SYNTHESIS OF 6-HALOGEN-SUBSTITUTED 2-METHYLENE-2,3-DIHYDRO-1,4-OXAZEPINE DERIVATIVES

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY

ÖZGE İBİŞ

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
CHEMISTRY

NOVEMBER 2017

Approval of the thesis

SYNTHESIS OF 6-HALOGEN-SUBSTITUTED 2-METHYLENE-2,3-DIHYDRO-1,4-OXAZEPINE DERIVATIVES

submitted by **ÖZGE İBİŞ** in partial fulfillment of the requirement for the degree of **Master of Science in Department of Chemistry, Middle East Technical University** by,

Prof. Dr. Gülbin Dural Ünver
Dean, Graduate School of **Natural and Applied Sciences** _____

Prof. Dr. Cihangir Tanyeli
Head of Department, **Chemistry** _____

Prof. Dr. Metin Zora
Supervisor, **Chemistry Dept., METU** _____

Examining Committee Members:

Prof. Dr. Fatma Sevin Düz
Chemistry Dept., Hacettepe Üniversitesi _____

Prof. Dr. Metin Zora
Chemistry Dept., METU _____

Assoc. Prof. Dr. Akın Akdağ
Chemistry Dept., METU _____

Assoc. Prof. Dr. E. Görkem Günbaş
Chemistry Dept., METU _____

Assist. Prof. Dr. Salih Özçubukçu
Chemistry Dept., METU _____

Date: 24.11.2017

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.

Name, Last name: Özge İBİŞ

Signature:

ABSTRACT

SYNTHESIS OF 6-HALOGEN-SUBSTITUTED 2-METHYLENE-2,3-DIHYDRO-1,4-OXAZEPINE DERIVATIVES

İbiş, Özge

M. Sc., Department of Chemistry

Supervisor: Prof. Dr. Metin Zora

November 2017, 233 pages

Heterocyclic compounds are important since they are present in life naturally or synthetically. Among heterocyclic compounds, seven-membered 1,4-oxazepines are giving more attention than ever due to their wide range of biological and medicinal activities. There are many studies about their synthesis and new ones continue to appear.

In this study, synthesis of halogen-substituted 1,4-oxazepine derivatives was investigated, which may have potential for biological studies. For this purpose, *α*,*β*-alkynic ketone derivatives were prepared by the reaction of aryloyl chlorides with terminal alkynes in the presence of a Pd catalyst. After that, by conjugate addition reaction between *α*,*β*-alkynic ketones and propargylamine, 23 *N*-propargylic *β*-enaminone derivatives were synthesized.

Secondly, *α*-halogen substitution reactions of *N*-propargylic *β*-enaminone derivatives were studied with NCS and Selectfluor® for chlorine and fluorine substitution, respectively. By these reactions, 23 novel *α*-chloro-substituted and 5

novel α-fluoro-substituted *N*-propargylic β-enaminone derivatives were synthesized in good yields.

In the final stage of this study, electrophilic cyclizations of halogen-substituted *N*-propargylic β-enaminones were investigated. When treated with zinc chloride by refluxing chloroform, they afforded 6-halo-substituted 1,4-oxazepines in good yields. In conclusion, 23 novel chloro-substituted and 5 novel fluoro-substituted 1,4-oxazepine derivatives were synthesized.

Keywords: Heterocyclic compounds, seven-membered rings, *N*-propargylic β-enaminones, 1,4-oxazepines, electrophilic cyclization.

ÖZ

6-HALOJEN SÜBSTİTÜYE 2-METİLEN-2,3-DİHİDRO-1,4-OKSAZEPİN TÜREVLERİNİN SENTEZİ

İbiş, Özge

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Zora

Kasım 2017, 233 sayfa

Heterosiklik bileşikler doğal veya sentetik olarak yaşam açısından önemlidirler. Heterosiklik kimyada yedi-üyeli 1,4-oksazepinler geniş biyolojik ve tıbbi aktiviteler göstermeleri nedeniyle her geçen gün daha fazla ilgi çekmektedirler. Bunlarla ilgili birçok çalışma vardır ve yenileri de ortaya çıkmaya devam etmektedir.

Bu çalışmada biyolojik çalışmalar için potansiyeli olan halojen-sübstitüye 1,4-oksazepin türevlerinin sentezi araştırılmıştır. Bu amaçla, ariloil klorürler ve terminal alkinlerin Pd katalizörlüğündeki reaksiyonlarından α,β-alkinik keton türevleri hazırlanmıştır. Daha sonra, proparjilaminin ve α,β-alkinik ketonlar arasındaki konjüge katılma reaksiyonları ile 23 tane *N*-proparjilik β-enaminon türevi sentezlenmiştir.

Projenin ikinci kısmında *N*-proparjilik β-enaminon türevlerinin *N*-klorosüksinimid ve Selekflor® ile α-klor- ve α-flor-sübstitüsyon tepkimeleri çalışılmıştır. Bu

reaksiyonlar ile 23 yeni α-klor-sübstitüye ve 5 yeni α-flor-sübstitüye *N*-proparjilik β-enaminon türevi iyi verimlerle sentezlenmiştir.

Projenin son kısmında ise halojen-sübstitüye *N*-proparjilik β-enaminonların elektrofilik halkalaşması araştırılmıştır. Bu bileşikler kloroform içerisinde geri-soğutucu altında çinko klorür varlığında kaynatıldıklarında 6-halojen-sübstitüye 1,4-oksazepin bileşiklerini iyi verimlerle üretmiştir. Sonuç olarak, 23 yeni klor-sübstitüye ve 5 yeni flor-sübstitüye 1,4-oksazepin türevi sentezlenmiştir.

Anahtar Kelimeler: Heterosiklik bileşikler, yedi-üyeli halkalar, *N*-proparjilik β-enaminonlar, oksazepinler, elektrofilik halkalaşma.

To my family…

ACKNOWLEDGEMENTS

Firstly, I would like to thank my supervisor Prof. Dr. Metin Zora for giving me opportunity to study my Master thesis in his group and I am sincerely grateful for his generous support with constitutive comments. I hope I will still have him as my mentor in the future.

I would like to thank research assistants Yılmaz Kelgökmen and Eda Karadeniz for their generous help with their experiences and comments. Their help was also as important as my supervisor. There are no sufficient words to express my gratitude to them.

I would like to thank my other labmates Elif Serel Yılmaz and Esra Korkmaz for their friendship and their support throughout this period. We have shared the same struggles and we have grown up together in this laboratory.

Family is important and they are who makes life meaningful which is a soil for someone to grow, so I would like to express my appreciation to my family for their valuable supports and presence in my life, whenever I look back they were always there for me.

After family, friends are also very important in life if family is my soil, so my friends are water. I would like to thank Negar Sioofy, Nigar Shiralizade and Sinem Ulusan, who were very close to me as a family member.

METU was my favorite place in this world. I hope I will love some other places as I loved this campus.

Finally, I would like to thank TÜBİTAK for a fellowship to me through my Master studies and financial support for this project (Project No: 114Z811).

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ABBREVIATIONS

ACN	acetonitrile
br	broad (spectral)
d	doublet (spectral)
DCM	dichloromethane
DCE	dichloroethane
dd	doublet of doublets (spectral)
dt	doublet of triplets (spectral)
FT	fourier transform
Hz	Hertz
J	coupling constant
m	multiplet (spectral)
min	minute(s)
NCS	*N*-chlorosuccinimide
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)
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, having a great significance of existence in living organisms. Carbon compounds are present as structural, chemical or organic functions in living organisms. Carbon forms strong bond with other carbons, forming chains and rings, which yields various organic molecules. Importantly, proteins, lipids, DNA and many other parts of a human body are composed of organic compounds [1].

Organic chemistry made a breakthrough when the vitalism lost its significance [2]. Vitalism defends that all organic compounds come from living organisms or synthesized by living organisms. Likewise, inorganic compounds come from non-living sources. In oppose to that belief, in 1828, Friedrich Wöhler managed to produce urea (an organic compound) from ammonium cyanate (an inorganic compound). Procedure was simply evaporation of the aqueous ammonium cyanate (Figure 1). This phenomenon brought out the organic chemistry to a scientific approach [2].

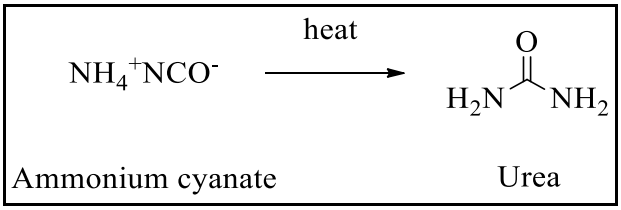


Figure 1. Synthesis of urea from ammonium cyanate by Friedrich Wöhler.

Organic chemistry is the study of carbon compounds in every manner, having a great significance of existence in living organisms. Carbon compounds are present as structural, chemical or organic functions in living organisms. Carbon forms strong bond with other carbons, forming chains and rings, which yields various organic molecules. Importantly, proteins, lipids, DNA and many other parts of a human body are composed of organic compounds [1].

Organic compounds can be synthesized in laboratory conditions as well. Modern chemists developed many methods for the synthesis of organic compounds which can be used as medicines, dyes, polymers and other substances [3].

Most of the compounds have ring systems which are composed of carbon and additional one or more than one heteroatom. These heteroatom-containing ring structures are called as heterocyclic compounds (Figure 2) [4].

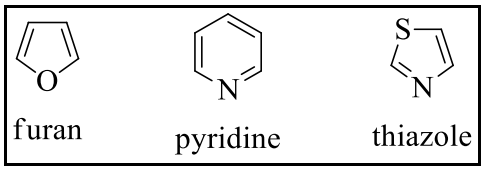


Figure 2. Some examples of heterocyclic compounds.

1.1 Heterocyclic Compounds

Most of the heterocyclic compounds are found in nature and there is no doubt that they have fundamental functions in living organisms since they have significant roles in biological systems [4]. For example, nucleic-acid bases, which provide replication, have pyrimidine and purine moieties in their structures. Chlorophyll (components of photosynthesis) and heme (components of oxygen transport) are other examples of heterocyclic compounds which have porphyrin ring in their structures. Vitamin B_1 (thiamin), vitamin B_2 (ribofavin), vitamin B_3 (nicotinamide), vitamin B_6 (pyridoxol) and vitamin C (ascorbic acid), and also tryptophan and histidine (essential amino acids) are further examples for heterocyclic compounds (Figure 3). Because of their importance in living systems, chemists try to find out information about their structures, properties and synthethetic methods to determine their biological function and design medical assistances [4].

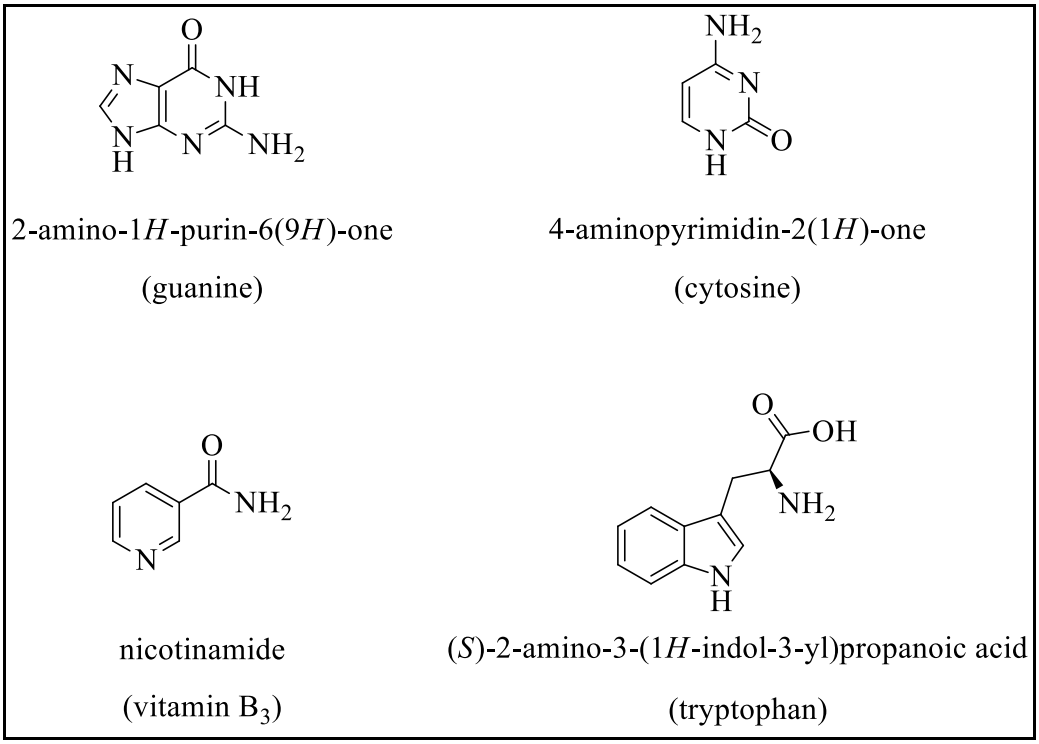


Figure 3. Some heterocyclic compounds that are found in living systems.

Heterocyclic molecules are classified as three-, four-, five-, six- and seven-membered according to their ring size (Figure 4). Their reactivity can change as ring size changes; for example, three-membered heterocycles have the highest ring strain. So, they are very reactive. In general, the reactivity of three- and four-membered heterocycles are higher than other heterocyclic compounds that have higher number of members in their rings [5]. Five- and six-membered heterocycles are often more stable and they are commonly found in nature. Pyrrole, furan, thiophene and pyridine are their well-known examples. On the other hand, seven-membered heterocycles have been less investigated as compared to five- or six-membered heterocycles, yet they are stable and have useful applications [6].

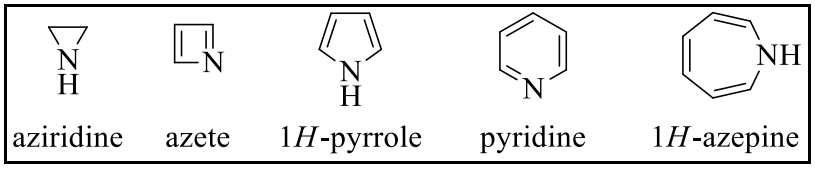


Figure 4. Some examples of three-, four-, five-, six- and seven-membered heterocyclic compounds.

1.2 Seven-membered Heterocyclic Compounds

When the number of atoms that build the ring of heterocycles increases, diversity of compounds get higher with the number of heteroatoms and their location in the structure. For instance, thiepane, azepane and oxepane are composed of one sulfur, nitrogen or oxygen atom, respectively, and six carbon atoms (Figure 5). These three examples of seven-membered heterocyclic compounds are all saturated. Their unsaturated forms are thiepine, azepine and oxepine, respectively (Figure 5) [7].

Seven-membered heterocyclic compounds have gained importance due to their wide range of biological applications [8].

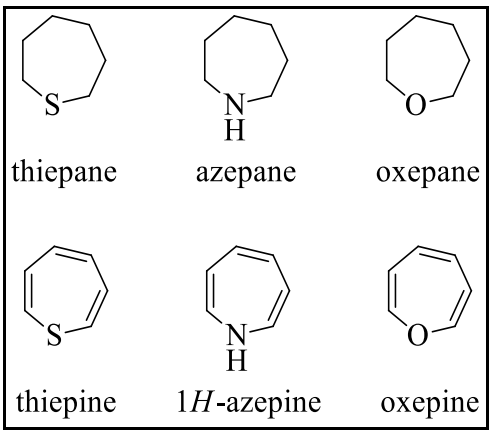


Figure 5. Saturated and unsaturated seven-membered heterocyclic compounds.

Azepine and oxepine are extensively found in nature, particularly in alkaloids. For example, caprolactam (Figure 6), which is an azepine derivative, shows biological activity, such as growth-inhibiting property and allelopathy (influencing germination, growth, survival, and reproduction). Moreover, it is widely used in nylon 6 polymerization process (Figure 6) [9-12].

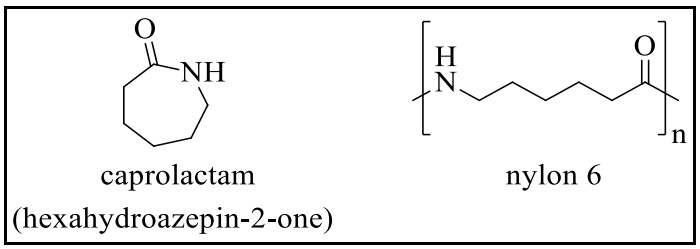


Figure 6. Structure of caprolactam and nylon 6.

There are fused-ring derivatives of azepine as well. 1*H*-Benzo[*b*]azepines (Figure 7), which are examples of such derivatives, are anti-HIV agents and inhibit acetylcholinesterase (used for Alzheimer's disease treatment) [13,14].

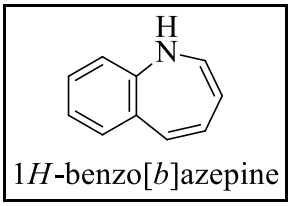


Figure 7. The structure of 1*H*-benzo[*b*]azepine.

Oxepine was first synthesized in 1964 by Vogel, Boell and Schubart [15]. Monocyclic oxepines are instable, so their direct applications are not prevalent, but they take part in metabolism and biosynthesis of products of nature and xenobiotics (chemicals that are not present or produced in the organism naturally, like antibiotics) as important intermediates [16].

Monocyclic thiepanes have not been observed. Nevertheless, their fused dibenzo derivatives have been characterized as pharmaceutical molecules, which display anti-inflammatory, antihistamic, antidepressant, neuroleptic and antischizophrenic properties [17, 18].

Three examples of nitrogen, oxygen and sulphur containing seven-membered drugs are shown in Figure 8. Perlapine is an azepine derivative and it has antipsychotic and sedative activity. Artocarpol is an oxepine derivative, showing anti-inflammatory action. Monatepil is a thiepine derivative which is a calcium antagonist.

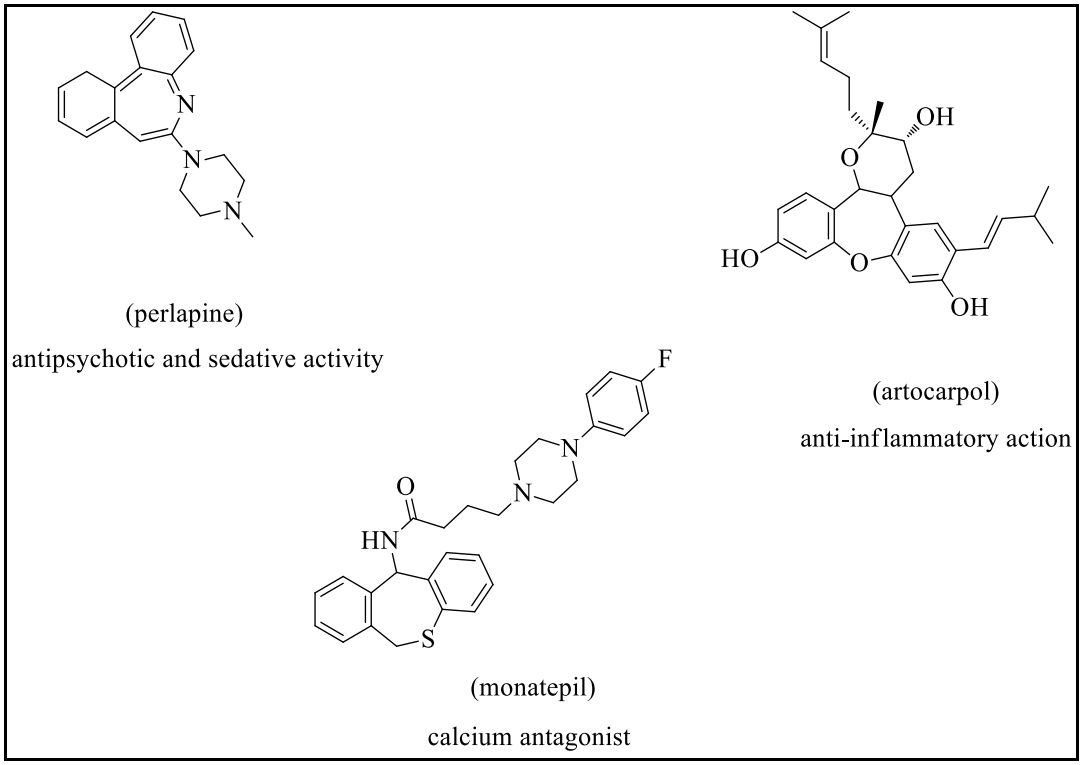


Figure 8. Examples for azepine, oxepine and thiepine derivatives that have pharmacological activity.

Consequently, seven-membered rings are gaining importance in chemistry since they are known to have various biological activities. Among them, one oxygen and one nitrogen heteroatom containing seven membered heterocyclic molecules, namely oxazepines, are main scope in synthetic organic chemistry [22].

1.2.1 Oxazepines

Oxazepines are very important member of seven-membered heterocyclic compounds composed of one nitrogen and one oxygen atoms. They are called 1,2-oxazepine, 1,3-oxazepine and 1,4-oxazepine according to the position of these two heteroatoms in the ring (Figure 9) [23].

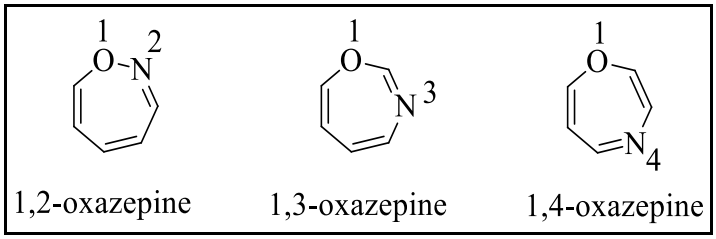


Figure 9. Structure of oxazepines.

1,4-Oxazepines are important compounds showing histone deacetylase inhibition and antitumor properties. They find application in antidepressant, anticonvulsant (antiepileptic), antiviral, antimicrobial, antifungal, anticancer, antithrombotic (preventing blood clot), sedative, and hypnotic agents and drugs. Moreover, they are active in the treatment of Alzheimer's disease and type 2 diabetes. Sintamil (nitroxazepine), Amoxazpine and Loxazepine are the well-known examples of 1,4-oxazepine containing drugs (Figure 10) [24-26]. Because of their important medicinal activities and physiological properties, they draw the attention of chemists.

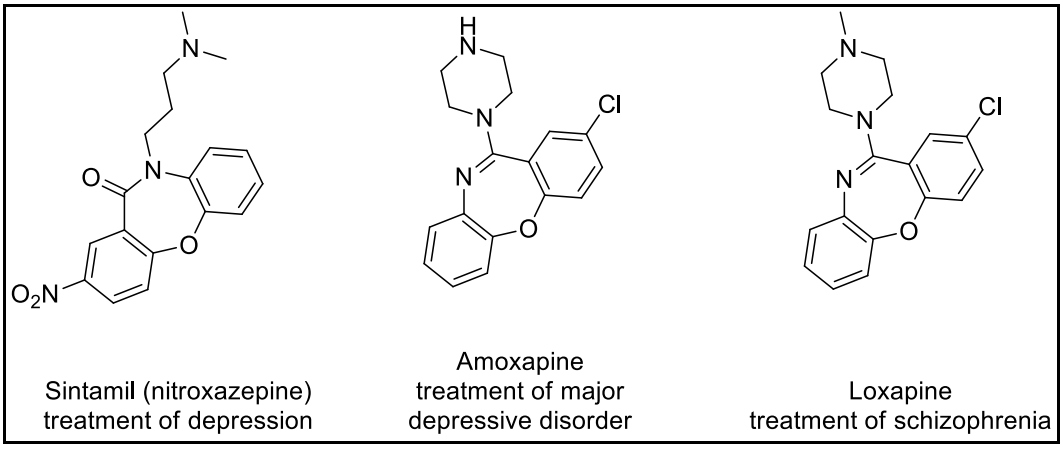


Figure 10. Some examples for 1,4-oxazepine bearing drugs.

Alternations on parent unit of oxazepine and their fused ring systems are also the active area of chemistry [27]. For example, tricyclic (hetero)arene-fused benzo[1,4]oxazepines have shown various medicinal properties in drug applications (Figure 11) [28]. In addition, they have been used in asymmetric synthesis of monoterpenoid alkaloids and secoiridoids [29].

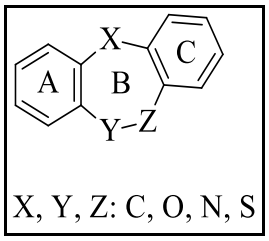
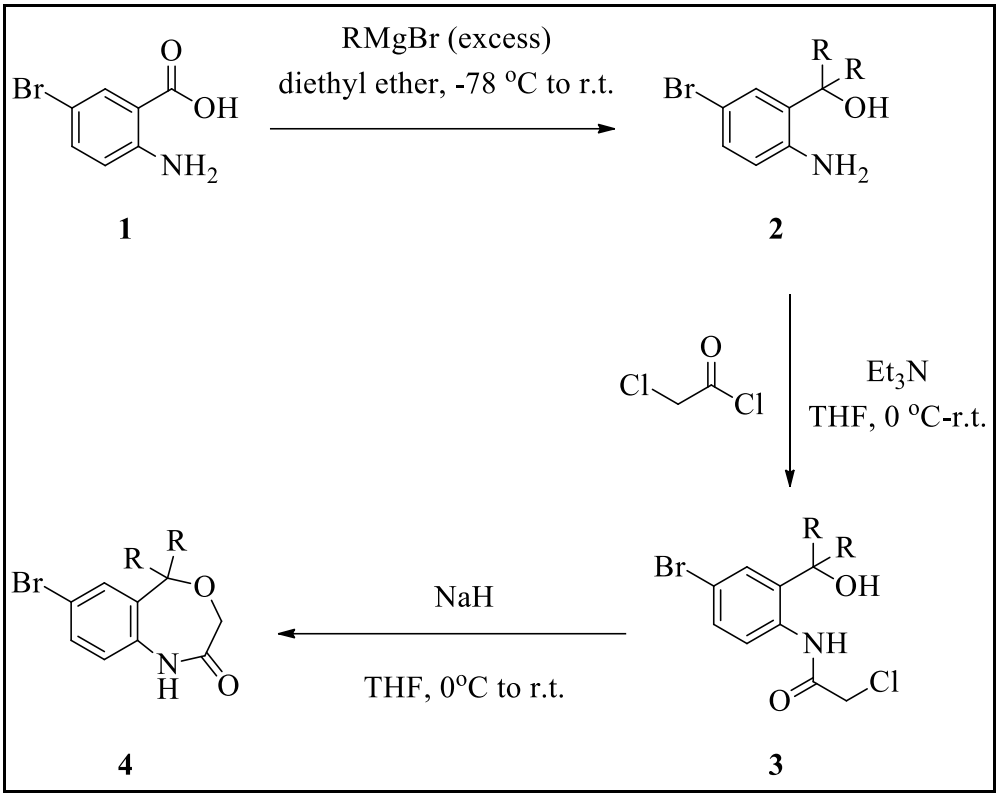


Figure 11. General structure for tricyclic 1,4-oxazepine scaffolds.

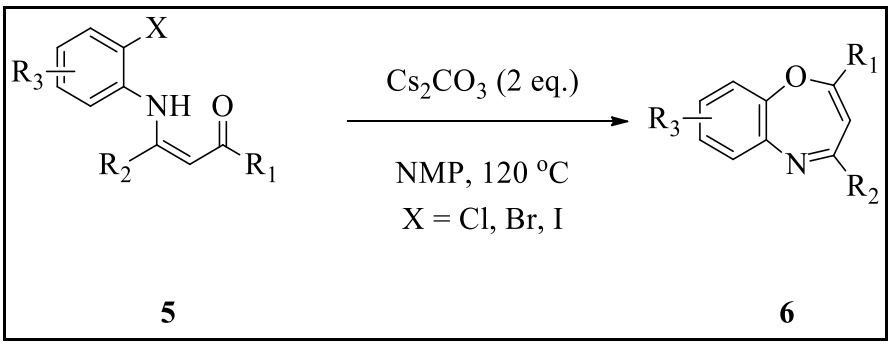
1.2.2 Synthesis of 1,4-Oxazepines

There are many studies concerning the synthesis of 1,4-oxazepines. For example, Zhang and et al. synthesized benzo[1,4]oxazepin-2-one derivatives **4** and then studied their activity as non-steroidal progesterone receptor (PR), regulator in female reproduction and modulator (Scheme 1) [30].



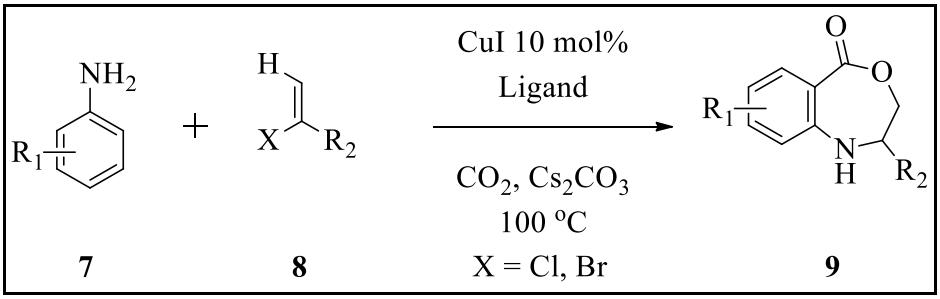
Scheme 1. Synthesis of benzo[1,4]oxazepin-2-one derivatives **4**.

Shen research group carried out the synthesis of benzo[b][1,4]oxazepine **6** from *N*-(2-haloaryl)enaminones **5** in high yield via Cs_2CO_3–mediated cyclization in NMP (*N*-methyl-2-pyrrolidone) at 120˚C (Scheme 2) [31].



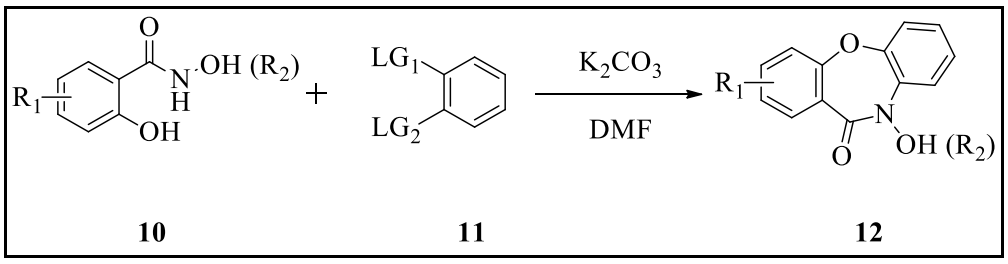
Scheme 2. Synthesis of benzo[b][1,4]oxazepine **6**.

Zhao research group performed tandem reaction for the synthesis of benzo-1,4-oxazepine **9** (Scheme 3). Reaction was performed by employing phenylamine derivatives **7** and 1-halo-vinyl derivatives **8** in the presence of Cu catalyst and Cs_2CO_3 base at 100 ˚C (Scheme 3) [32].



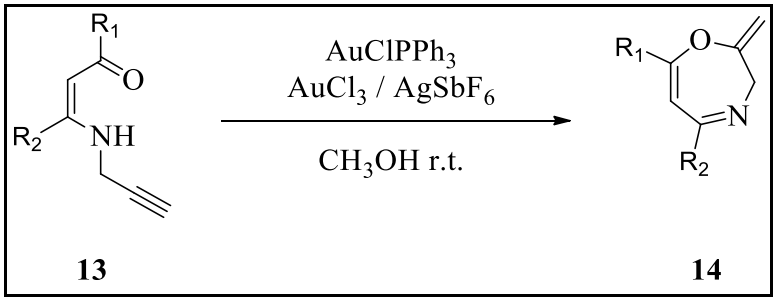
Scheme 3. Synthesis of benzo-1,4-oxazepine **9**.

Sapegin also studied the synthesis of fused benzo[1,4]oxazepines [33]. *N*-Alkoxy-2-hydroxybenzamides **10** were reacted with two leaving group-containing (hetero)aromatic substrates **11** in the presence of K_2CO_3 in DMF giving tricyclic *N*-alkoxy benzo[1,4]oxazepines **12** (Scheme 4) [33].



Scheme 4. Synthesis of tricyclic *N*-alkoxybenzo[1,4]oxazepines **12**.

Recently, Gautham investigated the cyclization of *N*-propargylic *β*-enaminone **13** into 1,4-oxazepine derivative **14** via 7-exo-dig cyclization in the presence of gold and silver catalyst (Scheme 5) [34]. The reaction proceeded well and produced 1,4-oxazepine **14** in high yield.

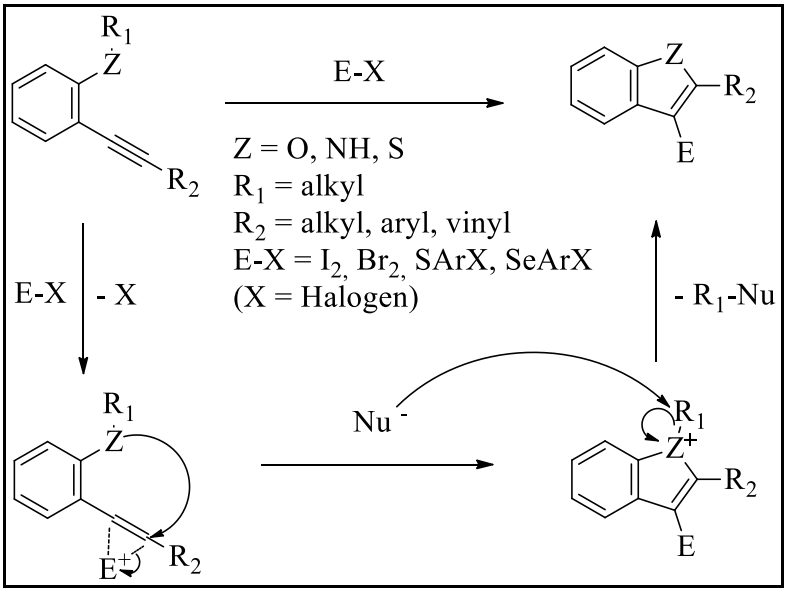


Scheme 5. Cyclization of *N*-propargylic *β*-enaminone **13** to 1,4-oxazepine **14**.

1.3 Electrophilic Cyclization

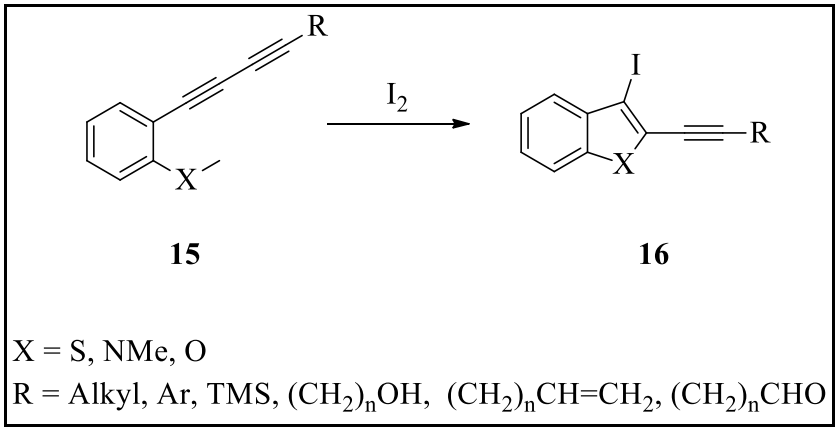
A broad series of cyclic compounds have been prepared by electrophilic cyclization of substituted alkynes in the presence of proper Lewis acids and transition metals [35]. Electrophilic cyclizations are very effective and take place under mild conditions and in short times, and tolerate nearly all functional groups [36].

Over the past decade, there has been an increase in the cyclization of functionally-substituted acetylene derivatives, which is a common method for the synthesis of heterocycles, including isoquinolines, chromones and oxazoles [37]. The mechanism for electrophilic cyclization first requires the activation of the triple bond with an electrophile. Then intramolecular nucleophilic attack on activated triple bond occurs. Finally, reaction is completed with leaving group elimination via a S_N2 substitution (Scheme 6) [38].



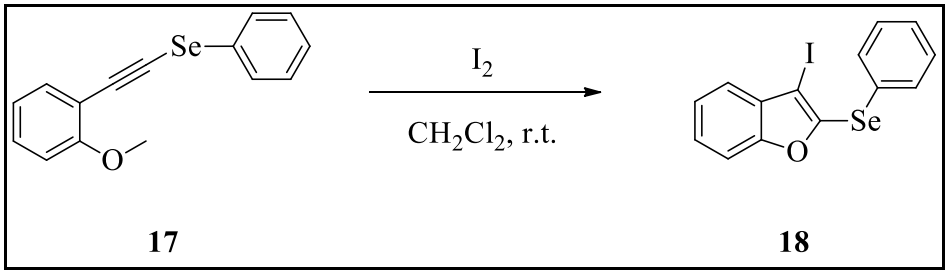
Scheme 6. General mechanism for electrophilic cyclization.

Danilkina research group studied formation of asymmetrically-substituted enediynes fused to benzothiophene, benzofuran and indole by electrophilic cyclization. The reaction of ortho-functionalized (buta-1,3-diynyl)arenes **15** afforded 2-ethynyl-3-iodoheteroindenes **16** (Scheme 7) [39].



Scheme 7. Electrophilic cyclization of ortho-functionalized (buta-1,3-diynyl)arenes **15**.

Manarin research group has carried out the synthesis of 2-chalcogen-3-substituted-benzo[b]furan derivatives **18** via electrophilic cyclization of 2-chalcogenealkynyl anisoles **17** by using I_2, ICl, Br_2 and PhSeBr (Scheme 8) [40]. Notably, benzo[b]furan is valuable heterocycle since it is found in a wide range of biologically active compounds such as anti-HIV, anticancer and antiinflamator agents [41].



Scheme 8. Synthesis of 2-chalcogen-3-substituted-benzo[b]furan **18**.

1.4 *β*-Enaminones

The conjugated O=C−C=C−N structure, which is called as *β*-enaminones, has rich applications in synthesis because of their high reactivity [42]. Their various intra- and intermolecular reactions have been studied intensely. In particular, *N*-propargylic *β*-enaminones **19**, the structure of which is shown in Figure 12, are very reactive to intramolecular cyclization in the presence of transition metals, such as gold, platinum and silver. These metals coordinate and form positive ions with the C–C triple bond [43-45]. The resulting positive ion is sufficiently electrophilic, so it initiates the attacks of nucleophiles. As a result, heterocyclic compounds are obtained [46]. Moreover, *N*-propargylic *β*-enaminones **19** have an attractive structure since they include various functional groups, such as enone, enaminone, enamine, alkene and alkyne [47].

In summary, *β*-enaminones are very valuable substrates for the formation of many heterocyclic compounds. Importantly, they have potential to produce five-, six- and seven-membered ring systems [48].

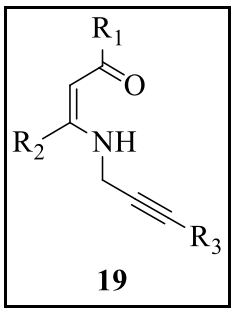
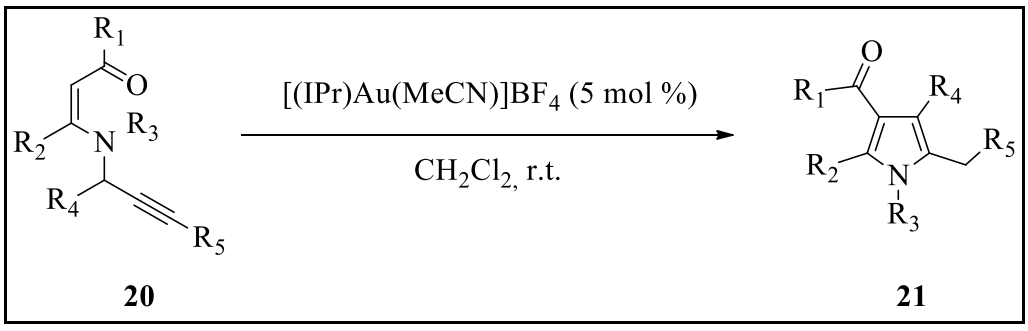


Figure 12. The structure of *N*-Propargylic *β*-enaminones **19**.

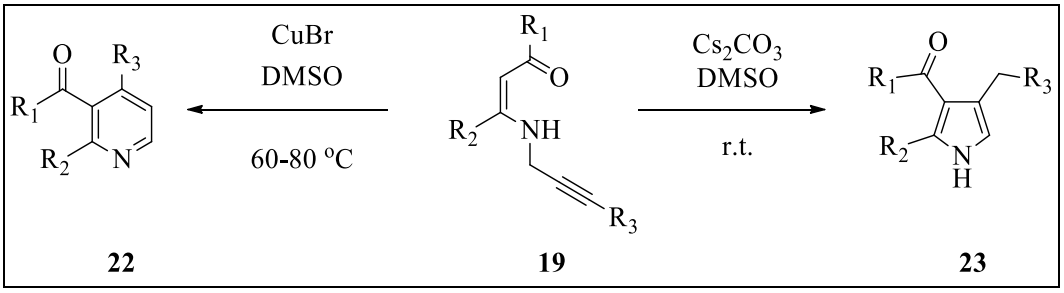
1.4.1 Cyclization of *N*-propargylic *β*-enaminones

There are many studies that involve the cyclizations of *N*-propargylic *β*-enaminones **19** through metal catalysts giving 1,2-dihydropyridine and pyrrole products [49-51]. For example, Saito and co-workers synthesized pyrrole derivatives **21** from *N*-propargylic *β*-enaminones **20** with a gold catalyst (Scheme 9) [50].



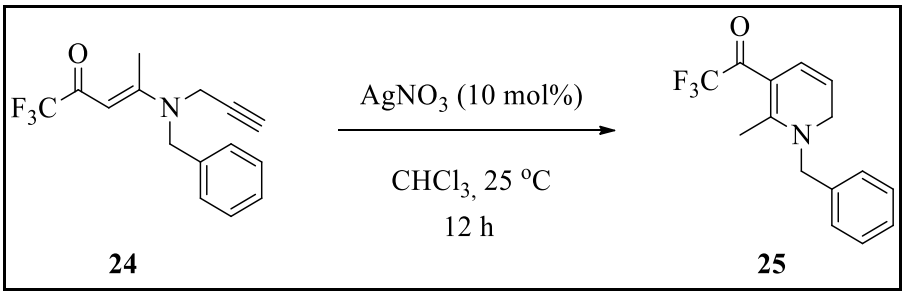
Scheme 9. Synthesis of pyrrole derivatives **21** from *N*-propargylic *β*-enaminones **20**.

Cacchi and his group also studied the cyclizations *N*-propargylic *β*-enaminones **19** (Scheme 10). They reported that pyrrole products **23** were resulted from *N*-propargylic *β*-enaminones **19** when they treated them with Cs_2CO_3 in the presence of DMSO at room temperature. Their other study was the synthesis of pyridines **22** from *N*-propargylic *β*-enaminones **19** in the presence of CuBr in DMSO (Scheme 10) [45].



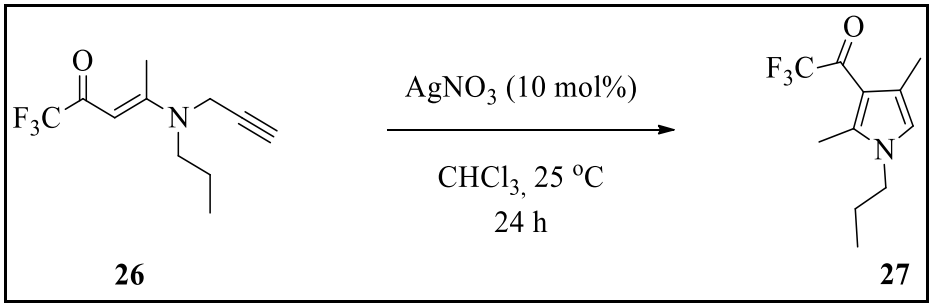
Scheme 10. Synthesis of pyrrole **23** and pyridine **22** derivatives from *N*-propargylic *β*-enaminones **19**.

Martins and co-workers have reported a method for the synthesis of dihydropyridines **25**. When treated with silver nitrate (10 mol%) in chloroform, trifluoromethylated *N*-propargylic *β*-enaminones **24** produced 1,2-dihydropyridines **25** (Scheme 11) [51].



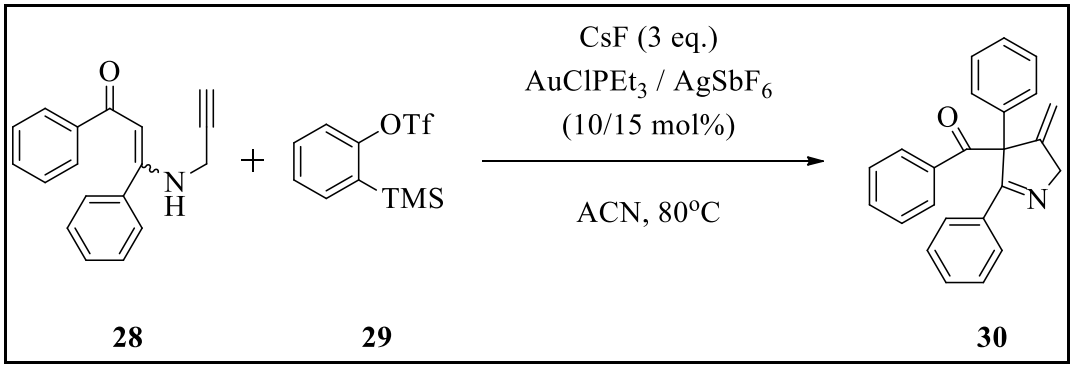
Scheme 11. Cyclization of trifluoromethylated *N*-propargylic *β*-enaminone **24** into 1,2-dihydropyridine **25**.

When *N*-propargylic *β*-enaminone **26** was subjected to same conditions, polysubstituted pyrrole **27** was observed (Scheme 12) [51]. For the account of having two different products from different *N*-propargylic *β*-enaminone derivatives, Martin and co-workers proposed that the formation of 1,2-dihydropyridine **25** goes through 6-endo-dig mechanism while pyrrole **27** forms via 5-exo-dig mechanism [51].



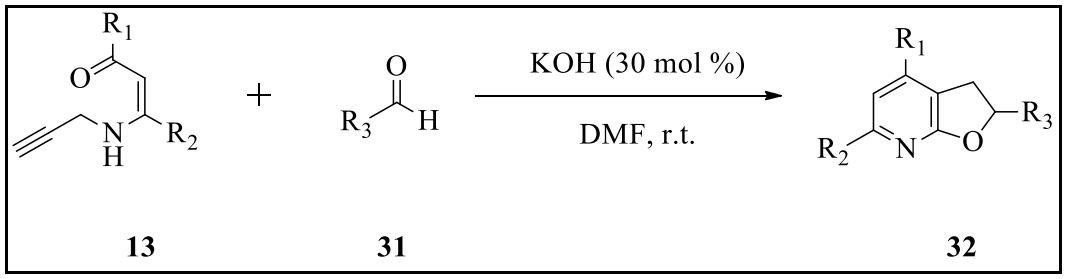
Scheme 12. Cyclization of trifluoromethylated *N*-propargylic *β*-enaminone **26** into pyrrole **27**.

1-Pyrrolines are used in many medicinal research as preliminary compounds. For example, they are found in medicines showing anti-inflammator, anticonvulsant and cyclooxygenase enzyme inhibition activities [52-55]. Goutham research group reported the synthesis of 1-pyrroline **30** via a gold catalysed cyclization of *N*-propargylic *β*-enaminone **28** (Scheme 13) [56].

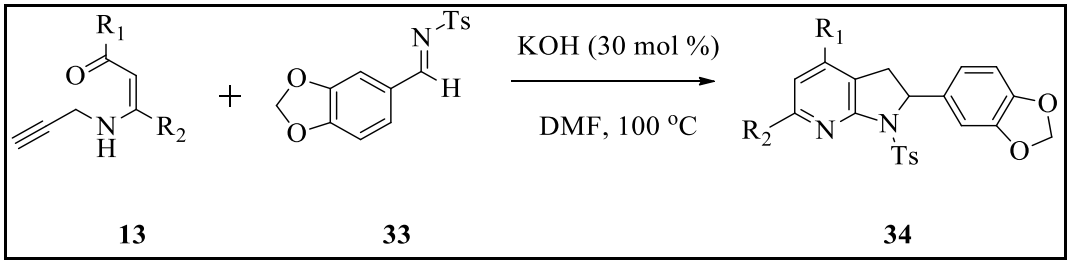


Scheme 13. Synthesis of 1-pyrroline **30** from *N*-propargylic *β*-enaminone **28**.

Yang and his colleagues have carried out the synthesis of dihydrofuropyridine **32** and dihydropyrrolopyridine **34** from *N*-propargylic *β*-enaminone **13** and arylaldehydes **31** or *N*-sulfonyl imine (**33**) with KOH catalization (Scheme 14 andScheme 15). In the first study, 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13**) and aldehydes **31** was reacted in DMF with KOH catalyst to yield 2,3-dihydrofuro[2,3-b]pyridines (**32**) (Scheme 14). In the second study, *N*-propargylic *β*-enaminone **13** was treated with *N*-sulfonyl imine (**33**) in similar conditions to give 2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridine (**34**) (Scheme 15) [57].



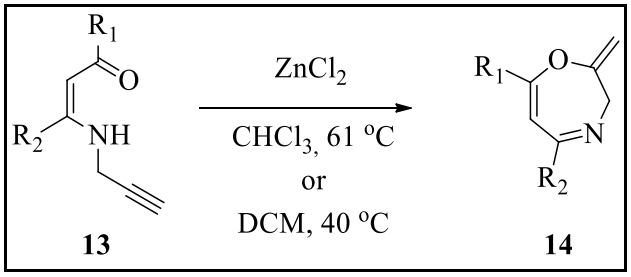
Scheme 14. Synthesis of 2,3-dihydrofuro[2,3-b]pyridine derivatives (**32**).



Scheme 15. Synthesis of 2,3-dihydro-1*H*-pyrrolo[2,3-b]pyridine derivatives (**34**).

1.5 Aim of the project

So far, the studies on heterocyclic compounds, importance of their applications were shown. There are mostly five- and six-membered heterocycles in literature. However, there is a growing interest towards seven- and higher number-membered heterocyclic compounds. In Zora research group, five- and six-membered heterocycles were studied; however, we have also managed to develop a new method for the synthesis of seven-membered heterocycles. Recently, 2-methylene-2,3-dihydro-1,4-oxazepine (**14**) was synthesized from *N*-propargylic *β*-enaminone **13** via $ZnCl_2$–mediated cyclization (Scheme 16) [58].

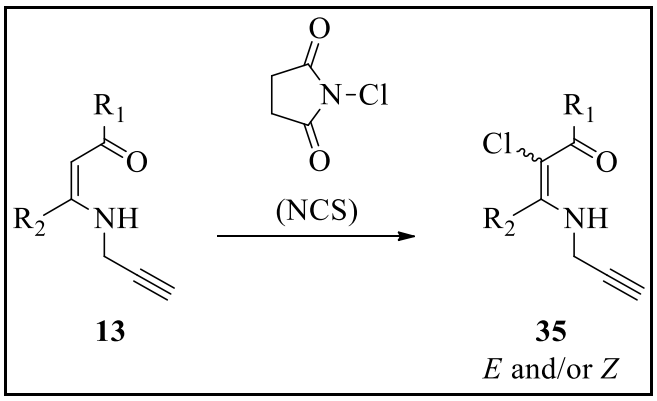


Scheme 16. Synthesis of 2-methylene-2,3-dihydro-1,4-oxazepines **14**.

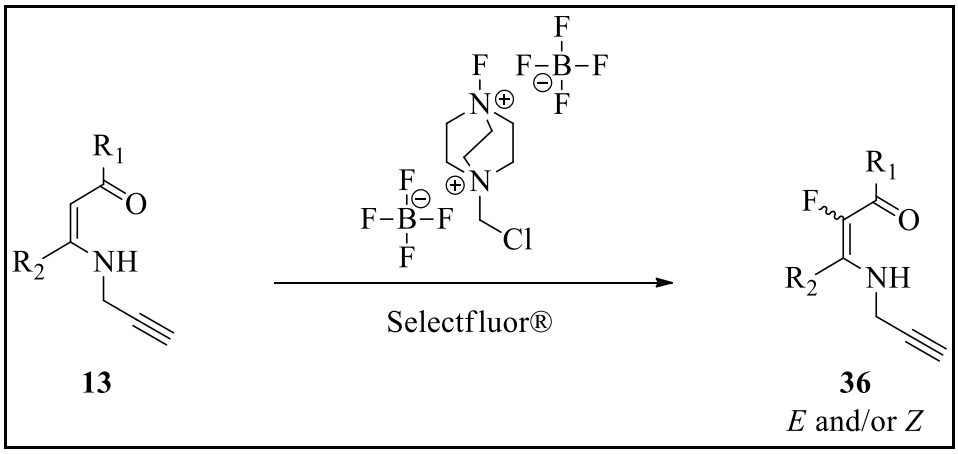
This study showed remarkable results. Thus, it was decided to expand and diversify this work. First, it was aimed to functionalize the starting *N*-propargylic *β*-

enaminone **13** further, since they could provide functionalized 1,4-oxazepines **14** when treated with $ZnCl_2$ in refluxing $CHCl_3$ or refluxing DCM.

For this reason, *N*-propargylic *β*-enaminones **13** will be subjected to the reaction with NCS and Selectfluor®, which should afford chloro- and fluoro-substituted *N*-propargylic *β*-enaminones **35** and **36**, respectively, as shown in Scheme 17 and Scheme 18.

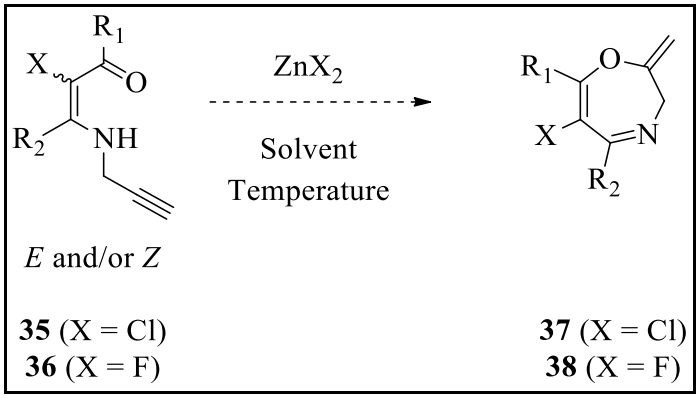


Scheme 17. Synthesis of chloro-substituted *N*-propargylic *β*-enaminones **35**.



Scheme 18. Synthesis of fluoro-substituted *N*-propargylic *β*-enaminones **36**.

At the final stage, $ZnCl_2$–mediated cyclizations of halogen-substituted *N*-propargylic *β*-enaminone derivatives **35** and **36** will be investigated, which could produce 6-chloro and 6-fluoro-substituted 2-methylene-2,3-dihydro-1,4-oxazepines **37** and **38**, respectively (Scheme 19).



Scheme 19. Synthesis of halogen-substituted 2,3-dihydro-1,4-oxazepines **37** and **38**.

In short, in this thesis, optimization studies, substrate scope and mechanisms of these reactions, i.e. cyclization of halogen-substituted *N*-propargylic *β*-enaminones **35** and **36** into halogen-substituted 2,3-dihydro-1,4-oxazepines **37** and **38,** will be discussed in more detail.

CHAPTER 2

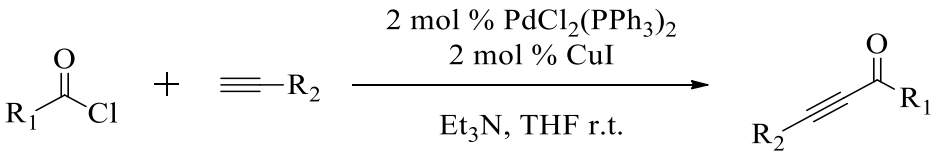
RESULTS AND DISCUSSION

2.1 Synthesis of *N*-propargylic *β*-enaminone derivatives

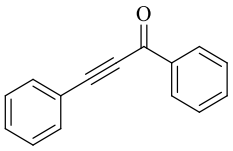
In the first phase of this study, we synthesized starting materials *N*-propargylic *β*-enaminones **13** in two steps according to well-known literature procedures (Table 1 and 2) [46, 58, 60]. First, we have prepared *α*,*β*-alkynic ketones **41** by the reaction of aryloyl chlorides **39** with terminal alkynes **40** in the presence of a Pd catalyst (Table 1). For this purpose, typical Sonogashira coupling conditions [58, 60] were used by employing $PdCl_2(Ph_3)_2$ (catalyst), CuI (cocatalyst), Et_3N (base) and THF (solvent).

The structures of these compounds were identified by ^{1}H and ^{13}C NMR spectroscopy.

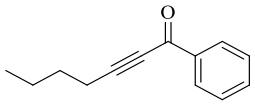
Table 1. Synthesis of *α,β*-alkynic ketone derivatives **41**. [a]



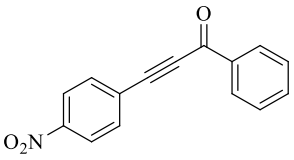
39 **40** **41**



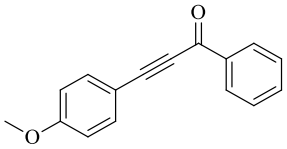
41A (97%)



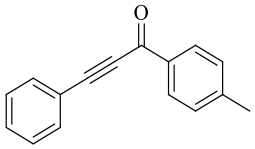
41B (78%)



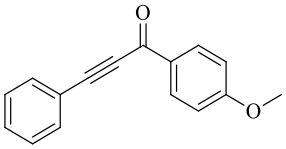
41C (45%)



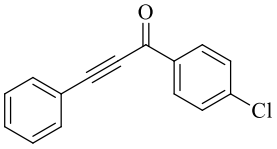
41D (71%)



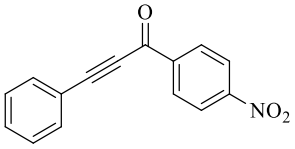
41E (86%)



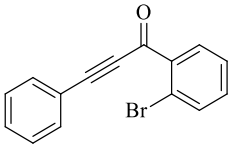
41F (99%)



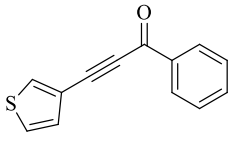
41G (83%)



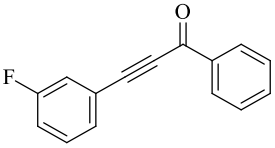
41H (74%)



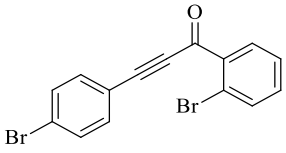
41I (56%)



41J (90%)

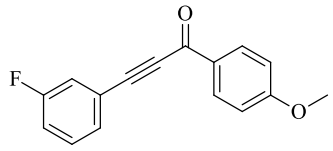
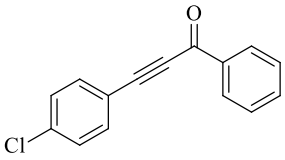
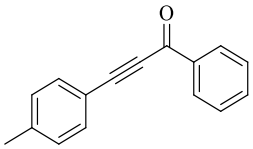
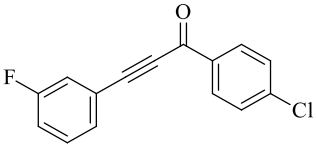
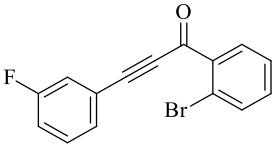
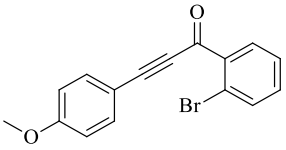
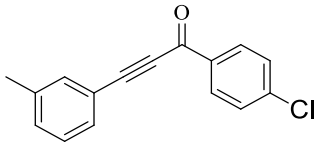
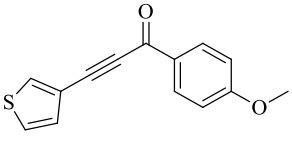
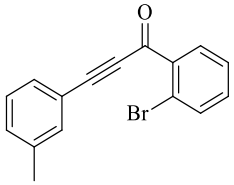
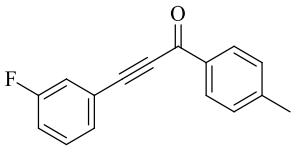
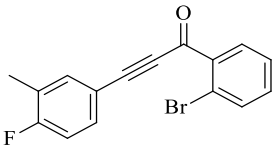


41K (74%)



41L (85%)

Table 1. Continued.

		
41M (96%)	**41N** (86%)	**41O** (68%)
		
41P (61%)	**41Q** (54%)	**41R** (72%)
		
41S (72%)	**41T** (64%)	**41U** (88%)
		
41V (94%)	**41W** (81%)	

[a] Yields of the isolated products.

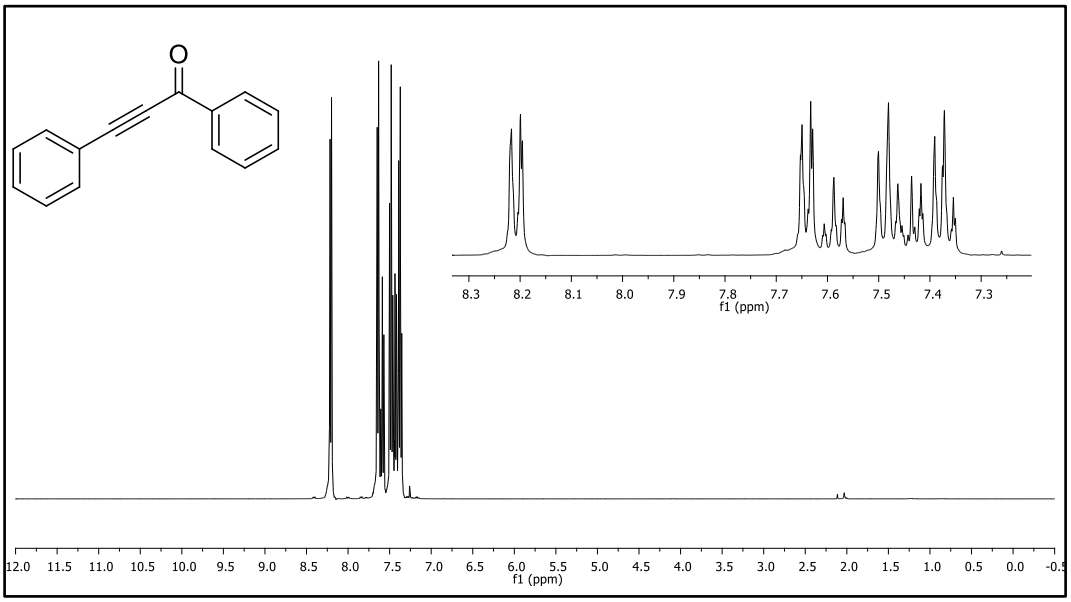


Figure 13. ^{1}H NMR spectrum of 1,3-diphenylprop-2-yn-1-one (**41A**).

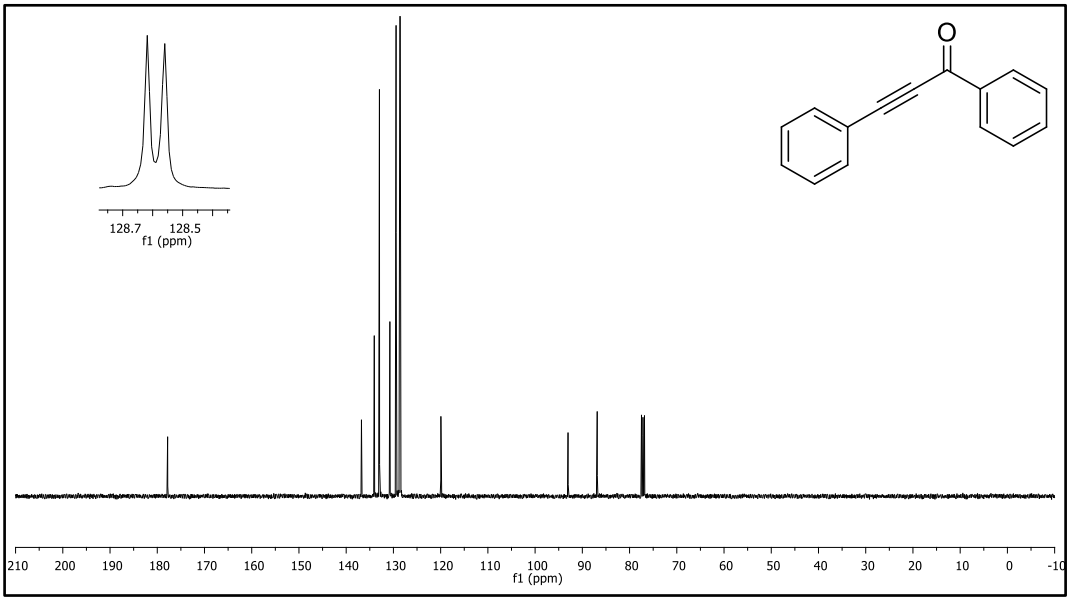
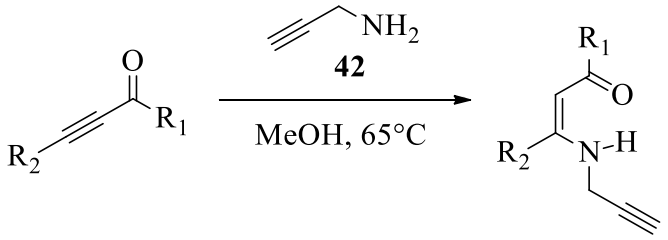


Figure 14. ^{13}C NMR spectrum of 1,3-diphenylprop-2-yn-1-one (**41A**).

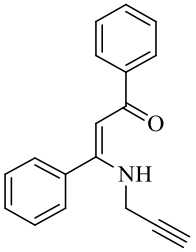
As an example, ^{1}H and ^{13}C NMR spectra of 1,3-diphenylprop-2-yn-1-one (**41A**) are shown in Figure 13 and 14. As depicted in Figure 13, in the ^{1}H NMR spectrum, aromatic ten hydrogens of two phenyl groups resonate between 7.34–8.27 ppm. In the ^{13}C NMR spectrum, aromatic eight carbons of two phenyl groups resonate between 119.9–136.8 ppm (Figure 14). On the other hand, two alkynic carbons appear at 86.9 and 93.0 ppm while the peak of carbonyl carbon comes at 177.8 ppm.

Next, we have subjected *α*,*β*-alkynic ketones **41** to conjugate addition with propargylamine (**42**) to prepare *N*-propargylic *β*-enaminones **13** (Table 2). When treated with propargylamine in refluxing methanol, *α*,*β*-alkynic ketones afforded *N*-propargylic *β*-enaminones **13** in good to high yields [58, 60].

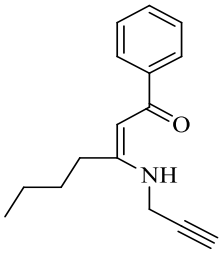
Table 2. Synthesis of *N*-propargylic *β*-enaminone derivatives **13**. [a]



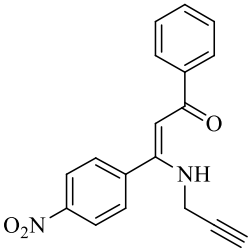
41 **13**



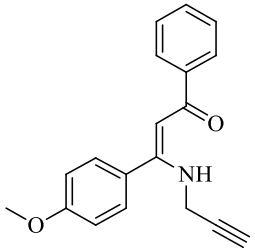
13A (80%)



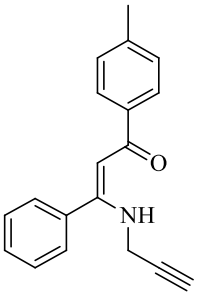
13B (92%)



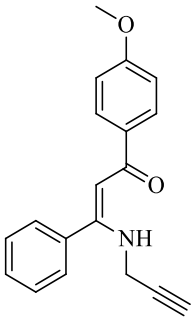
13C (87%)



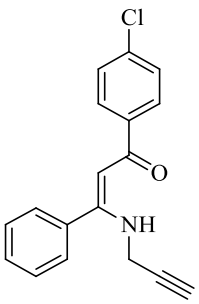
13D (89%)



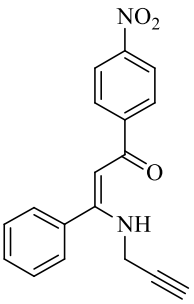
13E (99%)



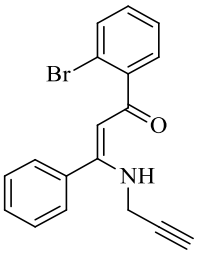
13F (92%)



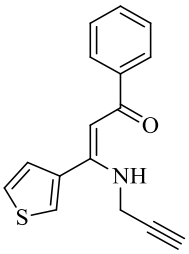
13G (93%)



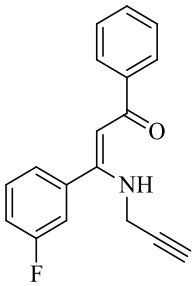
13H (92%)



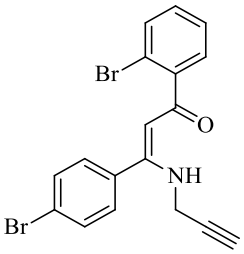
13I (98%)



13J (91%)

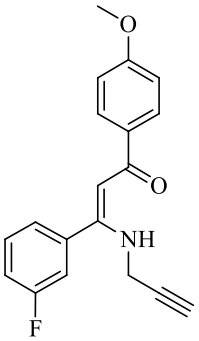
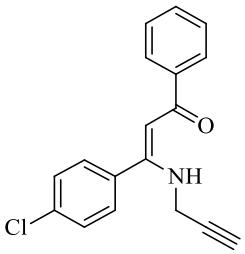
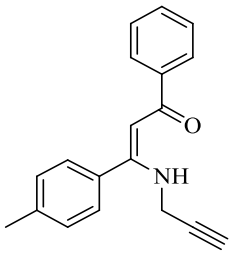
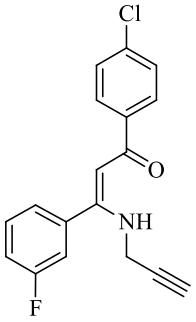
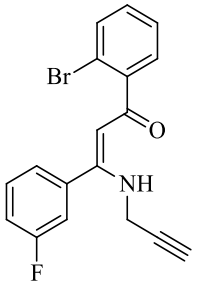
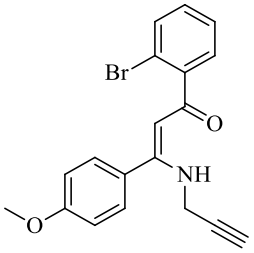
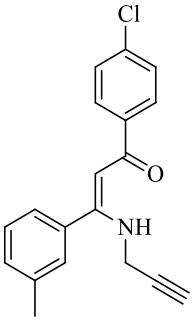
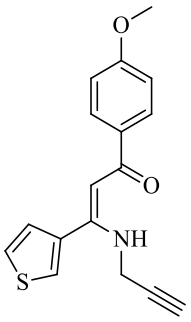
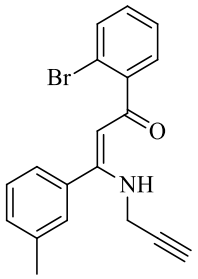
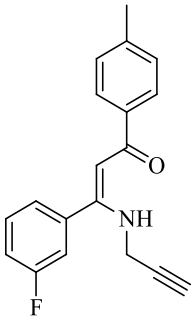
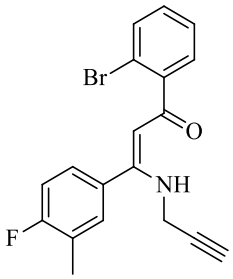


13K (94%)



13L (90%)

Table 2. Continued.

			
13M (92%)	**13N** (96%)	**13O** (97%)	**13P** (86%)
			
13Q (94%)	**13R** (75%)	**13S** (94%)	**13T** (86%)
			
13U (93%)	**13V** (84%)	**13W** (97%)	

[a] Yields of the isolated products.

By using conjugate addition reaction between *α,β*-alkynic ketone derivatives **41** and propargylamine (**42**), we have synthesized 23 derivatives of *N*-propargylic *β*-

enaminones **13**, containing a large variety of aryl groups with electron-withdrawing and electron-donating substituents (Table 2).

It should be pointed out that from this reaction we isolated *Z* isomers of *N*-propargylic *β*-enaminone derivatives **13** as illustrated in Table 2. The observed *Z* stereochemistry was assigned by NOESY experiments on representative compounds by Cacchi research group [46] and our research group [60]. NOESY experiments have also shown the presence of intramolecular hydrogen bonding between carbonyl oxygen and amine hydrogen (N–H ··· O=C) [46, 60].

As an example, ^{1}H and ^{13}C NMR spectra of (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13A**) is given in Figures 15 and 16. As seen in ^{1}H NMR spectrum (Figure 15), acetylenic hydrogen resonates at 2.32 ppm as a triplet while two methylene hydrogens (CH_2) appear at 3.86 ppm as a doublet of doublets. The vinylic *α*-hydrogen gives a singlet at 5.82 ppm. The amine hydrogen gives a triplet at 11.39 ppm due to the hydrogen bonding with carbonyl oxygen. Finally, aromatic ten hydrogens of phenyl groups give peaks between 7.29–7.89 ppm (Figure 15).

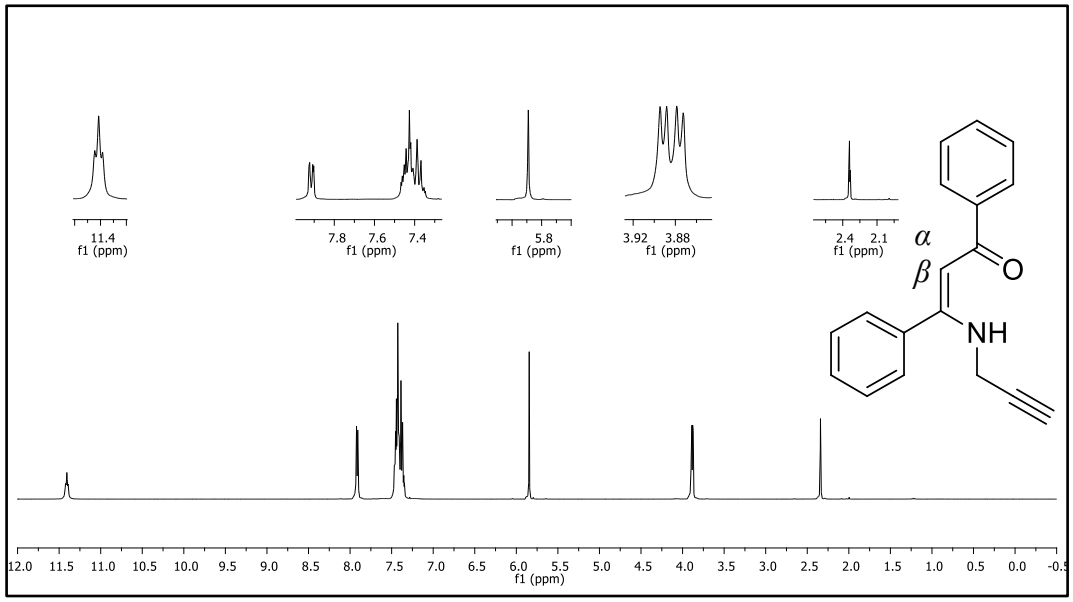


Figure 15. ^{1}H NMR spectrum of (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13A**).

In ^{13}C NMR spectrum of compound **13A** (Figure 16), the peaks of two alkynic carbons come at 72.4 and 79.6 ppm. Methylene carbon appears at 33.9 ppm. Double bond α-carbon resonates at 94.3 ppm while β-carbon resonates at 165.5 ppm. The aromatic carbons of phenyl groups give peaks between 126.9–139.6 ppm. Finally, carbonyl carbon peak appears at 188.6 ppm (Figure 16).

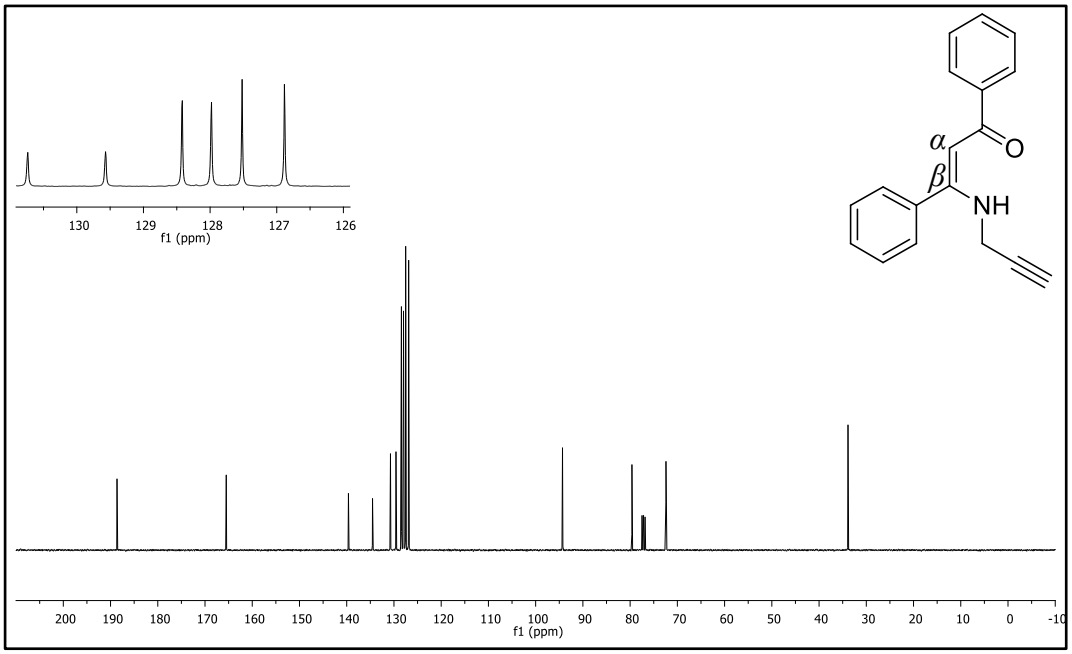


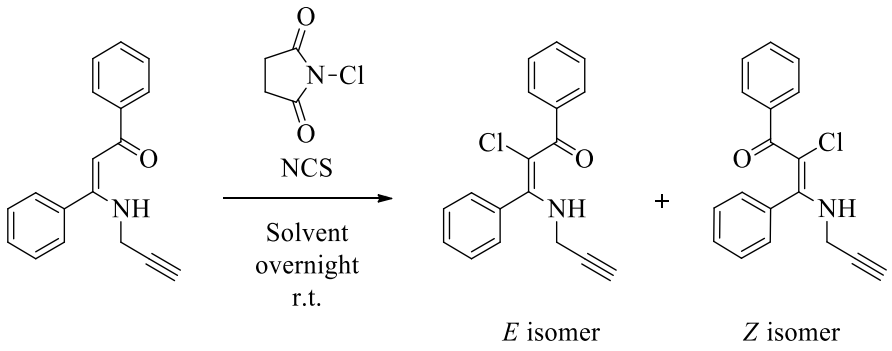
Figure 16. ^{13}C NMR spectrum of (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13A**).

2.2 *α*-Halogenation of *N*-propargylic *β*-enaminones

After synthesizing starting *N*-propargylic *β*-enaminone derivatives **13**, we investigated *α*-halogenation of these compounds with *N*-chlorosuccinimide (NCS) and Selectfluor® for chlorine and fluorine substitution as shown in Table 3 and 5, respectively.

Initially, we have examined several chlorine substitution reactions with NCS (Table 3). Best result (85%) was obtained with 1.2 equivalent of NCS in acetonitrile at room temperature (Table 3, Entry 2). In general, the reactions were so slow that they took overnight (the progress of the reaction was monitored by routine TLC for the consumption of starting *N*-propargylic *β*-enaminone **13A**). Interestingly, from these reactions, chloro-substituted *N*-propargylic *β*-enaminone **35A** was obtained as an inseparable diastereomeric mixture of *E* and *Z* isomers. *E/Z* ratio was found to be 11.1/1.0 by calculating from the integration values of methylene hydrogens (CH_2) of the corresponding isomers. In all reactions, *E* isomer was resulted as the major isomer, presumably due to the intramolecular hydrogen bonding between amine hydrogen and carbonyl oxygen, which increases the stability of this isomer relative to *Z* isomer. On the other hand, as seen from its structure, minor *Z* isomer lacks such an intramolecular hydrogen bonding.

Table 3. Synthesis of 2-chloro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35A**). [a]



13A **35A**

Entry	Amount of NCS (eq.)	Solvent	Total Yield (%) [a,b]
1	1.0 eq.	ACN	56
2	1.2 eq.	ACN	85
3	1.2 eq.	ACN	72 [c]
4	1.2 eq.	DCM	66
5	1.2 eq.	DCE	63
6	2.0 eq.	ACN	0 [d]

[a] Total yield of the isolated products of mixture isomers.

[b]Chloro-substituted *N*-propargylic *β*-enaminone **35A** was obtained from this reaction as an inseparable mixture of *E* and *Z* isomers. (*E/Z* ratio was calculated to be 11.1:1.0 from integration values).

[c] Reaction was performed at 50 ˚C.

[d] Amine group cleavage was observed.

^{1}H and ^{13}C NMR spectra of 2-chloro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35A**) are given in Figure 17 and Figure 18. In the ^{1}H NMR spectrum (Figure 17), the peaks of major *E* isomer are as follows: Acetylenic hydrogen resonates at 2.37 ppm as a triplet while methylene hydrogens appear at 3.83 ppm as a doublet of doublets. Amine hydrogen gives a broad singlet (pseudo triplet) at 11.56 ppm. The peaks of aromatic hydrogens come at between 7.42–7.79 ppm.

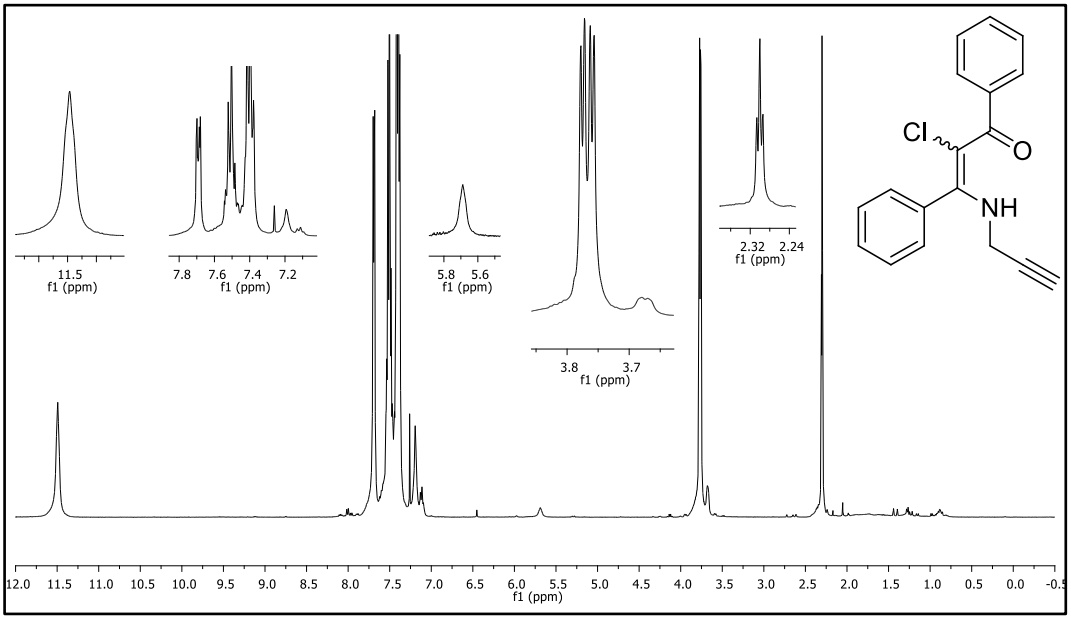


Figure 17. ^{1}H NMR spectrum of 2-chloro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35A**).

Notably, there are some additional low intense peaks in ^{1}H NMR spectrum which belong to minor *Z* isomer of 2-chloro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35A**). In some cases, this low intense peaks overlapped with the peaks of major *E* isomer. Thus, the characterization of the minor *Z* isomer could not be fully achieved. As much as we can analyze, the following peaks are belong to *Z* isomer: Methylene hydrogens of this isomer appear at 3.67 ppm as a doublet of doublets. Because *Z* isomer is lack of hydrogen bonding, amine hydrogen comes at 5.69 ppm as a broad singlet (pseudo triplet).

In ^{13}C NMR spectrum of 2-chloro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35A**), (Figure 18) methylene carbon resonates at 34.9 ppm. Two alkynic carbons appear at 72.8 and 79.2 ppm. The *α*-carbon comes at 101.1 ppm while *β*-carbon appear at 163.9 ppm. The remaining eight aromatic carbons resonate between 127.7–140.7 ppm. Finally, the carbonyl carbon peak shows at 192.6 ppm (Figure 18).

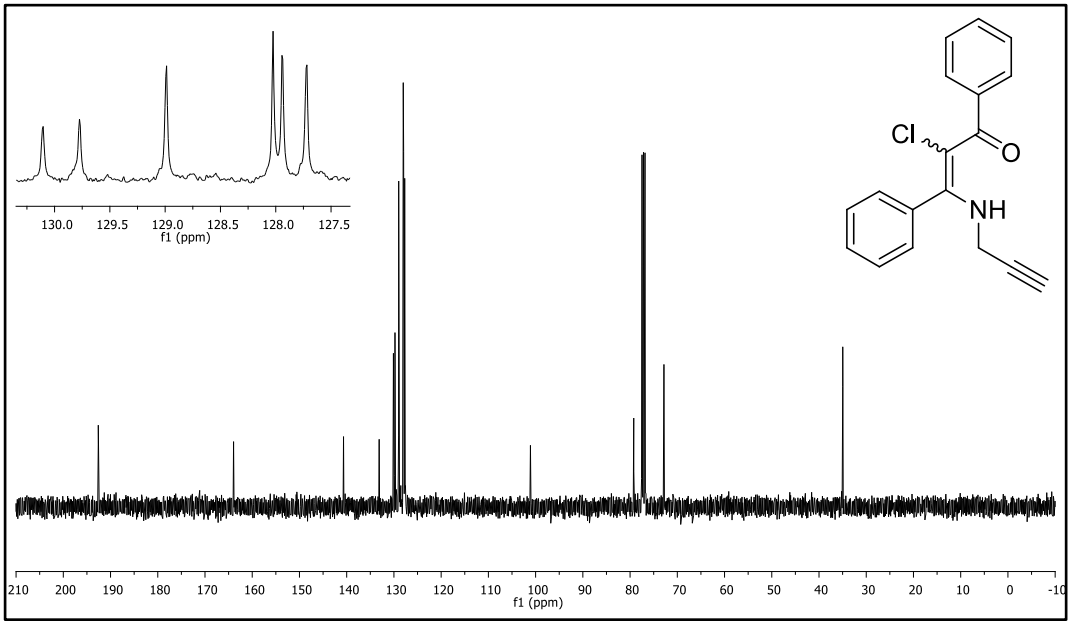
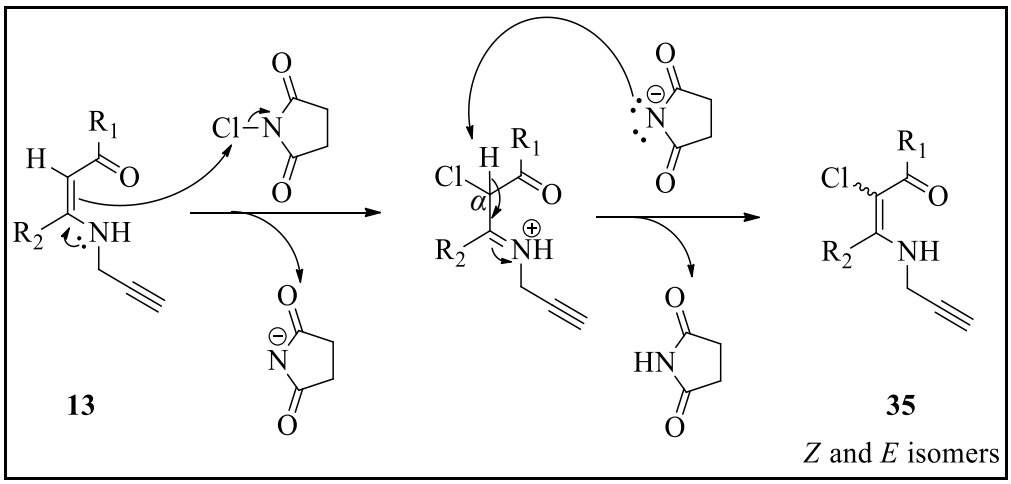


Figure 18. ^{13}C NMR spectrum of 2-chloro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35A**).

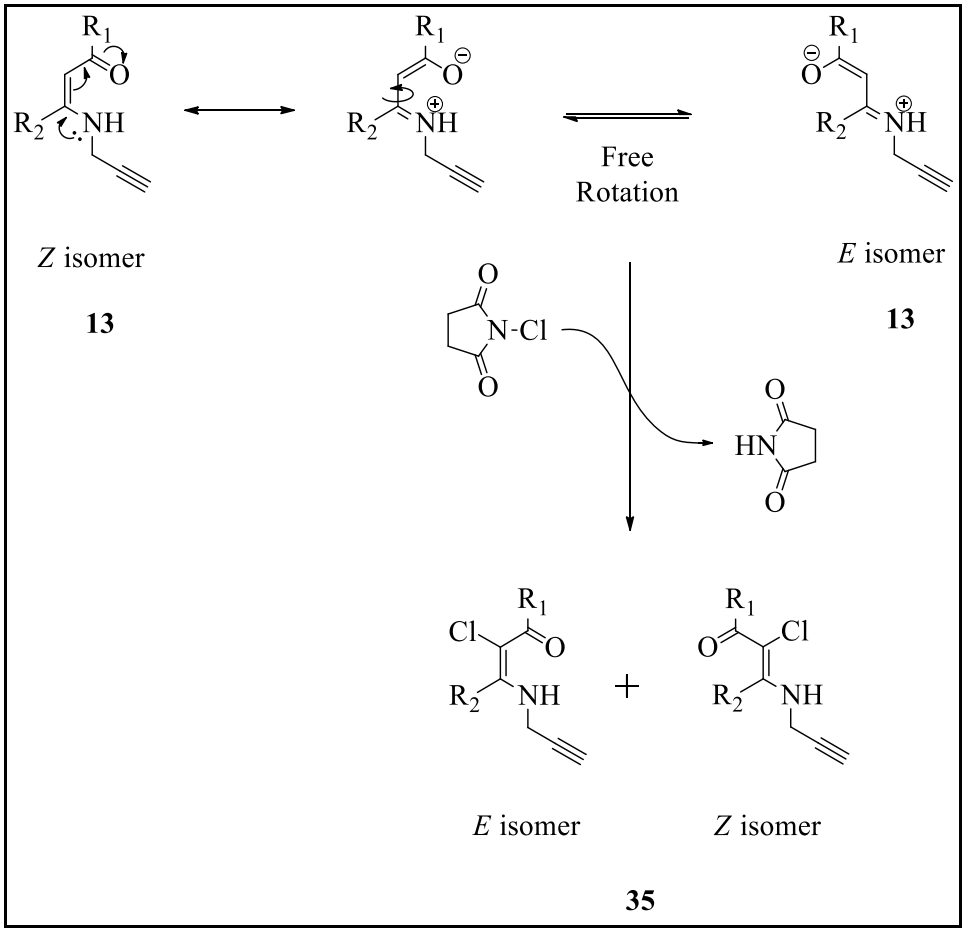
For the synthesis of *α*-chloro-substituted *N*-propargylic *β*-enaminone **35**, the proposed mechanism is shown in Scheme 20. According to this mechanism, the lone pair on nitrogen atom undergoes resonance interaction and *α*-carbon attacks the chlorine of *N*-chlorosuccinimide, forming the succinimide ion. Afterwards, this succinimide ion abstracts *α*-hydrogen, and *α*-*β* double bond is formed again. At last, succinimide and the corresponding *α*-chloro-substituted *N*-propargylic *β*-enaminone **35** are formed. As mentioned before, *α*-chloro-substituted *N*-propargylic

β-enaminone **35** were obtained from these reactions as a diasteroisomeric mixture of *E* and *Z* isomers.



Scheme 20. Proposed mechanism for chloro-substitution of *N*-propargylic *β*-enaminones **13** with NCS.

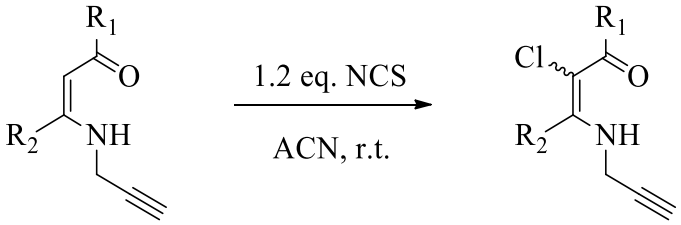
As shown in Scheme 21, diastereoisomers *Z* and *E* isomers can convert into each other by resonance interaction, followed by a free rotation around *α*,*β*-single bond. Finally, these *Z* and *E* isomer of **13** can react with NCS to provide *E* and *Z* isomers of **35**, respectively (Scheme 21).



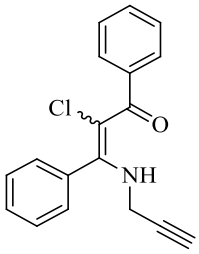
Scheme 21. Formation of *E* and *Z* isomers of *N*-propargylic *β*-enaminones **13** and **35**.

We have synthesized 23 novel *α*-chloro-substituted *N*-propargylic *β*-enaminones **35** in good yields as a mixture of *E* and *Z* isomers (Table 4). For all *α*-chloro-substituted *N*-propargylic *β*-enaminone **35**, *E* isomer was obtained as the major product.

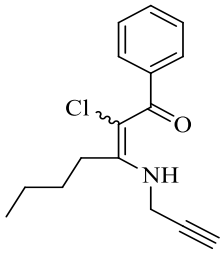
Table 4. Synthesis of α-chloro-substituted *N*-propargylic β-enaminone derivatives **35**. [a]



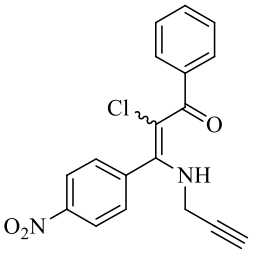
13 **35**



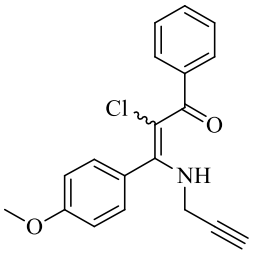
35A (85%)



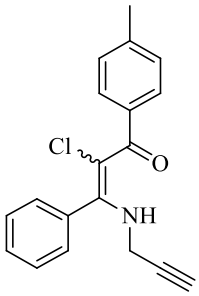
35B (67%)



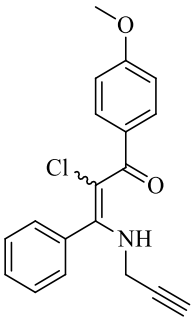
35C (45%)



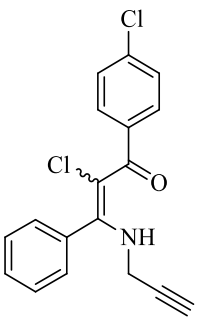
35D (67%)



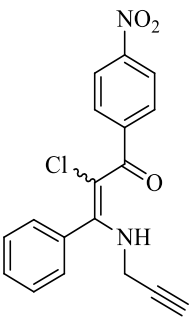
35E (60%)



35F (78%)



35G (78%)



35H (68%)

Table 4. Continued.

