DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR INDOLE DERIVATIVES: CHEMISTRY OF HOMOPHTHALIC ACID

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AHMET ALPER KILIKLI

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DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR INDOLE DERIVATIVES: CHEMISTRY OF HOMOPHTHALIC ACID

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

Name, Last name : Ahmet Alper KILIKLI

Signature :

To my parents and sisters...

ABSTRACT

DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR INDOLE DERIVATIVES: CHEMISTRY OF HOMOPHTHALIC ACID

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Synthesizing nitrogen containing heterocyclic compounds is one of the leading research areas throughout the organic chemistry due to their significant activities on biological systems. Among the various biologically active molecules, indole derivatives are of prime importance on the grounds of their proven clinical roles.

Objective of this study is to synthesize new indole derivatives those may contribute treatment of several diseases like their analogues via a recently developed synthetic methodology. Besides this, another objective is to observe and discuss effects of two different substituents on the homophtalic acid system through the synthetic route.

Initially starting from homophtalic and 3-methoxybenzoic acid two different homophtalic acid derivatives were synthesized as starting materials. Then the corresponding acyl azide and isocyanate derivatives were generated which might further be used as a precursor to construct a variety of indole derivatives. After synthesizing urea derivatives, ring-closure under the basic conditions generated the heterocyclic units. Whole products were conscientiously purified and characterized.

Keywords: homophtalic acid, indole, isocyanate, ring-closure reaction

ÖZ

İNDOL VE TÜREVLERİNİN SENTEZİ İÇİN YENİ SENTEZ YÖNTEMLERİNİN GELİŞTİRİMESİ: HOMOFTALİK ASİT KİMYASI

Kılıklı, Ahmet Alper

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Balcı

Şubat 2010, 130 sayfa

Azot içeren heterosiklik yapıların sentezi, bu yapıların biyolojik sistemler üzerinde gösterdikleri önemli aktivitelerden dolayı organik kimya alanında önde gelen çalışma alanlarından birisidir. Birçok biyolojikçe aktif molekül içerisinde, kanıtlanmış klinik rollerinden dolayı indol türevlerinin sentezi ile alakalı çalışmalar çok önemlidir.

Bu çalışmanın amacı; yakın geçmişte geliştirilmiş sentetik bir method kullanarak, benzeri yapılar gibi çeşitli hastalıkların tedavisine katkı sağlayabilecek yeni indol türevleri sentezlemektir. Bunun yanı sıra bir başka amaç da iki farklı substitüentin sentetik rota boyunca homoftalik asit sistemi üzerindeki etkisini gözlemlemektir.

İlk olarak iki farklı homoftalik asit türevi olan başlangıç materyalleri, homoftalik asit ve 3-metoksibenzoik asitten yola çıkılarak sentezlendi. Daha sonra, ileride birçok indol türevinin oluşturulmasında öncül olabilecek açil azid ve izosiyanat türevleri sentezlendi. Üre türevlerinin sentezinden sonra, bazik şartlarda halka kapanma reaksiyonu heterosiklik yapıları oluşturdu. Bütün ürünler özenle saflaştırıldı ve karakterize edildi.

Anahtar Kelimeler: homoftalik asit, indole, izosiyanat, halka kapanma reaksiyonu

ACKNOWLEDGEMENT

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DMSO : Dimethylsulfoxide

THF : Tetrahydrofuran

m-CPBA: Metachloroperbenzoic Acid

NMR : Nuclear magnetic resonance

IR : Infrared

J : Coupling constant

HRMS : High resolution mass spectrum

Hz: Hertz

ppm : Parts per million

mg : miligram

mmol : milimol

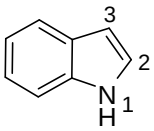
CHAPTER 1

INTRODUCTION

1.1 Indoles

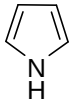
1.1.1 Definition of Indole and General Properties of Indoles

Indole **1** is a heterocyclic organic compound. Fundamental skeleton of an indole derivative has a bicycylic structure containing a benzene ring **2** fused to a pyrrole ring **3**. Indole can be classified as π-excessive aromatic compound and it is isoelectronic with naphthalene **4**.

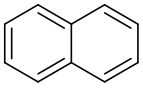


indole **1**

benzene **2**



pyrrole **3**



naphtalene **4**

The aromaticity of the indole ring is located at the center of succession for many synthetic methods. Driving force for most of the indole ring formations is stabilization of the system after formation of the pyrrole ring which is combined to the benzene ring.[1]

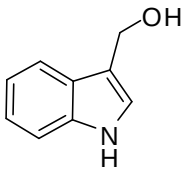
Contribution of the nitrogen lone pair electrons into the aromatic ring prevents the strong base behavior of indoles and also indoles do not behave as a simple amine. Besides this, indole is a very weak base just like pyrrole. The conjugate acid is estimated to have a pK_a= -2.4 because aromaticity is compromised by protonation at nitrogen.[2] As a result of these indoles and some of simple indole derivatives are quite reactive toward strong acids instead of protonation at C-3 position.

Many synthetic methodologies have been developed over substitution reactions on the indole ring. Electrophilic substitution preferably takes place at C-3 carbon as a result of various molecular orbital calculations which shows the highest electron

density is sited at C-3 and electrophilic attack tendency of the C-3 position is estimated to be 10^{13} times greater than the benzene ring.[3] C-2 position is the second reactive site toward electrophiles. Most nucleophilic site of the indole skeleton is N-1 as nitrogen proton is waekly acidic. Therefore N-1 substitution like alkylation, acylation takes place under basic conditions.

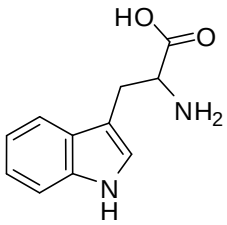
The indole structure can be found in many natural products. Several naturally occurring indole derivatives have clinical importance and experimental studies have shown that they have significant biological activities.

One of the important indole derivatives is indole-3-carbinol **4** which occurs naturally in cruciferous vegetables such as cabbage and broccoli. Controlled studies have been performed on some animals such as rats and mice by addition of indole-3-carbinol into their daily diet. Studies with animals have demonstrated that indole-3-carbinol **4** reduces the carcinogenic affects of aflatoxins.[4] Indole-3-carbinol blocks estrogen receptor sites on the membranes of breast and other cells, so reduces the risk of breast cancer.[5] Some studies also showed its beneficial effect on the treatment of skin cancer.[6]



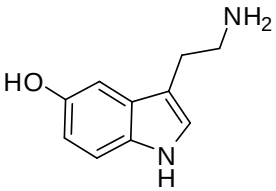
indole-3-carbinol (4)

The indole skeleton appears in the tryptophan **5** which is one of the 20 naturally occurring amino acids. For many organisms including human being, tryptophan is an essential amino acid. This means that it cannot be synthesized by the organism and therefore must be obtained from different dietary sources. Plants and microorganisms synthesize tryptophan by starting from shikimic acid[7] or anthranilate.[8] Amino acids, including tryptophan, act as building blocks in protein biosynthesis and also functions as a biochemical precursor for many biologically important compounds.



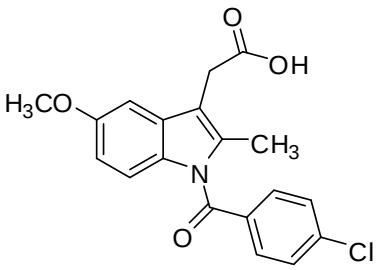
tryptophan (5)

One of another significant indole derivative is serotonin **6**. It acts as a chemical messenger that transmits nerve signals between nerve cells and that causes blood vessels to narrow, so serotonin is a biochemical messenger and regulator.[9] It is synthesized from L-tryptophan by hydroxylation and decarboxylation.[10]

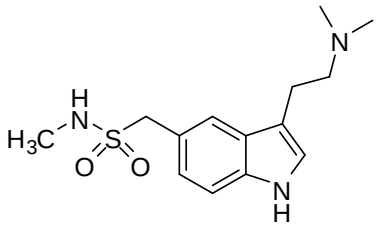


serotonin (6)

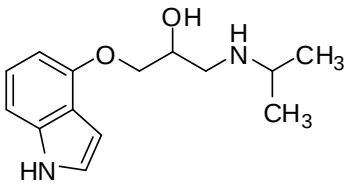
Among the indole derivatives those are commonly being used as drugs, some of them comes to the fore such as; indomethacin **7**, one of the first non-steroidal anti-inflammatory agents,[11] sumatriptan **8**, which is being used to treatment of migrane headaches[12] and pindolol **9**, one of the nonselective β-adrenergic blockers.[13]



indomethacin (7)

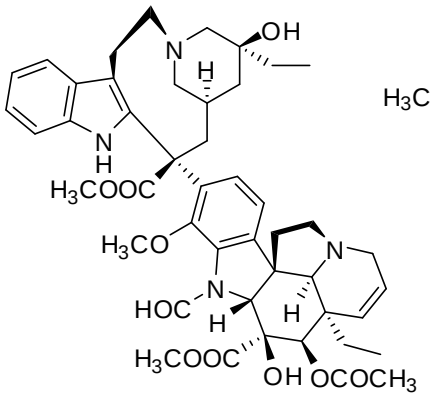


sumatriptan (8)

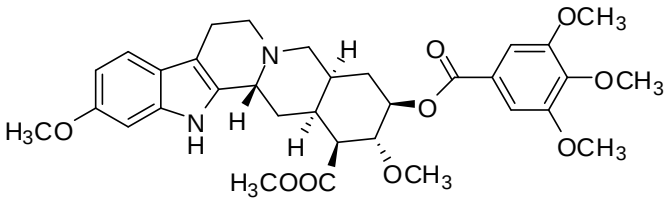


pindolol (9)

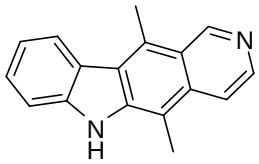
Some of major naturally occurring indoles which exhibits biological activities should be mentioned. Vincristine **10**, which is isolated from Madagascar periwinkle, is a dimeric *vinca* alkaloid and it has a proven clinical importance in cancer chemotherapy due to its mitotic inhibitor function.[14] Ellipticine **11** is another naturally occurred indole derivative obtained from *ochrosia elliptic* and it shows anti-tumor activity.[15] Reserpine **12** is also an important natural indole derivative that has been used for treatment of mental disorders.[16] But due to its various side effects, newly developed drugs are commonly being used instead of reserpine.



vincristine (10)



reserpine (12)



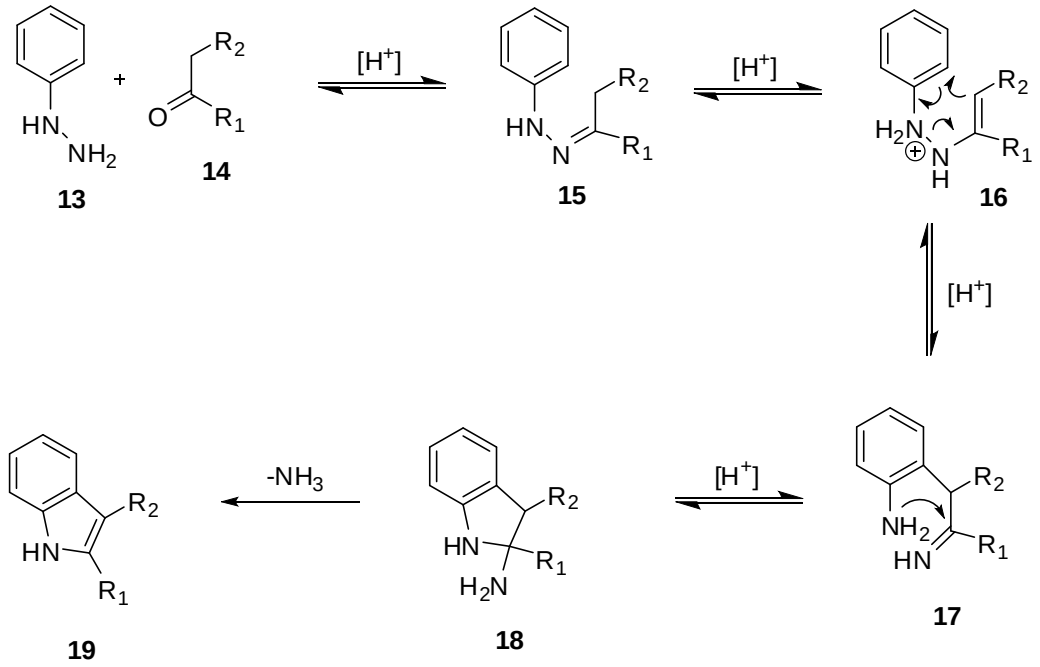
ellipticine (11)

1.1.2 Synthesis of Indoles

1.1.2.1 Fischer Indole Synthesis

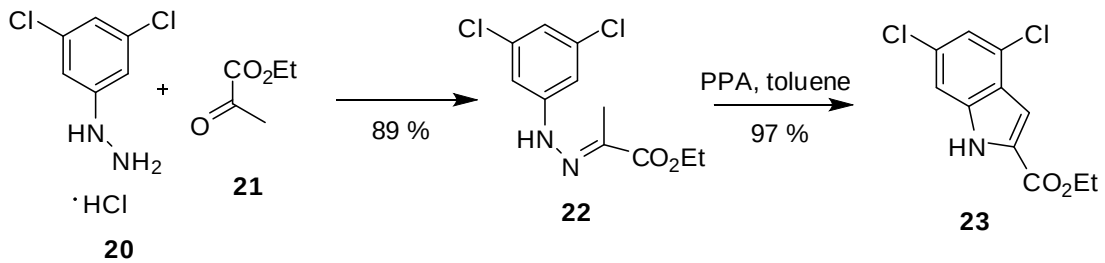
The Fischer indole synthesis is one of very useful and important method for the synthesis of numerous indole intermediates which has been using for over a century.[17] This method was first discovered by a German chemist, Hermann Emil Fischer, in 1883.[18] Fischer indole synthesis is a well established procedure for the synthesis of substituted indoles. The synthetic route of the method initiates by the reaction of (substituted) arylhydrazine **13** with an aldehyde or ketone **14** under acidic conditions in order to form a arylhydrazone **15**. [3,3]-sigmatropic rearrangement that involves cleavage of N-N bond is a key step after the protonation of the enamine **16**

to produce an imine **17**. Cyclization of the imine to form an cyclic aminoacetal **18** and aromatization with loss of ammonia provides the indole **19** product. (Scheme 1)



Scheme 1

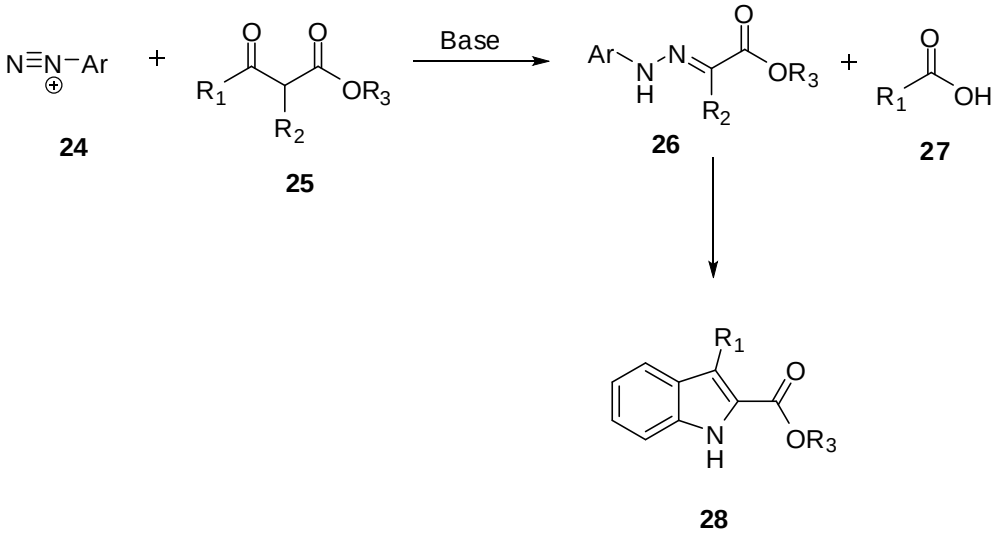
Watson and co-workers carried out an efficient three step synthesis based on Fischer indolization method.[19] Starting from commercially available 3,5 dichloro-phenylhydrazine hydrochloride **20**, treatment with ethyl pyruvate **21** in ethanol gave the hydrazone **22** as an *E*/*Z* mixture. [3,3]-sigmatropic rearrangement followed by cyclization using PPA (polyphosphoric acid) as a catalyst in toluene at 95-100 °C provided the indole ethylcarboxylate **23** in 97% yield as a crystalline solid. (Scheme 2)



Scheme 2

1.1.2.2 Japp-Klingemann Reaction

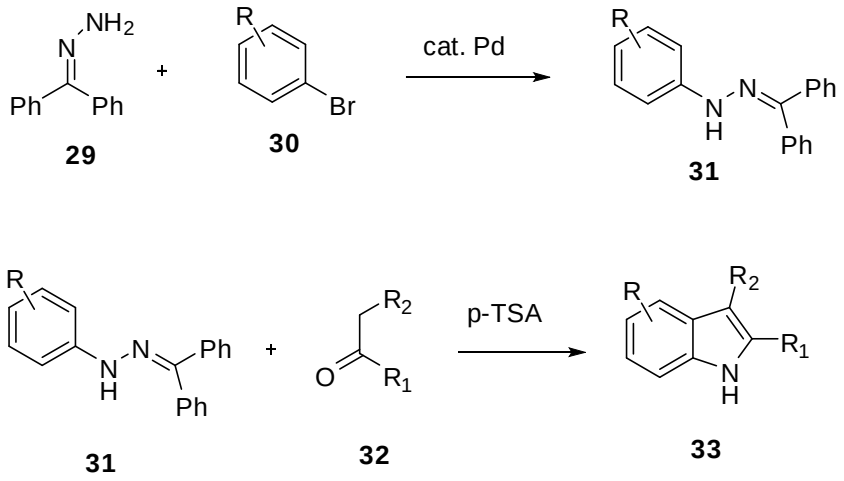
The Japp-Klingemann reaction provides a very useful alternative route to produce a number of arylhydrazones which can be used in the Fischer indolization process.[20] Initially coupling of aryldiazonium ions **24** with especially β-ketoesters **25** yields arylhydrazones **26** in the presence of base. At this step deacylation takes place and it is followed by indole **28** formation as shown in Scheme 3. Prevent the formation and usage of arylhydrazines which can be difficult to handle is an advantage of the Japp-Klingemann reaction over Fischer indolization process.



Scheme 3

1.1.2.3 Metal Catalyzed Arylation of Benzophenone Hydrazone

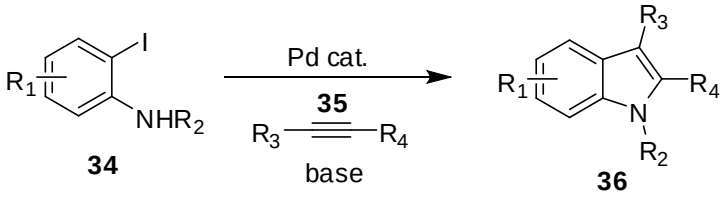
Accessibility of certain substituted arylhydrazine or arylhydrazone intermeiates is one of the important restrictions of Fischer indolization method. In order to overcome this limitation Buchwald and co-workers reported a palladium catalyzed coupling method starting from commercially available benzophenone hydrazone **29** and aryl bromides **30** to produce *N*-arylbenzophenone hydrazones **31**.[21] Acid catalyzed treatment of *N*-arylbenzophenone hydrazones and corresponding ketones **32** provide indole structures **33**. (Scheme 4)



Scheme 4

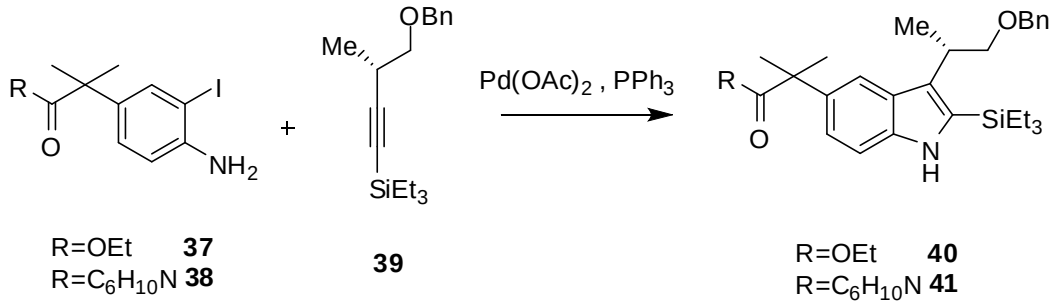
1.1.2.4 Indole Synthesis via the Larock Heteroannulation

The Larock heteroannulation is one of the practical method to construct indole structures **36** via a palladium catalyzed reaction of *o*-iodoanilines **34** and internal alkynes **35**.[22] First advantage of this method is its readily accessible starting materials. Both *o*-iodoanilines and corresponding alkynes are commercially available and easily can be handled. Second advantage is the method involves just one step and enables to produce complex indole structures in a single operation. This reaction is regioselective and more sterically hindered group almost occupies the 2 position of the indole ring.



Scheme 5

Walsh and co-workers reported the preparation of indoles **40**, **41** which were utilized in the synthesis of the gonadotropin releasing hormone antagonist.[23] Their study involves the Larock heteroannulation of *o*-iodoanilines **37**, **38** and with chiral alkynylsilane **39** in the presence of $Pd(OAc)_2$ and PPh_3 as shown in Scheme 6.



R=OEt **37**
R=$C_6H_{10}N$ **38**

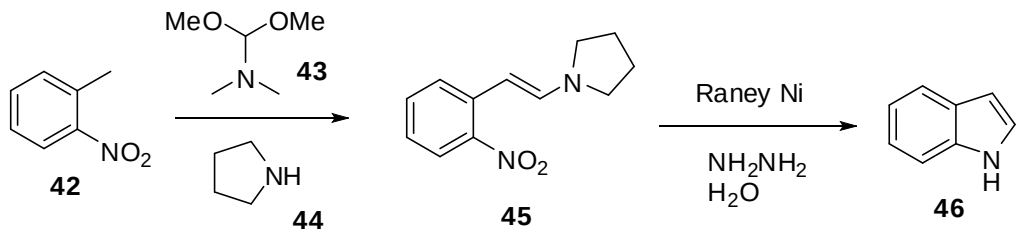
39

R=OEt **40**
R=$C_6H_{10}N$ **41**

Scheme 6

1.1.2.5 The Leimgruber-Batcho Indole Synthesis

Another effective method for synthesizing indole derivatives is the reductive cyclization of aromatic nitro compounds. Leimgruber Batcho synthesis is a two step method which provides indoles that are only substituted at the benzene ring via reductive cyclization.[24] The pyrrole part of the indole remains unsubstituted as a result of this method. In the first step enamine **45** formation takes place after a condensation of an o-nitrotoluene **42** with N,N-dimethylformamide dimethylacetal (DMFADMA) **43** and pyrrolidine **44**. In the second step nitro group is reduced to NH_2 using hydrogen and a Raney nickel catalyst, then desired indole **46** is obtained after cyclization.

