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SYNTHESIS OF NEW PYRROLE DERIVATIVES FROM *N*-PROPARGYLIC β-ENAMINONES

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

BY

NILAY KANOVA

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

JULY 2020

Approval of the thesis:

SYNTHESIS OF NEW PYRROLE DERIVATIVES FROM *N*-PROPARGYLIC β-ENAMINONES

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ABSTRACT

SYNTHESIS OF NEW PYRROLE DERIVATIVES FROM *N*-PROPARGYLIC β-ENAMINONES

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Master of Science, Chemistry
Supervisor : Prof. Dr. Metin Zora

July 2020, 187 pages

Heterocyclic compounds are a momentous area of synthetic organic chemistry because of their existence in bioactive molecules. Pyrroles, which are one of the most important classes of heterocyclic compounds, have great importance in pharmaceutical chemistry due to their biological activities. Having these characteristics makes them drawn attention of most chemists to develop new methodologies for the synthesis of pyrroles. Recently, the cyclization of *N*-propargylic β-enaminones has been used for the synthesis of heterocyclic compounds, especially pyrroles.

In this study, we have investigated the synthesis of new 2-acetylpyrrole derivatives which may have potential biological activities. Various pyrrole derivatives have been synthesized with two unprecedented way which are synthesis method from 1,4-oxazepines and one-pot two-step synthesis method from *N*-propargylic β-enaminones.

Firstly, α,β-alkynic ketone derivatives have been synthesized via Sonogashira coupling reaction between benzoyl chlorides and terminal alkynes. After synthesizing α,β-alkynic ketone derivatives, *N*-propargylic β-enaminone derivatives

have been synthesized by the conjugate addition between propargylamine and the corresponding α,β-alkynic ketones.

Secondly, the cyclization of *N*-propargylic β-enaminones have been carried out for the synthesis of 2-methylene-2,3-dihydro-1,4-oxazepines. A number of 2-methylene-2,3-dihydro-1,4-oxazepine derivatives have been synthesized in the presence of $ZnCl_2$.

Lastly, we have investigated the synthesis of 2-acetylpyrroles by using 1,4-oxazepines and *N*-propargylic β-enaminones as starting materials. We have achieved that the synthesis of the mentioned pyrroles via two original synthesis procedures. In the light of these two methods, 19 novel pyrrole derivatives have been synthesized.

Keywords: Heterocyclic compounds, *N*-propargylic β-enaminones, pyrroles, 1,4-oxazepines.

ÖZ

YENİ PİROL TÜREVLERİNİN *N*-PROPARJİLİK β-ENAMİNONLARDAN SENTEZİ

Kanova, Nilay
Yüksek Lisans, Kimya
Tez Yöneticisi: Prof. Dr. Metin Zora

Temmuz 2020, 187 sayfa

Heterohalkalı bileşikler biyoaktif moleküllerin yapısında bulunmaları nedeniyle sentetik kimyanın önemli alanlarından biridir. Heterohalkalı bileşiklerin çok önemli sınıflarından biri olan pirollerin ilaç kimyasındaki önemi onların biyolojik aktifliklerinden dolayı oldukça büyüktür. Bu karakteristik özelliğinden dolayı piroller birçok kimyacının ilgisini sentezleri için yeni yöntemler geliştimek için çekmişlerdir. Son zamanlarda, *N*-proparjilik β-enaminonların halkalaşması heterohalkalı bileşiklerin, özellikle pirollerin sentezleri için kullanılmıştır.

Bu çalışmada, biyolojik aktiviteye sahip olabilecek yeni 2-asetil pirol türevlerinin sentezlerini araştırılmıştır. 1,4 oxazepinlerden sentezleme yöntemi ve *N*-proparjilik β-enaminonlardan tek kap iki aşamalı sentezleme yöntemi olmak üzere iki yeni sentez yolları kullanılarak çeşitli pirol türevleri sentezlenmiştir.

İlk olarak, Sonogashira kenetlenme tepkimesi kullanılarak ariloyil klorürlerden ve terminal alkinlerden α,β-alkinik keton bileşikleri sentezlenmiştir. α,β-alkinik keton bileşiklerinin sentezinden sonra, proparjilamin ve ilgili α,β-alkinik ketonlar arasındaki konjuge katılma tepkimesi ile *N*-proparjilik β-enaminon bileşikleri sentezlenmiştir.

İkinci aşamada, *N*-proparjilik β-enaminon bileşiklerinin halkalaşması sonucunda 2-metilen-2,3-dihidro-1,4-oksazepinler elde edilmiştir. Birçok 2-metilen-2,3-dihidro-1,4-oksazepin türevi $ZnCl_2$ varlığında sentezlenmiştir.

Son olarak, 2-asetil pirollerin sentezi 1,4-oxazepin ve *N*-proparjilik β-enaminon bileşikleri başlangıç maddesi olarak kullanılarak araştırılmıştır. Bahsi geçen pirollerin sentezinin iki orjinal sentez prosedürü ile mümkün olduğu gösterilmiştir. Bu bulguların ışığında, 19 yeni pirol türevleri sentezlendi.

Anahtar Kelimeler: Heterohalkalı bileşikler, *N*-proparjilik β-enaminonlar, piroller, 1,4-oksazepinler.

To my Dear Devoted Family

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The greatest gratitude is to my perfect family. My mother, father and sister are always the biggest supporter of me. They always believed my success and they were with me in every situation all the time. They were supportive without questioning my decisions anytime and this made me more ambitious and self-confident. Shortly, without their endless encouragement and unconditional love there was no possibility to me to be successful in this project.

Finally, I would like to thank the Scientific and Technological Research Council of Turkey (TUBITAK, grant no. 118Z428) and the Middle East Technical University (METU, grant no. GAP-103-2018-2770) for supporting the project financially.

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ABBREVIATIONS

br	broad (spectral)
δ	chemical shift
J	coupling constant
DCM	dichloromethane
d	doublet (spectral)
dd	doublet of doublets (spectral)
FT	fourier transform
Hz	hertz
mL	milliliter(s)
mmol	milimole
m	multiplet (spectral)
ppm	parts per million (in NMR)
q	quartet (spectral)
rt	room temperature
s	singlet (spectral)
THF	tetrahydrofuran
TLC	thin layer chromatography
t	triplet (spectral)
NMP	*N*-methyl-2-pyrrolidone

CHAPTER 1

INTRODUCTION

Organic chemistry is the study of the carbon-containing compounds.[1] Besides carbon atom, organic molecules can include all atoms in periodic table in their structures. Organic compounds are found in living organisms such as DNA, lipids and proteins.[2]

It is also possible to synthesize organic molecules in laboratory conditions. In addition, organic molecules can be used as starting materials for synthesizing important compounds which can be used in manufacturing polymers, pharmaceuticals, food additives, dyes and related industrial important compounds.[3]

One of the most important branches of organic chemistry is heterocyclic chemistry which deals with the properties, applications and synthesis of the heterocyclic compounds. More than half of the organic compounds which are identified until the end of the second millennium are heterocycles.[4] That's why heterocyclic compounds have great importance.

1.1 Heterocyclic Compounds

Heterocyclic compounds are cyclic compounds which have at least one heteroatom, such as sulfur, oxygen, nitrogen, in their ring skeletons (Figure 1).[5] Heterocyclic compounds can be classified as nitrogen, oxygen and sulfur based heterocycles according to the type of heteroatom in their ring skeletons; within each of these classes the compounds are arranged by the ring size such as three-, four-, five-, six- and seven-membered.[6] Their physical and chemical properties depend on both the size of the ring and the heteroatom in the ring.

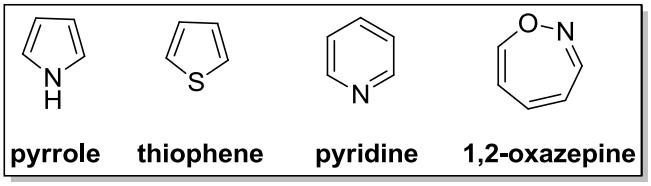


Figure 1. Some examples of heterocyclic compounds.

Heterocycles play very important role on biological systems. They are the core components of the many natural products such as nucleic acids, carbohydrates, amino acids, alkaloids, and vitamins.[7] Some important heterocycles are present in amino acids are proline, histidine and tryptophan; some other like vitamin and coenzymes are riboflavin, biotin, pyridoxine, thiamine, folic acid, vitamin B12 and vitamin E (Figure 2).[8]

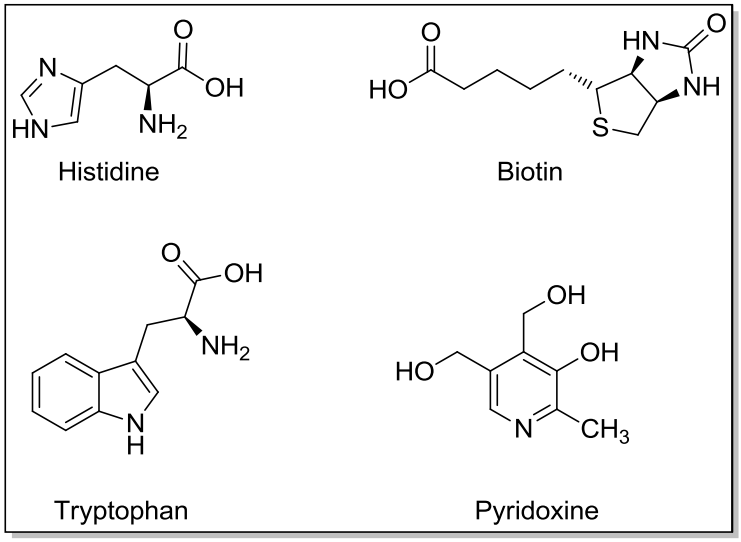


Figure 2. Some examples of amino acids, vitamins and coenzymes.

Heterocyclic compounds are very important for medicinal chemistry, especially for drug design. They have a broad range of biological activities such as antifungal, analgesic and anti-inflammatory, antibacterial, neurological, antiallergic, anticancer

and cardiovascular properties.[9] For example, coumarin containing compounds have anticancer properties.[10] New derivatives of coumarin containing compounds have been synthesized lately (Figure 3).[11] These compounds have anticancer activity against two human tumor cell lines.

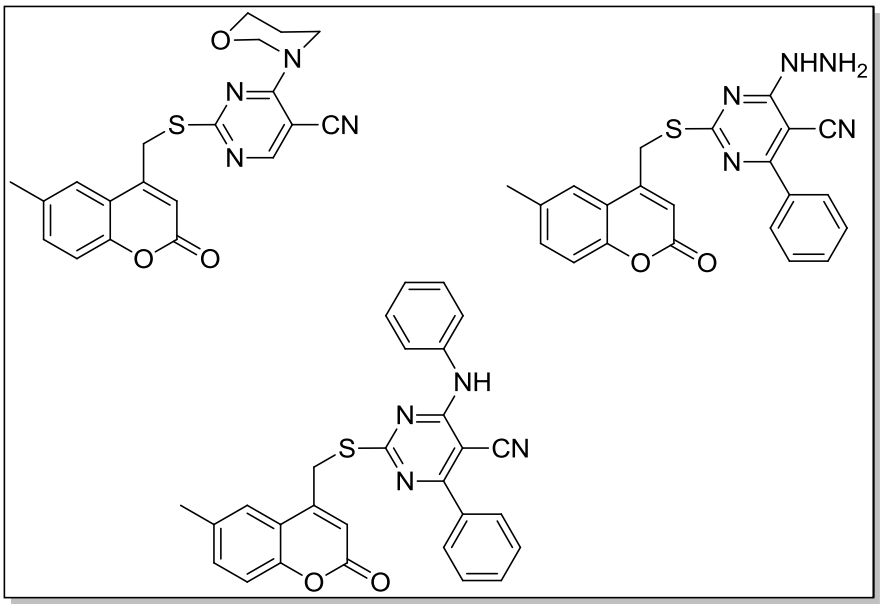


Figure 3. Some examples of coumarin containing anticancer compounds.

In addition, heterocyclic compounds are found in many natural and synthetic drugs. Theobromine, theophylline, procaine, atropine, emetine, reserpine and morphine are heterocyclic compounds and they are also some examples of natural drugs. Azidothymidine, antipyrine, metronidazole, barbiturates, diazepam and methotrexate are also heterocycles and they are known as synthetic drugs (Figure 4).[4]

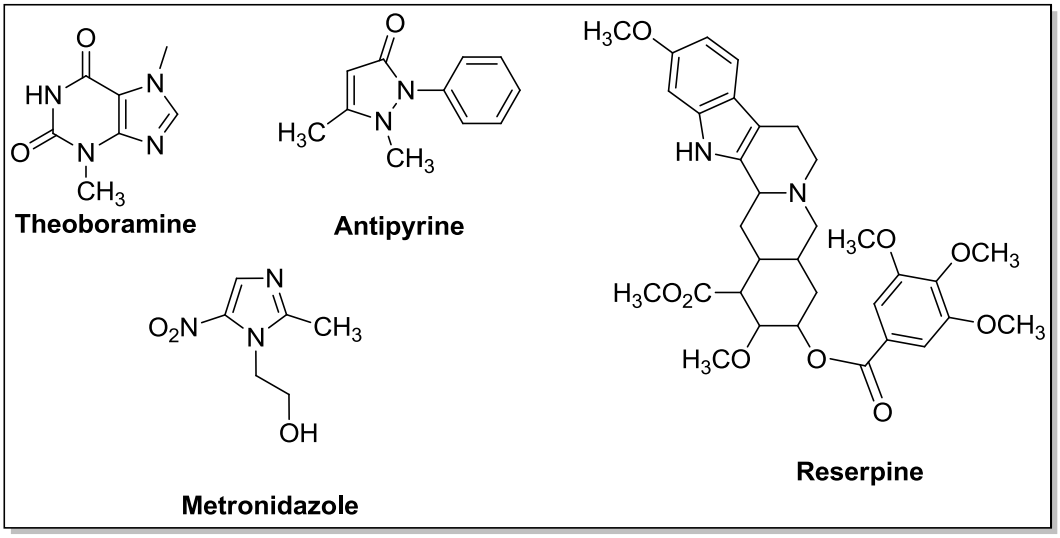


Figure 4. Some examples of natural and synthetic drugs.

1.2 Nitrogen Containing Heterocyclic Compounds

Nitrogen containing heterocyclic molecules are very important heterocycles for natural products, pharmacologically and biologically active molecules.[12] Due to these properties, this topic always caught attention of organic chemists in synthesis, materials science and medicinal chemistry. Some examples for nitrogen-based heterocycles are pyridines, piperidines, pyrroles, azepines, pyrrolines and oxazepines (Figure 5).

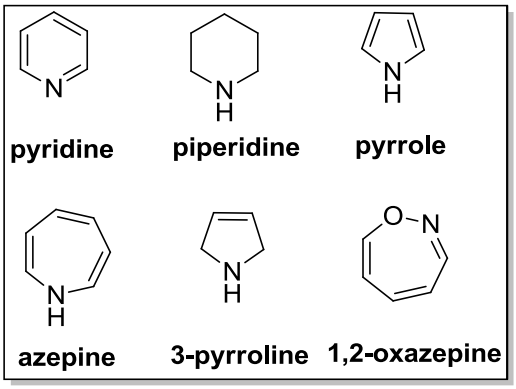


Figure 5. Some examples of nitrogen containing heterocyclic compounds.

Pyridines are a class of six-membered nitrogen containing aromatic compounds. They are found in many drugs because of having biological importance (Figure 6).[1] They can be used as anticancer, antidiabetic, antioxidant, antiviral and antimicrobial agents.[13]

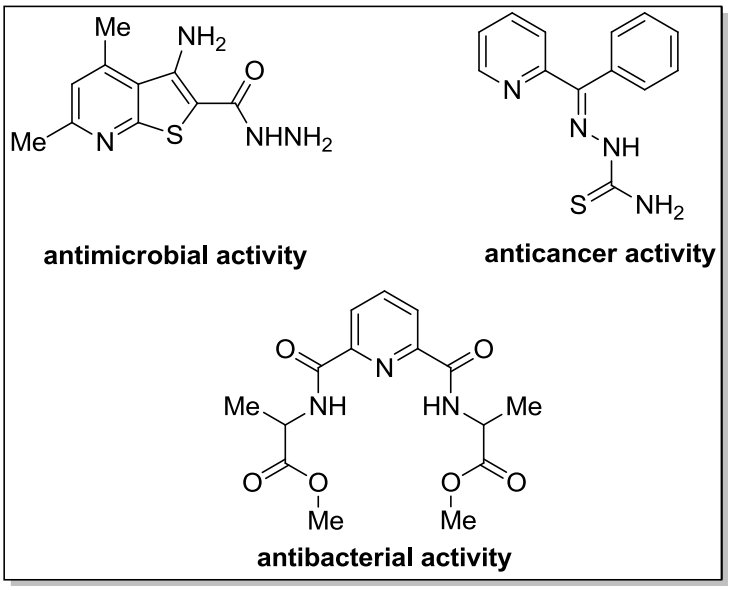


Figure 6. Pyridine containing molecules found in various drugs.

Oxazepines are another class of nitrogen-based heterocycles. 1,4-oxazepines, especially, are important compounds in terms of having biological activities. They are found in mostly antidepressant, antiviral, hypnotic and anticancer drugs.[14] Some of the examples for 1,4-oxazepine containing drugs are Loxapine and Amoxapine (Figure 7).[15]

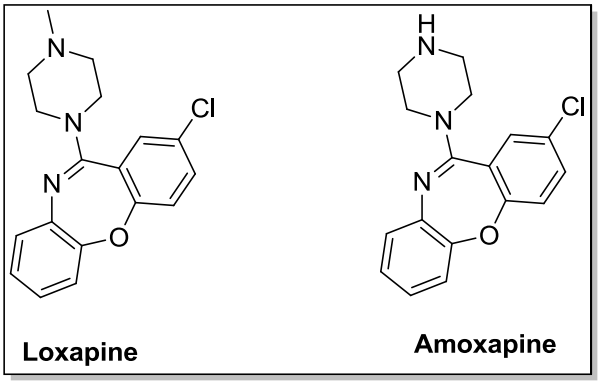


Figure 7. 1,4-Oxazepine containing drugs.

Pyrrolines and pyrroles are also important nitrogen containing heterocycles. They have great importance due to their biological applications. 1-Pyrrolines are found in many natural products such as Gelsenicine, Broussonetine U etc (Figure 8).[16] They are also used as synthetic building blocks for catalysts, drugs and alkaloids.[17] In addition, pyrroles have many important biological properties. In other respects, they have significant role in material science and synthetic organic chemistry.[18]

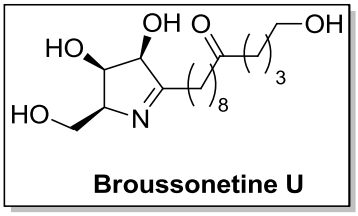


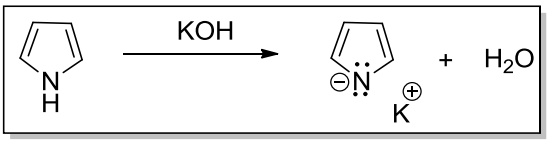
Figure 8. An example of 1-pyrroline containing natural product.

Consequently, heterocyclic molecules which are containing nitrogen are important class of organic chemistry. Pyrroles, which are one of the nitrogen-based heterocycles, are the main area of focus in synthetic chemistry.

1.3 Pyrroles

Pyrroles are one of the most important classes of heterocyclic compounds. They are five-membered heterocyclic compounds, and the core general formulas are C_4H_4NH.[19]

Pyrrole belongs to the group of aromatic heterocyclic compounds. Also, pyrrole is a basic compound, but its basicity is less than that of amine because of the delocalization of electrons of nitrogen atom in the aromatic ring.[21] Pyrrole is best described as the weak acid by generating potassium and sodium salts (Figure 10).[22] It is a colorless volatile liquid and it is unstable upon exposure to air. When it reacts with air, its color turns to darker.



Scheme 1. Acidic property of pyrrole.

Pyrrole is first detected by F.F. Runge in 1834 as a component of coal.[23] Later, it is discovered in bone for the first time, in 1857.[24] Pyrroles are found in many natural products and cofactors. They are constituents of vitamin B12, heme, chlorophyll, bacteriochlorins and biliverdin. However, pyrroles are not naturally occurred compounds.[25]

Pyrrole unit contained molecules have various kind of activities such as being biologically active compounds.[26] Pyrroles have a great importance for the synthesis of pharmaceutical and natural compounds such as medicines, agrochemicals, dyes, photographic chemicals and perfumes.[19] They are found in important pharmaceutical products like aloracetam for treatment of Alzheimer' disease and tolmetin which is

a rheumatoid arthritis pain drugs (Figure 11). In addition to these, they show anticancer, antibacterial, anti-fungal, anti-viral and antioxidant activities.[27]

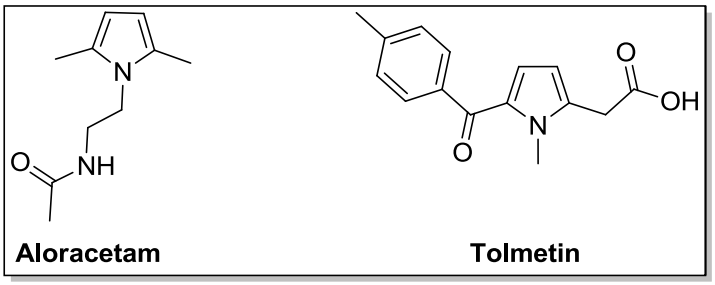
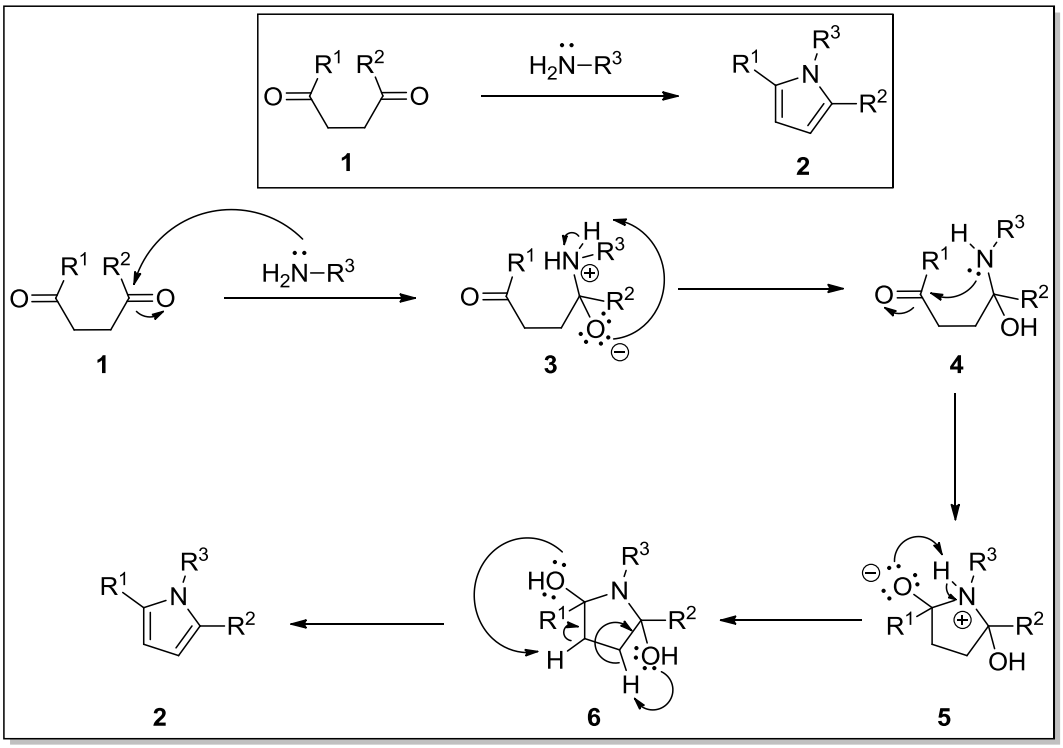


Figure 9. Some examples of pyrrole containing drugs.

Furthermore, pyrroles are used as a corrosion inhibitor, preservative, and catalyst for polymerization process.[27] They can be functionalized in luminescence chemistry, metallurgical operation and spectrochemical analysis.[19] Because of widely usage range of pyrrole, it is an important area for chemists to work.

Several methods have been improved for the synthesis of pyrrole and its derivatives. Some of them are Hantzsch procedure, 1,3-dipolar cycloaddition reaction, aza-Wittig reaction, conjugate addition, transition metal-mediated cyclization and Paal-Knorr reaction.[21] Paal-Knorr reaction, which contains the condensation of 1,4 dicarbonyl with ammonia or a primary amine, is accepted as the most important and simple method for synthesis of pyrroles (Scheme 2).

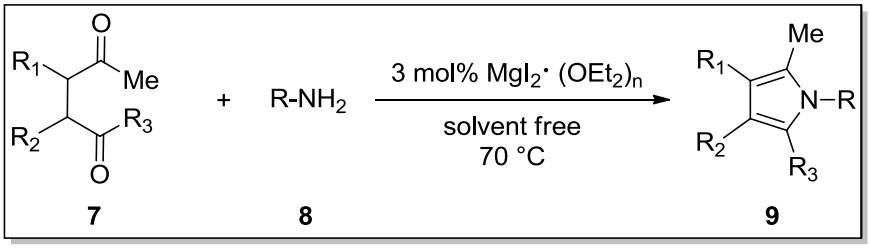


Scheme 2. Mechanism of Paal Knorr pyrrole synthesis.

1.4 Synthesis of Pyrroles

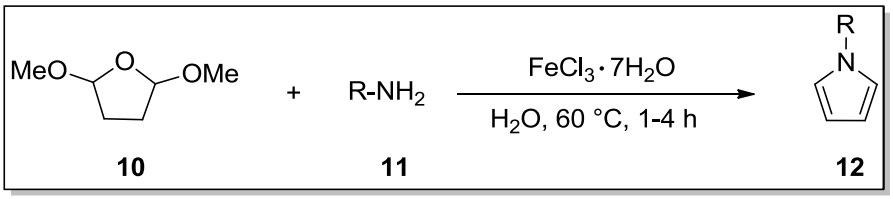
Several methods were developed for the synthesis of pyrrole derivatives.

First, Zhang research group synthesized *N*-substituted pyrroles **9** under solvent free conditions by using Paal-Knorr reaction. Then, they investigated the reaction scope by using different substituted 1,4-dicarbonyl compounds with different primary amines (Scheme 3).[28]



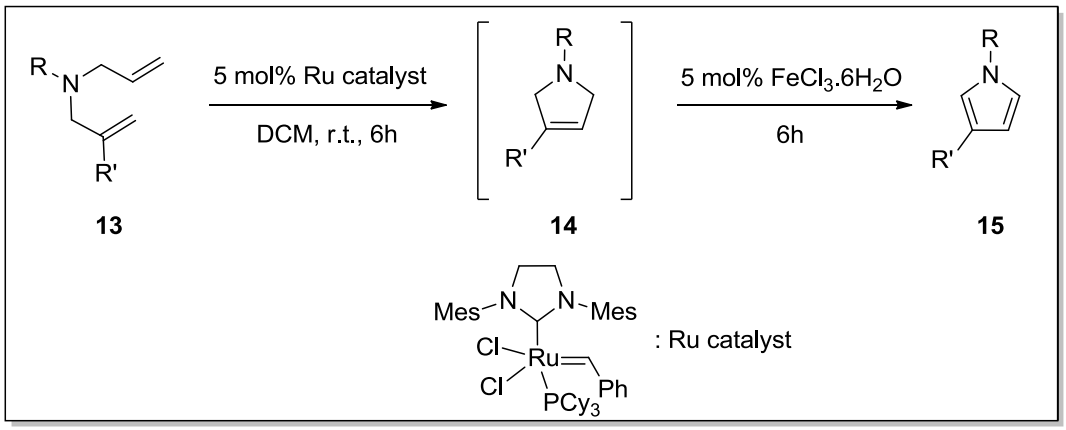
Scheme 3. Synthesis of *N*-substituted pyrrole derivatives.

Aziz et al. also synthesized *N*-substituted pyrroles **12** by using 2,5-dimethoxytetrahydrofuran **10** and primary aromatic amides **11** as the starting materials in the presence of catalytic amount of iron (III) chloride and water. This method is an example to practical and inexpensive synthesis of pyrrole derivatives (Scheme 4).[29]



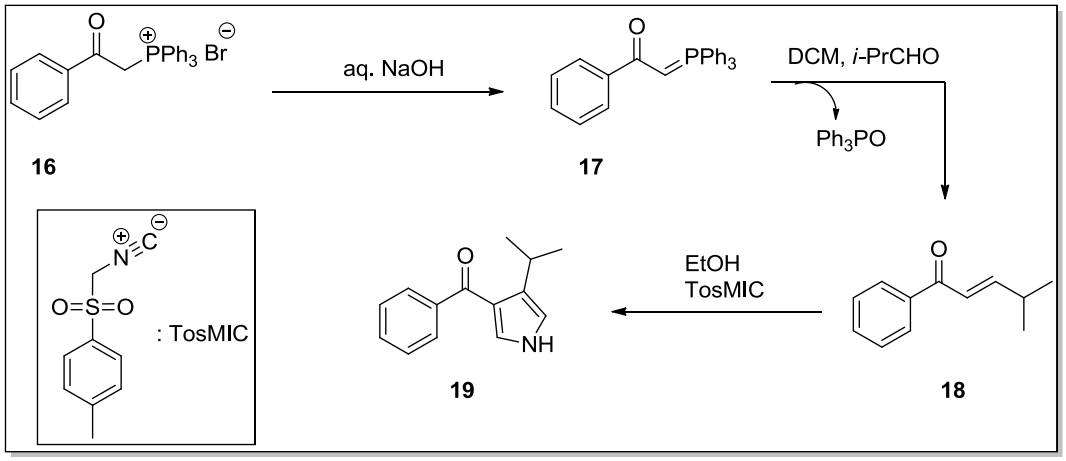
Scheme 4. Synthesis of iron catalyzed *N*-substituted pyrrole derivatives.

Bunrit et al. developed a new method for the synthesis of β-substituted pyrroles **15** in the presence of transition metal catalysts. They used Pd, Fe and Ru catalysts to get the pyrroles in high yields (Scheme 5).[30]



Scheme 5. Synthesis of iron-catalyzed *N*-substituted pyrrole derivatives.

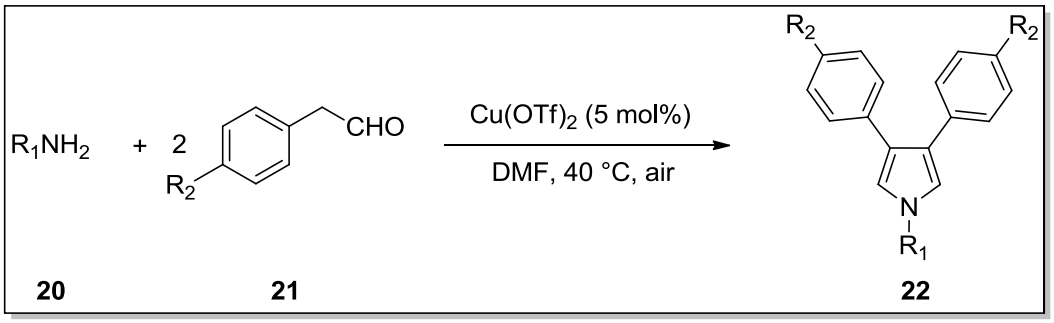
Kumar research group carried out the synthesis of 4-alkyl-3-benzoylpyrroles **19** from tosylmethylisocyanide and aromatic aldehydes with the Wittig approach. The reaction was performed as one-pot reaction under mild basic conditions with good yields (Scheme 6).[31]



Scheme 6. Synthesis of 4-alkyl-3-benzoylpyrroles.

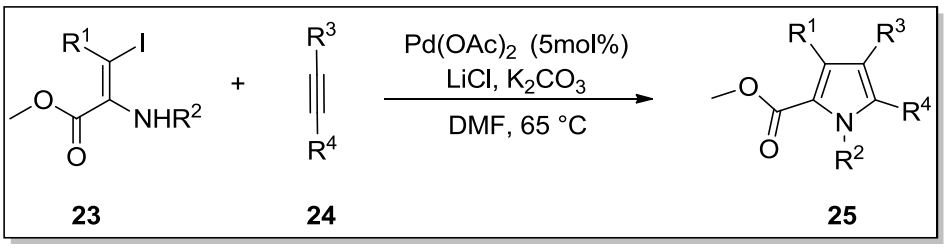
Huang and coworkers synthesized 1,3,4-trisubstituted pyrroles with the reaction of aliphatic amines **20** and substituted phenylacetaldehydes **21** under copper-catalyzed

and aerobic conditions. The reaction produced trisubstituted pyrroles **22** in good to high yields (Scheme 7).[32]



Scheme 7. Synthesis of 1,3,4-trisubstituted pyrrole derivatives.

A new type of cyclization of acetylenes or alkynes has been achieved to synthesize 2-amino-3-iodoacrylates **25** in the presence of palladium catalyst, LiCl, K_2CO_3 and DMF. In this reaction, pyrrole has been obtained in one step and regioselective manner (Scheme 8).[33]



Scheme 8. Regioselective synthesis of substituted pyrroles.

1.5 *N*-Propargylic β-Enaminones

β-Enaminones are widely used in the synthesis of heterocyclic compounds because they have high reactivity due to having O=C–C=C–N conjugated structure.[34] β-Enaminones also are important intermediates for synthetic organic chemistry because of their dual behavior. They show both nucleophilic and electrophilic character resulting from enamine and enone functional groups, respectively.[35] Intermolecular and intramolecular reactions of β-enaminones by utilizing their electronic properties have been investigated intensely.[36]

In particular, *N*-propargylic β-enaminones **26**, are reactive compounds for intramolecular reactions because they have different functional groups such as alkyne, alkene, enamine, enone, enaminone and propargylamine (Figure 12).[37] Five-, six- and seven-membered heterocyclic molecules can be obtained by the cyclization of *N*-propargylic β-enaminones under proper conditions.

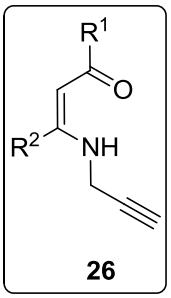
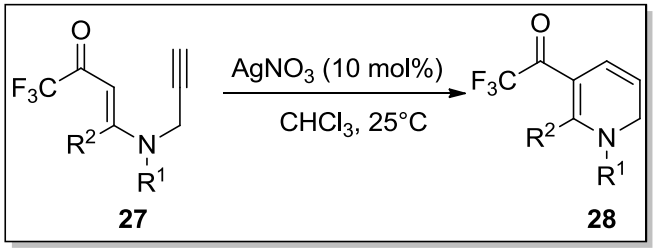


Figure 10. Structure of *N*-propargylic β-enaminones.

1.6 Reactions of *N*-propargylic β-enaminones

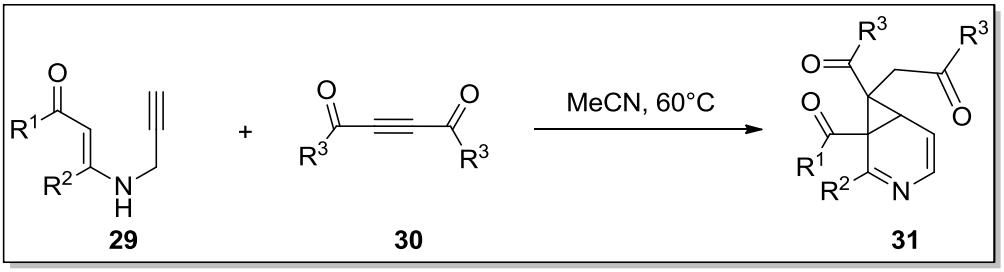
There are many studies that show the usage of *N*-propargylic β-enaminones as intermediates for the synthesis of 1,2-dihydropyridines, pyrroles, pyrrolidinones, oxazepines and thiazepines. In literature, their cyclization can be seen frequently.

Martins et al. synthesized dihydropyridines from trifluoromethylated *N*-propargylic β-enaminones **27**. The cyclization of *N*-propargylic β-enaminones was achieved by silver nitrate (10 mol%) in chloroform at 25 °C to obtain 1,2-dihydropyridines **28** (Scheme 9).[38]



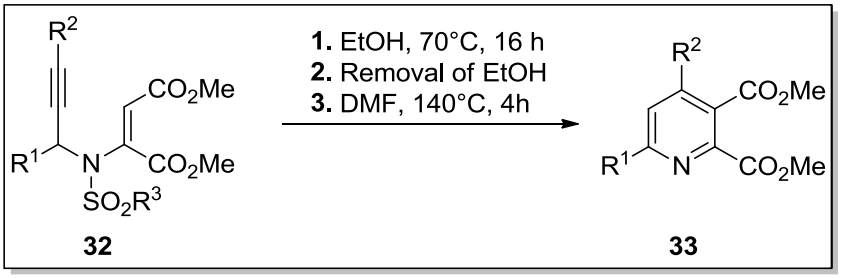
Scheme 9. Ag-catalyzed cyclization of trifluoromethylated *N*-propargylic β-enaminones.

Karunakar and co-workers showed that synthesis of fused pyridines **31** is possible by the reaction of *N*-propargylic β-enaminones **29** with acetylenecarboxylates **30**. The reaction was achieved under catalyst free conditions in acetonitrile (Scheme 10).[37]



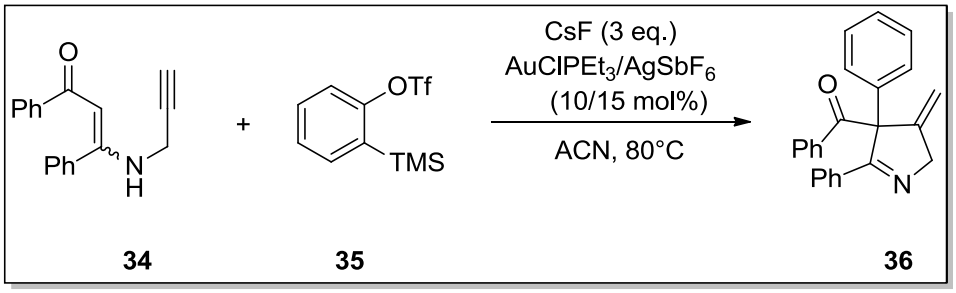
Scheme 10. Synthesis of fused pyridine ring systems.

Xin et al. reported a new method for the synthesis of pyridines from *N*-sulfonyl, *N*-propargylic β-enaminones. They have indicated that the cyclization proceeds via one-pot three-step reaction. Substituted pyridine derivatives **33** were obtained from *N*-sulfonyl, *N*-propargylic β-enaminones **32** by aza-Claisen rearrangement, electrocyclization and elimination, respectively (Scheme 10).[39]



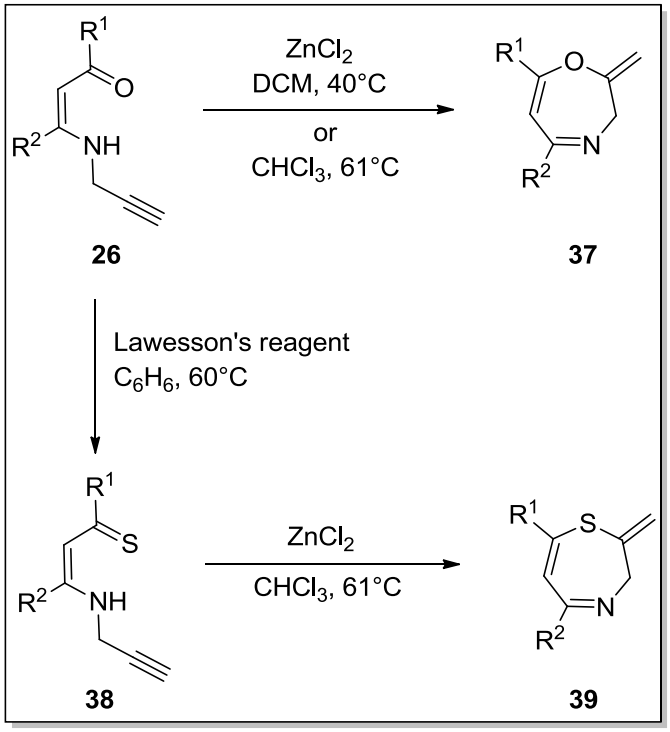
Scheme 11. Synthesis of pyridine derivatives.

In another study of Karunakar and co-workers, they reported that 1-pyrrolines **36** can be synthesized by the cyclization of *N*-propargylic β-enaminones **34** under gold-catalyzed condition. First, they investigate the reaction conditions with different catalysts and solvents and then they explored substrate scope for the synthesis of 1-pyrroline derivatives (Scheme 12).[40]



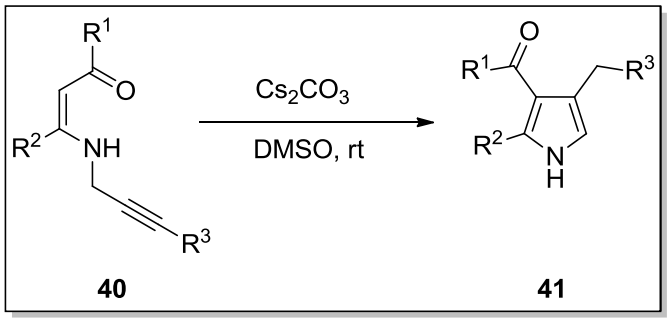
Scheme 12. Synthesis of 4-methylene-1-pyrroline derivatives.

Zora research group developed a new methodology for the synthesis of 1,4 oxazepines (Scheme 12).[41] In this study, the aim was to show 7-exo-dig cyclization of *N*-propargylic β-enaminones **26** to synthesize corresponding 2-methylene-2,3-dihydro-1,4 oxazepines **37** in the presence of $ZnCl_2$ and dichloromethane or chloroform. After this study, this research group also showed the synthesis of 1,4-thiazepines under similar conditions. They showed that when *N*-propargylic β-enaminothiones **38** reacted with $ZnCl_2$, 2-methylene-2,3-dihydro-1,4-thiazepines **39** can be obtained in good to high yields (Scheme 13).[42]



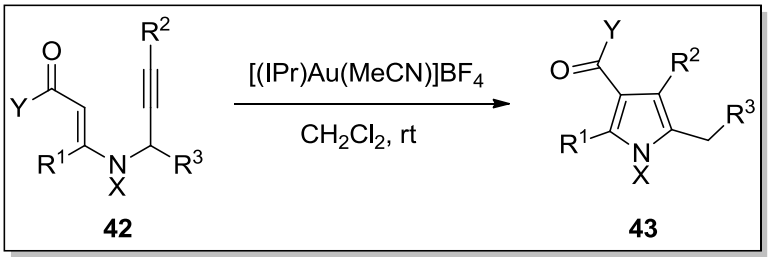
Scheme 13. Synthesis of 1,4-oxazepine and 1,4-thiazepine derivatives.

Cacchi et al. showed that *N*-propargylic β-enaminones could be used for the synthesis of pyrrole and pyridine derivatives. They developed a new method for the synthesis of polysubstituted pyrrole derivatives **41** by the cyclization of *N*-propargylic β-enaminones **40** in the presence of Cs_2CO_3 in DMSO (Scheme 14).[36]



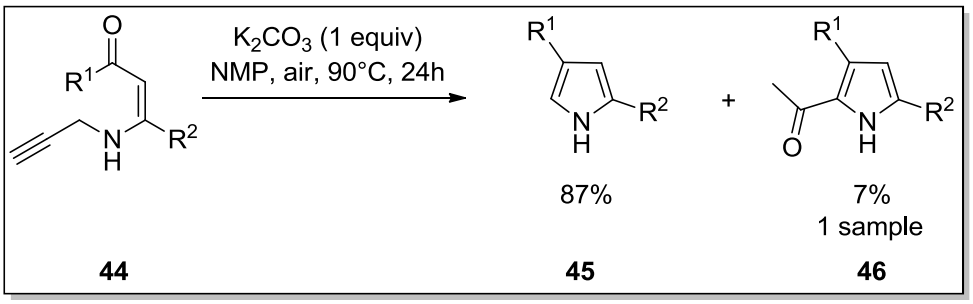
Scheme 14. Synthesis of polysubstituted pyrroles.

Saito and Hanzawa showed a new synthetic method for the synthesis of pyrroles **43**. They reported that when *N*-propargylic β-enaminones **42** were catalyzed with gold(I) in CH_2Cl_2, they underwent amino-claisen rearrangement to yield pyrroles **43** (Scheme 15).[43]



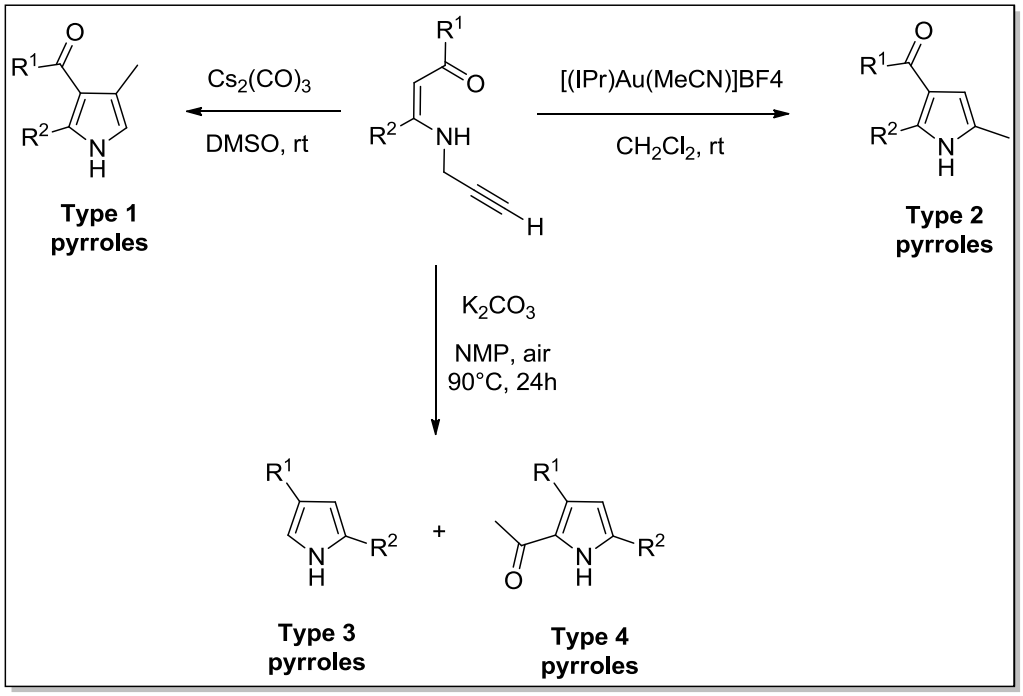
Scheme 15. Synthesis of pyrroles by gold(I) catalyzed amino-claisen rearrangement.

Synthesis of 2,4-disubstituted pyrrole derivatives **45** was accomplished by Cheng research group. Base-promoted cyclization of *N*-propargylic β-enaminones **44** in NMP at 90℃ yielded the target molecule **45**. However, in one case, they reported that the formation of 2-acetylpyrrole **46** as minor product with the yield of 7% (Scheme 16).[44] Although 2-acetylpyrroles have great potential in terms of derivatization, pyrrole **46** has obtained as minor product.



Scheme 16. Synthesis of 2,4-disubstituted pyrroles.

In summary, it is clearly seen that three types of pyrroles according to the arrangement of substituents have been synthesized from *N*-propargylic β-enaminones up to now. In addition to them, there is also fourth pyrrole type that have not been synthesize as major product in the literature yet. The general scheme of the synthesis of the different types of pyrroles from same starting compounds which are different derivatives of *N*-propargylic β-enaminones is shown below (Scheme 17).[36,43,44]

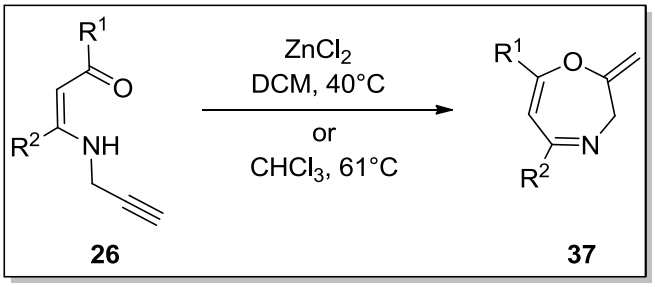


Scheme 17. Synthesis of types of pyrroles from *N*-propargylic β-enaminones.

1.7 Aim of the Study

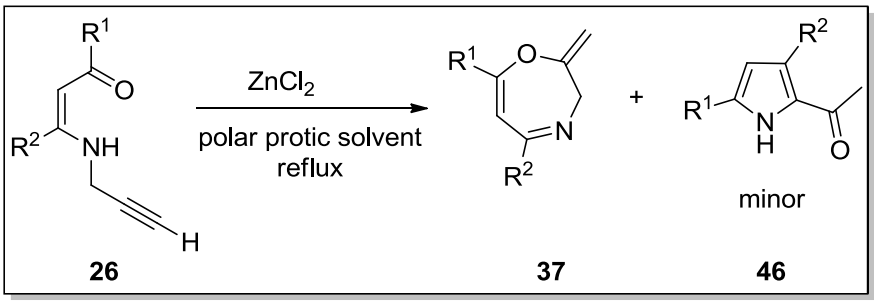
So far, the importance of heterocyclic compounds and the studies on them have been shown. It is clearly seen that *N*-propargylic β-enaminones are very important compounds for synthetic organic chemistry and they are commonly used as the starting materials for the synthesis of *N*-heterocycles. In this regard, our research group have also used *N*-propargylic β-enaminones as the starting compounds for the synthesis of desired pyrrole derivatives.

In our research group, generally five-, six- and seven-membered heterocyclic compounds are studied. We try to develop new methodologies for the synthesis of new heterocyclic molecules. Previously, in Zora research group, 2-methylene-2,3-dihydro-1,4-oxazepine **37** have been synthesized from *N*-propargylic β-enaminone **26** (Scheme 18).[41]



Scheme 18. Synthesis of 2-methylene-2,3-dihydro-1,4-oxaepines **37**.

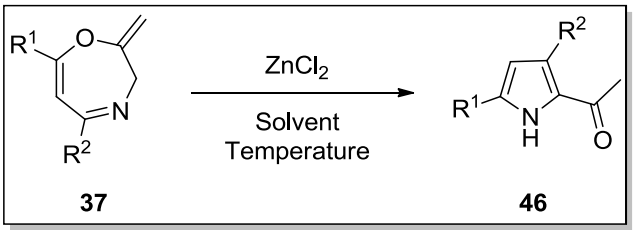
This work had remarkable results. Then, it was decided to repeat same work by using a polar protic solvent instead of halogenated solvents. After doing the experiment, it was seen that a type of pyrrole has been obtained as minor product (Scheme 19). Thus, it was aimed to synthesize this type of pyrrole as major product.



Scheme 19. Synthesis of pyrrole **42** as minor product.

For this reason, we try to develop new methodology for the synthesis of desired pyrrole derivatives. In this study, our aim is to synthesize a new type of 2-acetylpyrrole derivatives by using two unprecedented ways.

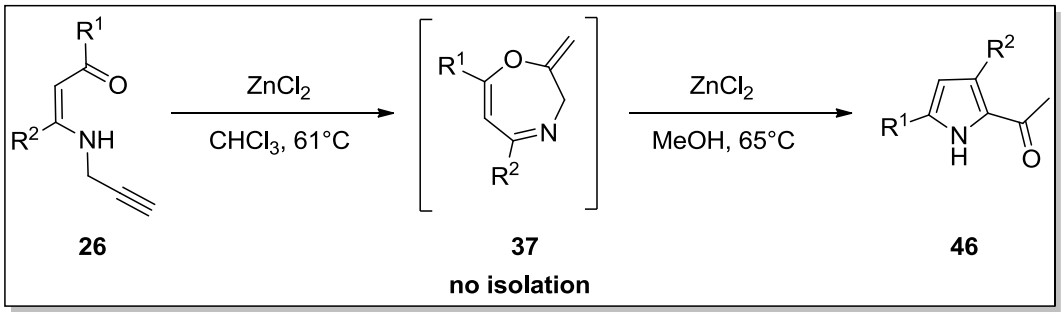
For the first part of this study, synthesis method from 1,4-oxazepines **37** will be applied to synthesize desired pyrrole. 2-Methylene-2,3-dihydro-1,4-oxazepines will be synthesized by using *N*-propargylic β-enaminones **26** according to our previous studies (Scheme 18).[41] Then, we will convert 2-methylene-2,3-dihydro-1,4-oxazepines into pyrrole derivatives (Scheme 20).



Scheme 20. Synthesis of pyrrole derivatives from 2-methylene-2,3-dihydro-1,4-oxazepines (**37**).

For the second part of the study, one-pot two-step synthesis of the same pyrrole derivatives will be performed. In this method, *N*-propargylic β-enaminones **26** will be used as starting materials, and then 1,4-oxazepines **37** will be obtained as the intermediates in the reaction medium. Finally, the in situ formed 2-methylene-2,3-

dihydro-1,4-oxazepines will be converted into desired pyrrole derivatives (Scheme 21).



Scheme 21. Synthesis of pyrrole derivatives from *N*-propargylic β-enaminones **26** via one-pot two-step synthesis method.

In brief, in this thesis, optimization studies and suggested mechanism for the synthesis of pyrrole derivatives **46** will be discussed in detail.

CHAPTER 2

RESULTS AND DISCUSSION

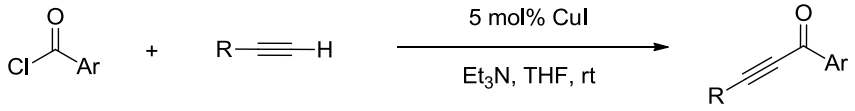
2.1 Synthesis of α,β-alkynic ketones

In the first phase of the project, we synthesized α,β-alkynic ketones **49**. For their synthesis, benzoyl chlorides **47** with terminal alkynes **48** coupled by sonogashira cross coupling reaction. $PdCl_2(PPh_3)_2$, CuI, Et_3N and THF were used as catalyst, co-catalyst, base and solvent, respectively (Scheme 22).

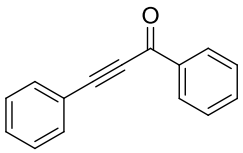
Scheme 22. Synthesis of α,β-alkynic ketones **49**.

The synthesis of 20 derivatives of α,β-alkynic ketones **49** were achieved in 60-98% yields by employing Sonogashira cross coupling reaction as depicted in Table 1.

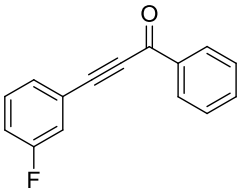
Table 1. Synthesis of α,β-alkynic ketone derivatives **49**. [a]



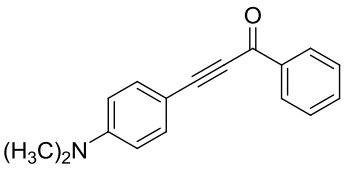
47 **48** **49**



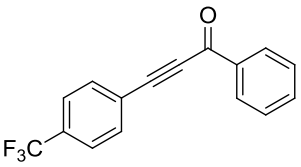
49a (97%)



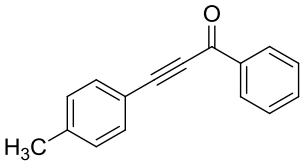
49b (78%)



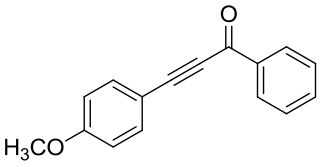
49c (87%)



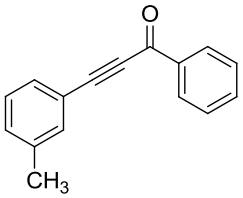
49d (60%)



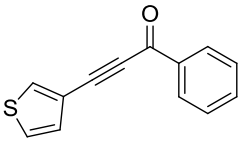
49e (88%)



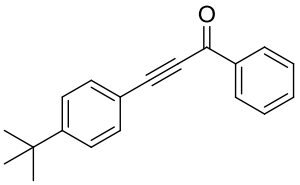
49f (78%)



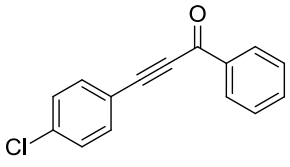
49g (93%)



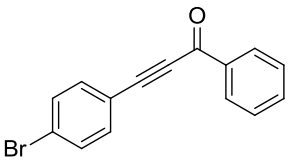
49h (88%)



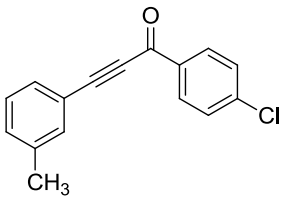
49i (97%)



49j (85%)

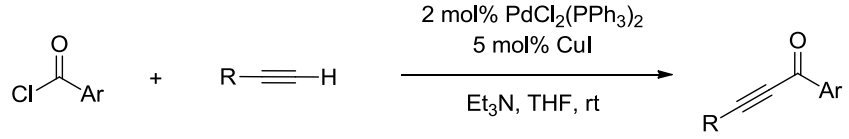


49k (78%)

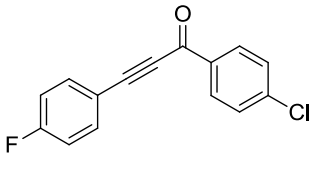


49l (77%)

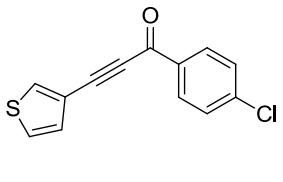
Table 1. Continued.



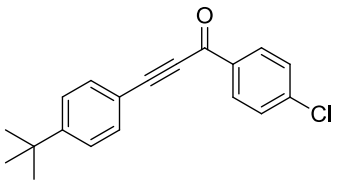
47 **48** **49**



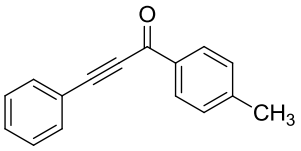
49m (90%)



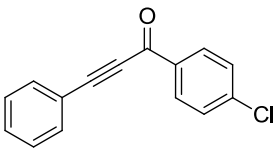
49n (80%)



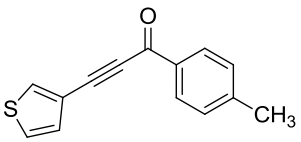
49o (85%)



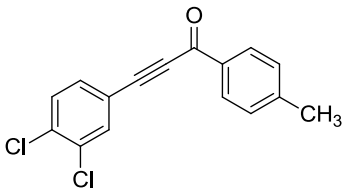
49p (93%)



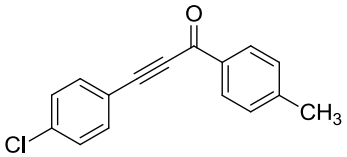
49q (98%)



49r (77%)



49s (74%)



49t (81%)

[a]Isolated yields.

^1H and ^{13}C NMR spectra were used to identify the structures of the synthesized compounds. As an example, ^1H and ^{13}C NMR spectra of 1,3-diphenylprop-2-yn-1-one (**49a**) are illustrated in Figures 13 and 14, respectively. In the ^1H NMR spectrum of compound **49a,** ten aromatic hydrogens resonate as multiplet at 7.36-8.24 ppm (Figure 13). In Figure 14, which shows the ^{13}C spectrum of compound **49a**, carbonyl

carbon resonates at 177.9 ppm and two alkynic carbons appear at 86.9 and 93.1 ppm. The remaining eight carbons of phenyl groups are observed at 120.0-136.8 ppm.

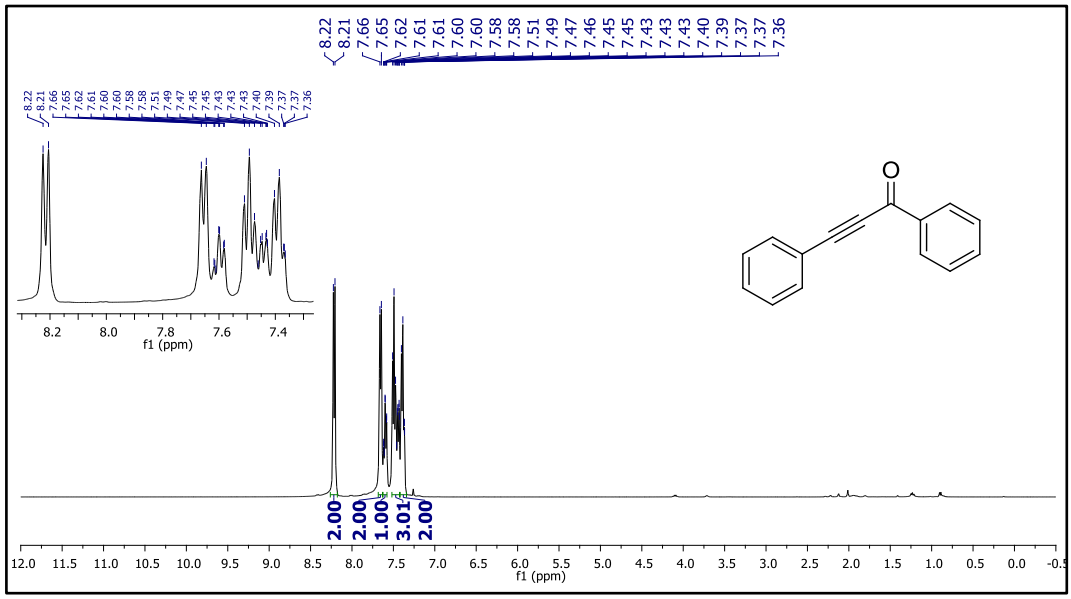


Figure 11. ^{1}H NMR spectrum of 1,3-diphenylprop-2-yn-1-one **(49a)**.

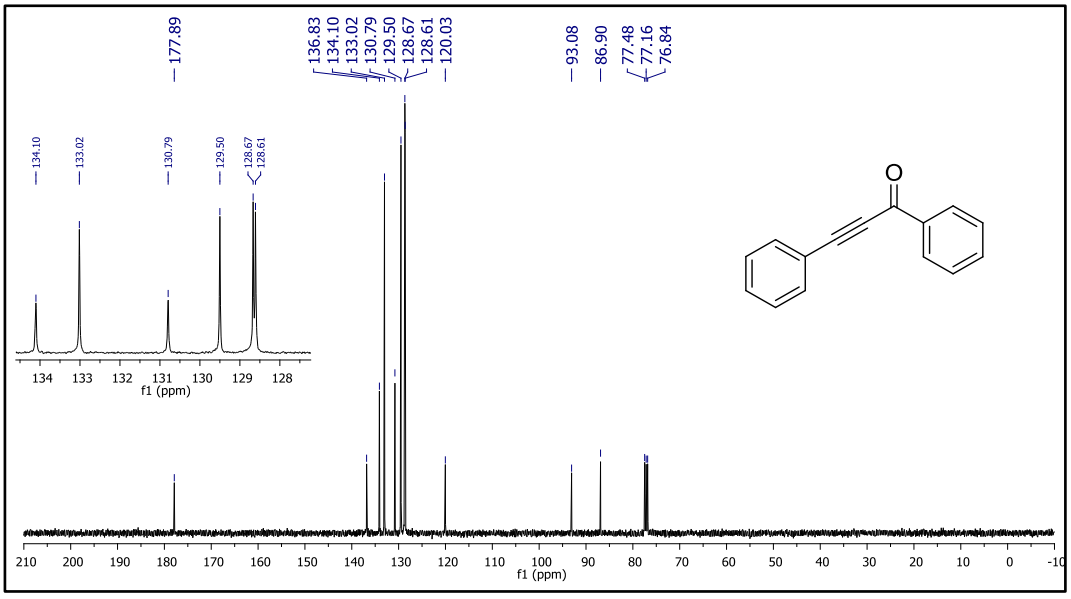
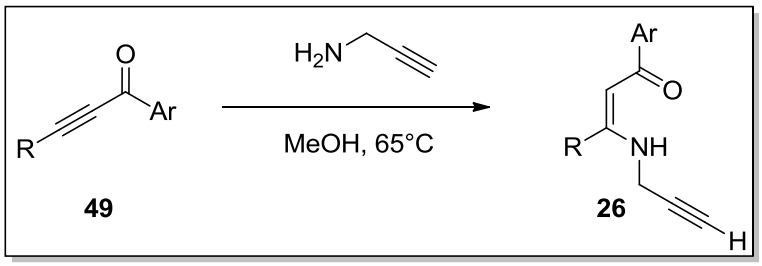


Figure 12. ^{13}C NMR spectrum of 1,3-diphenylprop-2-yn-1-one (**49a**).

2.2 Synthesis of *N*-propargylic β-enaminones

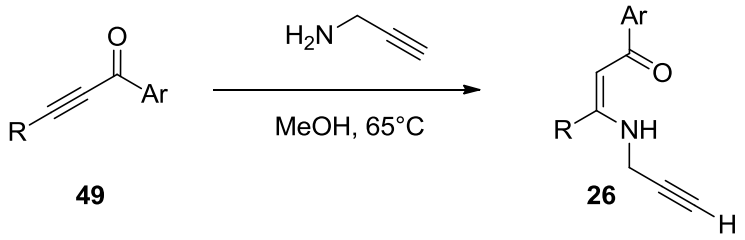
After synthesizing α,β-alkynic ketones **49**, we have prepared *N*-propargylic β-enaminones **26** via conjugate addition of propargylamine to α,β-alkynic ketones **49** in refluxing methanol (Scheme 23). It is very important to say that we have isolated only *Z* isomers of *N*-propargylic β-enaminones derivatives. Cacchi and coworkers[36] and Zora research group[45] have assigned the formation of single *Z* isomer by NOESY experiments. NOESY experiments have also demonstrated the presence of intramolecular hydrogen bonding. Clearly, H-bonding between amine hydrogen and carbonyl oxygen plays an important role in the formation of *Z* isomers of *N*-propargylic β-enaminones.



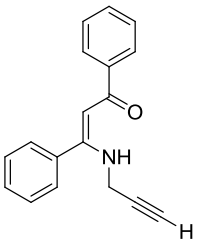
Scheme 23. Synthesis of *N*-propargylic β-enaminones **26**.

Twenty derivatives of *N*-propargylic β-enaminones **26** containing different electron-withdrawing and electron-donating groups were synthesized in 70-97% by employing this conjugate addition reaction (Table 2).

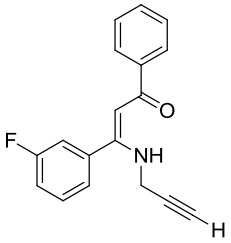
Table 2. Synthesis of *N*-propargylic β-enaminone derivatives **26**. [a]



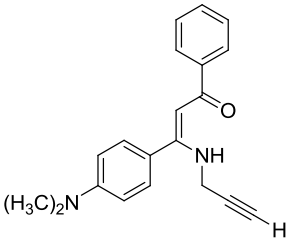
49 **26**



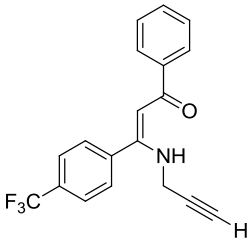
26a (97%)



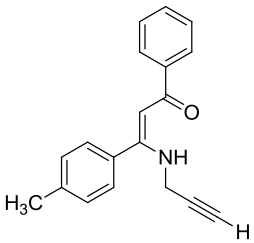
26b (89%)



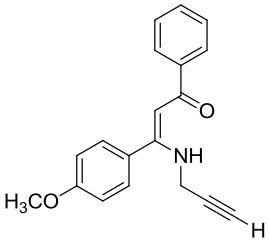
26c (78%)



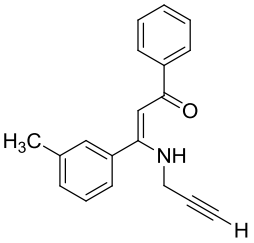
26d (93%)



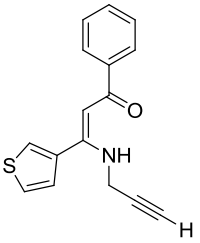
26e (93%)



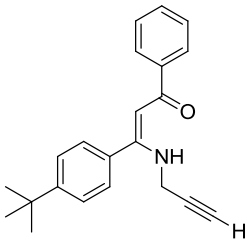
26f (92%)



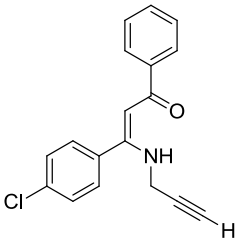
26g (91%)



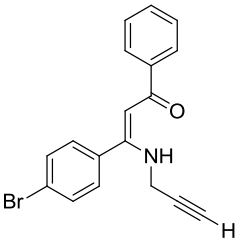
26h (92%)



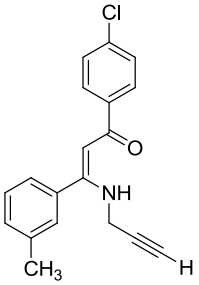
26i (93%)



26j (92%)

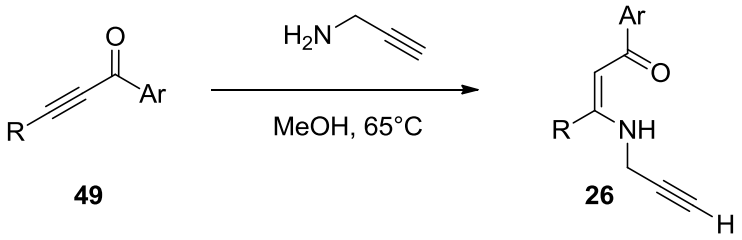


26k (91%)

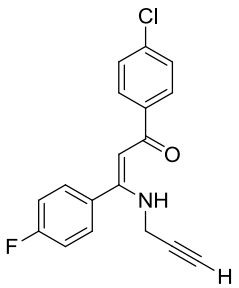


26l (89%)

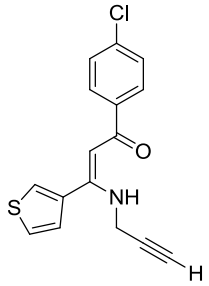
Table 2. Continued.



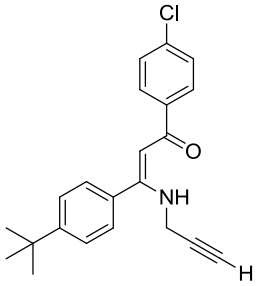
49 **26**



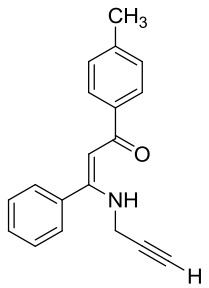
26m (92%)



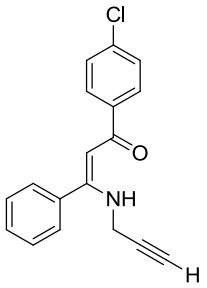
26n (80%)



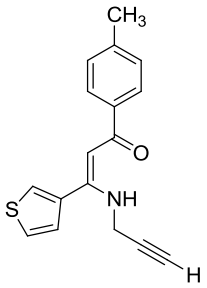
26o (90%)



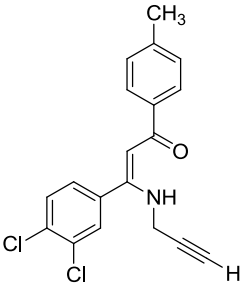
26p (87%)



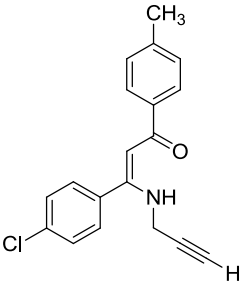
26q (86%)



26r (86%)



26s (70%)



26t (71%)

[a]Isolated yields.

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 (**26a**) are shown in figures 15 and 16, respectively. In ^{1}H NMR spectrum of compound **26a** (Figure 15), N-H proton gives a triplet peak at 11.34 ppm. As we discussed earlier, due to hydrogen bonding between amine hydrogen and carbonyl oxygen, amine hydrogen resonates at lower field. Aromatic hydrogens give multiplet signals between 7.93-7.36 as expected. Vinylic hydrogen

appears as a singlet at 5.85 ppm. Acetylenic hydrogen resonates as a triplet at 2.31 ppm. In ^{13}C NMR spectrum of compound **26a** (Figure 16), 14 different signals are seen. One peak belongs to carbonyl carbon which resonates at 189.1 ppm. The aromatic carbons give signals between 127.2-140.0 ppm. At 165.9 ppm, β-carbon peak is observed while α-carbon appears at 94.7 ppm. The other signals resonating at 79.8, 72.5 and 34.2 ppm belongs to two alkynic and methylene protons, respectively.

