activity of these compounds.[10]

1.2.1 Synthesis of Pyrrole Derivatives

Over the years, many synthetic methods have been developed for the synthesis of pyrrole ring.[11] Among them, there are important classical methodologies which are widely applied for the synthesis of pyrrole compounds.

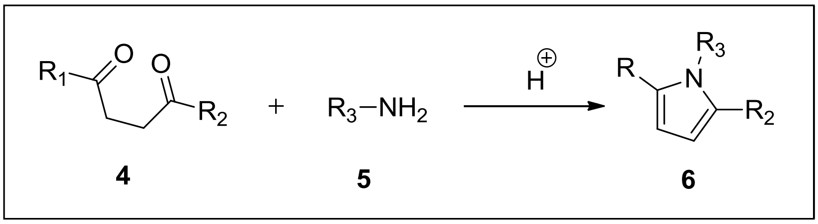
One of them is Hantzch pyrrole synthesis which is based on the reaction between β-ketoesters **1,** α-haloketones **2** and ammonia to provide substituted pyrroles **3**.[12]



Scheme 1. Hantzsch synthesis of pyrroles.

Knorr reaction is one of the widely employed methods for the synthesis of substituted pyrroles. This method is based on the reaction of *α*-aminoketones with *β*-ketoesters.[13,14]

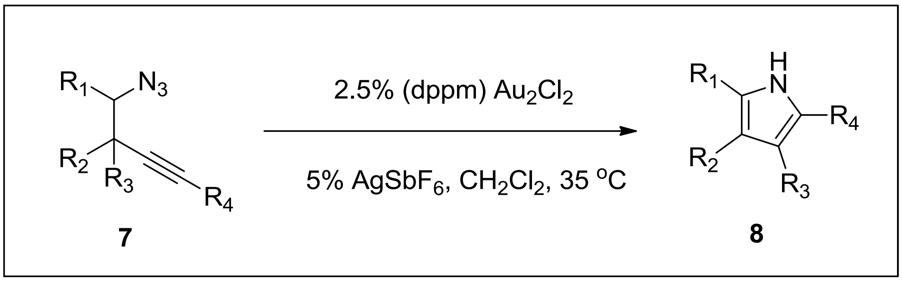
Paal-Knorr pyrrole synthesis is the another classical method.[15] In this method, the condensation of 1,4-dicarbonyl compound **4** with an excess amount of primary amine **5** or ammonia provides pyrroles **6** (Scheme 2).[15]



Scheme 2. Paal-Knorr synthesis of pyrroles.

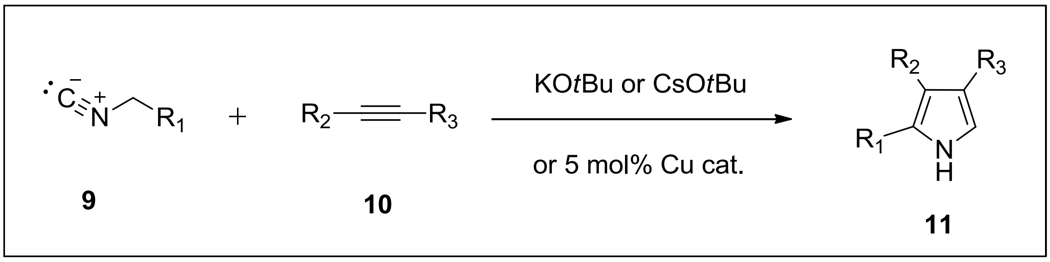
Recently, many new methodologies for the synthesis of these compounds have been developed.[9] Some examples are summarized below.

In 2005, Toste and co-workers have reported a method for the synthesis of substituted pyrroles. In this method, gold(I)-catalyzed Schmidt reaction of homopropargyl azides **7** generated pyrroles **8** (Scheme 3).[16]



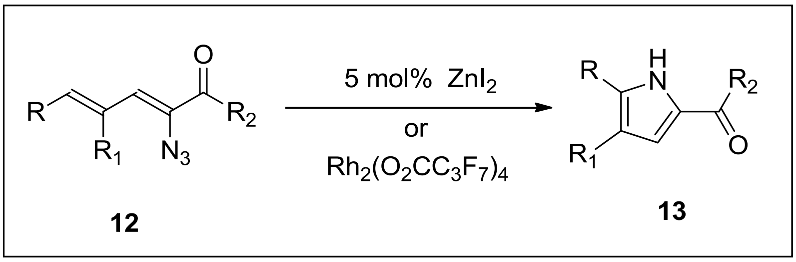
Scheme 3. Synthesis of substituted pyrroles via gold(I)-catalysis.

In the same year, Meijere and co-workers described the synthesis of 2,3,4-trisubstituted pyrroles **11** by the reaction of methyl isocyanides **9** and acetylenes **10** under basic medium or copper catalysis (Scheme 4).[17]



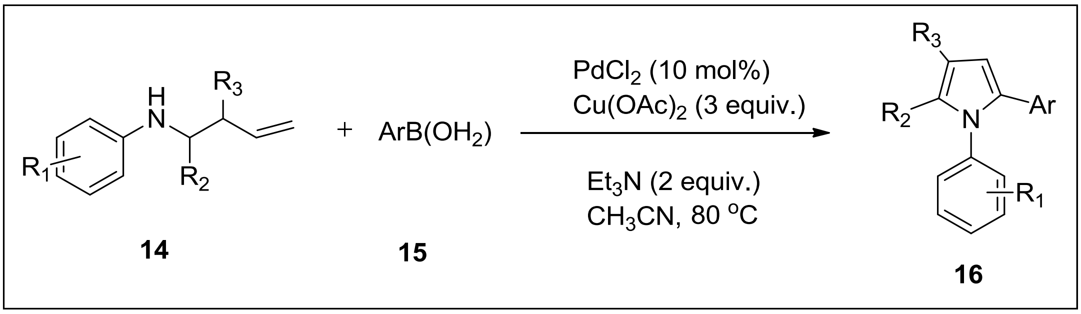
Scheme 4. Synthesis of 2,3,4-trisubstituted pyrroles.

In 2007, Driver research group has developed a method for the synthesis of 2,4,5-trisubstituted pyrroles **13** from dienyl azides **12** by using ZnI_2 or $Rh_2(O_2CC_3F_7)_4$ as the catalyst (Scheme 5).[18]



Scheme 5. Synthesis of 2,4,5-trisubstituted pyrrole derivatives.

In 2015, Zheng and co-workers reported the synthesis of polysubstituted pyrrole derivatives from *N*-homoallylicamines **14** and arylboronic acids **15** (Scheme 6).[19] In this study, $PdCl_2$ was used as the catalyst. This Pd(II)-catalyzed oxidative reaction allowed the conversion of starting materials to substituted pyrroles **16**.



Scheme 6. Synthesis of polysubstituted pyrrole derivatives.

1.3 Thiazepines

Seven-membered heterocycles have been considered as important structural skeletons in medicinal chemistry. Among them, thiazepines are one of the most important heterocycles containing sulfur and nitrogen heteroatoms, so they possess a broad spectrum of pharmacological activities. Depending on the position of sulfur and nitrogen atoms, they are called 1,2- 1,3- or 1,4-thiazepines (Figure 6).[20] Thiazepines are biologically active compounds againist different type of targets, and their distictive features make these molecules very valuable.[20,21]

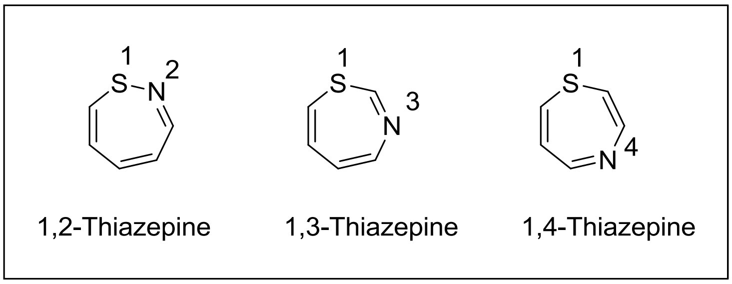
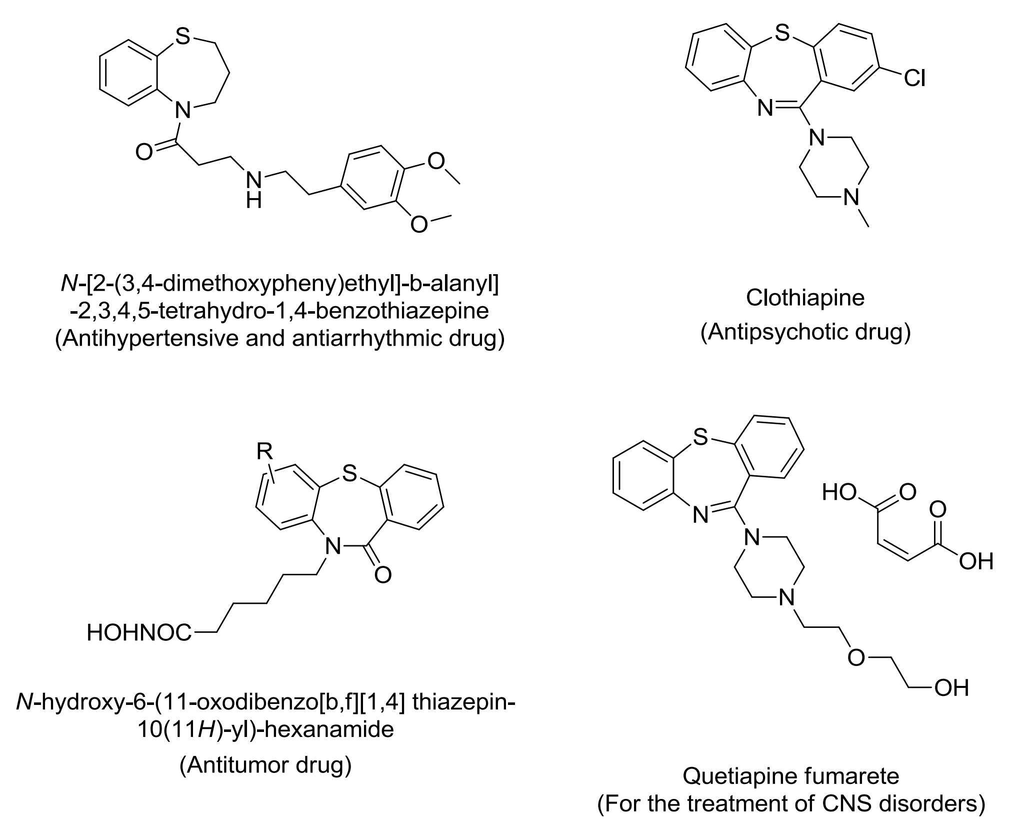


Figure 6. Structures of thiazepines.

1.3.1 1,4-Thiazepines

1,4-Thiazepines are one of the most prominent nitrogen and sulfur containing seven-membered heterocyclic compounds which have immense worth in the field of drug discovery and development because of their biological activities.[22]

As mentioned above, 1,4-thiazepines play a vital role in pharmaceutical chemistry because 1,4-thiazepine scaffold is found in many bioactive molecules. They have shown significant biological activities such as antifungal, antiinflammatory, antibacterial, anticonvulsant, antiallergic and anticancer properties.[23] There are numerous derivatives of 1,4-thiazepines that possess antiarrhythmic, antispasmodic, angiogenic and central nervous system (CNS) activities (Figure 7). For example, Quetiapine, which is the dibenzothiazepine derivative, is known as antipsychotic drug for the treatment of CNS disorder.[24] In addition, 1,4-benzothiazepine moieties have been used as the calcium channel blockers, HIV-1 integrase and reverse transcriptase inhibitors.[20] For this reason, substantial efforts have been spent for the synthesis of 1,4-thiazepine derivatives.



N-[2-(3,4-dimethoxypheny)ethyl]-b-alanyl] -2,3,4,5-tetrahydro-1,4-benzothiazepine (Antihypertensive and antiarrhythmic drug)

Clothiapine (Antipsychotic drug)

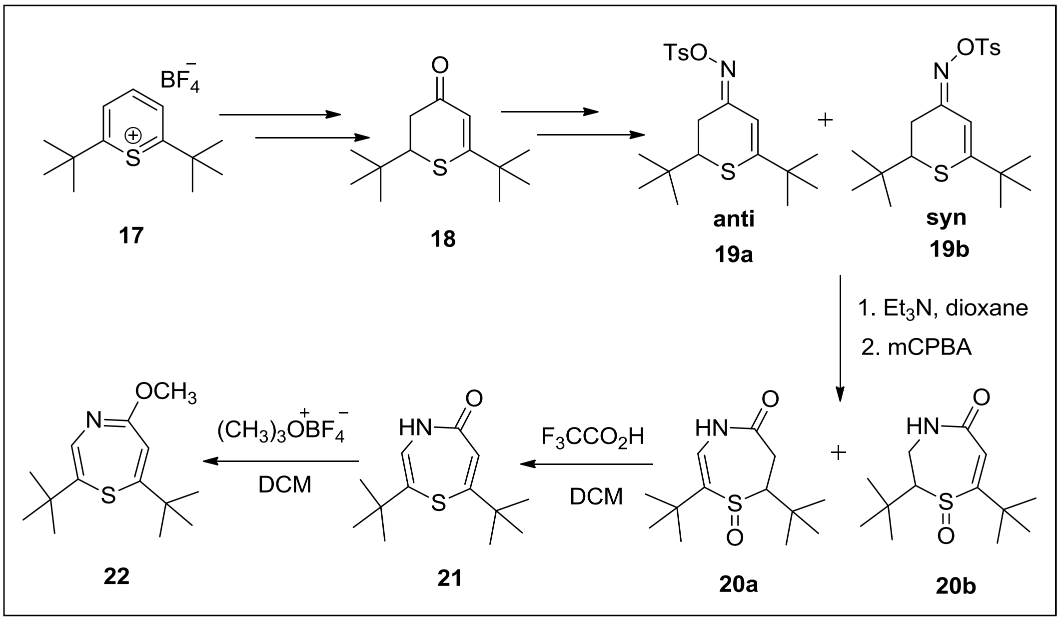
N-hydroxy-6-(11-oxodibenzo[b,f][1,4] thiazepin-10(11*H*)-yl)-hexanamide (Antitumor drug)

Quetiapine fumarete (For the treatment of CNS disorders)

Figure 7. Some examples of pharmacologically active 1,4-thiazepine derivatives.

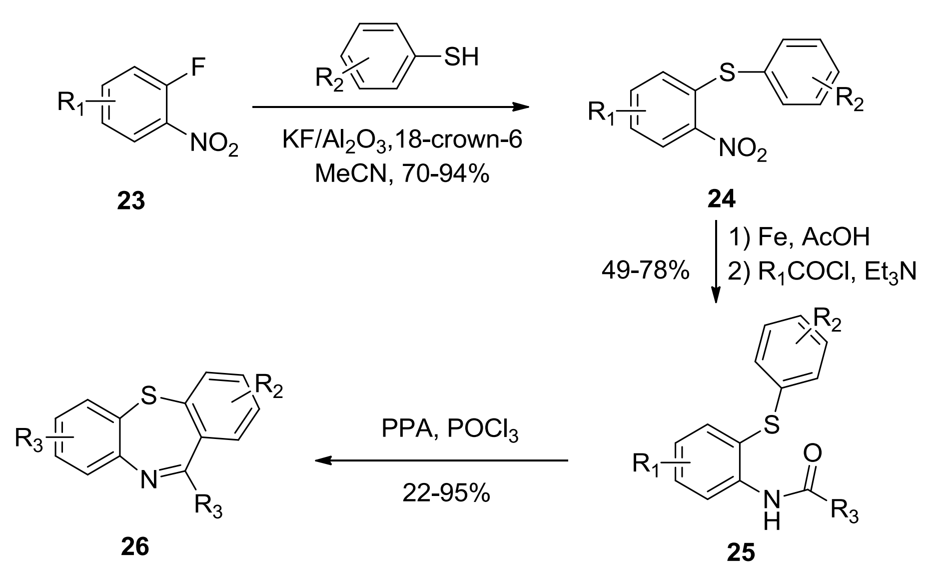
1.3.2 Synthesis of 1,4-Thiazepines

In 1986, Murata research group reported a multistep synthesis of monocyclic stable 2,7-di-*tert*-butyl-5-methoxy-1,4-thiazepine **22** starting from 2,6-di–*tert*-butylthiopyrylium tetrafluoroborate **17** (Scheme 7).[25] In this study, after dihydrothiopyranone **18** was obtained, the synthesis of a mixture of *anti*-**19a** and *syn* -**19b** oximes was achieved by the reaction of dihydrothiopyranone **18** with NH_2OH, followed by tosylation reaction. Lactams **20a** and **20b** were then obtained by Beckmann Rearrangement with Et_3N, followed by oxidation with mCPBA. Subsequently, the diene form of product **21** was obtained from the major isomer of sulfoxides (**20a** and **20b)** via Pummerer reaction. The resulting product was then converted into desired stable 1,4-thiazepine **22** in the presence of Me_3O^- BF_4^+ with 65 % yield (Scheme 7).



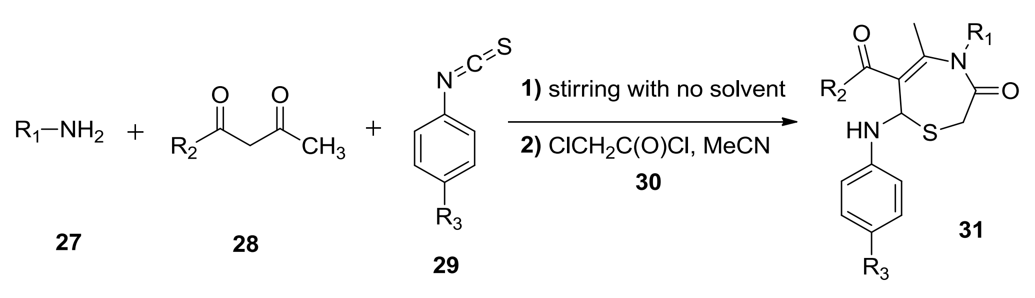
Scheme 7. Synthesis of a monocyclic stable 1,4-thiazepine.

In 2013, Guo and co-workers synthesized dibenzothiazepines according to the reaction pathway given in Scheme 8.[26] First, o-fluoronitrobenzenes **23** were reacted with substituted thiophenols by using KF/Al_2O_3 in the presence of 18-crown-6 to afford diphenyl thioether derivatives **24**. Subsequently, nitro groups were reduced to amines by Fe/AcOH. Then, acylation with acyl chloride gave amide derivatives **25.** In the final step, dibenzothiazepines **26** were obtained via cyclization with polyphosphoric acid (PPA) and $POCl_3$ (Scheme 8).



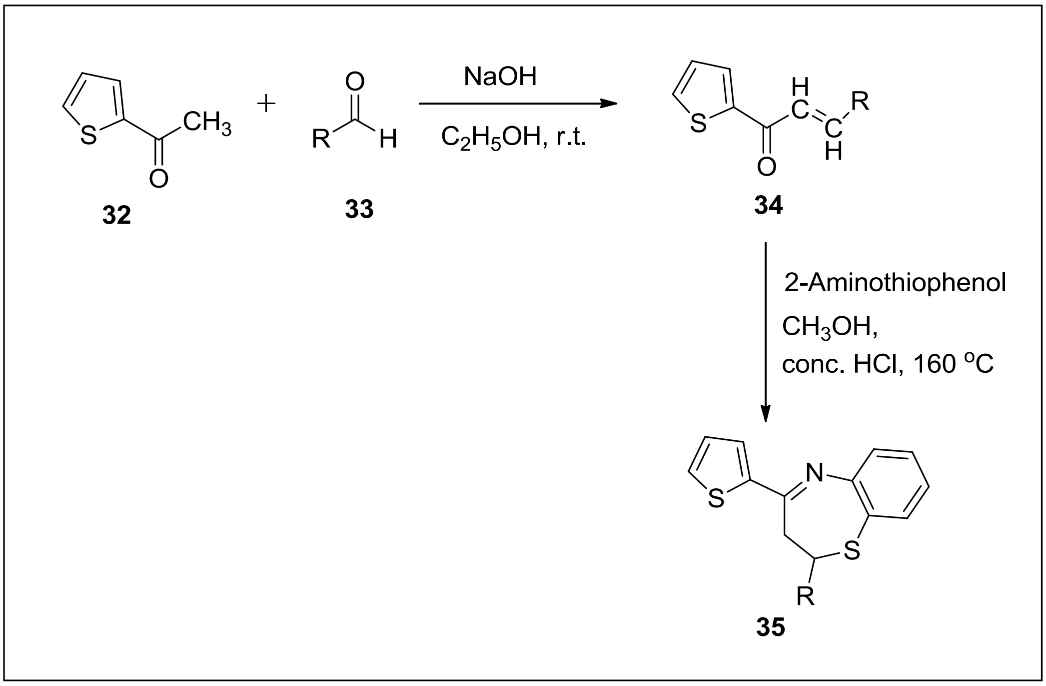
Scheme 8. Synthesis of 1,4-dibenzothiazepines.

In 2014, Alizadeh reported one-pot sequential synthesis of substituted 1,4-thiazepines (Scheme 9).[27] In this study, after primary amine **27**, 1,3 dicarbonyl compound **28** and aryl isothiocyanate **29** were reacted with each other under solvent free-conditions, the resulting intermediate was reacted with chloroacetyl chloride **(30)** to yield thiazepines **31** (Scheme 9).



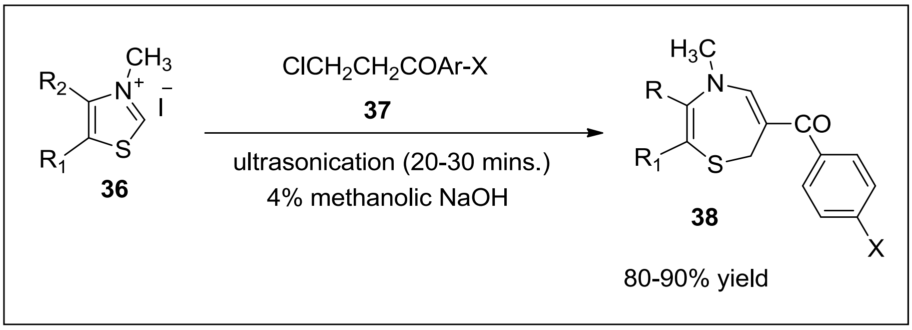
Scheme 9. Synthesis of substituted 1,4-thiazepine derivatives.

Kumar and co workers also synthesized 1,4-benzothiazepine derivatives (Scheme 10).[28] First, the reaction of 2-acetylthiophene **32** with aromatic aldeyhdes **33** in basic medium produced *α,β*-unsaturated ketones (chalcones) **34**. Then, *α,β*-unsaturated ketones were treated with 2-aminothiophenol in the presence of concentrated HCl in methanol in reflux conditions to afford 1,4-benzothiazepines **35**.



Scheme 10. Synthesis of 1,4-benzothiazepines.

In a recent study, Cannoo and Preet achieved the synthesis of thiazepine derivatives by applying ultrasonication method via intramolecular ring expansion (Scheme 11).[29] They firstly prepared ionic liquid-based 1,3-dialkyl-substituted thiazolium iodide **36**. When thiazolium salts were reacted with 3-chloro-1-(substituted phenyl)-propan-1-one **37** under basic medium, they obtained desired thiazepine derivatives **38** (Scheme 11).[29]



Scheme 11. Synthesis of thiazepine derivatives.

1.4 Lawesson's Reagent (LR) and Phosphorus Sulfide (P_4S_{10}) in Organic Synthesis

Synthetic organic chemists have interested in the conversion of carbonyl groups into thiocarbonyls over the years**.** For this transformation, phosphorus sulfide P_4S_{10} and Lawesson's Reagent (LR) have been commonly used as thionating agents. Moreover, they have been in the synthesis of various heterocyclic compounds.[30,31]

Compared to $P_4S_{10,}$ Lawesson's reagent, the structure of which is given in Figure 8, is favored for many chemists because of its diverse applications. Commercially availability, easy usage and mild reaction conditions make LR more popular over $P_4S_{10.}$ LR [2,4-bis(*p*-methoxyphenyl)-1,3,2,4 dithiadiphosphetane-2,4-disulfide] plays a significant role in organic synthesis. It can be used in the various transformations, rearrangements, cyclization processes and synthesis of many heterocyclic compunds.[32] The general thionation mechanism with LR is given in Scheme 12. Firstly, LR **39** decomposes to produce molecule **40**, which then reacts with carbonyl compound **41** to generate four-membered intermediate **42**. After the decomposition of intermediate **42**, thioketone **43** is obtained (Scheme 12). Driving force for this reaction is attributed to formation of strong P-O bonds as compared to P-S bonds.[30,32]

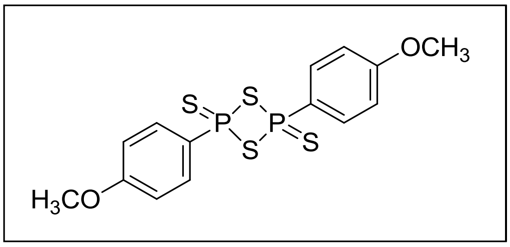
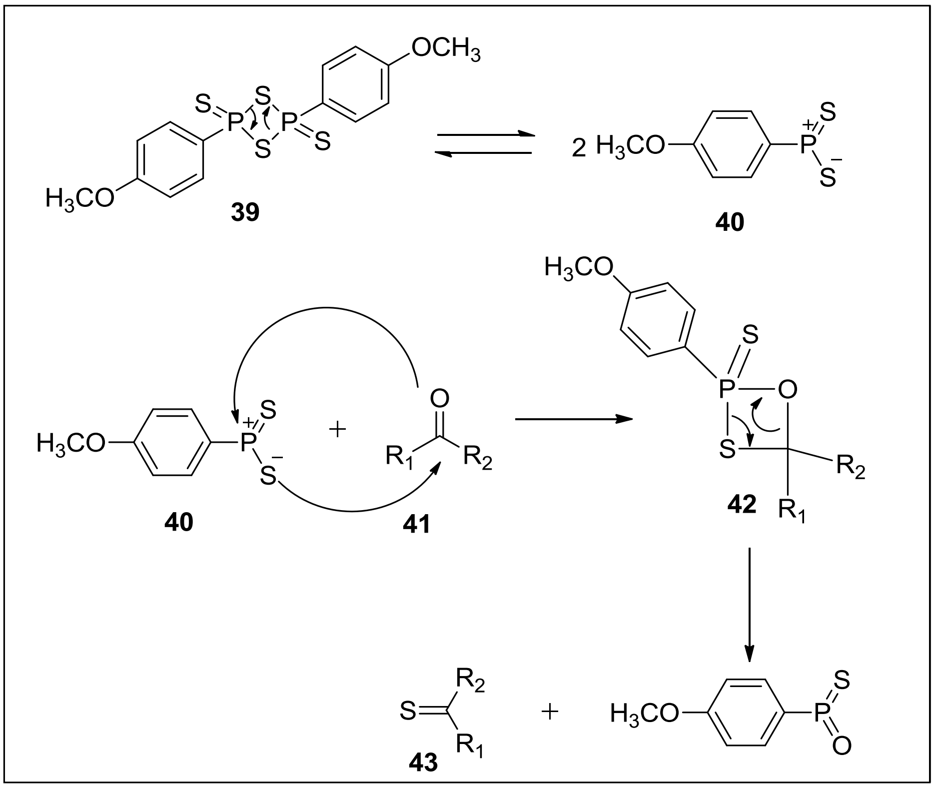


Figure 8. Structure of Lawesson's Reagent, (LR).



Scheme 12. Thionation mechanism of carbonyl groups with LR.

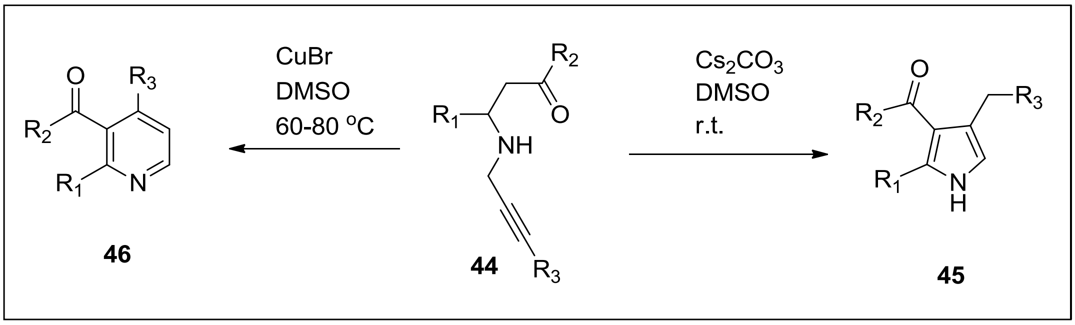
1.5 *N*-Propargylic *β*-Enaminones

β-Enaminones, which have basic structural unit N–C=C–C=O, play a important role in organic synthesis.[33] In particular, *N*-propargylic *β*-enaminones have been used as valuable intermediates in the synthesis of a broad range of heterocyclic compounds. They have attracted considerable attention because they show both nucleophilic and electrophilic character due to the presence of enamine and enone moieties in their structures.[34]

In literature, there are many studies regarding the new reactivity patterns of *N*-propargylic *β*-enaminones since their cyclizations lead to many important heterocycles such as pyrroles and pyridines.[35,36]

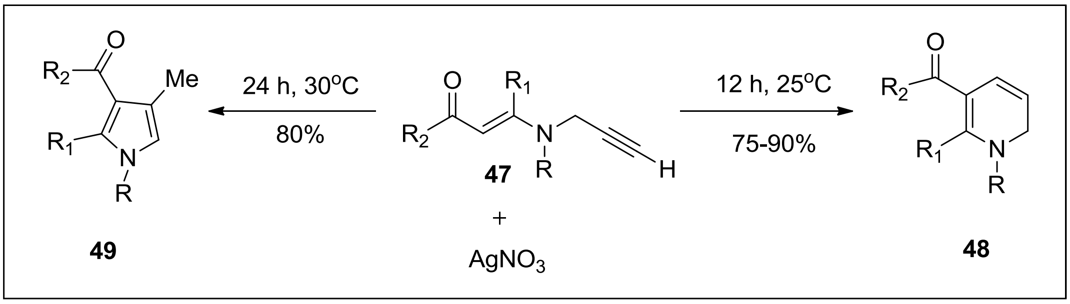
1.5.1 *N*-Propargylic *β*-Enaminones in Organic Synthesis

Recently, the cyclizations of functionally-substituted alkynes have emerged as a valuable tool in the preparation of diverse heterocyclic and carbocyclic compounds. In this regard, *N*-propargylic *β*-enaminones have provided to be useful. Therefore, researchers focused on the discovery of new methodologies to form many heterocyclic compounds by using *N*-propargylic *β*-enaminone compounds.[37] In this regard, pionnering study, was done by Cacchi and co-workers. (Scheme 13).[35] Cyclization of *N*-propargylic *β*-enaminones **44** with Cs_2CO_3 in DMSO at room temperature afforded pyrrole compounds **45**. However, when CuBr is used as a catalyst by heating in DMSO, pyridine compounds **46** were obtained from *N*-propargylic *β*-enaminones (Scheme 13).[35]



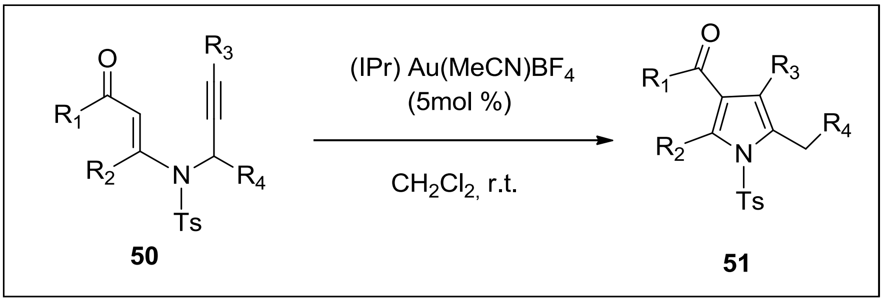
Scheme 13. Synthesis of pyrroles and pyridines.

Martins research group have achieved 6-*endo-dig* intramolecular cyclization of *N*-propargylic *β*-enaminones **47** by using $AgNO_3$ as a catalyst to produce 1,2-dihydropyridines **48** (Scheme 14).[37] In one case, pyrrole **49** was obtained.



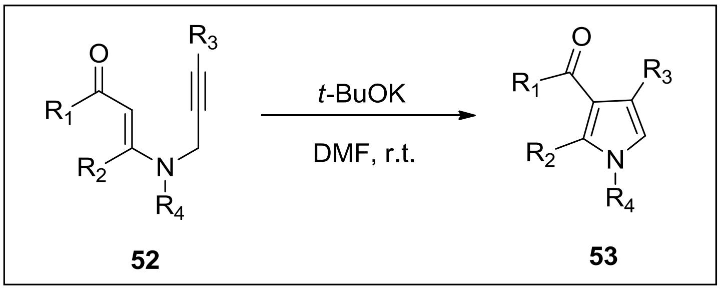
Scheme 14. Synthesis of 1,2-dihydropyridines and pyrroles.

Saito and research group have investigated gold(I)-catalyzed amino-Claisen rearrangement of *N*-tosyl, *N*-propargylic *β*-enaminones **50** which led to the formation of pyrroles **51** (Scheme 15).[34]



Scheme 15. Synthesis of pyrroles from *N*-tosyl, *N*-propargylic *β*-enaminones.

Recently, Hu and co-workers have shown that base-mediated intramolecular 5-*exo-dig* cyclization of *N*-alkyl, *N*-propargylic *β*-enaminones **52** under metal free conditons generated pyrrole derivatives **53** (Scheme 16).[38]



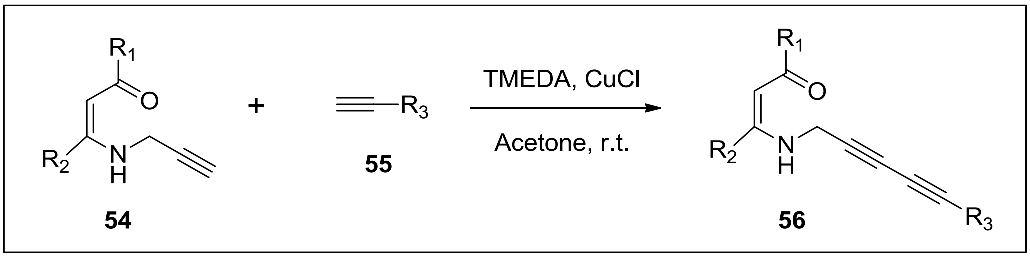
Scheme 16. Synthesis of pyrroles from *N*-alkyl, *N*-propargylic *β*-enaminones.

1.6 Aim of Thesis

Our research group have concentrated on the synthesis of five-, six- and seven-membered heterocyclic compounds. In this thesis work, we aimed to work on two projects. First study includes the synthesis of propargyl-substituted pyrrole derivatives and second work comprises the synthesis of seven-membered 1,4-thiazepine derivatives.

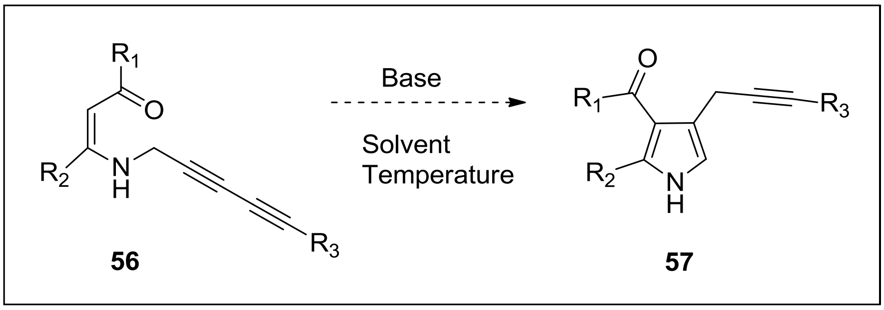
Recently, various heterocyclic and carbocyclic compounds have been synthesized via cyclizations of functionally-substituted alkynes which are recognized as precious substrates. In this regard, *N*-propargylic *β*-enaminones are worthwhile to use.

Initially, we prepared our starting materials (Scheme 17). First, we synthesized *N*-(2,4-pentadiynyl)-*β*-enaminones **56** by the copper-catalyzed coupling reaction of *N*-propargylic *β*-enaminones **54** with terminal alkynes **55** (Scheme 17).



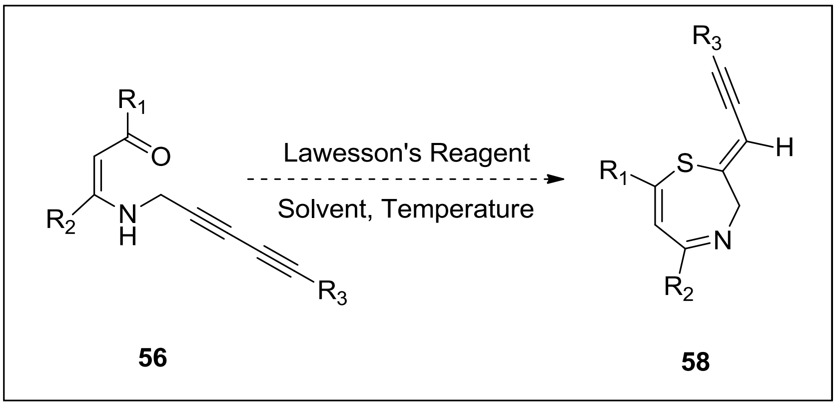
Scheme 17. Synthesis of *N*-(2,4-pentadiynyl)-*β*-enaminones.

In the first part of our study, we have anticipated that under basic conditions, cyclizations of *N*-(2,4-pentadiynyl)-*β*-enaminones **56** would produce propargyl-substituted pyrroles **57**, which have great potential for biological studies and further intramolecular cyclizations to generate new derivatives with significant, new and/or novel properties. (Scheme 18). We have explored 5-*exo-dig* cyclization of *N*-(2,4-pentadiynyl)-*β*-enaminones **56** under basic condition to obtain propargyl-substituted pyrroles.



Scheme 18. Strategy for the synthesis of propargyl-substituted pyrroles.

In the second part of our study, we have anticipated that the reaction of *N*-(2,4-pentadiynyl)-*β*-enaminones **56** with Lawesson's reagent, would produce *in situ N*-(2,4-pentadiynyl)-*β*-enaminothiones that may undergo intramolecular cyclization to afford 2-(2-propyn-1-ylidene)-2,3-dihydro-1,4-thiazepines **58** in one-pot manner (Scheme 19). Hence, we explored the reactions of *N*-(2,4-pentadiynyl)-*β*-enaminones **56** with Lawesson's reagent to yield 2-(2-propyn-1-ylidene)-2,3-dihydro-1,4-thiazepines **58**.



Scheme 19. Strategy for the synthesis of 1,4-thiazepines.

Briefly, in this thesis, the scope, limitations and proposed mechanisms for the synthesis of propargyl-substituted pyrroles **57** and 2-(2-propyn-1-ylidene)-2,3-dihydro-1,4-thiazepines **58** will be discussed in detail.

CHAPTER 2

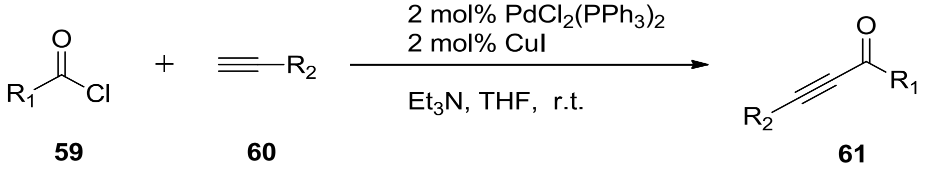
RESULTS AND DISCUSSION

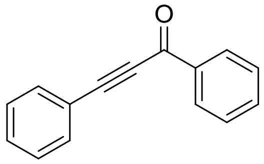
2.1 Synthesis of *α,β*-Alkynic Ketones

In the first part of our study, we synthesized *α,β*-alkynic ketones **61** from aryloyl chlorides **59** and terminal alkynes **60** via Pd-catalyzed coupling reaction (Table 1).[39-41] In this reaction, $PdCl_2(PPh_3)_2$ and CuI were used as catalyst and cocatalyst, respectively, Et_3N was used as a base. In fact, this Pd-catalzed reaction is known as Sanogashira cross-coupling reaction.[39-41] By employing this reaction, we prepared 12 *α,β*-alkynic ketone derivatives with different substitution in 45 to 98% yields (Table 1). Moreover, this coupling reaction tolerated the presence of variety of groups with electron-withdrawing and electron-donating substituents.

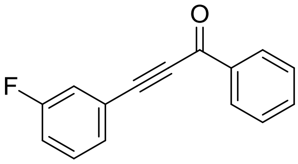
The structures of *α,β*-alkynic ketones were assigned by ^1H and ^{13}C NMR spectroscopy.

Table 1. Synthesis of *α,β*-alkynic ketone derivatives **61**.[a]

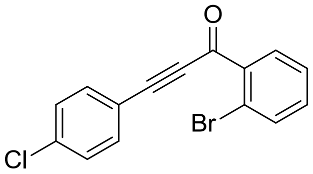




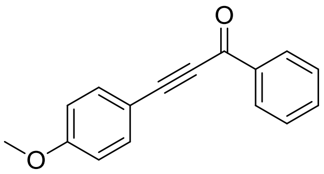
61A (90%)



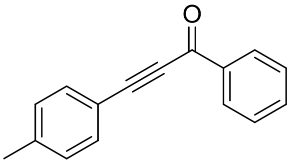
61B (75%)



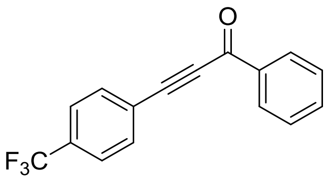
61C (45%)



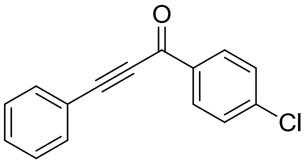
61D (96%)



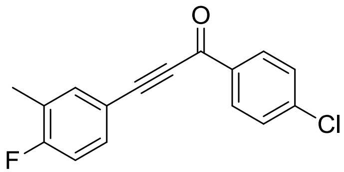
61E (68%)



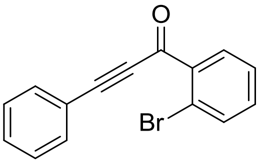
61F(67%)



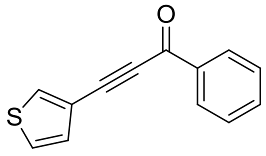
61G (72%)



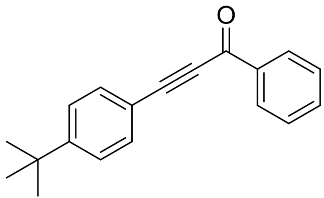
61H (76%)



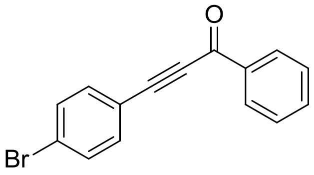
61I (70%)



61J (98%)



61K (94%)



61L (71%)

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[a] Yields of the isolated products.

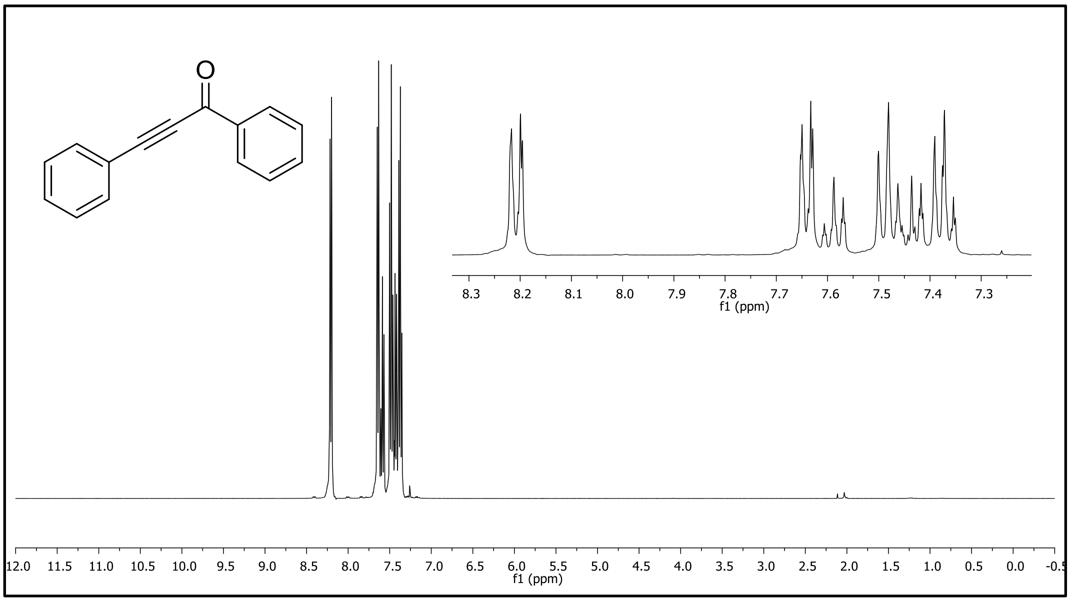


Figure 9. ^{1}H NMR spectrum of 1,3-diphenylprop-2-yn-1-one (**61A**).

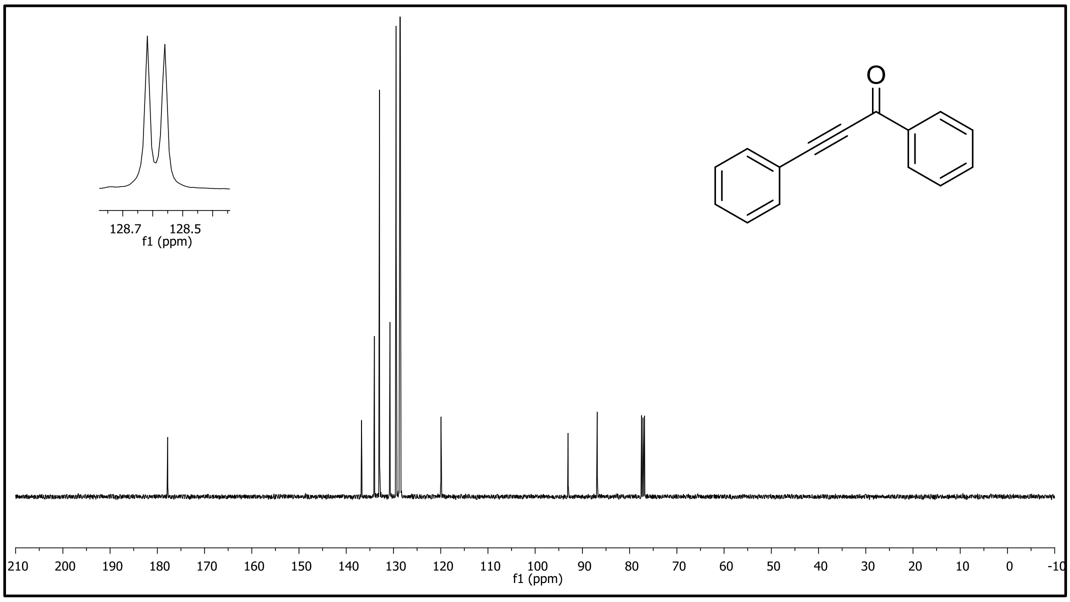


Figure 10. ^{13}C NMR spectrum of 1,3-diphenylprop-2-yn-1-one (**61A**).

In ^1H NMR spectrum of 1,3-diphenylprop-2-yn-1-one (**61A**), ten aromatic phenyl protons resonate between 8.27-7.34 ppm (Figure 9).

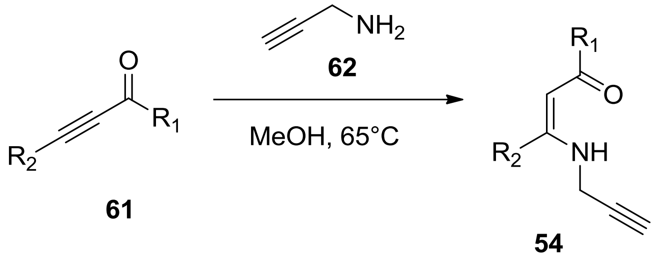
In ^{13}C NMR spectrum of 1,3-diphenylprop-2-yn-1-one (**61A**), carbonyl carbon (C=O) appears at 177.8 ppm. Two alkynic carbons resonate at 86.9 and 93.0 ppm. The remaining eight phenyl carbons appear between 119.9–136.8 ppm (Figure 10).

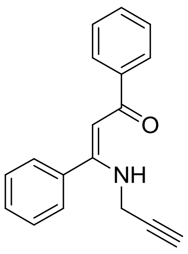
2.2 Synthesis of *N*-Propargylic *β*-Enaminone Compounds

We synthesized *N*-propargylic *β*-enaminones **54** by 1,4-conjugate addition of propargylamine (**62**) to α,*β*-alkynic ketones **61** in refluxing methanol (Table 2)[35] In fact, this is an example of Michael additon reaction.

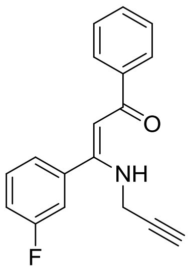
The synthesized *N*-propargylic *β*-enaminones **54** have *Z* stereochemistry due to intramolecular H-bonding between amine hydrogen and carbonyl oxygen, which also makes the molecule more stable.[35] In the *Z* form of the molecule, N-H peak appears around 11.0 ppm in ^1H NMR spectrum. By employing a variety of α,*β*-alkynic ketones **61**, we synthesized a diverse range of *N*-propargylic *β*-enaminones **54** (Table 2). The yields of *β*-enaminones altered between 77 to 99%.

Table 2. Synthesis of *N*-propargylic *β*-enaminone derivatives **54**.[a]

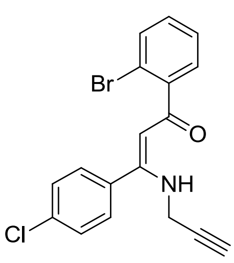




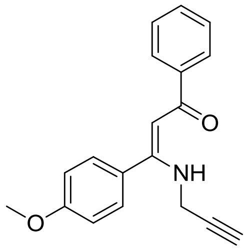
54A (95%)



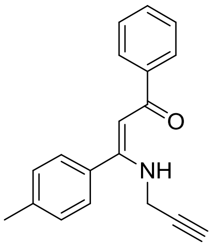
54B (94%)



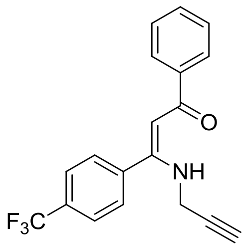
54C (95%)



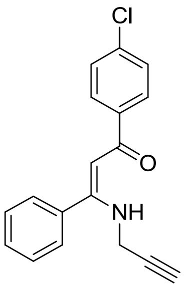
54D (98%)



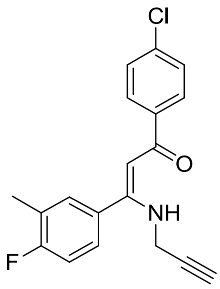
54E (97%)



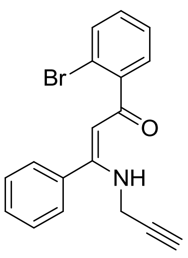
54F (86%)



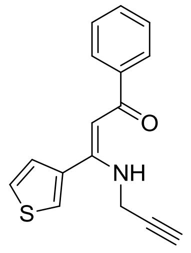
54G (93%)



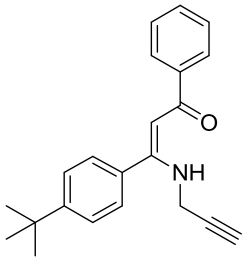
54H (88%)



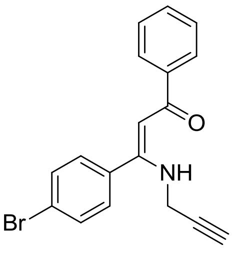
54I (99%)



54J (77%)



54K (98%)



54L (79%)

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[a] Yields of the isolated products.

^{1}H and ^{13}C NMR spectra of (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54A**) are shown in Figures 11 and 12. As seen in the ^{1}H NMR spectrum of **54A** (Figure 11), N-H proton appears at 11.39 ppm because of hydrogen bonding (N−H····O) as a broad singlet. The signals of aromatic hydrogens appear between 7.89 and 7.29 ppm. Vinylic hydrogen resonates at 5.82 ppm as a singlet. Methylenic hydrogen resonates at 3.86 ppm as doublet of doublet and alkynyl proton comes at 2.32 as triplet.

In ^{13}C NMR spectrum of **54A** (Figure 12), carbonyl carbon (C=O) resonates at 188.6 ppm. The signal of *β*-carbon (C-N) appears at 165.5 ppm. Aromatic phenyl carbons resonate between 126.9 and 139.6 ppm. *α*-CH carbon resonates at 94.3 ppm. Alkynyl carbons come at 79.9 and 72.4 ppm, respectively. Methylenic carbon (CH_2) resonates at 33.9 ppm.

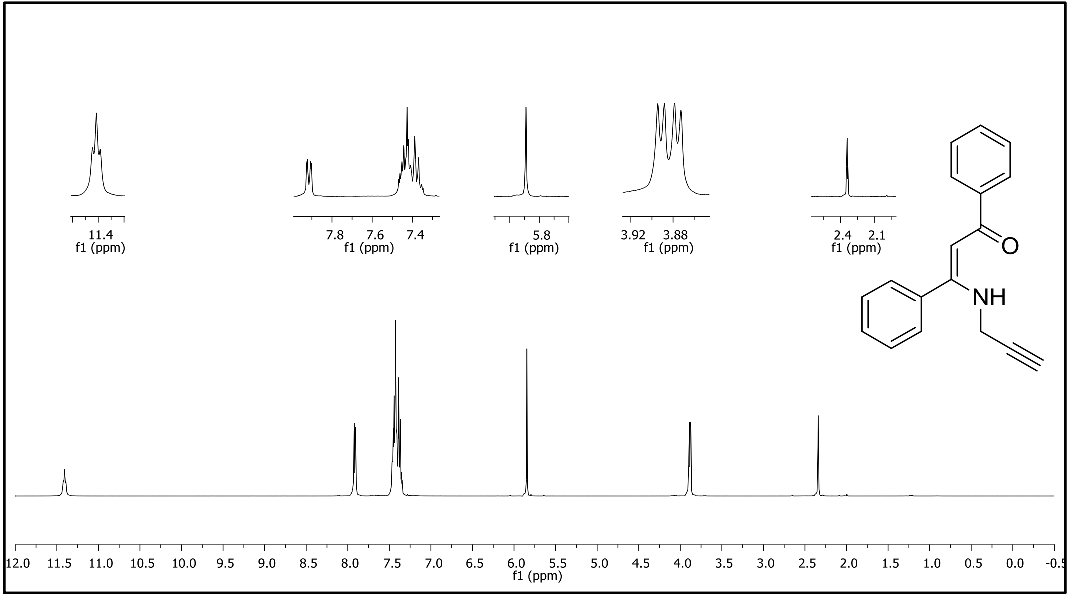


Figure 11. ^{1}H NMR spectrum of (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2 en-1-one (**54A**).

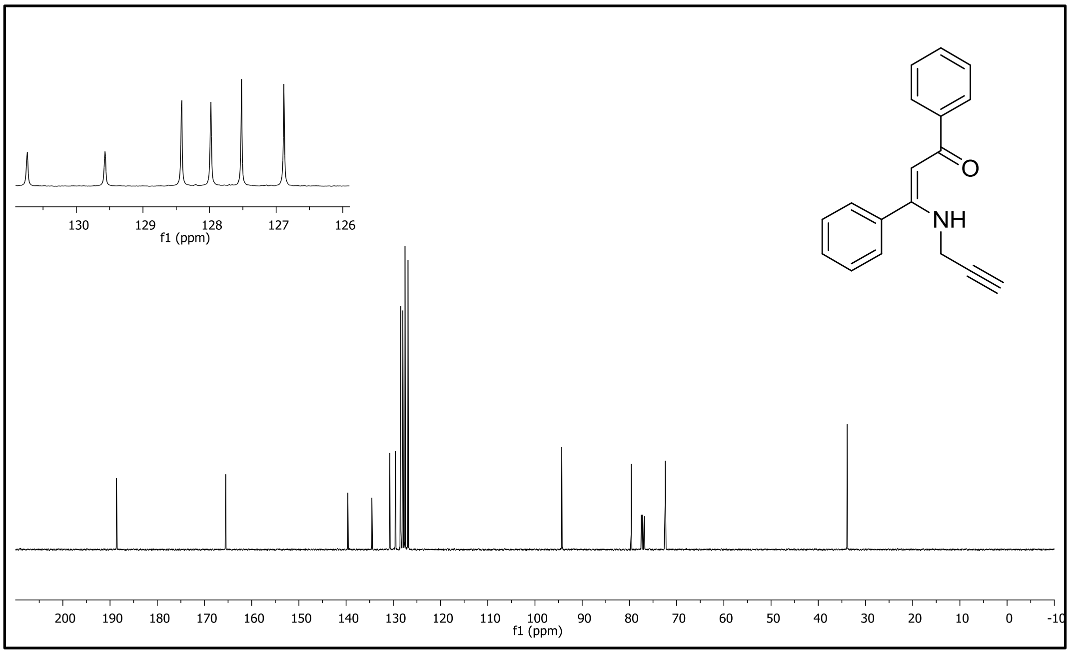


Figure 12. ^{13}C NMR spectrum of (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54A**).

