SYNTHESIS OF 2-IODOMETHYLENE-2,3-DIHYDRO-1,4-OXAZEPINE DERIVATIVES

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EZEL DİKMEN

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SYNTHESIS OF 2-IODOMETHYLENE-2,3-DIHYDRO-1,4-OXAZEPINE DERIVATIVES

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

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ABSTRACT

SYNTHESIS OF 2-IODOMETHYLENE-2,3-DIHYDRO-1,4-OXAZEPINE DERIVATIVES

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Seven-membered heterocyclic compounds containing two heteroatoms are at least as important as one heteroatom-containing heterocycles in many applications. Oxazepine derivatives are one of such seven-membered heterocyclic compounds. Therefore, the construction of oxazepine derivatives has attracted considerable attention among researchers because of providing useful treatments for many diseases with their pharmaceutical compositions. Accordingly, our research group has aimed to synthesize seven-membered heterocyclic compounds. In this manner, we have developed a new methodology for the synthesis of iodo-substituted 1,4-oxazepine derivatives. First of all, the synthesis of alkynyl ketones was achieved and then the preparation of *N*-propargylic β-enaminone derivatives was performed from the reaction of alkynyl ketones and propargyl amine. The reaction of *N*-propargylic β-enaminones via zinc chloride and iodine has afforded iodo-substituted 1,4-oxazepine molecules. For this study, $ZnCl_2$ was used as a Lewis acid catalyst in order to initiate electrophilic cyclization.

Keywords: Seven-membered heterocyclic compounds, oxazepine, *N*-propargylic *β*-enaminone, electrophilic cyclization

ÖZ

2-İYODOMETİLEN-2,3-DİHİDRO-1,4-OKZAZEPİN TÜREVLERİNİN SENTEZİ

Dikmen, Ezel
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Zora
Eylül 2014, 92 sayfa

2 Farklı atom içeren 7'li heterosiklik bileşikler, bir çok alanda 7'li halkaya sahip ve 2 farklı atom içeren heterosiklik bileşikler kadar önemlidir. Okzazepin türevleri 7'li heterosiklik bileşiklerden biridir. Okzazepin bileşiklerinin farmasotik kompozisyonlarıyla bir çok hastalığa tedavi sunduğundan dolayı, bu bileşiklerin sentezi araştırmacılar arasında önemli ölçüde dikkat çekmektedir. Bu yüzden, gurubumuz yeni 7'li heterosiklik moleküllerin sentezi üzerine yoğunlaşmıştır. Bu amaçla iyot bağlı okzazepin türevlerinin sentezi için yeni bir yöntem geliştirilmiştir. Öncelikle, alkinil keton türevlerinin sentezi gerçekleştirilmiştir, sonra alkinil keton ve proparjilik amin reaksiyonu ile *N*-proparjilik *β*-enaminonları sentezlenmiştir. *N*-Proparjilik *β*-enaminon türevleri ile $ZnCl_2$ ve I_2'un tepkimesi sonucunda okzazepine moleküllerini elde edilmiştir. Bu çalışmada, elektrofilik halkalaşma için $ZnCl_2$ Lewis asit katalizörü olarak kullanılmıştır.

Anahtar Kelimeler: Yedili halka heterosiklik bileşikler, okzazepin, *N*-proparjilik *β*-enaminon, elektrofilik halkalaşma.

To My Dear Family

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SCHEMES

ABBREVIATIONS

ACN	acetonitrile
br	broad (spectral)
d	doublet (spectral)
DCM	dichloromethane
dd	doublet of doublet (spectral)
FT	fourier transform
Hz	hertz
J	coupling constant
mmultiplet (spectral)	
ppm	parts per million (in NMR)
q	quartet (spectral)
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)
THF	tetrahydrofuran
TLC	thin layer chromatography
δ	chemicalshift in partspermilliondownfieldfrom

CHAPTER 1

INTRODUCTION

Organic chemistry is a comprehensive and continually evolving scientific discipline that focuses on carbon compounds. Over the years, chemists have paid much attention to carbon compounds on account of the electronic structure of carbon and its incidental position in the periodic table [1]. Carbon atoms constitute long chains by bonding to one another. Therefore, a great variety of compounds are formed from simple to complex. For instance, ethane has the shortest carbon chain whereas DNA has very long carbon chains. Another important macromolecular organic compound is the proteins, which contain many amino acids in their chains. Proteins have many functions in living organisms, such as catalyzing metabolic reactions, DNA replications, transporting molecules and so on [2].

Actually, all compounds of carbon do not come from living organisms. Over the past decades, chemists have tried to design and synthesize new functional molecules such as drugs, dyes, food additives, pesticides and polymers in the laboratory. In other words, organic chemistry has an important effect on the every area of our lives [3].

Many organic compounds include ring systems. There may be elements other than carbon in their cyclic structure. Then, these type of compounds are known as heterocyclic compounds (Figure 1) [4].

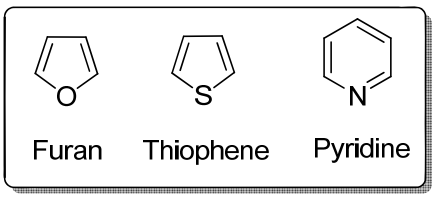


Figure 1. Examples of heterocyclic compounds.

1.1 Heterocyclic Compounds

Heterocyclic compounds incorporate not only one or more carbon atoms but also at least one heteroatom, such as oxygen, nitrogen or sulfur, in their ring skeletons [5]. Heterocycles vary depending on the number of their rings, types, and the positions of heteroatoms [6].

It is noteworthy that heterocyclic compounds have important utilizations in many areas, including biological systems, medicine, agriculture, industry and technology, polymers, dyes and pigments [6]. Because of the vital role of heterocycles in life and society, these molecules are inspirational for scientific and technological studies.

Heterocycles have also a great significance in biochemical processes. Fundamentally, DNA and RNA, both carry genetic information, contain heterocyclic pyrimidine and purine bases such as cytosine, thymine, uracil, adenine and guanine, the structures of which are depicted in Figure 2 [7].

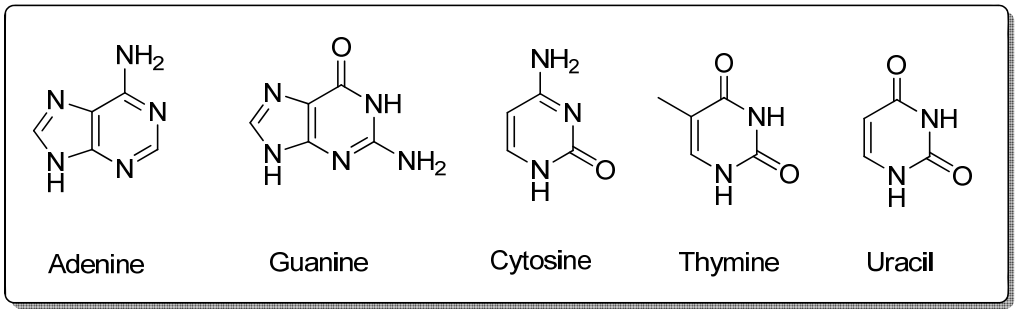


Figure 2. Structures of purine and pyrimidine bases.

Applications of heterocyclic molecules in medicinal chemistry are indisputable. In the present day, many diseases have been treated by the heterocyclic drugs.

The five of the top 20 best selling medicines for 2009 are illustrated in Figure 3, which are atorvastatin (lipitor; used for reducing blood cholesterol), rosuvastatin (crestor; a statin for treatment of cardiovascular disease), clopidogrel (plavix; anti-platelet agent), esomeprazole (nexium; a proton-pump inhibitor to prevent gastric acid formation) and montelukast (singulair; for treatment of asthma and seasonal allergies) [8].

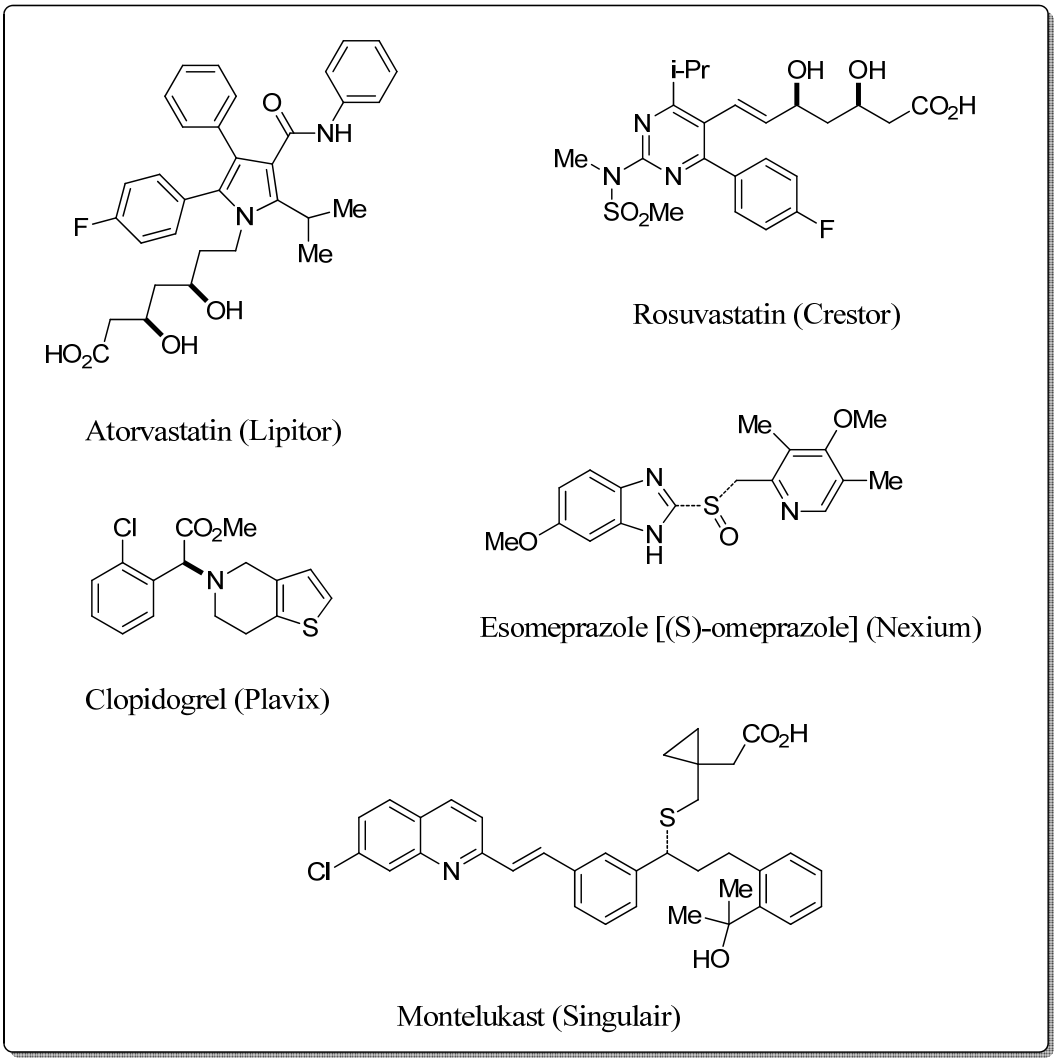


Figure 3. Structures of the five best selling heterocyclic medicines for 2009.

According to all the statements referred previously, it can be concluded that heterocyclic compounds have a great contribution to research area, technological developments and mediately human life.

1.2 Seven-membered Heterocyclic Compounds

In recent years, heterocyclic molecules with seven-membered rings have been a quickly evolving curiosity among chemists as compared to five and six-membered heterocyclic compounds. The more size of ring increases, the more range of compounds can be acquired by altering the type, location and number of the heteroatoms [9]. For instance, azepines are one nitrogen containing seven-membered heterocycles. Similarly, oxepines and thiepines are one oxygen or sulfur-containing seven-membered rings, respectively (Figure 4) [10].

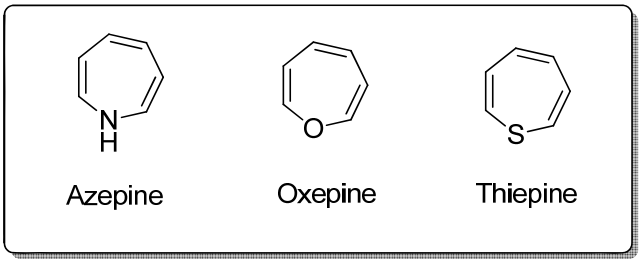


Figure 4. Examples of seven-membered heterocycles.

It is obvious that fused-ring derivatives based on the azepine system are important in medicinal chemistry due to their wide range of pharmacological applications. For example, 1*H*-2-benzazepine derivatives play an important role as an inhibitor of acetylcholinesterase [11] and the potential anti-HIV agent [12].

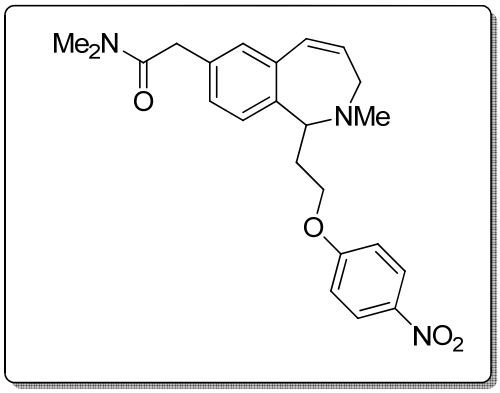


Figure 5. Structure of a 1*H*-2-benzazepine derivative.

Significantly, methyl-substituted oxepines are known as potential intermediates in the arene metobolism by enzymatic systems of liver [13]. Furthermore, dibenzo[b,f]thiepine derivatives are employed in many pharmacological applications, incorporating antischizophrenic, antiflammatory, antidepressant and antihistaminic properties [14,15].

Seven-membered heterocyclic compounds containing two heteroatoms are at least as important as one heteroatom-containing heterocycles in many applications. Oxazepine derivatives are one of such seven-membered heterocyclic compounds [10].

1.2.1 Oxazepines

Oxazepines are seven-membered heterocyclic systems composed of mixed heteroatoms, nitrogen and oxygen. There are three types of oxazepine, 1,2-oxazepine, 1-3-oxazepine and 1,4-oxazepine as illustrated in Figure 6 [16].

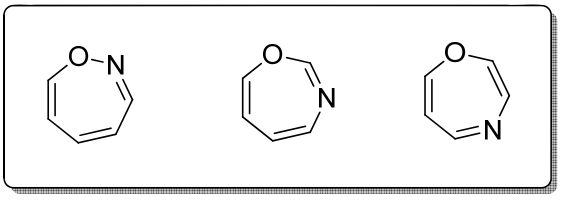


Figure 6. Structures of oxazepines.

Furthermore, benzoxapines are bicyclic heterocyclic compounds containing benzene ring fused to oxazepine ring as shown in Figure 7 [16].

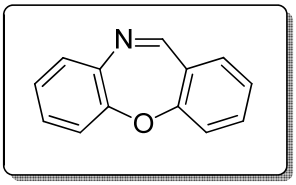


Figure 7. Structures of dibenz(b,f)[1,4]oxazepine.

A pharmaceutical composition including oxazepine ring structure provides useful treatments for many diseases. For instance, loxapine shown in Figure 8 is effective antipsycotic drug for schizophrenia [17].

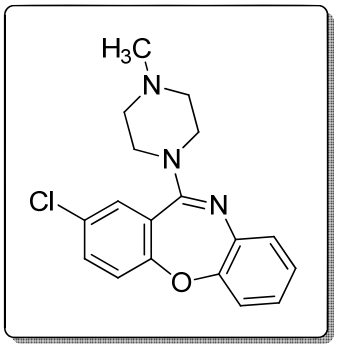


Figure 8. Structure of loxapine.

In addition, oxazepine-containing medicines, such as 5,11-dihydrodibenzo[b,e][1,4]-oxazepine derivatives, represent outstanding effects as therapeutic agents for abnormal motor functions of gastrointestinal tracts, particularly irritable bowel syndrome (Figure 9) [18].

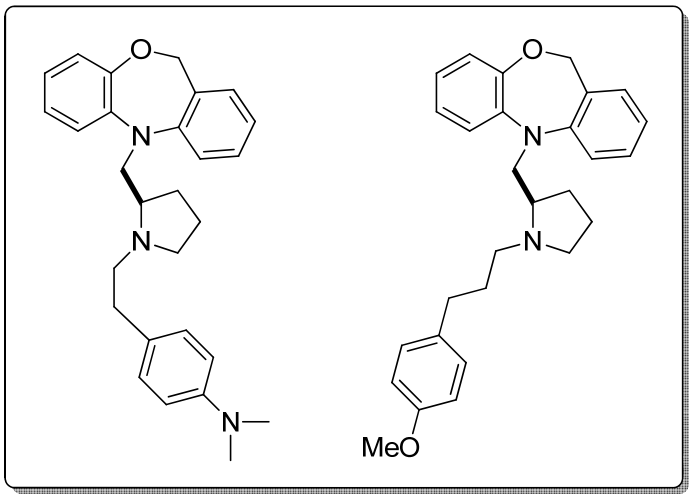
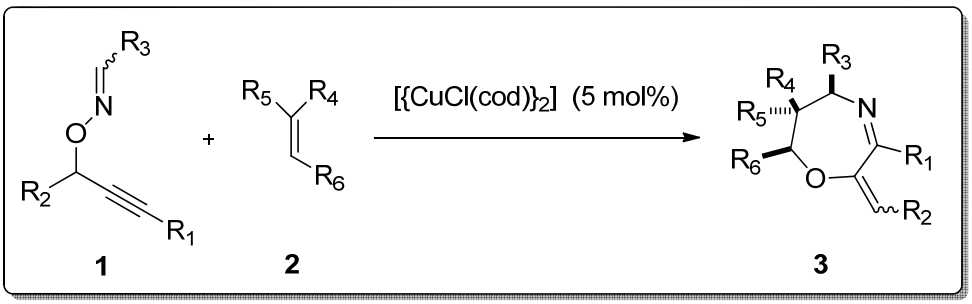


Figure 9. Structures of 5,11-dihydrodibenzo[b,e][1,4]oxazepine derivatives.

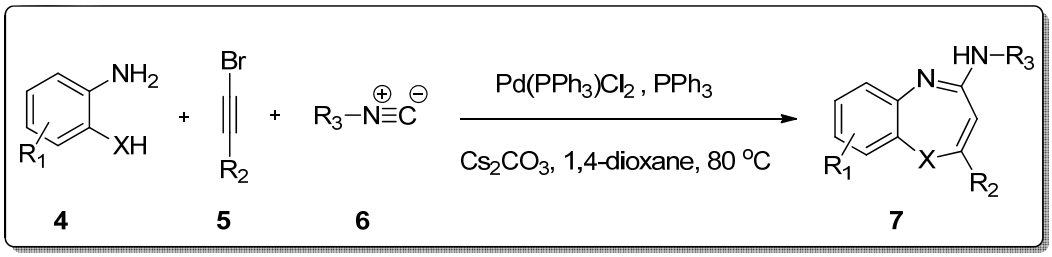
1.2.2 Synthesis of Oxazepines

It is obvious that the construction of oxazepine derivatives has attracted considerable attention among researchers. Nakamura and coworkers recently employed the copper-catalyzed reactions of the *O*-propargylic oximes (**1**) with dipolarophiles (**2**), such as maleimides and fumaric acid esters, to synthesize multisubstituted oxazepine derivatives (**3**) as shown in Scheme 1. This single operation contains in turn 2,3-rearrangement, [3+2] cycloaddition and 1,3-oxygen migration [19].



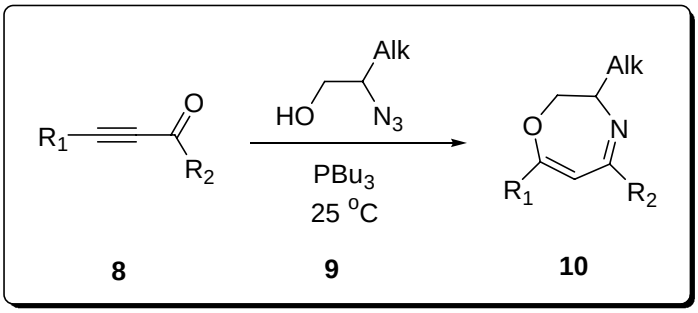
Scheme 1. Copper-catalyzed synthesis of oxazepines.

Another important study was conducted by Jiang and coworkers. This research group synthesized 4-aminobenzo[b][1,4]oxazepine derivatives **7** by employing palladium-catalyzed sequential reaction of o-aminophenols **4**, bromoalkynes **5** and isocyanides **6** as represented in Scheme 2 [20].



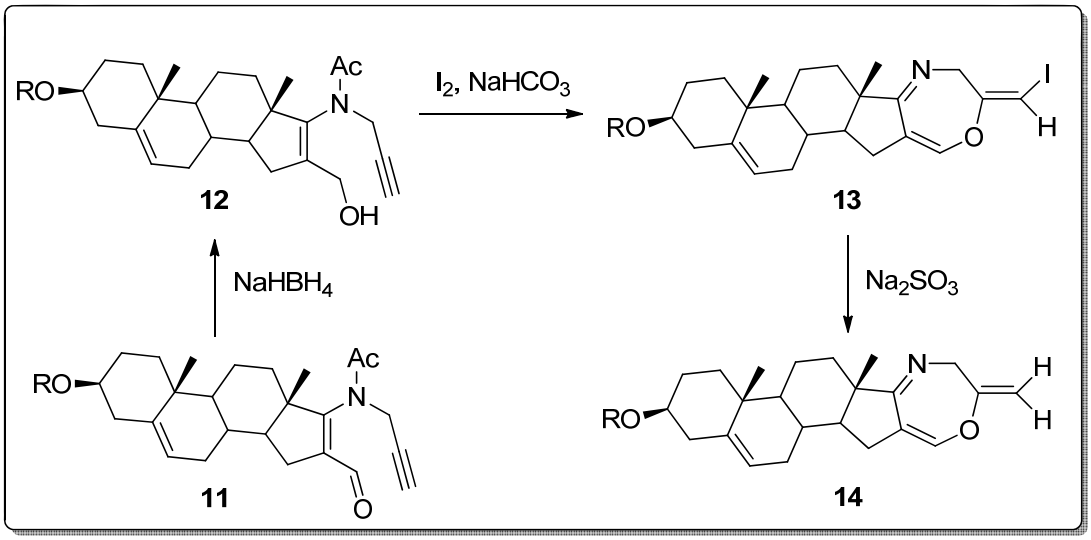
Scheme 2. Palladium-catalyzed synthesis of benzoxazepines.

Oxazepines can also be constructed by aza-Wittig reaction followed by intramolecular cyclization. Phosphine mediated tandem reaction of ynones **8** with 2-azido alcohols **9** generated biologically important seven-membered 1,4-oxazepines **10** (Scheme 3) [21].



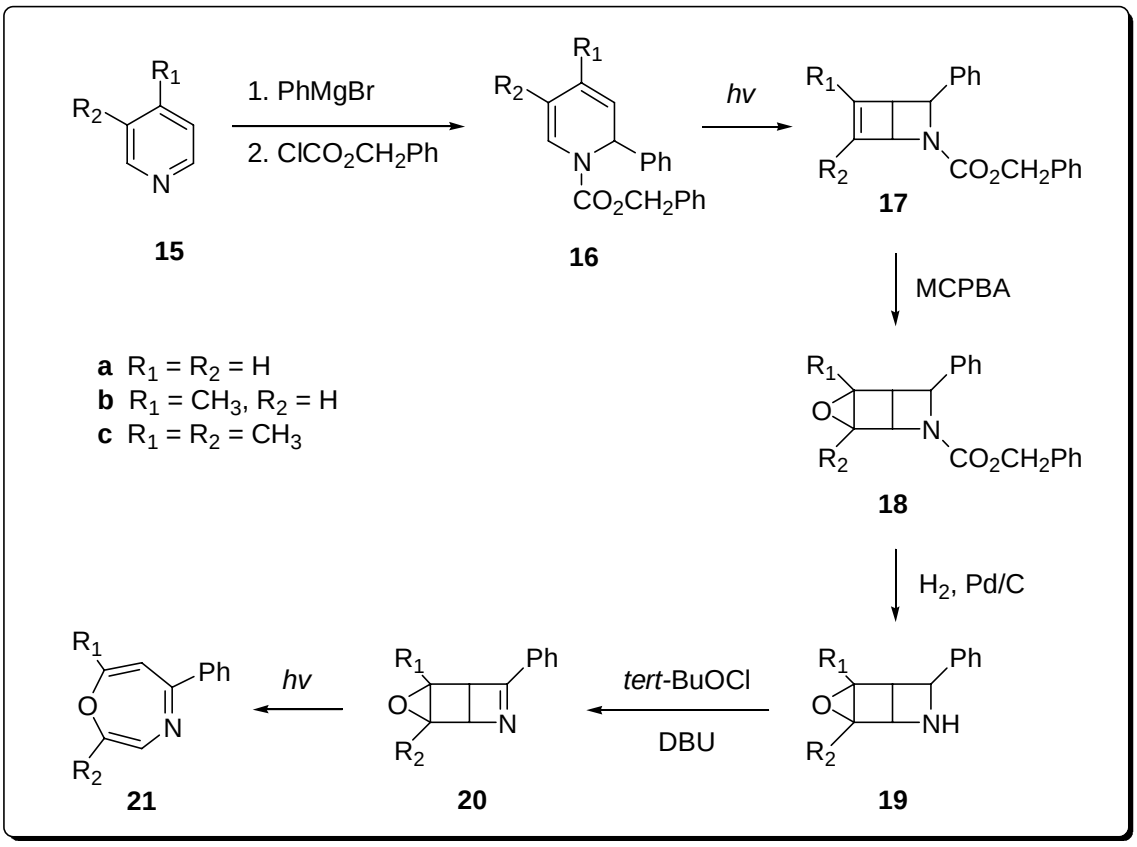
Scheme 3. Construction of 1,4-oxazepines from ynones and 2-azido alcohols.

Another efficient synthetic methodology for the preparation of 1,4-oxazepines **14** involves the intramolecular cyclization of *N*-progargyl-β-formylenamides **11** (Scheme 4). First ketone functionality is reduced by $NaBH_4$, and then the resulting alcohol **12** is subjected to cyclization by I_2 in the presence of $NaHCO_3$. Finally, the reductive dehalogenation of **13** produces 1,4-oxazepines **14** [22].



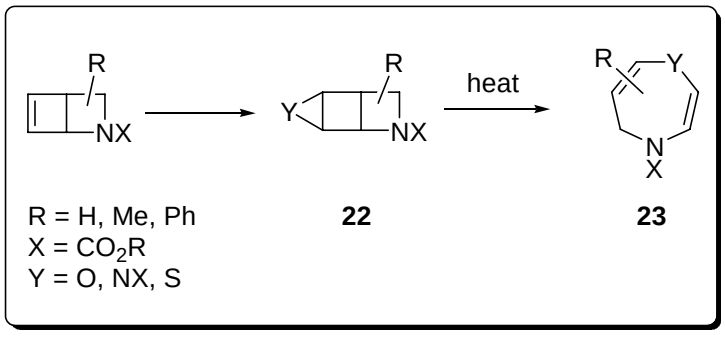
Scheme 4. Synthesis of 1,4-oxazepines from *N*-progargyl-β-formylenamides.

First example of fully unsaturated monocyclic 1,4-oxazepines was synthesized in six steps by Tsuchiya and coworkers in 1986 (Scheme 5) [23]. Initially, pyridine **15** was converted to corresponding dihidropyridine **16**, electrocyclic ring closure of which under photochemical conditions provided 2-azabicyclo[2.2.0]hex-5-ene **17**. Its oxidation with MCPBA, followed by reduction with H_2 in the presence of Pd/C provided 3-oxa-6-azatricyclo[3.2.0.0^{2,4}]heptane **19**. It was then converted to 3-oxa-6-azatricyclo[3.2.0.0^{2,4}]hept-6-ene **20**. Finally, electrocyclic ring opening afforded 1,4-oxazepine **21** (Scheme 5). The yield of final product was low since it was not so stable that it started to decompose during purification [23].



Scheme 5. Synthesis of fully unsaturated monocyclic 1,4-oxazepines.

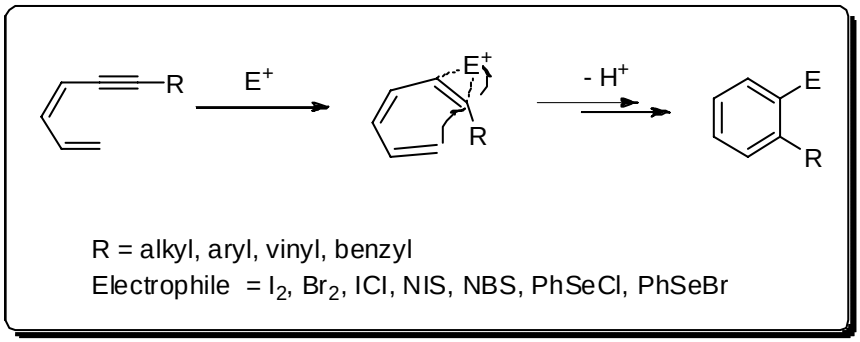
Tsuchiya and coworkers also reported the construction of novel dihydro-1,4-diheteroepins **23** from the corresponding tricyclic compounds **22** as shown in Scheme 6 [24]. Tricyclic compounds **22** were acquired from pyridines via a similar pathway depicted in Scheme 5.



Scheme 6. Synthesis of dihydro-1,4-diheteroepins.

1.3 Electrophilic Cyclization

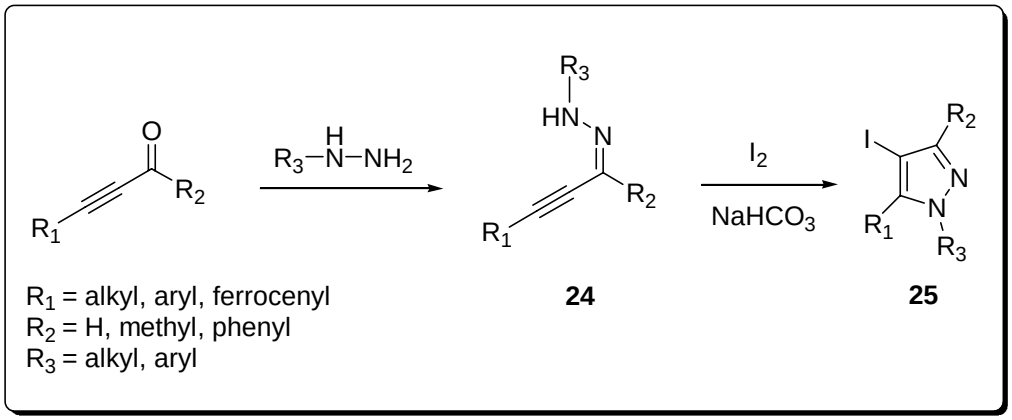
A general example of electrophilic cyclizations is represented in Scheme 7. I_2, Br_2, ICI, NBS, NIS, PhSeCl and PhSeBr are among the commonly used electrophiles. In cyclizations, electrophiles activate the alkyne functionality, which initiates the attack of nucleophiles such as hydroxyl, hydroxylate, carboxyl, carboxylate, amino and amido groups, resulting in the formation of cyclic compounds. Admittedly, electrophilic cyclizations are versatile methods in synthetic chemistry [25,26].



Scheme 7. General representation of electrophilic cyclizations.

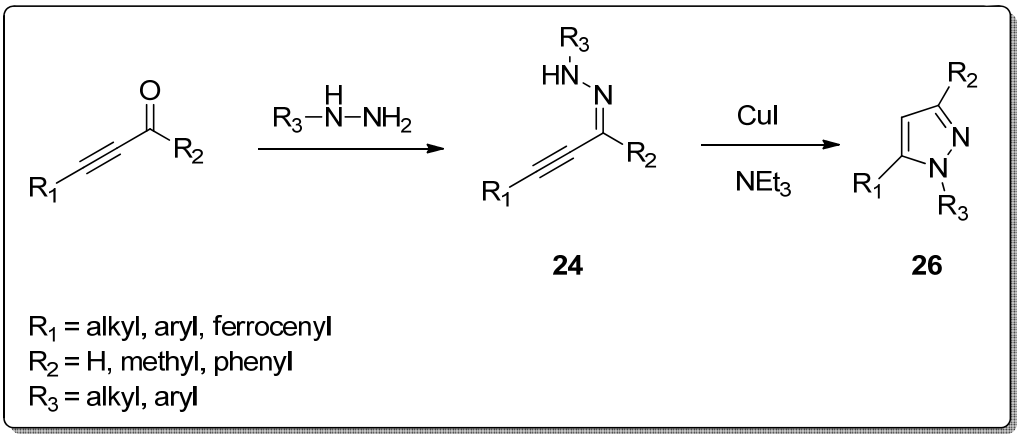
Electrophilic cyclizations are generally influenced by the nature of the electrophile and nucleophile, C-C triple bond polarizability and geometrical orientation of the functional groups. Length of chain and substitution type provide *endo*-dig or *exo*-dig cyclization for the formation of cyclic molecules [27].

Zora research group has recently reported the synthesis of α,β-alkynic hydrazones **24** and their regioselective conversion to 4-iodopyrazoles **25** via molecular iodine-mediated electrophilic cyclization (Scheme 8) [28]. These cyclizations were found to be general for a variety of α,β-alkynic hydrazones and allowed the presence of aliphatic, aromatic, heteroaromatic and ferrocenyl moieties with electron-withdrawing and electron-donating substituents.



