NUCLEOPHILIC AND ELECTROPHILIC CYCLIZATION REACTIONS OF *N*-ALKYNE SUBSTITUTED PYRROLE DERIVATIVES

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BY

IŞIL YENİCE

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FOR
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Approval of the thesis:

NUCLEOPHILIC AND ELECTROPHILIC CYCLIZATION REACTIONS OF *N*-ALKYNE SUBSTITUTED PYRROLE DERIVATIVES

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

Name, Last name: Işıl Yenice

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ABSTRACT

NUCLEOPHILIC AND ELECTROPHILIC CYCLIZATION REACTIONS OF *N*-ALKYNE SUBSTITUTED PYRROLE DERIVATIVES

Yenice, Işıl

M.S., Department of Chemistry

Supervisor: Prof. Dr. Metin Balcı

February 2016, 100 pages

Pyrrolopyrazinone, triazinone and oxazinone derivatives were synthesized via practical methodologies. In the study, *N*-alkyne substituted pyrrole esters were synthesized and isolated as key compounds via copper catalyzed cross-coupling reaction. Then, key compounds underwent nucleophilic cyclization reaction with hydrazine monohydrate to yield pyrrolopyrazinone and/or pyrrolotriazinone derivatives according to electronic properties of group attached to alkyne unit. Additional study was the synthesis of pyrrolooxazinone derivatives. Key compounds were treated with iodine to achieve electrophilic cyclization reactions and iodine substituted 6-*endo*-dig cyclization products were obtained.

Keywords: pyrrolopyrazinone, pyrrolotriazinone, pyrrolooxazinone, hydrazine monohydrate, iodine

ÖZ

N-ALKİN SÜBSTİTÜE PİROL TÜREVLERİNİN NÜKLEOFİLİK VE ELECTROFİLİK HALKALAŞMA REAKSİYONLARI

Yenice, Işıl
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Balcı

Şubat 2016, 100 sayfa

Pirolopirazinon, triazinon ve oksazinon türevleri pratik metodlar eşliğinde sentezlendi. Çalışmada, *N*-alkin sübstitüe pirol esterler anahtar molekül olarak bakır katalizli çapraz kenetlenme reaksiyonuyla sentezlendi ve izole edildi. Ardından, anahtar moleküllerin hidrazin monohidrat ile nükleofilik halkalaşma reaksiyonları gerçekleştirildi, alkine bağlı grubun elektronik özelliğine göre pirolopirazinon ve/veya pirolotriazinon türevleri sentezlendi. Bir diğer çalışma ise pirolooksazinon türevlerinin sentezlenmesidir. Anahtar moleküller iyotla muamele edilerek elektrofilik halkalaşma reaksiyonları gerçekleştirildi ve iyot sübstitüe 6-*endo*-dig haklaşma ürünleri elde edildi.

Anahtar Kelimeler: pirolopirazinon, pirolotriazinon, pirolooksazinon, hidrazin monohidrat, iyot

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To my beloved family and friends …

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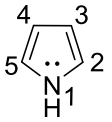
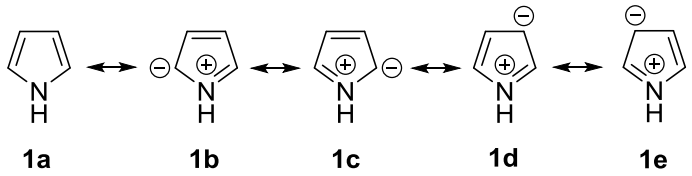
1.1. Pyrrole



Pyrrole

1

Nitrogen atom containing five-membered aromatic ring is called pyrrole (**1**). Two electrons contribution of the nitrogen atom and one electron contributions of each carbon atoms of pyrrole ring constitute 6π electron system. This property is combined with planarity of the pyrrole structure to generate aromaticity. Contribution to delocalization of lone pair electrons of nitrogen atom, as shown in Scheme 1, lowers the basicity of pyrrole ring.[1]



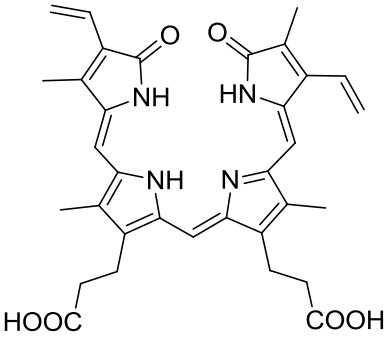
1a **1b** **1c** **1d** **1e**

Scheme 1. Resonance structures of pyrrole

Non-charged pyrrole structure **1a** makes the major contribution to the resonance hybrid, consequently it is drawn as this structure.[2]

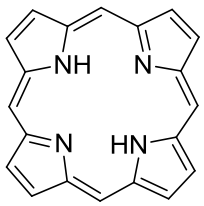
Pyrrole has a great range of applications in organic synthesis since most of the drugs and the natural products contain pyrrole moiety. There are many pyrrole containing essential pigments. For instance, Biliverdin (**2**), which causes greenish color in bruises,

has anti-oxidant property in mammals[3] and Chlorin (**3**) is essential for photodynamic therapy to be used as photosentisizing agent.[4]



Biliverdin

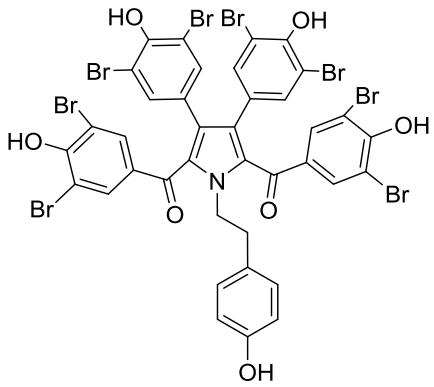
2



Chlorin

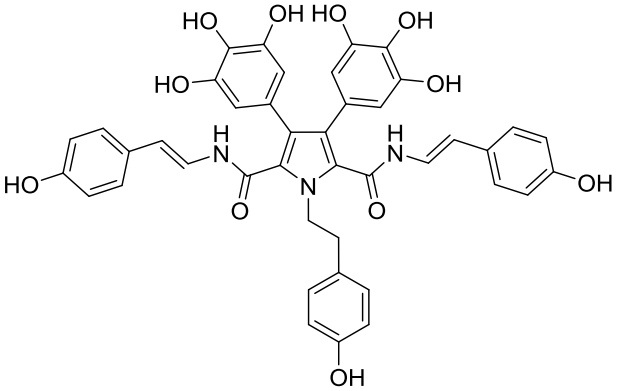
3

Additionally, central pyrrole ring containing marine alkaloids isolated from oceanic organism have seen great pharmacological interest. Polycitone A (**4**) isolated from a sea squirt, *Polycitor*, strongly has an inhibition capacity towards DNA polymerases directed by both RNA and DNA.[5] Peptide originated Storniamide A (**5**) isolated from a sponge, *Cliona*, is antibiotically active towards Gram-positive bacteria.[6]



Polycitone A

4

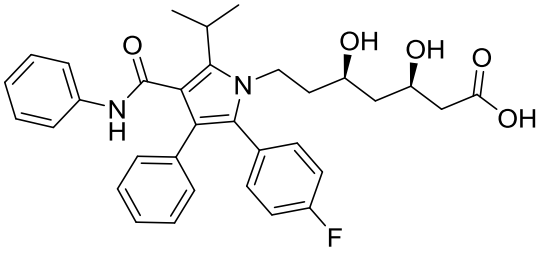


Storniamide A

5

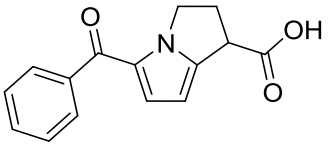
Besides these natural occurring pyrrole containing products, pyrrole derivatives constitute backbone of a lot of widely used synthetic drugs. By inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase, Atorvastatin (**6**) detains the biosynthesis of cholesterol.[7] Also, Ketorolac (**7**), which has analgesic and anti-

inflammatory properties, is used as a pain reliever for moderate to severe levels of pain.[8] Pyrrole has an important role in material sciences, 4,4-difluoro-4-boradipyrrin derivatives (BODIPY), which is highly applicable in sensors, lasers and image diagnosis, absorbs strongly light in the UV and emit intense fluorescence.[9]



Atorvastatin

6

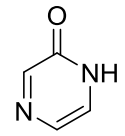


Ketorolac

7

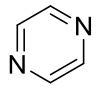
1.2. Pyrazinones

Pyrazinone (**8**) is a six-membered, para-positioned two nitrogen atom containing, non-aromatic heterocyclic ring. In chemical aspect, oxidizing one of the carbon atoms of pyrazine (**9**) yields pyrazinone ring.



Pyrazinone

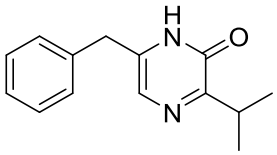
8



Pyrazine

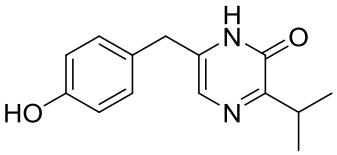
9

The pyrazinones have a biological importance because they can be biosynthesized by considerable amount of microbes.[10] Phevalin (**10**) and Tyrvalin (**11**) are synthesized by a serious human pathogen, *Staphylococcus aureus*, resulting in morbidity and mortality.[11] These pyrazinones have command on the virulence factors of the pathogen which may provide scopes of anti-infective methodologies.[12]



Phevalin

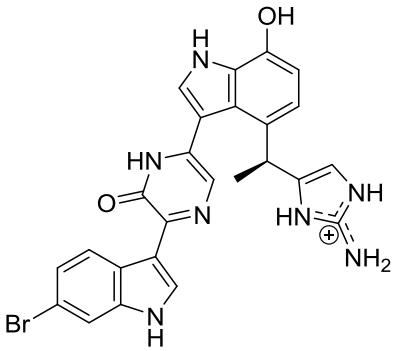
10



Tyrvalin

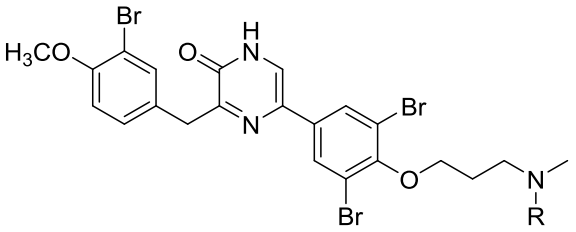
11

Discovery of pyrazinone containing marine alkaloids attracts great attention from scientists looking through their wide range of biological activities. For example, Dragmacidin D (**12**) isolated from *Dragmacidon*, a marine sponge, selectively inhibits neural nitric oxide synthase.[13] Neurodegeneration diseases, like Alzheimer, Prakinson or Huntington, can be cured with drugs including Dragmacidin D.[14] Additionally, Ma'deamines A (**13**) and B (**14**), showing cytotoxic activity against murine leukemia and epidermoid carcinoma cells, are isolated from a marine sponge, *Suberea*.[15]



Dragmacidin D

12

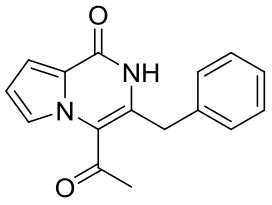


R:CH_3, Ma'edamines A; R:H, Ma'edamines B

13 **14**

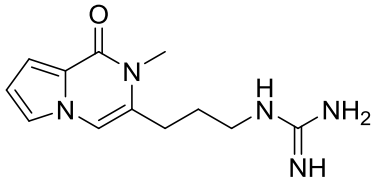
1.2.1. Methodologies for the synthesis of pyrrolopyrazinones

Pyrrole fused pyrazinone heterocycles and their synthesis have great interest due to their natural presence and potent pharmacological and biological activities. Pyrrolopyrazinone moiety containing natural product Nannozinone B (**15**) was isolated from a myxobacteria, *Nannocystis pusilla*.[16] In the similar way, alkaloid Peramine (**16**), isolated from endophyte-infected perennial ryegrass, has a feeding deterrant activity against insects.[17]



Nannozinone B

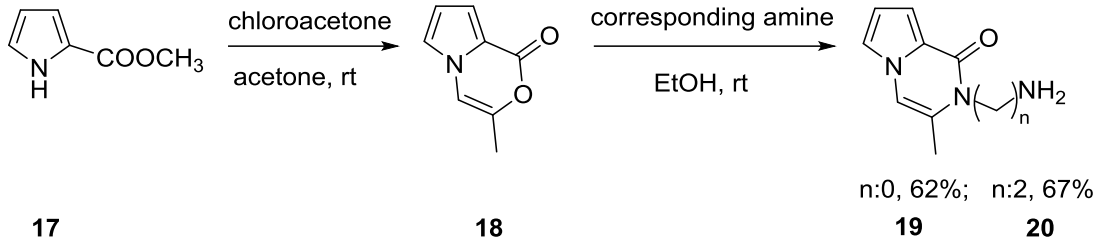
15



Peramine

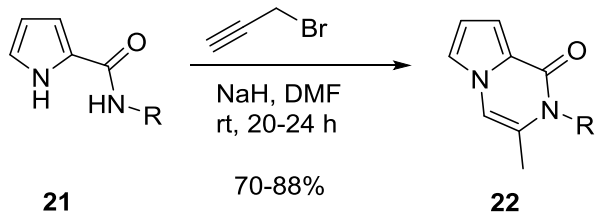
16

Meng and coworkers developed a new synthetic pathway for pyrrolopyrazinone skeleton and evaluated their potent antitumor activity.[18] Starting from the pyrrole ester **17**, they first achieved cyclization to corresponding pyrrolo-oxazinone derivative **18** by using chloroacetone. Then they treated compound **18** with corresponding amines to yield pyrrolopyrazinone derivatives **19**, **20** (Scheme 2).



Scheme 2. Synthesis of pyrrolopyrazinone derivatives **19** and **20**

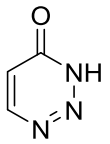
Recently, another synthetic pathway was developed by Balcı et al.[19] Derivatives of pyrrole substituted amides **21** were treated with propargyl bromide and sodium hydride in DMF at room temperature to give corresponding pyrrolopyrazinone derivatives **22** in yields of 70- 88% (Scheme 3).



Scheme 3. Synthesis of pyrrolopyrazinone derivative **22**

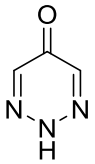
1.3. Triazinones

Six-membered, three nitogen atoms containing heterocyclic rings with an oxidized carbon atom are called triazinones. The positions of nitrogen atoms are named as 1,2,3- , 1,2,4- and 1,3,5-triazinones and addition of the positions of the carbonyl group and the proton attached to the nitrogen atom completes the naming of the isomeric triazinones **23-25** as shown below.



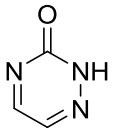
1,2,3-triazin-4(3*H*)-one

23a



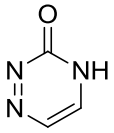
1,2,3-triazin-5(2*H*)-one

23b



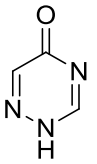
1,2,4-triazin-3(2*H*)-one

24a



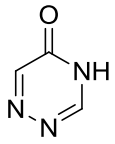
1,2,4-triazin-3(4*H*)-one

24b



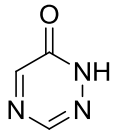
1,2,4-triazin-5(2*H*)-one

24c



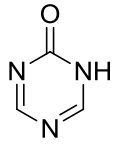
1,2,4-triazin-5(4*H*)-one

24d



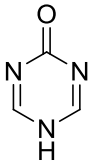
1,2,4-triazin-6(1*H*)-one

24e



1,3,5-triazin-2(1*H*)-one

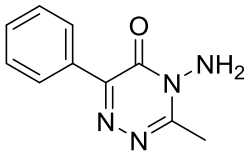
25a



1,3,5-triazin-2(5*H*)-one

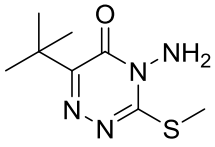
25b

Triazinone heterocycles are essential in organic synthesis regarding to their herbicide, anti-cancer, antimicrobial and antimetastatic activities. Metamitron (**26**) and Metribuzin (**27**), 1,2,4-triazinone herbicides, are absorbed by roots of the plants and inhibit the photosynthesis. They are used to control grasses in plants in pre- and post-emergence.[20]



Metamitron

26

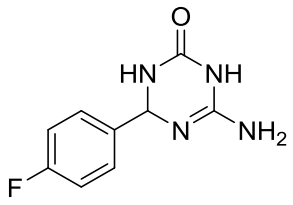


Metribuzin

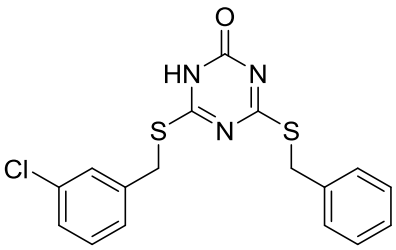
27

Recently, 1,3,5-triazinone derivatives were synthesized and their pharmacological activities were investigated. For example, triazinone scaffold containing compound **28** showed well-balanced inhibition activity without neurotoxicity towards both BACE-1

(aspartyl protease β-secretase) and GSK-3β (glycogen synthase kinase-3β) which are known as key enzymes for causing Alzheimer's disease.[21] Another 1,3,5-triazinone, compound **29**, inhibits human DNA topoisomerase IIα which is a notified anticancer agent target.[22]



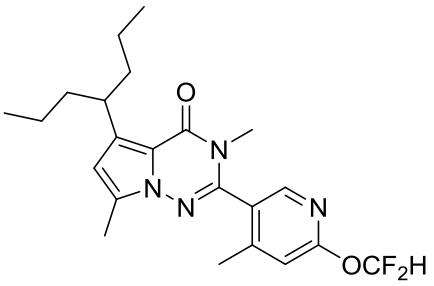
28



29

1.3.1. Methodologies for the synthesis of pyrrolotriazinones

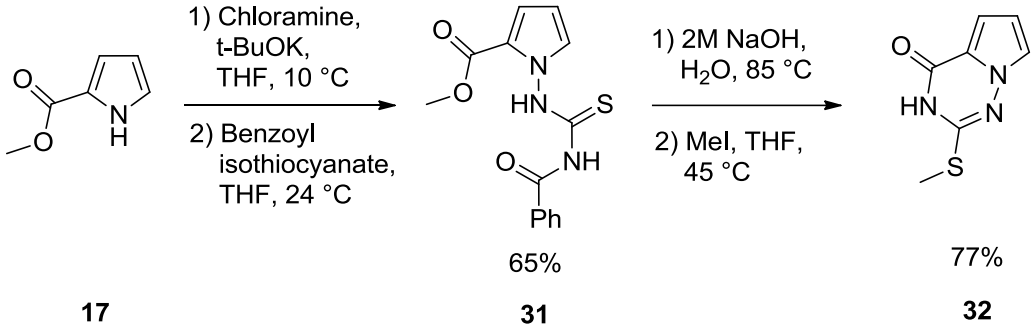
Synthesis of pyrrolotriazinone containing compounds are persued in organic synthesis because they have pharmaceutical activities and they are precursor to pyrrolotriazines which have medicinal activities. In recent studies, pyrrolotriazinone moiety containing compound **30** was synthesized and showed CRF (corticotropin-releasing factor) antagonist activity which can provide a drug treatment against stress-related disorders, like, depression, anxiety or obsessive-compulsive disorder.[23]



30

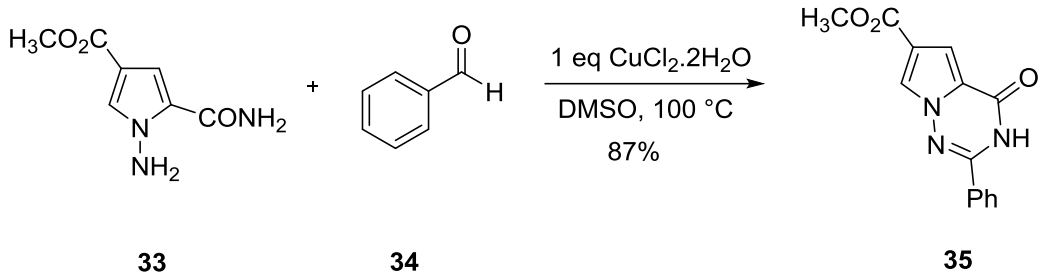
Thieu and coworkers synthesized pyrrolotriazinone derivative **32** starting from methyl-2-pyrrole carboxylate (**17**).[24] Firstly, they treated pyrrole ester **17** with chloramine in the presence of potassium *tert*-butoxide and without any purification crude product was treated with benzoylisothiocyanate and compound **31** was synthesized in overall yield of 65%. Sodium hydroxide was used to achieve hydrolytic

cyclization of compound **31** and following with the methylation reaction, pyrrolotriazinone derivative **32** was formed in 77% yield (Scheme 4).



Scheme 4. Synthesis of pyrrolotriazinone derivative **32**

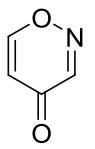
Another practical annulation reaction to synthesize pyrrolotriazinone subunit was achieved with pyrrole carboxamides and aldehydes by Chen and coworkers.[25] For instance, they reacted 1-amino-1*H*-pyrrole-2-carboxamide derivative **33** and benzaldehyde (**34**) with copper catalyst to afford corresponding annulation product **35** in 87% yield (Scheme 5).



Scheme 5. Synthesis of pyrrolotriazinone derivative **35**

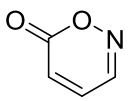
1.4. Oxazinones

Compounds formed from oxidation of one carbon atom of oxazine ring are called as oxazinones. Isomeric structures of oxazinone can be named via pointing the positions of the oxygen and nitrogen atoms of the ring as 1,2-, 1,3- and 1,4-oxazinones **36-38** as shown below.



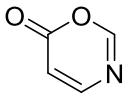
4*H*-1,2-oxazin-4-one

36a



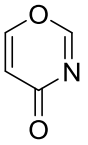
6*H*-1,2-oxazin-6-one

36b



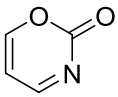
6*H*-1,3-oxazin-6-one

37a



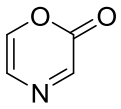
4*H*-1,3-oxazin-4-one

37b



2*H*-1,3-oxazin-2-one

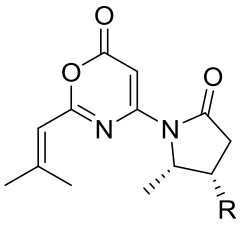
37c



2*H*-1,4-oxazin-2-one

38

Oxazinone subunits have been attracted scientists' interest due to their occurance in natural products and biological activities. Salinazinone A (**39**) and B (**40**), natural alkaloids were recently isolated from broth culture of a marine bacteria specie, *Streptomyces*, and they have an importance due to being first example of oxazinone-pyrrolidine structure containing alkaloids.[26]

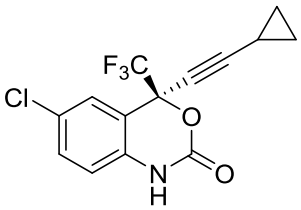


R:OH, Salinazinone A; R:H, Salinazinone B

39 **40**

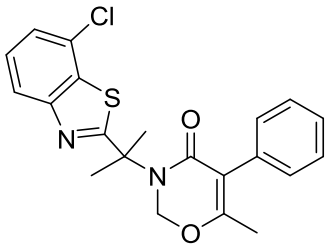
Besides the natural occurance of oxazinone moeity including compounds, their potent medicinal biological activities are making them worth to synthesize. For example, oxazinone substructure containing drug, Efavirenz (**41**), shows reverse transcriptase inhibitory activity to treat HIV-1 (human immunodeficiency virus-1). It inhibits the enzyme capability of turning viral RNA into DNA.[27] On the other hand, compound **42** has herbicide activity against a barndyardgrass, *Echinochloa oryzicola*, which comes from the same family with rice. These two are hard to differentiate during the seedling

process and compound **42** alleviates the growing of the barnyardgrass to provide control for rice cultivation.[28]



Efavirenz

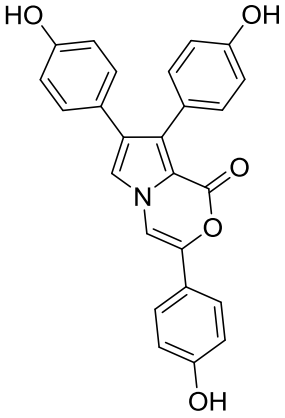
41



42

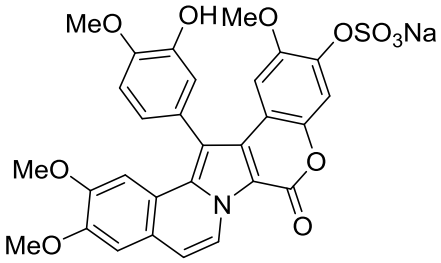
1.4.1. Methodologies for the synthesis of pyrrolooxazinones

Pyrrole fused oxazinone scaffolds have a synthetic importance due to its natural occurance and potent biological acitivities. From a tunicate, a primitive marine animal, pyrrolooxazinone centered alkaloid Lukianol A (**43**) was isolated from a tunicate and it showed cytotoxicity towards human epidermatoid carcinoma.[29] Lamellarin metabolites were isolated from a marine mollusk, *Lamellaria* sp.[30] Another member of lamellarin family, lamellarin α 20-sulfate (**44**) was elucidated with the activity against HIV-1 virus.[31]



Lukianol A

43

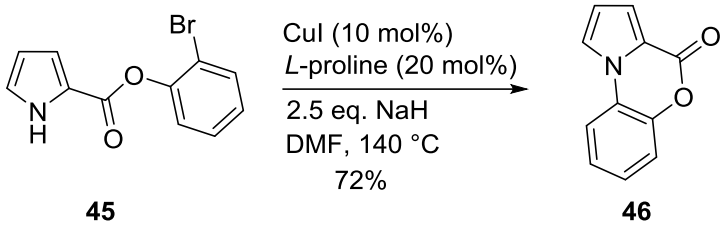


Lamellarin α 20-sulfate

44

Pyrrolooxazinone derivatives were synthesized via intramolecular cyclization reaction of pyrrole carboxamides by Vaillard and coworkers.[32] Pyrrole carboxamide derivative

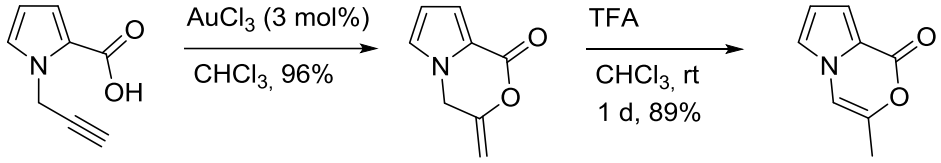
45 was treated with NaH in the presence of CuI catalyst and *L*-proline ligand to afford pyrrolooxazinone subunit containing product **46** in a yield of 77% (Scheme 6).



45 **46**

Scheme 6. Synthesis of pyrrolooxazinone derivative **46**

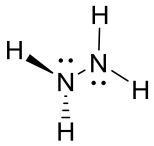
Balcı et al. recently published a facile method for the synthesis of pyrrolooxazinone derivatives.[33] *N*-propargyl-pyrrole-2-carboxylic acid **47** was firstly treated with $AuCl_3$ catalyst to achieve cyclization as corresponding *exo*-dig product **48** in high yield. Then trifluoroacetic acid was used to isomerize double bond to afford desired pyrrolooxazinone derivative **18** (Scheme 7).



47 **48** **18**

Scheme 7. Synthesis of pyrrolooxazinone derivative **18**

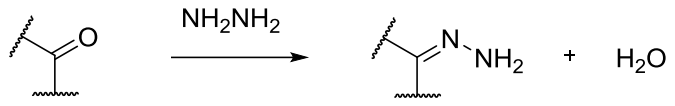
1.5. Hydrazine



Hydrazine

49

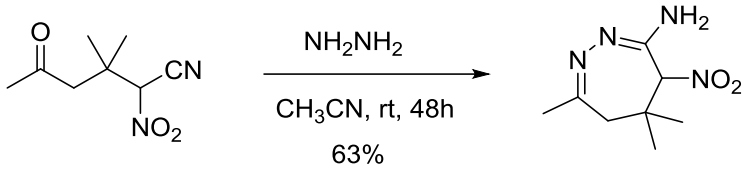
Hydrazine (**49**) is a simple molecular structured inorganic compound with the chemical formula of N_2H_4. It is an important reagent in organic synthesis in consequence of its basic property.[34] Hydrazines react with carbonyl groups **50** to form hydrazones **51** containing C=N double bond (Scheme 8).



50 **51**

Scheme 8. Hydrazone formation of carbonyl groups

Cyclization reactions with hydrazine over hydrazone formation are very common in literature. A very mild condition for cyclization reaction of α-nitro-δ-keto nitrile (**52**) with hydrazine was achieved by Hirao and coworkers.[35] Hydrazone formation allows a pseudo-intramolecular cyclization reaction to yield corresponding product **53** in a yield of 63% (Scheme 9).



52 **53**

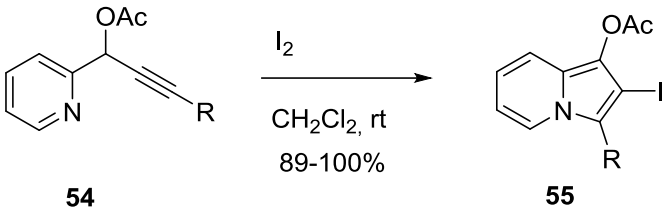
Scheme 9. Cyclization reaction of compound **52** via hydrazine

1.6. Iodine

Molecular iodine usage is very common in cyclization reactions due to its low price, non-toxicity and availability. Iodine is able to coordinate alkyne unit to promote electrophilic cyclization reactions (Scheme 10).

Scheme 10. Iodine coordination to alkyne unit

Indolizine derivatives **55** were synthesized via iodocyclization reactions by Mphahlele.[36] Propargylic group substituted pyridine derivatives **54** were treated with molecular iodine to afford corresponding *endo*-dig cyclization products **55** in good yields (Scheme 11).

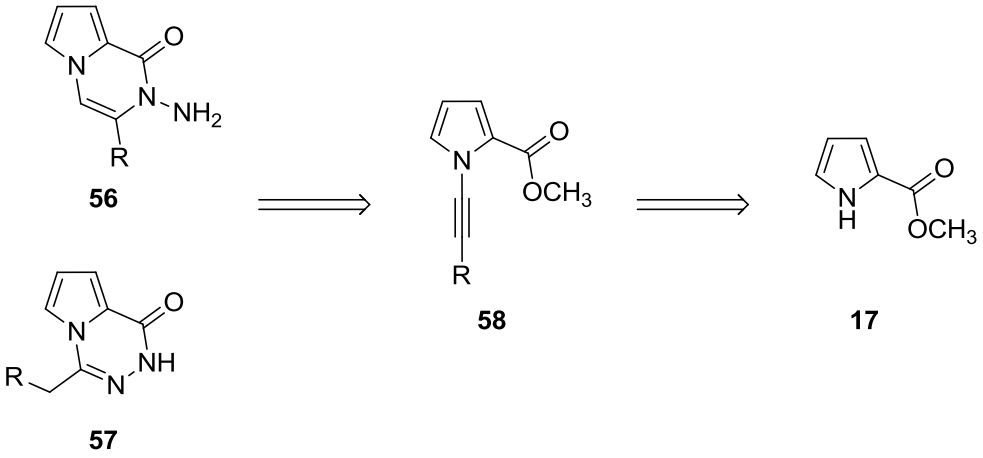


54 **55**

Scheme 11. Cyclization reaction of compound **54** via iodine

1.7. Aim of the study

The purpose of the study was to synthesize pyrrolopyrazinone, triazinone and oxazinone skeletons **56-57** via practical and low-cost methods. We aimed to attain pyrrolopyrazinone and triazinone heterocycles starting from pyrrole ester **17**. As key compounds, synthesis of *N*-alkyne substituted pyrrole ester derivatives **58** was aimed (Scheme 12).

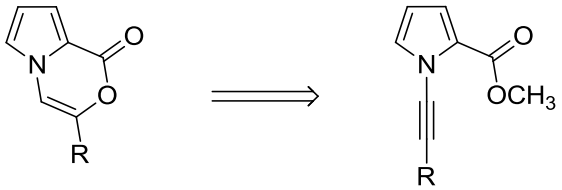


56 **58** **17**

57

Scheme 12. Pathway to synthesize pyrrolopyrazinone and triazinone skeletons

Additionally, pyrrolooxazinone skeleton **59** synthesis was aimed starting from the same key compounds **58** via practical and low-cost synthetic pathway (Scheme 13).



59 **58**

Scheme 13. Pathway to synthesis pyrrolooxazinone skeleton

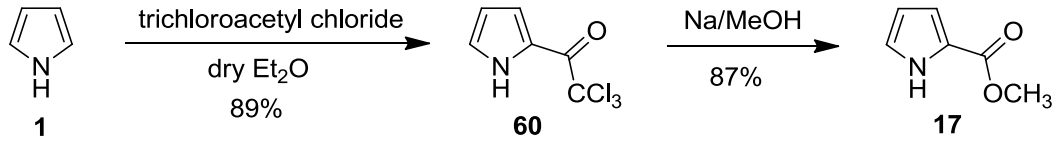
CHAPTER 2

RESULTS AND DISCUSSION

2.1. Synthesis of *N*-alkyne substituted methyl 1*H*-pyrrole-2-carboxylate derivatives

2.1.1. Synthesis of methyl 1*H*-pyrrole-2-carboxylate (17)[37]

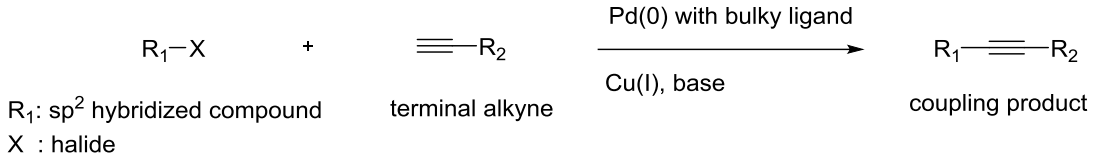
Electron rich pyrrole ring generally undergoes electrophilic substitution reaction at the α-position due to the formation of more stable protonated intermediate. Pyrrole (**1**) was acetylated at C-2 carbon atom via trichloroacetyl chloride in diethyl ether to afford compound **60** in a yield of 89%. In the following step, compound **60** was reacted with NaOMe in methanol to achieve pyrrole ester **17** (Scheme 14).



Scheme 14. Synthesis of methyl 1*H*-pyrrole-2-carboxylate (**17**)

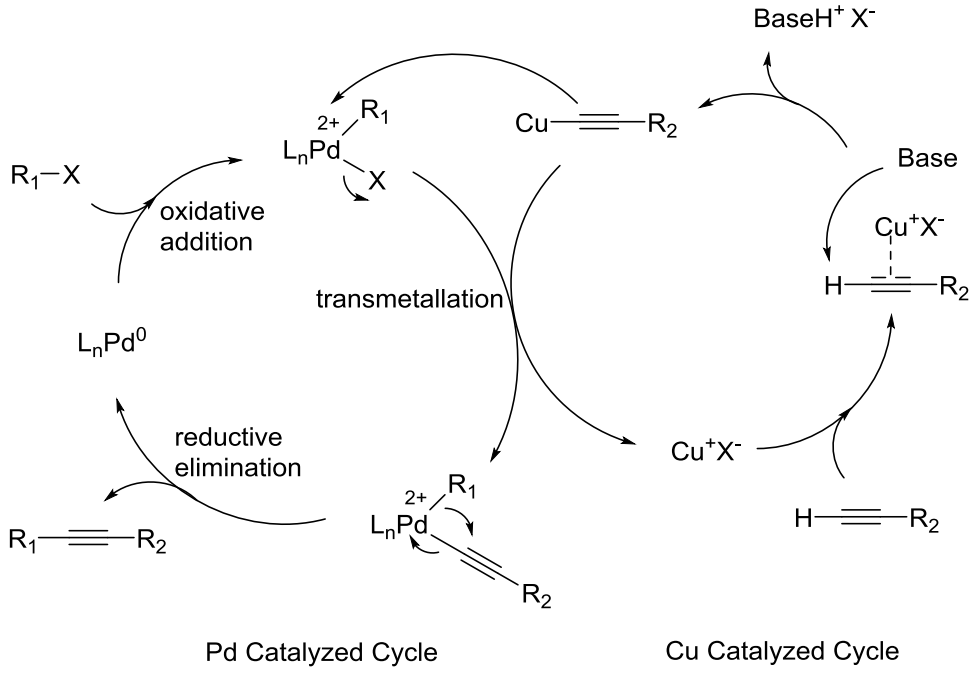
2.1.2. Synthesis of arylalkyne derivatives, 62 and 64, via Sonogashira coupling reaction

N-alkyne substituted pyrrole ester derivatives were synthesized via Sonogashira coupling reaction which forms a carbon-carbon bond between sp^2 hybridized carbon halides and terminal alkynes via Pd-Cu catalysis (Scheme 15).[38] It is a very convenient method to synthesize complex conjugated molecules with a wide range of applications.



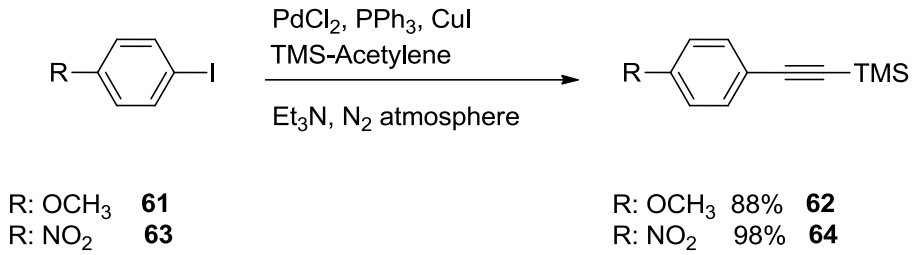
Scheme 15. Sonogashira coupling reaction

Looking through the mechanism of Sonogashira coupling reaction, it is divided into two catalytic cycles which are Pd and Cu catalyzed cycles. Starting with the oxidative addition of sp^2 hybridized carbon halide with Pd(0) and ligand complex gives the Pd(II) and ligand complex. Cu catalyzed cycle starts with the coordination of Cu(I) to terminal alkyne and followed by the abstraction of the terminal proton of alkyne via base to give corresponding organocopper product. Cycles are combined in the transmetallation step and mechanism is completed with reductive elimination step to yield coupled product (scheme 16).



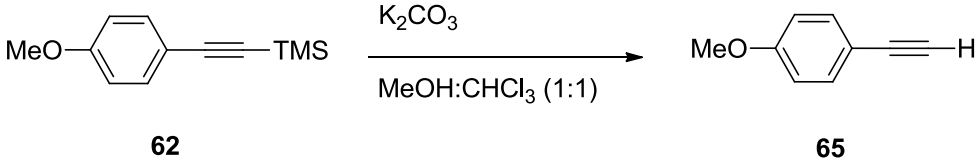
Scheme 16. Mechanism of Sonogashira coupling reaction

Under the light of this cross-coupling reaction, we synthesized two arylalkyne derivatives **62** and **64** via literature methods by using $PdCl_2$, PPh_3 and CuI as catalysts and triethylamine as both solvent and base (Scheme 17).[39]



Scheme 17. Synthesis of arylalkyne derivatives **62** and **64**

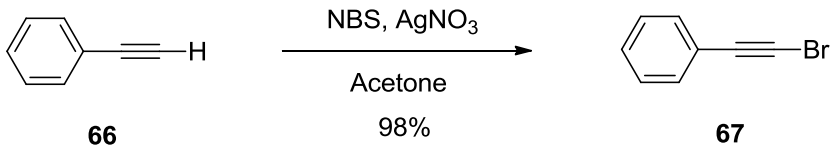
Compound **62** was then treated with K_2CO_3 in MeOH/ $CHCl_3$ (1:1) to be hydrolyzed to corresponding terminal alkyne derivative **65** (Scheme 18).[40]



Scheme 18. Hydrolysis of compound **62**

2.1.3. Synthesis of bromoalkyne derivatives

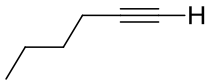
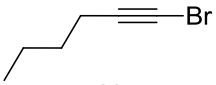
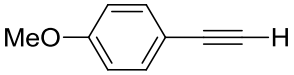
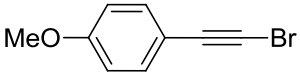
It is essential to use bromoalkynes for *N*-alkyne substitution of pyrrole ester. Fortunately, terminal alkynes can be easily converted into bromoalkynes with *N*-bromosuccinimide in the presence of silver nitrate. Phenylacetylene **66** was converted into (bromoethynyl)benzene (**67**) as reported in the literature (Scheme 19).[41]



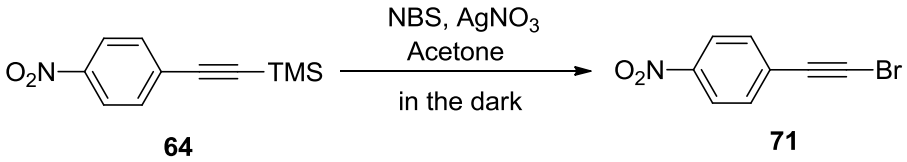
Scheme 19. Synthesis of (bromoethynyl)benzene (**67**)

Synthesis of another two bromoalkyne derivatives **69** and **70** were also accomplished according to the literature methods (Table 1).