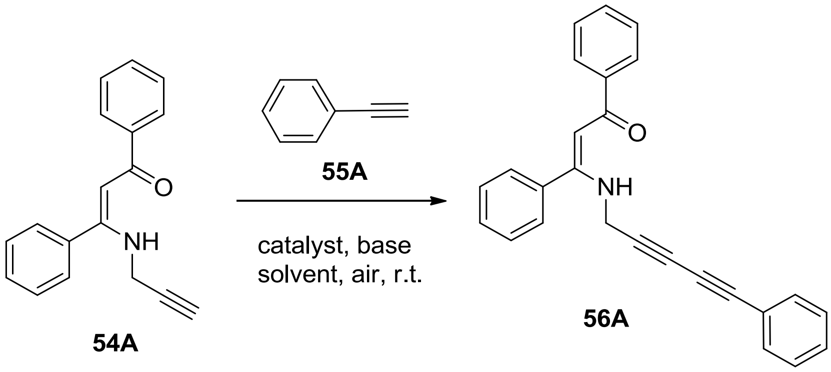
2.3 Synthesis of *N*-(2,4-Pentadiynyl)-*β*-enaminones

After preparing *N*-propargylic *β*-enaminone compounds **54**, we aimed to synthesize *β*-enaminones containing double alkyne functionality, such as *N*-(2,4-pentadiynyl)-*β*-enaminones **56**. Therefore, metal-catalyzed oxidative coupling of *N*-propargylic *β*-enaminones **54** with terminal acetylenes were performed to yield to *N*-(2,4-pentadiynyl)-*β*-enaminones **56**.

In this regard, there are many studies in the literature including heterocoupling reactions via Glaser Hay type reaction.[42-46] The synthesis of unsymmetrical 1,3-diynes by the coupling of two different alkynes is not straightforward because of the poor selectivity.[43] Therefore, we have had to optimize the reaction conditions. We used different catalysts, bases and solvents to optimize the cross-coupling reaction of *N*-propargylic *β*-enaminone compounds with terminal acetylenes (Table 3). On the basis of the Lei's coupling method,[47] when the reaction was carried out in the presence of $NiCl_2.6H_2O$, CuI and TMEDA in THF at room temperature under aerobic condition for 20 h. The reaction gave 38% yield of product **56A** (Table 3, entry 1). When we increased the amount of phenylacetylene to 1.5 to 3.0 equiv., the yield of product increased slightly (44%) (Table 3, entry 2). Higher equivalent of phenylacetylene did not improve the yield of **56A** (45%) (Table 3, entry 3). Thus, we performed the reaction by using TMEDA/NEt_3 together but we could not observe any satisfying result (30%) (Table 3, entry 4). We also applied Kesavan's coupling method.[42] Accordingly, $Cu(OAc)_2.H_2O$ and piperidine were used in DCM under aerobic condition. However, we could not observe any product formation (Table 3, entry 8). Finally, we tried Okada's coupling method,[48] which provided to the highest yield (%59) (Table 3, entry 5). In this reaction CuCl was used as a catalyst in the presence of TMEDA and the reaction was carried out with 1.5 equiv. of phenylacetylene (Table 3, entry 5).

By employing the optimized conditions, we synthesized 13 derivatives of *N*-(2,4-pentadiynyl)-*β*-enaminones **56** from *N*-propargylic *β*-enaminone derivatives **54** and terminal alkynes **55** in moderate to good yields (31-67%) (Table 4).

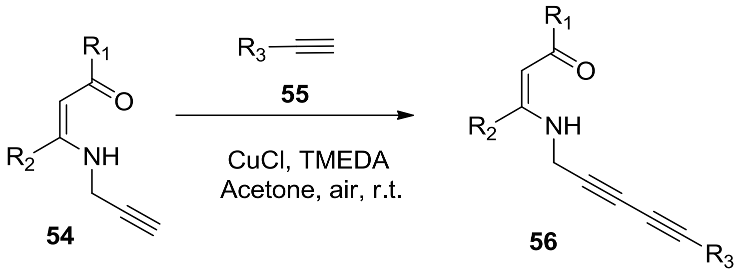
Table 3. Optimization of reaction conditions for synthesis of *N*-(2,4-pentadiynyl)-*β*-enaminones **56A**.[a]

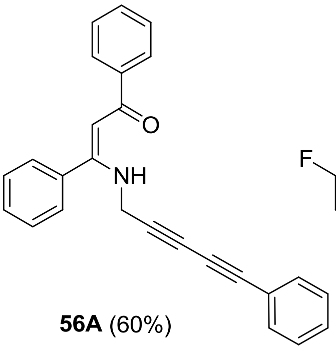


Entry	Phenylacetylene (equiv.)	Catalyst	Base	Solvent	Yield[b](%)
1	1.5	$NiCl_2.6H_2O/CuI$	TMEDA	THF	38
2	3.0	$NiCl_2.6H_2O/CuI$	TMEDA	THF	44
3	5.0	$NiCl_2.6H_2O/CuI$	TMEDA	THF	45
4	1.5	$NiCl_2.6H_2O/CuI$	$TMEDA/NEt_3$	THF	30
5	**1.5**	**CuCl**	**TMEDA**	**Acetone**	**59**
6	2.0	CuCl	TMEDA	Acetone	52
7	2.5	CuCl	TMEDA	Acetone	46
8	1.5	$Cu(OAc)_2.H_2O$	Piperidine	DCM	NR[c]

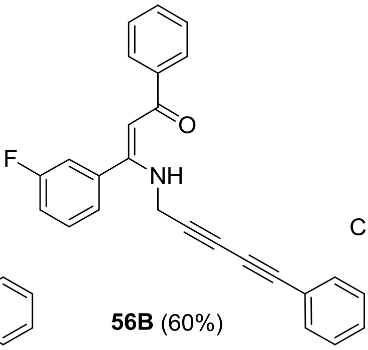
[a]The reactions were carried out at room temperature and extractions were done with saturated NH_4Cl solution. [b]Yields of isolated products. [c]NR = No reaction.

Table 4. Synthesis of *N*-(2,4-pentadiynyl)-*β*-enaminone derivatives **56**.[a]

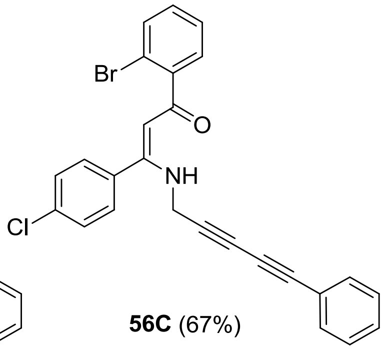




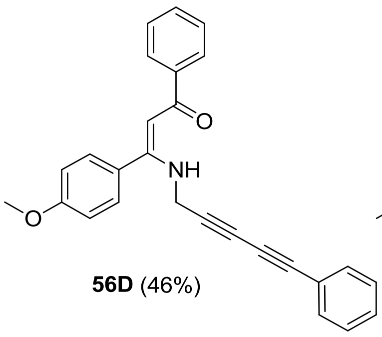
56A (60%)



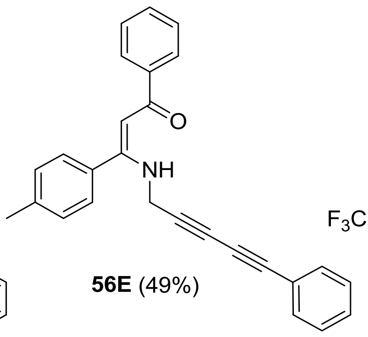
56B (60%)



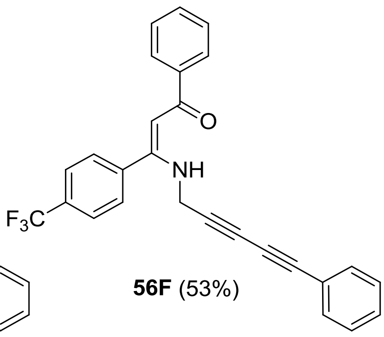
56C (67%)



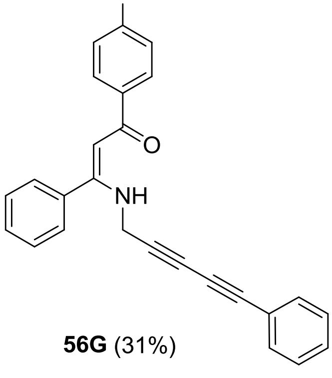
56D (46%)



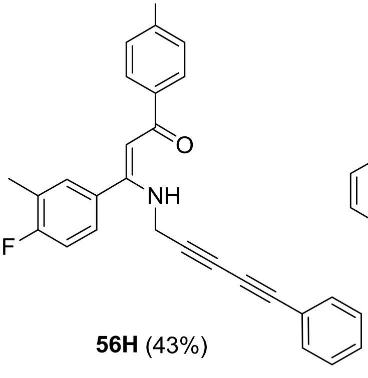
56E (49%)



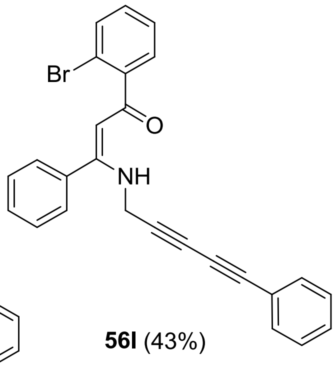
56F (53%)



56G (31%)

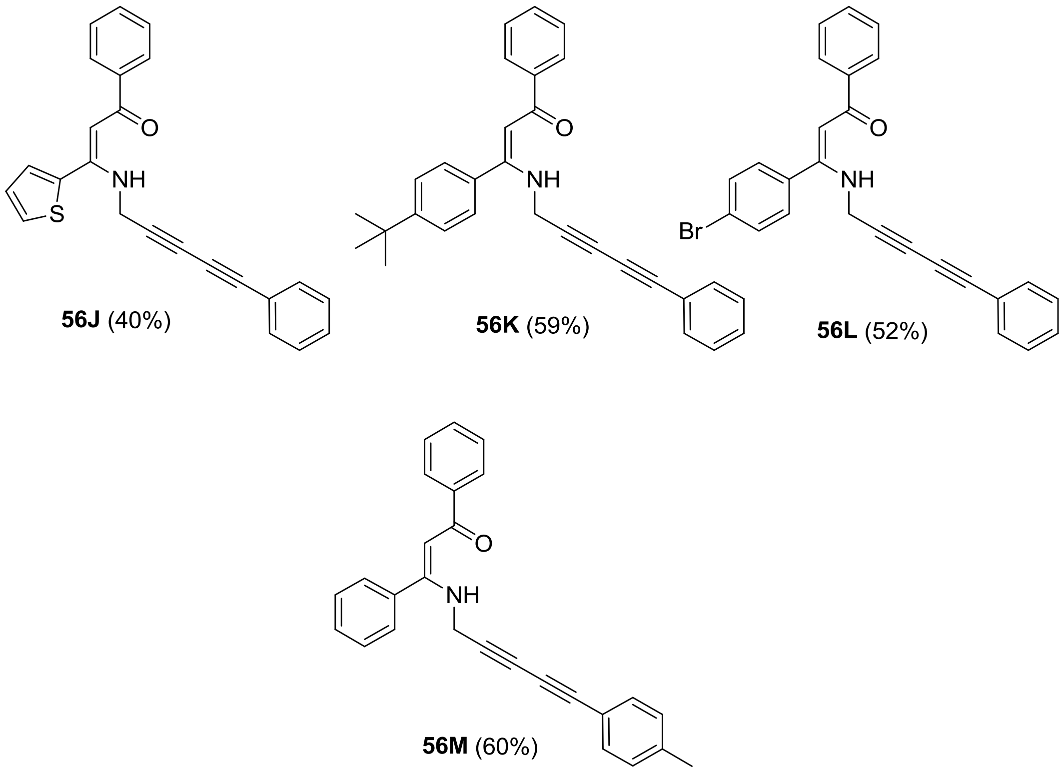


56H (43%)



56I (43%)

Table 4. Continued.



56J (40%)

56K (59%)

56L (52%)

56M (60%)

[a]Yields of isolated products.

The structures of *N*-(2,4-pentadiynyl)-*β*-enaminones **56** were identified on the basis of ^1H and ^{13}C NMR spectra. ^1H and ^{13}C NMR spectra of (*Z*)-1,3-diphenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56A**) are depicted in Figures 13 and 14. In the ^1H NMR spectrum of **56A** (Figure 13), methylene hydrogens resonate at 4.11 ppm as doublet while double bond hydrogen on the ring comes at 5.88 ppm as a singlet. The remaining fifteen hydrogens of three phenyl groups resonate between 7.28 and 7.92 ppm. Finally, N-H appears at 11.38 ppm as a triplet. (Figure 13).

In ^{13}C NMR spectrum of **56A** (Figure 14), four alkynyl carbons appear between 78.6 and 69.0 ppm. Carbonyl carbon (C=O) resonates at 189.2 ppm. Metylene carbon (CH_2) comes at 35.1 ppm. Double bond carbon (=CH) appears at 165.6

ppm. The remaining aromatic carbon atoms resonate between 121.4 and 139.9 ppm (Figure 14).

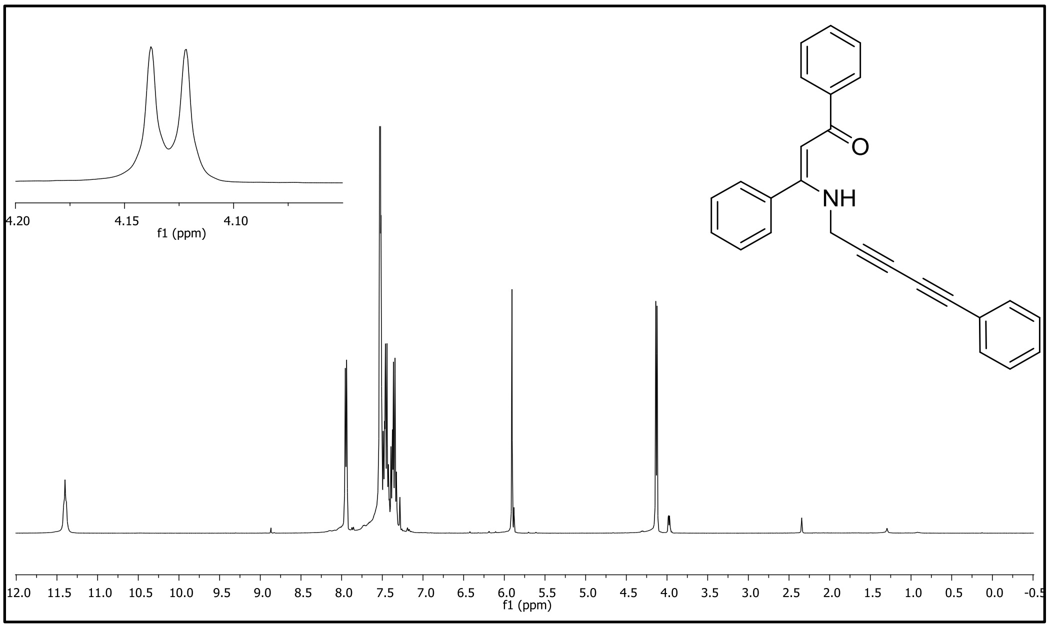


Figure 13. ^{1}H NMR spectrum of (*Z*)-1,3-diphenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56A**).

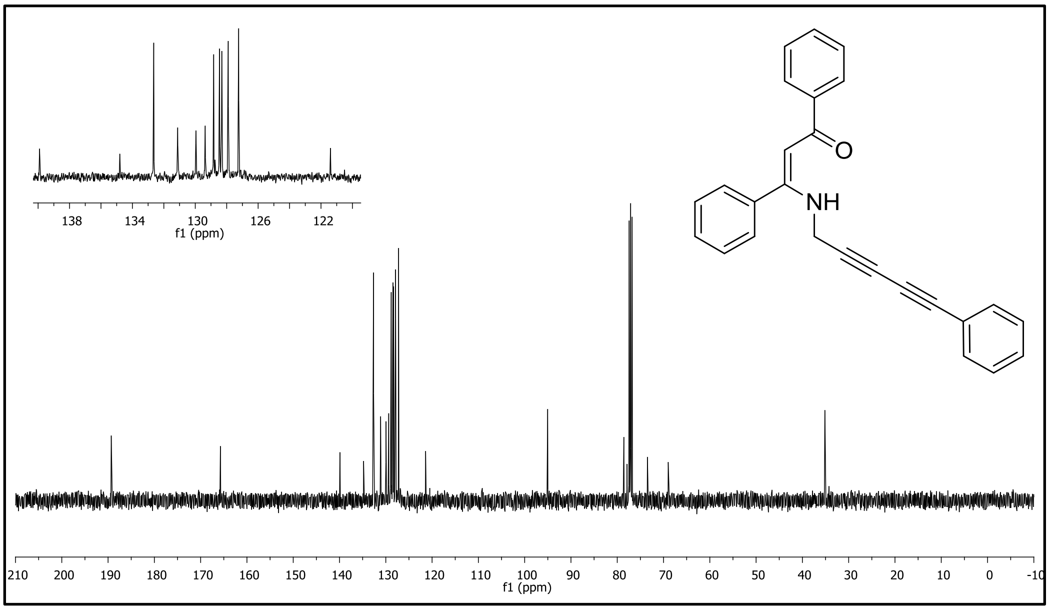
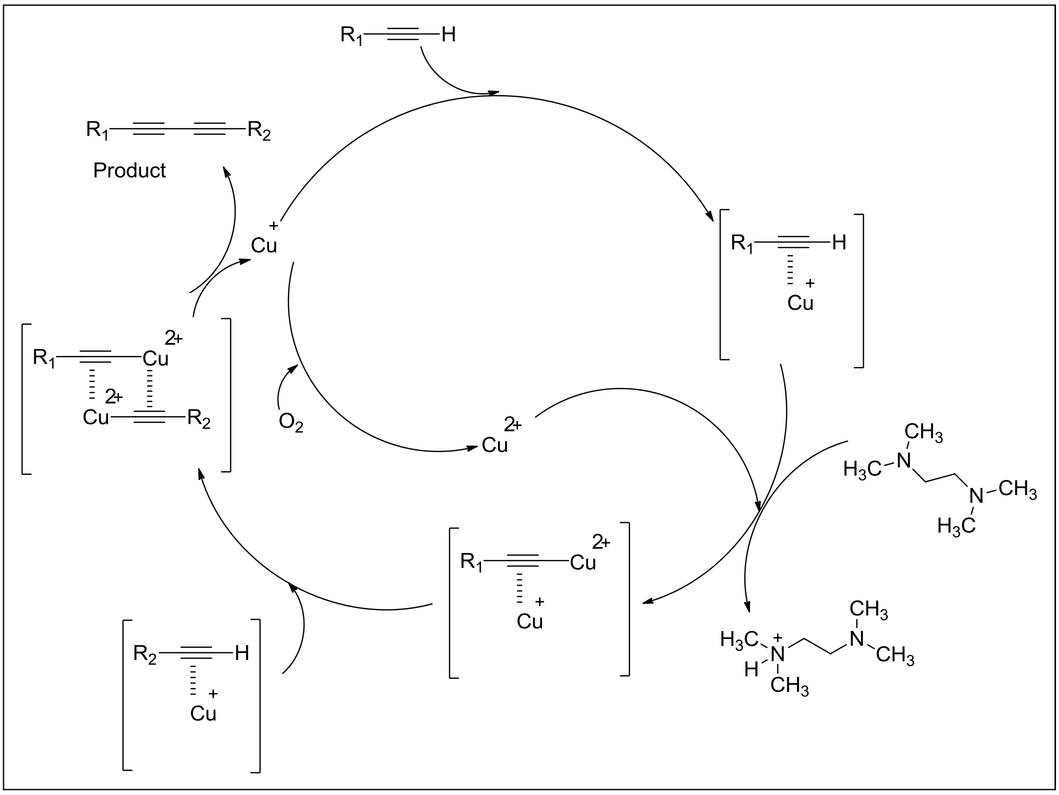


Figure 14. ^{13}C NMR spectrum of (*Z*)-1,3-diphenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56A**).

On the basis of Okada's study[48], the mechanism proposed for copper-catalyzed oxidative coupling of terminal alkynes is shown in Scheme 20.[49] In this reaction, firstly, Cu(I) is coordinated with terminal alkyne to generate Cu(I) acetylene intermediate under basic medium. Then, in aerobic condition, the oxidative coupling of the intermediate occurs and yields the final diyne products (Scheme 20).[49]



Scheme 20. Proposed mechanism for copper-catalzed oxidative coupling of terminal alkynes.

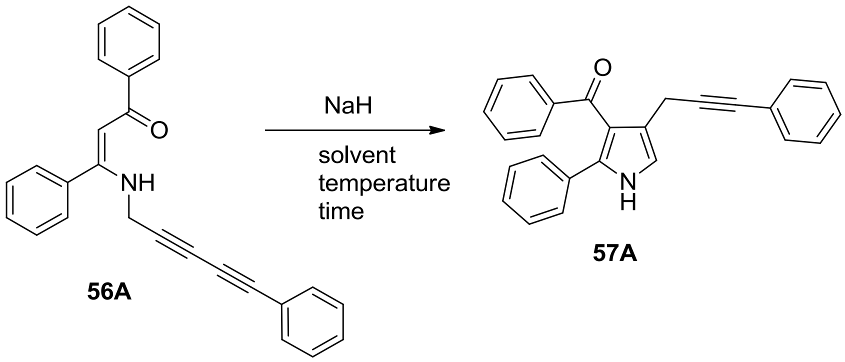
2.4 Synthesis of Propargyl-Substituted Pyrroles

In the first phase of our study, we investigated the synthesis of alkynyl-substituted pyrroles **57**. For this reason, we optimized the reaction conditions by performing the reaction of (*Z*)-1,3-diphenyl-3-((5-phenylpenta-2,4-diyn-1-

yl)amino)prop-2-en-1-one (**56A**) under basic conditions (Table 5). In all cases, cyclization of **56A** under basic conditions afforded the expected alkynyl-substituted pyrrole **57A**, namely phenyl(2-phenyl-4-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrol-3-yl)methanone (**57A**) (Table 5). We used NaH as base because of the ongoing research projects in group.

We performed several optimization studies in order to afford pyrrole **57A** under basic medium. Firstly, the cyclization reaction of *N*-(2,4-pentadiynyl)-*β*-enaminones **56A** in the presence of 2.0 eq. of NaH in benzene at 80 ^{o}C was carried out. Unfortunately, this reaction gave the desired product **57A** in low yield (12%) (Table 5, entry 1). Then, we used DMF as a reaction solvent but the yield of this reaction increased slightly (17%) (Table 5, entry 2). Since the yield of the reaction was low at higher temperatures, we conducted the same reaction at room temperature. However, the yield (26%) did not increase so much (Table 5, entry 3). In order to obtain higher yields, this time DCM was used as a reaction solvent. Initially, at 40^{o}C, using 1.0 equiv. of NaH, reaction product **57A** was formed in 48% yield (Table 5, entry 4). In additon, there was no effect of using 2.0 equiv. of NaH in reflux condition (Table 5, entry 5). However, 3.0 equiv. of NaH affected the efficiency of the product negatively (Table 5, entry 6). As a result of these optimization reactions, the best yield of **57A** (48%) was obtained by using 1.0 equiv. of NaH in DCM under reflux conditions for 2 h (Table 5, entry 4).

Table 5. Optimization of the reaction conditions for the synthesis of propargyl-substituted pyrroles.



Entry	**NaH (equiv.)**	**Solvent**	**Temp. (°C)**	**Time (h)**	**Yield(%)**[a]
1	2.0	Benzene	80	1.0	12
2	2.0	DMF	50	2.0	17
3	2.0	DMF	25	2.0	26
4	**1.0**	**DCM**	**40**	**2.0**	**48**
5	2.0	DCM	40	2.0	47
6	3.0	DCM	40	2.0	44
7	2.0	ACN	82	1.0	13
8	1.0	ACN	25	1.0	25
9	2.0	ACN	25	2.0	8
10	2.0	DCE	84	1.0	24
11	1.0	THF	66	2.0	17

[a]Yields of isolated products.

As representative examples, ^{1}H and ^{13}C NMR spectra of pyrrole **57A** are shown in Figures 15 and 16, respectively. As seen in ^{1}H NMR spectrum (Figure 15), N-H hydrogen resonates around 8.42 ppm as a broad singlet and methylene hydrogens appear at 3.77 ppm as a singlet. In addition, α-hydrogen of pyrrole resonates at 6.93 ppm as a singlet. The remaining fifteen aromatic hydrogens give peaks between 7.02-7.55 ppm (Figure 15).

In ^{13}C NMR spectrum of **57A** (Figure 16), carbonyl carbon (C=O) comes around 194.0 ppm and two alkynyl carbons (C) resonate at 88.4 and 81.3 ppm. Methylene carbon (CH_2) comes at 17.2 ppm. Finally, sixteen aromatic carbon atoms resonate between 117.7-139.3 ppm (Figure 16).

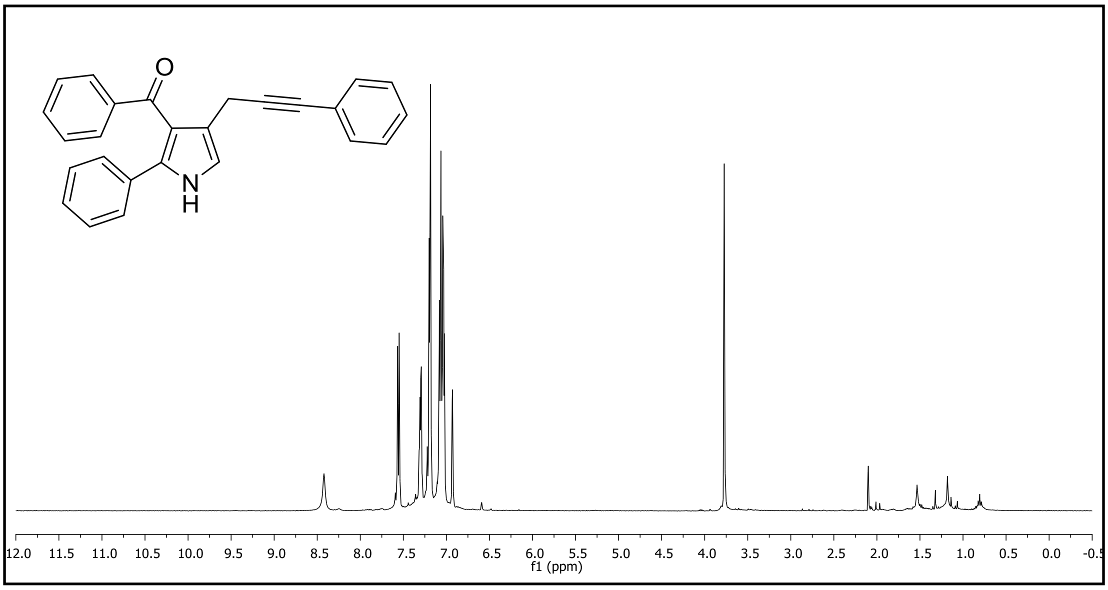


Figure 15. ^{1}H NMR spectrum of propargyl-subtituted pyrrole **57A**.

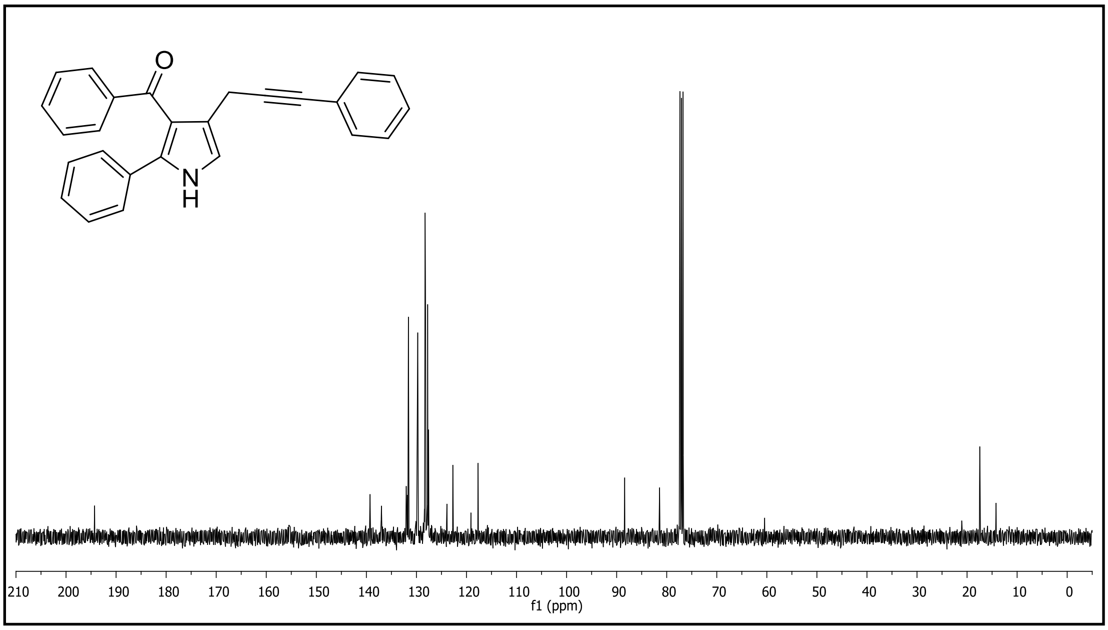
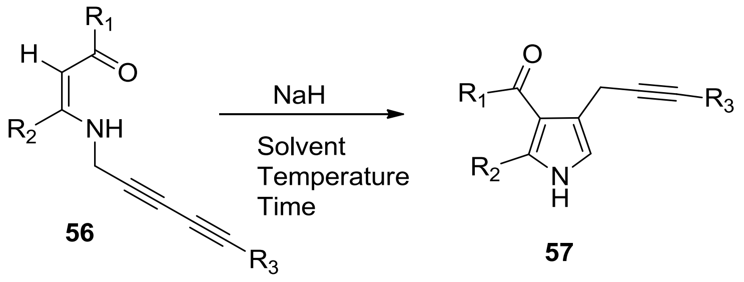
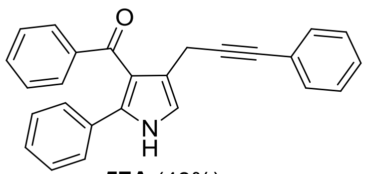


Figure 16. ^{13}C NMR spectrum of propargyl-substituted pyrrole **57A**.

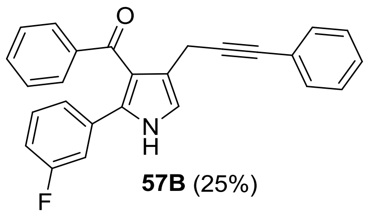
In conclusion, by employing a variety of *N*-(2,4-pentadiynyl)-*β*-enaminones **56**, 7 novel propargyl-substituted pyrroles **57** with different substituents were synthesized in yields ranging from 25 to 52% (Table 6). Notably, some proaprgyl-substituted pyrroles **57** were isolated from these reactions in relatively low yields. These low yields can be the result of high reactivity of double alkyne-containing *β*-enaminones **56** since, in these reactions, some decomposition of **56** were observed.

Table 6. Synthesis of propargyl-substituted pyrroles **57**.[a]

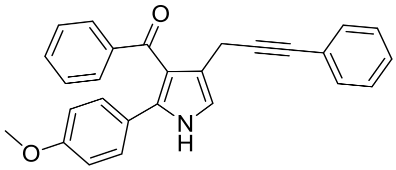




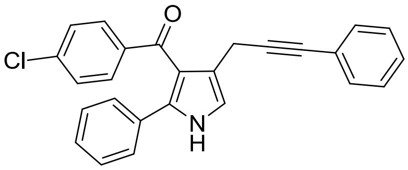
57A (48%)



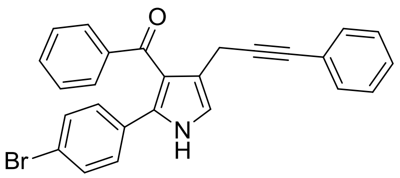
57B (25%)



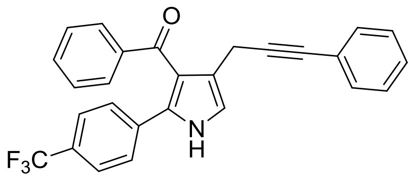
57C (52%)



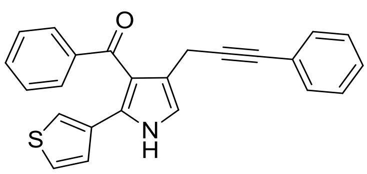
57D (47%)



57E (45%)



57F (46%)



57G (43%)

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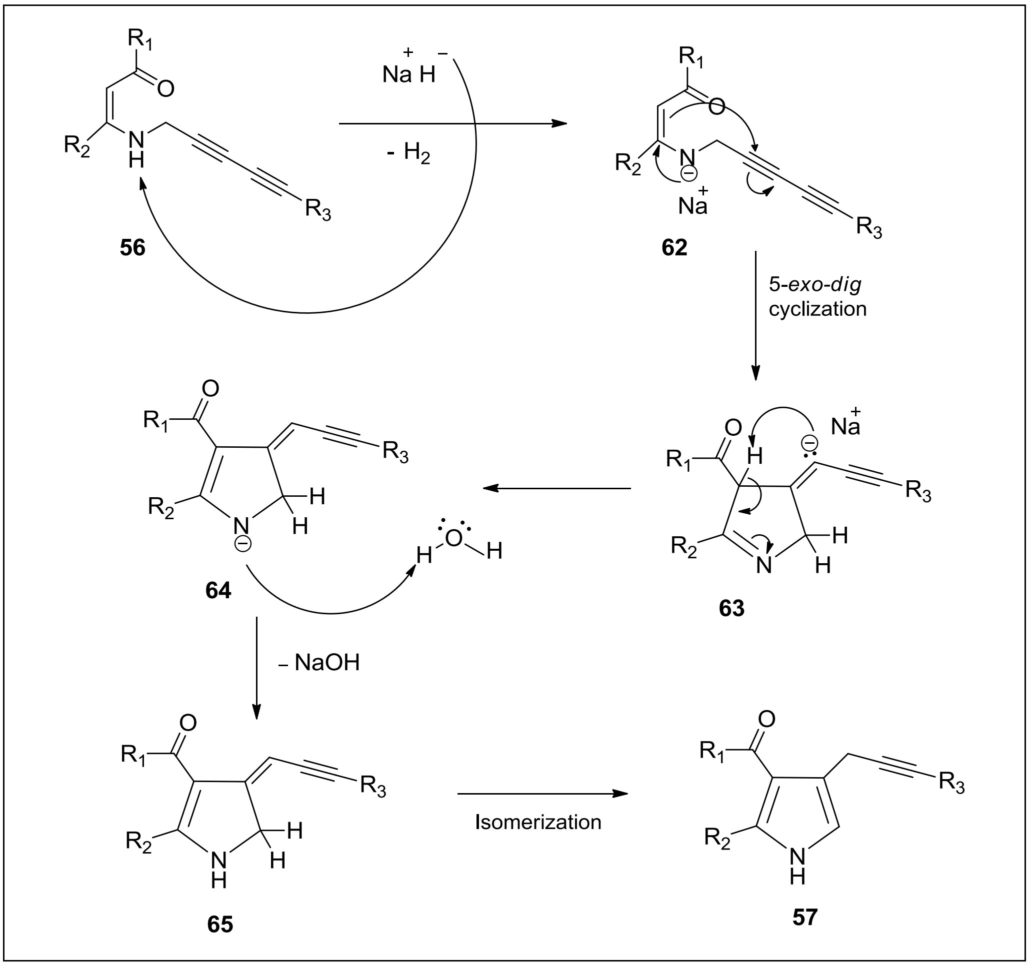
[a] Yields of isolated products.

The mechanism proposed for the synthesis of alkynyl-substituted pyrroles **57** is outlined in Scheme 21. According to the mechanism, hyride abstracts amine hydrogen of *N*-(2,4-pentadiynyl)-*β*-enaminone **56A** to produce anion on nitrogen atom of intermediate **62**. After resonance interaction, intramolecular nucleophilic attack of *α*-carbon onto closer acetylenic carbon atom, i.e. 5-*exo*-*dig* cyclization process, yields nitrogen containing five-membered intermediate **63**. Then, anion abstracts acidic *α*-hydrogen to form intermediate **64**. Finally, quenching **64** with water, dihydropyrrole **65** is obtained. The compound isomerizes to the desired propargyl-substituted pyrrole **57** (Scheme 21).



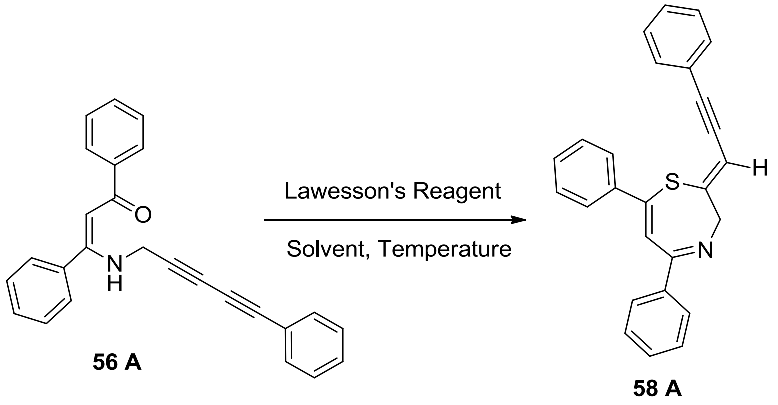
Scheme 21. Proposed mechanism for the synthesis of propargyl-substituted pyrroles.

2.5 Synthesis of 2-(2-Propyn-1-ylidene)-2,3-dihydro-1,4-thiazepines

In the second part, we investigated the synthesis of 1,4-thiazepines **58** from same starting compounds **56**. In this work, we used Lawesson's reagent **39** as thionating agent. In fact, our goal was to obtain thionated *β*-enaminones at first and after isolation of *β*-enaminothiones, we aimed to investigate their cyclizations to afford 1,4-thiazepines according to our previous studies.[50] However, there happened different reaction pathway than we expected. In fact, as soon as our starting compunds were thionated, the resulting *β*-enaminothiones were immediately cyclized *in-situ* to produce seven-membered 1,4-thiazepine rings depending upon high nucleophilicity of sulfur atom. In fact, this one-pot synthesis of 1,4-thiazepines **58** has been an advantage for us without isolating intermediate *β*-enaminothiones. Optimization of the reaction conditions for the synthesis of 1,4-thiazepines **58** is summarized in Table 7. Thus, we performed many reactions with *β*-enaminones **56A** to increase the yield of expected product **58A**. When reactions were performed at room temperature, the yields were not good (21-25%) (Table 7, entries 1 and 2). Moreover, under reflux condition, desired product **58A** was resulted in lower yield (11%) (Table 7, entry 3). This can be due to the decomposition of **58A**. A decrease in temperature from 82 °C to 65 °C by using 0.5 equiv of LR led to rise in yield (58%) (Table 7, entry 4). The highest result (64%) was obtained by using 1.0 equiv of LR in benzene at 65 °C (Table 7, entry 5). However, higher equivalents of LR did not work well (Table 7, entry 6). When the reaction was performed in different solvents like toluene and pyridine, no satisfying results could be observed (Table 7, entries 7 and 8). In addition, we would like to see the effect of base in the yield of product **58A**. When reaction was performed with 0.5 and 1.0 equiv of NaH with LR, it yielded 1,4-thiazepine **58A** in 6 and 36% yields, respectively. (Table 7, entries 9 and 10).

We also conducted experiment with P_4S_{10} as thionating agent instead of LR, but we could not observe any product **58A** because of the low solubility of P_4S_{10}.

Table 7. Optimization studies for the synthesis of 2-(2-propyn-1-ylidene)-2,3-dihydro-1,4-thiazepine **58A**.



Entry	LR (equiv.)	NaH (equiv.)	Solvent	Temp. (^{o}C)	Time	Yield(%)[a]
1	0.5	-	Benzene	25	20 h	21
2	1.0	-	Benzene	25	20 h	25
3	0.5	-	Benzene	82	2 h	11
4	0.5	-	Benzene	65	20 min	58
5	**1.0**	**-**	**Benzene**	**65**	**20 min**	**64**
6	1.5	-	Benzene	65	20 min	30
7	1.0	-	Toluene	65	20 min	25
8	0.5	-	Pyridine	25	20 h	NR[b]
9	0.5	0.5	Benzene	25	4 h	6
10	0.5	1.0	Benzene	65	2 h	36

[a] Yields of isolated products.
[b] NR = No reaction.

The structure of 2-(2-propyn-1-ylidene)-2,3-dihydro-1,4-thiazepine **58A** was proved by ^{1}H and ^{13}C NMR spectra (Figures 17 and 18). According to ^{1}H NMR spectrum of **58A** (Figure 17), *exo*-double bond hydrogen resonates at 5.71 ppm while methylene hydrogens on the ring appear at 4.80 ppm. Olefinic proton on the ring appears at 6.87 ppm. The remaining phenyl hydrogens appear between 7.18 and 7.73 ppm.

^{13}C NMR spectrum of **58A** (Figure 18), carbon atom of C=N bond resonates at 168.0 ppm. Two alkynyl carbons come at 98.4 and 85.2 ppm. Methylene carbon resonates at 58.5 ppm. The remaning carbons give peaks between 103.6 and 150.5 ppm (Figure 18).

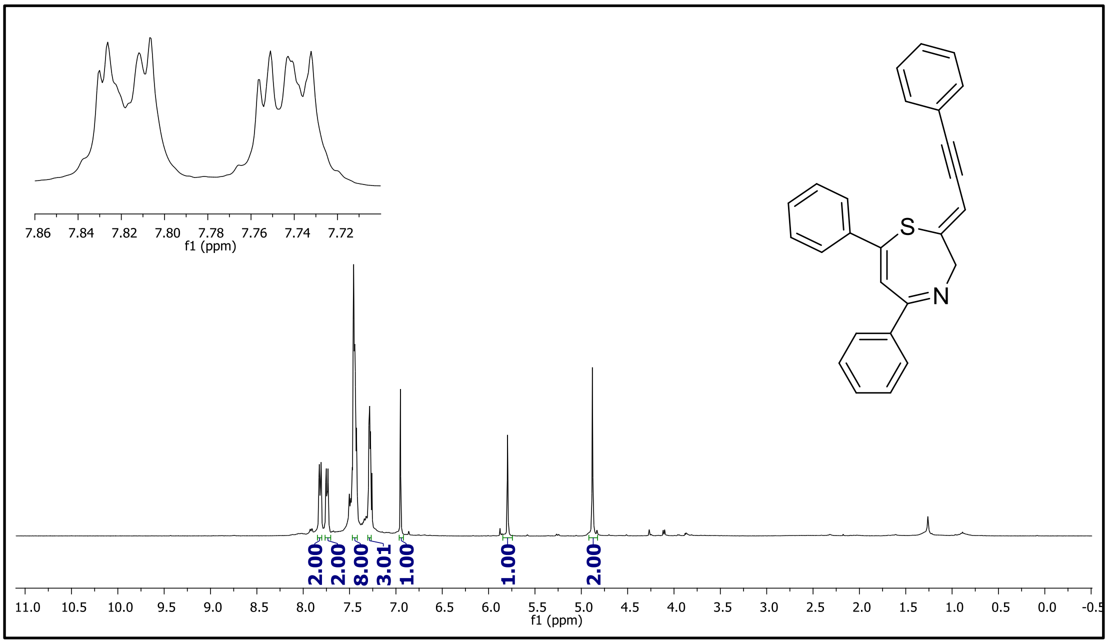


Figure 17. ^{1}H NMR spectrum of (*Z*)-5,7-diphenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58A**).

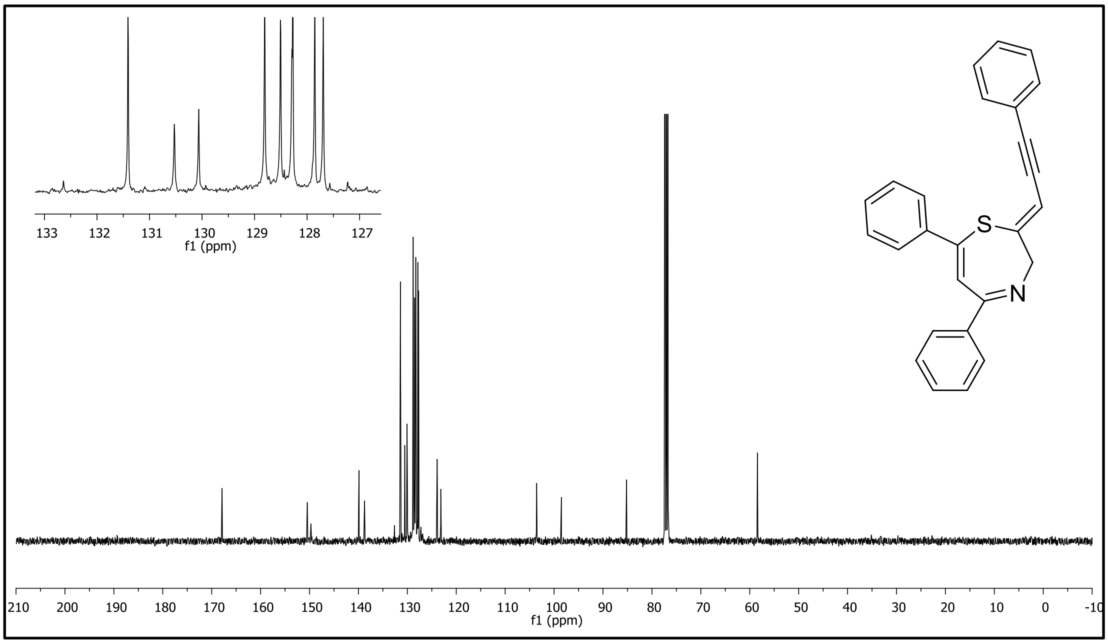


Figure 18. ^{13}C NMR spectrum of (*Z*)-5,7-diphenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58A**).

In order to assign the the stereochemistry of (*Z*)-5,7-diphenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58A**), we carried out NOESY experiment (Figure 19). According to NOESY spectrum of **58A**, an NOE interaction was observed between methylene hydrogens and exo-double bond hydrogen. In summary, we concluded that our target molecule 1,4-thiazepine molecule has *Z* stereochemistry according to NOESY results (Figure 19).

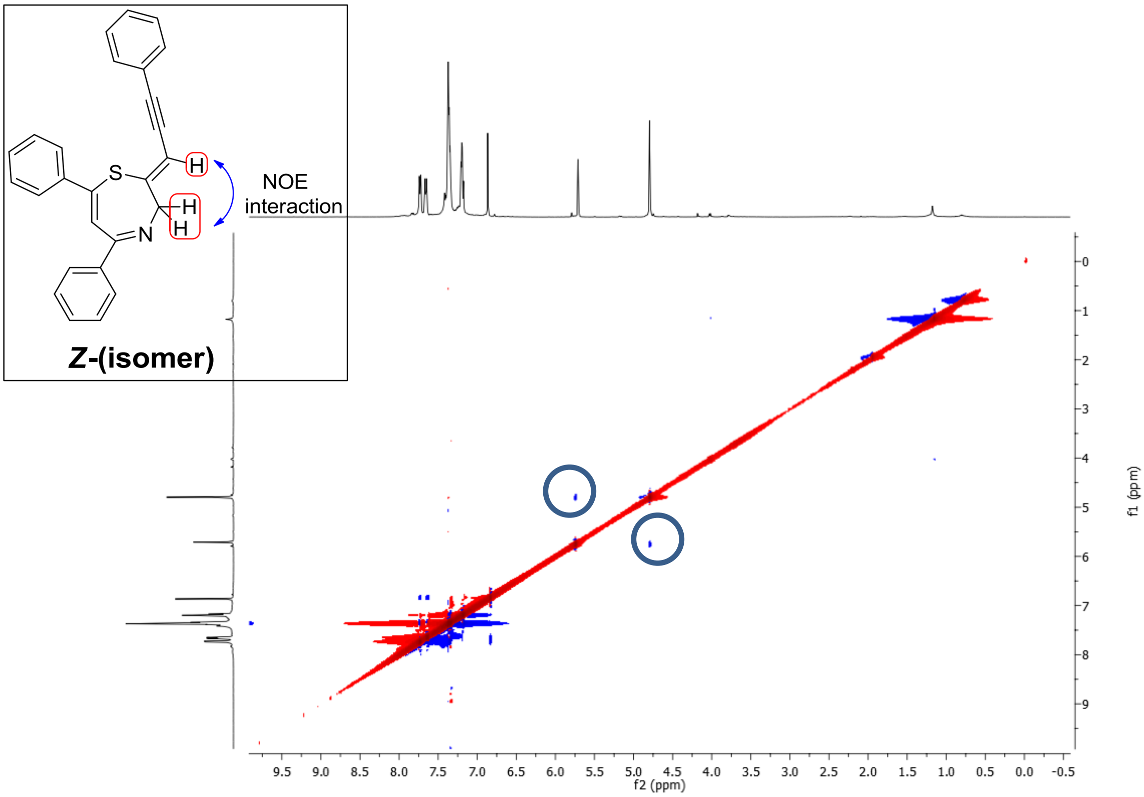
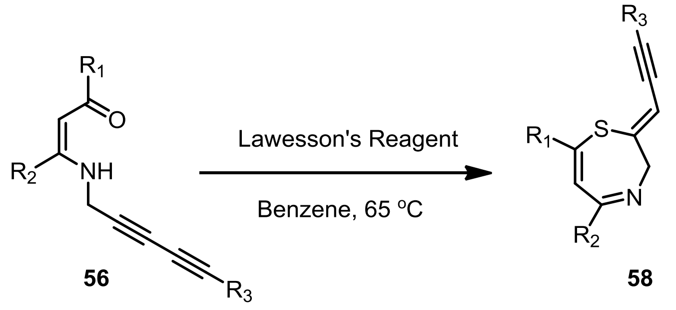


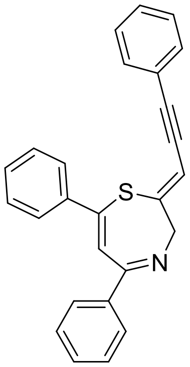
Figure 19. NOESY NMR spectrum of 1,4-thiazepine **58A**.

(Cross peaks in circles represent the NOE interaction shown on the structure).

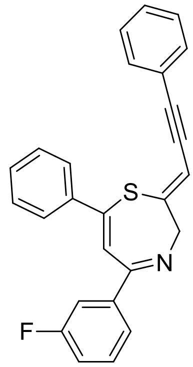
By employing a variety of β-enaminones **56**, we synthesized 12 novel 1,4-thiazapine derivatives with yields changing between 15 to 64% with various substitution pattern (Table 8). In some cases, final 1,4-thiazepine derivatives **58** were obtained in low yields. As mentioned before, low yields of these products can be presumably attributed to high reactivity of starting β-enaminones **56** since during the course of the reactions, some decomposition occurred.

Table 8. Synthesis of 1,4-thiazepine derivatives **58**.[a]

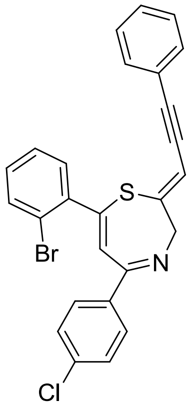




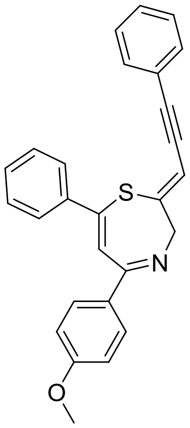
58A (64%)



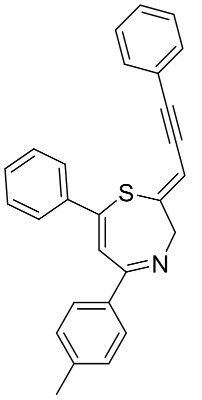
58B (57%)



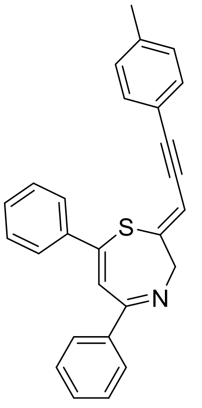
58C (46%)



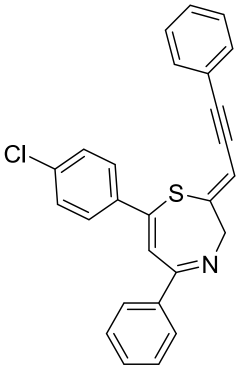
58D (43%)



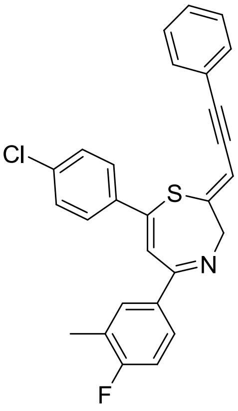
58E (25%)



58F (30%)

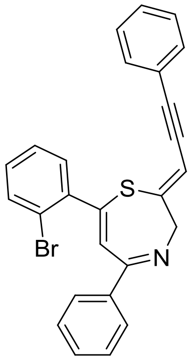


58G (23%)

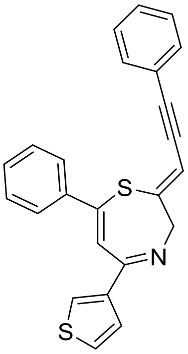


58H (49%)

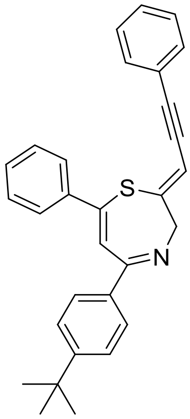
Table 8. Continued.



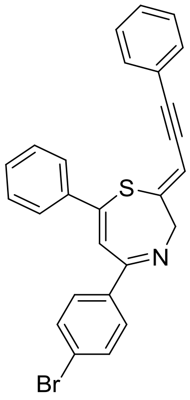
58I (46%)



58J (15%)



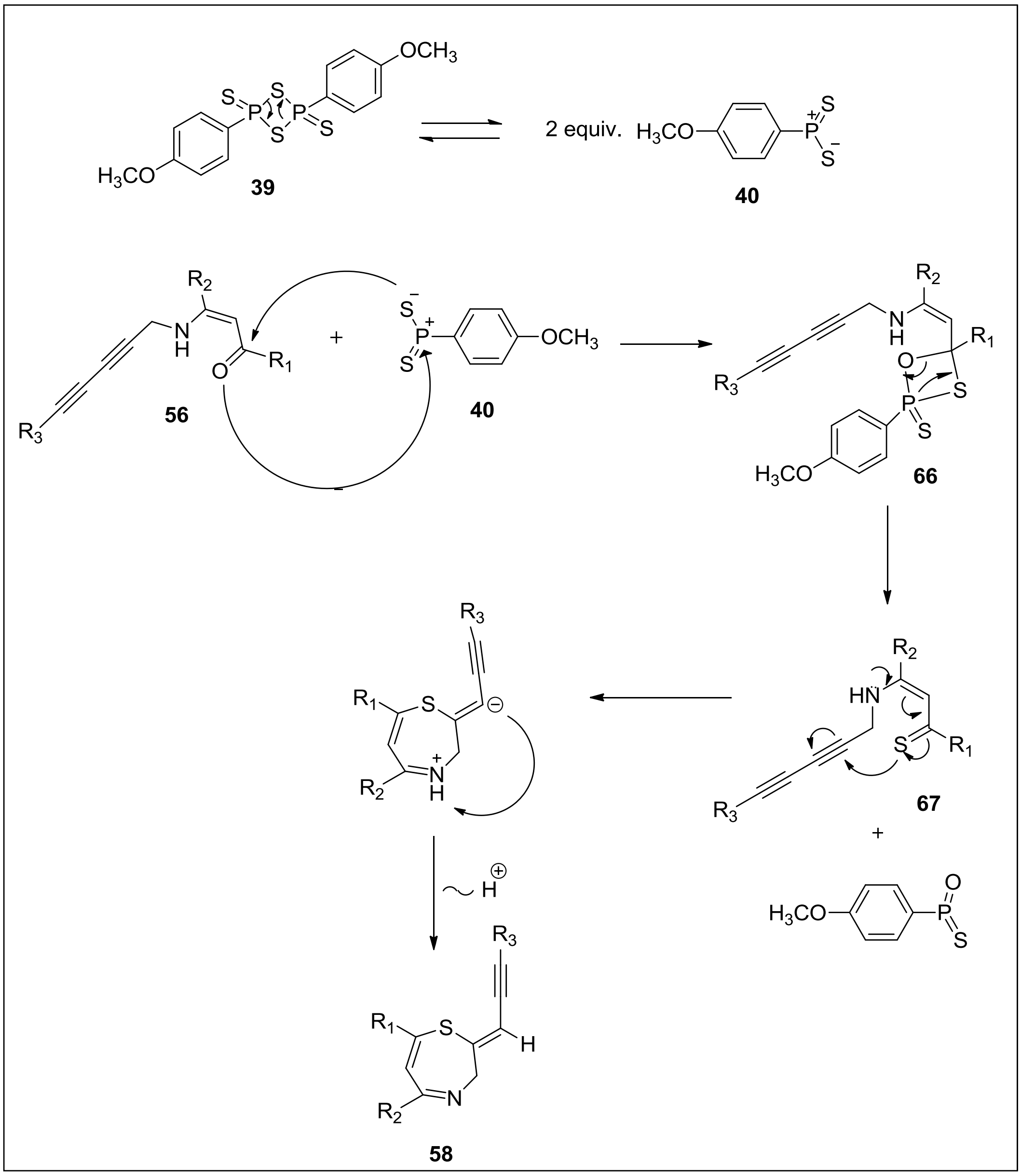
58K (36%)



58L (30%)

[a]Yields of isolated products.

Proposed mechanism for the synthesis of 1,4-thiazepines **58** is given in Scheme 22. After LR decomposed to its monomer, it reacted with carbonyl group of *β*-enaminone **56** to form four-membered intermediate **66.** After decomposition of four-membered intermediate **66**, thionated *β*-enaminone **67** was obtained. As soon as *β*-enaminothione was formed, it was immediately cyclized *in situ* to afford seven-membered intermediate compound as the result of high nucleophilic character of sulfur atom. Finally, desired 1,4-thiazepine derivative **58** was obtained by proton exchange (Scheme 22).