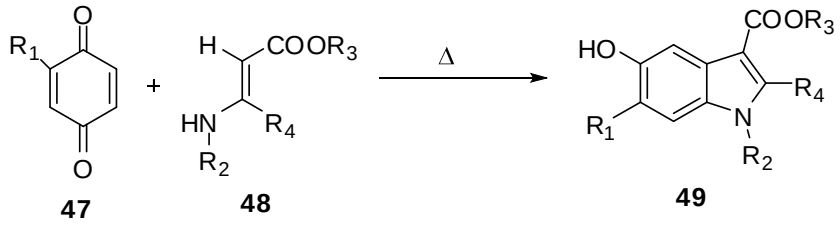


Scheme 7

1.1.2.6 Nenitzescu Indole Synthesis

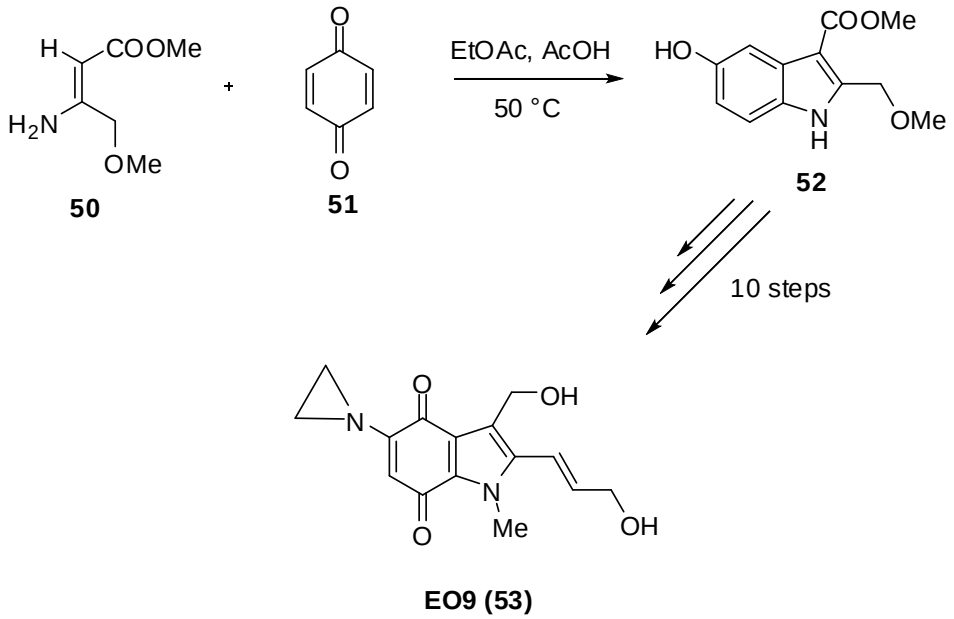
The Nenitzescu indole synthesis enables an easy way to synthesize functionalized 5-hydroxyindole derivatives **49** from (substituted)benzoquinone **47** and β-amino-

crotonic esters **48** as shown in Scheme 8.[25] Due to various possible side product formations, yields of this method is quite low.



Scheme 8

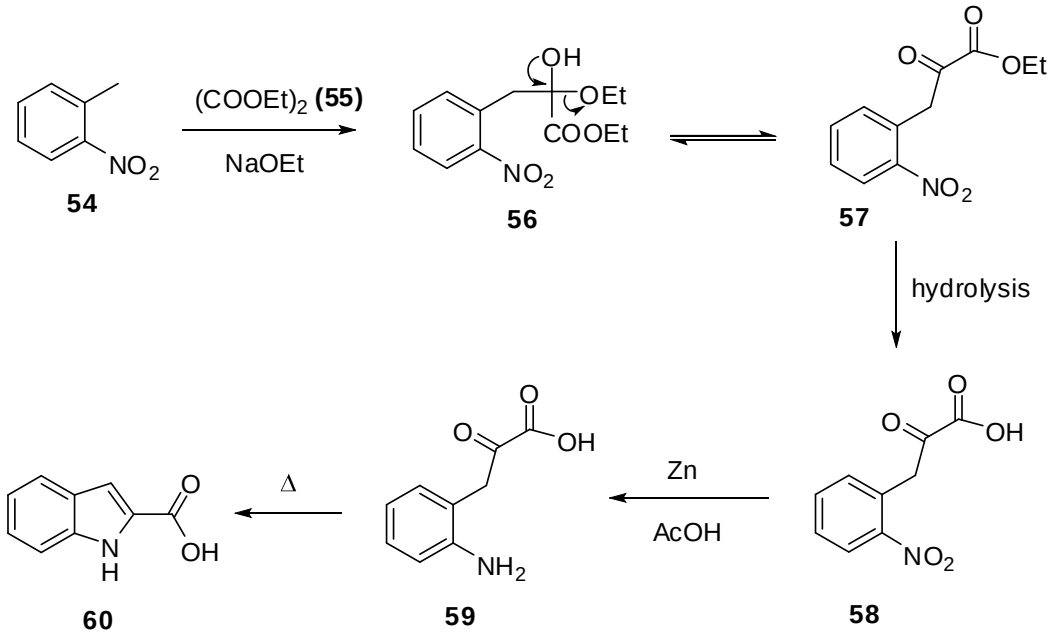
As shown in Scheme 9, Kasai *et al. r*eported preparation of an 5-hydroxyindole derivative **52** which is further utilized to synthesize antitumor indolequinone EO9 **53**.[26] The Nenitzescu indole synthesis methodhology was used to construct the desired indole precursor in this study. Reaction of **50** and benzoquinone **51** yielded the indole derivative which was then converted into EO9 in 10 additional steps.



Scheme 9

1.1.2.7 Reissert Indole Synthesis

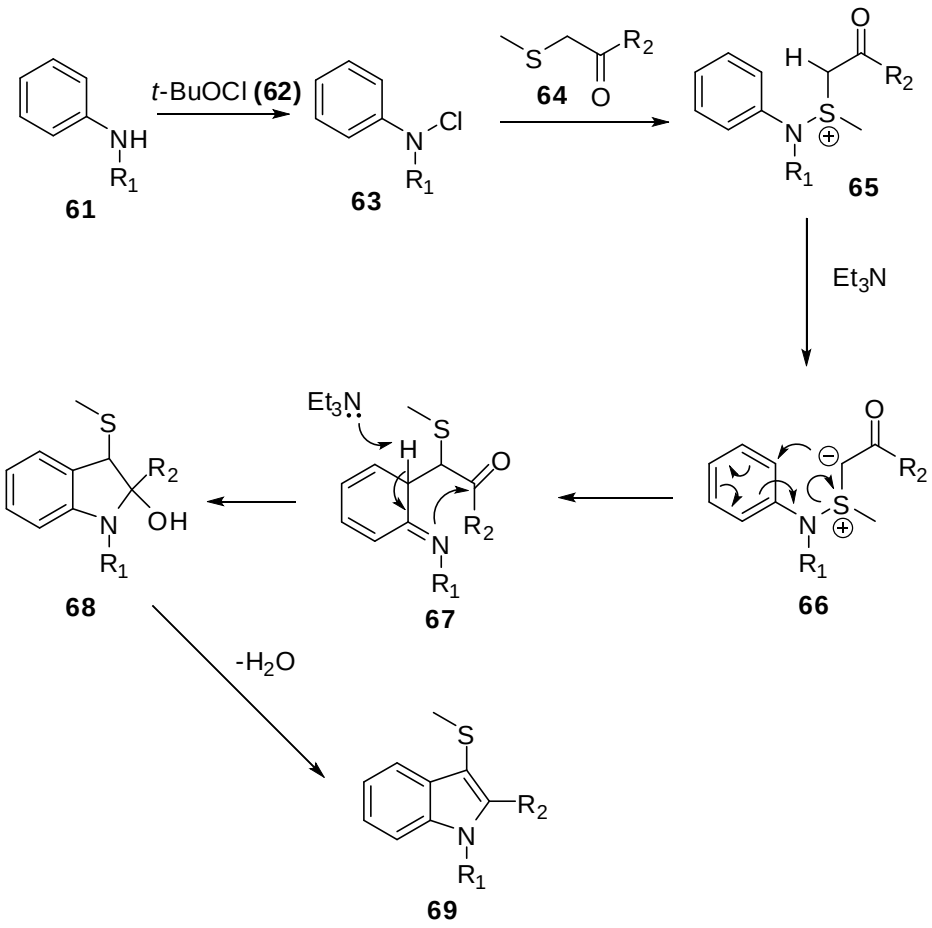
The Reissert indole synthesis involves base catalyzed condensation of o-nitrotoluene **54** and diethyl oxalate **55**. Hydrolysis of the ester group in **57** followed by reduction of the nitro group in **58** to the amine gave **59** which was converted into indole **60**.[27] (Scheme 10)



Scheme 10

1.1.2.7 Gassman Indole Synthesis

Substituted indoles can be synthesized starting from aniline via Gassman indole synthesis.[28] First step of the synthetic route of this method shown in Scheme 11 starts with the reaction of aniline **61** and *t*-BuOCl **62**. After formation of the chloramine **63**, addition of the β-carbonyl sulfide derivative **64** yields the sulfonium ion **65**. Finally treatment of the sulfonium ion by Et_3N creates the sulfonium ylide **66** which turns into the ketone **67** after a [2,3] sigmatropic rearrangement and desired indole derivative **69** is produced in the presence of the base.

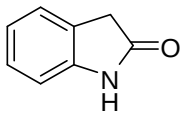


Scheme 11

1.2 Oxindoles

1.2.1 Definition of Oxindoles

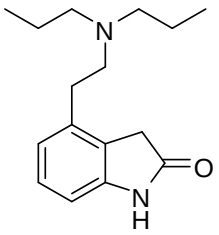
Oxindole **70** is an aromatic heterocyclic organic compound. It consists of a six membered benzene ring and a five membered nitrogen containing ring attached to the benzene ring.



70

Oxindoles represent an important pattern found in a number of natural products and pharmaceutical targets. They exhibit biological activity against anti-tumor[29] and anti-

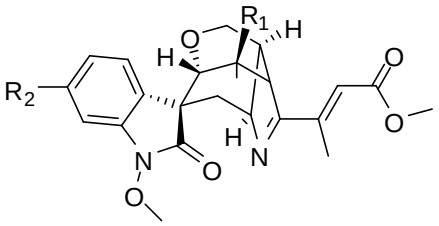
HIV[30] properties. As an example, ropinirole **71** is an important oxindole derivative which has been using for parkinson treatment.[31]

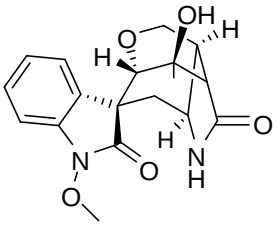


ropinirole (71)

Various naturally occurring oxindole alkaloids represent biological activity like indoles.

Gelsemium elegans Benth. (Loganiaceae), a toxic plant widely distributed in Southeast Asia, was used in traditional Chinese medicine. This plant was used as a medicine for certain kinds of skin ulcers in traditional Chinese medicine and is assumed to have been used as an external medication for dermatitis for more than 1250 years in Japan.[32] New alkaloids named as, gelsecrotonidine **72**, 14-hydroxy-gelsecrotonidine **73**, 11-methoxygelsecrotonidine **74**, and 14-hydroxygelsedilam **75**, were isolated from G. elegans which contains oxindole skeleton inside their structures.[33]





14-hydroxy-gelsedilam (75)

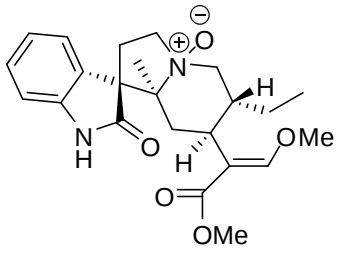
R_1=H, R_2=H :gelsecrotonidine (72)

R_1=OH, R_2=H :14-hydroxy-gelsecrotonidine (73)

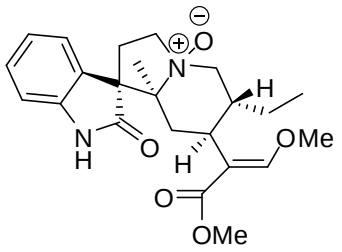
R_1=H, R_2=OMe :11-methoxygelsecrotonidine (74)

The leaves of *Uncaria rhynchophylla* were used as a folk medicine in China for the treatment of hypertension, headache, and stroke.[34] Two of several alkaloids isolated

from this plant named as (4S)-corynoxeine N-oxide **76** and isocorynoxeine N-oxide **77** involves oxindole inside their structure.

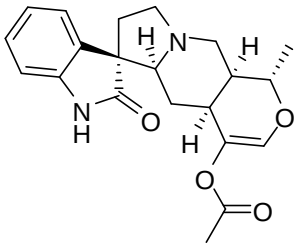


(4S)-corynoxeine N-oxide (76)

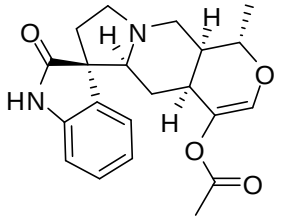


isocorynoxeine N-oxide (77)

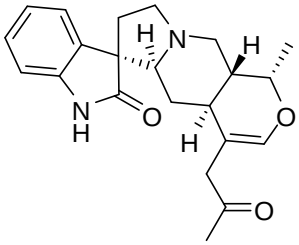
The *Uncaria tomentosa* that grows in the Amazonian forests had been used as medicine by the Andean populations. They used the bark as a local and systemic anti-inflammatory agent and as inmunostimmulant. Oxindole alkaloids, namely isopteropodine **78**, pteropodine **79**, and mitraphylline **80** obtained from *Uncaria tomentosa*. These alkaloids inhibited increasing of acute lymphoblastic leukaemia cells.[35]



isopteropodine (78)



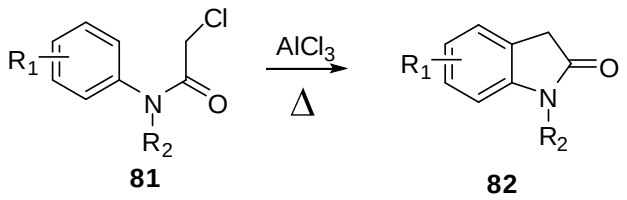
pteropodine (79)



mitraphylline (80)

1.2.2 Synthesis of Oxindoles

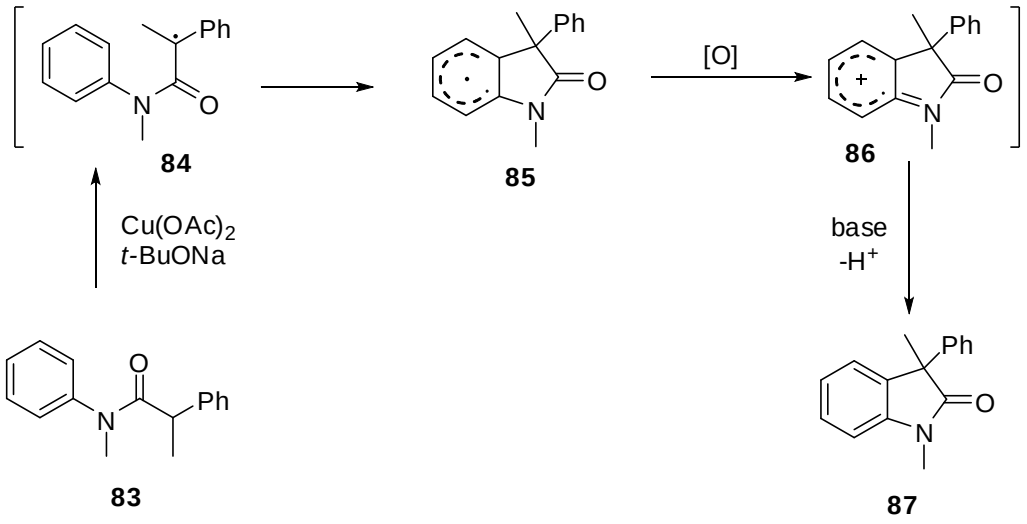
Intramolecular Freidel-Crafts substitution is one of the prominent method for synthesizing oxindoles **82** from α-haloacetanilides **81**. Cyclization takes place via heating the reagent with $AlCl_3$ (Scheme 12).[36]



81 **82**

Scheme 12

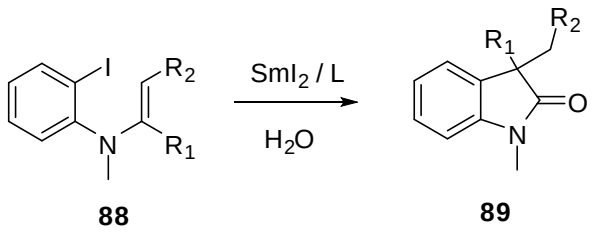
Among the numerous methods those have been reported for the syntheses of oxindoles, radicalic cyclizations play an important role in order to synthesize oxindoles. As shown in Scheme 13, Kündig *et al*. performed a study based on radical cyclization starting with N-methyl-N-2-diphenylpropanamide **83**.[37] Formation of the radical **84** starting from **83** is followed by cyclizaiton onto the benzene to obtain corresponding oxindole derivative **87**.



84 **85** **86** **83** **87**

Scheme 13

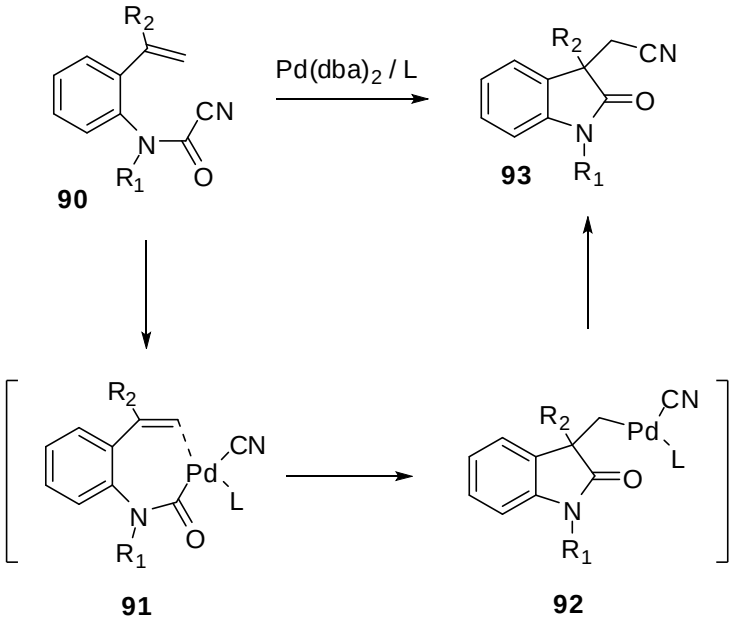
Another example for radicalic cyclization was published by Cabri and co-workers. Samarium diiodide mediated cyclization of aryliodides **88** yielded the oxindole derivatives **89** (Scheme 14).[38]



88 **89**

Scheme 14

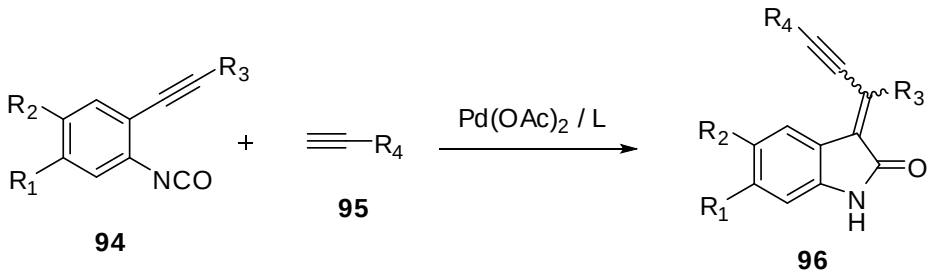
Takemoto *et al.* published another efficient method to synthesize oxindoles via palladium catalyzed cyanoamidation. Cyanoformamide **90** was treated with $Pd(dba)_2$ and different ligands in order to synthesize oxindole derivatives **93** (Scheme 15).[39]



90 **93** **91** **92**

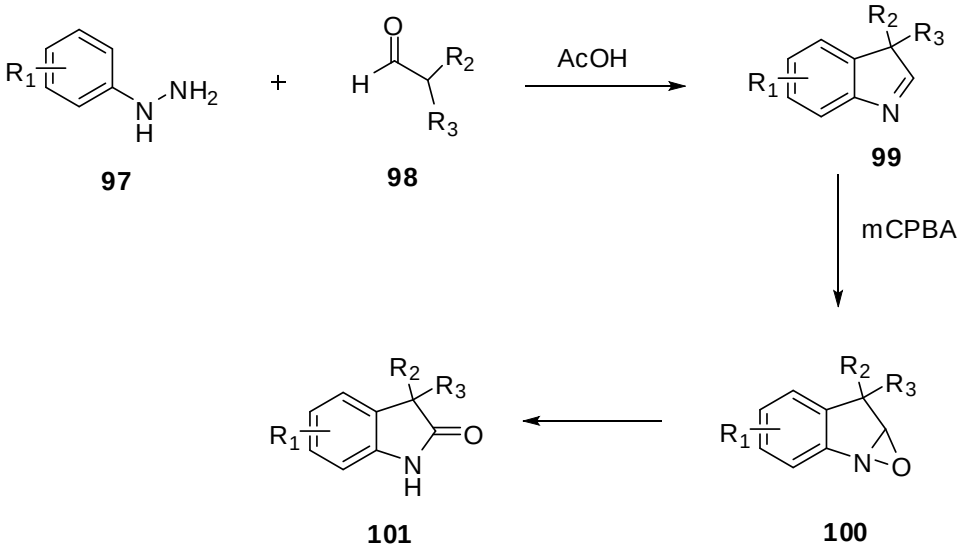
Scheme 15

Among many different examples carried out with palladium catalysts aims to synthesize oxindoles, one of the recent articles was published by Yamamoto and Kamijo.[40] They reported the first example of intramolecular nucleophilic vinyl-palladation of isocyanates to produce oxindoles as shown in Scheme 16. Coupling reaction between 2-(alkynyl)phenylisocyanates **94** and terminal alkynes **95** in the presence of $Pd(OAc)_2$ yields the corresponding oxindole derivatives **96**.



Scheme 16

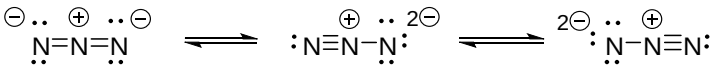
Oxidation of the indole derivatives is another easy and common method for the synthesis of oxindoles. A recent example of this method was carried out and published by Lui *et al*. as shown in Scheme 17. Indole derivatives **99** which can be readily synthesized via Fischer indolization is subjected into a reaction with m-CPBA to obtain oxaziridines **100**.[41] After a simple rearrangement on the oxaziridines, corresponding 3,3-di-substituted oxindole derivatives **101** can be easily handled.



