SYNTHESIS OF INDOLE-FUSED NEW HETEROCYCLES VIA ALKYNE CYCLIZATIONS

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

BY

ALİ FATİH ŞEYBEK

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

SEPTEMBER 2015

Approval of the thesis:

SYNTHESIS OF INDOLE-FUSED NEW HETEROCYCLES VIA ALKYNE CYCLIZATIONS

submitted by **ALİ FATİH ŞEYBEK** in partial fulfillment of the requirements for the degree of **Master of Sciences in Chemistry Department, Middle East Technical University** by,

Prof. Dr. Gülbin Dural Ünver _____

Dean, Graduate School of **Natural and Applied Sciences**

Prof. Dr. Cihangir Tanyeli _____

Head of Department, **Chemistry**

Prof. Dr. Metin Balcı _____

Supervisor, **Chemistry Dept., METU**

Examining Committee Members:

Prof. Dr. Metin Zora _____

Chemistry Dept., METU

Prof. Dr. Metin Balcı _____

Chemistry Dept., METU

Prof. Dr. Adnan Bulut _____

Chemistry Dept., Kırıkkale University

Assist. Prof. Dr. Salih Özçubukçu _____

Chemistry Dept., METU

Assist. Prof. Dr. Yasin Çetinkaya _____

Dept. of Food Technology, Atatürk University

Date: 01.09.2015

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

Name, Last name: Ali Fatih Şeybek

Signature :

ABSTRACT

SYNTHESIS OF INDOLE-FUSED NEW HETEROCYCLES VIA ALKYNE CYCLIZATIONS

Şeybek, Ali Fatih

M.Sc., Department of Chemistry

Supervisor: Prof. Dr. Metin Balcı

September 2015, 97 pages

It is known that many natural and synthetic structures including indole ring have important biological activities. In this thesis, synthesis of pyridine, pyrazine and pyrazinone rings condensed to indole was carried out via alkyne cyclization reactions. In the first part, oxindole was synthesized by reduction of isatin. Then, aldehyde group and chlorine atom was introduced to the C-3 and C-2 positions via Vilsmeier-Haack reaction. After that, Sonagashira coupling reaction led to functionalize C-3 position with an alkyne group. Reaction of the resulting compound with hydrazine gave γ-carboline derivative. In the second part, C-2 and C-3 positions were functionalized by ester and alkyne groups, respectively. We attempted to synthesize diazepinone derivative by using ring closure reaction with hydrazine, but the desired compound could not obtained. In the final part, C-2 position was substituted by an aldehyde group and N-1 position was substituted by a propargyl group starting from indole-2-carboxylic acid. Then, as a result of the reactions of this key compound with variety of amines, indolopyrazine and indolopyrazinone derivatives were synthesized.

Keywords: indole, γ-carboline, pyrazine, pyrazinone, alkyne cyclization

ÖZ

İNDOLE KONDENZE YENİ HETEROSİKLİK BİLEŞİKLERİN ALKİN HALKALAŞMASIYLA SENTEZİ

Şeybek, Ali Fatih
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Balcı

Eylül 2015, 97 sayfa

İndol içeren birçok doğal veya sentetik yapının önemli biyolojik aktiviteye sahip olduğu bilinmektedir. Bu çalışmada indole kondenze bazı piridin, pirazin ve pirazinon bileşiklerinin sentezi alkin halkalaşma reaksiyonları kullanılarak gerçekleştirildi. İlk olarak isatin bileşiğinden yola çıkılarak indirgeme reaksiyonu sonucu oxindol sentezlendi ve ardından Vilsmeier-Haack reaksiyonu ile C-2 pozisyonuna aldehit bağlanması sağlandı ve C-3 pozisyonuna Cl grubu bağlandı. Daha sonra Sonagashira kenetlenme reaksiyonu ile alkin fonksiyonel grubu indolün C-3 pozisyonuna bağlandı. Oluşan ürünün hidrazin ile reaksiyonu sonucu γ-karbolin türevi sentezlendi. Çalışmanın ikinci kısmında, C-2 ve C-3 pozisyonu sırasıyla ester ve alkin grupları kullanılarak fonksiyonlandırıldı. Hydrazin ile kapanma reaksiyonu denenerek diazepinone türevi sentezlenmeye çalışıldı fakat olumlu sonuçlar alınamadı. Son olarak indol-2-karboksilik asitten yola çıkılarak indolün C-2 pozisyonu aldehit grubu ile N-1 pozisyonu ise proparjil grubu ile bağlandı ve istenilen anahtar bileşik elde edildi. Daha sonra, bu bileşiğin çeşitli aminlerle reaksiyonu sonucu indole kondenze pirazin ve pirazinone bileşikleri sentezlendi.

Anahtar Kelimeler: indol, γ-karbolin, pirazin, pirazinon, alkin halkalaşması

ACKNOWLEDGEMENT

I would like to express my genuine gratitude and thanks to my supervisor Prof. Dr. Metin Balcı for his guidance, priceless advices, and worthful encouragements. It is a proud privilege to be one of his graduate students.

I wish to thank Serdal Kaya for his help and valuable advices during this research.

I would like to thank Emre Hoplamaz for his help and intimate friendship.

I would like to thank to all the members of SYNTHOR Research Group especially to Özlem, Nurettin, Başak, Selin, Sultan, Sinem, Nalan, Selbi, Yasemin, Meltem, Erol Can, Furgan, Işıl, Kübra, Tolga. Their friendship and company during whole work make everything easier and enjoyable.

I would like to thank NMR specialists Betül for the NMR experiments.

I would like to thank TÜBİTAK (Scientific and Technological Research Council of Turkey, Program no: 2211 and also Project no: TBAG 112 T360) for scholarship during my graduate study and their financial support.

Finally, I would like to thank my beautiful wife and family for their presence in my life.

For my precious wife …

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DBTCE: 1,2-dibromotetrachloroethane

DDQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DIPA: Diisopropylamine

DIPEA: *N*,*N*-Diisopropylethylamine

DMF: Dimethylformamide

HBTU: 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

NCS: N-Chlorosuccinimide

NBS: N-Bromosuccinimide

THF: Tetrahydrofuran

XPhos: 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-bipheyl

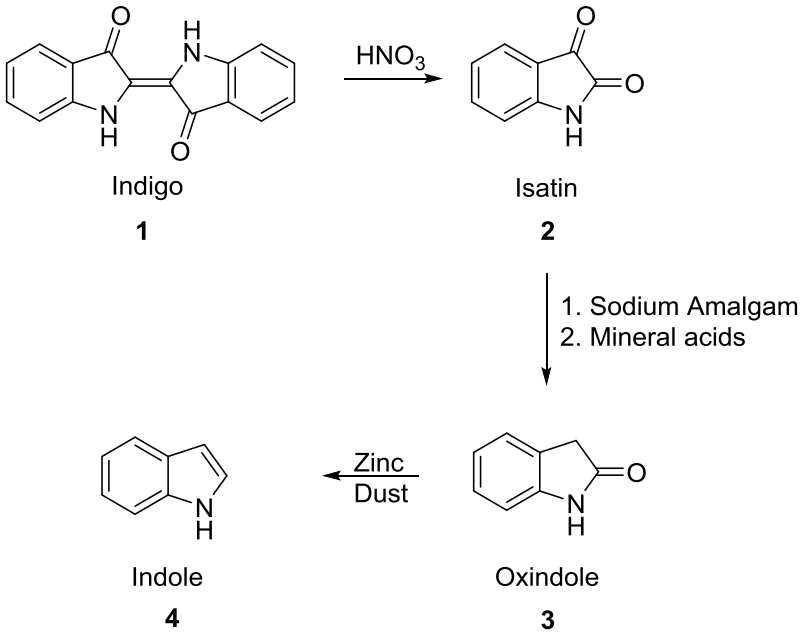
CHAPTER 1

INTRODUCTION

1.1. Indoles

1.1.1. General Properties of Indole

Indole is a bicyclic molecule containing pyrrole fused benzene skeleton, so indoles can also be called as benzo[b]pyrrole.[1] Indole (**4**) is firstly discovered by Adolf von Baeyer in 1866 and its name is coming from the dye pigment, indigo (**1**). Indigo is firstly oxidized to isatin (**2**) (with HNO_3) which is a reddish compound and following reduction causes to formation of oxindole (**3**) and using zinc dust as reducing agent leads to formation of indole (Scheme 1).[2,3]

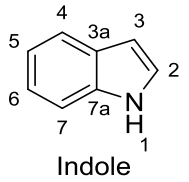


Scheme 1

This heterocyclic molecule is a colorless crystalline solid and it has fecal odor under normal conditions; however, in certain concentrations it can give nice flowery smells. Indole molecule can be soluble in hot water and its melting point and boiling point are 52 °C and 253 °C, respectively.[1,4]

1.1.2. Reactivity of Indole

Indole ring system contains 10 π electrons and obeys the Hückel rules to show proper aromaticity. One of the electron pair comes from the nitrogen atom of five membered ring. As a result of this, protonation of nitrogen of indole ring causes to disruption of aromaticity, therefore indole shows weak basic properties.[4]



Indole

4

These 10 π electrons are distributed over 9 atoms of indole ring; therefore, indole is a π-excessive heterocyclic compound which makes it more reactive than benzene ring. As seen in Table 1, the proton H-2 resonates at 7.05 ppm whereas the proton resonance of H-3 appears at 6.52 ppm. In the ^{13}C NMR spectrum of indole, the carbon atoms C-2 and C-3 resonate at 124.3 ppm and at 102.2 ppm, respectively.[1] The fact that the C-3 carbon atom resonates at higher field compared to the C-2 carbon atom indicates the increased electron density at C-3, which makes this carbon atom more reactive. However, pyrrole is more reactive at the C-2 carbon atom.

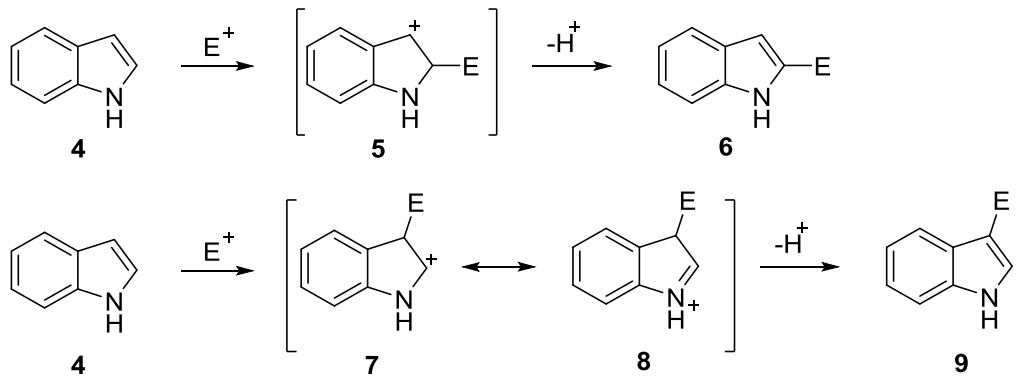
Table 1: ^{1}H and ^{13}C Shifts of Indole

	N-1	C-2	C-3	C-4	C-5	C-6	C-7	C-3a	C-7a
H shifts	7.81	7.05	6.52	7.64	7.12	7.18	7.27	X	X
C shifts	X	124.3	102.2	120.6	121.9	119.7	111.1	127.7	135.7

1.1.2.1. Reactivity of C-3 Position

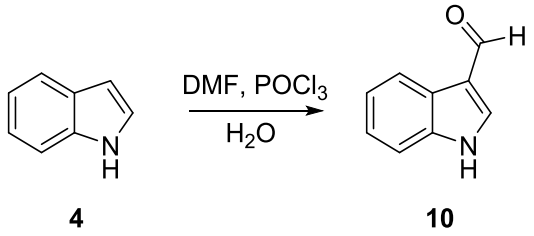
As discussed above, the C-3 carbon atom of indole has more tendency to react with electrophiles compared to other positions. As a result of this situation, there are many literature examples about the selective reactivity of indole at C-3 position. In certain cases, there is even no need to use catalyst or harsh conditions for the reaction of this position with an electrophile.

As seen in Scheme 2, the higher reactivity of C-3 compared to C-2 is arising from the resonance structures. After an electrophilic attack on the C-3 carbon atom of indole (**4**), the intermediate **7** can be stabilized by the lone pair on the nitrogen atom without disrupting aromaticity of benzene ring. However, in case of electrophilic attack on C-2 position, it is not possible.[4]



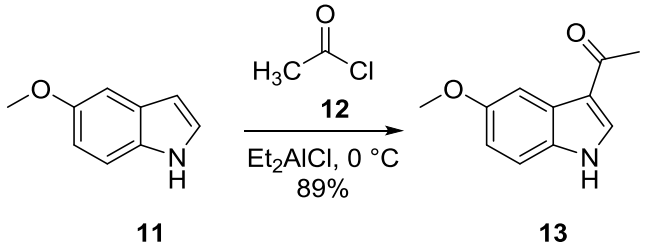
Scheme 2

To gain functionality, attaching an aldehyde to indole ring can be accomplished by using Vilsmeier-Haack reaction.[5] During the course of this reaction, firstly, iminium ion will be formed due to reaction of DMF and $POCl_3$. Then, reactive C-3 part of indole will react with this ion and aldehyde group will selectively be bonded to the C-3 position to give **10** (Scheme 3).



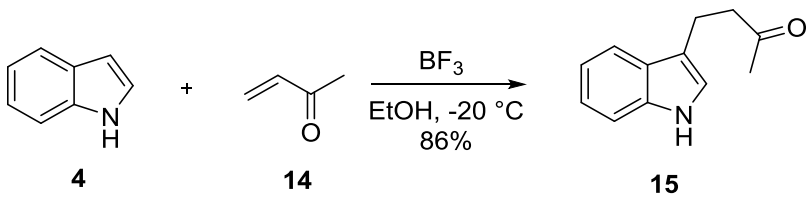
Scheme 3

Another useful reaction to gain functionality at the C-3 position is Friedel-Craft acylation. Acetyl chloride **12** can be reacted with indole derivative **11** in the presence of dialkylaluminum chloride as Lewis acid to form **13**.[6] Acidic conditions can cause dimerization[4] of indole derivatives, therefore liberated HCl during the progress of reaction should be quenched by using excess Lewis acid (Scheme 4).



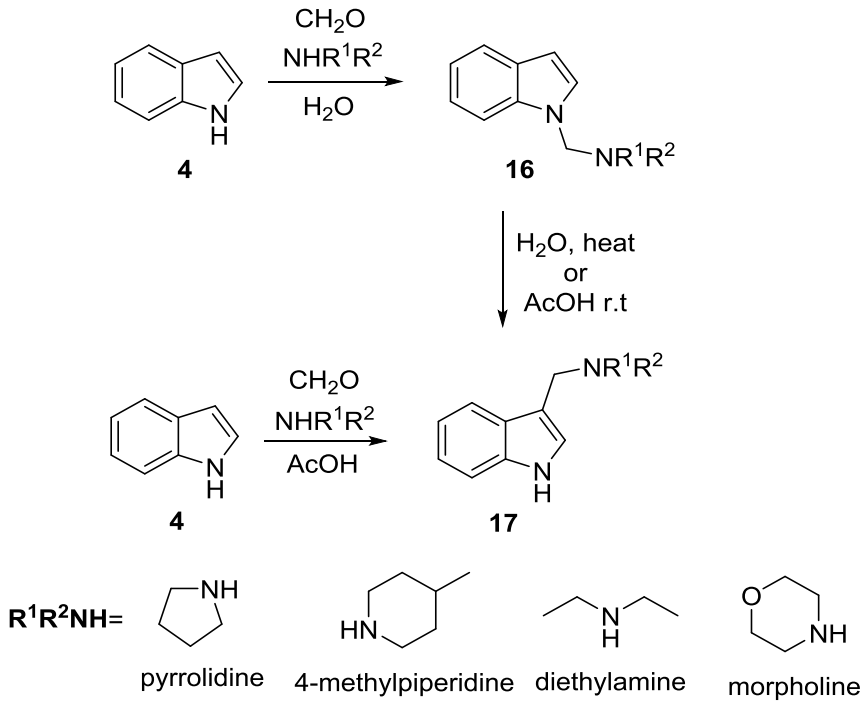
Scheme 4

Michael addition reaction is another applicable way to substitute indole ring system. Usage of α,β- unsaturated ketone **14** in the presence of a Lewis acid is a good way to form 3-substituted indole derivative **15**. After Lewis acid coordination to electron deficient α-β unsaturated ketones, electron rich C-3 will attack the double bond at the β-position to complete the reaction (Scheme 5).[7]



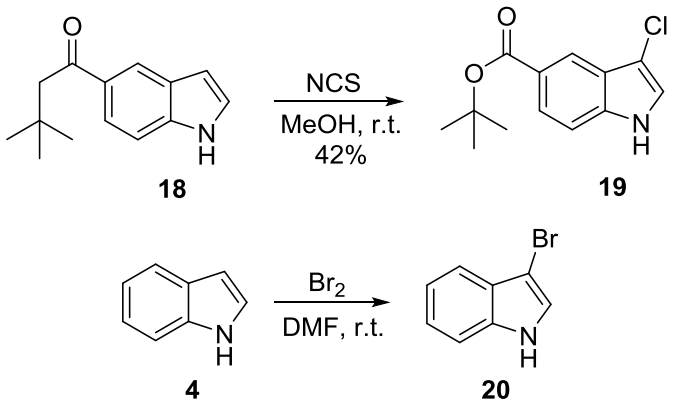
Scheme 5

Mannich reaction can also be applied to indole ring system to synthesize gramines **17** which are quite important precursor to get biologically active indole derivatives. Katritzky *et al.*[8] emphasized the balance between C-3- and *N*-substituted indoles caused by Mannich reaction. At low temperatures and under aqueous conditions kinetically controlled *N*-substituted indole **16** was formed, but treatment with acetic acid or running the reaction at higher temperatures resulted in the formation of thermodynamically more favored gramines (3-substituted indole). Also, further Mannich reaction of gramines leads to formation of 1,3-disubstituted indoles (Scheme 6).[9]



Scheme 6

Halogenation reaction of indoles also causes substitution selectively at C-3 position and makes this position functional for further possible reactions. While NCS[10] can be used to synthesize 3-chlorinated indole derivative **19**, bromine[11] can be used to form 3-brominated indole **20** (Scheme 7).

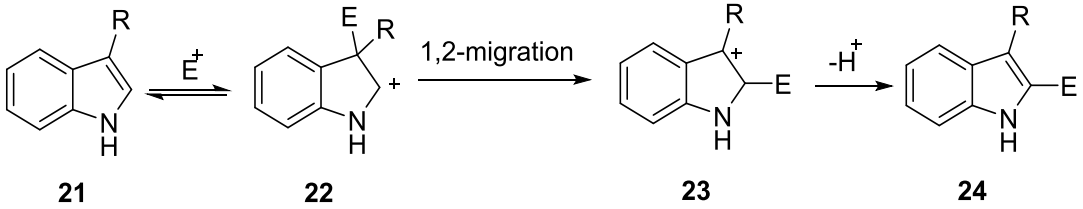


Scheme 7

1.1.2.2. Reactivity of C-2 Position

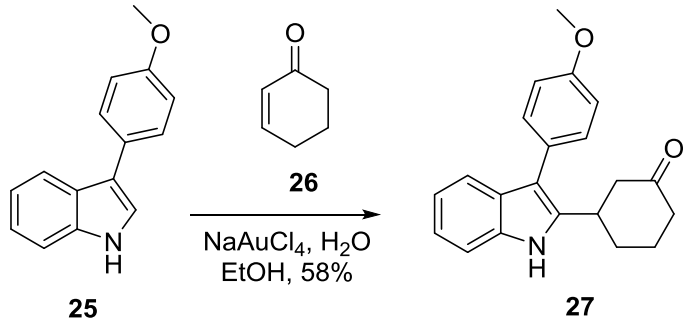
It is known that C-2 position is next most reactive part of indole. However, C-3 position should be substituted before trying to attach a group to C-2 position. Due to higher reactivity of C-3 than C-2, there are comparatively less example for the electrophilic attack on the C-2 position.

In fact, Jackson and Smith showed that even during the reaction of 3-substituted indoles, an electrophile can attack on the C-3 position. Then, two attached groups on C-3 will compete to migrate to C-2 position. The group with higher electron density will migrate from C-3 to C-2 position (Scheme 8).[12]



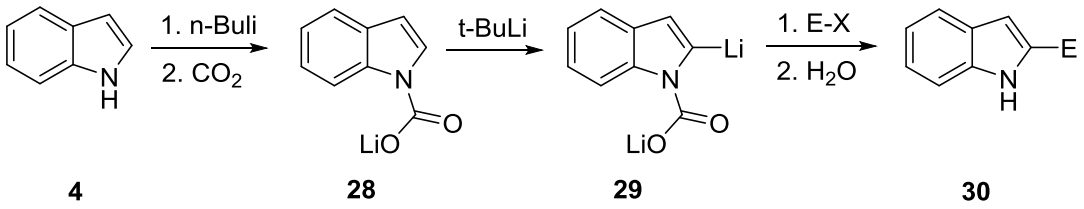
Scheme 8

When 3-substituted indole **25** was reacted with α-β unsaturated ketone **26**, the formation of Michael addition product was formed in low yield. However, gold-catalyzed reaction formed the expected addition product **27**[13] in a yield of 58% (Scheme 9).



Scheme 9

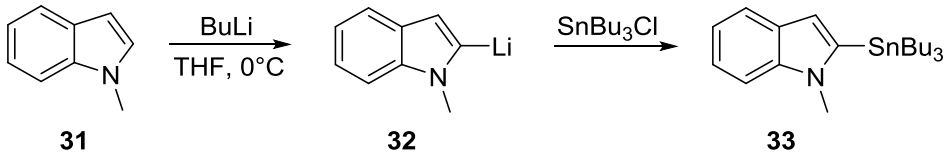
Bergmann developed an alternative synthetic methodology to substitute the C-2 position of indole without requiring any C-3 substitution. The H-2 proton of indole is the next most acidic proton after N-H proton. Treatment of indole with *n*-BuLi followed by CO_2 reaction forms *N*-carboxylate **28**. Reaction of this salt with a powerful base such as *t*-BuLi can lead to removal of H-2 and lithation of that position. Coordination of carboxylate anion with Li bonded C-2 position will stabilize the intermediate **29**. After lithation of C-2 position, C_2Cl_6 or DBTCE (1,2-dibromotetrachloroethane) can be used for chlorination and bromination reaction as an electrophile. Deprotection will lead to the formation of the halogenated product **30** (Scheme 10).[14]



E-X : C_2Cl_6 (chlorination) , DBTCE (bromination)

Scheme 10

Previous reaction showed that a coordinating group attached to N-1 position is required to substitute C-2 position. Following example illustrates that attachment of non-coordinating groups to N-1 position also has effects on C-2 substitution of indole.



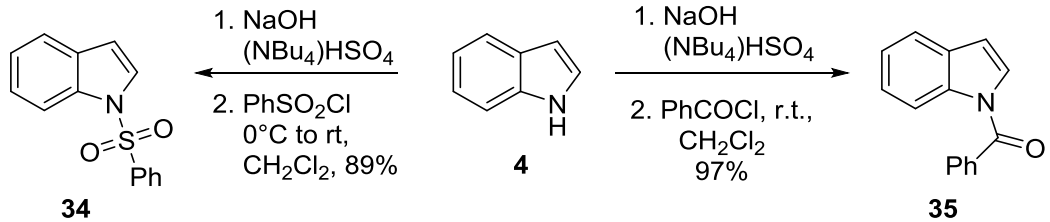
Scheme 11

While crowded non-coordinating groups attached to N-1 atom cause to lithation of C-3 position, C-2 lithated product **32** can be produced by attaching non-bulky alkyl groups to N-1 position. After lithation of C-2 position via treating with n-BuLi, desired group can be bonded to C-2 position to give **33** (Scheme 11).[15]

1.1.2.3. Reactivity of N-1 position

Indole shows weak base properties because using electron pair on nitrogen disrupts indole molecule aromaticity so that direct reaction of indoles at N-1 position with an electrophile is not likely. Besides, indole is a weak acid and its p*K*a value is 16.7 in water[16] so strong bases can be used to remove the N-H proton of indole. The indolyl anion is open to attack of electrophiles. The electronic nature of the substituents attached to N-atom can affect the electron density on the five-membered ring so that the reactivity of indole can be manipulated.

Acylation[17] and sulfonation[18] reactions of indole at N-1 position is very useful and these compounds can be used for multistep reactions. These groups not only change the reactivity of indole but also serve to carry out selective reactions. In the presence of a phase transfer catalyst, NaOH in aqueous phase can be used as a base to abstract N-H proton. Reaction of the intermediate formed with suitable electrophiles can form the compounds **34** and **35** (Scheme 12).

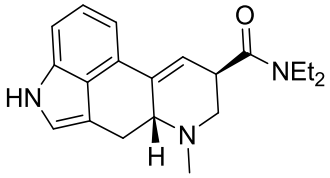


Scheme 12

1.1.3. Biological Activity of Indole

Indoles and its derivatives are widely studied by researchers because of their high potential of biological activities. Indole is the most widely used heterocyclic compound which shows therapeutic activity.[19,20] It is well known that the heterocyclic part of indole is responsible for activities in most cases.

Lysergic acid diethylamide (LSD) (**36**) is a well-known indole derivative. Even it has many beneficial therapeutic usages; it generally has reputation about narcotic properties. LSD can cause to fast chance in mood, change in time perception, illusion and hallucinations (Scheme 13).[21]



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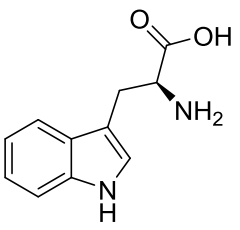
Scheme 13

Another famous and vital indole derivative is tryptophan which is required for human life. Tryptophan (**37**) is one of the 22 essential aminoacids and it cannot be synthesized by human organism.[22] Besides this vital property of tryptophan, it is biochemical precursor of serotonin (**38**) and melatonin (**39**). Serotonin[23] is neurotransmitter and plays an important role for brain functionality, whereas melatonin[24] is responsible for biological rhythm of body (Scheme 14).



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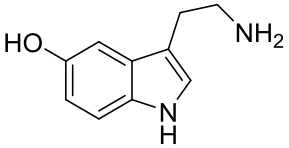

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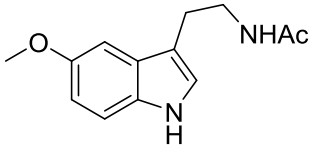
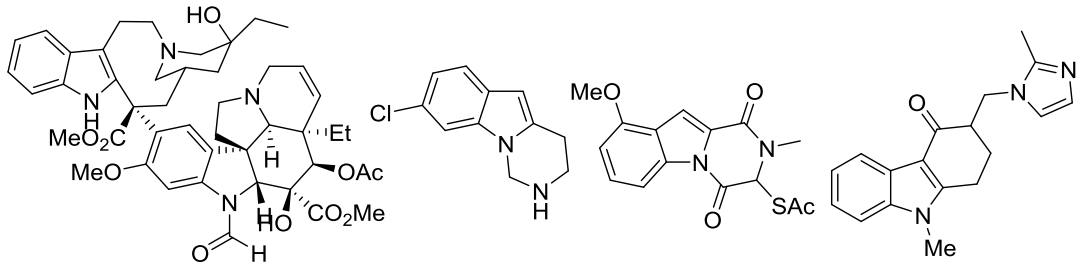


39

Scheme 14

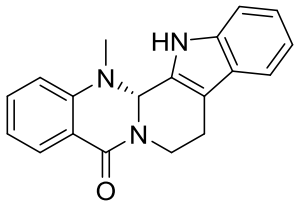
Vincristine (**40**) is a drug which has antitumor activity against certain kinds of cancers such as leukemia and lymphoma.[25] Another one is compound **41** which has pyrazino indole skeleton and used widely for the treatment of obesity and central nervous system disorders.[26] The compound **42** is also a pyrazino indole derivative with two carbonyls and it is used for effective antimicrobial activity.[27] Ondensetron (**43**) is also a marketable drug used for the treatment of side effects caused by cancer therapies (Scheme 15).[28]



40 **41** **42** **43**

Scheme 15

Besides these biologically active compounds, many alkaloids includes indole ring and traditionally used for treatments of diseases. Evodiamine (**44**) is one of the popular alkaloids derived from herbs to cure headaches, different muscular pains and diarrhea (Scheme 16).[29]



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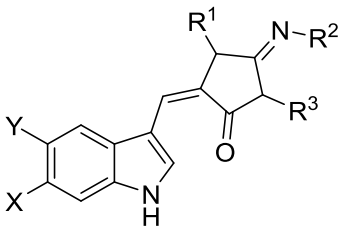
Scheme 16

In the literature, it is not hard to find marine products containing indole skeleton which shows pharmaceutical activities. Aplysinopsins (**45**) can be derived from tryptophan and it is natural marine product isolated from sponges. It shows antitumor activity and also is used against microbial diseases (Scheme 17).[30]



X=Y= H,Br
R^1= H, CH_3
R^2= H, CH_3, CH_2CH_3
R^3= H, CH_3

45

Scheme 17

1.2. Pyrazine and Pyrazinone

Pyrazine (**46**) is a six membered diazine ring showing aromatic properties but it has lower resonance energy than benzene (Scheme 18).

Pyrazine **46**

Pyrazinone **47**

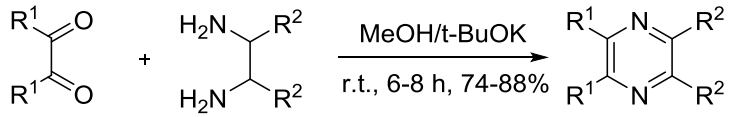
Scheme 18

Due to electronegative property of nitrogen atoms on ring, pyrazine is an electron deficient system and it means that sp^2 hybridized carbons are more positively charged compared to benzene. Melting point of pyrazine is 57 °C and boiling point is 116 °C and its pKa value is about 26.[1,4] One of the most characteristic properties of these molecules is that even in very low concentrations they are responsible for odor or flavor of foods. Pyrazinone (**47**), an oxidation product of pyrazine, exists in many biologically active compounds.

1.2.1. Synthesis of Pyrazine and Pyrazinone

If retrosynthetic pathway is thought for pyrazine synthesis, the first direct way is the reaction of 1,2-diketones **48** with 1,2-diamines **49** and then following oxidation reaction. Symmetrical 1,2-diketones and symmetrical 1,2-diamines undergo

condensation reaction and forming intermediate which can be oxidized easily in MeOH/t-BuOK solution to form **50**[31] (Scheme 19).

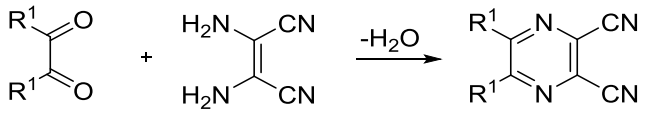


48 **49** **50**

R^1= alkyl, aryl, furyl, hydrogen
R^2= H, CH_3, CN

Scheme 19

To synthesize pyrazines in one step reaction, 1,2-diketones should be trapped with 1,2-diaminoalkenes, but 1,2-diaminoalkenes are very rare so diaminomaleonitrile **52** is very convenient for this purpose to obtain cyano substituted pyrazine derivatives **53** without requiring any oxidation step (Scheme 20).[32]

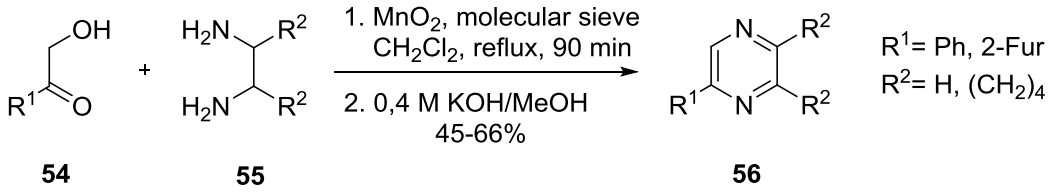


51 **52** **53**

R= H, CH_3, C_6H_5

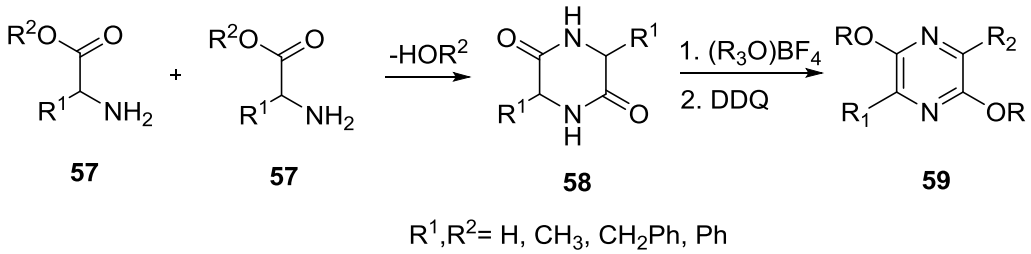
Scheme 20

It is known that 1,2-dicarbonyls are highly reactive and it is hard to isolate these products. However, 1,2-dicarbonyls can be synthesized in situ by oxidation of α-hydroxy ketones **54** and then it can be trapped with 1,2-diamines. MnO_2 is used as oxidizing agent for in situ oxidation of α-hydroxy ketones. Then, reaction of α-hydroxy ketones with 1,2-diamines in the presence of KOH in MeOH yields pyrazine derivative **56** (Scheme 21).[33]



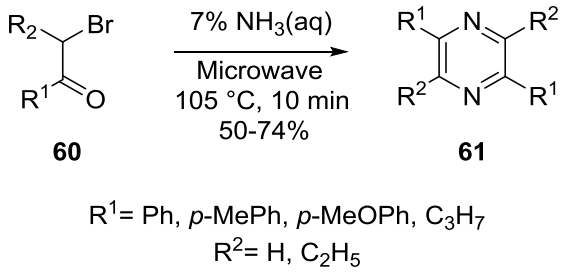
Scheme 21

α-Aminoacids or esters are also starting materials to produce pyrazine derivatives via self-condensation reaction. 2,5-Dioxopiperazines **58** formed by self-condensation of **57** can be easily converted to alkoxy substituted pyrazine derivatives **59**[34] by the reaction with trialkyloxonium salts which are alkylating agents, followed by oxidation by DDQ (Scheme 22).



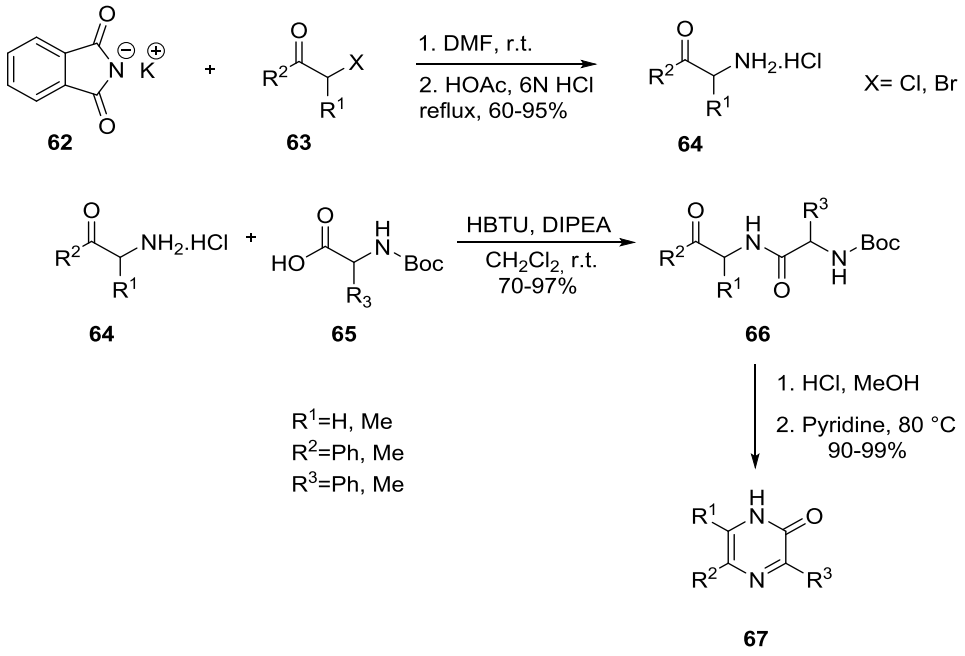
Scheme 22

α-Bromo ketones **60** reacts with aqueous NH_3 solution under microwave radiation in very short times to yield pyrazine derivatives **61**[35] (Scheme 23).



Scheme 23

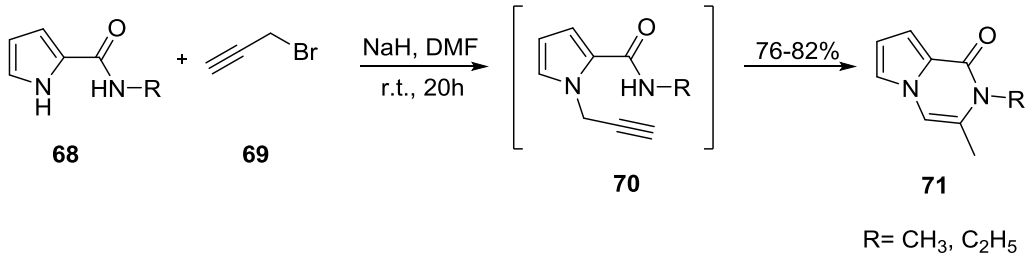
Following pathway is another example for the synthesis of pyrazinone derivatives by starting from α-bromo or α-chloro ketones **63**.