Scheme 22. Proposed mechanism for the synthesis of 1,4-thiazepine **58.**

CHAPTER 3

CONCLUSION

In summary, we conducted two studies. In the first part, we synthesized alkynyl-substituted pyrroles **57** under basic medium from *N*-(2,4-pentadiynyl)-*β*-enaminones **56**. As a second study, we accomplished one-pot synthesis of functionalized 1,4-thiazepine derivatives by intramolecular cyclization reaction of intermediate thionated *β*-enaminones.

Initially, aryloyl chlorides **61** and terminal alkynes **55** were coupled to give α,*β*-alkynic ketone **61** via Sonogashira coupling reaction. Afterwards, 1,4-conjugate addition of propargylamine (**62)** to the corresponding ketones **61**, generated *N*-propargylic *β*-enaminones **54**. Then, *N*-(2,4-pentadiynyl)-*β*-enaminones **56** were obtained via metal-catalyzed cross-coupling of *N*-propargylic *β*-enaminones **54** with terminal alkynes.

For the alkynyl-substituted pyrrole synthesis, the cyclization of *N*-(2,4-pentadiynyl)-*β*-enaminones **56** was investigated in various condition. Optimization reactions were performed by changing the reaction solvent, amount of base and the temperature. As a result of these optimization reactions, the best yield (48%) was obtained by using 1.0 equiv. of NaH in DCM in reflux conditions.

In the second part, we anticipated that cyclization reactions of thionated *β*-enaminones would produce 1,4-thiazepines. For this purpose, we first prepared *N*-(2,4-pentadiynyl)-*β*-enaminone derivatives **56**. We have shown that when treated with Lawesson's reagent, the resulting *β*-enaminones **56** produce *in situ* *N*-(2,4-pentadiynyl)-*β*-enaminothiones **67** that undergo immediately intramolecular cyclization to afford 2-(2-propyn-1-ylidene)-2,3-dihydro-1,4-thiazepines **58** in moderate to good yields in one-pot manner. To conclude, the highest yield (64%) was obtained by employing 1.0 equiv. of LR in benzene at reflux condition in argon atmosphere.

In conclusion, we anticipate that new insights will be of value in the design of new and novel molecular entities and/or structural leads for drug discovery.

CHAPTER 4

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded with Bruker Spectrospin Avance DPX400 Ultrashield spectrometer at 400 and 100 MHz. The chemical shift reports are in parts per million (ppm) downfield in TMS (trimethylsilane) reference point and coupling constants (*J*) are in hertz (Hz), spin multiplicities are in singlet (s), doublet (d), triplet (t), quartet (q), pentet, sextet, m (multiplet), and broad (br), doublet of doublets (dd), doublet of triplets (dt), triplet of triplets (tt), triplet of doublets (td), triplet of doublet of doublets (tdd). After reactions the crude samples were purified using silica gel (Merck 230-400) with flash chromatography. TLC (thin layer chromatography) of 0.25 mm commercially available silica gel plates used for monitoring the reactions and visualized with UV lamp. Different hexane-ethyl acetate solvent mixtures were eluent for flash chromatography and their employments were changed with respect to volume:volume ratio. These solvents were distilled whether the presence of impurity. Inert atmosphere was provided with Argon gas (ca. 0.1 psi). All glassware and other equipments were washed with care and dried in oven.

4.1 General Procedure 1. Synthesis of *α,β*-Alkynic Ketone Derivatives 61

Aryloyl chloride (1.2 mmol) was dissolved in THF, and $PdCl_2(PPh_3)_2$ (0.02 mmol) and Et_3N (1.2 mmol) were added to the solution. The solution was stirred at room temperature for ten minutes. CuI (0.02 mmol) was added to the solution and then was stirred at room temperature for ten minutes. Lastly, after phenyl acetylene was added to solution, the solution was stirred at room temperature for six hours. After completing reaction, THF was removed by rotary evaporator. Then, extraction was done by using ethyl acetate and water. After organic phase was separated and dried over $MgSO_4$, the solution was filtered and ethyl acetate was removed by rotary evaporator. Finally, the residue was purified by column chromatography using hexane/ethyl acetate (19:1) mixture.

4.1.1 Synthesis of 1,3-Diphenylprop-2-yn-1-one (61A)

General Procedure **1** was followed by using benzoyl chloride (1.228 g, 8.73 mmol) $PdCl_2(PPh_3)_2$ (39 mg, 0.15 mmol), Et_3N (890 mg, 8.73 mmol), CuI (28 mg, 0.15 mmol) and phenylacetylene (744 mg, 7.28 mmol) were employed to afford 1.350 g (90%) of the indicated product of 1,3-diphenylprop-2-yn-1-one (**61A**) as yellow liquid (R_f = 0.54 in 4:1 hexane/ethyl acetate).

61A: ^1H NMR (400 MHz, $CDCl_3$) δ 8.27–8.16 (m, 2H), 7.64 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.61-7.55 (m, 1H), 7.52-7.45 (m, 2H), 7.43 (dt, *J* = 2.8, 2.1 Hz, 1H), 7.40-7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (CO), 136.8 (C), 134.1 (CH), 132.9 (CH), 130.8 (CH), 129.4 (CH), 128.6 (CH), 128.6 (CH), 119.9 (C), 93.0 (C), 86.9 (C); IR (neat): 3059, 3032, 2195, 1638, 1597, 1579, 1488, 1448, 1314, 1284, 1239, 1208, 1171, 1096, 1069, 1031, 1011, 995, 920, 846, 814, 794, 757, 696 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[39,51]

4.1.2 Synthesis of 3-(3-Fluorophenyl)-1-phenylprop-2-yn-1-one (61B)

General Procedure **1** was followed by using benzoyl chloride (750 mg, 5.33 mmol) $PdCl_2(PPh_3)_2$ (62 mg, 0.09 mmol), Et_3N (540 mg, 5.33 mmol), CuI (17 mg, 0.09 mmol) and 1-ethynyl-3-fluorobenzene (534 mg, 4.44 mmol) were employed to afford 750 mg (75%) of the indicated product of 3-(3-fluorophenyl)-1-phenylprop-2-yn-1-one (**61B**) as yellow solid (R_f = 0.68 in 4:1 hexane/ethyl acetate); mp 60.1–61.0 ^oC.

61B: ^1H NMR (400 MHz, $CDCl_3$) δ 8.28–8.05 (m, 2H), 7.64-7.55 (m, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.41 (d, J = 7.7 Hz, 1H), 7.37-7.27 (m, 2H), 7.17-7.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C=O), 162.2 (d, ^1J = 248.3 Hz, CF), 136.6 (CH), 134.3 (CH), 130.4 (d, ^3J = 8.4 Hz, CH), 129.5 (CH), 128.9 (d, ^4J = 3.0 Hz, CH), 128.7 (C), 121.9 (d, ^3J = 9.3 Hz, C), 119.6 (d, ^2J = 23.3 Hz, CH), 118.2 (d, ^2J = 21.1 Hz, CH), 90.9 (d, ^4J = 3.3 Hz, C), 87.1 (C); IR (neat): 3259, 3000, 2458, 2201, 1649, 1597, 1579, 1485, 1468, 1446, 1426, 1338, 1314, 1299, 1267, 1251, 1228, 1169, 1144, 1077, 1029, 1015, 998, 923, 867, 781, 765, 691 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[52]

4.1.3 Synthesis of 1-(2-bromophenyl)-3-(4-chlorophenyl)prop-2-yn-1-one (61C)

General Procedure **1** was followed by using 2-bromo benzoyl chloride (1.574 mg, 7.17 mmol) $PdCl_2(PPh_3)_2$ (101 mg, 0.14 mmol), Et_3N (731 mg, 7.17 mmol), CuI (27 mg, 0.14 mmol) and 1-chloro-4-etynyl benzene (816 mg, 5.98 mmol) were employed to afford 903 mg (45%) of the indicated product of 1-(2-bromophenyl)-3-(4-chlorophenyl)prop-2-yn-1-one (**61C**) as light brown solid (R_f = 0.65 in 4:1 hexane/ethyl acetate); mp 95.8-97.0 ^oC.

61C:^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.7, 1.6 Hz, 1H), 7.50 (dd, J = 8.1, 2.2 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.34-7.24 (m, 2H), 7.22 (d, J = 8.5 Hz, 2H) ;^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (C=O), 137.4 (C), 137.1 (CBr), 135.0 (CH), 134.3 (CH), 133.6 (CH), 132.8 (CH), 129.1 (CH), 127.5 (CH), 121.3 (CCl), 118.4 (C), 92.7 (C), 88.6 (C); IR (neat): 3081, 2349, 2196, 2155, 2063, 1968, 1646, 1582, 1480, 1427, 1298, 1200, 1085, 1059, 1035, 1011, 999, 829, 775, 728, 666, 634, 533, 480, 456, 423, 412 cm^{-1}; MS (ESI, m/z): 318.95 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_9BrClO$: 318.95198 $[M+H]^+$, found: 318.95318.

4.1.4 Synthesis of 3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (61D)

General Procedure **1** was followed by using benzoyl chloride (857 mg, 6.09 mmol) $PdCl_2(PPh_3)_2$ (71 mg, 0.10 mmol), Et_3N (621 mg, 6.09 mmol), CuI (19 mg, 0.10 mmol) and 4-ethynylanisole (970 mg, 5.08 mmol) were employed to afford 1.152 g (96%) of the indicated product of 3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-one (**61D**) as yellow solid (R_f = 0.41 in 4:1 hexane/ethyl acetate).

61D: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.14 (m, 2H), 7.68-7.56 (m, 3H), 7.53-7.47 (m, 2H), 6.91 (tt, J = 9.3, 2.3 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0 (C=O), 161.8 (C), 137.1 (C), 135.2 (CH), 133.9 (CH), 129.5 (CH), 128.6 (CH), 114.5 (CH), 111.9 (C), 94.4 (C), 86.9 (C), 55.5 (CH_3); IR (neat): 3198, 3096, 3077, 3052, 3014, 2978, 2941, 2842, 2594, 2555, 2424, 2325, 2185, 2083, 2068, 1979, 1911, 1825, 1783, 1730, 1659, 1622, 1597, 1568, 1510, 1459, 1441, 1315, 1293, 1253, 1210, 1189, 1168, 1113, 1009, 833, 793, 695 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[40]

4.1.5 Synthesis of 1-Phenyl-3-(*p*-tolyl)prop-2-yn-1-one (61E)

General Procedure **1** was followed by using benzoyl chloride (919 mg, 6.54 mmol) $PdCl_2(PPh_3)_2$ (77 mg, 0.11 mmol), Et_3N (662 mg, 6.54 mmol), CuI (21 mg, 0.11 mmol) and 1-ethynyl-4-methylbenzene (633 mg, 5.45 mmol) were employed to afford 821 mg (68%) of the indicated product of 1-phenyl-3-(*p*-tolyl)prop-2-yn-

1-one (**61E**) as brownish-orange solid (R_f = 0.56 in 4:1 hexane/ethyl acetate); mp 58.3–59.6 ^{o}C.

61E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.59-7.28 (m, 5H), 7.06 (d, *J* = 7.9 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4 (C=O), 141.2 (C), 136.6 (C), 133.7 (CH), 132.8 (CH), 129.2 (CH), 129.1 (CH), 128.3 (CH), 116.6 (C), 93.4 (C), 86.6 (C), 21.3 (CH_3); IR (neat): 3066, 3025, 2915, 2854, 2442, 2325, 2303, 2193, 2125, 1969, 1916, 1826, 1731, 1671, 1626, 1596, 1577, 1507, 1488, 1448, 1409, 1375, 1314, 1293, 1245, 1206, 1168, 1119, 1106, 1072, 1029, 1007, 958, 939, 855, 814, 793, 765, 696 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[40]

4.1.6 Synthesis of 1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (61F)

General Procedure **1** was followed by using benzoyl chloride (615 mg, 4.4 mmol) $PdCl_2(PPh_3)_2$ (51 mg, 0.07 mmol), Et_3N (443 mg, 4.4 mmol), CuI (14 mg, 0.07 mmol) and 4-Ethynyl-*α,α,α*-trifluorotoluene (621 mg, 3.65 mmol) were employed to afford 670 mg (67%) of the indicated product of 1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (**61F**) as brown solid (R_f = 0.75 in 4:1 hexane/ethyl acetate); mp 82.9-83.7 ^{o}C.

61F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.9 Hz, 2H), 7.82-7.48 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (C=O), 136.5 (C), 134.5 (CH), 133.2 (CH), 132.2 (q, ^2J = 32.4 Hz, CH), 129.6 (CH), 128.7 (CH), 125.6 (q, ^3J = 3.6 Hz, CH), 123.9 (C), 123.6 (q, ^1J = 272.6 Hz, CF_3), 90.2 (C), 88.1 (C); IR (neat): 3052, 2205, 1638, 1596, 1578, 1449, 1405, 1314, 1290, 1212, 1165, 1105, 1066, 1028, 1008, 938, 844, 792, 760, 695, 632, 597, 526 cm^{-1}; MS (ESI, m/z): 275.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{10}F_3O$: 275.06783 $[M+H]^+$, found: 275.06850.

4.1.7 Synthesis of 1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one (61G)

General Procedure **1** was followed by using 4-chlorobenzoyl chloride (870 mg, 4.97 mmol) $PdCl_2(PPh_3)_2$ (58 mg, 0.08 mmol), Et_3N (503 mg, 4.97 mmol), CuI (16 mg, 0.08 mmol) and phenylacetylene (422 mg, 4.14 mmol) were employed to afford 720 mg (72%) of the indicated product of 1-(4-chlorophenyl)-3-phenylprop-2-yn-1-one (**61G**) as yellow solid (R_f = 0.68 in 4:1 hexane/ethyl acetate).

61G: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.6 Hz, 2H), 7.73-7.59 (m, 2H), 7.55-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (C=O), 140.7 (CCl), 135.3 (C), 133.1 (CH), 131.0 (C), 130.9 (CH), 129.0 (CH), 128.8 (CH), 119.9 (CH), 93.7 (C), 86.6 (C); IR (neat): 3262, 3085, 3061, 3032, 3032, 2472, 2197, 1953, 1649, 1582, 1480, 1445, 1398, 1301, 1276, 1205, 1168, 1108, 1089, 1029, 1007, 994, 913, 847, 812, 749, 738, 680 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[40]

4.1.8 Synthesis of 1-(4-chlorophenyl)-3-(4-fluoro-3-methylphenyl)prop-2-yn-1-one (61H)

General Procedure **1** was followed by using 4-chloro benzoyl chloride (770 mg, 4.4 mmol) $PdCl_2(PPh_3)_2$ (52 mg, 0.07 mmol), Et_3N (445 mg, 4.4 mmol), CuI (14 mg, 0.07 mmol) and 4-ethynyl-1-fluoro-2-methylbenzene (496 mg, 3.67 mmol) were employed to afford 760 mg (76%) of the indicated product of 1-(4-chlorophenyl)-3-(4-fluoro-3-methylphenyl)prop-2-yn-1-one (**61H**) as yellow solid (R_f = 0.83 in 4:1 hexane/ethyl acetate); mp 186.9-187.7 ^{o}C

61H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.2 Hz, 2H), 7.54-7.42 (m, 4H), 7.03 (t, J = 8.7 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (C=O), 162.8 (d, ^1J = 262.1 Hz, CF), 140.6 (CCl), 136.6 (d, ^3J = 6.0 Hz, CH), 135.2 (C) ,132.8 (d, ^3J = 8.8 Hz, CH), 130.7 (CH), 129.3 (CH), 126.1 (d, ^2J = 19.3 Hz, C), 115.8 (d, ^2J = 23.4 Hz, CH), 115.6 (d, ^4J = 3.5 Hz, C), 93.0 (C), 86.3 (C), 14.33 (d, ^4J = 2.9 Hz, CH_3); IR (neat): 3079, 2196, 1784, 1676, 1588, 1488, 1420, 1398, 1281, 1221, 1172, 1127, 1111, 1089, 1005, 923, 850, 759, 741, 681, 628, 545, 521, 470 cm^{-1}; MS (ESI, m/z): 273.04 [M+H]$^+$; HRMS (ESI) calcd. for $C_{16}H_{11}ClFO$: 273.0477 [M+H]$^+$, found: 273.04870.

4.1.9 Synthesis of 1-(2-Bromophenyl)-3-phenylprop-2-yn-1-one (61I)

General Procedure **1** was followed by using 2-bromobenzoyl chloride (877 mg, 4.0

mmol) $PdCl_2(PPh_3)_2$ (47 mg, 0.06 mmol), Et_3N (405 mg, 4.0 mmol), CuI (13 mg, 0.06 mmol) and phenylacetylene (340 mg, 3.33 mmol) were employed to afford 700 mg (70%) of the indicated product of 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (**61I**) as yellow oil (R_f = 0.3 in 4:1 hexane/ethyl acetate).

61I: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.66-7.60 (m, 2H), 7.54-7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C=O), 137.5 (C), 134.9 (CH), 133.5 (CH), 133.2 (CH), 132.8 (CH), 131.1 (CH), 128.8 (CH), 127.5 (CH), 121.3 (CBr), 119.9 (C), 94.3 (C), 87.9 (C); IR (neat): 3059, 2192, 1733, 1648, 1584, 1562, 1488, 1464, 1443, 1431, 1372, 1297, 1201, 1128, 1062, 1026, 1007, 994, 814, 757, 736, 688 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[53]

4.1.10 Synthesis of 1-Phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (61J)

General Procedure **1** was followed by using benzoyl chloride (953 mg, 6.78 mmol) $PdCl_2(PPh_3)_2$ (79 mg, 0.11 mmol), Et_3N (686 mg, 6.78 mmol), CuI (21 mg, 0.11 mmol) and 3-ethynylthiophene (611 mg, 5.65 mmol) were employed to afford 1.176 mg (98%) of the indicated product of 1-phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (**61J**) as orange-brown oil (R_f = 0.67 in 4:1 hexane/ethyl acetate).

61J: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23-8.14 (m, 2H), 7.98-7.72 (m, 1H), 7.64-7.58 (m, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.43-7.33 (m, 1H), 7.32–7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0 (C=O), 136.8 (C), 134.2 (CH), 134.0 (CH), 130.3 (CH), 129.6 (CH), 128.7 (CH), 126.4 (CH), 119.4 (C), 88.6 (C), 87.2 (C); IR (neat): 3105, 3063, 2148, 1631, 1596, 1546, 1514, 1487, 1448, 1409, 1359, 1312, 1266, 1217, 1167, 1080, 1032, 1014, 924, 872, 827, 784, 695 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[40]

4.1.11 Synthesis of 3-(4-(*tert*-butyl)phenyl)-1-phenylprop-2-yn-1-one (61K)

General Procedure **1** was followed by using benzoyl chloride (643 mg, 4.57 mmol) $PdCl_2(PPh_3)_2$ (54 mg, 0.08 mmol), Et_3N (463 mg, 4.57 mmol), CuI (15 mg, 0.08 mmol) and 4-*tert*-butylphenylacetylene (603 mg, 381 mmol) were employed to afford 940 mg (94%) of the indicated product of 3-(4-(*tert*-butyl)phenyl)-1-phenylprop-2-yn-1-one (**61K**) as yellow oil (R_f = 0.75 in 4:1 hexane/ethyl acetate).

61K: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.47, 1.41 Hz, 2H), 7.44-7.36 (m, 3H), 7.49-7.43 (m, 2H), 7.38 (dd *J* = 8.34, 1.54 Hz, 2H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (C=O), 154.5 (C), 136.9 (C), 134.0 (CH), 133.0 (CH), 129.5 (CH), 128.6 (CH), 125.8 (CH), 116.9 (C), 93.7 (C), 86.8 (C), 34.9 (C), 31.0 (CH_3); IR (neat): 3065, 2961, 2904, 2867, 2192, 1637, 1597, 1578, 1504, 1448, 1394, 1363, 1313, 1288, 1212, 1171, 1107, 1029, 1008, 834, 792, 697, 650, 563, 524, 414 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[54,55]

4.1.12 Synthesis of 3-(4-bromophenyl)-1-phenylprop-2-yn-1-one (61L)

General Procedure **1** was followed by using benzoyl chloride (887 mg, 6.31 mmol) $PdCl_2(PPh_3)_2$ (74 mg, 0.11 mmol), Et_3N (639 mg, 6.31 mmol), CuI (21 mg, 0.11 mmol) and 1-bromo-4-ethynyl benzene (952 mg, 5.26 mmol) were employed to afford 1.066 g (71%) of the indicated product of 3-(4-bromophenyl)-1-phenylprop-2-yn-1-one (**61L**) as brownish yellow (*R_f* = 0.67 in 4:1 hexane/ethyl acetate); mp 114.1-115.7 ^{o}C.

61L: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.1 Hz, 2H), 7.56-7.35 (m, 7H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (C=O), 136.7 (C), 134.6 (CH), 134.3 (CH), 132.1 (CH), 129.6 (CH), 128.7 (CH), 125.6 (C), 119.1 (C), 91.6 (C), 87.7 (C); IR (neat): 3053, 2195, 1629, 1577, 1473, 1447, 1393, 1325, 1292, 1205, 1170, 1062, 1029, 1007, 817, 791, 692, 639, 628, 528, 438 cm^{-1}. MS (ESI, m/z): 284.99 [M+H]$^{+}$; HRMS (ESI) calcd. for $C_{15}H_{10}BrO$: 284.99095 [M+H]$^{+}$, found: 284.99160.

4.2 General Procedure 2. Synthesis of *N*-Propargylic *β*-Enaminones

α,*β*-Alkynic ketones **61** (1.0 mmol) and propargylamine (**62**) (1.2 mmol) were mixed in refluxing methanol (5 mL) in a round-bottomed flask, reaction duration was about 2 hours and reaction is monitored by TLC (9:1 hexane:EtOAc). After reaction was finished, methanol was removed with rotary evaporator and the crude sample is prufied with flash chromatography with silica gel using 9:1 hexane: EtOAc as eluent.

4.2.1 Synthesis of (*Z*)-1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (54A)

General Procedure **2** was followed by using 1,3-diphenylprop-2-yn-1-one (**61A**) (1.200 g, 5.83 mmol) and propargylamine (385 mg, 6.99 mmol) were employed to afford 1.341 g (95%) of the indicated product of (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54A**) as yellow solid (*R_f* = 0.44 in 4:1 hexane/ethyl acetate).

54A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (t, *J* = 6.0 Hz, 1H), 7.89 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.50-7.29 (m, 8H), 5.82 (s, 1H), 3.86 (dd, *J* = 6.3, 2.5 Hz, 2H), 2.32

(t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6 (C=O), 165.5 (C), 139.6 (C), 134.5 (C), 130.7 (CH), 129.6 (CH), 128.4 (CH), 127.9 (CH), 127.5 (CH), 126.9 (CH), 94.3 (CH), 79.6 (C), 72.4 (CH), 33.9 (CH_2); IR (neat): 3224, 3055, 3022, 2113, 1596, 1585, 1547, 1478, 1443, 1429, 1346, 1324, 1294, 1266, 1242, 1219, 1139, 1053, 1026, 924, 803, 775, 763, 729, 703, 676 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[35]

4.2.2 Synthesis of (*Z*)-3-(3-Fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (54B)

General Procedure **2** was followed by using 3-(3-fluorophenyl)-1-phenylprop-2-yn-1-one (**61B**) (454 mg, 2.02 mmol) and propargylamine (134 mg, 2.43 mmol) were employed to afford 528 mg (94%) of the indicated product of (*Z*)-3-(3-fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54B**) as pale yellow solid (R_f = 0.5 in 4:1 hexane/ethyl acetate); mp 93.8–94.8 °C.

54B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (br s, 1H), 8.06-7.80 (m, 2H), 7.52-7.36 (m, 4H), 7.28 (d, J = 7.6 Hz, 1H), 7.23 (dt, J = 9.0, 2.1 Hz, 1H), 7.17 (td, J = 8.4, 2.3 Hz, 1H), 5.85 (s, 1H), 3.92 (dd, J = 6.3, 2.4 Hz, 2H), 2.35 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3 (C=O), 164.1 (C), 162.5 (d, ^{1}J = 248.3 Hz, CF), 139.7 (C), 136.9 (d, ^{3}J = 7.5 Hz, C), 131.1 (CH), 130.5 (d, ^{3}J = 8.3 Hz, CH), 128.2 (CH), 127.2 (CH), 123.6 (d, ^{4}J = 3.0 Hz, CH), 116.8 (d, ^{2}J = 21.0 Hz, CH), 115.1 (d, ^{2}J = 22.7 Hz, CH), 94.7 (CH), 79.6 (C), 72.7 (CH), 34.1 (CH_2); IR (neat): 3222, 3055, 2939, 2111, 1974, 1939, 1875, 1804, 1747, 1599, 1548, 1519, 1474, 1431, 1348, 1323, 1299, 1284, 1265, 1250, 1227, 1203, 1179, 1158, 1123, 1054, 1026, 999, 965, 929, 888, 877, 788, 736, 707, 675 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.

4.2.3 Synthesis of (*Z*)-1-(2-bromophenyl)-3-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (54C)

General Procedure **2** was followed by using 1-(2-bromophenyl)-3-(4-chlorophenyl) prop-2-yn-1-one (**61C**) (903 mg, 2.7 mmol) and propargylamine (178 mg, 3.24 mmol) were employed to afford 958 mg (95%) of the indicated product of (*Z*)-1-(2-bromophenyl)-3-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54C**) as brown solid (R_f = 0.45 in 4:1 hexane/ethyl acetate); mp 82.3-83.6 °C.

54C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.49-7.38 (m, 5H), 7.30 (td, *J* = 7.5, 1.0 Hz, 1H), 7.19 (td, *J* = 7.7, 1.7 Hz, 1H), 5.44 (s, 1H), 3.94 (dd, *J* = 6.5, 2.5 Hz, 2H), 2.34 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1 (C=O), 164.4 (C), 142.8 (CCl), 136.2 (C), 134.5 (CH), 133.4 (C), 132.7 (CH), 130.5 (CH), 129.3 (CH), 129.2 (CH) 129.0 (CH), 119.4 (CBr), 94.4 (CH), 76.3 (C), 71.9 (CH), 32.7 (CH_2); IR (neat): 3297, 3053, 2930, 2349, 1589, 1554, 1478, 1420, 1364, 1320, 1260, 1216, 1145, 1084, 1015, 923, 871, 831, 778, 753, 738, 656, 638, 624, 562, 522, 471, 415 cm^{-1}; MS (ESI, m/z): 371.97 [M-H]$^-$; HRMS (ESI) calcd. for $C_{18}H_{12}BrClNO$: 371.97983 [M-H]$^-$, found: 371.97963.

4.2.4 Synthesis of (*Z*)-3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (54D)

General Procedure **2** was followed by using 3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-one (**61D**) (932 mg, 3.94 mmol) and propargylamine (260 mg, 4.73 mmol) were employed to afford 1.122 g (98%) of the indicated product of (*Z*)-3-(4-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54D**) as reddish orange oil (R_f = 0.29 in 4:1 hexane/ethyl acetate).

54D: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.37 (bs, 1H), 7.90 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.49–7.35 (m, 5H), 7.00–6.95 (m, 2H), 5.84 (s, 1H), 3.97 (dd, *J* = 6.3, 2.5 Hz, 2H), 3.84 (s, 3H), 2.32 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

188.9 (C=O), 165.9 (C), 160.9 (C), 140.1 (C), 130.9 (C), 129.5 (CH), 128.3 (CH), 127.2 (CH), 114.1 (CH), 94.6 (CH), 80.0 (C), 72.5 (CH), 55.4 (OCH_3), 34.3 (CH_2), (Note that two CH peaks overlap on each other); IR (neat): 3285, 3057, 3020, 3003, 2959, 2933, 2907, 2837, 2167, 2120, 2104, 1909, 1731, 1668, 1583, 1559, 1497, 1328, 1293, 1247, 1174, 1142, 1056, 1023, 836, 808, 757, 689, 653, 555, 418 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[40]

4.2.5 Synthesis of (*Z*)-1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (54E)

General Procedure **2** was followed by using 1-phenyl-3-(p-tolyl)prop-2-yn-1-one (**61E**) (523 mg, 2.37 mmol) and propargylamine (157 mg, 2.85 mmol) were employed to afford 637 mg (97%) of the indicated product of (*Z*)-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (**54E**) as reddish orange oil (R_f = 0.50 in 4:1 hexane/ethyl acetate).

54E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.38 (br s, 1H), 7.93 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.50–7.38 (m, 5H), 7.29 (d, *J* = 7.7 Hz, 2H), 5.87 (s, 1H), 3.98 (dd, *J* = 6.3, 2.4 Hz, 2H), 2.44 (s, 3H), 2.34 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C=O), 166.2 (C), 140.1 (C), 132.1 (C), 130.9 (C), 129.4 (CH), 128.3 (CH), 127.8 (CH), 127.2 (CH), 94.6 (CH), 79.9 (C), 72.5 (CH), 34.3 (CH_2), 21.4 (CH_3) (Note that two CH peaks overlap on each other); IR (neat): 3287, 3056, 3026, 2919, 2861, 1666, 1579, 1555, 1499, 1482, 1446, 1356, 1327, 1289, 1266, 1248, 1181, 1142, 1055, 1022, 1001, 972, 926, 872, 825, 755, 689 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[40]

4.2.6 Synthesis of (*Z*)-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluorometyl)phenyl)prop-2-en-1-one (54F)

General Procedure **2** was followed by using 1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (**61F**) (545 mg, 1.99 mmol) and propargylamine (131 mg, 2.39 mmol) were employed to afford 566 mg (86%) of the indicated product of (*Z*)-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**54F**) light brown solid (R_f = 0.69 in 4:1 hexane/ethyl acetate); mp 99.1-99.8 ^{o}C.

54F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 7.89 (d, *J* = 7.2 Hz, 2 H), 7.69 (dd, *J* = 44.4, 8.1 Hz, 4H), 7.51 – 7.36 (m, 3H), 5.83 (s, 1H), 3.90 (dd, *J* = 6.4, 2.3 Hz, 2H), 2.32 (t, *J* = 2.3 Hz, 1H);^{13}C NMR (101 MHz, $CDCl_3$) δ 189.4 (C=O), 164.0 (C), 139.6 (C), 138.4 (C), 131.8 (q, ^{2}J = 33.0 Hz, CH), 131.3 (CH), 128.4 (CH), 128.3 (CH), 127.2 (CH), 125.7 (q, ^{3}J = 3.6 Hz, CH), 123.8 (q, ^{1}J = 271.0 Hz, CF_3), 94.9 (CH), 79.5 (C), 72.8 (CH), 34.2 (CH_2); IR (neat): 3286, 2930, 1597, 1580, 1541, 1323, 1293, 1226, 1193, 1122, 1105, 1072, 1053, 1017, 921, 848, 759, 747, 707, 682, 647, 631, 599, 554, 489, 469, 421 cm^{-1}; MS (ESI, m/z): 330.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}F_3NO$: 330.11120 $[M+H]^+$, found: 330.11120.

4.2.7 Synthesis of (*Z*)-1-(4-Chlorophenyl)-3-phenyl-3-(prop-2-yn-ylamino)prop-2-en-1-one (54G)

General Procedure **2** was followed by using 1-(4-chlorophenyl)-3-phenylprop-2-yn-1-one (**61G**) (935 mg, 3.87 mmol) and propargylamine (256 mg, 4.65 mmol) were employed to afford 1.060 g (93%) of the indicated product of (*Z*)-1-(4-chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54G**) as yellow solid (R_f = 0.45 in 4:1 hexane/ethyl acetate).

54G: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.34 (br s, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.46 (s, 5H), 7.35 (d, *J* = 8.5 Hz, 2H), 5.77 (s, 1H), 3.93 (dd, *J* = 6.3, 2.4 Hz, 2H), 2.32 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5 (CO), 166.2 (C), 138.3 (C), 137.1 (C), 134.7 (C), 129.9 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.8 (CH), 94.3 (CH), 79.7 (C), 72.7 (CH), 34.3 (CH_2); IR (neat): 3229, 3065, 3027, 2184, 2164, 2114, 2026, 1983, 1895, 1593, 1561, 1543, 1518, 1477, 1431, 1395, 1352, 1327, 1295, 1267, 1144, 1091, 1074, 1015, 927, 838, 801, 774, 753, 698 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[35]

4.2.8 Synthesis of (*Z*)-1-(4-chlorophenyl)-3-(4-fluoro-3-methylphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (54H)

General Procedure **2** was followed by using 1-(4-chlorophenyl)-3-(4-fluoro-3-methylphenyl)prop-2-yn-1-one (**61H**) (1.229 g, 4.51 mmol) and propargylamine (299 mg, 5.41 mmol) were employed to afford 1.306 g (88%) of the indicated product of (*Z*)-1-(4-chlorophenyl)-3-(4-fluoro-3-methylphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54H**) as yellow solid (R_f = 0.45 in 4:1 hexane/ethyl acetate); mp 92.6-93.7 °C.

54H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (t, *J* = 6.1 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.24 (m, 4H), 7.07 (t, *J* = 8.8 Hz, 1H), 5.74 (s, 1H), 3.92 (dd, *J* = 6.3, 2.5 Hz, 2H), 2.35 (t, *J* = 2.4 Hz, 1H), 2.32 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7 (C=O), 165.3 (C), 162.1 (d, ^1J = 248.9 Hz, CF), 138.2 (CCl), 137.1 (C), 131.2 (d, ^3J = 5.46 Hz, CH), 130.5 (d, ^4J = 3.63 Hz, C), 128.6 (CH), 128.4 (CH), 127.2 (d, ^3J = 8.54 Hz, CH), 125.7 (d, ^2J = 17.9 Hz, C), 115.4 (d, ^2J = 22.8 Hz, CH), 94.1 (CH), 79.5 (C), 72.7 (CH), 34.2 (CH_2), 14.5 (d, ^3J = 3.0 Hz, CH_3); IR (neat): 3057,3031, 2926, 2241, 2206, 1963, 1732, 1567, 1428, 1442, 1325, 1224, 1140, 1051, 1023, 999, 918, 843, 809, 750, 686, 608, 526 cm-1; MS (ESI, m/z): 328.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}ClFNO$: 328.08990 $[M+H]^+$, found: 328.09044.

4.2.9 Synthesis of (*Z*)-1-(2-Bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (56I)

General Procedure **2** was followed by using 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (**61I**) (1.184 g, 3.94 mmol) and propargylamine (261 mg, 4.73 mmol) were employed to afford 1.327 g (99%) of the indicated product of (*Z*)-1-(2-bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54I**) as reddish orange oil (*Rf* = 0.31 in 4:1 hexane/ethyl acetate).

54I: 1H NMR (400 MHz, $CDCl_3$) δ 11.11 (br s, 1H), 7.56 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.50-7.40 (m, 6H), 7.30 (td, *J* = 7.5, 1.0 Hz, 1H), 7.18 (td, *J* = 7.7, 1.7 Hz, 1H), 5.47 (s, 1H), 3.96 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.35 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9 (C=O), 165.7 (C), 142.9 (C), 134.3 (C), 133.3 (CH), 130.2 (CH), 129.9 (CH), 129.1 (CH), 128.6 (CH), 127.8 (CH), 127.1 (CH), 119.3 (CBr), 98.3 (CH), 79.5 (C), 72.7 (CH), 34.3 (CH_2); IR (neat): 3288, 3055, 2119, 1732, 1588, 1560, 1484, 1461, 1427, 1359, 1319, 1269, 1218, 1182, 1146, 1123, 1084, 1025, 1000, 949, 927, 873, 755, 701, 669 cm-1; MS (ESI, m/z): 340.03 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{16}BrNO$: 340.0332 $[M+H]^+$, found: 340.0333.

4.2.10 Synthesis of (*Z*)-1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (54J)

General Procedure **2** was followed by using 1-phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (**61J**) (1.434 g, 6.76 mmol) and propargylamine (447 mg, 8.10 mmol) were employed to afford 1.387 mg (77%) of the indicated product of (*Z*)-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**54J**) as yellow solid (R_f = 0.5 in 4:1 hexane/ethyl acetate); mp 77.4–78.3 °C.

54J: ^1H NMR (400 MHz, $CDCl_3$) δ 11.42 (br s, 1H), 7.98-7.85 (m, 2H), 7.63 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.47-7.37 (m, 4H), 7.27 (dd, *J* = 5.0, 1.3 Hz, 1H), 5.94 (s, 1H), 4.02 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.38 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (C=O), 160.5 (C), 139.9 (C), 135.4 (C), 130.9 (CH), 128.2 (CH), 127.2 (CH), 127.0 (CH), 126.6 (CH), 126.2 (CH), 94.2 (CH), 79.9 (C), 72.6 (CH), 34.1 (CH_2); IR (neat): 3249, 3102, 2921, 2119, 2064, 1985, 1953, 1896, 1769, 1576, 1553, 1497, 1425, 1393, 1371, 1314, 1289, 1248, 1227, 1131, 1079, 1057, 1021, 924, 894, 864, 823, 799, 784, 754, 713, 695 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[40]

4.2.11 Synthesis of (*Z*)-3-(4-(*tert*-butyl)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (54K)

General Procedure **2** was followed by using 3-(4-(*tert*-butyl) phenyl)-1-phenylprop-2-yn-1-one (**61K**) (788 mg, 3.00 mmol) and propargylamine (198 mg, 3.60 mmol) were employed to afford 934 mg (98%) of the indicated product of (*Z*)-3-(4-(*tert*-butyl)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54K**) as yellow solid (R_f = 0.63 in 4:1 hexane/ethyl acetate); mp 108.8-109.8°C. **54K:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (br s, 1H), 7.96-7.81 (m, 2H), 7.56-7.35 (m, 7H), 5.88 (s, 1H), 4.01 (dd, *J* = 6.3, 2.5 Hz, 2H), 2.35 (t, *J* = 2.5 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (C=O), 166.1 (C), 153.2 (C), 140.1 (C), 132.0 (C), 130.9 (CH), 128.2 (CH), 127.6 (CH), 127.2 (CH), 125.6 (CH), 94.6 (CH), 79.9 (C), 72.5 (CH), 34.8 (C), 34.3 (CH_2), 31.3 (CH_3); IR (neat): 3287, 3252, 2953, 2863, 1578, 1547, 1497, 1353, 1326, 1290, 1266, 1221, 1147, 1107, 1054, 1022, 930, 840, 806, 756, 742, 706, 687, 636, 592, 559, 489, 458, 420 cm^{-1}; MS (ESI, m/z): 318.18 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{24}NO$: 318.18524 $[M+H]^+$, found: 318.18594.

4.2.12 Synthesis of (*Z*)-3-(4-bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (54L)

General Procedure **2** was followed by using 3-(4-bromophenyl)-1-phenylprop-2-yn-1-one (**61L**) (1.033 mg, 3.62 mmol) and propargylamine (239 mg, 4.35 mmol) were employed to afford 972 mg (79%) of the indicated product of (*Z*)-3-(4-

bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54L**) as light brown solid (R_f = 0.58 in 4:1 hexane/ethyl acetate); mp 92.6-93.8 ^{o}C.

54L: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.25 (br s, 1H), 7.88 (dd, *J* = 5.1, 3.2 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.34 (m, 5H), 5.81 (s, 1H), 3.90 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.32 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3 (C=O), 164.5 (C), 139.8 (C), 133.8 (C), 132.0 (CH), 131.1 (CH), 129.6 (CH), 128.3 (CH), 127.1 (CH), 124.3 (CBr), 94.7 (CH), 79.5 (C), 72.9 (CH), 34.2 (CH_2); IR (neat): 3226, 2990, 2937, 2349, 1594, 1577, 1546, 1473, 1321, 1295, 1239, 1220, 1176, 1138, 1073, 1050, 1021, 1008, 944, 926, 831, 789, 692, 678, 623, 560, 472, 460 cm^{-1}; MS (ESI, m/z): 338.01 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}BrNO$: 338.01860 $[M+H]^+$, found: 338.01729.

4.3 General Procedure 3. Synthesis of *N*-(2,4-Pentadiynyl)-*β*-enaminones

N-propargylic *β*-enaminone (1.0 mmol) was dissolved in 5.0 ml of acetone. Then, TMEDA (2.0 mmol) and CuCl (1.0 mmol) was added subsequently and stirred in a round bottom flask at room temperature in aerobic condition. After 10 mins terminal acetylene (1.5-2.0) mmol was added drop by drop to the solution. The solution was stirred for 24 hours. After completing reaction, acetone was removed by rotary evaporator. Finally, the residue was purified by column chromatography using hexane/ethyl acetate (10:1) mixture.

4.3.1 Synthesis of (*Z*)-1,3-diphenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (56A)

General Procedure **3** was followed by using (*Z*)-1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54A**) (265 mg, 1.02 mmol), TMEDA (236 mg, 2.03 mmol), CuCl (101 mg, 1.02 mmol) and phenylacetylene (156 mg, 1.53 mmol) were employed to afford 157 mg (60%) of the indicated product of (*Z*)-1,3-

diphenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56A**) as orange oil (R_f = 0.53 in 4:1 hexane/ethyl acetate).

56A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.38 (t, *J* = 5.8 Hz, 1H), 7.92 (d, *J* = 6.6 Hz, 2H), 7.56-7.28 (m, 13H), 5.88 (s, 1H), 4.11 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2 (C=O), 165.6 (C), 139.9 (C), 134.8 (C), 132.6 (CH), 131.1 (CH), 129.9 (CH), 129.4 (CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 127.9 (CH), 127.2 (CH), 121.4 (C), 95.0 (CH), 78.6 (C), 77.9 (C), 73.5 (C), 69.0 (C), 35.1 (CH_2). IR (neat): 3057, 3031, 2926, 2241, 2206, 1732, 1557, 1478, 1442, 1325, 1224, 1140, 1051, 1023, 999, 918, 843, 809, 750, 686, 608, 526 cm^{-1}; MS (ESI, m/z): 362.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{26}H_{20}NO$: 362.15394 $[M+H]^+$, found: 362.15372.

4.3.2 Synthesis (*Z*)-3-(3-fluorophenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (56B)

General Procedure **3** was followed by using (*Z*)-3-(3-Fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54B**) (291 mg, 1.04 mmol), TMEDA (241 mg, 2.09 mmol), CuCl (103 mg, 1.04 mmol) and phenylacetylene (159 mg, 1.56 mmol) were employed to afford 174 mg (60%) of the indicated product of (*Z*)-3-(3-fluorophenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56B**) as red oil (R_f = 0.47 in 4:1 hexane/ethyl acetate).

56B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 8.01 (d, *J* = 6.9 Hz, 2H), 7.65-7.21 (m, 12H), 5.96 (s, 1H), 4.17 (d, *J* = 2.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7 (C=O), 164.0 (d, ^4J = 3.8 Hz, C), 162.3 (d, ^1J = 241.1 Hz, CF), 139.6 (C), 136.8 (d, ^3J = 6.8 Hz, C), 132.6 (CH), 131.6 (CH), 130.6 (d, ^3J = 8.3 Hz, CH), 129.4 (CH), 128.5 (CH), 128.4 (CH), 127.3 (CH), 123.7 (d, ^4J = 2.9 Hz, CH), 121.3 (C), 116.9 (d, ^2J = 20.3 Hz, CH), 115.2 (d, ^2J = 17.9 Hz, CH), 95.1 (CH), 78.3 (C), 78.1 (C), 73.4 (C), 69.2 (C), 35.4 (CH_2); IR (neat): 3055, 2920, 2203, 1668, 1569, 1474, 1444, 1395, 1362, 1229, 1052, 1022, 873, 753, 686, 520 cm^{-1}. MS (ESI, m/z): 380.24 [M+H]$^+$; HRMS (ESI) calcd. for $C_{26}H_{19}FNO$: 380.14547 [M+H]$^+$, found: 380.14547.

4.3.3 Synthesis of (*Z*)-1-(2-bromophenyl)-3-(4-chlorophenyl)-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (56C)

General Procedure **3** was followed by using (*Z*)-1-(2-bromophenyl)-3-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54C**) (220 mg, 0.59 mmol), TMEDA (160 mg, 1.17 mmol), CuCl (58 mg, 0.59 mmol) and phenylacetylene (90 mg, 0.88 mmol) were employed to afford 147 mg (67%) of the indicated product of (*Z*)-1-(2-bromophenyl)-3-(4-chlorophenyl)-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56C**) as orange-brown oil (R_f = 0.58 in 4:1 hexane/ethyl acetate).

56C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.06 (br s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.54- 7.41 (m, 7H), 7.39-7.28 (m, 4H), 7.21 (t, *J* = 7.5 Hz, 1H), 5.48 (s, 1H), 4.10 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2 (C=O), 164.1 (C), 142.6 (CCl), 136.3 (C), 133.4 (C), 132.6 (CH), 130.5 (CH), 129.5 (CH), 129.4 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.5 (CH), 127.2 (CH), 121.2 (C), 119.4 (CBr), 98.5 (CH), 78.2 (C), 78.1 (C), 73.3 (C), 72.9 (C), 35.4 (CH_2). IR (neat): 3059, 2913, 2363, 2110, 1733, 1626, 1578, 1550, 1477, 1439, 1317, 1280, 1202, 1088, 1012, 830, 752, 687, 525, 480, 441 cm^{-1}; MS (ESI, m/z): 474.02 [M+H]$^+$; HRMS (ESI) calcd. for $C_{26}H_{18}BrClNO$: 474.02548 [M+H]$^+$, found: 474.02438.

4.3.4 Synthesis of (*Z*)-3-(4-methoxyphenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (56D)

General Procedure **3** was followed by using of (*Z*)-3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54D**) (280 mg, 0.96 mmol), TMEDA (224 mg, 1.92 mmol), CuCl (95 mg, 0.96 mmol) and phenylacetylene (147 mg, 1.44 mmol) were employed to afford 130 mg (46%) of the indicated product of (*Z*)-3-(4-methoxyphenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56D**) as orange-yellow oil (R_f = 0.42 in 4:1 hexane/ethyl acetate).

56D: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (t, *J* = 6.2 Hz, 1H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.52-7.40 (m, 7H), 7.37-7.29 (m, 3H), 7.00 (d, *J* = 8.7 Hz, 2H), 5.87 (s, 1H), 4.13 (d, *J* = 6.4 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3 (C=O), 165.9 (C), 160.9 (C), 132.8 (C),132.6 (CH), 131.0 (C), 129.5 (CH), 129.4 (CH), 128.5 (CH), 128.3 (CH), 127.2 (CH), 127.0 (CH), 121.3 (C), 114.3 (CH), 94.9 (CH), 78.8 (C), 77.8 (C), 73.6 (C), 68.8 (C), 55.5 (OCH_3), 35.2 (CH_2); IR (neat): 3055, 2920, 2203, 1668, 1569, 1474, 1444, 1395, 1362, 1229, 1052, 873, 753, 686, 520 cm^{-1}; MS (ESI, m/z): 392.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{27}H_{22}NO_2$: 392.16451 $[M+H]^+$, found: 392.16587.

4.3.5 Synthesis of (*Z*)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)-3-(p-tolyl)prop-2-en-1-one (56E)

General Procedure **3** was followed by using (*Z*)-1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (**54E**) (215 mg, 0.78 mmol), TMEDA (181 mg, 1.56 mmol), CuCl (101 mg, 0.78 mmol) and phenylacetylene (159 mg, 1.56 mmol) were employed to afford 105 mg (49%) of the indicated product of (*Z*)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)-3-(p-tolyl)prop-2-en-1-one (**56E**) as brown oil

(R_f = 0.66 in 4:1 hexane/ethyl acetate).

56E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.37 (t, *J* = 6.0 Hz, 1H), 7.91 (dd, *J* = 6.8, 1.6 Hz, 2H), 7.50 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.46-7.38 (m, 5H), 7.35-7.27 (m, 4H) 5.87 (s, 1H), 4.12 (d, *J* = 6.3 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4 (C=O), 165.9 (C), 140.1 (C), 140.0 (C), 132.6 (CH), 131.9 (C), 131.0 (CH), 129.5 (CH), 129.4 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.2 (CH), 121.4 (C), 94.9 (CH), 78.7 (C), 77.8 (C), 73.6 (C), 72.4 (C), 35.4 (CH_2), 21.3 (CH_3); IR (neat): 3052, 3028, 2920, 1685, 1582, 1558, 1442, 1289, 1224, 1176, 1040, 1020, 818, 754, 687, 654, 527 cm^{-1}; MS (ESI, m/z): 376.17 [M+H]$^+$; HRMS (ESI) calcd. for $C_{27}H_{22}NO$: 376.16959 [M+H]$^+$, found: 376.17020.

4.3.6. Synthesis of (*Z*)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (56F)

General Procedure **3** was followed by using (*Z*)-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**54F**) (265 mg, 0.80 mmol), TMEDA (187 mg, 1.61 mmol), CuCl (79 mg, 0.80 mmol) and phenylacetylene (164 mg, 1.61 mmol) were employed to afford 140 mg (53%) of the indicated product of (*Z*)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**56F**) as reddish brown oil (R_f = 0.65 in 4:1 hexane/ethyl acetate).

56F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (s, 1H), 7.96-7.60 (m, 7H), 7.54-7.28 (m, 7H), 5.85 (s, 1H), 4.05 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6 (C=O), 163.8 (C), 139.6 (C), 138.4 (C), 132.6 (q, ^2J = 30.7 Hz, C), 132.1 (CH), 131.4 (CH), 129.4 (CH), 129.1 (CH), 128.7 (CH), 128.4 (CH), 127.3 (CH), 125.8 (q, ^3J = 3.2 Hz, CH), 123.1 (q, ^1J = 282.3 Hz, CF_3), 121.3 (C), 95.4 (CH), 78.1 (C), 73.3 (C), 69.3 (C), 35.1 (CH_2); (Note that two (≡C) peaks overlap on each other); IR (neat): 3062, 2197, 2160, 1688, 1679, 1563, 1502, 1445, 1406, 1322, 1167, 1125, 1067, 1017, 848, 755, 687, 527, 465 cm^{-1}; MS (ESI, m/z): 376.14 [M+H]$^+$; HRMS (ESI) calcd. for $C_{27}H_{19}F_3NO$: 430.13995 [M+H]$^+$, found: 430.14133.

4.3.7 Synthesis of (*Z*)-1-(4-chlorophenyl)-3-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (56G)

General Procedure **3** was followed by using (*Z*)-1-(4-Chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54G**) (300 mg, 1.01 mmol), TMEDA (235 mg, 2.02 mmol), CuCl (100 mg, 1.01 mmol) and phenylacetylene (155 mg, 1.52 mmol) were employed to afford 92 mg (31%) of the indicated product of (*Z*)-1-(4-chlorophenyl)-3-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56G**) as orange-brown (R_f = 0.56 in 4:1 hexane/ethyl acetate).

56G: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.36 (br s, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.55-7.42 (m, 6H), 7.40-7.27 (m, 6H), 5.81 (s, 1H), 4.11 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6 (C=O), 166.2 (C), 138.3 (CCl), 137.2 (C), 134.6 (C), 132.6 (CH), 130.1 (CH), 129.4 (CH), 128.9 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 121.4 (C), 94.6 (CH), 78.4 (C), 78.0 (C), 73.4 (C), 69.5 (C), 35.1 (CH_2). IR (neat): 3058, 2918, 2210, 1731, 1671, 1585, 1563, 1475, 1441, 1320, 1293, 1173, 1140, 1088, 1010, 964, 917, 873, 844, 754, 687, 628, 549, 525, 474 cm^{-1}; MS (ESI, m/z): 396.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{26}H_{19}ClNO$: 396.114570 $[M+H]^+$, found: 396.11497.

4.3.8 Synthesis of (*Z*)-1-(4-chlorophenyl)-3-(4-fluoro-3-methylphenyl)-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (56H)

General Procedure **3** was followed by using (*Z*)-1-(4-chlorophenyl)-3-(4-fluoro-3-methylphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54H**) (265 mg, 0.81 mmol), TMEDA (188 mg, 1.62 mmol), CuCl (80 mg, 0.81 mmol) and phenylacetylene (165 mg, 1.62 mmol) were employed to afford 114 mg (43%) of the indicated product of (*Z*)-1-(4-chlorophenyl)-3-(4-fluoro-3-methylphenyl)-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56H**) as reddish brown oil (R_f = 0.71 in 4:1 hexane/ethyl acetate).

56H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (br s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 6.9 Hz, 2H), 7.32-7.19 (m, 7H), 7.03 (t, *J* = 8.8 Hz, 1H), 5.69 (s, 1H), 4.01 (d, *J* = 5.8 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2 (C=O), 165.0 (C), 160.8 (d, ^1J = 179.6 Hz, CF), 140.0 (C), 132.6 (CH), 131.3 (d, ^3J = 5.7 Hz, CH), 131.2 (C), 130.6 (d, ^4J = 3.6 Hz, C), 129.4 (CH), 128.5 (CH), 128.3 (CH), 127.2 (CH), 127.1 (d, ^3J = 3.6 Hz, CH), 125.8 (d, ^2J = 17.8 Hz, C), 121.2 (C), 115.5 (d, ^2J = 22.0 Hz, CH), 95.0 (CH), 78.6 (C), 77.9 (C), 73.4 (C), 69.0 (C), 35.1 (CH_2), 14.6 (d, ^3J = 2.8 Hz, CH_3); IR (neat): 3061, 2920, 2421, 2213, 1961, 1686, 1672, 1570, 1491, 1399, 1234, 1171, 1088, 1010, 895, 879, 822, 778, 753, 687, 626, 578, 525, 474, 439, 412 cm^{-1}; MS (ESI, m/z): 428.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{27}H_{20}ClFNO$: 428.12120 $[M+H]^+$, found: 428.12124.

4.3.9 Synthesis of (*Z*)-1-(2-bromophenyl)-3-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (56I)

General Procedure **3** was followed by using (*Z*)-1-(2-Bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54I**) (300 mg, 0.88 mmol), TMEDA (205 mg, 1.76 mmol), CuCl (87 mg, 0.88 mmol) and phenylacetylene (180 mg, 1.76 mmol) were employed to afford 130 mg (43%) of the indicated product of (*Z*)-1-(2-bromophenyl)-3-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56I**) as orange oil (R_f = 0.49 in 4:1 hexane/ethyl acetate).

56I: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (br s, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.55-7.41 (m, 8H), 7.38-7.30 (m, 4H), 7.20 (t, *J* = 7.2 Hz, 1H), 5.51 (s, 1H), 4.13 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2 (C=O), 165.6 (C), 142.9 (C), 134.3 (C), 133.4 (CH), 132.6 (CH), 130.4 (CH), 130.1 (CH), 129.4 (CH), 129.2 (CH), 128.8 (CH), 128.5 (CH), 127.9 (CH), 127.2 (CH), 121.4 (C), 119.5 (CBr) 98.5 (CH), 78.3 (C), 78.0 (C), 73.4 (C), 69.2 (C), 35.3 (CH_2); IR (neat): 3057, 2916, 2848, 2199, 1730, 1682, 1586, 1560, 1483, 1317, 1144, 1068, 1022, 998, 915, 872, 839, 750, 687, 645, 610, 526, 447 cm^{-1}; MS (ESI, m/z): 440.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{26}H_{19}BrNO$: 440.06445 $[M+H]^+$, found: 440.06445.

4.3.10 Synthesis of (*Z*)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)-3-(thiophen-3-yl)prop-2-en-1-one (56J)

General Procedure **3** was followed by using (*Z*)-1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**54J**) (265 mg, 0.99 mmol), TMEDA

(230 mg, 1.98 mmol), CuCl (98 mg, 0.99 mmol) and phenylacetylene (202 mg, 1.98 mmol) were employed to afford 107 mg (40%) of the indicated product of (*Z*)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)-3-(thiophen-3-yl)prop-2-en-1-one (**56J**) as dark brown oil (R_f = 0.47 in 4:1 hexane/ethyl acetate).

56J: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.41 (br s, 1H), 7.90 (dd, *J* = 14.4, 13.0 Hz, 2H), 7.67 – 7.62 (m, 1H), 7.54 – 7.27 (m, 10H), 5.96 (s, 1H), 4.19 (d, *J* = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2 (C=O), 160.3 (C), 140.0 (C), 135.5 (C), 132.7 (CH), 131.1 (CH), 129.4 (CH), 128.5 (CH), 128.3 (CH), 127.3 (CH), 127.2 (CH), 126.8 (CH), 126.5 (CH), 121.4 (C), 94.6 (CH), 78.7 (C), 78.0 (C), 73.5 (C), 69.1 (C), 35.4 (CH_2); IR (neat): 3099, 3058, 2921, 2203, 1707, 1576, 1500, 1442, 1363, 1274, 1221, 1131, 1053, 1022, 999, 916, 866, 797, 751, 686, 642, 589, 527, 484, 457 cm^{-1}; MS (ESI, m/z): 368.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{18}NOS$: 368.11036 $[M+H]^+$, found: 368.11094.

4.3.11 Synthesis of (*Z*)-3-(4-(*tert*-butyl)phenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (56K)

General Procedure **3** was followed by using (*Z*)-3-(4-(tert-butyl)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54K**) (262 mg, 0.87 mmol), TMEDA (202 mg, 1.74 mmol), CuCl (86 mg, 0.87 mmol) and phenylacetylene (177 mg, 1.74 mmol) were employed to afford 155 mg (59%) of the indicated product of (*Z*)-3-(4-(tert-butyl)phenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56K**) as reddish brown oil (R_f = 0.69 in 4:1 hexane/ethyl acetate).

56K: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (t, *J* = 6.0 Hz, 1H), 7.84 (dd, *J* = 13.6, 7.0 Hz, 2 H), 7.45-7.20 (m, 12H), 5.80 (s, 1H), 4.06 (d, *J* = 6.4 Hz, 2H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1 (C=O), 165.9 (C), 153.3 (C), 140.0 (C), 132.6 (CH), 131.9 (C), 131.1 (CH), 129.4 (CH), 128.5 (CH), 128.3 (CH), 127.7 (CH), 127.2 (CH), 125.7 (CH), 121.4 (C), 94.9 (CH), 78.8 (C), 77.9 (C) ,73.6 (C), 69.0 (C), 35.2 (C), 35.0 (CH_2), 31.3 (CH_3); IR (neat): 3057, 2960, 2866, 2202, 1734, 1675, 1578, 1549, 1498, 1362, 1325, 1292, 1266, 1224, 1145, 1107, 1052, 1022, 840, 754, 687, 636, 556, 526 cm^{-1}; MS (ESI, m/z): 418.21 [M+H]$^+$; HRMS (ESI) calcd. for $C_{30}H_{28}NO$: 418.21654 [M+H]$^+$, found: 418.21808.