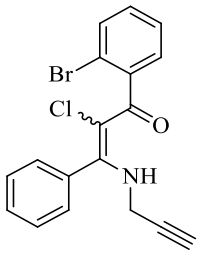
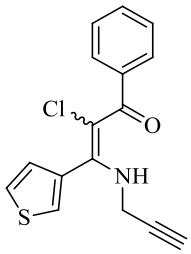
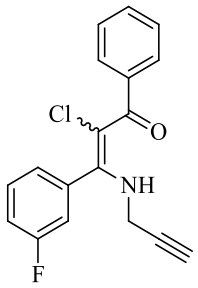
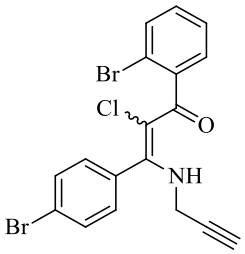
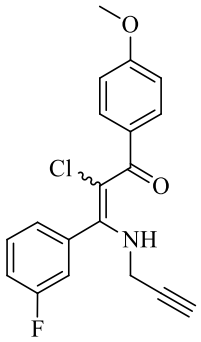
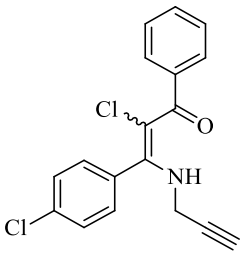
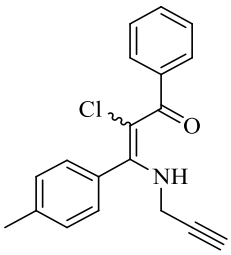
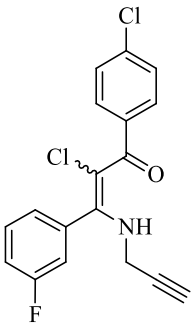
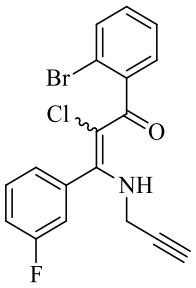
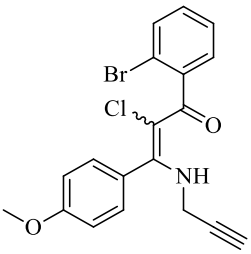
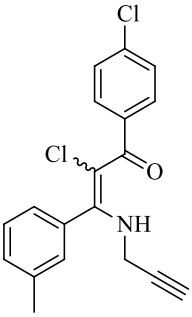
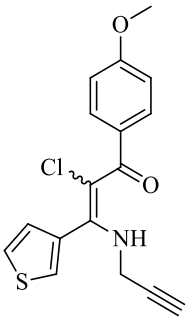
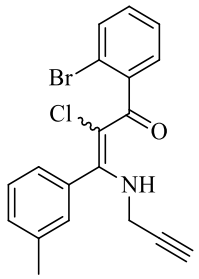
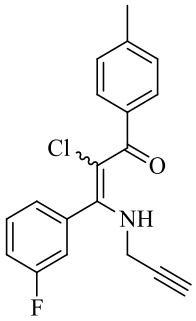
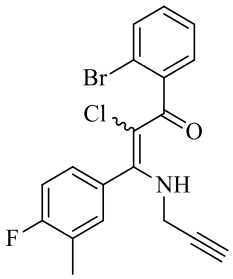
			
35I (68%)	**35J** (63%)	**35K** (74%)	**35L** (65%)
			
35M (62%)	**35N** (68%)	**35O** (73%)	**35P** (68%)
			
35Q (78%)	**35R** (67%)	**35S** (77%)	**35T** (46%)

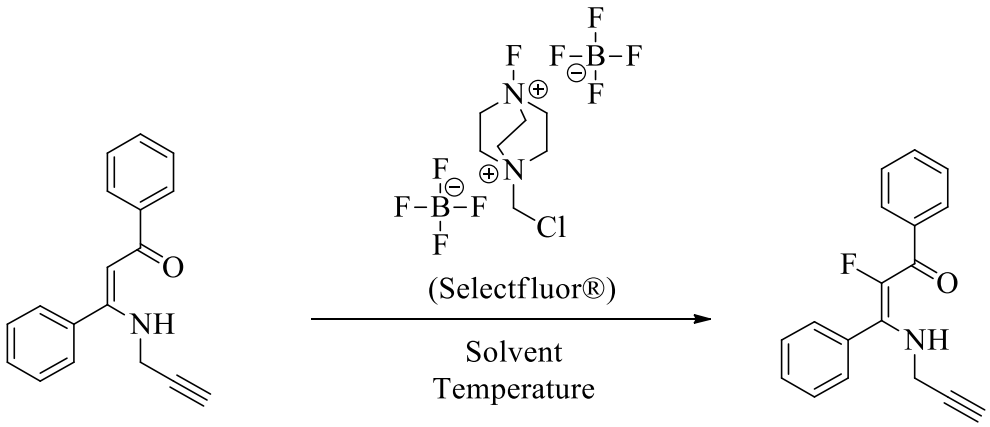
Table 4. Continued.

		
35U (76%)	**35V** (83%)	**35W** (63%)

[a] Total yield of the isolated products as a mixture of *Z* and *E* isomers.

In addition to *α*-chloro substitution of *N*-propargylic *β*-enaminone derivatives **13**, we have studied their *α*-fluorine substitution (Table 5). For this purpose, we used Selectfluor® as fluorine source. The yields for this reaction were low and the best result was 31%, which was obtained by using 1 equivalent of Selectfluor® in ACN at 0 ˚C in 4 h reaction period (Table 5, Entry 2). While examining the reaction conditions, we used ACN:H_2O solvent system, since Selectfluor® is a salt (Table 5, Entries 4–6). The use of water may dissolve this salt very well and increase the yields, but it did not improve the yields.

Table 5. Synthesis of 2-fluoro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**36A**). [a]



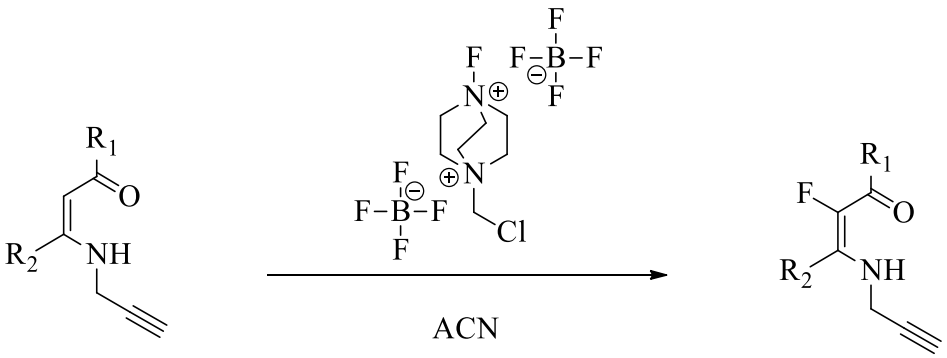
13 **36**

Entry	Amount of Selectfluor® (eq.)	Solvent	Temperature (˚C)	Time (h)	Yield (%) [a]
1	1 eq.	ACN	r.t.	25	21
2	1 eq.	ACN	0	4	31
3	2 eq.	ACN	0	24	18
4	1 eq.	ACN:H_2O (20:1)	r.t./50/82	13	trace amount
5	2 eq.	ACN:H_2O (20:1)	0	3	trace amount
6	2 eq.	ACN:H_2O (20:1)	0	0.10	8
7	1 eq.	CH_3NO_2	70	4.09	15

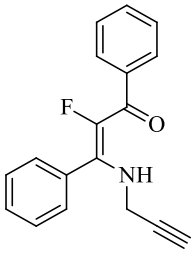
[a] Yield of the isolated products.

We have synthesized 5 novel α-fluoro-substituted *N*-propargylic *β*-enaminones **36** with the yields changing between 15% to 31% (Table 6). In all reactions, we recovered much of the starting *N*-propargylic *β*-enaminone derivatives **13** with some decomposition. We surprisingly did not obtain *Z* isomers of fluoro-substituted derivatives **36** from these reactions. The isolated products were the sole *E* isomers of fluoro-substituted *N*-propargylic *β*-enaminones **36**.

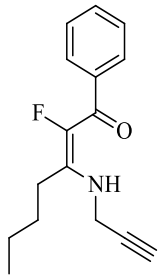
Table 6. Synthesis of *α*-fluoro-substituted *N*-propargylic *β*-enaminones **36**. [a]



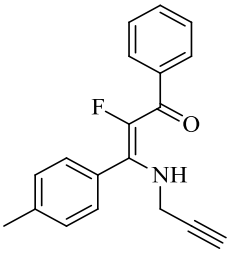
13 **36**



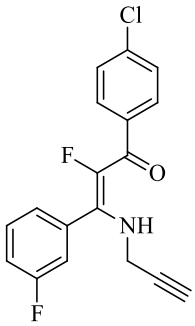
36A (31%)



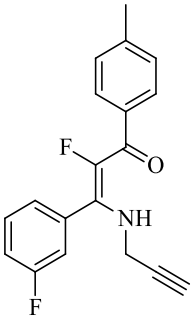
36B (21%)



36O (15%)



36P (17%)



36V (15%)

[a] Yield of the isolated products.

^{1}H and ^{13}C NMR spectra of 2-fluoro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**36A**) is given in Figure 19 and 20. As seen in ^{1}H NMR spectrum (Figure 19), acetylenic hydrogen resonates at 2.29 ppm as a triplet while methylene hydrogens appear at 3.79 ppm as a doublet of doublets. Amine hydrogen gives a broad singlet at 10.10 ppm. Aromatic ten hydrogens of two phenyl groups give peaks between 7.39–7.94 ppm. Notably, the singlet peak of α-hydrogen of *N*-propargylic β-enaminones **13A** at 5.82 ppm was disappeared in the spectrum as the result of α-fluorination (Figure 19).

In ^{13}C NMR spectrum of **36A** (Figure 20), two alkynic carbons resonate at 72.6 and 79.9 ppm while methylene carbon comes at 34.9 ppm. α-Carbon peak appears at 140.2 ppm as a doublet while β-carbon peak comes at 153.1 ppm as a doublet. The carbonyl carbon peak shows at 185.2 ppm as a doublet. Finally, the remaining peaks between 140.2–128.8 ppm belong to aromatic carbons of two phenyl rings of compound **36A** (Figure 20).

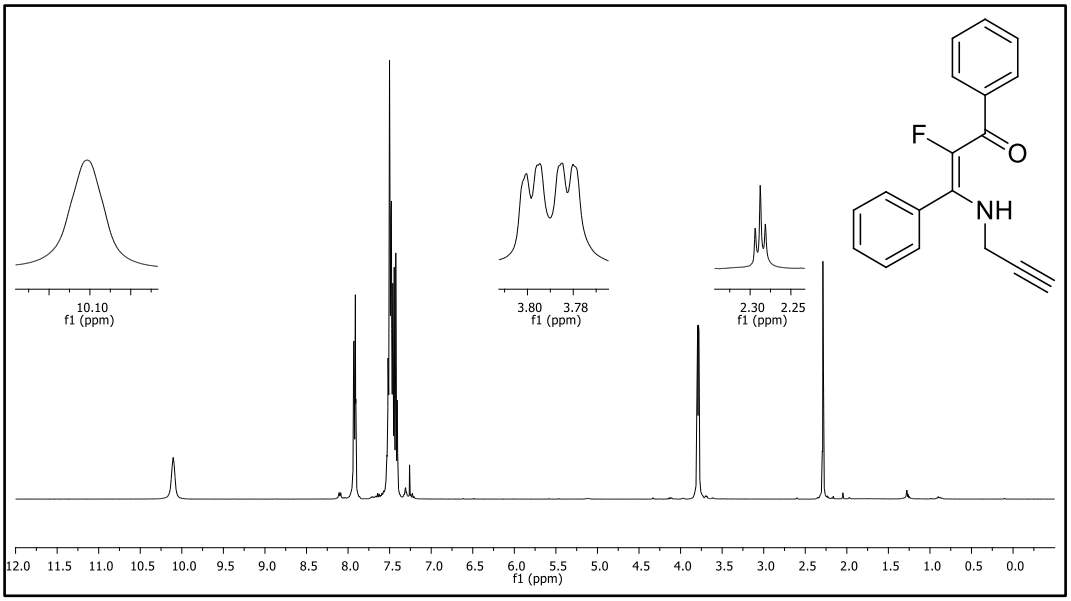


Figure 19. ^{1}H NMR spectrum of 2-fluoro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**36A**).

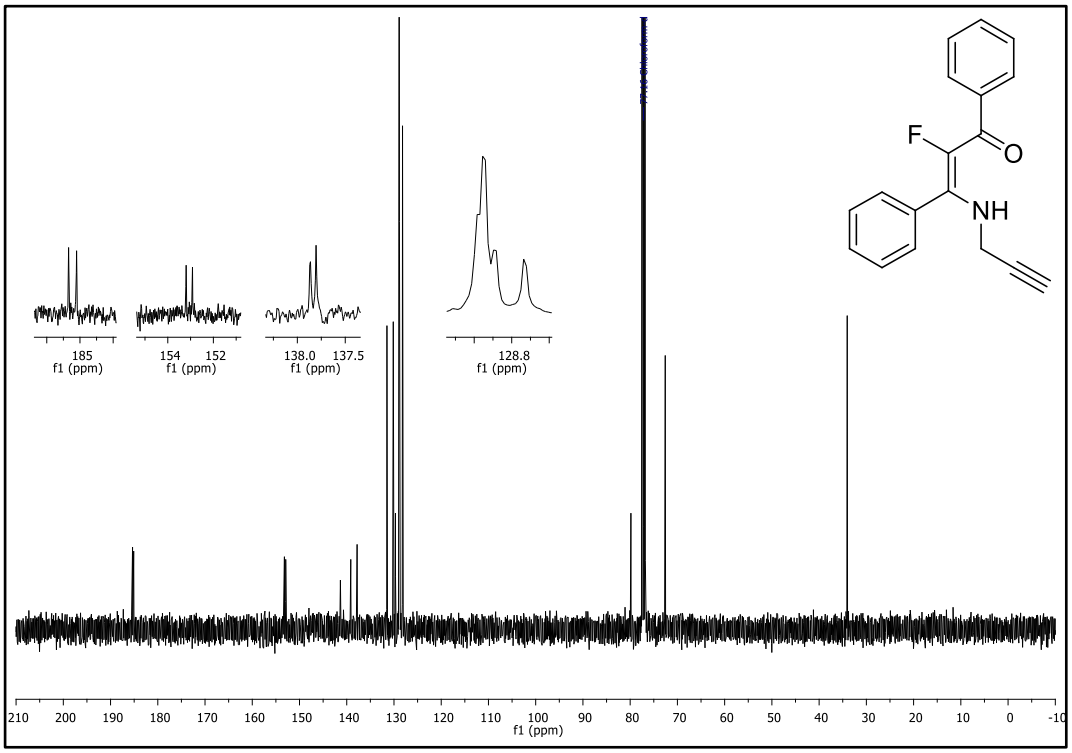
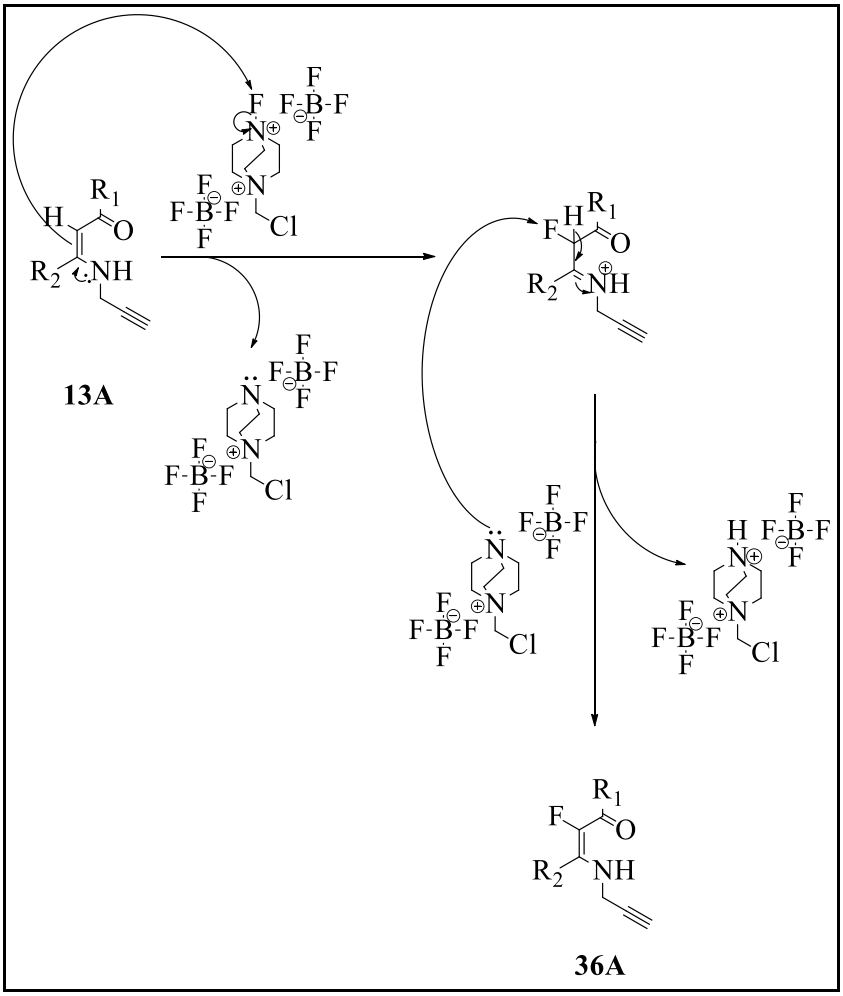


Figure 20. ^{13}C NMR spectrum of 2-fluoro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**36A**).

The mechanism proposed for α-fluorination of *N*-propargylic β-enaminones **13** with Selectfluor® is given in Scheme 22 and it is similar to that for α-chloro substitution of *N*-propargylic β-enaminones **13** with NCS (Scheme 22). In this reaction, the fluorine bonded to nitrogen in Selectfluor® was attacked by α-carbon of **13**. Then, hydrogen loss provided α-fluoro-substituted *N*-propargylic β-enaminones **36** (Scheme 22).



Scheme 22. Proposed mechanism for α-fluoro-substitution of *N*-propargylic β-enaminones **13** with Selectfluor®.

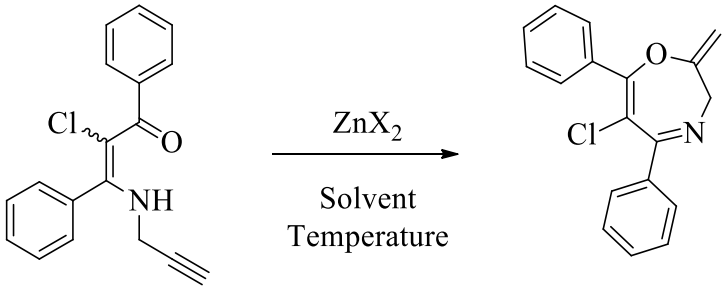
After the synthesis of chloro- and fluoro-substituted *N*-propargylic β-enaminones **35** and **36**, respectively, we investigated their electrophilic cyclizations with $ZnCl_2$ into 6-halo-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **37** and **38**.

2.3 Cyclization of halogen-substituted *N*-propargylic *β*-enaminones

In the final phase of this study, we investigated electrophilic cyclization of halogen-substituted *N*-propargylic *β*-enaminones **35** and **36** into seven-membered 6-halo-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **37** and **38**. Considering our previous work about the synthesis of 2,3-dihydro-1,4-oxazepine [58], we performed these cyclization reactions in the presence of Zn salts. Accordingly, optimization reactions were carried out to determine the best reaction conditions for electrophilic cyclizations of halogen-substituted *N*-propargylic *β*-enaminones **35** and **36** (Table 7 and 9).

Initially, we studied electrophilic cyclization of **35A**. Results of these experiments are summarized in Table 7. All of these reactions gave the desired 6-chloro-2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**37A**), but the best result (49%) was obtained by using 2 equivalents of $ZnCl_2$ in refluxing chloroform (Table 7, Entry 2). We also tested other zinc salts, such as $ZnBr_2$ and ZnI_2; however, their yields were very low (Table 7, Entries 4 and 5). Besides chloroform, we used DCE, DCM and ACN as solvent for this reaction, but they afforded **37A** in 43, 32 and 15%, respectively (Table 7, Entries 6–8).

Table 7. Synthesis of 6-chloro-2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**37A**). [a]



E and *Z* isomer

35A **37A**

Entry	ZnX_2 (eq.)	Solvent	Temperature (˚C)	Time (h)	Yield (%) [a]
1	$ZnCl_2$ (1 eq.)	$CHCl_3$	61	3.5	37
2	$ZnCl_2$ (2 eq.)	$CHCl_3$	61	5	49
3	$ZnCl_2$ (3 eq.)	$CHCl_3$	61	6.5	35
4	$ZnBr_2$ (1 eq.)	$CHCl_3$	61	6	19
5	ZnI_2 (1 eq.)	$CHCl_3$	61	4	18
6	$ZnCl_2$ (2 eq.)	DCE	84	4.5	43
7	$ZnCl_2$ (2 eq.)	DCM	39	6	32
8	$ZnCl_2$ (2 eq.)	ACN	82	3	15
9	$ZnCl_2$ (2 eq.)	$CHCl_3$	61	6	42 [e]
10	$ZnCl_2$ (2 eq.)	ACN	82	5	12 [e]

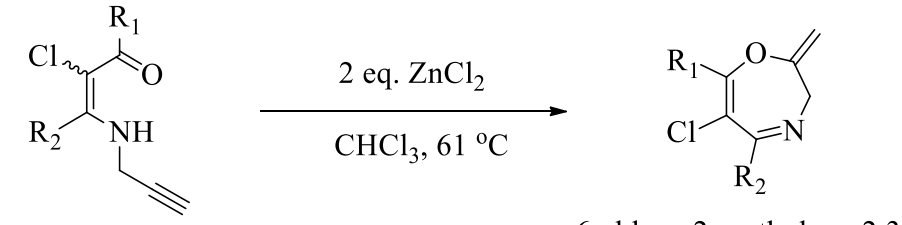
[a] Yield of the isolated products.

[e] One-pot reactions were carried out without isolation at previous step.

As seen in Table 7, one-pot reactions were also performed, starting from *N*-propargylic *β*-enaminone **13** without isolation of α-chloro-substituted *N*-propargylic *β*-enaminone **35** (Table 7, Entries 9 and 10). These reactions were conducted in $CHCl_3$ and ACN, but they gave the product in low yields (42 and 12%, respectively).

Finally, it can be concluded that the condition using 2 equivalents of $ZnCl_2$ in refluxing chloroform gave the best yield (49%) for the formation of 6-chloro-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **37** (Table 7, Entry 2). So, we performed the synthesis of other chloro-substituted 1,4-oxazepine derivatives **37** by using these conditions (Table 8). We achieved the synthesis of 23 novel 6-chloro-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **37** in moderate to good yields (Table 8). Yields were between 31 to 80%.

Table 8. Synthesis of 6-chloro-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **37**. [a]

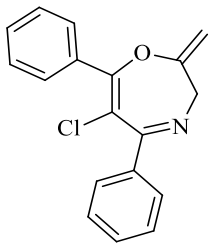


E and *Z* isomers

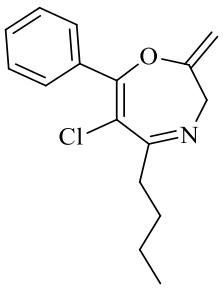
35

6-chloro-2-methylene-2,3-dihydro-1,4-oxazepine

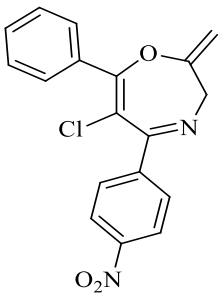
37



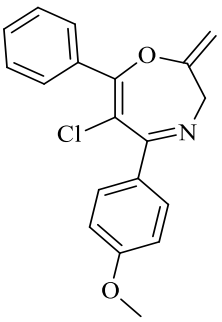
37A (49%)



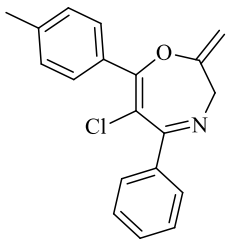
37B (44%)



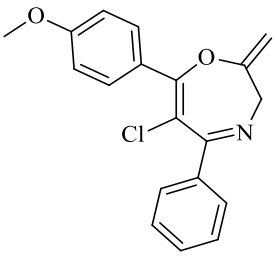
37C (41%)



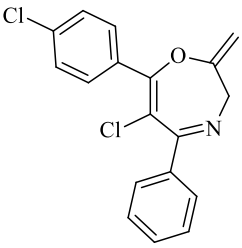
37D (31%)



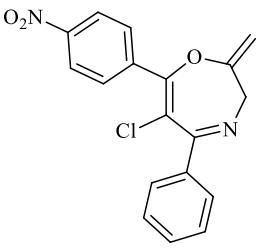
37E (46%)



37F (39%)



37G (42%)



37H (65%)

Table 8. Continued.

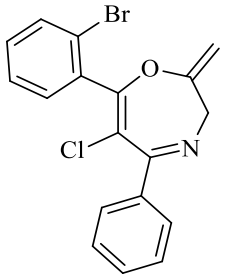
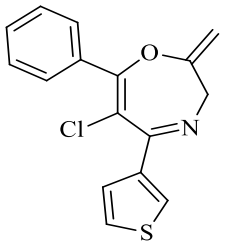
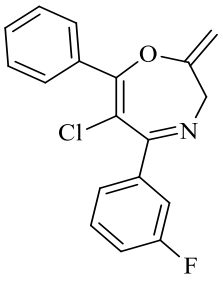
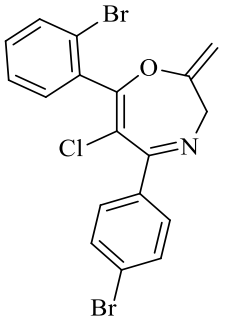
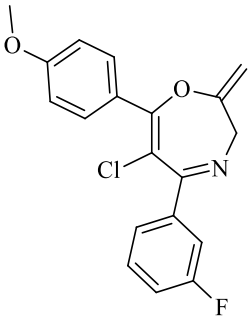
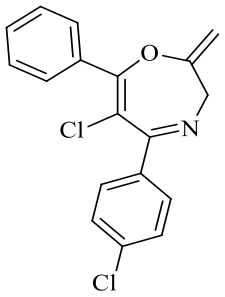
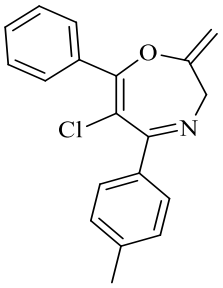
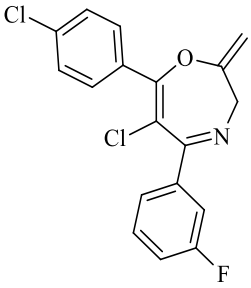
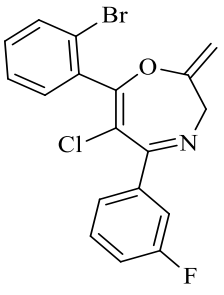
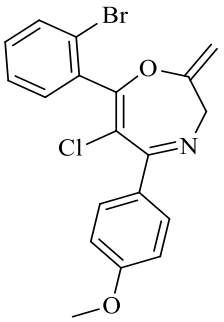
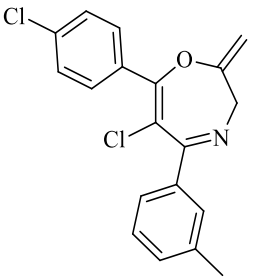
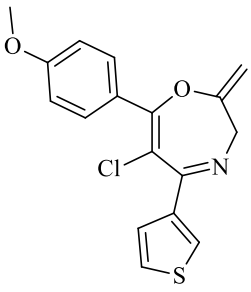
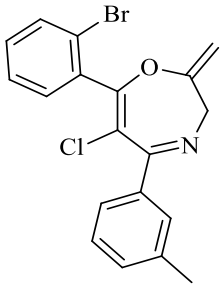
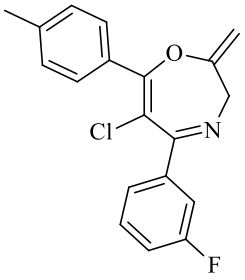
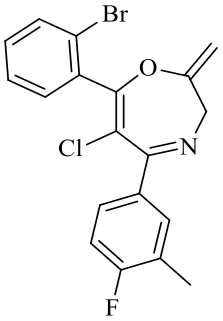
			
37I (78%)	**37J** (32%)	**37K** (51%)	**37L** (46%)
			
37M (39%)	**37N** (51%)	**37O** (48%)	**37P** (53%)
			
37Q (80%)	**37R** (68%)	**37S** (46%)	**37T** (31%)

Table 8. Continued.

		
37U (71%)	**37V** (54%)	**37W** (39%)

[a] Yield of the isolated products.

As an example, ^{1}H and ^{13}C NMR spectra of 6-chloro-2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**37A**) are given in Figure 21 and Figure 22. As seen in ^{1}H NMR spectrum (Figure 21), methylene hydrogens on the ring resonate at 4.59 ppm as a singlet while exo-double bond hydrogens appear at 4.34 and 4.59 ppm as doublets. Finally, the peaks of aromatic ten hydrogens of phenyl groups come at between 7.36–7.83 ppm (Figure 21).

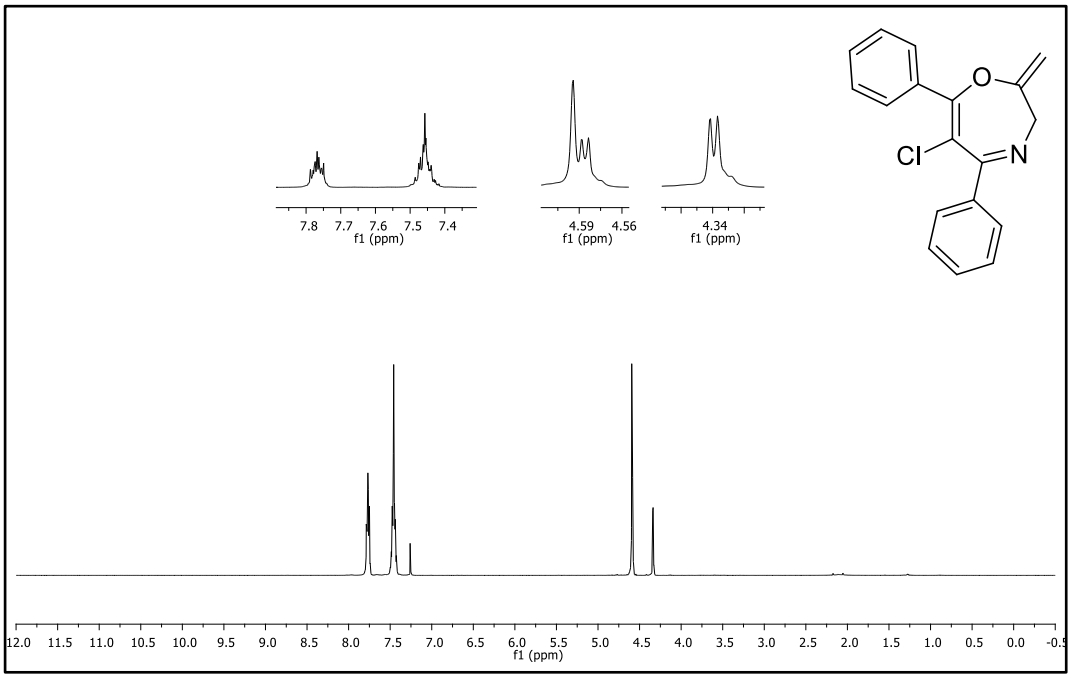


Figure 21. ^{1}H NMR spectrum of 6-chloro-2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**37A**).

In ^{13}C NMR spectrum of 6-chloro-2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**37A**) (Figure 22), methylene carbon resonates at 54.5 ppm while exo-double bond carbon, bonded to two hydrogens, appears at 91.6 ppm. The olefinic carbon, which bonded to chlorine comes at 110.6 ppm. The remaining carbon peaks between 128.3–168.2 ppm belong to two phenyl and oxazepine rings of **37A** (Figure 22).

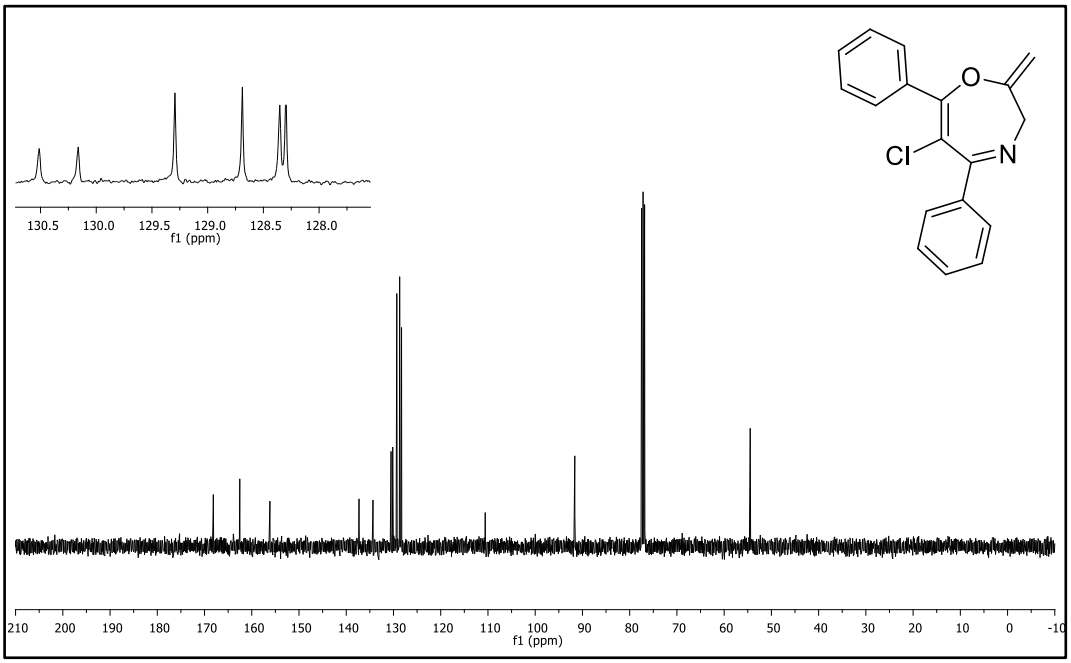
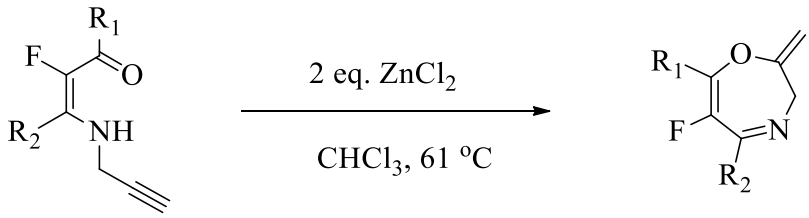


Figure 22. ^{13}C NMR spectrum of 6-chloro-2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**37A**).

We performed the synthesis of fluoro-substituted 1,4-oxazepine derivatives **38** by using the same conditions for the synthesis of chloro-substituted 1,4-oxazepine derivatives **37** (Table 9). We synthesized 5 novel 6-fluoro-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **38** in good to high yields (Table 9). Yields change from 59 to 93%.

Table 9. Synthesis of 6-fluoro-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **38**. [a]

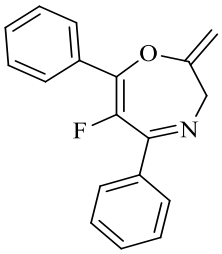


E isomer

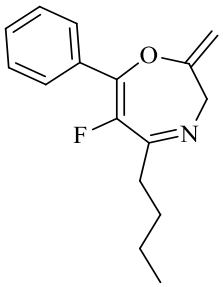
36

6-fluoro-2-methylene-2,3-dihydro-1,4-oxazepine

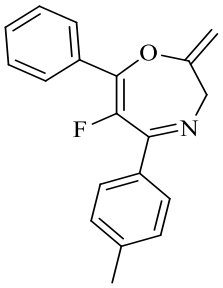
38



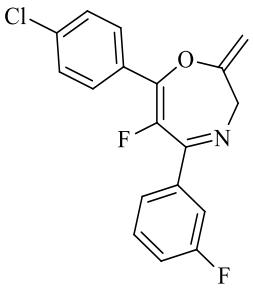
38A (74%)



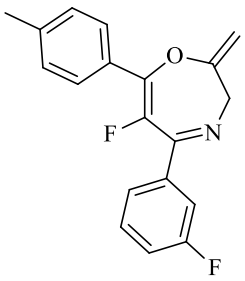
38B (59%)



38O (93%)



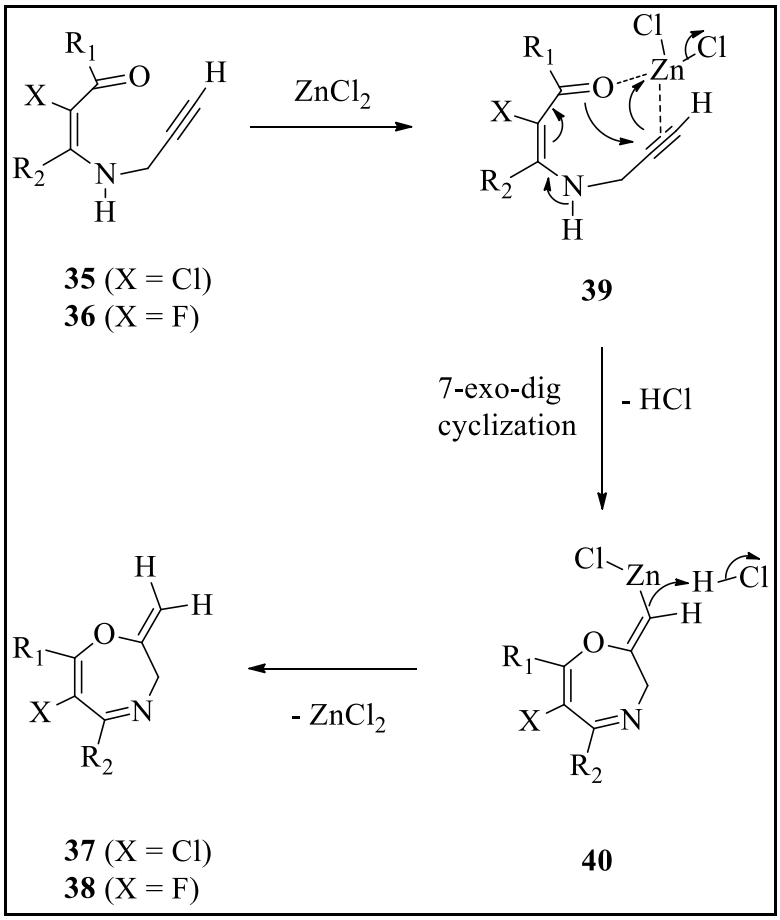
38P (81%)



38V (74%)

[a] Yield of the isolated products.

Proposed mechanism for electrophilic cyclization of halogen-substituted *N*-propargylic *β*-enaminones **35** and **36** into 6-halo-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **37** and **38** is given in Scheme 23. According to proposed mechanism, $ZnCl_2$ coordinates with carbonyl oxygen and triple bond, bringing them closer to each other, and forms the intermediate complex **39** (Scheme 23). Then 7-exo-dig cyclization occurs giving complex **40**. Finally, its reaction with in situ generated HCl produces the target products **37** and **38** (Scheme 23).



Scheme 23. Proposed mechanism for electrophilic cyclization of *N*-propargylic *β*-enaminones **35** and **36** into 6-halo-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **37** and **38**.

CHAPTER 3

CONCLUSION

To summarize, in this study, electrophilic cyclizations of halogen-substituted *N*-propargylic *β*-enaminones **35** and **36** were investigated, which afforded 6-halo-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **37** and **38**.

In the first part of the study, starting compounds, *N*-propargylic *β*-enaminones **13**, were synthesized. Firstly, *α*,*β*-alkynic ketone derivatives **41** were synthesized via Sonogashira cross-coupling reaction of aryloyl chlorides **39** with terminal alkynes **40**. After that, conjugate addition reactions of propargylamine **42** to *α*,*β*-alkynic ketones **41** were performed to obtain *N*-propargylic *β*-enaminones **13**. We synthesized 23 different *N*-propargylic *β*-enaminones **13** in good yields.

In the second part, we studied halogen-substitution reactions of *N*-propargylic *β*-enaminone derivatives **13** by using NCS for chlorine substitution and Selectfluor® for fluorine substitution. We obtained the best result for chloro-substituted *N*-propargylic *β*-enaminones **35** with 1.2 equivalent of NCS in acetonitrile at room temperature. On the other hand, fluoro-substituted *N*-propargylic *β*-enaminones **36** were obtained with 1 equivalent of Selectfluor® in acetonitrile at 0 ˚C. We synthesized 28 novel halo-substituted *N*-propargylic *β*-enaminones **35** and **36** in moderate to good yields.

In final stage of this study, we investigated electrophilic cyclizations of halogen-substituted *N*-propargylic *β*-enaminones **35** and **36**. These reactions afforded the expected 6-halo-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **37** and **38**.

These reactions were achieved by using 2 equivalents of $ZnCl_2$ in refluxing chloroform. Seven-membered ring forming reaction was found to be general for a range of *N*-propargylic *β*-enaminones and tolerated the presence of various aryl groups with electron-withdrawing and electron-donating substituents. In brief, we synthesized 28 novel 6-halo-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **37** and **38** in good yields.

The structures of these novel compounds were identified by ^{1}H and ^{13}C NMR, IR spectroscopy and HRMS.

Finally, as the future work, these 6-halo-2-methylene-2,3-dihydro-1,4-oxazepine derivatives **37** and **38** will be tested for biological activity by a collaborative work.

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 41

Aryloyl chlorides **39** (1.2 mmol) was dissolved in THF (5.0 mL) and $PdCl_2(PPh_3)_2$ (0.02 mmol) and Et_3N (1.2 mmol), and CuI (0.02 mmol) added orderly and stirred in a round bottom flask at room temperature under argon atmosphere. After 10 min. later terminal alkyne **40** (1.0 mmol) was added to the reaction and reaction is started to monitored by TLC (19:1 hexane:EtOAc). When the reaction finished, extraction with ethyl acetate (50 mL), saturated NH_4Cl solution (50 mL) and 0.1 N HCl solution was performed and the separated organic phase was dried with $MgSO_4$ and filtered. Finally, with flash chromatography using hexane as eluent was performed to purify the crude product.

4.1.1 Synthesis of 1,3-Diphenylprop-2-yn-1-one (41A)

General Procedure **1** was followed by using benzoyl chloride (1.636 g, 11.64 mmol) $PdCl_2(PPh_3)_2$ (136 mg, 0.19 mmol), Et_3N (1.177 g, 11.64 mmol), CuI (37 mg, 0.19 mmol) and phenylacetylene (990 mg, 9.70 mmol) were employed to afford 1.935 g (97%) of the indicated product of 1,3-diphenylprop-2-yn-1-one **41A**. as yellow liquid (R_f = 0.54 in 4:1 hexane/ethyl acetate).

41A: ^{1}H 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 [59].

4.1.2 Synthesis of 1-Phenylhept-2-yn-1-one (41B)

General Procedure **1** was followed by using benzoyl chloride (815 mg, 5.80 mmol) $PdCl_2(PPh_3)_2$ (68 mg, 0.12 mmol), Et_3N (586 mg, 5.80 mmol), CuI (22 mg, 0.12 mmol) and 1-hexyne (397 mg, 4.80 mmol) were employed to afford 703 mg (78%) of the indicated product of 1-phenylhept-2-yn-1-one (**41B**) as pale orange liquid (R_f = 0.71 in 4:1 hexane/ethyl acetate).

41B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17–8.08 (m, 2H), 7.61–7.54 (m, 1H), 7.49–7.42 (m, 2H), 2.48 (t, *J* = 7.1 Hz, 2H), 1.69–1.59 (m, 2H), 1.55–1.42 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (CO), 136.9 (C), 133.8 (CH), 129.4 (CH), 128.4 (CH), 96.7 (C), 79.6 (C), 29.8 (CH_2), 21.9 (CH_2), 18.8 (CH_2), 13.4 (CH_3). IR (neat): 3062, 3031, 2958, 2872, 2377, 2236, 2199, 1641, 1597, 1579, 1488, 1449, 1422, 1379, 1312, 1262, 1174, 1114, 1069, 1054, 1024, 999, 985, 961, 910, 844, 795, 745, 699 cm^{-1}. The spectral data were in agreement with those reported previously for this compound [60].

4.1.3 Synthesis of 3-(4-Nitrophenyl)-1-phenylprop-2-yn-1-one (41C)

General Procedure **1** was followed by using benzoyl chloride (278 mg, 1.98 mmol) $PdCl_2(PPh_3)_2$ (23 mg, 0.03 mmol), Et_3N (200 mg, 1.98 mmol), CuI (6 mg, 0.03 mmol) and 1-ethynyl-4-nitrobenzene (243 mg, 1.65 mmol) were employed to afford 185 mg (45%) of the indicated product of 3-(4-nitrophenyl)-1-phenylprop-2-yn-1-one (**41C**) as bright yellow solid (R_f = 0.50 in 4:1 hexane/ethyl acetate).

41C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dt, *J* = 8.9, 1.9 2H), 8.23–8.17 (m, 2H), 7.84 (dt, *J* = 8.9, 1.9 2H), 7.67 (tt, *J* = 2.4, 1.2 Hz, 1H), 7.57–7.52 (dd, *J* = 10.7, 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (CO), 148.7 (C), 136.5 (C), 134.8 (CH), 133.8 (C), 129.8 (CH), 128.9 (CH), 126.9 (CH), 123.9 (CH), 89.9 (C), 89.3 (C); IR (neat): 3104, 3067, 2934, 2844, 2696, 2444, 2322, 2289, 2205, 2145, 1980, 1935, 1811, 1782, 1733, 1685, 1633, 1592, 1519, 1449, 1402, 1370, 1341, 1312, 1287, 1211, 1169, 1102, 1027, 1007, 855, 804, 751, 711, 681, 642, 525, 426 cm^{-1}. The spectral data were in agreement with those reported previously for this compound [60].

4.1.4 Synthesis of 3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (41D)

General Procedure **1** was followed by using benzoyl chloride (319 mg, 2.27 mmol) $PdCl_2(PPh_3)_2$ (27 mg, 0.04 mmol), Et_3N (231 mg, 2.27 mmol), CuI (7 mg, 0.04 mmol) and 4-ethynylanisole (250 mg, 1.89 mmol) were employed to afford 317 mg (71%) of the indicated product of 3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-one (**41D**) as yellow solid (R_f = 0.41 in 4:1 hexane/ethyl acetate).

41D: ^{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 (CO), 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. [60]

4.1.5 Synthesis of 3-Phenyl-1-(p-tolyl)prop-2-yn-1-one (41E)

General Procedure **1** was followed by using p-toluoyl chloride (505 mg, 3.26 mmol) $PdCl_2(PPh_3)_2$ (38 mg, 0.05 mmol), Et_3N (330 mg, 3.26 mmol), CuI (10 mg, 0.05 mmol) and phenylacetylene (278 mg, 2.72 mmol) were employed to afford 522 mg (86%) of the indicated product of 3-phenyl-1-(p-tolyl)prop-2-yn-1-one (**41E**) as orange-yellow solid (R_f = 0.67 in 4:1 hexane/ethyl acetate).

41E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.2 Hz, 2H), 7.70–7.64 (m, 2H), 7.50–7.35 (m, 3H), 7.30 (d, *J* = 8.1 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (CO), 145.3 (C), 134.7 (C), 133.1 (CH), 130.8 (CH), 129.8 (CH), 129.4 (CH), 128.7 (CH), 120.3 (C), 92.7 (C), 87.0 (C), 21.9 (CH_3); IR (neat): 3257, 3063, 3022, 2198, 1633, 1601, 1569, 1505, 1487, 1442, 1406, 1382, 1308, 1283, 1207, 1167, 1113, 1070, 1030, 1010, 995, 971, 926, 851, 831, 778, 759, 736, 689 cm^{-1}. The spectral data were in agreement with those reported previously for this compound [60].

4.1.6 Synthesis of 1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-one (41F)

General Procedure **1** was followed by using 4-methoxybenzoyl chloride (520 mg, 3.05 mmol) $PdCl_2(PPh_3)_2$ (36 mg, 0.05 mmol), Et_3N (308 mg, 3.05 mmol), CuI (10 mg, 0.05 mmol) and phenylacetylene (259 mg, 2.54 mmol) were employed to afford 598 mg (99%) of the indicated product of 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one (**41F**) as yellow solid (R_f = 0.46 in 4:1 hexane/ethyl acetate).

41F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.12 (m, 2H), 7.67–7.59 (m, 2H), 7.47–7.32 (m, 3H), 7.03–6.84 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (CO), 164.5 (C), 132.9 (CH), 131.9 (CH), 130.6 (CH), 130.2 (C), 128.6 (CH), 120.2 (C), 113.9 (CH), 92.2 (C), 86.9 (C), 55.5 (CH_3); IR (neat): 3009, 2956, 2847, 2195, 1627, 1594, 1569, 1508, 1486, 1456, 1439, 1419, 1332, 1291, 1257, 1213, 1172, 1156, 1029, 1009, 993, 838, 820, 759, 681 cm^{-1}. The spectral data were in agreement with those reported previously for this compound [60].

4.1.7 Synthesis of 1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one (41G)

General Procedure **1** was followed by using 4-chlorobenzoyl chloride (525 mg, 3.0 mmol) $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), Et_3N (304 mg, 3.0 mmol), CuI (10 mg, 0.05 mmol) and phenylacetylene (255 mg, 2.5 mmol) were employed to afford 496 mg (83%) of the indicated product of 1-(4-chlorophenyl)-3-phenylprop-2-yn-1-one (**41G**) as yellow solid (R_f = 0.68 in 4:1 hexane/ethyl acetate).

41G: ^{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 (CO), 140.7 (C), 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 [60].

4.1.8 Synthesis of 1-(4-Nitrophenyl)-3-phenylprop-2-yn-1-one (41H)

General Procedure **1** was followed by using 4-nitrobenzoyl chloride (532 mg, 2.87 mmol) $PdCl_2(PPh_3)_2$ (34 mg, 0.05 mmol), Et_3N (290 mg, 2.87 mmol), CuI (9 mg, 0.05 mmol) and phenylacetylene (244 mg, 2.39 mmol) were employed to afford 447 mg (74%) of the indicated product of of 1-(4-nitrophenyl)-3-phenylprop-2-yn-1-one (**41H**) as yellow solid (R_f = 0.5 in 4:1 hexane/ethyl acetate).

41H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42–8.34 (m, 4H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0 (CO), 150.9 (C), 141.1 (C), 133.42 (CH), 131.6 (CH), 130.6 (CH), 128.9 (CH), 124.0 (CH), 119.5 (C), 95.6 (C), 86.7 (C); IR (neat): 3280, 3112, 3048, 2918, 2854, 2194, 1993, 1644, 1594, 1517, 1484, 1443, 1407, 1343, 1321, 1299, 1278, 1201, 1171, 1105, 1071, 1025, 1008, 992, 927, 867, 856, 827, 808, 759, 704, 688 cm^{-1}. The spectral data were in agreement with those reported previously for this compound [61].

4.1.9 Synthesis of 1-(2-Bromophenyl)-3-phenylprop-2-yn-1-one (41I)

General Procedure **1** was followed by using 2-bromobenzoyl chloride (555 mg, 2.53 mmol) $PdCl_2(PPh_3)_2$ (30 mg, 0.04 mmol), Et_3N (256 mg, 2.53 mmol), CuI (8 mg, 0.04 mmol) and phenylacetylene (215 mg, 2.11 mmol) were employed to afford 338 mg (56%) of the indicated product of 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (**41I**) as yellow oil (R_f = 0.3 in 4:1 hexane/ethyl acetate).

41I: ^{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 (CO), 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 (C), 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 [61].

4.1.10 Synthesis of 1-Phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (41J)

General Procedure **1** was followed by using benzoyl chloride (477 mg, 3.39 mmol) $PdCl_2(PPh_3)_2$ (40 mg, 0.06 mmol), Et_3N (344 mg, 3.39 mmol), CuI (11 mg, 0.06 mmol) and 3-ethynylthiophene (306 mg, 2.83 mmol) were employed to afford 539 mg (90%) of the indicated product of 1-phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (**41J**) as orange-brown oil (R_f = 0.67 in 4:1 hexane/ethyl acetate).

41J: ^{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 (CO), 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 [60].

4.1.11 Synthesis of 3-(3-Fluorophenyl)-1-phenylprop-2-yn-1-one (41K)

General Procedure **1** was followed by using benzoyl chloride (452 mg, 3.22 mmol) $PdCl_2(PPh_3)_2$ (37 mg, 0.05 mmol), Et_3N (325 mg, 3.22 mmol), CuI (10 mg, 0.05 mmol) and 1-ethynyl-3-fluorobenzene (322 mg, 2.68 mmol) were employed to afford 443 mg (74%) of the indicated product of 3-(3-fluorophenyl)-1-phenylprop-2-yn-1-one (**41K**) as yellow solid (R_f = 0.68 in 4:1 hexane/ethyl acetate); mp 60.1–61.0 ^oC.

41K: ^{1}H 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 (CO), 162.22 (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 [63].

4.1.12 Synthesis of 1-(2-Bromophenyl)-3-(4-bromophenyl)prop-2-yn-1-one (41L)

General Procedure 1 was followed by using 2-bromobenzoyl chloride (270 mg, 1.23 mmol) $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), Et_3N (125 mg, 1.23 mmol), CuI (4 mg, 0.02 mmol) and 1-bromo-4-ethynylbenzene (185 mg, 1.02 mmol) were employed to afford 315 mg (85%) of the indicated product of 1-(2-bromophenyl)-3-(4-bromophenyl)prop-2-yn-1-one (**41L**) as yellow solid (R_f = 0.63 in 4:1 hexane/ethyl acetate); mp 88.0–89.1 ºC.

41L: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.56 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.43–7.29 (m, 5H), 7.25 (td, *J* = 7.6, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (CO), 137.1 (C), 134.9 (CH), 134.3 (CH), 133.5 (CH), 132.8 (CH), 132.1 (CH), 127.4 (CH), 125.8 (C), 121.2 (C), 118.8 (C), 92.7 (C), 88.7 (C); IR (neat): 3233, 3088, 3068, 2401, 2359, 2306, 2195, 1903, 1825, 1728, 1631, 1580, 1482, 1426, 1391, 1299, 1202, 1174, 1059, 1025, 1006, 823, 809, 772, 731, 687 cm^{-1}; MS (ESI, m/z): 362.90 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_9{}^{79}Br_2O$: 362.9014 $[M+H]^+$, found: 362.9001; MS (ESI, m/z): 364.90 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_9{}^{79}Br^{81}BrO$: 364.8994 $[M+H]^+$, found: 364.8991; MS (ESI, m/z): 366.90 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_9{}^{81}Br_2O$: 366.8974 $[M+H]^+$, found: 366.8970.

4.1.13 Synthesis of 3-(3-Fluorophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-one (41M)

General Procedure 1 was followed by using 4-methoxybenzoyl chloride (966 mg, 5.66 mmol) $PdCl_2(PPh_3)_2$ (66 mg, 0.09 mmol), Et_3N (573 mg, 5.66 mmol), CuI (18 mg, 0.09 mmol) and 1-ethynyl-3-fluorobenzene (566 mg, 4.72 mmol) were employed to afford 1.147 g (96%) of the indicated product of 3-(3-fluorophenyl)-

1-(4-methoxyphenyl)prop-2-yn-1-one (**41M**) as pale orange solid (R_f = 0.48 in 4:1 hexane/ethyl acetate); mp 92.8–93.3 °C.

41M: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.13 (m, 2H), 7.44 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.41–7.31 (m, 2H), 7.17 (tdd, *J* = 8.4, 2.6, 1.0 Hz, 1H), 7.01–6.94 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (CO), 164.8 (C), 162.4 (d, ^{1}J = 248.1 Hz, CF), 132.1 (CH), 130.5 (d, ^{3}J = 8.5 Hz, CH), 130.2 (C), 128.9 (d, ^{4}J = 2.9 Hz, CH), 122.3 (d, ^{3}J = 9.4 Hz, C), 119.6 (d, ^{2}J = 23.1 Hz, CH), 118.1 (d, ^{2}J = 21.3 Hz, CH), 114.1 (CH), 90.4 (d, ^{4}J = 3.1 Hz, C), 87.3 (C), 55.7 (CH_3); IR (neat): 3074, 3032, 2939, 2901, 2842, 3198, 1946, 1916, 1809, 1748, 1630, 1595, 1572, 1508, 1485, 1421, 1332, 1304, 1258, 1233, 1191, 1159, 1143, 1025, 999, 919, 872, 837, 780, 750, 676 cm^{-1}; MS (ESI, m/z): 255.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{12}FO_2$: 255.0816 $[M+H]^+$, found: 255.0823.

4.1.14 Synthesis of 3-(4-Chlorophenyl)-1-phenylprop-2-yn-1-one (41N)

General Procedure **1** was followed by using benzoyl chloride (337 mg, 2.39 mmol) $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol), Et_3N (243 mg, 2.39 mmol), CuI (8 mg, 0.04 mmol) and 1-chloro-4-ethynylbenzene (273 mg, 1.99 mmol) were employed to afford 414 mg (86%) of the indicated product of 3-(4-chlorophenyl)-1-phenylprop-2-yn-1-one (**41N**) as yellow solid (R_f = 0.63 in 4:1 hexane/ethyl acetate).

41N: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.54–7.39 (m, 3H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (CO), 137.1 (C), 136.6 (C), 134.2 (CH), 129.4 (CH), 129.0 (CH), 128.6 (CH), 118.5 (C), 91.5 (C), 87.5 (C). (Note that two CH peaks overlap on each other); IR (neat): 3408, 3251,3211, 3157, 3083, 3054, 3031, 3002, 2504, 2433, 2327, 2309, 2196, 2116, 2032, 1966, 1915, 1825, 1786, 1733, 1697, 1659, 1629, 1598, 1578, 1489, 1478, 1447, 1399, 1316, 1294, 1205, 1170, 1085, 1030, 1008, 939, 821, 791, 722, 692 cm^{-1}. The spectral data were in agreement with those reported previously for this compound [60].

4.1.15 Synthesis of 1-Phenyl-3-(p-tolyl)prop-2-yn-1-one (41O)

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 (**41O**) as brownish-orange solid (R_f = 0.56 in 4:1 hexane/ethyl acetate); mp 58.3–59.6 ºC.

41O: ^{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 (CO), 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 [60].

4.1.16 Synthesis of 1-(4-Chlorophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (41P)

General Procedure **1** was followed by using 4-chlorobenzoyl chloride (1.237 g, 7.07 mmol) $PdCl_2(PPh_3)_2$ (83 mg, 0.118 mmol), Et_3N (715 mg, 7.07 mmol), CuI (22 mg, 0.12 mmol) and 1-ethynyl-3-fluorobenzene (708 mg, 5.89 mmol) were employed to afford 920 mg (61%) of the indicated product of 1-(4-chlorophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (**41P**) as pale orange solid (R_f = 0.70 in 4:1 hexane/ethyl acetate); mp 125.7–126.3 ºC.

41P: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.5 Hz, 2H), 7.52–7.44 (m, 3H), 7.44–7.33 (m, 2H), 7.24–7.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (CO), 162.4 (d, ^1J = 248.6 Hz, CF), 141.1 (C), 135.2 (C), 131.0 (CH), 130.6 (d, ^3J = 8.6 Hz, CH), 129.2 (CH), 129.1 (d, ^4J = 3.0 Hz, CH), 121.8 (d, ^3J = 9.2 Hz, C), 119.8 (d, ^2J = 23.4 Hz, CH), 118.6 (d, ^2J = 21.2 Hz, CH), 91.7 (d, ^4J = 3.2 Hz, C), 86.9 (C); IR (neat): 3251, 3090, 3078, 3059, 3040, 2454, 2324, 2202, 1941, 1923,

1867, 1788, 1722, 1682, 1633, 1607, 1582, 1481, 1428, 1398, 1304, 1268, 1223, 1168, 1154, 1108, 1087, 1030, 1008, 922, 889, 842, 783, 738, 718, 671 cm^{-1}; MS (ESI, m/z): 259.03 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_9ClFO$: 259.0320 $[M+H]^+$, found: 259.0319.

4.1.17 Synthesis of 1-(2-Bromophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (41Q)

General Procedure **1** was followed by using 2-bromobenzoyl chloride (1.321 g, 6.02 mmol) $PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol), Et_3N (609 mg, 6.02 mmol), CuI (19 mg, 0.10 mmol) and 1-ethynyl-3-fluorobenzene (602 mg, 5.01 mmol) were employed to afford 808 mg (54%) of the indicated product of 1-(2-bromophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (**41Q**) as orange solid (R_f = 0.58 in 4:1 hexane/ethyl acetate); mp 61.5–62.5 ºC.

41Q: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 7.7, 1.5 Hz, 1H), 7.64–7.53 (m, 1H), 7.43–7.35 (m, 1H), 7.33–7.25 (m, 3H), 7.23–7.17 (m, 1H), 7.13–7.05 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (CO), 161.9 (d, ^1J = 248.2 Hz, CF), 136.5 (C), 134.8 (CH), 133.4 (CH), 132.8 (CH), 130.3 (d, ^3J = 8.4 Hz, CH), 128.7 (d, ^4J = 3.0 Hz, CH), 127.3 (CH), 121.4 (d, ^3J = 9.4 Hz, C), 120.9 (C), 119.3 (d, ^2J = 23.1 Hz, CH), 118.2 (d, ^2J = 21.1 Hz, CH), 91.7 (d, ^4J = 3.4 Hz, C), 87.8 (C); IR (neat): 3069, 2195, 1648, 1579, 1520, 1484, 1429, 1336, 1301, 1263, 1222, 1167, 1149, 1079, 1059, 1011, 922, 872, 785, 736, 697 cm^{-1}; MS (ESI, m/z): 302.98 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_9{}^{79}BrFO$: 302.9815$[M+H]^+$, found: 302.9823.

4.1.18 Synthesis of 1-(2-Bromophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-one (41R)

General Procedure **1** was followed by using 2-bromobenzoyl chloride (501 mg, 2.28 mmol) $PdCl_2(PPh_3)_2$ (33 mg, 0.04 mmol), Et_3N (231 mg, 2.28 mmol), CuI (9 mg, 0.04 mmol) and 1-ethynyl-4-methoxybenzene (252 mg, 1.90 mmol) were employed to afford 432 mg (72%) of the indicated product of 1-(2-bromophenyl)-3-(4-

methoxyphenyl)prop-2-yn-1-one (**41R**) as pale yellow solid (R_f = 0.33 in 4:1 hexane/ethyl acetate); mp 52.2–53.0 °C.

41R: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.72–7.61 (m, 1H), 7.60–7.54 (m, 2H), 7.47–7.40 (m, 1H), 7.35 (td, *J* = 7.7, 1.8 Hz, 1H), 6.95–6.85 (m, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4 (CO), 161.9 (C), 137.7 (C), 135.2 (CH), 134.8 (CH), 133.2 (CH), 132.5 (CH), 127.4 (CH), 120.9 (C), 114.4 (CH), 111.5 (C), 95.6 (C), 88.1 (C), 55.4 (CH_3); IR (neat): 3096, 3069, 3054, 3009, 2973, 2958, 2931, 2908, 2843, 2554, 2424, 2322, 2185, 2084, 2045, 1956, 1895, 1841, 1805, 1732, 1647, 1619, 1585, 1563, 1506, 1461, 1447, 1426, 1317, 1305, 1292, 1252, 1209, 1191, 1172, 1109, 1062, 1024, 827, 766, 729, 704, 679 cm^{-1}. The spectral data were in agreement with those reported previously for this compound [62].

4.1.19 Synthesis of 1-(4-Chlorophenyl)-3-(m-tolyl)prop-2-yn-1-one (41S)

General Procedure **1** was followed by using 4-chlorobenzoyl chloride (989 mg, 5.65 mmol) $PdCl_2(PPh_3)_2$ (66 mg, 0.09 mmol), Et_3N (572 mg, 5.65 mmol), CuI (18 mg, 0.09 mmol) and 3-ethynyltoluene (547 mg, 4.71 mmol) were employed to afford 865 mg (72%) of the indicated product of 1-(4-chlorophenyl)-3-(m-tolyl)prop-2-yn-1-one (**41S**) as pale yellow solid (R_f = 0.67 in 4:1 hexane/ethyl acetate); mp 80.4–81.5 °C.

41S: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20–8.11 (m, 2H), 7.52–7.46 (m, 4H), 7.35–7.28 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (CO), 140.6 (C), 138.6 (C), 135.4 (C), 133.6 (CH), 131.9 (CH), 130.9 (CH), 130.3 (CH), 128.9 (CH), 128.7 (CH), 119.7 (C), 94.1 (C), 86.4 (C), 21.2 (CH_3); IR (neat): 3244, 3194, 3089, 3058, 2951, 2916, 2853, 2185, 1925, 1793, 1668, 1627, 1597, 1583, 1479, 1453, 1397, 1363, 1312, 1301, 1283, 1222, 1164, 1106, 1088, 1033, 1007, 913, 897, 881, 839, 781, 741, 715, 685 cm^{-1}; MS (ESI, m/z): 255.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{12}ClO$: 255.0571 $[M+H]^+$, found: 255.0568.

4.1.20 Synthesis of 1-(4-Methoxyphenyl)-3-(thiophen-3-yl)prop-2-yn-1-one (41T)

General Procedure **1** was followed by using 4-methoxybenzoyl chloride (1.267 g, 7.43 mmol) $PdCl_2(PPh_3)_2$ (87 mg, 0.12 mmol), Et_3N (752 mg, 7.43 mmol), CuI (24 mg, 0.12 mmol) and 3-ethynylthiophene (670 mg, 6.12 mmol) were employed to afford 961 mg (64%) of the indicated of 1-(4-methoxyphenyl)-3-(thiophen-3-yl)prop-2-yn-1-one (**41T**) product as pale yellow solid (R_f = 0.37 in 4:1 hexane/ethyl acetate); mp 100.9–102.3 °C.

41T: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.9 Hz, 2H), 7.75 (dd, *J* = 2.9, 1.0 Hz, 1H), 7.33–7.25 (m, 1H), 7.23 (dd, *J* = 5.0, 1.0 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (CO), 164.5 (C), 133.7 (CH), 131.9 (CH), 130.2 (CH), 130.1 (CH), 126.3 (C), 119.4 (CH), 113.9 (C), 87.8 (C), 87.2 (C), 55.6 (CH_3); IR (neat): 3095, 3079, 3012, 2993, 2956, 2899, 2842, 2226, 2185, 2052, 1625, 1596, 1571, 1506, 1474, 1435, 1421, 1361, 1301, 1280, 1256, 1222, 1179, 1156, 1031, 1011, 926, 876, 839, 823, 791, 752, 712, 680 cm^{-1}; MS (ESI, m/z): 243.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{11}O_2S$: 243.0474 $[M+H]^+$, found: 243.0477.

4.1.21 Synthesis of 1-(2-Bromophenyl)-3-(m-tolyl)prop-2-yn-1-one (41U)

General Procedure **1** was followed by using 2-bromobenzoyl chloride (1.041 g, 4.74 mmol) $PdCl_2(PPh_3)_2$ (56 mg, 0.08 mmol), Et_3N (480 mg, 4.74 mmol), CuI (15 mg, 0.08 mmol) and 1-ethynyl-3-methylbenzene (459 mg, 3.95 mmol) were employed to afford 1.041 g (88%) of the indicated product of 1-(2-bromophenyl)-3-(m-tolyl)prop-2-yn-1-one (**41U**) as yellow liquid (R_f = 0.54 in 4:1 hexane/ethyl acetate).

41U: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.51–7.39 (m, 3H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.30–7.19 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (CO), 138.4 (C), 137.3 (C), 134.8 (CH), 133.4 (CH), 133.3 (CH), 132.7 (CH), 131.9 (CH), 130.1 (CH), 128.5 (CH), 127.4 (CH), 121.0 (C), 119.6 (C), 94.4 (C), 87.7 (C), 21.1 (CH_3); IR (neat): 3057, 3025,

2948, 2919, 2342, 2186, 2051, 1982, 1646, 1584, 1562, 1482, 1463, 1431, 1379, 1300, 1262, 1221, 1165, 1127, 1094, 1063, 1017, 901, 784, 737, 688 cm^{-1}; MS (ESI, m/z): 299.01 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{12}{}^{79}BrO$: 299.0066 $[M+H]^+$, found: 299.0070.

4.1.22 Synthesis of 3-(3-Fluorophenyl)-1-(p-tolyl)prop-2-yn-1-one (41V)

General Procedure **1** was followed by using p-toluoyl chloride (1.169mg, 7.56 mmol) $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol), Et_3N (765 mg, 7.56 mmol), CuI (24 mg, 0.13 mmol) and 1-ethynyl-3-fluorobenzene (757 mg, 6.30 mmol) were employed to afford 1.406 g (94%) of the indicated product of 3-(3-fluorophenyl)-1-(p-tolyl)prop-2-yn-1-one (**41V**) as yellow solid (R_f = 0.63 in 4:1 hexane/ethyl acetate); mp 64.7–65.6 ºC.

41V: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.2 Hz, 2H), 7.35 (dt, J = 7.7, 1.2 Hz, 1H), 7.32–7.27 (m, 1H), 7.25–7.18 (m, 3H), 7.08 (tdd, J = 8.4, 2.6, 1.1 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.00 (CO), 162.1 (d, ^1J = 248.1 Hz, CF), 145.3 (C), 134.2 (C), 130.3 (d, ^3J = 8.4 Hz, CH), 129.5 (CH), 129.2 (CH), 128.7 (d, ^4J = 3.0 Hz, CH), 121.8 (d, ^3J = 9.4 Hz, C), 119.4 (d, ^2J = 23.0 Hz, CH), 117.9 (d, ^2J = 21.1 Hz, CH), 90.3 (d, ^4J = 3.4 Hz, C), 87.1 (C), 21.57 (CH_3); IR (neat): 3063, 3042, 2948, 2911, 2204, 1982, 1944, 1865, 1824, 1796, 1738, 1625, 1599, 1579, 1504, 1479, 1440, 1426, 1407, 1374, 1300, 1233, 1167, 1150, 1118, 1082, 1031, 1011, 920, 899, 835, 784, 739, 679 cm^{-1}; MS (ESI, m/z): 239.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{12}FO$: 239.0867 $[M+H]^+$, found: 239.0875.

4.1.23 Synthesis of 1-(2-Bromophenyl)-3-(4-fluoro-3-methylphenyl)prop-2-yn-1-one (41W)

General Procedure **1** was followed by using 2-bromobenzoyl chloride (988 mg, 4.50 mmol) $PdCl_2(PPh_3)_2$ (53 g, 0.08 mmol), Et_3N (456 mg, 4.50 mmol), CuI (14 mg, 0.08 mmol) and 4-ethynyl-1-fluoro-2-methylbenzene (504 mg, 3.75 mmol) were employed to afford 962 mg (81%) of the indicated product of 1-(2-Bromophenyl)-

3-(4-fluoro-3-methylphenyl)prop-2-yn-1-one (**41W**) as yellow solid (R_f = 0.64 in 4:1 hexane/ethyl acetate); mp 64.7–66.1 ºC.

41W: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.43–7.23 (m, 4H), 6.96–6.82 (m, 1H), 2.14 (d, *J* = 1.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9 (CO), 162.7 (d, ^{1}J = 252.8 Hz, CF), 137.1 (C), 136.5 (d, ^{3}J = 6.1 Hz, CH), 134.9 (CH), 133.5 (CH), 132.8 (CH), 132.7 (CH), 127.5 (CH), 125.9 (d, ^{2}J = 18.3 Hz, C), 121.1 (C), 115.7 (d, ^{2}J = 23.4 Hz, CH), 115.6 (d, ^{4}J = 3.6 Hz, C), 93.4 (C), 87.6 (C), 14.2 (d, ^{3}J = 3.3 Hz, CH_3); IR (neat): 3264, 3094, 3063, 2924, 2325, 1642, 1606, 1585, 1561, 1494, 1466, 1430, 1398, 1378, 1311, 1291, 1263, 1229, 1156, 1117, 1059, 1033, 1014, 989, 955, 923, 888, 816, 775, 731, 712, 677 cm^{-1}; MS (ESI, m/z): 316.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{11}{}^{79}BrFO$: 316.9982 $[M+H]^+$, found: 316.9981; MS (ESI, m/z): 318.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{11}{}^{81}BrFO$: 318.9962 $[M+H]^+$, found: 318.9962.

4.2 General Procedure 2. Synthesis of *N*-Propargylic *β*-Enaminones 13

α,*β*-Alkynic ketones **41** (1.0 mmol) and propargylamine (**42**) (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 (13A)

General Procedure **2** was followed by using 1,3-diphenylprop-2-yn-1-one (**41A**) (1.660 g, 8.05 mmol) and propargylamine (532 mg, 9.66 mmol) were employed to afford 1.688 g (80%) of the indicated product of (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-

ylamino)prop-2-en-1-one (**13A**) as yellow solid (R_f = 0.44 in 4:1 hexane/ethyl acetate).

13A: ^{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 (CO), 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 [46].

4.2.2 Synthesis of (*Z*)-1-Phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (13B)

General Procedure **2** was followed by using 1-phenylhept-2-yn-1-one (**41B**) (703 mg, 3.80 mmol) and propargylamine (251 mg, 4.56 mmol) were employed to afford 837 mg (92%) of the indicated product of (*Z*)-1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (**13B**) as orange-yellow solid (R_f = 0.48 in 4:1 hexane/ethyl acetate); mp 43.0–43.6 °C.

13B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (br s, 1H), 7.86 (dt, *J* = 3.9, 2.3 Hz, 2H), 7.47–7.34 (m, 3H), 5.75 (s, 1H), 4.08 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.41–2.34 (m, 2H), 2.32 (t, *J* = 2.5 Hz, 1H), 1.62 (tt, *J* = 7.9, 6.8 Hz, 2H), 1.44 (sextet, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7 (CO), 168.2 (C), 140.4 (C), 130.7 (CH), 128.3 (CH), 127.1 (CH), 92.2 (CH), 79.2 (C), 72.5 (CH), 32.3 (CH_2), 31.9 (CH_2), 30.2 (CH_2), 22.7 (CH_2), 13.9 (CH_3); IR (neat): 3207, 3084, 3058, 3036, 2954, 2931, 2895, 2869, 2808, 2119, 1593, 1572, 1548, 1485, 1467, 1453, 1412, 1372, 1339, 1313, 1282, 1246, 1213, 1179, 1155, 1102, 1081, 1061, 1023, 936, 853, 807, 725, 678 cm^{-1}; MS (ESI, m/z): 242.15 $[M+H]^+$; HRMS (ESI): calc. for $C_{16}H_{20}NO$: 242.1545 $[M+H]^+$, found: 242.1524.

4.2.3 Synthesis of (*Z*)-3-(4-Nitrophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino) prop-2-en-1-one (13C)

General Procedure **2** was followed by using 3-(4-nitrophenyl)-1-phenylprop-2-yn-1-one (**41C**) (180 mg, 0.72 mmol) and propargylamine (47 mg, 0.86 mmol) were employed to afford 120 mg (87%) of the indicated product of (*Z*)-3-(4-nitrophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13C**) as bright yellow solid (R_f = 0.25 in 4:1 hexane/ethyl acetate); mp 125.4–126.5 ^{o}C.

13C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (br s, 1H), 8.33 (tt, *J* = 8.9, 1.9 Hz, 2H), 7.90–7.86 (m, 2H), 7.69 (tt, *J* = 8.8, 1.9 Hz, 2H), 7.50–7.37 (m, 3H), 5.83 (s, 1H), 3.88 (dd, *J* = 6.5, 2.5 Hz, 2H), 2.33 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8 (CO), 162.9 (C), 148.7 (C), 141.2 (C), 139.5 (C), 131.6 (CH), 129.2 (CH), 128.5 (CH), 127.3 (CH), 124.1 (CH), 95.3 (CH), 79.5 (C), 73.1 (CH), 34.3 (CH_2); IR (neat): 3243, 3109, 3076, 3052, 3036, 3019, 2974, 2943, 2848, 2448, 2116, 1808, 1730, 1684, 1608, 1595, 1572, 1551, 1511, 1492, 1477, 1444, 1427, 1345, 1319, 1296, 1242, 1225, 1179, 1141, 1107, 1073, 1051, 1022, 926, 855, 803, 762, 743, 690 cm^{-1}; MS (ESI, m/z): 307.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}N_2O_3$: 307.1077 $[M+H]^+$, found: 307.1088.

4.2.4 Synthesis of (*Z*)-3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13D)

General Procedure **2** was followed by using 3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-one (**41D**) (210 mg, 0.89 mmol) and propargylamine (59 mg, 1.07 mmol) were employed to afford 221 mg (89%) of the indicated product of (*Z*)-3-(4-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13D**) as reddish orange oil (R_f = 0.29 in 4:1 hexane/ethyl acetate).

13D: ^{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 (CO), 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 (CH_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 [60].

4.2.5 Synthesis of (*Z*)-3-Phenyl-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (13E)

General Procedure **2** was followed by using 3-phenyl-1-(p-tolyl)prop-2-yn-1-one (**41E**) (522 mg, 2.37 mmol) and propargylamine (157 mg, 2.84 mmol) were employed to afford 651 mg (99%) of the indicated product (*Z*)-3-phenyl-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (**13E**) as yellowish orange solid (R_f = 0.48 in 4:1 hexane/ethyl acetate).

13E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (bs, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.52–7.43 (m, 5H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.84 (s, 1H), 3.93 (dd, *J* = 6.3, 2.5 Hz, 2H), 2.38 (s, 3H), 2.31 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (CO), 165.6 (C), 141.5 (C), 137.3 (C), 135.0 (C), 129.8 (CH), 129.0 (CH), 128.7 (CH), 127.9 (CH), 127.3 (CH), 94.6 (CH), 79.9 (C), 72.5 (CH), 34.2 (CH_2), 21.5 (CH_3); IR (neat): 3243, 3063, 3029, 2995, 2973, 2938, 2914, 2857, 2116, 1596, 1583, 1561, 1522, 1479, 1447, 1403, 1369, 1350, 1326, 1298, 1282, 1270, 1245, 1205, 1177, 1143, 1114, 1071, 1018, 998, 928, 875, 836, 779, 758, 747, 702, 685 cm^{-1}. The spectral data were in agreement with those reported previously for this compound [60].

4.2.6 Synthesis of (*Z*)-1-(4-Methoxyphenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13F)

General Procedure **2** was followed by using 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one (**41F**) (455 mg, 1.93 mmol) and propargylamine (127 mg, 2.31 mmol) were employed to afford 518 mg (92%) of the indicated product of (*Z*)-1-(4-

methoxyphenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13F**) as orange solid (R_f = 0.32 in 4:1 hexane/ethyl acetate).

13F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (t, *J* = 5.5 Hz, 1H), 7.98–7.77 (m, 2H), 7.56–7.40 (m, 5H), 6.98–6.81 (m, 2H), 5.80 (s, 1H), 3.91 (dd, *J* = 6.3, 2.5 Hz, 2H), 3.81 (s, 3H), 2.30 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3 (CO), 165.3 (C), 162.1 (C), 135.1 (C), 132.7 (C), 129.8 (CH), 129.1 (CH), 128.7 (CH), 127.9 (CH), 113.5 (CH), 94.4 (CH), 80.0 (C), 72.4 (CH), 55.3 (CH_3), 34.2 (CH_2); IR (neat): 3263, 3068, 3040, 2999, 2939, 2928, 2844, 2116, 1956, 1903, 1592, 1511, 1482, 1419, 1368, 1326, 1298, 1251, 1224, 1172, 1140, 1074, 1060, 1029, 919, 870, 843, 769, 738, 695 cm^{-1}. The spectral data were in agreement with those reported previously for this compound [46].

4.2.7 Synthesis of (*Z*)-1-(4-Chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13G)

General Procedure **2** was followed by using 1-(4-chlorophenyl)-3-phenylprop-2-yn-1-one (**41G**) (293 mg, 1.22 mmol) and propargylamine (80 mg, 1.46 mmol) were employed to afford 335 mg (93%) of the indicated product of (*Z*)-1-(4-chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13G**) as yellow solid (R_f = 0.45 in 4:1 hexane/ethyl acetate).

13G: ^{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 [46].

4.2.8 Synthesis of (*Z*)-1-(4-Nitrophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13H)

General Procedure **2** was followed by using 1-(4-nitrophenyl)-3-phenylprop-2-yn-1-one (**41H**) (398 mg, 1.58 mmol) and propargylamine (105 mg, 1.90 mmol) were employed to afford 444 mg (92%) of the indicated product of (*Z*)-1-(4-nitrophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13H**) as yellow solid (R_f = 0.29 in 4:1 hexane/ethyl acetate); mp 159.9–162.0 ºC.

13H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (br s, 1H), 8.22 (d, *J* = 8.7 Hz, 2H), 8.00 (d, *J* = 8.7 Hz, 2H), 7.49 (s, 5H), 5.81 (s, 1H), 3.98 (dd, *J* = 6.2, 2.3 Hz, 2H), 2.35 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2 (CO), 167.4 (C), 149.2 (C), 145.4 (C), 134.3 (C), 130.4 (CH), 128.9 (CH), 128.1 (CH), 127.8 (CH), 123.6 (CH), 94.7 (CH), 79.3 (C), 73.0 (CH), 34.5 (CH_2); IR (neat): 3229, 3109, 3085, 2938, 2844, 2114, 1735, 1590, 1556, 1511, 1480, 1443, 1432, 1405, 1347, 1328, 1297, 1265, 1145, 1109, 1074, 929, 869, 849, 813, 788, 745, 699 cm^{-1}; MS (ESI, m/z): 307.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}N_2O_3$: 307.1077 $[M+H]^+$, found: 307.1085.

4.2.9 Synthesis of (*Z*)-1-(2-Bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13I)

General Procedure **2** was followed by using 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (**41I**) (327 mg, 1.15 mmol) and propargylamine (76 mg, 1.38 mmol) were employed to afford 383 mg (98%) of the indicated product of (*Z*)-1-(2-bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13I**) as reddish-orange oil (Rf = 0.31 in 4:1 hexane/ethyl acetate).

13I: 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) δ 190.9 (CO), 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 (C), 98.3 (CH), 79.5 (C), 72.7 (CH), 34.3 (CH2); 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 C18H1579BrNO: 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 (13J)

General Procedure **2** was followed by using 1-phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (**41J**) (415 mg, 1.96 mmol) and propargylamine (129 mg, 2.35 mmol) were employed to afford 476 mg (91%) of the indicated product of (*Z*)-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**13J**) as yellow solid (R_f = 0.5 in 4:1 hexane/ethyl acetate); mp 77.4–78.3 ºC.

13J: ^{1}H 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 (CO), 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 [60].

4.2.11 Synthesis of (*Z*)-3-(3-Fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13K)

General Procedure **2** was followed by using 3-(3-fluorophenyl)-1-phenylprop-2-yn-1-one (**41K**) (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 (**13K**) as pale yellow solid (R_f = 0.5 in 4:1 hexane/ethyl acetate); mp 93.8–94.8 ºC.

13K: ^{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 (CO), 164.1 (C), 162.5 (d, ^1J = 248.3 Hz, CF), 139.7 (C), 136.9 (d, ^3J = 7.5 Hz, C), 131.1 (CH), 130.5 (d, ^3J = 8.3 Hz, CH), 128.2 (CH), 127.2 (CH), 123.6 (d, ^4J = 3.0 Hz, CH), 116.8 (d, ^2J = 21.0 Hz, CH), 115.1 (d, ^2J = 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.

4.2.12 Synthesis of (*Z*)-1-(2-Bromophenyl)-3-(4-bromophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13L)

General Procedure **2** was followed by using 1-(2-bromophenyl)-3-(4-bromophenyl)prop-2-yn-1-one (**41L**) (258 mg, 0.71 mmol) and propargylamine (47 mg, 0.85 mmol) were employed to afford 266 mg (90%) of the indicated product of (*Z*)-1-(2-bromophenyl)-3-(4-bromophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13L**) as orange solid (R_f = 0.46 in 4:1 hexane/ethyl acetate); mp 88.3–89.1 ºC.

13L: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (br s, 1H), 7.65–7.51 (m, 3H), 7.45 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.42–7.36 (m, 2H), 7.31 (td, *J* = 7.5, 1.0 Hz, 1H), 7.20 (td, *J* = 7.7, 1.7 Hz, 1H), 5.44 (s, 1H), 3.94 (dd, *J* = 6.5, 2.5 Hz, 2H), 2.35 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1 (CO), 164.3 (C), 142.8 (C), 133.4 (CH), 133.2 (C), 131.9 (CH), 130.4 (CH), 129.5 (CH), 129.2 (CH), 127.2 (CH), 124.5 (C), 119.4 (C), 98.4 (CH), 79.5 (C), 72.9 (CH), 34.3 (CH_2); IR (neat): 3267, 2975, 2916, 2855, 2122, 1920, 1811, 1734, 1584, 1546, 1510, 1476, 1439, 1394, 1357, 1321, 1287, 1239, 1181, 1145, 1107, 1071, 1022, 1008, 934, 833, 798, 750, 700, 662 cm^{-1}; MS (ESI, m/z): 417.94 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{79}Br_2NO$: 417.9436 $[M+H]^+$, found: 417.94309; MS (ESI, m/z): 419.94 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}{}^{79}Br^{81}BrNO$: 419.9416 $[M+H]^+$, found:

419.9429; MS (ESI, m/z): 421.94 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}{}^{81}Br_2NO$: 421.9396 $[M+H]^+$, found: 421.9424.

4.2.13 Synthesis of (*Z*)-3-(3-Fluorophenyl)-1-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13M)

General Procedure **2** was followed by using 3-(3-fluorophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-one (**41M**) (1.053 g, 4.14 mmol) and propargylamine (274 mg, 4.97 mmol) were employed to afford 1.175 g (92%) of the indicated of (*Z*)-3-(3-fluorophenyl)-1-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13M**) product as yellow solid (R_f = 0.27 in 4:1 hexane/ethyl acetate); mp 84.2–85.0 ºC.

13M: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (t, *J* = 6.0 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.42 (dd, *J* = 13.8, 7.8 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 9.1 Hz, 1H), 7.19–7.12 (m, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.80 (s, 1H), 3.90 (dd, *J* = 6.3, 2.2 Hz, 2H), 3.81 (s, 3H), 2.33 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4 (CO), 163.6 (C), 162.5 (d, ^1J = 248.0 Hz, CF), 162.1 (C), 137.0 (d, ^3J = 7.5 Hz, C), 132.3 (C), 130.4 (d, ^3J = 8.2 Hz, CH), 129.1 (CH), 123.7 (d, ^4J = 3.0 Hz, CH), 116.7 (d, ^2J = 20.9 Hz, CH), 115.1 (d, ^2J = 22.7 Hz, CH), 113.4 (CH), 94.3 (CH), 79.8 (C), 72.6 (CH), 55.3 (CH_3), 34.1 (CH_2); IR (neat): 3224, 3061, 2957, 2931, 2908, 2836, 2112, 1597, 1572, 1516, 1502, 1474, 1433, 1352, 1329, 1299, 1232, 1200, 1168, 1127, 1116, 1071, 1032, 931, 909, 891, 877, 836, 814, 772, 708, 664 cm^{-1}; MS (ESI, m/z): 310.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}FNO_2$: 310.1238 $[M+H]^+$, found: 310.1249.

4.2.14 Synthesis of (*Z*)-3-(4-Chlorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13N)

General Procedure **2** was followed by using 3-(4-chlorophenyl)-1-phenylprop-2-yn-1-one (**41N**) (364 mg, 1.51 mmol) and propargylamine (100 mg, 1.81 mmol) were employed to afford 429 mg (96%) of the indicated product of (*Z*)-3-(4-

chlorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13N**) as pale yellow solid (R_f = 0.50 in 4:1 hexane/ethyl acetate); mp 91.9–93.1 °C.

13N: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (br s, 1H), 7.95–7.83 (m, 2H), 7.51–7.34 (m, 7H), 5.81 (s, 1H), 3.91 (dd, *J* = 6.3, 2.3 Hz, 2H), 2.32 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3 (CO), 164.6 (C), 139.8 (C), 136.1 (C), 133.3 (C), 131.3 (CH), 129.4 (CH), 129.1 (CH), 128.4 (CH), 127.2 (CH), 94.8 (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}; MS (ESI, m/z): 296.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}ClNO$: 296.0837 $[M+H]^+$, found: 296.0848.

4.2.15 Synthesis of (*Z*)-1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (13O)

General Procedure **2** was followed by using 1-phenyl-3-(p-tolyl)prop-2-yn-1-one (**41O**) (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 (**13O**) as reddish orange oil (R_f = 0.50 in 4:1 hexane/ethyl acetate).

13O: ^{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 (CO), 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 [60].

4.2.16 Synthesis of (*Z*)-1-(4-Chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13P)

General Procedure **2** was followed by using 1-(4-chlorophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (**41P**) (812 mg, 3.14 mmol) and propargylamine (208 mg, 3.77 mmol) were employed to afford 851 mg (86%) of the indicated product of *(Z)*-1-(4-chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13P**) as pale yellow solid (Rf = 0.48 in 4:1 hexane/ethyl acetate); mp 132.8–133.6 oC.

13P: 1H NMR (400 MHz, CDCl3) δ 11.28 (br s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.52–7.43 (m, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.2 Hz, 1H), 7.26–7.16 (m, 2H), 5.79 (s, 1H), 3.95 (dd, J = 6.3, 2.2 Hz, 2H), 2.35 (s, 1H); 13C NMR (100 MHz, CDCl3) δ 187.9 (CO), 164.7 (C), 162.7 (d, 1J = 248.6 Hz, CF), 138.1 (C), 137.4 (C), 136.8 (d, 3J = 8.2 Hz, C), 130.7 (d, 3J = 8.3 Hz, CH), 128.7 (CH), 128.6 (CH), 123.7 (d, 4J = 3.1 Hz, CH), 117.1 (d, 2J = 20.9 Hz, CH), 115.2 (d, 2J = 22.8 Hz, CH), 94.4 (CH), 79.5 (C), 72.9 (CH), 34.3 (CH2); IR (neat): 3231, 3063, 2115, 2038, 1598, 1544, 1470, 1433, 1351, 1325, 1281, 1252, 1230, 1201, 1169, 1129, 1092, 1063, 1014, 931, 891, 871, 837, 793, 764, 736, 704, 684 cm-1; MS (ESI, m/z): 314.07 [M+H]+; HRMS (ESI) calcd. for C18H14ClFNO: 314.0743 [M+H]+, found: 314.0746.

4.2.17 Synthesis of (*Z*)-1-(2-Bromophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13Q)

General Procedure **2** was followed by using 1-(2-bromophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (**41Q**) (661 mg, 2.18 mmol) and propargylamine (144 mg, 2.62 mmol) were employed to afford 733 mg (94%) of the indicated product of (*Z*)-1-(2-bromophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13Q**) as dark orange solid (R_f = 0.5 in 4:1 hexane/ethyl acetate); mp 45.0–46.8 ºC.

13Q: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.01 (br s, 1H), 7.56 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.47–7.39 (m, 2H), 7.33–7.26 (m, 2H), 7.24–7.12 (m, 3H), 5.47 (s, 1H),

3.95 (dd, J = 6.4, 2.5 Hz, 2H), 2.35 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1 (CO), 163.9 (C), 162.3 (d, ^1J = 248.3 Hz, CF), 142.6 (C), 136.1 (d, ^3J = 7.6 Hz, C), 133.2 (CH), 130.4 (d, ^3J = 8.3 Hz, CH), 130.4 (CH), 129.0 (CH), 127.1 (CH), 123.6 (d, ^4J = 3.1 Hz, CH), 119.2 (C), 116.9 (d, ^2J = 21.0 Hz, CH), 114.9 (d, ^2J = 22.8 Hz, CH), 98.2 (CH), 79.3 (C), 72.9 (CH), 34.2 (CH_2); IR (neat): 3311, 3296, 3263, 3178, 3066, 2986, 2928, 2906, 2115, 1935, 1885, 1818, 1735, 1591, 1549, 1477, 1462, 1422, 1365, 1322, 1289, 1247, 1225, 1195, 1131, 1080, 1024, 927, 884, 867, 791, 759, 745, 705, 684 cm^{-1}; MS (ESI, m/z): 358.02 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{79}BrFNO$: 358.0237 $[M+H]^+$, found: 358.0239.

4.2.18 Synthesis of (*Z*)-1-(2-Bromophenyl)-3-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13R)

General Procedure **2** was followed by using 1-(2-bromophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-one (**41R**) (624 mg, 1.98 mmol) and propargylamine (131 mg, 2.37 mmol) were employed to afford 548 mg (75%) of the indicated product of (*Z*)-1-(2-bromophenyl)-3-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13R**) as dark red oil (R_f = 0.25 in 4:1 hexane/ethyl acetate).

13R: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (br s, 1H), 7.55 (dd, J = 8.0, 0.9 Hz, 1H), 7.45 (dd, J = 10.6, 4.1 Hz, 3H), 7.29 (td, J = 7.5, 1.1 Hz, 1H), 7.20–7.14 (m, 1H), 6.98–6.92 (m, 2H), 5.45 (s, 1H), 4.00 (dd, J = 6.4, 2.5 Hz, 2H), 3.83 (s, 3H), 2.35 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6 (CO), 165.8 (C), 160.9 (C), 143.1 (C), 133.3 (CH), 130.2 (CH), 129.5 (CH), 129.1 (CH), 127.1 (CH), 126.4 (C), 119.4 (C), 114.1 (CH), 98.1 (CH), 79.8 (C), 72.7 (CH), 55.3 (CH_3), 34.4 (CH_2); IR (neat): 3288, 3051, 3002, 2962, 2935, 2905, 2837, 2118, 2045, 1731, 1588, 1560, 1491, 1439, 1370, 1359, 1323, 1297, 1248, 1176, 1147, 1114, 1083, 1024, 948, 927, 873, 838, 810, 794, 761, 670 cm^{-1}; MS (ESI, m/z): 370.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}{}^{79}BrNO_2$: 370.0437 $[M+H]^+$, found: 370.0440.

4.2.19 Synthesis of (*Z*)-1-(4-Chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (13S)

General Procedure **2** was followed by using 1-(4-chlorophenyl)-3-(m-tolyl)prop-2-yn-1-one (**41S**) (821 mg, 3.22 mmol) and propargylamine (213 mg, 3.87 mmol) were employed to afford 936 mg (94%) of the indicated product of (*Z*)-1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**13S**) as pale yellow solid (R_f = 0.54 in 4:1 hexane/ethyl acetate); mp 119.4–120.0 ^{o}C.