Scheme 24

After transformation of these compounds to α-amino ketones **64**, it is reacted with amino acid **65** to form **66**. Deprotection of Boc group followed by cyclization reaction leads to formation of pyrazinone derivative **67** (Scheme 24).[36]

In case of synthesis of pyrazinone, amide substituted pyrroles **68** can be used as starting compound. Attaching of a propargyl group to nitrogen atom causes to immediate cyclization to produce pyrrolopyrazinone derivatives **71** in quite good yields (Scheme 25).[37]

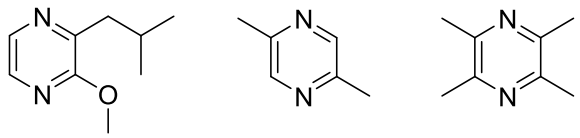


Scheme 25

1.2.2. Biological Activities of Pyrazine and Pyrazinone

Pyrazine and pyrazinone derivatives show variety of pharmaceutical effects on human body and also some simple pyrazine derivatives give taste and odor to foods. In addition, some small creatures biosynthesize pyrazinone derivatives to attack human beings by using these molecules as weapons.

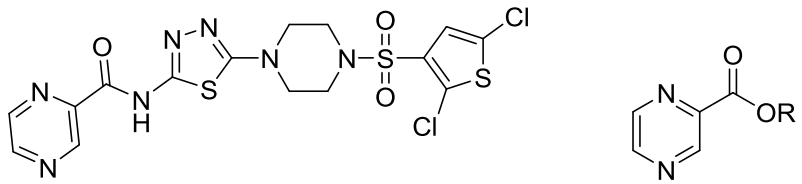
First, the well-known property of simple pyrazines is about their responsibility in flavor and aroma in foods or drinks. Generally, alkyl pyrazines shows this behavior. **72** is a famous example which is responsible for the taste of wine.[38] Also, **73** gives flavor to potato chips and **74** is the source of the smell of soybean and these are caused from very low concentration of pyrazine derivatives (Scheme 26).[39]



72 **73** **74**

Scheme 26

Besides these natural products, some synthetic pyrazine derivatives can be used as medicine. **75** is a synthetic molecule and it is known that it shows anticonvulsant activity on human organism.[40] Also ester substituted pyrazine derivative **76** which exhibit antituberculosis activity is another example for the medicinal importance of pyrazines (Scheme 27).[41]

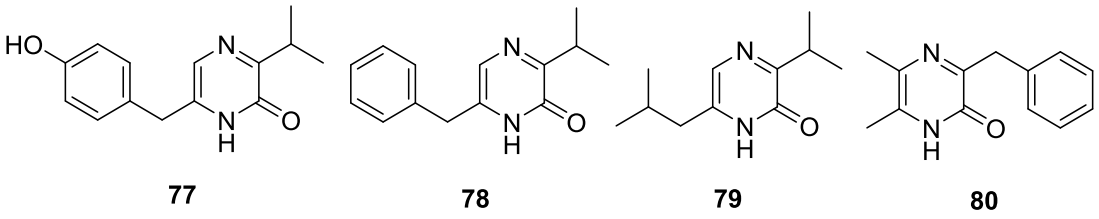


75 **76**

Scheme 27

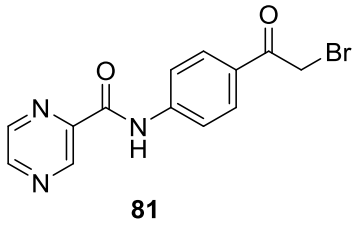
Some natural products which include pyrazinone skeleton can be synthesized by skin microbes. It has been shown that these creatures produce pyrazinone derivatives

during the infection process. *Staphylococcus aureus* which is responsible for thousands of deaths biosynthesizes three pyrazinone derivatives; tryvalin (**77**), phevalin (**78**), leuvalin (**79**).[42] Additionally, butrepyrazinone (**80**) biosynthesized by *Verrucosispora sp.* has interaction with skin microbes synthesized by *S. aureus* (Scheme 28).[43]



Scheme 28

While some pyrazinone derivatives can be responsible for microbial activities as seen in previous example, some pyrazine derivatives show antimicrobial activities. **81** is a pyrazine derivative and inhibits the growth of *Leuconostoc sp* (Scheme 29).[44]



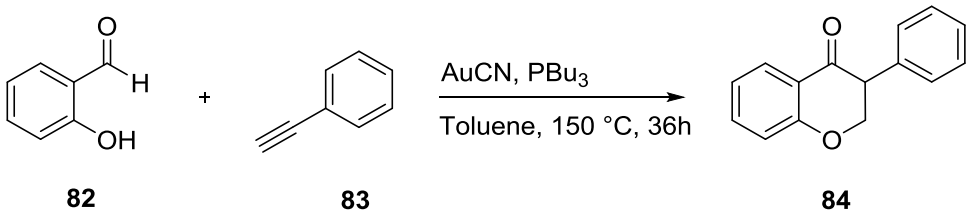
Scheme 29

1.3. Alkyne Cyclization Reactions

Alkyne cyclization reactions are very popular in recent years. By using alkyne reactivity, many different heterocyclic compounds can be synthesized. Alkyne cyclization reactions generally handled via two ways; metal catalyzed reaction or non-metal catalyzed reaction.

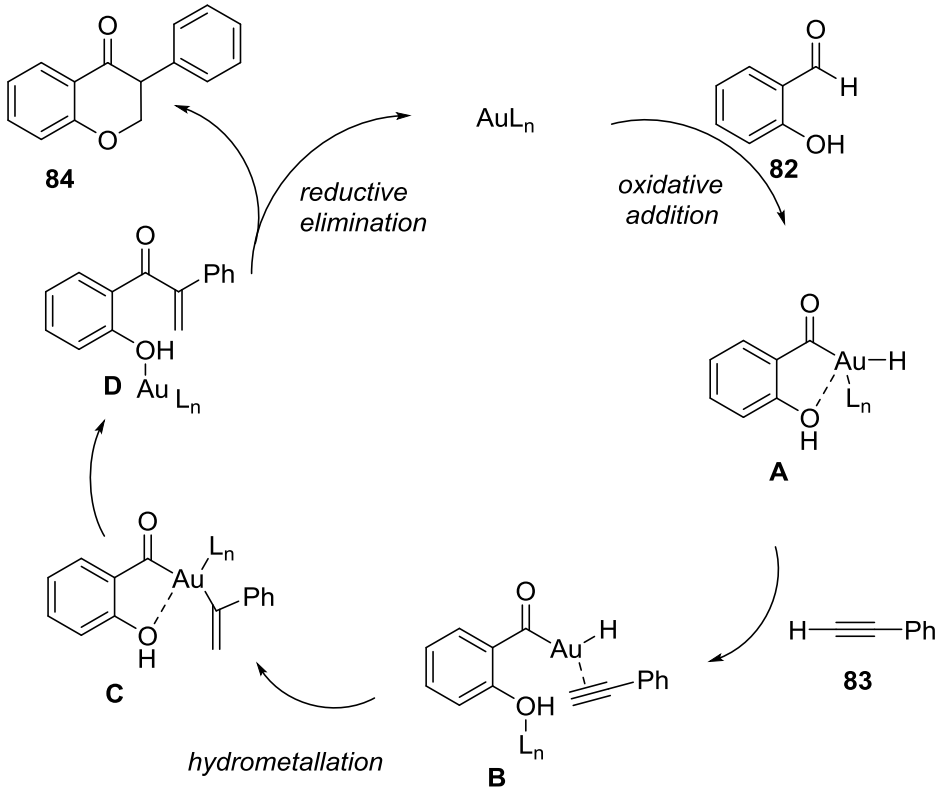
1.3.1. Metal Catalyzed Reactions

Gold(I) is an actively used metal catalyst to initiate alkyne cyclization reactions. For example, the reaction of gold(I) with salicylaldehyde (**82**) and phenylacetylene forms isoflavone derivative **84**[45] (Scheme 30). First, gold(I) reacts with salicylaldehyde and generates an insertion product; gold(III) complex **A**, which then forms a complex by coordinating with phenylacetylene (**83**) to form **B**. Hydrometallation of **B** leads to the formation of **C**. After reductive elimination, hydroxyl group attacks to α-β unsaturated ketone to yield product **84** (Scheme 31).



82 **83** **84**

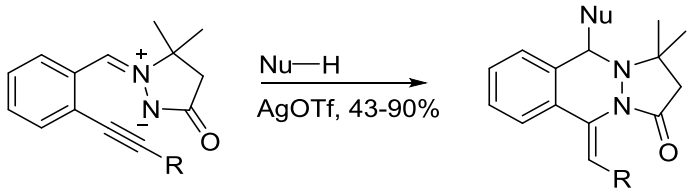
Scheme 30



84 **82** **D** **A** **C** **B** **83**

Scheme 31

The next example about Ag(I) catalyst is the coordination with the triple bond of **85** to increase its reactivity. First, negatively charged nitrogen atom attacks the triple bond followed by attack a soft nucleophile on imine carbon atom to generate this six-*exo*-dig selective cyclization product **86** (Scheme 32).[46]

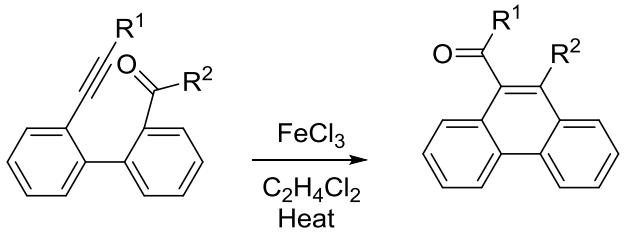


85 **86**

R= ^{n}Pr, ^{n}Bu, ^{i}Bu, H, CH_2OMe, C_6H_5, 2-ClC_6H_4, 4-$OMeC_6H_4$
NuH= ketone, nitroalkane, water, terminal alkyne

Scheme 32

Fe(III) catalyst was also used for the metal catalyst alkyne cyclization reaction. [2+2] cycloaddition reaction is forbidden according to Woodward-Hoffmann rules. However, in the presence of metal catalyst, cycloaddition reactions can take place. Phenanthrene derivative **88** was formed after cycloaddition reaction followed by cycloreversion reaction (Scheme 33).[47]



87 **88**

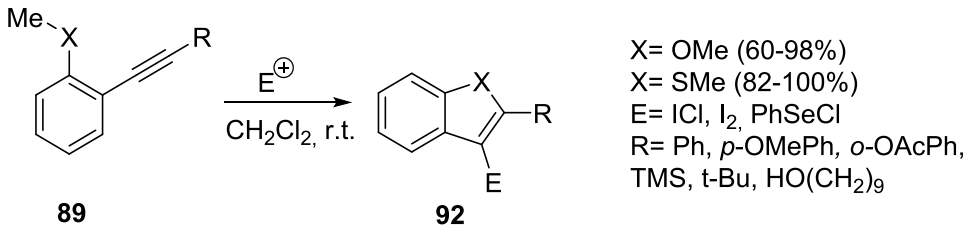
R^1= *p*-MePh, *p*-ClPh, *m*-NO_2Ph, C_6H_{13}, CH_2CH_2OMe, C_6H_{11}
R^2= H, Me

Scheme 33

1.3.2. Non-Metal Catalyst Reactions

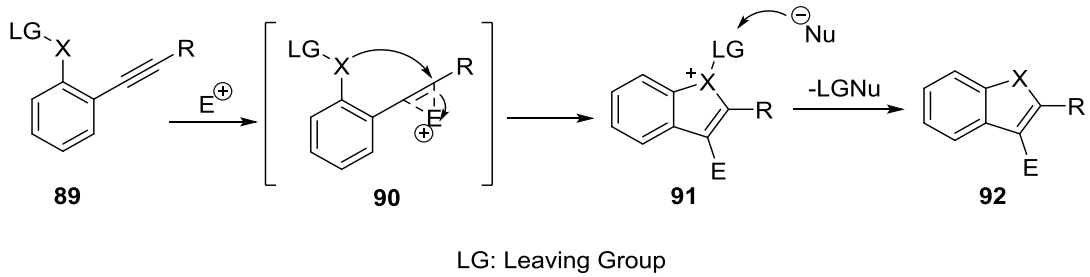
This type of alkyne cyclization reactions can also be catalyzed generally by an electrophile instead of a metal catalyst or can be triggered by a nucleophile.

Following example includes electrophiles such as ICl, I_2 and PhSeCl (Scheme 34). These groups coordinate with the triple bond of **89** by forming a positively charged triangular cyclic intermediate **90**, which undergoes an intramolecular ring-opening reaction to give **91**. The leaving group can be removed by a nucleophile such as OMe or SMe to form furan[48] or thiophene[49] derivatives (Scheme 35).



89 **92**

Scheme 34

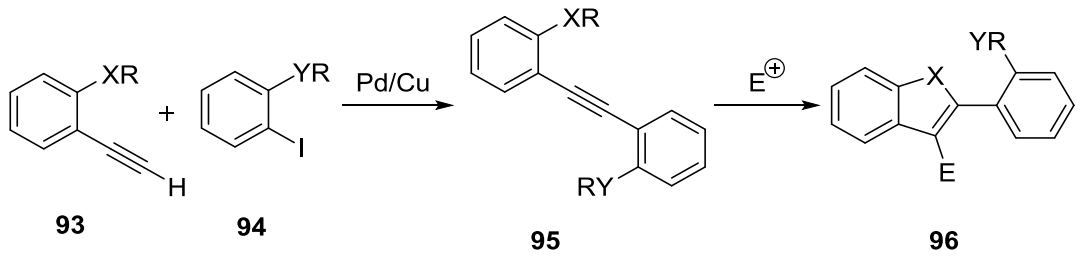


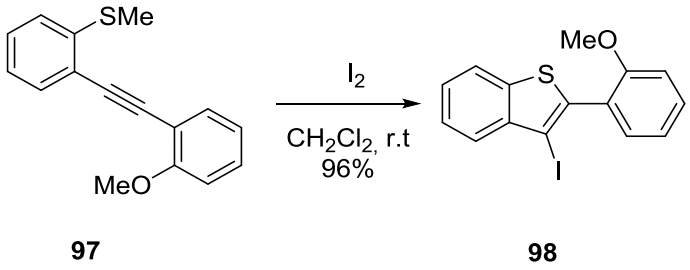
89 **90** **91** **92**

LG: Leaving Group

Scheme 35

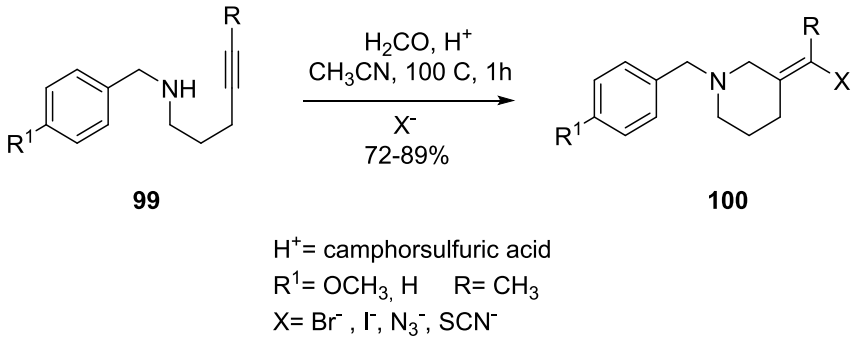
The product **95** was synthesized by Sonogashira-type coupling reaction starting from **93** and **94**. It can undergo cyclization reaction by activation of triple bond. X and Y groups will compete based on their nucleophilicity for cyclization reaction. According to this reaction system, sulfur and oxygen atoms on compound **97** compete for cyclization reaction which leads to formation thiophene derivative **98** due to higher nucleophilicity of sulfur atom (Scheme 36).[50]





Scheme 36

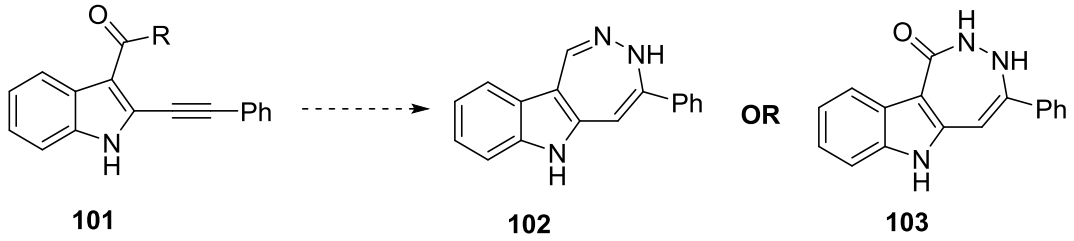
A nucleophile-assisted electrophilic cyclization reaction can be encountered in the synthesis of **100**. First, an imine is formed between the reaction of formaldehyde and amine functional group. Then, nucleophiles such as bromide, iodide or azide anions attack alkyne functionality to initiate cyclization reaction to yield **100.**[51] (Scheme 37)



Scheme 37

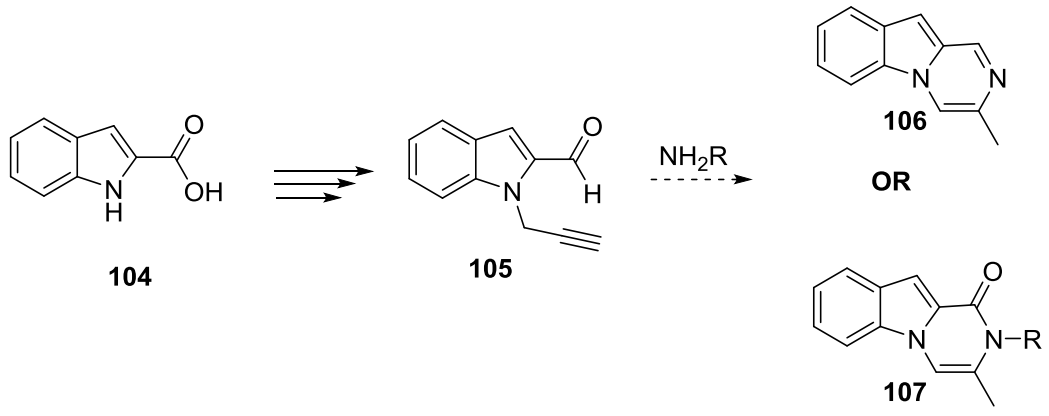
1.4. Aim of Study

This study emphasizes alkyne cyclization reactions of indole ring to produce indole fused heterocyclic compounds. First, our aim was to synthesize 7-membered heterocycles condensed to indole molecule by starting from 2- and 3- substituted indole derivatives. We planned to benefit from aldehyde and ester reactivities toward alkyne functional groups (Scheme 38).



Scheme 38

Second, we focused on C-2 and N-substituted indoles which are functionalized by aldehyde and propargyl groups, respectively. Our goal was to develop new synthetic pathways to produce indole fused heterocycles via using variety of amines. We planned to react propargyl aldehyde **105** with different amines to synthesize indolopyrazine **106** and indolopyrazinone **107** derivatives (Scheme 39).



Scheme 39

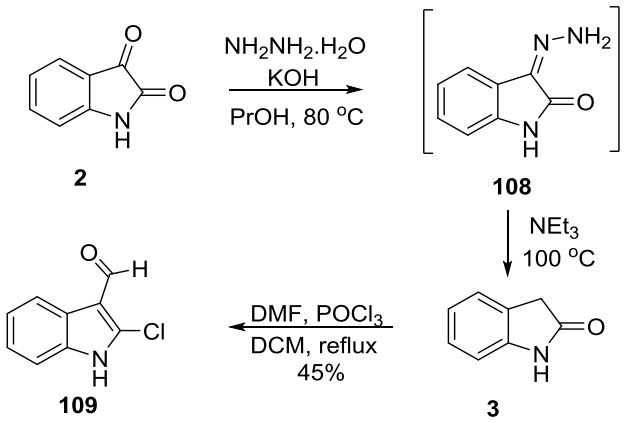
CHAPTER 2

RESULT AND DISCUSSION

2.1. Synthesis of γ-carboline moiety

2.1.1. Synthesis of 2-chloro-1*H*-indole-3-carbaldehyde

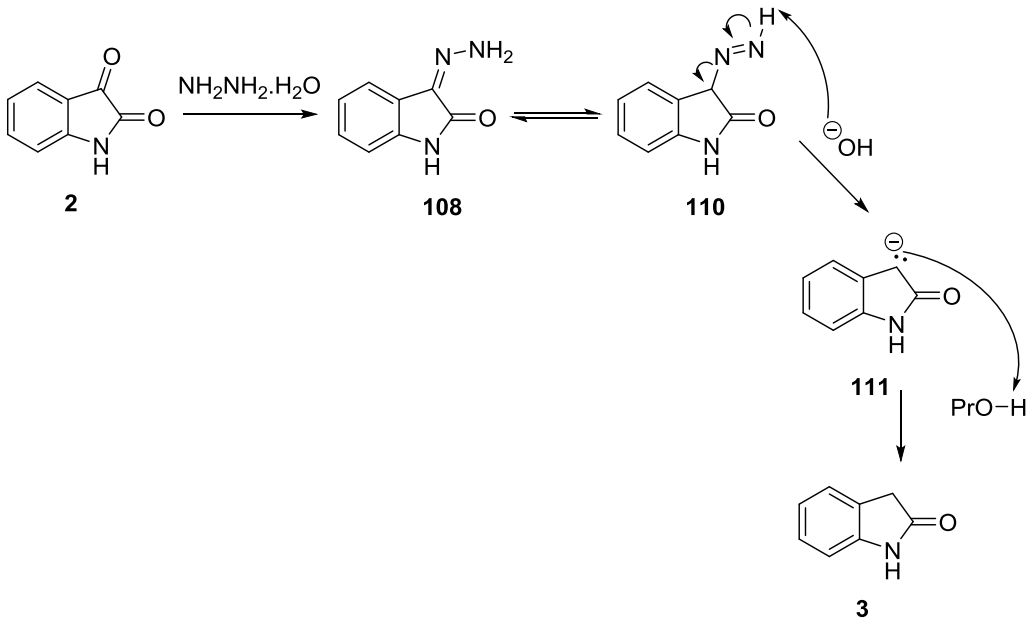
In the first part of our studies we were interested in the synthesis of indole derivatives having an aldehyde group connected to the C-3 carbon atom and alkyne functionality connected to the C-2 carbon atom in order to carry out cyclization reactions. We chose aldehyde group because aldehydes can be converted easily into different functional groups with different reactivities toward an alkyne group. In order to introduce the aldehyde group into the indole molecule, we started with **2** as the starting material which is an oxidized indole derivative. First of all, **2** was converted into **3** by using Wolff-Kischner-Huang reduction reaction[52] called as modified Wolff-Kischner reaction which works at higher temperatures by using relatively high boiling solvents (Scheme 40).



Scheme 40

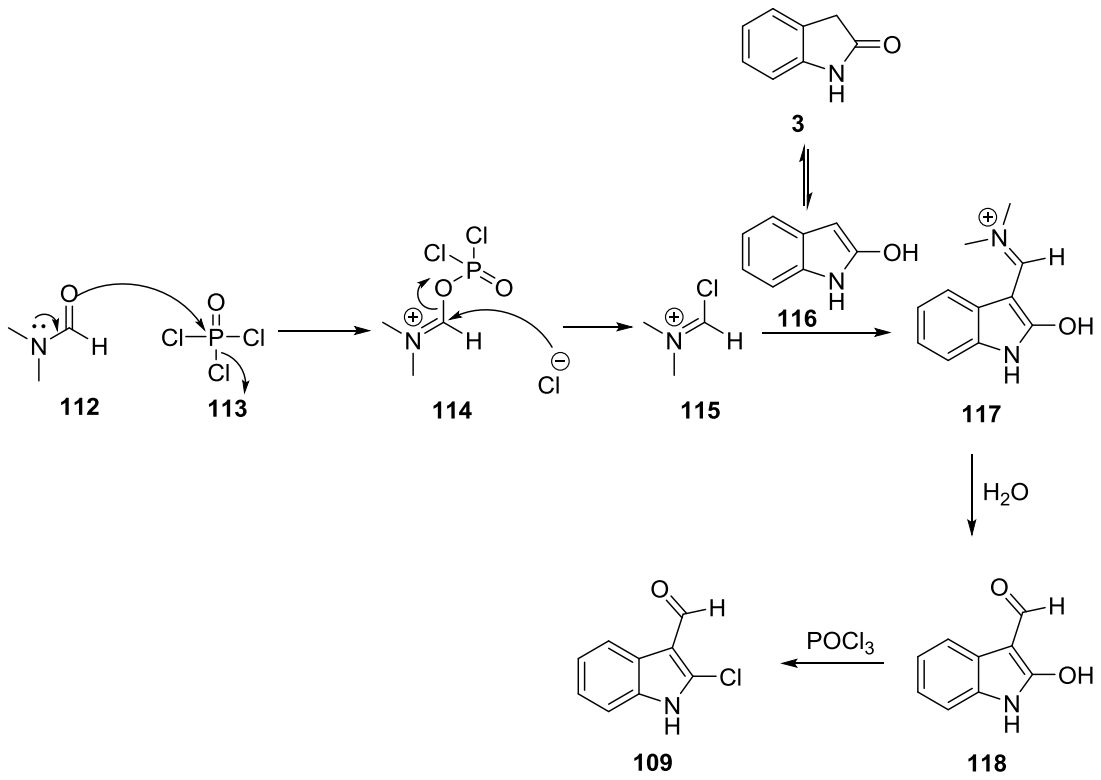
Reduction of **2** involves firstly the formation of hydrazone (**108**) on C-3 position of indole in the presence of hydrazine and KOH in n-propanol. Actually, there are two carbonyl groups on indole molecule but the carbonyl group on C-2 which can be thought as amide carbonyl is less reactive than carbonyl on C-3. Therefore, C-3 carbonyl group was selectively reduced.

After hydrazone formation, tautomerization of compound **108** gives rise to formation of diazo compound **110**. The base, hydroxide anion abstracts a proton. After extrusion of N_2, the carbanion **111** takes a proton from solvent to finalize the reaction to form oxindole (**3**) (Scheme 41).[53]



Scheme 41

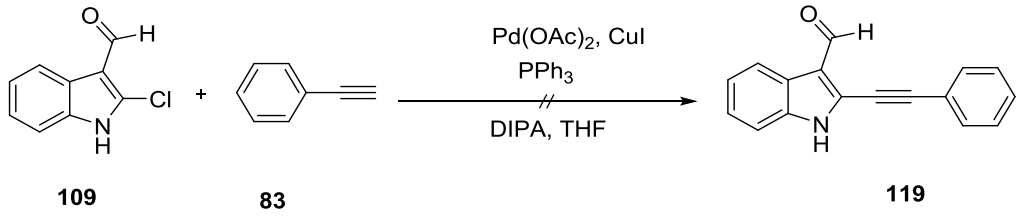
After the formation of **3**, Vilsmeier-Haack reaction was used to functionalize indole molecule on C-2 and C-3 positions at the same time. Vilsmeier-Haack reaction is a good way to attach an aldehyde group to electron rich aromatic compound.[54] First, DMF and $POCl_3$ are mixed in dichloromethane and then oxindole is added to react with in situ generated iminium ion **115**. As seen in Scheme 42, hydrolysis of the intermediate **117** and substitution of hydroxyl group gave the desired product **109**.



Scheme 42

2.1.2. Synthesis of 2-(phenylethynyl)-1*H*-indole-3-carbaldehyde

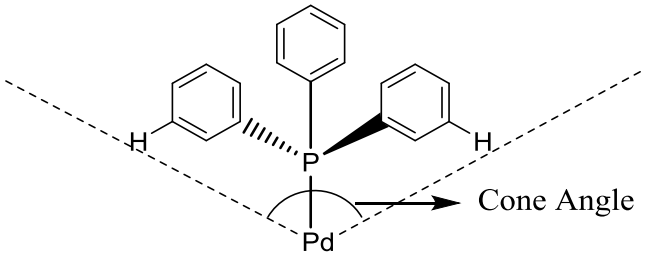
The compound **109** contains the desired functionalities for introduction of an alkyne group. Presence of chlorine atom at C-2 position gave us a possibility to replace this group with an alkyne group by using Sonogashira coupling reaction. Sonogashira coupling reaction generally includes Pd(II) and CuI as metal catalysts and PPh_3 as ligand for the coupling of aromatic halide with many terminal alkyne derivatives as in case of **109**. Chloroaldehyde **109** was reacted with phenyl acetylene (**83**) in the presence of $Pd(OAc)_2$, CuI and PPh_3 by using DIPA as base to form desired coupling product **119**, but it failed under this condition (Scheme 43).



109 83 119

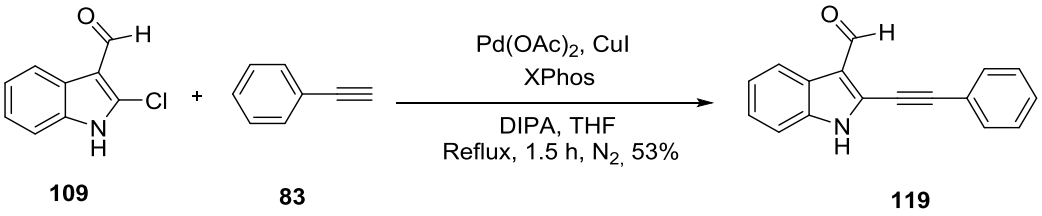
Scheme 43

We assume that chlorine atom is responsible for this failure. Generally, chlorine is less reactive than bromine and iodine, toward Sonogashira coupling reaction.[55] However, aryl-chloride bond can be activated by using different ligands. Especially, bulkier and electron richer ligands can activate aryl-chloride bonds (Scheme 44).[56]

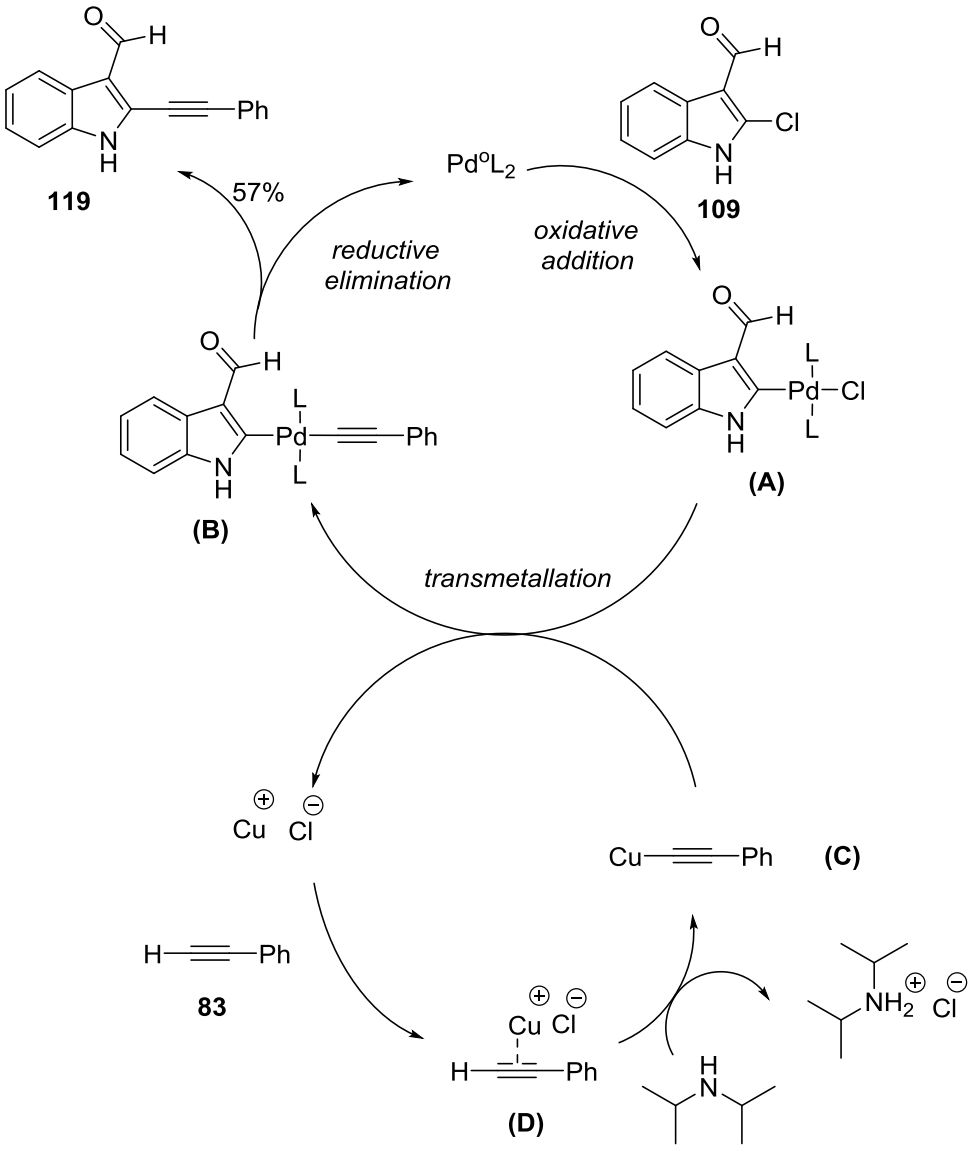


Scheme 44

When a ligand coordinate in carbon-halide bond it will increase the length of bond so that the carbon-halide bond will be weakened. Bulkier ligands have higher cone angle which weakens carbon-halide bond easier so coupling reactions can be done by using these kinds of ligands. While becoming electron rich ligand facilitates oxidative addition step, becoming bulkier ligand makes reductive elimination step easier.[55] Therefore, for the synthesis of **119** starting from **109**, 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-bipheyl (XPhos) was used as phosphine ligand beside $Pd(OAc)_2$ and CuI as metal catalysts (Scheme 45). Sonogashira coupling reaction proceeded smoothly and the desired compound **119** having aldehyde and alkyne functionalities were formed in 57% yield. The mechanism of formation of **119** is presented in Scheme 46.[57]



Scheme 45

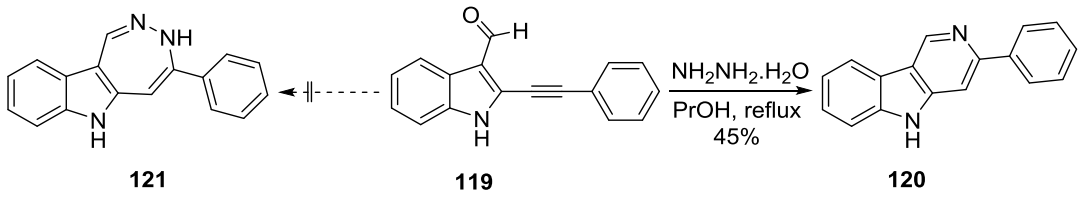


Scheme 46

2.1.3. Synthesis of 3-phenyl-5*H*-pyrido[4,3-*b*]indole

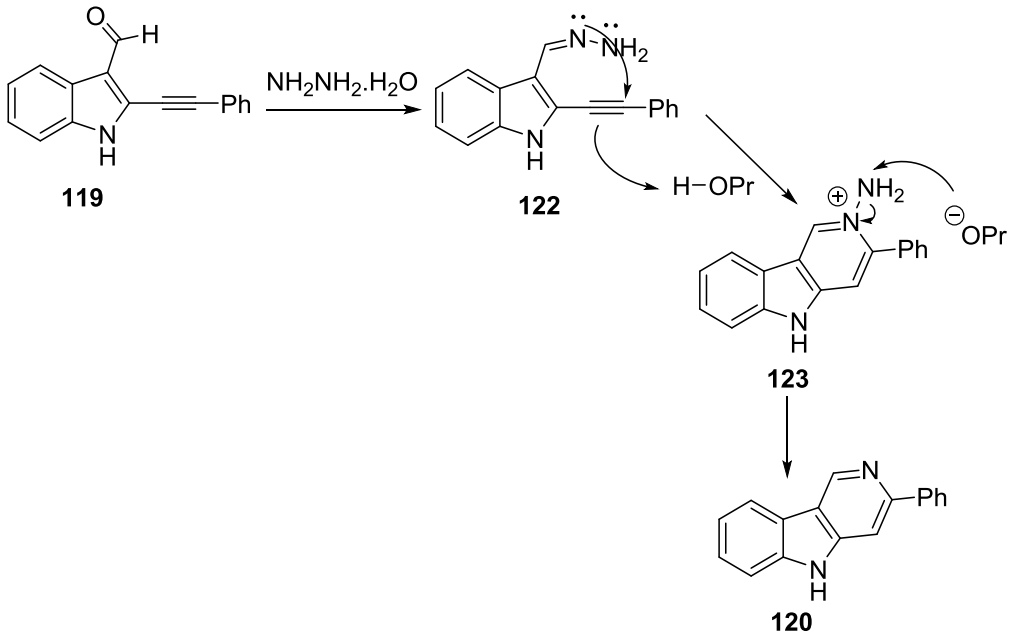
After successful synthesis of **119**, we tried ring-closure reactions between the aldehyde and alkyne groups. We were interested in generation of a seven-membered ring, diazepine derivatives, using hydrazine. **119** was reacted with hydrazine monohydrate in *n*-propanol under the reflux temperature. γ-Carboline product **120** was formed as a single product instead of the expected indolo-diazepine derivative **121** (Scheme 47).

Larock *et al*. synthesized this γ-carboline derivative **120** by reacting **119** with tert-butylamine.[57] Also there are examples for the similar synthetic pathways of β-carbolines synthesis with ammonia[58] and hydroxylamine[59] in literature. In the case of our reaction, we did not expect removal of one of NH_2 group of hydrazine during the reaction due to the low living group properties.



Scheme 47

We have proposed the following reaction mechanism for the formation of the product (Scheme 48). First hydrazine reacts with aldehyde to form hydrazone **122** which has two different nitrogen atoms and they will compete to react with alkyne for cyclization reaction. Actually, amine nitrogen is more electronegative than imine nitrogen atom because sp^3 hybridized nitrogen is more nucleophilic than sp^2 hybridized nitrogen.