4.3.12 Synthesis of (*Z*)-3-(4-bromophenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (56L)

General Procedure **3** was followed by using (*Z*)-3-(4-bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54L**) (260 mg, 0.78 mmol), TMEDA (181 mg, 1.56 mmol), CuCl (77 mg, 0.78 mmol) and phenylacetylene (159 mg, 1.56 mmol) were employed to afford 136 mg (52%) of the indicated product of (*Z*)-3-(4-bromophenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56L**) as reddish brown (R_f = 0.57 in 4:1 hexane/ethyl acetate).

56L: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (br s, 1H), 7.90 (d, *J* = 6.9 Hz, 2H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.55-7.27 (m, 10H), 5.84 (s, 1H), 4.07 (d, *J* = 4.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4 (CO), 164.1 (C), 139.6 (C), 133.7 (CH), 132.7 (CH), 132.1 (CH), 131.2 (CH), 129.6 (CH), 129.4 (CH), 128.5 (CH), 128.4 (CH), 127.3 (C), 124.3 (C), 121.3 (C), 95.2 (CH), 78.4 (C), 78.0 (C), 73.3 (C), 69.2 (C), 35.4 (CH_2); IR (neat): 3050, 2917, 2345, 2150, 1974, 1735, 1671, 1592, 1576, 1550, 1472, 1441, 1390, 1323, 1290, 1223, 1139, 1050, 1022, 1009, 829, 751, 686, 616, 524, 465, 411 cm^{-1}; MS (ESI, m/z): 440.06 [M+H]$^+$; HRMS (ESI) calcd. for $C_{26}H_{19}BrNO$: 440.06445 [M+H]$^+$, found: 440.06497.

4.3.13 Synthesis of (*Z*)-1,3-diphenyl-3-((5-(p-tolyl)penta-2,4-diyn-1-yl)amino)prop-2-en-1-one (56M)

General Procedure **3** was followed by using (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**54M**) (200 mg, 0.77 mmol), TMEDA (178 mg, 1.53 mmol), CuCl (76 mg, 0.77 mmol) and 4-ethynyl toluene (133 mg, 1.15 mmol) were employed to afford 100 mg (50%) of the indicated product of (*Z*)-1,3-diphenyl-3-((5-(p-tolyl)penta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56M**) as reddish brown oil (R_f = 0.60 in 4:1 hexane/ethyl acetate).

56M: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H), 7.93 (d, *J* = 7.3 Hz, 2H), 7.54 – 7.26 (m, 12H), 5.88 (s, 1H), 4.12 (d, *J* = 6.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2 (C=O), 165.6 (C), 139.9 (C), 139.7 (C), 134.8 (C), 132.6 (CH), 131.1 (CH), 129.9 (CH), 129.2 (CH), 128.8 (CH), 128.3 (CH), 127.9 (CH), 127.2 (CH), 118.2 (C), 95.0 (CH), 78.3 (C), 78.2 (C), 73.0 (C), 69.2 (C), 35.1 (CH_2), 21.6 (CH_3); IR (neat): 3056, 3028, 2918, 2241, 1907, 1733, 1555, 1476, 1324, 1292, 1223, 1178, 1139, 1052, 1023, 999, 813, 745, 688, 525, 461 cm^{-1}; MS (ESI, m/z): 376.17 $[M+H]^+$; HRMS (ESI) calcd. for $C_{27}H_{22}NO$: 376.16959 $[M+H]^+$, found: 376.17059.

4.4 General procedure 4. Synthesis of propargyl-substituted pyrroles

N-(2,4-pentadiynyl)-*β*-enaminone (0.24 mmol) was dissolved in DCM (4.0 mL) at room temperature under argon and then NaH (0.24 or 0.48 mmol) was added to the reaction mixture. The resulting mixture was carried at reflux condition for 2 hours. (Note that reaction was continued until *N*-(2,4-pentadiynyl)-*β*-enaminone was completely consumed as monitored by routine TLC). After completing reaction, extraction was done with ethyl acetate (50 mL) and saturated aqueous solution ammonium chloride. (30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator. Finally, the residue was purified by column chromatography using hexane/ethyl acetate (12:1) mixture.

4.4.1 Synthesis of phenyl(2-phenyl-4-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrol-3-yl)methanone (57A)

General Procedure **4** was followed by using (*Z*)-1,3-diphenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56A**) (86 mg, 0.24 mmol) and NaH (% 60 in oil) (9.5 mg, 0.24 mmol) were employed to afford 41 mg (48 %) of the indicated product of phenyl(2-phenyl-4-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrol-3-yl)methanone (**57A**) as brown solid (R_f = 0.47 in 4:1 hexane/ethyl acetate); mp 116.5-117.0 °C.

57A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.55 (dd, *J* = 5.1, 3.2 Hz, 2H), 7.33–7.27 (m, 2H), 7.23–7.16 (m, 4H), 7.09–7.02 (m, 7H), 6.93 (s, 1H), 3.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 194.5 (C=O), 139.3 (C), 137.0 (C), 132.0 (C), 131.8 (C), 131.6 (CH), 129.7 (CH), 128.3 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 123.9 (CH), 122.7 (C), 119.1 (C), 117.7 (CH), 88.4 (C), 81.3 (C), 17.2 (CH_2). (Note that two CH peaks overlap on each other); IR (neat): 3117, 2912, 2848, 2349, 2152, 1732, 1591, 1561, 1456, 1426, 1346, 1324, 1222, 906, 758, 742, 691, 658, 639, 608, 530, 467 cm^1; MS (ESI, m/z): 362.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{26}H_{20}NO$: 362.15394 $[M+H]^+$, found: 362.15394.

4.4.2 Synthesis of (2-(3-fluorophenyl)-4-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrol-3-yl)(phenyl)methanone (57B)

General Procedure **4** was followed by using (*Z*)-3-(3-fluorophenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56B**) (84 mg, 0.22 mmol) and NaH (% 60 in oil) (17.7 mg, 0.44 mmol) were employed to afford 21 mg (25 %) of the indicated product of (2-(3-fluorophenyl)-4-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrol-3-yl)(phenyl)methanone (**57B**) as yellow solid (R_f = 0.55 in 4:1 hexane/ethyl acetate); mp 146.1 -147.3 °C.

57B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.57 (dd, *J* = 8.1, 1.1 Hz, 2H), 7.33-7.23 (m, 3H), 7.20-7.18 (m, 3H), 7.13-7.08 (m, 2H), 7.02-6.95 (m, 1H), 6.93 (s, 1H), 6.86-6.83 (m, 1H), 6.82-6.77 (m, 1H), 6.72 (tdd, *J* = 8.5, 2.5, 0.8 Hz, 1H), 3.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 194.1 (C=O), 162.4 (d, ^1J = 246.6 Hz, CF), 139.2 (C), 135.2 (d, ^4J = 1.92 Hz, C), 134.0 (d, ^3J = 8.31 Hz, C), 132.0 (C), 131.6 (CH), 129.8 (d, ^3J = 8.68 Hz, CH), 129.6 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 123.9 (d, ^4J = 2.76 Hz, CH), 123.8 (CH), 122.8 (C), 119.7 (C), 118.0 (CH), 114.9 (d, ^2J = 22.7 Hz, CH), 114.5 (d, ^2J = 21.0 Hz, CH), 88.1 (C), 81.5 (C), 17.4 (CH_2). (Note that two CH peaks overlap on each other); IR (neat): 3188, 2917, 2849, 2341, 1733, 1585, 1486, 1453, 1426, 1406, 1327, 1262, 1208, 1154, 935, 912, 849, 783, 773, 754, 741, 686, 671, 660, 641, 605, 576, 528, 450 cm^{-1}; MS (ESI, m/z): 380.14 [M+H]$^+$; HRMS (ESI) calcd. for $C_{26}H_{19}FNO$: 380.14452 [M+H]$^+$, found: 380.14430.

4.4.3 Synthesis of 2-(4-methoxyphenyl)-4-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrol- 3-yl)(phenyl)methanone (57C)

General Procedure **4** was followed by using (*Z*)-3-(4-methoxyphenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56C**) (66 mg, 0.17 mmol) and NaH (% 60 in oil) (13.5 mg, 0.34 mmol) were employed to afford 34 mg (52 %) of the indicated product of 2-(4-methoxyphenyl)-4-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrol-3-yl)(phenyl)methanone (**57C**) as yellow solid (R_f = 0.27 in 4:1 hexane/ethyl acetate); mp 126.1-127.0°C.

57C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.67–7.63 (m, 2H), 7.43–7.38 (m, 2H), 7.31–7.27 (m, 4H), 7.18 (t, *J* = 7.7 Hz, 2H), 7.15-7.13 (m, 2H), 7.11 (s, 1H), 7.02 (d, *J* = 1.2 Hz, 2H), 3.87 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 193.8 (C=O), 159.0 (C), 139.3 (C), 137.1 (C), 131.7 (C), 131.6 (CH), 129.7 (CH), 129.6 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 124.7 (CH), 123.9 (C), 122.7 (C) 118.7 (C), 117.1 (CH), 113.8 (CH), 88.5 (C), 81.1 (C), 55.3 (OCH_3), 17.4 (CH_2); IR (neat): 3117, 2985, 2363, 2240, 1700, 1592, 1562, 1528, 1491, 1449, 1438,1407, 1326, 1286, 1247, 1173, 1028, 907, 833, 756, 745, 693, 669, 596, 575, 529, 514, 493, 471, 449, 418 cm^{-1}; MS (ESI, m/z): 392.16 [M+H]$^+$; HRMS (ESI) calcd. for $C_{27}H_{22}NO_2$: 392.16451 [M+H]$^+$, found: 392.16501.

4.4.4 Synthesis of (4-chlorophenyl)(2-phenyl-4-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrol-3-yl)methanone (57D)

General Procedure **4** was followed by using (*Z*)-1-(4-chlorophenyl)-3-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56D**) (80 mg, 0.20 mmol) and NaH (% 60 in oil) (16.2 mg, 0.40 mmol) were employed to afford 38 mg (48 %) of the indicated product of (4-chlorophenyl)(2-phenyl-4-(3-phenylprop-2-yn-

1-yl)-1*H*-pyrrol-3-yl)methanone (**57D**) as orange solid (R_f = 0.48 in 4:1 hexane/ethyl acetate); mp: 137.0-138.0 °C.

57D: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.31–7.25 (m, 2H), 7.22–7.16 (m, 4H), 7.10–6.95 (m, 7H), 6.89 (s, 1H), 3.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 193.0 (C=O), 138.0 (C), 137.6 (CCl), 137.0 (C), 131.8 (C), 131.6 (CH), 131.1(CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 123.8 (C), 122.8 (C), 118.8 (C), 117.8 (CH), 88.4 (C), 81.6 (C), 17.2 (CH_2); IR (neat): 3201, 3050, 2574, 2181, 1727, 1585, 1561, 1487, 1453, 1428, 1326, 1222, 1084, 1012, 954, 910, 841, 754 cm^{-1}; MS (ESI, m/z): 396.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{26}H_{19}ClNO$: 396.11497 $[M+H]^+$, found: 396.11564.

4.4.5 Synthesis of (2-(4-bromophenyl)-4-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrol-3-yl)(phenyl)methanone (57E)

General Procedure **4** was followed by using (*Z*)-3-(4-bromophenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56E**) (119 mg, 0.27 mmol) and NaH (% 60 in oil) (21.6 mg, 0.54 mmol) were employed to afford 22 mg (30 %) of the indicated product of (2-(4-bromophenyl)-4-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrol-3-yl)(phenyl)methanone (**57E**) as orange solid (R_f = 0.72 in 4:1 hexane/ethyl acetate); mp 160.0-161.6 °C.

57E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.65 (dd, *J* = 8.3, 1,3 Hz, 2H), 7.41–7.34 (m, 3H), 7.31–7.18 (m, 7H), 7.04 (d, *J* = 8.5 Hz, 2H), 7.01 (s, 1H), 3.81 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 194.0 (C=O), 139.1 (C), 135.0 (C), 132.1 (CH), 131.6 (C), 131.5 (C), 130.9 (C), 129.6 (CH), 129.5 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 123.7 (CH), 121.8 (CBr), 122.8 (C), 119.6 (C), 118.0 (CH), 88.1 (C), 81.7 (C), 17.2 (CH_2). (Note that two CH peaks overlap on each other); IR (neat): 3202, 2928, 2827, 2345, 2168, 1736, 1589, 1560, 1448, 1328, 1069, 1080, 946, 907, 828, 736, 713, 691, 665, 607, 525, 474, 452, 412 cm^{-1}; MS (ESI, m/z): 440.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{26}H_{19}BrNO$: 440.06445 $[M+H]^+$, found: 440.06472.

4.4.6 Synthesis of phenyl(4-(3-phenylprop-2-yn-1-yl)-2-(4-(trifluoromethyl)phenyl)-1*H*-pyrrol-3-yl)methanone (57F)

General Procedure **4** was followed by using (*Z*)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**56F**) (125 mg, 0.29 mmol) and NaH (% 60 in oil) (23.3 mg, 0.58 mmol) were employed to afford 32 mg (26%) of the indicated product of phenyl(4-(3-phenylprop-2-yn-1-yl)-2-(4-(trifluoromethyl)phenyl)-1*H*-pyrrol-3-yl)methanone (**57F**) as orange solid (R_f = 0.51 in 4:1 hexane/ethyl acetate); mp 138.0-139.7 °C.

56F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.78-7.74 (m, 1H), 7.70-7.62 (m, 2H), 7.40-7.33 (m, 4H), 7.31-7.28 (m, 5H), 7.21 (t, *J* = 7.7 Hz, 2H), 7.06 (s, 1H), 3.81 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 194.0 (C=O), 139.0 (C), 135.4 (C), 134.6 (C), 132.3 (CH), 131.7 (q, ^2J =12.6 Hz, C), 131.6 (C), 129.6 (CH), 128.4 (CH), 128.2 (C), 128.0 (CH), 126.9 (CH), 125.2 (q, ^3J = 3.7 Hz, CH), 123.7 (CH), 123.0 (C), 121.7 (q, ^1J = 270 Hz, CH), 120.3 (C), 118.4 (CH), 88.0 (C), 81.6 (C), 17.4 (CH_2); IR (neat): 3182, 3059, 2349, 2225, 1731, 1594, 1565, 1490, 1451, 1405, 1321, 1167, 1123, 1064, 1015, 908, 845, 753, 733, 691, 667 cm^{-1}; MS (ESI, m/z): 430.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{27}H_{19}F_3NO$: 430.14133 $[M+H]^+$, found: 430.14195.

4.4.7 Synthesis of phenyl(4-(3-phenylprop-2-yn-1-yl)-2-(thiophen-3-yl)-1*H*-pyrrol-3-yl)methanone (57G)

General Procedure **4** was followed by using (*Z*)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)-3-(thiophen-3-yl)prop-2-en-1-one (**56G**) (103 mg, 0.28 mmol) and NaH (% 60 in oil) (22.4 mg, 0.56 mmol) were employed to afford 31 mg (30 %) of the indicated product of phenyl(4-(3-phenylprop-2-yn-1-yl)-2-(thiophen-3-yl)-1*H*-pyrrol-3-yl)methanone (**57G**) as light brown (R_f = 0.39 in 4:1 hexane/ethyl acetate); mp 143.0-144.0 °C.

56G: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.73-7.66 (m, 2H), 7.42-7.35 (m, 2H), 7.32-7.22 (m, 6H), 7.15-7.13 (m, 1H), 7.10-7.07 (m, 1H), 6.93 (s, 1H), 6.89 (dd, $J = 5.0, 1.1$ Hz, 1H), 3.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 194.1 (C=O), 139.4 (C), 132.6 (C), 132.1 (CH), 131.9 (CH), 131.6 (CH), 129.9 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 125.6 (CH), 123.8 (C), 123.0 (CH), 122.2 (C), 119.2 (C), 117.2 (CH), 88.3 (C), 81.4 (C), 17.6 (CH_2); IR (neat): 3149, 3058, 2973, 2349, 2165, 1733, 1593, 1563, 1488, 1449, 1333, 1223, 1169, 1070, 936, 912, 853, 784, 742, 730, 687, 648, 520 cm^{-1}; MS (ESI, m/z): 368.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{18}NOS$: 368.11036 $[M+H]^+$, found: 368.11127.

4.5 General procedure 5. Synthesis of 1,4-Thiazepine

N-(2,4-pentadiynyl)-*β*-enaminone (0.25 mmol) in benzene (5.0 mL) was stirred at room temperature under argon and then Lawesson's reagent (0.25 mmol) was added to the reaction mixture. The resulting mixture was then refluxed (Note that reaction was continued until *N*-(2,4-pentadiynyl)-*β*-enaminone 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 (9:1 hexane/ethyl acetate as the eluent to afford the corresponding 1,4-thiazepine derivatives.

4.5.1 Synthesis of (*Z*)-5,7-diphenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (58A)

General Procedure **5** was followed by using (*Z*)-1,3-diphenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56A**) (90 mg, 0.25 mmol) and Lawesson's reagent (101 mg, 0.25 mmol) were employed to afford 58 mg (64%) of the indicated product of (*Z*)-5,7-diphenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58A**) as orange-brown solid (R_f = 0.53 in 4:1 hexane/ethyl acetate); mp 94.0-95.0 °C.

58A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.66 (dd, *J* = 6.8, 2.8 Hz, 2H), 7.44-7.30 (m, 8H), 7.22-7.18 (m, 3H), 6.87 (s, 1H), 5.71 (s, 1H), 4.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9 (C), 150.4 (C), 149.8 (C), 139.9 (C), 138.7 (C), 131.4 (CH), 130.5 (CH), 130.1 (CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 123.9 (C), 123.2 (CH), 103.6 (CH), 98.4 (C), 85.2 (C), 58.5 (CH_2). (Note that two CH peaks overlap on each other); IR (neat): 3021, 2917, 2849, 2240, 2051, 1607, 1569, 1486, 1323, 1293, 1246, 1174, 1158, 1112, 1067, 1025, 935, 915, 839, 814, 779, 755, 689, 663, 620, 572, 562, 526, 417 cm^{-1}; MS (ESI, m/z): 376.11 [M-H]$^-$; HRMS (ESI) calcd. for $C_{26}H_{18}NS$: 376.11654 [M-H]$^-$, found: 376.11743.

4.5.2 Synthesis of (*Z*)-5-(3-fluorophenyl)-7-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (58B)

General Procedure **5** was followed by using (*Z*)-3-(3-fluorophenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56B**) (140 mg, 0.37 mmol) and Lawesson's reagent (150 mg, 0.37 mmol) were employed to afford 80 mg (57%) of the indicated product of (*Z*)-5-(3-fluorophenyl)-7-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58B**) as reddish brown solid (R_f = 0.58 in 4:1 hexane/ethyl acetate); mp 44.1-45.1 °C.

58B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 6.2, 2.9 Hz, 2H), 7.51–7.42 (m, 2H), 7.39–7.26 (m, 7H), 7.24–7.16 (m, 3H), 7.06 (td, *J* = 8.3, 2.5 Hz, 1H), 6.80 (s, 1H), 5.69 (s, 1H), 4.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (d, ^4J = 2.23 Hz, CH), 161.8 (d, ^1J = 246.4 Hz, CF), 148.7 (C), 148.2 (C), 139.3 (d, ^3J = 7.01 Hz, C), 137.9 (C), 129.7 (C), 128.5 (CH), 128.3 (d, ^3J = 7.99 Hz, C) ,127.8 (CH), 127.3 (CH), 127.2 (CH), 126.7 (CH), 122.4 (d, ^4J = 2.73 Hz, CH) 122.2 (CH), 122.0 (C), 116.3 (d, ^2J = 21.4 Hz, CH), 113.5 (d, ^2J = 22.7 Hz, CH), 102.8 (CH), 94.5 (C), 84.1 (C), 57.5 (CH_2); IR (neat): 3026, 2961, 2849, 2192, 1733, 1577, 1485, 1440, 1296, 1259, 1172, 1023, 937, 875, 789, 754, 686, 616, 568, 524, 480 cm^{-1}; MS (ESI, m/z): 394.10 [M+H]$^+$; HRMS (ESI) calcd. for $C_{26}H_{19}FNS$: 394.10712 [M+H]$^+$, found: 394.10783.

4.5.3 Synthesis of (*Z*)-7-(2-bromophenyl)-5-(4-chlorophenyl)-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (58C)

General Procedure **5** was followed by using (*Z*)-1-(2-bromophenyl)-3-(4-chlorophenyl)-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56C**) (140 mg, 0.37 mmol) and Lawesson's reagent (150 mg, 0.37 mmol) were employed to afford 80 mg (57%) of the indicated product of (*Z*)-7-(2-bromophenyl)-5-(4-chlorophenyl)-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58C**) as reddish orange solid (R_f = 0.55 in 4:1 hexane/ethyl acetate); mp 87.2-88.1 °C.

58C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dt, *J* = 9.1, 2.3 Hz, 3H), 7.72 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.52 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.47 – 7.41 (m, 3H), 7.36 – 7.29 (m, 3H), 6.69 (s, 1H), 5.78 (s, 1H), 4.98 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (C), 150.7 (C), 149.5 (C), 140.5 (C), 137.0 (C), 136.8 (CCl), 133.4 (CH), 131.5 (CH), 130.8 (CH), 130.5 (CH), 129.0 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 126.4 (CBr), 123.0 (C), 122.5 (CH), 104.2 (CH), 98.6 (C), 85.0 (C), 58.5 (CH_2); IR (neat): 3053, 2926, 2848, 2201, 1732, 1610, 1590, 1486, 1462, 1398, 1370, 1239, 1174, 1089, 1045, 1011, 932, 829, 754, 733, 688, 644, 527, 502, 478, 444 cm^{-1}; MS (ESI, m/z): 487.98 [M-H]$^-$; HRMS (ESI) calcd. for $C_{26}H_{16}BrClNS$: 487.98808 [M-H]$^-$, found: 487.98808.

4.5.4 Synthesis of (*Z*)-5-(4-methoxyphenyl)-7-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (58D)

General Procedure **5** was followed by using (*Z*)-3-(4-methoxyphenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56D**) (86 mg, 0.22 mmol) and Lawesson's reagent (89 mg, 0.22 mmol) were employed to afford 37 mg (43%) of the indicated product of (*Z*)-5-(4-methoxyphenyl)-7-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58D**) as orange-yellow solid (R_f = 0.37 in 4:1 hexane/ethyl acetate); mp 58.0-59.0 °C.

58D: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.9 Hz, 2H), 7.67–7.64 (m, 2H), 7.38–7.34 (m, 3H), 7.29 (d, *J* = 4.6 Hz, 1H), 7.22–7.19 (m, 3H), 6.89 – 6.84 (m, 3H), 5.70 (s, 1H), 4.75 (s, 1H), 4.62 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C), 161.6 (C), 151.0 (C), 149.2 (C), 140.9 (C), 131.4 (CH), 130.0 (CH), 129.3 (CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 127.9 (CH), 127.6 (C), 126.9 (CH), 124.1 (CH), 123.2 (C), 113.8 (CH), 103.0 (CH), 98.5 (C), 85.2 (C), 65.2 (OCH3), 55.6 (CH_2); IR (neat): 3056, 3023, 2926, 2842, 2191, 1718, 1594, 1567, 1508, 1486, 1441, 1332, 1296, 1247, 1167, 1111, 1080, 1025, 934, 830, 756, 687, 614, 570, 527, 474 cm^{-1}; MS (ESI, m/z): 408.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{27}H_{22}NOS$: 408.14166 $[M+H]^+$, found: 408.14107.

4.5.5 Synthesis of (*Z*)-7-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-5-(*p*-tolyl)-2,3-dihydro-1,4-thiazepine (58E)

General Procedure **5** was followed by using (*Z*)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)-3-(*p*-tolyl)prop-2-en-1-one (**56E**) (91mg, 0.24 mmol) and Lawesson's reagent (98 mg, 0.24 mmol) were employed to afford 23 mg (25%) of the indicated product of (*Z*)-7-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-5-(*p*-tolyl)-2,3-dihydro-1,4-thiazepine (**58E**) as dark brown solid (R_f = 0.56 in 4:1 hexane/ethyl acetate); mp 78.8-79.5 °C.

58E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.71 (m, 4H), 7.52-7.44 (m, 6H), 7.36-7.25 (m, 4H), 6.98 (s, 1H), 5.81 (s, 1H), 4.89 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7 (C), 150.4 (C), 149.6 (C), 140.9 (C), 139.9 (C), 135.8 (C), 131.4 (CH), 130.0 (CH), 129.2 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 124.0 (C), 123.2 (CH), 103.3 (CH), 98.5 (C), 85.4 (C), 58.0 (CH_2), 21.6 (CH_3); IR (neat): 3025, 2993, 2846, 2341, 2180, 2161, 2027, 1979, 1737, 1600, 1564, 1486, 1441, 1293, 1249, 1179, 1112, 1082, 1018, 933, 855, 823, 802, 762, 750, 683, 660, 568, 527, 503, 476, 435, 422 cm^{-1}; MS (ESI, m/z): 390.13 [M-H]; HRMS (ESI) calcd. for $C_{27}H_{20}NS$: 390.13219 [M-H]$^-$, found: 390.13071.

4.5.6 Synthesis of (*Z*)-5,7-diphenyl-2-(3-(*p*-tolyl)prop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (58F)

General Procedure **5** was followed by using (*Z*)-1,3-diphenyl-3-((5-(*p*-tolyl)penta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56F**) (113 mg, 0.38 mmol) and Lawesson's reagent (153 mg, 0.38 mmol) were employed to afford 34 mg (30%) of the indicated product of (*Z*)-5,7-diphenyl-2-(3-(*p*-tolyl)prop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58F**) as dark brown solid (R_f = 0.56 in 4:1 hexane/ethyl acetate); mp 75.5-76.5 ^oC.

58F: ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.75 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.52 – 7.41 (m, 6H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.94 (s, 1H), 5.79 (s, 1H), 4.88 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.9 (C), 150.0 (C), 149.8 (C), 139.9 (C), 138.7 (C), 138.5 (C), 131.3 (CH), 130.5 (CH), 130.0 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 123.7 (C), 120.0 (CH), 103.8 (CH), 98.8 (C), 84.6 (C), 58.6 (CH_2), 21.6 (CH_3); IR (neat): 3023, 2917, 2848, 2345, 2190, 1734, 1563, 1489, 1442, 1294, 1242, 1176, 1097, 1026, 934, 813, 753, 690, 753, 690, 558, 525 cm^{-1}; MS (ESI, m/z): 392.14 [M+H]$^+$; HRMS (ESI) calcd. for $C_{27}H_{22}NS$: 392.14675 [M+H]$^+$, found: 392.14808.

4.5.7 Synthesis of (*Z*)-7-(4-chlorophenyl)-5-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (58G)

General Procedure **5** was followed by using (*Z*)-1-(4-chlorophenyl)-3-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56G**) (64 mg, 0.16 mmol) and Lawesson's Reagent (65 mg, 0.16 mmol) were employed to afford 15 mg (23%) of the indicated product of (*Z*)-7-(4-chlorophenyl)-5-phenyl-2-(3-

phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58G**) as orange-brown solid (R_f = 0.50 in 4:1 hexane/ethyl acetate); mp 68.1-69.2 ^{o}C.

58G: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.48–7.39 (m, 7H), 7.31–7.27 (m, 3H), 6.92 (s, 1H), 5.79 (s, 1H), 4.86 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7 (C), 150.2 (C), 150.1 (C), 138.6 (C), 138.3 (CCl), 136.0 (C), 131.4 (CH), 130.5 (CH), 129.1 (CH), 129.0 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 124.3 (C), 123.1 (CH), 103.9 (CH), 98.5 (C), 84.9 (C), 58.3 (CH_2); IR (neat): 3055, 3019, 2930, 2849, 2012, 1973, 1734, 1655, 1569, 1484, 1441, 1398, 1294, 1253, 1175, 1088, 1011, 905, 823, 753, 727, 687, 524, 468, 407 cm^{-1}; MS (ESI, m/z): 412.09 [M+H]$^+$; HRMS (ESI) calcd. for $C_{26}H_{19}ClNS$: 412.09212 [M+H]$^+$, found: 412.09324.

4.5.8 Synthesis of (*Z*)-7-(4-chlorophenyl)-5-(4-fluoro-3-methylphenyl)-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (58H)

General Procedure **5** was followed by using (*Z*)-1-(4-chlorophenyl)-3-(4-fluoro-3-methylphenyl)-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56H**) (88 mg, 0.21 mmol) and Lawesson's reagent (83 mg, 0.21 mmol) were employed to afford 43 mg (49%) of the indicated product of (*Z*)-7-(4-chlorophenyl)-5-(4-fluoro-3-methylphenyl)-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58H**) as orange-brown solid (R_f = 0.66 in 4:1 hexane/ethyl acetate); mp 79.8-80.1 ^{o}C.

58H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.5 Hz, 2H), 7.50 – 7.43 (m, 1H), 7.40 – 7.30 (m, 4H), 7.24 – 7.19 (m, 3H), 6.97 (t, *J* = 8.9 Hz, 1H), 6.80 (s, 1H), 5.70 (s, 1H), 4.75 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (C), 162.9 (d, ^1J = 257.8 Hz, CF), 150.3 (C), 148.2 (C), 138.2 (CCl), 136.1 (C), 134.6 (d, ^4J = 2.72 Hz, C), 131.4 (CH), 130.9 (d, ^3J = 5.8 Hz, CH), 129.1 (CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 127.0 (d, ^3J = 8.7 Hz, CH), 125.2 (d, ^2J = 17.7 Hz, C), 124.1 (C), 123.1 (CH), 115.0 (d, ^2J = 22.7 Hz, CH), 103.6 (CH), 98.5 (C), 84.6 (C), 58.6 (CH_2), 14.5 (d, ^3J = 3.4 Hz, CH_3); IR (neat): 3023, 2922, 2848, 2196, 2016, 1702, 1587, 1484, 1441, 1397, 1322, 1296, 1251, 1158, 1113, 1090, 1011, 933, 908, 813, 751, 686, 632, 591, 565, 525, 472, 452 cm^{-1}; MS (ESI, m/z): 442.08 [M-H]$^-$; HRMS (ESI) calcd. for $C_{27}H_{18}ClFNS$: 442.08380 [M-H]$^-$, found: 442.08552.

4.5.9 Synthesis of (*Z*)-7-(2-bromophenyl)-5-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (58I)

General Procedure **5** was followed by using (*Z*)-1-(2-bromophenyl)-3-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56I**) (114 mg, 0.26 mmol) and Lawesson's reagent (105 mg, 0.26 mmol) were employed to afford 43 mg (46%) of the indicated product of (*Z*)-7-(2-bromophenyl)-5-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58I**) as orange solid (R_f=0.52 in 4:1 hexane/ethyl acetate); mp 68.1-69.0 °C.

58I: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.59 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.43–7.26 (m, 7H), 7.24–7.13 (m, 4H), 6.67 (s, 1H), 5.71 (s, 1H), 4.91 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C), 151.2 (C), 148.6 (C), 140.6 (C), 138.6 (C), 133.3 (CH), 131.4 (CH), 130.8 (CH), 130.4 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CBr), 123.0 (C), 122.6 (CH), 103.6 (CH), 98.2 (C), 85.1 (C), 58.3 (CH_2). (Note that two CH peaks overlap on each other); IR (neat): 3026, 2923, 2850, 2160, 1721, 1609, 1595, 1570, 1486, 1461, 1441, 1323, 1294, 1244, 1114, 1024, 933, 817, 751, 686, 584, 525, 439 cm^{-1}; MS (ESI, m/z): 454.02 [M-H]$^-$; HRMS (ESI) calcd. for $C_{26}H_{17}BrNS$: 454.02706 [M-H]$^-$, found: 454.02588.

4.5.10 Synthesis of (*Z*)-7-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-5-(thiophen-3-yl)-2,3-dihydro-1,4-thiazepine (58J)

General Procedure **5** was followed by using (*Z*)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)-3-(thiophen-3-yl)prop-2-en-1-one (**56J**) (102 mg, 0.28 mmol) and Lawesson's reagent (112 mg, 0.28 mmol) were employed to afford 15 mg (15%) of the indicated product of (*Z*)-7-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-

5-(thiophen-3-yl)-2,3-dihydro-1,4-thiazepine (**58J**) as orange-brown solid (R_f = 0.50 in 4:1 hexane/ethyl acetate); mp: 95.0-95.0 ^{o}C. ^{1}H NMR (400 MHz, CDCl3) δ 7.70 (dd, J = 7.4, 2.0 Hz, 2H), 7.59 (d, J = 4.5 Hz, 1H), 7.48–7.39 (m, 6H), 7.35 (dd, J = 5.0, 2.9 Hz, 2H), 7.31–7.27 (m, 3H), 6.96 (s, 1H), 5.85 (s, 1H), 4.86 (s, 2H).^{13}C NMR (100 MHz, $CDCl_3$), δ 163.2 (C), 155.4 (C), 149.3 (C), 139.8 (C), 131.4 (CH), 130.6 (C), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 126.8 (CH), 126.3 (CH), 123.1 (C), 122.8 (CH), 104.6 (CH), 98.5 (C), 85.1 (C), 57.8 (CH_2). (Note that two CH peaks overlap on each other); IR (neat): 3020, 2916, 2847, 2189, 1593, 1565, 1486, 1441, 1414, 1294, 1247, 1176, 1081, 1023, 935, 909, 865, 840, 792, 754, 687, 614, 598, 526, 430 cm^{-1}; MS (ESI, m/z): 382.07 [M-H]$^{-}$; HRMS (ESI) calcd. for $C_{24}H_{16}NS_2$: 382.07296 [M-H]$^{-}$, found: 382.07176.

4.5.11 Synthesis of (*Z*)-5-(4-(*tert*-butyl)phenyl)-7-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (58K)

General Procedure **5** was followed by using (*Z*)-3-(4-(*tert*-butyl)phenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56K**) (110 mg, 0.26 mmol) and Lawesson's reagent (107 mg, 0.26 mmol) were employed to afford 40 mg (36%) of the indicated product of (*Z*)-5-(4-(*tert*-butyl)phenyl)-7-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58K**) as reddish brown solid (R_f = 0.61 in 4:1 hexane/ethyl acetate); mp 76.9-77.9 ^{o}C.

58K: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.70 (m, 4H), 7.50-7.41 (m, 7H), 7.30-7.26 (m, 3H), 6.97 (s, 1H), 5.79 (s, 1H), 4.87 (s, 2H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.6 (C), 153.9 (C), 150.7 (C), 149.2 (C), 139.9(C), 135.6 (C), 131.4 (CH), 129.9 (CH), 128.8 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH),127.5 (CH), 125.4 (CH), 124.2 (C), 123.2 (CH), 103.3 (CH), 98.2 (C), 85.4 (C), 58.3 (CH_2), 34.8 (C), 31.2 (CH_3); IR (neat): 2950, 2862, 2239, 2168, 2018, 1897, 1733, 1599, 1559, 1507, 1487, 1457, 1442, 1362, 1294, 1257, 1187, 1110, 1071, 1022, 934, 827, 753, 688, 553, 526, 468 cm^{-1}; MS (ESI, m/z): 434.19 [M+H]$^{+}$; HRMS (ESI) calcd. for $C_{30}H_{28}NS$: 434.19370 [M+H]$^{+}$, found: 434.19524.

4.5.12 Synthesis of (*Z*)-5-(4-bromophenyl)-7-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (58L)

General Procedure **5** was followed by using (*Z*)-3-(4-bromophenyl)-1-phenyl-3-((5-phenylpenta-2,4-diyn-1-yl)amino)prop-2-en-1-one (**56L**) (72 mg, 0.16 mmol) and Lawesson's reagent (66 mg, 0.16 mmol) were employed to afford 21 mg (30%) of the indicated product of (*Z*)-5-(4-bromophenyl)-7-phenyl-2-(3-phenylprop-2-yn-1-ylidene)-2,3-dihydro-1,4-thiazepine (**58L**) as orange-yellow solid (R_f = 0.60 in 4:1 hexane/ethyl acetate); mp 98.1-98.7 ^{o}C.

58L: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.65 (m, 4H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.46-7.42 (m, 5H), 7.31-7.26 (m, *J* = 7.7, 4.6 Hz, 3H), 6.88 (s, 1H), 5.78 (s, 1H), 4.86 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (C), 150.2 (C), 150.0 (C), 139.8 (C), 137.8 (C), 131.6 (CH), 131.4 (CH), 130.1 (CH), 129.2 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 124.9 (CBr), 123.2 (C), 123.1 (CH), 103.6 (CH), 98.2 (C), 85.2 (C), 58.6 (CH_2); IR (neat): 3020, 2923, 2868, 2349, 2138, 2029, 1742, 1606, 1485, 1441, 1392, 1325, 1295, 1254, 1174, 1069, 1007, 934, 918, 818, 757, 690, 526, 481, 422 cm^{-1}; MS (ESI, m/z): 456.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{26}H_{19}BrNS$: 456.04161 $[M+H]^+$, found: 456.0416.

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APPENDICES A

NMR SPECTRA

Bruker Spectrospin Avance DPX400 Ultrashield spectromer was employed for the records of ^{1}H, ^{13}C and NOESY NMR spectroscopy of synthesized compounds.

^{1}H and ^{13}C NMR spectra of all compounds are shown at below.

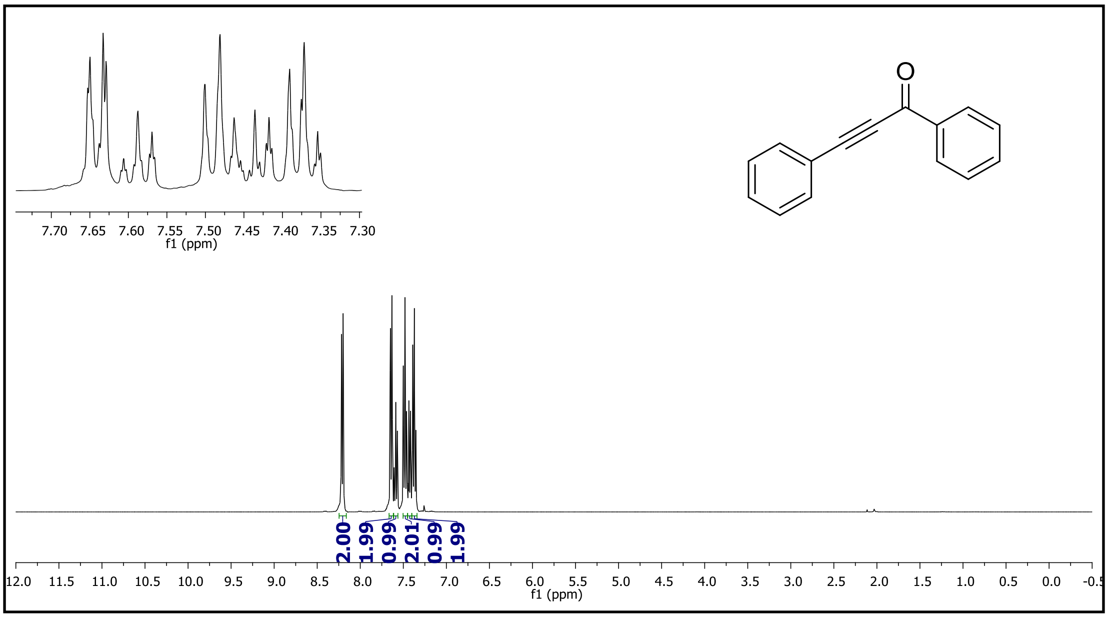

Figure 20. ^{1}H NMR spectrum of compound **61A**.

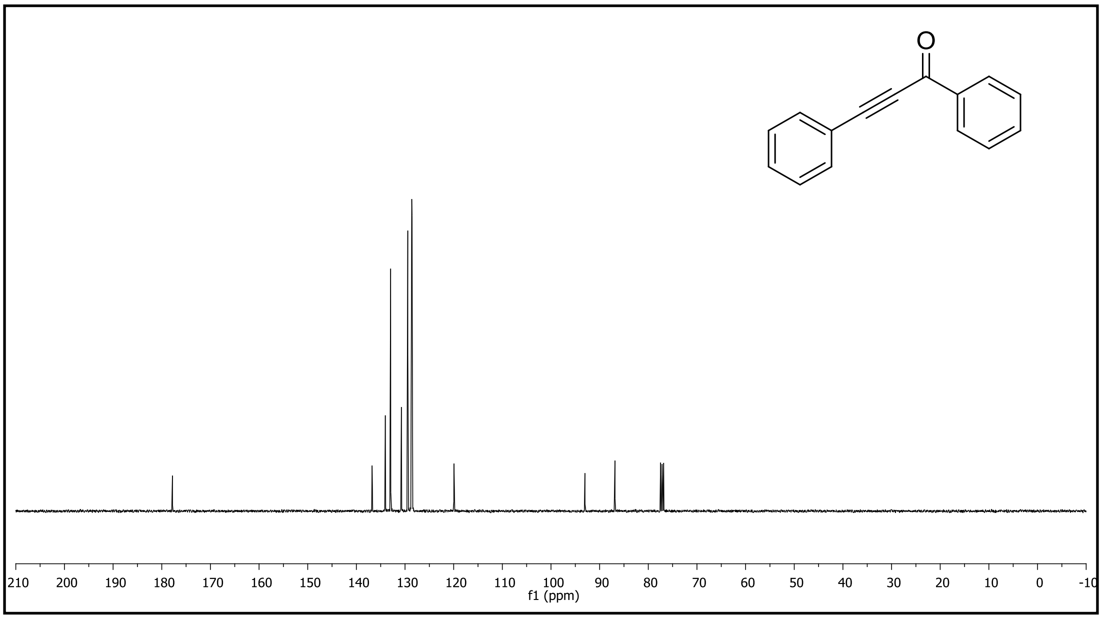

Figure 21. ^{13}C NMR spectrum of compound **61A**.

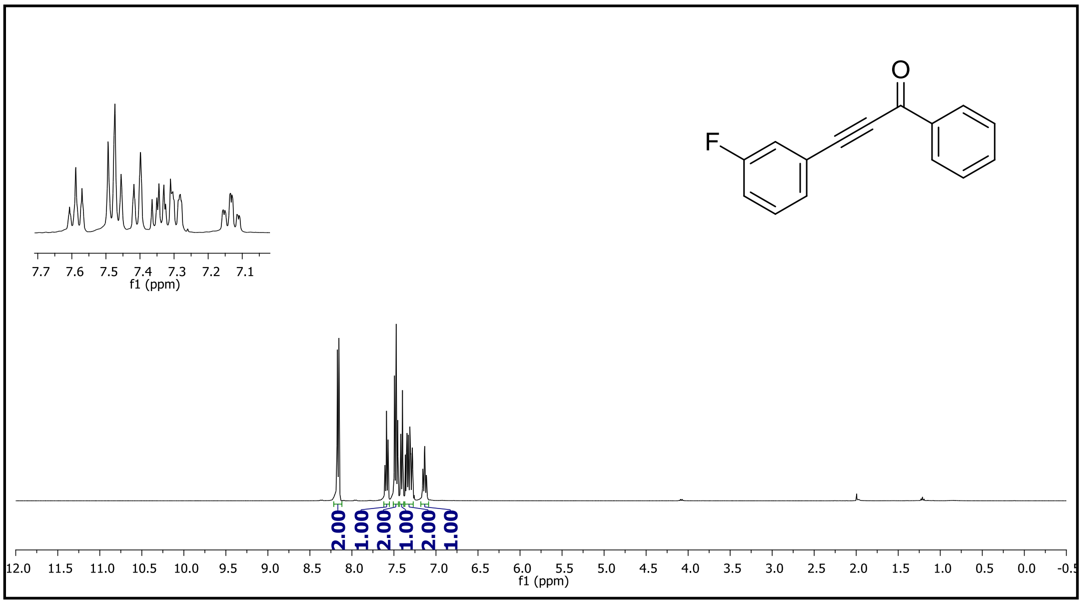

Figure 22. ^{1}H NMR spectrum of compound **61B**.

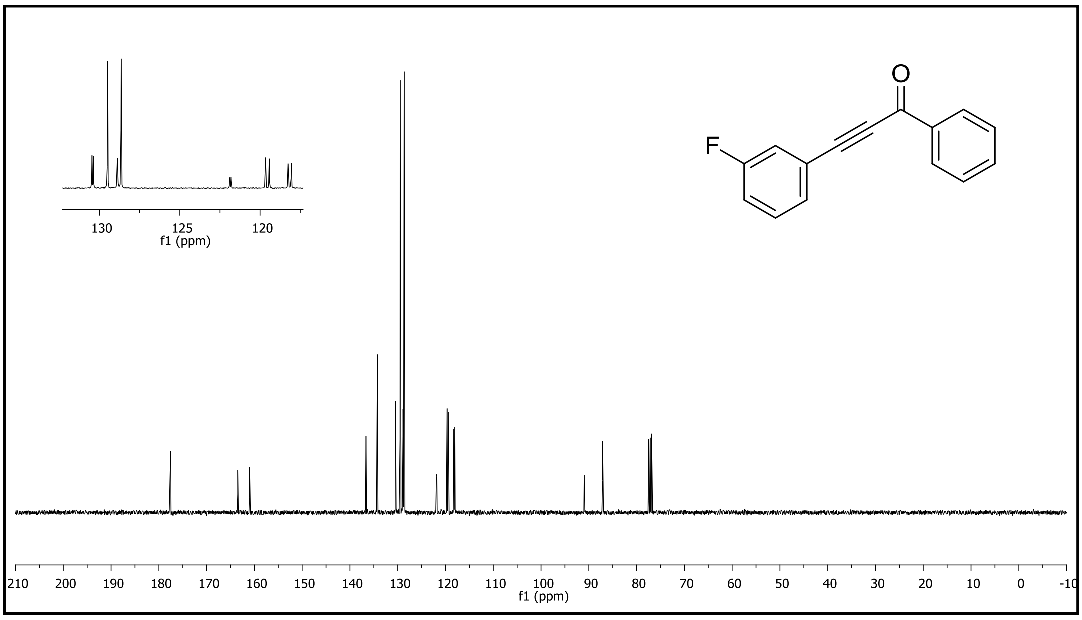

Figure 23. ^{13}C NMR spectrum of compound **61B**.

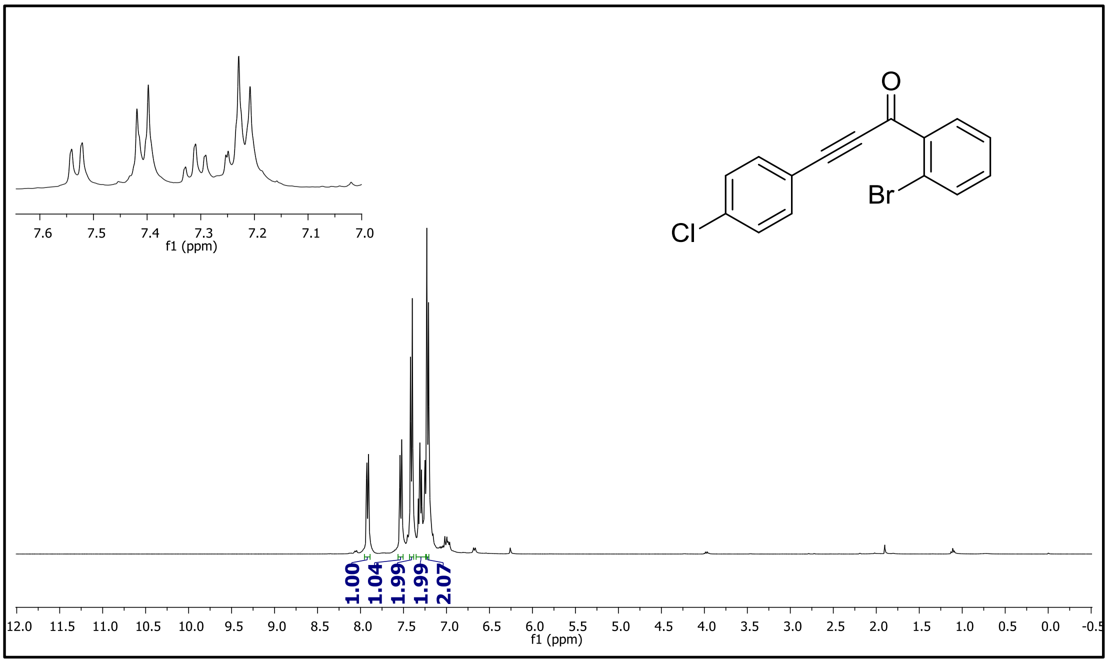

Figure 24. ^{1}H NMR spectrum of compound **61C**.

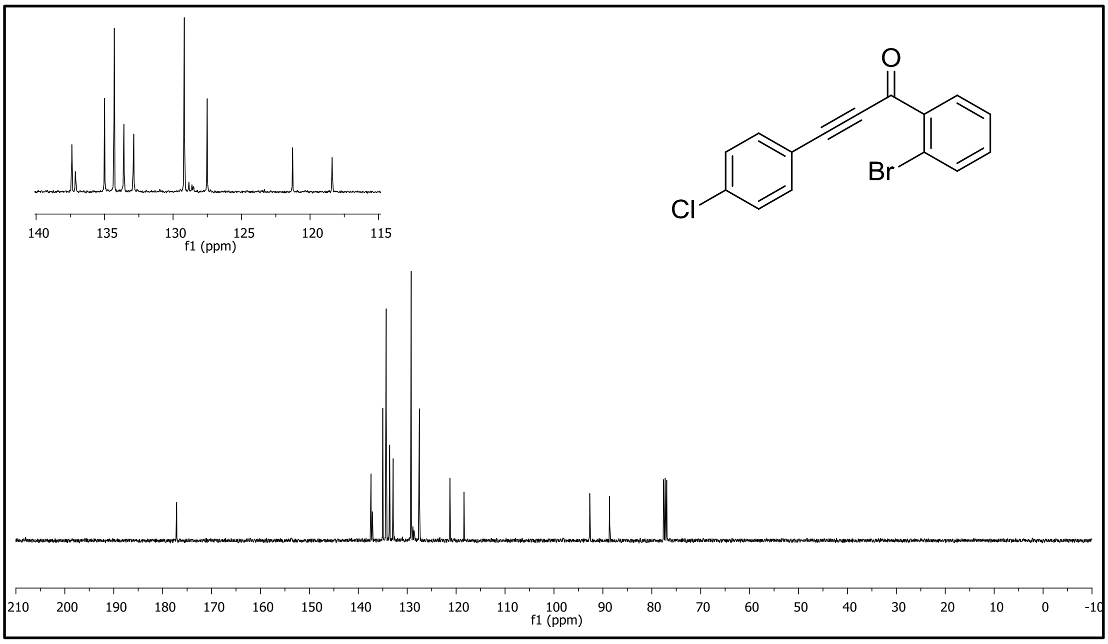

Figure 25. ^{13}C NMR spectrum of compound **61C**.

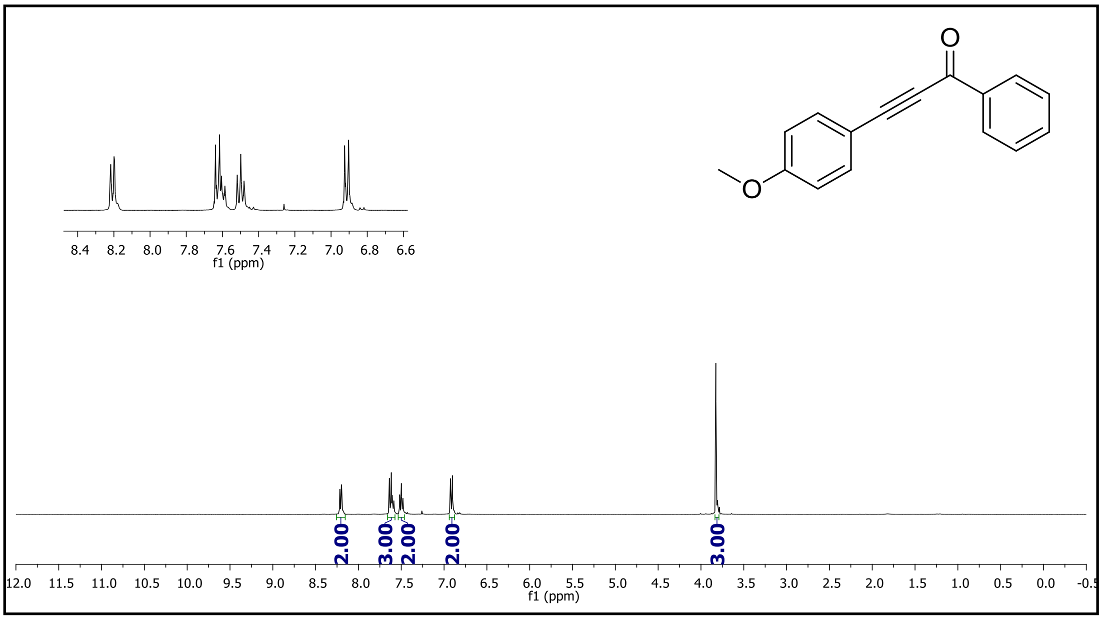

Figure 26. ^{1}H NMR spectrum of compound **61D**.

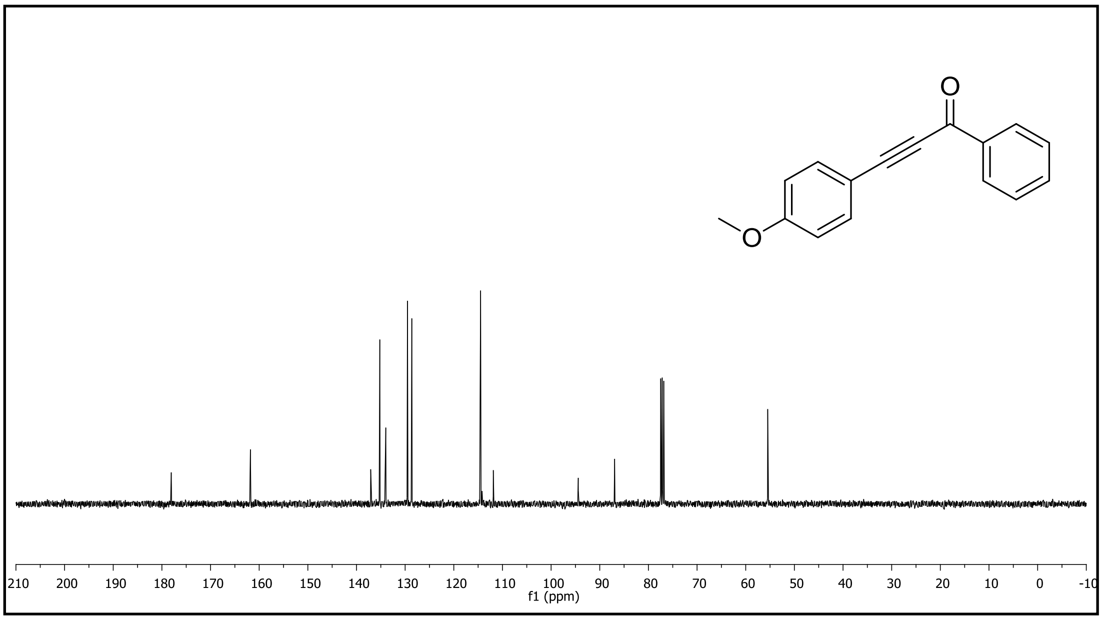

Figure 27. ^{13}C NMR spectrum of compound **61D**.

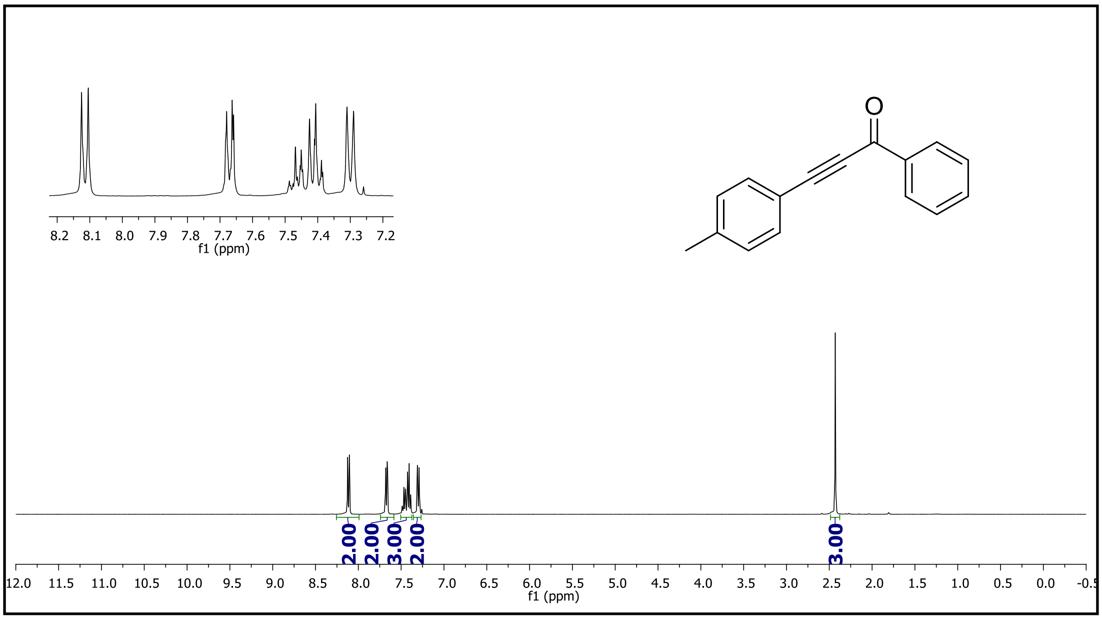

Figure 28. ^{1}H NMR spectrum of compound **61E**.