13S: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.38 (t, *J* = 5.8 Hz, 1H), 7.91–7.78 (m, 2H), 7.40–7.32 (m, 3H), 7.32–7.23 (m, 3H), 5.79 (s, 1H), 3.95 (dd, *J* = 6.3, 2.5 Hz, 2H), 2.42 (s, 3H), 2.35 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3 (CO), 166.4 (C), 138.6 (C), 138.3 (C), 136.9 (C), 134.6 (C), 130.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 124.8 (CH), 94.0 (CH), 79.7 (C), 72.6 (CH), 34.2 (CH_2), 21.4 (CH_3); IR (neat): 3242, 3223, 3089, 3059, 3029, 2974, 2939, 2914, 2857, 2112, 1589, 1566, 1518, 1474, 1429, 1394, 1352, 1325, 1293, 1269, 1229, 1174, 1134, 1105, 1088, 1072, 1011, 961, 929, 914, 887, 872, 838, 797, 786, 762, 719, 696 cm^{-1}; MS (ESI, m/z): 310.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO$: 310.0993 $[M+H]^+$, found: 310.0989.

4.2.20 Synthesis of (*Z*)-1-(4-Methoxyphenyl)-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (13T)

General Procedure **2** was followed by using 1-(4-methoxyphenyl)-3-(thiophen-3-yl)prop-2-yn-1-one (**41T**) (859 mg, 3.55 mmol) and propargylamine (234 mg, 4.26 mmol) were employed to afford 908 mg (86%) of the indicated product of (*Z*)-1-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one **(13T**) as orange solid (R_f = 0.33 in 4:1 hexane/ethyl acetate); mp 74.2–76.1 ^{o}C.

13T: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (t, *J* = 5.4 Hz, 1H), 7.94–7.78 (m, 2H), 7.62 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.41 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.27 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.03–6.77 (m, 2H), 5.88 (s, 1H), 4.00 (dd, *J* = 6.4, 2.5 Hz, 2H), 3.83 (s, 3H), 2.33 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9 (CO), 161.8 (C), 159.9 (C), 135.5 (C), 132.4 (C), 128.9 (CH), 127.2 (CH), 126.5 (CH), 126.1

(CH), 113.3 (CH), 93.7 (CH), 80.1 (C), 72.5 (CH), 55.1 (CH_3), 34.0 (CH_2); IR (neat): 3268, 3097, 3001, 2962, 2934, 2834, 2116, 1577, 1537, 1511, 1492, 1462, 1439, 1416, 1392, 1366, 1351, 1313, 1292, 1255, 1225, 1166, 1132, 1087, 1069, 1024, 968, 925, 898, 869, 845, 774, 736, 674 cm^{-1}; MS (ESI, m/z): 298.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{16}NO_2S$: 298.0896 $[M+H]^+$, found: 298.0889.

4.2.21 Synthesis of (*Z*)-1-(2-Bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (13U)

General Procedure **2** was followed by using 1-(2-bromophenyl)-3-(m-tolyl)prop-2-yn-1-one (**41U**) (765 mg, 2.63 mmol) and propargylamine (174 mg, 3.15 mmol) were employed to afford 862 mg (93%) of the indicated product of (*Z*)-1-(2-bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**13U**) as dark red oil (R_f = 0.36 in 4:1 hexane/ethyl acetate).

13U: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (br s, 1H), 7.48 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.37 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.25–7.16 (m, 5H), 7.10 (td, *J* = 7.7, 1.7 Hz, 1H), 5.37 (s, 1H), 3.88 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.30 (s, 3H), 2.25 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1 (CO), 166.2 (C), 143.2 (C), 138.7 (C), 134.4 (C), 133.5 (CH), 130.9 (CH), 130.3 (CH), 129.3 (CH), 128.7 (CH), 128.5 (CH), 127.2 (CH), 125.0 (CH), 119.5 (C), 98.3 (CH), 79.8 (C), 72.7 (CH), 34.5 (CH_2), 21.5 (CH_3); IR (neat): 3288, 3053, 2917, 2858, 1731, 1561, 1479, 1461, 1427, 1359, 1322, 1289, 1257, 1224, 1139, 1123, 1083, 1023, 999, 928, 874, 790, 759, 745, 708, 688 cm^{-1}; MS (ESI, m/z): 354.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}{}^{79}BrNO$: 354.0488 $[M+H]^+$, found: 354.0490.

4.2.22 Synthesis of (*Z*)-3-(3-Fluorophenyl)-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (13V)

General Procedure **2** was followed by using 3-(3-fluorophenyl)-1-(p-tolyl)prop-2-yn-1-one (**41V**) (1.096 g, 4.60 mmol) and propargylamine (304 mg, 5.52 mmol) were employed to afford 1.139 mg (84%) of the indicated product of (*Z*)-3-(3-

fluorophenyl)-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (**13V**) as pale yellow solid (R_f = 0.52 in 4:1 hexane/ethyl acetate); mp 102.9–103.3 ºC.

13V: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (t, *J* = 6.1 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.41 (td, *J* = 7.9, 5.8 Hz, 1H), 7.33–7.11 (m, 5H), 5.83 (s, 1H), 3.90 (dd, *J* = 6.4, 2.4 Hz, 2H), 2.36 (s, 3H), 2.34 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (CO), 163.70 (C), 162.4 (d, ^1J = 248.1 Hz, CF), 141.5 (C), 136.9 (d, ^3J = 7.1 Hz, C), 136.9 (C), 130.3 (d, ^3J = 8.2 Hz, CH), 128.9 (CH), 127.1 (CH), 123.6 (d, ^4J = 3.0 Hz, CH), 116.6 (d, ^2J = 21.0 Hz, CH), 114.9 (d, ^2J = 22.7 Hz, CH), 94.4 (CH), 79.7 (C), 72.5 (CH), 33.9 (CH_2), 21.3 (CH_3); IR (neat): 3222, 3064, 3033, 2996, 2971, 2940, 2911, 2111, 1882, 1600, 1568, 1545, 1522, 1474, 1431, 1349, 1326, 1286, 1266, 1251, 1235, 1212, 1175, 1157, 1124, 1066, 1017, 965, 929, 907, 889, 874, 839, 789, 756, 707, 662 cm^{-1}; MS (ESI, m/z): 294.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}FNO$: 294.1289 $[M+H]^+$, found: 294.1284.

4.2.23 Synthesis of (*Z*)-1-(2-Bromophenyl)-3-(4-fluoro-3-methylphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (13W)

General Procedure **2** was followed by using 1-(2-bromophenyl)-3-(4-fluoro-3-methylphenyl)prop-2-yn-1-one (**41W**) (855 mg, 2.69 mmol) and propargylamine (178 mg, 3.24 mmol) were employed to afford 969 mg (97%) of the indicated product of (*Z*)-1-(2-bromophenyl)-3-(4-fluoro-3-methylphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13W**) as dark red oil (R_f = 0.44 in 4:1 hexane/ethyl acetate).

13W: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (t, *J* = 5.6 Hz, 1H), 7.57 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.38–7.24 (m, 3H), 7.19 (td, *J* = 7.7, 1.7 Hz, 1H), 7.07 (t, *J* = 8.8 Hz, 1H), 5.44 (s, 1H), 3.97 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.37 (t, *J* = 2.5 Hz, 1H), 2.31 (d, *J* = 1.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9 (CO), 165.0 (C), 162.2 (d, ^1J = 249.0 Hz, CF), 142.9 (C), 133.4 (CH), 131.2 (d, ^3J = 5.7 Hz, CH), 130.3 (CH), 130.1 (d, ^4J = 3.7 Hz, C), 129.1 (CH), 127.3 (CH), 127.2 (CH), 125.6 (d, ^2J = 17.9 Hz, C), 119.4 (C), 115.4 (d, ^2J = 22.8 Hz, CH), 98.3 (CH), 79.6 (C), 72.8 (CH), 34.3 (CH_2), 14.6 (d, ^3J = 3.0 Hz, CH_3); IR (neat): 3291,

3052, 2979, 2925, 2858, 2324, 2122, 1981, 1892, 1733, 1614, 1564, 1487, 1462, 1428, 1399, 1358, 1324, 1298, 1273, 1234, 1183, 1119, 1082, 1024, 896, 828, 795, 758, 670 cm^{-1}; MS (ESI, m/z): 372.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}{}^{79}BrFNO$: 372.0393 $[M+H]^+$, found: 372.0394; MS (ESI, m/z): 374.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}{}^{81}BrFNO$: 374.0373 $[M+H]^+$, found: 374.0378.

4.3 General Procedure 3. Synthesis of Chloro-substituted N-Propargylic β-Enaminone Derivatives 35

N-Propargylic *β*-enaminones **13** (1.0 mmol) and *N*-chlorosuccinimide (1.2 mmol) were mixed in acetonitrile (10 mL) in a round-bottomed flask, reaction duration was about 24 hours and reaction is monitored by TLC (19:1 hexane:EtOAc). When the reaction was finished, extraction with ethyl acetate (50 mL) and saturated NH_4Cl solution (50 mL) was performed. The separated organic phase was dried with $MgSO_4$ and filtered. Finally, with flash chromatography using 19:1 hexane:EtOAc as eluent was performed to purify the crude product.

4.3.1 Synthesis of 2-Chloro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35A)

General Procedure **3** was followed by using (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13A**) (153 mg, 0.59 mmol) and NCS (94 mg, 0.70 mmol) were employed to afford the indicated product of 2-chloro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35A**) as *E/Z* mixture of isomers (ratio: 11.1:1.0) in 85% (147 mg) combined yield as a red oil (R_f = 0.43 in 4:1 hexane/ethyl acetate).

35A: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.56 (t, 1H), 7.79–7.73 (m, 2H), 7.63–7.53 (m, 3H), 7.51–7.42 (m, 5H), 3.83 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.37 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6 (CO), 163.9 (C), 140.7 (C), 133.1 (C), 130.1 (CH), 129.8 (CH), 128.9 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 101.1 (CCl), 79.2 (C), 72.8 (CH), 34.9 (CH_2); IR (neat): 2891, 2828, 1737,

1646, 1629, 1606, 1578, 1548, 1523, 1490, 1447, 1357, 1317, 1267, 1189, 1107, 1059, 811, 758, 683 cm^{-1}; MS (ESI, m/z): 296.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}ClNO$: 296.0837 $[M+H]^+$, found: 296.0837. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.2 Synthesis of 2-Chloro-1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (35B)

General Procedure **3** was followed by using (*Z*)-1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (**13B**) (369 mg, 1.53 mmol) and NCS (245 mg, 1.83 mmol) were employed to afford the indicated product of 2-chloro-1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (**35B**) as *E/Z* mixture of isomers (ratio 100.0:1.0) in 67% (282 mg) combined yield as a dark red oil (R_f = 0.77 in 4:1 hexane/ethyl acetate).

35B: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.78 (br s, 1H), 7.62–7.53 (m, 2H), 7.43–7.34 (m, 3H), 4.11 (dd, *J* = 6.0, 2.5 Hz, 2H), 2.75–2.59 (m, 2H), 2.37 (t, *J* = 2.5 Hz, 1H), 1.73–1.60 (m, 2H), 1.49 (sextet, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5 (CO), 166.7 (C), 141.1 (C), 129.6 (CH), 127.7 (CH), 127.6 (CH), 101.3 (CCl), 78.8 (C), 73.0 (CH), 33.2 (CH_2), 29.9 (CH_2), 28.9 (CH_2), 22.9 (CH_2), 13.8 (CH_3); IR (neat): 3290, 3245, 3059, 3026, 2957, 2871, 2715, 2335, 2325, 2166, 2117, 2017, 1980, 1719, 1684, 1576, 1448, 1263, 1082, 699 cm^{-1}; MS (ESI, m/z): 276.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{19}ClNO$: 276.1150 $[M+H]^+$, found: 276.1155. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.3 Synthesis of 2-Chloro-3-(4-nitrophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35C)

General Procedure **3** was followed by using (*Z*)-3-(4-nitrophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13C**) (101 mg, 0.35 mmol) and NCS (71 mg, 0.53 mmol) were employed to afford the indicated product of 2-chloro-3-(4-nitrophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35C**) as *E/Z*

mixture of isomers (ratio 7.1:1.0) in 45% (54 mg) combined yield as a bright-yellow solid (R_f = 0.28 in 4:1 hexane/ethyl acetate); mp 99.0–101.0 ºC.

35C: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (br s, 1H), 8.41–8.34 (m, 2H), 7.70–7.64 (m, 2H), 7.63–7.57 (m, 2H), 7.48–7.36 (m, 3H), 3.72 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.32 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0 (CO), 160.9 (C), 148.6 (C), 139.9 (C), 139.2 (C), 130.6 (CH), 129.6 (CH), 128.1 (CH), 127.8 (CH), 124.3 (CH), 101.1 (CCl), 78.9 (C), 73.3 (CH), 34.9 (CH_2); IR (neat): 3272, 3103, 3079, 3060, 3022, 2967, 2923, 2848, 2445, 2169, 2134, 2041, 1934, 1881, 1813, 1724, 1694, 1599, 1566, 1543, 1519, 1447, 1429, 1402, 1345, 1318, 1293, 1233, 1158, 1098, 1073, 1028, 1013, 947, 919, 855, 795, 775, 758, 706, 678 cm^{-1}; MS (ESI, m/z): 341.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClN_2O_3$: 341.0688 $[M+H]^+$, found: 341.0694. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.4 Synthesis of 2-Chloro-3-(4-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35D)

General Procedure **3** was followed by using (*Z*)-3-(4-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13D**) (133 mg, 0.46 mmol) and NCS (73 mg, 0.55 mmol) were employed to afford the indicated prıoduct of 2-chloro-3-(4-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35D**) as *E/Z* mixture of isomers (ratio 10.0:1.0) in 67% (99 mg) combined yield as an orange oil (R_f = 0.37 in 4:1 hexane/ethyl acetate).

35D: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.51 (br s, 1H), 7.75–7.60 (m, 2H), 7.44–7.29 (m, 5H), 7.02 (d, *J* = 8.6 Hz, 2H), 3.86 (s, 3H), 3.80 (dd, *J* = 5.9, 2.2 Hz, 2H), 2.30 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3 (CO), 164.0 (C), 160.5 (C), 140.8 (C), 129.9 (CH), 129.6 (CH), 127.9 (CH), 127.6 (CH), 125.1 (C), 114.3 (CH), 101.4 (CCl), 79.3 (C), 72.7 (CH), 55.3 (CH_3), 34.9 (CH_2); IR (neat): 3378, 3288, 3057, 3005, 2961, 2934, 2837, 2546, 2114, 1896, 1711, 1672, 1608, 1548, 1511, 1447, 1347, 1287, 1246, 1176, 1164, 1099, 1074, 1026, 945, 912, 836, 809, 790, 750, 718, 696 cm^{-1}; MS (ESI, m/z): 326.10 $[M+H]^+$;

HRMS (ESI) calcd. for $C_{19}H_{17}ClNO_2$: 326.0942 $[M+H]^+$, found: 326.0951. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.5 Synthesis of 2-Chloro-3-phenyl-3-(prop-2-yn-1-ylamino)-1-(p-tolyl) prop-2-en-1-one (35E)

General Procedure **3** was followed by using (*Z*)-3-phenyl-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (**13E**) (70 mg, 0.25 mmol) and NCS (41 mg, 0.31 mmol) were employed to afford the indicated product of 2-chloro-3-phenyl-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (**35E**) as *E/Z* mixture of isomers (ratio 12.5:1.0) in 60% (48 mg) combined yield as a dark red oil (R_f = 0.48 in 4:1 hexane/ethyl acetate).

35E: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.44 (br s, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.55–7.45 (m, 3H), 7.38 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 3.75 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.39 (s, 3H), 2.29 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5 (CO), 163.7 (C), 140.5 (C), 137.9 (C), 133.3 (C), 129.7 (CH), 128.9 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 101. (CCl), 79.3 (C), 72.8 (CH), 34.9 (CH_2), 21.6 (CH_3); IR (neat): 3289, 3245, 3054, 3029, 2978, 2952, 2922, 2715, 2589, 2349, 2121, 1704, 1676, 1604, 1581, 1548, 1495, 1445, 1374, 1348, 1312, 1293, 1265, 1246, 1180, 1162, 1098, 1020, 1001, 946, 919, 879, 829, 775, 757, 701, 605 cm^{-1}; MS (ESI, m/z): 310.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO$: 310.0993 $[M+H]^+$, found: 310.0997. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.6 Synthesis of 2-Chloro-1-(4-methoxyphenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35F)

General Procedure **3** was followed by using (*Z*)-1-(4-methoxyphenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13F**) (305 mg, 1.05 mmol) and NCS (168 mg, 1.25 mmol) were employed to afford the indicated product of 2-chloro-1-(4-methoxyphenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35F**) as *E/Z*

mixture of isomers (ratio 9.1:1.0) in 78% (258 mg) combined yield as an orange solid (R_f = 0.33 in 4:1 hexane/ethyl acetate); mp 71.7–73.3 °C.

35F: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.43 (t, *J* = 5.7 Hz, 1H), 7.84–7.75 (m, 2H), 7.57–7.44 (m, 3H), 7.41–7.39 (m, 2H), 6.95–6.89 (m, 2H), 3.83 (s, 3H), 3.75 (dd, *J* = 6.3, 2.3 Hz, 2H), 2.32 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4 (CO), 163.3 (C), 161.2 (C), 133.2 (C), 132.9 (C), 130.4 (CH), 129.6 (CH), 128.8 (CH), 127.9 (CH), 112.8 (CH), 100.9 (CCl), 79.3 (C), 72.7 (CH), 55.3 (CH_3), 34.8 (CH_2); IR (neat): 3287, 3244, 3141, 3057, 2935, 2838, 1732, 1701, 1671, 1601, 1582, 1550, 1509, 1443, 1372, 1292, 1248, 1175, 1161, 1097, 1028, 943, 914, 880, 841, 811, 775, 749, 702, 681 cm^{-1}; MS (ESI, m/z): 326.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO_2$: 326.0942 $[M+H]^+$, found: 326.0948. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.7 Synthesis of 2-Chloro-1-(4-chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35G)

General Procedure **3** was followed by using (*Z*)-1-(4-chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13G**) (117 mg, 0.39 mmol) and NCS (63 mg, 0.47 mmol) were employed to afford the indicated product of 2-chloro-1-(4-chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35G**) as *E/Z* mixture of isomers (ratio 11.1.1.0) in 78% (101 mg) combined yield as an orange solid (R_f = 0.48 in 4:1 hexane/ethyl acetate); mp 64.3–65.3 °C.

35G: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.55 (br s, 1H), 7.69–7.64 (m, 2H), 7.57–7.48 (m, 3H), 7.44–7.34 (m, 4H), 3.79 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.33 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9 (CO), 164.4 (C), 138.9 (C), 136.1 (C), 132.9 (C), 129.9 (CH), 129.6 (CH), 129.0 (CH), 127.9 (CH), 127.8 (CH), 100.8 (CCl), 79.0 (C), 72.9 (CH), 35.0 (CH_2); IR (neat): 3266, 3151, 3058, 3031, 2969, 2913, 2834, 2126, 1579, 1545, 1486, 1447, 1423, 1391, 1355, 1305, 1293, 1259, 1177, 1163, 1106, 1095, 1083, 1025, 1013, 999, 969, 956, 944, 914, 849, 837, 788, 762, 724, 696 cm^{-1}; MS (ESI, m/z): 330.05 $[M+H]^+$; HRMS

(ESI) calcd. for $C_{18}H_{14}Cl_2NO$: 330.0447 $[M+H]^+$, found: 330.0457. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.8 Synthesis of 2-Chloro-1-(4-nitrophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35H)

General Procedure **3** was followed by using (*Z*)-1-(4-nitrophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13H**) (85 mg, 0.28 mmol) and NCS (45 mg, 0.33 mmol) were employed to afford the indicated product of 2-chloro-1-(4-nitrophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35H**) as *E/Z* mixture of isomers (ratio 14.3:1.0) in 68% (64 mg) combined yield as a bright yellow solid (R_f = 0.31 in 4:1 hexane/ethyl acetate); mp 100.2–101.4 ºC.

35H: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.62 (br s, 1H), 8.35–8.15 (m, 2H), 7.83–7.71 (m, 2H), 7.61–7.45 (m, 3H), 7.42–7.33 (m, 2H), 3.82 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.33 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9 (CO), 165.4 (C), 148.4 (C), 146.5 (C), 132.5 (C), 130.2 (CH), 129.2 (CH), 128.9 (CH), 127.8 (CH), 123.2 (CH), 100.7 (CCl), 78.7 (C), 73.3 (CH), 35.2 (CH_2); IR (neat): 3295, 3272, 3105, 3063, 3028, 2959, 2933, 2855, 2457, 2123, 1603, 1583, 1545, 1511, 1446, 1427, 1349, 1305, 1258, 1242, 1166, 1098, 1026, 1011, 957, 946, 909, 856, 785, 762, 736, 700, 673 cm^{-1}; MS (ESI, m/z): 341.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClN_2O_3$: 341.0688 $[M+H]^+$, found: 341.0697. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.9 Synthesis of 1-(2-Bromophenyl)-2-chloro-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35I)

General Procedure **3** was followed by using (*Z*)-1-(2-bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13I**) (359 mg, 1.06 mmol) and NCS (169 mg, 1.27 mmol) were employed to afford the indicated product of 1-(2-bromophenyl)-2-chloro-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35I**) as *E/Z* mixture of isomers (ratio 12.5:1.0) in 68% (269 mg) combined yield as a yellow solid (R_f = 0.36 in 4:1 hexane/ethyl acetate); mp 114.9–116. 6 ºC.

35I: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.44 (br s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.52–7.43 (m, 3H), 7.43–7.28 (m, 4H), 7.24–7.18 (m, 1H), 3.79 (dd, *J* = 6.0, 2.3 Hz, 2H), 2.33 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4 (CO), 164.1 (C), 142.5 (C), 132.4 (C), 132.3 (CH), 129.9 (CH), 128.9 (CH), 127.7 (CH), 127.6 (CH), 127.1 (CH), 118.8 (C), 101.6 (CCl), 78.9 (C), 73.1 (CH), 34.9 (CH_2) (Note that two CH peaks overlap on each other); IR (neat): 3291, 3118, 3048, 3025, 2930, 2138, 2125, 1951, 1811, 1704, 1576, 1544, 1469, 1453, 1414, 1349, 1315, 1272, 1241, 1112, 1073, 1039, 1022, 959, 907, 849, 806, 788, 757, 734, 699 cm^{-1}; MS (ESI, m/z): 373.99 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{79}BrClNO$: 373.9942 $[M+H]^+$, found: 373.9943; MS (ESI, m/z): 375.99 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{81}BrClNO$: 375.9921 $[M+H]^+$, found: 375.9925. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.10 Synthesis of 2-Chloro-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (35J)

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 (**13J**) (111 mg, 0.42 mmol) and NCS (67 mg, 0.49 mmol) were employed to afford the indicated product of 2-chloro-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**35J**) as *E/Z* mixture of isomers (ratio 7.1:1.0) in 63% (78 mg) combined yield as a red oil (R_f = 0.41 in 4:1 hexane/ethyl acetate).

35J: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.48 (br s, 1H), 7.67 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.53–7.49 (m, 1H), 7.46 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.44–7.36 (m, 3H), 7.16 (dd, *J* = 5.0, 1.0 Hz, 1H), 3.83 (dd, *J* = 6.1, 2.4 Hz, 2H), 2.32 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3 (CO), 159.7 (C), 140.6 (C), 132.6 (C), 130.1 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 126.7 (CH), 126.3 (CH), 101.6 (CCl), 79.5 (C), 72.9 (CH), 35.0 (CH_2); IR (neat): 3288, 3101, 1704, 1670, 1553, 1525, 1448, 1387, 1361, 1316, 1247, 1211, 1179, 1158, 1099, 1074, 1026, 1001, 963, 909, 863, 826, 790, 718, 696 cm^{-1}; MS (ESI, m/z): 302.04 $[M+H]^+$;

HRMS (ESI) calcd. for $C_{16}H_{13}ClNOS$: 302.0401 $[M+H]^+$, found: 302.0407. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.11 Synthesis of 2-Chloro-3-(3-fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35K)

General Procedure **3** was followed by using (*Z*)-3-(3-fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13K**) (123 mg, 0.44 mmol) and NCS (71 mg, 0.53 mmol) were employed to afford the indicated product of 2-chloro-3-(3-fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35K**) as *E/Z* mixture of isomers (ratio 9.1:1.0) in 74% (103 mg) combined yield as an orange oil (R_f = 0.36 in 4:1 hexane/ethyl acetate).

35K: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.37 (br s, 1H), 7.71–7.66 (m, 2H), 7.56–7.36 (m, 4H), 7.21–7.11 (m, 3H), 3.76 (dd, J = 6.2, 2.5 Hz, 2H), 2.31 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8 (CO), 162.9 (d, ^1J = 248.6 Hz, CF), 162.1 (C), 140.4 (C), 134.9 (d, ^3J = 7.9 Hz, C), 130.9 (d, ^3J = 8.2 Hz, CH), 130.3 (CH), 128.0 (CH), 127.7 (CH), 123.8 (d, ^4J = 3.2 Hz, CH), 116.9 (d, ^2J = 21.0 Hz, CH), 115.5 (d, ^2J = 22.9 Hz, CH), 101.1 (CCl), 79.1 (C), 73.0 (CH), 34.9 (CH_2); IR (neat): 3294, 3265, 3151, 3056, 2128, 1708, 1681, 1583, 1549, 1487, 1449, 1431, 1353, 1314, 1302, 1262, 1244, 1215, 1136, 1099, 1069, 1026, 1001, 960, 918, 880, 824, 786, 748, 725, 692 cm^{-1}; MS (ESI, m/z): 314.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClFNO$: 314.0743 $[M+H]^+$, found: 314.0754. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.12 Synthesis of 1-(2-Bromophenyl)-3-(4-bromophenyl)-2-chloro-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35L)

General Procedure **3** was followed by using (*Z*)-1-(2-bromophenyl)-3-(4-bromophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13L**) (89 mg, 0.21 mmol) and NCS (34 mg, 0.25 mmol) were employed to afford the indicated product of 1-(2-bromophenyl)-3-(4-bromophenyl)-2-chloro-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35L**) as *E/Z* mixture of isomers (ratio 11.1:1.0) in 65% (63 mg) combined

yield as a pale yellow solid (R_f = 0.41 in 4:1 hexane/ethyl acetate); mp 145.0–146.9 ^{o}C.

35L: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.34 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.33–7.28 (m, 3H), 7.28–7.22 (m, 1H), 3.83 (dd, *J* = 6.1, 2.3 Hz, 2H), 2.35 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9 (CO), 162.9 (C), 142.5 (C), 132.7 (CH), 132.4 (CH), 131.3 (C), 130.1 (CH), 129.8 (CH), 127.7 (CH), 127.3 (CH), 124.5 (C), 118.9 (C), 101.9 (CCl), 78.9 (C), 73.3 (CH), 35.1 (CH_2); IR (neat): 3298, 3130, 3086, 3061, 2961, 2938, 2849, 2524, 2371, 2357, 2322, 2275, 2222, 2127, 2090, 2039, 2025, 2003, 1987, 1973, 1955, 1941, 1919, 1901, 1803, 1786, 1734, 1590, 1576, 1544, 1469, 1449, 1415, 1356, 1356, 1309, 1272, 1244, 1180, 1159, 1107, 1072, 1038, 1010, 956, 907, 830, 781, 757, 729, 670 cm^{-1}; MS (ESI, m/z): 451.91 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}{}^{79}Br_2ClNO$: 451.9047 $[M+H]^+$, found: 451.9054; MS (ESI, m/z): 453.90 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}{}^{79}Br^{81}BrClNO$: 453.9027 $[M+H]^+$, found: 453.9033; MS (ESI, m/z): 455.90 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}{}^{81}Br_2ClNO$: 455.9008 $[M+H]^+$, found: 406.9013. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.13 Synthesis of 2-Chloro-3-(3-fluorophenyl)-1-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35M)

General Procedure **3** was followed by using (*Z*)-3-(3-fluorophenyl)-1-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13M**) (179 mg, 0.58 mmol) and NCS (93 mg, 0.69 mmol) were employed to afford the indicated product of 2-chloro-3-(3-fluorophenyl)-1-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino) prop-2-en-1-one (**35M**) as *E/Z* mixture of isomers (ratio 7.1:1.0) in 62% (123 mg) combined yield as a dark red oil (R_f = 0.29 in 4:1 hexane/ethyl acetate).

35M: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (t, *J* = 5.5 Hz, 1H), 7.80–7.71 (m, 2H), 7.57–7.44 (m, 1H), 7.21–7.10 (m, 3H), 6.90 (dd, *J* = 9.3, 2.3 Hz, 2H), 3.82 (s, 3H), 3.73 (dd, *J* = 6.2, 2.5 Hz, 2H), 2.30 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6 (CO), 162.8 (d, ^{1}J = 248.7 Hz, CF), 162.3 (C),

161.5 (C), 135.2 (d, ^{3}J = 7.8 Hz, C), 132.7 (C), 130.8 (d, ^{3}J = 8.3 Hz, CH), 130.5 (CH), 123.9 (d, ^{4}J = 3.1 Hz, CH), 116.7 (d, ^{2}J = 20.9 Hz, CH), 115.5 (d, ^{2}J = 22.8 Hz, CH), 112.9 (CH), 101.0 (CCl), 79.2 (C), 72.9 (CH), 55.3 (CH_3), 34.8 (CH_2); IR (neat): 3292, 3246, 3067, 3006, 2958, 2934, 2835, 2717, 2114, 2051, 2023, 1707, 1672, 1585, 1556, 1509, 1488, 1452, 1421, 1374, 1301, 1248, 1215, 1170, 1093, 1026, 963, 879, 834, 790, 766, 673 cm^{-1}; MS (ESI, m/z): 344.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}ClFNO_2$: 344.0848 $[M+H]^+$, found: 344.0849. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.14 Synthesis of 2-Chloro-3-(4-chlorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35N)

General Procedure **3** was followed by using (*Z*)-3-(4-chlorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13N**) (184 mg, 0.62 mmol) and NCS (100 mg, 0.75 mmol) were employed to afford the indicated product of 2-chloro-3-(4-chlorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35N**) as *E/Z* mixture of isomers (ratio 12.5:1.0) in 68% (138 mg) as a bright orange solid (R_f = 0.40 in 4:1 hexane/ethyl acetate); mp 66.1–68.1 ^{o}C.

35N: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.41 (t, *J* = 5.2 Hz, 1H), 7.71–7.67 (m, 2H), 7.52–7.46 (m, 2H), 7.44–7.37 (m, 3H), 7.36–7.31 (m, 2H), 3.74 (dd, *J* = 6.2, 2.5 Hz, 2H), 2.31 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6 (CO), 162.5 (C), 140.4 (C), 135.9 (C), 131.3 (C), 130.2 (CH), 129.5 (CH), 129.3 (CH), 127.9 (CH), 127.7 (CH), 101.1 (CCl), 79.1 (C), 72.9 (CH), 34.9 (CH_2); IR (neat): 3267, 3083, 3055, 3022, 2967, 2895, 2840, 2129, 1909, 1707, 1684, 1597, 1543, 1491, 1445, 1427, 1349, 1318, 1303, 1291, 1236, 1178, 1160, 1102, 1086, 1072, 1027, 1013, 967, 947, 918, 831, 795, 777, 735, 719, 694 cm^{-1}; MS (ESI, m/z): 330.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}Cl_2NO$: 330.0447 $[M+H]^+$, found: 330.0449. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.15 Synthesis of 2-Chloro-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (35O)

General Procedure **3** was followed by using (*Z*)-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (**13O**) (214 mg, 0.78 mmol) and NCS (125 mg, 0.93 mmol) were employed to afford the indicated product of 2-chloro-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (**35O**) as *E/Z* mixture of isomers (ratio 11.1:1.0) in 73% (176 mg) combined yield as an orange oil (R_f = 0.55 in 4:1 hexane/ethyl acetate).

35O: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.53 (br s, *J* = 45.6 Hz, 1H), 7.74–7.68 (m, 2H), 7.46–7.38 (m, 3H), 7.36–7.25 (m, 4H), 3.78 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.43 (s, 3H), 2.31 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5 (CO), 164.3 (C), 140.8 (C), 139.9 (C), 130.2 (C), 130.1 (CH), 129.7 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 101.2 (CCl), 79.3 (C), 72.8 (CH), 34.9 (CH_2), 21.6 (CH_3); IR (neat): 3316, 3284, 3054, 3023, 2928, 2868, 2349, 2121, 2022, 1999, 1983, 1962, 1909, 1707, 1678, 1611, 1584, 1544, 1512, 1447, 1416, 1348, 1303, 1271, 1242, 1179, 1162, 1096, 1020, 953, 909, 823, 784, 734, 698 cm^{-1}; MS (ESI, m/z): 310.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO$: 310.0993 $[M+H]^+$, found: 310.1000. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.16 Synthesis of 2-Chloro-1-(4-chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35P)

General Procedure **3** was followed by using (*Z*)-1-(4-chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13P**) (222 mg, 0.71 mmol) and NCS (113 mg, 0.85 mmol) were employed to afford the indicated product of 2-chloro-1-(4-chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35P**) as *E/Z* mixture of isomers (ratio 10.0:1.0) in 68% (138 mg) combined yield as a dark orange solid (R_f = 0.42 in 4:1 hexane/ethyl acetate); mp 64.0–66.0 ^{o}C.

35P: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (br s, 1H), 7.66–7.59 (m, 2H), 7.55–7.41 (m, 1H), 7.39–7.33 (m, 2H), 7.23–7.08 (m, 3H), 3.76 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.32 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2 (CO), 162.8 (d, ^{1}J = 248.8 Hz, CF), 162.5 (C), 138.6 (C), 136.3 (C), 134.7 (d, ^{3}J = 7.9 Hz, C), 130.9 (d, ^{3}J = 8.2 Hz, CH), 129.7 (CH), 128.0 (CH), 123.7 (d, ^{4}J = 3.1 Hz, CH), 116.9 (d, ^{2}J = 20.8 Hz, CH), 115.4 (d, ^{2}J = 23.0 Hz, CH), 100.7 (CCl), 78.9 (C), 73.1 (CH), 34.9 (CH_2); IR (neat): 3286, 3166, 3073, 3034, 2957, 2932, 2319, 2166, 2120, 1915, 1873, 1797, 1712, 1682, 1579, 1545, 1487, 1453, 1422, 1343, 1281, 1245, 1216, 1136, 1095, 1013, 965, 948, 909, 887, 865, 838, 758, 719, 676 cm^{-1}; MS (ESI, m/z): 348.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}Cl_2FNO$: 348.0353 $[M+H]^+$, found: 348.0366. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.17 Synthesis of 1-(2-Bromophenyl)-2-chloro-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35Q)

General Procedure **3** was followed by using (*Z*)-1-(2-bromophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13Q**) (373 mg, 1.04 mmol) and NCS (167 mg, 1.25 mmol) were employed to afford the indicated product of 1-(2-bromophenyl)-2-chloro-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**35Q**) as *E/Z* mixture of isomers (ratio 10.0:1.0) in 78% (318 mg) combined yield as a pale orange solid (R_f = 0.40 in 4:1 hexane/ethyl acetate); mp 104.5–106.2 °C.

35Q: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (br s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.49 (td, *J* = 7.9, 5.7 Hz, 1H), 7.38–7.32 (m, 1H), 7.29 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.25–7.10 (m, 4H), 3.81 (dd, *J* = 6.2, 2.5 Hz, 2H), 2.33 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8 (CO), 162.7 (d, ^{1}J = 248.7 Hz, CF), 162.3 (C), 142.3 (C), 134.1 (d, ^{3}J = 7.8 Hz, C), 132.5 (CH), 130.9 (d, ^{3}J = 8.2 Hz, CH), 130.0 (CH), 127.6 (CH), 127.2 (CH), 123.6 (d, ^{4}J = 3.0 Hz, CH), 118.8 (C), 117.0 (d, ^{2}J = 20.8 Hz, CH), 115.3 (d, ^{2}J = 23.0 Hz, CH), 101.6 (CCl), 78.7 (C), 73.2 (CH), 34.9 (CH_2); IR (neat): 3291, 3127, 2929, 2323, 2124, 1868, 1579, 1545,

1454, 1428, 1414, 1347, 1317, 1280, 1246, 1221, 1160, 1143, 1108, 1040, 1022, 956, 908, 890, 871, 763, 736, 703, 669 cm^{-1}; MS (ESI, m/z): 391.99 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}{}^{79}BrClFNO$: 391.9848 $[M+H]^+$, found: 391.9857; MS (ESI, m/z): 393.98 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}{}^{81}BrClFNO$: 393.9827 $[M+H]^+$, found: 393.9840. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.18 Synthesis of 1-(2-Bromophenyl)-2-chloro-3-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35R)

General Procedure **3** was followed by using (*Z*)-1-(2-bromophenyl)-3-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13R**) (112 mg, 0.30 mmol) and NCS (49 mg, 0.36 mmol) were employed to afford the indicated product of 1-(2-bromophenyl)-2-chloro-3-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino) prop-2-en-1-one (**35R**) as *E/Z* mixture of isomers (ratio 12.5:1.0) in 67% (82 mg) combined yield as a yellow solid (R_f = 0.29 in 4:1 hexane/ethyl acetate); mp 97.5–99.1 ^oC.

35R: Major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 11.44 (br s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.38–7.28 (m, 4H), 7.23–7.18 (m, 1H), 7.01 (d, *J* = 8.6 Hz, 2H), 3.84 (s, 5H), 2.32 (t, *J* = 2.3 Hz, 1H. ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3 (CO), 164.4 (C), 160.7 (C), 142.7 (C), 132.5 (CH), 129.9 (CH), 129.6 (CH), 127.7 (CH), 127.2 (CH), 124.5 (C), 118.9 (C), 114.3 (CH), 102.6 (CCl), 79.1 (C), 72.9 (CH), 55.4 (CH_3), 35.1 (CH_2); IR (neat): 3120, 3054, 3000, 2961, 2933, 2905, 2837, 2558, 2506, 2466, 2297, 2162, 2135, 2104, 2065, 2014, 1928, 1902, 1870, 1734, 1654, 1606, 1571, 1511, 1465, 1437, 1419, 1372, 1305, 1245, 1173, 1147, 1112, 1075, 1029, 986, 963, 835, 782, 755, 682 cm^{-1}; MS (ESI, m/z): 404.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}{}^{79}BrClNO_2$: 404.0047 $[M+H]^+$, found: 404.0043; MS (ESI, m/z): 406.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}{}^{81}BrClNO_2$: 406.0027 $[M+H]^+$, found: 406.0026. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.19 Synthesis of 2-Chloro-1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (35S)

General Procedure **3** was followed by using (*Z*)-1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**13S**) (300 mg, 0.97 mmol) and NCS (155 mg, 1.16 mmol) were employed to afford the indicated product of 2-chloro-1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**35S**) as *E/Z* mixture of isomers (ratio 11.1:1.0) in 77% (255 mg) combined yield as a pale orange solid (R_f = 0.48 in 4:1 hexane/ethyl acetate); mp 89.6–92.5 ºC. Major isomer:

35S: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.53 (br s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.47–7.32 (m, 3H), 7.32–7.25 (m, 1H), 7.20–7.08 (m, 2H), 3.77 (dd, *J* = 6.0, 2.4 Hz, 2H), 2.42 (s, 3H), 2.31 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8 (CO), 164.6 (C), 138.9 (C), 138.8 (C), 135.9 (C), 132.8 (C), 130.6 (CH), 129.6 (CH), 128.9 (CH), 128.2 (CH), 127.9 (CH), 124.8 (CH), 100.7 (CCl), 79.1 (C), 72.9 (CH), 34.9 (CH_2), 21.5 (CH_3); IR (neat): 3287, 3142, 3053, 3014, 2962, 2930, 2854, 2252, 2184, 2173, 2163, 2125, 2041, 1897, 1787, 1681, 1544, 1487, 1456, 1418, 1361, 1311, 1276, 1247, 1215, 1176, 1149, 1101, 1013, 966, 910, 883, 873, 833, 787, 758, 707, 676 cm^{-1}; MS (ESI, m/z): 344.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}Cl_2NO$: 344.0604 $[M+H]^+$, found: 344.0614. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.20 Synthesis of 2-Chloro-1-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (35T)

General Procedure **3** was followed by using (*Z*)-1-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**13T**) (144 mg, 0.49 mmol) and NCS (78 mg, 0.58 mmol) were employed to afford the indicated product of 2-chloro-1-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**35T**) as *E/Z* mixture of isomers (ratio 5.3:1.0) in 46% (74 mg) combined yield as dark orange oil (R_f = 0.29 in 4:1 hexane/ethyl acetate).

35T: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (t, J = 5.4 Hz, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.53–7.44 (m, 2H), 7.17 (dd, J = 5.0, 1.2 Hz, 1H), 6.92 (d,

J = 8.8 Hz, 2H), 3.83 (s, 3H), 3.81 (dd, J = 6.2, 2.5 Hz, 2H), 2.34 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1 (CO), 161.2 (C), 159.1 (C), 132.8 (CH), 130.9 (CH), 130.4 (CH), 127.5 (C), 126.5 (C), 126.2 (CH), 112.8 (CH), 101.5 (CCl), 79.6 (C), 72.7 (CH), 55.3 (CH_3), 34.9 (CH_2); IR (neat): 3287, 3102, 3001, 2955, 2933, 2837, 1731, 1601, 1559, 1452, 1415, 1387, 1360, 1301, 1285, 1244, 1210, 1171, 1146, 1094, 1026, 962, 909, 839, 792, 766, 621 cm^{-1}; MS (ESI, m/z): 332.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{15}ClNO_2S$: 332.0507 $[M+H]^+$, found: 332.0512. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.21 Synthesis of 1-(2-Bromophenyl)-2-chloro-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (35U)

General Procedure **3** was followed by using (*Z*)-1-(2-bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**13U**) (444 mg, 1.25 mmol) and NCS (201 mg, 1.50 mmol) were employed to afford the indicated product of 1-(2-bromophenyl)-2-chloro-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**35U**) as *E/Z* mixture of isomers (ratio 9.1:1.0) in 76% (369 mg) combined yield as an orange solid (R_f = 0.38 in 4:1 hexane/ethyl acetate); mp 102.6–104.2 ºC.

35U: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.33 (br s, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.32–7.15 (m, 4H), 7.14–7.03 (m, 3H), 3.71 (dd, *J* = 5.9, 2.4 Hz, 2H), 2.31 (s, 3H), 2.23 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5 (CO), 164.5 (C), 142.6 (C), 138.8 (C), 132.5 (C), 132.4 (CH), 130.7 (CH), 129.9 (CH), 128.9 (CH), 128.2 (CH), 127.7 (CH), 127.2 (CH), 124.8 (CH), 118.9 (C), 101.7 (CCl), 78.9 (C), 72.9 (CH), 35.1 (CH_2), 21.5 (CH_3); IR (neat): 3294, 3143, 3128, 3050, 3020, 2929, 2350, 2342, 2323, 2280, 2268, 2184, 2117, 2087, 2040, 2023, 2012, 1953, 1731, 1553, 1470, 1453, 1428, 1416, 1354, 1313, 1268, 1241i 1218, 1156, 1111, 1074, 1022, 959, 909, 818, 798, 746, 709, 688 cm^{-1}; MS (ESI, m/z): 388.01 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}{}^{79}BrClFNO$: 388.0098 $[M+H]^+$, found: 388.0105; MS (ESI, m/z): 390.01 $[M+H]^+$; HRMS (ESI) calcd. for

$C_{19}H_{16}{}^{81}BrClFNO$: 390.0078 $[M+H]^+$, found: 390.0087. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.22 Synthesis of 2-Chloro-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (35V)

General Procedure **3** was followed by using (*Z*)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (**13V**) (250 mg, 0.85 mmol) and NCS (137 mg, 1.02 mmol) were employed to afford the indicated product of 2-chloro-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (**35V**) as *E/Z* mixture of isomers (ratio 10.0:1.0) in 83% (232 mg) combined yield as a reddish-orange oil (R_f = 0.50 in 4:1 hexane/ethyl acetate).

35V: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.34 (br s, 1H), 7.63 (d, J = 8.1 Hz, 2H), 7.49 (td, J = 7.9, 5.8 Hz, 1H), 7.23–7.11 (m, 5H), 3.75 (dd, J = 6.2, 2.5 Hz, 2H), 2.39 (s, 3H), 2.31 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6 (CO), 162.8 (d, ^1J = 248.4 Hz, CF), 161.8 (C), 140.7 (C), 137.5 (C), 134.9 (d, ^3J = 7.9 Hz, C), 130.9 (d, ^3J = 8.5 Hz, CH), 128.4 (CH), 128.3 (CH), 123.8 (d, ^4J = 3.2 Hz, CH), 116.8 (d, ^2J = 20.8 Hz, CH), 115.5 (d, ^2J = 22.9 Hz, CH), 101.1 (CCl), 79.1 (C), 72.9 (CH), 34.9 (CH_2), 21.6 (CH_3); IR (neat): 3293, 3064, 3030, 2922, 2865, 2324, 2217, 2172, 2120, 2983, 1733, 1608, 1581, 1547, 1491, 1452, 1421, 1375, 1348, 1313, 1294, 1250, 1217, 1181, 1093, 1020, 964, 877, 829, 791, 757, 672, 584, 557, 672 cm^{-1}; MS (ESI, m/z): 328.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}ClFNO$: 328.0899 $[M+H]^+$, found: 328.0908. The peaks of minor isomer could not be properly resolved due to weak intensity.

4.3.23 Synthesis of 1-(2-Bromophenyl)-2-chloro-3-(4-fluoro-3-methylphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (35W)

General Procedure **3** was followed by using (*Z*)-1-(2-bromophenyl)-3-(4-fluoro-3-methylphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13W**) (271 mg, 0.73 mmol) and NCS (117 mg, 0.87 mmol) were employed to afford the indicated product of 1-(2-bromophenyl)-2-chloro-3-(4-fluoro-3-methylphenyl)-3-(prop-2-

yn-1-ylamino)prop-2-en-1-one (**35W**) as *E/Z* mixture of isomers (ratio 7.1:1.0) in 63% (187 mg) combined yield as a pale orange solid (R_f = 0.38 in 4:1 hexane/ethyl acetate); mp 91.4–93.4 ºC.

35W: Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (t, *J* = 5.5 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.37–7.28 (m, 2H), 7.25–7.15 (m, 3H), 7.12 (t, *J* = 8.8 Hz, 1H), 3.80 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.33 (dd, *J* = 5.6, 2.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5 (CO), 163.5 (C), 161.9 (d, ^{1}J = 249.0 Hz, CF), 142.5 (C), 132.5 (CH), 131.1 (d, ^{3}J = 5.6 Hz, CH), 129.9 (CH), 128.0 (d, ^{4}J = 3.7 Hz, C), 127.6 (CH), 127.3 (d, ^{3}J = 8.5 Hz, CH), 127.2 (CH), 125.9 (d, ^{2}J = 17.9 Hz, C), 118.8 (C), 115.7 (d, ^{2}J = 23.1 Hz, CH), 101.9 (CCl), 78.9 (C), 73.1 (CH), 34.9 (CH_2), 14.6 (d, ^{3}J = 2.7 Hz, CH_3); IR (neat): 3291, 3248, 3055, 2979, 2956, 2928, 2870, 2121, 1732, 1545, 1502, 1469, 1452, 1428, 1399, 1307, 1233, 1198, 1161, 1104, 1068, 1038, 943, 899, 869, 826, 799, 757, 739, 670 cm^{-1}; MS (ESI, m/z): 406.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}{}^{79}BrClFNO$: 406.0004 $[M+H]^+$, found: 406.0010; MS (ESI, m/z): 408.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}{}^{81}BrClFNO$: 407.9983 $[M+H]^+$, found: 407.9995.

4.4 General Procedure 4. Synthesis of Fluoro-substituted *N*-Propargylic *β*-Enaminone Derivatives 36

N-Propargylic *β*-enaminones **13** (1.0 mmol) and Selectfluor® (1.0 mmol) were mixed in acetonitrile (10 mL) at 0 ˚C in a round-bottomed flask, reaction duration was about 4 hours and reaction is monitored by TLC (9:1 hexane:EtOAc). When the reaction was finished, extraction with ethyl acetate (50 mL), distilled H_2O (50 mL) was performed and the separated organic phase was dried with $MgSO_4$ and filtered. Finally, with flash chromatography using 15:1 hexane:EtOAc as eluent was performed to purify the crude product.

4.4.1 Synthesis of 2-Fluoro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (36A)

General Procedure **4** was followed by using (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13A**) (114 mg, 0.44 mmol) and Selectfluor® (154 mg, 0.44 mmol) were employed to afford 38 mg (31%) of the indicated product of 2-fluoro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**36A**) as orange oil (R_f = 0.54 in 4:1 hexane/ethyl acetate).

36A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (br s, 1H), 7.94–7.90 (m, 2H), 7.55–7.39 (m, 8H), 3.79 (dd, *J* = 6.2, 2.0 Hz, 2H), 2.29 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.2 (d, ^{2}J = 24.1 Hz, CO), 153.1 (d, ^{2}J = 28.0 Hz, C), 140.2 (d, ^{1}J = 220.8 Hz, CF), 137.8 (d, ^{3}J = 6.2 Hz, C), 131.5 (CH), 130.2 (CH), 129.7 (CH), 128.9 (CH), 128.9 (d, ^{3}J = 4.4 Hz, C), 128.8 (CH), 128.2 (CH), 79.9 (C), 72.6 (CH), 34.1 (CH_2); IR (neat): 3304, 3276, 3059, 2929, 2117, 1697, 1610, 1598, 1575, 1554, 1462, 1427, 1336, 1285, 1246, 1157, 1071, 1027, 1001, 912, 852, 789, 697 cm^{-1}; MS (ESI, m/z): 280.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}FNO$: 280.1132 $[M+H]^+$, found: 280.1141.

4.4.2 Synthesis of 2-Fluoro-1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (36B)

General Procedure **4** was followed by using (*Z*)-1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (**13B**) (359 mg, 1.49 mmol) and Selectfluor® (528 mg, 1.49 mmol) were employed to afford 81 mg (21%) of the indicated product of 2-fluoro-1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (**36B**) as dark orange oil (R_f = 0.48 in 4:1 hexane/ethyl acetate).

36B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (br s, 1H), 7.93–7.73 (m, 2H), 7.52–7.34 (m, 3H), 4.05 (dd, *J* = 5.9, 2.2 Hz, 2H), 2.64–2.52 (m, 2H), 2.34 (t, *J* = 2.5 Hz, 1H), 1.69–1.57 (m, 2H), 1.47 (sextet, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.3 (d, ^{2}J = 23.5 Hz, CO), 156.4 (d, ^{2}J = 26.9 Hz, C), 141.4 (d, ^{1}J = 216.9 Hz, CF), 138.1 (d, ^{3}J = 6.3 Hz, C), 130.9 (CH), 128.6 (d, ^{4}J = 7.8 Hz, CH), 128.1 (CH), 79.4 (C), 72.7 (CH), 32.4 (CH_2), 29.9 (CH_2),

25.6 (d, ^{3}J = 5.4 Hz, CH_2), 22.8 (CH_2), 13.8 (CH_3); IR (neat): 3292, 3062, 2958, 2931, 2872, 1686, 1601, 1579, 1542, 1449, 1329, 1248, 1171, 1086, 701 cm^{-1}; MS (ESI, m/z): 260.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{19}FNO$: 260.1445 $[M+H]^+$, found: 260.1448.

4.4.3 Synthesis of 2-Fluoro-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (36O)

General Procedure **4** was followed by using (*Z*)-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (**13O**) (544 mg, 1.97 mmol) and Selectfluor® (699 mg, 1.97 mmol) were employed to afford 87 mg (15%) of the indicated product of 2-fluoro-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (**36O**) as orange solid (R_f = 0.48 in 4:1 hexane/ethyl acetate); mp 76.6–78.6 °C.

36O: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (br s, 1H), 7.96–7.88 (m, 2H), 7.50–7.40 (m, 3H), 7.34 (dd, *J* = 21.8, 8.0 Hz, 4H), 3.81 (dd, *J* = 6.2, 2.0 Hz, 2H), 2.43 (s, 3H), 2.29 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9 (d, ^{2}J = 24.1 Hz, CO), 153.4 (d, ^{2}J = 27.6 Hz, C), 140.3 (C), 140.3 (d, ^{1}J = 220.2 Hz, CF), 137.9 (d, ^{3}J = 6.3 Hz, C), 131.4 (CH), 129.5 (CH), 128.8 (d, ^{4}J = 3.3 Hz, CH), 128.7 (d, ^{4}J = 2.2 Hz, CH), 128.1 (CH), 126.6 (C), 79.9 (C), 72.5 (CH), 33.9 (CH_2), 21.5 (CH_3); IR (neat): 3304, 3217, 3059, 3028, 2968, 2932, 2038, 1979, 1909, 1602, 1577, 1549, 1492, 1469, 1332, 1286, 1251, 1185, 1157, 1023, 1003, 914, 827, 791, 763, 737, 695 cm^{-1}; MS (ESI, m/z): 294.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}FNO$: 294.1289 $[M+H]^+$, found: 294.1298.

4.4.4 Synthesis of 1-(4-Chlorophenyl)-2-fluoro-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (36P)

General Procedure **4** was followed by using (*Z*)-1-(4-chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**13P**) (309 mg, 0.99 mmol) and Selectfluor® (349 mg, 0.99 mmol) were employed to afford 57 mg (17%) of the indicated product of 1-(4-chlorophenyl)-2-fluoro-3-(3-fluorophenyl)-

3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**36P**) as bright yellow solid (R_f = 0.68 in 4:1 hexane/ethyl acetate); mp 107.1–109.0 ºC.

36P: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (br s, 1H), 7.81–7.76 (m, 2H), 7.45–7.40 (m, 1H), 7.34–7.30 (m, 2H), 7.20–7.09 (m, 3H), 3.71 (dd, *J* = 6.1, 2.2 Hz, 2H), 2.22 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.9 (d, ^{2}J = 23.7 Hz, CO), 162.8 (d, ^{1}J = 248.3 Hz, CF), 151.7 (d, ^{2}J = 27.2 Hz, C), 140.1 (d, ^{1}J = 222.5 Hz, CF), 137.9 (C), 135.9 (d, ^{3}J = 6.4 Hz, C), 131.5 (d, ^{3}J = 8.0 Hz, C), 130.7 (d, ^{3}J = 8.3 Hz, CH), 130.4 (d, *J* = 8.6 Hz), 128.6 (CH), 124.7 (t, ^{4}J = 2.5 Hz, CH), 117.4 (d, ^{2}J = 20.9 Hz, CH), 116.3 (dd, ^{2}J = 22.8, ^{4}J = 2.1 Hz, CH), 79.5 (C), 72.9 (CH), 34.1 (CH_2); IR (neat): 3238, 2117, 1899, 1683, 1599, 1569, 1539, 1460, 1433, 1397, 1322, 1294, 1252, 1214, 1174, 1091, 1009, 920, 882, 833, 794, 766, 745, 697 cm^{-1}; MS (ESI, m/z): 332.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}ClF_2NO$: 332.0648 $[M+H]^+$, found: 332.0661.

4.4.5 Synthesis of 2-Fluoro-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (36V)

General Procedure **4** was followed by using (*Z*)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (**13V**) (373 mg, 1.27 mmol) and Selectfluor® (451 mg, 1.27 mmol) were employed to afford 61 mg (15%) of the indicated product of 2-fluoro-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (**36V**) as light orange solid (R_f = 0.42 in 4:1 hexane/ethyl acetate); mp 97.3– 98.4 ºC.

36V: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (br s, 1H), 7.74 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.38 (dd, *J* = 13.6, 7.8 Hz, 1H), 7.19–7.05 (m, 5H), 3.66 (dd, *J* = 6.0, 1.9 Hz, 2H), 2.30 (s, 3H), 2.19 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4 (d, ^{2}J = 23.9 Hz, CO), 162.8 (d, ^{1}J = 248.2 Hz, CF), 150.7 (d, ^{2}J = 27.4 Hz, C), 142.3 (C), 140.3 (d, ^{1}J = 224.3 Hz, CF), 134.9 (d, ^{3}J = 6.7 Hz, C), 131.8 (t, ^{3}J = 7.0 Hz, C), 130.6 (d, ^{3}J = 8.1 Hz, CH), 128.9 (CH), 128.9 (d, ^{4}J = 8.1 Hz, CH), 124.7 (t, ^{4}J = 2.5 Hz, CH), 117.1 (d, ^{2}J = 20.9 Hz, CH), 116.3 (dd, ^{2}J = 22.8, ^{4}J = 2.2 Hz, CH), 79.8 (C), 72.7 (CH), 34.0 (CH_2), 21.7 (CH_3); IR (neat): 3233, 2112, 1601, 1571,

1543, 1461, 1432, 1329, 1289, 1250, 1211, 1180, 1139, 1008, 882, 827, 789, 741, 698 cm^{-1}; MS (ESI, m/z): 312.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}F_2NO$: 312.1195 $[M+H]^+$, found: 312.1188.

4.5 General Procedure 5. Synthesis of 6-Halo-2-methylene-2,3-dihydro-1,4-oxazepine Derivatives 37 and 38

Halogen-substituted *N*-propargylic *β*-enaminones **35** and **36** (1.0 mmol) and $ZnCl_2$ (2.0 mmol) were mixed in refluxing chloroform (15 mL) in a round-bottomed flask, reaction duration was about 5 hours and reaction is monitored by TLC (9:1 hexane:EtOAc). When the reaction finished extraction with ethyl acetate (50 mL), saturated NH_4Cl solution (50 mL) was performed and the separated organic phase was dried with $MgSO_4$ and filtered. Finally, with flash chromatography using 9:1 hexane:EtOAc as eluent was performed to purify the crude product.

4.5.1 Synthesis of 6-Chloro-2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (37A)

General Procedure **5** was followed by using 2-chloro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 11.1:1.0) (**35A**) (101 mg, 0.34 mmol) and $ZnCl_2$ (93 mg, 0.68 mmol) were employed to afford 49 mg (49%) of the indicated product of 6-chloro-2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**37A**) as orange-yellow oil (R_f = 0.45 in 4:1 hexane/ethyl acetate).

37A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.69 (m, 4H), 7.54–7.36 (m, 6H), 4.59 (s, 2H), 4.59 (d, *J* = 1.9 Hz, 1H), 4.34 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2 (C), 162.5 (C), 156.2 (C), 137.3 (C), 134.3 (C), 130.5 (CH), 130.2 (CH), 129.3 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 110.6 (CCl), 91.6 (CH_2), 54.5 (CH_2); IR (neat): 3058, 3031, 2975, 2926, 2856, 1703, 1656, 1601, 1575, 1491, 1446, 1409, 1372, 1313, 1288, 1249, 1193, 1176, 1143, 1114, 1080, 1066, 1028, 999, 986, 959, 921, 847, 810, 762, 729, 694 cm^{-1}; MS (ESI, m/z): 296.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}ClNO$: 296.0837 $[M+H]^+$, found: 296.0835.

4.5.2 Synthesis of 5-Butyl-6-chloro-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (37B)

General Procedure **5** was followed by using 2-chloro-1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one as *E/Z* mixture of isomers (ratio100.0:1.0) (**35B**) (282 mg, 1.02 mmol) and $ZnCl_2$ (279 mg, 2.05 mmol) were employed to afford 125 mg (44%) of the indicated product 5-butyl-6-chloro-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**37B**) as orange oil (R_f = 0.56 in 4:1 hexane/ethyl acetate).

37B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.57 (m, 2H), 7.47–7.37 (m, 3H), 4.49 (d, *J* = 1.7 Hz, 1H), 4.37 (s, 2H), 4.23 (d, *J* = 1.7 Hz, 1H), 2.65 (t, *J* = 7.8 Hz, 2H), 1.67 (pentet, *J* = 7.6 Hz, 2H), 1.41 (sextet, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C), 161.8 (C), 153.9 (C), 134.7 (C), 129.8 (CH), 129.1 (CH), 128.2 (CH), 111.6 (CCl), 90.9 (CH_2), 54.1 (CH_2), 37.0 (CH_2), 29.2 (CH_2), 22.5 (CH_2), 14.0 (CH_3); IR (neat): 3150, 3055, 2958, 2930, 2872, 2164, 2121, 2042, 2021, 1974, 1685,1597, 1580, 1520, 1491, 1448, 1408, 1378, 1317, 1261, 1245, 1173, 1123, 1070, 1027, 1001, 922, 764, 693, 646, 615 cm^{-1}; MS (ESI, m/z): 276.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{19}ClNO$: 276.1150 $[M+H]^+$, found: 276.1148.

4.5.3 Synthesis of 6-Chloro-2-methylene-5-(4-nitrophenyl)-7-phenyl-2,3-dihydro-1,4-oxazepine (37C)

General Procedure **5** was followed by using 2-chloro-3-(4-nitrophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 7.1:1.0) (**35C**) (58 mg, 0.17 mmol) and $ZnCl_2$ (46 mg, 0.34 mmol) were employed to afford 23 mg (41%) of the indicated product of 6-chloro-2-methylene-5-(4-nitrophenyl)-7-phenyl-2,3-dihydro-1,4-oxazepine (**37C**) as yellow solid (R_f = 0.41 in 4:1 hexane/ethyl acetate); mp 131.1–133.1 ^{o}C.

37C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.6 Hz, 2H), 7.91 (d, *J* = 8.6 Hz, 2H), 7.79–7.72 (m, 2H), 7.54–7.42 (m, 3H), 4.68–4.60 (m, 3H), 4.38 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (C), 161.7 (C), 157.2 (C), 149.0 (C), 143.3 (C), 133.9 (C), 130.5 (CH), 129.8 (CH), 129.3 (CH), 128.4 (CH), 123.6 (CH),

109.2 (CCl), 92.6 (CH_2), 54.9 (CH_2); IR (neat): 3114, 3089, 3056, 3042, 2988, 2924, 2849, 2168, 1975, 1711, 1652, 1613, 1596, 1579, 1514, 1491, 1446, 1406, 1347, 1307, 1287, 1257, 1190, 1146, 1115, 1068, 1029, 1013, 983, 933, 855, 803, 760, 733, 709, 694 cm^{-1}; MS (ESI, m/z): 341.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClN_2O_3$: 341.0688 $[M+H]^+$, found: 341.0676.

4.5.4 Synthesis of 6-Chloro-2-methylene-5-phenyl-7-(p-tolyl)-2,3-dihydro-1,4-oxazepine (37D)

General Procedure **5** was followed by using 2-chloro-3-(4-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 10.0:1.0) (**35D**) (124 mg, 0.38 mmol) and $ZnCl_2$ (104 mg, 0.76 mmol) were employed to afford 39 mg (31%) of the indicated product of 6-Chloro-2-methylene-5-phenyl-7-(p-tolyl)-2,3-dihydro-1,4-oxazepine (**37D**) as pale yellow solid (R_f = 0.41 in 4:1 hexane/ethyl acetate); mp 80.0–81.7 ºC.

37D: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.64 (m, 4H), 7.54–7.39 (m, 3H), 7.02–6.88 (m, 2H), 4.56 (d, *J* = 1.8 Hz, 1H), 4.55 (s, 2H), 4.33 (d, *J* = 1.8 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4 (C), 162.9 (C), 161.6 (C), 155.9 (C), 134.4 (C), 130.3 (CH), 130.1 (CH), 129.7 (C), 129.3 (CH), 128.3 (CH), 113.7 (CH), 110.9 (CCl), 91.3 (CH_2), 55.5 (CH_2), 54.3 (CH_3); IR (neat 3122, 3053, 3003, 2972, 2933, 2907,2839, 2563, 1956, 1894, 1644, 1605, 1595, 1583, 1511, 1491, 1459, 1446, 1416, 1369, 1302, 1251, 1170, 1138, 1113, 1067, 1027, 985, 957, 851, 829,778, 756, 741, 692 cm^{-1}; MS (ESI, m/z): 326.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO_2$: 326.0942 $[M+H]^+$, found: 326.0955.

4.5.5 Synthesis of 6-Chloro-2-methylene-5-phenyl-7-(p-tolyl)-2,3-dihydro-1,4-oxazepine (37E)

General Procedure **5** was followed by using 2-chloro-3-phenyl-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one s *E/Z* mixture of isomers (ratio 12.5:1.0) (**35E**) (61 mg, 0.20 mmol) and $ZnCl_2$ (54 mg, 0.40 mmol) were employed to afford 28 mg (46%) of the indicated product of 6-chloro-2-methylene-5-phenyl-7-(p-

tolyl)-2,3-dihydro-1,4-oxazepine (**37E**) as yellow solid (R_f = 0.5 in 4:1 hexane/ethyl acetate); mp 71.7–73.7 ^{o}C.

37E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.64 (m, 2H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.43–7.30 (m, 3H), 7.18 (d, *J* = 8.3 Hz, 2H), 4.49 (s, 3H), 4.24 (d, *J* = 1.5 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4 (C), 162.6 (C), 156.4 (C), 140.5 (C), 137.3 (C), 131.4 (C), 130.6 (CH), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.4 (CH), 110.1 (CCl), 91.6 (CH_2), 54.4 (CH_2), 21.6 (CH_3); IR (neat): 3119, 3060, 3031, 2986, 2918, 2838, 2353, 2149, 2114, 2049, 2000, 1914, 1820, 1672, 1648, 1608,1585, 1507, 1492, 1447, 1292, 1252, 1185, 1139, 1079, 1064, 1021, 982, 956, 837, 811, 776, 757, 731, 695 cm^{-1}; MS (ESI, m/z): 310.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO$: 310.0993 $[M+H]^+$, found: 310.1007.

4.5.6 Synthesis of 6-Chloro-7-(4-methoxyphenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (37F)

General Procedure **5** was followed by using 2-chloro-1-(4-methoxyphenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 9.1:1.0) (**35F**) (171 mg, 0.52 mmol) and $ZnCl_2$ (143 mg, 1.05 mmol) were employed to afford 67 mg (39%) of the indicated product 6-chloro-7-(4-methoxyphenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (**37F**) as bright yellow solid (R_f = 0.42 in 4:1 hexane/ethyl acetate); mp 81.5–82.8 ^{o}C.

37F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.69 (m, 4H), 7.55–7.38 (m, 3H), 7.08–6.84 (m, 2H), 4.58 (d, *J* = 1.8 Hz, 1H), 4.56 (s, 2H), 4.33 (d, *J* = 1.8 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3 (C), 162.7 (C), 160.9 (C), 155.7 (C), 137.4 (C), 130.9 (CH), 130.4 (CH), 128.7 (CH), 128.3 (CH), 126.4 (C), 113.6 (CH), 109.6 (CCl), 91.3 (CH_2), 55.5 (CH_2), 54.4 (CH_3); IR (neat): 3121, 3036, 3000, 2958, 2936, 2914, 2837, 2064, 1982, 1919, 1898, 1814, 1773, 1735, 1714, 1687, 1657, 1619, 1605, 1573, 1504, 1466, 1446, 1414, 1381, 1304, 1271, 1248, 1187, 1175, 1141, 1111, 1083, 1064, 1032, 984, 958, 826, 811, 780, 760, 729, 697 cm^{-1}; MS (ESI, m/z): 326.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO_2$: 326.0942 $[M+H]^+$, found: 326.0944.

4.5.7 Synthesis of 6-Chloro-7-(4-chlorophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (37G)

General Procedure **5** was followed by using 2-chloro-1-(4-chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 11.1.1.0) (**35G**) (90 mg, 0.27 mmol) and $ZnCl_2$ (74 mg, 0.55 mmol) were employed to afford 38 mg (42%) of the indicated product of 6-cloro-7-(4-chlorophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (**37G**) as brown solid (R_f = 0.5 in 4:1 hexane/ethyl acetate); mp 88.9–90.9 ºC.

37G: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.65 (m, 4H), 7.59–7.37 (m, 5H), 4.61–4.55 (m, 3H), 4.34 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9 (C), 162.5 (C), 154.9 (C), 137.1 (C), 136.2 (C), 132.7 (C), 130.7 (CH), 130.6 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 111.0 (CCl), 91.9 (CH_2), 54.4 (CH_2); IR (neat): 3120, 3082, 3055, 3027, 2924, 2850, 2676, 2561, 2112, 1910, 1892, 1808, 1663, 1615, 1595, 1522, 1486, 1446, 1427, 1398, 1314, 1284, 1255, 1183, 1145, 1090, 1062, 1027, 1014, 981, 960, 925, 860, 817, 770, 729, 717, 694 cm^{-1}; MS (ESI, m/z): 330.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}Cl_2NO$: 330.0447 $[M+H]^+$, found: 330.0440.

4.5.8 Synthesis of 6-Chloro-2-methylene-7-(4-nitrophenyl)-5-phenyl-2,3-dihydro-1,4-oxazepine (37H)

General Procedure **5** was followed by using 2-chloro-1-(4-nitrophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 14.3:1.0) (**35H**) (63 mg, 0.86 mmol) and $ZnCl_2$ (51 mg, 0.37 mmol) were employed to afford 41 mg (65%) of the indicated product of 6-chloro-2-methylene-7-(4-nitrophenyl)-5-phenyl-2,3-dihydro-1,4-oxazepine (**37H**) as dark orange liquid (R_f = 0.29 in 4:1 hexane/ethyl acetate).

37H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.9 Hz, 2H), 7.95 (d, *J* = 8.9 Hz, 2H), 7.73 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.57–7.36 (m, 3H), 4.62 (d, *J* = 2.1 Hz, 1H), 4.61 (s, 2H), 4.40 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6 (C), 162.3 (C), 153.8 (C), 148.4 (C), 140.4 (C), 136.8 (C), 130.8 (CH), 130.5 (CH),

128.6 (CH), 128.5 (CH), 123.6 (CH), 112.7 (CCl), 92.5 (CH_2), 54.4 (CH_2); IR (neat): 3291, 31.08, 3055, 2980, 2931, 2858, 2453, 2120, 1959, 1939, 1729, 1659, 1598, 1547, 1518, 1446, 1372, 1345, 1303, 1288, 1243, 1101, 1066, 1014, 853, 762, 696, 460 cm^{-1}; MS (ESI, m/z): 341.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClN_2O_3$: 341.0688 $[M+H]^+$, found: 341.0700.

4.5.9 Synthesis of 7-(2-Bromophenyl)-6-chloro-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (37I)

General Procedure **5** was followed by using 1-(2-bromophenyl)-2-chloro-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 12.5:1.0) (**35I**) (133 mg, 0.35 mmol) and $ZnCl_2$ (97 mg, 0.71 mmol) were employed to afford 103 mg (78%) of the indicated product of 7-(2-bromophenyl)-6-chloro-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (**37I**) as orange oil (R_f = 0.48 in 4:1 hexane/ethyl acetate).

37I: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.72 (m, 2H), 7.70 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.51 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.49–7.40 (m, 4H), 7.36–7.29 (m, 1H), 4.79 (s, 2H), 4.56 (d, *J* = 2.0 Hz, 1H), 4.33 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6 (C), 161.6 (C), 156.4 (C), 137.3 (C), 136.3 (C), 133.1 (CH), 131.2 (CH), 131.1 (CH), 130.4 (CH), 128.6 (CH), 128.3 (CH), 127.7 (CH), 122.3 (C), 111.7 (CCl), 92.2 (CH_2), 54.9 (CH_2); IR (neat): 3056, 3027, 2976, 2927, 2846, 2177, 2121, 1949, 1886, 1808, 1734, 1655, 1620, 1596, 1574, 1492, 1467, 1445, 1373, 1307, 1290, 1245, 1191, 1148, 1082, 1067, 1045, 1029, 984, 963, 927, 843, 816, 753, 732, 718, 694 cm^{-1}; MS (ESI, m/z): 373.99 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{79}BrClNO$: 373.9942 $[M+H]^+$, found: 373.9950; MS (ESI, m/z): 375.99 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}{}^{81}BrClNO$: 375.9921 $[M+H]^+$, found: 375.9931.

4.5.10 Synthesis of 6-Chloro-2-methylene-7-phenyl-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (37J)

General Procedure **5** was followed by using 2-chloro-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 7.1:1.0) (**35J**) (77 mg, 0.26 mmol) and $ZnCl_2$ (70 mg, 0.51 mmol) were employed to afford 25 mg (32%) of the indicated product of 6-chloro-2-methylene-7-phenyl-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (**37J**) as brown oil (R_f = 0.46 in 4:1 hexane/ethyl acetate).

37J: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.8 Hz, 1H), 7.74 (dd, *J* = 6.4, 2.9 Hz, 2H), 7.50 (t, *J* = 6.3 Hz, 1H), 7.47–7.42 (m, 3H), 7.32 (dd, *J* = 4.9, 2.9 Hz, 1H), 4.57 (d, *J* = 1.2 Hz, 1H), 4.55 (s, 2H), 4.34 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (C), 162.6 (C), 155.7 (C), 139.3 (C), 134.3 (C), 130.2 (CH), 129.3 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 125.5 (CH), 110.6 (CCl), 91.6 (CH_2), 54.0 (CH_2); IR (neat): 3107, 3058, 3033, 2974, 2919, 2855, 2601, 2349, 2337, 2256, 2181, 2161, 2127, 2104, 2091, 2052, 2036, 2004, 1981, 1958, 1901, 1884, 1695, 1658, 1599, 1580, 1511, 1490, 1445, 1414, 1311, 1249, 1133, 1070, 1028, 992, 970, 931, 851, 825, 795, 761, 692 cm^{-1}; MS (ESI, m/z): 302.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{13}ClNOS$: 302.0401 $[M+H]^+$, found: 302.0406.

4.5.11 Synthesis of 6-Chloro-5-(3-fluorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (37K)

General Procedure **5** was followed by using 2-chloro-3-(3-fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 9.1:1.0) (**35K**) (148 mg, 0.47 mmol) and $ZnCl_2$ (129 mg, 0.94 mmol) were employed to afford 75 mg (51%) of the indicated product of 6-chloro-5-(3-fluorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**37K**) as yellow solid (R_f = 0.41 in 4:1 hexane/ethyl acetate); mp 78.3–80.2 °C.

37K: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.70 (m, 2H), 7.54 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.51–7.45 (m, 4H), 7.40 (td, *J* = 8.0, 5.7 Hz, 1H), 7.15 (tdd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 4.62–4.57 (m, 3H), 4.35 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 166.9 (d, ^4J = 2.5 Hz, C), 162.8 (d, ^1J = 246.1 Hz, CF), 162.3 (C), 156.5 (C), 139.5 (d, ^3J = 7.5 Hz, C), 134.2 (C), 130.3 (CH), 129.9 (d, ^3J = 8.0 Hz, CH), 129.3 (CH), 128.3 (CH), 124.5 (d, ^4J = 2.9 Hz, CH), 117.4 (d, ^2J = 21.3 Hz, CH), 115.6 (d, ^2J = 23.0 Hz, CH), 110.0 (CCl), 91.9 (CH_2), 54.6 (CH_2); IR (neat): 3119, 3081, 3065, 3005, 2953, 2923, 2852, 1706, 1657, 1609, 1576, 1482, 1441, 1313, 1293, 1258, 1204, 1187, 1121, 1072, 1026, 989, 972, 883, 845, 794, 781, 758, 734, 692 cm^{-1}; MS (ESI, m/z): 314.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClFNO$: 314.0743 $[M+H]^+$, found: 314.0750.

4.5.12 Synthesis of 7-(2-Bromophenyl)-5-(4-bromophenyl)-6-chloro-2-methylene-2,3-dihydro-1,4-oxazepine (37L)

General Procedure **5** was followed by using 1-(2-bromophenyl)-3-(4-bromophenyl)-2-chloro-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 11.1:1.0) (**35L**) (180 mg, 0.40 mmol) and $ZnCl_2$ (108 mg, 0.79 mmol) were employed to afford 82 mg (46%) of the indicated product of 7-(2-bromophenyl)-5-(4-bromophenyl)-6-chloro-2-methylene-2,3-dihydro-1,4-oxazepine (**37L**) as yellow solid (R_f = 0.56 in 4:1 hexane/ethyl acetate); mp 105.1–105.7 °C.

37L: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.64–7.59 (m, 2H), 7.59–7.53 (m, 2H), 7.49 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.43 (td, *J* = 7.5, 1.1 Hz, 1H), 7.36–7.29 (m, 1H), 4.76 (s, 2H), 4.55 (d, *J* = 2.0 Hz, 1H), 4.33 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (C), 161.5 (C), 156.8 (C), 136.3 (C), 133.2 (C), 131.5 (CH), 131.3 (CH), 131.1 (CH), 130.3 (CH), 127.8 (CH), 124.9 (C), 122.3 (C), 111.3 (CCl), 92.5 (CH_2), 55.0 (CH_2) (Note that two CH peaks overlap on each other); IR (neat): 3056, 2975, 2848, 2120, 2038, 1982, 1921, 1796, 1737, 1710, 1655, 1618, 1589, 1563, 1484, 1466, 1434, 1395, 1313, 1292, 1246, 1189, 1149, 1104, 1071, 1043, 1012, 982, 927, 874, 840, 811, 759, 738, 725, 681 cm^{-1}; MS (ESI, m/z): 451.91 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}{}^{79}Br_2ClNO$: 451.9047 $[M+H]^+$, found: 451.9056; MS (ESI, m/z): 453.90 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}{}^{79}Br{}^{81}BrClNO$: 453.9027 $[M+H]^+$, found: 453.9043; MS (ESI,

m/z): 455.90 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}{}^{81}Br_2ClNO$: 455.9008 $[M+H]^+$, found: 406.0006.

4.5.13 Synthesis of 6-Chloro-5-(3-fluorophenyl)-7-(3-methoxyphenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (37M)

General Procedure **5** was followed by using 2-chloro-3-(3-fluorophenyl)-1-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 7.1:1.0) (**35M**) (123 mg, 0.36 mmol) and $ZnCl_2$ (98 mg, 0.72 mmol) were employed to afford 48 mg (39%) of the indicated product of 6-chloro-5-(3-fluorophenyl)-7-(3-methoxyphenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**37M**) as dark orange solid (R_f = 0.52 in 4:1 hexane/ethyl acetate); mp 87.0–89.0 ^oC.

37M: ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.9 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.47 (dd, *J* = 9.6, 1.6 Hz, 1H), 7.40 (td, *J* = 7.9, 5.8 Hz, 1H), 7.15 (td, *J* = 8.4, 2.5 Hz, 1H), 6.97 (d, *J* = 8.9 Hz, 2H), 4.59 (d, *J* = 1.8 Hz, 1H), 4.56 (s, 2H), 4.33 (d, *J* = 1.7 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2 (d, ^4J = 2.6 Hz, C), 162.8 (d, ^1J = 246.3 Hz, CF), 162.4 (C), 161.1 (C), 156.1 (C), 139.5 (d, ^3J = 7.3 Hz, C), 130.9 (CH), 129.9 (d, ^3J = 8.1 Hz, CH), 126.2 (C), 124.5 (d, ^4J = 2.8 Hz, CH), 117.4 (d, ^2J = 21.4 Hz, CH), 115.7 (d, ^2J = 22.8 Hz CH, 113.7 (CH), 108.9 (CCl), 91.7 (CH_2), 55.5 (CH_2), 54.5 (CH_3); IR (neat): 3691, 3619, 2961, 2936, 2854, 1708, 1691, 1663, 1600, 1577, 1509, 1483, 1441, 1396, 1376, 1306, 1254, 1221, 1171, 1112, 1073, 1008, 938, 911, 857, 843, 828, 818, 805, 791, 758, 738, 695 cm^{-1}; MS (ESI, m/z): 344.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}ClFNO_2$: 344.0848 $[M+H]^+$, found: 344.0855.

4.5.14 Synthesis of 6-Chloro-5-(4-chlorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (37N)

General Procedure **5** was followed by using 2-chloro-3-(4-chlorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 12.5:1.0) (**35N**) (139 mg, 0.42 mmol) and $ZnCl_2$ (115 mg, 0.84 mmol) were employed to

afford 70 mg (51%) of the indicated product of 6-chloro-5-(4-chlorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**37N**) as dark orange solid (R_f = 0.64 in 4:1 hexane/ethyl acetate); mp 86.2–87.7 ^{o}C.

37N: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.73 (m, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.51–7.44 (m, 3H), 7.43–7.38 (m, 2H), 4.60 (d, *J* = 1.9 Hz, 1H), 4.58 (s, 2H), 4.35 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C), 162.3 (C), 156.4 (C), 136.6 (C), 135.7 (C), 134.1 (C), 130.3 (CH), 130.1 (CH), 129.2 (CH), 128.6 (CH), 128.3 (CH), 110.0 (CCl), 91.8 (CH_2), 54.5 (CH_2); IR (neat): 3119, 3061, 3036, 3006, 2986, 2861, 2577, 2266, 2190, 2121, 2015, 1656, 1584, 1487, 1445, 1398, 1310, 1291, 1258, 1189, 1141, 1091, 1071, 1027, 1015, 1001, 987, 960, 853, 836, 808, 758, 737, 691 cm^{-1}; MS (ESI, m/z): 330.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}Cl_2NO$: 330.0447 $[M+H]^+$, found: 330.0454.

4.5.15 Synthesis of 6-Chloro-2-methylene-7-phenyl-5-(p-tolyl)-2,3-dihydro-1,4-oxazepine (37O)

General Procedure **5** was followed by using 2-chloro-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 11.1:1.0) (**35O**) (176 mg, 0.57 mmol) and $ZnCl_2$ (154 mg, 1.13 mmol) were employed to afford 85 mg (48%) of the indicated product of 6-chloro-2-methylene-7-phenyl-5-(p-tolyl)-2,3-dihydro-1,4-oxazepine (**37O**) as dark orange solid (R_f = 0.52 in 4:1 hexane/ethyl acetate); mp 116.7–118.0 ^{o}C.

37O: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.79 (m, 2H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.54–7.45 (m, 3H), 7.33–7.25 (m, 2H), 4.61 (d, *J* = 1.8 Hz, 3H), 4.37 (d, *J* = 1.8 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9 (C), 162.6 (C), 155.9 (C), 140.8 (C), 134.4 (C), 134.3 (C), 130.1 (CH), 129.3 (CH), 129.1 (CH), 128.6 (CH), 128.3 (CH), 110.7 (CCl), 91.5 (CH_2), 54.3 (CH_2), 21.6 (CH_3); IR (neat): 3062, 3023, 2985, 2921, 2856, 2325, 2194, 2178, 2104, 1993, 1941, 1919, 1895, 1879, 1811, 1736, 1690, 1649, 1607, 1587, 1567, 1492, 1443, 1310, 1293, 1249, 1187, 1135, 1110, 1069, 1032, 983, 955, 925, 831, 774, 758, 733, 686 cm^{-1};

MS (ESI, m/z): 310.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO$: 310.0993 $[M+H]^+$, found: 310.0997.

4.5.16 Synthesis of 6-Chloro-7-(4-chlorophenyl)-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (37P)

General Procedure **5** was followed by using 2-chloro-1-(4-chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 10.0:1.0) (**35P**) (129 mg, 0.37 mmol) and $ZnCl_2$ (101 mg, 0.74 mmol) were employed to afford 68 mg (53%) of the indicated product of 6-chloro-7-(4-chlorophenyl)-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**37P**) as yellow solid (R_f = 0.54 in 4:1 hexane/ethyl acetate); mp 91.1–93.1 ºC.

37P: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.67 (m, 2H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.47–7.36 (m, 4H), 7.16 (td, *J* = 8.3, 2.0 Hz, 1H), 4.60 (d, *J* = 2.0 Hz, 1H), 4.57 (s, 2H), 4.36 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (C), 162.8 (d, ^1J = 246.5 Hz, CF), 162.2 (C), 155.3 (C), 139.3 (d, ^3J = 6.9 Hz, C), 136.4 (C), 132.5 (C), 130.7 (CH), 129.9 (d, ^3J = 8.0 Hz, CH), 128.7 (CH), 124.5 (d, ^4J = 2.8 Hz, CH), 117.6 (d, ^2J = 21.3 Hz, CH), 115.6 (d, ^2J = 23.0 Hz, CH), 110.4 (CCl), 92.2 (CH_2), 54.5 (CH_2); IR (neat): 3067, 3014, 2989, 2845, 2531, 2374, 2165, 2049, 2014, 2005, 1944, 1920, 1884, 1871, 1657, 1613, 1582, 1485, 1445, 1399, 1307, 1293, 1253, 1190, 1120, 1092, 1073, 1011, 989, 975, 885, 846, 825, 795, 782, 737, 690 cm^{-1}; MS (ESI, m/z): 348.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}Cl_2FNO$: 348.0353 $[M+H]^+$, found: 348.0352.

4.5.17 Synthesis of 7-(2-Bromophenyl)-6-chloro-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (37Q)

General Procedure **5** was followed by using 1-(2-bromophenyl)-2-chloro-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 10.0:1.0) (**35Q**) (238 mg, 0.61 mmol) and $ZnCl_2$ (165 mg, 1.21 mmol) were employed to afford 190 mg (80%) of the indicated product of 7-(2-bromophenyl)-

6-chloro-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**37Q**) as orange oil (R_f = 0.48 in 4:1 hexane/ethyl acetate).

37Q: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.52-7.37 (m, 4H), 7.32 (td, *J* = 7.8, 1.8 Hz, 1H), 7.15 (tdd, *J* = 8.3, 2.5, 0.6 Hz, 1H), 4.79 (s, 2H), 4.57 (d, *J* = 2.0 Hz, 1H), 4.34 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (d, ^{4}J = 2.3 Hz, C), 162.6 (d, ^{1}J = 246.3 Hz, CF), 161.4 (C), 156.7 (C), 139.5 (d, ^{3}J = 7.4 Hz, C), 136.2 (C), 133.1 (CH), 131.2 (CH), 131.1 (CH), 129.8 (d, ^{3}J = 7.4 Hz, CH), 127.7 (CH), 124.4 (d, ^{4}J = 2.8 Hz, CH), 122.2 (CBr), 117.3 (d, ^{2}J = 21.2 Hz, CH), 115.6 (d, ^{2}J = 22.8 Hz, CH), 111.2 (CCl), 92.5 (CH_2), 54.9 (CH_2); IR (neat): 3068, 2979, 2846, 1733, 1659, 1618, 1580, 1484, 1467, 1442, 1372, 1297, 1269, 1247, 1195, 1160, 1132, 1078, 1065, 1045, 1012, 989, 975, 929, 889, 845, 784, 755, 735, 720, 696 cm^{-1}; MS (ESI, m/z): 391.98 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}{}^{79}BrClFNO$: 391.9848 $[M+H]^+$, found: 391.9836; MS (ESI, m/z): 393.98 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{13}{}^{81}BrClFNO$: 393.9827 $[M+H]^+$, found: 393.9814.

4.5.18 Synthesis of 7-(2-Bromophenyl)-6-chloro-5-(4-methoxyphenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (37R)

General Procedure **5** was followed by using 1-(2-bromophenyl)-2-chloro-3-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 12.5:1.0) (**35R**) (135 mg, 0.33 mmol) and $ZnCl_2$ (91 mg, 0.67 mmol) were employed to afford 91 mg (68%) of the indicated product of 7-(2-bromophenyl)-6-chloro-5-(4-methoxyphenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**37R**) as pale orange oil (R_f = 0.32 in 4:1 hexane/ethyl acetate).

37R: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.62 (m, 3H), 7.50 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.43 (td, *J* = 7.5, 1.1 Hz, 1H), 7.33–7.29 (m, 1H), 6.98–6.92 (m, 2H), 4.75 (s, 2H), 4.53 (d, *J* = 1.9 Hz, 1H), 4.32 (d, *J* = 2.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C), 162.1 (C), 161.5 (C), 156.2 (C), 136.4 (C), 133.1 (CH), 131.2 (CH), 131,1 (CH), 130.2 (CH), 129.7 (C), 127.7 (CH), 122.3 (C), 113.6 (CH), 112.1 (CCl), 91.8 (CH_2), 55.4 (CH_2), 54.6 (CH_3); IR (neat): 3120, 3054,

3000, 2961, 2933, 2905, 2837, 2558, 2297, 2162, 2135, 2104, 2065, 2014, 1928, 1902, 1870, 1734, 1654, 1606, 1571, 1511, 1465, 1437, 1419, 1372, 1305, 1245, 1173, 1147, 1112, 1075, 1029, 986, 963, 835, 782, 755, 682 cm^{-1}; MS (ESI, m/z): 404.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}{}^{79}BrClNO_2$: 404.0047 $[M+H]^+$, found: 404.0046; MS (ESI, m/z): 406.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}{}^{81}BrClNO_2$: 406.0027 $[M+H]^+$, found: 406.0026.

4.5.19 Synthesis of 6-Chloro-7-(4-chlorophenyl)-2-methylene-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (37S)

General Procedure **5** was followed by using 2-chloro-1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one as *E/Z* mixture of isomers ratio (11.1:1.0) (**35S**) (127 mg, 0.37 mmol) and $ZnCl_2$ (100 mg, 0.74 mmol) were employed to afford 58 mg (46%) of the indicated product of 6-chloro-7-(4-chlorophenyl)-2-methylene-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (**37S**) as orange solid (R_f = 0.42 in 4:1 hexane/ethyl acetate); mp 60.3–62.3 ^oC.

37S: ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.61 (m, 2H), 7.47 (s, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.36–7.31 (m, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.20–7.16 (m, 1H), 4.48 (d, *J* = 2.0 Hz, 1H), 4.47 (s, 2H), 4.24 (d, *J* = 1.9 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1 (C), 162.5 (C), 154.7 (C), 138.2 (C), 137.1 (C), 136.1 (C), 132.7 (C), 131.4 (CH), 130.7 (CH), 128.9 (CH), 128.6 (CH), 128.3 (CH), 125.9 (CH), 111.1 (CCl), 91.8 (CH_2), 54.4 (CH_2), 21.5 (CH_3); IR (neat): 3296, 3118, 3051, 2979, 2952, 2920, 2861, 2838, 2249, 2165, 2139, 2110, 2084, 2042, 2014, 1981, 1949, 1906, 1797, 1786, 1733, 1680, 1642, 1594, 1487, 1399, 1374, 1307, 1294, 1251, 1187, 1132, 1092, 1072, 1014, 985, 966, 872, 851, 820, 794, 778, 734, 717, 694 cm^{-1}; MS (ESI, m/z): 344.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}Cl_2NO$: 344.0603 $[M+H]^+$, found: 344.0606.

4.5.20 Synthesis of 6-Chloro-7-(4-methoxyphenyl)-2-methylene-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (37T)

General Procedure **5** was followed by using 2-chloro-1-(4-methoxyphenyl)-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 5.3:1.0) (**35T**) (102 mg, 0.31 mmol) and $ZnCl_2$ (84 mg, 0.61 mmol) were employed to afford 32 mg (31%) of the indicated product of 6-chloro-7-(4-methoxyphenyl)-2-methylene-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (**37T**) as dark yellow solid (R_f = 0.38 in 4:1 hexane/ethyl acetate); mp 84.4–85.8 ^oC.

37T: ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 2.9, 1.1 Hz, 1H), 7.79–7.70 (m, 2H), 7.50 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.31 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.05–6.89 (m, 2H), 4.55 (d, *J* = 1.8 Hz, 1H), 4.51 (s, 2H), 4.32 (d, *J* = 1.8 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (C), 162.8 (C), 160.9 (C), 155.1 (C), 139.6 (C), 130.9 (CH), 128.2 (CH), 127.7 (CH), 126.4 (C), 125.5 (CH), 113.7 (CH), 109.7 (CCl), 91.3 (CH_2), 55.5 (CH_2), 54.1 (CH_3); IR (neat): 3107, 3072, 3048, 3009, 2962, 2930, 2893, 2836, 2551, 2042, 1899, 1653, 1606, 1585, 1505, 1451, 1439, 1410, 1373, 1304, 1248, 1209, 1173, 1132, 1110, 1065, 1025, 988, 970, 923, 869, 823, 793, 729, 664 cm^{-1}; MS (ESI, m/z): 332.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{15}ClNO_2S$: 332.0507 $[M+H]^+$, found: 332.0510.

4.5.21 Synthesis of 7-(2-Bromophenyl)-6-chloro-2-methylene-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (37U)

General Procedure **5** was followed by using 1-(2-bromophenyl)-2-chloro-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 9.1:1.0) (**35U**) (225 mg, 0.58 mmol) and $ZnCl_2$ (158 mg, 1.16 mmol) were employed to afford 160 mg (71%) of the indicated product of 7-(2-bromophenyl)-6-chloro-2-methylene-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (**37U**) as pale orange oil (R_f = 0.64 in 4:1 hexane/ethyl acetate).

37U: ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.62–7.51 (m, 3H), 7.44 (td, *J* = 7.5, 0.9 Hz, 1H), 7.37–7.27 (m, 3H), 4.80 (s, 2H), 4.56 (d, *J* = 1.9 Hz, 1H), 4.34 (d, *J* = 2.0 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

167.7 (C), 161.7 (C), 156.3 (C), 138.0 (C), 137.3 (C), 136.3 (CH), 133.1 (C), 131.2 (CH), 131.12 (CH), 131.09 (CH), 128.9 (CH), 128.1 (CH), 127.6 (CH), 125.8 (CH), 122.2 (CBr), 111.9 (CCl), 92.0 (CH_2), 54.8 (CH_2), 21.5 (CH_3); IR (neat): 3055, 3022, 2975, 2919, 2848, 2322, 2179, 2107, 1932, 1734, 1656, 1620, 1595, 1580, 1467, 1434, 1373, 1300, 1247, 1190, 1140, 1072, 1045, 1029, 987, 938, 844, 797, 779, 754, 734, 719, 700, 683 cm^{-1}; MS (ESI, m/z): 388.01 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}{}^{79}BrClFNO$: 388.0098 $[M+H]^+$, found: 388.0104; MS (ESI, m/z): 390.01 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}{}^{81}BrClFNO$: 390.0078 $[M+H]^+$, found: 390.0085.

4.5.22 Synthesis of 6-Chloro-5-(3-fluorophenyl)-2-methylene-7-(p-tolyl)-2,3-dihydro-1,4-oxazepine (37V)

General Procedure **5** was followed by using 2-chloro-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 10.0:1.0) (**35V**) (107 mg, 0.33 mmol) and $ZnCl_2$ (89 mg, 0.65 mmol) were employed to afford 58 mg (54%) of the indicated product of 6-chloro-5-(3-fluorophenyl)-2-methylene-7-(p-tolyl)-2,3-dihydro-1,4-oxazepine (**37V**) as pale yellow solid (R_f = 0.68 in 4:1 hexane/ethyl acetate); mp 105.5–106.3 ºC.