Scheme 48

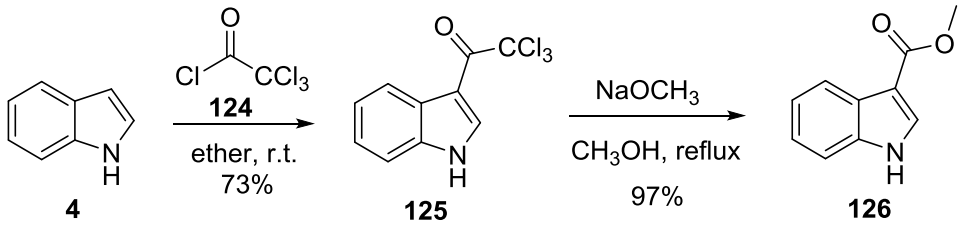
However, we were not able to observe any product, seven-membered ring, arising from the attack of more electronegative nitrogen atom. Exclusively, imine nitrogen atom was involved in the cyclization reaction. Of course the transition state for the formation of a six-membered ring will always be favored about the formation of a seven-membered ring. Furthermore, we assume that the configuration of amine group may be trans. In this case the formation of a seven-membered ring will be hindered. Attack of less reactive imine nitrogen to alkyne causes the formation of cationic amino γ-carboline intermediate **123** and then attack of propoxyl group to remove amino group forms **120**. Obviously, the directing force for the formation of γ-carboline product is formation of an aromatic ring condensed to indole ring.

2.2. Attempt for the synthesis of indolodiazepinone moiety

2.2.1. Synthesis of 2,2,2-trichloro-1-(1*H*-indol-3-yl)ethanone and methyl 1*H*-indole-3-carboxylate

In the second part of alkyne cyclization studies we decided to replace the aldehyde functional group in **118** with an ester. Ester groups are relatively less reactive than aldehyde but it can be modified by using hydrazine to form seven membered rings

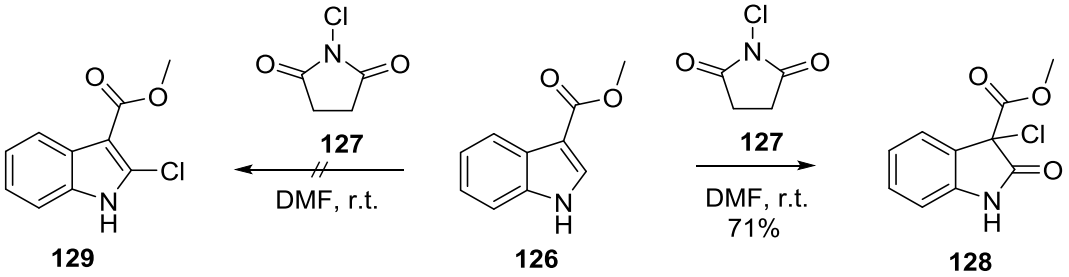
condensed to indole molecule.[60] First, we tried to substitute C-3 position of indole with ester group so indole (**4**) was reacted with trichloroacetyl chloride (**124**) to form **125**. As mentioned in introduction part, indole has π excessive character and C-3 position of indole is reactive toward electrophilic attacks.[61] Trichloroacetyl group was attached to indole which can be turned to ester group easily. Reaction of **125** with sodium methoxide in methanol gave the desired ester **126** in good yield (Scheme 49).[62]



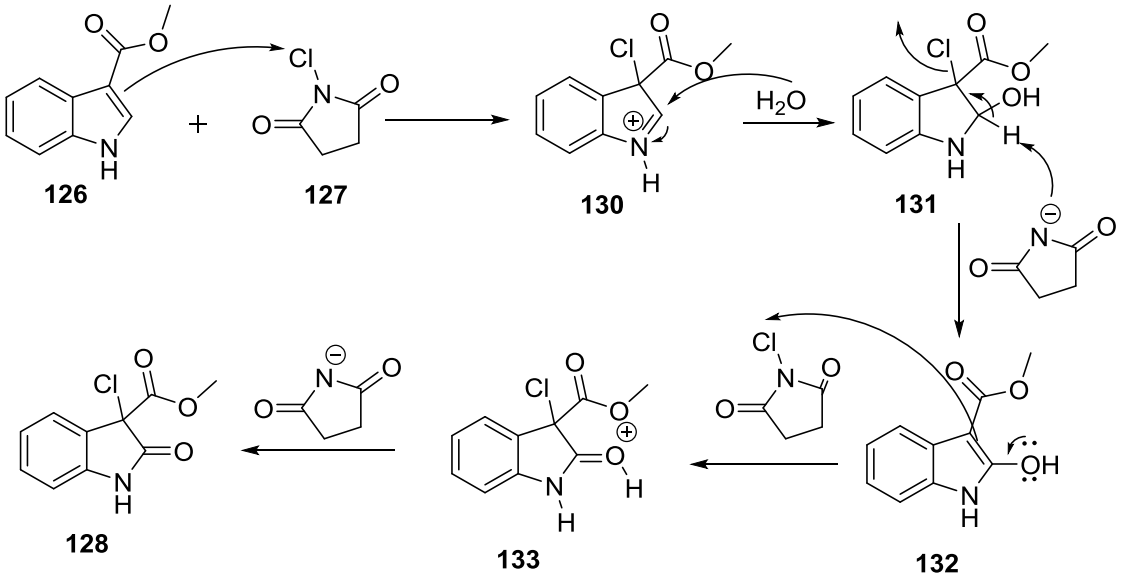
Scheme 49

2.2.2. Synthesis of methyl 3-chloro-2-oxoindoline-3-carboxylate

Next, we tried to introduce chlorine atom to C-2 position of indole using a literature procedure. Indole ester **126** was reacted with NCS (**127**) in DMF as described in the literature.[63] Unfortunately, we were not able to get desired product **129** although the reaction was repeated many times. Instead of the described product **129**, we isolated **128** as the major product of NCS reaction (Scheme 50). The structure of **128** was proved by NMR studies and elemental analysis. The presence of carbon resonance at 66.3 ppm demonstrates the existence of a quaternary carbon atom which is attached to an electronegative atom, chlorine. The presence of ester and amide groups was also established by resonances appearing at 173.2 and 167.0 ppm (Figure 1). Indeed, it was quite interesting to isolate an oxindole derivative. For the formation of **128** we proposed the following mechanism as depicted in Scheme 51. Unfortunately, we could not use this important component for further studies.



Scheme 50



Scheme 51

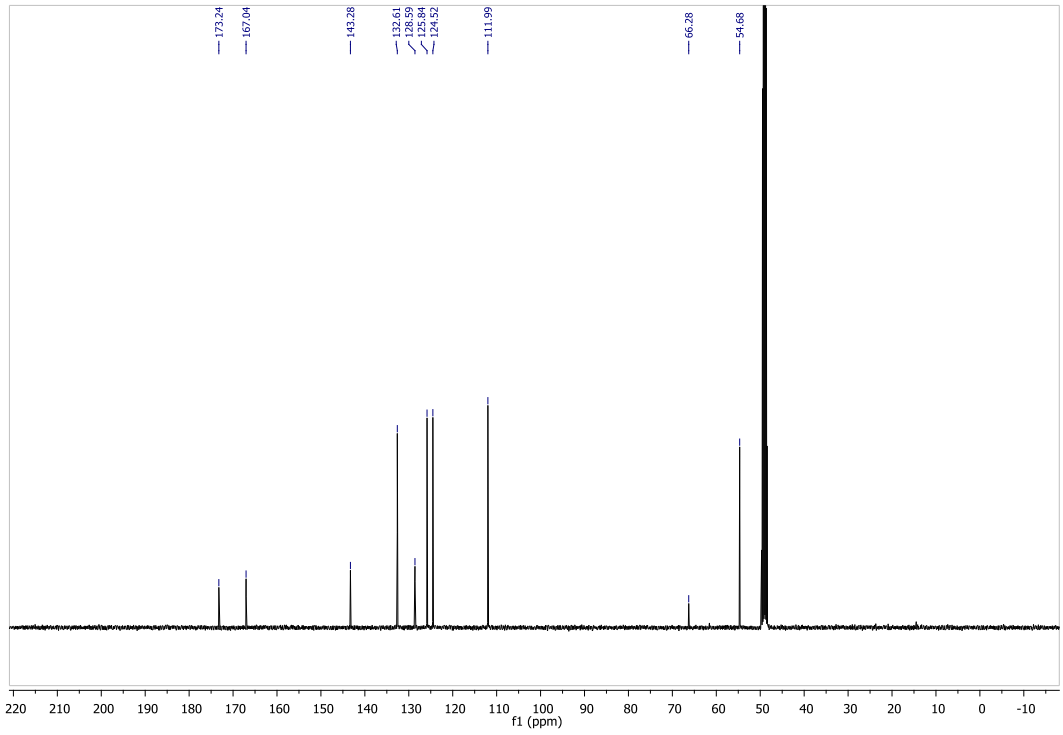
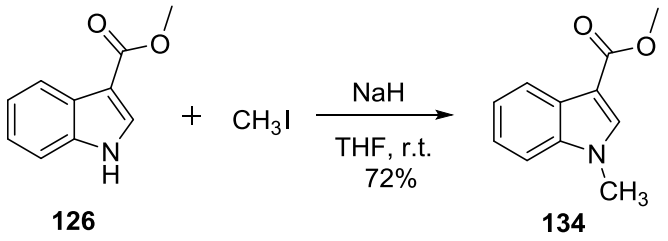


Figure 1 ^{13}C NMR spectrum of compound **128**

2.2.3. Synthesis of methyl 1-methyl-1*H*-indole-3-carboxylate

We assumed that the NH group could prevent the formation **129**. Therefore, it could be useful to protect this NH group by a methyl group and see whether NH group has any effect on the mode of the reaction or not. The indoloester was reacted first with NaH to generate the corresponding anion and then with methyliodide.[64] As explained in the introduction part, NaH is a quite effective base to remove the proton of weakly acidic indole derivatives, so at the end of reaction, **134** was formed easily by following the procedure (Scheme 52).

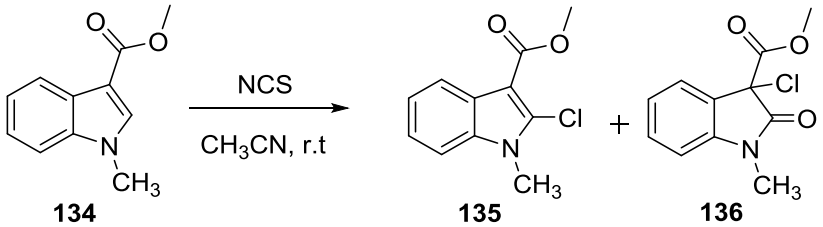


126 **134**

Scheme 52

2.2.4. Synthesis of methyl 2-chloro-1-methyl-1*H*-indole-3-carboxylate

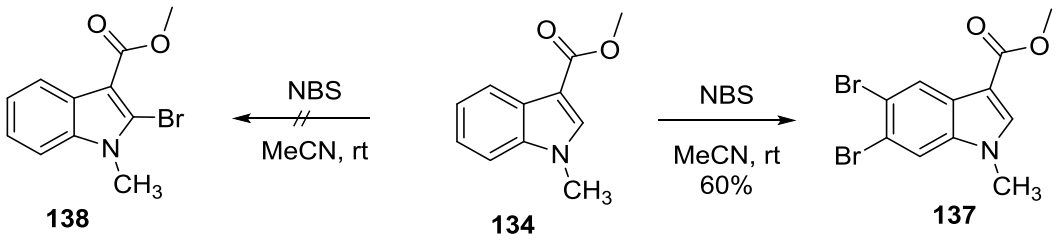
After protecting the NH group, **134** was submitted to the reaction with NCS under the similar reaction conditions as described above. After completion of the reaction we isolated the desired product **135** as the major product in 67% isolated yield which was separated by recrystallization. The ^{1}H NMR spectral studies indicated that oxindole derivative **136** was also formed as the side product (Scheme 53).



Scheme 53

2.2.5. Synthesis of methyl 5,6-dibromo-1-methyl-1*H*-indole-3-carboxylate

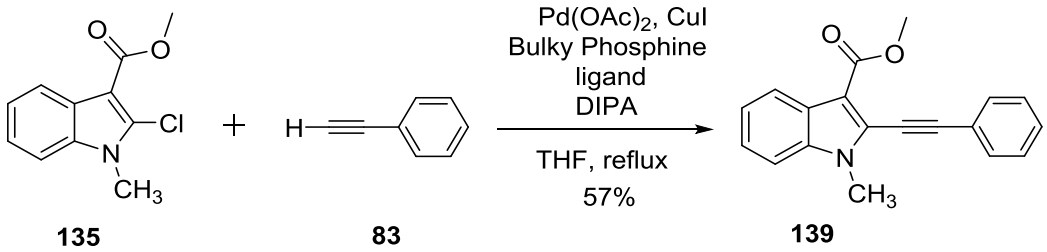
Since brominated compounds undergo Sonogashira-coupling reactions much easier than chlorinated compounds, we attempted to brominate **134** with NBS. **134** was reacted with NBS in acetonitrile. Instead of expected 2-bromo substituted indole derivative **138**, we isolated dibromo substituted indole derivative **137**, where the aromatic ring was brominated instead of the five-membered ring (Scheme 54).



Scheme 54

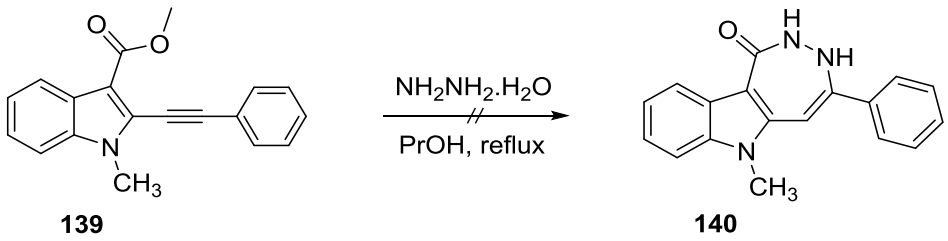
2.2.6. Synthesis of methyl 1-methyl-2-(phenylethynyl)-1*H*-indole-3-carboxylate

After failure of bromination reaction of **134** we decided to continue our coupling reaction with chlorinated isomer **135**, which was submitted to Sonogashira coupling reaction. As in the previous alkyne cyclization study, we used same bulky phosphine ligand, 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-bipheyl, along with Pd and Cu catalysts. After completion of Sonogashira reaction, **139** was isolated as the expected product in 57% yield (Scheme 55).



Scheme 55

After the synthesis of key compound **139**, we reacted **139** with hydrazine with the expectation of the formation of diazepinone derivative **140** condensed to indole molecule. Ester part of compound was supposed to form hydrazide and more reactive second nitrogen should react with alkyne to form expected diazepinone derivative. Unfortunately, we were not able to observe any trace of a cyclization product even after 24 hours (Scheme 56).



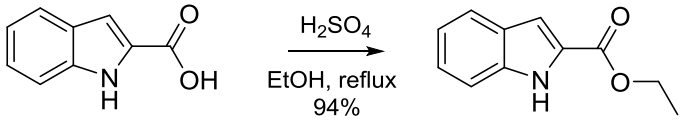
Scheme 56

2.3. Synthesis of indolopyrazine and indolopyrazinone derivatives

2.3.1. Synthesis of ethyl-1H-indole-2-carboxylate

After failure of the cyclization reactions with an alkyne group attached to C-2 carbon atom of indole moiety, we decided to change our strategy and change the position of the carbonyl group as well as the position of alkyne group. We planned to attach a propargyl group to the nitrogen atom and aldehyde group to the C-2 atom and then perform a cyclization reaction with these functional groups to synthesize new indole-condensed heterocyclic compounds.

The reason why we chose these functional groups is their reactivity. Aldehyde groups are more reactive than other carboxylic groups. Especially, this reactivity towards amine groups has crucial importance for our synthetic pathway. Furthermore propargyl groups can be turned into allene functional groups which are quite reactive for nucleophilic attacks at central carbon atom. To synthesize the key product, we started with **104**. Indole carboxylic acid **104** was reacted in ethanol under acidic condition and the corresponding ester **141** was obtained in 94% yield as described in the literature (Scheme 57) .[65]



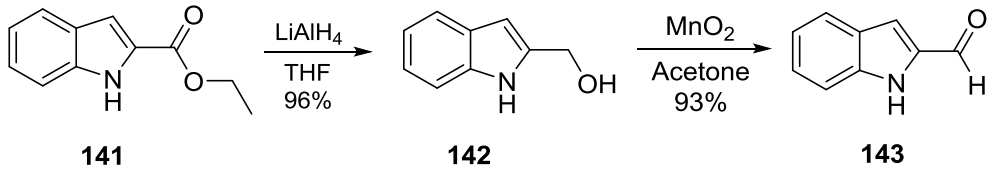
104 **141**

Scheme 57

2.3.2. Synthesis of 1*H*-indol-2-ylmethanol and 1H-indole-2-carbaldehyde

For the synthesis of **143**, first ester **141** was reacted with $LiAlH_4$ in THF to give the corresponding alcohol **142**. $LiAlH_4$ is a good reducing agent for conversion of ester to alcohol under very mild conditions.[66] The next step was the formation of aldehyde functionality at C-2 position of indole ring.

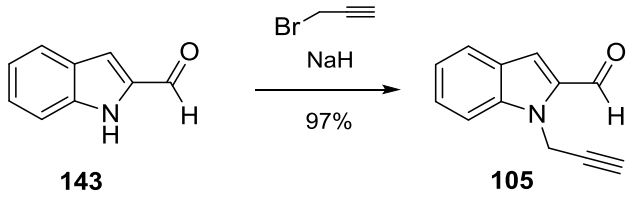
To oxidize alcohol group to aldehyde by one step oxidation reaction MnO_2 was used as oxidizing reagent.[67] MnO_2 is known as selective oxidizer for allyl, benzyl and also propargyl alcohols to synthesize corresponding aldehydes. In the light of this information, **142** was oxidized to **143** with MnO_2 in acetone at room temperature in 93% yield (Scheme 58).



Scheme 58

2.3.3. Synthesis of 1-prop-2-ynyl-1H-indole-2-carbaldehyde

After having aldehyde **143** in hand, we reacted it with propargyl bromide in the presence of NaH as a base at room temperature. The key product **105** was synthesized in 97% yield. As mentioned before, indoles are weak acids so it is needed to use strong bases to remove the proton bonded to the nitrogen atom. NaH is a strong base and works for the removal of NH proton. Acid-base reaction leads to formation of anionic nitrogen, and this intermediate attack propargyl bromide and substitutes bromide to form **105 (**Scheme 59**)**.[68]



Scheme 59

2.3.4. Synthesis of 3-methylpyrazino[1,2-*a*]indole

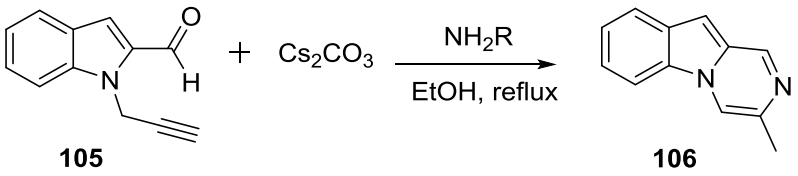
After getting the key compound we were ready to apply ring-closure reactions by using primary amines. We first, reacted **105** in ethanol with ammonia in the presence

of Cs_2CO_3 as base and obtained 3-methylpyrazino[1,2-*a*]indole (**106**) in 76% yield. In 2005, Abbiati *et al.* reacted 1-prop-2-ynyl-1*H*-indole-2-carbaldehyde **105** with ammonia in sealed tubes at high temperatures (100 ˚C) and got pyrazino indole derivative **106** in 80% isolated yield (Scheme 60).[69]

After successful ring-closure reaction, we wanted to extend this reaction to different primarily substituted amines and introduced an alkyl group into the molecule. Firstly, allylamine and propargylamine were used for this purpose. Again **105** was reacted with allylamine and propargylamine in ethanol under the reflux temperature with Cs_2CO_3 as a base. (Table 2)

Table 2: Yields of pyrazine derivative with ammonia and β-unsaturated amines

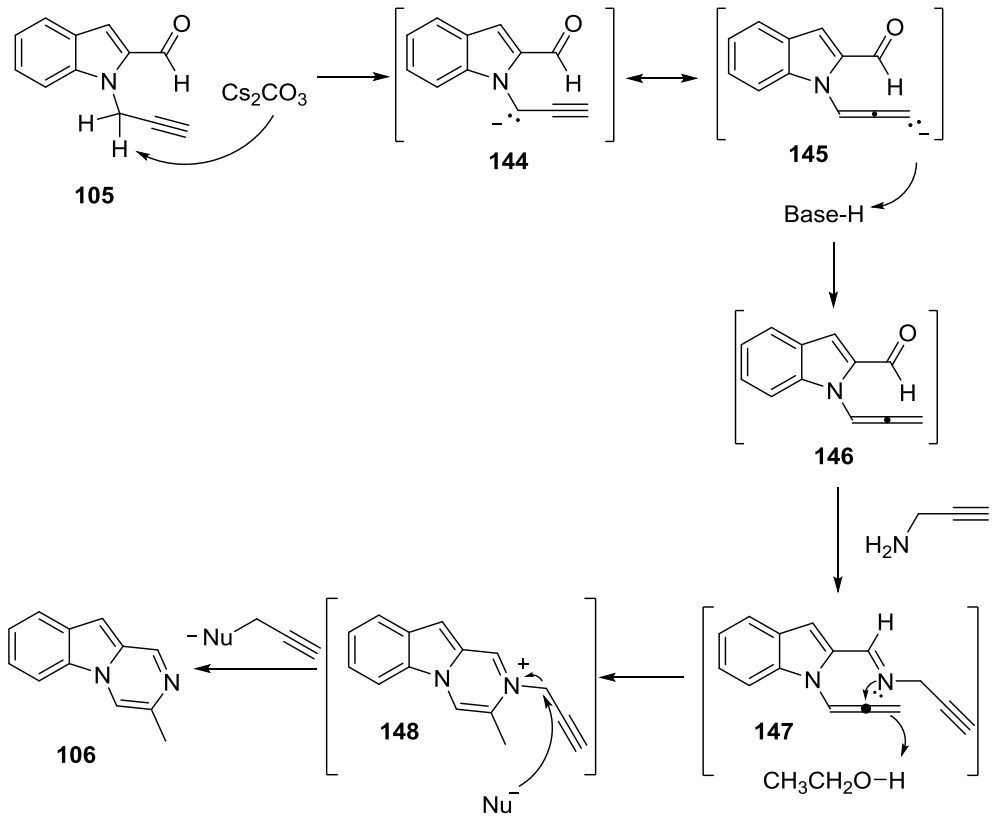
Reactant	Amine	Product	İsolated Yield
105	Ammonia	**106**	76%
105	Allyl amine	**106**	65%
105	Propargyl amine	**106**	51%



105 **106**

Scheme 60

Unexpectedly, both allylamine and propargylamine reactions with the key compound **105** gave the same compound, 3-methylpyrazino[1,2-*a*]indole (**106**) which was isolated by the reaction of **105** with ammonia. All these findings demonstrate that the R groups attached to the amine are removed during reaction. This means that the allyl and propargyl groups behave as leaving groups during the cyclization reaction. Under the light of this information, we proposed the following reaction mechanism for the formation of **106** with different substituted amines (Scheme 61).



Scheme 61

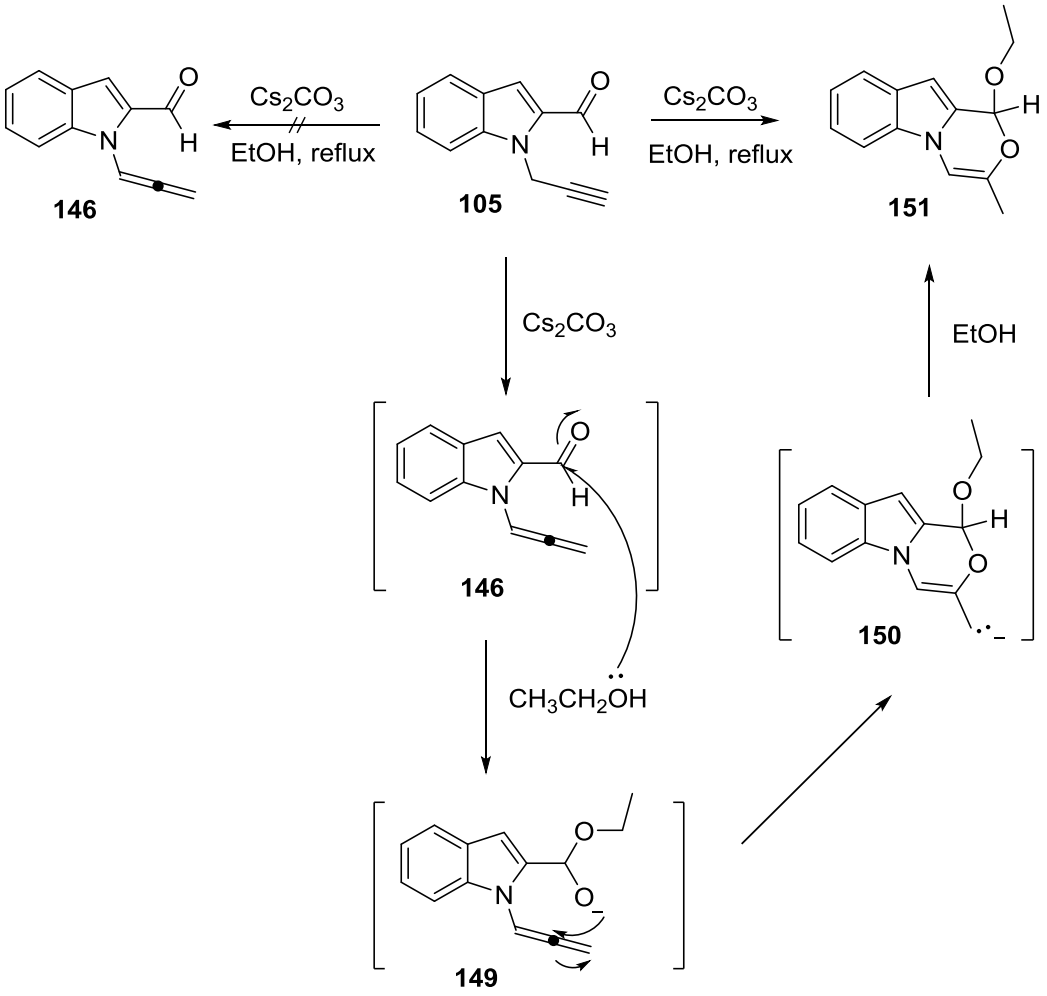
The methylene protons in **105** are acidic because of connection to nitrogen as well as to sp-hybridized carbon atom. Therefore, Cs_2CO_3 removes one of them and newly formed propargylic anion **144** can be turned into allene intermediate **146**. The presence of propargyl amine in the reaction medium causes the formation of imine intermediate **147** by reacting with aldehyde. This intermediate **147** has two very reactive parts; an allene part and an imine part. As discussed before, the allene central carbon has electropositive character so it is open to any nucleophilic attack. Imine lone pair attacks on the central carbon atom of allene followed by the taking a hydrogen from solvent gives rise to a cationic indolopyrazine intermediate **148**. Any nucleophilic attack on the methylene carbon atom of propargyl group, activated by the positive charge located on the nitrogen atom, will remove the propargyl group and form the final product **106**.

This proposed reaction mechanism contains two intermediates; imine group derived from aldehyde and allene group derived from propargyl part of molecule. To ensure

this proposed mechanism we decided to isolate the allene unit and run the reaction with allene.

2.3.5. Reaction of 105 with Cs_2CO_3: Attempted Synthesis of 146 and formation of 1-ethoxy-3-methyl-1*H*-[1,4]oxazino[4,3-*a*]indole

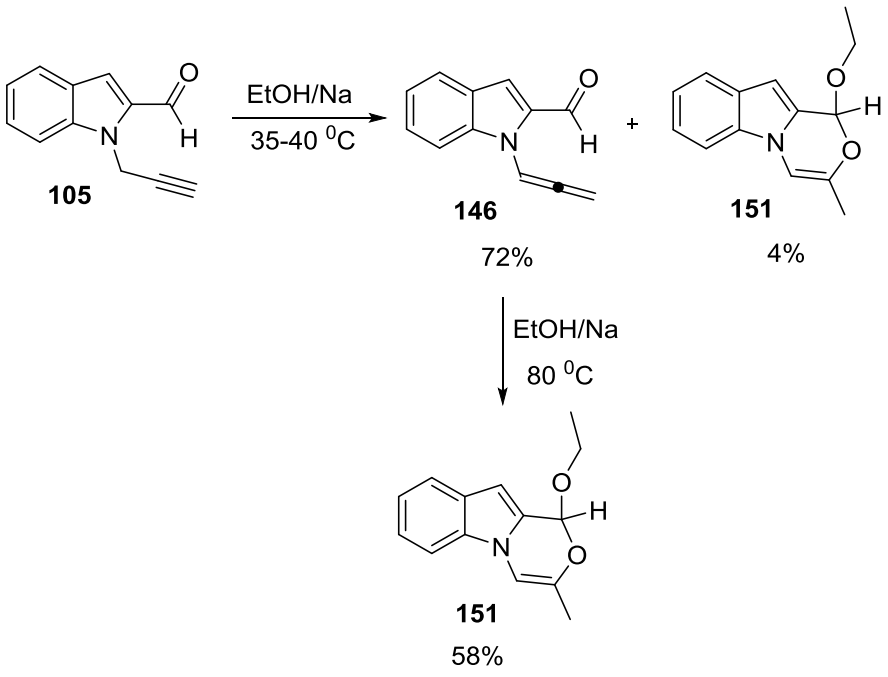
First of all, we tried to isolate allene **146**. Forming only allene intermediate by starting from key compound **105** may be possible if we use only Cs_2CO_3 for the transformation of propargyl group into allene.



Scheme 62

Propargyl aldehyde **105** was reacted with Cs_2CO_3 in ethanol in the absence of primary amine under the same reaction conditions. The desired allene derivative **146**

could not be isolated. Instead of that, we observed the formation of **151**, an indolo-oxazine derivative, where ethanol was incorporated into the molecule. We propose the following reaction mechanism for the formation of this unexpected product (Scheme 62). The allene intermediate **146** is formed under the basic conditions. This highly reactive intermediate can react with any nucleophile. Attack of ethoxide ion formed under the reaction conditions on the aldehyde group generates anionic intermediate **149** which is in close proximity to the allene functionality so that an attack from alkoxide ion on the allene units takes place to give the final product **151**. Similar reactions were done by Abbiati et al. in 2005 by using sodium ethoxide as base which also support our findings about the failure of isolating allene intermediate (Scheme 63).[70]

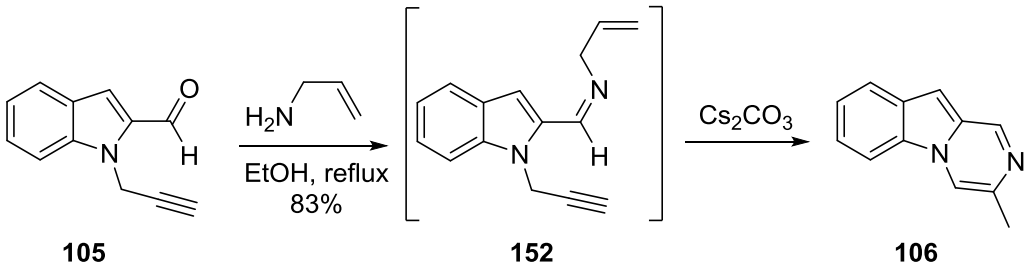


Scheme 63

2.3.6. Synthesis of *N*-[(1E-prop-2-ynyl-1*H*-indol-2-yl)methylidene]prop-2-en-1-amine

At this stage we decided to isolate the imine **152** as the intermediate. The propargyl aldehyde **105** was reacted in ethanol with allylamine again under the same reaction conditions and in the absence of Cs_2CO_3. The ^1H NMR spectral studies indicated the

complete consumption of the starting material and the formation of imine **152** as a single product in quite high yield. However, we were not able to isolate imine in pure state. Attempted chromatography hydrolyzed imine **152** back to the starting aldehyde. Upon standing in solution at room temperature, it was decomposed.



Scheme 64

The structure of **152** was determined by analysis of the ^{1}H NMR spectrum (Figure 2). The peak resonating at 8.26 ppm belongs to the imine hydrogen. The peaks appearing at 5.21 and 5.08 ppm as doublet of quartet belong to the terminal vinyl protons. The other proton resonances are also in agreement with the proposed structure.

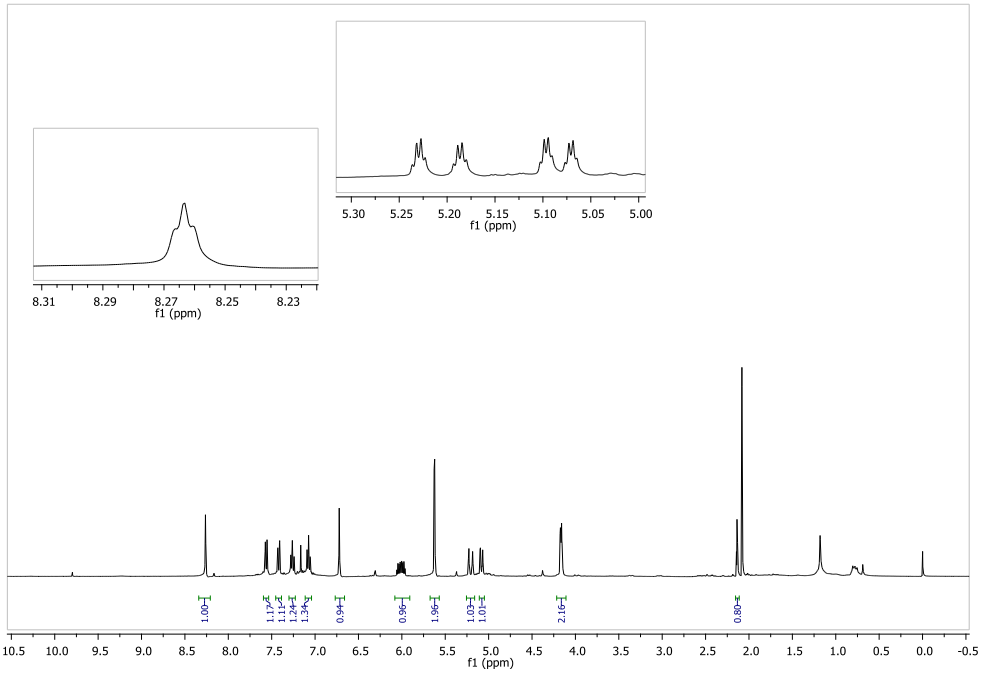
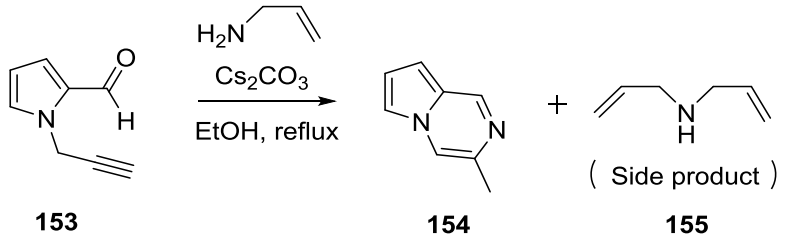


Figure 2 ^{1}H NMR spectrum of compound **152**

After synthesis of imine **152**, Cs_2CO_3 was added to the reaction mixture and the reaction was continued as described above. The product **106** was obtained as the single product (Scheme 64).

After getting the information about that imine was involved in the formation of the final product **106**, we were still curious how the R groups of primary amines are removed. In Scheme 61, we discussed that the intermediate **148** is formed which can be attacked by any nuchleophile present in the reaction medium. Actually, any nucleophile can accomplish the formation of **106** because there is a certain directing force which is the formation of neutral aromatic product from cationic intermediate **148**.



Scheme 65

We carefully analyzed the reaction mixture to determine the fate of the leaving group. We run similar reaction with pyrrole system. The compound **153** was synthesized as described in the literature.[60] The reaction was carried out under the similar reaction conditions with excess of allyl amine. As seen in Scheme 65, analysis of the reaction mixture by GC-MS indicated the formation of expected pyrrolopyrazine derivative **154** and diallylamine **155** as a byproduct (Figure 3).

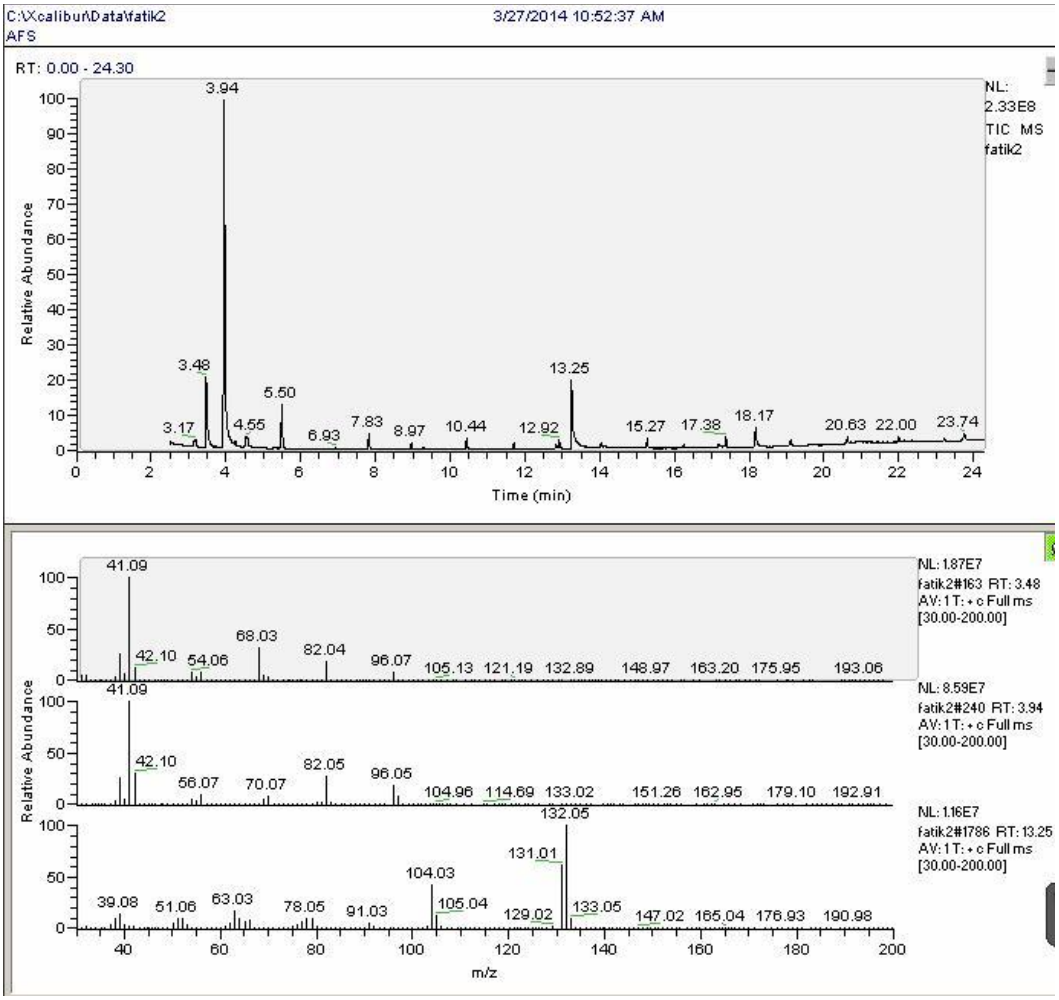
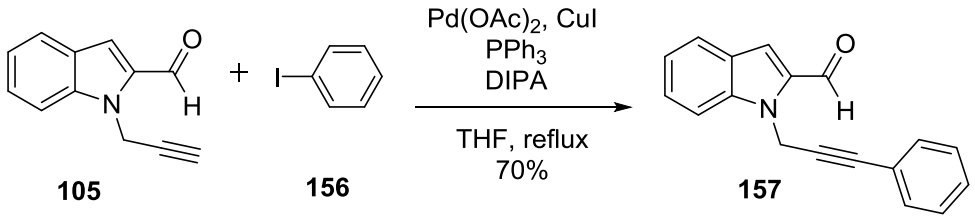


Figure 3 GC-MS spectrum of compound **155**

Mass Spectroscopy results were compared with the library and the fragmentation patterns were in agreement with the published one.