Scheme 17

1.3 Chemistry of Azide and Isocyanate

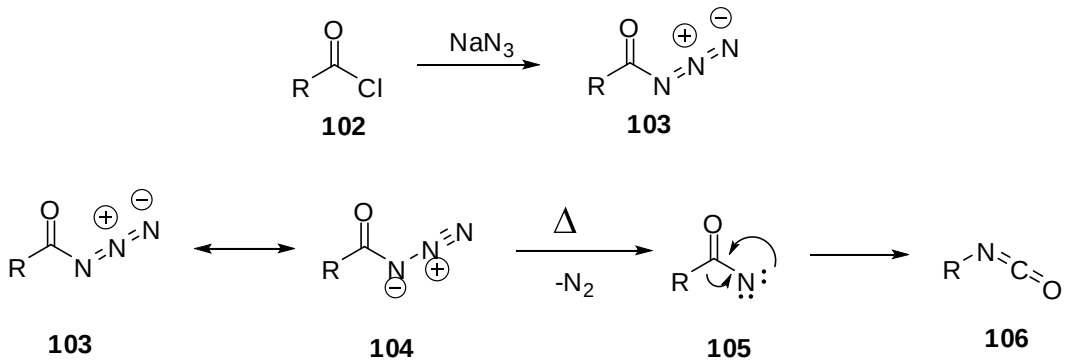
Azide is the anion with the formula N_3^-. It is the conjugate base of hydrazoic acid and it is also a functional group in organic chemistry.[42] Azide can be described by several resonance structures as shown in Scheme 18.



Scheme 18

The principal source of the azide family is sodium azide. Most inorganic and organic azides are prepared directly or indirectly from sodium azide.

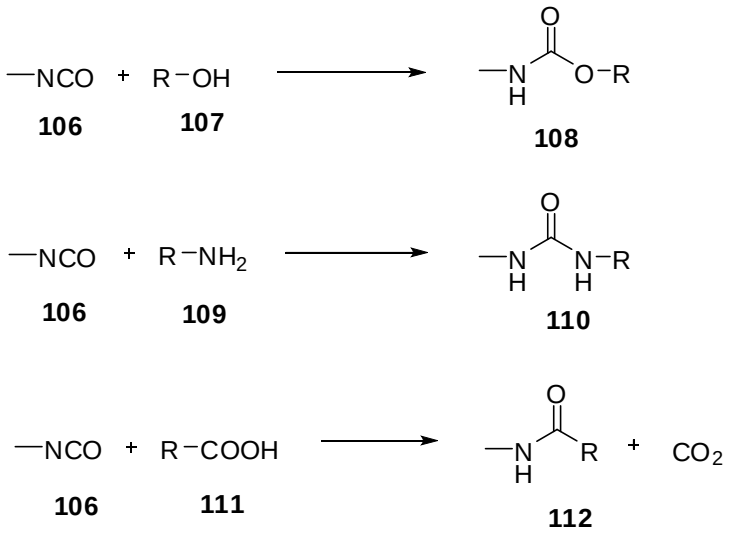
Alkyl or aryl acyl chlorides **102** react with sodium azide in aqueous solution to give acyl azides **103**, which give isocyanates **106** in the Curtius rearrangement which is first defined by Theodor Curtius (Scheme 19).[43]



Scheme 19

The first step of the Curtius rearrangement is the loss of nitrogen gas forming an acyl nitrene **105** which can very quickly rearrange by migration of R group forming the desired isocyanate **106** .

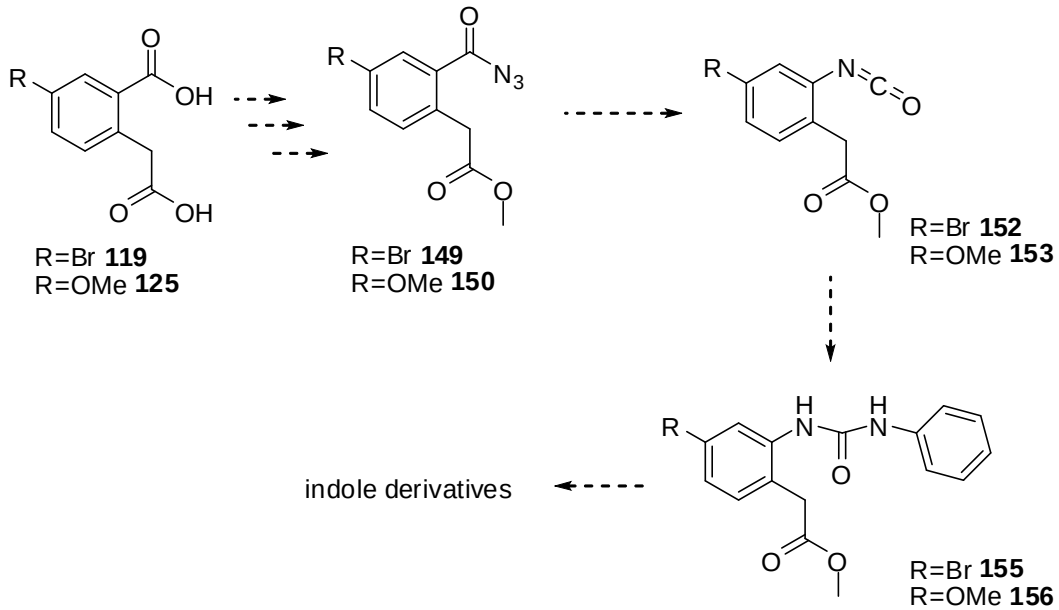
Isocyanate is the functional group of atoms –N=C=O. The most prominent characteristic of isocyanate is its high reactivity towards nucleophiles. It gives rapid reactions with alcohols **107** to produce urethane **108**, amines **109** to produce urea **110**, carboxylic acids **111** to produce amide **112** and so on (Scheme 20).



Scheme 20

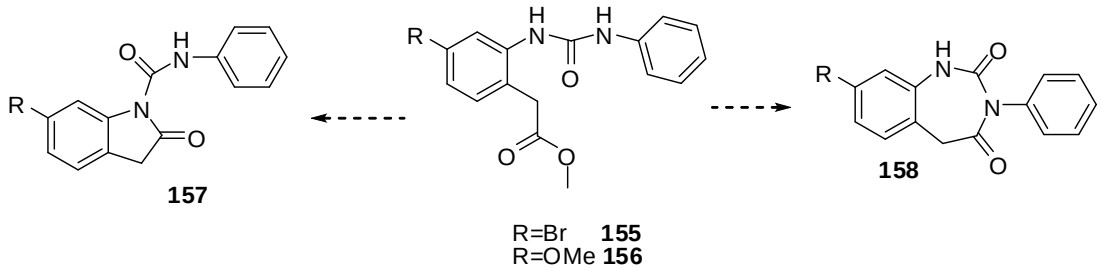
1.4 Aim of the Thesis

Main aim of this thesis is construction of new indole derivatives via ring-closure reactions starting from substituted homophtalic acids **119**, **125**. Acyl azide **149**, **150** and isocyanate **152**, **153** precursors will play an important role throughout the synthetic route. The corresponding isocyanate derivatives **152**, **153** will be trapped with aniline to generate urea derivatives **155**, **156** which will be subjected into ring-closure reactions under basic conditions.



Scheme 21

The urea derivatives **155**, **156** have two possible ring closure pathway leading to five or seven membered rings. Reveal the preference of this system is another objective during this study.



Scheme 22

Effect of the two different substituents on the cyclization process will be discussed in detail according to the experimental results.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of Starting Materials

2.1.1 The synthesis of Bromine Substituted Homophthalic Acid: The Reaction of Homophthalic Acid with Potassium Bromate

Potassium and sodium bromates are both powerful bromination agents for aromatic molecules which contains deactivating substituents like carboxylic acid. This method is usefull especially for disubstituted benzene rings.[44] Aqueous solution of a strong acid, preferably sulphuric acid, leads to the production of active brominating species upon treatment with sodium or potassium bormates.[45] Potassium bromate **113** was used as bromine source in this study. Initially participation of acidic proton provides the formation of bromic acid **114**.

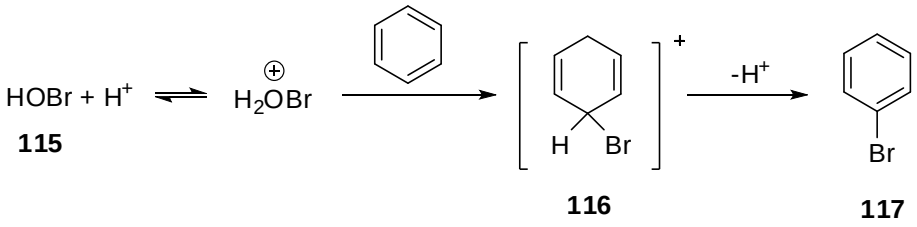
$$\underset{\mathbf{113}}{KBrO_3} \rightleftharpoons K^+ + BrO_3^-$$

$$BrO_3^- + H^+ \rightleftharpoons \underset{\mathbf{114}}{HBrO_3}$$

After the formation of the bromic acid a decomposition takes place to form hypobromous acid **115** and perbromic acid **116**.

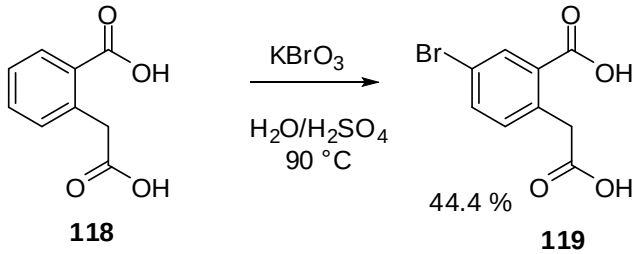
$$\underset{\mathbf{114}}{3HBrO_3} \rightleftharpoons \underset{\mathbf{115}}{HOBr} + \underset{\mathbf{116}}{2HBrO_4}$$

Finally hypobromous acid **115** was activated in the presence of acidic protons and this step is followed by a nucleophilic attack from the benzene ring. Elimination of a proton from the intermediate **116** yields the bromine substituted product **117**. (Scheme 23)



Scheme 23

Preparation of the desired bromine substituted homophthalic **119** acid was carried out by this method starting from the homophthalic acid **118**. As the carboxylic acid behaves as meta director, substitution takes place at the meta position. Isolated yield was quite low that is % 44.4 due to some possible side products those are soluble in water.

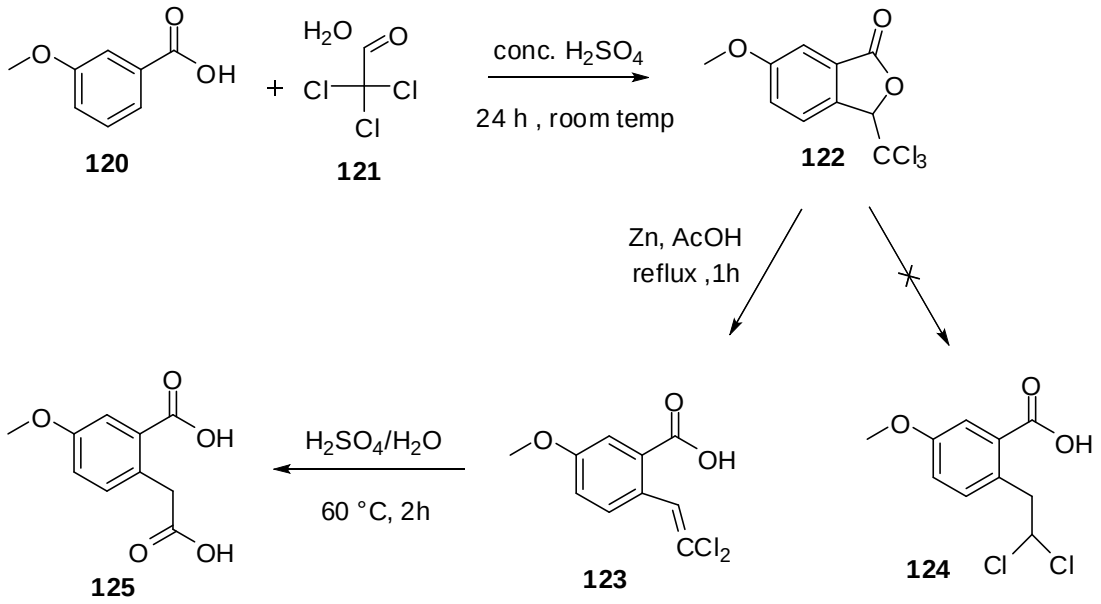


Scheme 24

2.1.2 The synthesis of Methoxy Substituted Homophthalic Acid: The reaction of 3-Methoxybenzoic Acid and Chloral Hydride

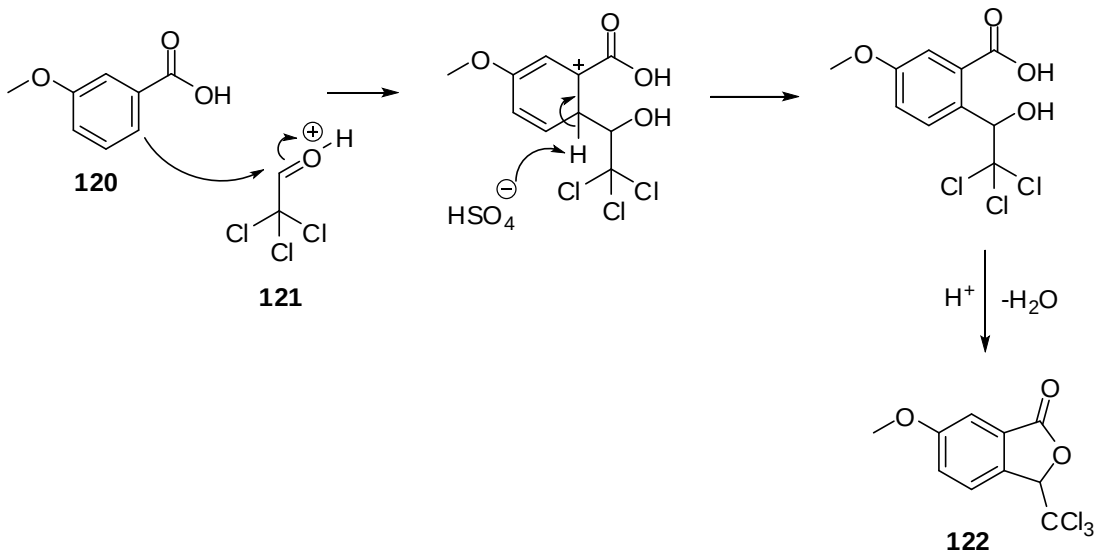
For the synthesis of methoxy substituted homophthalic acid **125**, an efficient procedure published in the literature was followed by the help of just a few modifications.[46] The procedure consists of three steps.

Initially 3-methoxybenzoic acid **120** and chloral hydrate **121** was subjected into a condensation reaction in the presence of sulphuric acid in order to obtain the corresponding lactone **122**. As a second step the lactone derivative was reduced by zinc in acetic acid to produce dichlorovinyl derivative **123** instead of a saturated compound **124**. Finally the desired compound **125** was synthesized by the treatment of sulphuric acid and the dichlorovinyl derivative. (Scheme 25)



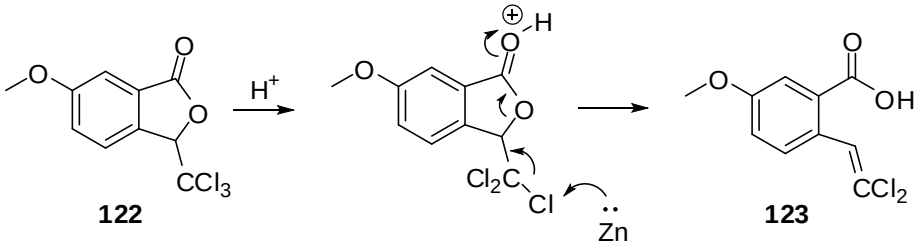
Scheme 25

First of all, double bond of the benzene ring **120** attacks to the carbonyl carbon of the chloral hydride **121** which was activated by the acid. In order to regaining aromaticity a proton is eliminated from the benzene ring. Consequently corresponding lactone derivative **122** was produced via acid catalyzed Fischer esterification.



Scheme 26

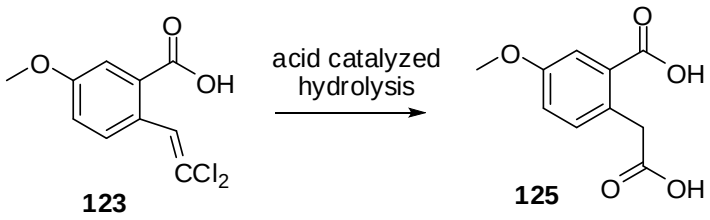
Second step of the formation involves an oxidation reduction reaction in the presence of acetic acid and zinc dust. After activation of the carbonyl carbon of the lactone **122**, a nucleophilic attack of lone pair electrons of the zinc through one of the chlorine atoms yields the dichlorovinyl derivative **123**.



122 **123**

Scheme 27

Finally desired methoxy substituted homophthalic acid **125** is formed via acid catalyzed hydrolysis.

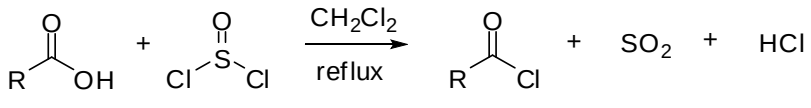


123 **125**

Scheme 28

2.2 Reaction of Homophthalic Acid with Thionyl Chloride

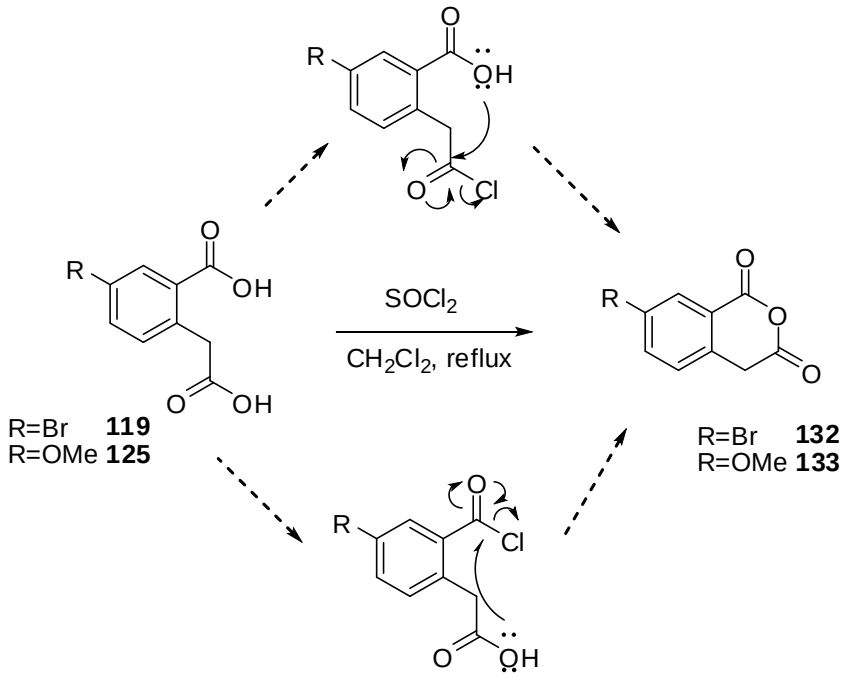
Thionyl chloride **127** is an inorganic compound and it has been using as one of the well known chlorination agents in organic synthesis. Carboxylic acid derivatives **126** can be easily converted into acyl chloride derivatives **128** by using thionyl chloride.[47]



126 **127** **128**

Scheme 29

In our case, initially thionyl chloride was reacted with the substituted homophthalic acid derivatives **119**, **125**. Characterization of the resulting product showed that anhydride derivatives **132**, **133** were formed instead of diacyl chloride derivatives **134**, **135**. Formation of those products were somewhat reasonable due to an instantaneous attack of the lone pair electrons of one of the hydoxy group towards chlorinated side just after chlorination of one of the branches as shown in Scheme 30.

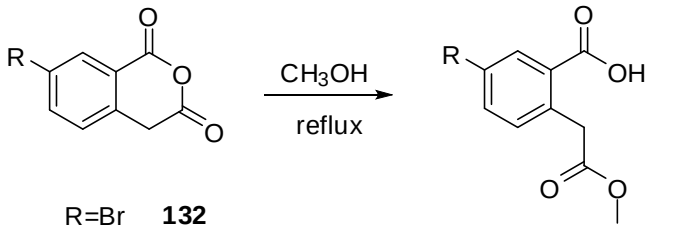


Scheme 30

In addition to the NMR spectra, IR spectrum proves the disappearance of the –OH groups. Comparing the IR spectra of the homophthalic acid and the anhydride derivatives, broad –OH stretching vanishes as a result of this reaction

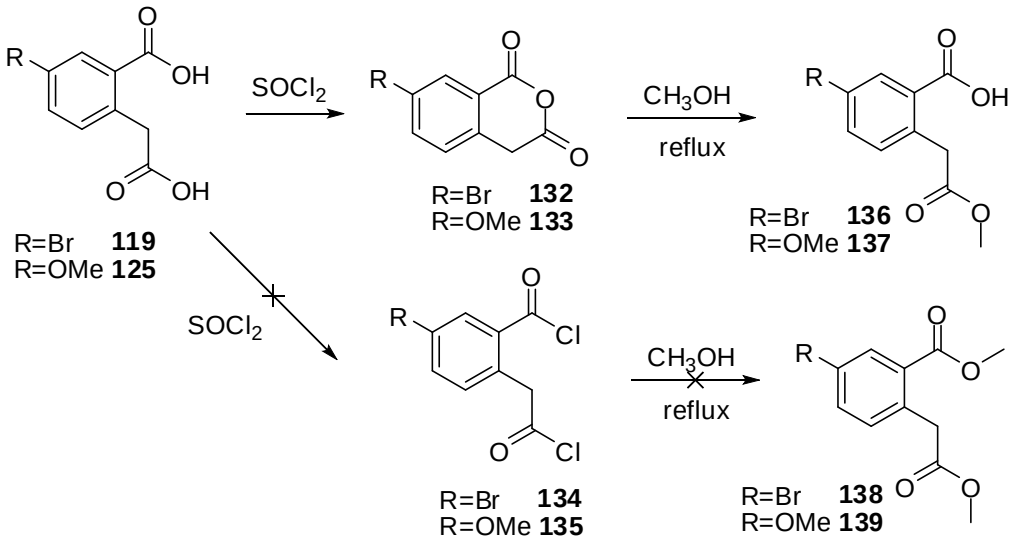
2.3 Reaction of Anhydride Derivatives with Methanol

When the corresponding anhydride derivatives **132**, **133** were refluxed with methanol, regioselectively formed half esters **136**, **137** were isolated. Conjugation between the aromatic benzene ring and carbonyl group that is closer to the ring, makes the other carbonyl goup more reactive towards nucleophiles so that methoxy group attacks regioselectively to the more reactive carbonyl carbon. (Scheme 31)



Scheme 31

Methoxy protons and hydroxy protons observed from ^{1}H-NMR spectrum clearly indicates the formation of half ester. Besides this, ratios of the integration values shows an absolute regioselective ring opening process. This step can also assumed as an evidence for formation of the anhydride derivatives upon treatment of the diacids **119** and **125** as shown in Scheme 32. Because if the compounds were diacyl chlorides **134**, **135** after treatment with thionyl chloride, at this step diester **138**, **139** should be isolated and one additional methoxy signal should be observed from the ^{1}H-NMR spectrum (Figure 1) instead of –OH signal.