Scheme 8. Synthesis of 4-iodopyrazoles via I_2-mediated electrophilic cyclization of α,β-alkynic hydrazones.

Correspondingly, Zora research group has also investigated the synthesis of pyrazole derivatives **26** via copper (I) iodide-mediated electrophilic cyclizations of α,β-alkynic hydrazones **23** as illustrated in Scheme 9 [29].



Scheme 9. Synthesis of pyrazoles via CuI-mediated electrophilic cyclization of α,β alkynic hydrazones.

1.4 β-Enaminones

β-Enaminones, containing the structural units of N–C=C–C=O, have an important place in organic synthesis. Particularly, *N*-propargylic β-enaminones are frequently used as substrates for the synthesis of heterocyclic and pharmaceutical compounds,

such as pyrrole, pyridine, benzodiazepine and indole derivatives and many healing agents (Figure 10) [30,31].

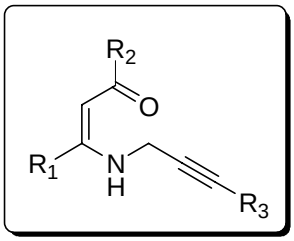
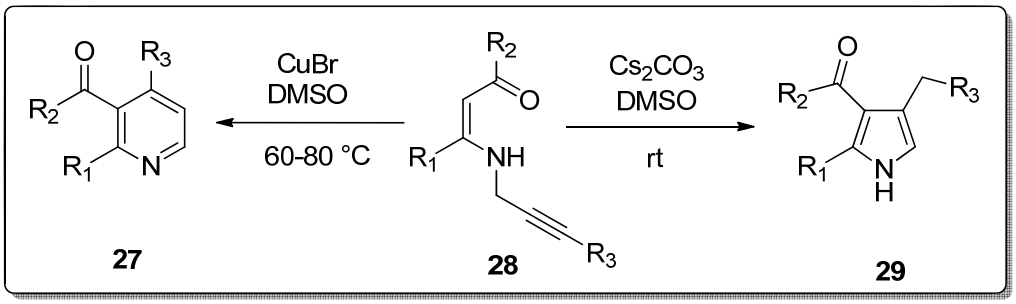


Figure 10. Structure of *N*-propargylic β-enaminone.

1.4.1 Cyclization of *N*-propargylic β-enaminones

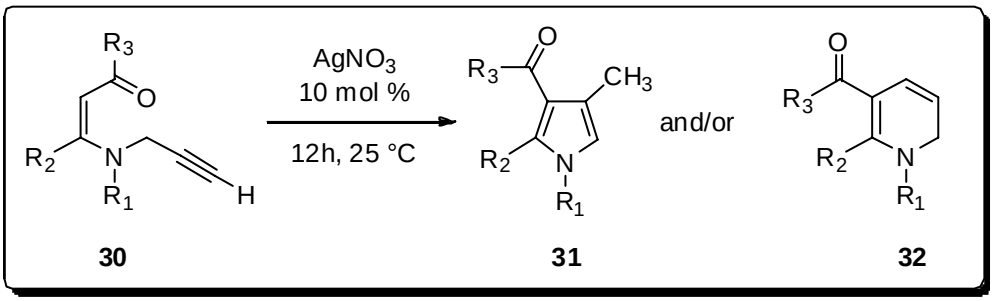
Because of the ambident nucleophilic feature of enamine moiety and the electrophilic feature of enone moiety, *N*-propargylic β-enaminones have emerged as valuable substrates and intermediates in cyclization reactions [34].

In this respect, an important study was reported by Cacchi research group (Scheme 10) [33]. When treated with CuBr in DMSO, *N*-propargylic β-enaminones **28** yielded pyridine derivatives **27.** However, when treated with Cs_2CO_3 in DMSO, they produced pyrrole derivatives **29** in good to high yields, as depicted in Scheme 10 [33].



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

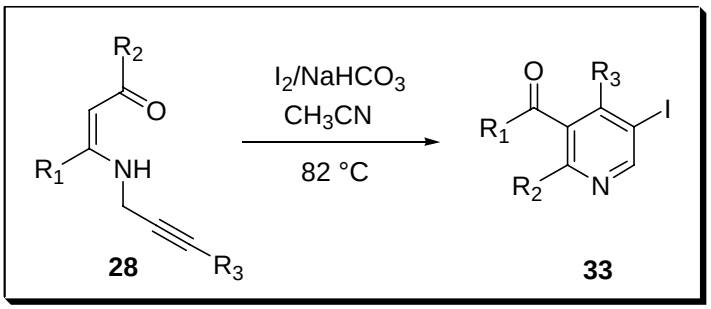
A similar study was conducted by Martins and coworkers. They investigated Ag-catalyzed intramolecular cyclization of *N*-propargylic β-enaminones **30**, which provided pyrroles **31** and/or 1,2-dihydropyridines **32** (Scheme 11) [34].



Scheme 11. Ag-catalyzed intramolecular cyclization of *N*-propargylic β-enaminones.

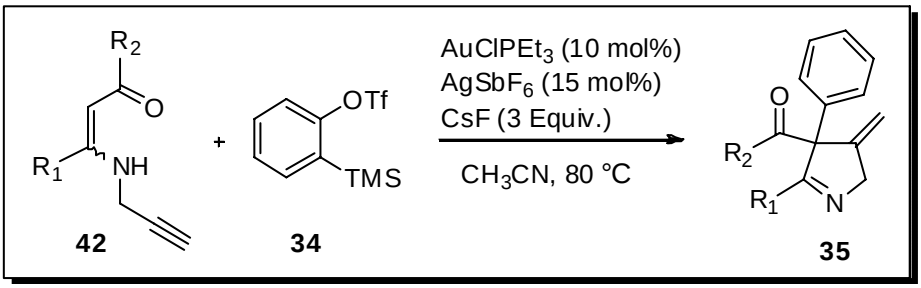
Zora research group has recently developed a new method for the synthesis of iodo-substituted pyridine derivatives, the initial results of which were presented [35]. When treated with molecular iodine in the presence of $NaHCO_3$, *N*-propargylic β-enaminones **28** underwent electrophilic cyclization to afford iodopyridines **33** in good to high yields (Scheme 12) [35].

Significantly, iodopyridines are very useful synthetic intermediates due to their capability of being converted to more complex structures by metal-catalyzed coupling reactions [36].



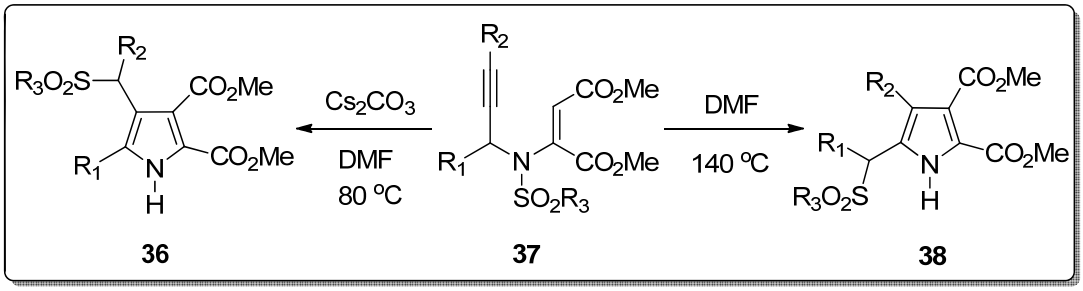
Scheme 12. Synthesis of iodo-substituted pyridines via electrophilic cyclization.

Synthesis of 3-methylene-3,4-dihydro-2*H*-pyrroles was also accomplished from *N*-propargylic β-enaminones. In the presence of Au(I) and Ag(I) catalysts, *N*-propargylic β-enaminones reacted with aryne precursor **34** to generate 3-methylene-3,4-dihydro-2*H*-pyrroles **35** as depicted in Scheme 13. These products have substantial role in many applications, such as flavouring agent for various food products, alkaloids and natural products [37].



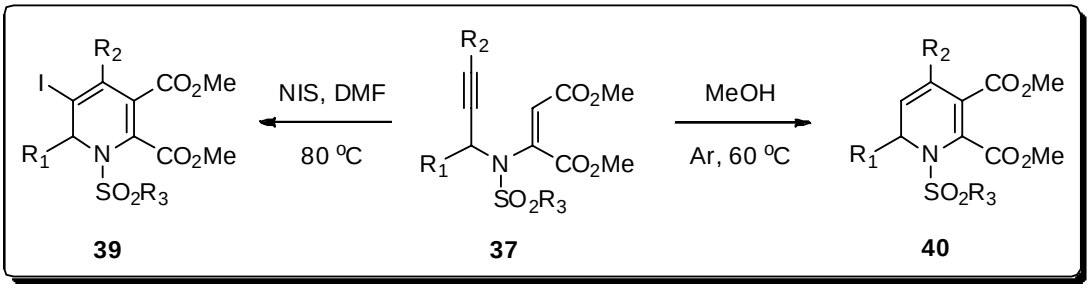
Scheme 13. Synthesis of 3-methylene-3,4-dihydro-2*H*-pyrroles.

Wan and coworkers developed new routes for the synthesis of highly functionalized pyrrole derivatives. Under proper conditions, *N*-sulfonyl azaenyne derivatives **37** produced α-(arylsulfonyl)methyl pyrroles **36** and β-(arylsulfonyl)methyl pyrroles **38** as shown in Scheme 14 [38]. Importantly, during these reactions, sulfonyl group migration was observed.



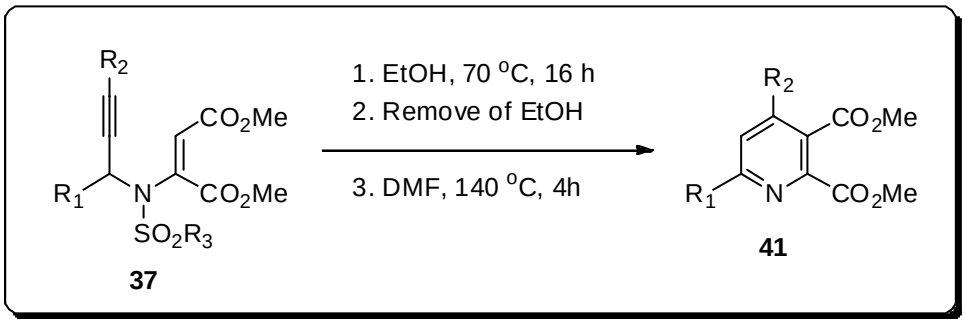
Scheme 14. Synthesis of highly functionalized pyrroles from 3-aza-1,5-enynes.

In addition, Wan and coworkers achieved the synthesis of pyridine derivatives from the same starting materials. When treated with NIS in DMF at 80 °C or heated in refluxing methanol, 3-aza-1,5-enynes **37** produced 3-iodo-1,2-dihydropyridines **39** and 1,2-dihydropyridines **40**, respectively (Scheme 15) [39].



Scheme 15. Synthesis of 1,2-dihydropyridines and 3-iodo-1,2-dihydropyridines from 3-aza-1,5-enynes.

Wan and coworkers also reported one-pot synthesis of substituted pyridines **41** from 3-aza-1,5-enynes **37** (Scheme 16) [40]. The reaction first produced in situ 1,2-dihydropyridines which, upon elimination of sulfinic acid, afforded pyridines.



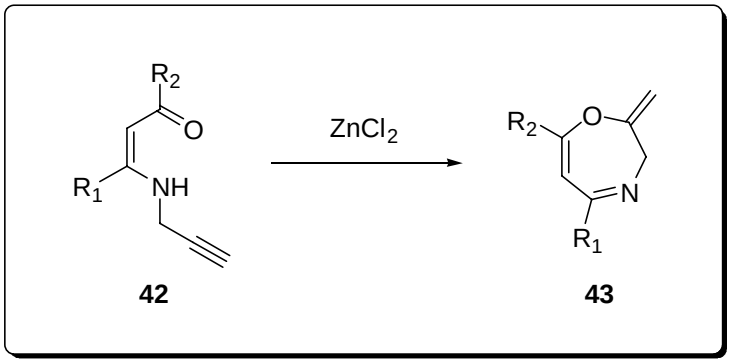
Scheme 16. Synthesis of pyridines from 3-aza-1,5-enynes.

Notably, the popularity of *N*-propargylic β-enaminones as synthetic intermediates has risen considerably in organic synthesis [41] since the important heterocyclic compounds, such as pyrroles, pyrrolines and pyridines, were resulted from the cyclization of these β-enaminones and their 3-aza-1,5-enyne derivatives [42].

As exemplified above, different kinds of five and six-membered heterocycles were obtained from the cyclization of *N*-propargylic β-enaminones. However, from these cyclizations, no seven-membered ring formation, such as oxazepine, was reported.

1.5 Aim of the study

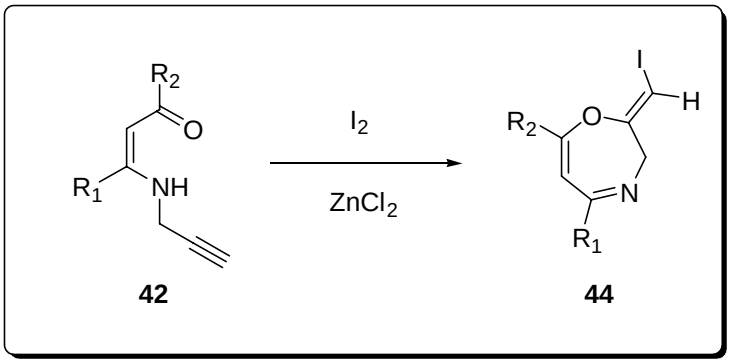
So far, the syntheses of five and six-membered heterocyclic compounds were generally reported from *N*-propargylic β-enaminones. On the other hand, there are quite a few studies for the construction of seven-membered rings with two heteroatoms, especially monocyclic oxazepine molecules. Our research group has recently achieved the synthesis of 2-methylene-2,3-dihydro-1,4-oxazepines **43** via $ZnCl_2$-mediated cyclization of *N*-propargylic β-enaminones **42** in one-pot manner (Scheme 17).



Scheme 17. Synthesis of 2-methylene-2,3-dihydro-1,4-oxazepines **43**.

In the light of this study, we have planned the synthesis of monocyclic iodo-substituted oxazepine derivatives. Importantly, iodine-containing derivatives are very useful intermediates for the synthesis of various products since they can be easily elaborated to more complex structures by metal-catalyzed coupling reactions. In the first part of the study, α,β-alkynic ketones will be synthesized via Sonogashira cross-coupling reaction of terminal alkynes with aryloyl chlorides. Then, conjugate addition of propargylamine to α,β-alkynic ketones will be employed to afford *N*-propargylic β-enaminones as starting materials. At the final stage, the cyclizations of

N-propargylic β-enaminones **42** will be investigated in the presence of molecular iodine and $ZnCl_2$, which is expected to give monocyclic iodo-substituted 2,3-dihydro-1,4-oxazepine derivatives **44** as presented in Scheme 18.



Scheme 18. Synthesis of iodo-substituted 2,3-dihydro-1,4-oxazepines **44**.

In brief, the scope, limitations and proposed mechanism of the above mentioned cyclization of *N*-propargylic β-enaminones **42** to 2-iodomethylene-2,3-dihydro-1,4-oxazepine derivatives **44** will be discussed in detail.

CHAPTER 2

RESULTS AND DISCUSSION

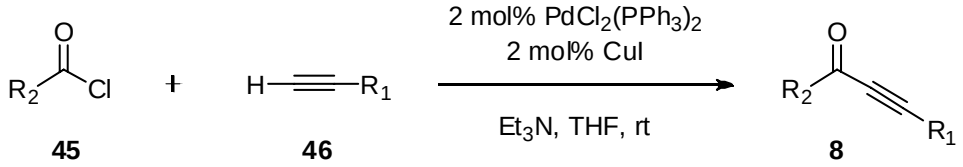
2.1 Synthesis of N-propargylic β-enaminone derivatives

At the first stage of the study, the starting materials, namely *N*-propargylic β-enaminone derivatives **42**, were synthesized from terminal alkynes **46** in two steps according to literature procedures [33]. First step of the synthesis was the preparation of alknyl ketones **8** through Sonogashira cross-coupling of benzoyl chloride derivatives **45** with terminal alkynes **46** in the presence of a Pd catalyst (Table 1) [33]. Importantly, $PdCl_2(PPh_3)_2$ was employed as catalyst, CuI as co-catalyst and NEt_3 as base for this coupling reaction, which are generally used in Sonogashira reactions.

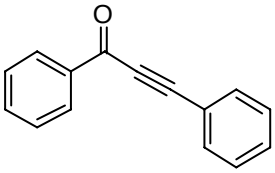
By means of these coupling reactions, eleven derivatives of alkynyl ketones **8**, including electron-withdrawing and electron-donating groups, were prepared. The yields of alkynyl ketones **8** changed from 54 to 99% (Table 1).

Structural assignments of alkynyl ketones **8** were elucidated by ^{1}H and ^{13}C NMR spectroscopy. As a representative example, ^{1}H and ^{13}C NMR spectra of 1,3-diphenylprop-2-yn-1-one (**8A**) are given in Figures 11 and 12. As shown in ^{1}H NMR spectrum (Figure 11), phenyl hydrogens resonate approximately between 7.39 and 8.31 ppm. On the other hand, as depicted in ^{13}C NMR spectrum (Figure 12), alkynic carbons peaks appear at 87.0 and 93.2 ppm while carbonyl peak shows up at 178.2 ppm. The remaining phenyl carbons resonate approximately between 120.3 and 137.1 ppm.

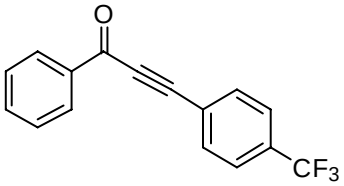
Table 1. Synthesis of alkynyl ketones **8**.[a]



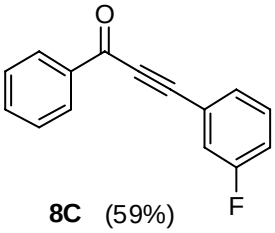
45 **46** **8**



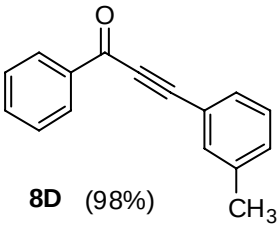
8A (90%)



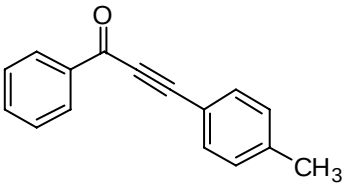
8B (85%)



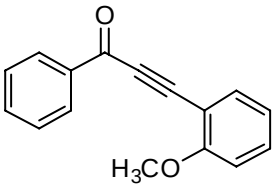
8C (59%)



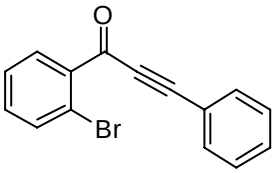
8D (98%)



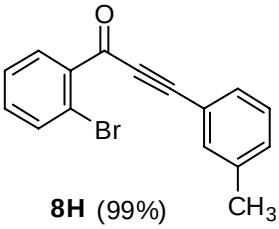
8E (72%)



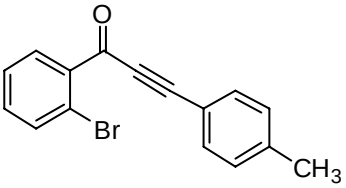
8F (90%)



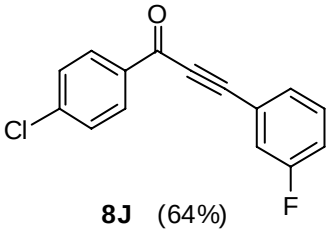
8G (55%)



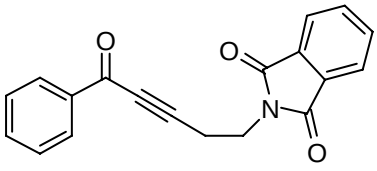
8H (99%)



8I (93%)



8J (64%)



8K (54%)

[a]Yield are of isolated products.

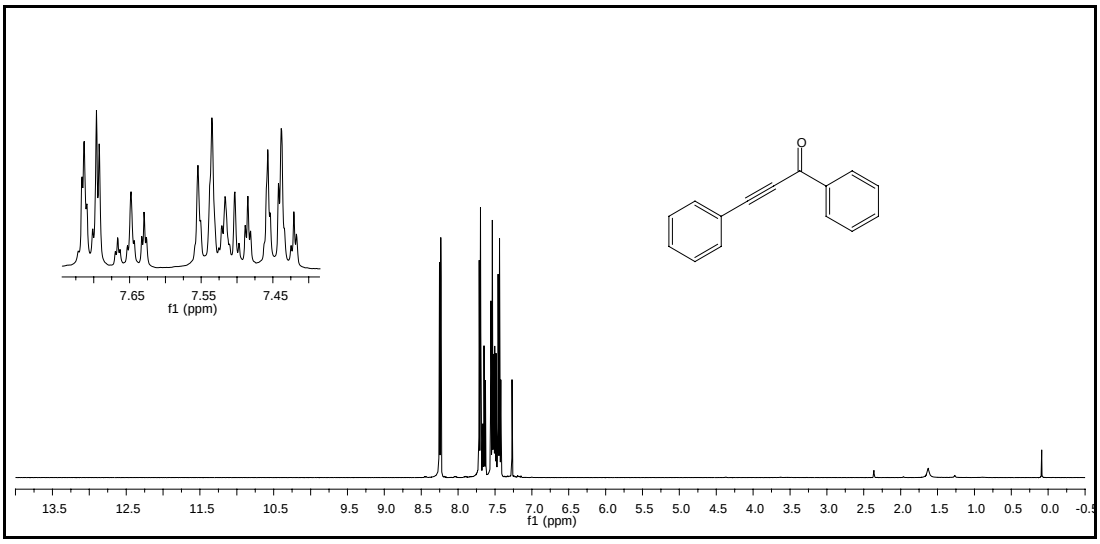


Figure 11. ^{1}H NMR spectrum of 1,3-diphenylprop-2-yn-1-one (**8A**).

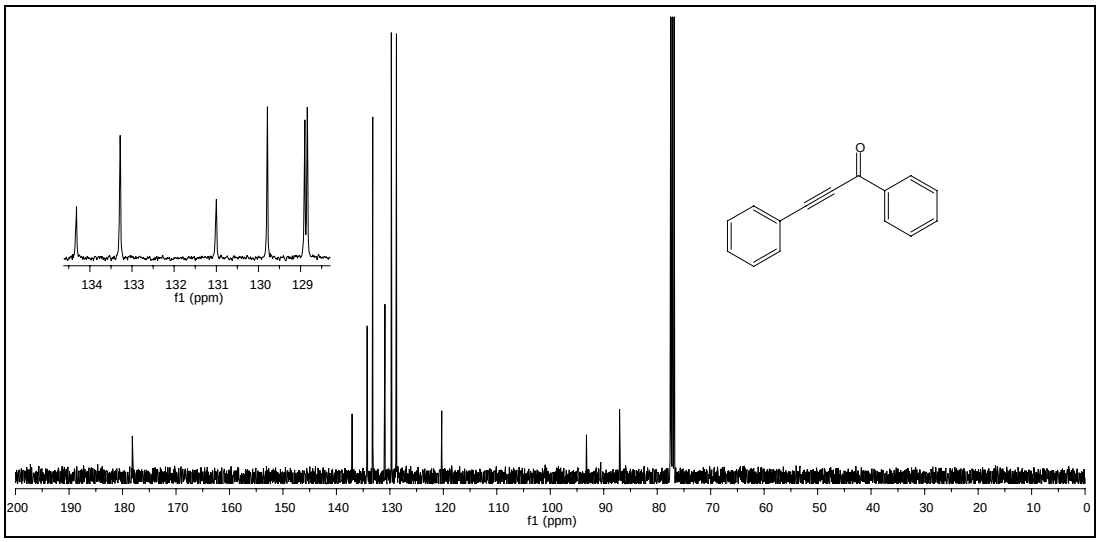
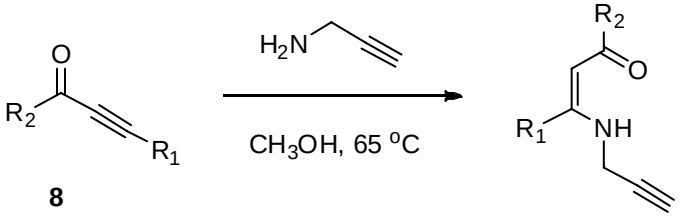


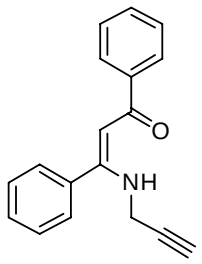
Figure 12. ^{13}C NMR spectrum of 1,3-diphenylprop-2-yn-1-one (**8A**).

Subsequently, as illustrated in Table 2, we synthesized *N*-propargylic *β*-enaminones **42** by conjugate addition of propargylamine to alkynyl ketones **8** [33]. The reaction of alkynyl ketones **8** with propargylamine in methanol at 65 ^{o}C for approximately 2 h afforded *N*-propargylic *β*-enaminones **42** in good to high yields.

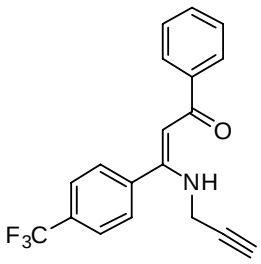
Table 2. Synthesis of *N*-propargylic β-enaminones **42**.[a]



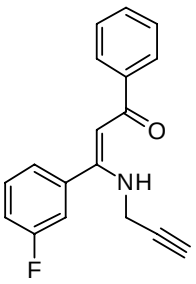
8 **42**



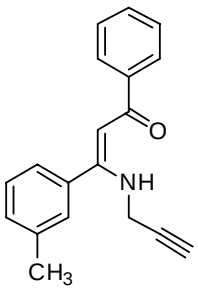
42A (98%)



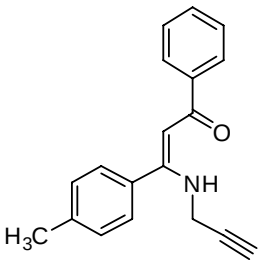
42B (98%)



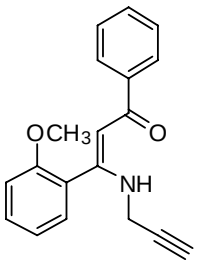
42C (90%)



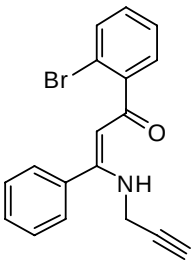
42D (78%)



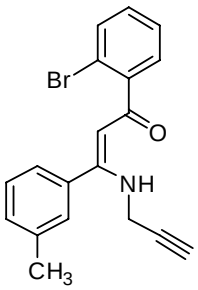
42E (93%)



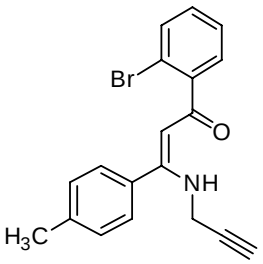
42F (80%)



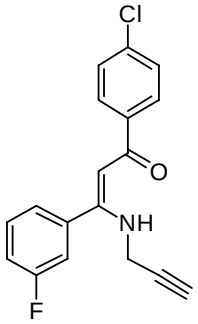
42G (90%)



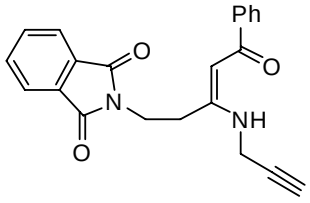
42H (97%)



42I (94%)



42J (91%)



42K (53%)

[a]Yield are of isolated products.

By employing these reactions, eleven derivatives of *N*-propargylic *β*-enaminones **42** were synthesized. The yields of *N*-propargylic *β*-enaminones **42** altered from 53 to 98% (Table 2). It should be mentioned that β-enaminones **42** were obtained as single isomers from these reactions, The stereochemistry of the double bonds in β-enaminones **42** was assigned as Z on the basis of NOESY experiments of the Cacchi research group using the same and/or similar compounds [33]. NOESY experiments showed the presence of an intramolecular hydrogen bond (N-H•••O) in these compounds as well. Obviously, the presence of such an intramolecular hydrogen bond in β-enaminones **42** increases their stability. As a result, NH peak of β-enaminones **42** generally appears over 11.00 ppm in their ^{1}H NMR spectra.

The structures of *N*-propargylic *β*-enaminones **42** were analyzed by ^{1}H and ^{13}C NMR spectroscopy. As a representative example, ^{1}H and ^{13}C NMR spectra of *N*-propargylic *β*-enaminone **42A** are given in Figures 13 and 14. As expected, in the ^{1}H NMR spectrum (Figure 13), acetylenic hydrogen resonates at 2.31 ppm while double bond hydrogen resonates at 5.87 ppm. Methylene hydrogens between amine and alkyne groups appear at 3.97. ppm. The remaining phenyl hydrogen peaks come approximately between 7.39 and 7.97 ppm (Figure 13).

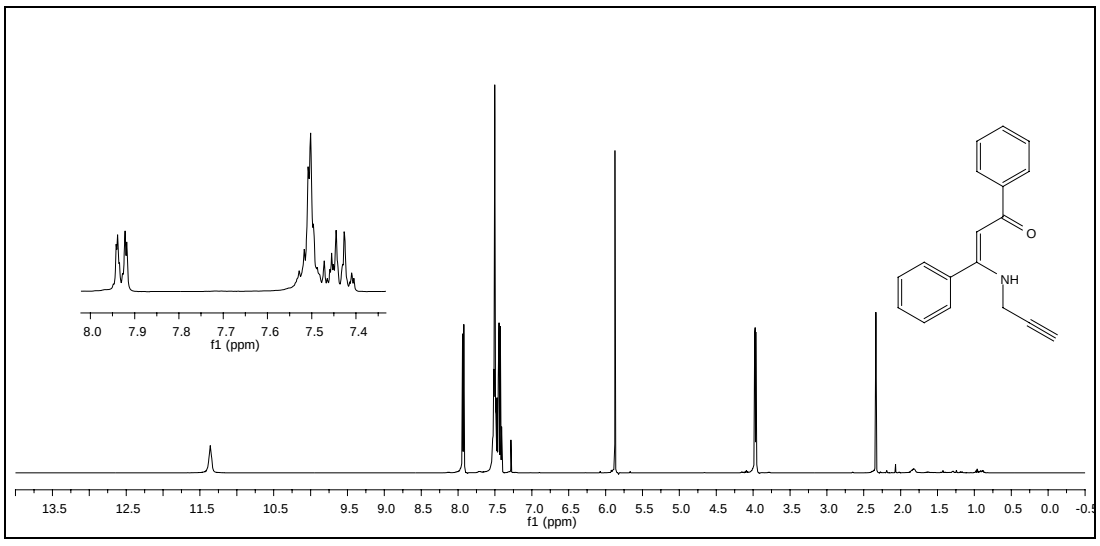


Figure 13. ^{1}H NMR spectrum of 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**42A**).

On the other hand, as shown in the ^{13}C NMR spectrum (Figure 14), two alkynic carbon peaks are observed at 72.6 and 79.9 ppm while carbonyl peak is observed at 189.3 ppm. Methylene carbon between amine and alkyne groups appears at 34.3 ppm. The remaining phenyl carbon peaks are seen between 127.3 and 140.1 ppm (Figure 14).

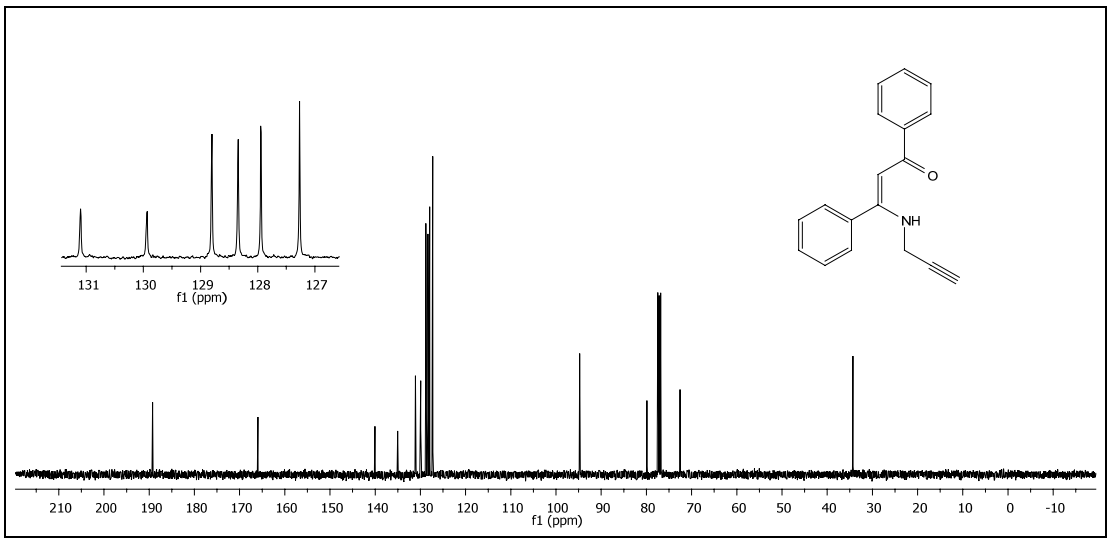


Figure 14. ^{13}C NMR spectrum of 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one **42A.**

2.2 Synthesis of 2-iodomethylene-2,3-dihydro-1,4-oxazepines

At the final stage, for the synthesis of iodo-substituted oxazepine derivatives, we investigated the cyclizations of *N*-propargylic β-enaminones **42**. In the light of our previous studies, these cyclizations were carried out in the presence of molecular iodine and $ZnCl_2$. Recently, in organic reactions, popularity of Zn based lewis acids have increased significantly due to their abundance, affordability and environmetal friendliness [43]. Therefore, we chose $ZnCl_2$ as a Lewis acid for this study.