Table 1 Yields of bromoalkyne derivatives **69** and **70**

Adduct	Product	Yield
 **68**	 **69**	93%
 **65**	 **70**	89%

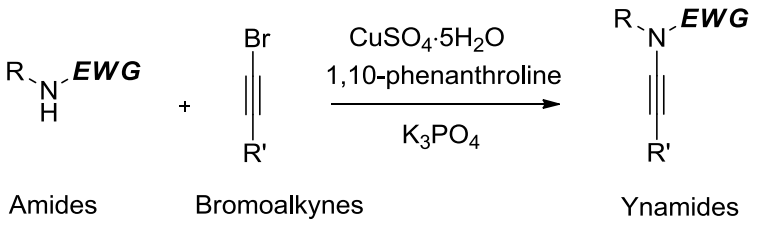
Besides terminal alkynes, ethynyltrimethylsilane derivatives can also be converted into bromoalkynes. Compound **64** was treated with *N*-bromosuccinimide in the presence of silver nitrate in the dark to yield corresponding bromoalkyne derivative **71** (Scheme 20).[42]



Scheme 20. Synthesis of 1-(bromoethynyl)-4-nitrobenzene (**71**)

2.1.4. *N*-alkyne substitution of methyl 1*H*-pyrrole-2-carboxylate derivatives via copper catalyzed cross coupling reaction

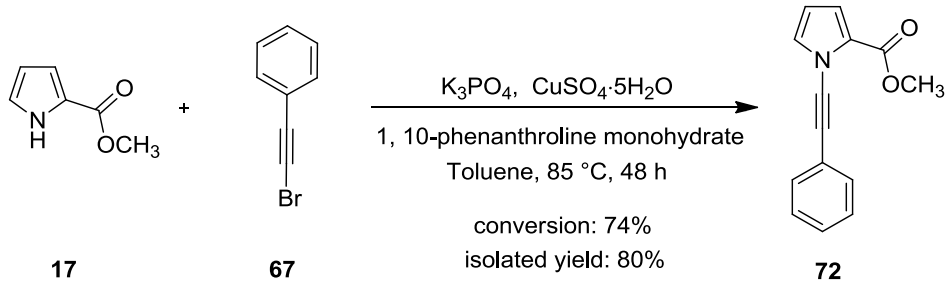
Zhang and coworkers developed a low-priced and ecofriendly copper catalytic method for cross-coupling reaction to form C-N bond.[43] They used $CuSO_4.5H_2O$, instead of CuCN or other copper halides, with 1,10-phenanthroline as the ligand and K_3PO_4 as the base (Scheme 21).



Scheme 21. Copper catalyzed cross-coupling reaction to afford ynamides

Although they did not propose a catalytic cycle for this coupling reaction, mechanism could possibly be like that base abstracts a proton which is attached to the nitrogen atom and nucleophilic pyrrole compound undergoes anion exchange reaction with copper sulfate-ligand complex. In the following step bromoalkyne could undergo oxidative addition with newly formed copper complex and reductive elimination of pyrrole moiety and alkyne unit could give ynamides.

Under the light of this cross-coupling reaction, we decided to apply this procedure to methyl 1*H*-pyrrole-2-carboxylate (**17**) to achieve teh synthesis of our key compounds. Proper conditions were established using (bromoethynyl)benzene (**67**) as the model compound (Scheme 22).



Scheme 22. Proper *N*-alkynylation reaction conditions

Characterization of the compound **72** was achieved by ^{1}H-NMR, ^{13}C-NMR, IR and HRMS data. Disappearance of N-H proton resonance at 9.74 ppm in the ^{1}H-NMR spectrum of pyrrole ester **17** (Figure 1) and appearance of two carbon signals in the ^{13}C-NMR spectrum at 69.7 and 81.4 ppm (sp-hybridized carbon atom resonance region) proved this product (Figure 2).

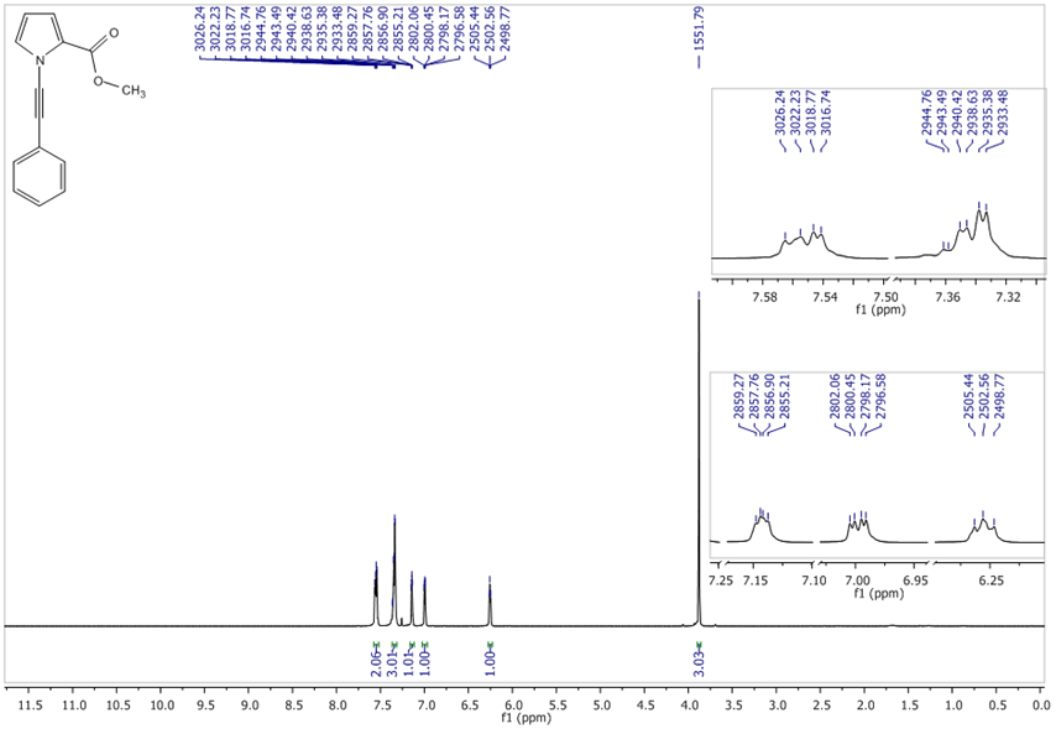


Figure 1 ^{1}H-NMR spectrum of compound **72** in $CDCl_3$

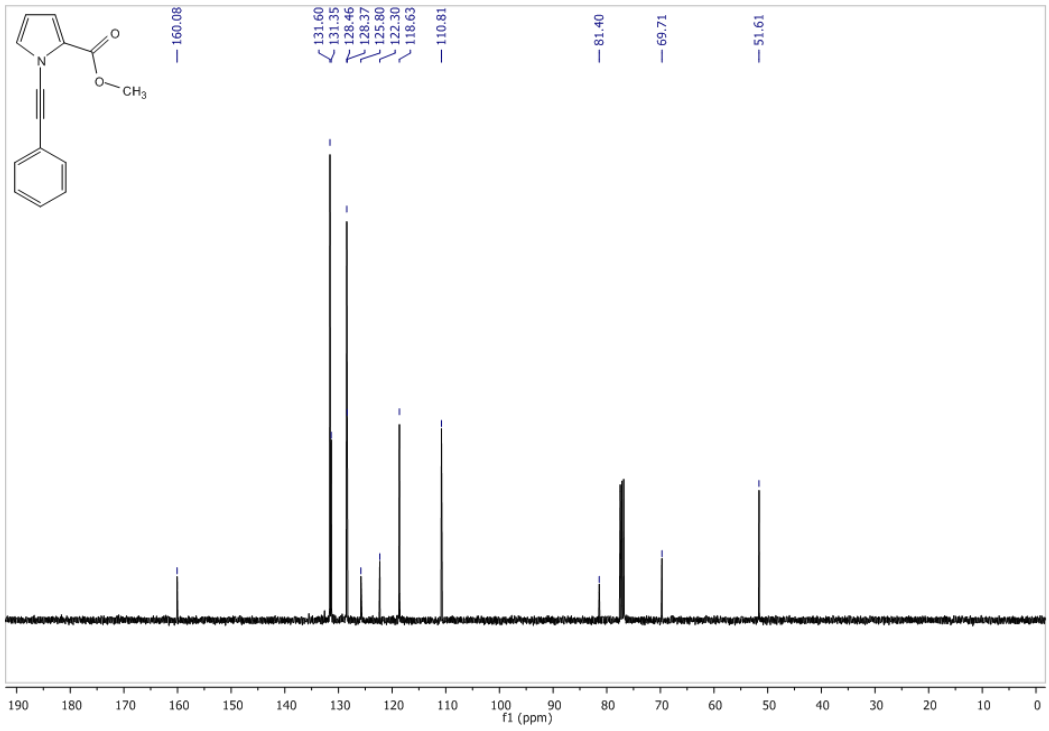
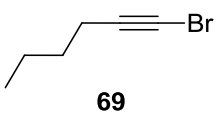
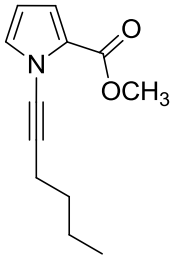
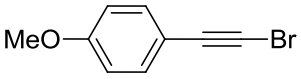
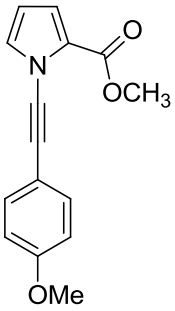
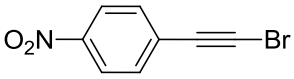
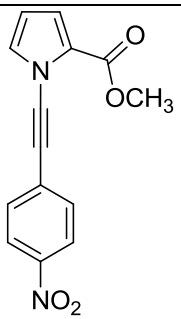


Figure 2 ^{13}C-NMR spectrum of compound **72** in $CDCl_3$

Same procedure was applied to other bromoalkyne derivatives to obtain corresponding *N*-alkyne substituted pyrrole ester derivatives **73-75** (Table 2). Characterizations of compounds **73-75** were proceeded in the same way by ^{1}H-NMR, ^{13}C-NMR, IR and HRMS spectra discussed in the case of compound **72**.

Table 2 N-alkyne substituted methyl 1H-pyrrole-2-carboxlate derivatives **73-75**

Bromoalkyne	Product	Conversion	Isolated Yield*
 **69**	 **73**	63%	92%
 **70**	 **74**	12%	92%
 **71**	 **75**	59%	92%

* Based on conversions

As shown in Table 2, compound **74** was formed in very low yield, the reason for the low conversion should arise from mesomeric effect of electron donating methoxy

group which makes oxidative addition, on terminal alkyne carbon, difficult. To increase the yield, the reaction was carried out at higher temperatures. We were able to increase conversion hardly up to 35% at reflux temperature of anisole (Table 3).

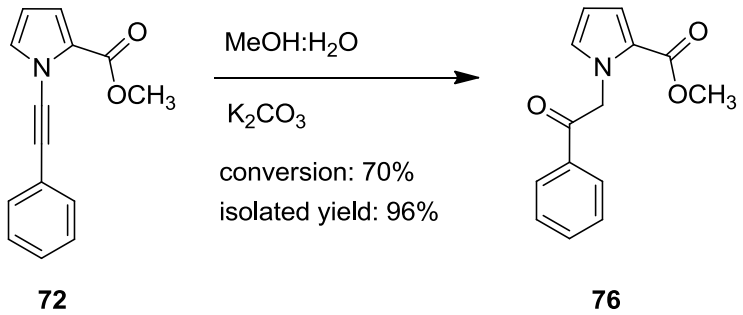
Table 3 Yields for compound **74** at different temperatures

Solvent - Temperature	Conversion	Isolated Yield*
Toluene - 110 °C	20%	87%
Anisole - 155 °C	35%	99%

* Based on conversions

2.2. An attempt to hydrolyze methyl 1-(phenylethynyl)-1*H*-pyrrole-2-carboxylate (72)

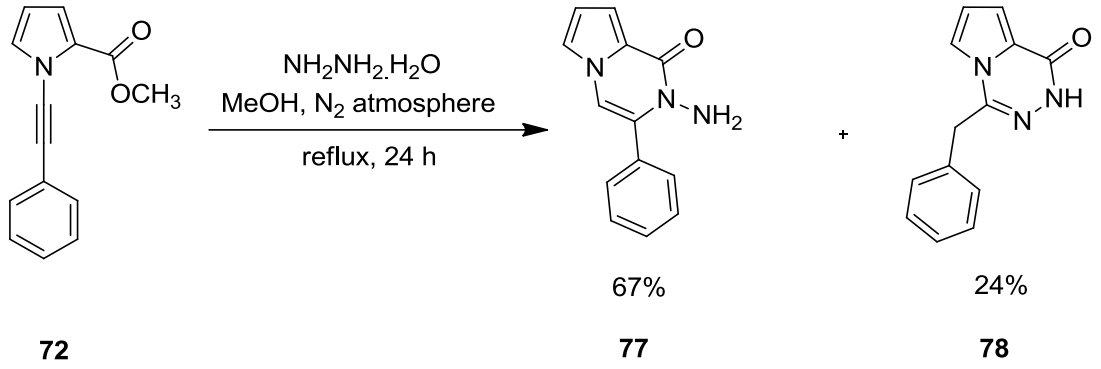
After the synthesis of key compounds, we decided to hydrolyze the ester functionalities to the corresponding carboxylic acids to make them more tended to be cyclyzed via metal catalysts. We tried to hydrolyze methyl 1-(phenylethynyl)-1*H*-pyrrole-2-carboxylate (**72**) by using potassium carbonate in MeOH/H_2O solution. Unfortunately the desired carboxylic acid was not formed, instead ketone **76** was formed by addition of water to the triple bond in **72** (Scheme 23). The compound was easily characterized by comparison of the spectral data with those of **76** reported in the literature.[44]



Scheme 23. Attempt to hydrolyze compound **72**

2.3. Nucleophilic cyclization reactions of *N*-alkyne substituted methyl 1*H*-pyrrole-2-carboxylate derivatives via hydrazine monohydrate

After failure of hydrolysis of methyl 1-(phenylethynyl)-1*H*-pyrrole-2-carboxylate (**72**), we decided to conduct cyclization reaction of key compounds **72-75** via hydrazine monohydrate. Methyl 1-(phenylethynyl)-1*H*-pyrrole-2-carboxylate (**72**) was treated with hydrazine monohydrate in MeOH under N_2 atmosphere at reflux temperature. Pyrrolopyrazinone and pyrrolotriazinone skeletons **77**, **78** were formed in 67% and 24% yields, respectively (Scheme 24).



Scheme 24. Nucleophilic cyclization reaction of compound **72**

Structures of compounds **77** and **78** were proven by ^{1}H-NMR, ^{13}C-NMR, IR and HRMS spectra. Looking through the H^{1}-NMR spectrum of pyrrolopyrazinone derivative, compound **77**, two -NH_2 protons resonates at 4.41 ppm as broad singlet and one double bond proton resonance of newly formed pyrazinone ring appears at 6.94 ppm as singlet (Figure 3). Furthermore, disappearance of two carbon signals in sp-hybridized carbon atom resonance region strongly supports the formation of **77** (Figure 4).

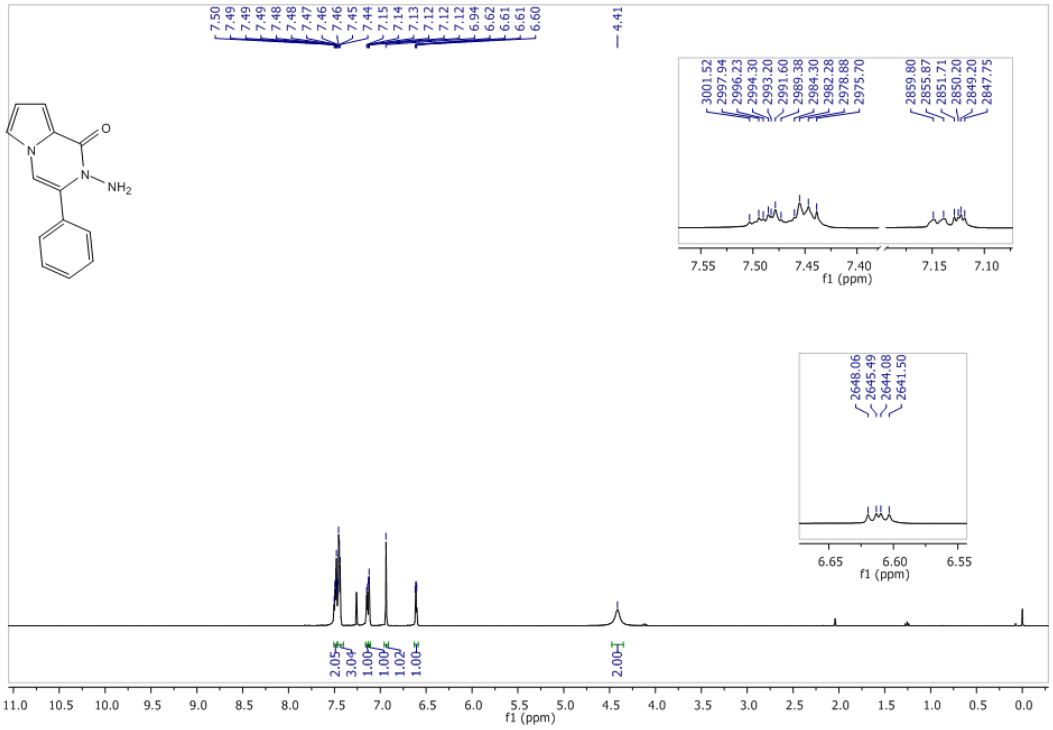


Figure 3 ^{1}H-NMR spectrum of compound **77** in $CDCl_3$

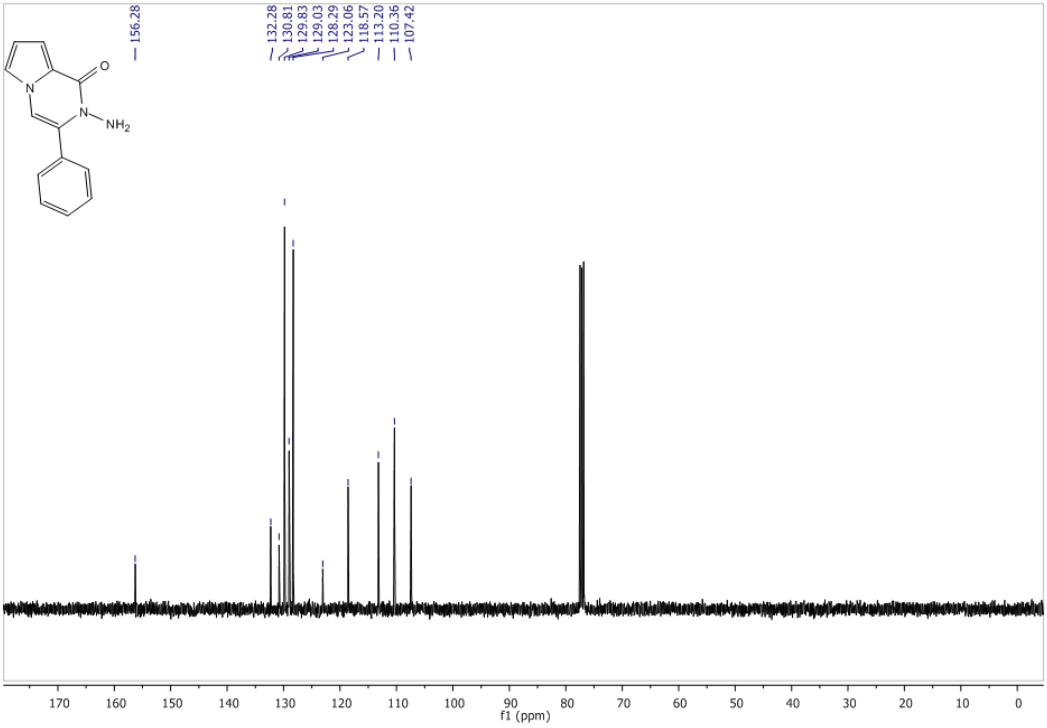
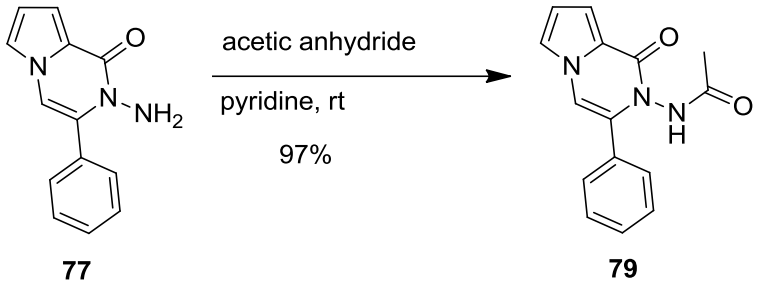


Figure 4 ^{13}C-NMR spectrum of compound **77** in $CDCl_3$

For further proof of the structure **77**, we submitted the compound to acetylation reaction with acetic anhydride in pyridine and obtained acetylated compound **79** in 97% yield (Scheme 25).



Scheme 25. Acetylation reaction of compound **77**.

Acetylated -NH- proton resonance was now shifted to the lower field (9.12 ppm) as expected, since electron density is decreased via mesomeric effect of the attached carbonyl group (Figure 5).

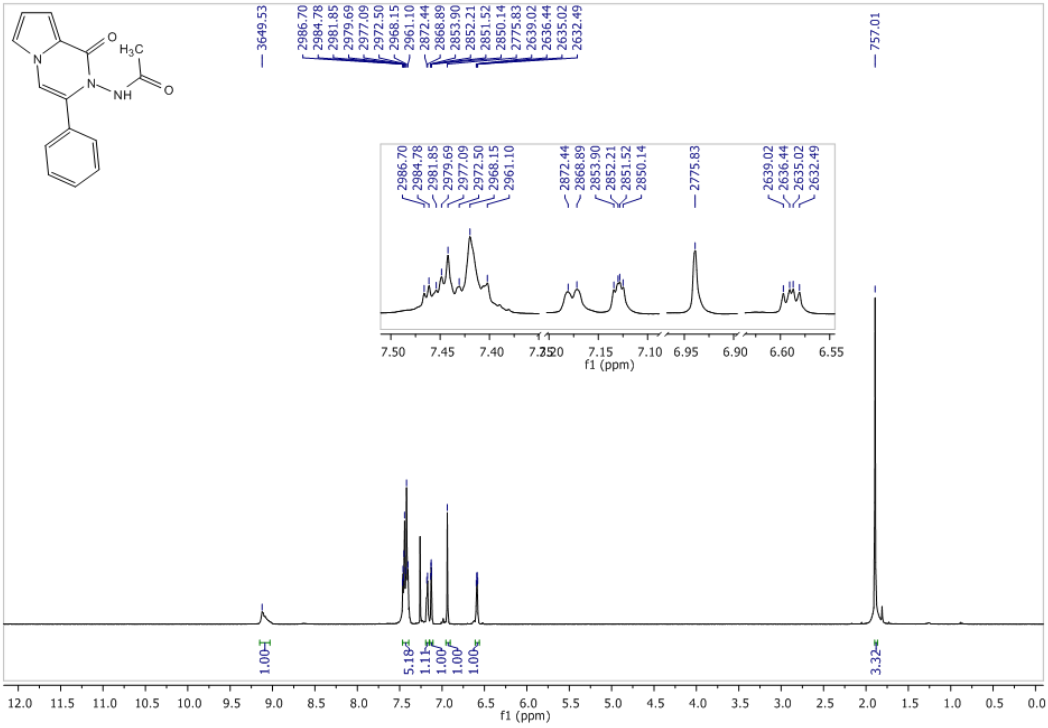


Figure 5 ^{1}H-NMR spectrum of compound **79** in $CDCl_3$

Analysis of HMBC spectrum of this compounds proved us the structure via correlation between -NH- proton and C-3 carbon atoms (Figure 6).

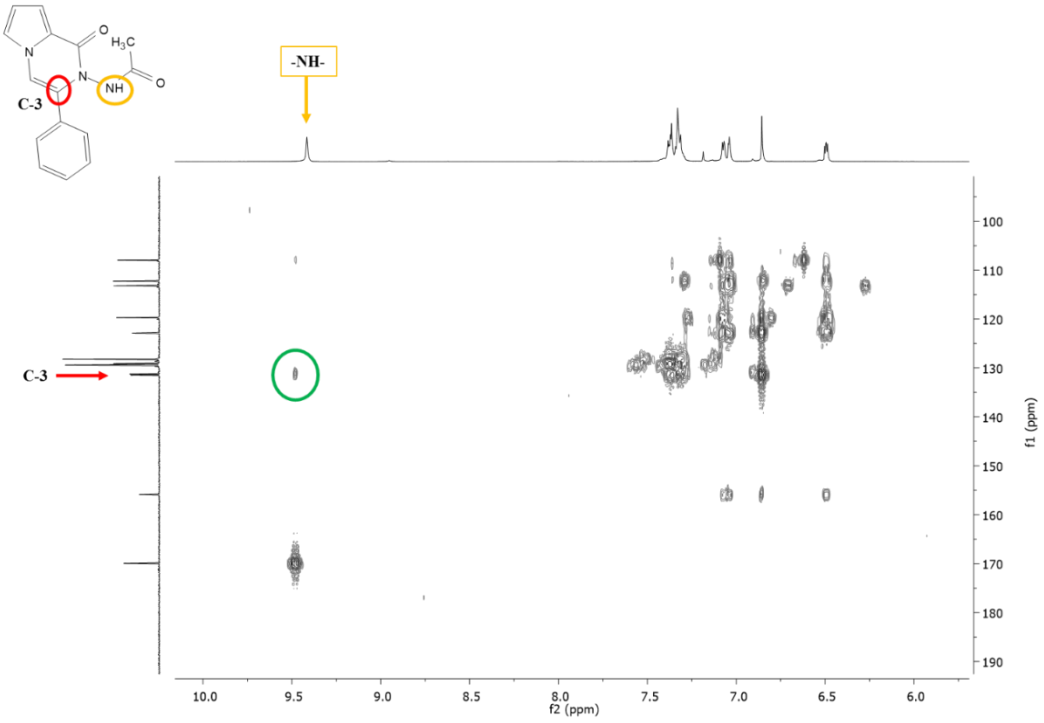


Figure 6 HMBC spectrum of compound **79**

On the other hand, pyrrolotriazinone derivative **78**, was identified via resonances of methylene protons at 4.26 ppm and -NH- proton at 11.78 ppm (Figure 7). In the same way, disappearance of two sp-hybridized carbon atom resonances of **78** in the ^{13}C-NMR spectrum provided strong evidence for structure **78** (figure 8).

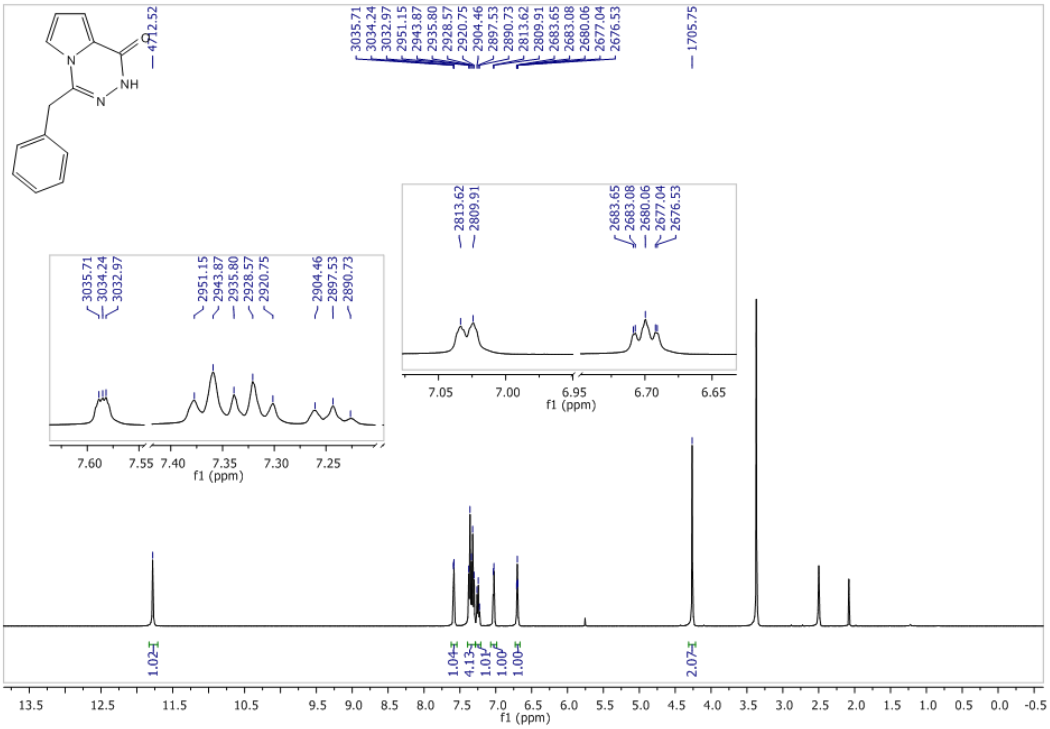


Figure 7 ^{1}H-NMR spectrum of compound **78** in DMSO-d_6

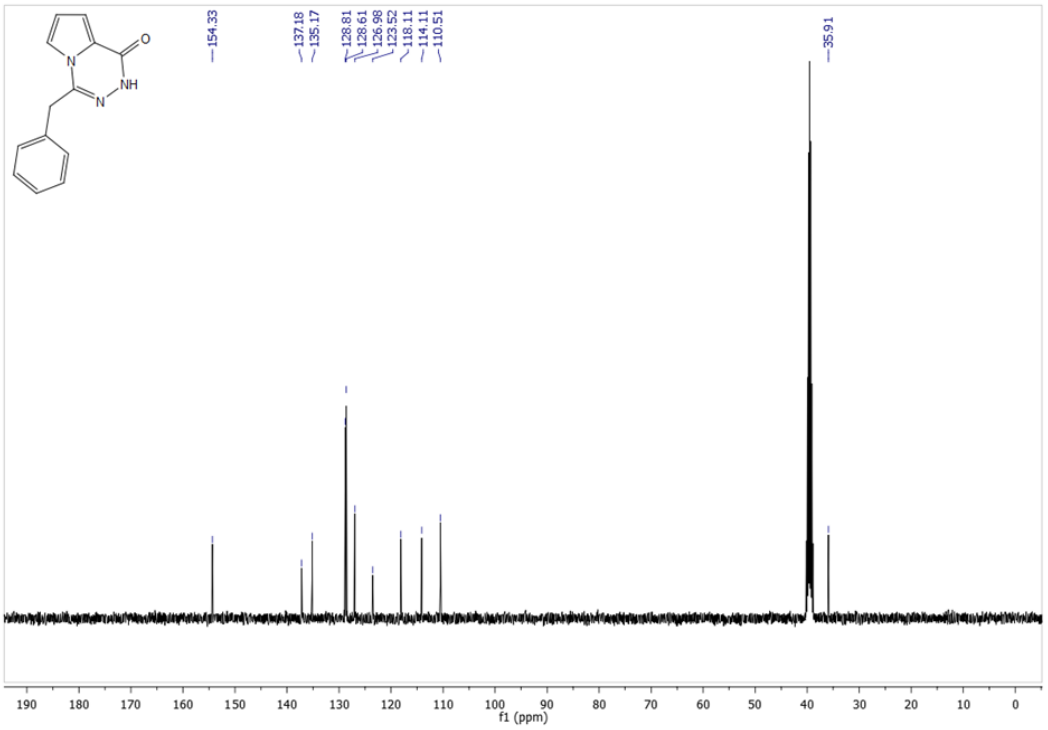
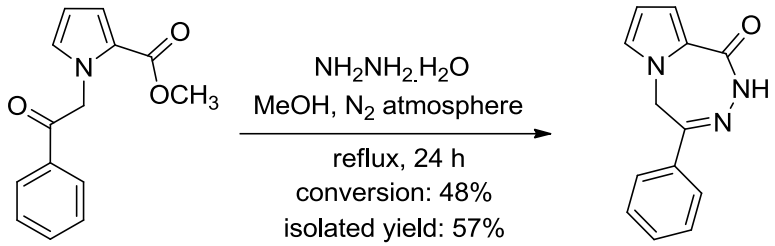


Figure 8 ^{13}C-NMR spectrum of compound **78** in DMSO-d_6

Determined ^{1}H-NMR data of compound **78** showed that this compound could also have the structure **80**. In order to assign the correct structure to the product obtained by the reaction of **72** with hydrazine as the second product (Scheme 24), to distinguish between six- and seven-membered rings (**78** and **80**), we decided to synthesize pyrrolotriazepinone derivative on an independent way and compare the spectral data. For this reason compound **76** was treated with hydrazine monohydrate in methanol to obtain methyl 4-phenyl-2,5-dihydro-1*H*-pyrrolo[2,1-*d*][1,2,5]triazepin-1-one (**80**) (Scheme 26).



76 **80**

Scheme 26. Synthesis of methyl 4-phenyl-2,5-dihydro-1*H*-pyrrolo[2,1-*d*][1,2,5]triazepin-1-one (**80**)

^{1}H-NMR, ^{13}C-NMR, IR and HRMS data were used for the characterization of compound **80**. ^{1}H-NMR and ^{13}C-NMR spectra of these two compounds **78** and **80** were completely different. The methylene protons of compound **78** resonate at 4.26 ppm while the methylene proton resonance in compound **80** is shifted to lower field, to 5.28 ppm due to directly attachment to nitrogen atom which decreases electron density around protons (Figure 9).

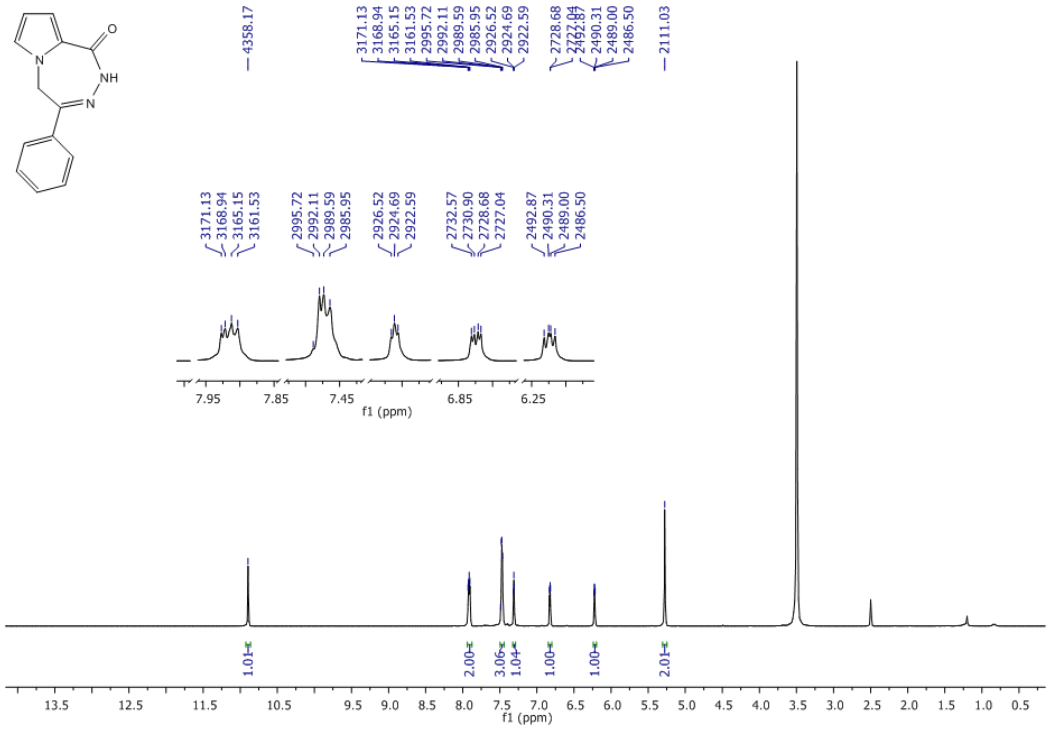
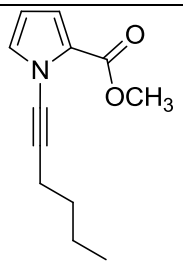
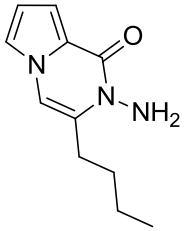
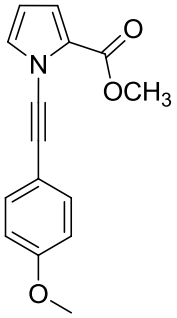
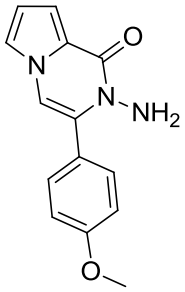
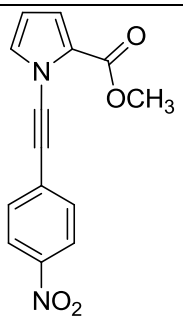
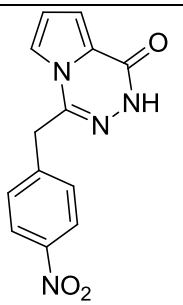


Figure 9 ^{1}H-NMR spectrum of compound **80** in DMSO-d_6

After correct assignments of the structure of **77** and **78**, we applied the same cyclization methodology on key compounds **73-75** and isolated corresponding cyclization products in good yields (Table 4). Identifications of the compounds **81-83** were established via ^{1}H-NMR, ^{13}C-NMR, IR and HRMS spectra. As shown in the Table 4, products dominate over the other one depending on the electronic properties of the substituents attached to the alkyne group. In substituted arylalkyne derivatives **74** and **75**, mesomeric effect dominates due to resonance structures. Since, electron donating methoxy group leads to the formation of *N*-amino pyrazinone derivative **82**, while electron withdrawing nitro group yields triazinone derivative **83**. In the case of alkyl group substituted compound **73**, *N*-amino pyrazinone derivative **81** was formed. Because, alkyne carbon attached to nitrogen atom must be more electropositive and prone to accept nucleophilic attack, but somehow alkyl group attached carbon atom accepts nucleophilic attack to afford compound **81**. We assume that an allenic intermediate may be responsible for the formation of **81**. Since the central carbon atom of allene unit is more electropositive, the carbon atom can undergo an attack by amide

nitrogen atom to form a six-membered ring. Formation of allenic intermediate in case **74** and **75** is out of the question.

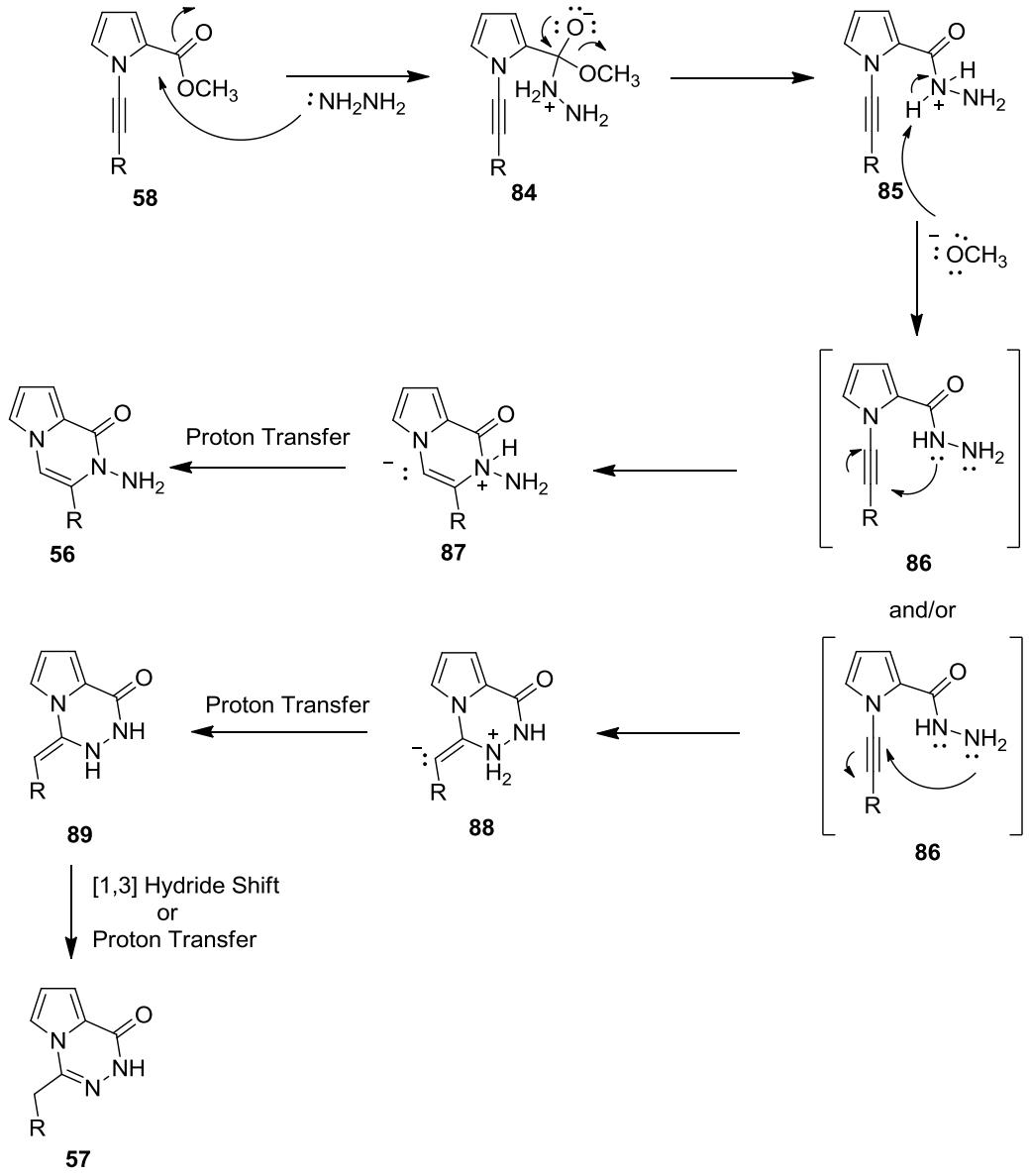
Table 4 Nucleophilic cyclization products of key compounds **73-75**

Adduct	Product	Isolated Yield
 **73**	 **81**	87%
 **74**	 **82**	90%
 **75**	 **83**	97%

2.3.1. Proposed reaction mechanism

All informations collected during characterization and derivatization of the nucleophilic cyclization products give us a rough draft of the reaction mechanism which is shown below (Scheme 27). Nucleophilic attack of hydrazine on carbonyl carbon of ester unit starts the reaction and leads methoxy group to leave the compound to form hydrazide **86** through the intermediates **84-85**. Anionic methoxy group takes

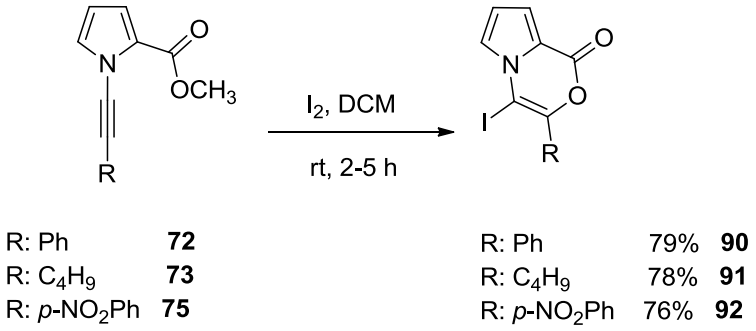
one proton from cationic hydrazide compound **85** to yield non-charged reaction intermediate **86**. Electronic properties of the susbstituents designate the fate of the reaction at this step. Intermediate undergoes either 6-*endo* or –*exo*-dig cyclizations to form corresponding products by attack of lone pair electrons of internal nitrogen or terminal nitrogen atoms respectively. 6-*endo*-dig cyclization follows only proton shift to yield pyrrolopyrazinone skeleton **56**, while 6-*exo*-dig follows first proton shift and then [1,3] hydride shift to afford pyrrolotriazinone moiety **57**.