2.3.7. Synthesis of 1-(3-phenylprop-2-ynyl)-1*H*-indole-2-carbaldehyde

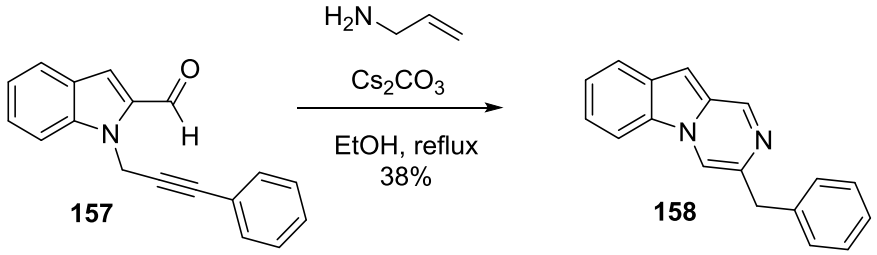
To see the feasibility of the procedure to the similar system, we tried to substitute terminal carbon of triple bond in **105** with a phenyl group by using Sonogashira coupling reaction. **105** was reacted with iodobenzene (**156**) in the presence of CuI and $Pd(OAc)_2$ metal catalysts and PPh_3 as a ligand to give **157** (Scheme 66).[68]



Scheme 66

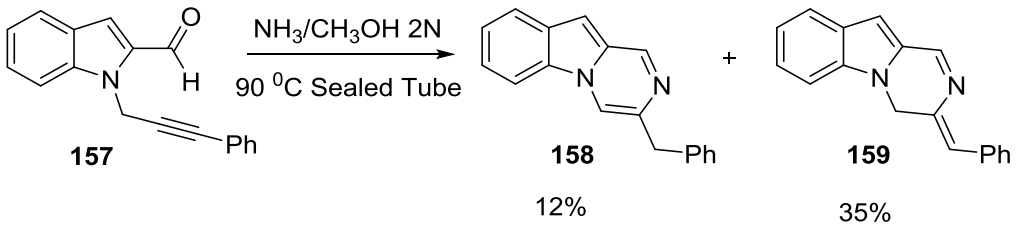
2.3.8. Synthesis of 3-benzylpyrazino[1,2-*a*]indole

Coupling product **157** was reacted with allylamine and Cs_2CO_3 in ethanol and the expected product **158** was synthesized as major product in 38% isolated yield (Scheme 67).



Scheme 67

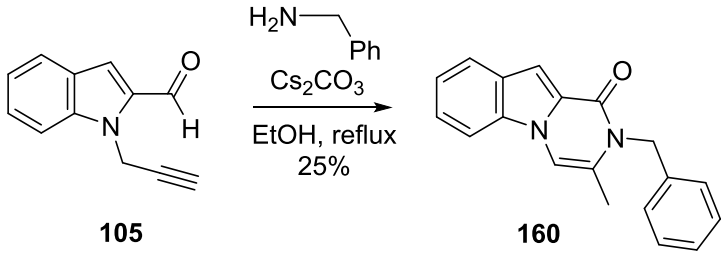
Similar reaction has been described in the literature. Abbiati *et al.* reacted **157** with ammonia in a sealed tube and they reported the formation of **158** and 3-[1-phenylmeth-(Z)-ylidine]-3,4-dihydropyrazino[1,2-α]indole (**159**) in 12% and 35% yields, respectively (Scheme 68).[69] We produced **158** with higher yield and other cyclization product was not observed in the reaction medium.



Scheme 68

2.3.9. Synthesis of 2-benzyl-3-methylpyrazino[1,2-*a*]indol-1(2*H*)-one, 2-methyl-3-methylpyrazino[1,2-*a*]indol-1(2*H*)-one and 2-hexyl-3-methylpyrazino[1,2-*a*]indol-1(2*H*)-one

As the next, another β-unsaturated primary amine was choosen to react with **105**. We expected that benzylamine follow the same reaction pathway like other β-unsaturated primary amines; allylamine and propargylamine to give **106**. Benzylamine was reacted with **105** in ethanol under the reflux temperature with benzylamine and Cs_2CO_3 as described before. Analysis of the product revealed the formation of indolo-pyrazinone derivative (**160**) instead of expected indolo-pyrazine (**106**) compound (Scheme 69). The product **160** was isolated by column chromatography and characterization was done by NMR spectral studies.



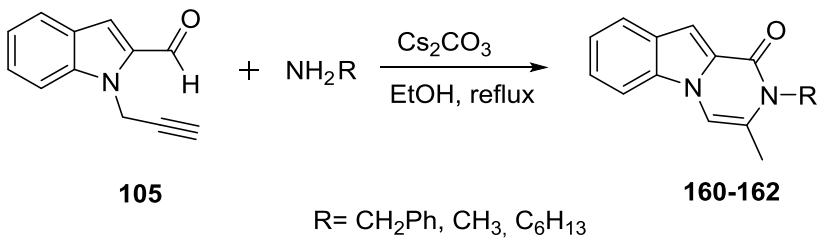
Scheme 69

After completion of the cyclization reactions of **105** with primary amines having unsaturated substituents, we decided to run reactions with saturated unbranched alkyl amines such as methyl, ethyl and hexyl amine in order to compare the results and get additional information about the removal of the substituents. Allyl or propargyl groups can act as good leaving groups while formation of pyrazine derivatives but removal of methyl, ethyl or hexyl groups must be much more difficult compared to them. First of all, methyl amine was reacted with **105** in the presence of Cs_2CO_3 in ethanol and we isolated the indolo-pyrazinone derivative **161** as an isolable product, its formation is unusual. The isolated yield was low and about 10% after column chromatography. The interesting feature of this reaction was the fact that the methyl group was not removed and was incorporated into the molecule. Furthermore, we

carried out a similar reaction with hexylamine and we observed the formation of **162** in 21% isolated yield, where again the hexyl group was not removed (Scheme 70).

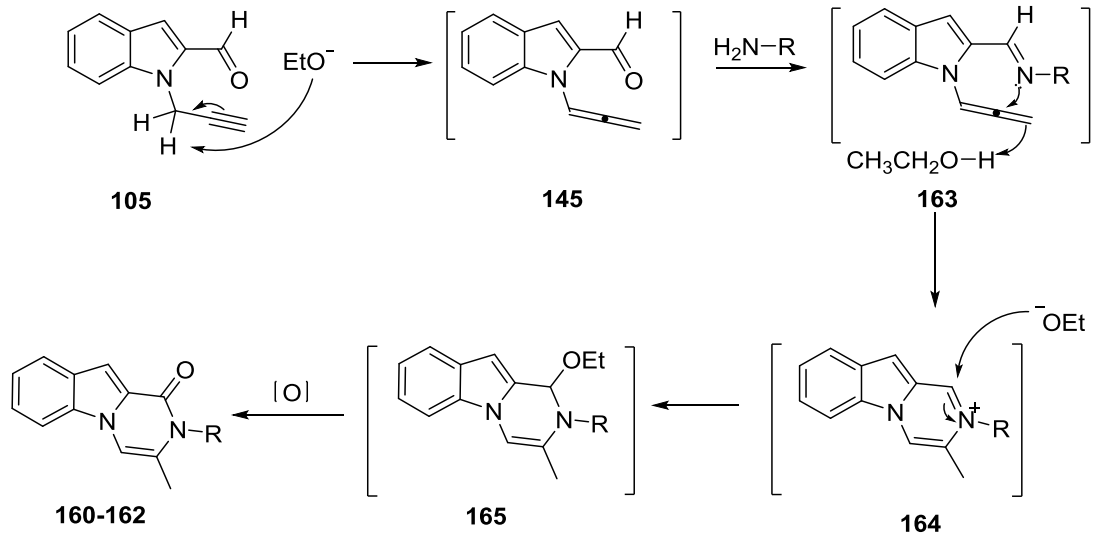
Table 3: Yields of Pyrazinone derivatives with β-unsaturated and saturated alkyl amines

Reactant	Amine	R	Product	İsolated Yield
105	Benzyl amine	CH_2Ph	**160**	25%
105	Methyl amine	CH_3	**161**	10%
105	Hexyl amine	C_6H_{13}	**162**	21%



Scheme 70

Formation of indolo-pyrazinone derivatives **160-162** is quite unusual. We propose the following reaction mechanism for the formation of these products. The details are given in Scheme 71. The proposed mechanism: Cs_2CO_3 catalyzes the isomerization of propargyl group to allene via H-transfer. Alkyl amines react first with aldehyde to form imine derivative (**163**) where alkyne group is isomerized to the corresponding allene. Lone pairs on imine nitrogen attacks the central carbon atom of allene to form the ion **164**. Now this ion is open to attack by nucleophiles at two different positions. Any attack on R groups would result in the formation of **106**. If R group contain a double bond or triple bond, the methylene group can be attacked easily. Probably the methyl group connected to the nitrogen atom is not electrophilic enough for a nucleophilic attack. However, the nucleophiles, probably ethoxide ion, can attacks the imine carbon atom to form **165** which can undergo easily oxidation reaction in the presence of air oxygen to form imide functionalities (**160-162**).



Scheme 71

The structure of pyrazinone derivatives were secured with the help of 2D NMR spectral studies. The HMBC spectrum shows a strong correlation between the methyl protons attached to the nitrogen atom with carbonyl carbon and quaternary alkene carbon which is substituted by methyl group. The other correlations were also in complete agreement with the proposed structure (Figure 4).

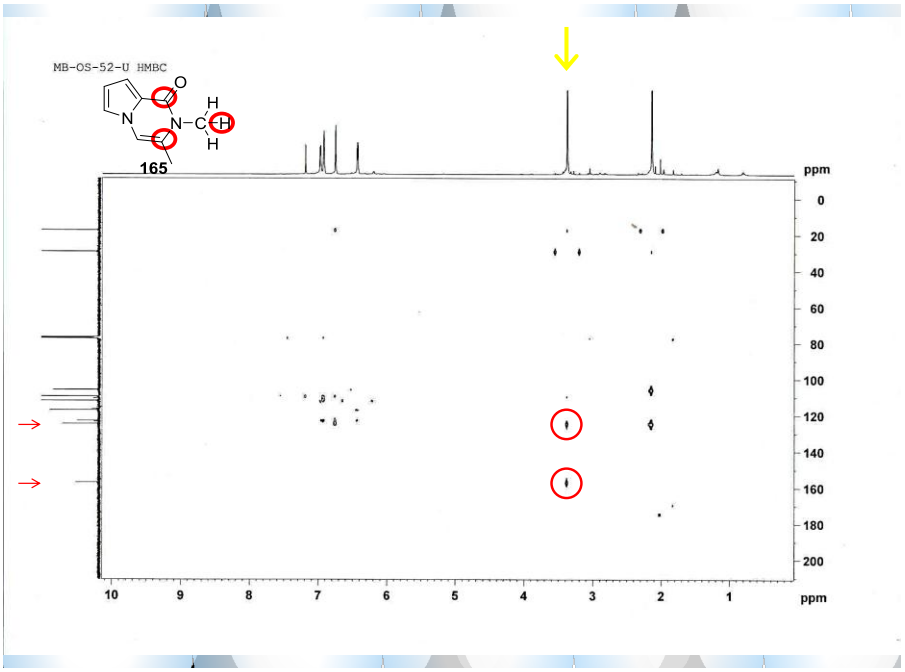
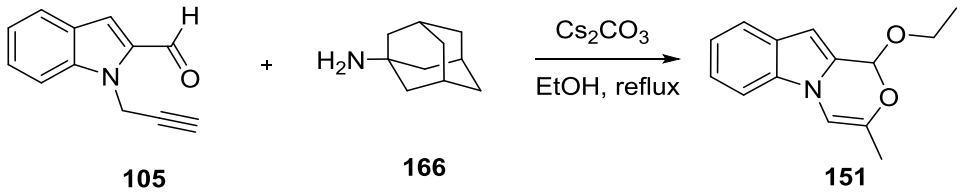


Figure 4 HMBC spectrum of compound **166**

2.3.10. Further Amine Studies

Lastly, we tried the cyclization reaction of **105** with primary amines having a tertiary or quaternary carbon atoms attached directly to the amine nitrogen such as *i*-propylamine, *t*-butylamine and 1-adamantylamine. First, 1-adamentylamine (**167**) was reacted with **105** under the same conditions of other amine reactions, and then we observed formation of **151** as the main product and no pyrazine or pyrazinone derivatives were detected. Formation of **151** states that 1-adamantylamine did not involve in reaction and the solvent molecule was incorporated into the compound (Scheme 72).



105 **166** **151**

Scheme 72

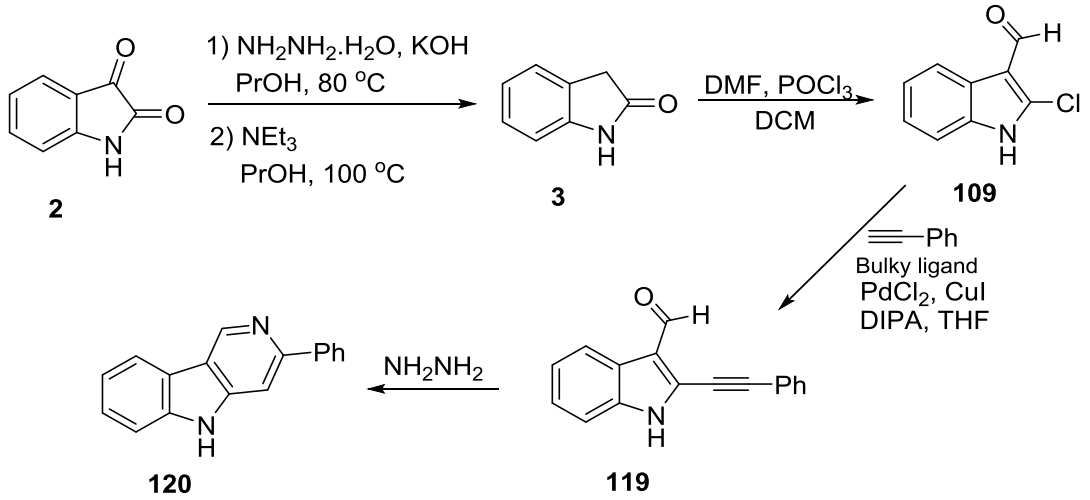
Unfortunately, neither isopropylamine nor tertbutylamine gave positive results for the formation of expected skeletons. As in the alkylamine reactions, we observed high amount of decomposed product and remaining organic contents were very low amount.

CHAPTER 3

CONCLUSION

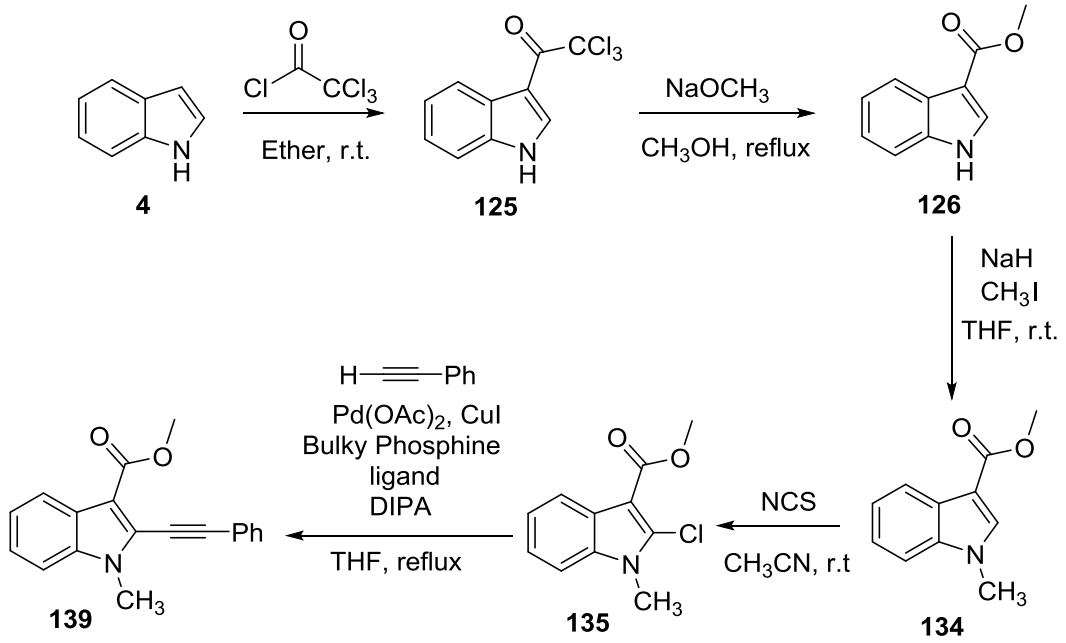
We developed a new synthetic route for the formation of indolopyrazine and indolopyrazinone derivatives. In addition, synthesis of γ-carboline derivative and possible precursor for diazepinone derivatives were achieved. During the course of this study, indole skeleton was used to be condensed by new heterocyclic systems by the help of alkyne cyclization reactions. Synthesized final products have great potential to show biological activity because there are many biologically active compounds with similar structures in the literature.

In the first part of thesis, oxindole was synthesized by starting from isatin via Wolff-Kischner-Huang reduction. Vilsmeier-Haack reaction was used to attach aldehyde and chloride at the same time to the indole molecule and then Sonogashira coupling of phenyl acetylene was carried out for the formation of key compound **119**. Finally, γ-carboline derivative **120** was formed as a result of alkyne and aldehyde reaction in the presence of hydrazine (Scheme 73).



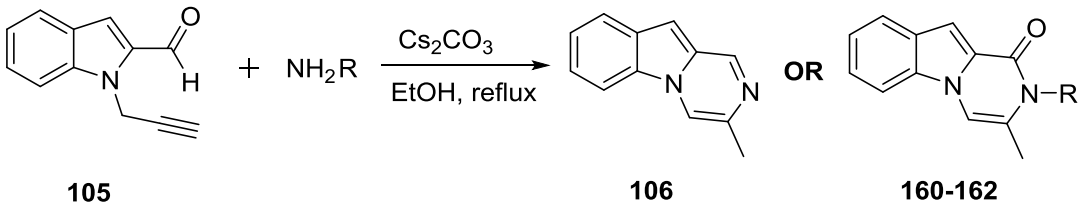
Scheme 73

In the second part of the thesis, attachment of an ester functionality to the indole was accomplished by electrophilic substitution of C-3 position and following simple esterification reaction. Then, C-2 position is halogenated by reacting with NCS and Sonogashira coupling was applied to halogenated indole derivative **135** to get key compound **139** which is a possible precursor of diazepinone derivatives (Scheme 74).



Scheme 74

In the last part of thesis, C-2 position was substituted by aldehyde and N-1 position was attached by propargyl group. The compound **105** was treated with different amines to produce indolopyrazine and indolopyrazinone derivatives. While reaction of β-unsaturated amines except benzylamine caused to formation of pyrazine skeleton condensed to indole ring, unbranched alkyl amines gave rise to formation of pyrazinone skeletons (Scheme 75).



Scheme 75

CHAPTER 4

EXPERIMENTAL SECTION

4.1. General

^{1}H-NMR and ^{13}C-NMR spectrums were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in $CDCl_3$, CD_3OD, DMSO-d_6, and with TMS as internal reference. Chemical shifts (δ) were reported in units parts per million (ppm). Spin multiplicities were specified as singlet (s), broad singlet (bs), doublet (d), broad doublet (bd), doublet of doublet (dd), doublet of triplet (dt), doublet of quartet (dq), doublet of doublet of doublet (ddd), triplet (t),triplet of doublet (td), quintet (quint), quasi triplet (quasi t) and multiplet (m) and coupling constants (J) were reported in Hertz (Hz).

Infrared spectra were recorded on a Bruker Platinum ATR FT-IR spectrometer in the range of 600-4000 cm-1.

Melting points were reported by operating Gallenkamp electronic melting point apparatus.

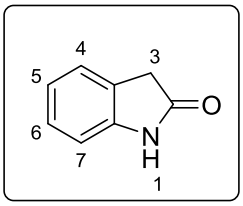
Column chromatography separations were done by using 60-mesh silica gel. Thin layer chromatography (TLC) was performed by using 0.20 mm silica gel 60 F254 aluminum plates.

Names of the compounds were established by using ACD/NMR.

All solvents and chemicals were commercially available and used without further purification.

4.2. Synthesis of 1,3-dihydro-2*H*-indol-2-one (3)[52]

To a stirring solution of 1*H*-indole-2,3-dione (**2**) (442 mg, 3 mmol) in propanol (10 mL), hydrazine monohydrate was added (0.18 mL, 3.6 mmol) dropwise and stirred for 5 hours at 80 °C. Then, triethylamine (0,85 mL, 6 mmol) was added to the reaction mixture and stirred for 2 days at reflux temperature. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, 1,3-dihydro-2*H*-indol-2-one (**3**) (300 mg, 78%) was isolated as broken white solid.

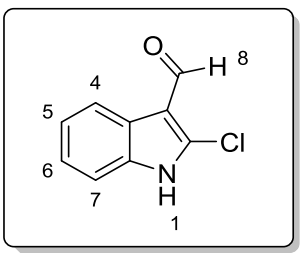


^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.27 – 7.17 (m, 2H), 7.02 (td, *J*=7.6, *J*=0.8 Hz, 1H), 6.92 (d, *J*=8.2 Hz, 1H), 3.55 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.6, 142.9, 127.9, 125.4, 124.5, 122.3, 110.0, 36.4.

4.3. Synthesis of 2-chloro-1*H*-indole-3-carbaldehyde (109)[54]

To a stirring solution of DMF (0.77 mL, 10 mmol) in CH_2Cl_2 (10 mL), phosphorous oxychloride in CH_2Cl_2 (7 mL) was added dropwise (0.5 mL, 5.4mmol) during 30 min at 0 °C. Then, 1,3-dihydro-2*H*-indol-2-one (**3**) (265 mg, 2 mmol) was added portionwise to the reaction mixture and stirred for 2 hours at reflux temperature. The reaction was quenched by ice-cold water and then the mixture was stirred for 15 min. Aqueous layer was neutralized by K_2CO_3. The yellow solid precipitate was filtered and dried to give 2-chloro-1*H*-indole-3-carbaldehyde (**109**) (160 mg, 45%), m.p. 229-231 ˚C (lit. m.p. 223-225 ˚C).

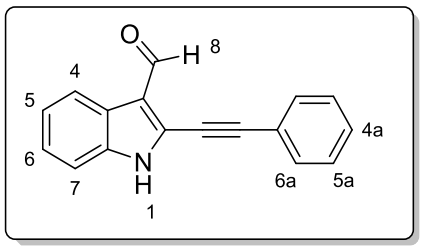


^{1}H-NMR (400 MHz, MeOD) δ 9.99 (s, 1H), 8.15 – 8.08 (m, 1H), 7.41 – 7.34 (m, 1H), 7.32 – 7.21 (m, 2H).

^{13}C-NMR (100 MHz, MeOD) δ 185.7, 137.2, 136.4, 126.0, 125.2, 124.1, 121.6, 113.9, 112.4.

4.4. Synthesis of 2-(phenylethynyl)-1*H*-indole-3-carbaldehyde (119)[57]

Cuprous Iodide (15 mg, 0,08 mmol), 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (76 mg, 0,16 mmol), palladium acetate (18 mg, 0.08 mmol) and dry diisopropyl amine (6 mL, 0.043 mmol) were added to a solution of 2-chloro-1*H*-indole-3-carbaldehyde (**109**) (360 mg, 2mmol) in dry THF (25 mL) under nitrogen atmosphere. Then phenyl acetylene (0,26 mL, 2,4 mmol) dissolved in THF (5 mL) was added to the reaction mixture dropwise at room temperature. The mixture was heated at reflux temperature and stirred for 1.5 hours. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the product was chromatographed on silica gel column eluting with hexane/EtOAc (7:1) to give 2-(phenylethynyl)-1*H*-indole-3-carbaldehyde (**119**) (261 mg, 53%) as yellow solid.



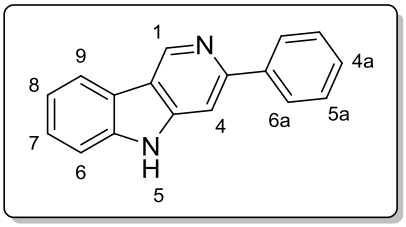
^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H, H-8), 9.48 (bs, 1H, H-1), 8.26 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.37 – 7.16 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 185.8, 136.0, 131.9, 129.8, 129.6, 128.6, 125.4, 124.5, 123.6, 122.0, 121.2, 120.7, 111.3, 98.3, 78.3.

4.5. Synthesis of 3-phenyl-5*H*-pyrido[4,3-*b*]indole (120)[57]

To a stirring solution of (phenylethynyl)-1*H*-indole-3-carbaldehyde (**119**) (0.245 g, 1.0 mmol) in PrOH (10 mL), hydrazine monohydrate (0,25 mL, 5 mmol) in PrOH (5 ml) was added dropwise. The reaction mixture was stirred overnight at reflux temperature. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over

$MgSO_4$, then filtered. After evaporation of the solvent, the product was chromatographed on silica gel column eluting with hexane/EtOAc (3:1) to give 3-phenyl-5*H*-pyrido[4,3-*b*]indole (**120**). Yellow solid (110 mg, 45%) from chloroform/n-hexane, m.p. 272-274 ˚C (lit. m.p. 272-273 ˚C).

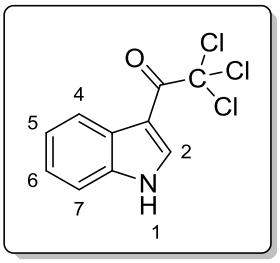


^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.77 (s, 1H), 9.41 (s, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 8.18 (d, *J* = 7.2 Hz, 2H), 7.96 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.54 – 7.45 (m, 3H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H).

^{13}C-NMR ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.7, 144.8, 142.4, 140.2, 139.9, 128.6, 128.2, 126.6, 126.6, 120.6, 120.6, 120.1, 118.6, 111.5, 102.3.

4.6. Synthesis of 2,2,2-trichloro-1-(1*H*-indol-3-yl)ethanone (125)[61]

To a stirring solution of 1*H*-indole (**4**) (2,4 g, 20.5 mmol) dissolved in diethyl ether (25 mL), trichloroacetyl chloride (**124**) (2,52 mL, 22,6 mmol) in ether (10 mL) was added dropwise. The reaction mixture was stirred for 3 hours at room temperature. After completion of the reaction monitoring by TLC, 1 M K_2CO_3 solution was slowly added until pH reached to 7 which is controlled by Litmus paper. The resulting mixture was extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the crude product was recrystallized in ether/hexane mixture to give 2,2,2-trichloro-1-(1*H*-indol-3-yl)ethanone (**125**) (3.9 g, 73%) as pale yellow needle crystals, m.p. 235-237 ˚C (lit. m.p. 228 ˚C).

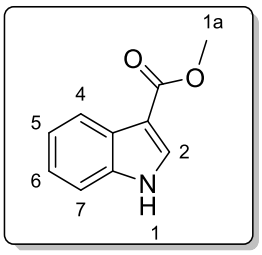


^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.54 (bs, 1H, H-1), 8.59 (s, 1H), 8.34 – 8.11 (m, 1H), 7.68 – 7.50 (m, 1H), 7.40 – 7.22 (m, 2H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ 176.7, 136.6, 136.1, 127.1, 123.7, 123.0, 121.2, 112.9, 104.7, 96.5.

4.7. Synthesis of methyl 1*H*-indole-3-carboxylate (126)[62]

To a stirring solution of 2,2,2-trichloro-1-(1*H*-indol-3-yl)ethanone (**125**) (525 mg, 2mmol) in methanol (15 mL), sodium methoxide (120 mg, 2.2mmol) was added piecewise. The reaction mixture was stirred for 3 hours at reflux temperature. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, methyl 1*H*-indole-3-carboxylate (**126**) was obtained. White powder (340 mg, 97%) from diethyl ether/n-hexane, m.p. 148-150 ˚C (lit. m.p. 149-152 ˚C).

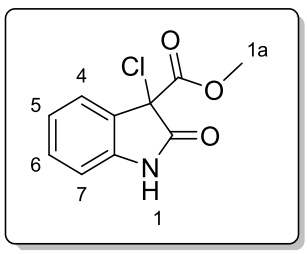


^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.15 – 8.06 (m, 1H), 7.81 (d, *J* = 3.0 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.24 – 7.13 (m, 2H), 3.85 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.0, 136.2, 131.3, 125.8, 123.2, 122.1, 121.4, 111.7, 108.6, 51.2.

4.8. Synthesis of methyl 3-chloro-2-oxoindoline-3-carboxylate (128)

To a stirring solution of methyl 1*H*-indole-3-carboxylate (**126**) (350 mg, 2 mmol) in DMF (12 mL), NCS (**127**) (400 mg, 3 mmol) was added piecewise at room temperature. The reaction mixture was stirred for 1.5 hour. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the residue was purified by recrystallization in diethyl ether/hexane mixture to give methyl 2-chloro-1-methyl-1*H*-indole-3-carboxylate (**128**) (320 mg, 71%) as colorless cubic crystals, m.p. 154-155 ˚C.



^{1}H-NMR (400 MHz, MeOD) δ 7.43 – 7.33 (m, 2H), 7.11 (td, *J* = 7.7, 0.9 Hz, 1H), 6.97 (dd, *J* = 7.7, 0.9 Hz, 1H), 3.78 (s, 3H, H-1a).

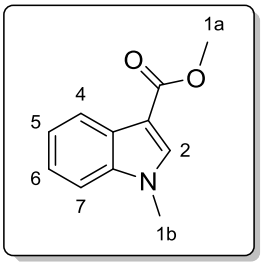
^{13}C-NMR (100 MHz, MeOD) δ 173.2, 167.0, 143.3, 132.6, 128.6, 125.8, 124.5, 112.0, 66.3, 54.7.

IR (ATR) 1759, 1723, 1614, 1223, 1018, 750, 617

Elemental Analysis Anal. Calcd. for $C_{10}H_8ClNO_3$; C 53.23, H 3.57, N 6.21; Found: C 53.31, H 3.54, N 6.16.

4.9. Synthesis of methyl 1-methyl-1*H*-indole-3-carboxylate (134)[64]

To a stirring solution of methyl 1*H*-indole-3-carboxylate (**126**) (175 mg, 1 mmol) in dry THF (15 mL), sodium hydride (29 mg, 1.2mmol) was added piecewise for 15 min in ice bath. Then, methyl iodide (0.07 ml, 1.1mmol) was added dropwise to the reaction medium. The reaction mixture was stirred for 5 hour at room temperature. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, methyl 1-methyl-1*H*-indole-3-carboxylate (**134**) was obtained. Pale orange crystals (136 mg, 72%) from chloroform/n-hexane, m.p. 87-88 ˚C (Lit. m.p. 88-89 ˚C).

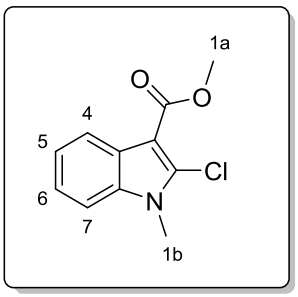


^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.11 (m, 1H), 7.78 (s, 1H), 7.43 – 7.22 (m, 3H), 3.94 (s, 3H, H-), 3.80 (s, 3H, H-);
^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.5, 137.2, 135.2, 126.6, 122.8, 121.9, 121.6, 109.8, 106.8, 50.9, 33.4.

4.10. Synthesis of methyl 2-chloro-1-methyl-1*H*-indole-3-carboxylate (135)[71]

To a stirring solution of methyl 1-methyl-1*H*-indole-3-carboxylate (**134**) (190 mg, 1mmol) in DMF (6 mL), NCS (200 mg, 1.5mmol) was added piecewise. The reaction mixture was stirred for 1 hour at room temperature. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the residue was purified by recrystallization in diethyl ether/hexane mixture

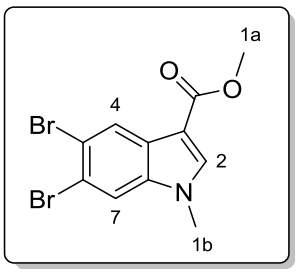
to give methyl 2-chloro-1-methyl-1*H*-indole-3-carboxylate (**135**) (150 mg, 67%) as colorless snowflake crystals, m.p. 116-118 ˚C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.28 – 7.97 (m, 1H), 7.39 – 7.16 (m, 3H), 3.94 (s, 3H, H-), 3.73 (s, 3H, H-).
^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.3, 135.4, 132.5, 125.6, 123.1, 122.4, 121.4, 109.4, 103.4, 51.1, 30.1.

4.11. Synthesis of methyl 5,6-dibromo-1-methyl-1*H*-indole-3-carboxylate (137)

To a stirring solution of methyl 1-methyl-1*H*-indole-3-carboxylate (**134**) (380 mg, 2 mmol) in DMF (10 mL), NBS (750 mg, 4.2 mmol) was added piecewise. The reaction mixture was stirred for 1.5 hour at room temperature. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the residue was purified by recrystallization in diethyl ether/hexane mixture to give methyl 5,6-dibromo-1-methyl-1*H*-indole-3-carboxylate (**137**) (420 mg, 60%) as pure white powder, m.p. 181-183 ˚C

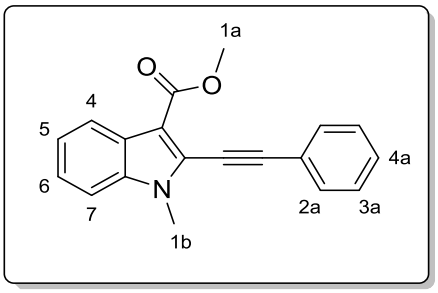


^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.65 (s, 1H), 7.51 (s, 1H), 3.83 (s, 3H), 3.71 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.6, 136.8, 136.5, 127.0, 126.0, 118.2, 117.7, 114.7, 106.7, 51.2, 33.7.
IR (ATR) 2946, 1685, 1530, 1471, 1226, 1114, 773, 596
HRMS calcd for $C_{11}H_9Br_2NO_2$ $[M+H]^+$: 345.90728. Found: 345.91201

4.12. Synthesis of methyl 1-methyl-2-(phenylethynyl)-1*H*-indole-3-carboxylate (139)

Cuprous iodide (8 mg, 0,04 mmol), 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (38 mg, 0,08 mmol), palladium acetate (9 mg, 0.04 mmol) and

dry diisopropyl amine (4 mL, 0.031 mmol) were added in a solution of methyl 2-chloro-1-methyl-1*H*-indole-3-carboxylate (**135**) (224 mg, 1 mmol) in dry THF (20 mL) under nitrogen atmosphere. Then phenyl acetylene (**83**) (0,13 ml, 1,2 mmol) was added to the the reaction mixture dropwise at room temperature. The mixture was heated to reflux temperature and stirred for 3 hours. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the product was chromatographed on silica gel column eluting with hexane/EtOAc (7:1) to give methyl 1-methyl-2-(phenylethynyl)-1*H*-indole-3-carboxylate (**139**). Yellow solid (165 mg, 57%) from diethyl ether/n-hexane, m.p. 87-89 ˚C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.12 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.35 – 7.30 (m, 3H), 7.27 – 7.16 (m, 3H), 3.91 (s, 3H, H-), 3.83 (s, 3H, H-);

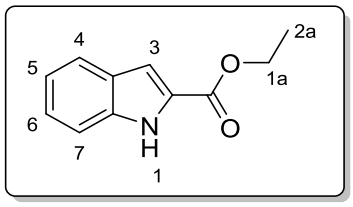
^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.1, 135.2, 130.0, 127.4, 126.7, 125.3, 124.2, 122.2, 120.6, 120.4, 120.3, 108.3, 107.8, 98.7, 78.2, 49.2, 29.2.

IR (ATR) 2915, 2849, 1729, 1627, 1453, 1393, 1179, 745

HRMS calcd for $C_{19}H_{15}NO_2$ $[M+H]^+$: 290.11756, Found: 290.11690

4.13. Synthesis of ethyl-1*H*-indole-2-carboxylate (141)[65]

Starting material indole-2-carboxylic acid (**104**) **(**3 g, 18.6 mmol) was dissolved in ethanol (50 mL) and sulfuric acid (1 mL) was added as catalyst. The solution was refluxed at 78 °C, and then it was stirred overnight. After completion of the reaction, solvent was removed and sat. $NaHCO_3$ was added until reaching pH=7. The resulting mixture was extracted with ethyl acetate (3 × 50 mL). The organic phases were combined and dried over $MgSO_4$. Then, the solvent was evaporated under reduced pressure to give ethyl-1*H*-indole-2-carboxylate (**141**). White solid (3.31 g, 94%) from ethyl acetate/n-hexane, m.p 118-119 ˚C (lit. m.p. 124-125 ˚C).