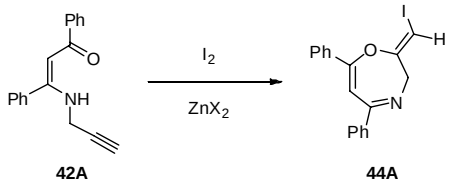
Initially, for the optimization of reaction conditions, the cyclization of *N*-propargylic β-enaminone **42A** was examined in detail. The results are summarized in Table 3. First, the reaction was carried out in the presence of 1.0 eq. I_2 with varying amount of $ZnCl_2$ in DCM at 40 ^oC (Table 3, Entries 1-4).

These reactions went to completion in approximately 6 h on average. Importantly, all of these reactions afforded the expected seven-membered ring product 2-iodomethylene-2,3-dihydro-1,4-oxazepine **44A** in varying yields (52-81%). However, best result (81%) was obtained with 1.0 eq. I_2 and 2.5 eq. $ZnCl_2$ (Table 3, Entry 4). Clearly, the use of higher amounts of $ZnCl_2$ increased the yield of **44A** considerably. However, the use of higher amounts of I_2 with varying amounts of $ZnCl_2$ did not increase or did lower the yield of **44A** (23-56%) (Table 3, Entries 5-7).

Subsequently, the reaction in Entry 4 was also performed in different solvents such as ACN, 1,4-dioxane, DCE and THF (Table 3, Entries 8-11), but mostly lower yields of **44A** were obtained with these solvents (12-56%), indicating that DCM was the most suitable solvent for this reaction. The reaction in Entry 4 was also carried out with ZnI_2 and $ZnBr_2$, instead of $ZnCl_2$ (Table 3, Entries 12 and 13), but no higher yields of **44A** were observed with these Lewis acids (39-52%). In summary, the cyclization reactions were carried out with 1.0 eq. I_2 and 2.5 eq. $ZnCl_2$ in refluxing DCM (i.e. with the reaction condition present in Entry 4 of Table 3).

The results from a systematic study are given in Table 5. A variety of *N*-propargylic β-enaminones **42**, bearing electron-withdrawing and electron-donating groups, were employed in these reactions and eleven derivatives of 2-iodomethylene-2,3-dihydro-1,4-oxazepines **44** were synthesized in mostly moderate to good yields.

Table 3. Optimization of reaction conditions for the synthesis of 2-iodomethylene-2,3-dihydro-1,4-oxazepine **44A**.[a]

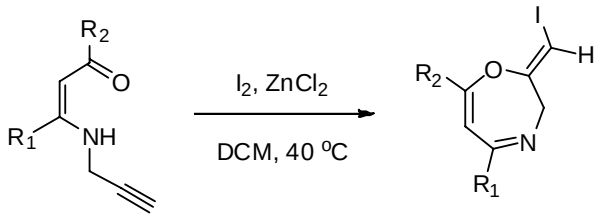


42A **44A**

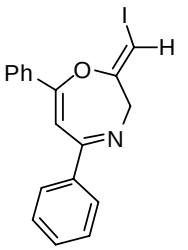
Entry	Amount of I_2	Amount of ZnX_2	Solvent	Temp. (^oC)	Time (h)	Yield (%)[a]
1	1.0 eq. I_2	1.0 eq. $ZnCl_2$	DCM	40	5.0	52
2	1.0 eq. I_2	1.5 eq. $ZnCl_2$	DCM	40	7.0	62
3	1.0 eq. I_2	2.0 eq. $ZnCl_2$	DCM	40	5.0	76
4	1.0 eq. I_2	2.5 eq. $ZnCl_2$	DCM	40	6.0	81
5	1.5 eq. I_2	2.0 eq. $ZnCl_2$	DCM	40	6.0	56
6	2.0 eq. I_2	1.0 eq. $ZnCl_2$	DCM	40	6.0	23
7	2.0 eq. I_2	2.0 eq. $ZnCl_2$	DCM	40	5.0	46
8	1.0 eq. I_2	2.5 eq. $ZnCl_2$	ACN	82	5.5	12
9	1.0 eq. I_2	2.5 eq. $ZnCl_2$	1,4-Dioxane	101	3.5	56
10	1.0 eq. I_2	2.5 eq. $ZnCl_2$	DCE	84	3.5	19
11	1.0 eq. I_2	2.5 eq. $ZnCl_2$	THF	66	5.0	40
12	1.0 eq. I_2	2.5 eq. ZnI_2	DCM	40	5.0	39
13	1.0 eq. I_2	2.5 eq. $ZnBr_2$	DCM	40	5.0	52

[a]Yields are of isolated products.

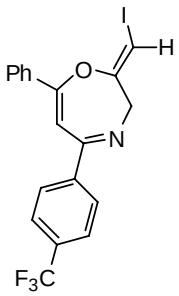
Table 4. Synthesis of 2-iodomethylene-2,3-dihydro-1,4-oxazepines **44**.[a]



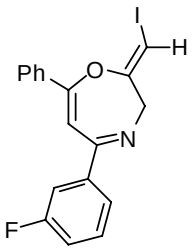
42 **44**



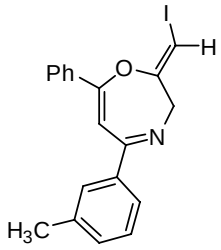
44A (81%)



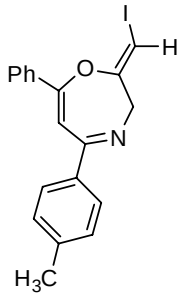
44B (72%)



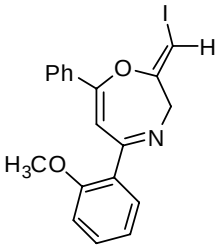
44C (85%)



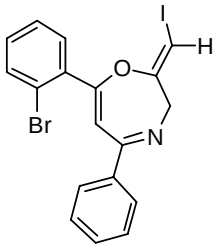
44D (78%)



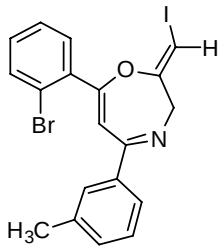
44E (42%)



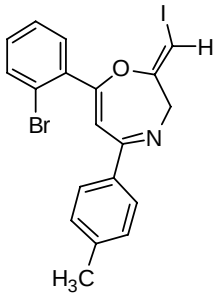
44F (23%)



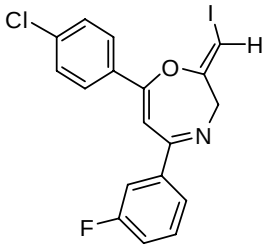
44G (66%)



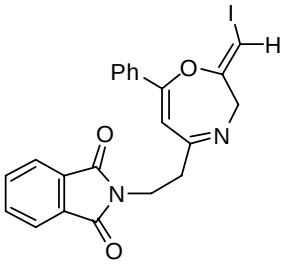
44H (59%)



44I (55%)



44J (68%)



44K (28%)

[a]Yield are of isolated products.

Structural assignments of 2-iodomethylene-2,3-dihydro-1,4-oxazepines **44** were made by ^{1}H and ^{13}C NMR spectroscopy. As a representative illustration, ^{1}H NMR, NOESY and ^{13}C NMR spectra of 2,3-dihydro-1,4-oxazepine **44A** are exhibited in Figures 15-17.

As seen in the ^{1}H NMR spectrum of 2,3-dihydro-1,4-oxazepine **44A** (Figure 15), The peak of methylene hydrogens appears at 4.71 ppm. The exo double bond hydrogen, near iodine atom, resonates at 5.90 ppm while the olefinic hydrogen on the ring skeleton resonates at 6.36 ppm. The protons of phenyl groups appear approximately between 7.28 and 7.79 ppm.

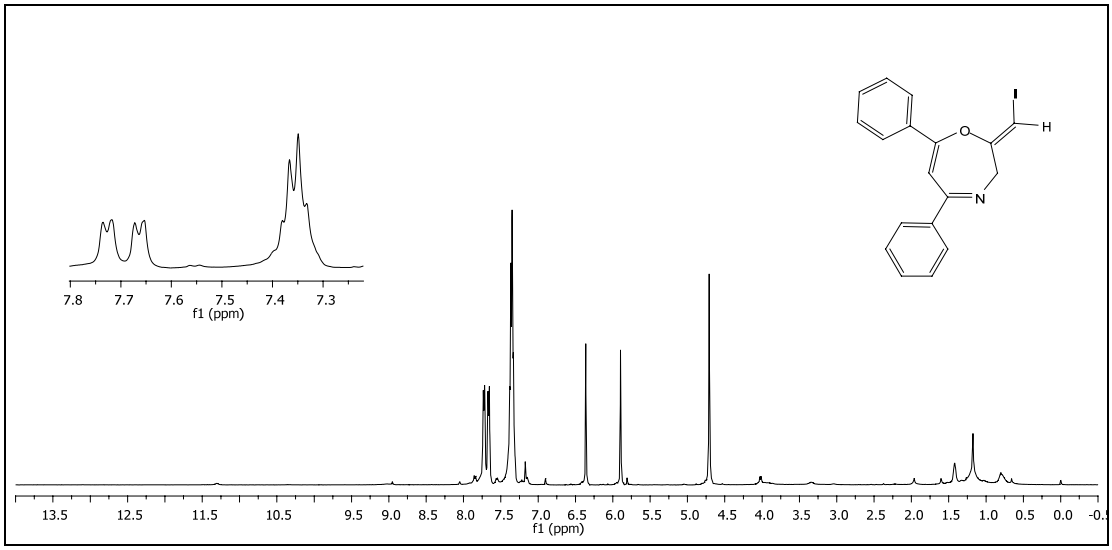


Figure 15. ^{1}H NMR spectrum of 2-iodomethylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**44A**).

It should be mentioned that 2-iodomethylene-2,3-dihydro-1,4-oxazepines **44** were obtained as single isomers from these reactions. The stereochemistry of the exo double bonds in oxazepines **44** was assigned as *Z* on the basis of NOESY experiment performed on oxazepine **44A**. In the NOESY spectrum of **44A** (Figure 16), a NOE interaction was observed between the exo double bond hydrogen and the methylene hydrogens, which is shown in circles in Figure 16, proving the *Z* configuration of the exo double bond.

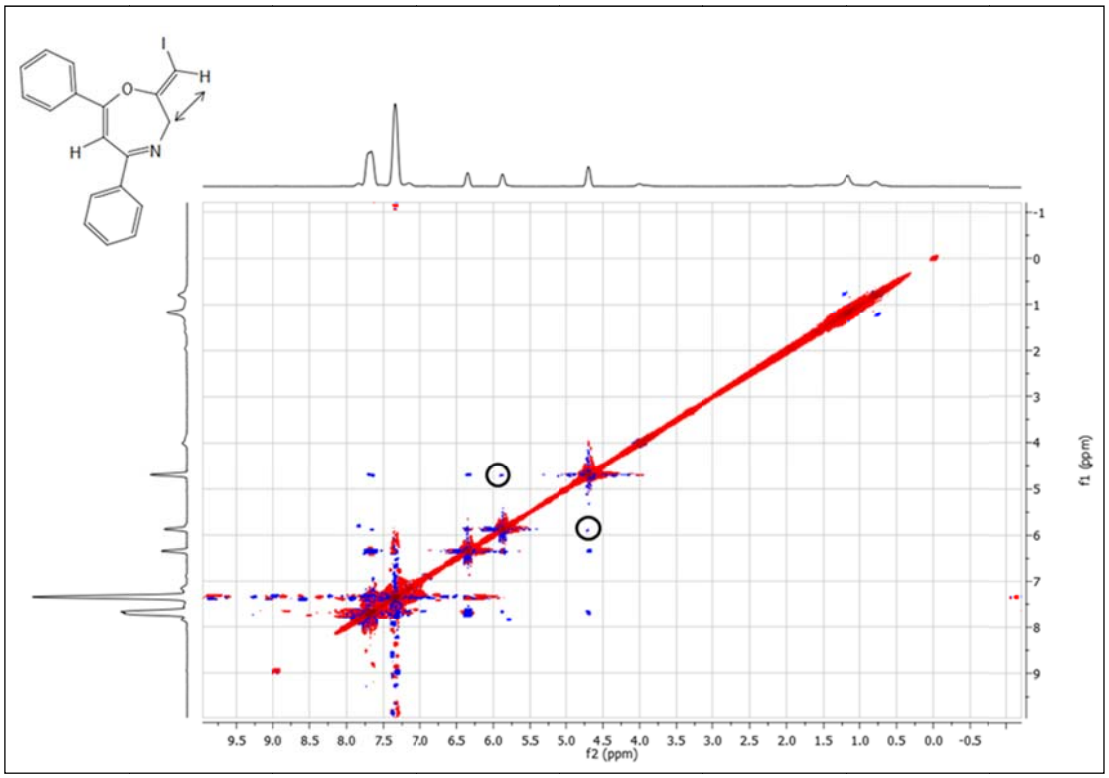


Figure 16. NOESY spectrum of 2-iodomethylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**44A**).

On the other hand, in ^{13}C NMR spectrum of **44A** shown in Figure 17, methylene carbon resonates at 54.8 ppm. The exo double bond carbon, which is attached to iodine atom, appears at 59.9 ppm. The olefinic CH carbon on the ring skeleton appears at 100.2 ppm. The remaining carbon atoms, including phenyl carbons, are observed between 126.5 and 167.6 ppm.

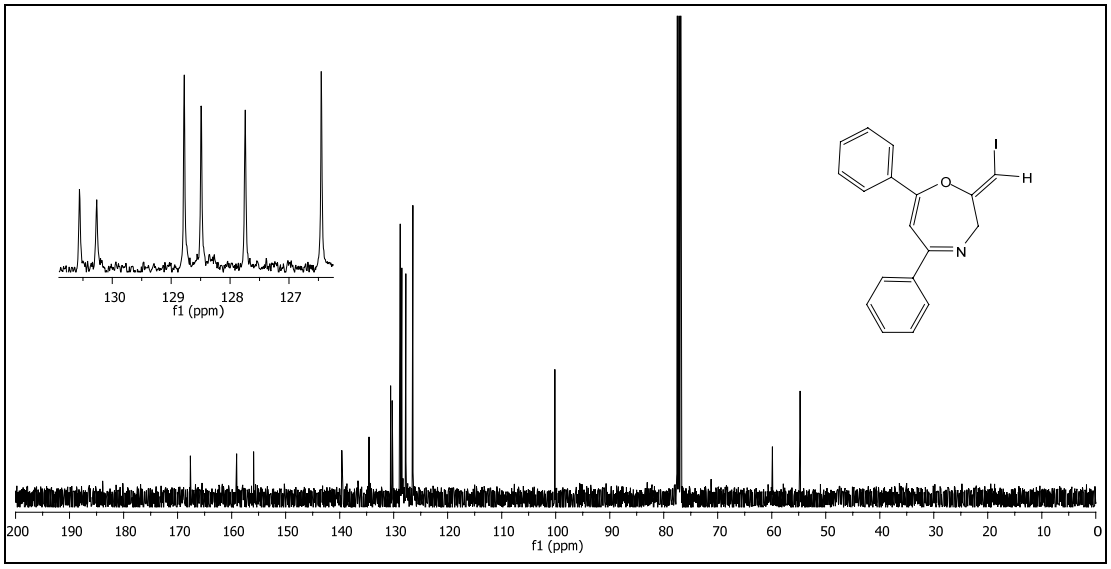
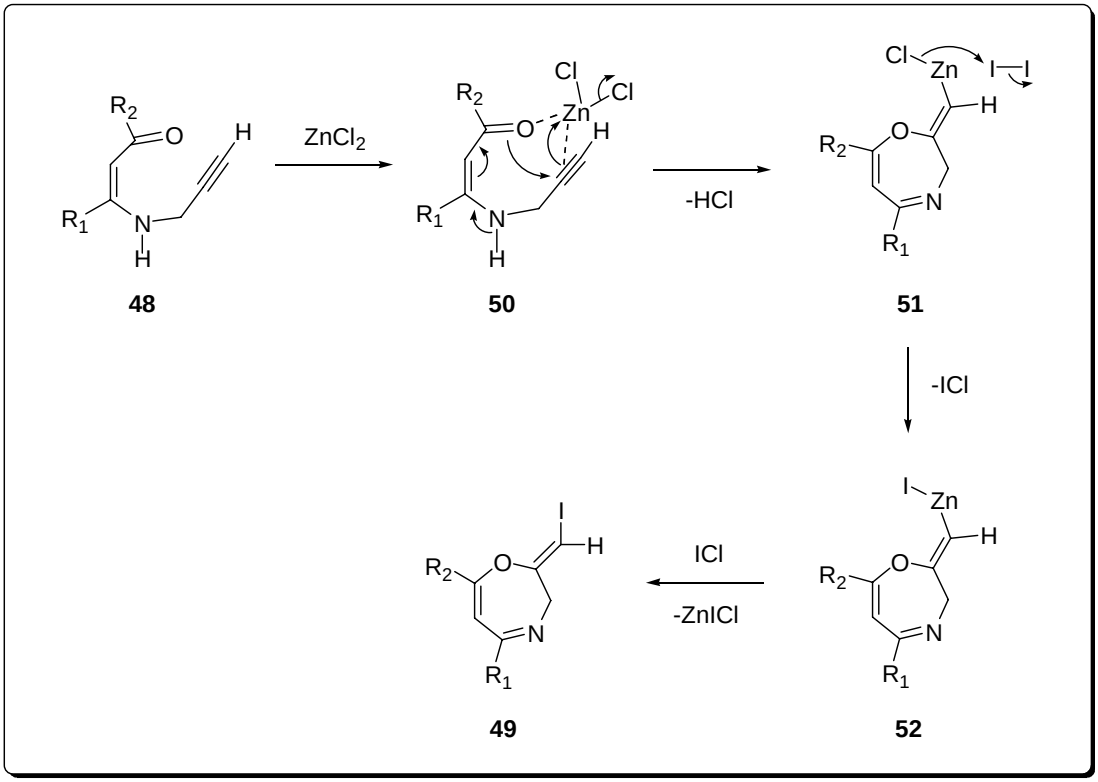


Figure 17. ^{13}C NMR spectrum of 2-iodomethylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**44A**).

2.3 Proposed mechanism for the formation of 2-iodomethylene-2,3-dihydro 1,4-oxazepines 44.

A possible mechanism for the formation of 2-iodomethylene-2,3-dihydro-1,4-oxazepines **44** is outlined in Scheme 18. Initial coordination of alkyne and carbonyl functionalities of *N*-propargylic β-enaminone **42** to $ZnCl_2$ forms the intermediate complex **50**, in which alkyne and carbonyl functionalities come close to each other. 7-Exo-dig cyclization then occurs to give complex **51**. The interaction of Zn moiety of **51** with molecular iodine produces complex **52**. Finally, reductive elimination affords 2-iodomethylene-2,3-dihydro-1,4-oxazepine derivative **44**. Importantly, the stereochemistry of the exo double bond is set at the formation of complex **51**, in which Zn and oxygen moieties end up on the same side, presumably as a result of oxygen coordination to Zn during the course of the reaction.



Scheme 19. Proposed mechanism for the formation of 2-iodomethylene-2,3-dihydro-1,4-oxazepines **44**.

CHAPTER 3

CONCLUSION

To sum up, one-pot synthesis of 2-iodomethylene-2,3-dihydro-1,4-oxazepines were achieved from *N*-propargylic β-enaminones in the presence of molecular iodine and zinc chloride.

In the first part of the study, α,β-alkynic ketones were prepared via Sonogashira cross-coupling of terminal alkynes with aryloyl chlorides, which then subjected to conjugate addition of propargylamine to yield *N*-propargylic β-enaminones. Through this procedure, eleven derivatives of *N*-propargylic β-enaminones were synthesized.

In the second part of the study, 7-exo-dig cyclizations of *N*-propargylic β-enaminones were investigated. When treated with molecular iodine and zinc chloride in refluxing DCM, *N*-propargylic β-enaminones afforded 2-iodomethylene-2,3-dihydro-1,4-oxazepines. Optimization studies for reaction conditions showed that best results were obtained with 1.0 eq. I_2 and 2.5 eq. $ZnCl_2$ over 6 h.

Consequently, eleven derivatives of 2-iodomethylene-2,3-dihydro-1,4-oxazepines were synthesized from *N*-propargylic β-enaminones in one-pot cyclization using I_2 and $ZnCl_2$. Although the yields of final products altered between 23 and 85%, they were in moderate to good yields in most cases.

The biological activity tests of the synthesized 2-iodomethylene-2,3-dihydro-1,4-oxazepine derivatives, which may have some potential for pharmaceutical benefit, will be carried out by a collaborative work.

CHAPTER 4

EXPERIMENTAL

The record of ^{1}H and ^{13}C NMR spectra were made at 400 and 100 MHz by a Bruker Spectrospin Avance DPX400 Ultrashield spectrometer. The chemical shifts are reported in parts per million (ppm) downfield from an internal TMS (trimethylsilane) reference. Coupling constants (*J*) are given in hertz (Hz), and the spin multiplicities are presented by the following symbols: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet) and br (broad). The reactions were accomplished by using Flash chromatography involving thick-walled glass columns using silica gel (Merck 230-400). Thin layer chromatography (TLC) was performed by using commercially available 0.25 mm silica gel plates and visualizing was effected with short wavelength UV lamp. Ethyl acetate-hexane solvent mixtures were used as eluent in Flash chromatography and their polarities were employed according to volume:volume ratio. In case of necessity, solvents used in reactions were distilled for purity. The inert atmosphere was supplied by slight positive pressure (ca. 0.1 psi) of argon gas in some reactions. All equipments and glassware were dried in oven prior to use.

4.1 General Procedure 1. Synthesis of alkynyl ketones (8)

In a round-bottomed flask, the corresponding benzoyl chloride (**45**) (0.70 mmol) was dissolved in THF (1.0 mL) and to the solution, $PdCl_2(PPh_3)_2$ (0.01 mmol) and Et_3N (0.1 mL), and CuI (0.01 mmol) were added, respectively, and stirred at room temperature under argon atmosphere. After 20 min later, terminal alkyne (**46**) (0.58 mmol) was added slowly and the resulting mixture was continued to be stirred for additional 40 min. When the reaction was over, water (50 mL) was added to the flask and the organic layer was extracted with ethyl acetate (2 x 25 mL). The separated organic phase was washed with water (2 x 50 mL) and then dried over $MgSO_4$ and filtered. The obtained crude product was purified by flash chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent.

4.1.1 Synthesis of 1,3-diphenylprop-2-yn-1-one (8A)

General Procedure 1 was followed by using benzoyl chloride (**45)** (100 mg, 0.70 mmol), $PdCl_2(PPh_3)_2$ (7 mg , 0.01 mmol), triethylamine (0.1 ml), CuI (2 mg, 0.01 mmol) and ethynylbenzene (59 mg, 0.58 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 1,3-diphenylprop-2-yn-1-one (**8A**) (yellow oil, 129 mg, 90% yield).

8A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.22 (m, 2H), 7.73-7.68 (m, 2H), 7.67-7.62 (m, 1H), 7.57-7.48 (m, 3H), 7.47-7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2 (CO), 137.1 (C), 134.3 (CH), 133.3 (CH), 131.0 (CH), 129.8 (CH), 128.9 (CH), 128.8 (CH), 120.4 (C), 93.3 (C), 87.1 (C). The spectral data are in agreement with those reported previously for this compound [44].

4.1.2 Synthesis of 1-phenyl-3-(4-(trifluoromethyl)-phenyl)prop-2-yn-1-one (8B)

General Procedure 1 was followed by using benzoyl chloride (**45**) (100 mg, 0.70 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), triethylamine (0.1 ml), CuI (2 mg, 0.01 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (98 mg, 0.58 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 1-phenyl-3-(4-(trifluoromethyl)-phenyl)prop-2-yn-1-one (**8B**) (brown-yellow oil, 162 mg, 85% yield).

8B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (m, 2H), 7.80 (d, J = 8.1 Hz, 2H), 7.74-7.63 (m, 3H), 7.59-7.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (CO), 136.7 (C), 134.6 (CH), 133.3 (CH), 132.3 (q, ^{2}J = 33.0 Hz, C), 129.7 (CH), 128.8 (CH), 125.7 (q, ^{3}J = 4.0 Hz, CH), 124.1 (C), 123.7 (q, ^{1}J = 270.0 Hz, CF_3), 90.5 (C), 88.2 (C). The spectral data are in agreement with those reported previously for this compound [45].

4.1.3 Synthesis of 3-(3-fluorophenyl)-1-phenylprop-2-yn-1-one (8C)

General Procedure 1 was employed using benzoyl chloride (**45**) (100 mg, 0.70 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), triethylamine (0.1 ml), CuI (2 mg, 0.01 mmol) and 1-ethynyl-3-fluorobenzene (70 mg, 0.58 mmol). Purification of the crude product by flash column chromatography on silica gel using 15:1 hexane/ethyl acetate as the eluent afforded 3-(2-fluorophenyl)-1-phenylprop-2-yn-1-one (**8C**) (yellow solid, 77 mg, 59% yield).

8C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.01 (m, 1H), 7.53 – 7.45 (m, 1H), 7.42 – 7.34 (m, 1H), 7.30 (dt, J = 7.7, 1.2 Hz, 1H), 7.25 – 7.14 (m, 1H), 7.03 (m, J = 8.4, 2.6, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (CO), 162.2 (d, ^{1}J = 246.0 Hz, CF), 136.6 (C), 134.2 (CH), 130.4 (d, ^{3}J = 9.0 Hz, CH), 129.43 (CH), 128.8 (d, ^{4}J = 3.0 Hz, CH), , 128.6 (CH), 121.8 (d, ^{3}J = 10.0 Hz, C), 119.5 (d, ^{2}J = 22.0 Hz, CH), 118.1 (d, ^{2}J = 21.0 Hz, CH), 90.9 (d, ^{4}J = 4.0 Hz, C), 87.1 (C): IR (neat): 3053,

2201, 1649, 1597, 1579, 1485, 1445, 1426, 1314, 1299, 1267, 1251, 1228, 1169, 1144, 1077, 1029, 1015, 998, 922, 867, 781, 765, 690, 673, 623, 541, 515.

4.1.4 Synthesis of 1-phenyl-3-(m-tolyl)prop-2-yn-1-one (8D)

General Procedure 1 was employed using benzoyl chloride (**45)** (100 mg, 0.70 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), triethylamine (0.1 ml), CuI (2 mg, 0.01 mmol) and 3-ethynyl toluene (67 mg, 0.58 mmol). Purification of the crude product by flash column chromatography on silica gel using 15:1 hexane/ethyl acetate as the eluent afforded 1-phenyl-3-(m-tolyl)prop-2-yn-1-one (**8D**) (yellow solid, 125 mg, 98% yield).

8D: ^{1}H NMR (400 MHz, $CDCl_3$ δ 8.29-8.20 (m, 2H), 7.68-7.59 (m, 5H), 7.56-7.45 (m, 1H), 7.35-7.22 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 138.7, 136.9, 134.0, 133.5, 131.8, 130.2, 129.5, 128.6, 128.6, 119.9, 93.5, 86.7, 21.1; IR (neat): 3059, 3032, 2188, 1630, 1596, 1578, 1479, 1450, 1377, 1314, 1294, 1280, 1225, 1165, 1092, 1036, 1016, 988, 935, 900, 883, 784, 759, 685, 626, 548, 520.

4.1.5 Synthesis of 1-phenyl-3-(p-tolyl)prop-2-yn-1-one (8E)

General Procedure 1 was employed using benzoyl chloride (**45**) (100.0 mg, 0.70 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), triethylamine (0.1 ml), CuI (2 mg, 0.01 mmol) and 4-ethynyl toluene (67 mg, 0.58 mmol). Purification of the crude product by flash column chromatography on silica gel using 15:1 hexane/ethyl acetate as the eluent afforded 1-phenyl-3-(p-tolyl)prop-2-yn-1-one (**8E**) (yellow solid, 92 mg, 72% yield).

8E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37-7.96 (m, 2H), 7.51 (tt, J = 31.6, 7.4 Hz, 5H), 7.17 (t, J = 9.0 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 141.7, 137.1, 134.1, 133.2, 129.7, 129.6, 128.7, 117.2, 93.9, 86.9, 21.9.

4.1.6 Synthesis of 3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-one (8F)

General Procedure 1 was followed by using benzoyl chloride (**45**) (100 mg, 0.70 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), triethylamine (0.1 ml), CuI (2 mg, 0.01 mmol) and 1-ethynyl-2-methoxybenzene (76 mg, 0.58 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-one (**8F**) (brown solid, 148 mg, 99% yield).

8F: ^{1}H NMR (400 MHz, $CDCl_3$ δ 7.85-6.96 (m, 9H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 160.9, 134.5, 134.3, 129.2, 128.7, 124.0, 121.0, 111.2, 96.1, 88.2, 55.4; IR (neat): 3065, 3004, 2939, 2834, 2194, 1642, 1592, 1576, 1511, 1487, 1458, 1448, 1426, 1314, 1296, 1277, 1249, 1229, 1205, 1159, 1112, 1041, 1008, 933, 828, 811, 745, 693, 623, 580, 516.

4.1.7 Synthesis of 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (8G)

General Procedure 1 was employed using 2-bromobenzoyl chloride (**45**) (100.0 mg, 0.46 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), triethylamine (0.1 ml), CuI (2 mg, 0.01 mmol) and ethynylbenzene (39 mg, 0.38 mmol) . Purification of the crude product by flash column chromatography on silica gel using 15:1 hexane/ethyl acetate as the eluent afforded 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (**8G**) (brown oil, 59 mg, 55% yield).

. **8G:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, J = 7.7, 1.7 Hz, 1H), 7.96 (dd, J = 7.9, 1.0 Hz, 1H), 7.90 (m, J = 9.2, 4.3 Hz, 2H), 7.79-7.61 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 137.4, 135.0, 133.5, 133.1, 132.8, 131.1, 128.8, 127.5, 121.2, 119.9, 94.2, 88.0; IR (neat): 3057, 2192, 1648, 1584, 1561, 1488, 1465, 1430, 1297, 1272, 1201, 1163, 1128, 1061, 1026, 1007, 994, 920, 814, 757, 736, 711, 688, 654, 619, 551, 535, 516.

4.1.8 Synthesis of 1-(2-bromophenyl)-3-(m-tolyl)prop-2-yn-1-one (8H)

General Procedure 1 was employed using 2-bromobenzoyl chloride (**45**) (100 mg, 0.46 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), triethylamine (0.1 ml), CuI (2 mg, 0.01 mmol) and 3-ethynyl toluene (45 mg, 0.38 mmol) Purification of the crude product by flash column chromatography on silica gel using 15:1 hexane/ethyl acetate as the eluent afforded 1-(2-bromophenyl)-3-(m-tolyl)prop-2-yn-1-one (**8I**) (yellow oil, 113 mg, 99% yield).

8I: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.63 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.46-7.43 (m, 1H), 7.43-7.39 (m, 1H), 7.38 (d, *J* = 0.9 Hz, 2H), 7.35-7.30 (m, 1H), 7.25-7.21 (m, 2H), 2.30 (s, 3H), 2.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 138.3, 137.1, 134.7, 133.3, 133.2, 132.6, 131.8, 130.0, 128.4, 127.3, 120.9, 119.4, 94.3, 87.5, 20.9; IR (neat): 3064, 2966, 2916, 2179, 1991, 1956, 1922, 1894, 1638, 1581, 1561, 1480, 1464, 1431, 1410, 1377, 1301, 1264, 1218, 1169, 1127, 1094, 1059, 1036, 1010, 987, 899, 874, 789, 774, 728, 685, 674, 654, 623, 552, 521.

4.1.9 Synthesis of 1-(2-bromophenyl)-3-(p-tolyl)prop-2-yn-1-one (8I)

General Procedure 1 was employed using 2-bromobenzoyl chloride (**45**) (100.0 mg, 0.46 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), triethylamine (0.1 ml), CuI (2 mg, 0.01 mmol) and 4-ethynyl toluene (45 mg, 0.38 mmol) Purification of the crude product by flash column chromatography on silica gel using 15:1 hexane/ethyl acetate as the eluent afforded 1-(2-bromophenyl)-3-(p-tolyl)prop-2-yn-1-one (**8I**) (light yellow solid, 106 mg, 93% yield).

8I: ^{1}H NMR (400 MHz, $CDCl_3$)) δ 8.06 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.70 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.45 (td, *J* = 7.5, 1.2 Hz, 1H), 7.37 (td, *J* = 7.6, 1.8 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 142.3, 138.2, 135.3, 133.6, 133.6, 133.1, 129.9, 127.8, 121.6, 117.3, 95.4, 88.4, 22.2; IR (neat): 2190, 1643, 1601, 1583, 1560, 1507, 1465, 1430, 1300, 1200, 1178, 1129, 1060, 1035, 1001, 823, 775, 730, 685, 674, 647, 610, 538, 517.