Scheme 32

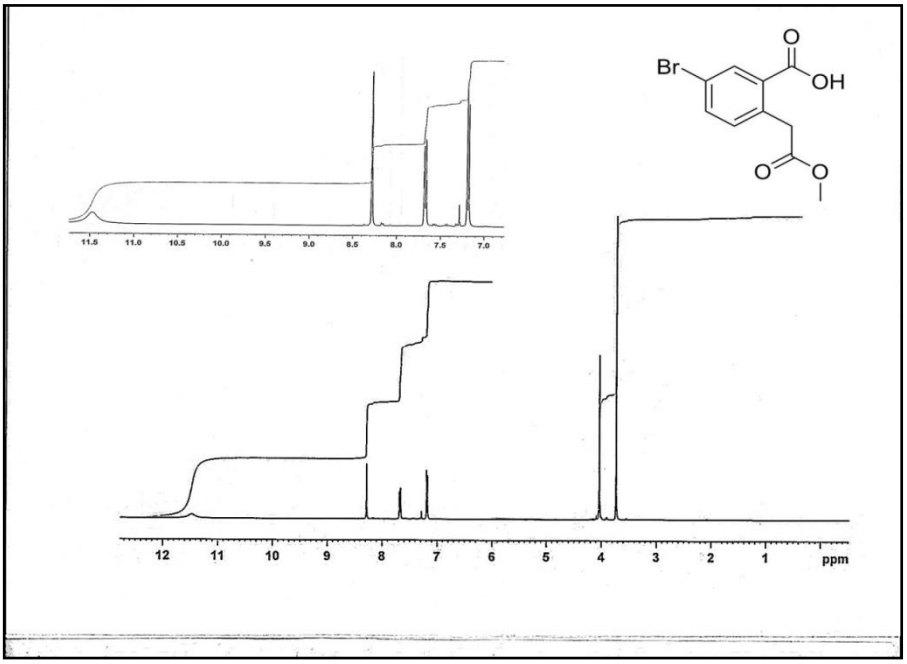
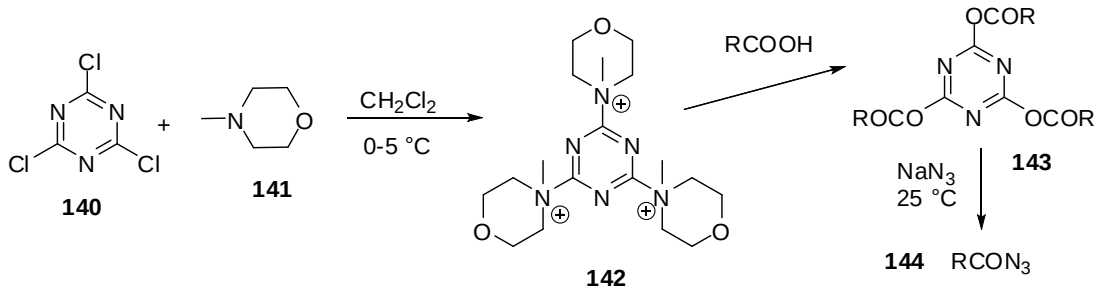


Figure 1 ^{1}H-NMR spectrum of the compound **136**

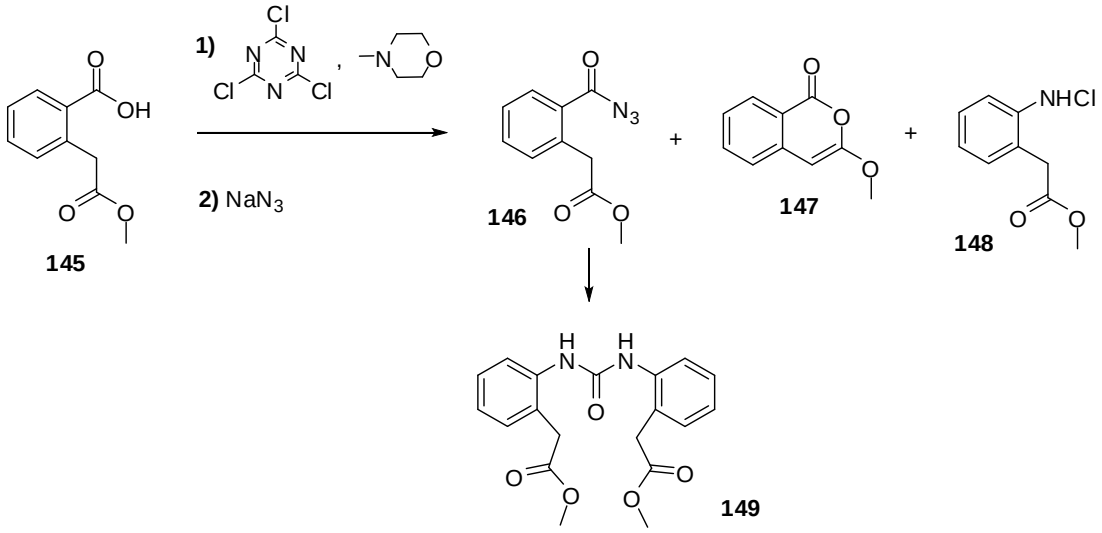
2.4 Reaction of Substituted Half-Esterificated Homophthalic Acid Derivatives: Synthesis of Acyl Azides

The most critical step of the study was to find out a way to incorporate a nitrogen atom into the the structure. One of the best method to achieve this goal is the conversion of the carboxylic acids into the corresponding azides which are important synthetic intermediates. In the literature there are procedures published for conversion of carboxylic acids to acyl azides **144.** One of these methods was performed by using cyanuric chloride **140** and N-methyl morpholine oxide **141**.[48] According to this literature, activating of the carboxylic acid derivatives is followed by addition of the aqueous sodium azide to produce desired acyl azide derivatives.



Scheme 33

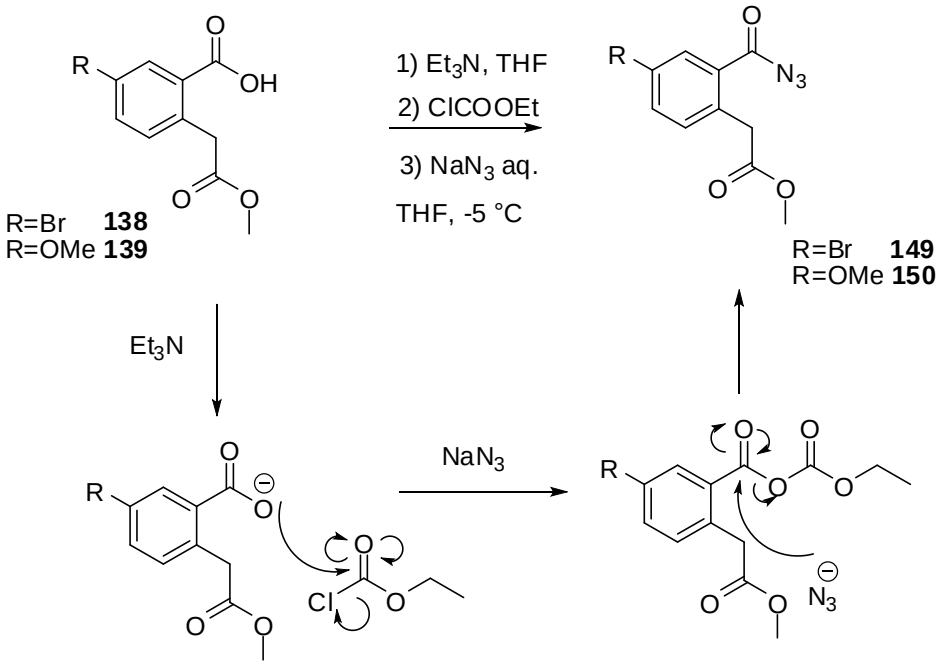
This procedure was applied on nonsubstituted homophthalic acid **145**.[49] Unfortunately three additional unexpected products **147**, **148** and **149** were formed beside the desired azide **146**.



Scheme 34

Another procedure to convert carboxylic acids into acyl azides is the reaction of acids with ethyl chloroformate in the presence of triethyl amine followed by addition of sodium azide.[50] This procedure was successfully applied on nonsubstituted homophthalic **145** and it served desired sole acy azide product **146.**

This succeeded procedure was applied on the substituted half esterificated compounds **138**, **139**. Initially acidic proton of the carboxylic acid was abstracted by triethylamine and addition of the ethyl choloroformate provided a better leaving group which is further converted into azide **149**, **150** after addition of aqueous sodium azide solution.



Scheme 35

IR spectroscopy played an important role for the characterization of the acyl azide compounds besides NMR spectra. The characteristic frequency values of the azide appeared around 2270 and 2140 cm^{-1} (Figure 2).

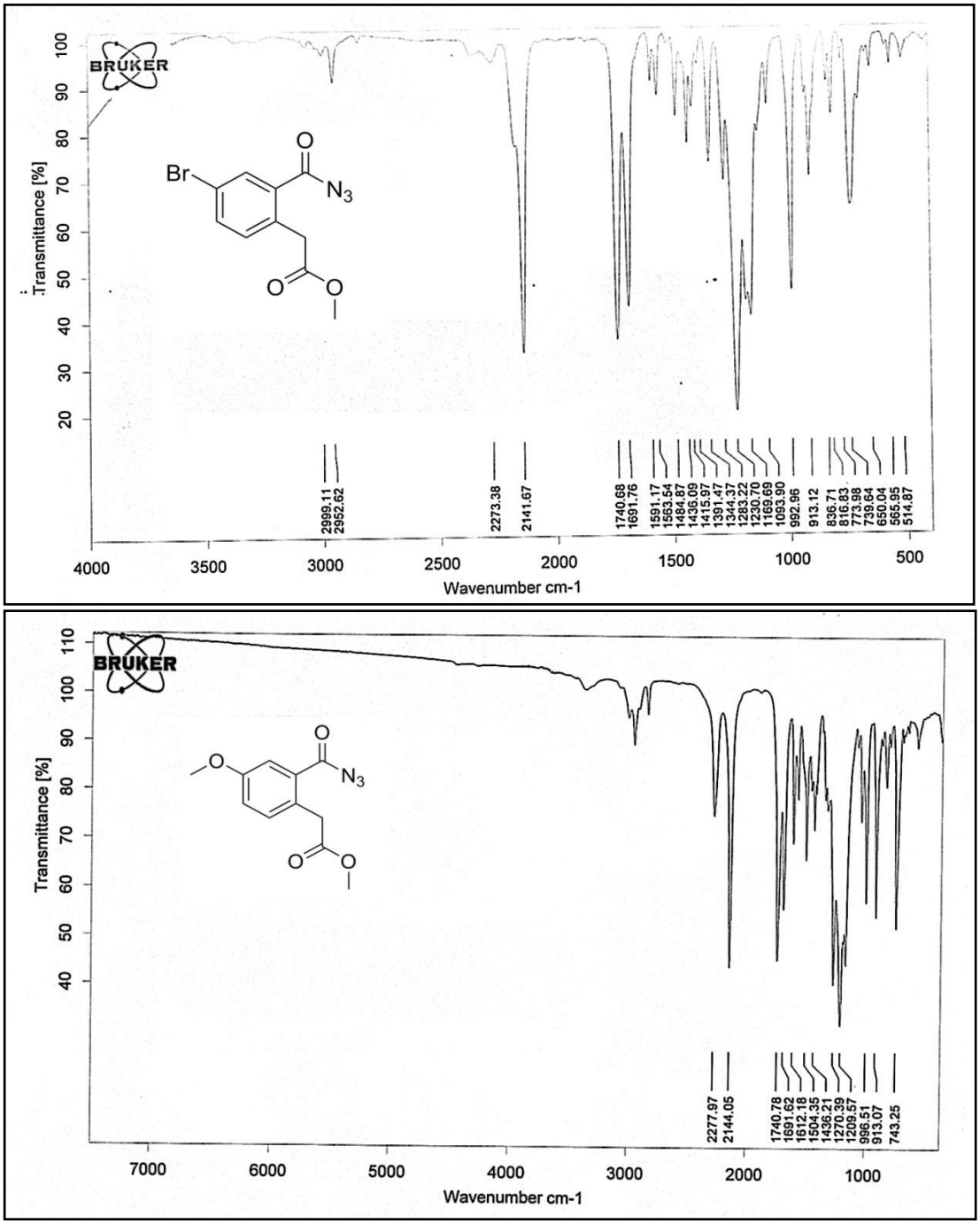
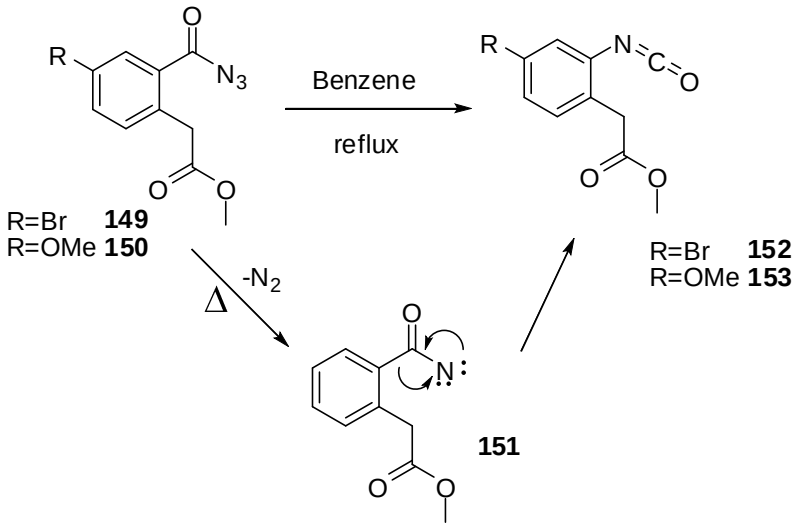


Figure 2 IR spectra of the compounds **149** and **150**

2.5 Reaction of Acyl Azides: Synthesis of Isocyanates

Isocyanate formation is another crucial step due to its strong electrophilicity. By using different nucleophiles, various molecules which can serve as important precursors for construction of indole derivatives can be synthesized. The synthesized

azides **149**, **150** are converted into isocyanates **152**, **153** by refluxing in benzene via Curtius rearrangement. Initially acyl nitrenes **151** are formed after nitrogen gas evolution those are readily rearrange to produce isocyanates **152**, **153** as shown in Scheme 36.

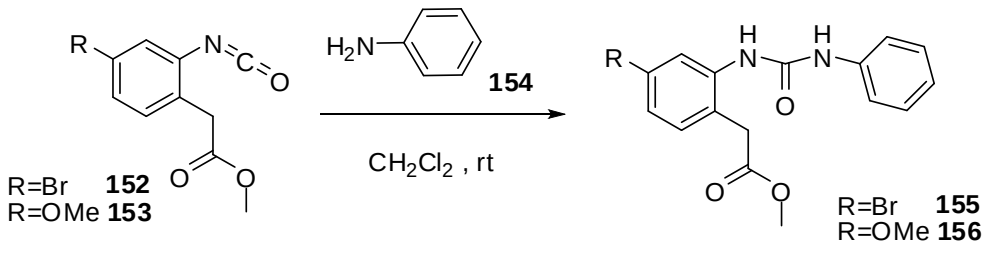


Scheme 36

Expected isocyanates were isolated and characterizated by ^{1}H-NMR and IR spectroscopy. Characteristic frequency values of isocyanates in IR spectra were observed around 2270-2280 cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were also in agreement with the proposed structures.

2.6 Reaction of Isocyanates: Synthesis of Urea Derivatives

To synthesize the precursors of indole derivatives, isocyanate **152**, **153** was reacted with aniline **154** and corresponding urea derivatives **155**, **156** were produced.

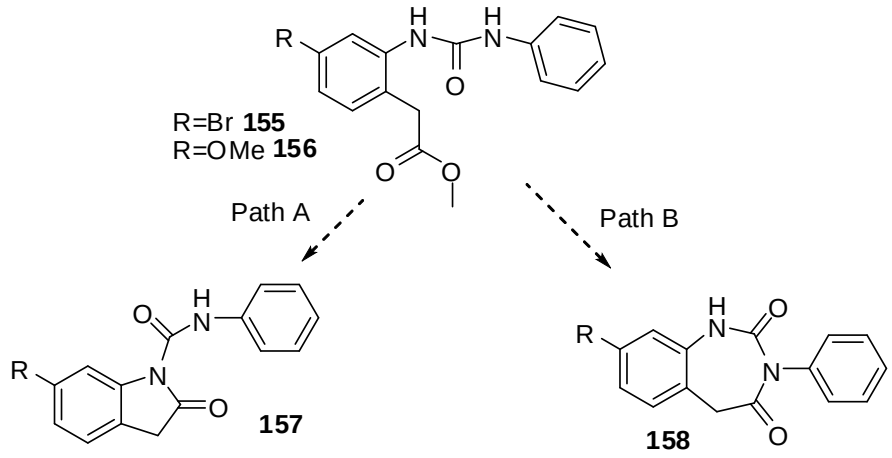


Scheme 37

After a short time the reaction was completed and white precipitate was filtered to handle the desired urea derivatives. Characterization of the products are mostly based on ^{1}H-NMR and ^{13}C-NMR spectra. It was easy to determine from the ^{1}H-NMR spectra that the compounds **155**, **156** contain two aromatic rings. Also two different NH signals support the formation. In addition to this, fourteen and fifteen different carbon signals were observed from ^{13}C-NMR spectra of the bromine **155** and methoxy substituted **156** derivatives respectively. For both cases, two different carbonyl carbon and aromatic carbons are apparent and the only difference is methoxy substituted compound **156** has one additional signal which belongs to the methoxy carbon. On the other hand, elemental analysis result were in agreement with the theoretical results.

2.7 Synthesis of Indole and Indolinone Derivatives

When the urea derivatives **155**, **156** were reacted with a base, obviously a ring closure was expected by the abstraction of one of the two acidic nitrogen protons. For this cyclization two possible pathway can be predicted. The question needed to be answered is which path will be chosen for the cyclization? Path A for the formation of indolinone derivatives **157** which are expected in the light of a previous studies published by Balci *et al.*[51] or Path B for the formation of seven membered ring, benzodiazepine derivatives **158** due to a substituent effect.

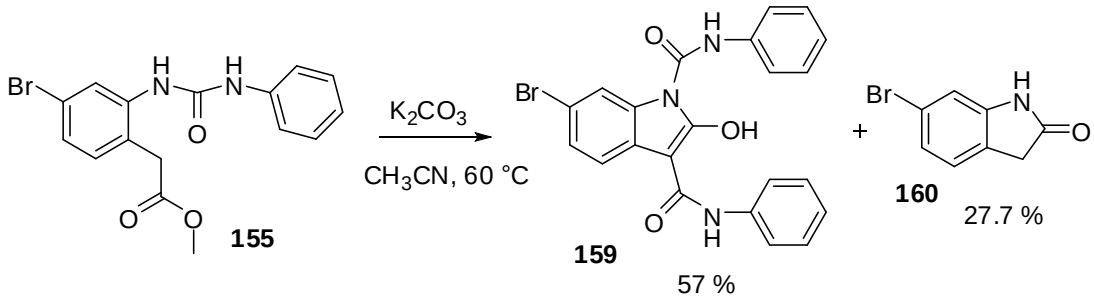


Scheme 38

Experimental studies were performed to clarify this problem. Bromine and methoxy substituted urea derivatives were separately treated with relevant bases, products were isolated and characterized.

2.7.1 Reaction of the Bromine Substituted Urea Derivative with Potassium Carbonate

A TLC controlled reaction of the urea derivative **155** with potassium carbonate in acetonitrile at 60 °C was carried out up to the disappearance of the initial spot of the reagent. Products arised from this reaction were separated and purified by solubility difference and coloumn chromatography. According to ^{1}H-NMR spectra of the products, major product contains three aromatic rings where the minor product contains just one aromatic ring. The products were stated as an indole **159** and indolinone derivative **160** by the help of the spectral data. Hereby formation of five membered rings was preferred instead of formation of the seven membered ring at this case.



Scheme 39

The ^{1}H-NMR spectrum of the major product **159** represents presence of three aromatic rings where two of them belong to a phenyl ring according to the integration values 2:2:1. Absence of the $-CH_2$ peak is a good point to locate this additional phenyl ring. In order to determine the correct structure a carbon signal resonating at 86.6 gives an important clue about the presence of a double bond inside the five membered pyrrole ring. All other proton and carbon signals were compatible with the structure.