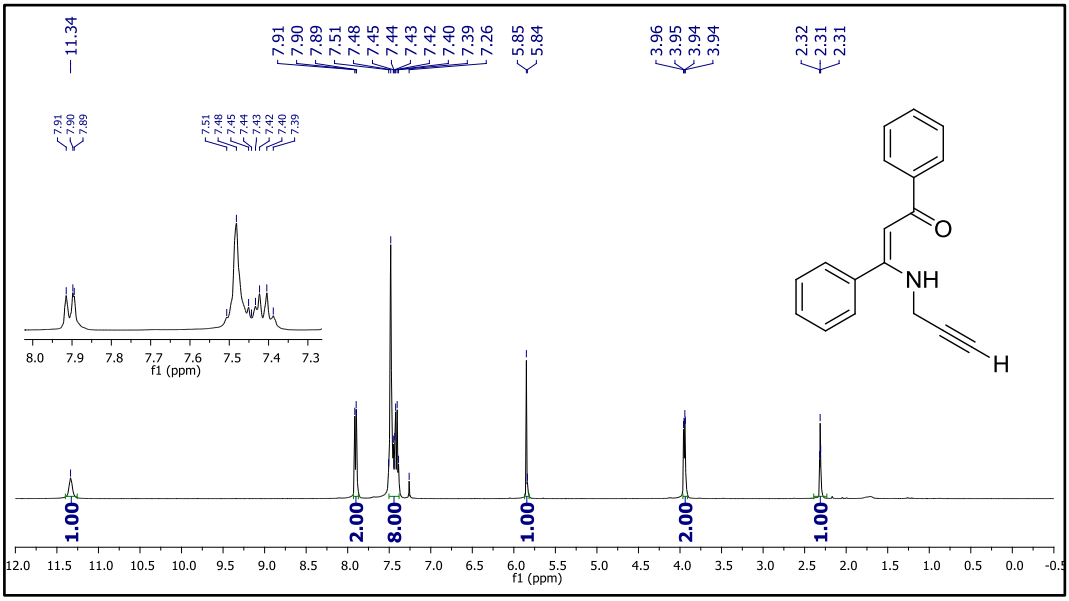


Figure 13. ^{1}H NMR spectrum of (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26a**).

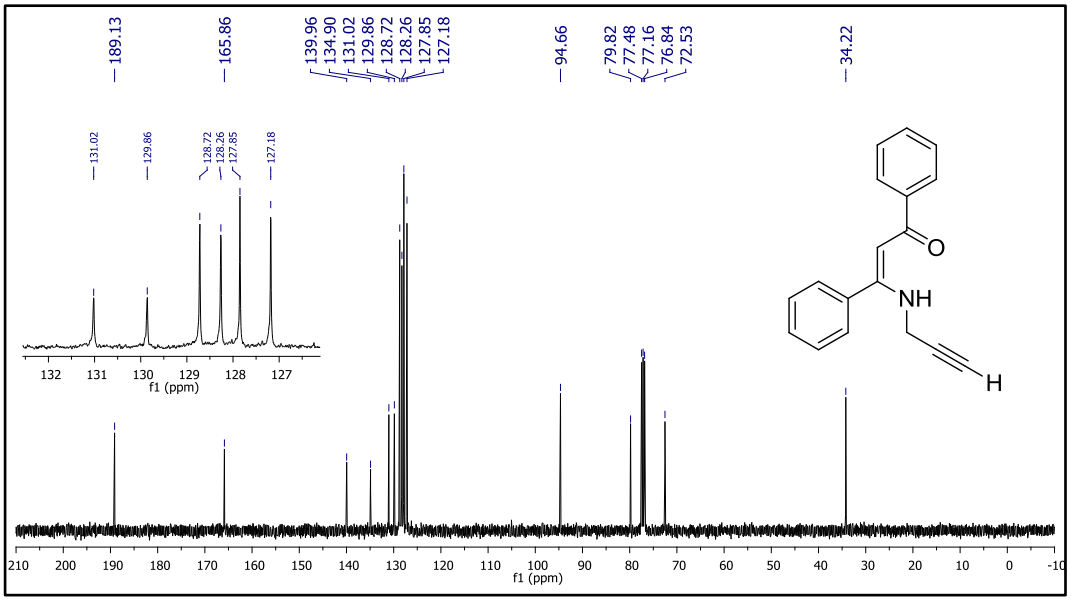
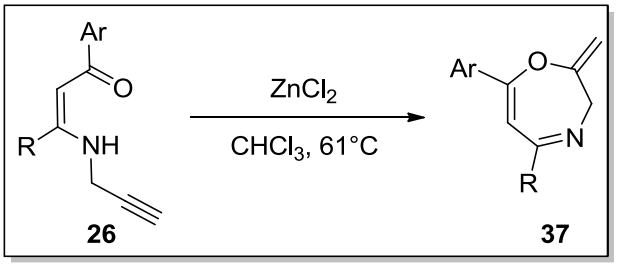


Figure 14. ^{13}C NMR spectrum of (*Z*)-1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26a**).

2.3 Synthesis of 1,4-Oxazepines

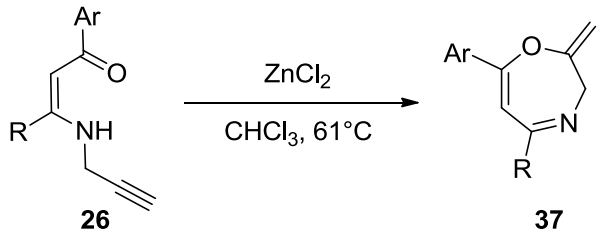
In this part of the project, 1,4-oxazepine derivatives **37** have been synthesized via zinc-mediated cyclization of *N*-propargylic β-enaminones **26**. Our group have shown that synthesis of 2,3-dihydro-1,4-oxazepines is possible by $ZnCl_2$ mediated cyclization of *N*-propargylic β-enaminones in refluxing chloroform (Scheme 24).[41] The reaction time is nearly 1.5 h and yields are good to high. That's why this method has been convenient way for the synthesis of our starting materials.



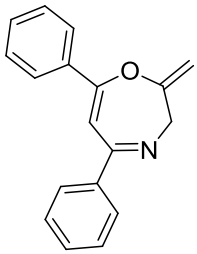
Scheme 24. Synthesis of 1,4-oxazepines **37**.

By using this method, synthesis of twenty different derivatives of 2-methylene-2,3-dihydro-1,4-oxazepines (**37**) with different electron-withdrawing and electron-donating groups were achieved in good to high yields (Table 3).

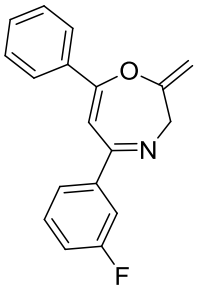
Table 3. Synthesis of 1,4-oxazepines derivatives **37**. [a]



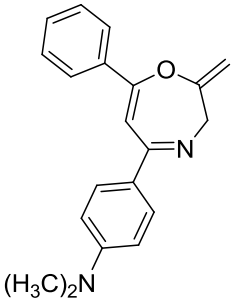
26 **37**



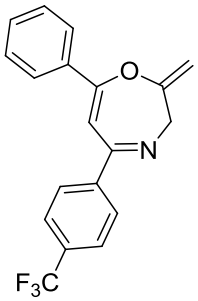
37a (95%)



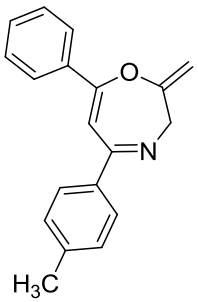
37b (84%)



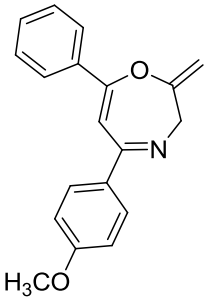
37c (61%)



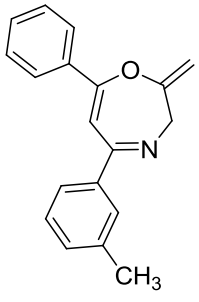
37d (75%)



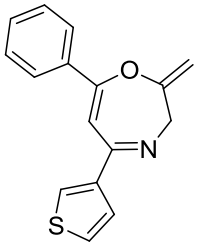
37e (70%)



37f (72%)

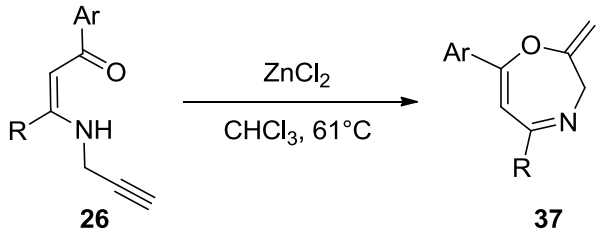


37g (74%)

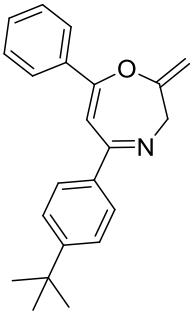


37h (82%)

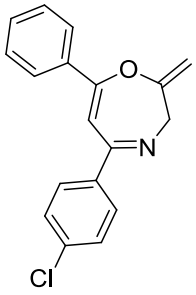
Table 3. Continued.



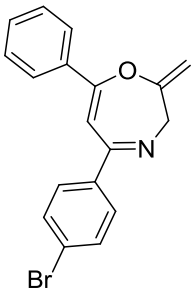
26 **37**



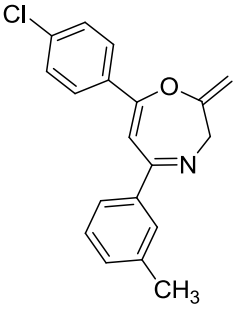
37i (88%)



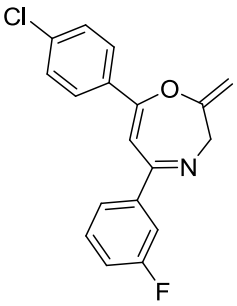
37j (85%)



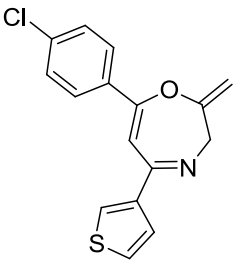
37k (87%)



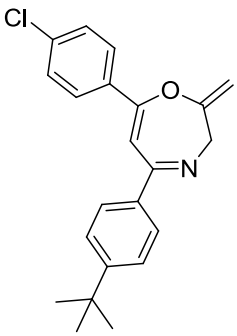
37l (87%)



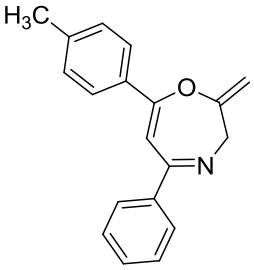
37m (74%)



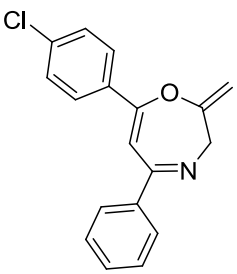
37n (87%)



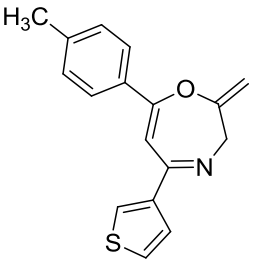
37o (82%)



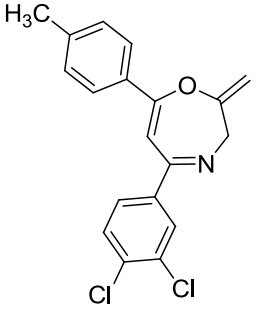
37p (64%)



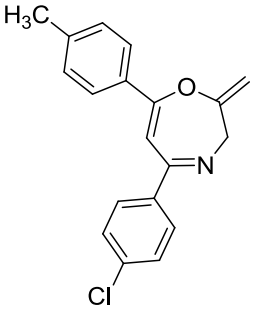
37q (84%)



37r (79%)



37s (80%)



37t (80%)

[a]Isolated yields.

The structures of 2,3-dihydro-1,4-oxazepine derivatives were mainly identified with analysis of their ^{1}H and ^{13}C NMR spectra. For example, ^{1}H and ^{13}C NMR spectra of 2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**37a**) were illustrated in Figures 17 and 18, respectively. In the ^{1}H NMR spectrum (Figure 17), ten aromatic hydrogens give peaks as multiplets between 7.94-7.37 ppm as expected. The olefinic hydrogen resonates as singlet at 6.40 ppm. In the higher field of the spectrum, there are 3 characteristic peaks for 1,4-oxazepine **37a**. The exo-methylenic hydrogens give signal as singlet and doublets at 4.76 and 4.39 ppm, respectively. The third signal, which is in between these peaks, is originated from two methylenic hydrogens on the ring. They resonate as singlet at 4.57 ppm. In the ^{13}C NMR spectrum (Figure 18), there are three peaks which belong to the endo-olefinic carbons of the oxazepine ring, which appear at 167.1, 158.9 and 158.2 ppm. Eight different aromatic carbons resonate between 126.3 and 136.8 ppm. The signals seen at 99.8, 93.9 and 55.6 ppm belong to exo-double bond carbons and methylenic carbon on the ring, respectively.

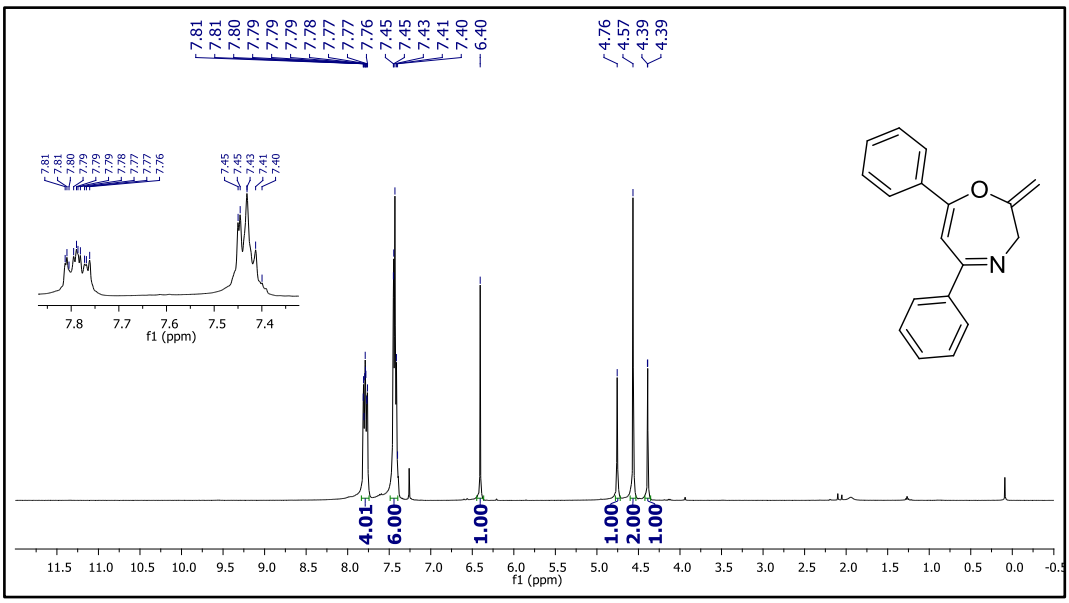


Figure 15. ^{1}H NMR spectrum of 2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**37a**).

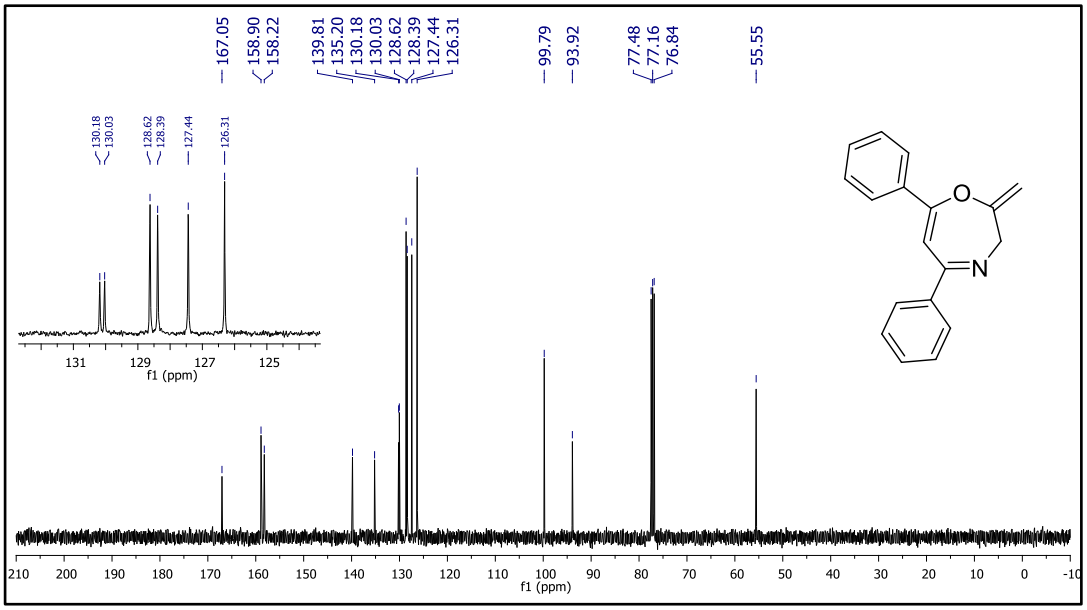
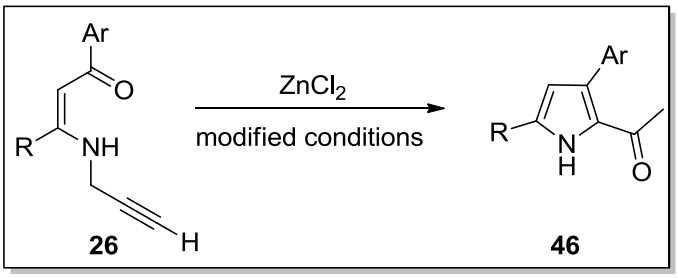


Figure 16. ^{13}C NMR spectrum of 2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**37a**).

2.4 Synthesis of Pyrroles

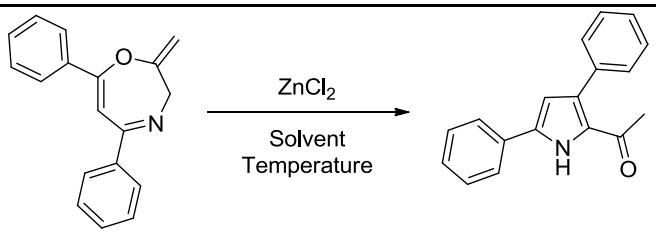
After synthesizing *N*-propargylic β-enaminones, we have investigated the synthesis of pyrroles by using the cyclization of *N*-propargylic β-enaminones. We were inspired by previous work of our research group about the synthesis of 2,3-dihydro-1,4-oxazepines.[41] We tried to analyze cyclization of *N*-propargylic β-enaminones by using $ZnCl_2$ as in the 1,4-oxazepine synthesis. However, in pyrrole synthesis, different type of solvents was used to achieve cyclization. Therefore, optimization reactions were employed in order to determine the best reaction conditions for the synthesis of target pyrrole compounds.



Scheme 25. Synthesis of pyrroles **46** in modified conditions.

In this regard, pyrroles have been synthesized by using 1,4-oxazepines **37** as starting material firstly. According to our previous study, we thought that formation of 2,3-dihydro-1,4-oxazepines are important step for the synthesis of desired pyrroles. That's why, firstly we synthesized 2,3-dihydro-1,4-oxazepines **37** via known procedure in literature.[41] Then, 1,4-oxazepine compound was isolated after performing work-up and column chromatography. After taking the pure product, we treated it with $ZnCl_2$ in different protic solvents at reflux conditions. Various optimization conditions were studied to find best reaction condition (Table 4).

Table 4. Optimization studies for synthesis of pyrroles **46** from 1,4-oxazepines **37**.



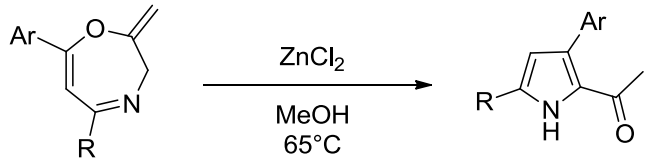
37a **46a**

Entry	$ZnCl_2$ (equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	-	MeOH	65	35.0	77
2	1.0	MeOH	65	3.0	88
3	1.5	MeOH	65	1.5	84
4	2.0	MeOH	65	1.0	80
5	1.0	EtOH	78	3.0	71
6	1.0	*n*-PrOH	97	3.5	74
7	1.0	*n*-BuOH	116	2.0	63

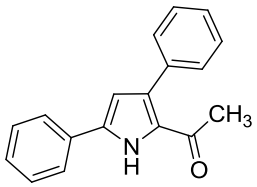
We used various amount of $ZnCl_2$ in different solvents at this study. First, we performed the reaction in refluxing methanol without using $ZnCl_2$ (Table 4, entry 1). The reaction took very long time (35 h). The obtained yield was 77%. The yield was not poor, but this try was not very useful because of its reaction time. And then, we tried the same reaction by using 1.0 equiv. of $ZnCl_2$ in MeOH at reflux condition (Table 4, entry 2). The yield of pyrrole product was 88% in 3 h. In addition, we did the same reaction by using 1.5 equiv. of $ZnCl_2$ (Table 4, entry 3). The reaction time was decreased, but the yield was also decreased in this experiment (1.5 h, 84%). Then, 2.0 equiv. of $ZnCl_2$ was employed to optimize the reaction conditions (Table 4, entry 4). After performing reaction by using 2.0 equiv. of $ZnCl_2$ in refluxing MeOH, the yield of the product was 80%. After that, solvent was changed to carry out the reaction at higher temperature than 65°C. By refluxing EtOH at 78 °C for 3.0 h, the target product was obtained in 71% yield (Table 4, entry 5). Notably, changing the solvent to *n*-PrOH did not increase the yield so much (74%) (Table 4, entry 6).

As the last optimization study, we performed the reaction in *n*-BuOH at 116 °C by using 1.0 equiv. of $ZnCl_2$ (Table 4, entry 7). The yield was decreased to 63% at the end of this reaction. By using the best reaction condition from Table 4, which is entry 2, derivatives of pyrroles have been synthesized as depicted in Table 5.

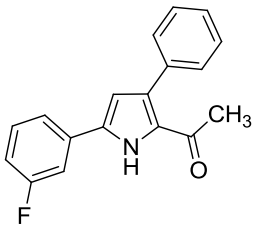
Table 5. Synthesis of pyrrole derivatives **46** from 1,4-oxazepines **37**. [a]



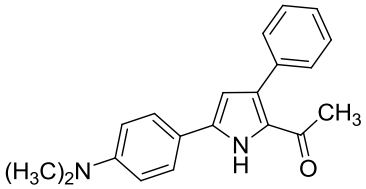
37 **46**



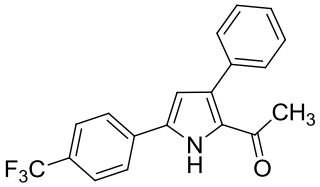
46a (88%)



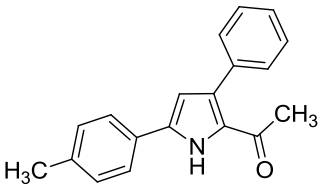
46b (76%)



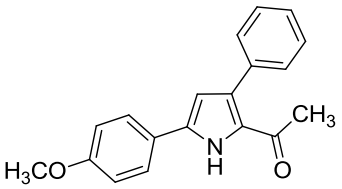
46c (64%)



46d (88%)

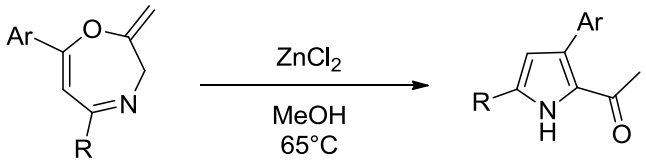


46e (79%)

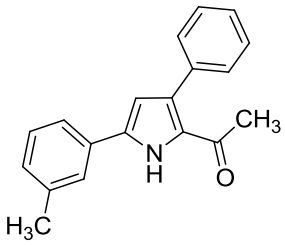


46f (73%)

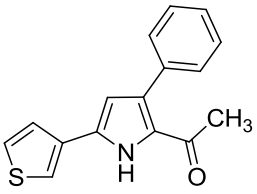
Table 5. Continued.



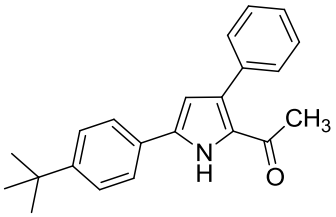
37 **46**



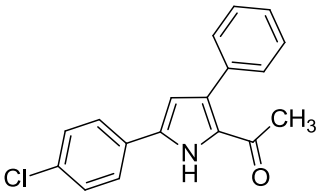
46g (73%)



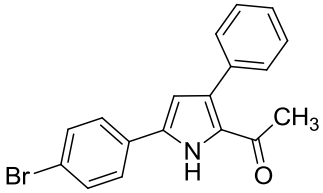
46h (67%)



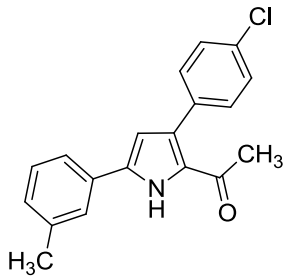
46i (79%)



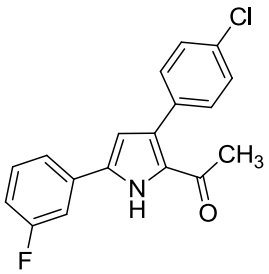
46j (75%)



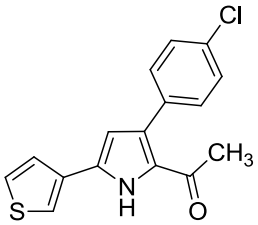
46k (82%)



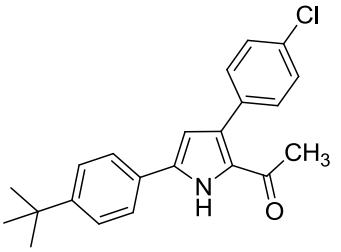
46l (81%)



46m (78%)

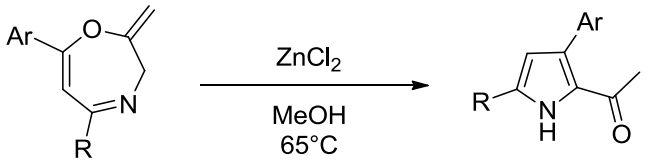


46n (85%)

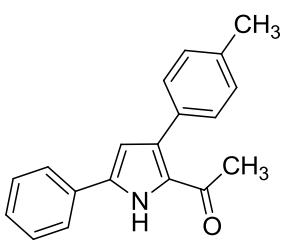


46o (78%)

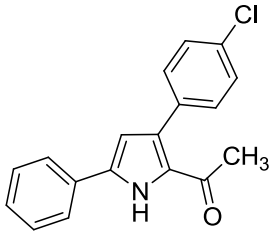
Table 5. Continued.



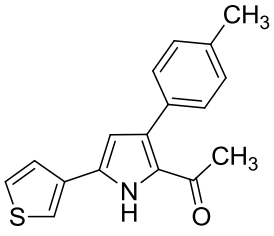
37 **46**



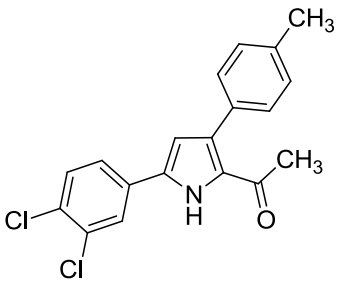
46p (81%)



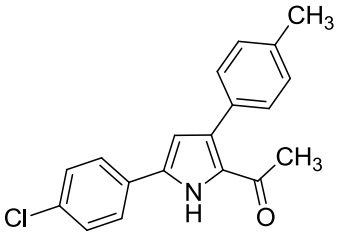
46q (77%)



46r (83%)



46s (69%)



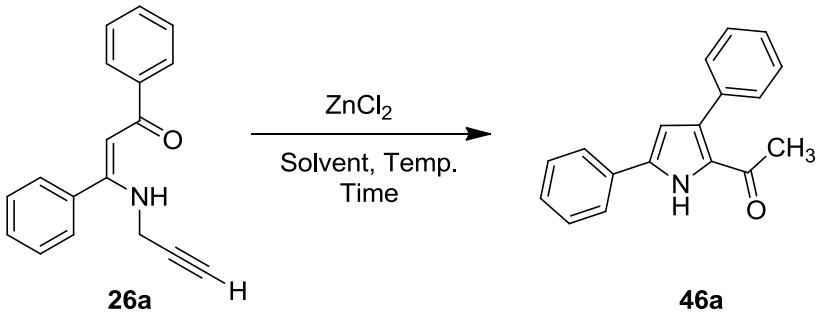
46t (63%)

[a]Isolated yields.

After carrying the reactions in Table 4, we decided to change the reaction pathway to decrease time in total and to prevent the usage of some extra chemicals (usage of extra silica gel, EtOH etc.). In this regard, one-pot reactions were carried out (Table 6). Therefore, it was aimed to obtain target pyrrole by using the same procedure as in the oxazepine case, but with different type of solvents. In this regard, all reactions were performed by using 1.0 equiv. of *N*-propargylic β-enaminone with varying amounts of $ZnCl_2$ in different solvents. All reactions were carried out in reflux

conditions. At the end of the reactions, column chromatography was used to purify the products.

Table 6. Optimization studies for synthesis of pyrroles **46** via one-pot reactions.



26a **46a**

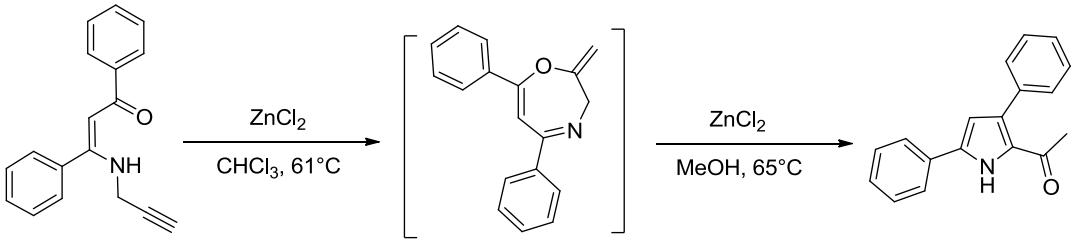
Entry	$ZnCl_2$ (equiv.)	Solvent	Temperature	Time	Yield (%)
1	1.0	MeOH	65	24	46
2	1.5	MeOH	65	12	51
3	2.0	MeOH	65	11	51
4	2.5	EtOH	78	8	46
5	2.5	*n*-PrOH	97	5	34

In these optimization studies, equivalent of $ZnCl_2$ and solvents were changed to obtain best yield. Firstly, we used 1.0 equiv. of $ZnCl_2$ in refluxing methanol for 24 h. At the end of this reaction, the product was obtained in 46% yield (Table 6, entry 1). Then the same reaction was performed by using 1.5 equiv. of $ZnCl_2$ to increase the yield and decrease the reaction time; the yield was 51% (Table 6, entry 2). Moreover, the reaction was repeated by 2.0 equiv. $ZnCl_2$ in methanol and there was no change in the yield (Table 6, entry 3). Then we decided to try different solvent and we replaced MeOH with EtOH to achieve cyclization at higher temperature. We used 2.5 equiv. of $ZnCl_2$ in refluxing EtOH to increase the yield, but instead it was decreased to 46% (Table 6, entry 4). For the relatively low yield, the possible reason

might be decomposition of the product at higher temperature. As a last optimization reaction, we used 2.5 equiv. of $ZnCl_2$ in refluxing *n*-PrOH (Table 6, entry 5). The yield was decreased to 34% due to the same reason with the EtOH case. Clearly, higher temperatures have decreased the yield of the pyrrole product.

After carrying the reactions in Table 6, it is seen that the yields were relatively low. Therefore, we decided to change the reaction pathway. We thought that, in one-pot reactions, the formation of 1,4-oxazepine **37** cannot be achieved properly because of using polar protic solvents. This situation might be the reason of the low yields. That's why we decided to improve yields by performing reactions as one-pot two-step reactions. In the light of optimization Table 6, we decided to continue with MeOH as solvent; because the best reaction condition was achieved by using MeOH as solvent. That's why we carried out the reaction as one-pot two-steps in refluxing methanol (Table 7). Firstly, we synthesized 2,3-dihydro-1,4-oxazepines **37** by the cyclization of *N*-propargylic β-enaminones **26** and then the product from the first reaction was used as the starting material for the synthesis of the targeting pyrrole. It means that 1,4-oxazepine was used as intermediate in this experiment. After all the starting material is gone, the solvent was removed. Without doing any work-up or column chromatography, $ZnCl_2$ and MeOH were added to the reaction medium. Then the reaction scope was investigated to achieve the best reaction conditions.

Table 7. Optimization studies for synthesis of pyrroles **46** from *N*-propargylic β-enaminones **26** via one-pot two-step reactions.



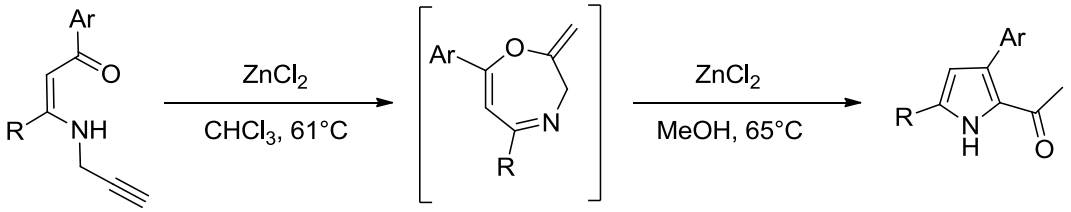
26a **37a** **46a**

no isolation

Entry	$ZnCl_2$ (equiv.)	Solvent	Temperature	Time	Yield (%)
1	-	MeOH	65	3.0	57
2	0.5	MeOH	65	1.5	75
3	1.0	MeOH	65	1.0	85
4	1.5	MeOH	65	1.0	75

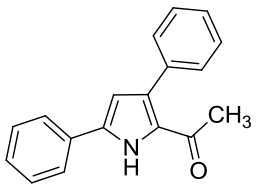
First, we carried out the synthesis without using $ZnCl_2$ (Table 7, entry 1). However, the product was obtained in low yield, which was 57%. Then, 0.5 equiv. $ZnCl_2$ was added to reaction medium in methanol (Table 7, entry 2), and the reaction was carried out in refluxing methanol for 1.5 h. This reaction afforded the product in 75% yield. To increase yield and decrease reaction time, we decided to increase the amount of $ZnCl_2$ more in the same solvent. When we increased the amount of $ZnCl_2$ to 1.0 equiv., the reaction time was decreased to 1.0 h. The obtained yield from this reaction was 85% (Table 7, entry 3). Then we performed the same reaction by adding 1.5 equiv. of $ZnCl_2$, but the reaction time stayed same and the yield was decreased (1h, 75%) (Table 7, entry 4). The reaction conditions of entry 3 from Table 7 was used to synthesize different derivatives of pyrrole.

Table 8. Synthesis of pyrrole derivatives **46** from *N*-propargylic β-enaminones **26** via one-pot two-step reactions. [a]

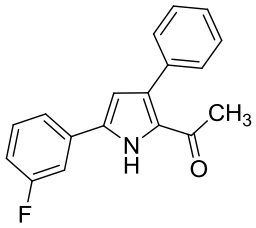


26 **37** **46**

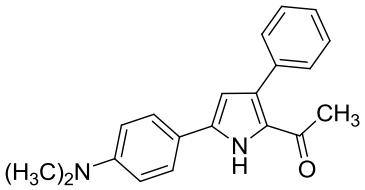
no isolation



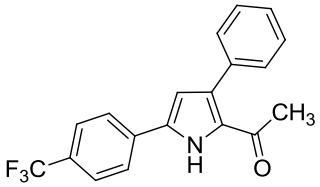
46a (85%)



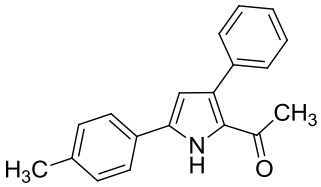
46b (63%)



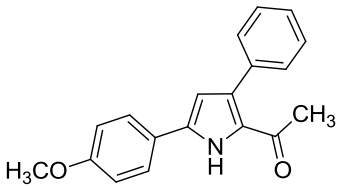
46c (51%)



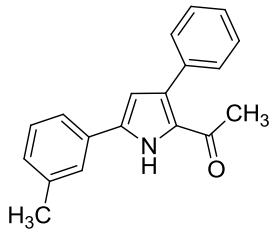
46d (69%)



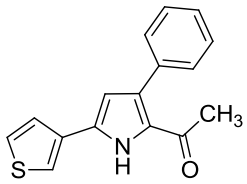
46e (62%)



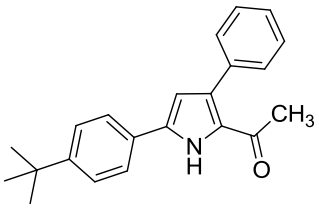
46f (66%)



46g (73%)

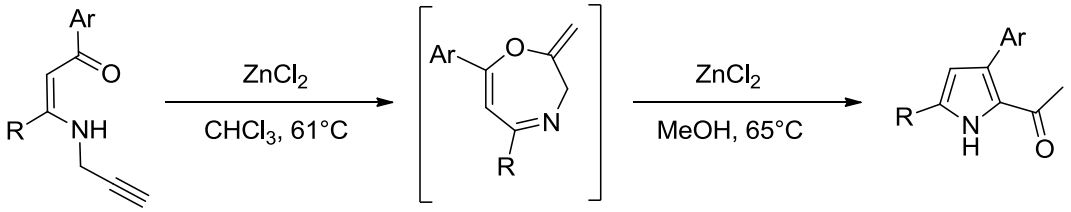


46h (76%)



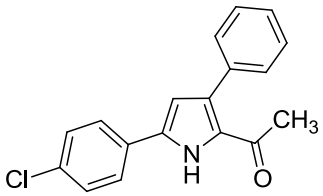
46i (85%)

Table 8. Continued.

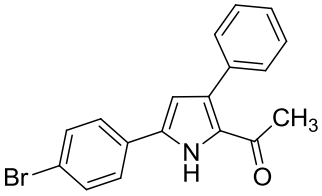


26 **37** **46**

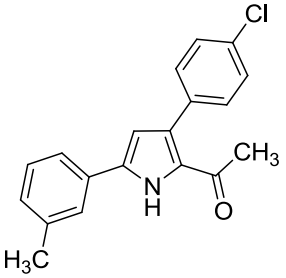
no isolation



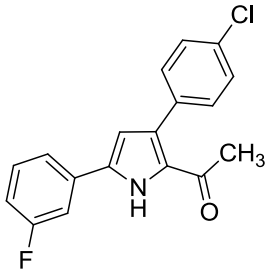
46j (67%)



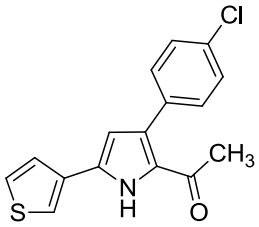
46k (75%)



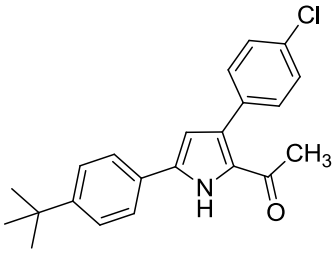
46l (71%)



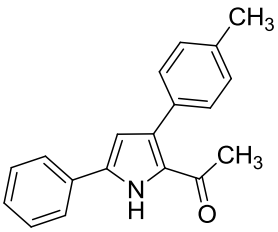
46m (72%)



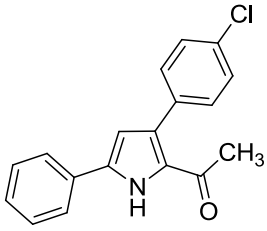
46n (77%)



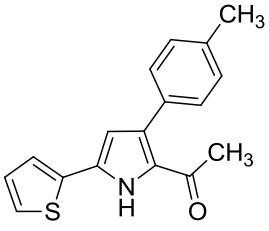
46o (78%)



46p (53%)

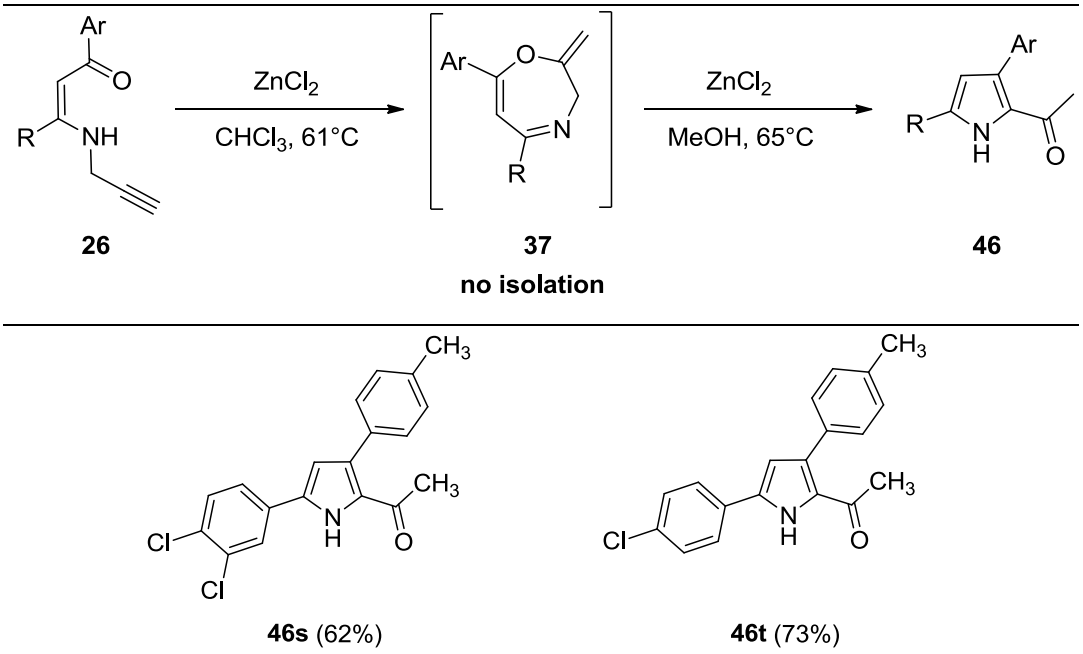


46q (75%)



46r (67%)

Table 8. Continued.



[a]Isolated yields.

Twenty derivatives of the pyrroles have been synthesized by using the determined optimization conditions which is obtained from Table 4 and Table 7. Different derivatives of the desired pyrrole compound have been synthesized by using different electron donating and electron withdrawing groups. When we evaluate the yield of the pyrrole derivatives from 1,4-oxazepines **37**, the lowest yield (63%) also was belonged to pyrrole **46t**. The highest yield was 88% and this yield was obtained for pyrroles **46a** and **46d**. On the other hand, when we look at the yields of the pyrrole derivatives from of *N*-propargylic β-enaminones **26** via one-pot two-step reactions, the lowest yield was obtained as 51% for pyrrole **46c**. On the contrary, the highest yield (85%) was belonged to pyrroles **46a** and **46i**.

The structures of compounds were identified by NMR spectra of compounds. As an example, ^{1}H and ^{13}C NMR spectra of pyrrole **46a** are given in Figures 19 and 20. In the ^{1}H NMR spectrum (Figure 19), N-H proton appears at 10.17 ppm as a broad

singlet. Ten aromatic hydrogens are seen as multiplets between 7.70 and 7.33 ppm as expected. In addition, β-hydrogen of pyrrole gives a peak at 6.58 ppm as doublet. Methyl hydrogens resonate at 2.12 ppm as a singlet. In the ^{13}C NMR spectrum (Figure 20), carbonyl carbon resonates at 188.8 ppm. One of pyrrole carbons on the ring (=CH) resonates at 110.9 ppm. Eleven different aromatic carbons on pyrrole and phenyl rings appear between 136.7 and 125.3 ppm. Methyl carbon gives a peak at 27.6 ppm.

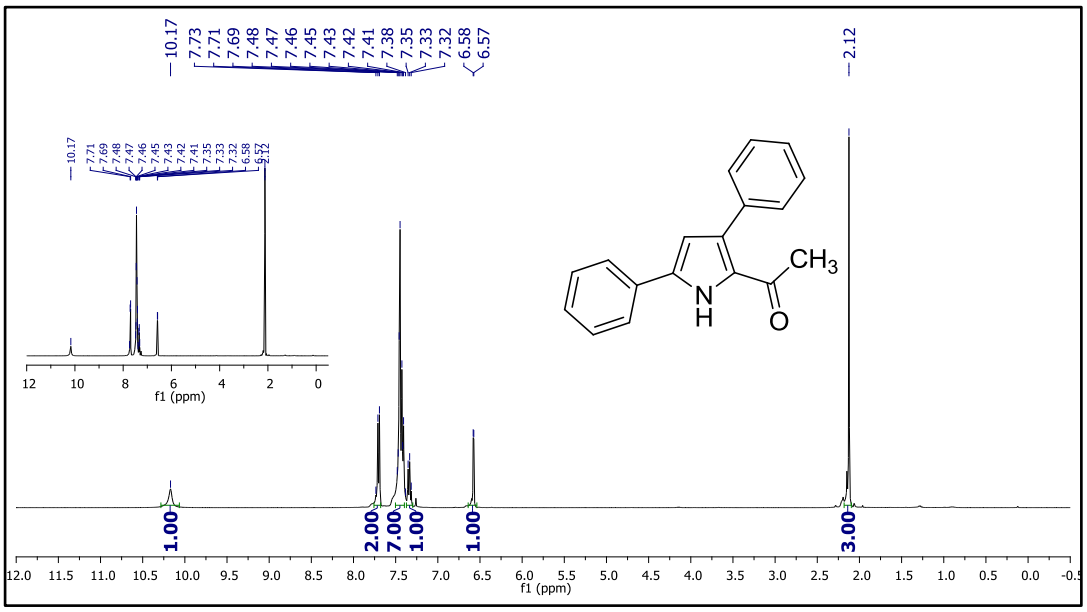


Figure 17. ^{1}H NMR spectra of 1-(3,5-diphenyl-1*H*-pyrrol-2-yl)ethanone (**46a**).

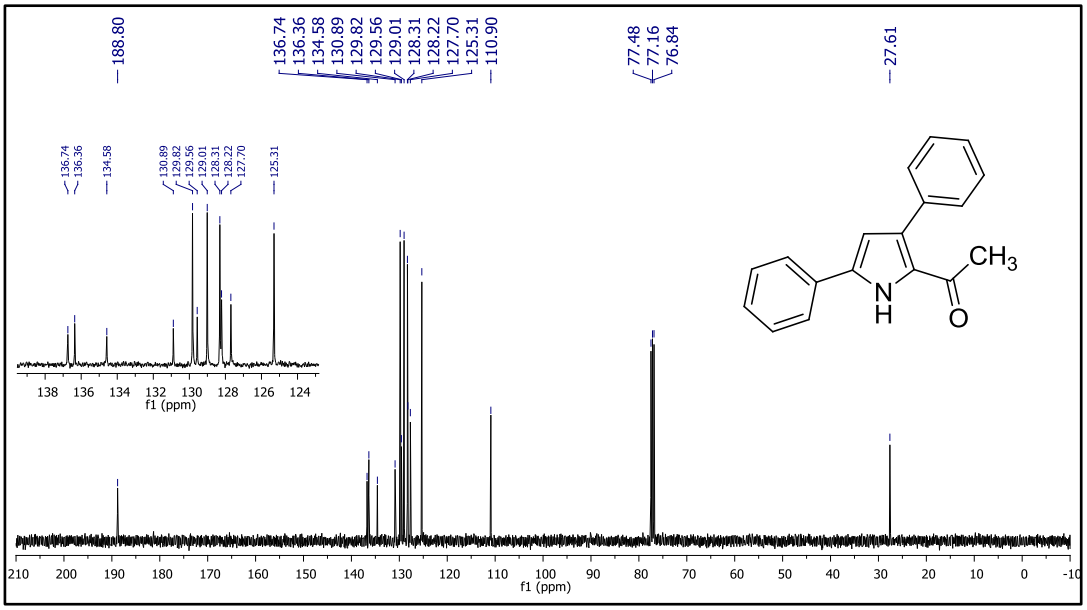
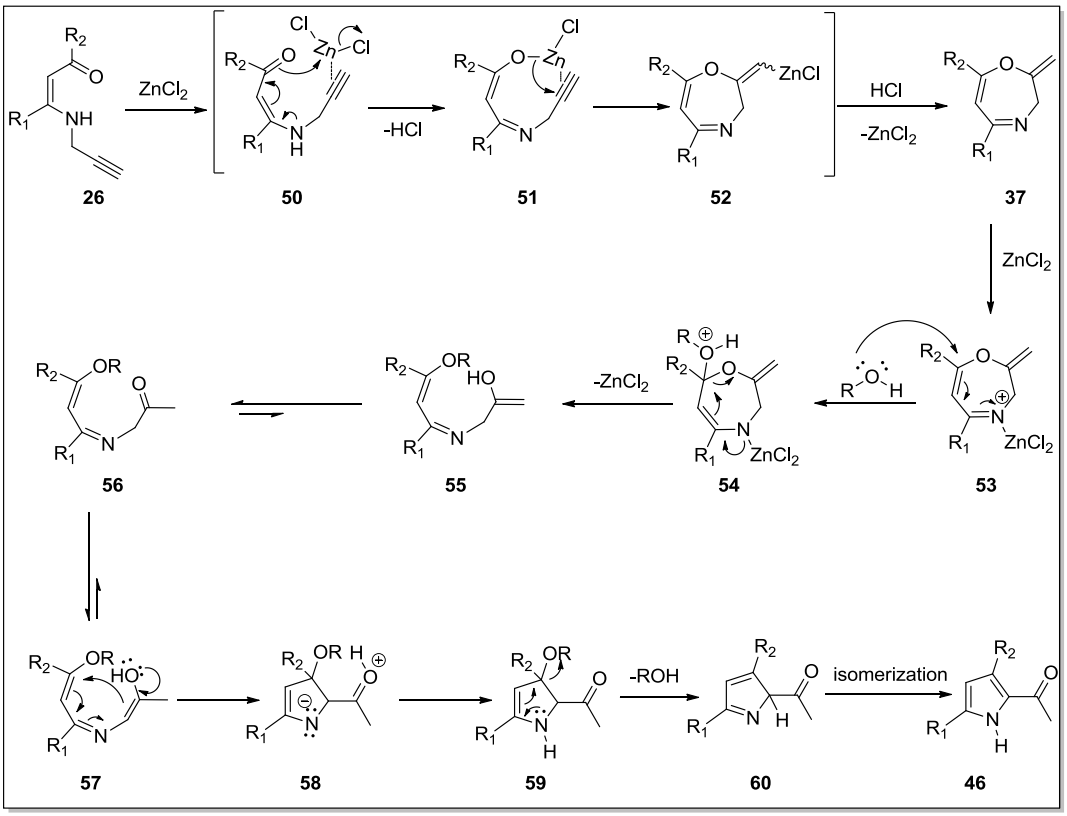


Figure 18. ^{13}C NMR spectra of 1-(3,5-diphenyl-1*H*-pyrrol-2-yl)ethanone (**46a**).

The suggested mechanism for the synthesis of pyrrole derivatives is shown in Scheme 25. Firstly, coordination of zinc chloride through triple bond of *N*-propargylic β-enaminone **26** gives intermediate **50**. And then, carbonyl oxygen is coordinated by zinc and it generates intermediate **51**, providing closeness of carbonyl oxygen to the alkynyl group. After that, vinyl zinc intermediate **52** is formed by *7-exo-dig* cyclization. Afterwards, 2,3-dihydro-1,4-oxazepine **37** is generated due to in situ quenching by HCl. Enhancement of electrophilicity of α carbon because of coordination of zinc chloride through nitrogen enables nucleophilic attack of protic solvent to intermediate **53** in order to give hemiketal **54**. Then, ring opening occurs to produce intermediate **55**, which becomes to be isomer **56** via enol-keto tautomerization. Intermediate **57** is formed via enol-keto tautomerization to get rid of carbonyl group. After that, cyclization is achieved to afford compound **58**, which rearranges to **59** via intramolecular hydrogen shift. Subsequently, compound **59** gives the isomer of 1*H*-pyrrole derivatives **46** via eliminating an alcohol. Lastly, isomerization of compound **60** gives 1*H*-pyrrole derivatives **46**.

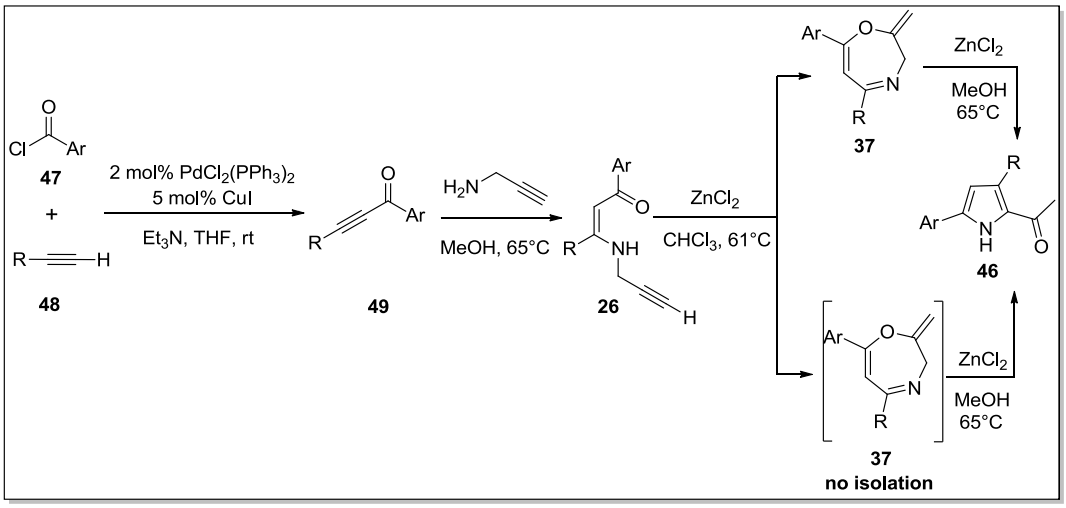


Scheme 26. Proposed mechanism for the desired pyrrole **46**.

CHAPTER 3

CONCLUSION

In summary, potentially biologically active pyrrole derivatives **46** have been synthesized from 1,4-oxazepines **37** and *N*-propargylic β-enaminones **26**. General synthetic pathway for the synthesis of pyrroles **46** is shown in Scheme 26.



Scheme 27. General synthetic pathway for the synthesis of pyrroles **46**.

Firstly, synthesis of starting compounds was described in detail (Scheme 26). α,β-Alkynic ketones have been synthesized via Sonogashira cross coupling reaction. Benzoyl chlorides were coupled with corresponding terminal alkynes under palladium and copper catalyzed conditions to achieve derivatives of α,β-alkynic ketone. The yields were between 60% and 98%. Then, *N*-propargylic β-enaminone derivatives were synthesized by the conjugate addition of propargylamine to the corresponding α,β-alkynic ketones. Therefore, derivatives of *N*-propargylic β-

enaminone have been synthesized in good to high yields which were between 70%-93%.

After synthesis of starting materials, suitable reaction conditions for the preparation of target pyrrole derivatives have been investigated. After carrying out optimization studies, it was seen that desired pyrrole derivatives can be synthesized in good to high yields via two original synthesis procedures.

In the first part of the study, we used 1,4-oxazepines **37** as starting compounds for the synthesis of pyrrole derivatives. In this regard, *N*-propargylic β-enaminones **26** were treated with $ZnCl_2$ in refluxing $CHCl_3$ to give 2-methylene-2,3-dihydro-1,4-oxazepines via cyclization. Derivatives of 2-methylene-2,3-dihydro-1,4-oxazepine were synthesized with the yields ranging between 61%-88%. After 1,4-oxazepines have been isolated, reaction scope was investigated for the synthesis of pyrrole derivatives from 1,4-oxazepines. As a result of the optimization reactions, the best yield (88%) was obtained by using 1.0 eq. of $ZnCl_2$ in refluxing MeOH. By using this reaction condition, 19 novel derivatives of pyrrole have been synthesized.

In the second part of the study, our aim was to decrease total time and the usage of some extra chemicals (usage of extra silica gel, EtOH etc.). Therefore, in this part we synthesized pyrrole derivatives via one-pot two-step reactions from *N*-propargylic β-enaminones **26**. In this study, 2-methylene-2,3-dihydro-1,4-oxazepine derivatives **37** were obtained as intermediate in the reaction medium. Then, the in-situ formed 1,4-oxazepines were converted into desired pyrrole by using several optimization reaction conditions. Consequently, the highest yield (85%) was obtained by using 1.0 eq. of $ZnCl_2$ in refluxing MeOH. 19 novel derivatives of pyrrole have been synthesized with the optimized reaction conditions.

The structures of the new compounds were identified by using ^{1}H and ^{13}C NMR spectra, IR and HRMS spectroscopy.

CHAPTER 4

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz. Chemical shifts are indicated in parts per million (ppm) by using TMS (trimethylsilane) as reference point. Spin multiplicities are reported as 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) and coupling constants (*J*) are indicated in hertz (Hz). Attenuated total reflection (ATR) was used to record Infrared spectra (IR). High resolution mass spectra (HRMS) was performed using Electrospray Ionization (ESI). Thin layer chromatography (TLC) was performed with commercially obtained 0.25 mm silica gel plates and it was visualized by UV lamp. Flash chromatography was carried out using silica gel (Merck 230-400 mesh). Different proportions of solvents are represented in volume:volume ratio. All solvents, which are used in flash chromatography, were used after distillation process; while all commercially available solvents were used directly. Argon gas (ca. 0.1 psi) was used to generate inert atmosphere. All equipments were clean and all glassware were dried in oven.

4.1 General procedure 1 for the synthesis of α,β-alkynic ketone Derivatives 49

To a stirred solution of corresponding benzoyl chloride (1.2 mmol), $PdCl_2(PPh_3)_2$ (0.2 mmol), Et_3N (1.2 mmol) and CuI (0.2 mmol) in anhydrous THF (5.0 ml) were added at room temperature under argon atmosphere for 10 min. Then, proper terminal alkyne (1.0 mmol) was added to the reaction mixture. The resulting mixture was stirred for approximately 4 h. During the reaction, the progress was monitored by TLC (19:1 hexane/ethyl acetate) (Note that the reaction was continued until terminal alkyne was completely consumed). When the reaction was over, the solvent was removed by rotary evaporator and extraction was performed with ethyl acetate (50 ml), 0.1 N HCl (10 ml) and saturated NH_4Cl (10 ml). After the separation of organic and aqueous phases, aqueous phase was extracted with ethyl acetate (50 ml). After combining organic phases, organic phase dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product. Flash chromatography on silica gel was used to purify crude product by using hexane/ethyl acetate (19:1) as the eluent and to afford corresponding α,β-alkynic ketone derivative **49**.

4.1.1 1,3-Diphenylprop-2-yn-1-one (49a)

General procedure **1** was followed by employing benzoyl chloride (407.7 mg, 2.9 mmol), $PdCl_2(PPh_3)_2$ (35.1 mg, 0.05 mmol), Et_3N (295.5 mg, 2.9 mmol), CuI (9.5 mg, 0.05 mmol) and phenylacetylene (247.2 mg, 2.4 mmol), which yielded 485.1 mg (97%) of the indicated product **49a** as a yellow oil (R_f = 0.38 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24–8.19 (m, 2H), 7.69–7.64 (m, 2H), 7.63–7.57 (m, 1H), 7.53–7.42 (m, 3H), 7.42–7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (C=O), 136.8 (C), 134.1 (CH), 133.0 (CH), 130.8 (CH), 129.5 (CH), 128.7 (CH), 128.6 (CH), 120.0 (C), 93.1 (C), 86.9 (C). The spectral data were in agreement with those reported previously for this compound.[46]

4.1.2 3-(3-Fluorophenyl)-1)phenylprop-2-yn-1-one (49b)

General procedure **1** was followed by employing benzoyl chloride (295.3 mg, 2.1 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol), Et_3N (214.0 mg, 2.1 mmol), CuI (7.6 mg, 0.04 mmol) and 1-ethynyl-3-fluorobenzene (216.2 mg, 1.8 mmol), which yielded 314.7 mg (78%) of the indicated product **49b** as a yellow solid (R_f = 0.68 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.05 (m, 2H), 7.57–7.53 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.32–7.26 (m, 2H), 7.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (C=O), 162.4 (d, ^1J = 248.2 Hz, CF), 136.8 (C), 134.4 (CH), 130.6 (d, ^3J = 8.4 Hz, CH), 129.7 (CH), 129.0 (d, ^4J = 3.1 Hz, CH), 128.8 (CH), 122.0 (d, ^3J = 9.1 Hz, C), 119.7 (d, ^2J = 23.3 Hz, CH), 118.3 (d, ^2J = 21.2 Hz, CH), 91.1 (d, ^4J = 3.4 Hz, C), 87.2 (C). The spectral data were in agreement with those reported previously for this compound.[46]

4.1.3 3-(4-(Dimethylamino)phenyl)-1-phenylprop-2-yn-1-one (49c)

General procedure **1** was followed by employing benzoyl chloride (337.4 mg, 2.4 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol), Et_3N (244.6 mg, 2.4 mmol), CuI (7.6 mg, 0.04 mmol) and 4-ethynyl-N,N-dimethylaniline (290.4 mg, 2.0 mmol), which yielded 435.0 mg (87%) of the indicated product **49c** as a yellowish green oil (R_f = 0.41 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27–8.23 (m, 2H), 7.61–7.55 (m, 3H), 7.52 (t, *J* = 7.4 Hz, 2H), 6.70–6.62 (m, 2H), 3.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5(C=O), 151.5 (C), 137.1 (C), 134.9 (CH), 133.3 (CH), 129.0 (CH), 128.3 (CH), 111.3 (CH), 104.9 (C), 97.8 (C), 87.8 (C), 39.6 ($N(CH_3)_2$). The spectral data were in agreement with those reported previously for this compound.[47]

4.1.4 1-Phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (49d)

General procedure **1** was followed by employing benzoyl chloride (309.3 mg, 2.2 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol), Et_3N (224.2 mg, 2.2 mmol), CuI (7.6 mg, 0.04 mmol) and 4-ethynyl-α,α,α-trifluorotoluene (306.2 mg, 1.8 mmol), which yielded 300.5 mg (60%) of the indicated product **49d** as a yellow solid (R_f = 0.66 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24–8.20 (m, 2H), 7.80–7.76 (m, 2H), 7.70–7.60 (m, 3H), 7.53 (t, *J* = 7.7Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C=O), 136.5 (C), 134.4 (CH), 133.1 (CH), 132.1 (q, ^2J = 32.5 Hz, C), 129.5 (CH), 128.7 (CH), 125.5 (q, ^3J = 3.5 Hz, CH), 124.9 (C), 123.9 (q, ^1J = 272.7 Hz, CF_3), 90.3 (C), 88.0 (C). The spectral data were in agreement with those reported previously for this compound.[48]

4.1.5 1-Phenyl-3-(*p*-tolyl)prop-2-yn-1-one (49e)

General procedure **1** was followed by employing benzoyl chloride (379.6 mg, 2.7 mmol), $PdCl_2(PPh_3)_2$ (35.1 mg, 0.05 mmol), Et_3N (275.1 mg, 2.7 mmol), CuI (9.5 mg, 0.05 mmol) and 4-ethynyltoluene (267.2 mg, 2.3 mmol), which yielded 440.5 mg (88%) of the indicated product **49e** as a brownish-orange solid (R_f = 0.56 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–8.10 (m, 2H), 7.58–7.49 (m, 3H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0 (C=O), 141.6 (C), 136.9 (C), 134.0 (CH), 133.1 (CH), 129.5 (CH), 128.6 (CH), 116.9 (C), 93.8 (C), 86.8 (C), 21.7 (CH_3) (Note that two CH peaks overlap on each other). The spectral data were in agreement with those reported previously for this compound.[49]

4.1.6 3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (49f)

General procedure **1** was followed by employing benzoyl chloride (351.5 mg, 2.5 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol), Et_3N (254.8 mg, 2.5 mmol), CuI (7.6

mg, 0.04 mmol) and 4-ethynylanisole (277.5 mg, 2.1 mmol), which yielded 390.5 mg (78%) of the indicated product **49f** as a yellow solid (R_f = 0.40 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29–8.18 (m, 2H), 7.70 – 7.60 (m, 3H), 7.53 (t, *J* = 7.6 Hz, 2H), 6.97–6.91 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (C=O), 161.7 (C), 137.0 (C), 135.1 (CH), 133.9 (CH), 129.4 (CH), 128.6 (CH), 114.4 (CH), 111.7 (C), 94.4 (C), 86.9 (C), 55.4 (OCH_3). The spectral data were in agreement with those reported previously for this compound.[49]

4.1.7 1-Phenyl-3-(*m*-tolyl)prop-2-yn-1-one (49g)

General procedure **1** was followed by employing benzoyl chloride (379.6 mg, 2.7 mmol), $PdCl_2(PPh_3)_2$ (35.1 mg, 0.05 mmol), Et_3N (275.1 mg, 2.7 mmol), CuI (9.5 mg, 0.05 mmol) and 3-ethynytoluene (266.9 mg, 2.3 mmol), which yielded 465.0 mg (93%) of the indicated product **49g** as a green solid (R_f = 0.63 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29–8.19 (m, 2H), 7.67–7.60 (m, 1H), 7.56–7.47 (m, 4H), 7.34–7.28 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (C=O), 138.4 (C), 136.8 (C), 134.0 (CH), 133.5 (CH), 131.8 (CH), 130.2 (CH), 129.5 (CH), 128.57 (CH), 128.55 (CH), 119.8 (C), 93.5 (C), 86.6 (C), 21.11 (CH_3). The spectral data were in agreement with those reported previously for this compound.[49]

4.1.8 1-Phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (49h)

General procedure **1** was followed by employing benzoyl chloride (393.7 mg, 2.8 mmol), $PdCl_2(PPh_3)_2$ (35.1 mg, 0.05 mmol), Et_3N (285.3 mg, 2.8 mmol), CuI (9.5 mg, 0.05 mmol) and 3-ethynythiophene (248.8 mg, 2.3 mmol), which yielded 441.8 mg (88%) of the indicated product **49h** as a orange-brown oil (R_f = 0.67 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.02 (m, 2H), 7.71–7.65 (m, 1H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.19 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.14 (dd, *J* = 4.9, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (C=O), 136.6 (C), 134.01 (CH), 133.96 (CH), 130.1 (CH), 129.4 (CH), 128.5 (CH), 126.3

(CH), 119.1 (C), 88.5 (C), 87.1(C). The spectral data were in agreement with those reported previously for this compound.[49]

4.1.9 3-(4-(*tert*-Butyl)phenyl)-1-phenylprop-2-yn-1-one (49i)

General procedure **1** was followed by employing benzoyl chloride (323.4 mg, 2.3 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol), Et_3N (234.4 mg, 2.3 mmol), CuI (7.6 mg, 0.04 mmol) and 1-(*tert*-butyl)-4-ethynylbenzene (300.7 mg, 1.9 mmol), which yielded 460.0 mg (97%) of the indicated product **49i** as a yellow oil (R_f = 0.68 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.08 (m, 2H), 7.53–7.44 (m, 3H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0 (C=O), 154.6 (C), 137.0 (C), 134.0 (CH), 133.0 (CH), 129.5 (CH), 128.6 (CH), 125.8 (CH), 117.0 (C), 93.8 (C), 86.8 (C), 35.1 (C), 31.0 (CH_3); IR (neat): 3065, 2961, 2867, 1637, 1597, 1448, 1394, 1313, 1288, 1171, 1107, 1029, 1008, 834, 792, 697, 650, 563, 524, 414 cm^{-1}; MS (ESI, m/z): 263.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{19}O$: 263.1430 $[M+H]^+$, found: 263.1430.

4.1.10 3-(4-Chlorophenyl)-1-phenylprop-2-yn-1-one (49j)

General procedure **1** was followed by employing benzoyl chloride (351.5 mg, 2.5 mmol), $PdCl_2(PPh_3)_2$ (35.1 mg, 0.05 mmol), Et_3N (254.8 mg, 2.5 mmol), CuI (9.5 mg, 0.05 mmol) and 1-chloro-4-ethynylbenzene (286.8 mg, 2.1 mmol), which yielded 425.3 mg (85%) of the indicated product **49j** as a yellow solid (R_f = 0.63 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–7.99 (m, 2H), 7.47–7.37 (m, 3H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C=O), 137.0 (C), 136.5 (C), 134.1 (CH), 129.4 (CH), 129.0 (CH), 128.6 (CH), 118.4 (C), 91.5 (C), 87.5 (C) (Note that two CH peaks overlap on each other). The spectral data were in agreement with those reported previously for this compound.[49]

4.1.11 3-(4-Bromophenyl)-1-phenylprop-2-yn-1-one (49k)

General procedure **1** was followed by employing benzoyl chloride (295.2 mg, 2.1 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol), Et_3N (214.0 mg, 2.1 mmol), CuI (7.6 mg, 0.04 mmol) and 1-bromo-4-ethynylbenzene (325.9 mg, 1.8 mmol), which yielded 387.7 mg (78%) of the indicated product **49k** as a pale yellow solid (R_f = 0.66 in 4:1 hexane/ethyl acetate); mp 117.1–119.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–8.13 (m, 2H), 7.62–7.56 (m, 1H), 7.52–7.44 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6 (C=O), 136.6 (C), 134.3 (C), 134.2 (CH), 132.0 (C), 129.5 (CH), 128.6 (CH), 125.6 (CH), 118.9 (CH), 91.6 (C), 87.7 (C); IR (neat): 3054, 2195, 1912, 1630, 1598, 1578, 1474, 1447, 1394, 1315, 1292, 1205, 1170, 1062, 1030, 1007, 817, 791, 711, 692,639 cm^{-1}; MS (ESI, m/z): 284.99 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{10}{}^{79}BrO$: 284.9910 $[M+H]^+$, found: 284.9916.

4.1.12 1-(4-Chlorophenyl)-3-(*m*-tolyl)prop-2-yn-1-one (49l)

General procedure **1** was followed by employing 4-chlorobenzoyl chloride (420.0 mg, 2.4 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol), Et_3N (244.6 mg, 2.4 mmol), CuI (7.6 mg, 0.04 mmol) and 3-ethynyltoluene (223.3 mg, 2.0 mmol), which yielded 384.7 mg (77%) of the indicated product **49l** as a pale yellow solid (R_f = 0.67 in 4:1 hexane/ethyl acetate); mp 80.1–81.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 6.8, 1.8 Hz, 2H), 7.30–7.23 (m, 4H), 7.11–7.05 (m, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2 (C=O), 140.4 (C), 138.4 (C), 135.1 (C), 133.4 (CH), 131.8 (CH), 130.6 (CH), 130.1 (CH), 128.8 (CH), 128.5 (CH), 119.4 (C), 93.8 (C), 86.2 (C), 21.0 (CH_3); IR (neat): 2853, 2185, 1668, 1627, 1583, 1479, 1453, 1397, 1283, 1222, 1033, 1007, 913, 897, 839, 781, 745, 715, 685 cm^{-11}; MS (ESI, m/z): 255.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{12}ClO$: 255.0571 $[M+H]^+$, found: 255.0568.

4.1.13 1-(4-Chlorophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (49m)

General procedure **1** was followed by employing 4-chlorobenzoyl chloride (402.5 mg, 2.3 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol), Et_3N (234.4 mg, 2.3 mmol), CuI (7.6 mg, 0.04 mmol) and 1-ethynyl-3-fluorobenzene (228.2 mg, 1.9 mmol), which yielded 449.3 mg (90%) of the indicated product **49m** as a pale orange solid (R_f = 0.70 in 4:1 hexane/ethyl acetate); mp 125.1–126.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–8.07 (m, 2H), 7.49–7.42 (m, 3H), 7.41–7.36 (m, 1H), 7.35–7.30 (m, 1H), 7.21–7.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (C=O), 162.3 (d, ^1J = 248.7 Hz, CF), 141.0 (C), 135.1 (C), 130.9 (CH), 130.6 (d, ^3J = 8.4 Hz, CH), 129.1 (CH), 129.0 (d, ^4J = 3.1 Hz, CH), 121.7 (d, ^3J = 9.3 Hz, C), 119.7 (d, ^2J = 23.3 Hz, CH), 118.6 (d, ^2J = 20.9 Hz, CH), 91.6 (d, ^4J = 3.2 Hz, C), 86.8 (C); IR (neat): 3059, 2203, 1634, 1538, 1481, 1428, 1399, 1360, 1305, 1248, 1168, 1154, 1108, 1088, 1031, 1009, 954, 890, 784 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.