Scheme 27. Proposed reaction mechanism of nucleophilic cyclization reaction

2.4. Electrophilic cyclization reactions of *N*-alkyne substituted methyl 1*H*-pyrrole-2-carboxylate derivatives via iodine

After completion of the nucleophilic cyclization reactions of the key compounds **72**-**75**, we desired to activate triple bond via iodine to synthesize pyrrolooxazinone derivatives via electrophilic intramolecular cyclization reaction. For this purpose, *N*-alkyne substituted methyl 1*H*-pyrrole-2-carboxylate derivatives **72**, **73**, **75** were treated with iodine in dichloromethane to yield corresponding pyrrolooxazinone derivatives **90**-**92** in yields of 76-79% (Scheme 28).



Scheme 28. Electrophilic cyclization reactions of key compounds **72**, **73**, **75**

Characterizations of the cyclization products **90**, **91**, **92** were done by ^{1}H-NMR, ^{13}C-NMR, IR and HRMS spectra. As we expected for compound **90**, proton signals observed in the ^{1}H-NMR spectrum where the pyrrole and phenyl protons were overlapped, which made difficult to determine the exact structure. Therefore, we recorded HMBC spectrum (Figure 10). A quaternary carbon resonance at 69.4 ppm was a proof for presence of an iodine attached sp^{2}-hybridized carbon atom, because iodine attached carbon atoms resonate at high fields due to heavy atom effect[45] (Figure 11).

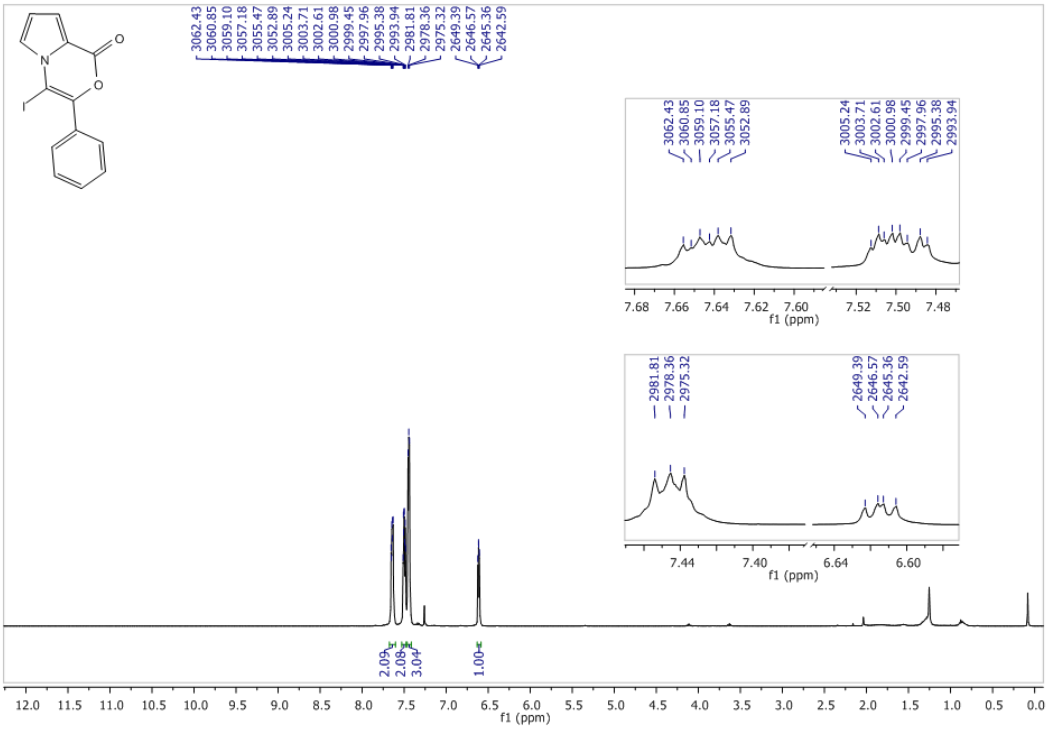


Figure 10 ^{1}H-NMR spectrum of compound **90** in $CDCl_3$

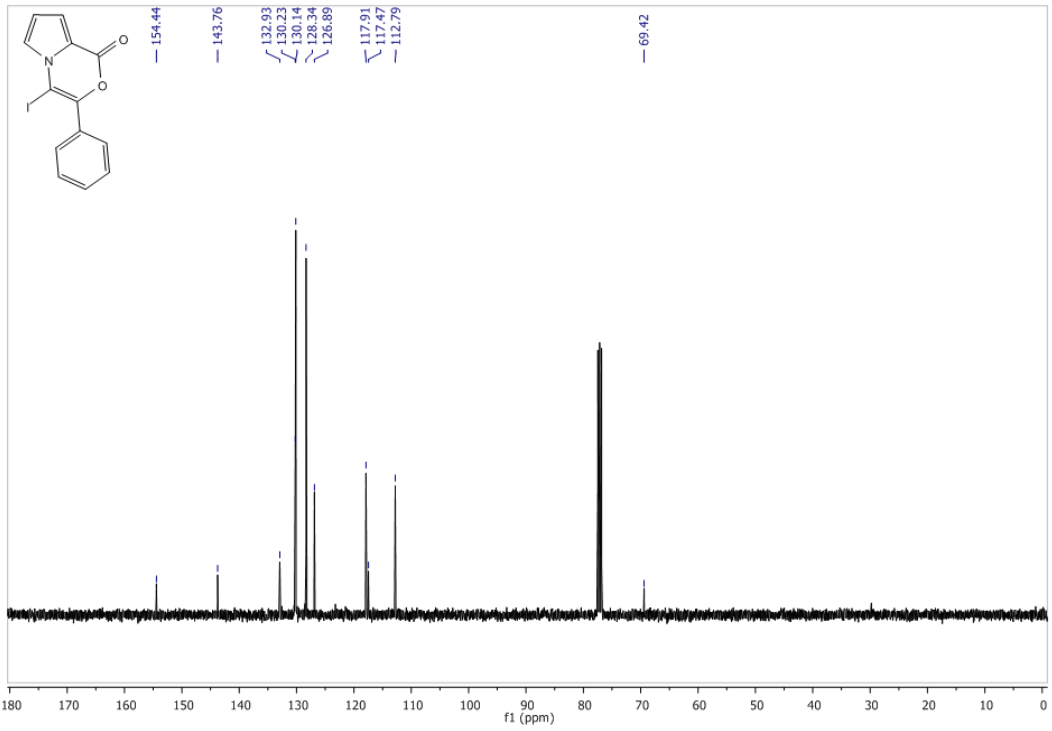


Figure 11 ^{13}C-NMR spectrum of compound **90** in $CDCl_3$

Although these were strong evidences for structure **90**, for a clear-cut differentiation between **90** other possible structures we carried out an X-ray analysis of the compound **90**, which clearly supported the proposed structure as shown in Figure 12.

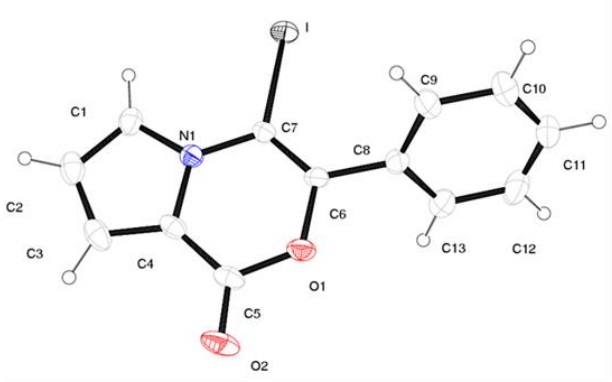
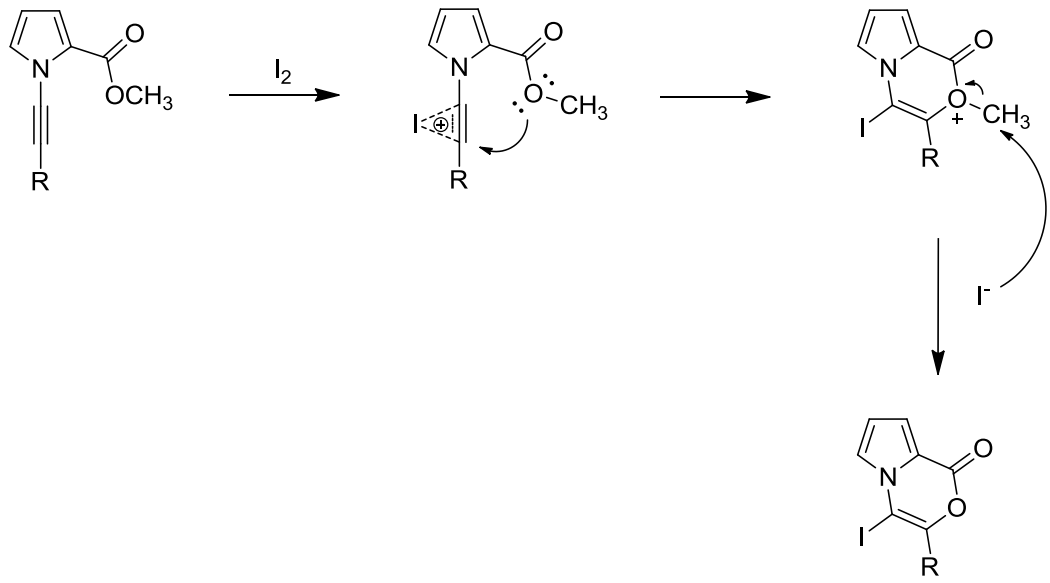


Figure 12 X-ray analysis of compound **90**

2.4.1. Proposed reaction mechanism



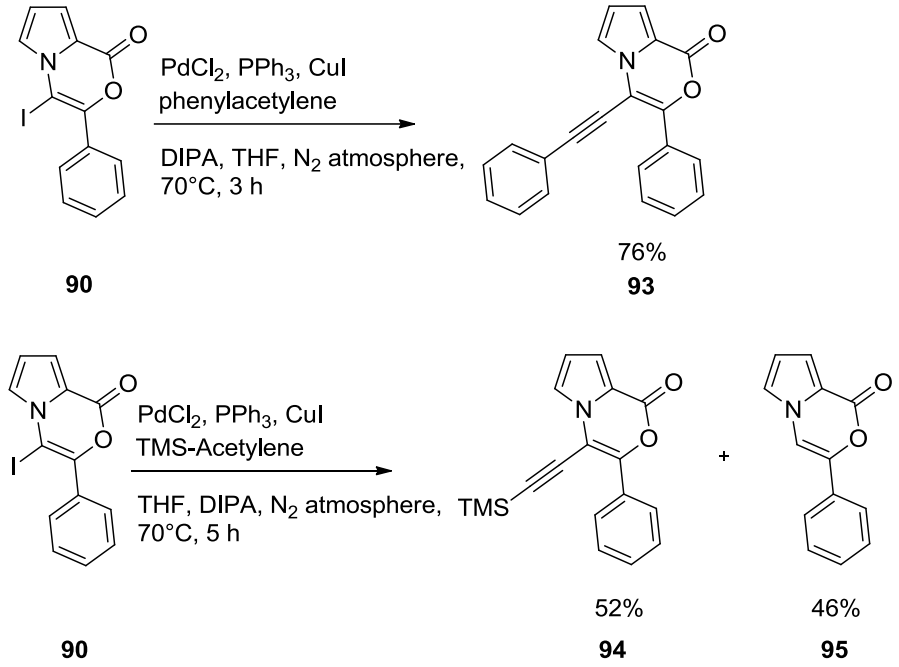
Scheme 29. Proposed reaction mechanism of electrophilic cyclization reaction

Iodine substituted products lead us to propose a plausable mechanism for this electrophilic cyclization reaction. In the beginning of the reaction iodine coordinates to alkyne unit to achieve π-activation. Lone pair electrons of methoxy oxygen attack on alkyne to yield 6-*endo*-dig cyclization product while iodine stays on the structure.

And iodide anion which is already existing in reaction media attacks protonated methoxy group and removes methyl group from structure to yield corresponding pyrrolooxazinone skeletons **90-92** (Scheme 29).

2.4.2. Derivatization of 4-iodo-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (90) via Sonogashira coupling reaction

After successful synthesis of 4-iodo-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (**90**), we decided to apply Sonogashira coupling reaction to attach another alkyne unit which may lead to further functionalization as well as cyclization reaction over phenyl ring. We used phenylacetylene and TMS-acetylene for coupling reactions and desired products **93** and **94** were obtained (Scheme 30). By using TMS-acetylene as the coupling product, we isolated a side product **95** which was known in literature.



Scheme 30. Sonogashira coupling reactions of 4-iodo-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (**90**)

Corresponding coupling products **93** and **94** were proved by ^{1}H-NMR, ^{13}C-NMR, IR and HRMS spectra. The ^{1}H-NMR spectrum of compound 93 showed 13 aromatic

proton resonances. The ^{13}C-NMR spectrum revealed the presence of 14 distinct sp^2-hybridized carbon resonances beside of one carbonyl and two alkyne carbon resonances. All this data were in agreement with the proposed structure and incorporation of alkyne unit into the molecule.

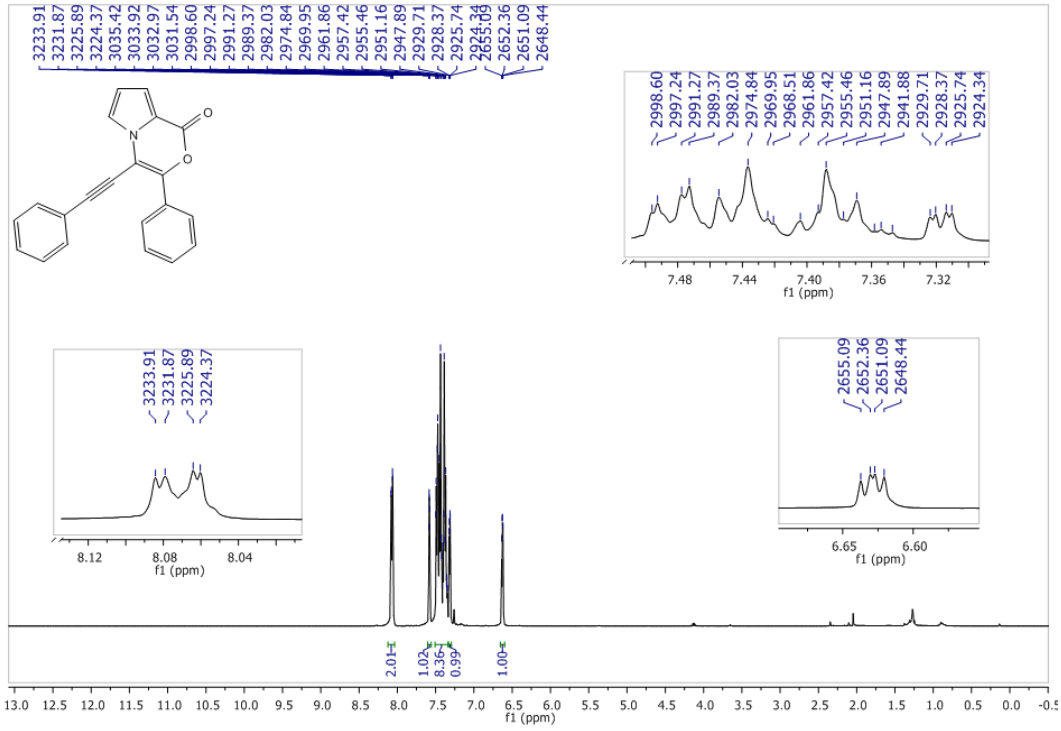


Figure 13 ^{1}H-NMR spectrum of compound **93** in $CDCl_3$

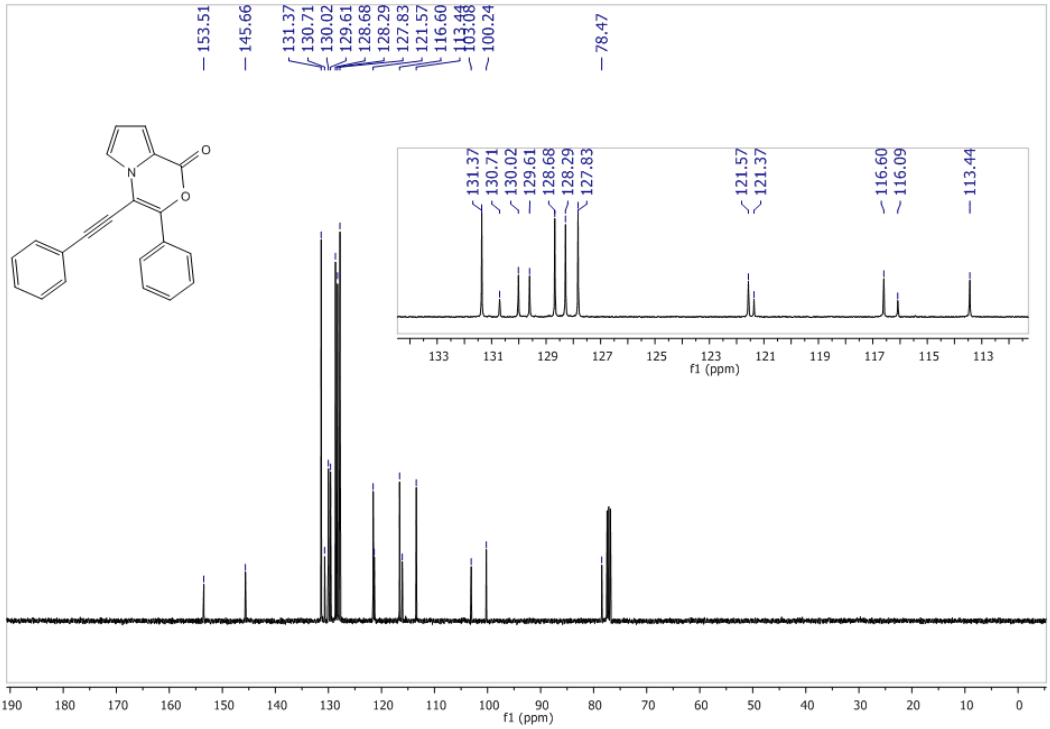
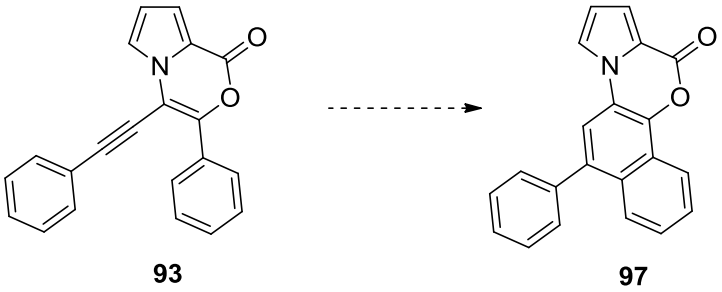


Figure 14 ^{13}C-NMR spectrum of compound **93** in $CDCl_3$

2.5. Further cyclization attempts of alkyne substituted 3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one derivative 93

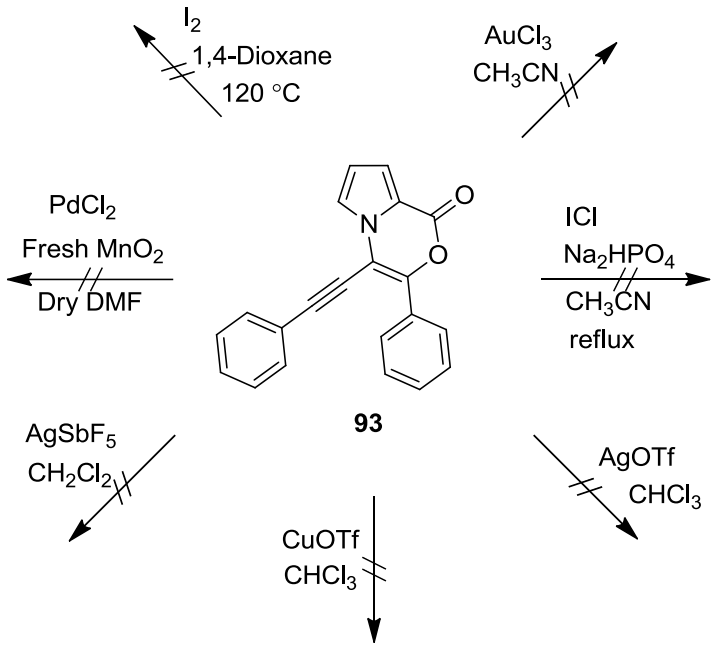
The idea of synthesis of naphthopyrrolooxazinone skeleton led us to try cyclization of 3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one derivative **93** (Scheme 31).



Scheme 31. The idea of further cyclization

We conducted reactions with different catalysts to achieve this challenge. Firstly, compound **93** was treated with $AuCl_3$ in acetonitrile which did not react in any way,

then ICl was used in the presence of Na_2HPO_4 that did not change the result. AgOTf and CuOTf were also tried separately which were also not successful for cyclization. Even they are used in literature for this type of annulations, $AgSbF_5$ or I_2 (at high temperature) did not help us to achieve our desired cyclization product. Treatment with $PdCl_2$ in the presence of freshly synthesized MnO_2 did not work for compound **93** (Scheme 32). This is unfortunate that we could not achieved this type of cyclization.



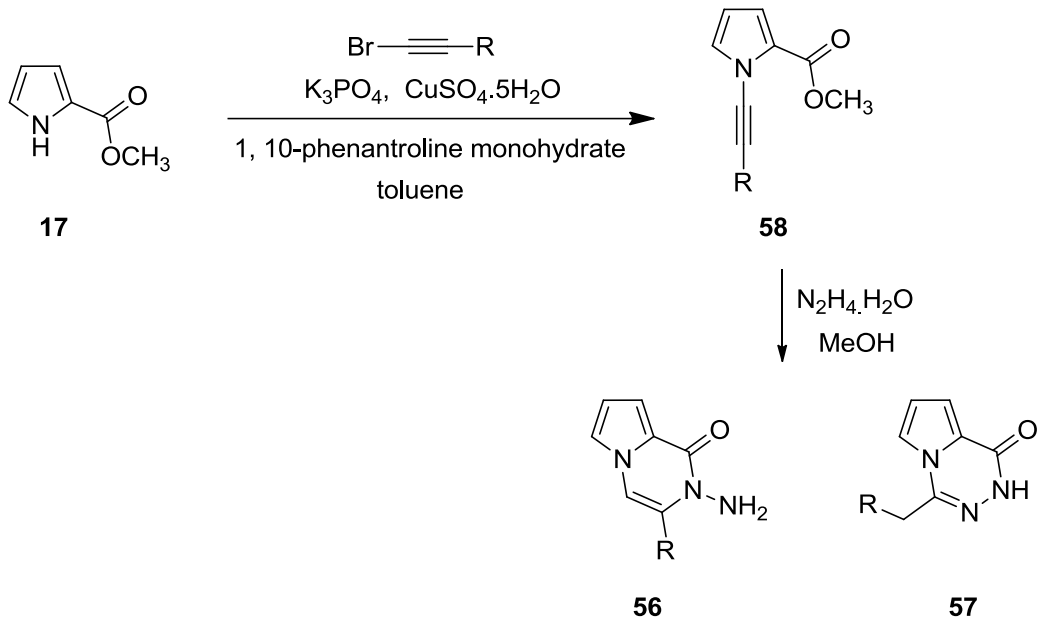
Scheme 32. Attempts to cyclize compound **93**

CHAPTER 3

CONCLUSION

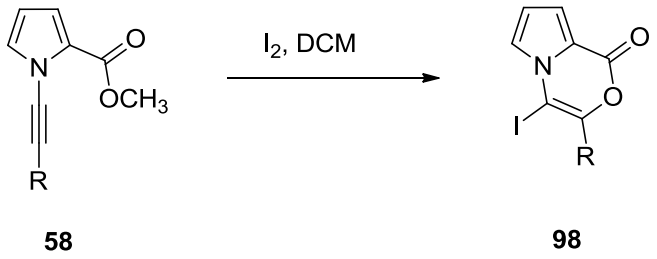
Pyrrolopyrazinone, triazinone and oxazinone moiety containing compounds have potent biological and pharmacological activities. Therefore, their synthesis have a great importance in chemical aspect. In our study, we synthesized these skeletons via low-cost and practical methods.

For the synthesis of pyrrolopyrazinone and triazinone derivatives, pyrrole ester **17** was first synthesized via literature methods. Then, copper catalyzed cross-coupling reaction was applied to ester **17** to achieve C-N bond formation with bromoalkynes. After isolation of coupling products which are our key compounds **58**, nucleophilic cyclization reaction via hydrazine monohydrate yielded pyrrolopyrazinone and/or triazinone products **56**, **57**. For this reaction, electronic effects of substituents designate formation of either one of the products **56**, **57** or both. In aryl derivatives, mesomerically electron donating groups led to formation of *N*-amino pyrazinone derivative **56** while electron withdrawing groups yielded triazinone derivative **57**. Formation of both products can occur when the electropositivities of alkyne carbons are close to each other. Combination of all these information let us to propose a plausable mechanism for this reaction.



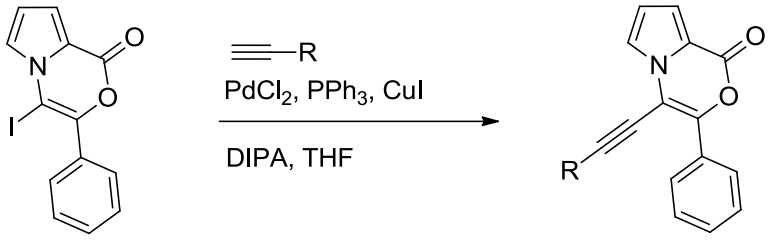
Scheme 33. Nucleophilic cyclization reaction via hydrazine monohydrate

Additionally, electrophilic cyclization reactions of key compounds **58** were achieved via alkyne activation. Iodine was used for this purpose. 6-*endo*-dig cyclization products, iodine containing pyrrolooxazinone derivatives **98** were synthesized and isolated successfully. A reasonable mechanism was also stated for this study.



Scheme 34. Electrophilic cyclization reaction via iodine

Further functionalizations of the compound **90** were achieved via Sonogashira coupling reactions with phenylacetylene and TMS-acetylene to replace iodine with alkyne derivatives **99**.



90 **99**

Scheme 35. Further functionalizations of compound **90**

CHAPTER 4

EXPERIMENTAL SECTION

4.1.General Methods

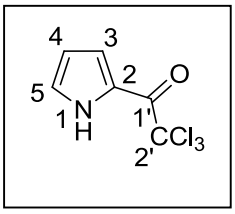
1H NMR spectra were recorded on Bruker Instrument Avance Series with 400 MHz in solvents DMSO-d6 or CDCl3 and chemical shifts (δ) were reported in units of parts per million (ppm) with internal standart of TMS. 13C-NMR spectra were recorded on the same instrument with 100 MHz and chemical shifts (δ) were reported in ppm. HRMS spectra were recorded by LC/MS Q-TOF with electrospray ionization method. ATR diamond FT-IR was used for recording infrared spectra with the band locations between 4000 and 6000 cm-1.

Column chromatography methodologies were applied on Merck silica gel (60-mesh with 0.063-0.200 mm particle sizes). TLC was applied on 0.25 mm Merck silica gel aluminum plates. Uncorrected melting points were recorded via Gallenkamp variable heater. All reagents were used without further purification since purchased from suppliers. Solvents were evaporated on rotary vacuum.

4.2.Synthesis of 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone (60)[37]

To a solution of trichloroacetyl chloride (14.3 g, 78.6 mmol) in dry diethyl ether (20 mL), pyrrole (**1**) (4.80 g, 71.6 mmol) was added over 1 h. The reaction mixture was stirred for an additional hour at room temperature, and then the reaction mixture was neutralized with an aqueous potassium carbonate solution (6.10 g, 44.1 mmol in 20 mL water). Then the extraction was performed with diethyl ether (3 × 25 mL) and the organic phase was dried over Na_2SO_4. After the filtration and evaporation of the solvent, the crude product was purified via column chromatography (SiO_2, ethyl

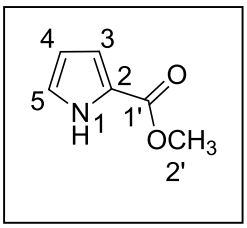
acetate/n-hexane, 1:7) and concentrated in vacuum to obtain 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone (**60**) (13.52 g, 89% isolated yield) and recrystallized as colorless needles from ethyl acetate/n-hexane. Mp. 74.8-76.4 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.60 (bs, 1H, N-H), 7.39 (ddd, J = 3.7, 2.4, 1.1 Hz, 1H, H-4), 7.19-7.16 (m, 1H, arom.), 6.41–6.37 (m, 1H, arom.); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.4, 127.3, 123.1, 121.3, 112.0, 95.1.

4.3.Synthesis of methyl 1H-pyrrole-2-carboxylate (17)[37]

In dry methanol (40 mL), sodium (0.14 g, 6.20 mmol) was dissolved and trichloroacetyl-1*H*-pyrrole (**60**) (9.440 g, 44.43 mmol) was added in small quantities over 30 min. Then the reaction mixture was stirred for additional 2 hours at room temperature, and then the solvent was removed and resulting crystals were dissolved in diethyl ether (50 mL). Ether solution was washed with HCl (4 mL, 3N) & $NaHCO_3$ (10 mL) solution. Then the organic phase was dried over Na_2SO_4. After the filtration and evaporation of the solvent, the crude product was purified via column chromatography (SiO_2, ethyl acetate/hexane, 2:3) and concentrated in vacuum to obtain methyl 1*H*-pyrrole-2-carboxylate (**17**) (4.83 g, 87% isolated yield) and recrystallized as colorless pellets from ethyl acetate/hexane. Mp. 71.9-72.7 °C.

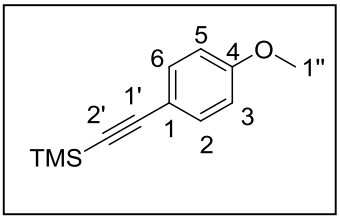


^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.74 (bs, 1H, N-H), 6.97 (ddd, J = 4.1, 2.7, 1.5 Hz, 1H, H-4), 6.95-6.91 (m, 1H, arom.), 6.31-6-21 (m, 1H, arom.), 3.86 (s, 3H, -OCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.0, 123.3, 122.6, 115.5, 110.4, 51.5.

4.4.Synthesis of [(4-methoxyphenyl)ethynyl]trimethylsilane (62)[39]

To a solution of $PdCl_2$ (30.00 mg, 0.171 mmol), PPh_3 (90.00 mg, 0.342 mmol), CuI (16.00 mg, 0.085 mmol), in triethylamine (30 mL) was added 4-iodoanisole **61** (1.00 g, 4.27 mmol) under N_2 atmosphere, the mixture was stirred for 10 minutes and trimethylsilylacetylene (0.839 g, 8.540 mmol) was added. Then, the reaction mixture

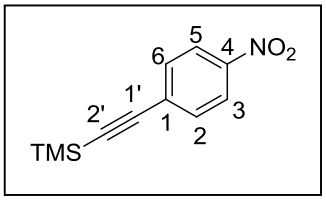
was stirred at 80 °C for 3 hours. After completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated in vacuum. The resulting crude mixture was eluted through a SiO_2 column (ethylacetate/hexane, 1:10) and concentrated in vacuum to obtain [(4-methoxyphenyl)ethynyl]trimethylsilane (**62**) (0.768 g, 88% isolated yield) as a yellowish liquid.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.9 Hz, 2H, arom.), 6.82 (d, J = 8.9 Hz, 2H, arom.), 3.80 (s, 3H, -CH_3), 0.24 (s, 9H, TMS); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.9, 133.6, 115.4, 113.9, 105.3, 92.6, 55.4, 0.2.

4.5.Synthesis of [(4-nitrophenyl)ethynyl]trimethylsilane (64)[39]

To a solution of $PdCl_2$ (29.00 mg, 0.163 mmol), PPh_3 (85.00 mg, 0.326 mmol), CuI (15.00 mg, 0.082 mmol), in triethylamine (30 mL) was added 1-iodo-4-nitrobenzene (**63**) (2.036 g, 8.176 mmol) under N_2 atmosphere, the mixture was stirred for 10 minutes and then trimethylsilylacetylene (0.964 g, 9.815 mmol) was added. The reaction mixture was stirred at 80 °C for 4 h. After completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated in vacuum. The resulting crude mixture was elueted through a SiO_2 column (ethylacetate/hexane, 1:10) and concentrated in vacuum to obtain [(4-nitrophenyl)ethynyl]trimethylsilane (**64**) (1.614 g, 90% isolated yield) and recrystallized as yellowish solid from chloroform. Mp. 98-99 °C.[46]

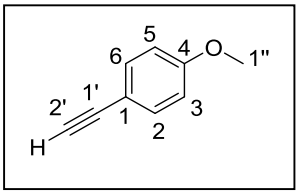


^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.9 Hz, 2H, arom.), 7.59 (d, J = 8.9 Hz, arom.), 0.27 (s, 9H, TMS); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.3, 132.8, 130.1, 123.6, 102.8, 100.8, -0.2.

4.6.Synthesis of 1-ethynyl-4-methoxybenzene (65)[40]

To a solution of MeOH/$CHCl_3$ (30 mL, 1:1) was added ((4-methoxyphenyl)ethynyl)trimethylsilane (**62**) (0.768 g, 3.760 mmol) and then K_2CO_3

(0.624 g, 4.510 mmol). The reaction mixture was stirred at room temperature for an hour. After completion of the reaction, the reaction mixture was concentrated in vacuum. The residue was diluted with EtOAc (50 mL) and washed with HCl (4N, 40 mL) then with brine (3 × 40 mL). The resulting crude mixture was eluted through a SiO_2 column (hexane) and concentrated in vacuum to obtain 1-ethynyl-4-methoxybenzene (**65**) (0.487 g, 98% isolated yield) as a colorless oil.



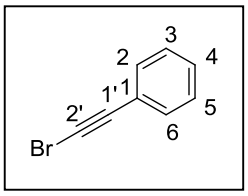
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.6 Hz, 2H, arom.), 6.85 (d, J = 8.6 Hz, 2H, arom.), 3.81 (s, 3H, O-CH_3), 3.01 (s, 1H, H-2'); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.1, 133.7, 114.3, 114.1, 83.8, 75.9, 55.4.

4.7.General procedure for synthesis of bromoalkyne derivatives

To a solution of terminal alkyne derivatives (1.0 eq.) in acetone (30 mL) were added NBS (1.1 eq.) and $AgNO_3$ (0.1 eq.) and the resulting mixture was stirred at room temperature for 4 hours. After completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated in vacuum. Then, the resulting crude mixture was added to distilled water (20 mL) and extracted with diethyl ether (3 × 25 mL) and washed with brine. Then the organic phase was dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified via column chromatography (SiO_2, hexane) and concentrated in vacuum to obtain bromoalkyne derivatives**.**

4.7.1. Synthesis of (bromoethynyl)benzene (67)[41]

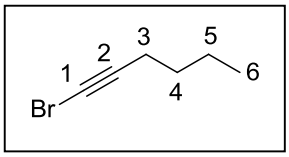
A solution of phenylacetylene (**66**) (0.58 g, 5.68 mmol) in acetone (30 mL) were treated with NBS (1.11 g, 6.25 mmol) in the presence of $AgNO_3$ (0.11 g 0.57 mmol) as described above to obtain (bromoethynyl)benzene (**67**) (1.01 g, 98% isolated yield) as a yellowish liquid.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50–7.41 (m, 2H, arom.), 7.37–7.28 (m, 3H, arom.); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 132.1, 128.8, 128.5, 122.8, 80.2, 49.9.

4.7.2. Synthesis of 1-bromohex-1-yne (69)[47]

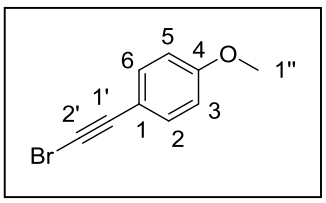
A solution of 1-hexyne (**68**) (3.50 g, 42.6 mmol) in acetone (150 mL) were added $AgNO_3$ (0.84 g 4.30 mmol) and stirred for 5 minutes. To the resulting mixture was added NBS (9.09 g, 51.1 mmol) and stirred at room temperature for 90 min and 1-bromohex-1-yne (**69**) (6.38 g, 39.6 g, 93% crude yield) was obtained as a colorless liquid as described above.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.20 (t, J = 7.1 Hz, 2H, H-3), 1.54-1.44 (m, 2H, H-4), 1.44-1.34 (m, 2H, H-5), 0.91 (t, J = 7.1 Hz, 3H, H-6); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 80.5, 37.5, 30.5, 22.0, 19.5, 13.6.

4.7.3. Synthesis of 1-(bromoethynyl)-4-methoxybenzene (70)[39]

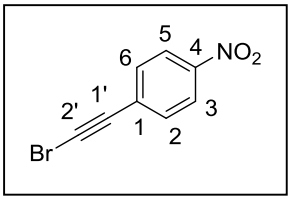
A solution of 1-ethynyl-4-methoxybenzene (**65**) (0.51 g, 3.86 mmol) in acetone (30 mL) were treated with NBS (0.76 g, 4.25 mmol) in the presence of $AgNO_3$ (0.065 g 0.386 mmol) as described above to obtain 1-(bromoethynyl)-4-methoxybenzene (**70**) (0.72 g, 89% isolated yield) as a yellowish oil.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.62-7.47 (m, 2H, arom.), 6.76 – 6.60 (m, 2H, arom.), 3.78 (s, 3H, O-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.6, 138.3, 133.6, 116.5, 82.8, 55.4, 29.8.

4.7.4. Synthesis of 1-(bromoethynyl)-4-nitrobenzene (71)[42]

To a solution of [(4-nitrophenyl)ethynyl]trimethylsilane (**64**) (0.654 g, 2.980 mmol) in acetone (30 mL) were added $AgNO_3$ (0.151 g 0.890 mmol) and NBS (0.637 g, 3.580 mmol), then the resulting mixture was stirred at room temperature in the dark for 2 hours. After completion of the reaction, the reaction mixture was concentrated in vacuum. Then, the resulting crude mixture was purified via column chromatography (SiO_2, DCM:hexane, 2:3) and concentrated in vacuum to obtain 1-(bromoethynyl)-4-nitrobenzene (**71**) (0.658 g, 98% isolated yield) as a light yellowish solid. Mp. 165-166 °C.[48]



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.8 Hz, 2H, arom.), 7.59 (d, J = 8.8 Hz, 2H, arom.); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.5, 133.0, 129.6, 123.7, 78.6, 56.5.