37V: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 26.9, 20.2 Hz, 2H), 7.42 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.36 (dq, *J* = 9.7, 1.7 Hz, 1H), 7.29 (td, *J* = 8.0, 5.7 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.04 (tdd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 4.47 (d, *J* = 1.9 Hz, 1H), 4.46 (s, 2H), 4.22 (d, *J* = 1.9 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (d, ^4J = 2.7 Hz, C), 162.8 (d, ^1J = 246.0 Hz, CF), 162.3 (C), 156.5 (C), 140.6 (C), 139.6 (d, ^3J = 7.5 Hz, C), 131.2 (C), 129.8 (d, ^3J = 8.0 Hz, CH), 129.2 (CH), 129.0 (CH), 124.5 (d, ^4J = 2.8 Hz, CH), 117.4 (d, ^2J = 21.3 Hz, CH), 115.6 (d, ^2J = 22.8 Hz, CH), 109.6 (CCl), 91.8 (CH_2), 54.6 (CH_2), 21.6 (CH_3). IR (neat): 3119, 3079, 3049, 3028, 3006, 2922, 2854, 1660, 1609, 1577, 1506, 1483, 1441, 1381, 1312, 1294, 1258, 1204, 1182, 1122, 1070, 1019, 1009, 988, 972, 884, 854, 811, 791, 759, 736, 717, 695 cm^{-1}; MS (ESI, m/z): 328.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{16}ClFNO$: 328.0899 $[M+H]^+$, found: 328.0901.

4.5.23 Synthesis of 7-(2-Bromophenyl)-6-chloro-5-(4-fluoro-3-methylphenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (37W)

General Procedure **5** was followed by using 1-(2-bromophenyl)-2-chloro-3-(4-fluoro-3-methylphenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one as *E/Z* mixture of isomers (ratio 7.1:1.0) (**35W**) (91 mg, 0.22 mmol) and $ZnCl_2$ (61 mg, 0.45 mmol) were employed to afford 36 mg (39%) of the indicated product of 7-(2-bromophenyl)-6-chloro-5-(4-fluoro-3-methylphenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**37W**) as yellow oil (R_f = 0.50 in 4:1 hexane/ethyl acetate).

37W: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.59 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.56–7.51 (m, 1H), 7.50 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.44 (td, *J* = 7.5, 1.0 Hz, 1H), 7.35–7.30 (m, 1H), 7.05 (t, *J* = 8.9 Hz, 1H), 4.75 (s, 2H), 4.54 (d, *J* = 2.0 Hz, 1H), 4.31 (d, *J* = 2.0 Hz, 1H), 2.32 (d, *J* = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (C), 162.8 (d, ^1J = 249.2 Hz, CF), 161.6 (C), 156.6 (C), 136.4 (C), 133.2 (CH), 133.1 (d, ^4J = 3.4 Hz, C), 131.9 (CH), 131.8 (CH), 131.2 (d, ^3J = 9.5 Hz, CH), 128.2 (d, ^3J = 8.7 Hz, CH), 127.7 (CH), 125.1 (d, ^2J = 17.8 Hz, C), 122.3 (C), 114.9 (d, ^2J = 23.0 Hz, CH), 111.7 (CCl), 92.3 (CH_2), 54.8 (CH_2), 14.7 (d, ^3J = 3.4 Hz, CH_3); IR (neat): 3289, 3245, 3056, 3028, 2921, 2120, 1706, 1677, 1604, 1581, 1548, 1497, 1445, 1374, 1348, 1312, 1245, 1181, 1162, 1097, 1021, 1001, 945, 916, 881, 829, 775, 758, 701, 613 cm^{-1}; MS (ESI, m/z): 406.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}{}^{79}BrClFNO$: 406.0004 $[M+H]^+$, found: 406.0006; MS (ESI, m/z): 407.99 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}{}^{81}BrClFNO$: 407.9983 $[M+H]^+$, found: 407.9990.

4.5.24 Synthesis of 6-Fluoro-2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (38A)

General Procedure **5** was followed by using 2-fluoro-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**36A**) (70 mg, 0.25 mmol) and $ZnCl_2$ (68 mg, 0.50 mmol) were employed to afford 52 mg (74%) of the indicated product of 6-fluoro-2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**38A**) as light yellow solid (R_f = 0.52 in 4:1 hexane/ethyl acetate); mp 59.1–60.5 °C.

38A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.0, 1.3 Hz, 2H), 7.79–7.75 (m, 2H), 7.51–7.42 (m, 6H), 4.69 (d, *J* = 1.7 Hz, 1H), 4.59 (s, 2H), 4.35 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6 (d, ^{2}J = 25.6 Hz, C), 160.7 (C), 146.6 (d, ^{2}J = 30.5 Hz, C), 142.2 (d, ^{1}J = 250.6 Hz, CF), 136.3 (d, ^{3}J = 3.5 Hz, C), 132.0 (d, ^{3}J = 5.1 Hz, C), 130.8 (CH), 130.1 (CH), 128.5 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 92.1 (CH_2), 55.0 (CH_2); IR (neat): 3116, 3053, 3004, 2980, 2918, 2852, 2349, 1981, 1963, 1915, 1897, 1816, 1657, 1634, 1586, 1568, 1494, 1446, 1388, 1332, 1314, 1263, 1204, 1147, 1078, 1040, 1026, 999, 973, 943, 924, 867, 822, 777, 765, 695 cm^{-1}; MS (ESI, m/z): 280.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}FNO$: 280.1132 $[M+H]^+$, found: 280.1129.

4.5.25 Synthesis of 5-Butyl-6-fluoro-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (38B)

General Procedure **5** was followed by using 2-fluoro-1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (**36B**) (81 mg, 0.31 mmol) and $ZnCl_2$ (85 mg, 0.62 mmol) were employed to afford 47 mg (59%) of the indicated product of 5-butyl-6-fluoro-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**38B**) as dark orange oil (R_f = 0.40 in 4:1 hexane/ethyl acetate).

38B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.68 (m, 2H), 7.46–7.38 (m, 3H), 4.63 (d, *J* = 1.4 Hz, 1H), 4.35 (s, 2H), 4.27 (d, *J* = 1.6 Hz, 1H), 2.60–2.53 (m, 2H), 1.69–1.59 (pentet, *J* = 7.7 Hz, 2H), 1.46–1.35 (sextet, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7 (d, ^{2}J = 26.4 Hz, C), 158.9 (C), 144.9 (d, ^{2}J = 32.7 Hz, C), 141.9 (d, ^{1}J = 245.7 Hz, CF), 132.1 (d, ^{3}J = 4.4 Hz, C), 129.9 (CH), 128.3 (d, ^{4}J = 3.9 Hz, CH), 128.2 (CH), 92.4 (CH_2), 54.7 (CH_2), 35.6 (CH_2), 29.1 (d, ^{4}J = 1.2 Hz, CH_2), 22.6 (CH_2), 14.0 (CH_3); IR (neat): 3061, 2958, 2931, 2871, 1657, 1494, 1447, 1263, 1154, 846, 692 cm^{-1}; MS (ESI, m/z): 260.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{19}FNO$: 260.1445 $[M+H]^+$, found: 260.1436.

4.5.26 Synthesis of 6-Fluoro-2-methylene-7-phenyl-5-(p-tolyl)-2,3-dihydro-1,4-oxazepine (38O)

General Procedure **5** was followed by using 2-fluoro-1-phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (**36O**) (82 mg, 0.28 mmol) and $ZnCl_2$ (76 mg, 0.56 mmol) were employed to afford 52 mg (93%) of the indicated product of 6-fluoro-2-methylene-7-phenyl-5-(p-tolyl)-2,3-dihydro-1,4-oxazepine (**38O**) as yellow oil (R_f = 0.60 in 4:1 hexane/ethyl acetate);

38O: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.1, 1.2 Hz, 2H), 7.56 (dd, *J* = 8.2, 2.1 Hz, 2H), 7.39–7.33 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 2H), 4.56 (d, *J* = 1.7 Hz, 1H), 4.47 (s, 2H), 4.23 (d, *J* = 1.7 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4 (d, ^2J = 25.5 Hz, C), 160.9 (C), 146.4 (d, ^2J = 30.4 Hz, C), 142.5 (d, ^1J = 251.5 Hz, CF), 141.1 (C), 133.5 (d, ^3J = 3.8 Hz, C), 132.1 (d, ^3J = 5.4 Hz, C), 130.0 (CH), 129.2 (CH), 128.5 (CH), 128.4 (d, ^4J = 2.7 Hz, CH), 128.1 (d, ^4J = 8.4 Hz, CH), 91.9 (CH_2), 54.9 (CH_2), 21.6 (CH_3); IR (neat): 3056, 3029, 2974, 2919, 2838, 2352, 2174, 1735, 1652, 1612, 1586, 1510, 1493, 1446, 1408, 1374, 1329, 1310, 1259, 1203, 1165, 1147, 1077, 1041, 972, 939, 834, 766, 729, 691 cm^{-1}; MS (ESI, m/z): 294.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}FNO$: 294.1289 $[M+H]^+$, found: 294.1292.

4.5.27 Synthesis of 7-(4-Chlorophenyl)-6-fluoro-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (38P)

General Procedure **5** was followed by using 1-(4-chlorophenyl)-2-fluoro-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**36P**) (56 mg, 0.17 mmol) and $ZnCl_2$ (46 mg, 0.34 mmol) were employed to afford 46 mg (81%) of the indicated product of 7-(4-chlorophenyl)-6-fluoro-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**38P**) as light yellow solid (R_f = 0.48 in 4:1 hexane/ethyl acetate); mp 99.1–100.4 °C.

38P: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 1H), 7.55–7.36 (m, 3H), 7.16 (tdd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 4.69 (d, *J* = 1.9 Hz, 1H), 4.57 (s, 1H), 4.36 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2 (d, ^2J = 28.1 Hz, C), 162.9

(d, ^{1}J = 246.2 Hz, CF), 160.3 (C), 145.9 (d, ^{2}J = 30.1 Hz, C), 141.9 (d, ^{1}J = 251.6 Hz, CF), 138.2 (dd, ^{3}J = 7.4, ^{4}J = 3.7 Hz, C), 136.3 (C), 130.2 (d, ^{3}J = 5.3 Hz, C), 130.1 (d, ^{3}J = 8.0 Hz, CH), 129.5 (d, ^{4}J = 8.7 Hz, CH), 128.9 (CH), 124.3 (t, ^{4}J = 3.0 Hz, CH), 117.8 (d, ^{2}J = 21.3 Hz, CH), 115.4 (dd, ^{2}J = 23.1, ^{4}J = 2.5 Hz, CH), 92.8 (CH_2), 55.1 (CH_2); IR (neat): 3132, 3070, 3013, 2921, 2853, 1917, 1737, 1661, 1641, 1615, 1573, 1487, 1444, 1399, 1313, 1259, 1218, 1199, 1151, 1088, 1011, 985, 883, 860, 836, 795, 782, 741, 723, 694 cm^{-1}; MS (ESI, m/z): 332.06 $[M+H]^{+}$; HRMS (ESI) calcd. for $C_{18}H_{13}ClF_2NO$: 332.0648 $[M+H]^{+}$, found: 332.0641.

4.5.28 Synthesis of 6-Fluoro-5-(3-fluorophenyl)-2-methylene-7-(p-tolyl)-2,3-dihydro-1,4-oxazepine (38V)

General Procedure **5** was followed by using 2-fluoro-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)-1-(p-tolyl)prop-2-en-1-one (**36V**) (61 mg, 0.20 mmol) and $ZnCl_2$ (53 mg, 0.39 mmol) were employed to afford 45 mg (74%) of the indicated product of 6-fluoro-5-(3-fluorophenyl)-2-methylene-7-(p-tolyl)-2,3-dihydro-1,4-oxazepine (**38V**) as light yellow solid (R_f = 0.50 in 4:1 hexane/ethyl acetate); mp 82.6–83.7 ^{o}C.

38V: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.41 (dd, *J* = 18.9, 8.7 Hz, 2H), 7.29 (td, *J* = 8.0, 5.8 Hz, 1H), 7.20–7.15 (m, 2H), 7.06 (td, *J* = 8.3, 2.2 Hz, 1H), 4.58 (d, *J* = 1.6 Hz, 1H), 4.47 (s, 2H), 4.24 (d, *J* = 1.7 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5 (dd, ^{2}J = 26.1, ^{4}J = 2.5 Hz, C), 162.9 (d, ^{1}J = 246.1 Hz, CF), 160.4 (C), 147.1 (d, ^{2}J = 30.4 Hz, C), 141.5 (d, ^{1}J = 249.1 Hz, CF), 140.6 (C), 138.48 (dd, ^{3}J = 10.5, ^{4}J = 2.9 Hz, CH), 129.9 (d, ^{3}J = 8.0 Hz, C), 129.3 (CH), 128.9 (d, ^{3}J = 5.2 Hz, CH), 128.1 (d, ^{4}J = 8.2 Hz, CH), 124.3 (t, ^{4}J = 3.0 Hz, CH), 117.6 (d, ^{2}J = 21.3 Hz, CH), 115.4 (d, ^{2}J = 25.7 Hz, CH), 92.3 (CH_2), 55.1 (CH_2), 21.6 (CH_3); IR (neat): 3127, 3077, 3031, 2921, 2852, 2201, 1911, 1661, 1633, 1575, 1509, 1485, 1446, 1381, 1308, 1264, 1214, 1193, 1151, 1019, 987, 938, 893, 880, 854, 837, 811, 792, 764, 736, 705, 678 cm^{-1}; MS (ESI, m/z): 312.12 $[M+H]^{+}$; HRMS (ESI) calcd. for $C_{19}H_{16}F_2NO$: 312.1194 $[M+H]^{+}$, found: 312.1191.

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APPENDIX A

NMR DATA

^{1}H and ^{13}C NMR spectra were reported in 400 and 100 MHz, respectively, with Bruker Spectrospin Avance DPX400 Ultrashield spectrometer.

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

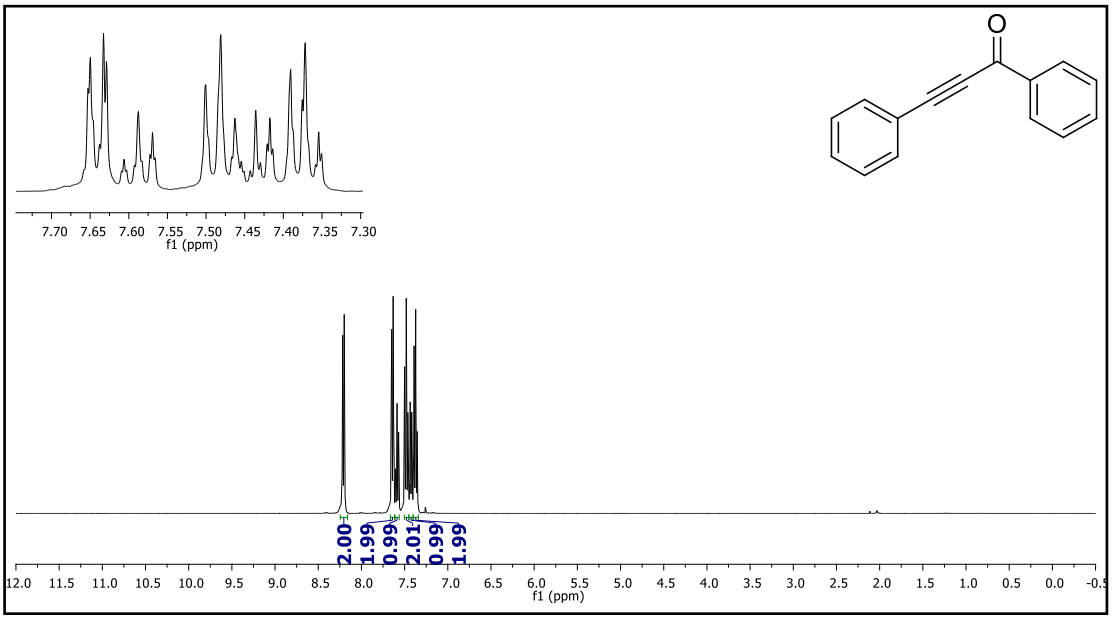

Figure 23. ^{1}H NMR spectrum of compound **41A**.

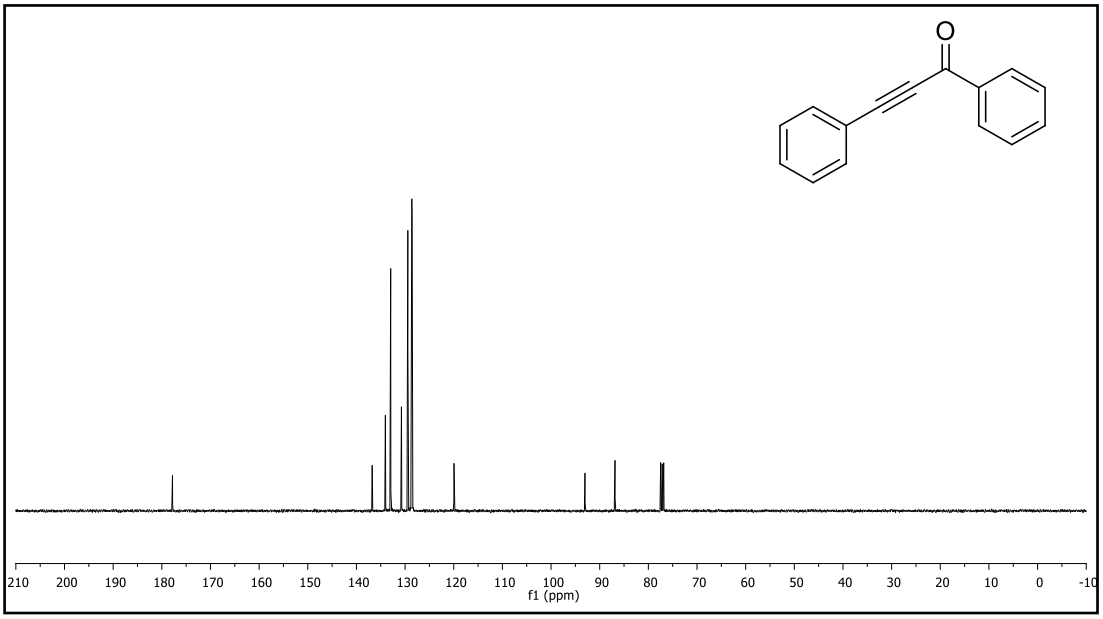

Figure 24. ^{13}C NMR spectrum of compound **41A**.

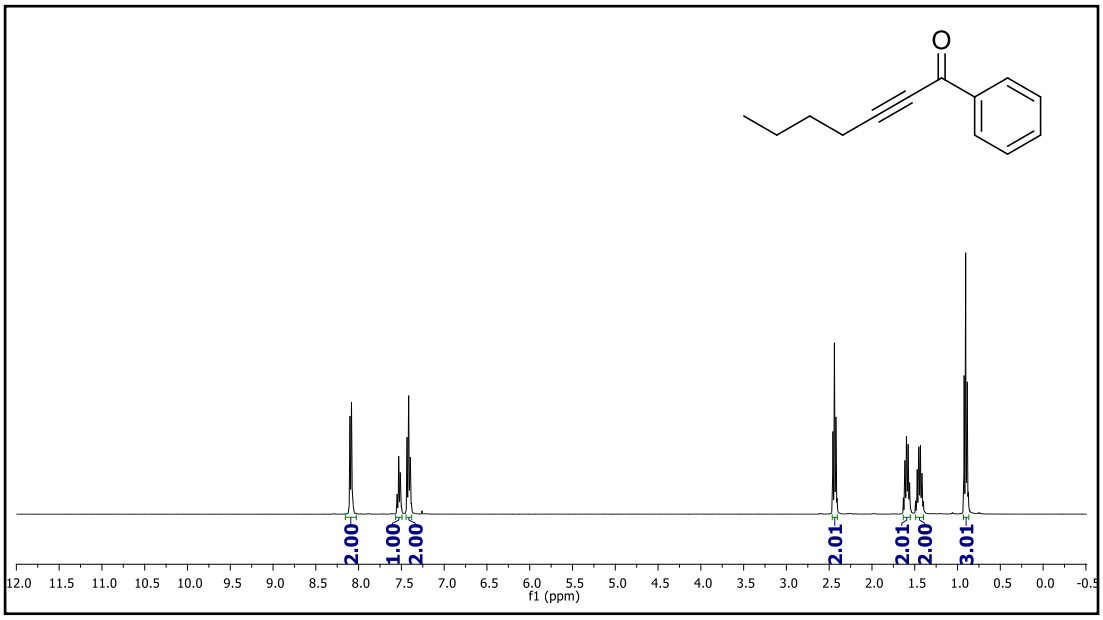

Figure 25. ^{1}H NMR spectrum of compound **41B**.

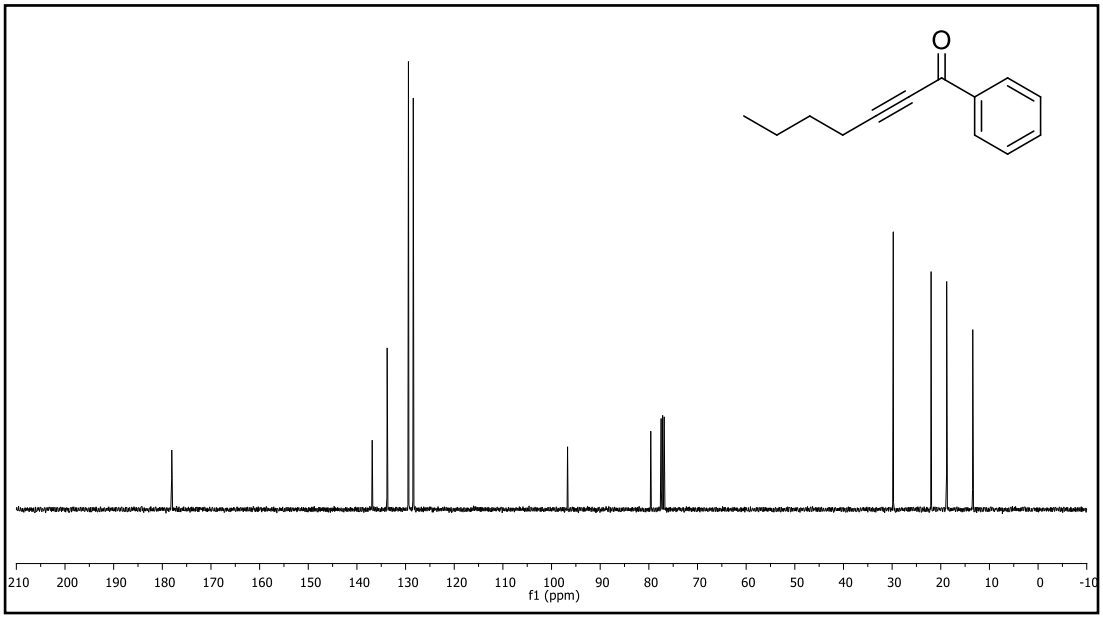

Figure 26. ^{13}C NMR spectrum of compound **41B**.

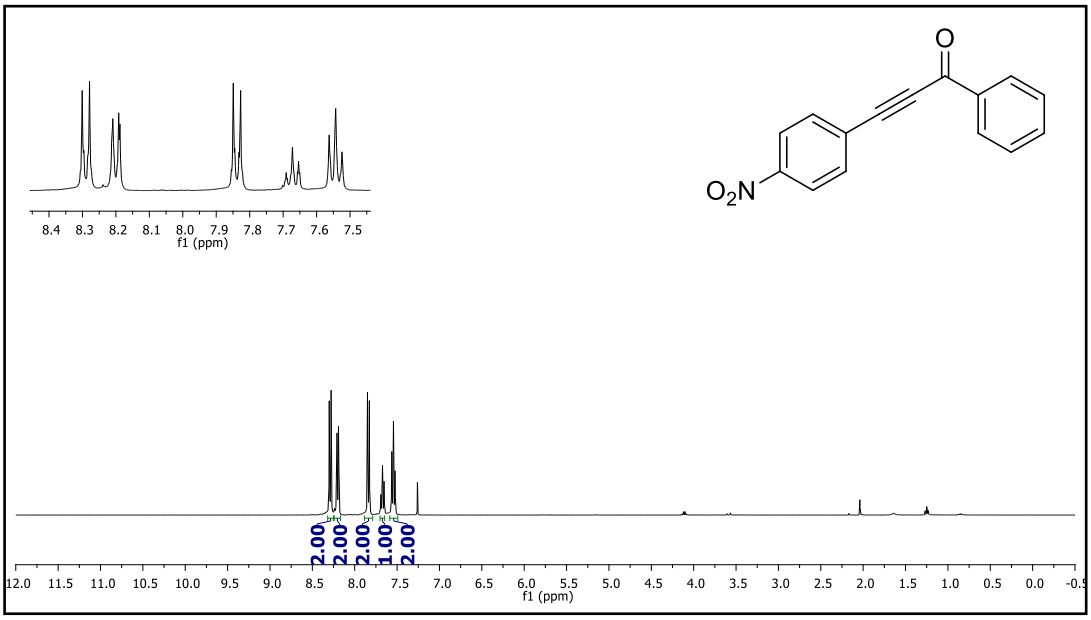

Figure 27. ^{1}H NMR spectrum of compound **41C**.

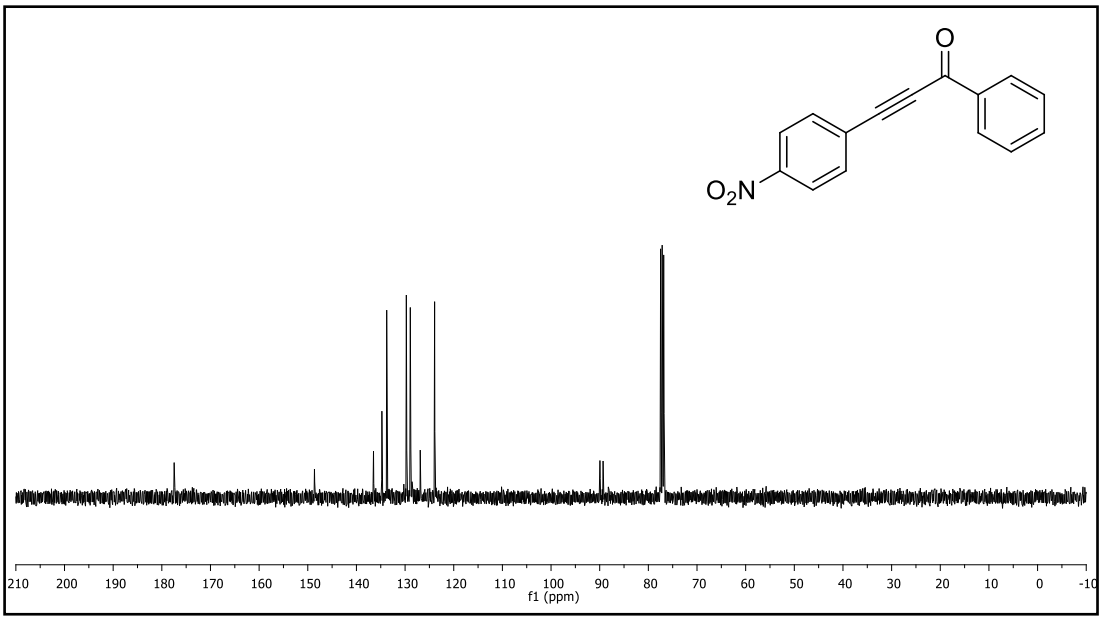

Figure 28. ^{13}C NMR spectrum of compound **41C**.

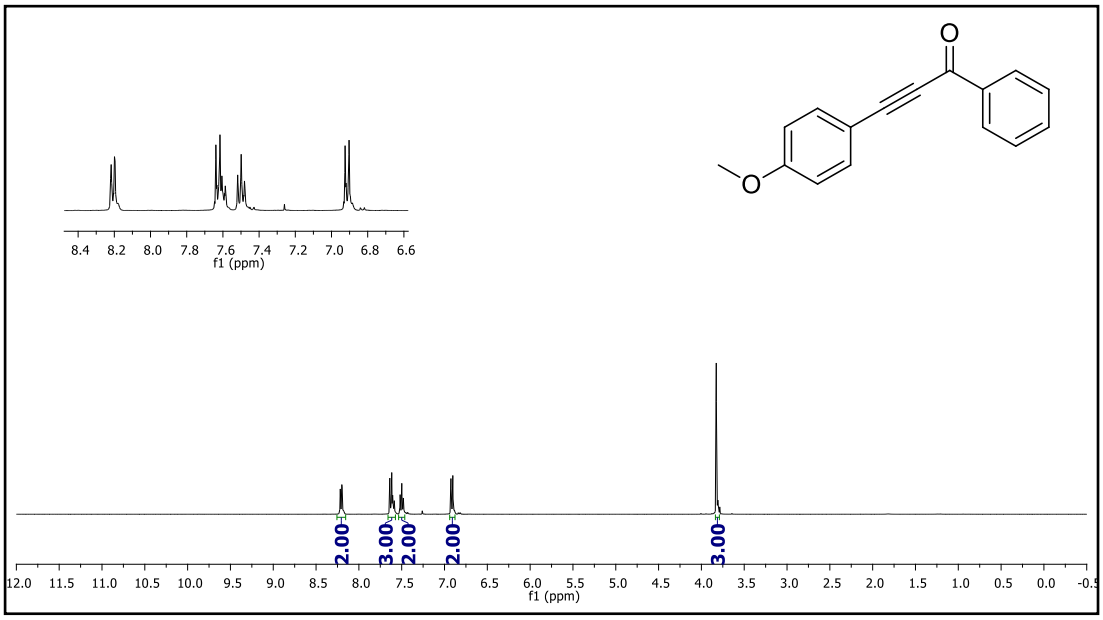

Figure 29. ^{1}H NMR spectrum of compound **41D**.

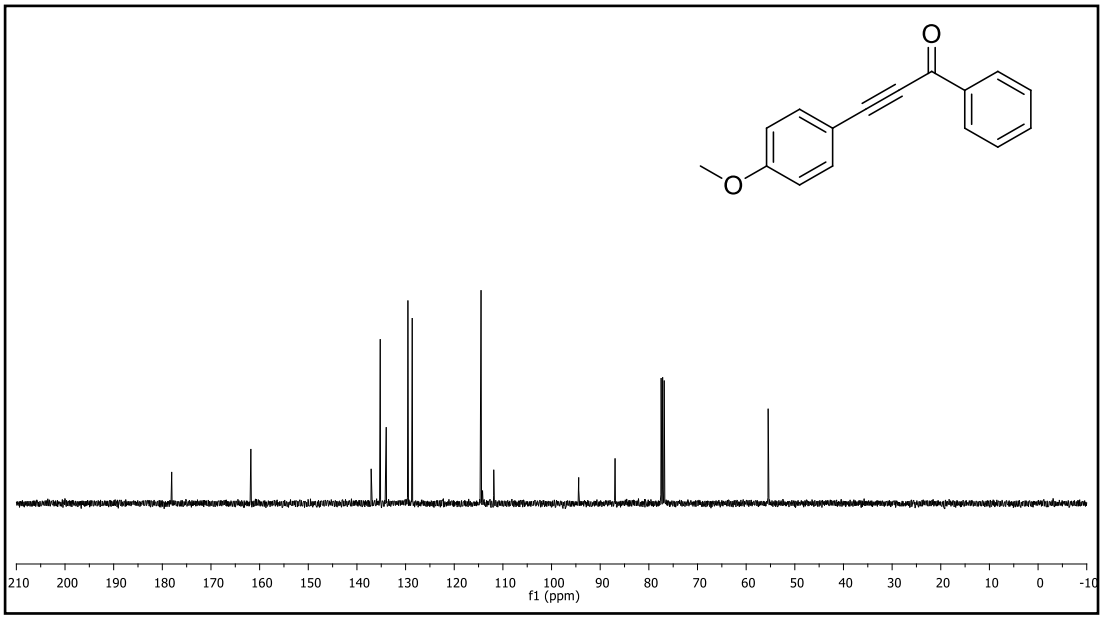

Figure 30. ^{13}C NMR spectrum of compound **41D**.

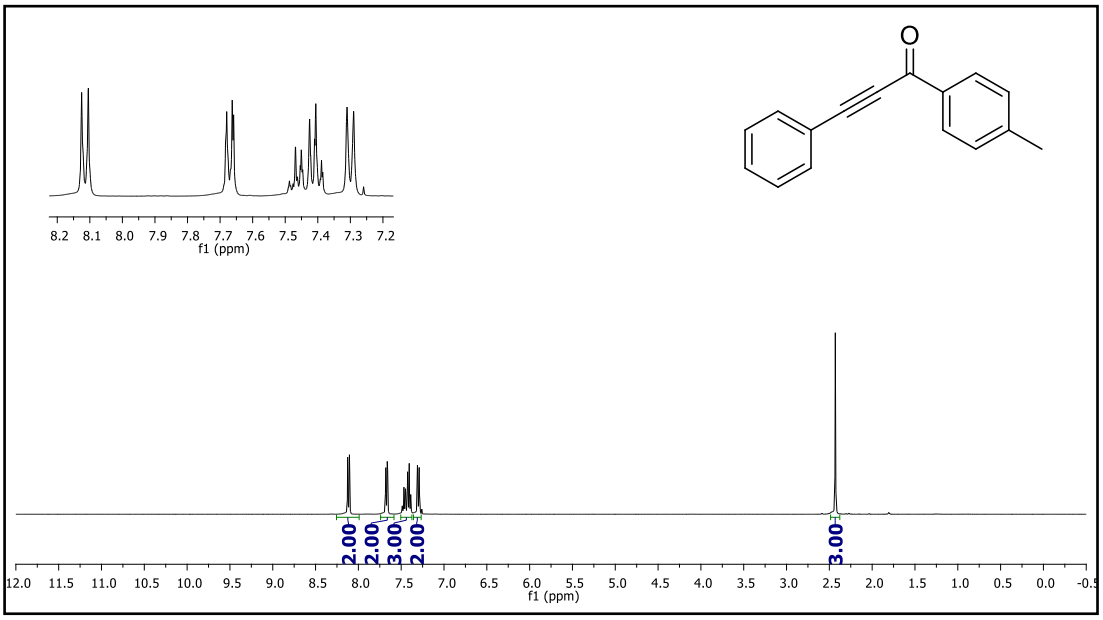

Figure 31. ^{1}H NMR spectrum of compound **41E**.

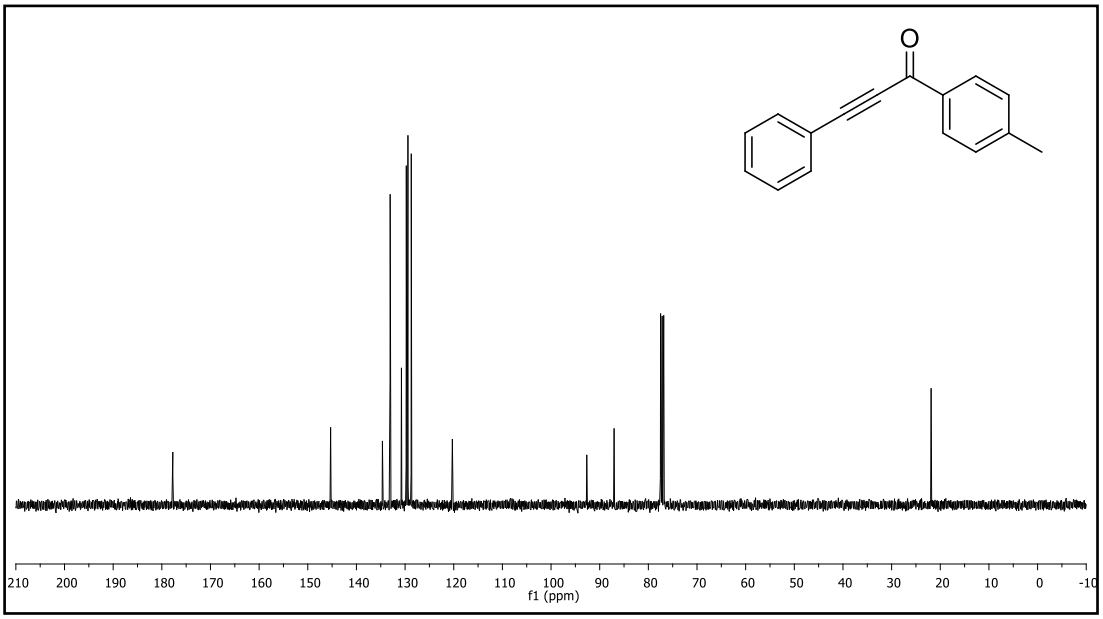

Figure 32. ^{13}C NMR spectrum of compound **41E**.

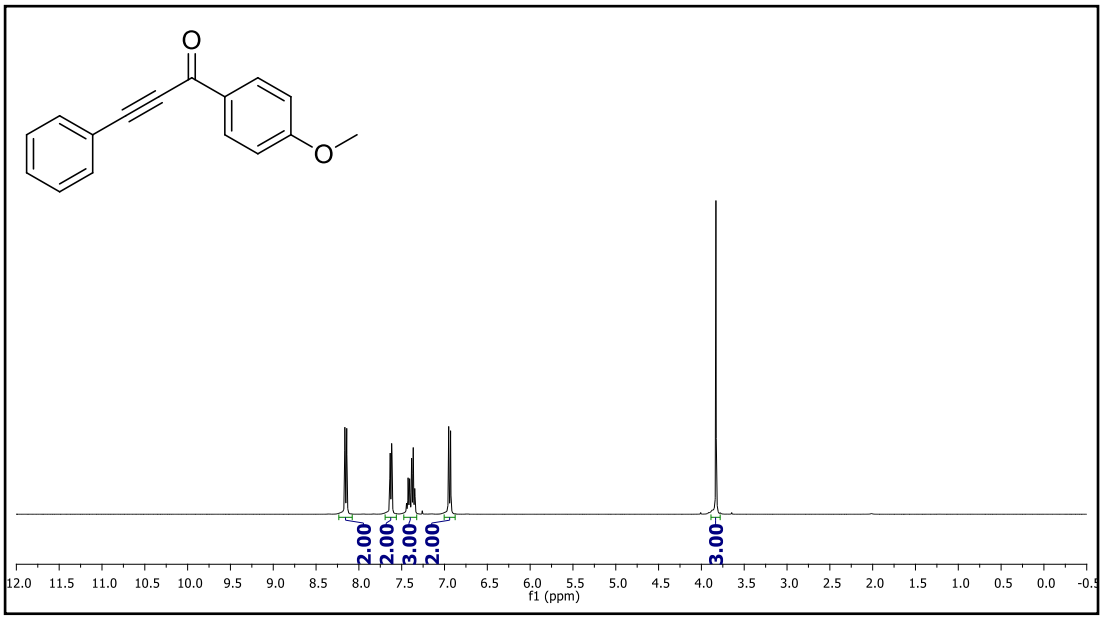

Figure 33. ^{1}H NMR spectrum of compound **41F**.

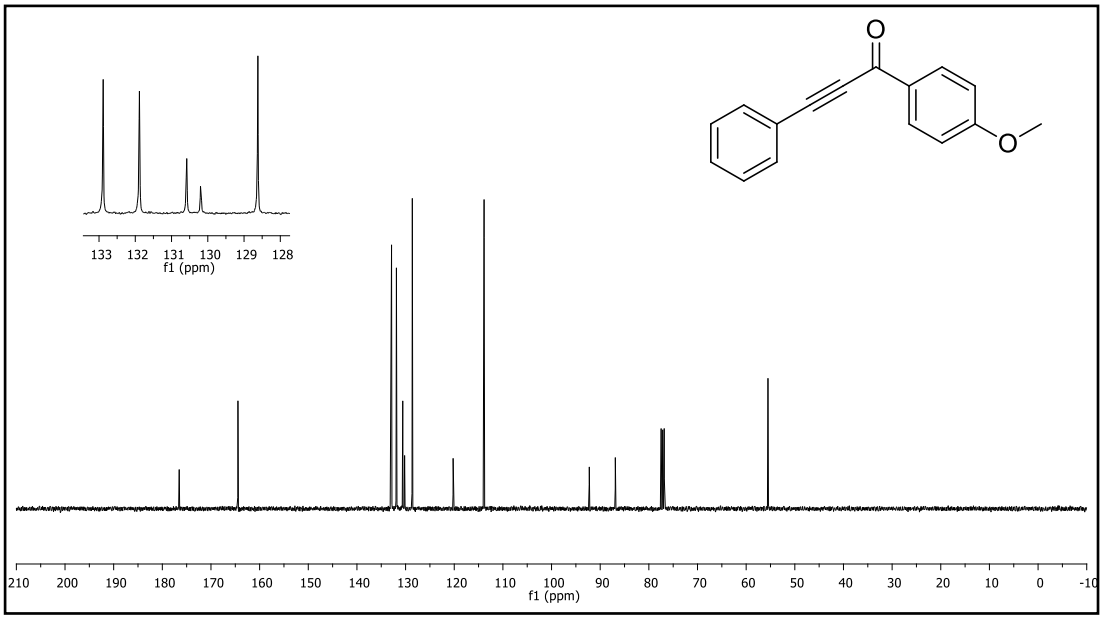

Figure 34. ^{13}C NMR spectrum of compound **41F**.

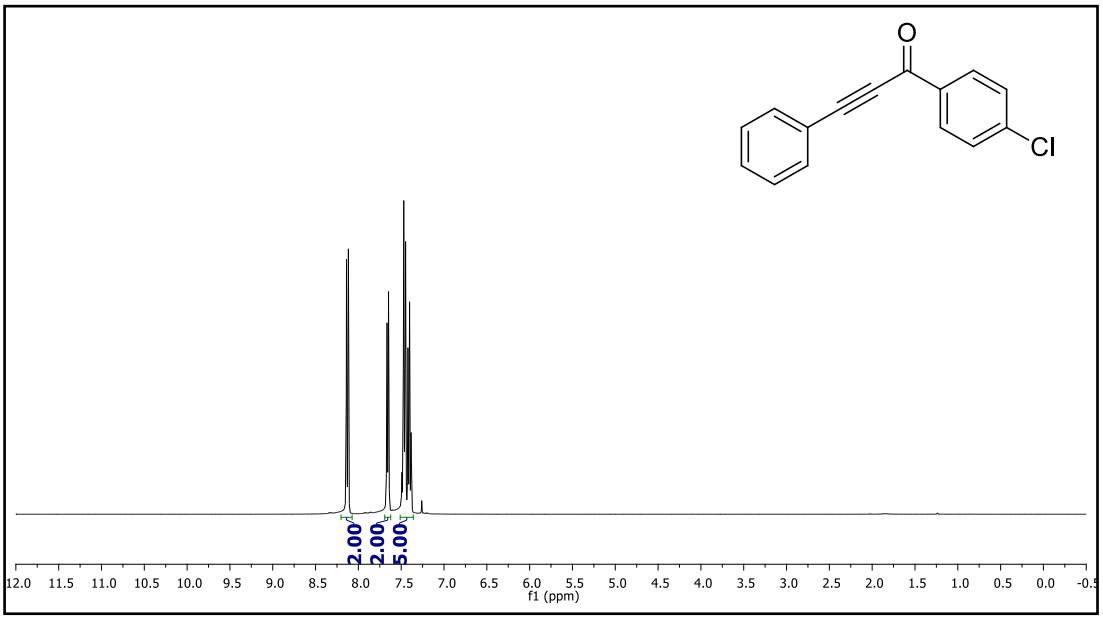

Figure 35. ^{1}H NMR spectrum of compound **41G**.

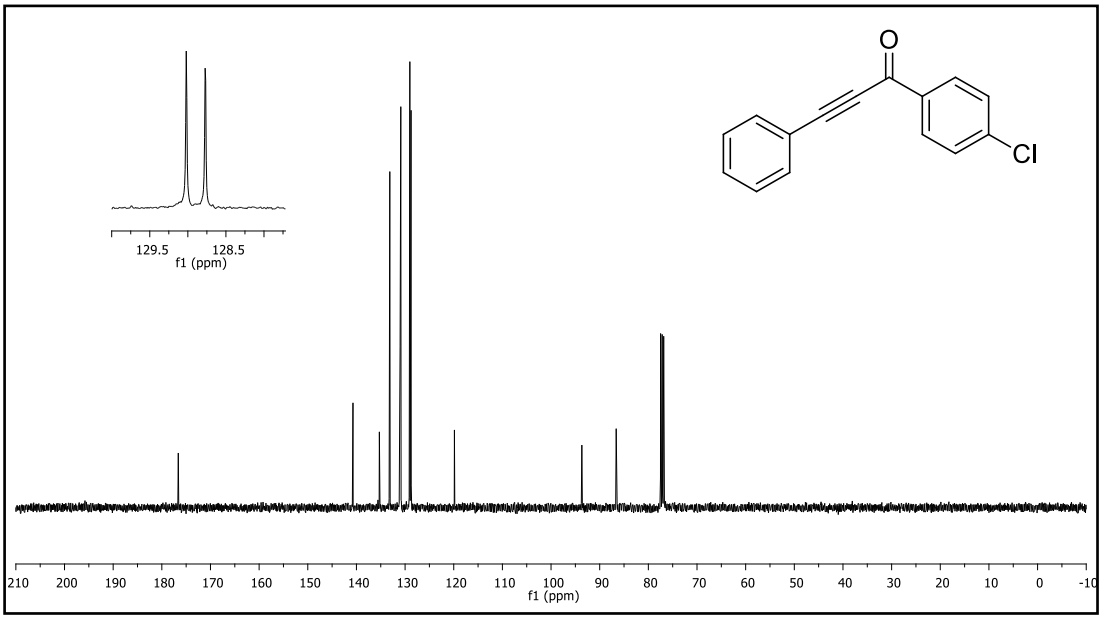

Figure 36. ^{13}C NMR spectrum of compound **41G**.

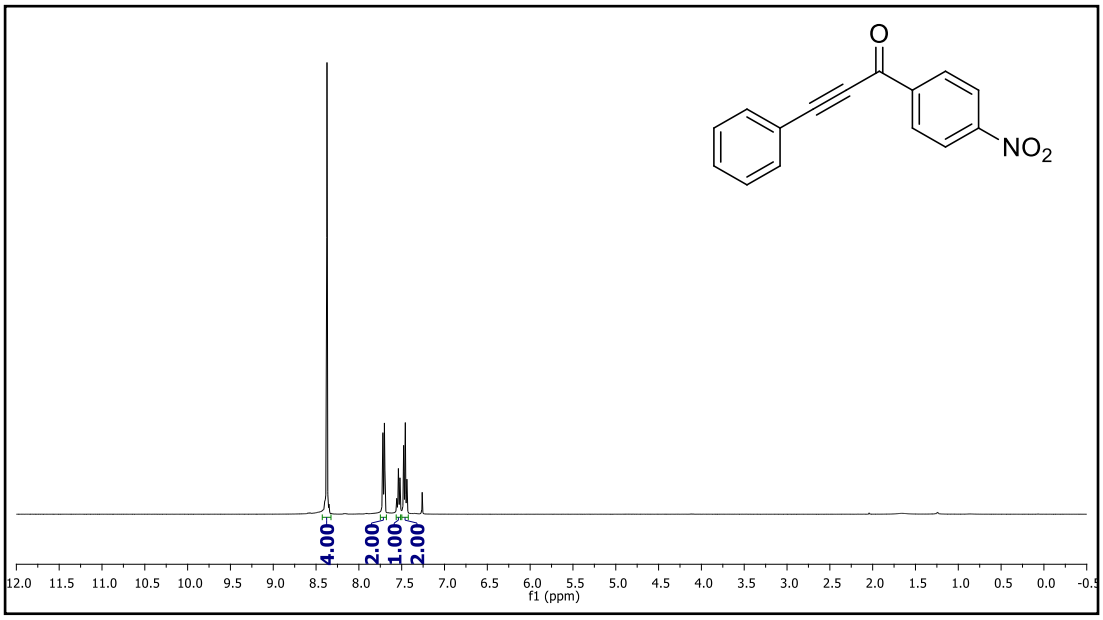

Figure 37. ^{1}H NMR spectrum of compound **41H**.

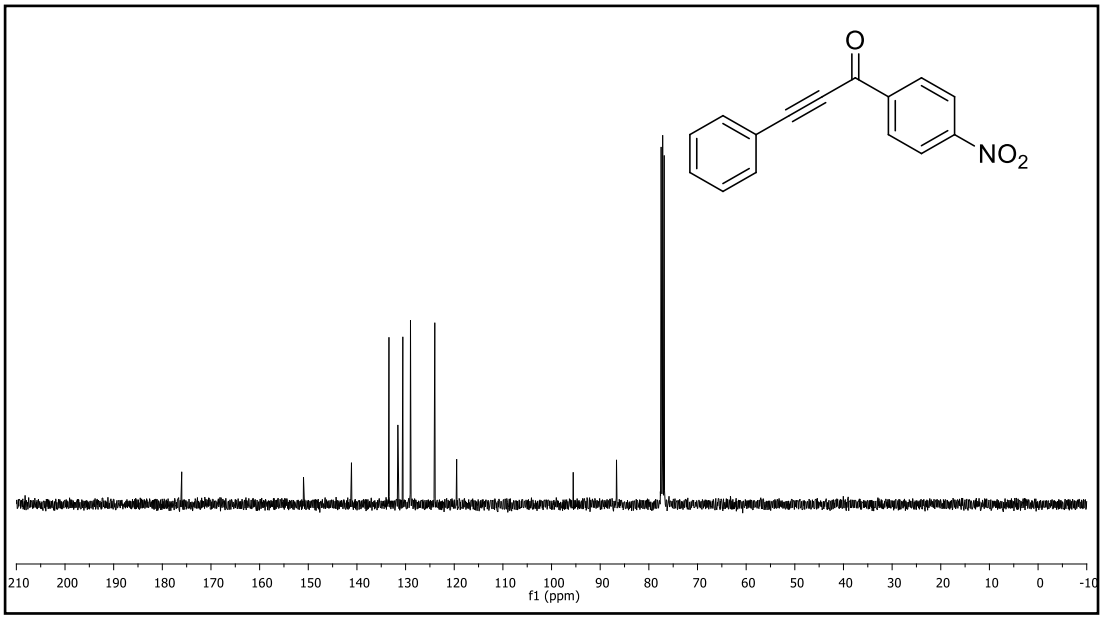

Figure 38. ^{13}C NMR spectrum of compound **41H**.

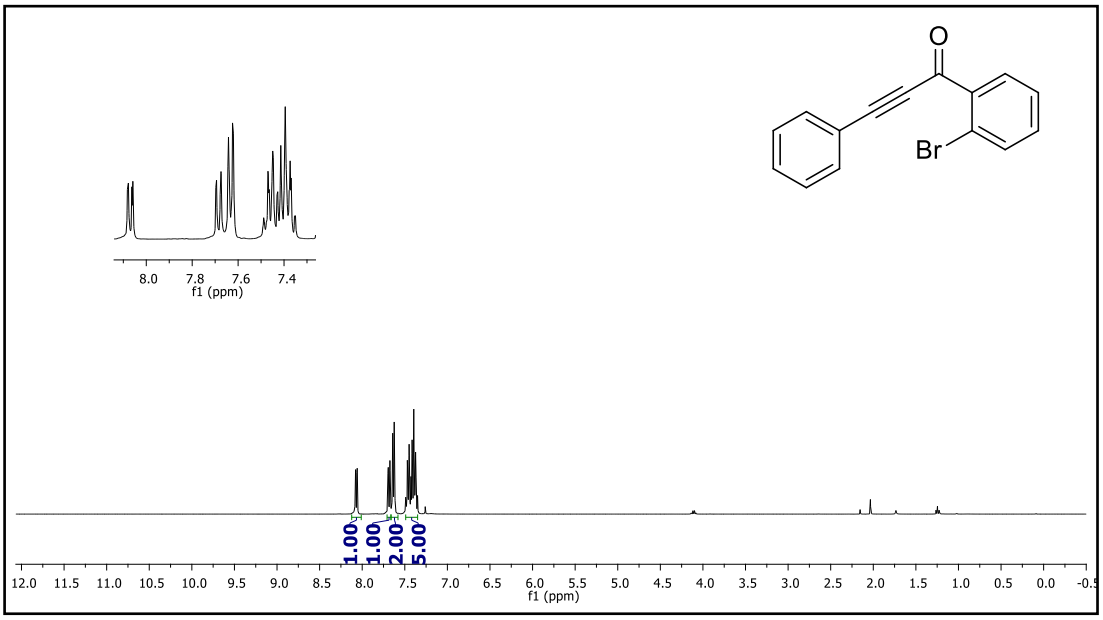

Figure 39. ^{1}H NMR spectrum of compound **41I**.

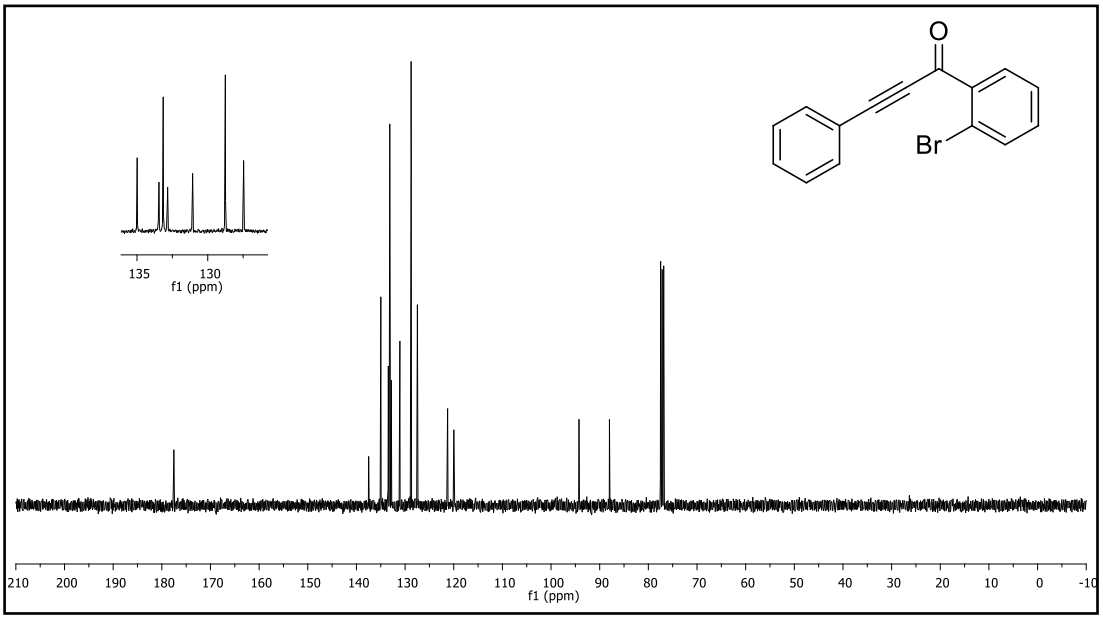

Figure 40. ^{13}C NMR spectrum of compound **41I**.

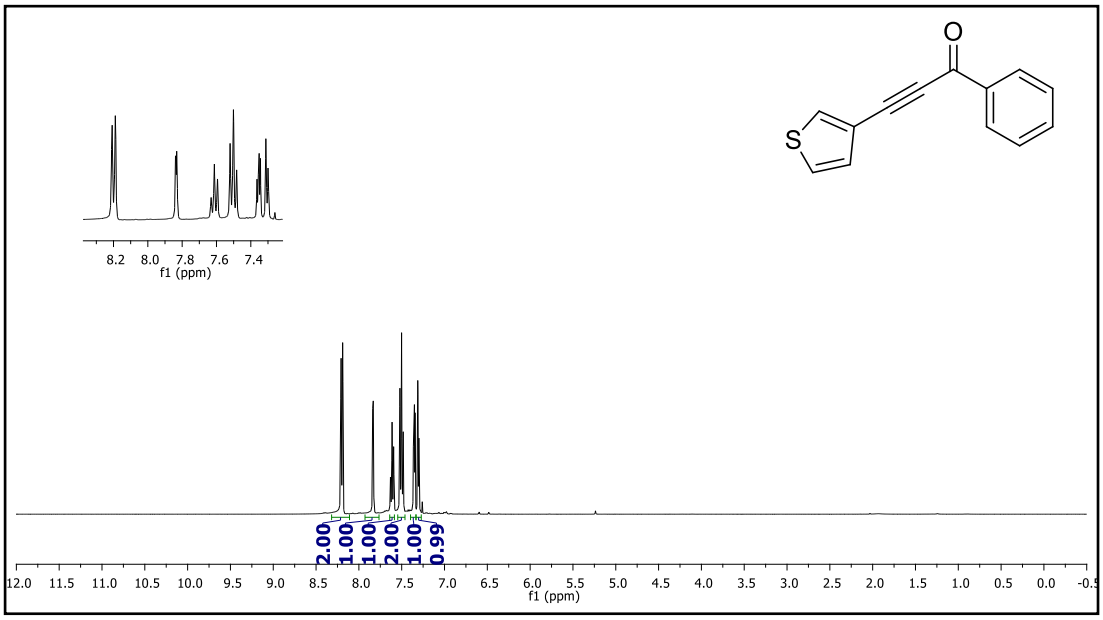

Figure 41. ^{1}H NMR spectrum of compound **41J**.

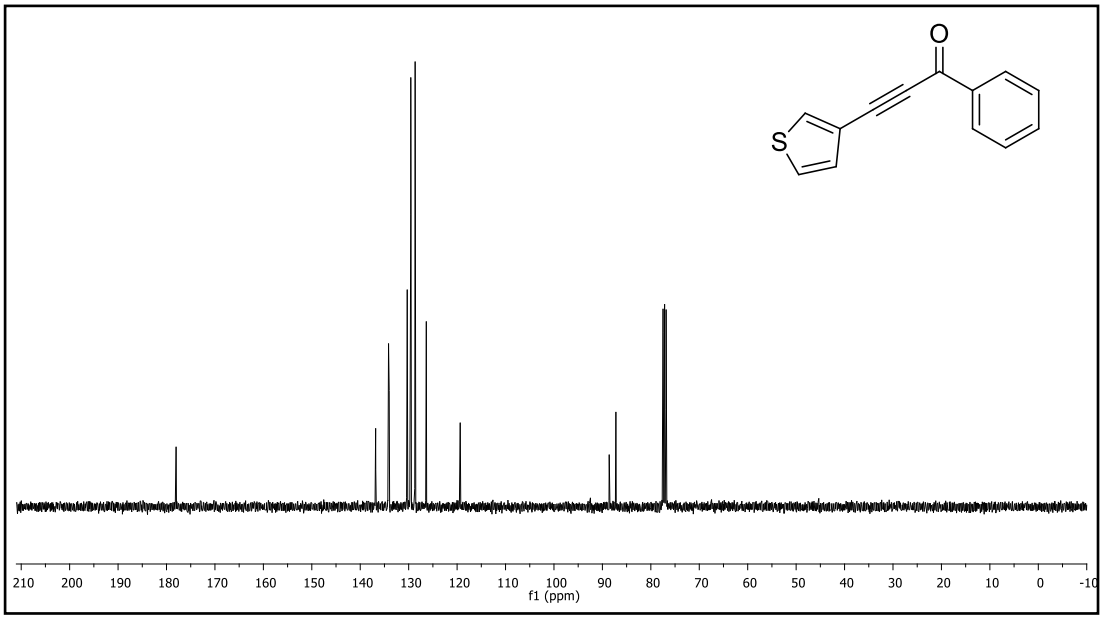

Figure 42. ^{13}C NMR spectrum of compound **41J**.

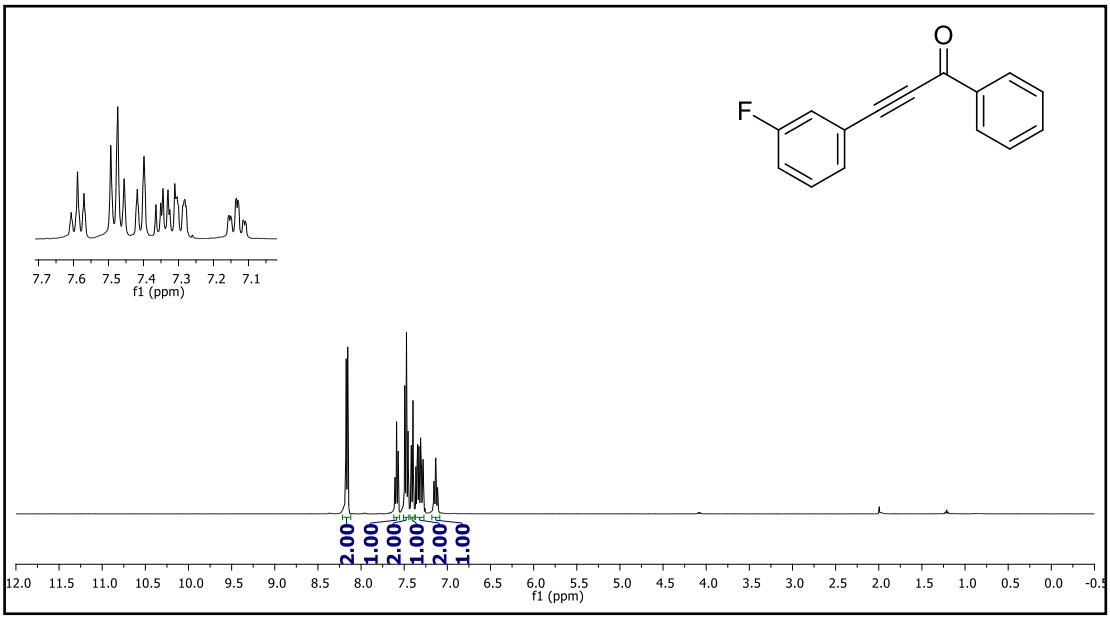

Figure 43. ^{1}H NMR spectrum of compound **41K**.

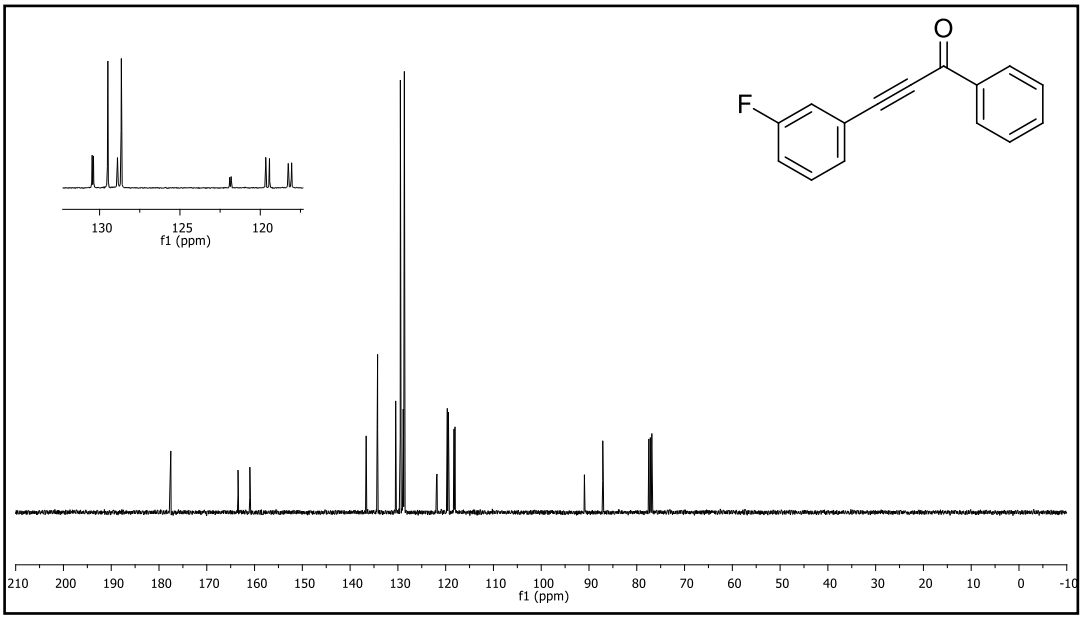

Figure 44. ^{13}C NMR spectrum of compound **41K**.

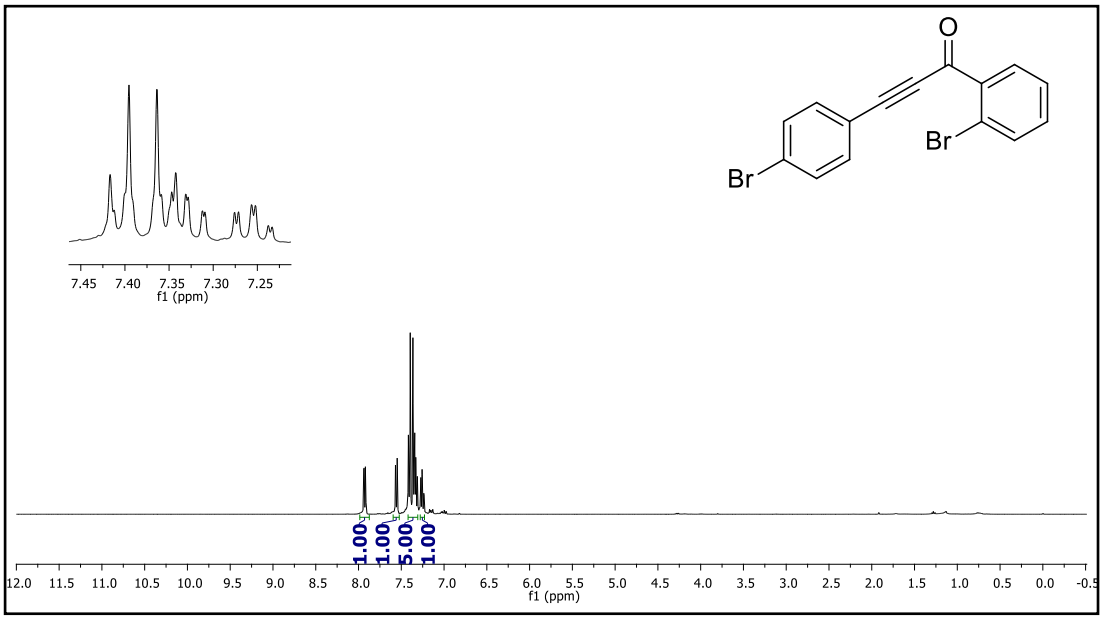

Figure 45. ^{1}H NMR spectrum of compound **41L**.

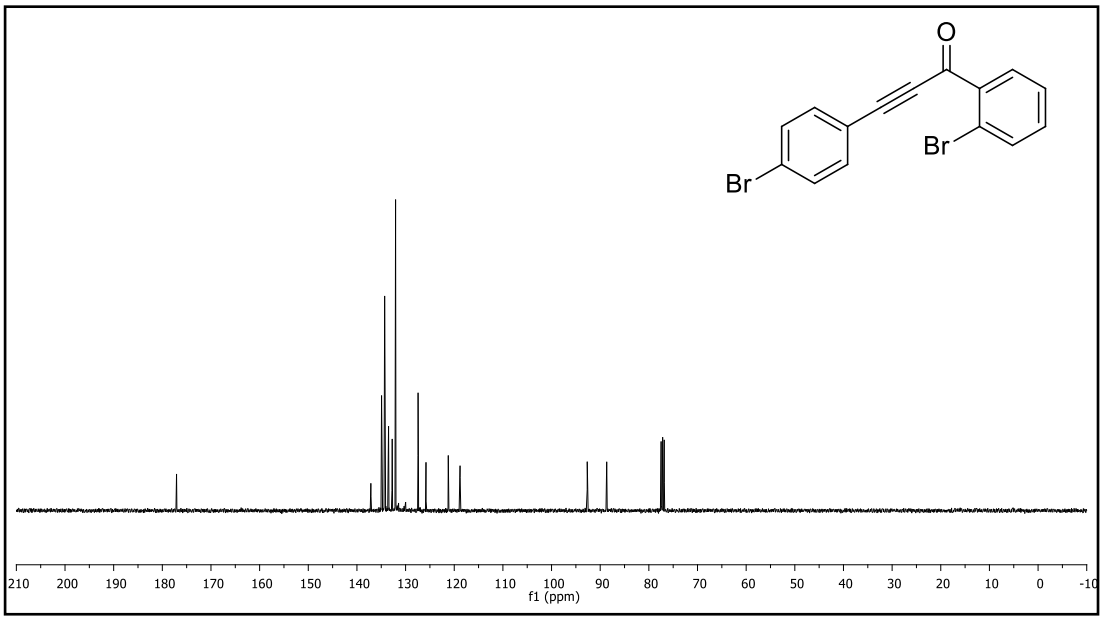

Figure 46. ^{13}C NMR spectrum of compound **41L**.

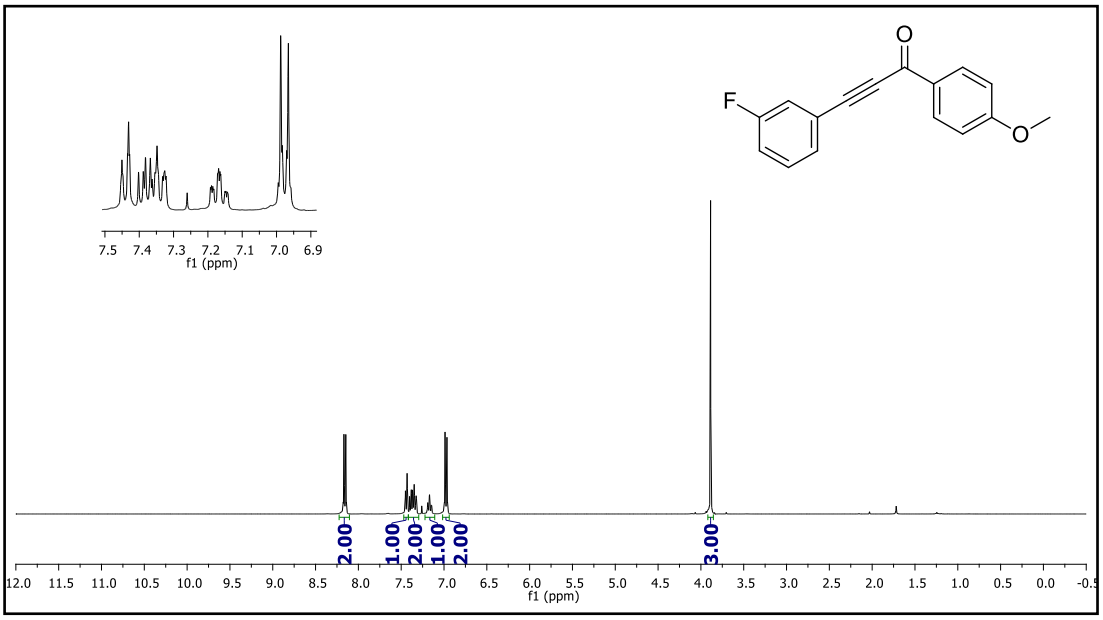

Figure 47. ^{1}H NMR spectrum of compound **41M**.

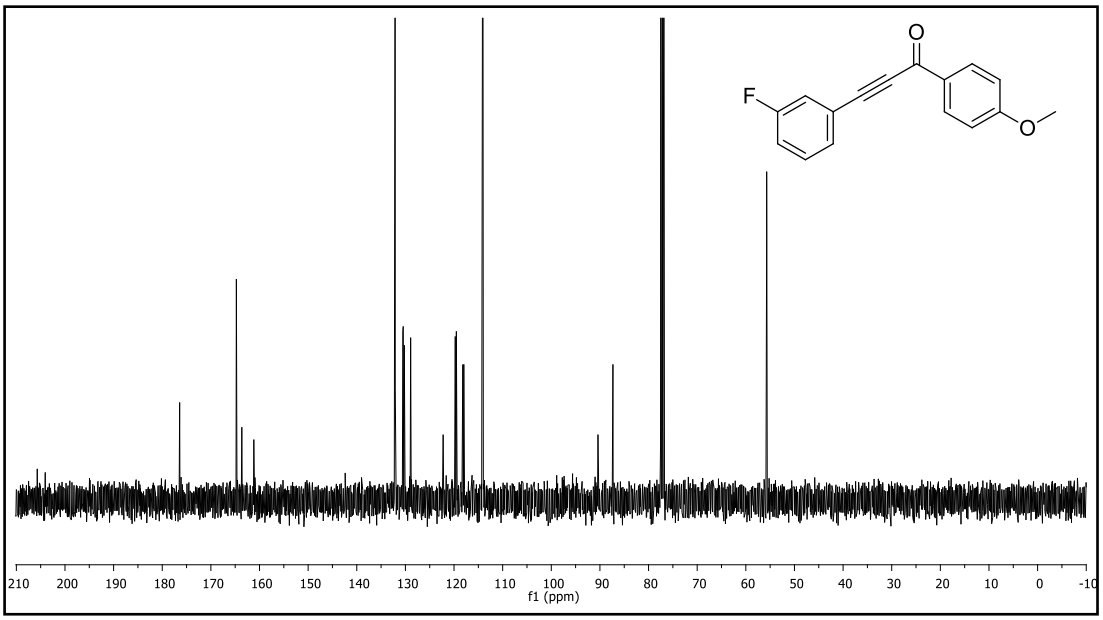

Figure 48. ^{13}C NMR spectrum of compound **41M**.

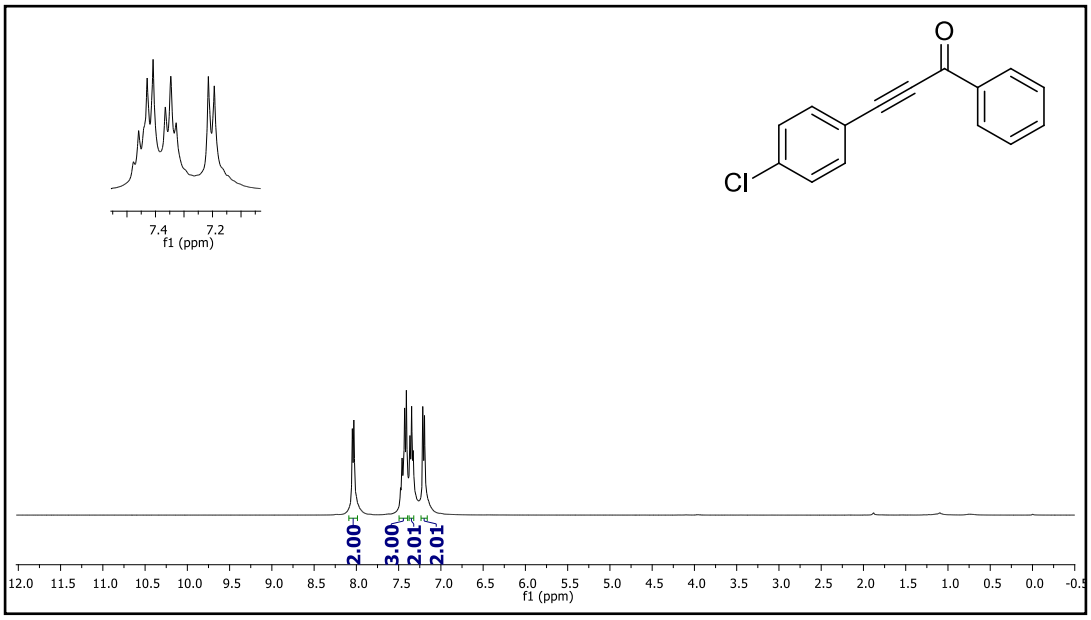

Figure 49. ^{1}H NMR spectrum of compound **41N**.

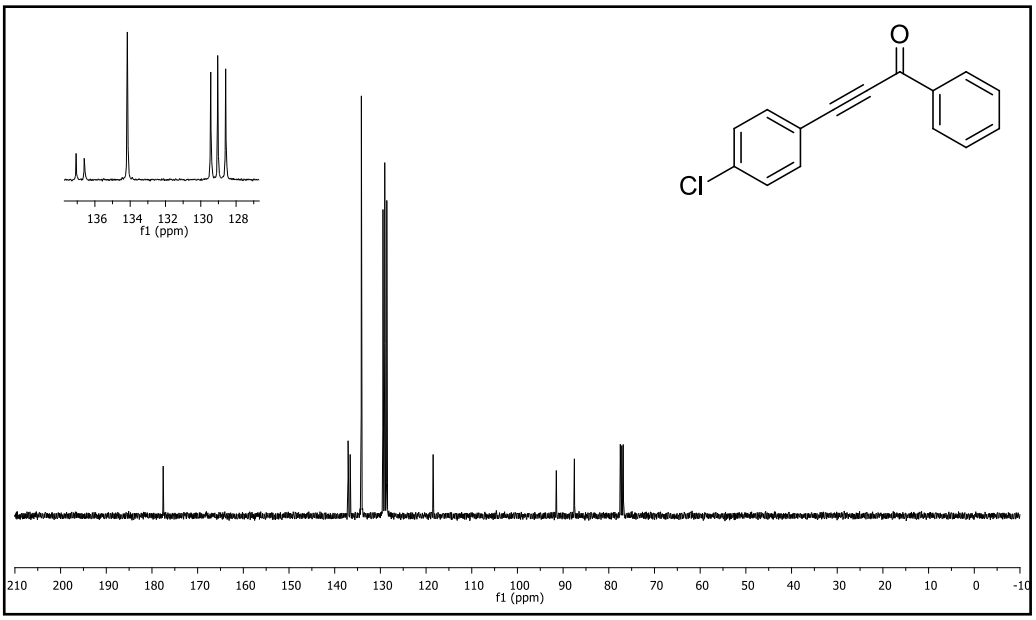

Figure 50. ^{13}C NMR spectrum of compound **41N**.

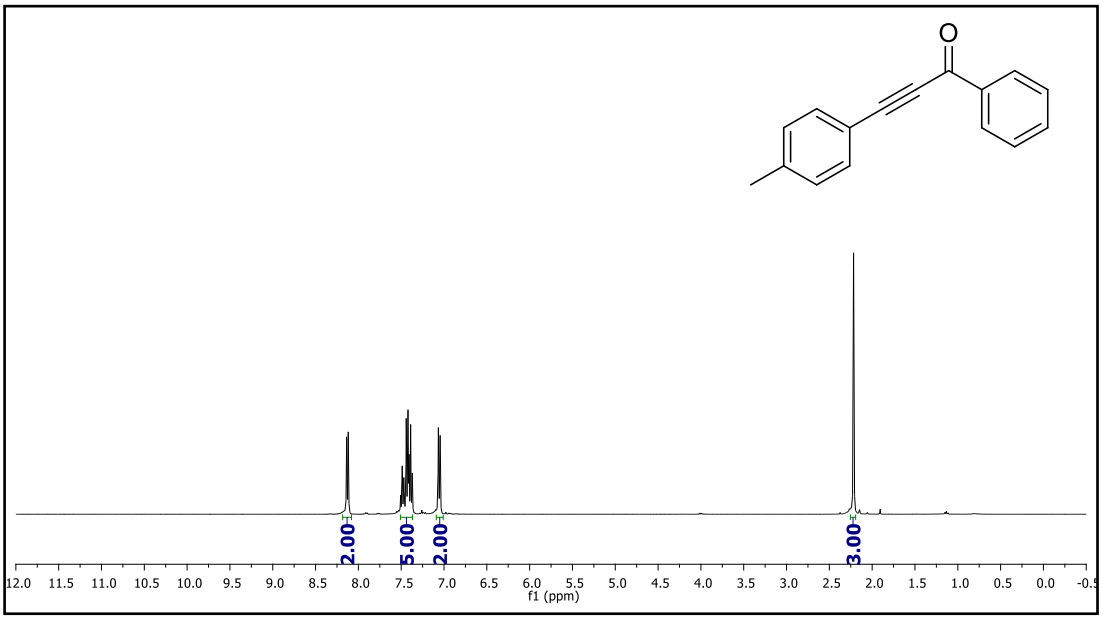

Figure 51. ^{1}H NMR spectrum of compound **41O**.

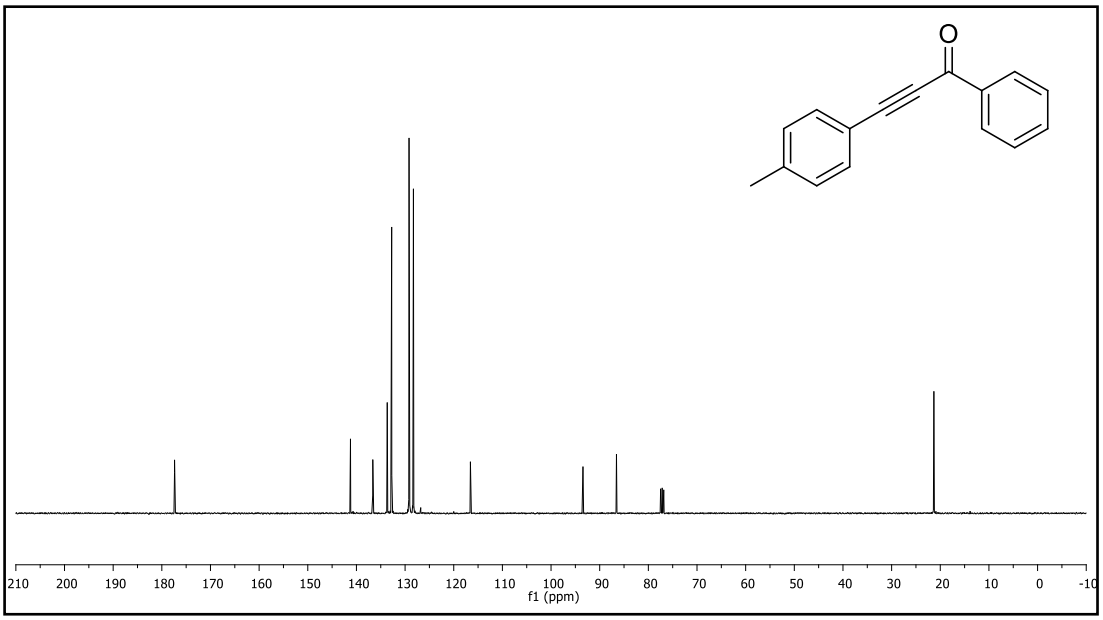

Figure 52. ^{13}C NMR spectrum of compound **41O**.

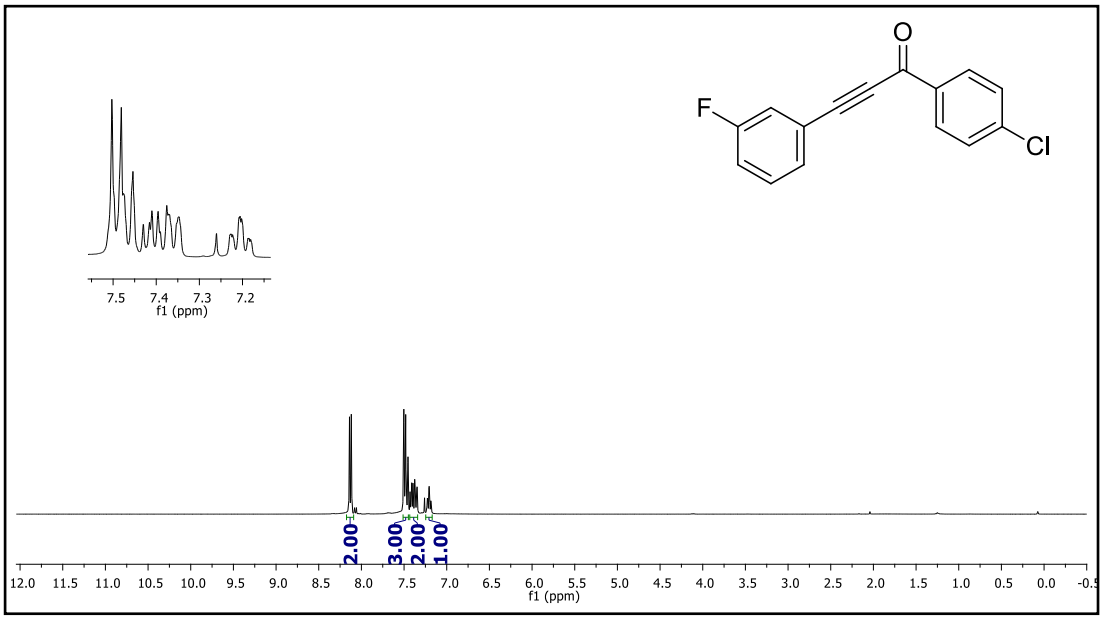

Figure 53. ^{1}H NMR spectrum of compound **41P**.

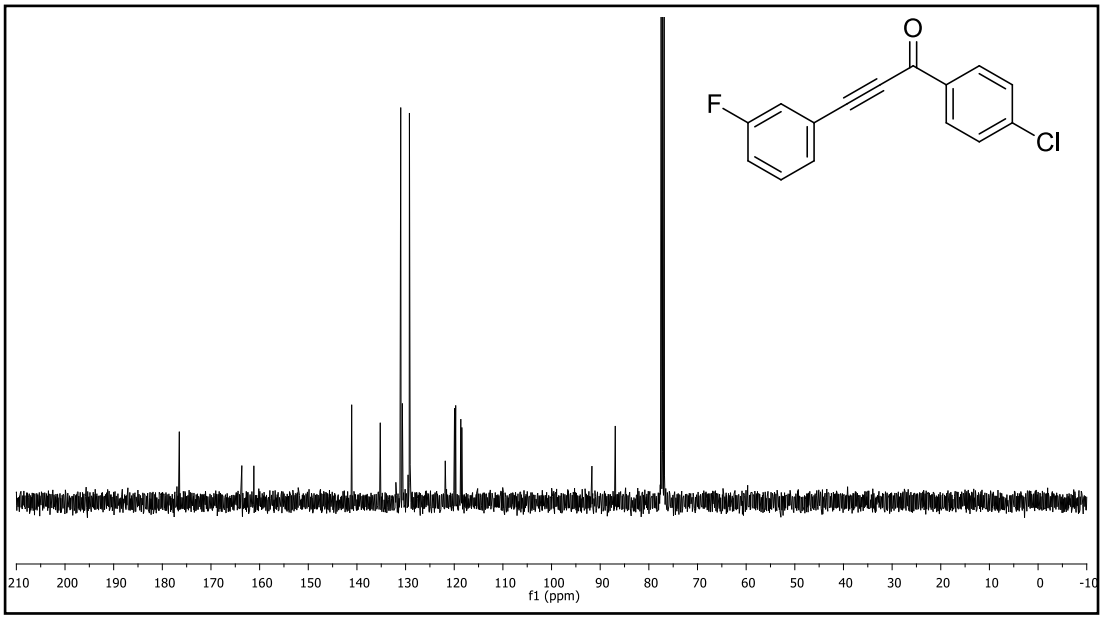

Figure 54. ^{13}C NMR spectrum of compound **41P**.

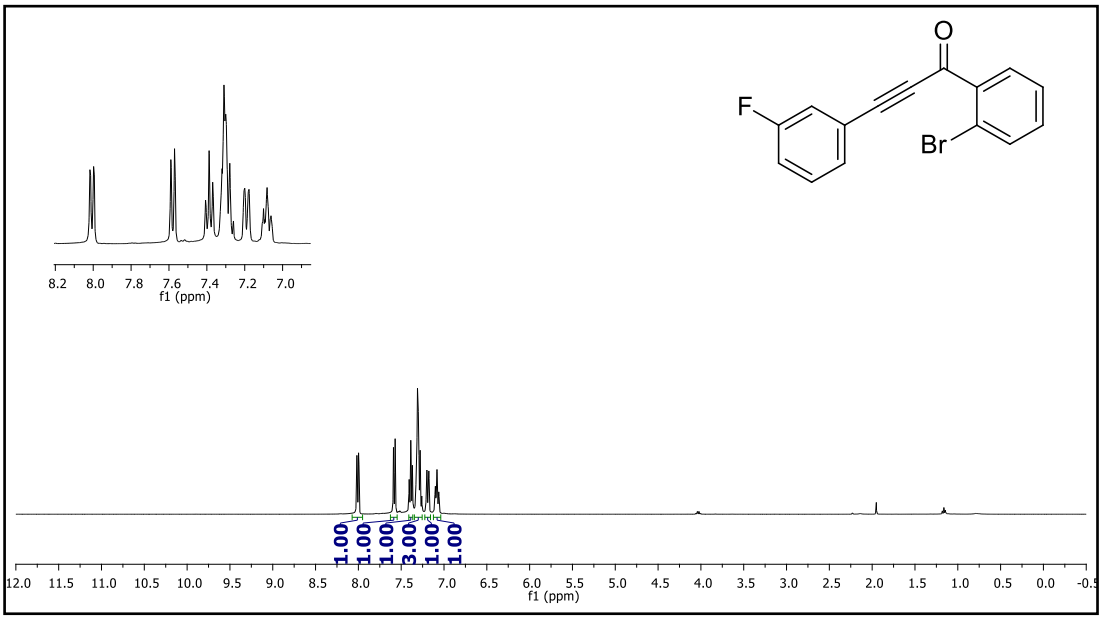

Figure 55. ^{1}H NMR spectrum of compound **41Q**.

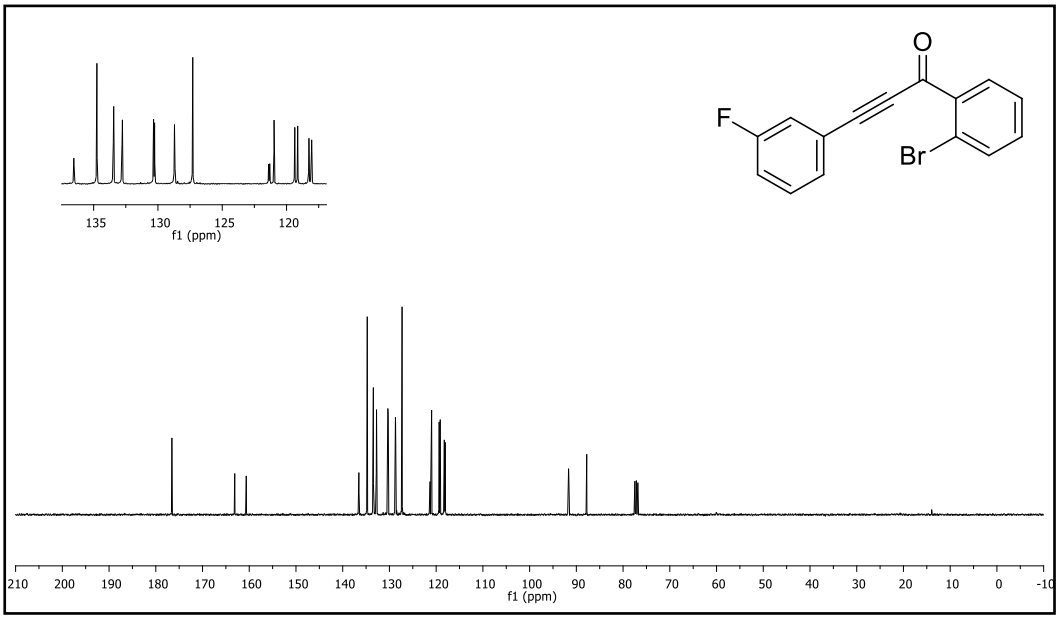

Figure 56. ^{13}C NMR spectrum of compound **41Q**.

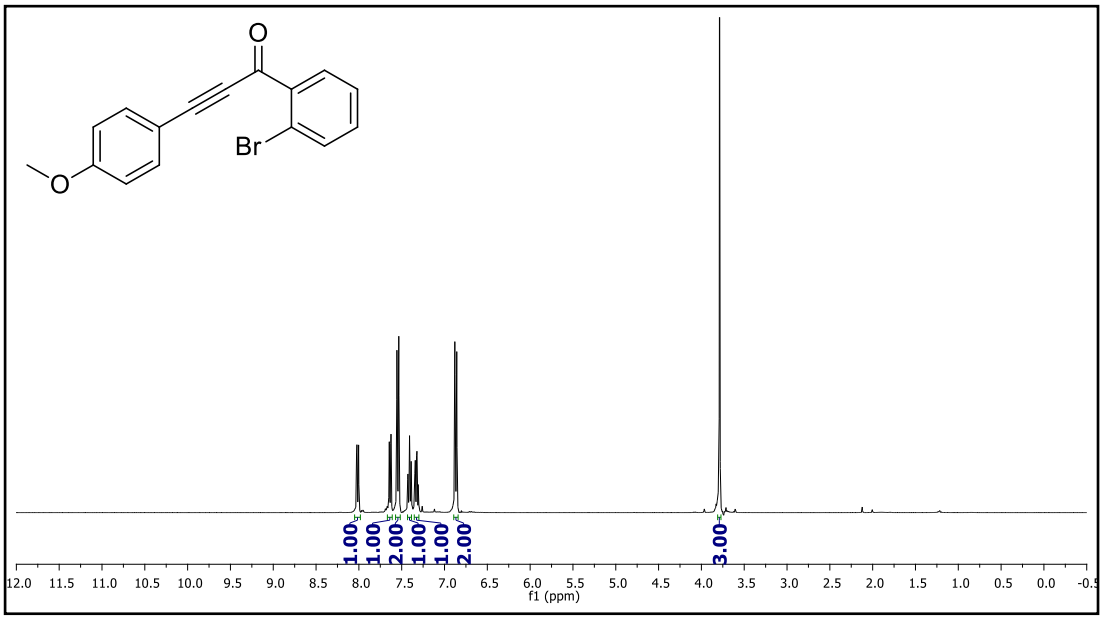

Figure 57. ^{1}H NMR spectrum of compound **41R**.

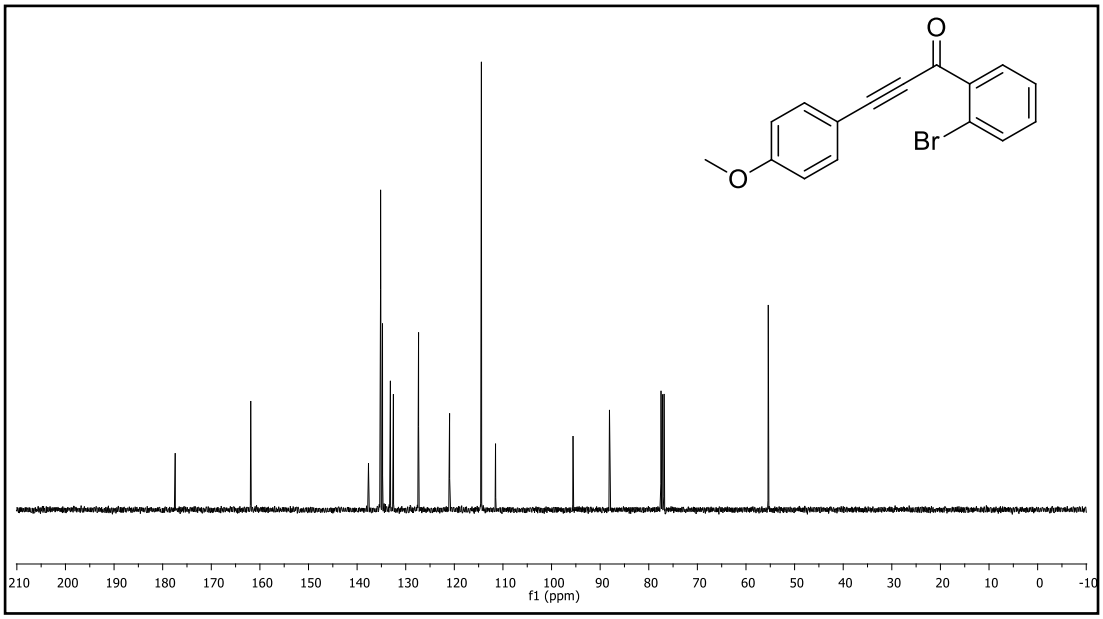

Figure 58. ^{13}C NMR spectrum of compound **41R**.

