DEVELOPMENT OF A NEW METHOD FOR THE SYNTHESIS OF BENZO[*h*][1,6]NAPHTHYRIDINE DERIVATIVES AND CHROMENOPYRAZINONE SKELETON

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DEVELOPMENT OF A NEW METHOD FOR THE SYNTHESIS OF BENZO[*h*][1,6]NAPHTHYRIDINE DERIVATIVES AND CHROMENOPYRAZINONE SKELETON

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ABSTRACT

DEVELOPMENT OF A NEW METHOD FOR THE SYNTHESIS OF BENZO[*h*][1,6]NAPHTHYRIDINE DERIVATIVES AND CHROMENOPYRAZINONE SKELETON

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In the first part of this thesis, a new methodology was developed for the synthesis of benzo[*h*][1,6]naphthyridine derivatives. Firstly, 2-(diprop-2-ynylamino)benzaldehyde was synthesized starting from 2-aminobenzoic acid in three steps. Then, cyclization reaction was achieved in the presence of propargyl amine and DBU. The expected 3-methylbenzo[*h*][1,6]naphthyridine was obtained. To generalize this methodology, several derivatives of 2-(diprop-2-ynylamino)benzaldehyde were synthesized by applying Sonogashira coupling reaction in good yields. Cyclization reaction of these derivatives were succeeded by using propargyl amine and DBU. Finally, aryl and methyl substituted benzo[*h*][1,6]naphthyridine derivatives were obtained in good yields.

In the second part, a new synthetic method for the synthesis of a chromenopyrazine and a chromenopyrazinone derivative was developed. Firstly, acetonitrile group was introduced to salicylaldehyde. Then, reaction of this aldehyde with propargyl amine gave imine. DBU-supported cyclization reaction afforded the product, 3-methyl-5*H*-chromeno[3,4-*b*]pyrazine. Finally, cyclization product was oxidized with CrO_3/pyridine to yield 3-methyl-5*H*-chromeno[3,4-*b*]pyrazin-5-one. In order to generalize this reaction, two different aldehyde substituted at the benzene ring were employed. Same procedure for cyclization reaction was applied to get chromenopyrazine derivatives. Unfortunately, expected chromenopyrazine and chromenopyrazinone derivatives were not obtained.

Keywords: Sonogashira coupling, Aza-Diels-Alder reaction, benzo-naphthyridine, chromenopyrazine, chromenopyrazinone

ÖZ

BENZO[*h*][1,6]NAFTİRİDİN TÜREVLERİNİN VE KROMENOPİRAZİNON İSKELETİNİN SENTEZİ İÇİN YENİ YÖNTEMLERİN GELİŞTİRİLMESİ

Hoplamaz, Emre
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Balcı

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Çalışmanın ilk kısmında, benzo[*h*][1,6]naftiridin türevlerinin sentezi için yeni bir yöntem geliştirildi. İlk olarak, 2-aminobenzoik asitten başlayarak üç basamakta 2-(diprop-2-inilamino)benzaldehit sentezlendi. Ardından, propargil amin ve DBU kullanılarak halkalaşma tepkimesi gerçekleştirildi. Beklenen halkalaşma ürünü 3-metilbenzo[*h*][1,6]naftiridin elde edildi. Bu yöntemin genel bir metot olduğunu gösterebilmek için Sonogashira kenetlenme tepkimesi kullanılarak başlangıç maddesi olan 2-(diprop-2-inilamino)benzaldehit'in çeşitli türevleri sentezlendi. Propargil amin ve DBU kullanılarak bu türevlerin halkalaşma tepkimeleri başarıyla gerçekleştirildi. Sonuç olarak yeni bir yöntem kullanarak aril and metil sübstitüe benzo[*h*][1,6]naftiridin'in türevleri iyi verimlerle sentezlendi.

Çalışmanın ikinci kısmında, kromenopirazin ve kromenopirazinon iskeletinin sentezi için yeni bir sentetik metot geliştirildi. İlk olarak, asetonitril grubu salisilaldehide takıldı. Ardından, aldehit ile propargil amin reaksiyona sokularak imin türevi elde edildi. İminin DBU eşliğinde kapanma reaksiyonu sonucu 3-metil-5*H*-kromeno[3,4-*b*]pirazin elde edildi. Sonuç olarak, kapanma ürününün CrO_3/piridin ile yükseltgenmesiyle 3-metil-5*H*-kromeno[3,4-*b*]pirazin-5-on bileşiği elde edildi. Bu kapanma reaksiyonunu genellemek için iki farklı aldehit kullanıldı. Kapanma tepkimesi için aynı prosedür uygulandı. Maalesef, beklenen kromenopirazin and kromenopirazinon türevleri elde edilemedi.

Keywords: Sonogashira kenetlenmesi, Aza-Diels-Alder tepkimesi, benzo-naftiridin, kromenopirazin, kromenopirazino

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To my lovely wife …

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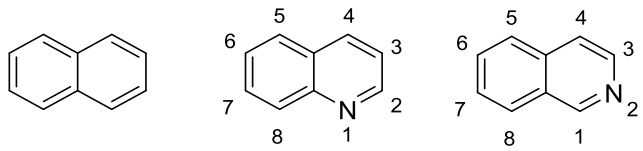
CHAPTER 1

BENZONAPTHYRIDINES

1.1. INTRODUCTION

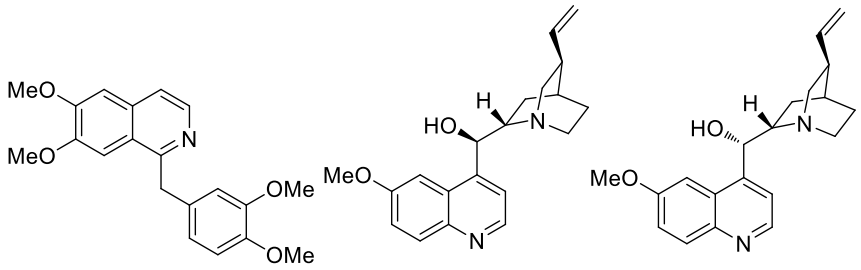
1.1.1. Quinolines

Quinoline is a heterocyclic aromatic molecule with the chemical formula C_9H_7N. It is the simplest *N*-heteropolycyclic aromatic compound. In quinoline, one of the carbon atoms (except bridge carbon atoms) of naphthalene (**1**) is replaced with a nitrogen atom. There are two structural isomers of benzopyridine which are quinoline (**2**) and isoquinoline (**3**). Quinoline is also named as a 1-azanaphtalene and isoquinoline is named as a 2-azanaphtalene.



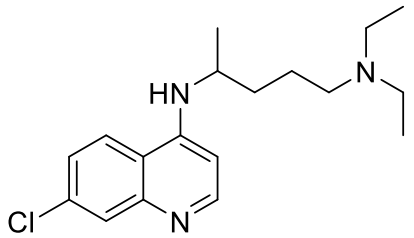
1 **2** **3**

Among many aromatic compounds, quinoline derivatives are one of the most important aromatic compounds. Because, most of natural products and drugs contain quinolines skeleton. For example, papaverine (**4**) being isolated from opium plant is used for the treatment of heart spasm and erectile dysfunction.[1,2,3]



4 **5** **6**

Quinine (**5**) which is isolated from cinchona tree is used as an antimalarial and an analgesic drug. In addition to these, quinidine (**6**) which is a diastereoisomer of quinine is one of most potent of the antiarrhythmic compounds.[4] Chloroquine (**7**) has long been used in the treatment of malaria and autoimmune disorders.[5] It was reported that compound **8a** and compound **8b** show good anticancer activity against different cancer cell lines like colon cancer, breast cancer, and lung cancer.[6,7]



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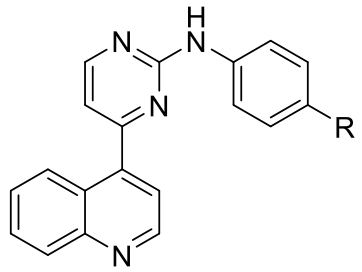
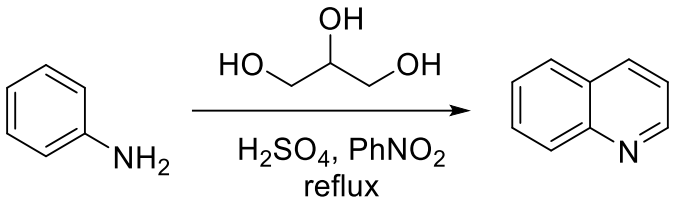


8a R = CH_3
8b R = OCH_3

1.1.1.1. Synthesis of quinoline derivatives

There are many methods which are reported in literature for the synthesis of quinoline derivatives. Two of them; Skraup quinoline synthesis and Pfitzinger quinoline synthesis are shown below.

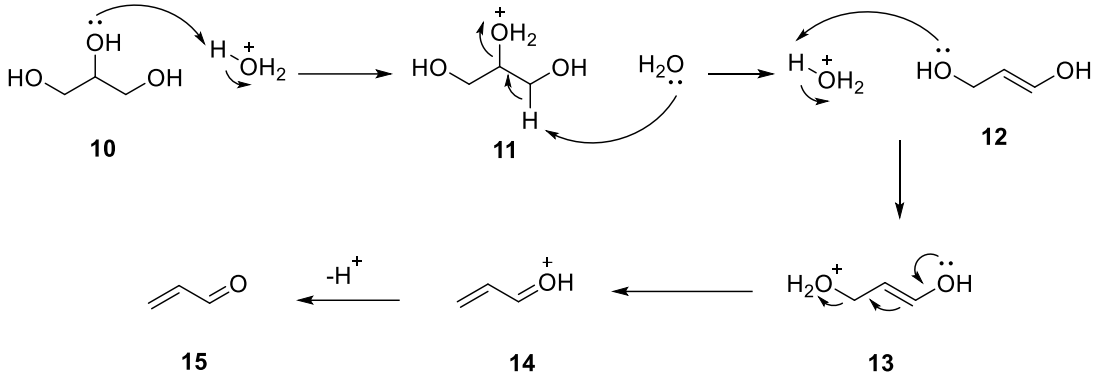
In the Skraup reaction, a mixture of aniline (**9**), glycerol, and nitro benzene was heated in the presence of sulphuric acid, where nitrobenzene acts as oxidizing agent and solvent (Scheme 1).[8]



9 **2**

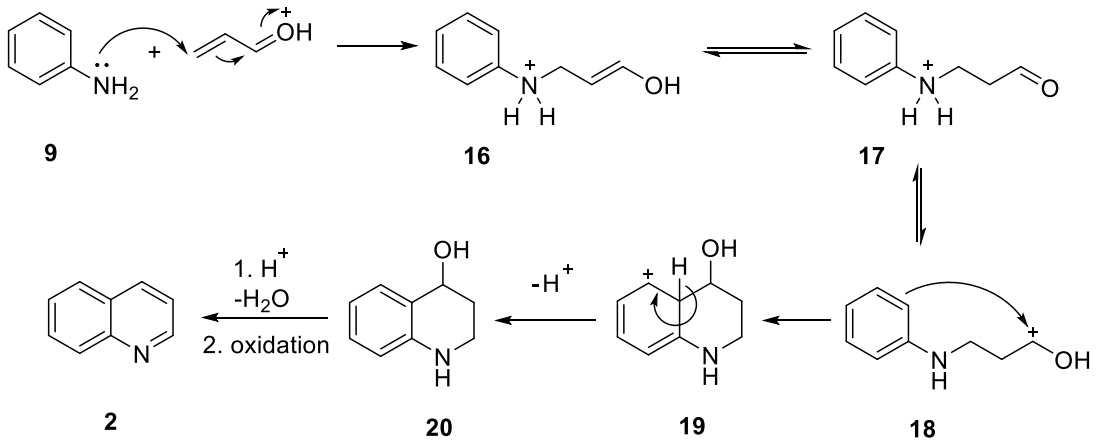
Scheme 1

Suggested mechanism for the synthesis of quinoline starts with formation of acrolein (**15**) from glycerol and sulphuric acid (Scheme 2).



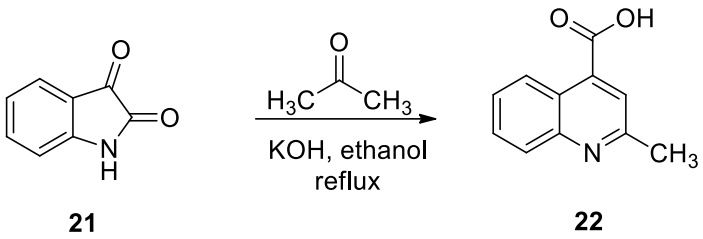
Scheme 2

Since acrolein underwent polymerization reaction with itself, it could not be used directly for this reaction. Therefore, it was preferred to generate acrolein during the reaction. Acrolein abstracts proton from sulphuric acid. When it is formed, it reacts immediately with aniline to yield the condensation product **16**. Then, intramolecular cyclization takes place to form product **20**. Elimination of water followed by oxidation results in the formation of quinoline (**2**) (Scheme 3).



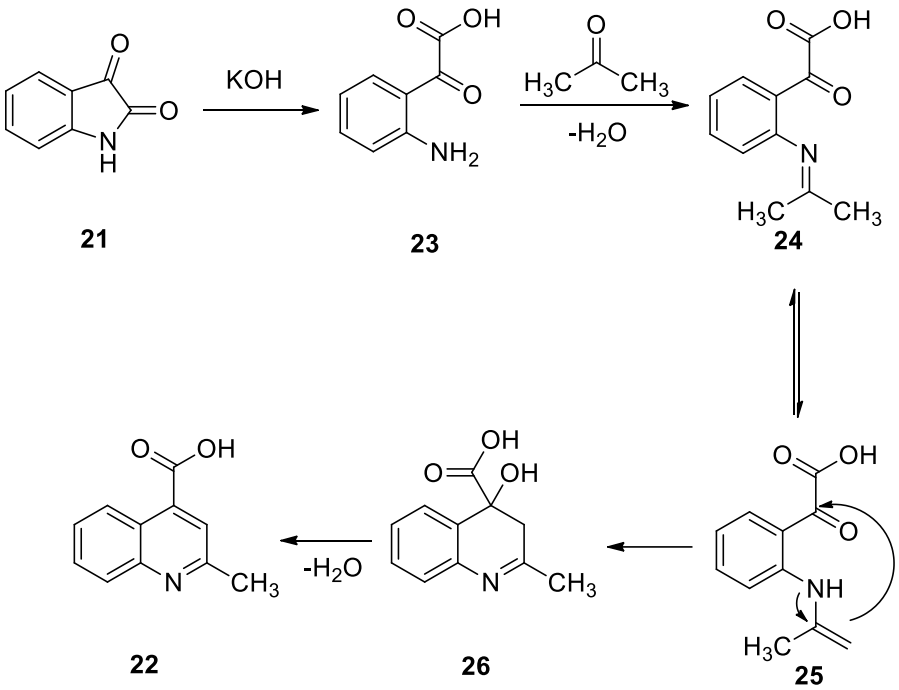
Scheme 3

Pfitzinger and coworkers synthesized quinoline-4-carboxylic derivative **22** by using isatin (**21**) and carbonyl containing compound in the presence of a base (Scheme 4).[9]



Scheme 4

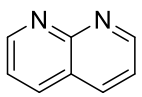
Firstly, isatin (**21**) was reacted with KOH to form 2-(2-aminophenyl)-2-oxoacetic acid (**23**), which then underwent a condensation reaction with a carbonyl containing compound to yield imine **24**. Isomerization of imine **24** to enamine **25** took place. Intramolecular cyclization reaction of **25** followed by elimination of water gave quinoline-4-carboxylic derivative **22** (Scheme 5).



Scheme 5

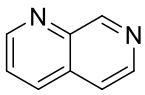
1.1.2. Naphthyridines

Naphthyridine is *N*-heterocyclic compound that consists of naphthalene ring in which two of carbon atoms (excluding bridge carbon atoms) are replaced with nitrogen. There are six isomers of naphthyridine and they are named according to the position of nitrogen atoms.



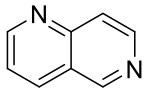
1,8-naphthyridine

27



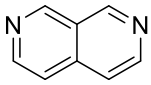
1,7-naphthyridine

28



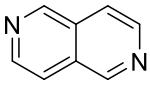
1,6-naphthyridine

29



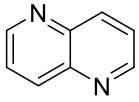
2,7-naphthyridine

30



2,6-naphthyridine

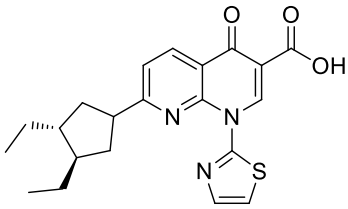
31



1,5-naphthyridine

32

Among the nitrogen heterocycles, naphthyridine derivatives have attracted great attention due to their broad spectrum of biological activities.[10] There are several publications showing that naphthyridine derivatives possess anticancer, antibacterial, anticonvulsant, and analgesic activities.[11,12] It was recently found that vosaroxin (**33**) shows activity for cancer cell line by inhibiting topoisomerase II.[13] Gemifloxacin (**34**) is antibacterial agent for treatment of chronic bronchitis and pneumonia.[14] Nalidixic acid (**35**) also play important role in the treatment of serious bacterial infections.[15]



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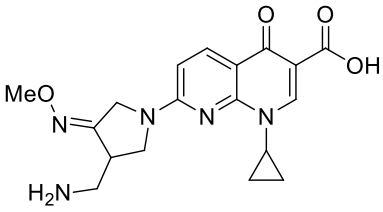

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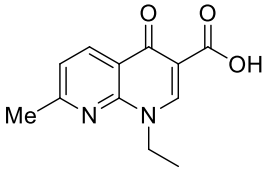
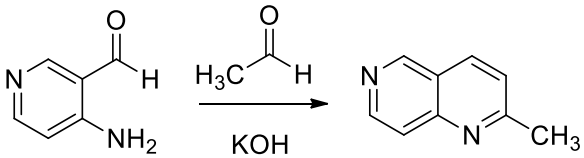


35

1.1.2.1. Synthesis of naphthyridines

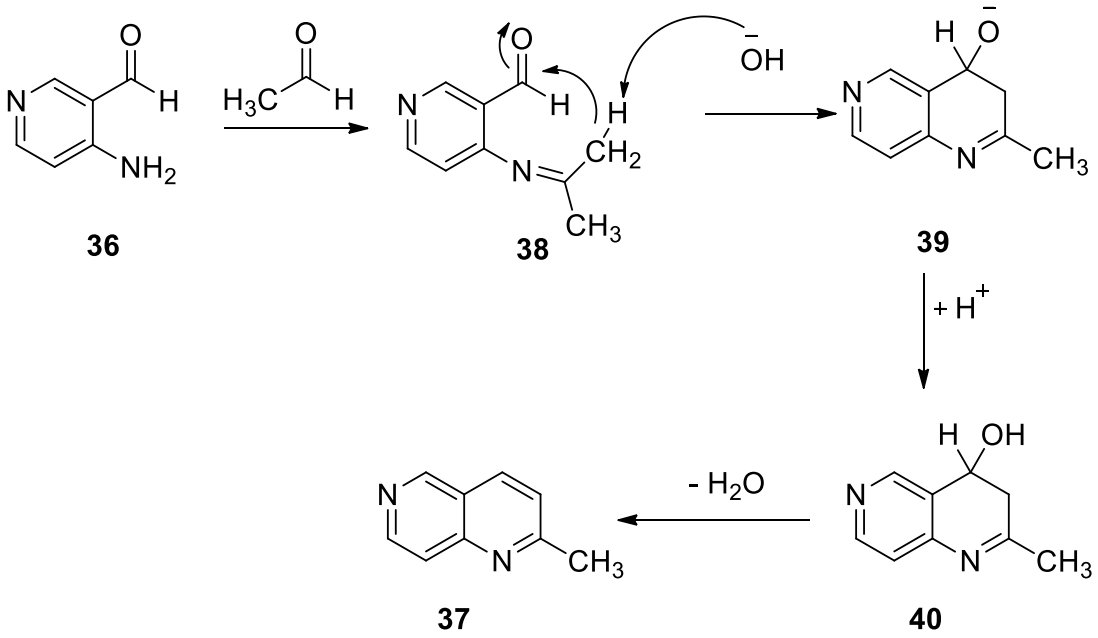
Cheng *et al.* developed a new methodology for the synthesis of naphthyridine by Friedlander synthesis. 4-Aminonicotinaldehyde (**36**) was reacted with acetaldehyde in the presence of KOH to afford [1,6]naphthyridine derivative **37** (Scheme 6).



36 **37**

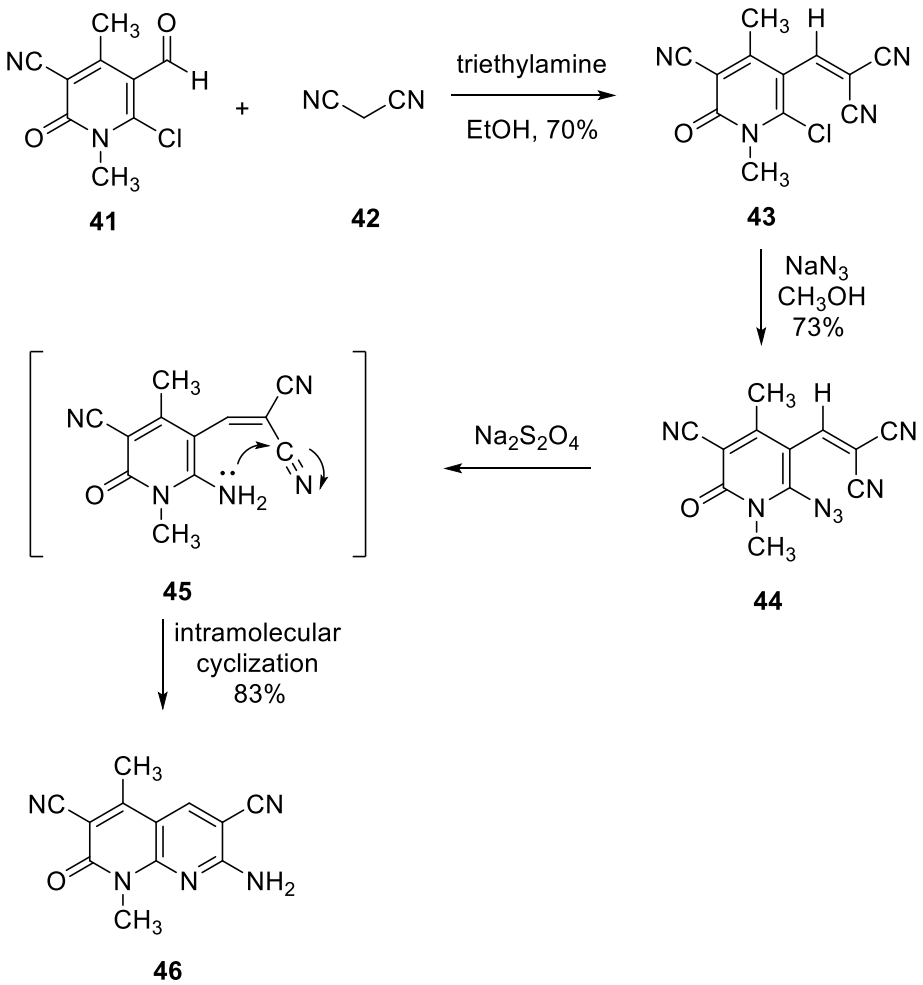
Scheme 6

Suggested mechanism starts with formation of imine. Then, base abstracts proton from CH_3 followed by intramolecular cyclization to give corresponding alcohol **40**. Water elimination yields [1,6]naphthyridine **37** (Scheme 7).



Scheme 7

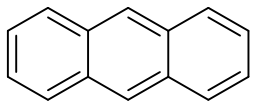
Sadek and coworkers synthesized [1,8]naphthyridine-2-one derivative **46** starting from compound **41**. Firstly, aldehyde **41** in EtOH was reacted with malononitrile (**42**) in the presence of a base at room temperature for two hours to give the corresponding methylenemalononitrile compound **43**. Then, reaction of compound **43** with sodium azide in MeOH at room temperature for two hours yielded corresponding azide **44** in 73% yield. Finally, the transformation of azide functionality in **44** into amino group with the help of sodium dithionate followed by intramolecular cyclization afforded [1,8]naphthyridine-2-one derivative **46** in a yield of 83% (Scheme 8).[16]



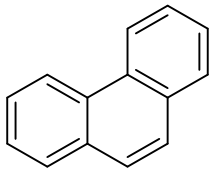
Scheme 8

1.1.3. Benzonaphthyridines

Benzonaphthyridine is a tricyclic compound in which naphthyridine unit is fused to a benzene ring. The structures of benzonaphthyridine resemble anthracene (**47**) and phenanthrene (**48**) structures depending on the position of benzene ring.

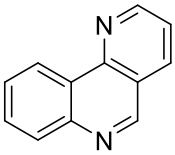


47



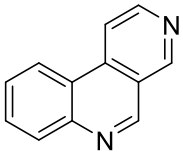
48

There are 10 structural isomers of benzonaphthyridines. The structures and names of them are shown below. Numbers denote the position of nitrogen atoms and the letter comes from the position of benzene ring.



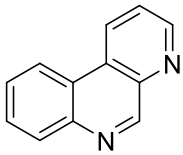
benzo[*h*][1,6]naphthyridine

49



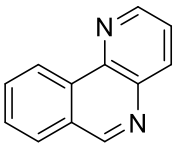
benzo[*c*][2,7]naphthyridine

50



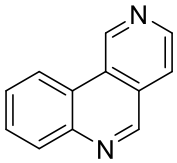
benzo[*f*][1,7]naphthyridine

51



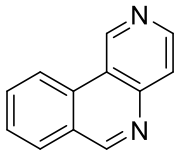
benzo[*c*][1,5]naphthyridine

52



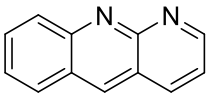
benzo[*c*][2,6]naphthyridine

53



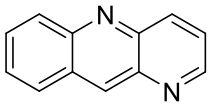
benzo[*c*][1,6]naphthyridine

54



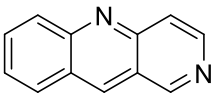
benzo[*b*][1,8]naphthyridine

55



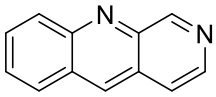
benzo[*b*][1,5]naphthyridine

56



benzo[*b*][1,6]naphthyridine

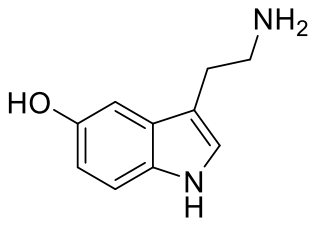
57



benzo[*b*][1,7]naphthyridine

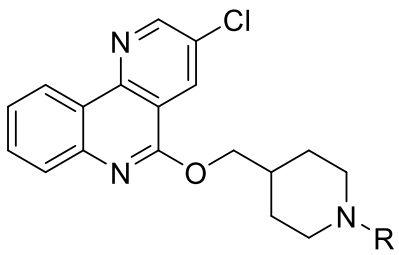
58

Benzonaphthyridine derivatives have potential activities such as antimalarial, analgesic, anticancer, and antibacterial.[17,18] In addition to these, Hinschberger and coworkers reported that compound **60a** and **60b** are used as selective antagonists of 5-HT_4 (**59**) receptors in central nervous system.[19]



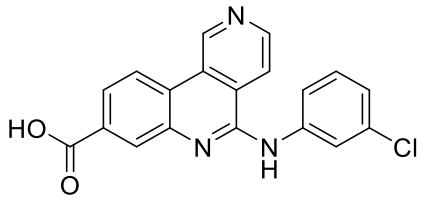
serotonin or 5-HT

59



60a R = CH_2CH_3
60b R = $(CH_2)_2CH_3$

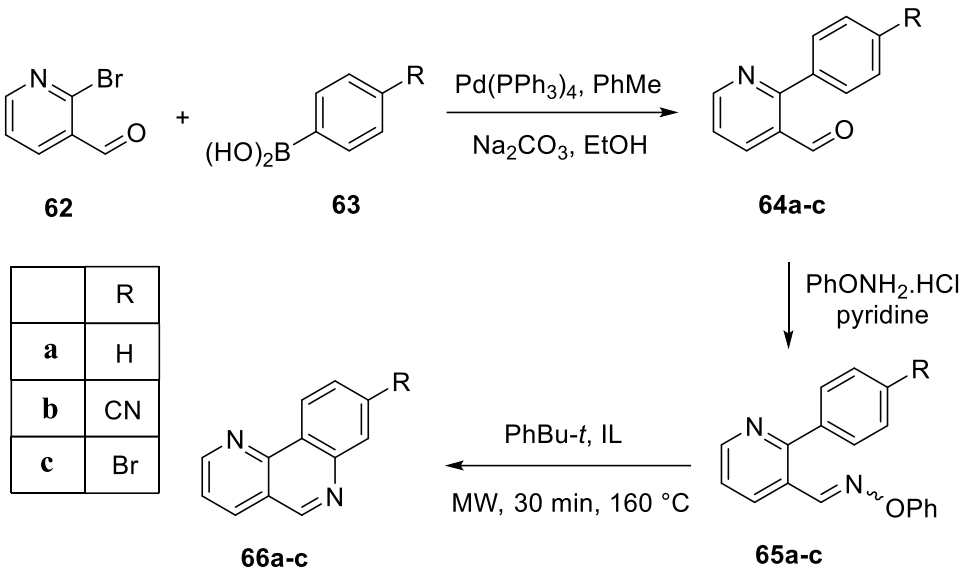
Also, Pierre and coworkers synthesized several benzonaphthyridine derivatives in order to search anticancer activity of these compounds. They reported that 5-(3-chlorophenylamino)benzo[*c*][2,6]naphthyridine (**61**) inhibits protein kinase CK2 for the treatment of cancer.[20]



61

1.1.3.1. Synthesis of benzonaphthyridine derivatives

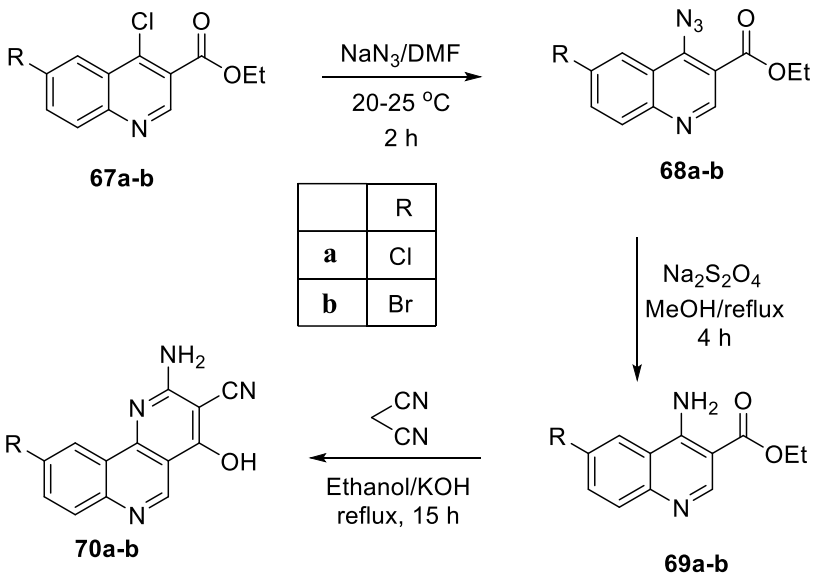
Portela-Cubillo and coworkers developed a new synthetic method for the synthesis of benzo[*h*][1,6]naphthyridine derivatives. 2-Bromonicotinaldehyde (**62**) was reacted with phenyl boronic acids **63a-c** via Suzuki coupling reaction to afford 2-aryl-3-formyl-pyridine derivatives **64a-c** which are then converted to corresponding oxime ethers **65a-c**. These oxime ethers **65a-c** were subjected to the microwave radiation in the presence of 1-ethyl-3-methylimidazolium hexafluorophosphate which is increasing the microwave absorbance level of solvent, to yield the expected benzo[*h*][1,6]naphthyridine derivatives **66a-c** (Scheme 9).[21]



	R
a	H
b	CN
c	Br

Scheme 9

Ghotekar and coworkers synthesized benzo[*h*][1,6]naphthyridine derivatives **70a-b** in three steps. Corresponding chloroquinoline derivatives **67a-b** were reacted with NaN_3 to furnish azidoquinoline derivatives **68a-b**. Reduction of azide group to amino group was achieved with $Na_2S_2O_4$ to give the expected 4-aminoquinoline-3-carboxylates **69a-b**. Reaction of carboxylate derivatives **69a-b** with malononitrile in the presence of a base gave the desired benzo[*h*][1,6]naphthyridine derivatives **70a-b** (Scheme 10).[22]

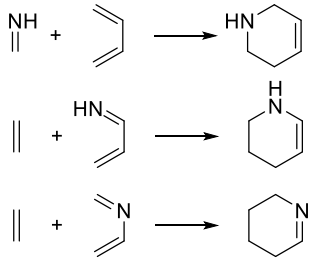


	R
a	Cl
b	Br

Scheme 10

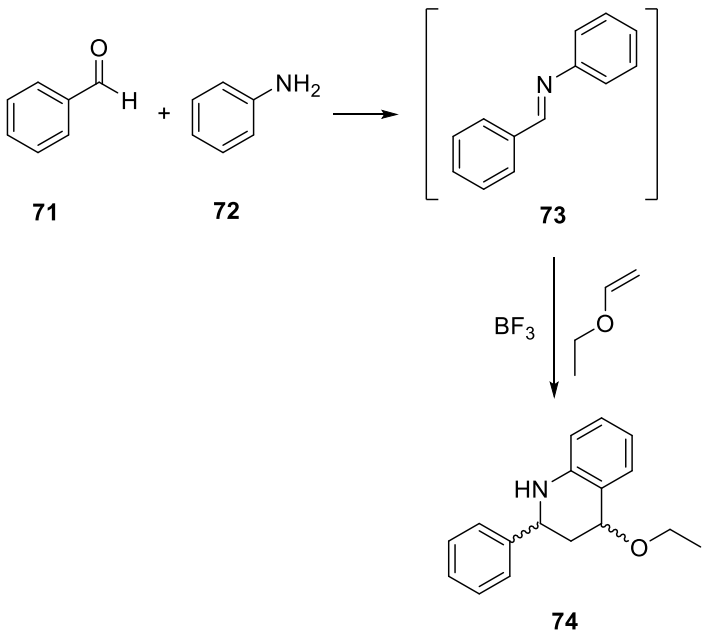
1.1.4. Aza-Diels-Alder reactions

The Diels-Alder (DA) reaction is one of the most useful named reactions in synthetic organic chemistry. Aza-Diels-Alder (ADA) is the modification of DA reaction. Unlike DA reaction, ADA reaction contains at least one nitrogen atom which can be part of the diene unit or the dienophile unit (Scheme 11).[23]



Scheme 11

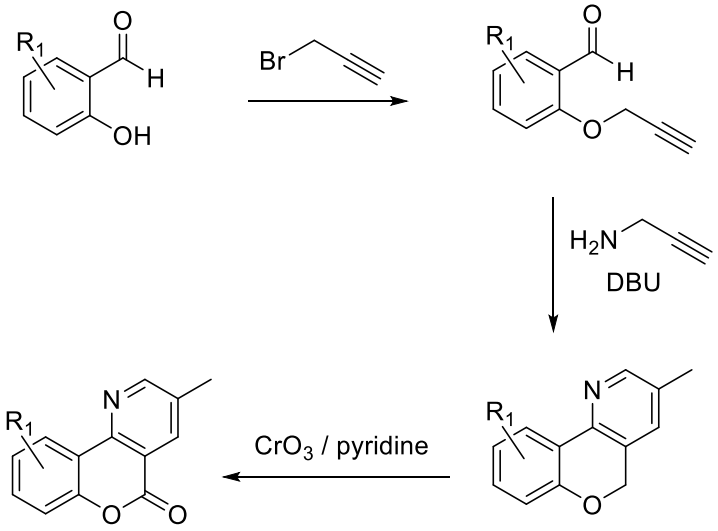
There are several examples of ADA reaction in literature. One of them is the Povarov reaction. The condensation reaction between benzaldehyde (**71**) and aniline (**72**) took place to yield an aromatic imine **73** which later was reacted with an alkene in the presence of a lewis acid. BF_3, used as a Lewis acid, activates the imine for electrophilic addition of electron rich alkene. Hydroquinoline derivative **74** was obtained at the end of the reaction (Scheme 12).[24]



Scheme 12

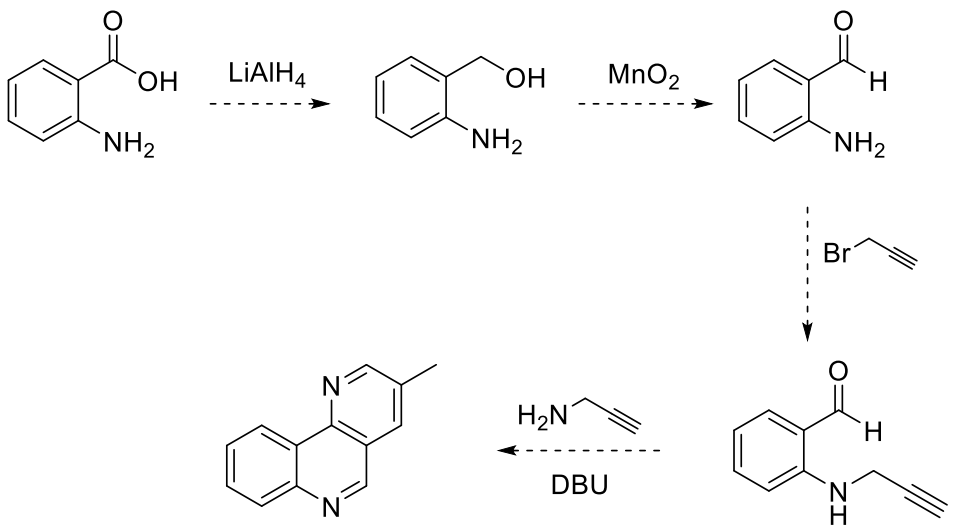
1.1.5. Aim of Study

The synthesis of chromenopyridinone derivatives were achieved by our group. Starting from salicylaldehyde derivatives, several chromenopyridines were synthesized by using propargyl amine and DBU. After then, these derivatives were oxidized to the corresponding chromenopyridinone in high yield (Scheme 13).[25]



Scheme 13

Our aim was to replace oxygen atom in salicylaldehyde with nitrogen and to investigate the generality of this cyclization reaction. This methodology would open up an entry to the synthesis of the corresponding benzonaphthyridine derivatives.



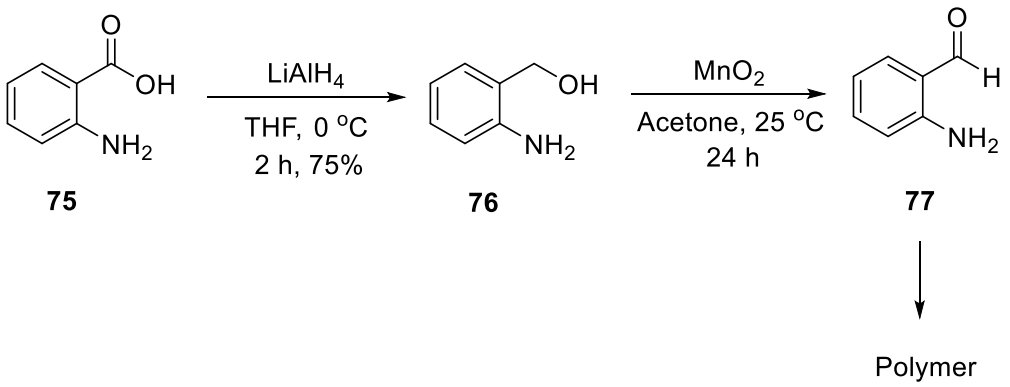
Scheme 14

We will start from 2-amino benzoic acid and synthesize 2-aminobenzaldehyde. 2-Aminobenzoic acid will be reduced to 2-aminobenzyl alcohol followed by oxidation of 2-aminobenzyl alcohol to give 2-aminobenzaldehyde. Then, propargyl group will be introduced to 2-aminobenzaldehyde to yield *N*-propargylated aldehyde. Finally, its cyclization reaction with propargyl amine and DBU will be investigated (Scheme 14).

1.2. RESULTS AND DISCUSSION

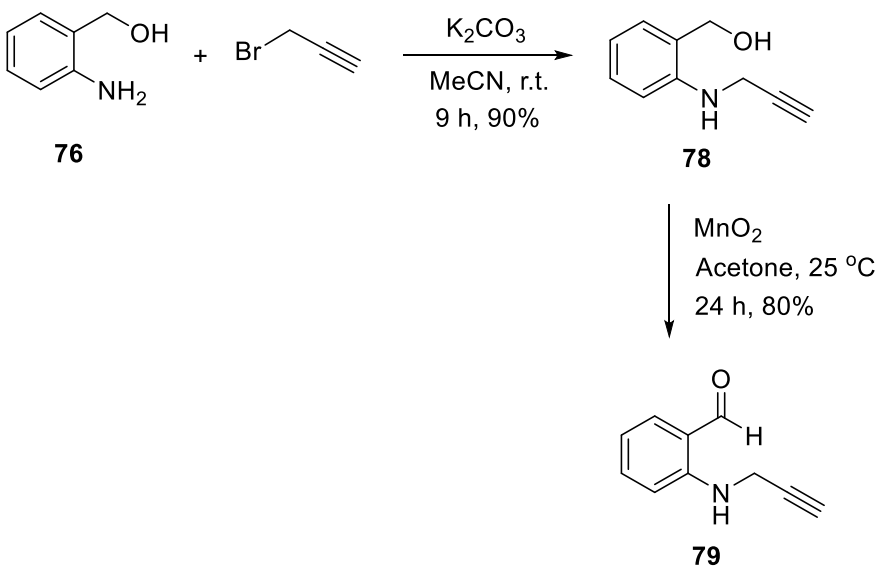
1.2.1. Synthesis of 2-(prop-2-ynylamino)benzaldehyde

For the synthesis of compound **77**, a straightforward procedure was applied. 2-Aminobenzoic acid (**75**) was reduced by using $LiAlH_4$ to yield 2-amino benzyl alcohol.[26] Then, corresponding alcohol **76** was oxidized with MnO_2.[27] Unfortunately, under these reaction conditions expected aldehyde **77** was not obtained. Because compound **77** was rapidly polymerized via condensation reaction (Scheme 15).



Scheme 15

The route for the synthesis of starting material was changed. According to the literature procedure[28], propargyl group was introduced to nitrogen atom by the reaction of aminoalcohol **76** with propargyl bromide in the presence of K_2CO_3.



Scheme 16

After then, *N*-propargylated alcohol **78** was oxidized with MnO_2 to give corresponding *N*-propargylated aldehyde **79** in a yield of 80% by using literature procedure[27] (Scheme 16).

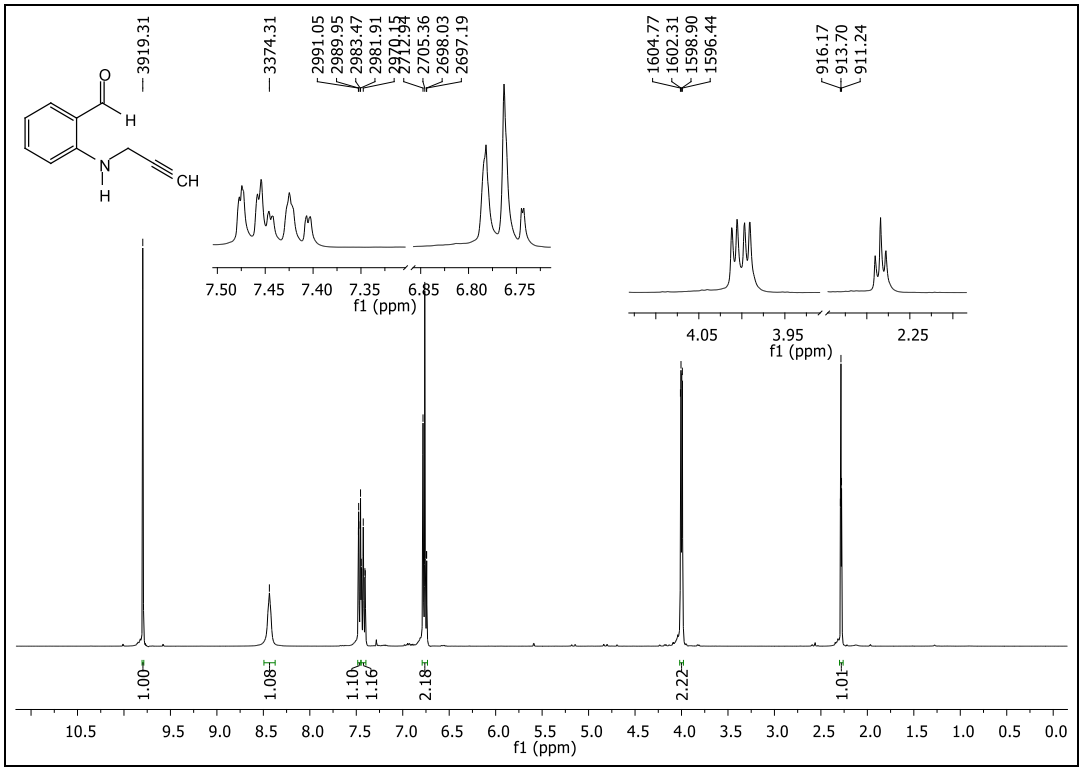
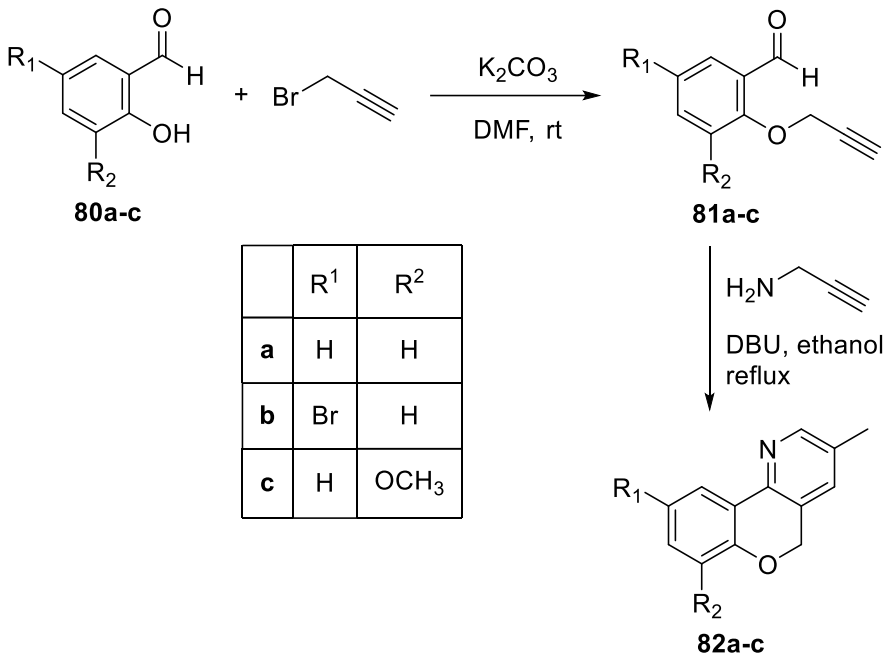


Figure 1 ^{1}H-NMR Spectrum of compound **79** in $CDCl_3$

Compound **79** was characterized by ^{1}H-NMR and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrum of compound **79**, aldehyde proton resonates at 9.80 ppm as a singlet. In addition, the proton attached to the nitrogen atom resonates at 8.44 ppm as a broad singlet and alkyne proton resonating at 2.28 ppm splits into triplet with a coupling constant of J = 2.5 Hz arising from the long-range coupling with methylene protons (Figure 1). The CH_2 protons resonate as doublet of doublets with the coupling constants of 5.9 and 2.5 Hz due to the coupling with NH proton and alkyne proton, respectively.

1.2.2. An attempt for the cyclization reaction of 2-(prop-2-ynylamino) benzaldehyde with propargyl amine and DBU

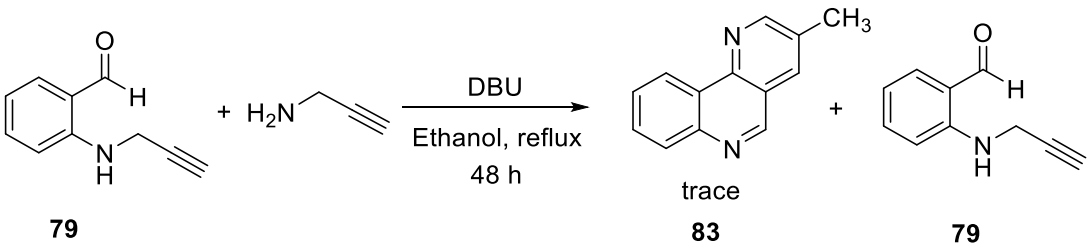
Balcı *et al*. described a concise synthetic methodology for the synthesis of chromenopyridine derivatives **82a-c** starting from salicylaldehyde derivatives **80a-c** in two steps by using necessary reagents (Scheme 17).[25]



	R^1	R^2
a	H	H
b	Br	H
c	H	OCH_3

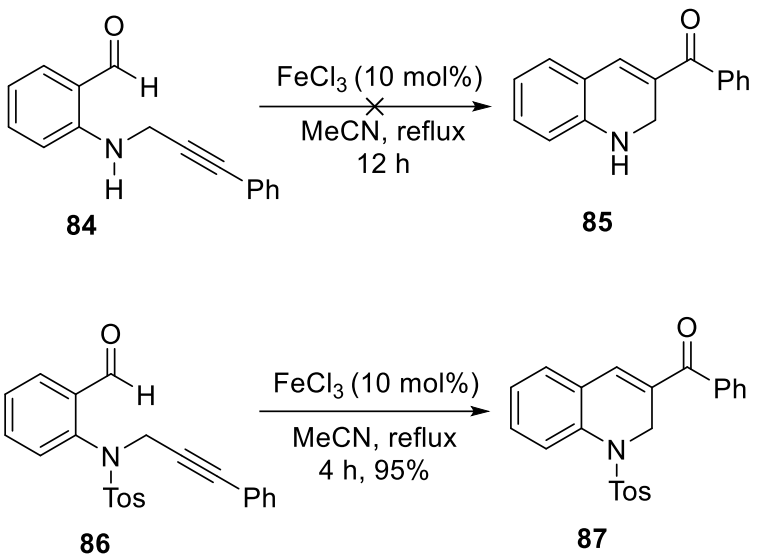
Scheme 17

DBU is a non-nucleophilic base used in isomerization reaction of alkyne to allene. According to the procedure by Balci *et al.*[25], 2-(prop-2-ynylamino)benzaldehyde (**79**) was reacted with propargyl amine in the presence of DBU at reflux temperature of ethanol for 48 h. After monitoring with TLC, expected cyclization product **83** was obtained in a trace amount and starting material **79** was recovered (Scheme 18).



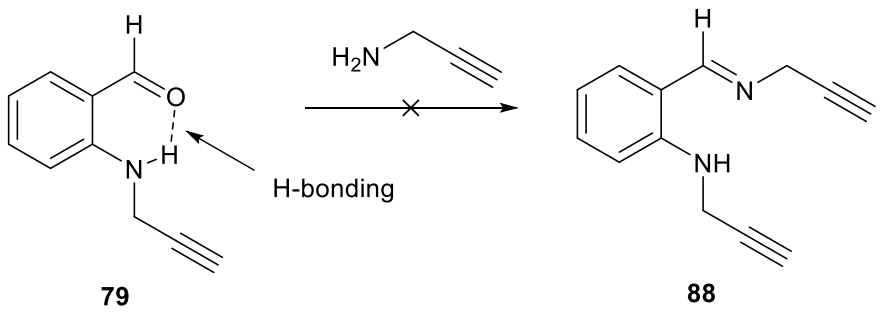
Scheme 18

Jalal *et al.*[29] synthesized quinolines via an iron(III) chloride catalyzed intramolecular alkyne-carbonyl metathesis of alkyne tethered 2-amino benzaldehyde/acetophenone derivatives. While *N*-tosylated aldehyde **86** was reacted with $FeCl_3$ to afford expected acetophenone **87**, compound **84** did not give the expected compound under the same reaction conditions (Scheme 19). They revealed that free amine did not work because it lowered the reactivity of carbonyl group due to the H-bonding.