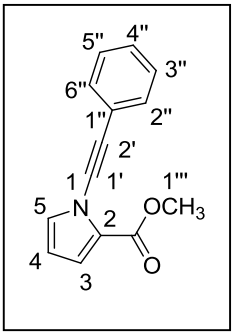
4.8. General procedure for *N*-alkyne substituted methyl 1*H*-pyrrole-2-carboxylate derivatives

To a solution of bromoalkyne derivatives (1.1 eq.) in freshly distilled anhydrous toluene (20 mL), methyl 1*H*-pyrrole-2-carboxylate (**17**) (1.0 eq.), K_3PO_4 (2 eq.), $CuSO_4.5H_2O$ (0.1 eq.) and 1,10-phenanthroline monohydrate (0.2 eq.) were added under N_2 atmosphere. The reaction mixture was heated to 85 °C and stirred for 48 h. Then, the reaction mixture was cooled to room temperature and diluted with DCM (30 mL). The resulting mixture was filtered through celite and filtrate was concentrated in vacuum. Then, the crude product was purified via column chromatography (SiO_2, hexane) to obtain *N*-alkyne substituted methyl 1*H*-pyrrole-2-carboxylate derivatives.

4.8.1. Synthesis of methyl 1-(phenylethynyl)-1*H*-pyrrole-2-carboxylate (72)

To a solution of (bromoethynyl)benzene (**67**) (0.91 g, 5.02 mmol) in freshly distilled anhydrous toluene (20 mL), methyl 1*H*-pyrrole-2-carboxylate (**17**) (0.57 g, 4.56

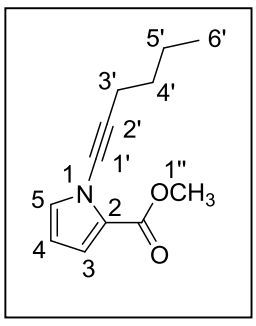
mmol), K_3PO_4 (1.94 g, 9.12 mmol), $CuSO_4.5H_2O$ (0.11 g, 0.46 mmol) and 1,10-phenanthroline monohydrate (0.18 g, 0.91 mmol) were added and the resulting mixture was reacted as described above to obtain methyl 1-(phenylethynyl)-1*H*-pyrrole-2-carboxylate (**72**) (0.61 g, 80% isolated yield based on 74% conversion) as a yellowish liquid.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61-7.47 (m, 2H, arom.), 7.39-7.29 (m, 3H, arom.), 7.18-7.10 (m, 1H, arom.), 7.00 (dd, J = 3.9, 1.6 Hz, 1H, H-3), 6.28-6.22 (m, 1H, arom.), 3.88 (s, 3H, -OCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.1, 131.6, 131.4, 128.5, 128.4, 125.8, 122.3, 118.6, 110.8, 81.4, 69.7, 51.6; IR (ATR) 2259, 1719, 1458, 1438, 1360, 1264, 1168, 1100, 1069, 751, 733, 689; HRMS Calculated for $C_{14}H_{11}NO_2$ $[M+H]^+$: 226.08626. Found: 226.08840.

4.8.2. Synthesis of methyl 1-(hex-1-yn-1-yl)-1*H*-pyrrole-2-carboxylate (73)

To a solution of 1-bromohex-1-yne (**69**) (1.23 g, 7.65 mmol) in freshly distilled anhydrous toluene (30 mL), methyl 1*H*-pyrrole-2-carboxylate (**17**) (0.87 g, 6.95 mmol), K_3PO_4 (2.95 g, 13.9 mmol), $CuSO_4.5H_2O$ (0.17 g, 0.69 mmol) and 1,10-phenantroline monohydrate (0.27 g, 1.39 mmol) were added and the resulting mixture was reacted as described above to obtain methyl 1-(hex-1-yn-1-yl)-1*H*-pyrrole-2-carboxylate (**73**) (0.83 g, 92% isolated yield based on 63% conversion) as a colorless liquid.

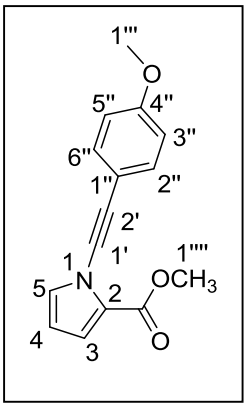


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, J = 2.8, 1.7 Hz, 1H, H-5), 6.90 (dd, J = 3.9, 1.7 Hz, 1H, H-3), 6.16 (dd, J = 3.9, 2.8 Hz, 1H, H-4), 3.84 (s, 3H, 0-CH_3), 2.41 (t, J = 7.2 Hz, 2H, H-3'), 1.60 (q, J = 7.2 Hz, 2H, H-4'), 1.48 (h, J = 7.2 Hz, 2H, H-5'), 0.94 (t, J = 7.3 Hz, 3H, H-6'); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.3, 131.8, 125.5, 118.0, 110.0, 72.6, 69.7, 51.5, 30.9, 22.1,

18.2, 13.7; IR (ATR) 2955, 2872, 2273, 1720, 1542, 1464, 1438, 1416, 1197, 1105, 926, 732, 601; HRMS Calculated for $C_{12}H_{15}NO_2$ $[M+H]^+$: 206.11756. Found: 206.11960.

4.8.3. Synthesis of methyl 1-[(4-methoxyphenyl)ethynyl]-1*H*-pyrrole-2-carboxylate (74)

To a solution of 1-(bromoethynyl)-4-methoxybenzene (**70**) (0.272 g, 1.290 mmol) in freshly distilled anhydrous toluene (20 mL), methyl 1*H*-pyrrole-2-carboxylate (**17**) (0.147 g, 1.170 mmol), K_3PO_4 (0.497 g, 2.340 mmol), $CuSO_4.5H_2O$ (0.030 g, 0.120 mmol) and 1,10-phenantroline monohydrate (0.045 g, 0.230 mmol) were added and the mixture was reacted as described above. Then, the crude product was purified via column chromatography (SiO_2, hexane/EtOAc, 20:1) to obtain methyl 1-[(4-methoxyphenyl)ethynyl]-1H-pyrrole-2-carboxylate (**74**) (0.033 g, 92% isolated yield based on 12% conversion) as a yellowish liquid.

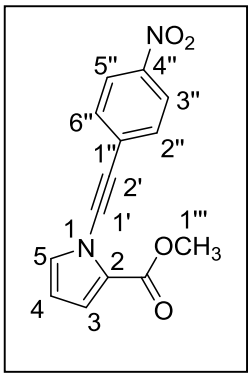


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52-7.43 (m, 2H, arom.), 7.12 (dd, J = 2.8, 1.7 Hz, 1H, H-5), 6.98 (dd, J = 3.9, 1.7 Hz, 1H, H-3), 6.90-6.83 (m, 2H, arom.), 6.24 (dd, J = 3.9, 2.8 Hz, 1H, H-4), 3.86 (s, 3H, O-CH_3), 3.81 (s, 3H, O-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.2, 159.8, 133.3, 131.4, 125.7, 118.5, 114.3, 114.1, 110.6, 80.2, 69.5, 55.4, 51.6; IR (ATR) 2951, 2257, 1719, 1605, 1543, 1515, 1458, 1438, 1416, 1361, 1334, 1265, 1246, 1179, 1168, 1100, 1069, 1027, 948, 830, 735, 598, 583; HRMS Calculated for $C_{14}H_{11}NO_2$ $[M+H]^+$: 256.09682. Found: 256.09730.

4.8.4. Synthesis of methyl 1-[(4-nitrophenyl)ethynyl]-1*H*-pyrrole-2-carboxylate (75)

To a solution of 1-(bromoethynyl)-4-nitrobenzene (**71**) (0.658 g, 2.910 mmol) in freshly distilled anhydrous toluene (40 mL), methyl 1*H*-pyrrole-2-carboxylate (**17**) (0.330 g, 2.640 mmol), K_3PO_4 (1.121 g, 5.280 mmol), $CuSO_4.5H_2O$ (0.065 g, 0.260 mmol) and 1,10-phenantroline monohydrate (0.105 g, 0.530 mmol) were added and

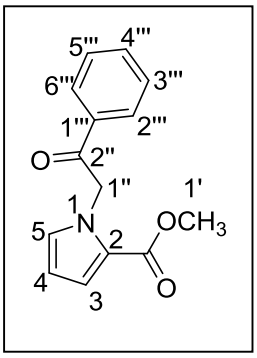
reacted as described above. Then, the crude product was purified via column chromatography (SiO_2, hexane/EtOAc, 20:1) to obtain methyl 1-[(4-nitrophenyl)ethynyl]-1H-pyrrole-2-carboxylate (**75**) (0.394 g, 92% isolated yield) and recrystallized as yellowish needle from chloroform. Mp. 103-104 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.9 Hz, 2H, arom.), 7.67 (d, J = 8.9 Hz, 2H, arom.), 7.16 (dd, J = 2.9, 1.6 Hz, 1H, H-5), 7.02 (dd, J = 3.8, 1.6 Hz, 1H, H-3), 6.31 (dd, J = 3.8, 2.9 Hz, 1H, H-4), 3.89 (s, 3H, O-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.0, 147.0, 131.9, 131.2, 129.6, 126.1, 123.8, 119.3, 111.6, 86.4, 68.9, 51.8; IR (ATR) 3135, 3107, 2259, 1717, 1594, 1512, 1456, 1440, 1420, 1338, 1265, 1188, 1170, 1100, 1071, 943, 852, 754, 743, 686, 593, 517; HRMS Calculated for $C_{14}H_{10}N_2O_4$ $[M+H]^+$: 271.07133. Found: 271.07200.

4.9.Synthesis of methyl 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carboxylate (76)

To a solution of K_2CO_3 (0.246 g, 1.780 mmol) in water (15 mL) was added a solution of methyl 1-(phenylethynyl)-1*H*-pyrrole-2-carboxylate (**72**) (0.250 g, 1.110 mmol) in MeOH (15 mL) and the reaction mixture was stirred at room temperature overnight. Then HCl (25 mL, 3N) was added to the reaction mixture and extracted with EtOAc (3 × 25 mL) and the combined organic phase was washed with brine. Resulting mixture was dried over Na_2SO_4 and concentrated in vacuum. Then, the product was elueted over SiO_2 (hexane) and concentrated in vacuum to obtain methyl 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carboxylate (**76**) (0.182 g, 0.748 mmol, 96% isolated yield) and recrystallized as white needles from chloroform. Mp. 109-110 °C.[44]



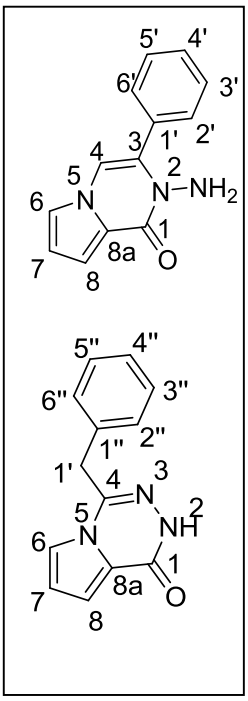
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.5 Hz, 2H, arom.), 7.62 (t, J = 7.5 Hz, 1H, H-4’’’), 7.51 (t, J = 7.5 Hz, 2H, arom.), 7.10-7.00 (m, 1H, arom.), 6.85 (s, 1H, arom.), 6.26 (dd, J = 3.5, 2.5 Hz, 1H, H-4), 5.76 (s, 2H, H-1’’), 3.72 (s, 3H, H-1’); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.5, 161.9, 135.0, 133.7, 129.9, 129.0, 128.1, 122.3, 118.4, 108.9, 55.2, 51.2.

4.10. General procedure for nucleophilic cyclization reactions of *N*-alkyne substituted methyl 1*H*-pyrrole-2-carboxylate derivatives via hydrazine monohydrate

To a solution of *N*-alkyne substituted methyl 1H-pyrrole-2-carboxylate derivatives **72-75** (1.0 eq.) in dry MeOH (15 mL), hydrazine monohydrate (10 eq.) was added under N_2 atmosphere. The reaction mixture was stirred at reflux Temperature for 24 h. After completion of the reaction, water (20 mL) was added to the reaction mixture. Then, MeOH was removed from the resulting mixture in vacuum. Residue was extracted with ethyl acetate (3 × 25 mL) and organic phase was concentrated in vacuum. The resulting crude mixture was separated gradiently via column chromatography (SiO_2, ethyl acetate/hexane, 1:4 to 1:1) and concentrated in vacuum to obtain corresponding pyrrolopyrazinone and/or pyrrolotriazinone derivatives.

4.10.1. Synthesis of 2-amino-3-phenylpyrrolo[1,2-a]pyrazin-1-(2*H*)-one (77) and 4-benzylpyrrolo[1,2-*d*][1,2,4]triazin-1(2*H*)-one (78)

Methyl 1-(phenylethynyl)-1*H*-pyrrole-2-carboxylate (**72**) (0.32 g, 1.42 mmol) in dry MeOH (15 mL) reacted with hydrazine monohydrate (0.71 g, 14.2 mmol) as described above to obtain 2-amino-3-phenylpyrrolo[1,2-*a*]pyrazin-1-(2*H*)-one (**77**) (0.21g, 67% isolated yield) as colorless cubics from ethyl acetate (Mp. 167-168 °C) and 4-benzylpyrrolo[1,2-*d*][1,2,4]triazin-1(2*H*)-one (**78**) (0.077 g, 24% isolated yield) and recrystallized as white needles from chloroform. Mp. 199-200 °C.

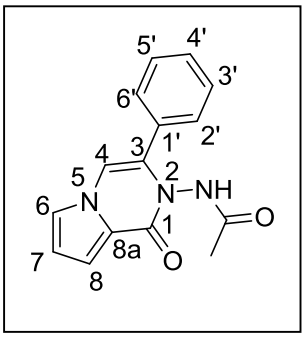


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.51-7.47 (m, 2H, arom.), 7.47-7.42 (m, 3H, arom.), 7.14 (d, J = 4.0 Hz, 1H, H-8), 7.12 (dd, J = 2.5, 1.5 Hz, 1H, H-6), 6.94 (s, 1H, H-4), 6.61 (dd, J = 4.0, 2.5 Hz, 1H, H-7), 4.41 (bs, 2H, NH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.3, 132.3, 130.8, 129.8, 129.0, 128.3, 123.1, 118.6, 113.2, 110.4, 107.4; IR (ATR) 3297, 3097, 1664, 1630, 1430, 1376, 1347, 1294, 1184, 1009, 753, 732, 697, 627; HRMS Calculated for $C_{13}H_{11}N_3O$ $[M+H]^+$: 226.09749. Found: 226.09990.

^{1}H-NMR (400 MHz, DMSO) δ 11.78 (s, 1H, N-H), 7.72-7.46 (m, 1H, arom.), 7.34 (dt, J = 15.2, 7.6 Hz, 4H, arom.), 7.24 (t, J = 6.9 Hz, 1H, H-4'), 7.03 (d, J = 3.7 Hz, 1H, H-8.), 6.82-6.53 (m, 1H, arom.), 4.26 (s, 2H, H-1'); ^{13}C-NMR (100 MHz, DMSO) δ 154.3, 137.2, 135.2, 128.8, 128.6, 126.9, 123.5, 118.1, 114.1, 110.5, 35.9; IR (ATR) 3668, 3170, 3120, 2987, 2902, 1644, 1554, 1455, 1415, 1380, 1072, 846, 803, 695, 642, 598; HRMS Calculated for $C_{13}H_{11}N_3O$ $[M+H]^+$: 226.09749. Found: 226.09760.

4.10.2. *N*-(1-oxo-3-phenylpyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)acetamide (79)

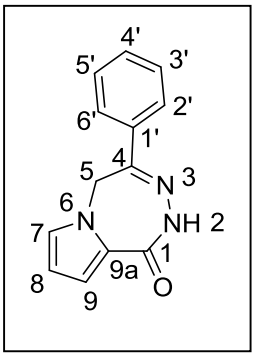
2-Amino-3-phenylpyrrolo[1,2-*a*]pyrazin-1-(2*H*)-one (**77**) (0.200 g, 0.888 mmol) was dissolved in pyridine (5 mL) and then acetic anhydride (0.136 g, 1.332 mmol) was added at room temperature. The reaction mixture was stirred over 2 days, and then HCl (10 mL, 3N) was added to the reaction mixture and extracted with EtOAc (3 × 20 mL) and washed with brine. Resulting mixture was dried over Na_2SO_4 and concentrated in vacuum. Then, the product was elueted over SiO_2 (ethyl acetate/hexane, 1:3) and concentrated in vacuum to obtain methyl *N*-(1-oxo-3-phenylpyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)acetamide (**79**) (0.229 g, 0.856 mmol, 97% isolated yield) and recrystallized as snowflakes from chloroform. Mp. 169.7-170.5 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H, NH), 7.51-7.35 (m, 5H, arom.), 7.18 (d, J = 3.8 Hz, 1H, H-8), 7.13 (dd, J = 2.4, 1.5 Hz, 1H, H-6), 6.94 (s, 1H, H-4), 6.59 (dd, J = 3.8, 2.4 Hz, 1H, H-7), 1.89 (s, 3H, -CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.1, 155.9, 131.5, 131.4, 129.5, 129.3, 128.4, 123.0, 119.9, 113.4, 112.5, 108.0, 20.6; IR (ATR) 3367, 2971, 1473, 1373, 1341, 1315, 1281, 1081, 1040, 774, 722, 710, 632, 546; HRMS Calculated for $C_{15}H_{13}N_3O_2$ $[M+H]^+$: 268.10805. Found: 268.11080.

4.10.3. Synthesis of 4-phenyl-2,5-dihydro-1*H*-pyrrolo[2,1-*d*][1,2,5]triazepin-1-one (80)

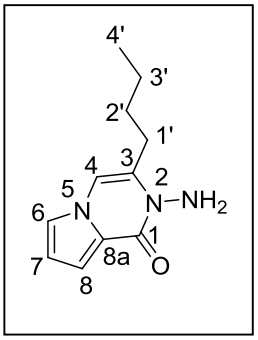
To a solution of methyl 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carboxylate (**76**) (0.127 g, 0.522 mmol) in dry MeOH (10 mL), hydrazine monohydrate (0.261 g, 5.220 mmol) was added under N_2 atmosphere. The reaction mixture was stirred at reflux temperature for 24 h, then water (20 mL) was added. The solvent was removed from the resulting mixture in vacuum. Residue was extracted with ethyl acetate (3 × 20 mL) and organic phase was concentrated in vacuum. The resulting crude mixture was separated gradiently via column chromatography (SiO_2, ethyl acetate/hexane, 1:4 to 1:1) and concentrated in vacuum to obtain methyl 4-phenyl-2,5-dihydro-1*H*-pyrrolo[2,1-*d*][1,2,5]triazepin-1-one (**80**) (0.032 g, 0.142 mmol, 57% isolated yield) and recrystallized as white solids from chloroform. Mp. 224-225 °C.



^{1}H-NMR (400 MHz, DMSO) δ 10.89 (s, 1H, NH), 7.95-7.87 (m, 2H, arom.), 7.51-7.43 (m, 3H, arom.), 7.34-7.27 (m, 1H), 6.82 (dd, J = 3.8, 1.7 Hz, 1H, H-9), 6.22 (dd, J = 3.8, 2.5 Hz, 1H, H-8), 5.28 (s, 2H, H-5); ^{13}C-NMR (100 MHz, DMSO) δ 159.7, 155.1, 134.7, 130.5, 129.0, 126.7, 126.4, 125.0, 115.7, 109.7, 44.9; (ATR) 3206, 3069, 2929, 1634, 1604, 1537, 1409, 1372, 1347, 1307, 1179, 1074, 1023, 875, 831, 816, 749, 735, 687, 626, 577; HRMS Calculated for $C_{13}H_{11}N_3O$ $[M+H]^+$: 226.09749. Found: 226.09850.

4.10.4. Synthesis of 2-amino-3-butylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (81)

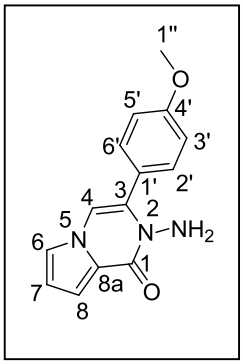
Methyl 1-(hex-1-yn-1-yl)-1*H*-pyrrole-2-carboxylate (**73**) (0.30 g, 1.46 mmol) in dry MeOH (15 mL) was reacted with hydrazine monohydrate (0.73 g, 14.6 mmol) as described above to obtain 2-amino-3-butylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (**81**) (0.26g, 87% isolated yield) and recrystallized as colorless needles from chloroform. Mp. 119-120 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.09-6.93 (m, 2H, arom.), 6.71 (s, 1H, H-4), 6.52-6.46 (m, 1H, arom.), 4.54 (s, 2H, NH_2), 2.59 (t, J = 7.4 Hz, 2H, H-1'), 1.58 (q, J = 7.4 Hz, 2H, H-2'), 1.40 (h, J = 7.4 Hz, 2H, H-3'), 0.93 (t, J = 7.4 Hz, 3H, H-4'); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.8, 130.7, 122.9, 117.7, 112.3, 109.5, 104.8, 30.7, 29.5, 22.3, 13.9; IR (ATR) 3287, 3204, 3111, 2950, 2934, 2867, 1670, 1618, 1596, 1414, 1371, 1346, 1232, 1071, 971, 878, 742, 690, 639; HRMS Calculated for $C_{11}H_{15}N_3O$ $[M+H]^+$: 206.12879. Found: 206.13010.

4.10.5. Synthesis of 2-amino-3-(4-methoxyphenyl)pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (82)

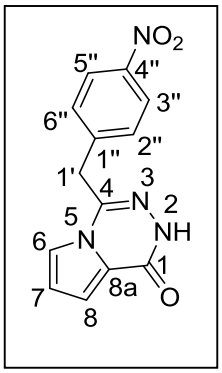
Methyl 1-[(4-methoxyphenyl)ethynyl]-1*H*-pyrrole-2-carboxylate (**74**) (0.080 g, 0.313 mmol) was reacted with hydrazine monohydrate (0,157 g, 3.130 mmol) as described above and the resulting crude mixture was separated gradiently via column chromatography (SiO_2, ethyl acetate/hexane, 1:10 to 1:2) and concentrated in vacuum to obtain to obtain 2-amino-3-(4-methoxyphenyl)pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (**82**) (0.072g, 0.282 mmol, 90% isolated yield) as brownish needles from chloroform. Mp. 168-169 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.7 Hz, 2H, arom.), 7.13 (d, J = 4.0 Hz, 1H, H-8), 7.11 (dd, J = 2.5, 1.4 Hz, 1H, H-6), 6.96 (d, J = 8.7 Hz, 2H, arom.), 6.91 (s, 1H, H-4), 6.60 (dd, J = 4.0, 2.5 Hz, 1H, H-7), 4.56 (bs, 2H, NH_2), 3.84 (s, 3H, O-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.2, 156.2, 131.2, 130.4, 124.4, 123.0, 118.4, 113.7, 113.1, 110.2, 107.2, 55.4; IR (ATR) 3314, 3107, 2920, 1670, 1605, 1510, 1473, 1373, 1341, 1242, 1176, 1021, 965, 830, 800, 736, 634, 595; HRMS Calculated for $C_{13}H_8INO_2$ $[M+H]^+$: 256.10805. Found: 256.10860.

4.10.6. Synthesis of 4-(4-nitrobenzyl)pyrrolo[1,2-*d*][1,2,4]triazin-1(2*H*)-one (83)

Methyl 1-[(4-nitrophenyl)ethynyl]-1H-pyrrole-2-carboxylate (**75**) (0.30 g, 1.46 mmol) in dry MeOH (15 mL) was reacted with hydrazine monohydrate (0.205 g, 0.758 mmol) as described above to obtain 4-(4-nitrobenzyl)pyrrolo[1,2-*d*][1,2,4]triazin-1(2*H*)-one (**83**) (0.190g, 0.703 mmol, 97% isolated yield) and recrystallized as yellowish pellets from chloroform. Mp. 237-238 °C.



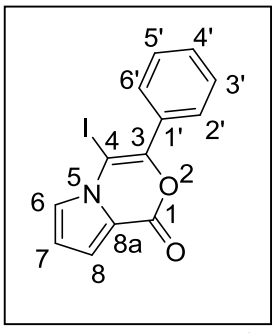
^{1}H-NMR (400 MHz, DMSO) δ 10.92 (s, 1H, NH), 7.42-7.25 (m, 2H, arom.), 6.86-6.71 (m, 3H, arom.), 6.19 (dd, J = 3.7, 1.2 Hz, 1H, H-8), 5.88 (dd, J = 3.7, 3.1 Hz, 1H, H-7), 3.59 (s, 2H, H-1'); ^{13}C-NMR (100 MHz, DMSO) δ 154.4, 146.7, 143.2, 136.6, 130.6, 123.6, 123.6, 118.1, 114.4, 110.8, 35.5; IR (ATR) 3144, 3110, 2259, 1717, 1594, 1512, 1457, 1440, 1420, 1339, 1265, 1220, 1170, 1100, 1071, 943, 852, 754, 743, 686, 593 ; HRMS Calculated for $C_{13}H_{10}N_4O_3$ $[M+H]^+$: 271.08257. Found: 271.08380.

4.11. General procedure for electrophilic cyclization reactions of *N*-alkyne substituted methyl 1*H*-pyrrole-2-carboxylate derivatives via iodine

To a solution of *N*-alkyne substituted methyl 1H-pyrrole-2-carboxylate derivatives in DCM (10 mL), I_2 (1.0 eq.) was added. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the mixture was concentrated in vacuum. Then, the crude product was purified via column chromatography (SiO_2, ethyl acetate/hexane, 1:5) and concentrated in vacuum to obtain corresponding iodine substituted pyrrolo-oxazinone derivatives.

4.11.1. Synthesis of 4-iodo-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (90)

To a solution of methyl 1-(phenylethynyl)-1*H*-pyrrole-2-carboxylate (**72**) (50.0 mg, 0.22 mmol) in DCM (10 mL), I_2 (56.3 mg, 0.22 mmol) was added and treated as described above to obtain 4-iodo-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (**90**) (58.9 mg, 79% isolated yield) and recrystallized as colorless cubics from chloroform. Mp. 176-178 °C.

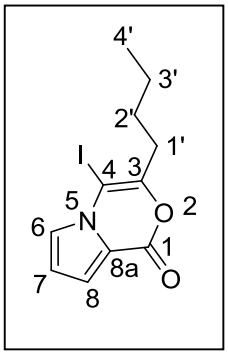


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69-7.59 (m, 2H, arom.), 7.52-7.47 (m, 2H, arom.), 7.47-7.42 (m, 3H, arom.), 6.61 (dd, J = 4.0, 2.8 Hz, 1H, H-7); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.3, 142.6, 131.8, 129.1, 129.0, 127.2, 125.8, 116.8, 116.4, 111.7, 68.3; IR (ATR) 3664, 2969, 2918, 1708, 1450, 1371, 1332, 1089, 1055, 766, 729, 696, 685; HRMS Calculated for $C_{13}H_8INO_2$ $[M+H]^+$: 337.96791. Found: 337.97070.

4.11.2. Synthesis of 4-iodo-3-butyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (91)

To a solution of methyl 1-(hex-1-yn-1-yl)-1*H*-pyrrole-2-carboxylate (**73**) (0.120 g, 0.585 mmol) in $CHCl_3$ (15 mL), I_2 (0.15g, 0.59 mmol) was added and the reaction

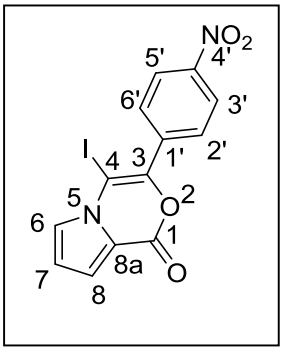
mixture was stirred for 5 h. The crude product was purified as described above to obtain 4-iodo-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (**91**) (58.9 mg, 79% isolated yield) and recrystallized as colorless cubics from chloroform. Mp. 176-178 °C



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 4.1, 1.6 Hz, 1H, H-8), 7.33 (dd, J = 2.7, 1.6 Hz, 1H, H-6), 6.52 (dd, J = 4.1, 2.7 Hz, 1H, H-7), 2.70 (t, J = 7.5 Hz, 2H, H-1'), 1.66 (q, J = 7.5 Hz, 2H, H-2'), 1.39 (h, J = 7.5 Hz, 2H, H-3'), 0.93 (t, J = 7.5 Hz, 3H, H-4'); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.7, 145.7, 125.9, 117.6, 117.4, 112.3, 68.6, 34.0, 29.3, 22.1, 13.9; IR (ATR) 2956, 2928, 2869, 1635, 1534, 1455, 1402, 1339, 1229, 1023, 1084, 1027, 997, 896, 620, 596; HRMS Calculated for $C_{11}H_{12}INO_2$ $[M+H]^+$: 317.99855. Found: 317.99880.

4.11.3. Synthesis of 4-iodo-3-(4-nitrophenyl)-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (92)

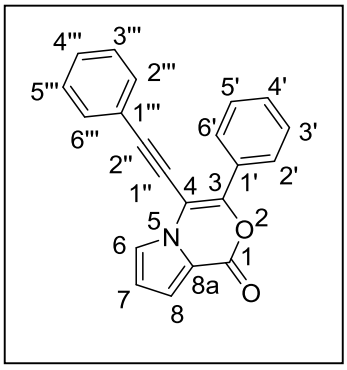
To a solution of methyl 1-[(4-nitrophenyl)ethynyl]-1*H*-pyrrole-2-carboxylate (**75**) (0.108 g, 0.400 mmol) in DCM (20 mL), I_2 (0.101 g, 0.400 mmol) was added and the reaction mixture was stirred for 5 h. The crude product was purified as described above to obtain 4-iodo-3-(4-nitrophenyl)-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (**92**) (0.116 g, 76% isolated yield) and recrystallized as yellowish needle from chloroform. Mp. 171-172 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.9 Hz, 2H, arom.), 7.90 (d, J = 8.9 Hz, 2H, arom.), 7.58-7.48 (m, 2H, arom.), 6.67 (dd, J = 3.9, 2.9 Hz, 1H, H-7); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.5, 148.4, 141.4, 138.9, 131.2, 127.2, 123.5, 118.6, 117.3, 113.3, 70.8; IR (ATR) 3144, 1731, 1594, 1447, 1406, 1332, 1249, 1182, 1107, 1074, 1033, 1011, 939, 855, 738, 707, 694, 676, 598; HRMS Calculated for $C_{13}H_7IN_2O_4$ $[M+H]^+$: 382.95233, Found: 382.95660.

4.12. Synthesis of 3-phenyl-4-(phenylethynyl)-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (93)

To a mixture of $PdCl_2$ (4.300 mg, 0.024 mmol), PPh_3 (12.60 mg, 0.048 mmol), CuI (2.300 mg, 0.012 mmol) was added 4-iodo-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (**90**) (0.200 g, 0.590 mmol), phenylacetylene (72.51 mg, 0.710 mmol) and DIPA (119.0 mg, 1.180 mmol) in dry THF (30 mL) under N_2 atmosphere. The mixture was stirred at 70 °C for 3 h. After completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated in vacuum. Then, the resulting crude mixture was eluted gradiently through a SiO_2 column (EtOAc/hexane, 1:10-1:5) and concentrated in vacuum to obtain 3-phenyl-4-(phenylethynyl)-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (**93**) (0.140 g, 76% isolated yield) and recrystallized as a white powder from chloroform. Mp. 164-165 °C.

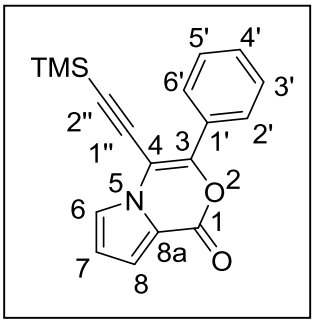


^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, J = 7.8, 1.8 Hz, 2H, arom.), 7.58 (dd, J = 2.5, 1.4 Hz, 1H, H-6), 7.52-7.33 (m, 8H, arom.), 7.32 (dd, J = 4.0, 1.4 Hz, 1H, H-8), 6.63 (dd, J = 4.0, 2.5 Hz, 1H, H-7); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.5, 145.7, 131.4, 130.7, 130.0, 129.6, 128.7, 128.3, 127.8, 121.6, 121.4, 116.6, 116.1, 113.4, 103.1, 100.2, 78.5; IR (ATR) 2988, 1745, 1489, 1464, 1444, 1405, 1319, 1232, 1190, 1099, 1079, 1036, 1002, 896, 753, 731, 695, 685, 606, 554; HRMS Calculated for $C_{21}H_{13}NO_2$ $[M+H]^+$: 312.10191, Found: 312.10070.

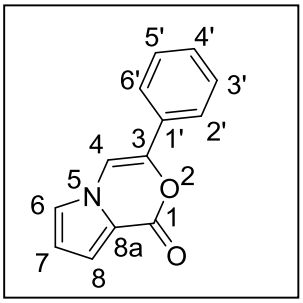
4.13. Synthesis of 4-((trimethylsilyl)ethynyl)-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (94) and 3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (95)

To a mixture of $PdCl_2$ (8.500 mg, 0.048 mmol), PPh_3 (24.90 mg, 0.095 mmol), CuI (4.600 mg, 0.024 mmol) was added 4-iodo-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (**90**) (0.400 g, 1.190 mmol), phenylacetylene (140.3 mg, 1.428 mmol) and DIPA (240.8 mg, 2.380 mmol) in dry THF (30 mL) under N_2 atmosphere. Then, the reaction

mixture was stirred at 70 °C for 5 h. After completion of the reaction, the mixture was filtered and the filtrate was concentrated in vacuum. Then, the resulting crude mixture was eluted gradiently through a SiO_2 column (EtOAc/hexane, 1:10-1:5) and concentrated in vacuum to obtain 4-((trimethylsilyl)ethynyl)-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (**94**) (0.190 g, 52% isolated yield) and recrystallized as a yellowish needles from ethanol (Mp. 119-121 °C) and 3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (**95**) (0.115 g, 46% isolated yield) and recrystallized as a yellowish solid from chloroform (Mp. 133-134 °C).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.12-8.01 (m, 2H, arom.), 7.53 (dd, J = 2.6, 1.4 Hz, 1H, H-6), 7.48-7.39 (m, 3H, arom.), 7.32 (dd, J = 4.0, 1.4 Hz, 1H, H-8), 6.63 (dd, J = 4.0, 2.6 Hz, 1H, H-7), 0.30 (s, 9H, -TMS); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.5, 146.6, 130.5, 130.2, 128.2, 127.9, 121.8, 116.7, 116.0, 113.5, 108.2, 103.0, 93.5, -0.5; IR (ATR) 2969, 2901, 1733, 1464, 1393, 1348, 1335, 1301, 1249, 1145, 1091, 1049, 1038, 848, 834, 764, 730, 682, 606; HRMS Calculated for $C_{18}H_{17}SiNO_2$ $[M+H]^+$: 308.11013, Found: 308.10980.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57-7.49 (m, 2H, arom.), 7.35 (s, 1H, H-4), 7.29-7.19 (m, 3H, arom.), 7.11 (d, J = 4.0 Hz, 1H, H-8), 7.08 (dd, J = 2.5, 1.4 Hz, 1H, H-6), 6.43 (dd, J = 4.0, 2.5 Hz, 1H, H-7); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.8, 141.9, 130.4, 129.3, 128.8, 124.2, 121.7, 116.7, 115.6, 113.6, 104.5.