4.1.14 1-(4-Chlorophenyl)-3-(thiophen-3-yl)prop-2-yn-1-one (49n)

General procedure **1** was followed by employing 4-chlorobenzoyl chloride (420.0 mg, 2.4 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol), Et_3N (244.6 mg, 2.4 mmol), CuI (7.6 mg, 0.04 mmol) and 3-ethynythiophene (216.3 mg, 2.0 mmol), which yielded 400.4 mg (80%) of the indicated product **49n** as a brownish yellow solid (R_f = 0.63 in 4:1 hexane/ethyl acetate); mp 109.5–111.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 2H), 7.74–7.63 (m, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.23–7.18 (m,1H), 7.14 (d, J = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (C=O), 140.5 (C), 135.1 (CH), 134.2 (CH), 130.7 (CH), 130.2 (CH), 128.9 (C), 126.4 (CH), 119.0 (C), 89.1 (C), 86.9 (C); IR (neat): 3200, 2376, 2178, 1629, 1582, 1481, 1398, 1357, 1267, 1213, 1161, 1088, 1023, 1007, 921, 873, 840, 826, 779, 741, 710, 675, 621 cm^{-1}; MS (ESI, m/z): 247.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{13}H_8ClOS$: 246.9977 $[M+H]^+$, found: 246.9979.

4.1.15 3-(4-(*tert*-Butyl)phenyl)-1-(4-chlorophenyl)prop-2-yn-1-one (49o)

General procedure **1** was followed by employing 4-chlorobenzoyl chloride (350.0 mg, 2.0 mmol), $PdCl_2(PPh_3)_2$ (21.1 mg, 0.03 mmol), Et_3N (203.8 mg, 2.0 mmol), CuI (5.7 mg, 0.03 mmol) and 1-(*tert*-butyl)-4-ethynylbenzene (269.0 mg, 1.7 mmol), which yielded 425.9 mg (85%) of the indicated product **49o** as a yellow solid (R_f = 0.78 in 4:1 hexane/ethyl acetate); mp 104.0–106.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–8.00 (m, 2H), 7.51–7.46 (m, 2H), 7.35–7.29 (m, 4H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (C=O), 154.8 (C), 140.5 (C), 135.4 (C), 133.1 (CH), 130.8 (CH), 129.0 (CH), 125.8 (CH), 116.8 (C), 94.3 (C), 86.5 (C), 35.1 (C), 31.0 (CH_3); IR (neat): 2964, 2193, 1629, 1584, 1571, 1504, 1484, 1399, 1363, 1300, 1289, 1265, 1215, 1190, 1162, 1108, 1090, 1025, 1005, 838, 746, 675 cm^{-1}; MS (ESI, m/z): 297.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}ClO$: 297.1041 $[M+H]^+$, found: 297.1046.

4.1.16 3-Phenyl-1-(*p*-tolyl)prop-2-yn-1-one (49p)

General procedure **1** was followed by employing 4-methylbenzoyl chloride (355.6 mg, 2.3 mmol), $PdCl_2(PPh_3)_2$ (35.1 mg, 0.05 mmol), Et_3N (234.4 mg, 2.3 mmol), CuI (9.5 mg, 0.05 mmol) and phenylacetylene (194.0 mg, 1.9 mmol), which yielded 389.2 mg (93%) of the indicated product **49p** as a orange-yellow solid (R_f = 0.67 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.8 Hz, 2H), 7.58–7.47 (m, 2H), 7.35–7.30 (m, 1H), 7.29–7.23 (m, 2H), 7.15 (d, J = 7.2 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6 (C=O), 145.2 (C), 134.5 (C), 133.0 (CH), 130.7 (CH), 129.6 (CH), 129.3 (CH), 128.6 (CH), 120.1 (C), 92.6 (C), 87.0 (C), 21.8 (CH_3). The spectral data were in agreement with those reported previously for this compound.[49]

4.1.17 1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one (49q)

General procedure **1** was followed by employing 4-chlorobenzoyl chloride (437.5 mg, 2.5 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol), Et_3N (254.8 mg, 2.5 mmol), CuI (7.6 mg, 0.04 mmol) and phenylacetylene (214.5 mg, 2.1 mmol), which yielded 495.1 mg (98%) of the indicated product **49q** as a yellow solid (R_f = 0.68 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17–8.07 (m, 2H), 7.69–7.60 (m, 2H), 7.49–7.42 (m, 3H), 7.42–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (C=O), 140.6 (C), 135.2 (C), 133.1 (CH), 131.0 (CH), 130.8 (CH), 129.0 (CH), 128.7 (CH), 119.8 (C), 93.6 (C), 86.6 (C). The spectral data were in agreement with those reported previously for this compound.[49]

4.1.18 3-(Thiophen-3-yl)-1-(*p*-tolyl)prop-2-yn-1-one (49r)

General procedure **1** was followed by employing 4-methylbenzoyl chloride (417.4 mg, 2.7 mmol), $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol), Et_3N (275.1 mg, 2.7 mmol), CuI (7.6 mg, 0.04 mmol) and 3-ethynythiophene (238.0 mg, 2.2 mmol), which yielded 386.6 mg (77%) of the indicated product **49r** as a yellow solid (R_f = 0.49 in 4:1 hexane/ethyl acetate); mp 96.9–97.9 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.2 Hz, 2H), 7.77 (dd, J = 2.9, 1.2 Hz, 1H), 7.30 (dd, J = 5.0, 3.0 Hz, 1H), 7.25–7.19 (m, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3 (C=O), 145.0 (C), 134.3 (C), 133.6 (CH), 130.0 (CH), 129.4 (CH), 129.2 (CH), 126.2 (CH), 119.2 (C), 87.9 (C), 87.1 (C), 21.6 (CH_3); IR (neat): 2349, 2182, 1987, 1617, 1600, 1357, 1317, 1276, 1166, 1032, 1015, 923, 871, 833, 807, 734, 711, 679, 627 cm^{-1}; MS (ESI, m/z): 227.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{11}OS$: 227.0531 $[M+H]^+$, found: 227.0536.

4.1.19 3-(3,4-Dichlorophenyl)-1-(*p*-tolyl)prop-2-yn-1-one (49s)

General procedure **1** was followed by employing 4-methylbenzoyl chloride (324.6 mg, 2.1 mmol), $PdCl_2(PPh_3)_2$ (21.1 mg, 0.03 mmol), Et_3N (214.0 mg, 2.1 mmol), CuI (5.7 mg, 0.03 mmol) and 1,2-dichloro-4-ethynylbenzene (290.7 mg, 1.7 mmol), which yielded 363.6 mg (74%) of the indicated product **49s** as a yellow solid (R_f = 0.58 in 4:1 hexane/ethyl acetate); mp 124.5–125.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.1 Hz, 2H), 7.61–7.58 (m, 1H), 7.38–7.34 (m, 2H), 7.19 (t, J = 7.9 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (C=O), 145.7 (C), 135.4 (C), 134.4 (CH), 134.3 (C), 133.1 (C), 132.0 (CH), 130.8 (CH), 129.7 (CH), 129.5 (CH), 120.2 (C), 89.3 (C), 88.1 (C), 21.9 (CH_3); IR (neat): 3390, 2610, 2212, 2196, 2147, 2134, 2036, 1993, 1847, 1595, 1046, 942, 838, 812, 741, 716, 693, 624 cm^{-1}; MS (ESI, m/z): 289.02 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{11}Cl_2O$: 289.0182 $[M+H]^+$, found: 289.0187.

4.1.20 3-(4-Chlorophenyl)-1-(*p*-tolyl)prop-2-yn-1-one (49t)

General procedure **1** was followed by employing 4-methylbenzoyl chloride (324.6 mg, 2.1 mmol), $PdCl_2(PPh_3)_2$ (21.1 mg, 0.03 mmol), Et_3N (214.0 mg, 2.1 mmol), CuI (5.7 mg, 0.03 mmol) and 1-chloro-4-ethynylbenzene (232.2 mg, 1.7 mmol), which yielded 350.8 mg (81%) of the indicated product **49t** as a white solid (R_f = 0.64 in 4:1 hexane/ethyl acetate); mp 126.3–127.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02–7.91 (m, 2H), 7.52–7.40 (m, 2H), 7.31–7.11 (m, 4H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4 (C=O), 145.4 (C), 137.0 (C), 134.4 (C), 134.2 (CH), 129.7 (CH), 129.4 (CH), 129.1 (CH), 118.7 (C), 91.1 (C), 87.7 (C), 21.9 (CH_3); IR (neat): 2915, 2195, 1626, 1587, 1485, 1397, 1310, 1287, 1207, 1166, 1085, 1009, 832, 816, 781, 736, 680, 636 cm^{-1}; MS (ESI, m/z): 255.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{12}ClO$: 255.0571 $[M+H]^+$, found: 255.0576.

4.2 General procedure 2 for the synthesis of *N*-propargylic β-enaminones 26

To a stirred solution of corresponding α,β-alkynic ketone **49** (1.0 mmol) in MeOH (5.0 ml) was added propargylamine (1.2 mmol). Then, the reaction mixture was refluxed for approximately 2 h. During the course of the reaction, the progress was monitored by TLC (9:1 hexane/ethyl acetate) (Note that the reaction was continued until α,β-alkynic ketone **49** was completely consumed). When the reaction was over, the solvent was removed by using rotary evaporator to give the crude product. Flash chromatography on silica gel was used to purify crude product by using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent and to afford corresponding β-enaminone derivative **26**.

4.2.1 1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (26a)

General procedure **2** was followed by employing 1,3-diphenylprop-2-yn-1-one (**49a**) (450.0 mg, 2.2 mmol) and propargylamine (143.2 mg, 2.6 mmol), which yielded 556.9 mg (97%) of the indicated product **26a** as a yellow solid (R_f = 0.44 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.34 (s, 1H), 7.93–7.87 (m, 2H), 7.52–7.36 (m, 8H), 5.85 (s, 1H), 3.95 (dd, *J* = 6.3, 2.3 Hz, 2H), 2.31 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1 (C=O), 165.9 (C), 140.0 (C), 134.9 (C), 131.0 (CH), 129.9 (CH), 128.7 (CH), 128.3 (CH), 127.9 (CH), 127.2 (CH), 94.7 (CH), 79.8 (C), 72.5 (CH), 34.2 (CH_2). The spectral data were in agreement with those reported previously for this compound.[36]

4.2.2 3-(3-Fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (26b)

General procedure **2** was followed by employing 3-(3-fluorophenyl)-1-phenylprop-2-yn-1-one (**49b**) (336.3 mg, 1.5 mmol)and propargylamine (99.1 mg, 1.8 mmol),

which yielded 373.8 mg (89%) of the indicated product **26b** as a pale yellow solid (R_f = 0.50 in 4:1 hexane/ethyl acetate); mp 93.8–94.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (s, 1H), 7.85–7.73 (m, 2H), 7.36–7.24 (m, 4H), 7.20–7.00 (m, 3H), 5.72 (s, 1H), 3.79 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.21 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5 (C=O), 164.2 (C), 162.6 (d, ^1J = 248.4 Hz, CF), 139.8 (C), 137.0 (d, ^3J = 7.6 Hz, C), 131.3 (CH), 130.6 (d, ^3J = 8.2 Hz, CH), 128.4 (CH), 127.3 (CH), 123.7 (d, ^4J = 3.2 Hz, CH), 116.9 (d, ^2J = 21.0 Hz, CH), 115.2 (d, ^2J = 22.6 Hz, CH), 94.8 (CH), 79.7 (C), 72.7 (CH), 34.2 (CH_2); IR (neat): 3222, 1600, 1570, 1549, 1520, 1474, 1431, 1323, 1299, 1284, 1265, 1250, 1226, 1203, 1025, 1000, 965, 876, 788 cm^{-1}; MS (ESI, m/z): 280.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}FNO$: 280.1132 $[M+H]^+$, found: 280.1134.

4.2.3 3-(4-(Dimethylamino)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (26c)

General procedure **2** was followed by employing 3-(4-(dimethylamino)phenyl)-1-phenylprop-2-yn-1-one **(49c)** (623.3 mg, 2.5 mmol) and propargylamine (165.2 mg, 3.0 mmol), which yielded 593.6 mg (78%) of the indicated product **26c** as a yellow oil (R_f = 0.10 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (s, 1H), 8.01–7.80 (m, 2H), 7.48–7.30 (m, 5H), 6.73 (d, *J* = 8.9 Hz, 2H), 5.88 (s, 1H), 4.06 (dd, *J* = 6.3, 2.5 Hz, 2H), 3.00 (s, 6H), 2.34 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2 (C=O), 166.9 (C), 151.4 (C), 140.4 (C), 130.6 (CH), 129.2 (CH), 128.1 (CH), 127.0 (CH), 121.7 (C), 111.5 (CH), 94.0 (CH), 80.3 (C), 72.3 (CH), 40.1 ($N(CH_3)_2$), 34.4 (CH_2). IR (neat): 3208, 2884, 2805, 2111, 1614, 1579, 1502, 1481, 1446, 1328, 1264, 1233, 1194, 1141, 1054, 928, 815, 797, 743, 729 cm^{-1}; MS (ESI, m/z): 305.17 $[M+H]^+$; HRMS (ESI) calcd. for $C_{20}H_{21}N_2O$: 305.1648 $[M+H]^+$, found: 305.1653.

4.2.4 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (26d)

General procedure **2** was followed by employing 1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (**49d**) (521.1 mg, 1.9 mmol) and propargylamine (126.7 mg, 2.3 mmol), which yielded 582.1 mg (93%) of the indicated product **26d** as a brown solid (R_f = 0.63 in 4:1 hexane/ethyl acetate); mp 100.9–102.0 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.30 (t, J = 5.8 Hz, 1H), 7.96–7.86 (m, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.64–7.57 (m, 2H), 7.47–7.35 (m, 3H), 5.84 (m, 1H), 3.94–3.78 (m, 2H), 2.36 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3 (C=O), 163.9 (C), 139.5 (C), 138.4 (C), 131.6 (q, ^2J = 32.7 Hz, C), 131.2 (CH), 128.4 (CH), 128.3 (CH), 127.1 (CH), 125.6 (q, ^3J = 3.7 Hz, CH), 125.1 (q, ^1J = 272.4 Hz, CF_3), 94.8 (CH), 79.5 (C), 72.7 (CH), 34.1 (CH_2); IR (neat): 3055, 2116, 1600, 1583, 1548, 1502, 1430, 1321, 1294, 1240, 1225, 1163, 1104, 1072, 1050, 1015, 925, 849, 737 cm^{-1}; MS (ESI, m/z): 330.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}F_3NO$: 330.1100 $[M+H]^+$, found: 330.1100.

4.2.5 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-en-1-one (26e)

General procedure **2** was followed by employing 1-phenyl-3-(*p*-tolyl)prop-2-yn-1-one (**49e**) (396.5 mg, 1.8 mmol) and propargylamine (121.2 mg, 2.2 mmol), which yielded 462.5 mg (93%) of the indicated product **26e** as a reddish orange oil (R_f = 0.50 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (s, 1H), 7.85–7.79 (m, 2H), 7.40–7.27 (m, 5H), 7.22–7.18 (m, 2H), 5.76 (s, 1H), 3.89 (dd, J = 6.3, 2.5 Hz, 2H), 2.34 (s, 3H), 2.23 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (C=O), 166.1 (C), 140.0 (C), 131.9 (C), 130.9 (C), 129.3 (CH), 128.2 (CH), 127.8 (CH), 127.1 (CH), 94.5 (CH), 79.9 (C), 72.5 (CH), 34.2 (CH_2), 21.4 (CH_3) (Note that two CH peaks overlap on each other); IR (neat): 3288, 3056, 3025, 2919, 1579, 1554, 1498, 1326, 1295, 1141, 1055, 1023, 825, 754, 690 cm^{-1}; MS (ESI, m/z):

376.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1390.

4.2.6 3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (26f)

General procedure **2** was followed by employing 3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-one (**49f**) (496.2 mg, 2.1 mmol) and propargylamine (137.7 mg, 2.5 mmol), which yielded 565.1 mg (92%) of the indicated product **26f** as a reddish orange oil (R_f = 0.29 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.36 (s, 1H), 7.90 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.47–7.36 (m, 5H), 7.00–6.95 (m, 2H), 5.84 (s, 1H), 3.98 (dd, *J* = 6.3, 2.5 Hz, 2H), 3.86 (s, 3H), 2.32 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7 (C=O), 165.8 (C), 160.8 (C), 140.0 (C), 130.8 (CH), 129.3 (CH), 128.1 (CH), 127.0 (CH), 126.9 (C), 114.0 (CH), 94.4 (CH), 79.9 (C), 72.4 (CH), 55.2 (OCH_3), 34.2 (CH_2). IR (neat): 3285, 3056, 2931, 2837, 1593, 1559, 1497, 1247, 1173, 1142, 1023, 836, 757, 689 cm^{-1}; MS (ESI, m/z): 292.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO_2$: 292.1332 $[M+H]^+$, found: 292.1337.

4.2.7 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (26g)

General procedure **2** was followed by employing 1-phenyl-3-(m-tolyl)prop-2-yn-1-one (**49g**) (506.6 mg, 2.3 mmol) and propargylamine (154.2 mg, 2.8 mmol), which yielded 573.5 mg (91%) of the indicated product **26g** as a red oil (R_f = 0.51 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.37 (s, 1H), 7.95–7.91 (m, 2H), 7.49–7.28 (m, 7H), 5.86 (s, 1H), 3.97 (dd, *J* = 6.2, 2.4 Hz, 2H), 2.44 (s, 3H), 2.34 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (C=O), 166.1 (C), 139.8 (C), 138.4 (C), 134.7 (C), 130.9 (CH), 130.5 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.0 (CH), 124.8 (CH), 94.3 (CH), 79.8 (C), 72.4 (CH), 34.1 (CH_2), 21.3 (CH_3); IR (neat): 3224, 3055, 2113, 1667, 1594, 1550, 1476, 1324, 1270, 1226,

1173, 1134, 1054, 1024, 789, 733 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1380

4.2.8 1-Phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (26h)

General procedure **2** was followed by employing 1-phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (**49h**) (552.0 mg, 2.6 mmol) and propargylamine (170.7 mg, 3.1 mmol), which yielded 639.3 mg (92%) of the indicated product **26h** as a yellow solid (R_f = 0.50 in 4:1 hexane/ethyl acetate); mp 77.4–78.3 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.43 (s, 1H), 7.94 – 7.89 (m, 2H), 7.66–7.63 (m, 1H), 7.48–7.39 (m, 4H), 7.31–7.27 (m, 1H), 5.95 (s, 1H), 4.04 (dd, *J* = 6.3, 2.2 Hz, 2H), 2.38 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C=O), 160.6 (C), 139.9 (C), 135.5 (C), 131.0 (CH), 128.3 (CH), 127.3 (CH), 127.1 (CH), 126.7 (CH), 126.3 (CH), 94.2 (CH), 80.0 (C), 72.7 (CH), 34.2 (CH_2); IR (neat): 3249, 3214, 1653, 1593, 1577, 1290, 1247, 1227, 1079, 1057, 799, 754, 720 cm^{-1}; MS (ESI, m/z): 268.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{14}NOS$: 268.0796 $[M+H]^+$, found: 268.0775.

4.2.9 3-(4-(*tert*-Butyl)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (26i)

General procedure **2** was followed by employing 3-(4-(*tert*-butyl)phenyl)-1-phenylprop-2-yn-1-one (**49i**) (397.3 mg, 1.6 mmol) and propargylamine (104.7 mg, 1.9 mmol), which yielded 436.6 mg (86%) of the indicated product **26i** as a yellow solid (R_f = 0.57 in 4:1 hexane/ethyl acetate); mp 108.8–109.8 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (s, 1H), 7.83–7.75 (m, 2H), 7.36–7.24 (m, 7H), 5.73 (s, 1H), 3.84 (dd, *J* = 6.3, 2.4 Hz, 2H), 2.20 (t, *J* = 2.4 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (C=O), 166.0 (C), 153.1 (C), 140.0 (C), 131.9 (C), 130.9 (CH), 128.2 (CH), 127.6 (CH), 127.1 (CH), 125.6 (CH), 94.5 (CH), 79.9 (C), 72.5 (CH), 34.8 (C), 34.3 (CH_2), 31.2 (CH_3); IR (neat): 3252, 2953, 2863, 1578, 1547, 1497,

1353, 1290, 1266, 1147, 1107, 1054, 1022, 930, 840, 806, 756, 742, 706, 687 cm^{-1}; MS (ESI, m/z): 318.18 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{24}NO$: 318.1852 $[M+H]^+$, found: 318.1859.

4.2.10 3-(4-Chlorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (26j)

General procedure **2** was followed by employing 3-(4-chlorophenyl)-1-phenylprop-2-yn-1-one (**49j**) (385.1 mg, 1.6 mmol) and propargylamine (104.7 mg, 1.9 mmol), which yielded 425.5 mg (90%) of the indicated product **26j** as a pale yellow solid (R_f = 0.50 in 4:1 hexane/ethyl acetate); mp 91.9–93.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (s, 1H), 7.94–7.82 (m, 2H), 7.48–7.37 (m, 7H), 5.81 (s, 1H), 3.92 (dd, *J* = 6.4, 2.4 Hz, 2H), 2.32 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1 (C=O), 164.4 (C), 139.6 (C), 135.8 (C), 133.2 (C), 131.1 (CH), 129.2 (CH), 128.9 (CH), 128.2 (CH), 127.1 (CH), 94.6 (CH), 79.6 (C), 72.7 (CH), 34.1 (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.

4.2.11 3-(4-Bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (26k)

General procedure **2** was followed by employing 3-(4-bromophenyl)-1-phenylprop-2-yn-1-one (**49k**) (342.2 mg, 1.2 mmol) and propargylamine (77.1 mg, 1.4mmol), which yielded 378.8 mg (93%) of the indicated product **26k** as a brown solid (R_f = 0.51 in 4:1 hexane/ethyl acetate); mp 95.1–96.9 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.45–7.30 (m, 5H), 5.80 (s, 1H), 3.88 (dd, *J* = 6.2, 1.9 Hz, 2H), 2.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1 (C=O), 164.4 (C), 139.6 (C), 133.6 (C), 131.9 (C), 131.1 (CH), 129.4 (CH),

128.2 (CH), 127.1 (CH), 124.1 (CH), 94.6 (CH), 79.6 (C), 72.7 (CH), 34.1 (CH_2). The spectral data were in agreement with those reported previously for this compound.[50]

4.2.12 1-(4-Chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-en-1-one (26l)

General procedure **2** was followed by employing 1-(4-chlorophenyl)-3-(m-tolyl)prop-2-yn-1-one (**49l**) (458.5 mg, 1.8 mmol) and propargylamine (121.2 mg, 2.2 mmol), which yielded 498.0 mg (89%) of the indicated product **26l** as a pale yellow solid (R_f = 0.54 in 4:1 hexane/ethyl acetate); mp 119.4–120.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (t, *J* = 5.8 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.41–7.23 (m, 6H), 5.78 (s, 1H), 3.94 (dd, *J* = 6.2, 2.4 Hz, 2H), 2.41 (s, 3H), 2.35 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2 (C=O), 166.4 (C), 138.5 (C), 138.2 (C), 136.9 (C), 134.5 (C), 130.6 (CH), 128.51 (CH), 128.48 (CH), 128.3 (CH), 128.2 (CH), 124.7 (CH), 93.9 (CH), 79.7 (C), 72.5 (CH), 34.2 (CH_2), 21.3 (CH_3); IR (neat): 3242, 3089, 3059, 3029, 2974, 2857, 2112, 1589, 1518, 1394, 1352, 1293, 1269, 1229, 1174, 1134, 1105, 1088, 1072, 1011, 961, 929, 914, 887, 872, 838, 797, 786, 762, 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.

4.2.13 1-(4-Chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (26m)

General procedure **2** was followed by employing 1-(4-chlorophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (**49m**) (388.0 mg, 1.5 mmol) and propargylamine (99.1 mg, 1.8 mmol), which yielded 431.8 mg (92%) of the indicated product **26m** as a pale yellow solid (R_f = 0.48 in 4:1 hexane/ethyl acetate); mp 132.8–133.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (s, 1H), 7.90–7.78 (m, 2H), 7.49–7.41 (m, 1H), 7.30–7.26 (m, 2H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.24–7.15 (m, 2H), 5.78 (s, 1H), 3.98–

3.88 (m, 2H), 2.36 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8 (C=O), 164.6 (C), 162.6 (d, ^1J = 248.4 Hz, CF), 138.1 (C), 137.3 (C), 136.7 (d, ^3J = 7.8 Hz, C), 130.6 (d, ^3J = 8.3 Hz, CH), 128.6 (CH), 128.5 (CH), 123.7 (d, ^4J = 3.0 Hz, CH), 117.0 (d, ^2J = 21.1 Hz, CH), 115.2 (d, ^2J = 22.9 Hz, CH), 94.3 (CH), 79.5 (C), 72.9 (CH), 34.3 (CH_2); IR (neat): 3232, 1570, 1545, 1473, 1325, 1282, 1265, 1231, 1092, 1065, 898, 764 cm^{-1}; MS (ESI, m/z): 314.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClFNO$: 314.0743 $[M+H]^+$, found: 314.0746.

4.2.14 1-(4-Chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (26n)

General procedure **2** was followed by employing 1-(4-chlorophenyl)-3-(thiophen-3-yl)prop-2-yn-1-one (**49n**) (444.1 mg, 1.8 mmol) and propargylamine (121.2 mg, 2.2 mmol),which yielded 431.9 mg (80%) of the indicated product **26n** as a yellow solid (R_f = 0.51 in 4:1 hexane/ethyl acetate); mp 110.0–112.0 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.68–7.62 (m, 1H), 7.43 (dd, J = 4.8, 2.9 Hz, 1H), 7.37 (d, J = 7.7 Hz, 2H), 7.30–7.26 (m,1H), 5.87 (s, 1H), 4.10–3.99 (m, 2H), 2.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4 (C=O), 161.0 (C), 138.3 (C), 137.1 (C), 135.3 (C), 128.6 (CH), 128.5 (CH), 127.3 (CH), 126.8 (CH), 126.5 (CH), 93.9 (CH), 79.9 (C), 72.8 (CH), 34.3 (CH_2); IR (neat): 3219, 1574, 1548, 1497, 1479, 1412, 1369, 1312, 1274, 1246, 1224, 1169, 1130, 1091, 1059, 1013, 931, 898, 869, 840, 826, 793, 760, 732, 708, 676, 627 cm^{-1}; MS (ESI, m/z): 302.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{13}NOS$: 302.0401 $[M+H]^+$, found: 302.0410.

4.2.15 3-(4-(*tert*-Butyl)phenyl)-1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (26o)

General procedure **2** was followed by employing 3-(4-(*tert*-butyl)phenyl)-1-(4-chlorophenyl)prop-2-yn-1-one (**49o**) (385.8 mg, 1.3 mmol) and propargylamine (88.1 mg, 1.6 mmol), which yield 410.6 mg (90%) of the indicated product **26o** as a

reddish brown oil (R_f = 0.63 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 5.67 (s, 1H), 3.86 (dd, *J* = 6.2, 2.3 Hz, 2H), 2.22 (t, *J* = 2.3 Hz, 1H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3 (C=O), 166.4 (C), 153.3 (C), 138.4 (C), 136.9 (C), 131.7 (C), 128.6 (CH), 128.4 (CH), 127.6 (CH), 125.7 (CH), 94.1 (CH), 79.8 (C), 72.6 (CH), 34.8 (C), 34.3 (CH_2), 31.2 (CH_3); IR (neat): 3296, 2961, 1575, 1548, 1498, 1478, 1397, 1362, 1324, 1295, 1267, 1147, 1107, 1090, 1058, 1011, 841, 776, 660 cm^{-1}; MS (ESI, m/z): 352.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{23}ClNO$: 352.1463 $[M+H]^+$, found: 352.1471.

4.2.16 3-Phenyl-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (26p)

General procedure **2** was followed by employing 3-phenyl-1-(*p*-tolyl)prop-2-yn-1-one (**49p**) (506.6 mg, 2.3 mmol) and propargylamine (154.2 mg, 2.8 mmol), which yielded 550.6 mg (87%) of the indicated product **26p** as a yellowish orange solid (R_f = 0.48 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.51–7.42 (m, 5H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.83 (s,1H), 3.93 (dd, *J* = 6.3, 2.5 Hz, 2H), 2.36 (s,3H), 2.31 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C=O), 165.6 (C), 141.4 (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). The spectral data were in agreement with those reported for this compound.[45]

4.2.17 1-(4-Chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (26q)

General procedure **2** was followed by employing 1-(4-chlorophenyl)-3-phenylprop-2-yn-1-one (**49q**) (433.2 mg, 1.8 mmol) and propargylamine (121.2 mg, 2.2 mmol), which yielded 459.2 mg (86%) of the indicated product **26q** as a yellow solid (R_f = 0.45 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.37 (s, 1H), 7.88–

7.80 (m, 2H), 7.49 (s, 5H), 7.40–7.34 (m, 2H), 5.80 (s, 1H), 3.96 (dd, *J* = 6.3, 2.5 Hz, 2H), 2.35 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5 (C=O), 166.2 (C), 138.3 (C), 137.1 (C), 134.7 (C), 130.0 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.8 (CH), 94.2 (CH), 79.7 (C), 72.7 (CH), 34.3 (CH_2). The spectral data were in agreement with those reported previously for this compound.[36]

4.2.18 3-(Prop-2-yn-1-ylamino)-3-(thiophen-3-yl)-1-(*p*-tolyl)prop-2-en-1-one (26r)

General procedure **2** was followed by employing 3-(thiophen-3-yl)-1-(*p*-tolyl)prop-2-yn-1-one (**49r**) (407.3 mg, 1.8 mmol) and propargylamine (121.2 mg, 2.2 mmol), which yielded 435.2 mg (86%) of the indicated product **26r** as a brown oil (R_f = 0.31 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.66–7.55 (m, 1H), 7.47–7.34 (m, 1H), 7.27 (d, *J* = 5.0 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 2H), 5.93 (s, 1H), 4.01 (d, *J* = 5.7 Hz, 2H), 2.37 (s, 3H), 2.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7 (C=O), 160.2 (C), 141.3 (C), 137.2 (C), 135.5 (C), 128.9 (CH), 127.2 (CH), 127.1 (CH), 126.5 (CH), 126.1 (CH), 94.0 (CH), 80.1 (C), 72.5 (CH), 34.1 (CH_2), 21.4 (CH_3); IR (neat): 3286, 3100, 2917, 1667, 1573, 1487, 1369, 1278, 1178, 1132,1057, 1016, 768, 635 cm^{-1}; MS (ESI, m/z): 282.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{16}NOS$: 282.0953 $[M+H]^+$, found: 282.0948.

4.2.19 3-(3,4-Dichlorophenyl)-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (26s)

General procedure **2** was followed by employing 3-(3,4-dichlorophenyl)-1-(*p*-tolyl)prop-2-yn-1-one (**49s**) (318.1 mg, 1.1 mmol) and propargylamine (71.6 mg, 1.3 mmol), which yielded 265.1 mg (70%) of the indicated product **26s** as a yellow solid (R_f = 0.44 in 4:1 hexane/ethyl acetate); mp 116.5–117.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (t, *J* = 6.0 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 1.9 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.34 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.79

(s, 1H), 3.88 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.37 (s, 3H), 2.33 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3 (C=O), 162.7 (C), 141.9 (C), 136.9 (C), 134.9 (C), 134.2 (C), 133.1 (C), 130.8 (CH), 129.9 (CH), 129.1 (CH), 127.3 (CH), 94.9 (CH), 79.7 (C), 72.8 (CH), 34.2 (CH_2), 21.5 (CH_3) (Note that two CH peaks overlap on each other); IR (neat): 3210, 2960, 1596, 1570, 1544, 1459, 1372, 1297, 1258, 1182, 1140, 1054, 1015, 891, 795, 768, 664, 628 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: 344.0612.

4.2.20 3-(4-Chlorophenyl)-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (26t)

General procedure **2** was followed by employing 3-(4-chlorophenyl)-1-(*p*-tolyl)prop-2-yn-1-one (**49t**) (280.2 mg, 1.1 mmol) and propargylamine (71.6 mg, 1.3 mmol), which yielded 241.9 mg (71%) of the indicated product **26t** as a brown oil (R_f = 0.53 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (t, *J* = 5.9 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.43 (s, 4H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.80 (s, 1H), 3.89 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.37 (s, 3H), 2.31 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1 (C=O), 164.2 (C), 141.6 (C), 137.0 (C), 135.9 (C), 133.4 (C), 129.3 (CH), 129.02 (CH), 128.99 (CH), 127.3 (CH), 94.7 (CH), 79.8 (C), 72.6 (CH), 34.2 (CH_2), 21.5 (CH_3); IR (neat): 3290, 2216, 1658, 1576, 1554, 1323, 1299, 1179, 1141, 1088, 1055, 1014, 835, 769, 661 cm^{-1}; MS (ESI, m/z): 310.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO$: 310.0993 $[M+H]^+$, found: 310.1002.

4.3 General procedure 3 for the synthesis of 2,3-dihydro-1,4-oxazepines 37

To a stirred solution of corresponding *N*-propargylic β-enaminone **26** (1.0 mmol) in $CHCl_3$ (10.0 ml) was added $ZnCl_2$ (1.0 mmol). Then, the reaction mixture was refluxed under argon atmosphere for approximately 2 h. During the course of the reaction, the progress was monitored by TLC (9:1 hexane/ethyl acetate) (Note that the reaction was continued until *N*-propargylic β-enaminone **26** was completely

consumed). When the reaction was over, the solvent removed by rotary evaporator and extraction was performed with ethyl acetate (40 ml) and saturated NH_4Cl (15 ml). After the separation of organic and aqueous phases, aqueous phase was extracted with ethyl acetate (2 x 35 ml). After combining organic phases, organic phase dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product. Flash chromatography on silica gel was used to purify crude product by using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent and to afford corresponding 2,3-dihydro-1,4-oxazepine derivative **37**.

4.3.1 2-Methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (37a)

General procedure **3** was followed by employing 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26a**) (287.5 mg, 1.1 mmol) and $ZnCl_2$ (149.9 mg, 1.1 mmol), which yielded 273.2 mg (95%) of the indicated product **37a** as a brown solid (R_f = 0.26 in 4:1 hexane/ethyl acetate); mp 94.2–95.9 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94–7.69 (m, 4H), 7.53–7.37 (m, 6H), 6.40 (s, 1H), 4.76 (s, 1H), 4.57 (s, 2H), 4.39 (d, J = 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C), 158.9 (C), 158.2 (C), 139.8 (C), 135.2 (C), 130.2 (CH), 130.0 (CH), 128.6 (CH), 128.4 (CH), 127.4 (CH), 126.3 (CH), 99.8 (CH), 93.9 (CH_2), 55.6 (CH_2); IR (neat): 3104, 3059, 2994, 2955, 2837, 1656, 1627, 1587, 1570, 1491, 1446, 1361, 1313, 1290, 1260, 1230, 1191, 1176, 1110, 1076, 1055, 1027, 999, 946, 926, 882, 832, 804, 762 cm^{-1}; MS (ESI, m/z): 262.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{16}NO$: 262.1226 $[M+H]^+$, found: 262.1236. The spectral data were in agreement with those reported previously for this compound.[41]

4.3.2 5-(3-Fluorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (37b)

General procedure **3** was followed by employing 3-(3-fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26b**) (251.4 mg, 0.9 mmol) and $ZnCl_2$

(122.7 mg, 0.9 mmol), which yielded 211.3 mg (84%) of the indicated product **37b** as an orange solid (R_f = 0.45 in 4:1 hexane/ethyl acetate); mp 67.7–68.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.74 (m, 2H), 7.59–7.56 (m, 1H), 7.55–7.51 (m, 1H), 7.47–7.41 (m, 3H), 7.37 (td, J = 8.0, 5.9 Hz, 1H), 7.13 (ddd, J = 8.3, 5.1, 1.8 Hz, 1H), 6.35 (s, 1H), 4.78 (s, 1H), 4.56 (s, 2H), 4.41 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0 (C), 162.9 (d, ^1J = 246.3 Hz, CF), 159.4 (C), 158.0 (C), 142.1 (d, ^3J = 7.1 Hz, C), 135.1 (C), 130.4 (CH), 130.0 (d, ^3J = 8.0 Hz, CH), 128.7 (CH), 126.4 (CH), 123.2 (d, ^4J = 2.6 Hz, CH), 117.0 (d, ^2J = 21.6 Hz, CH), 114.5 (d, ^2J = 22.7 Hz, CH), 99.2 (CH), 94.4 (CH_2), 55.6 (CH_2); IR (neat): 3102, 2993, 2951, 2837, 1731, 1704, 1656, 1624, 1569, 1483, 1447, 1431, 1361, 1313, 1296, 1261, 1248, 1196, 1174, 1104, 1077, 1055, 874, 825, 790, 762 cm^{-1}; MS (ESI, m/z): 280.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}FNO$: 280.1132 $[M+H]^+$, found: 280.1137.

4.3.3 N,N-Dimethyl-4-(2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepin-5-yl)aniline (37c)

General procedure **3** was followed by employing 3-(4-(dimethylamino)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26c**) (334.8 mg, 1.1 mmol) and $ZnCl_2$ (149.9 mg, 1.1 mmol), which yielded 204.5 mg (61%) of the indicated product **37c** as a brownish yellow oil (R_f = 0.30 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.75 (m, 2H), 7.74–7.69 (m, 2H), 7.49–7.40 (m, 3H), 6.70 (d, J = 8.9 Hz, 2H), 6.43 (s, 1H), 4.69 (s, 1H), 4.51 (s, 2H), 4.35 (d, J = 1.2 Hz, 1H), 3.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (C), 159.0 (C), 158.5 (C), 151.8 (C), 135.5 (C), 130.0 (CH), 128.8 (CH), 128.6 (CH), 127.2 (C), 126.3 (CH), 111.5 (CH), 100.3 (CH), 93.2 (CH_2), 54.8 (CH_2), 40.3 ($N(CH_3)_2$); IR (neat): 2891, 2828, 1737, 1646, 1629, 1606, 1578, 1548, 1523, 1490, 1447, 1357, 1317, 1267, 1189, 1107, 1059, 811, 758, 683 cm^{-1}; MS (ESI, m/z): 305.17 $[M+H]^+$; HRMS (ESI) calcd. for $C_{20}H_{21}N_2O$: 305.1648 $[M+H]^+$, found: 305.1662.

4.3.4 2-Methylene-7-phenyl-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1,4-oxazepine (37d)

General procedure **3** was followed by employing 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**26d**) (230.5 mg, 0.7 mmol) and $ZnCl_2$ (95.4 mg, 0.7 mmol), which yielded 172.9 mg (75%) of the indicated product **37d** as a yellowish orange solid. (R_f = 0.67 in 4:1 hexane/ethyl acetate); mp 101.9–103.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 2H), 7.79–7.74 (m, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.50–7.40 (m, 3H), 6.35 (s, 1H), 4.79 (d, J = 0.6 Hz, 1H), 4.58 (s, 2H), 4.42 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (C), 159.6 (C), 157.8 (C), 143.1 (C), 134.9 (C), 131.7 (q, ^2J = 32.4 Hz, C), 130.4 (CH), 128.7 (CH), 127.8 (CH), 126.3 (CH), 125.3 (q, ^3J = 3.7 Hz, CH), 124.1 (q, ^1J = 272.2 Hz, CF_3), 98.9 (CH), 94.5 (CH_2), 55.8 (CH_2); IR (neat): 3109, 3085, 3054, 3039, 1660, 1623, 1568, 1565, 1491, 1446, 1408, 1365, 1326, 1315, 1264, 1201, 1183, 1153, 1105, 1067, 1014, 947, 884, 861, 819, 759 cm^{-1}; MS (ESI, m/z): 330.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}F_3NO$: 330.1100 $[M+H]^+$, found: 330.1101.

4.3.5 2-Methylene-7-phenyl-5-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (37e)

General procedure **3** was followed by employing 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-en-1-one (**26e**) (220.3 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 154.1 mg (70%) of the indicated product **37e** as a brownish solid (R_f = 0.48 in 4:1 hexane/ethyl acetate); mp 73.0–75.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.74 (m, 2H), 7.69 (d, J = 8.1 Hz, 2H), 7.46–7.41 (m, 3H), 7.21 (d, J = 8.0 Hz, 2H), 6.39 (s, 1H), 4.73 (s, 1H), 4.54 (s, 2H), 4.37 (d, J = 1.4 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (C), 158.6 (C), 158.3 (C), 140.0 (C), 136.9 (C), 135.1 (C), 130.0 (CH), 129.0 (CH), 128.5 (CH), 127.3 (CH), 126.2 (CH), 99.8 (CH), 93.5 (CH_2), 55.3 (CH_2), 21.3 (CH_3); IR (neat): 3112, 3055, 3025, 3000, 2962, 2836, 1659, 1624, 1584, 1561, 1508, 1492, 1446, 1362, 1316, 1292, 1264, 1229, 1198, 1179, 1109, 1063, 1028, 950, 882, 854, 812, 758 cm^{-1}; MS (ESI, m/z):

276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1386.

4.3.6 5-(4-Methoxyphenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (37f)

General procedure **3** was followed by employing 3-(4-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26f**) (203.9 mg, 0.7 mmol) and $ZnCl_2$ (95.4 mg, 0.7 mmol), which yielded 146.8 mg (72%) of the indicated product **37f** as a yellow solid (R_f = 0.21 in 4:1 hexane/ethyl acetate); mp 112.0–113.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.73 (m, 4H), 7.46–7.40 (m, 3H), 6.92 (d, J = 8.7 Hz, 2H), 6.39 (s, 1H), 4.72 (s, 1H), 4.52 (s, 2H), 4.37 (d, J = 1.1 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 (C), 161.1 (C), 158.54 (C), 158.49 (C), 135.1 (C), 132.2 (C), 130.0 (CH), 128.8 (CH), 128.5 (CH), 126.2 (CH), 113.5 (CH), 99.8 (CH), 93.3 (CH_2), 55.2 (OCH_3), 55.1 (CH_2); IR (neat): 3081, 3052, 2996, 2953, 2835, 1656, 1630, 1604, 1586, 1562, 1510, 1492, 1462, 1432, 1367, 1315, 1299, 1254, 1199, 1172, 1109, 1063, 1029, 999 869, 856, 820 762 cm^{-1}; MS (ESI, m/z): 292.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO_2$: 292.1332 $[M+H]^+$, found: 292.1346.

4.3.7 2-Methylene-7-phenyl-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (37g)

General procedure **3** was followed by employing 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**26g**) (385.5 mg, 1.4 mmol) and $ZnCl_2$ (190.8 mg, 1.4 mmol), which yielded 285.3 mg (74%) of the indicated product **37g** as an orange oil (R_f = 0.48 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.79 (m, 2H), 7.70 (s, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.52–7.45 (m, 3H), 7.38–7.26 (m, 2H), 6.44 (s, 1H), 4.81 (s, 1H), 4.60 (s, 2H), 4.44 (d, J = 1.3 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C), 158.7 (C), 158.2 (C), 139.7 (C), 138.0 (C), 135.1 (C), 130.7 (CH), 130.1 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 126.2 (CH), 124.6 (CH), 99.8 (CH), 93.8 (CH_2), 55.4 (CH_2), 21.4 (CH_3); IR (neat): 3056,

3026, 2920, 1707, 1657, 1622, 1596, 1546, 1491, 1447, 1373, 1315, 1260, 1198, 1067, 1044, 1024, 999, 907, 831, 787, 764 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1394.

4.3.8 2-Methylene-7-phenyl-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (37h)

General procedure **3** was followed by employing 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**26h**) (294.1 mg, 1.1 mmol) and $ZnCl_2$ (149.9 mg, 1.1 mmol), which yielded 241.1 mg (82%) of the indicated product **37h** as a yellow solid (R_f = 0.42 in 4:1 hexane/ethyl acetate); mp 98.0–100.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.75 (m, 2H), 7.70–7.67 (m, 1H), 7.60 (d, J = 5.0 Hz, 1H), 7.46 (s, 3H), 7.35–7.29 (m, 1H), 6.42 (s, 1H), 4.78 (s, 1H), 4.55 (s, 2H), 4.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1 (C), 158.3 (C), 158.0 (C), 142.7 (C), 135.0 (C), 130.1 (CH), 128.5 (CH), 126.7 (CH), 126.2 (CH), 125.9 (CH), 125.6 (CH), 99.3 (CH), 93.9 (CH_2), 55.2 (CH_2); IR (neat): 3098, 2989, 2954, 2832, 1656, 1626, 1577, 1492, 1448, 1352, 1312, 1283, 1261, 1194, 1110, 1057, 1028, 872, 764, 689 cm^{-1}; MS (ESI, m/z): 268.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{14}NOS$: 268.0791 $[M+H]^+$, found: 268.0791.

4.3.9 5-(4-(*tert*-Butyl)phenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (37i)

General procedure **3** was followed by employing 3-(4-(*tert*-butyl)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26i**) (253.9 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol),which yielded 223.8 mg (88%) of the indicated product **37i** as a brownish orange oil (R_f = 0.58 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.75 (m, 4H), 7.52–7.43 (m, 5H), 6.47 (s, 1H), 4.79 (s, 1H), 4.60 (s, 2H), 4.42 (d, J = 1.3 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C), 158.6 (C), 158.3 (C), 153.3 (C), 137.0 (C), 135.2 (C), 130.1 (CH), 128.6 (CH),

127.2 (CH), 126.3 (CH), 125.3 (CH), 99.9 (CH), 93.7 (CH_2), 55.5 (CH_2), 34.8 (C), 31.3 (CH_3). IR (neat): 2960, 1654, 1622, 1573, 1493, 1448, 1361, 1313, 1291, 1261, 1192, 1106, 1061, 1019, 999, 946, 820, 763, 731, 683, 613 cm^{-1}; MS (ESI, m/z): 318.19 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{24}NO$: 318.1859 $[M+H]^+$, found: 318.1852.

4.3.10 5-(4-Chlorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (37j)

General procedure **3** was followed by employing 3-(4-chlorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26j**) (207.0 mg, 0.7 mmol) and $ZnCl_2$ (95.4 mg, 0.7 mmol), which yielded 175.9 mg (85%) of the indicated product **37j** as a brown solid (R_f = 0.61 in 4:1 hexane/ethyl acetate); mp 112.9–114.8 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.66 (m, 4H), 7.46–7.30 (m, 5H), 6.32 (s, 1H), 4.77 (s, 1H), 4.54 (s, 2H), 4.39 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (C), 159.2 (C), 158.0 (C), 138.1 (C), 136.0 (C), 134.9 (C), 130.2 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 126.2 (CH), 99.1 (CH), 94.0 (CH_2), 55.5 (CH_2); IR (neat): 2961, 1660, 1624, 1584, 1559, 1487, 1446, 1397, 1363, 1315, 1290, 1263, 1197, 1115, 1103, 1083, 1062, 1026, 1011, 944, 881, 855, 815, 760, 730, 688, 606 cm^{-1}; MS (ESI, m/z): 296.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}ClNO$: 296.0842 $[M+H]^+$, found: 296.0837.

4.3.11 5-(4-Bromophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (37k)

General procedure **3** was followed by employing 3-(4-bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26k**) (204.1 mg, 0.6 mmol) and $ZnCl_2$ (81.8 mg, 0.6 mmol), which yielded 177.9 mg (87%) of the indicated product **37k** as an orange solid (R_f = 0.42 in 4:1 hexane/ethyl acetate); mp 120.3–121.9 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.74 (m, 2H), 7.69 (t, J = 7.8 Hz, 2H), 7.58–7.51 (m,

2H), 7.50–7.41 (m, 3H), 6.34 (d, *J* = 7.2 Hz, 1H), 4.79 (d, *J* = 7.1 Hz, 1H), 4.56 (d, *J* = 7.3 Hz, 2H), 4.45–4.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0 (C), 159.3 (C), 158.0 (C), 138.6 (C), 135.0 (C), 131.5 (CH), 130.3 (CH), 129.0 (CH), 128.6 (CH), 126.3(CH), 124.6 (C), 99.1 (CH), 94.2 (CH_2), 55.6 (CH_2); IR (neat): 2960, 1661, 1623, 1585, 1557, 1483, 1446, 1393, 1363, 1315, 1297, 1262, 1197, 1114, 1102, 1068, 1025, 1008, 949, 883, 855, 826, 814, 760, 723, 688 cm^{-1}; MS (ESI, m/z): 340.03 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}{}^{79}BrNO$: 340.0334 $[M+H]^+$, found: 340.0332.

4.3.12 7-(4-Chlorophenyl)-2-methylene-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (37l)

General procedure **3** was followed by employing 1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**26l**) (247.8 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 214.8 mg (87%) of the indicated product **37l** as a pale yellow solid (R_f = 0.42 in 4:1 hexane/ethyl acetate); mp 89.0–91.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.7 Hz, 2H), 7.65 (s, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.35–7.25 (m, 2H), 6.38 (s, 1H), 4.77 (s, 1H), 4.57 (s, 2H), 4.42 (d, *J* = 1.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C), 158.1 (C), 157.6 (C), 139.6 (C), 138.1 (C), 136.2 (C), 133.6 (C), 130.9 (CH), 128.8 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 124.6 (CH), 100.0 (CH), 94.1 (CH_2), 55.5 (CH_2), 21.5 (CH_3); IR (neat): 3053, 2960, 1645, 1624, 1572, 1491, 1404, 1361, 1318, 1262, 1200, 1114, 1087, 1063, 1010, 908, 874, 934, 809, 779, 696, 668, 631, 607 cm^{-1}; MS (ESI, m/z): 310.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO$: 310.1000 $[M+H]^+$, found: 310.0993.

4.3.13 7-(4-Chlorophenyl)-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (37m)

General procedure **3** was followed by employing 1-(4-chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26m**) (219.6 mg, 0.7 mmol) and $ZnCl_2$ (95.4 mg, 0.7 mmol), which yielded 163.0 mg (74%) of the indicated product **37m** as an orange solid (R_f = 0.48 in 4:1 hexane/ethyl acetate); mp 114.5.0–115.6 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.6 Hz, 2H), 7.55–7.47 (m, 2H), 7.40–7.32 (m, 3H), 7.15–7.07 (m, 1H), 6.30 (s, 1H), 4.76 (s, 1H), 4.54 (s, 2H), 4.40 (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 (C), 162.8 (d, ^1J = 246.6 Hz, CF), 158.1 (C), 157.8 (C), 141.9 (d, ^3J = 7.1 Hz, C), 136.4 (C), 133.4 (C), 129.9 (d, ^3J = 8.1 Hz, CH), 128.9 (CH), 127.6 (CH), 123.1 (d, ^4J = 2.6 Hz, CH), 117.0 (d, ^2J = 21.6 Hz, CH), 114.3 (d, ^2J = 22.7 Hz, CH), 99.3 (CH), 94.5 (CH_2), 55.6 (CH_2); IR (neat): 3297, 2997, 1657, 1623, 1591, 1573, 1484, 1439, 1402, 1362, 1314, 1259, 1178, 1090, 1055, 1010, 984, 881, 819, 783 cm^{-1}; MS (ESI, m/z): 314.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClFNO$: 314.0743 $[M+H]^+$, found: 314.0750.

4.3.14 7-(4-Chlorophenyl)-2-methylene-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (37n)

General procedure **3** was followed by employing 1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**26n**) (241.5 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 210.6 mg (87%) of the indicated product **37n** as a yellow solid (R_f = 0.32 in 4:1 hexane/ethyl acetate); mp 121.0–122.9 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.5 Hz, 3H), 7.55 (dd, J = 5.0, 1.1 Hz, 1H), 7.37 (d, J = 8.6 Hz, 2H), 7.31–7.28 (m, 1H), 6.35 (s, 1H), 4.74 (s, 1H), 4.51 (s, 2H), 4.40 (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (C), 157.8 (C), 157.1 (C), 142.5 (C), 136.0 (C), 133.4 (C), 128.7 (CH), 127.5 (CH), 126.7 (CH), 125.9 (CH), 125.6 (CH), 99.4 (CH), 94.1 (CH_2), 55.1 (CH_2); IR (neat): 3100, 3952, 2834, 1652, 1621, 1578, 1520, 1488, 1402, 1349, 1312, 1260, 1231, 1194, 1111, 1088,

1055, 1011, 874, 837, 818, 787, 693, 605 cm^{-1}; MS (ESI, m/z): 302.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{13}ClNOS$: 302.0410 $[M+H]^+$, found: 302.0401.

4.3.15 5-(4-(*tert*-Butyl)phenyl)-7-(4-chlorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (37o)

General procedure **3** was followed by employing 3-(4-(*tert*-butyl)phenyl)-1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26o**) (246.3 mg, 0.7 mmol) and $ZnCl_2$ (95.4 mg, 0.7 mmol), which yielded 202.3 mg (82%) of the indicated product **37o** as an orange oil (R_f = 0.48 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.70 (m, 4H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 6.41 (s, 1H), 4.76 (s, 1H), 4.57 (s, 2H), 4.41 (d, *J* = 1.3 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6 (C), 158.2 (C), 157.5 (C), 153.4 (C), 136.9 (C), 136.1 (C), 133.7 (C), 128.8 (CH), 127.6 (CH), 127.2 (CH), 125.4 (CH), 100.0 (CH), 94.0 (CH_2), 55.4 (CH_2), 34.8 (C), 31.3 (CH_3); IR (neat): 2960, 1737, 1654, 1623, 1581, 1489, 1405, 1361, 1313, 1260, 1192, 1092, 1059, 1012, 909, 813, 736, 682, 632 cm^{-1}; MS (ESI, m/z): 352.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{23}ClNO$: 352.1473 $[M+H]^+$, found: 352.1463.

4.3.16 2-Methylene-5-phenyl-7-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (37p)

General procedure **3** was followed by employing 3-phenyl-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (**26p**) (220.3 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 140.6 mg (64%) of the indicated product **37p** as a yellow solid (R_f = 0.42 in 4:1 hexane/ethyl acetate); mp 81.0–83.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.81 (m, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.49–7.43 (m, 3H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.41 (s, 1H), 4.79 (s, 1H), 4.59 (s, 2H), 4.42 (d, *J* = 1.2 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C), 159.0 (C), 158.2 (C), 140.4 (C), 139.9 (C), 132.3 (C), 130.0 (CH), 129.3 (CH), 128.3 (CH), 127.4 (CH), 126.2 (CH), 99.1 (CH), 93.7 (CH_2), 55.5 (CH_2), 21.4 (CH_3); IR (neat): 3106, 2995, 2837, 1657,

1626, 1588, 1569, 1509, 1445, 1359, 1312, 1292, 1261, 1193, 1113, 1076, 1055, 1028, 952, 926, 908, 882, 813, 765, 705, 692, 616 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1386 $[M+H]^+$, found: 276.1383.

4.3.17 7-(4-Chlorophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (37q)

General procedure **3** was followed by employing 1-(4-chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26q**) (236.6 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 197.9 mg (84%) of the indicated product **37q** as a yellow solid (R_f = 0.42 in 4:1 hexane/ethyl acetate); mp 125.8–127.1 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.75 (m, 2H), 7.72–7.63 (m, 2H), 7.47–7.35 (m, 5H), 6.35 (s, 1H), 4.75 (d, J = 0.6 Hz, 1H), 4.54 (s, 2H), 4.40 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (C), 158.0 (C), 157.6 (C), 139.6 (C), 136.1 (C), 133.5 (C), 130.0 (CH), 128.8 (CH), 128.3 (CH), 127.5 (CH), 127.3 (CH), 99.8 (CH), 94.1 (CH_2), 55.4 (CH_2); IR (neat): 2953, 2837, 1656, 1625, 1587, 1569, 1488, 1445, 1402, 1362, 1312, 1290, 1258, 1192, 1110, 1088, 1054, 1028, 1010, 885, 858, 820, 769, 714, 691, 601 cm^{-1}; MS (ESI, m/z): 296.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}ClNO$: 296.0842 $[M+H]^+$, found: 296.0837.

4.3.18 2-Methylene-5-(thiophen-3-yl)-7-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (37r)

General procedure **3** was followed by employing 3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)-1-(*p*-tolyl)prop-2-en-1-one (**26r**) (225.1 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 188.7 mg (84%) of the indicated product **37r** as a yellow solid (R_f = 0.23 in 4:1 hexane/ethyl acetate); mp 88.0–90.1 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.65 (m, 3H), 7.57 (dd, J = 5.1, 1.1 Hz, 1H), 7.35–7.31 (m, 1H), 7.26 (d, J = 8.0 Hz, 2H), 6.40 (s, 1H), 4.76 (s, 1H), 4.54 (s, 2H), 4.41 (d, J = 1.1 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (C), 158.7 (C),

158.1 (C), 143.0 (C), 140.5 (C), 132.3 (C), 129.3 (CH), 126.9 (CH), 126.3 (CH), 125.9 (CH), 125.7 (CH), 98.8 (CH), 93.9 (CH_2), 55.4 (CH_2), 21.4 (CH_3); IR (neat): 2196, 1623, 1580, 1409, 1345, 1312, 1266, 1200, 1182, 1110, 1059, 1017, 865, 805, 778, 753, 695, 654 cm^{-1}; MS (ESI, m/z): 282.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{16}NOS$: 282.0942 $[M+H]^+$, found: 282.0947.

4.3.19 5-(3,4-Dichlorophenyl)-2-methylene-7-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (37s)

General procedure **3** was followed by employing 3-(3,4-dichlorophenyl)-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (**26s**) (275.4 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 220.3 mg (80%) of the indicated product **37s** as a yellow solid (R_f = 0.53 in 4:1 hexane/ethyl acetate); mp 119.0–120.8 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 2.0 Hz, 1H), 7.59–7.52 (m, 3H), 7.39 (d, J = 8.4 Hz, 1H), 7.19–7.14 (m, 2H), 6.18 (s, 1H), 4.69 (d, J = 0.5 Hz, 1H), 4.45 (s, 2H), 4.32 (d, J = 1.5 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9 (C), 159.9 (C), 157.8 (C), 140.8 (C), 139.8 (C), 134.1 (C), 132.7 (C), 132.0 (C), 130.3 (CH), 129.41 (CH), 129.39 (CH), 126.7 (CH), 126.3 (CH), 97.9 (CH), 94.4 (CH_2), 55.7 (CH_2), 21.5 (CH_3); IR (neat): 2915, 1655, 1579, 1469, 1372, 1317, 1264, 1233, 1191, 1062, 1027, 854, 809, 754, 717, 676, 644 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: 344.0613.

4.3.20 5-(4-Chlorophenyl)-2-methylene-7-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (37t)

General procedure **3** was followed by employing 3-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (**26t**) (247.8 mg, 0.8 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 198.3 mg (80%) of the indicated product **37t** as an orange solid (R_f = 0.50 in 4:1 hexane/ethyl acetate); mp 115.4–116.0 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.60 (m, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.28–7.24

(m, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 6.19 (s, 1H), 4.65 (s, 1H), 4.42 (s, 2H), 4.28 (d, *J* = 1.5 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 (C), 159.5 (C), 158.1 (C), 140.7 (C), 138.3 (C), 136.1 (C), 132.2 (C), 129.4 (CH), 128.8 (CH), 128.6 (CH), 126.3 (CH), 98.5 (CH), 94.1 (CH_2), 55.6 (CH_2), 21.4 (CH_3); IR (neat): 2961, 1650, 1583, 1488, 1409, 1366, 1312, 1260, 1196, 1088, 1060, 1011, 863, 843, 802, 727, 679 cm^{-1}; MS (ESI, m/z): 310.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO$: 310.0993 $[M+H]^+$, found: 310.0996.

4.4 General procedure 4 for the synthesis of 2-acetyl-1*H*-pyrroles 46

a. Synthesis method from 1,4-oxazepines 37.

To a stirred solution of corresponding 2,3-dihydro-1,4-oxazepine **37** (0.5 mmol) in MeOH (5.0 ml) was added $ZnCl_2$ (0.5 mmol). Then, the reaction mixture was refluxed under argon atmosphere for approximately 2 h. During the course of the reaction, the progress was monitored by TLC (19:1:0.2 hexane/ethyl acetate/acetone) (Note that the reaction was continued until *N*-propargylic β-enaminone **26** was completely consumed). When the reaction was over, the solvent removed by rotary evaporator and extraction was performed with ethyl acetate (40 ml) and saturated NH_4Cl (15 ml). After the separation of organic and aqueous phases, aqueous phase was extracted with ethyl acetate (2 x 35 ml). After combining organic phases, organic phase dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product. Flash chromatography on silica gel was used to purify crude product by using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent and to afford corresponding pyrrole derivatives **46**.

b. One-pot two-step synthesis method from *N*-propargylic β-enaminones 26.

To a stirred solution of corresponding *N*-propargylic β-enaminone **26** (0.5 mmol) in $CHCl_3$ (5.0 ml) was added $ZnCl_2$ (0.5 mmol). Then, the reaction mixture was refluxed under argon atmosphere for approximately 2 h. During the course of the

reaction, the progress was monitored by TLC (9:1 hexane/ethyl acetate) (Note that the reaction was continued until *N*-propargylic β-enaminone **26** was completely consumed). After the reaction was over, $CHCl_3$ is removed by rotary evaporator. Subsequently, MeOH (5 ml) and $ZnCl_2$ (0.5 mmol) were added to the crude product. Then, the reaction mixture was refluxed under argon atmosphere for approximately 2 h. During the course of the reaction, the progress was monitored by TLC (19:1:0.2 hexane/ethyl acetate/acetone) (Note that the reaction was continued until 2,3-dihydro-1,4-oxazepine **37** was completely consumed). When the reaction was ended, the solvent was removed by rotary evaporator and extraction was performed with ethyl acetate (40 ml) and saturated NH_4Cl (15 ml). After the separation of organic and aqueous phases, aqueous phase was extracted with ethyl acetate (2 x 35 ml). After combining organic phases, organic phase dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product. Flash chromatography on silica gel was used to purify crude product by using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent and to afford corresponding pyrrole derivative **46**.

4.4.1 1-(3,5-Diphenyl-1*H*-pyrrol-2-yl)ethanone (46a)

a. General procedure **4a** was followed by employing 2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**37a**) (130.7 mg, 0.5 mmol) and $ZnCl_2$ (68.1 mg, 0.5 mmol), which yielded 115.0 mg (88%) of the indicated product **46a** as a white crystal solid.

b. General procedure **4b** was followed by employing 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26a**) (130.7 mg, 0.5 mmol) and $ZnCl_2$ (111.1 mg, 1.0 mmol), which yielded 113.1 mg (85%) of the indicated product **46a** as a white crystal solid.

(R_f = 0.26 in 4:1 hexane/ethyl acetate); mp 147.0–149.0 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.70 (d, *J* = 7.4 Hz, 2H), 7.52–7.38 (m, 7H), 7.33 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 2.9 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (C=O), 136.7 (C), 136.4 (C), 134.6 (C), 130.9 (C), 129.8 (CH), 129.6 (C), 129.0

(CH), 128.3 (CH), 128.2 (CH), 127.7 (CH), 125.3 (CH), 110.9 (CH), 27.6 (CH_3); IR (neat): 3251, 1612, 1597, 1492, 1461, 1438, 1356, 1291, 1269, 1184, 1075, 992, 956, 914, 826, 760, 703, 688, 671, 613 cm^{-1}; MS (ESI, m/z): 262.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{16}NO$: 262.1226 $[M+H]^+$, found: 262.1232.

4.4.2 1-(5-(3-Fluorophenyl)-3-phenyl-1*H*-pyrrol-2-yl)ethanone (46b)

a. General procedure **4a** was followed by employing 5-(3-fluorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**37b**) (111.8 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 85.0 mg (76%) of the indicated product **46b** as a white solid.

b. General procedure **4b** was followed by employing 3-(3-fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26b**) (139.8 mg, 0.5 mmol) and $ZnCl_2$ (136.3 mg, 1.0 mmol), which yielded 88.1 mg (63%) of the indicated product **46b** as a white solid.

(R_f = 0.38 in 4:1 hexane/ethyl acetate); mp 176.0–177.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.48–7.34 (m, 8H), 7.05–6.98 (m, 1H), 6.57 (d, J = 3.0 Hz, 1H), 2.12 (d, J = 0.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2 (C=O), 163.4 (d, ^1J = 246.2 Hz, CF), 136.2 (C) , 135.5 (C), 134.6 (C), 133.2 (d, ^3J = 8.3 Hz, C) , 130.6 (d, ^3J = 8.5 Hz, CH), 129.92 (CH), 129.86 (C), 128.4 (CH), 127.9 (CH), 121.0 (d, ^4J = 1.9 Hz, CH), 115.1 (d, ^2J = 21.3 Hz, CH), 112.4 (d, ^2J = 23.1 Hz, CH), 111.5 (CH), 27.7 (CH_3); IR (neat): 3301, 3288, 3062, 1628, 1489, 1454, 1434, 1414, 1357, 1271, 1206, 1176, 1107, 1076, 991, 977, 957, 892, 848, 814, 784, 766, 729, 704, 680, 613 cm^{-1}; MS (ESI, m/z): 280.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}FNO$: 280.1132 $[M+H]^+$, found: 280.1136.

4.4.3 1-(5-(4-(Dimethylamino)phenyl)-3-phenyl-1*H*-pyrrol-2-yl)ethanone (46c)

a. General procedure **4a** was followed by employing N,N-dimethyl-4-(2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepin-5-yl)aniline (**37c**) (121.8 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 78.0 mg (64%) of the indicated product **46c** as a yellow solid.

b. General procedure **4b** was followed by employing 3-(4-(dimethylamino)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26c**) (152.2 mg, 0.5 mmol) and $ZnCl_2$ (136.3 mg, 1.0 mmol), which yielded 77.7 mg (51%) of the indicated product **46c** as a yellow solid.

(R_f = 0.22 in 4:1 hexane/ethyl acetate); mp 193.6–195.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.56 (d, *J* = 8.9 Hz, 2H), 7.46–7.38 (m, 5H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.44 (d, *J* = 3.0 Hz, 1H), 3.00 (s, 6H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9 (C=O), 150.4 (C), 137.8 (C), 136.7 (C), 135.0 (C), 129.8 (CH), 128.6 (C), 128.2 (CH), 127.6 (CH), 126.3 (CH), 118.7 (C), 112.4 (CH), 109.3 (CH), 40.4 ($N(CH_3)_2$), 27.4 (CH_3); IR (neat): 3303, 3276, 2802, 1594, 1498, 1463, 1411, 1383, 1353, 1272, 1209, 1184, 1102, 1069, 948, 819, 798, 766, 699, 676, 632, 612 cm^{-1}; MS (ESI, m/z): 305.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{20}H_{21}N_2O$: 305.1648 $[M+H]^+$, found: 305.1651.

4.4.4 1-(3-Phenyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrrol-2-yl)ethanone (46d)

a. General procedure **4a** was followed by employing 2-methylene-7-phenyl-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1,4-oxazepine (**37d**) (131.7 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 115.4 mg (88%) of the indicated product **46d** as a yellowish white solid.

b. General procedure **4b** was followed by employing 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**26d**) (131.7 mg, 0.4

mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 91.0 mg (69%) of the indicated product **46d** as a yellowish white solid.

(R_f = 0.41 in 4:1 hexane/ethyl acetate); mp 196.0–198.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.49–7.38 (m, 5H), 6.64 (d, *J* = 3.0 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3 (C=O), 136.0 (C), 134.9 (C), 134.5 (C), 134.3 (C), 130.3 (C), 130.2 (q, ^2J = 32.4 Hz, C), 129.9 (CH), 128.5 (CH), 128.0 (CH), 126.1 (q, ^3J = 3.5 Hz, CH), 125.4 (CH), 124.2 (q, ^1J = 272.0 Hz, CF_3), 112.1 (CH), 27.8 (CH_3); IR (neat): 3290, 1618, 1465, 1450, 1411, 1318, 1295, 1262, 1159, 1106, 1062, 1017, 957, 841, 815, 767, 704, 676, 626, 612 cm^{-1}; MS (ESI, m/z): 280.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{15}F_3NO$: 330.1100 $[M+H]^+$, found: 330.1109.

4.4.5 1-(3-Phenyl-5-(*p*-tolyl)-1*H*-pyrrol-2-yl)ethanone (46e)

a. General procedure **4a** was followed by employing 2-methylene-7-phenyl-5-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (**37e**) (110.1 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 87.1 mg (79%) of the indicated product **46e** as an off white solid.

b. General procedure **4b** was followed by employing 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(*p*-tolyl)prop-2-en-1-one (**26e**) (110.1 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 67.9 mg (62%) of the indicated product **46e** as an off white solid.

(R_f = 0.38 in 4:1 hexane/ethyl acetate); mp 164.5–165.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.48–7.38 (m, 5H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.53 (d, *J* = 2.9 Hz, 1H), 2.38 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6 (C=O), 138.3 (C), 136.9 (C), 136.5 (C), 134.6 (C), 129.8 (CH), 129.7 (C), 129.3 (CH), 128.3 (CH), 128.1 (CH), 127.7 (C), 125.2 (CH), 110.5 (CH), 27.6 (CH_3), 21.3 (CH_3); IR (neat): 3299, 3277, 1620, 1495, 1462, 1409, 1287, 1262, 1181,

1100, 1071, 1017, 952, 801, 766, 700, 634, 610 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1391.

4.4.6 1-(5-(4-Methoxyphenyl)-3-phenyl-1*H*-pyrrol-2-yl)ethanone (46f)

a. General procedure **4a** was followed by employing 5-(4-methoxyphenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**37f**) (116.5 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 84.8 mg (73%) of the indicated product **46f** as a yellowish white solid.

b. General procedure **4b** was followed by employing 3-(4-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26f**) (145.7 mg, 0.5 mmol) and $ZnCl_2$ (136.3 mg, 1.0 mmol), which yielded 96.4 mg (66%) of the indicated product **46f** as a yellowish white solid.

(R_f = 0.25 in 4:1 hexane/ethyl acetate); mp 174.1–177.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.66–7.62 (m, 2H), 7.46–7.37 (m, 5H), 6.97–6.92 (m, 2H), 6.47 (d, *J* = 3.0 Hz, 1H), 3.83 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5 (C=O), 159.8 (C), 136.9 (C), 136.5 (C), 134.8 (C), 129.8 (CH), 129.1 (C), 128.3 (CH), 127.7 (CH), 126.7 (CH), 123.6 (C), 114.5 (CH), 110.1 (CH), 55.4 (OCH_3), 27.5 (CH_3); IR (neat): 3274, 1612, 1599, 1495, 1463, 1440, 1421, 1387, 1294, 1275, 1245, 1175, 1103, 1071, 1027, 954, 824, 793, 765, 716, 699, 641, 608 cm^{-1}; MS (ESI, m/z): 292.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO_2$: 292.1332 $[M+H]^+$, found: 292.1340.

4.4.7 1-(3-Phenyl-5-(*m*-tolyl)-1*H*-pyrrol-2-yl)ethanone (46g)

a. General procedure **4a** was followed by employing 2-methylene-7-phenyl-5-(*m*-tolyl)-2,3-dihydro-1,4-oxazepine (**37g**) (137.7 mg, 0.5 mmol) and $ZnCl_2$ (68.1 mg, 0.5 mmol), which yielded 100.9 mg (73%) of the indicated product **46g** as an off white solid.

b. General procedure **4b** was followed by employing 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(*m*-tolyl)prop-2-en-1-one (**26g**) (137.7 mg, 0.5 mmol) and $ZnCl_2$ (136.3 mg, 1.0 mmol), which yielded 100.7 mg (73%) of the indicated product **46g** as an off white solid.