4.1.10 Synthesis of 1-(4-chlorophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (8J)

General Procedure 1 was employed using 2-chlorobenzoyl chloride (**45**) (100 mg, 0.570 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), triethylamine (0.1 ml), CuI (2 mg, 0.01 mmol) and 1-ethynyl-3-fluorobenzene (82 mg, 0.68 mmol). Purification of the crude product by flash column chromatography on silica gel using 15:1 hexane/ethyl acetate as the eluent afforded 1-(2-chlorophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (**8J**) (Brown-yellow solid, 112 mg, 64% yield).

. **8J:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.03 (m, 1H), 7.52-7.50 (m, 1H), 7.49-7.46 (m, 1H), 7.46 (t, *J* = 1.3 Hz, 1H), 7.43 (s, 1H), 7.40 (dd, *J* = 7.9, 2.4 Hz, 1H), 7.36 (m, *J* = 8.9, 2.4, 1.3 Hz, 1H), 7.21 (m, *J* = 8.4, 2.6, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (CO), 162.4 (d, ^{1}J = 247.0 Hz, CF), 141.1 (C), 135.2 (C), 131.0 (CH), 130.6 (d, ^{3}J = 8.0 Hz, CH), 129.2 (CH), 129.1 (d, ^{4}J = 3.0 Hz, CH), 121.8 (d, ^{3}J = 9.0 Hz, C), 119.8 (d, ^{2}J = 23.0 Hz, CH), 118.6 (d, ^{2}J = 21.0 Hz, CH), 91.7 (d, ^{4}J = 3.0 Hz, C), 86.9 (C); IR (neat): 3059, 2454, 2313, 2203, 1942, 1923, 1867, 1791, 1634, 1582, 1481, 1428, 1399, 1360, 1304, 1248, 1168, 1154, 1108, 1088, 1031, 1009, 954, 922, 890, 842, 784, 738, 718, 671, 641, 518.

4.1.11 Synthesis of 2-(5-oxo-5-phenylpent-3-yn-1-yl)isoindoline-1,3-dione (8K)

General Procedure 1 was employed using benzoyl chloride (**45**) (100 mg, 0.70 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), triethylamine (0.1 ml), CuI (2 mg, 0.01 mmol) and 2-(but-3-yn-1-yl)isoindoline-1,3-dione (116 mg, 0.58 mmol). Purification of the crude product by flash column chromatography on silica gel using 15:1 hexane/ethyl acetate as the eluent afforded 2-(5-oxo-5-phenylpent-3-yn-1-yl)isoindoline-1,3-dione (**8K**) (brown solid, 112 mg, 54% yield).

8K: ^{1}H NMR (400 MHz, $CDCl_3$ δ 8.12-7.93 (m, 1H), 7.90-7.62 (m, 2H), 7.58-7.47 (m, 1H), 7.44-7.31 (m, 1H), 3.98 (t, *J* = 6.9 Hz, 1H), 3.78-3.69 (m, 1H), 3.52 (dd, *J* = 6.2, 3.1 Hz, 1H), 3.49-3.40 (m, 1H), 2.92 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 167.8, 136.5, 134.2, 134.0, 133.5, 131.8, 130.1, 129.5, 128.5, 128.4, 126.3, 123.4, 91.6, 80.7, 35.7, 19.1; IR (neat): 3069, 2830, 2670, 2553, 2234, 2193,

1769, 1706, 1686, 1638, 1594, 1578, 1451, 1425, 1391, 1362, 1310, 1281, 1256, 1177, 1111, 1071, 993, 936, 917, 866, 797, 702, 666, 549, 530.

4.2 General Procedure 2. Synthesis of N-propargylic β-enaminones derivatives (42)

In a round-bottomed flask, the corresponding alkynyl ketone (**8**) (0.50 mmol) was dissolved in methanol (2.0 mL) and to the solution, propargylamine (0.60 mmol) was added. The resulting reaction mixture was refluxed in methanol at 65 ^{o}C for approximately 2 h under argon atmosphere. When the reaction was over, methanol was evaporated and the resulting crude product was purified by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent.

4.2.1 Synthesis of 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (42A)

General Procedure 2 was followed by using 1,3-diphenylprop-2-yn-1-one (**8A**) (103 mg, 0,50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**42A**) (brown-yellow solid, 128 mg, 98% yield).

42A: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.3 (br s, 1H), 7.8-7.3 (m, 10H), 5.9 (s,1H), 3.9 (dd J = 6.4, 2.4 Hz, 2H), 2.4 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.2, 165.6, 136.5, 134.2, 129.9, 128.2, 94.4, 72.4, 68.3, 34.2. The spectral data are in agreement with those reported previously for this compound [33].

4.2.2 Synthesis of 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)-phenyl)prop-2-en-1-one (42B)

General Procedure 2 was followed by using 1-phenyl-3-(4-(trifluoromethyl)-phenyl)prop-2-yn-1-one (**8B**) (137 mg, 0,50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 1-phenyl-3-(prop-2-

yn-1-ylamino)-3-(4-(trifluoromethyl)-phenyl)prop-2-en-1-one (**42B**) (yellow solid, 161 mg, 98% yield).

42B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.3 (br s, 1H), 7.9-7.4 (m, 9H), 5.9 (s,1H), 3.9 (dd J = 6.4, 2.4 Hz, 2H), 2.4 (t, J = 1.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.4 (CO), 164.0 (C), 139.6 (C), 138.4 (C), 131.8 (q, ^{2}J = 33.0 Hz, C), 131.3 (CH), 128.4 (CH), 128.3 (CH), 127.2 (CH), 125.7 (q, ^{3}J = 3.6 Hz, CH), 123.8 (q, ^{1}J = 271.0 Hz, CF_3), 94.9 (CH), 79.5 (C), 72.8 (C), 34.2 (CH_2).

4.2.3 Synthesis of 3-(3-fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (42C)

General Procedure 2 was followed by using 3-(3-fluorophenyl)-1-phenylprop-2-yn-1-one (**8C**) (112 mg, 0,50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 3-(3-fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**42C**) (brown-yellow solid, 126 mg, 90% yield).

42C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (s, 1H), 7.95-7.89 (m, 2H), 7.52-7.38 (m, 4H), 7.33-7.14 (m, 3H), 5.86 (s, 1H), 3.95 (dd, J = 6.4, 2.5 Hz, 2H), 2.35 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5 (CO), 164.2 (C), 162.6 (d, ^{1}J = 246.0 Hz, CF), 139.8 (C), 137.0 (d, ^{3}J = 7.0 Hz, C), 130.6 (d, ^{3}J = 8.0 Hz, CH), 131.3 (CH), 128.4 (CH), 127.3 (CH), 123.7 (d, ^{4}J = 3.0 Hz, CH), 116.9 (d, ^{2}J = 21.0 Hz, CH), 115.2 (d, ^{2}J = 23.0 Hz, CH), 94.8 (CH), 79.7 (C), 72.8 (CH), 34.3 (CH_2); IR (neat): 3222, 3055, 1600,1570, 1549, 1520, 1474, 1431, 1323, 1299, 1284, 1265, 1250, 1226, 1203, 1178, 1157, 1123, 1054, 1025, 1000, 965, 887, 876, 788, 736, 707, 675, 662, 578, 524.

4.2.4 Synthesis of 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (42D)

General Procedure 2 was followed by using 1-phenyl-3-(m-tolyl)prop-2-yn-1-one (**8D)** (110 mg, 0,50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product by flash column chromatography on silica gel using

9:1 hexane/ethyl acetate as the eluent afforded 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**42D)** (red oil, 107 mg, 78% yield).

42D: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (t, *J* = 6.0 Hz, 1H), 7.93 (dt, *J* = 3.9, 2.3 Hz, 2H), 7.49 – 7.24 (m, 7H), 5.86 (s, 1H), 3.93 (dd, *J* = 6.3, 2.5 Hz, 2H), 2.41 (s, 2H), 2.35 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 165.9, 139.8, 138.4, 134.6, 130.8, 130.4, 128.4, 128.2, 128.1, 127.0, 124.7, 94.3, 79.8, 77.5, 77.2, 76.8, 72.4, 34.0, 21.2.

4.2.5 Synthesis of 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (42E)

General Procedure 2 was followed by using 1-phenyl-3-(p-tolyl)prop-2-yn-1-one (**8E**) (110 mg, 0,50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (**42E**) (brown-yellow oil, 128 mg, 93% yield).

42E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.83 (m, 2H), 7.55-7.36 (m, 5H), 7.26 (dd, *J* = 17.7, 7.5 Hz, 2H), 5.87 (s, 1H), 4.04-3.88 (m, 2H), 2.42 (s, 3H), 2.38-2.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 166.1, 140.0, 131.9, 130.9, 129.3, 128.2, 127.7, 127.1, 94.5, 79.9, 72.4, 34.1, 21.3.

4.2.6 Synthesis of 3-(2-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (42F)

General Procedure 2 was followed by using 3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-one (**8F**) (118 mg, 0,50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 3-(2-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**42F**) (red oil, 116 mg, 80% yield).

42F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (br s, 1H), 7.95-7.86 (m, 2H), 7.52-7.26 (m, 5H), 7.03 (m, 2H), 5.91-5.65 (m, 1H), 3.97-3.81 (m, 2H), 3.85 (s, 3H), 2.27 (t, J

= 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 163.3, 156.1, 140.2, 131.3, 130.8, 129.9, 128.2, 127.1, 123.7, 121.0, 110.9, 94.1, 79.5, 72.2, 55.6, 33.9.

4.2.7 Synthesis of 1-(2-bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (42G)

General Procedure 2 was followed by using 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (**8G**) (142 mg, 0.50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 1-(2-bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**42G**) (red oil, 153 mg, 90% yield).

42G: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.51-7.41 (m, 6H), 7.30 (td, *J* = 7.5, 1.1 Hz, 1H), 7.22-7.15 (m, 1H), 5.54 (s, 1H), 3.96 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.33 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 165.7, 142.9, 134.4, 133.4, 130.3, 130.1, 129.2, 128.7, 127.9, 127.2, 119.5, 98.0, 79.6, 77.5, 76.8, 72.8; IR (neat): 3290, 3057, 1731, 1588, 1560, 1483, 1461, 1427, 1359, 1317, 1244, 1216, 1145, 1082, 1023, 949, 926, 872, 751, 698, 666, 647, 613, 564.

4.2.8 Synthesis of 1-(2-bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (42H)

General Procedure 2 was followed by using 1-(2-bromophenyl)-3-(m-tolyl)prop-2-yn-1-one (**8H**) (150 mg, 0.5 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent 1-(2-bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**42H**) (red oil, 172 mg, 97% yield).

42H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 2H), 7.78-7.72 (m, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.54-7.37 (m, 3H), 6.40 (s, 1H), 6.02 (s, 1H), 4.81 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 166.1, 143.1, 140.4, 133.5, 131.6, 130.3, 129.5, 129.3, 128.0, 127.3, 119.6, 98.4, 79.8, 72.7, 34.5, 21.5; IR (neat): 3289, 3054,

2920, 1731, 1712, 1680, 1561, 1479, 1426, 1359, 1321, 1256, 1223, 1139, 1123, 1082, 1023, 873, 789, 757, 744, 707, 669, 649, 574.

4.2.9 Synthesis of 1-(2-bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (42I)

General Procedure 2 was followed by using 1-(2-bromophenyl)-3-(p-tolyl)prop-2-yn-1-one (**8I**) (150 mg, 0.5 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent 1-(2-bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (**42I**) (brown-yellow solid, 166 mg, 94% yield).

42I: ^{1}H NMR (400 MHz, $CDCl_3$ δ 11.13 (s, 1H), 7.59 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.51-7.46 (m, 1H), 7.44-7.39 (m, 2H), 7.33 (ddd, *J* = 8.6, 5.8, 2.0 Hz, 1H), 7.28 (s, 1H), 7.24-7.18 (m, 1H), 5.48 (s, 1H), 4.01 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.42 (d, *J* = 5.5 Hz, 3H), 2.36 (q, *J* = 2.9 Hz, 1H), 2.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 166.2, 143.2, 140.4, 133.5, 131.6, 130.3, 129.5, 129.3, 128.0, 127.2, 119.6, 98.3, 79.8, 72.7, 34.5, 21.5; IR (neat): 3280, 1586, 1571, 1552, 1522, 1492, 1460, 1430, 1351, 1310, 1280, 1256, 1219, 1184, 1146, 1080, 1021, 949, 925, 872, 827, 791, 757, 734, 677, 666, 636, 564, 530.

4.2.10 Synthesis of 1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(3-fluorophenyl)prop-2-en-1-one (42J)

General Procedure 2 was followed by using 1-(4-chlorophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (**8J**) (129 mg, 0.5 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent 1-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(3-fluorophenyl)prop-2-en-1-one (**42J**) (brown yellow solid, 143 mg, 91% yield).

42J: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.34 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.54 (dt, *J* = 15.4, 7.7 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.30 (d,

J = 10.8 Hz, 1H), 5.86 (s, 1H), 4.02 (d, J = 4.2 Hz, 2H), 2.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1 (CO), 164.7 (C), 162.7 (d, ^1J = 247.0 Hz, CF), 138.2 (C), 137.5 (C), 136.8 (d, ^3J = 7.0 Hz, C), 130.7 (d, ^3J = 8.0 Hz, CH), 123.7 (d, ^4J = 3.0 Hz, CH), 117.1 (d, ^2J = 20.0 Hz, CH), 115.3 (d, ^2J = 22.0 Hz, CH), 128.7 (CH), 128.7 (CH), 94.5 (CH), 79.5 (C), 72.9 (CH), 34.4 (CH_2); IR (neat): 3233, 3064, 1598, 1570, 1545, 1520, 1473, 1433, 1395, 1351, 1325, 1282, 1265, 1253, 1231, 1202, 1170, 1158, 1128, 1106, 1092, 1065, 1014, 1001, 968, 933, 891, 878, 838, 793, 764, 704, 684, 665, 629, 583, 524.

4.2.11 Synthesis of 2-(5-oxo-5-phenyl-3-(prop-2-yn-1-ylamino)pent-3-en-1-yl)-1H-indene-1,3(2H)-dione (42K)

General Procedure 2 was followed by using 2-(5-oxo-5-phenylpent-3-yn-1-yl)isoindoline-1,3-dione (**8K**) (152 mg, 0,50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 2-(5-oxo-5-phenyl-3-(prop-2-yn-1-ylamino)pent-3-en-1-yl)-1H-indene-1,3(2H)-dione **(42K**) (yellow solid, 95 mg, 53% yield).

42K: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (t, J = 5.8 Hz, 1H), 7.81-7.71 (m, 4H), 7.68-7.58 (m, 2H), 7.41-7.27 (m, 4H), 5.74 (s, 1H), 4.19 (dd, J = 6.2, 2.4 Hz, 2H), 3.91 (dd, J = 8.8, 6.9 Hz, 2H), 2.91-2.61 (m, 2H), 2.45-2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 167.8, 162.8, 139.7, 134.7, 131.8, 130.8, 129.0, 128.3, 128.1, 126.9, 126.2, 123.3, 92.9, 79.1, 72.8, 35.9, 32.3, 30.7; IR (neat): 3260, 3061, 1775, 1713, 1594, 1581, 1550, 1521, 1463, 1438, 1426, 1392, 1354, 1337, 1316, 1290, 1247, 1233, 1188, 1173, 1098, 1077, 1063, 1024, 997, 971, 933, 872, 802, 784, 753, 710, 691, 652, 605, 550,528.

4.3 General procedure 3. Synthesis of iodo-substituted oxazepine derivatives (44)

In a round-bottomed flask, the corresponding *N*-propargylic *β*-enaminones derivatives (**42**) (0.38 mmol) was dissolved in DCM (10 mL) and to the solution,

$ZnCl_2$ (0.95 mmol) and I_2 (0.38 mmol) were added, respectively, and stirred at 40 ^oC under argon atmosphere. When the reaction was over, water (50 mL) was added to the flask and the organic layer was extracted with ethyl acetate (2 x 25 mL). The separated organic phase was washed with water (2 x 50 mL) and then dried over $MgSO_4$ and filtered. The obtained crude product was purified by flash chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent.

4.3.1 Synthesis of 2-(iodomethylene)-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (44A)

General Procedure 3 was followed by using 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**42A**) (100 mg, 0.38 mmol), $ZnCl_2$ (130 mg, 0.95 mmol) and I_2 (97 mg, 0.38 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 2-(iodomethylene)-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (**44A**) (brown solid, 119 mg, 81% yield, mp 112.5 ^oC).

44A: ^1H NMR (400 MHz, $CDCl_3$) δ 8.05-7.62 (m, 2H), 7.57-7.19 (m, 4H), 6.48 (d, J = 20.6 Hz, 1H), 6.10-5.83 (m, 1H), 4.82 (d, J = 20.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 159.1, 158.2, 155.9, 139.6, 134.6, 130.6, 130.3, 128.8, 128.5, 127.7, 126.5, 100.2, 59.9, 54.8; IR (neat): 3058, 3034, 2954, 2921, 2851, 1966, 1953, 1737, 1632, 1615, 1586, 1561, 1493, 1446, 1434, 1362, 1321, 1287, 1259, 1230, 1186, 1141, 1018, 994, 934, 836, 827, 758, 726, 693, 682, 669, 648, 583; MS (ESI, m/z): 387.01 $[M+H]^+$; HRMS (ESI): calc. For $C_{18}H_{14}INO$: 388.0198 $[M+H]^+$, found: 388.0196.

4.3.2 Synthesis of 2-(iodomethylene)-7-phenyl-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1,4-oxazepine (44B)

General Procedure 3 was followed by using 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)-phenyl)prop-2-en-1-one (**42B**) (125 mg, 0.38 mmol), $ZnCl_2$ (130 mg, 0.95 mmol) and I_2 (97 mg, 0.38 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the

eluent afforded 2-(iodomethylene)-7-phenyl-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1,4-oxazepine (**44B**) (yellow solid, 125 mg, 72% yield, mp 134.4 ^{o}C).

44B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.1 Hz, 1H), 7.78-7.72 (m, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.54-7.37 (m, 2H), 6.40 (s, 1H), 6.02 (s, 1H), 4.81 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C), 159.5 (C), 155.6 (C), 143.0 (C), 134.3 (C), 131.9 (q, ^{2}J = 33.0 Hz, C), 130.8 (CH), 128.8 (CH), 128.1 (CH), 126.5 (CH), 125.4 (q, ^{3}J = 4.0 Hz, CH), 124.1 (q, ^{1}J = 270.0 Hz, CF_3), 99.4 (CH), 60.5 (CH), 55.2 (CH_2); IR (neat): 3082, 2350, 2318, 1745, 1628, 1611, 1584, 1562, 1493, 1448, 1429, 1406, 1367, 1322, 1308, 1261, 1232, 1186, 1161, 1144, 1106, 1066, 992, 969, 930, 868, 849, 816, 775, 761, 731, 678, 648, 602, 590, 516.

4.3.3 Synthesis of 5-(3-fluorophenyl)-2-(iodomethylene)-7-phenyl-2,3-dihydro-1,4-oxazepine (44C)

General Procedure 3 was followed by 3-(3-fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**42C**) (106 mg, 0.38 mmol), $ZnCl_2$ (130 mg, 0.95 mmol) and I_2 (97 mg, 0.38 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 5-(3-fluorophenyl)-2-(iodomethylene)-7-phenyl-2,3-dihydro-1,4-oxazepine (**44C**) (brown-yellow solid, 131 mg, 85% yield, mp 115.2 ^{o}C).

44C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.70 (m, 1H), 7.55 (ddd, J = 9.8, 8.1, 6.8 Hz, 1H), 7.51-7.32 (m, 2H), 7.19-7.05 (m, 1H), 6.40 (s, 1H), 5.99 (s, 1H), 4.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3 (C), 161.3 (d, ^{1}J = 244.0 Hz, CF), 159.2 (C), 155.8 (C), 142.0 (d, ^{3}J = 7.0 Hz, C), 134.4 (C), 130.6 (CH), 129.9 (d, ^{3}J = 8.0 Hz, CH), 128.8 (CH), 126.4 (CH), 123.4 (d, ^{4}J = 4.0 Hz, CH), 117.0 (d, ^{2}J = 21.0 Hz, CH), 114.7 (d, ^{2}J = 22.0 Hz, CH), 99.6 (CH), 60.1 (CH), 55.0 (CH_2); IR (neat): 3065, 2969, 1661, 1632, 1617, 1562, 1496, 1481, 1445, 1429, 1365, 1319, 1305, 1289, 1253, 1179, 1038, 1021, 981, 929, 891, 873, 791, 758, 719, 684, 649, 628, 589, 525.

4.3.4 Synthesis of 2-(iodomethylene)-7-phenyl-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (44D)

General Procedure 3 was followed by 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**42D**) (105 mg, 0.38 mmol), $ZnCl_2$ (130 mg, 0.95 mmol) and I_2 (97 mg, 0.38 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 2-(iodomethylene)-7-phenyl—5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (**44D**) (red solid, 119 mg, 78% yield, mp 122.7 ^{o}C).

44D: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.75 (m, 2H), 7.66 (s, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.51-7.42 (m, 3H), 7.38-7.25 (m, 2H), 6.46 (s, 1H), 5.99 (s, 1H), 4.81 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 158.7, 156.0, 139.8, 138.2, 134.6, 130.9, 130.5, 128.8, 128.4, 128.3, 126.4, 124.9, 100.4, 59.6, 54.8, 21.5: IR (neat): 3061, 3023, 2948, 1735, 1617, 1596, 1562, 1491, 1477, 1437, 1340, 1324, 1281, 1261, 1215, 1173, 1133, 1104, 1019, 933, 869, 834, 784, 756, 685, 646, 616, 588, 530.

4.3.5 Synthesis of 2-(iodomethylene)-7-phenyl—5-(p-tolyl)-2,3-dihydro-1,4-oxazepine (44E)

General Procedure 3 was followed by 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (**42E**) (105 mg, 0.38 mmol), $ZnCl_2$ (130 mg, 0.95 mmol) and I_2 (97 mg, 0.38 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 2-(iodomethylene)-7-phenyl—5-(p-tolyl)-2,3-dihydro-1,4-oxazepine (**44E**) (brown solid, 64 mg, 42% yield, mp 121.1 ^{o}C).

44E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 -7.70 (m, 4H), 7.55-7.38 (m, 4H), 7.34-7.17 (m, 3H), 6.48 (d, *J* = 7.5 Hz, 1H), 5.98 (s, 1H), 4.80 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 158.8, 156.1, 140.5, 136.8, 134.7, 130.5, 129.5, 129.2, 128.8, 128.3, 127.9, 127.7, 127.3, 126.4, 100.3, 59.6, 54.6, 21.5; IR (neat): 3070, 3028, 2966, 1733, 1633, 1616, 1580, 1556, 1491, 1451, 1437, 1405, 1359,

1321, 1289, 1262, 1232, 1206, 1180, 1140, 1112, 1089, 1036, 1018, 996, 930, 867, 842, 817, 761, 714, 690, 674, 649, 624, 552.

4.3.6 Synthesis of 2-(iodomethylene)-5-(2-methoxyphenyl)-7-phenyl-2,3-dihydro-1,4-oxazepine (44F)

General Procedure 3 was followed by using 3-(2-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**42F**) (111 mg, 0.38 mmol), $ZnCl_2$ (130 mg, 0.95 mmol) and I_2 (97 mg, 0.38 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 2-(iodomethylene)-5-(2-methoxyphenyl)-7-phenyl-2,3-dihydro-1,4-oxazepine (**44F**) (light yellow solid, 36 mg, 23% yield, mp 102.6 ^{o}C).

44F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (ddd, *J* = 11.4, 6.8, 5.0 Hz, 1H), 7.59-7.31 (m, 3H), 7.15-6.83 (m, 1H), 5.81 (s, 1H), 4.00-3.68 (m, 2H), 2.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2, 163.6, 156.0, 140.4, 140.2, 136.2, 131.3, 131.0, 128.3, 127.4, 123.3, 121.1, 111.1, 101.4, 94.6, 80.3, 79.1, 55.7; IR (neat): 3059, 2971, 2918, 2839, 1594, 1567, 1549, 1511, 1480, 1462, 1449, 1436, 1347, 1318, 1292, 1271, 1234, 1215, 1183, 1146, 1115, 1078, 1053, 1042, 1020, 994, 929, 872, 802, 774, 741, 691, 673, 636, 617, 582, 529, 506.

4.3.7 Synthesis of 7-(2-bromophenyl)-2-(iodomethylene)-5-phenyl-2,3-dihydro-1,4-oxazepine (44G)

General Procedure 3 was followed by 1-(2-bromophenyl)-3-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**42G**) (129 mg, 0.38 mmol), $ZnCl_2$ (130 mg, 0.95 mmol) and I_2 (97 mg, 0.38 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 7-(2-bromophenyl)-2-(iodomethylene)-5-phenyl-2,3-dihydro-1,4-oxazepine (**44G**) (brown-yellow oil, 117 mg, 66% yield,).

44G: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.92 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.84 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.78 (ddd, *J* = 11.1, 7.6, 1.7 Hz, 2H), 7.73-7.62 (m, 6H), 7.60-7.42 (m, 2H), 6.35 (s, 1H), 6.17 (s, 1H), 5.80 (s, 1H), 5.18

(s, 1H), 4.44-4.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 156.4, 139.1, 137.2, 133.5, 131.1, 130.9, 130.4, 130.3, 130.0, 129.4, 129.2, 128.9, 128.5, 128.3, 127.6, 127.6, 127.2, 122.2, 119.6, 105.0, 99.4, 81.1, 60.0, 55.7, 54.9; IR (neat): 3060, 2974, 2840, 1732, 1636, 1588, 1562, 1482, 1467, 1427, 1356, 1320, 1297, 1250, 1217, 1178, 1137, 1084, 1059, 1018, 1000, 931, 872, 835, 755, 719, 696, 640, 611, 584, 545.

4.3.8 Synthesis of 7-(2-bromophenyl)-2-(iodomethylene)-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (44H)

General Procedure 3 was followed by 1-(2-bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(m-tolyl)prop-2-en-1-one (**42H**) (135 mg, 0.38 mmol), $ZnCl_2$ (130 mg, 0.95 mmol) and I_2 (97 mg, 0.38 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 7-(2-bromophenyl)-2-(iodomethylene)-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (**44H**) (yellow solid, 107 mg, 59% yield, mp 133.2 ^{o}C).

44H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.65 (m, 2H), 7.64-7.53 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.36-7.24 (m, 3H), 6.10 (s, 1H), 5.93 (s, 1H), 4.94 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 159.1, 156.5, 139.2, 138.2, 137.2, 133.5, 131.1, 131.0, 130.9, 128.3, 128.1, 127.6, 124.8, 122.2, 105.2, 59.8, 54.9, 21.5; IR (neat): 3061, 3043, 2953, 2325, 1637, 1622, 1585, 1571, 1464, 1433, 1357, 1319, 1300, 1258, 1238, 1207, 1187, 1136, 1095, 1080, 1057, 1018, 983, 948, 932, 866, 843, 799, 768, 756, 719, 710, 679, 634, 588, 520.

4.3.9 Synthesis of 7-(2-bromophenyl)-2-(iodomethylene)-5-(p-tolyl)-2,3-dihydro-1,4-oxazepine (44I)

General Procedure 3 was followed by 1-(2-bromophenyl)-3-(prop-2-yn-1-ylamino)-3-(p-tolyl)prop-2-en-1-one (**42I**) (135 mg, 0.38 mmol), $ZnCl_2$ (130 mg, 0.95 mmol) and I_2 (97 mg, 0.38 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 7-(2-bromophenyl)-2-(iodomethylene)-5-(p-tolyl)-2,3-dihydro-1,4-oxazepine (**44I**) (light yellow solid, 100 mg, 55% yield, mp 128.9 ^{o}C).

44I: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.66 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.53 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.39 (ddd, *J* = 8.7, 6.8 and 3.0 Hz, 1H), 7.33-7.27 (m, 1H), 7.21 (d, *J* = 7.9 Hz, 2H), 6.08 (s, 1H), 5.88(s, 1H), 4.90 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 159.0, 156.7, 140.5, 137.3, 136.5, 133.5, 131.1, 130.9, 129.2, 127.58, 127.56, 122.2, 105.2, 59.6, 54.8, 21.5; IR (neat): 3055, 3024, 2971, 2841, 1734, 1638, 1624, 1580, 1560, 1510, 1464, 1429, 1349, 1321, 1296, 1252, 1228, 1209, 1178, 1136, 1113, 1084, 1057, 1018, 997, 965, 947, 932, 845, 811, 776, 754, 721, 688, 663, 638, 624, 556, 547, 508.

4.3.10 Synthesis of 7-(4-chlorophenyl)-5-(3-fluorophenyl)-2-(iodometyhlene)-2,3-dihydro-1,4-oxazepine (44J)

General Procedure 3 was followed by 11-(4-chlorophenyl)-3-(prop-2-yn-1-ylamino)-3-(3-fluorophenyl)prop-2-en-1-one (**42J**) (119 mg, 0.38 mmol), $ZnCl_2$ (130 mg, 0.95 mmol) and I_2 (97 mg, 0.38 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 7-(2-chlorophenyl)-5-(fluorophenyl)-2-(iodometyhlene)-2,3-dihydro-1,4-oxazepine (**44J**) (light yellow solid, 114 mg, 68% yield, mp 136.4 ^{o}C).

44J: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.65 (m, 2H), 7.57-7.49 (m, 2H), 7.44-7.34 (m, 3H), 7.13 (m, *J* = 8.3, 2.5, 0.8 Hz, 1H), 6.36 (s, 1H), 5.99 (s, 1H), 4.78 (s, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2 (C), 162.9 (d, ^{1}J = 245.0 Hz, CF), 158.0 (C), 155.6 (C), 141.9 (d, ^{3}J = 7.0 Hz, C), 136.7 (C), 132.9 (C), 130.0 (d, ^{3}J = 8.0 Hz, CH), 129.1 (CH), 127.7 (CH), 123.3 (d, ^{4}J = 2.7 Hz, CH), 117.1 (d, ^{2}J = 21.2 Hz, CH), 114.6 (d, ^{2}J = 22.6 Hz, CH), 99.8 (CH), 60.3 (CH), 55.0 (CH_2); IR (neat): 3066, 2976, 1629, 1616, 1563, 1487, 1431, 1403, 1364, 1319, 1274, 1255, 1179, 1159, 1136, 1091, 1068, 1011, 982, 961, 929, 892, 878, 834, 817, 789, 760, 724, 711, 692, 666, 634, 621, 599, 555, 518; MS (ESI, m/z): 438.96 $[M+H]^+$; HRMS (ESI): calc. For $C_{18}H_{12}ClFINO$: 439.9714 $[M+H]^+$, found: 439.9785.

4.3.11 Synthesis of 2-(2(2-(iodomethylene)-7-phenyl-2,3-dihydro-1,4-oxazepin-5-yl)ethyl)-1H-indene-1,3(2H)-dione (44K)

General Procedure 3 was followed by 2-(5-oxo-5-phenyl-3-(prop-2-yn-1-ylamino)pent-3-en-1-yl)-1H-indene-1,3(2H)-dione (**42K**) (136 mg, 0.38 mmol), $ZnCl_2$ (130 mg, 0.95 mmol) and I_2 (97 mg, 0.38 mmol). Final purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 2-(2(2-(iodomethylene)-7-phenyl-2,3-dihydro-1,4-oxazepin-5-yl)ethyl)-1H-indene-1,3(2H)-dione (**44K**) (yellow solid, 52 mg, 28% yield).

44K: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 7.56 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.51-7.41 (m, 6H), 7.30 (td, *J* = 7.5, 1.1 Hz, 1H), 7.21-7.15 (m, 1H), 5.47 (s, 1H), 3.96 (dd, *J* = 6.4, 2.5 Hz, 2H), 2.33 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 165.8, 143.1, 134.4, 133.4, 130.3, 130.1, 129.2, 128.8, 127.9, 127.2, 119.5, 98.4, 79.6, 72.8, 34.4; IR (neat): 3060, 2919, 1769, 1703, 1634, 1615, 1572, 1493, 1435, 1392, 1354, 1294, 1261, 1237, 1211, 1188, 1177, 1135, 1093, 1064, 1026, 1000, 970, 941, 887, 863, 844, 764, 717, 689, 629, 603, 529, 505.

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APPENDIX A

NMR DATA

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker Spectrospin Avance DPX400 Ultrashield spectrometer.

^{1}H and ^{13}C NMR spectra of products are given below.