Minor product **160** involves a benzene ring, a nitrogen proton and two $-CH_2$ protons with respect to the ^{1}H-NMR spectrum. In addition to this ^{13}C-NMR shows existence of eight different carbon atoms that supports the structure. (Figure 3)

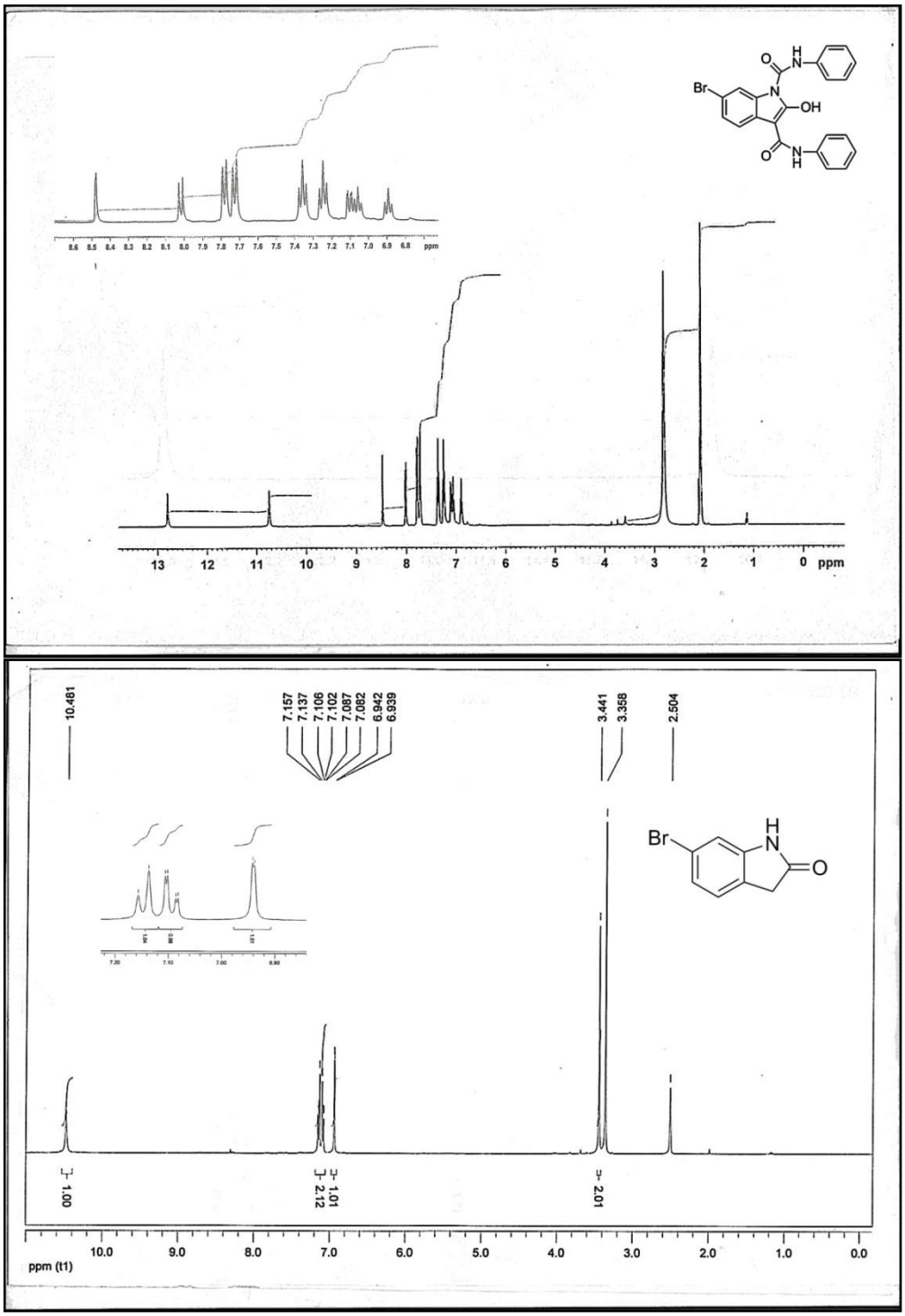
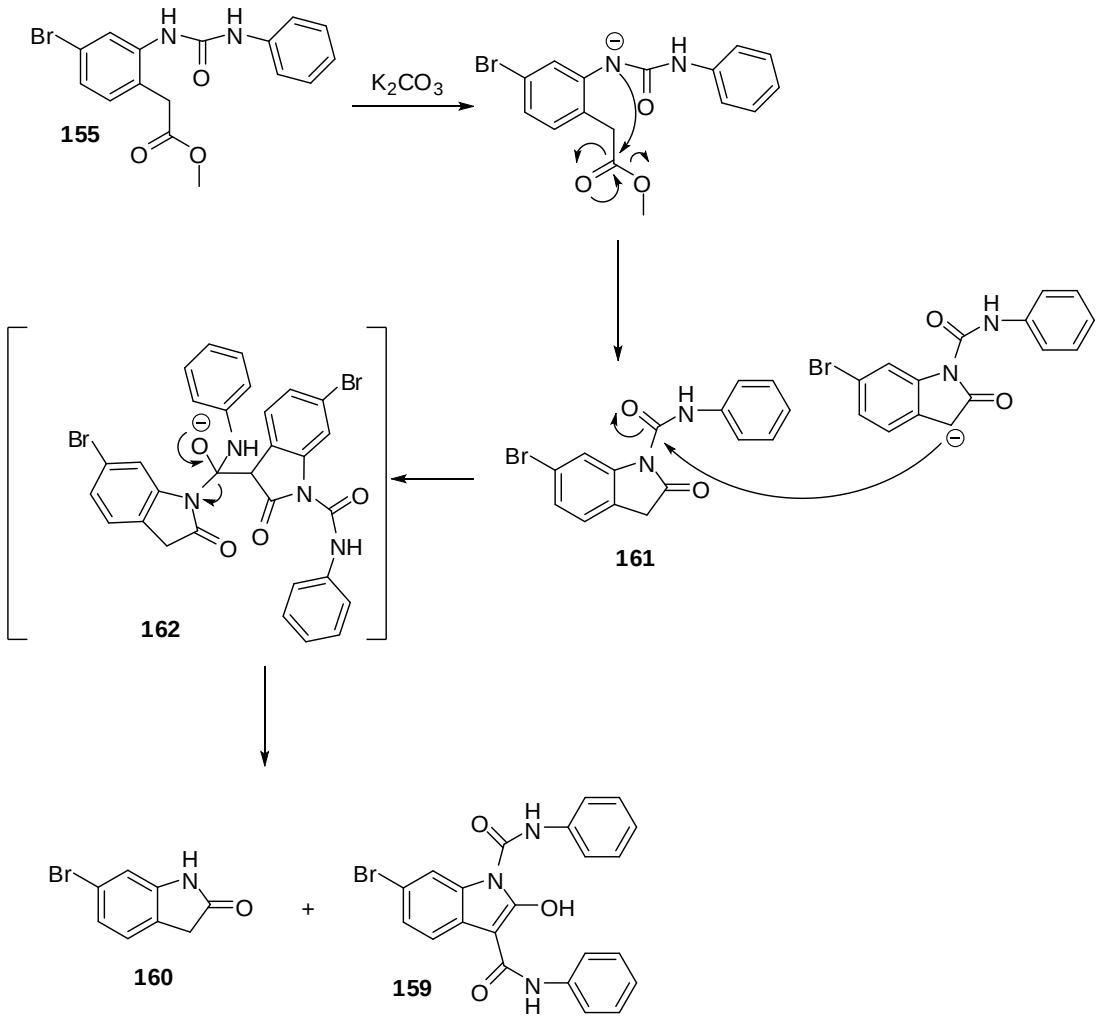


Figure 3 ^{1}H-NMR spectra of the products **159** and **160**

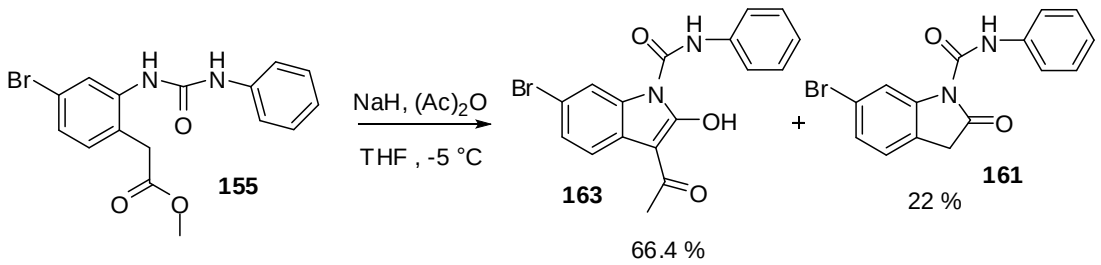
In order to clarify the formation of those products, a mechanism was suggested as shown in Scheme 39. Formation of the indolinone derivative **160** plays an important role at this point. First the base abstracts the acidic –NH proton and a cyclization takes place but the reaction is not over due to the presence of the excess base. Methylene proton of the five membered compound **161** was also abstracted by the base that causes an intermolecular attack through the carbonyl carbon of another cyclized compound and this action forms an dimeric intermediate **162**. Removal of the indolinone **160** from this intermediate formed the indole derivative **159**.



Scheme 40

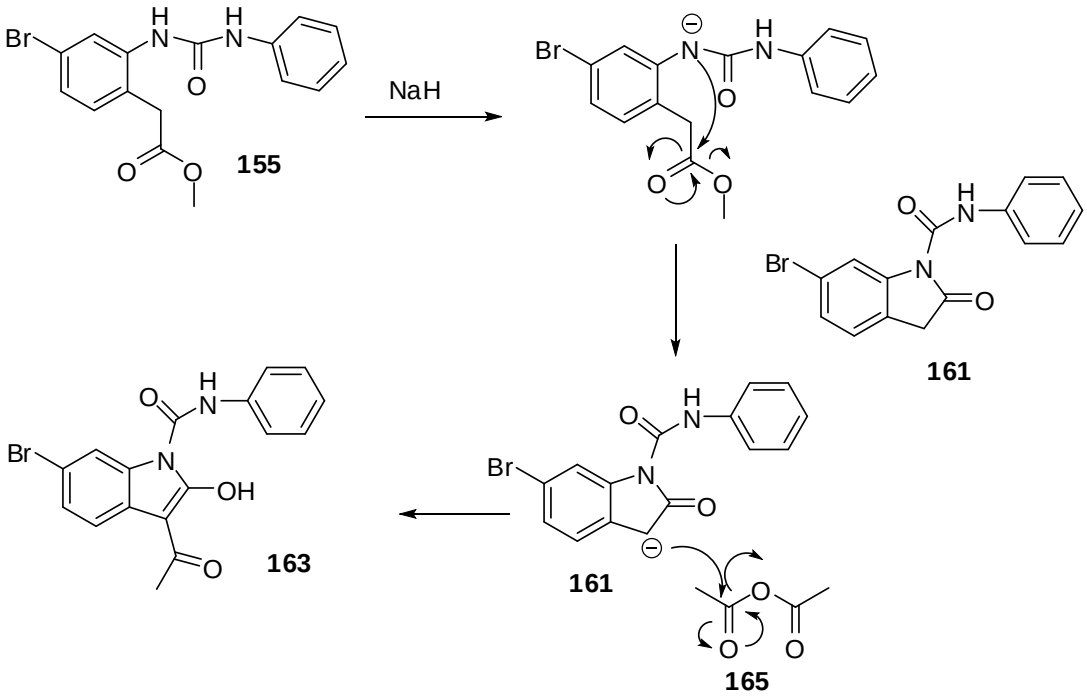
2.7.2 Reaction of the Bromine Substituted Urea Derivative with Sodium Hydride

Regarding the carbanion formation after abstraction of the methylene proton by excess base, another reaction was applied on the urethane derivative **155**. Aim of this step was to prove the formation of the carbanion via preventing the intermolecular attack by using a stronger electrophile as a trapping agent. Firstly reaction starts with the treatment of the urea derivative **155** with sodium hydride at -5 °C and followed by the addition of acetic anhydride half an hour later. Formed products were separated and purified by solubility difference and coloumn chromatography and characterized as an indole **163** and indolinone **161** derivatives.



Scheme 41

Suggested mechanism for the formation of the products starts with the abstraction of the –NH proton and followed by the cyclization. Similarly excess base abstracts the methylene proton of the five membered ring **161** here but at this time it attacks through acetic anhydride **165** instead of intermolecular attack. Finally an indole **163** and an indolinone **161** derivatives were yielded. (Scheme 42)



Scheme 42

For the major product **163**, absence of an additional phenyl ring and presence of the acetyl group can be observed from ^{1}H-NMR spectrum (Figure 4). Similar with the compound **159**, carbon signal resonated at 98.5 ppm proves the existence of double bond in the pyrrole ring.

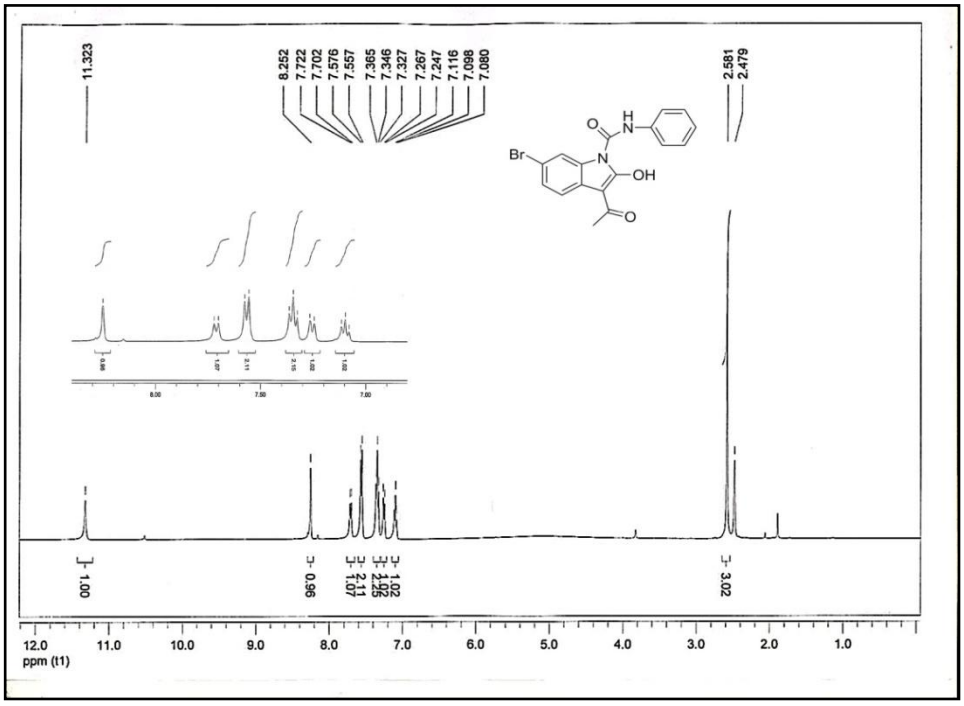


Figure 4 [1]H-NMR spectrum of the product **163**

The minor product did not reveal the presence of an acetyl group (Figure 5). The spectral data were in agreement with the indolinone structure **161**.

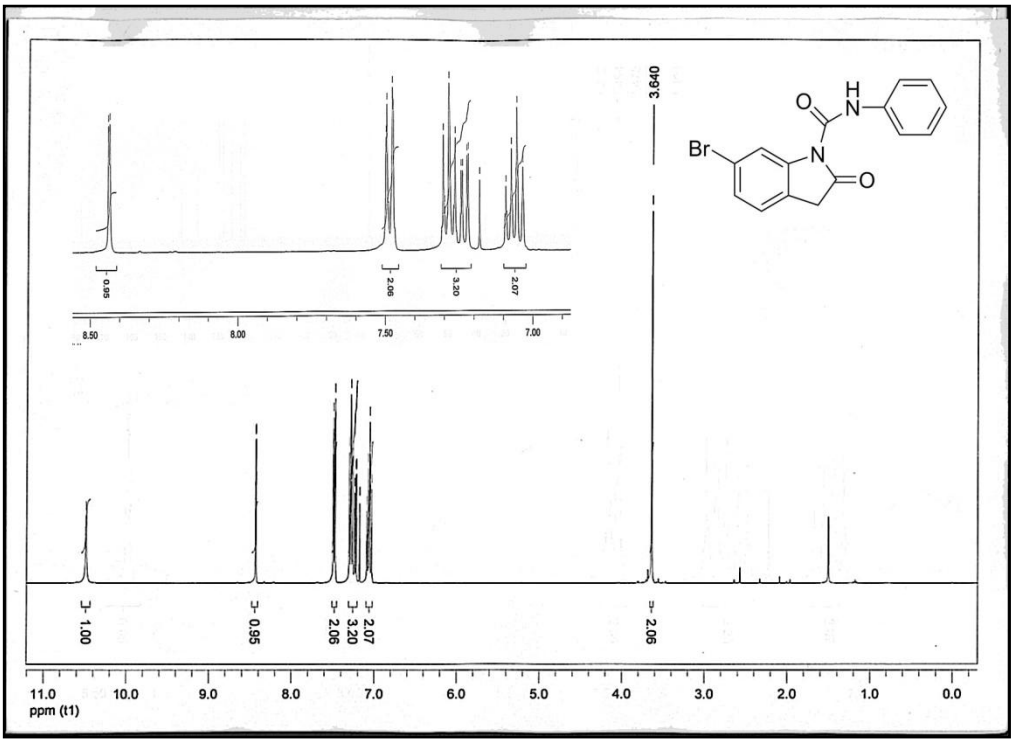
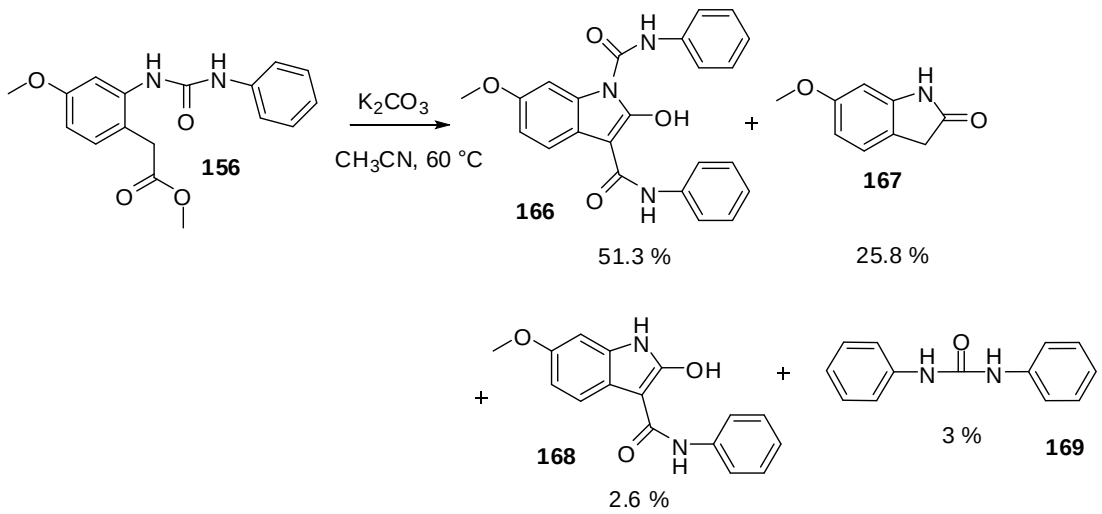


Figure 5 [1]H-NMR spectrum of the product **164**

2.7.3 Reaction of the Methoxy Substituted Urea Derivative with Potassium Carbonate

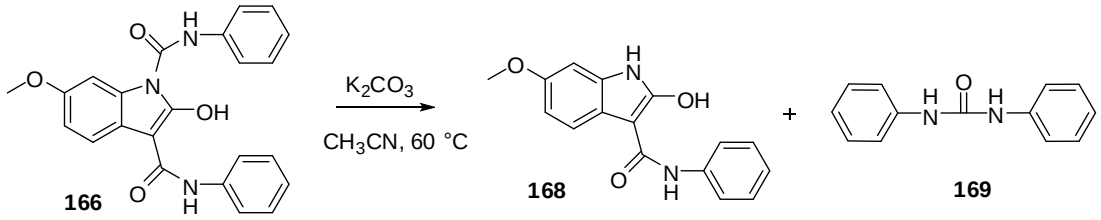
At this step methoxy substituted homophthalic acid derivative **156** was treated with potassium carbonate under same conditions that applied to the bromine substituted case. TLC controlled reaction was ended after disappearance of the initial spots. Major product **166** which is one of the four isolated compounds was separated again by solubility difference. Remaining side products were separated by coloumn chromatography and characterized on the basis of ^{1}H-NMR and ^{13}C-NMR data. In addition to the indolinone derivative **167**, another indole derivative **168** and a symmetric product **169** were isolated as distinct from the bromine substituted case.



Scheme 43

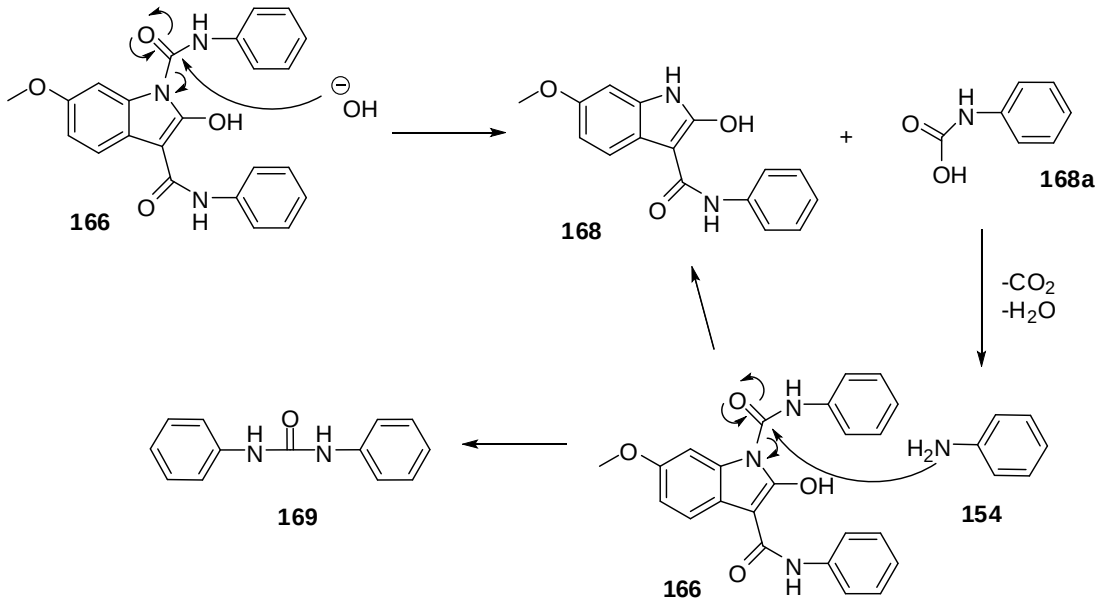
The indole **166** and indolinone **167** derivatives were the expected products. ^{1}H-NMR and ^{13}C-NMR spectra of those compounds were analogous with the bromine substituted compounds. The only differences were the additional signals arised from the methoxy substituent attached to the benzene ring. Suggested mechanism for the formation of those products is not different from the formation mechanism of their analogues **159** and **160**. The point should be emphasized for this step is that the secrets behind the formation of the other side products **168** and **169**.

The major product **166** was centered at the basis of the most reasonable mechanism for the formation of the side products due to a resemblance between their structures. Then the major product was reacted under same conditions to clarify the suspicions. Treatment of the indole derivative with potassium carbonate in acetonitrile served the same products **168**, **169** that accords with the proposed mechanism.



Scheme 44

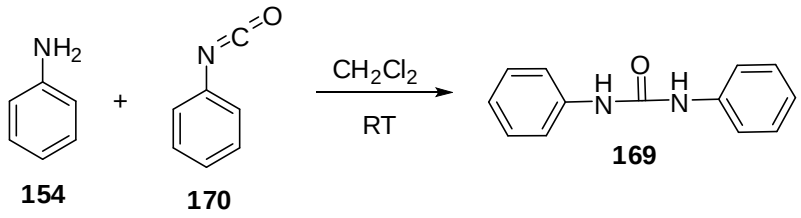
According to the mechanism shown in Scheme 45, hydrolysis of upper chain of the major product **166** under basic conditions is inevitable for the formation of indole derivative **168**. Then formation of aniline **154** upon another hydrolysis of **168a** is followed by an attack through **166** to yield the symmetric side product**169**.



Scheme 45

Although the ^{1}H-NMR spectrum of the compound **169** is not much complicated, characterization of its structure was not too easy to interpret. In addition to a

carbonyl carbon signal, presence of a phenyl ring and a nitrogen proton offered an important hint about the structure. As a providing reaction, phenyl isocynate **170** and aniline **154** were reacted and the same symmetric product **169** was produced.



Scheme 46

Comparison of the both ^{1}H-NMR spectra clearly indicated the correct structure. Prediction of the correct structure of the compound **168** was harder due to some unexpected signals resonat at ^{1}H-NMR spectrum those are marked with the stars as shown in the Figure 6.