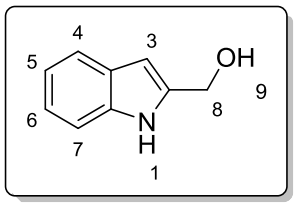


^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H, H-1), 7.69 (dd, $J_{4,5}$ = 8.1, $J_{4,6}$ = *0*.9 Hz, 1H, H-4), 7.43 (dd, $J_{7,6}$ = 8.3, $J_{7,5}$ = 0.9 Hz, 1H, H-7), 7.32 (ddd, $J_{6,7}$ = 8.3, $J_{6,5}$ = 7.0, $J_{6,4}$ = 0.9 Hz, 1H, H-6), 7.24 (dd, $J_{3,1}$ = 2.0, $J_{3,4}$ = 0.9 Hz, 1H, H-3), 7.15 (ddd, $J_{5,4}$ = 8.1, $J_{5,6}$ = 7.0, $J_{5,7}$ = 0.9 Hz, 1H, H-5), 4.42 (q, $J_{1a,2a}$ = 7.1 Hz, 2H, H-1a), 1.42 (t, $J_{2a,1a}$ = 7.1 Hz, 3H, H-2a).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 134.4, 133.5, 124.9, 122.8, 120.1, 118.3, 109.4, 106.3, 58.6, 11.9.

4.14. Synthesis of 1*H*-indol-2-ylmethanol (142)[66]

A solution of ethyl-1*H*-indole-2-carboxylate (**141**) (1 eq, 3.4 g, 17.6 mmol) in dry THF (30 mL) was added to a suspension of $LiAlH_4$ (1.37 g, 36 mmol) in dry THF (40 mL) dropwise while cooling in an ice bath. After the reaction was completed (2 h), saturated NH_4Cl solution was added slowly in order to quench excess $LiAlH_4$. Extraction was done with ethyl acetate (3 × 50 mL) and water (100 mL). The combined organic extracts were dried over $MgSO_4$. The solvent was evaporated to give 1*H*-indol-2-ylmethanol (**142**). White solid (2.54 g, 96%) from ethyl acetate/n-hexane, m.p. 75-77 ˚C (lit. m.p. 75 ˚C).



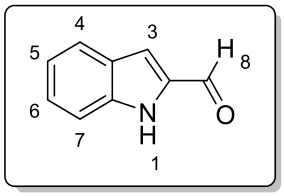
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (bs, 1H, H-1), 7.50 (bd, $J_{4,5}$ = 7.8 Hz, 1H, H-4), 7.23 (bd, $J_{7,6}$ = 8.0 Hz, 1H, H-7), 7.11 (ddd, $J_{6,7}$ = 8.0, $J_{6,5}$ = 7.0, $J_{6,4}$ = 1.0 Hz, 1H, H-6), 7.03 (ddd, $J_{5,4}$ = 7.8, $J_{5,6}$ = 7.0, $J_{5,7}$ = 1.1 Hz, 1H, H-5), 6.31 (d, $J_{3,4}$ = 0.8, 1H, H-3), 4.69 (s, 2H, H-8), 2.13 (bs, 1H, H-9).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 136.4, 128.0, 122.2, 120.7, 120.0, 111.1, 100.6, 58.5.

4.15. Synthesis of 1*H*-indole-2-carbaldehyde (143)[67]

To a stirred solution of 1*H*-indol-2-ylmethanol (**142**) (2.46 g, 16.7 mmol) in acetone (50 mL), molecular sieve and MnO_2 (10 eq, 14.52 g, 167 mmol) were added at 25 °C and the resulting mixture was stirred overnight. The reaction mixture was filtered over celite by using vacuum filtration and washed with CH_2Cl_2. The filtered solution

was evaporated to give 1*H*-indole-2-carbaldehyde (**143**) (2.26 g, 93%) as pale yellow solid, m.p. 75-76 ˚C.

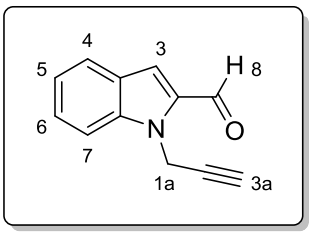


^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H, H-8), 9.00 (bs, 1H, H-1), 7.76 (dt, $J_{4,5}$ = 8.1, $J_{4,6}$ = $J_{4,3}$ = 0.8 Hz, 1H, H-4), 7.45 (dd, $J_{7,6}$ = 8.3, $J_{7,5}$ = 1.0 Hz, 1H, H-7), 7.40 (ddd, $J_{6,7}$ = 8.3, $J_{6,5}$ = 6.7, $J_{6,4}$ = 0.8 Hz, 1H, H-6), 7.29 (dd, $J_{3,1}$ = 1.9, $J_{3,4}$ = 0.8 Hz, 1H, H-3), 7.19 (ddd, $J_{5,4}$ = 8.1, $J_{5,6}$ = 6.7, $J_{5,7}$ = 1.0 Hz, 1H, H-5).

^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 138.0, 136.0, 127.4, 123.4, 121.3, 114.9, 112.5.

4.16. Synthesis of 1-prop-2-ynyl-1*H*-indole-2-carbaldehyde (105)[68]

To a stirred solution of 1*H*-indole-2-carbaldehyde (**143**) (2.64 g, 15.6 mmol) in dry DMF (20 mL), solid NaH was added (0.48 g, 20 mmol) piecewise over a period of 15 min while stirring in an ice bath. Propargyl bromide (80 wt. % in toluene) (2.4 mL, 21.8 mmol) was diluted with 1:3 ratio of DMF and added to the stirring the solution slowly at room temperature. After completion of the reaction (6 h), brine was added (50 mL) and extraction was done with ethyl acetate (3 × 50 mL). The organic extracts were dried over $MgSO_4$ and filtered. After evaporation of the solvent, the product 1-prop-2-ynyl-1*H*-indole-2-carbaldehyde (**105**) was obtained. Yellow solid (2.56 g, 97%) from ethyl acetate/n-hexane, m.p. 101-103 ˚C.



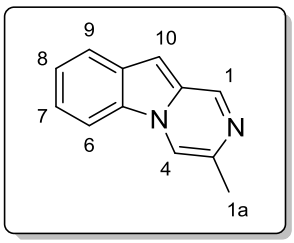
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H, H-8), 7.68 (dt, $J_{4,5}$ = 8.0, $J_{4,6}$ = $J_{4,3}$ = 0.9 Hz, 1H, H-4), 7.47 (dd, $J_{7,6}$ = 8.5, $J_{7,5}$ = 1.0 Hz, 1H, H-7), 7.40 (ddd, $J_{6,7}$ = 8.5, $J_{6,5}$ = 7.0, $J_{6,4}$ = 0.9 Hz, 1H, H-6), 7.22 (d, $J_{3,4}$ = 0.9 Hz, 1H, H-3), 7.15 (ddd, $J_{5,4}$ = 8.0, $J_{5,6}$ = 7.0, $J_{5,7}$ = 1.0 Hz, 1H, H-5), 5.39 (d, $J_{1a,3a}$ = 2.5 Hz, 2H, H-1a), 2.20 (t, $J_{3a,1a}$ = 2.5 Hz, 1H, H-3a).

^{13}C NMR (100 MHz, $CDCl_3$) δ 182.6, 140.1, 134.5, 127.4, 126.6, 123.5, 121.5, 118.7, 110.8, 78.2, 72.5, 33.9.

4.17. Synthesis of 3-methylpyrazino[1,2-*a*]indole (106)[69]

Procedure for allylamine reaction: To a stirred solution of 1-prop-2-ynyl-1*H*-indole-2-carbaldehyde (**105**) (0.360 g, 1.97 mmol) in EtOH (20 ml), solid Cs_2CO_3 was added (0.64 g, 1.97 mmol) piecewise. Allylamine (0.30 mL, 3.94 mmol) was diluted with EtOH (5 mL) and added to the stirring solution dropwise. The reaction mixture was stirred overnight. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the product was choromatographed on a silica gel column eluting with hexane/EtOAc (4:1) to give 3-methylpyrazino[1,2-*a*]indole (**106**). Yellow solid (0.233 g, 65%) from ethyl acetate/n-hexane, m.p. 163-165 ˚C (lit. m.p. 173 ˚C).

Procedure for propargylamine reaction: To a stirred solution of 1-prop-2-ynyl-1*H*-indole-2-carbaldehyde (**105**) (0.360 g, 1.97 mmol) in EtOH (20 mL), solid Cs_2CO_3 was added (0.64 g, 1.97 mmol) piecewise. Propargyl amine (0.25 mL, 3.94 mmol) was diluted with EtOH (5 mL) and added to the stirring solution dropwise. The reaction mixture was stirred overnight. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtrated. After evaporation of the solvent, the residue was chromatographed on a silica gel column eluting with hexane/EtOAc (4:1) to give 3-methylpyrazino[1,2-*a*]indole (**106**). Yellow solid (0.183 g, 51%) from ethyl acetate/n-hexane, m.p. 163-165 ˚C (lit. m.p. 173 ˚C).

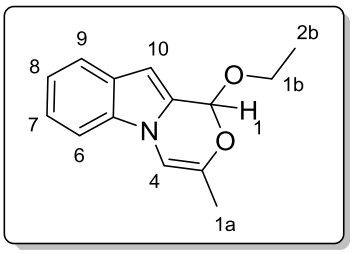


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, $J_{1,10}$ = 1.2 Hz, 1H, H-1), 7.98 (bs, 1H, H-4), 7.94 – 7.85 (m, 2H), 7.46 – 7.34 (m, 2H), 6.96 (s, J = 7.0 Hz, 1H, H-10), 2.51 (d, $J_{1a,4}$ = 1.0 Hz 3H, H-1a).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 132.3, 129.3, 129.0, 128.4, 123.5, 122.3, 122.1, 113.4, 110.8, 94.8, 20.7.

4.18. Synthesis of 1-ethoxy-3-methyl-1*H*-[1,4]oxazino[4,3-*a*]indole (151)[70]

To a stirred solution of 1-prop-2-ynyl-1*H*-indole-2-carbaldehyde (**105**) (0.360 g, 1.97 mmol) in EtOH (20 mL), solid Cs_2CO_3 was added (0.64 g, 1.97 mmol) piecewise. The reaction mixture was stirred overnight. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the crude product was chromatographed on a silica gel column, eluting with hexane/EtOAc (4:1) to give 1-ethoxy-3-methyl-1*H*-[1,4]oxazino[4,3-*a*]indole (**151**) (0.230 g, 51%) as brown solid.

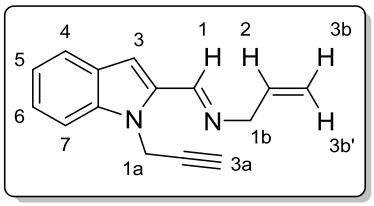


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dt, $J_{9,8}$ = 8.0, $J_{9,7}$ = 1.0 Hz, 1H, H-9), 7.36 (dd, $J_{6,7}$ = 8.4, $J_{6,8}$ = 1.0 Hz, 1H, H-6), 7.22 (ddd, $J_{7,6}$ = 8.4, $J_{7,8}$ = 7.0, $J_{7,9}$ = 1.0 Hz, 1H, H-7), 7.12 (ddd, $J_{8,9}$ = 8.0, $J_{8,7}$ = 7.0, $J_{8,6}$ = 1.0 Hz, 1H, H-8), 6.67 (bs, 1H, H-10), 6.48 (bs, 1H, H-4), 6.23 (s, 1H, H-1), 4.00 – 3.89 (A part of AB system, m, 1H, H-1b), 3.80 – 3.71 (B part of AB system, m, 1H, H-1b), 2.01 (d, $J_{1a,4}$ = 1.0 Hz, 3H, H-1a), 1.28 (t, $J_{2b,1b}$ = 7.2 Hz, 3H, H-2b).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 132.4, 128.0, 127.8, 122.3, 121.5, 120.4, 109.0, 101.3, 98.2, 94.7, 63.6, 17.5, 15.3.

4.19. Synthesis of *N*-[(1E-prop-2-ynyl-1*H*-indol-2-yl)methylidene]prop-2-en-1-amine (152)

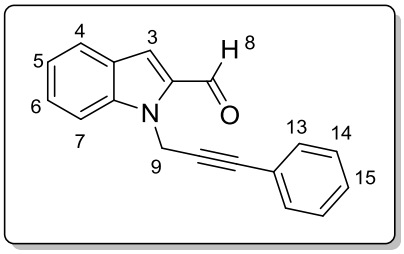
1-Prop-2-ynyl-1*H*-indole-2-carbaldehyde (**105**) (0.360 g, 1.97 mmol) dissolved in EtOH (20 mL) and diluted allylamine (0.30 mL, 3.94 mmol) in EtOH (5 mL) was added to the stirring solution dropwise. After completion of the reaction (2 h) at room temperature, extraction was done with ethyl acetate (30 mL) and water (10 mL) quickly. The organic extracts were dried over $MgSO_4$ and filtered. After evaporation of the solvent, the product *N*-[(1*E*)-(1-prop-2-ynyl-1*H*-indol-2-yl)methylidene]prop-2-en-1-amine (**152**) (0.360 g, 83%) was obtained as yellow solid.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (t, $J_{1,1b}$ = 1.1 Hz, 1H, H-1), 7.55 (dd, $J_{4,5}$ = 8.0, $J_{4,6}$ = 1.0 Hz, 1H, H-4), 7.42 (dd, $J_{7,6}$ = 8.5, $J_{7,5}$ = 1.0 Hz, 1H, H-7), 7.26 (ddd, $J_{6,7}$ = 8.5, $J_{6,5}$ = 7.0, $J_{6,4}$ = 1.0 Hz, 1H, H-6), 7.07 (ddd, $J_{5,4}$ = 8.0, $J_{5,6}$ = 7.0, $J_{5,7}$ = 1.0 Hz, 1H, H-5), 6.72 (bs, 1H, H-3), 6.08 – 5.91 (m, 1H, H-2), 5.63 (d, $J_{1a,3a}$ = 2.5 Hz, 2H, H-1a), 5.21 (A part of AB system, dq, $J_{3b',2}$ = 17.2, $J_{3b',3b}$ = $J_{3b',1b}$ = 1.8 Hz, 1H, H-3b'), 5.08 (B part of AB system, dq, $J_{3b,2}$ = 10.3, $J_{3b,3b'}$ = $J_{3b',1b}$ = 1.8 Hz, 1H, H-3b), 4.22 – 4.11 (m, 2H,H-1b), 2.14 (t, $J_{3a,1a}$ = 2.5 Hz, 1H, H-3a).

4.20. Synthesis of 1-(3-phenylprop-2-ynyl)-1*H*-indole-2-carbaldehyde (157)

Cuprous iodide (3,8 mg, 0.02 mmol), triphenylphosphine (13.1 mg, 0.05 mmol), palladium acetate (4,5 mg, 0.02 mmol), and dry diisopropylamine (1 mL, 7 mmol) were added in a solution of iodobenzene (0.24 mL, 2.18 mmol) in dry THF (25 mL) under nitrogen atmosphere. Then 1-prop-2-ynyl-1*H*-indole-2-carbaldehyde (**105**) (0.360 g, 1.97 mmol) dissolved in THF (10 mL) was added to the reaction mixture at room temperature. The mixture was heated to reflux temperature and stirred for 3 hours. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the product was chromatographed on silica gel column eluting with hexane/EtOAc (3:1) to isolate 1-(3-phenylprop-2-ynyl)-1*H*-indole-2-carbaldehyde (**157**). Yellow solid (0,357 g, 70%) from ethyl acetate/n-hexane, m.p. 101-103 ˚C.

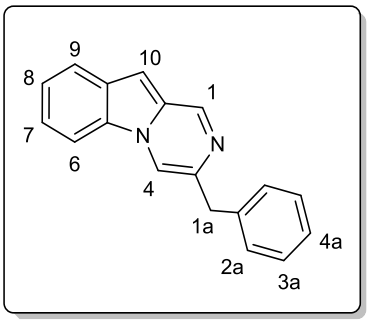


^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H, H-8), 7.75 (dt, $J_{4,5}$ = 8.0, $J_{4,6}$ = $J_{4,3}$= 0.9 Hz, 1H, H-4), 7.62 (dd, $J_{7,6}$ = 8.4, $J_{7,5}$ = 0.9 Hz, 1H, H-7), 7.46 (ddd, $J_{6,7}$ = 8.4, $J_{6,5}$ = 7.0, $J_{6,4}$ = 0.9 Hz, 1H, H-6), 7.34 (m, 2H), 7.28 (d, $J_{3,4}$ = 0.9 Hz, 1H, H-3), 7.26 – 7.19 (m, 4H), 5.66 (s, 2H, H-9).

^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 140.3, 134.6, 131.8, 128.4, 128.2, 127.3, 126.7, 123.5, 122.4, 121.5, 118.6, 111.1, 84.2, 83.7, 34.8.

4.21. Synthesis of 3-benzylpyrazino[1,2-*a*]indole (158)[72]

To a stirred solution of 1-(3-phenylprop-2-ynyl)-1*H*-indole-2-carbaldehyde (**157**) (0.260 g, 1 mmol) in EtOH (20 mL), solid Cs_2CO_3 was added (0.33 g, 1 mmol) piecewise. Allylamine (0.15 mL, 2 mmol) was dissolved in EtOH (5 mL) and added to the stirring solution dropwise. The reaction mixture was stirred overnight. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the product was chromatographed on silica gel column eluting with hexane/EtOAc (6:1) to give 3-benzylpyrazino[1,2-*a*]indole (**158**). Orange solid (0.098 g, 38%) from ethyl acetate/hexane, m.p. 86-87 ˚C (lit. m.p. 89˚C).



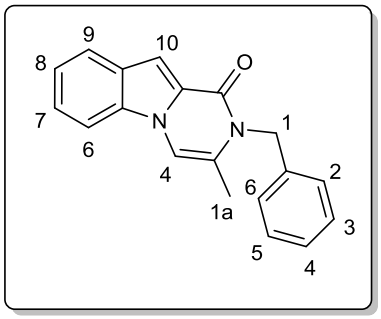
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (bs, 1H, H-1), 7.84 – 7.79 (m, 2H), 7.76 (d, J = 7.8 Hz, 1H), 7.35 – 7.27 (m, 5H), 7.22 – 7.15 (m, 2H), 6.90 (s, 1H, H-10), 4.05 (s, 2H, H-1a).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 139.0, 135.6, 129.3, 129.3, 129.1, 128.7, 128.6, 126.6, 123.6, 122.3, 122.3, 114.4, 110.8, 95.3, 40.9.

4.22. Synthesis of 2-benzyl-3-methylpyrazino[1,2-*a*]indol-1(2*H*)-one (160)[73]

To a stirred solution of 1-prop-2-ynyl-1*H*-indole-2-carbaldehyde (**105**) (0.360 g, 1.97 mmol) in EtOH (20 mL), solid Cs_2CO_3 was added (0.64 g, 1.97 mmol) piecewise. Benzylamine (1.08 mL, 9.85 mmol) was diluted with EtOH and added to the stirring solution dropwise. The reaction mixture was stirred overnight. After completion of the reaction monitoring by TLC, the solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The

organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the product was chromatographed on silica gel column eluting with hexane/EtOAc (6:1) to isolate 2-benzyl-3-methylpyrazino[1,2-*a*]indol-1(2*H*)-one (**160**) was obtained. Yellow solid (0,142 g, 25%) from ethyl acetate/n-hexane, m.p. 182-184 ˚C.

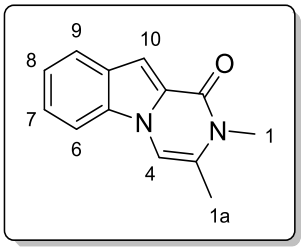


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dt, $J_{9,8}$ = 8.1, $J_{9,7}$ = $J_{9,10}$= 1.0 Hz, 1H, H-9), 7.57 (dd, $J_{6,7}$ = 8.4, $J_{6,8}$ = 1.0 Hz, 1H, H-6), 7.35 (bs, 1H, H-10), 7.32 (ddd, $J_{7,6}$ = 8.4, $J_{7,8}$ = 7.0, $J_{7,9}$ = 1.0 Hz, 1H, H-7), 7.27 – 7.12 (m, 6H), 7.08 (bs, 1H, H-4), 5.26 (s, 2H, H-1), 2.14 (d, $J_{1a,4}$ = 0.8, 3H, H-1a).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 137.3, 131.7, 128.8, 127.6, 127.3, 126.8, 126.4, 123.8, 122.7, 122.4, 122.3, 110.4, 104.1, 102.7, 45.7, 17.3.

4.23. Synthesis of 2-methyl-3-methylpyrazino[1,2-*a*]indol-1(2*H*)-one (161)[74]

To a stirred solution of 1-prop-2-ynyl-1*H*-indole-2-carbaldehyde (**105**) (0.360 g, 1.97 mmol) in EtOH (20 mL), solid Cs_2CO_3 was added (0.64 g, 1.97 mmol) piecewise. Methylamine (40% in H_2O, 0.85 ml, 9.85 mmol) was diluted with EtOH and added to the stirring solution dropwise. The reaction mixture was stirred overnight. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the product was chromatographed on silica gel column eluting with hexane/EtOAc (4:1) to give 2,3-dimethylpyrazino[1,2-*a*]indol-1(2*H*)-one (**161**) (42 mg, 10%) as a dark yellow solid. m.p. 198-201 ˚C (lit. m.p. 206-207.5 ˚C).



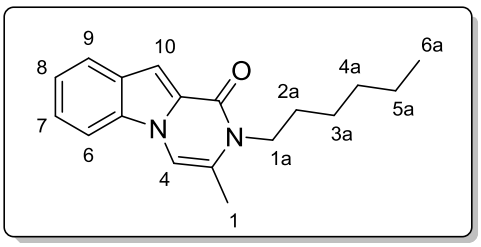
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dt, $J_{9,8}$ = 8.0, $J_{9,7}$ = $J_{9,10}$= 1.0 Hz, 1H, H-9), 7.59 (dd, $J_{6,7}$ = 8.4, $J_{6,8}$ = 1.0 Hz, 1H, H-6), 7.36 (ddd, $J_{7,6}$ = 8.4, $J_{7,8}$ = 7.0, $J_{7,9}$ = 1.0 Hz, 1H, H-7), 7.34 (bs, 1H, H-10), 7.28 (ddd, $J_{8,9}$ = 8.0, $J_{8,7}$ = 7.0,

$J_{8,6}$ = 1.0 Hz, 1H, H-8), 7.09 (bs, 1H, H-), 3.47 (s, 3H, H-1), 2.27 (d, $J_{1a,4}$ = 0.8, 3H, H-1a).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 131.5, 127.5, 126.9, 123.5, 122.6, 122.4, 122.1, 110.4, 103.6, 101.8, 29.5, 17.6.

4.24. Synthesis of 2-hexyl-3-methylpyrazino[1,2-*a*]indol-1(2*H*)-one (162)

To a stirred solution of 1-prop-2-ynyl-1*H*-indole-2-carbaldehyde (**105**) (0.360 g, 1.97 mmol) in EtOH (20 mL), solid Cs_2CO_3 was added (0.64 g, 1.97 mmol) piecewise. Hexylamine (1.3 ml, 9.85 mmol) was diluted with EtOH and added to the stirring solution dropwise. The reaction mixture was stirred overnight. After completion of the reaction monitoring by TLC, solvent was removed and water (50 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined and dried over $MgSO_4$, then filtered. After evaporation of the solvent, the crude product was chromatographed on a silica gel column, eluting with hexane/EtOAc (4:1) to give 2-hexyl-3-methylpyrazino[1,2-*a*]indol-1(2*H*)-one (**162**) (0.117 g, 21%) as a dark green viscous oil**.**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dt, $J_{9,8}$ = 8.0, $J_{9,7}$ = $J_{9,10}$ = 1.0 Hz, 1H, H-9), 7.55 (dd, $J_{6,7}$ = 8.4, $J_{6,8}$ = 1.0 Hz, 1H, H-6), 7.29 (ddd, $J_{7,6}$ = 8.4, $J_{7,8}$ = 7.0, $J_{7,9}$ = 1.0 Hz, 1H, H-7), 7.21 (ddd, $J_{8,9}$ = 8.0, $J_{8,7}$ = 7.0, $J_{8,6}$ = 1.0 Hz, 1H, H-8), 7.19 (bs, 1H, H-10), 7.05 (bs, 1H, H-9), 3.94 – 3.88 (quasi t, 2H, H-1a), 2.27 (d, J = 0.9 Hz, 3H, H-1), 1.63 (quint, J = 7.6 Hz, 2H), 1.38 – 1.17 (m, 6H), 0.82 (t, $J_{6a,5a}$ = 7.0 Hz, 3H, H-6a).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 130.5, 126.6, 126.2, 122.4, 121.6, 121.1, 121.0, 109.3, 102.9, 100.8, 42.0, 30.5, 28.3, 25.6, 21.5, 16.2, 13.0.

IR (ATR) 2916, 2850, 1707, 1637, 1457, 1391, 1195, 1179, 802, 740.