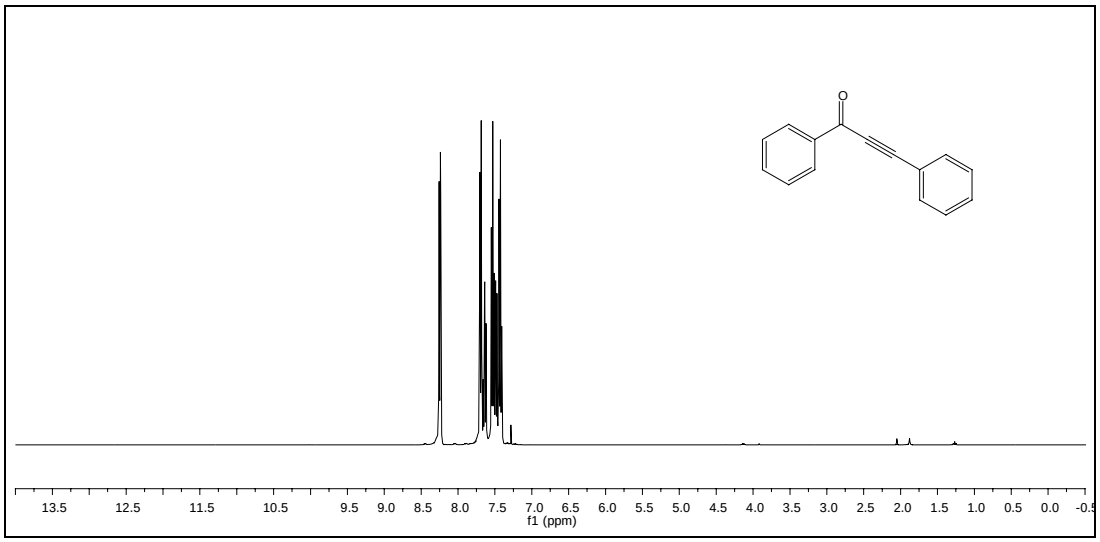

Figure 18A. ^{1}H NMR Spectrum of compound **8A**.

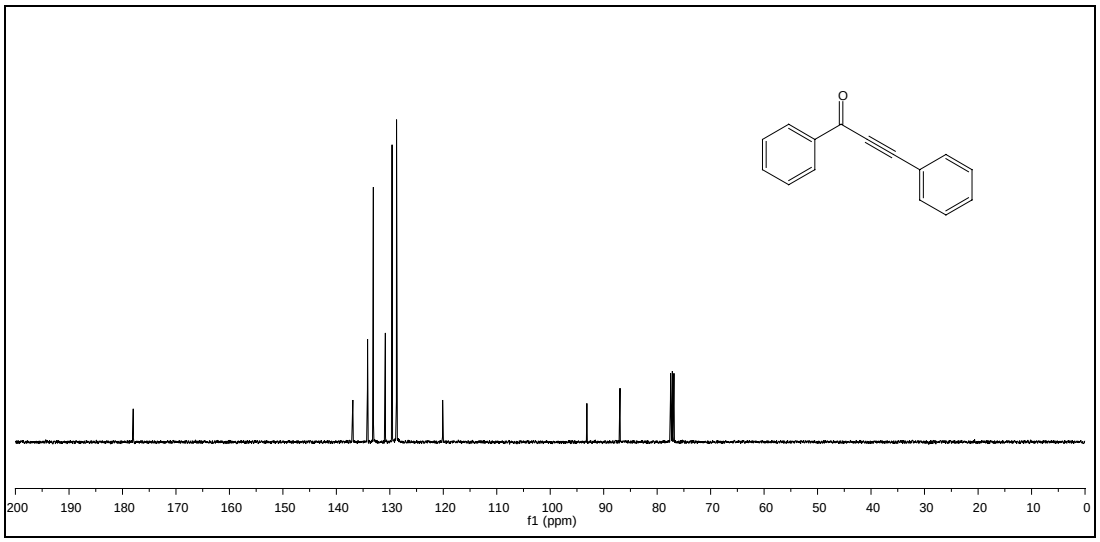

Figure 19A. ^{13}C NMR Spectrum of compound **8A**.