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APPENDIX A

SPECTRAL DATA

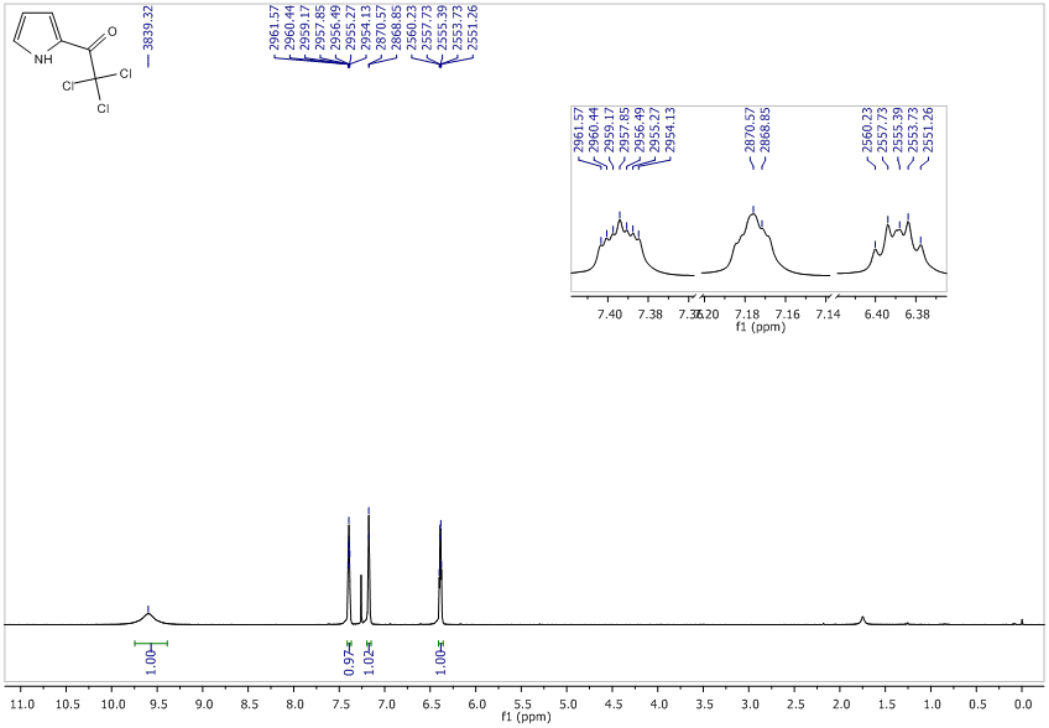

Figure 15 ^{1}H-NMR Spectrum of Compound **60** in $CDCl_3$

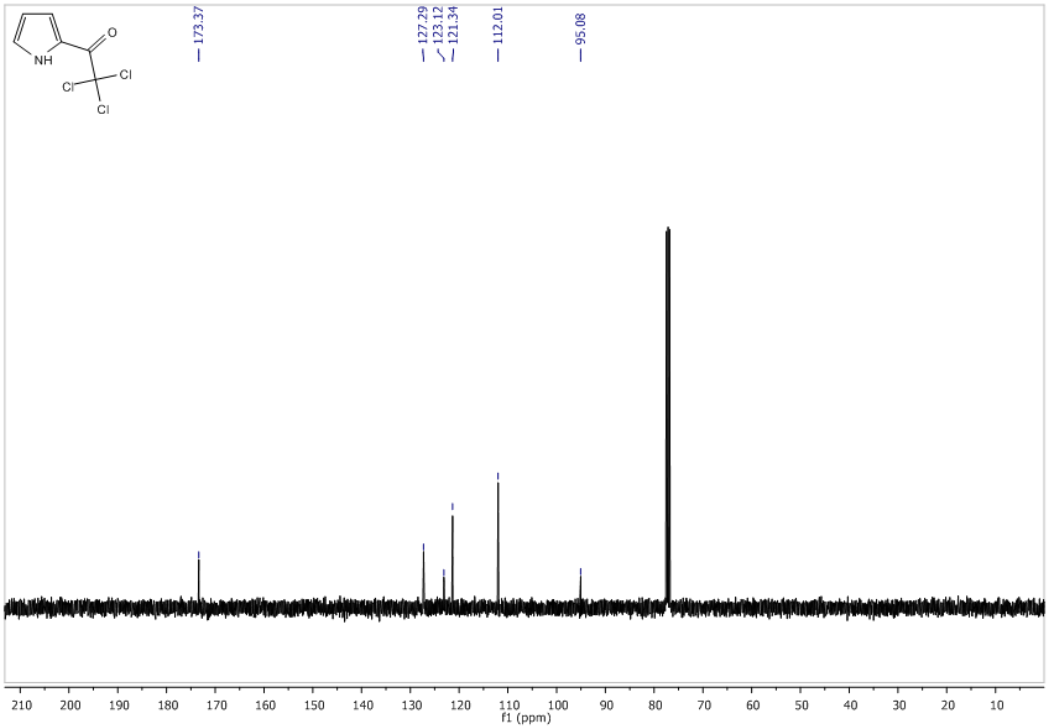

Figure 16 ^{13}C-NMR Spectrum of Compound **60** in $CDCl_3$

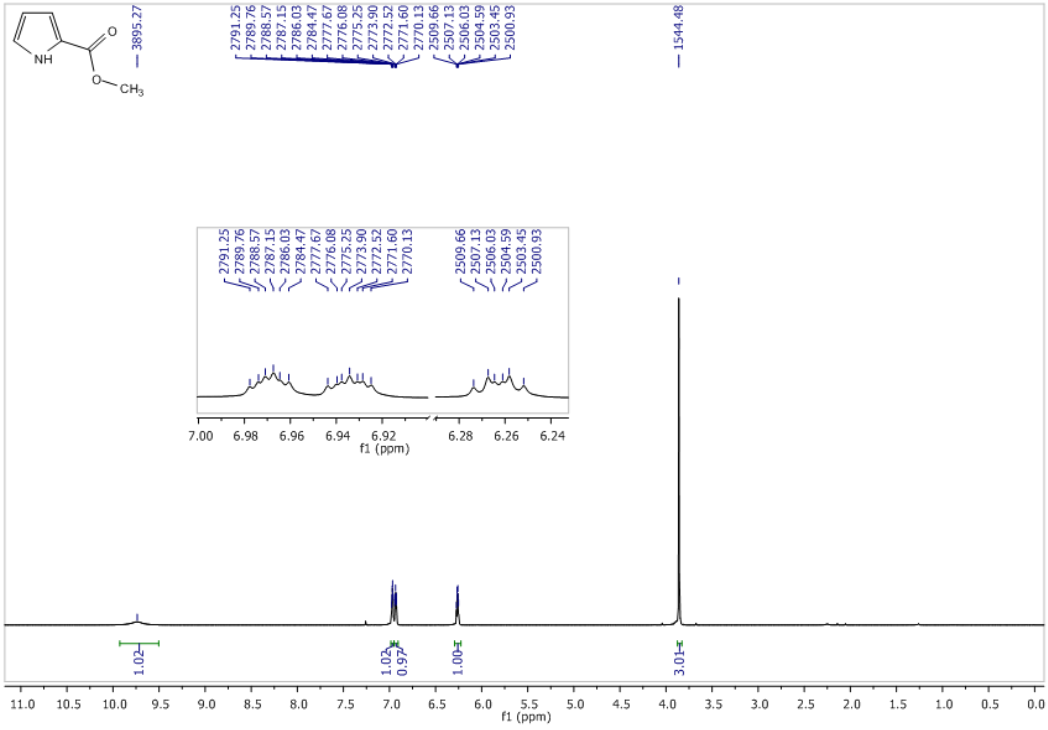

Figure 17 ^{1}H-NMR Spectrum of Compound **17** in $CDCl_3$

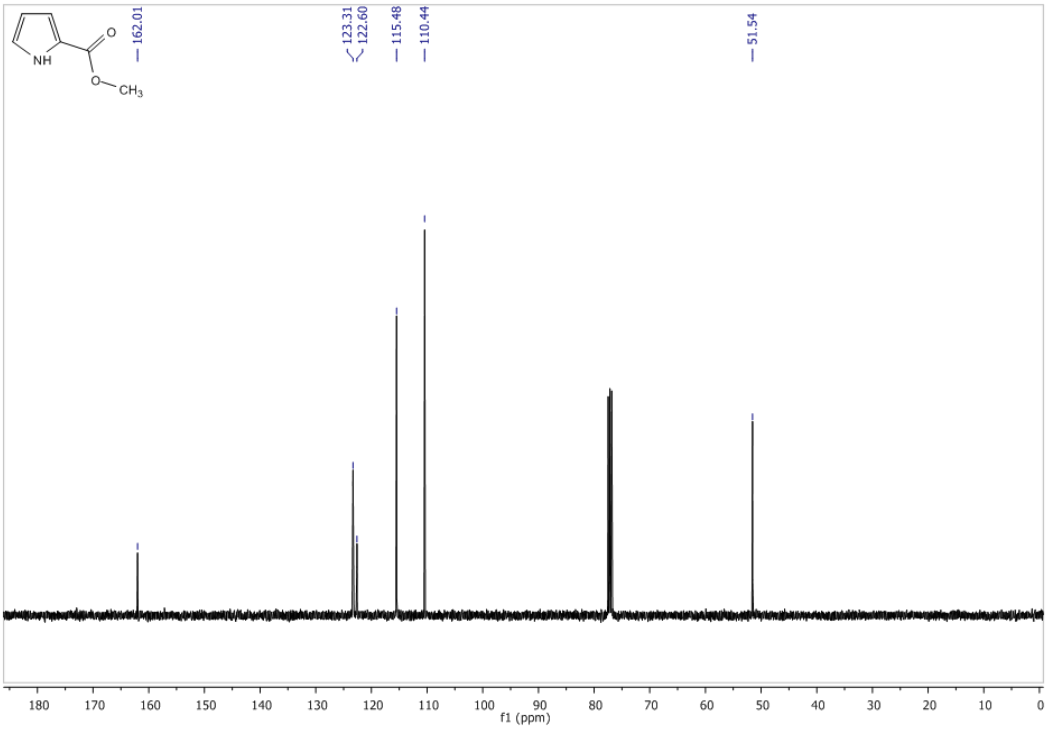

Figure 18 ^{13}C-NMR Spectrum of Compound **17** in $CDCl_3$

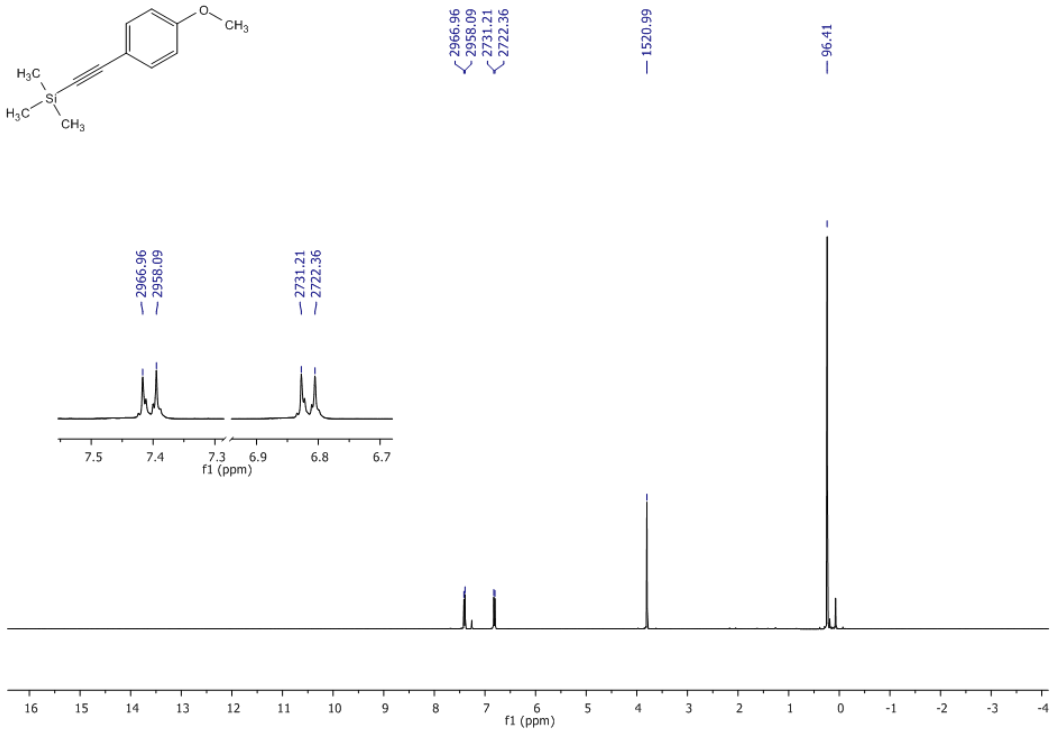

Figure 19 ^{1}H-NMR Spectrum of Compound **62** in $CDCl_3$

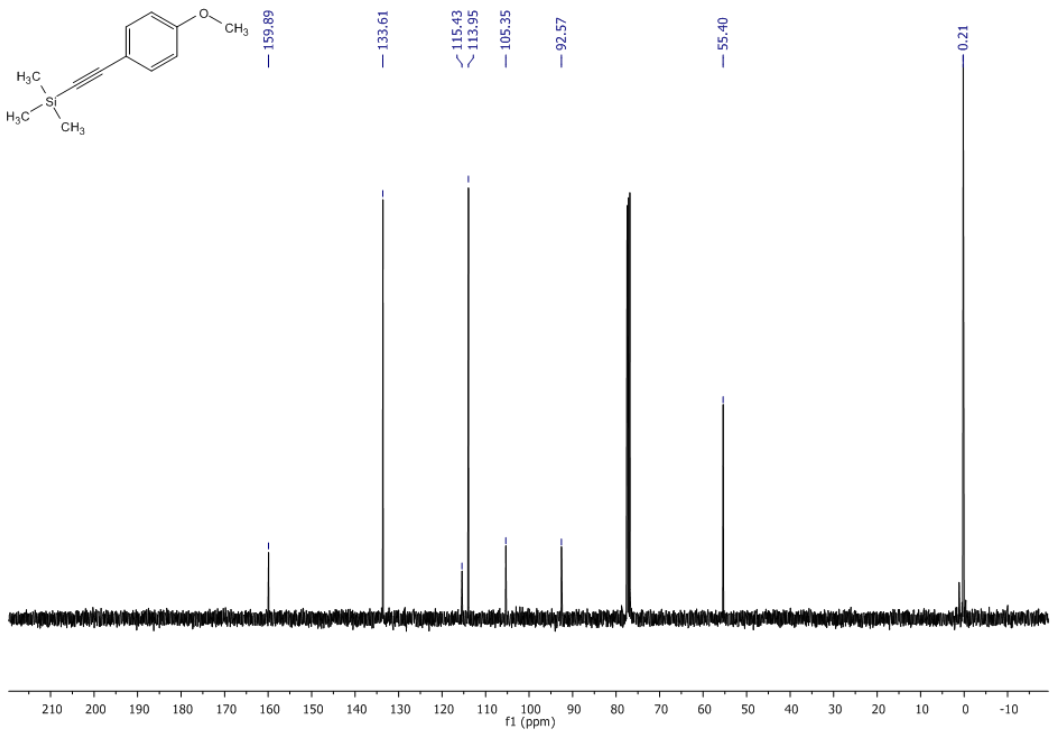

Figure 20 ^{13}C-NMR Spectrum of Compound **62** in $CDCl_3$

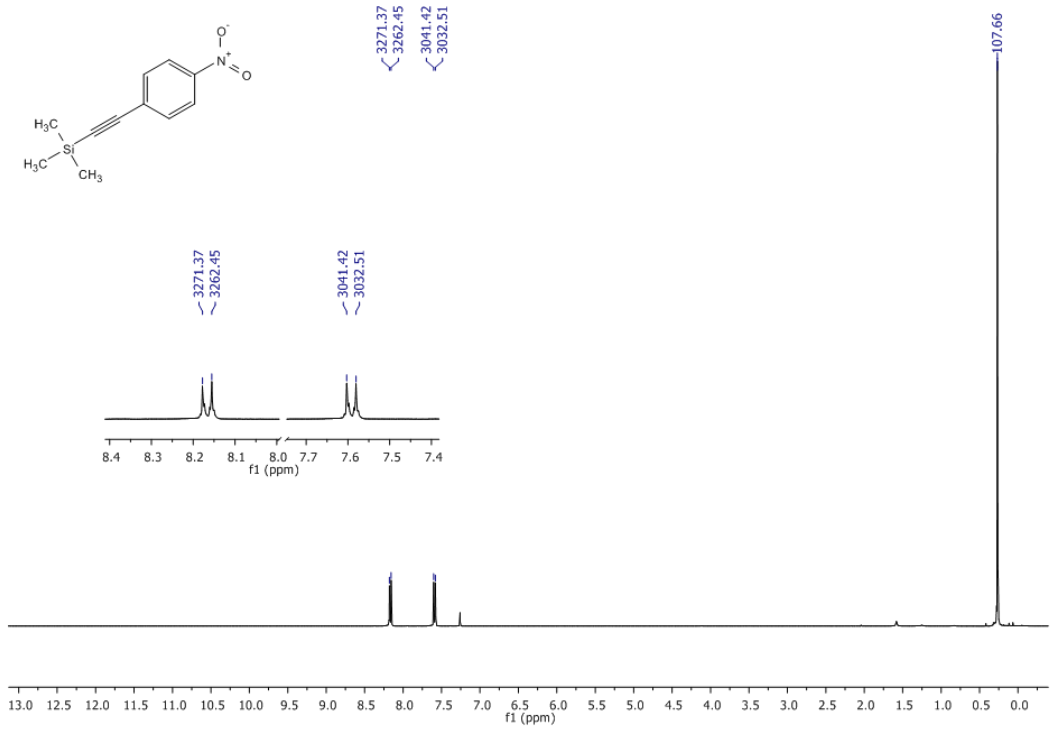

Figure 21 ^{1}H-NMR Spectrum of Compound **64** in $CDCl_3$

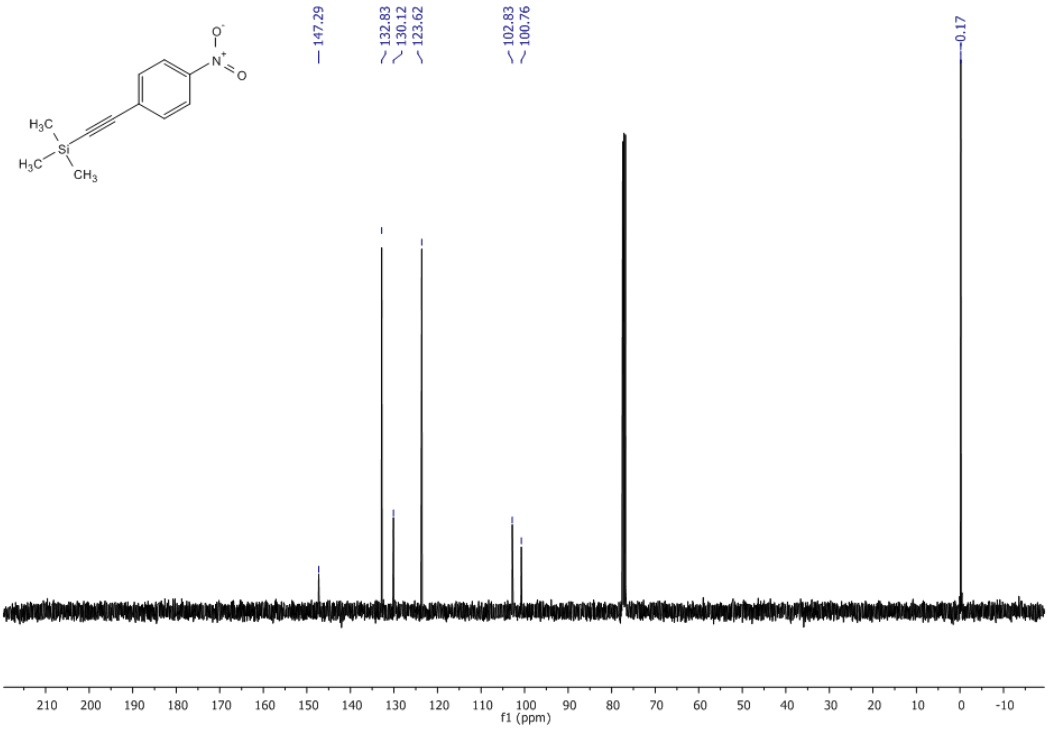

Figure 22 ^{13}C-NMR Spectrum of Compound **64** in $CDCl_3$

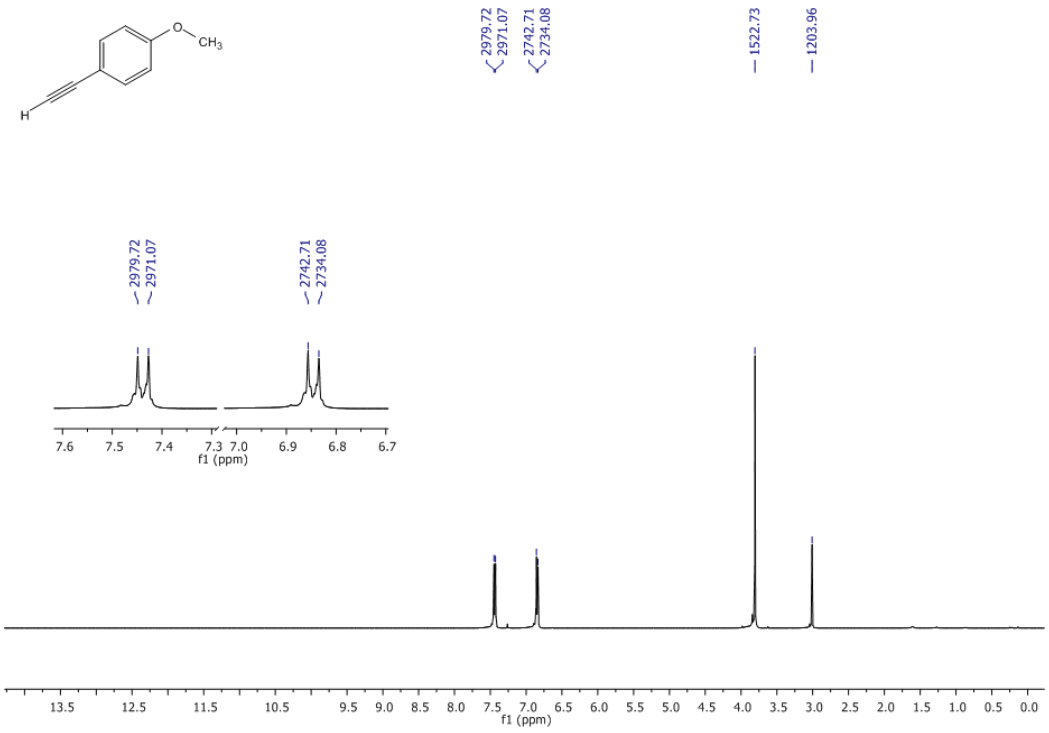

Figure 23 ^{1}H-NMR Spectrum of Compound **65** in $CDCl_3$

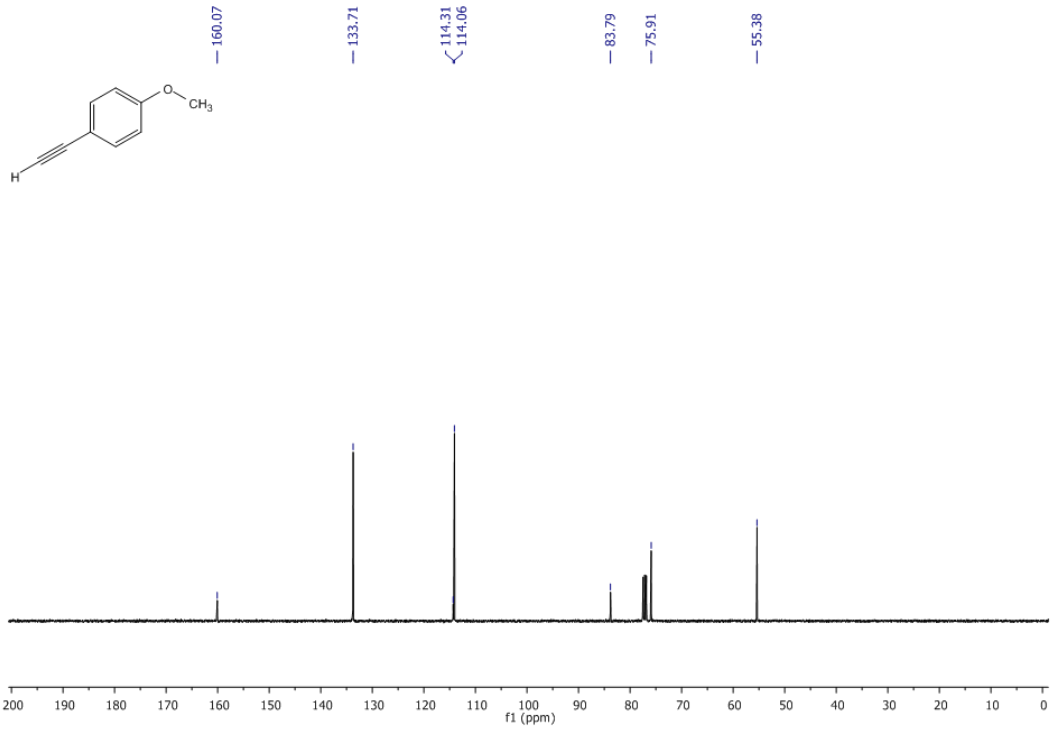

Figure 24 ^{13}C-NMR Spectrum of Compound **65** in $CDCl_3$

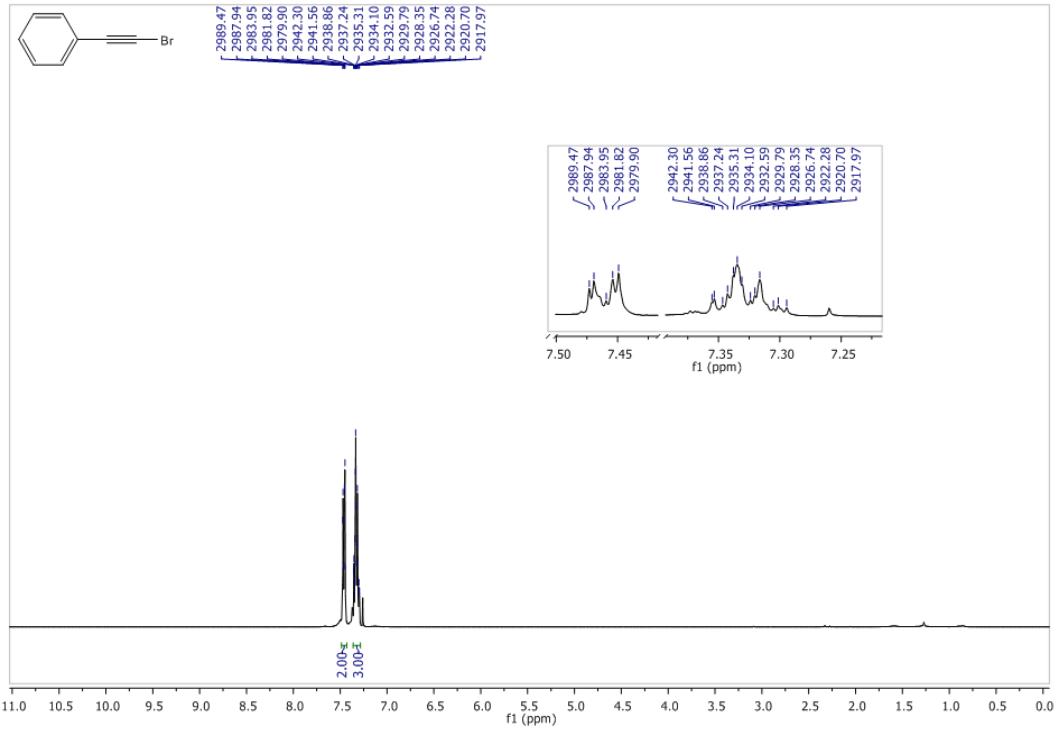

Figure 25 ^{1}H-NMR Spectrum of Compound **67** in $CDCl_3$

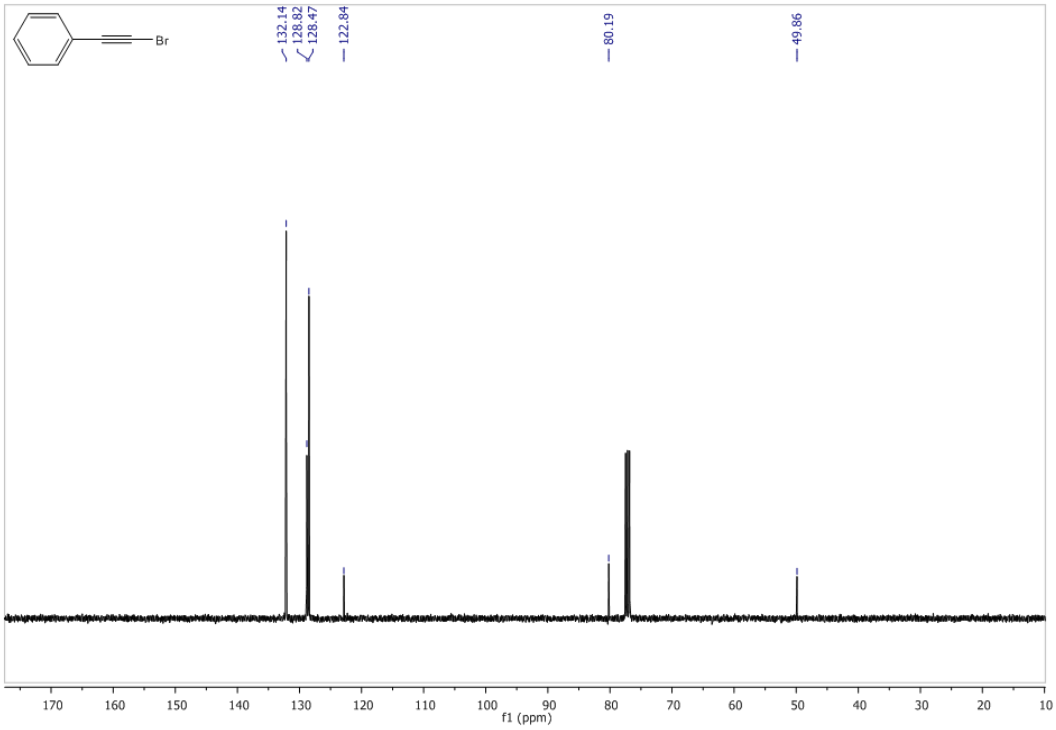

Figure 26 ^{13}C-NMR Spectrum of Compound **67** in $CDCl_3$

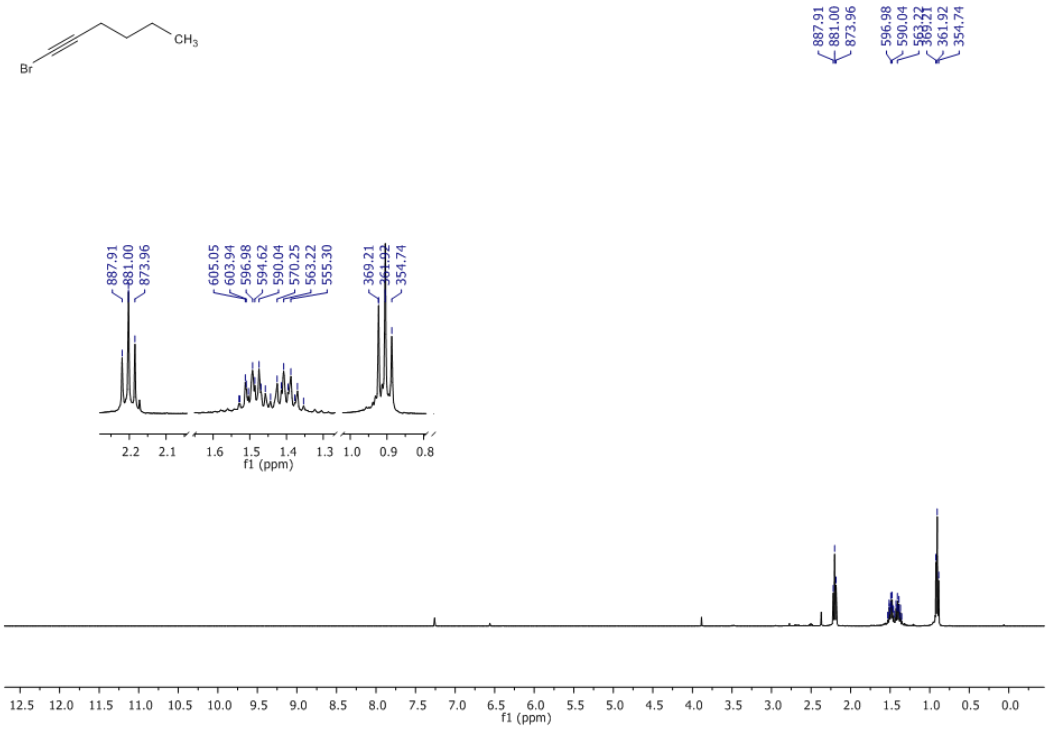

Figure 27 ^{1}H-NMR Spectrum of Compound **69** in $CDCl_3$

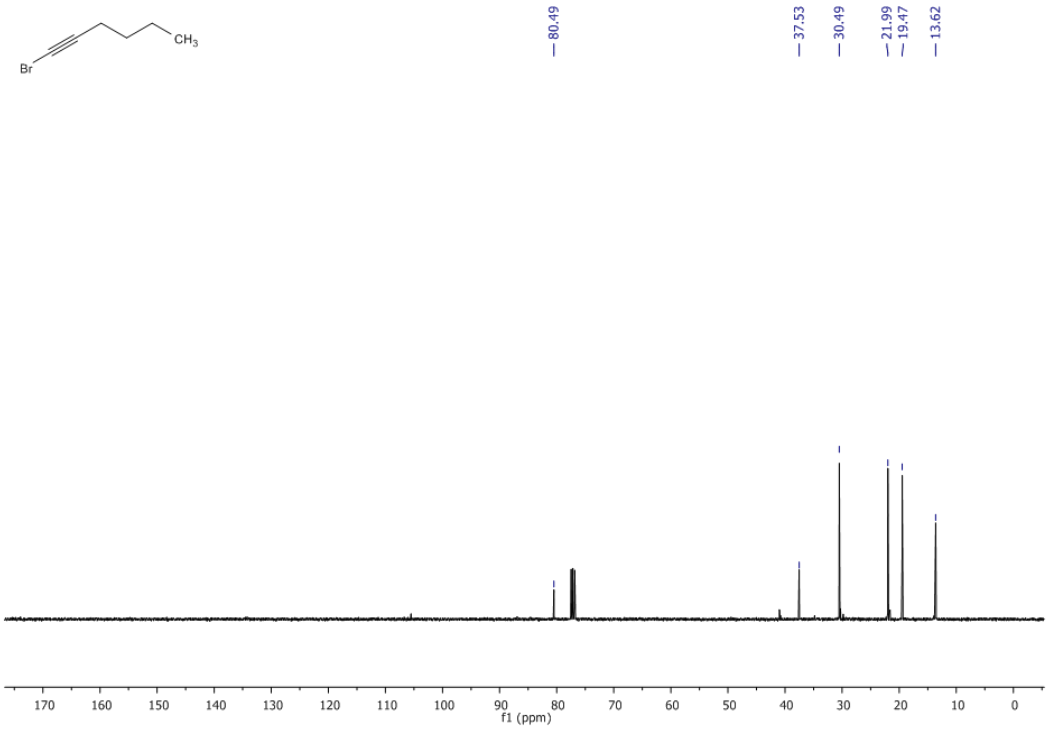

Figure 28 ^{13}C-NMR Spectrum of Compound **69** in $CDCl_3$

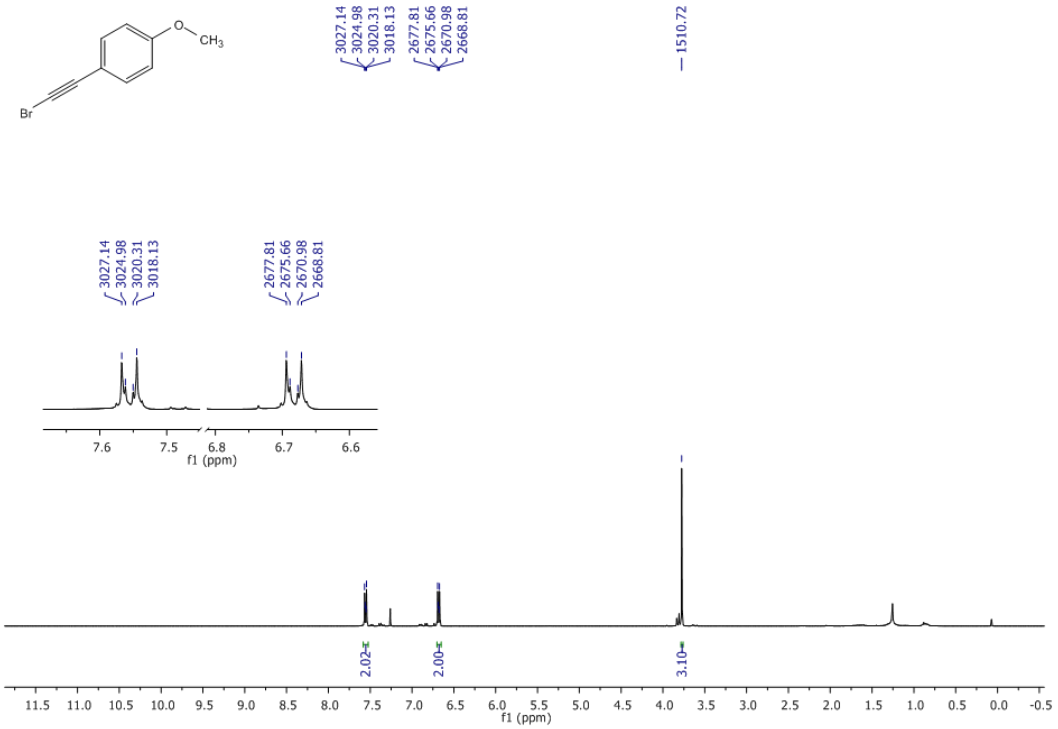

Figure 29 ^{1}H-NMR Spectrum of Compound **70** in $CDCl_3$

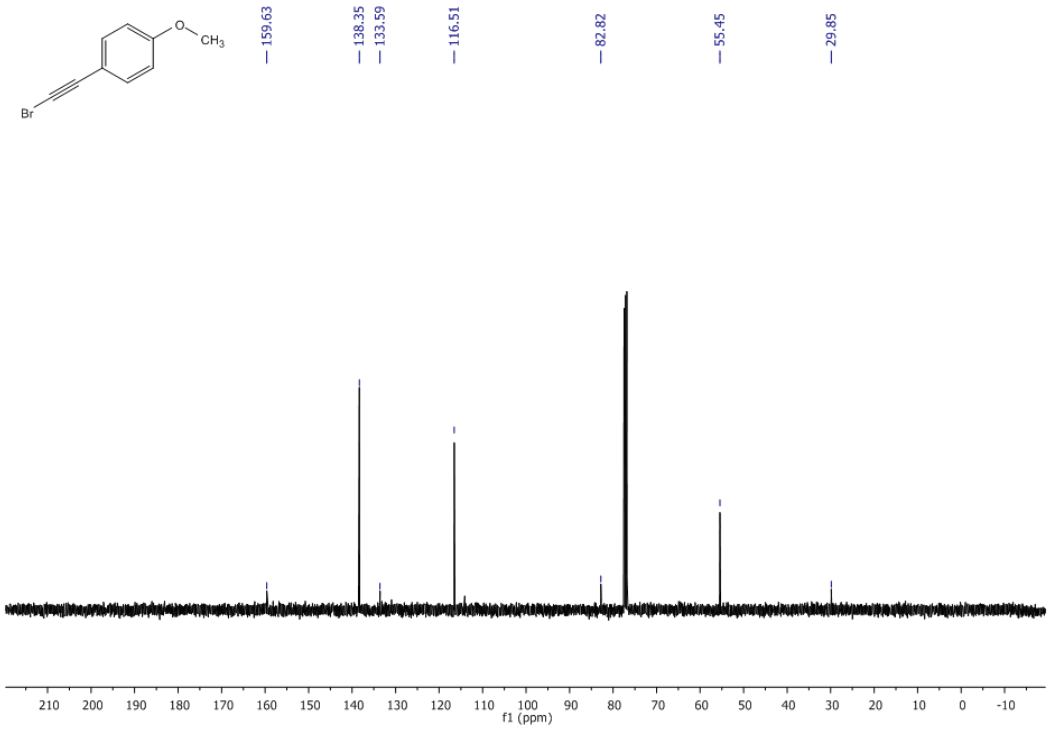

Figure 30 ^{13}C-NMR Spectrum of Compound **70** in $CDCl_3$