HRMS calcd for $C_{18}H_{22}N_2O$ $[M+H]^+$: 283.18049. Found: 283.18575

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APPENDIX A

SPECTRAL DATA

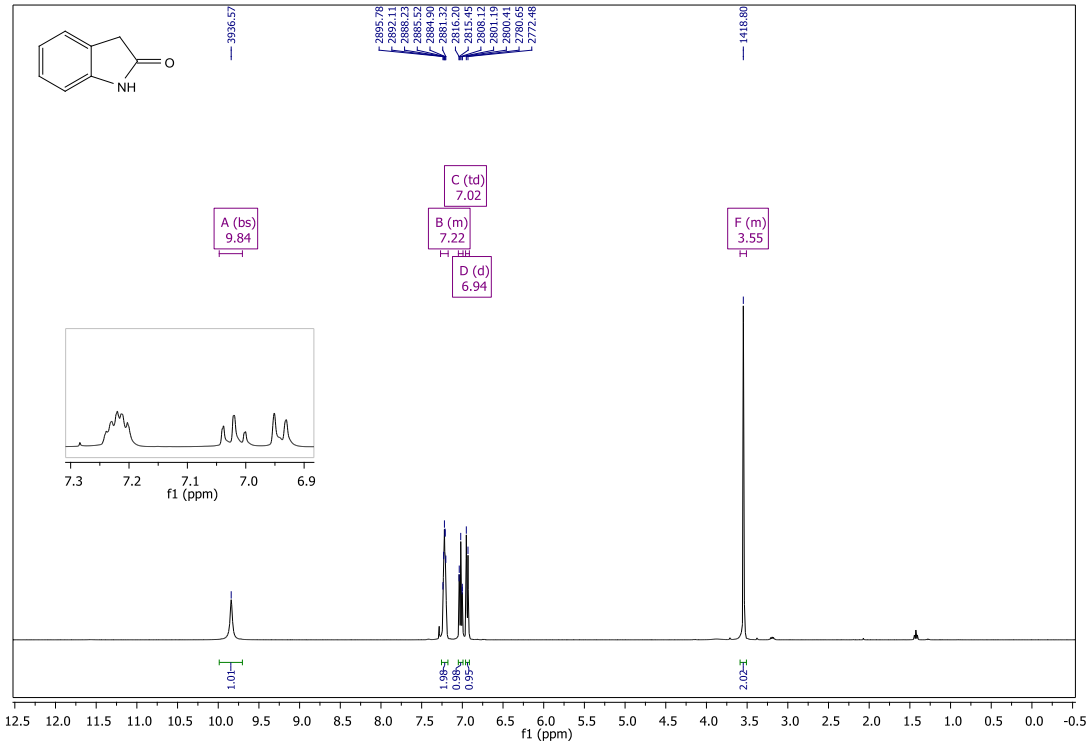

Figure 5 ^{1}H NMR Spectrum of Compound **3** in $CDCl_3$

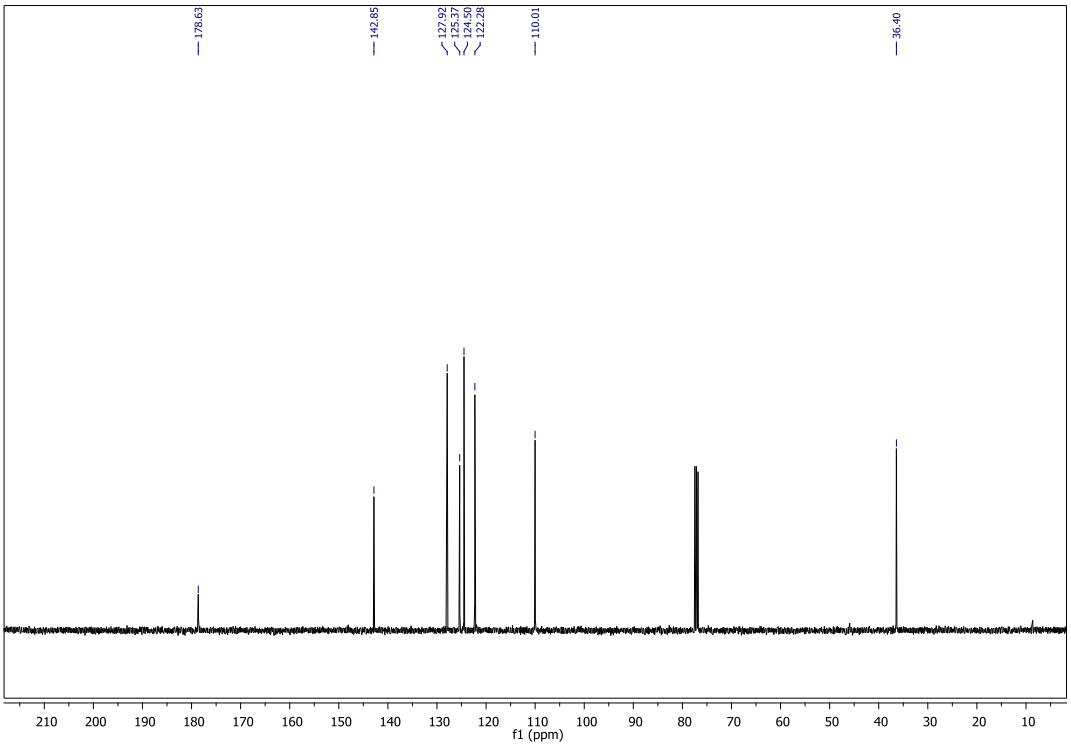

Figure 6 ^{13}C NMR Spectrum of Compound **3** in $CDCl_3$

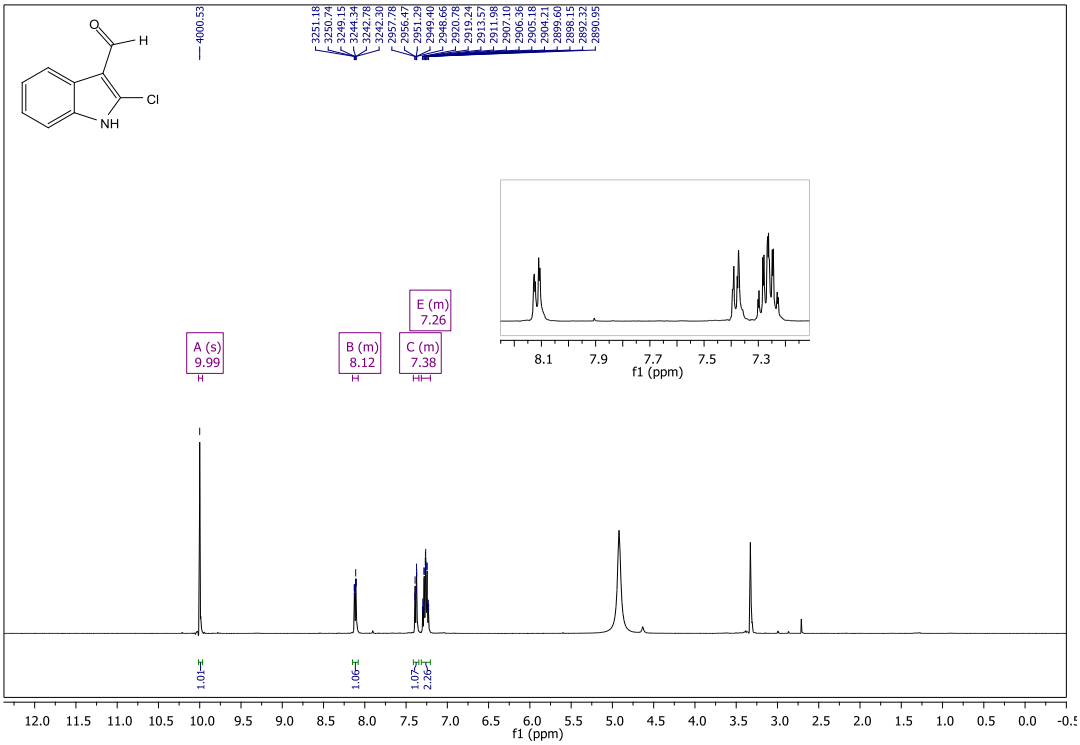

Figure 7 ^{1}H NMR Spectrum of Compound **109** in MeOD

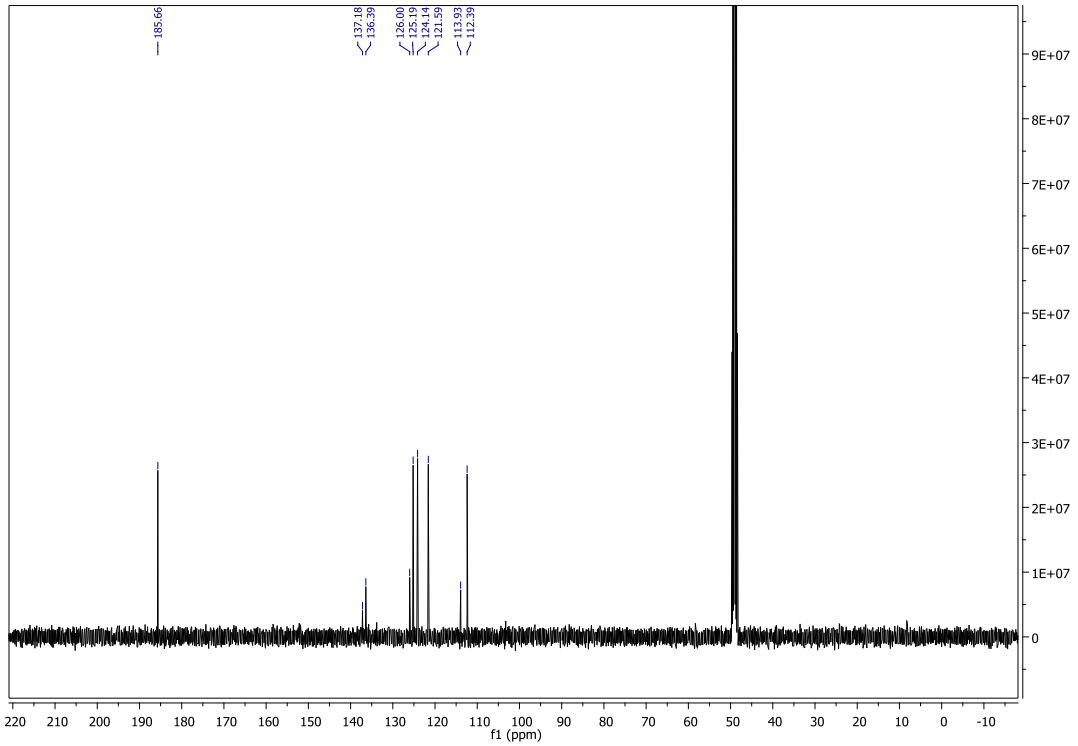

Figure 8 ^{13}C NMR Spectrum of Compound **109** in MeOD

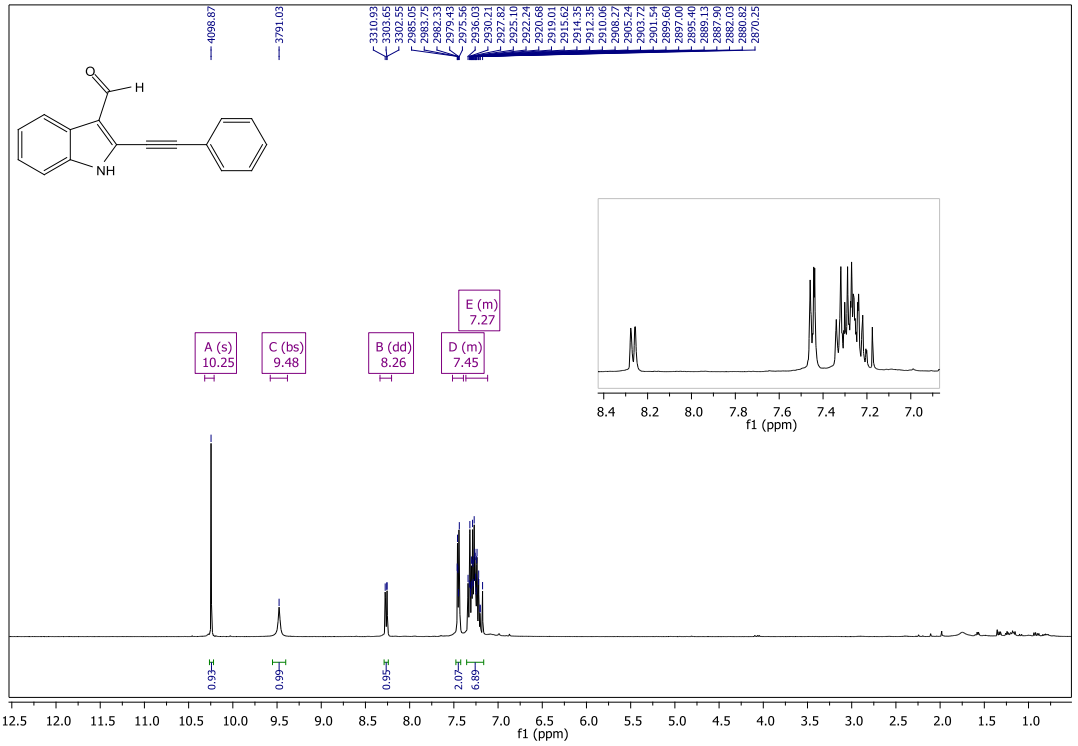

Figure 9 ^{1}H NMR Spectrum of Compound **119** in $CDCl_3$

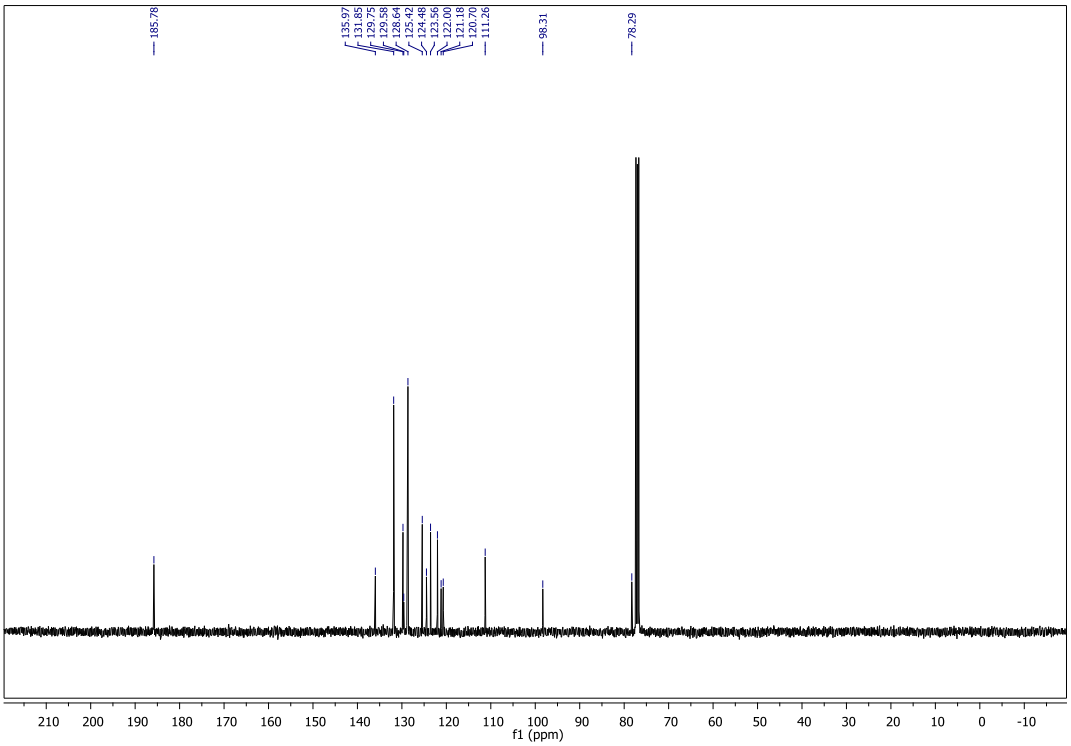

Figure 10 ^{13}C NMR Spectrum of Compound **119** in $CDCl_3$

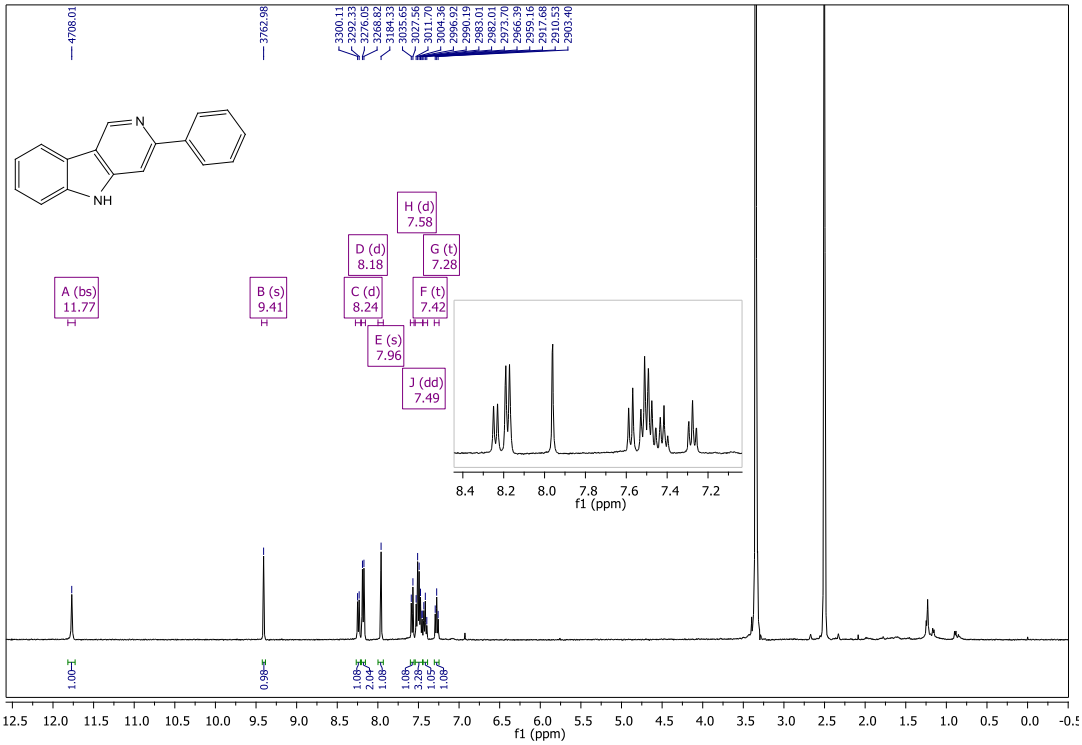

Figure 11 ^{1}H NMR Spectrum of Compound **120** in DMSO

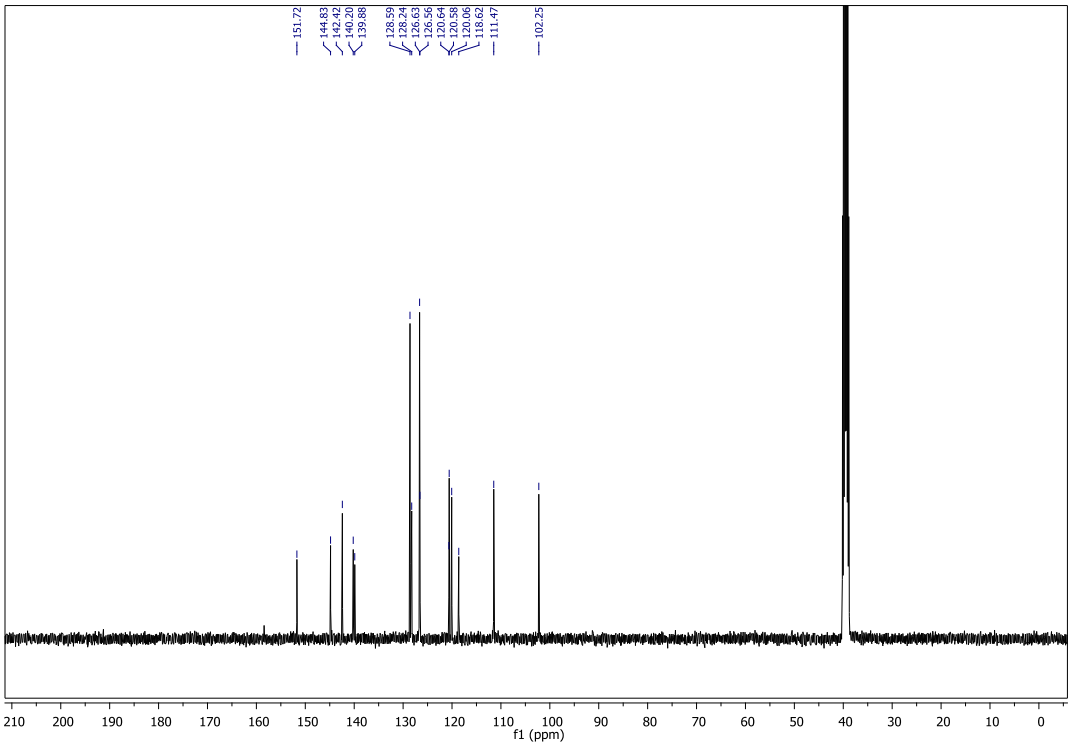

Figure 12 ^{13}C NMR Spectrum of Compound **120** in DMSO

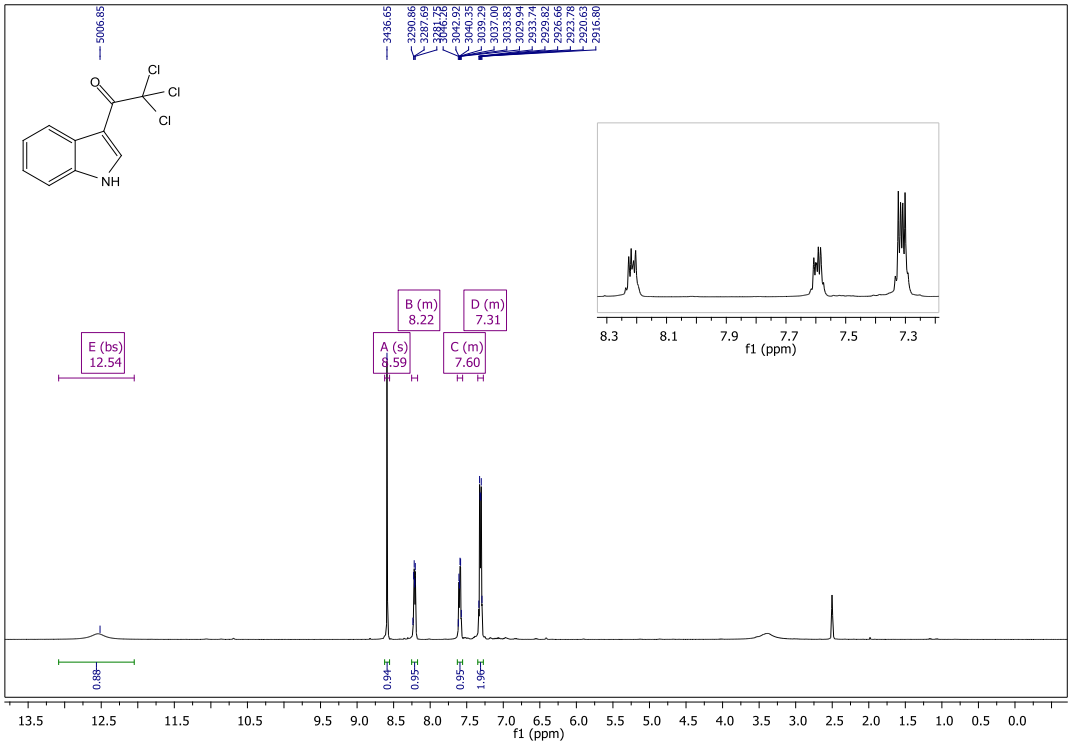

Figure 13 ^{1}H NMR Spectrum of Compound **125** in DMSO

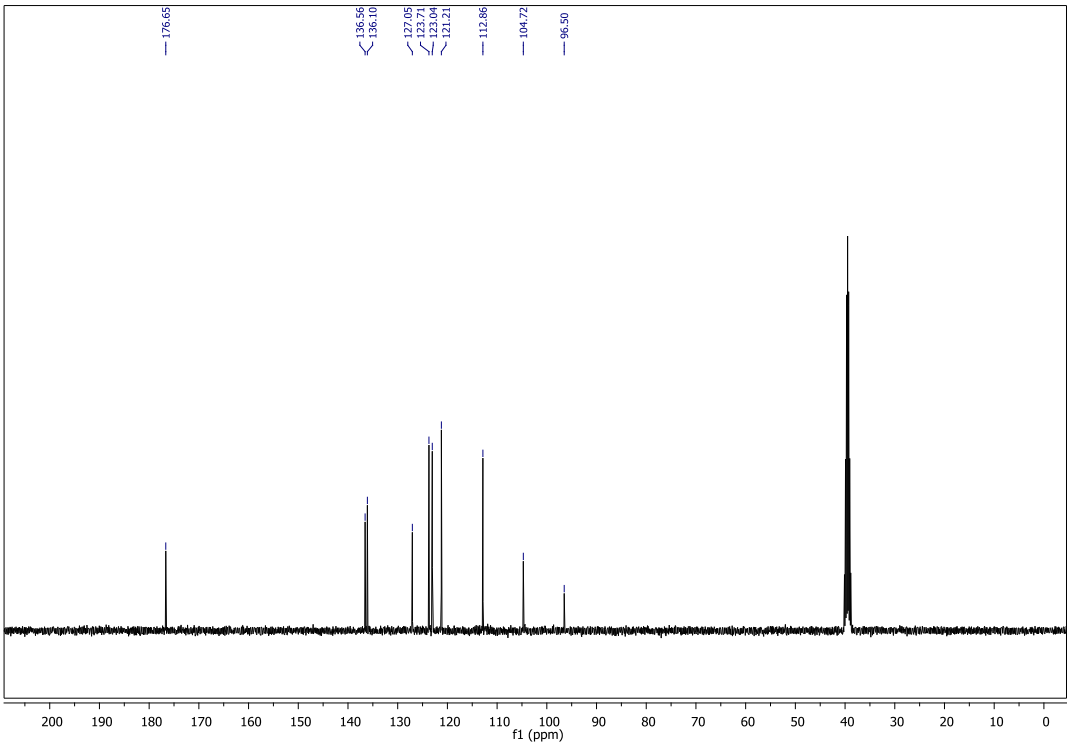

Figure 14 ^{13}C NMR Spectrum of Compound **125** in DMSO

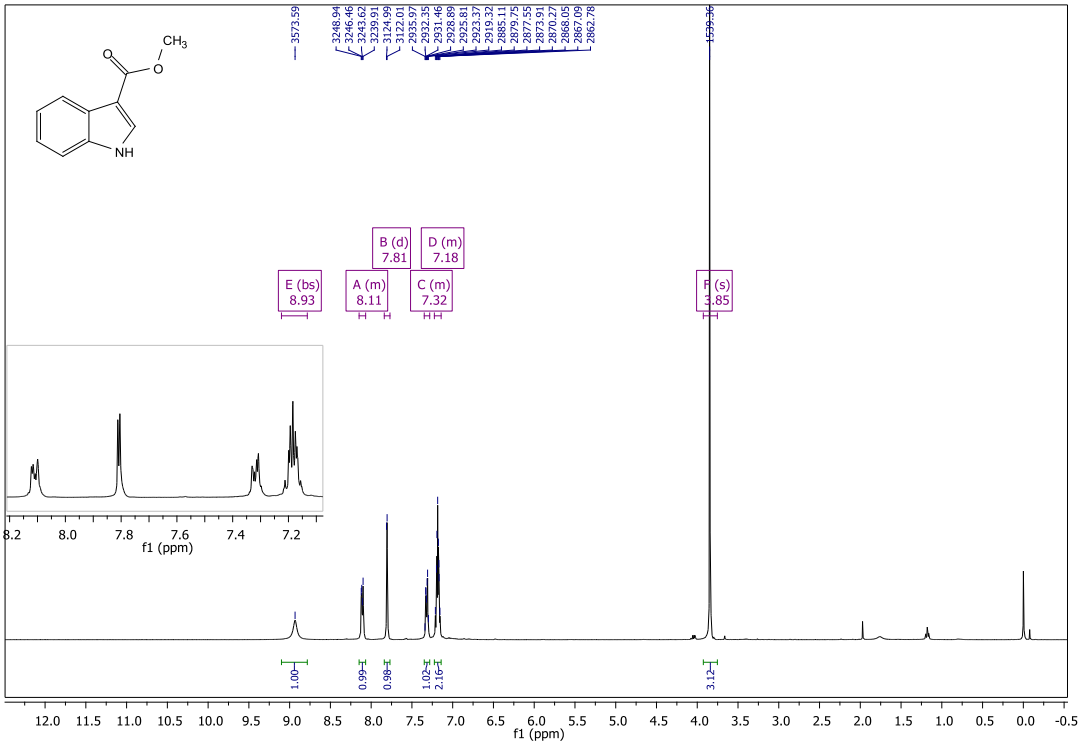

Figure 15 ^{1}H NMR Spectrum of Compound **126** in $CDCl_3$

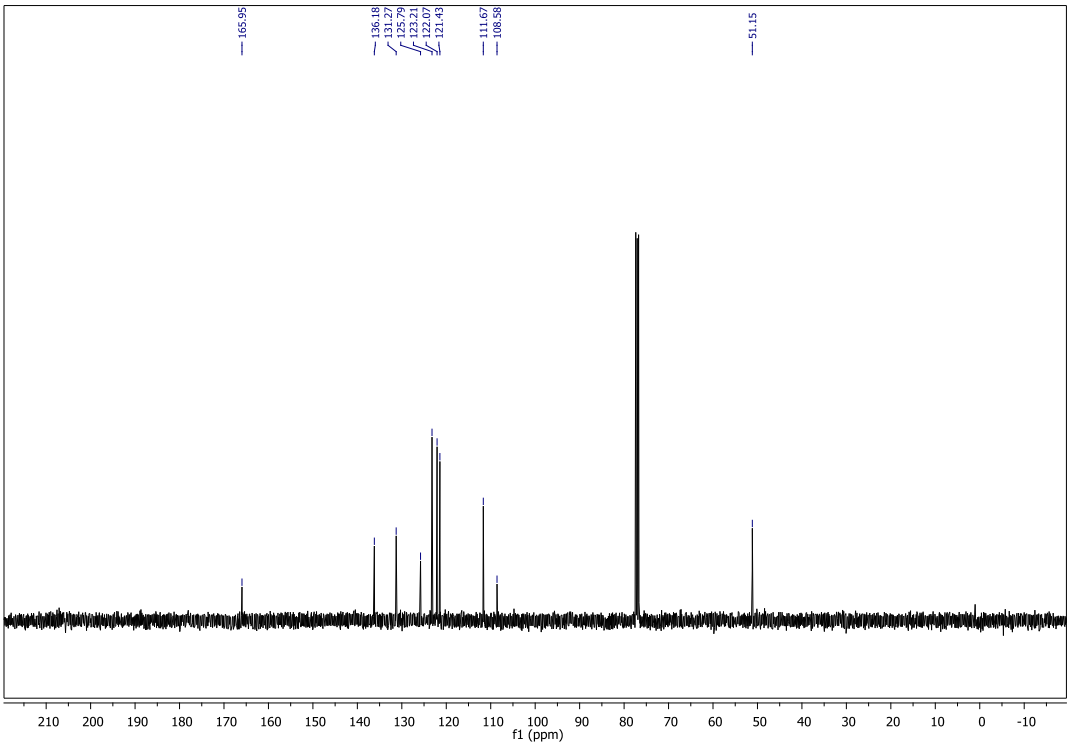

Figure 16 ^{13}C NMR Spectrum of Compound **126** in $CDCl_3$

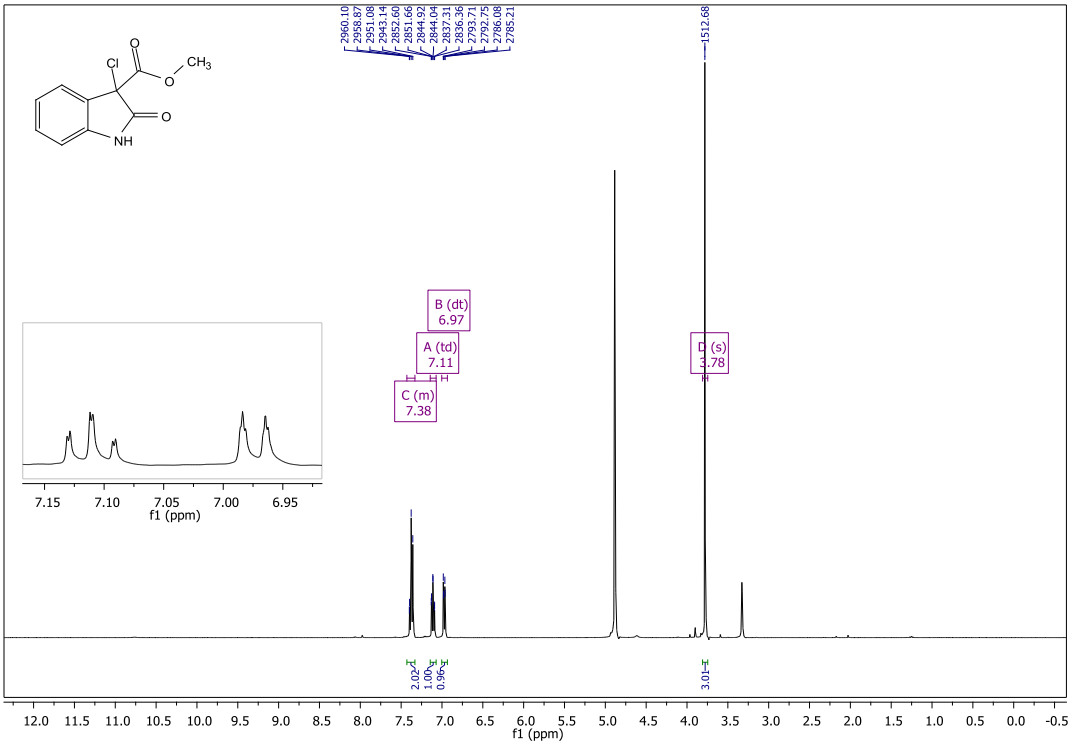

Figure 17 ^{1}H NMR Spectrum of Compound **128** in MeOD

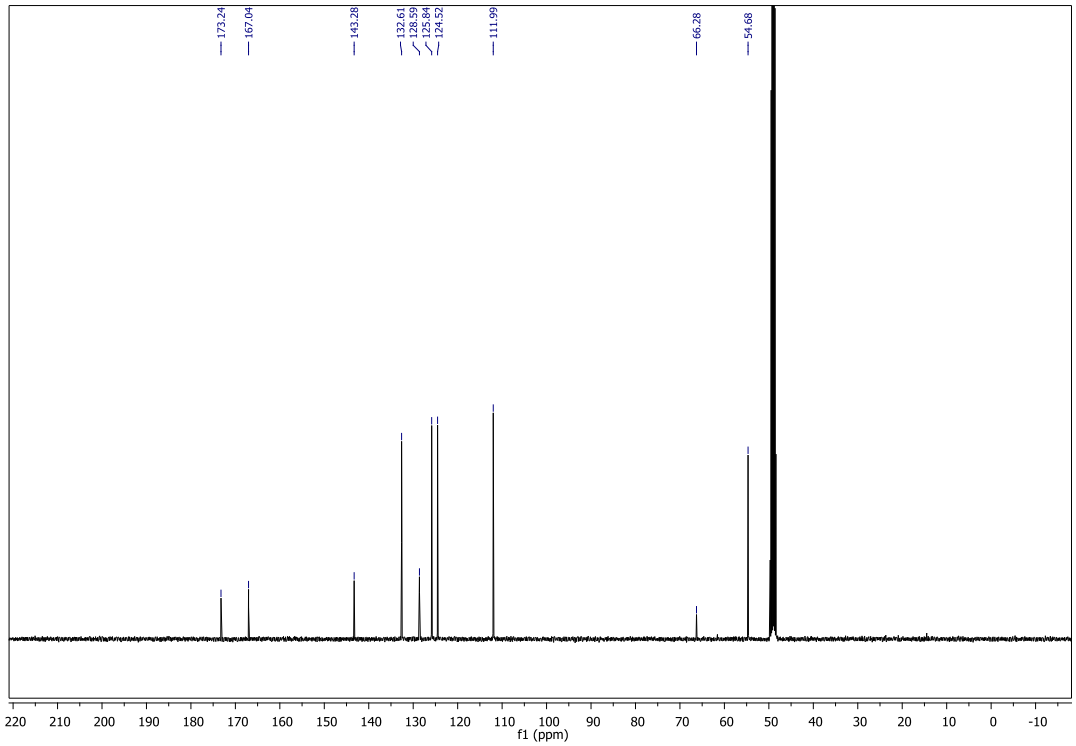

Figure 18 ^{13}C NMR Spectrum of Compound **128** in MeOD

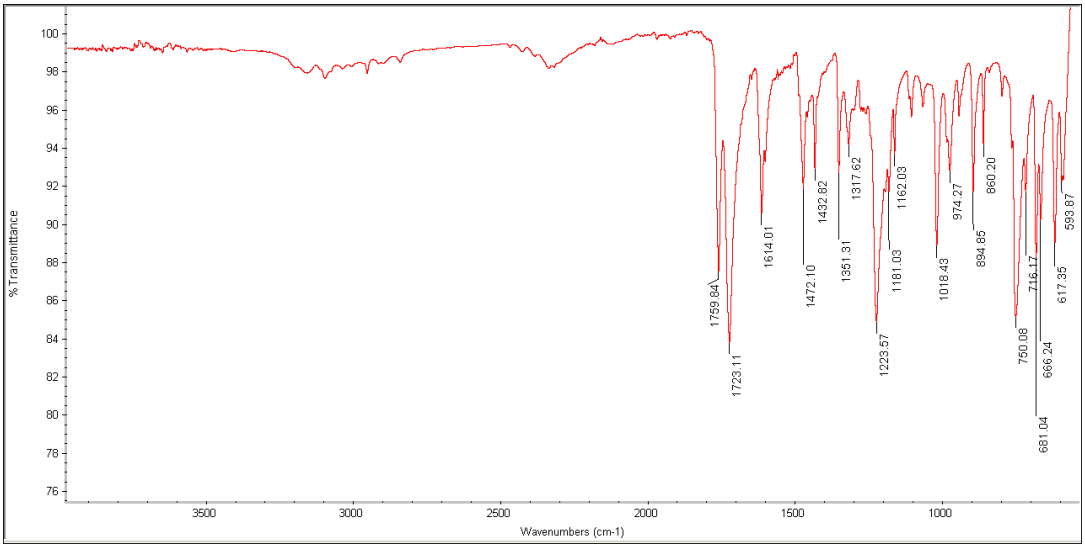

Figure 19 IR Spectrum of Compound **128**

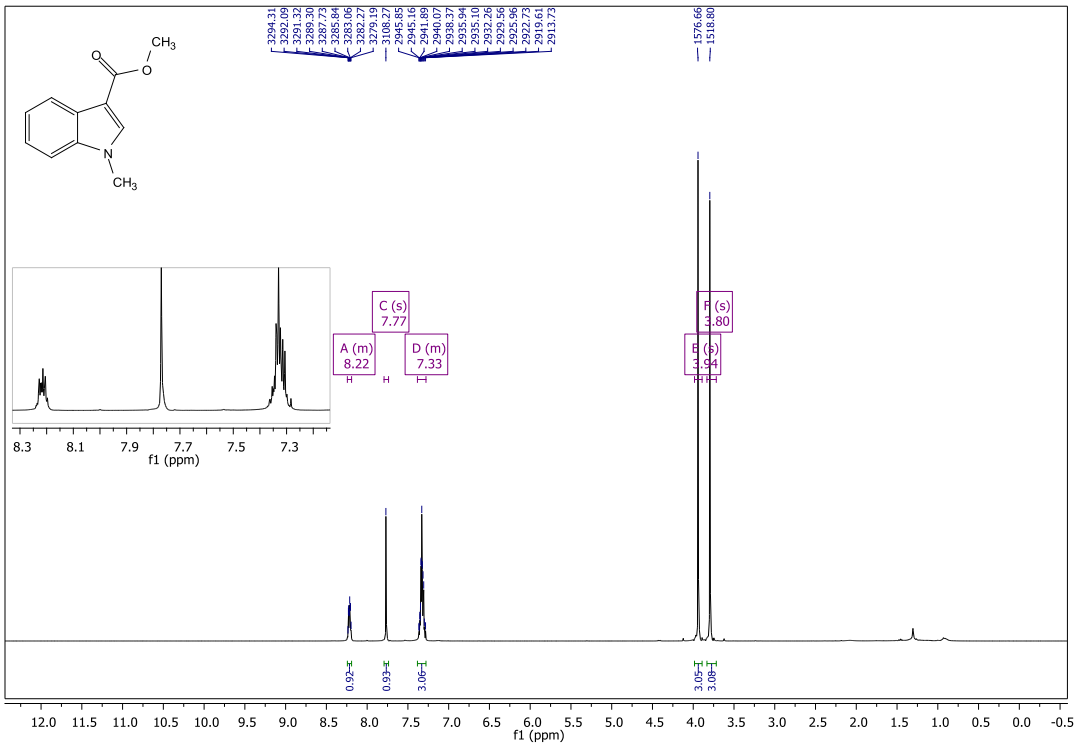