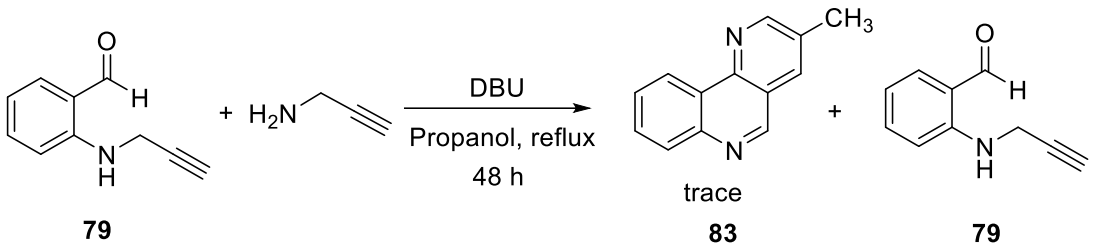
Scheme 19

We also assume that the formation of imine **88** which is necessary for cyclization is inhibited due to the H-bonding between oxygen and hydrogen. In other words, H-bonding prevents the formation of imine **88** as shown in Scheme 20.



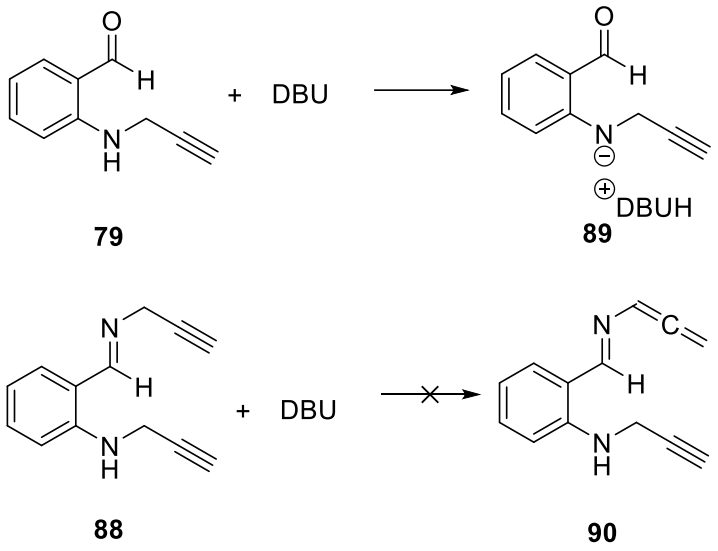
Scheme 20

It is well known fact that increasing temperature could eliminate H-bonding. In order to remove this H-bonding, propanol was used as a solvent instead of ethanol. Because reflux temperature of propanol is higher than that of ethanol. Unfortunately, expected cyclization product **83** was again obtained as a trace amount like in ethanol and starting material **79** was recovered (Scheme 21).



Scheme 21

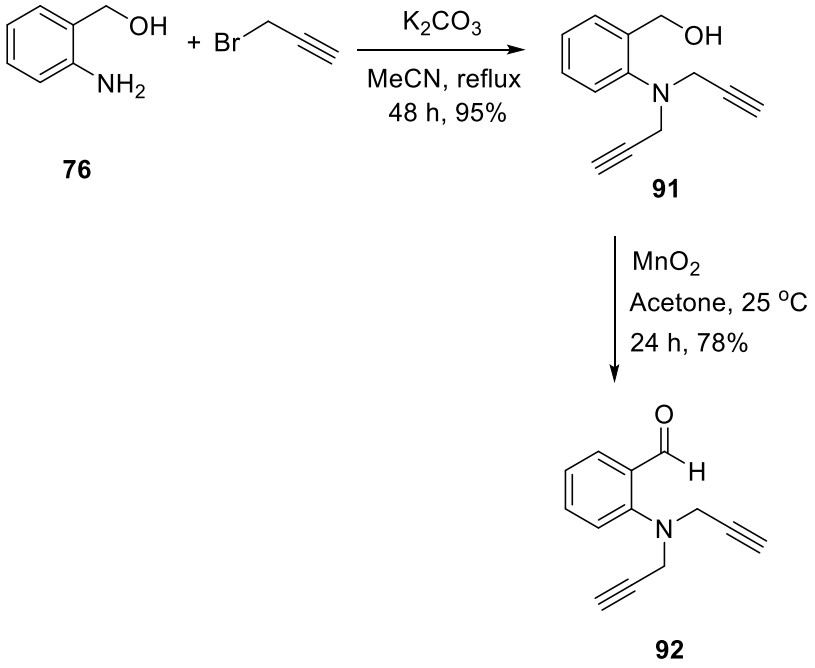
For cyclization reaction DBU is necessary because alkyne functionality must be transferred into allene **90**. However, the compound **79** contains an acidic proton bonded to the nitrogen atom. Therefore, DBU can abstract this proton and form organic salt **89** (Scheme 22). This can also prevent the reaction.



Scheme 22

1.2.3. Cyclization reaction of 2-(diprop-2-ynylamino)benzaldehyde with propargyl amine and DBU

Two propargyl groups were introduced to the free amine in order to eliminate H-bonding. By using literature procedure[28], double *N*-propargylated alcohol **91** was obtained by the reaction of **76** with excess propargyl bromide in a yield of 95%. According to the literature method[27], oxidation of alcohol group in **91** with MnO_2 furnished the corresponding aldehyde **92** in 78% of yield (Scheme 23).



Scheme 23

The characterization of compound **92** was achieved by using ^{1}H-NMR and ^{13}C-NMR spectra. The aldehyde proton resonates at 10.33 ppm as a singlet.

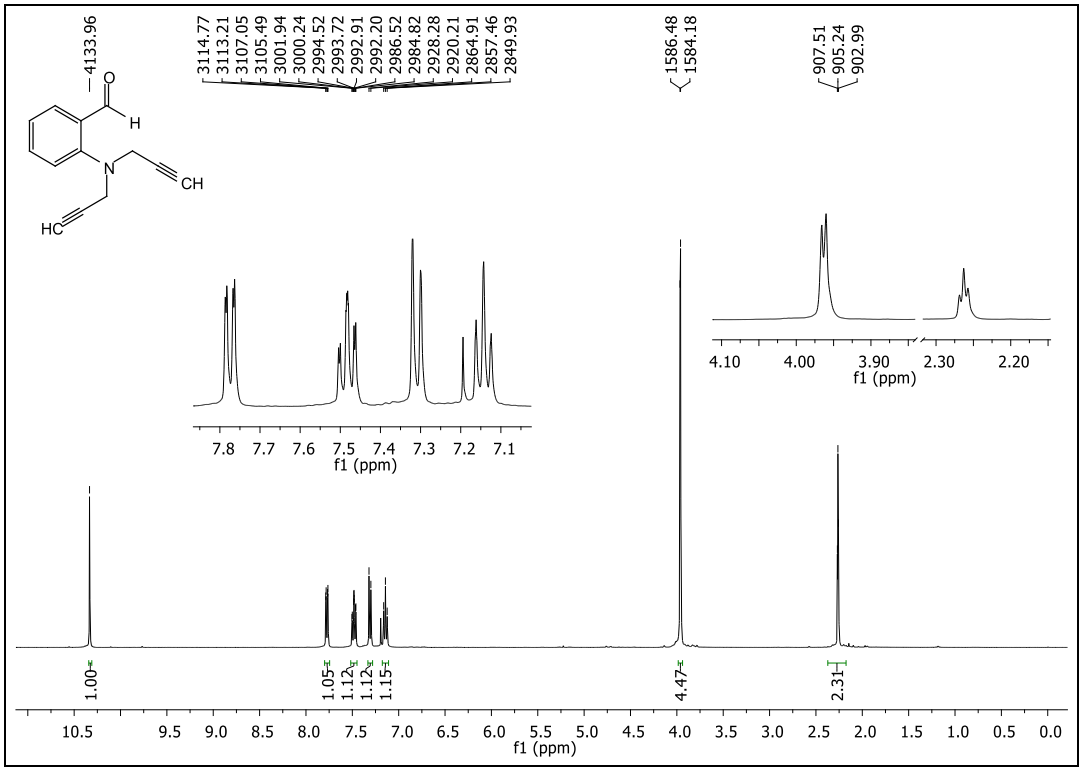
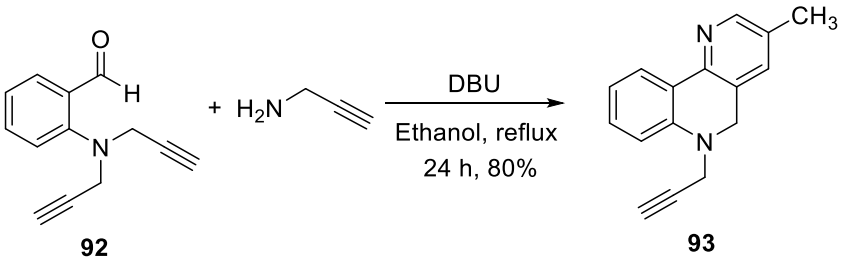


Figure 2 ^{1}H-NMR Spectrum of compound **92** in $CDCl_3$

The alkyne proton splits into triplet with a coupling constant of J = 2.3 Hz due to the long-range coupling with CH_2 protons which appears as a doublet (J = 2.3 Hz) as shown in Figure 2.

After synthesis of 2-(diprop-2-ynylamino)benzaldehyde (**92**), it was reacted with propargyl amine in the presence of DBU to afford the desired cyclization product **93** in a yield of 80% (Scheme 24). The compound **93** was characterized by using ^{1}H-NMR (Figure 3) and ^{13}C-NMR spectra.



Scheme 24

As one can see from the Figure 3, there are six separate aromatic proton resonances in the range of aromatic region which is in agreement with the structure of the expected product **93**. Two of the protons resonate at quite low field, at 8.37 ppm and 8.24 ppm. The doublet resonance at 8.37 ppm belongs to pyridine proton which is adjacent to the nitrogen atom. Doublet splitting (J = 1.2 Hz) is arising from the coupling with the other proton bonded to the pyridine ring. The low field signal at 8.24 ppm belongs to the proton of the benzene ring closer to pyridine ring. Doublet of doublets splitting is due to the coupling with ortho and meta protons (J = 7.7 Hz and 1.6 Hz). The quite low field shift of this proton can be explained by location of this proton in the deshielding zone of the benzene ring as well as of the pyridine ring. There are two CH_2 proton resonances in which one of them resonates as a doublet with the coupling constant of J = 2.4 Hz and other resonates as a singlet.

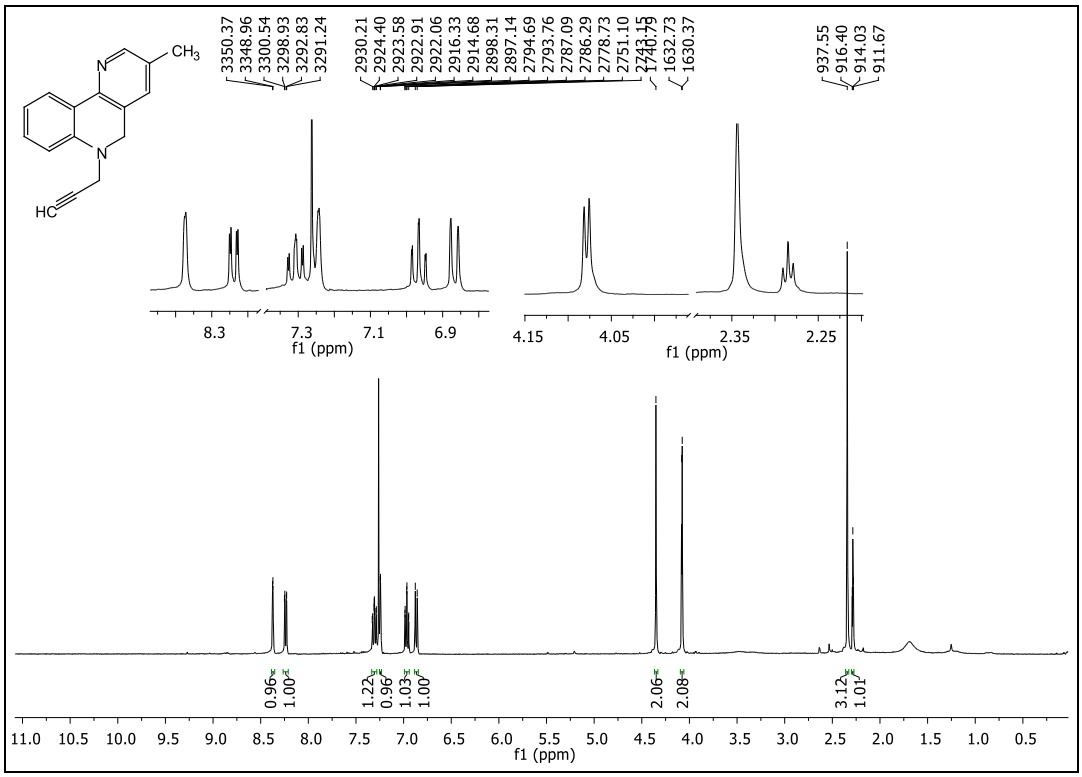
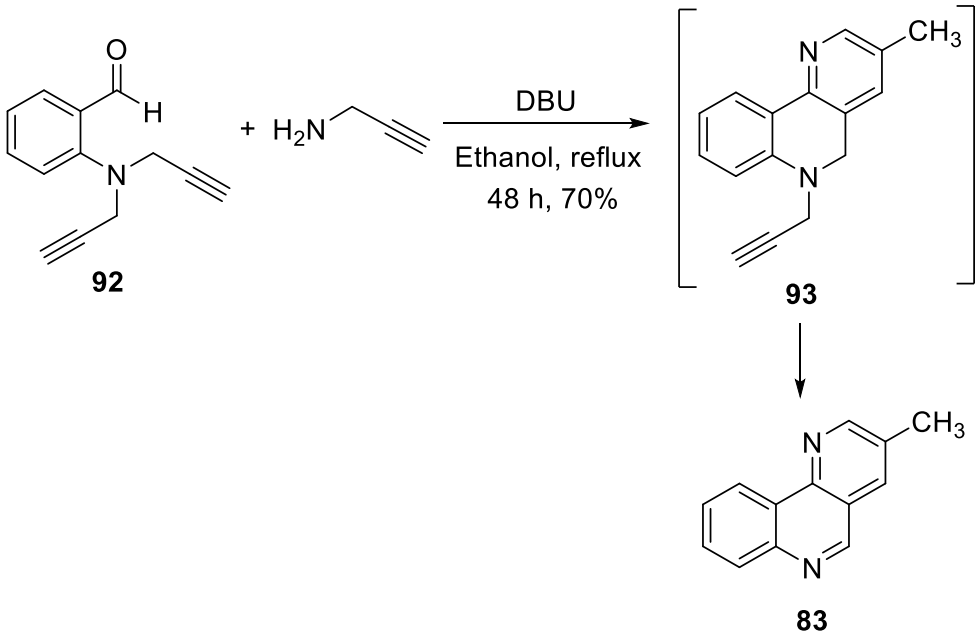


Figure 3 ^{1}H-NMR Spectrum of compound **93** in $CDCl_3$

It was interesting to notice that the remaining propargyl group was eliminated and an aromatization occurred when the reaction time was increased. Probably, the formation of an aromatic compound is the driving force of this reaction (Scheme 25).



Scheme 25

The ^{1}H-NMR and ^{13}C-NMR spectra were used to confirm the structure of aromatic compound **83.** Comparison of the ^{1}H-NMR spectra of compound **93** and **83** clearly shows that the propargyl group which resonate as a doublet and triplet in **93**, was removed from the molecule. Furthermore the resonance signals of methylene protons were also disappeared. The ^{1}H-NMR spectrum of compound **83** is shown in Figure 4. An additional aromatic proton resonances at 9.21 ppm appears in the range of aromatic proton resonances. The ^{1}H-NMR spectrum of compound **83** shows 7 aromatic proton resonances in which three of them shifted to the lower field. The imine protons and one of the α-protons are shifted to lower field due to the connection to an electronegative element nitrogen and the presence of the deshielding zone of the benzene and pyridine rings, respectively. The ^{13}C-NMR spectrum with 13 distinct signals is also in agreement with the proposed structure. All carbons and protons were assigned by analyzing the COSY, HMBC and HSQC spectra of compound **83**.

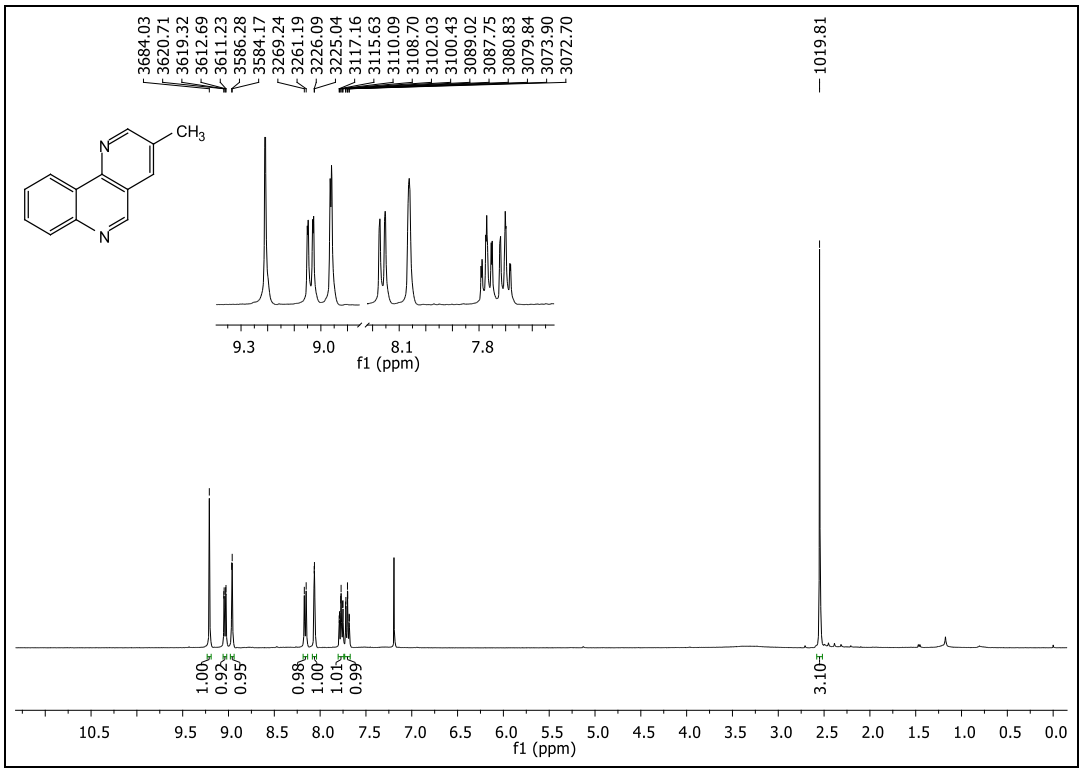
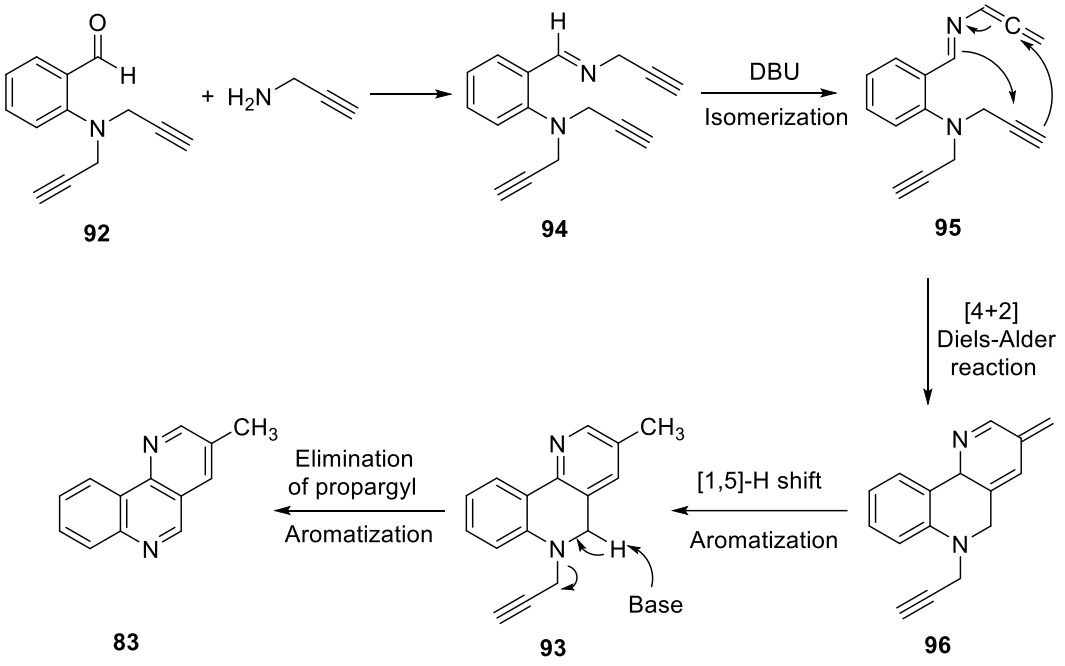


Figure 4 ^{1}H-NMR Spectrum of compound **83** in $CDCl_3$

1.2.4. Proposed mechanism for the formation of benzonaphthyridine derivative 83.

Proposed mechanism starts with formation of imine **94** via condensation reaction followed by isomerization of alkyne **94** to allene **95**.



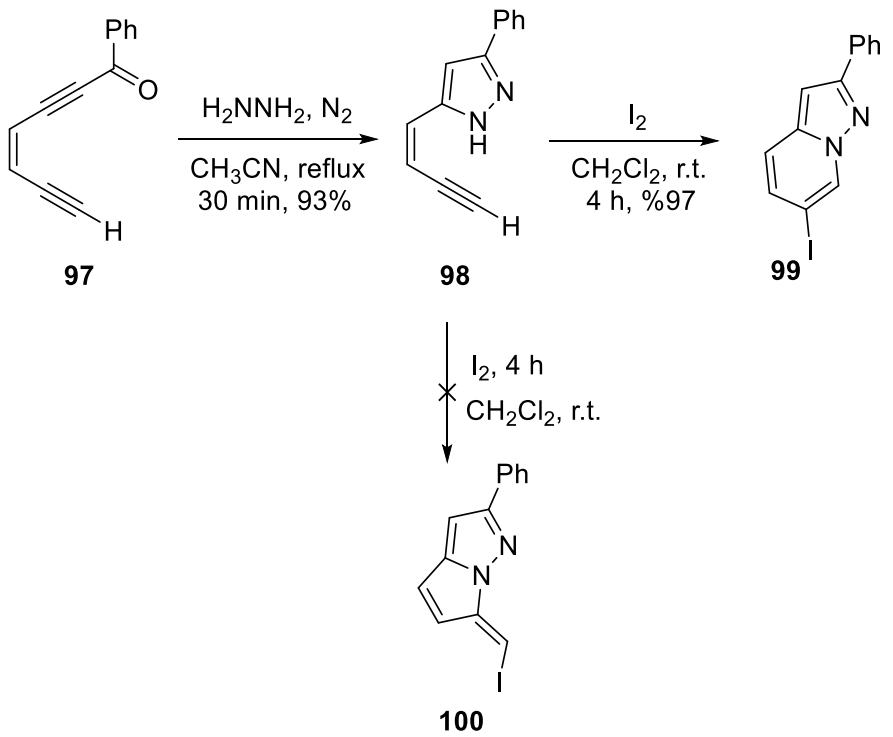
Scheme 26

There are two possible alkyne units which can undergo isomerization. The alkyne unit connected to the imine can easily isomerize than the alkyne unit bonded to the nitrogen atom. The methylene protons located between the imine and alkyne units are more acidic than the other methylene protons. Furthermore, isomerization of alkyne connected to imine functionality will generate an allene which will be in conjugation with the imine. Therefore, allene **95** will be thermodynamically more stable than the other allene. After formation of allene **95**, an Aza-Diels-Alder reaction takes place between diene and alkyne units to form corresponding intermediate **96**. Then, [1,5]-H shift occurs in order to afford cyclization product **93** with propargyl group. Finally, propargyl group is eliminated with the help of base to yield benzonaphthyridine derivative **83** (Scheme 26).

1.2.5. An attempt for the cyclization reaction of 3-methyl-6-prop-2-ynyl-5,6-dihydrobenzo[*h*][1,6]naphthyridine with iodine.

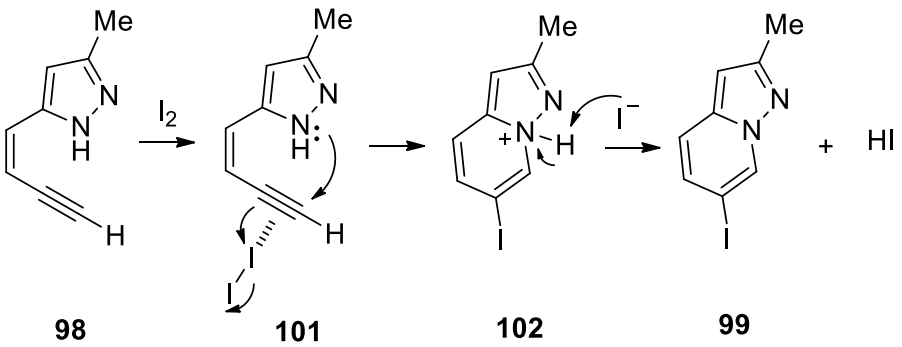
Electrophilic cyclization of alkynes mediated by iodine is well known reaction in the literature. There are many examples related with electrophilic iodine cyclization. The reaction starts with coordination of iodine to the unsaturated carbon-carbon triple bond which is followed by nucleophilic addition to the triple bond.

Wu *et al*.[30] investigated iodine-mediated cyclization of enynylpyrazoles to synthesize pyrazolo[1,5-a]pyridines (Scheme 27). Reaction of compound **97** with hydrazine at reflux temperature of CH_3CN afforded the corresponding enynylpyrazole **98** in a yield of 93%. Obtained product **98** was reacted with iodine to yield desired cyclization product **99**. According to the Baldwin's rules,[31] two possible products can be formed in cyclization reaction with iodine which are 5-*exo-dig* product **100** and 6-*endo-dig* product **99**. While 6-*endo-dig* product was formed, 5-*exo-dig* product was not observed. Because transition state for the formation 5-*exo-dig* product is more strained than that of 6-*endo-dig*. Furthermore, while compound **99** is an aromatic compound, **100** is not aromatic. This is another reason why only 6-*endo-dig* product was formed as the sole product.



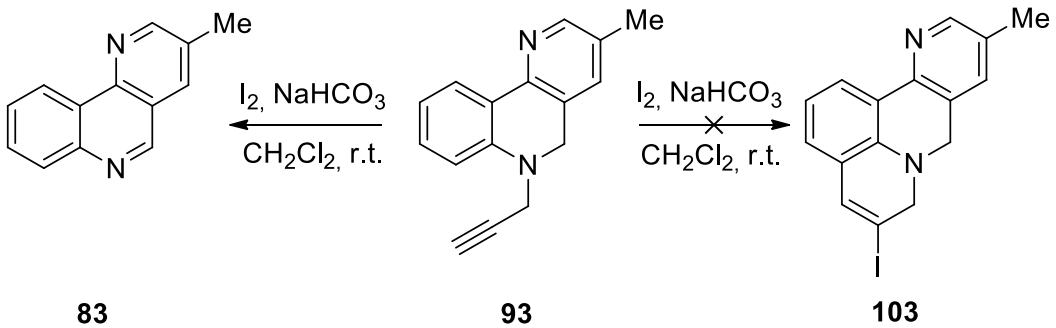
Scheme 27

Proposed mechanism of cyclization reaction starts with coordination of iodine to triple bond. Then, lone pairs of nitrogen attacks to activated triple bond followed by removal of the proton to give pyrazolo[1,5-a]pyridine derivative **99** as shown in Scheme 28.



Scheme 28

After successful synthesis of 3-methyl-6-prop-2-ynyl-5,6-dihydrobenzo[*h*][1,6]naphthyridine (**93**), the compound was submitted to electrophilic cyclization reaction with iodine. Unfortunately, expected cyclization product **103** was not formed. Instead, breaking of propargyl group was achieved to form fully aromatic 3-methylbenzo[*h*][1,6]naphthyridine (**83**) (Scheme 29).

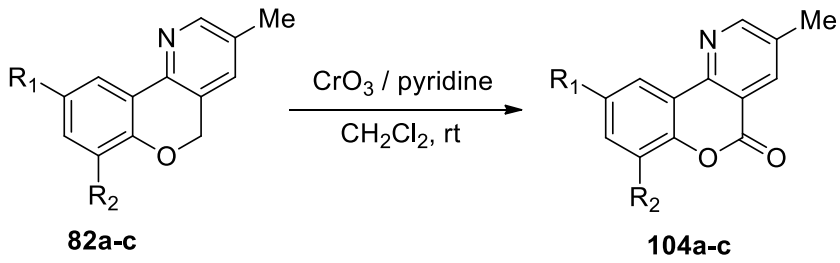


Scheme 29

Compound **93** was not stable under normal condition. By standing at room temperature, it undergoes elimination and forms aromatic 3-methylbenzo[*h*][1,6]naphthyridine (**83**). It was observed that iodine accelerates the elimination of propargyl group and shortens reaction time.

1.2.6. Oxidation reaction of 3-methyl-6-prop-2-ynyl-5,6-dihydrobenzo[*h*]-1,6-naphthyridine with CrO_3/pyridine

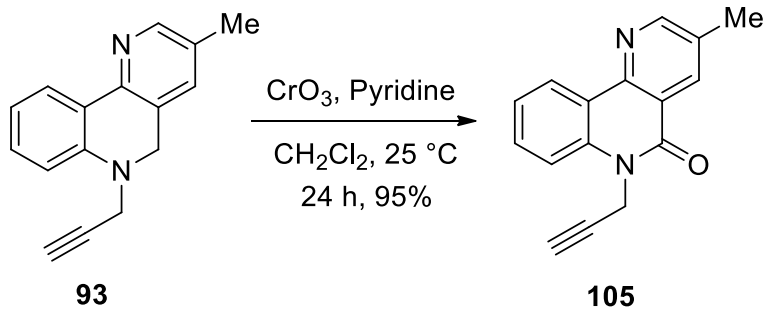
Balci *et al*. achieved oxidation of chromenopyrazine derivatives to chromenopyrazinone derivatives by using CrO_3/pyridine reagent. Oxidation products were obtained in a high yield (Scheme 30).[25]



	R^1	R^2
a	H	H
b	Br	H
c	H	OCH_3

Scheme 30

3-Methyl-6-prop-2-ynyl-5,6-dihydrobenzo[*h*][1,6]naphthyridine (**93**) was oxidized by using CrO_3/pyridine to afford 3-methyl-6-prop-2-ynylbenzo[*h*][1,6]naphthyridin-5(6*H*)-one (**105**) in a yield of 95% (Scheme 31).



Scheme 31

Characterization of oxidation product **105** was accomplished by analyzing the ^{1}H-NMR and ^{13}C-NMR spectra. There are two CH_2 protons in naphthyridine derivative **93**. One of them resonates as a doublet and other resonates as a singlet. The disappearance of CH_2 protons resonating as a singlet shown in Figure 5 reveals the formation of oxidation product, benzonapthyridinone derivative **105**.

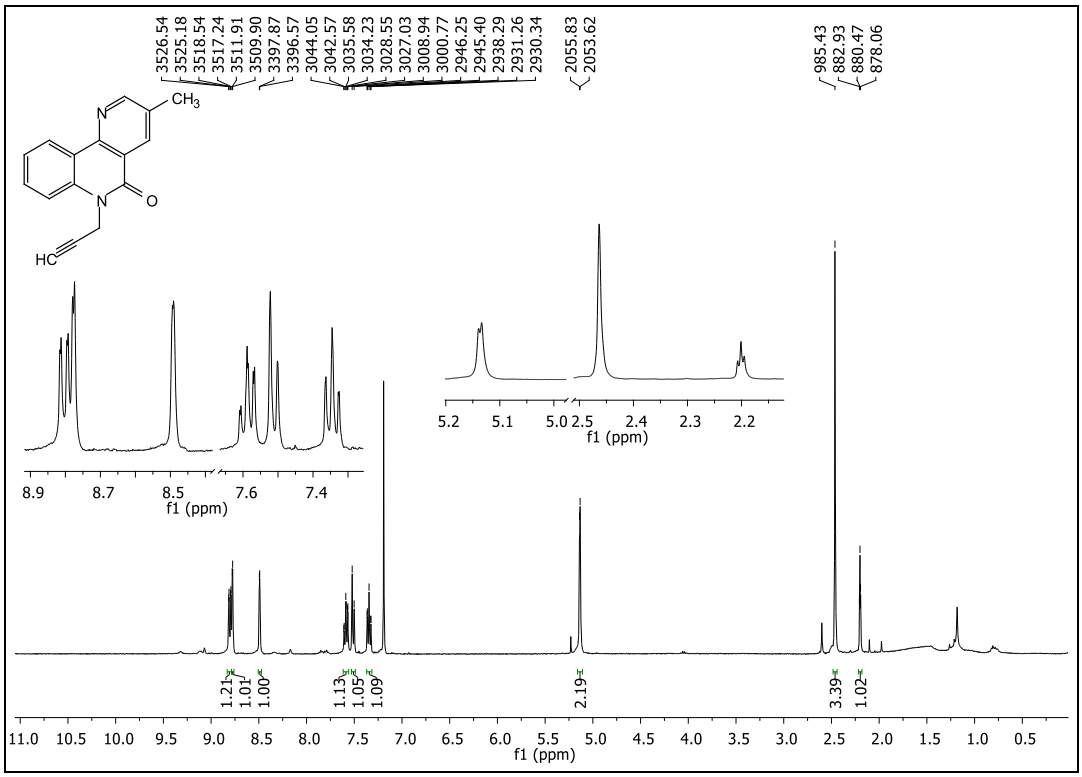
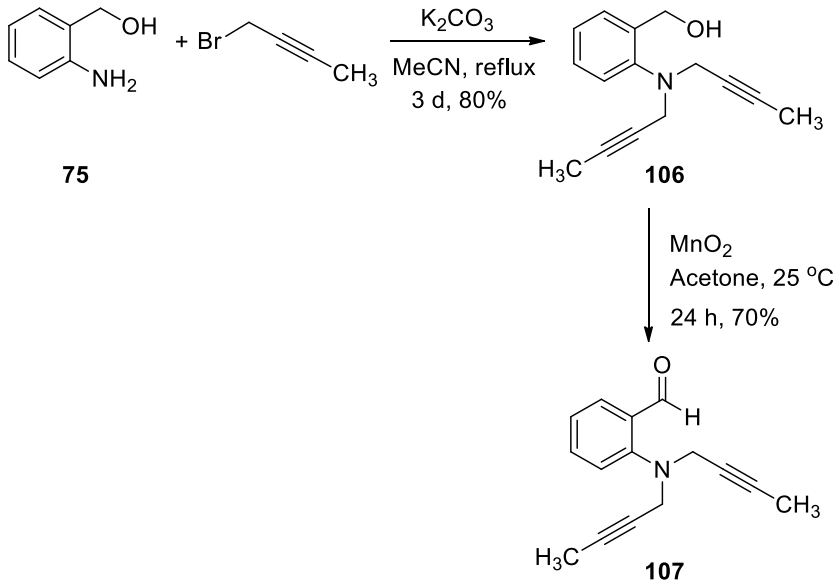


Figure 5 ^{1}H-NMR Spectrum of compound **105** in $CDCl_3$

Also, the disappearance of one of aliphatic carbon in the ^{13}C-NMR spectrum of 3-methyl-6-prop-2-ynyl-5,6-dihydrobenzo[*h*][1,6]naphthyridine (**93**) and appearance of new amide signal in the ^{13}C-NMR spectrum support the formation of oxidation product **105**.

In order to check the scope of this cyclization reaction, different derivative of starting material **92** was synthesized. 1-Bromobut-2-yne was chosen as a new alkyne derivative. Aminobenzyl alcohol **75** was reacted with excess of bromobut-2-yne in the presence of K_2CO_3. The desired compound **106** was formed in a yield of 80%.

The next step was the synthesis of corresponding aldehyde **107** by using MnO_2. The oxidation product **107** was synthesized in a yield of 70% (Scheme 32). The characterization of this aldehyde was done by analyzing the ^{1}H-NMR and ^{13}C-NMR spectra. The long range coupling between CH_3 protons and CH_2 protons can be seen easily from the ^{1}H-NMR spectrum of 2-[di(but-2-yn-1-yl)amino]benzaldehyde (**107**) as shown in Figure 6.



Scheme 32

The CH_3 protons resonate at 1.75 ppm as a triplet with the coupling constant of J = 2.2 Hz and CH_2 protons resonate at 4.00 ppm as a quartet with the coupling constant J = 2.2 Hz which indicate the incorporation of butyne group into the molecule and formation of compound **107** (Figure 6).

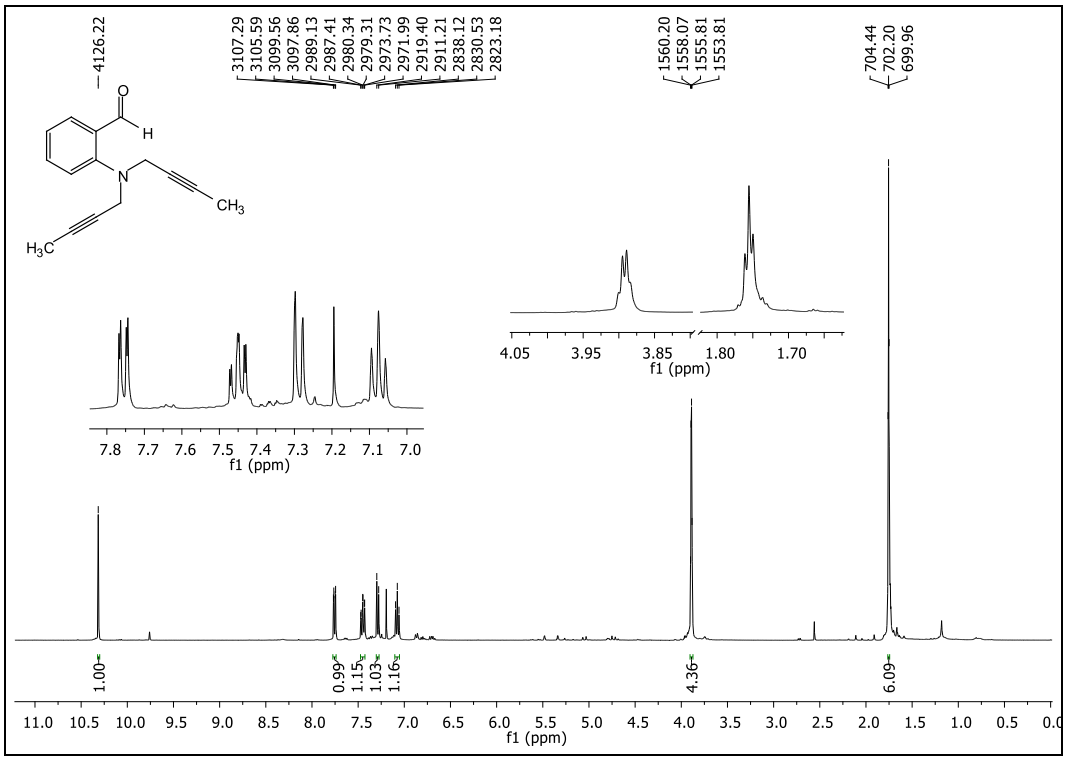
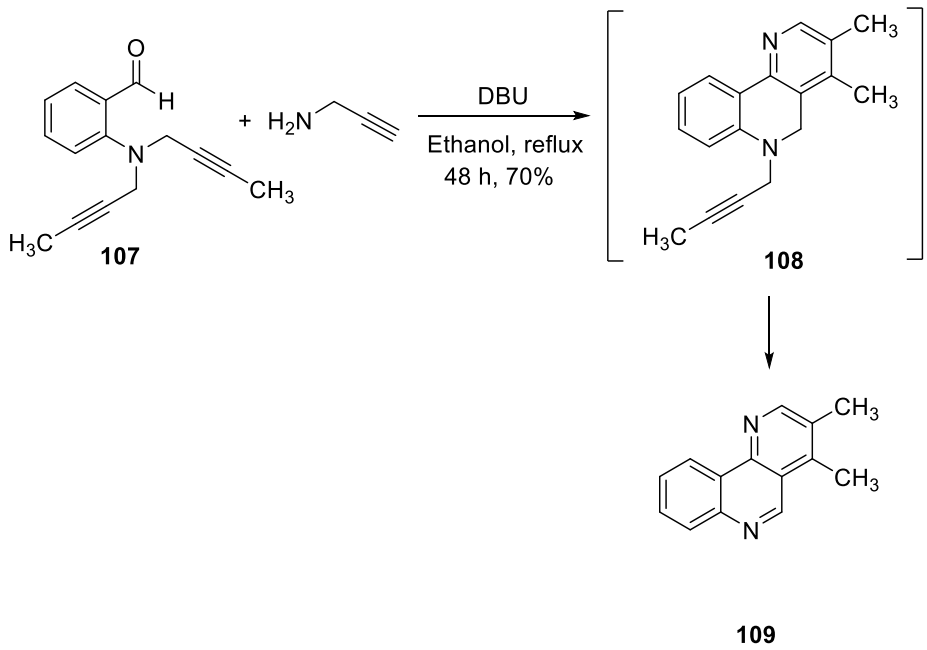


Figure 6 ^{1}H-NMR Spectrum of compound **107** in $CDCl_3$

Having obtained 2-[di(but-2-yn-1-yl)amino]benzaldehyde (**107**), it was reacted with propargyl amine in the presence of DBU. The aromatic product **109** was formed in a yield of 70% instead of cyclization product **108**.



Scheme 33

The elimination of 2-butynyl group took place under the reaction conditions to afford 3,4-dimethylbenzo[*h*][1,6]naphthyridine (**109**) (Scheme 33). Benzonaphthyridine derivative **109** was characterized by using the ^{1}H-NMR, ^{13}C-NMR and HRMS spectra. The ^{1}H-NMR spectrum (Figure 7) shows the presence of two distinct CH_3 protons which resonate as singlets at 2.71 ppm and 2.47 ppm. Six aromatic proton resonance are in agreement with the proposed structure. Three protons are shifted to lower field. Two of them are naphthyridine protons which are adjacent to the nitrogen atom. The other low field proton resonance which appears as doublet of doublets belongs to the α-proton of the benzene ring.

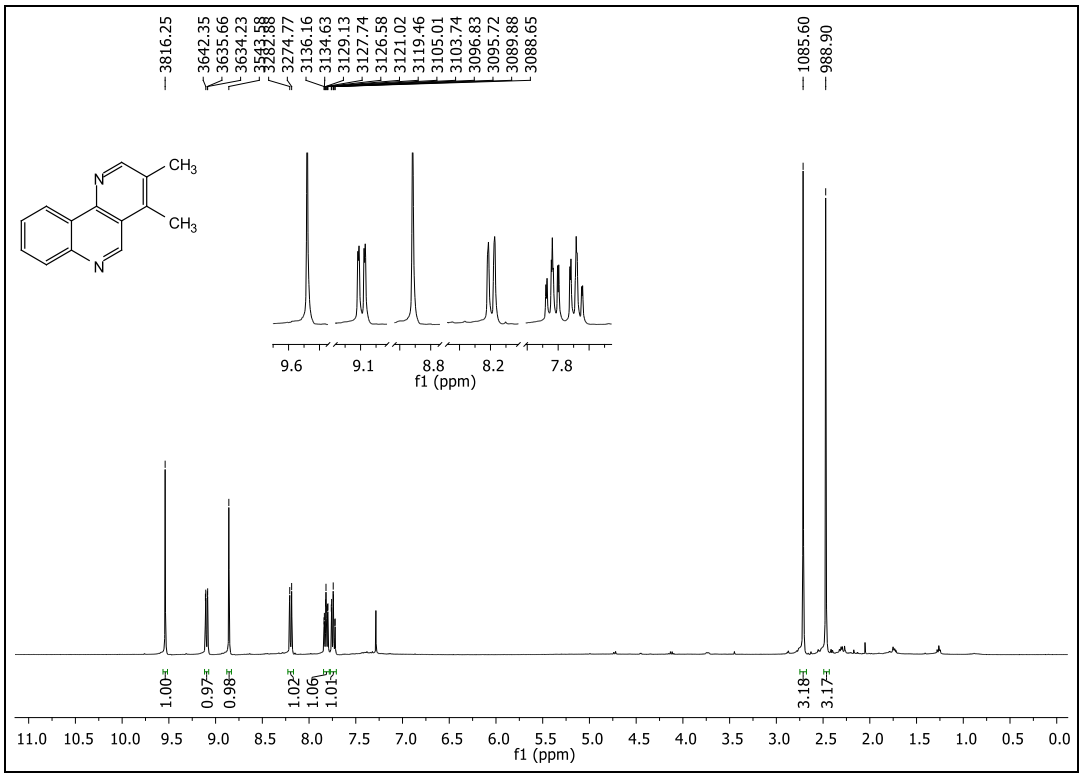
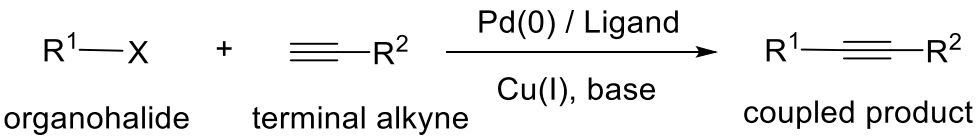


Figure 7 ^{1}H-NMR Spectrum of compound **109** in $CDCl_3$

1.2.7. Synthesis of other derivatives of 92 as starting materials by using Sonogashira coupling reaction and their cyclization reaction

Sonogashira coupling reaction[32] is a cross-coupling reaction used for formation of carbon-carbon bond between a terminal alkyne and aryl or vinyl halide by using a palladium catalyst, cupper catalyst, bulky ligand, and base (Scheme 34). It is a useful reaction to synthesize complex molecules such as pharmaceuticals, natural products, organic materials and nanomaterials.



Scheme 34

The mechanism of Sonogashira coupling reaction starts with oxidative addition of organohalide to the Pd(0)/ligand complex to form Pd(II)/ligand complex. Reaction of cupper catalyst with terminal alkyne in the presence of base generates organocupper

reagent which then performs transmetalation with Pd(II)/ligand complex. Finally, reductive elimination gives the final coupled product as shown in Figure 8.

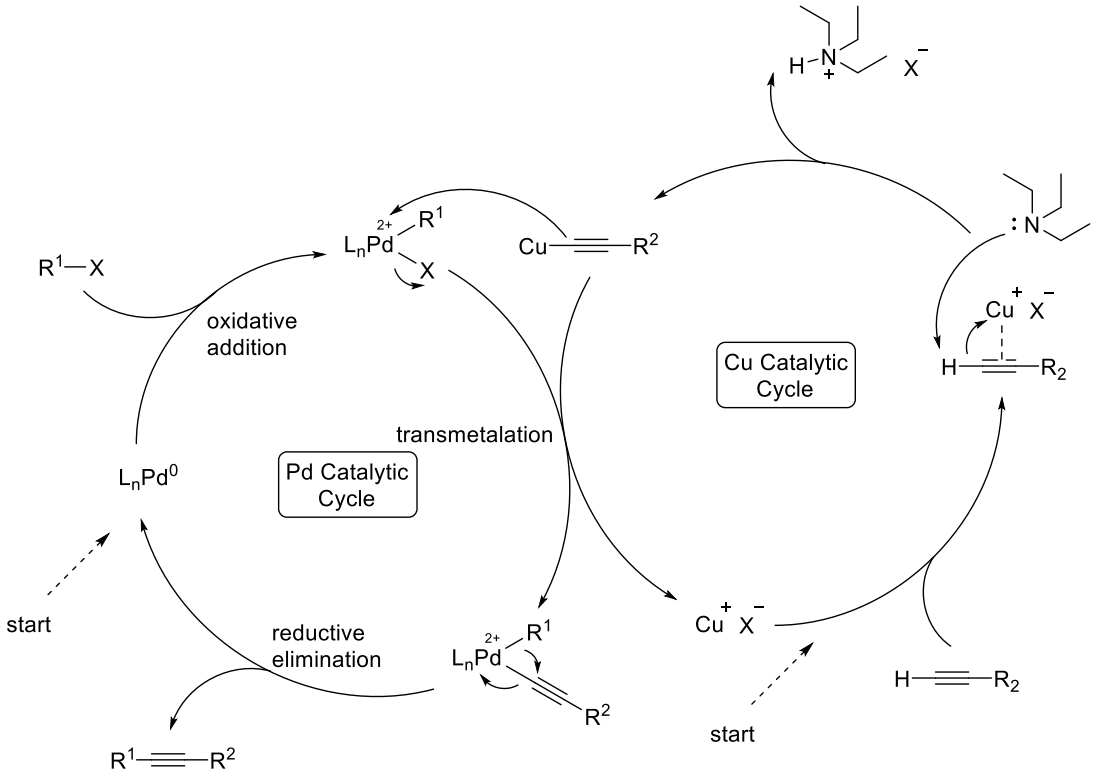
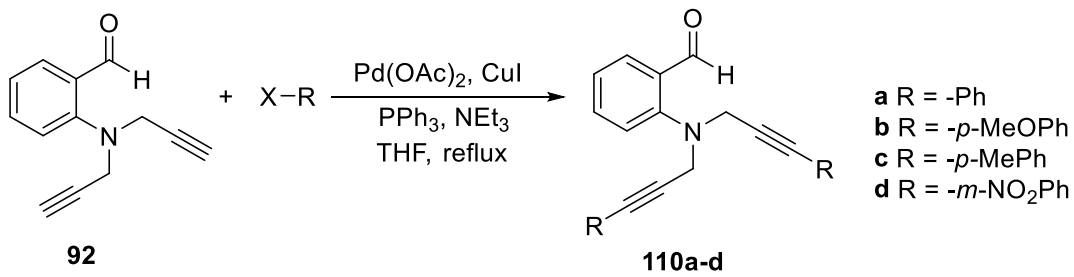


Figure 8 Catalytic cycle for Sonogashira coupling

For testing scope of this cyclization reaction, additional derivatives of starting material **110a-d** were synthesized by using Sonogashira coupling reaction procedure[33] (Scheme 35).

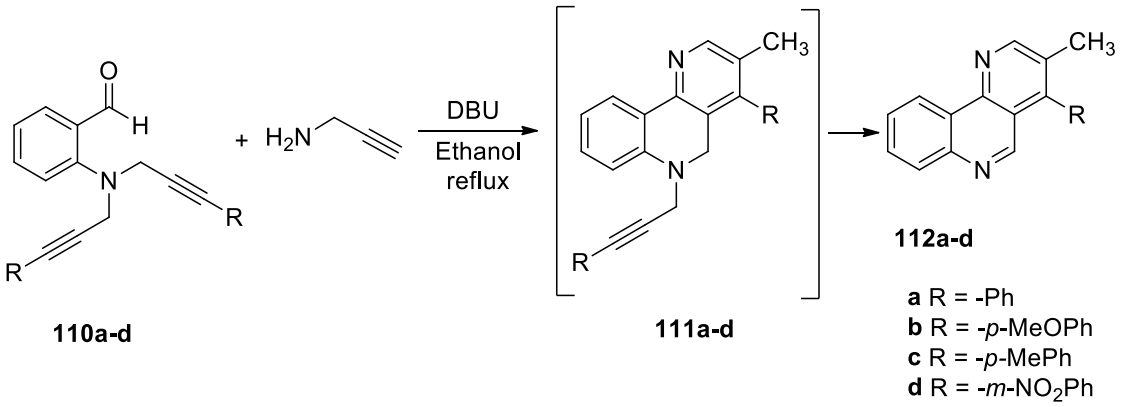


Scheme 35

Four different organohalides were used to synthesize different derivatives of aldehyde **92** as shown in Table 1. Because there are two alkyne units, two equivalents of

organohalide were used. Expected coupling products were obtained in high yields and their characterization was achieved by analyzing the ^{1}H-NMR, ^{13}C-NMR, IR, and HRMS spectra.

After getting several derivatives of starting material **110a-d**, they were reacted with propargyl amine in the presence of base to afford expected benzonaphthyridine derivatives **112a-d**. Cyclization products **111a-d** were not observed at the end of reaction. Again in this case, propargyl groups were easily eliminated from the molecule during the reaction to provide fully aromatized compounds **112a-d** (Scheme 36).



Scheme 36

Desired benzonaphthyridine derivatives **112a-d** were obtained in high yield which are shown in Table 1. Their characterization was accomplished by examining ^{1}H-NMR, ^{13}C-NMR, IR and HRMS spectra of them.