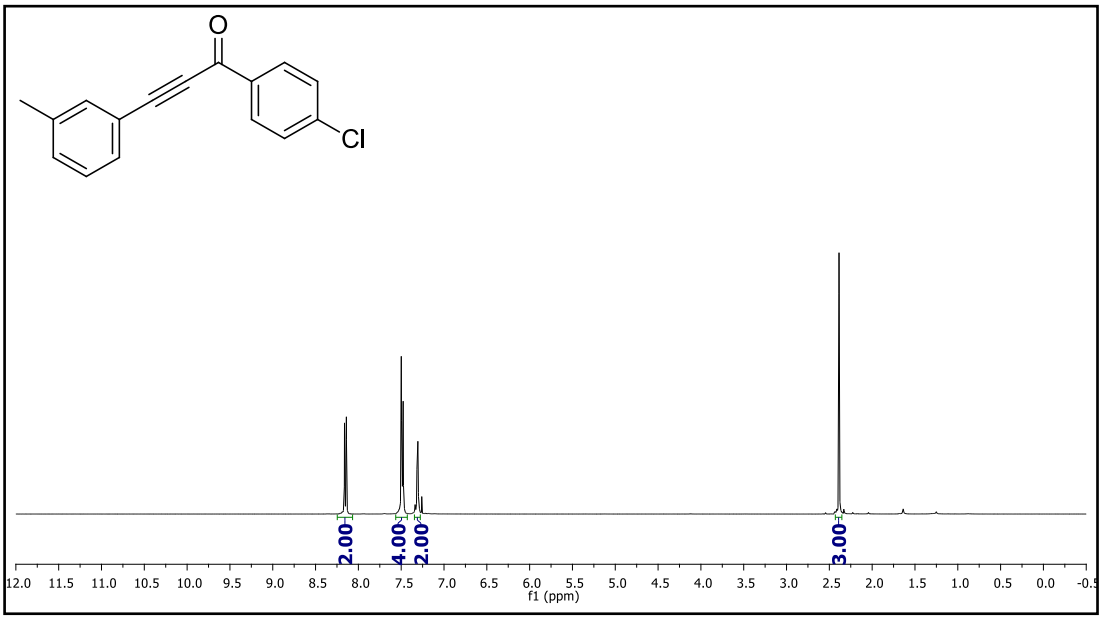

Figure 59. ^{1}H NMR spectrum of compound **41S**.

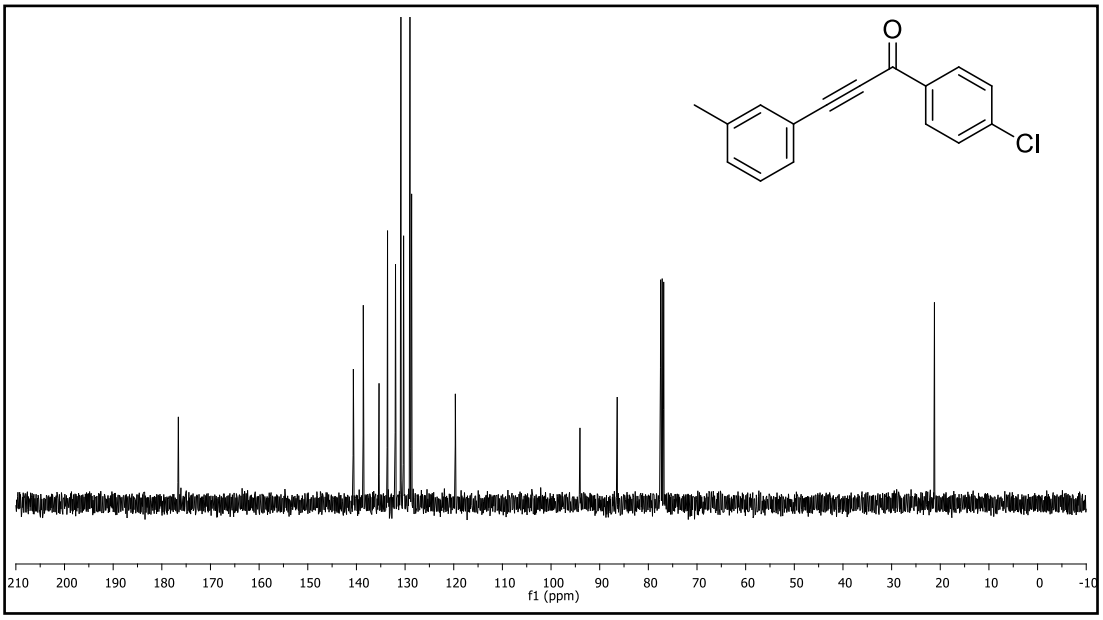

Figure 60. ^{13}C NMR spectrum of compound **41S**.

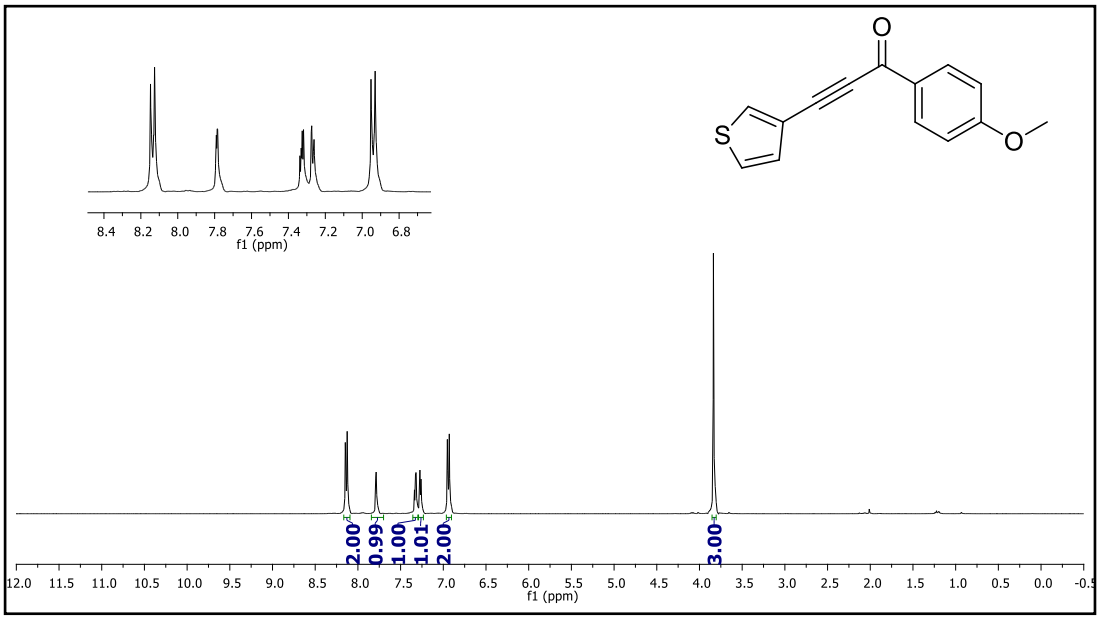

Figure 61. ^{1}H NMR spectrum of compound **41T**.

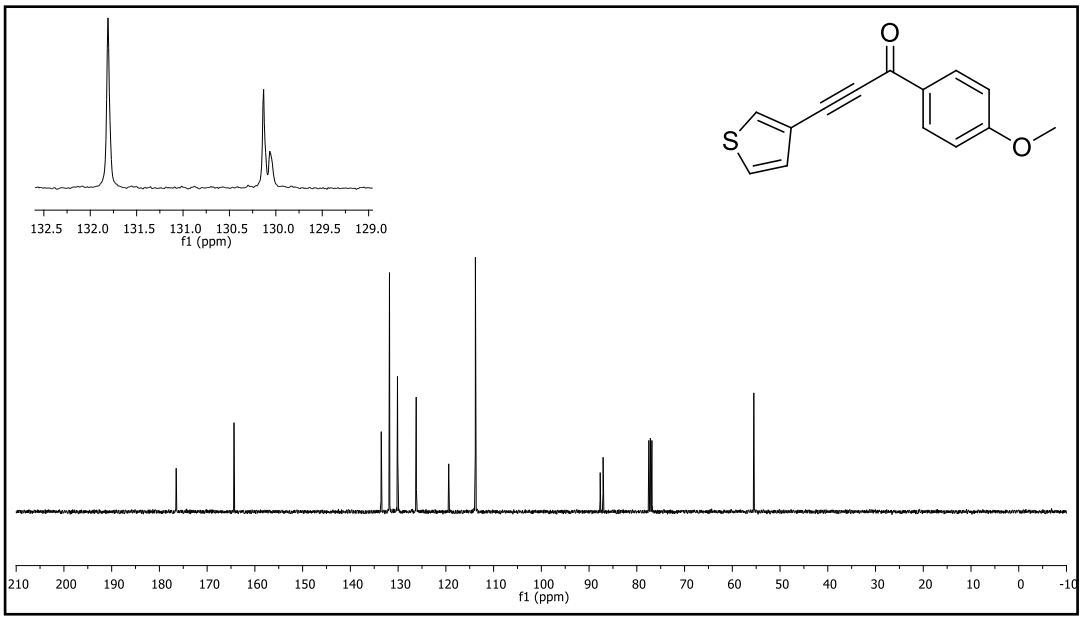

Figure 62. ^{13}C NMR spectrum of compound **41T**.

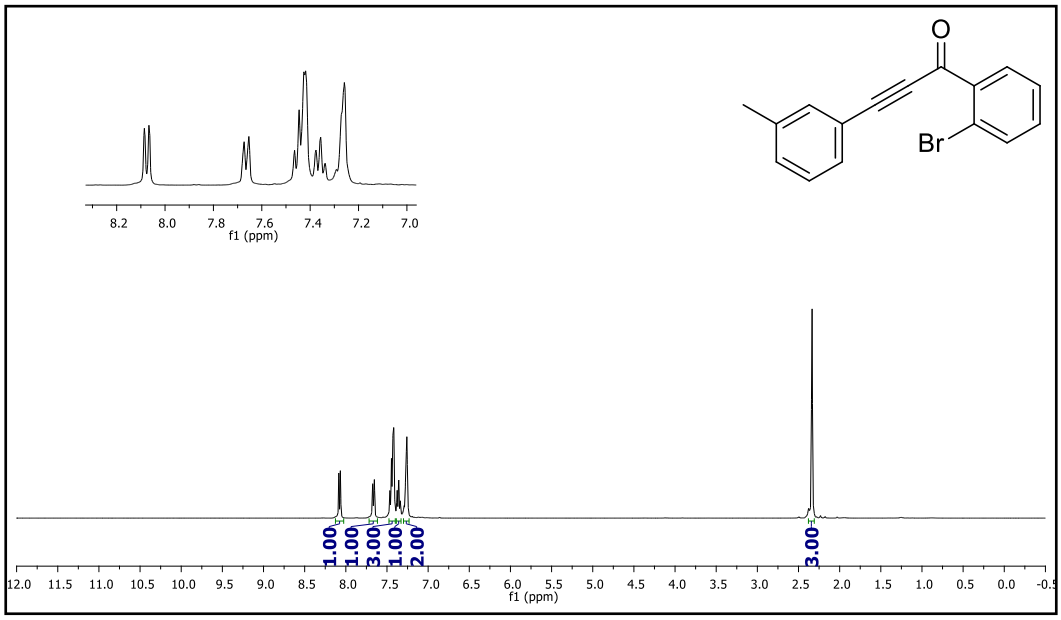

Figure 63. ^{1}H NMR spectrum of compound **41U**.

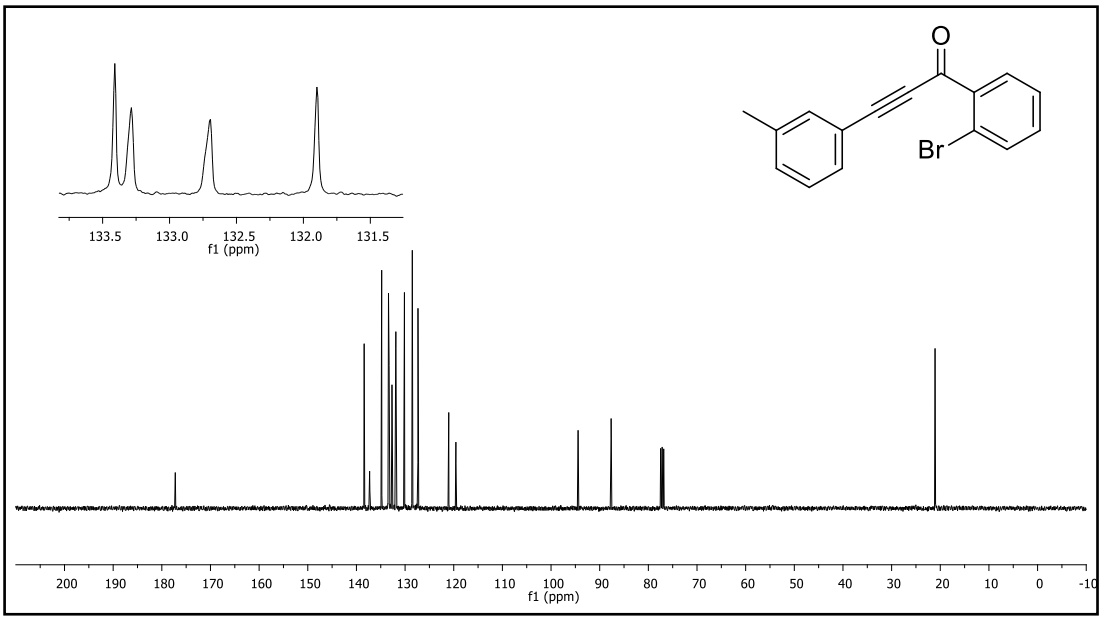

Figure 64. ^{13}C NMR spectrum of compound **41U**.

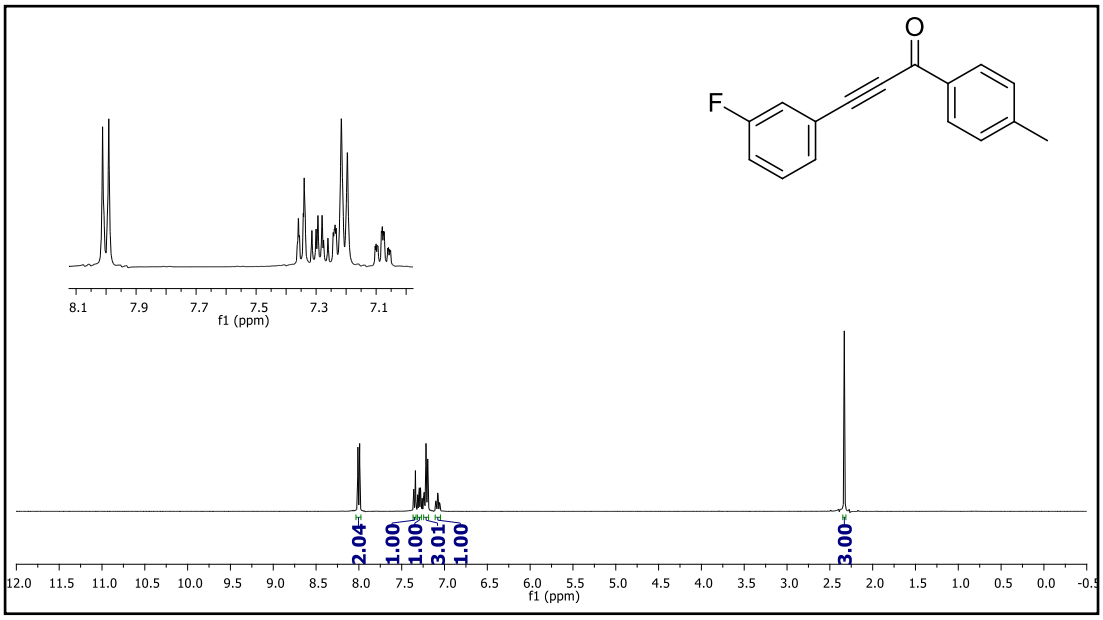

Figure 65. ^{1}H NMR spectrum of compound **41V**.

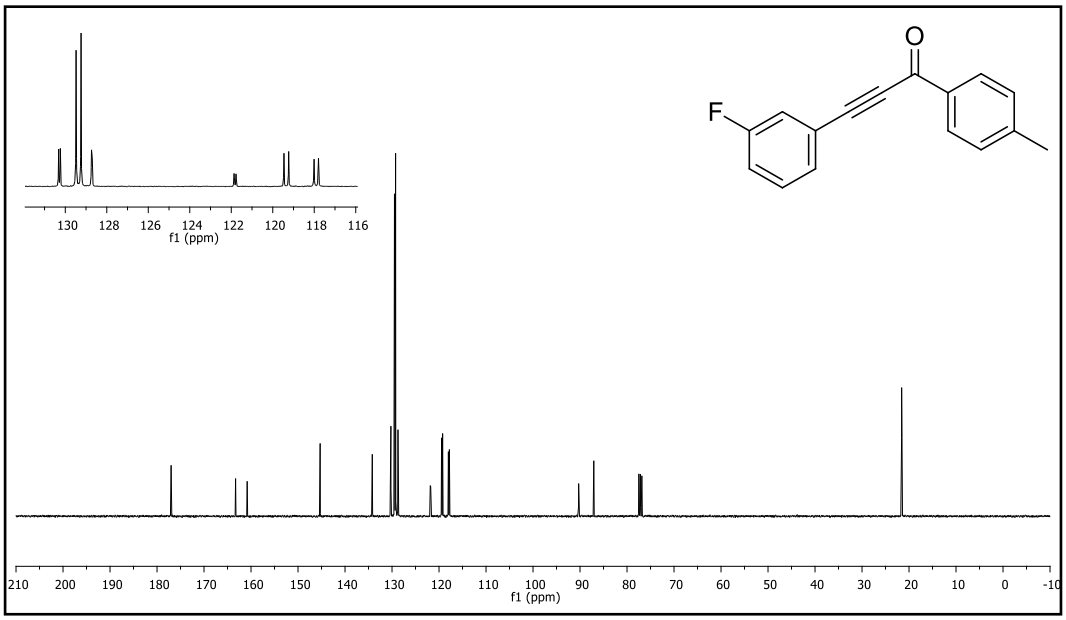

Figure 66. ^{13}C NMR spectrum of compound **41V**.

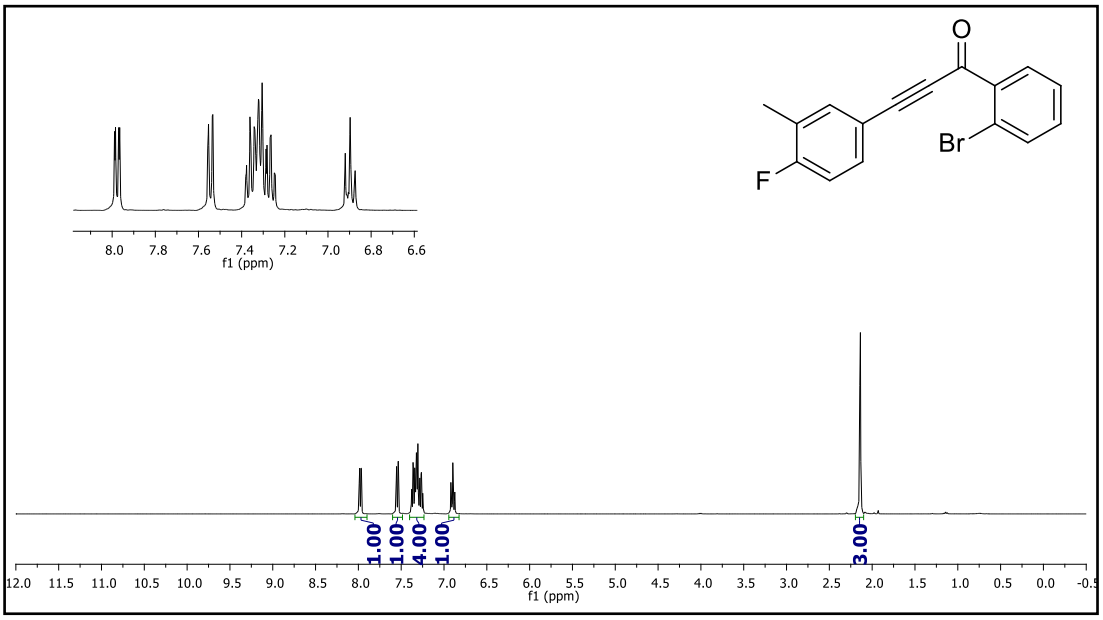

Figure 67. ^{1}H NMR spectrum of compound **41W**.

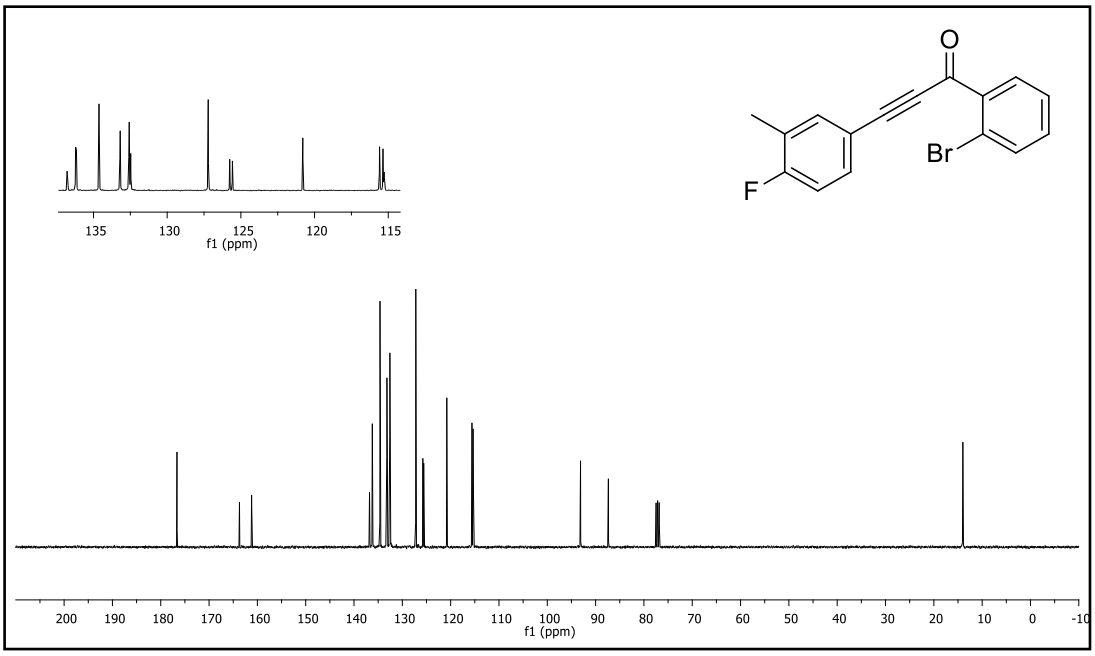

Figure 68. ^{13}C NMR spectrum of compound **41W**.

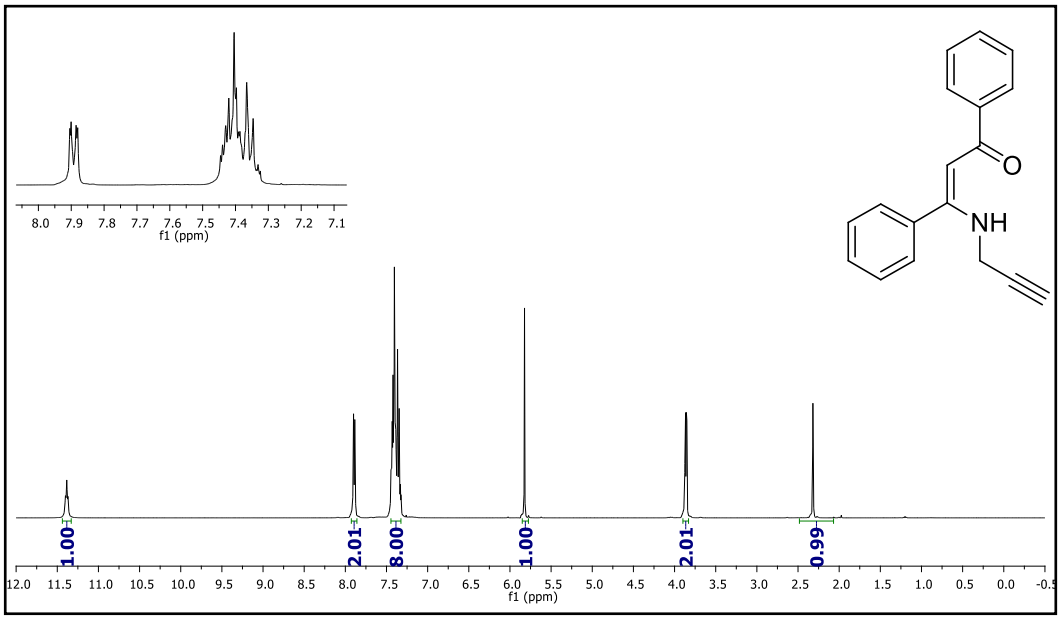

Figure 69. ^{1}H NMR spectrum of compound **13A**.

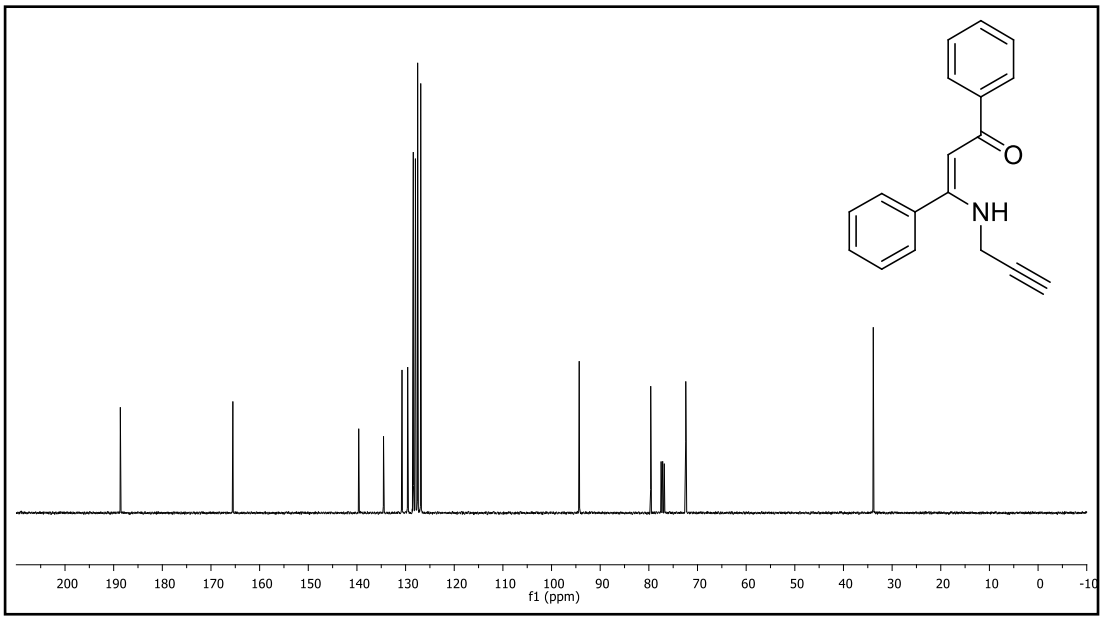

Figure 70. ^{13}C NMR spectrum of compound **13A**.

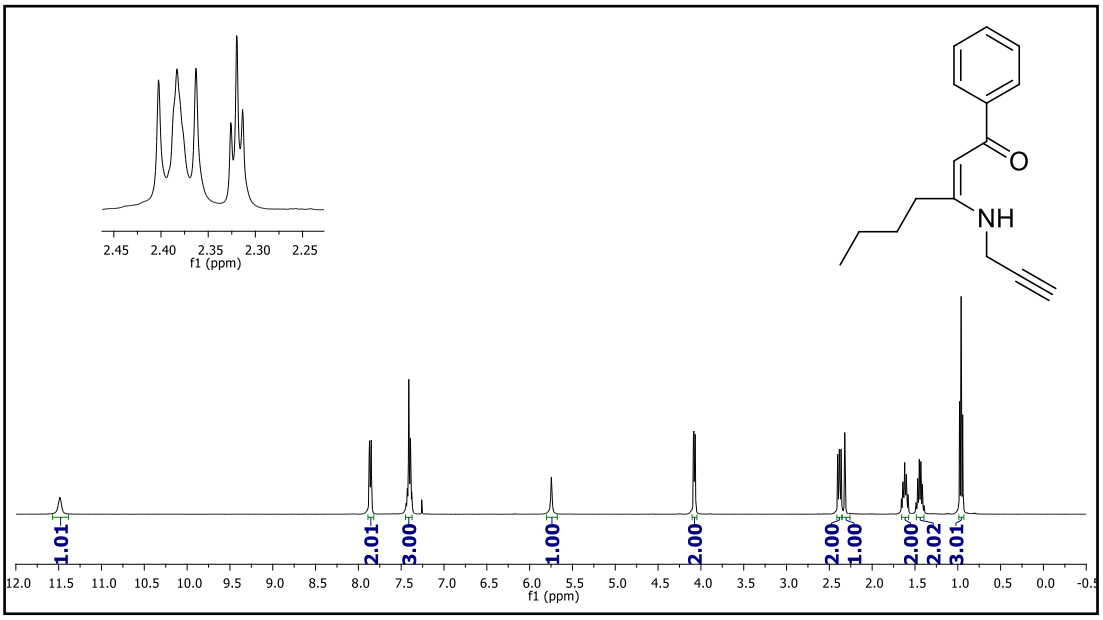

Figure 71. [1] H NMR spectrum of compound **13B**.

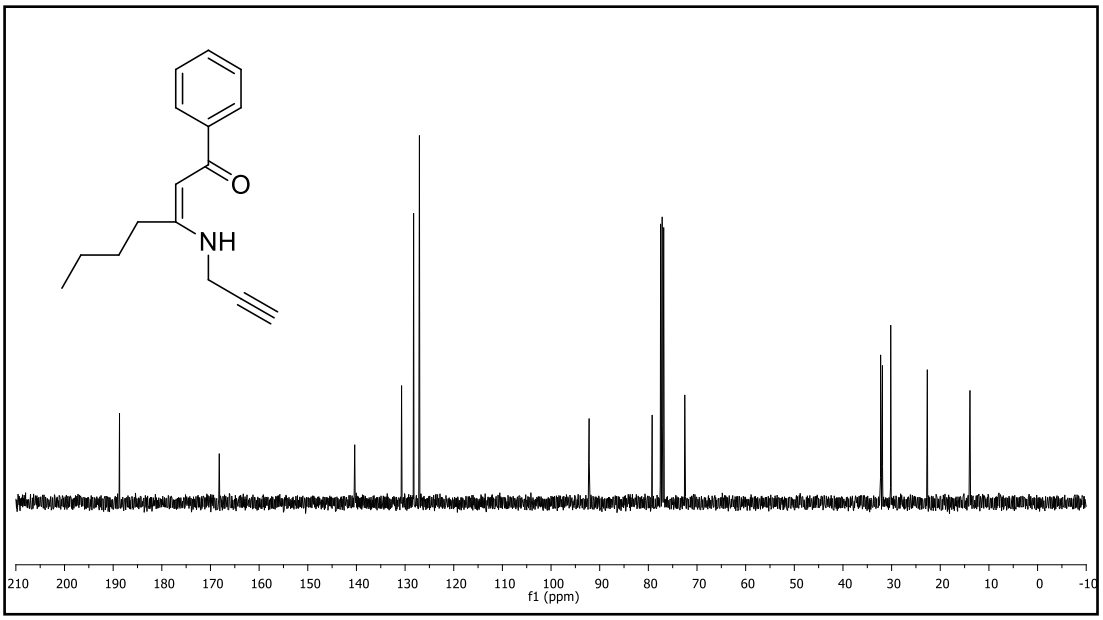

Figure 72. [13]C NMR spectrum of compound **13B**.

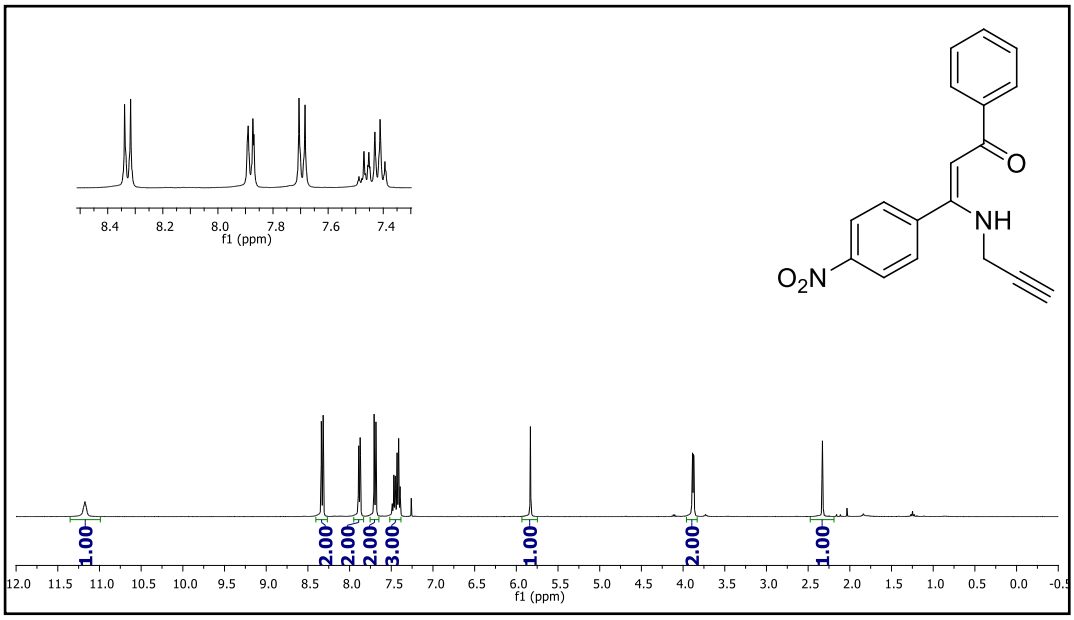

Figure 73. ^{1}H NMR spectrum of compound **13C**.

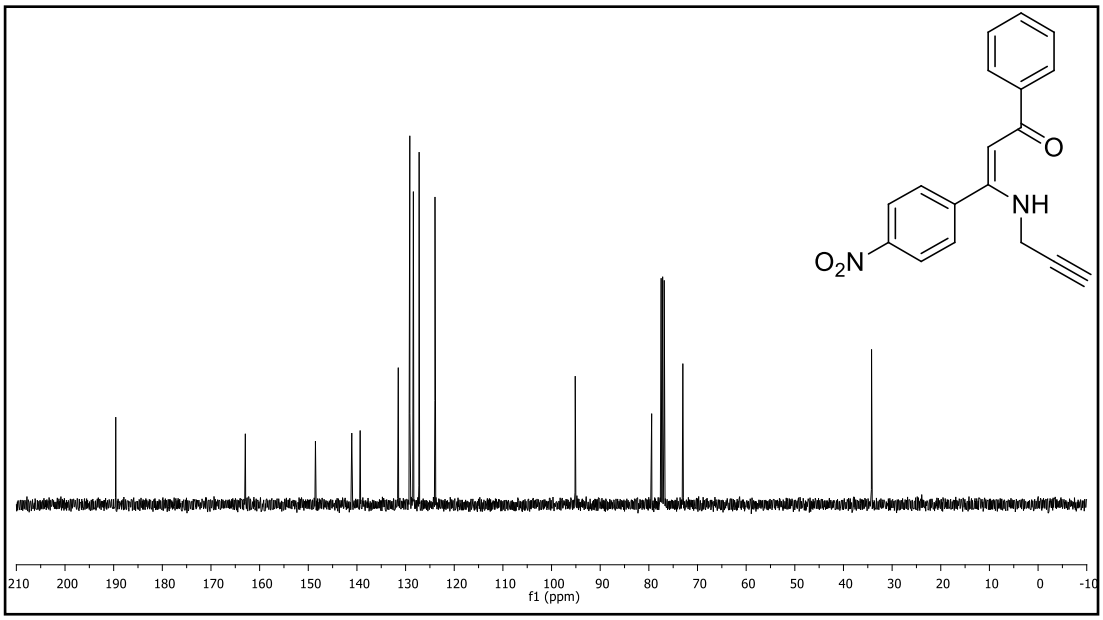

Figure 74. ^{13}C NMR spectrum of compound **13C**.

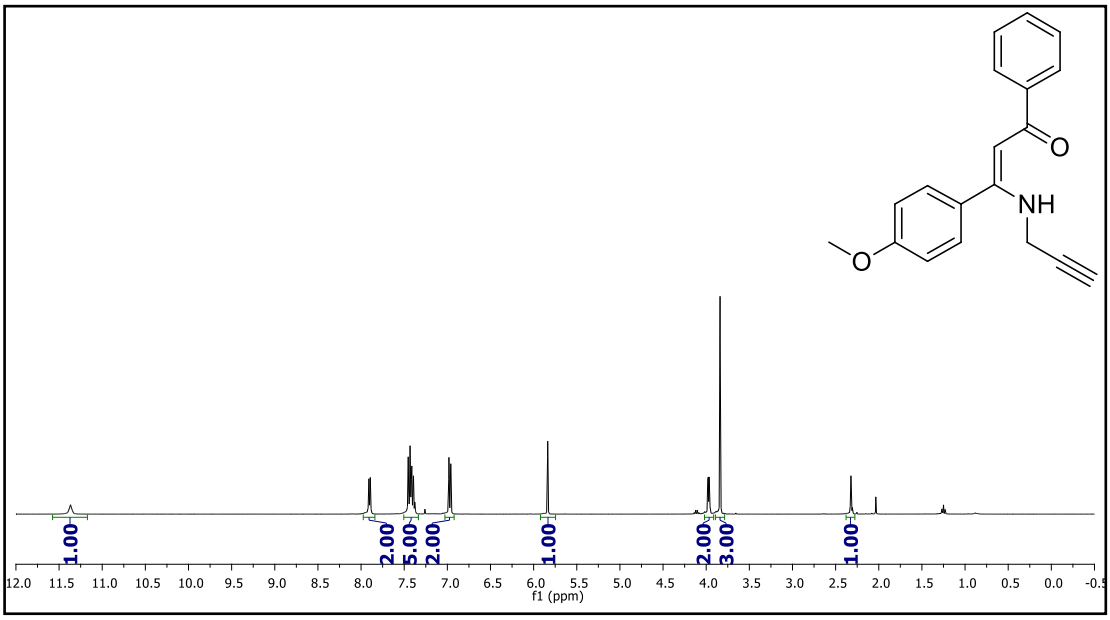

Figure 75. ^{1}H NMR spectrum of compound **13D**.

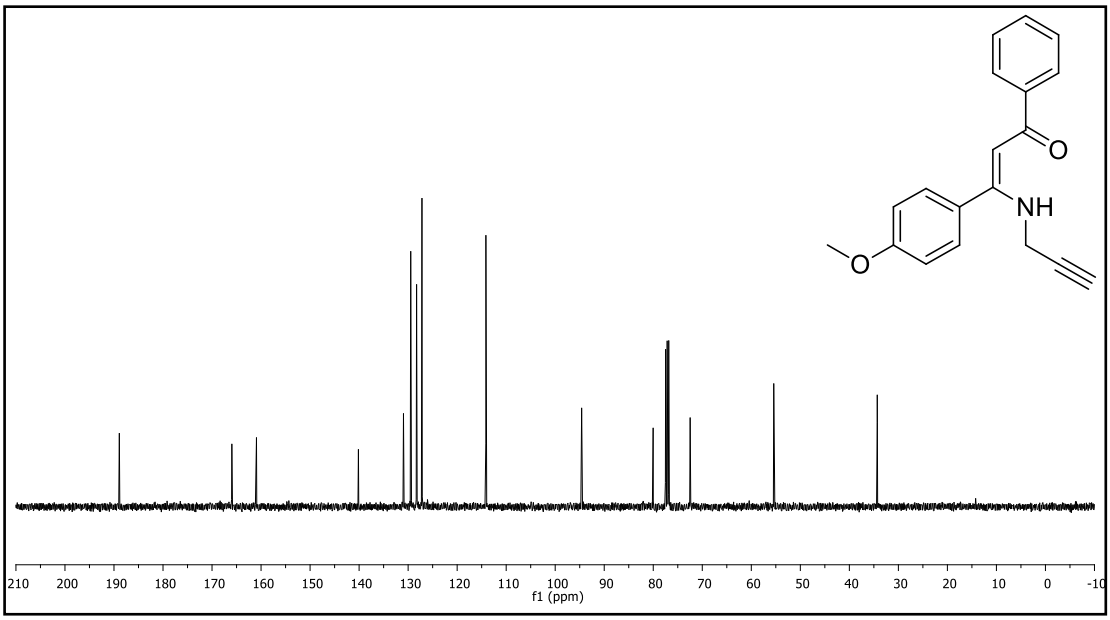

Figure 76. ^{13}C NMR spectrum of compound **13D**.

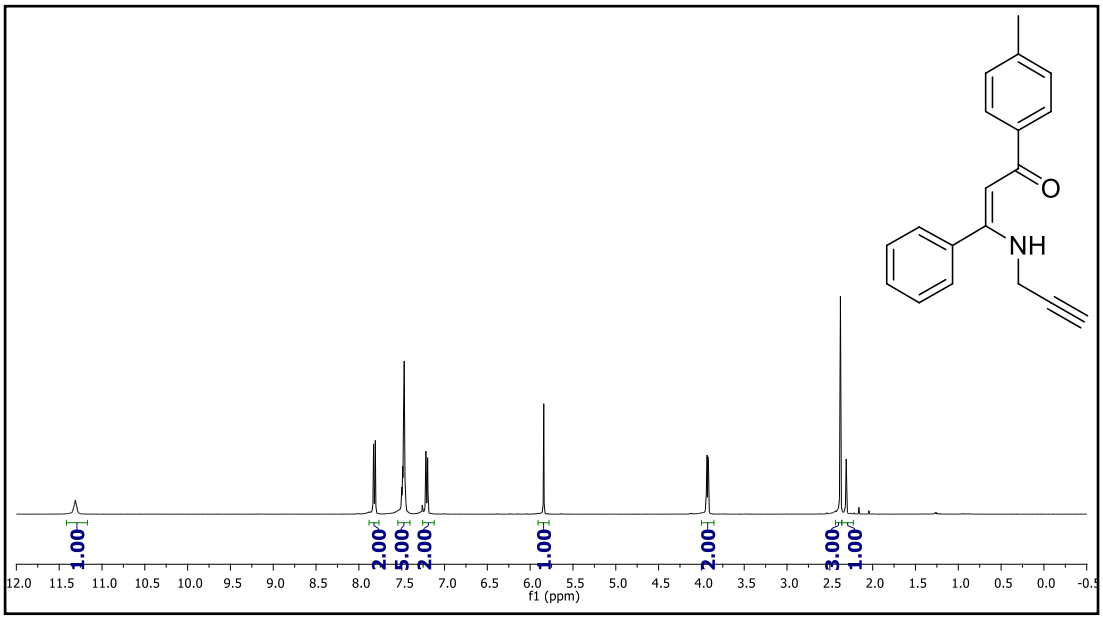

Figure 77. ^{1}H NMR spectrum of compound **13E**.

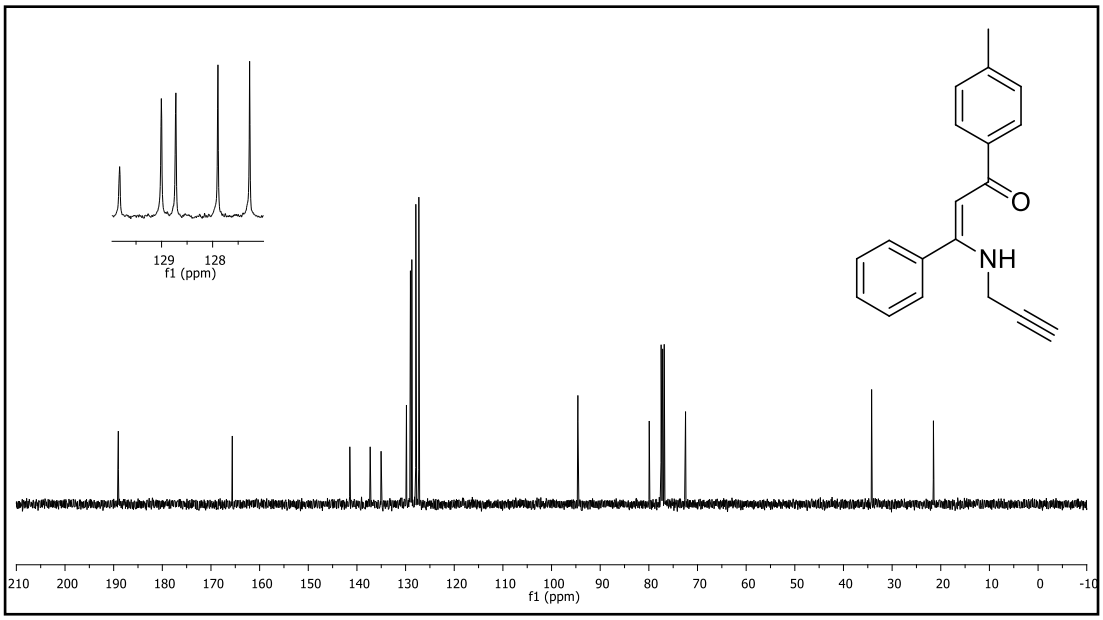

Figure 78. ^{13}C NMR spectrum of compound **13E**.

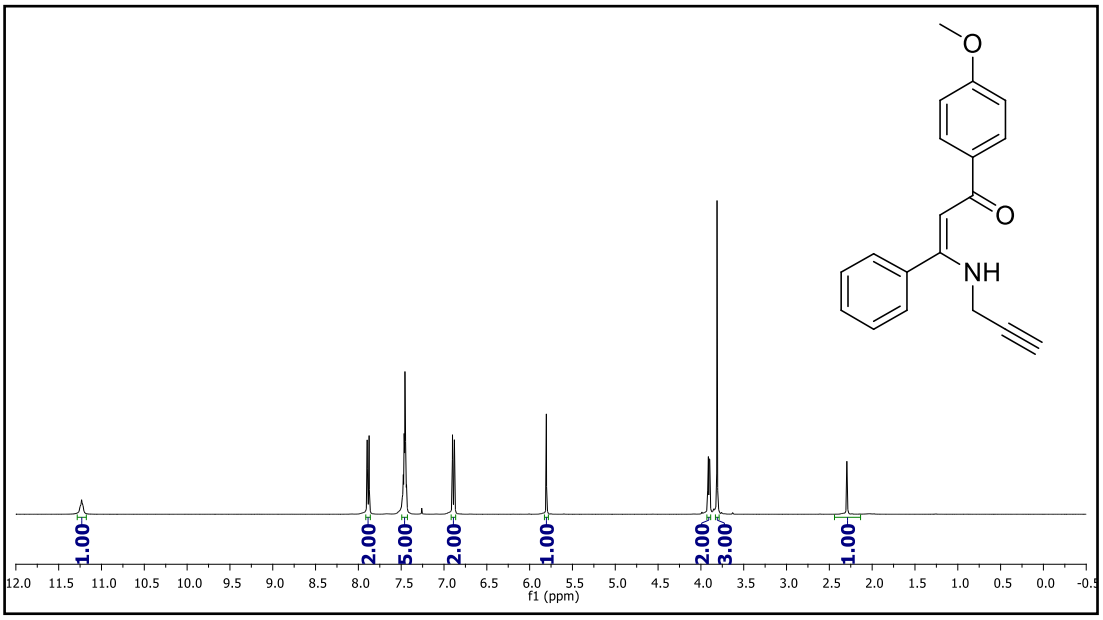

Figure 79. ^{1}H NMR spectrum of compound **13F**.

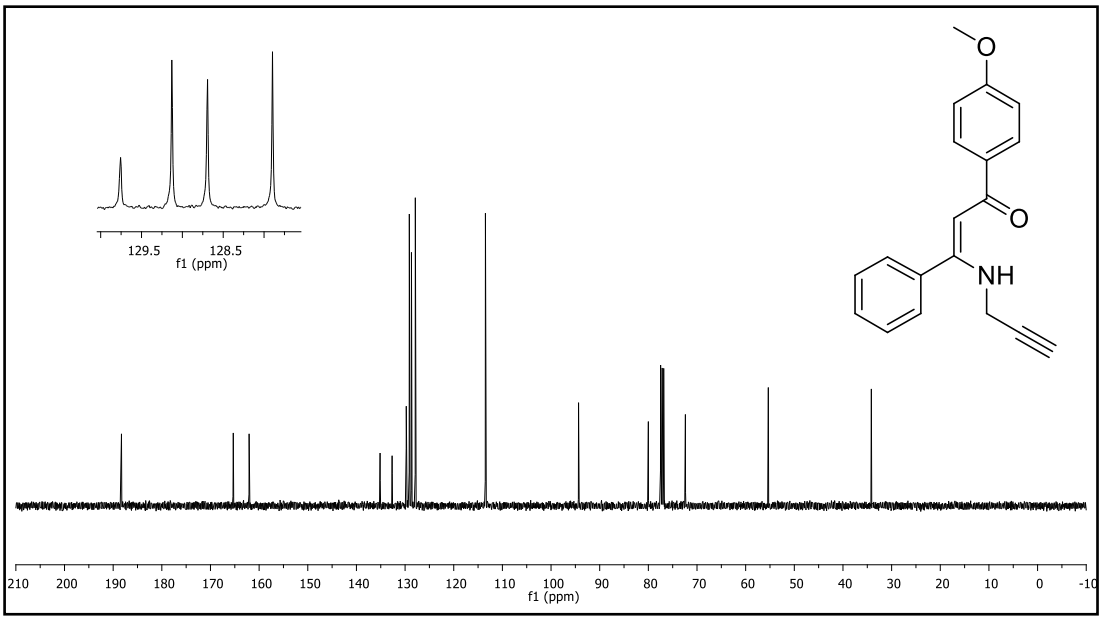

Figure 80. ^{13}C NMR spectrum of compound **13F**.

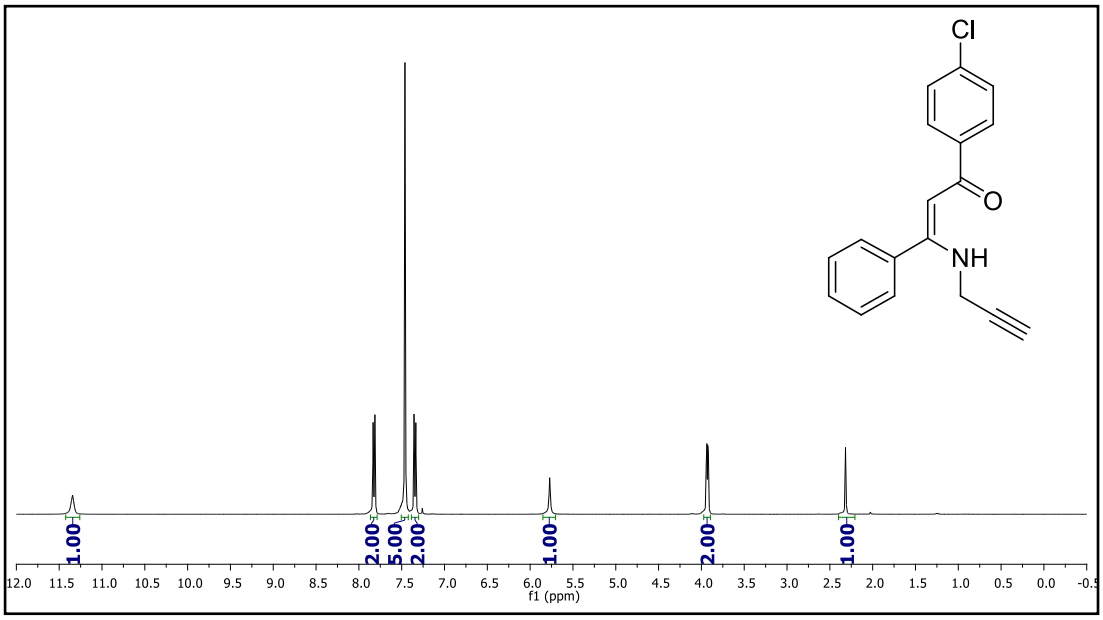

Figure 81. ^{1}H NMR spectrum of compound **13G**.

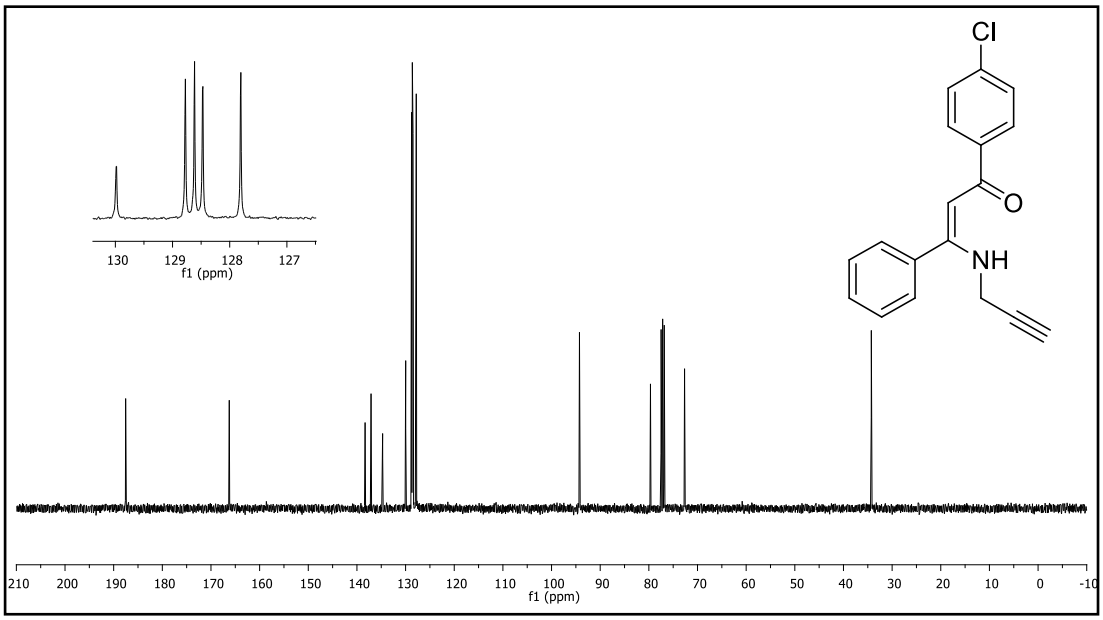

Figure 82. ^{13}C NMR spectrum of compound **13G**.

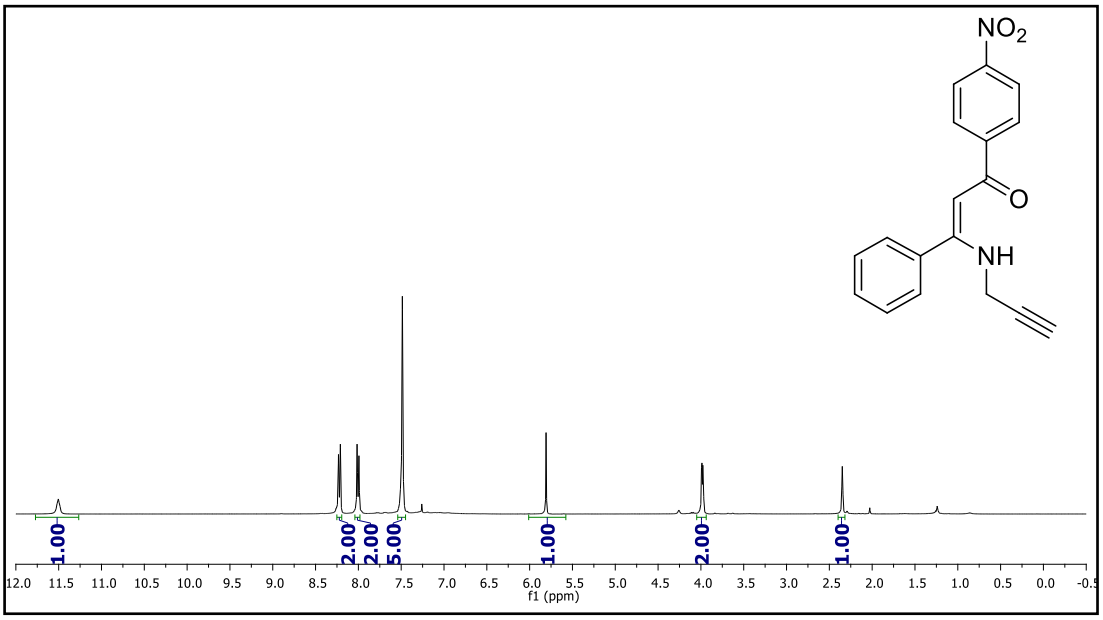

Figure 83. ^{1}H NMR spectrum of compound **13H**.

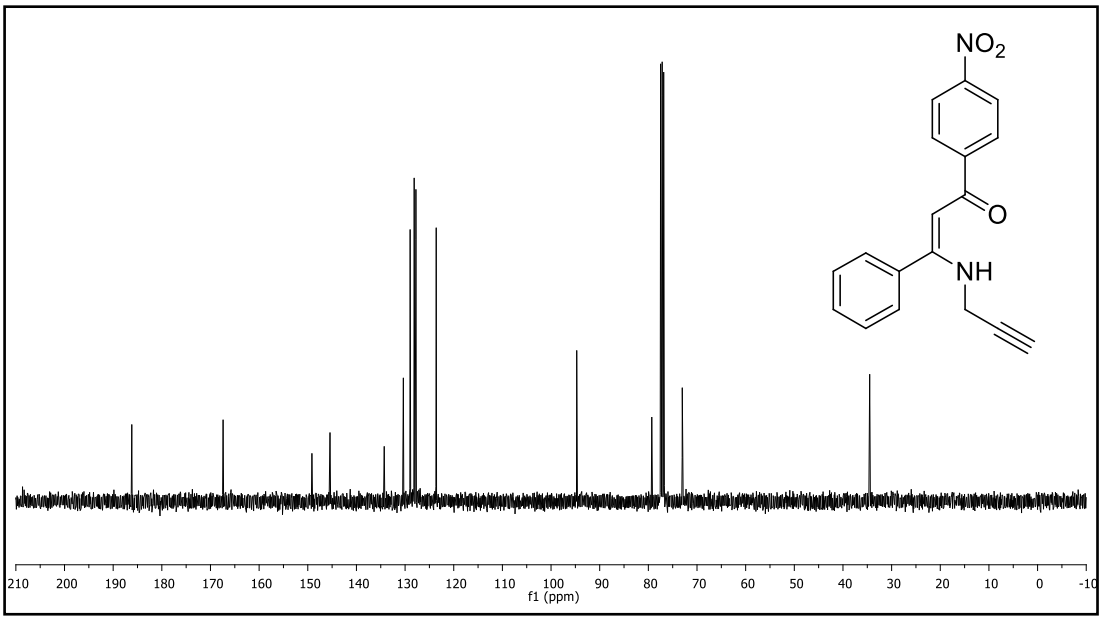

Figure 84. ^{13}C NMR spectrum of compound **13H**.

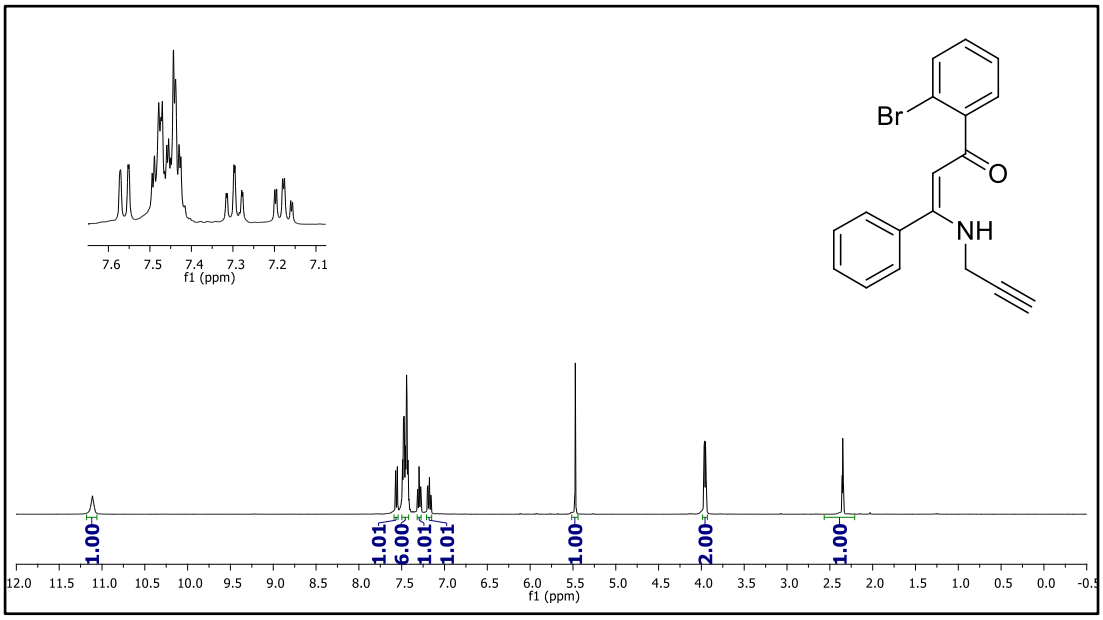

Figure 85. ^{1}H NMR spectrum of compound **13I**.

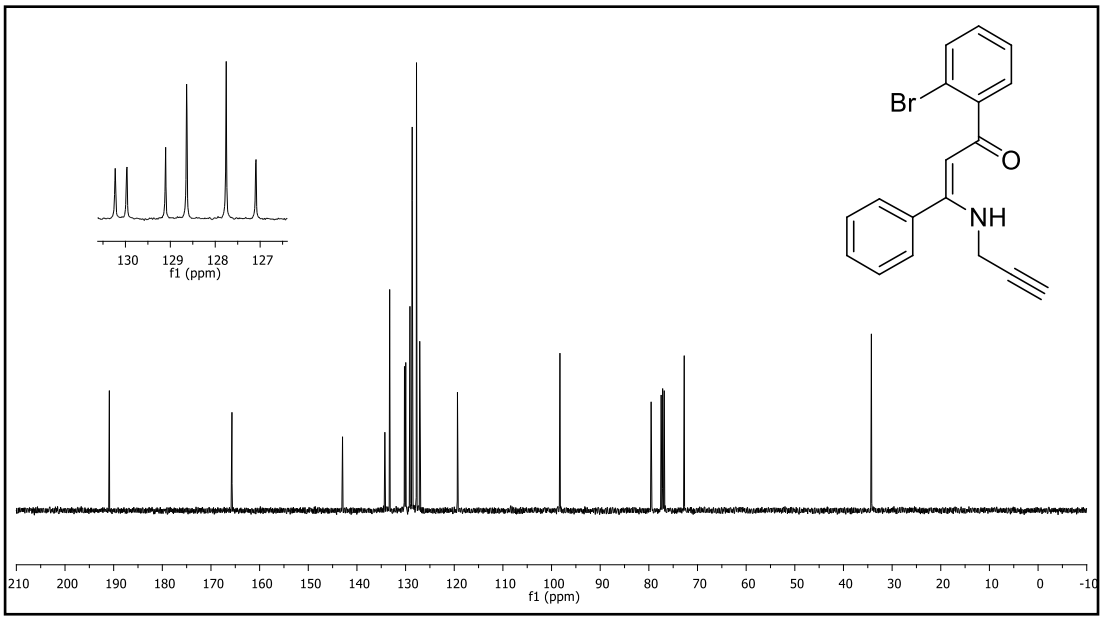

Figure 86. ^{13}C NMR spectrum of compound **13I**.

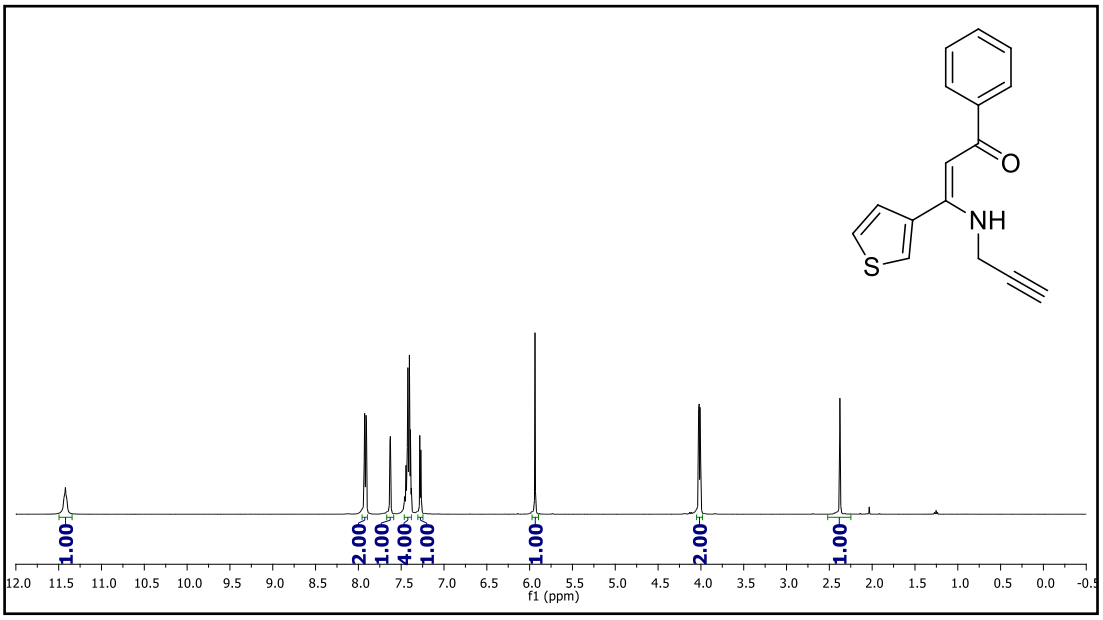

Figure 87. ^{1}H NMR spectrum of compound **13J**.

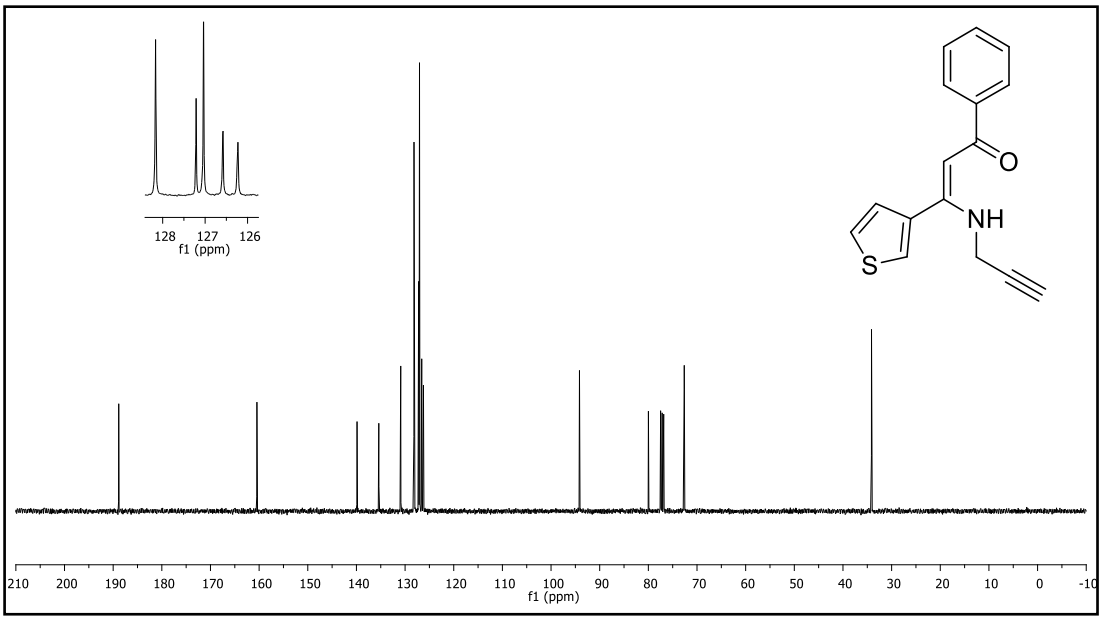

Figure 88. ^{13}C NMR spectrum of compound **13J**.

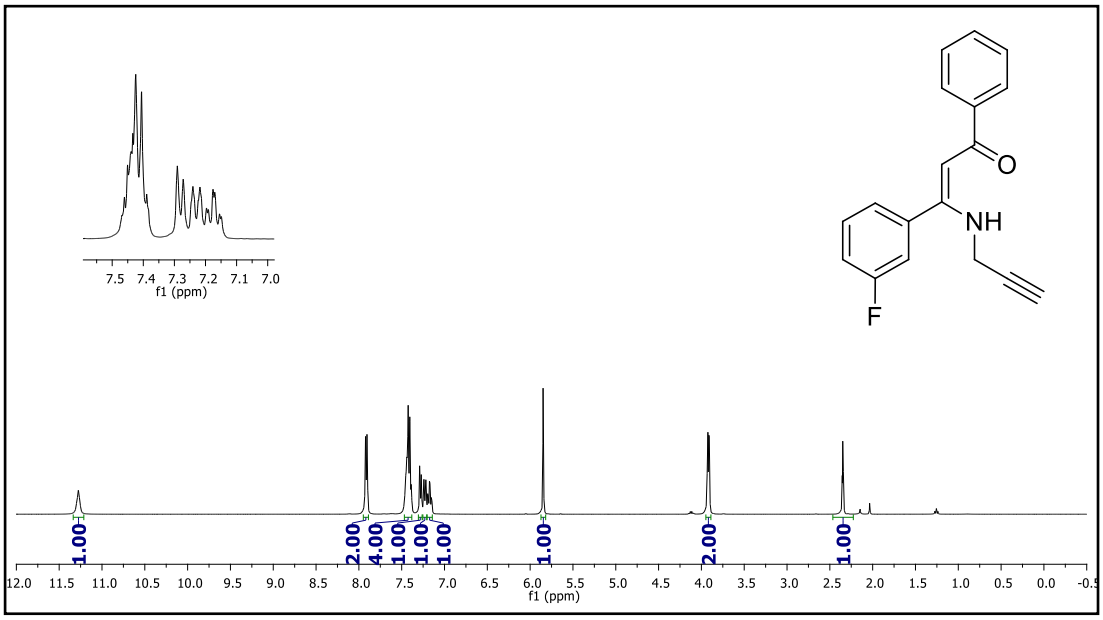

Figure 89. ^{1}H NMR spectrum of compound **13K**.

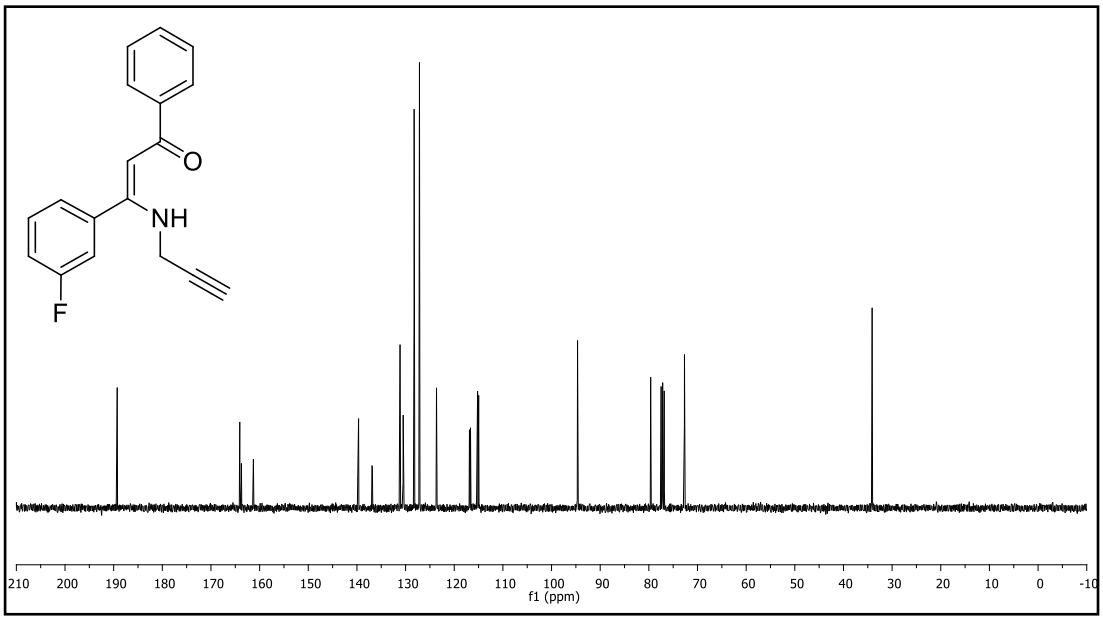

Figure 90. ^{13}C NMR spectrum of compound **13K**.

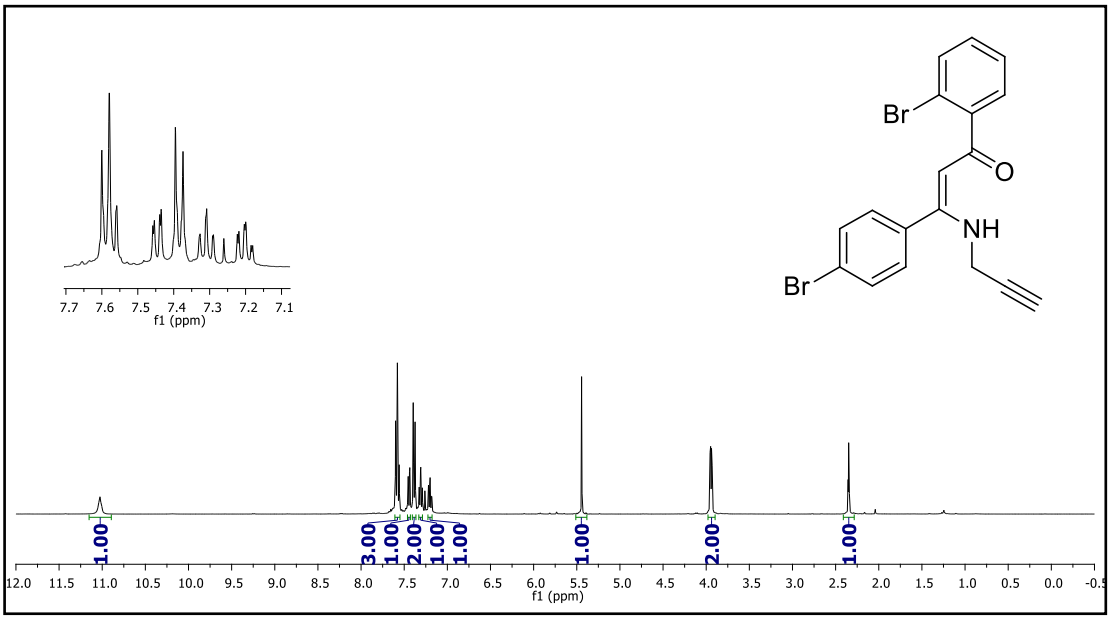

Figure 91. ^{1}H NMR spectrum of compound **13L**.

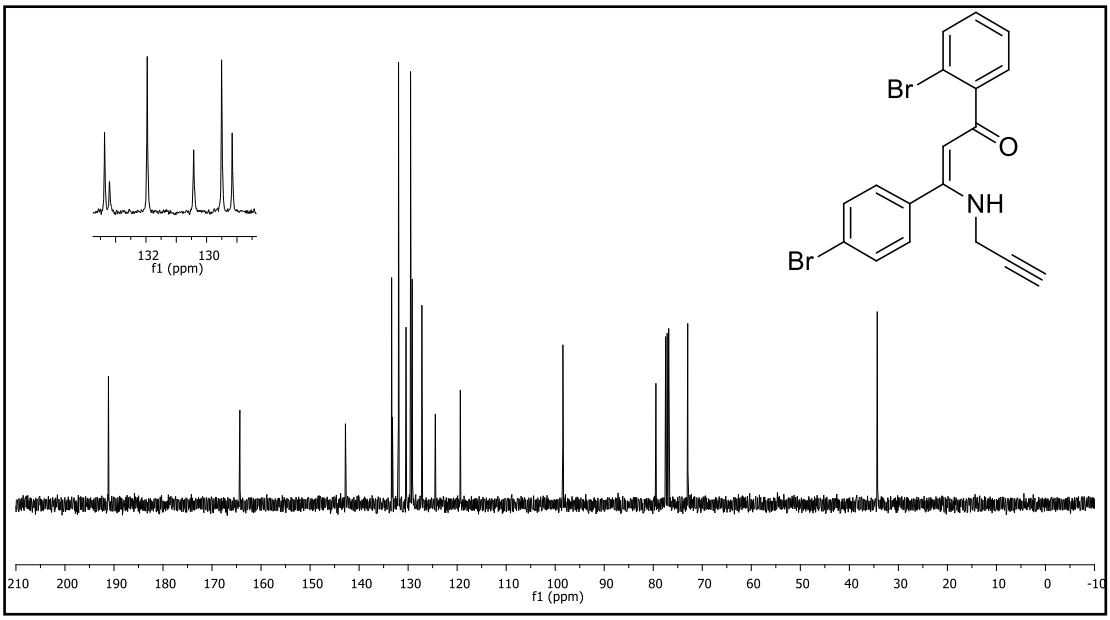

Figure 92. ^{13}C NMR spectrum of compound **13L**.

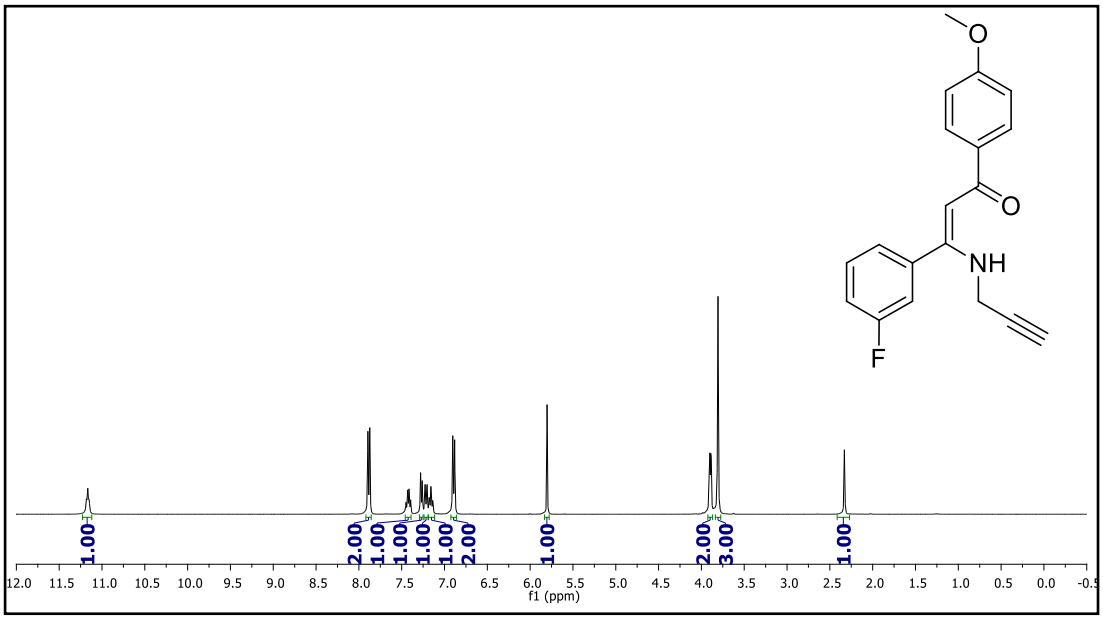

Figure 93. ^{1}H NMR spectrum of compound **13M**.

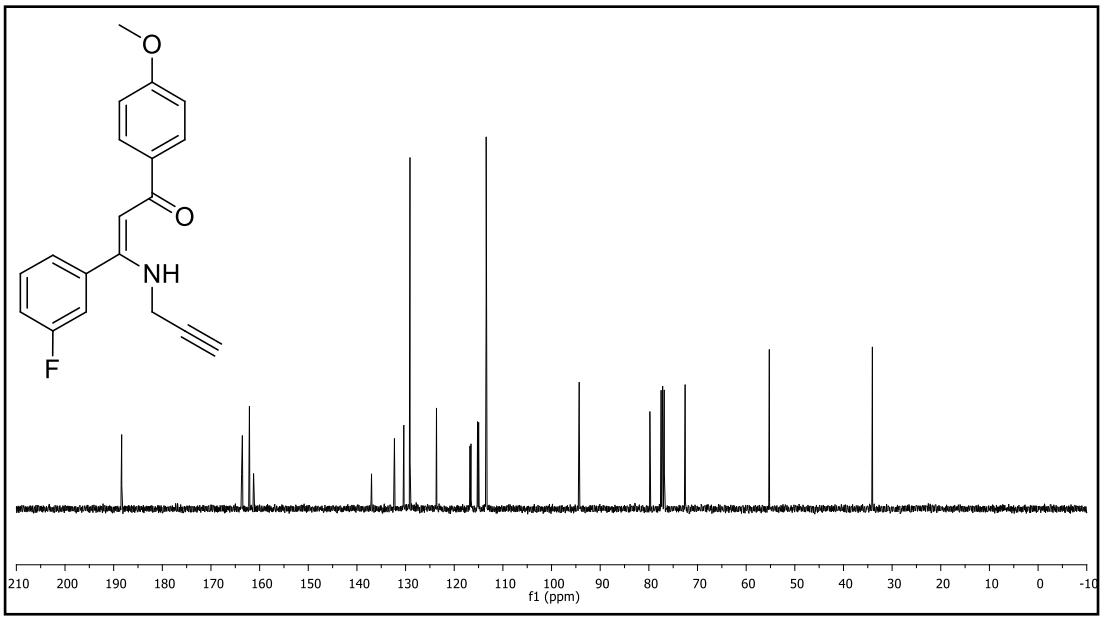

Figure 94. ^{13}C NMR spectrum of compound **13M**.

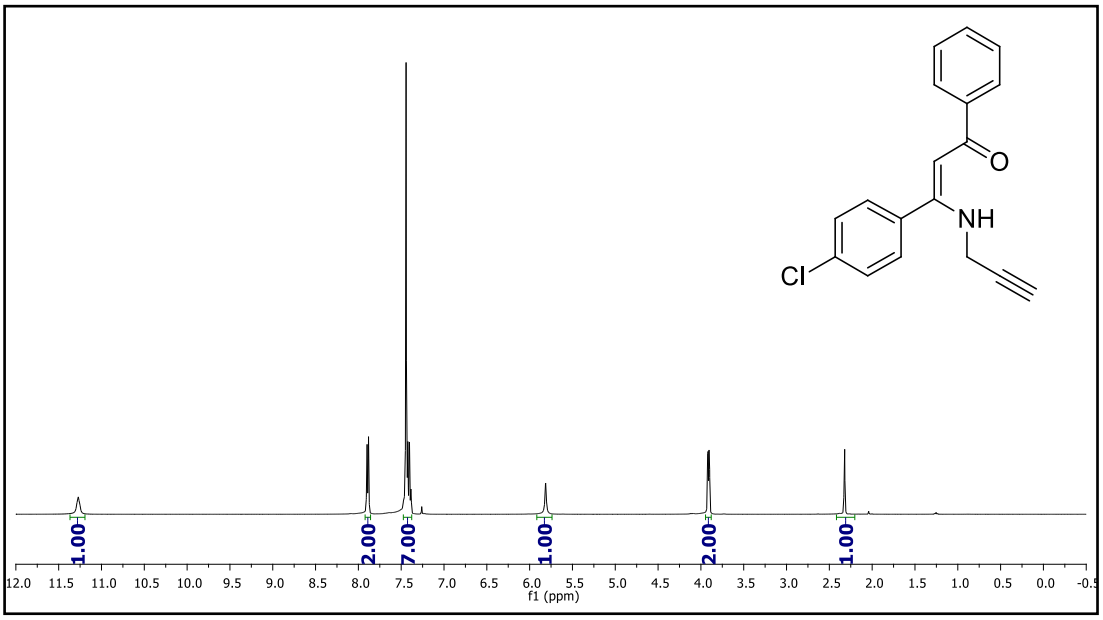

Figure 95. ^{1}H NMR spectrum of compound **13N**.

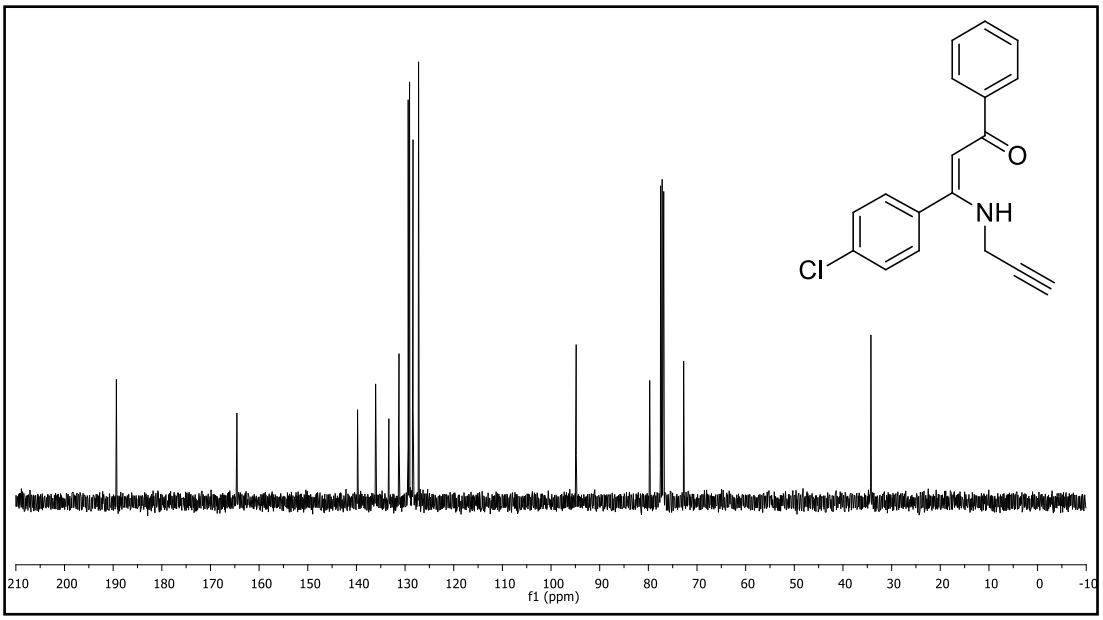

Figure 96. ^{13}C NMR spectrum of compound **13N**.

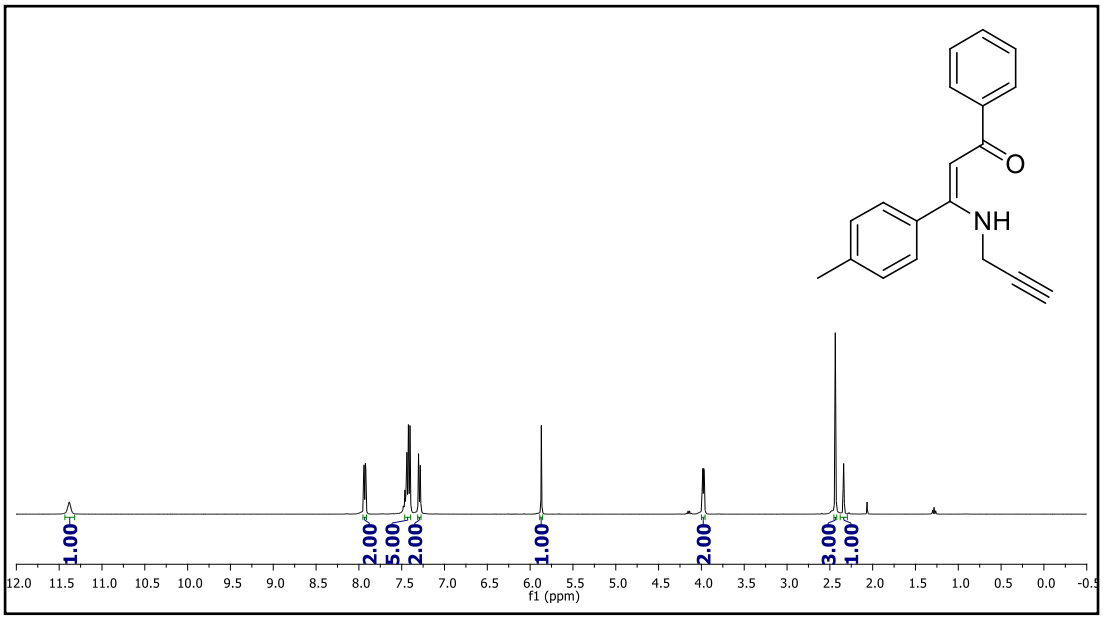

Figure 97. ^{1}H NMR spectrum of compound **13O**.

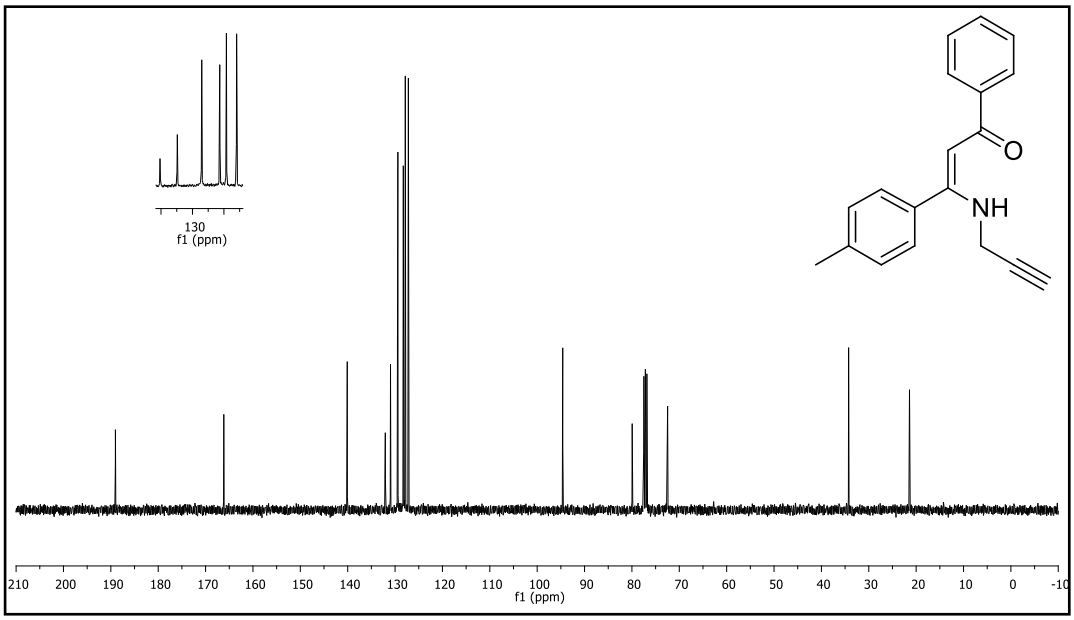

Figure 98. ^{13}C NMR spectrum of compound **13O**.

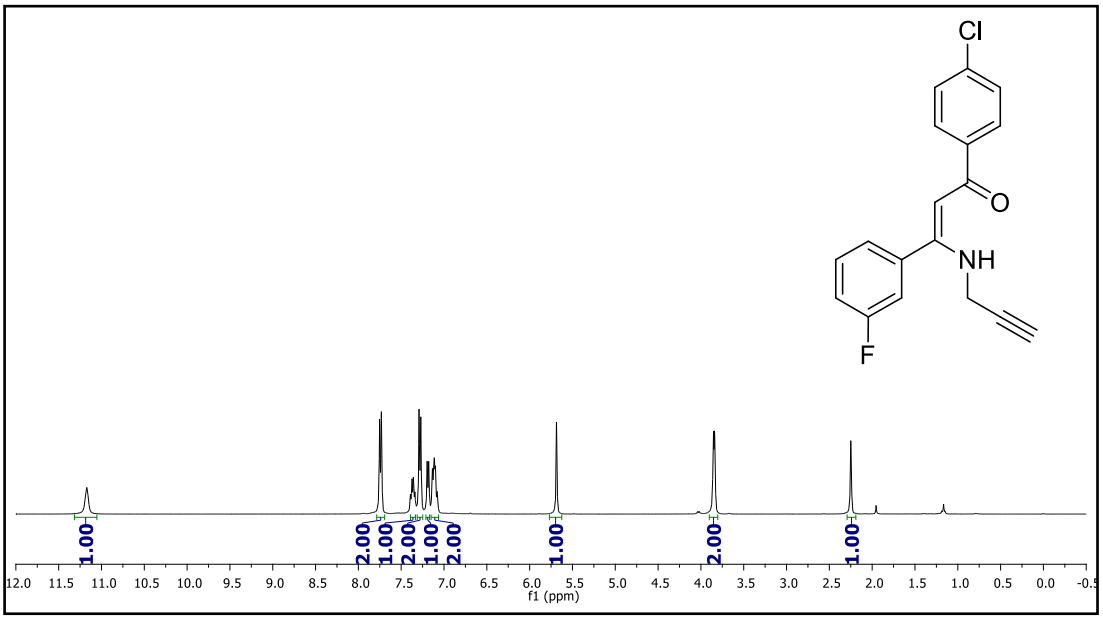

Figure 99. ^{1}H NMR spectrum of compound **13P**.

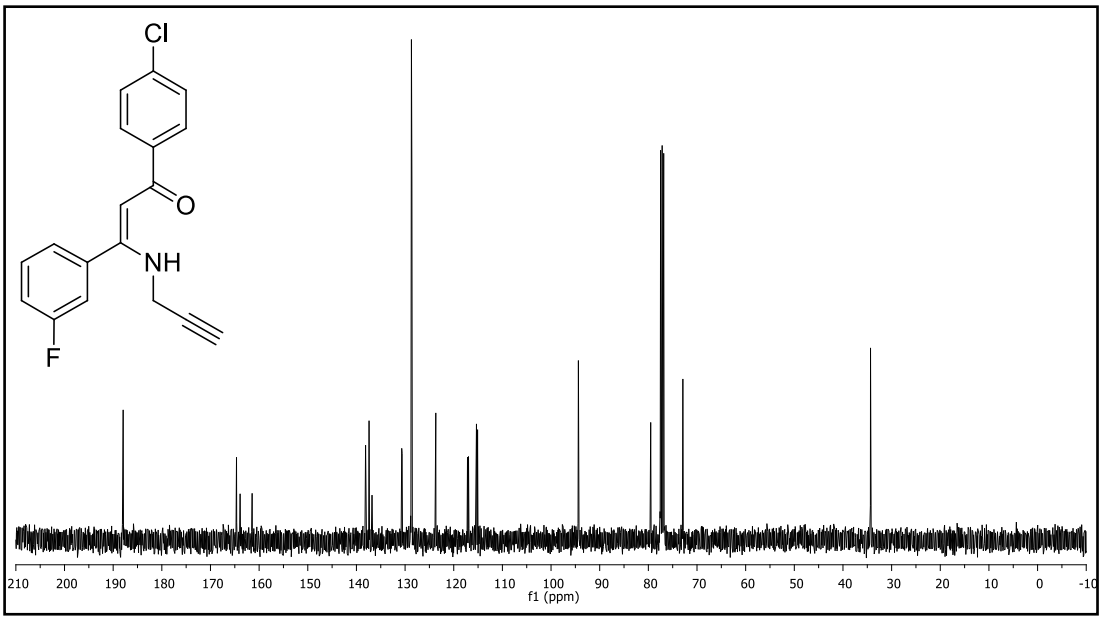

Figure 100. ^{13}C NMR spectrum of compound **13P**.