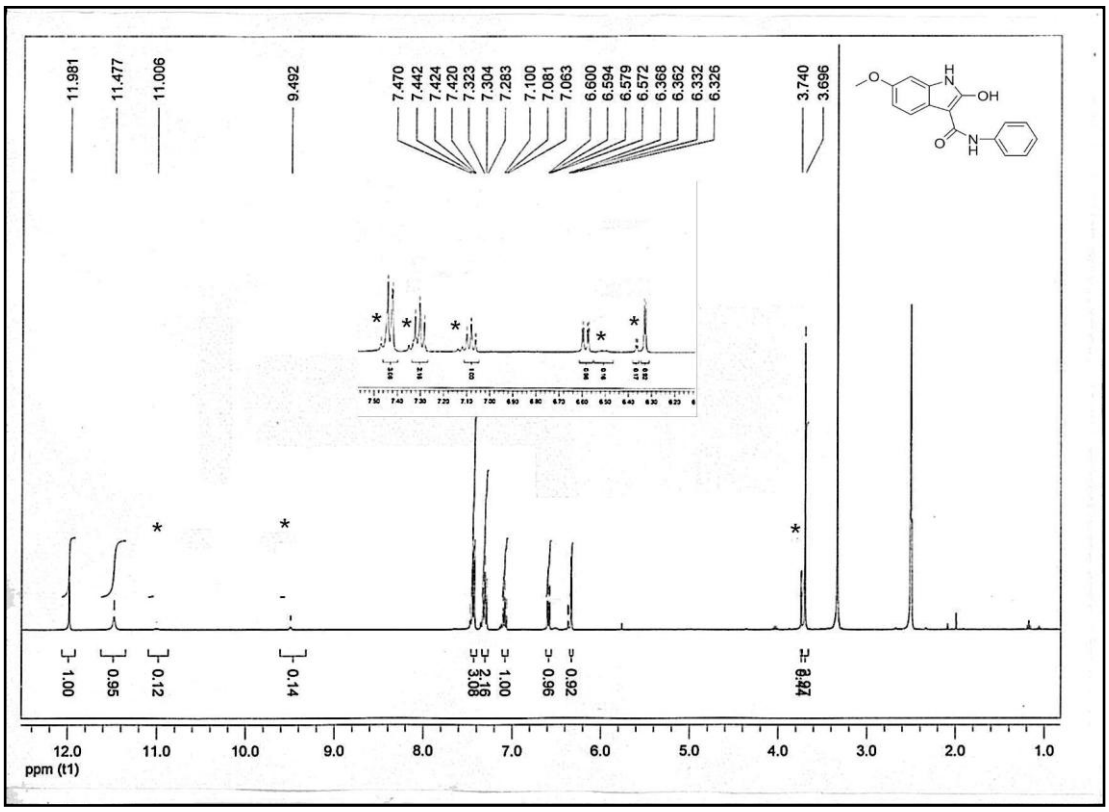


Figure 6 ^{1}H-NMR spectrum of the product **168**

Although their integration values are relatively small with respect to the other signals, consistency of the integration values among themselves had aroused a suspicion about the structure. Due to the proximity of the signals marked by stars and the remaining signals, probable existence of an isomer of the compound **168** had taken in account. Therefore the compound was heated and a new ^{1}H-NMR spectrum was taken to observe the differences. According to the new spectrum, rising of the integration values of the marked signals was observed in the same trend that supports the presence of an isomeric structure.

By comparison of the both spectra, biggest difference between the marked and unmarked signals were observed at downfield or in other words somewhere close to the nitrogen atoms. In the light of this observation possible resonance structure of the indole derivative **168** is stated as the indolinone derivative **171** as shown in the Scheme 47.

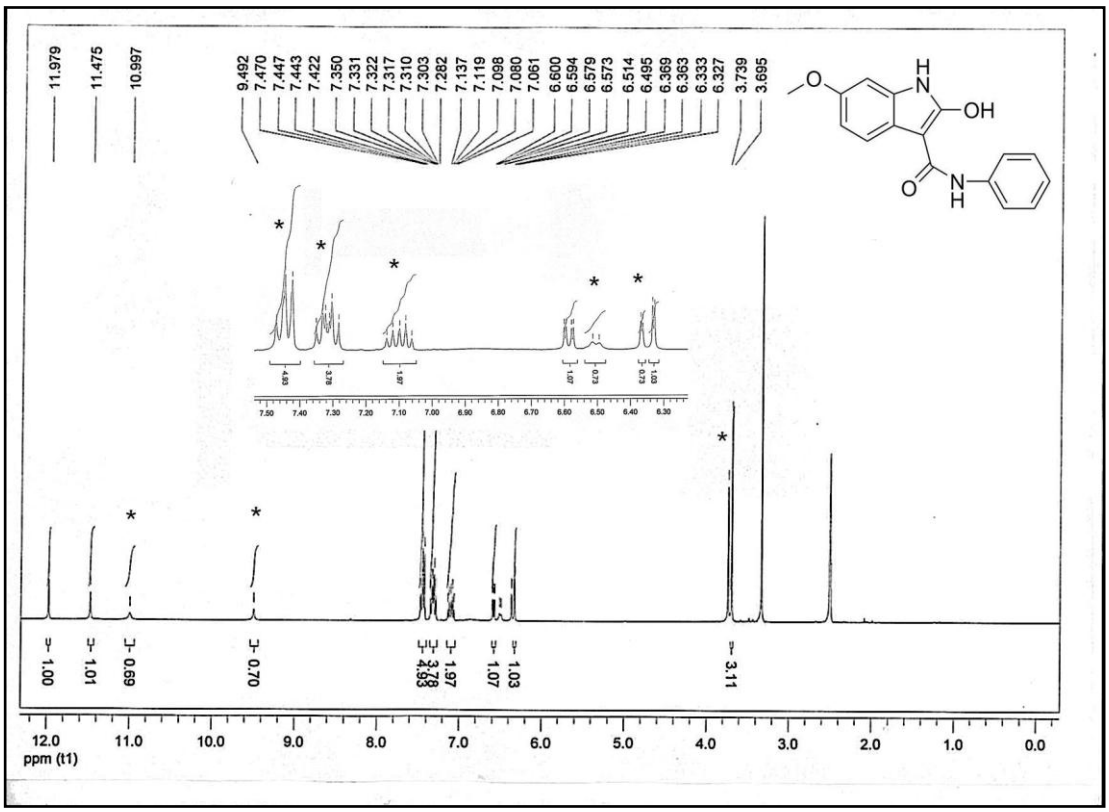
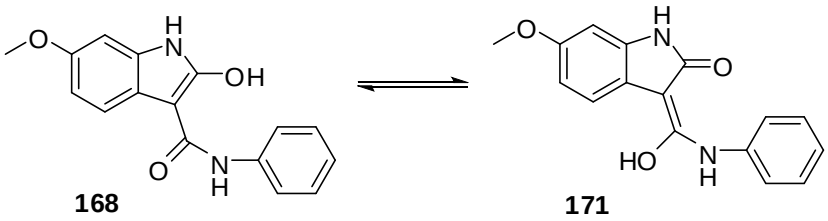


Figure 7 ^{1}H-NMR spectrum of the products **168** and **171**



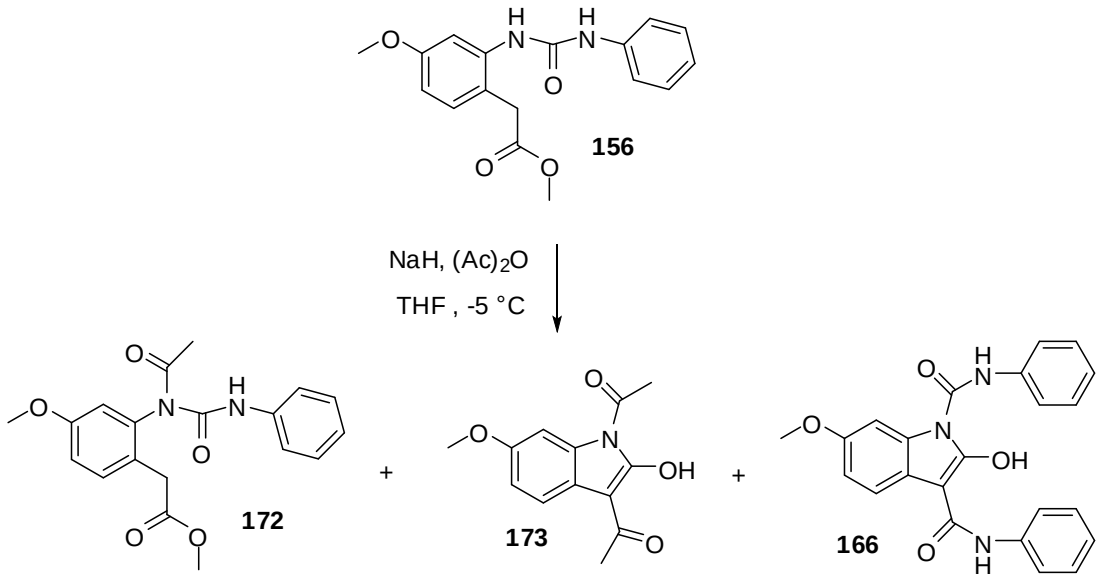
168 **171**

Scheme 47

Elemental analysis results of the compounds **168**, **171** are consistent with the proposed structures. As the compounds are isomeric structures, no any difference should be expected according to the result of the elemental analysis.

2.7.4 Reaction of the Methoxy Substituted Urea Derivative with Sodium Hydride

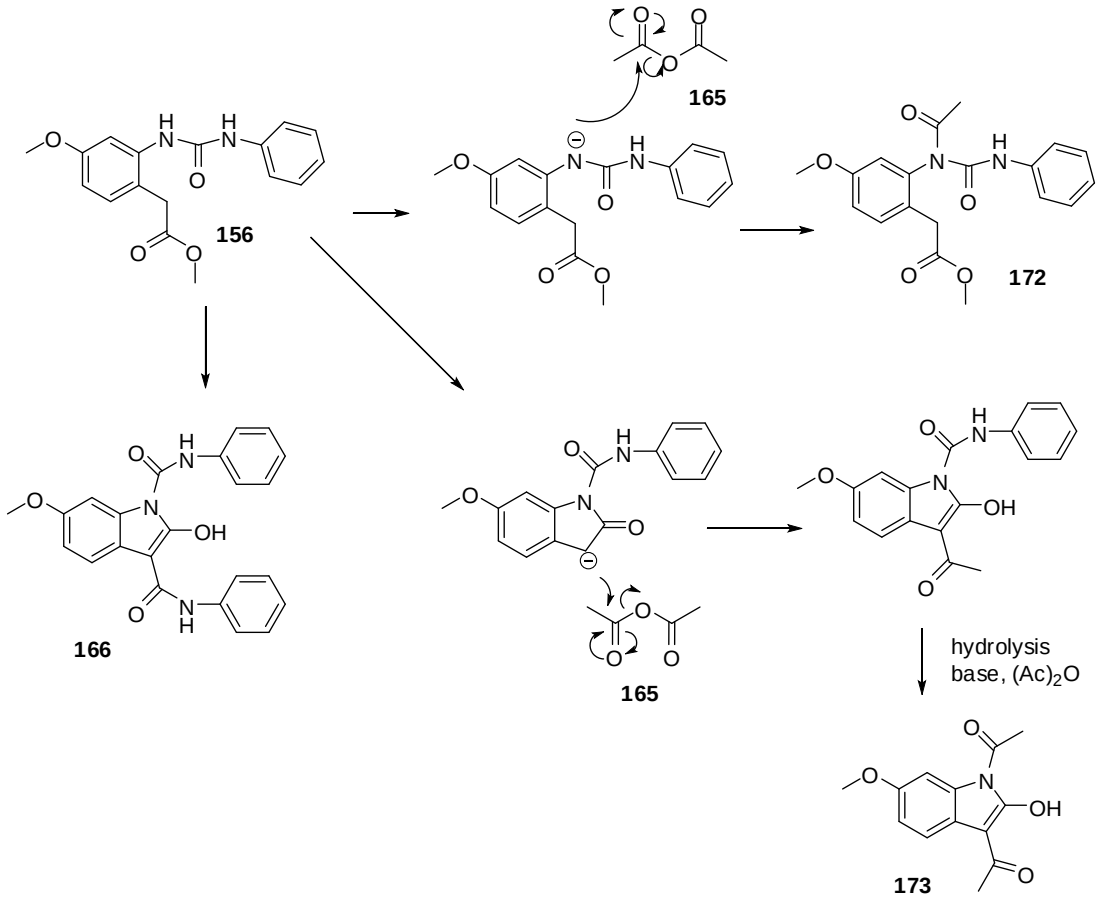
Another cyclization reaction was carried out on methoxy substituted urea **156** by using sodium hydride. Primary target of this step was to demonstrate the formation of the carbanion after the first cyclization as mentioned at bromine substituted case. Additionally presence of probable additional side products is another driving force to proceed this method. Firstly reaction starts with the treatment of the urea derivative **156** and sodium hydride at -5 °C and followed by the addition of acetic anhydride **165**. Then the products arised from this reaction were separated by coloumn chromatography and characterized on the basis of ^{1}H-NMR and ^{13}C-NMR spectra. Interestingly result of this reaction exhibited three unexpected products those are an acetylated urea derivative **172**, a diacetilated indole **173** derivative and a small amount of indole derivative **166** which was the major product of the potassium carbonate based cyclization process. (Scheme 48)



Scheme 48

Suggested mechanism for the formation of the compound **166** was analogous with the formation of the compound **159**. But here as the quantity of the compound is slightly lower, the side product **167** could not be isolated.

Formation of the compound **173** starts with a cyclization that is followed by formation of the carbanion and after addition of the acetic anhydride **165** acetylation takes place. Likely the formation of the compound **168**, hydrolysis occurs and abstraction of the nitrogen proton yields the compound **173** in the presence of the acetic anhydride. At this step acetic anhydride lacks cyclization. Just after the abstraction of the nitrogen proton of the urea derivative **156**, the anion prefers to attack acetic anhydride **165** instead of the cyclization that results in the formation of **172**. (Scheme 49)



Scheme 49

The ^{1}H-NMR spectrum of the compound **172** gives information about the existence of two benzene rings. The presence of two methoxy signals resonating at 3.74 and 3.69 ppm is the most important evidence about absence of five membered indolinone derivative (Figure 8). Comparing the ^{1}H-NMR spectra of the urea derivative **156** and the compound **172**, the only difference is addition of a methyl signal and disappearance of one of the nitrogen proton signals. According to ^{13}C-NMR spectrum of the compound **172**, additional two carbon signal those are belongs to a carbonyl and methyl carbons are effective as well to predict the correct structure.

The ^{1}H-NMR spectrum of the compound **173** is consistent with the predicted structure (Figure 9). Absence of the phenyl ring signals and presence of two methyl signals arised from the acetyl groups instead of the phenyl ring proves the hydrolysis and second acetylation processes.

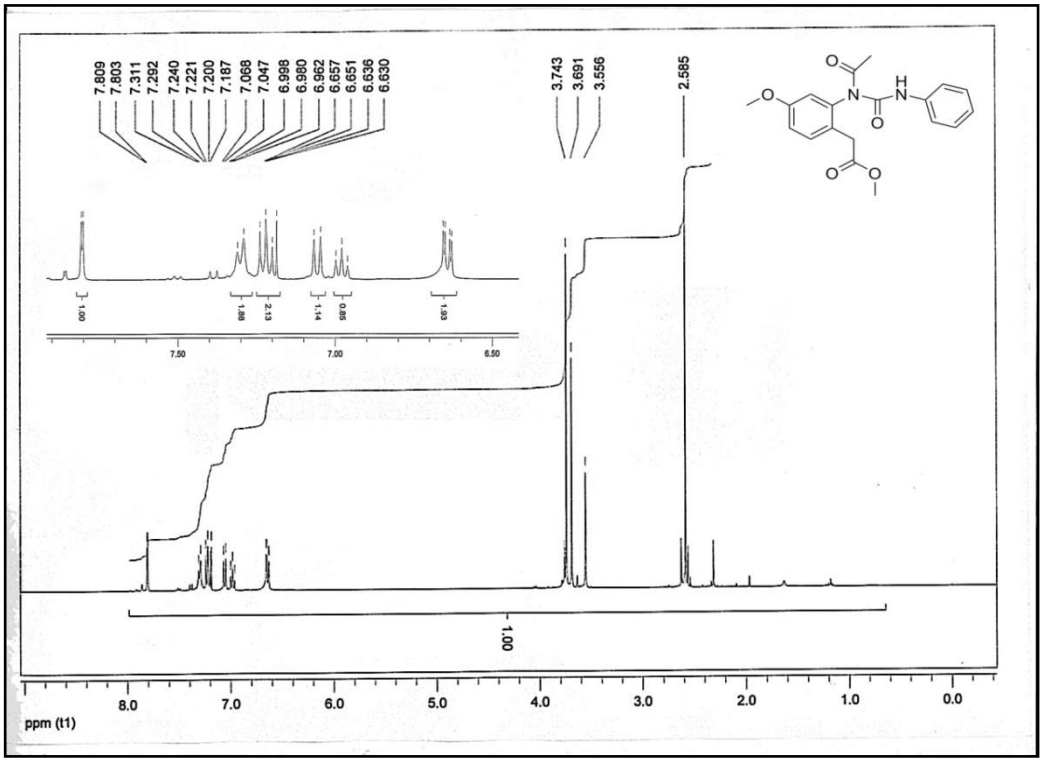


Figure 8 ^{1}H-NMR spectrums of the product **172**

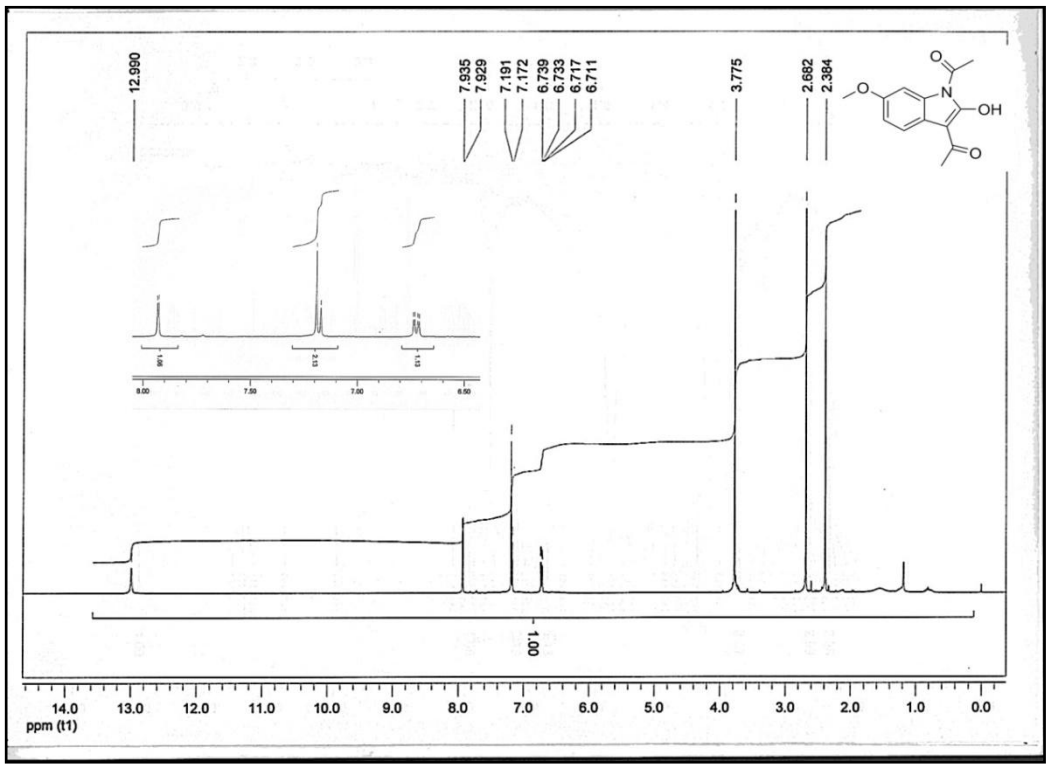


Figure 9 ^{1}H-NMR spectrums of the product **173**

2.8 Comparing the Cyclization Reactions of the Bromine and Methoxy Substituted Urea Derivatives.

At the end of the study all products arised from two different cases were isolated and characterized. Formation of the final products of the bromine substituted system were showed a similar trend with the non-substituted system. However methoxy substituted system provided some different products.

The most obvious difference is the formation of the side products via hydrolysis for the methoxy substituted system. Two main reasons can be stated for the formation of those products. First one is electron donating methoxy group may create somehow a partial positivity on the chain attached at the meta position, so enables hydrolysis. Second one is methoxy substituent increases the base activity via a interaction between the lone pair electrons of the methoxy oxygen and cation of the base.

Electron donating groups enhance the activation of the benzene ring which they are fused. In other words electron donating groups increase electron density on the benzene ring. Comparing the ^{1}H-NMR spectra of the bromine and methoxy substituted homophthalic acids, location of the aromatic protons proves this effect as well. At the methoxy substituted case aromatic protons shifts upwards due to the substituent effect. However, both bromine and methoxy groups are ortho-para directors. Their effects on the electron density of the meta position of the benzene ring is not differ each other (Table 1). So if the first statement was valid, then the same side products would have been observed at the bromine substituted case as well. Absence of the analogue products at the bromine substituted case failed the approach about polarization.

Table 1 Chemical shift values of the substituents attached to benzene ring in ppm[52]

Substituents	Position of the substituents		
	ortho	meta	para
Br	0.17	-0.11	-0.06
OMe	-0.49	-0.12	-0.44

In addition to this polarization effect of the methoxy substituent at the para position clarified the formation of the **168**. Due to a higher electron density at the para position than the meta position, hydrolysis reaction took place at the upper side of the indole derivative **166**

Second statement become dominant about the formation of the side products at the methoxy substituted case. Interaction between lone pair electrons of the oxygen and cation of the base led to a stronger base reactivity which enabled an easier hydrolysis process. Parallel to this prediction, comparatively lower base reactivity could not able to form side products at the bromine substituted case.

CHAPTER 3

EXPERIMENTAL

3.1 General Considerations

Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in DMSO-$_{d6}$ and $CDCl_3$ with TMS as internal reference. Chemical shifts (δ) were expressed in units parts per million (ppm). Spin multiplicities were specified as singlet (s), doublet (d), doublet of doublets (dd), triplet (t) and multiplet (m) and coupling constants (J) were reported in Hertz (Hz).

Infrared spectra were recorded on a Matson 1000 FT-IR spectrometer and Vertex 70 series FT-IR spectrometer. Band positions were reported in reciprocal centimeters (cm^{-1}).

Column chromatographic separations were performed by using Fluka Silica Gel 60 plates with a particle size of 0.063–0.200 mm. Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Fluka.

Atoms numbers, which were used for interpretation of coupling constants in ^{1}H-NMR spectra, do not competible with the IUPAC nomenclature.

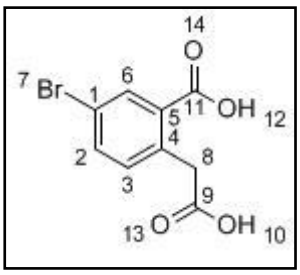
Compounds were named by using ChemDraw Ultra 8.0.

Solvents were purified as reported in the literature.[53]

3.2 Synthesis of 5-bromo-2-(carboxymethyl)benzoic acid (119)

Homophtalic acid **118** (5 g, 27 mmol) and potassium bromate (6.58 g, 40 mmol) were mixed in water (30 ml) and the mixture was heated at 90 °C. In a 100 ml dropping funnel, sulfuric acid (24 ml, 95%) added on water (40 ml) which is further dropped onto the mixture stirring at 90 °C along 30 min. After the dropwise addition of the acid finished, the reaction mixture was remained stirring for 2 h at the same temperature. Then the mixture cooled down to the room temperature and filtered by suction filtration followed by washing with thoroughly water (3 x 50 ml) in order to obtain the product **119** (3.2 g, 12 mmol, 44.4 %). The product was crystallized from EtOAc/hexane (4/1).