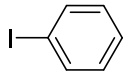
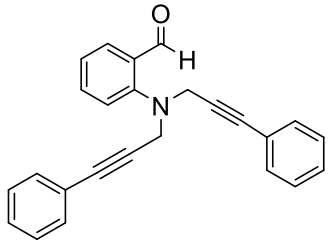
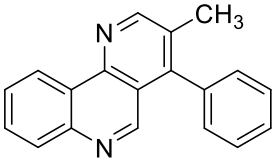
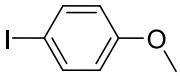
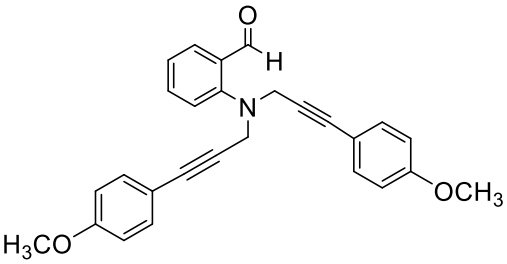
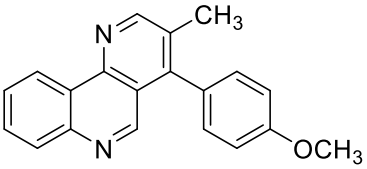
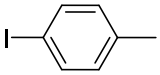
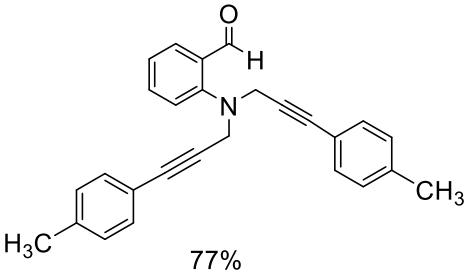
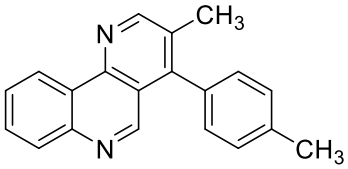
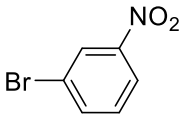
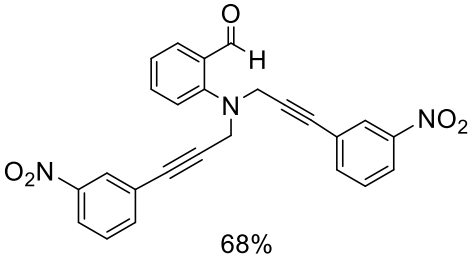
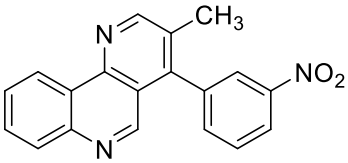
X−R	Coupling Product	Cyclization product
	 90%	 75%
	 75%	 75%
	 77%	 80%
	 68%	 65%

Table 1 Yields of coupling products and cyclization products

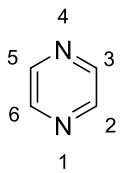
CHAPTER 2

CHROMENOPYRAZINONES

2.1. INTRODUCTION

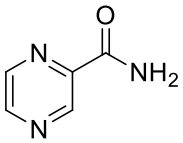
2.1.1. Pyrazines

Pyrazine (**113**) is a six-membered heterocyclic aromatic compound with two nitrogen atoms and the chemical formula of $C_4H_4N_2$. It is also named as a 1,4-diazine in which numbers indicate the position of nitrogen atoms.



113

Compounds containing pyrazine derivatives occur in many natural products, pharmaceuticals, and agricultural chemicals. They exhibit various biological activities such as antimycobacterial, antibacterial, antifungicidal, and antitubercular activity.[34] Pyrazinamide (**114**), derivatives of pyrazine, is used for treatment of tuberculosis. It is used as prodrug that prevents the growth of mycobacterium tuberculosis.[35] Phenazine (**115**) in which two benzene units are fused to pyrazine exhibits good antitumor and diuretic activities.[36] In addition, tetramethylpyrazine (**116**), isolated from chuanxiong, have characteristic flavor used as a food additive.[37]



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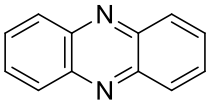

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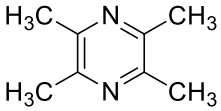
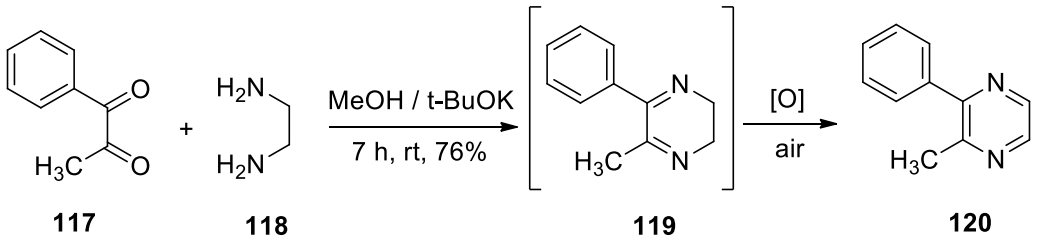


116

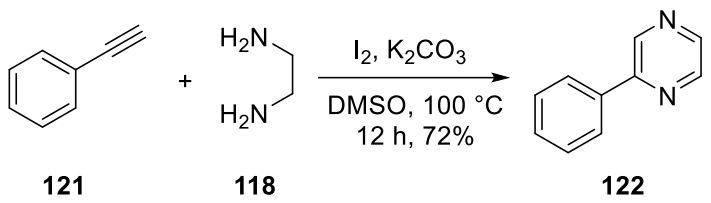
2.1.1.1. Synthesis of pyrazine derivatives

There are several methodologies for the synthesis of pyrazine derivatives. Ghosh *et al.* synthesized pyrazine derivatives starting from diketones.[38] Diketones were reacted with diamine in the presence of catalytic amount of a strong base to yield the corresponding pyrazine derivatives. For example, 1-phenylpropane-1,2-dione (**117**) was reacted with ethane-1,2-diamine (**118**) in the presence of *t*-BuOK to give 2-methyl-3-phenylpyrazine (**120**) in a yield of 76%. The mechanism for formation starts with the condensation reaction. Then oxidation of intermediate **119** with air affords compound **120** in a yield of 76% (Scheme 37).



Scheme 37

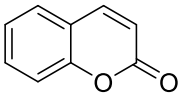
Viswanadham *et al*. achieved the synthesis of pyrazine derivative via iodine-mediated cyclization.[39] Reaction of phenylacetylene (**121**) with ethane-1,2-diamine (**118**) in the presence of I_2 and K_2CO_3 afforded desired cyclization product **122** in a yield of 72% (Scheme 38). DMSO was used as a solvent as well as oxidation reagent.



Scheme 38

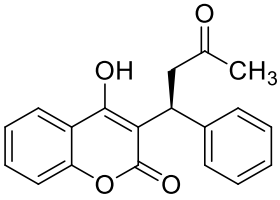
2.1.2. Coumarins

Coumarin (**123**), 2*H*-chromen-2-one, is the member of benzopyrano family in which a benzene ring is condensed to a 2*H*-pyran-2-one. Its derivatives play important role in perfume, agrochemical, and pharmaceutical industries. Also, some coumarin derivatives are used as an additives in foods and cosmetics.[40]



123

Coumarins have been shown to possess a broad spectrum of biological activities such as antibacterial, antifungal, anticoagulant, antitumor, anti-HIV. For example, warfarin (**124**) is an anticoagulant agent used in the prevention of the formation of clot clots in the blood vessels and the prevention of their migration elsewhere in the body.[41] Novobiocin (**125**) which is aminocoumarin is used as an antibiotic against staphylococcus epidermidis.[42]



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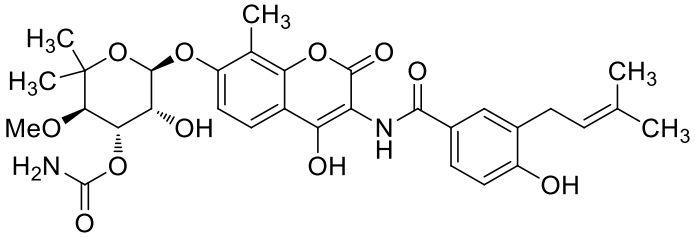
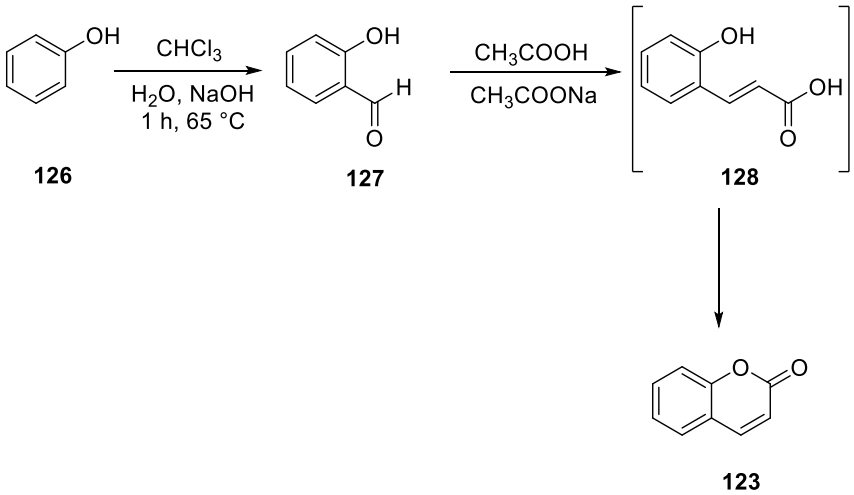


125

2.1.2.1. Synthesis of coumarin derivatives

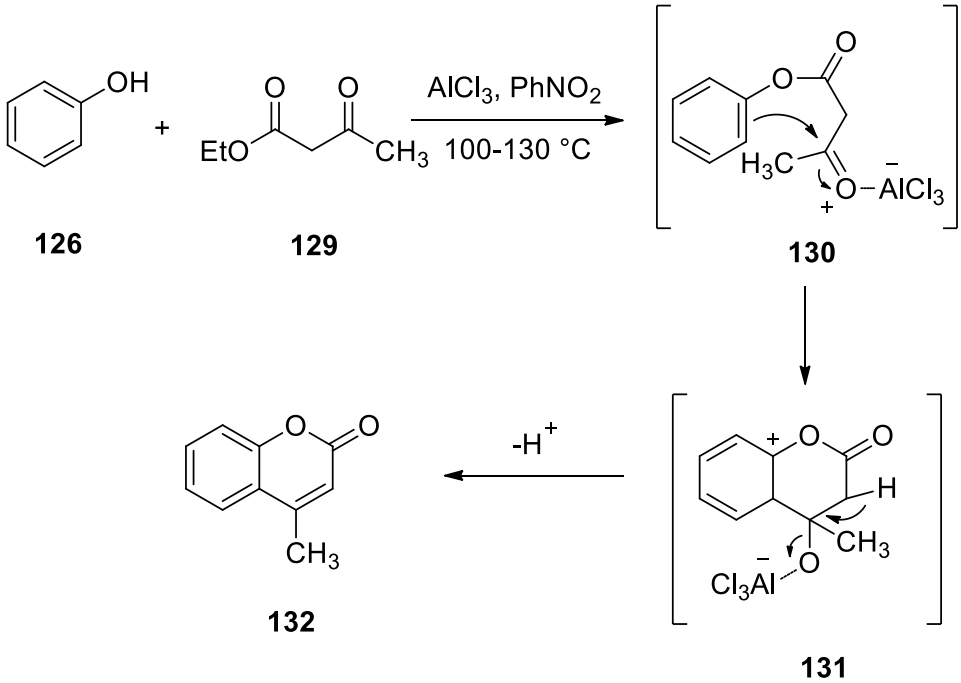
One of the methods for the synthesis of unsubstituted coumarin starts with Riemer-Tiemann reaction. Phenol (**126**) was reacted with chloroform in the presence of base to afford salicylaldehyde (**127**).



Scheme 39

Then, compound **127** underwent Perkin reaction with acetic acid and sodium acetate to give an unsaturated acid **128**. Finally, intramolecular esterification of unsaturated acid **128** yielded unsubstituted coumarin (**123**) (Scheme 39).

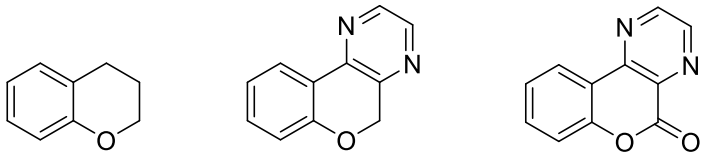
Pechmann condensation[43] is a general method for the synthesis of coumarin derivatives starting from a phenol and a carboxylic acid or ester containing a β-carbonyl group. The reaction was performed under acidic condition. Phenol (**126**) was reacted with ethyl acetoacetate (**129**) to form corresponding ester. After coordination of $AlCl_3$ to carbonyl group, intramolecular cyclization occurred. Finally, elimination of proton took place to give coumarin derivative **132** (Scheme 40).



Scheme 40

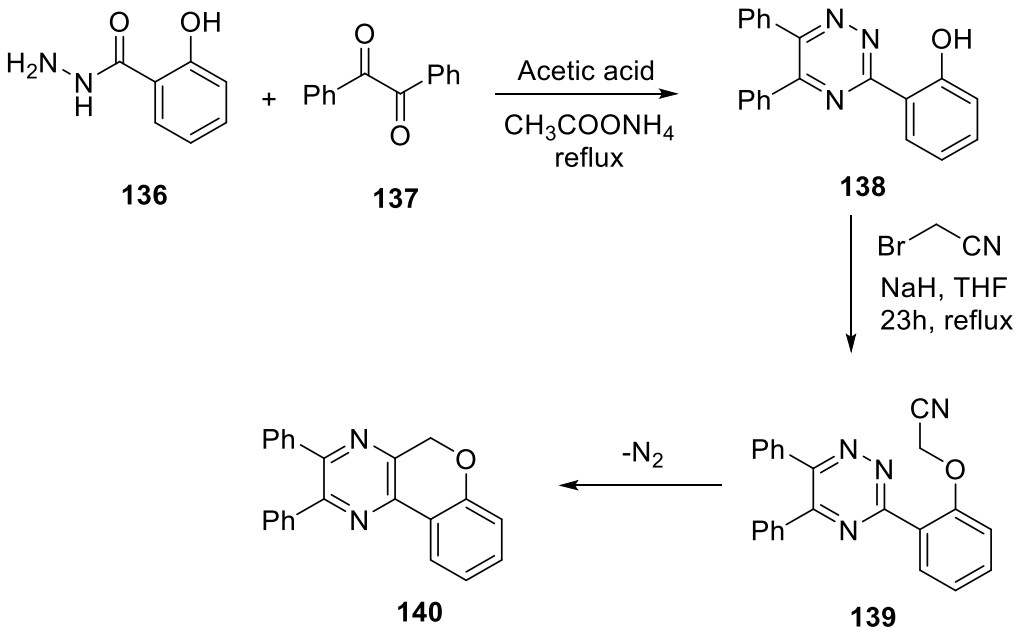
2.1.3. Chromenopyrazines and chromenopyrazinones

Chromane (**133**), also named as benzodihydropyran, is a heterocyclic organic compound with chemical formula of C_9H_9O. When chromane is fused to pyrazine, it is known as chromenopyrazine (**134**). It is a tricyclic organic compound with the chemical formula of $C_{11}H_8N_2O$. When CH_2 group in chromenopyrazine is oxidized to carbonyl group, it is named as chromenopyrazinone (**135**).



133 **134** **135**

Chromenopyrazine and chromenopyrazinone derivatives have not been investigated so much. There are a few examples of their derivatives reported in the literature. Taylor *et al*. synthesized the chromenopyrazine skeleton via intramolecular Diels-Alder reaction.[44] The reaction between salicylic acid hydrazide (**136**) and dicarbonyl compound **137** gave corresponding 1,2,4-triazine derivative **138**. Then, acetonitrile group was introduced to compound **138**.



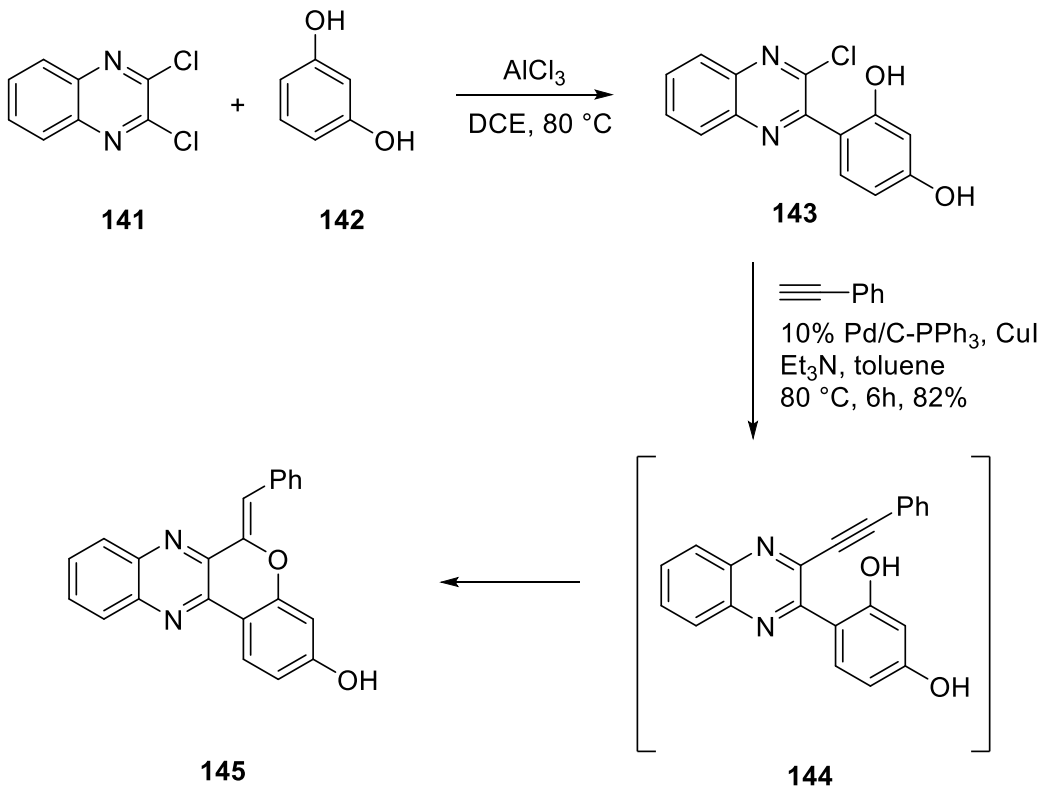
136 **137** **138** **139** **140**

Scheme 41

Finally, the synthesis was completed with an intramolecular Diels-Alder reaction in which 1,2,4-triazine part behaves as diene and nitrile part behaves as dienophile to yield diphenyl substituted chromenopyrazine derivative **140** (Scheme 41).

Kumar *et al*. investigated the synthesis of benzene fused chromenopyrazine derivative.[45] Quinoxaline derivative **141** was reacted with resorcinol (**142**) in the presence of Lewis acid to form compound **143**. It was then reacted with phenyl acetylene using coupling reagent to give cyclization product **145**. Coupling product

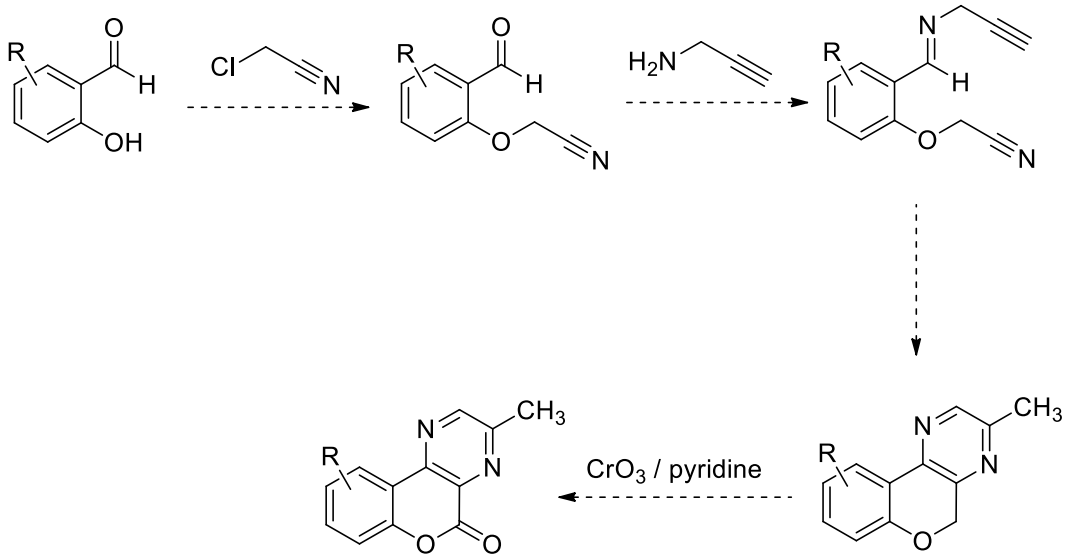
144 was not observed. Instead, cyclization product **145** was obtained in a yield of 82% (Scheme 42).



Scheme 42

2.1.4. Aim of study

In the second part of study, we were aiming to synthesize chromenopyrazine and chromepyrazinone derivatives. Because their analogues are reported in the literature to have potential biological activities such as antimycobacterial, antibacterial, antifungicidal, and antitubercular. First we will start with some salicylaldehyde derivatives and react them with chloroacetonitrile to attach acetonitrile functionality to the oxygen atom. Aldehyde will be condensed with propargyl amine to give the corresponding imines.



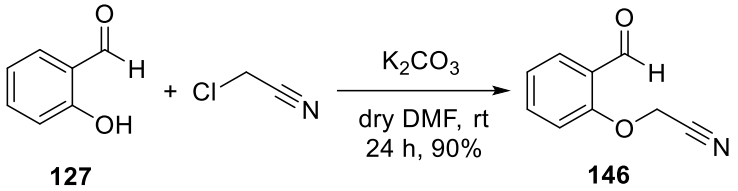
Scheme 23

Base-supported reaction of formed imines will form an allene as an intermediate. Intramolecular Diels-Alder reaction followed by H-shift should result in the formation of the desired chromenopyrazine derivatives. After getting these chromenopyrazine derivatives, their oxidation reaction with CrO_3 / pyridine will be searched (Scheme 43).

2.2. RESULTS AND DISCUSSION

2.2.1. Synthesis of (2-formylphenoxy)acetonitrile

To synthesize (2-formylphenoxy)acetonitrile (**146**), salicylaldehyde (**127**) was reacted with chloroacetonitrile in the presence of K_2CO_3. The expected product **146** was obtained in a yield of 90% after 24 hours (Scheme 44).[46]



Scheme 44

Its characterization was achieved by analyzing the ^{1}H-NMR and ^{13}C-NMR spectra. Appearance of CH_2 protons resonance as a singlet at 4.95 ppm indicates the formation of product **146** (Figure 9). Furthermore, there is an aliphatic carbon resonance for CH_2 at 53.8 ppm in the ^{13}C-NMR spectrum of **146** showing the attachment of acetonitrile group.

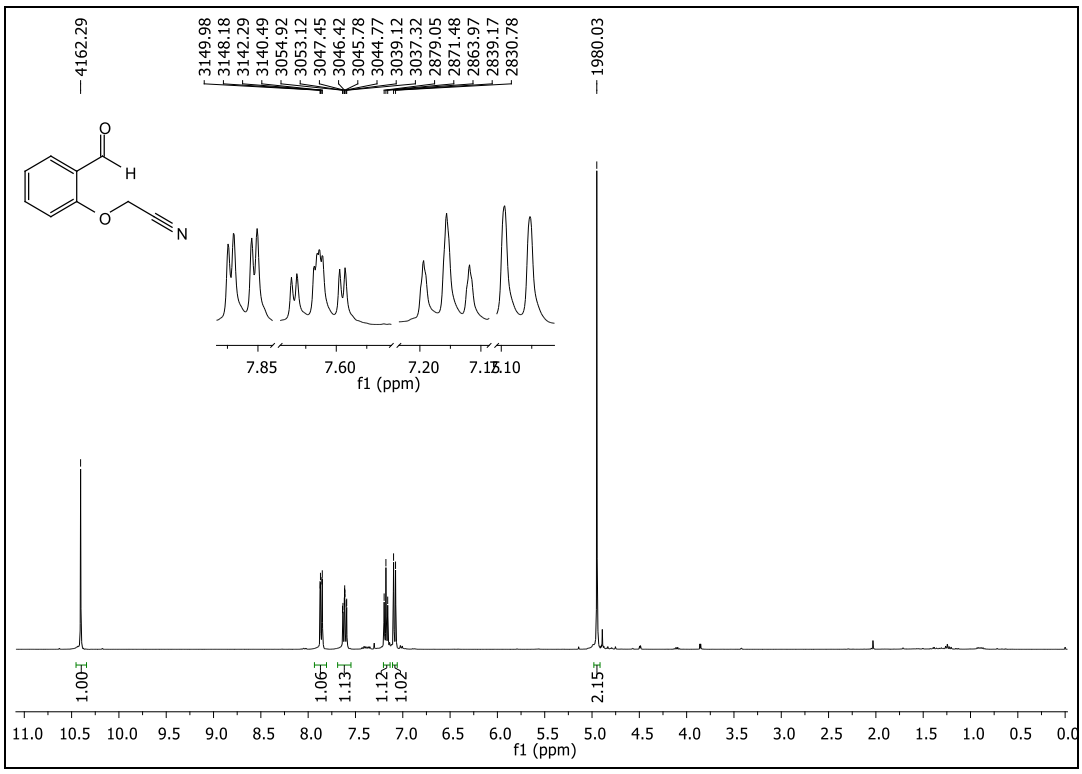
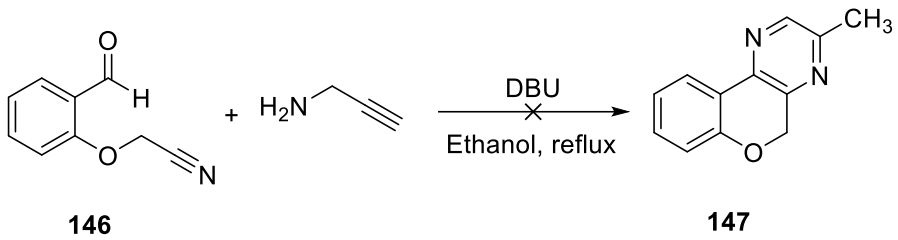


Figure 9 ^{1}H-NMR Spectrum of compound **146** in $CDCl_3$

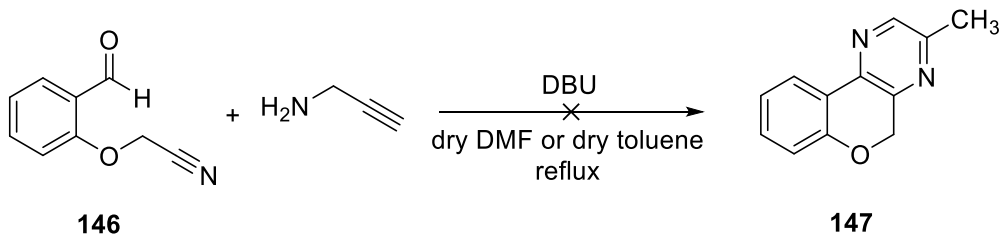
2.2.2. Cyclization reaction of (2-formylphenoxy)acetonitrile with propargyl amine in the presence of DBU

After getting (2-formylphenoxy)acetonitrile (**146**), its reaction with propargyl amine and DBU was investigated. Unfortunately, expected cyclization product **147** was not formed (Scheme 45).



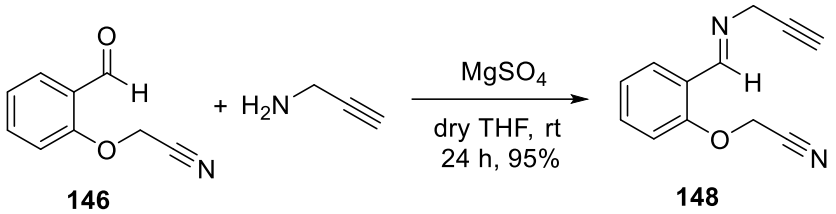
Scheme 45

To understand the effect of solvent, instead of a protic solvent, aprotic solvents such as DMF and toluene were used. Same procedure was applied, again, expected cyclization product **147** was not formed. Starting material **146** was recovered (Scheme 46).



Scheme 46

Then, we decided to change the reaction procedure. To get corresponding imine, literature procedure[26] was applied. Aldehyde **146** was reacted with propargyl amine without DBU in dry THF to afford corresponding imine **148** in a yield of 95% (Scheme 47). The formation of imine **148** was established by analyzing the ^{1}H-NMR and ^{13}C-NMR spectra of imine **148**.



Scheme 47

The imine peak in the ^{1}H-NMR spectrum appears at 8.95 ppm as a triplet with a coupling constant of J = 1.8 Hz. The alkyne proton resonating at 2.53 ppm is split into triplet with a coupling constant of J = 2.4 Hz resulting from the long-range coupling. The methylene proton resonance also splitted into doublet with the same coupling constant (Figure 10).

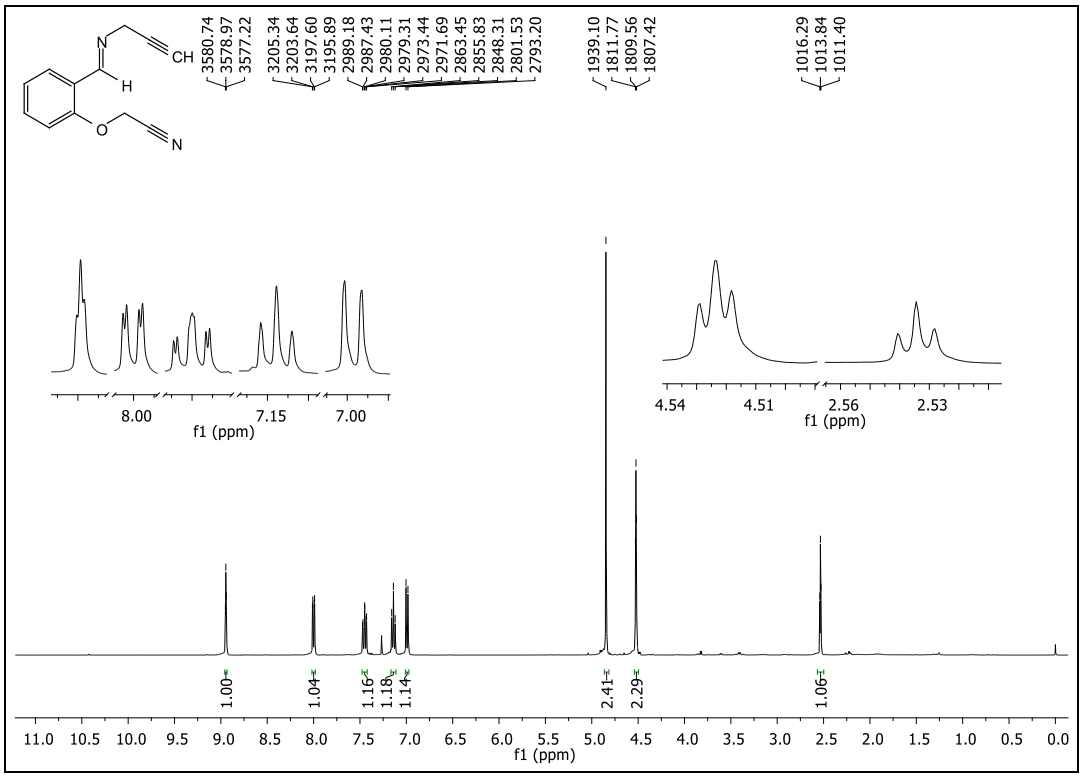
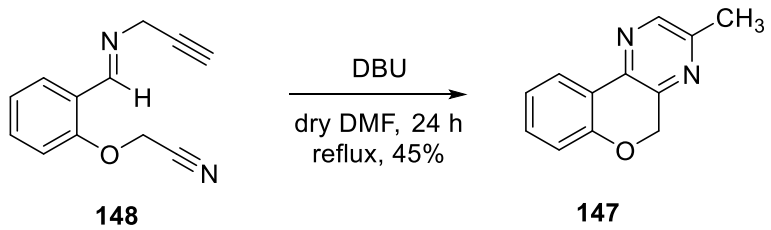


Figure 10 ^{1}H-NMR Spectrum of compound **148** in $CDCl_3$

Then, imine **148** was submitted to the cyclization reaction with DBU in dry DMF. The expected cyclization product **147** was formed in a yield of 45% which was properly characterized by ^{1}H-NMR and ^{13}C-NMR spectral analysis (Scheme 48).



Scheme 48

In the ^{1}H-NMR spectrum of compound **147**, one can easily see that there are five different aromatic protons. The resonance signal at 8.31 ppm is arising from the proton of pyrazine ring and shifted to the lower field. The proton resonance at 8.04 ppm appears as a doublet of doublets with coupling constants of J = 7.7 Hz and J = 1.6 Hz. The low field shield can be explained by the location of this proton in the deshielding zone of pyrazine ring.

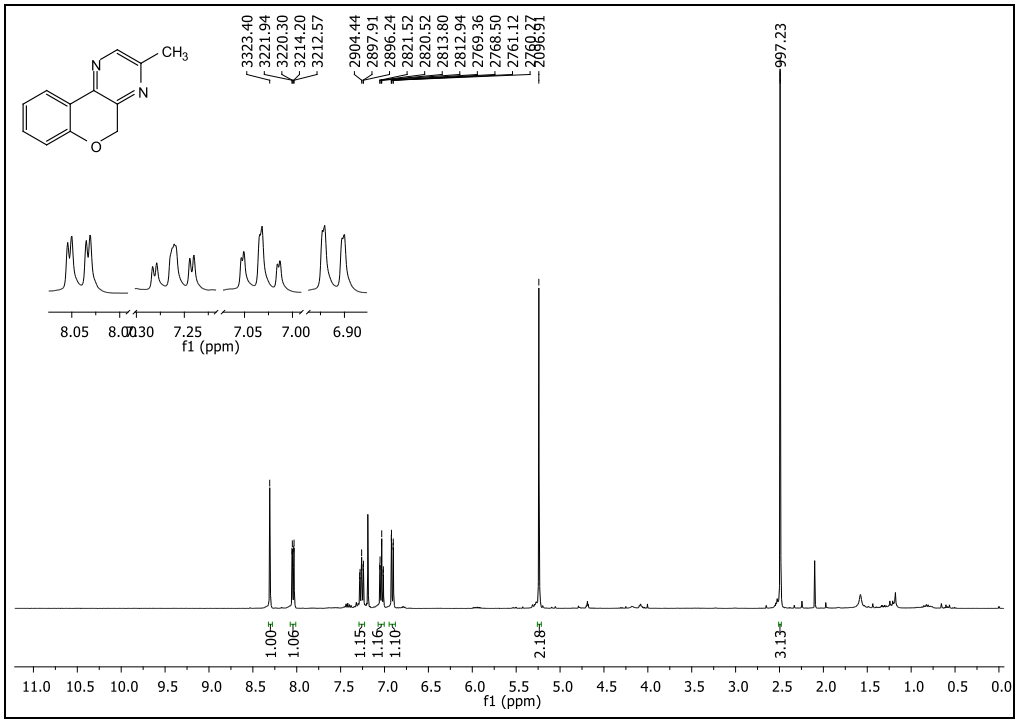
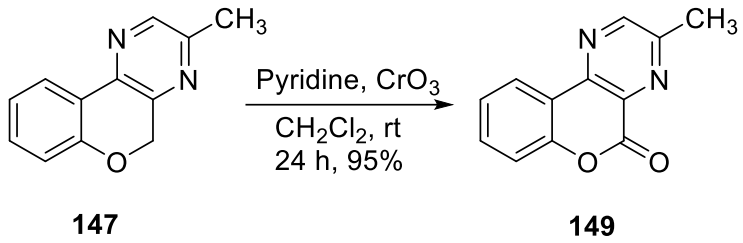


Figure 11 ^{1}H-NMR Spectrum of compound **147** in $CDCl_3$

In addition to these, appearance of CH_3 resonance a singlet at 2.49 ppm and CH_2 resonance as singlet 5.24 ppm confirm the structure of expected cyclization product **147** (Figure 11).

Cyclization product **147** was then submitted to oxidation reaction procedure[25] using CrO_3/pyridine reagent. As expected, methylene group in 3-methyl-5*H*-chromeno[3,4-*b*]pyrazine was oxidized to the corresponding carbonyl group in a yield of 95% (Scheme 49).



Scheme 49

The formation of oxidized product **149** was confirmed by examining the ^{1}H-NMR and ^{13}C-NMR spectra. Disappearance of methylene proton resonance in the ^{1}H-NMR spectrum of compound **147** (Figure 12) and appearance of a carbonyl group resonance in the ^{13}C-NMR spectrum of compound **149** clearly verify the formation of 3-methyl-5*H*-chromeno[3,4-*b*]pyrazin-5-one (**149**).

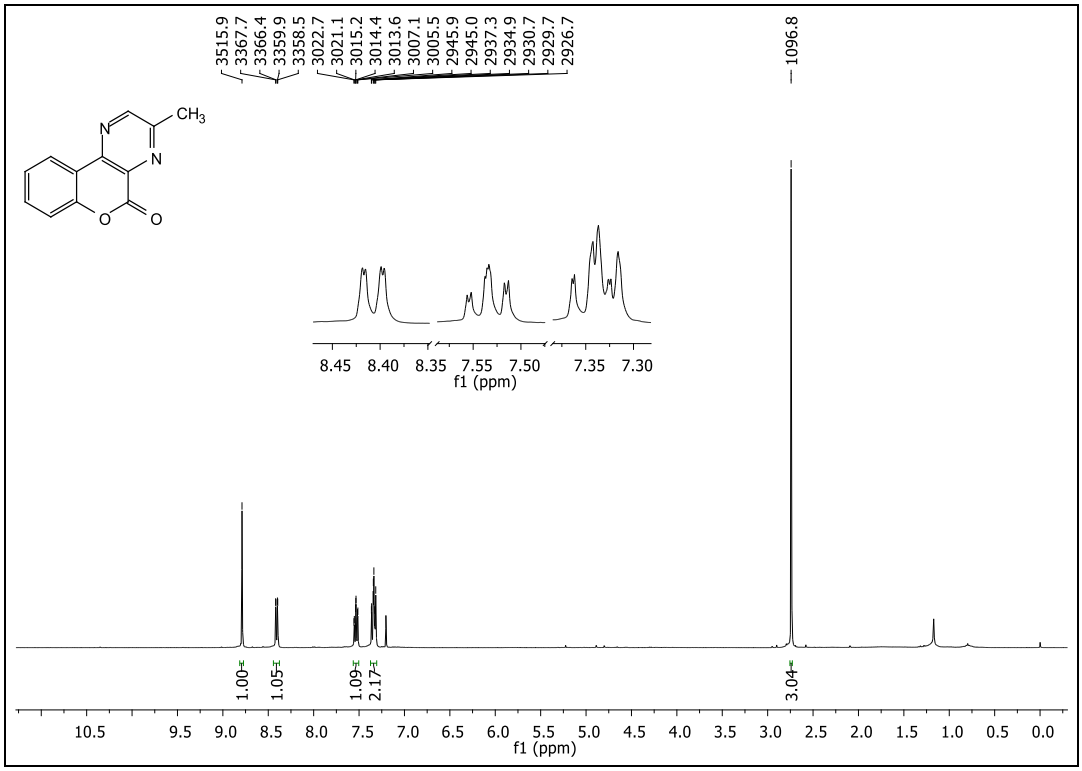
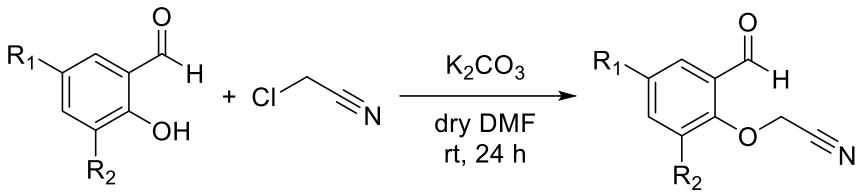


Figure 12 ^{1}H-NMR Spectrum of compound **149** in $CDCl_3$

2.2.3. Synthesis of imine derivatives

To test the scope of these cyclization reactions, two derivatives of starting material, **150** and **151**, reacted with chloroacetonitrile in the presence of K_2CO_3 according to the literature procedure[46]. Two aldehyde derivatives, (4-bromo-2-formylphenoxy)acetonitrile (**152**) and (2-formyl-6-methoxyphenoxy)acetonitrile (**153**) were obtained in yields of 85% and 80%, respectively (Scheme 50). Their characterization was achieved by analyzing their ^{1}H-NMR and ^{13}C-NMR spectra.

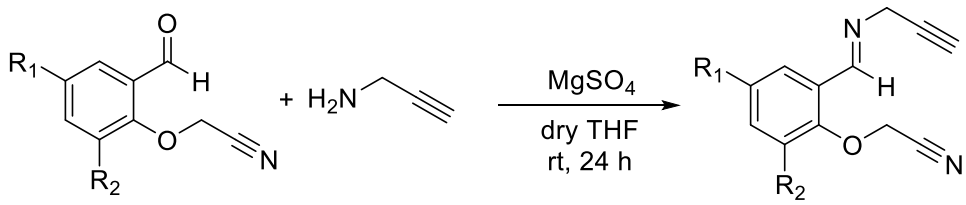


150 R_1 = Br, R_2 = H
151 R_1 = H, R_2 = OCH_3

152 R_1 = Br, R_2 = H (85%)
153 R_1 = H, R_2 = OCH_3 (80%)

Scheme 50

After getting corresponding aldehydes **152** and **153**, we applied imine formation procedure.[26] The reaction was performed by using propargyl amine in the presence of $MgSO_4$. Two distinct imine **154** and **155** were obtained in 85% and 88% yields, respectively (Scheme 51).



152 R_1 = Br, R_2 = H
153 R_1 = H, R_2 = OCH_3

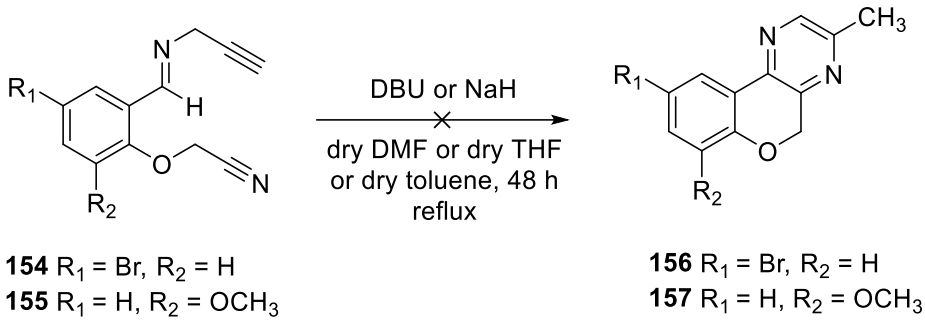
154 R_1 = Br, R_2 = H (85%)
155 R_1 = H, R_2 = OCH_3 (88%)

Scheme 51

In order to characterize imine **154** and **155**, the ^{1}H-NMR and ^{13}C-NMR spectra were analyzed. Their specific propargyl peaks were observed in the ^{1}H-NMR spectra as well as in the ^{13}C-NMR spectra.

2.2.4. An attempt for the synthesis of chromenopyrazine derivatives

Imines **154** and **155** were submitted to the cyclization reaction with DBU using three different solvent. Although three different solvent were employed and the reaction time was increased up to 48 h, expected chromenopyrazine derivatives **156** and **157** were not formed. Also, sodium hydride were used as a base instead of DBU, unfortunately, expected chromenopyrazine derivatives were not obtained (Scheme 52).

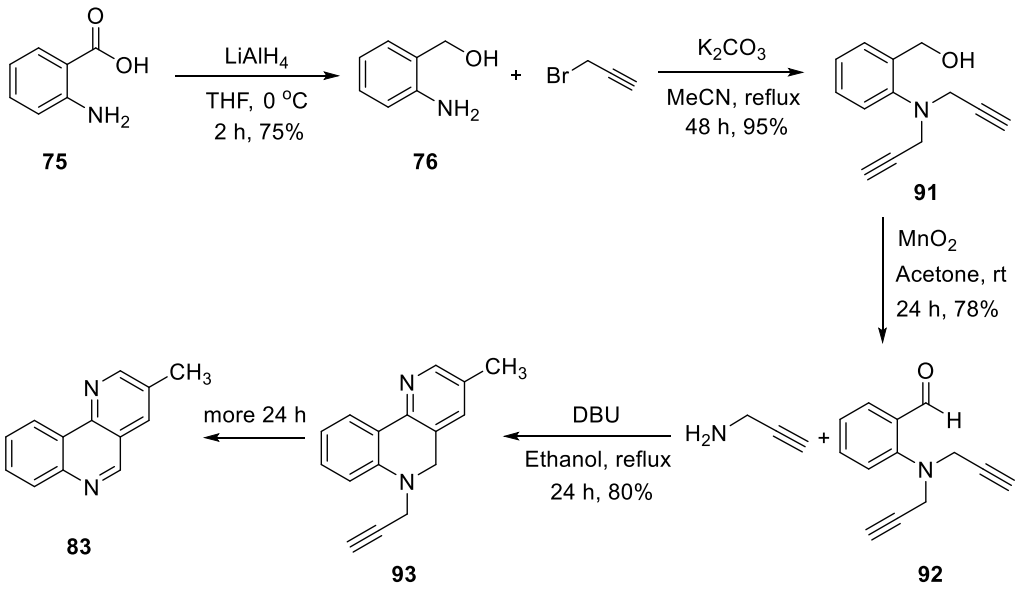


Scheme 52

CHAPTER 3

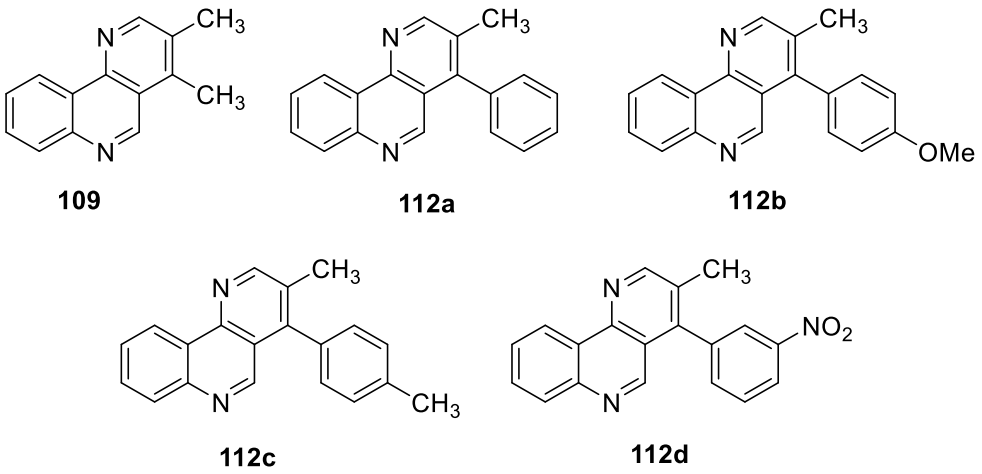
CONCLUSION

In the first part of study, we developed a new synthetic method for the synthesis of aryl and methyl substituted benzo[*h*][1,6]naphthyridine derivatives which may show potential biological activities such as anticancer, antibacterial, anti-HIV etc. Our method started with reduction of 2-aminobenzoic acid to 2-aminobenzylalcohol. After introducing of two propargyl group to amino group, expected double *N*-propargylated alcohol **91** was oxidized to the corresponding benzaldehyde derivative **92**. Its condensation reaction with propargyl amine and following cyclization reaction with DBU was explored. Expected cyclization product, 3-methyl-6-prop-2-ynyl-5,6-dihydrobenzo[*h*]-1,6-naphthyridine (**93**), was obtained. However, when the reaction time was increased, propargyl group was eliminated to yield fully aromatic 3-methylbenzo[*h*][1,6]naphthyridine (**83**) (Scheme53). Its characterization was achieved by analyzing their ^{1}H-NMR, ^{13}C-NMR, IR and HRMS spectra.

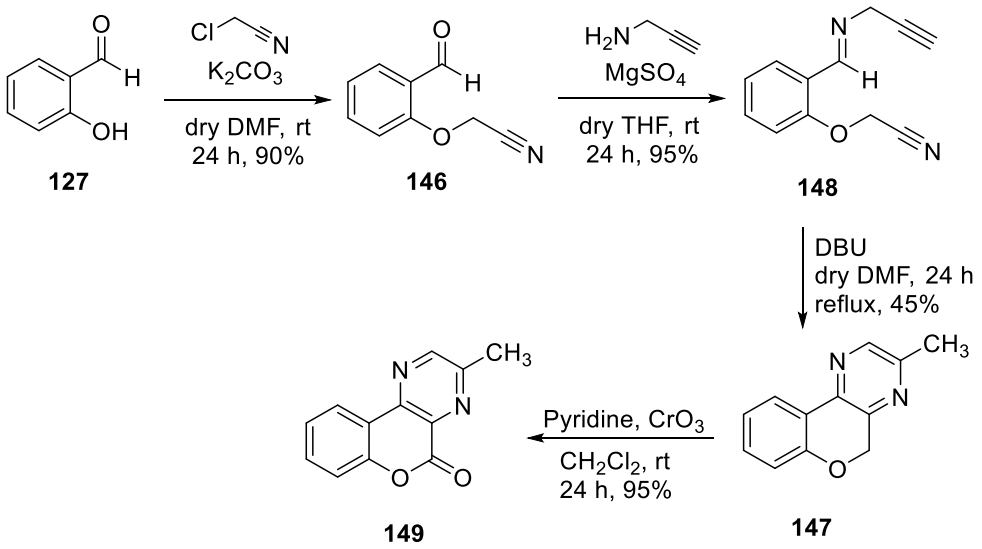


Scheme 33

To generalize this reaction, we synthesized 5 different derivatives of starting material **92**. They were submitted to cyclization reactions under the same reaction conditions to get expected aryl and methyl substituted benzo[*h*][1,6]naphthyridine derivatives. Obtained five cyclization products, **109** and **112a-d**, were analyzed by using ^{1}H-NMR and ^{13}C-NMR spectra.



In the second part of study, we explored a new reaction method to afford chromenopyrazine **147** and chromenopyrazinone **149**. We started with introduction of an acetonitrile group to salicylaldehyde. After getting corresponding aldehyde **146**, it was reacted with propargyl amine to give imine **148**.



Scheme 54

Reaction of imine **148** with DBU via aza-Diel-Alder type reaction gave the expected 3-methyl-5*H*-chromeno[3,4-*b*]pyrazine (**147**). Finally, It was oxidized by using CrO_3/pyridine to 3-methyl-5*H*-chromeno[3,4-*b*]pyrazin-5-one (**149**) (Scheme 54). Characterization of obtained chromenopyrazine and chromenopyrazinone derivative was achieved by analyzing ^{1}H-NMR and ^{13}C-NMR spectra.

CHAPTER 4

EXPERIMENTAL SECTION

4.1. General Methods

All reagents were used as purchased from commercial suppliers without further purification. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on an instrument 400 MHz and chemical shifts are reported in parts per million (ppm) downfield from TMS, using residual $CDCl_3$ as an internal standard. The ^{13}C-NMR spectra were recorded on an instrument 100 MHz and are reported in ppm using solvent as an internal standard ($CDCl_3$. Column chromatography was performed on silica gel (60-mesh). TLC was carried out on 0.2 mm silica gel 60 F254 analytical aluminum plates. High resolution Mass spectra were recorded by LC-MS TOF electrospray ionization technique.

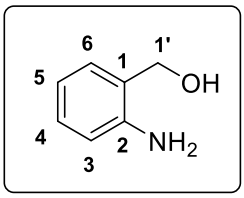
Infrared (IR) spectra were recorded in the range 4000-600 cm^{-1} via ATR diamond. Melting points were measured using melting point apparatus and were uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary vacuum evaporator.

Compounds were named by using ChemDraw Ultra 14.0 and ACD NMR.

4.2 Synthesis of (2-Aminophenyl)methanol (76)

To a solution of 2-amino-benzoic acid (2.00 g, 14.58 mmol) in dry THF (30 mL) was added dropwise a solution of $LiAlH_4$ in THF (1M, 30 mL) while the temperature was maintained at 0 °C. The resulting mixture was allowed to warm to room temperature and was stirred for 2 h. After completion of the reaction, the mixture was hydrolyzed by the addition of water (2 mL) and 5% NaOH (5 mL). The resulting suspension was filtered, and the precipitate was washed with ethyl acetate (3 × 50 mL). Then combined organic phase was dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The residue was recrystallized from chloroform, affording (2-

aminophenyl)methanol as a white tiny needles (1.35 g, 75%,) (mp 83-85 °C; Lit.[47] 81-83 °C).