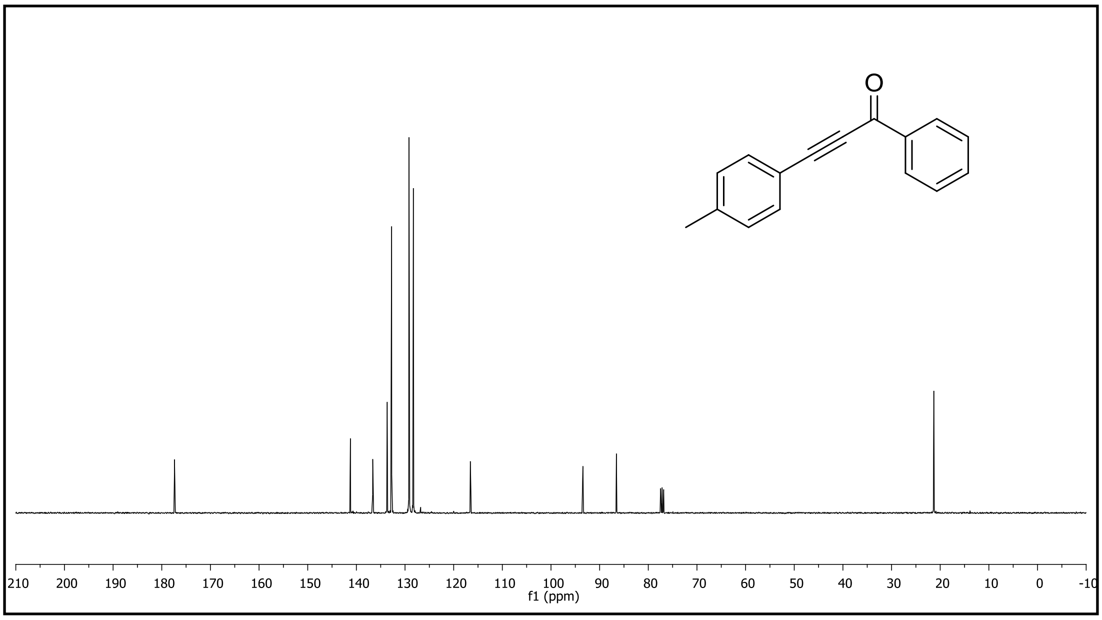

Figure 29. ^{13}C NMR spectrum of compound **61E**.

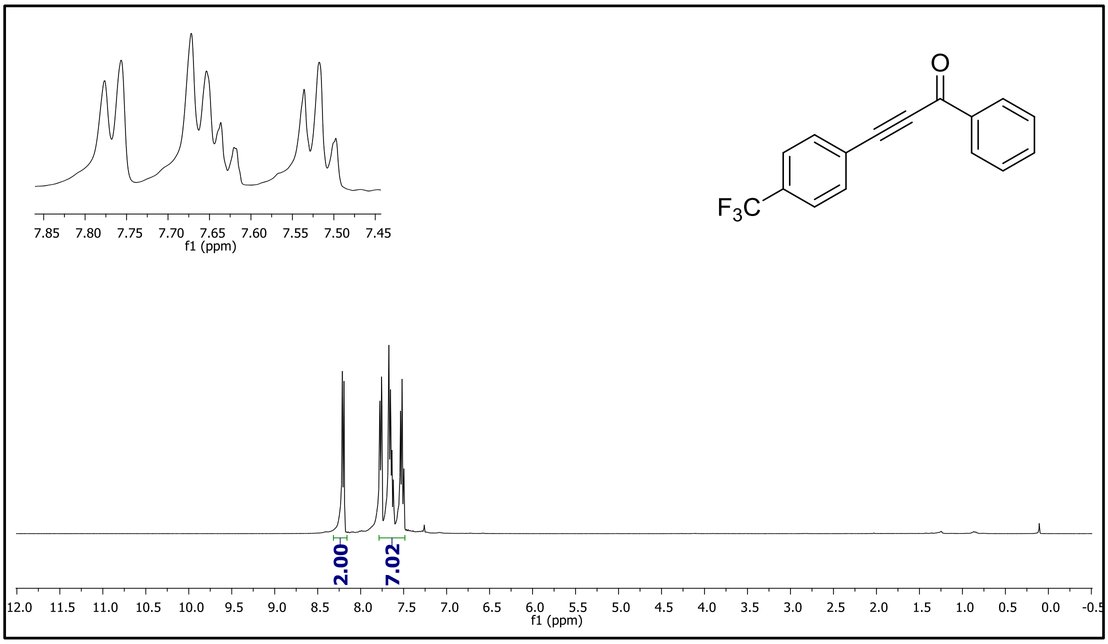

Figure 30. ^{1}H NMR spectrum of compound **61F**.

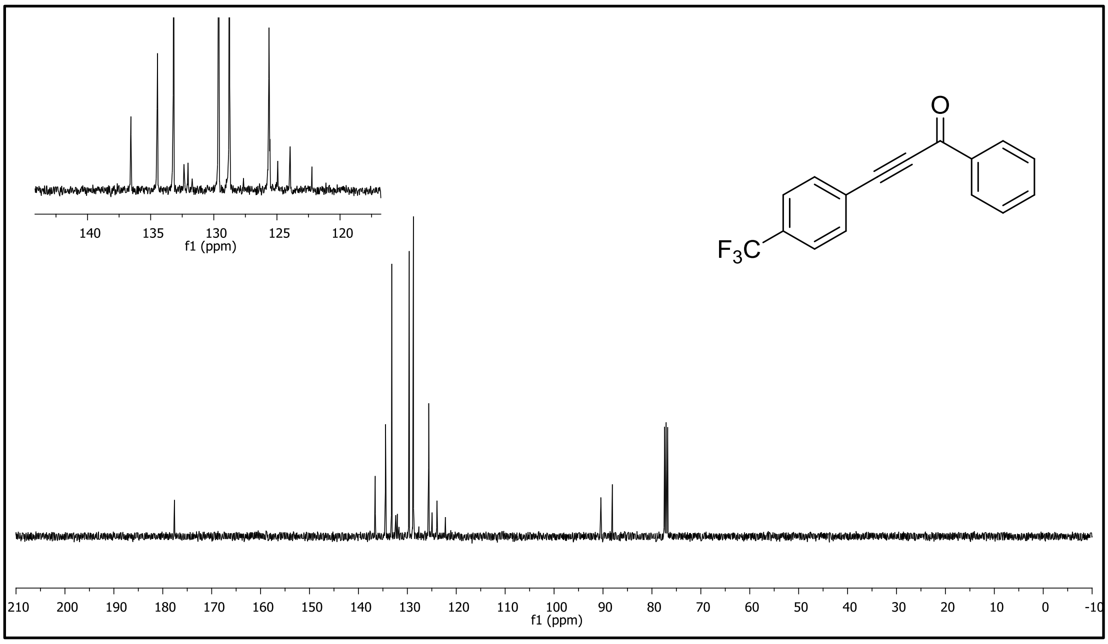

Figure 31. ^{13}C NMR spectrum of compound **61F**.

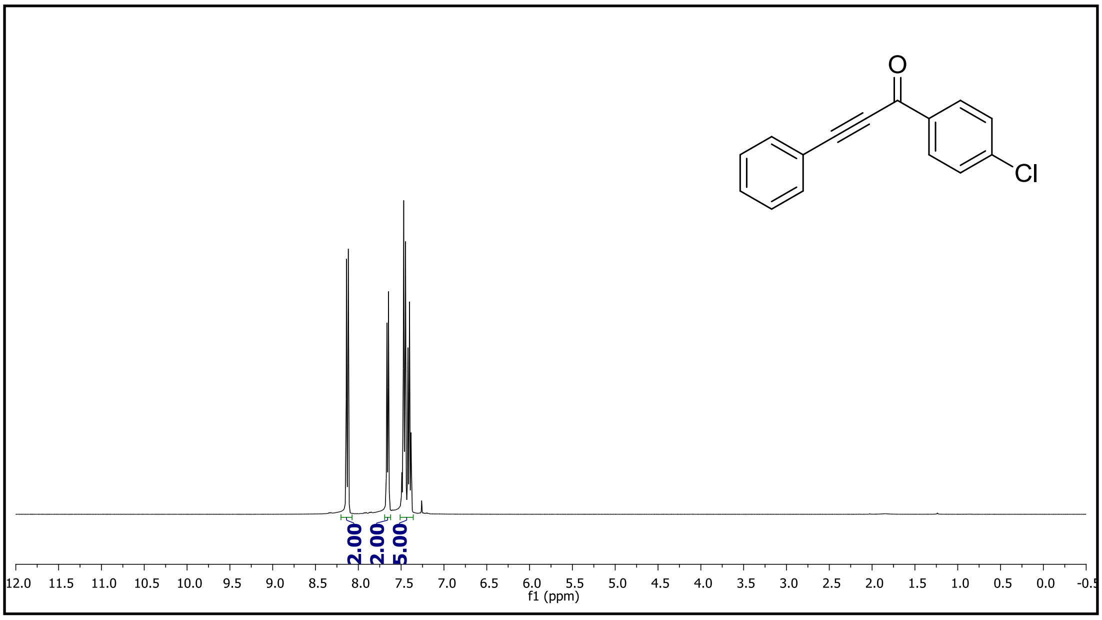

Figure 32. ^{1}H NMR spectrum of compound **61G**.

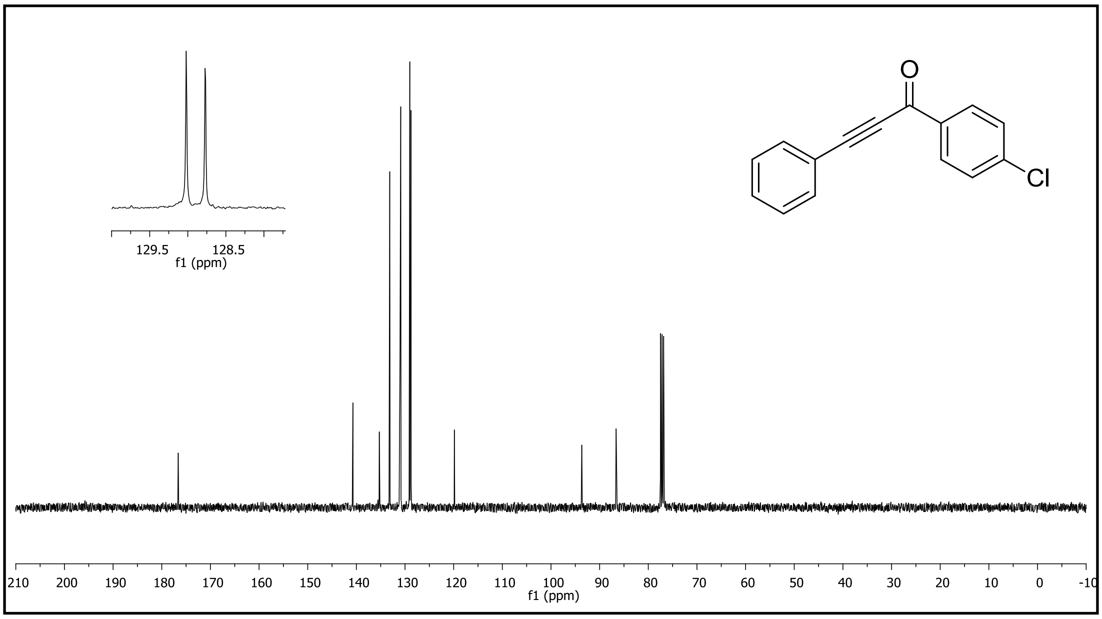

Figure 33. ^{13}C NMR spectrum of compound **61G**.

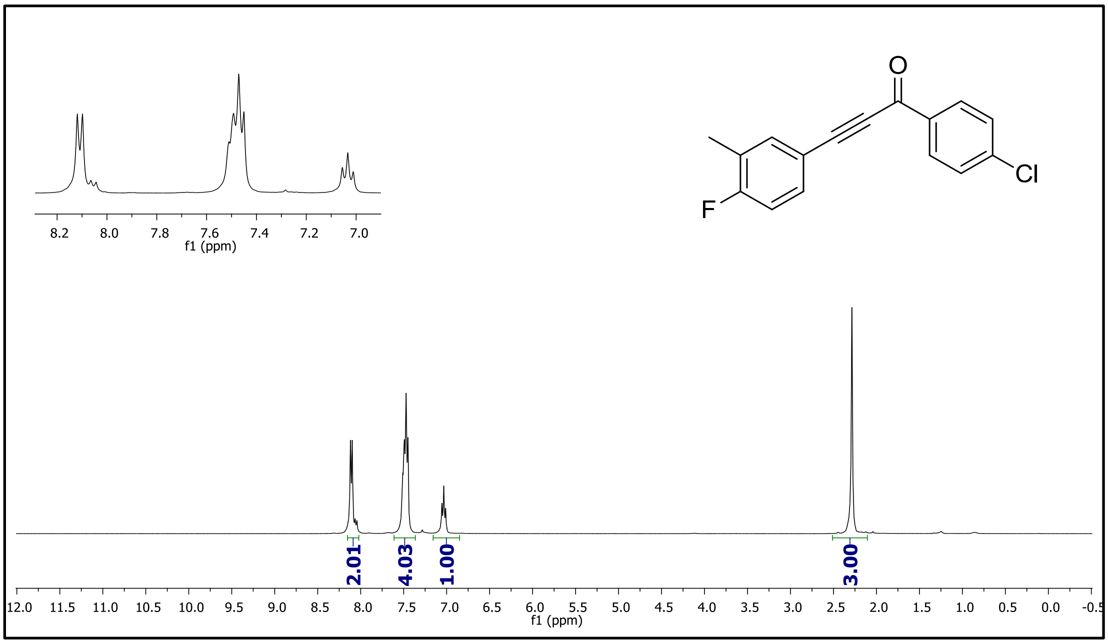

Figure 34. ^{1}H NMR spectrum of compound **61H**.

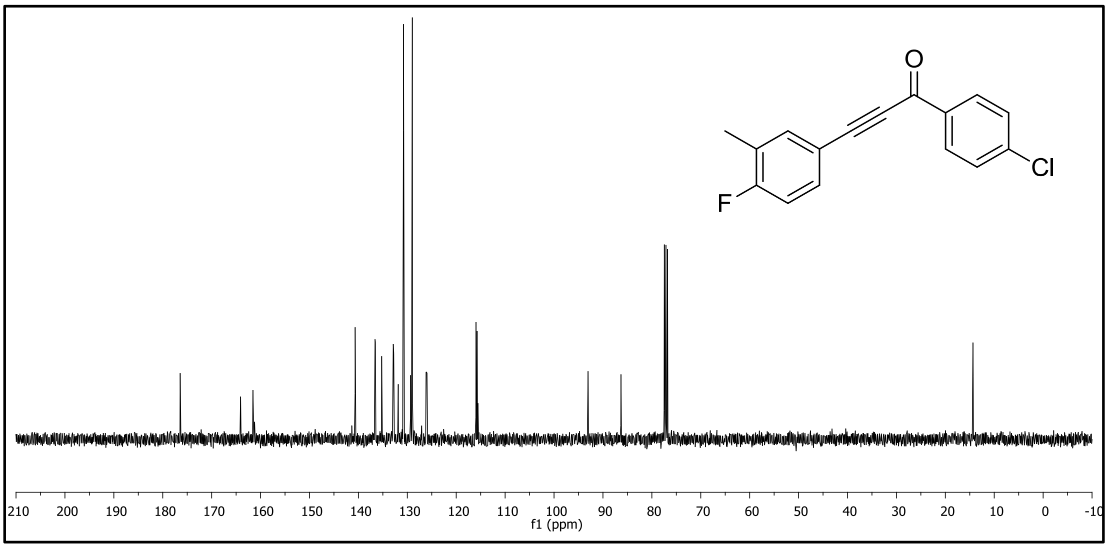

Figure 35. ^{13}C NMR spectrum of compound **61H**.

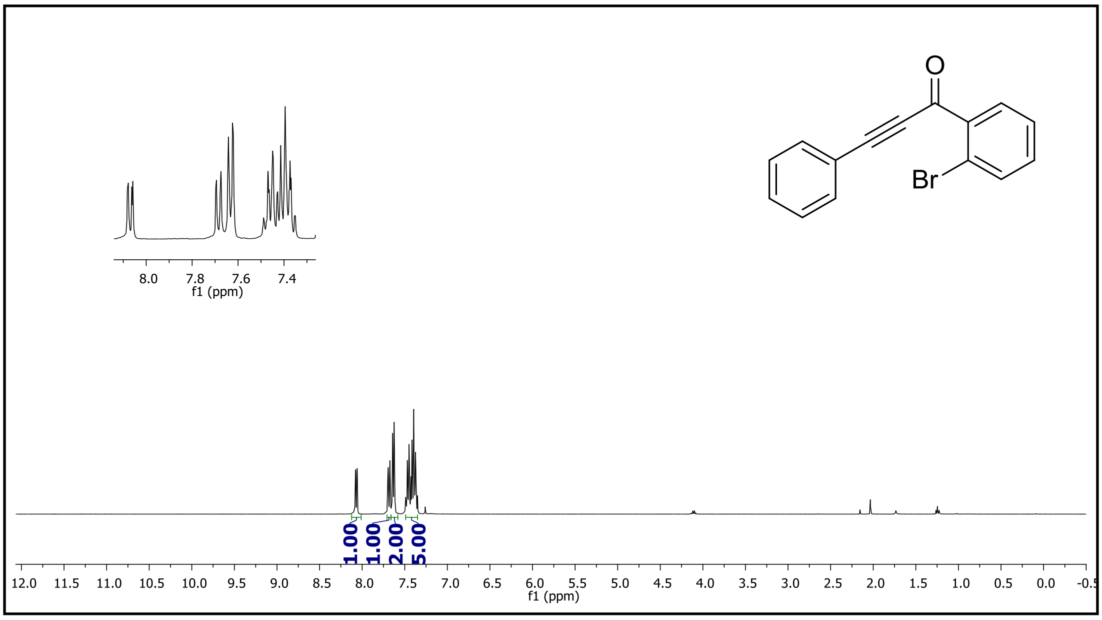

Figure 36. ^{1}H NMR spectrum of compound **61I**.

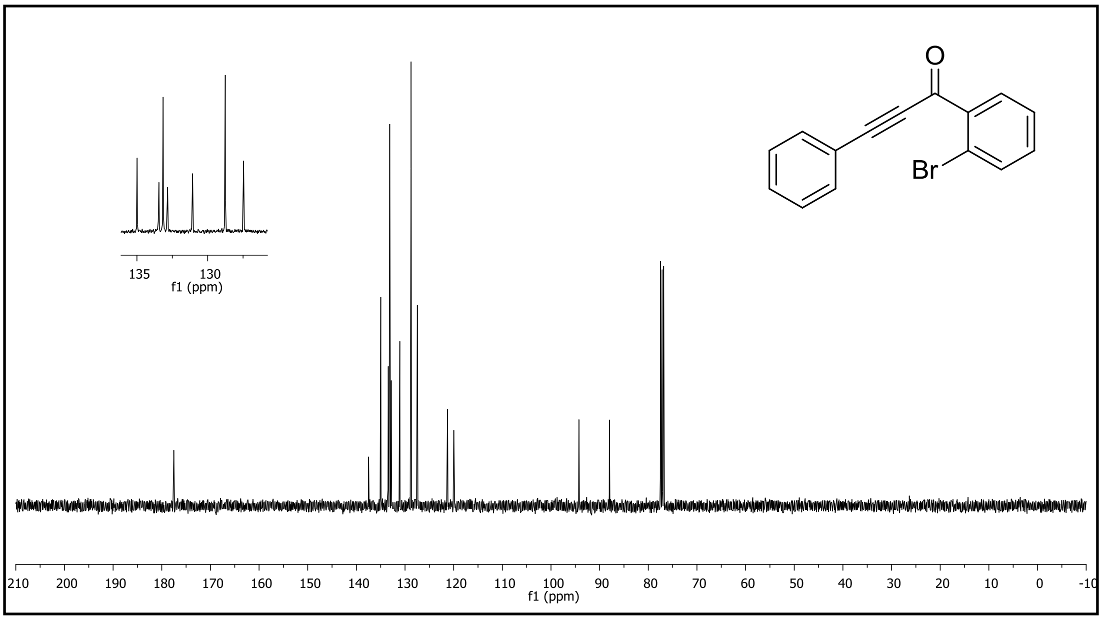

Figure 37. ^{13}C NMR spectrum of compound **61I**.

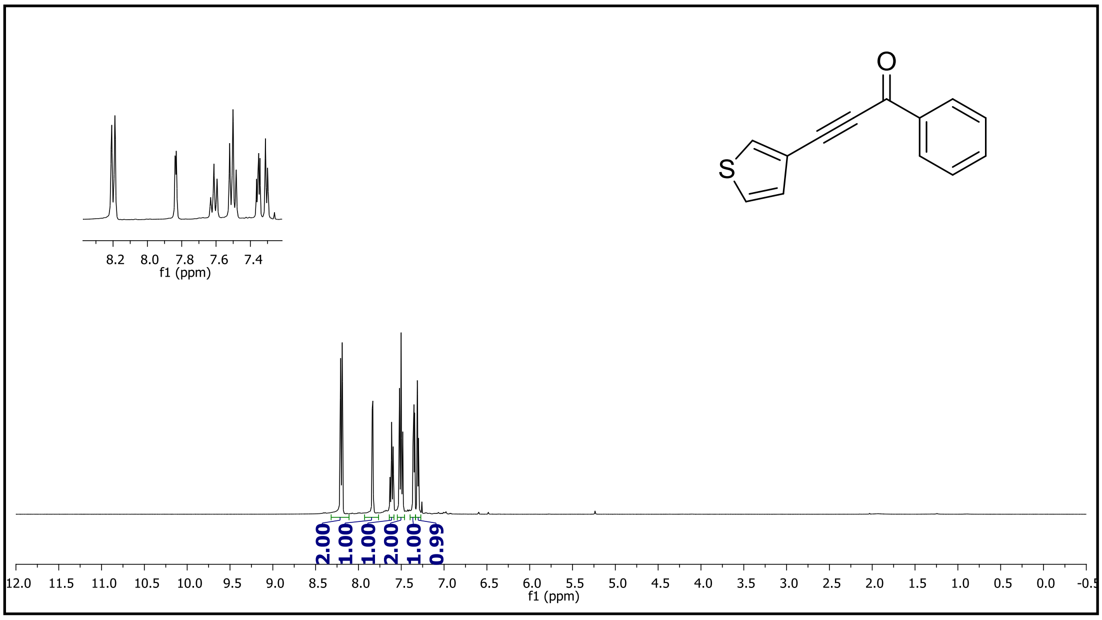

Figure 38. ^{1}H NMR spectrum of compound **61J**.

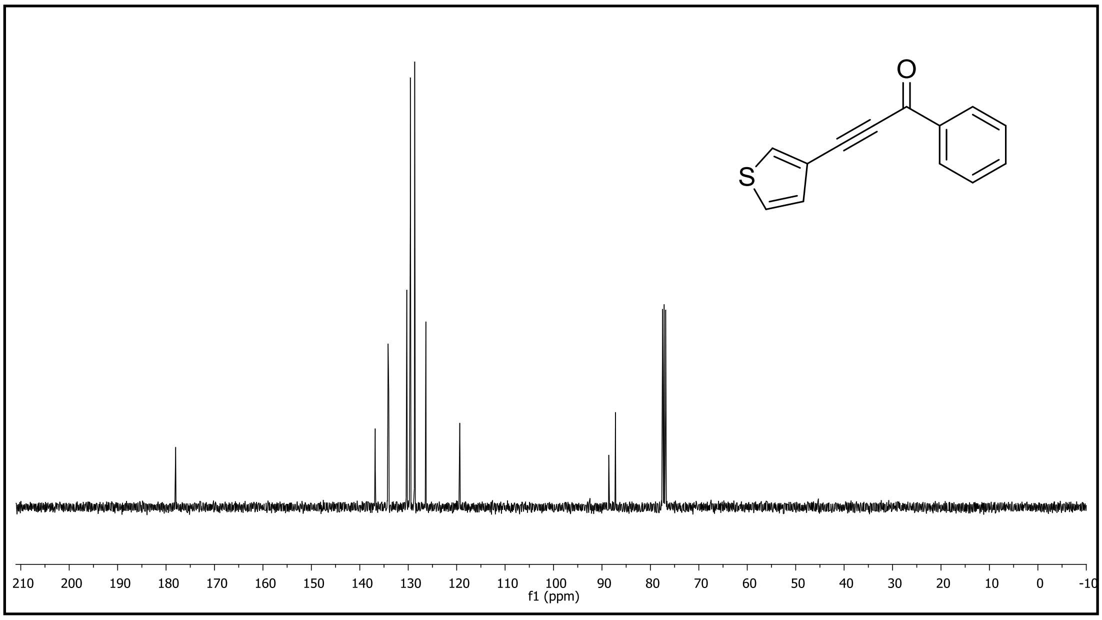

Figure 39. ^{13}C NMR spectrum of compound **61J**.

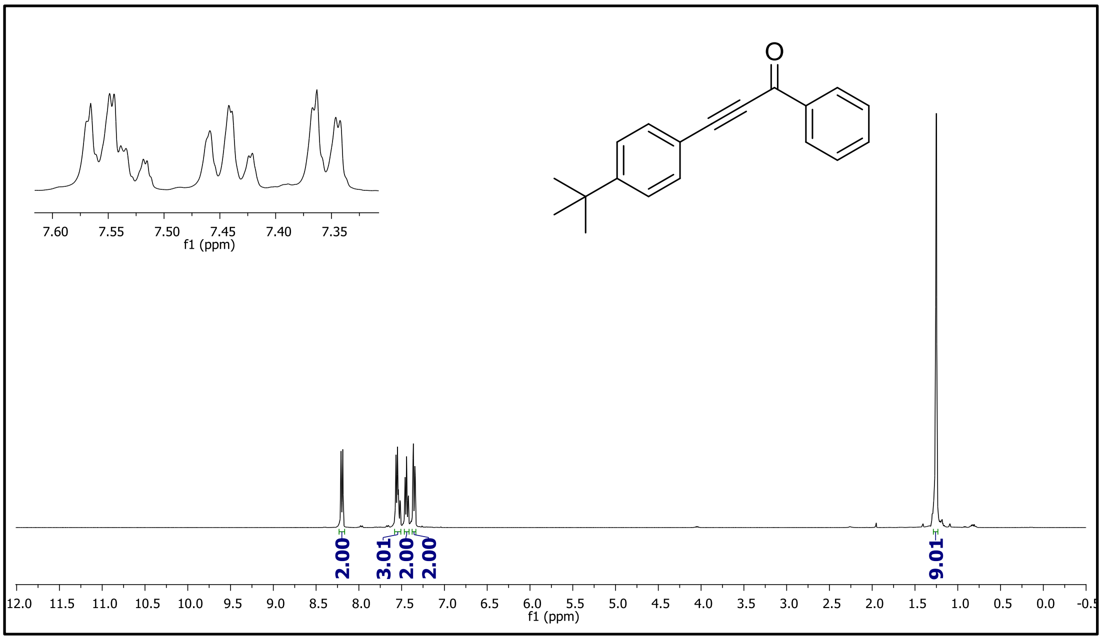

Figure 40. ^{1}H NMR spectrum of compound **61K.**

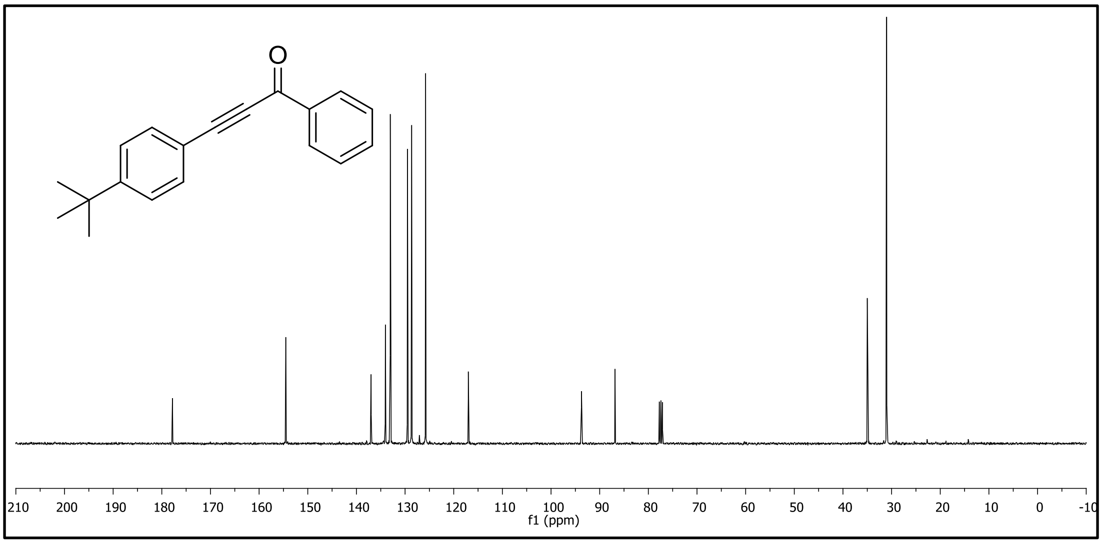

Figure 41. ^{13}C NMR spectrum of compound **61K**.

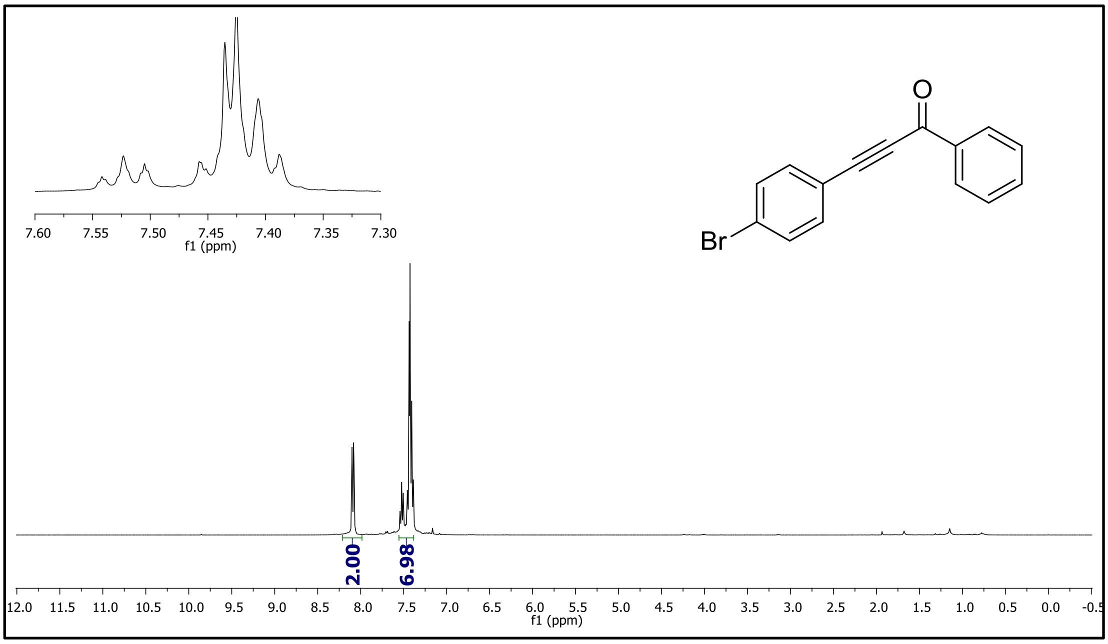

Figure 42. ^{1}H NMR spectrum of compound **61L**.

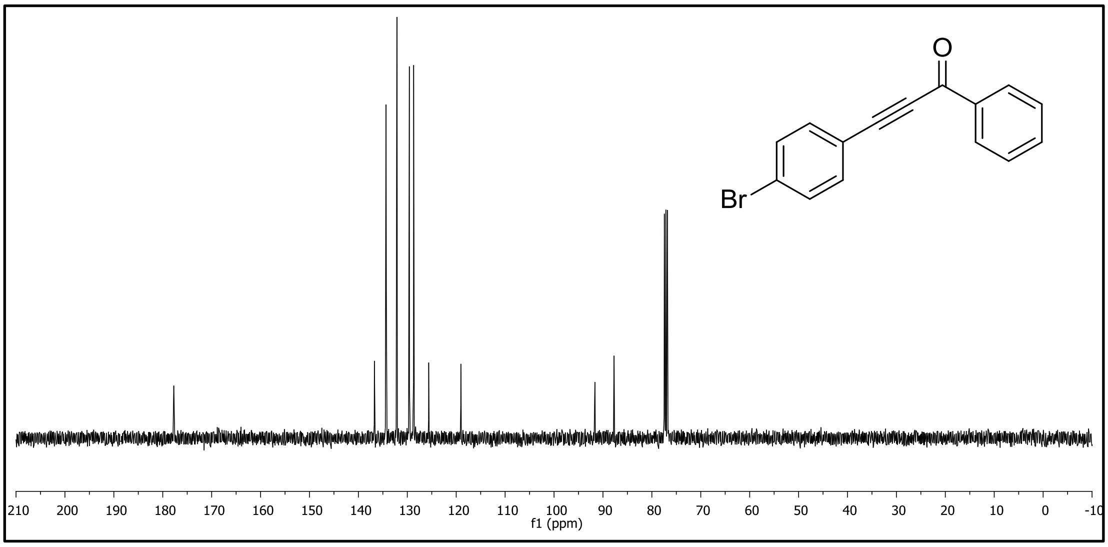

Figure 43. ^{13}C NMR spectrum of compound **61L**.

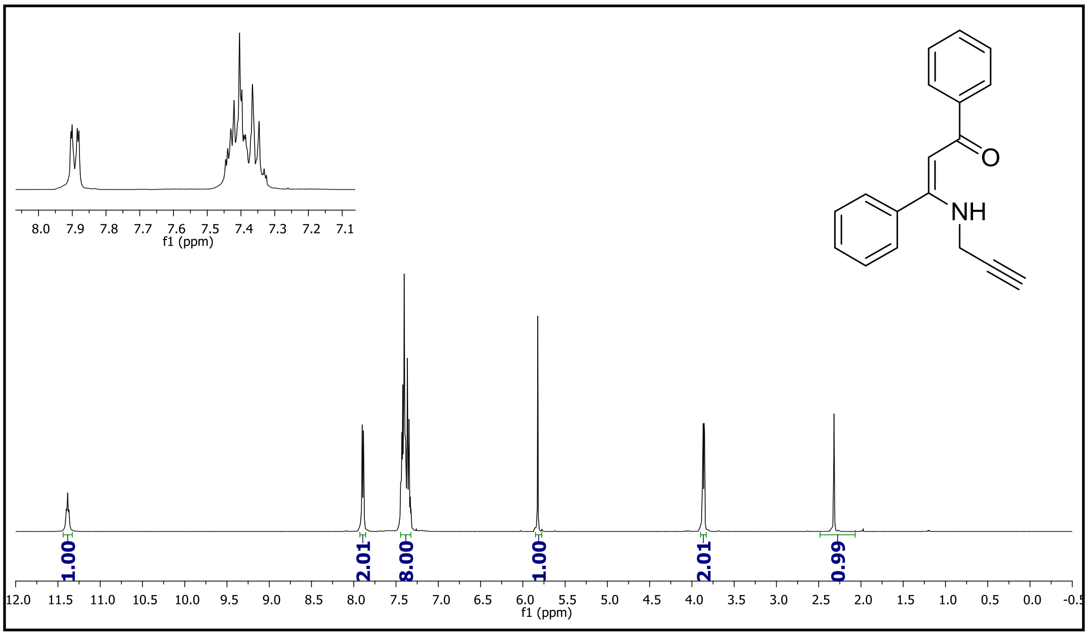

Figure 44. ^{1}H NMR spectrum of compound **54A**.

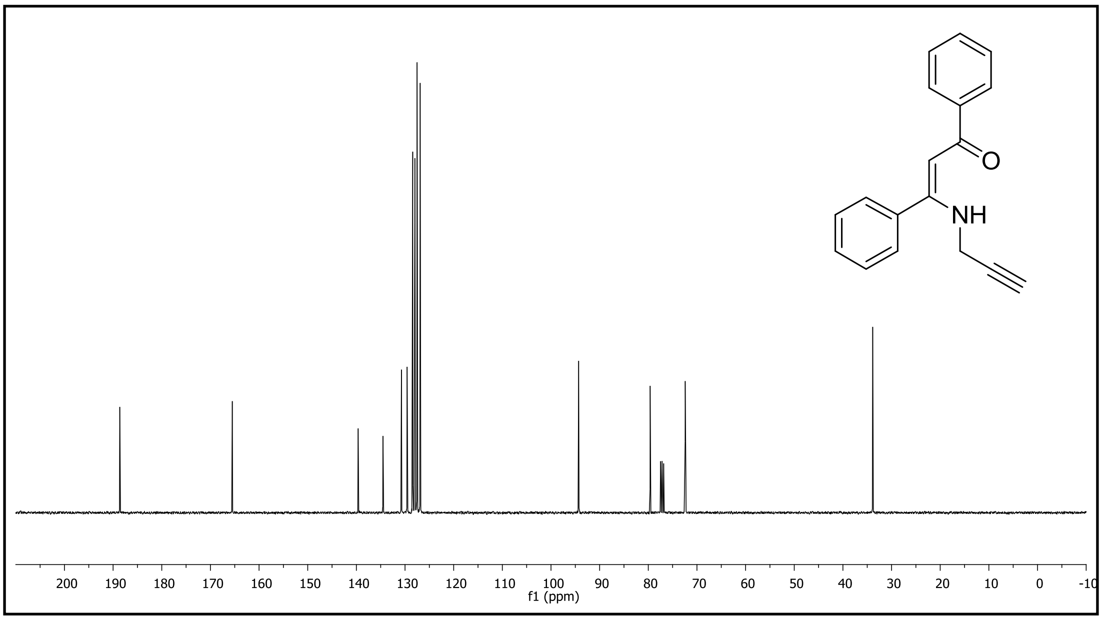

Figure 45. ^{13}C NMR spectrum of compound **54A**.

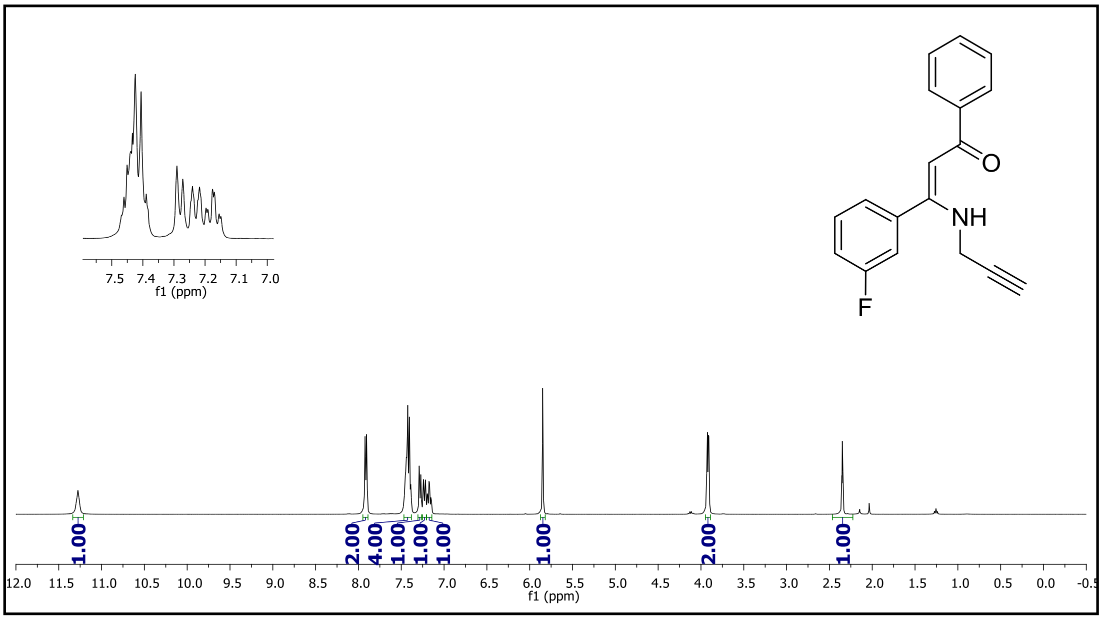

Figure 46. ^{1}H NMR spectrum of compound **54B**.

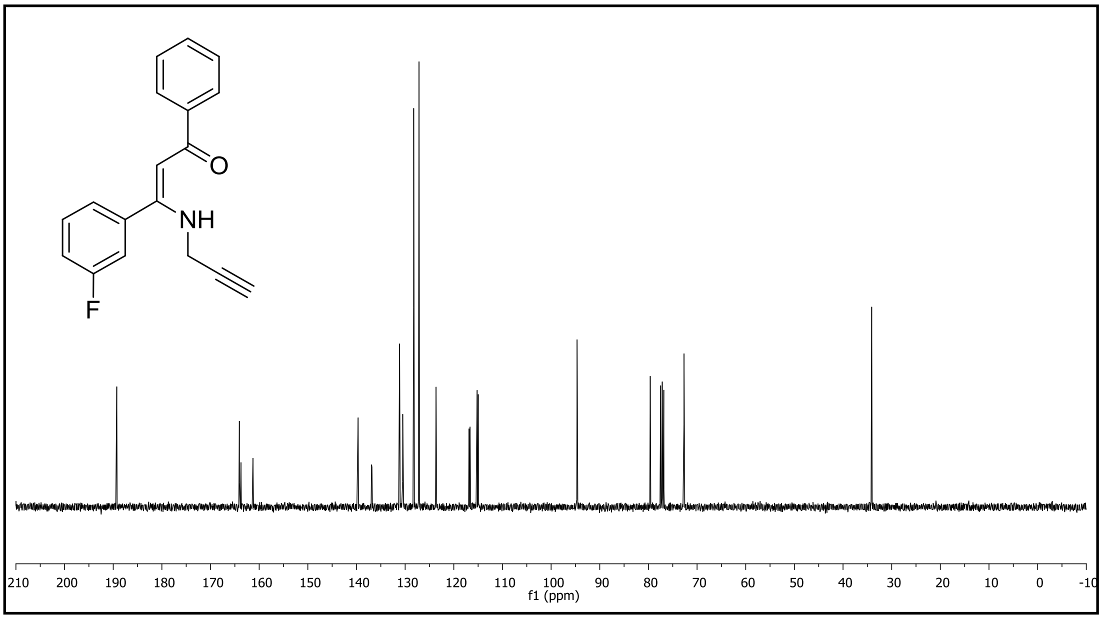

Figure 47. ^{13}C NMR spectrum of compound **54B**.

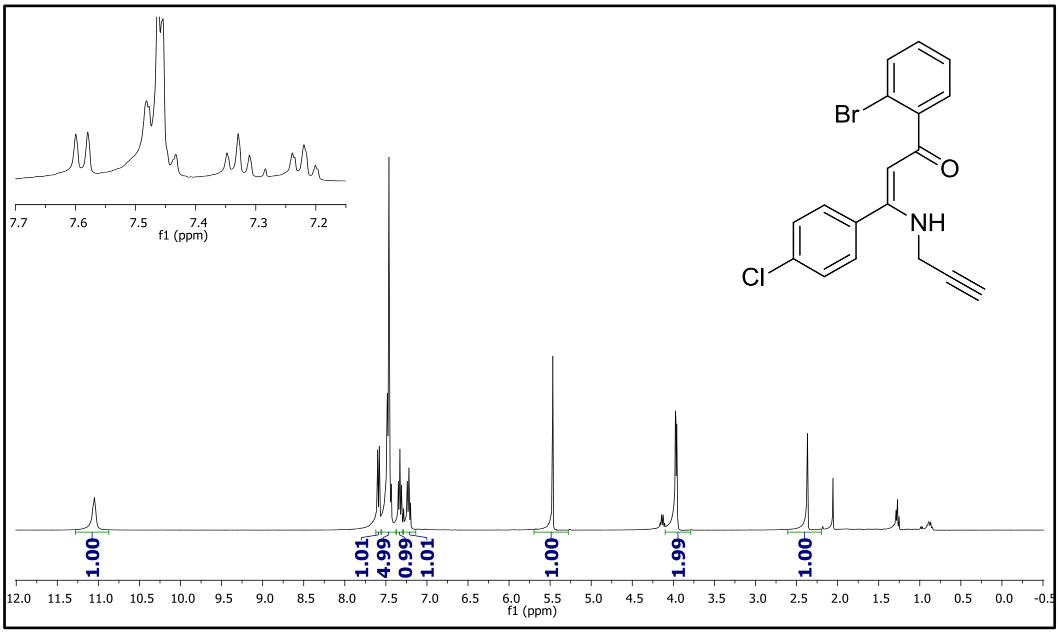

Figure 48. ^{1}H NMR spectrum of compound **54C**.

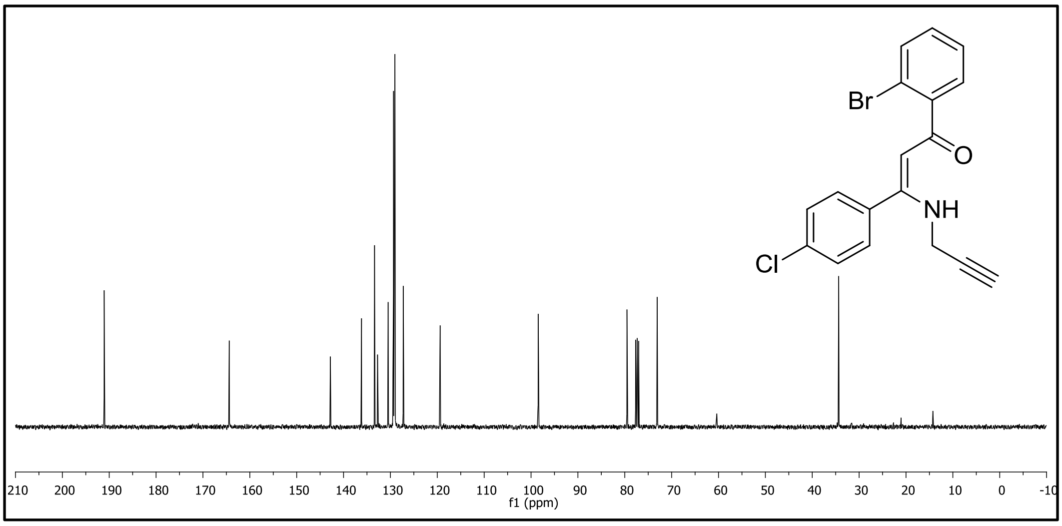

Figure 49. ^{13}C NMR spectrum of compound **54C**.

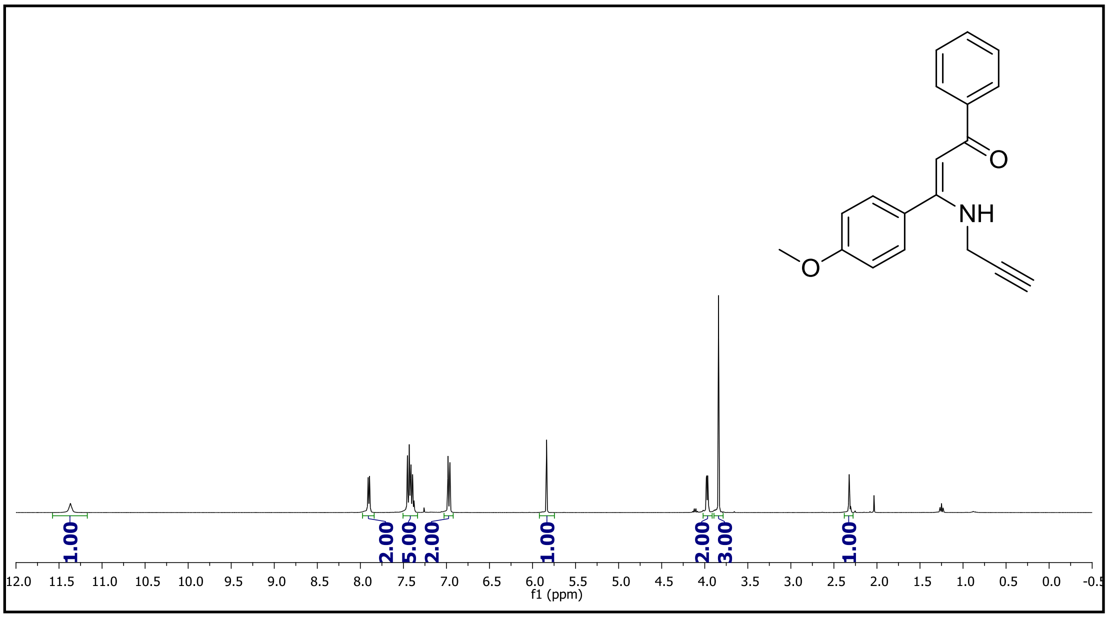

Figure 50. ^{1}H NMR spectrum of compound **54D**.

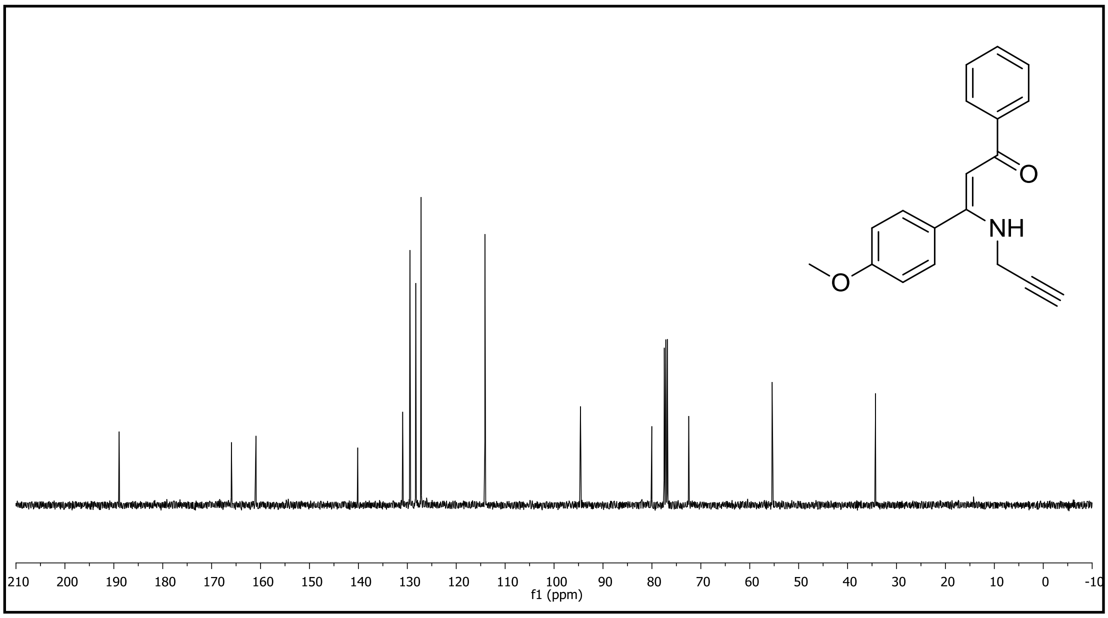

Figure 51. ^{13}C NMR spectrum of compound **54D.**

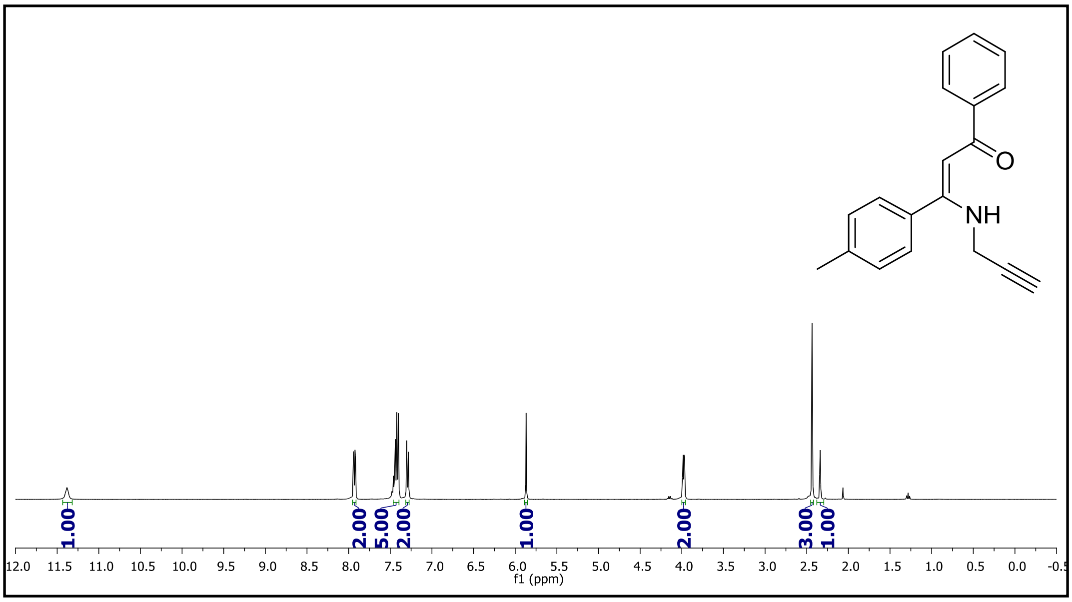

Figure 52. ^{1}H NMR spectrum of compound **54E**.

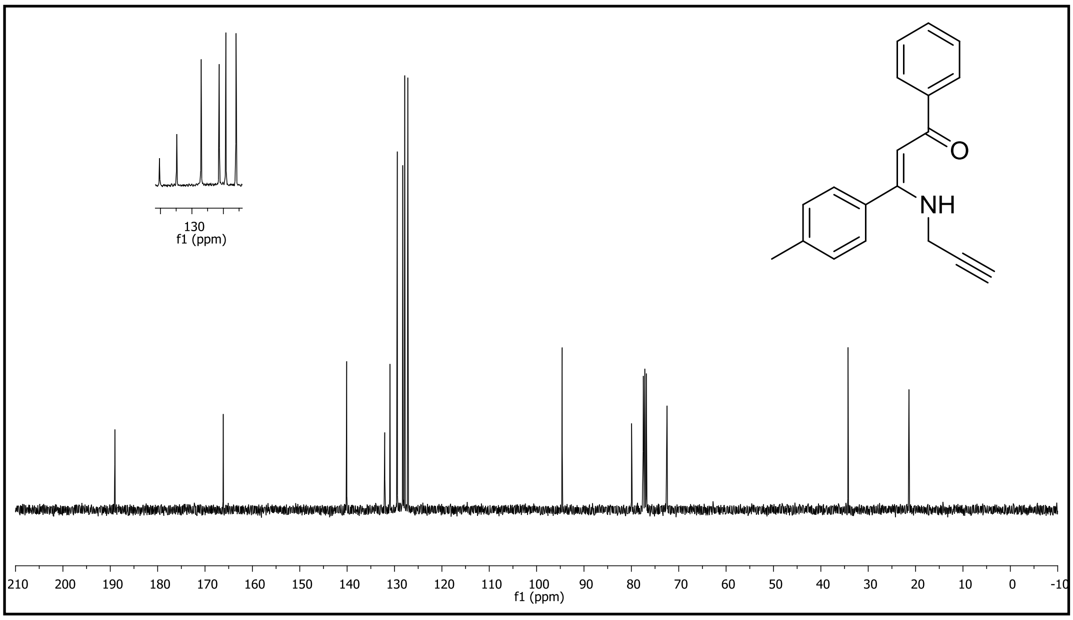

Figure 53. ^{13}C NMR spectrum of compound **54E**.

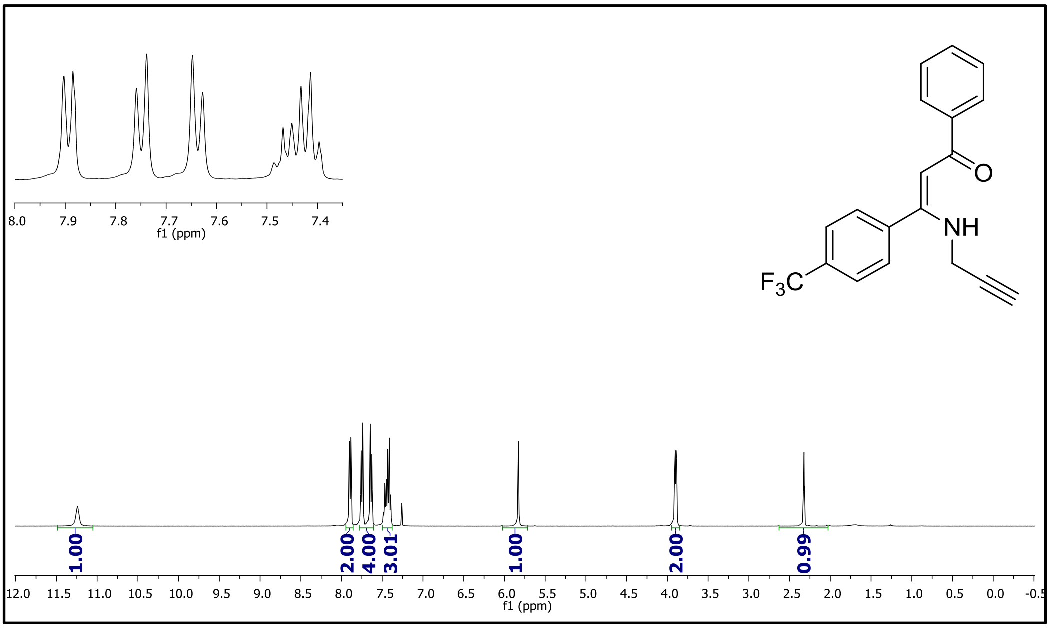

Figure 54. ^{1}H NMR spectrum of compound **54F**.