(R_f = 0.38 in 4:1 hexane/ethyl acetate); mp 130.0–131.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.58–7.51 (m, 2H), 7.49–7.39 (m, 5H), 7.35–7.28 (m, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.61–6.53 (m, 1H), 2.42 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7 (C=O), 138.6 (C), 136.9 (C), 136.4 (C), 134.6 (C), 130.8 (C), 129.8 (CH), 129.4 (C), 129.0 (CH), 128.9 (CH), 128.3 (CH), 127.6 (CH), 125.9 (CH), 122.5 (CH), 110.9 (CH), 27.6 (CH_3), 21.5 (CH_3); IR (neat): 3275, 3224, 1625, 1492, 1451, 1358, 1273, 1206, 1109, 994, 956, 909, 822, 786, 768, 694, 613 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1390.

4.4.8 1-(3-Phenyl-5-(thiophen-3-yl)-1*H*-pyrrol-2-yl)ethanone (46h)

a. General procedure **4a** was followed by employing 2-methylene-7-phenyl-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (**37h**) (133.7 mg, 0.5 mmol) and $ZnCl_2$ (68.1 mg, 0.5 mmol), which yielded 89.9 mg (67%) of the indicated product **46h** as a yellow solid.

b. General procedure **4b** was followed by employing 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**26h**) (133.7 mg, 0.5 mmol) and $ZnCl_2$ (136.3 mg, 1.0 mmol), which yielded 101.7 mg (76%) of the indicated product **46h** as a yellow solid.

(R_f = 0.38 in 4:1 hexane/ethyl acetate); mp 173.9–176.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 7.72–7.65 (m, 1H), 7.55–7.33 (m, 7H), 6.51–6.40 (m, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (C=O), 136.4 (C), 134.7 (C), 133.0 (C), 132.6 (C), 129.9 (CH), 128.9 (C), 128.4 (CH), 127.8 (CH), 126.7 (CH), 125.6 (CH), 120.9 (CH), 111.1 (CH), 27.6 (CH_3); IR (neat): 3286, 3092, 1620, 1473,

1450, 1409, 1380, 1266, 1212, 1075, 1021, 992, 957, 851, 818, 788, 764, 705, 679, 606 cm^{-1}; MS (ESI, m/z): 268.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{14}NOS$: 268.0791 $[M+H]^+$, found: 268.0795.

4.4.9 1-(5-(4-(tert-Butyl)phenyl)-3-phenyl-1*H*-pyrrol-2-yl)ethanone (46i)

a. General procedure **4a** was followed by employing 5-(4-(*tert*-butyl)phenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**37i**) (127.0 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 100.0 mg (79%) of the indicated product **46i** as a white solid.

b. General procedure **4b** was followed by employing 3-(4-(*tert*-butyl)phenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26i**) (127.0 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 108.5 mg (85%) of the indicated product **46i** as a white solid.

(R_f = 0.47 in 4:1 hexane/ethyl acetate); mp 168.0–169.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.52–7.39 (m, 7H), 6.60–6.56 (m, 1H), 2.16 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6 (C=O), 151.5 (C), 136.8 (C), 136.4 (C), 134.6 (C), 129.9 (CH), 129.3 (C), 128.3 (CH), 128.1 (C), 127.7 (CH), 126.0 (CH), 125.0 (CH), 110.6 (CH), 34.8 (C), 31.3 (CH_3), 27.6 (CH_3); IR (neat): 3273, 2961, 1626, 1494, 1452, 1415, 1289, 1261, 992, 957, 821, 772, 699, 673, 610 cm^{-1}; MS (ESI, m/z): 318.19 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{24}NO$: 318.1852 $[M+H]^+$, found: 318.1861.

4.4.10 1-(5-(4-Chlorophenyl)-3-phenyl-1*H*-pyrrol-2-yl)ethanone (46j)

a. General procedure **4a** was followed by employing 5-(4-chlorophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**37j**) (118.3 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 89.0 mg (75%) of the indicated product **46j** as an off white solid.

b. General procedure **4b** was followed by employing 3-(4-chlorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26j**) (118.3 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 79.7 mg (67%) of the indicated product **46j** as an off white solid.

(R_f = 0.40 in 4:1 hexane/ethyl acetate); mp 173.3–175.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.48–7.39 (m, 5H), 7.37 (d, *J* = 8.6 Hz, 2H), 6.55 (d, *J* = 2.9 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C=O), 136.2 (C), 135.8 (C), 134.8 (C), 134.0 (C), 129.83 (CH), 129.80 (C), 129.5 (CH), 129.2 (CH), 128.4 (CH), 127.8 (C), 126.7 (CH), 111.2 (CH), 27.7 (CH_3); IR (neat): 3286, 1621, 1488, 1462, 1411, 1355, 1284, 1261, 1086, 1013, 956, 832, 812, 765, 738, 702, 666, 611 cm^{-1}; MS (ESI, m/z): 296.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}ClNO$: 296.0837 $[M+H]^+$, found: 296.0844.

4.4.11 1-(5-(4-Bromophenyl)-3-phenyl-1*H*-pyrrol-2-yl)ethanone (46k)

a. General procedure **4a** was followed by employing 5-(4-bromophenyl)-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (**37k**) (102.1 mg, 0.3 mmol) and $ZnCl_2$ (40.9 mg, 0.3 mmol), which yielded 83.7 mg (82%) of the indicated product **46k** as an off white solid.

b. General procedure **4b** was followed by employing 3-(4-bromophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26k**) (136.1 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 102.3 mg (75%) of the indicated product **46k** as an off white solid.

(R_f = 0.43 in 4:1 hexane/ethyl acetate); mp 184.0–186.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.71–7.33 (m, 9H), 6.61–6.51 (m, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C=O), 136.1 (C), 135.7 (C), 134.7 (C), 132.1 (C), 129.88 (CH), 129.86 (C), 129.8 (CH), 128.4 (CH), 127.8 (CH), 126.9 (C), 122.2 (CH), 111.2 (CH), 27.7 (CH_3); IR (neat): 3854, 3284, 2008, 1618, 1485, 1462, 1408, 1282, 1261, 1068, 1007, 955, 810, 769, 739, 705, 611 cm^{-1}; MS (ESI, m/z): 340.03

$[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}{}^{79}BrNO$: 340.0332 $[M+H]^+$, found: 340.0333.

4.4.12 1-(3-(4-Chlorophenyl)-5-(m-tolyl)-1*H*-pyrrol-2-yl)ethanone (46l)

a. General procedure **4a** was followed by employing 7-(4-chlorophenyl)-2-methylene-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (**37l**) (123.9 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 100.2 mg (81%) of the indicated product **46l** as an off white solid.

b. General procedure **4b** was followed by employing 1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**26l**) (123.9 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 88.3 mg (71%) of the indicated product **46l** as an off white solid.

(R_f = 0.37 in 4:1 hexane/ethyl acetate); mp 178.8–179.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.51–7.46 (m, 2H), 7.43–7.34 (m, 4H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 6.53–6.50 (m, 1H), 2.40 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4 (C=O), 138.8 (C), 137.0 (C), 134.8 (C), 133.8 (C), 133.0 (C), 131.1 (CH), 130.6 (C), 129.4 (C), 129.2 (CH), 129.0 (CH), 128.6 (CH), 125.9 (CH), 122.5 (CH), 110.8 (CH), 27.7 (CH_3), 21.6 (CH_3); IR (neat): 3303, 3220, 1624, 1440, 1270, 1086, 1016, 952, 905, 837, 808, 782, 726, 694, 634, 613 cm^{-1}; MS (ESI, m/z): 310.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO$: 310.0993 $[M+H]^+$, found: 310.1001.

4.4.13 1-(3-(4-Chlorophenyl)-5-(3-fluorophenyl)-1*H*-pyrrol-2-yl)ethanone (46m)

a. General procedure **4a** was followed by employing 7-(4-chlorophenyl)-5-(3-fluorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**37m**) (94.1 mg, 0.3 mmol) and $ZnCl_2$ (40.9 mg, 0.3 mmol), which yielded 73.5 mg (78%) of the indicated product **46m** as an off white solid.

b. General procedure **4b** was followed by employing 1-(4-chlorophenyl)-3-(3-fluorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26m**) (125.5 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 90.7 mg (72%) of the indicated product **46m** as an off white solid.

(R_f = 0.40 in 4:1 hexane/ethyl acetate); mp 199.0–201.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 7.51–7.44 (m, 2H), 7.44–7.39 (m, 2H), 7.39–7.34 (m, 3H), 7.05–6.98 (m, 1H), 6.54 (d, J = 3.0 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C=O), 163.4 (d, ^1J = 246.0 Hz, CF), 135.7 (C), 134.6 (C), 134.0 (C), 133.1 (C), 133.0 (d, ^3J = 8.2 Hz, C), 131.2 (CH), 130.7 (d, ^3J = 8.4 Hz ,CH), 129.9 (C), 128.7 (CH), 121.0 (d, ^4J = 2.5 Hz, CH), 115.19 (d, ^2J = 21.3 Hz, CH), 112.38 (d, ^2J = 23.2 Hz, CH), 111.4 (CH), 27.8 (CH_3); IR (neat): 3294, 3060, 1631, 1491, 1432, 1356, 1274, 1204, 1175, 1089, 1014, 977, 955, 887, 841, 805, 777, 737, 720, 683, 627 cm^{-1}; MS (ESI, m/z): 314.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{14}ClFNO$: 314.0743 $[M+H]^+$, found: 314.0752.

4.4.14 1-(3-(4-Chlorophenyl)-5-(thiophen-3-yl)-1*H*-pyrrol-2-yl)ethanone (46n)

a. General procedure **4a** was followed by employing 7-(4-chlorophenyl)-2-methylene-5-(thiophen-3-yl)-2,3-dihydro-1,4-oxazepine (**37n**) (120.7 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 102.9 mg (85%) of the indicated product **46n** as a pale yellow solid.

b. General procedure **4b** was followed by employing 1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**26n**) (120.7 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 93.3 mg (77%) of the indicated product **46n** as a pale yellow solid.

(R_f = 0.34 in 4:1 hexane/ethyl acetate); mp 195.1–196.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.69–7.66 (m, 1H), 7.44–7.33 (m, 6H), 6.42 (d, J = 2.9 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5 (C=O), 134.8 (C) , 133.9

(C), 133.2 (C), 132.4 (C), 131.2 (CH), 128.9 (C), 128.6 (CH), 126.8 (CH), 125.6 (CH), 121.0 (CH), 111.0 (CH), 27.7 (CH_3) (Note that two C peaks overlap on each other); IR (neat): 3310, 3217, 3088, 2349, 2027, 1617, 1533, 1492, 1467, 1446, 1377, 1266, 1216, 1086, 1015, 993, 973, 952, 854, 829, 782, 735, 672, 648, 635, 605 cm^{-1}; MS (ESI, m/z): 302.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{13}ClNOS$: 302.0401 $[M+H]^+$, found: 302.0409.

4.4.15 1-(5-(4-(*tert*-Butyl)phenyl)-3-(4-chlorophenyl)-1*H*-pyrrol-2-yl)ethanone (46o)

a. General procedure **4a** was followed by employing 5-(4-(*tert*-butyl)phenyl)-7-(4-chlorophenyl)-2-methylene-2,3-dihydro-1,4-oxazepine (**37o**) (105.6 mg, 0.3 mmol) and $ZnCl_2$ (40.9 mg, 0.3 mmol), which yielded 82.4 mg (78%) of the indicated product **46o** as off white solid.

b. General procedure **4b** was followed by employing 3-(4-(*tert*-butyl)phenyl)-1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**26o**) (140.7 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 109.6 mg (78%) of the indicated product **46o** as an off white solid.

(R_f = 0.46 in 4:1 hexane/ethyl acetate); mp 222.0–224.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.47–7.35 (m, 6H), 6.51 (d, *J* = 3.0 Hz, 1H), 2.12 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3 (C=O), 151.7 (C), 137.0 (C), 134.9 (C), 133.8 (C), 133.1 (C), 131.2 (CH), 129.3 (C), 128.5 (CH), 127.9 (C), 126.0 (CH), 125.1 (CH), 110.5 (CH), 34.8 (C), 31.3 (CH_3), 27.7 (CH_3); IR (neat): 3279, 2947, 1619, 1491, 1460, 1413, 1358, 1290, 1259, 1185, 1085, 1016, 994, 954, 832, 812, 757, 723, 671, 634, 610 cm^{-1}; MS (ESI, m/z): 352.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{23}ClNO$: 352.1463 $[M+H]^+$, found: 352.1472.

4.4.16 1-(5-Phenyl-3-(*p*-tolyl)-1*H*-pyrrol-2-yl)ethanone (46p)

a. General procedure **4a** was followed by employing 2-methylene-5-phenyl-7-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (**37p**) (110.1 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 89.1 mg (81%) of the indicated product **46p** as an off white solid.

b. General procedure **4b** was followed by employing 3-phenyl-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (**26p**) (110.1 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 58.9 mg (53%) of the indicated product **46p** as an off white solid.

(R_f = 0.43 in 4:1 hexane/ethyl acetate); mp 148.7–150.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.76–7.68 (m, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.39–7.33 (m, 3H), 7.30–7.27 (m, 2H), 6.58 (d, *J* = 3.0 Hz, 1H), 2.46 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (C=O), 137.5 (C), 136.6 (C), 134.6 (C), 133.3 (C), 131.0 (C), 129.7 (CH), 129.6 (C), 129.0 (CH), 128.2 (CH), 125.3 (CH), 111.0 (CH), 27.6 (CH_3), 21.3 (CH_3) (Note that two CH peaks overlap on each other); IR (neat): 3281, 3227, 1624, 1497, 1460, 1438, 1358, 1289, 1268, 1106, 1021, 996, 955, 913, 839, 823, 806, 762, 690, 670, 637 cm^{-1}; MS (ESI, m/z): 276.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{19}H_{18}NO$: 276.1383 $[M+H]^+$, found: 276.1389.

4.4.17 1-(3-(4-Chlorophenyl)-5-phenyl-1*H*-pyrrol-2-yl)ethanone (46q)

a. General procedure **4a** was followed by employing 7-(4-chlorophenyl)-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine **(37q)** (118.3 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 91.1 mg (77%) of the indicated product **46q** as a yellowish white solid.

b. General procedure **4b** was followed by employing 1-(4-chlorophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one **(26q)** (118.3 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 89.1 mg (75%) of the indicated product **46q** as a yellowish white solid.

(R_f = 0.37 in 4:1 hexane/ethyl acetate); mp 173.0–174.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 7.72–7.67 (m, 2H), 7.45–7.31 (m, 7H), 6.53 (d, J = 3.0 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5 (C=O), 136.9 (C), 134.8 (C), 133.8 (C), 133.1 (C), 131.1 (CH), 130.7 (C), 129.5 (C), 129.1 (CH), 128.6 (CH), 128.4 (CH), 125.3 (CH), 110.8 (CH), 27.7 (CH_3); IR (neat): 3282, 3227, 1623, 1488, 1460, 1433, 1396, 1359, 1289, 1267, 1086, 1016, 994, 953, 914, 837, 809, 759, 688, 671, 632, 610 cm^{-1}; MS (ESI, m/z): 296.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{15}ClNO$: 296.0837 $[M+H]^+$, found: 296.0842.

4.4.18 1-(5-(Thiophen-3-yl)-3-(*p*-tolyl)-1*H*-pyrrol-2-yl)ethanone (46r)

a. General procedure **4a** was followed by employing 2-methylene-5-(thiophen-3-yl)-7-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (**37r**) (112.5 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 93.2 mg (83%) of the indicated product **46r** as a yellow solid.

b. General procedure **4b** was followed by employing 3-(prop-2-yn-1-ylamino)-3-(thiophen-3-yl)-1-(*p*-tolyl)prop-2-en-1-one (**26r**) (112.5 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 75.3 mg (67%) of the indicated product **46r** as a yellow solid.

(R_f = 0.37 in 4:1 hexane/ethyl acetate); mp 167.0–169.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 7.76–7.72 (m, 1H), 7.46 (dd, J = 5.0, 0.8 Hz, 1H), 7.39–7.32 (m, 3H), 7.27 (d, J = 7.9 Hz, 2H), 6.46 (d, J = 2.8 Hz, 1H), 2.45 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (C=O), 137.5 (C), 134.8 (C), 133.3 (C), 133.0 (C), 132.7 (CH), 129.7 (C), 129.1 (CH), 128.9 (C), 126.6 (CH), 125.7 (CH), 120.8 (CH), 111.1 (CH), 27.6 (CH_3), 21.4 (CH_3); IR (neat): 3286, 3100, 2917, 1667, 1573, 1486, 1369, 1277, 1178, 1132, 1058, 1016, 768, 653 cm^{-1}; MS (ESI, m/z): 282.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{16}NOS$: 282.0947 $[M+H]^+$, found: 282.0956.

4.4.19 1-(5-(3,4-Dichlorophenyl)-3-(*p*-tolyl)-1*H*-pyrrol-2-yl)ethanone (46s)

a. General procedure **4a** was followed by employing 5-(3,4-dichlorophenyl)-2-methylene-7-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (**37s**) (137.7 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 95.0 mg (69%) of the indicated product **46s** as a white solid.

b. General procedure **4b** was followed by employing 3-(3,4-dichlorophenyl)-3-(prop-2-yn-1-ylamino)-1-(*p*-tolyl)prop-2-en-1-one (**26s**) (137.7 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 85.4 mg (62%) of the indicated product **46s** as a white solid.

(R_f = 0.50 in 4:1 hexane/ethyl acetate); mp 224.0–226.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.76 (d, *J* = 1.8 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.20 (dd, *J* = 22.6, 8.3 Hz, 4H), 6.46 (d, *J* = 3.0 Hz, 1H), 2.35 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3 (C=O), 137.8 (C), 134.8 (C), 134.2 (C), 133.4 (C), 132.9 (C), 132.1 (C), 131.14 (C), 131.06 (CH), 130.2 (C), 129.7 (CH), 129.2 (CH), 127.1 (CH), 124.5 (CH), 111.8 (CH), 27.8 (CH_3), 21.4 (CH_3); IR (neat): 3271, 1617, 1485, 1442, 1417, 1359, 1281, 1180, 1134, 1107, 1027, 993, 954, 870, 814, 758, 697, 655 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: 344.0601.

4.4.20 1-(5-(4-Chlorophenyl)-3-(*p*-tolyl)-1*H*-pyrrol-2-yl)ethanone (46t)

a. General procedure **4a** was followed by employing 5-(4-chlorophenyl)-2-methylene-7-(*p*-tolyl)-2,3-dihydro-1,4-oxazepine (**37t**) (123.9 mg, 0.4 mmol) and $ZnCl_2$ (54.5 mg, 0.4 mmol), which yielded 78.1 mg (63%) of the indicated product **46t** as a white solid.

b. General procedure **4b** was followed by employing 3-(4-chlorophenyl)-1-(*p*-tolyl)prop-2-yn-1-one (**26t**) (123.9 mg, 0.4 mmol) and $ZnCl_2$ (109.0 mg, 0.8 mmol), which yielded 90.1 mg (73%) of the indicated product **46s** as a white solid.

(R_f = 0.58 in 4:1 hexane/ethyl acetate); mp 199.1–201.0 °C. ^{1}H NMR (400 MHz, CDCl3) δ 10.13 (s, 1H), 7.56–7.52 (m, 2H), 7.30–7.26 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.42 (d, *J* = 3.0 Hz, 1H), 2.33 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C=O), 137.7 (C), 135.5 (C), 134.8 (C), 134.0 (C), 133.1 (C), 129.8 (C), 129.7 (CH), 129.5 (C), 129.3 (CH), 129.1 (CH), 126.5 (CH), 111.2 (CH), 27.7 (CH_3), 21.4 (CH_3); IR (neat): 3290, 1631, 1493, 1443, 1356, 1284, 1260, 1181, 1087, 1011, 955, 831, 817, 799, 729, 656 cm^{-1}; MS (ESI, m/z): 310.10 [M+H]+; HRMS (ESI) calcd. for $C_{19}H_{17}ClNO$: 310.0993 [M+H]+, found: 310.1001.

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APPENDICES

NMR SPECTRA

^{1}H and ^{13}C NMR spectra were recorded in 400 and 100 MHz, respectively. Bruker Spectrospin Avance DPX400 Ultrashield spectrometer was used for recording ^{1}H and ^{13}C NMR spectra .

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

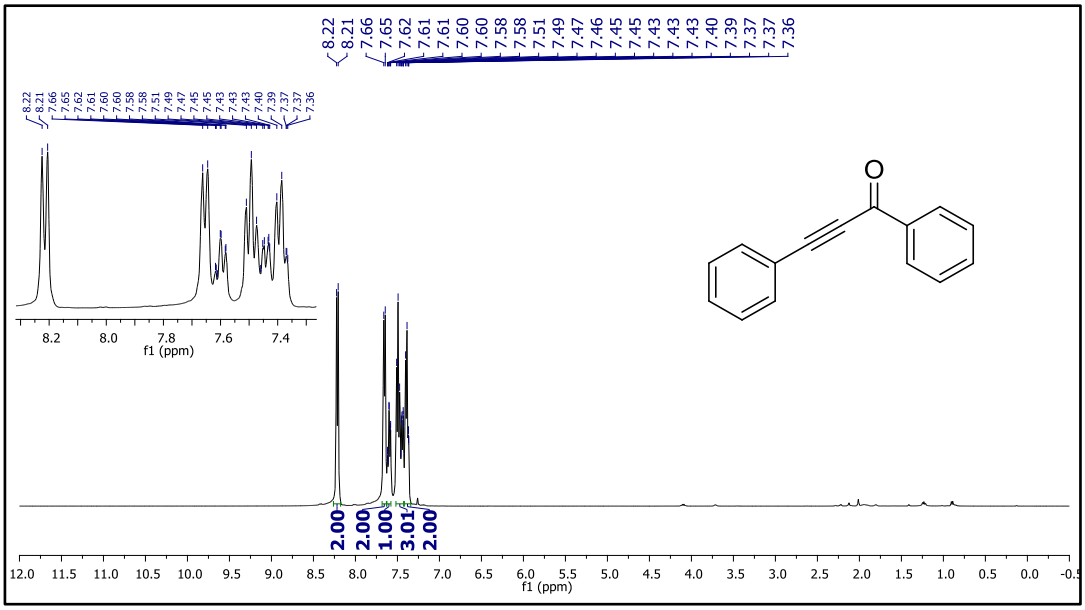

Figure 19. ^{1}H NMR spectrum of compound **49a**.

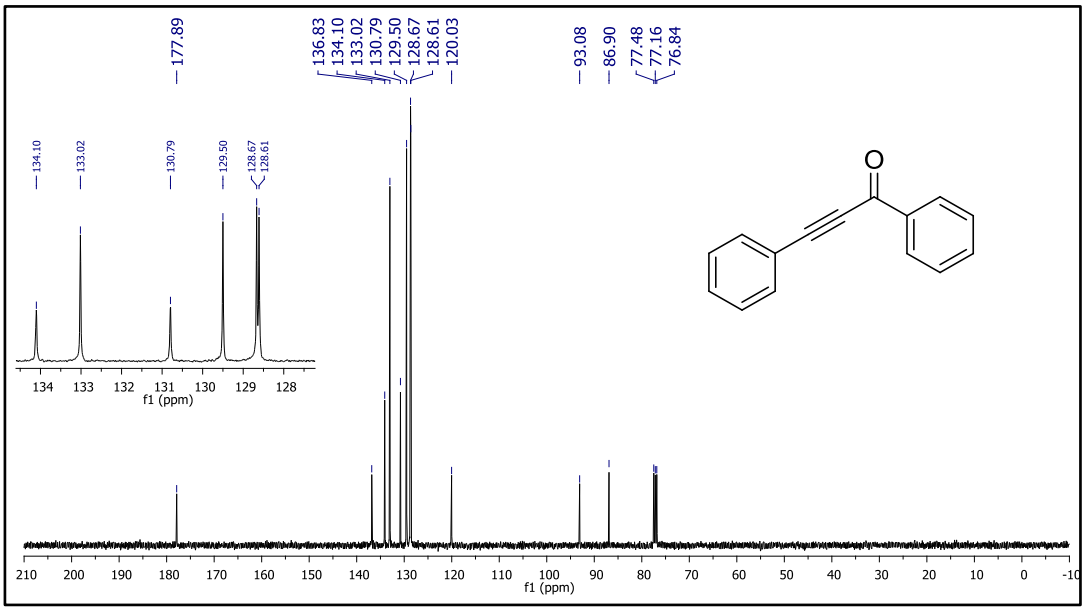

Figure 20. ^{13}C NMR spectrum of compound **49a**.

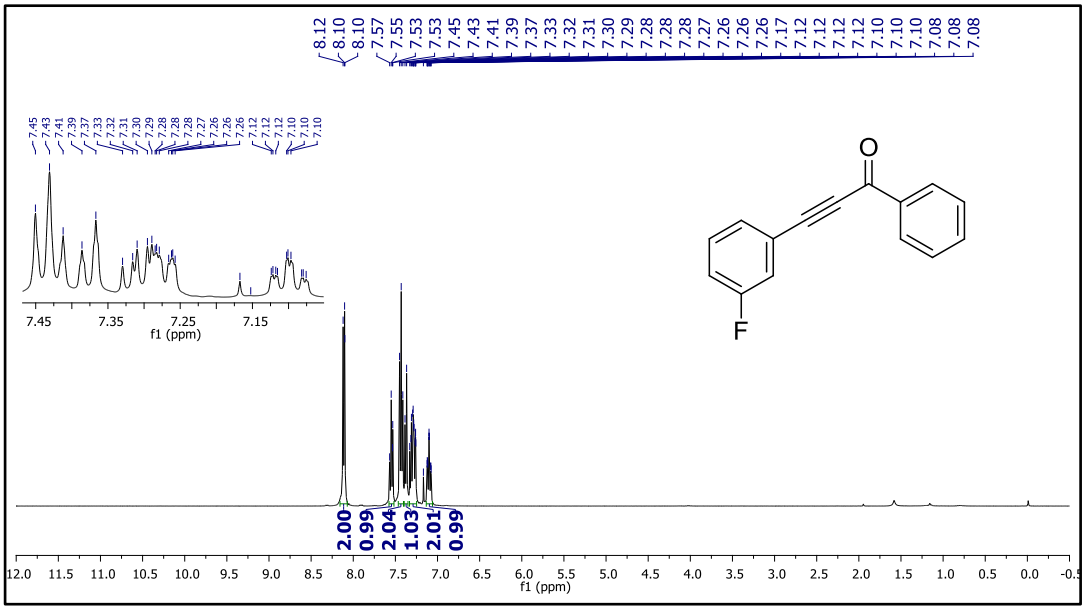

Figure 21. ^{1}H NMR spectrum of compound **49b**.

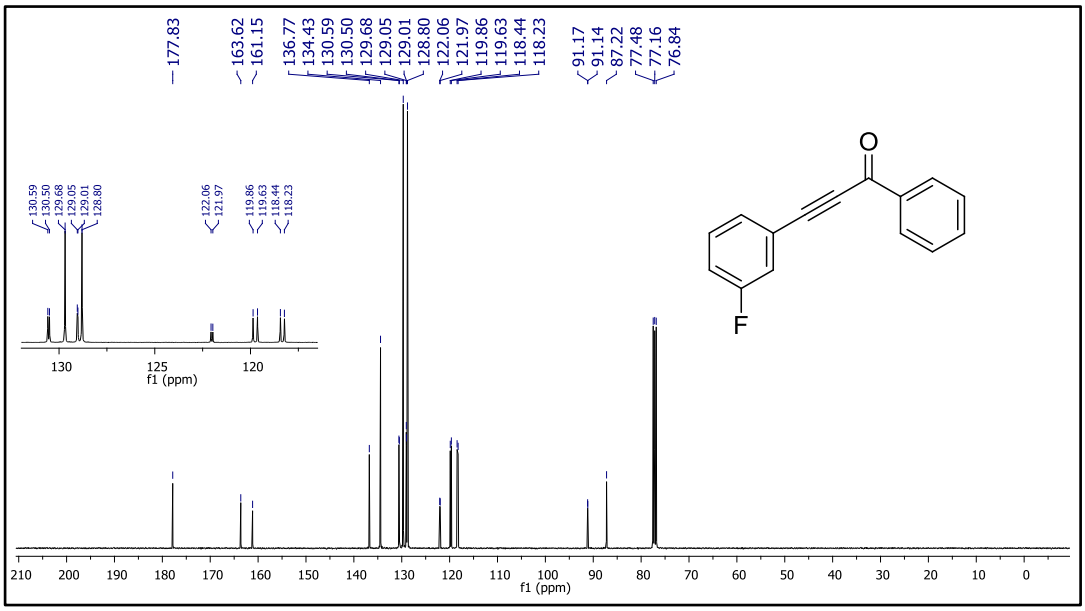

Figure 22. ^{13}C NMR spectrum of compound **49b**.

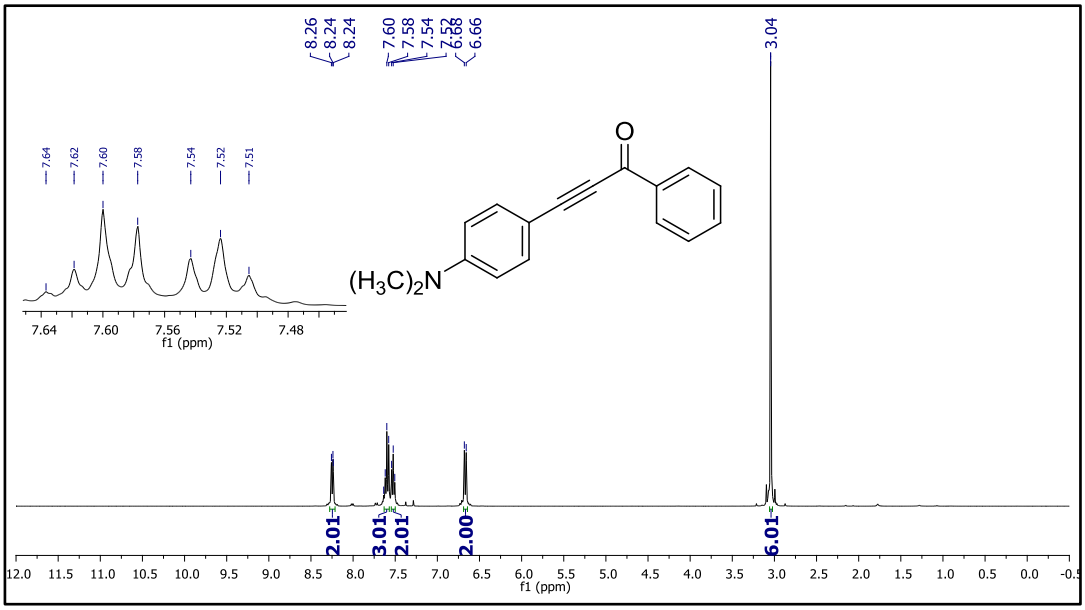

Figure 23. ^{1}H NMR spectrum of compound **49c**.

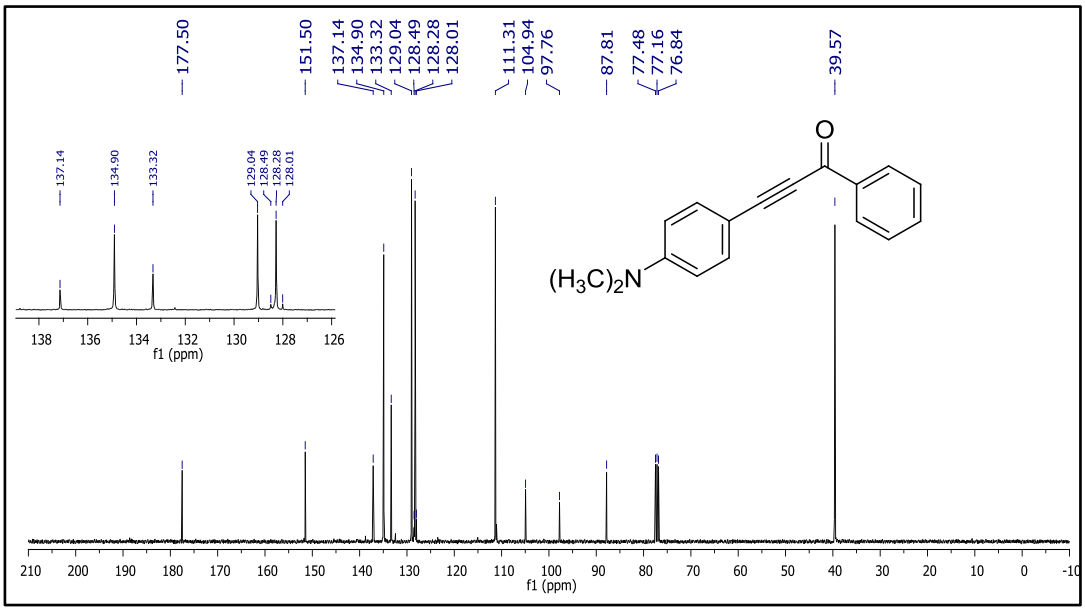

Figure 24. ^{13}C NMR spectrum of compound **49c**.

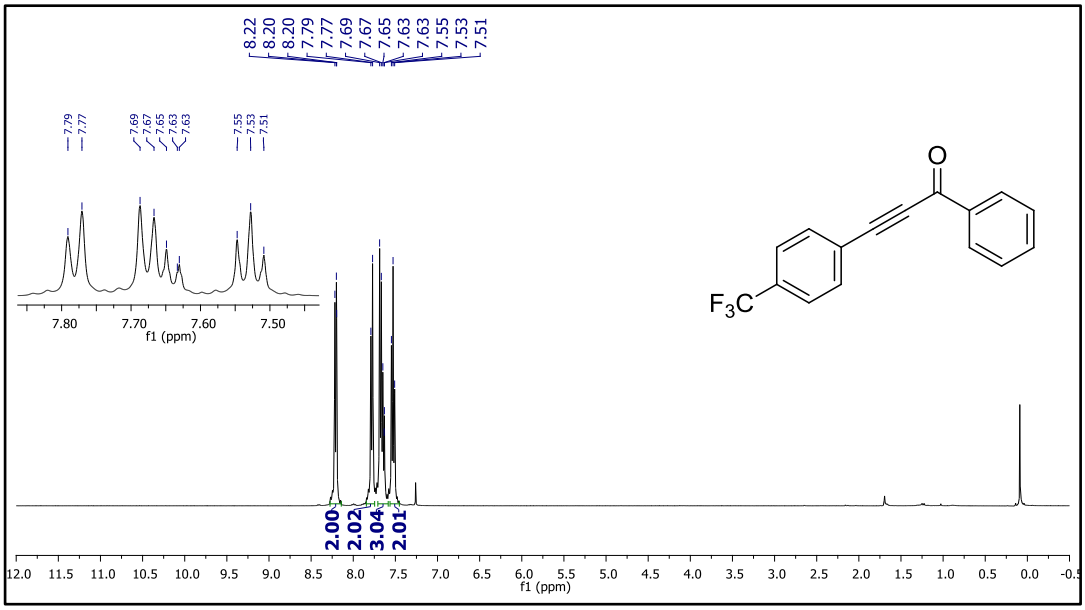

Figure 25. ^{1}H NMR spectrum of compound **49d**.

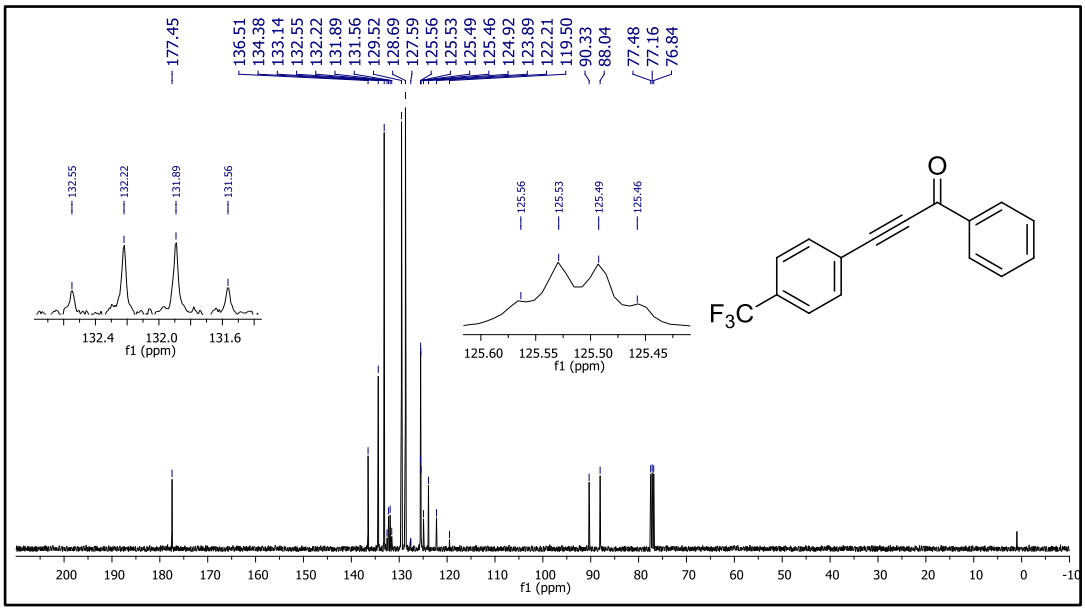

Figure 26. ^{13}C NMR spectrum of compound **49d**.

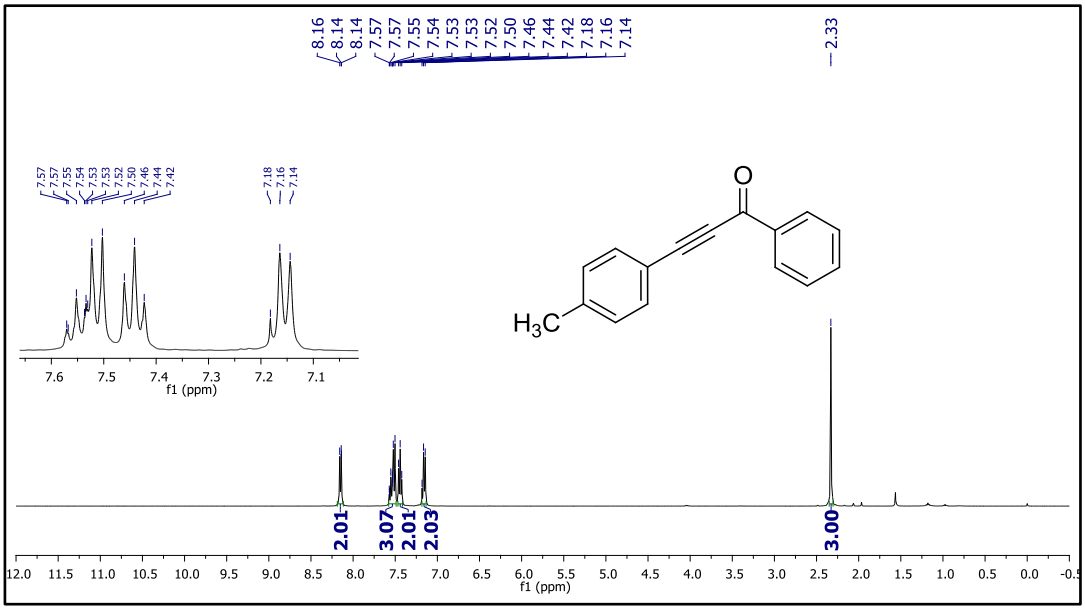

Figure 27. ^{1}H NMR spectrum of compound **49e**.

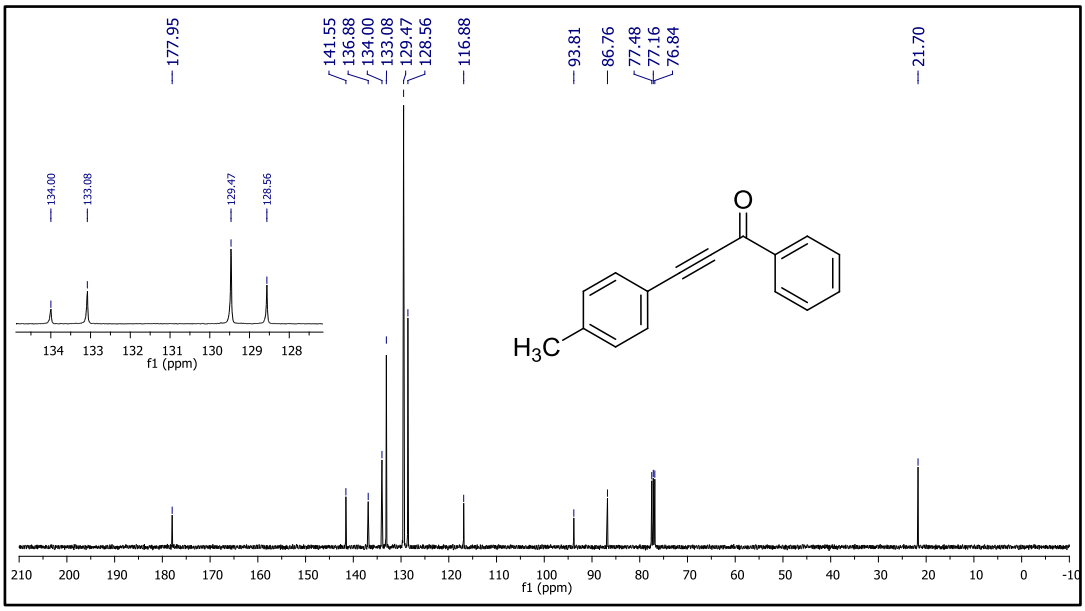

Figure 28. ^{13}C NMR spectrum of compound **49e**.

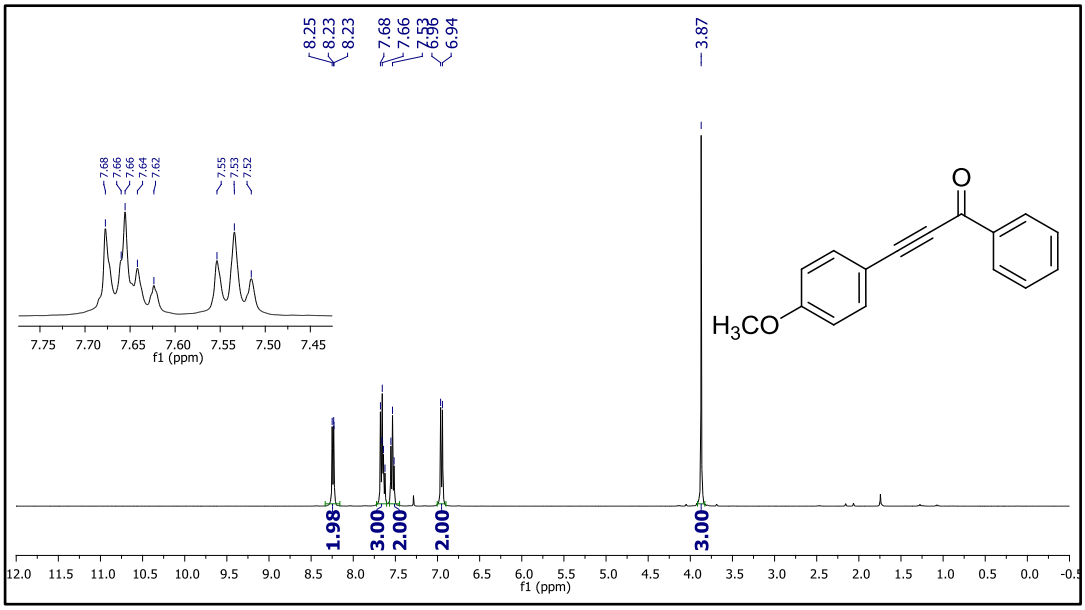

Figure 29. ^{1}H NMR spectrum of compound **49f**.

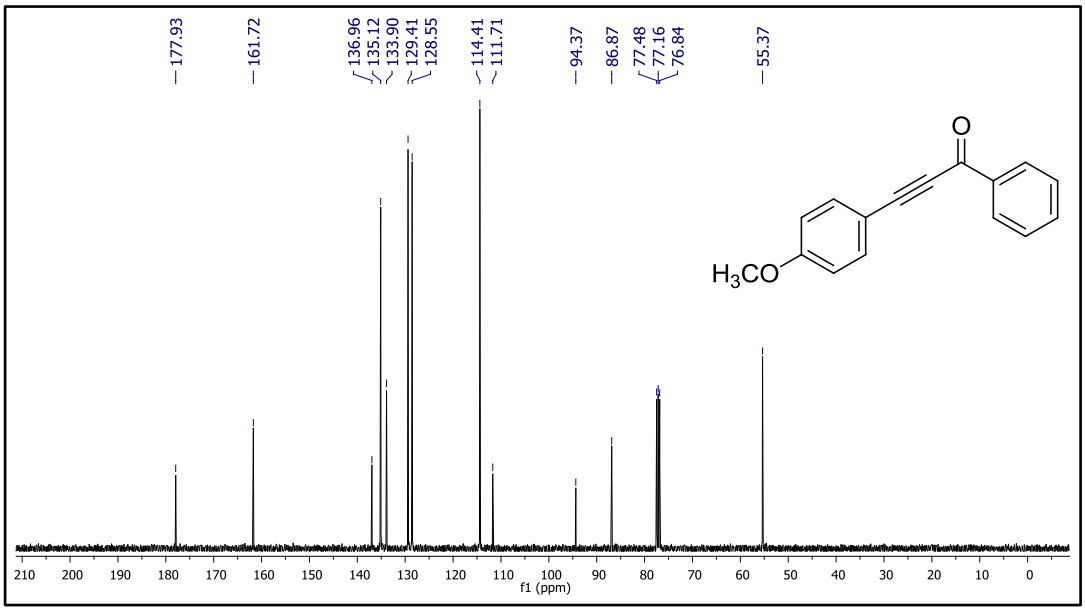

Figure 30. ^{13}C NMR spectrum of compound **49f**.

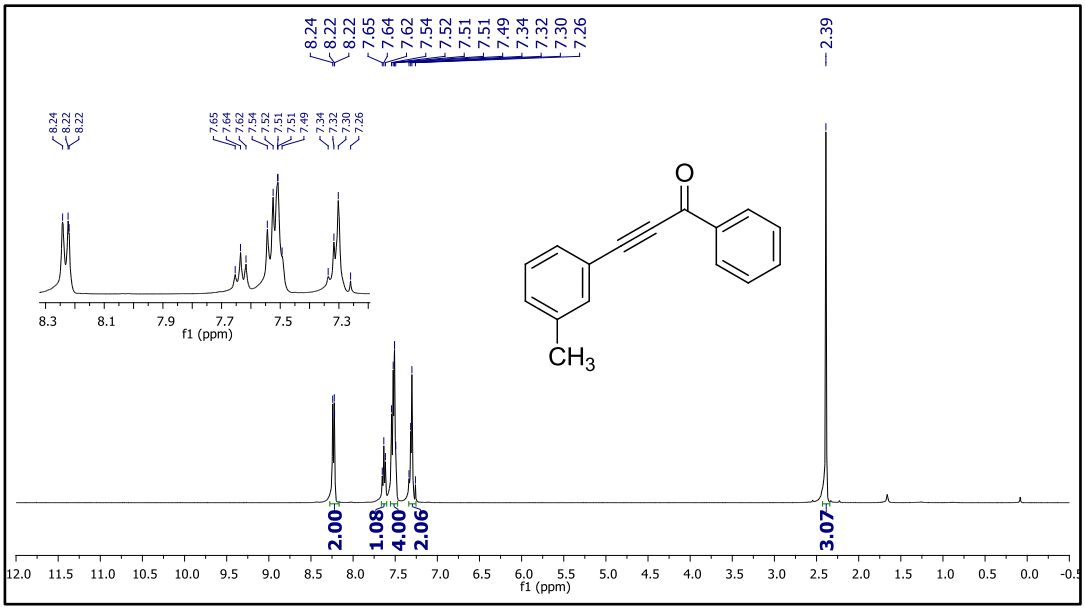

Figure 31. ^{1}H NMR spectrum of compound **49g**.

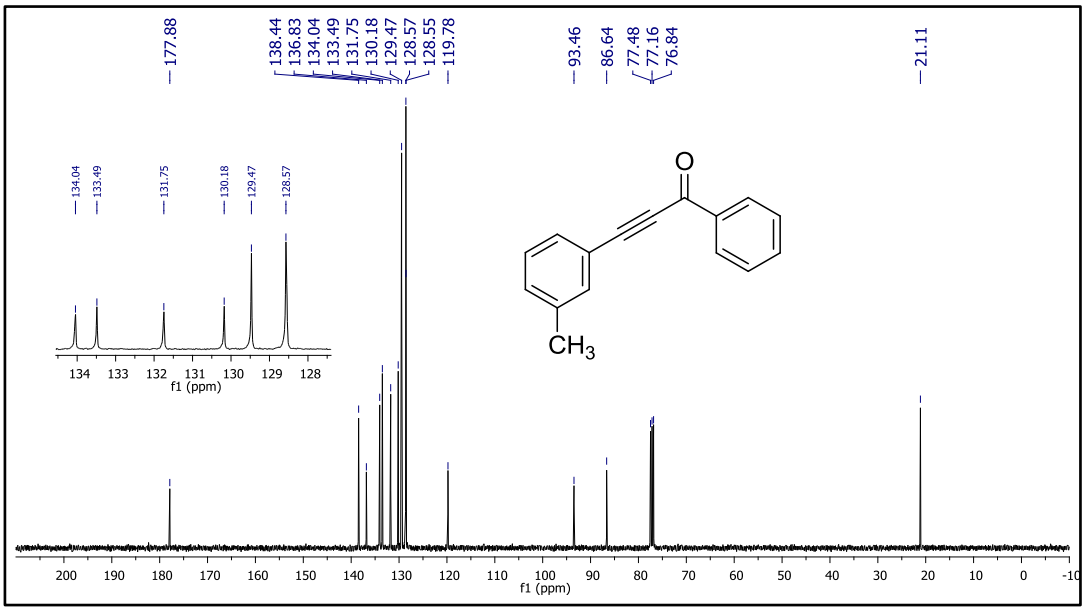

Figure 32. ^{1}H NMR spectrum of compound **49g**.

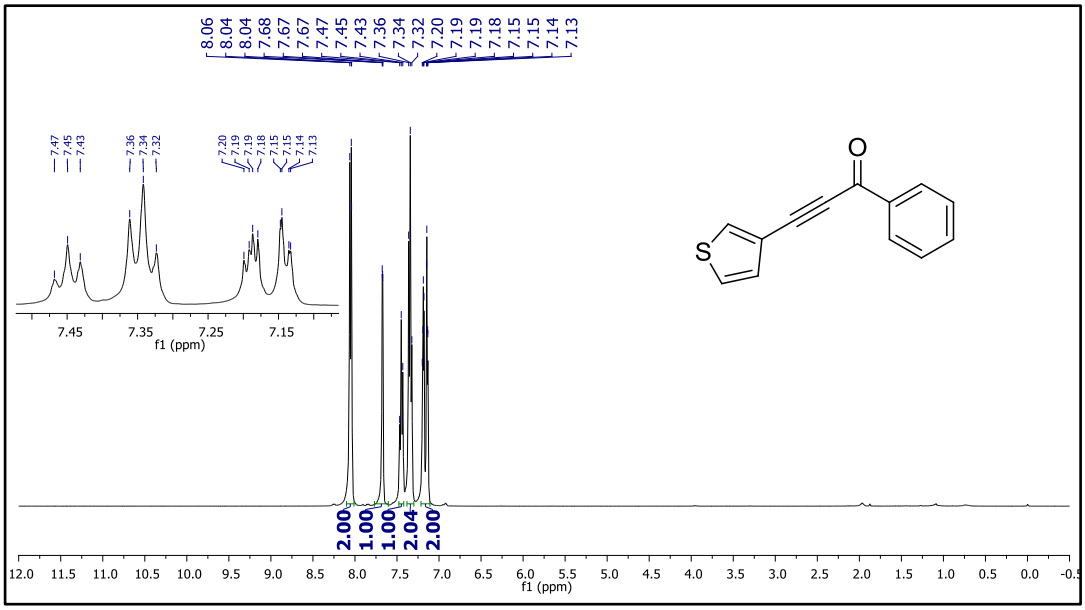

Figure 33. ^{1}H NMR spectrum of compound **49h**.

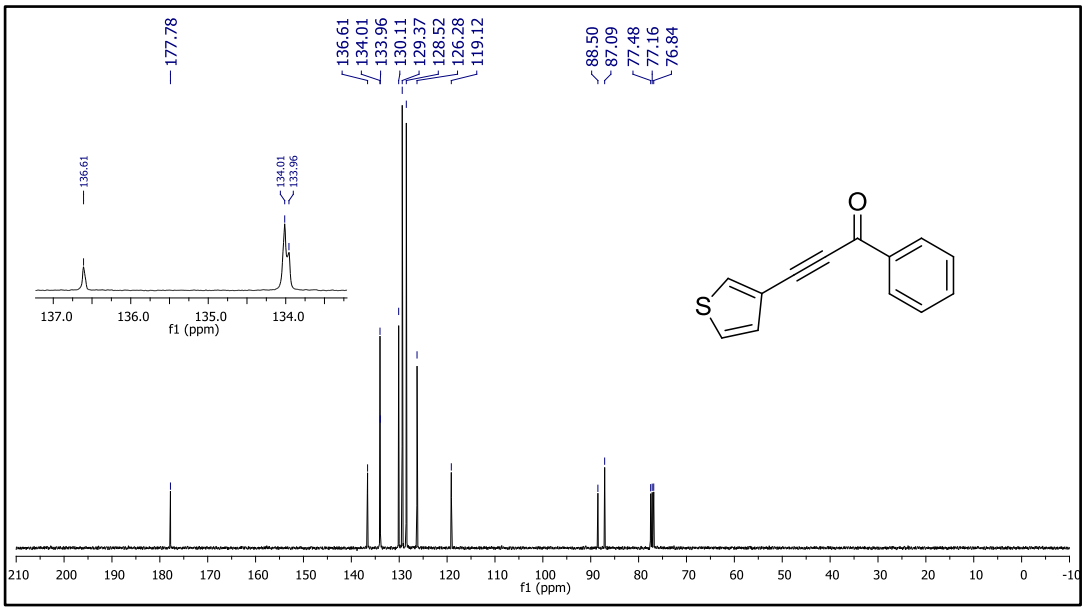

Figure 34. ^{13}C NMR spectrum of compound **49h**.

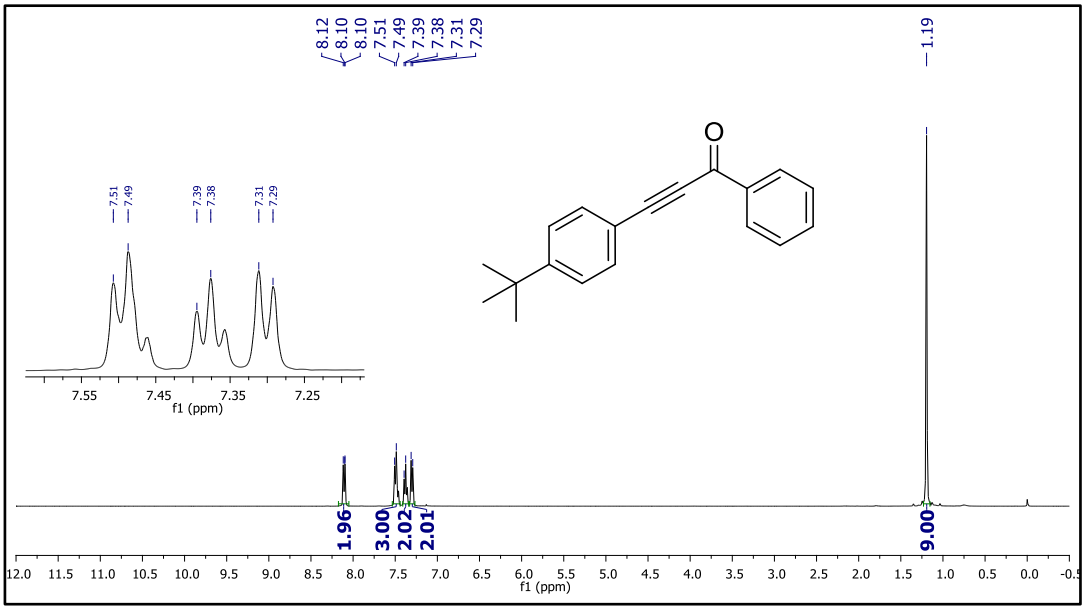

Figure 35. ^{1}H NMR spectrum of compound **49i**.

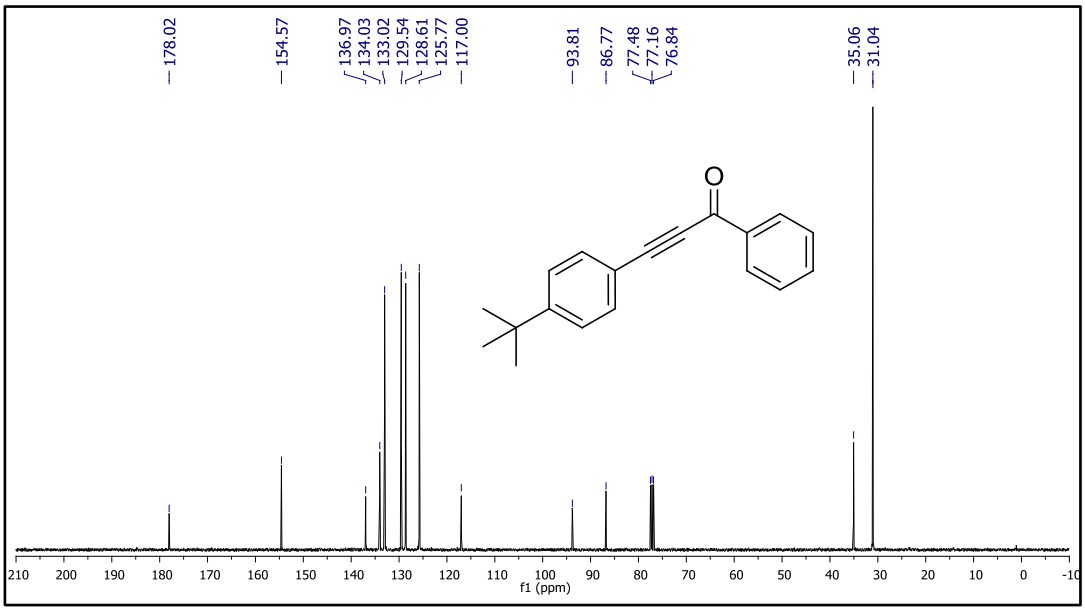

Figure 36. ^{13}C NMR spectrum of compound **49i**.

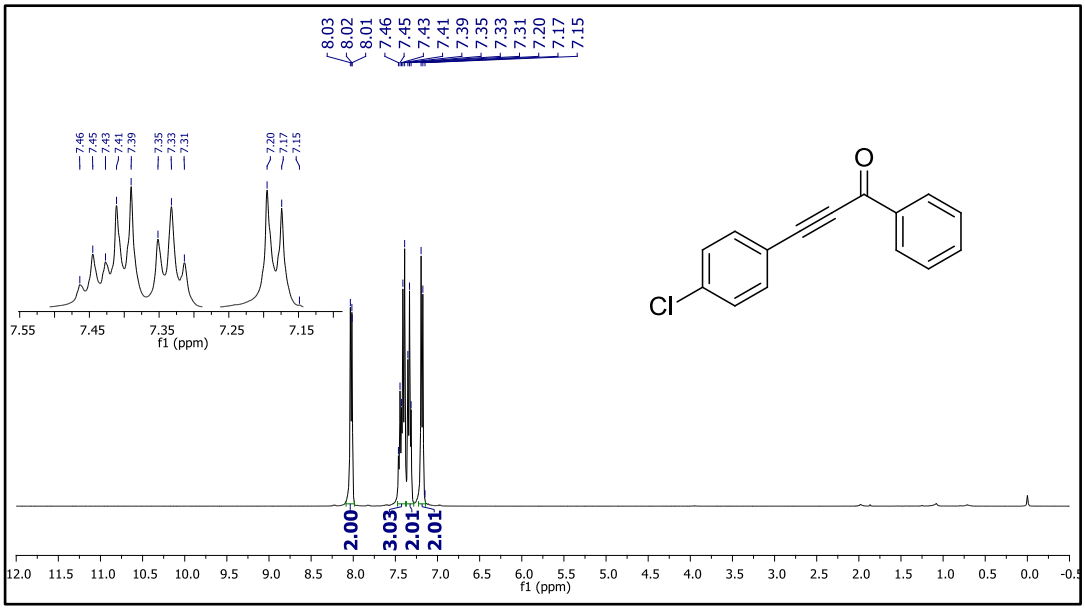

Figure 37. ^{1}HNMR spectrum of compound **49j**.

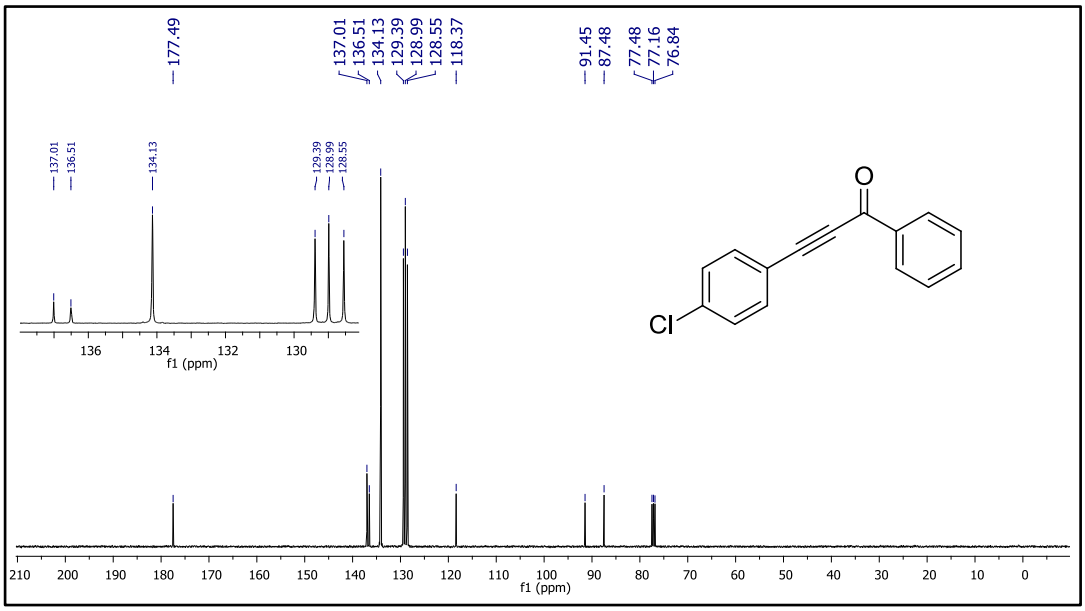

Figure 38. ^{13}C NMR spectrum of compound **49j**.

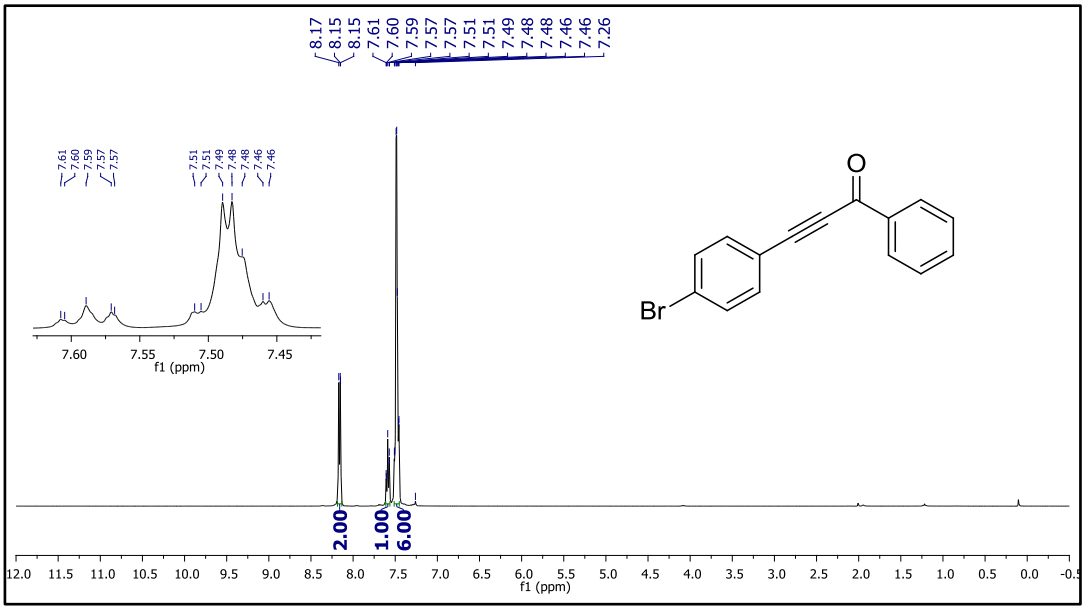

Figure 39. ^{1}H NMR spectrum of compound **49k**.

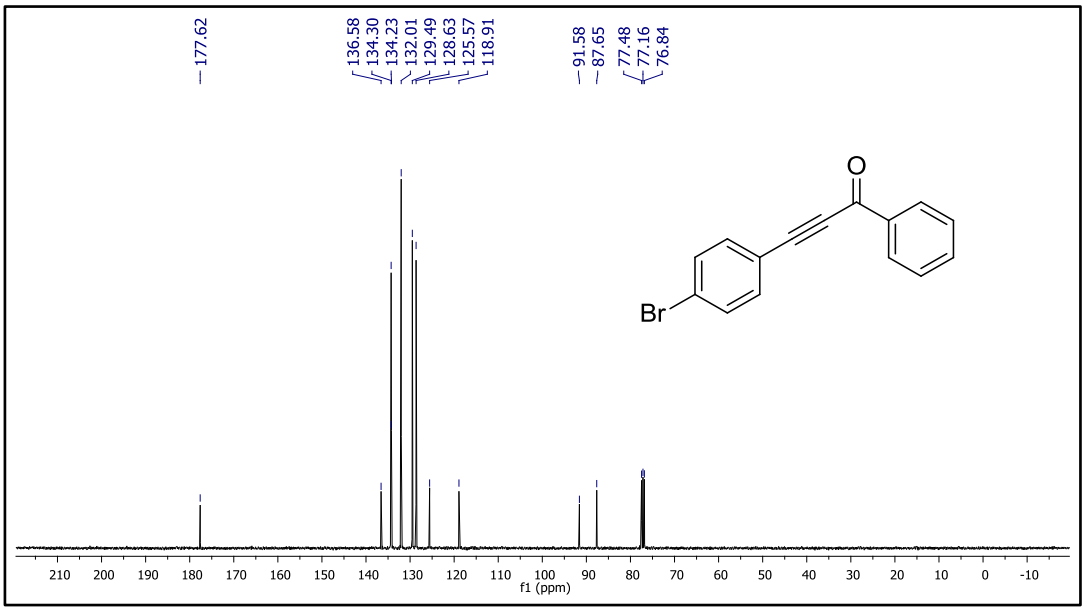

Figure 40. ^{13}C NMR spectrum of compound **49k**.

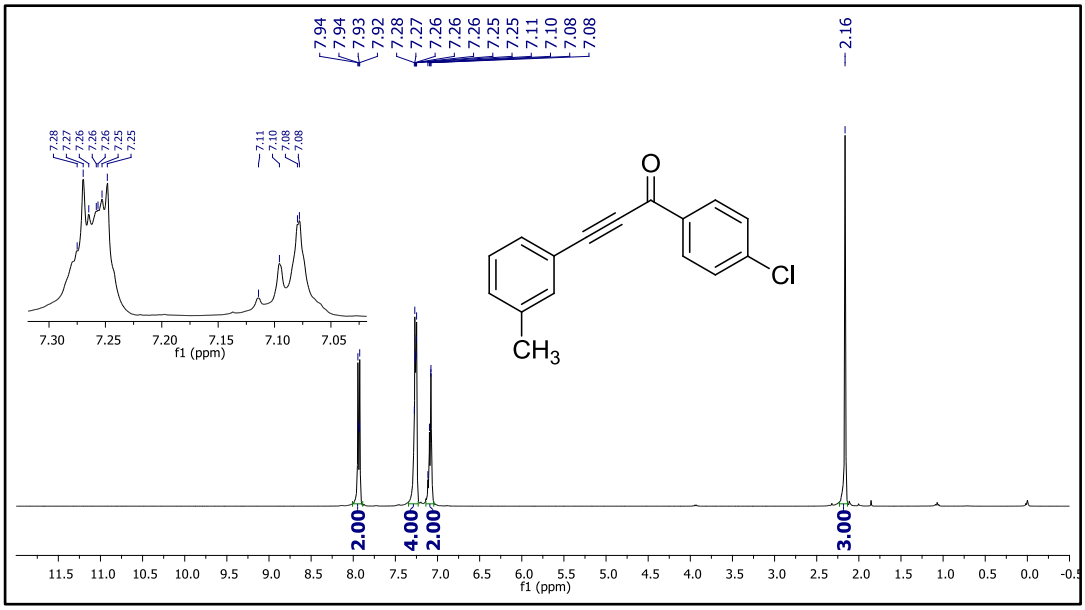

Figure 41. ^{1}H NMR spectrum of compound **49l**.

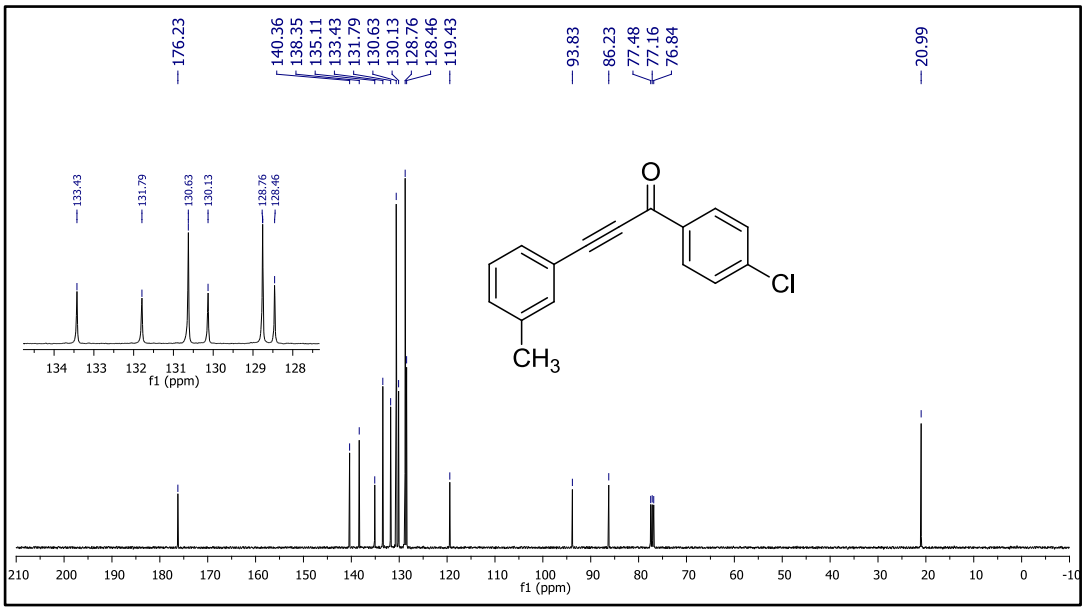

Figure 42. ^{13}C NMR spectrum of compound **49l**.

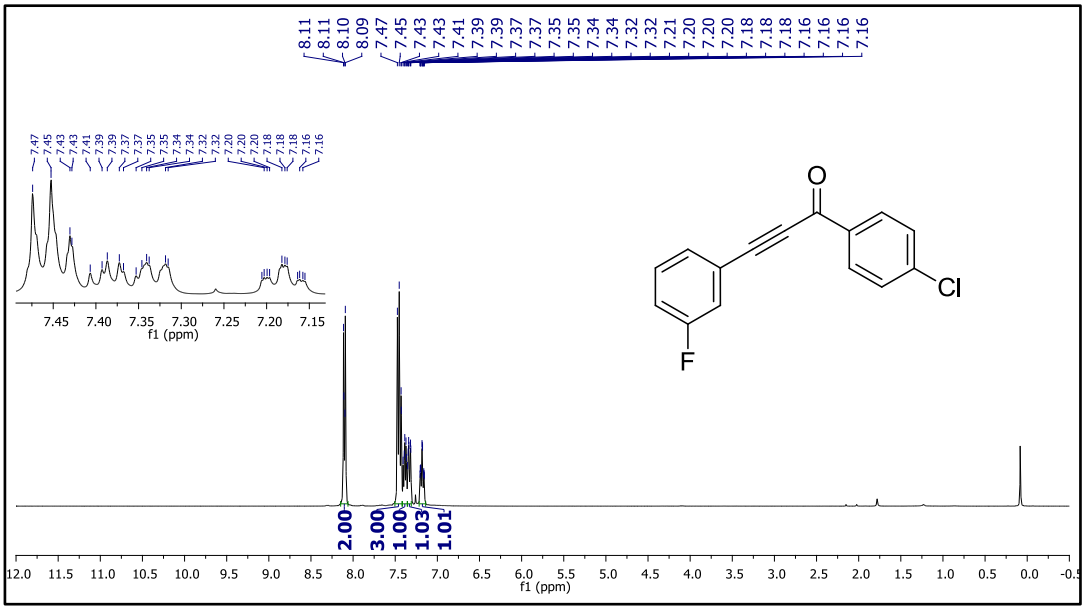

Figure 43. ^{1}H NMR spectrum of compound **49m**.