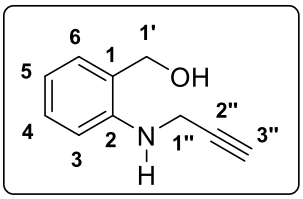


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (td, J = 7.7, $J_{4,6}$ = 1.4 Hz, 1H, H-4), 7.06 (dd, $J_{6,5}$ = 7.4, $J_{6,4}$ = 1.4 Hz, 1H, H-6), 6.75 (td, J = 7.4, $J_{5,3}$ = 1.0 Hz, 1H, H-5), 6.70 (d, $J_{3,4}$ = 7.4, 1H, H-3), 4.63 (s, 2H, H-1'), 3.49 (bs, 3H, NH_2, OH).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 129.3, 129.2, 125.0, 118.3, 116.2, 64.2

4.3. Synthesis of [2-(Prop-2-ynylamino)phenyl]methanol (78)

To a solution of (2-aminophenyl)methanol (0.50 g, 4.06 mmol) in MeCN (10 mL) was added K_2CO_3 (0.58 g, 4.26 mmol). The resulting mixture was stirred at room temperature for 15 min and to the reaction flask was added a solution of propargyl bromide (0.51 g, 4.26 mmol). The reaction mixture was stirred for 9 h at room temperature. After completion of the reaction, the reaction mixture was extracted with EtOAc (3 × 50 mL). Then combined organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from chloroform/hexane, affording [2-(prop-2-ynylamino)phenyl]methanol as a yellow needles (0.59 g, 90%) (mp 60-62 °C).

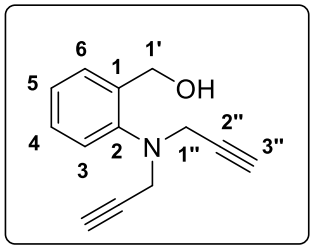


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (td, J = 7.8, $J_{4,6}$ = 1.5 Hz, 1H, H-4), 7.01 (dd, $J_{6,5}$ = 7.3, $J_{6,4}$ = 1.5 Hz, 1H, H-6), 6.76 – 6.69 (m, 2H, arom), 4.99 (bs, 1H, NH), 4.51 (s, 2H, H-1'), 3.88 (d, $J_{1'',3''}$ = 2.4 Hz, 2H, H-1''), 2.38 (bs, 1H, OH), 2.18 (t, $J_{3'',1''}$ = 2.4 Hz, 1H, H-3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 129.5, 129.1, 125.4, 117.8, 111.5, 81.3, 71.3, 64.39, 33.1.

4.4. Synthesis of [2-(Diprop-2-ynylamino)phenyl]methanol (91)

To a solution of (2-aminophenyl)methanol (1.00 g, 8.13 mmol) in MeCN (15 mL) was added K_2CO_3 (2.47 g, 17.89 mmol). The resulting mixture was stirred at room temperature for 30 min and to the reaction flask was added a solution of propargyl bromide (2.13 g, 17.89 mmol). The reaction mixture was stirred for 48 h at reflux temperature. After completion of the reaction, solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL). Then combined organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to afford [2-(diprop-2-ynylamino)phenyl]methanol as a yellow viscous oil (1.54 g, 95%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 1H, arom), 7.25 – 7.19 (m, 2H, arom), 7.13 – 7.09 (m, 1H, arom), 4.70 (s, 2H, H-1'), 3.86 (d, $J_{1'',3''}$ = 2.4 Hz, 4H, H-1''), 2.22 (t, $J_{3'',1''}$ = 2.3 Hz, 2H, H-3'').

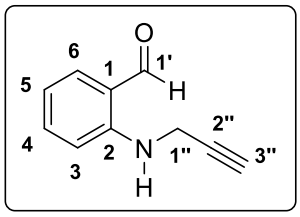
^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 136.7, 129.1, 128.2, 125.9, 123.0, 78.8, 73.7, 63.4, 42.6.

IR(ATR, cm^{-1}) 3382, 2918, 1599, 1490, 1451, 1362, 1332, 1208, 1189, 1151, 1093, 1024, 912, 759, 723, 596.

HRMS calcd for $C_{13}H_{13}NO$ $[M+H]^+$: 200.1069, found: 200.1070.

4.5. Synthesis of 2-(Prop-2-ynylamino)benzaldehyde (79)

To a solution of [2-(prop-2-ynylamino)phenyl]methanol (0.30 g, 1.86 mmol) in acetone (15 mL) was added MnO_2 (1.62 g, 18.60 mmol) and 3 Å molecular sieve. The resulting mixture was stirred at room temperature for 24 h. After completion of the reaction, the resulting mixture was filtered over a gauche and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel/hexane-EtOAc 5:1) and recrystallized from chloroform/hexane to give 2-(prop-2-ynylamino)benzaldehyde as a yellow solid (0.24 g, 80%) (mp 52-54 °C).



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H, H-1'), 8.44 (bs, 1H, NH), 7.47 (dd, $J_{6,5}$ = 7.8, $J_{6,4}$ = 1.3 Hz, 1H, H-6), 7.45 – 7.40 (m, 1H, H-4), 6.79 – 6.73 (m, 2H, arom), 4.00 (dd, J = 5.9, $J_{1'',3''}$ = 2.5 Hz, 2H, H-1''), 2.28 (t, $J_{3'',1''}$ = 2.5 Hz, 1H, H-3'').

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.09, 149.40, 136.62, 135.77, 119.13, 116.06, 111.19, 79.96, 71.70, 32.03.

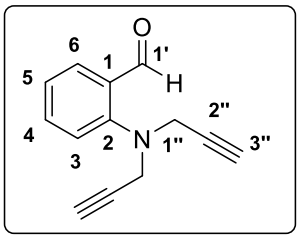
IR (ATR, cm^{-1}) 3342, 3279, 2747, 1658, 1609, 1574, 1502, 1462, 1420, 1396, 1358, 1313, 1198, 1181, 1162, 1129, 1067, 1046, 1009, 967, 937, 868, 743, 674, 660, 643.

HRMS calcd for $C_{10}H_9NO$ $[M+H]^+$: 160.0728, found: 160.0757.

4.6. Synthesis of 2-(Diprop-2-ynylamino)benzaldehyde (92)

To a solution of [2-(diprop-2-ynylamino)phenyl]methanol (0.50 g, 2.51 mmol) in acetone (15 mL) was added MnO_2 (2.18 g, 25.10 mmol) and 3 Å molecular sieve. The resulting mixture was stirred at room temperature for 24 h. After completion of the reaction, the resulting mixture was filtered over a gauche and evaporated under reduced pressure. The crude product was purified by column chromatography (silica

gel/hexane-EtOAc 4:1). Product was recrystallized from chloroform, affording 2-(diprop-2-ynylamino)benzaldehyde as a yellow crossed needles (0.39 g, 78%) (mp 70-72 °C).



^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H, H-1'), 7.77 (dd, $J_{6,5}$ = 7.7, $J_{6,4}$ = 1.7 Hz, 1H, H-6), 7.48 (ddd, $J_{4,3}$ = 8.1, $J_{4,5}$ = 7.4, $J_{4,6}$ = 1.7 Hz, 1H, H-4), 7.31 (d, $J_{3,4}$ = 8.1 Hz, 1H, H-3), 7.14 (t, J = 7.5 Hz, 1H, H-5), 3.96 (d, $J_{1'',3''}$ = 2.3 Hz, 4H, H-1''), 2.26 (t, $J_{3'',1''}$ = 2.3 Hz, 2H, H-3'').

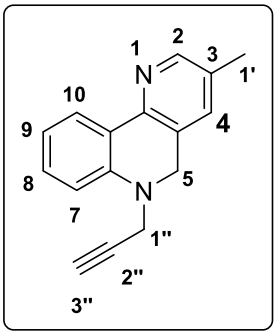
^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 152.5, 134.6, 130.0, 129.6, 124.3, 121.7, 78.4, 74.1, 43.8.

IR (ATR, cm^{-1}) 3285, 3269, 1652, 1593, 1481, 1455, 1397, 1368, 1350, 1296, 1281, 1206, 1191, 1165, 1142, 946, 761, 713, 681, 648.

HRMS calcd for $C_{13}H_{11}NO$ $[M+H]^+$: 198.0913, found: 198.0920.

4.7. Synthesis of 3-Methyl-6-prop-2-ynyl-5,6-dihydrobenzo[*h*][1,6]naphthyridine (93)

To a solution of 2-(diprop-2-ynylamino)benzaldehyde (0.20 g, 1.01 mmol) in EtOH (10 mL) was added propargyl amine (77 μL, 1.21 mmol) and DBU (181 μL, 1.21 mmol). The resulting mixture was stirred at reflux temperature for 24 h. After completion of the reaction, solvent was evaporated under pressure. The residue was extracted with EtOAc (3 × 50 mL). Then combined organic phase was dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized from chloroform/hexane, affording 3-methyl-6-prop-2-ynyl-5,6-dihydrobenzo[*h*][1,6]naphthyridine as a pale brown cubic crystal (0.20 g, 80%) (mp 162-164 °C).



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, $J_{2,4}$ = 1.3 Hz, 1H, H-2), 8.24 (dd, $J_{10,9}$ = 7.7, $J_{10,8}$ = 1.6 Hz, 1H, H-10), 7.31 (ddd, $J_{8,7}$ = 8.1, $J_{8,9}$ = 7.4, $J_{8,10}$ =1.6 Hz, 1H, H-8), 7.24 (d, $J_{4,2}$ = 1.3 Hz, 1H, H-4), 6.97 (td, J = 7.6, $J_{9,7}$ = 0.9 Hz, 1H, H-9), 6.87 (d, $J_{7,8}$ = 8.1 Hz, 1H, H-7), 4.35 (s, 2H, H-5), 4.08 (d, $J_{1'',3''}$ = 2.4 Hz, 2H, H-1''), 2.34 (s, 3H, H-1'), 2.28 (t, $J_{3'',1''}$ = 2.4 Hz, 1H, H-3'').

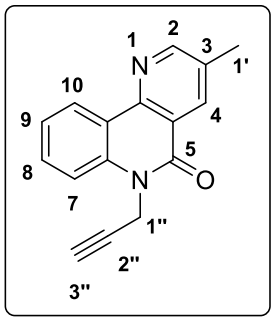
^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 147.5, 145.7, 133.7, 131.6, 130.3, 127.1, 124.9, 124.1, 119.7, 112.9, 78.0, 73.6, 51.8, 39.9, 18.3.

IR (ATR, cm^{-1}) 3265, 1597, 1494, 1458, 1434, 1324, 1299, 1238, 1223, 1170, 1138, 1105, 1061, 907, 891, 756, 748, 695, 677, 656, 626, 609, 592.

HRMS calcd for $C_{16}H_{14}N_2$ $[M+H]^+$: 235.1231, found: 235.1230.

4.8. Synthesis of 3-Methyl-6-prop-2-ynylbenzo[*h*][1,6]naphthyridin-5(6*H*)-one (105)

To a suspension of CrO_3 (1.92 g, 19.2 mmol) in 10 mL of DCM was added pyridine (0.76 g, 9.6 mmol) at room temperature. The mixture was stirred at room temperature for 20 min and cooled to 0 °C. Then, a solution of 3-methyl-6-prop-2-ynyl-5,6-dihydrobenzo[*h*][1,6]naphthyridine (0.15 g, 0.64 mmol) in 4 mL of DCM was added and the mixture was stirred at room temperature for 24 h. After completion of the reaction, the mixture was filtered over silica by using DCM as mobile phase. Solvent was evaporated under reduced pressure and the residue was recrystallized from chloroform/hexane to give 3-methyl-6-prop-2-ynylbenzo[*h*][1,6]naphthyridin-5(6*H*)-one as a white solid (95%) (mp 152-154 °C).



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (dd, $J_{10,9}$ = 8.0, $J_{10,8}$ = 1.4 Hz, 1H, H-10), 8.78 (d, $J_{2,4}$ = 1.7 Hz, 1H, H-2), 8.49 (d, $J_{4,2}$ = 1.7 Hz, 1H, H-4), 7.58 (ddd, $J_{8,7}$ = 8.4 Hz, $J_{8,9}$ = 7.2 Hz, $J_{8,10}$ = 1.4 Hz, 1H, H-8), 7.51 (d, $J_{7,8}$ = 8.4 Hz, 1H, H-7), 7.37 – 7.32 (m, 1H, H-9), 5.14 (d, $J_{1'',3''}$ = 2.3 Hz, 2H, H-1''), 2.46 (s, 3H, H-1'), 2.20 (t, $J_{3'',1''}$ = 2.3 Hz, 1H, H-3'').

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 155.8, 148.8, 138.0, 137.0, 133.8, 131.5, 125.8, 123.9, 121.7, 120.9, 115.6, 78.7, 73.1, 32.8, 19.2.

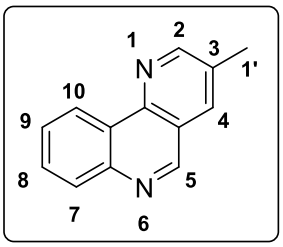
IR (ATR, cm^{-1}) 3257, 1647, 1607, 1587, 1505, 1468, 1456, 1428, 1370, 1352, 1309, 1258, 1202, 1134, 1121, 933, 914, 806, 752, 719, 699, 663, 649, 577.

HRMS calcd for $C_{16}H_{12}N_2O$ $[M+H]^+$: 249.1043, found: 249.1022.

4.9. Synthesis of 3-Methylbenzo[*h*][1,6]naphthyridine (83)

To a solution of 2-(diprop-2-ynylamino)benzaldehyde (0.20 g, 1.01 mmol) in EtOH (10 mL) was added propargyl amine (77 μL, 1.21 mmol) and DBU (181 μL, 1.21 mmol). The resulting mixture was stirred at reflux temperature for 48 h. After completion of the reaction, solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL) and dried over $MgSO_4$. Then combined organic phase was evaporated under reduced pressure and purified by column chromatography (silica gel/hexane-EtOAc 6:1) followed by recrystallization from

chloroform/hexane to afford 3-methylbenzo[*h*][1,6]naphthyridine as a yellow cubic crystal (0.14 g, 70%) (mp 138-140 °C; Lit.[48] 145-147 °C)



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H, H-5), 9.04 (dd, $J_{10,9}$ = 8.2, $J_{10,8}$ = 1.5 Hz, 1H, H-10), 8.96 (d, $J_{2,4}$ = 1.6 Hz, 1H, H-2), 8.16 (d, $J_{7,8}$ = 8.2 Hz, 1H, H-7), 8.06 (d, $J_{4,2}$ = 1.6 Hz, 1H, H-4), 7.77 (ddd, $J_{8,7}$ = 8.2 Hz, $J_{8,9}$ = 7.1 Hz, $J_{8,10}$ = 1.5 Hz, 1H, H-8), 7.70 (ddd, $J_{9,10}$ = 8.2 Hz, $J_{9,8}$ = 7.1 Hz, $J_{9,7}$ = 1.2 Hz, 1H, H-9), 2.55 (s, 3H, H-1').

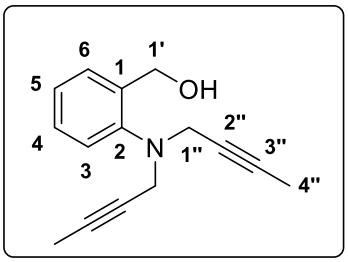
^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 152.3, 146.5, 145.7, 135.2, 132.7, 130.0, 129.0, 127.7, 125.4, 123.5, 120.6, 18.7.

IR (ATR, cm^{-1}) 1607, 1589, 1571, 1519, 1445, 1383, 1345, 1309, 1230, 1166, 1139, 1037, 1014, 965, 945, 931, 874, 865, 813, 788, 769, 728, 686, 614.

HRMS calcd for $C_{13}H_{10}N_2$ $[M+H]^+$: 195.0936, found: 195.0917.

4.10. Synthesis of {2-[Di(but-2-yn-1-yl)amino]phenyl}methanol (106)

To a solution of (2-aminophenyl)methanol (0.30 g, 2.44 mmol) in MeCN (5 mL) was added K_2CO_3 (1.06 g, 5.37 mmol). The resulting mixture was stirred at room temperature for 30 min and to the reaction flask was added a solution of 1-bromobut-2-yne (47 μL 5.37 mmol). The reaction mixture was stirred for 3 days at room temperature. After completion of the reaction, solvent was evaporated under pressure. The residue was extracted with EtOAc (3 × 50 mL). Then combined organic phase was dried over $MgSO_4$ and evaporated under reduced pressure, affording {2-[di(but-2-yn-1-yl)amino]phenyl}methanol as a pale brown viscous oil (0.44 g, 80%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, $J_{6,5}$ = 7.4 Hz, 1H, H-6), 7.30 – 7.22 (m, 2H), 7.15 (td, J = 7.5, $J_{5,3}$ = 1.0 Hz, 1H, H-5), 4.77 (s, 2H, H-1'), 4.44 (bs, 1H, OH), 3.85 (q, $J_{1'',4''}$ = 2.2 Hz, 4H, H-1''), 1.82 (t, $J_{4'',1''}$ = 2.2 Hz, 6H, H-4'').

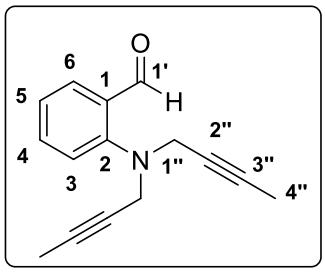
^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 136.6, 128.7, 127.8, 125.2, 122.8, 81.0, 74.3, 63.30, 42.8, 3.4.

IR (ATR, cm^{-1}) 3381, 2918, 1599, 1490, 1451, 1362, 1332, 1208, 1189, 1151, 1128, 1092, 1025, 912, 722, 597.

HRMS calcd for $C_{15}H_{17}NO$ $[M+H]^+$: 228.1386, found: 228.1383.

4.11. Synthesis of 2-[Di(but-2-yn-1-yl)amino]benzaldehyde (107)

To a solution of {2-[di(but-2-yn-1-yl)amino]phenyl}methanol (0.30 g, 1.32 mmol) in acetone (10 mL) was added MnO_2 (1.15 g, 13.20 mmol) and molecular sieve. The resulting mixture was stirred at room temperature for 24 h. After completion of the reaction, the resulting mixture was filtered over a gauche and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel/hexane-EtOAc 5:1) to afford 2-[di(but-2-yn-1-yl)amino]benzaldehyde as a pale yellow viscous oil (0.21 g, 70%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H, H-1'), 7.76 (dd, $J_{6,5}$ = 7.7, $J_{6,4}$ = 1.7 Hz, 1H, H-6), 7.45 (td, J = 7.7, $J_{4,6}$ = 1.7 Hz, 1H, H-4), 7.29 (d, $J_{3,4}$ = 8.2 Hz, 1H, H-3), 7.08 (t, J = 7.5 Hz, 1H, H-5), 3.89 (q, $J_{1'',4''}$ = 2.2 Hz, 4H, H-1''), 1.76 (t, $J_{4'',1''}$ = 2.2 Hz, 6H, H-4'').

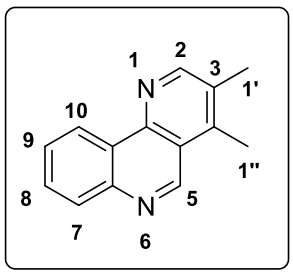
^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 153.4, 134.5, 129.6, 129.2, 123.3, 121.2, 81.7, 74.0, 44.3, 3.6.

IR (ATR, cm^{-1}) 2919, 1684, 1660, 1595, 1515, 1481, 1453, 1363, 1281, 1205, 1190, 1162, 1086, 1051, 1025, 913, 829, 756, 640.

HRMS calcd for $C_{15}H_{15}NO$ $[M+H]^+$: 226.1202, found: 226.1226.

4.12. Synthesis of 3,4-Dimethylbenzo[*h*][1,6]naphthyridine (109)

To a solution of 2-[di(but-2-yn-1-yl)amino]benzaldehyde (0.20 g, 89 mmol) in EtOH (10 mL) was added propargyl amine (68 μL, 1.07 mmol) and DBU (160 μL, 1.07 mmol). The resulting mixture was stirred at reflux temperature for 48 h. After completion of the reaction, solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL) and dried over $MgSO_4$. Then combined organic phase was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel/hexane-EtOAc 10:1) followed by recrystallization from chloroform/hexane, affording 3,4-dimethylbenzo[*h*][1,6]naphthyridine as a pale yellow needles (0.13 g, 70%) (mp 130-132 °C).



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H, H-5), 9.10 (dd, $J_{10,9}$ = 8.2, $J_{10,8}$ = 1.3 Hz, 1H, H-10), 8.86 (s, 1H, H-2), 8.20 (d, $J_{7,8}$ = 8.2 Hz, 1H, H-7), 7.82 (ddd, $J_{9,10}$ = 8.2, $J_{9,8}$ = 7.1, $J_{9,7}$ = 1.5 Hz, 1H), 7.74 (ddd, $J_{8,7}$ = 8.2, $J_{8,9}$ = 7.1, $J_{8,10}$ = 1.3 Hz, 1H), 2.71 (s, 3H, H-1''), 2.47 (s, 3H, H-1').

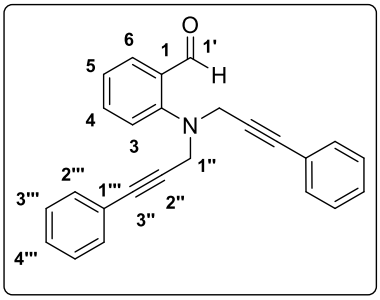
^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 149.2, 146.8, 145.3, 143.3, 131.1, 129.8, 128.9, 127.5, 125.5, 123.7, 119.8, 17.2, 13.7.

IR (ATR, cm^{-1}) 1579, 1517, 1445, 1384, 1295, 1148, 1024, 990, 976, 952, 929, 870, 856, 783, 771, 734, 694, 633, 593.

HRMS calcd for $C_{14}H_{12}N_2$ $[M+H]^+$: 209.1078, found: 209.1073.

4.13. Synthesis of 2-[Bis(3-phenylprop-2-ynyl)amino]benzaldehyde (110a)

A mixture of CuI (15.2 mg, 0.08 mmol), PPh_3 (53 mg, 0.20 mmol), and $Pd(OAc)_2$ (22 mg, 0.10 mmol) was stirred under nitrogen for 5 min. Then, a solution of 2-(diprop-2-ynylamino)benzaldehyde (0.20 g, 1,01 mmol), iodobenzene (0.43 g, 2.12 mmol), and DIPA (2 mL) in dry THF (15 mL) was added to the reaction medium. The reaction mixture was stirred at reflux temperature for 5 h. After completion of the reaction, solvent mixture was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane-EtOAc 7:1) to give 2-[bis(3-phenylprop-2-ynyl)amino]benzaldehyde as a pale brown viscous oil (0.32 g, 90%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H, H-1'), 7.86 (dd, $J_{6,5}$ = 7.7, $J_{6,4}$ = 1.6 Hz, 1H, H-6), 7.50 (ddd, $J_{4,3}$ = 8.4, $J_{4,5}$ = 7.1, $J_{4,6}$ = 1.6 Hz, 1H, H-4), 7.45 (d, $J_{3,4}$ = 8.4 Hz, 1H, H-3), 7.40 – 7.36 (m, 4H, arom), 7.26 – 7.21 (m, 6H, arom), 7.14 (t, J = 7.3 Hz, 1H, H-5), 4.26 (s, 4H, H-1'').

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 152.9, 134.7, 131.8, 130.2, 129.5, 128.5, 128.4, 124.2, 122.8, 122.0, 86.2, 84.4, 45.1.

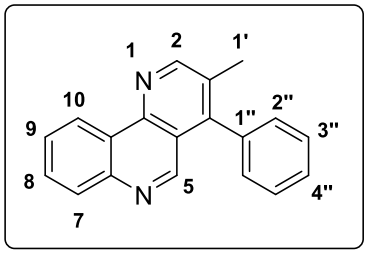
IR (ATR, cm^{-1}) 1684, 1594, 1488, 14811453, 1442, 1363, 1329, 1280, 1204, 1190, 1162, 1089, 1070, 913, 828, 689, 644.

HRMS calcd for $C_{25}H_{19}NO$ $[M+H]^+$: 350.1551, found: 350.1539.

4.14. Synthesis of 3-Methyl-4-phenylbenzo[*h*][1,6]naphthyridine (112a)

To a solution of 2-[bis(3-phenylprop-2-ynyl)amino]benzaldehyde (0.20 g, 0.57 mmol) in EtOH (10 mL) was added propargyl amine (43 μL, 0.68 mmol) and DBU (102 μL, 0.68 mmol). The resulting mixture was stirred at reflux temperature for 24 h. After completion of the reaction, solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL). Then combined organic phase was dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane-EtOAc 5:1) followed by

recrystallization from diethyl ether to afford 3-methyl-4-phenylbenzo[*h*][1,6]naphthyridine as a pale brown solid (0.12 g, 75%) (mp 139-141 °C).



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (dd, $J_{10,9}$ = 8.2, $J_{10,8}$ = 1.4 Hz, 1H, H-10), 9.08 (s, 1H, H-5), 8.99 (s, 1H, H-2), 8.17 (d, $J_{7,8}$ = 8.1 Hz, 1H, H-7), 7.83 (ddd, $J_{9,10}$ = 8.2, $J_{9,8}$ = 7.1, $J_{9,7}$ = 1.6 1H, H-9), 7.77 (ddd, $J_{8,7}$ = 8.1, $J_{8,9}$ = 7.1, $J_{8,10}$ = 1.4, 1H, H-8), 7.60 – 7.52 (m, 3H, arom), 7.35 – 7.32 (m, 2H, arom), 2.35 (s, 4H, H-1').

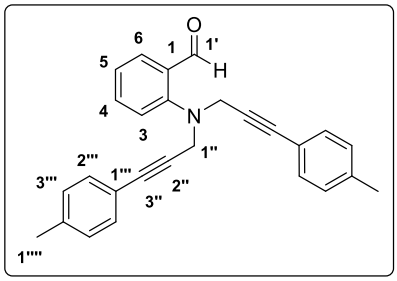
^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 151.3, 147.8, 146.9, 145.7, 135.0, 130.4, 130.0, 129.3, 129.2, 128.8, 128.6, 127.6, 125.2, 123.7, 119.4, 17.5.

IR (ATR, cm^{-1}) 3058, 2922, 1674, 1590, 1579, 1515, 1494, 1444, 1397, 1382, 1328, 1268, 1228, 1165, 1139, 1073, 1027, 969, 937, 865, 832, 816, 763, 743, 703, 694, 657.

HRMS calcd for $C_{19}H_{14}N_2$ $[M+H]^+$: 271.1260, found: 271.1230.

4.15. Synthesis of 2-{Bis[3-(4-methylphenyl)prop-2-ynyl]amino}benzaldehyde (110c)

A mixture of CuI (15.2 mg, 0.08 mmol), PPh_3 (53 mg, 0.20 mmol), and $Pd(OAc)_2$ (22 mg, 0.10 mmol) was stirred under nitrogen for 5 min. Then, a solution of 2-(diprop-2-ynylamino)benzaldehyde (0.20 g, 1.01 mmol), 1-iodo-4-methylbenzene (0.46 g, 2.12 mmol), and DIPA (2 mL) in dry THF (15 mL) was added to the reaction medium. The reaction mixture was stirred at reflux temperature for 5 h. After completion of the reaction, solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane-EtOAc 4:1) to give 2-{bis[3-(4-methylphenyl)prop-2-ynyl]amino}benzaldehyde as a pale brown viscous oil (0.29 g, 77%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H, H-1'), 7.78 (dd, $J_{6,5}$ = 7.7, $J_{6,4}$ = 1.6 Hz, 1H, H-6), 7.49 – 7.43 (m, 1H, H-4), 7.41 (dd, $J_{3,4}$ = 8.1, $J_{3,5}$ = 1.0 Hz, 1H, H-3), 7.24 – 7.18 (m, 4H, arom), 7.10 (t, J = 7.4 Hz, 1H, H-5), 7.04 – 6.97 (m, 4H, arom), 4.20 (s, 4H, H-1''), 2.24 (s, 6H, H-1'''').

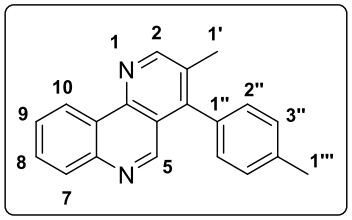
^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 153.1, 138.5, 134.5, 131.6, 130.1, 129.3, 129.1, 124.0, 121.9, 119.6, 86.2, 83.5, 45.0, 21.5.

IR (ATR, cm^{-1}) 1685, 1658, 1594, 1509, 1482, 1453, 1280, 1203, 1179, 1162, 1107, 1040, 1020, 961, 906, 868, 815, 754, 709, 661, 638.

HRMS calcd for $C_{27}H_{23}NO$ $[M+H]^+$: 378.1859, found: 378.1852.

4.16. Synthesis of 3-Methyl-4-(4-methylphenyl)benzo[*h*][1,6]naphthyridine (112c)

To a solution of 2-{bis[3-(4-methylphenyl)prop-2-ynyl]amino}benzaldehyde (0.20 g, 0.53 mmol) in EtOH (10 mL) was added propargyl amine (40 μL, 0.64 mmol) and DBU (96 μL, 0.64 mmol). The resulting mixture was stirred at reflux temperature for 24 h. After completion of the reaction, solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL). Then combined organic phase was dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane-EtOAc 10:1) followed by recrystallization from chloroform/hexane to give 3-methyl-4-(4-methylphenyl)benzo[*h*][1,6]naphthyridine as a yellow solid (0.12 g, 80%) (mp 165-167 °C).



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (dd, $J_{10,9}$ = 8.2, $J_{10,8}$ = 1.4 Hz, 1H), 8.99 (s, 1H, H-5), 8.94 (s, 1H, H-2), 8.10 (d, $J_{7,8}$ = 8.0 Hz, 1H, H-7), 7.75 (ddd, $J_{9,10}$ = 8.2, $J_{9,8}$ = 7.2, $J_{9,7}$ = 1.6 1H, H-9), 7.69 (ddd, $J_{8,7}$ = 8.0, $J_{8,9}$ = 7.2, $J_{8,10}$ = 1.4, 1H, H-8), 7.30 (d, J = 7.9 Hz, 2H, arom), 7.14 (d, J = 7.9 Hz, 2H, arom), 2.42 (s, 3H, H-1'), 2.28 (s, 3H, H-1''').

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 151.4, 148.1, 146.9, 145.6, 138.5, 131.9, 130.6, 129.9, 129.5, 129.3, 129.1, 127.5, 125.3, 123.7, 119.6, 21.4, 17.5.

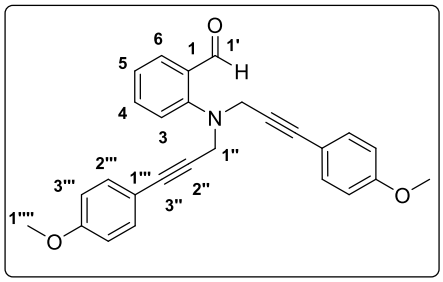
IR (ATR, cm^{-1}) 3025, 2919, 2851, 1666, 1578, 1511, 1444, 969, 813, 793, 768, 748, 628, 61, 590, 572, 553.

HRMS calcd for $C_{20}H_{16}N_2$ $[M+H]^+$: 285.1397, found: 285.1386.

4.17. Synthesis of 2-{Bis[3-(4-methoxyphenyl)prop-2-ynyl]amino}benzaldehyde (110b)

A mixture of CuI (15.2 mg, 0.08 mmol), PPh_3 (53 mg, 0.20 mmol), and $Pd(OAc)_2$ (22 mg, 0.10 mmol) was stirred under nitrogen for 5 min. Then, a solution of 2-(diprop-2-ynylamino)benzaldehyde (0.20 g, 1.01 mmol), 1-iodo-4-methoxy-benzene (0.50 g, 2.12 mmol), and DIPA (2 mL) in dry THF (15 mL) was added to the reaction medium. The reaction mixture was stirred at reflux temperature for 24 h. After completion of

the reaction, solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane-EtOAc 10:1) followed by recrystallization from chloroform/hexane to give 2-{bis[3-(4-methoxyphenyl)prop-2-ynyl]amino}benzaldehyde as a pale brown solid (0.31 g, 75%) (mp 105-107 °C).



^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H, H-1'), 7.86 (dd, $J_{6,5}$ = 7.7, $J_{6,4}$ = 1.7 Hz, 1H), 7.55 (ddd, $J_{4,3}$ = 8.3, $J_{4,5}$ = 7.2, $J_{4,6}$ = 1.7 Hz, 1H, H-4), 7.49 (d, $J_{3,4}$ = 8.3 Hz, 1H, H-3), 7.36 – 7.31 (m, 4H, arom), 7.18 (t, J = 7.4 Hz, 1H, H-5), 6.83 – 6.78 (m, 4H, arom), 4.28 (s, 4H, H-1''), 3.77 (s, 6H, H-1'''').

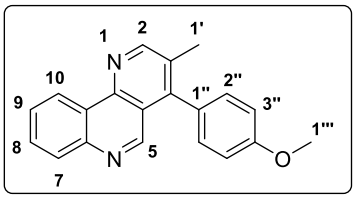
^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 159.7, 153.1, 134.6, 133.2, 130.1, 129.2, 123.9, 121.9, 114.8, 114.0, 85.9, 82.8, 55.3, 45.1.

IR (ATR, cm^{-1}) 2988, 2901, 1655, 1598, 1508, 1455, 1407, 1394, 1290, 1248, 1168, 1075, 1066, 1057, 1027, 831, 754, 664, 605, 578, 569, 540, 532, 526.

HRMS calcd for $C_{27}H_{23}NO_3$ $[M+H]^+$: 410.1762, found: 410.1751.

4.18. Synthesis of 4-(4-Methoxyphenyl)-3-methylbenzo[*h*][1,6]naphthyridine (112b)

To a solution of 2-{bis[3-(4-methoxyphenyl)prop-2-ynyl]amino}benzaldehyde (0.20 g, 0.49 mmol) in EtOH (10 mL) was added propargyl amine (37 μL, 0.59 mmol) and DBU (88 μL, 0.59 mmol). The resulting mixture was stirred at reflux temperature for 24 h. After completion of the reaction, solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL). Then combined organic phase was dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane-EtOAc 7:1) followed by recrystallization from diethyl ether to afford 4-(4-methoxyphenyl)-3-methylbenzo[*h*][1,6]naphthyridine as a yellow solid (0.11 g, 75%) (mp 122-124 °C).



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (dd, $J_{10,9}$ = 8.2, $J_{10,8}$ = 1.4 Hz, 1H, H-10), 9.07 (s, 1H, H-5), 9.05 (s, 1H, H-2), 8.17 (d, $J_{7,8}$ = 8.1 Hz, 1H, H-7), 7.82 (ddd, $J_{9,10}$ = 8.2, $J_{9,8}$ = 7.1, $J_{9,7}$ = 1.6, 1H, H-9), 7.76 (ddd, $J_{8,7}$ = 8.1, $J_{8,9}$ = 7.1, $J_{8,10}$ = 1.4, 1H, H-8), 7.28 – 7.25 (m, 2H, arom), 7.12 – 7.08 (m, 2H, arom), 3.93 (s, 3H, H-1'''), 2.37 (s, 3H, H-1').

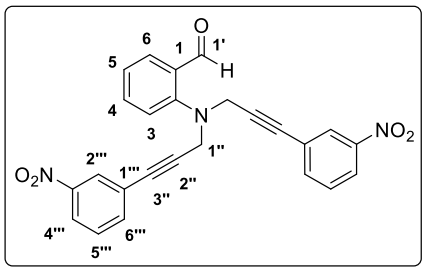
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 155.0, 151.5, 147.7, 147.0, 145.7, 130.7, 130.7, 129.9, 129.1, 127.5, 127.0, 125.3, 123.7, 119.8, 114.3, 55.4, 17.5.

IR(ATR, cm^{-1}) 2919, 2850, 1069, 1589, 1577, 1509, 1445, 1284, 1248, 1176, 1104, 1027, 1019, 963, 865, 846, 817, 794, 777, 769, 750, 693, 666, 618, 591, 550.

HRMS calcd for $C_{20}H_{16}N_2$ $[M+H]^+$: 301.1343, found: 301.1335.

4.19. Synthesis of 2-{Bis[3-(3-nitrophenyl)prop-2-ynyl]amino}benzaldehyde (110d)

A mixture of CuI (15.2 mg, 0.08 mmol), PPh_3 (53 mg, 0.20 mmol), and $Pd(OAc)_2$ (22 mg, 0.10 mmol) was stirred under nitrogen for 5 min. Then, solution of 2-(diprop-2-ynylamino)benzaldehyde (0.20 g, 1.01 mmol), 1-bromo-3-nitrobenzene (0.43 g, 2.12 mmol), and DIPA (2 mL) in dry THF (15 mL) was added to the reaction medium. The reaction mixture was stirred at reflux temperature for 24 h. After completion of the reaction, solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane-EtOAc 6:1) to give 2-{bis[3-(3-nitrophenyl)prop-2-ynyl]amino}benzaldehyde as a pale brown viscous oil (0.30 g, 68%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H, H-1'), 8.24 (s, 2H, H-2'''), 8.17 (dd, J = 7.9, 1.5 Hz, 2H, arom), 7.91 (dd, $J_{6,5}$ = 7.7, $J_{6,4}$ = 1.3 Hz, 1H, H-6), 7.70 (d, J = 7.7 Hz, 2H, arom), 7.66 – 7.61 (m, 1H, arom), 7.53 – 7.47 (m, 3H, arom), 7.30 (d, $J_{3,4}$ = 7.6 Hz, 1H, H-3), 4.35 (s, 4H, H-1'').

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 152.1, 148.1, 137.4, 134.8, 130.2, 130.1, 129.4, 126.6, 124.6, 124.3, 123.3, 121.8, 86.9, 83.9, 45.0.

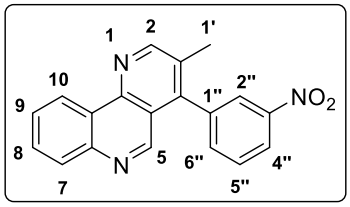
IR (ATR, cm^{-1}) 1684, 1594, 1525, 1481, 1453, 1347, 1280, 1204, 1163, 1120, 1094, 900, 869, 829, 806, 757, 734, 694, 672.

HRMS calcd for $C_{25}H_{17}N_3O_5$ $[M+H]^+$: 440.1313, found: 440.1241.

4.20. Synthesis of 3-Methyl-4-(3-nitrophenyl)benzo[*h*][1,6]naphthyridine (112d)

To a solution of 2-{bis[3-(3-nitrophenyl)prop-2-ynyl]amino}benzaldehyde (0.44 g, 1.00 mmol) in EtOH (10 mL) was added propargyl amine (77 μL, 1.20 mmol) and DBU (180 μL, 1.20 mmol). The resulting mixture was stirred at reflux temperature for 36 h. After completion of the reaction, solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (3 × 50 mL). Then combined organic phase

was dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane-EtOAc 6:1) followed by recrystallization from chloroform/hexane to give 3-methyl-4-(3-nitrophenyl)benzo[*h*][1,6]naphthyridine as a pale brown solid (0.21 g, 65%) (mp 189-191 °C).



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (dd, $J_{10,9}$ = 8.0, $J_{10,8}$ = 1.6 Hz, 1H, H-10), 9.14 (s, 1H, H-5), 8.88 (s, 1H, H-2), 8.45 (ddd, $J_{4",5"}$ = 8.3, J = 2.2, 1.0 Hz, 1H, H-4"), 8.28 (t, J = 1.9 Hz, 1H, H-2"), 8.19 (d, $J_{7,8}$ = 8.2 Hz, 1H, H-7), 7.81 (ddd, $J_{8,7}$ = 8.2, $J_{8,9}$ = 7.1, $J_{8,10}$ = 1.6 Hz, 1H, H-8), 7.78 – 7.72 (m, 2H, arom), 7.72 (dt, J = 7.59, $J_{5",2"}$ = 1.16 Hz, 1H, H-5"), 2.37 (s, 3H, H-1').,0

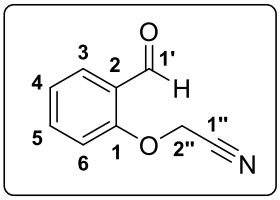
^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 150.2, 148.8, 147.2, 146.1, 144.9, 137.0, 135.6, 130.5, 130.3, 130.3, 129.6, 128.1, 125.2, 124.5, 123.9 (2C), 118.9, 17.6.

IR (ATR, cm^{-1}) 3662, 2988, 2900, 1579, 1527, 1444, 1394, 1348, 1300, 1229, 1078, 1066, 1057, 970, 896, 864, 805, 775, 750, 734, 710, 687, 656, 610, 598, 583.

HRMS calcd for $C_{19}H_{13}N_3O_2$ $[M+H]^+$: 316.1104, found: 316.1081.

4.21. Synthesis of (2-formylphenoxy)acetonitrile (146)

To a solution of 2-hydroxybenzaldehyde (0.50 g, 4.09 mmol) in dry DMF (10 mL) was added anhydrous K_2CO_3 (0.62 g, 4.50 mmol). After stirring for 30 min, chloroacetonitrile (0.34 g, 4.50 mmol) was added and the resulting mixture was stirred for 24 h at rt. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with brine (5 × 100 mL) and was dried over $MgSO_4$. The solvent was evaporated under the reduced pressure. The crude product was purified by column chromatography (silica gel/hexane-EtOAc 4:1) followed by recrystallization from diethyl ether to give (2-formylphenoxy)acetonitrile as a yellow needles (0.59 g, 90%) (mp 78-80 °C, Lit.[49] 82-84 °C).

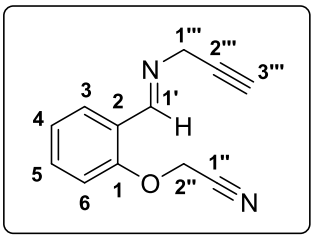


^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H, H-1'), 7.86 (dd, $J_{3,4}$ = 7.7, $J_{3,5}$ =1.8 Hz, 1H, H-3), 7.61 (ddd, $J_{5,6}$ = 8.5, $J_{5,4}$ = 7.5, $J_{5,3}$ = 1.8 Hz, 1H, H-5), 7.18 (t, J = 7.5 Hz, 1H, H-4), 7.09 (d, $J_{6,5}$ = 8.5 Hz, 1H, H-6), 4.95 (s, 2H, H-2").

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 158.3, 136.0, 129.5, 125.7, 123.3, 114.5, 112.7, 53.8.

4.22. Synthesis of {2-[(prop-2-ynylimino)methyl]phenoxy}acetonitrile (148)

To a solution of (2-formylphenoxy)acetonitrile (0.30 g, 1.86 mmol) in dry THF (15 mL) was added propargyl amine (0.11 g, 2.05 mmol) and anhydrous $MgSO_4$ (0.60 g, 4.98 mmol). The reaction mixture was stirred at room temperature for 24 h. After completion of the reaction, the solvent was evaporated under the reduced pressure followed by extraction with EtOAc (3 × 50 ml). The organic phase was dried over $MgSO_4$. The solvent was evaporated under the reduced pressure to afford {2-[(prop-2-ynylimino)methyl]phenoxy}acetonitrile as a yellow liquid (0.35 g, 95%).



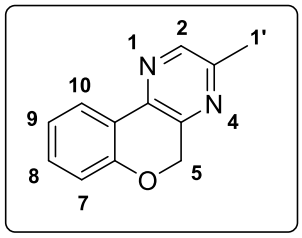
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (t, $J_{1',1'''}$ = 1.8 Hz, 1H, H-1'), 8.00 (dd, $J_{3,4}$ = 7.7, $J_{3,5}$ = 1.7 Hz, 1H, H-3), 7.48 – 7.42 (m, 1H, H-5), 7.14 (t, J = 7.6 Hz, 1H, H-4), 6.99 (d, $J_{6,5}$ = 8.3 Hz, 1H, H-6), 4.85 (s, 2H, H-2''), 4.52 (t, J = 2.2 Hz, 2H, H-1'''), 2.53 (t, $J_{3''',1'''}$ = 2.4 Hz, 1H, H-3''').

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 155.8, 132.3, 128.3, 125.5, 123.4, 114.8, 112.5, 79.1, 75.4, 54.1, 47.7.

IR (ATR, cm^{-1}) 1677, 1597, 1483, 1456, 1284, 1231, 1189, 1045, 1033, 843, 758, 652.

4.23. Synthesis of 3-methyl-5*H*-chromeno[3,4-*b*]pyrazine (147)

To a solution of {2-[(prop-2-ynylimino)methyl]phenoxy}acetonitrile (0.30 g, 1.51 mmol) in dry DMF (10 mL) was added DBU (0.28 g, 1.81 mmol). The resulting mixture was stirred for 24 h at 100 °C. After completion of the reaction by monitoring TLC, the reaction mixture was extracted with ethyl acetate (3 × 100 mL) and dried over $MgSO_4$. After removal of the solvent under the reduced pressure, the residue was purified by column chromatography (silica gel/hexane-EtOAc 5:1) to give 3-methyl-5*H*-chromeno[3,4-*b*]pyrazine as a yellow solid from diethyl ether (135 mg, 45%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H, H-2), 8.04 (dd, $J_{10,9}$ = 7.7, $J_{10,8}$ = 1.6 Hz, 1H, H-10), 7.29 – 7.24 (m, 1H, H-8), 7.03 (td, J = 7.6, $J_{9,7}$ = 1.0 Hz, 1H, H-9), 6.91 (dd, $J_{7,8}$ = 8.2, $J_{7,9}$ = 1.0 Hz, 1H, H-7), 5.24 (s, 2H, H-5), 2.49 (s, 3H, H-1').

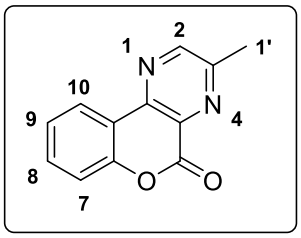
^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 152.1, 145.3, 143.8, 141.6, 131.7, 124.5, 122.6, 121.4, 117.2, 69.5, 21.3.

IR(ATR, cm^{-1}) 2923, 2853, 1603, 1512, 1476, 1332, 1302, 1225, 1143, 1101, 1087, 912, 890, 857, 753, 721, 668.

HRMS calcd for $C_{12}H_{10}N_2O$ $[M+H]^+$: 199.0890, found: 199.0866.

4.24. Synthesis of 3-methyl-5*H*-chromeno[3,4-*b*]pyrazin-5-one (149)

To a suspension of CrO_3 (0.20 g, 2 mmol) in 5 mL of CH_2Cl_2 was added dropwise pyridine (0.32 g, 4 mmol) at room temperature. The mixture was stirred at room temperature for 30 min and cooled to 0 °C. Then, a solution of 3-methyl-5*H*-chromeno[3,4-*b*]pyrazine (40.0 mg, 0.20 mmol) in 2 mL of dichloromethane was added and the mixture was stirred at rt overnight. After completion of the reaction, the mixture was filtered over silica by using dichloromethane as mobile phase. The solvent was evaporated under the reduced vacuum to give 3-methyl-5*H*-chromeno[3,4-*b*]pyrazin-5-one as a white solid from chloroform (40.3 mg, 95%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H, H-2), 8.41 (dd, $J_{10,9}$ = 7.9, $J_{10,8}$ = 1.3 Hz, 1H, H-10), 7.56 – 7.51 (m, 1H, H-8), 7.37 – 7.31 (m, 2H, arom), 2.74 (s, 3H, H-1').

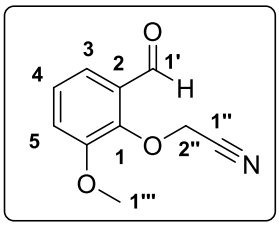
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 156.1, 152.0, 150.4, 145.6, 132.6 (2C), 125.2, 124.7, 118.3, 117.3, 22.1.

IR(ATR, cm^{-1}) 2973, 2935, 1712, 1634, 1462, 1329, 1298, 1162, 1020, 951, 820, 685, 657.

HRMS calcd for $C_{12}H_{10}N_2O$ $[M+H]^+$: 213.0664, found: 213.0657.

4.25. Synthesis of (2-formyl-6-methoxyphenoxy)acetonitrile (153)

To a solution of 3-methoxy-2-hydroxybenzaldehyde (0.50 g, 3.29 mmol) in dry DMF (10 mL) was added anhydrous K_2CO_3 (0.50 g, 3.62 mmol). After stirring for 30 min, chloroacetonitrile (0.27 g, 3.62 mmol) was added and the resulting mixture was stirred for 24 h at rt. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with brine (5 × 100 mL) and was dried over $MgSO_4$. The solvent was evaporated under the reduced pressure. The crude product was purified by column chromatography (silica gel/hexane-EtOAc 7:1) followed by recrystallization from diethyl ether to give (2-formyl-6-methoxyphenoxy)acetonitrile as a pale yellow tiny needles (0.50 g, 80%) (mp 116-118 °C, Lit.[49] 117-119 °C).

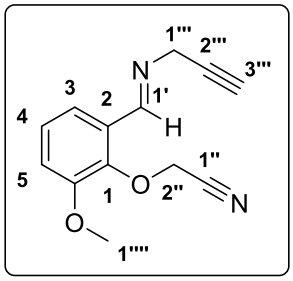


^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H, H-1'), 7.46 (dd, $J_{3,4}$ = 7.5, $J_{3,5}$ = 1.8 Hz, 1H, H-3), 7.28 – 7.19 (m, 2H, arom), 4.99 (s, 2H, H-2''), 3.94 (s, 3H, H-1''').

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 152.1, 147.9, 130.0, 125.9, 119.9, 118.2, 115.1, 58.0, 56.2.

4.26. Synthesis of {2-methoxy-6-[(prop-2-ynylimino)methyl]phenoxy}acetonitrile (155)

To a solution of (2-formyl-6-methoxyphenoxy)acetonitrile (0.20 g, 1.05 mmol) in dry THF (15 mL) was added propargyl amine (0.06 g, 1.16 mmol) and anhydrous $MgSO_4$ (0.60 g, 4.98 mmol). The reaction mixture was stirred at room temperature for 24 h. After completion of the reaction, the solvent was evaporated under the reduced pressure followed by extraction with EtOAc (3 × 50 ml). The organic phase was dried over $MgSO_4$. Solvent was evaporated under the reduced pressure to afford {2-methoxy-6-[(prop-2-ynylimino)methyl]phenoxy}acetonitrile as a pale yellow liquid (0.21 g, 88%).[26]



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (t, $J_{1',1'''}$ = 1.8 Hz, 1H, H-1'), 7.58 (dd, $J_{3,4}$ = 8.0, $J_{3,5}$ = 1.4 Hz, 1H, H-3), 7.18 (t, J = 8.1 Hz, 1H, H-4), 7.04 – 7.00 (m, 1H, H-5), 4.88 (s, 2H, H-2''), 4.55 (t, J = 2.2 Hz, 2H, H-1'''), 3.91 (s, 3H, H-1''''), 2.56 (t, $J_{3''',1'''}$ = 2.4 Hz, 1H, H-3''').

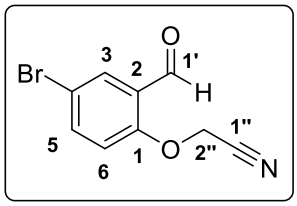
^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 151.9, 145.7, 129.9, 125.8, 119.3, 115.4, 114.6, 78.9, 75.7, 57.8, 55.9, 47.8.

IR (ATR, cm^{-1}) 2952, 1692, 1587, 1481, 1442, 1284, 1202, 1180, 1068, 1013, 923, 786, 749.

4.27. Synthesis of (4-bromo-2-formylphenoxy)acetonitrile (152)

To a solution of 5-bromo-2-hydroxybenzaldehyde (0.50 g, 2.49 mmol) in dry DMF (10 mL) was added anhydrous K_2CO_3 (0.38 g, 2.74 mmol). After stirring for 30 min, chloroacetonitrile (0.21 g, 2.74 mmol) was added and the resulting mixture was stirred for 24 h at rt. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with brine (5 × 100 mL) and was dried over $MgSO_4$. The solvent was evaporated under the reduced pressure. The crude product was purified by column chromatography (silica gel/hexane-EtOAc 3:1)

followed by recrystallization from chloroform/hexane to give (4-bromo-2-formylphenoxy)acetonitrile as an orange tiny neddles (0.51 g, 85%) (mp 106-108 °C, Lit.[49] 105-108 °C).

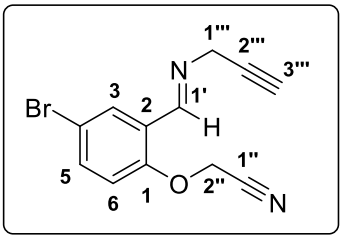


^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H, H-1'), 7.99 (d, $J_{3,5}$ = 2.6 Hz, 1H, H-3), 7.73 (dd, $J_{5,6}$ = 8.8, $J_{5,3}$ = 2.6 Hz, 1H, H-5), 7.00 (d, $J_{6,5}$ = 8.8 Hz, 1H, H-6), 4.93 (s, 2H, H-2'').