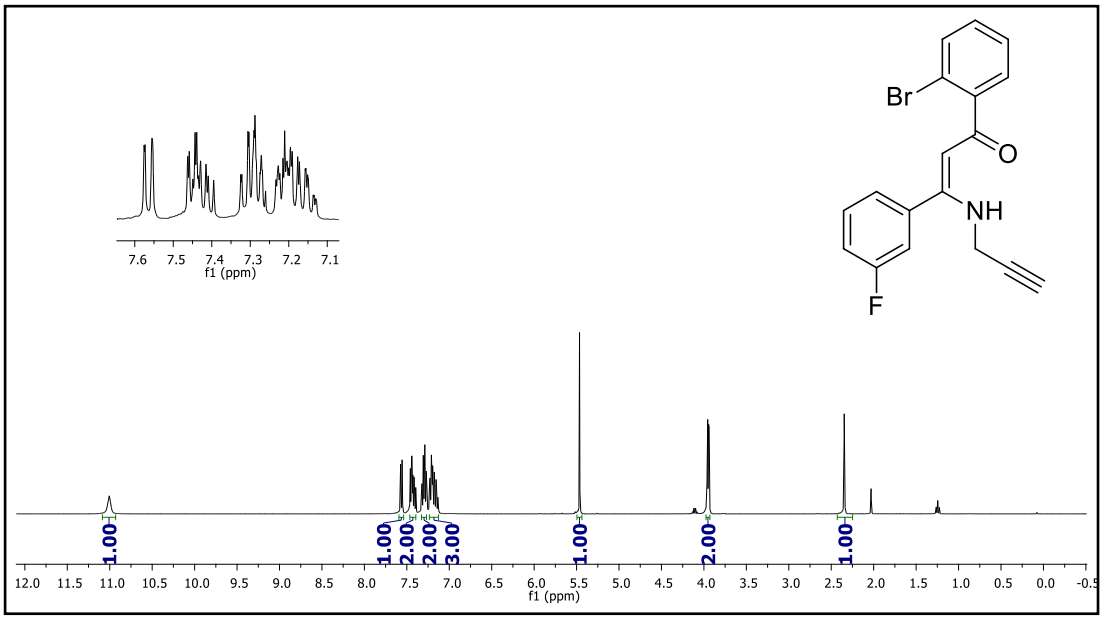

Figure 101. ^{1}H NMR spectrum of compound **13Q**.

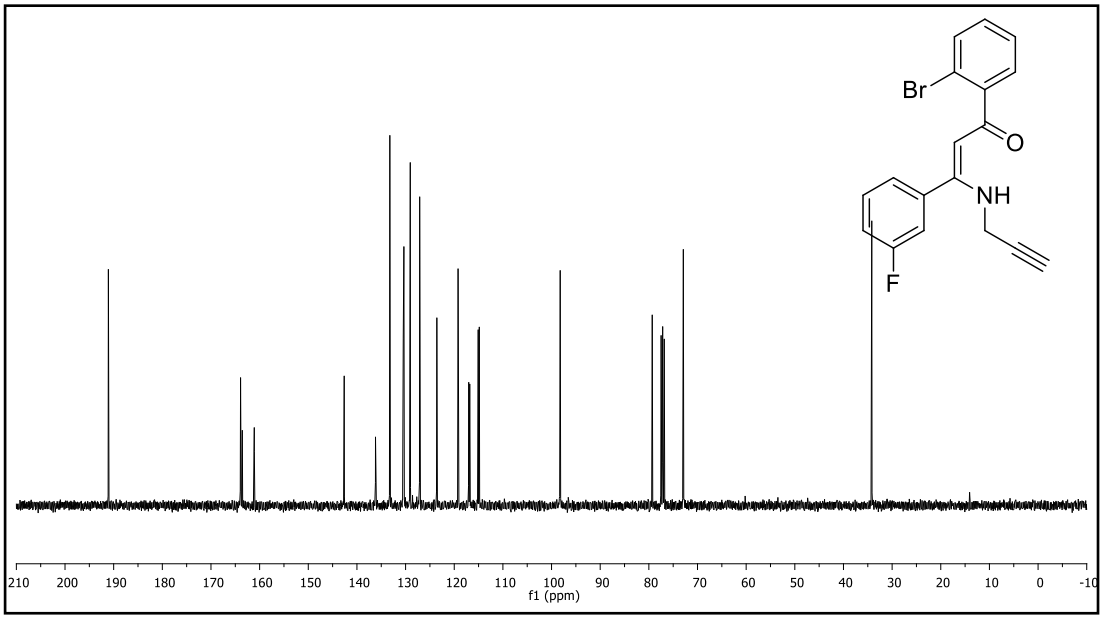

Figure 102. ^{13}C NMR spectrum of compound **13Q**.

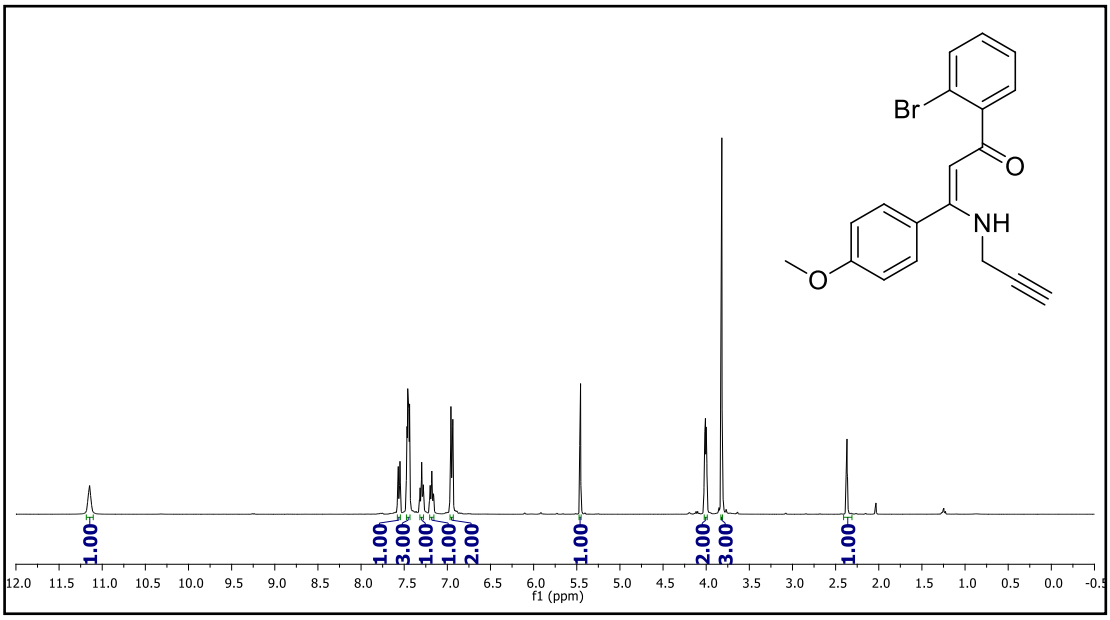

Figure 103. ^{1}H NMR spectrum of compound **13R**.

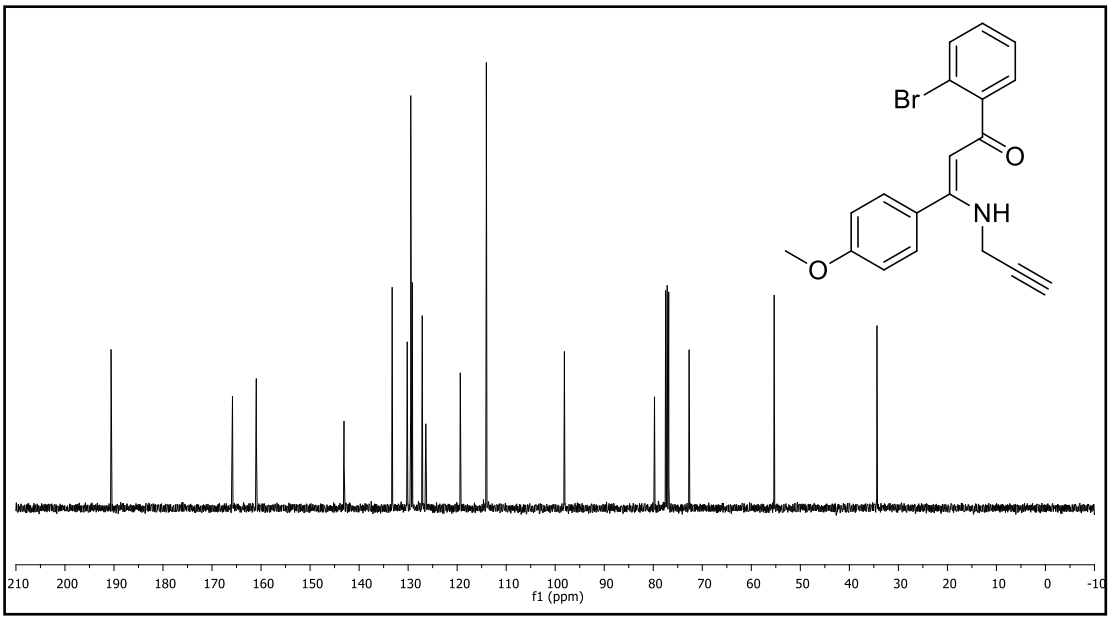

Figure 104. ^{13}C NMR spectrum of compound **13R**.

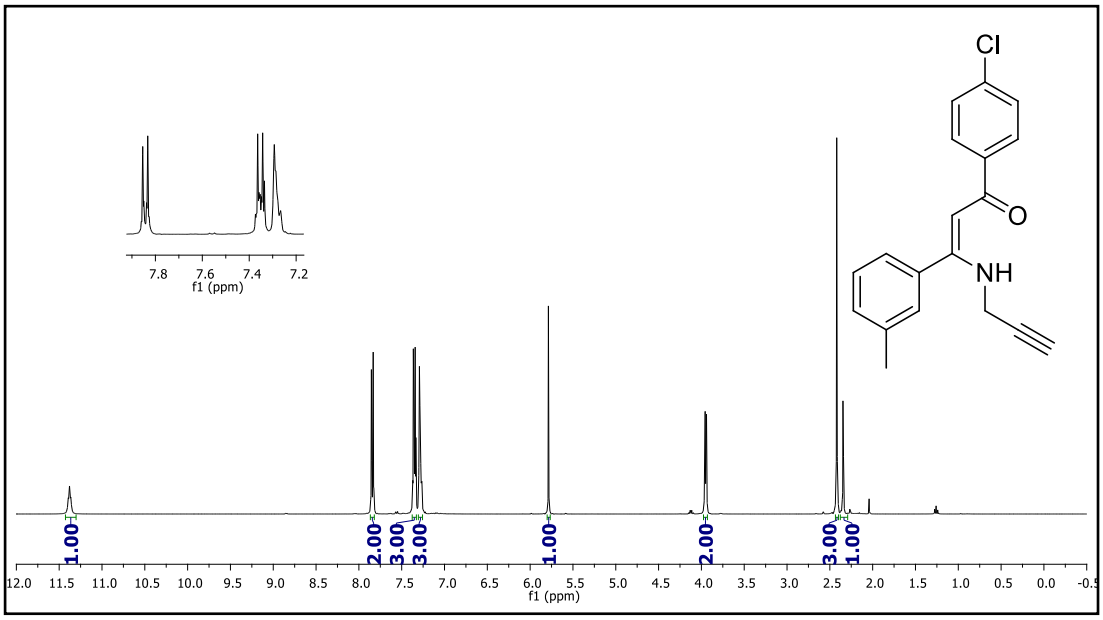

Figure 105. ^{1}H NMR spectrum of compound **13S**.

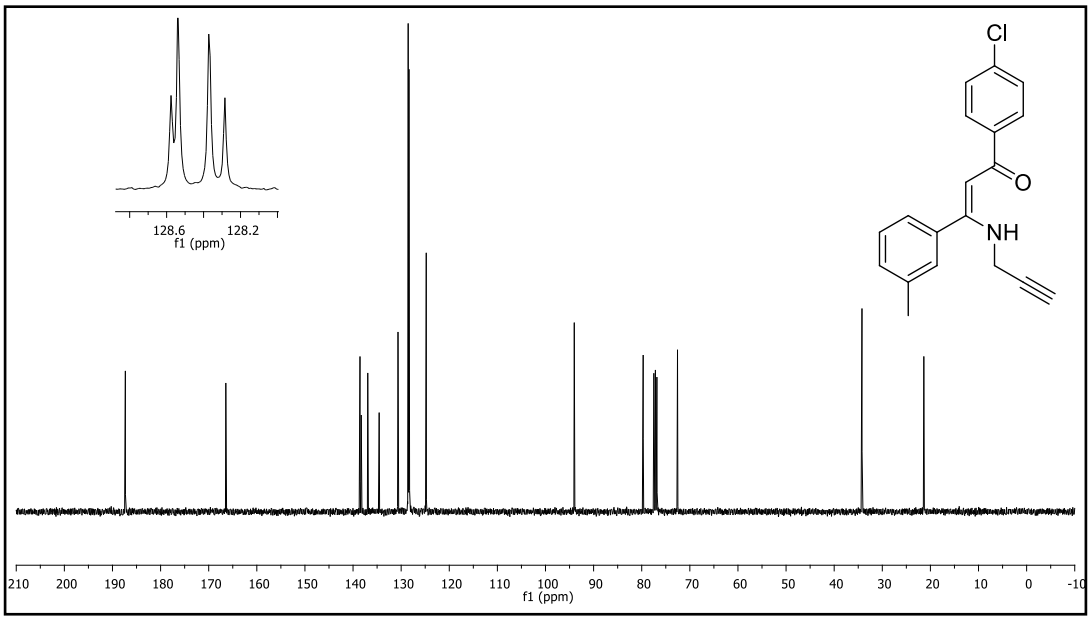

Figure 106. ^{13}C NMR spectrum of compound **13S**.

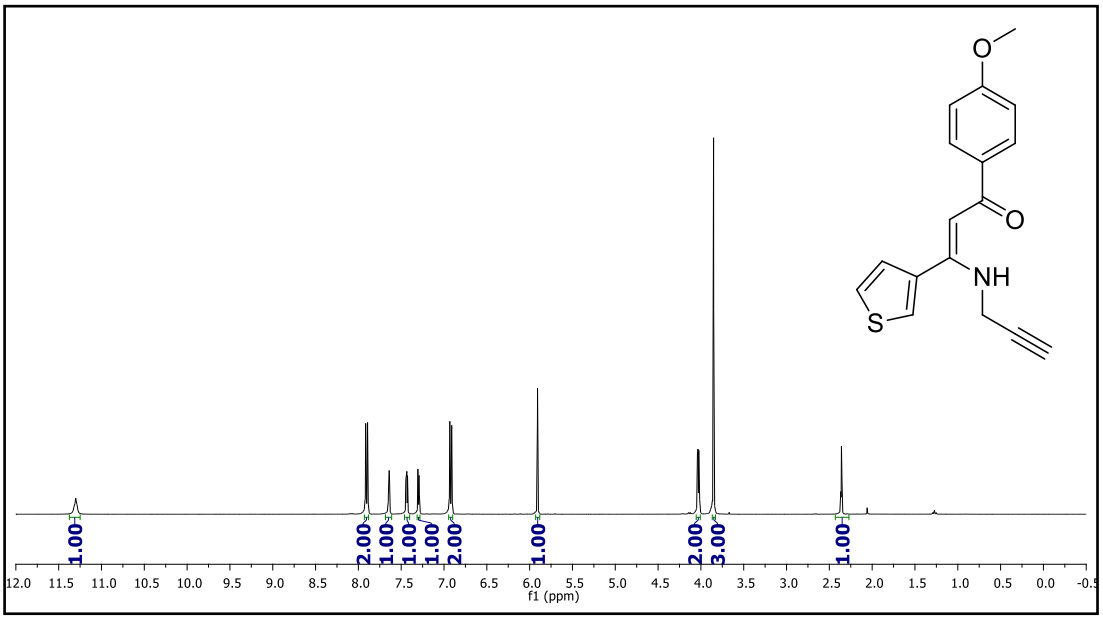

Figure 107. ^{1}H NMR spectrum of compound **13T**.

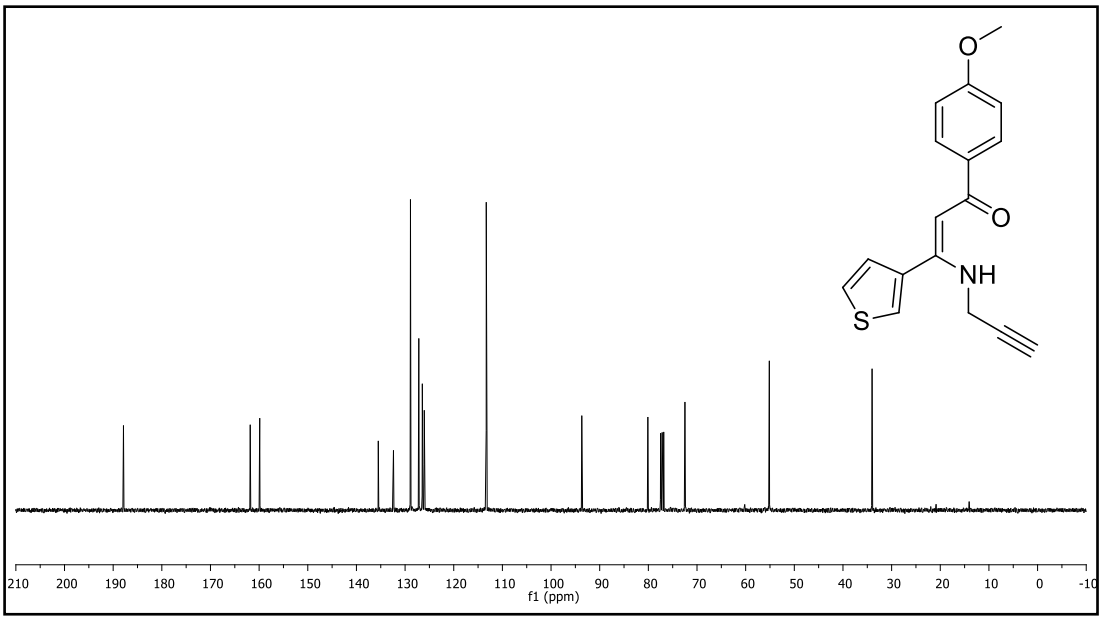

Figure 108. ^{13}C NMR spectrum of compound **13T**.

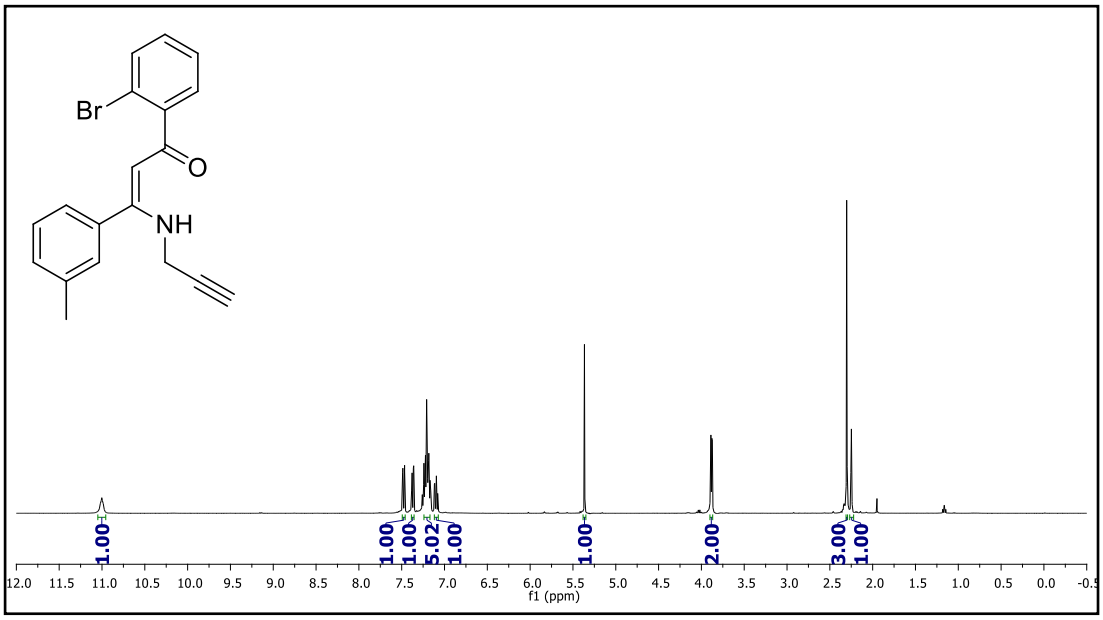

Figure 109. ^{1}H NMR spectrum of compound **13U**.

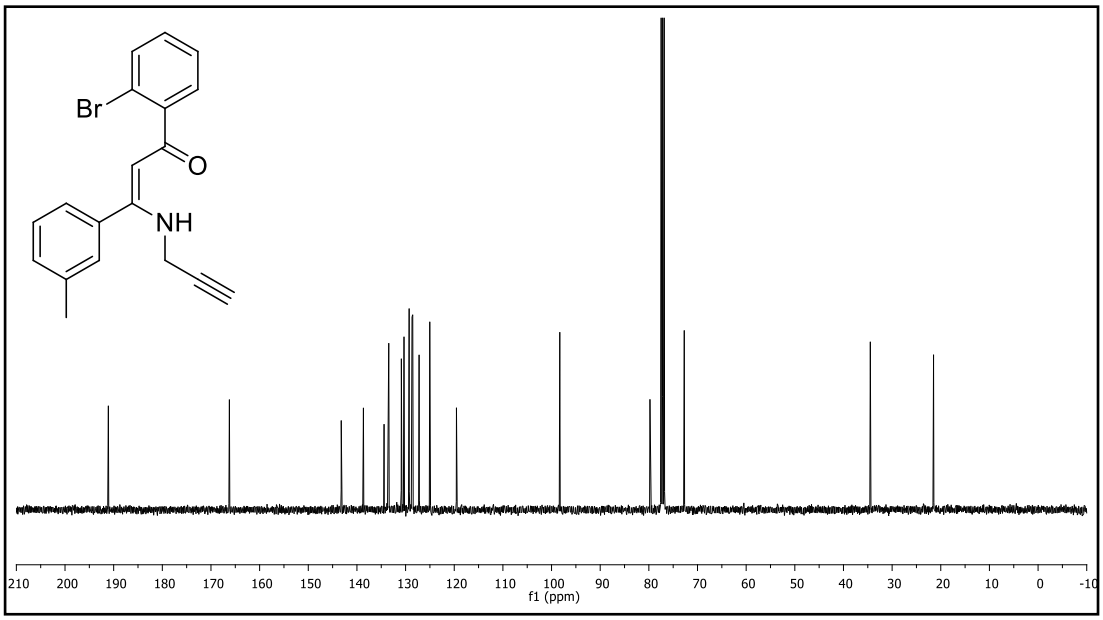

Figure 110. ^{13}C NMR spectrum of compound **13U**.

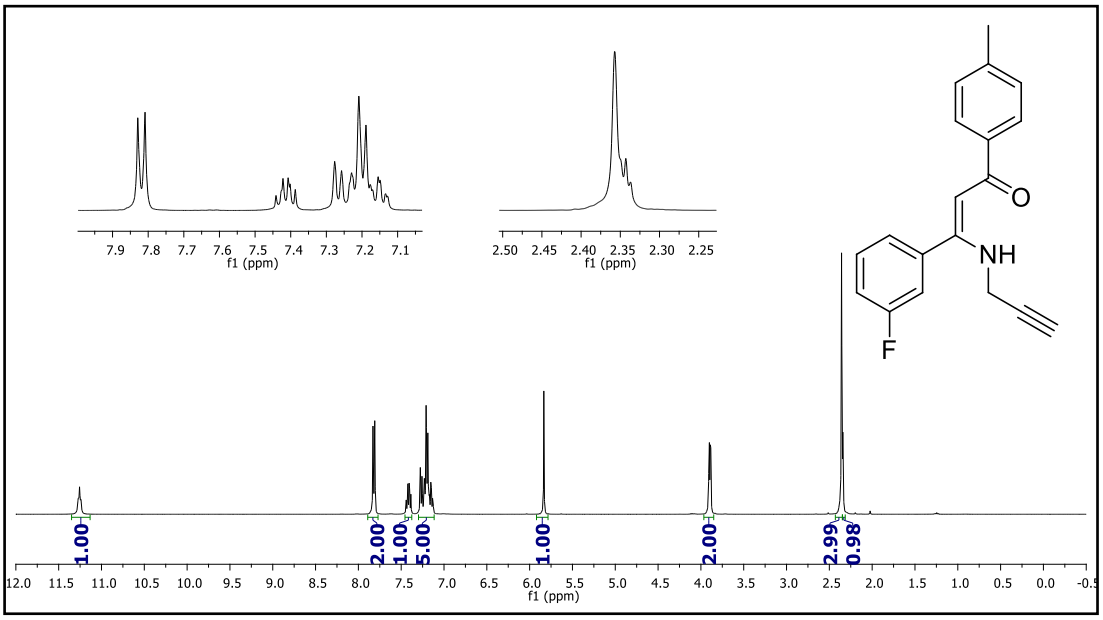

Figure 111. ^{1}H NMR spectrum of compound **13V**.

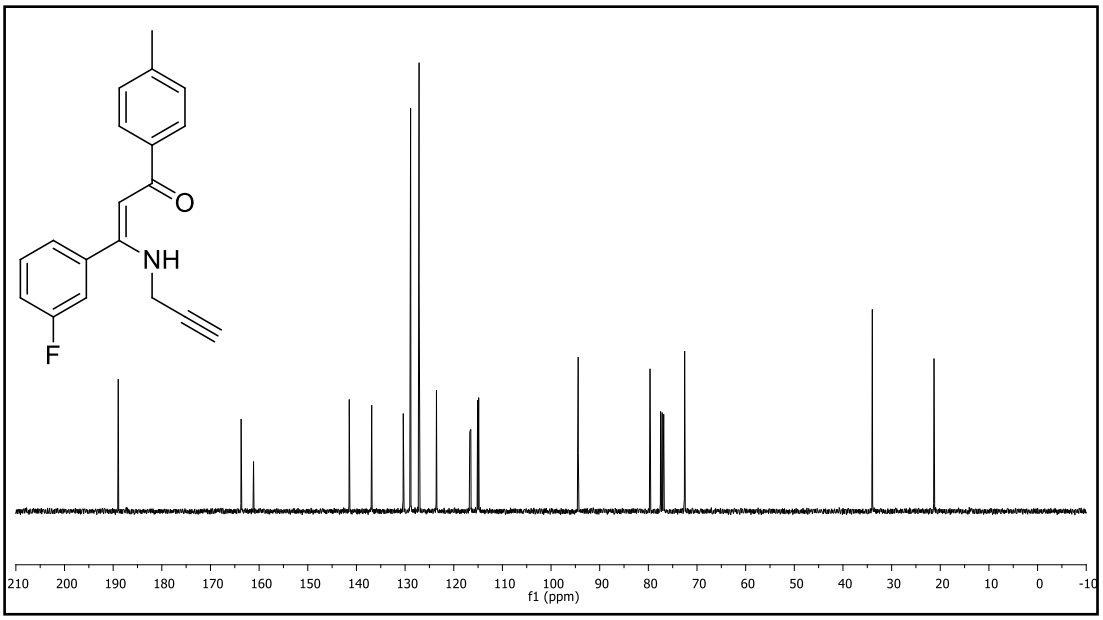

Figure 112. ^{13}C NMR spectrum of compound **13V**.

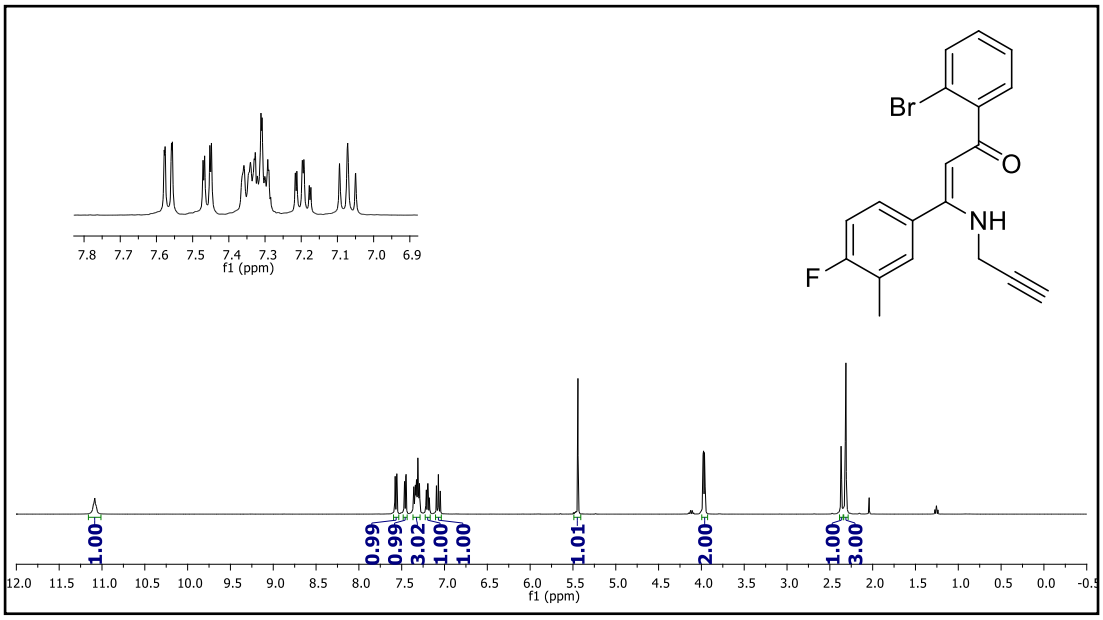

Figure 113. ^{1}H NMR spectrum of compound **13W**.

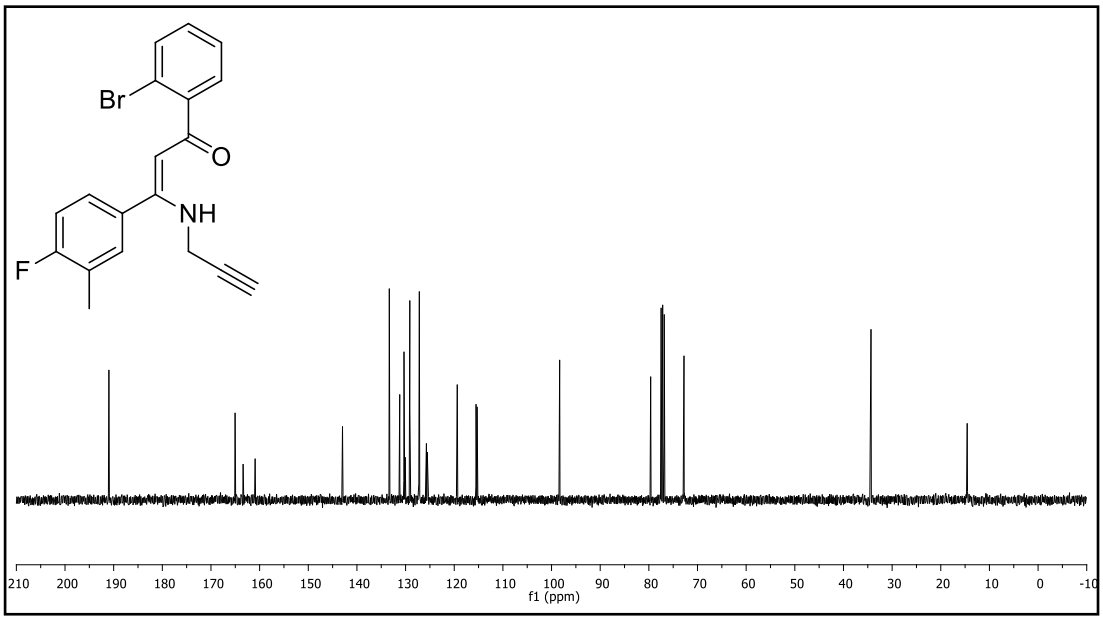

Figure 114. ^{13}C NMR spectrum of compound **13W**.

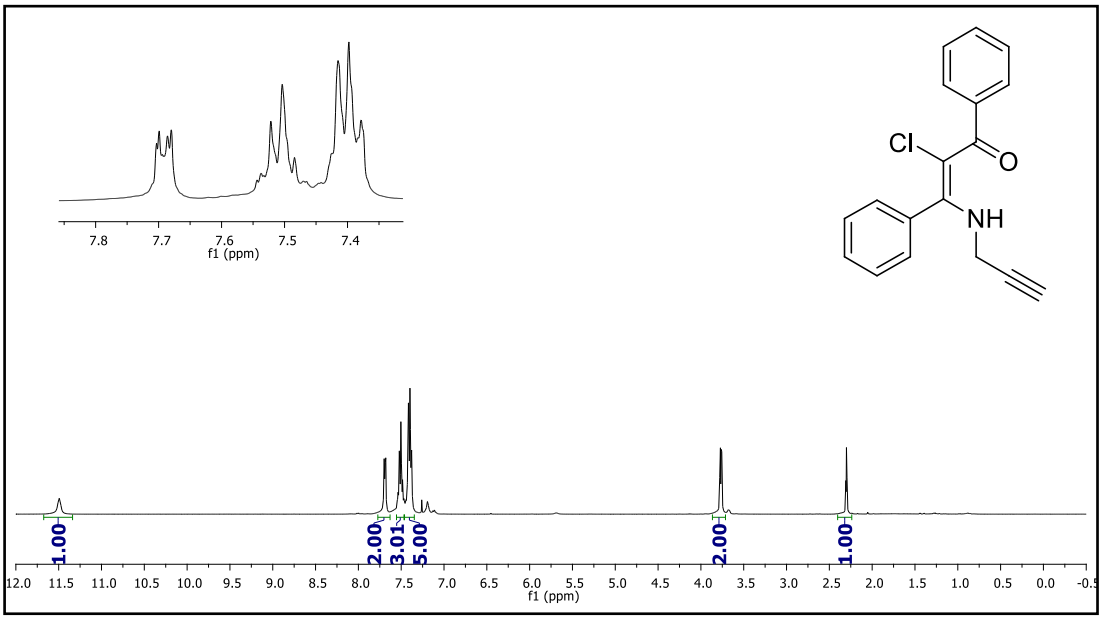

Figure 115. ^{1}H NMR spectrum of compound **35A**.

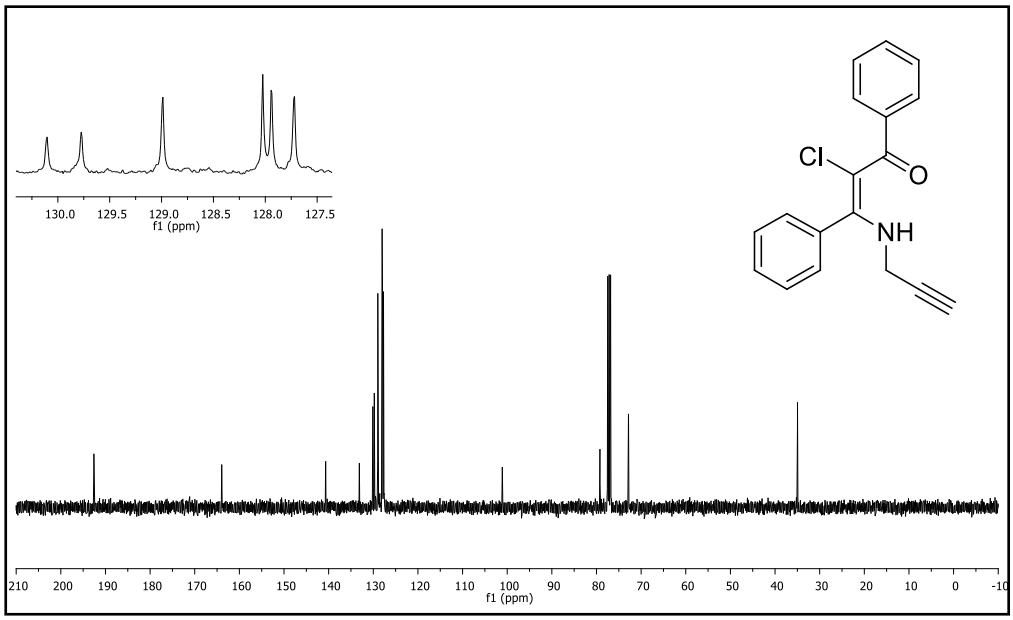

Figure 116. ^{13}C NMR spectrum of compound **35A**.

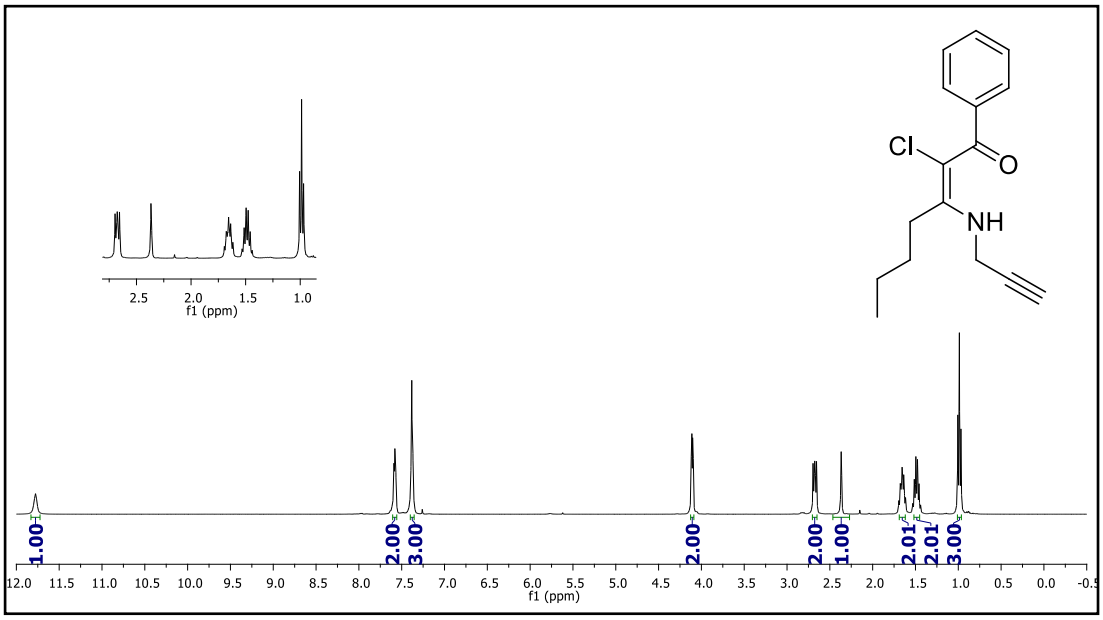

Figure 117. ^{1}H NMR spectrum of compound **35B**.

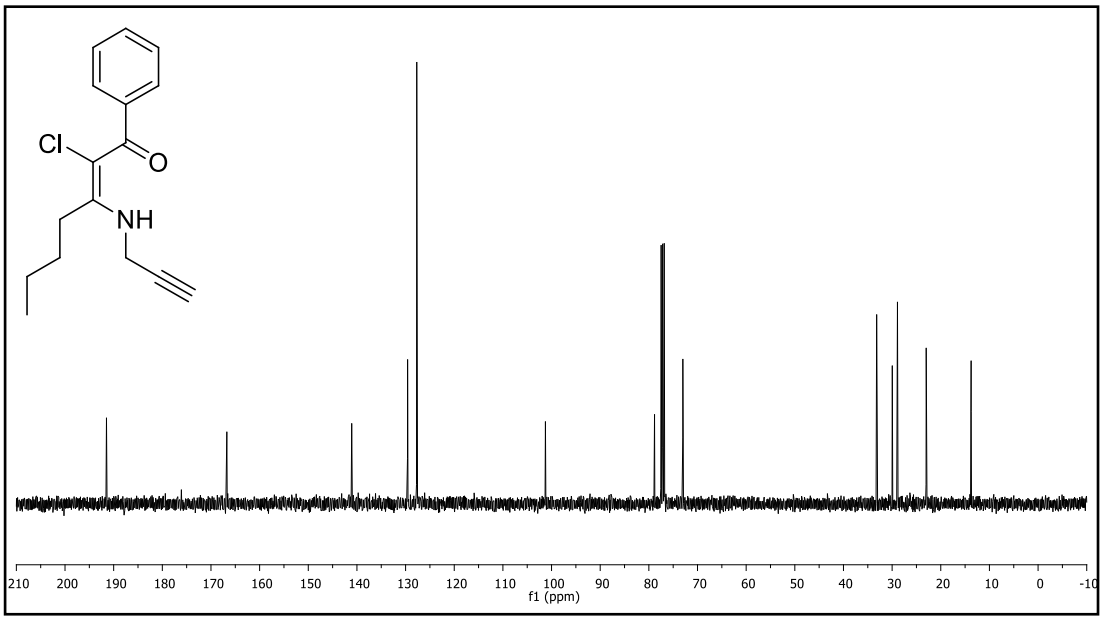

Figure 118. ^{13}C NMR spectrum of compound **35B**.

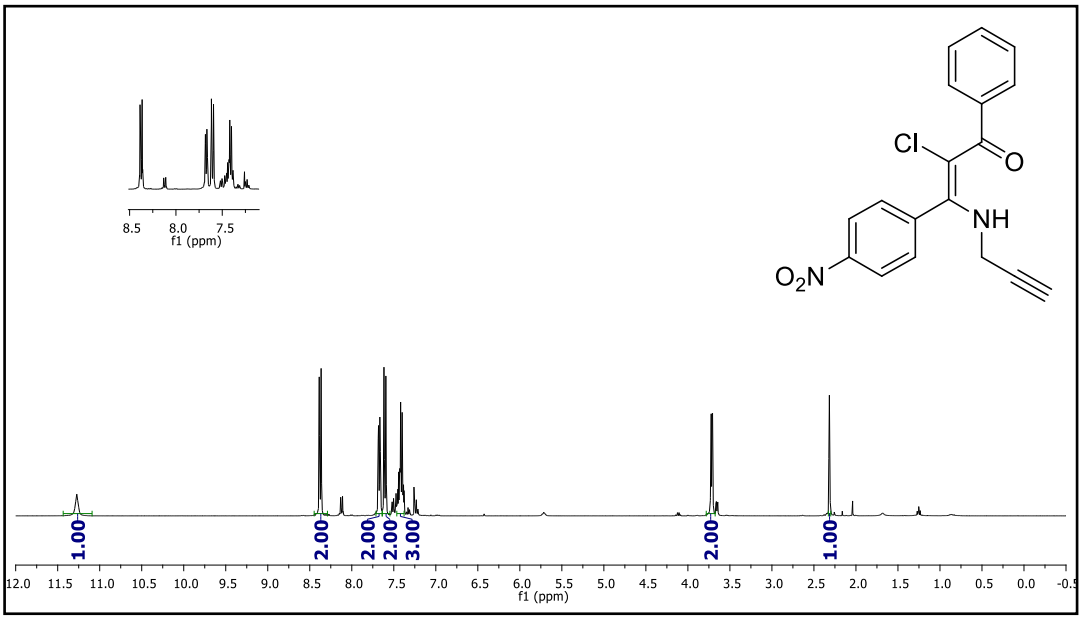

Figure 119. ^{1}H NMR spectrum of compound **35C**.

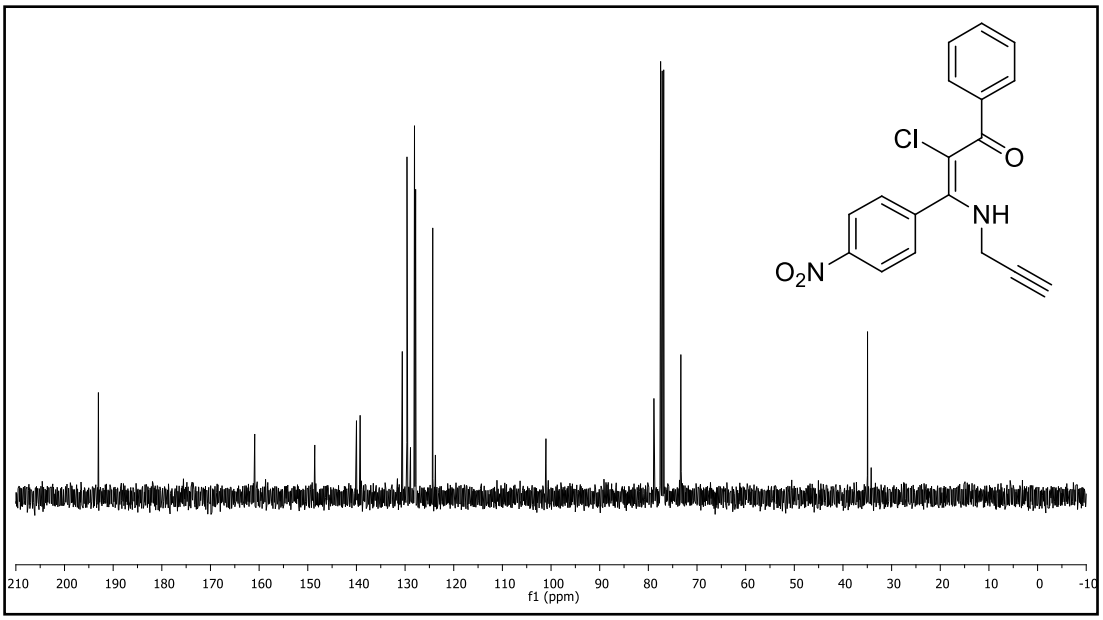

Figure 120. ^{13}C NMR spectrum of compound **35C**.

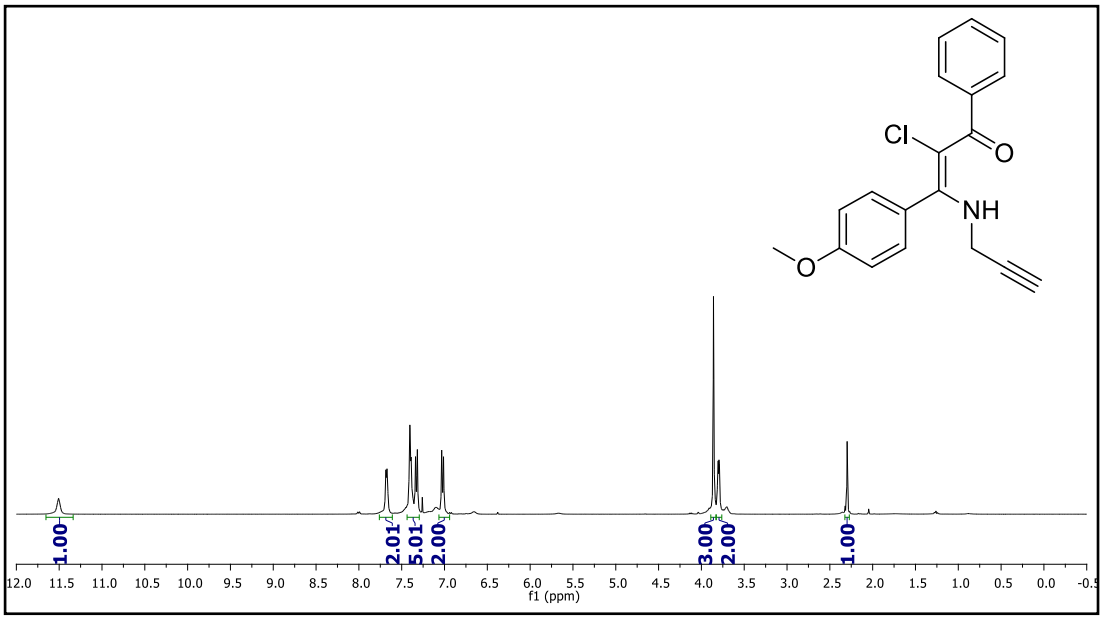

Figure 121. ^{1}H NMR spectrum of compound **35D**.

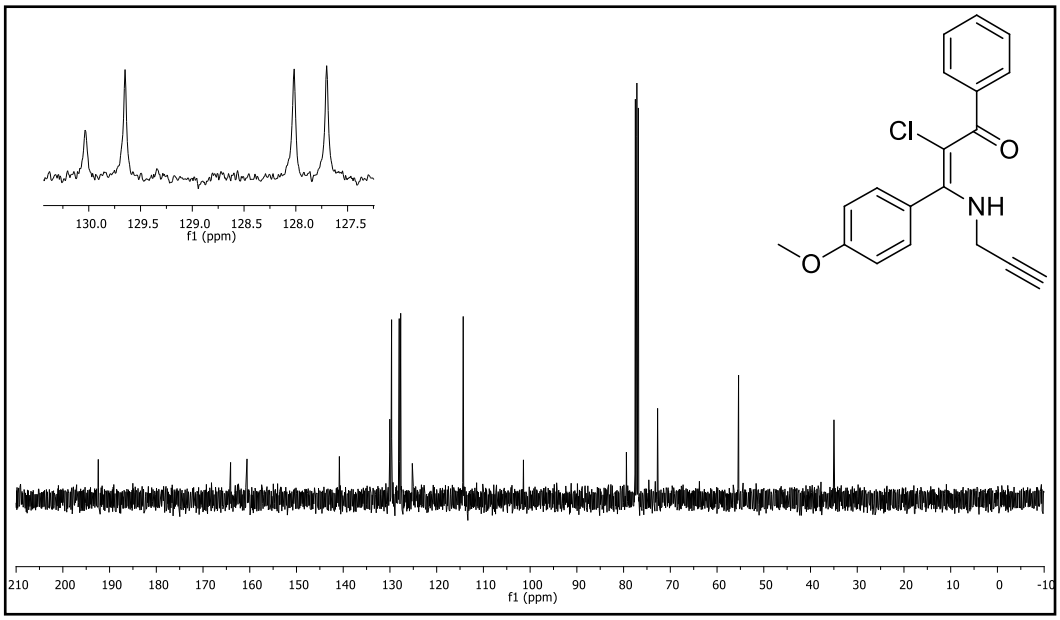

Figure 122. ^{13}C NMR spectrum of compound **35D**.

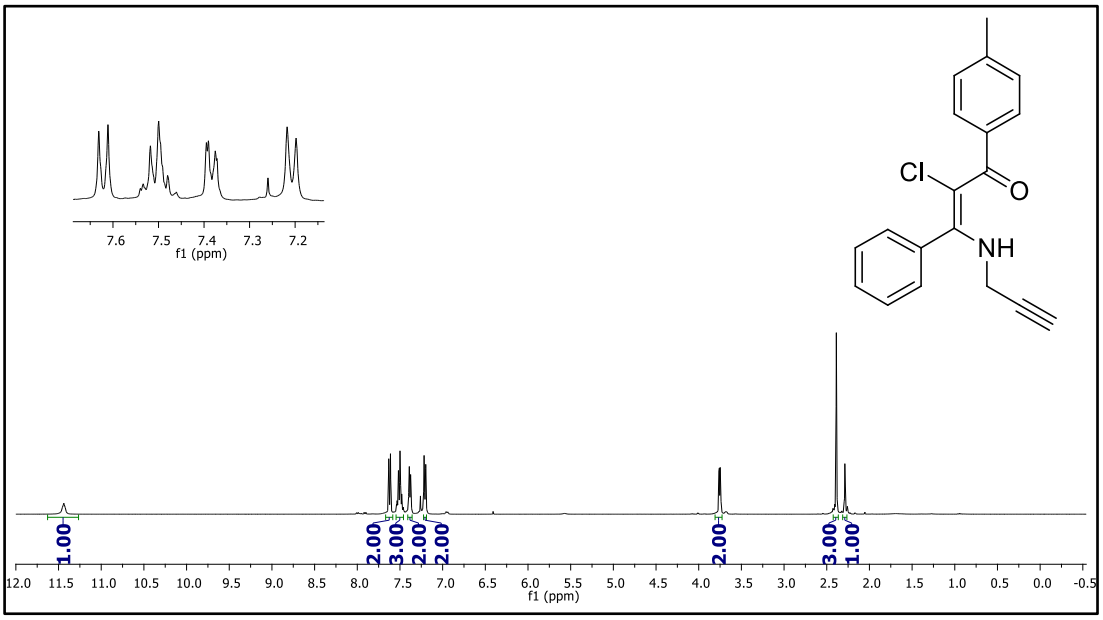

Figure 123. ^{1}H NMR spectrum of compound **35E**.

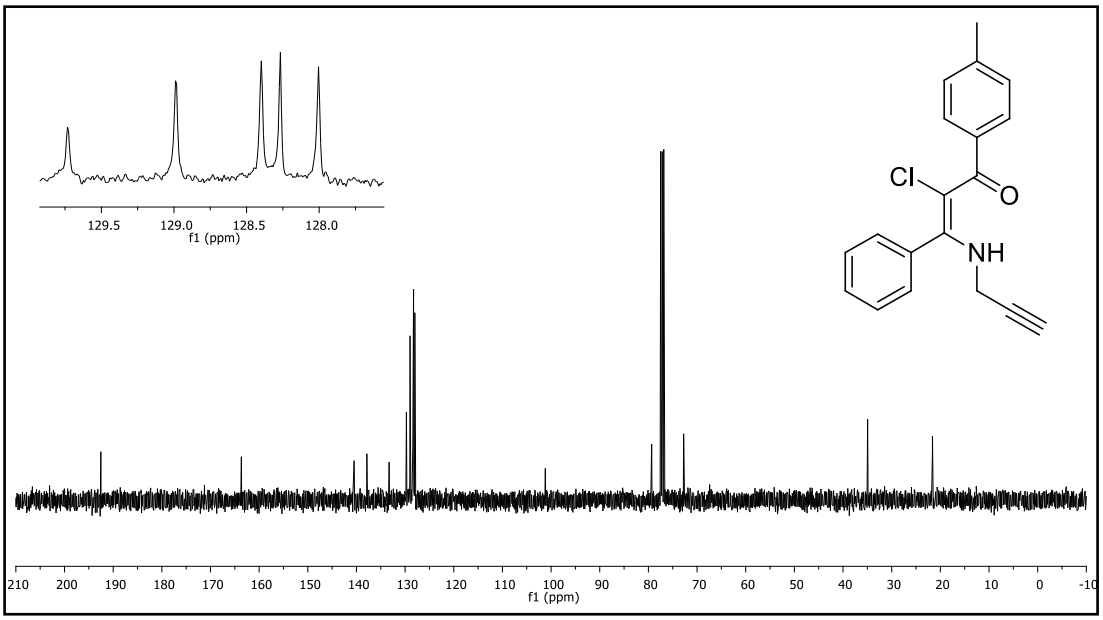

Figure 124. ^{13}C NMR spectrum of compound **35E**.

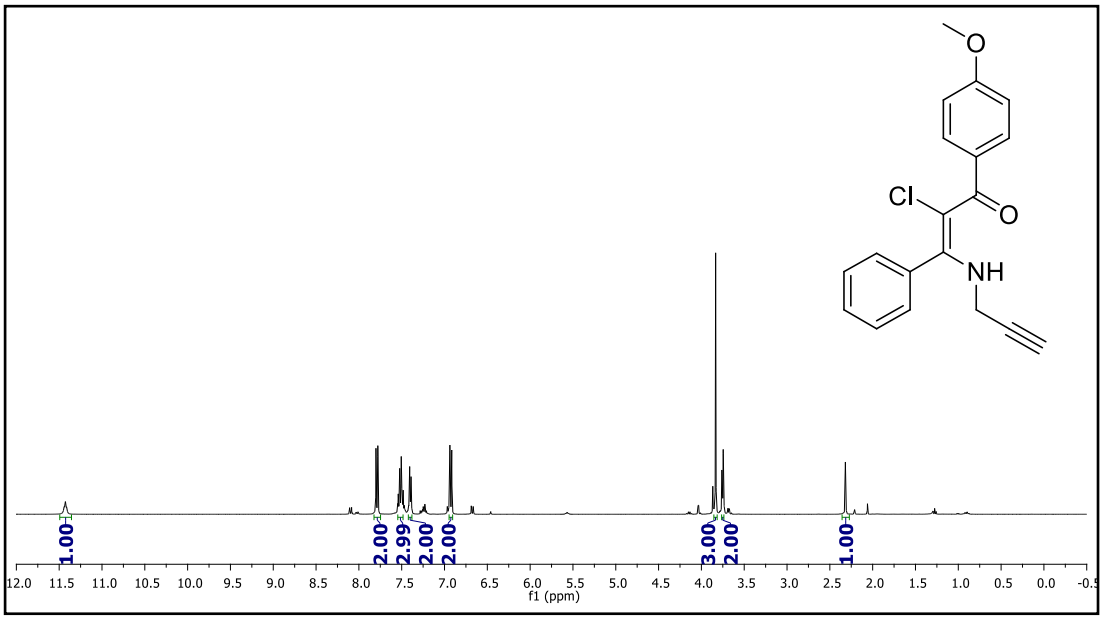

Figure 125. ^{1}H NMR spectrum of compound **35F**.

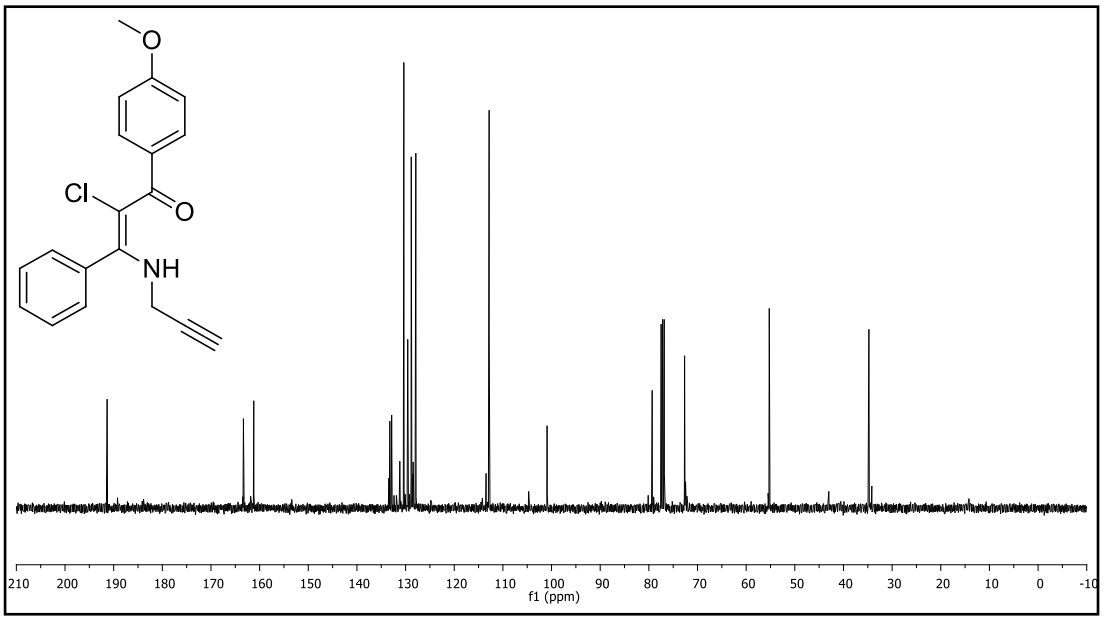

Figure 126. ^{13}C NMR spectrum of compound **35F**.

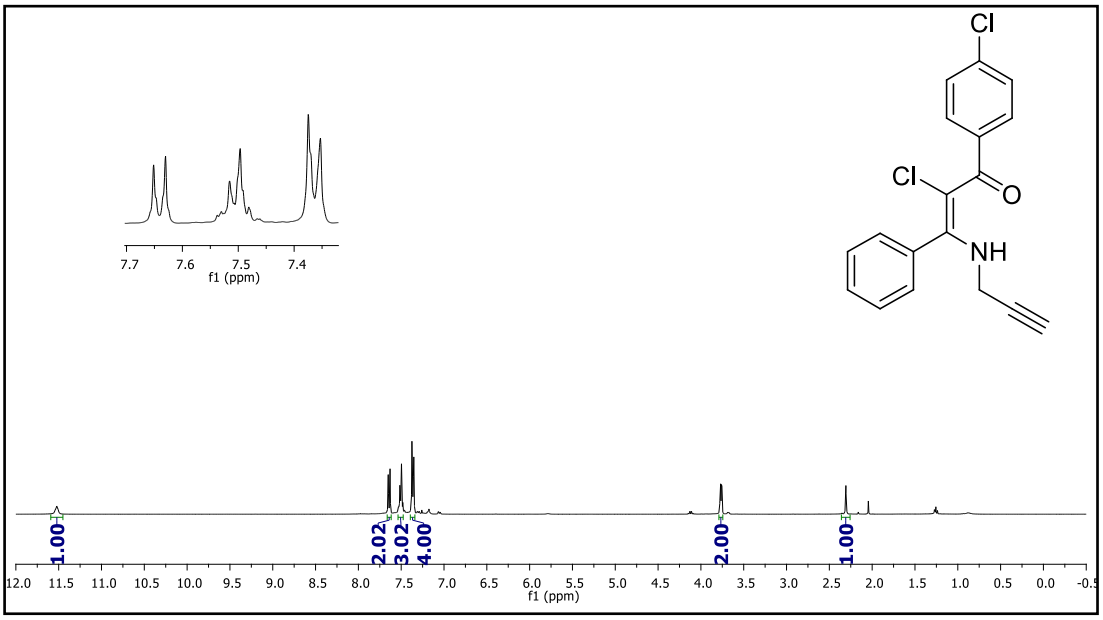

Figure 127. [1] H NMR spectrum of compound **35G**.

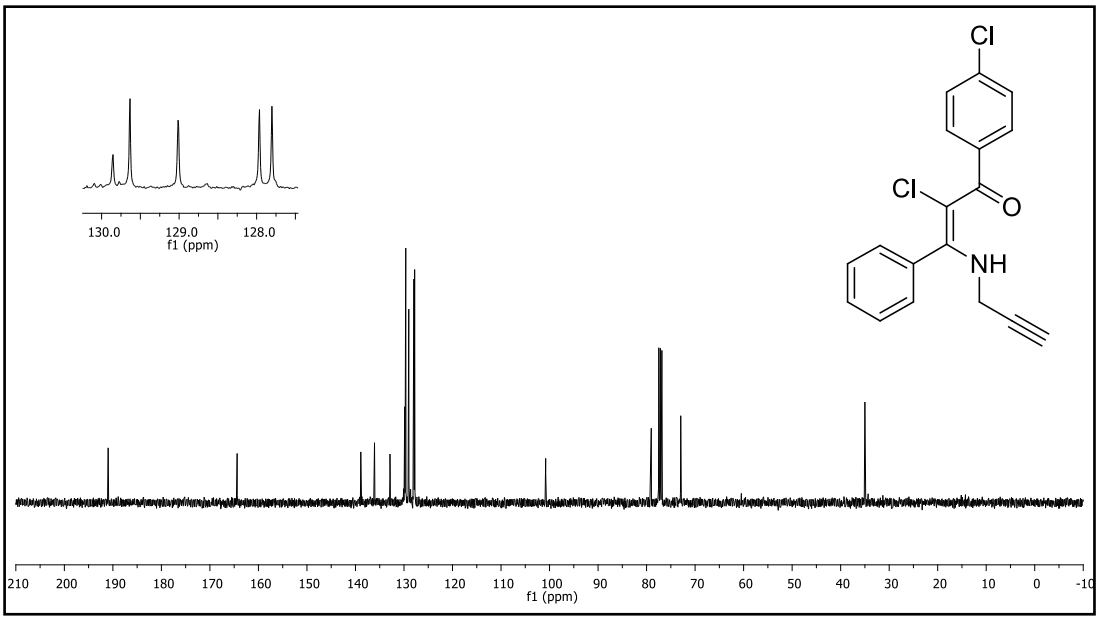

Figure 128. [13]C NMR spectrum of compound **35G**.

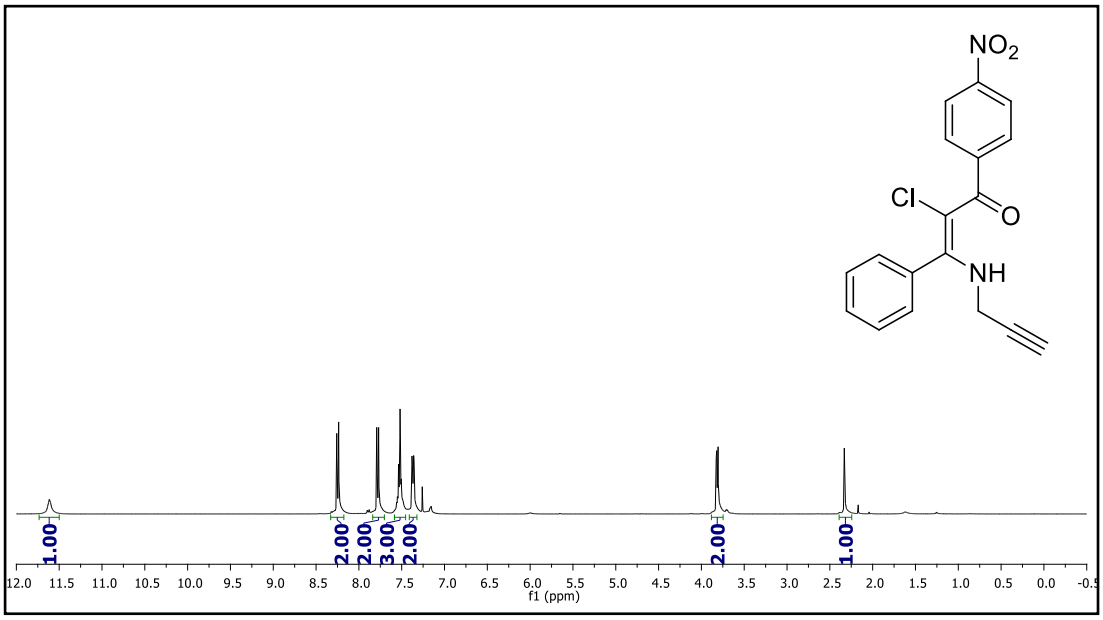

Figure 129. ^{1}H NMR spectrum of compound **35H**.

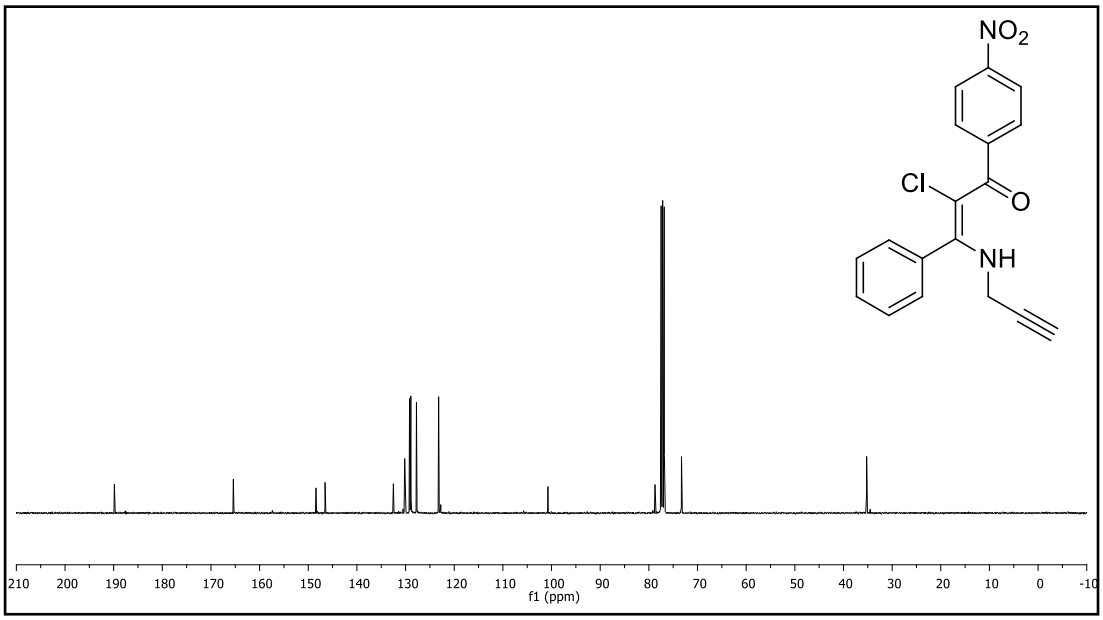

Figure 130. ^{13}C NMR spectrum of compound **35H**.

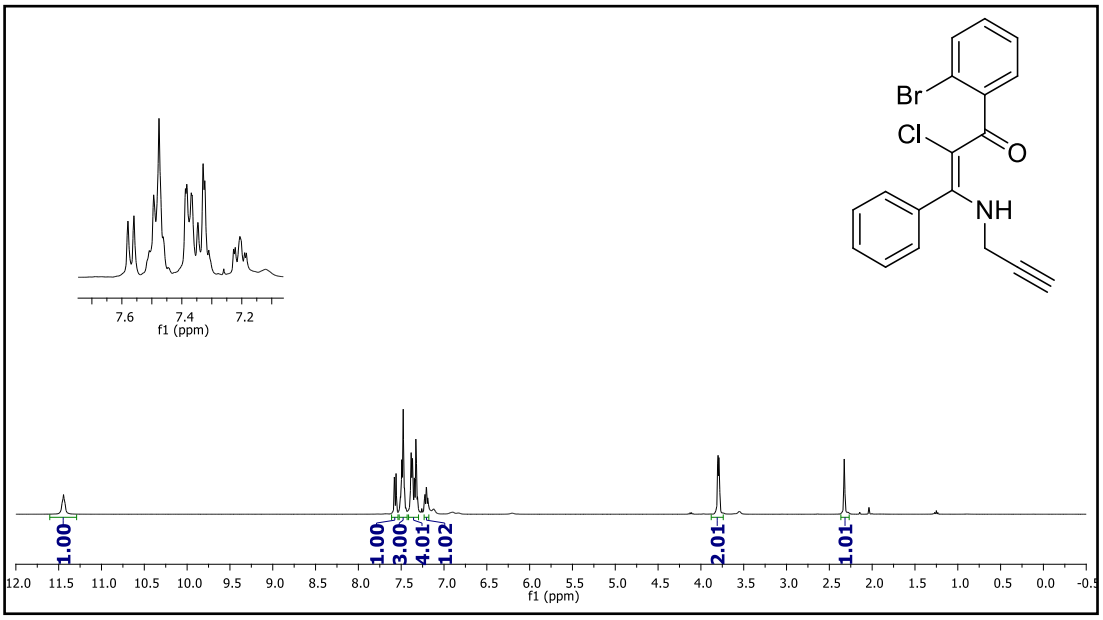

Figure 131. ^{1}H NMR spectrum of compound **35I**.

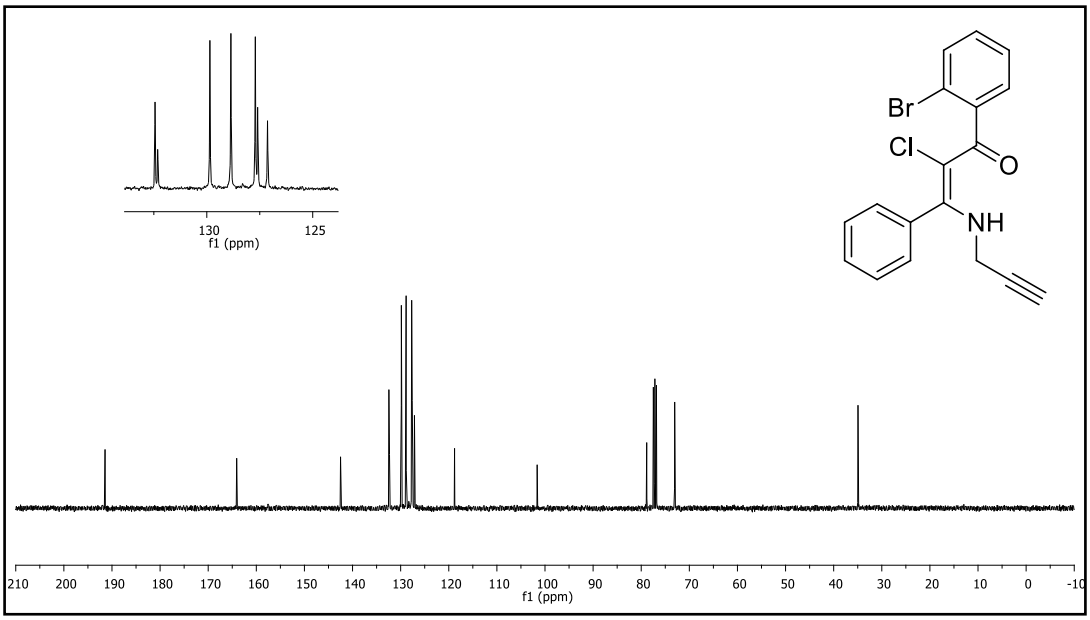

Figure 132. ^{13}C NMR spectrum of compound **35I**.

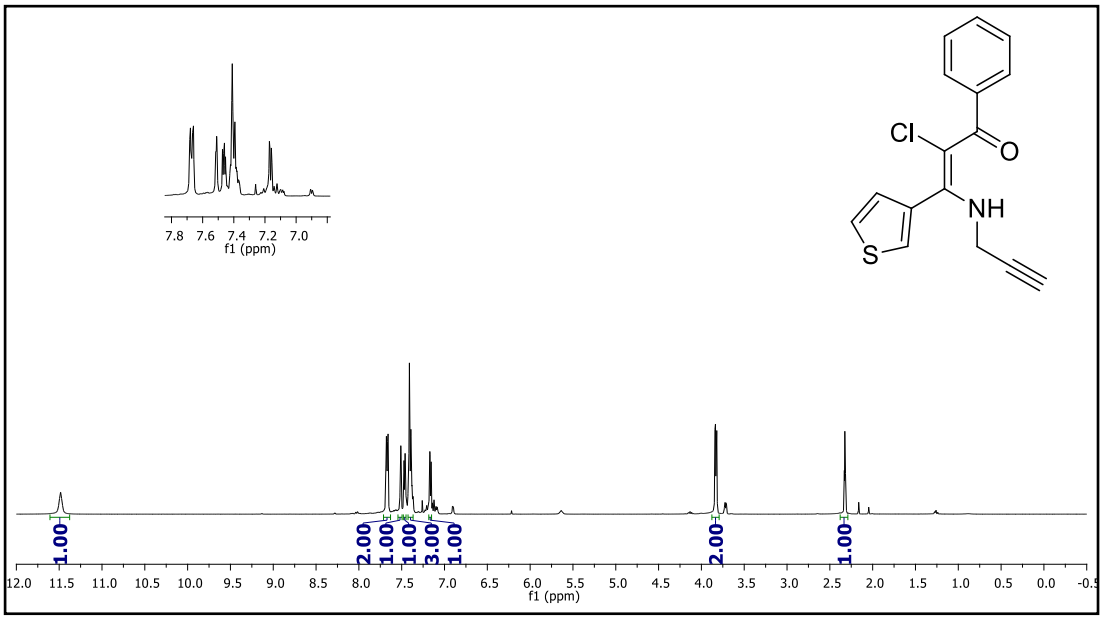

Figure 133. ^{1}H NMR spectrum of compound **35J**.

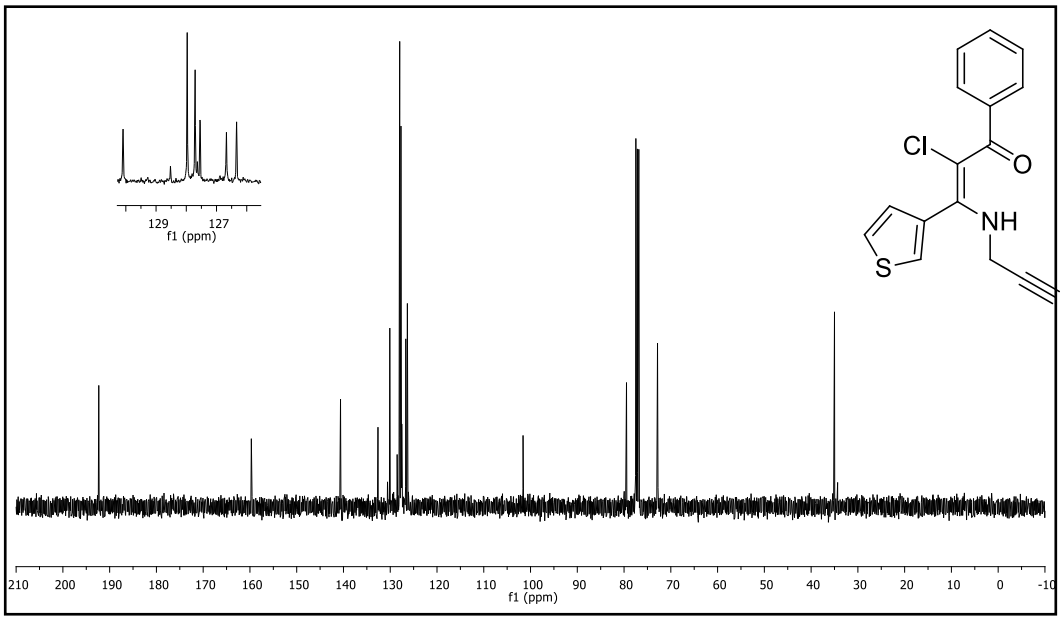

Figure 134. ^{13}C NMR spectrum of compound **35J**.

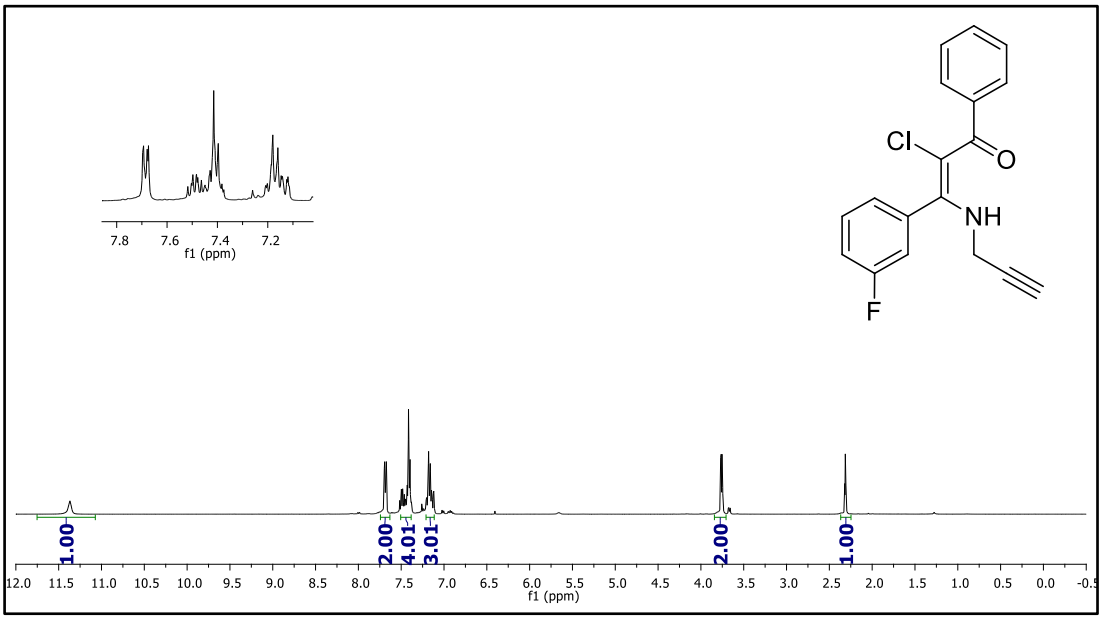

Figure 135. ^{1}H NMR spectrum of compound **35K**.

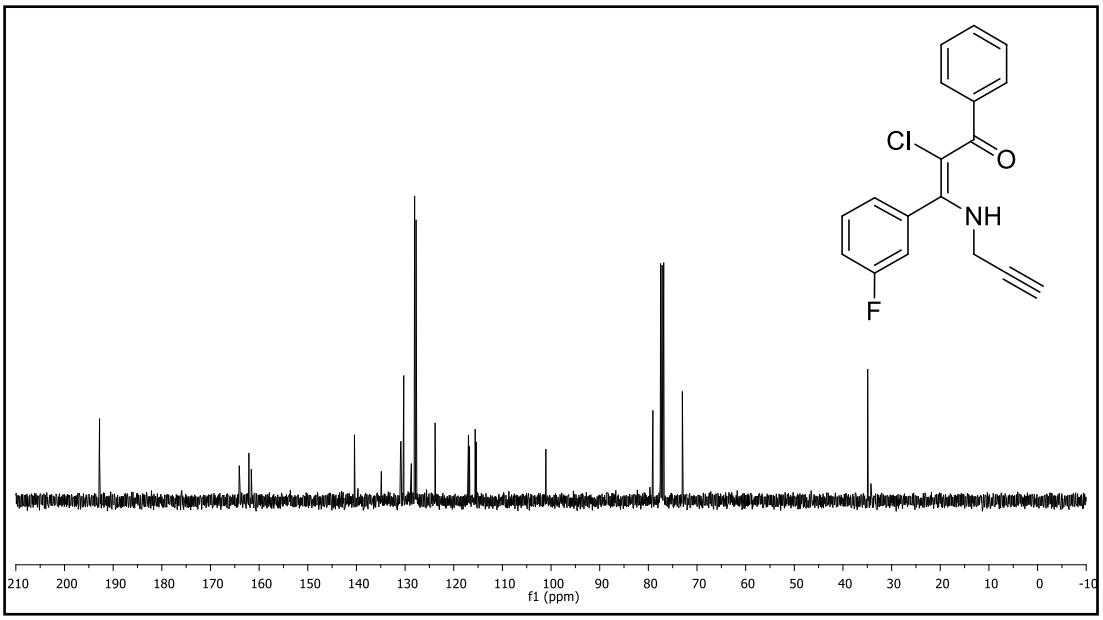

Figure 136. ^{13}C NMR spectrum of compound **35K**.

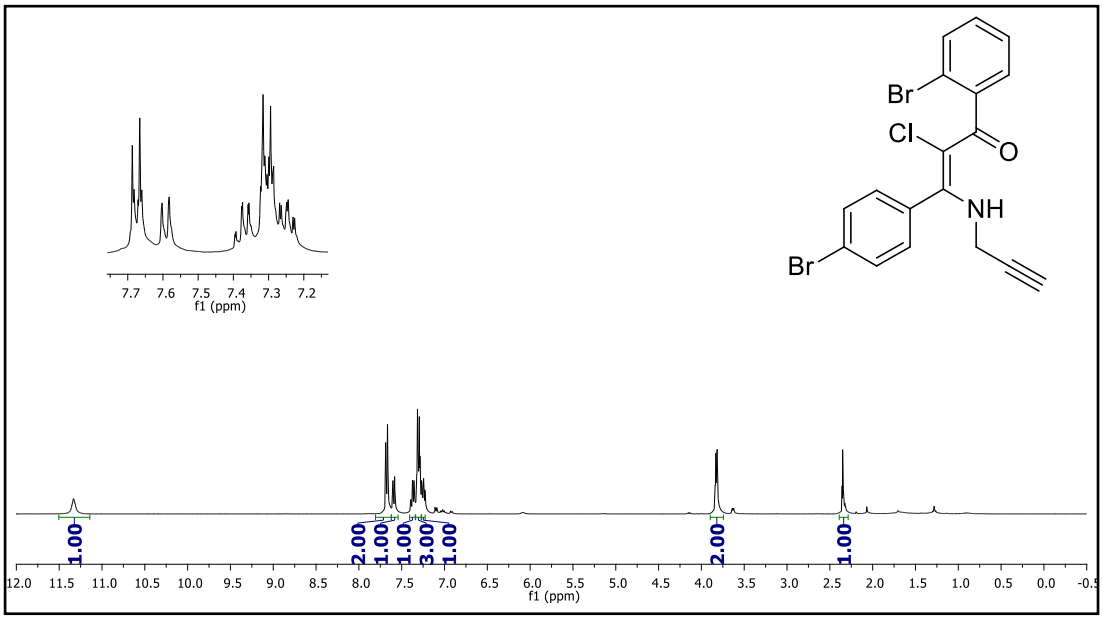

Figure 137. ^{1}H NMR spectrum of compound **35L**.

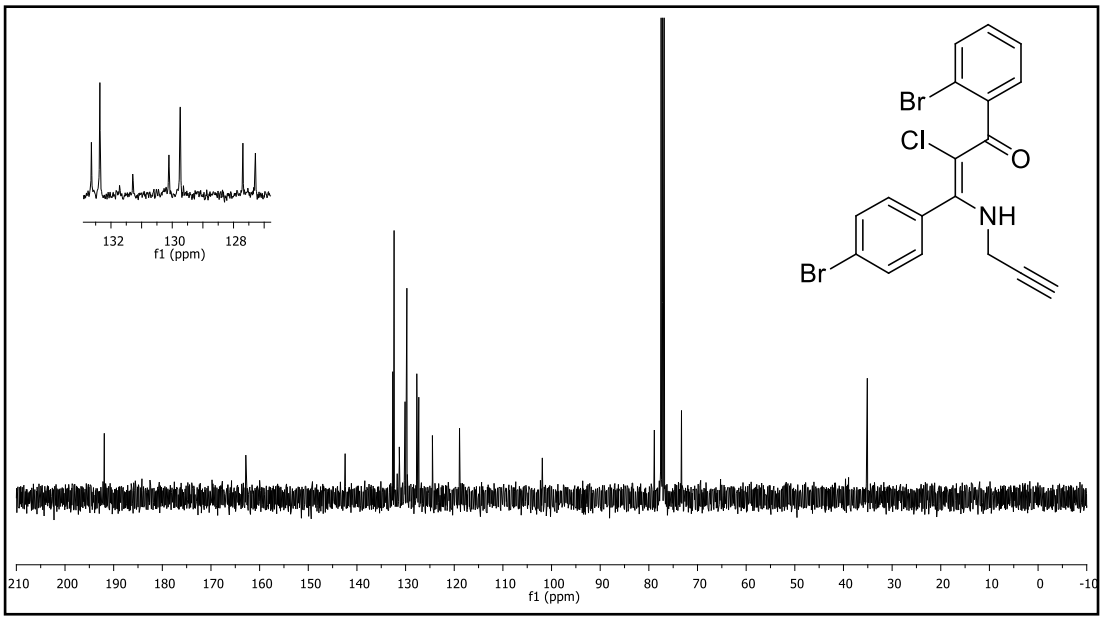

Figure 138. ^{13}C NMR spectrum of compound **35L**.

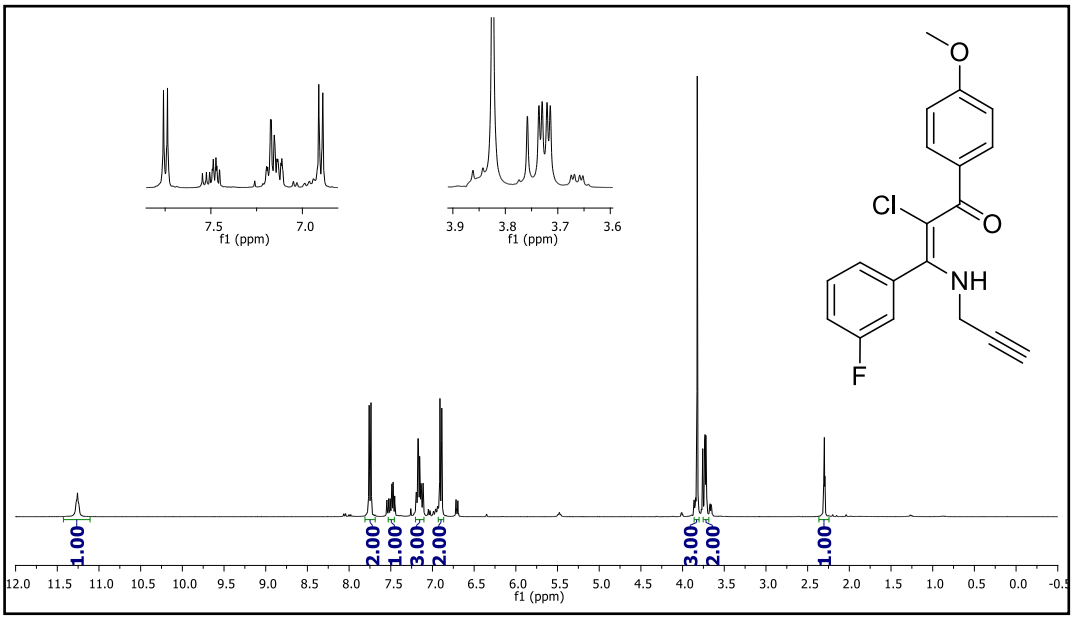

Figure 139. ^{1}H NMR spectrum of compound **35M**.

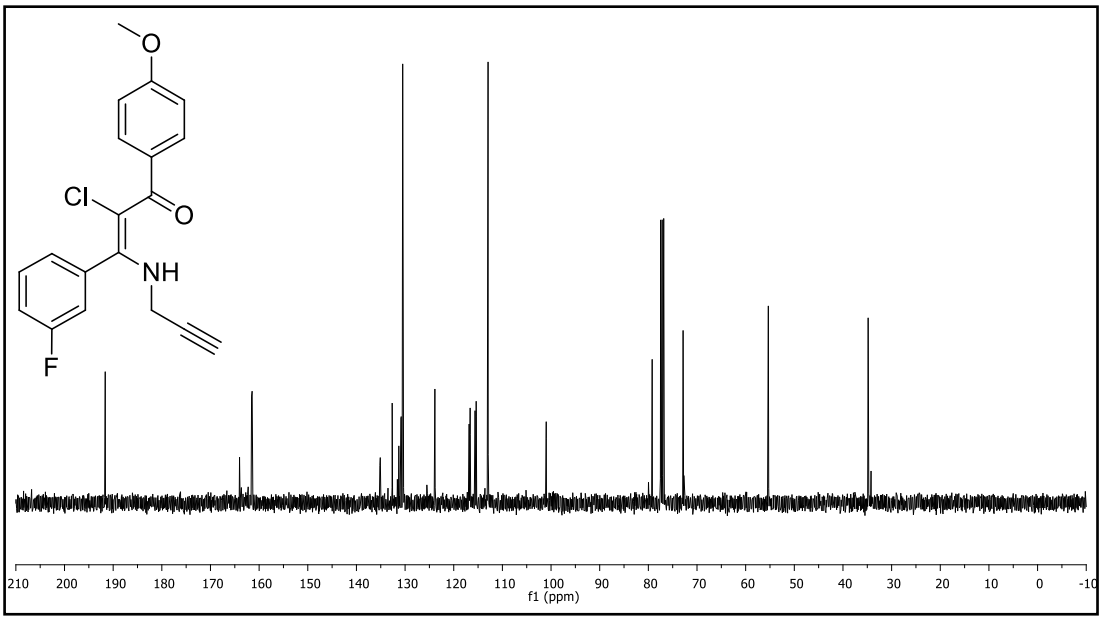

Figure 140. ^{13}C NMR spectrum of compound **35M**.

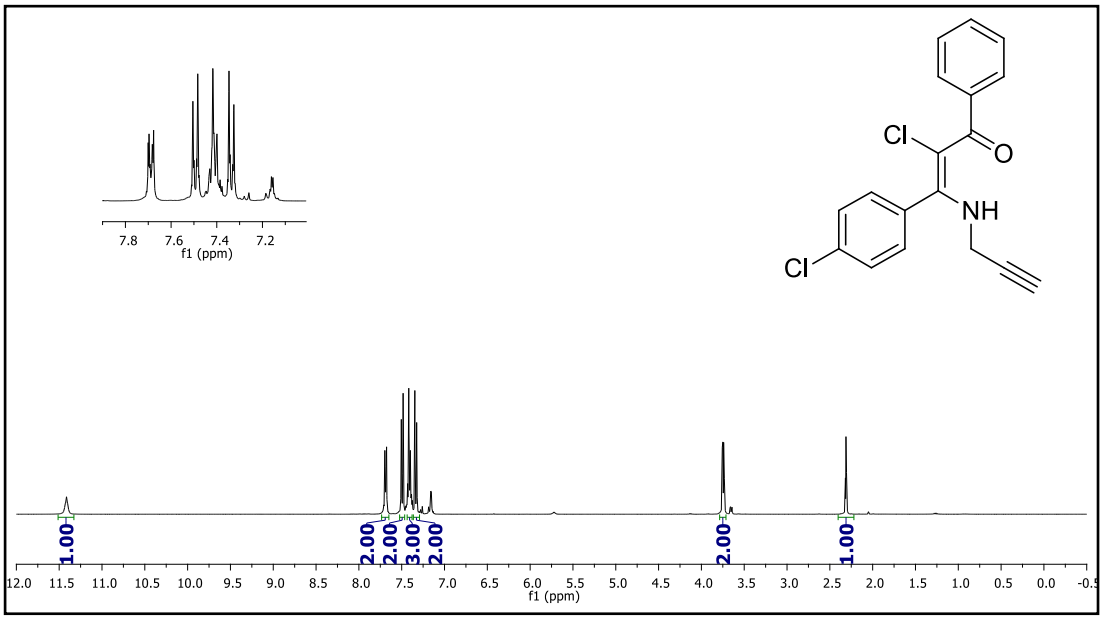

Figure 141. ^{1}H NMR spectrum of compound **35N**.

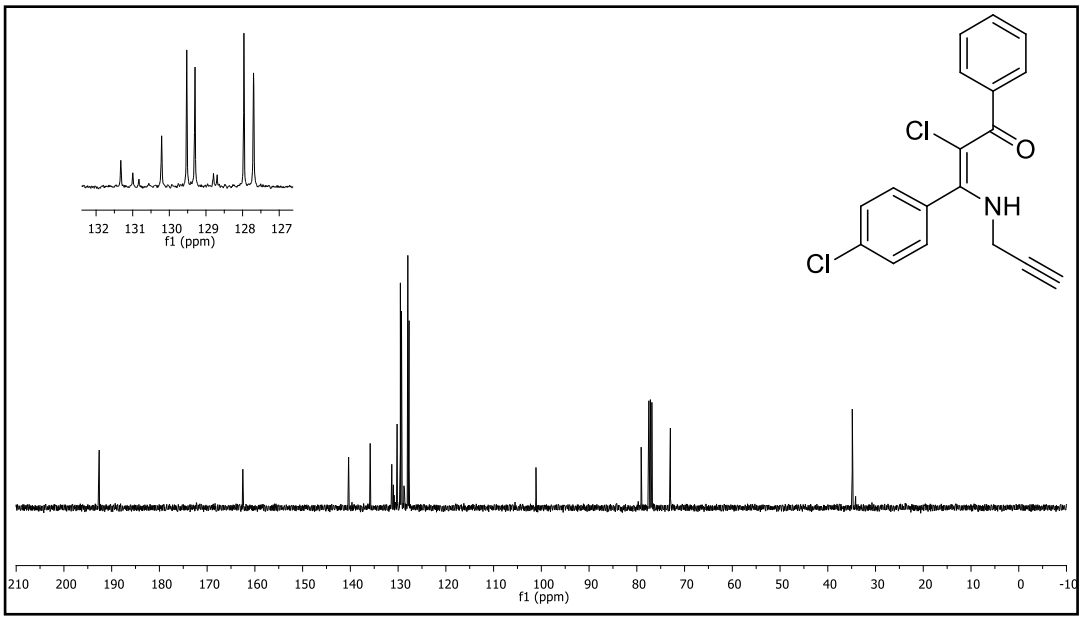

Figure 142. ^{1}H NMR spectrum of compound **35N**.