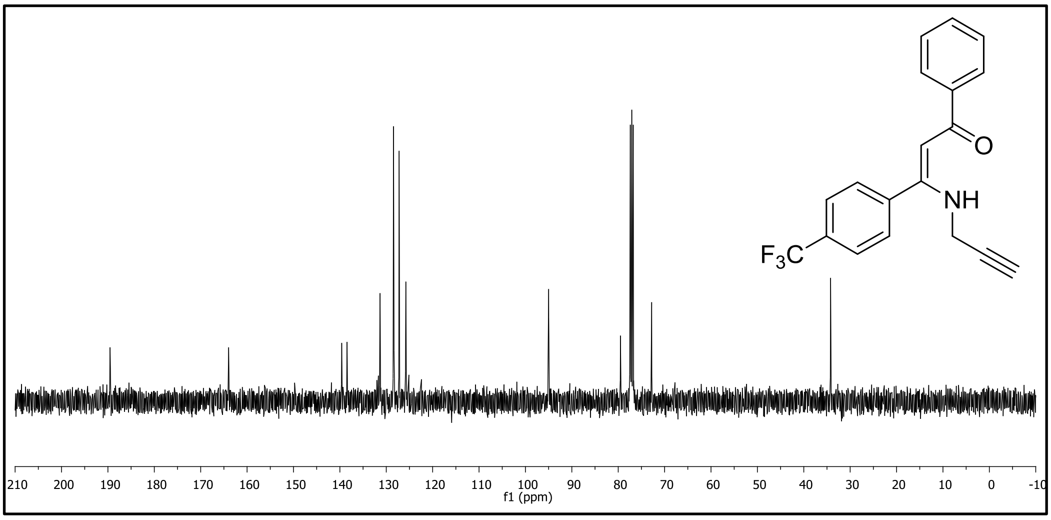

Figure 55. ^{13}C NMR spectrum of compound **54F**.

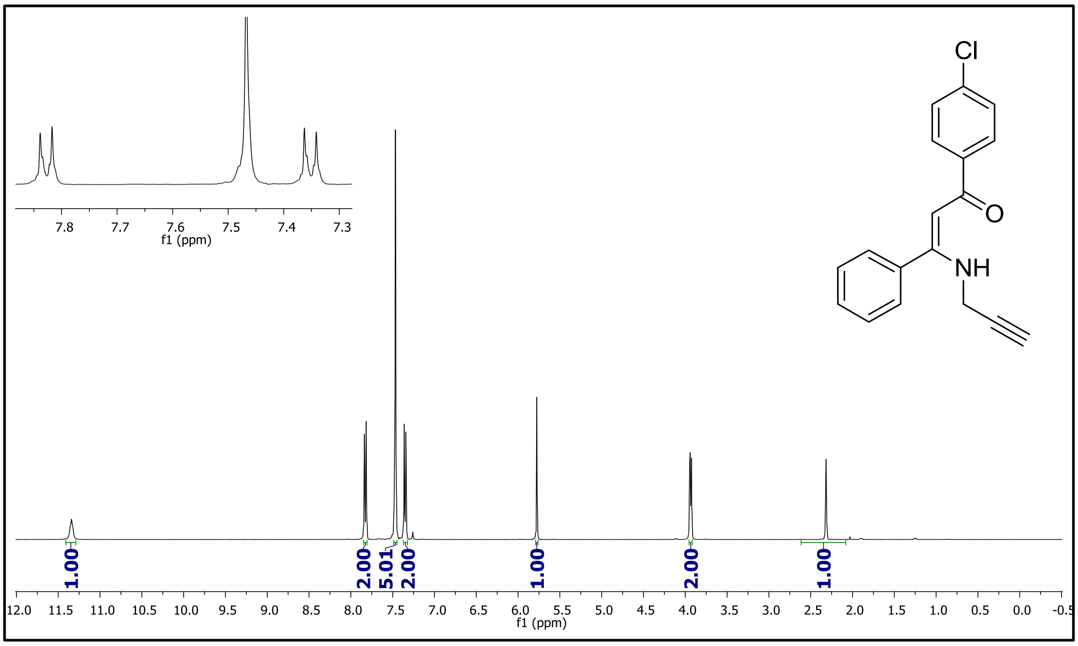

Figure 56. ^{1}H NMR spectrum of compound **54G**.

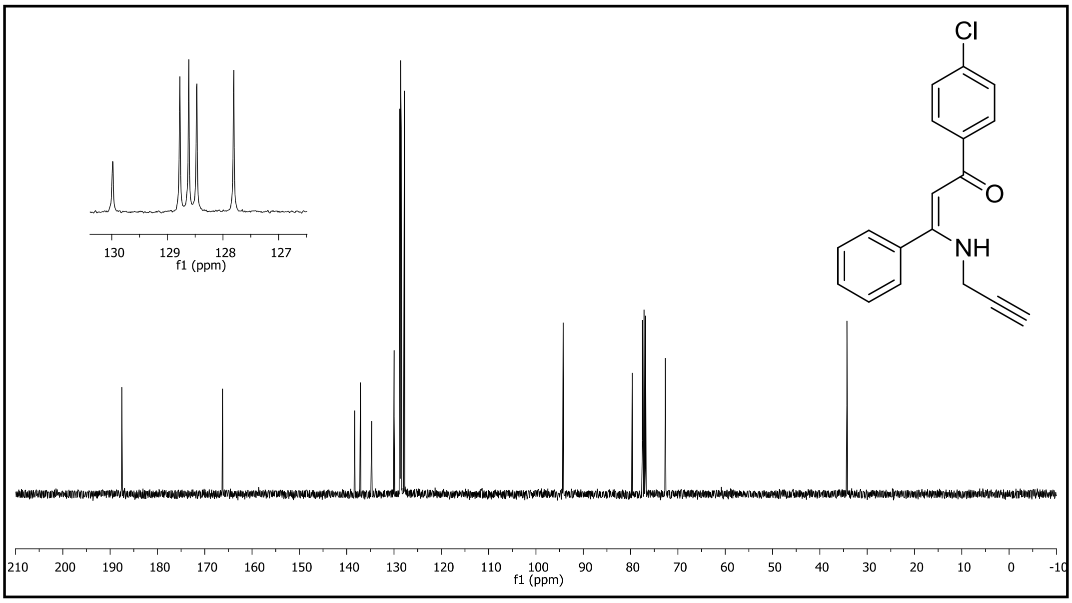

Figure 57. ^{13}C NMR spectrum of compound **54G**.

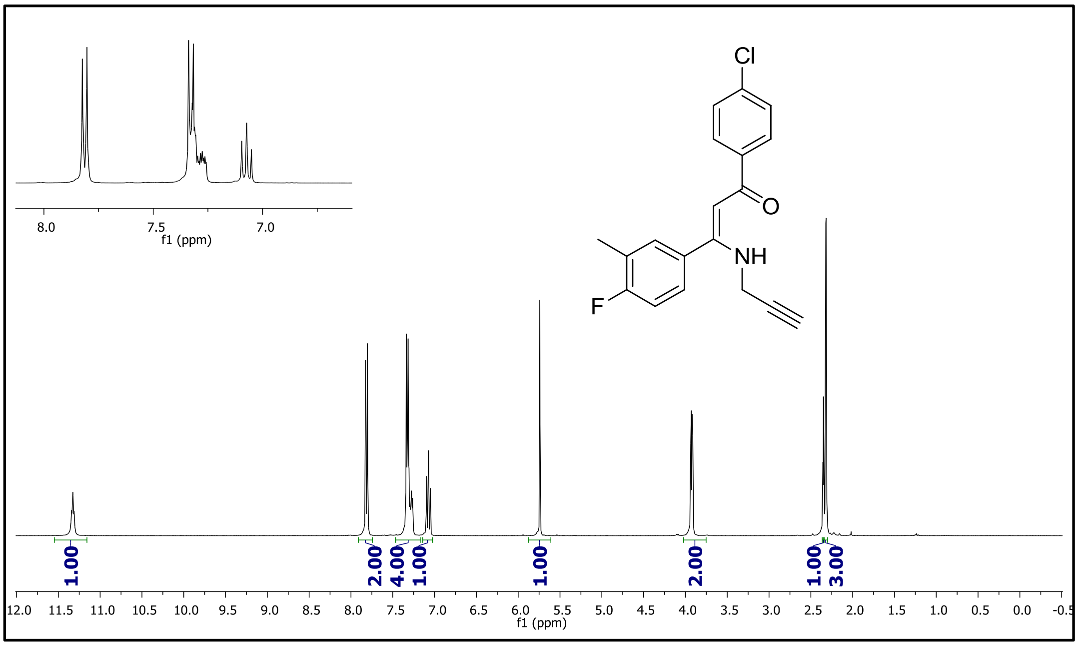

Figure 58. ^{1}H NMR spectrum of compound **54H**.

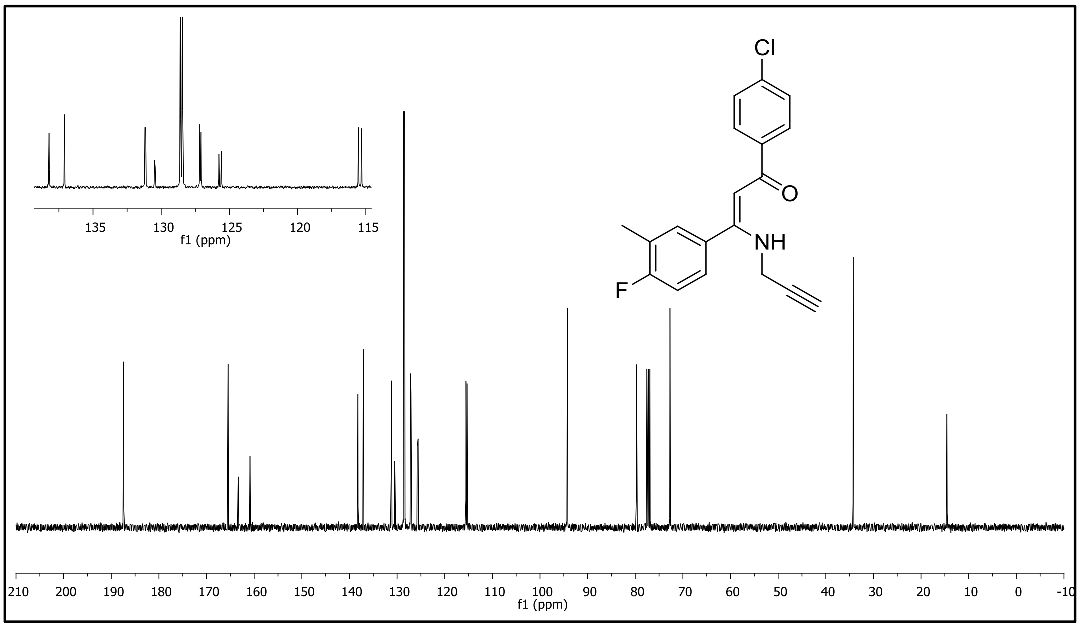

Figure 59. ^{13}C NMR spectrum of compound **54H**.

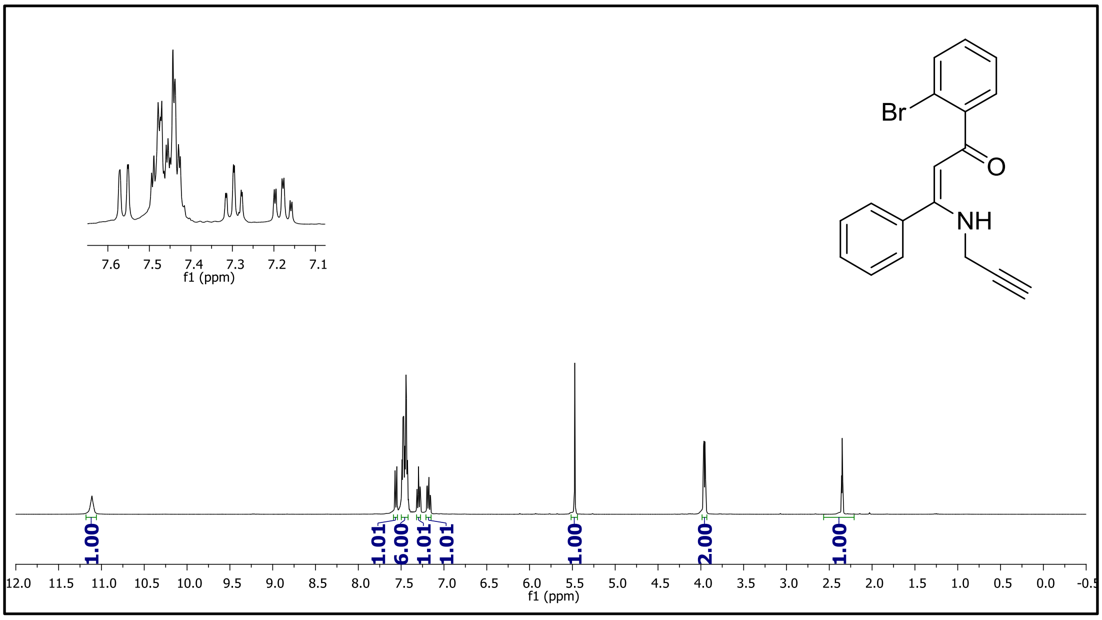

Figure 60. ^{1}H NMR spectrum of compound **54I**.

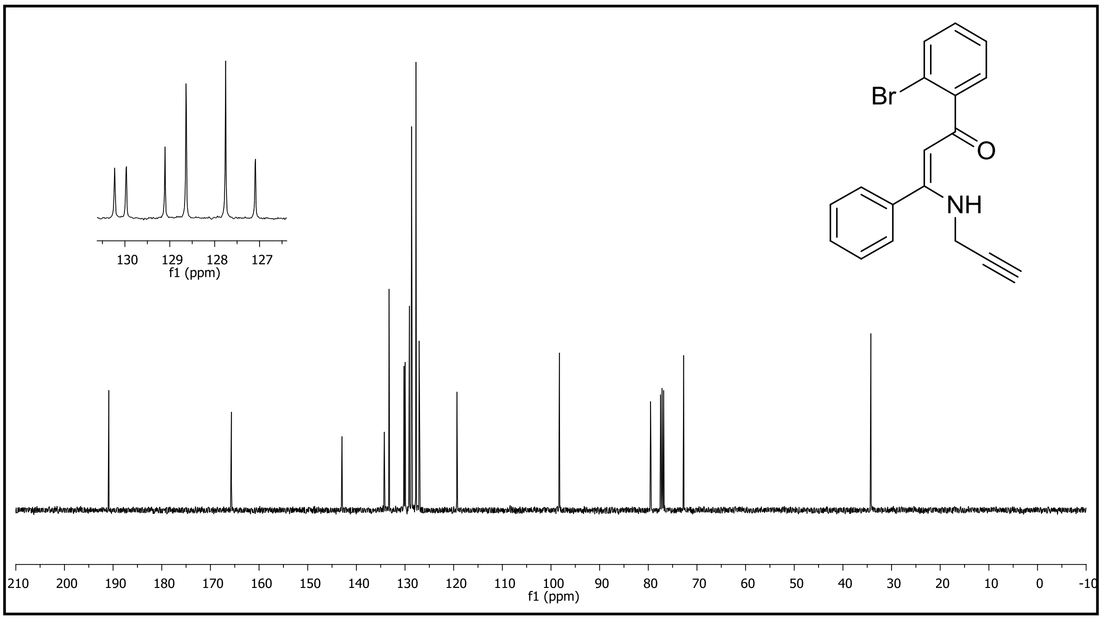

Figure 61. ^{13}C NMR spectrum of compound **54I**.

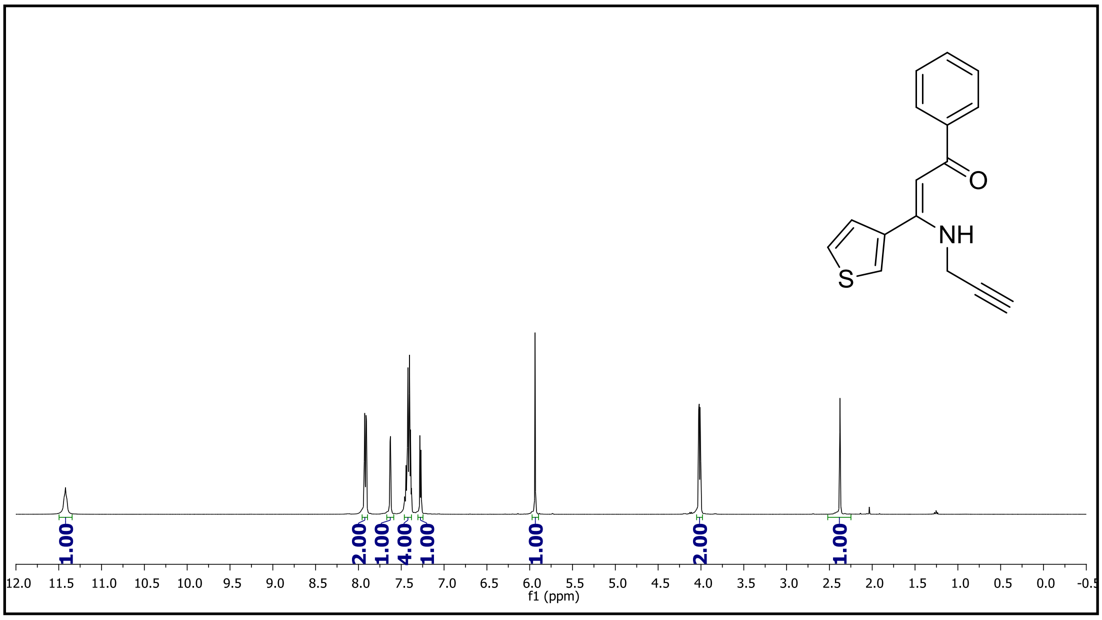

Figure 62. ^{1}H NMR spectrum of compound **54J**.

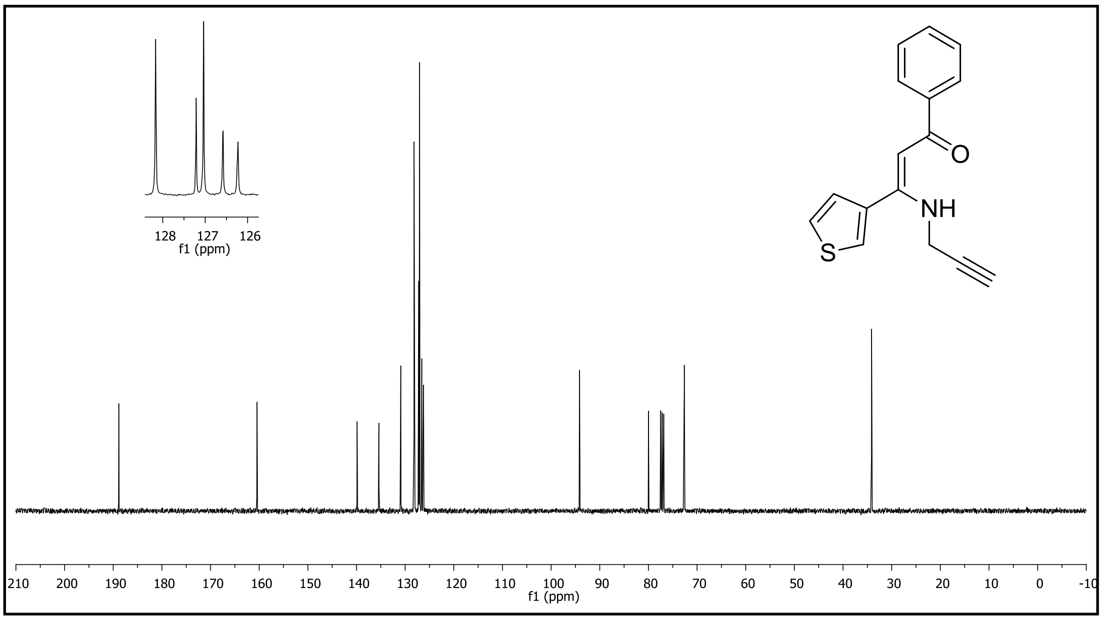

Figure 63. ^{13}C NMR spectrum of compound **54J**.

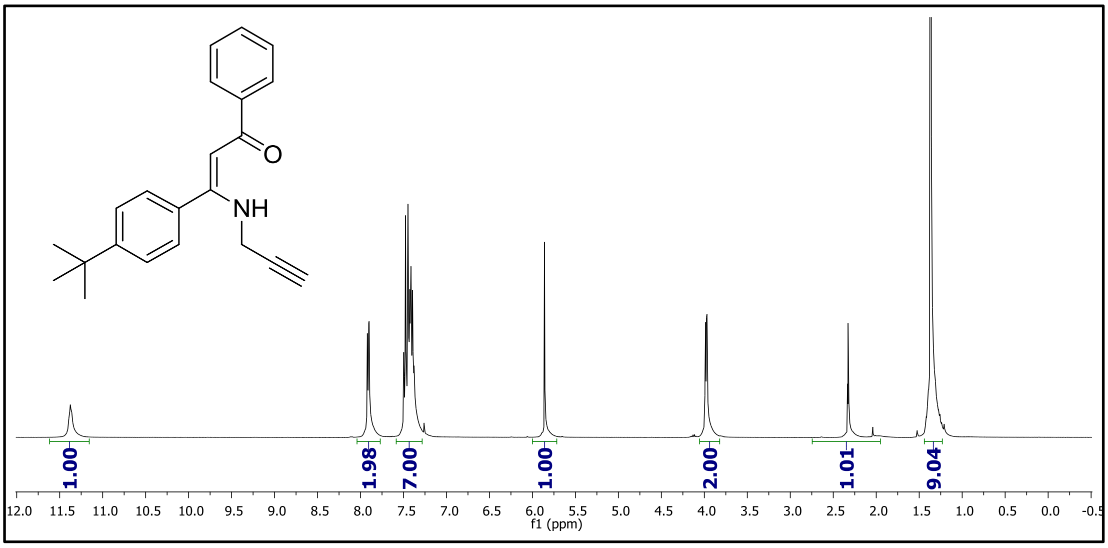

Figure 64. ^{1}H NMR spectrum of compound **54K**.

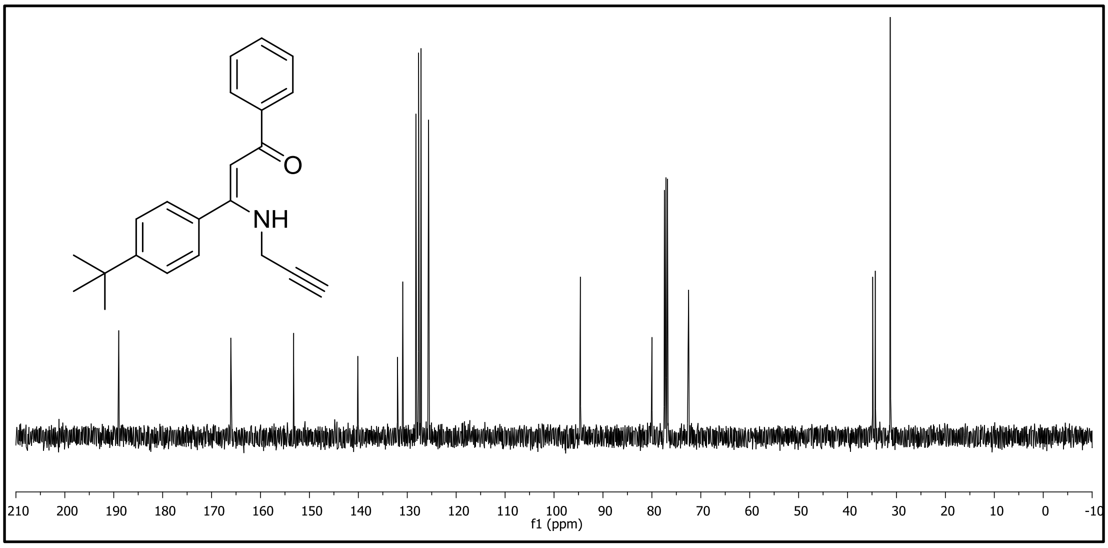

Figure 65. ^{13}C NMR spectrum of compound **54K**.

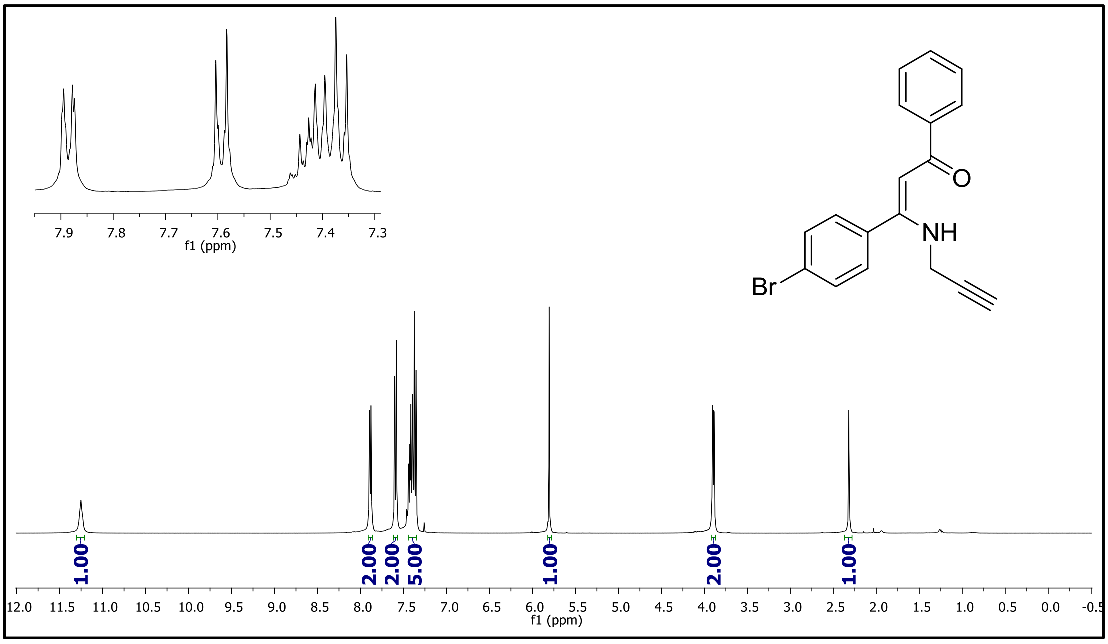

Figure 66. ^{1}H NMR spectrum of compound **54L**.

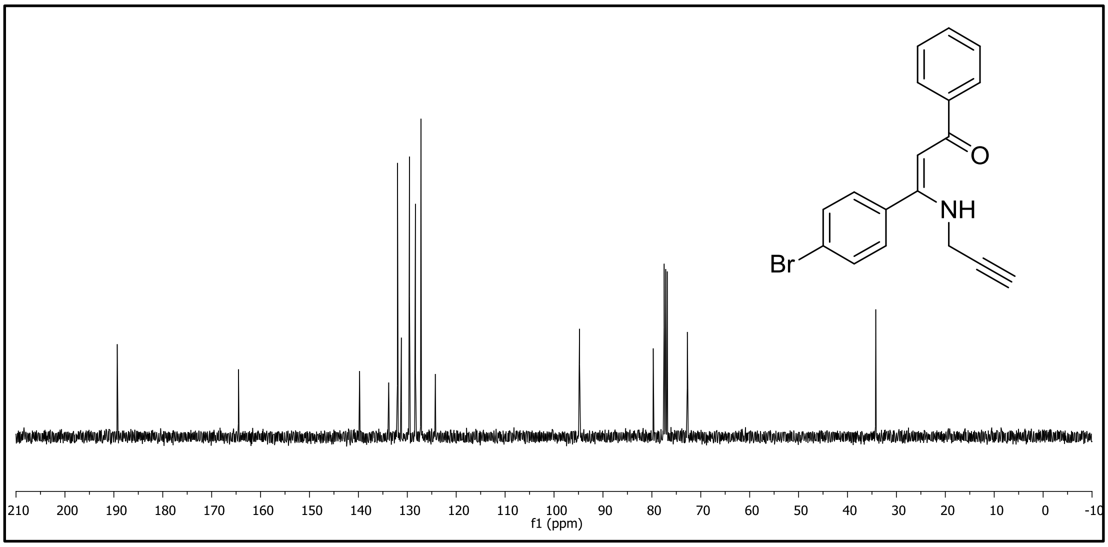

Figure 67. ^{13}C NMR spectrum of compound **54L**.

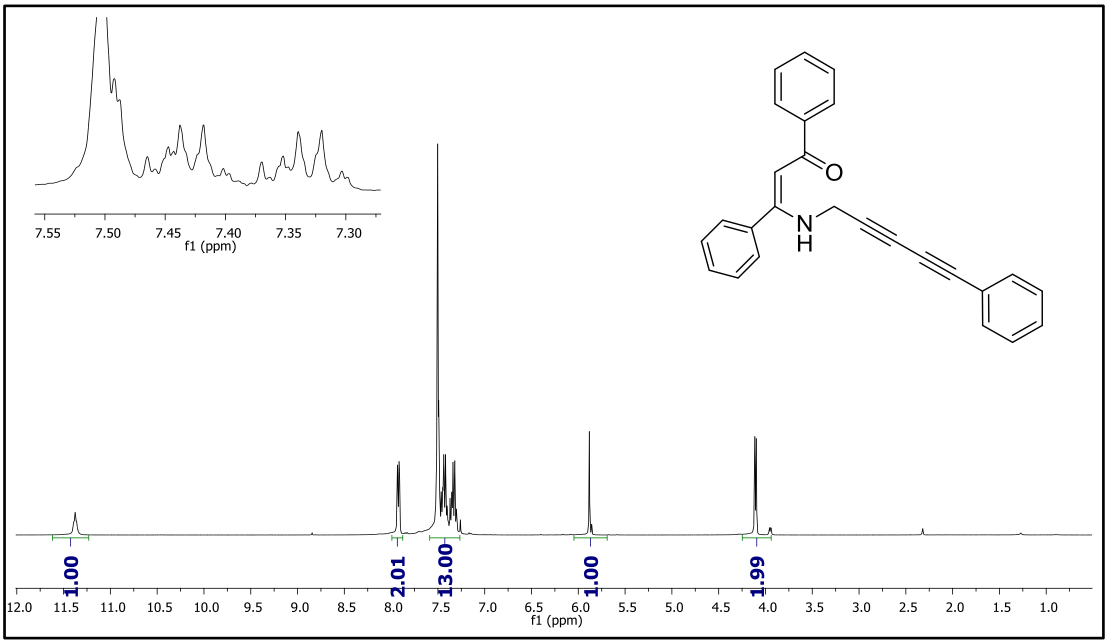

Figure 68. ^{1}H NMR spectrum of compound **56A**.

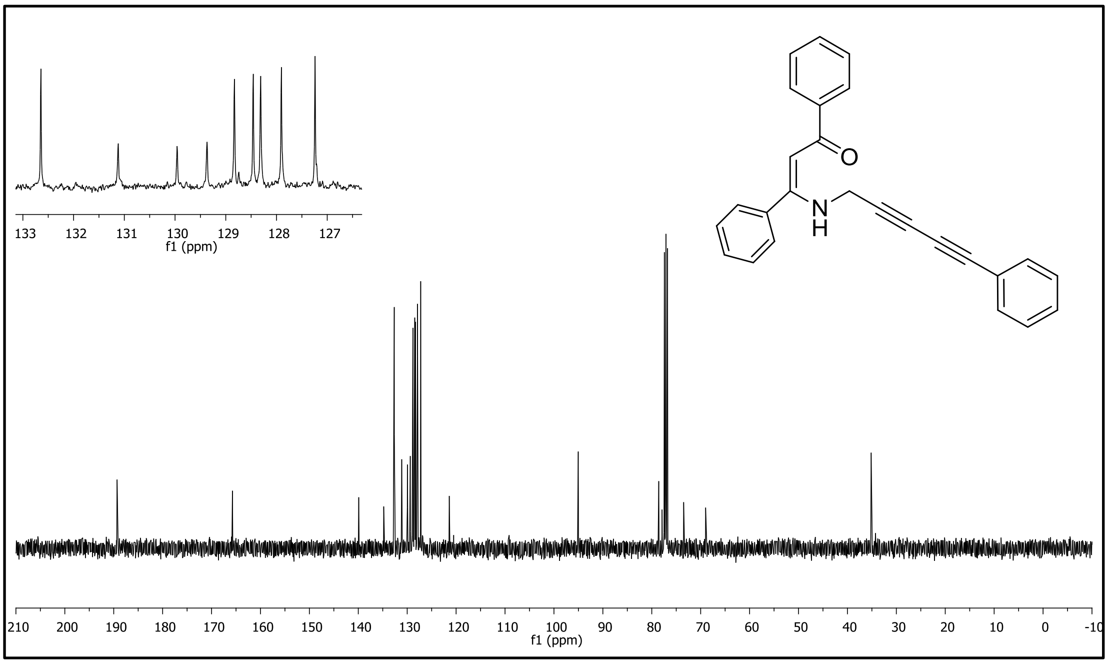

Figure 69. ^{13}C NMR spectrum of compound **56A**.

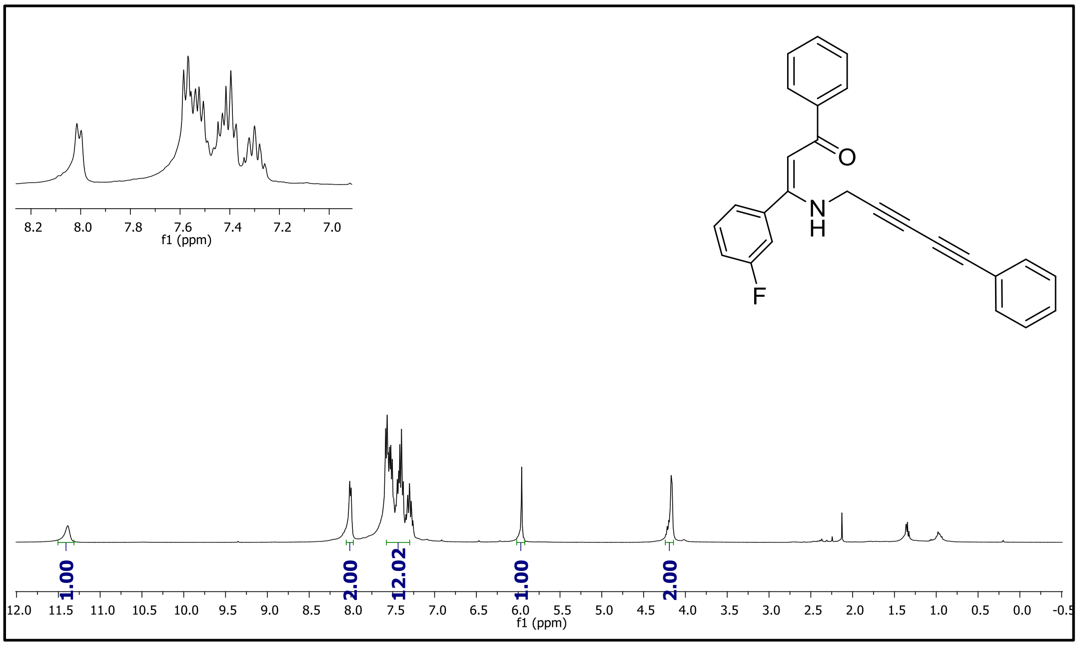

Figure 70. ^{1}H NMR spectrum of compound **56B**.

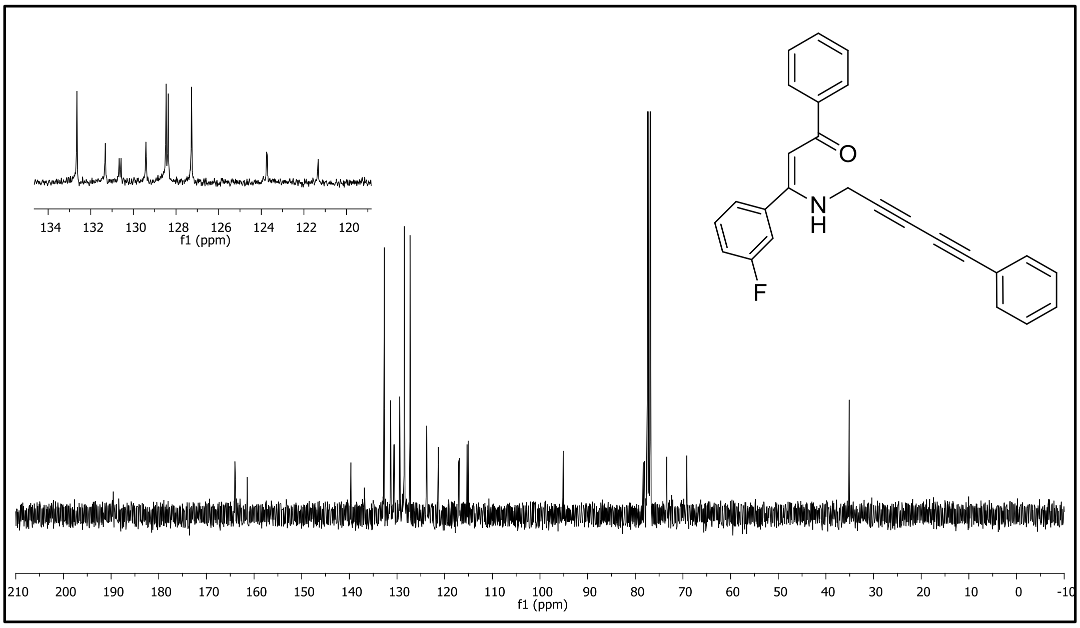

Figure 71. ^{13}C NMR spectrum of compound **56B**.

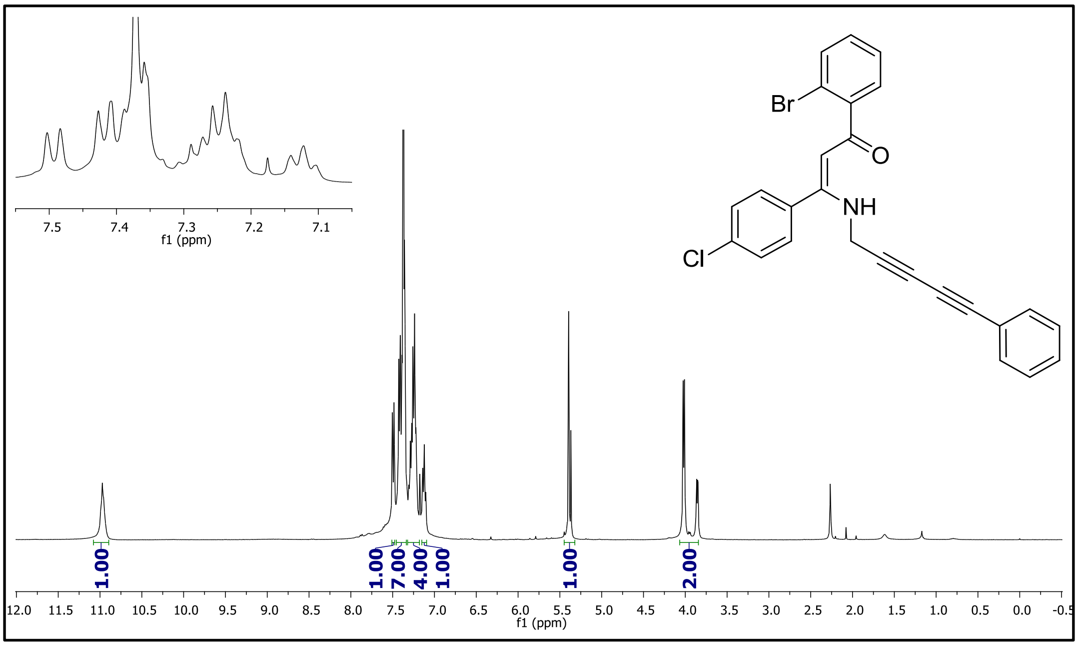

Figure 72. ^{1}H NMR spectrum of compound **56C**.

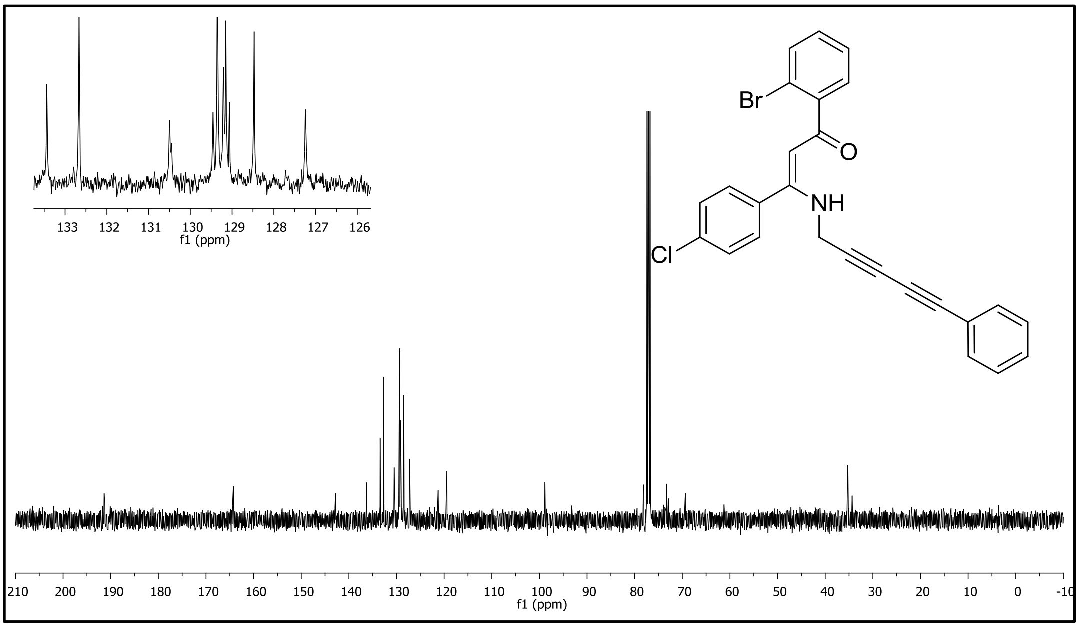

Figure 73. ^{13}C NMR spectrum of compound **56C**.

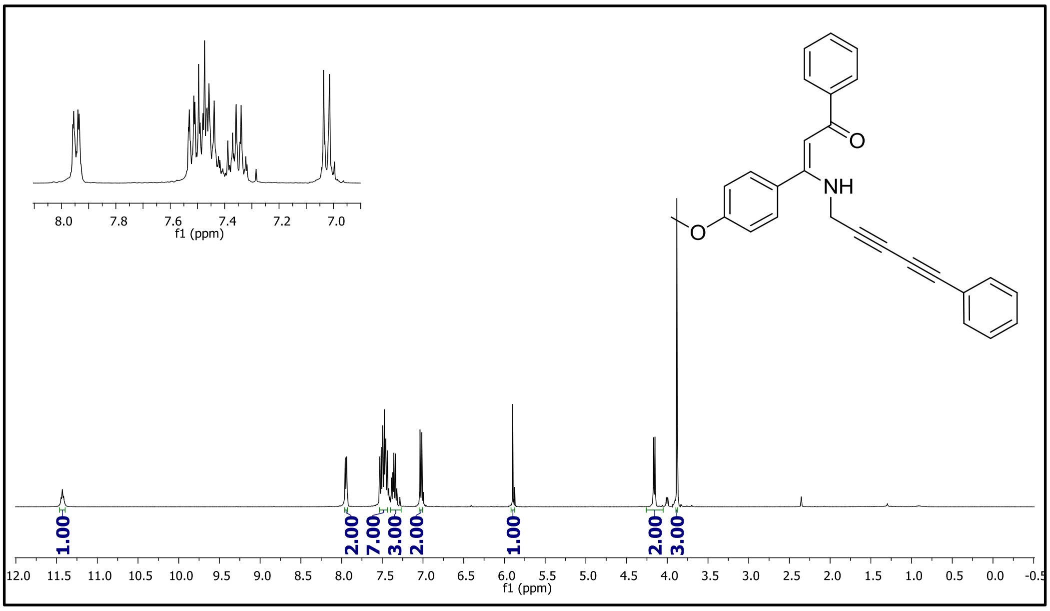

Figure 74. ^{1}H NMR spectrum of compound **56D**.

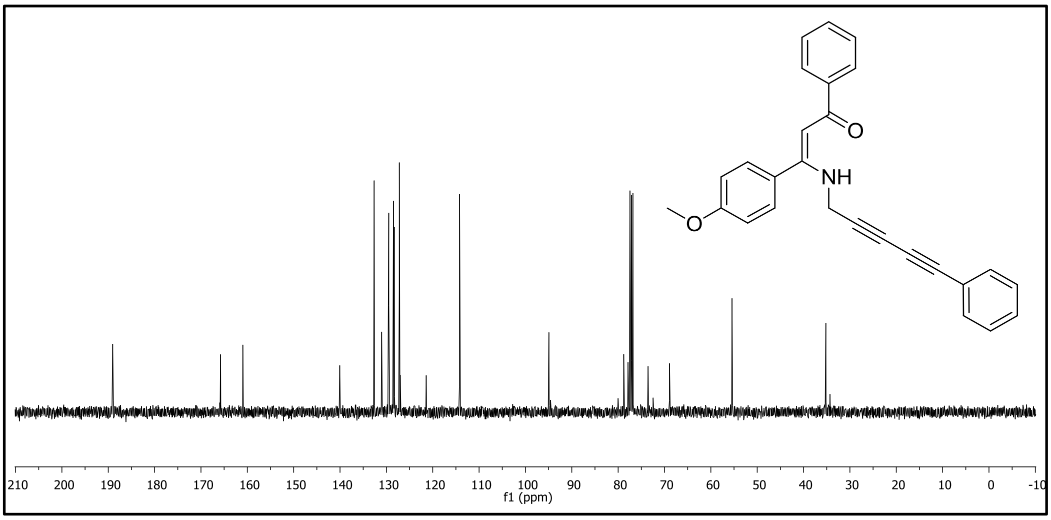

Figure 75. ^{13}C NMR spectrum of compound **56D**.

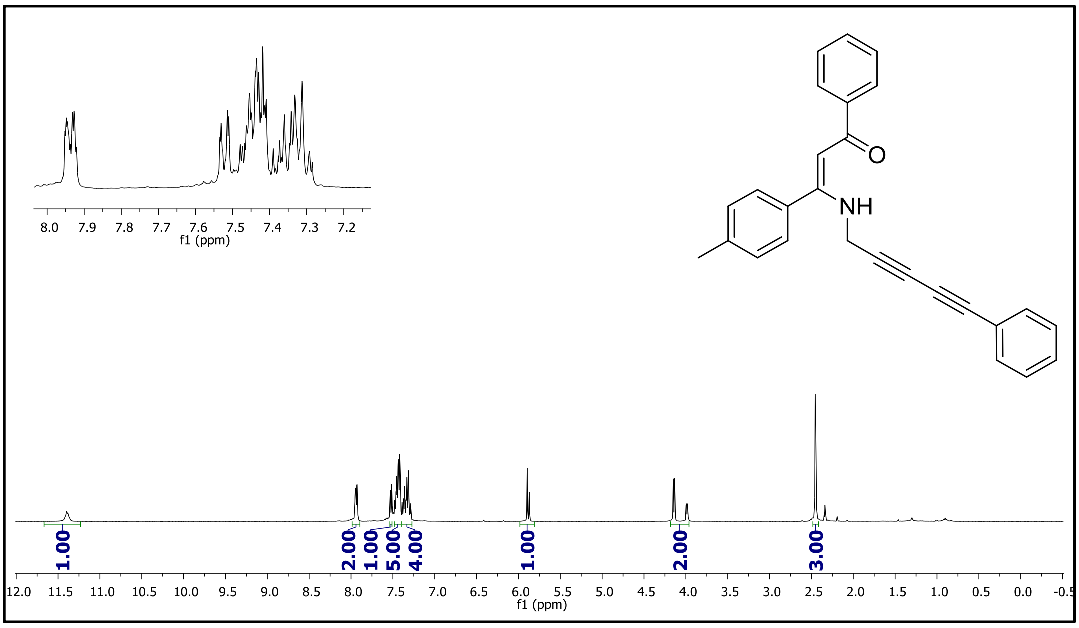

Figure 76. ^{1}H NMR spectrum of compound **56E**.

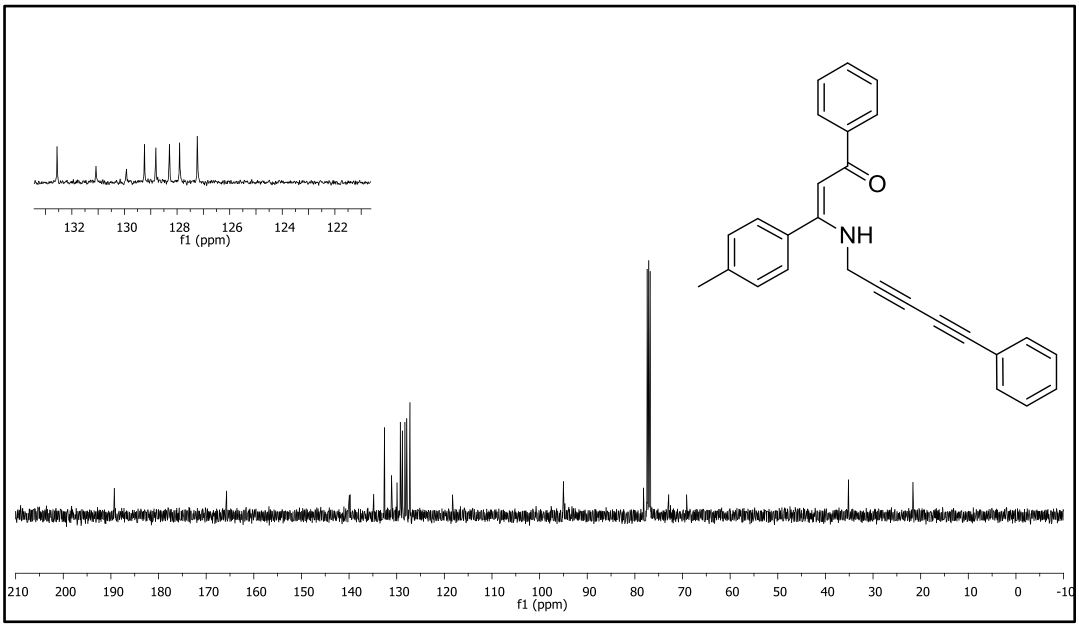

Figure 77. ^{13}C NMR spectrum of compound **56E**.

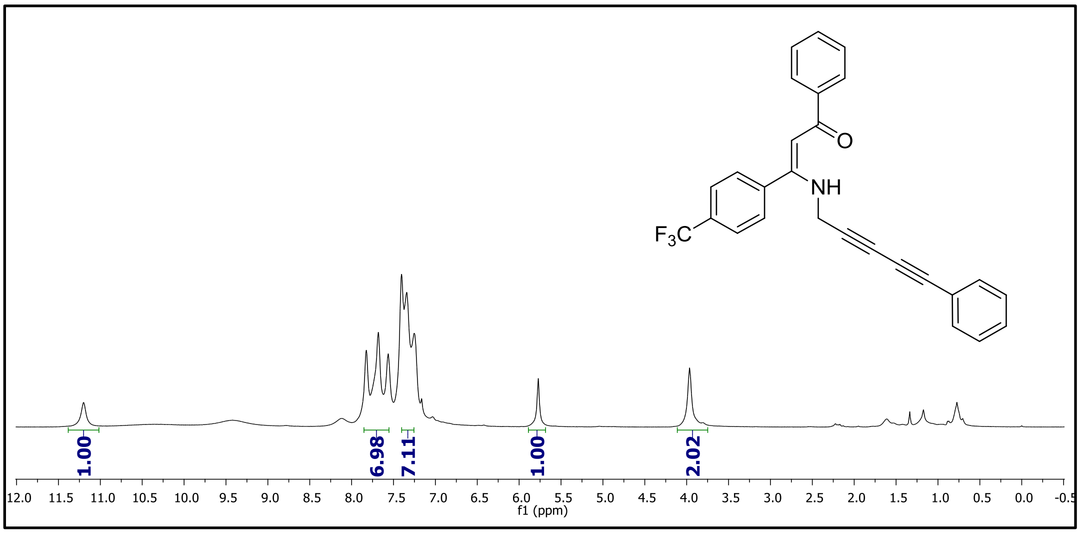

Figure 78. ^{1}H NMR spectrum of compound **56F**.

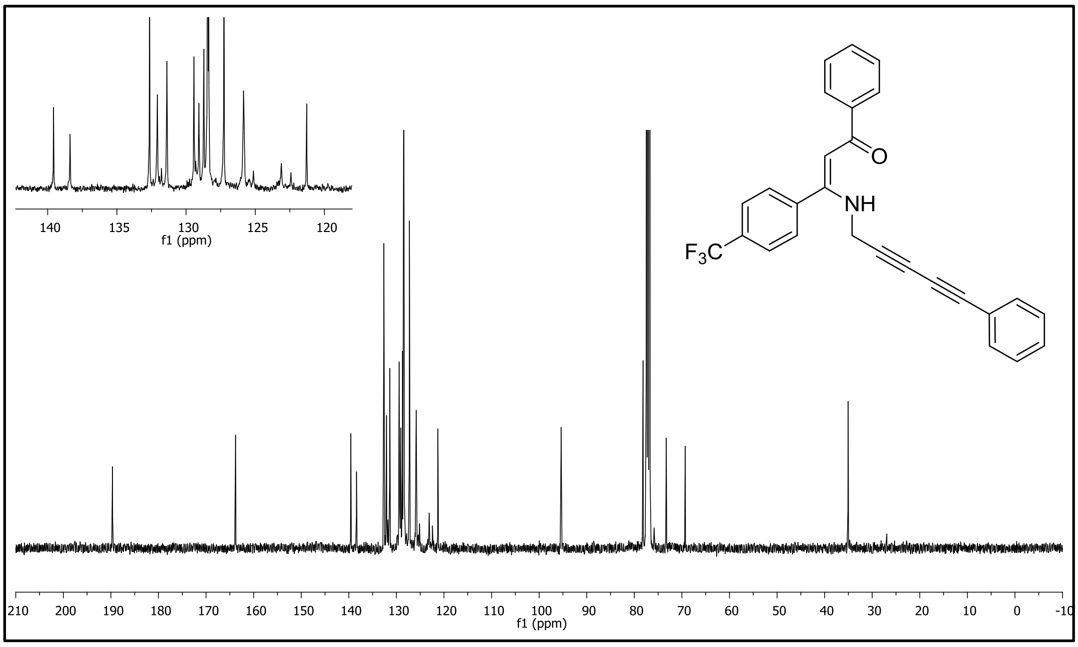

Figure 79. ^{13}C NMR spectrum of compound **56F**.

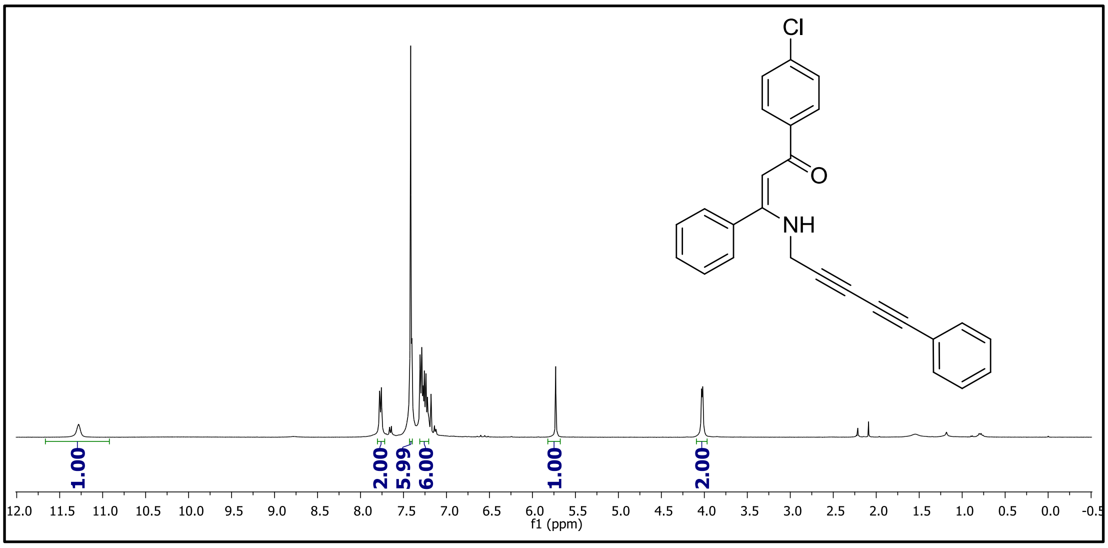

Figure 80. ^{1}H NMR spectrum of compound **56G**.

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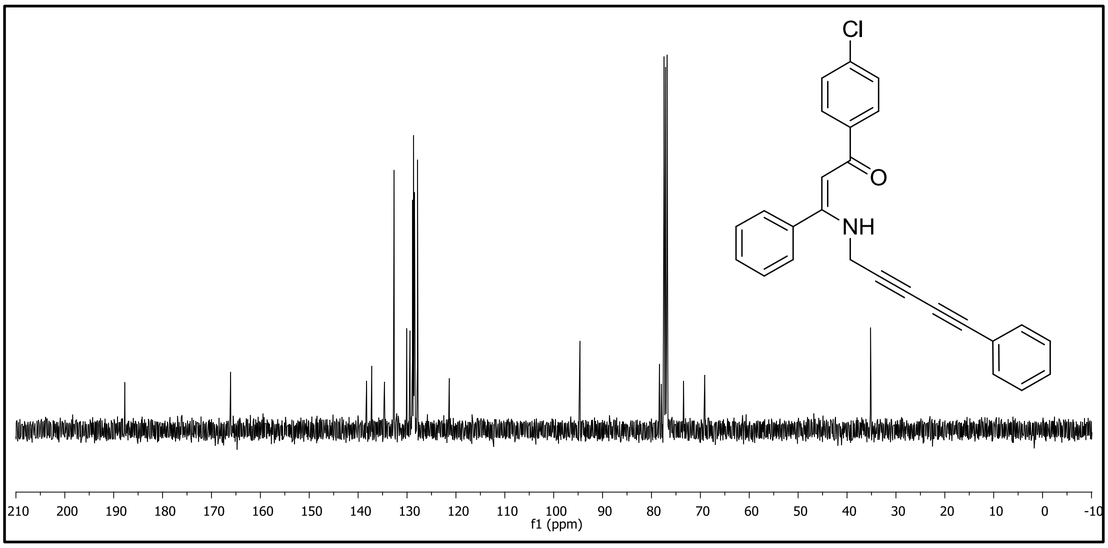

Figure 81. ^{13}C NMR spectrum of compound **56G**.