^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 157.2, 138.4, 132.0, 126.9, 116.3, 114.7, 114.1, 54.1.

4.28. Synthesis of {4-bromo-2-[(prop-2-ynylimino)methyl]phenoxy}acetonitrile (154)

To a solution of (4-bromo-2-formylphenoxy)acetonitrile (0.50 g, 2.08 mmol) in dry THF (15 mL) was added propargyl amine (0.13 g, 2.29 mmol) and anhydrous $MgSO_4$ (0.60 g, 4.98 mmol). The reaction mixture was stirred at room temperature for 24 h. After completion of the reaction, the solvent was evaporated under the reduced pressure followed by extraction with EtOAc (3 × 50 ml). The organic phase was dried over $MgSO_4$. The solvent was evaporated under the reduced pressure to afford {4-bromo-2-[(prop-2-ynylimino)methyl]phenoxy}acetonitrile as a yellow liquid (0.49 g, 85%).[26]



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (t, $J_{1',1'''}$ = 2.0 Hz, 1H, H-1'), 8.15 (d, $J_{3,5}$ = 2.6 Hz, 1H, H-3), 7.55 (dd, $J_{5,6}$ = 8.8, $J_{5,3}$ = 2.6 Hz, 1H, H-5), 6.89 (d, $J_{6,5}$ = 8.8 Hz, 1H, H-6), 4.85 (s, 2H, H-2''), 4.54 (t, J = 2.2 Hz, 2H, H-1'''), 2.55 (t, $J_{3''',1'''}$ = 2.4 Hz, 1H, H-3''').

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 154.6, 134.8, 131.1, 127.3, 116.5, 114.4, 114.3, 78.7, 75.8, 54.2, 47.6.

IR (ATR, cm^{-1}) 1676, 1596, 1455, 1256, 1190, 1158, 1046, 1034, 842, 808, 758, 652.

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APPENDIX A

SPECTRAL DATA

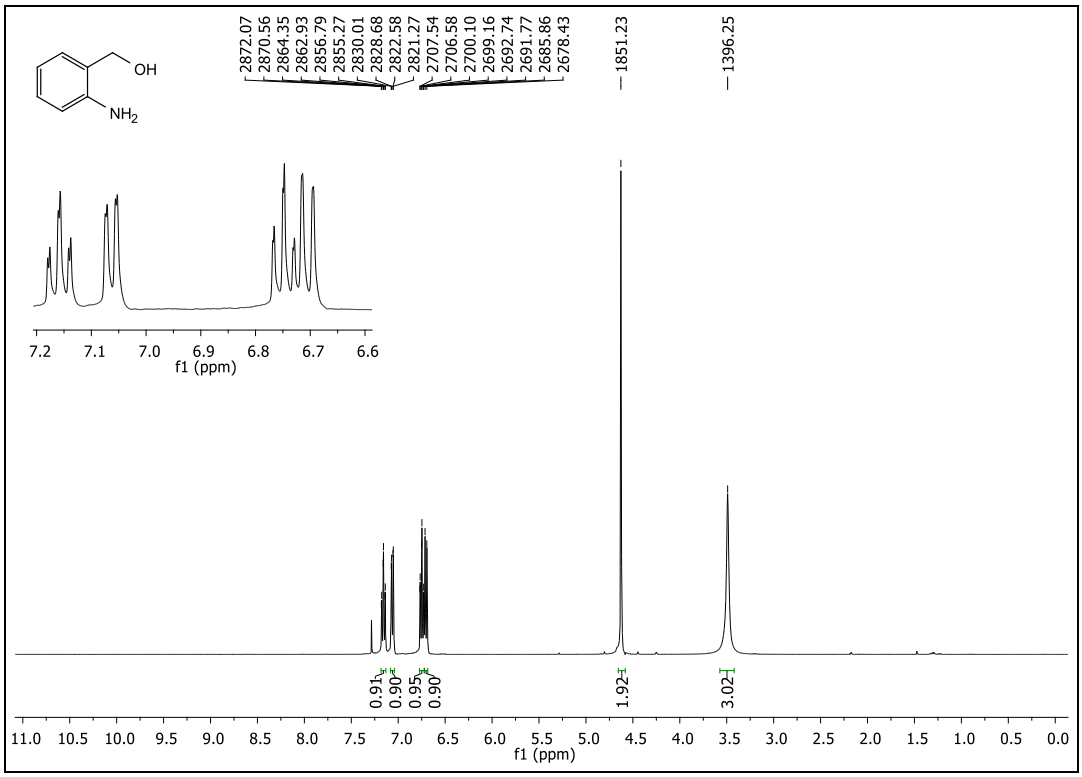


Figure 13 ^{1}H-NMR Spectrum of compound **76** in $CDCl_3$

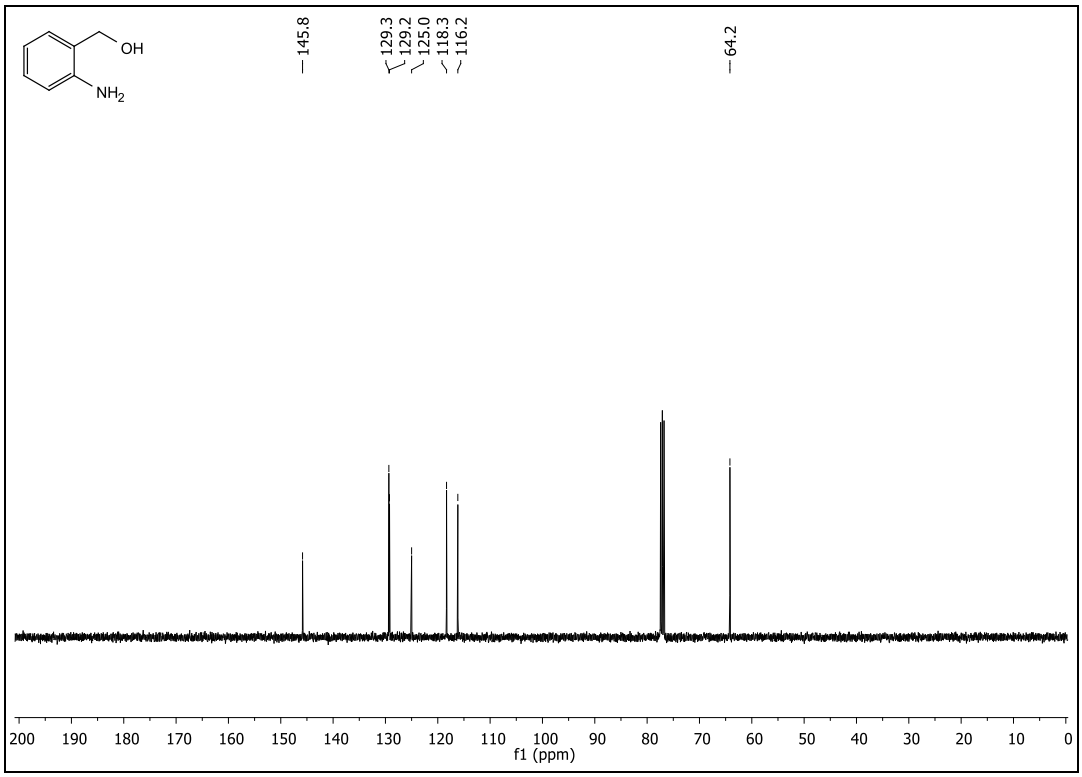


Figure 14 ^{13}C-NMR Spectrum of compound **76** in CDCl

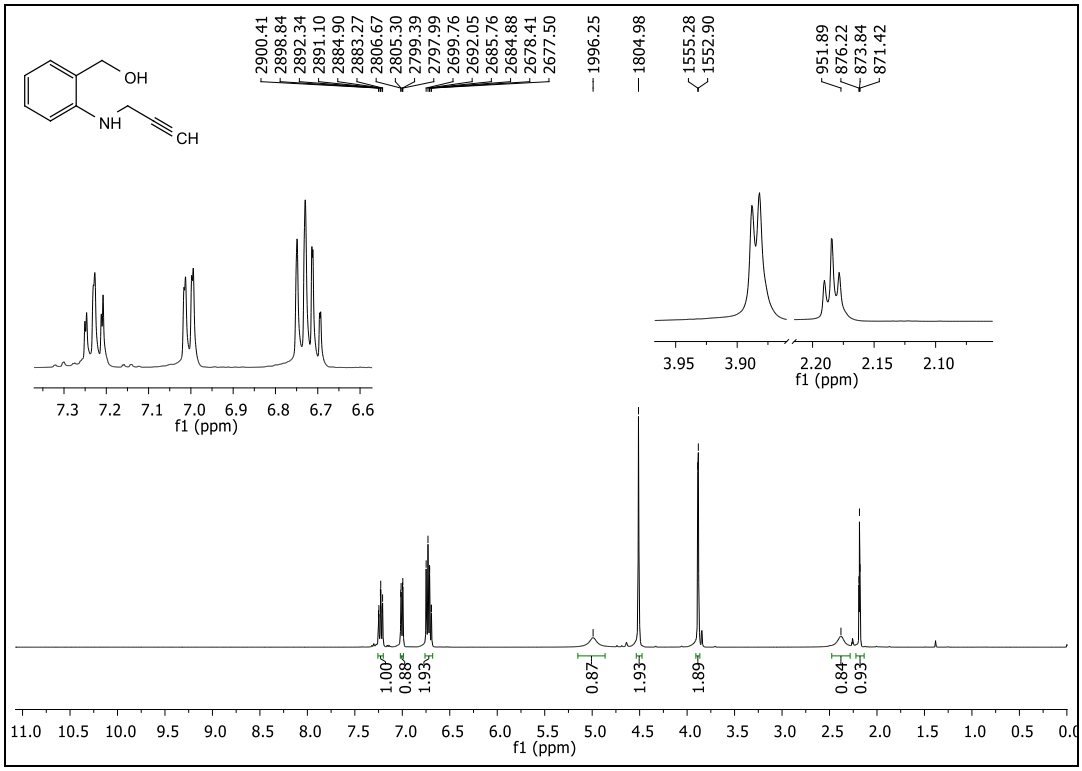


Figure 15 ^{1}H-NMR Spectrum of compound **78** in $CDCl_3$

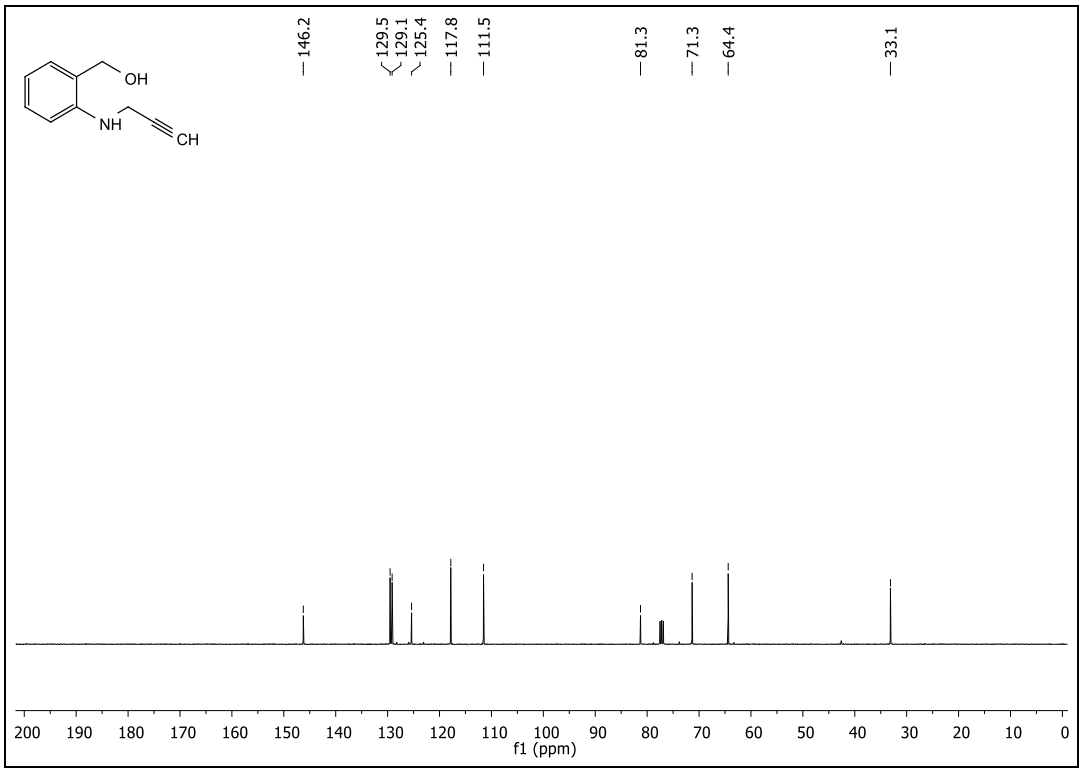


Figure 16 ^{13}C-NMR Spectrum of compound **78** in $CDCl_3$

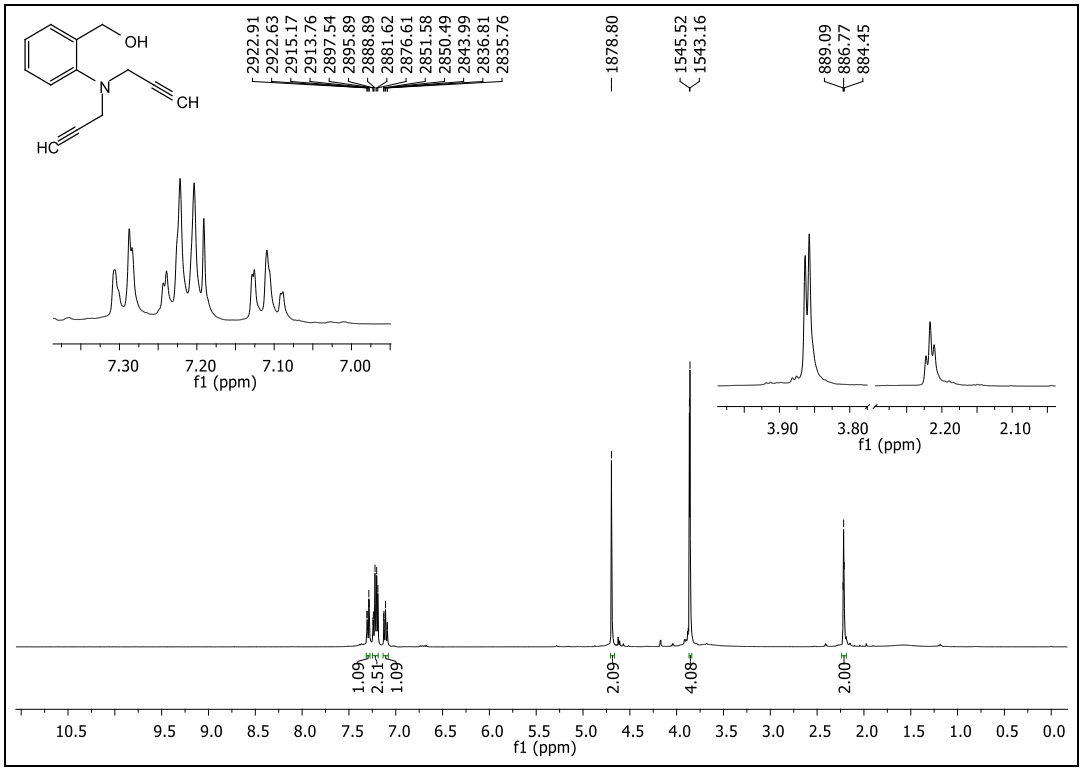


Figure 17 ^{1}H-NMR Spectrum of compound **91** in $CDCl_3$

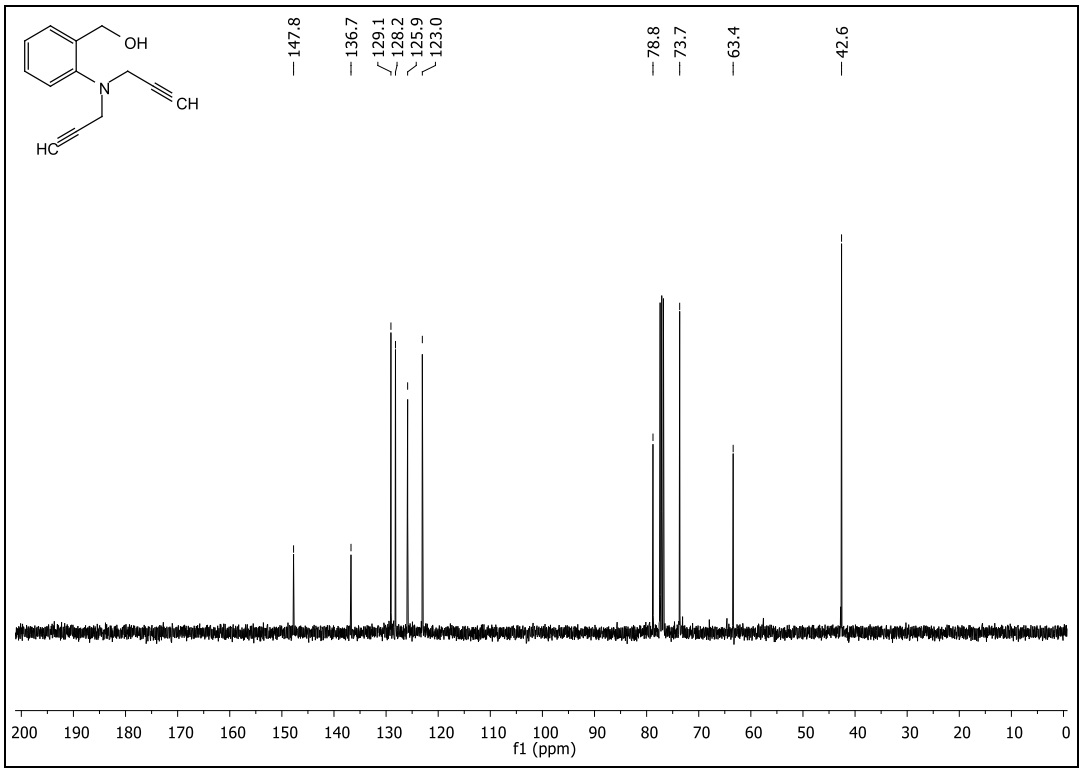


Figure 18 ^{13}C-NMR Spectrum of compound **91** in $CDCl_3$

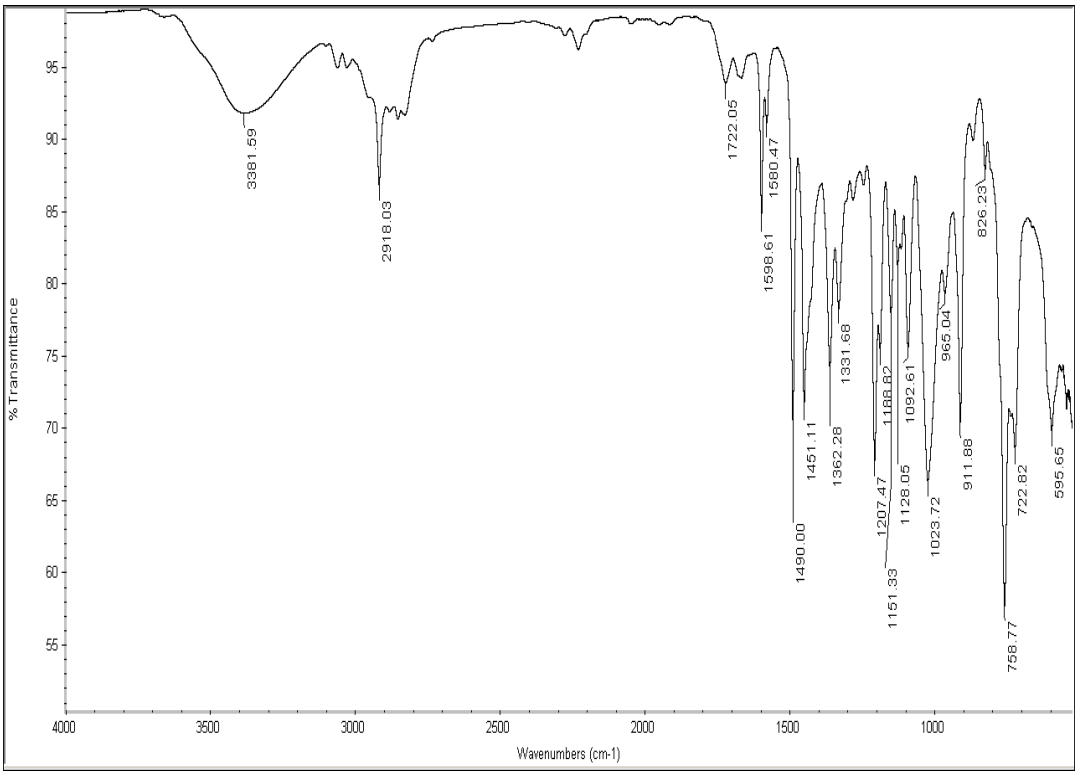


Figure 19 IR Spectrum of compound **91**

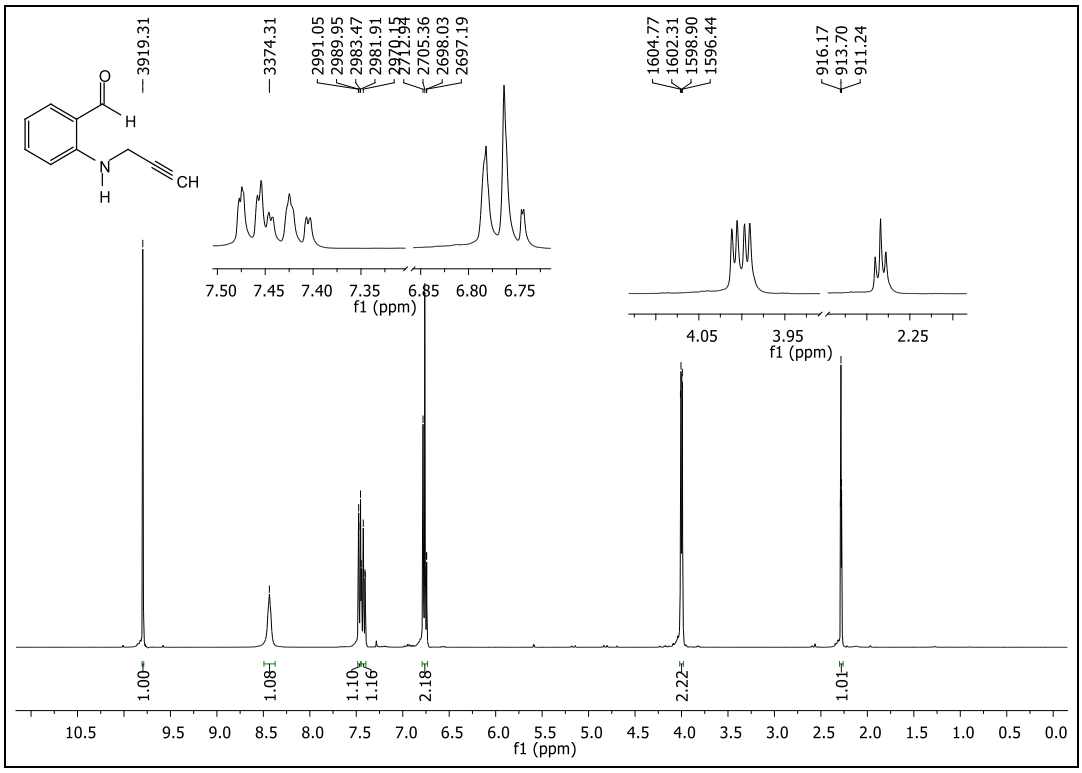


Figure 20 ^{1}H-NMR Spectrum of compound **79** in $CDCl_3$

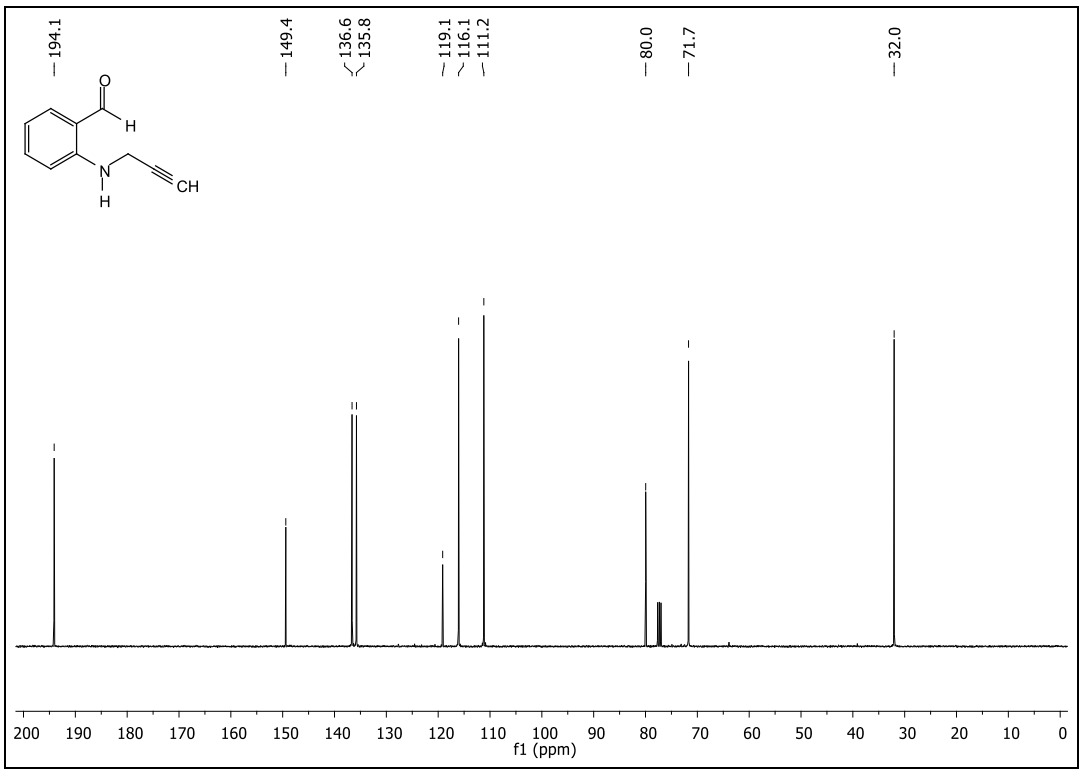


Figure 21 ^{13}C-NMR Spectrum of compound **79** in $CDCl_3$

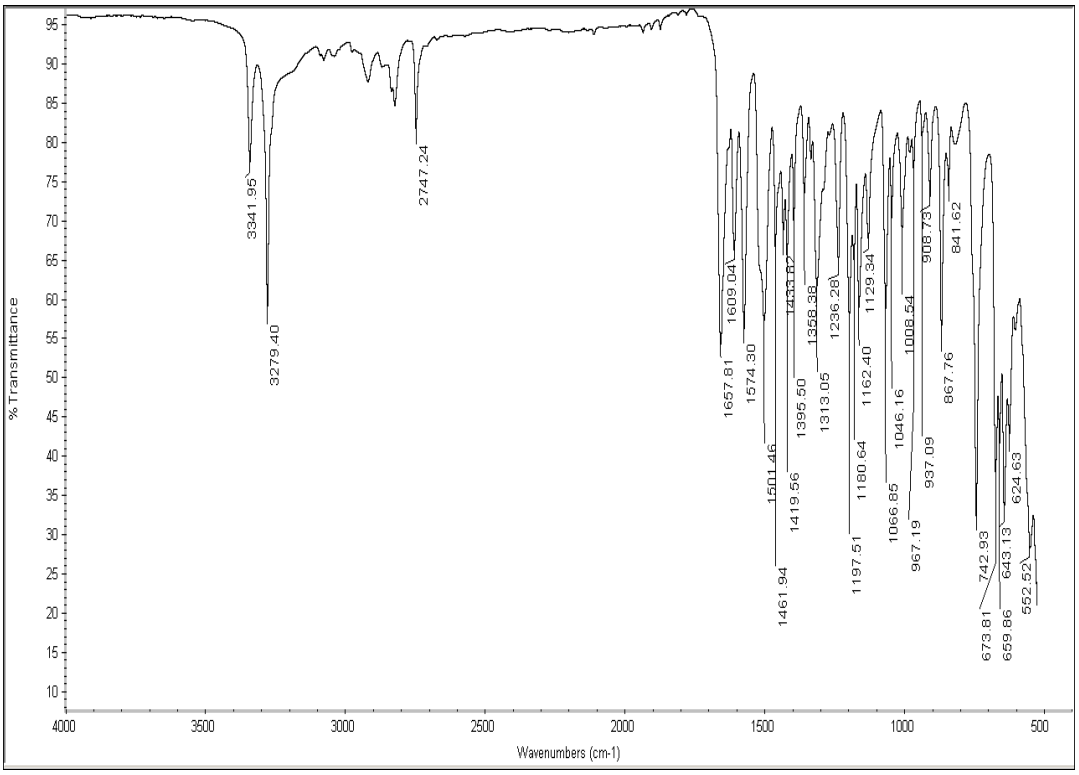
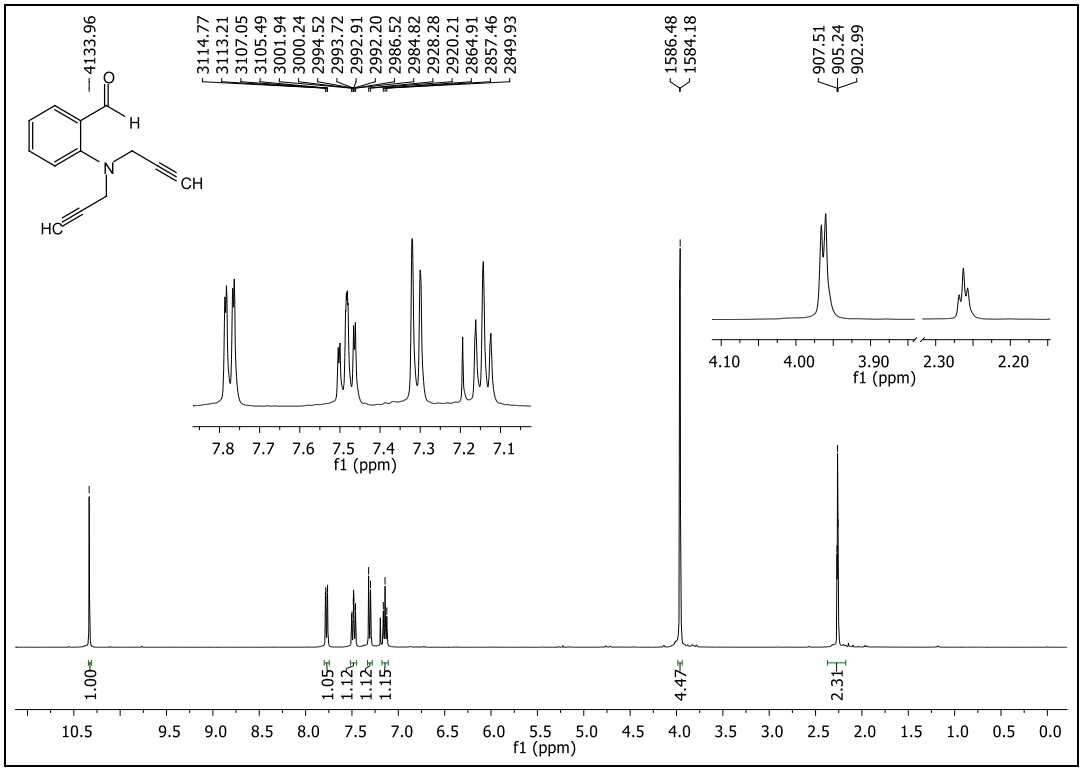


Figure 22 IR Spectrum of compound **79**



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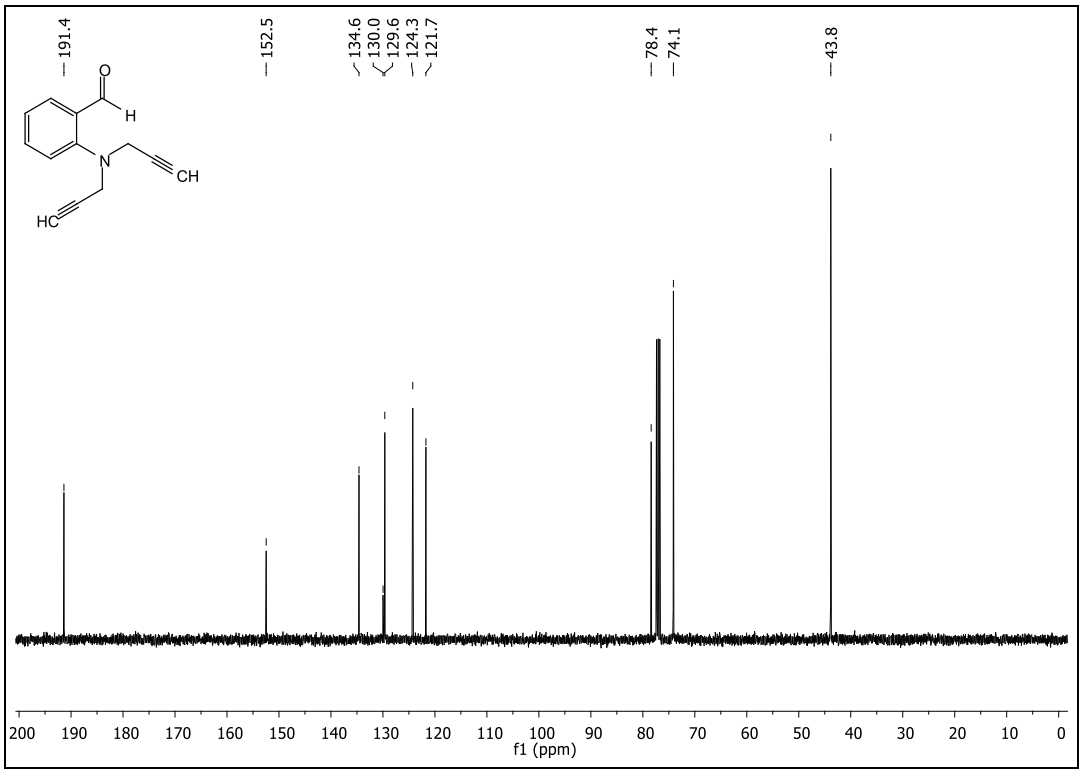