Figure 20 ^{1}H NMR Spectrum of Compound **134** in $CDCl_3$

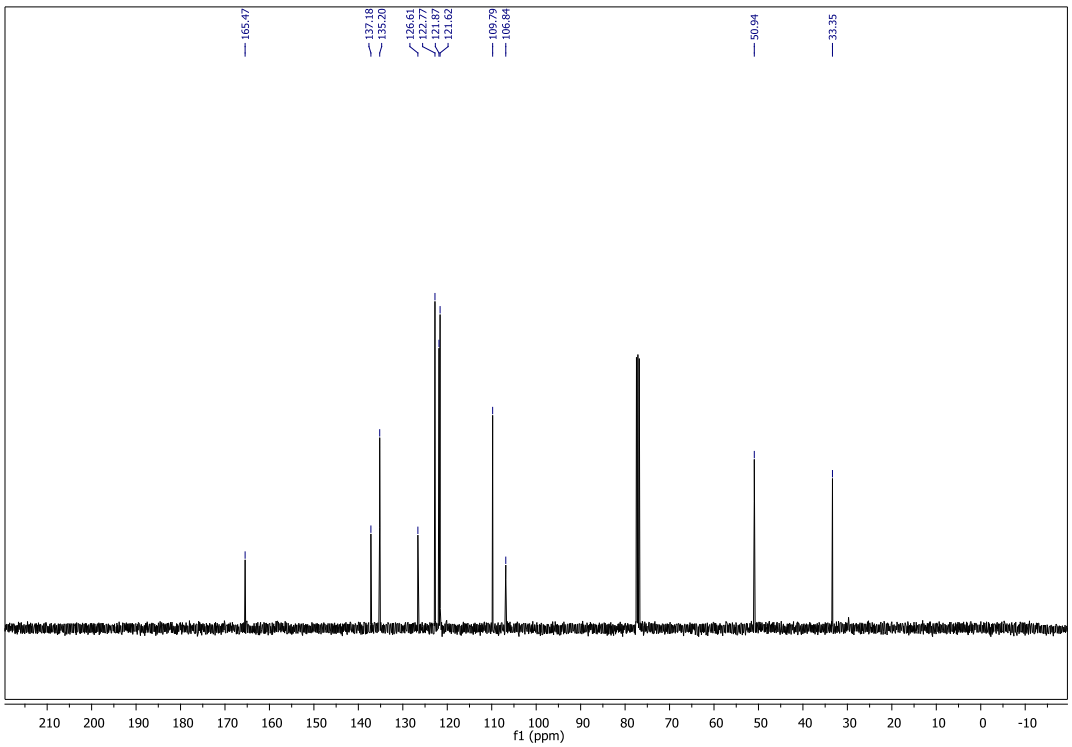

Figure 21 ^{13}C NMR Spectrum of Compound **134** in $CDCl_3$

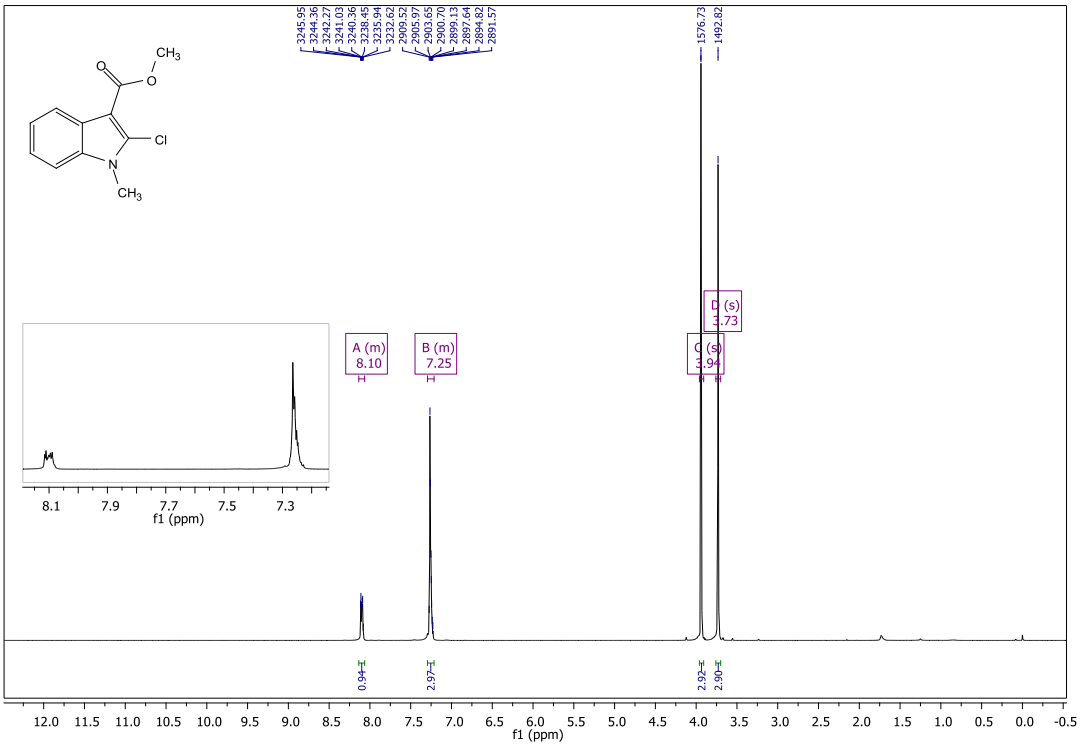

Figure 22 ^{1}H NMR Spectrum of Compound **135** in $CDCl_3$

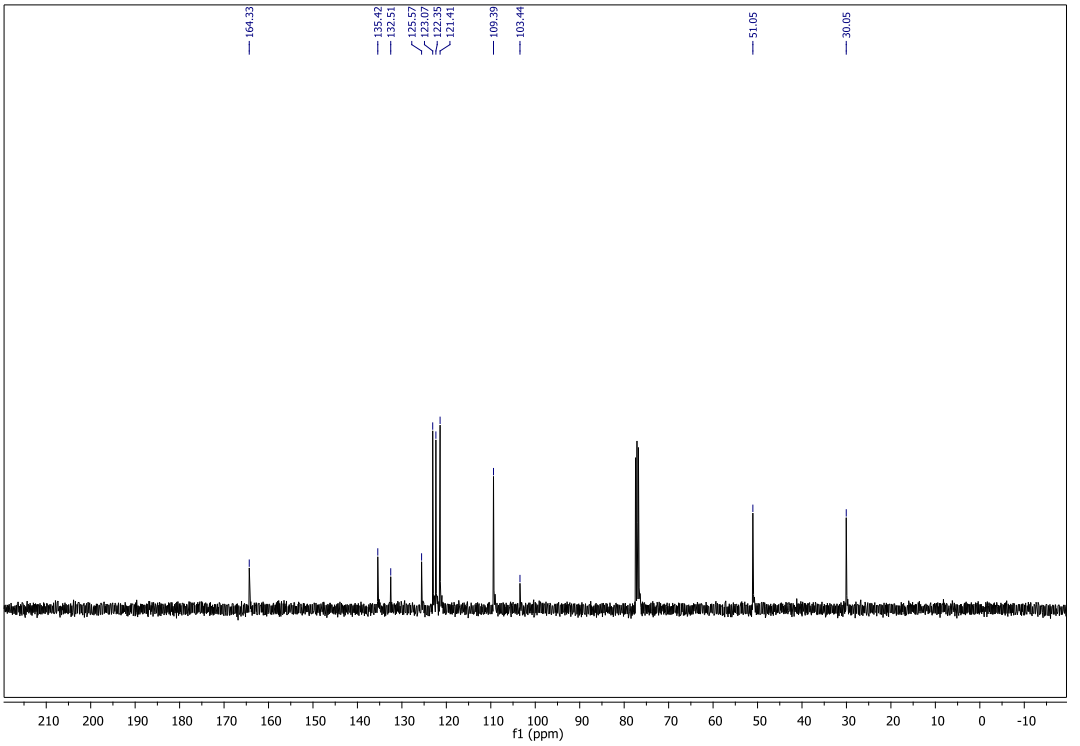

Figure 23 ^{13}C NMR Spectrum of Compound **135** in $CDCl_3$

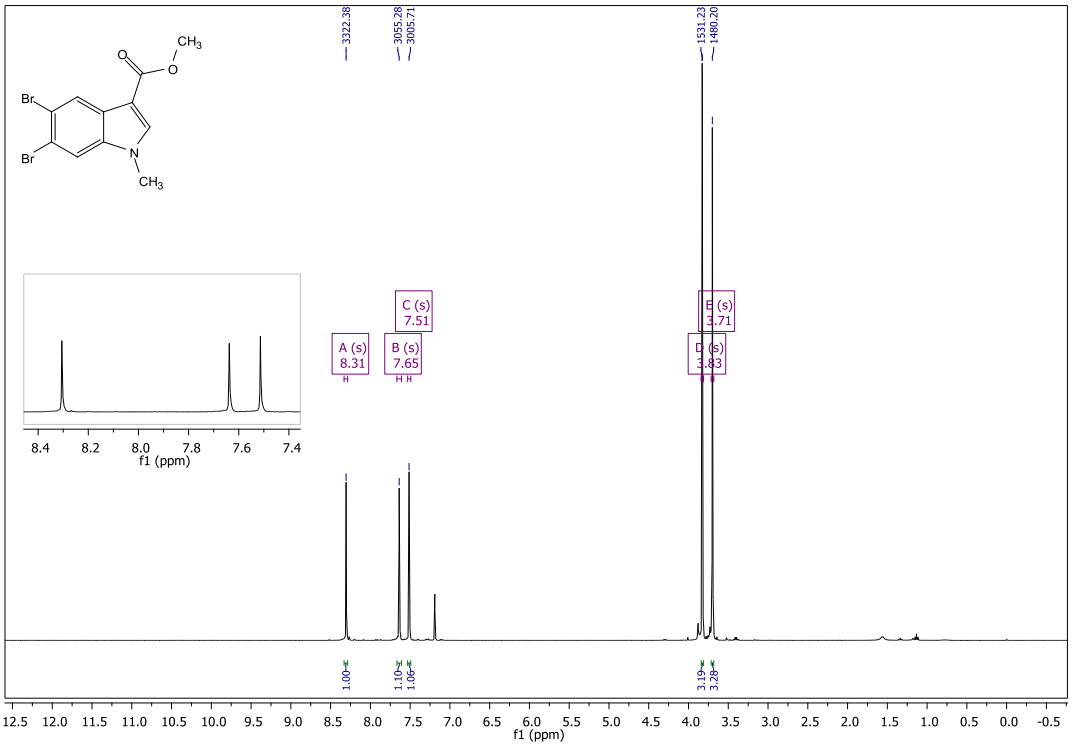

Figure 24 ^{1}H NMR Spectrum of Compound **137** in $CDCl_3$

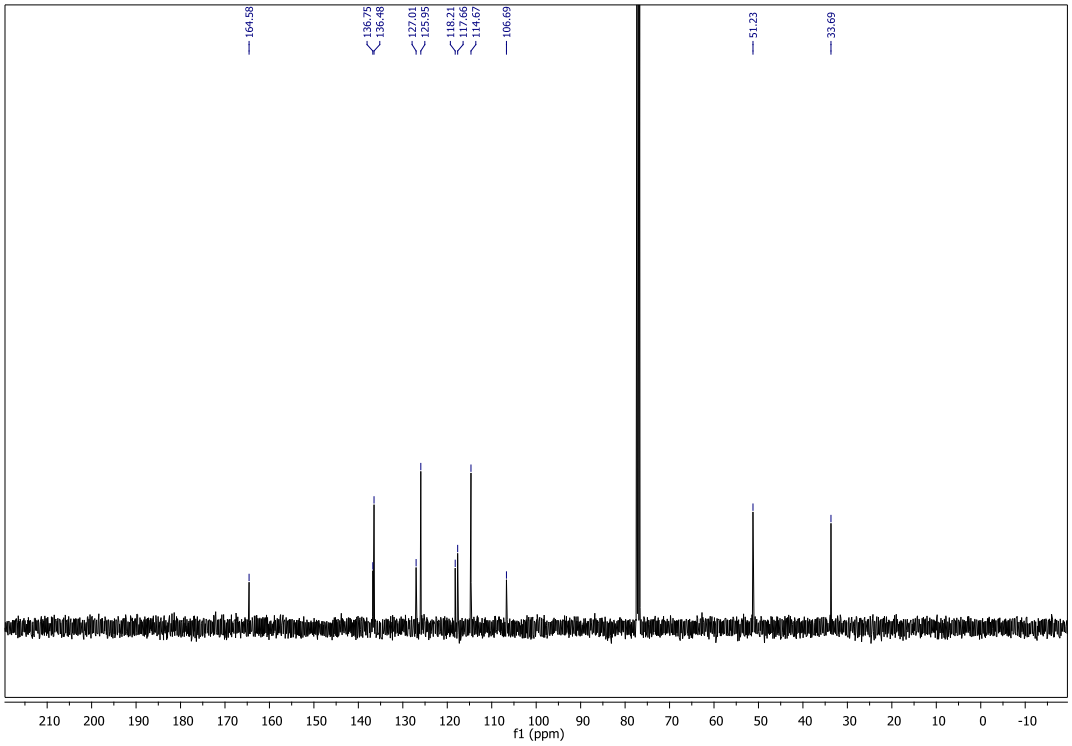

Figure 25 ^{13}C NMR Spectrum of Compound **137** in $CDCl_3$

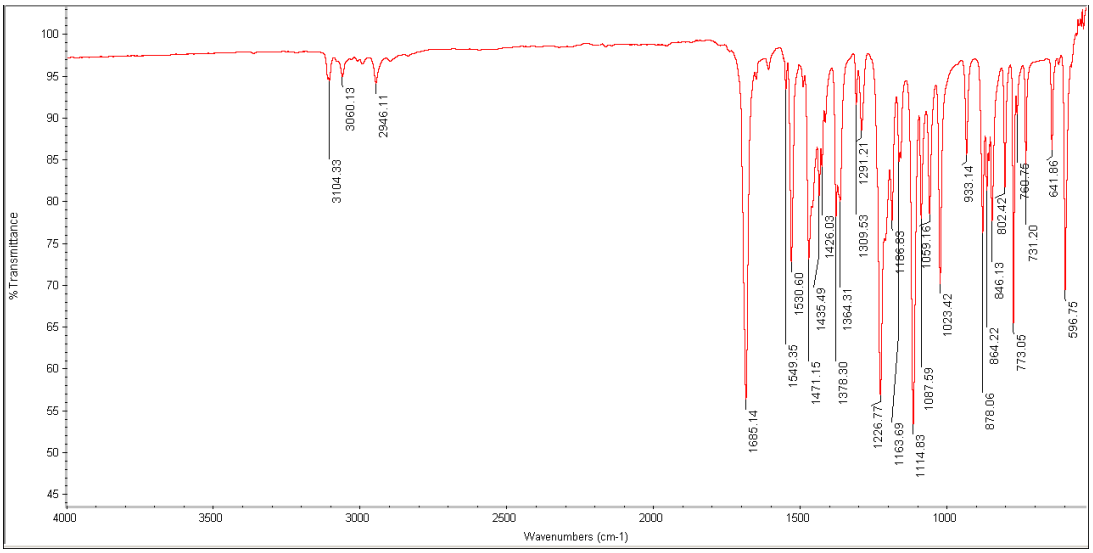

Figure 26 IR Spectrum of Compound **137**

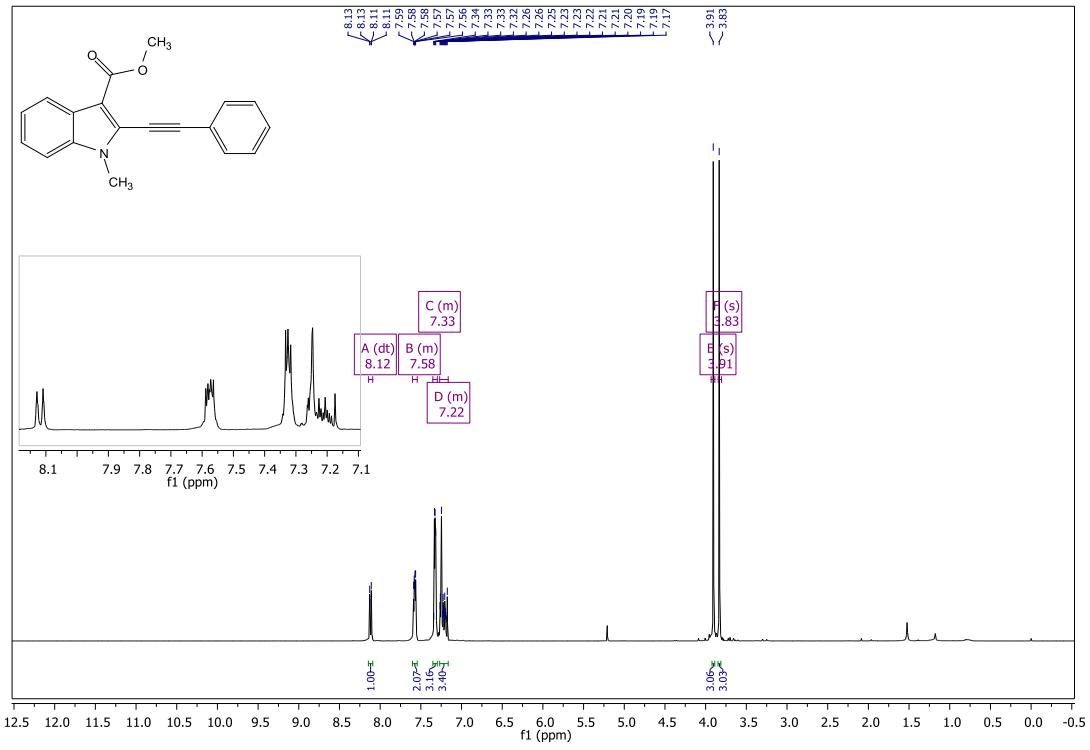

Figure 27 ^{1}H NMR Spectrum of Compound **139** in $CDCl_3$

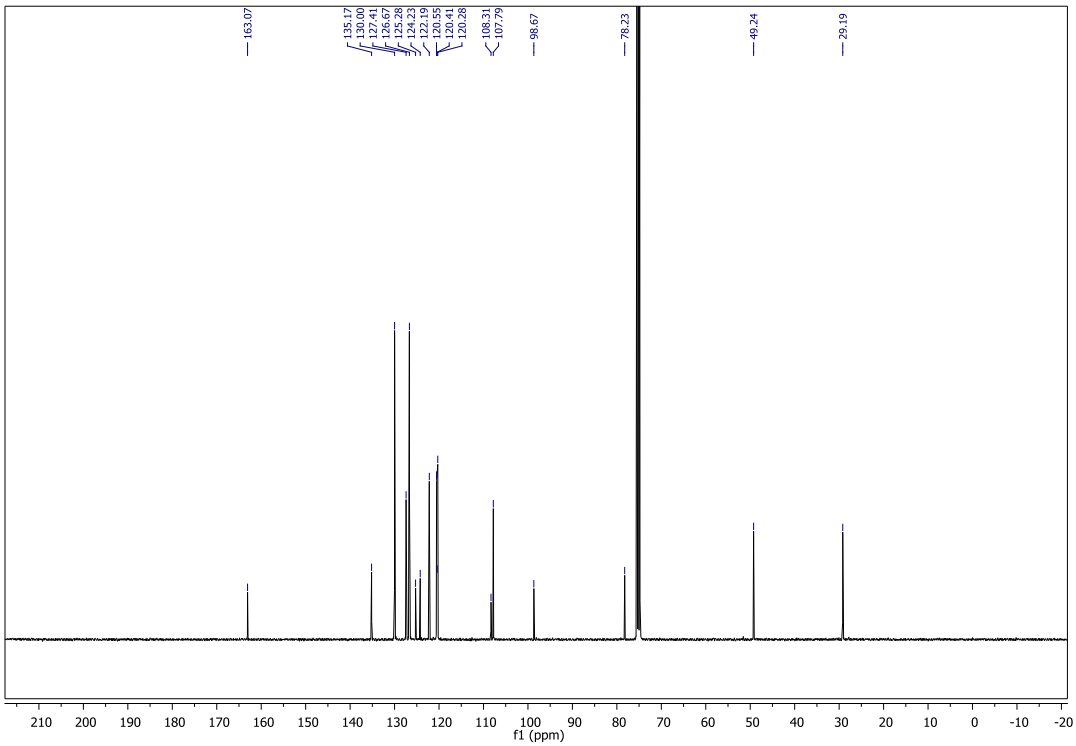

Figure 28 ^{13}C NMR Spectrum of Compound **139** in $CDCl_3$

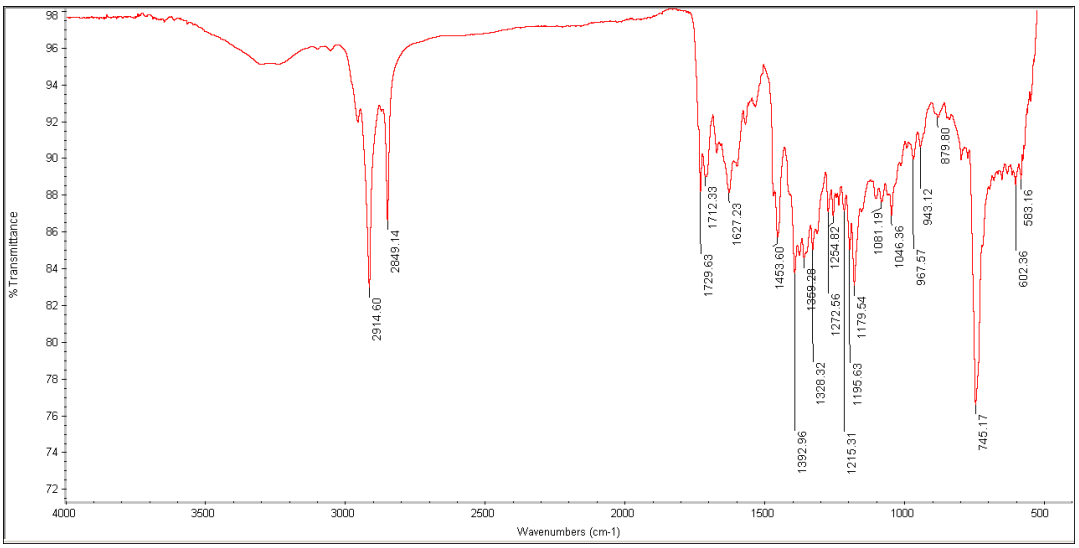

Figure 29 IR Spectrum of Compound **139**

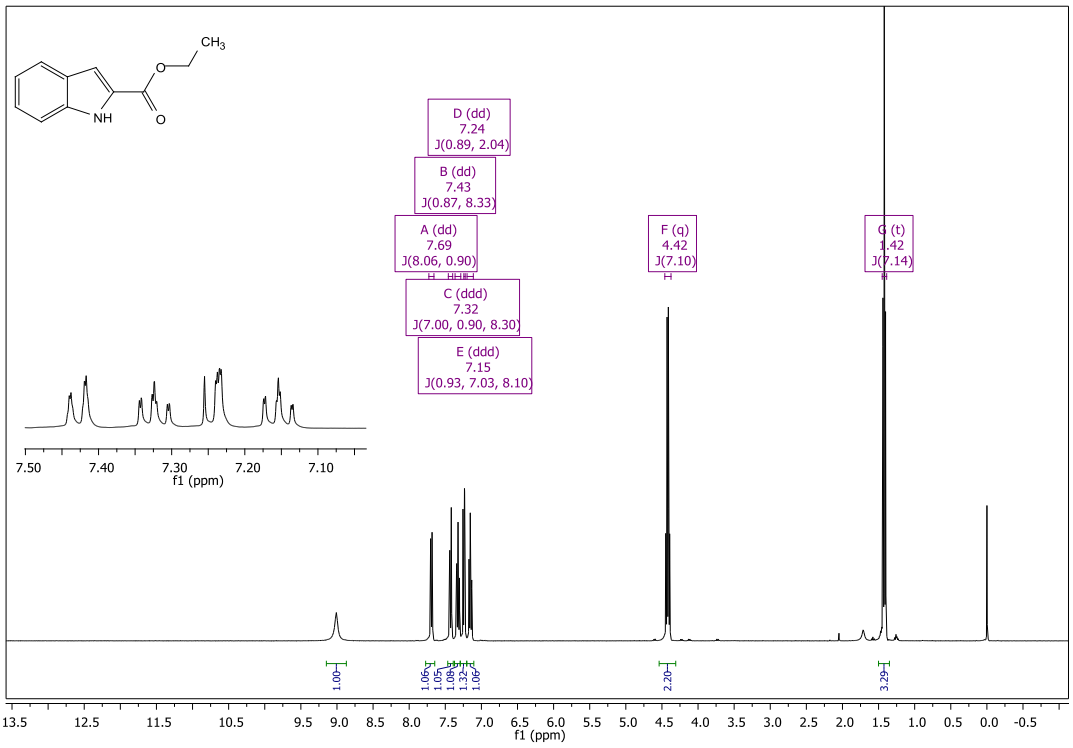

Figure 30 ^{1}H NMR Spectrum of Compound **141** in $CDCl_3$

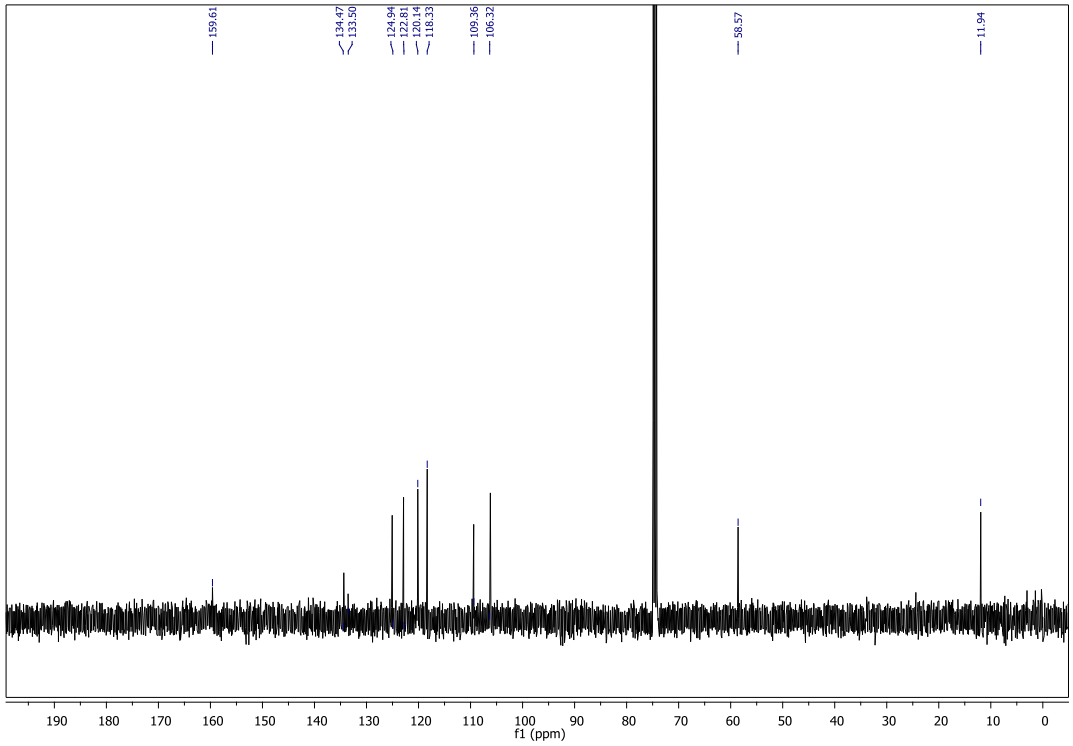

Figure 31 ^{13}C NMR Spectrum of Compound **141** in $CDCl_3$

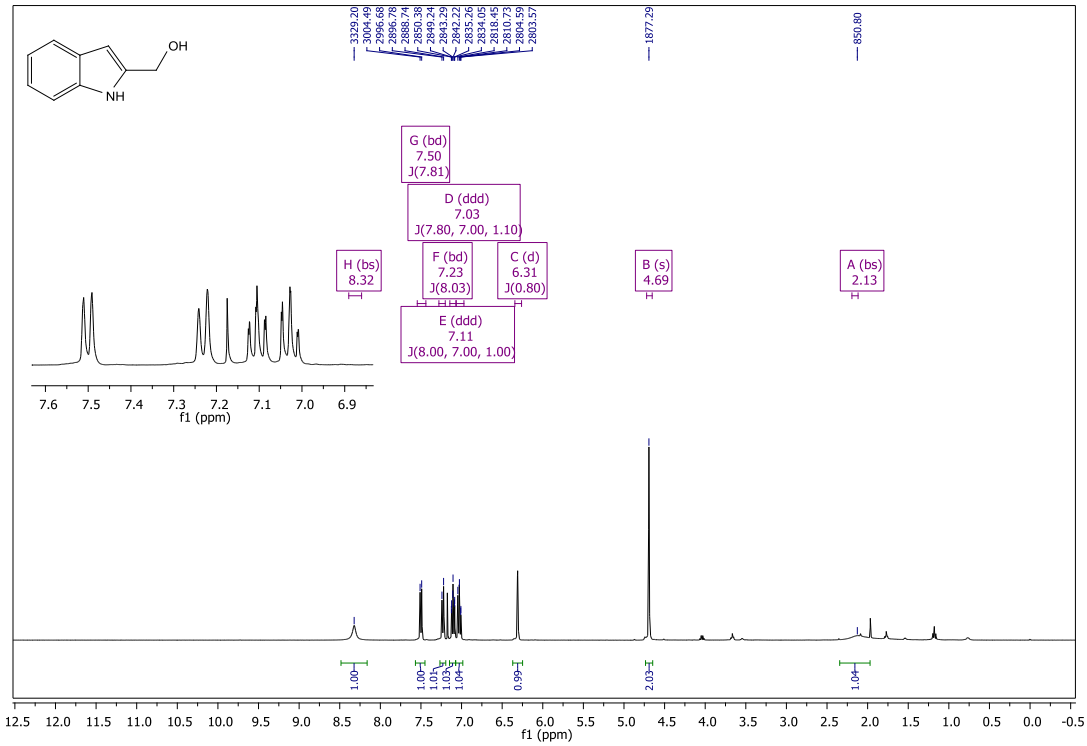

Figure 32 ^{1}H NMR Spectrum of Compound **142** in $CDCl_3$

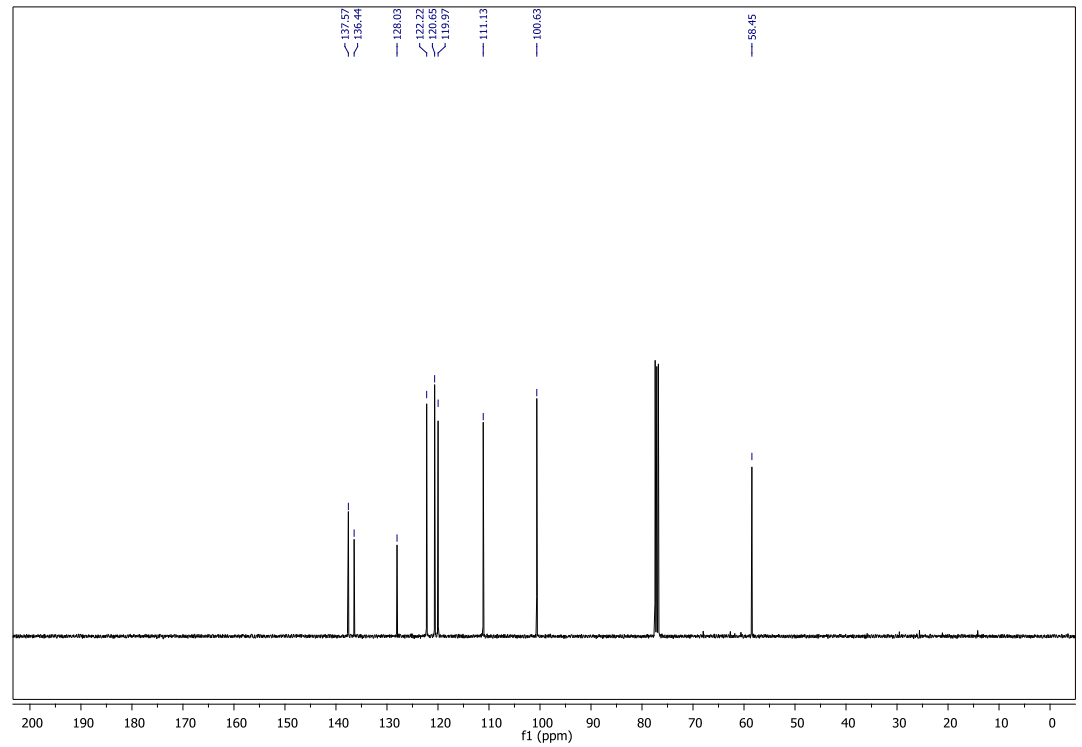

Figure 33 ^{13}C NMR Spectrum of Compound **142** in $CDCl_3$

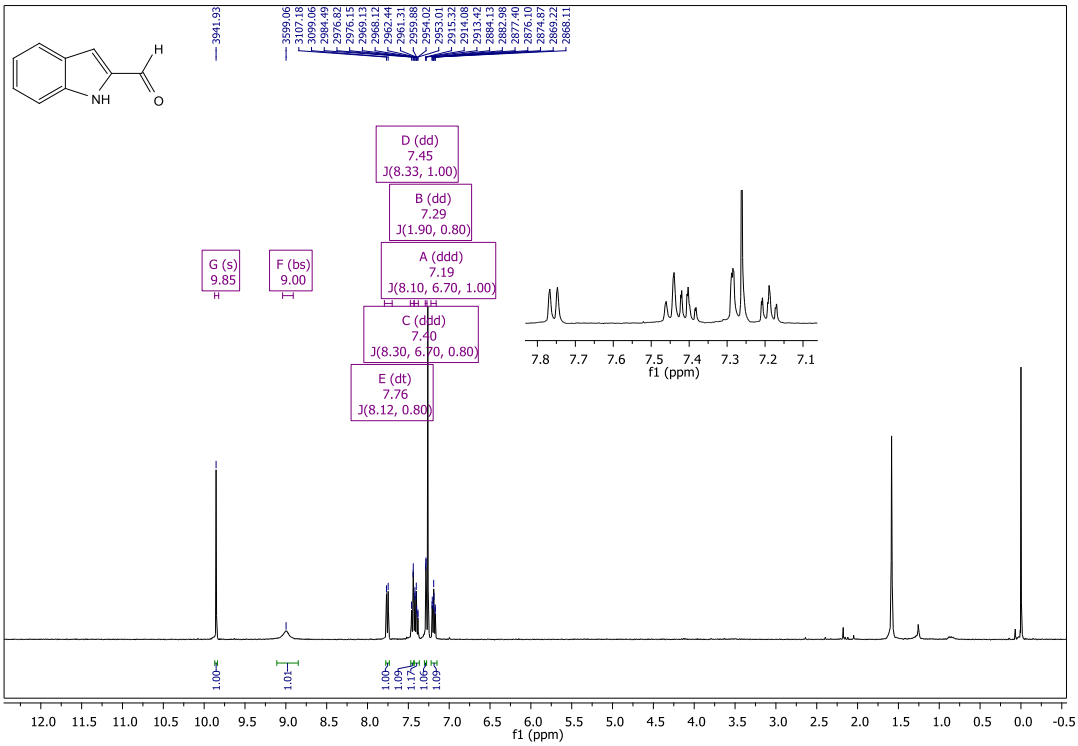

Figure 34 ^{1}H NMR Spectrum of Compound **143** in $CDCl_3$

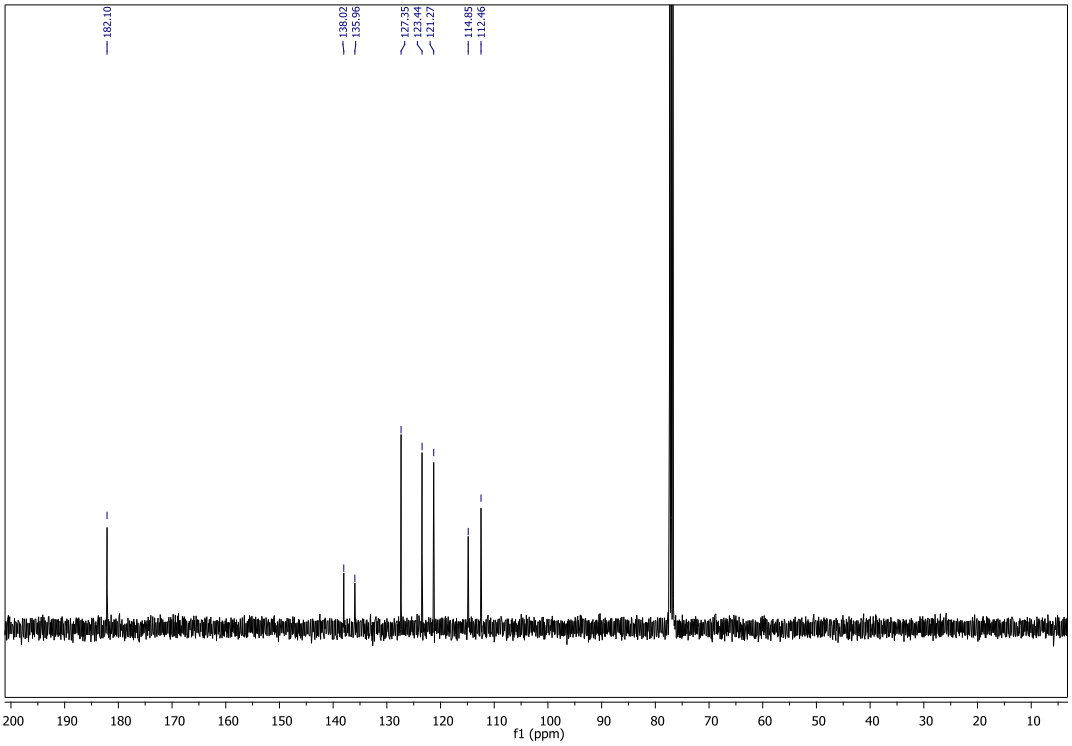

Figure 35 ^{13}C NMR Spectrum of Compound **143** in $CDCl_3$

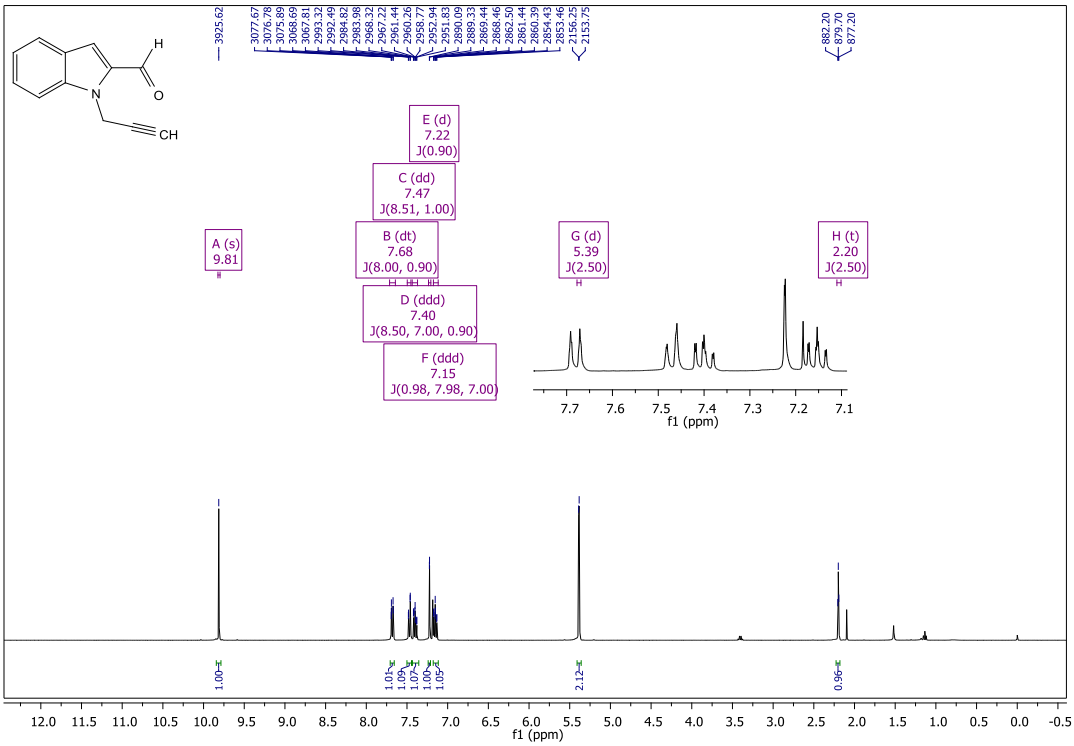

Figure 36 ^{1}H NMR Spectrum of Compound **105** in $CDCl_3$

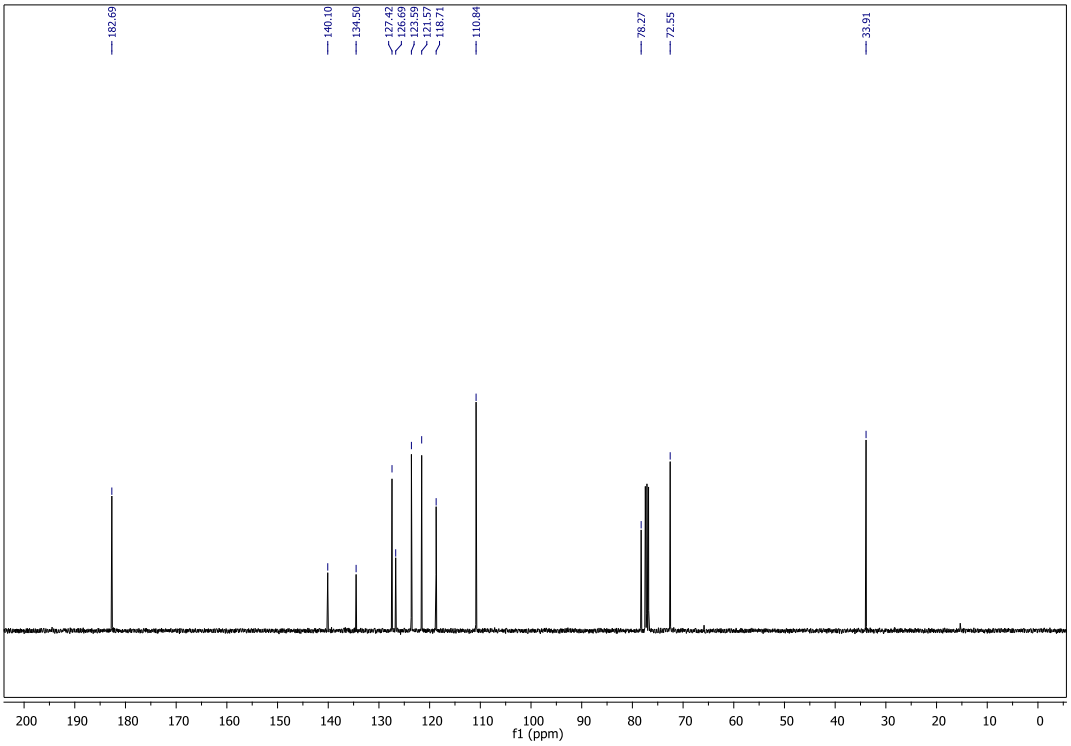