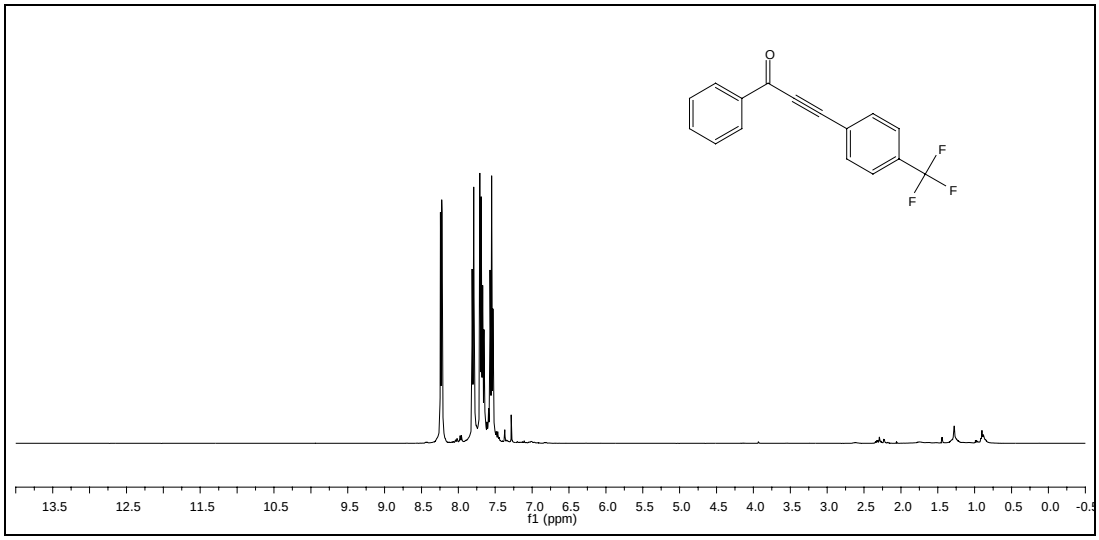

Figure 20A. ^{1}H NMR Spectrum of compound **8B.**

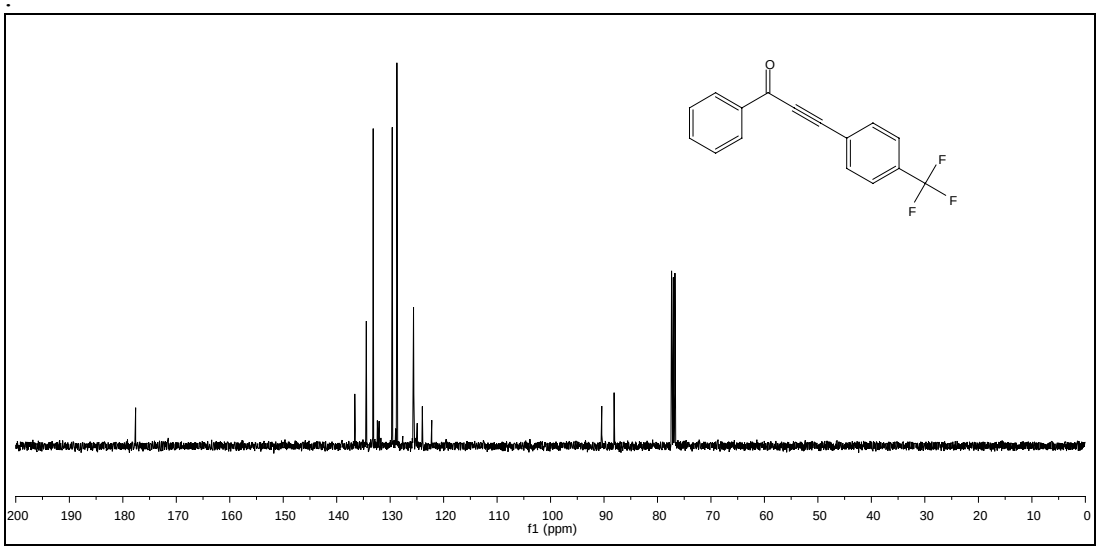

Figure 21A. ^{13}C NMR Spectrum of compound **8B.**

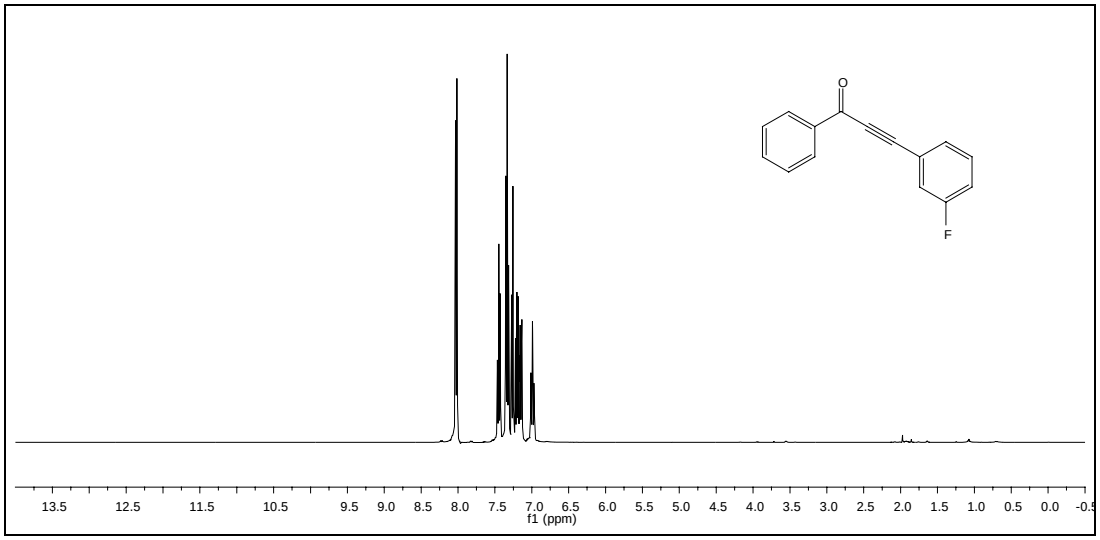

Figure 22A. ^{1}H NMR Spectrum of compound **8C.**

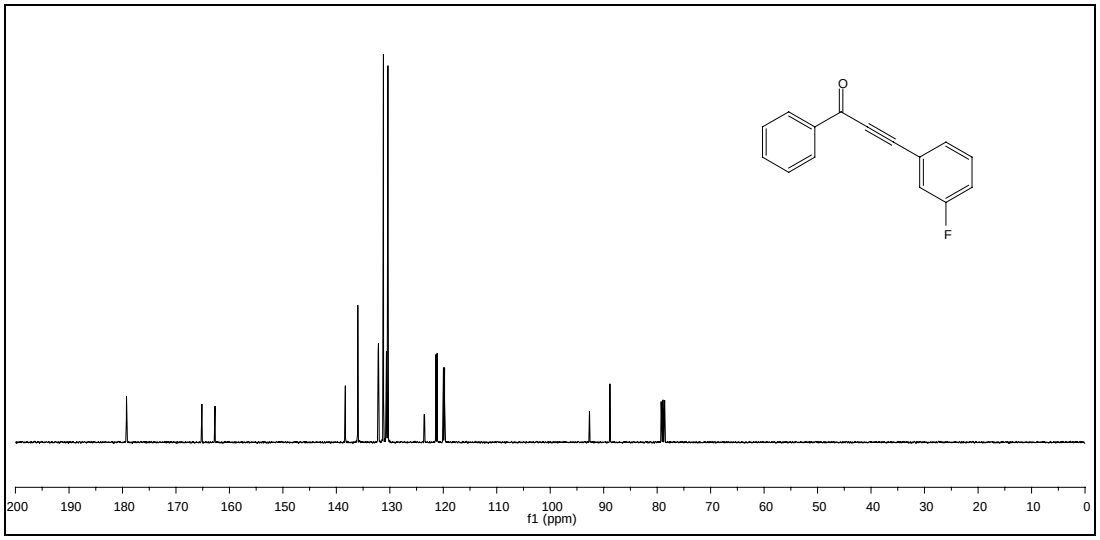

Figure 23A. ^{13}C NMR Spectrum of compound **8C.**

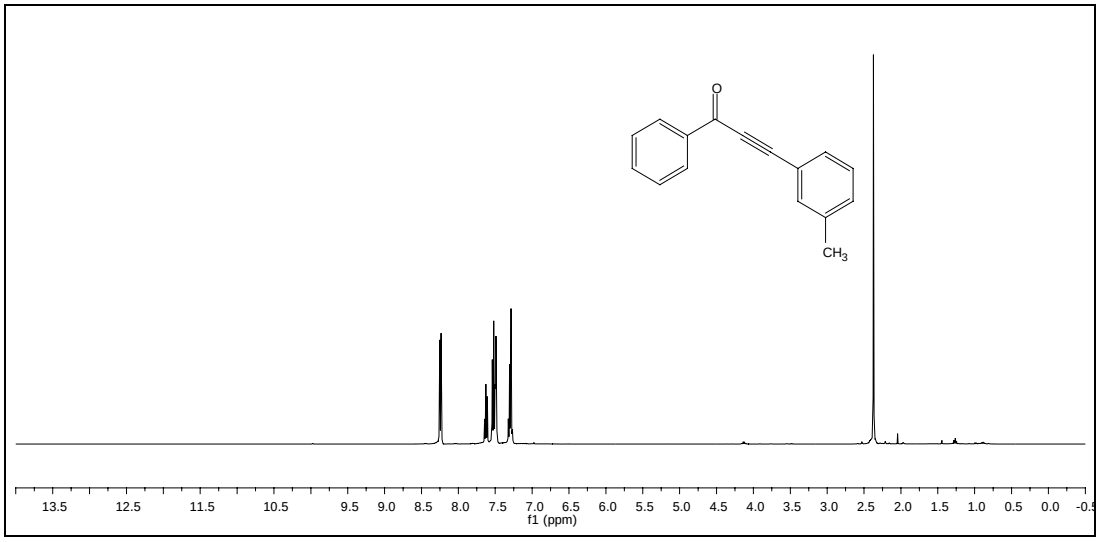

Figure 24A. ^{1}H NMR Spectrum of compound **8D.**

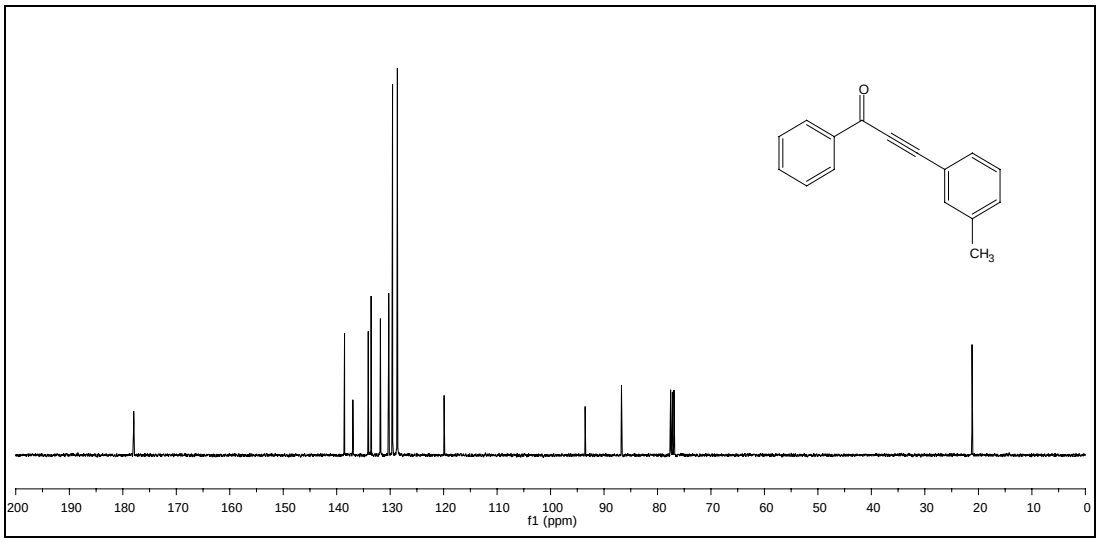

Figure 25A. ^{13}C NMR Spectrum of compound **8D.**

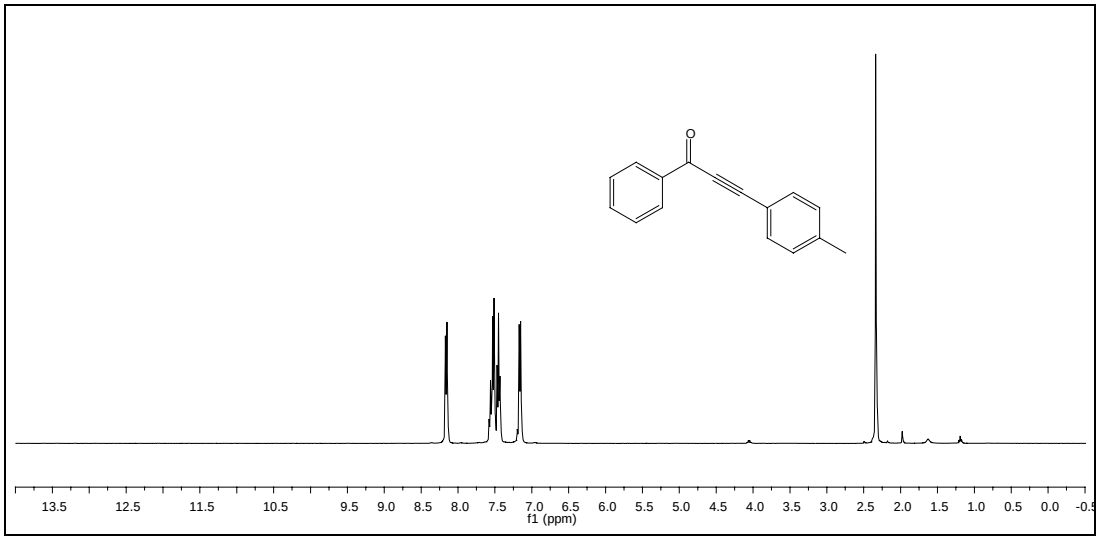

Figure 26A. ^{1}H NMR Spectrum of compound **8E.**

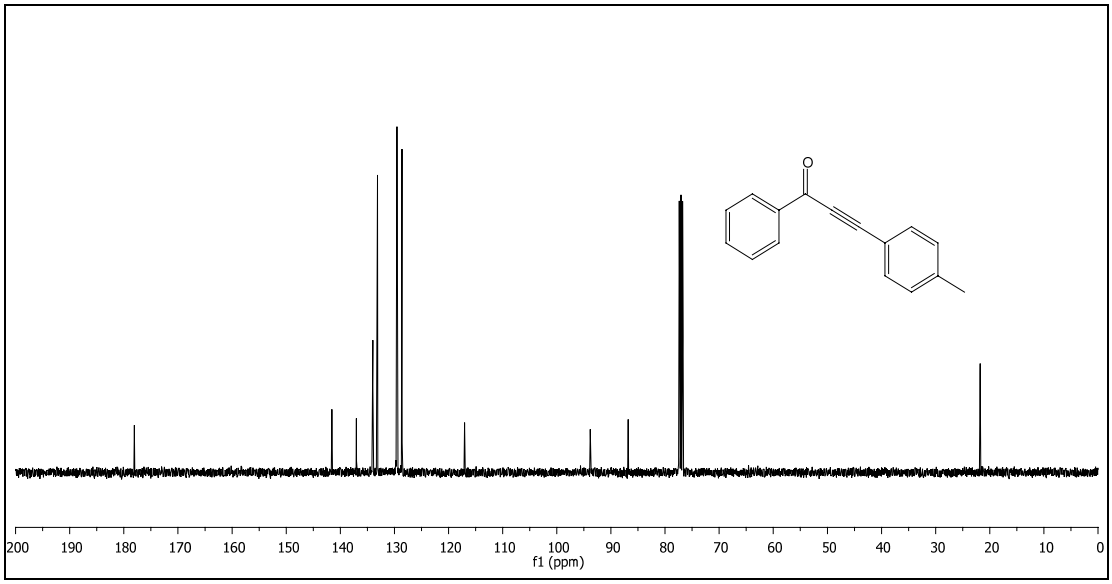

Figure 27A. ^{13}C NMR Spectrum of compound **8E.**

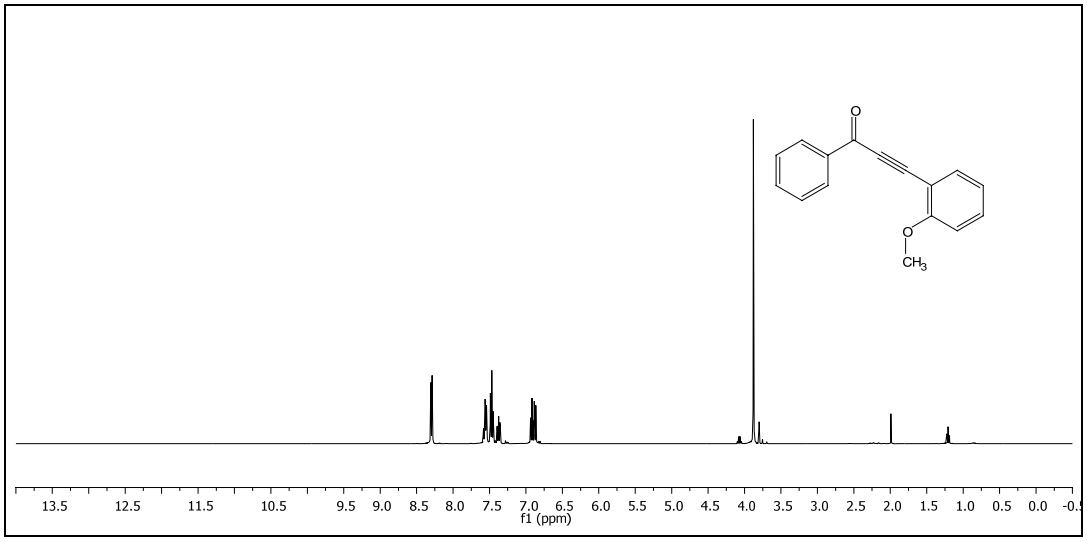

Figure 28A. ^{1}H NMR Spectrum of compound **8F.**

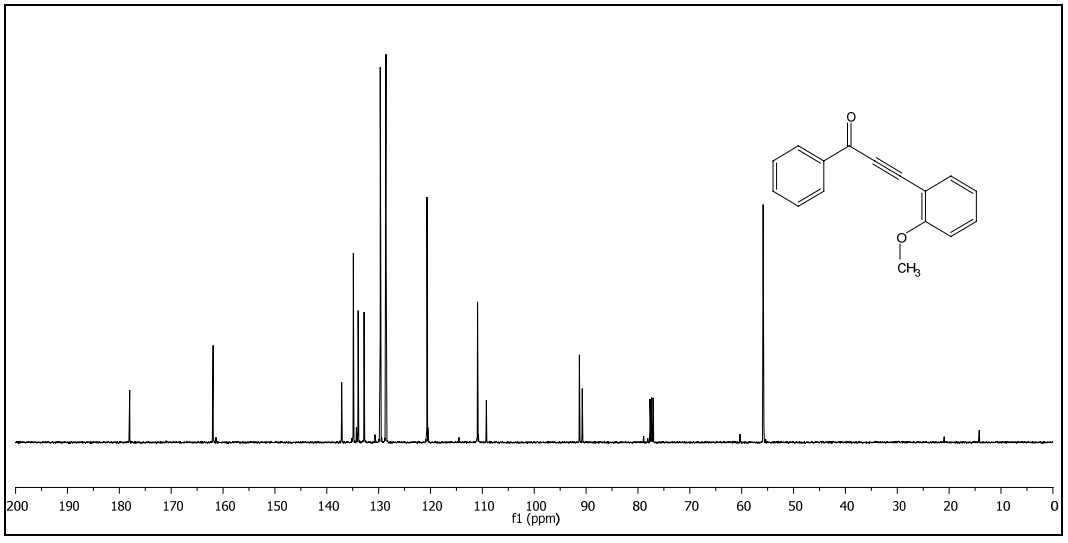

Figure 29A. ^{13}C NMR Spectrum of compound **8F.**

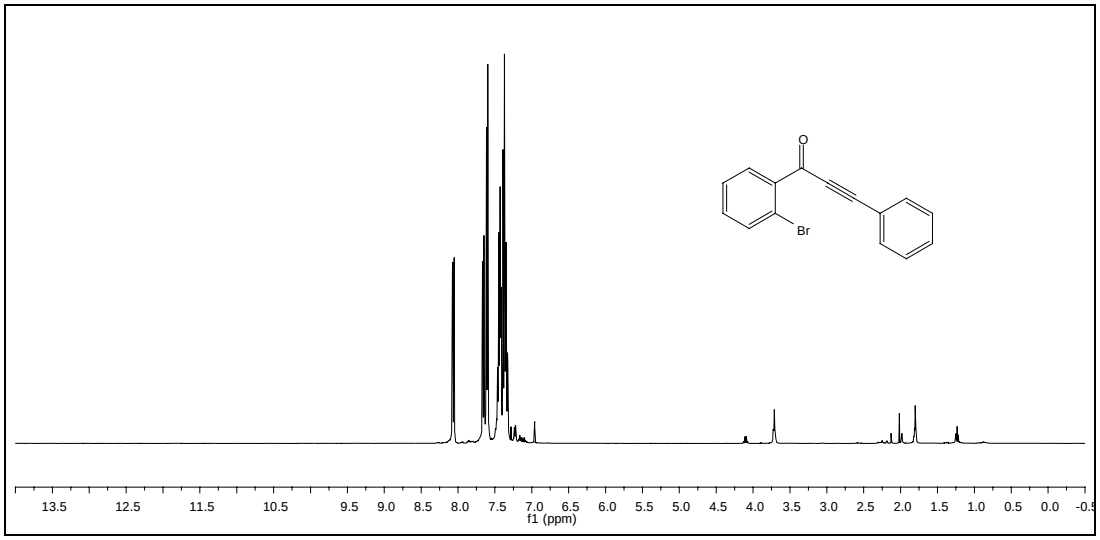

Figure 30A. ^{1}H NMR Spectrum of compound **8G.**

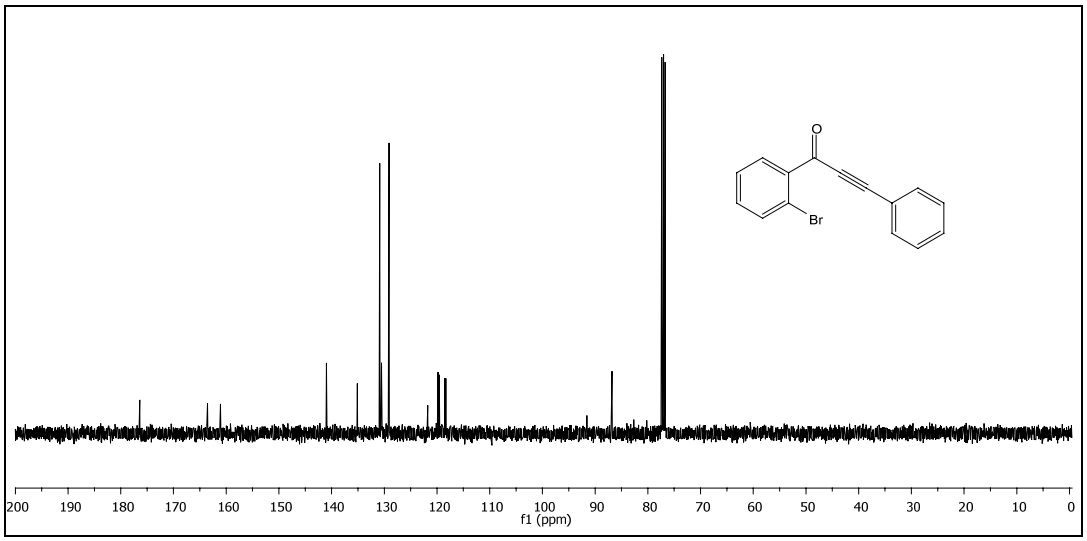

Figure 31A. ^{13}C NMR Spectrum of compound **8G.**

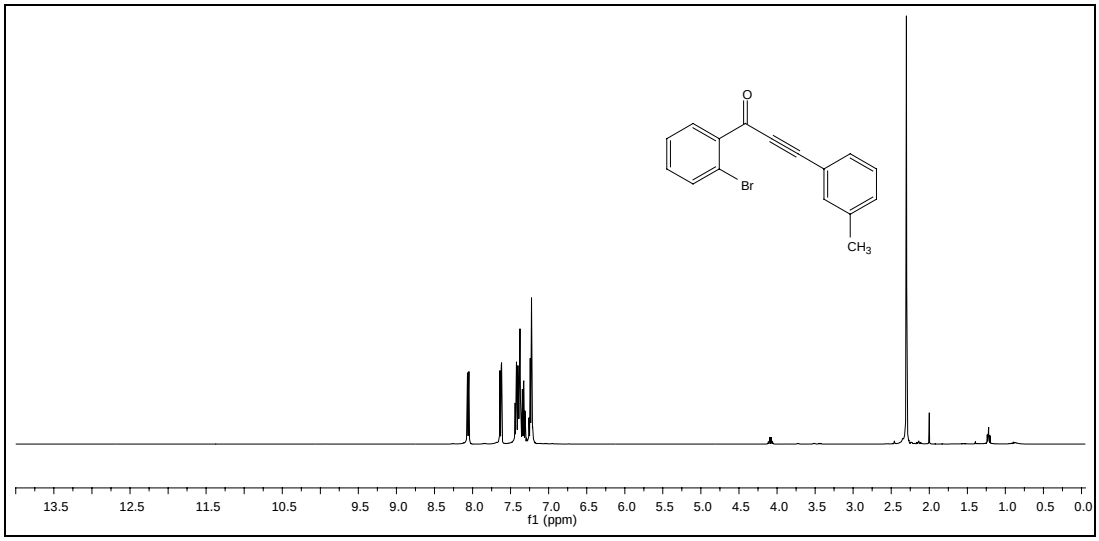

Figure 32A. ^{1}H NMR Spectrum of compound **8H.**

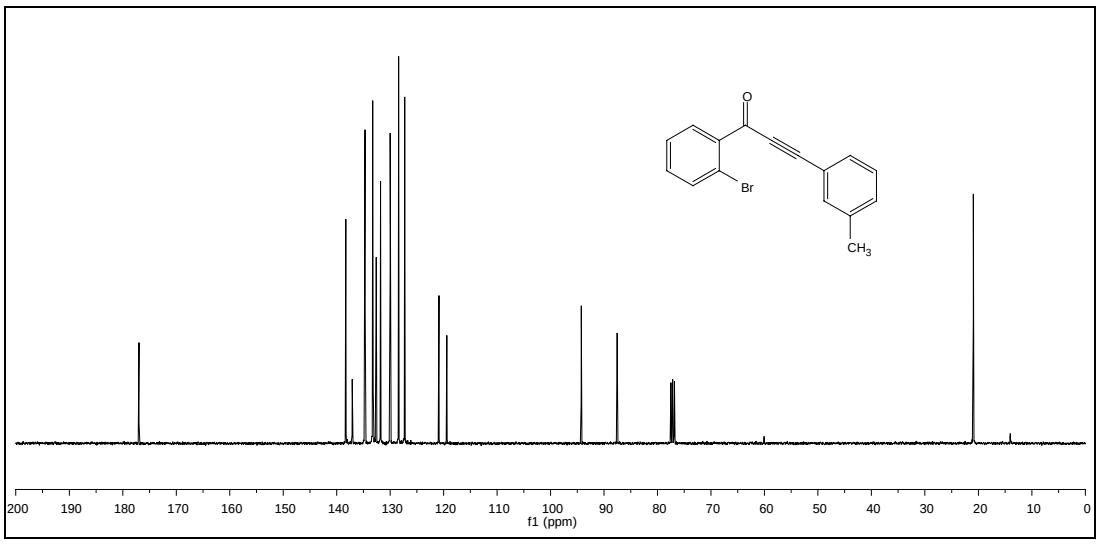

Figure 33A. ^{13}C NMR Spectrum of compound **8H.**

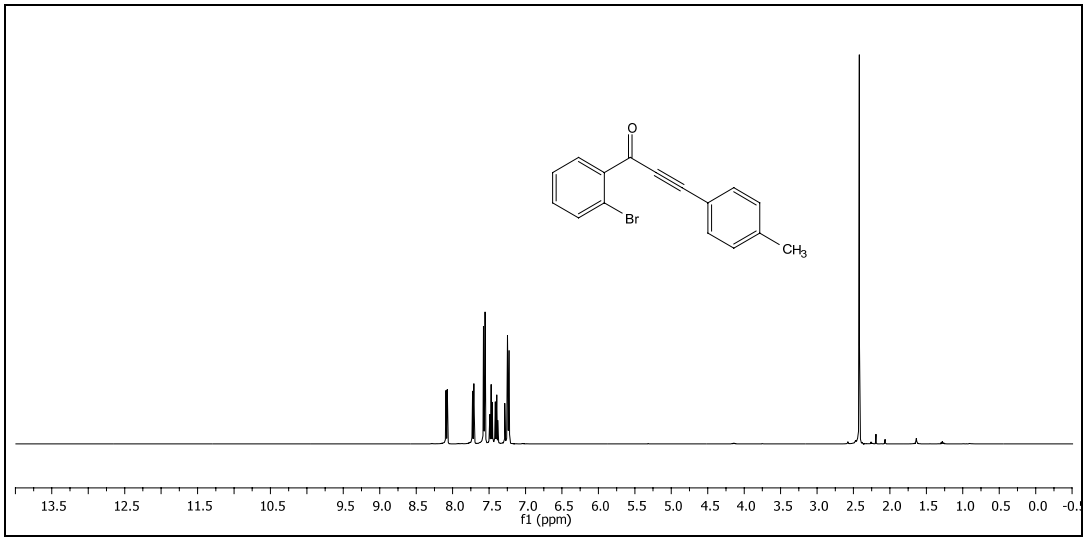

Figure 34A. ^{1}H NMR Spectrum of compound **8I.**

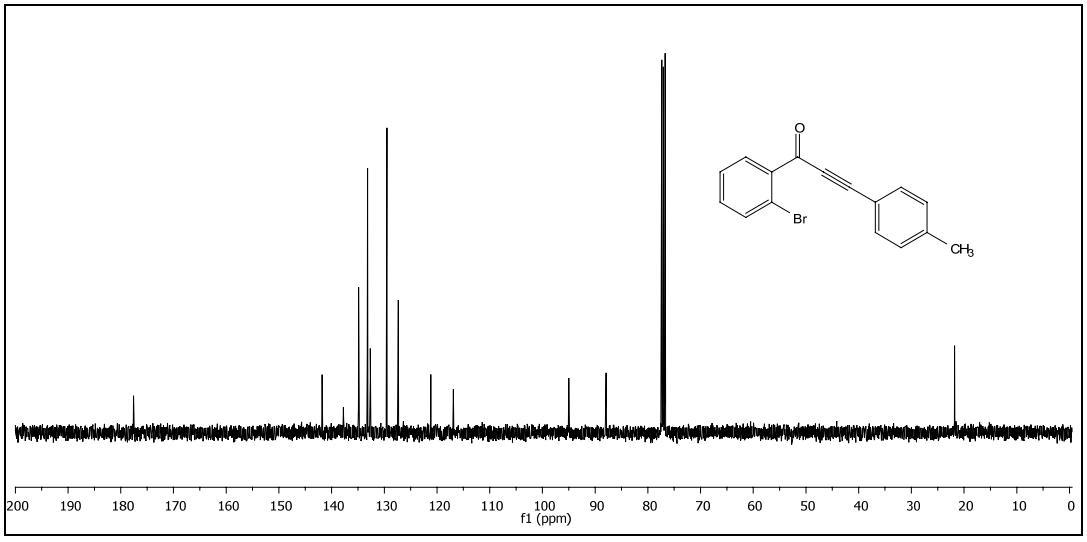

Figure 35A. ^{13}C NMR Spectrum of compound **8I.**

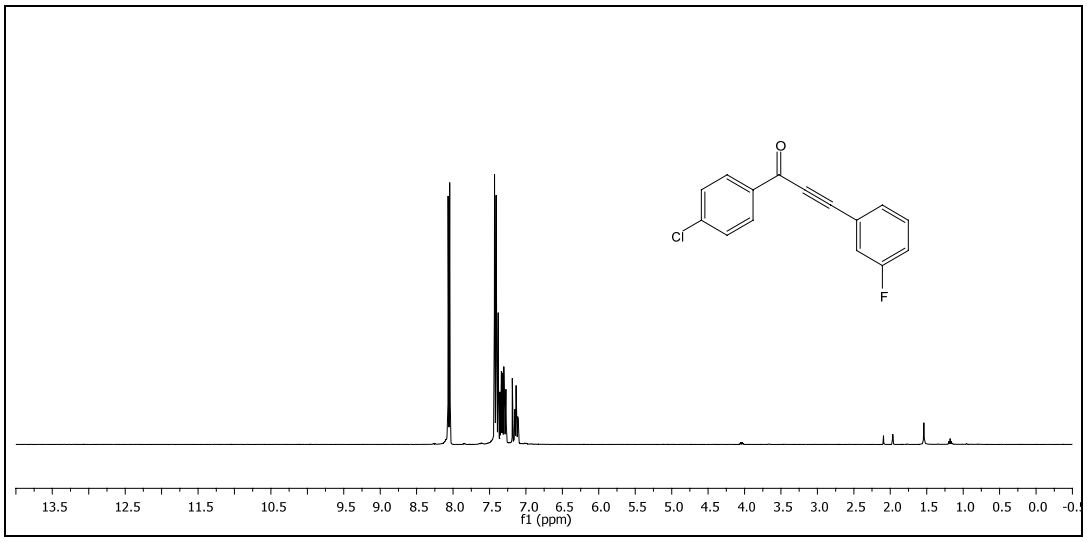

Figure 36A. ^{1}H NMR Spectrum of compound **8J.**

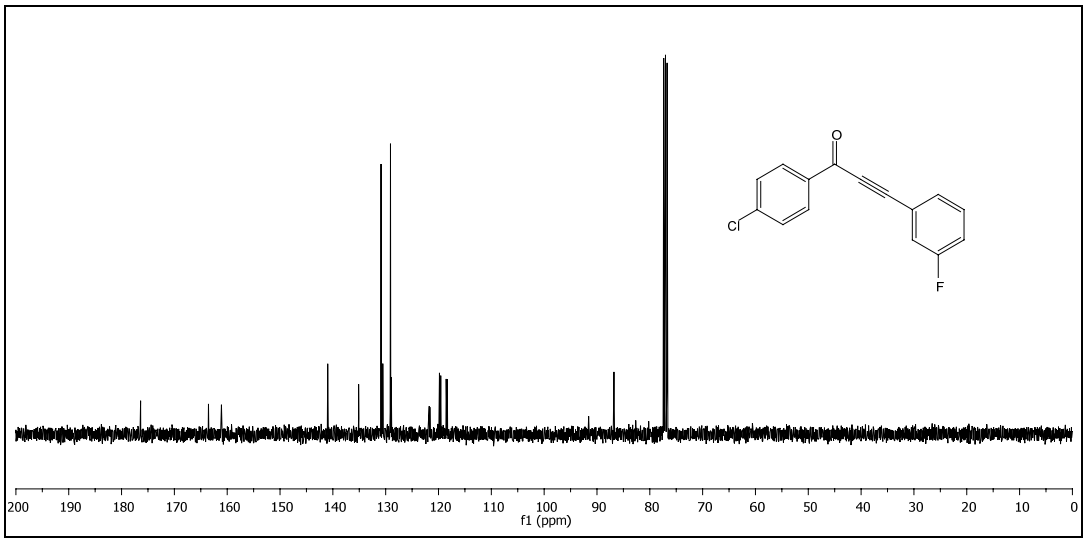

Figure 37A. ^{13}C NMR Spectrum of compound **8J.**

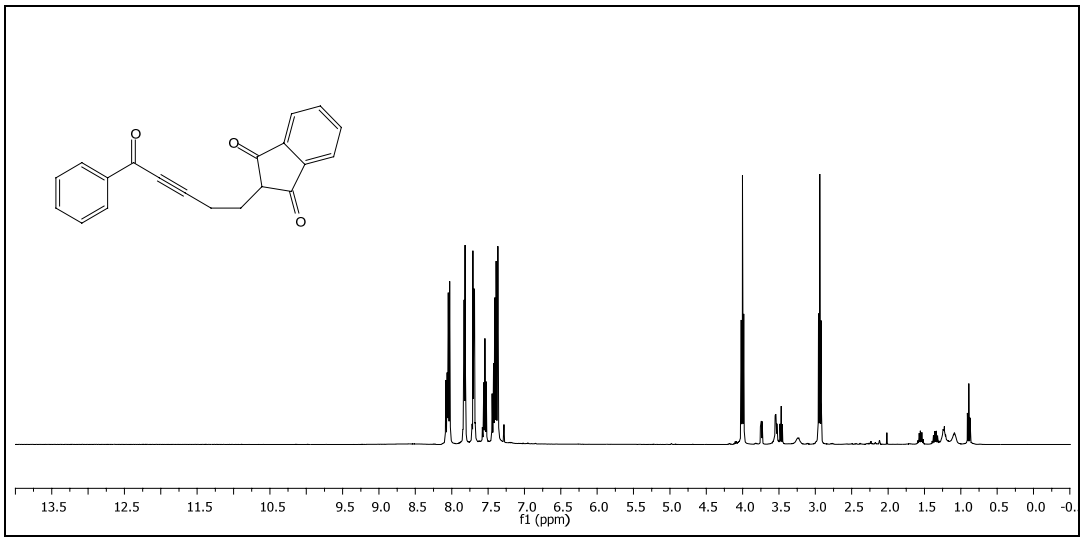

Figure 38A. ^{1}H NMR Spectrum of compound **8K.**

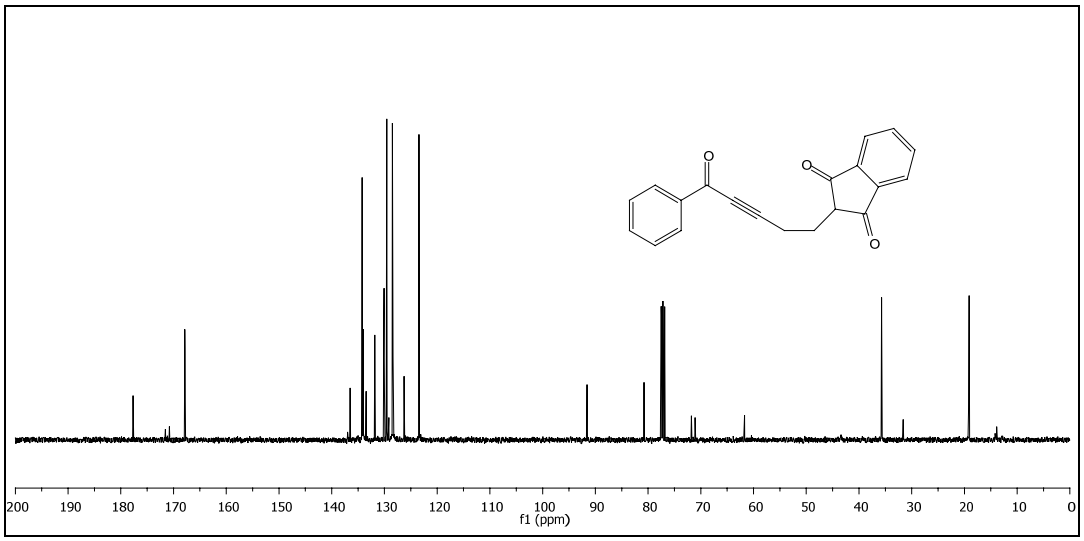

Figure 39A. ^{13}C NMR Spectrum of compound **8K.**

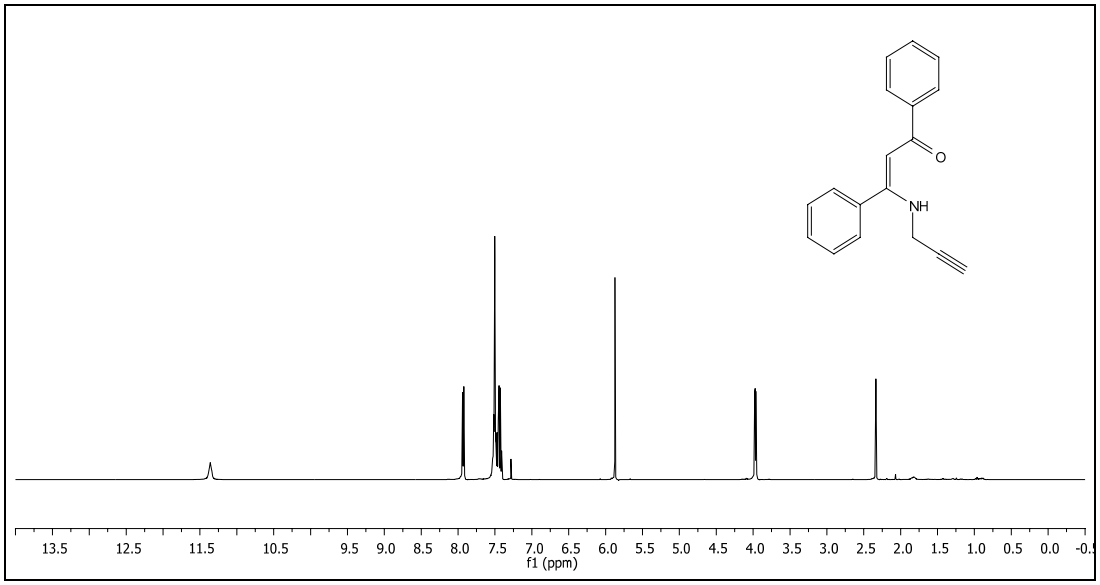

Figure 40A .[1]H NMR Spectrum of compound **42A.**

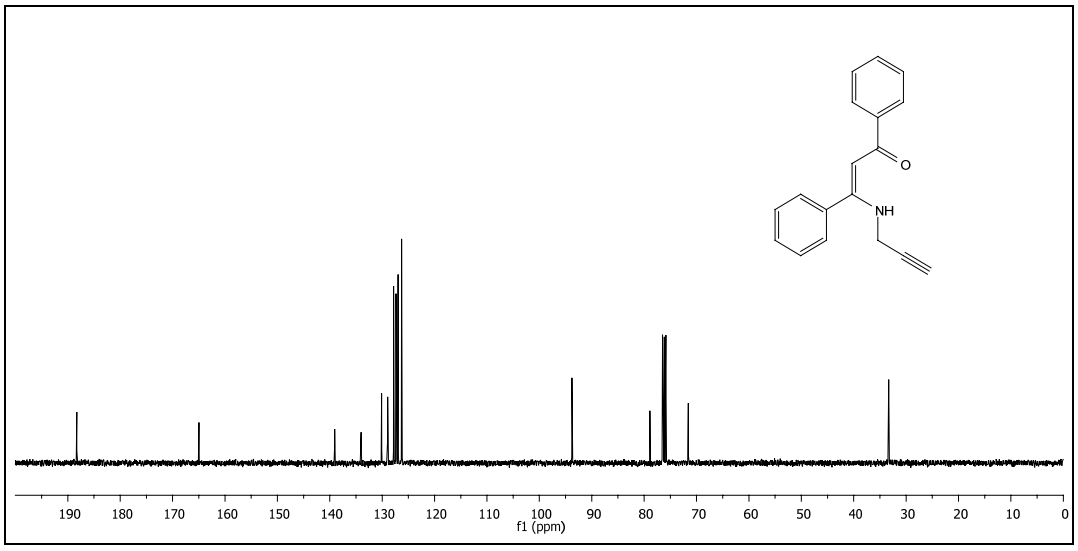

Figure 41A.[13]C NMR Spectrum of compound **42A.**

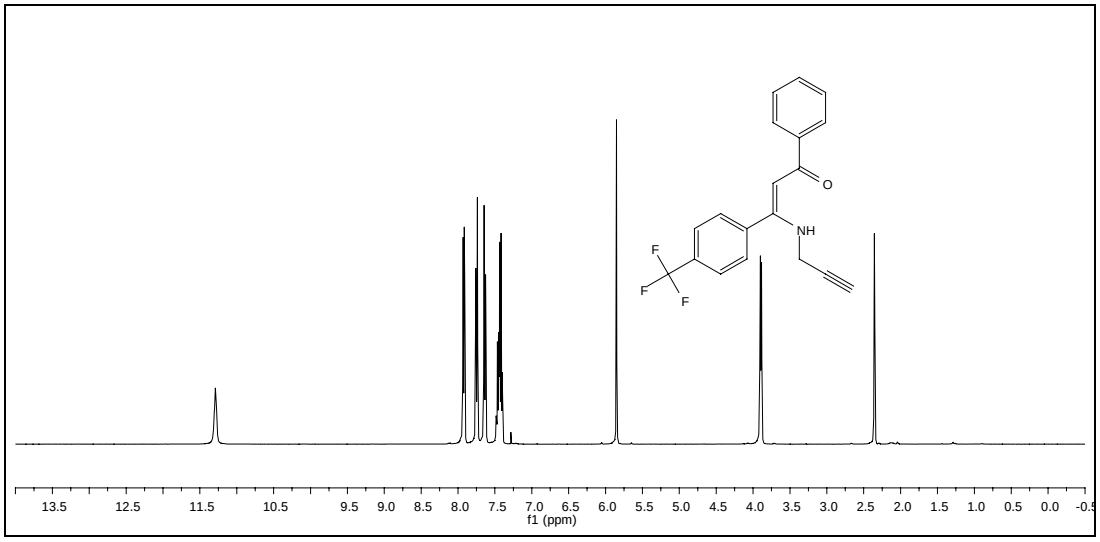

Figure 42A .[1]H NMR Spectrum of compound **42B**

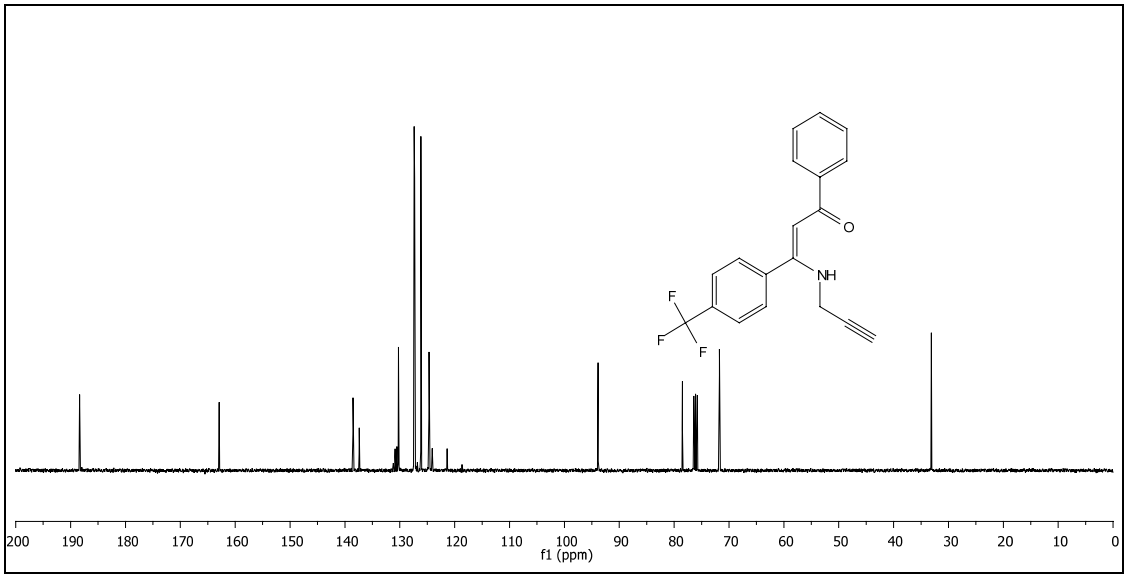

Figure 43A .[13]C NMR Spectrum of compound **42B.**

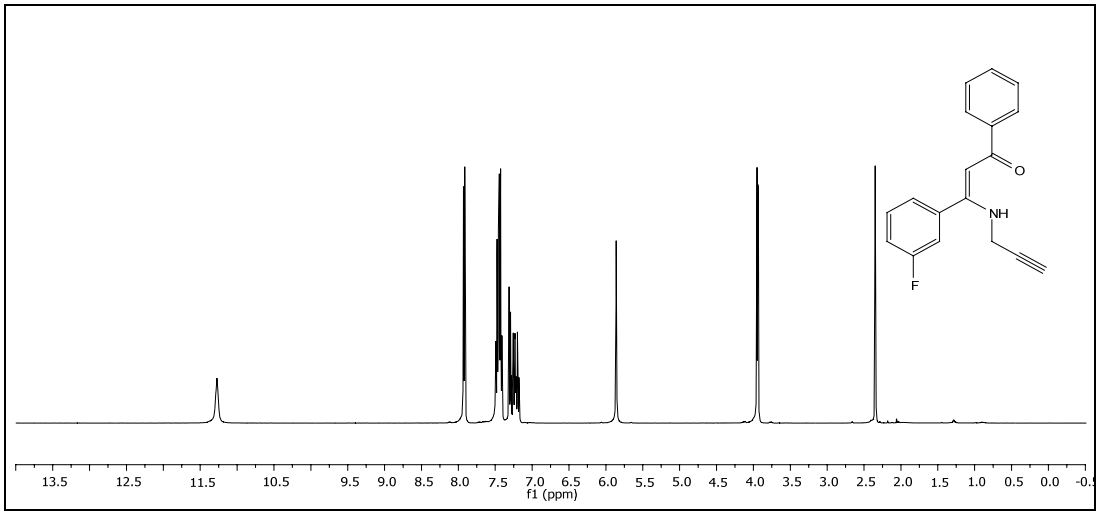

Figure 44A . ^{1}H NMR Spectrum of compound **42C.**

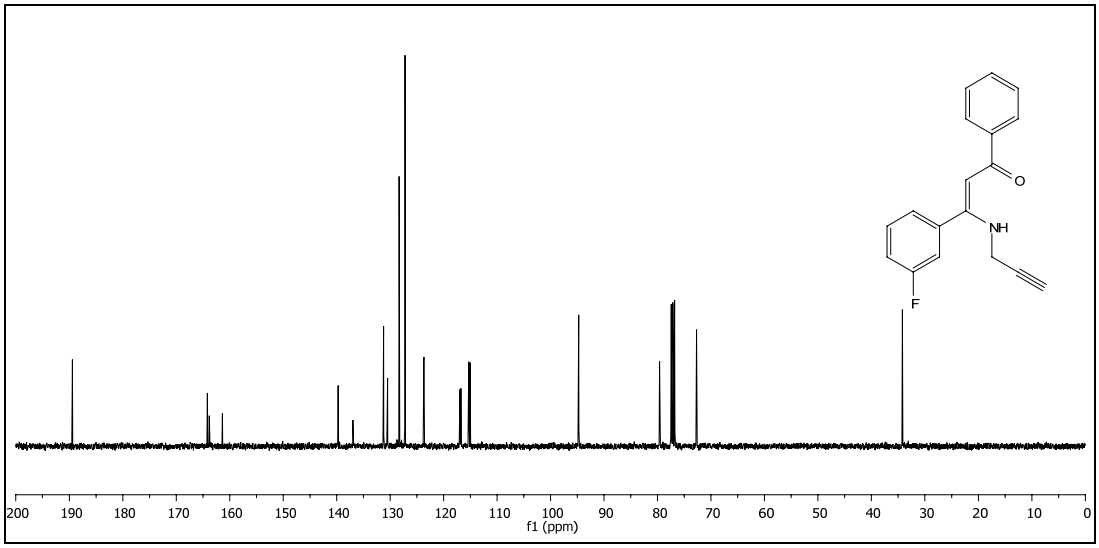

Figure 45A . ^{13}C NMR Spectrum of compound **42C.**

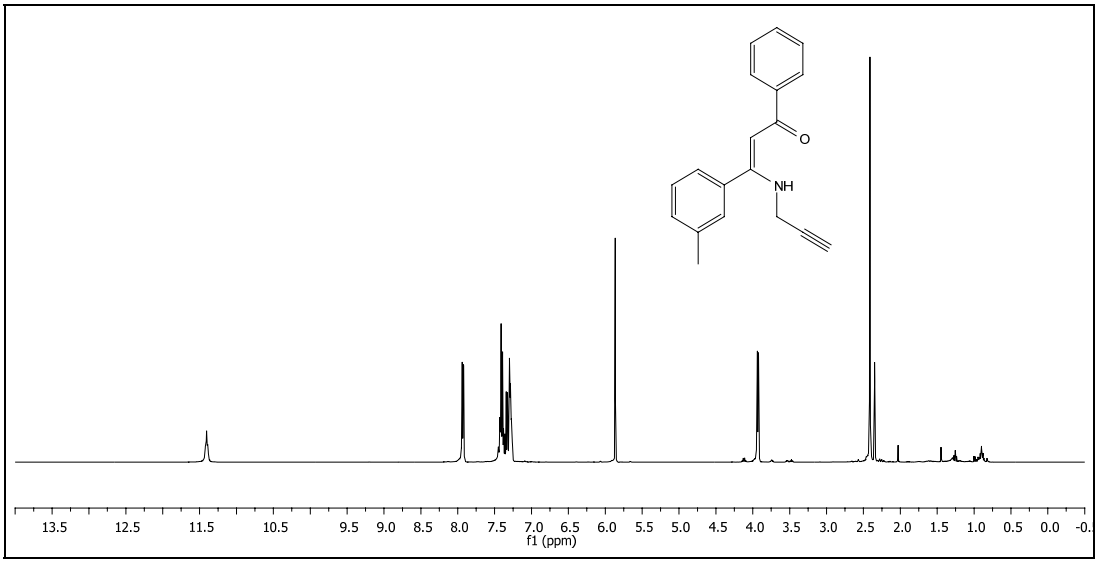

Figure 46A .[1]H NMR Spectrum of compound **42D.**

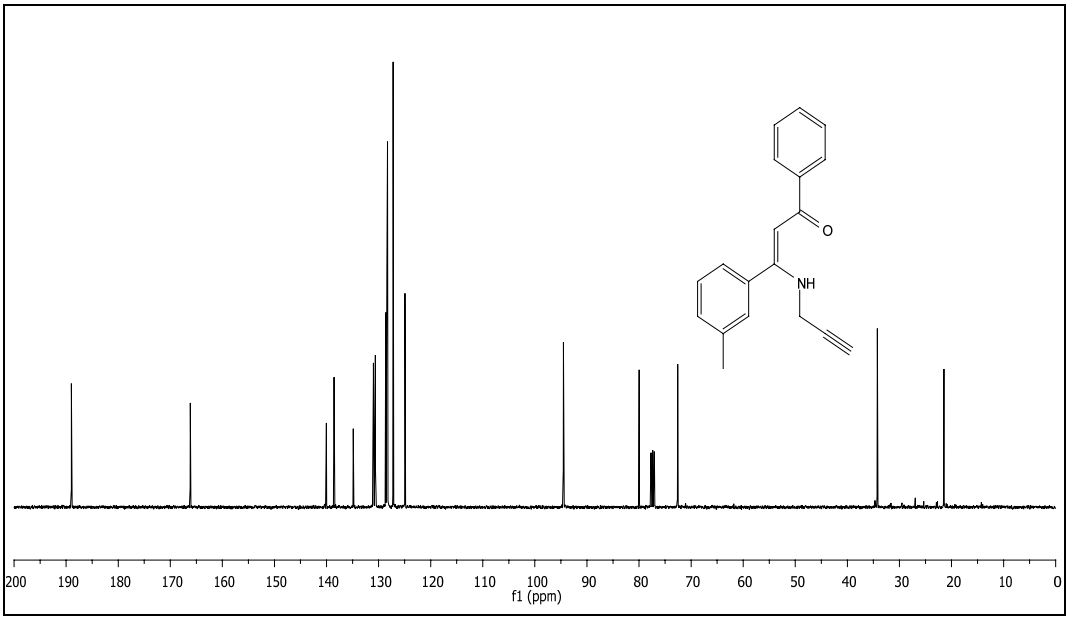

Figure 47A.[13]C NMR Spectrum of compound **42D**.