Figure 24 ^{13}C-NMR Spectrum of compound **92** in $CDCl_3$

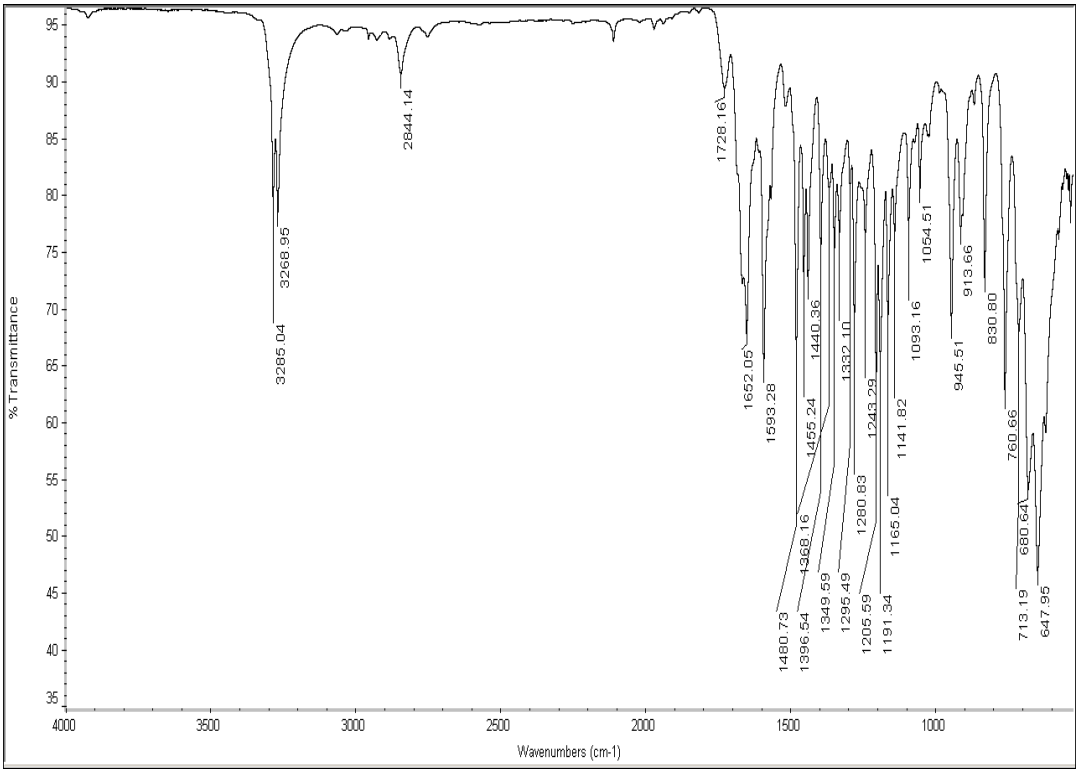

Figure 25 IR Spectrum of compound **92**

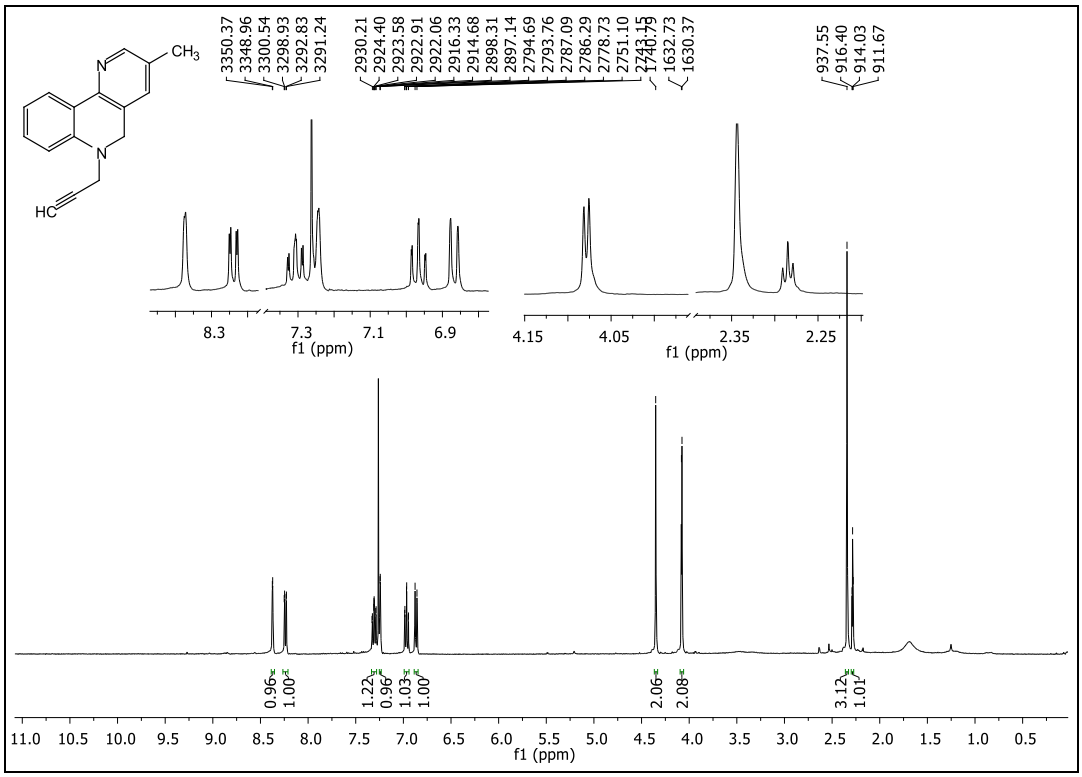

Figure 26 ^{1}H-NMR Spectrum of compound **93** in $CDCl_3$

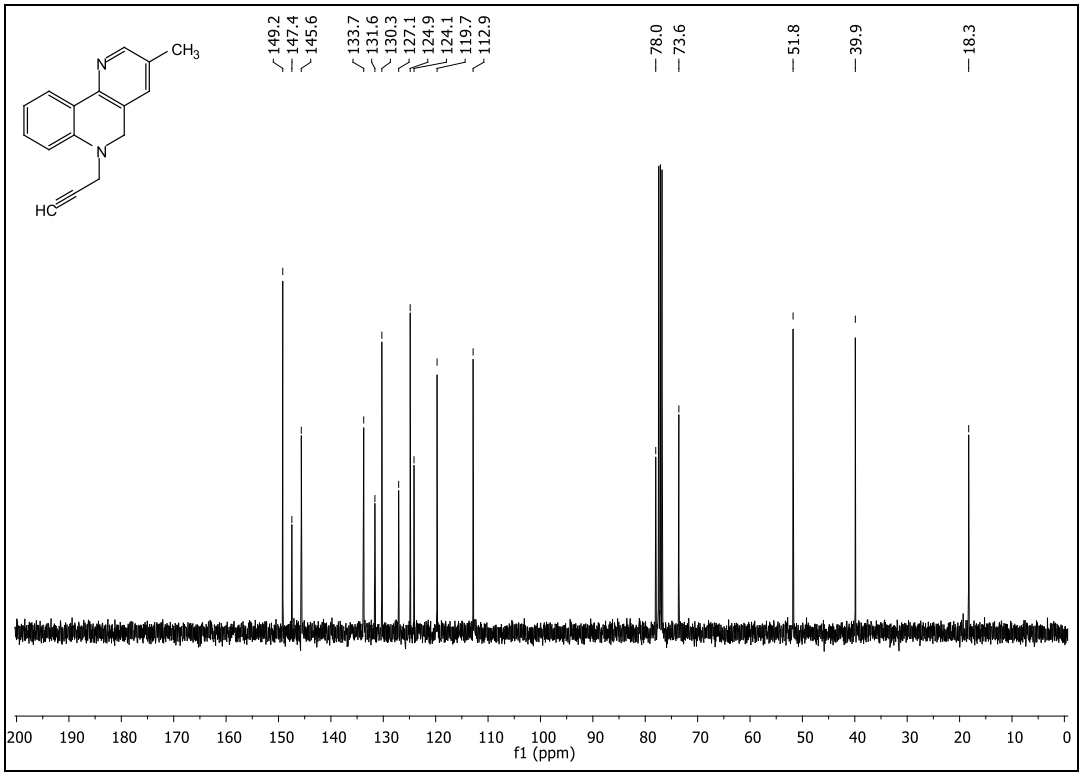

Figure 27 ^{13}C-NMR Spectrum of compound **93** in $CDCl_3$

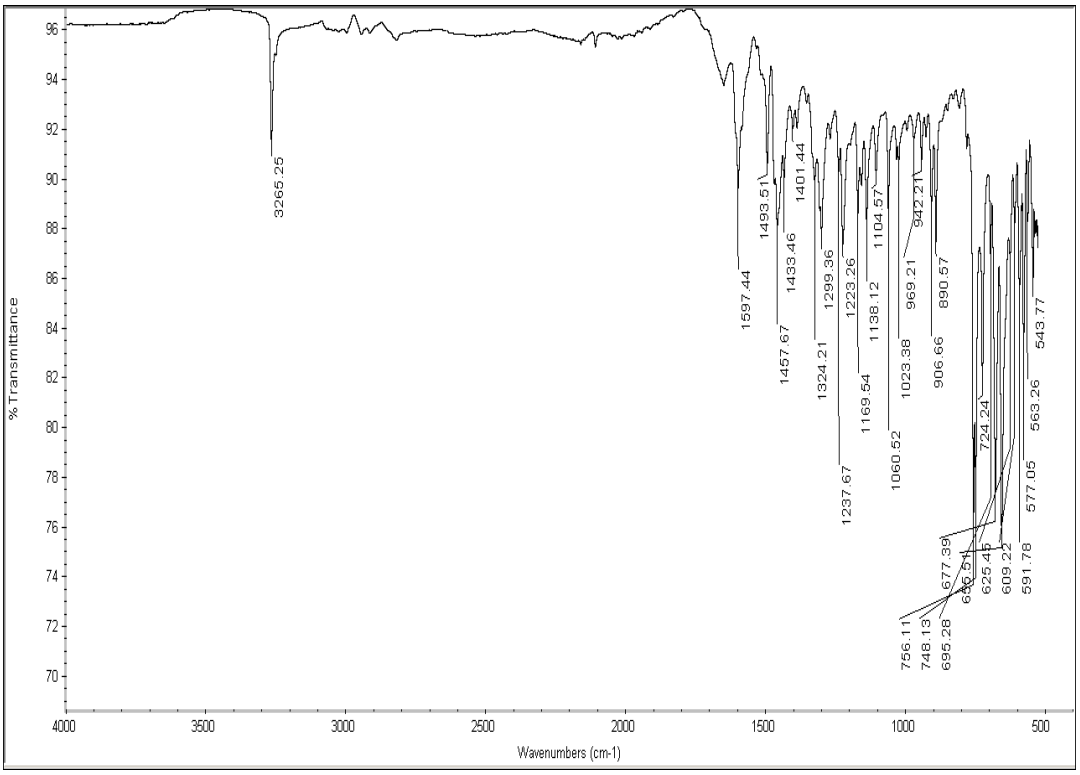

Figure 28 IR Spectrum of compound **93**

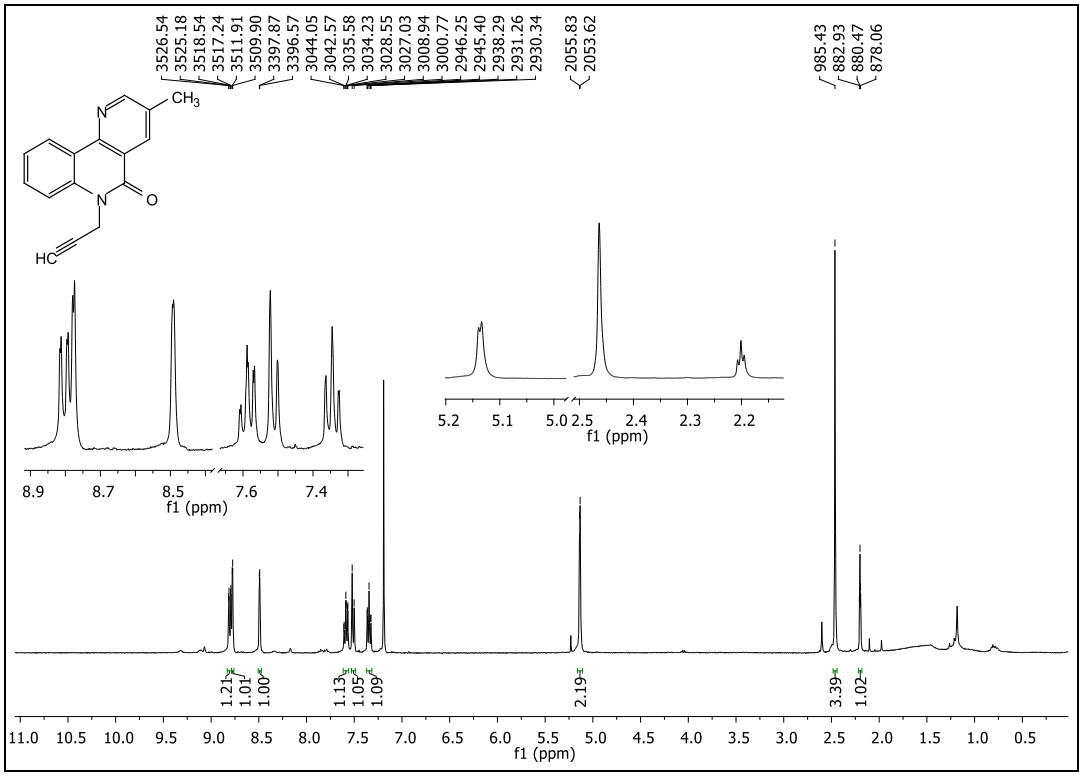

Figure 29 ^{1}H-NMR Spectrum of compound **105** in $CDCl_3$

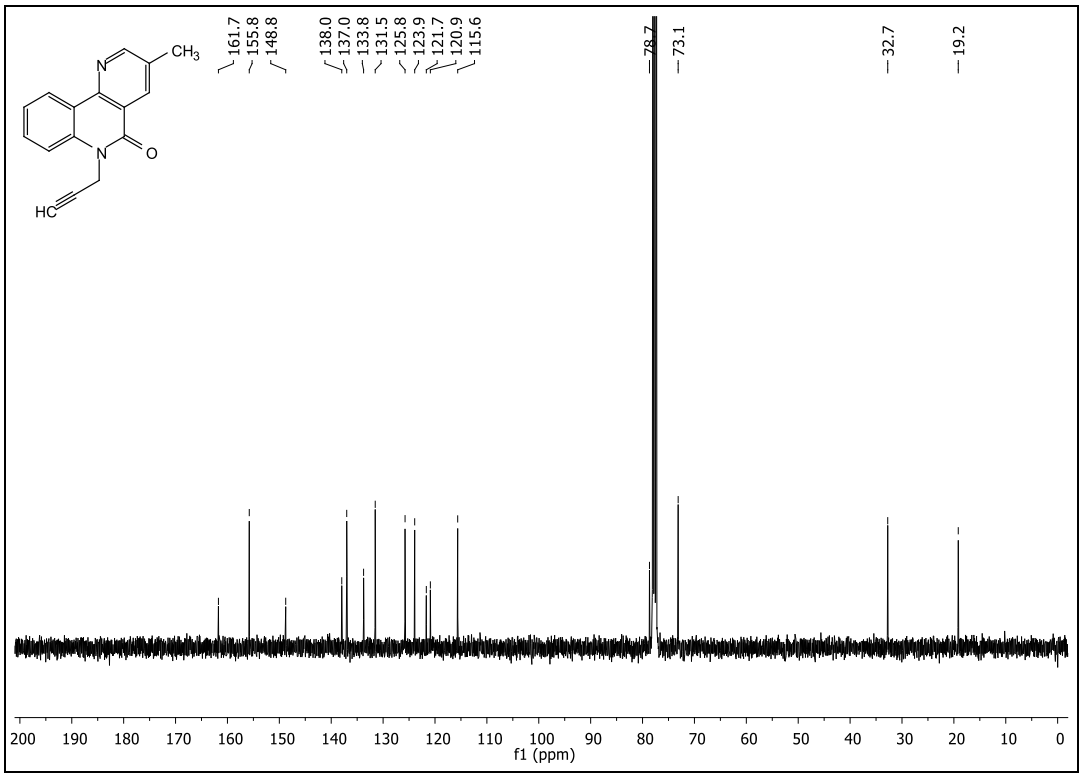

Figure 30 ^{13}C-NMR Spectrum of compound **105** in $CDCl_3$

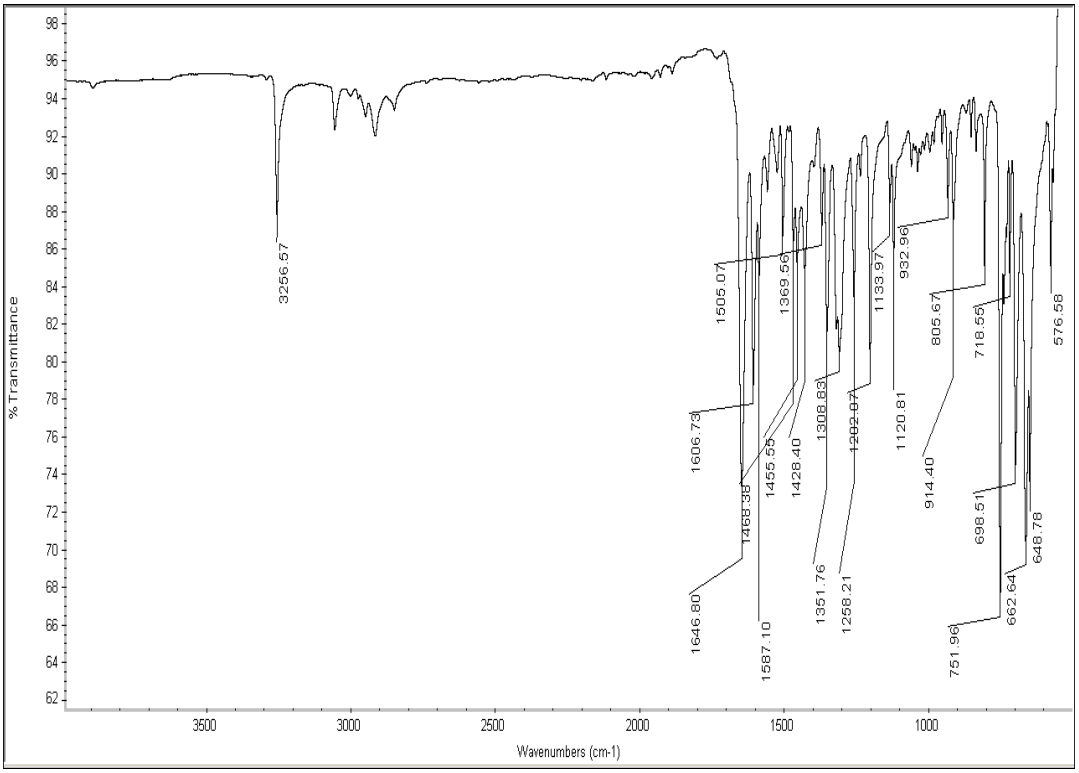

Figure 31 IR Spectrum of compound **105**

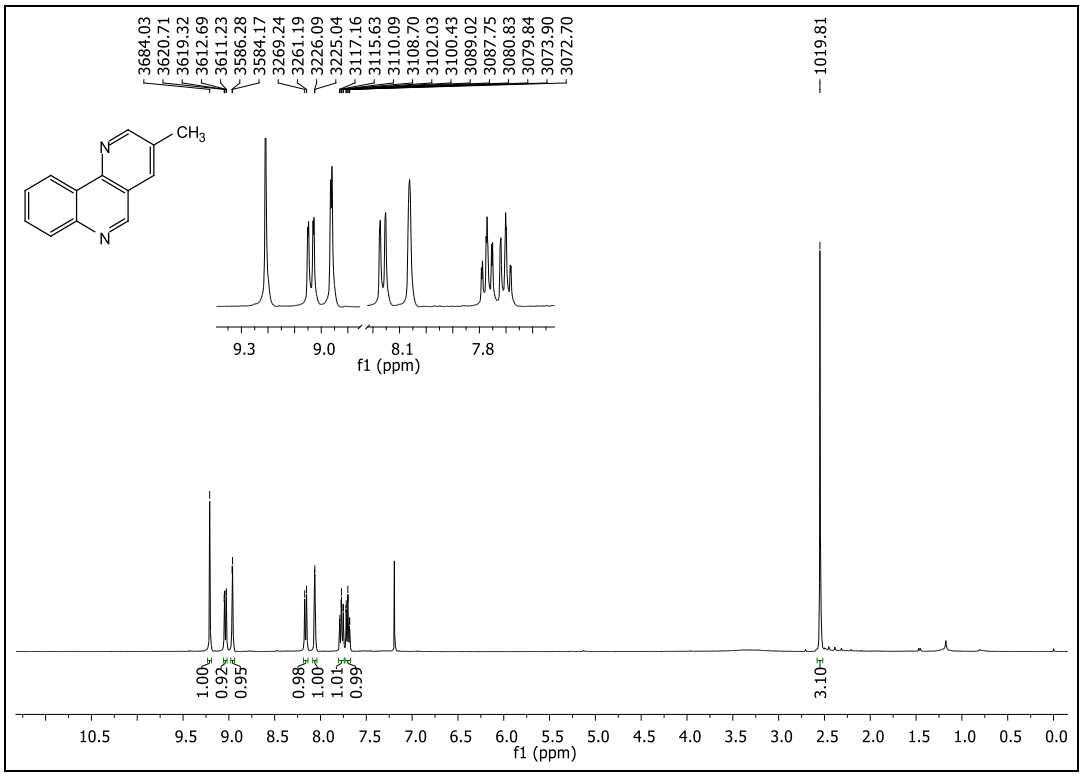

Figure 32 ^{1}H-NMR Spectrum of compound **83** in $CDCl_3$

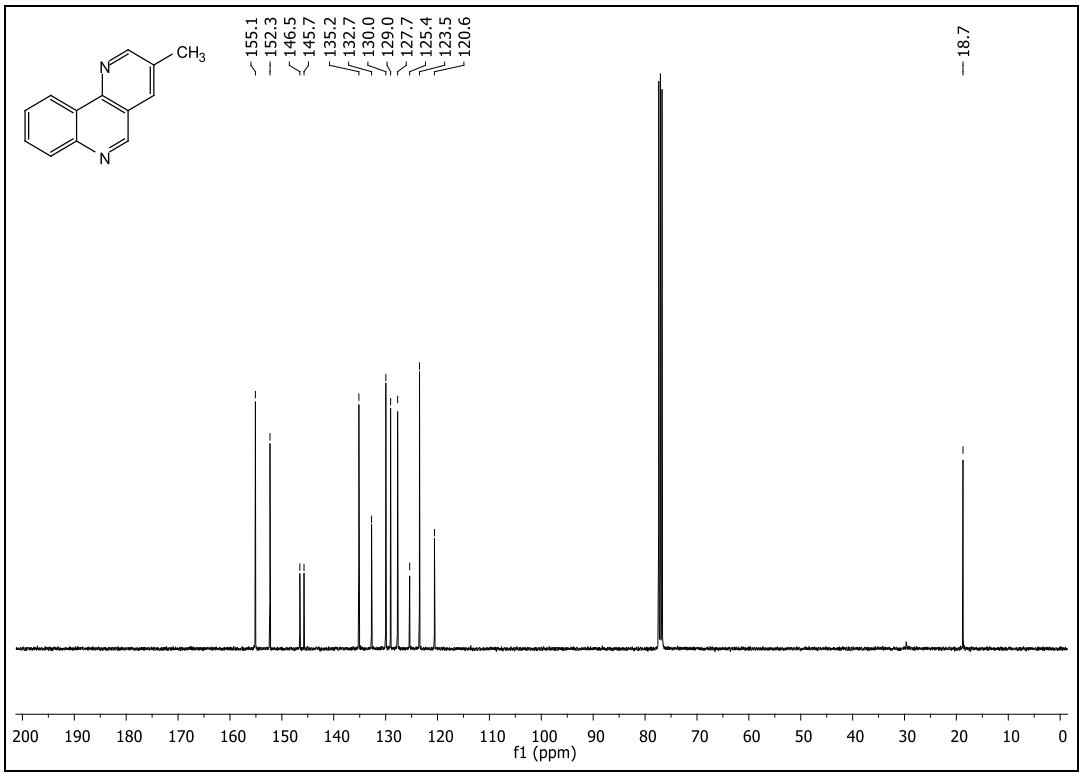

Figure 33 ^{13}C-NMR Spectrum of compound **83** in $CDCl_3$

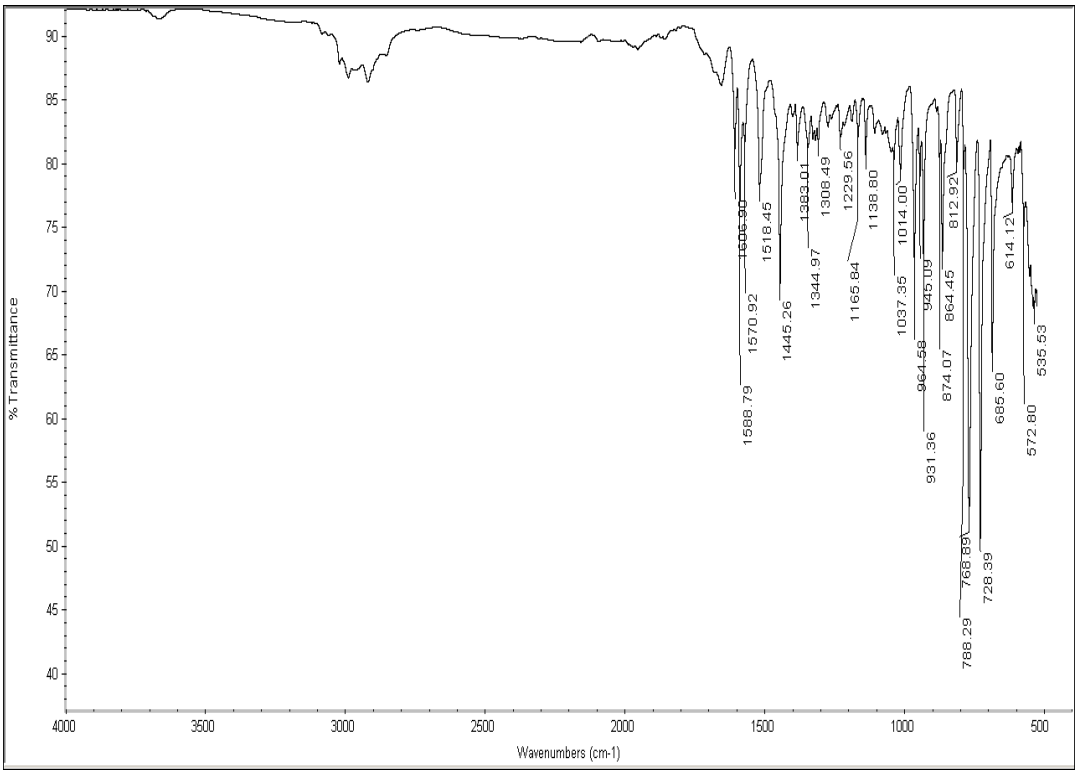

Figure 34 IR Spectrum of compound **83**

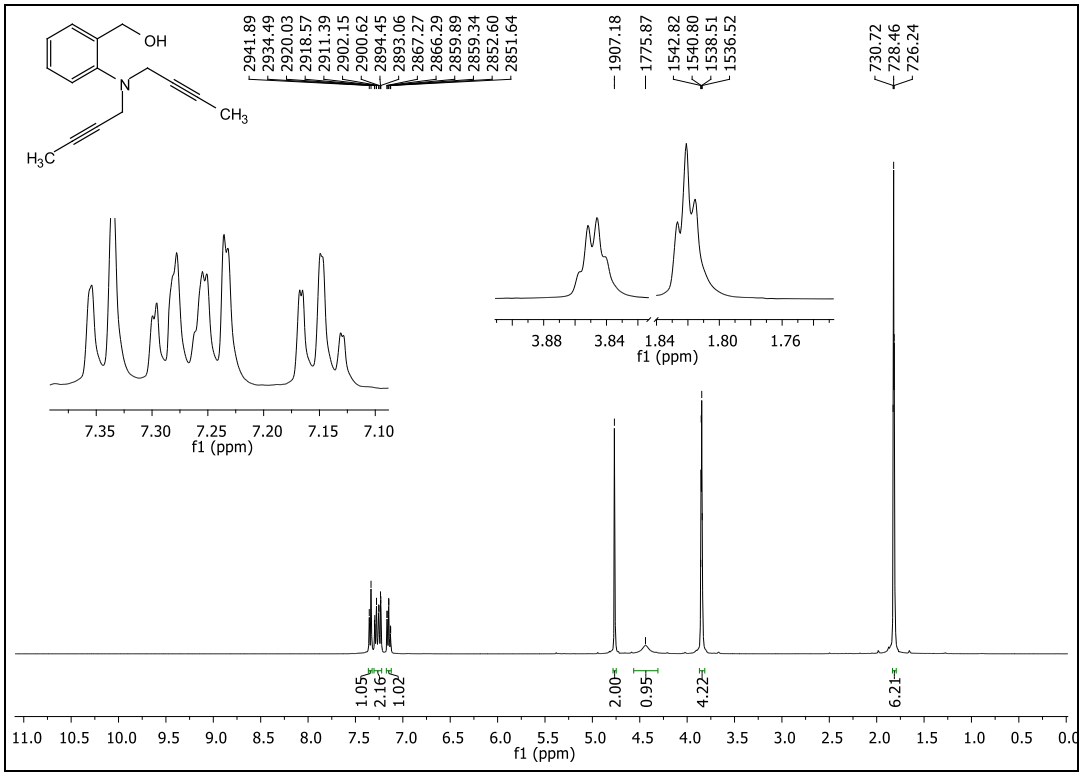

Figure 35 ^{1}H-NMR Spectrum of compound **106** in $CDCl_3$

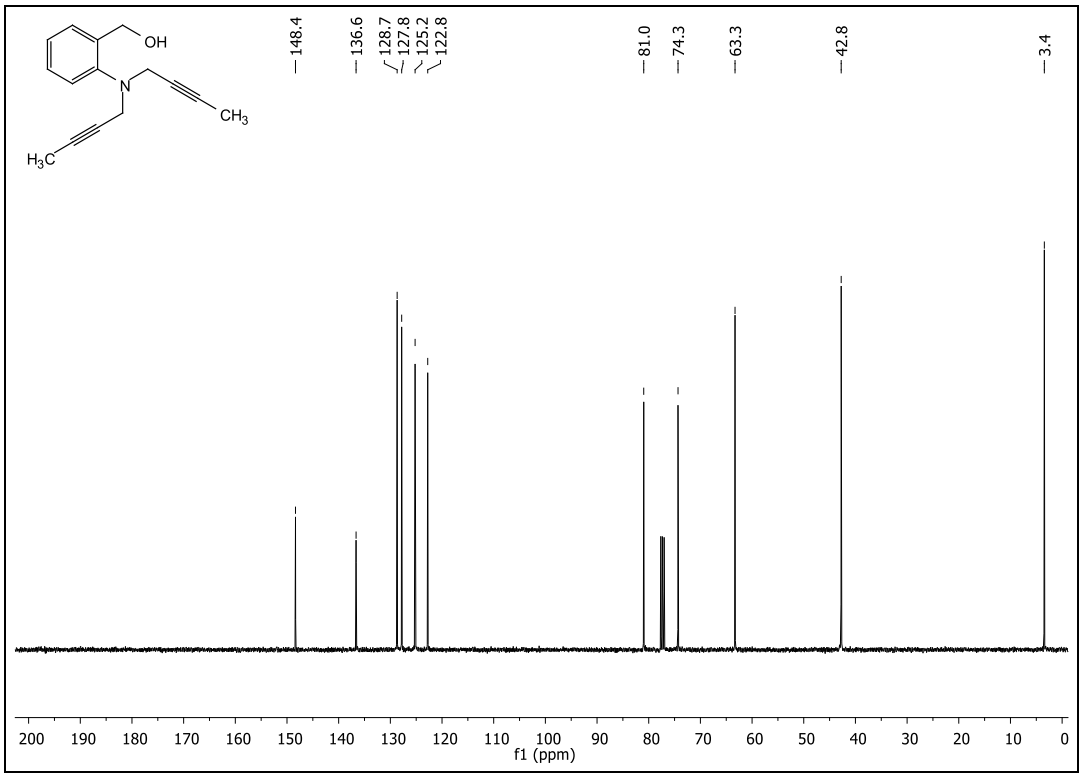

Figure 36 ^{13}C-NMR Spectrum of compound **106** in $CDCl_3$

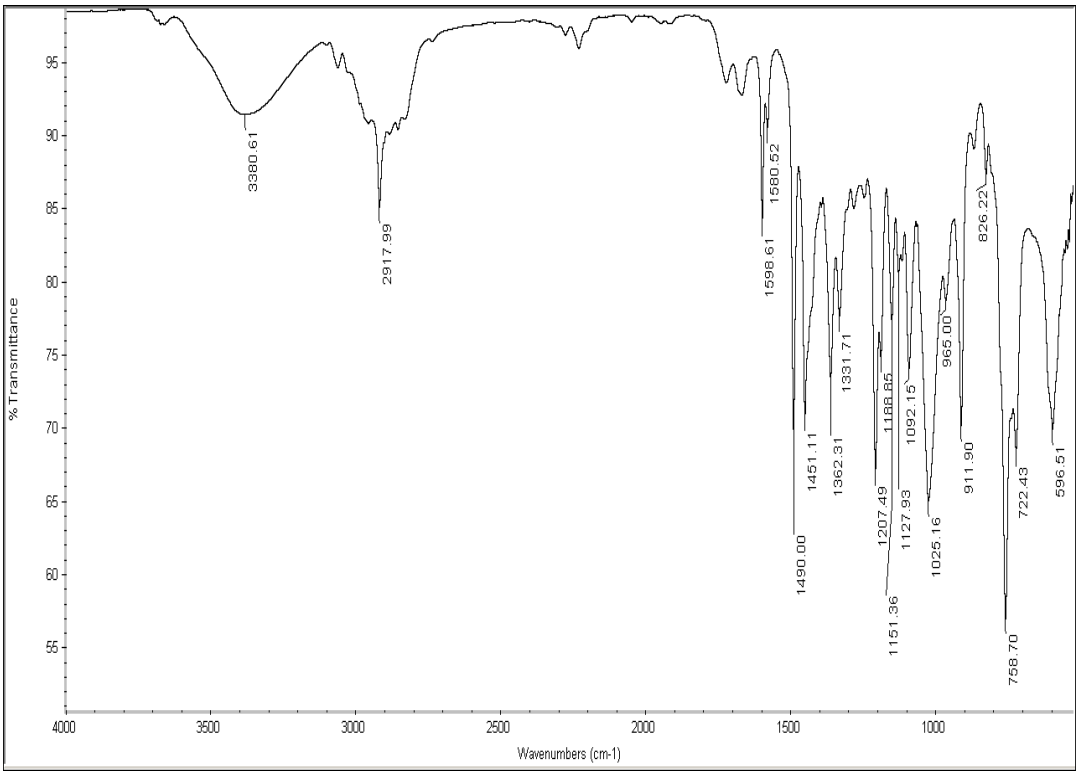

Figure 37 IR Spectrum of compound **106**

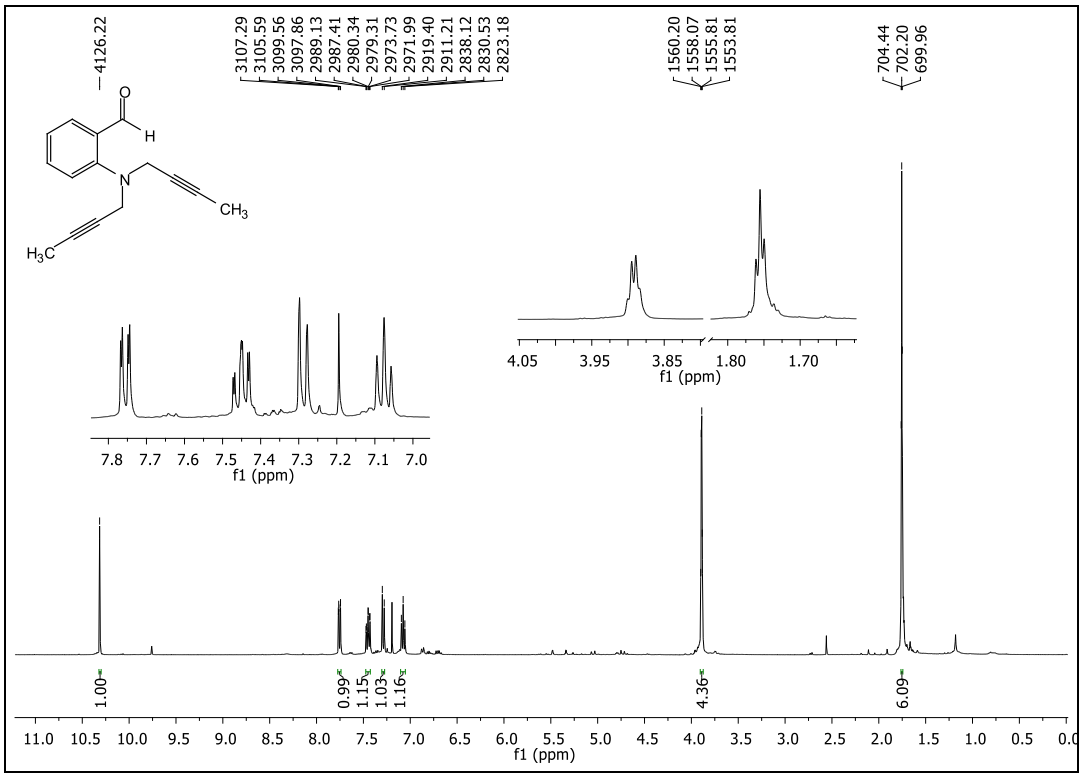

Figure 38 ^{1}H-NMR Spectrum of compound **107** in $CDCl_3$

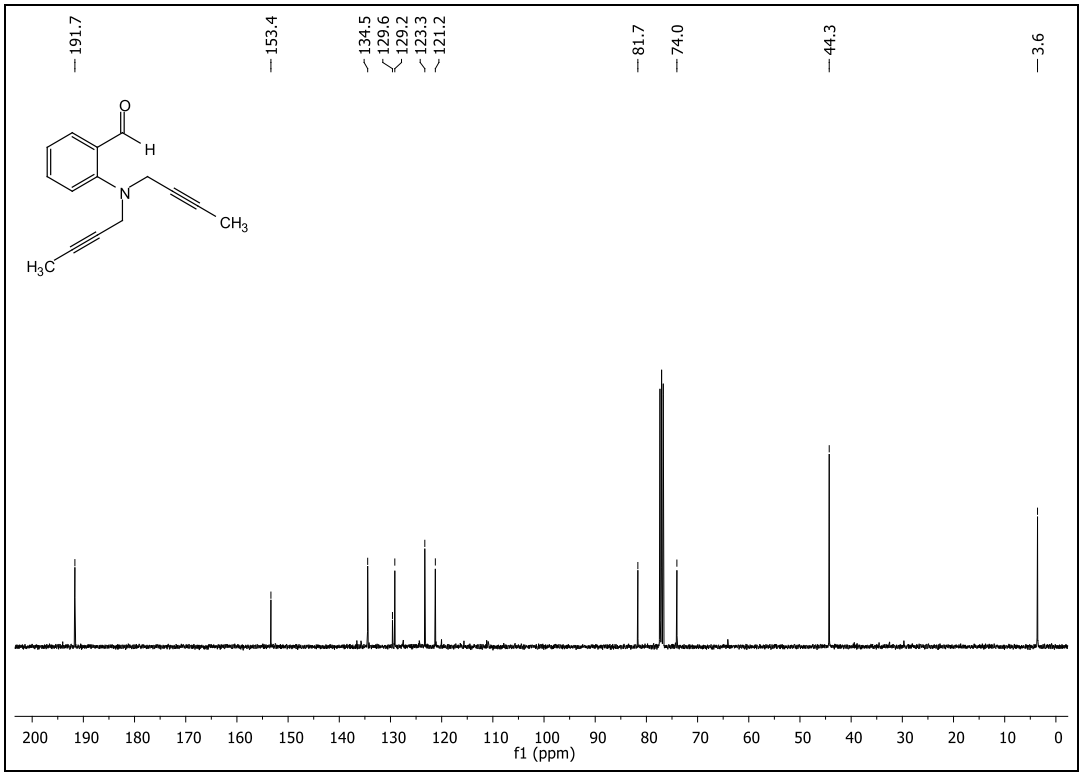

Figure 39 ^{13}C-NMR Spectrum of compound **107** in $CDCl_3$

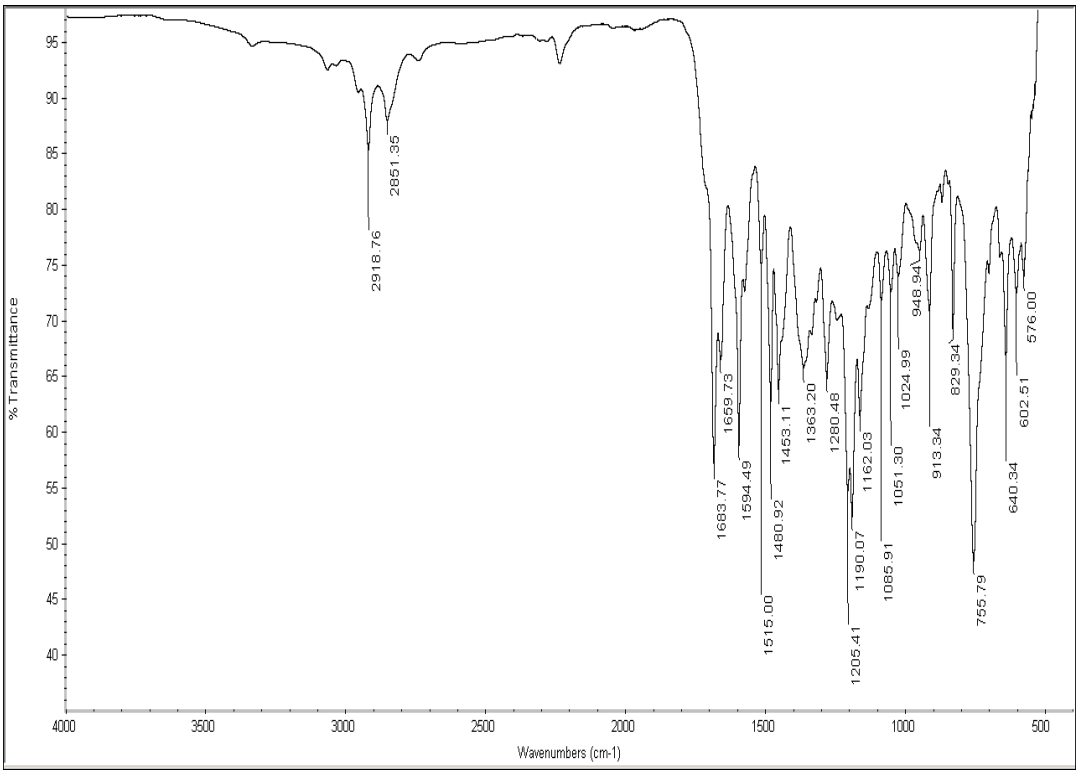

Figure 40 IR Spectrum of compound **107**

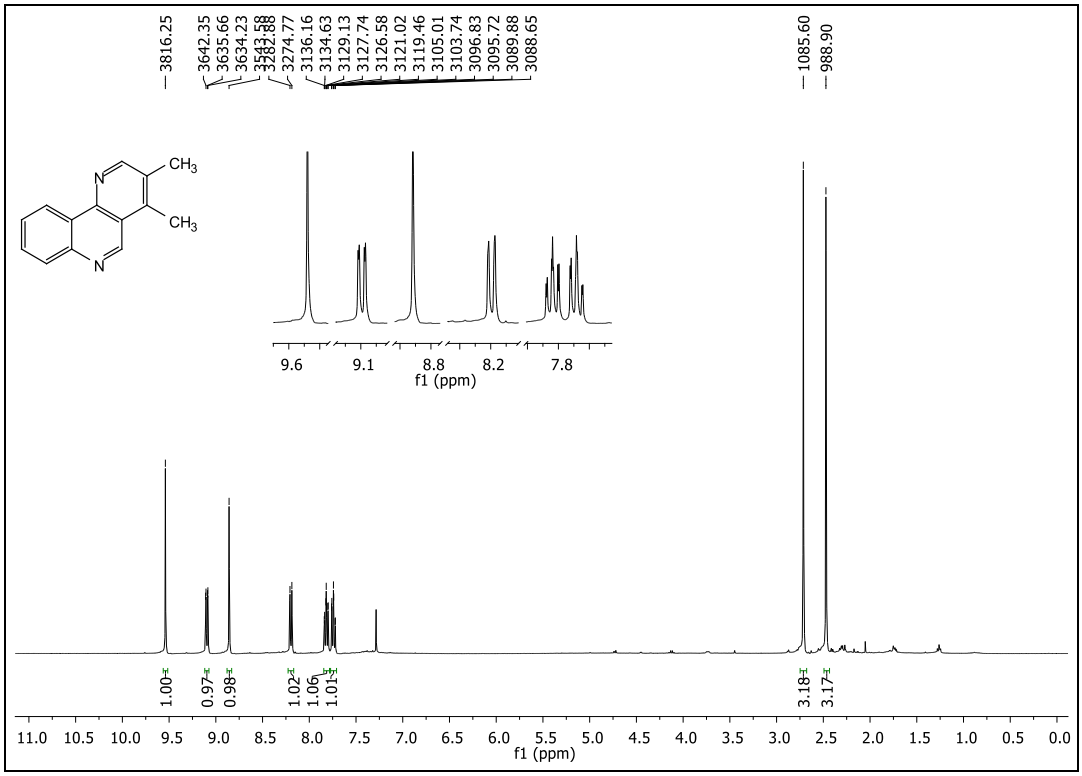

Figure 41 ^{1}H-NMR Spectrum of compound **109** in $CDCl_3$

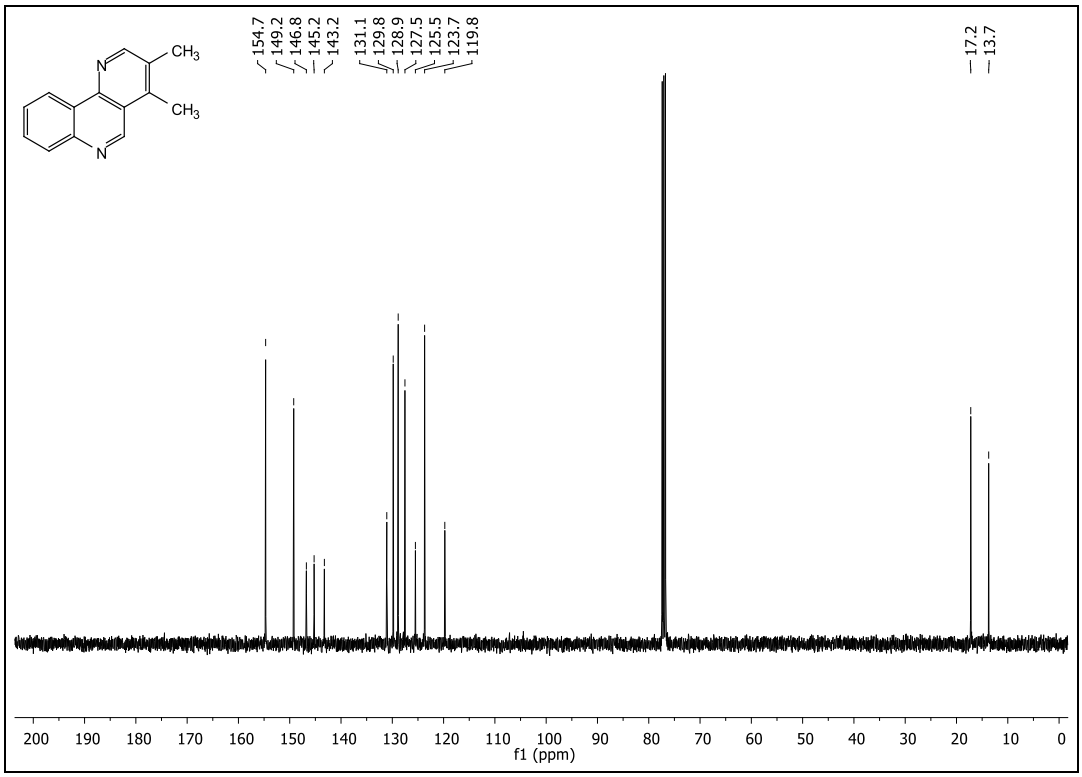

Figure 42 ^{13}C-NMR Spectrum of compound **109** in $CDCl_3$

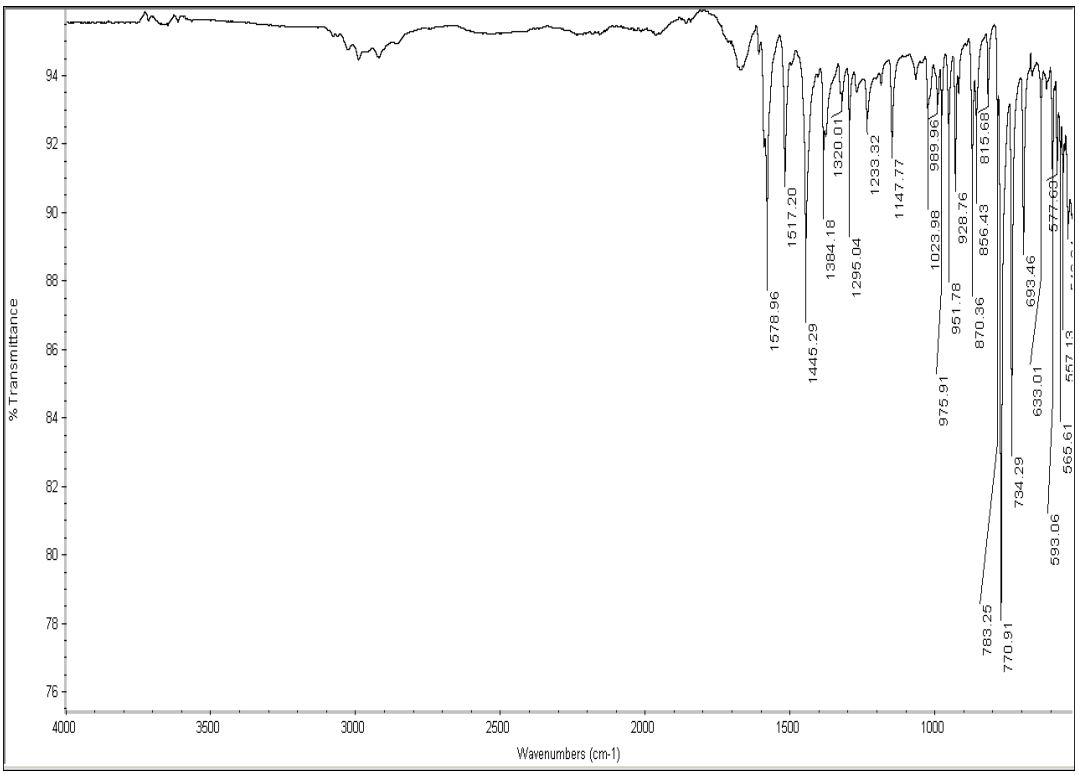

Figure 43 IR Spectrum of compound **109**

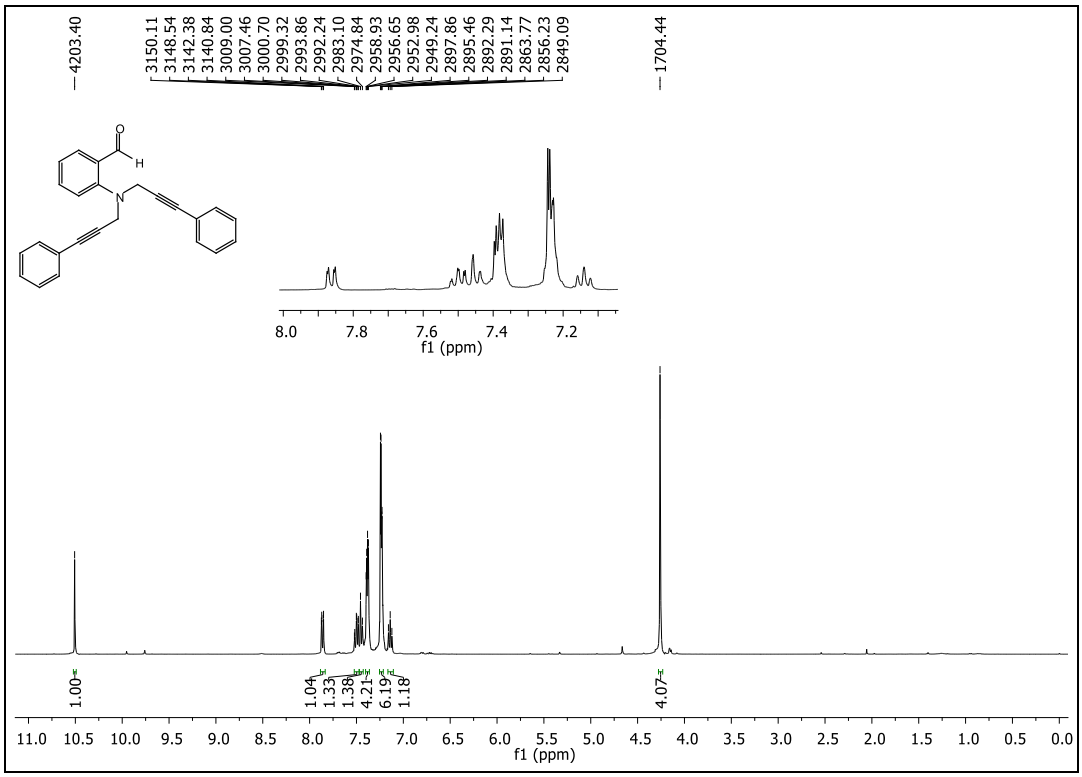

Figure 44 ^{1}H-NMR Spectrum of compound **110a** in $CDCl_3$

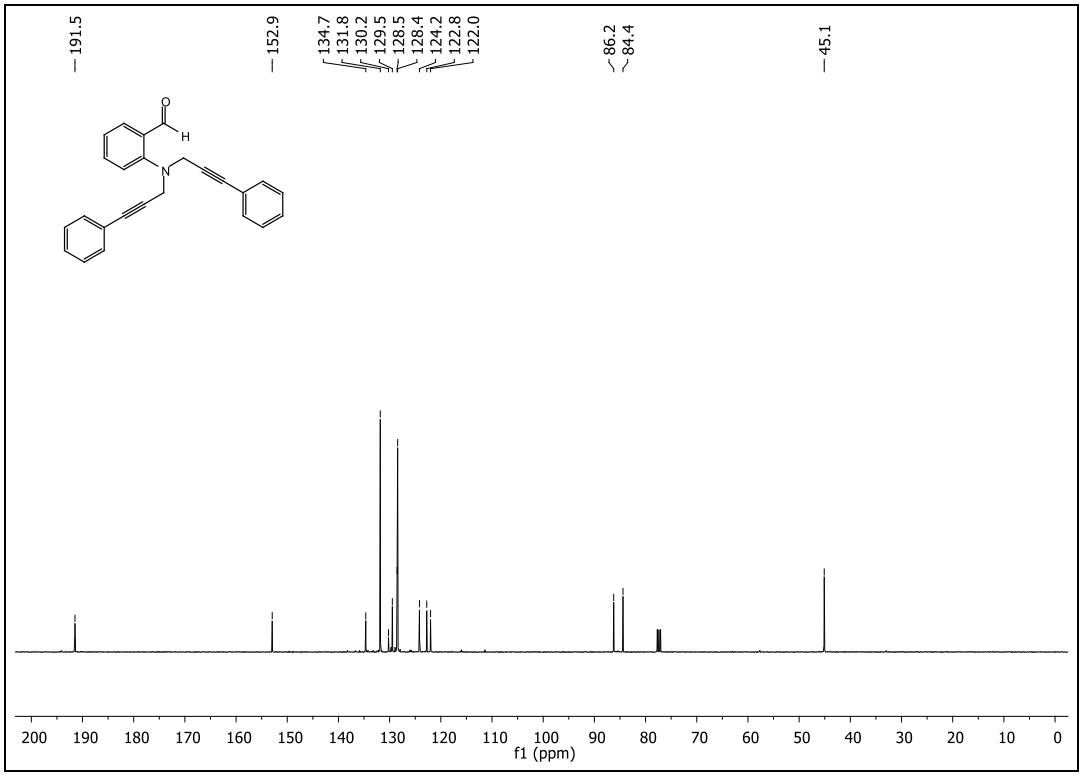

Figure 45 ^{13}C-NMR Spectrum of compound **110a** in $CDCl_3$

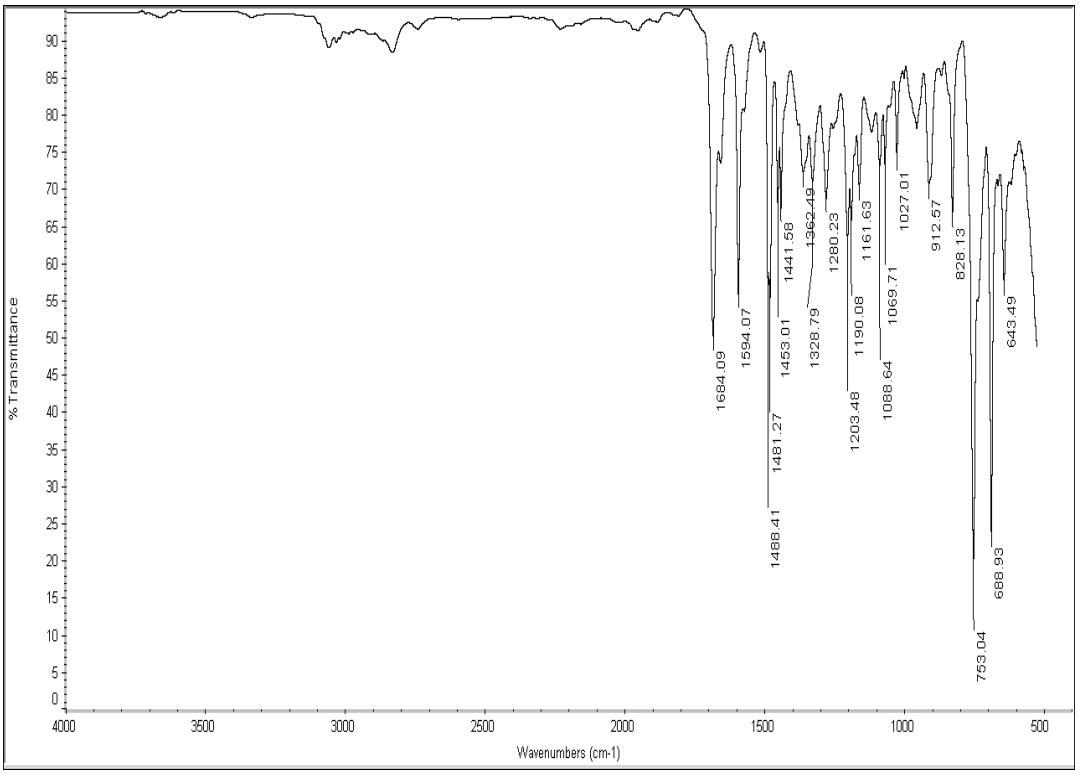