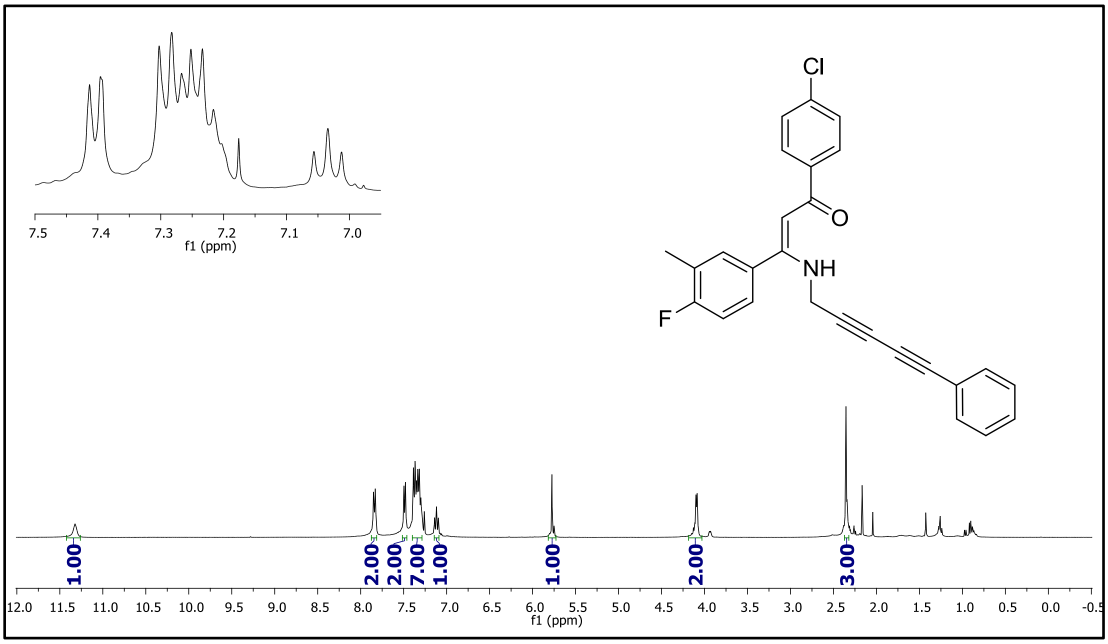

Figure 82. ^{1}H NMR spectrum of compound **56H**.

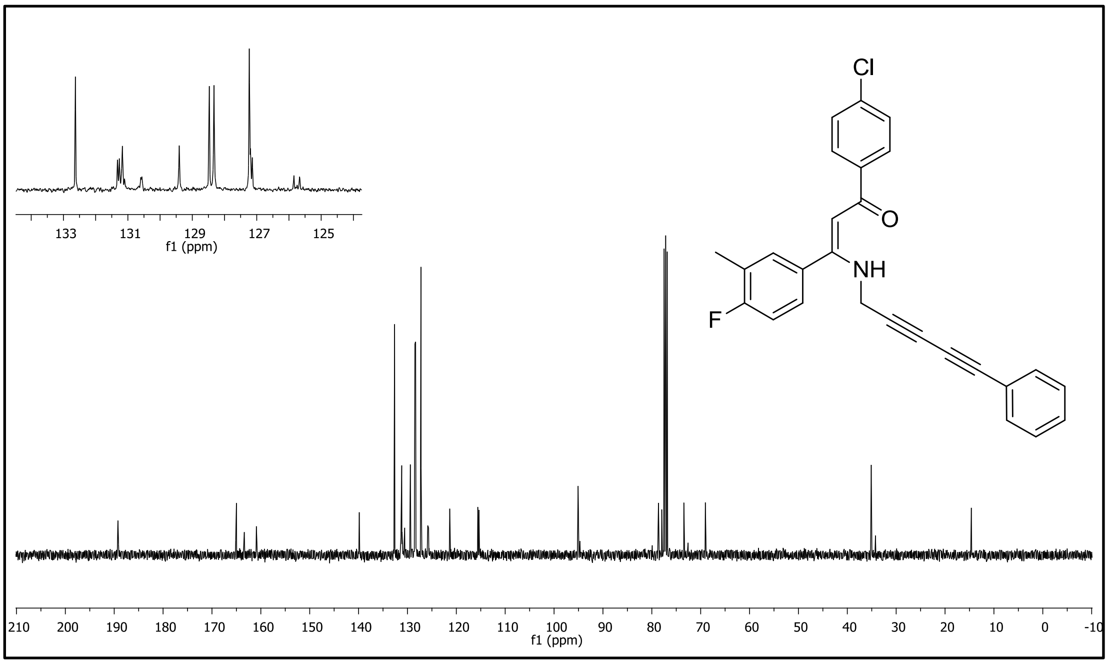

Figure 83. ^{13}C NMR spectrum of compound **56H**.

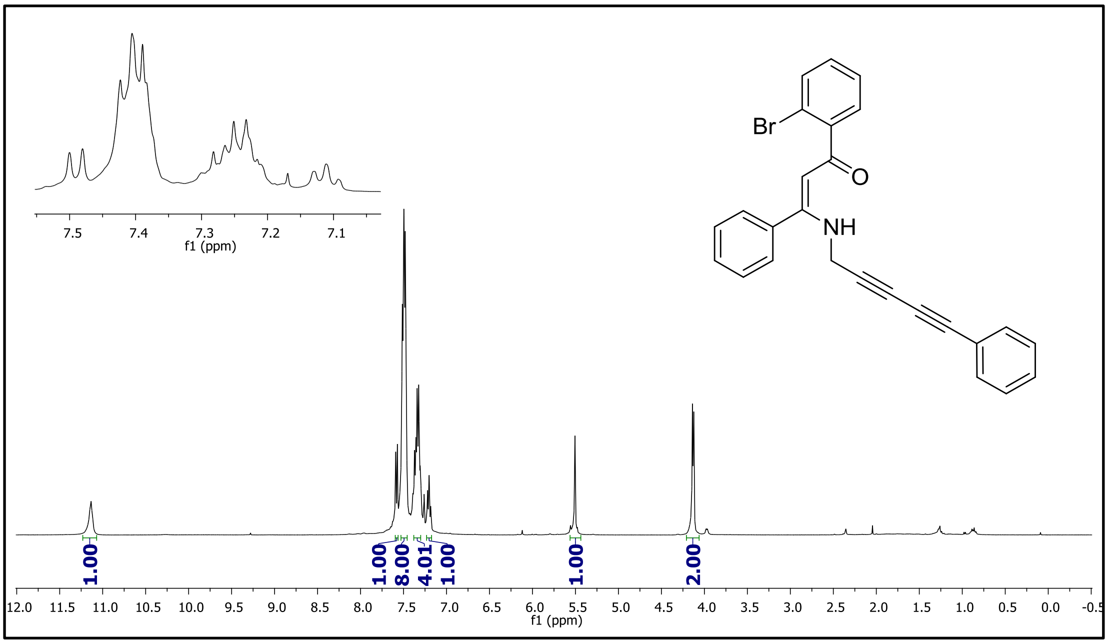

Figure 84. ^{1}H NMR spectrum of compound **56I**.

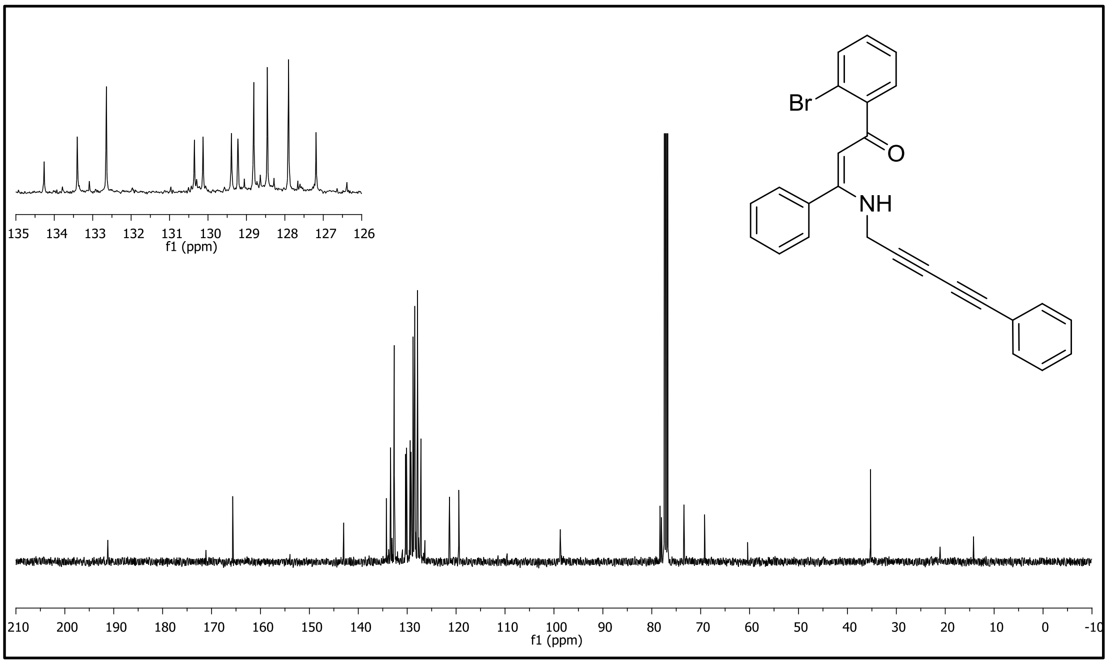

Figure 85. ^{13}C NMR spectrum of compound **56I**.

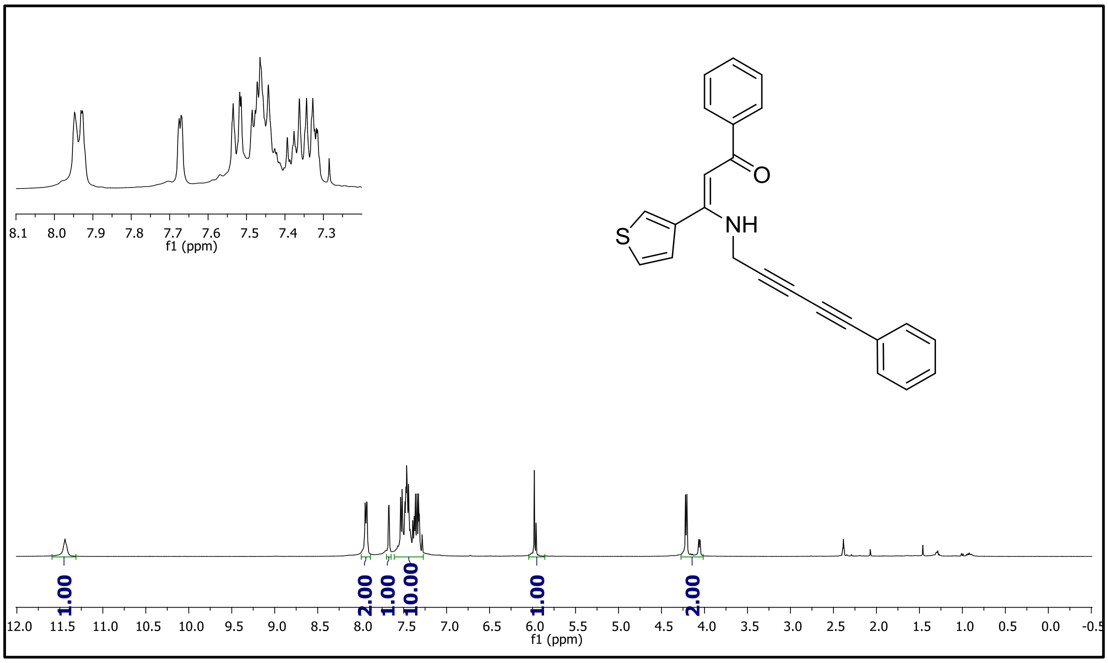

Figure 86. ^{1}H NMR spectrum of compound **56J**.

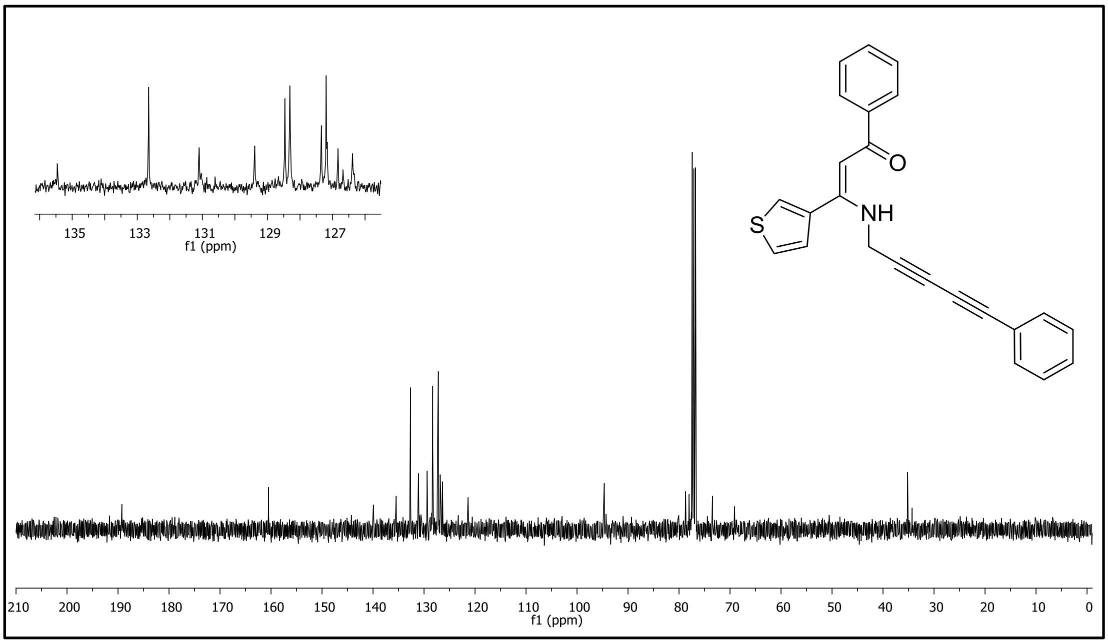

Figure 87. ^{13}C NMR spectrum of compound **56J**.

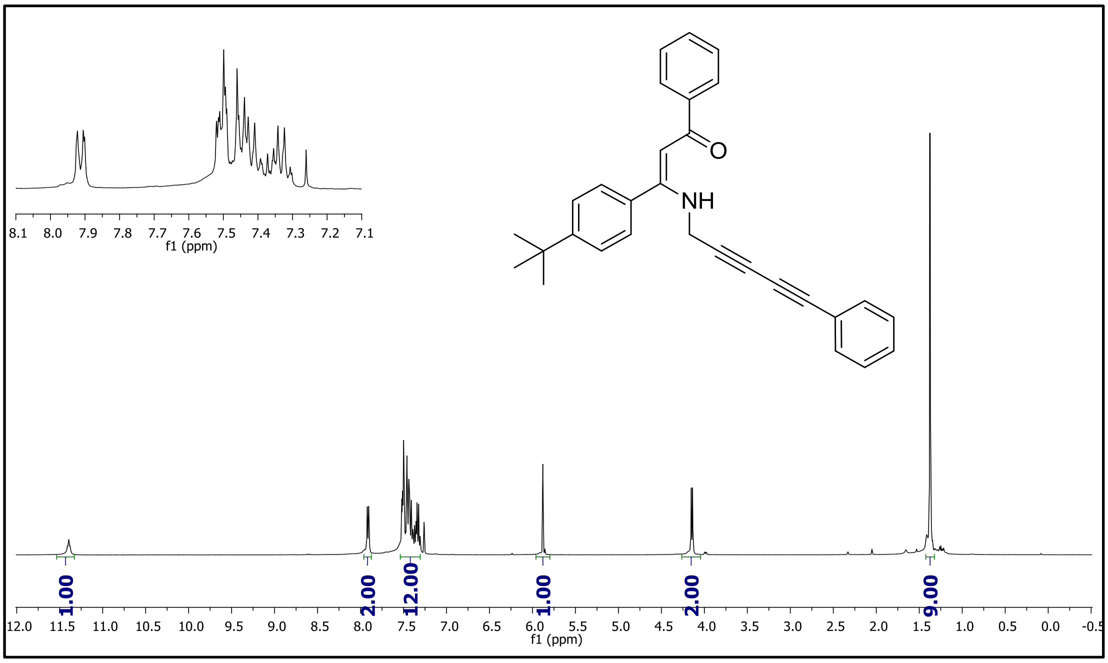

Figure 88. ^{1}H NMR spectrum of compound **56K**.

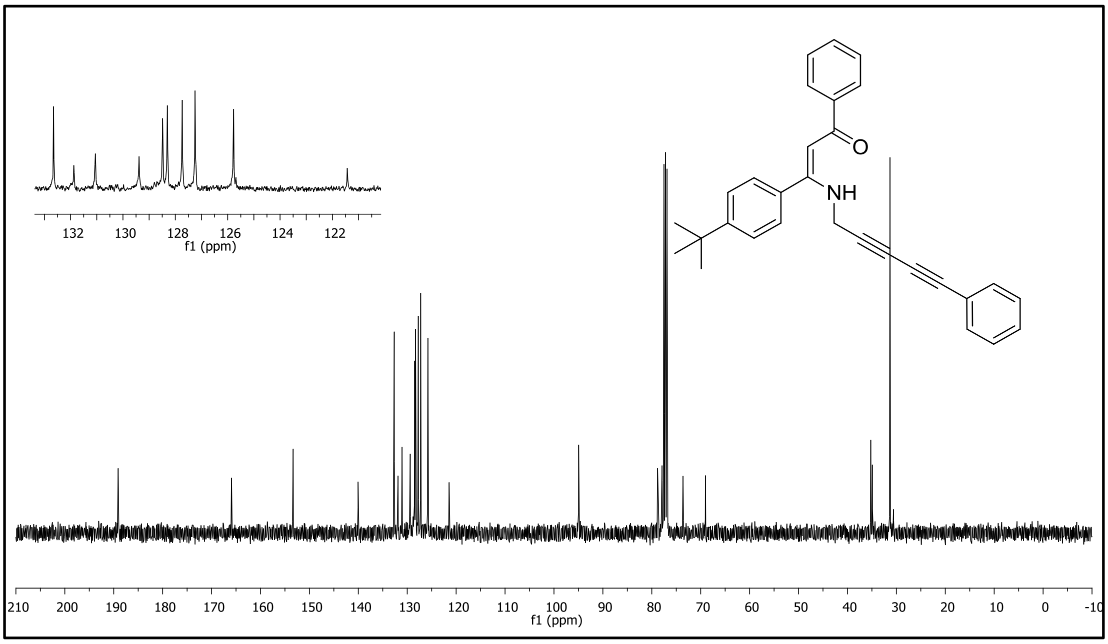

Figure 89. ^{13}C NMR spectrum of compound **56K**.

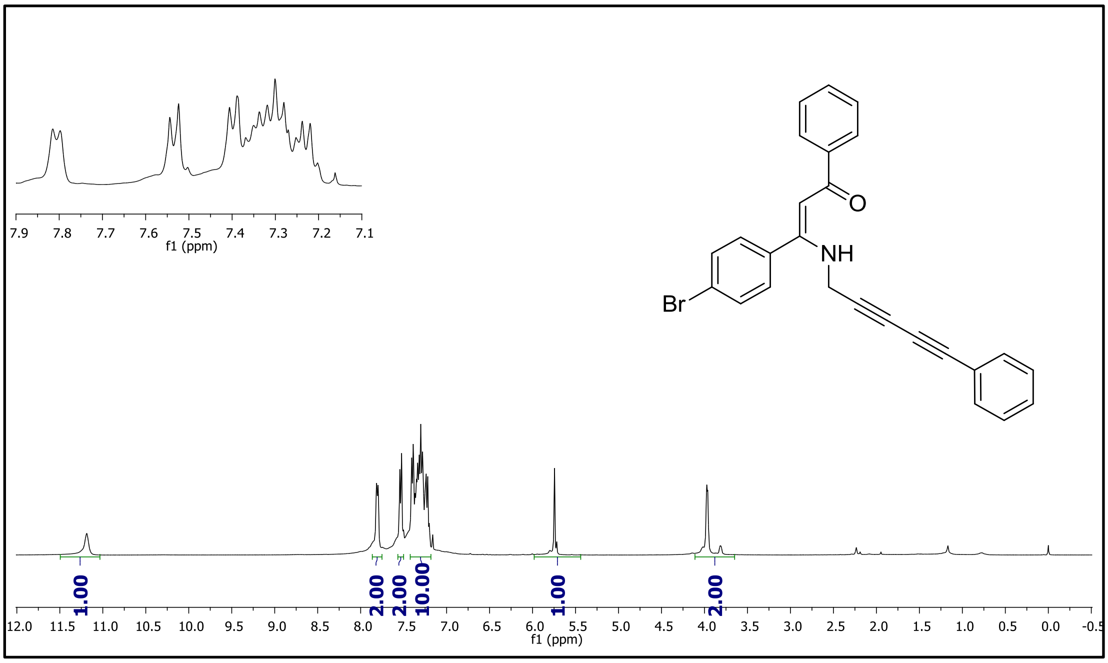

Figure 90. ^{1}H NMR spectrum of compound **56L**.

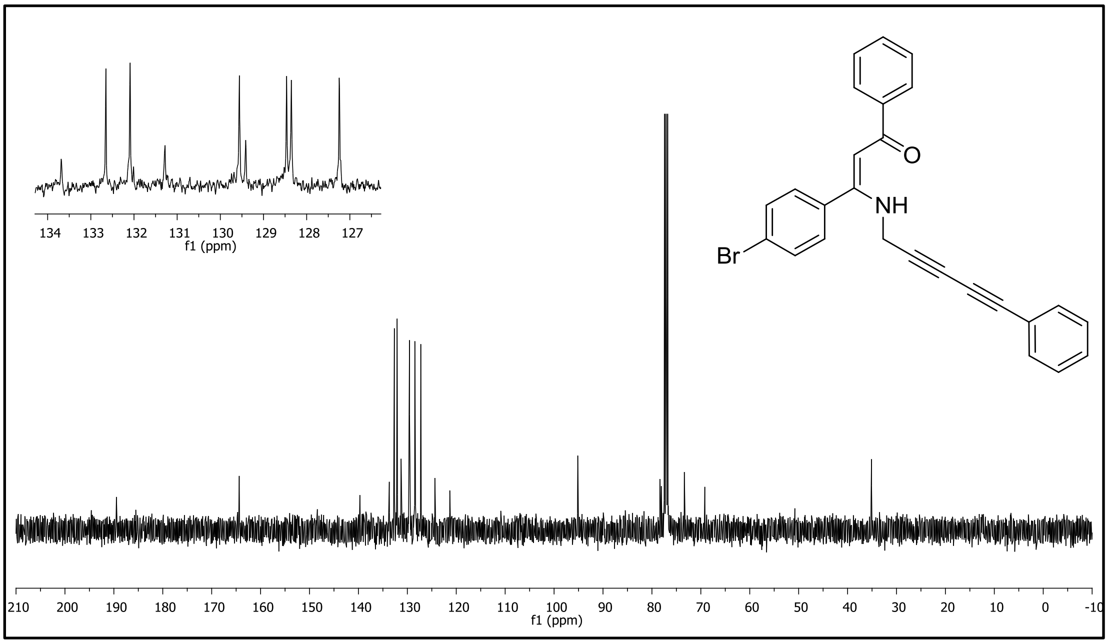

Figure 91. ^{13}C NMR spectrum of compound **56L**.

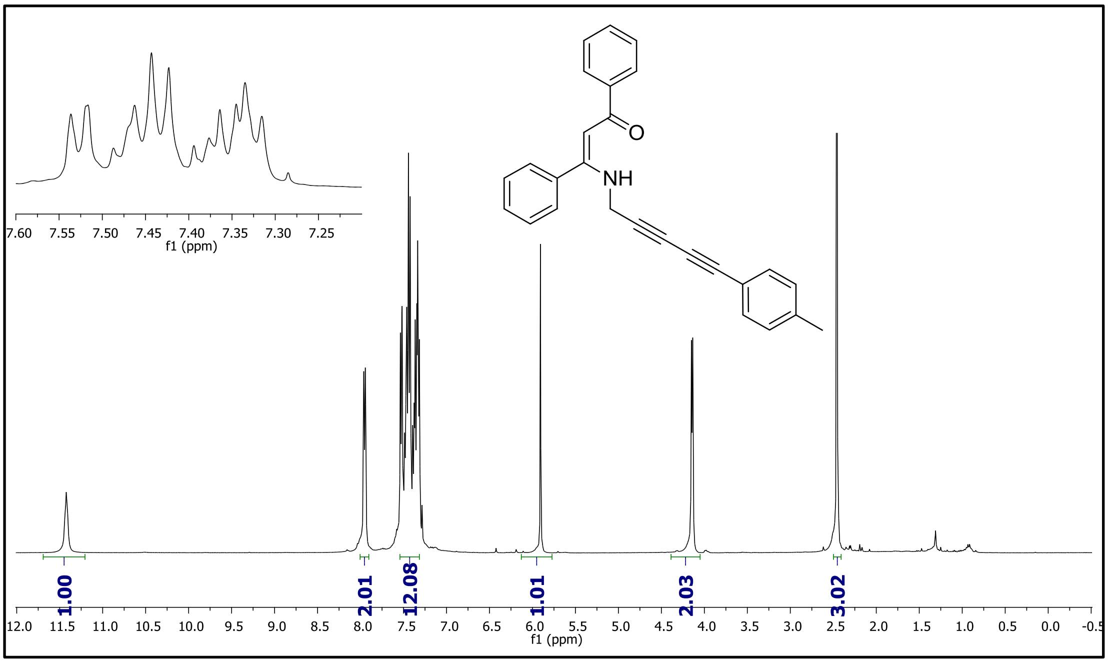

Figure 92. ^{1}H NMR spectrum of compound **56M.**

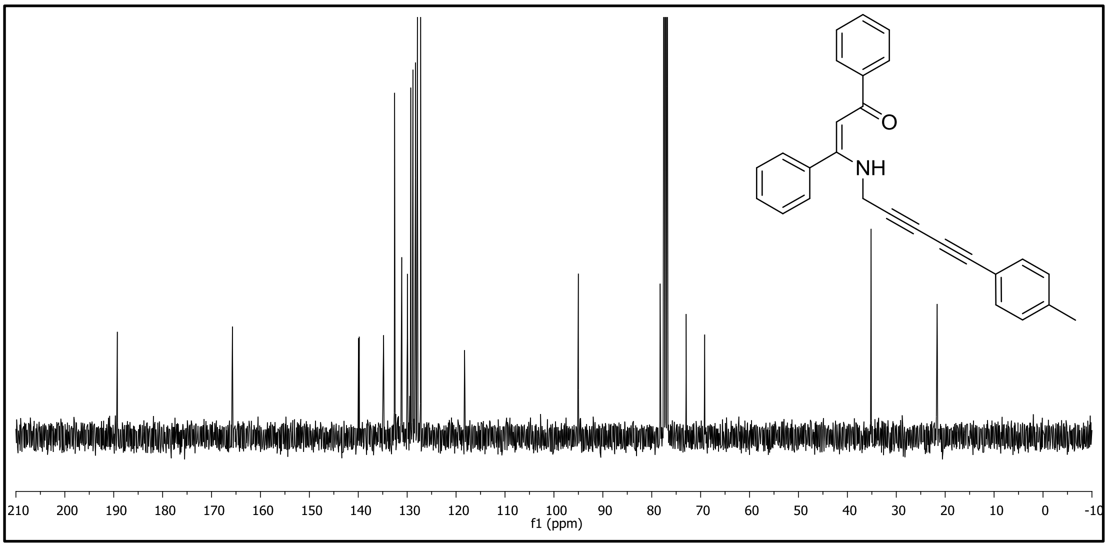

Figure 93. ^{13}C NMR spectrum of compound **56M**.

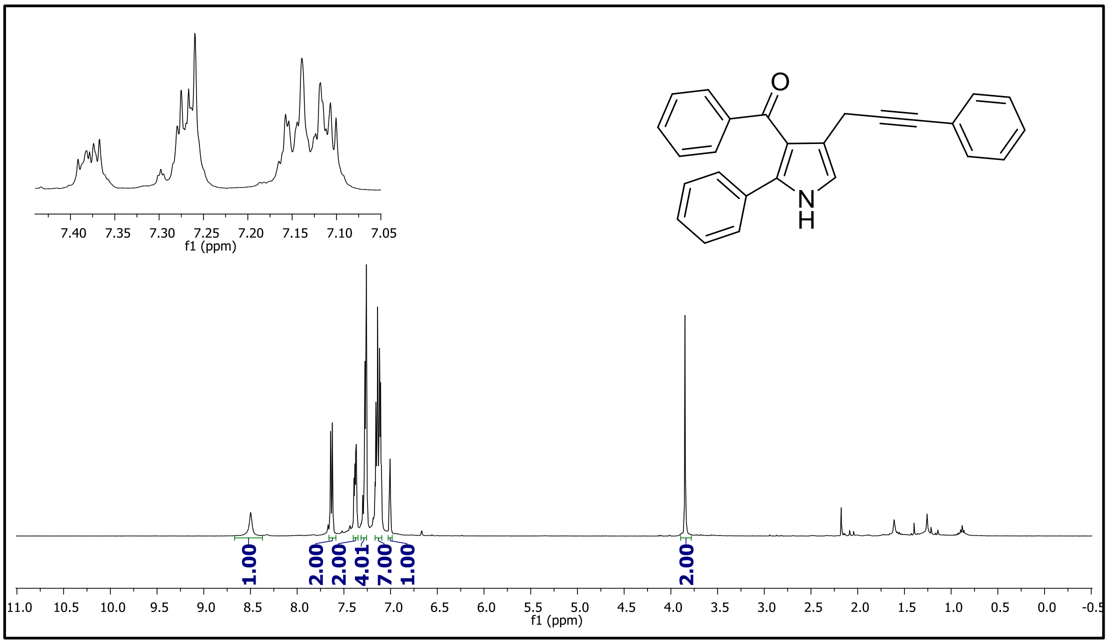

Figure 94. ^{1}H NMR spectrum of compound **57A**.

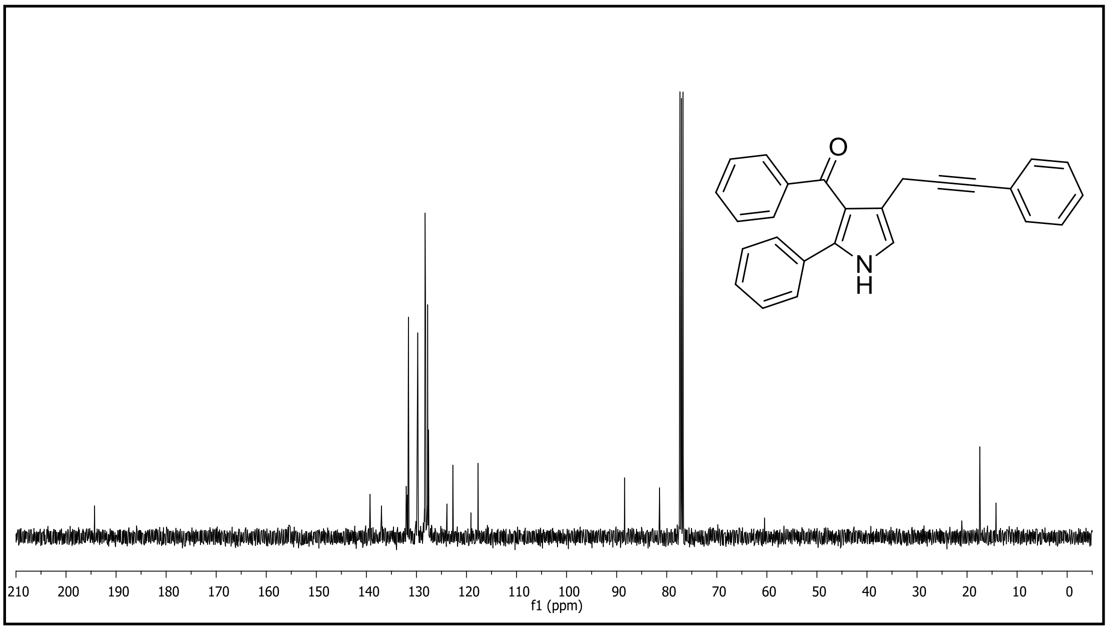

Figure 95. ^{13}C NMR spectrum of compound **57A**.

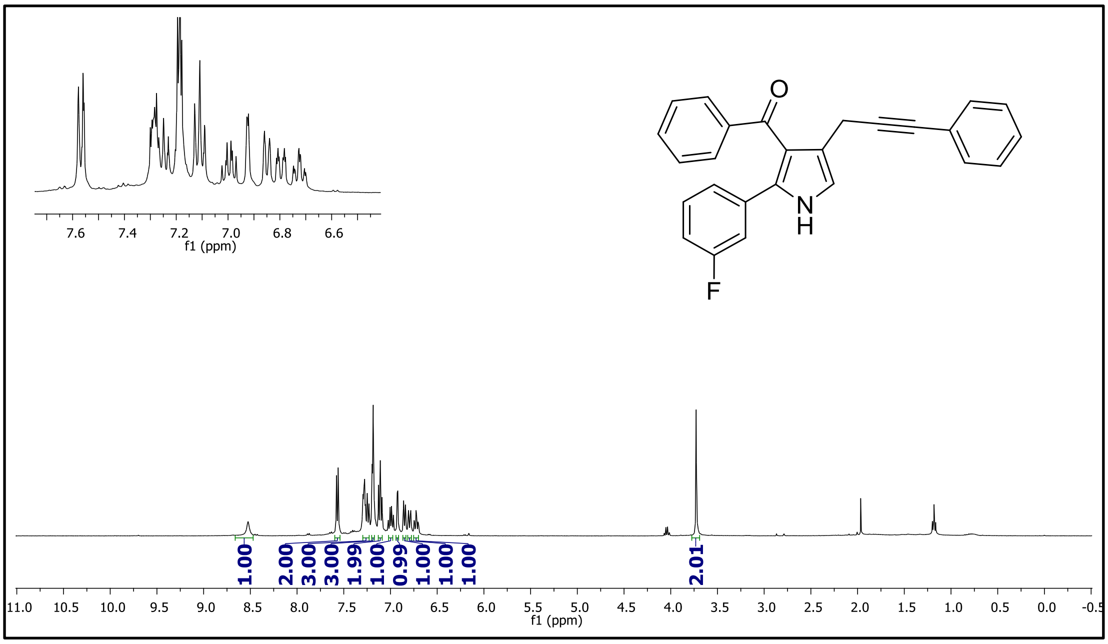

Figure 96. ^{1}H NMR spectrum of compound **57B**.

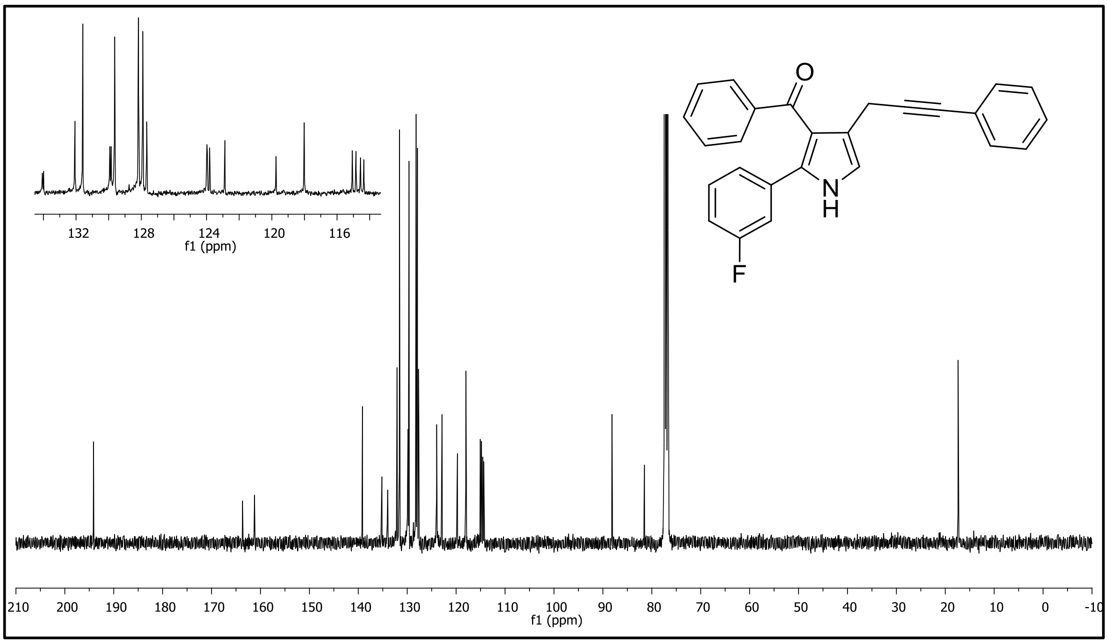

Figure 97. ^{13}C NMR spectrum of compound **57B**.

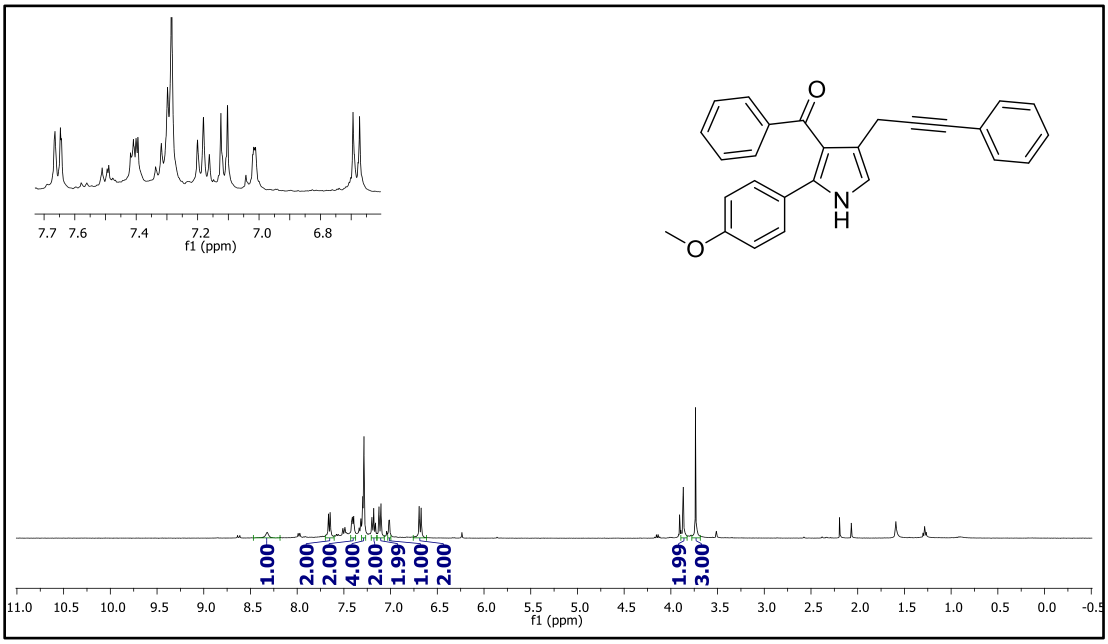

Figure 98. ^{1}H NMR spectrum of compound **57C**.

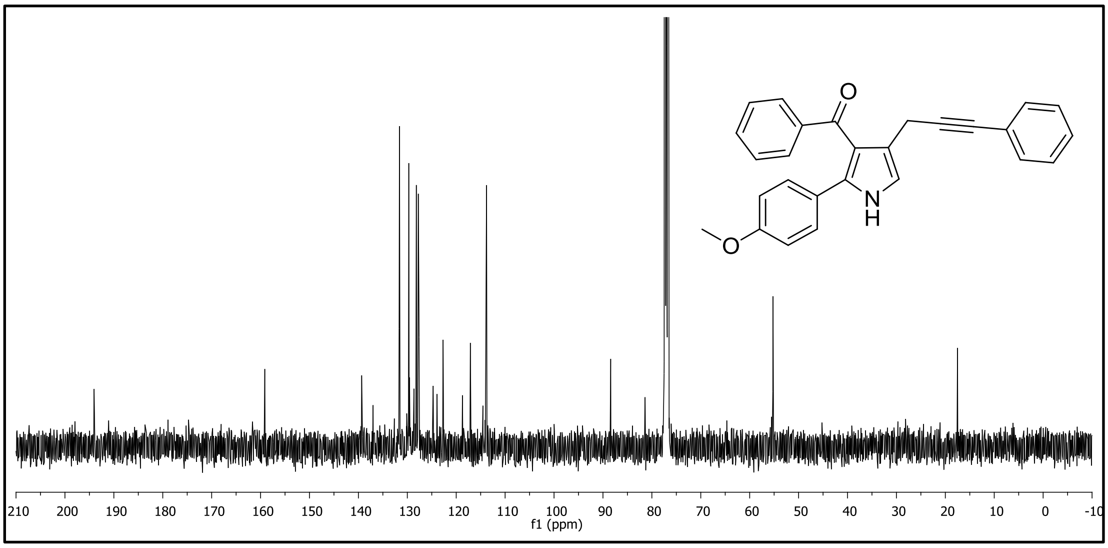

Figure 99. ^{13}C NMR spectrum of compound **57C**.

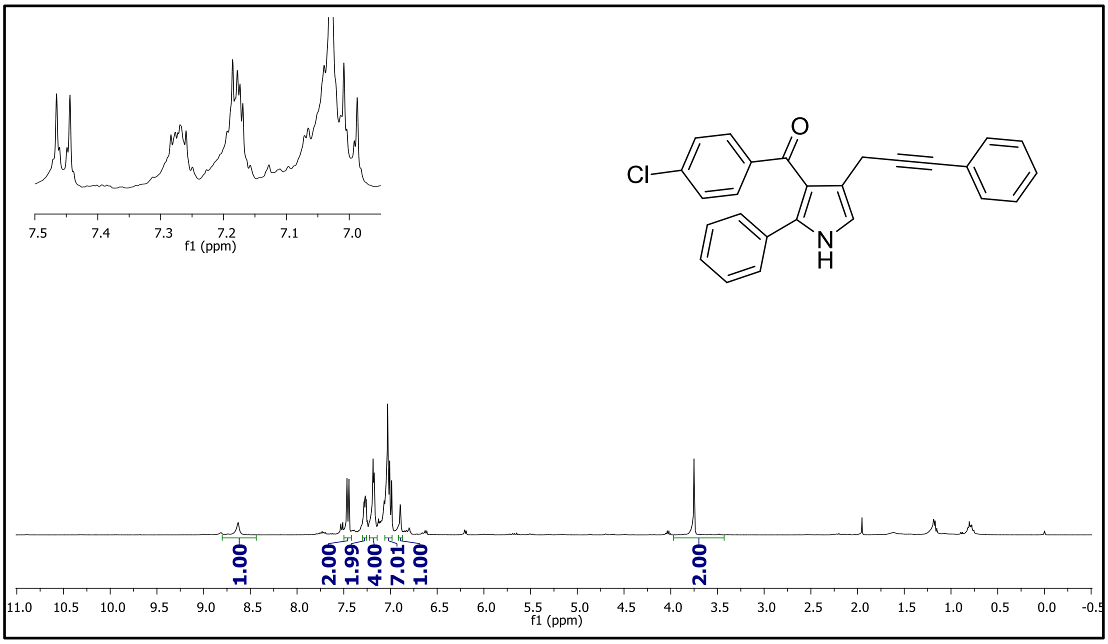

Figure 100. ^{1}H NMR spectrum of compound **57D**.

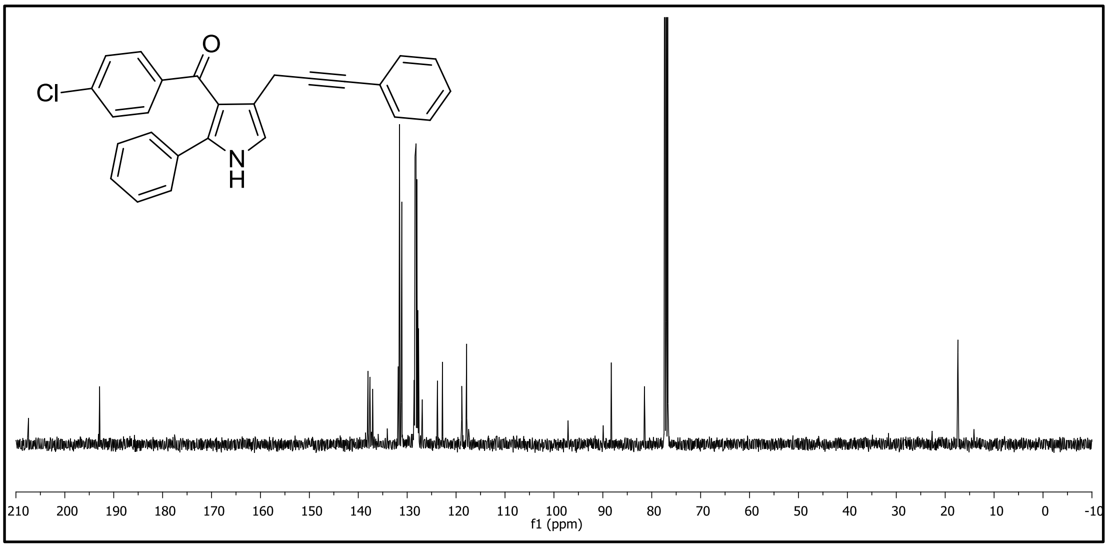

Figure 101. ^{13}C NMR spectrum of compound **57D**.

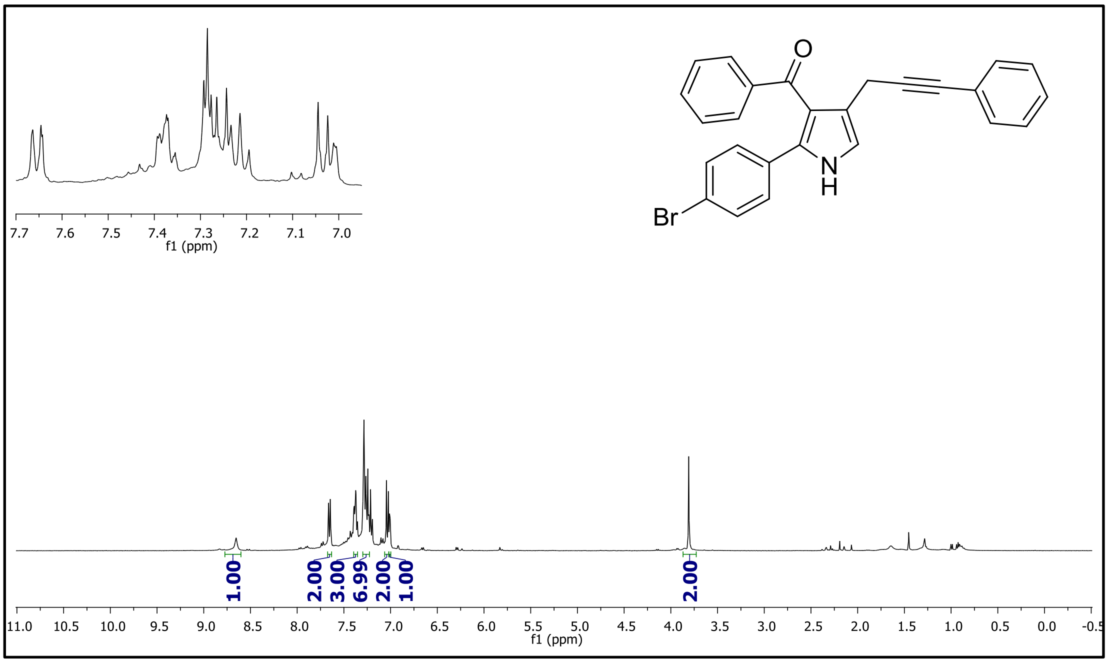

Figure 102. ^{1}H NMR spectrum of compound **57E**.

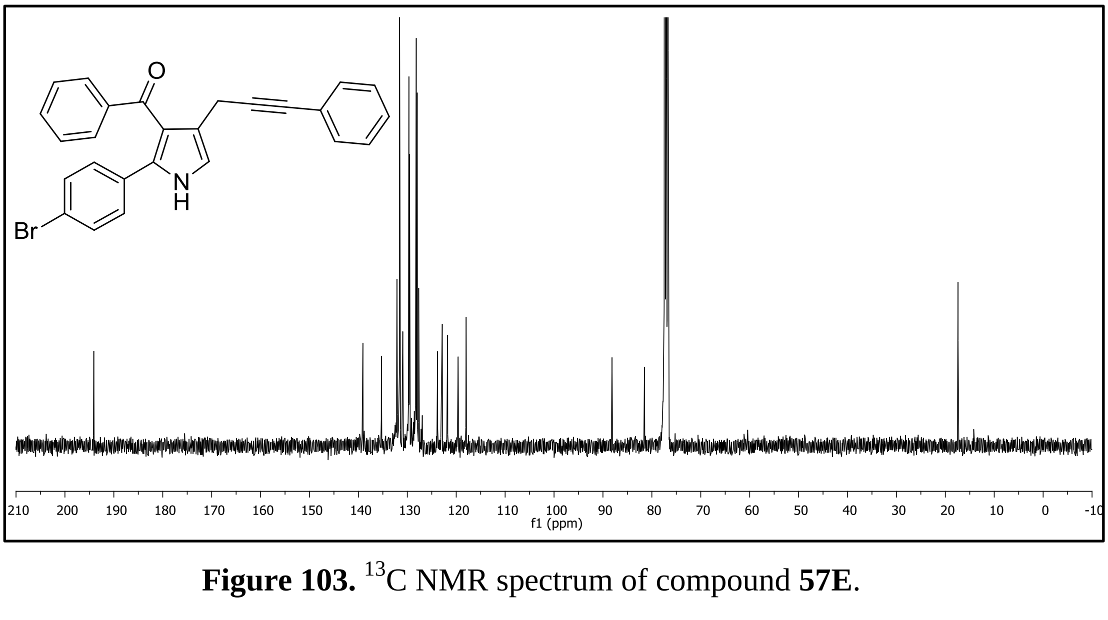

Figure 103. ^{13}C NMR spectrum of compound **57E**.

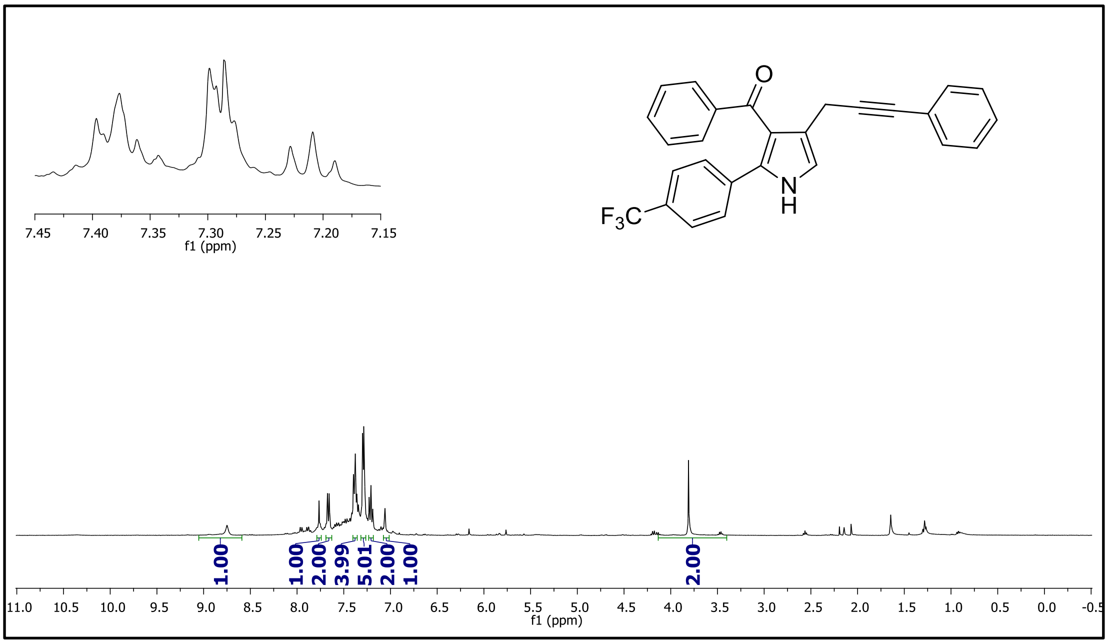

Figure 104. ^{1}H NMR spectrum of compound **57F**.

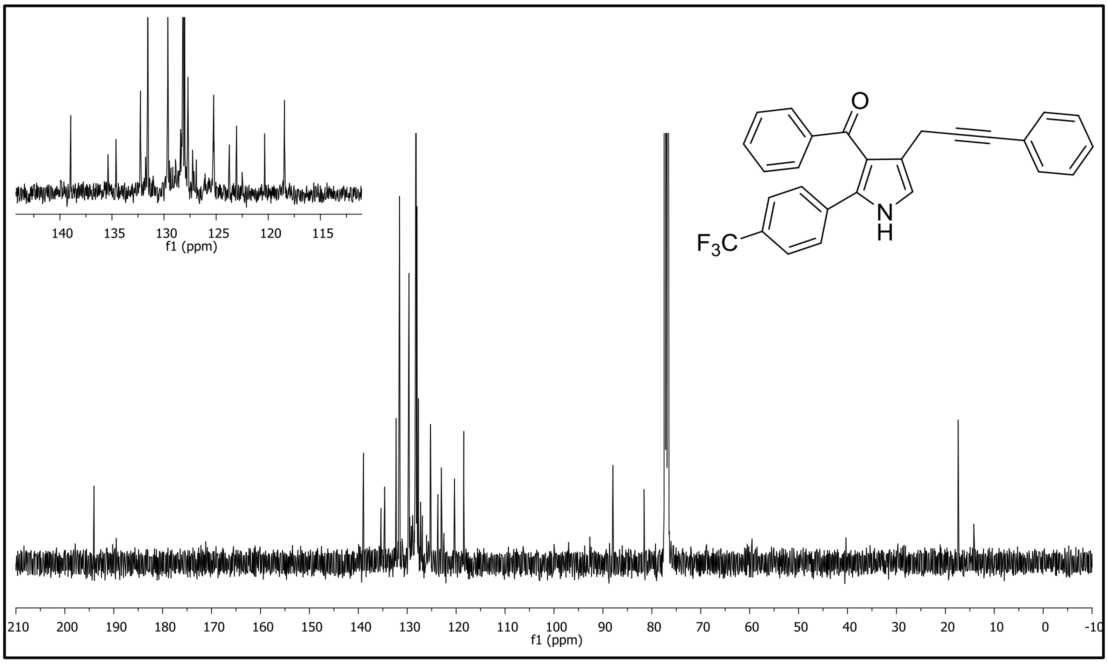

Figure 105. ^{13}C NMR spectrum of compound **57F**.

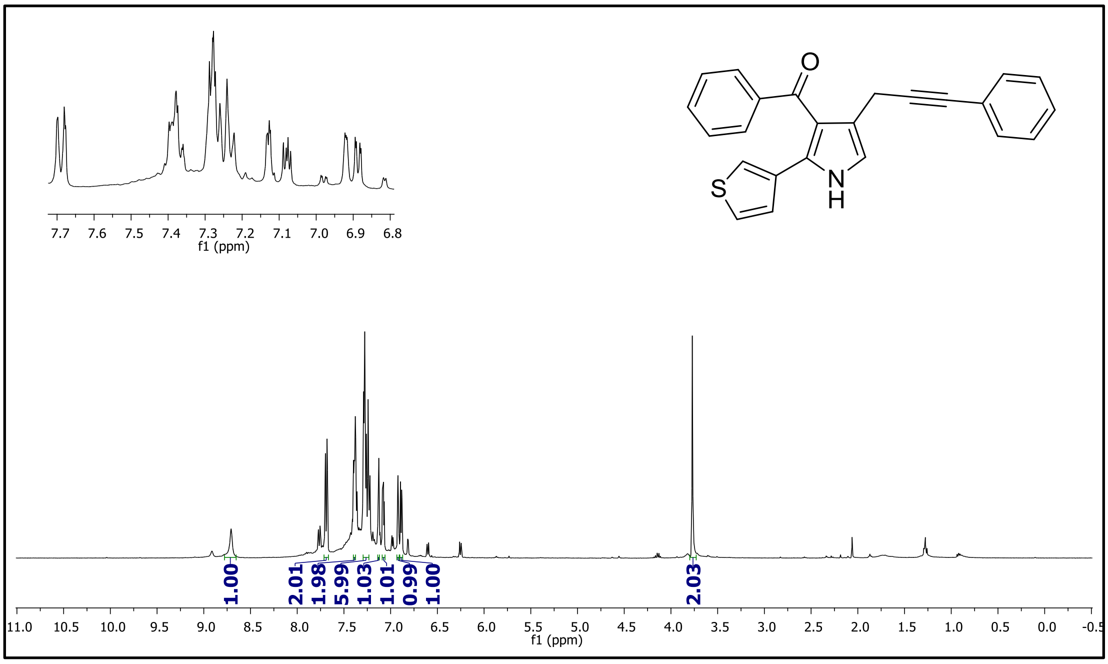

Figure 106. ^{1}H NMR spectrum of compound **57G**.