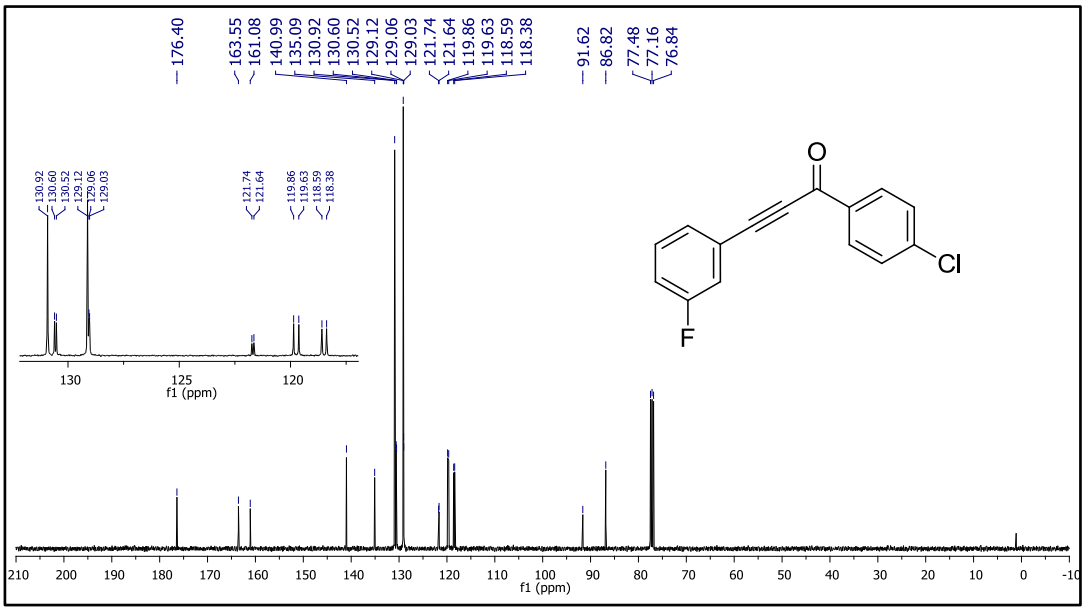

Figure 44. ^{13}C NMR spectrum of compound **49m**.

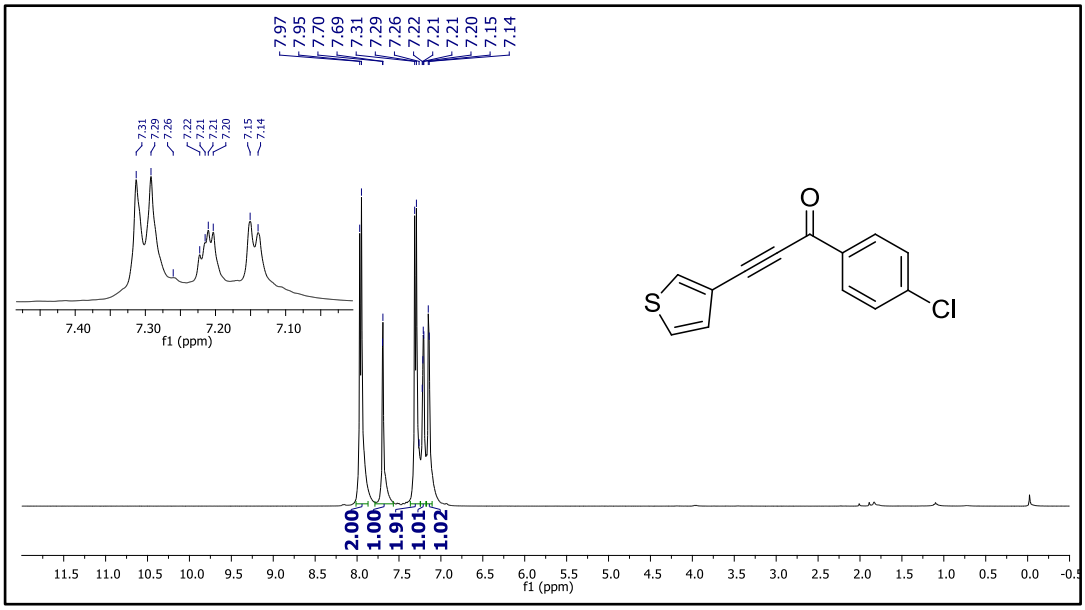

Figure 45. ^{1}H NMR spectrum of compound **49n**.

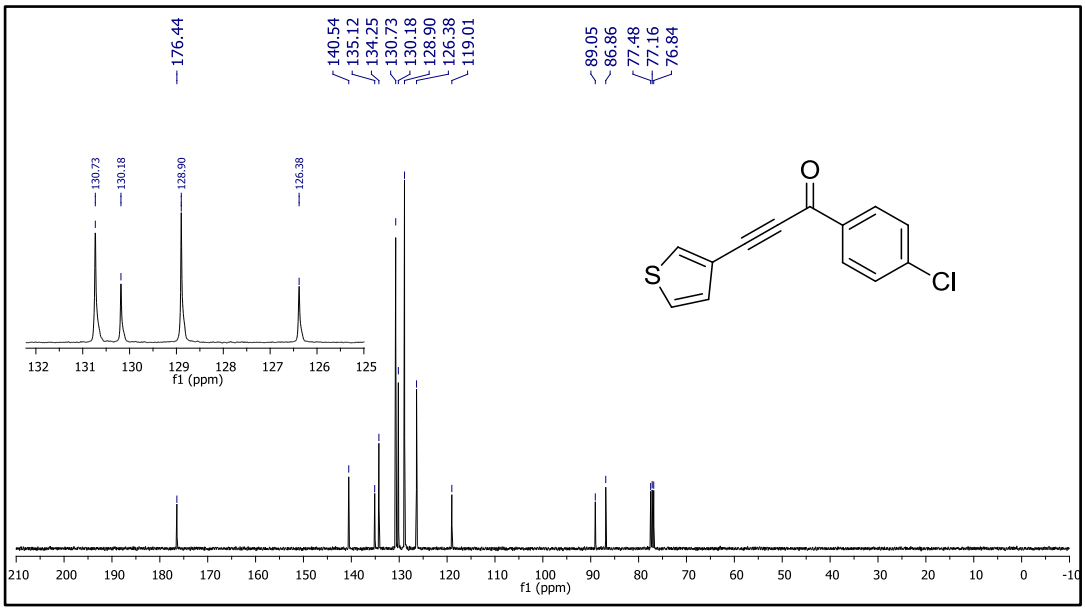

Figure 46. ^{13}C NMR spectrum of compound **49n**.

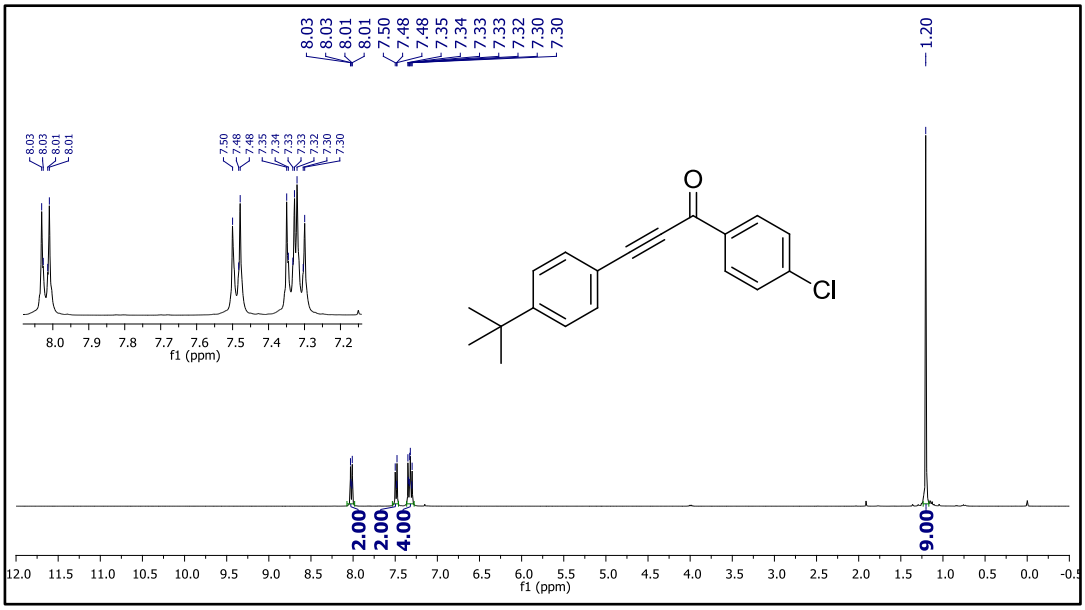

Figure 47. ^{1}H NMR spectrum of compound **49o**.

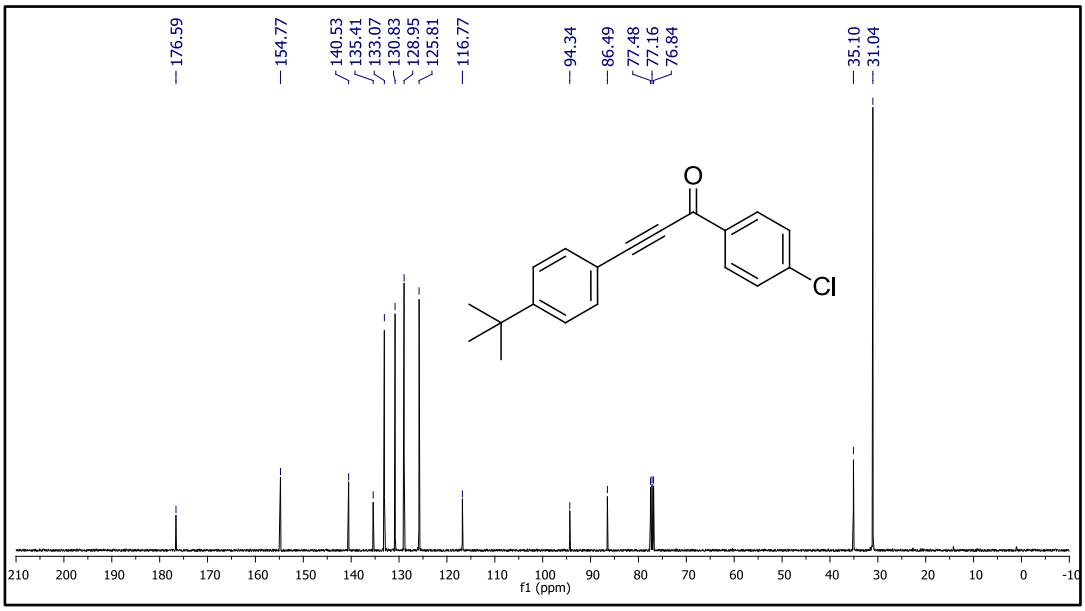

Figure 48. ^{13}C NMR spectrum of compound **49o**.

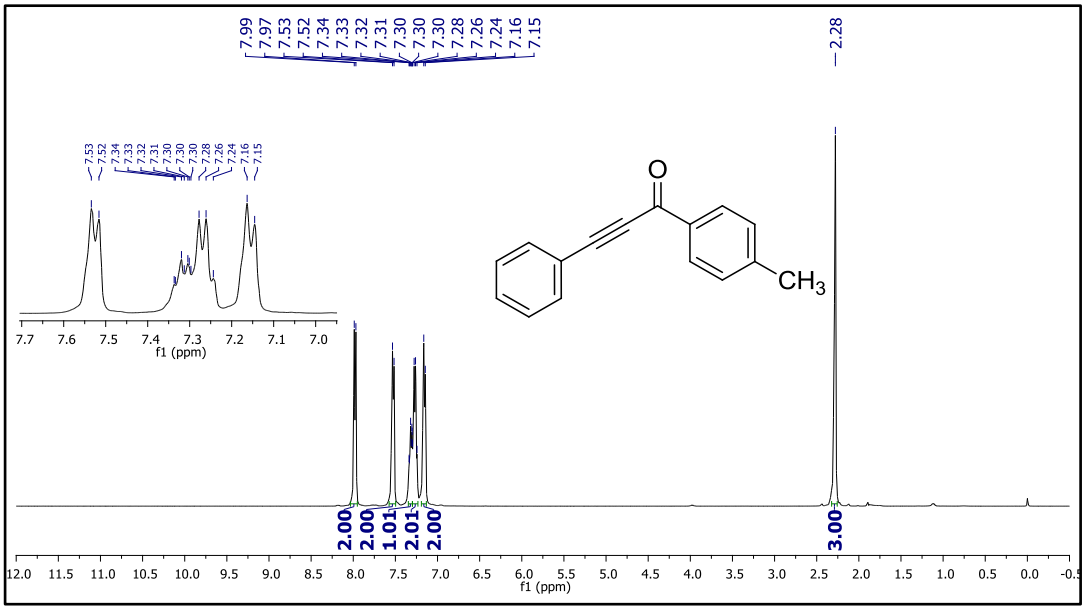

Figure 49. ^{1}H NMR spectrum of compound **49p**.

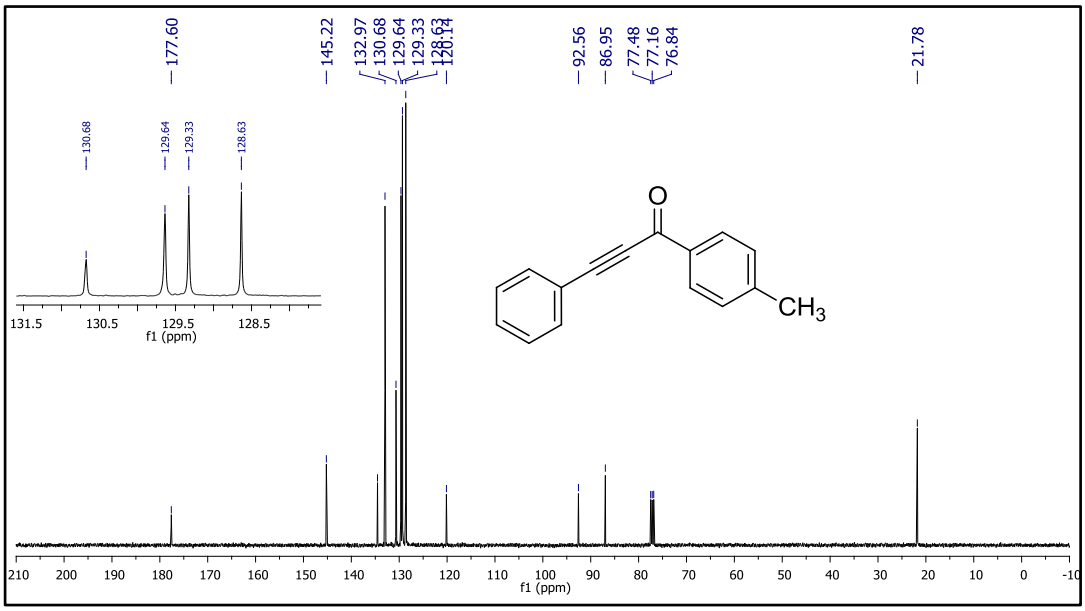

Figure 50. ^{13}C NMR spectrum of compound **49p**.

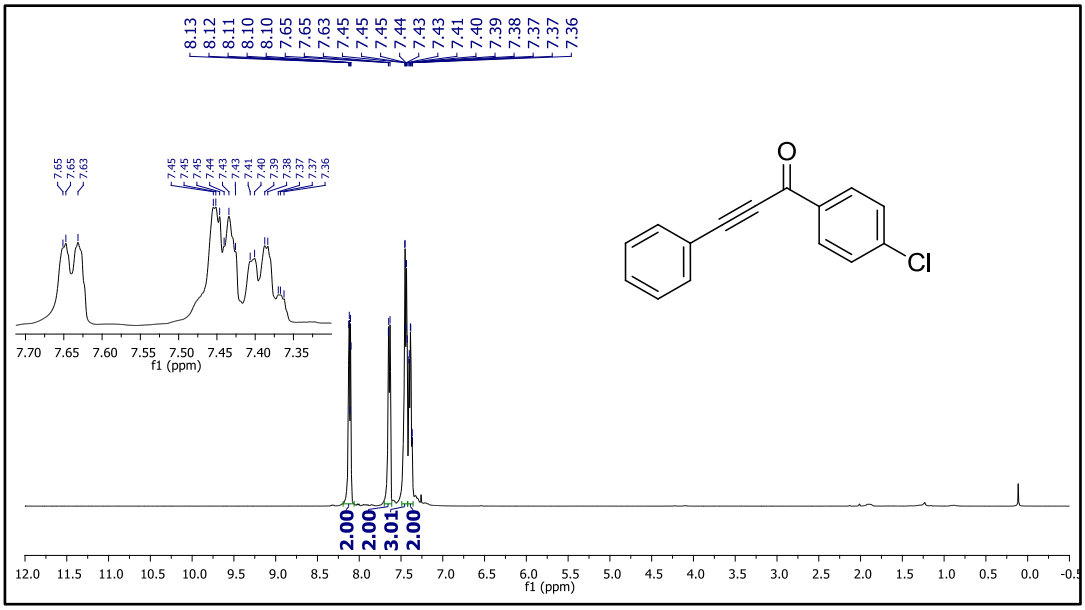

Figure 51. ^{1}H NMR spectrum of compound **49q**.

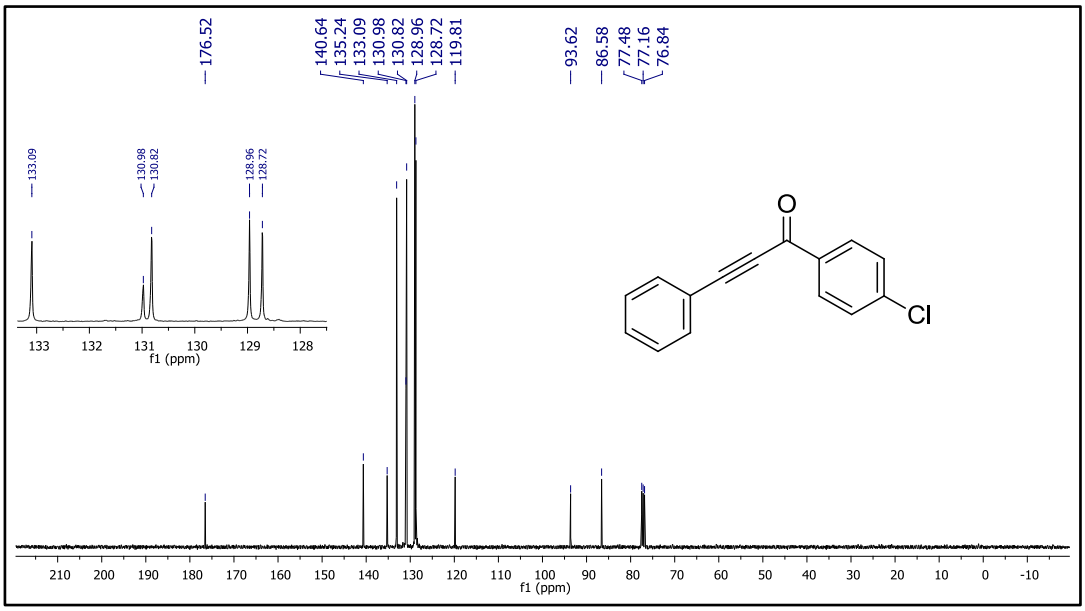

Figure 52. ^{13}C NMR spectrum of compound **49q**.

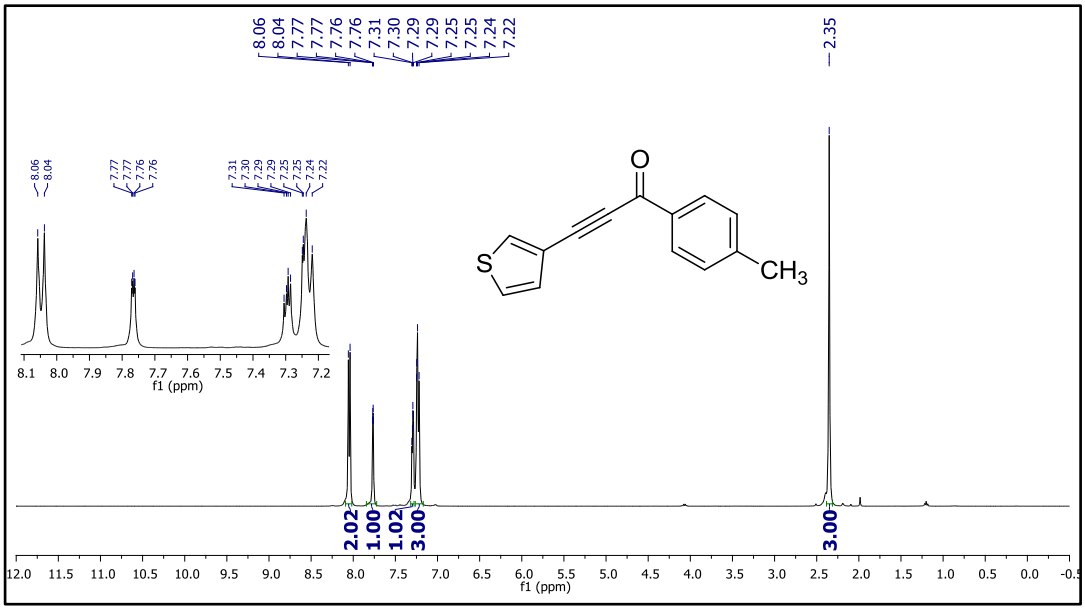

Figure 53. ^{1}H NMR spectrum of compound **49r**.

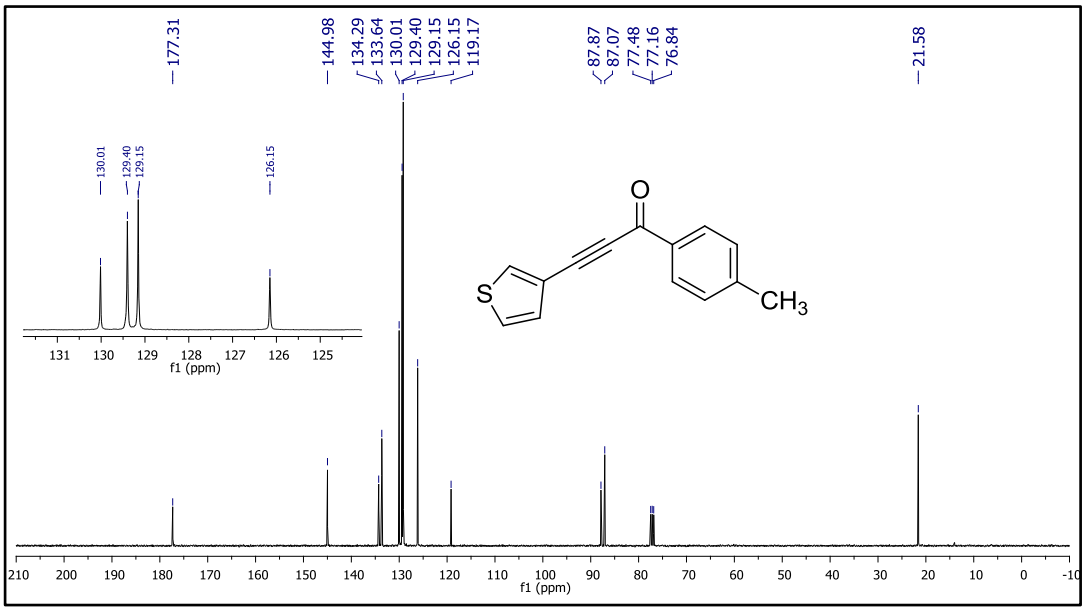

Figure 54. ^{13}C NMR spectrum of compound **49r**.

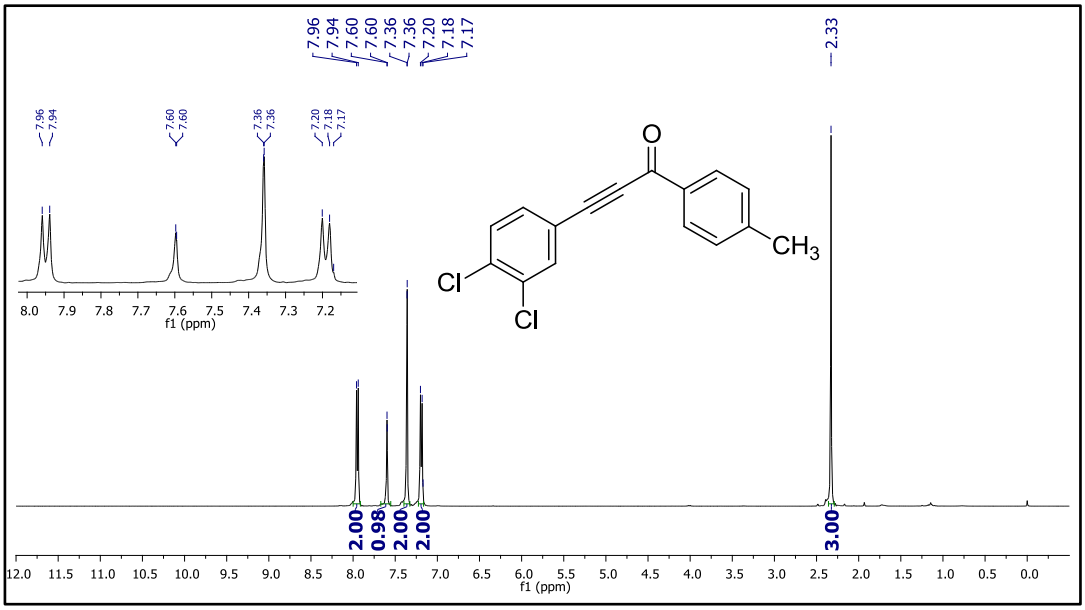

Figure 55. ^{1}H NMR spectrum of compound **49s**.

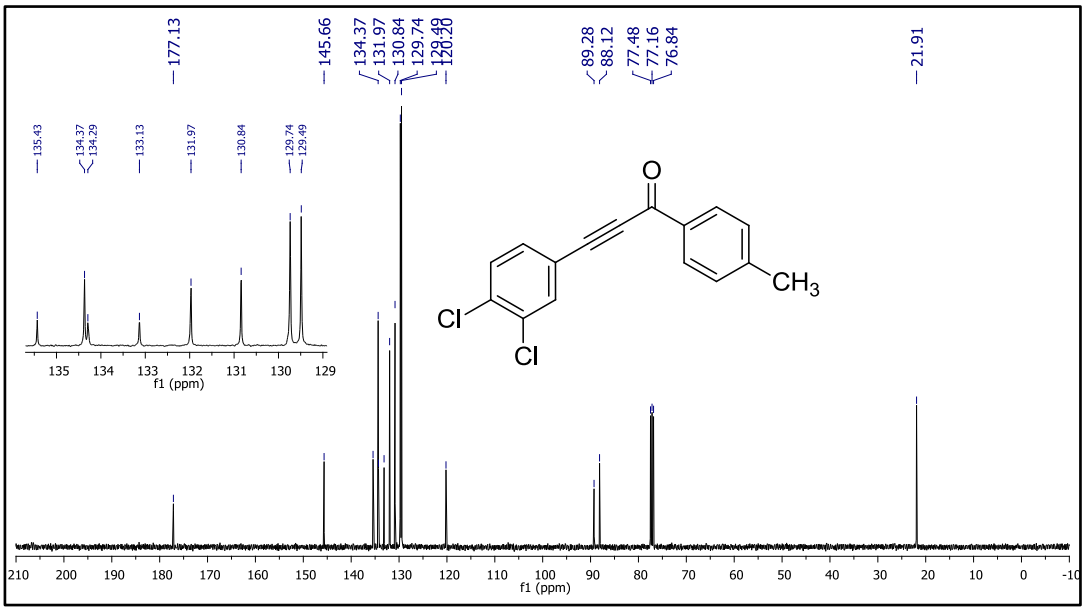

Figure 56. ^{13}C NMR spectrum of compound **49s**.

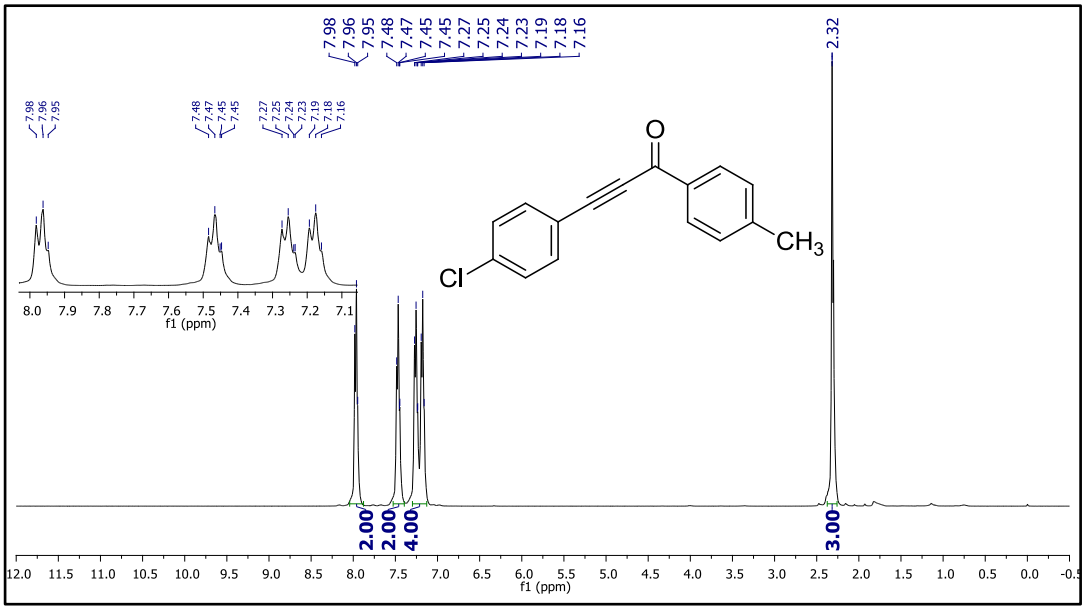

Figure 57. ^{1}H NMR spectrum of compound **49t**.

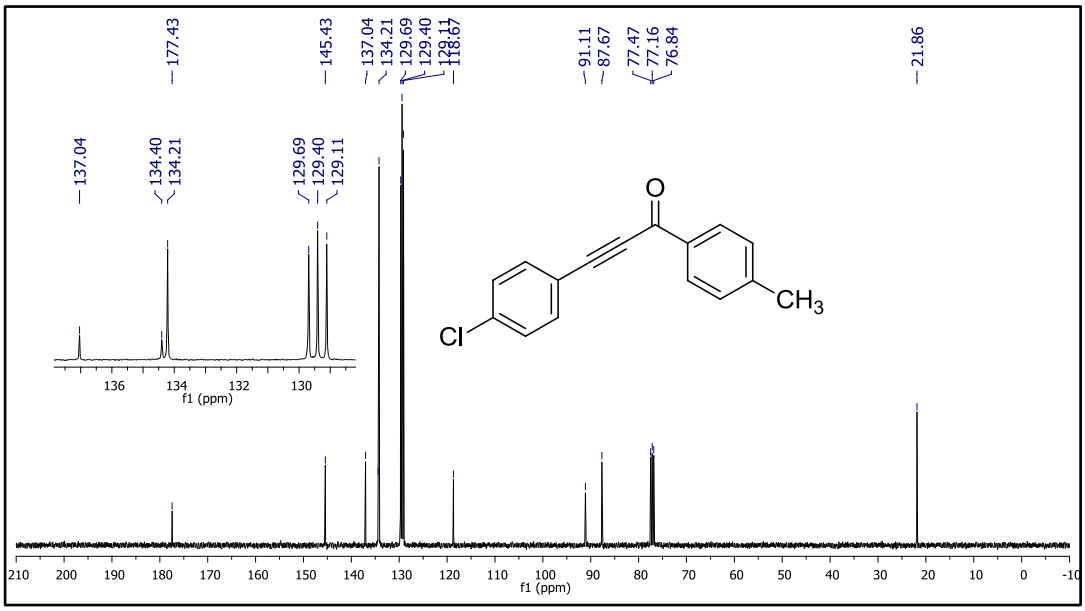

Figure 58. ^{13}C NMR spectrum of compound **49t**.

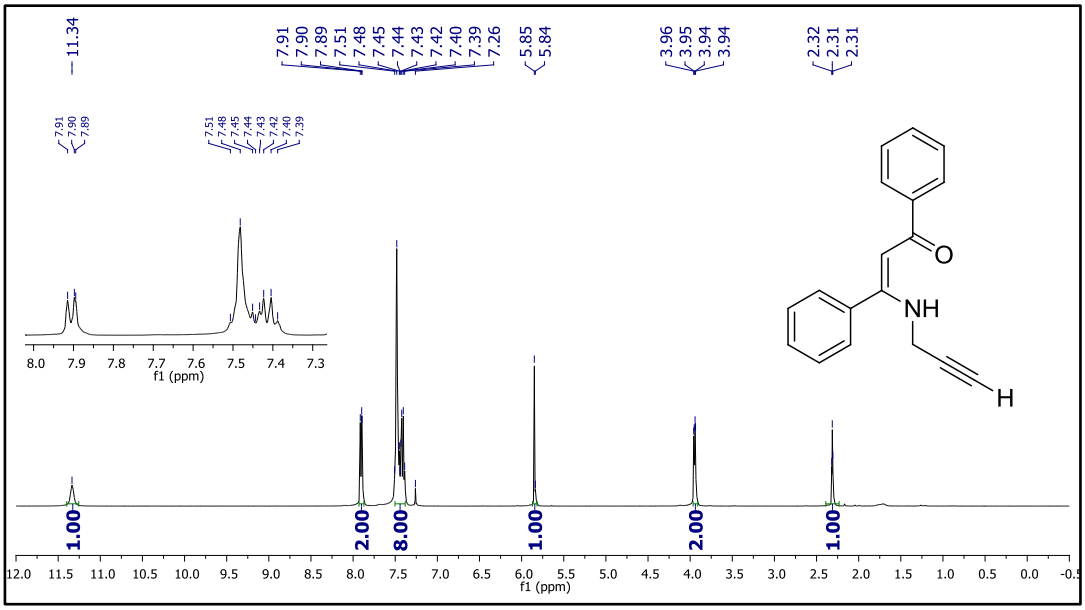

Figure 59. ^{1}H NMR spectrum of compound **26a**.

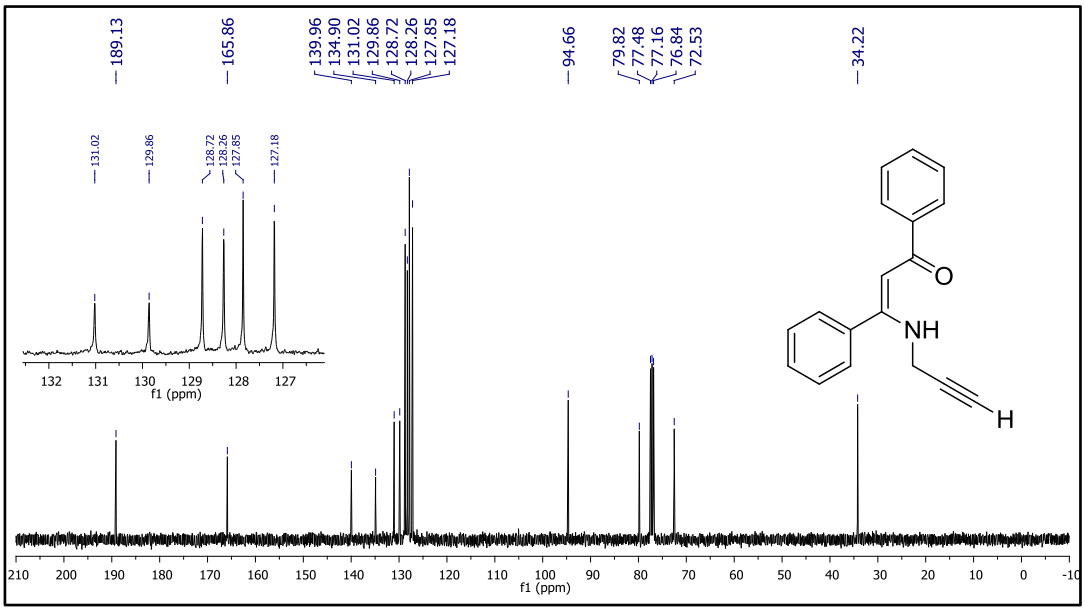

Figure 60. ^{13}C NMR spectrum of compound **26a**.

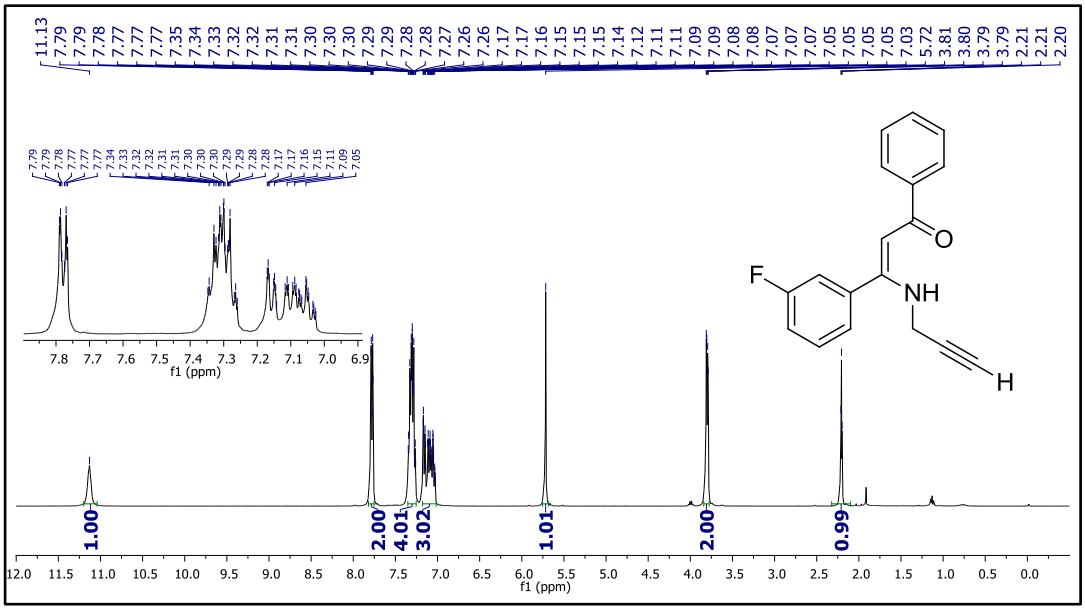

Figure 61. ^{1}H NMR spectrum of compound **26b**.

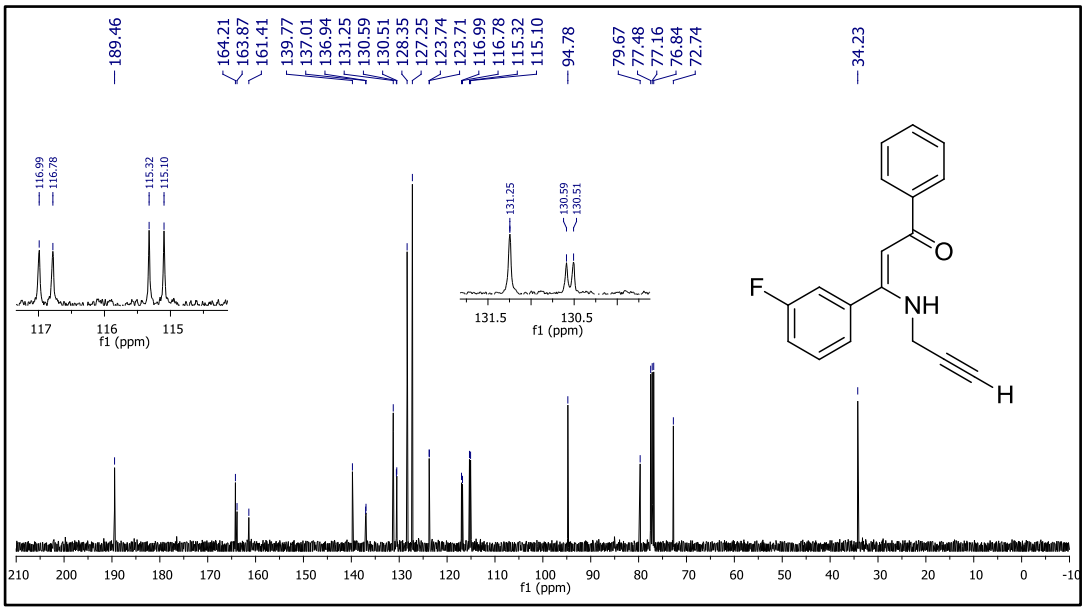

Figure 62. ^{13}C NMR spectrum of compound **26b**.

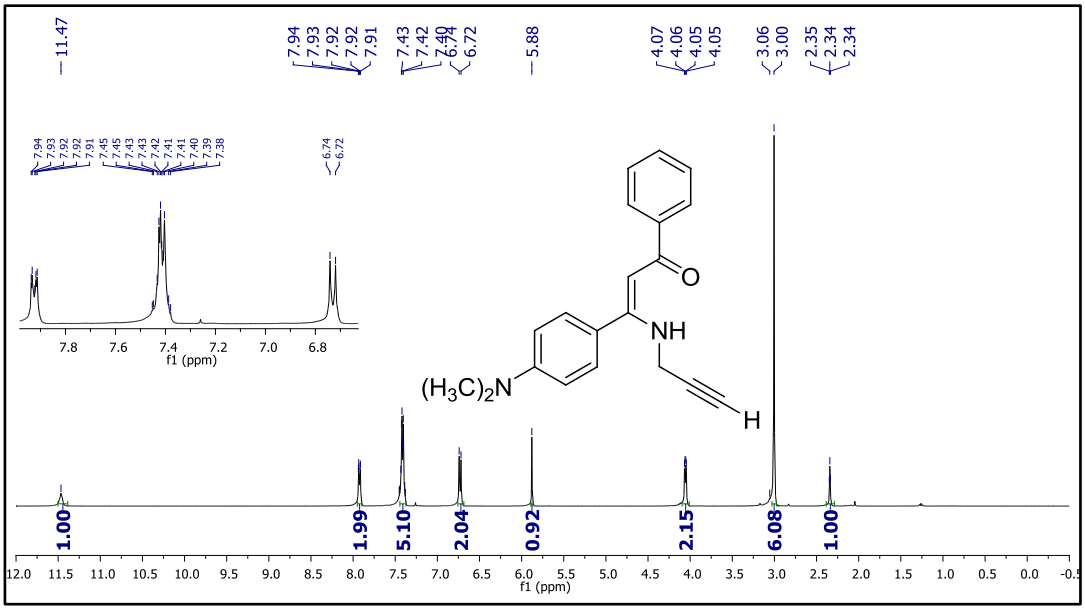

Figure 63. ^{1}H NMR spectrum of compound **26c**.

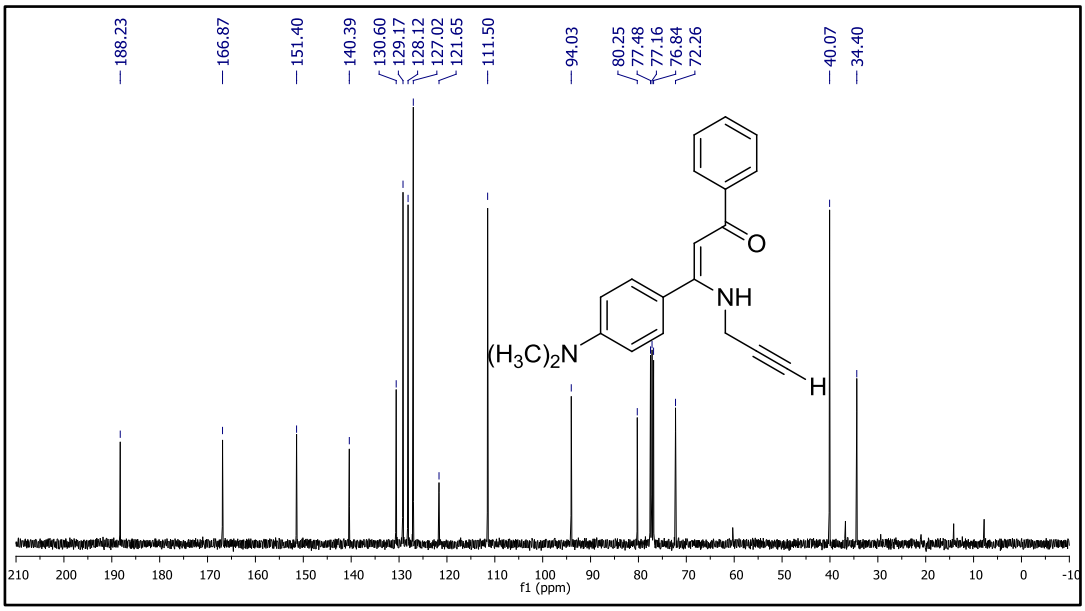

Figure 64. ^{13}C NMR spectrum of compound **26c**.

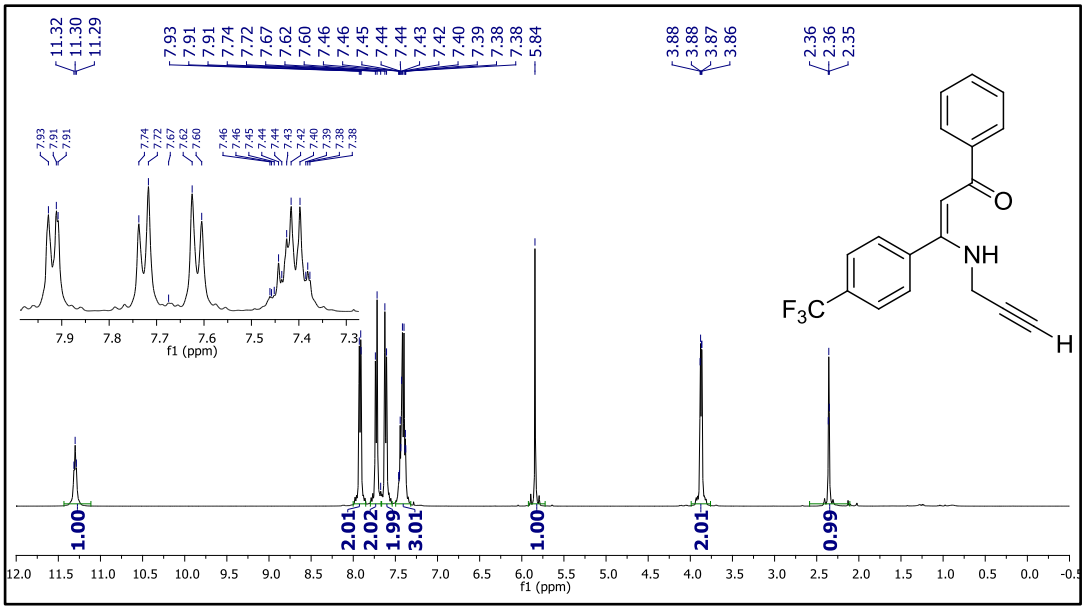

Figure 65. ^{1}H NMR spectrum of compound **26d**.

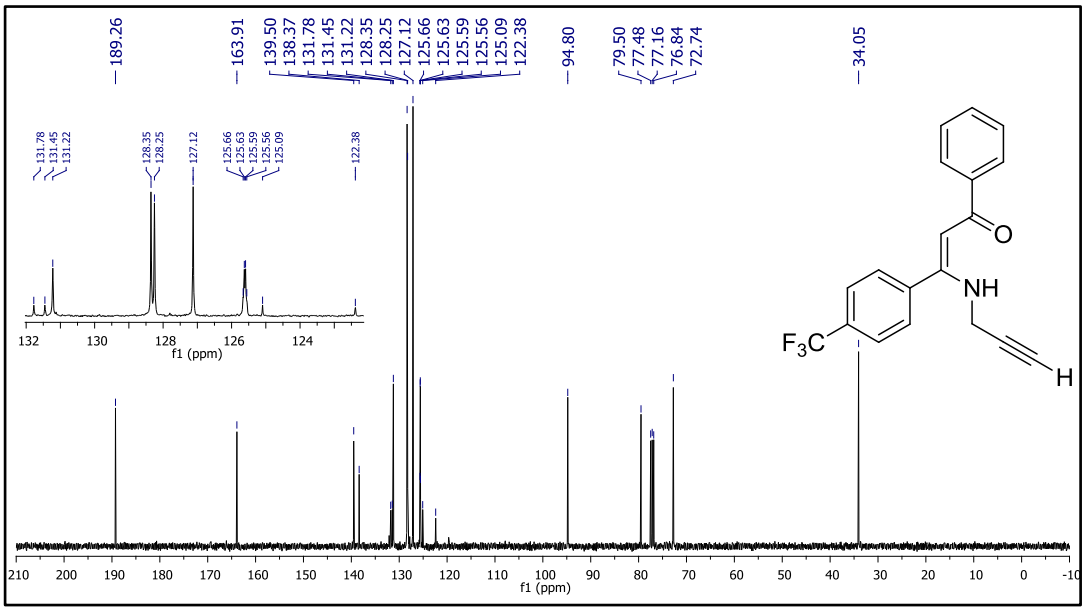

Figure 66. ^{13}C NMR spectrum of compound **26d**.

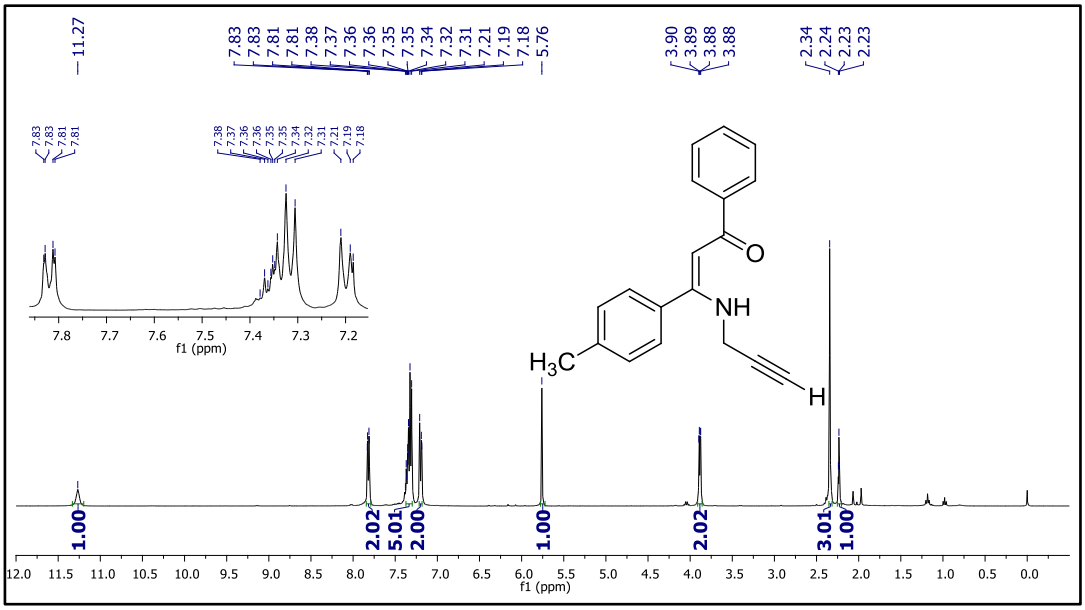

Figure 67. ^{1}H NMR spectrum of compound **26e**.

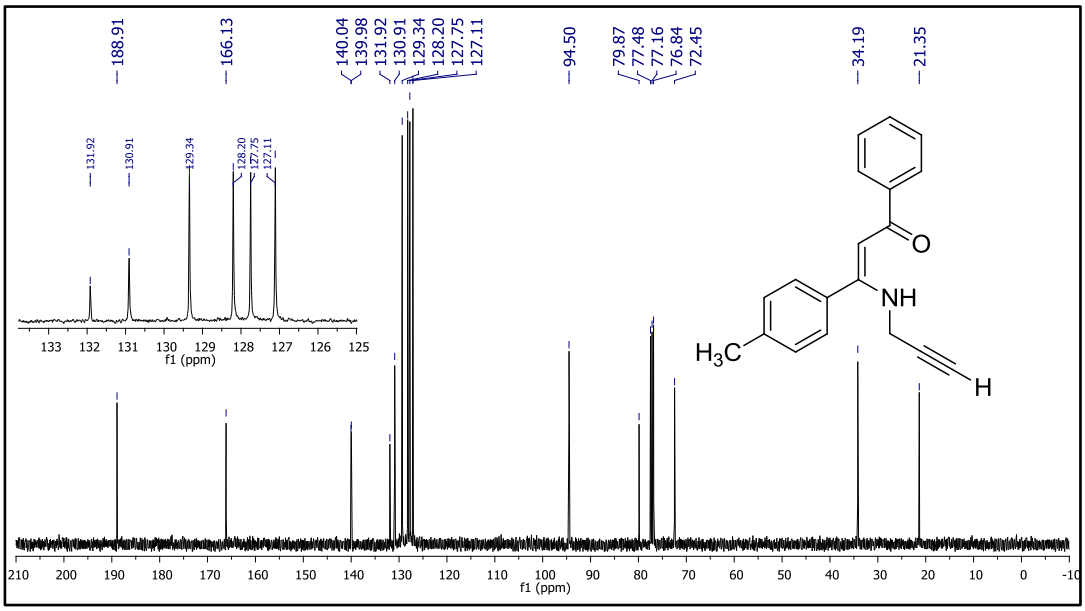

Figure 68. ^{13}C NMR spectrum of compound **26e**.

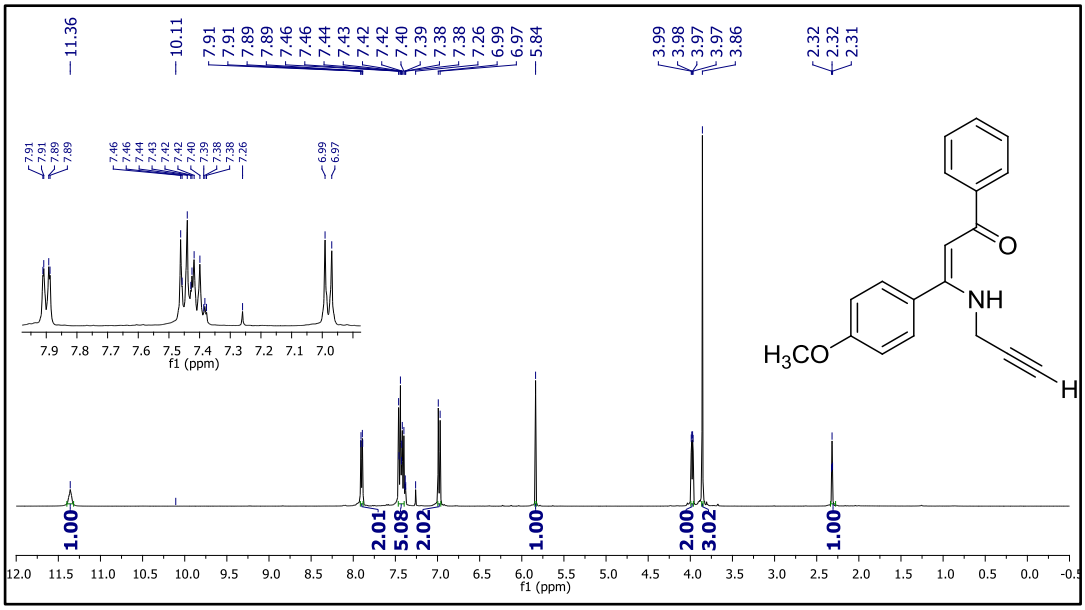

Figure 69. ^{1}H NMR spectrum of compound **26f**.

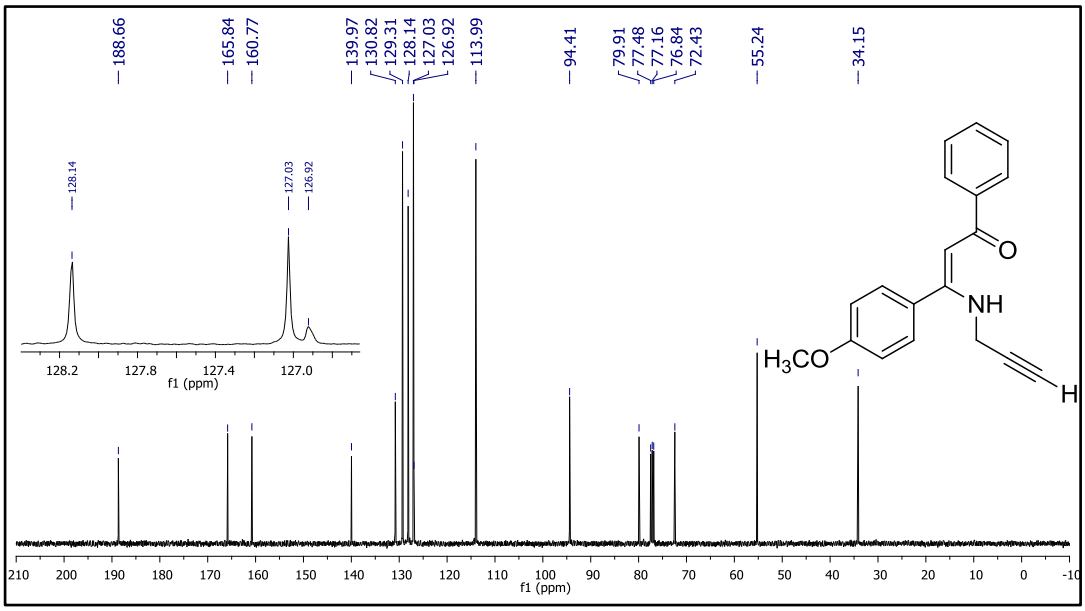

Figure 70. ^{13}C NMR spectrum of compound **26f**.

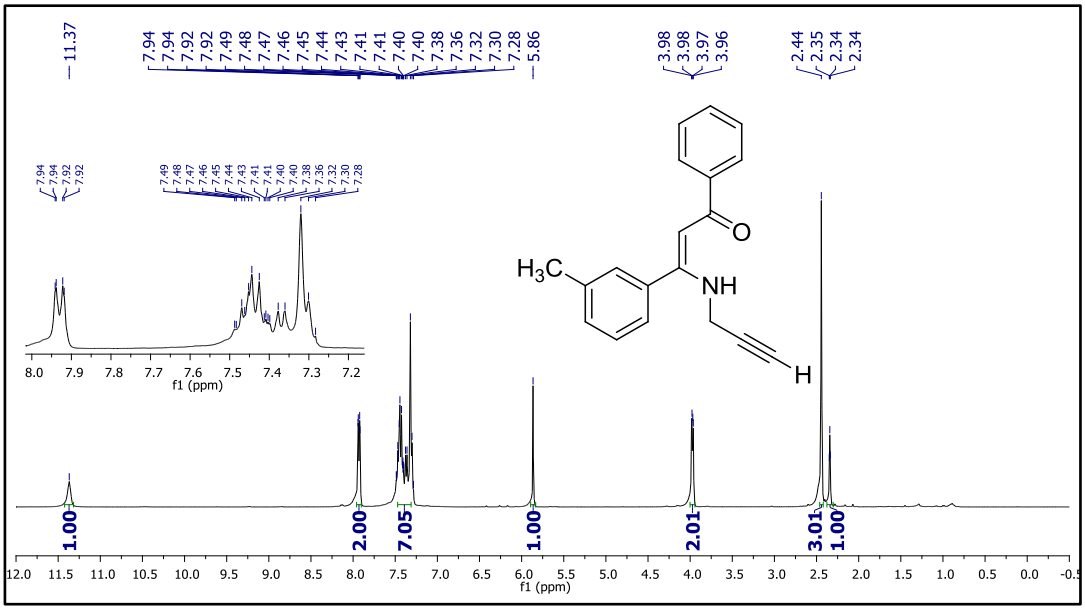

Figure 71. ^{1}H NMR spectrum of compound **26g**.

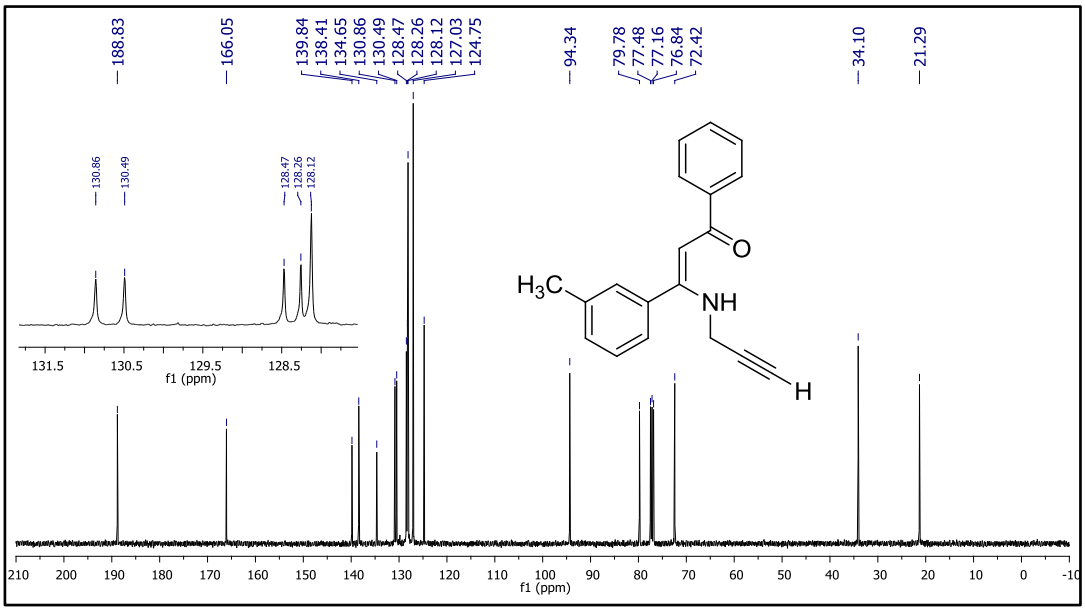

Figure 72. ^{13}C NMR spectrum of compound **26g**.

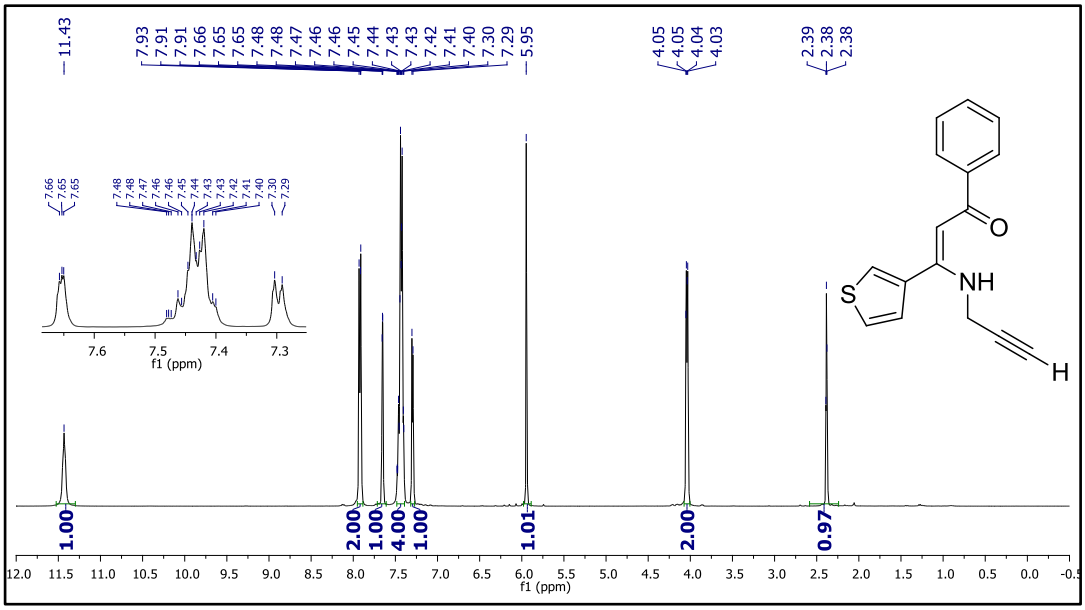

Figure 73. ^{1}H NMR spectrum of compound **26h**.

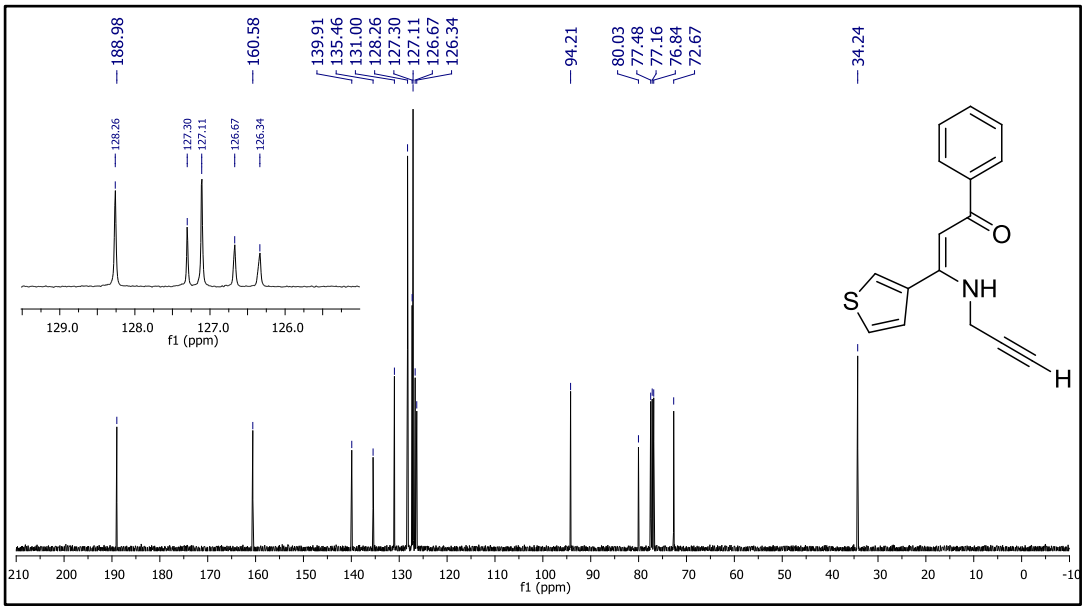

Figure 74. ^{13}C NMR spectrum of compound **26h**.

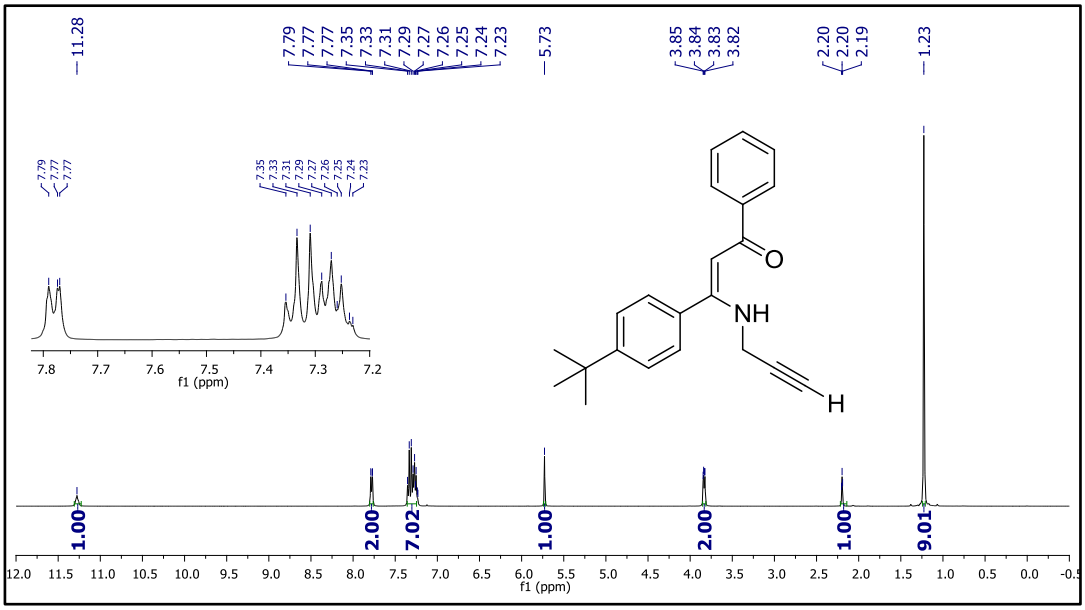

Figure 75. ^{1}H NMR spectrum of compound **26i**.

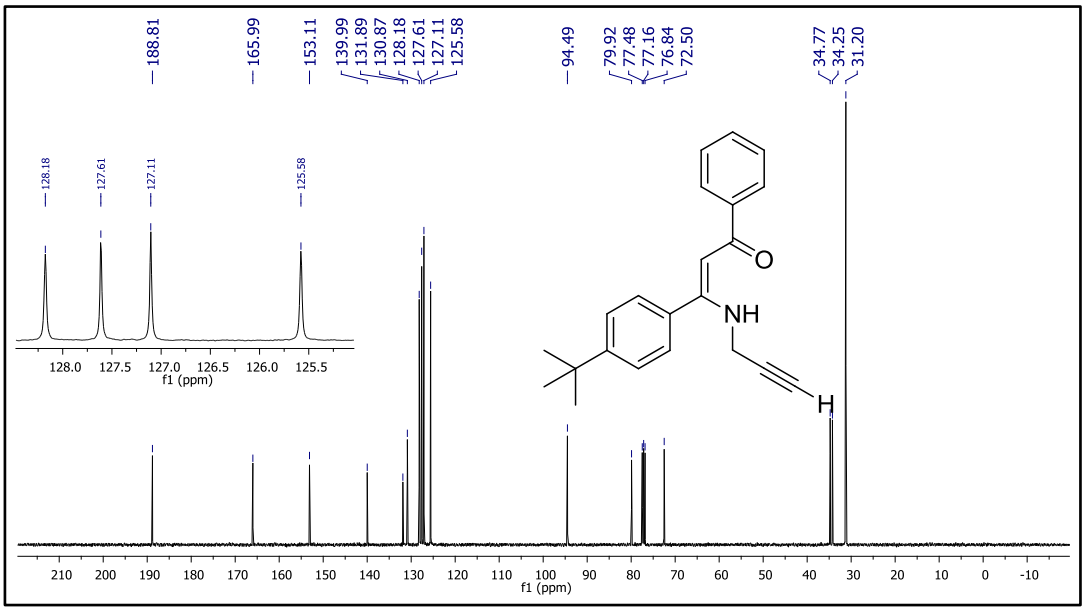

Figure 76. ^{13}C NMR spectrum of compound **26i**.