Figure 46 IR Spectrum of compound **110a**

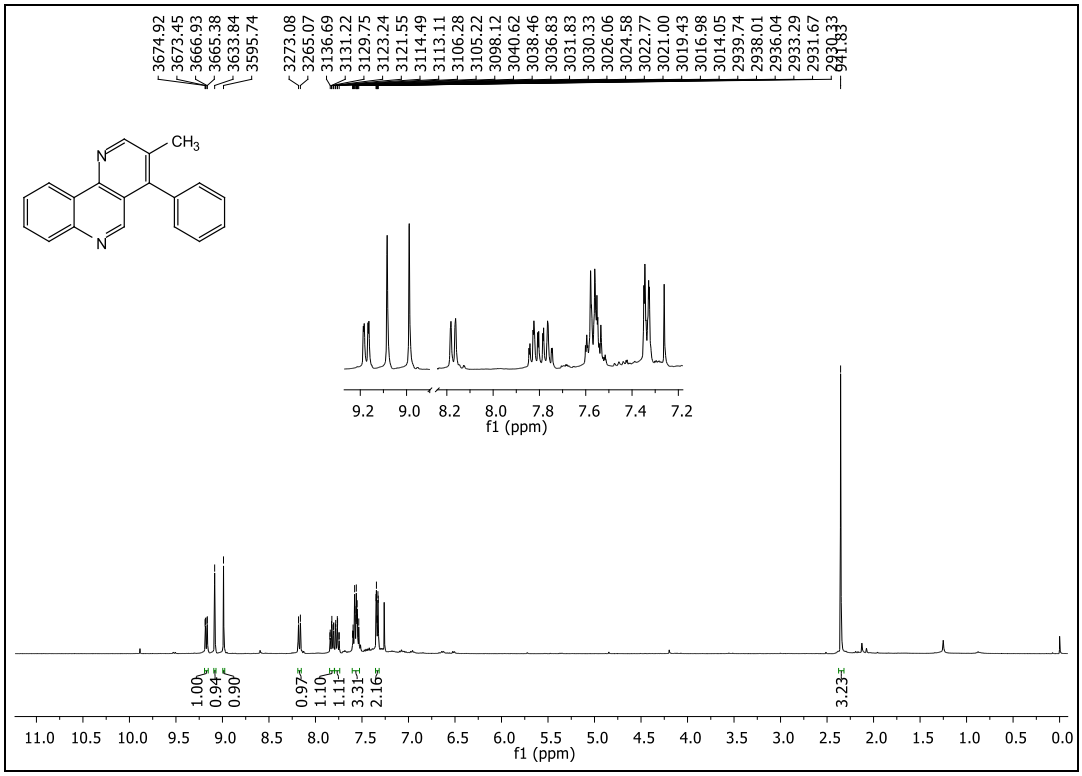

Figure 47 ^{1}H-NMR Spectrum of compound **112a** in $CDCl_3$

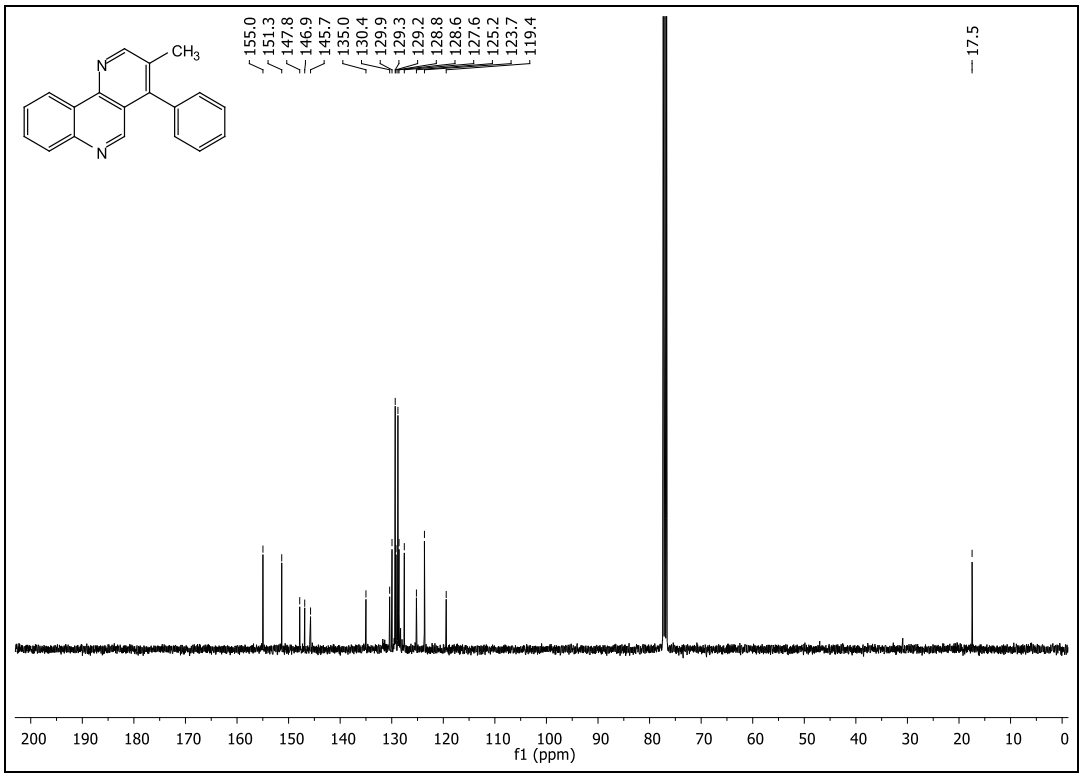

Figure 48 ^{13}C-NMR Spectrum of compound **112a** in $CDCl_3$

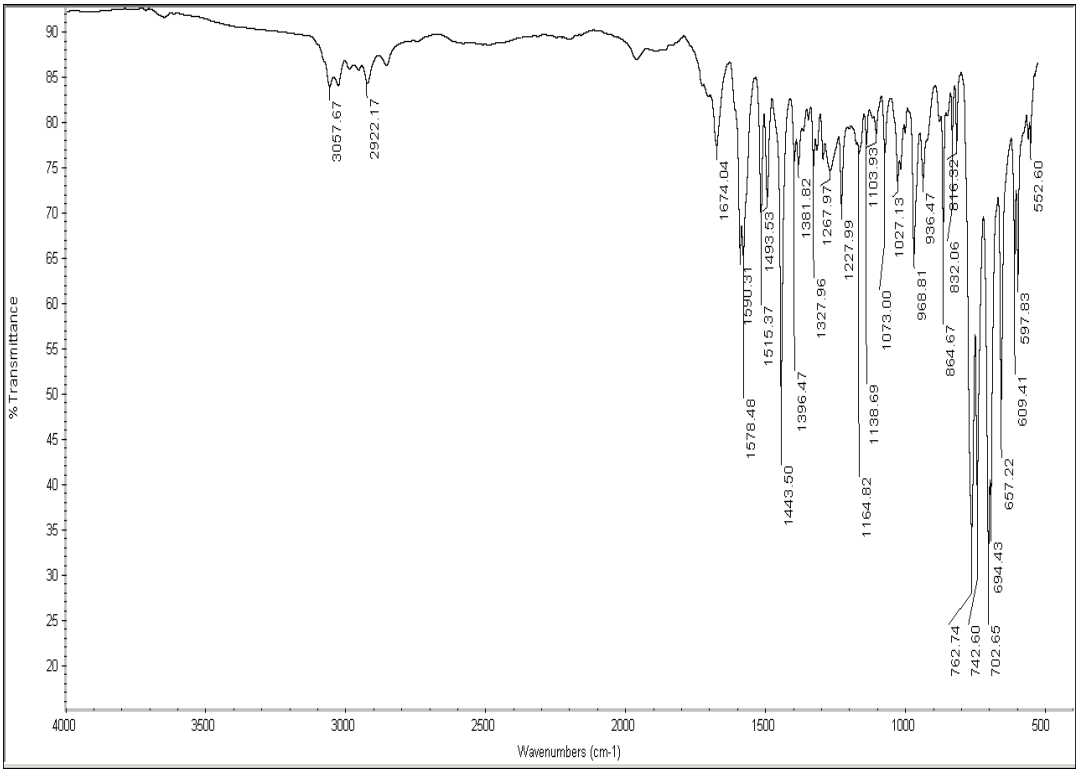

Figure 49 IR Spectrum of compound **112a** in $CDCl_3$

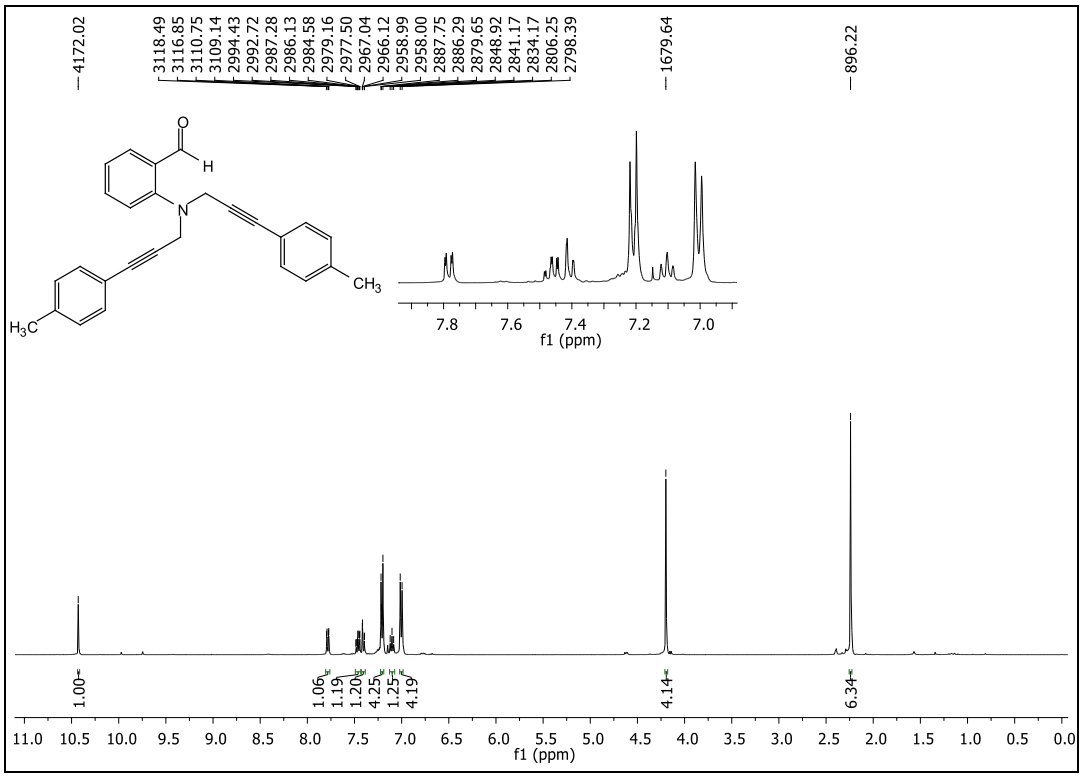

Figure 50 ^{1}H-NMR Spectrum of compound **110c** in $CDCl_3$

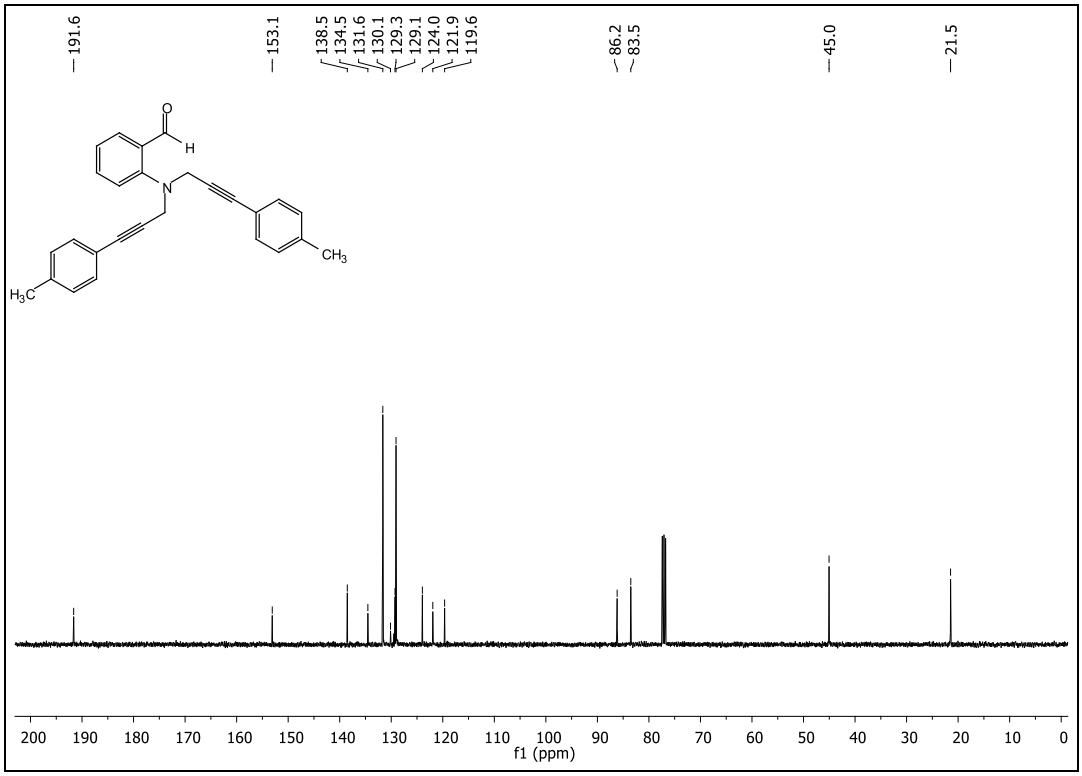

Figure 51 ^{13}C-NMR Spectrum of compound **110c** in $CDCl_3$

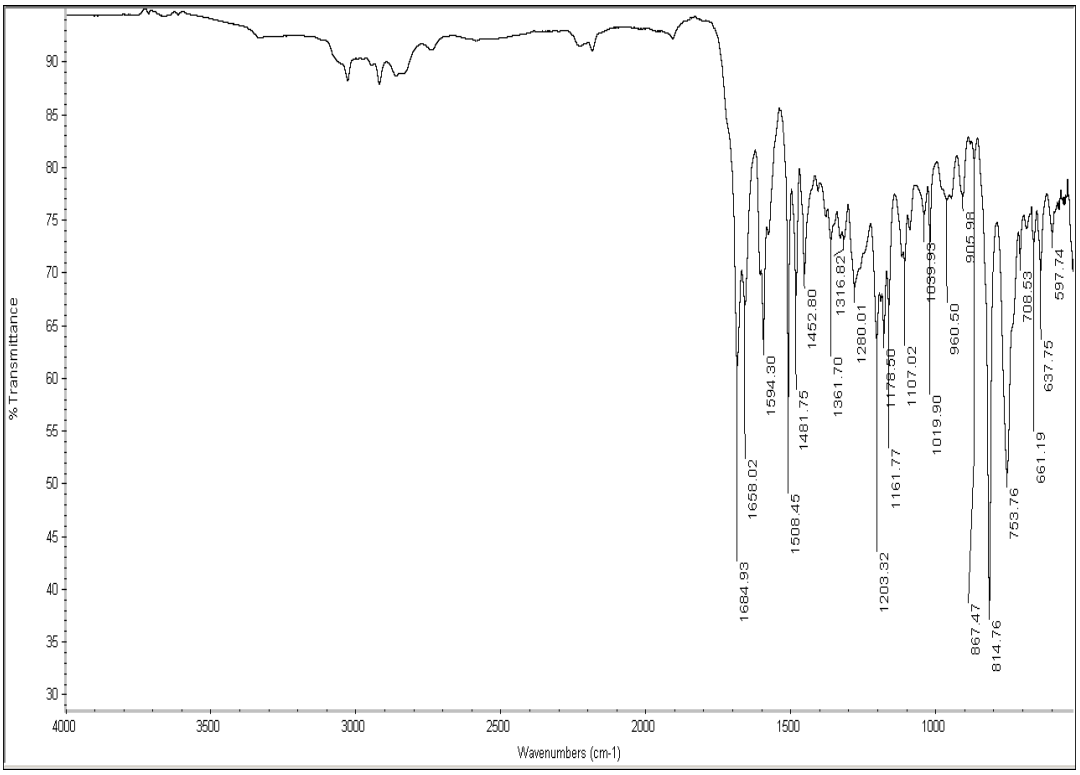

Figure 52 IR Spectrum of compound **110c**

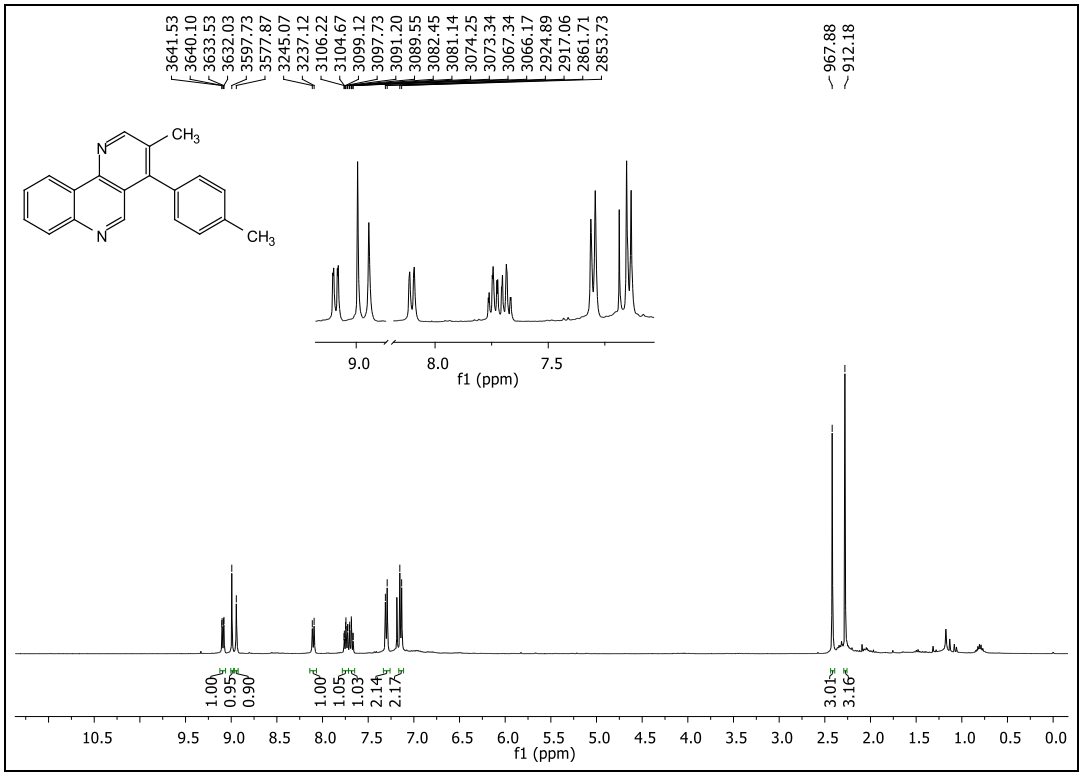

Figure 53 ^{1}H-NMR Spectrum of compound **112c** in $CDCl_3$

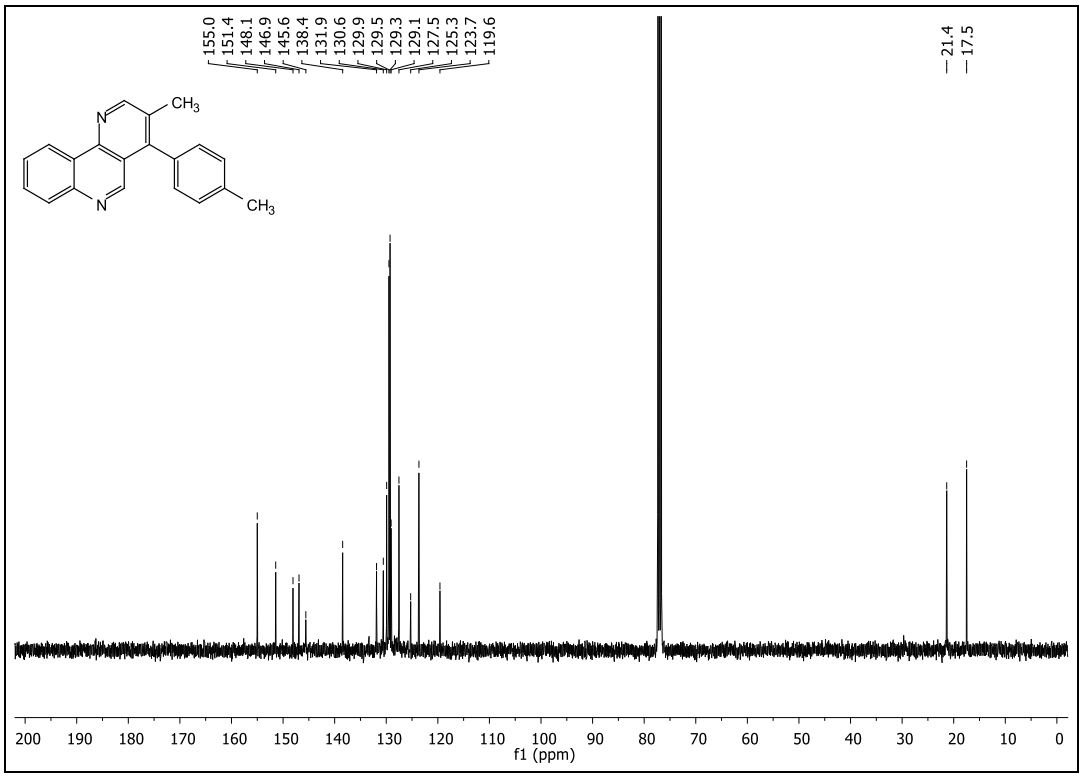

Figure 54 ^{13}C-NMR Spectrum of compound **112c** in $CDCl_3$

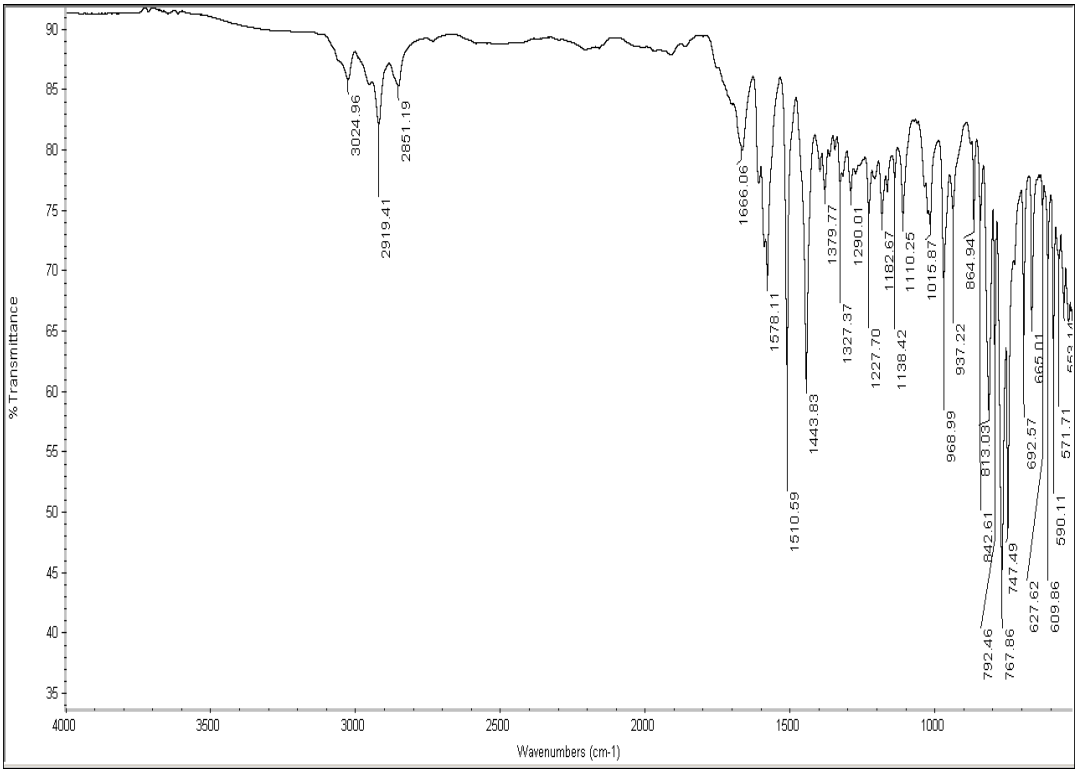

Figure 55 IR Spectrum of compound **112c**

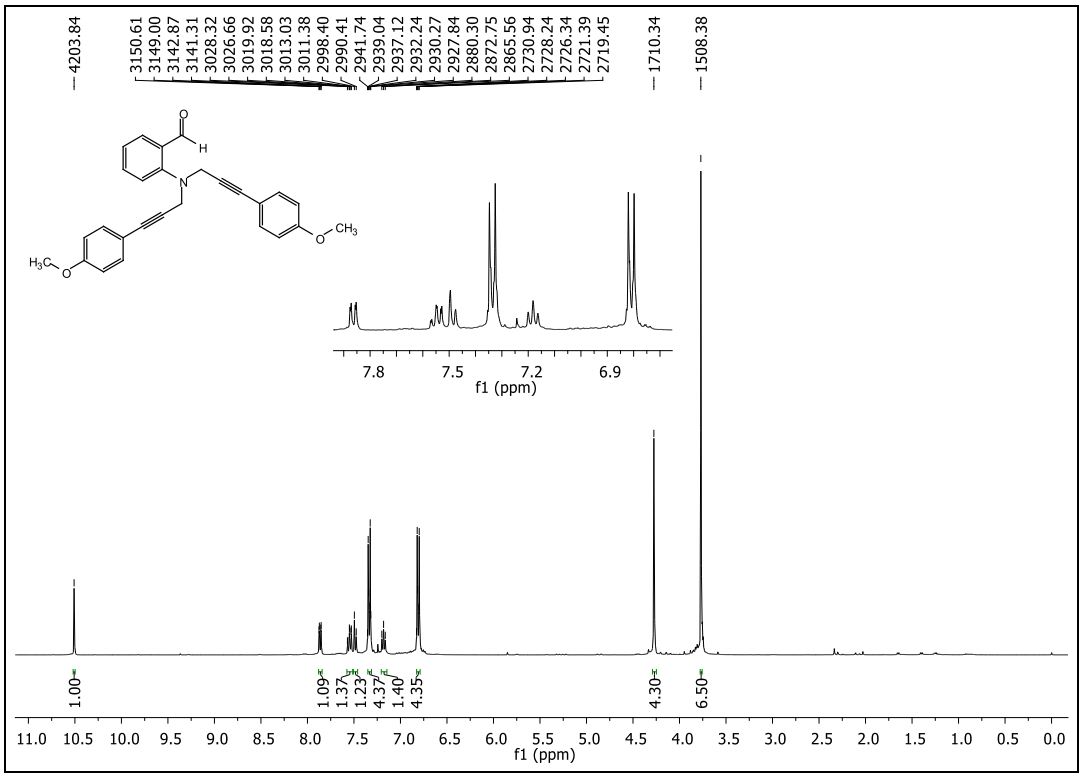

Figure 56 ^{1}H-NMR Spectrum of compound **110b** in $CDCl_3$

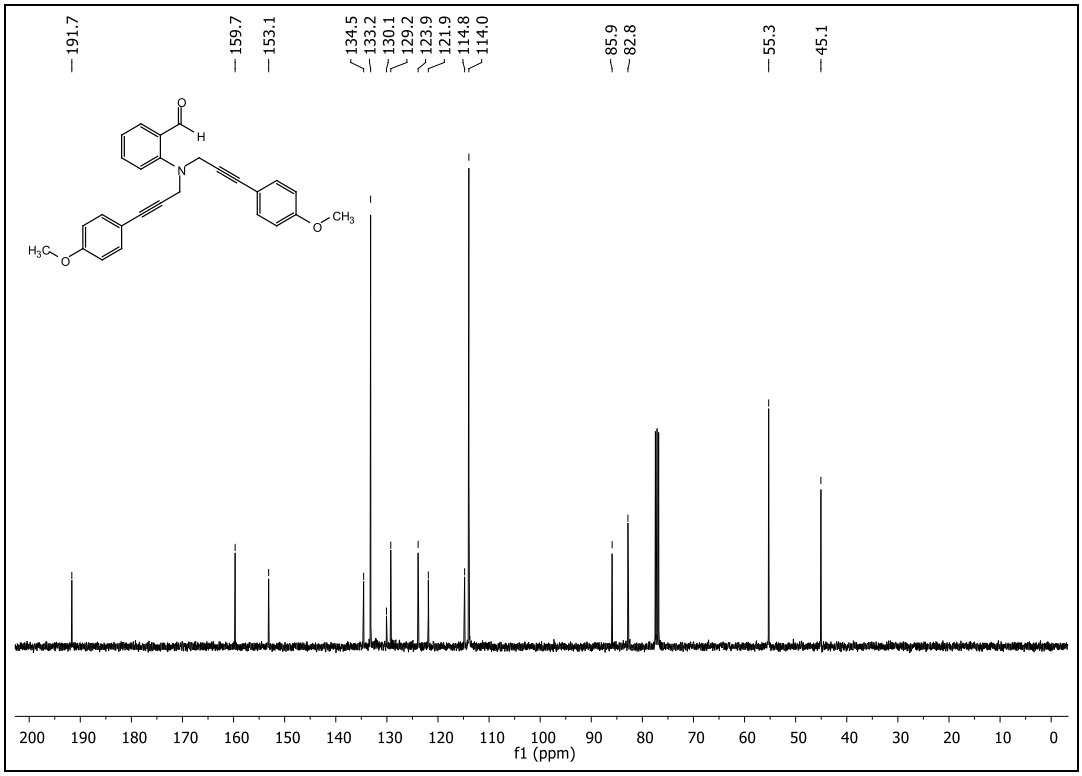

Figure 57 ^{13}C-NMR Spectrum of compound **110b** in $CDCl_3$

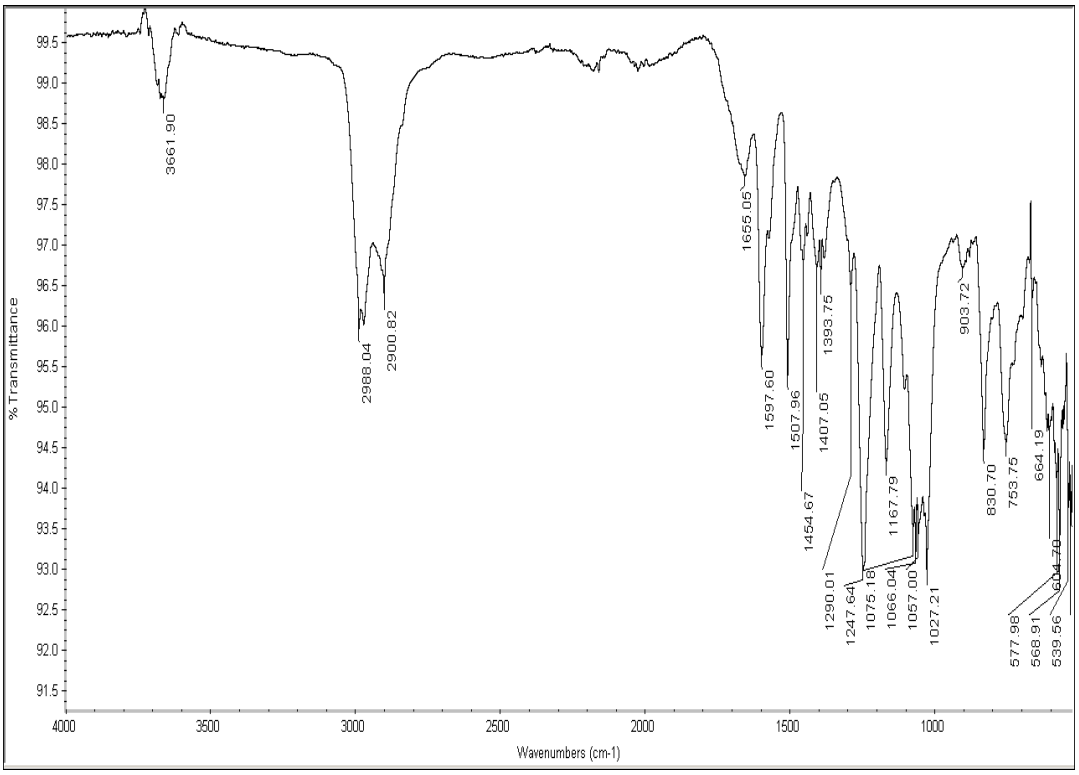

Figure 58 IR Spectrum of compound **110b**

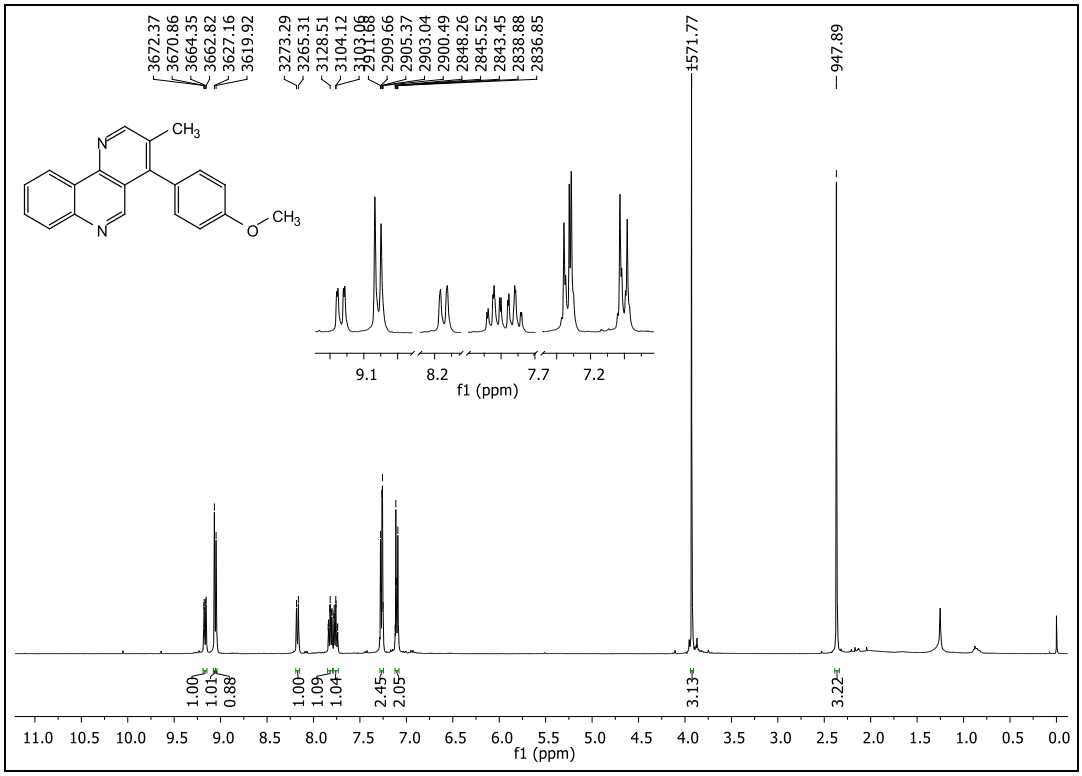

Figure 59 ^{1}H-NMR Spectrum of compound **112b** in $CDCl_3$

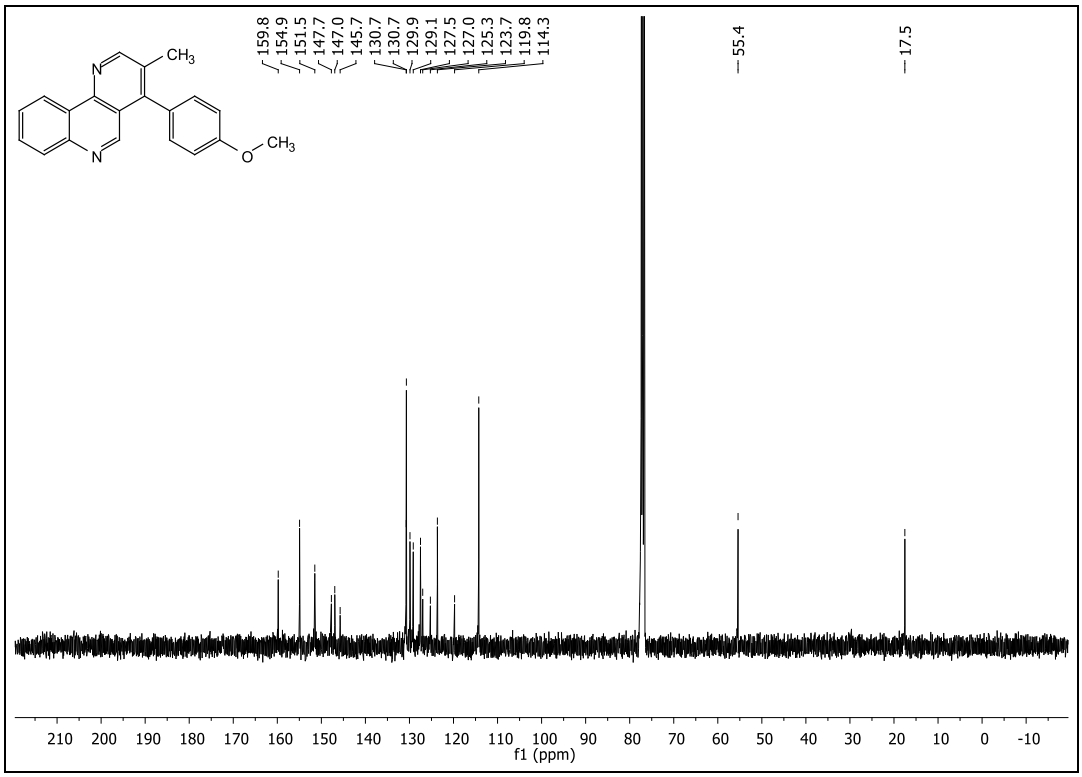

Figure 60 ^{13}C-NMR Spectrum of compound **112b** in $CDCl_3$

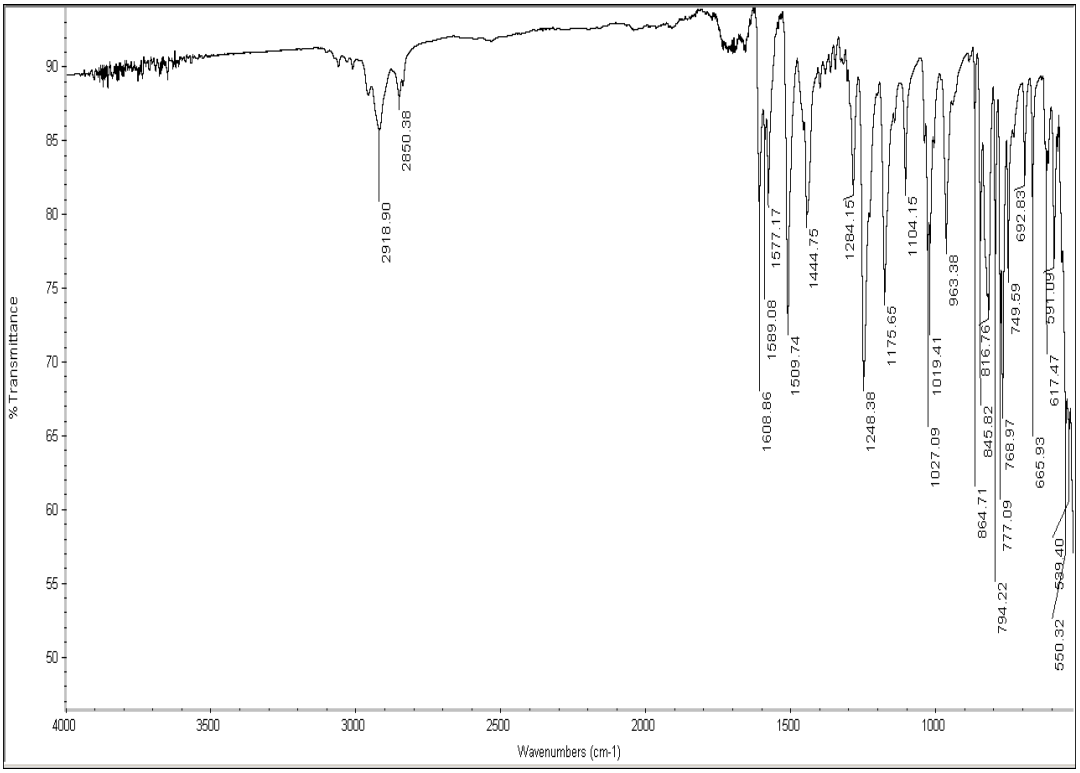

Figure 61 IR Spectrum of compound **112b**

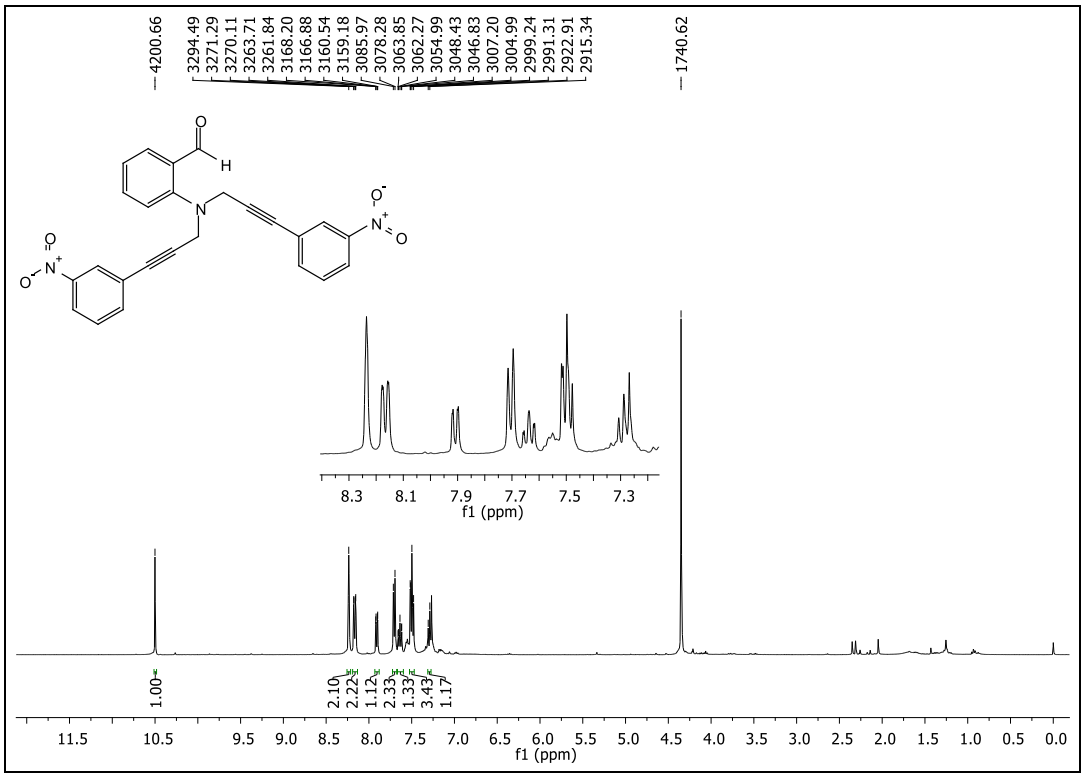

Figure 62 ^{1}H-NMR Spectrum of compound **110d** in $CDCl_3$

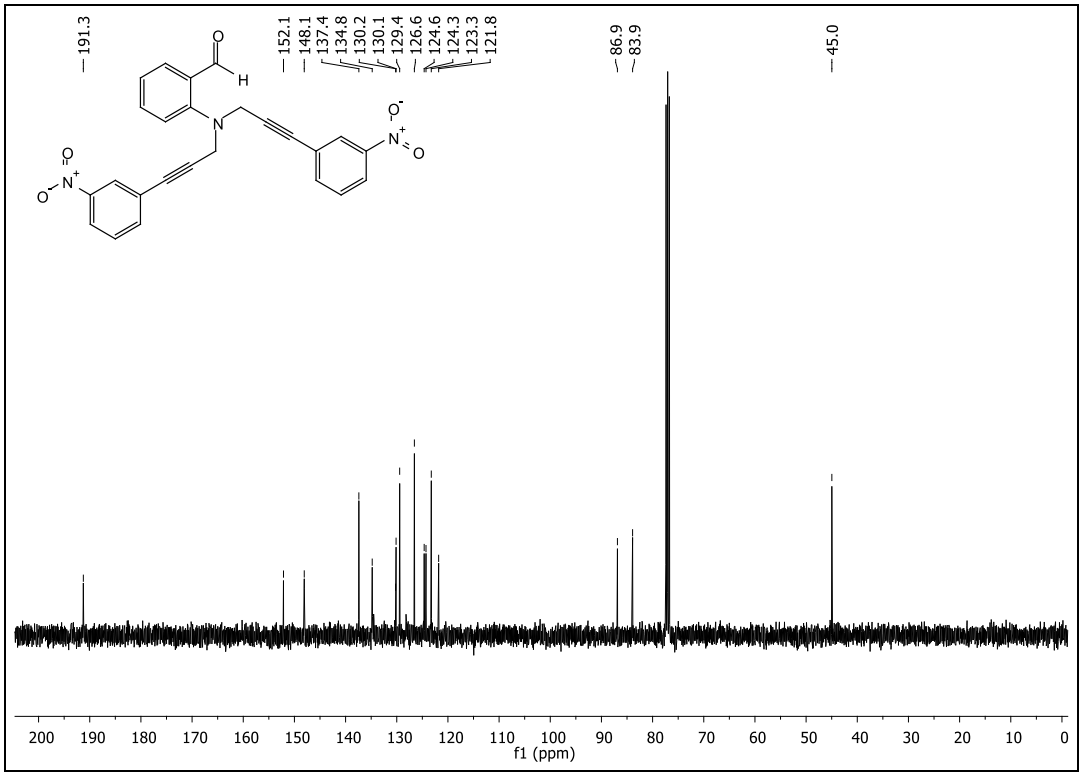

Figure 63 ^{13}C-NMR Spectrum of compound **110d** in $CDCl_3$

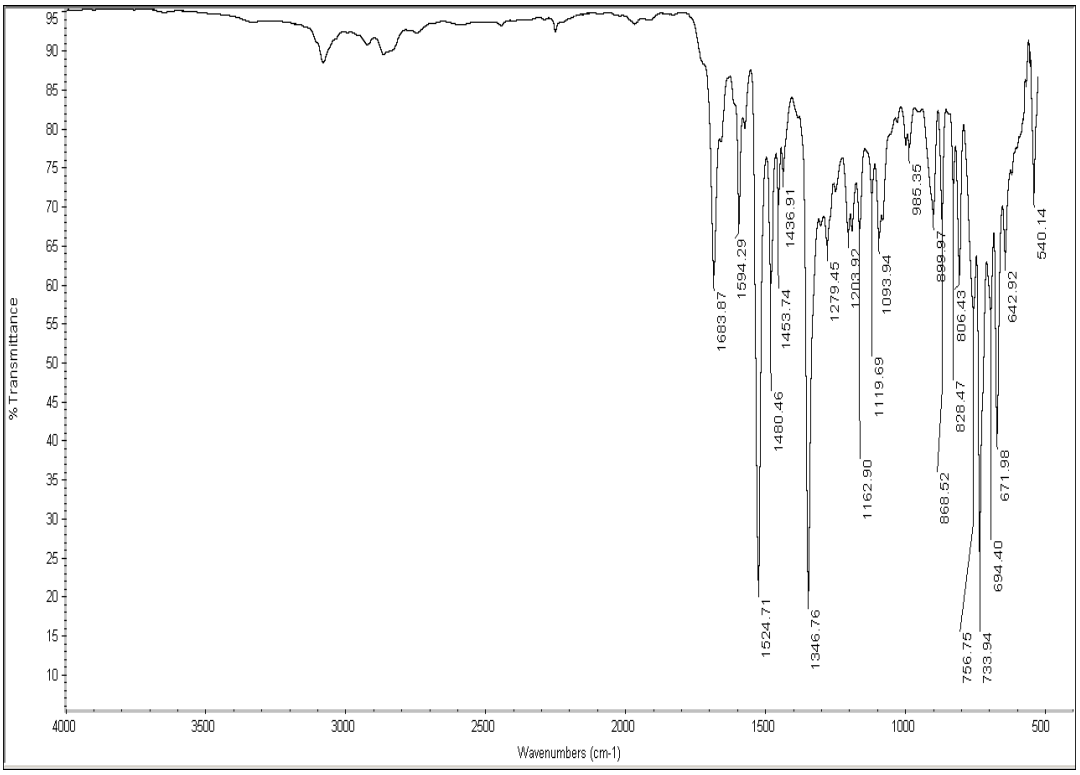

Figure 64 IR Spectrum of compound **110d**

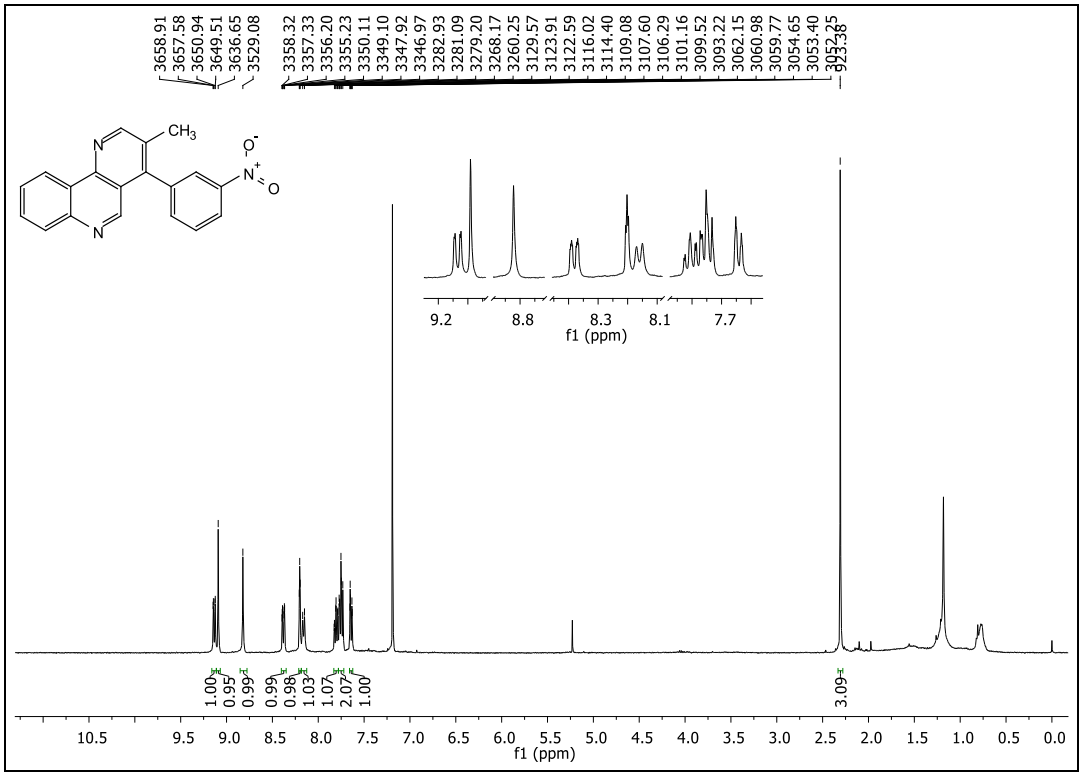

Figure 65 ^{1}H-NMR Spectrum of compound **112d** in $CDCl_3$

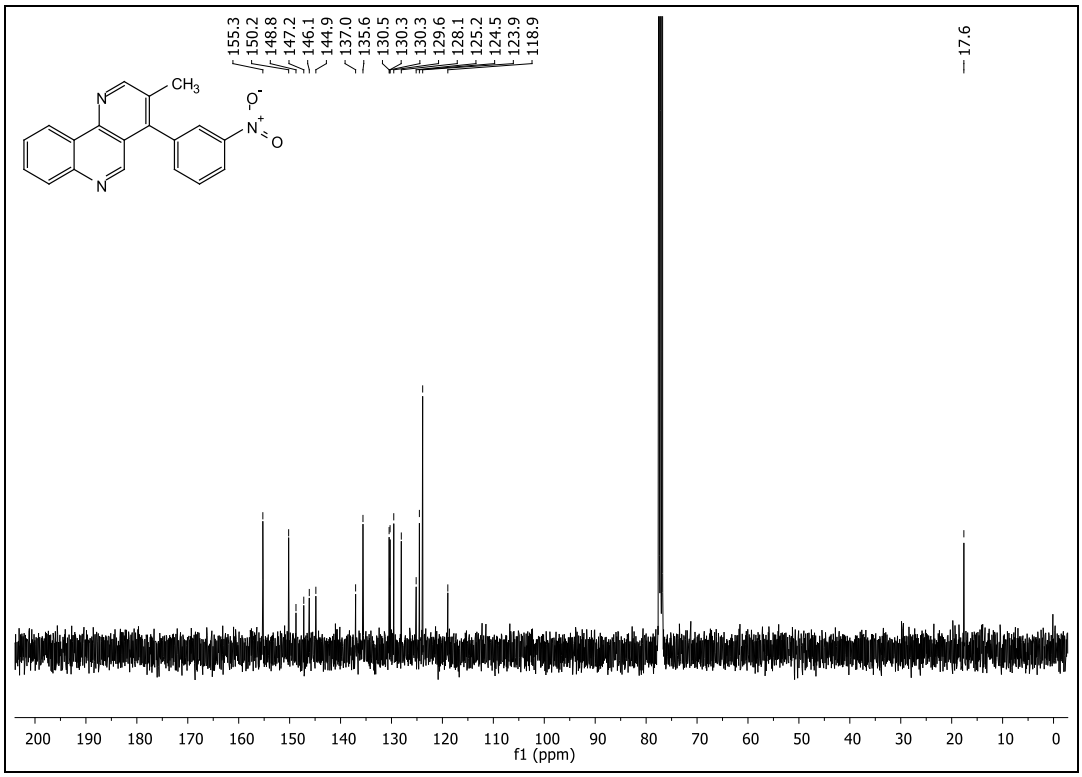

Figure 66 ^{13}C-NMR Spectrum of compound **112d** in $CDCl_3$

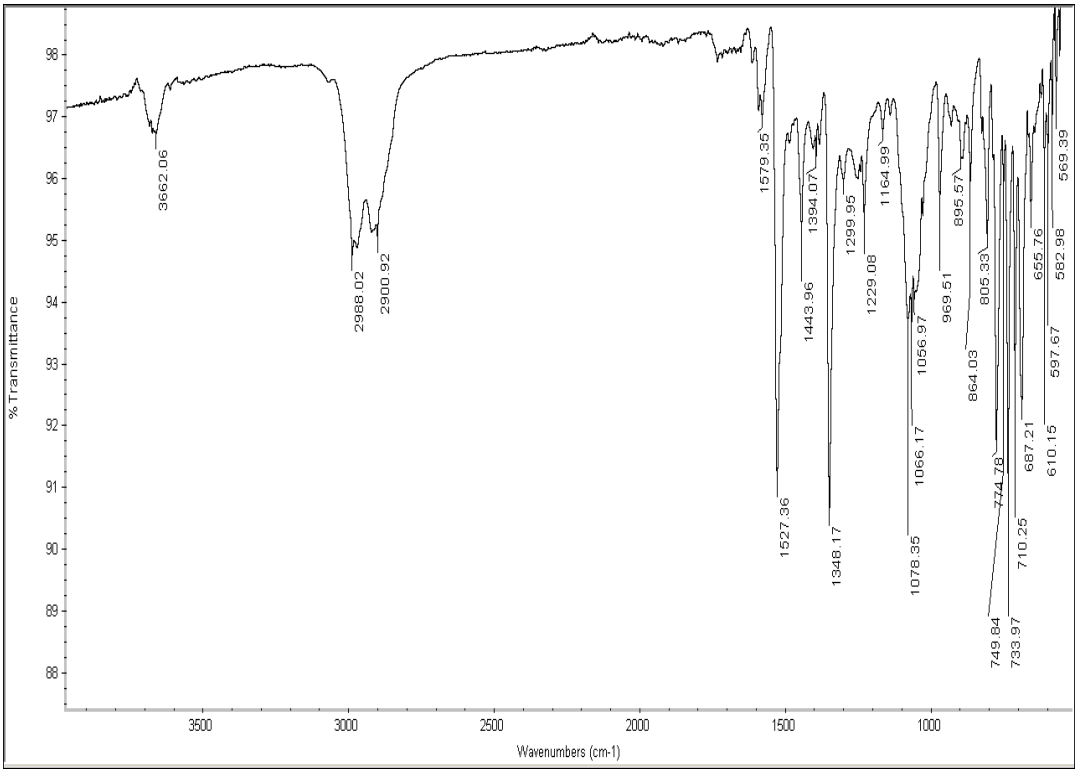

Figure 67 IR Spectrum of compound **112d**

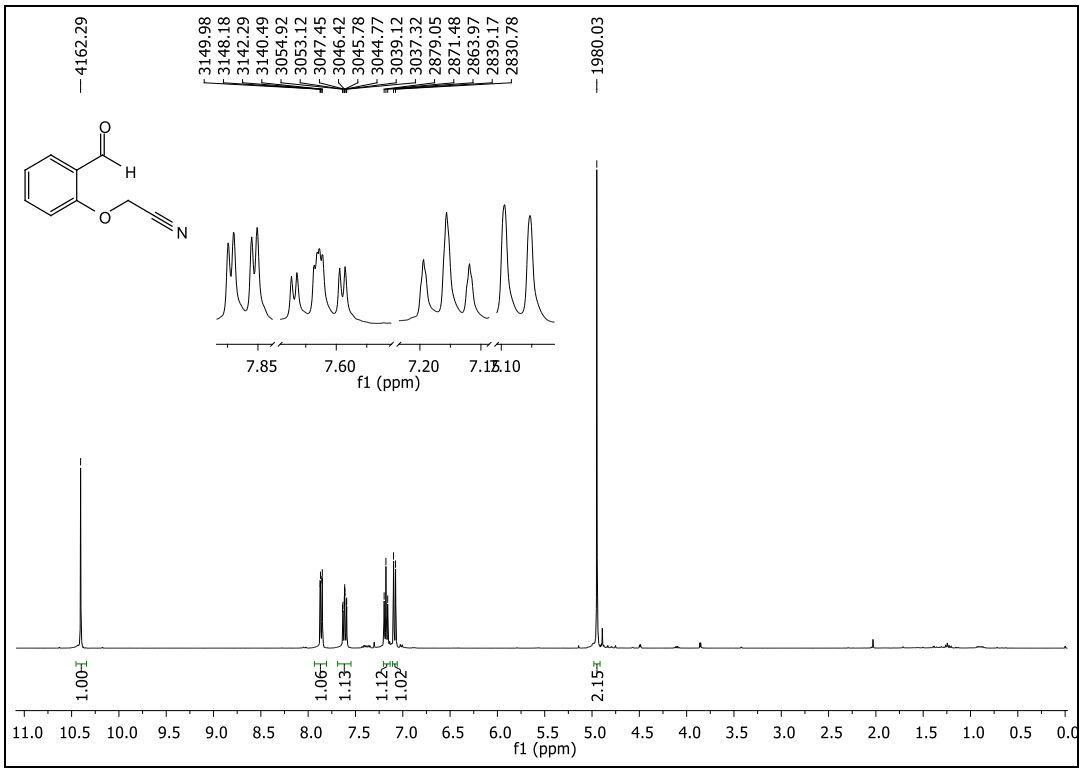