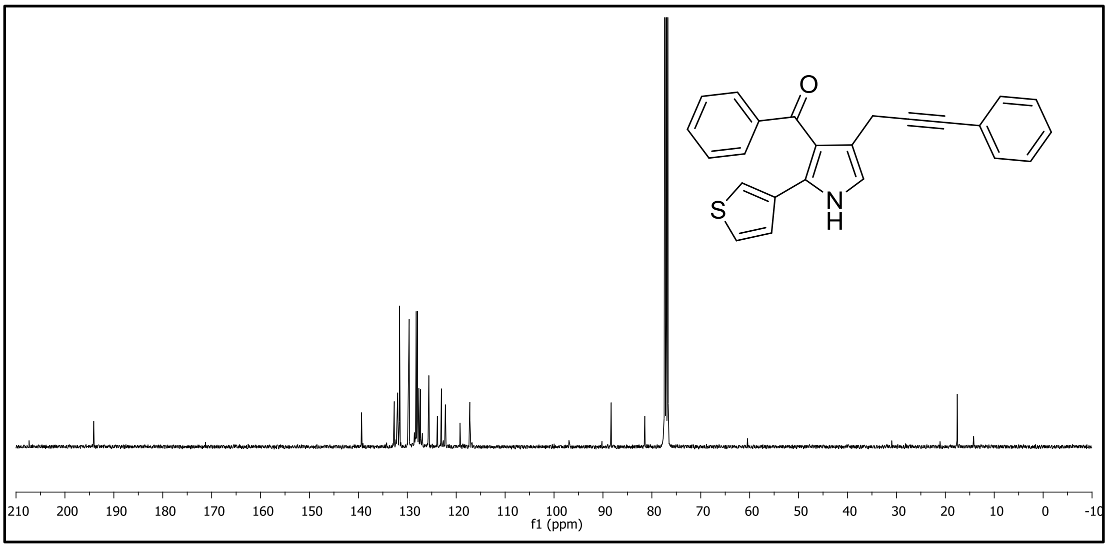

Figure 107. ^{13}C NMR spectrum of compound **57G**.

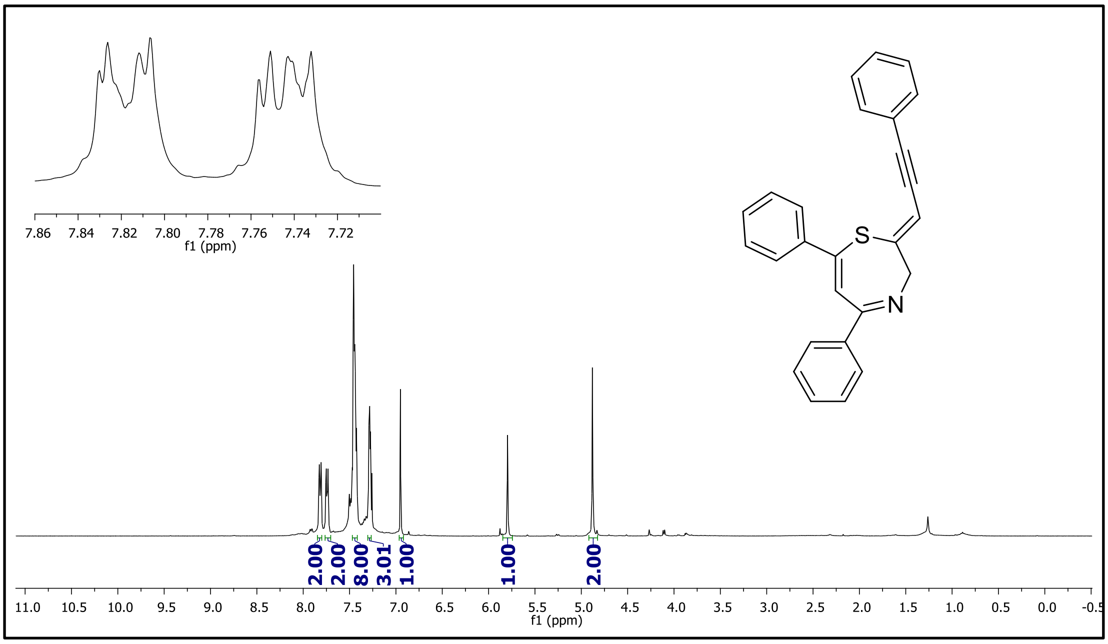

Figure 108. ^{1}H NMR spectrum of compound **58A**.

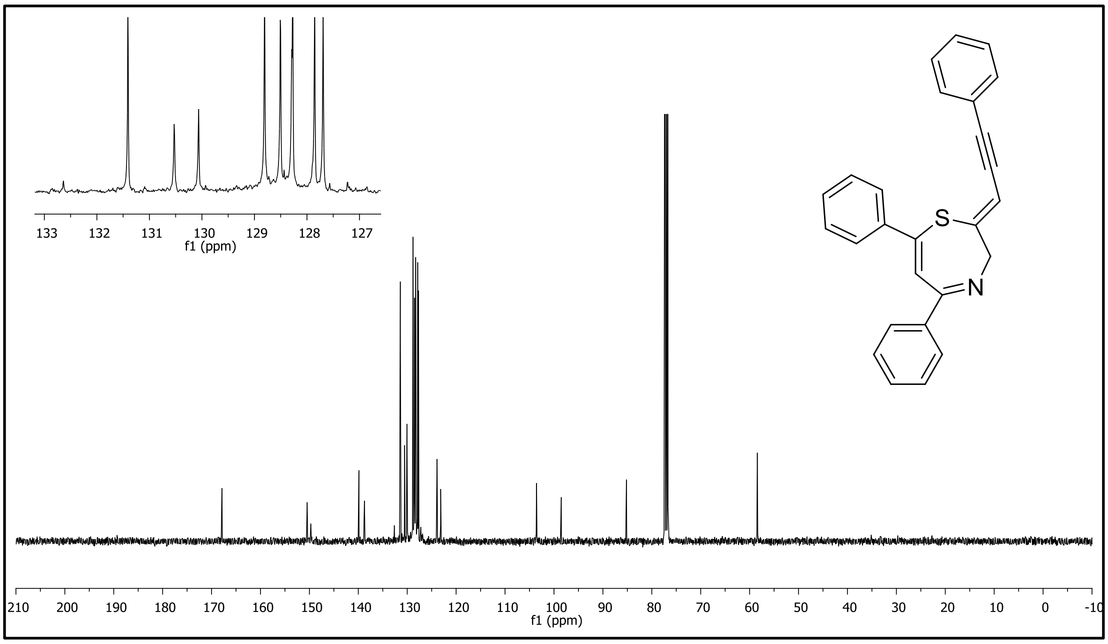

Figure 109. ^{13}C NMR spectrum of compound **58A**.

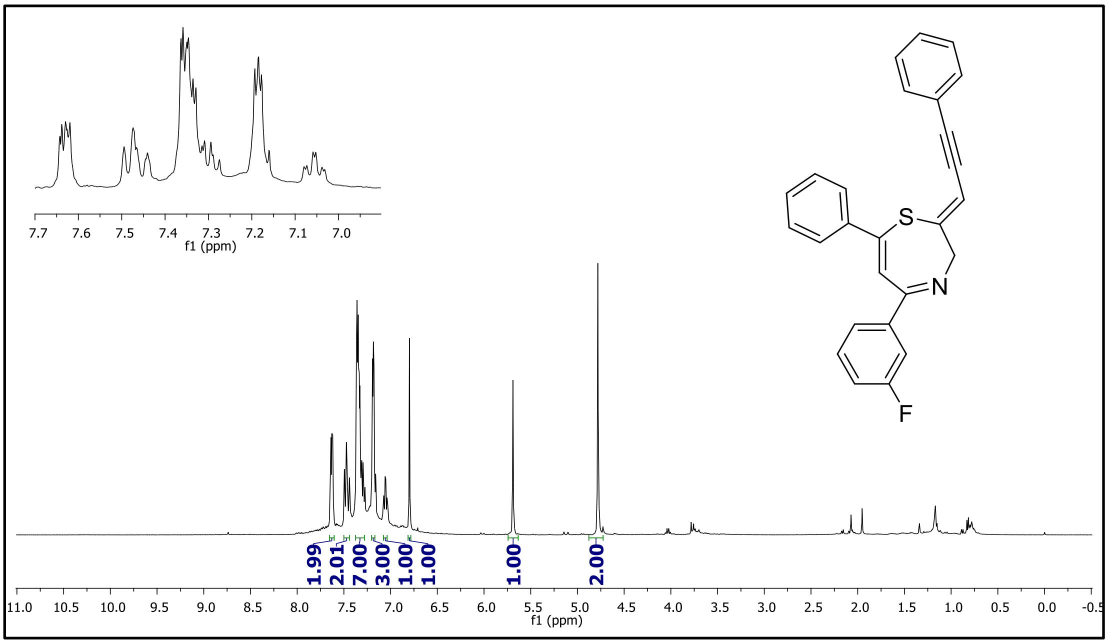

Figure 110. ^{1}H NMR spectrum of compound **58B**.

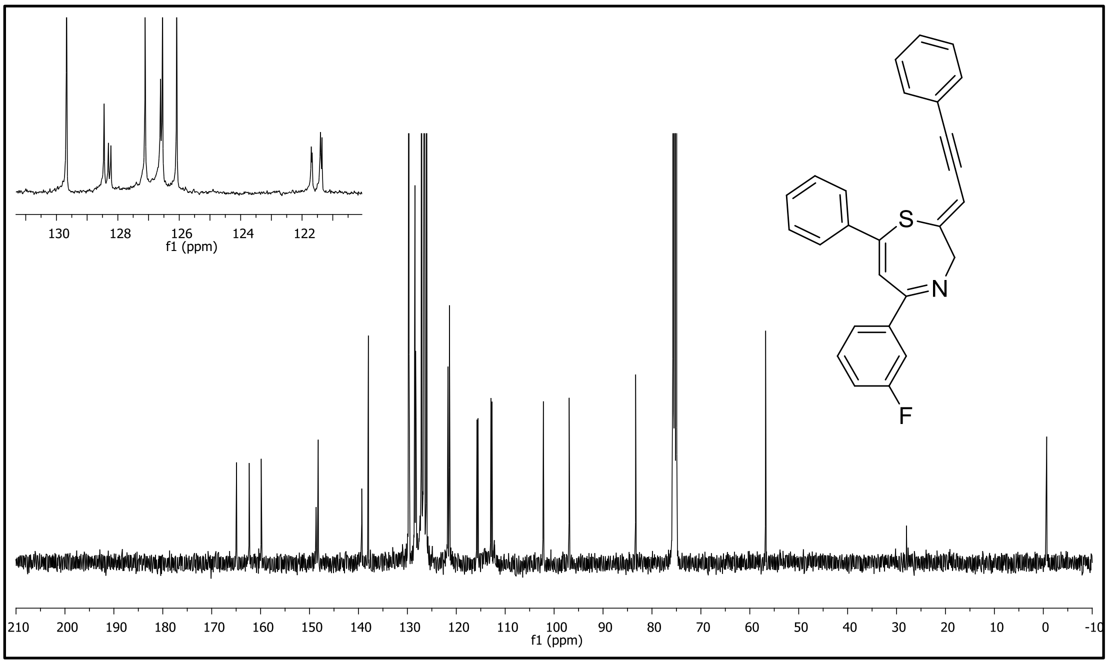

Figure 111. ^{13}C NMR spectrum of compound **58B**.

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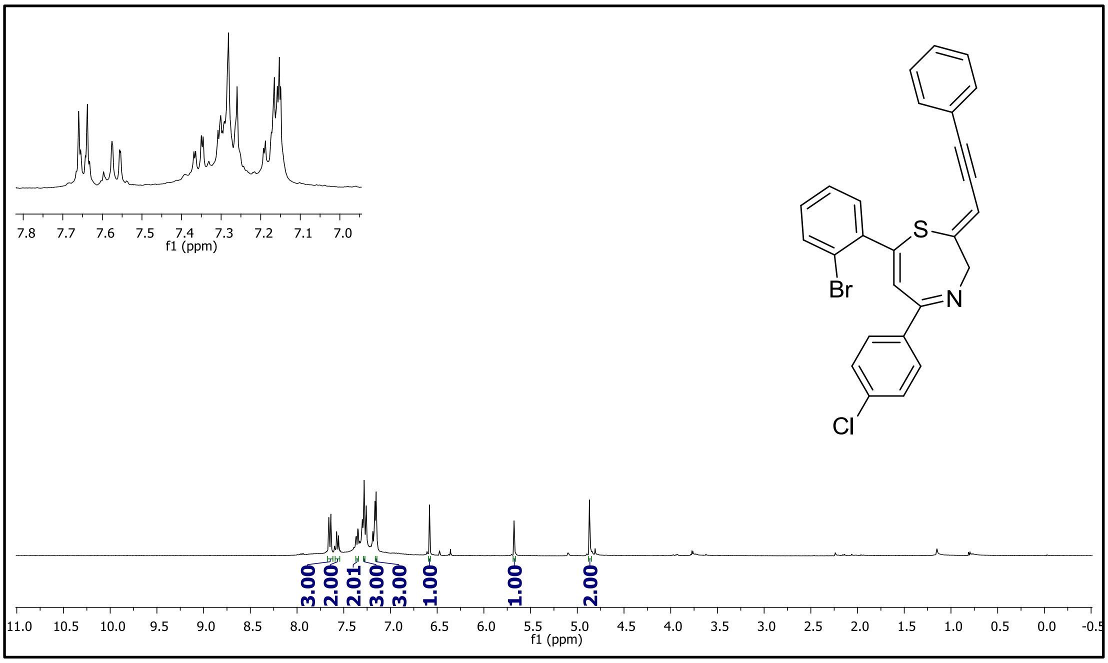

Figure 112. ^{1}H NMR spectrum of compound **58C**.

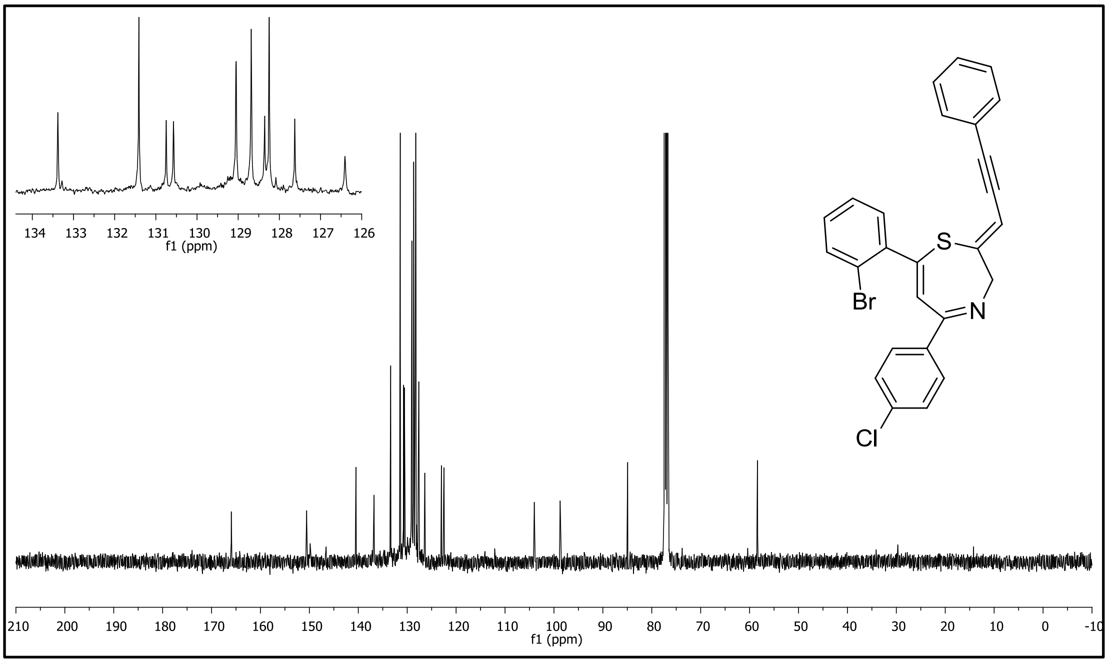

Figure 113. ^{13}C NMR spectrum of compound **58C**.

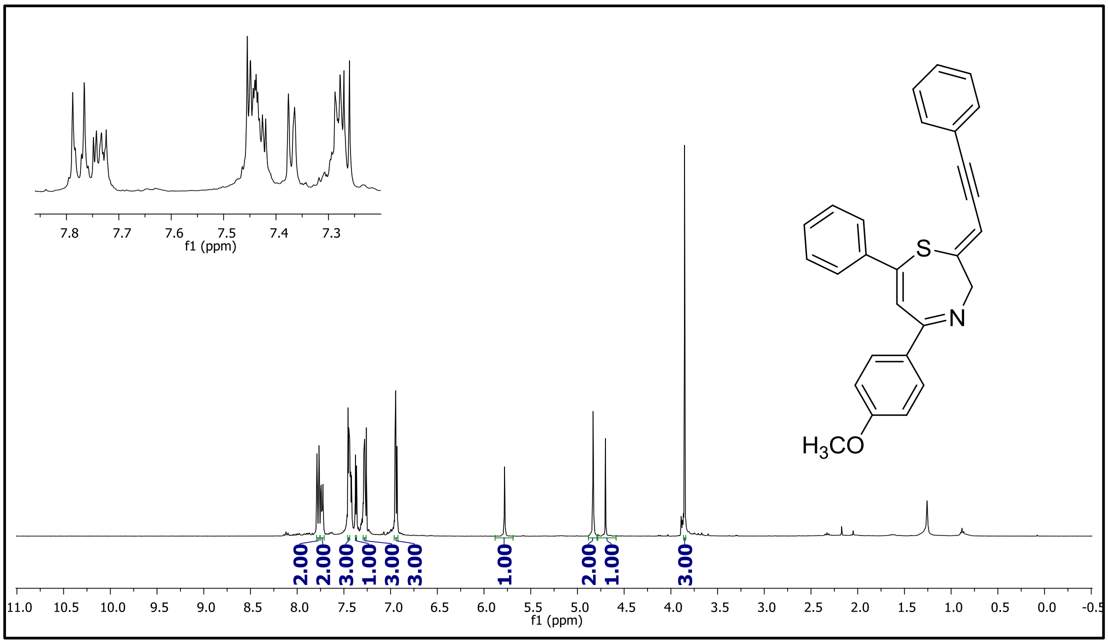

Figure 114. ^{1}H NMR spectrum of compound **58D**.

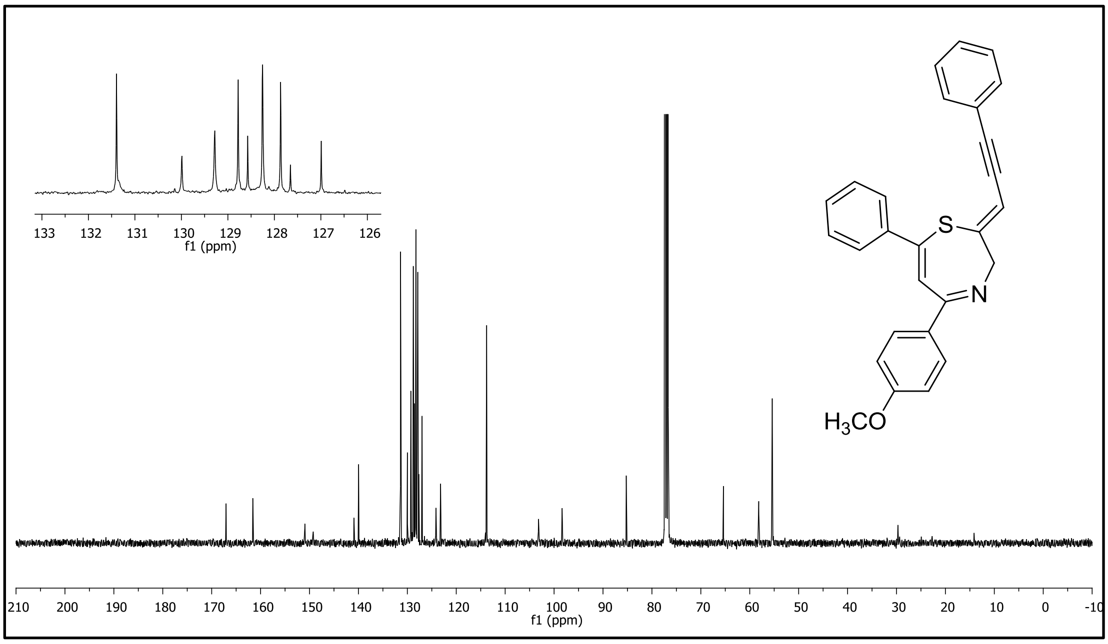

Figure 115. ^{13}C NMR spectrum of compound **58D**.

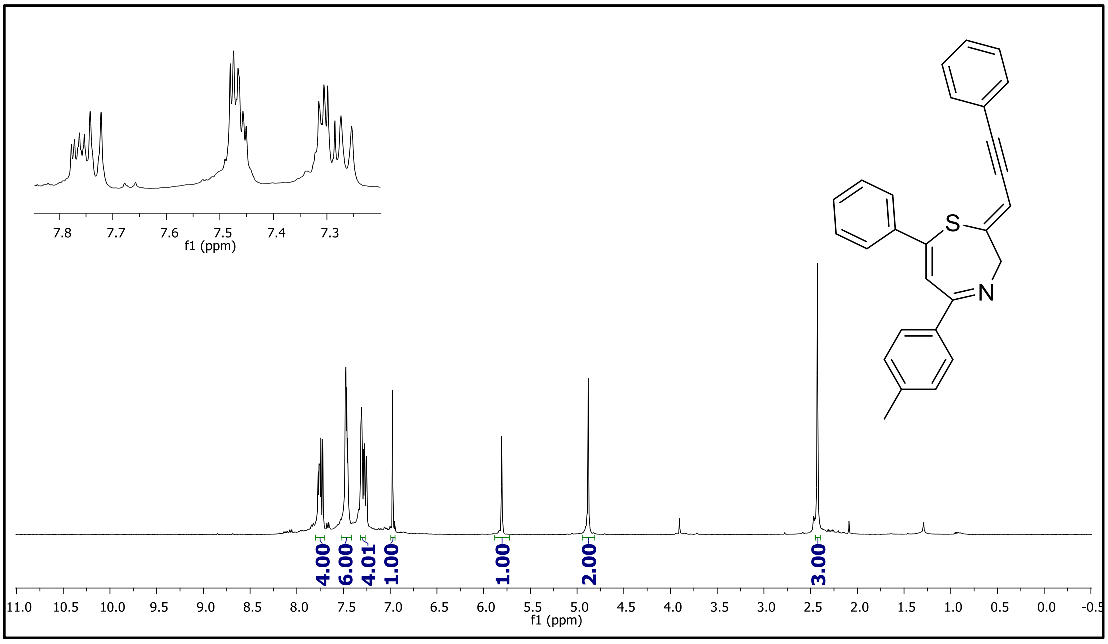

Figure 116. ^{1}H NMR spectrum of compound **58E**.

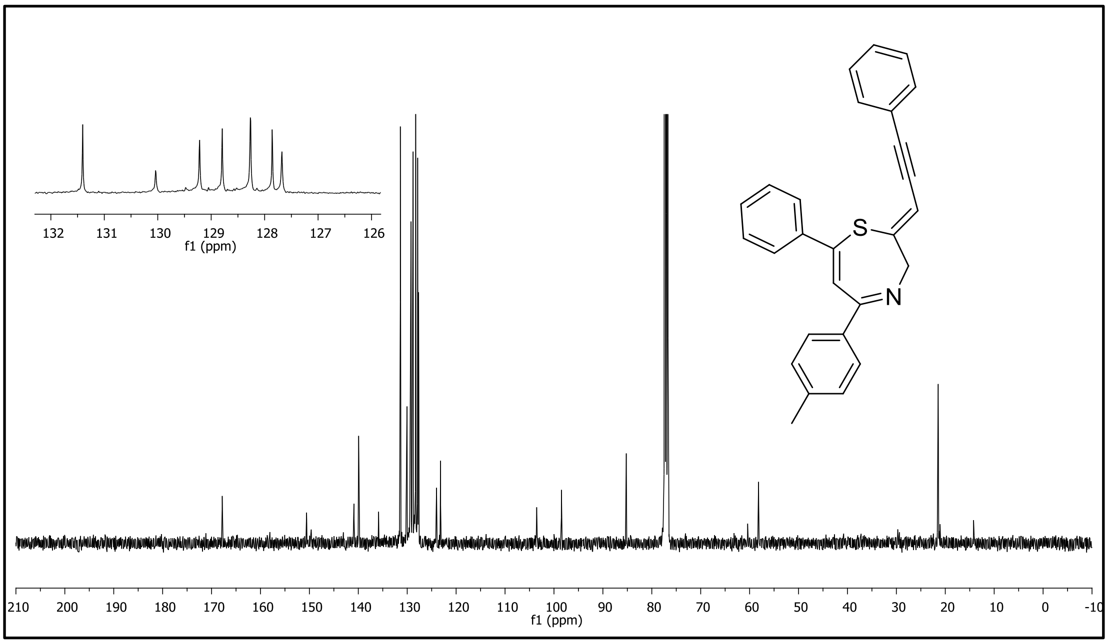

Figure 117. ^{13}C NMR spectrum of compound **58E**.

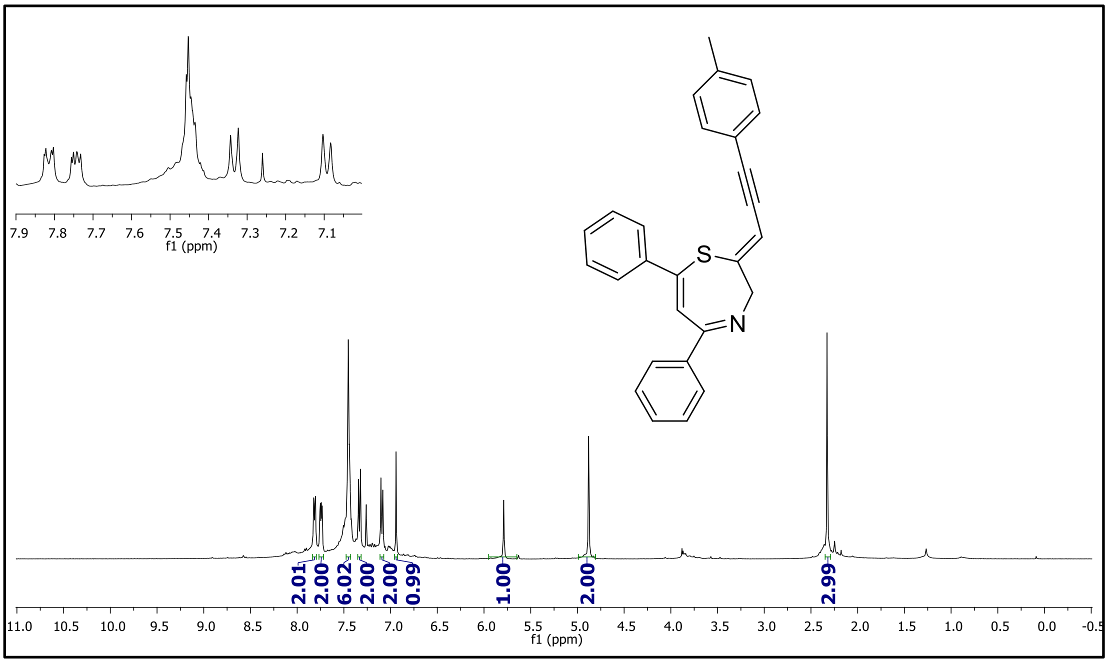

Figure 118. ^{1}H NMR spectrum of compound **58F**.

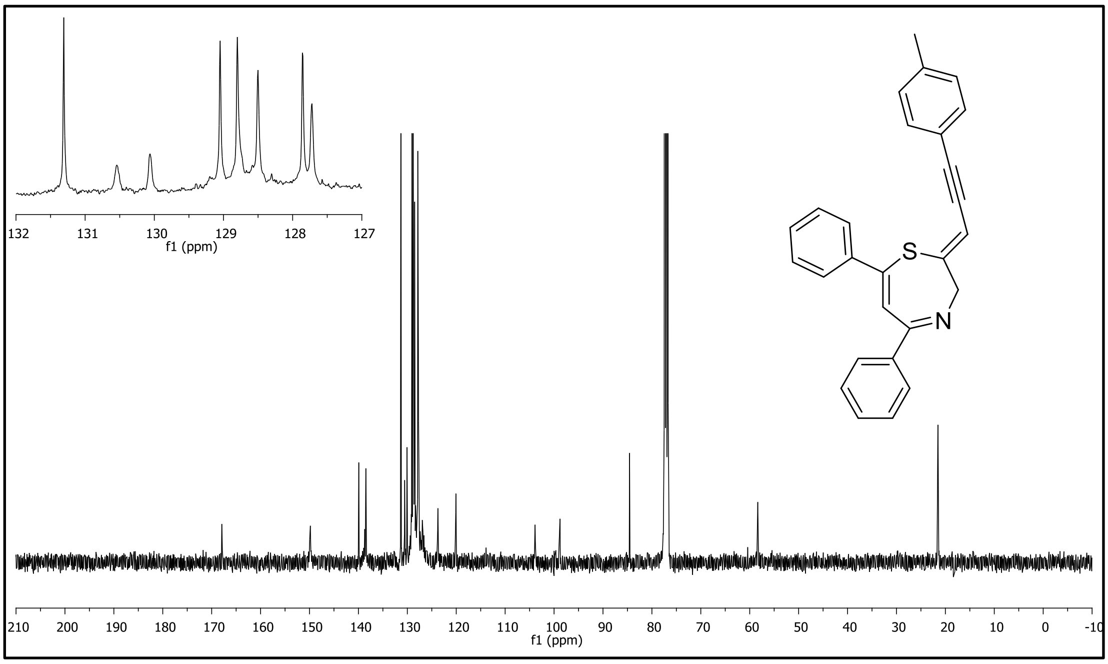

Figure 119. ^{13}C NMR spectrum of compound **58F**.

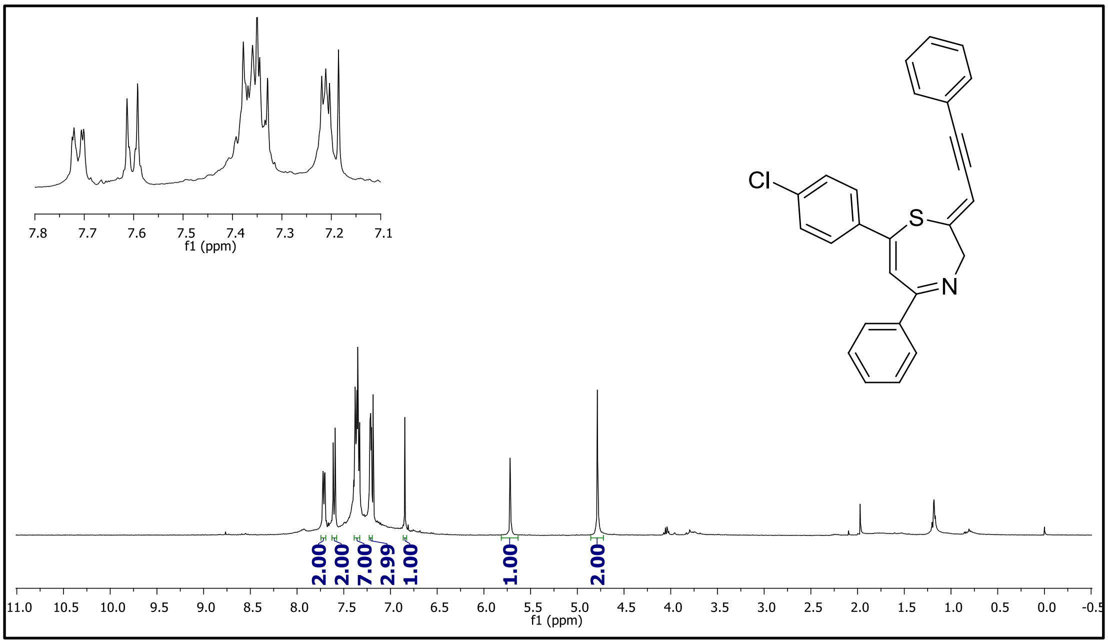

Figure 120. ^{1}H NMR spectrum of compound **58G**.

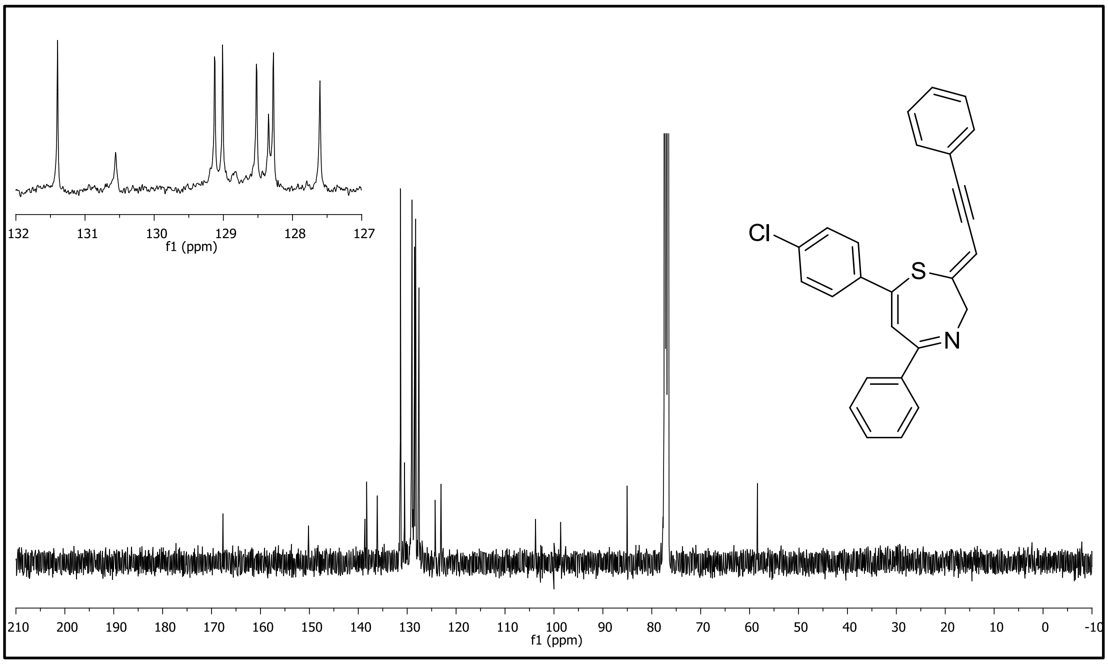

Figure 121. ^{13}C NMR spectrum of compound **58G**.

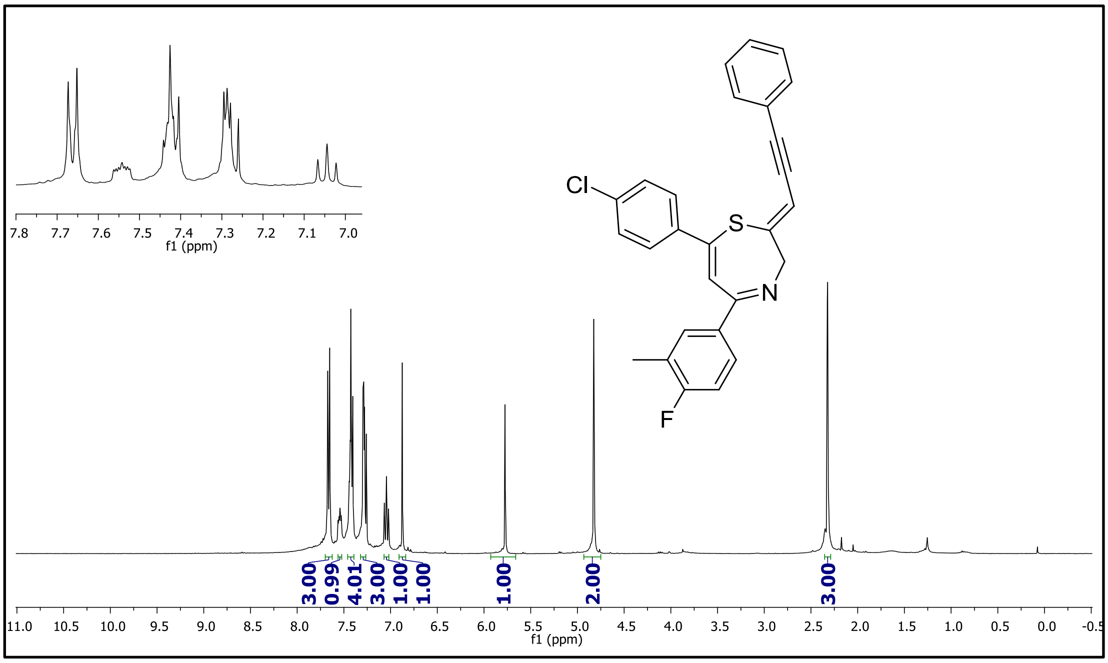

Figure 122. ^{1}H NMR spectrum of compound **58H**.

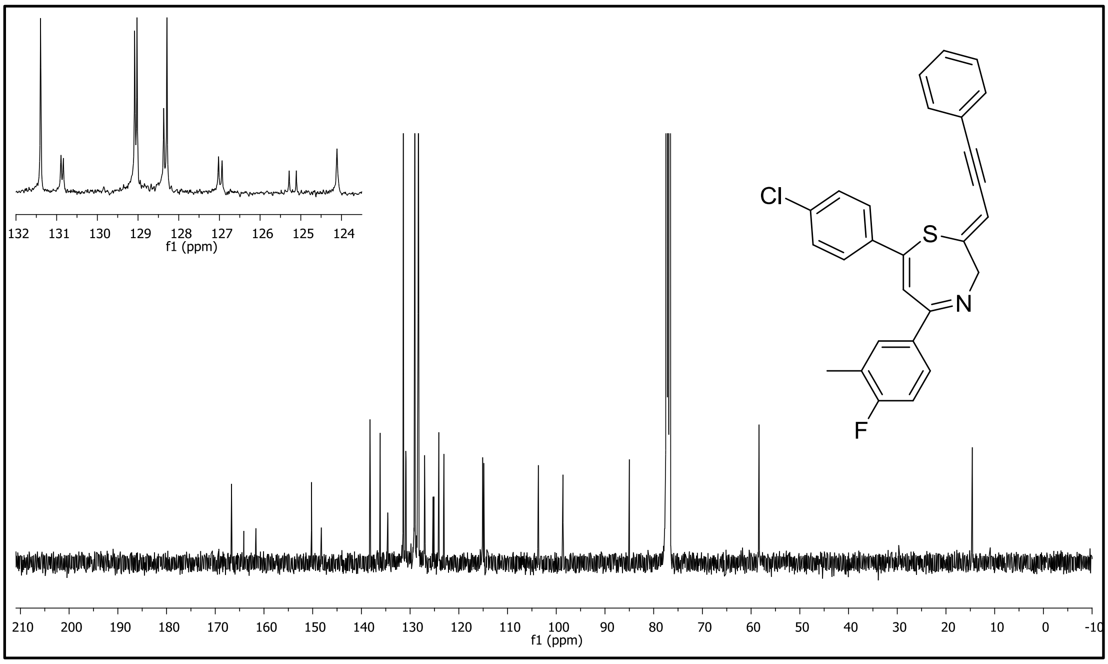

Figure 123. ^{13}C NMR spectrum of compound **58H**.

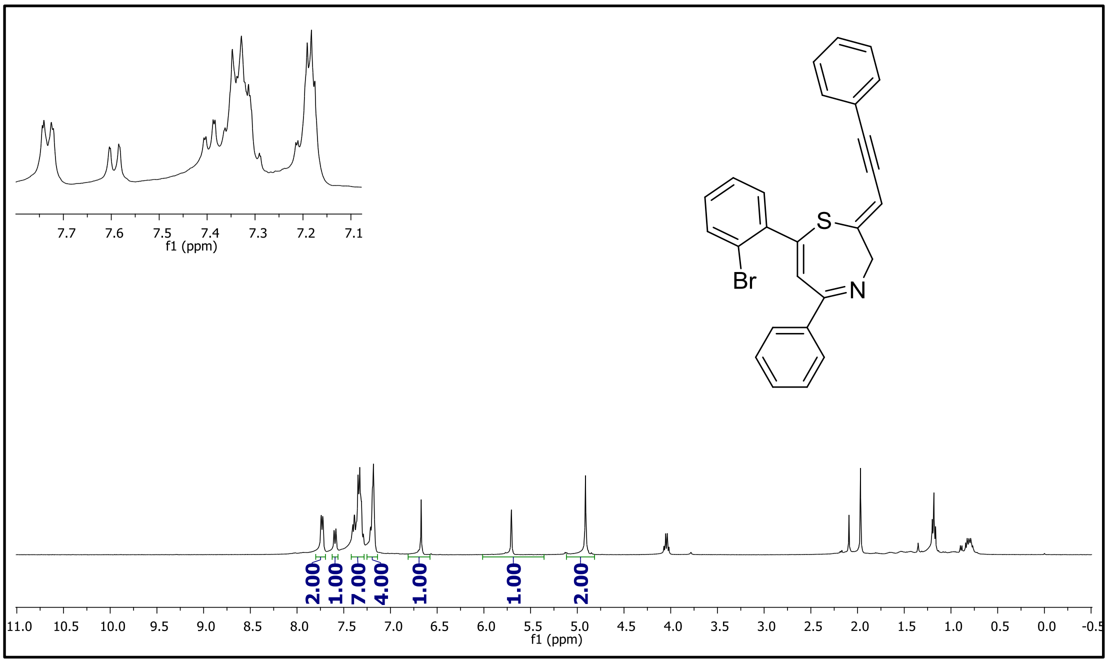

Figure 124. ^{1}H NMR spectrum of compound **58I**.

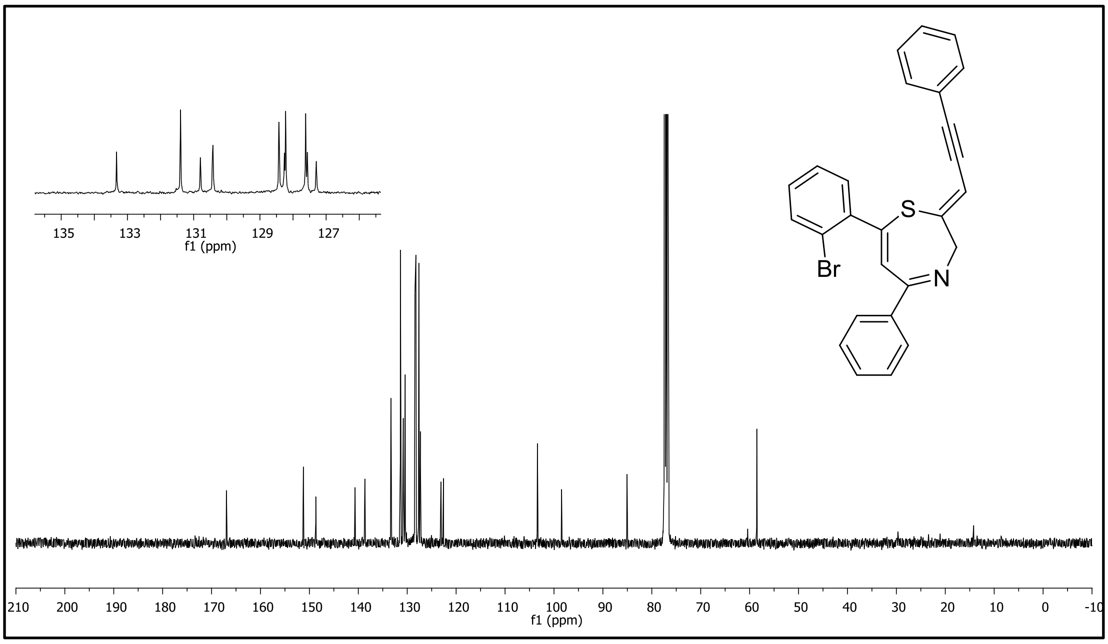

Figure 125. ^{13}C NMR spectrum of compound **58I**.

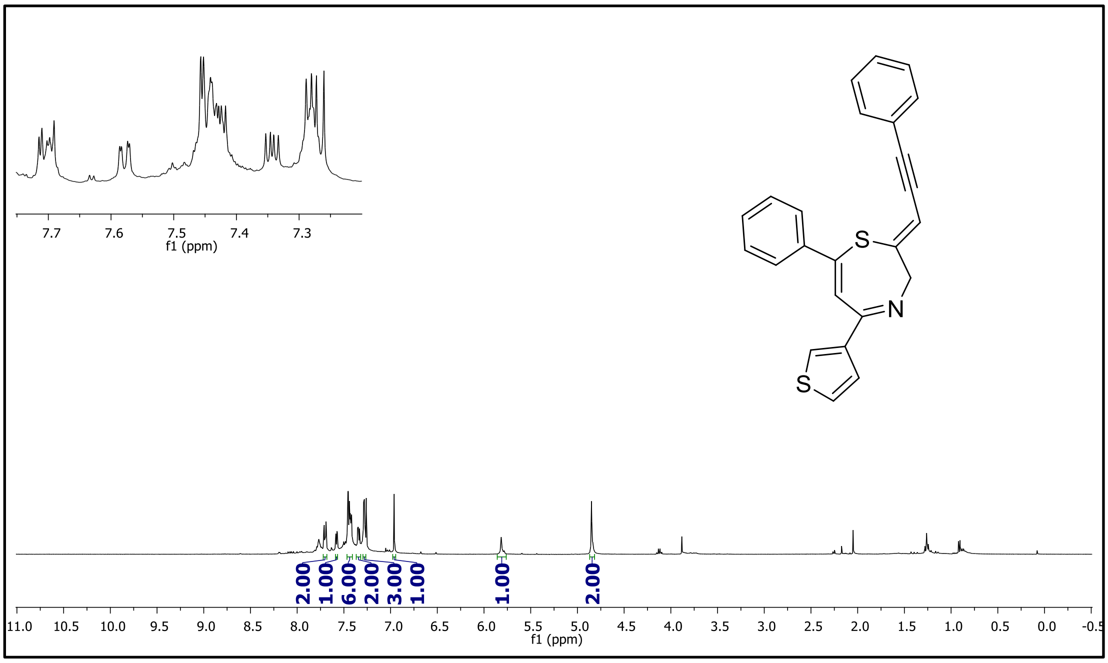

Figure 126. ^{1}H NMR spectrum of compound **58J**.

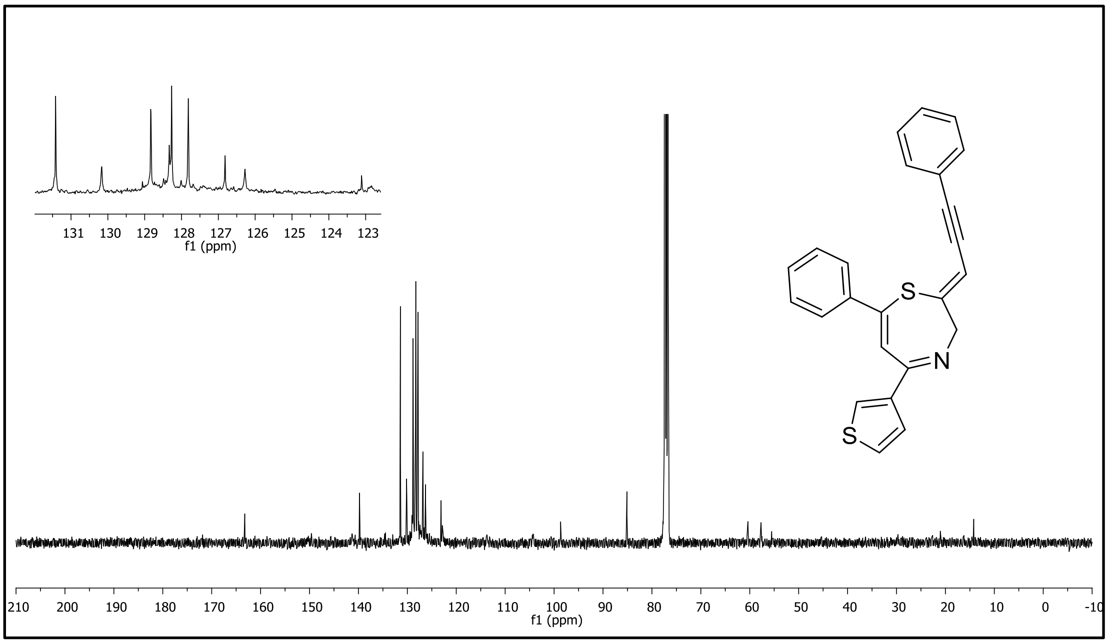

Figure 127. ^{13}C NMR spectrum of compound **58J**.

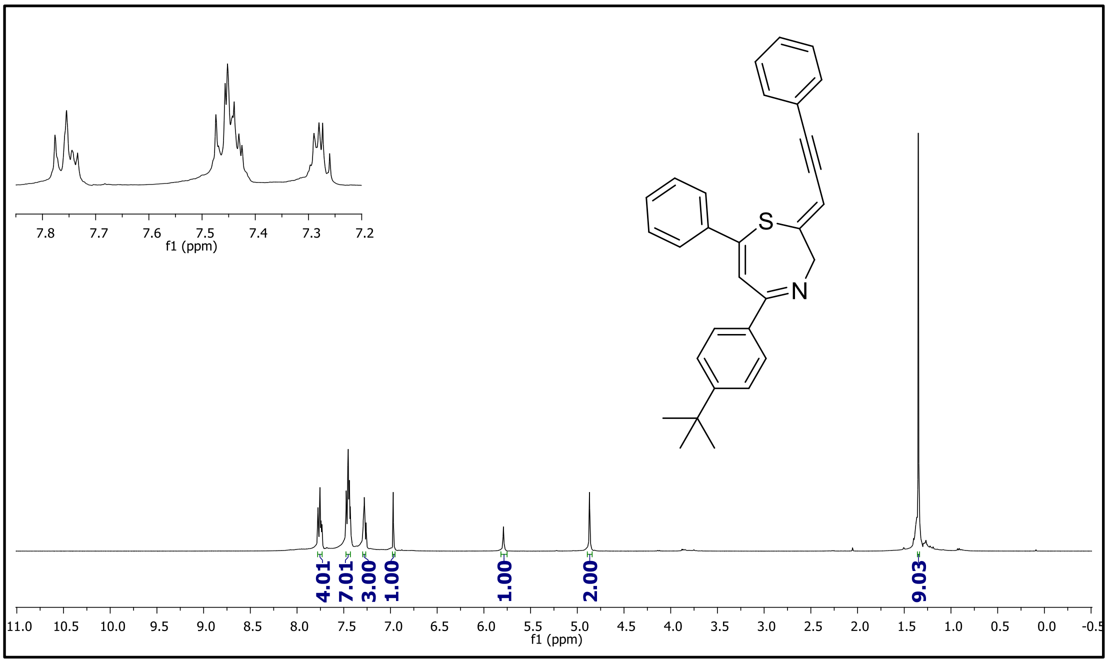

Figure 128. ^{1}H NMR spectrum of compound **58K**.

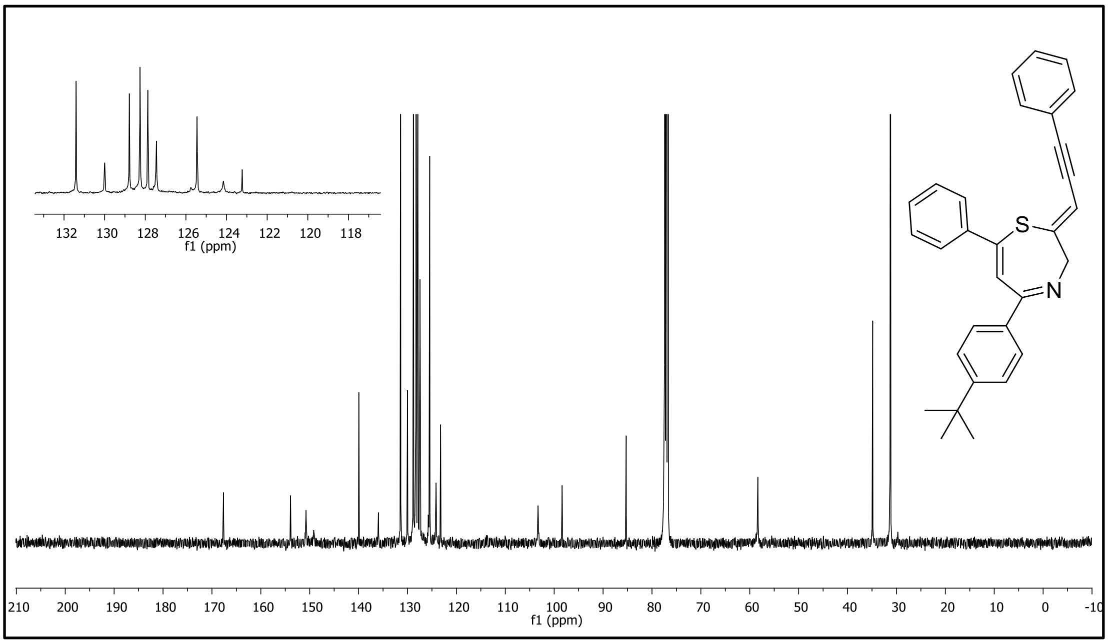

Figure 129. ^{13}C NMR spectrum of compound **58K**.

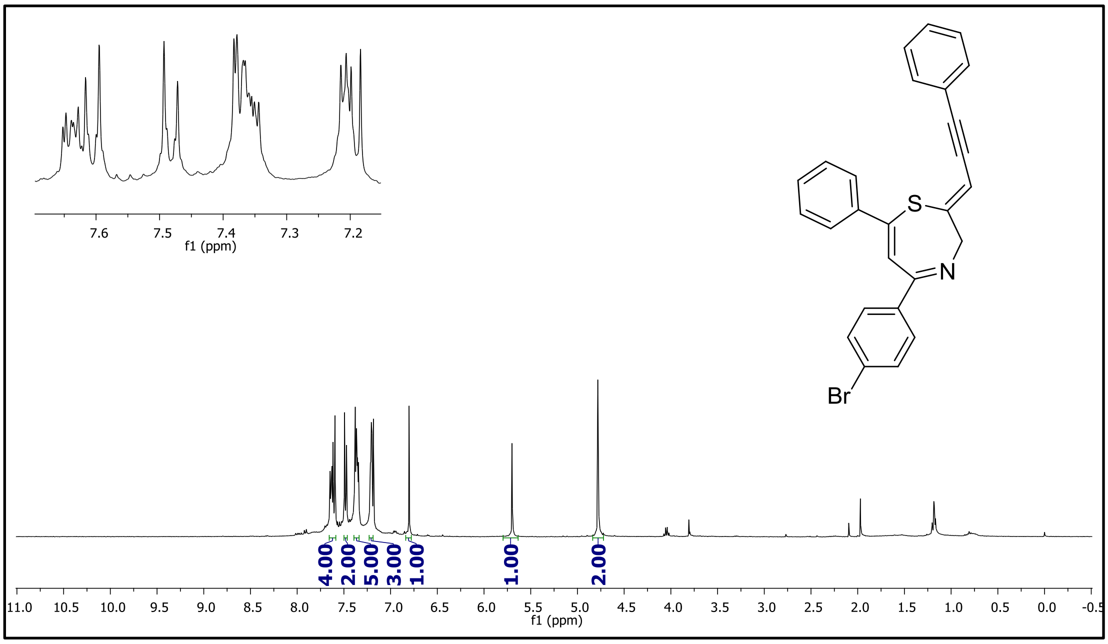

Figure 130. ^{1}H NMR spectrum of compound **58L**.

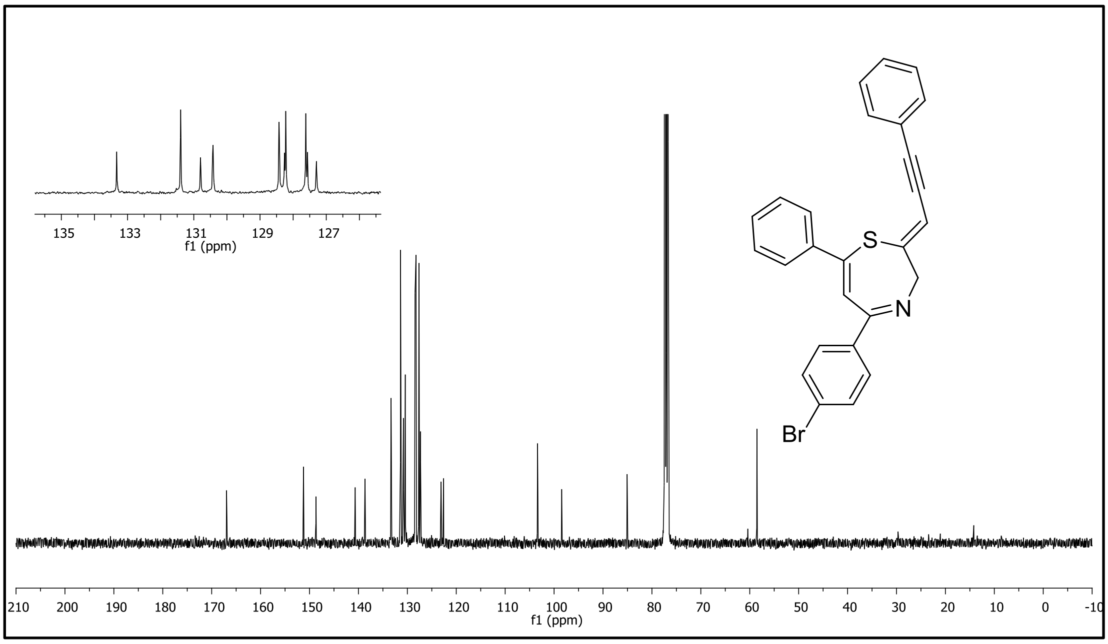

Figure 131. ^{13}C NMR spectrum of compound **58L**.