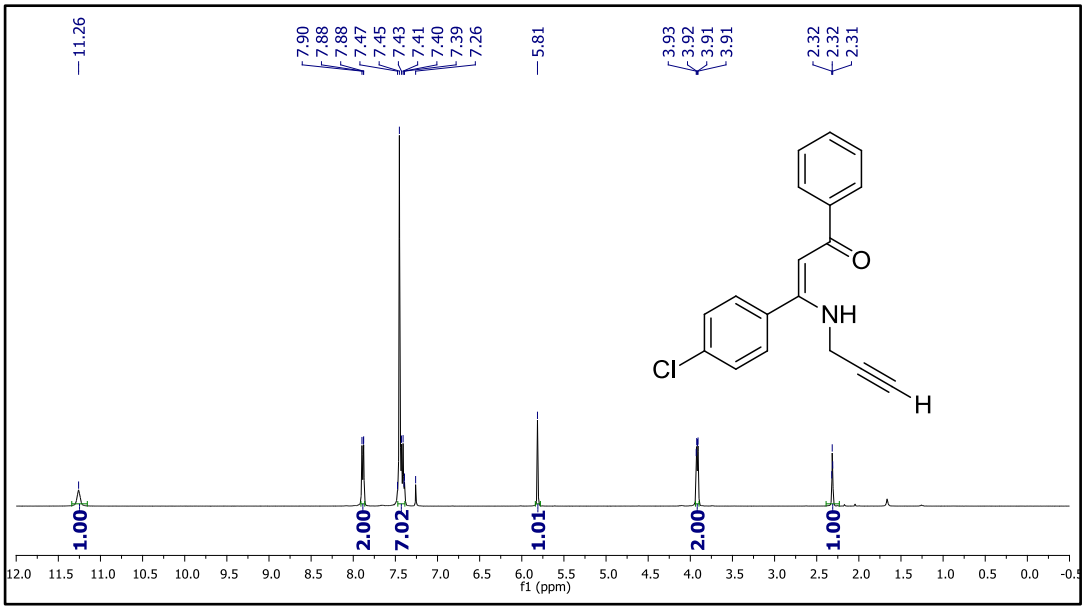

Figure 77. ^{1}H NMR spectrum of compound **26j**.

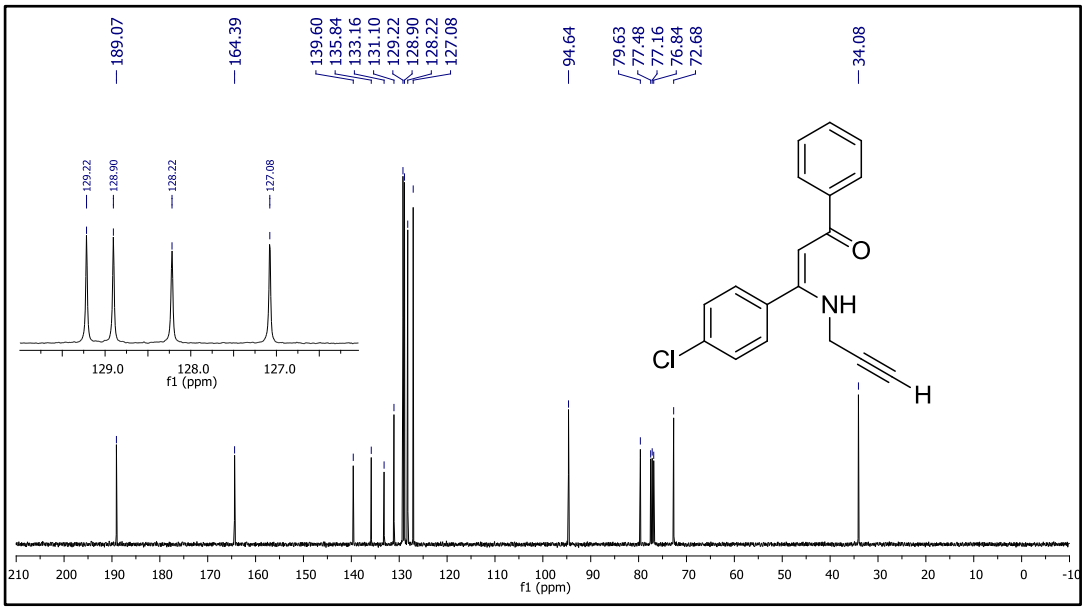

Figure 78. ^{13}C NMR spectrum of compound **26j**.

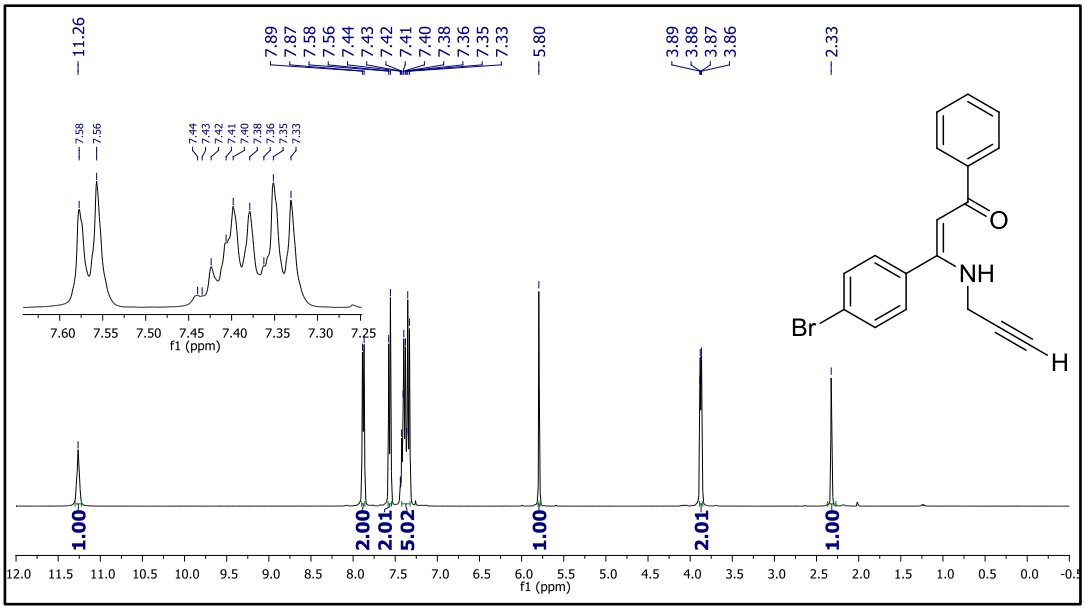

Figure 79. ^{1}H NMR spectrum of compound **26k**.

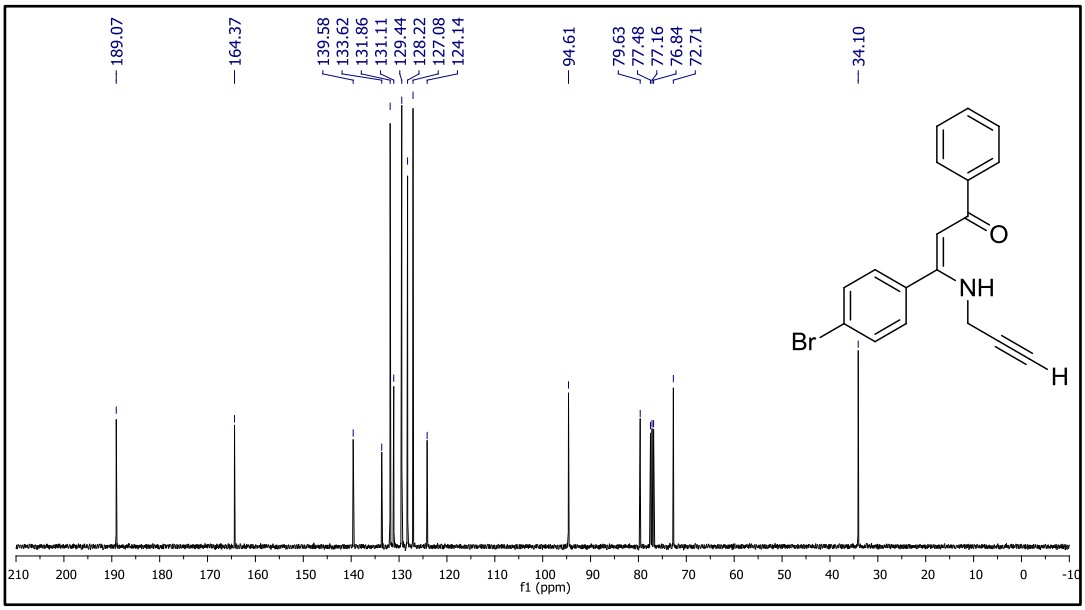

Figure 80. ^{13}C NMR spectrum of compound **26k**.

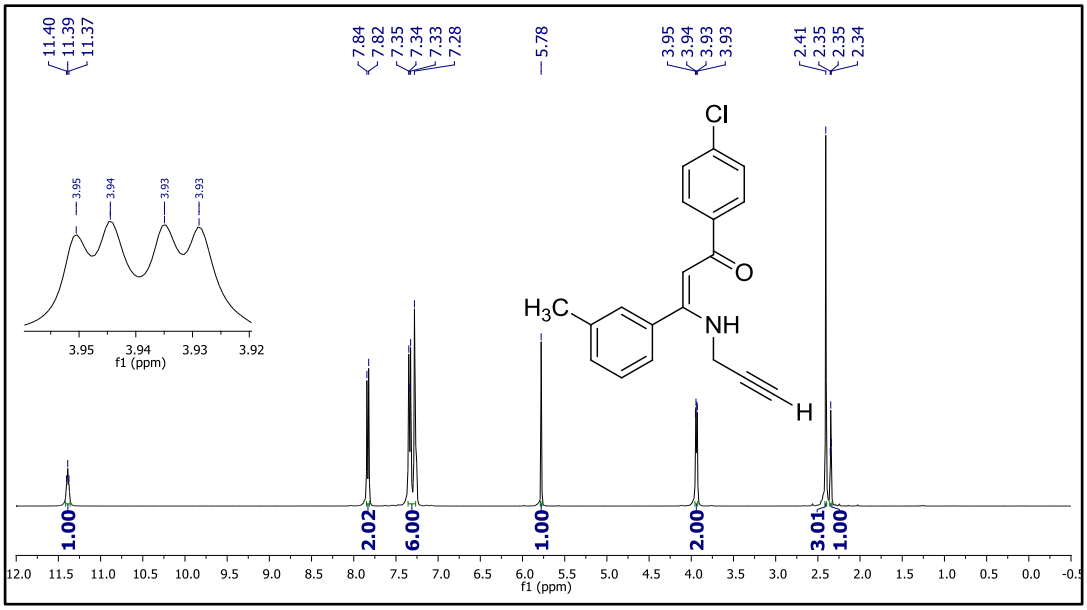

Figure 81. ^{1}H NMR spectrum of compound **26l**.

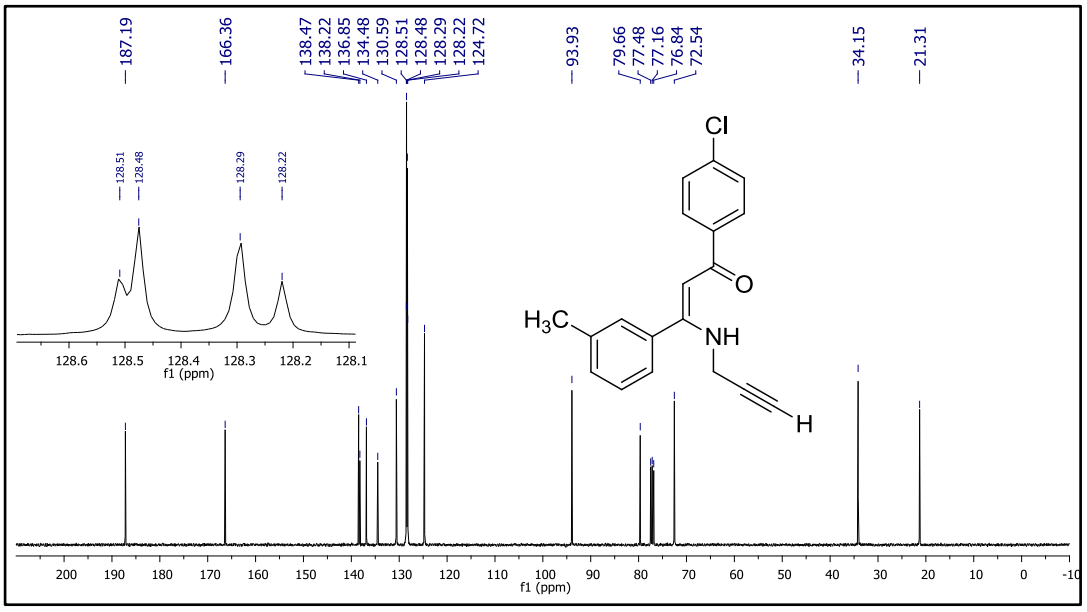

Figure 82. ^{13}C NMR spectrum of compound **26l**.

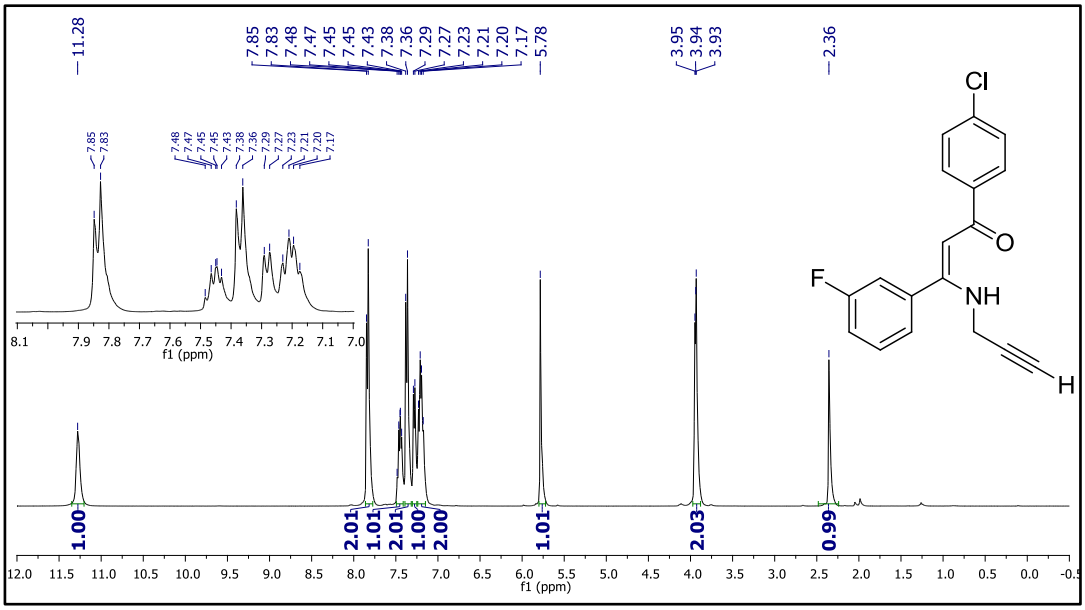

Figure 83. ^{1}H NMR spectrum of compound **26m**.

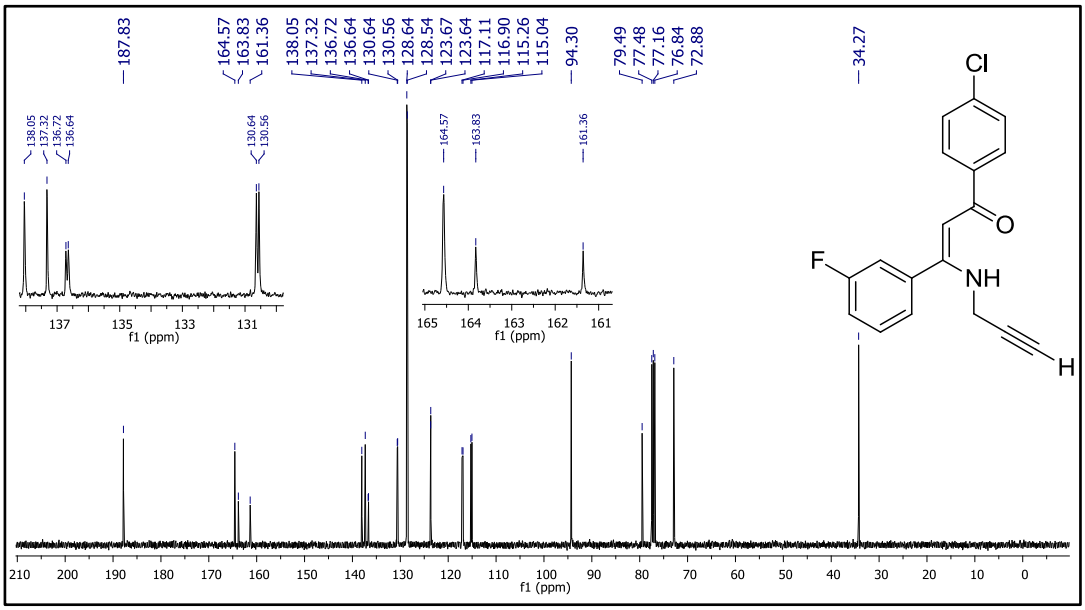

Figure 84. ^{13}C NMR spectrum of compound **26m**.

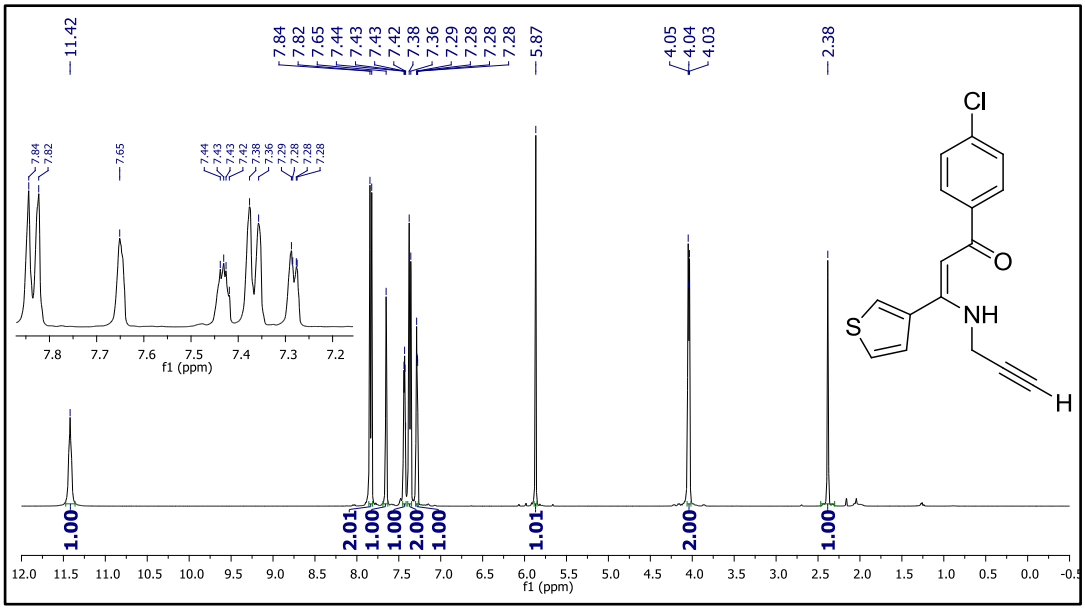

Figure 85. ^{1}H NMR spectrum of compound **26n**.

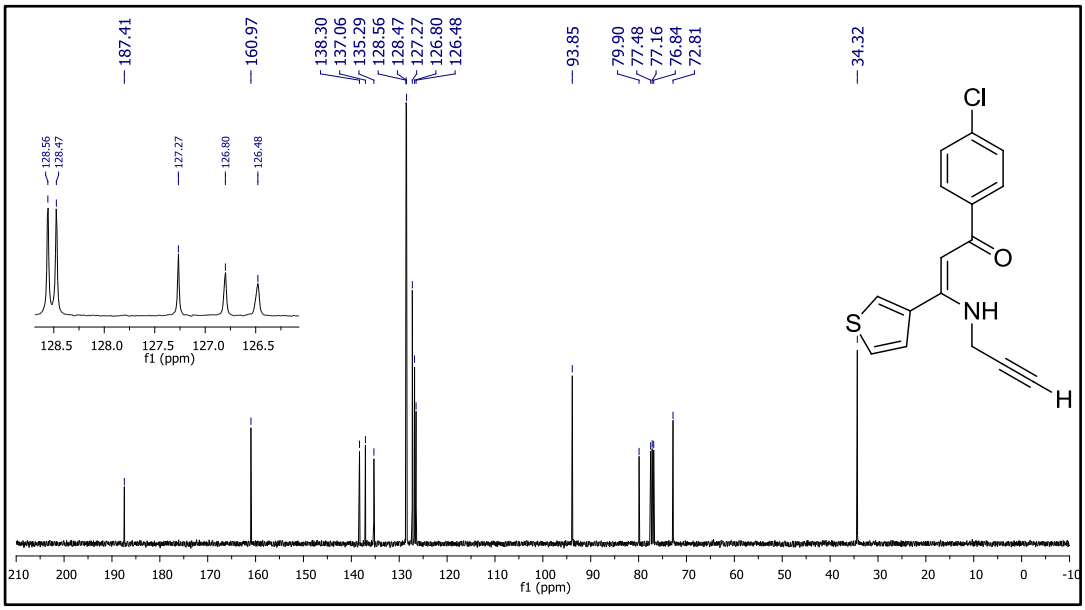

Figure 86. ^{13}C NMR spectrum of compound **26n**.

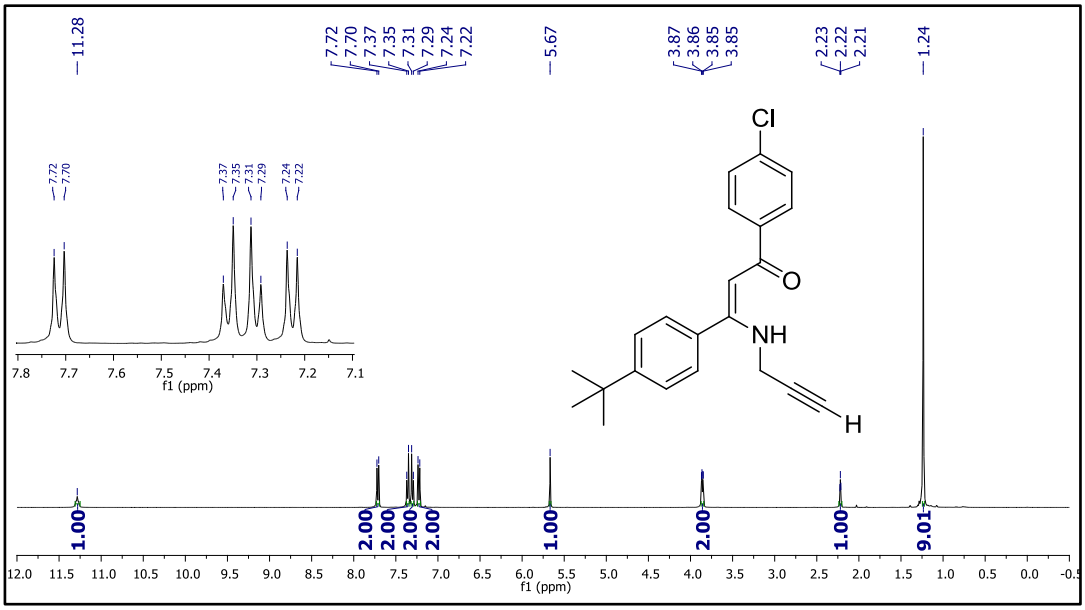

Figure 87. ^{1}H NMR spectrum of compound **26o**.

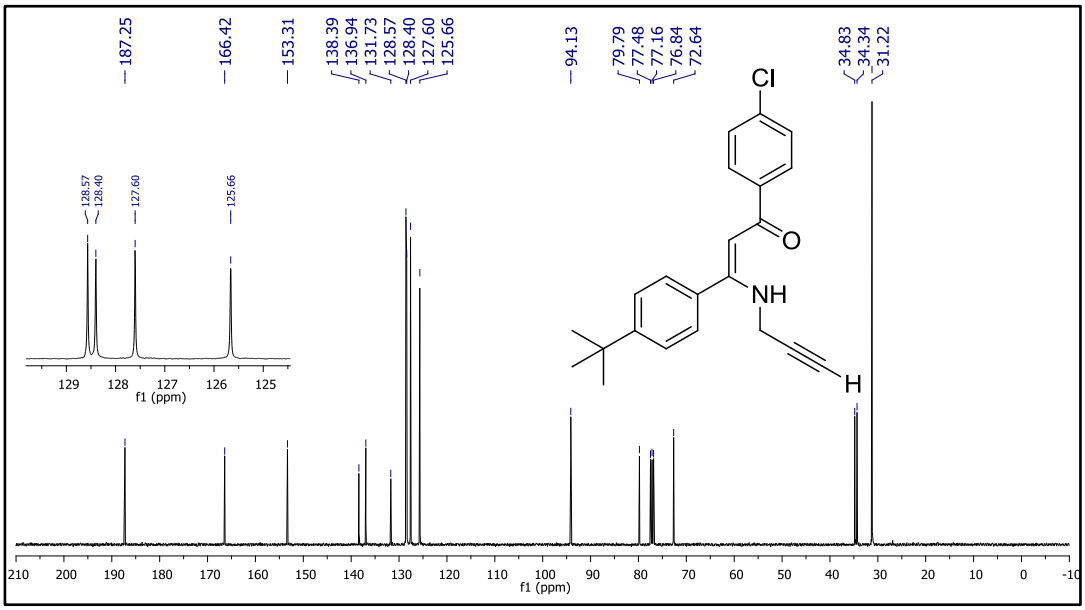

Figure 88. ^{13}C NMR spectrum of compound **26o**.

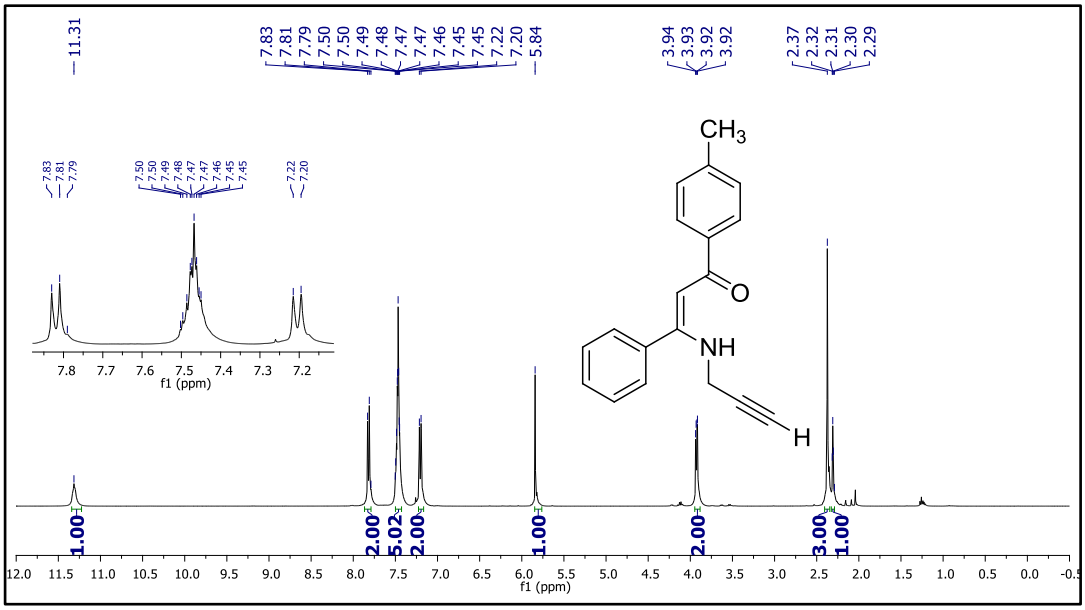

Figure 89. ^{1}H NMR spectrum of compound **26p.**

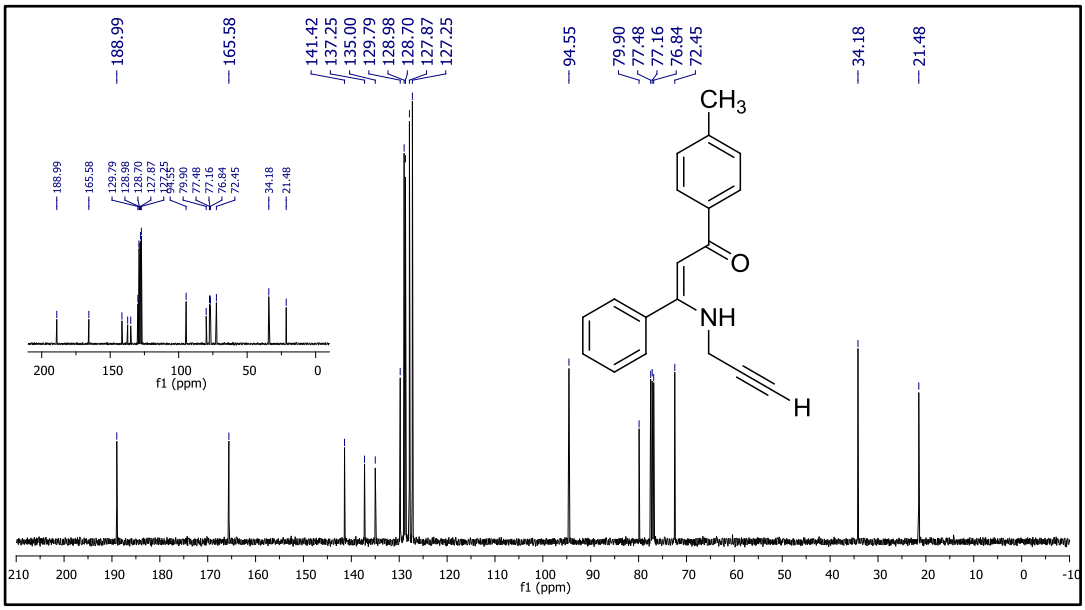

Figure 90. ^{13}C NMR spectrum of compound **26p**.

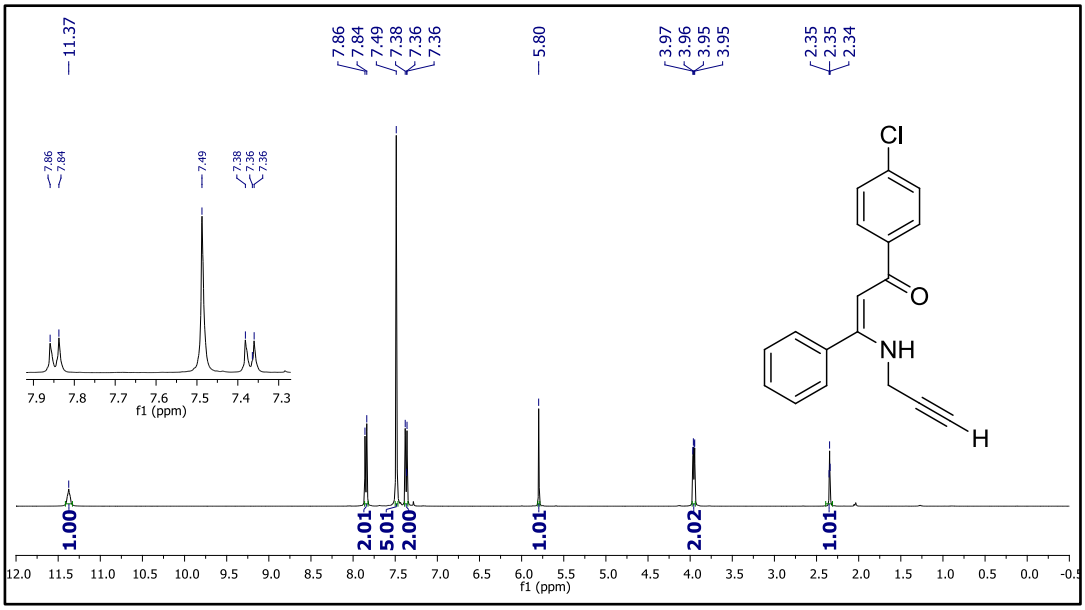

Figure 91. ^{1}H NMR spectrum of compound **26q**.

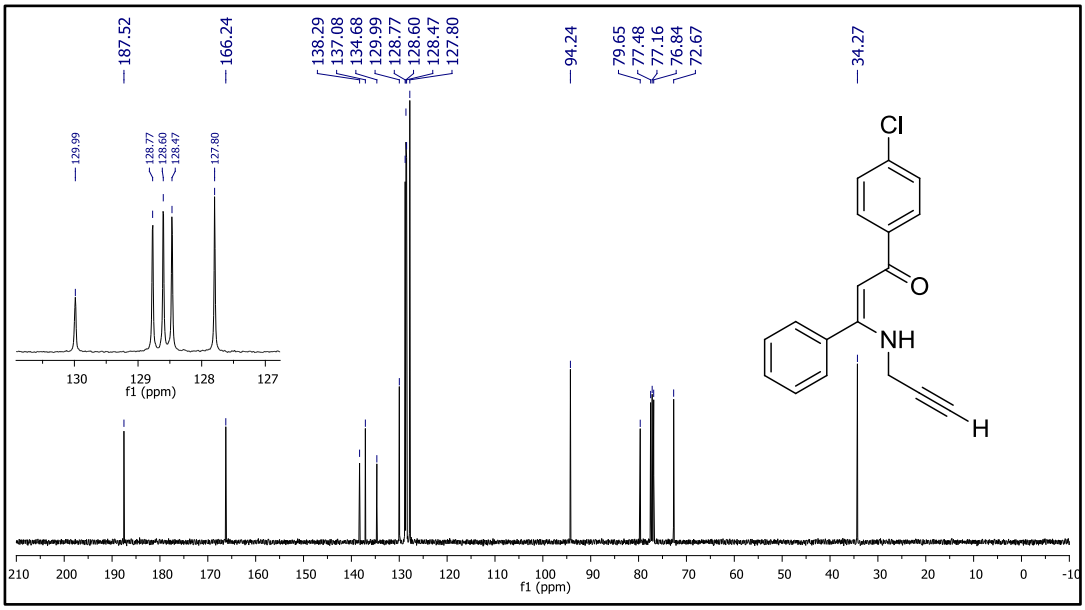

Figure 92. ^{13}C NMR spectrum of compound **26q**.

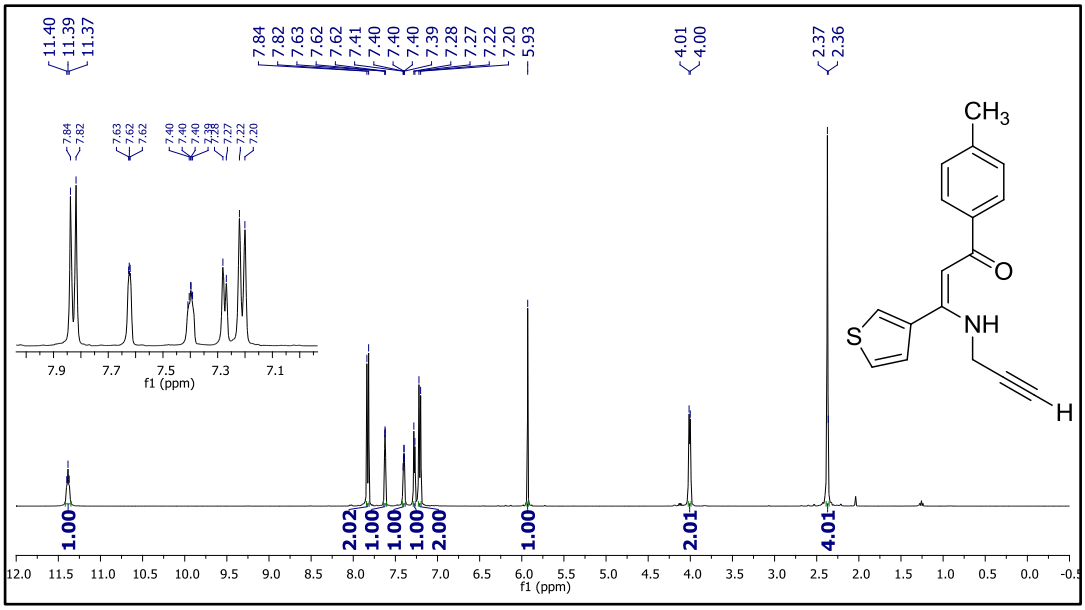

Figure 93. ^{1}H NMR spectrum of compound **26r**.

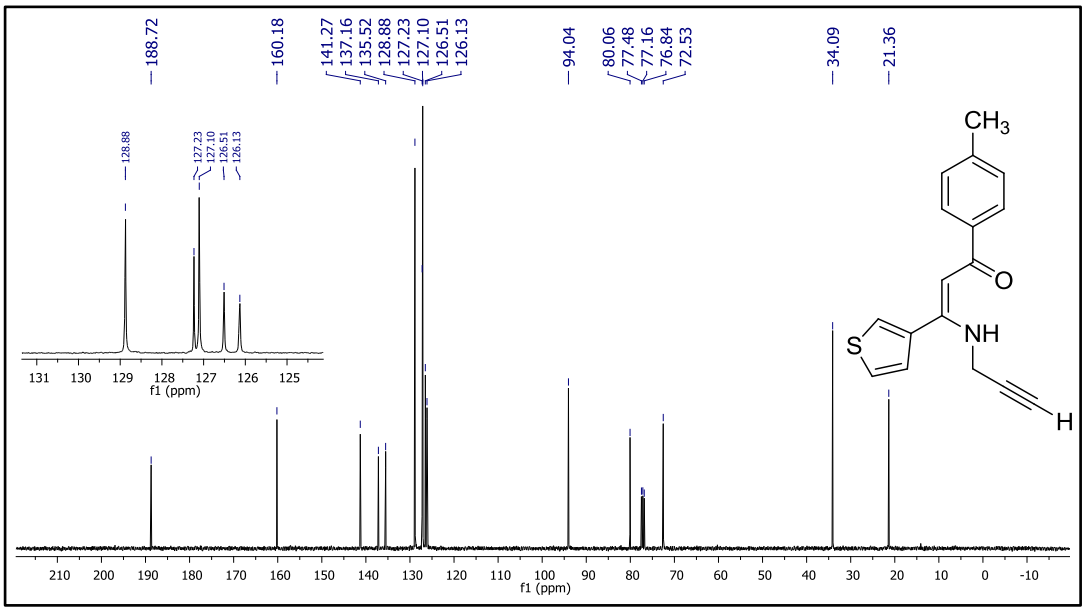

Figure 94. ^{13}C NMR spectrum of compound **26r**.

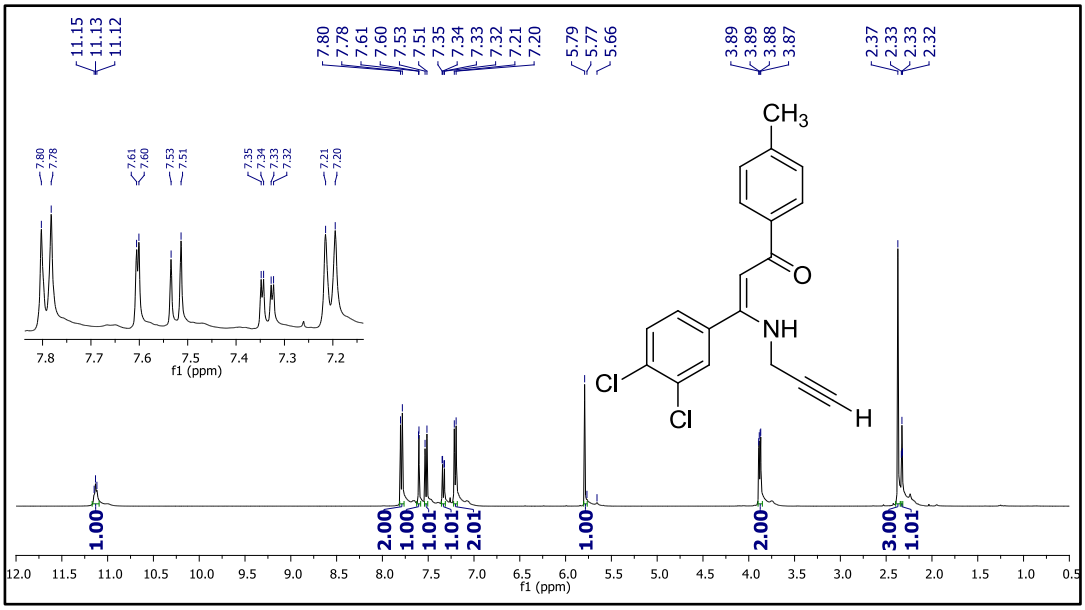

Figure 95. ^{1}H NMR spectrum of compound **26s**.

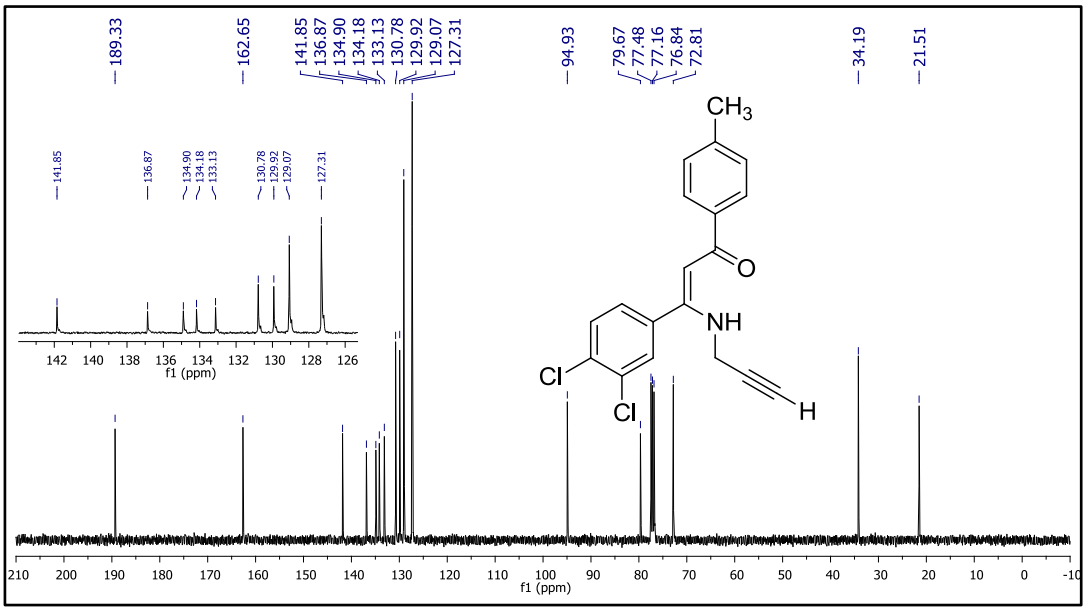

Figure 96. ^{13}C NMR spectrum of compound **26s**.

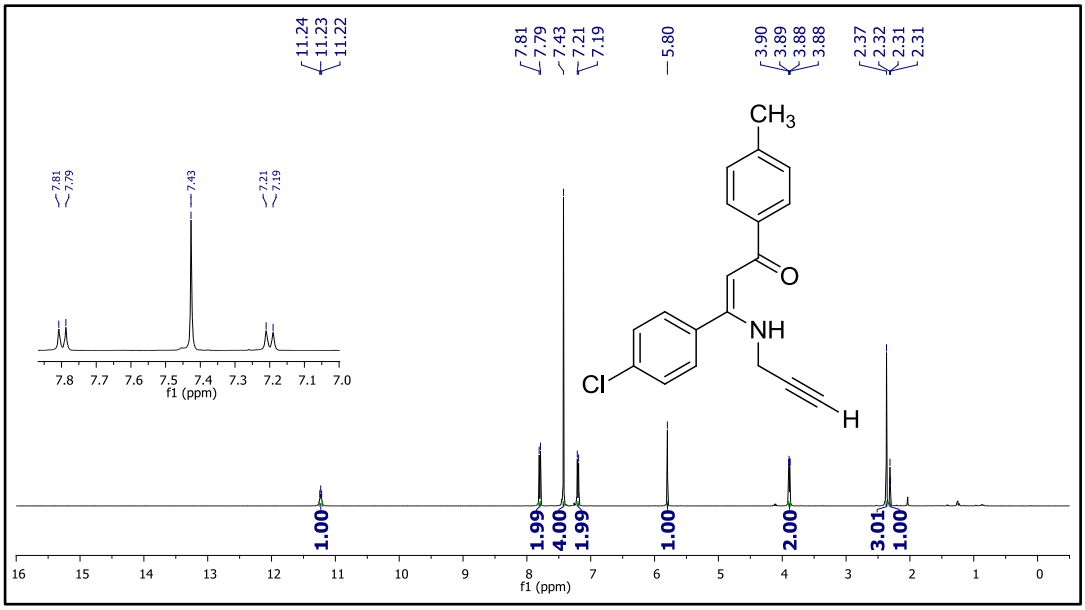

Figure 97. ^{1}H NMR spectrum of compound **26t**.

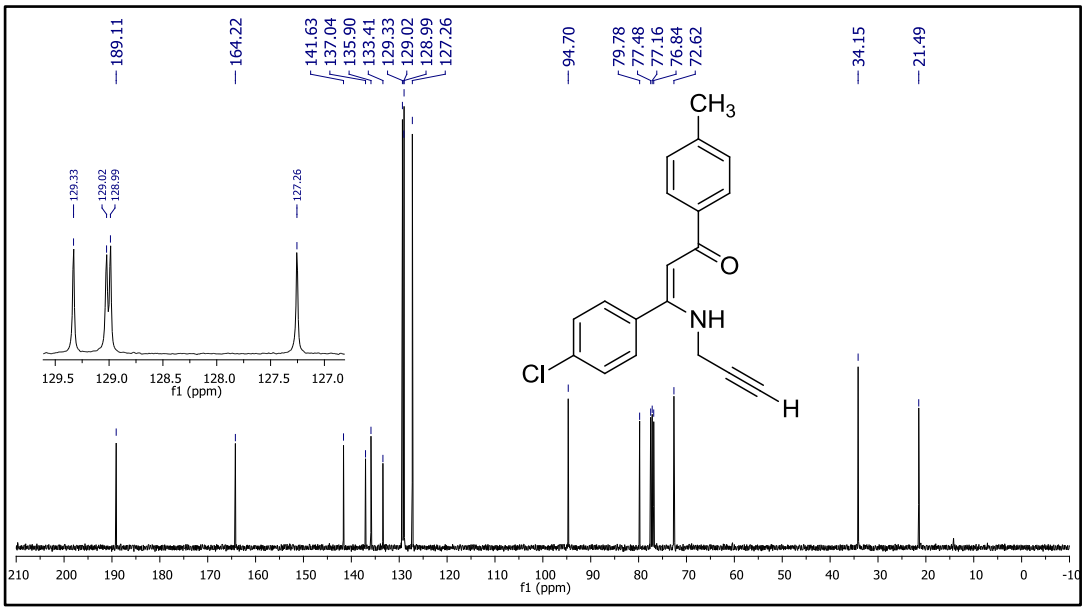

Figure 98. ^{13}C NMR spectrum of compound **26t**.

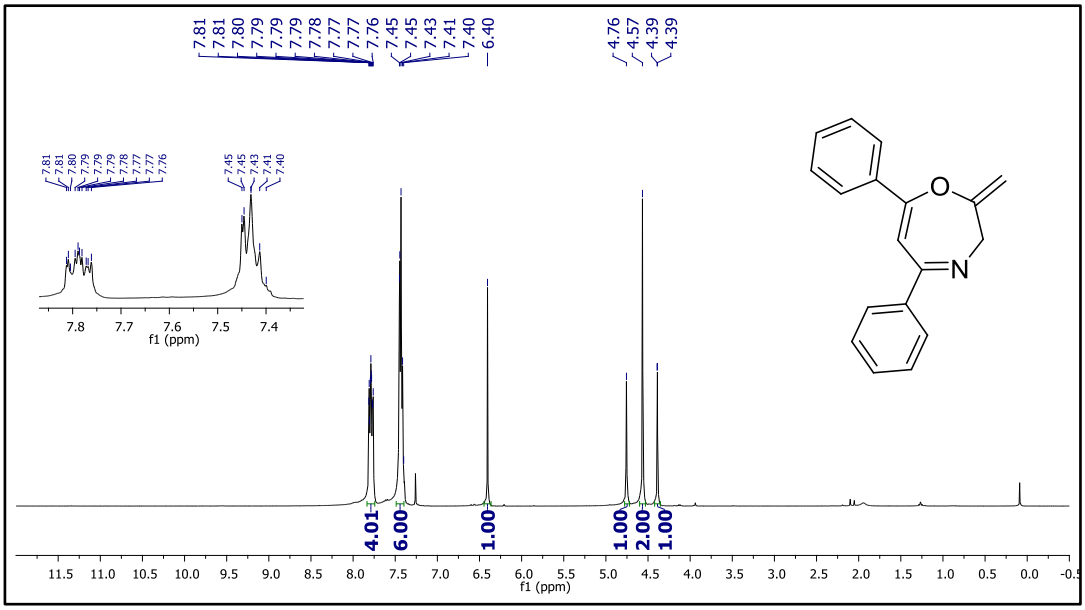

Figure 99. ^{1}H NMR spectrum of compound **37a**.

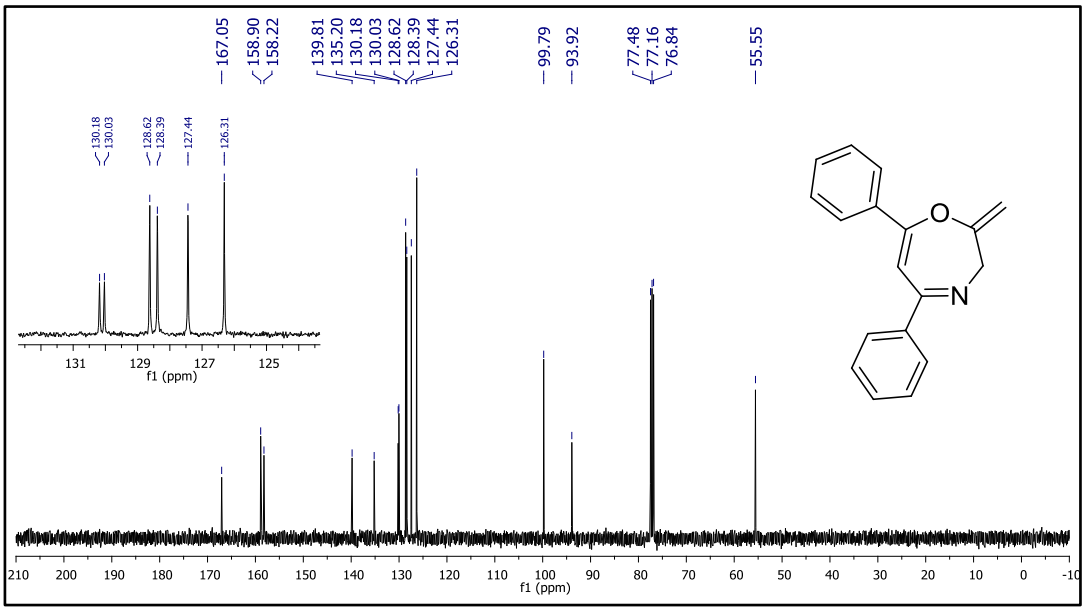

Figure 100. ^{13}C NMR spectrum of compound **37a**.

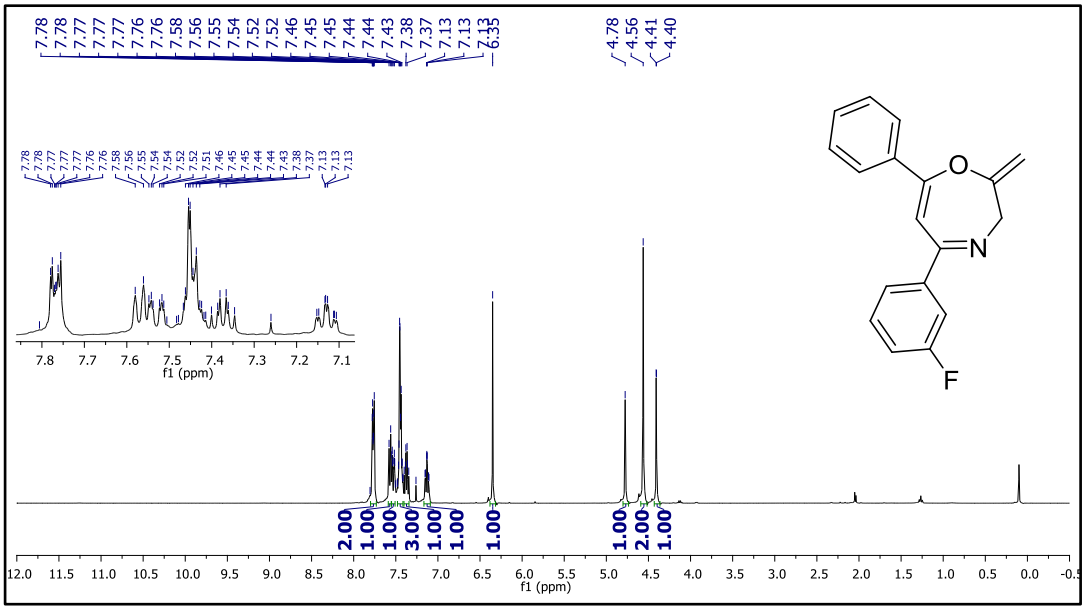

Figure 101. ^{1}H NMR spectrum of compound **37b**.

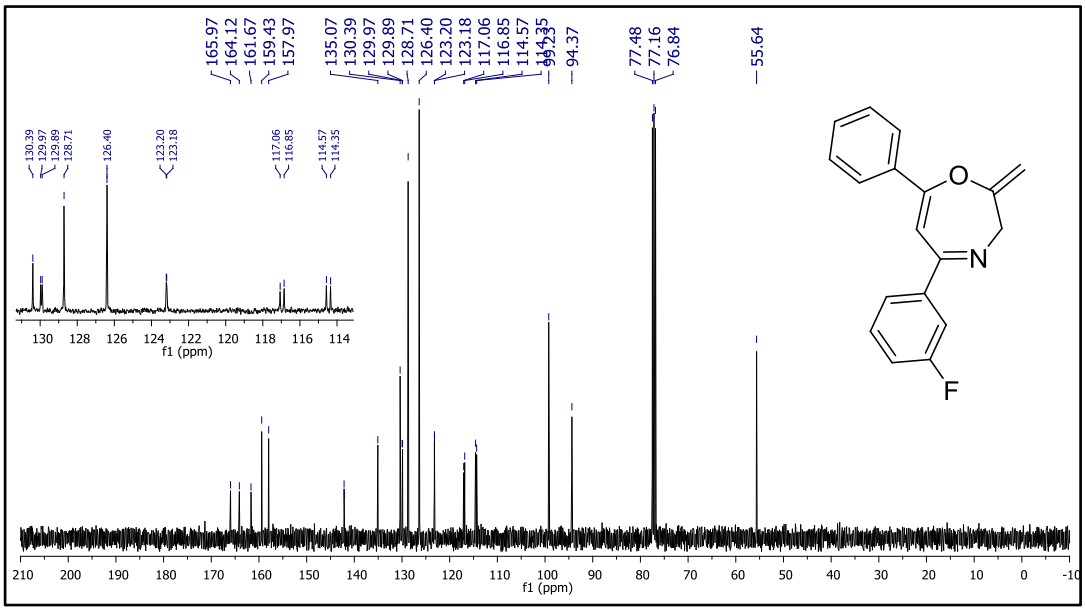

Figure 102. ^{13}C NMR spectrum of compound **37b**.

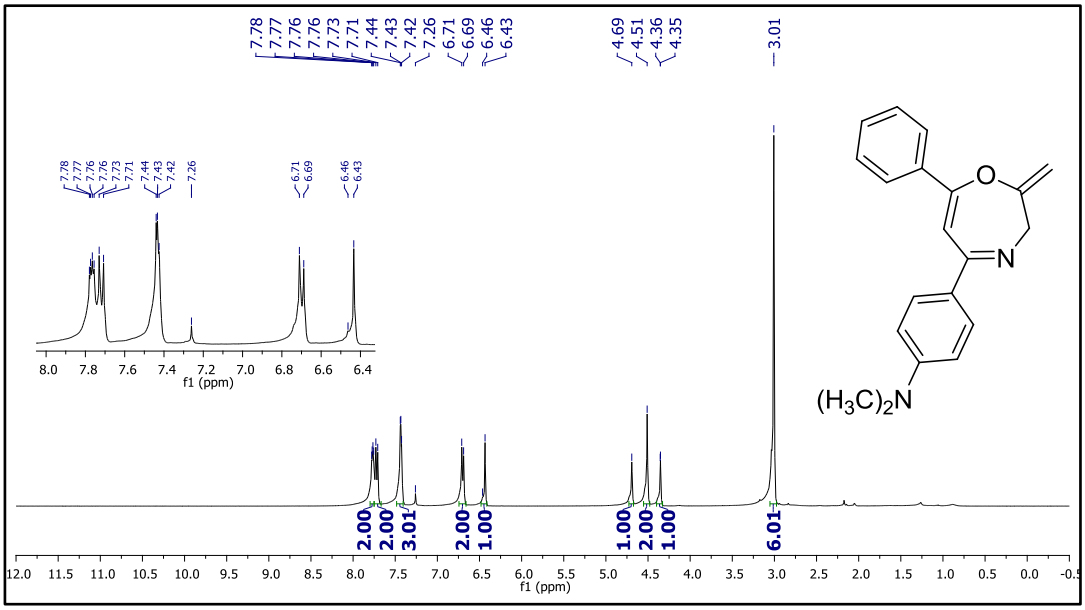

Figure 103. ^{1}H NMR spectrum of compound **37c**.

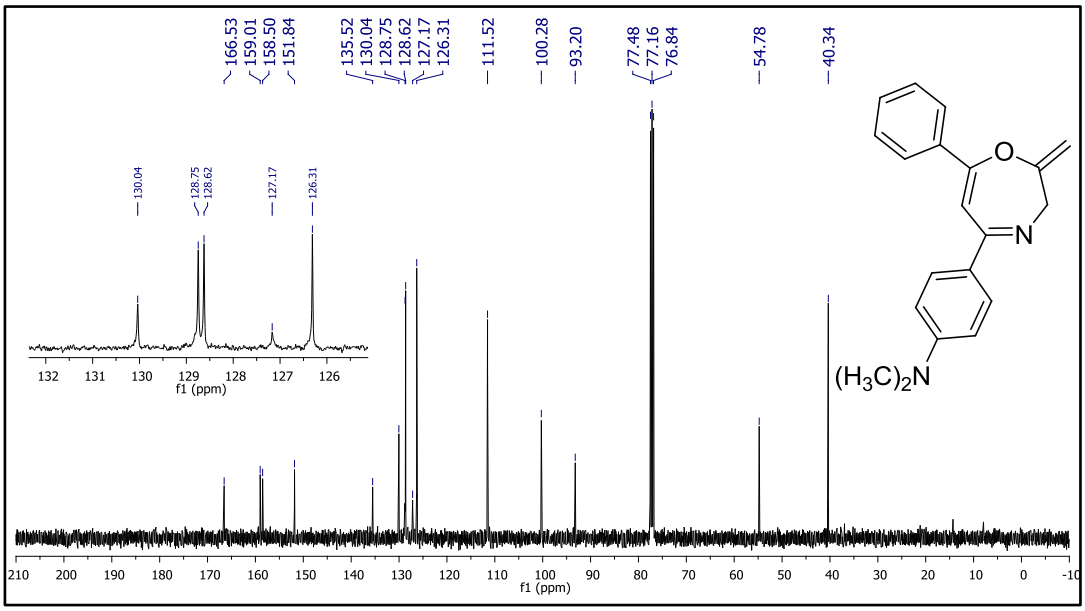

Figure 104. ^{13}C NMR spectrum of compound **37c**.

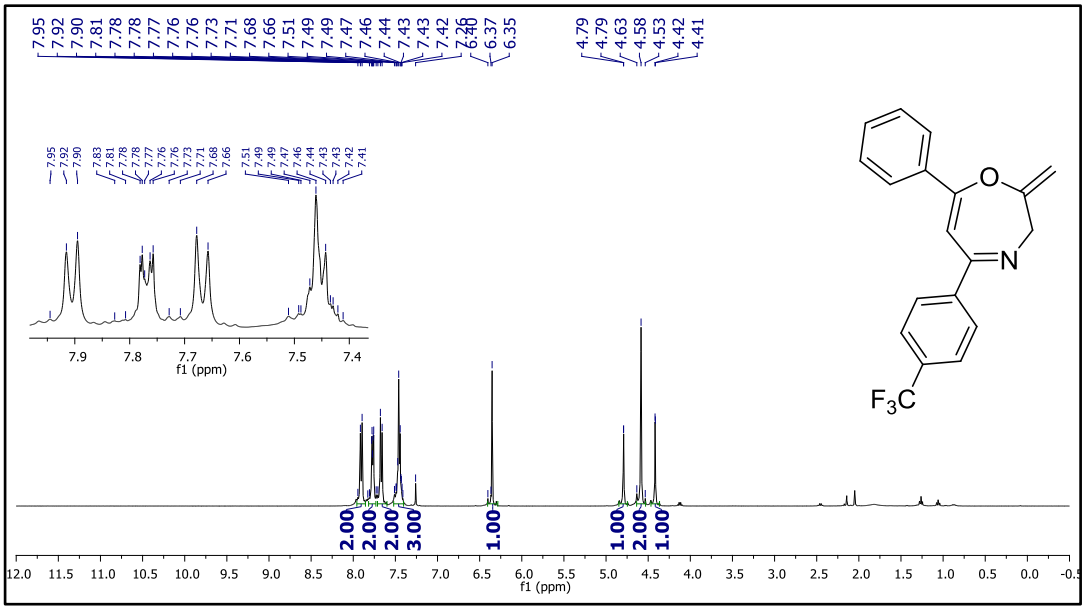

Figure 105. ^{1}H NMR spectrum of compound **37d**.

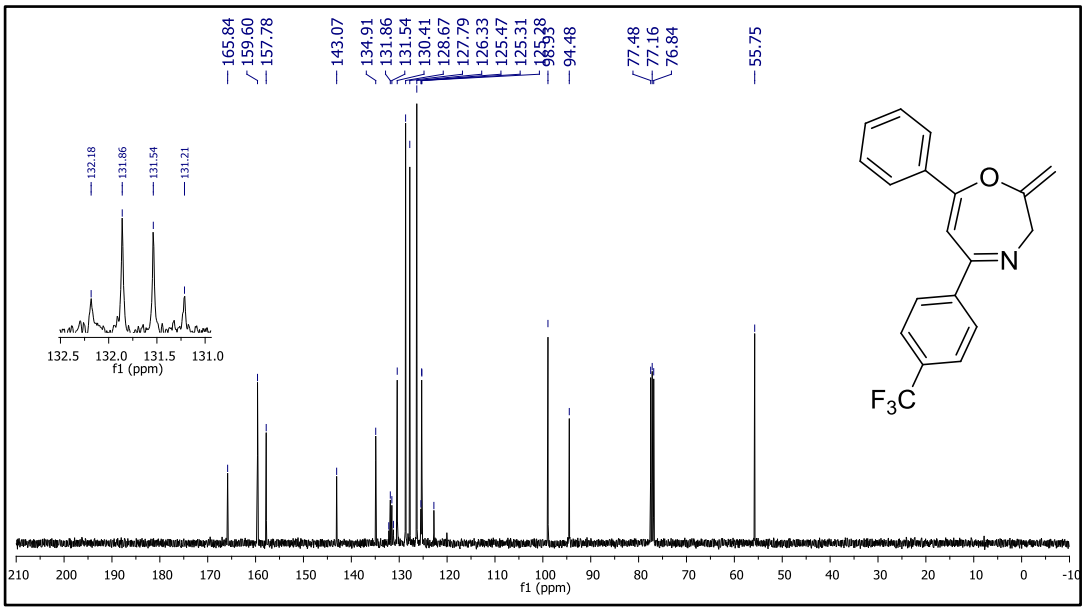

Figure 106. ^{13}C NMR spectrum of compound **37d**.

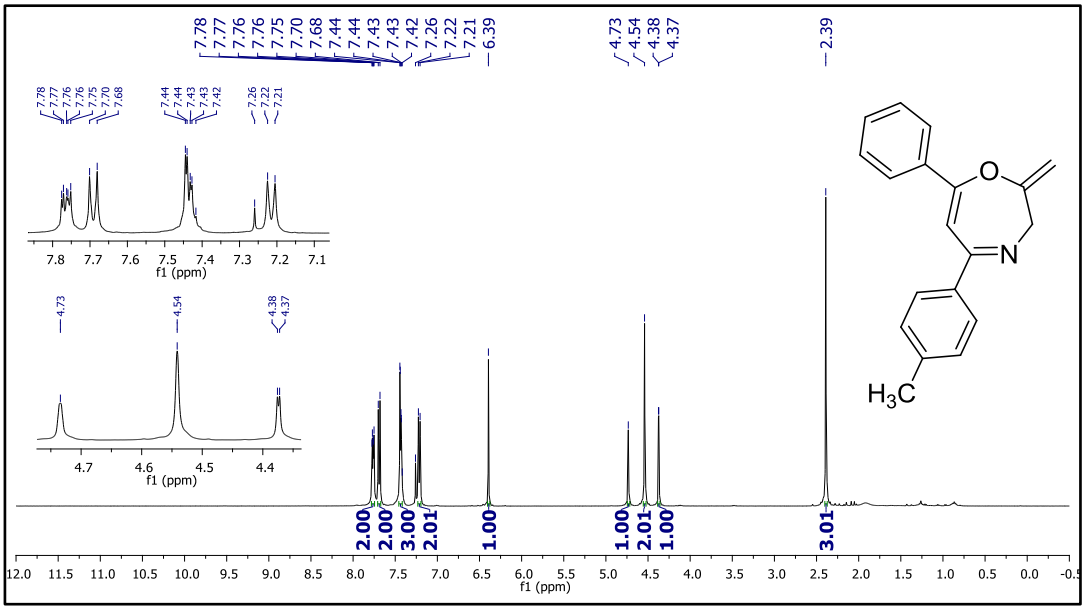

Figure 107. ^{1}H NMR spectrum of compound **37e**.

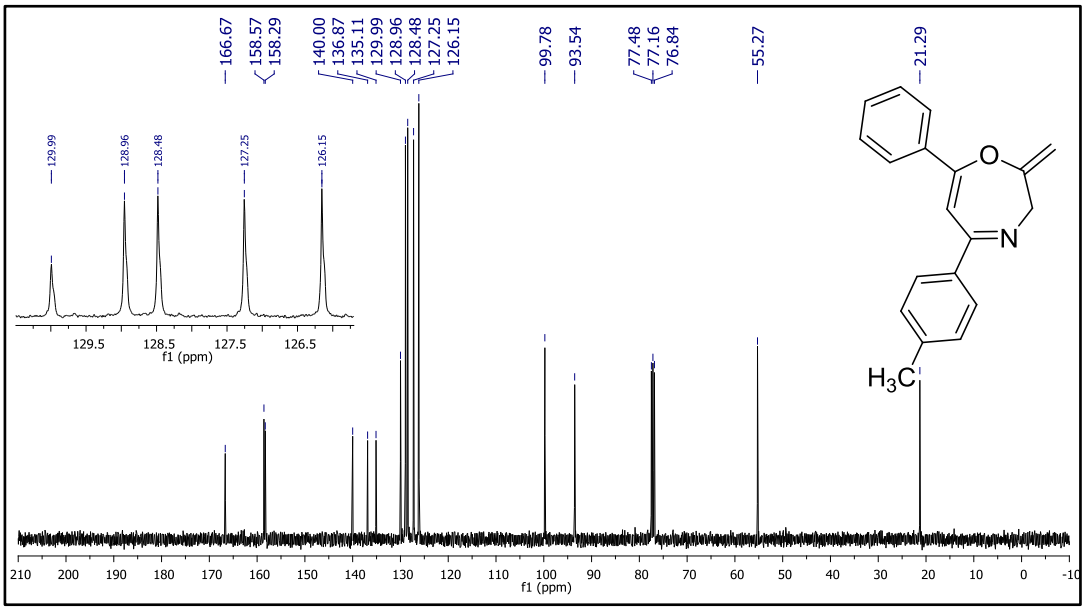

Figure 108. ^{13}C NMR spectrum of compound **37e**.

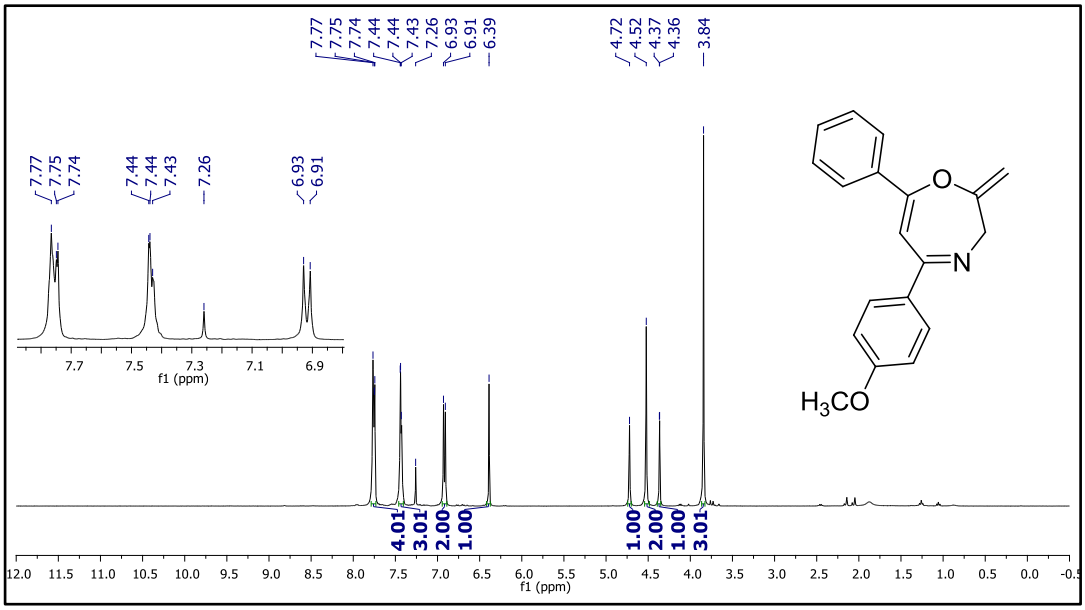

Figure 109. [1]H NMR spectrum of compound **37f**.

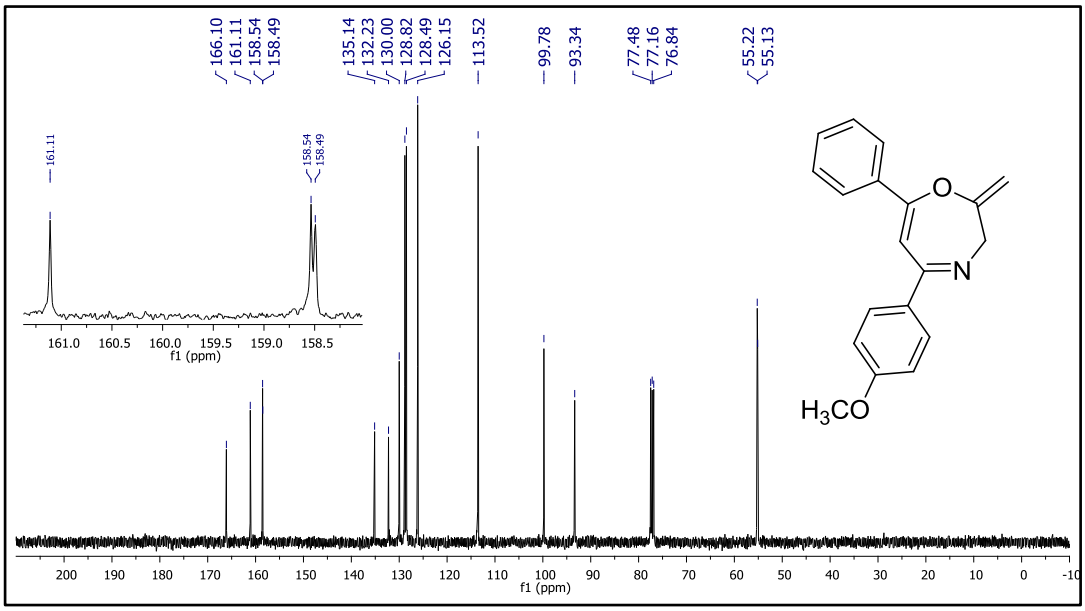

Figure 110. [13]C NMR spectrum of compound **37f**.