Figure 68 ^{1}H-NMR Spectrum of compound **146** in $CDCl_3$

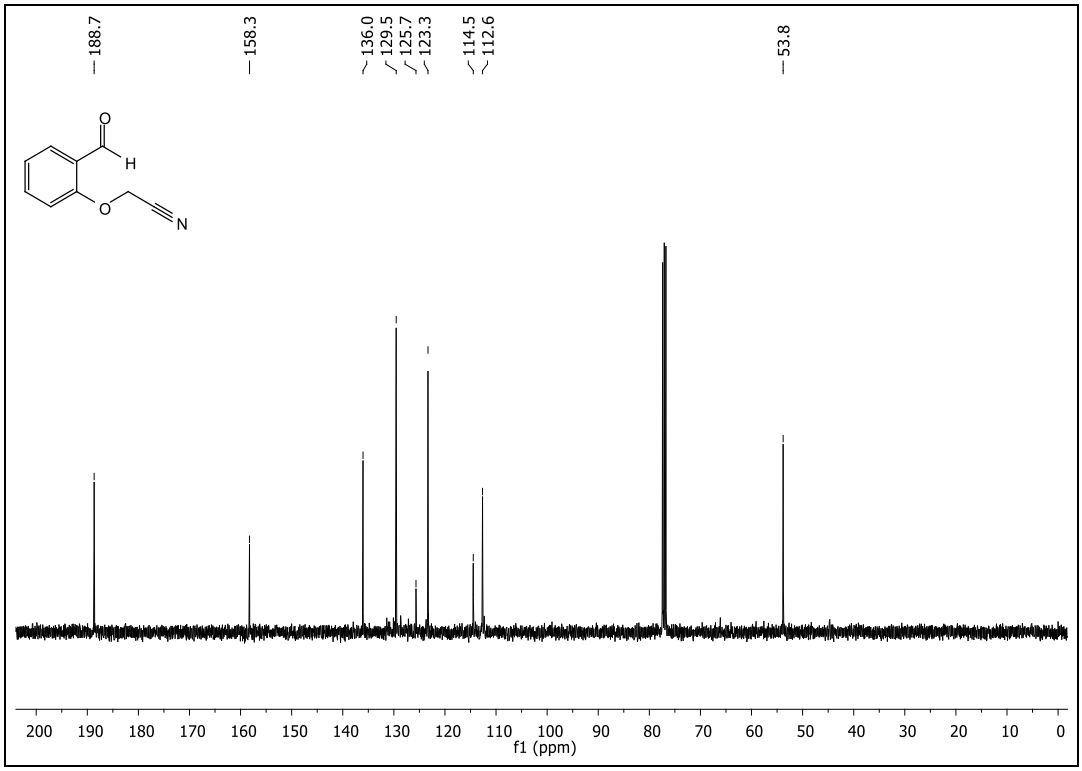

Figure 69 ^{13}C-NMR Spectrum of compound **146** in $CDCl_3$

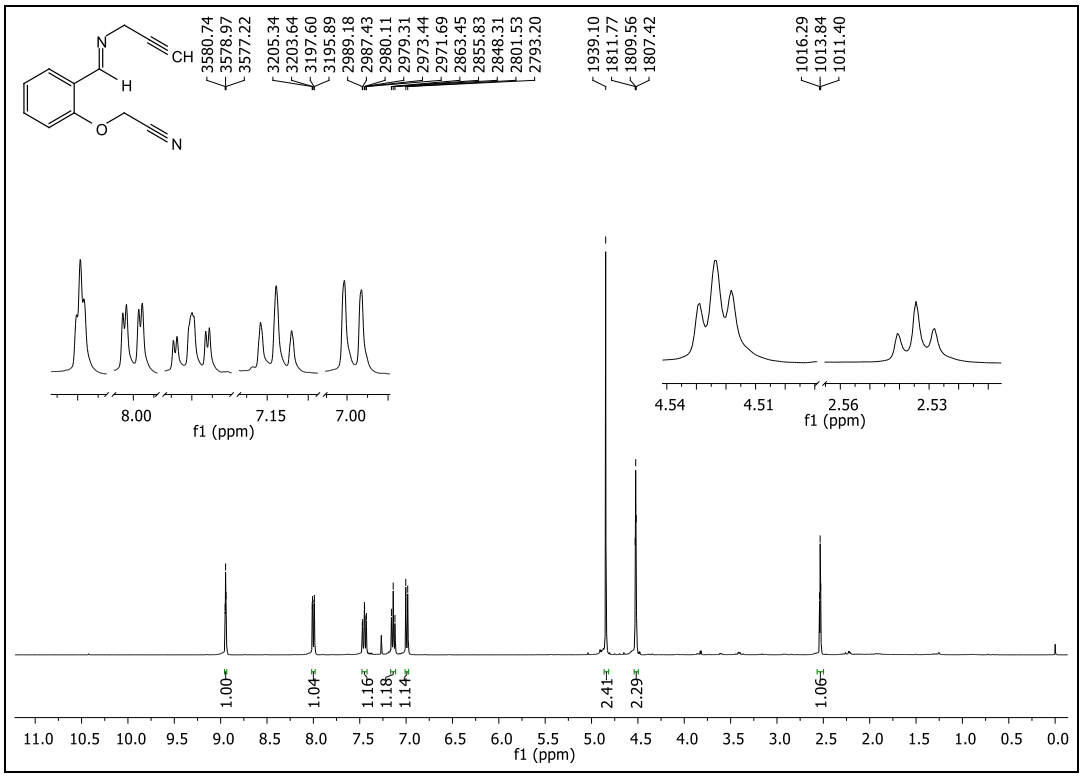

Figure 70 ^{1}H-NMR Spectrum of compound **148** in $CDCl_3$

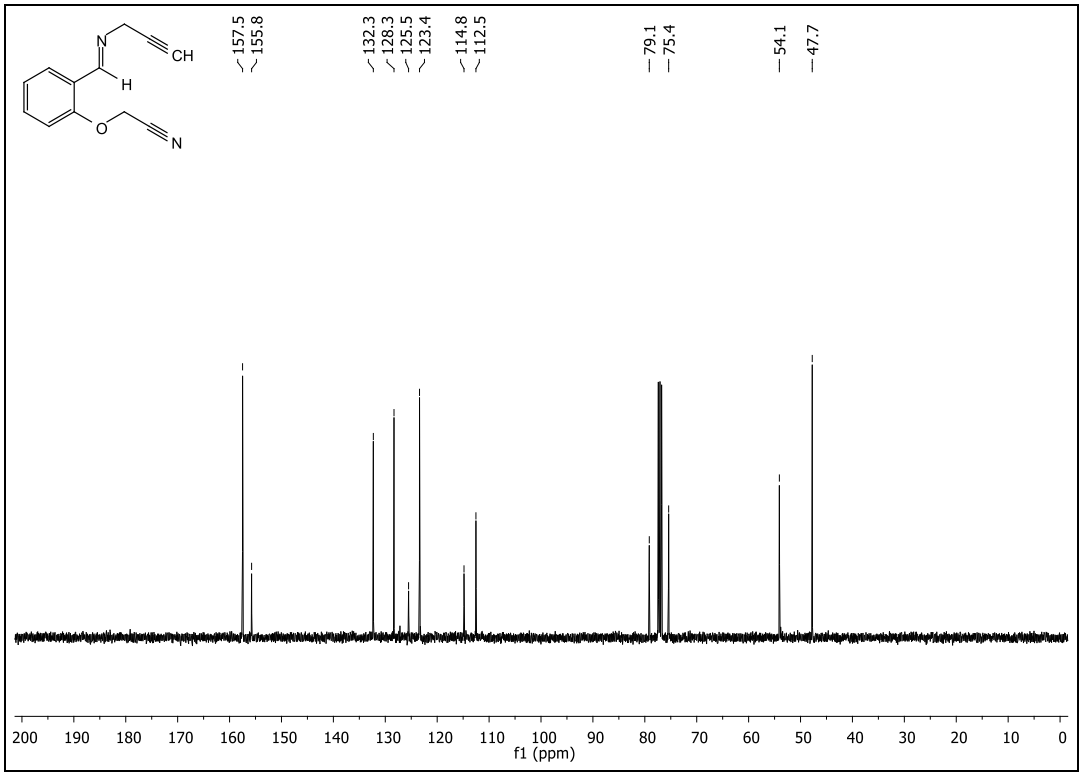

Figure 71 ^{13}C-NMR Spectrum of compound **148** in $CDCl_3$

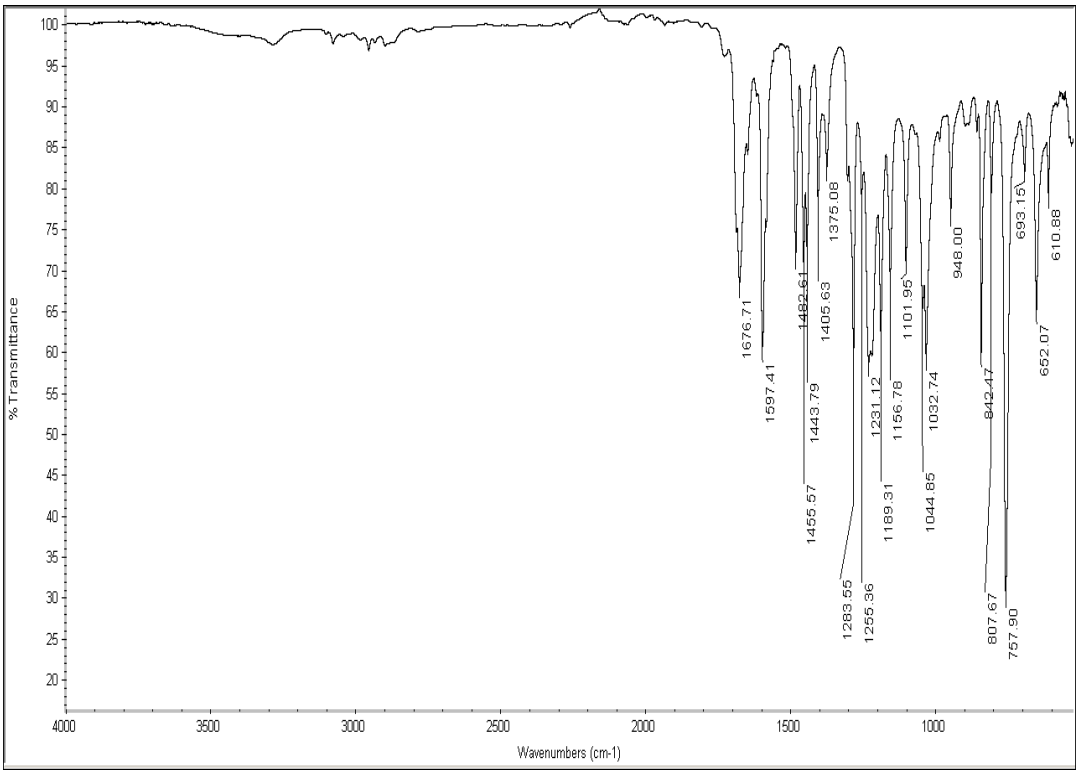

Figure 72 IR Spectrum of compound **148**

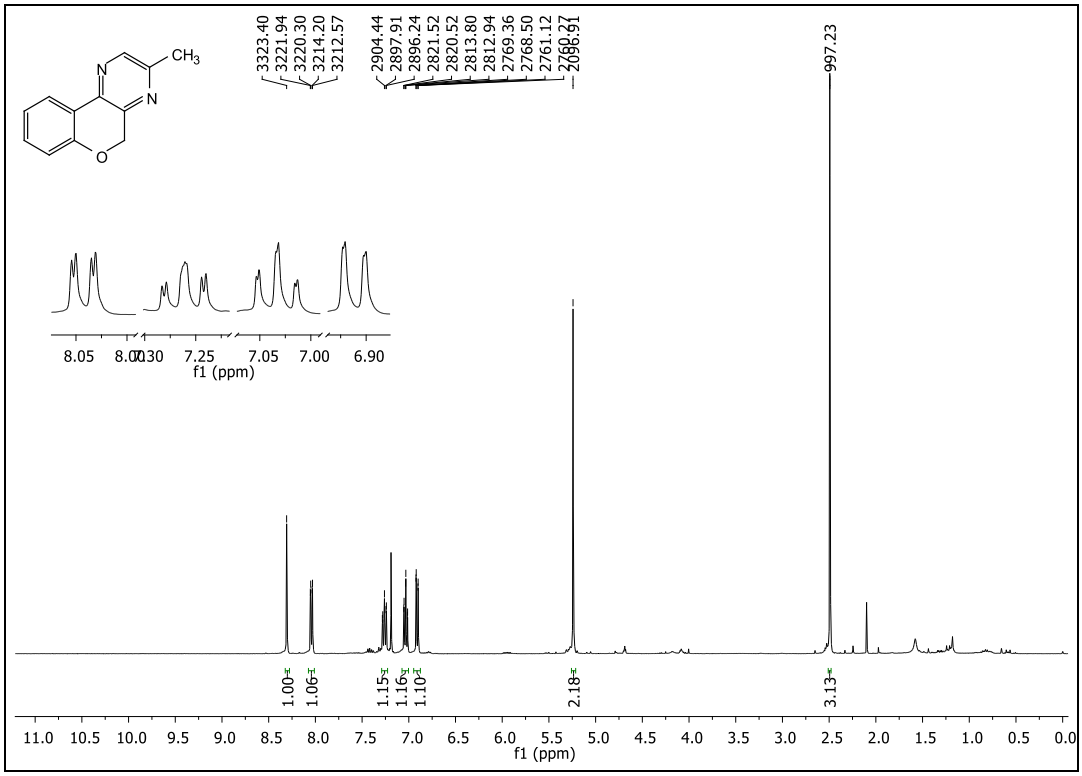

Figure 73 ^{1}H-NMR Spectrum of compound **147** in $CDCl_3$

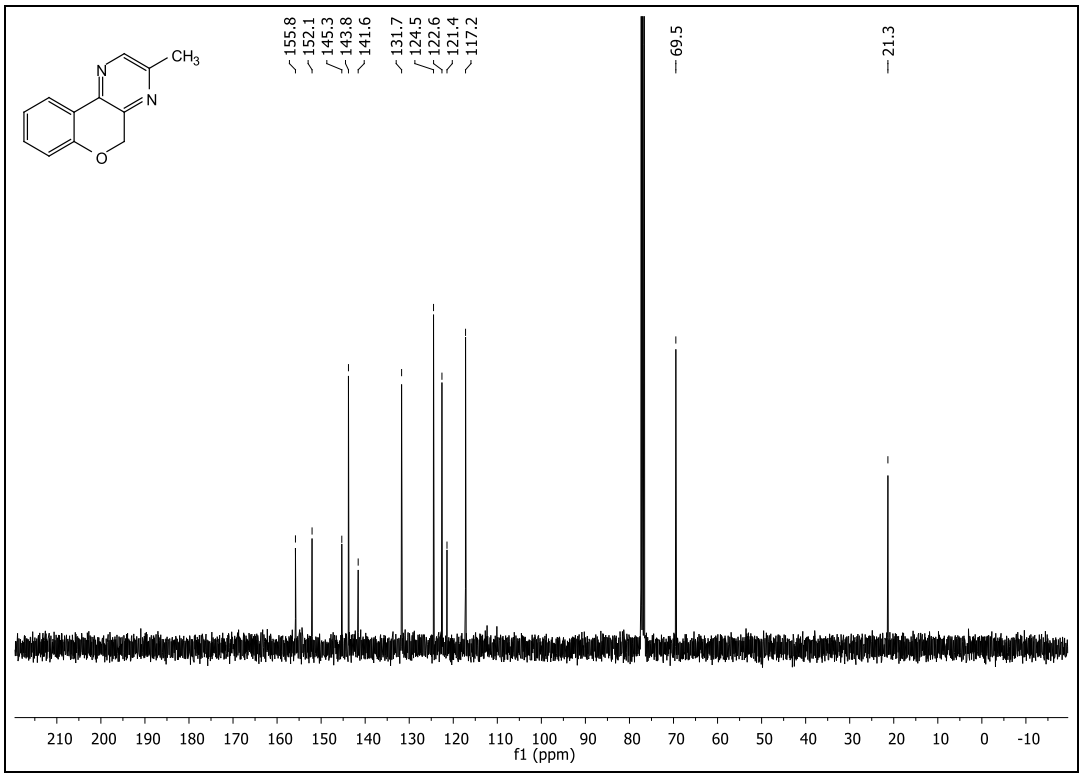

Figure 74 ^{13}C-NMR Spectrum of compound **147** in $CDCl_3$

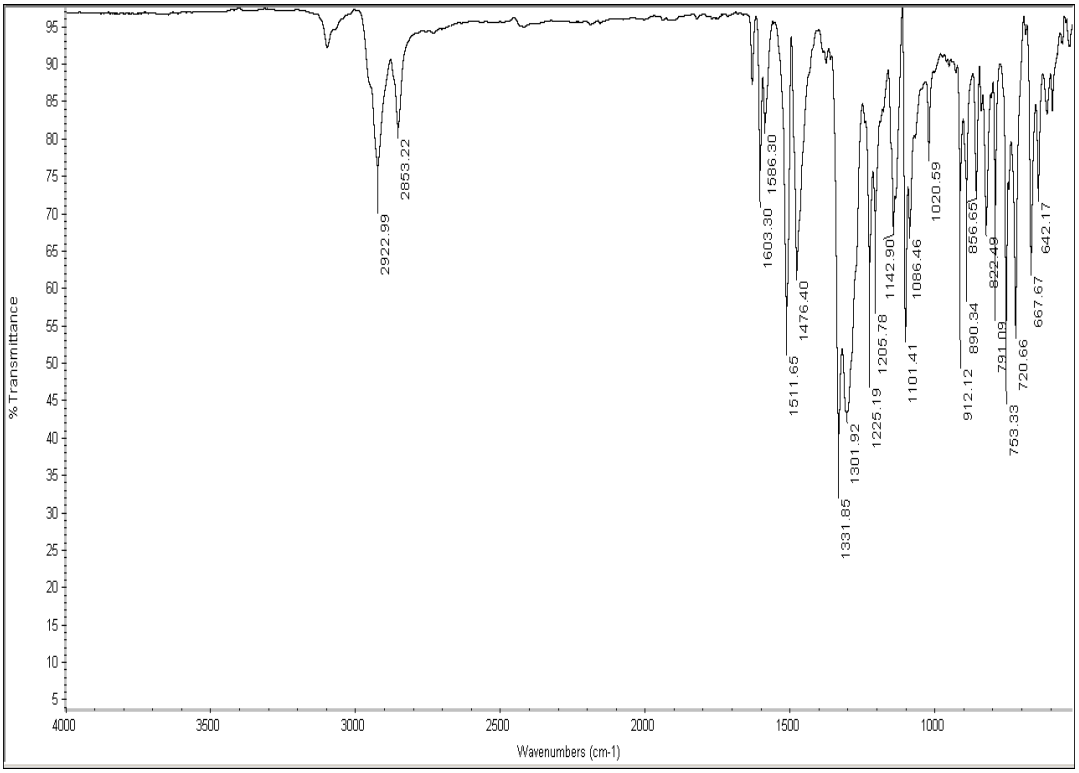

Figure 75 IR Spectrum of compound **147**

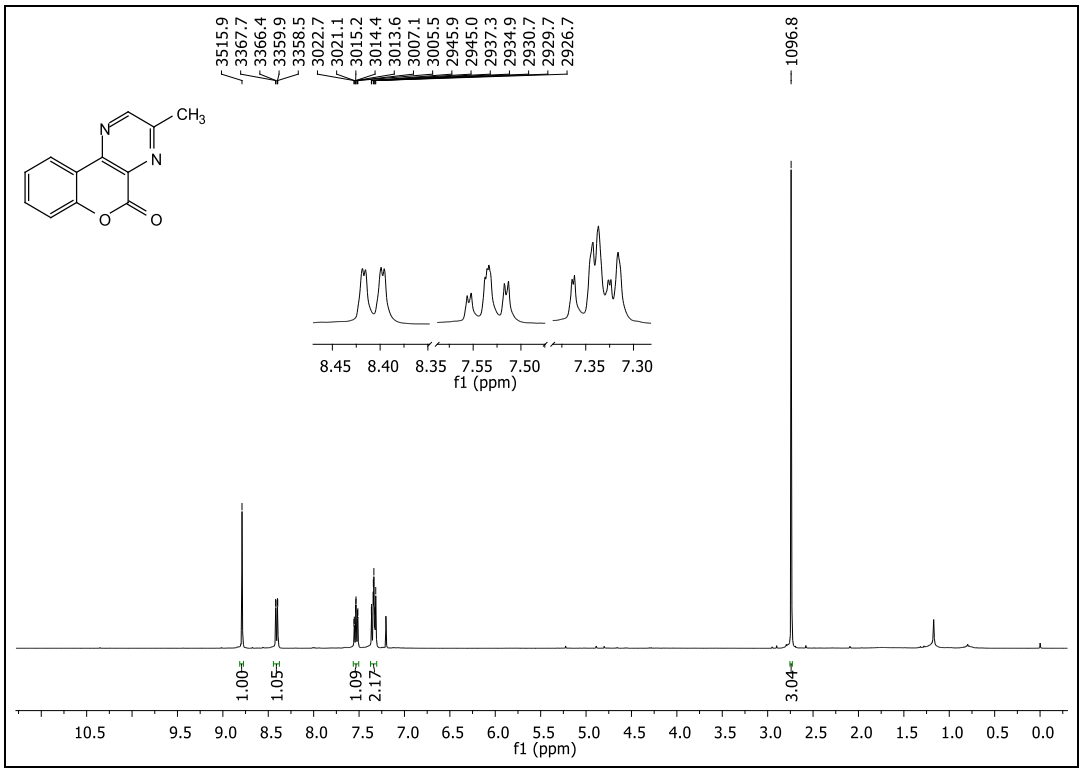

Figure 76 ^{1}H-NMR Spectrum of compound **149** in $CDCl_3$

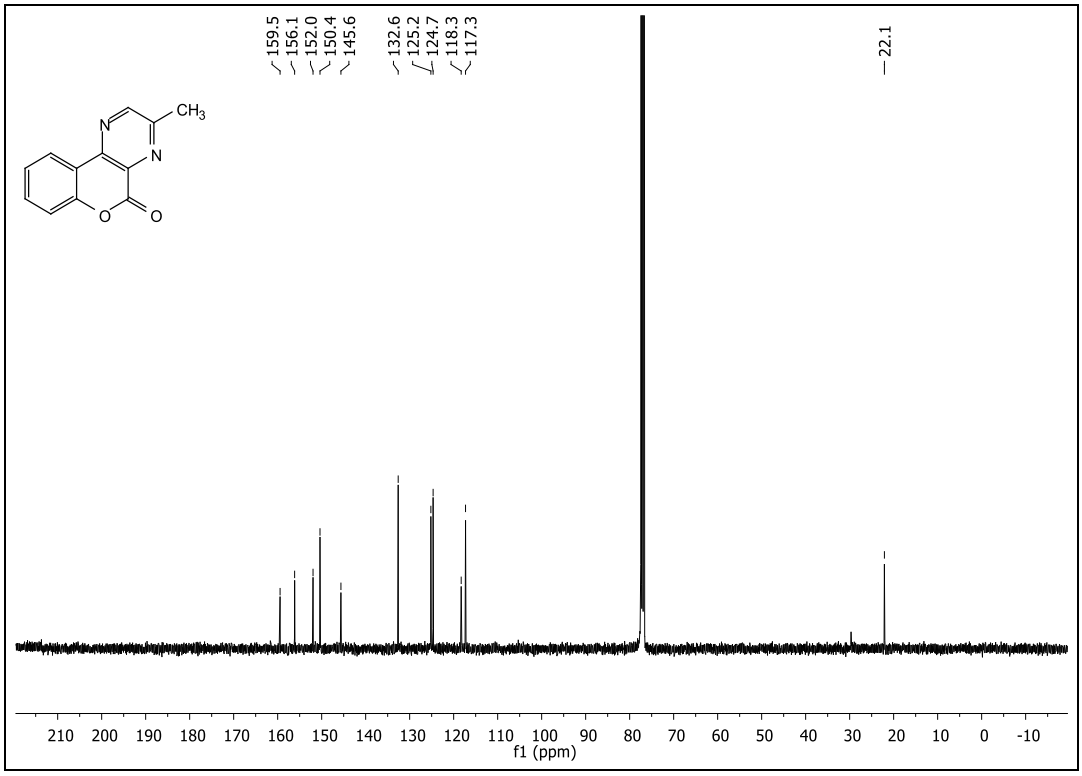

Figure 77 ^{13}C-NMR Spectrum of compound **149** in $CDCl_3$

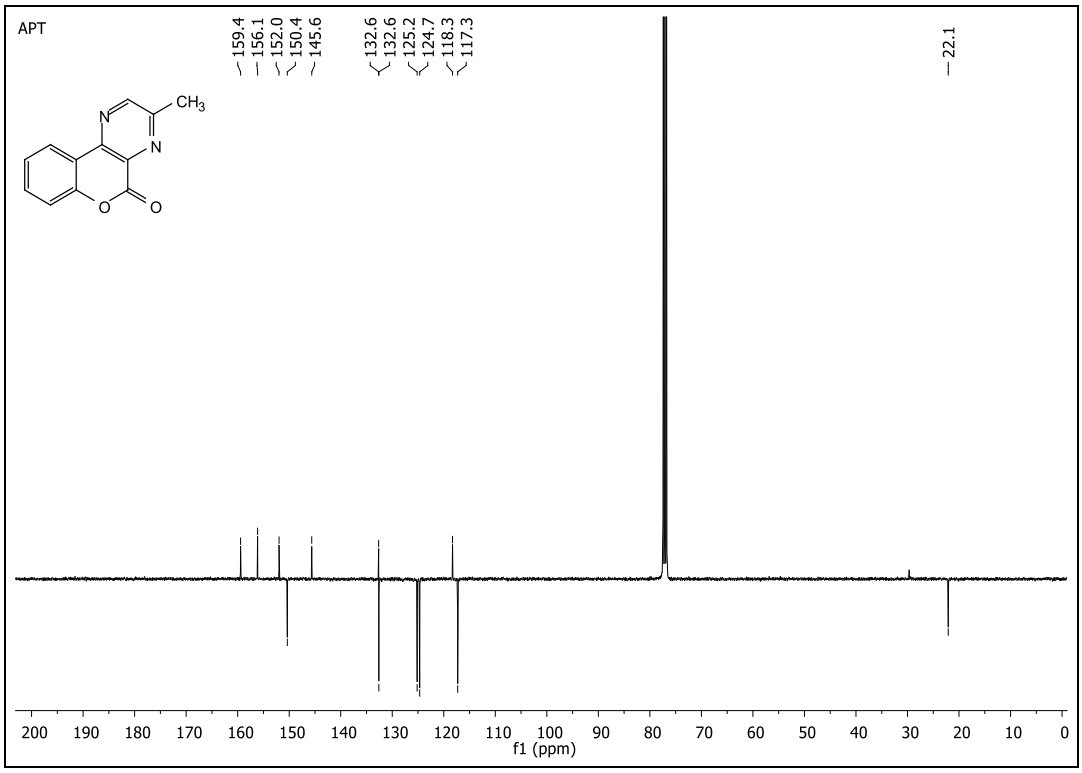

Figure 78 APT Spectrum of compound **149** in $CDCl_3$

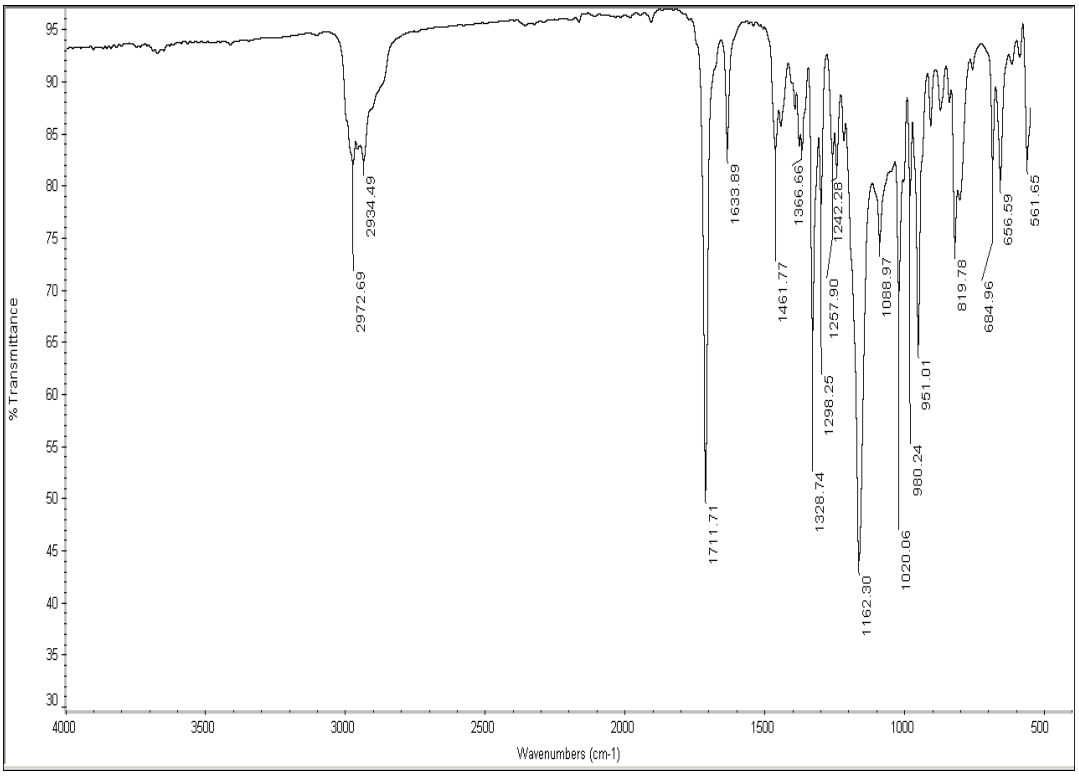

Figure 79 IR Spectrum of compound **149**

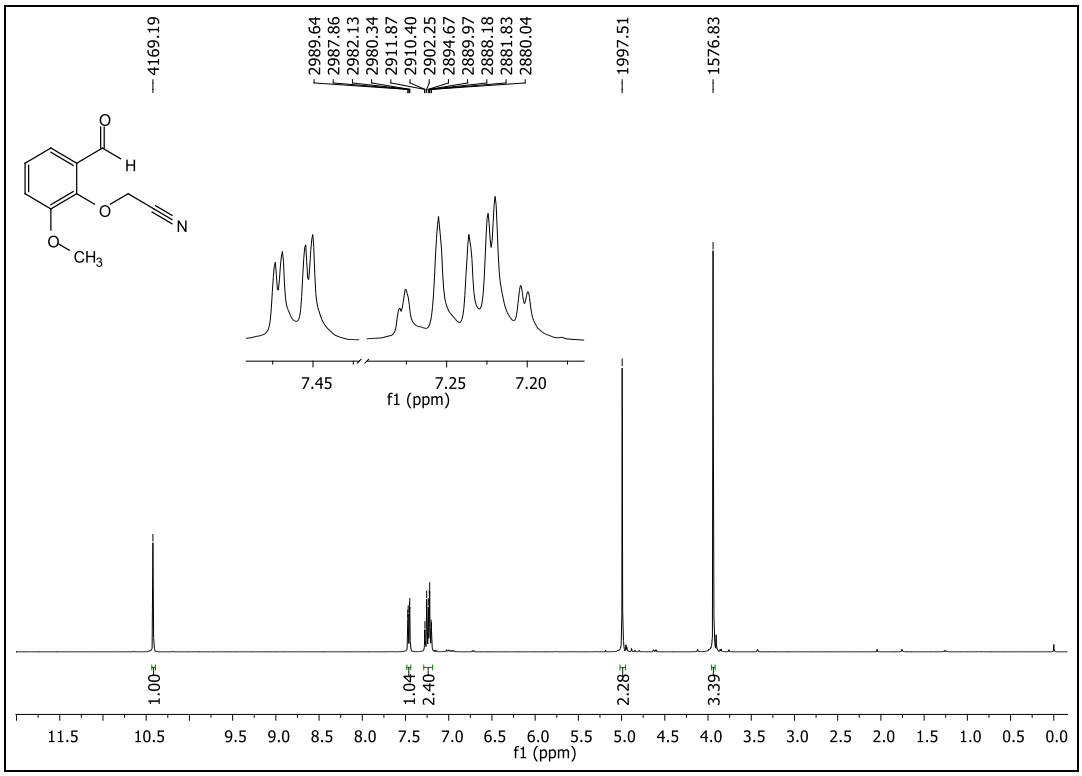

Figure 80 ^{1}H-NMR Spectrum of compound **153** in $CDCl_3$

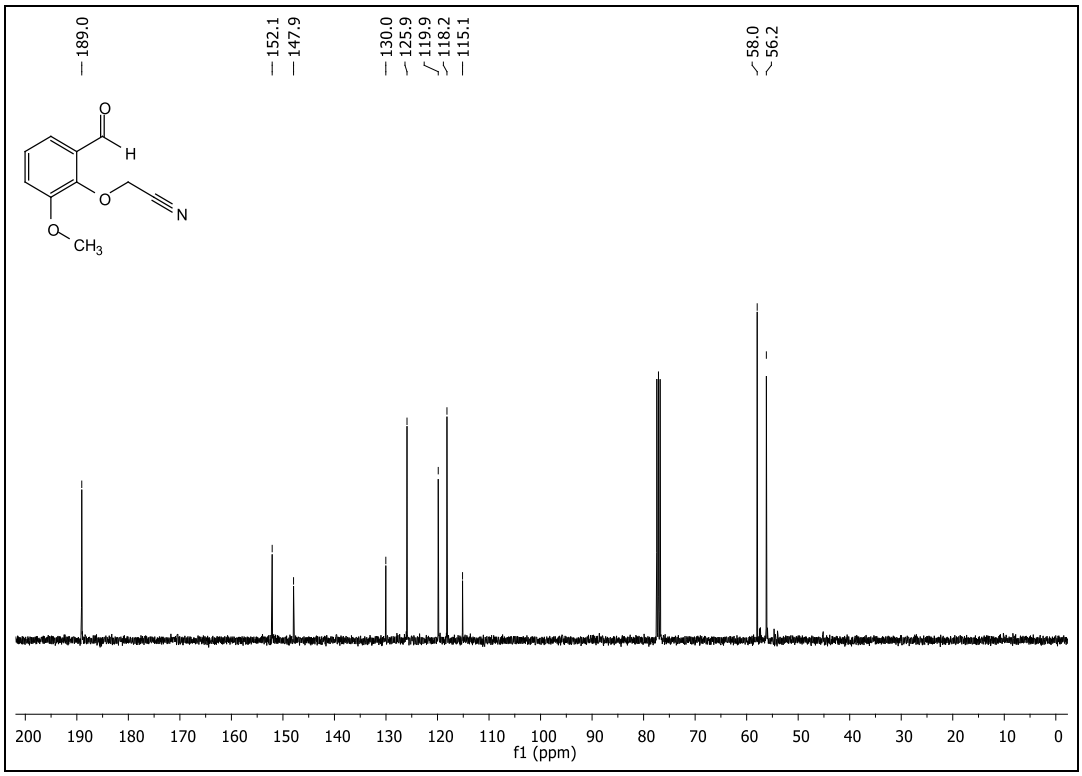

Figure 81 ^{13}C-NMR Spectrum of compound **153** in $CDCl_3$

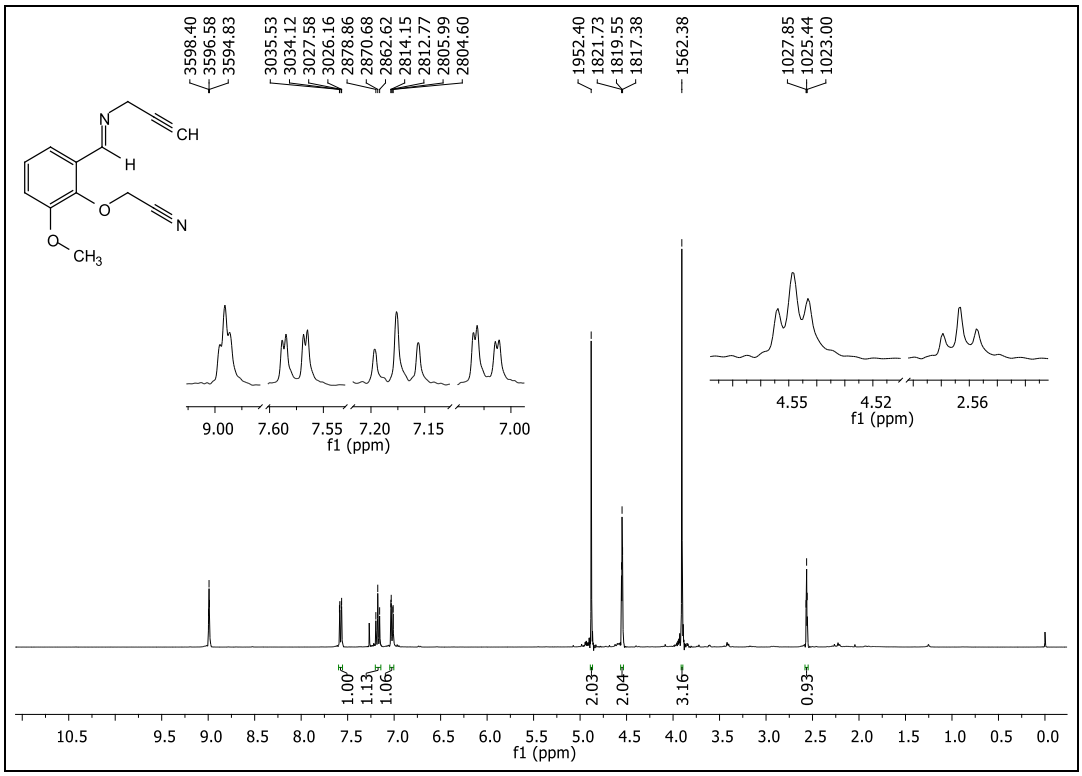

Figure 82 ^{1}H-NMR Spectrum of compound **155** in $CDCl_3$

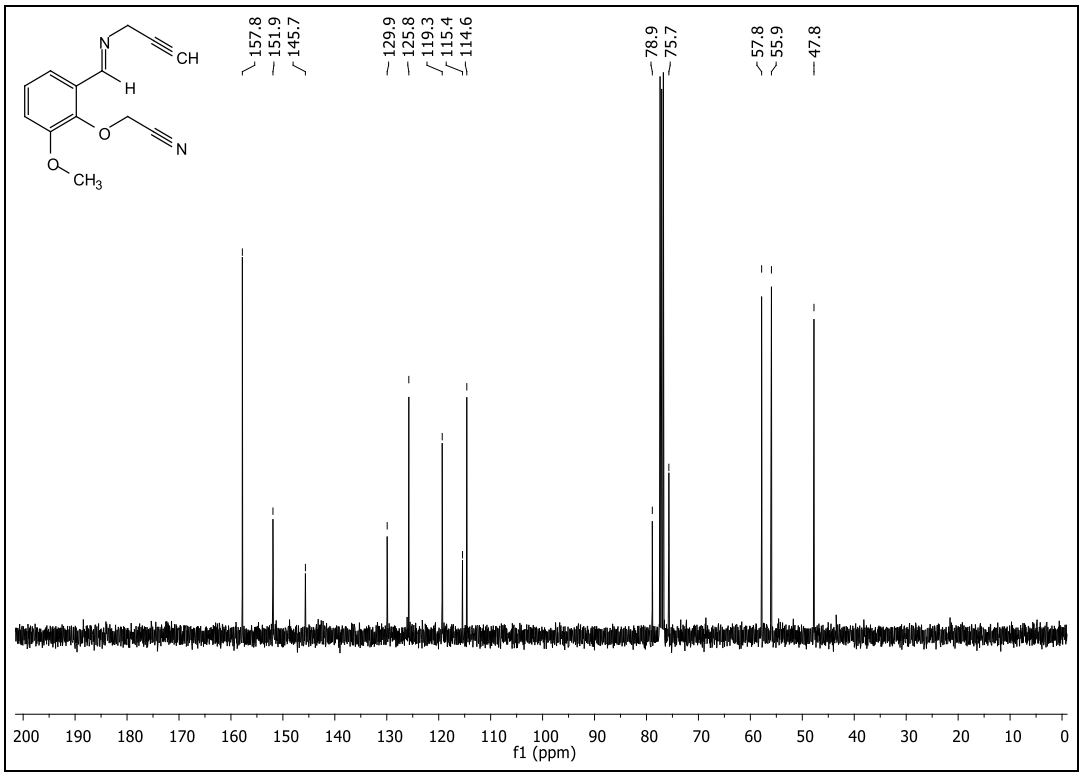

Figure 83 ^{13}C-NMR Spectrum of compound **155** in $CDCl_3$

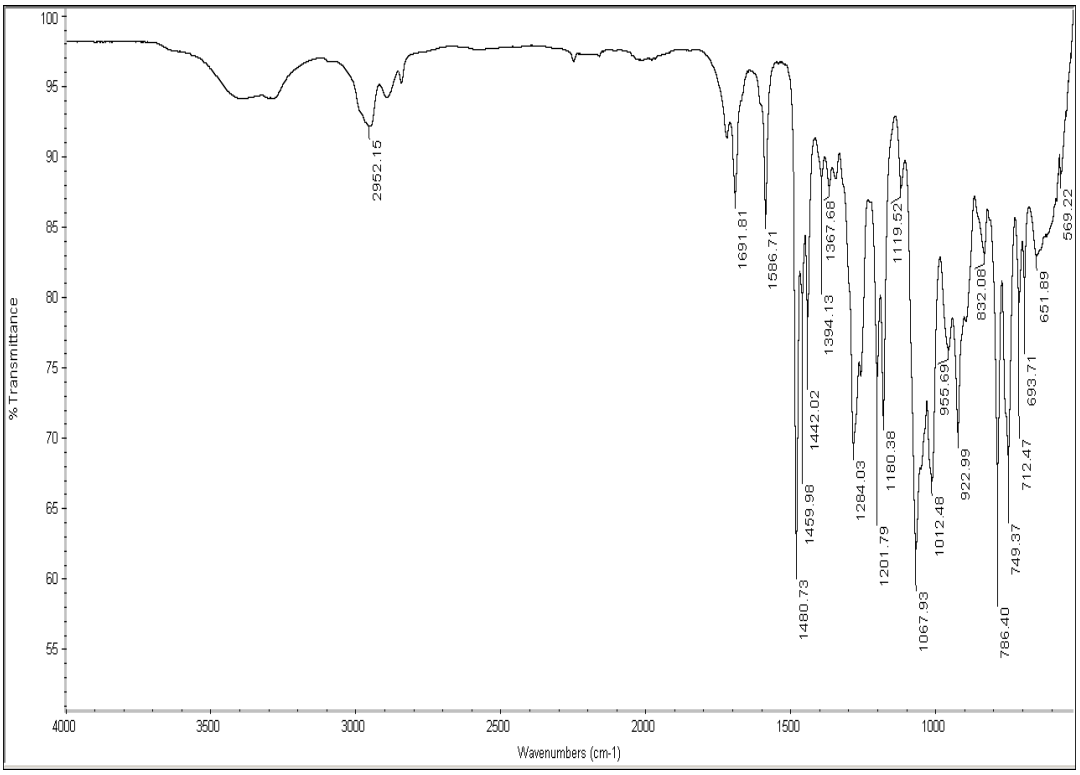

Figure 84 IR Spectrum of compound **155**

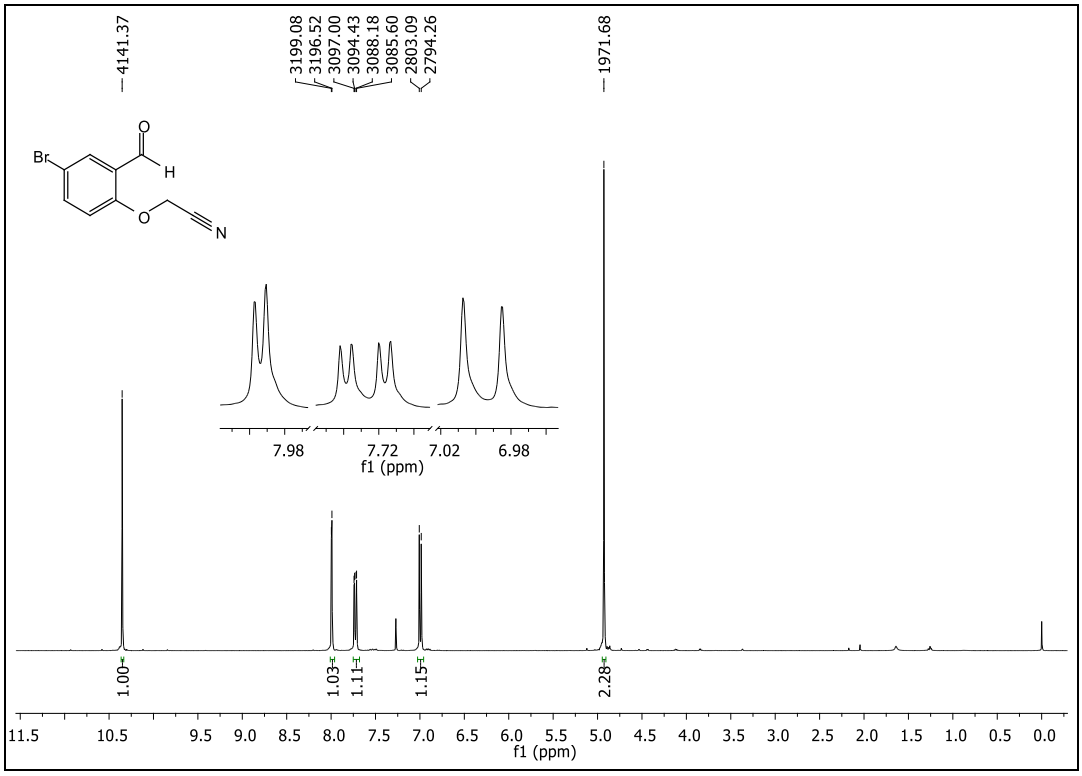

Figure 85 ^{1}H-NMR Spectrum of compound **152** in $CDCl_3$

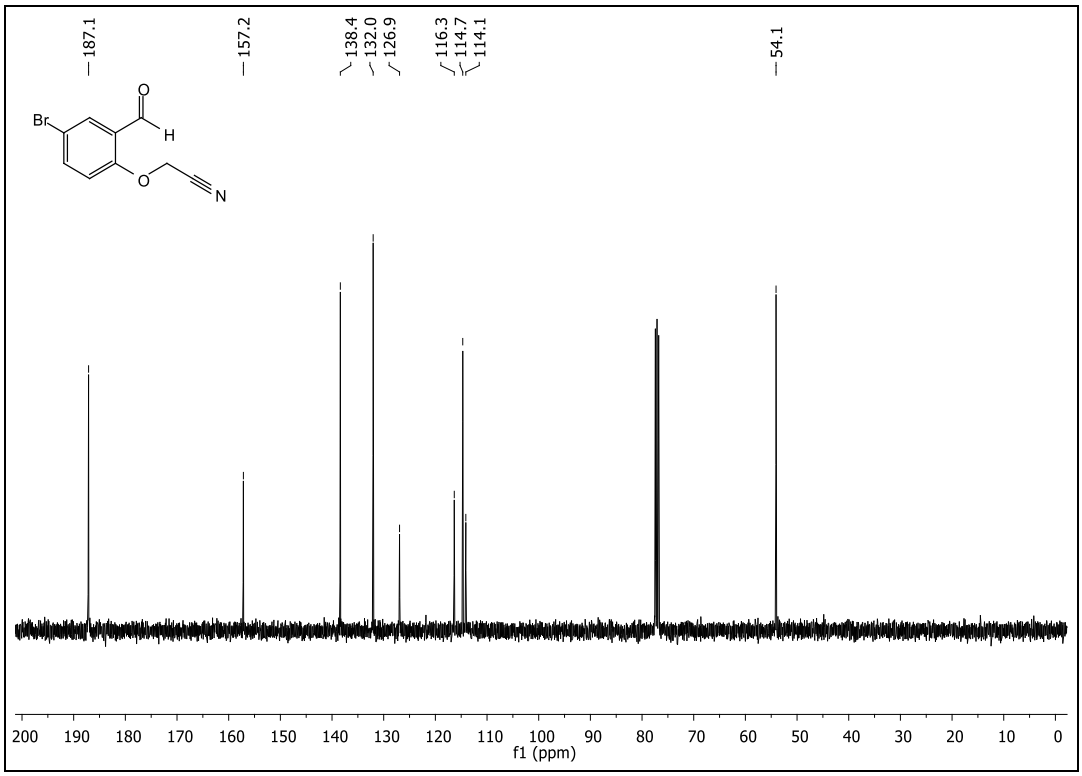

Figure 86 ^{13}C-NMR Spectrum of compound **152** in $CDCl_3$

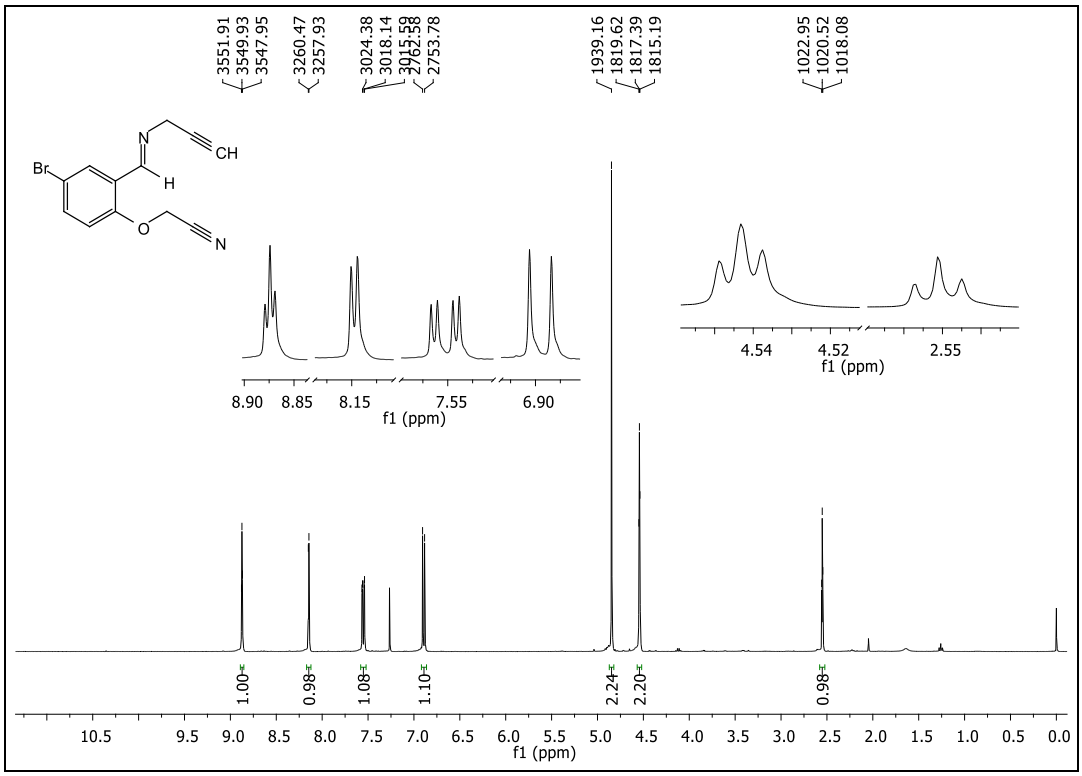

Figure 87 ^{1}H-NMR Spectrum of compound **154** in $CDCl_3$

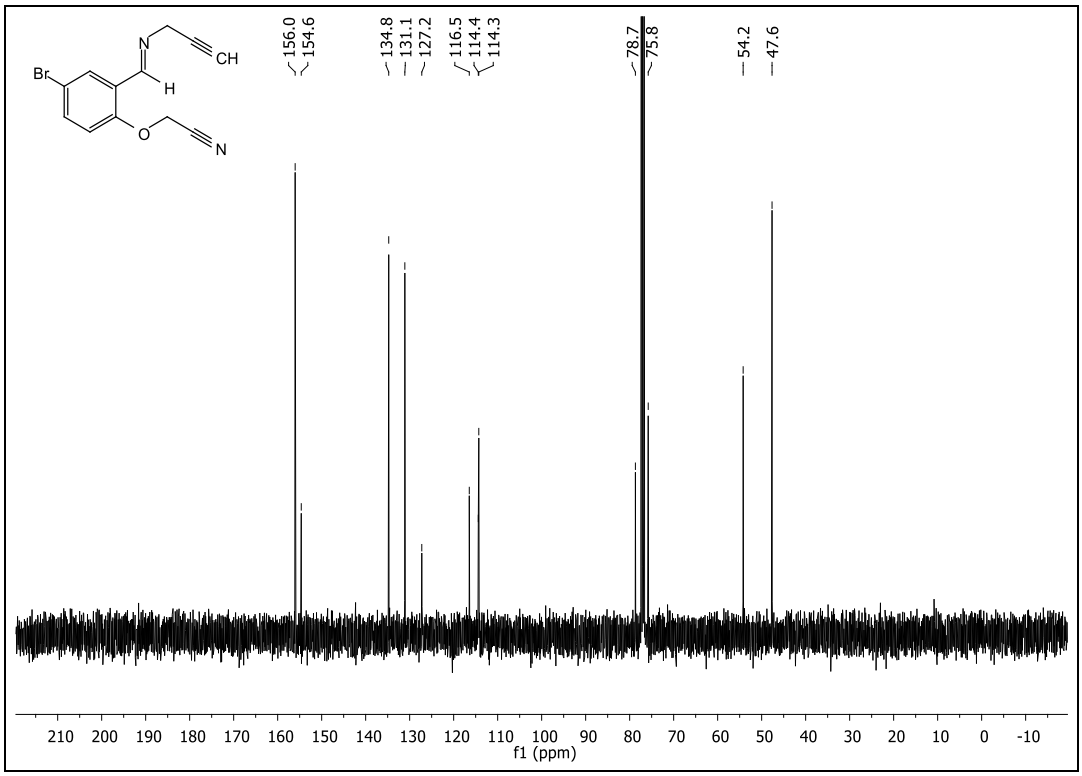

Figure 88 ^{13}C-NMR Spectrum of compound **154** in $CDCl_3$

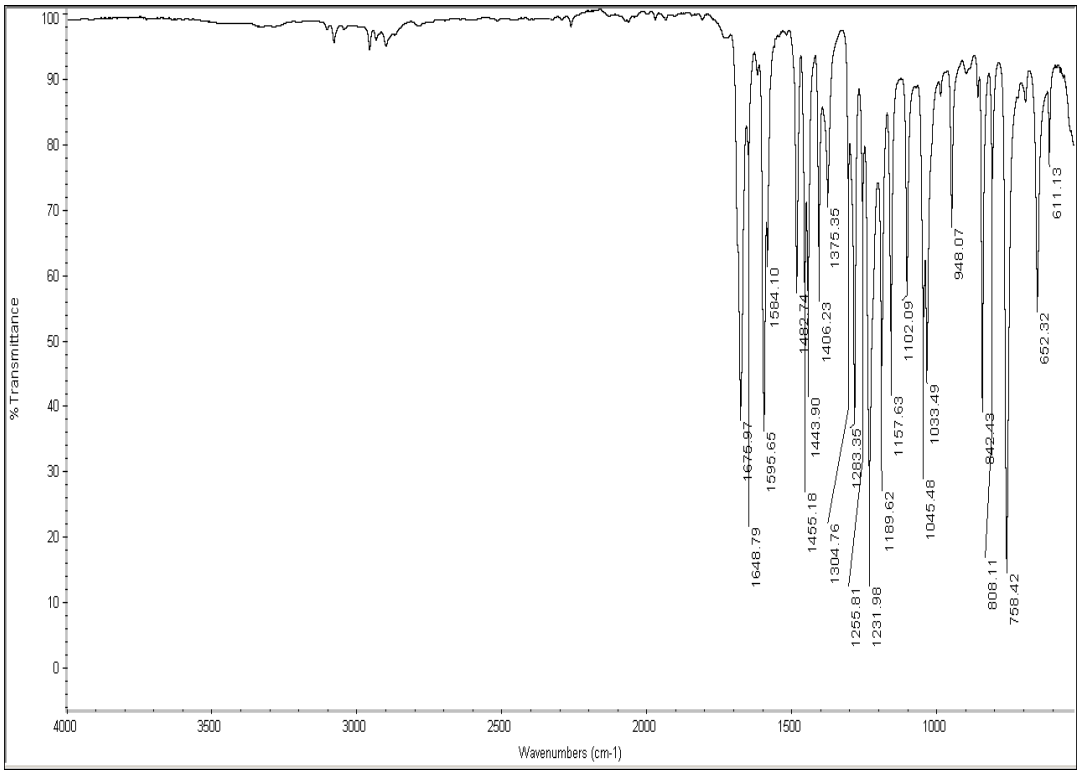

Figure 89 IR Spectrum of compound **154**