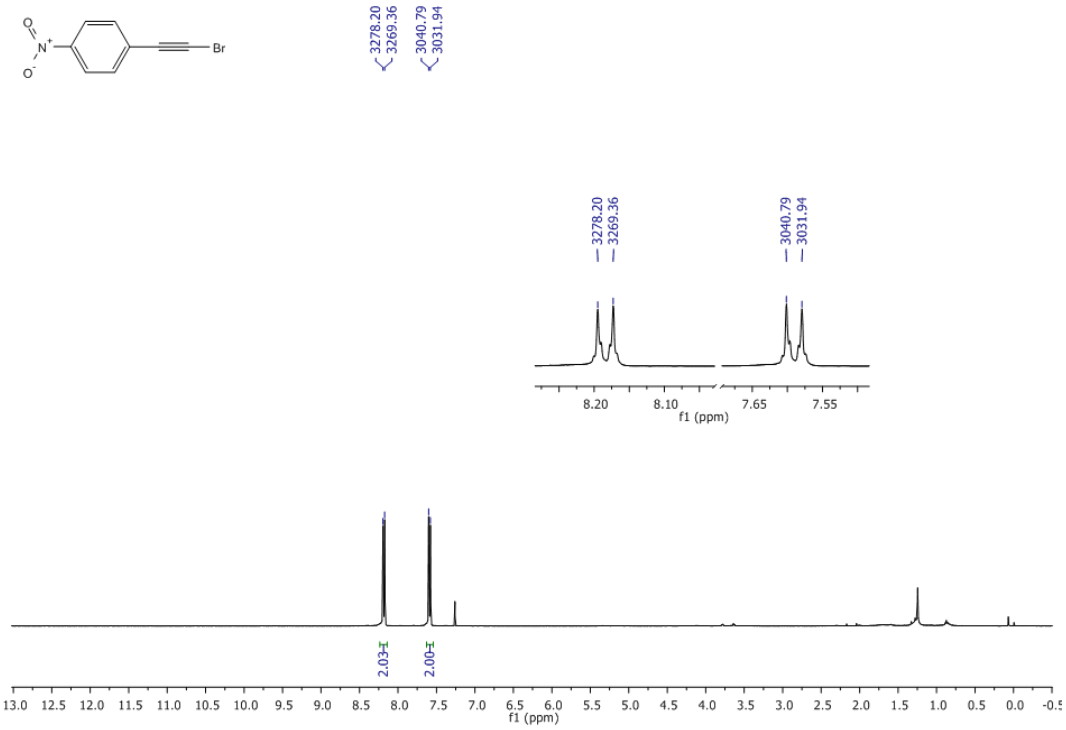

Figure 31 ^{1}H-NMR Spectrum of Compound **71** in $CDCl_3$

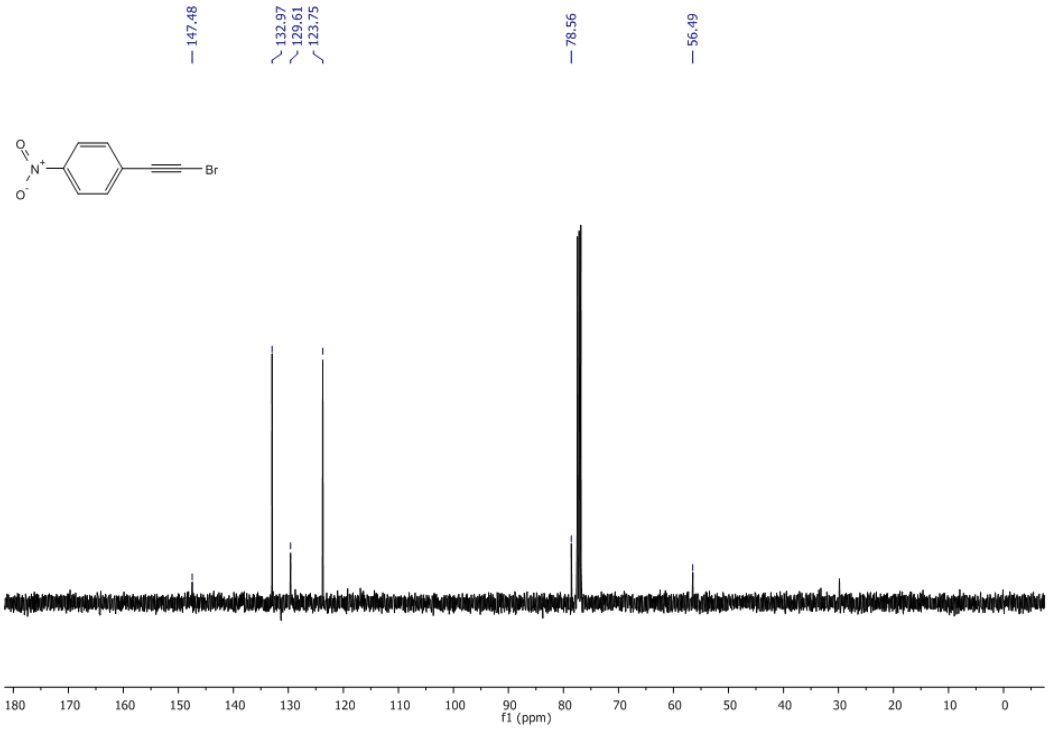

Figure 32 ^{13}C-NMR Spectrum of Compound **71** in $CDCl_3$

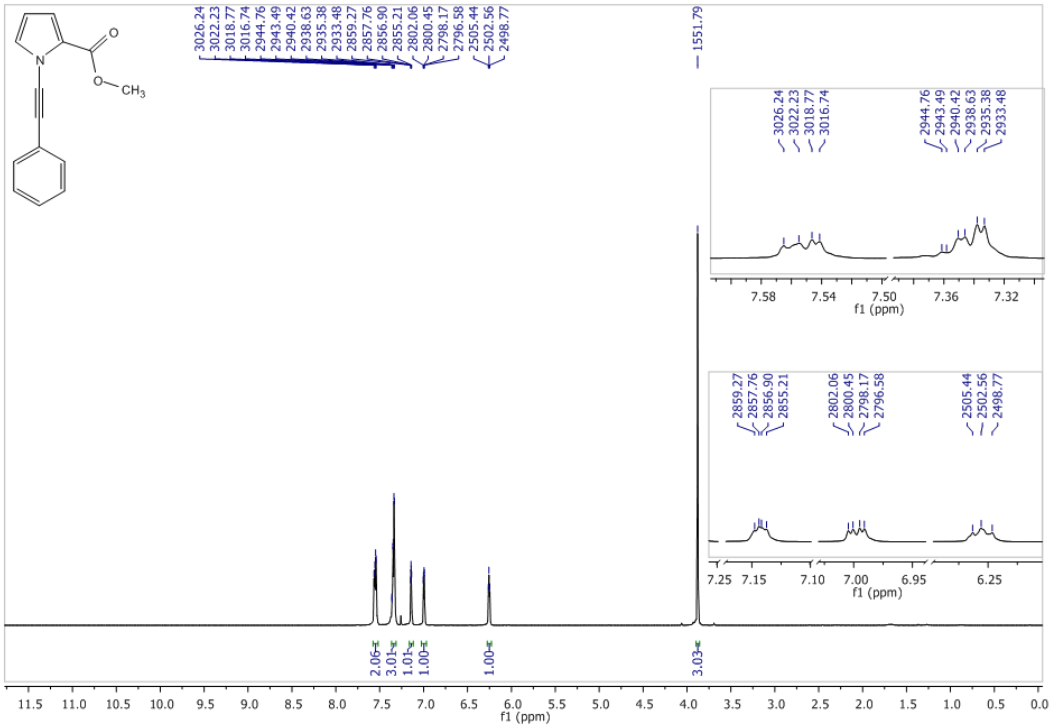

Figure 33 ^{1}H-NMR Spectrum of Compound **72** in $CDCl_3$

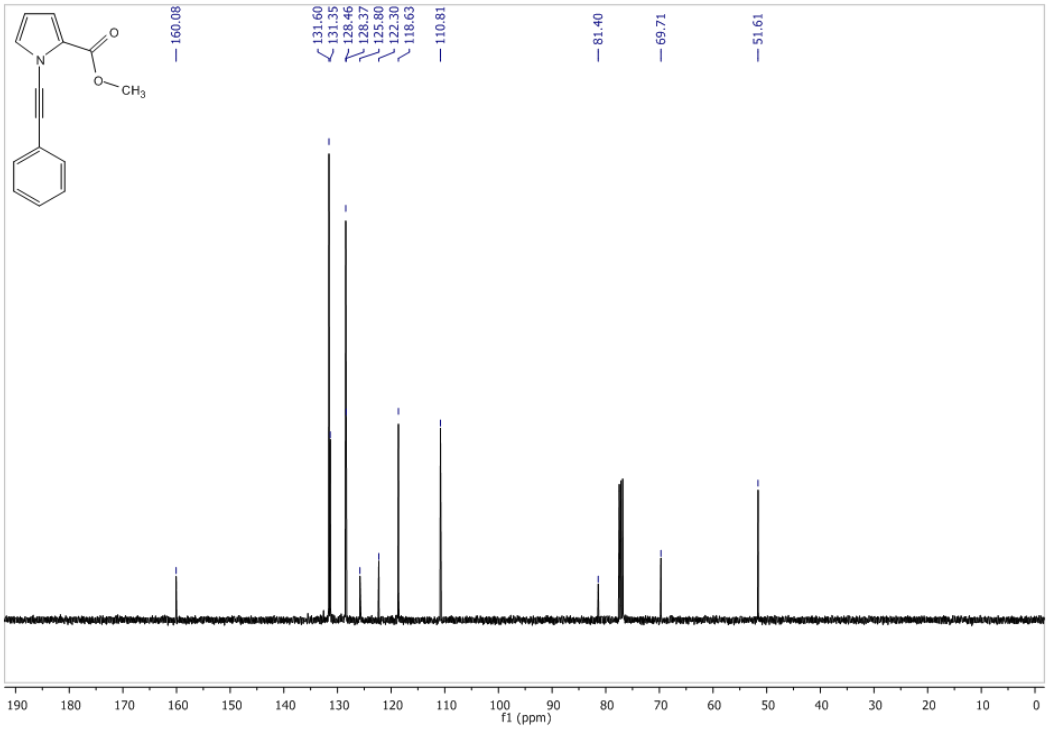

Figure 34 ^{13}C-NMR Spectrum of Compound **72** in CDCl3

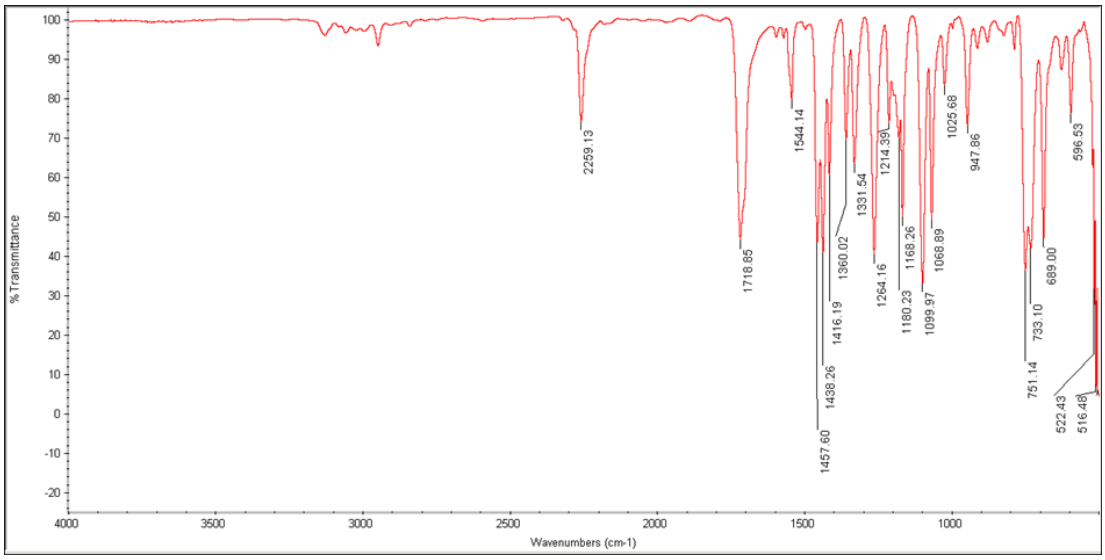

Figure 35 IR Spectrum of Compound **72**

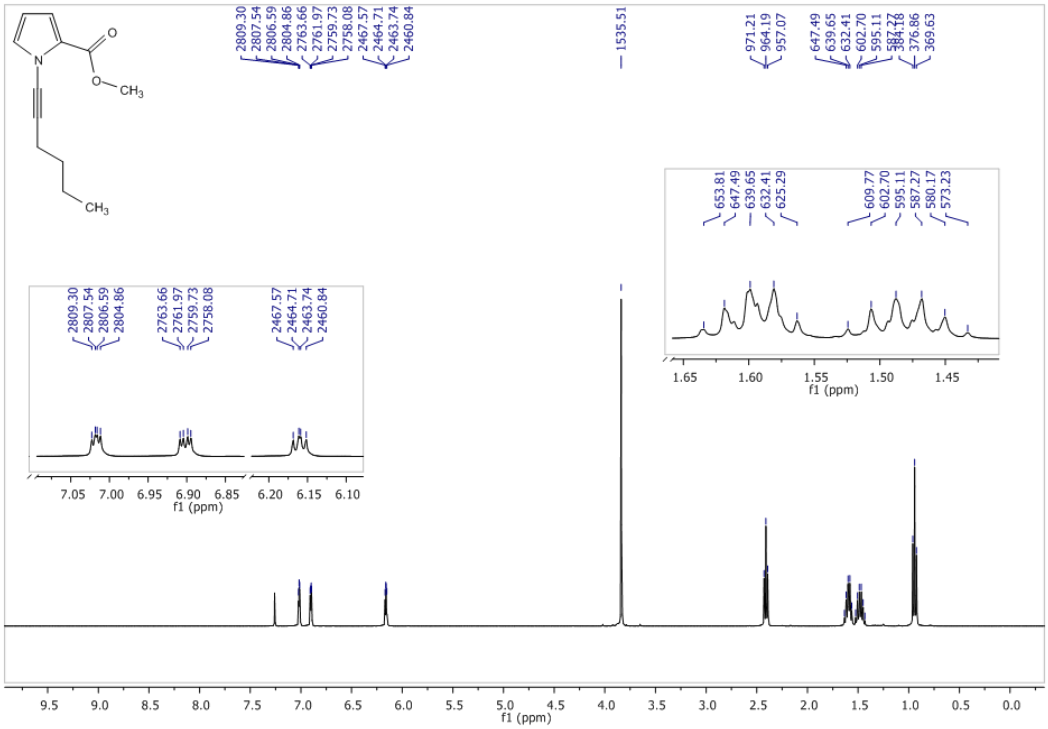

Figure 36 ^{1}H-NMR Spectrum of Compound **73** in $CDCl_3$

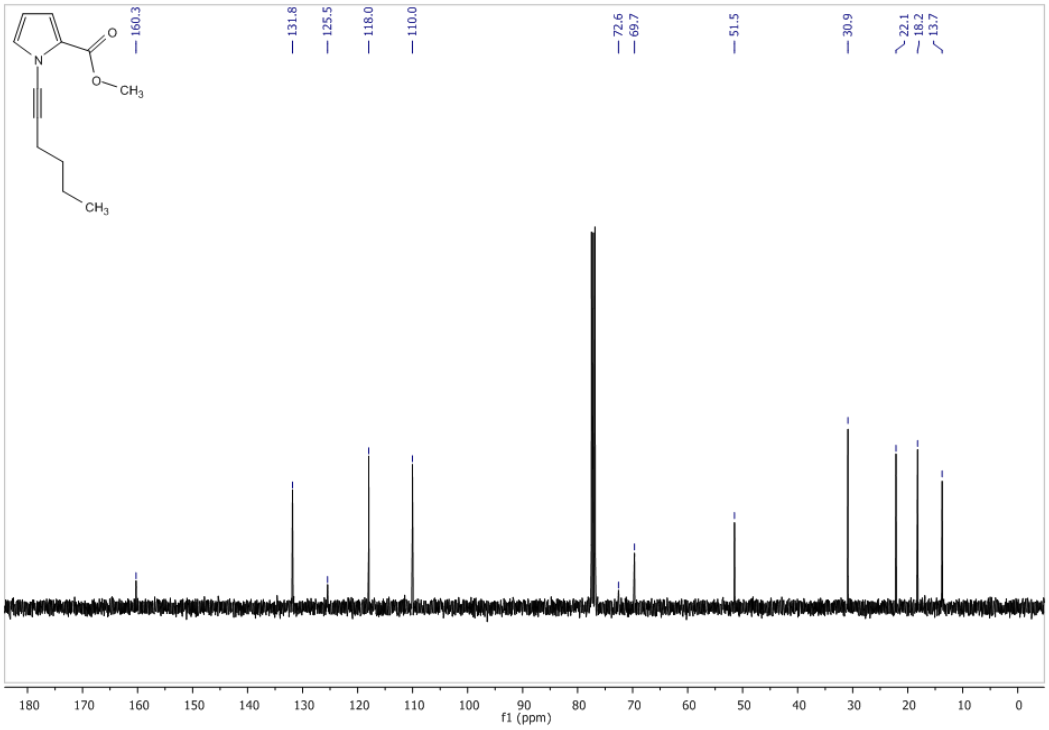

Figure 37 ^{13}C-NMR Spectrum of Compound **73** in $CDCl_3$

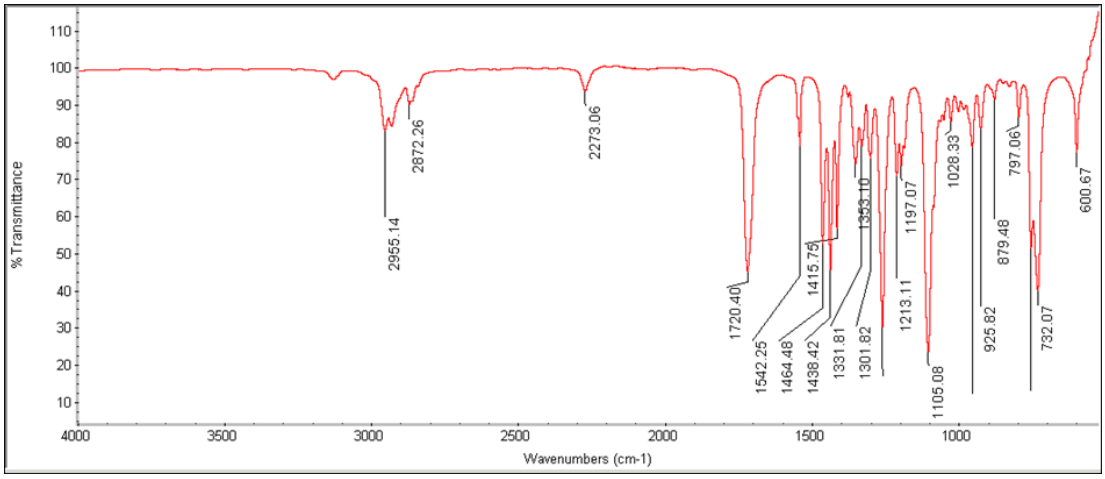

Figure 38 IR Spectrum of Compound **73**

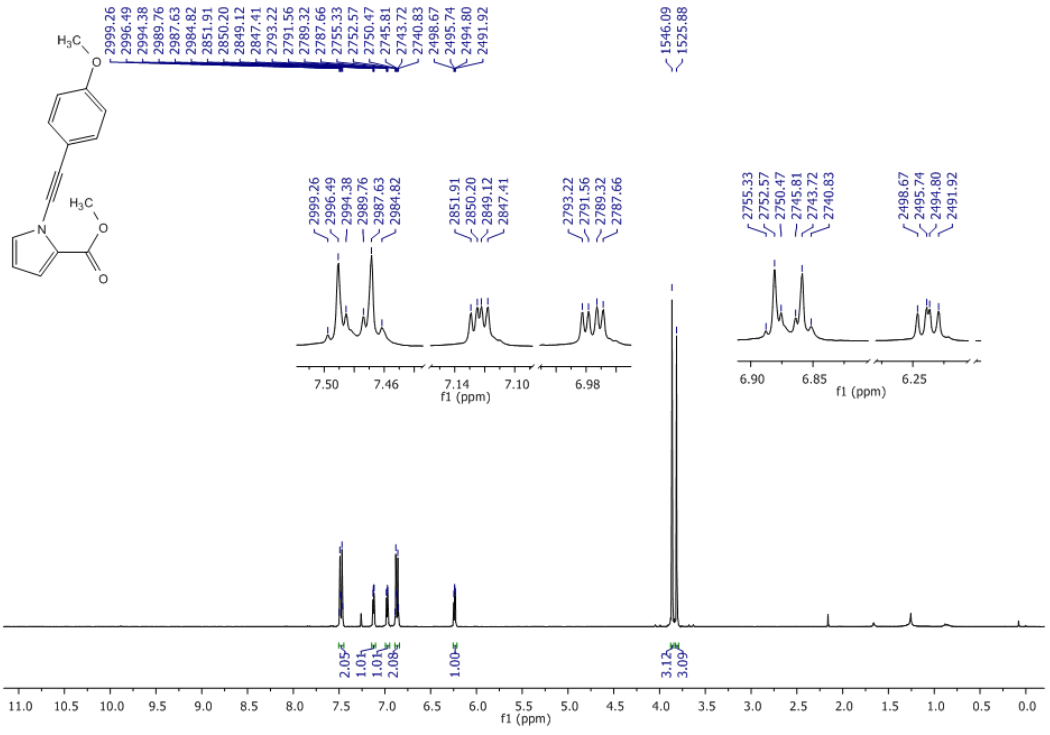

Figure 39 ^{1}H-NMR Spectrum of Compound **74** in $CDCl_3$

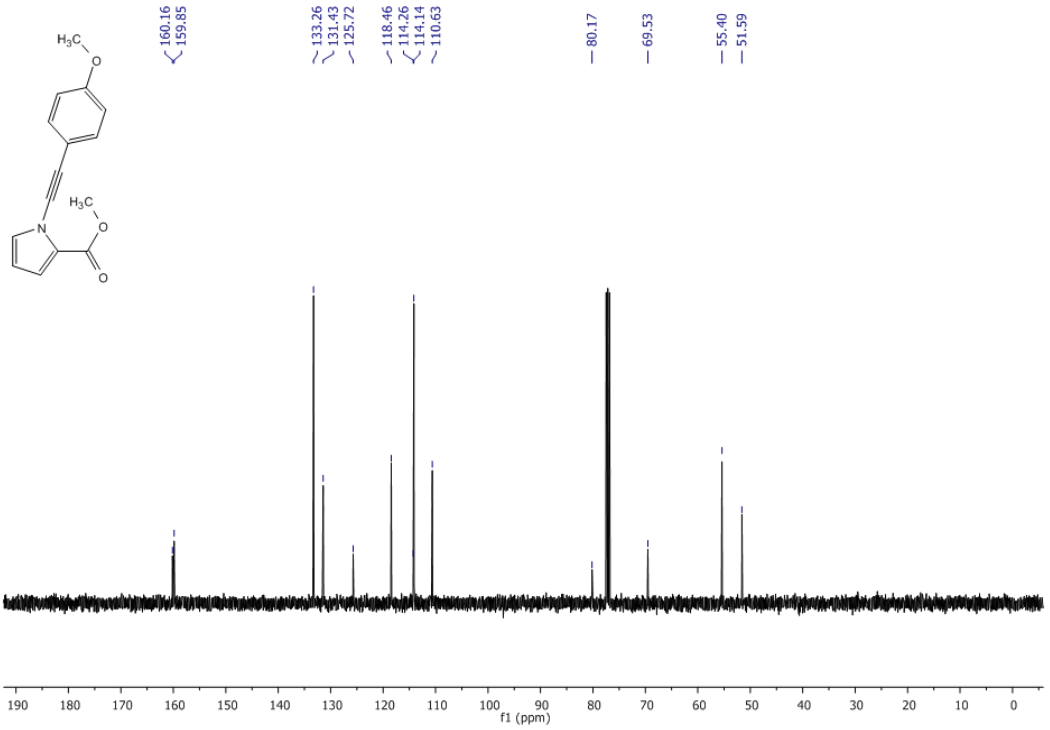

Figure 40 ^{13}C-NMR Spectrum of Compound **74** in $CDCl_3$

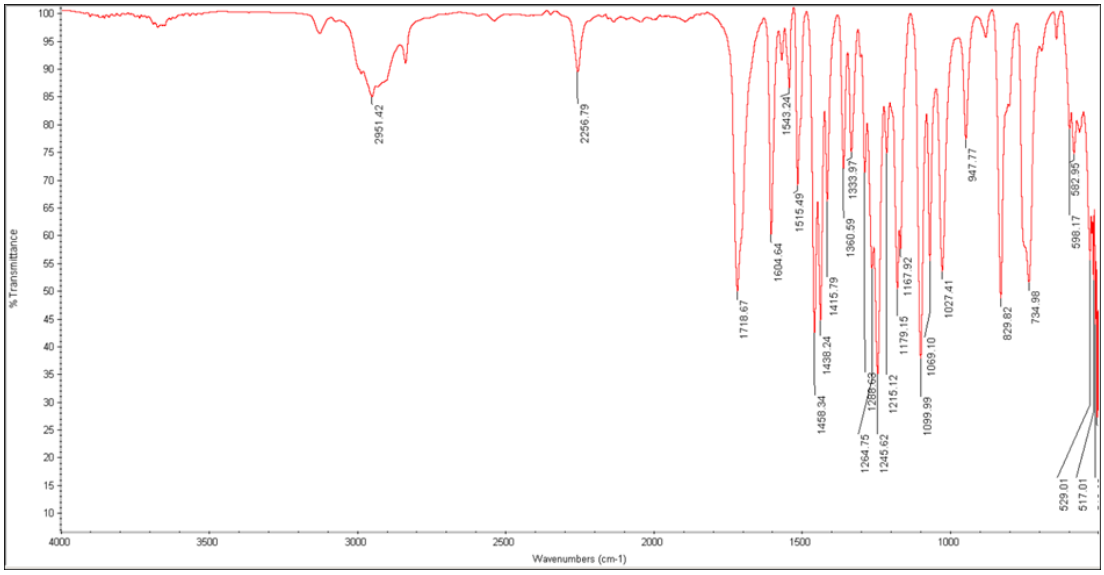

Figure 41 IR Spectrum of Compound **74**

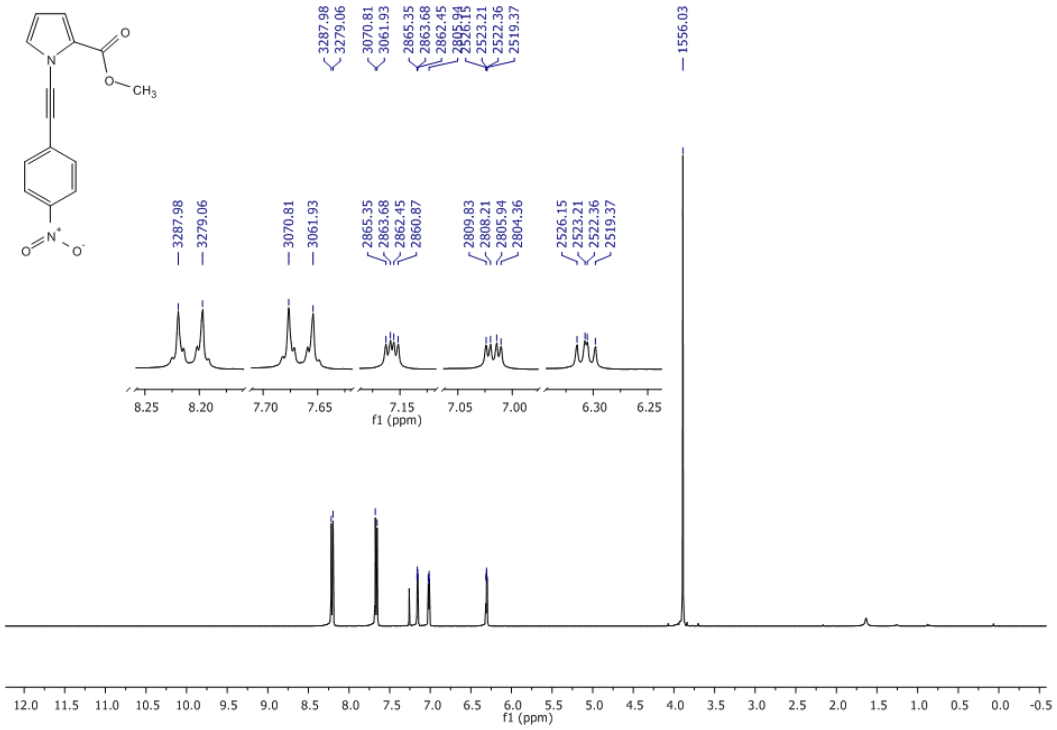

Figure 42 ^{1}H-NMR Spectrum of Compound **75** in $CDCl_3$

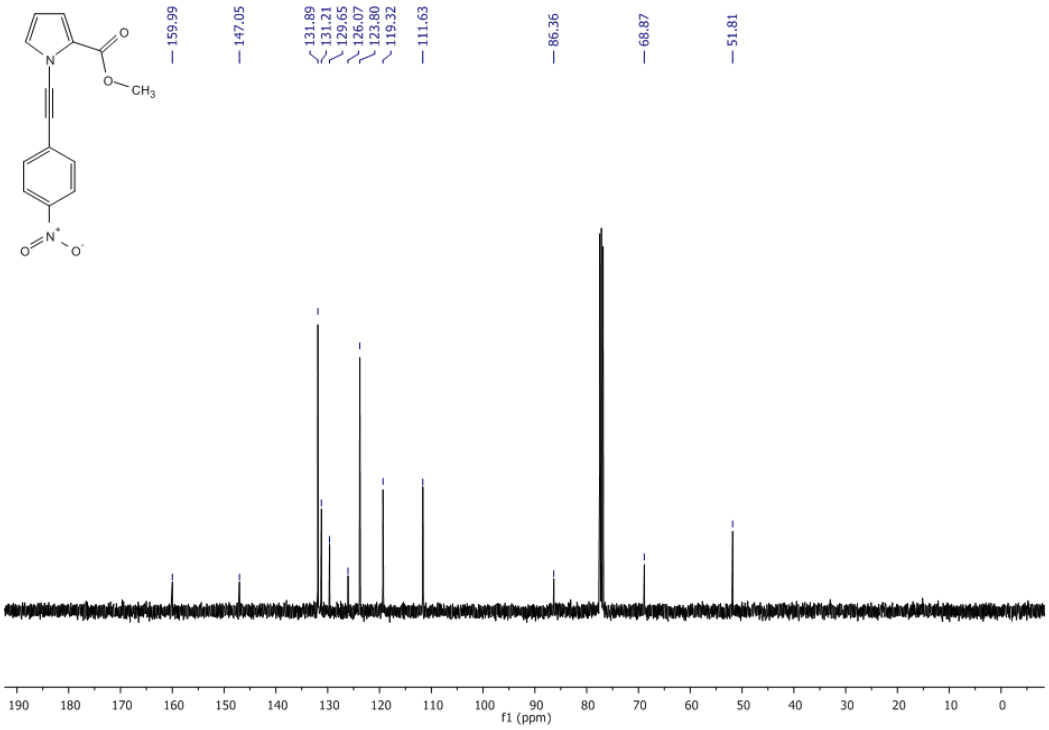

Figure 43 ^{13}C-NMR Spectrum of Compound **75** in $CDCl_3$

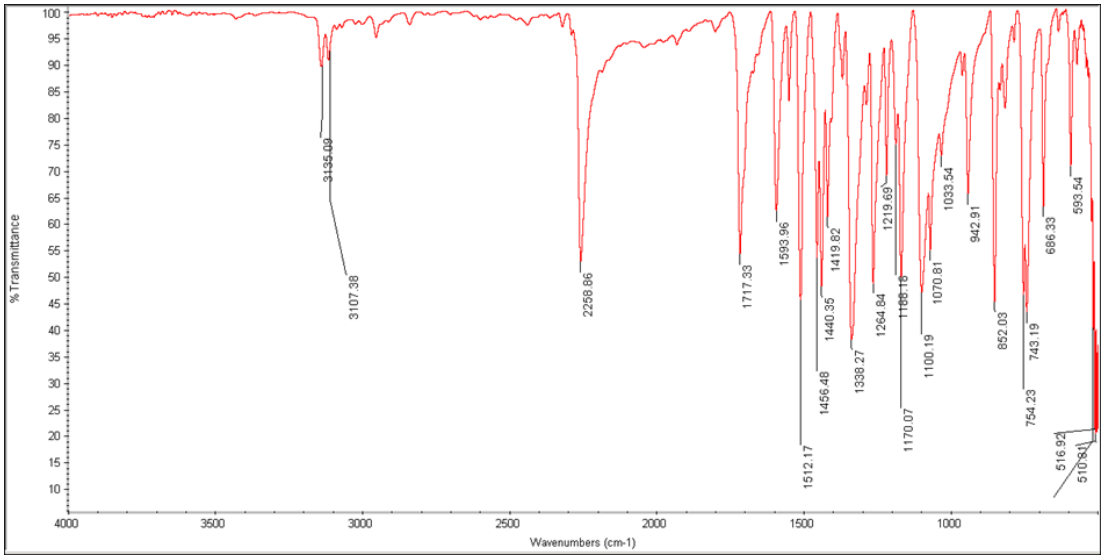

Figure 44 IR Spectrum of Compound **75**

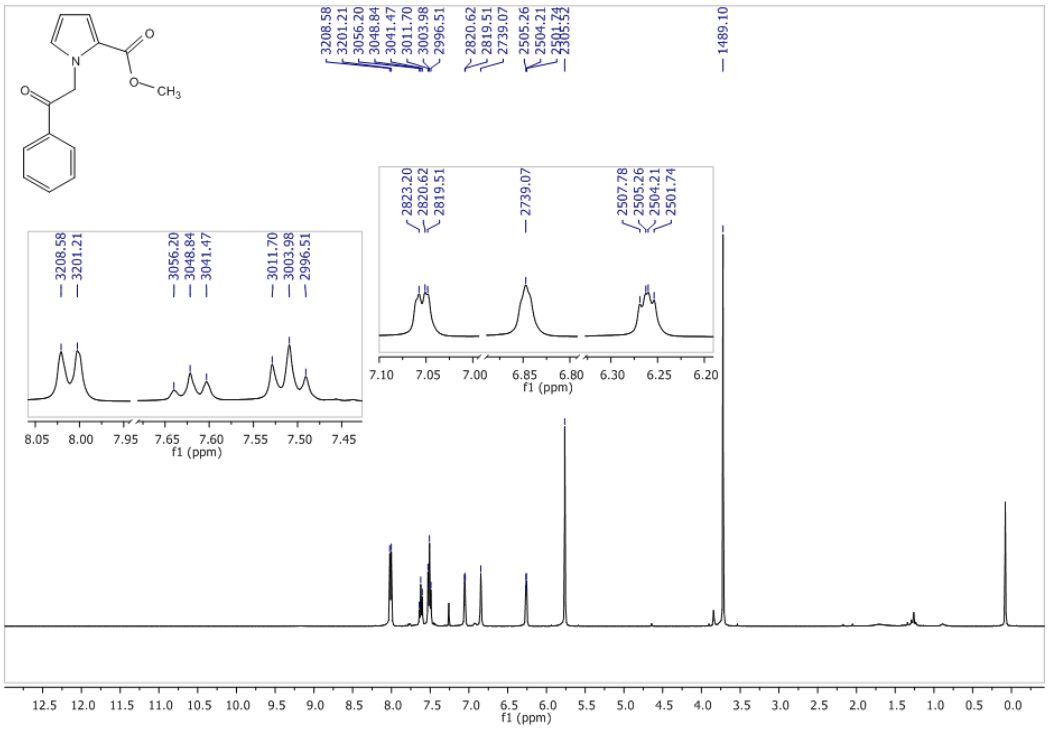

Figure 45 ^{1}H-NMR Spectrum of Compound **76** in $CDCl_3$

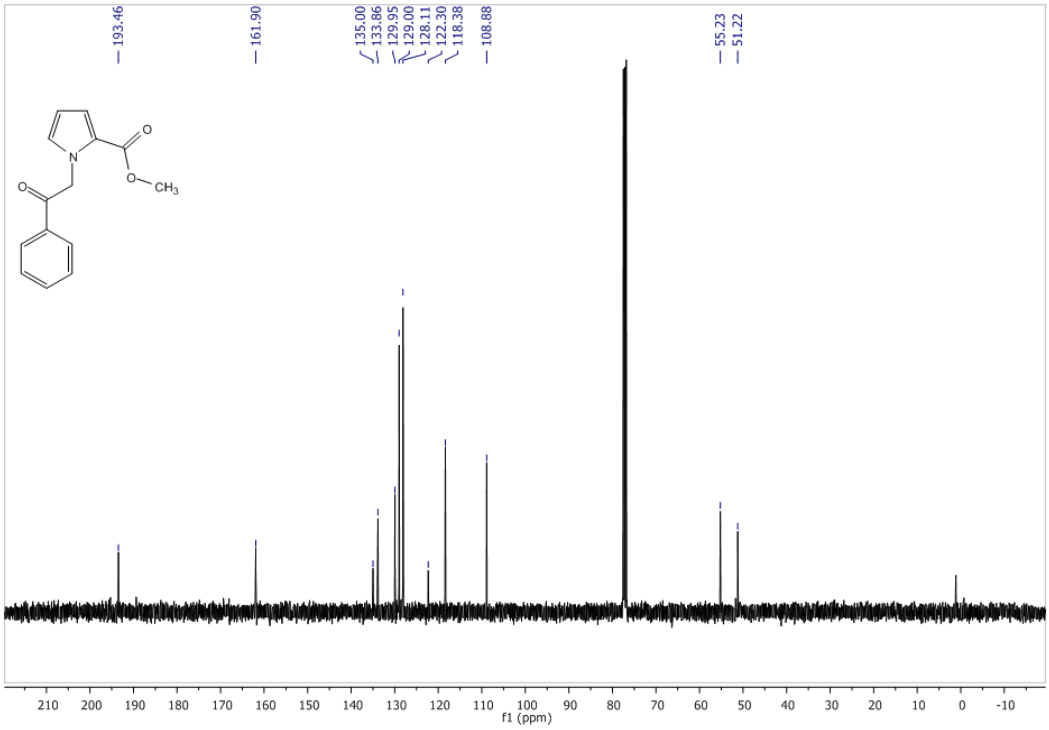

Figure 46 ^{13}C-NMR Spectrum of Compound **76** in $CDCl_3$

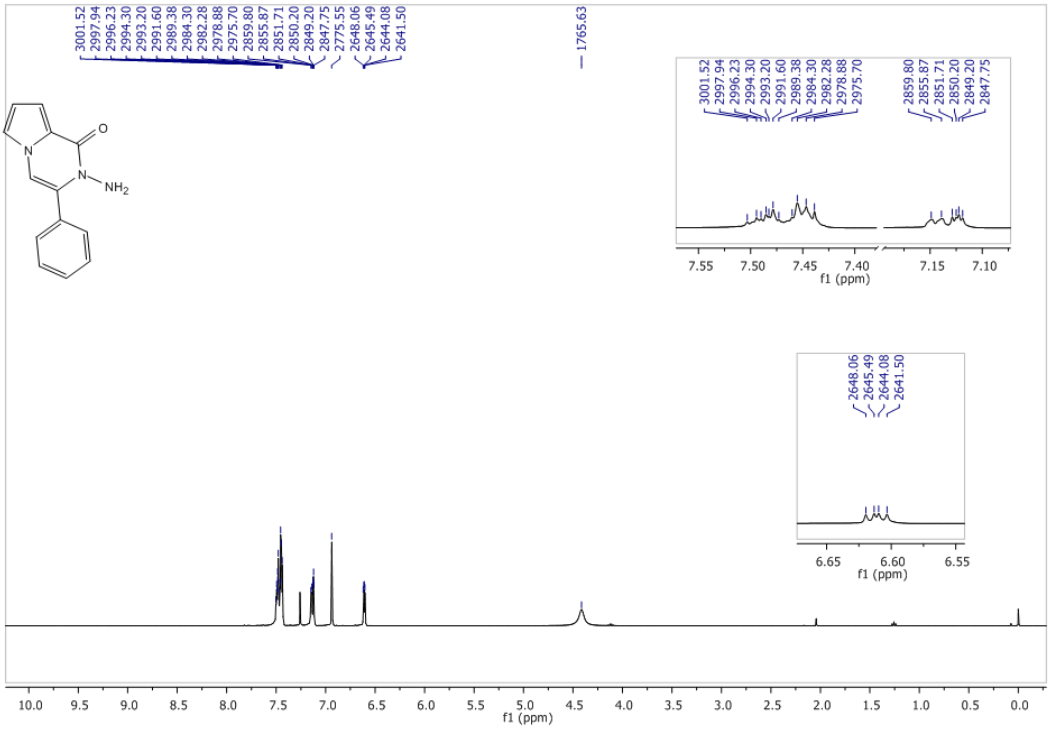

Figure 47 ^{1}H-NMR Spectrum of Compound **77** in $CDCl_3$

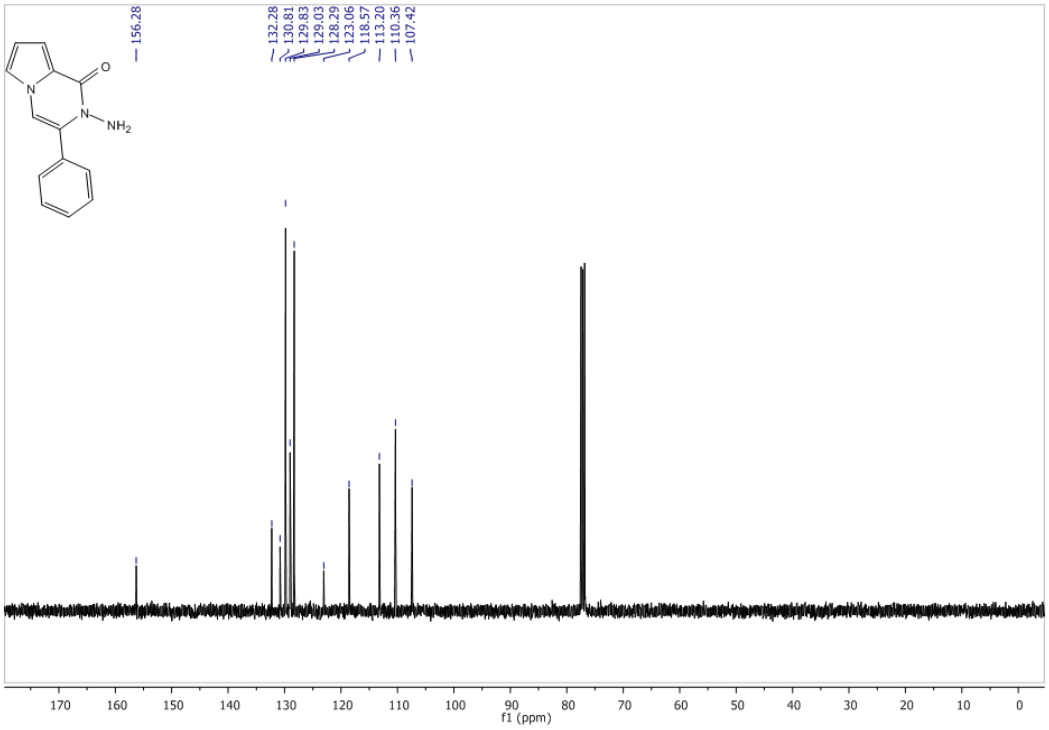

Figure 48 ^{13}C-NMR Spectrum of Compound **77** in $CDCl_3$