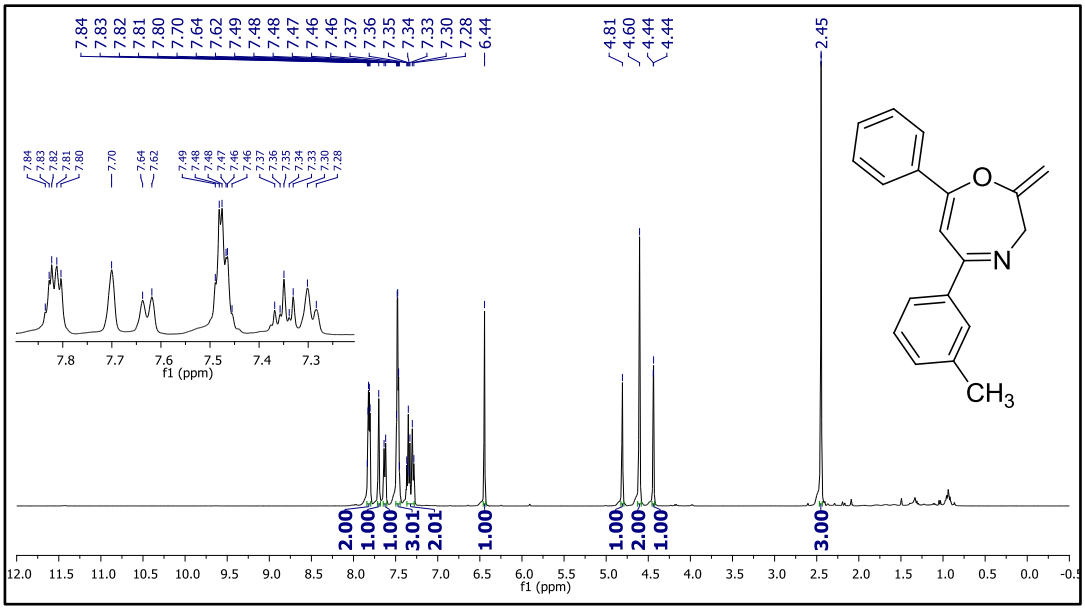

Figure 111. ^{1}H NMR spectrum of compound **37g**.

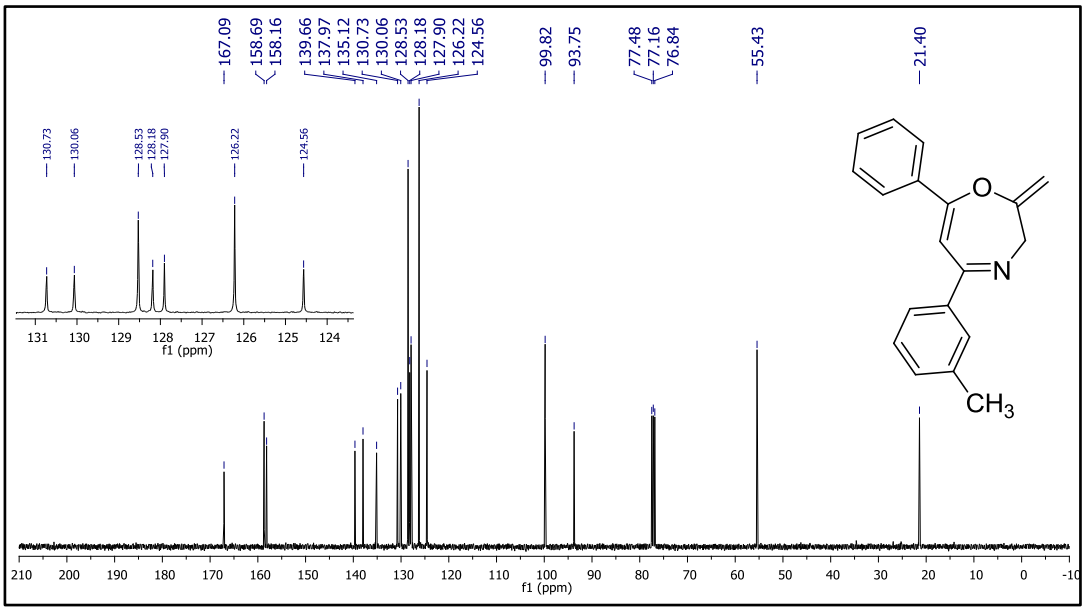

Figure 112. ^{13}C NMR spectrum of compound **37g**.

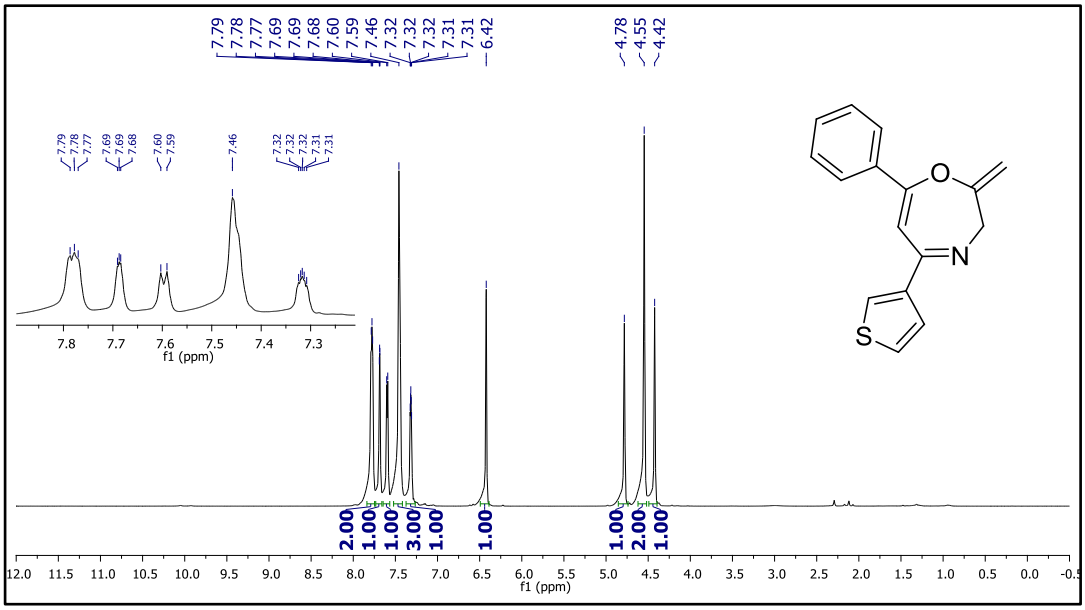

Figure 113. ^{1}H NMR spectrum of compound **37h**.

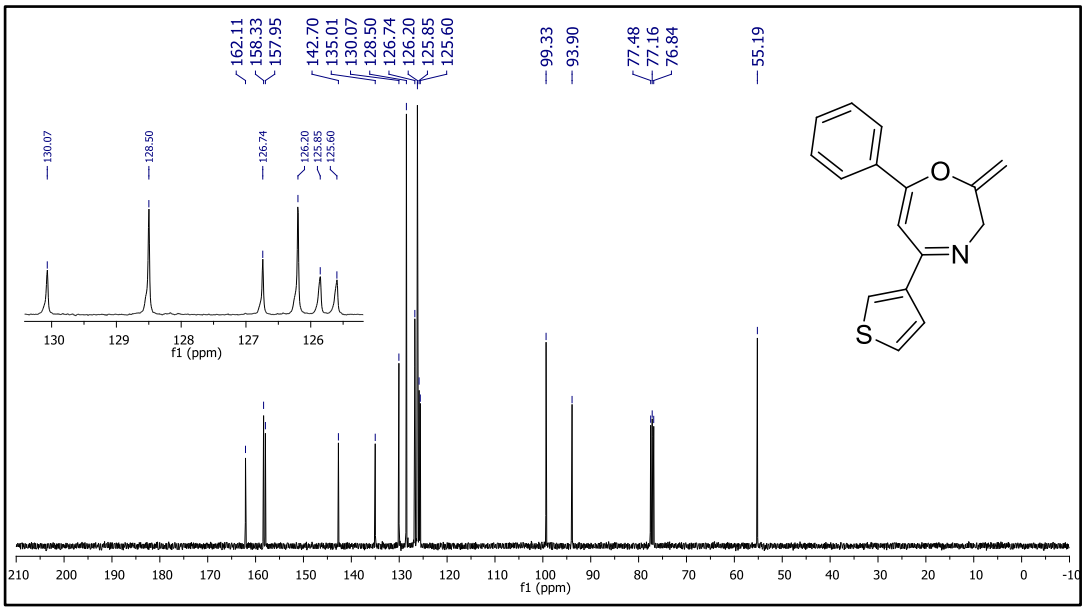

Figure 114. ^{13}C NMR spectrum of compound **37h**.

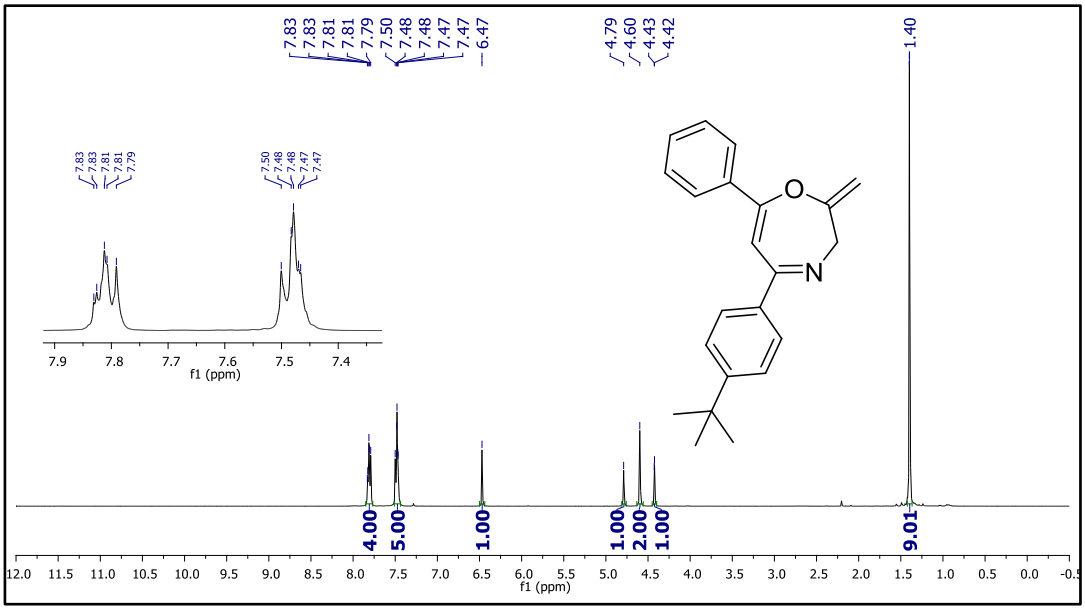

Figure 115. ^{1}H NMR spectrum of compound **37i**.

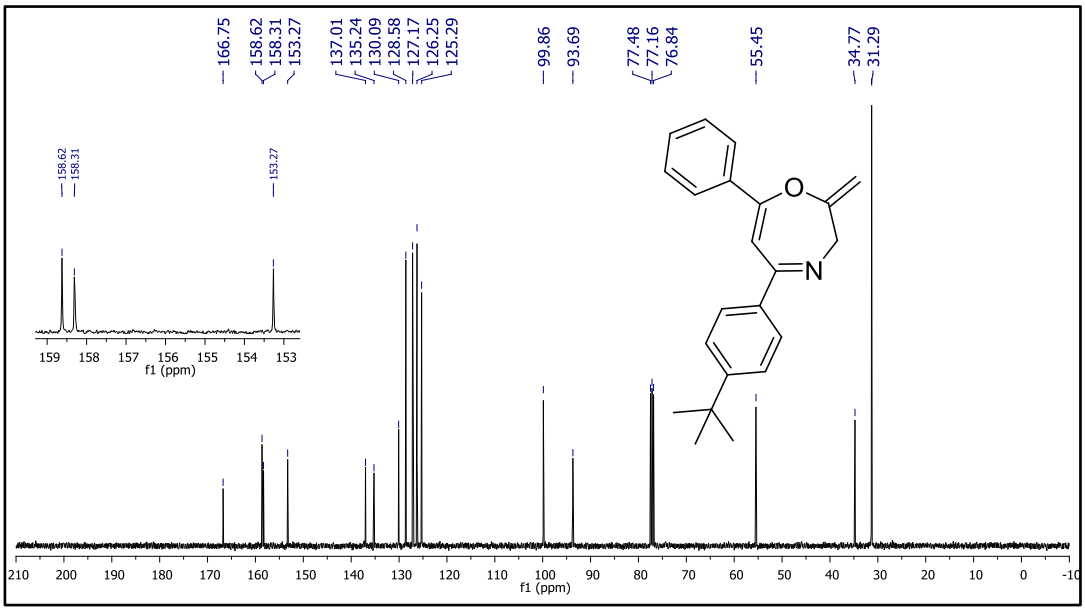

Figure 116. ^{13}C NMR spectrum of compound **37i**.

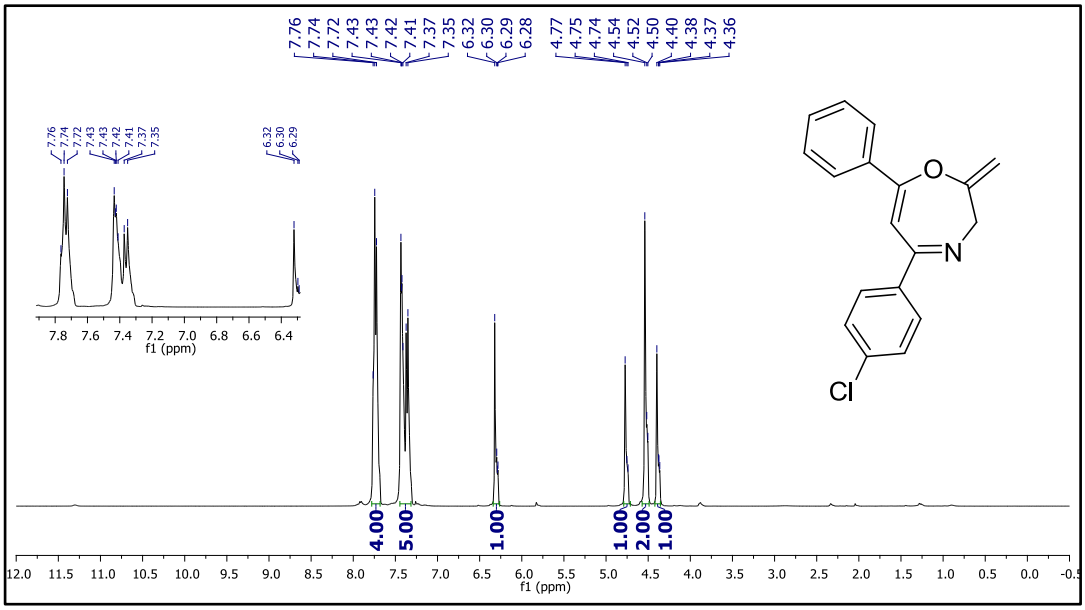

Figure 117. [1]H NMR spectrum of compound **37j**.

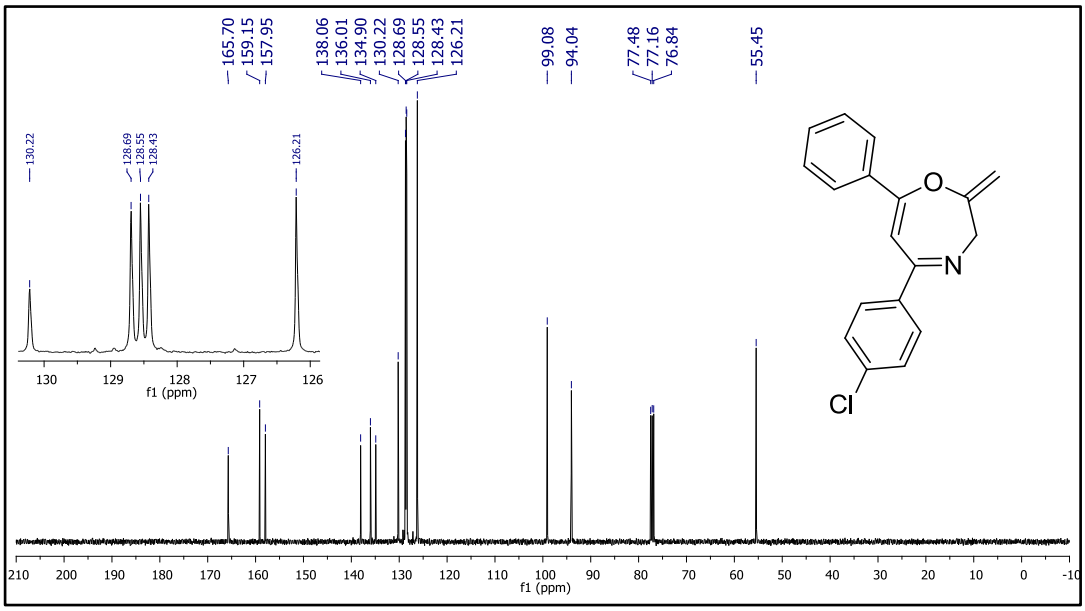

Figure 118. [13]C NMR spectrum of compound **37j**.

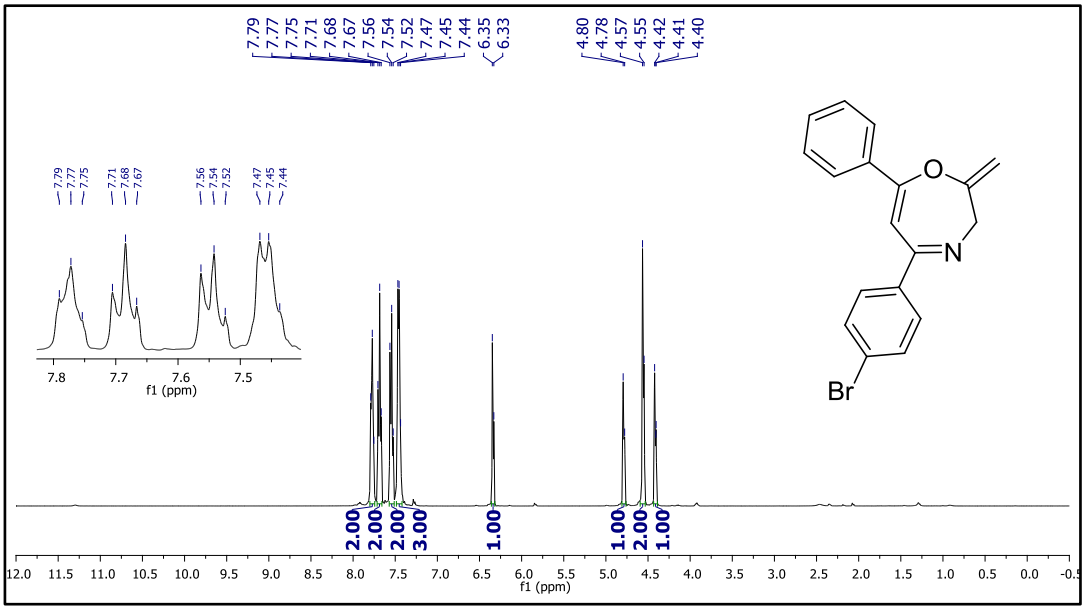

Figure 119. ^{1}H NMR spectrum of compound **37k**.

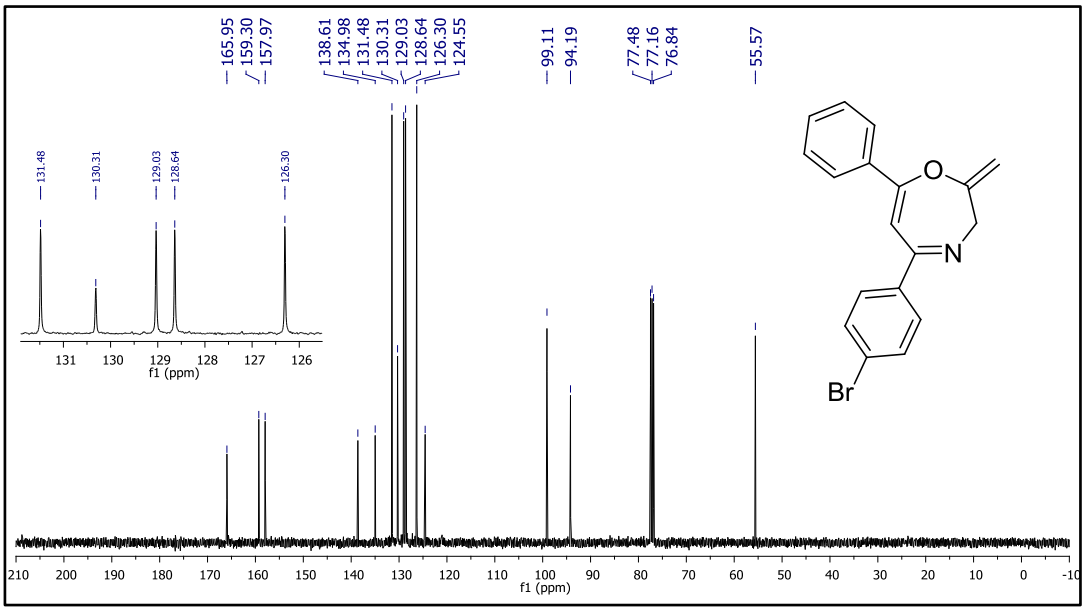

Figure 120. ^{13}C NMR spectrum of compound **37k**.

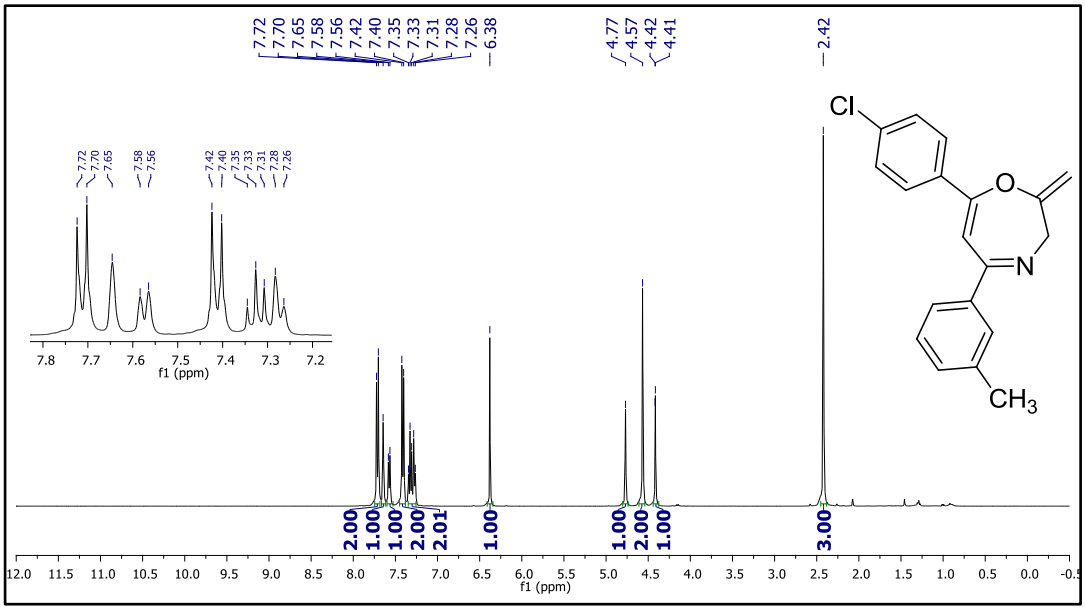

Figure 121. ^{1}H NMR spectrum of compound **37l**.

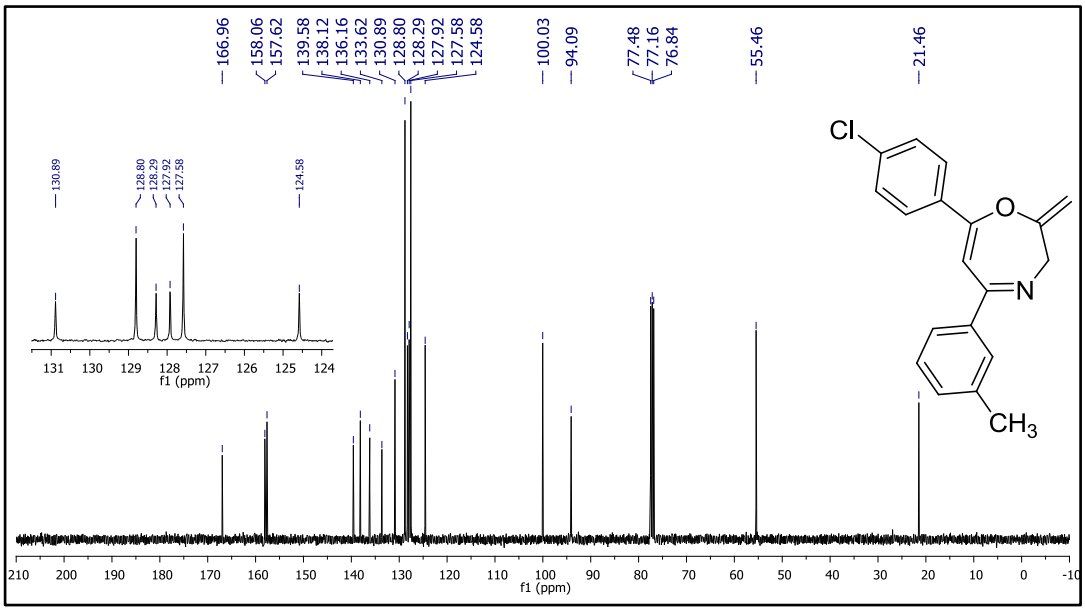

Figure 122. ^{13}C NMR spectrum of compound **37l**.

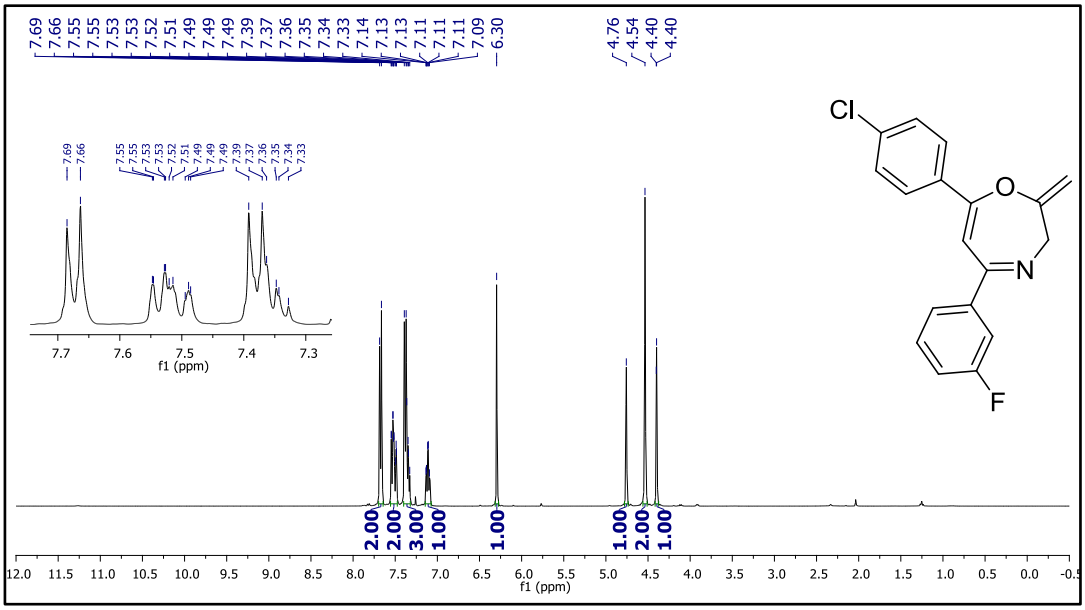

Figure 123. ^{1}H NMR spectrum of compound **37m**.

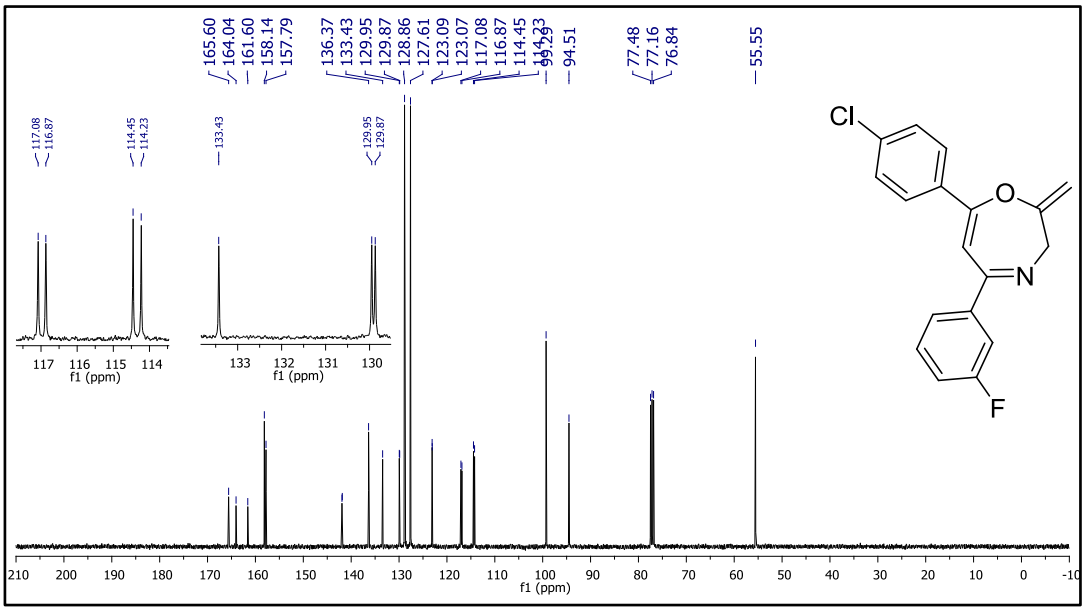

Figure 124. ^{13}C NMR spectrum of compound **37m**.

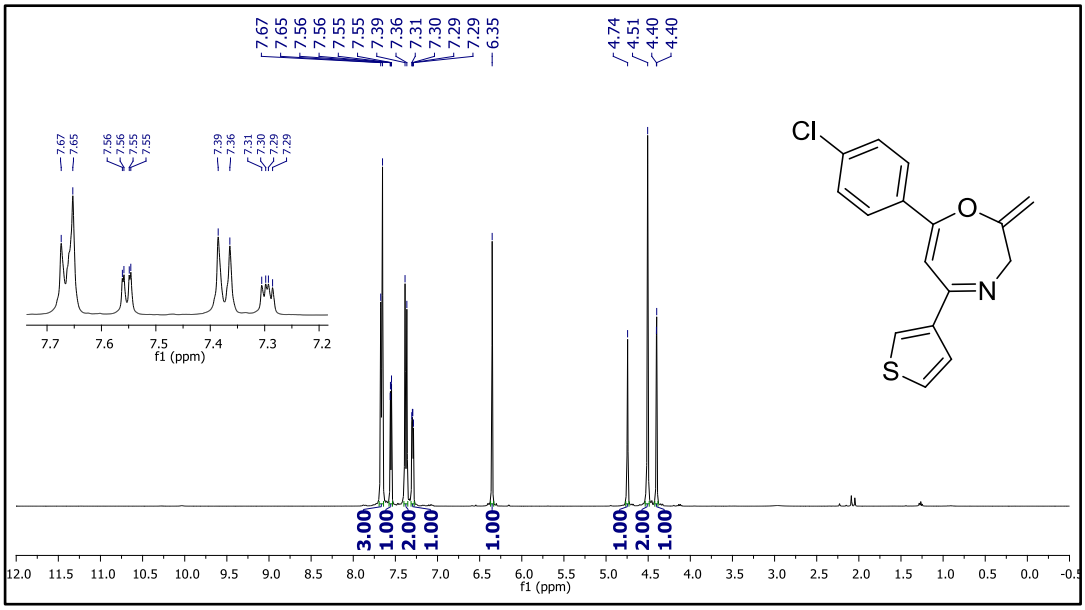

Figure 125. ^{1}H NMR spectrum of compound **37n**.

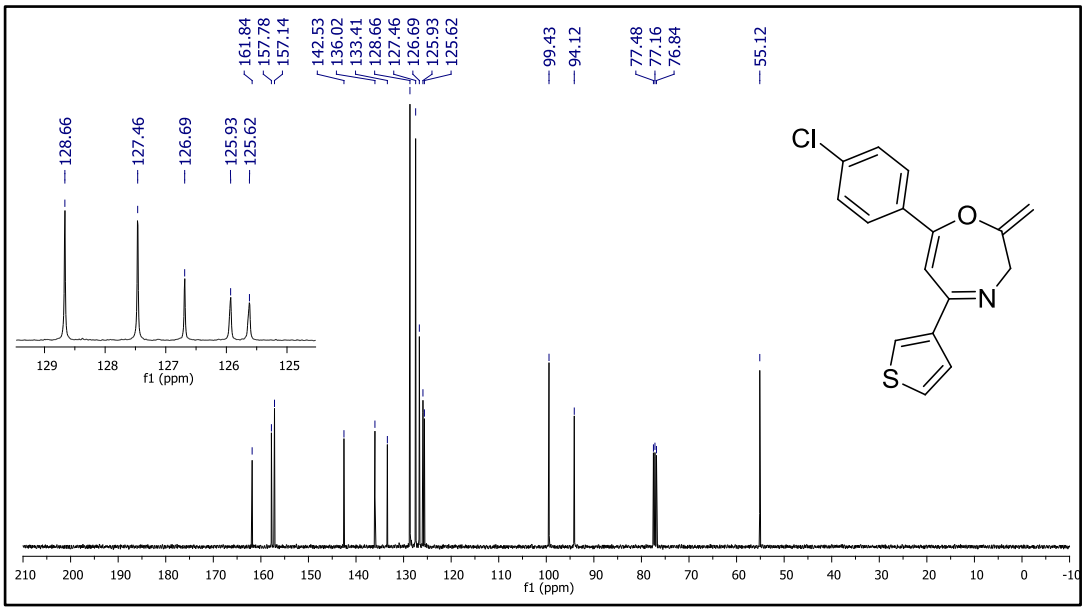

Figure 126. ^{13}C NMR spectrum of compound **37n**.

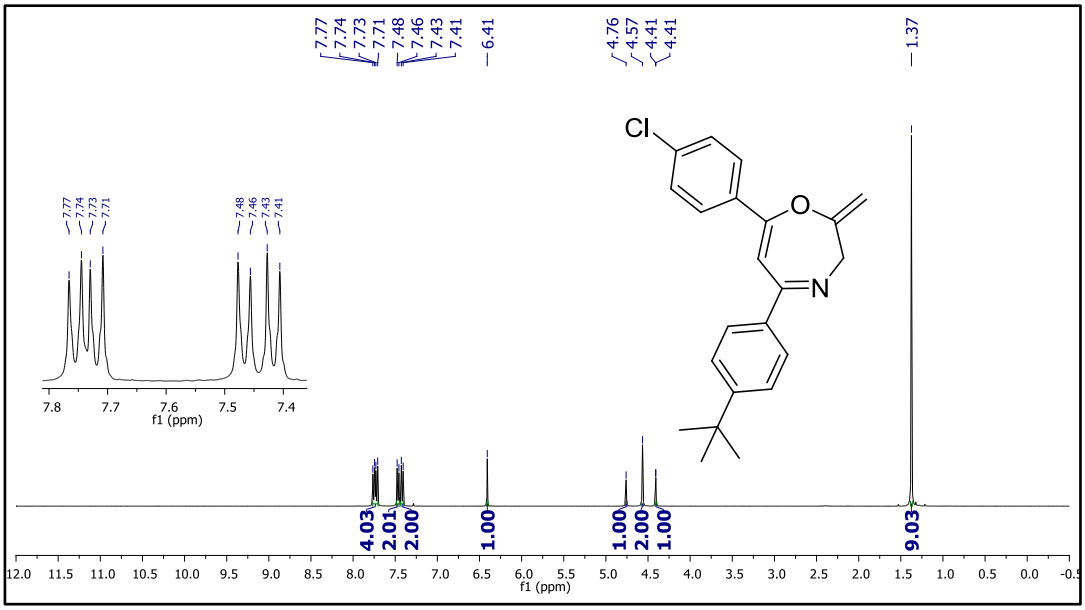

Figure 127. ^{1}H NMR spectrum of compound **37o**.

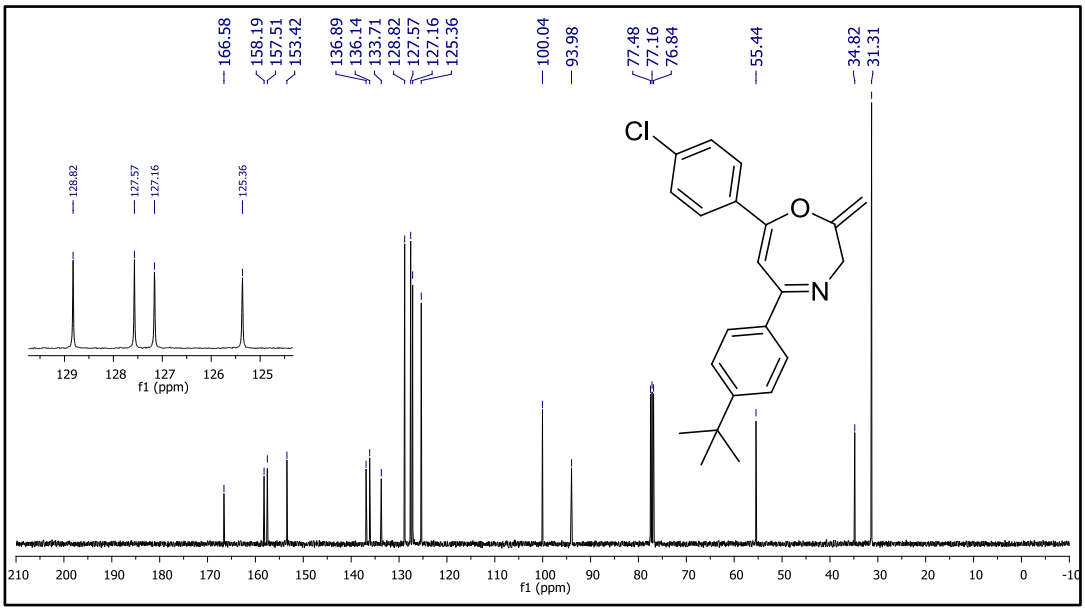

Figure 128. ^{13}C NMR spectrum of compound **37o**.

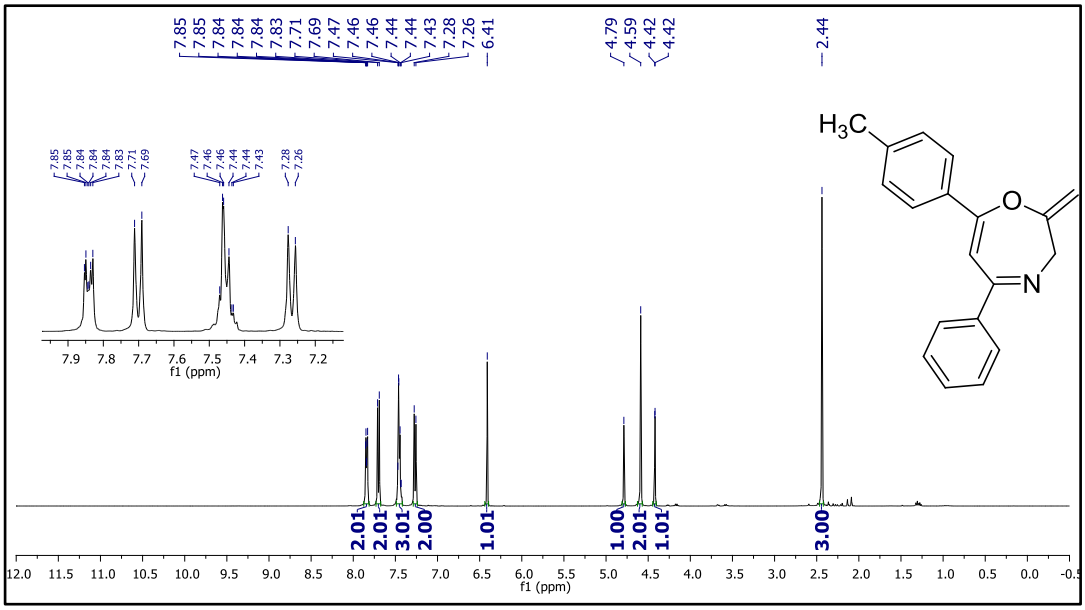

Figure 129. ^{1}H NMR spectrum of compound **37p**.

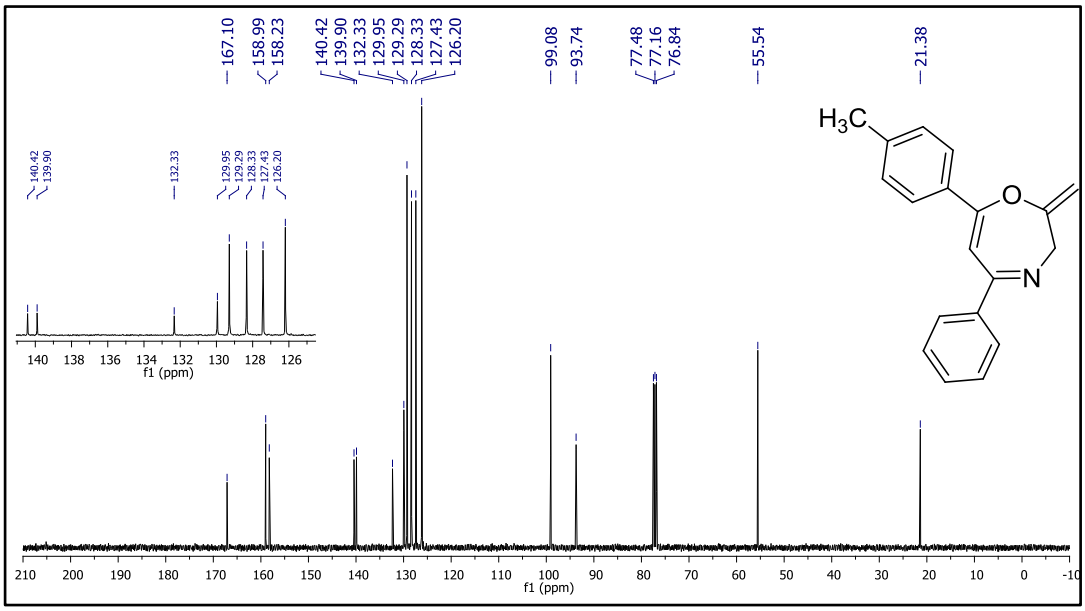

Figure 130. ^{13}C NMR spectrum of compound **37p**.

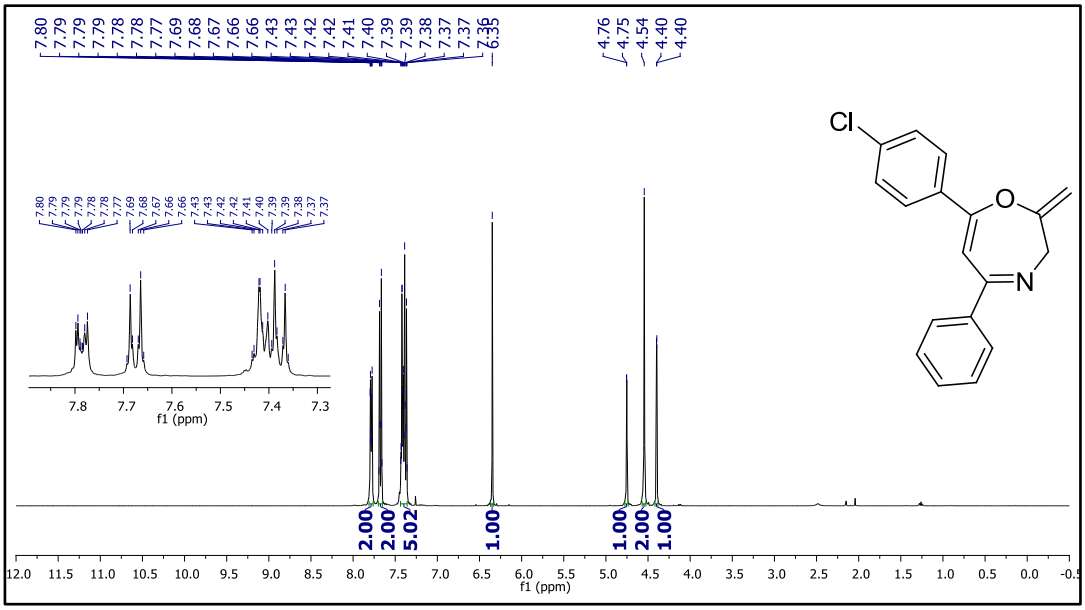

Figure 131. ^{1}H NMR spectrum of compound **37q**.

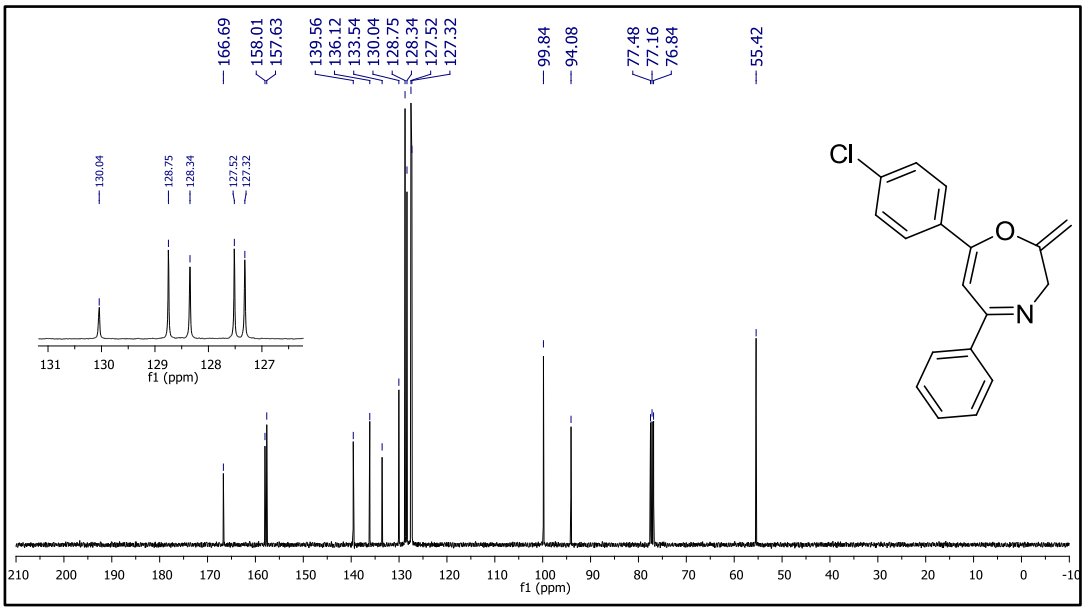

Figure 132. ^{13}C NMR spectrum of compound **37q**.

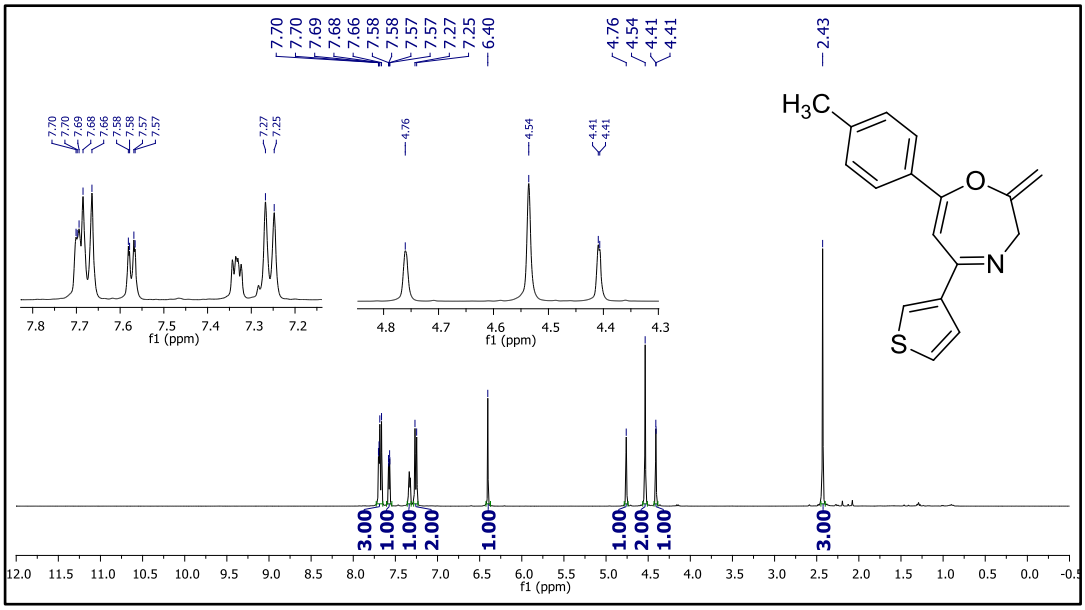

Figure 133. ^{1}H NMR spectrum of compound **37r**.

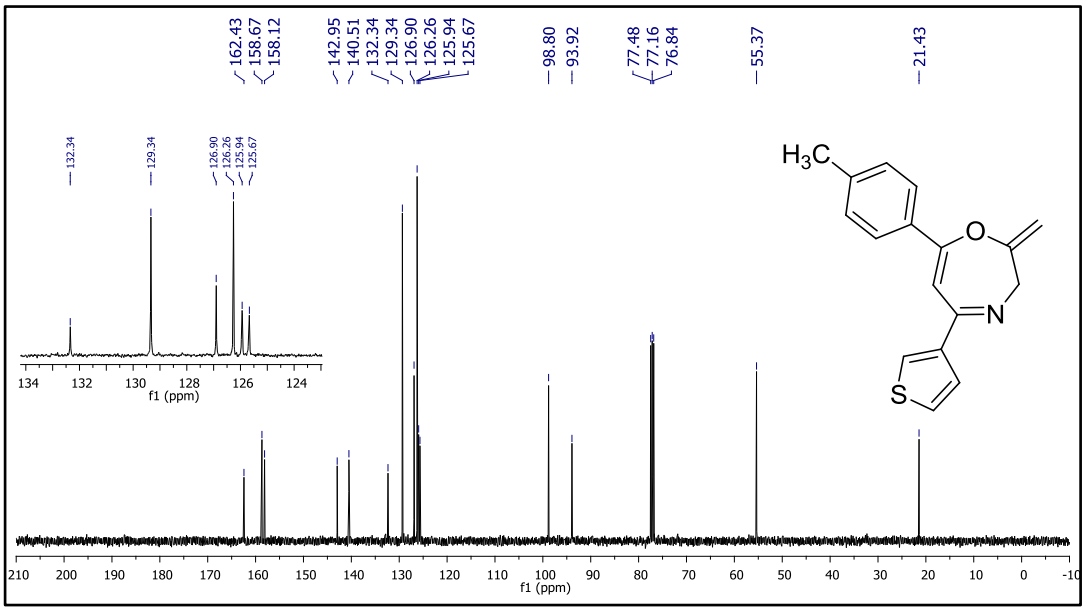

Figure 134. ^{13}C NMR spectrum of compound **37r**.

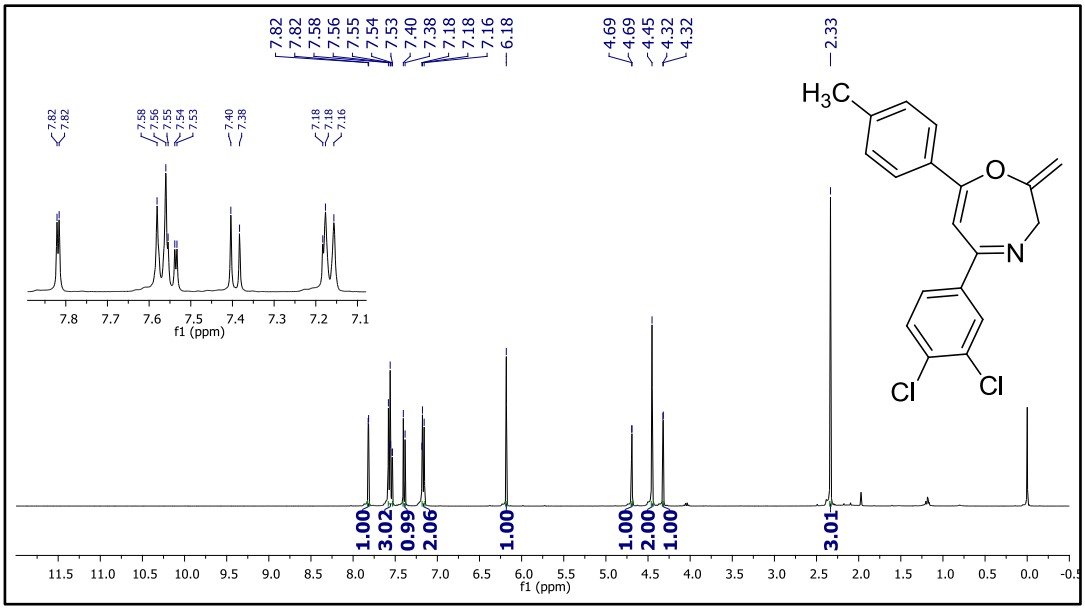

Figure 135. ^{1}H NMR spectrum of compound **37s**.

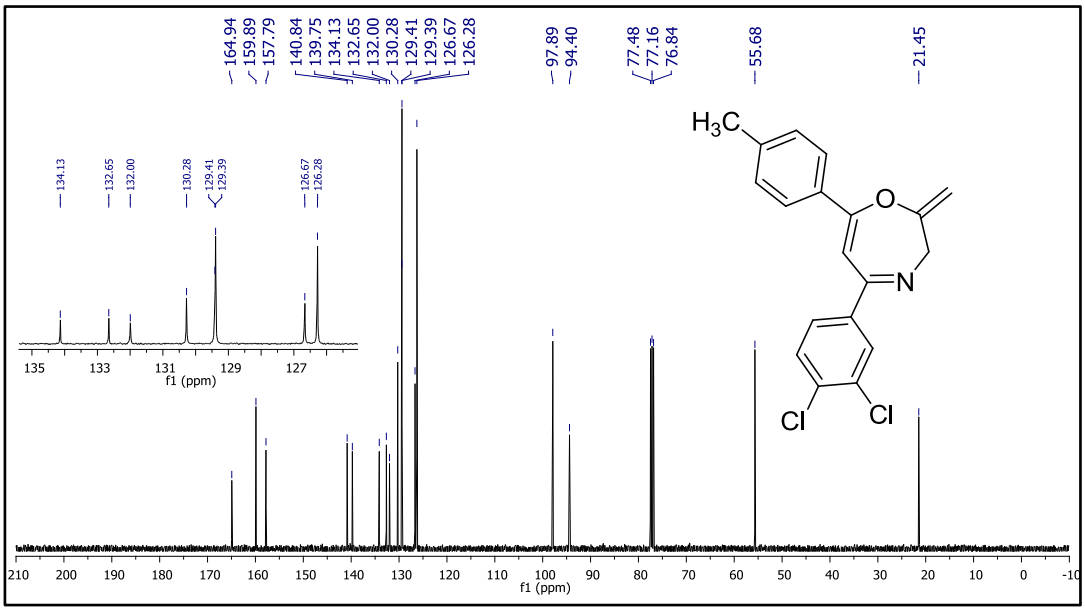

Figure 136. ^{13}C NMR spectrum of compound **37s**.

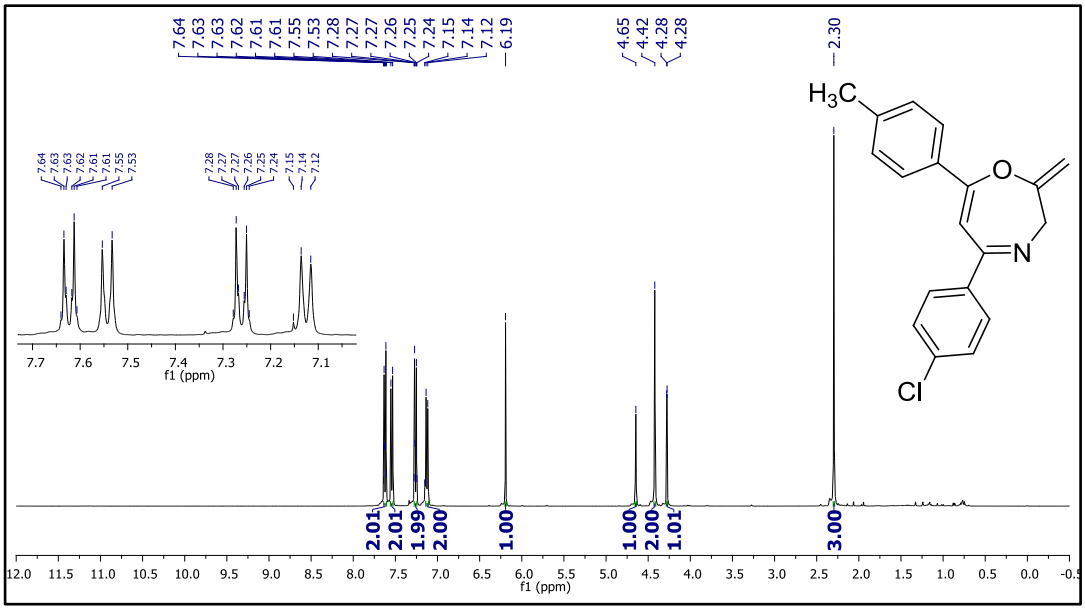

Figure 137. ^{1}H NMR spectrum of compound **37t**.

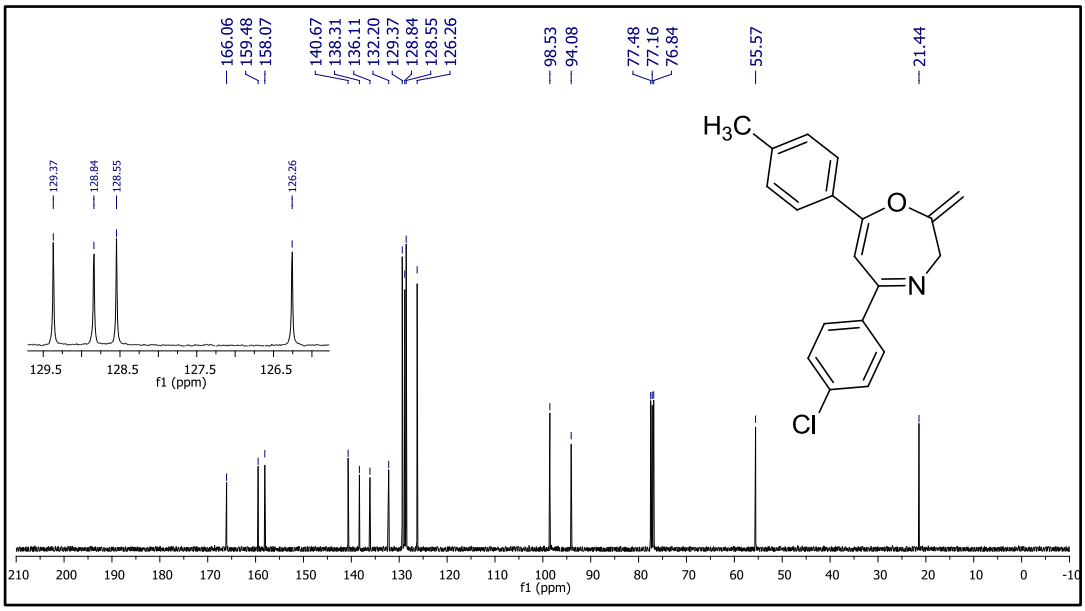

Figure 138. ^{13}C NMR spectrum of compound **37t**.

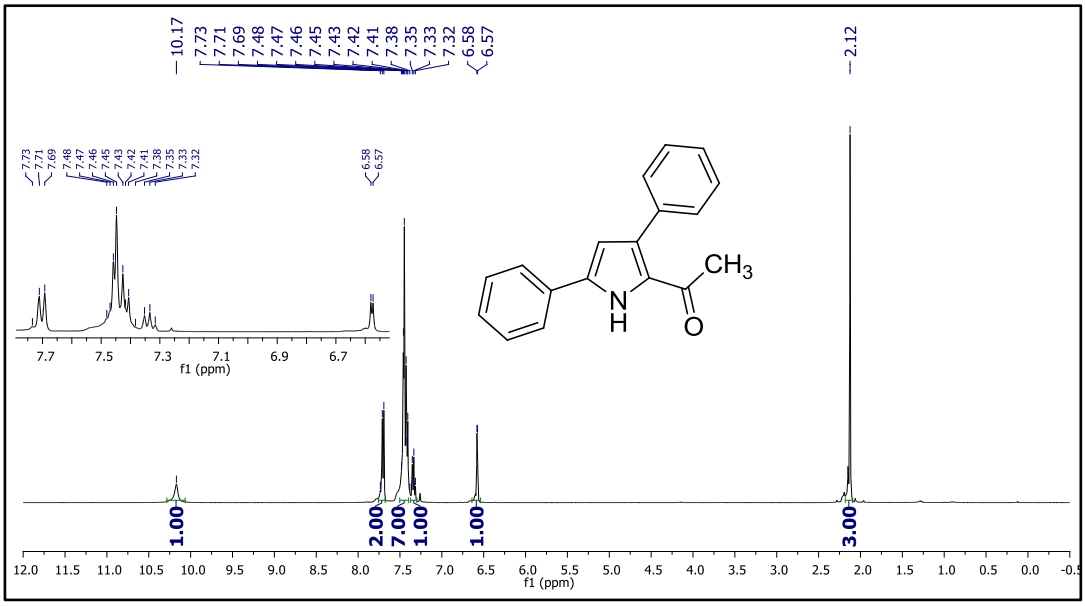

Figure 139. ^{1}H NMR spectrum of compound **46a**.

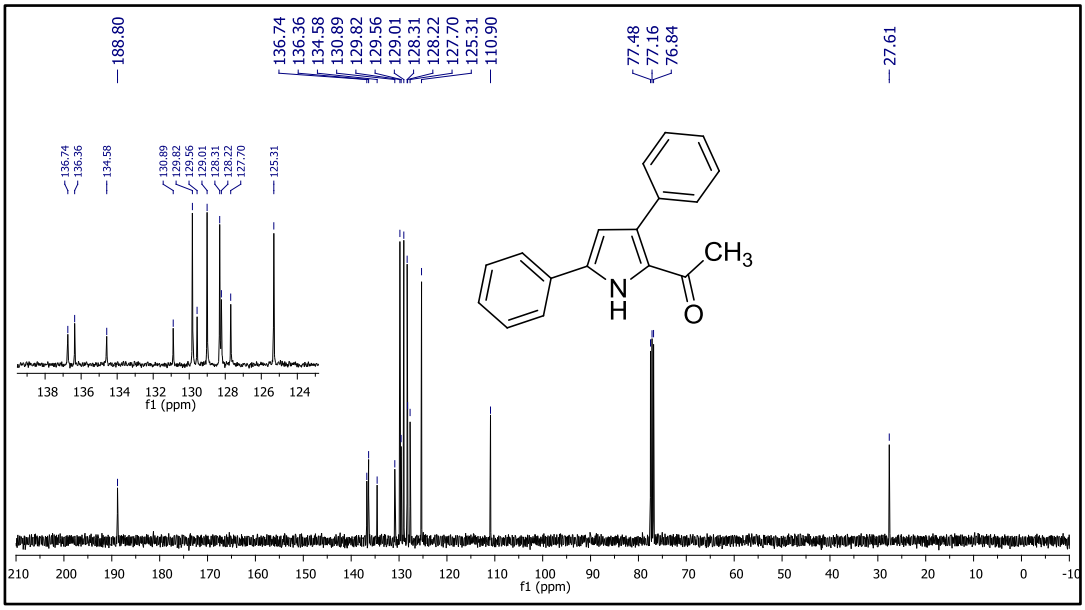

Figure 140. ^{13}C NMR spectrum of compound **46a**.

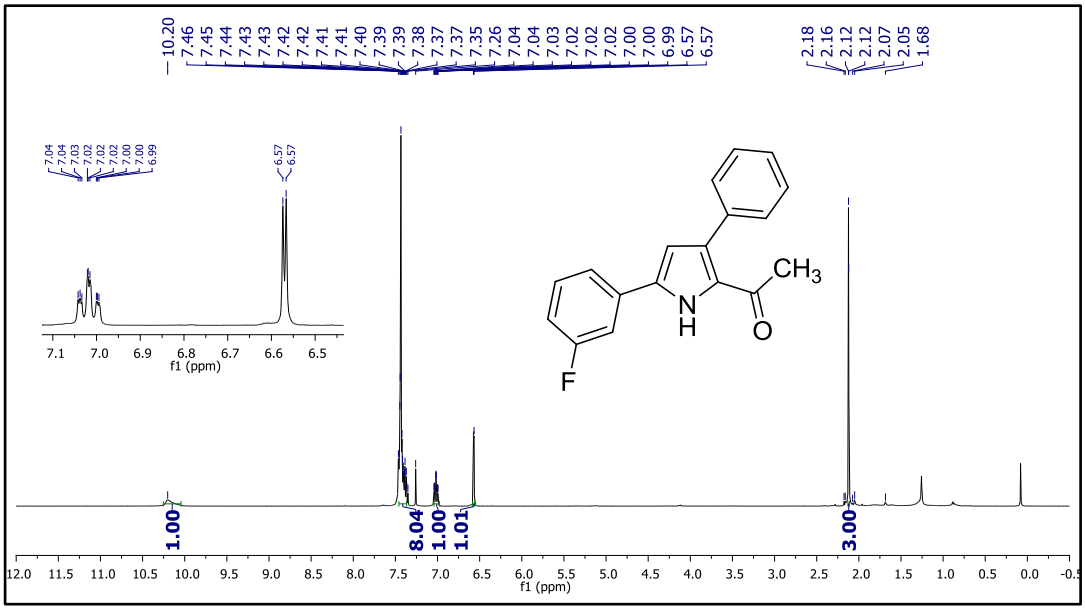

Figure 141. ^{1}H NMR spectrum of compound **46b**.

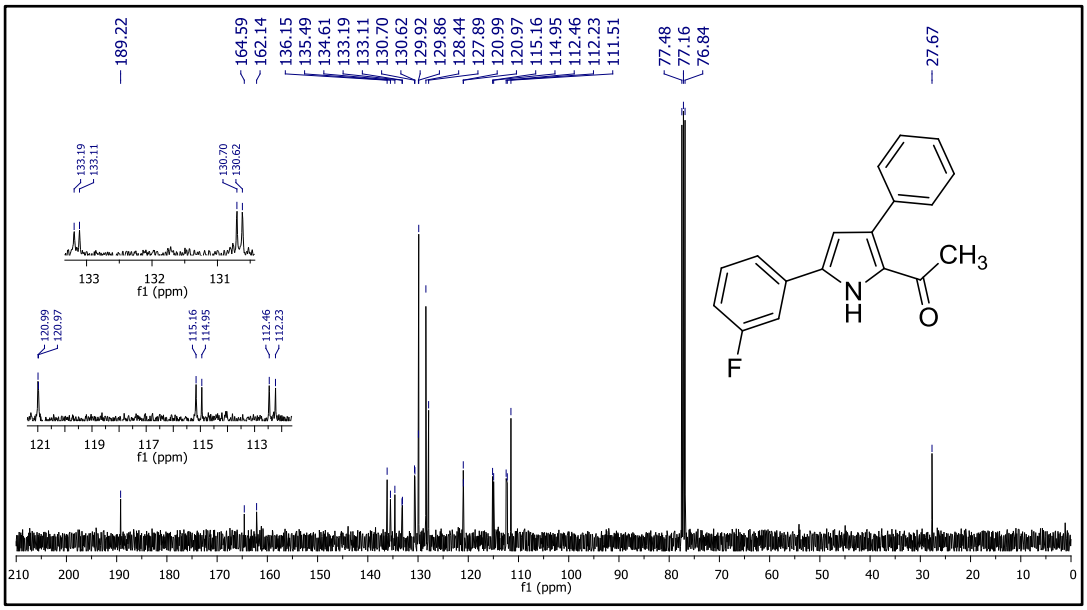

Figure 142. ^{13}C NMR spectrum of compound **46b**.

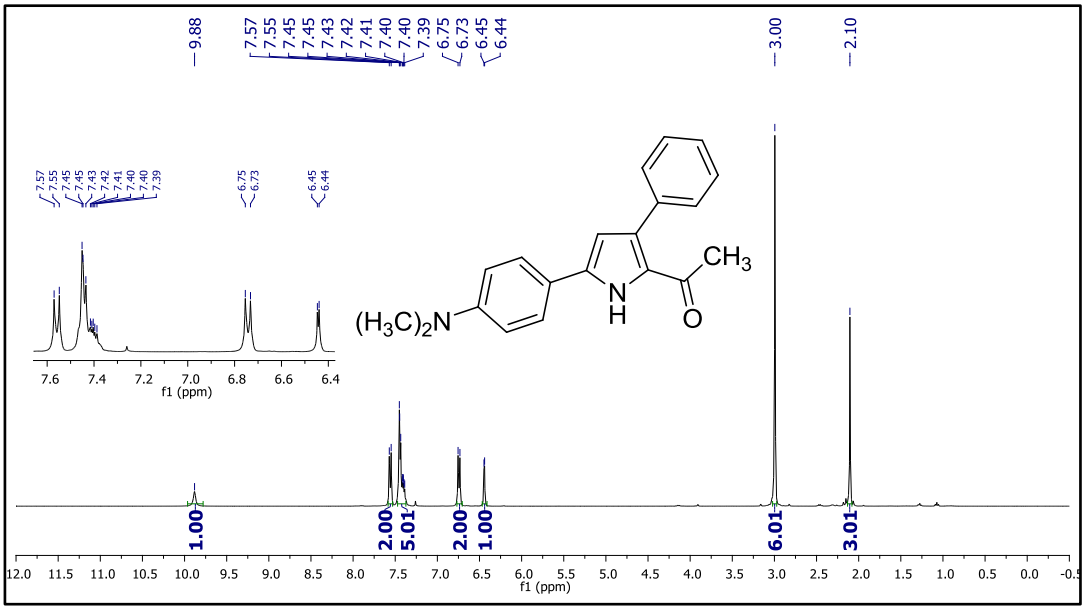

Figure 143. ^{1}H NMR spectrum of compound **46c**.

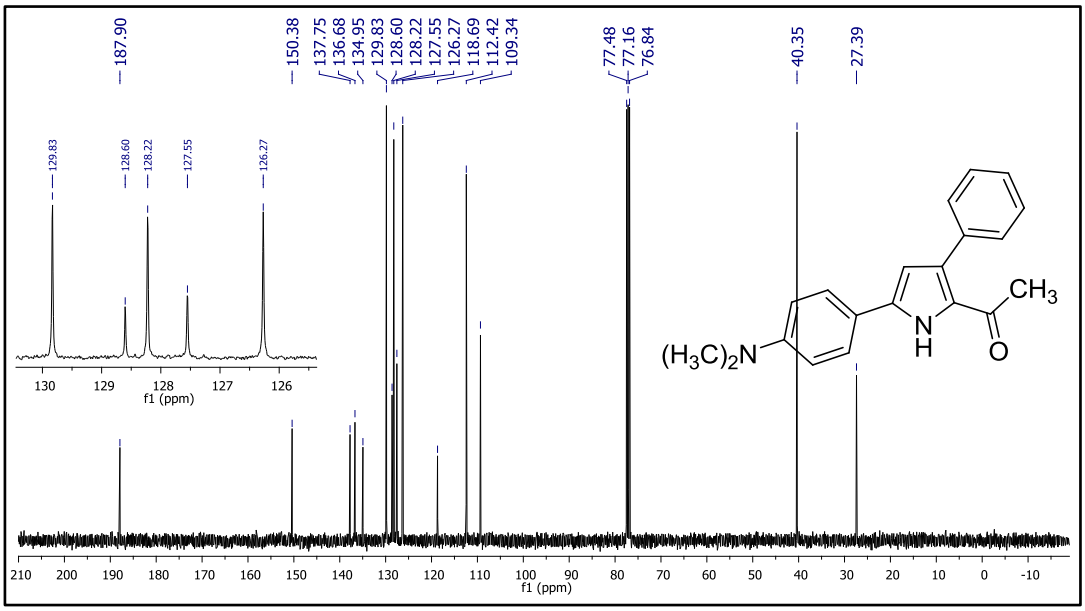

Figure 144. ^{1}H NMR spectrum of compound **46c**.