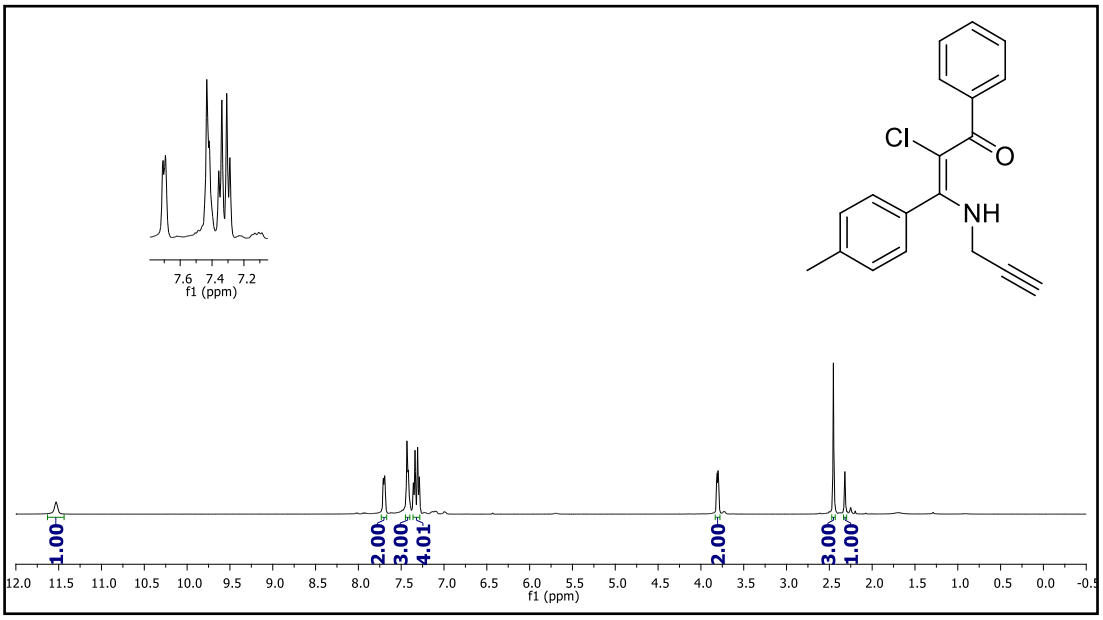

Figure 143. ^{1}H NMR spectrum of compound **35O**.

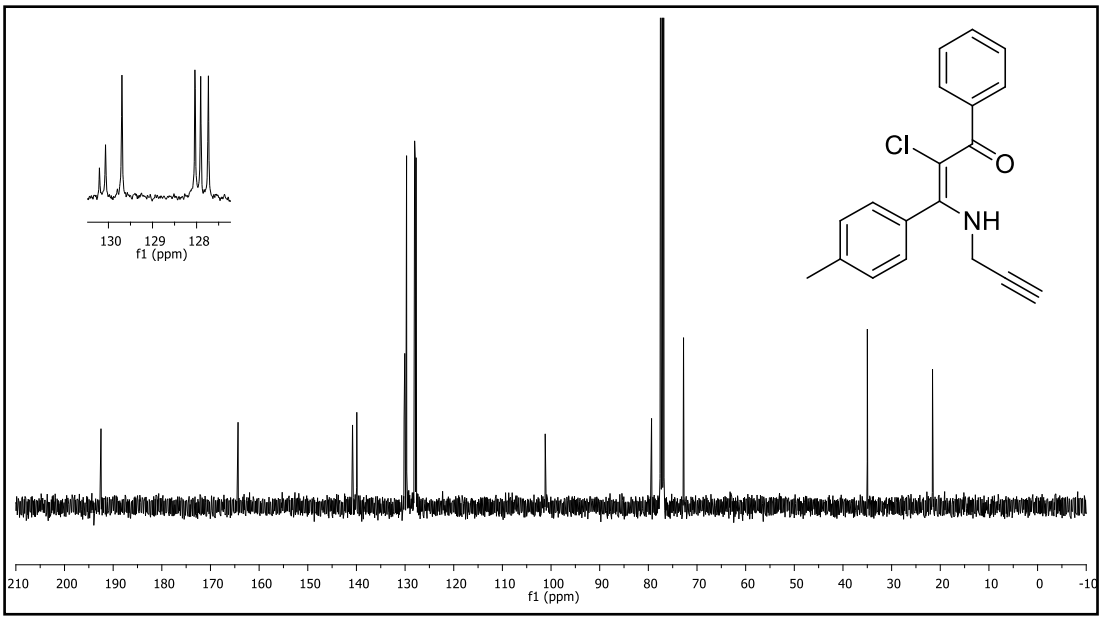

Figure 144. ^{13}C NMR spectrum of compound **35O**.

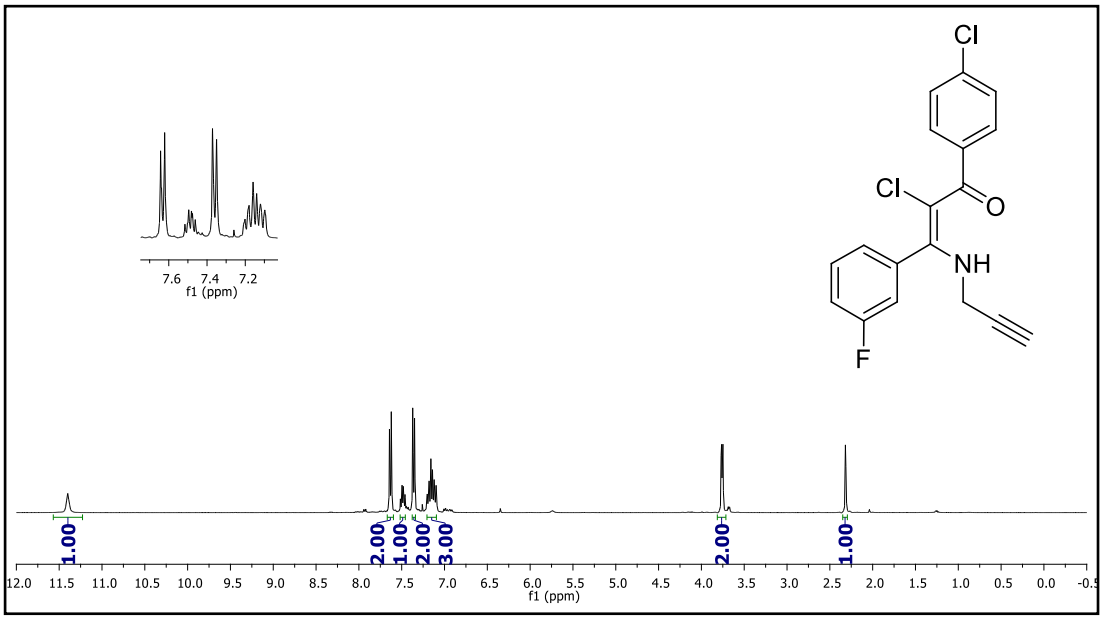

Figure 145. ^{1}H NMR spectrum of compound **35P**.

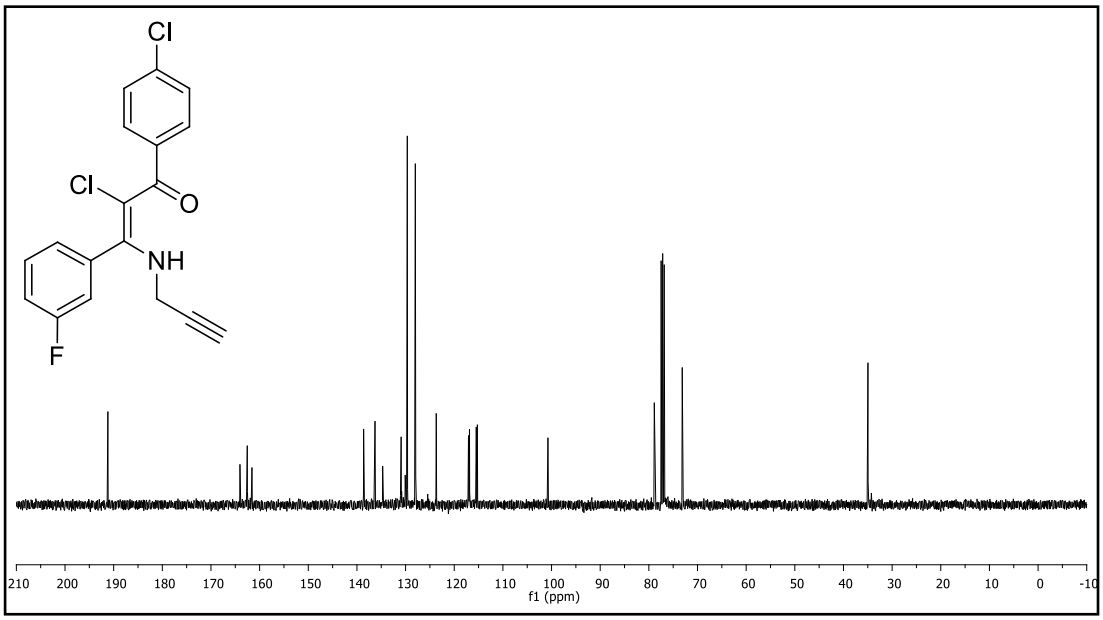

Figure 146. ^{13}C NMR spectrum of compound **35P**.

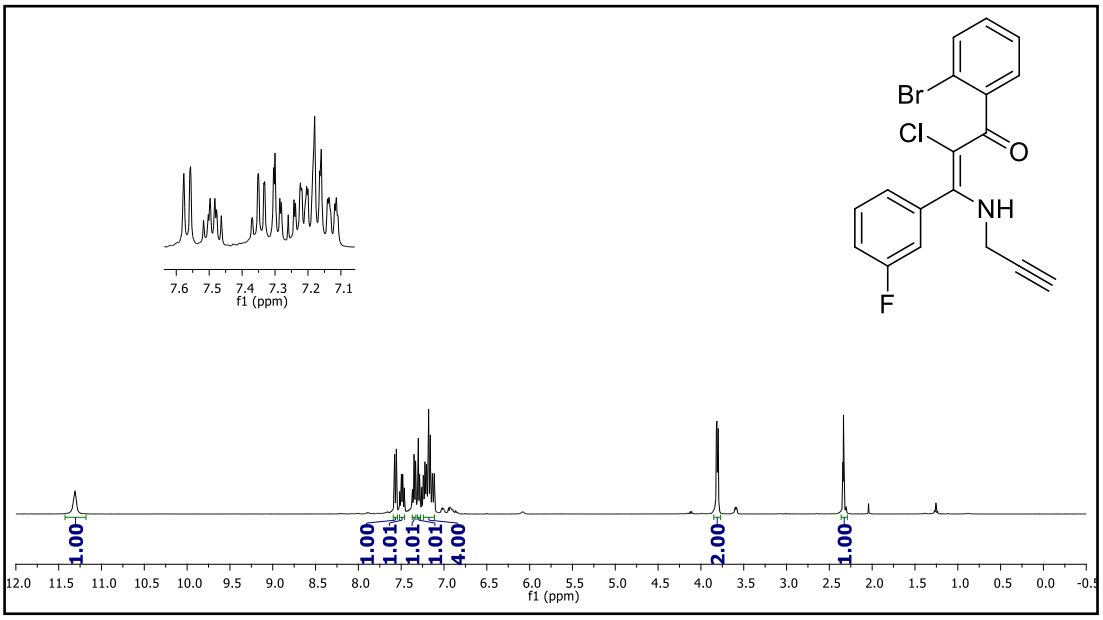

Figure 147. ^{1}H NMR spectrum of compound **35Q**.

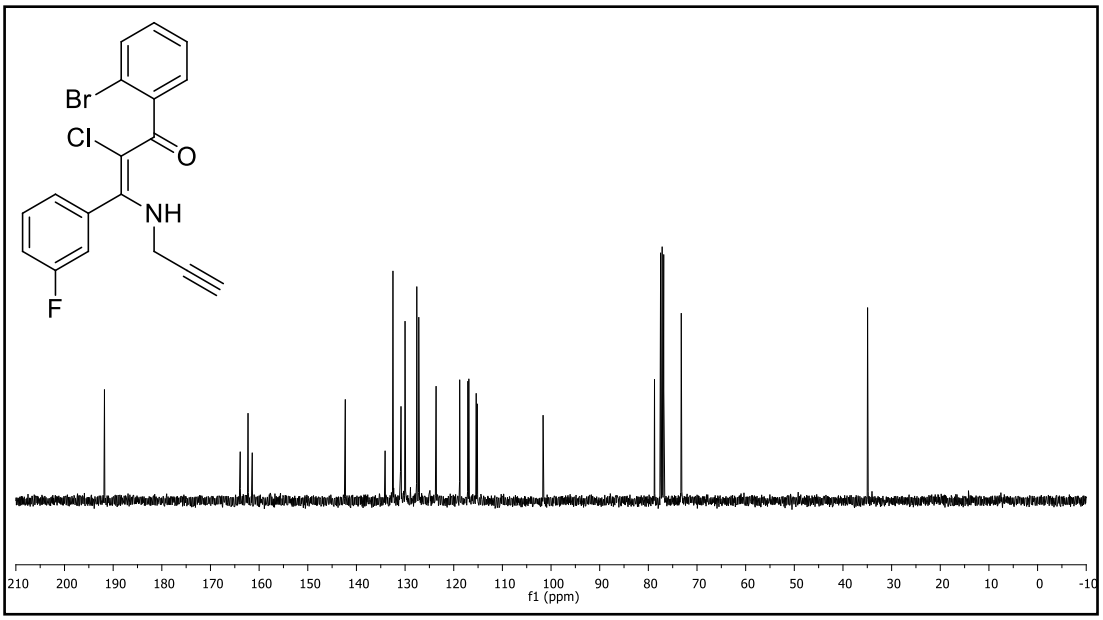

Figure 148. ^{13}C NMR spectrum of compound **35Q**.

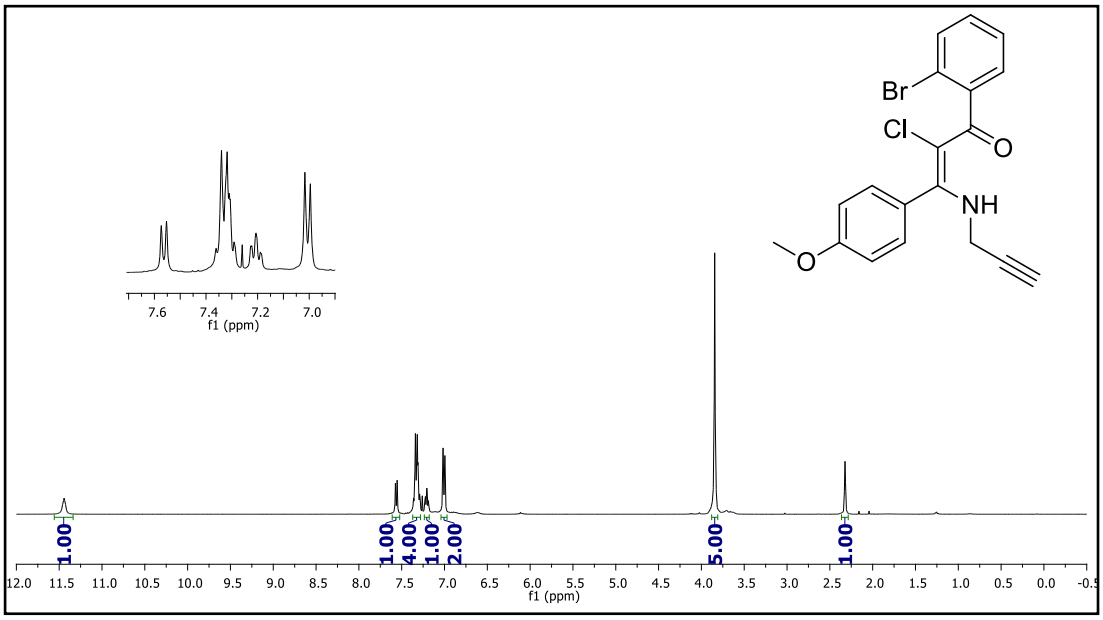

Figure 149. ^{1}H NMR spectrum of compound **35R**.

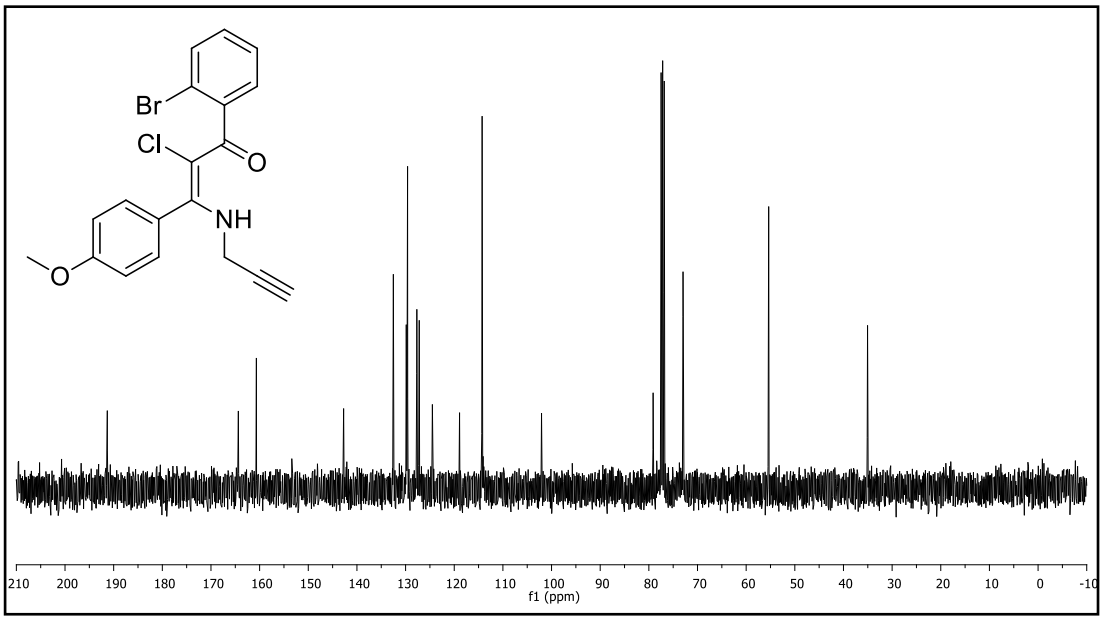

Figure 150. ^{13}C NMR spectrum of compound **35R**.

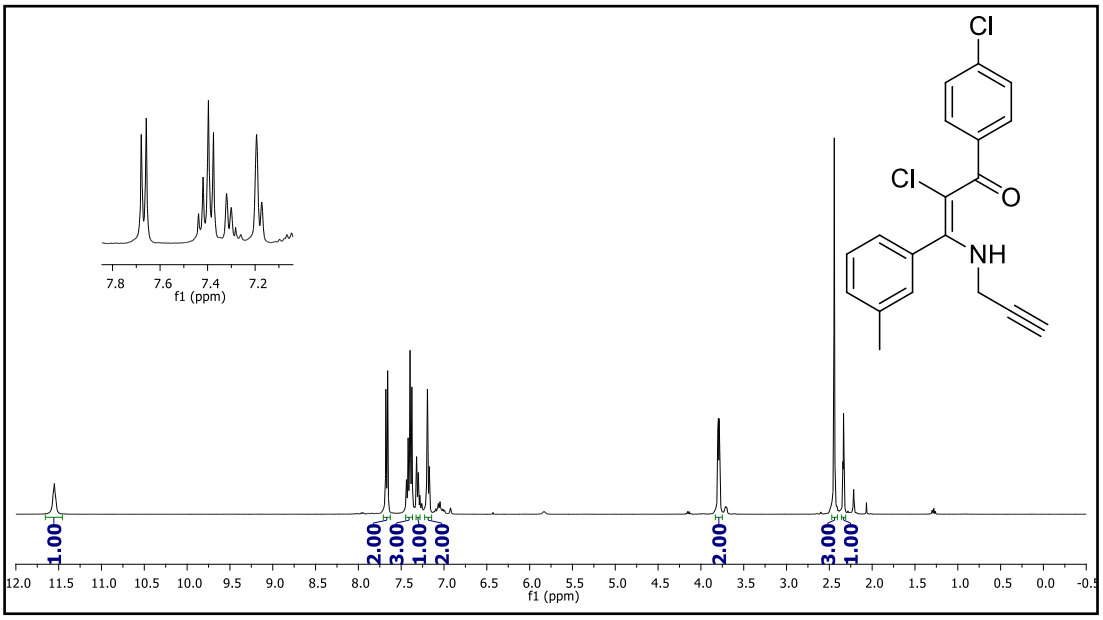

Figure 151. ^{1}H NMR spectrum of compound **35S**.

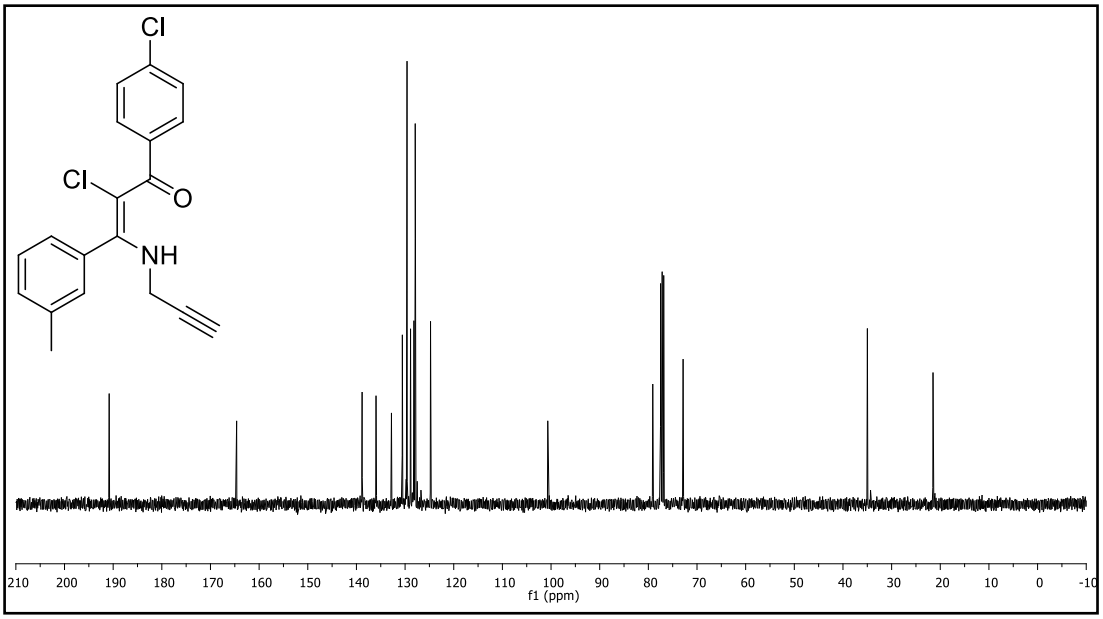

Figure 152. ^{13}C NMR spectrum of compound **35S**.

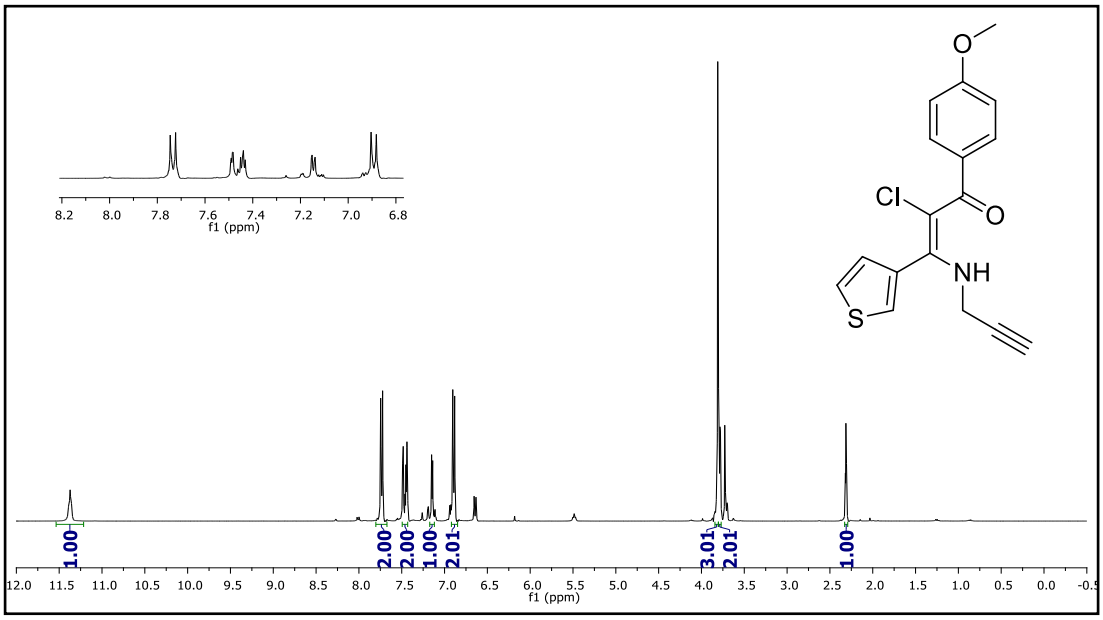

Figure 153. ^{1}H NMR spectrum of compound **35T**.

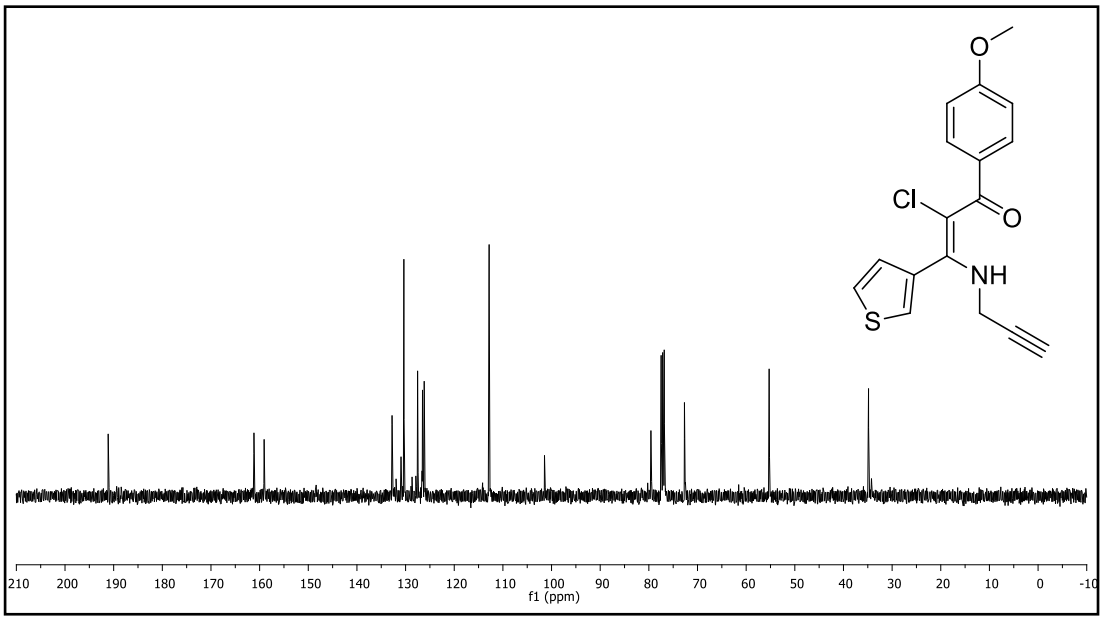

Figure 154. ^{13}C NMR spectrum of compound **35T**.

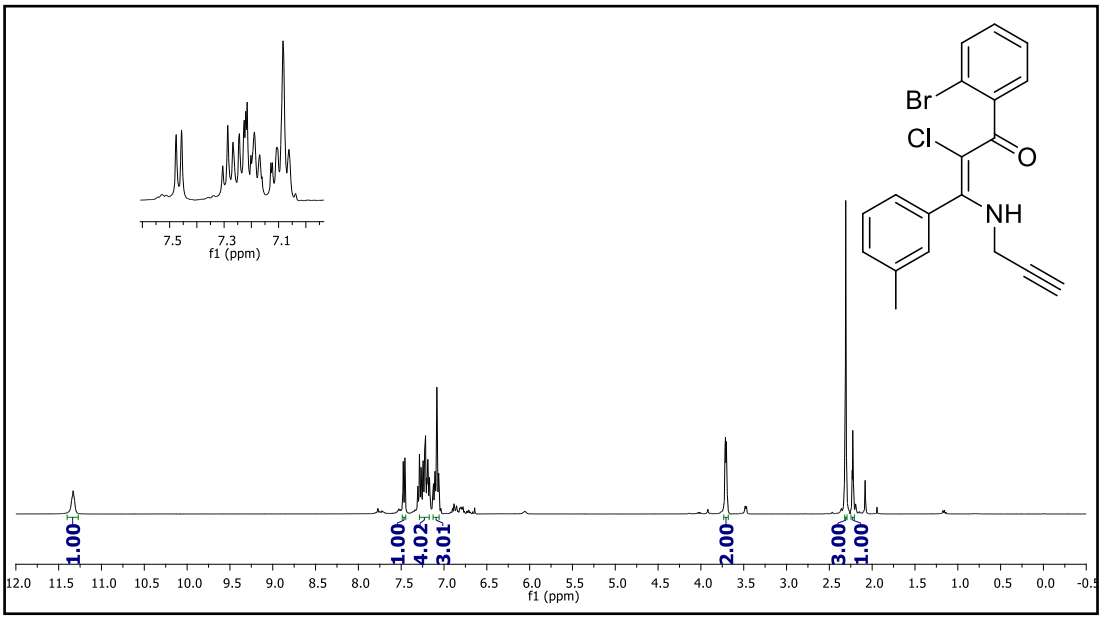

Figure 155. ^{1}H NMR spectrum of compound **35U**.

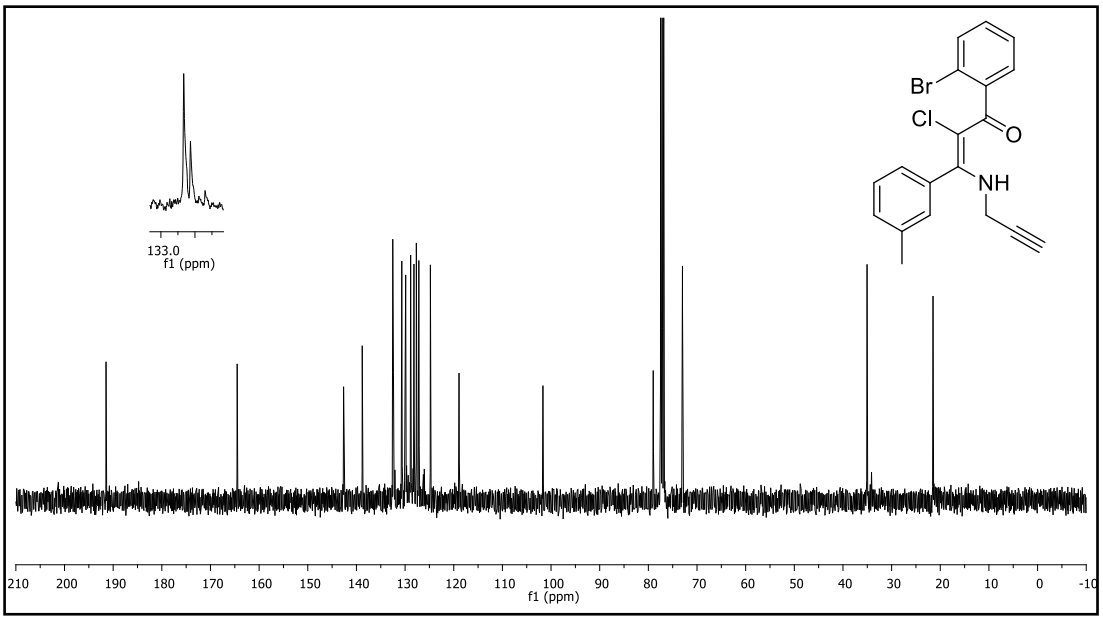

Figure 156. ^{13}C NMR spectrum of compound **35U**.

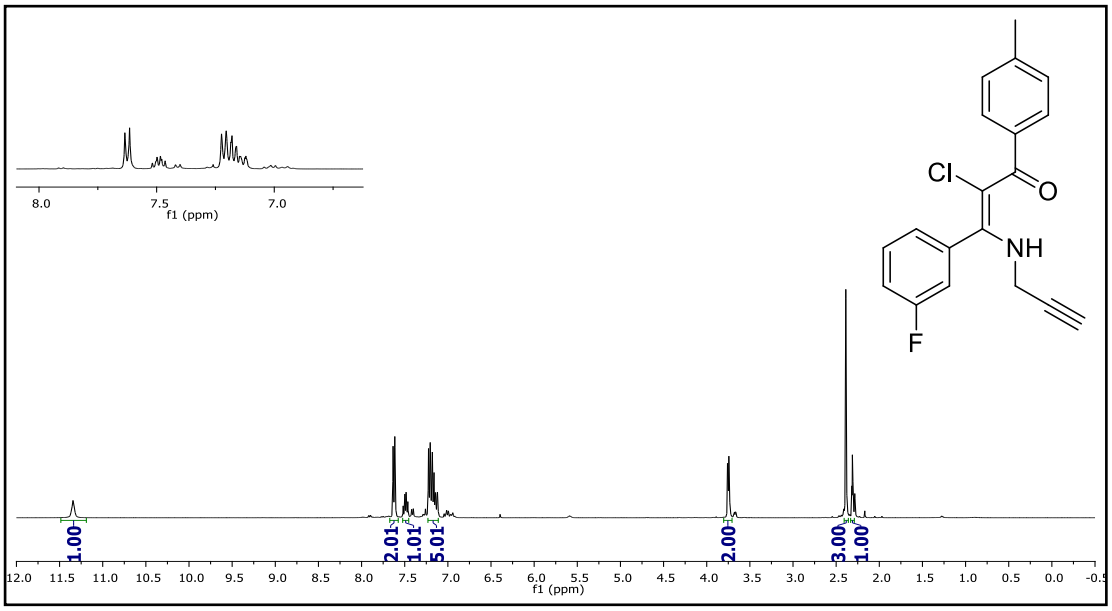

Figure 157. ^{1}H NMR spectrum of compound **35V**.

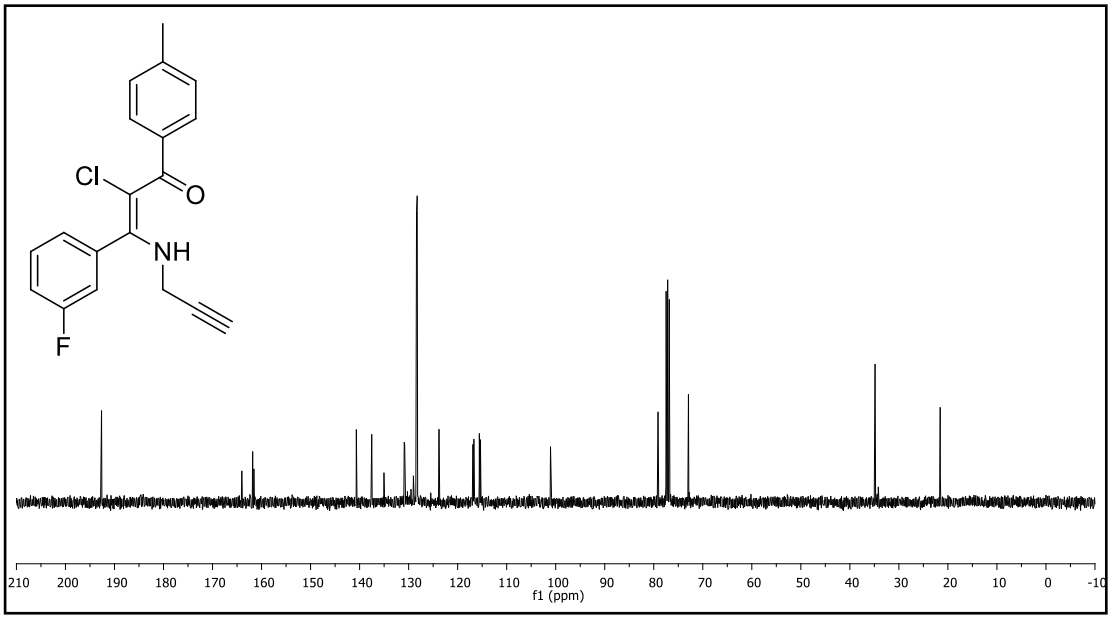

Figure 158. ^{13}C NMR spectrum of compound **35V**.

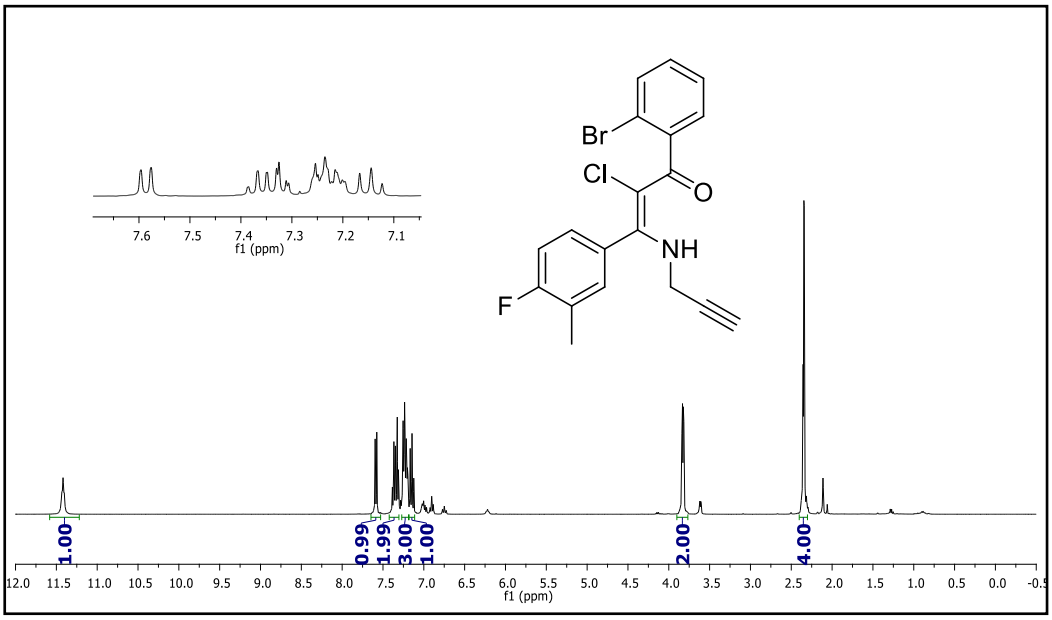

Figure 159. ^{1}H NMR spectrum of compound **35W**.

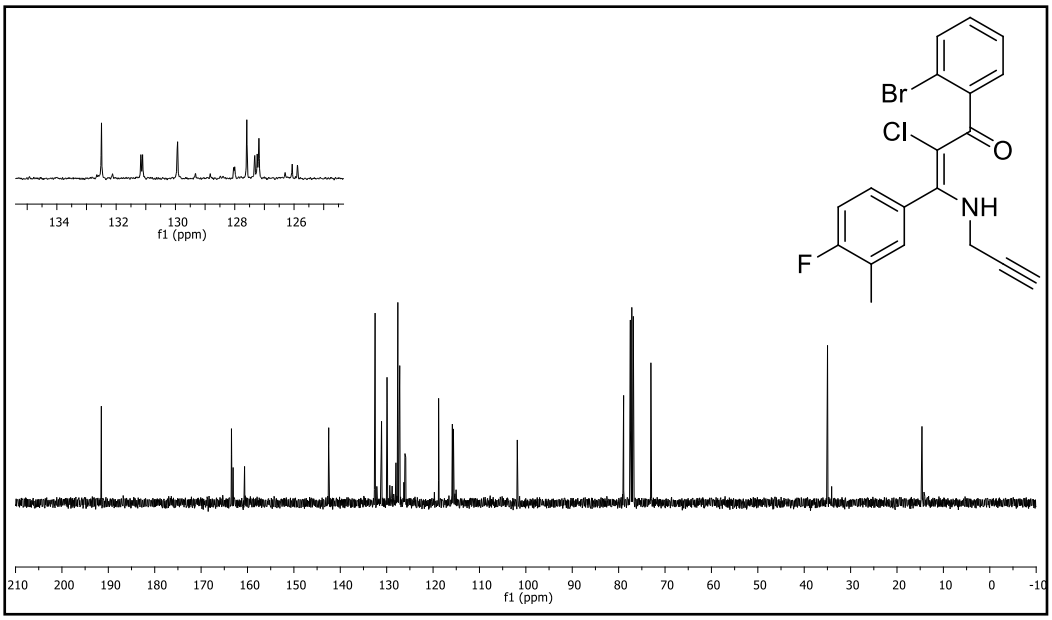

Figure 160. ^{13}C NMR spectrum of compound **35W**.

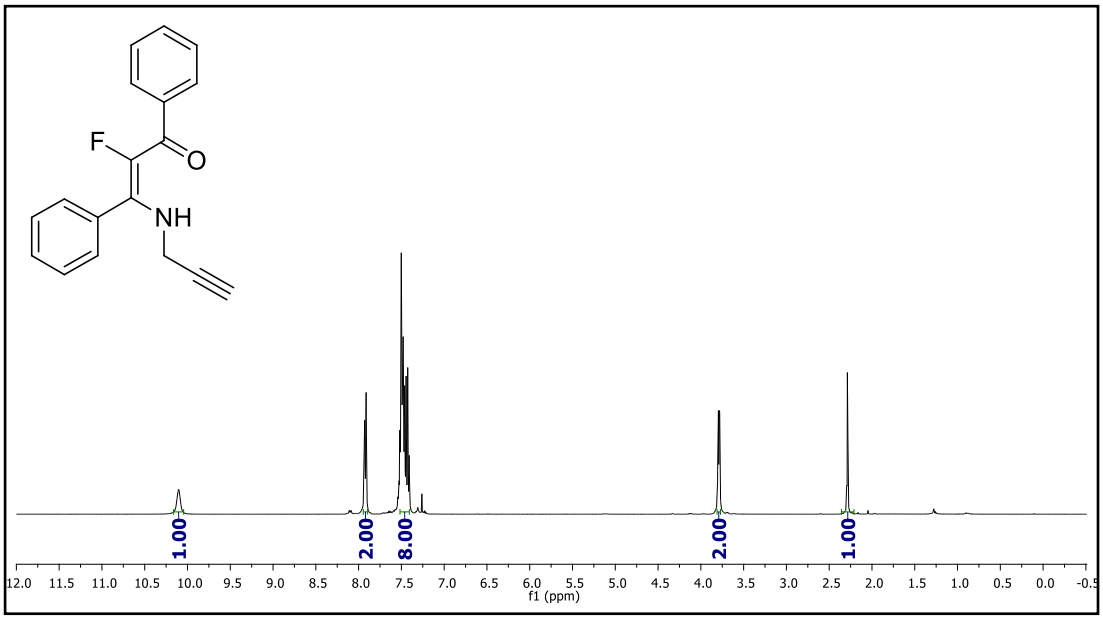

Figure 161. ^{1}H NMR spectrum of compound **36A**.

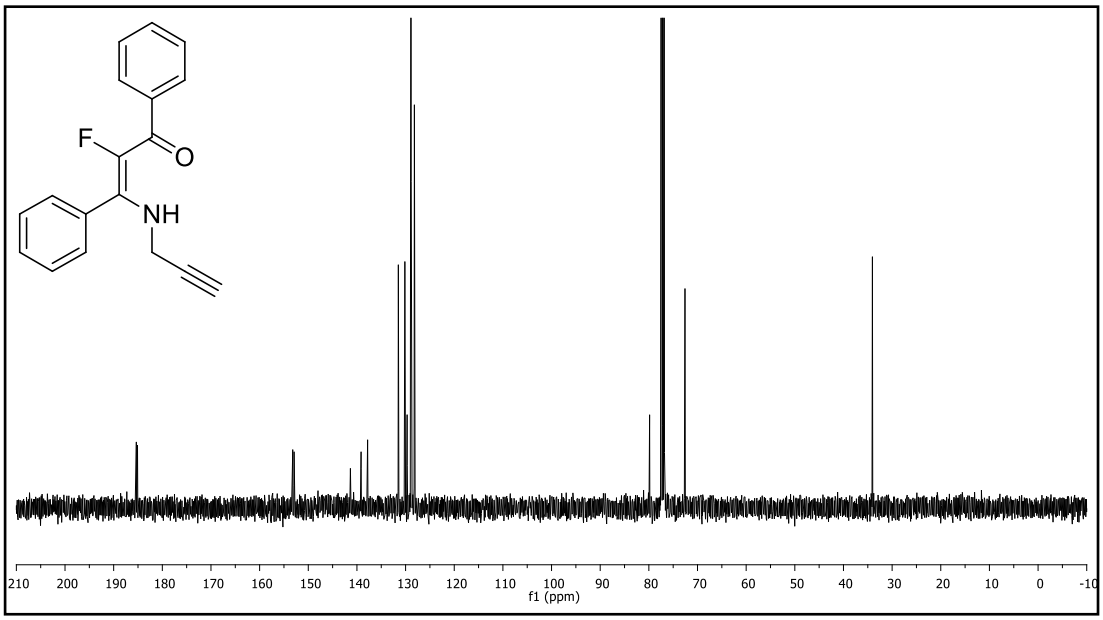

Figure 162. ^{13}C NMR spectrum of compound **36A**.

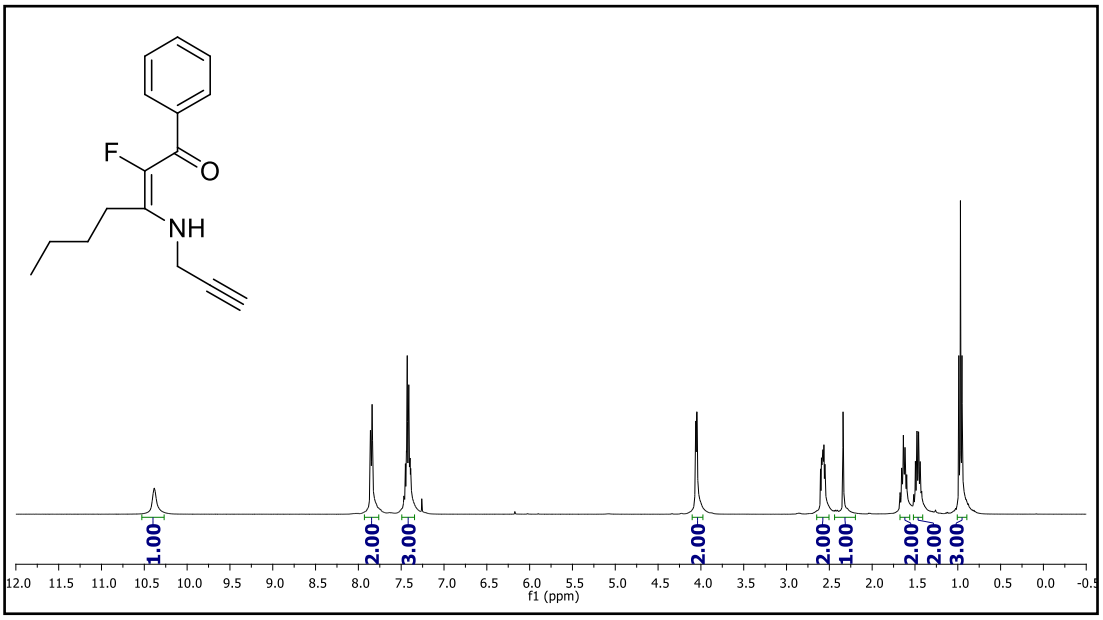

Figure 163. ^{1}H NMR spectrum of compound **36B**.

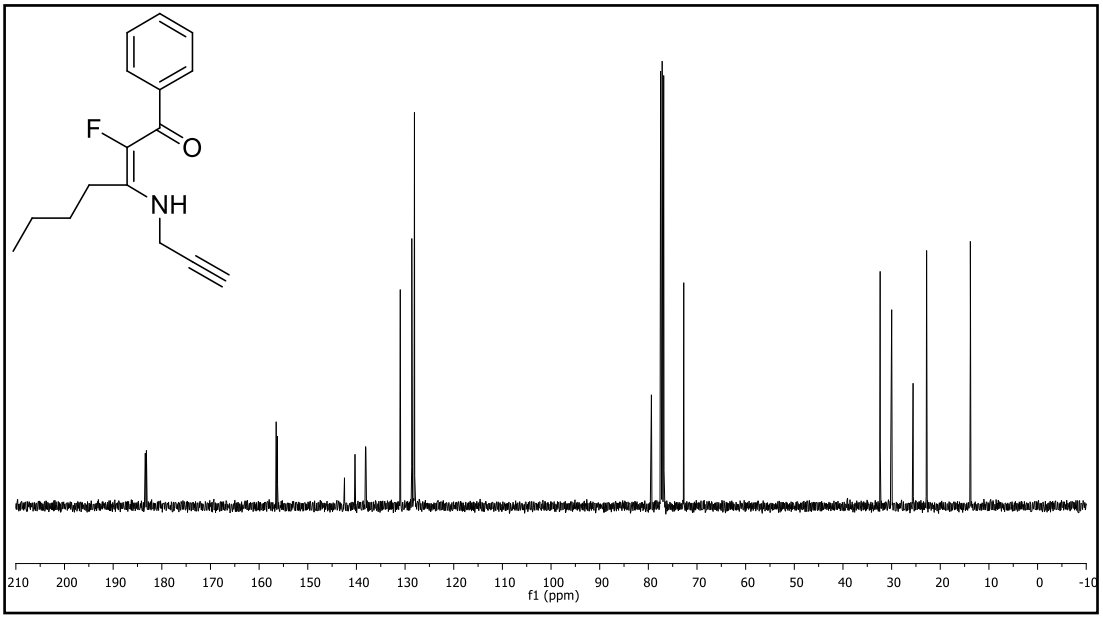

Figure 164. ^{13}C NMR spectrum of compound **36B**.

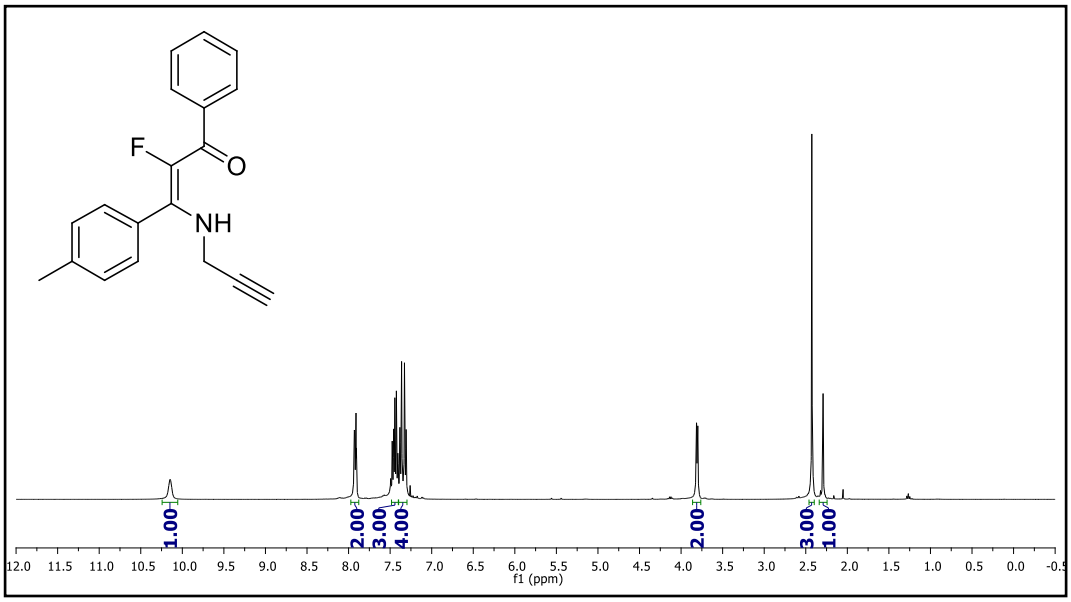

Figure 165. ^{1}H NMR spectrum of compound **36O**.

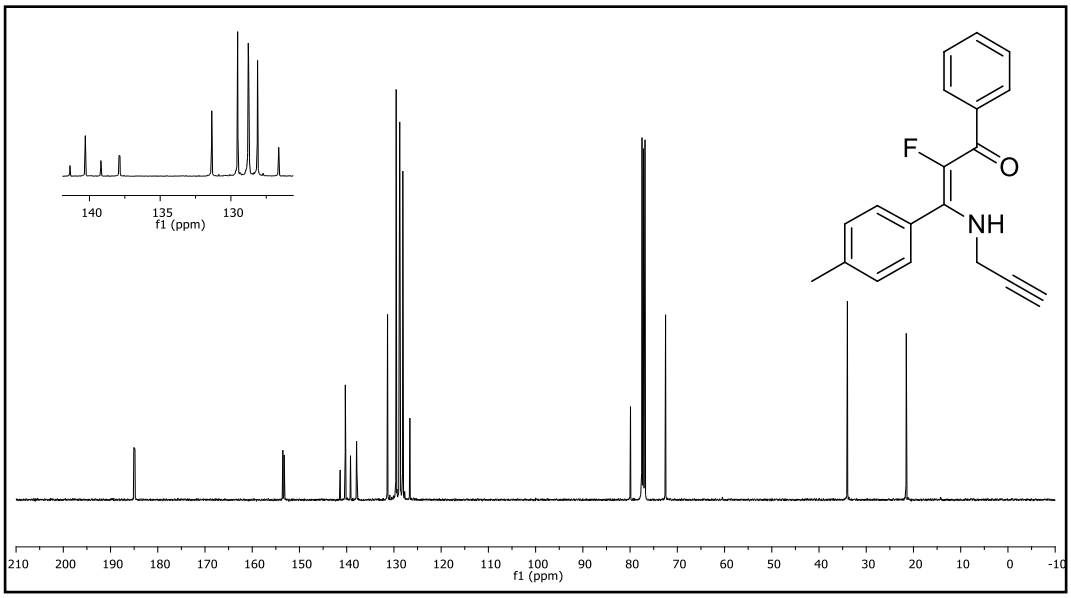

Figure 166. ^{13}C NMR spectrum of compound **36O**.

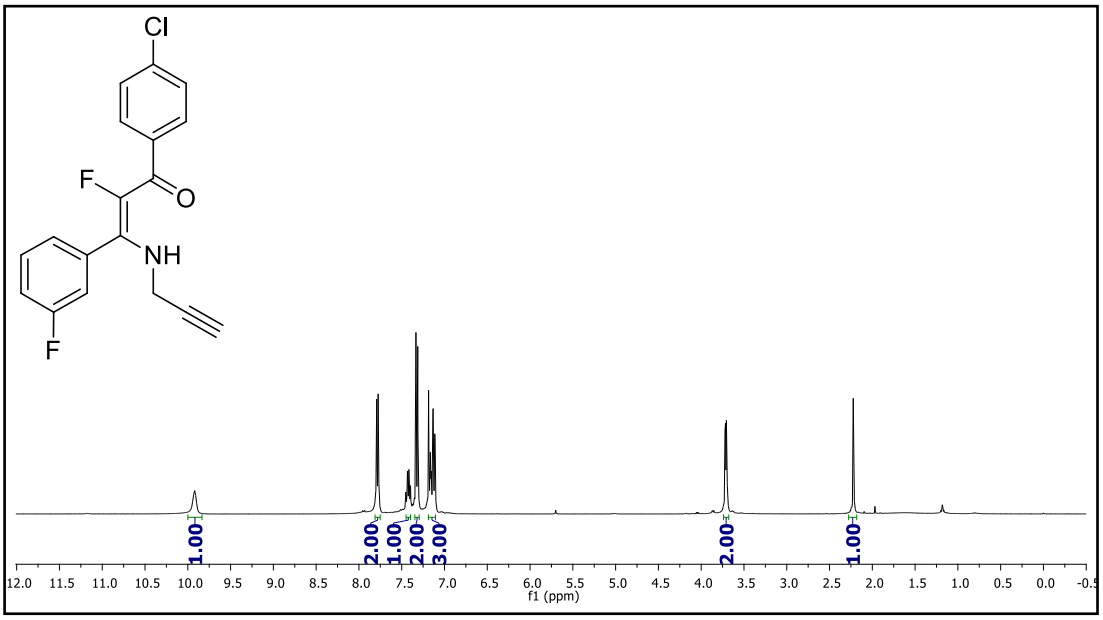

Figure 167. ^{1}H NMR spectrum of compound **36P**.

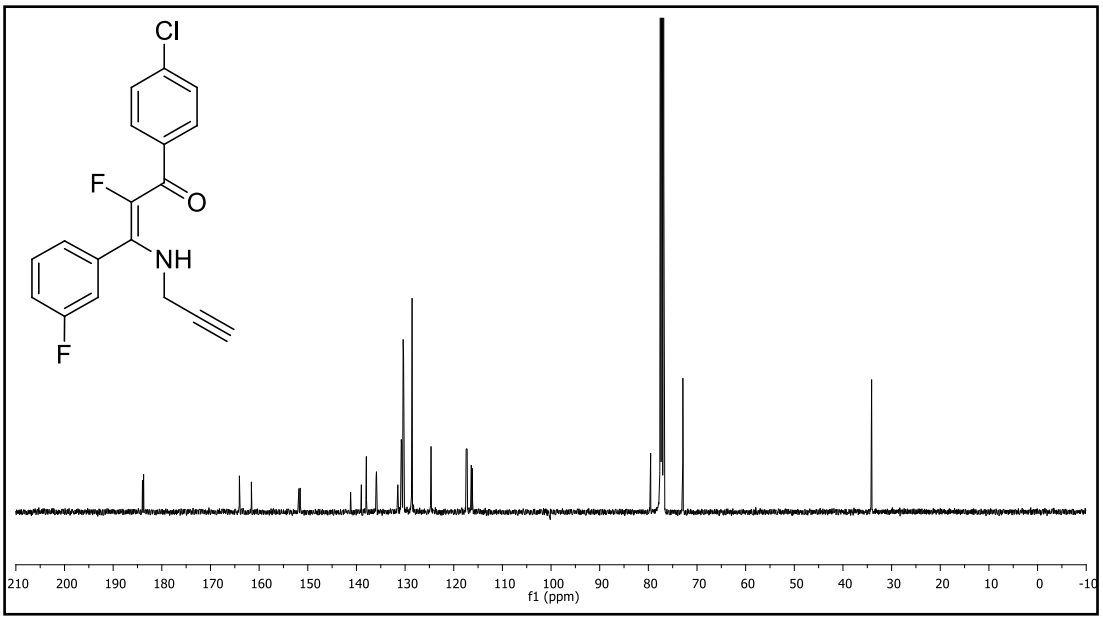

Figure 168. ^{13}C NMR spectrum of compound **36P**.

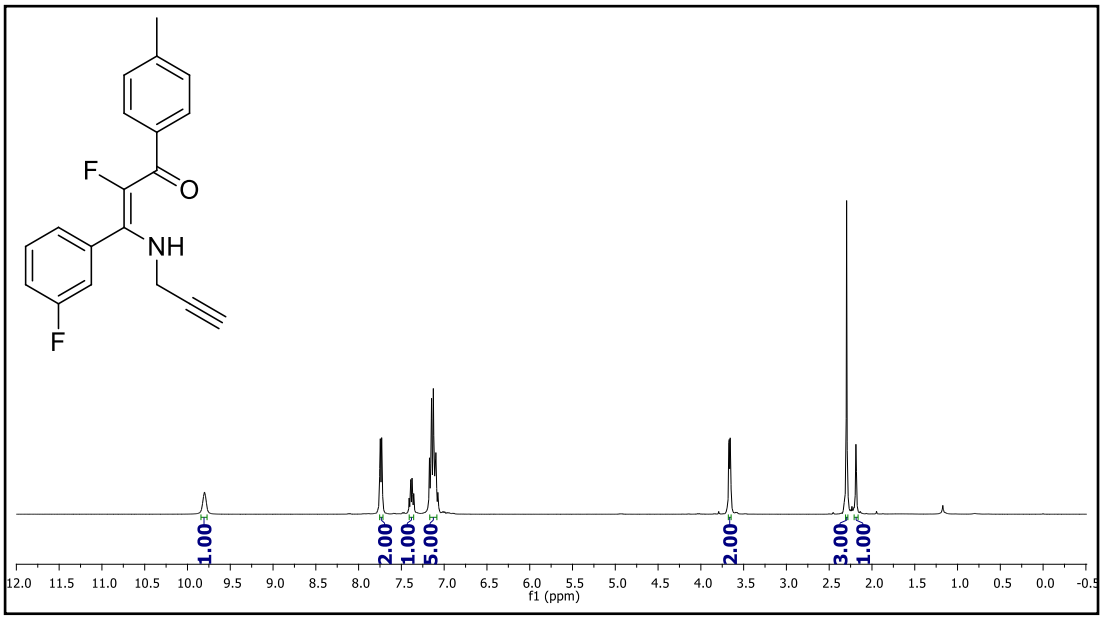

Figure 169. ^{1}H NMR spectrum of compound **36V**.

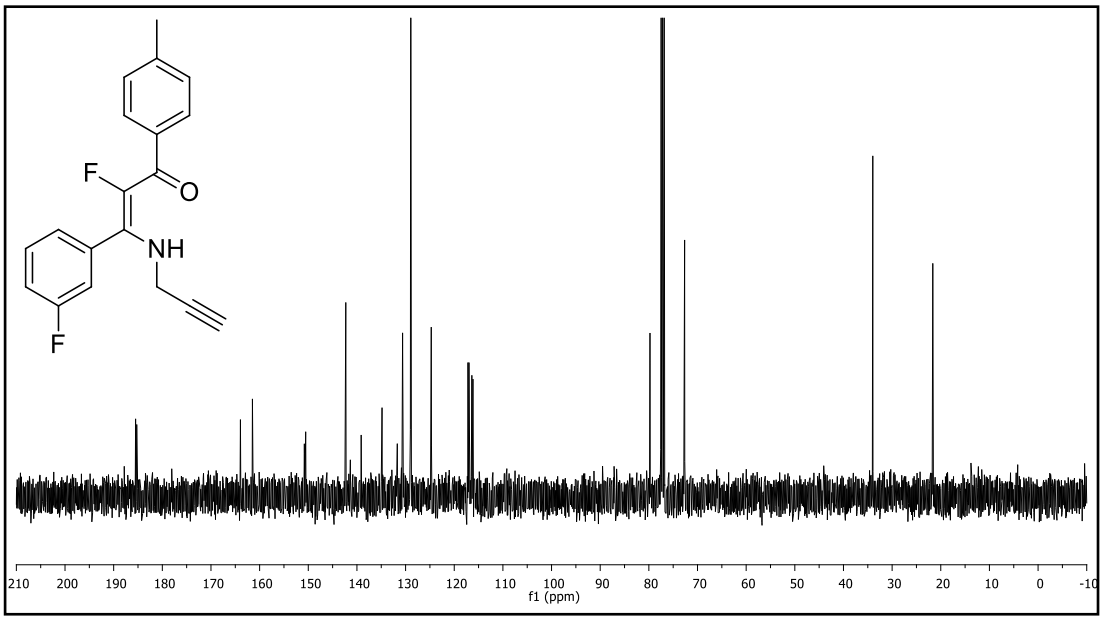

Figure 170. ^{13}C NMR spectrum of compound **36V**.

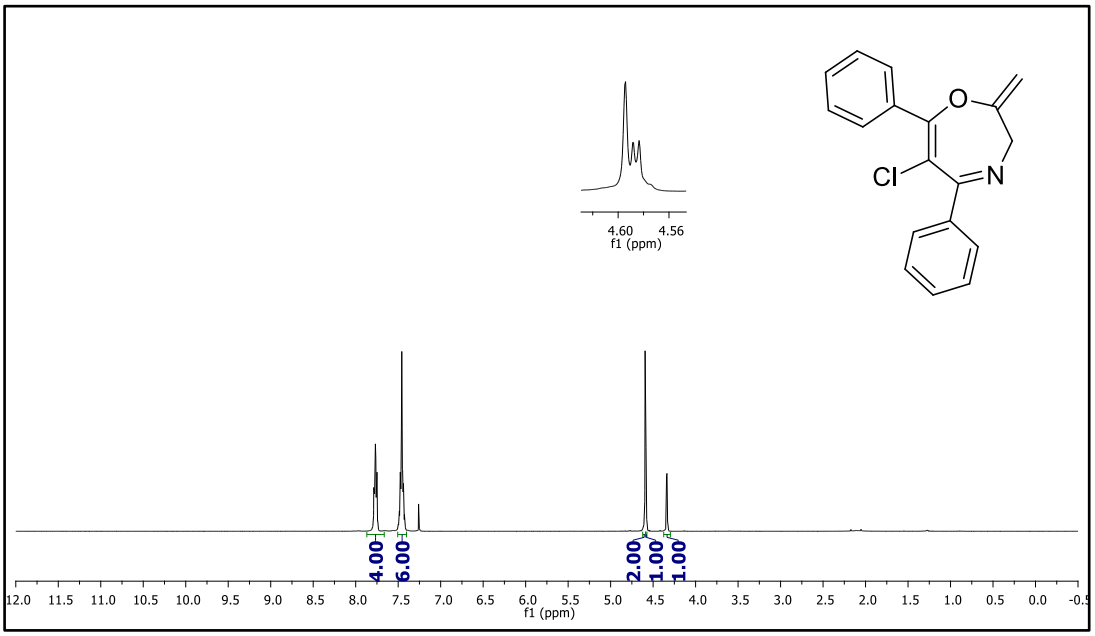

Figure 171. [1] H NMR spectrum of compound **37A**.

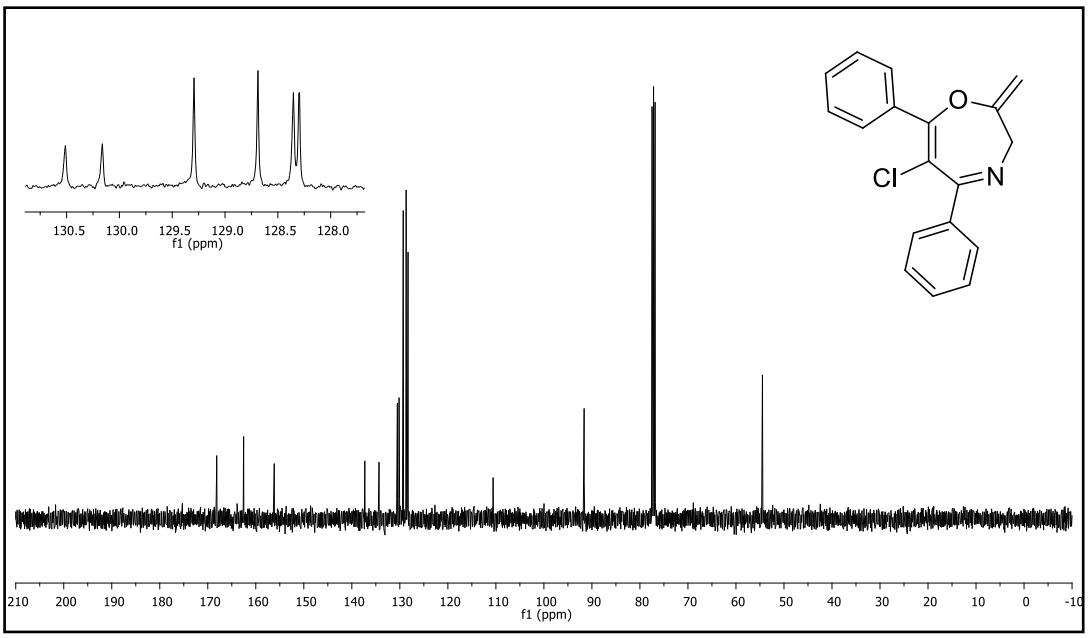

Figure 172. [13]C NMR spectrum of compound **37A**.

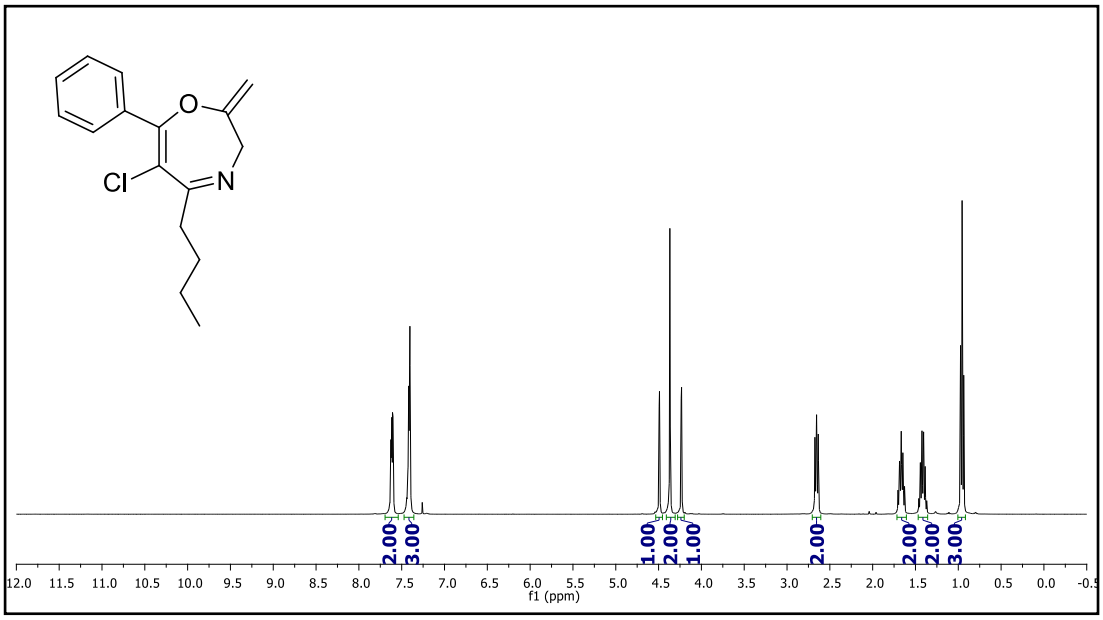

Figure 173. ^{1}H NMR spectrum of compound **37B**.

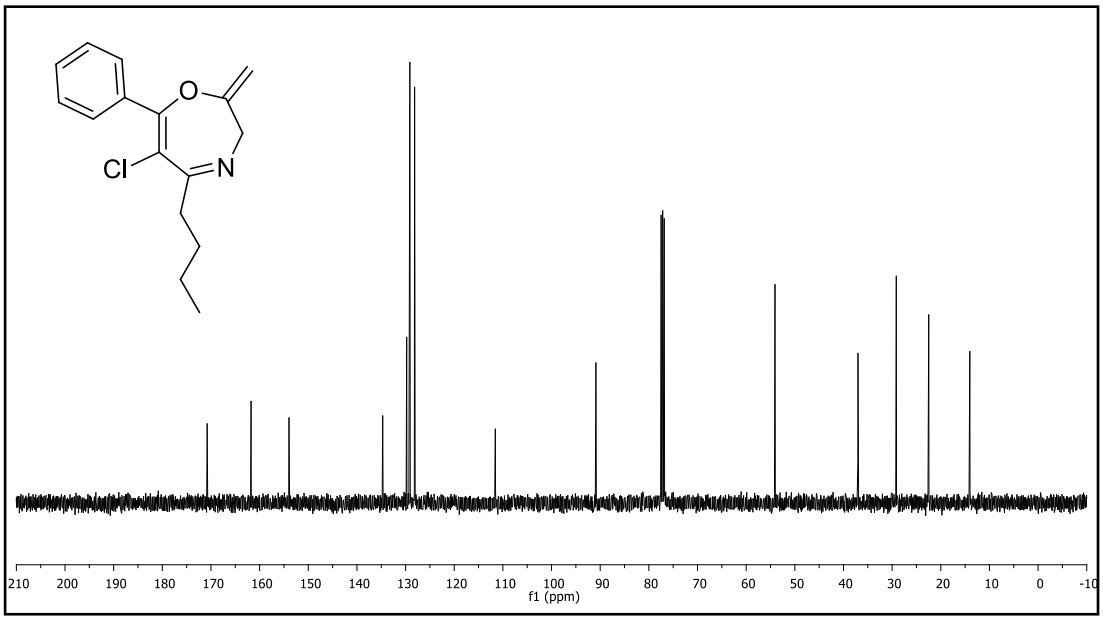

Figure 174. ^{13}C NMR spectrum of compound **37B**.

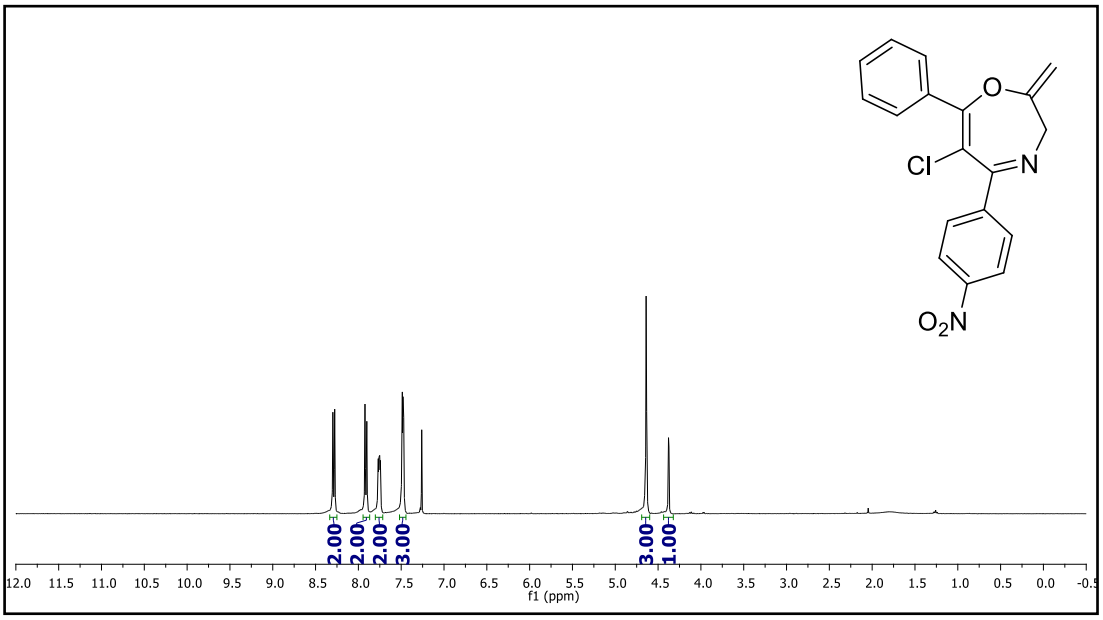

Figure 175. ^{1}H NMR spectrum of compound **37C**.

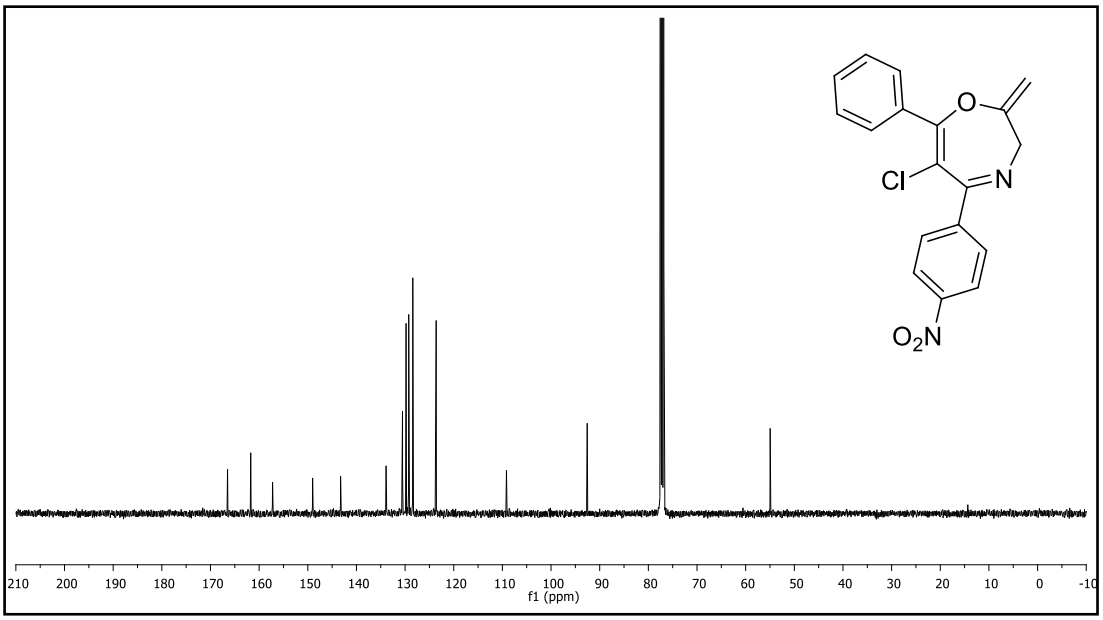

Figure 176. ^{13}C NMR spectrum of compound **37C**.

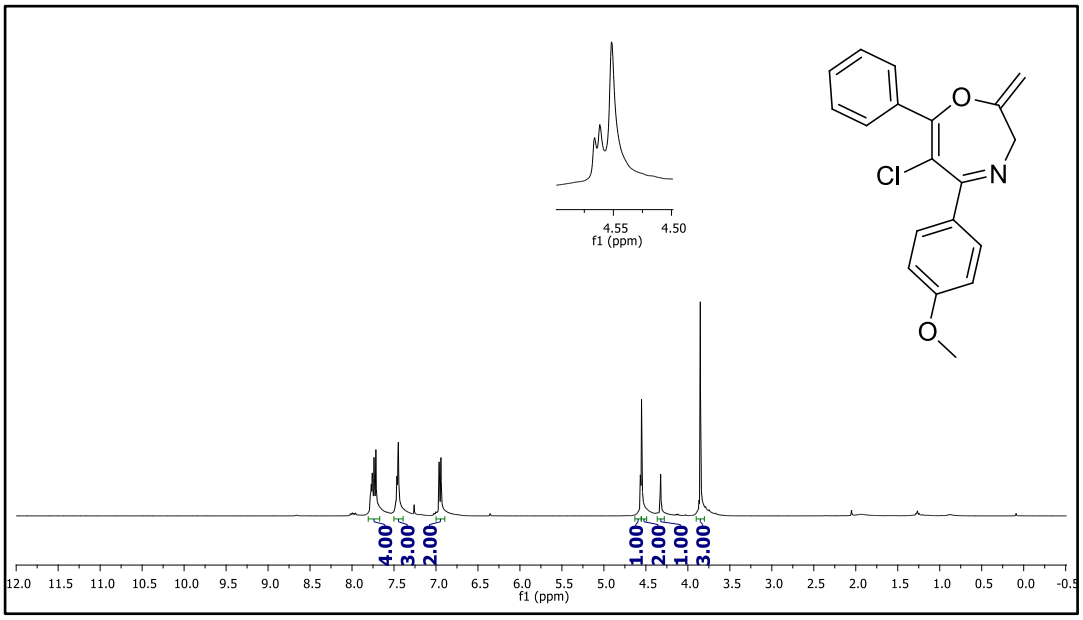

Figure 177. ^{1}H NMR spectrum of compound **37D**.

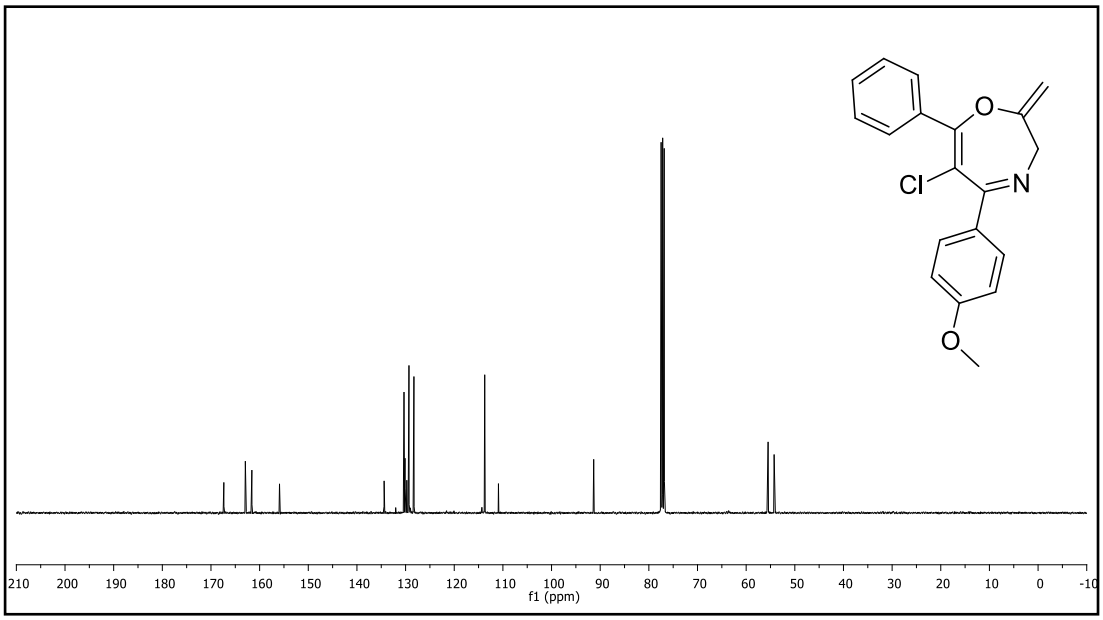

Figure 178. ^{13}C NMR spectrum of compound **37D**.

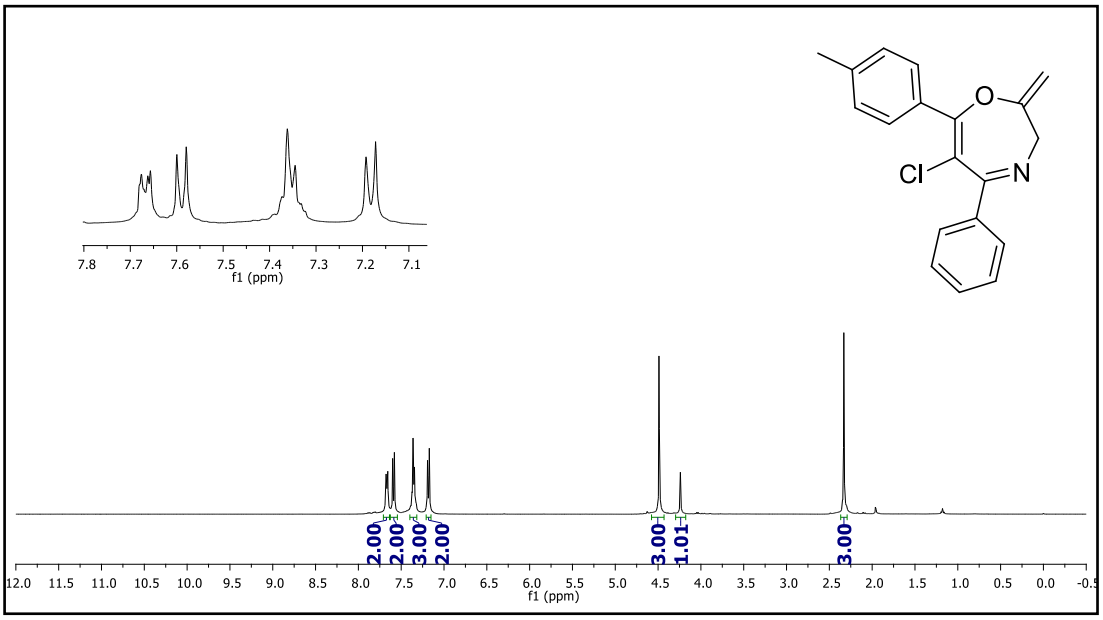

Figure 179. ^{1}H NMR spectrum of compound **37E**.

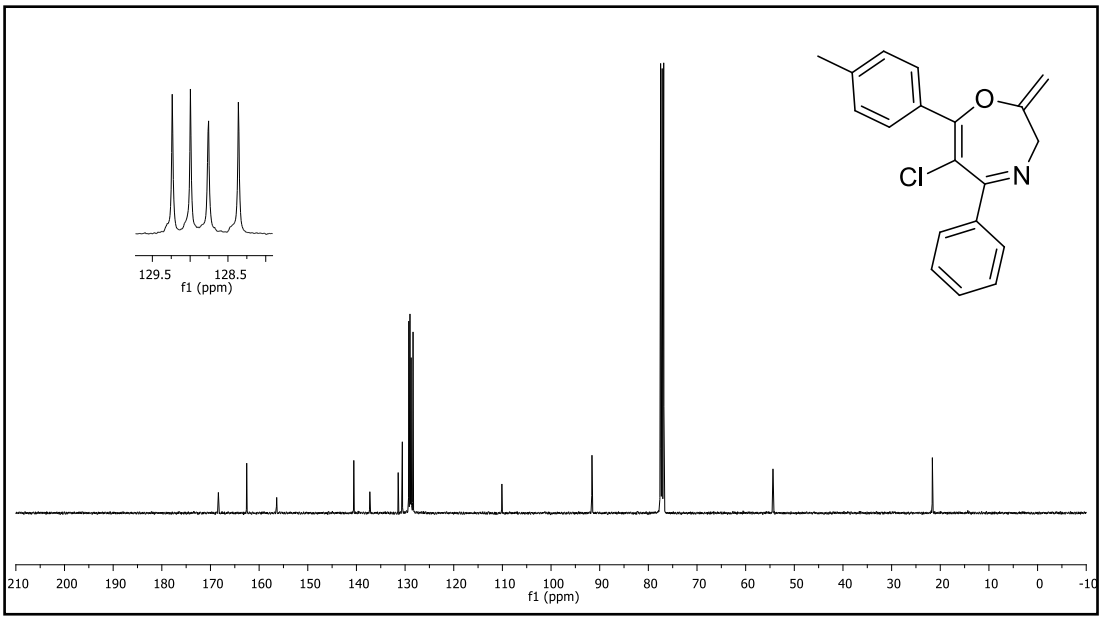

Figure 180. ^{13}C NMR spectrum of compound **37E**.

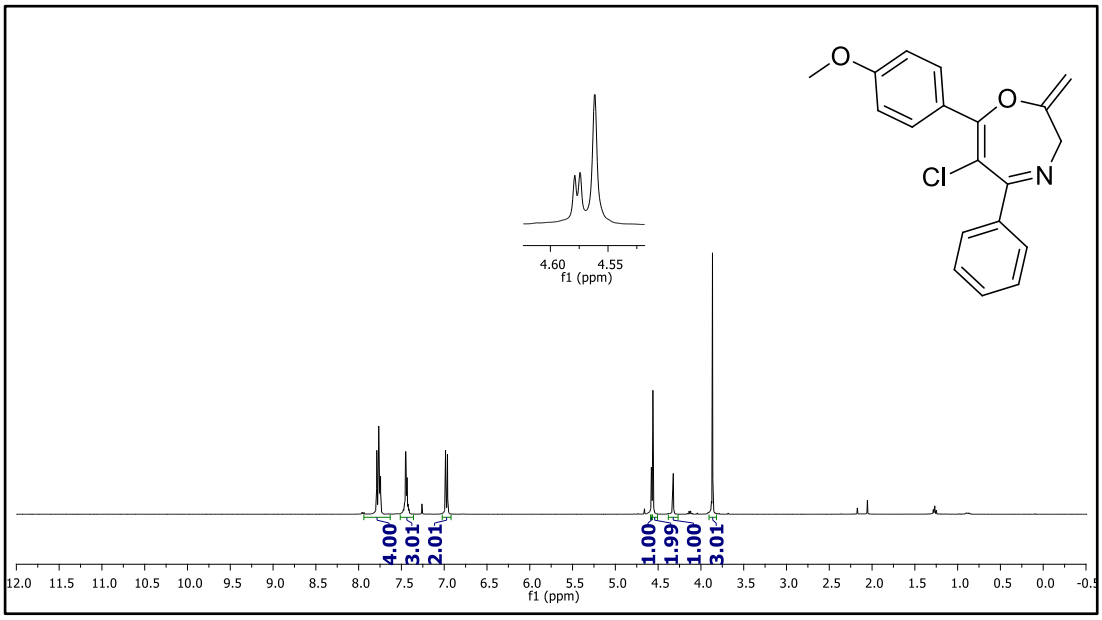

Figure 181. ^{1}H NMR spectrum of compound **37F**.

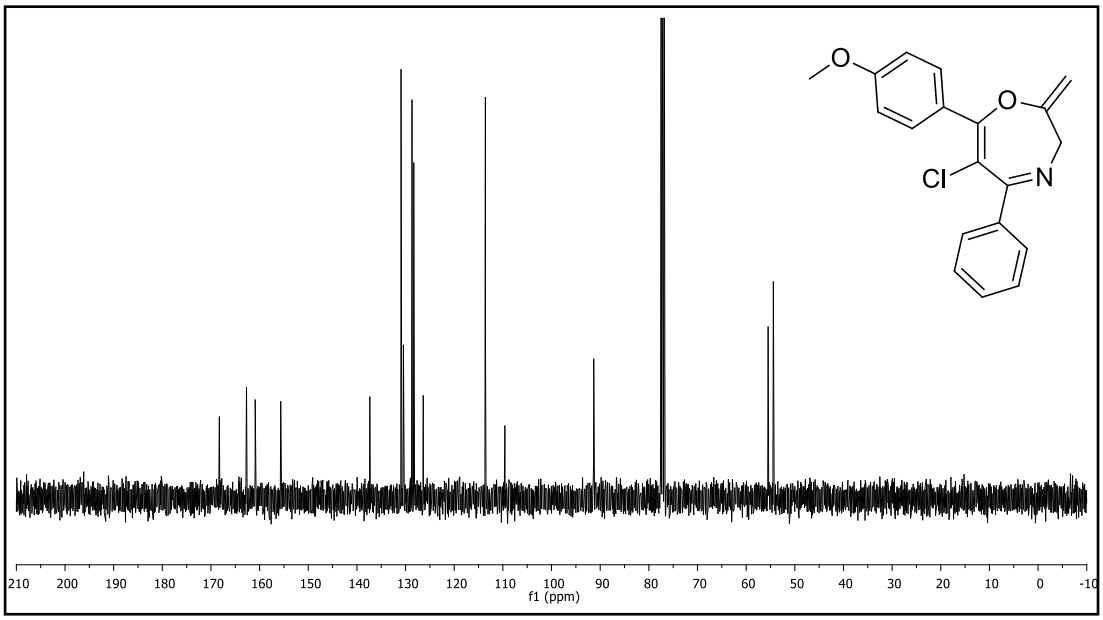

Figure 182. ^{13}C NMR spectrum of compound **37F**.

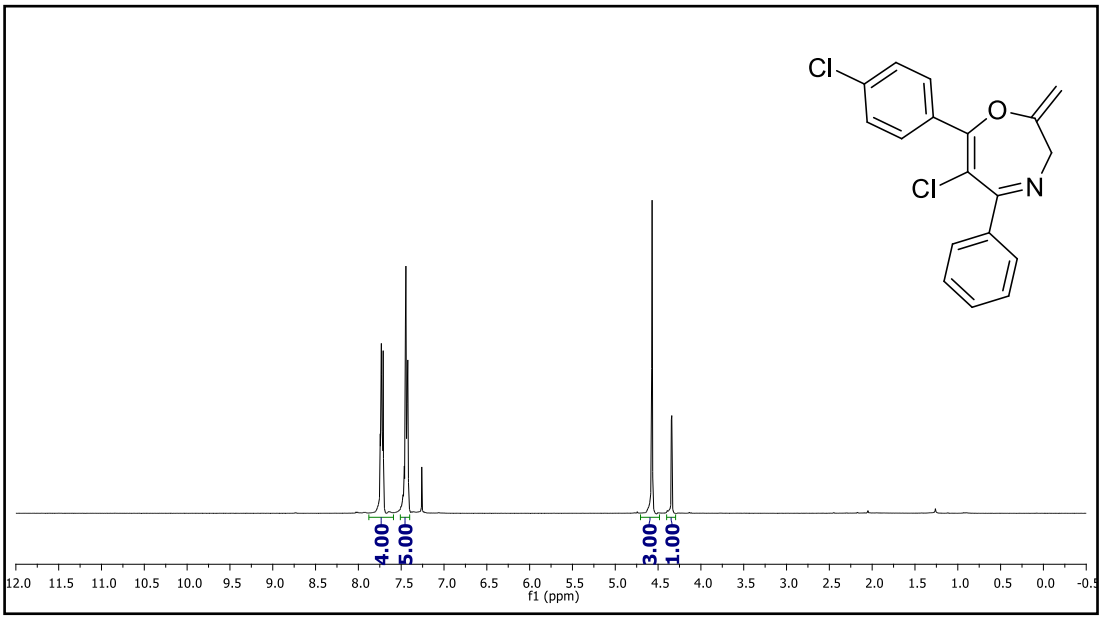

Figure 183. ^{1}H NMR spectrum of compound **37G**.

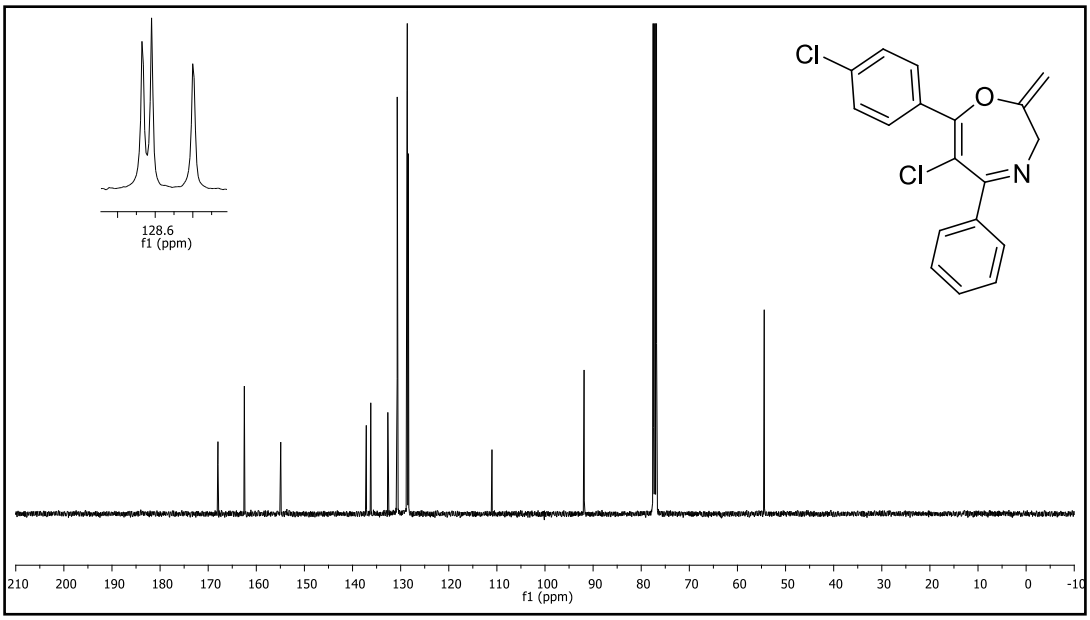

Figure 184. ^{13}C NMR spectrum of compound **37G**.