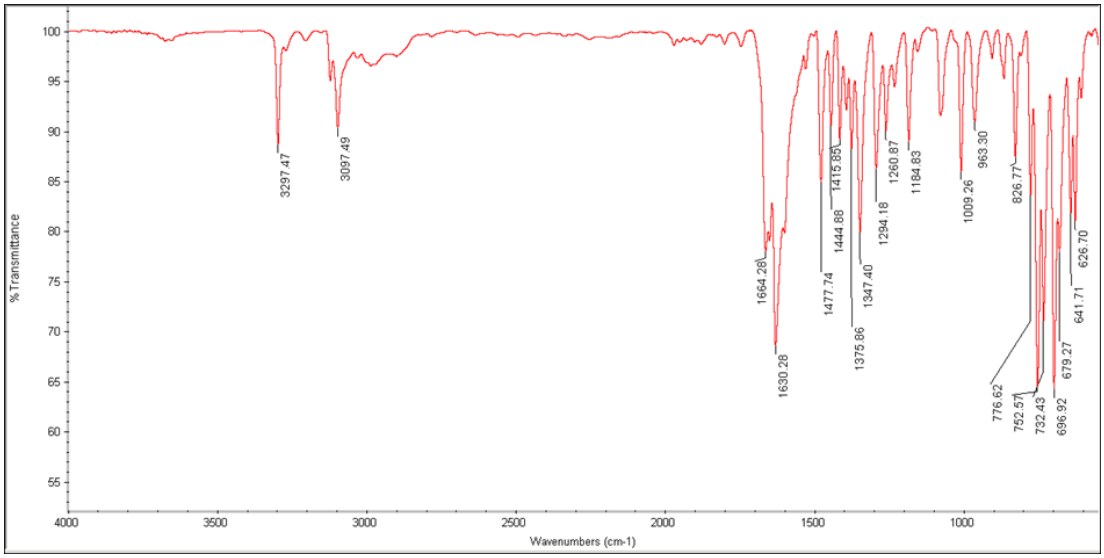

Figure 49 IR Spectrum of Compound **77**

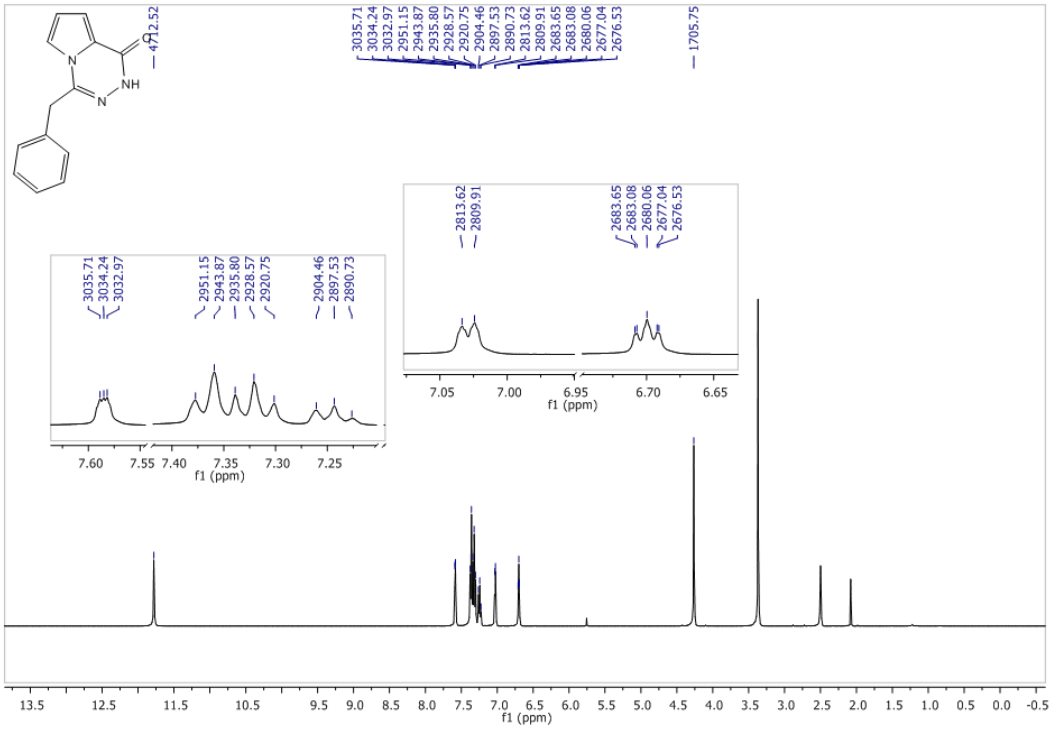

Figure 50 ^{1}H-NMR Spectrum of Compound **78** in DMSO-d_6

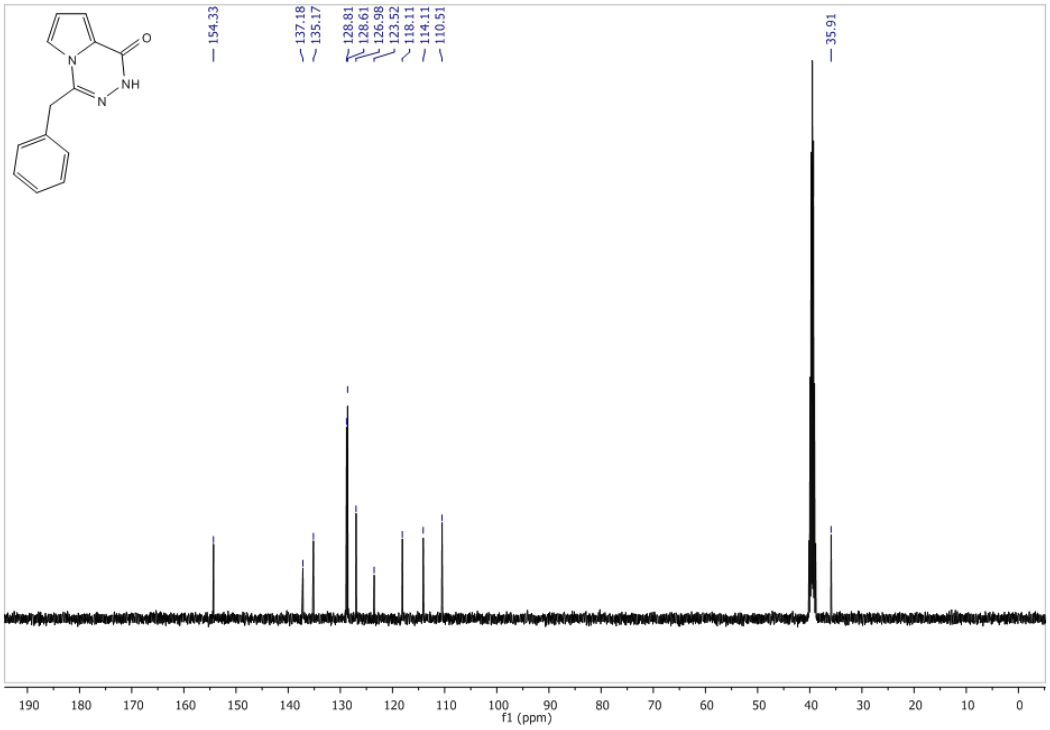

Figure 51 ^{13}C-NMR Spectrum of Compound **78** in DMSO-d_6

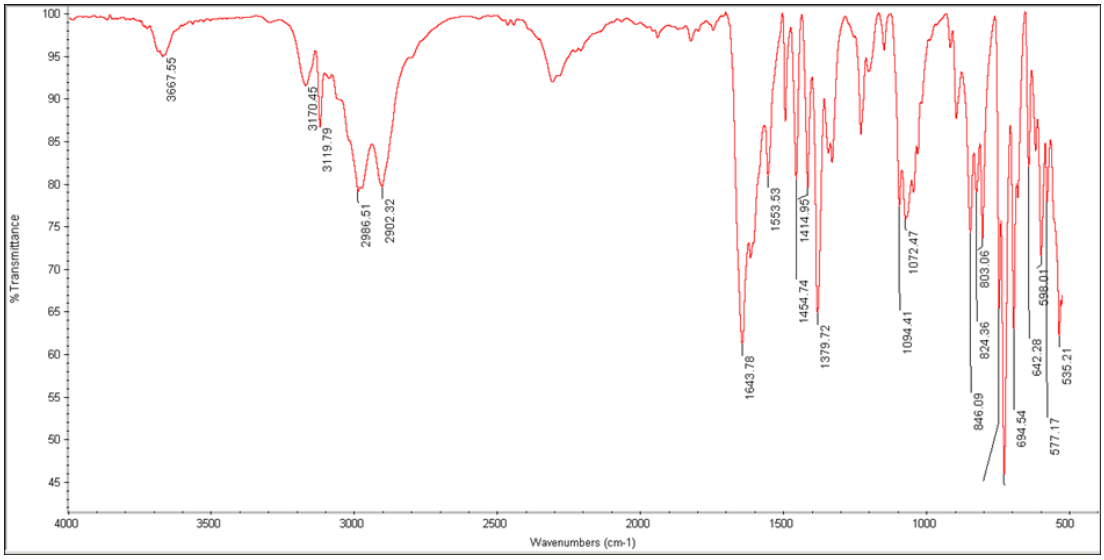

Figure 52 IR Spectrum of Compound **78**

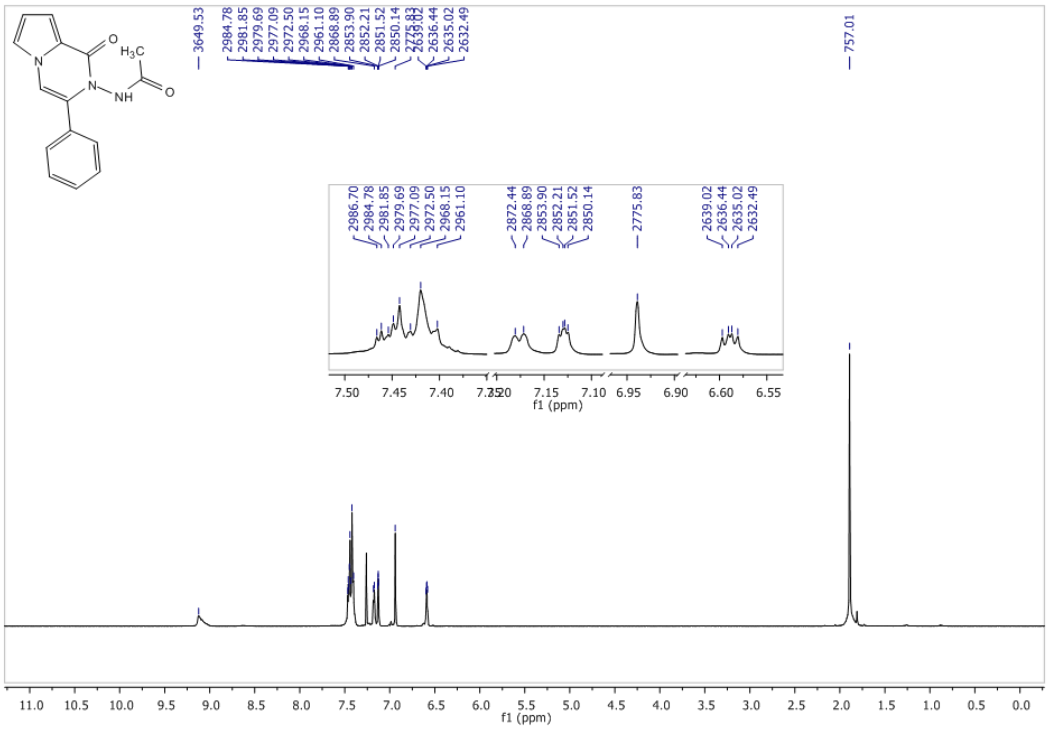

Figure 53 ^{1}H-NMR Spectrum of Compound **79** in $CDCl_3$

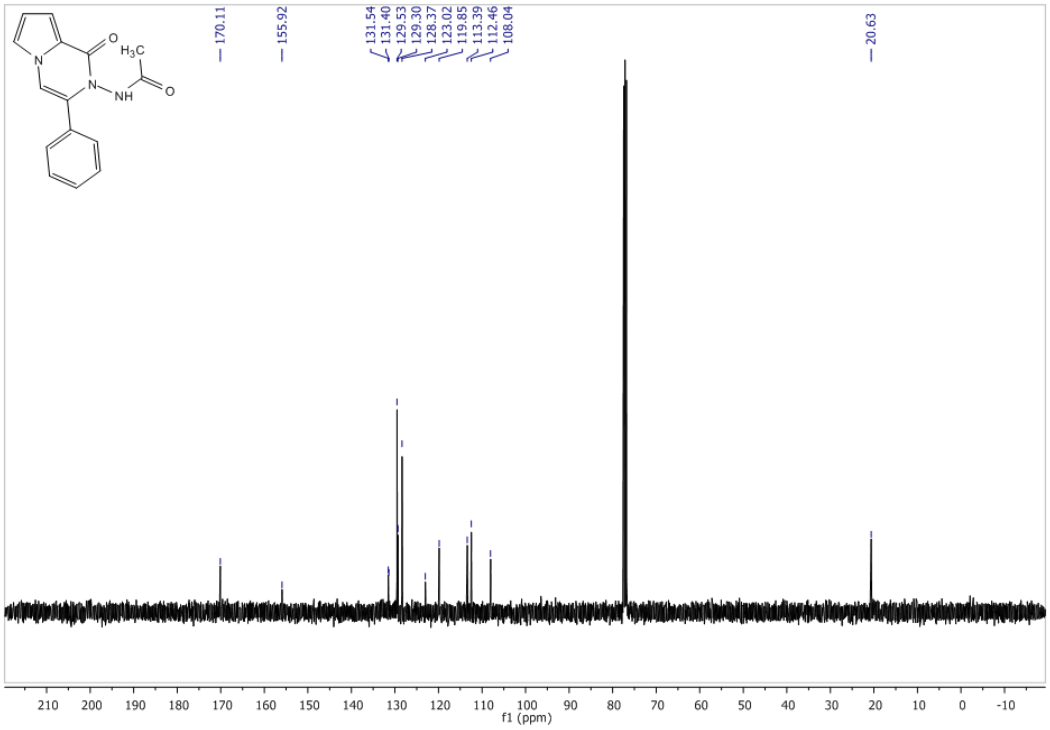

Figure 54 ^{13}C-NMR Spectrum of Compound **79** in $CDCl_3$

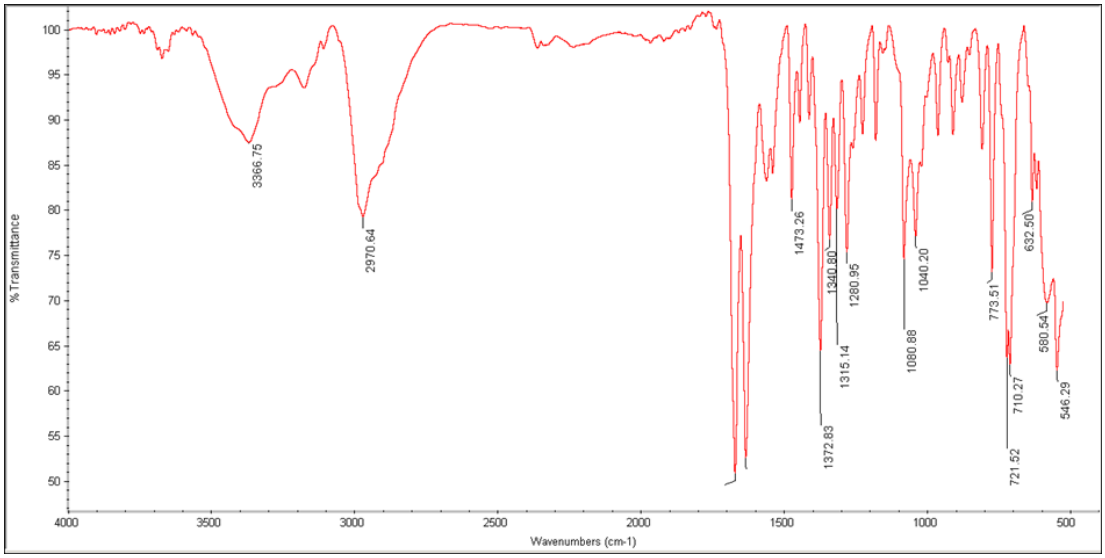

Figure 55 IR Spectrum of Compound **79**

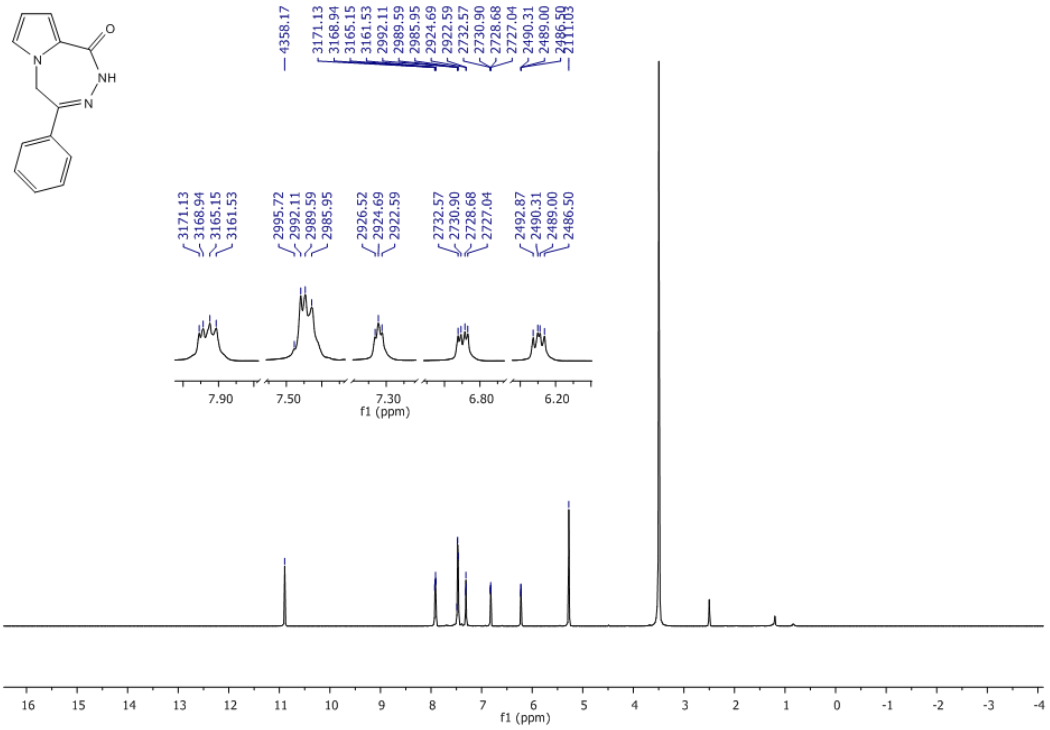

Figure 56 ^{1}H-NMR Spectrum of Compound **80** in DMSO-d_6

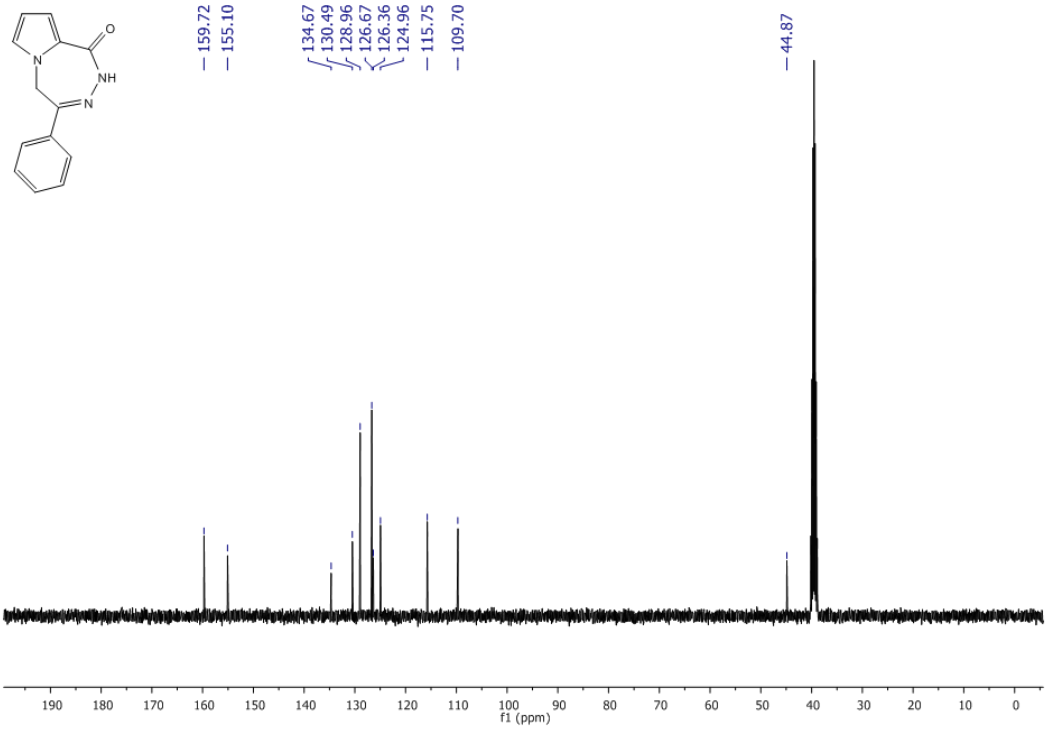

Figure 57 ^{13}C-NMR Spectrum of Compound **80** in DMSO-d_6

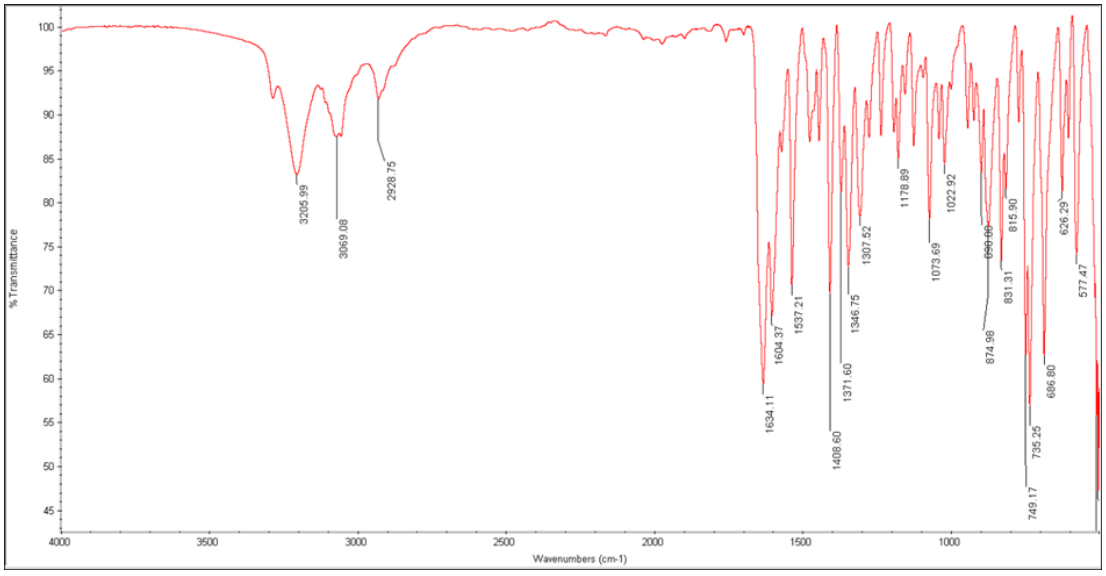

Figure 58 IR Spectrum of Compound **80**

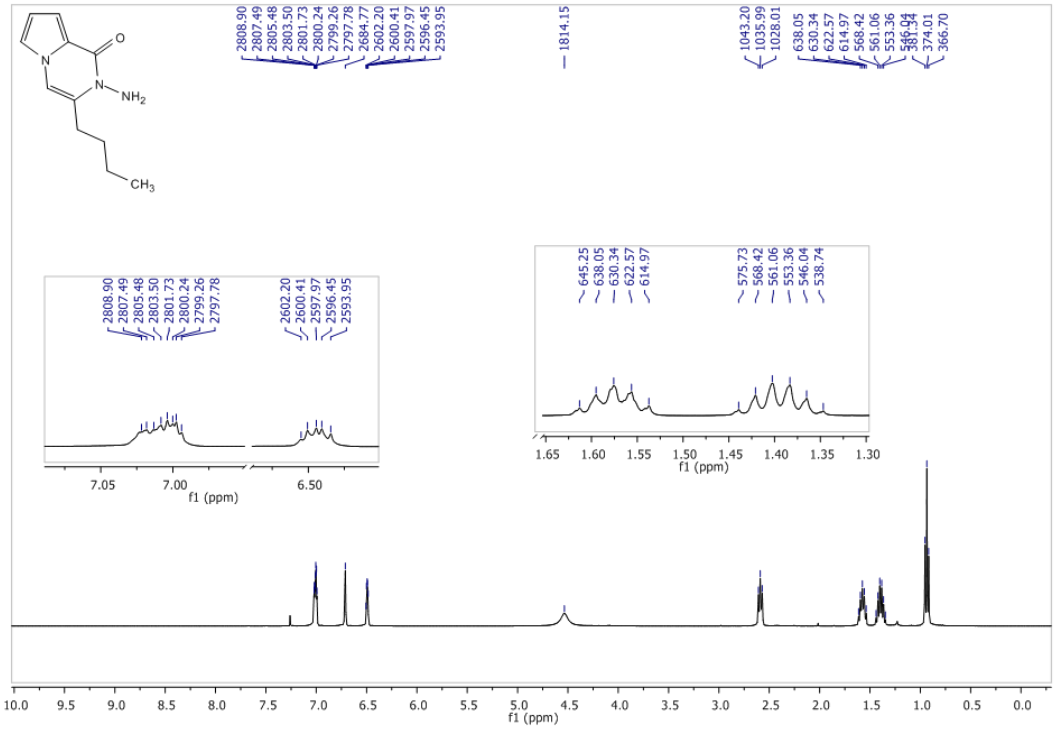

Figure 59 ^{1}H-NMR Spectrum of Compound **81** in $CDCl_3$

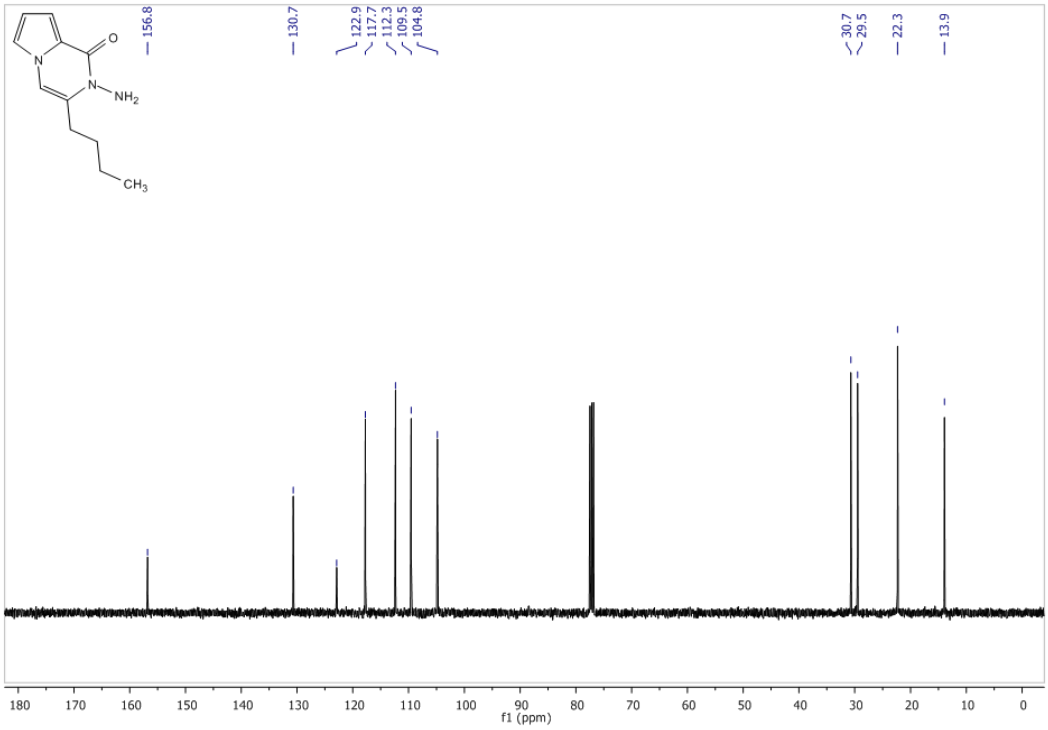

Figure 60 ^{13}C-NMR Spectrum of Compound **81** in $CDCl_3$

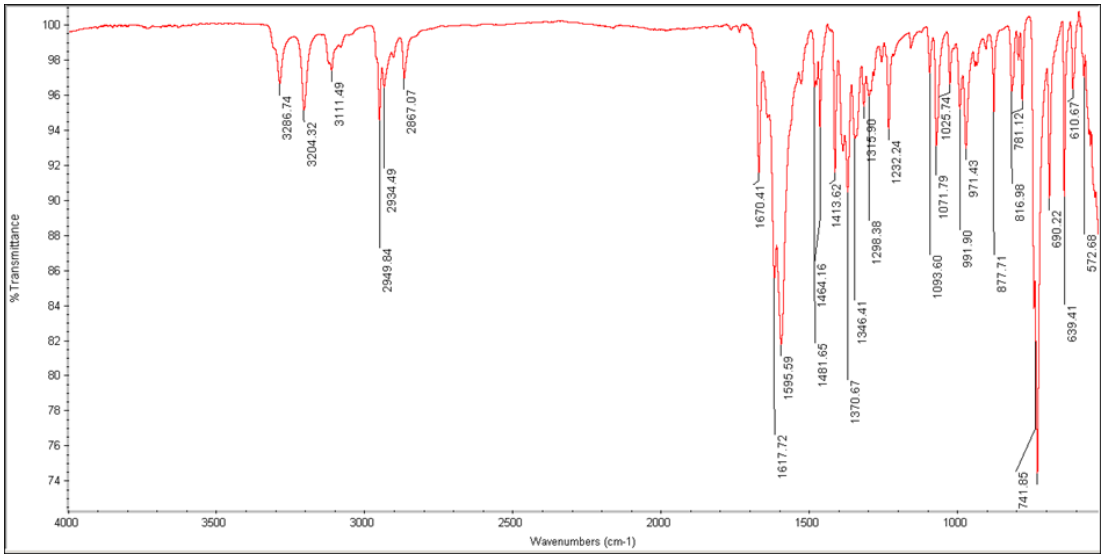

Figure 61 IR Spectrum of Compound **81**

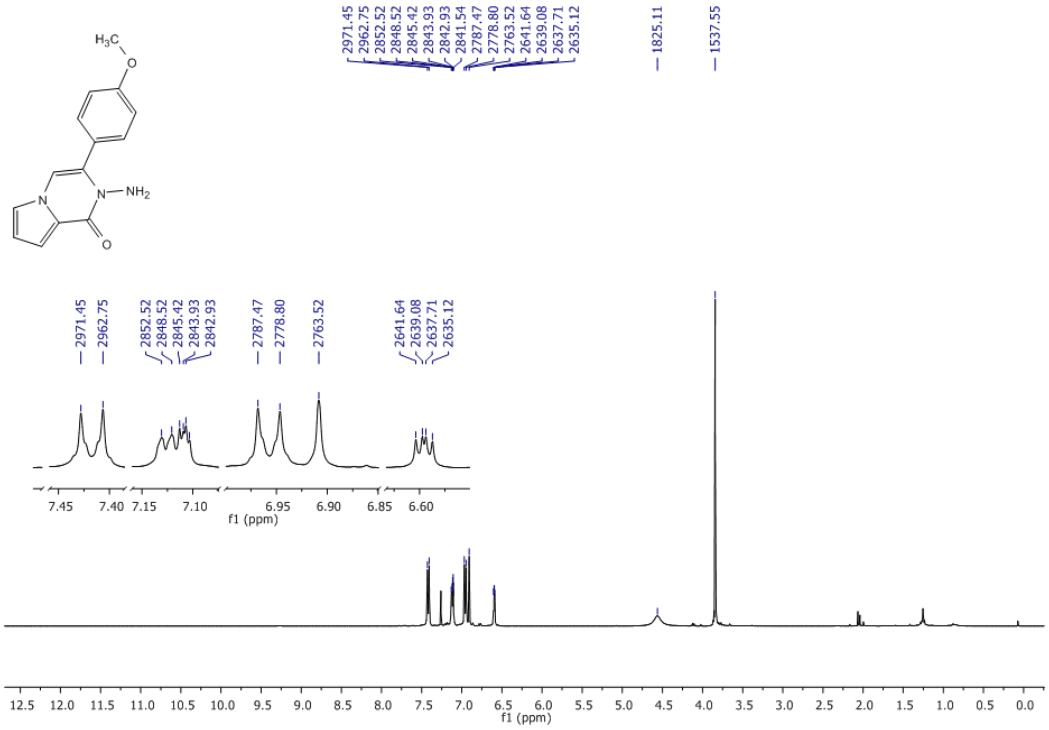

Figure 62 ^{1}H-NMR Spectrum of Compound **82** in $CDCl_3$

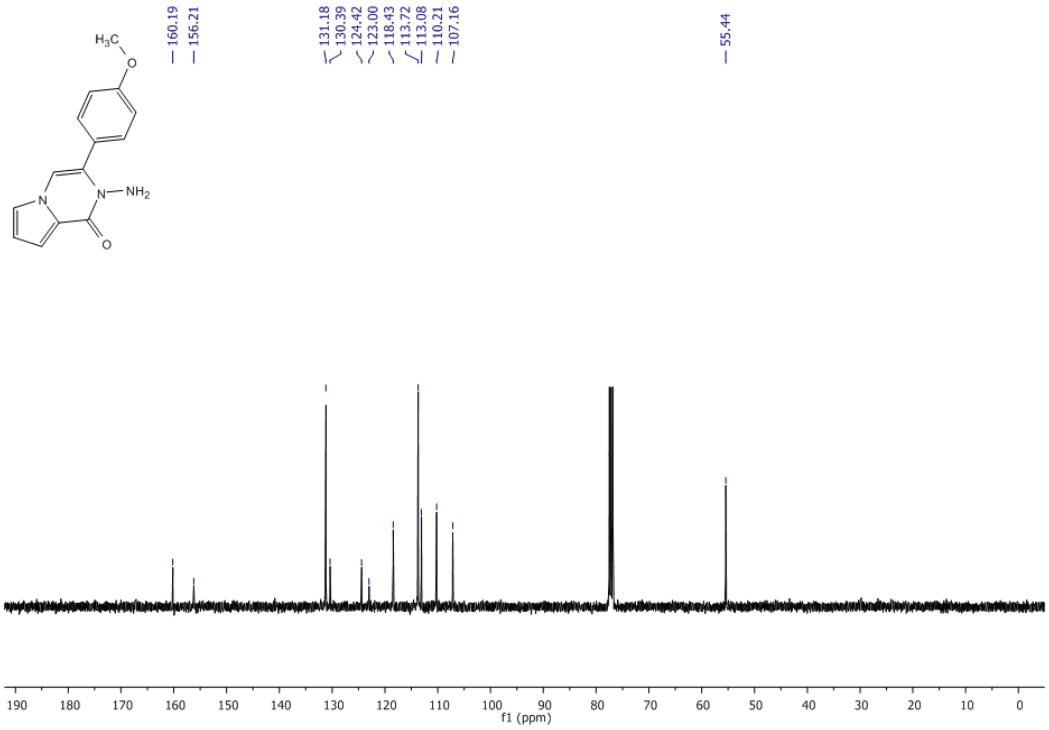

Figure 63 ^{13}C-NMR Spectrum of Compound **82** in $CDCl_3$

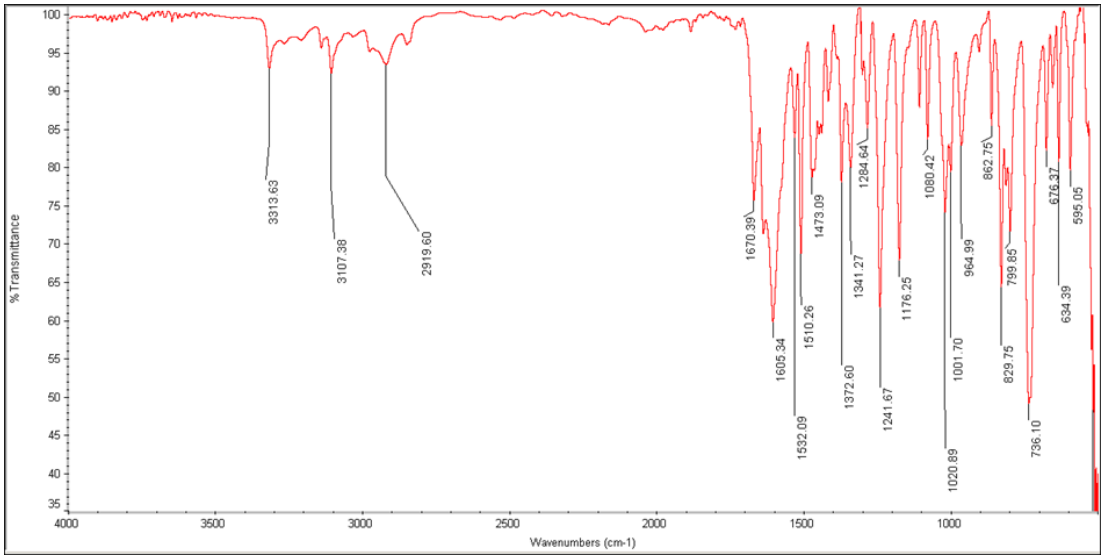

Figure 64 IR Spectrum of Compound **82**

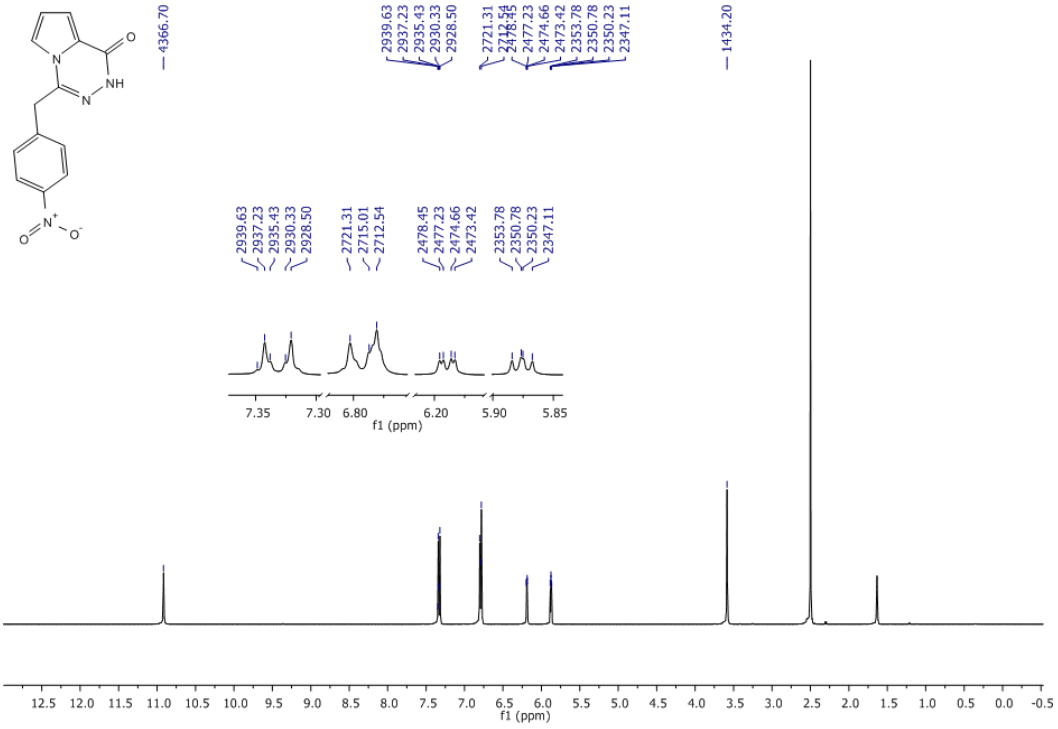

Figure 65 ^{1}H-NMR Spectrum of Compound **83** in DMSO-d_6

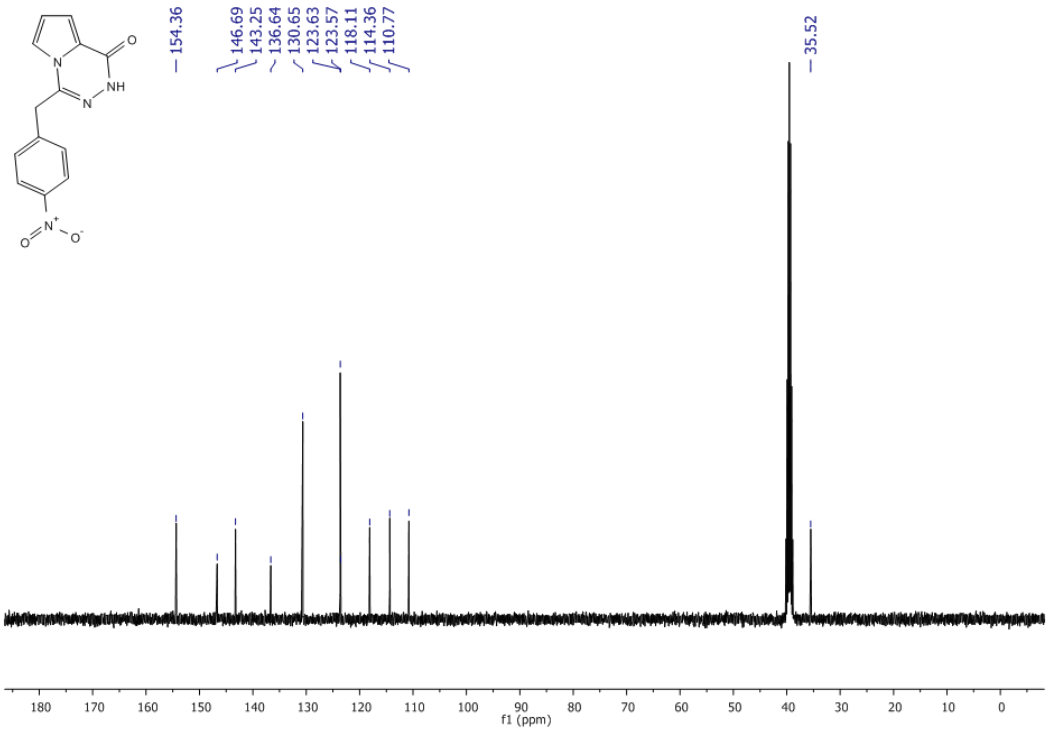

Figure 66 ^{13}C-NMR Spectrum of Compound **83** in DMSO-d_6