Figure 37 ^{13}C NMR Spectrum of Compound **105** in $CDCl_3$

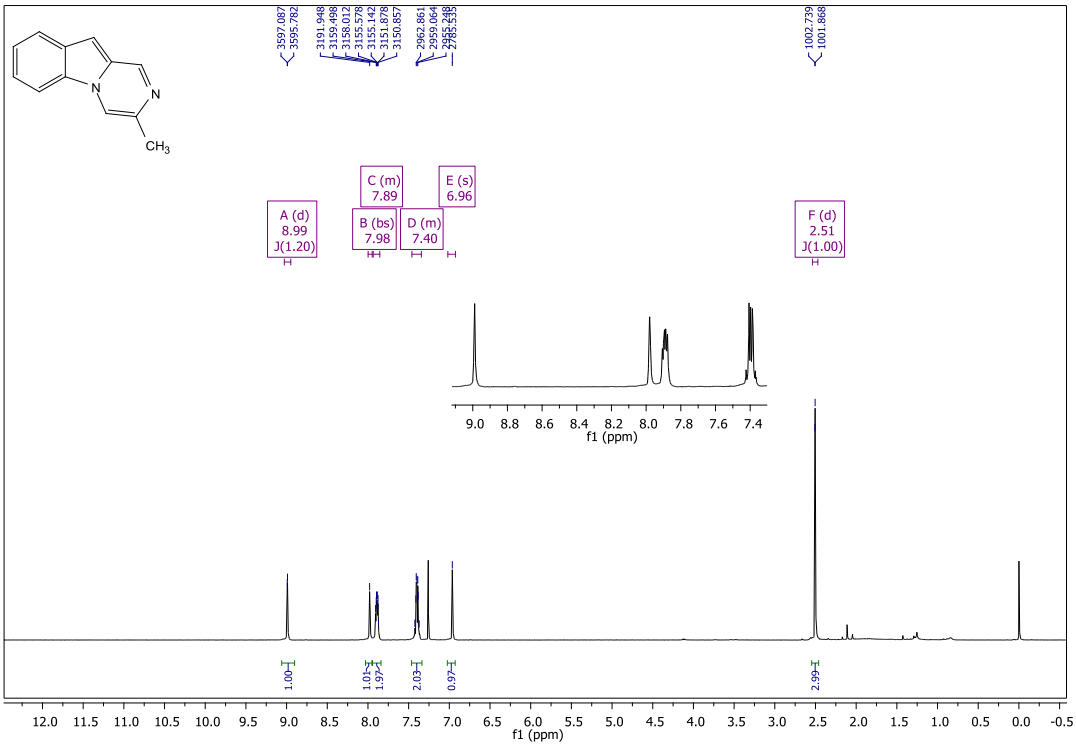

Figure 38 ^{1}H NMR Spectrum of Compound **106** in $CDCl_3$

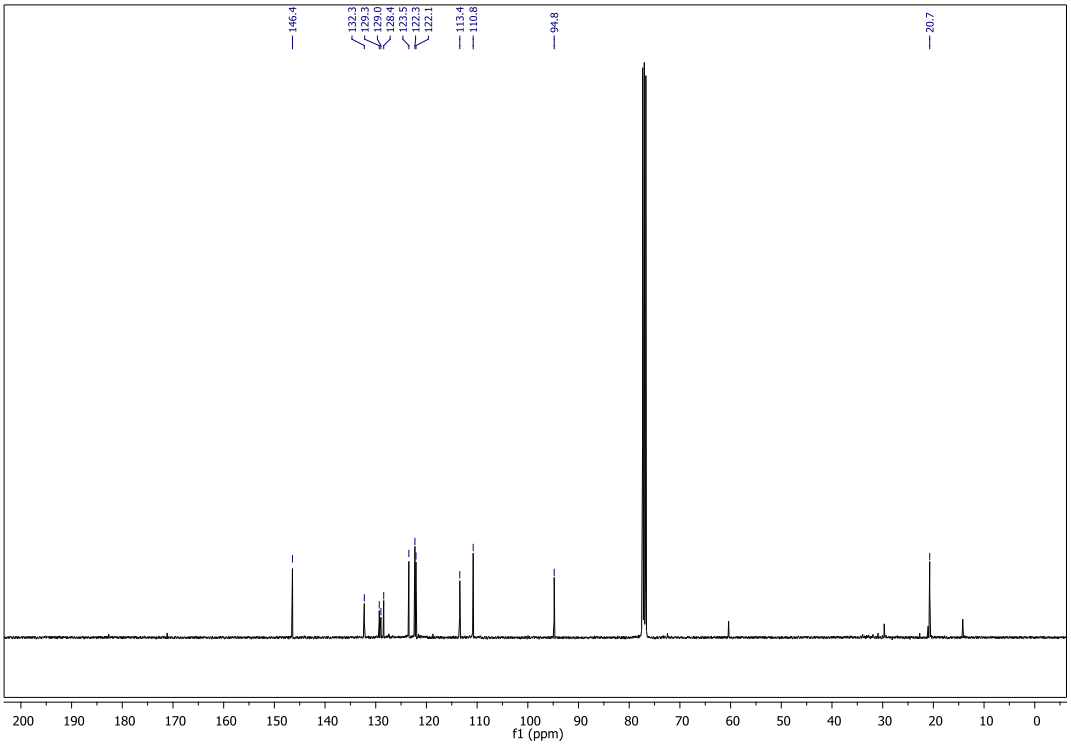

Figure 39 ^{13}C NMR Spectrum of Compound **106** in $CDCl_3$

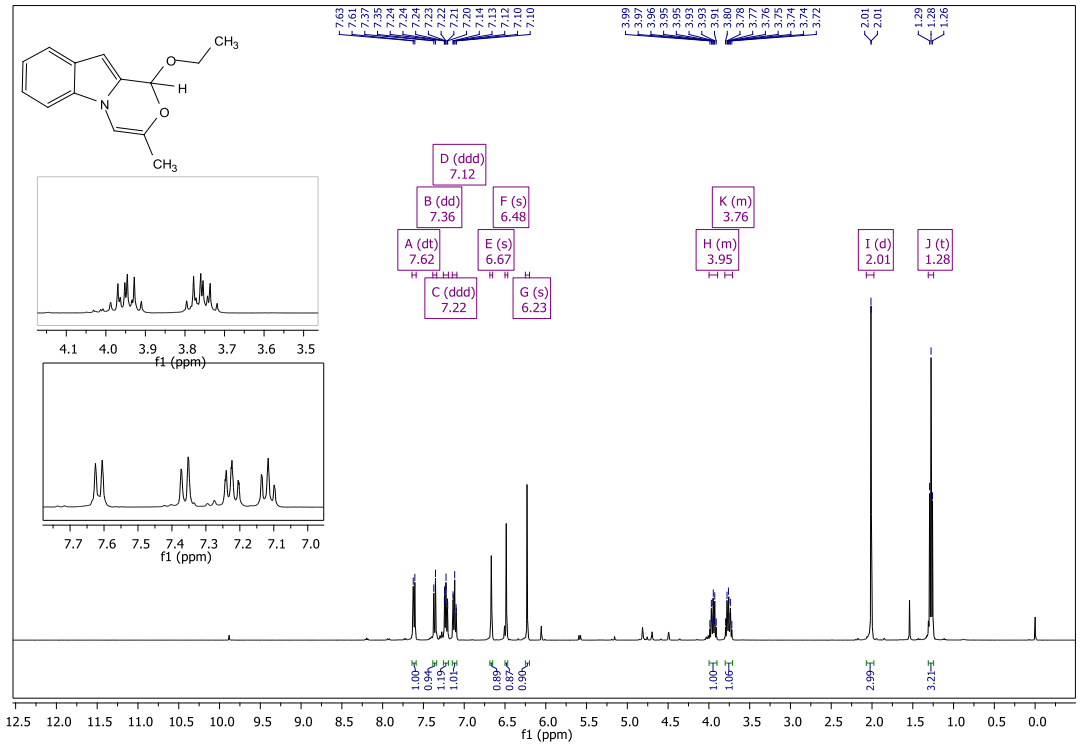

Figure 40 ^{1}H NMR Spectrum of Compound **151** in $CDCl_3$

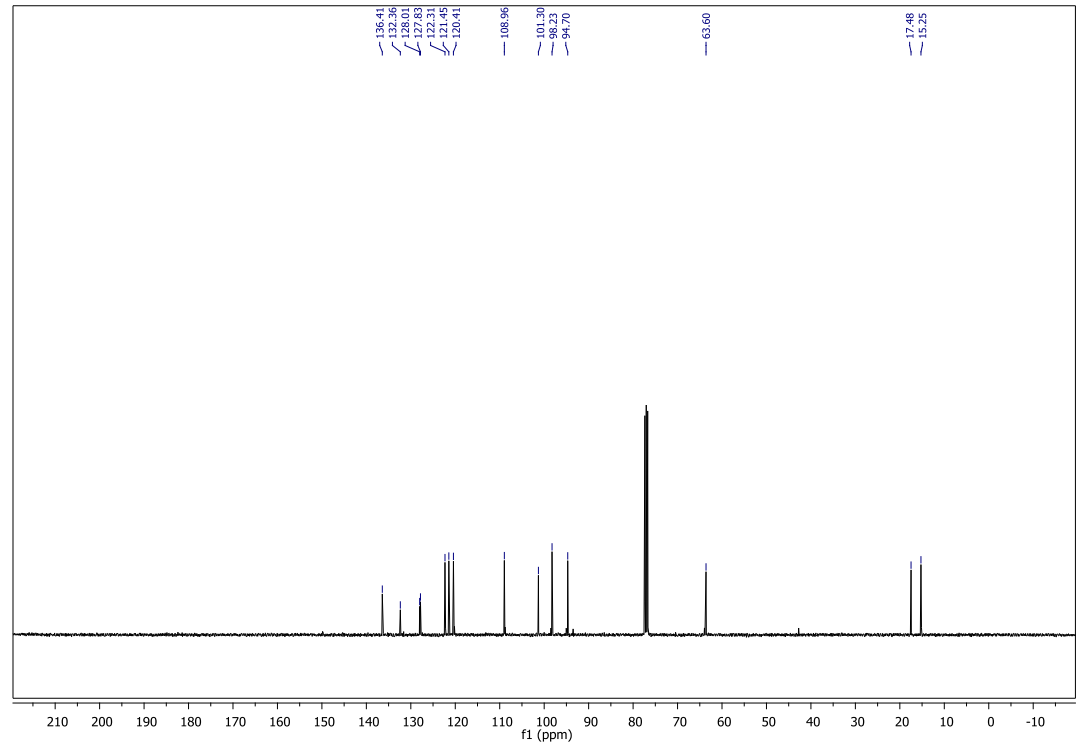

Figure 41 ^{13}C NMR Spectrum of Compound **151** in $CDCl_3$

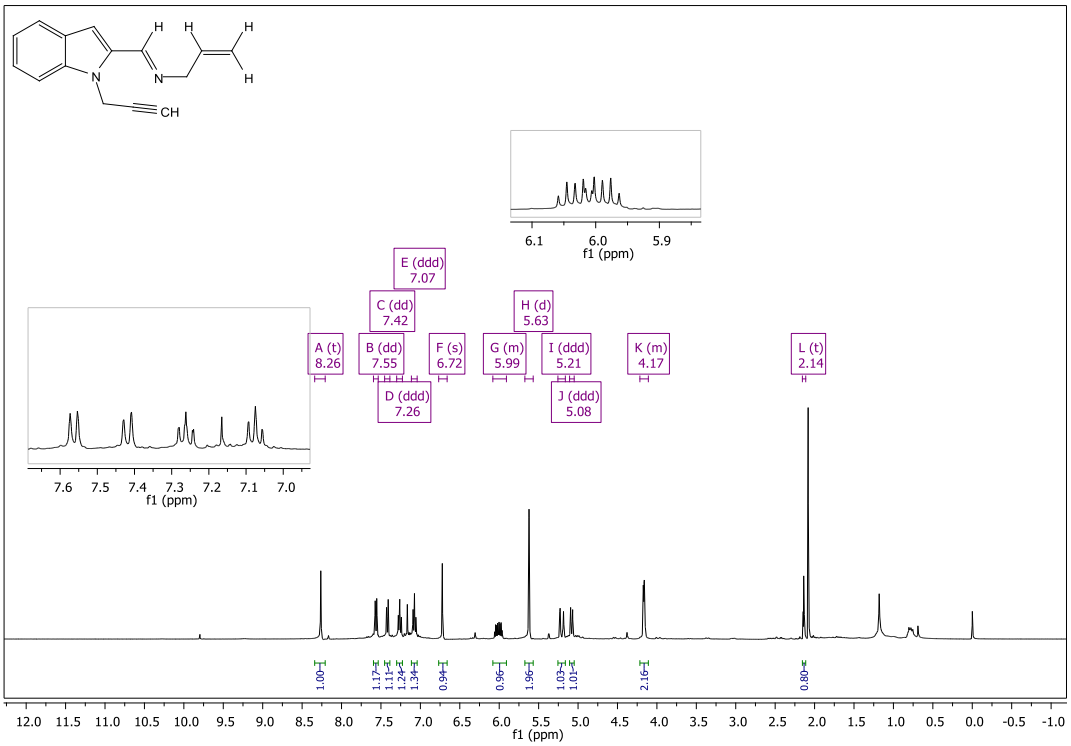

Figure 42 ^{1}H NMR Spectrum of Compound **152** in $CDCl_3$

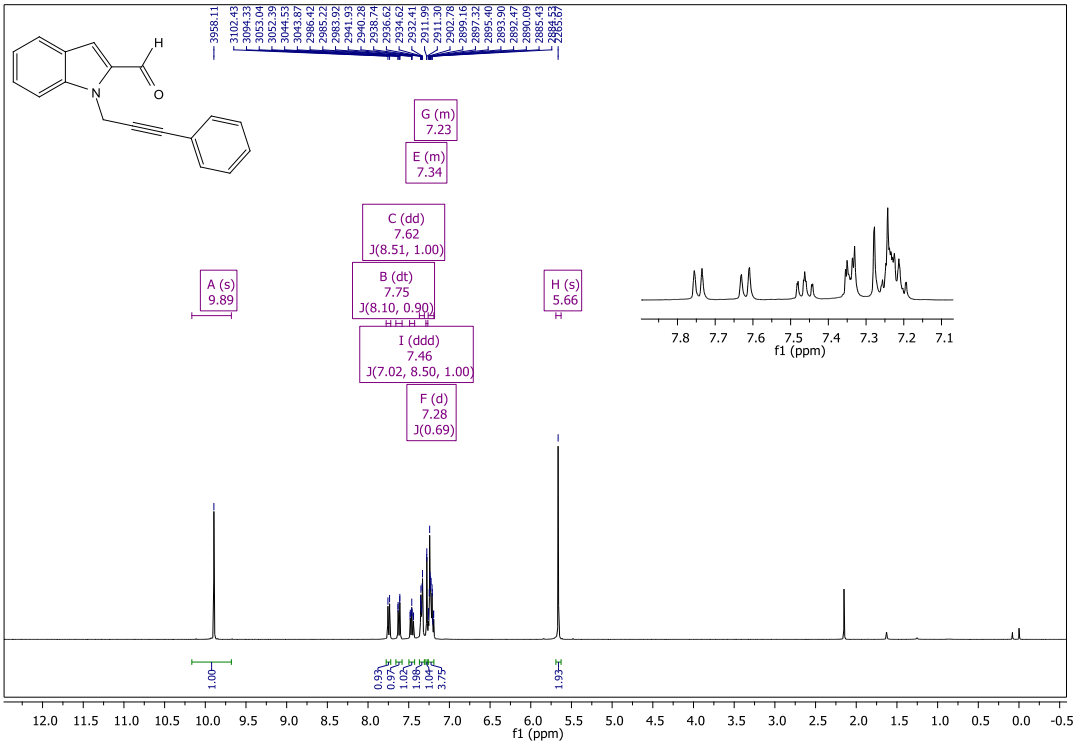

Figure 43 ^{1}H NMR Spectrum of Compound **157** in $CDCl_3$

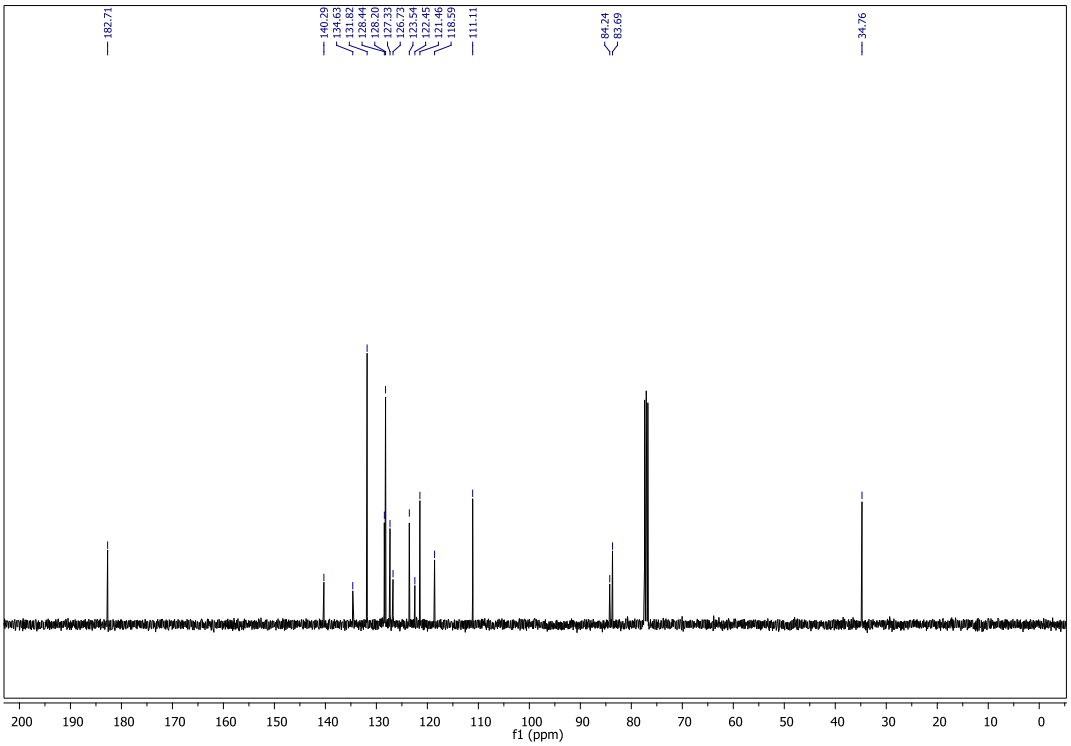

Figure 44 ^{13}C NMR Spectrum of Compound **157** in $CDCl_3$

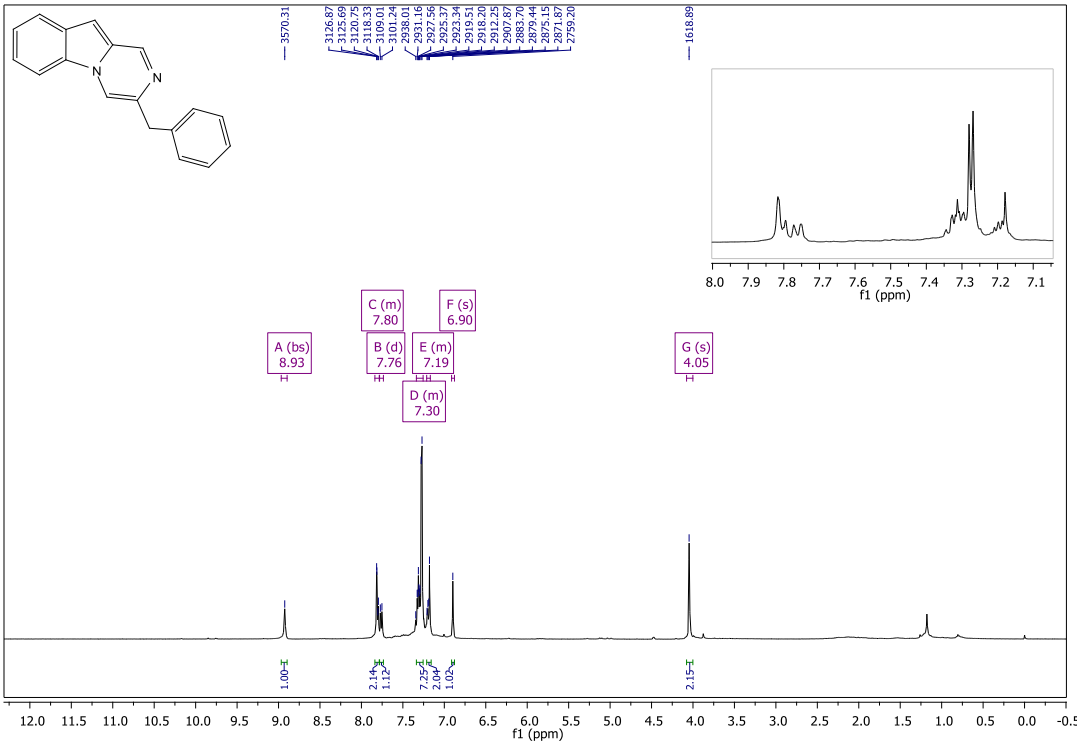

Figure 45 ^{1}H NMR Spectrum of Compound **158** in $CDCl_3$

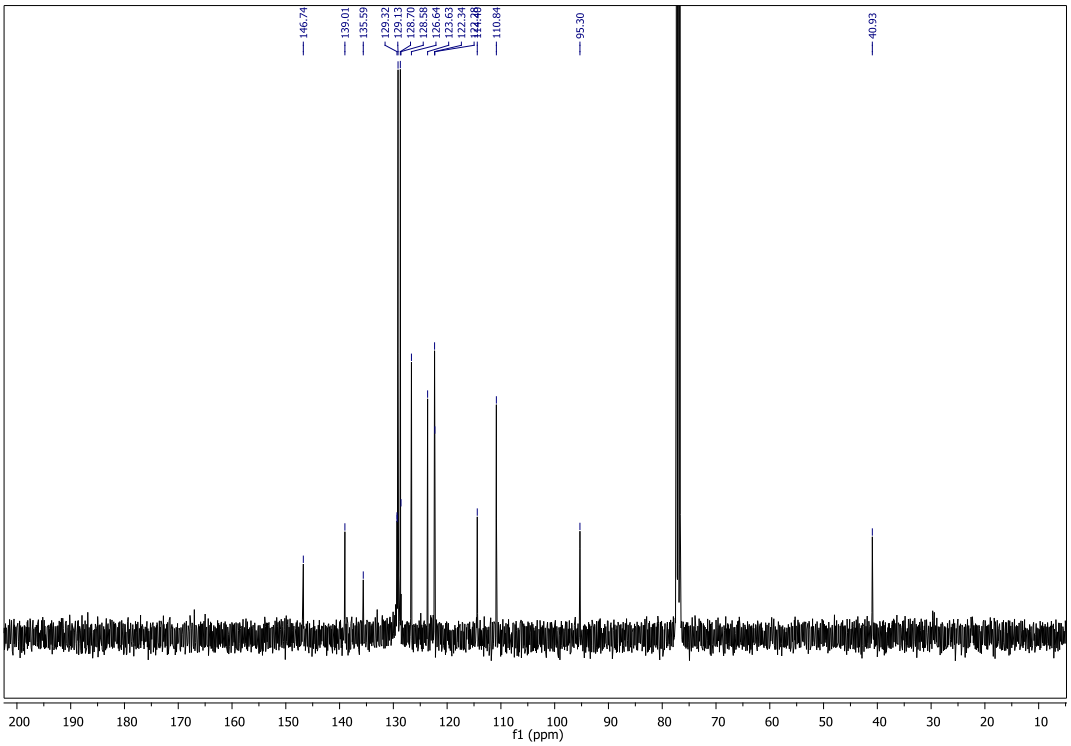

Figure 46 ^{13}C NMR Spectrum of Compound **158** in $CDCl_3$

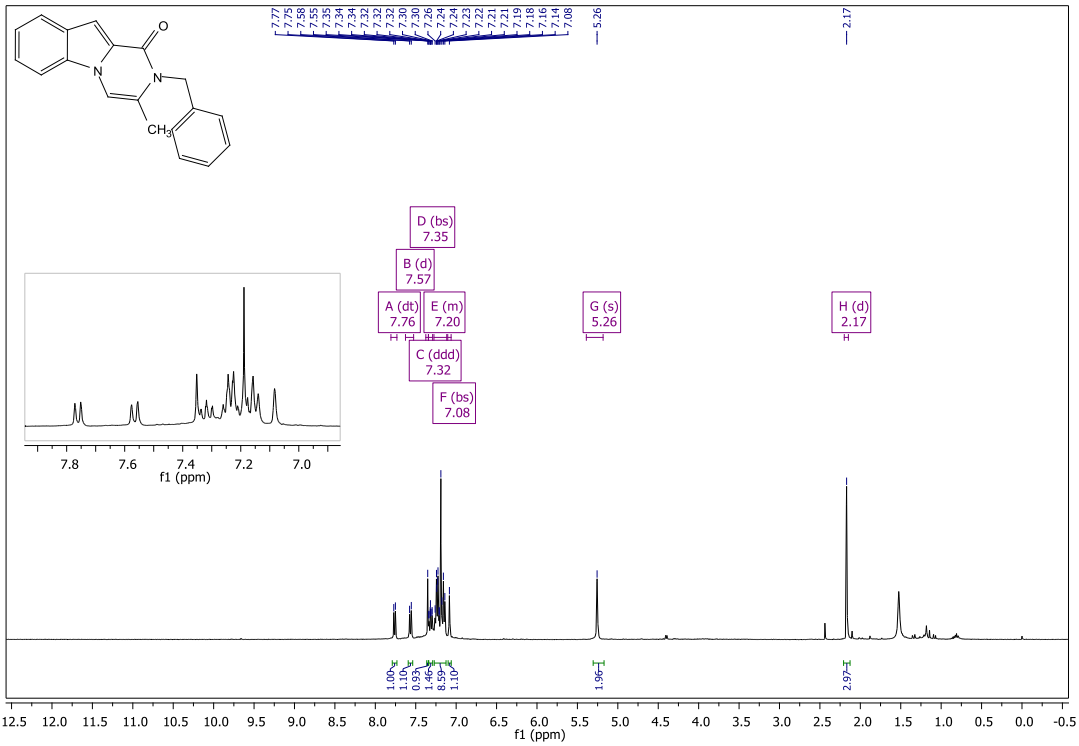

Figure 47 ^{1}H NMR Spectrum of Compound **160** in $CDCl_3$

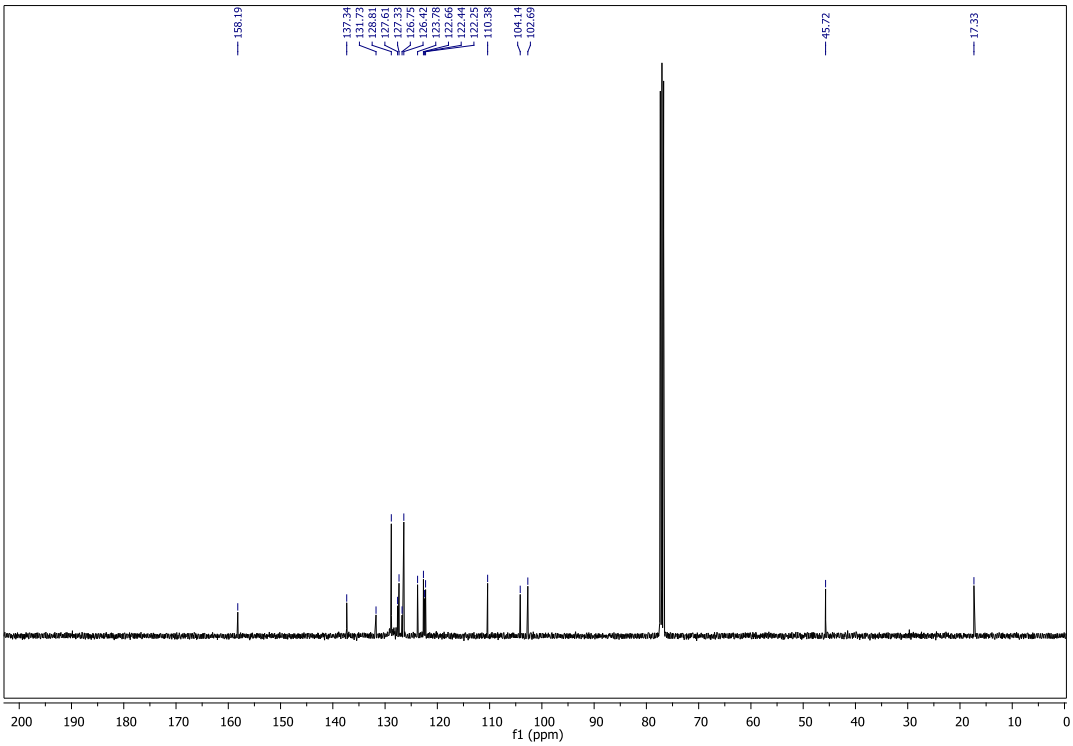

Figure 48 ^{13}C NMR Spectrum of Compound **160** in $CDCl_3$

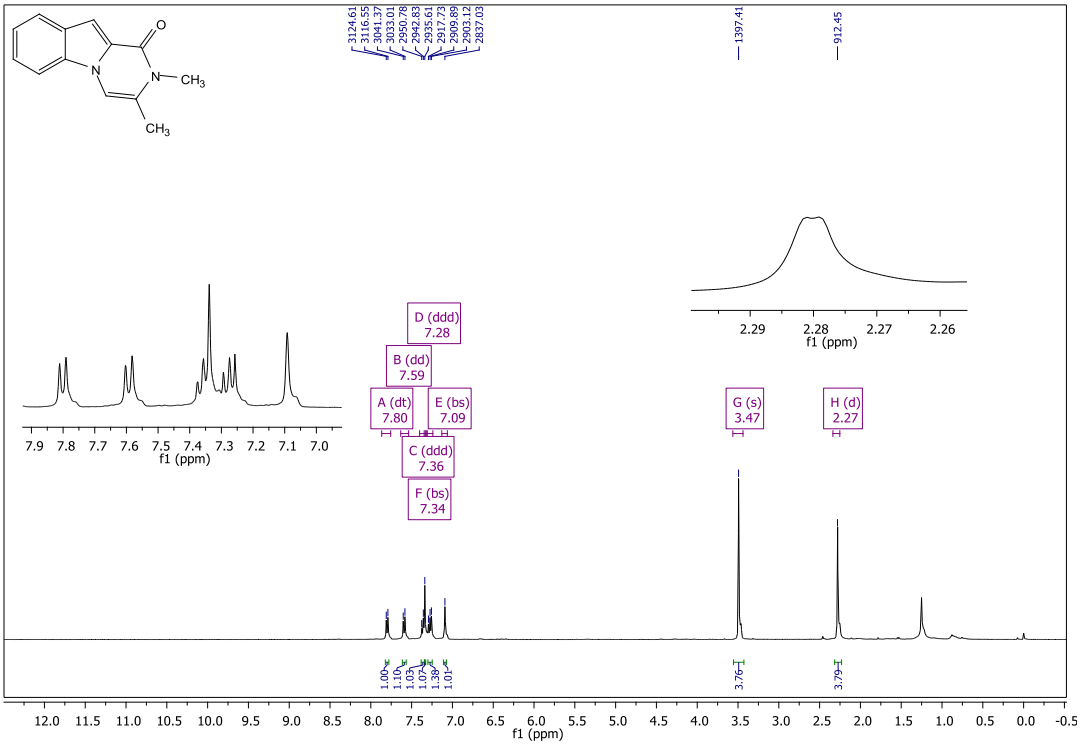

Figure 49 ^{1}H NMR Spectrum of Compound **161** in $CDCl_3$

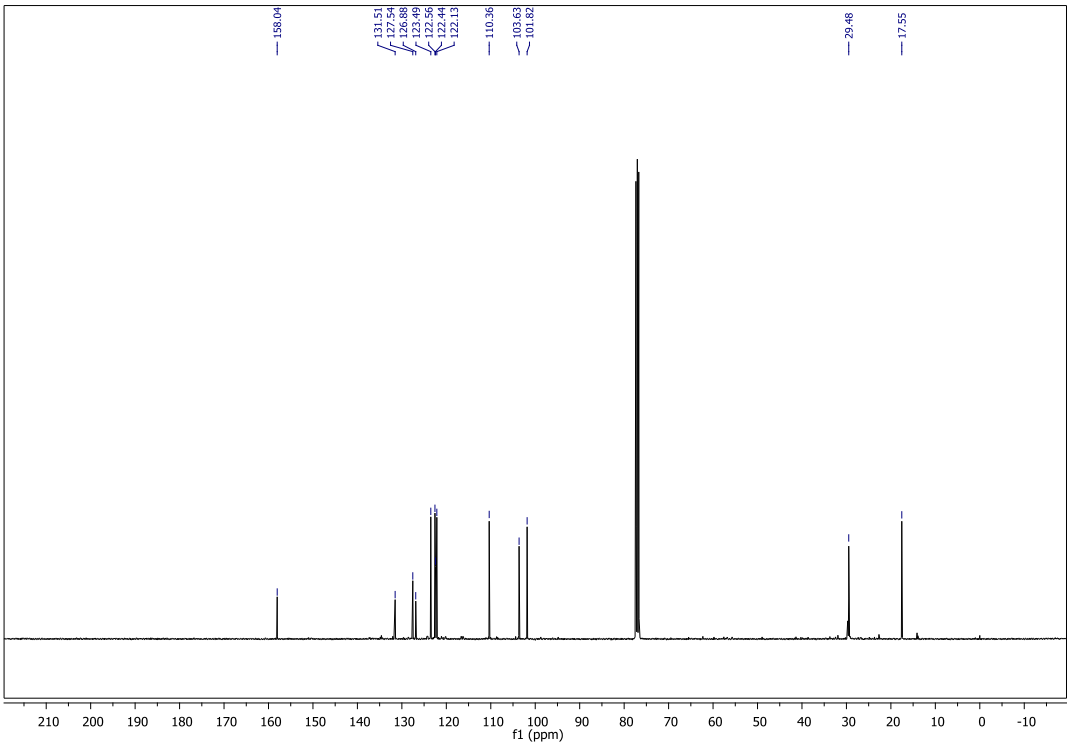

Figure 50 ^{13}C NMR Spectrum of Compound **161** in $CDCl_3$

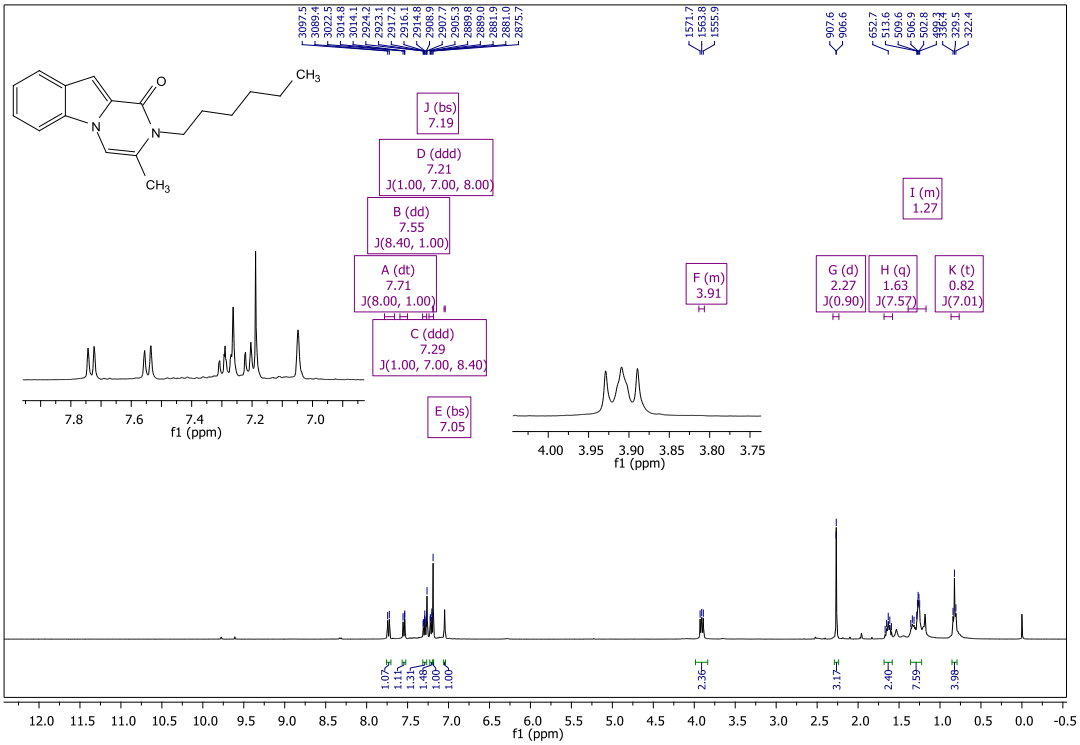

Figure 51 ^{1}H NMR Spectrum of Compound **162** in $CDCl_3$

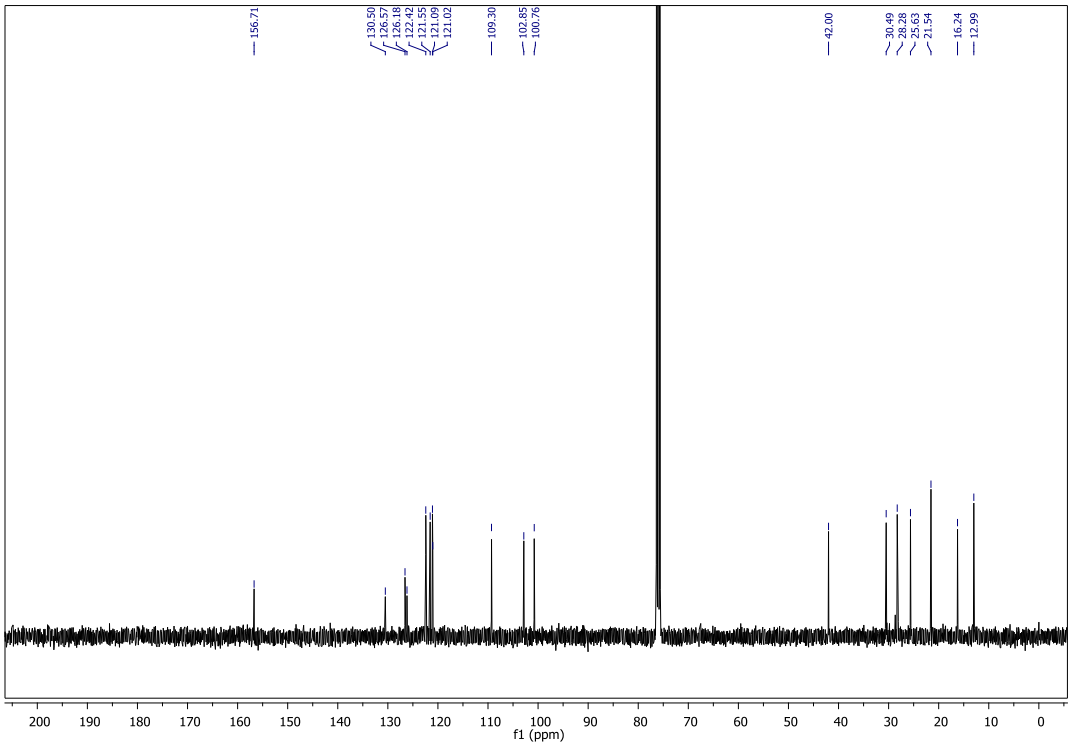

Figure 52 ^{13}C NMR Spectrum of Compound **162** in $CDCl_3$

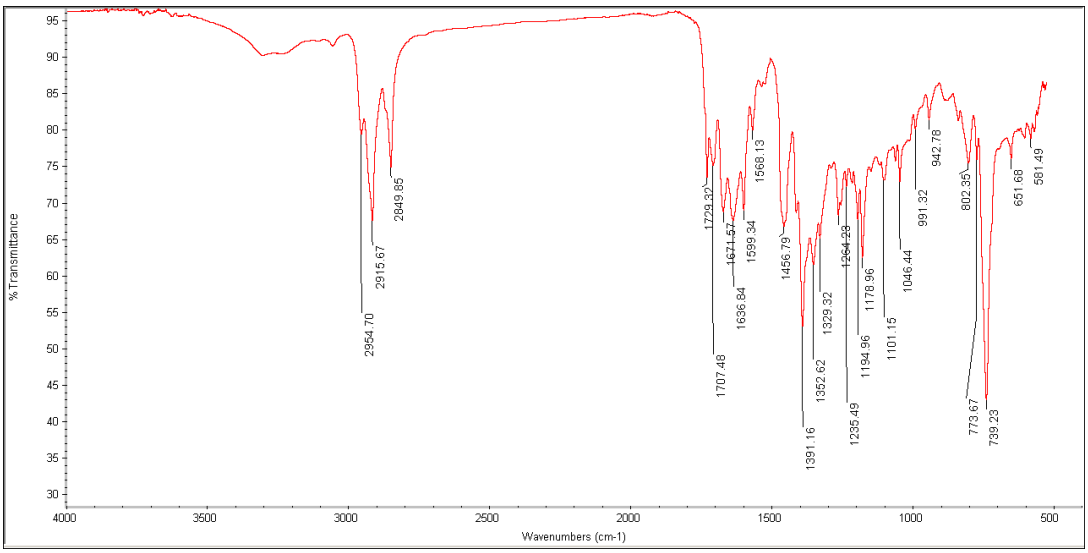

Figure 53 IR Spectrum of Compound **162**