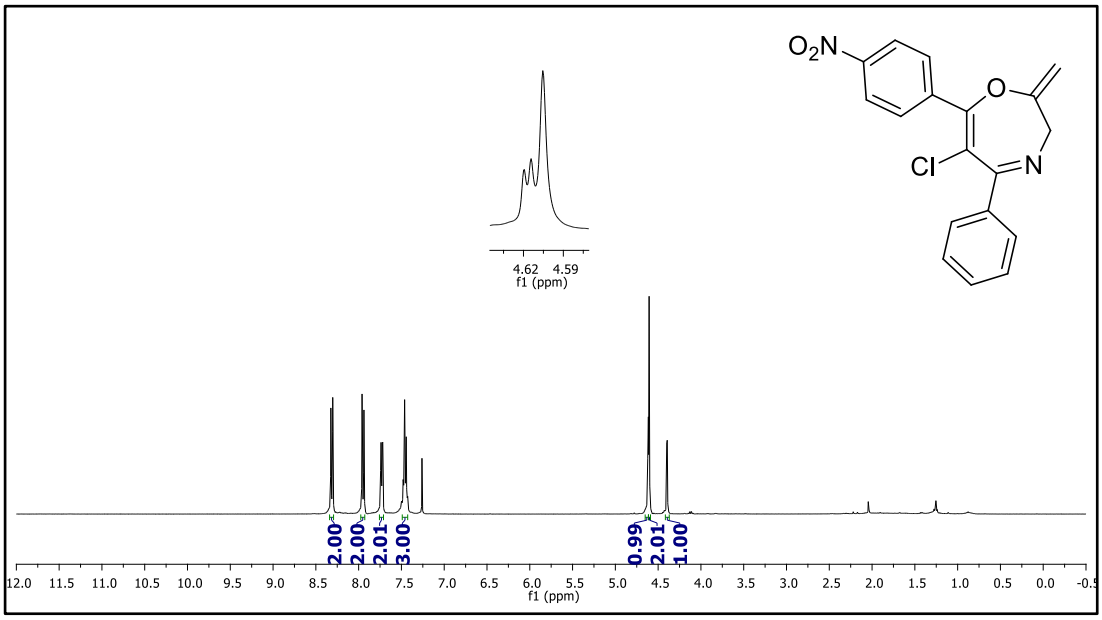

Figure 185. ^{1}H NMR spectrum of compound **37H**.

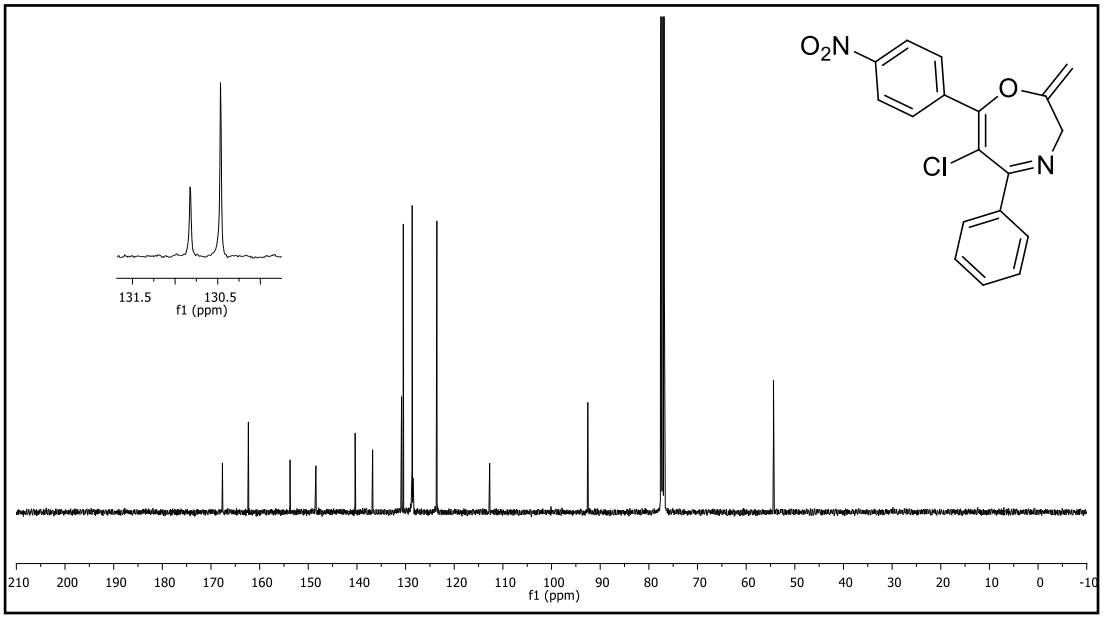

Figure 186. ^{13}C NMR spectrum of compound **37H**.

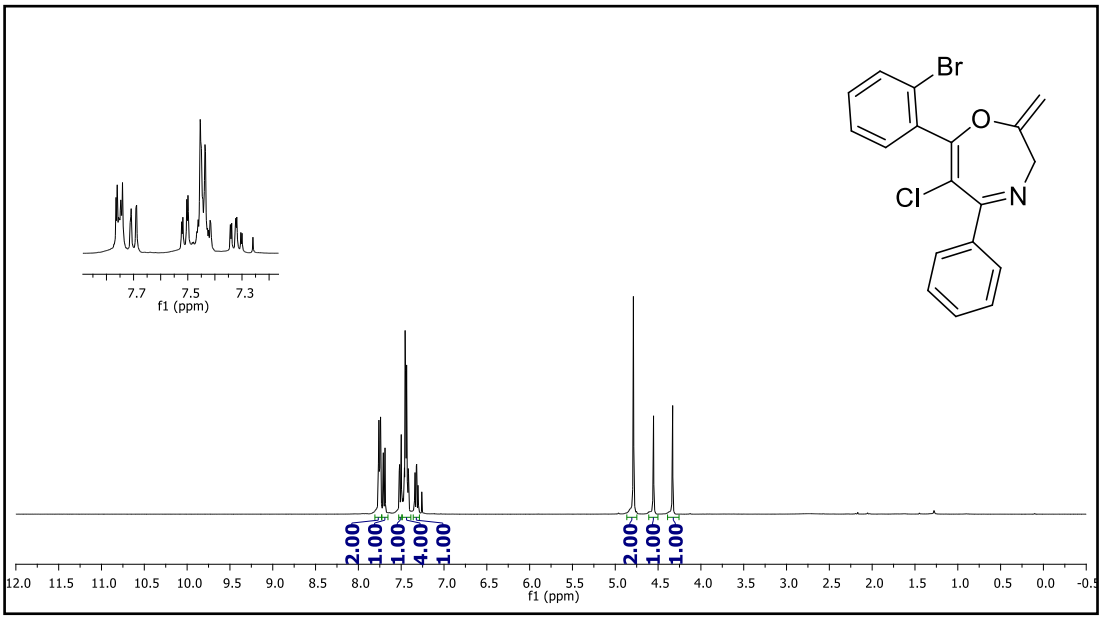

Figure 187. ^{1}H NMR spectrum of compound **37I**.

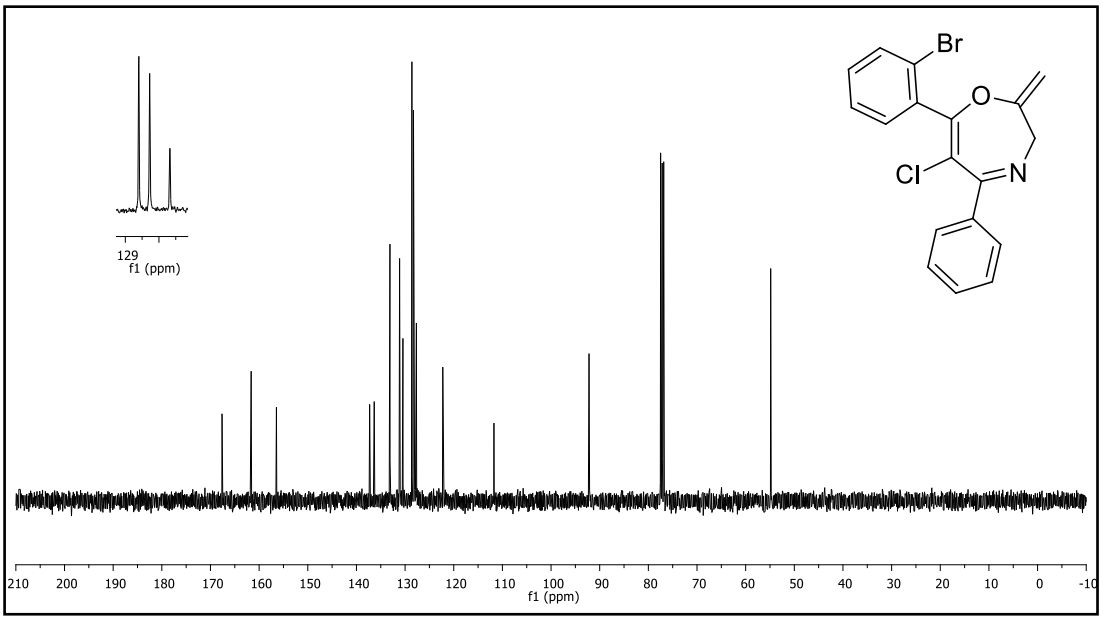

Figure 188. ^{13}C NMR spectrum of compound **37I**.

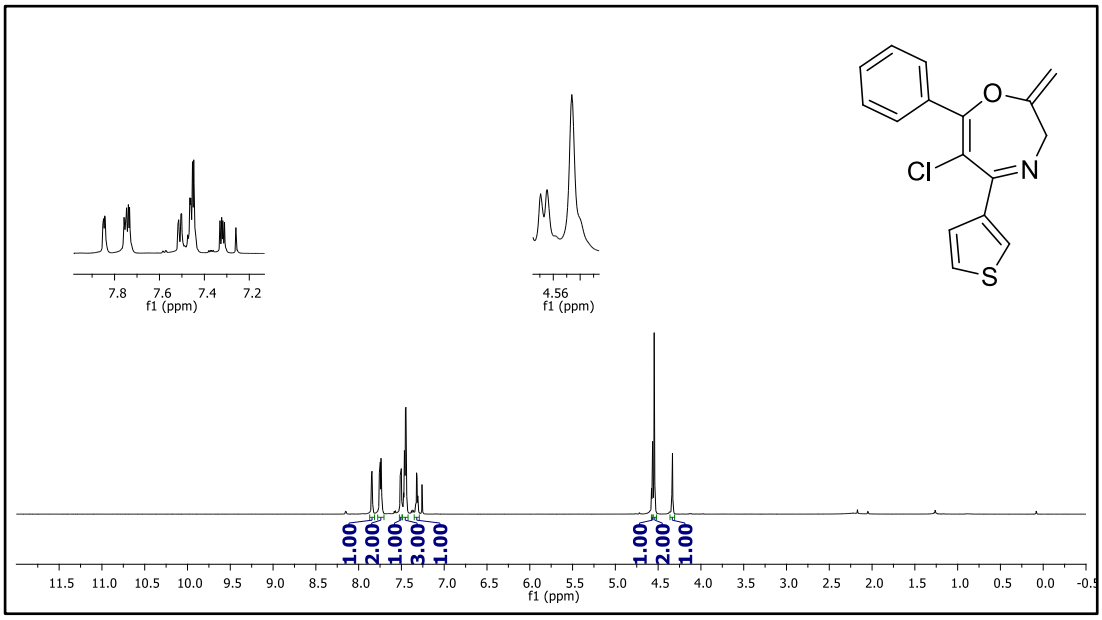

Figure 189. ^{1}H NMR spectrum of compound **37J**.

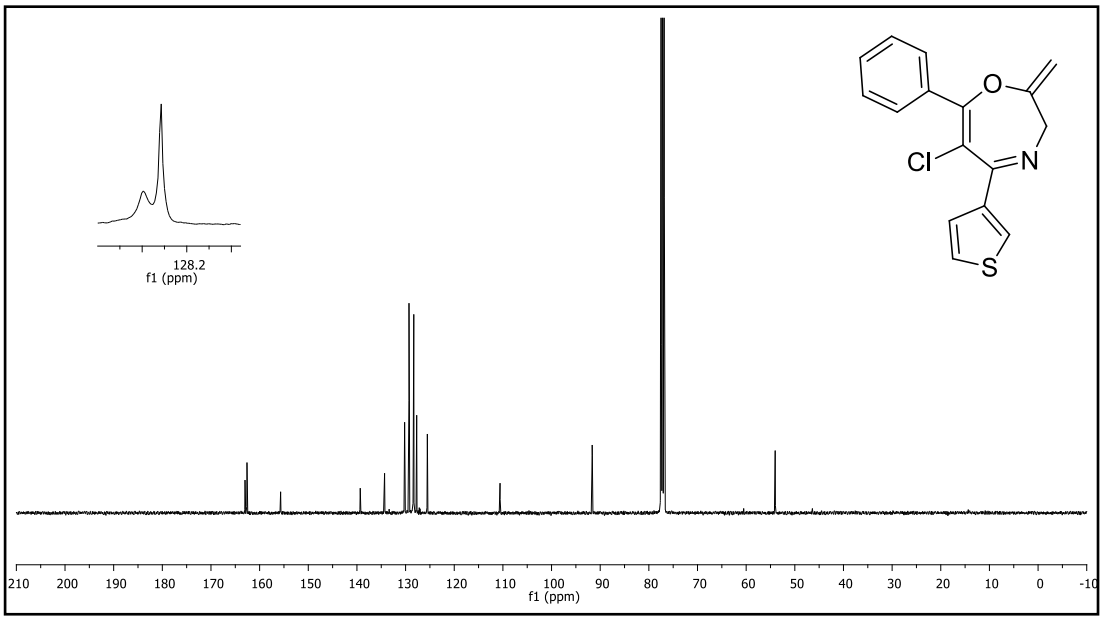

Figure 190. ^{13}C NMR spectrum of compound **37J**.

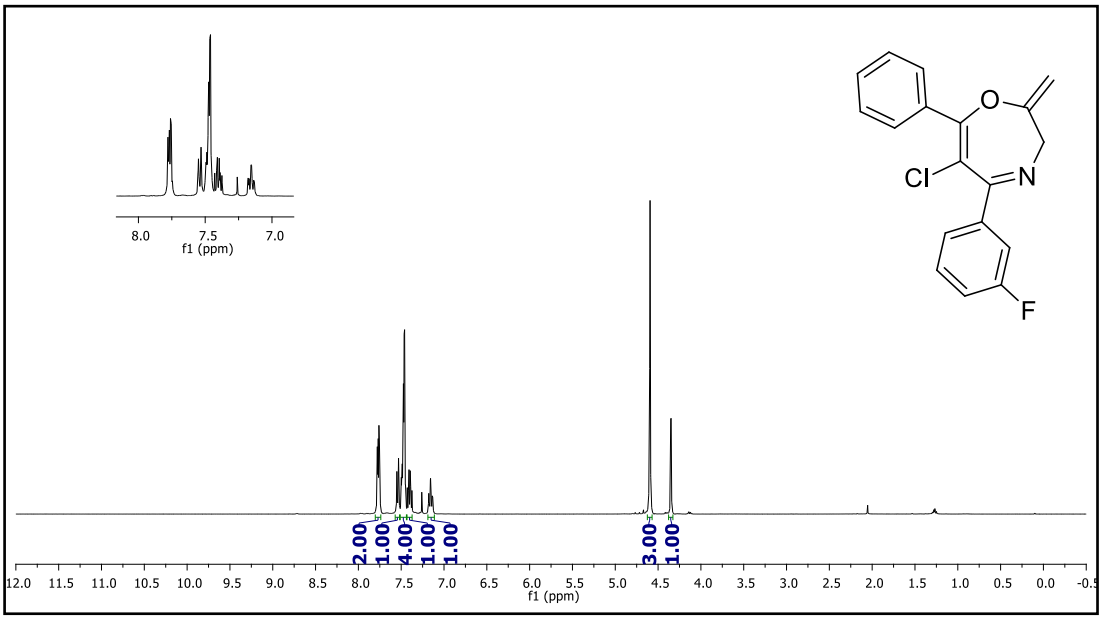

Figure 191. ^{1}H NMR spectrum of compound **37K**.

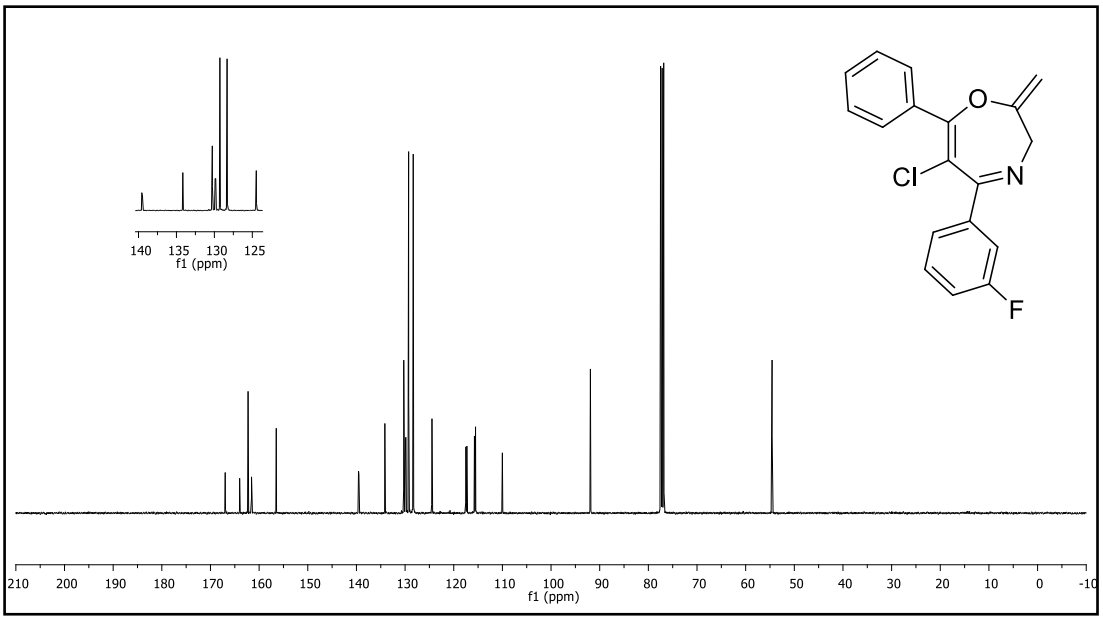

Figure 192. ^{13}C NMR spectrum of compound **37K**.

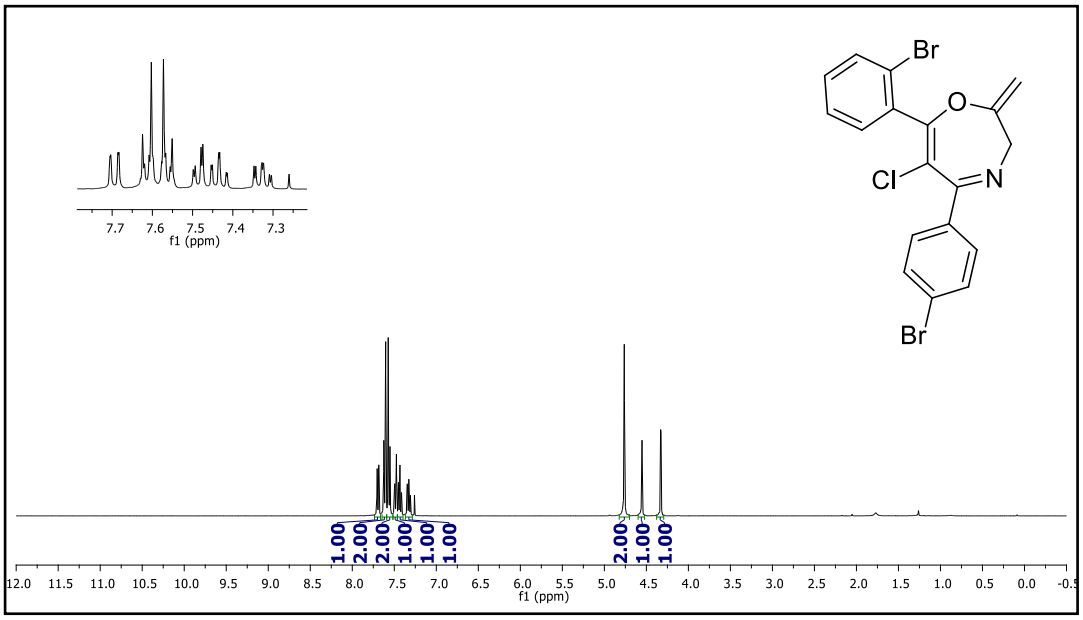

Figure 193. ^{1}H NMR spectrum of compound **37L**.

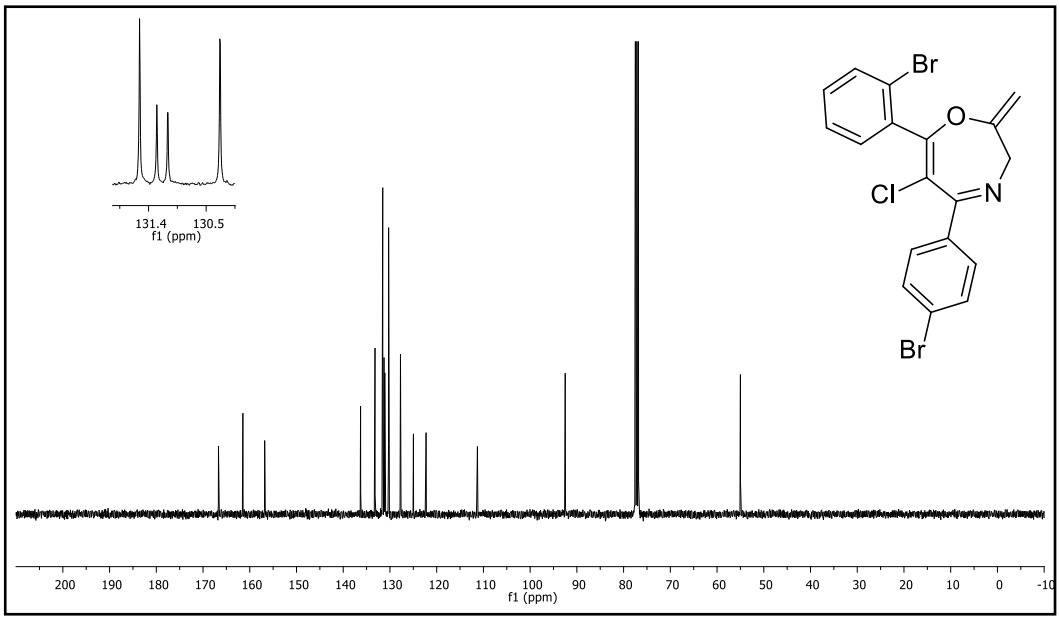

Figure 194. ^{13}C NMR spectrum of compound **37L**.

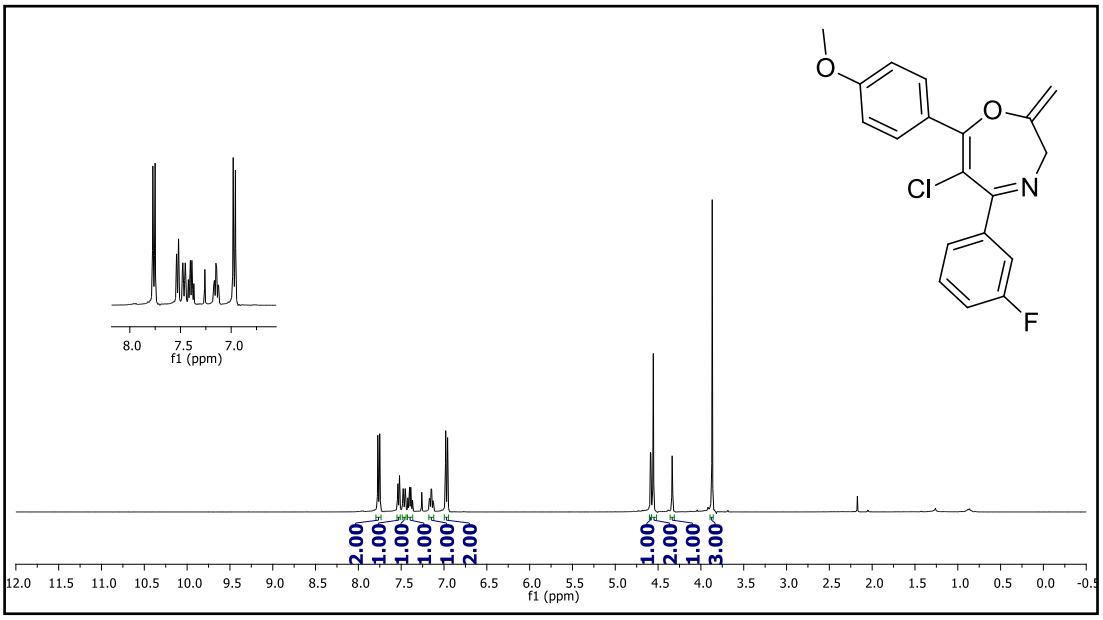

Figure 195. ^{1}H NMR spectrum of compound **37M**.

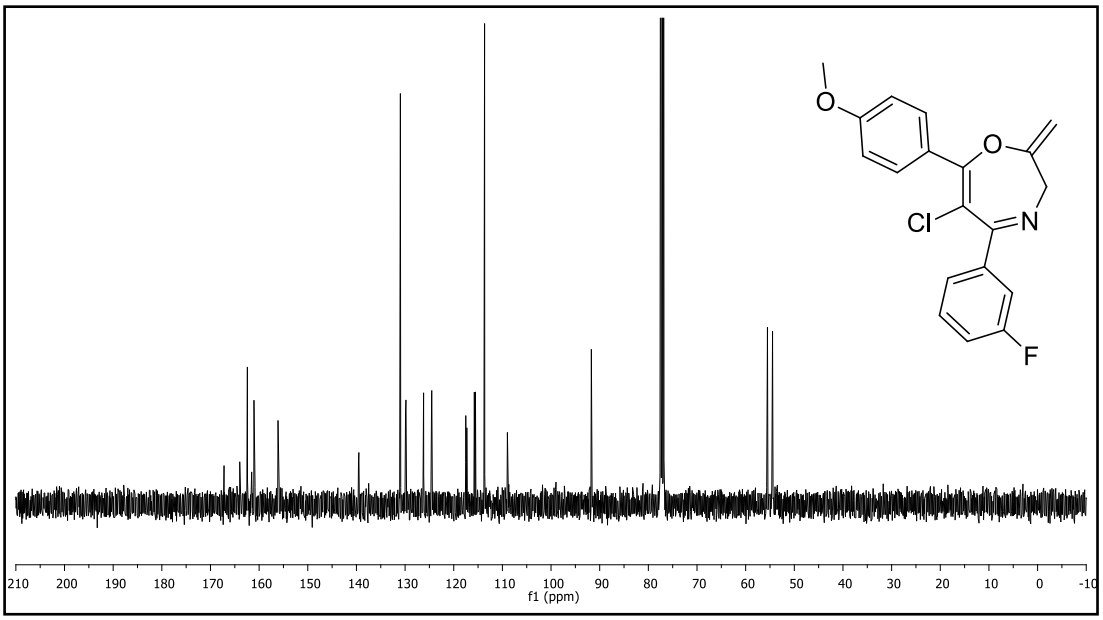

Figure 196. ^{13}C NMR spectrum of compound **37M**.

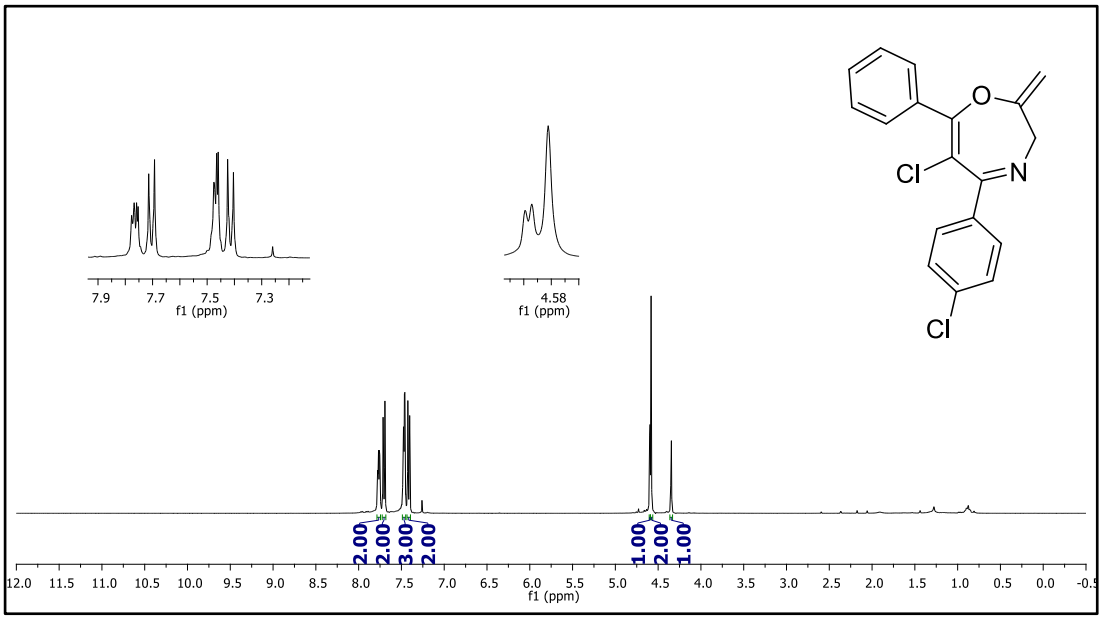

Figure 197. ^{1}H NMR spectrum of compound **37N**.

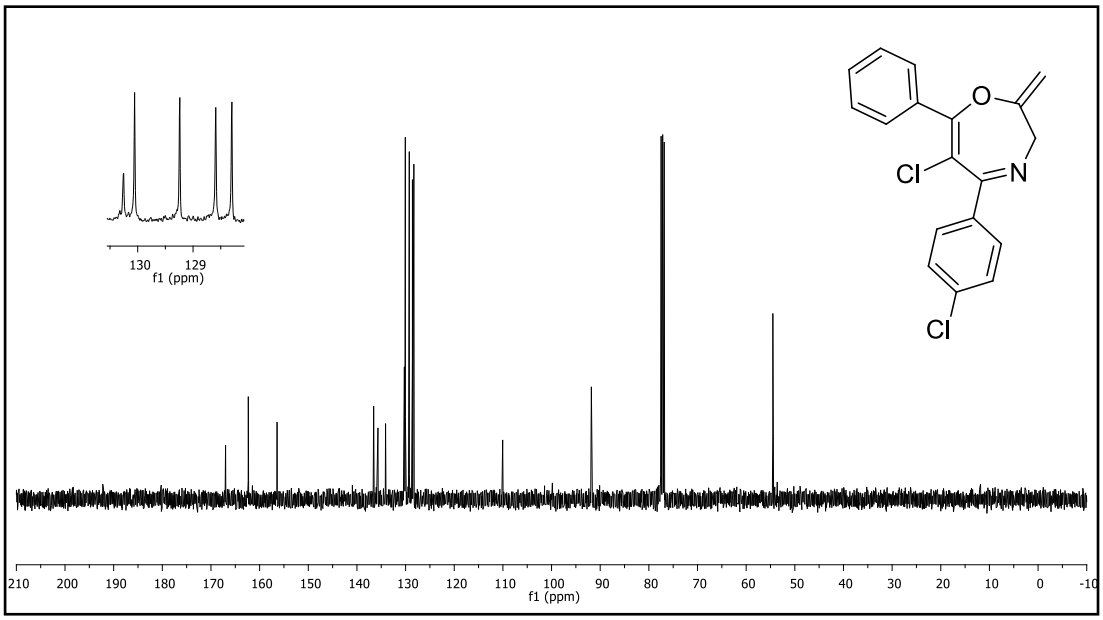

Figure 198. ^{13}C NMR spectrum of compound **37N**.

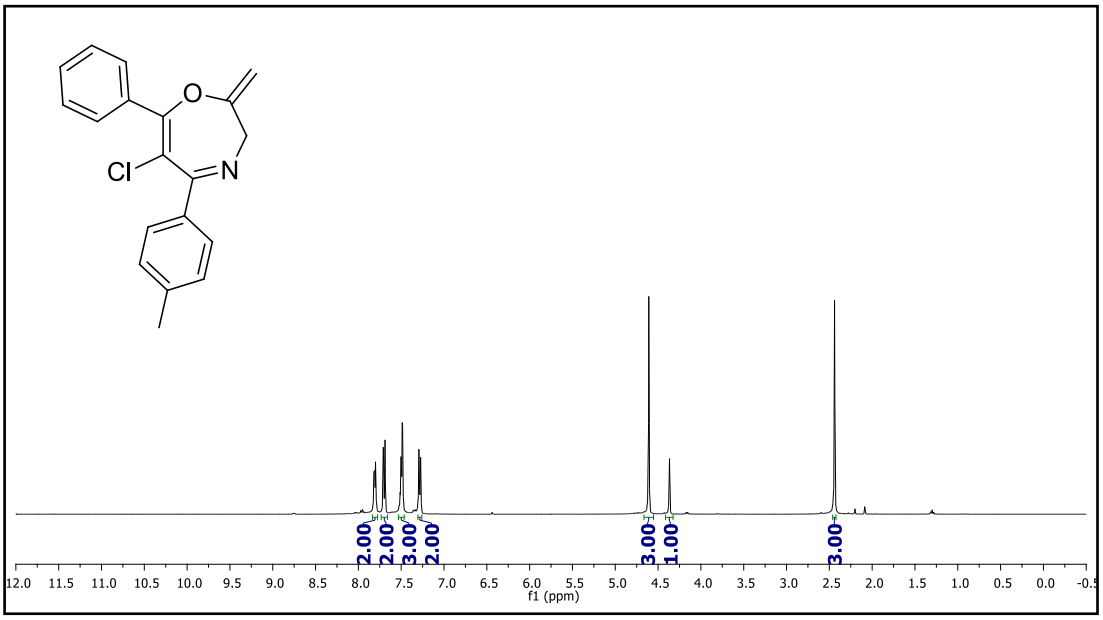

Figure 199. ^{1}H NMR spectrum of compound **37O**.

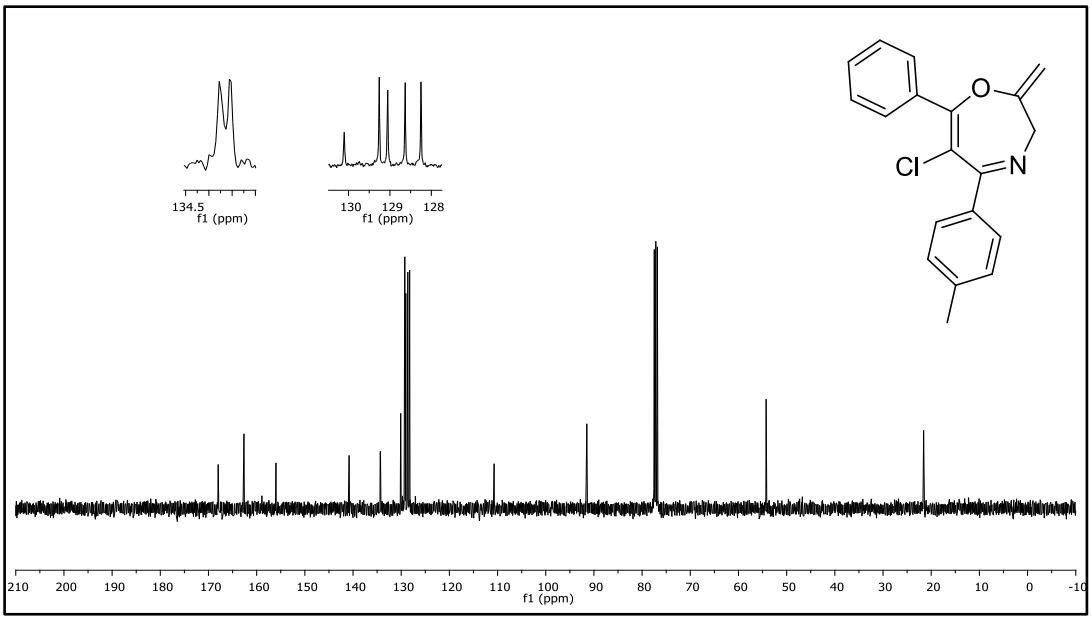

Figure 200. ^{13}C NMR spectrum of compound **37O**.

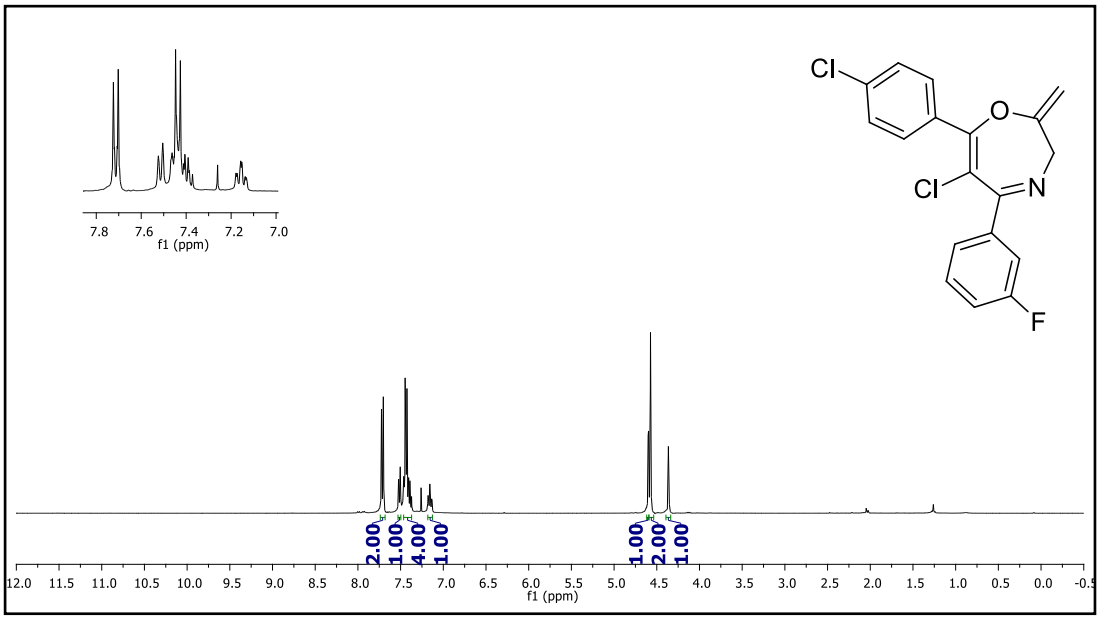

Figure 201. ^{1}H NMR spectrum of compound **37P**.

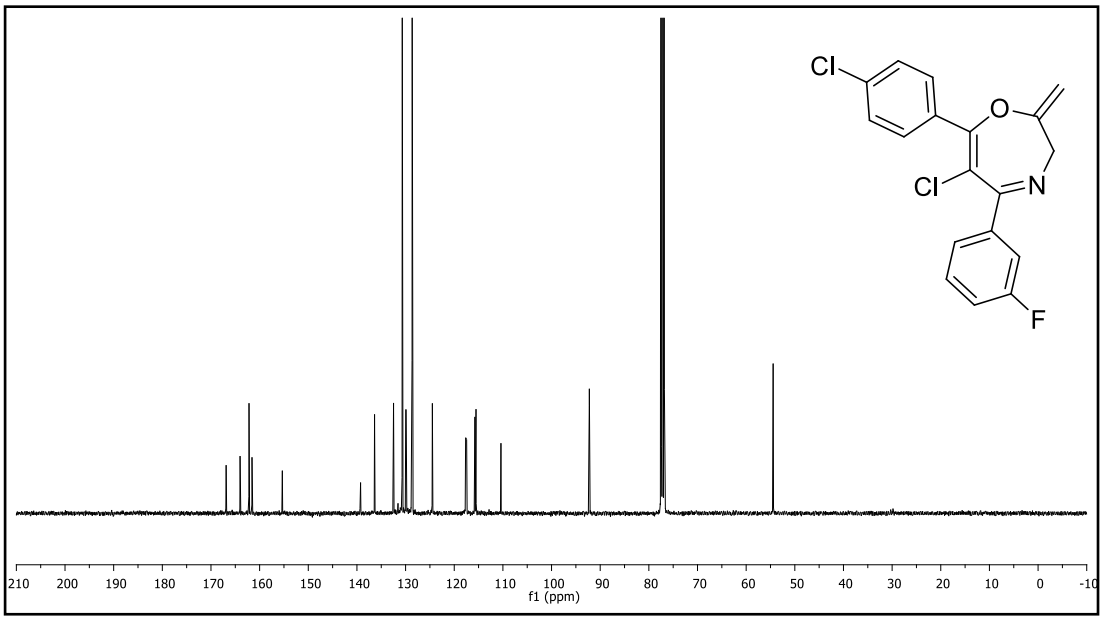

Figure 202. ^{13}C NMR spectrum of compound **37P**.

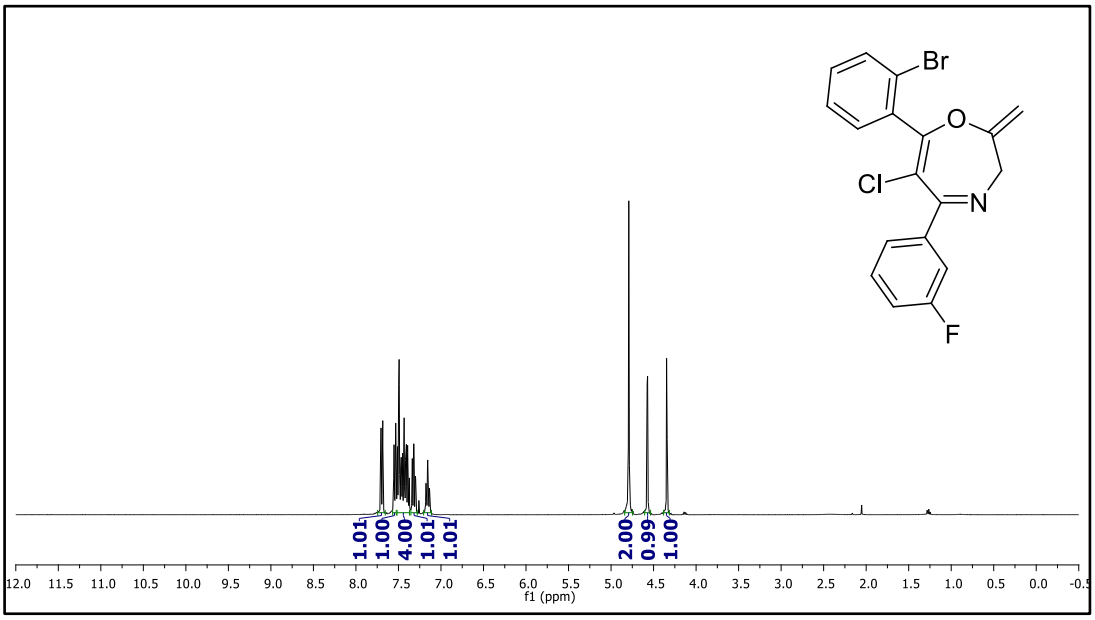

Figure 203. ^{1}H NMR spectrum of compound **37Q**.

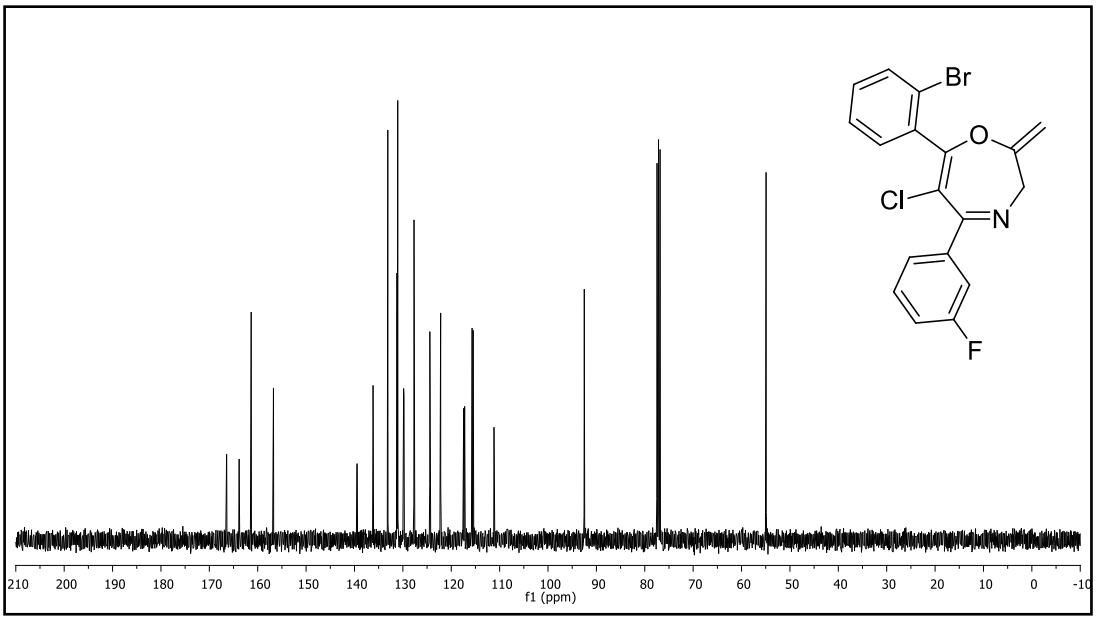

Figure 204. ^{13}C NMR spectrum of compound **37Q**.

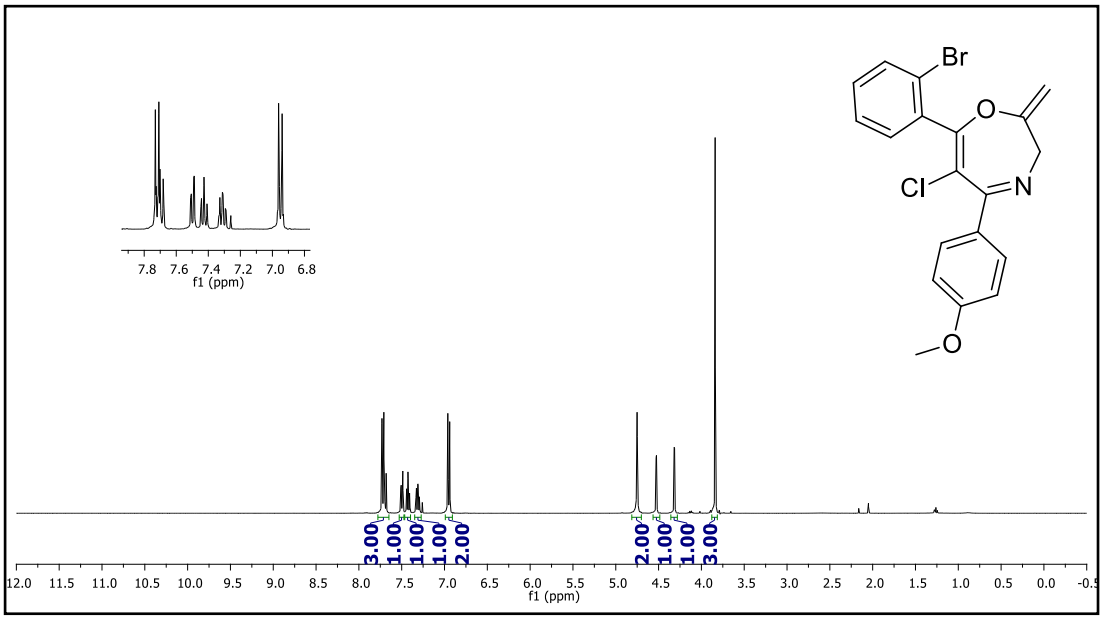

Figure 205. ^{1}H NMR spectrum of compound **37R**.

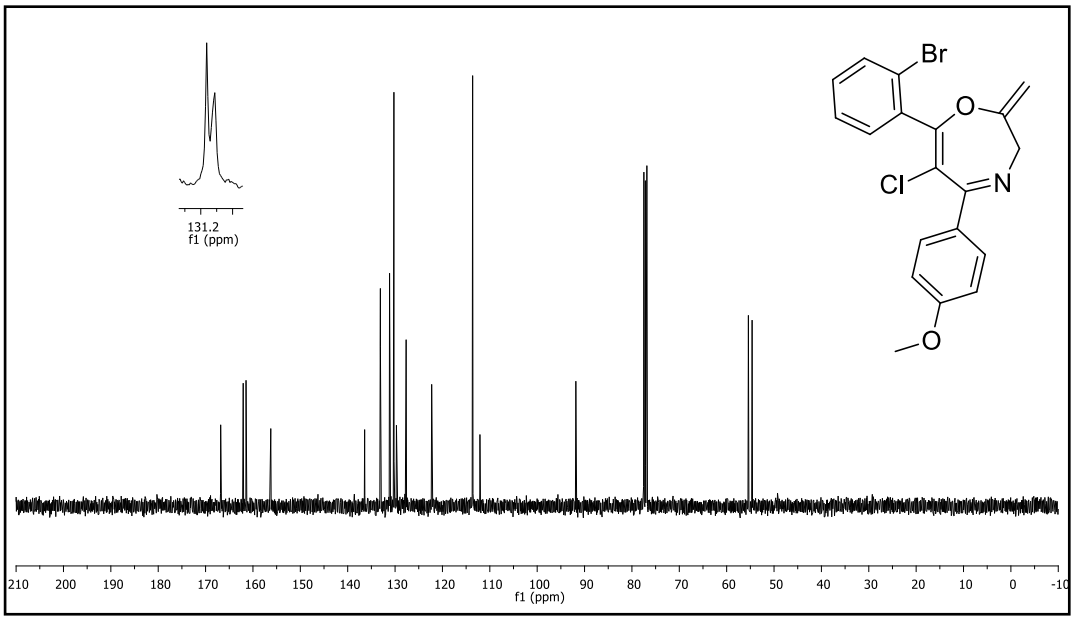

Figure 206. ^{13}C NMR spectrum of compound **37R**.

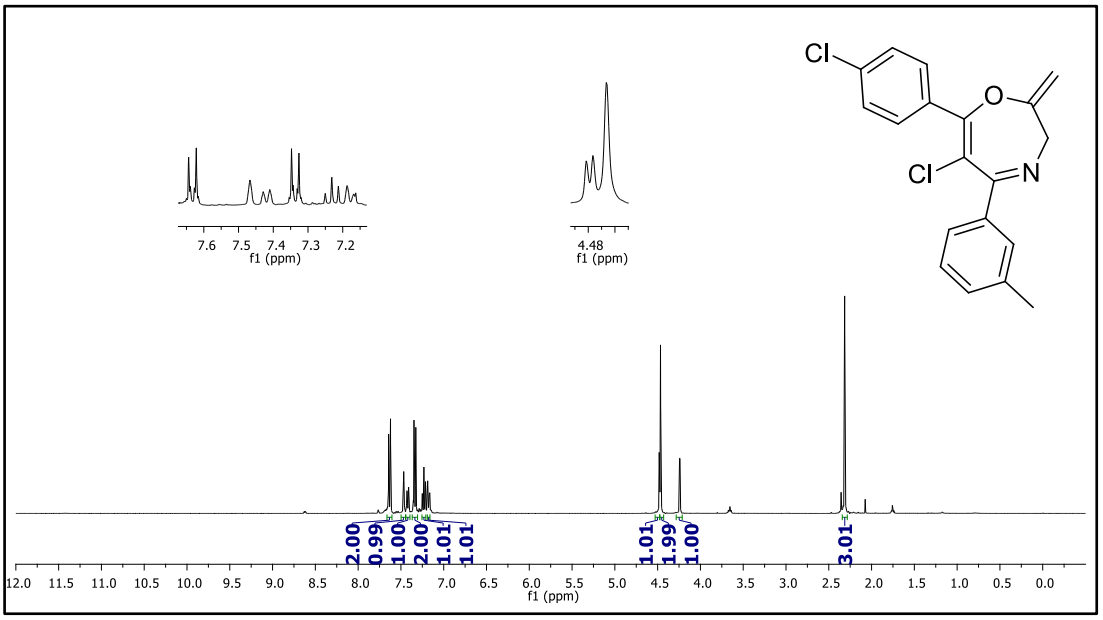

Figure 207. ^{1}H NMR spectrum of compound **37S**.

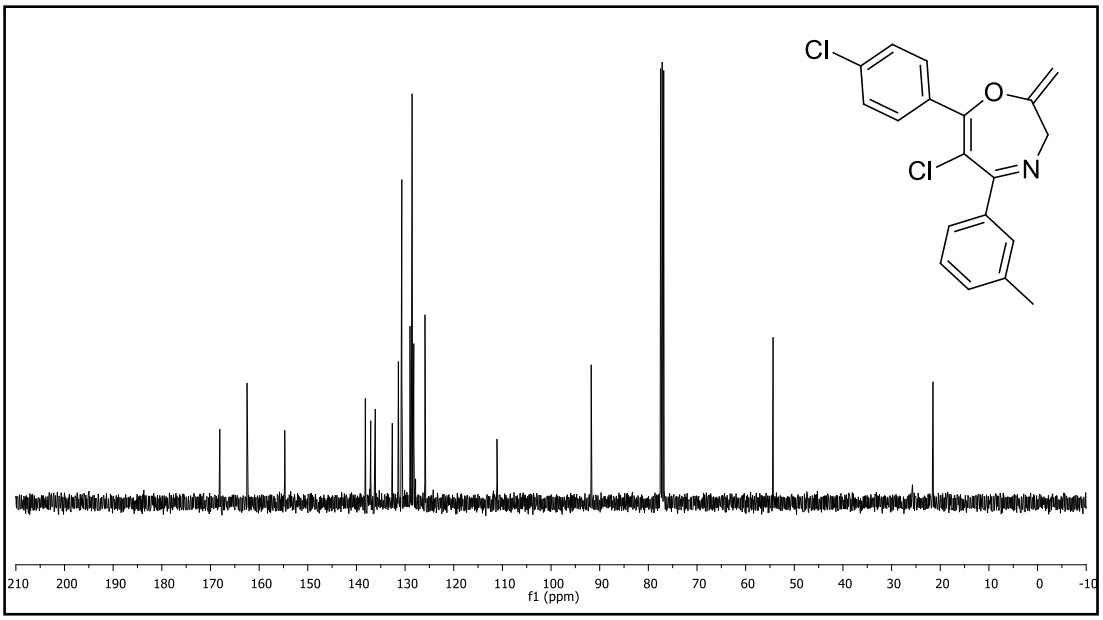

Figure 208. ^{13}C NMR spectrum of compound **37S**.

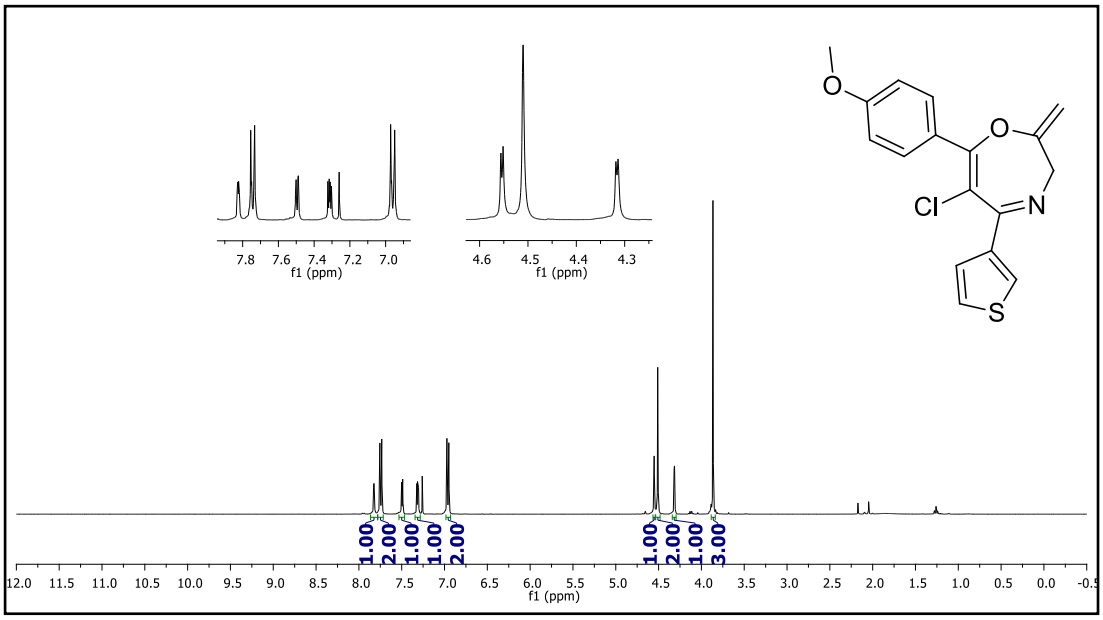

Figure 209. ^{1}H NMR spectrum of compound **37T**.

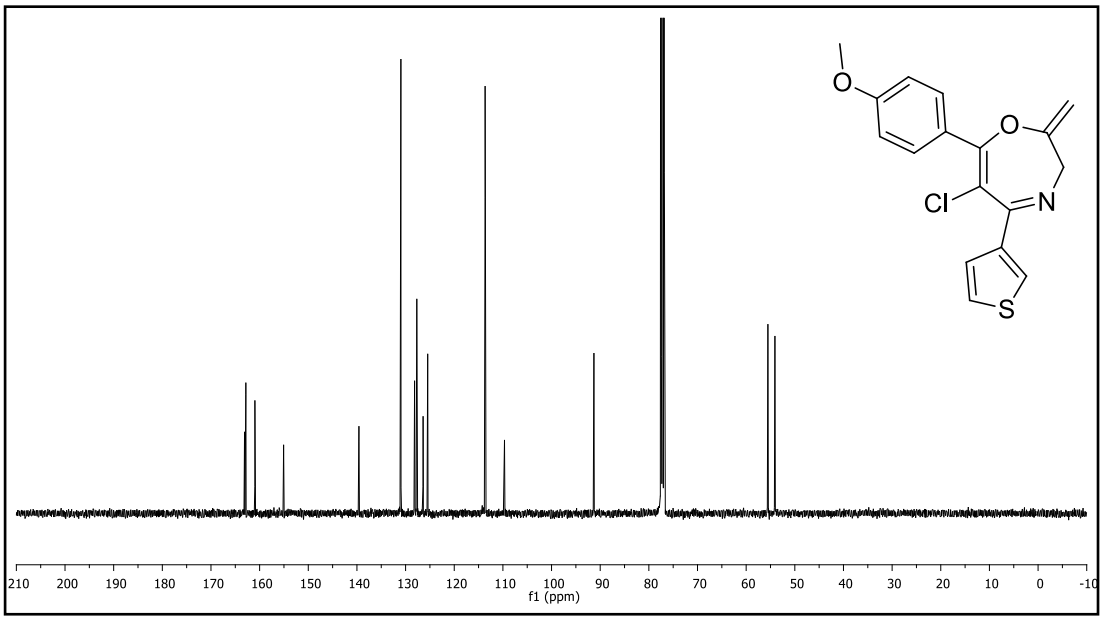

Figure 210. ^{13}C NMR spectrum of compound **37T**.

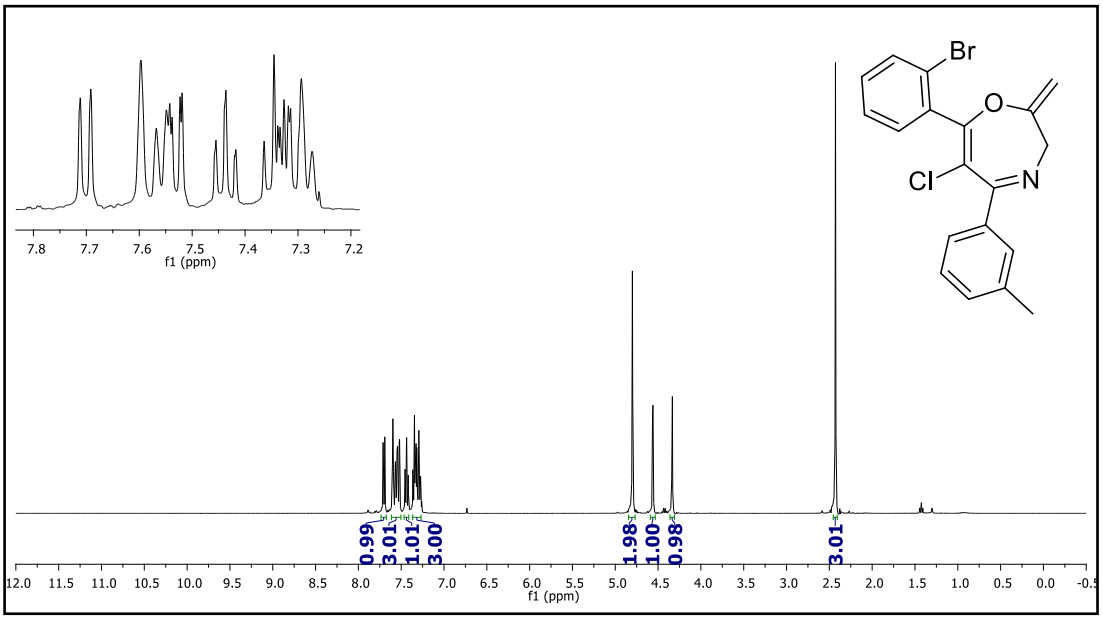

Figure 211. ^{1}H NMR spectrum of compound **37U**.

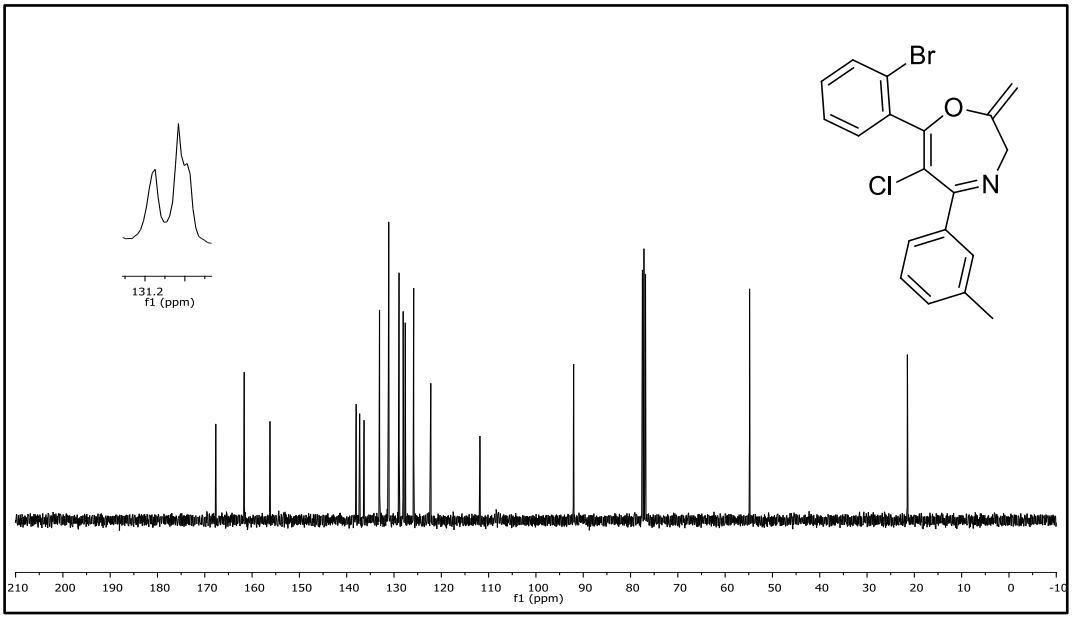

Figure 212. ^{13}C NMR spectrum of compound **37U**.

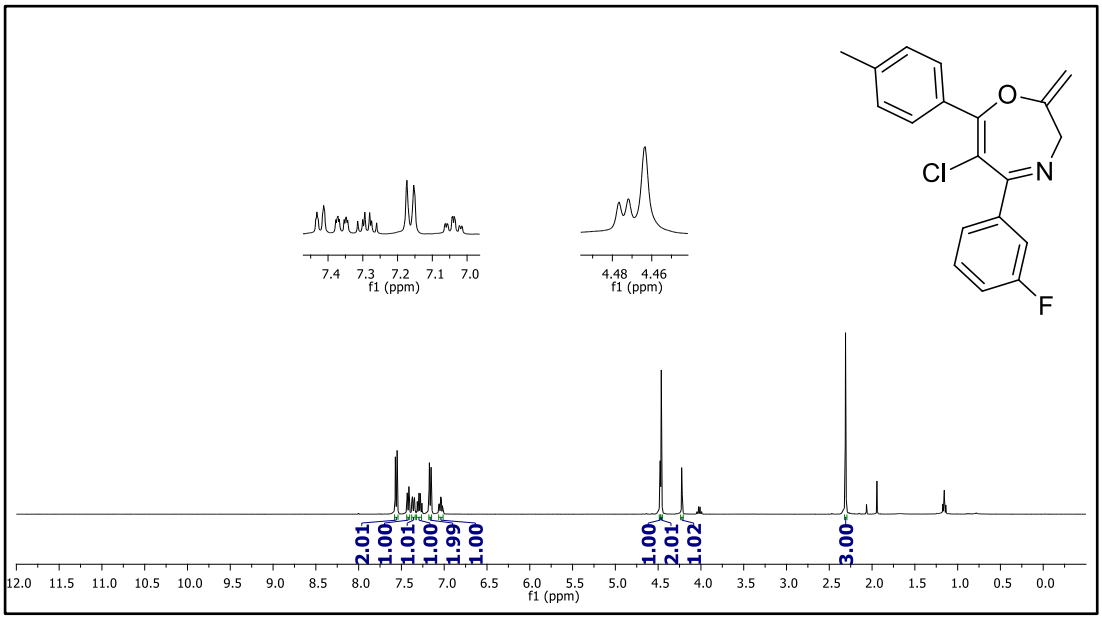

Figure 213. [1] H NMR spectrum of compound **37V**.

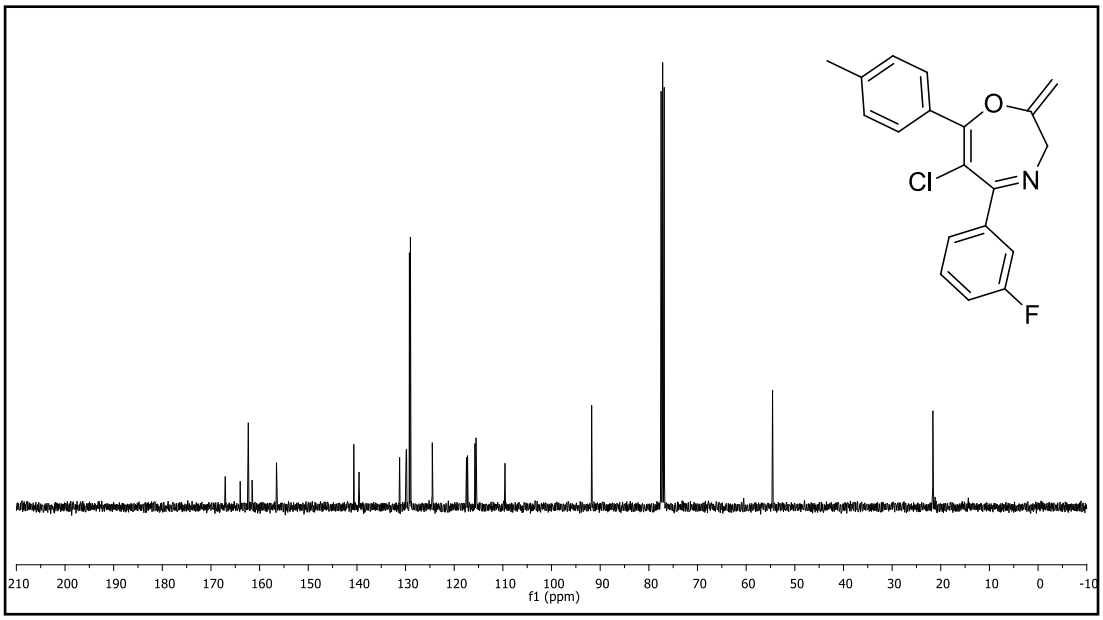

Figure 214. [13]C NMR spectrum of compound **37V**.

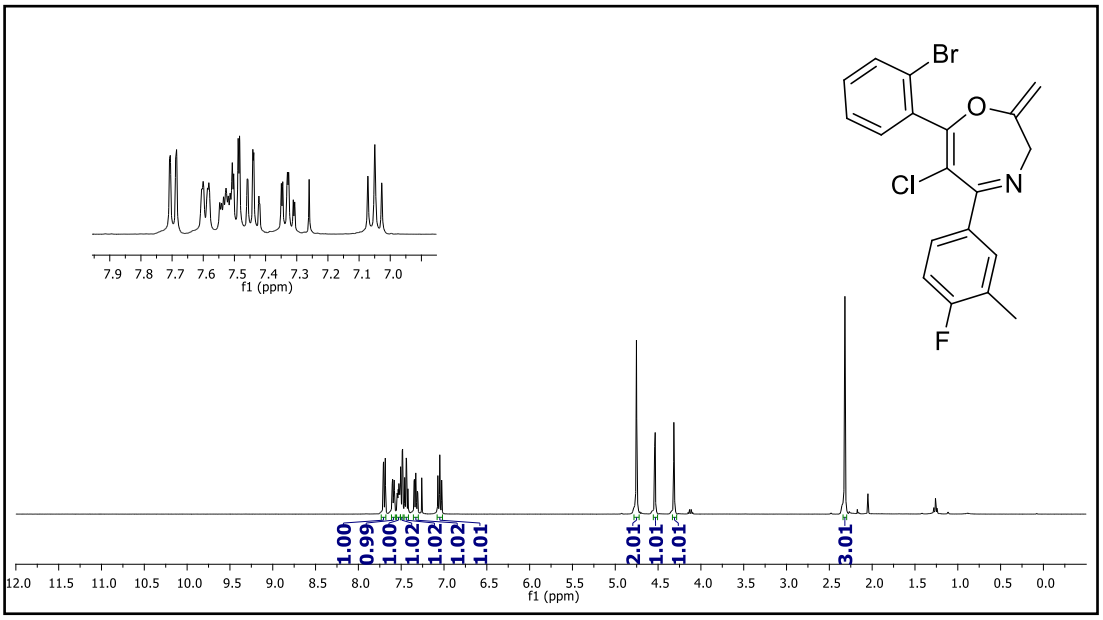

Figure 215. ^{1}H NMR spectrum of compound **37W**.

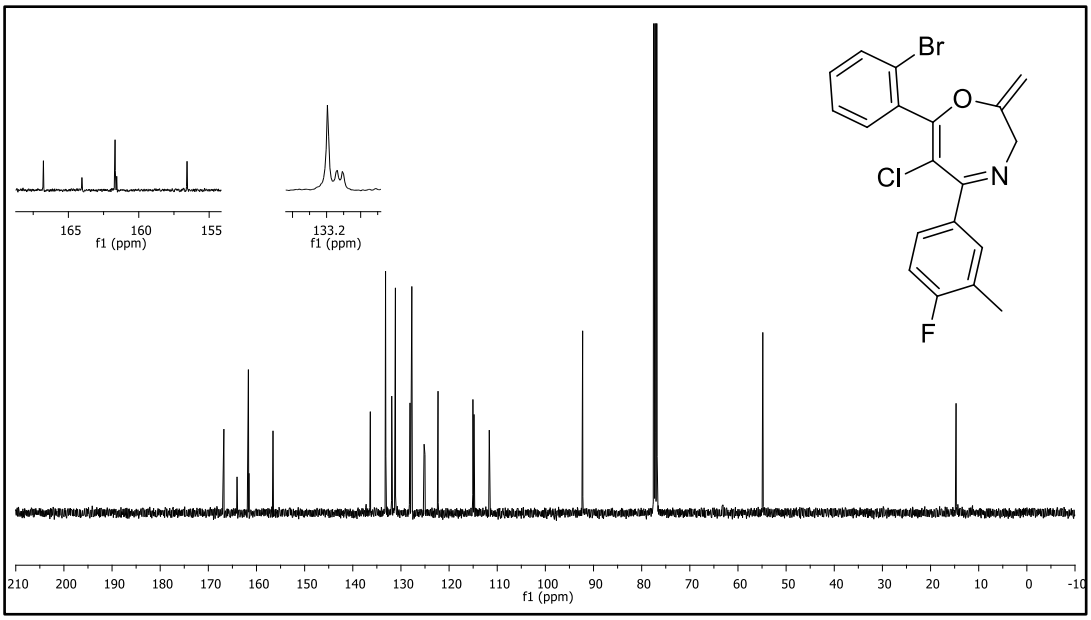

Figure 216. ^{13}C NMR spectrum of compound **37W**.

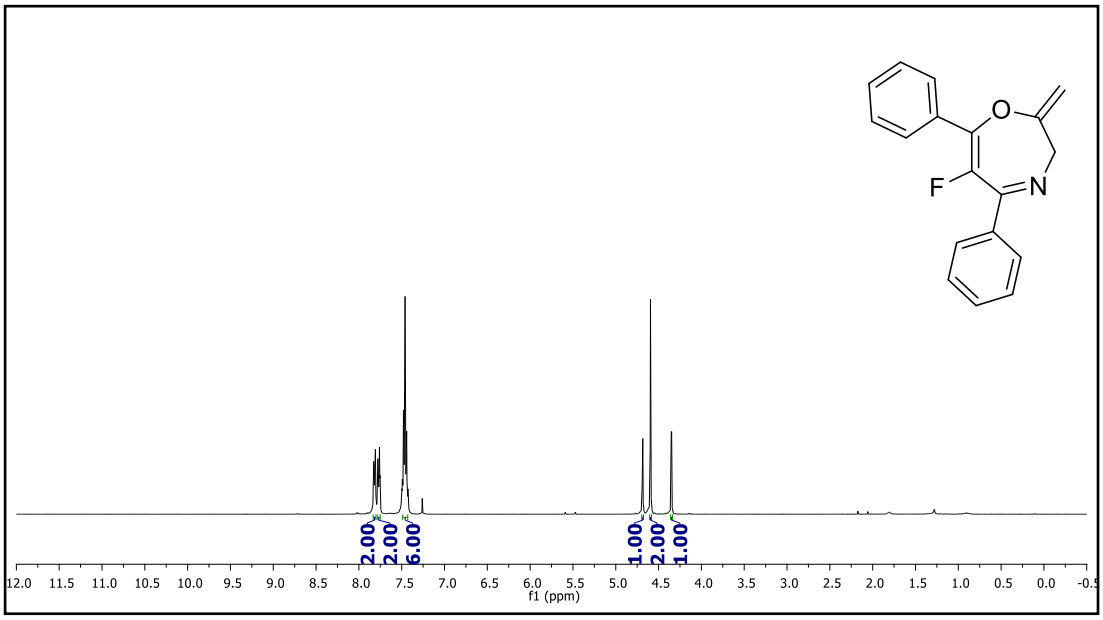

Figure 217. ^{1}H NMR spectrum of compound **38A**.

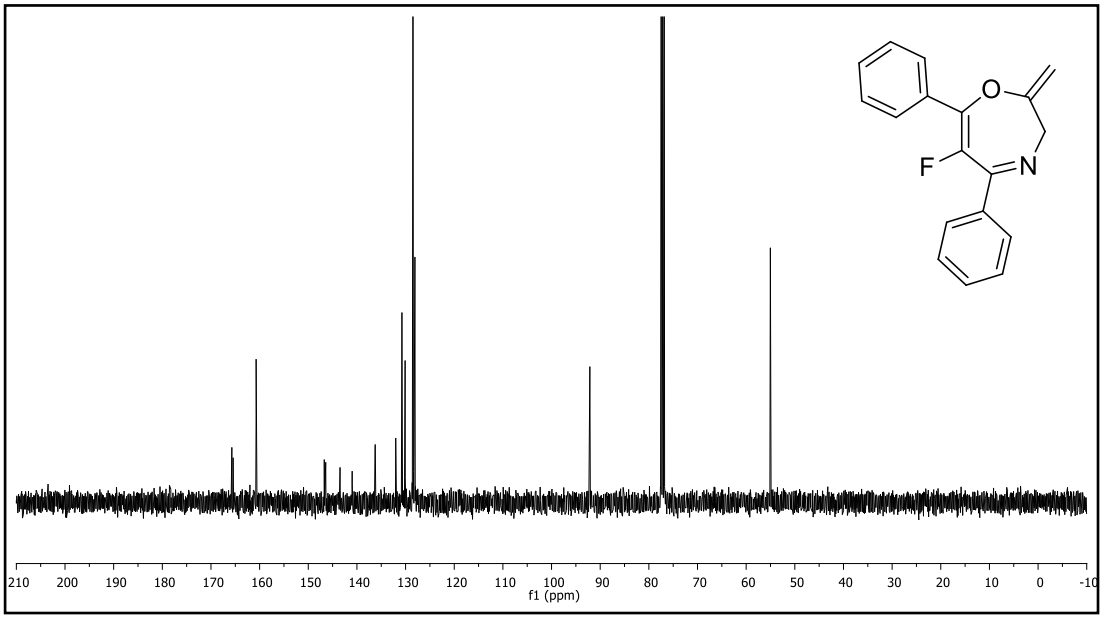

Figure 218. ^{13}C NMR spectrum of compound **38A**.

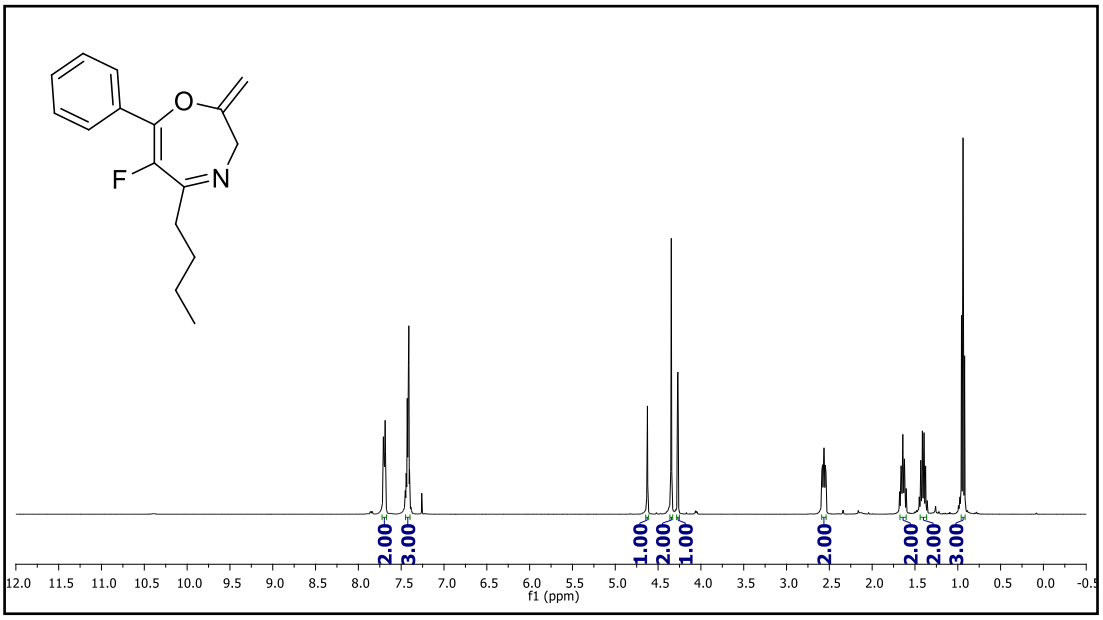

Figure 219. ^{13}C NMR spectrum of compound **38B**.

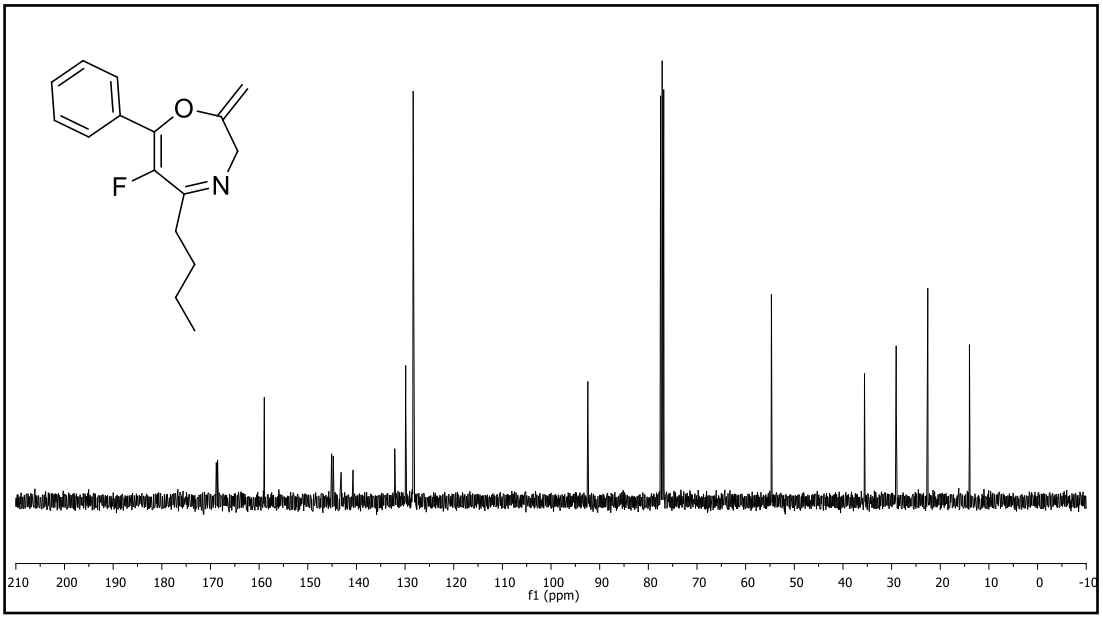

Figure 220. ^{13}C NMR spectrum of compound **38B**.

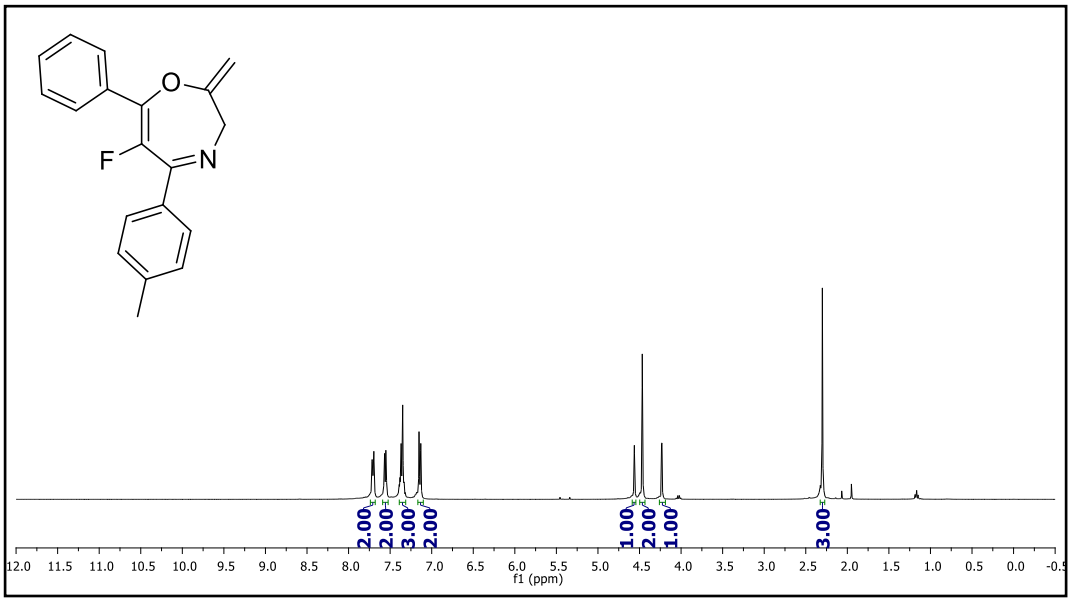

Figure 221. ^{1}H NMR spectrum of compound **38O**.

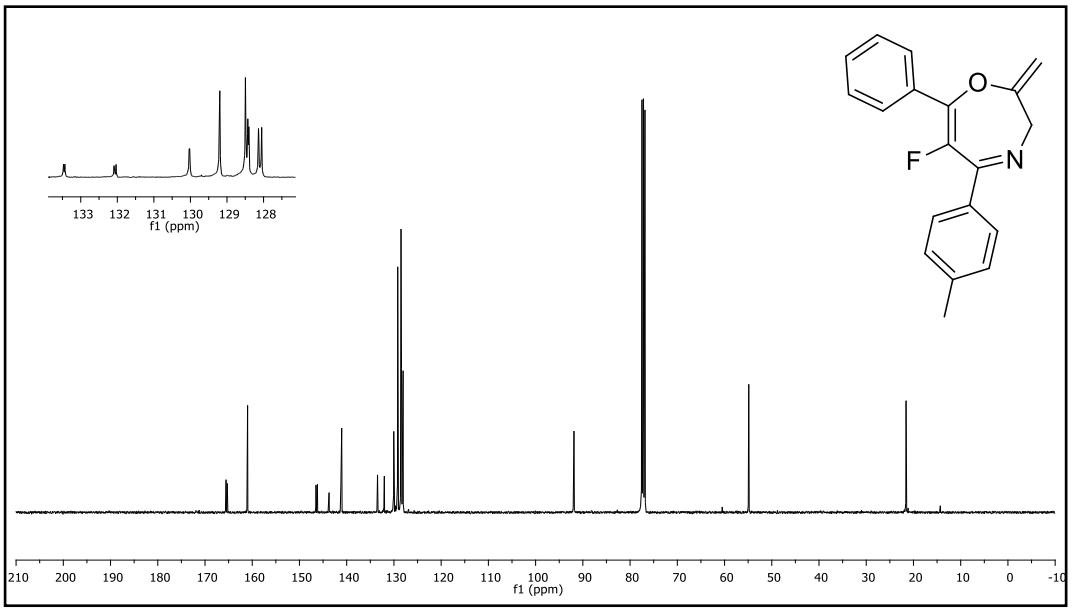

Figure 222. ^{13}C NMR spectrum of compound **38O**.

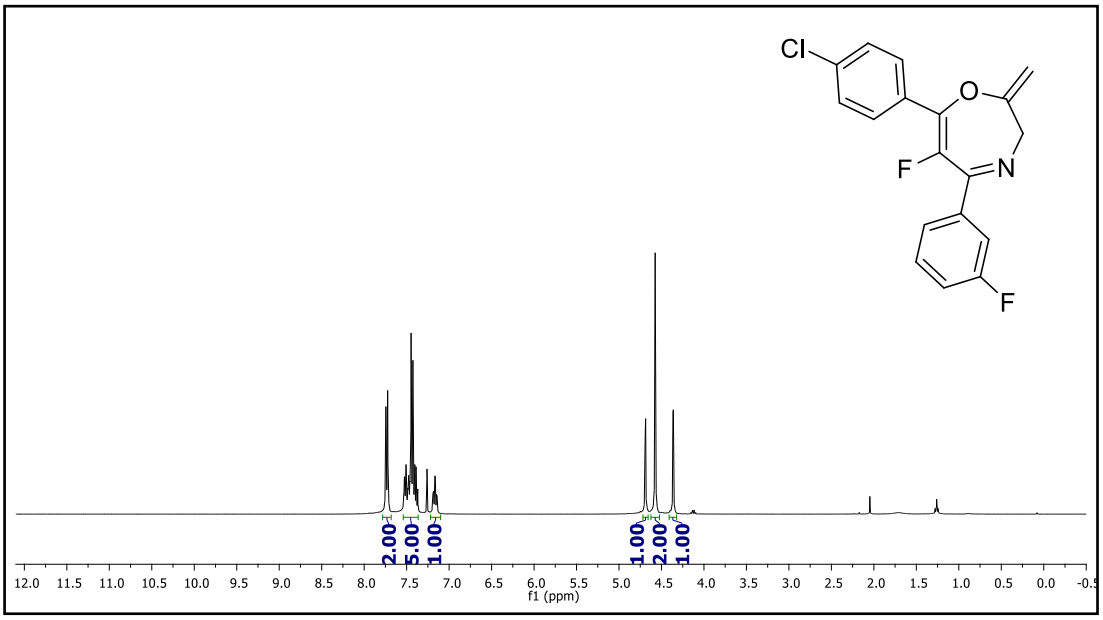

Figure 223. ^{1}H NMR spectrum of compound **38P**.

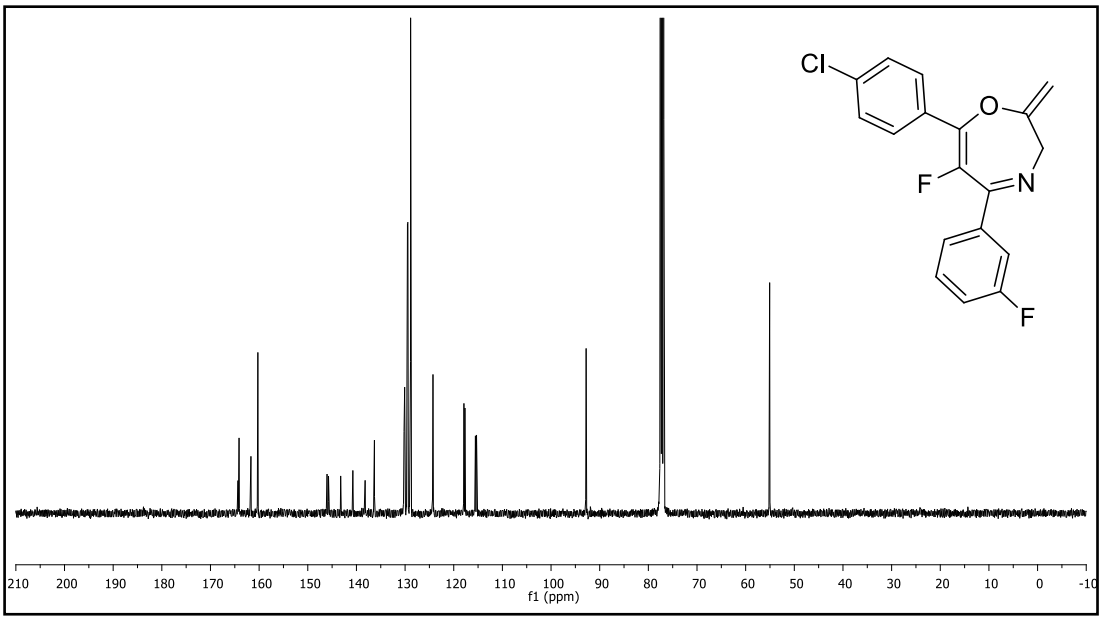

Figure 224. ^{13}C NMR spectrum of compound **38P**.

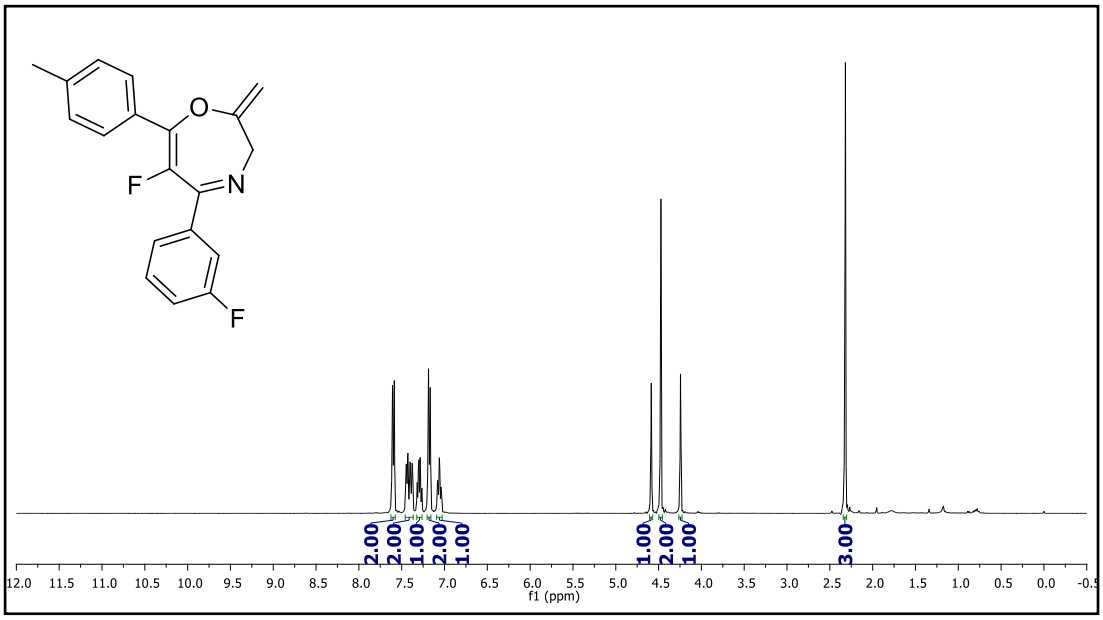

Figure 225. ^{1}H NMR spectrum of compound **38V**.

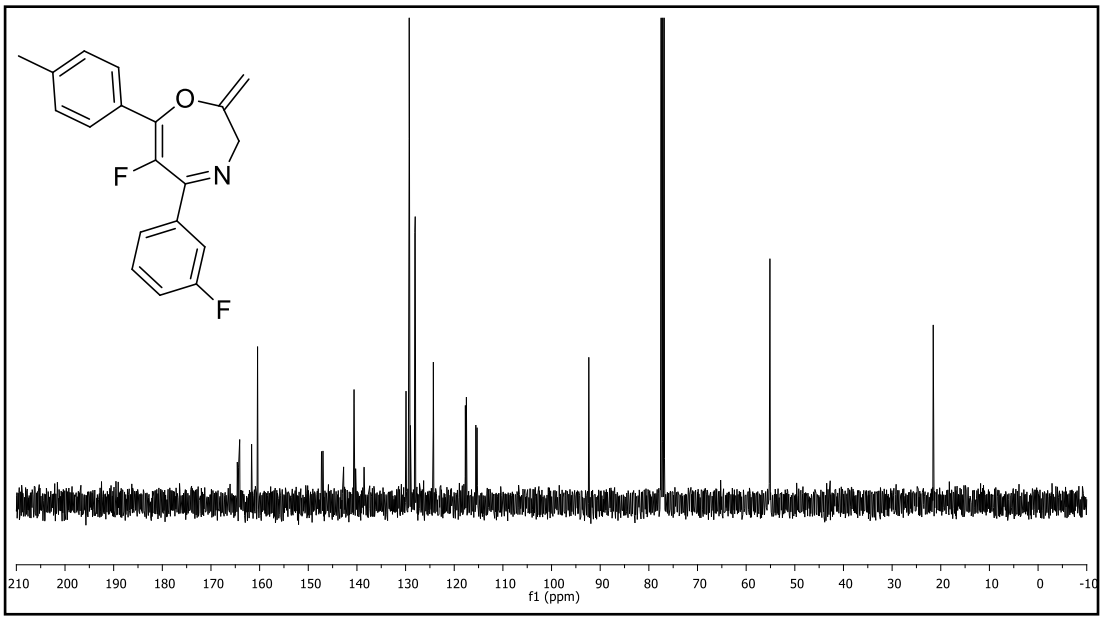

Figure 226. ^{13}C NMR spectrum of compound **38V**.