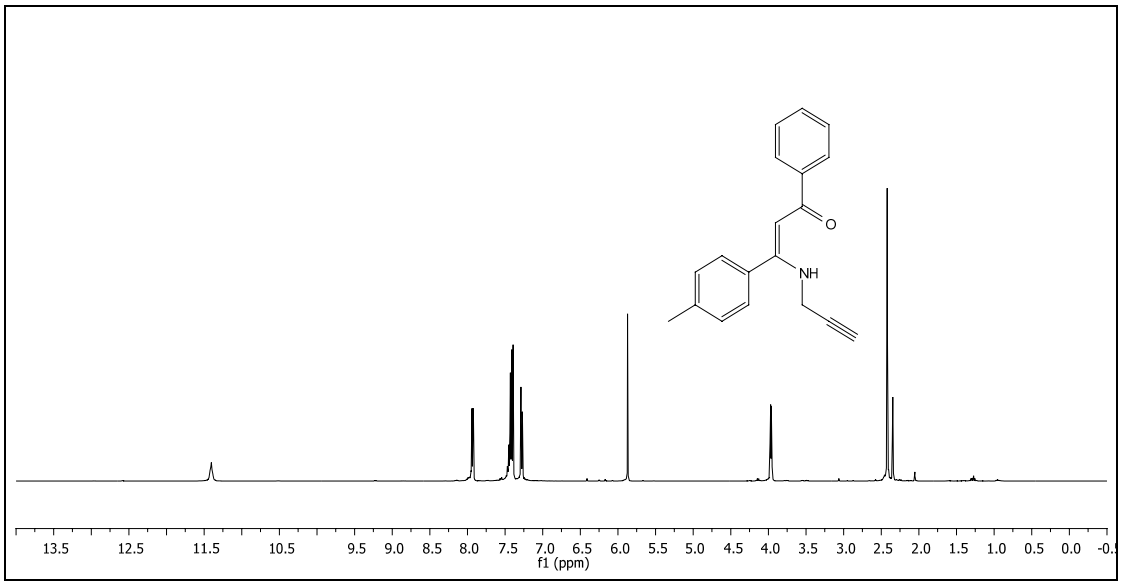

Figure 48A . ^{1}H NMR Spectrum of compound **42E.**

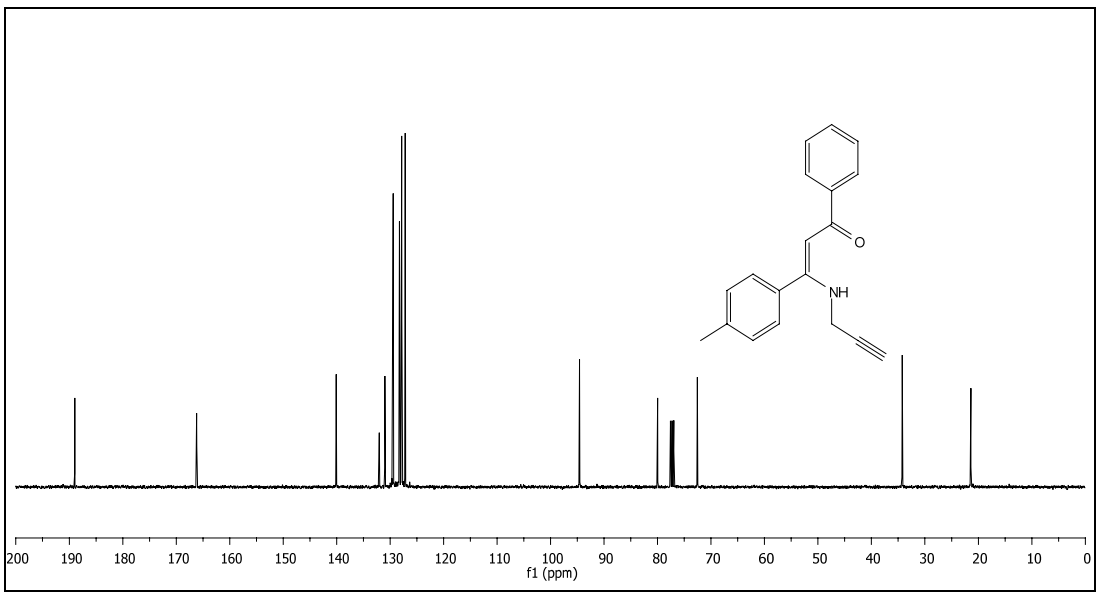

Figure 49A . ^{13}C NMR Spectrum of compound **42E.**

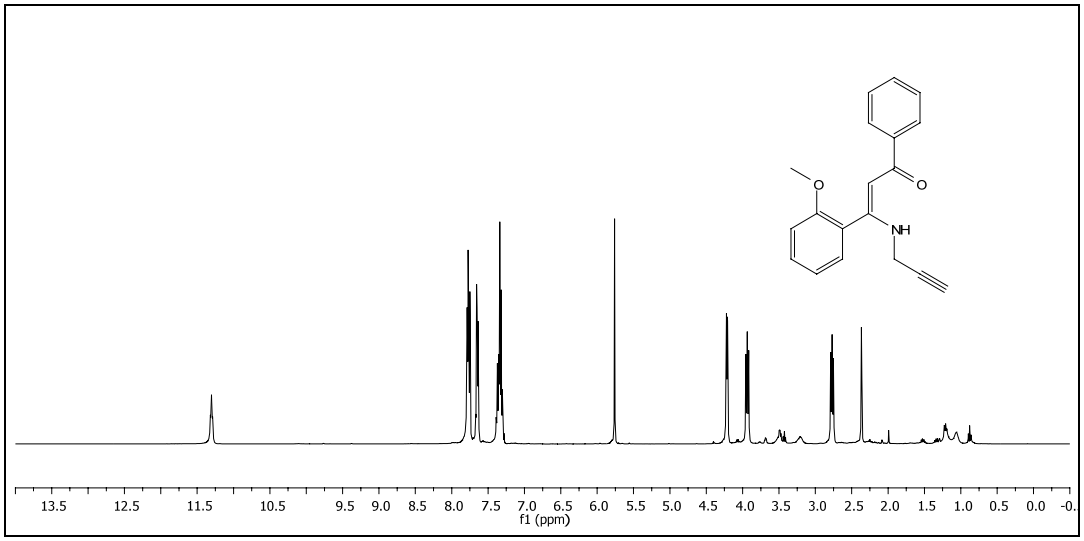

Figure 50A . ^{1}H NMR Spectrum of compound **42F.**

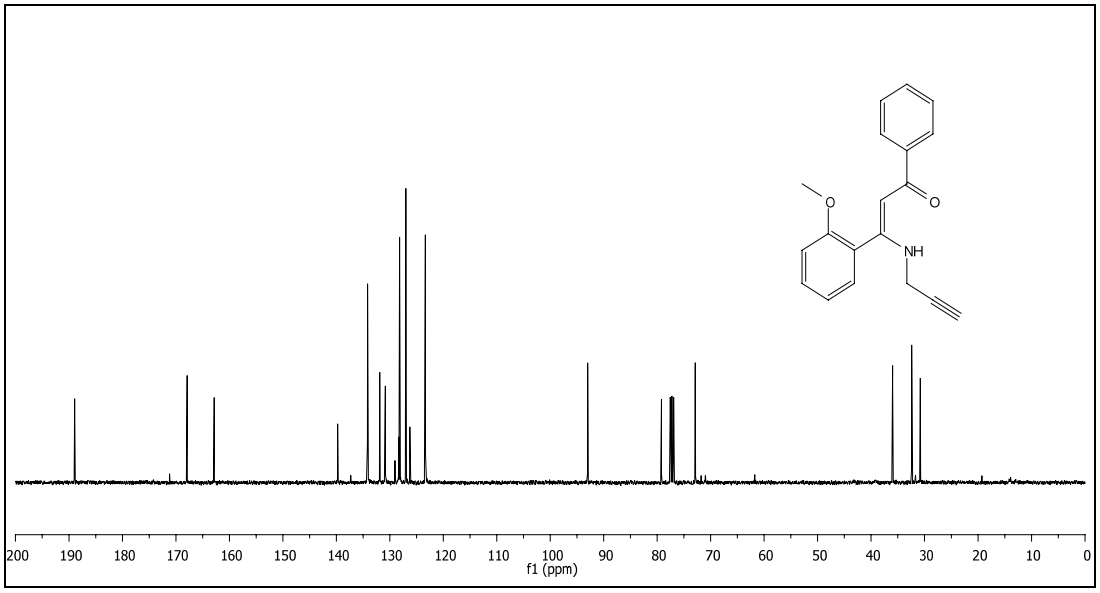

Figure 51A . ^{13}C NMR Spectrum of compound **42F.**

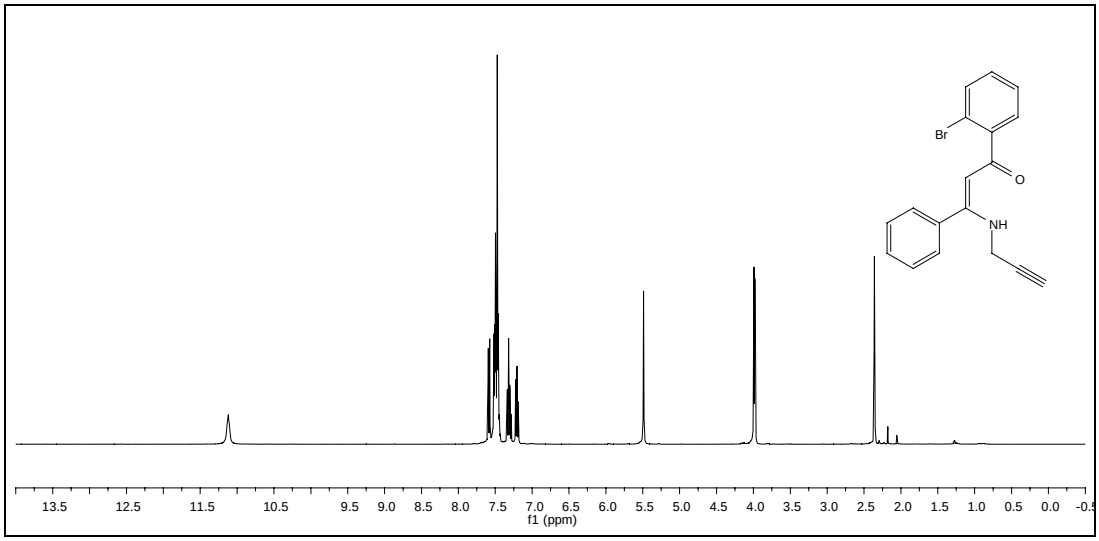

Figure 52A .^{1}H NMR Spectrum of compound **42G.**

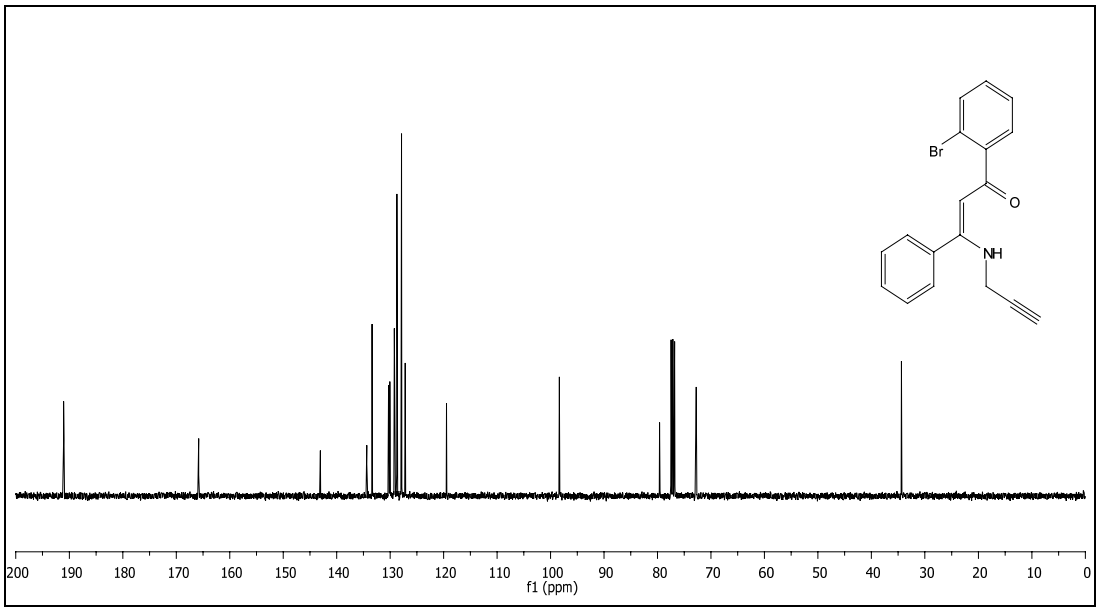

Figure 53A .^{13}C NMR Spectrum of compound **42G.**

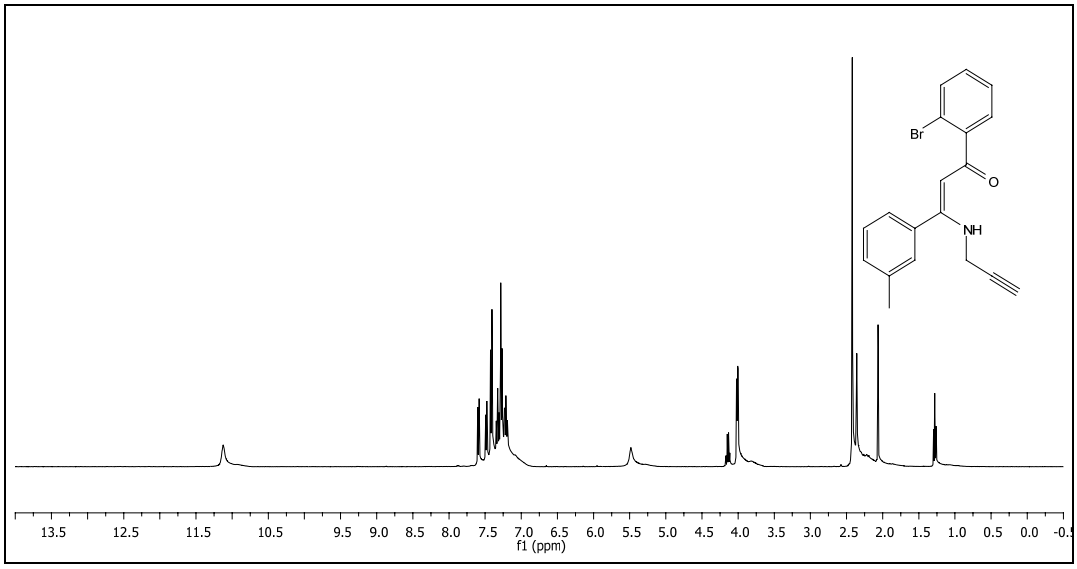

Figure 54A .[1]H NMR Spectrum of compound **42H.**

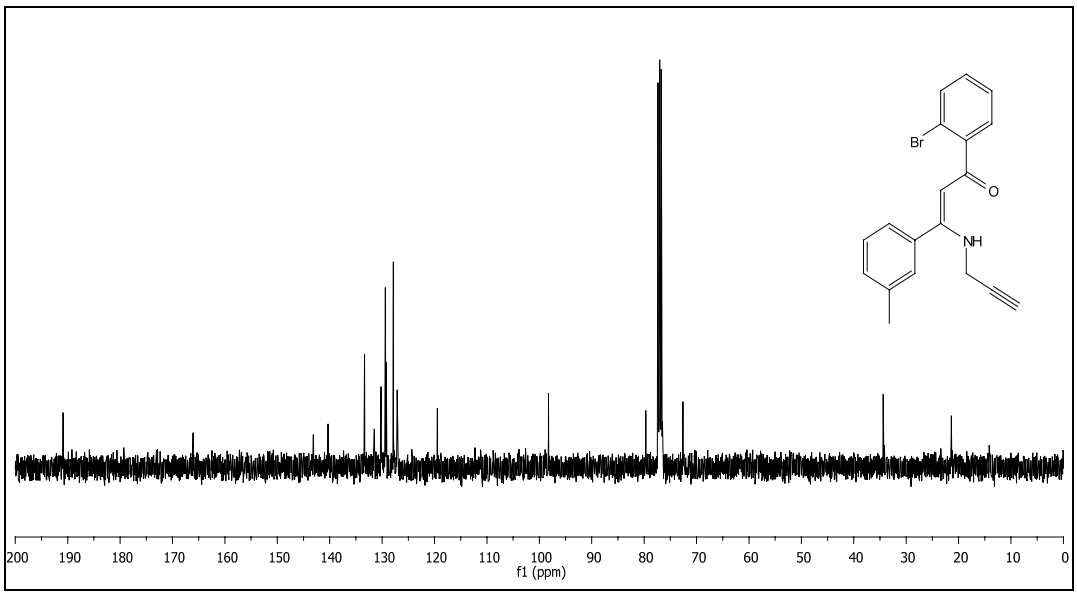

Figure 55A .[13]C NMR Spectrum of compound **42H.**

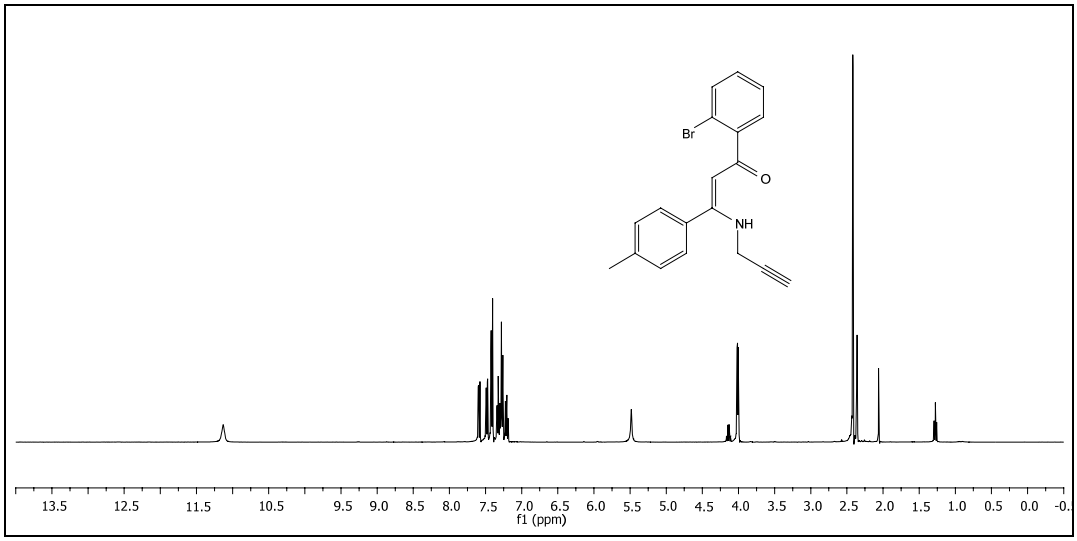

Figure 56A .^{1}H NMR Spectrum of compound **42I.**

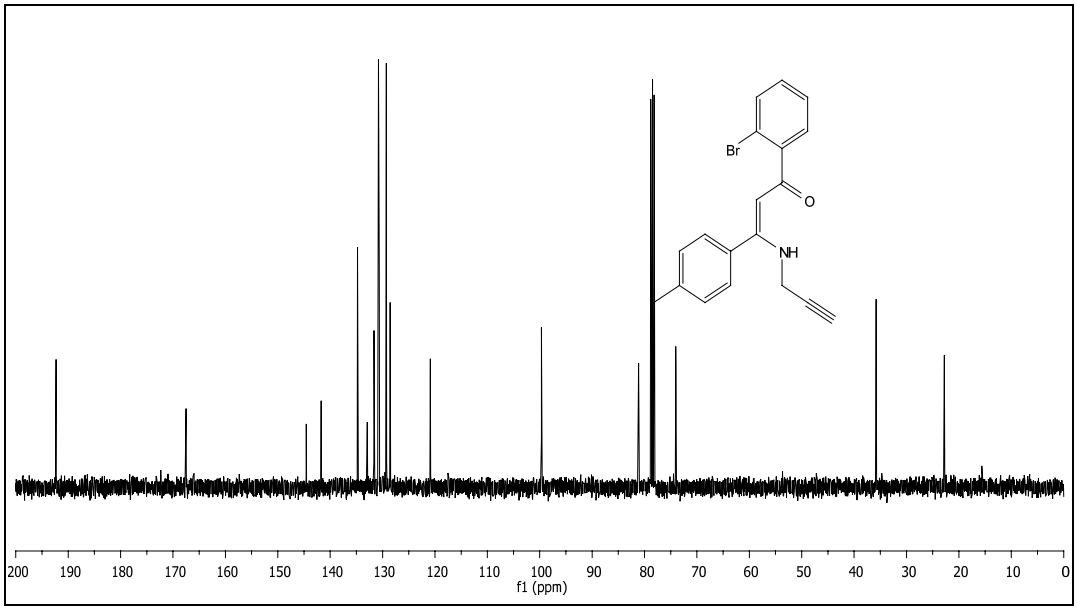

Figure 57A .^{13}C NMR Spectrum of compound **42I.**

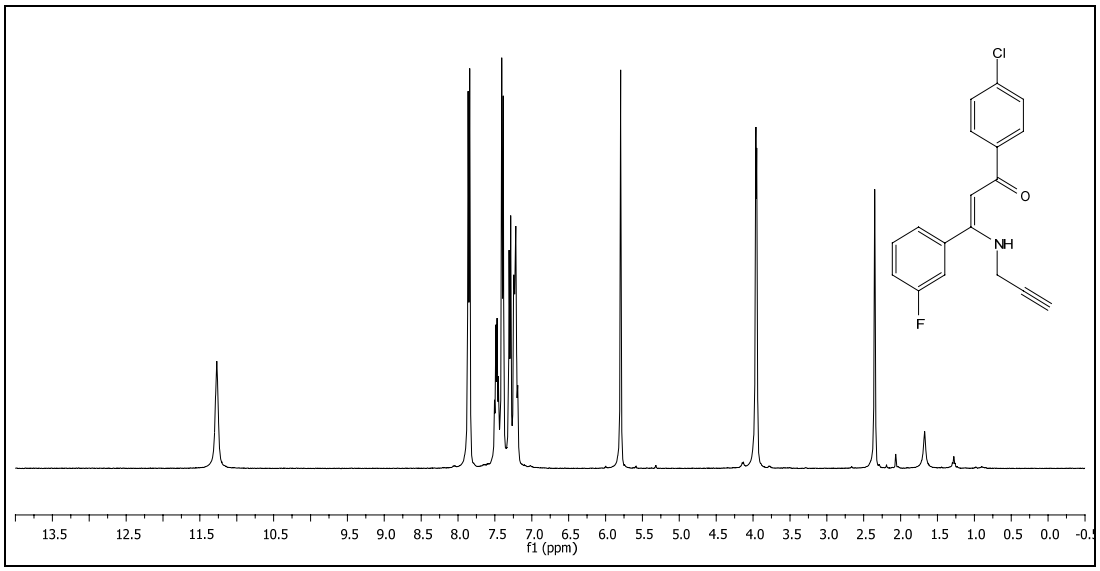

Figure 58A .[1]H NMR Spectrum of compound **42J.**

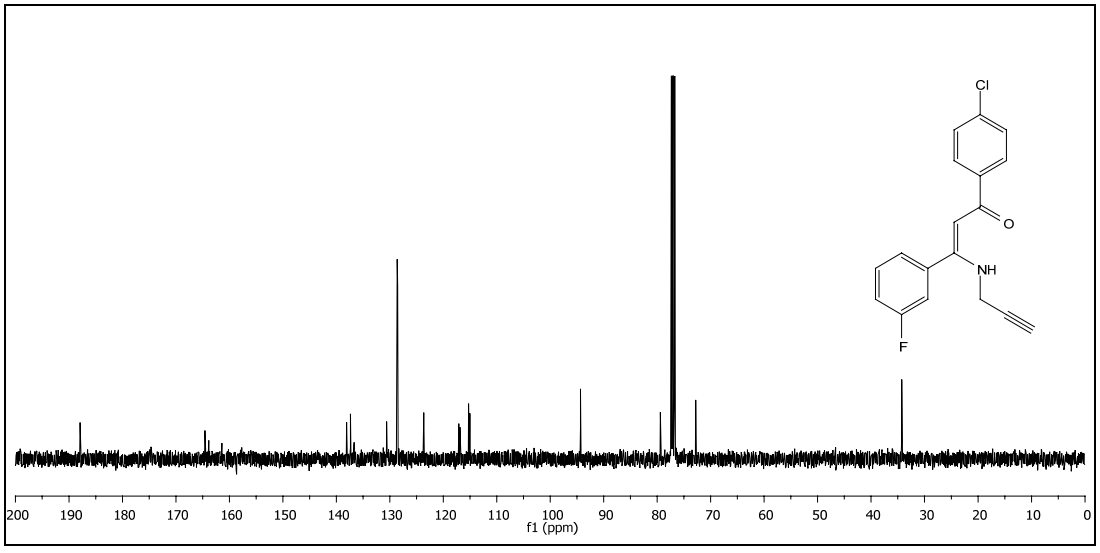

Figure 59A.[13]C NMR Spectrum of compound **42J.**

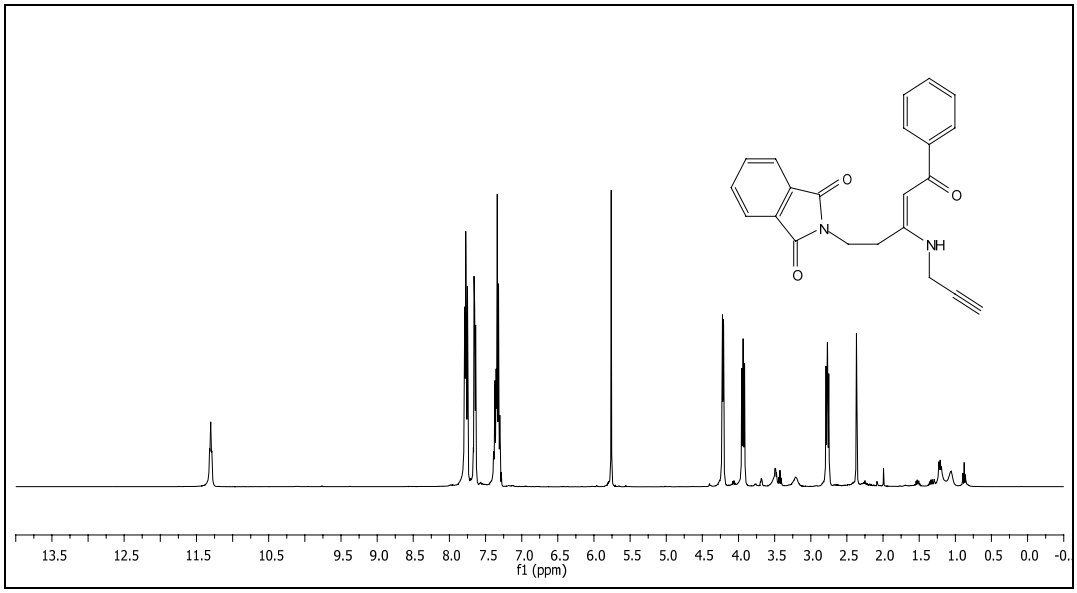

Figure 60A .^{1}H NMR Spectrum of compound **42K.**

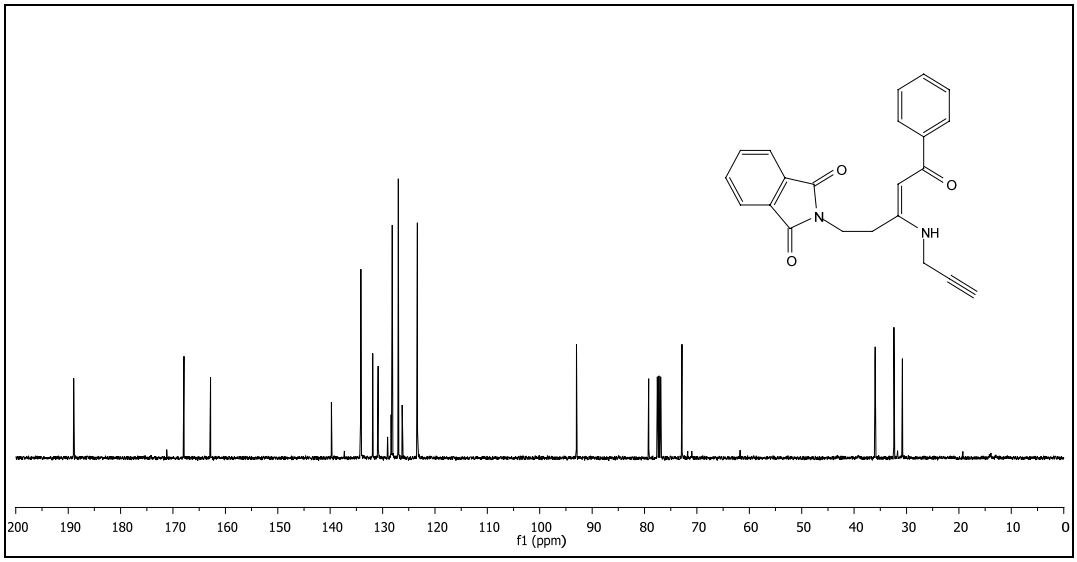

Figure 61A .^{13}C NMR Spectrum of compound **42K.**

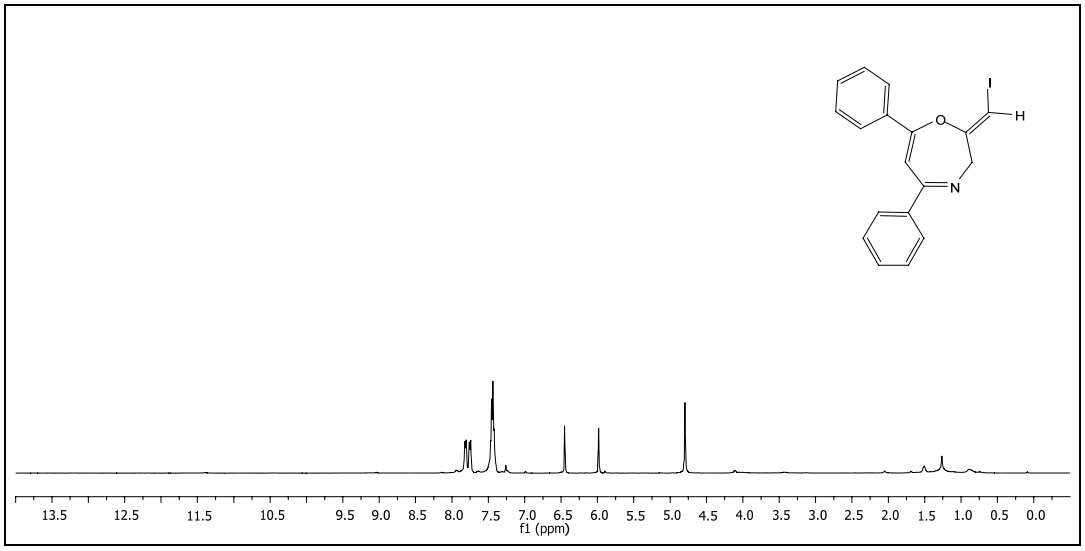

Figure 62A. ^{1}H NMR Spectrum of compound **44A.**

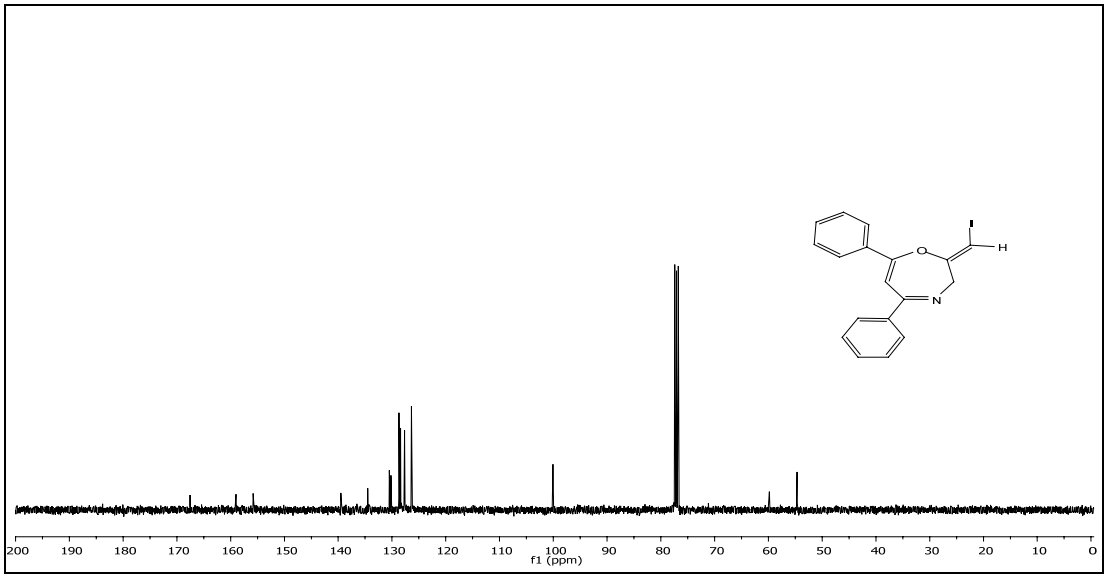

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Figure 63A. ^{13}C NMR Spectrum of compound **44A.**