119: White solid m.p. 213-215 °C



^{1}H-NMR (400 MHz, DMSO-$_{d6}$) δ 7.99 (d, $J_{6,2}$ = 2.4 Hz, 1H, H-6), 7.71 (br dd, $J_{2,3}$= 8.0 Hz, $J_{2,6}$ = 2.4 Hz, 1H, H-2), 7.31 (br d, $J_{3,2}$= 8.4 Hz, 1H, H-3), 3.92 (s, 2H, -CH_2)

^{13}C-NMR (100 MHz, DMSO-$_{d6}$) δ 172.0, 166.9, 135.9, 134.5, 134.4, 132.7, 132.6, 119.7, 39.2

IR (KBr, cm^{-1}) 2874 (br.), 2641 (w), 1592 (w), 1431 (m), 1274 (m), 1228 (m), 1191 (s), 1153 (m), 907 (s), 772 (s), 718 (s)

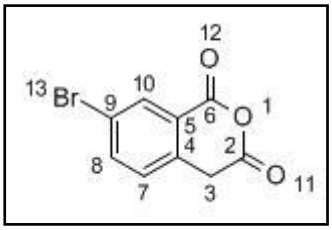
Anal. Calcd. for $C_9H_7BrO_4$; C, 41.73; H, 2.72; Br, 30.84; O, 24.70. Found: C, 41.83; H, 2.79.

3.3 Synthesis of 7-bromoisochroman-1,3-dione (132)

To a suspension of bromine substituted homophtalic acid **119** (5 g , 19 mmol) in dicholoromethane (100 ml) an excess amount of thionyl chloride (5 ml, 68 mmol) was added at room temperature. Then the mixture refluxed overnight. After the completion of the reaction which can be comprehended by the observation of the

clear solution, solvent and excess thionyl chloride was removed under vacuum pressure to give **132** (4.5 g, 18.6 mmol, 97.8 %)

132: Light yellow solid m.p. 171-173 °C



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.26 (br s, 1H, H-10), 7.73 (br dd, $J_{8,7}$= 8.2 Hz, $J_{8,10}$ = 1.6 Hz, 1H, H-8), 7.16 (br d, $J_{7,8}$= 8.2 Hz, 1H, H-7), 4.02 (s, 2H, -CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.2, 157.2, 136.0, 131.1, 130.5, 126.6, 120.9, 120.1, 31.6

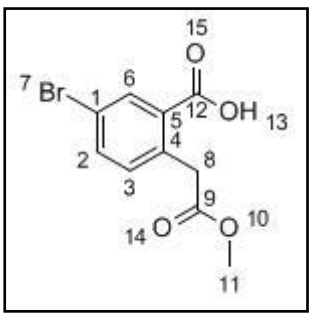
IR (KBr, cm^{-1}) 3094 (w), 2949 (w), 1796 (s), 1780 (s), 1296 (m), 1195 (m), 1177 (m), 1060 (m), 906 (s), 762 (s), 727 (m)

Anal. Calcd. for $C_9H_5BrO_3$; C, 44.85; H, 2.09; Br, 33.15; O, 19.91. Found: C, 41.69; H, 2.80

3.4 Synthesis of 7-bromoisochroman-1,3-dione 5-bromo-2-(2-methoxy-2-oxoethyl)benzoic acid (136)

The anhydride **132** (4.5 g, 18.6 mmol) was dissolved in methanol and refluxed for 2 h. After evaporation of the solvent, **136** (4.41 g, 16.1 mmol, 86.5 %) was obtained as a light yellow solid. The product was crystallized from EtOAc/hexane (4/1).

136: Light brown crystalline solid, m.p. 135-138 °C



^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.77 (br s, 1H, -OH), 8.26 (d, $J_{6,2}$ = 2.4 Hz, 1H, H-6), 7.65 (br dd, $J_{2,3}$= 8.0 Hz, $J_{2,6}$ = 2.4 Hz, 1H, H-2), 7.16 (br d, $J_{3,2}$= 8.0 Hz, 1H, H-3), 4.01 (s, 2H, -CH_2), 3.70 (s, 3H, -OCH_3)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.5, 170.8, 136.1, 135.6, 134.7, 133.9, 130.3, 121.3, 52.1, 39.9

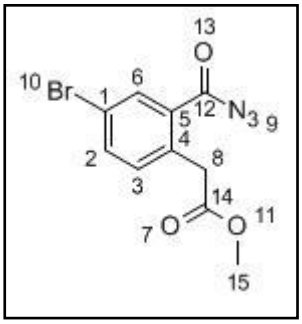
IR (KBr, cm^{-1}) 2923 (br.), 2661 (m), 2545 (m), 1728 (s), 1685 (s), 1591 (s), 1437 (m), 1259 (s), 1213 (m), 1102(m), 993 (m) 865 (m), 830 (m), 668 (m)

Anal. Calcd. for $C_{10}H_9BrO_4$; C, 43.98; H, 3.32; Br, 29.26; O, 23.44. Found: C, 43.46; H, 3.29

3.5 Synthesis of Methyl 2-(2-(azidocarbonyl)-4-bromophenyl)acetate (149)

Initially, half ester **136** (2.0 g, 7.3 mmol) was dissolved in freshly distilled THF (10 ml) at -5 °C and stirred for 10 min. In a 50 ml dropping funnel, a solution of triethylamine (1.22 ml, 8.7 mmol) and THF (10 ml) was prepared and slowly dropped onto the mixture and stirred for 30 min. Following this, a solution of ethyl chloroformate (0.82 ml, 8.7 mmol) in THF (10 ml) was added dropwise to the mixture and continuously stirred for 30 min. Finally (0.56 g, 8.7 mmol) sodium azide was dissolved in water (10 ml) and dropped to the mixture which was further stirred overnight at the same temperature. After removal of the THF under vacuum pressure, residual part of the mixture was extracted with two portions of ethyl acetate (2 x 30 ml) and the organic phase was dried over magnesium sulfate. Then solvent was evaporated and corresponding azide **149** was obtained (1.59 gr, 5.3 mmol, 72.6 %)

149: Light brown viscos liquid.



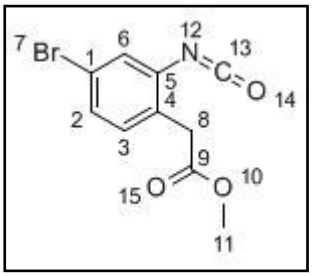
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (d, $J_{6,2}$ =1.9 Hz, 1H, H-6), 7.57 (br dd, $J_{2,3}$= 8.0 Hz, $J_{2,6}$=1.9 Hz, 1H, H-2), 7.07 (br d, $J_{3,2}$= 8.1 Hz, 1H, H-3), 3.91 (s, 2H, -CH_2), 3.62 (s, 3H, -OCH_3)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.0, 171.0, 136.4, 135.5, 134.1, 133.7, 131.2, 121.2, 52.0, 39.7

IR (KBr, cm^{-1}) 2952 (w), 2273 (m), 2141 (s), 1740 (s), 1691 (s), 1230 (s), 1169 (m), 1093 (m), 992 (m), 836 (m), 650 (m), 819 (m

3.6 Synthesis of Methyl 2-(4-bromo-2-isocyanatophenyl)acetate (152)

The acyl azide compound 1**49** (1.59 gr, 5.3 mmol) was refluxed in benzene for 1 h. Evaporation of the benzene under vacuum pressure gave the isocyanate **152** (1.41 g, 5.2 mmol, 98.1 %). **152**: Light brown viscos liquid.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23 (br s, 1H, H-6), 7.19 (br d, $J_{2,3}$= 9.5 Hz, 1H, H-2), 7.04 (br d, $J_{3,2}$= 7.5 Hz, 1H, H-3), 3.64 (s, 3H, -OCH_3), 3.55 (s, 2H, -CH_2)

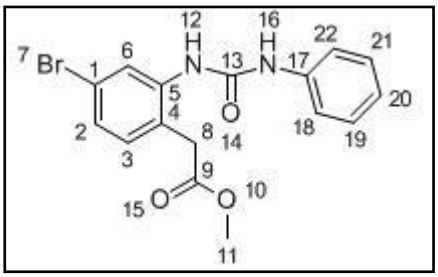
^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.5, 134.1, 132.1, 129.2, 128.8, 127.8, 121.4, 52.3, 37.0

IR (KBr, cm^{-1}) 2952 (w), 2270 (s), 2141 (s), 1739 (s), 1573 (m), 1253(m), 1218 (m), 930 (m), 673 (w)

3.7 Synthesis of Methyl 2-(4-bromo-2-(3-phenylureido)phenyl)acetate (155)

To a solution of isocyanate **152** (1.41 g, 5.2 mmol) in dichloromethane, aniline (0.56 ml, 6.2 mmol) was added and the solution was stirred for 2 h at room temperature. Filtration of the precipitate yielded the urea derivative **155** (1.77 g, 4.9 mmol, 94.2%) as a white solid.

155: White solid, m.p. 179-181°C



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83 (d, $J_{6,2}$ =1.6 Hz, 1H, H-6), 7.74 (br s, 1H, -NH), 7.32 (br s, 1H, -NH), 7.26 (m, 4H, H-18,19,20,21) 7.19 (br dd, $J_{2,6}$ =8.0 Hz, $J_{2,3}$ =1.6 Hz, 1H, H-2), 7.06 (br t, $J_{20,21}$ = $J_{20,19}$ = 6.8 Hz, 1H, H-20), 7.02 (br d, $J_{3,2}$ = 8.0 Hz, 1H, H-3), 3.60 (s, 3H , -OCH_3), 3.54 (s, 2H, -CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.4, 153.8, 138.1, 138.0, 132.0, 129.1, 128.4, 128.2, 126.2, 124.0, 121.7, 120.9, 52.5, 37.6

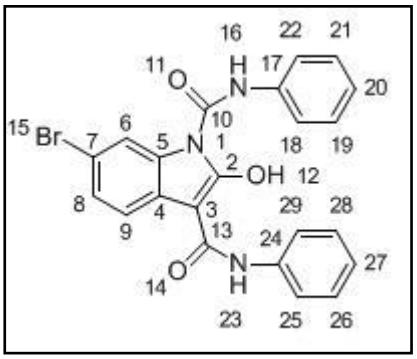
IR (KBr, cm^{-1}) 3277 (s), 1733 (s), 1640 (s), 1597 (s), 1578 (s), 1533 (s), 1445 (m), 1236 (m), 1154 (s)

Anal. Calcd. for $C_{16}H_{15}BrN_2O_3$; C, 52.91; H, 4.16; Br, 22.00; N, 7.71; O, 13.22. Found: C, 52.49; H, 4.12; N, 7.66

3.8 Synthesis of 6-bromo-2-hydroxy-N^1,N^3-diphenyl-1H-indole-1,3 dicarboxamide (159) and 6-bromoindolin-2-one (160)

The urea derivative **155** (1.5g, 4.12 mmol) was dissolved in acetonitrile (50 ml) and the mixture is heated up to 60 °C. After that at the same temperature excess amount of potassium carbonate (5 g, 36 mmol) was added to the reaction mixture. By the help of the TLC controlling, the reaction was ended after 1.5 hours. Excess potassium carbonate was filtered and solvent was evaporated under reduced pressure. Choloroform addition and filtration yielded the major product **159** (1.06 g, 2.35 mmol, 57.1 %). Remaining soluble part was concentrated and purified by silica gel eluting with EtOAc/Hexane (70/30) in order to obtain the minor product **160** (0.24 g, 1.13 mmol, 27.4 %).

159: Purple solid**,** m.p. > 320 °C



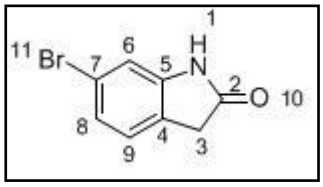
^{1}H-NMR (400 MHz, DMSO-$_{d6}$) δ 12.8 (br s, 1H, -NH), 10.74 (br s, 1H, -NH), 8.4 (d, $J_{6,8}$=1.4 Hz, 1H, H-6), 8.02 (br d, $J_{9,8}$ =8.1 Hz, 1H, H-9), 7.78 (br d, $J_{22,21} = J_{18,19}$ = 7.9 Hz, 2H, H-18,22), 7.72 (br d, $J_{29,28} = J_{25,26}$ = 7.8 Hz, 2H, H-29,25), 7.35 (br t, $J_{21,22} = J_{21,22} = J_{19,18} = J_{19,20}$ = 7.8 Hz, 2H, H-21,19), 7.24 (br t, $J_{28,29} = J_{28,27} = J_{26,25} = J_{26,27}$ = 7.8 Hz, 2H, H-28,16), 7.10 (br dd, $J_{8,9}$ =8.1 Hz, $J_{8,6}$ = 1.6 Hz, 1H, H-8), 7.05 (br t, $J_{20,21} = J_{20,29}$ = 7.3 Hz, 1H, H-20), 6.89 (br t, $J_{27,28} = J_{27,26}$ = 7.3 Hz, 1H, H-27)

^{13}C-NMR (100 MHz, DMSO-$_{d6}$) δ 166.0, 165.9, 152.9, 142.4, 140.3, 132.3, 130.3, 129.7, 129.4, 125.3, 123.5, 121.6, 120.4, 119.3, 119.1, 117.3, 111.1, 86.6

IR (KBr, cm^{-1}) 3604 (m), 3289 (br.), 1679(s), 1594 (s), 1583 (s), 1559 (s), 1445 (s), 1403 (s), 1247 (m), 1134 (m), 1097 (m), 749 (m), 686 (m)

HRMS $[M+H]^+$ calcd for $C_{22}H_{16}BrN_3O_3$; Exact mass: 448.0296; Found: 448.0309

160: Orange solid**,** m.p. 208-212 °C, 214-215 °C[54]

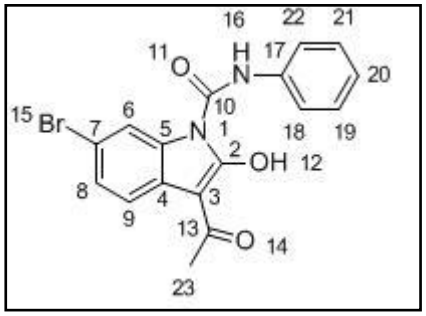


^{1}H-NMR (400 MHz, DMSO-$_{d6}$) δ 10.48 (br s, 1H, -NH), 7.14 (br d, $J_{9,8}$= 8.0 Hz, 1H, H-9), 7.09 (br dd, $J_{8,9}$= 8.0 Hz, $J_{8,6}$=1.6 Hz, 1H, H-8), 6.94 (d, $J_{6,9}$=1.2 Hz, 1H, H-6), 3.44 (s, 2H, -CH_2)

^{13}C-NMR (100 MHz, DMSO-$_{d6}$) δ 176.2, 145.3, 126.1, 125.2, 123.6, 119.9, 111.8, 35.3

3.9 Synthesis of 3-acetyl-6-bromo-2-hydroxy-N-phenyl-1H-indole-1-carboxamide (163) and 6-bromo-2-oxo-N-phenylindoline-1-carboxamide (161)

The urea derivative **155** (1.5g, 4.12 mmol) was dissolved in freshly distilled THF (20 ml) and the mixture is cooled down to -5 °C. At this temperature sodium hydride (0. 198 g ,8.24 mmol) added into the reaction and the mixture was continued stirring for 30 min. Then acetic anhydride (0.58 ml, 6.19 mmol) added to the solution which was further stirred overnight at room temperature. After solvent was evaporated under reduced pressure, choloroform addition and filtration yielded the major product **163** (1.02 g, 2.74 mmol, 66.4%). Remaining soluble part was concentrated and purified by silica gel eluting with EtOAc/Hexane (5/2) in order to obtain the minor product **161** (0.30 g , 0.90 mmol, 22.0%).



163: Pink solid, m.p. 245-248 °C

^{1}H-NMR (400 MHz, DMSO-$_{d6}$) δ 11.32 (br s, 1H, -NH), 8.25 (br s, 1H, H-6), 7.71 (br d, $J_{9,8}$ =8.0 Hz, 1H, H-9), 7.56 (br d, $J_{22,21}$ = $J_{18,19}$ = 7.6

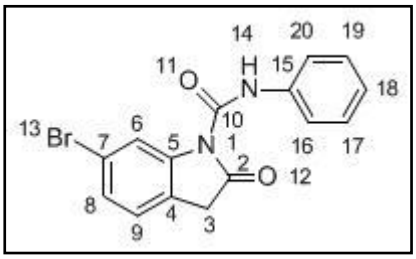
Hz, 2H, H-18,22), 7.34 (br t, $J_{21,22} = J_{21,22} = J_{19,18} = J_{19,20} = 7.6$ Hz, 2H, H-21,19), 7.25 (br d, $J_{8,9} = 8.0$ Hz, 1H, H-8), 7.09 (br t, $J_{20,21} = J_{20,29} = 7.2$ Hz, 1H, H-20), 2.58 (s, 3H, H-23)

^{13}C-NMR (100 MHz, DMSO-$_{d6}$) δ 180.6, 168.6, 150.2, 137.7, 134.1, 129.0, 125.7, 124.6, 123.7, 121.6, 119.7, 116.6, 115.2, 98.5, 22.4

IR (KBr, cm^{-1}) 3629 (m), 3201 (br.), 3033 (m), 1716 (m), 1596 (s), 1572 (s), 1470 (s), 1443 (s), 1414 (m), 1194 (m), 1284 (m), 1108 (m), 979 (m), 819 (m), 748 (m)

HRMS [M+H]$^+$ calcd for $C_{17}H_{13}BrN_2O_3$; Exact mass: 373.0187; Found: 373.0182

161: Light orange solid**,** m.p. 170-172 °C



^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.48 (br s, 1H, -NH), 8.43 (d, $J_{6,8}$=1.6 Hz, 1H, H-6), 7.48 (br d, $J_{20,19} = J_{16,17}$= 7.6 Hz, 2H, H-20,16), 7.28 (br t, $J_{19,20} = J_{19,18} = J_{17,16} = J_{17,18} = 7.6$ Hz, 2H, H-19,17), 7.23 (br dd, $J_{8,9} = 8.0$ Hz, $J_{8,6}$= 1.6 Hz, 1H, H-8), 7.07 (br t, $J_{18,19} = J_{18,17} = 7.6$ Hz, 1H, H-18), 7.04 (br d, $J_{9,8}$=8.0 Hz, 1H, H-9), 3.64 (s, 2H, -CH_2)

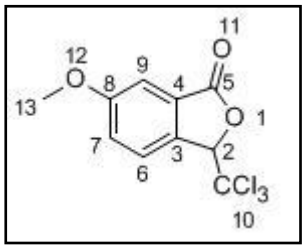
^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.1, 149.1, 142.4, 136.8, 129.1, 127.7, 125.1, 124.7, 122.0, 121.7, 120.5, 120.0, 36.7

IR (KBr, cm^{-1}) 3198 (m), 3132 (m), 2949 (m), 1742 (s), 1594 (s), 1556 (s), 1299 (m), 1473 (m), 1456 (m), 1204 (m), 1152 (m), 1098 (m), 991 (m)

Anal. Calcd. for $C_{15}H_{11}BrN_2O_2$; C, 54.40; H, 3.35; Br, 24.13; N, 8.46; O, 9.66. Found: C, 53.94; H, 3.20; N, 8.46

3.10 Synthesis of 6-methoxy-3-(trichloromethyl)isobenzofuran-1(3H)-one (122)

3-Methoxybenzoic acid **120** (12.5 g, 82 mmol), chloral hydride **121** (16g, 96 mmol) and sulphuric acid (38 ml, 95%) were mixed and stirred for 24 h at room temperature. Then the whole reaction mixture poured on ice and solid part was filtered by suction filtration. In order to remove excess acid, the solid was dissolved in ethyl acetate and washed with sodium bicarbonate solution. Then organic phase was separated and solvent was removed under reduced pressure to give **122** (21 g, 74 mmol, 90.2 %.)

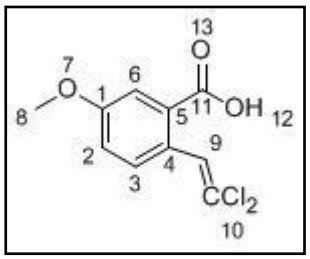


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (br d, $J_{6,7}$ = 8.4 Hz, 1H, H-6), 7.30 (d, $J_{9,7}$ = 2.4 Hz, 1H, H-9), 7.20 (br dd, $J_{7,6}$ = 8.4 Hz, $J_{7,9}$ = 2.4 Hz, 1H, H-7), 5.79 (s, 1H, -CH), 3.83 (s, 3H, --OCH_3)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.2, 162.1, 135.1, 129.1, 125.8, 122.9, 108.1, 97.8, 86.8, 55.9

3.11 Synthesis of 2-(2,2-dichlorovinyl)-5-methoxybenzoic acid (123)

To (19 g, 67 mmol) **122** in 140 ml acetic acid, (15 g, 229 mmol) zinc dust was added portionwise. Then the reaction was refluxed for 1 h, cooled to room temperature and zinc dust was filtered. The filtrate was diluted with water and the precipitate filtered to give **123** (14 g, 56 mmol, 83.5 %.)

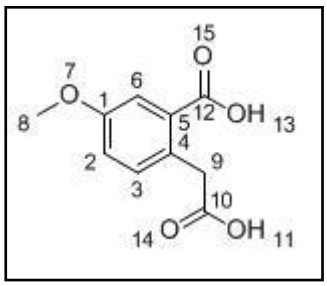


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (d, $J_{6,2}$ = 2.8 Hz, 1H, H-6), 7.49 (br d, $J_{3,2}$ = 8.4 Hz, 1H, H-3), 7.33 (s, 1H, -CH), 7.07 (br dd, $J_{2,3}$ = 8.8 Hz, $J_{2,6}$= 2.8 Hz, 1H, H-2), 3.81 (s, 3H, -OCH_3)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.5, 159.2, 132.0, 128.8, 128.2, 128.1, 121.2, 119.4, 116.0, 55.6

3.12 Synthesis of 2-(carboxymethyl)-5-methoxybenzoic acid (125)

To 20 ml 90% sulphuric acid, **123** (7 g, 23 mmol) was added portionwise at 60 °C and the whole mixture was stirred for 2 h at the same temperature. Then the mixture was poured on ice and filtered to give **125** (4.5 g, 21 mmol, 91.3 %).