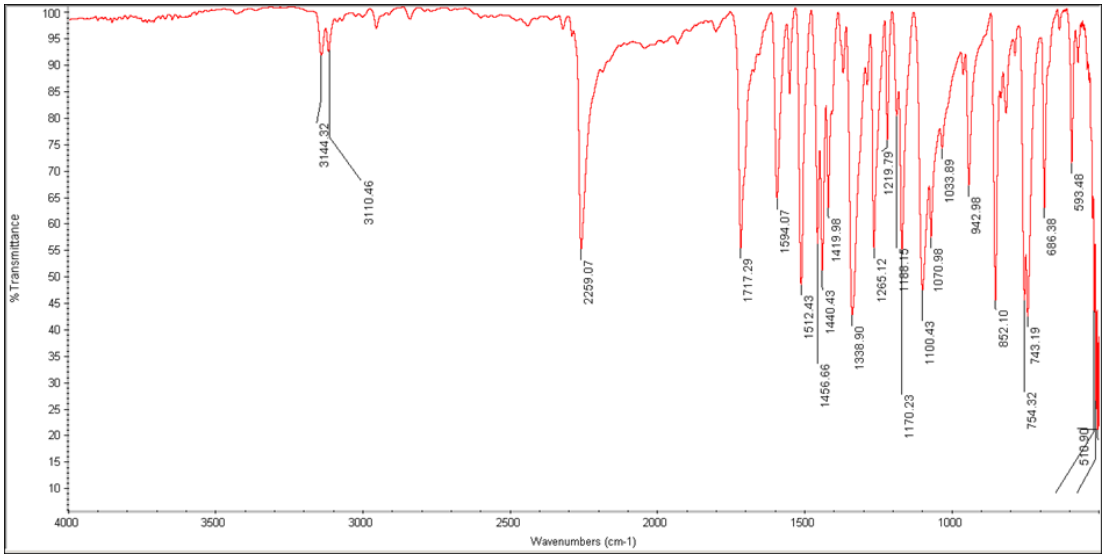

Figure 67 IR Spectrum of Compound **83**

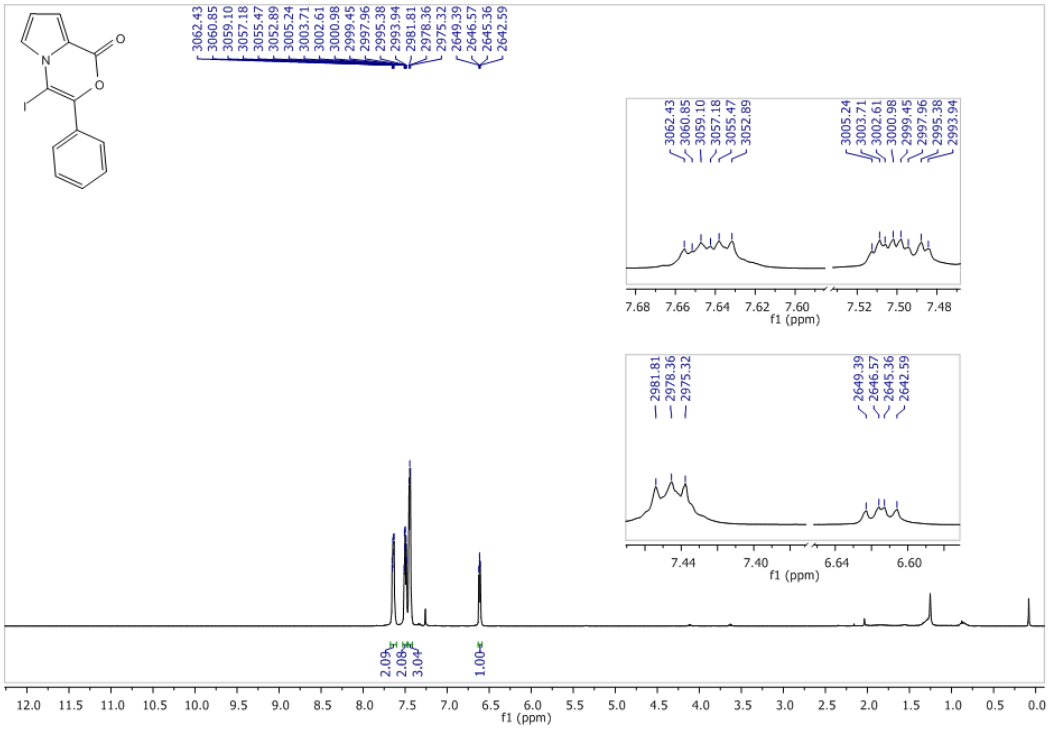

Figure 68 ^{1}H-NMR Spectrum of Compound **90** in $CDCl_3$

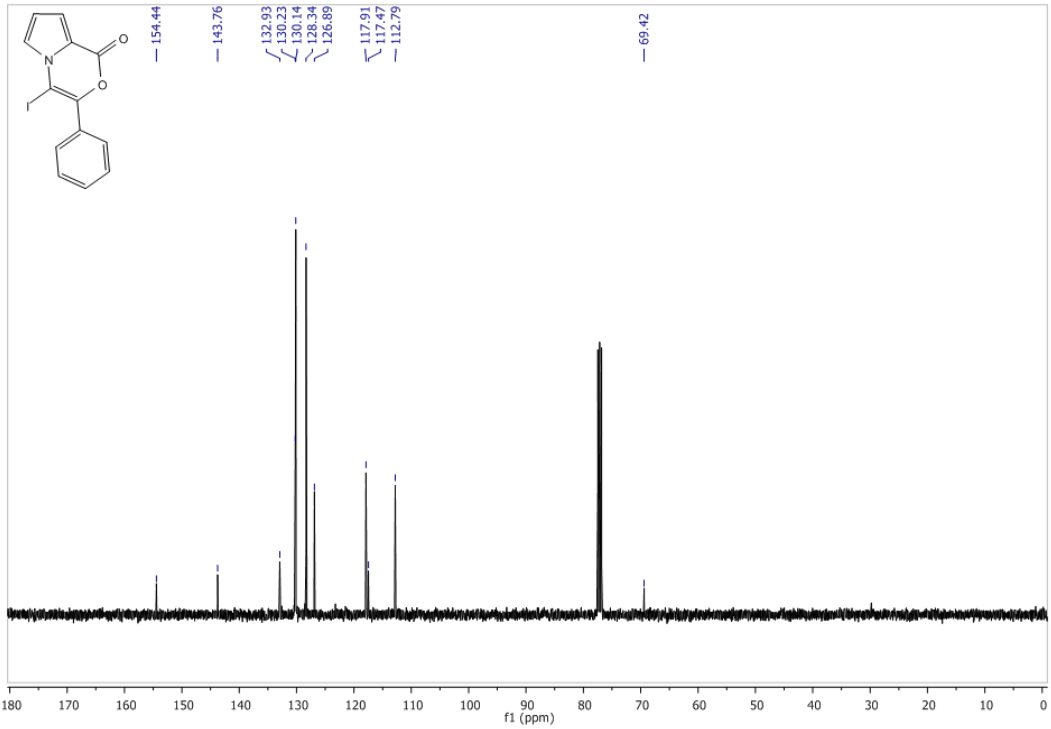

Figure 69 ^{13}C NMR Spectrum of Compound **90** in $CDCl_3$

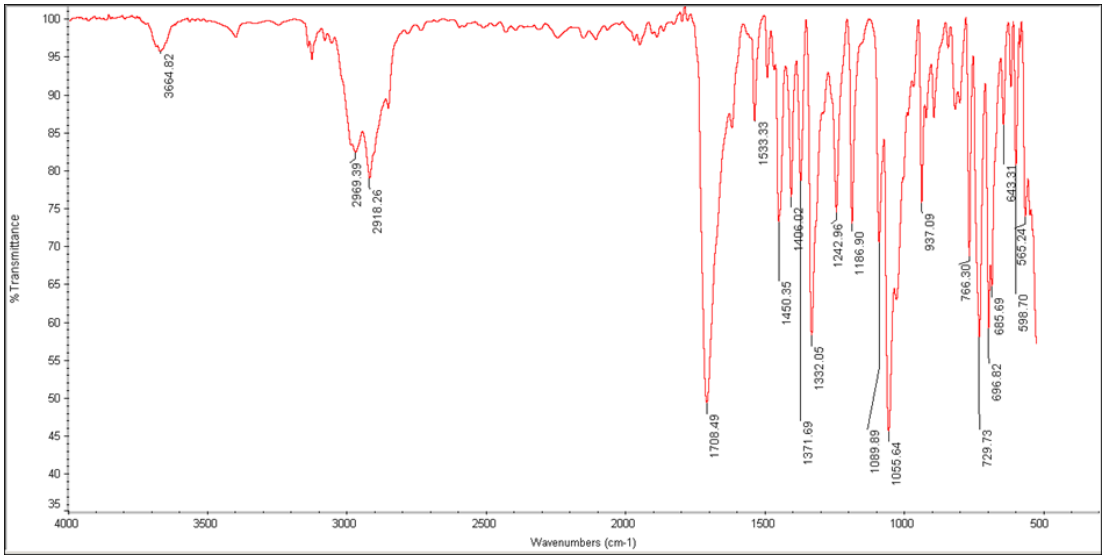

Figure 70 IR Spectrum of Compound **90**

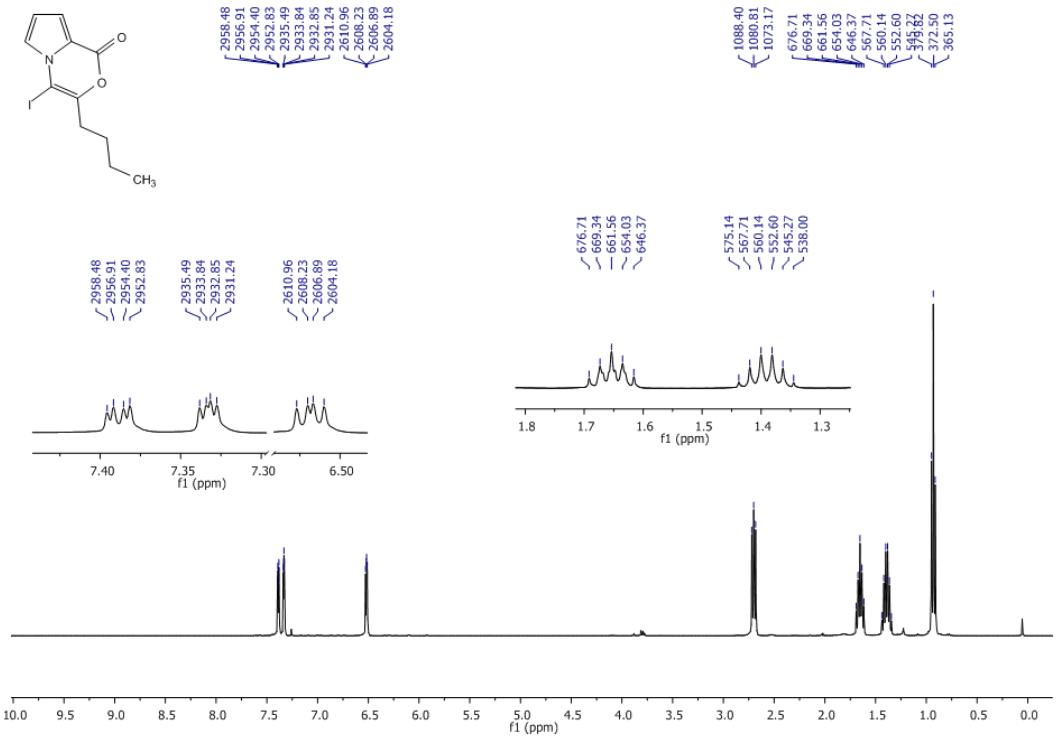

Figure 71 ^{1}H-NMR Spectrum of Compound **91** in $CDCl_3$

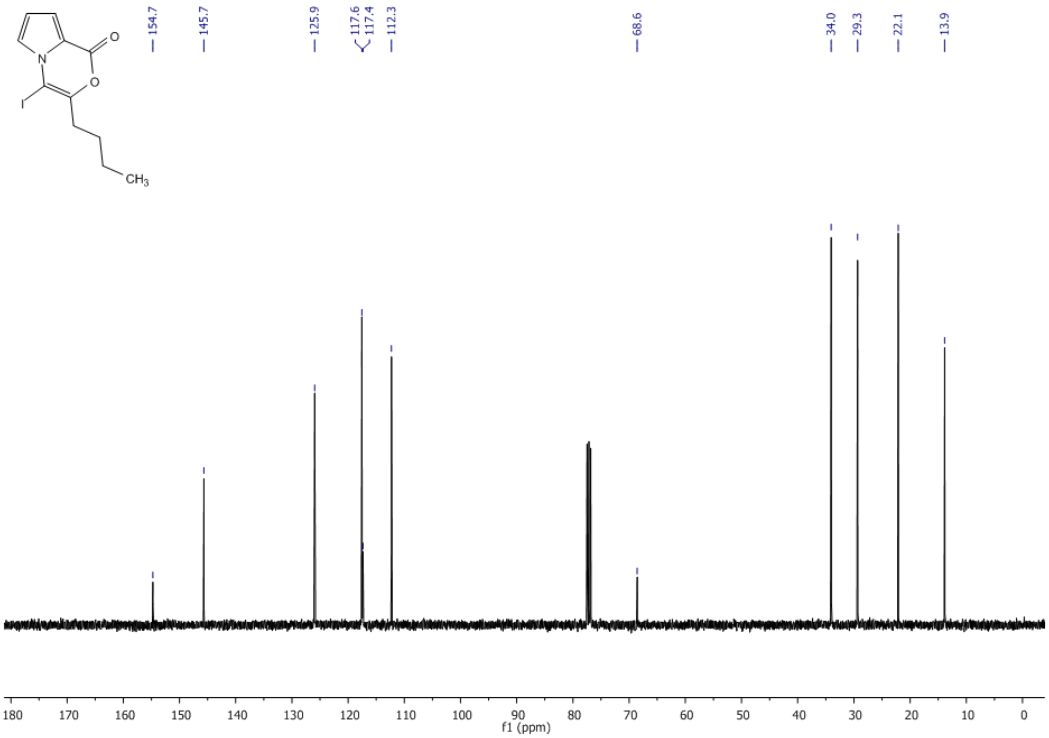

Figure 72 ^{13}C-NMR Spectrum of Compound **91** in $CDCl_3$

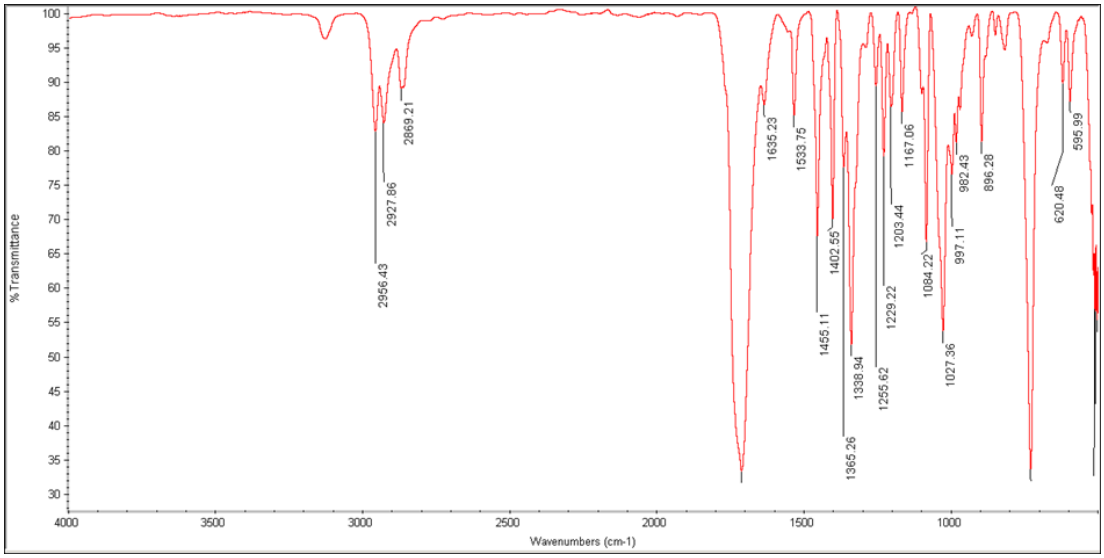

Figure 73 IR Spectrum of Compound **91**

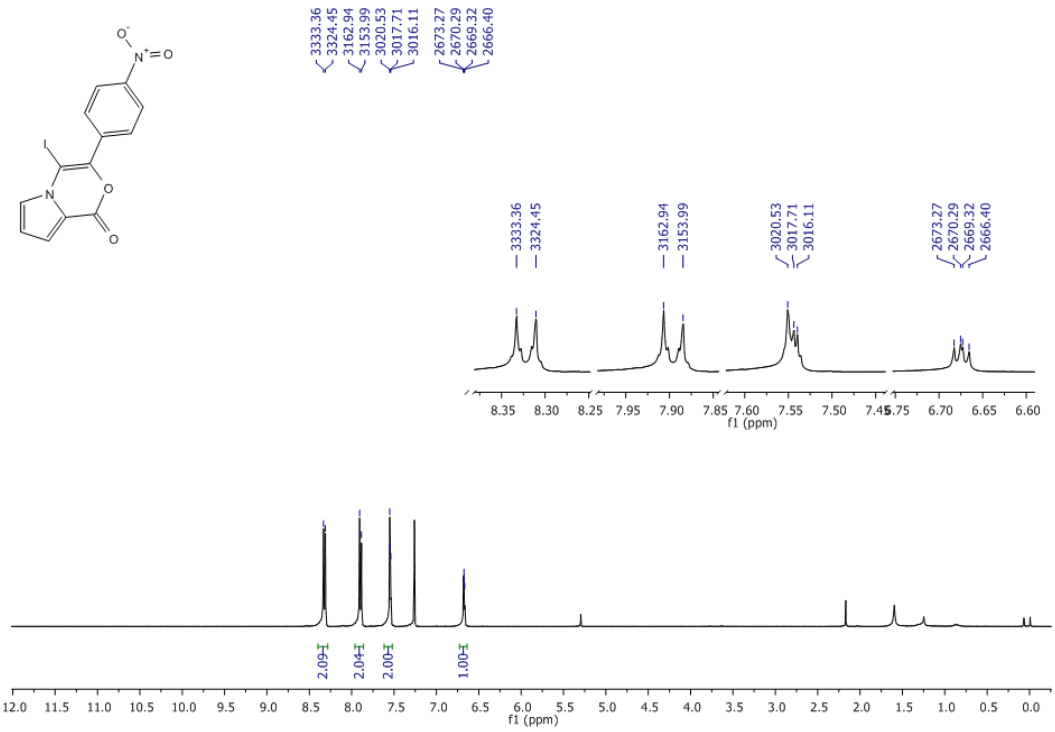

Figure 74 ^{1}H-NMR Spectrum of Compound **92** in $CDCl_3$

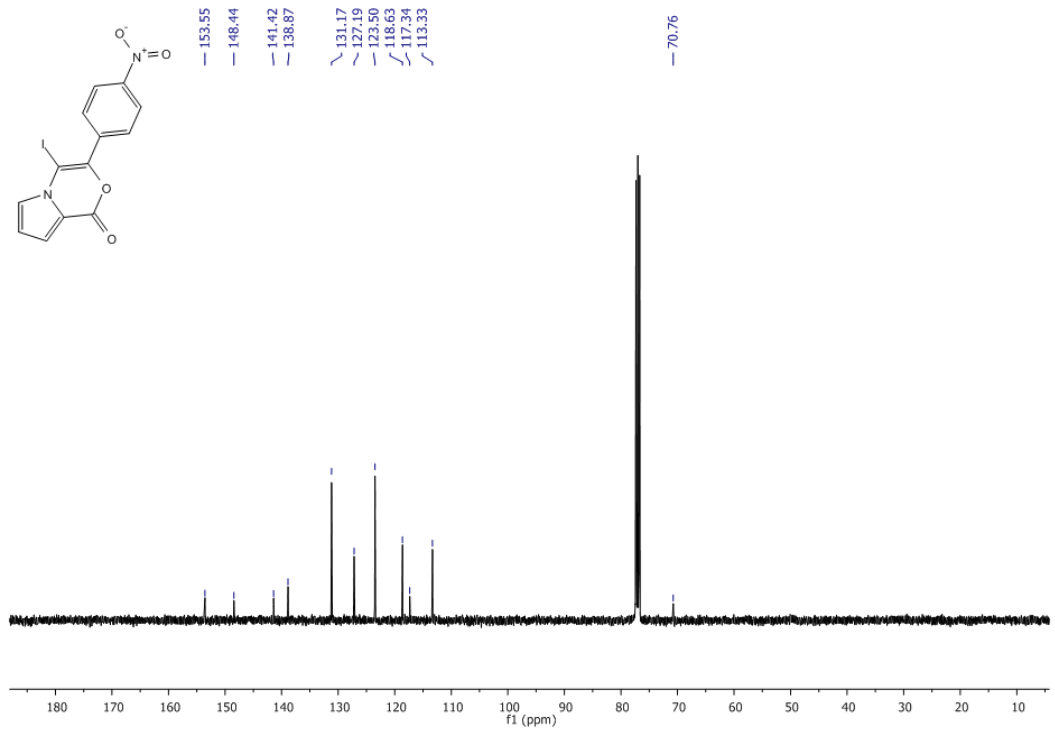

Figure 75 ^{13}C NMR Spectrum of Compound **92** in $CDCl_3$

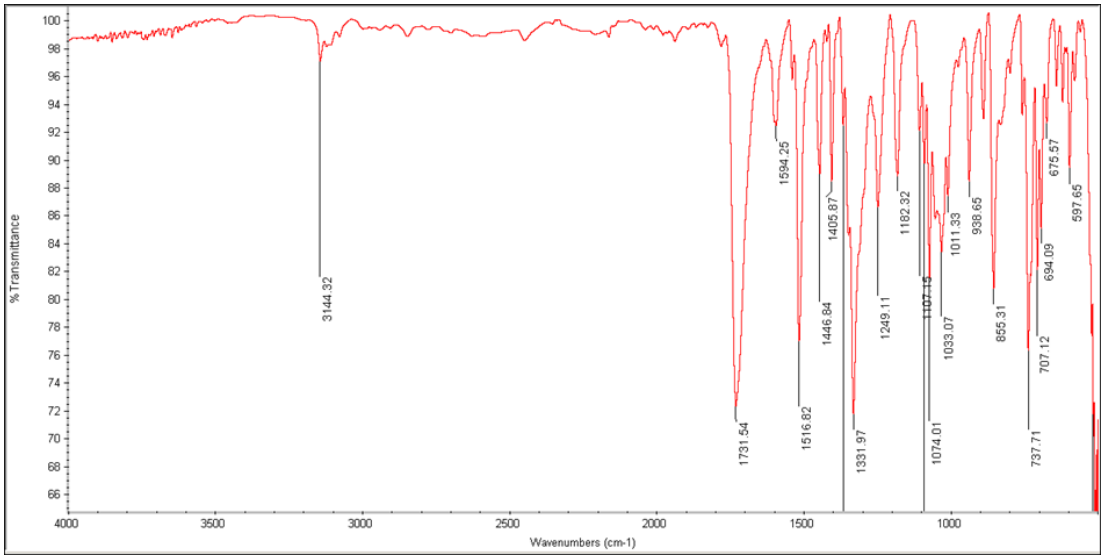

Figure 76 IR Spectrum of Compound **92**

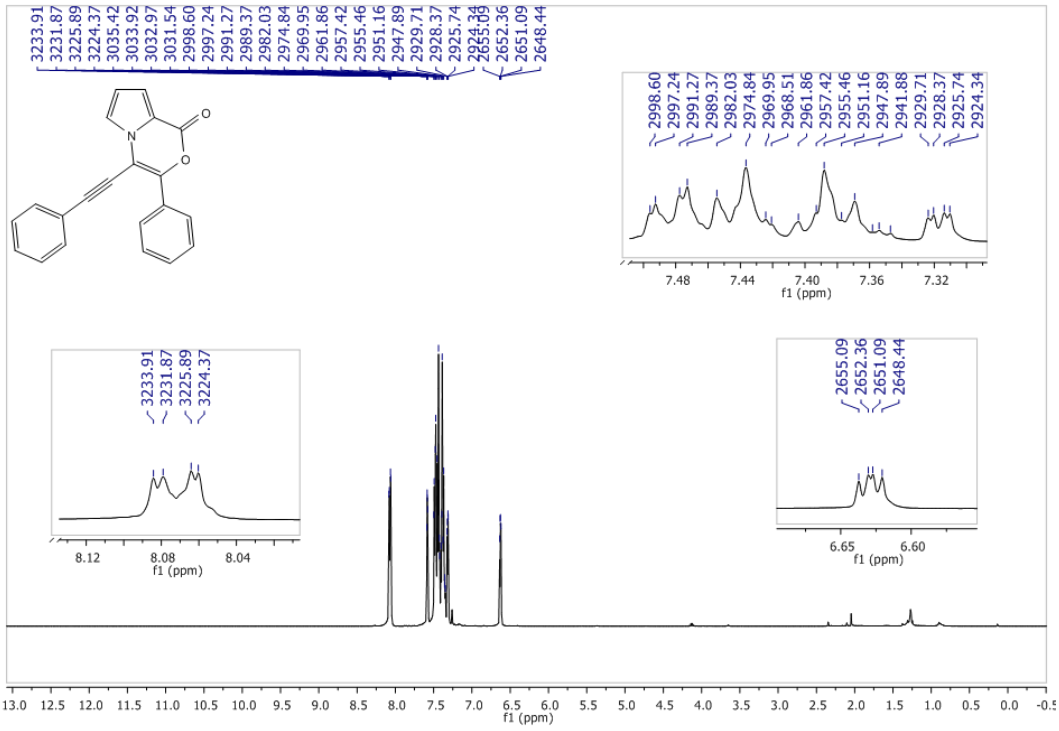

Figure 77 ^{1}H-NMR Spectrum of Compound **93** in $CDCl_3$

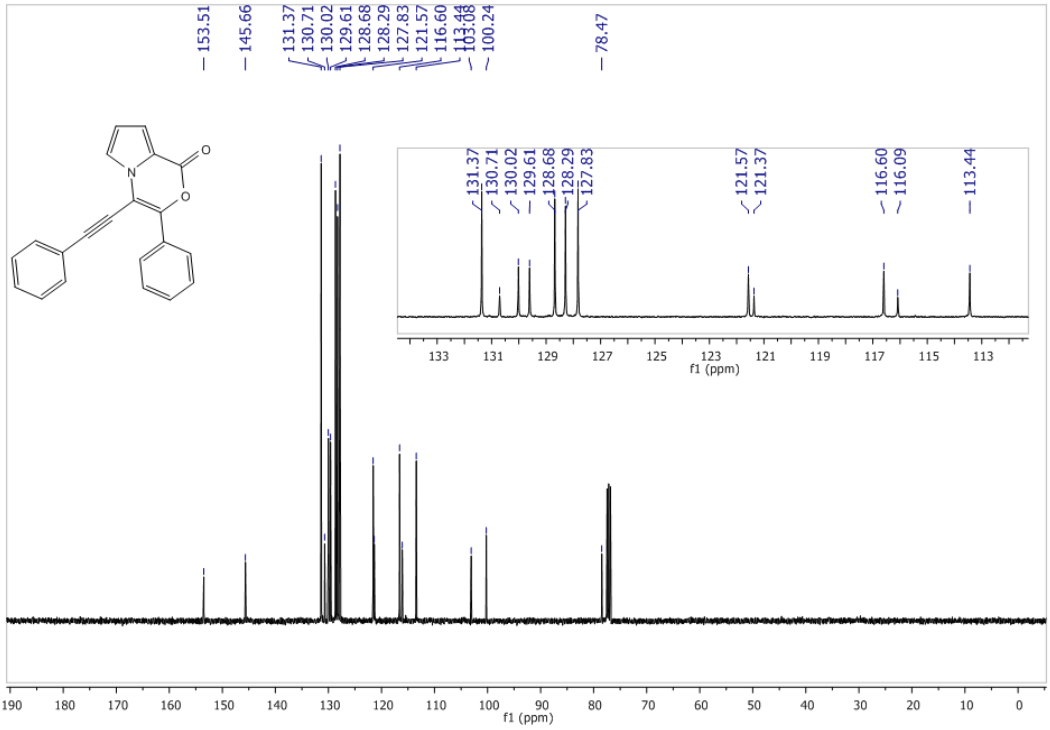

Figure 78 ^{13}C-NMR Spectrum of Compound **93** in $CDCl_3$

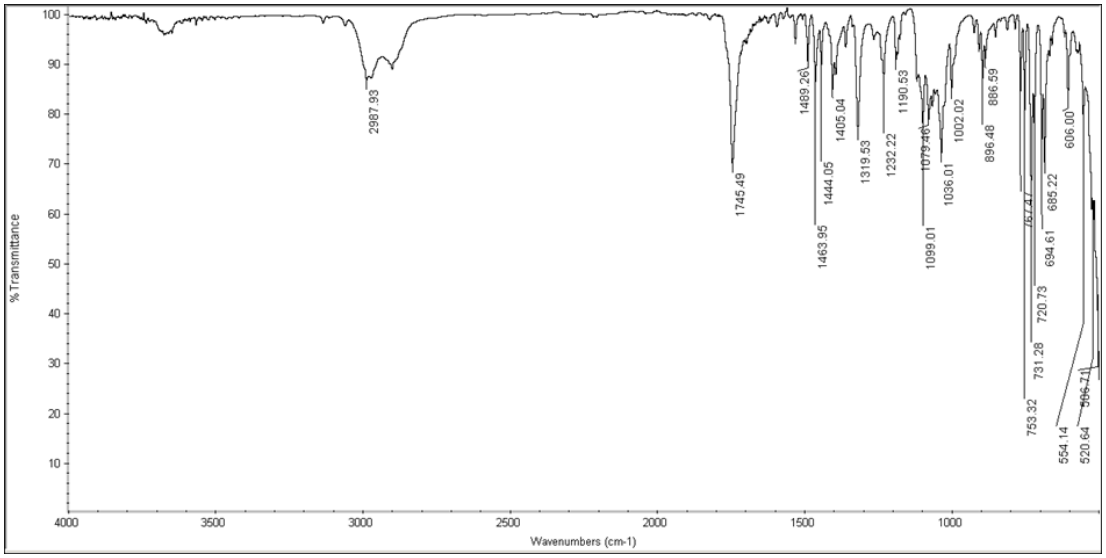

Figure 79 IR Spectrum of Compound **93**

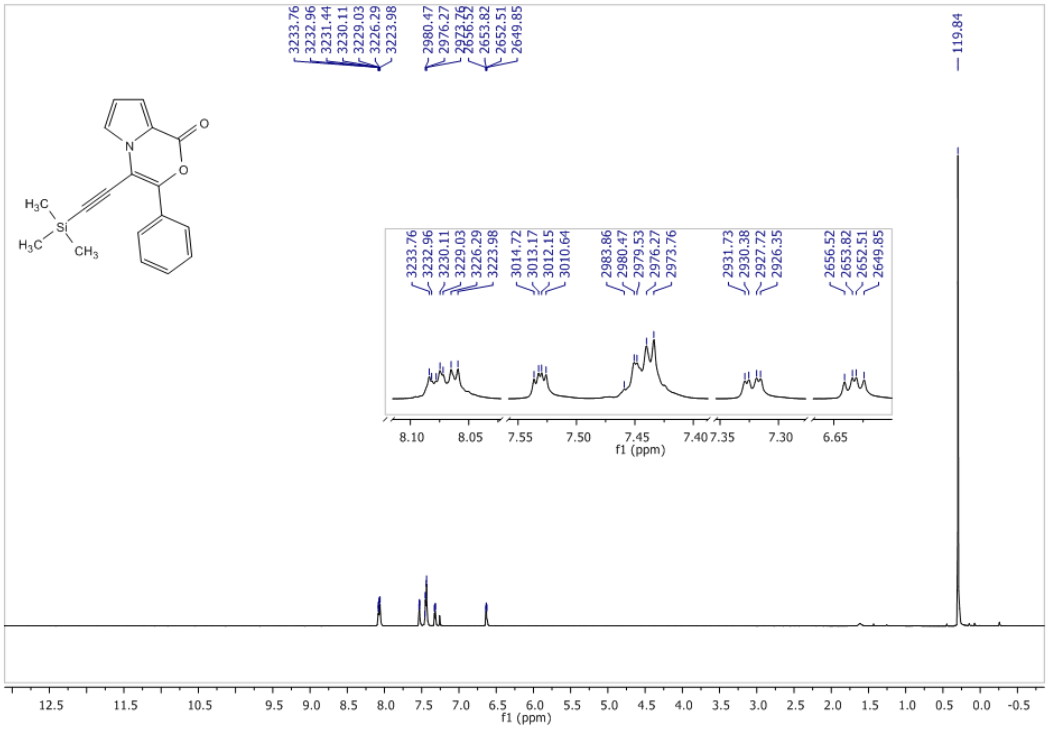

Figure 80 ^{1}H-NMR Spectrum of Compound **94** in $CDCl_3$

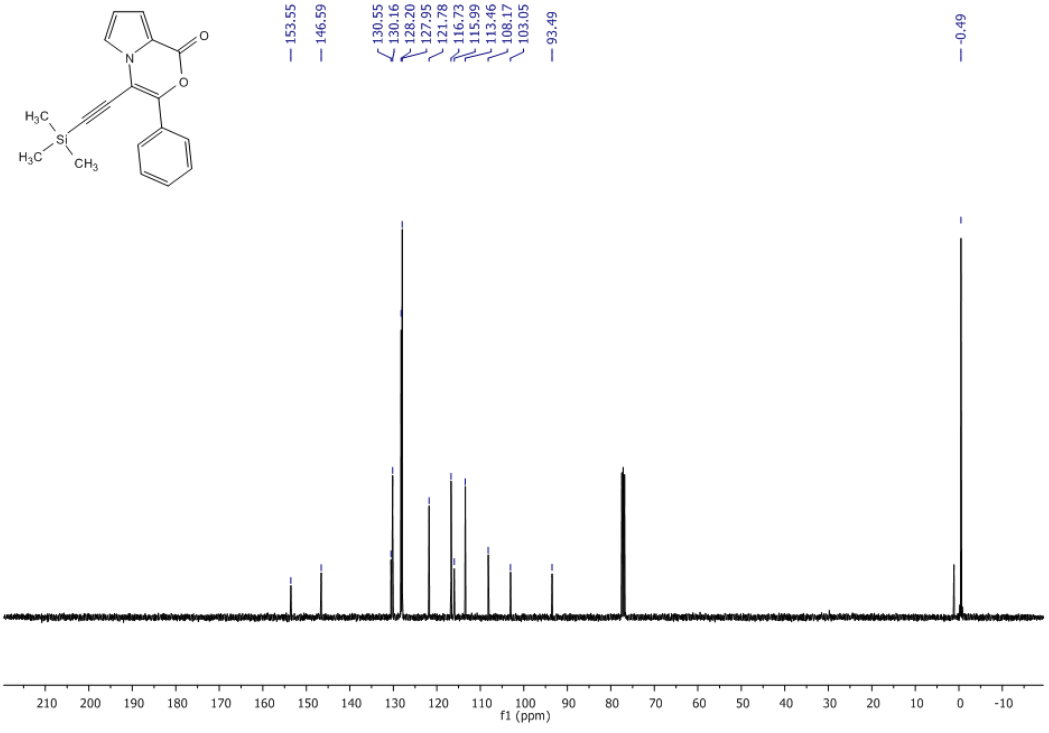

Figure 81 ^{13}C-NMR Spectrum of Compound **94** in $CDCl_3$

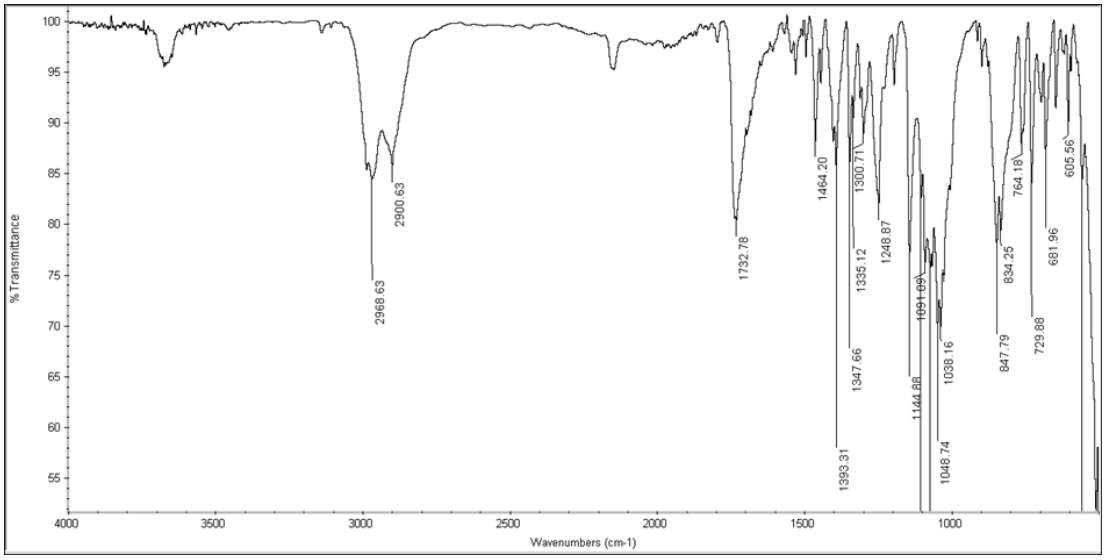

Figure 82 IR Spectrum of Compound **94**

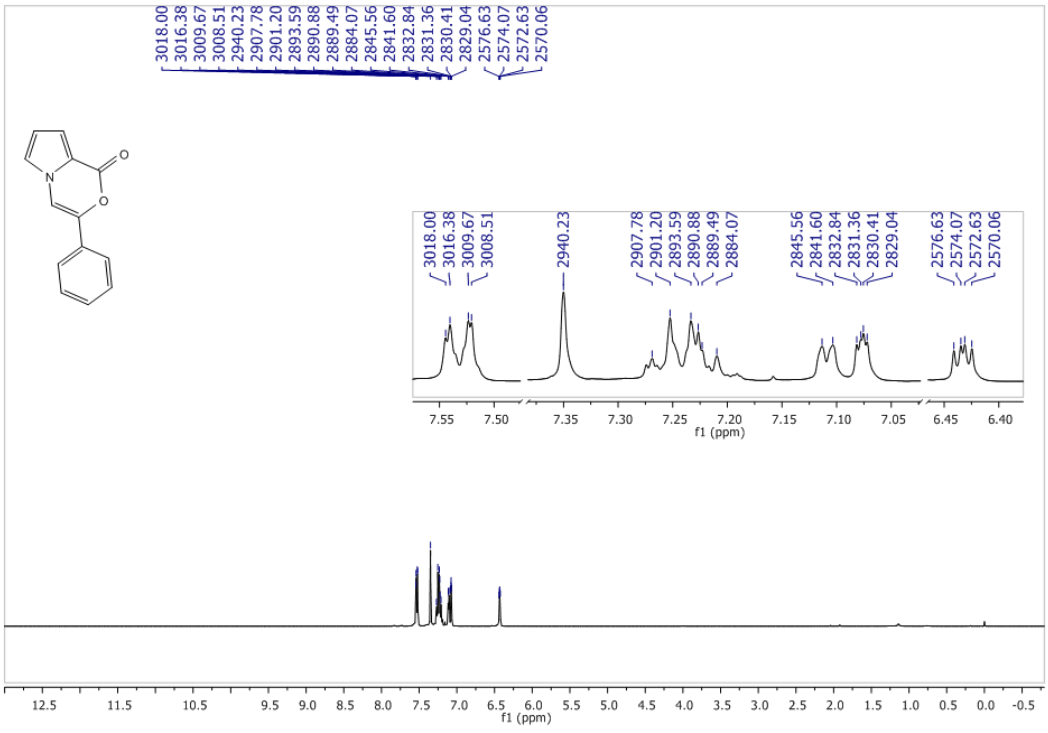

Figure 83 ^{1}H-NMR Spectrum of Compound **95** in $CDCl_3$

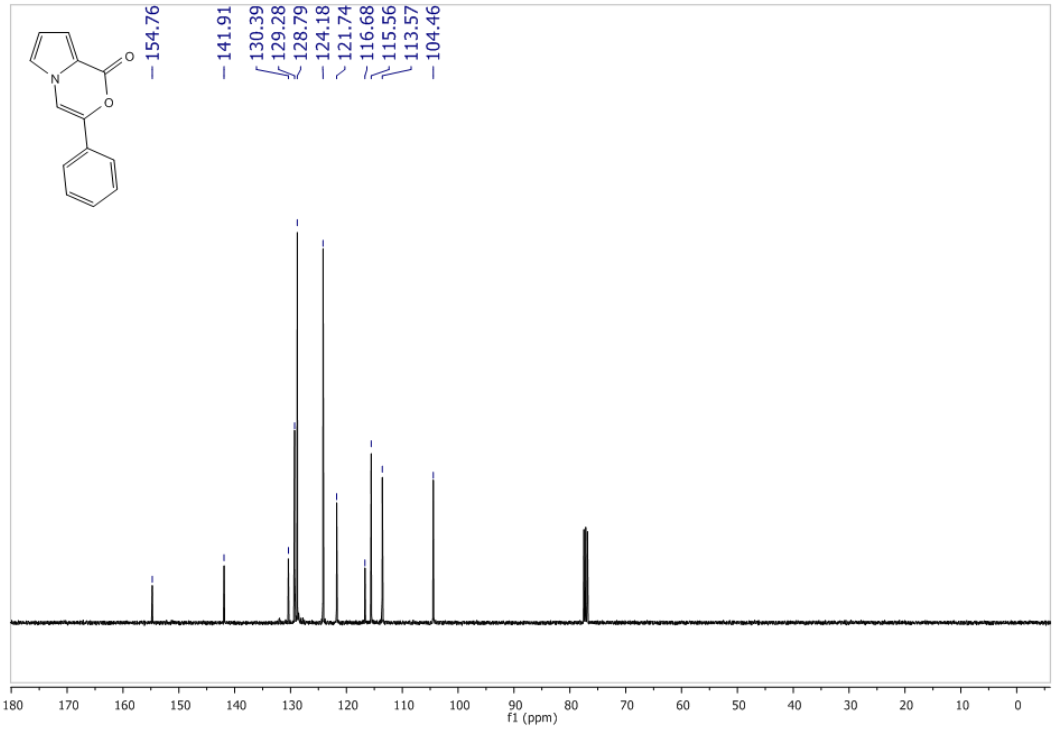

Figure 84 ^{13}C-NMR Spectrum of Compound **95** in $CDCl_3$