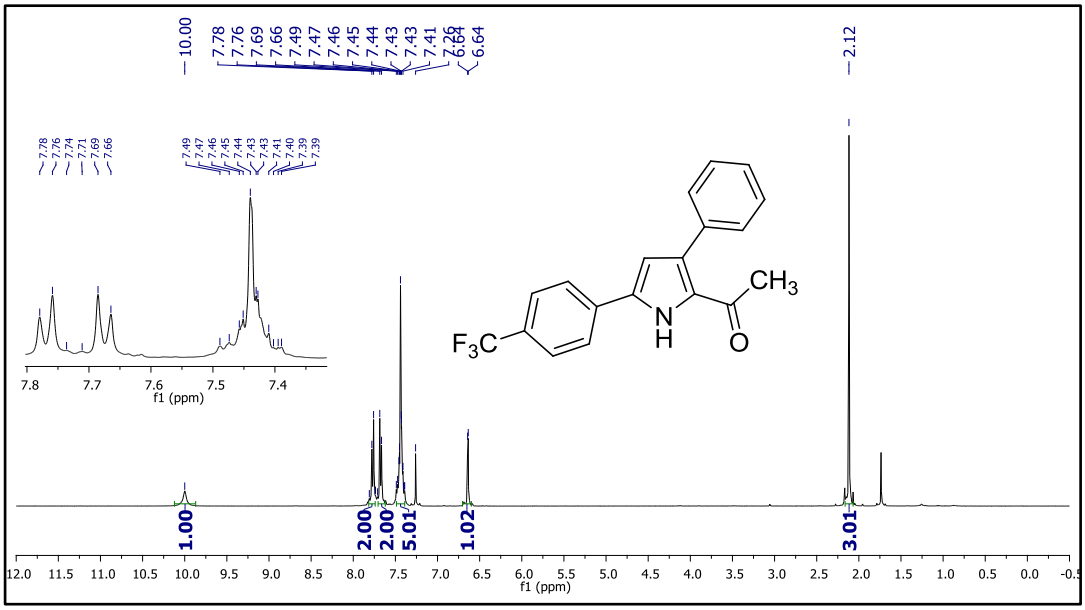

Figure 145. ^{1}H NMR spectrum of compound **46d**.

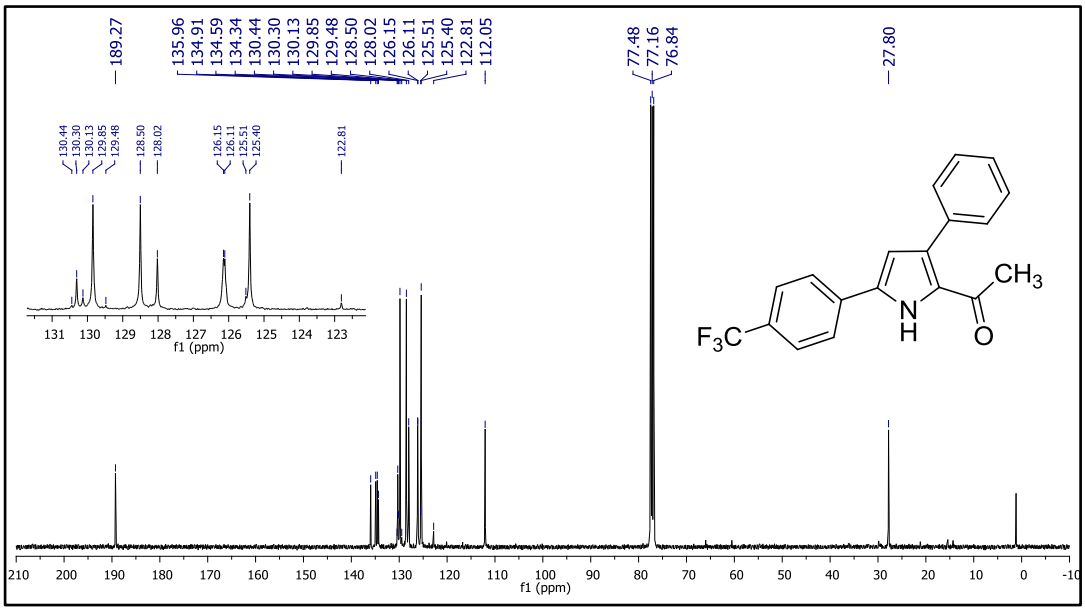

Figure 146. ^{13}C NMR spectrum of compound **46d**.

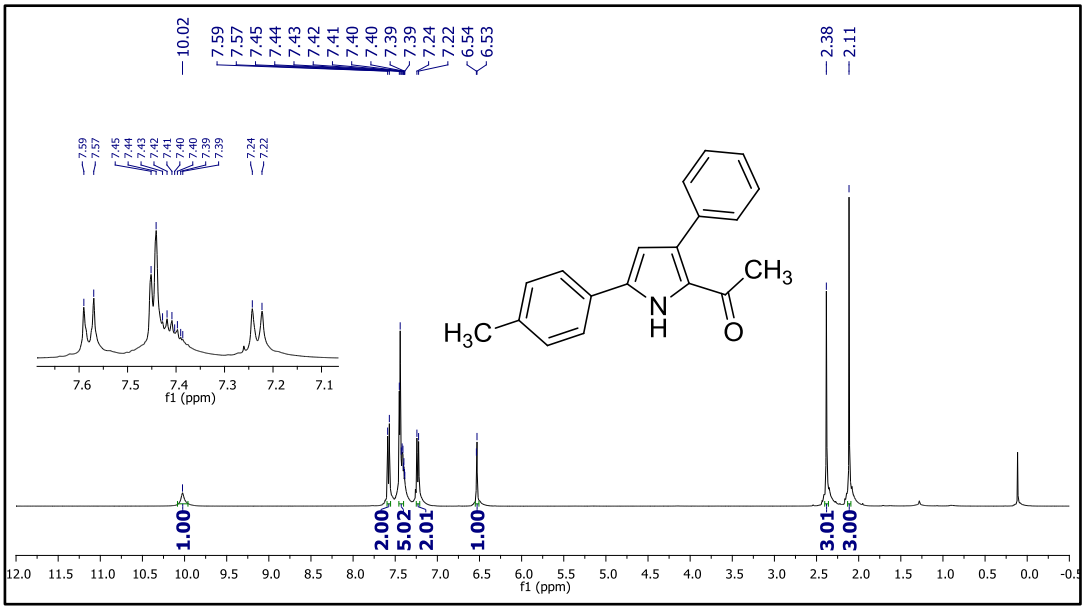

Figure 147. ^{1}H NMR spectrum of compound **46e**.

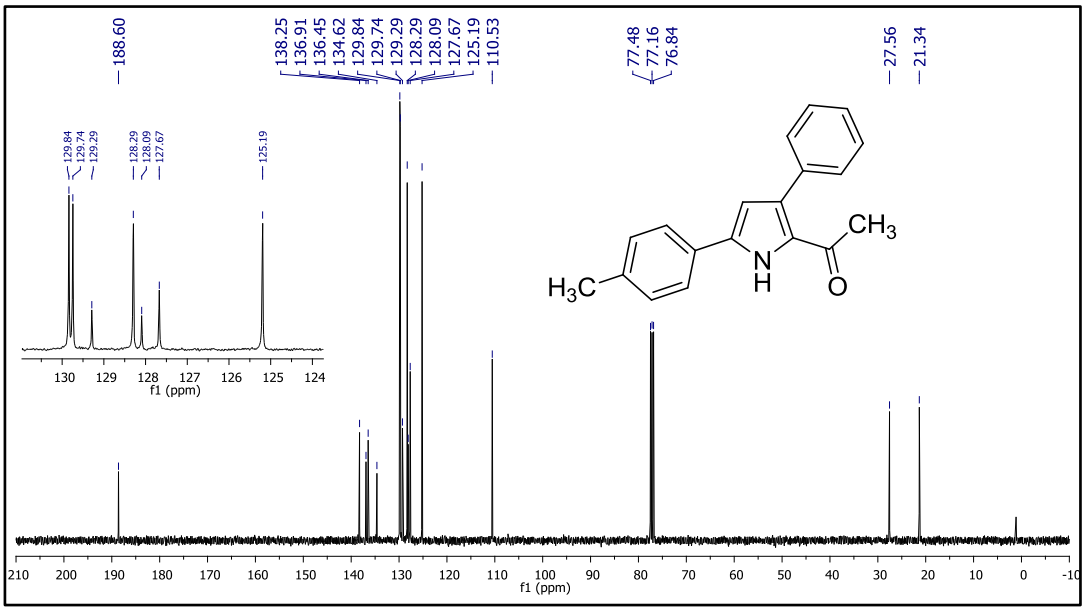

Figure 148. ^{13}C NMR spectrum of compound **46e**.

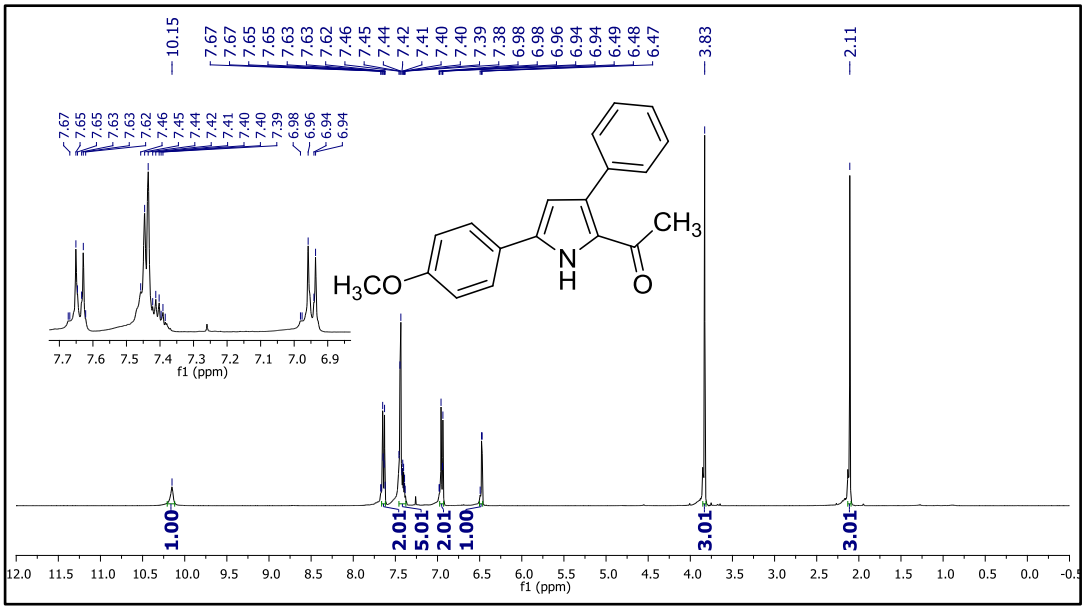

Figure 149. ^{1}H NMR spectrum of compound **46f**.

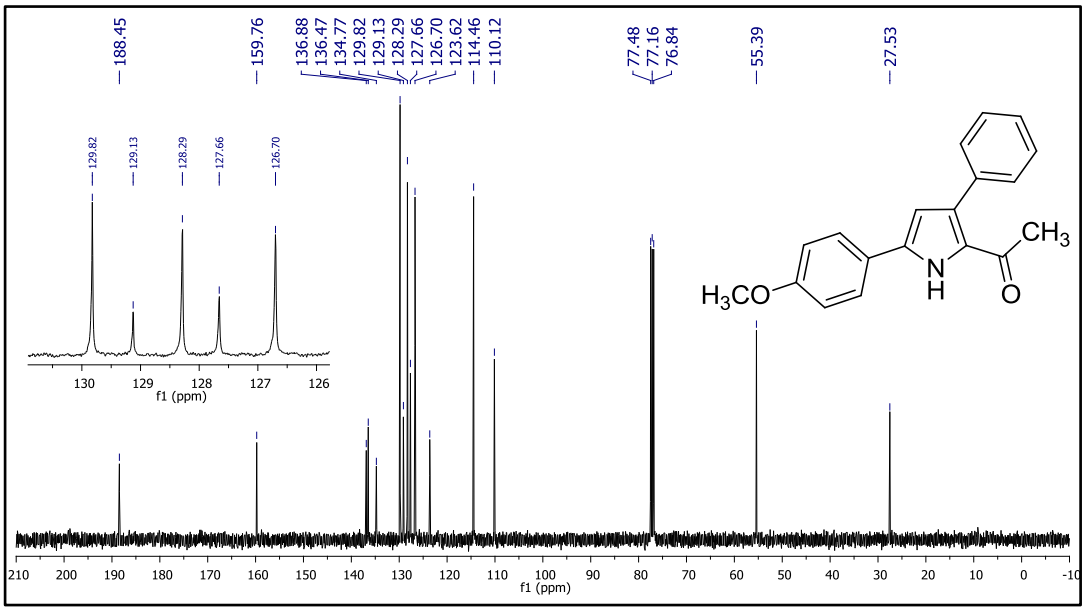

Figure 150. ^{13}C NMR spectrum of compound **46f**.

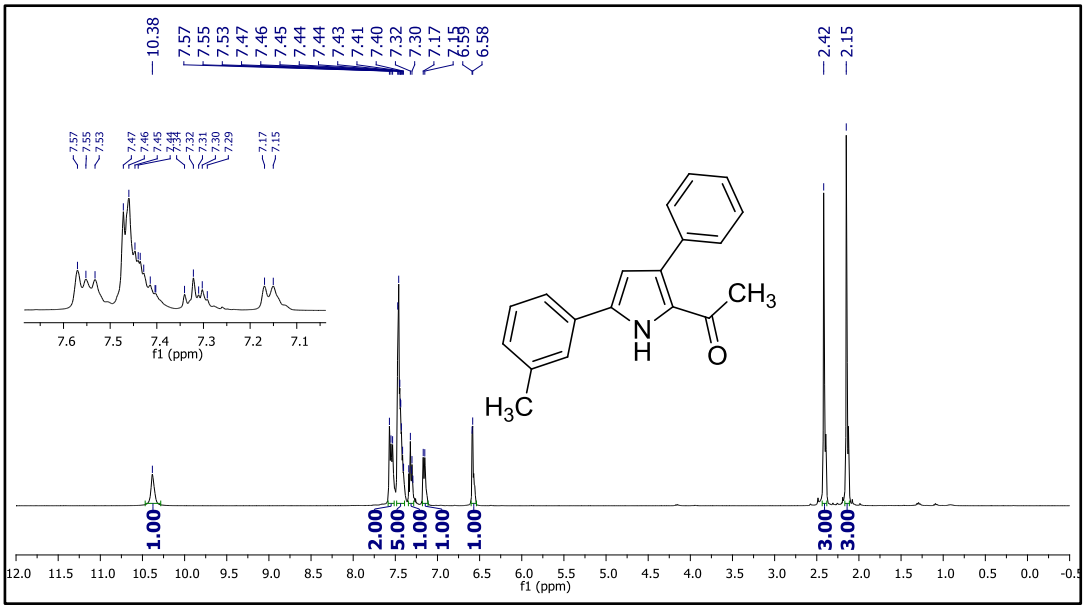

Figure 151. ^{1}H NMR spectrum of compound **46g**.

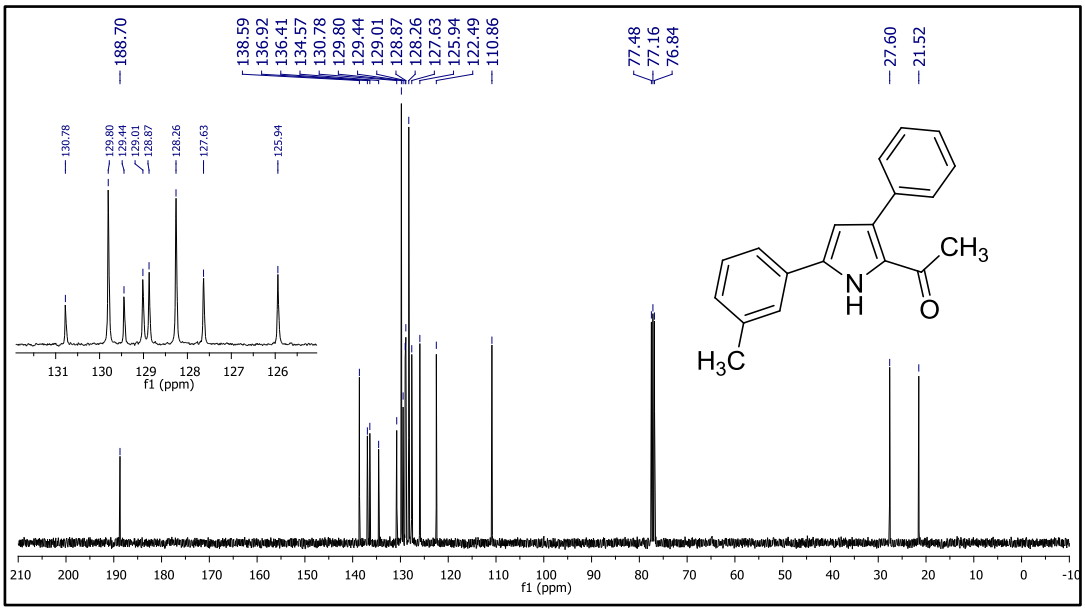

Figure 152. ^{13}C NMR spectrum of compound **46g**.

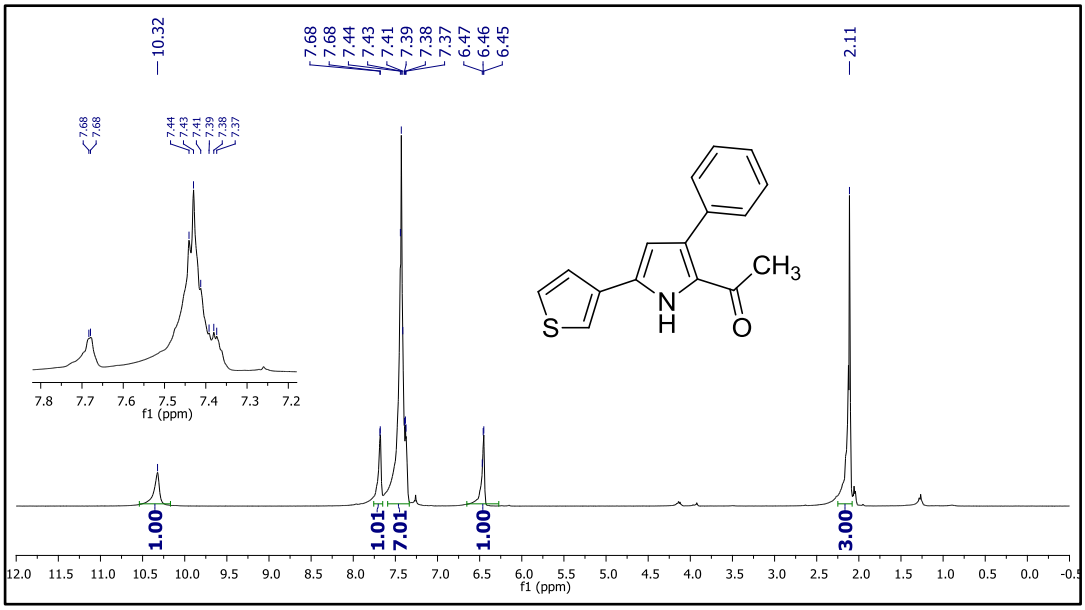

Figure 153. ^{1}H NMR spectrum of compound 46h.

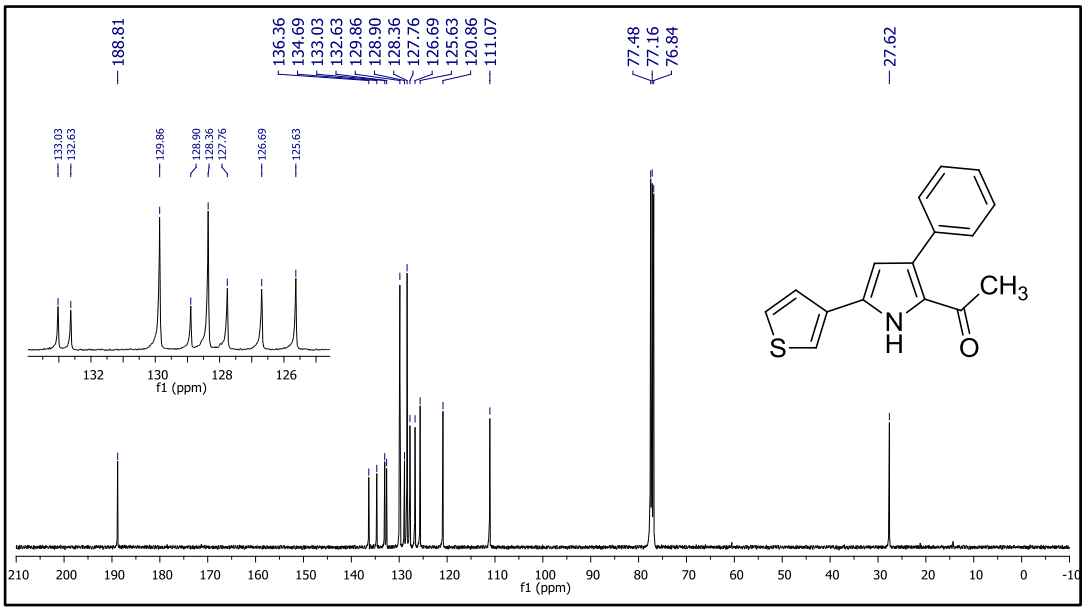

Figure 154. ^{13}C NMR spectrum of compound **46h**.

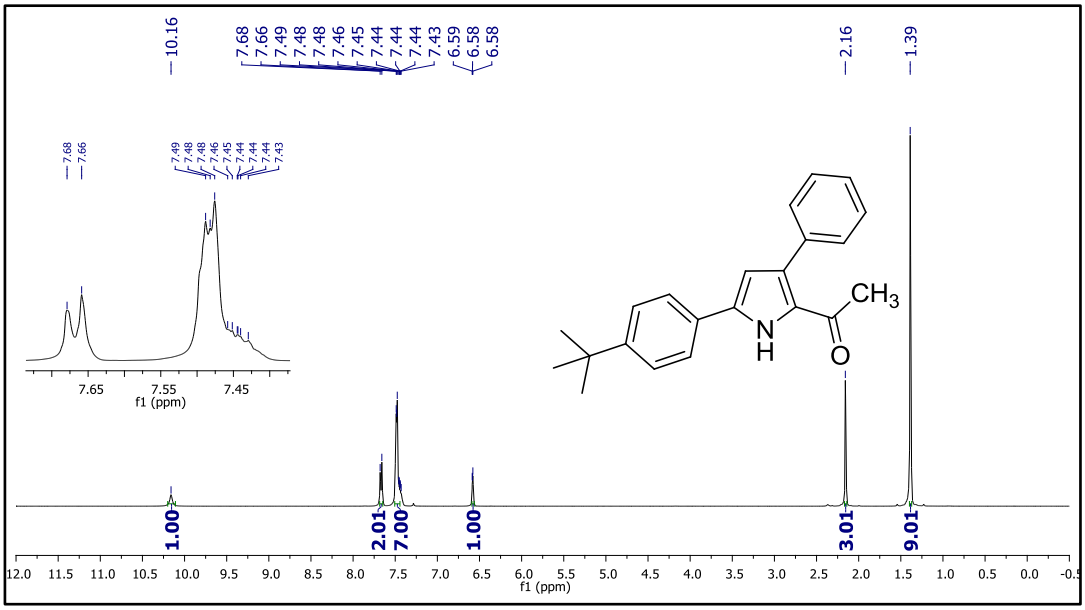

Figure 155. ^{1}H NMR spectrum of compound **46i**.

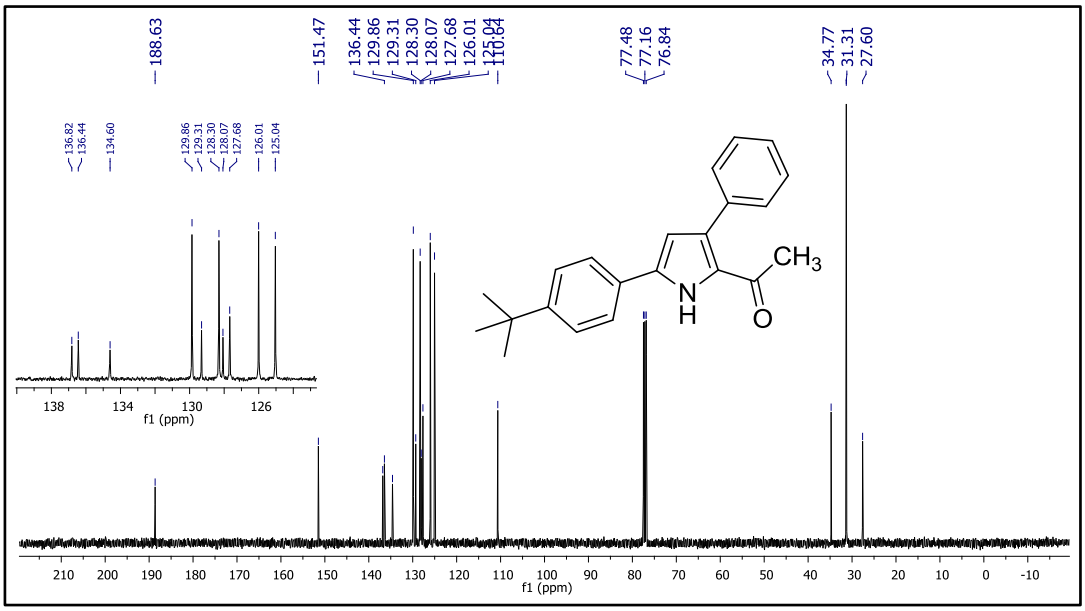

Figure 156. ^{13}C NMR spectrum of compound **46i**.

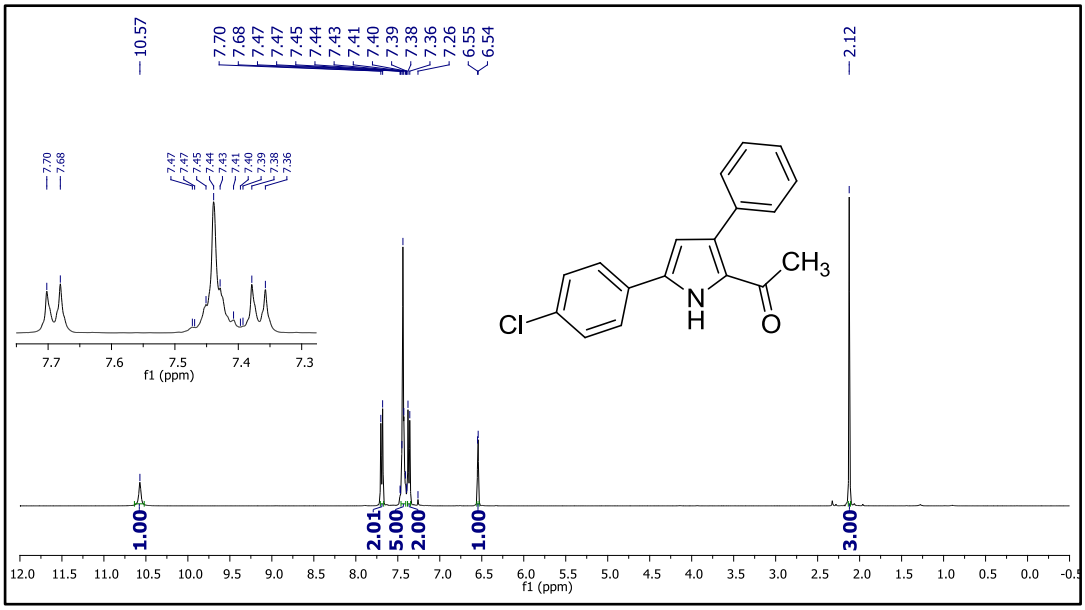

Figure 157. ^{1}H NMR spectrum of compound **46j**.

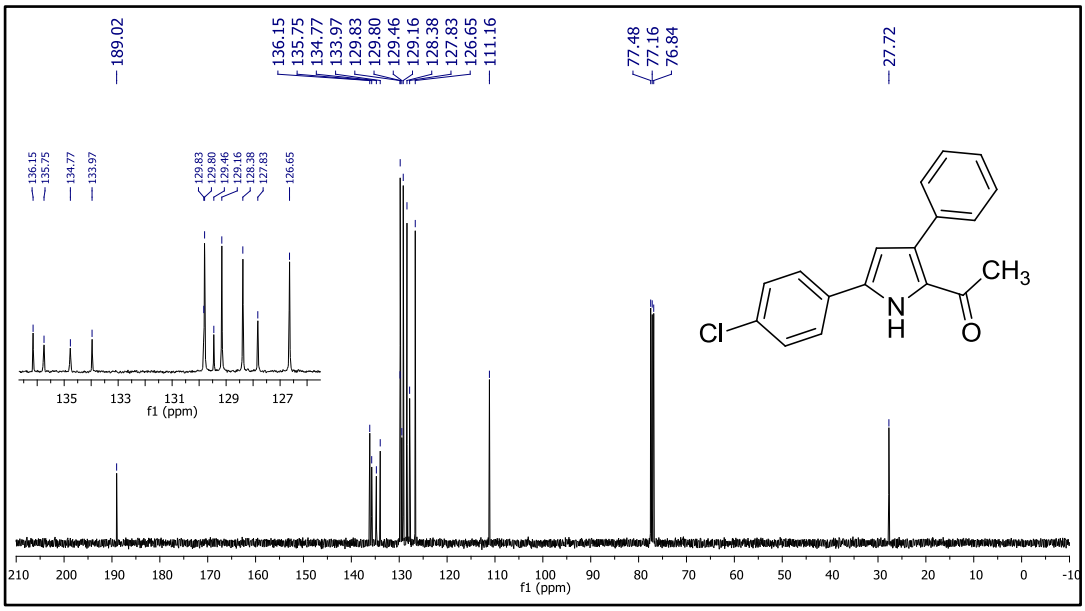

Figure 158. ^{13}C NMR spectrum of compound **46j**.

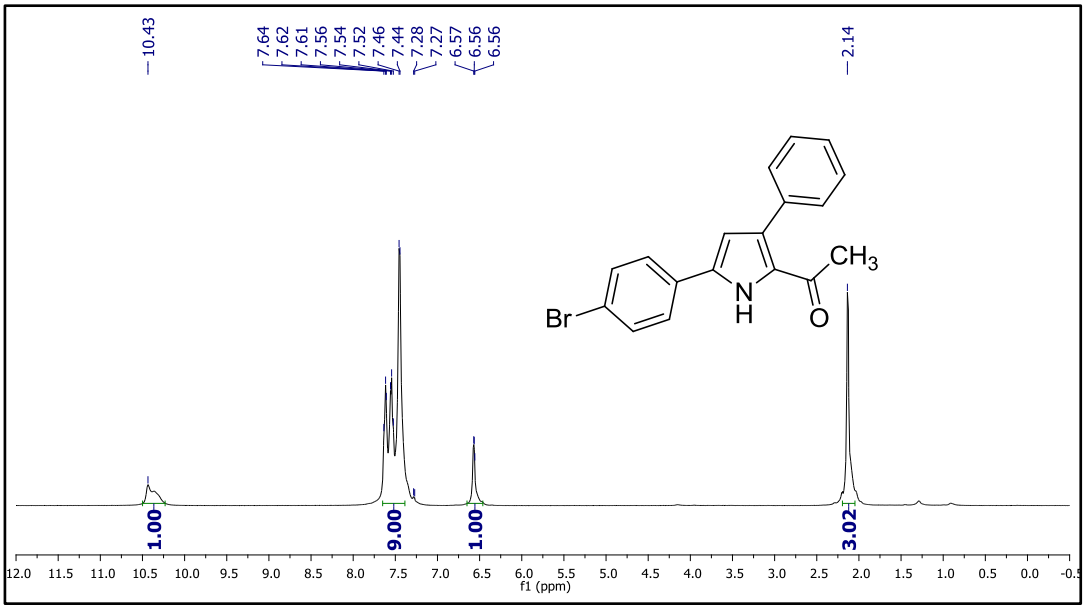

Figure 159. ^{1}H NMR spectrum of compound **46k**.

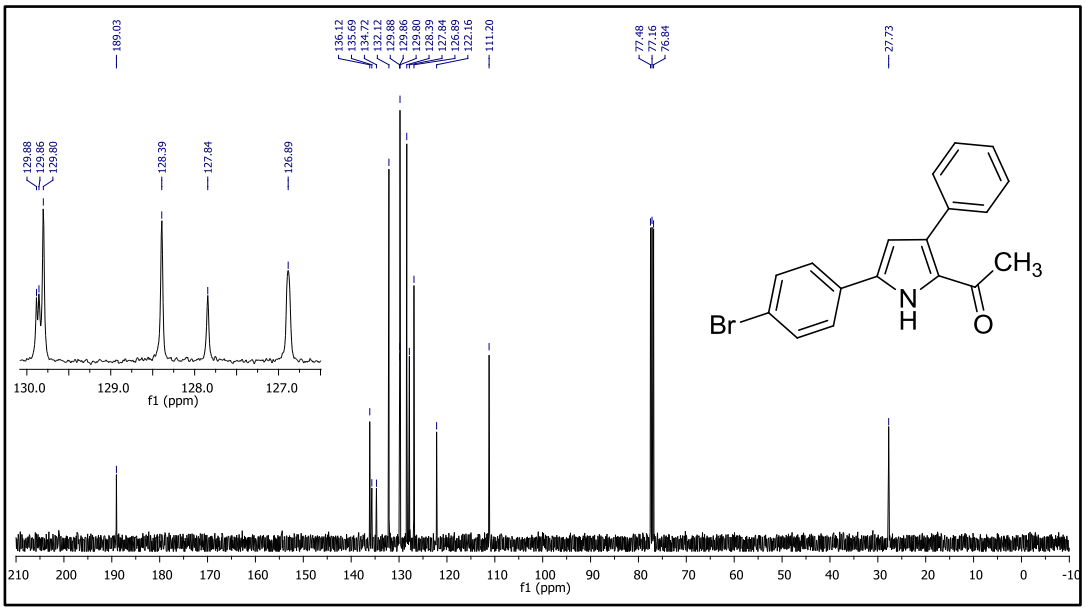

Figure 160. ^{13}C NMR spectrum of compound **46k**.

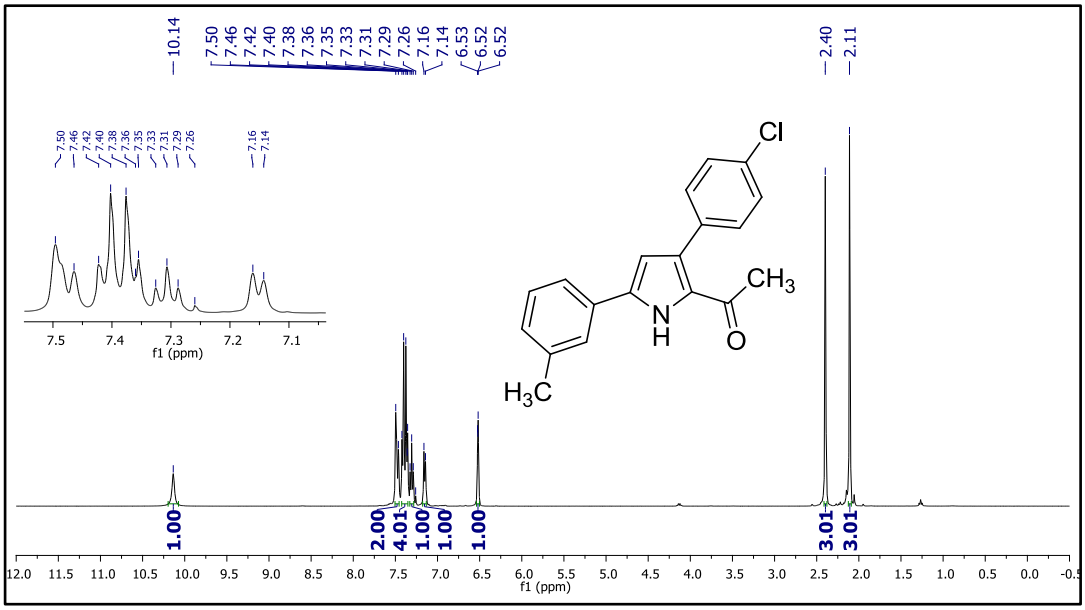

Figure 161. ^{1}H NMR spectrum of compound **46l**.

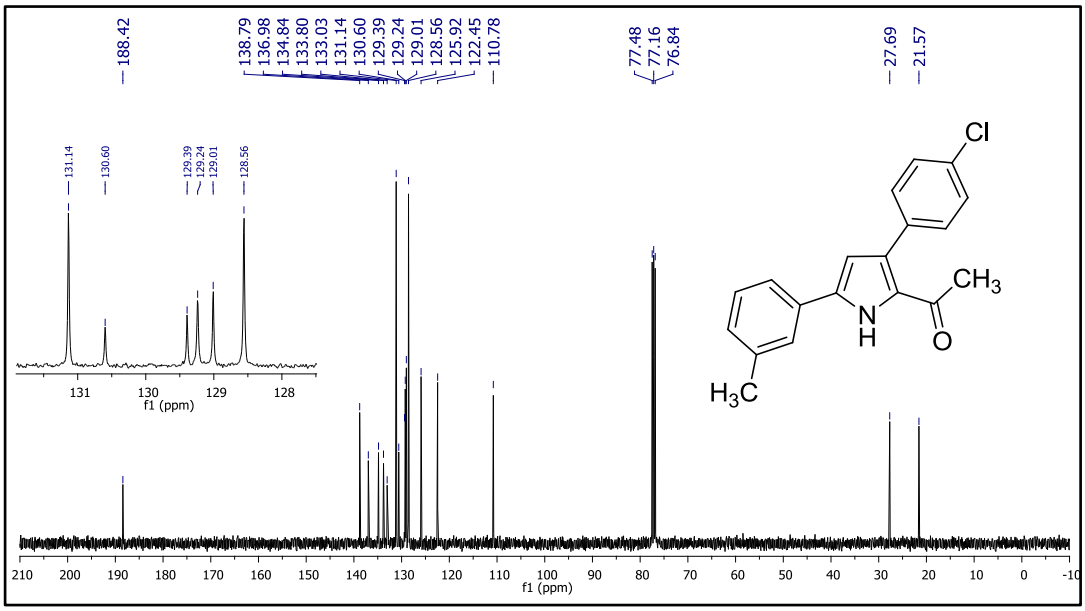

Figure 162. ^{13}C NMR spectrum of compound **46l**.

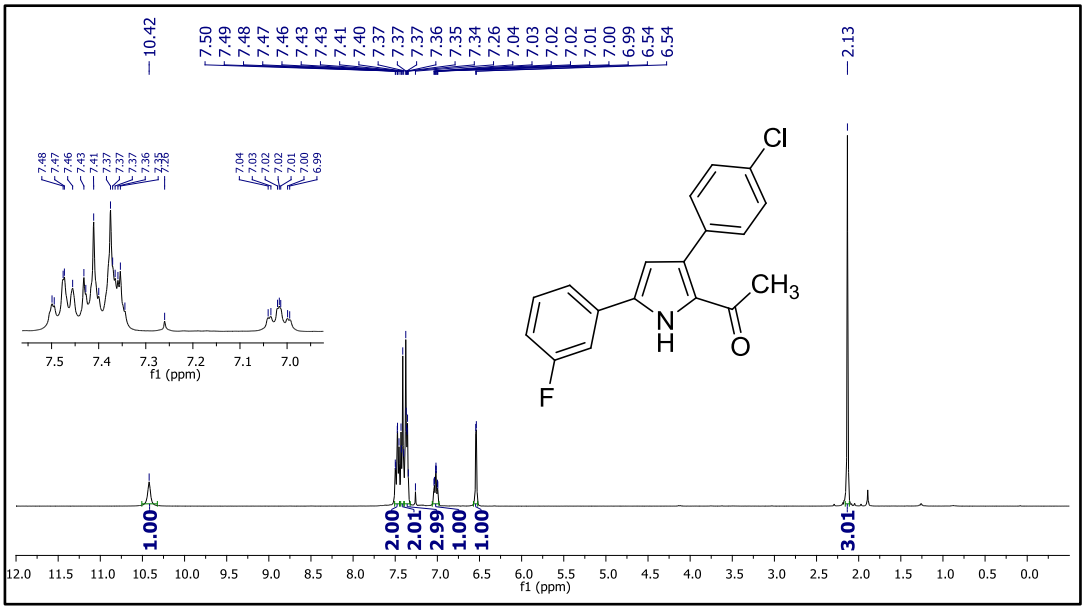

Figure 163. ^{1}H NMR spectrum of compound **46m**.

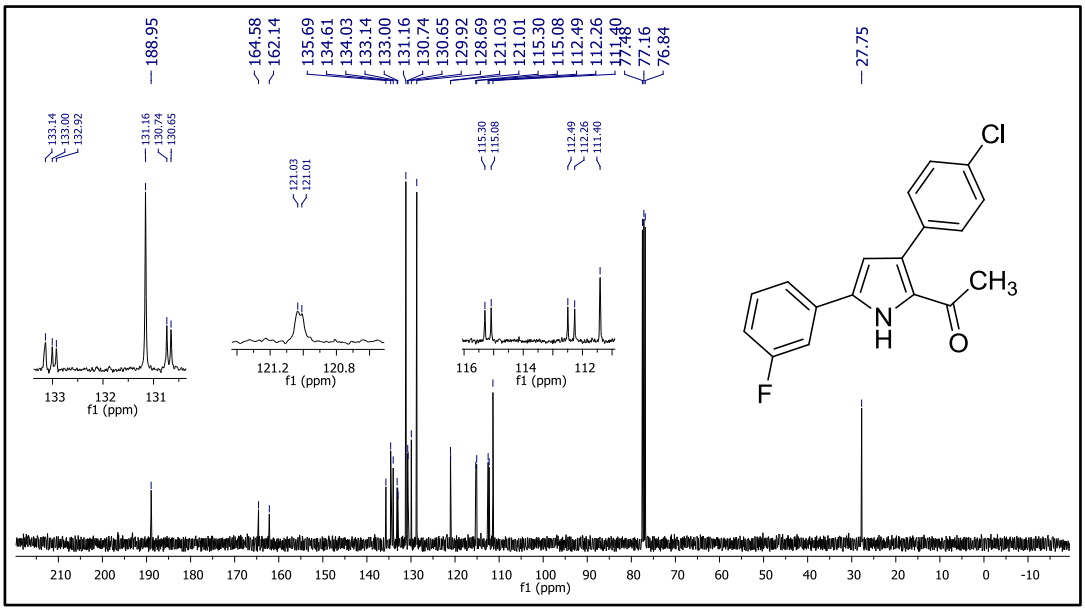

Figure 164. ^{13}C NMR spectrum of compound **46m**.

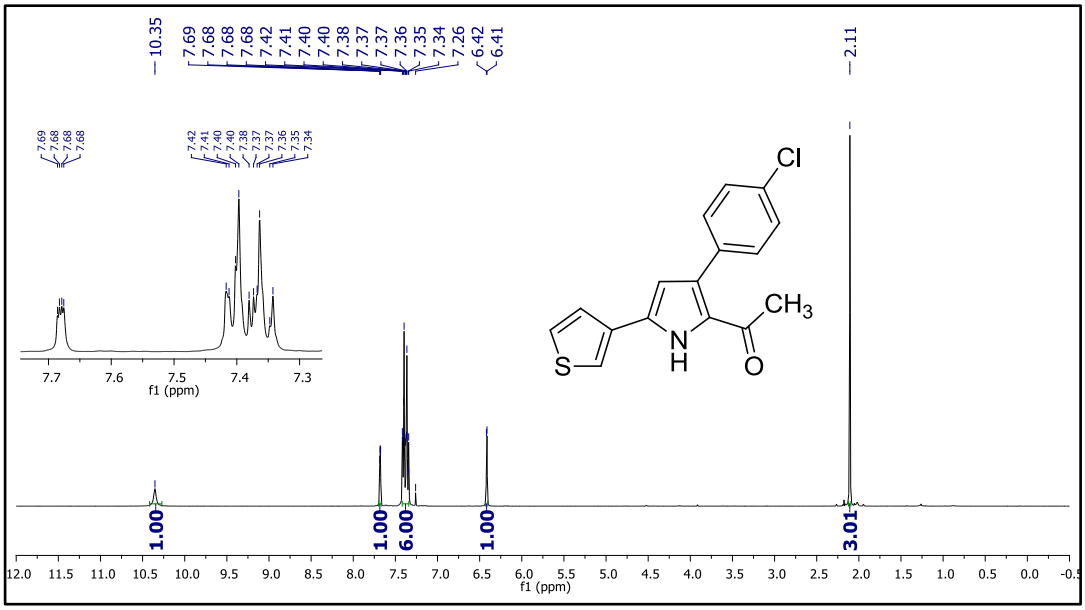

Figure 165. ^{1}H NMR spectrum of compound **46n**.

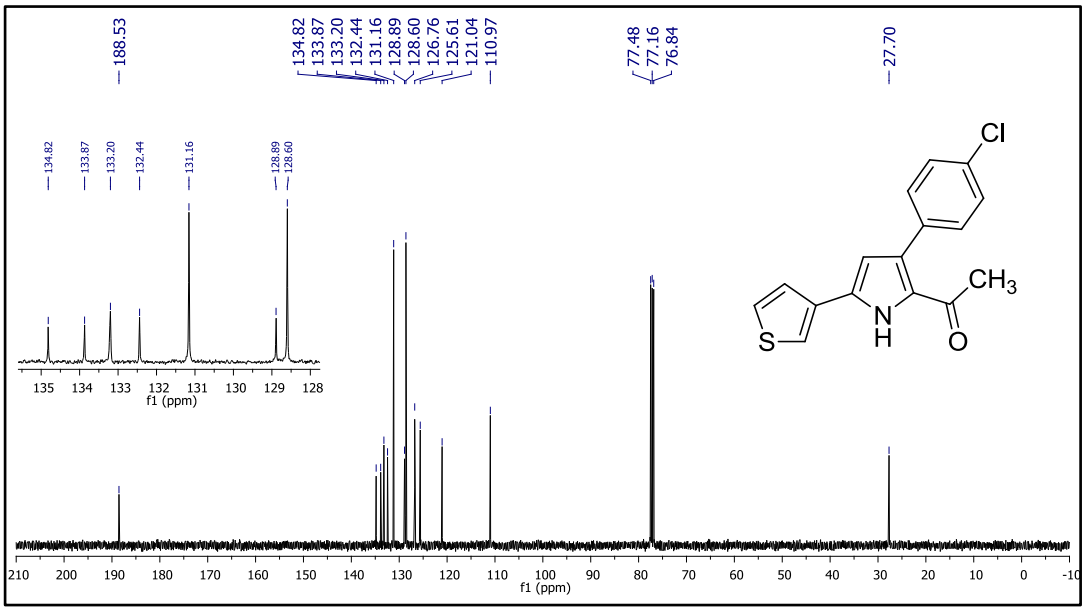

Figure 166. ^{13}C NMR spectrum of compound **46n**.

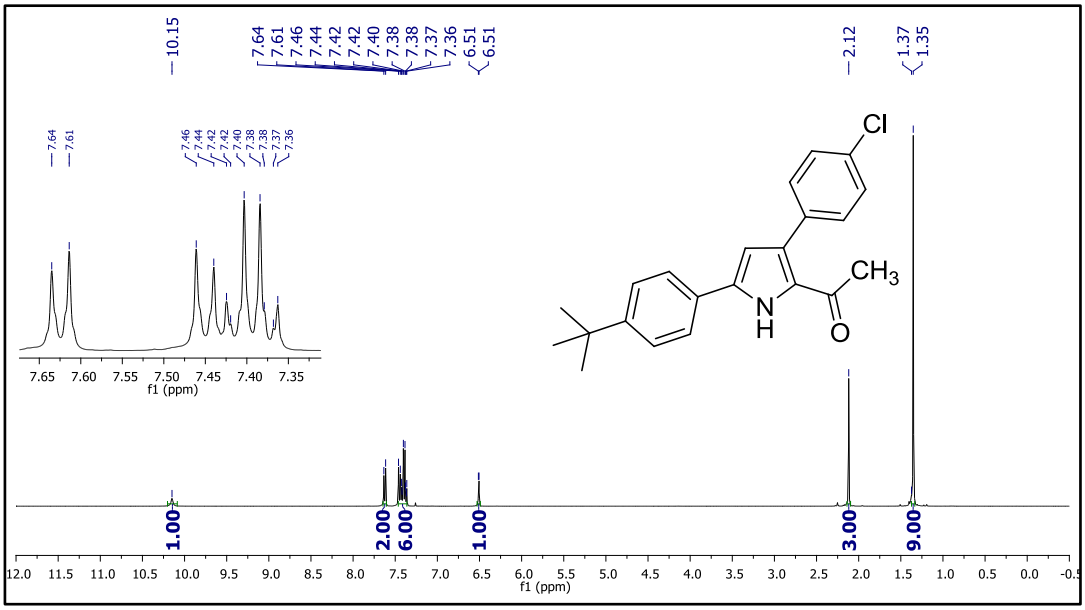

Figure 167. ^{1}H NMR spectrum of compound **46o**.

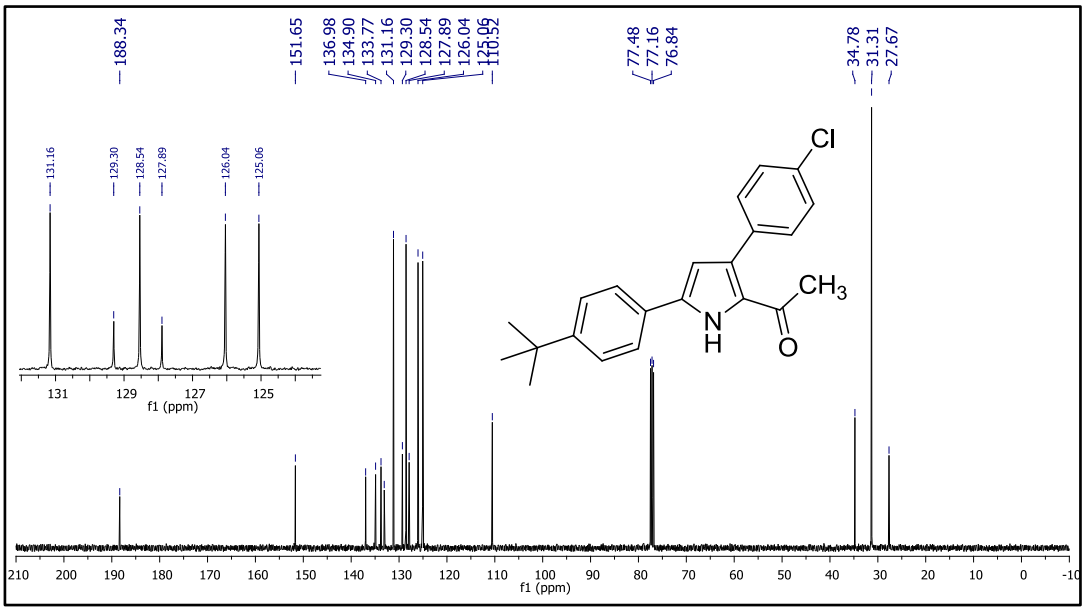

Figure 168. ^{13}C NMR spectrum of compound **46o**.

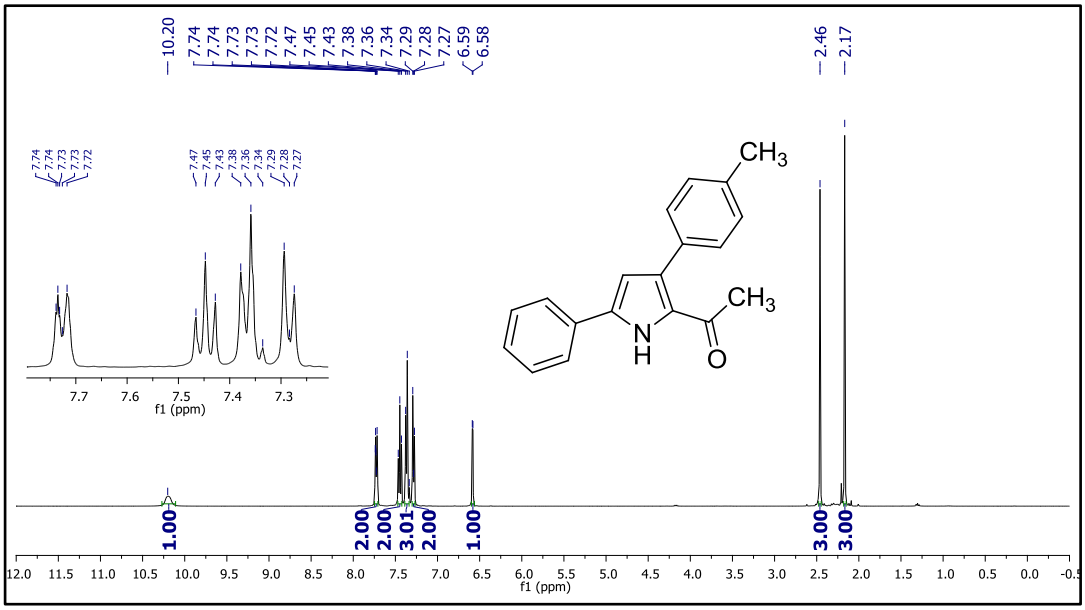

Figure 169. ^{1}H NMR spectrum of compound 46p.

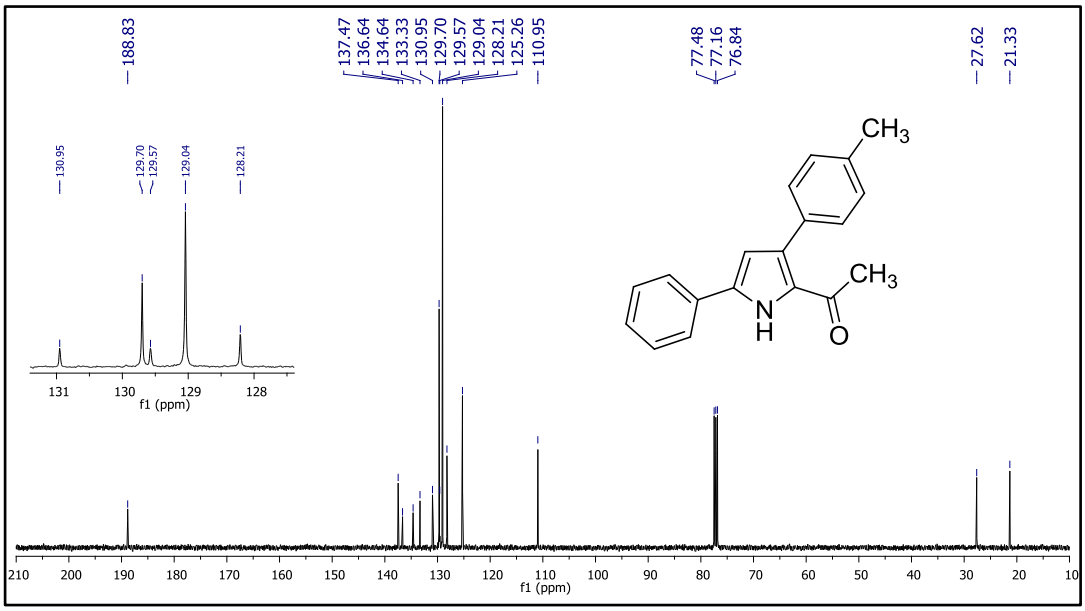

Figure 170. ^{13}C NMR spectrum of compound **46p**.

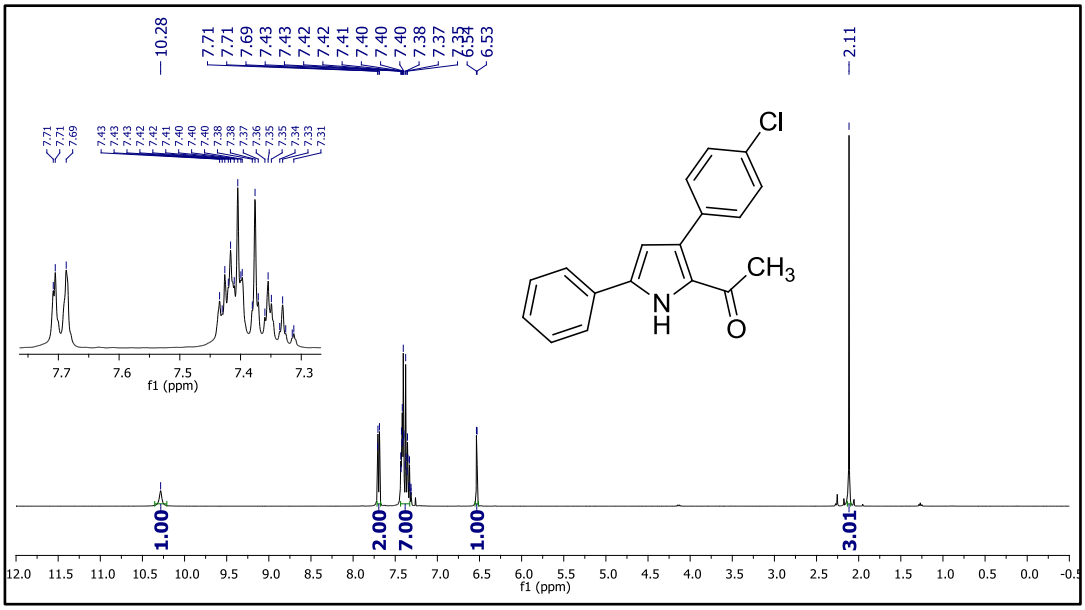

Figure 171. ^{1}H NMR spectrum of compound **46q**.

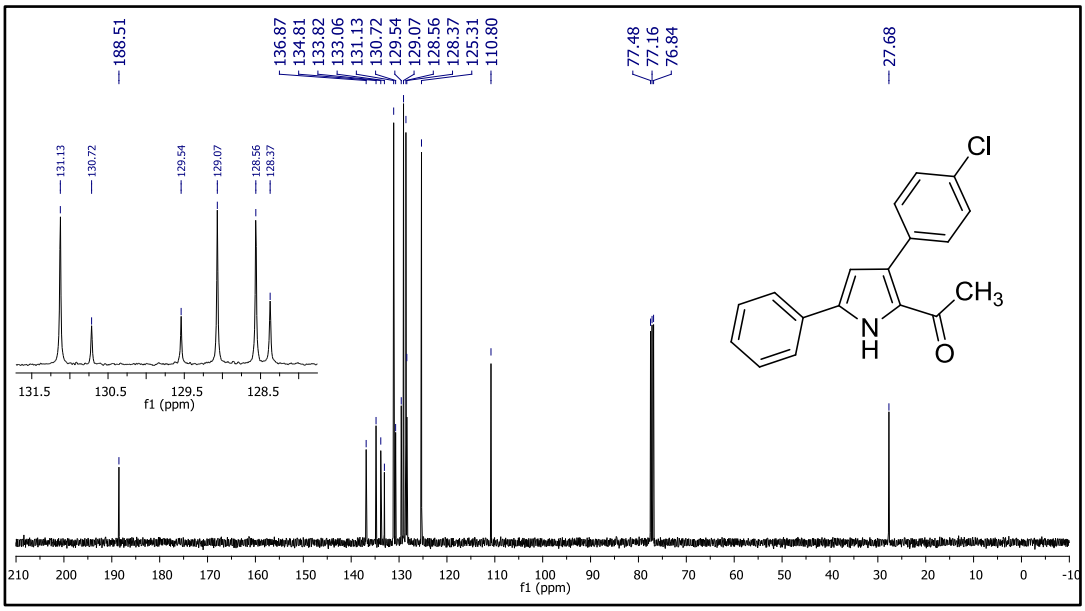

Figure 172. ^{13}C NMR spectrum of compound **46q**.

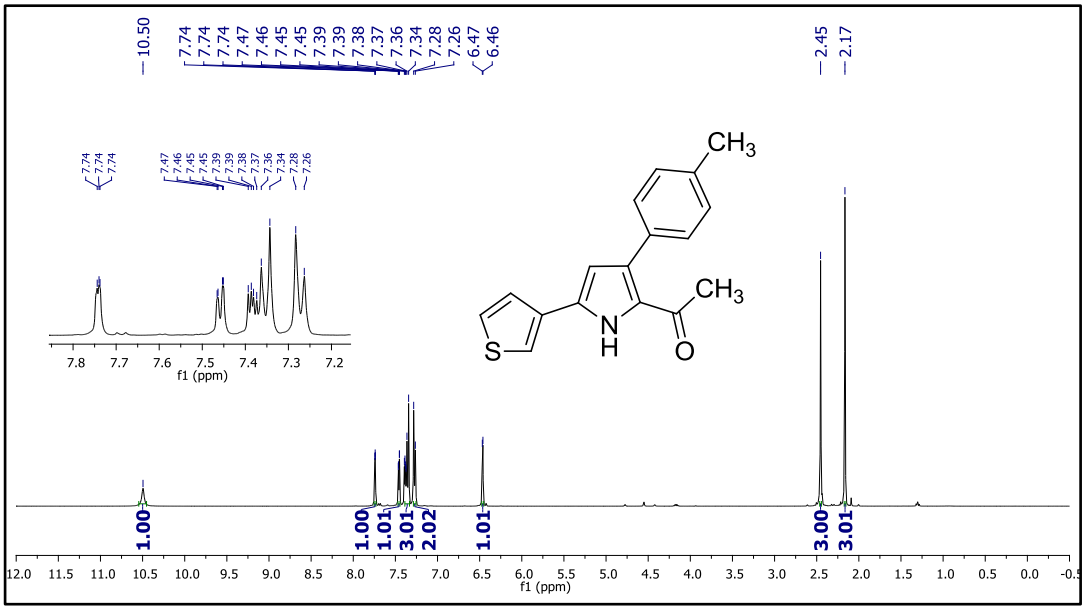

Figure 173. ^{1}H NMR spectrum of compound **46r**.

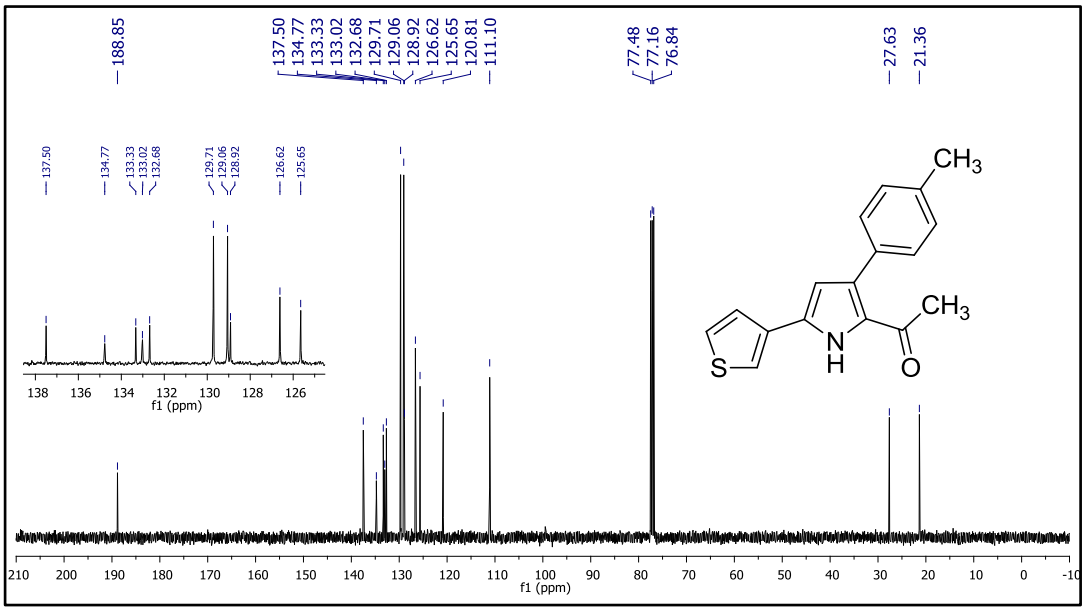

Figure 174. ^{13}C NMR spectrum of compound **46r**.

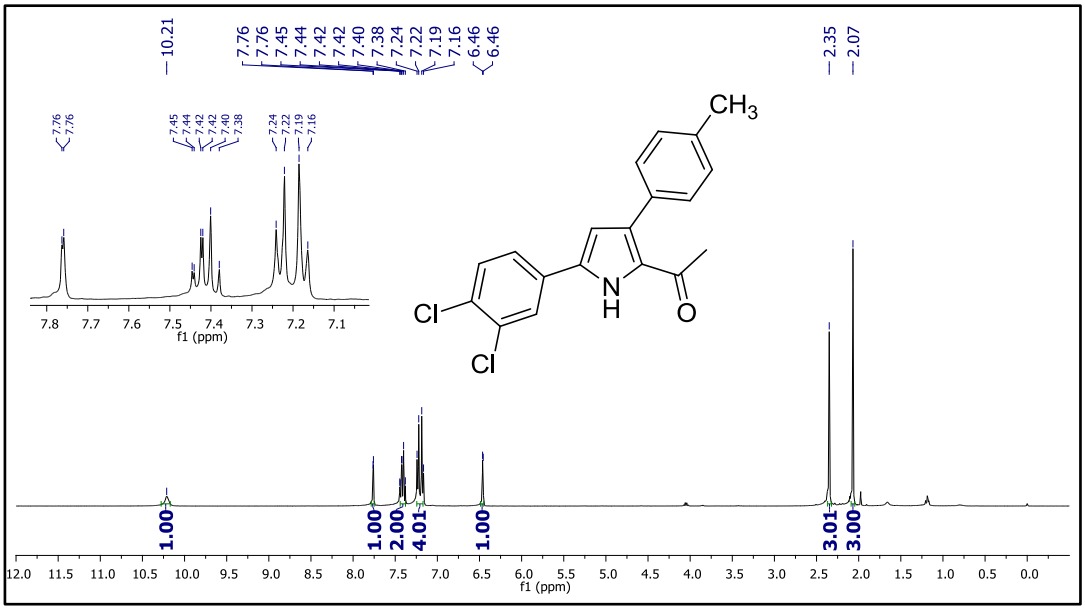

Figure 175. ^{1}H NMR spectrum of compound **46s**.

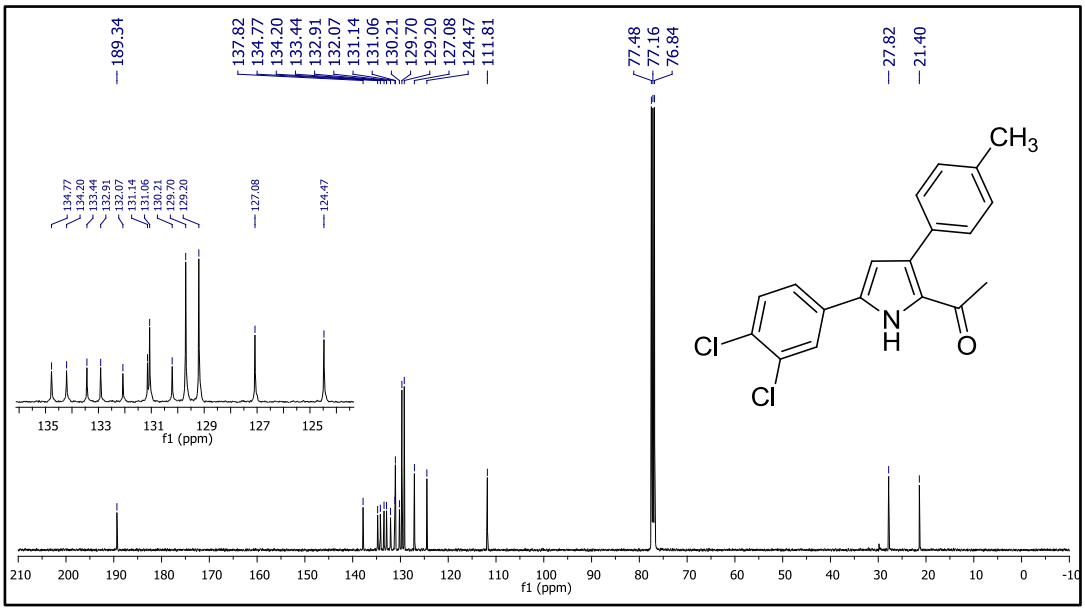

Figure 176. ^{13}C NMR spectrum of compound **46s**.

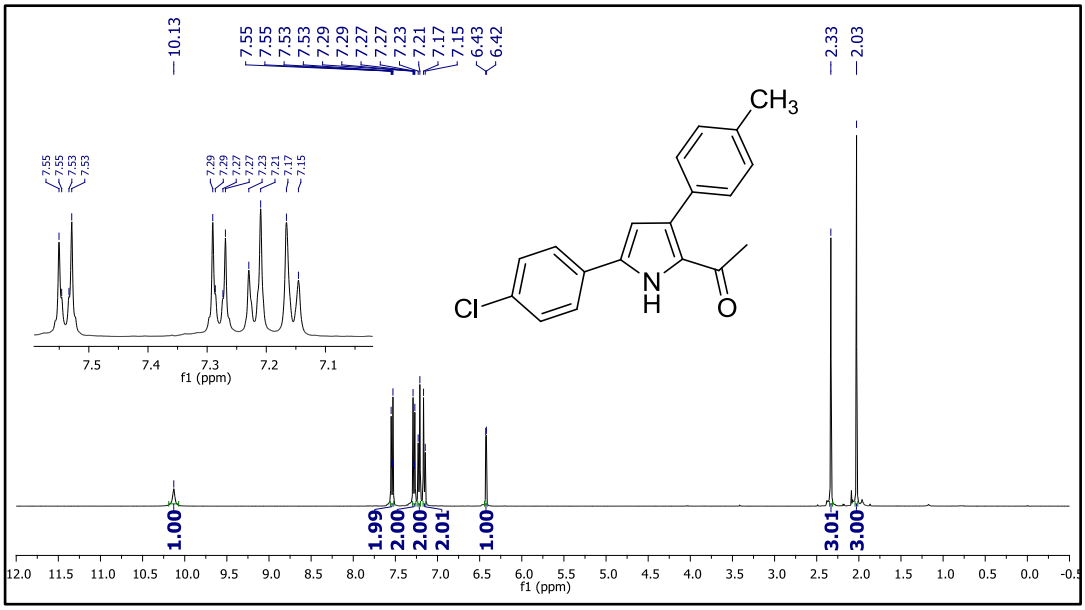

Figure 177. ^{1}H NMR spectrum of compound **46t**.

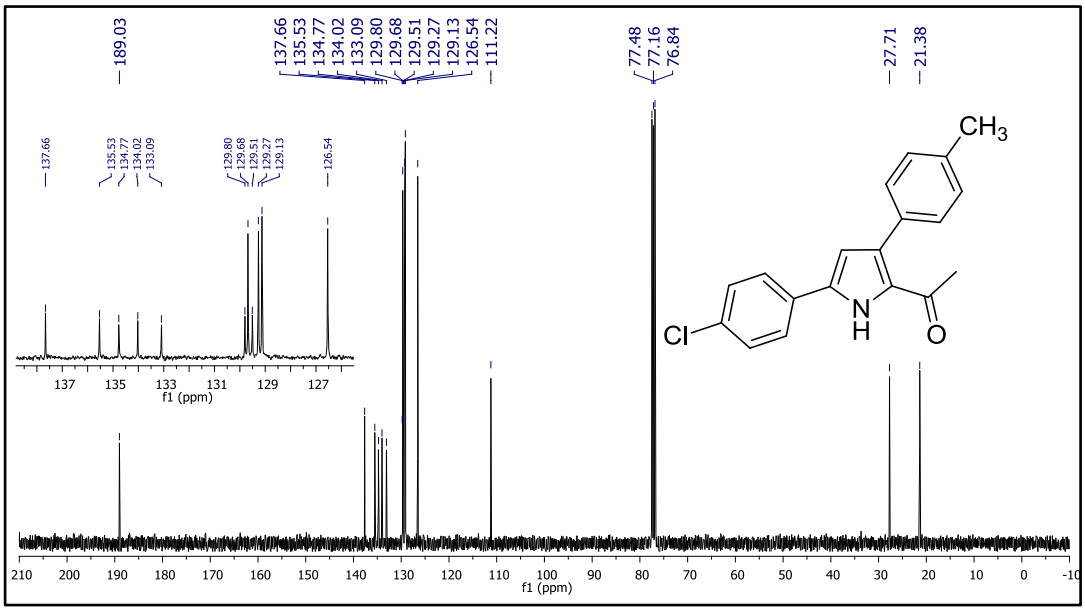

Figure 178. ^{13}C NMR spectrum of compound **46t**.