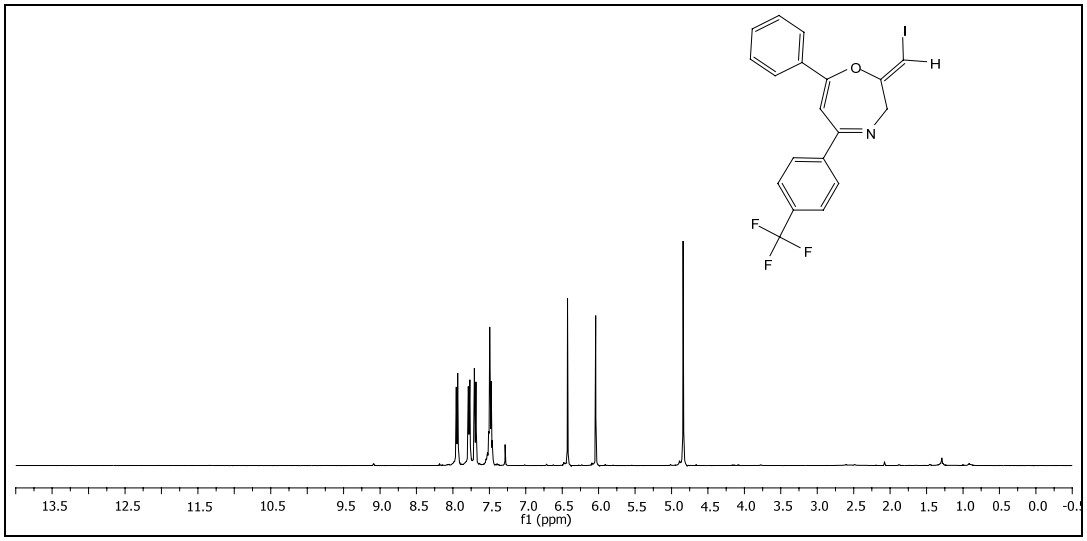

Figure 64A. ^{1}H NMR Spectrum of compound **44B.**

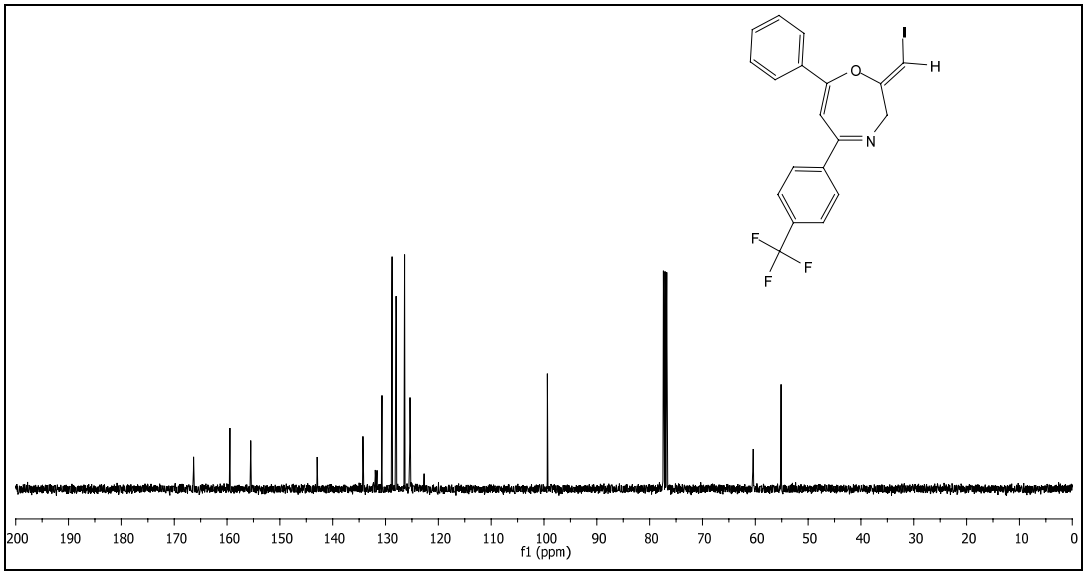

Figure 65A. ^{13}C NMR Spectrum of compound **44B.**

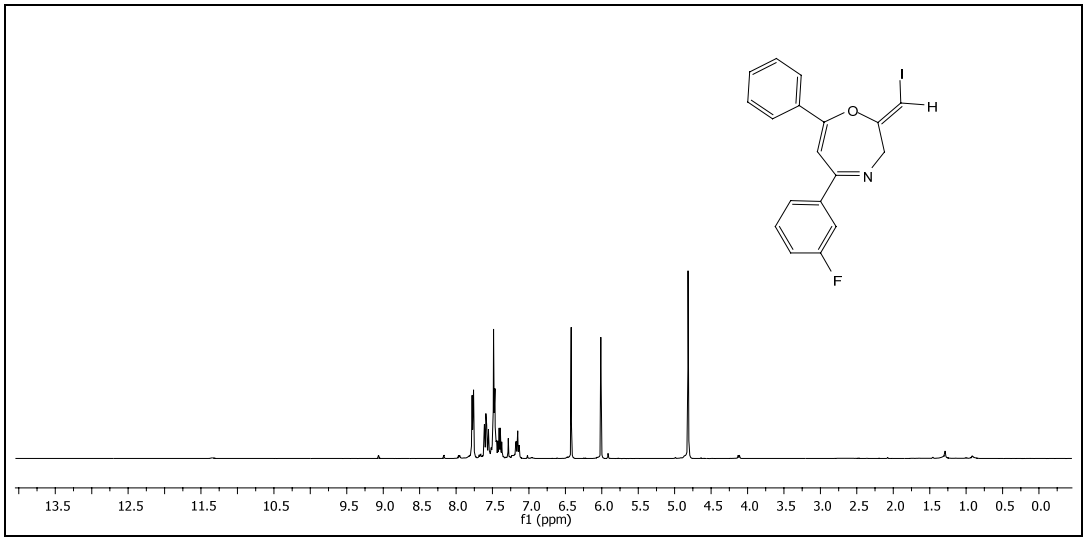

Figure 66A . ^{1}H NMR Spectrum of compound **44C.**

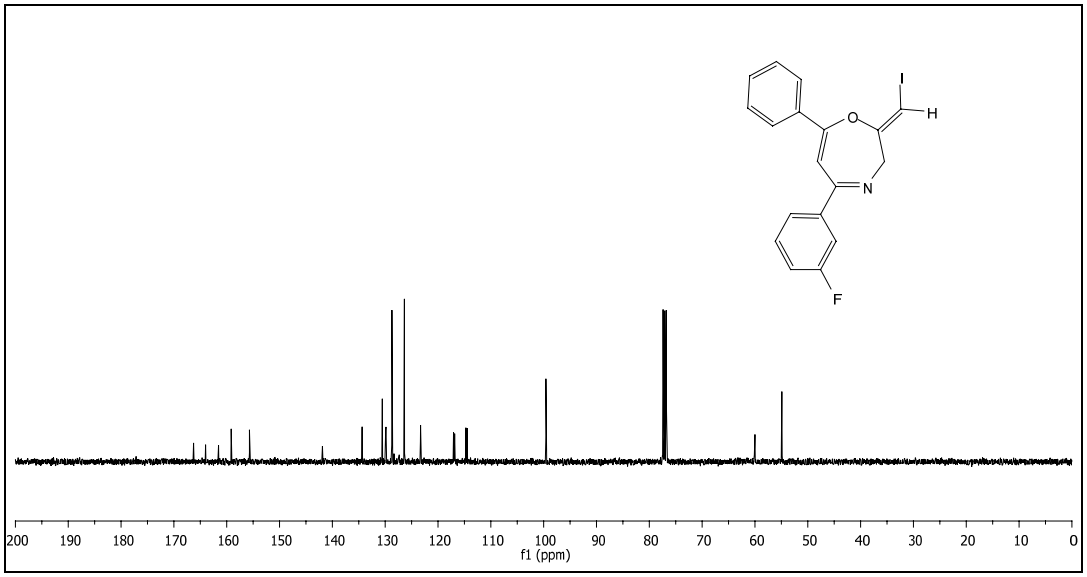

Figure 67A. ^{13}C NMR Spectrum of compound **44C.**

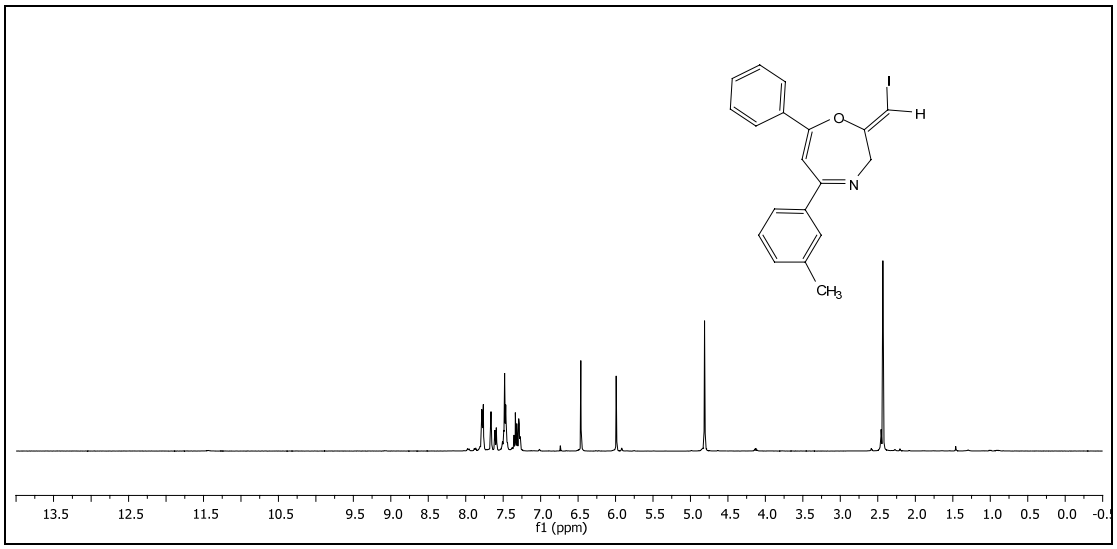

Figure 68A . ^{1}H NMR Spectrum of compound **44D.**

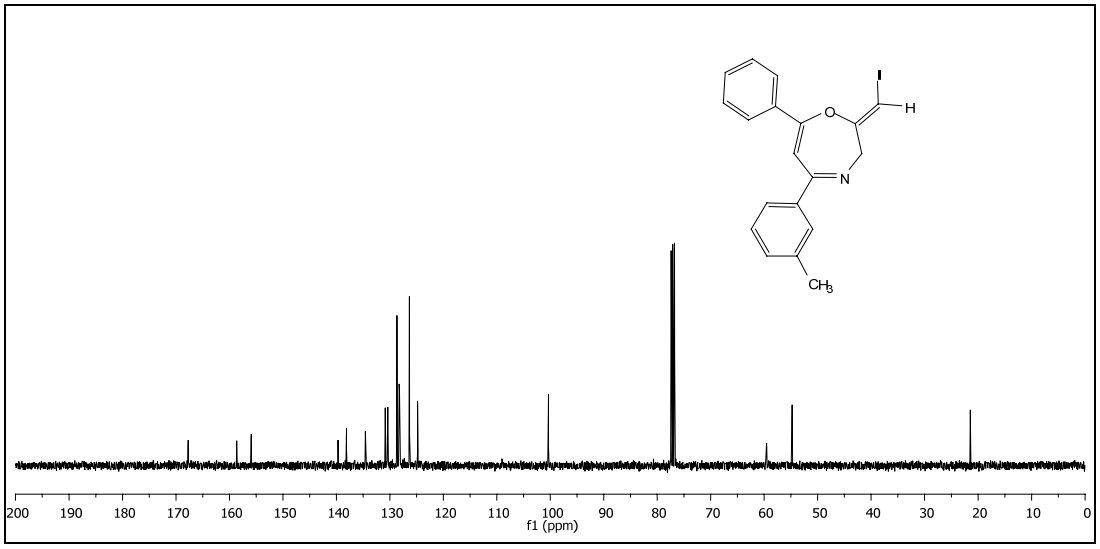

Figure 69A. ^{13}C NMR Spectrum of compound **44D.**

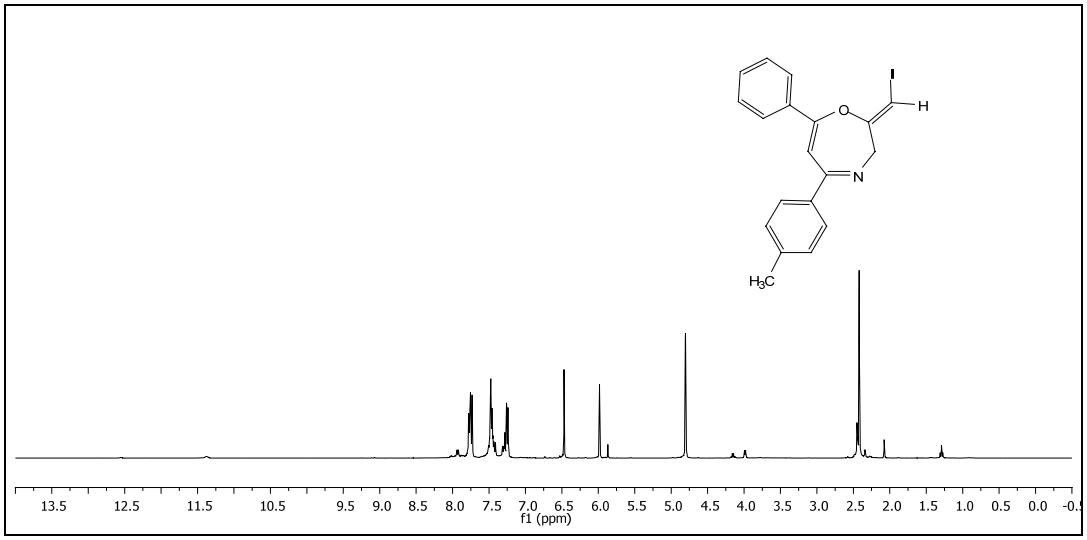

Figure 70A . ^{1}H NMR Spectrum of compound **44E.**

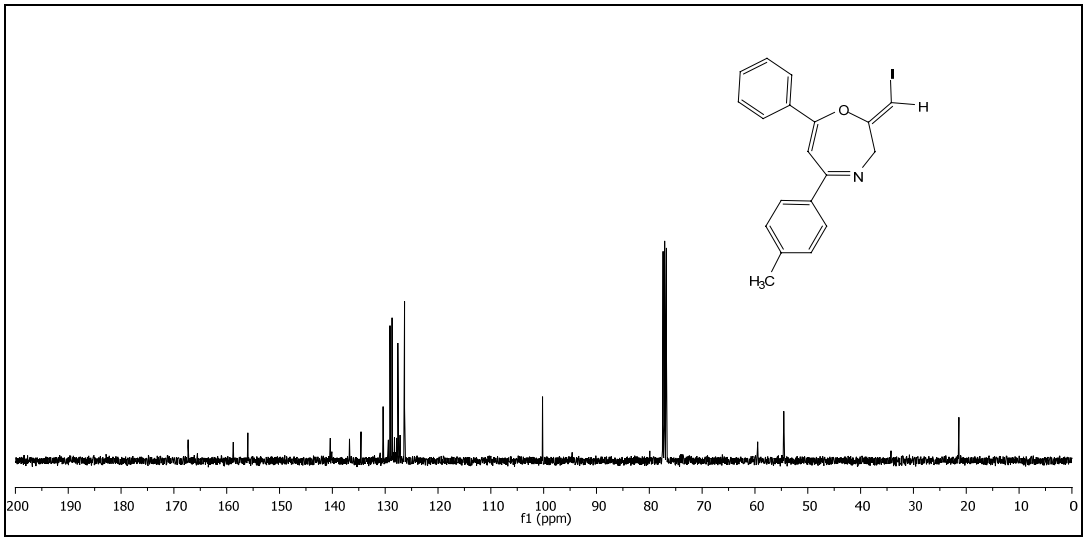

Figure 71A. ^{13}C NMR Spectrum of compound **44E.**

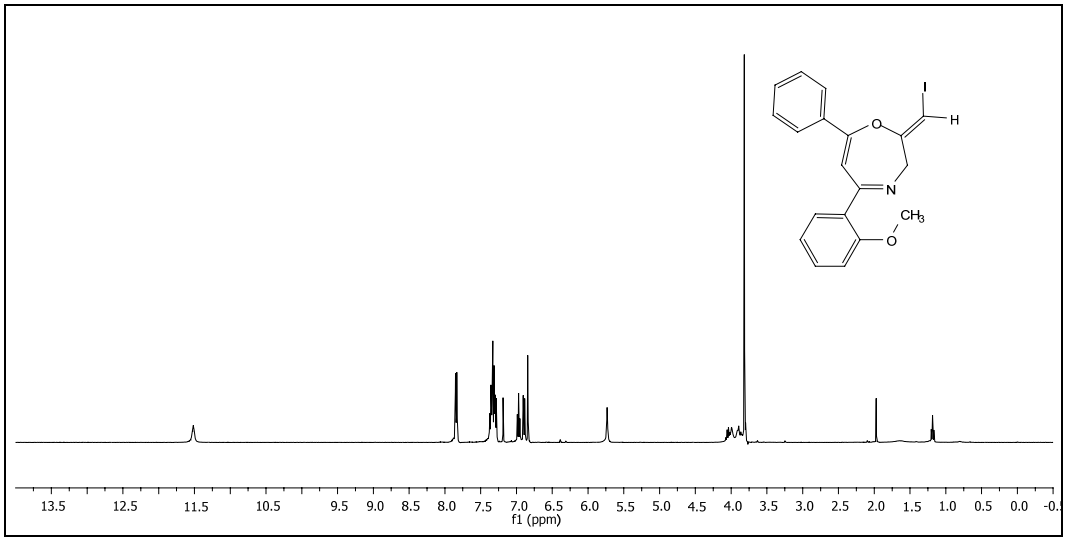

Figure 72A . ^{1}H NMR Spectrum of compound **44F.**

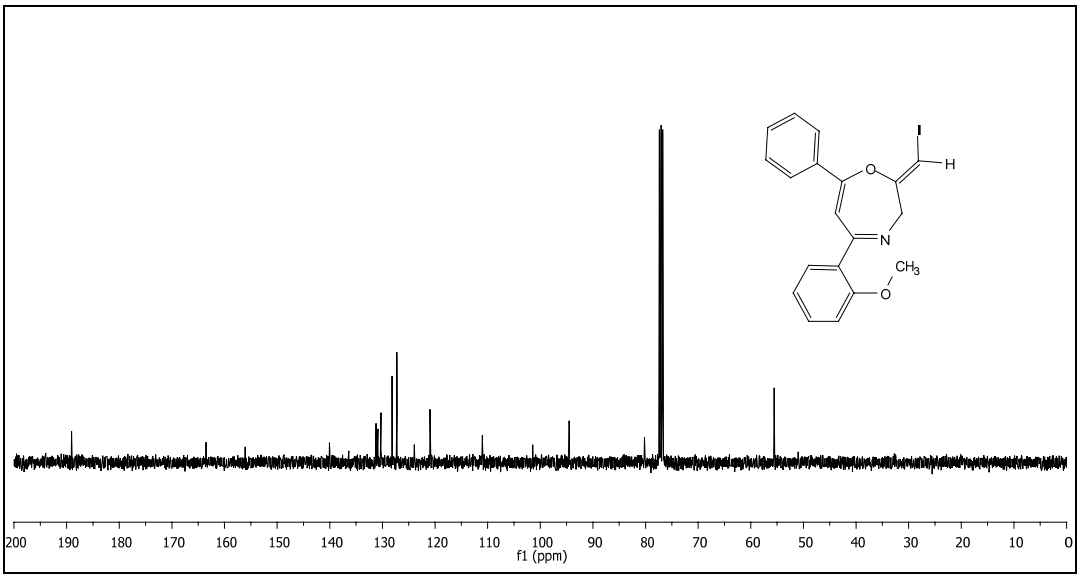

Figure 73A. ^{13}C NMR Spectrum of compound **44F.**

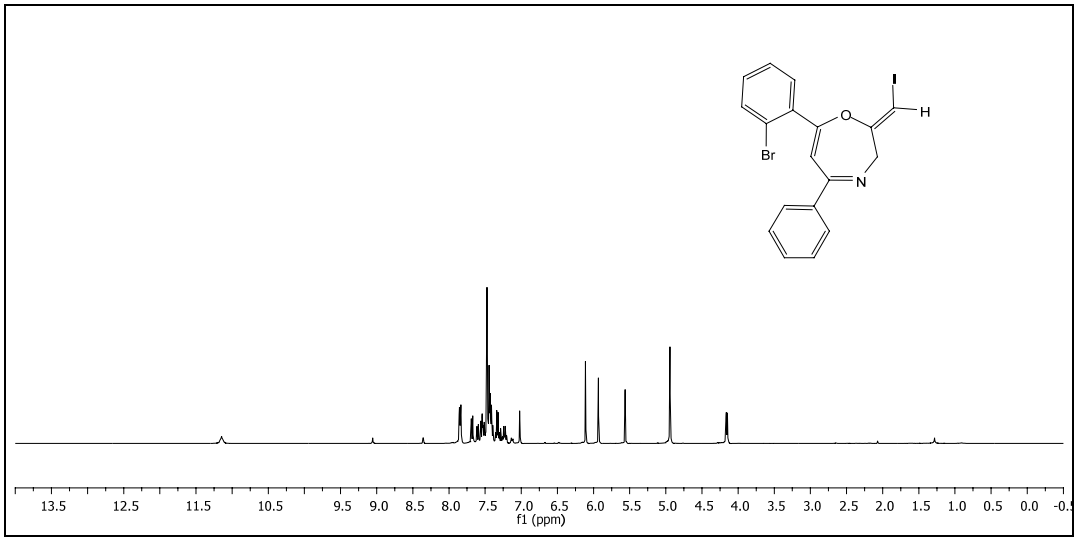

Figure 74A . ^{1}H NMR Spectrum of compound **44G.**

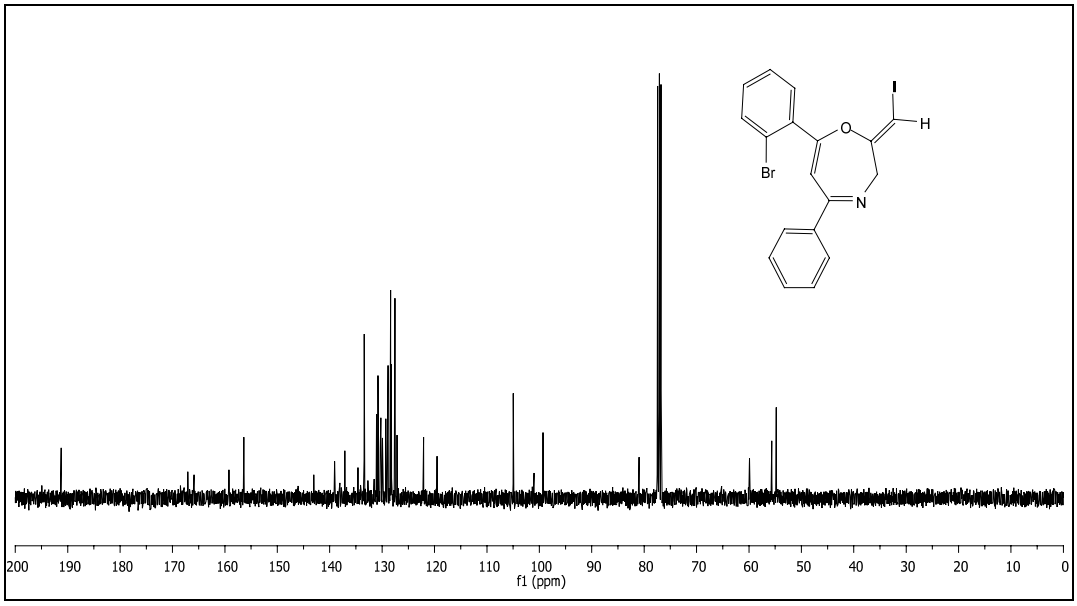

Figure 75A. ^{13}C NMR Spectrum of compound **44G.**

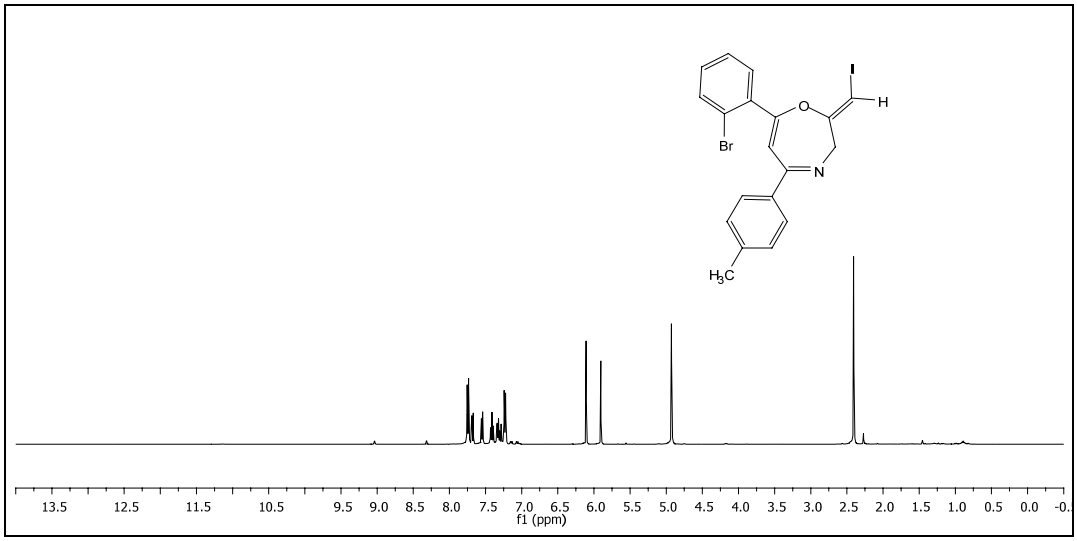

Figure 76A. ^{1}H NMR Spectrum of compound **44H.**

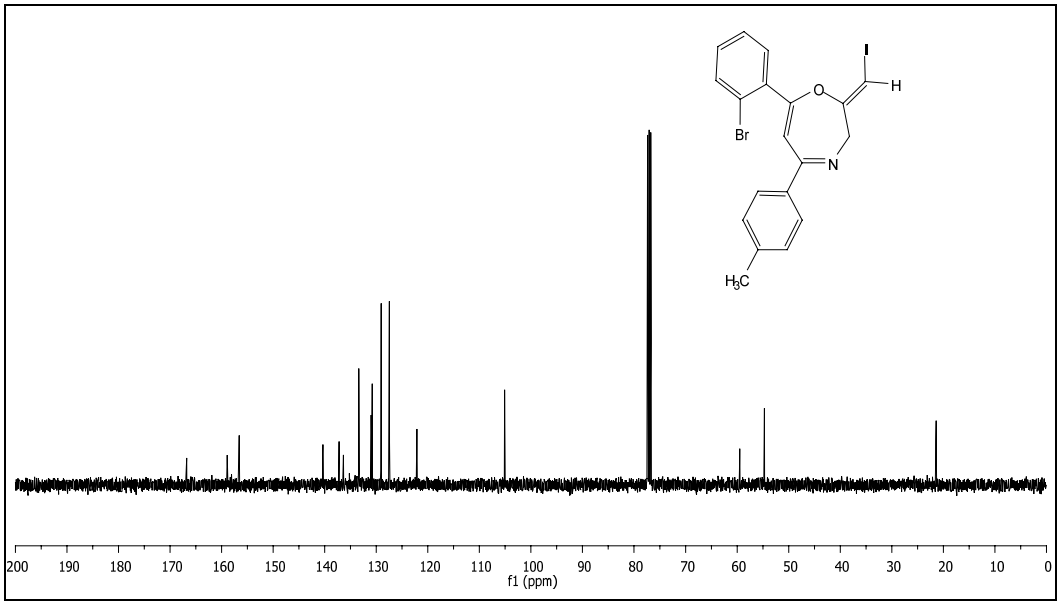

Figure 77A. ^{13}C NMR Spectrum of compound **44H.**

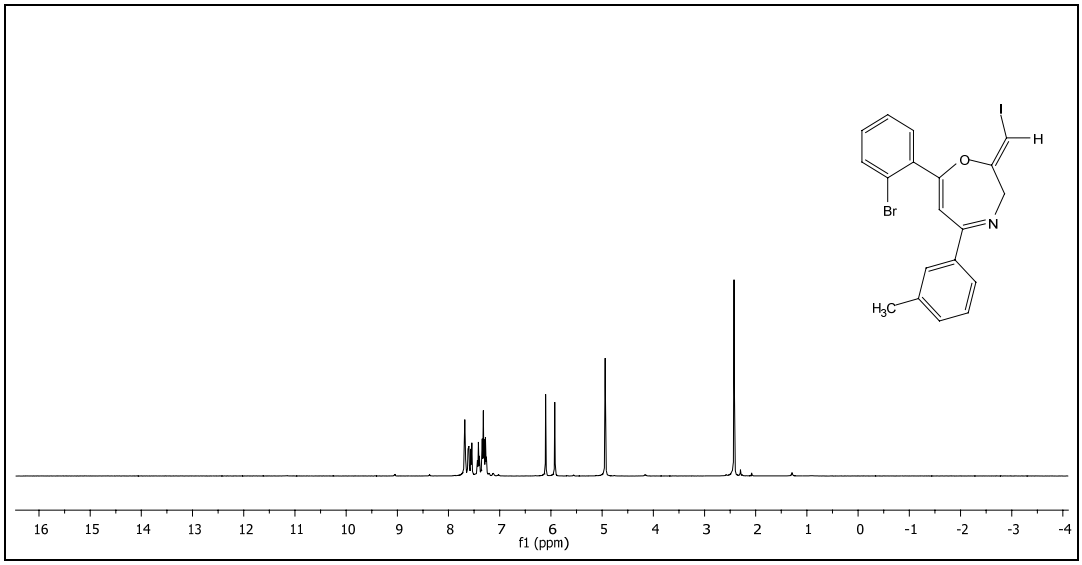

Figure 78A. ^{1}H NMR Spectrum of compound **44I.**

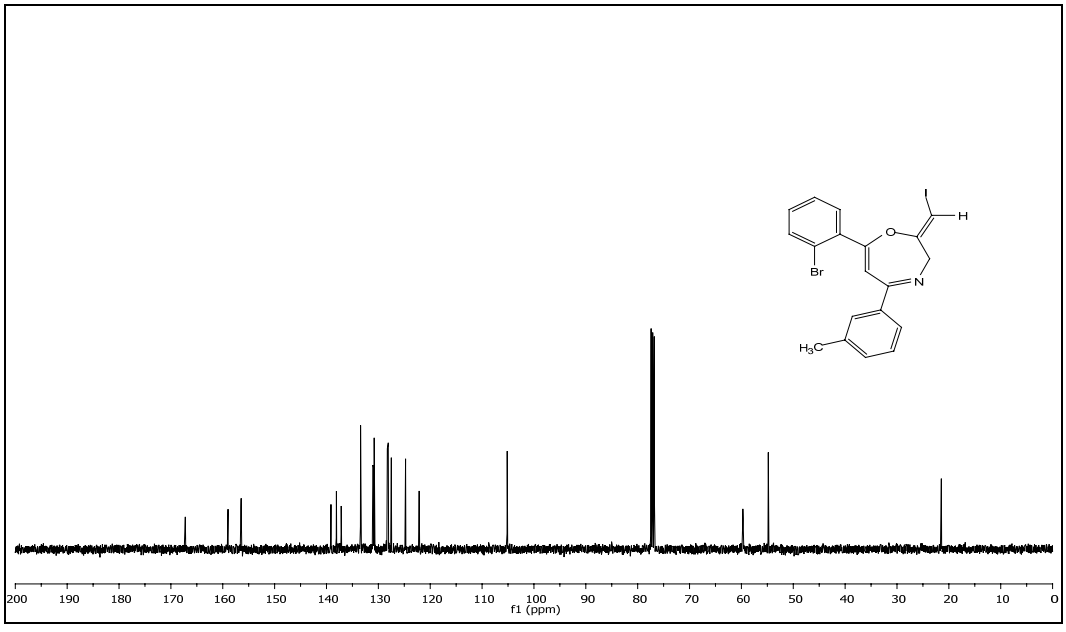

Figure 79A. ^{13}C NMR Spectrum of compound **44I**.

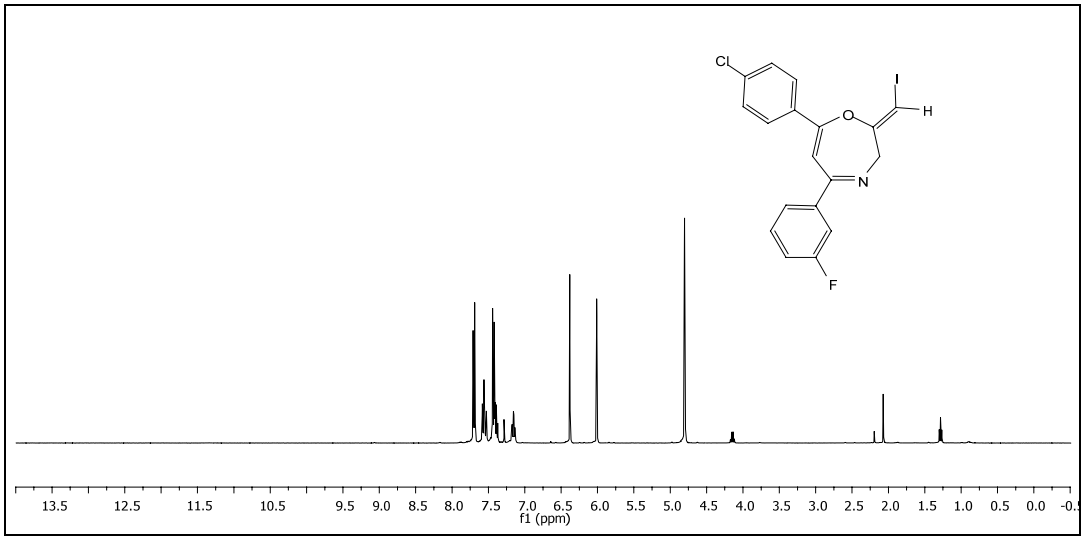

Figure 80A . ^{1}H NMR Spectrum of compound **44J.**

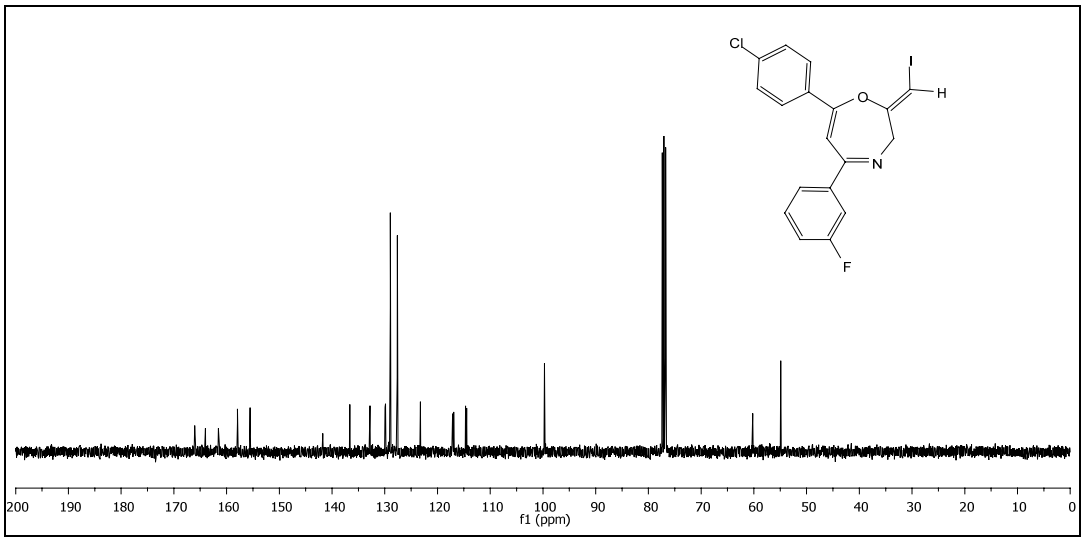

Figure 81A. ^{13}C NMR Spectrum of compound **44J.**

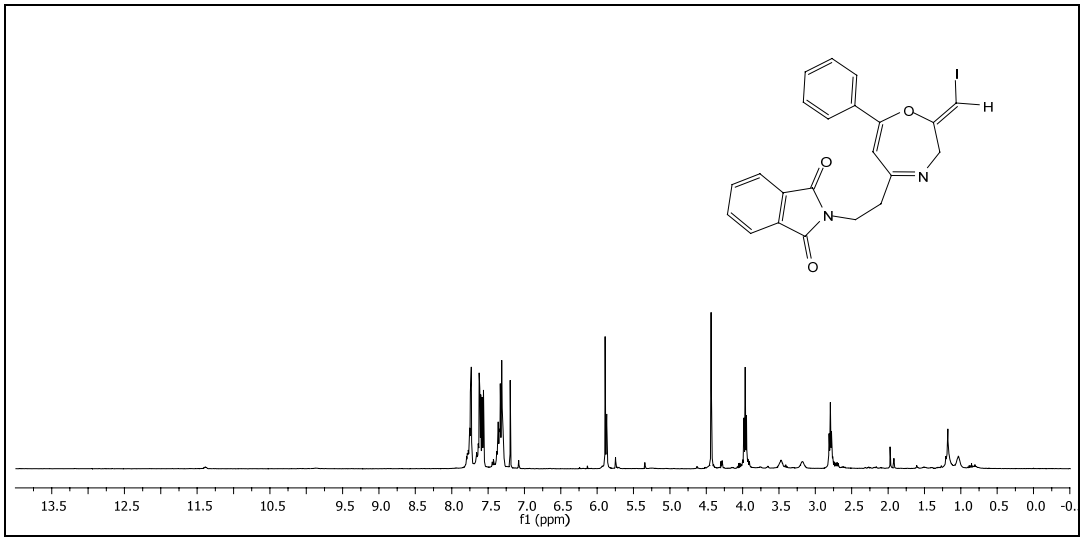

Figure 82A. ^{1}H NMR Spectrum of compound **44K.**

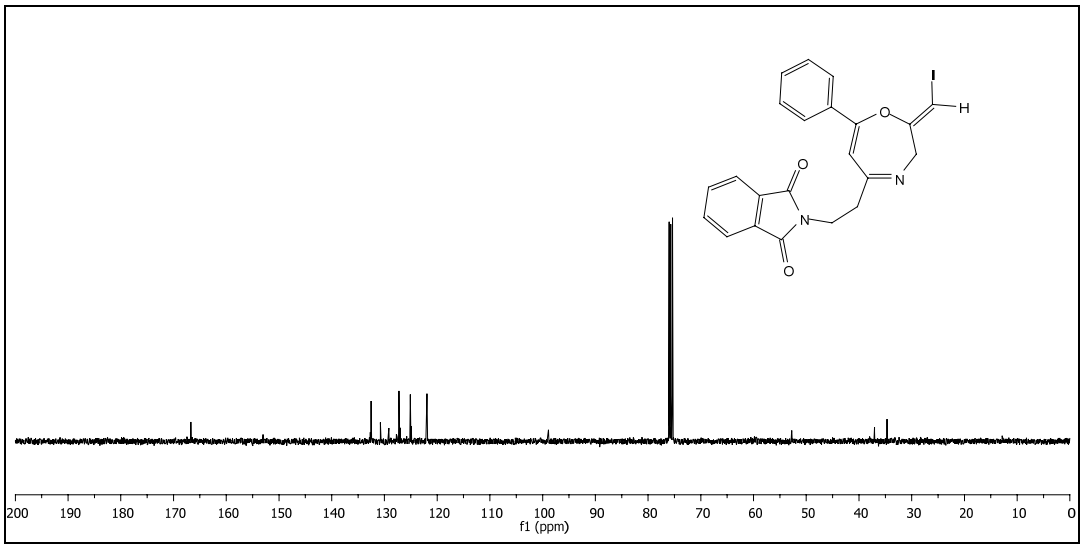

Figure 83A. ^{13}C NMR Spectrum of compound **44K.**