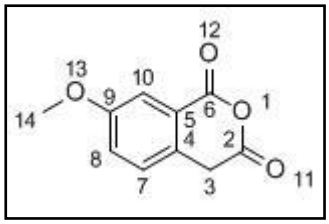


^{1}H-NMR (400 MHz, DMSO-$_{d6}$) δ 7.40 (d, $J_{6,2}$ = 2.8 Hz, 1H, H-6), 7.23 (br d, $J_{3,2}$ = 8.4 Hz, 1H, H-3), 7.07 (br dd, $J_{2,3}$ = 8.4 Hz, $J_{2,6}$= 2.8 Hz, 1H, H-2), 3.85 (s, 2H, -CH_2), 3.78 (s, 3H, -OCH_3)

^{13}C-NMR (400 MHz, DMSO-$_{d6}$) δ 172.7, 168.0, 157.8, 133.4, 131.5, 128.5, 117.4, 115.3, 55.2, 38.9

3.13 Synthesis of 7-methoxyisochroman-1,3-dione (133)

To a suspension of methoxy substituted homophthalic acid **125** (5 g, 23.7 mmol) in dicholoromethane (100 ml) an excess amount of thionyl chloride (5 ml, 68 mmol) was added at room temperature. Then the mixture refluxed up to the completion of the reaction which can be comprehended by the observation of the clear solution. Then solvent and excess thionyl chloride was removed under vacuum pressure to get **133** (4.4 g, 22.8 mmol, 95.8 %)



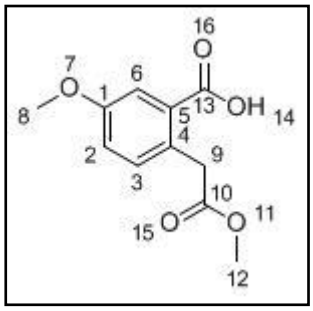
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (d, $J_{10,8}$ = 2.0 Hz, 1H, H-10), 7.19-7.17 (m, 2H, H-8,7), 4.01 (s, 2H, -CH_2), 3.82 (s, 3H, -OCH_3);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.9, 161.2, 159.9, 128.8, 126.6, 124.2, 122.7, 113.2, 56.0, 34.0

3.14 Synthesis of 5-methoxy-2-(2-methoxy-2-oxoethyl)benzoic acid (137)

The anhydride **133** (4.4 g, 22.8 mmol) was dissolved in methanol (100 ml) and refluxed for 2 h. After evaporation of the solvent, **137** (4.50 g, 20.1 mmol, 88.2 %)

obtained as a light yellow solid. The product was crystallized from EtOAc/hexane (3/1).

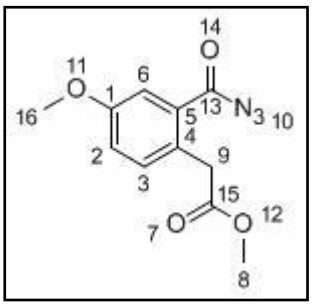


^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.87 (br s, 1H, -OH), 7.58 (d, $J_{6,2}$ = 2.8 Hz, 1H, H-6), 7.11 (br d, $J_{3,2}$= 8.4 Hz, 1H, H-3), 7.00 (br dd, $J_{2,3}$= 8.4 Hz, $J_{2,6}$ = 2.4 Hz, 1H, H-2), 3.91 (s, 2H, -CH_2), 3.77 (s, 3H, -OCH_3), 3.63 (s, 3H, -OCH_3)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.4, 158.7, 133.5, 129.4, 128.8, 119.5, 116.5, 55.5, 51.9, 39.7

3.15 Synthesis of methyl 2-(2-(azidocarbonyl)-4-methoxyphenyl)acetate (150)

Initially, half ester **137** (2 g, 8.9 mmol) was dissolved in freshly distilled THF (10 ml) at -5 °C and stirred for 10 min. In a 50 ml dropping funnel, a solution of triethylamine (1.49 ml, 10.6 mmol) and THF (10 ml) was prepared and slowly dropped onto the mixture and stirred for 30 min. Following this, a solution of ethyl chloroformate (1.00 ml, 10.6 mmol) in THF (10 ml) added dropwise to the mixture and continuously stirred for 30 min. Finally (0.68 g, 10.6 mmol) sodium azide was dissolved in water (10 ml) and dropped to the mixture which was further stirred overnight at the same temperature. After removal of the THF under vacuum pressure, residual part of the mixture was extracted with two portions of ethyl acetate (2 x 30 ml) and the organic phase was dried over magnesium sulfate. Then solvent was evaporated and corresponding azide **150** was obtained (1.77 gr, 7.1 mmol, 79.4 %)



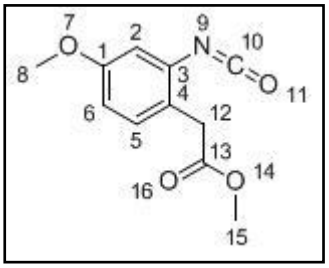
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (d, $J_{6,2}$ =2.8 Hz, 1H, H-6), 7.19 (br d, $J_{3,2}$= 8.4 Hz, 1H, H-3), 7.09 (br dd, $J_{2,3}$= 8.4 Hz, $J_{2,6}$=2.8 Hz, 1H, H-2), 3.97 (s, 2H, -CH_2), 3.84 (s, 3H, -OCH_3), 3.71 (s, 3H, -OCH_3)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.9, 171.9, 158.6, 133.7, 130.3, 128.7, 119.5, 116.1, 55.5, 55.4, 39.5;

IR (KBr, cm^{-1}) 3357 (br.), 2887 (w), 1648 (w), 1588 (w), 1448 (m), 1299 (m), 1260 (m), 1230 (s), 1194 (m), 1058 (s), 892 (m), 819 (m)

3.16 Synthesis of Methyl 2-(4-bromo-2-isocyanatophenyl)acetate (153)

The acyl azide compound **150** (1.77 gr, 7.1 mmol) was refluxed in benzene for 1 h. Evaporation of the benzene under vacuum gave the isocyanate **153** (1.53 g, 6.9 mmol, 97.2%).



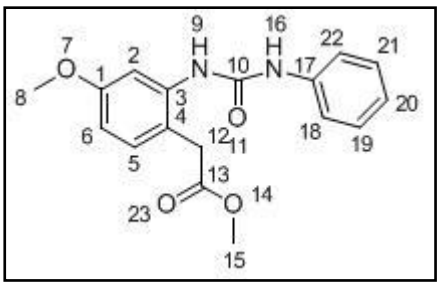
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.05 (br d, $J_{5,6}$= 8.4 Hz, 1H, H-5), 6.64 (br dd, $J_{6,5}$= 8.4 Hz, $J_{6,2}$= 2.8 Hz, 1H, H-6), 6.59 (d, $J_{2,6}$= 2.8 Hz, 1H, H-2), 3.69 (s, 3H, -OCH_3), 3.62 (s, 3H, -OCH_3), 3.52 (s, 2H, -CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.4, 159.6, 133.5, 131.6, 128.3, 120.9, 112.1, 111.4, 55.4, 52.1, 36.7

IR (KBr, cm^{-1}) 3357 (br.), 2887 (w), 1648 (w), 1588 (w), 1448 (m), 1299 (m), 1260 (m), 1230 (s), 1194 (m), 1058 (s), 892 (m), 819 (m)

3.17 Synthesis of Methyl 2-(4-methoxy-2-(3-phenylureido)phenyl)acetate (156)

To a solution of isocyanate **153** (1.53 g, 6.9 mmol) in dichloromethane (25 ml), aniline (1.00 ml, 11.0 mmol) was added and the solution was stirred for 2 h at room temperature. Filtration of the precipitate yielded the urea derivative **156** (2.07 g, 6.6 mmol, 95.6 %).



156: White solid, m.p. 168-170°C

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (br s, 1H, -NH), 7.30 (br d, $J_{22,21}$ = $J_{18,19}$ =7.6 Hz, 2H, H-22,18), 7.22 (m, 3H, H-21,19,2), 7.04 (br d, $J_{5,6}$ = 8.4 Hz, 1H, H-5), 7.00 (br t, $J_{20,21}$ = $J_{20,19}$ = 7.6 Hz, 1H, H-20), 6.71 (br s, 1H, -NH), 6.63 (br dd, $J_{6,5}$ = 8.4, $J_{6,2}$ = 2.4 Hz, 1H, H-6), 3.72 (s, 3H , -OCH_3), 3.56 (s, 3H , -OCH_3), 3.52 (s, 2H, -CH_2)

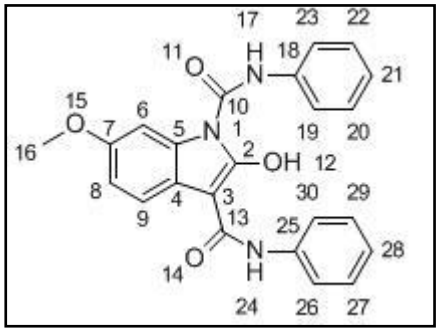
^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.1, 159.7, 153.9, 138.2, 137.7, 131.7, 129.1, 123.9, 120.7, 119.5, 111.9, 110.7, 55.4, 52.4, 37.3

IR (KBr, cm^{-1}) 3265 (s), 2896 (w), 1723 (s), 1618 (s), 1553 (s), 1462 (m), 1260 (m), 1243 (m), 1150 (s), 989 (s), 865(m), 811 (m)

Anal. Calcd. for $C_{17}H_{18}N_2O_4$; C, 64.96; H, 5.77; N, 8.91; O, 20.36. Found: C, 63.29; H, 5.56; N, 8.62

3.18 Synthesis of 2-hydroxy-6-methoxy-N^1,N^3-diphenyl-1H-indole-1,3-dicarboxamide (166), 6-methoxyindolin-2-one (167), 2-hydroxy-6-methoxy-N-phenyl-1H-indole-3-carboxamide (168) and 1,3-diphenylurea (169)

The urea derivative **156** (3.0 g, 9.54 mmol) was dissolved in acetonitrile (50 ml) and the mixture is heated up to 60 °C. After that at the same temperature excess amount of potassium carbonate (5 g, 36mmol) was added to the reaction mixture. By the help of the TLC controlling, the reaction was ended after 1.5 hours. Excess potassium carbonate was filtered and solvent was evaporated under reduced pressure. Product **166** (1.06 g, 2.35 mmol, 51.3 %) was obtained by precipitation in chloroform in one day. Remaining soluble part was concentrated and purified by silica gel eluting with EtOAc/DCM (40/60) in order to obtain the minor products; **167** (0.4 g , 2.46 mmol, 25.8 %), **168** (0.07 g , 0.25 mmol, 2.6 %), **169** (0.06 g , 0.28 mmol, 2.9 %)



166: Purple solid, m.p. 199-201 °C

^{1}H-NMR (400 MHz, DMSO-$_{d6}$) δ 12.69 (br s, 1H, -NH), 10.58 (br s, 1H, -NH), 7.87 (d, $J_{6,8}$=2.4 Hz, 1H, H-6), 7.80 (br d, $J_{9,8}$ =8.4 Hz, 1H, H-9), 7.67 (br d, $J_{23,22} = J_{19,20}$ = 7.6 Hz, 2H, H-23,19), 7.65 (br d, $J_{30,29} = J_{26,27}$ = 7.6 Hz, 2H, H-30,26), 7.37 (br t, $J_{22,23} = J_{22,21} = J_{20,19} = J_{20,21}$ = 7.6 Hz, 2H, H-22,20), 7.27 (br t, $J_{29,30} = J_{29,28} = J_{27,26} = J_{27,28}$ = 7.6 Hz, 2H, H-29,27), 7.08 (br t, $J_{21,22} = J_{21,20}$ = 7.2 Hz, 1H, H-21), 6.9 (br t, $J_{28,29} = J_{28,27}$ =

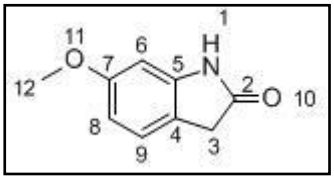
7.2 Hz, 1H, H-28), 6.65 (br dd, $J_{8,9}$ = 8.4 Hz, $J_{8,6}$ = 2.4 Hz, 1H, H-8), 3.74 (s, 3H, -OCH_3)

^{13}C-NMR (100 MHz, DMSO-$_{d6}$) δ 164.3, 164.1, 153.1, 151.7, 140.9, 138.6, 130.5, 128.9, 128.6, 122.9, 120.7, 119.4, 118.1, 116.8, 108.5, 100.7, 84.6, 55.3

IR (KBr, cm^{-1}) 3629 (m), 3201 (br.), 3033 (m) 1678 (s), 1596 (s), 1583 (s), 1550 (s), 1443 (s), 1414 (s), 1236 (m), 1173 (m), 1108 (m), 979 (m), 819 (m), 778 (m),748 (m)

HRMS $[M+K]^+$ calcd for $C_{23}H_{19}N_3O_4$; Exact mass: 440.1012; Found: 410.1007

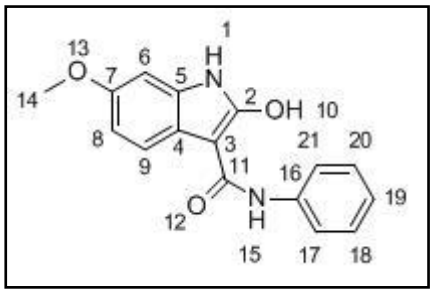
167: Light red solid**,** m.p. 157-159 °C, 162 °C[55]



^{1}H-NMR (400 MHz, DMSO-$_{d6}$) δ 10.31 (br s, 1H, -NH), 7.08 (br d, $J_{9,8}$= 8.4 Hz, 1H, H-9), 6.47 (br dd, $J_{8,9}$= 8.4 Hz, $J_{8,6}$=2.4 Hz, 1H, H-8), 6.37 (d, $J_{6,9}$=2.4 Hz, 1H, H-6), 3.71(s, 3H, -OCH_3), 3.37 (s, 2H, -CH_2)

^{13}C-NMR (100 MHz, DMSO-$_{d6}$) δ 176.9,159.1, 144.7, 124.8, 117.3, 106.0, 96.2, 55.1, 35.1

168: White crystalline solid**,** m.p. 250-252 °C



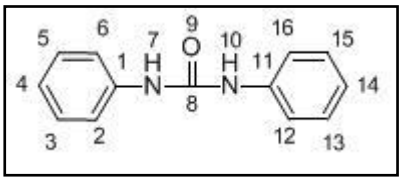
^{1}H-NMR (400 MHz, DMSO-$_{d6}$) δ 11.98 (br s, 1H, -NH), 11.47 (br s, 1H, -NH), 7.44 (m, 3H, H-9,17,21), 7.30 (br t, $J_{20,21}$ = $J_{20,19}$ = $J_{18,17}$ = $J_{18,19}$ = 7.6 Hz, 2H, H-20,18), 7.08 (br t, $J_{19,20}$ = $J_{19,18}$= 7.6 Hz, 1H, H-19), 6.58 (br dd, $J_{8,9}$ = 8.4 Hz, $J_{8,6}$ = 2.4 Hz, 1H, H-8), 6.33 (d, $J_{6,8}$ = 2.4 Hz, 1H, H-6), 3.69 (s, 3H, -OCH_3)

^{13}C-NMR (100 MHz, DMSO-$_{d6}$) δ 176.5, 165.4, 160.7, 143.7, 143.5, 138.0, 129.0, 128.8, 126.0, 124.3, 120.2, 119.7, 116.6, 108.1, 97.1, 63.9, 55.3

IR (KBr, cm^{-1}) 3446 (br.), 3268 (w), 3006 (w), 2249 (m), 2124 (m), 1715 (m), 1668 (m), 1626 (m), 1598 (m), 1217 (w), 1162 (w), 1005 (s), 820 (m), 757 (m)

Anal. Calcd. for $C_{16}H_{14}N_2O_3$; C, 68.07; H, 5.00; N, 9.92; O, 17.00. Found: C, 68.19; H, 4.74; N, 9.93

169: White crystal**,** m.p. 238-240 °C, 231-235 °C[56]



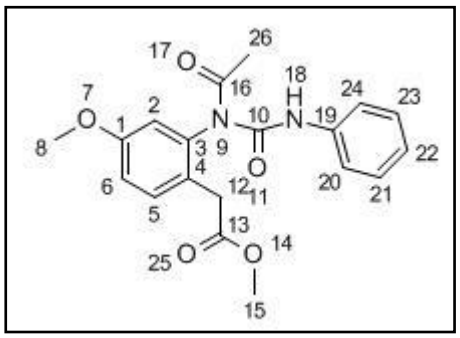
^{1}H-NMR (400 MHz, DMSO-$_{d6}$) δ 8.64 (br s, 2H, -NH), 7.45 (br d, $J_{6,5} = J_{2,3} = J_{16,15} = J_{12,13}$ = 7.6 Hz, 4H, H-2,6,12,16), 7.28 (br t, $J_{5,6} = J_{5,4} = J_{3,2} = J_{3,4} = J_{15,16} = J_{15,14} = J_{13,12} = J_{13,14}$= 7.6 Hz, 4H, H-3,5,13,15), 6.97 (br t, $J_{4,5} = J_{4,3} = J_{14,15} = J_{14,13}$= 7.2 Hz, 2H, H-4,14)

^{13}C-NMR (100 MHz, DMSO-$_{d6}$) δ 152.5, 139.7, 128.7, 121.8, 118.1

3.19 Synthesis of methyl 2-(4-methoxy-2-(N-(phenylcarbamoyl)acetamido)phenyl)acetate (172) and 1,1'-(2-hydroxy-6-methoxy-1H-indole-1,3-diyl)diethanone (173).

The urea derivative **156** (1.2 g, 3.81 mmol) was dissolved in freshly distilled THF (20 ml) and the mixture is cooled down to -5 °C. At this temperature sodium hydride (0. 175 g ,7.63 mmol) added into the reaction and the mixture was continued stirring for 30 min. Then acetic anhydride (0.53 ml, 5.72 mmol) added to the solution which was further stirred overnight at room temperature. After removal of the THF under vacuum pressure, residual part of the mixture was extracted with two portions of ethyl acetate (2 x 30 ml) and the organic phase was dried over magnesium sulfate. Organic phase was concentrated and purified by silica gel eluting with EtOAc/Hexane (3/2) to obtain the products **172** (0.38 g , 1.07 mmol, 28.1 %), **173** (0.26 g , 1.05 mmol, 27.6 %) and **166** (0.07 g , 0.17 mmol, 4.6 %).

172: Light brown solid**,** m.p. 107-109 °C

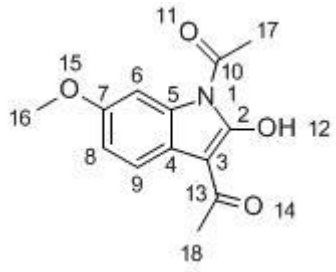


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80 (d, $J_{2,6}$ = 2.4 Hz 1H, H-2), 7.30 (br d, $J_{24,23}$ = $J_{20,21}$ =7.6 Hz, 2H, H-24,20), 7.22 (br t, $J_{23,24}$ = $J_{23,22}$ = $J_{21,20}$ = $J_{21,22}$ = 7.6 Hz, 2H, H-21,23), 7.05 (br d, $J_{23,24}$ = 8.4 Hz, 1H, H-5), 6.98 (br t, $J_{22,23}$ = $J_{22,21}$ = 7.6 Hz, 1H, H-22), 6.65-6.63 (m, 2H, -NH, H-6), 3.74 (s, 3H , -OCH_3), 3.69 (s, 3H , -OCH_3), 3.55 (s, 2H, -CH_2), 2.58 (s, 3H , H-26)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.0, 171.0, 159.7, 154.0, 137.9, 129.0, 124.4, 123.4, 118.7, 115.1, 110.8, 102.5, 110.7, 55.6, 52.3, 36.1, 26.7

IR (KBr, cm^{-1}) 3341 (br.), 3019 (m), 2953 (w), 1713 (s), 1660 (m), 1447 (m), 1372 (m), 1305 (m), 1215 (s), 1159 (m), 1029 (w), 698 (s), 667 (m)

173: Purple solid**,** m.p. 158-160 °C



^{1}H-NMR (400 MHz, $CDCl_3$) δ 13.00 (br s, 1H, -OH), 7.93 (d, $J_{22,21}$ = 2.4 Hz, 1H, H-6), 7.18 (br d, $J_{9,8}$ =8.8 Hz, 1H, H-9), 7.56 (dd, $J_{8,9}$ = 8.8 Hz, $J_{8,6}$= 2.4 Hz, 1H, H-8) 3.77 (s, 3H , -OCH_3), 2.68 (s, 3H , H-17), 2.38 (s, 3H, H-18)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.0, 172.4, 170.8, 158.4, 136.4, 119.8, 115.5, 111.1, 103.0, 101.5, 55.7, 26.9, 20.7

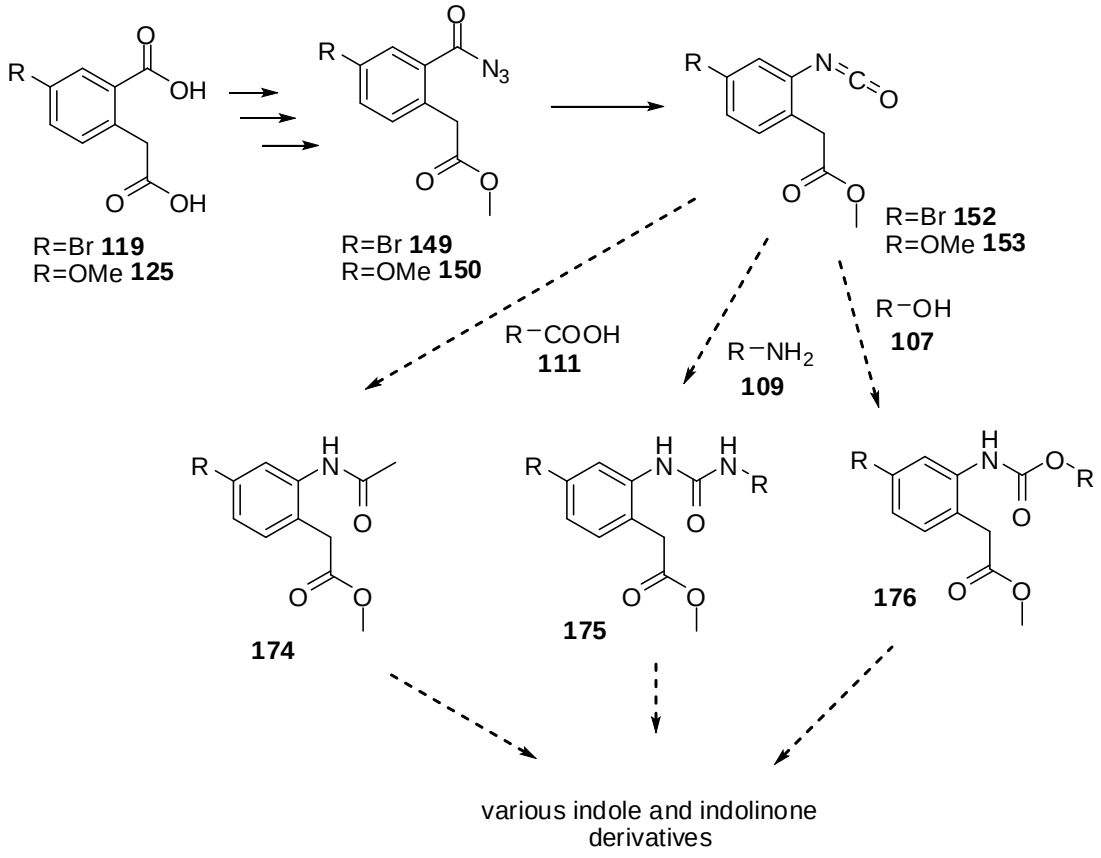
IR (KBr, cm^{-1}) 3019 (m), 1711 (w), 1623 (w), 1787 (w), 1307 (w), 1214 (s), 1162 (w), 711 (s), 668 (m)

HRMS $[M+H]^+$ calcd for $C_{13}H_{13}NO_4$; Exact mass: 248.0922 Found: 248.0917

CHAPTER 4

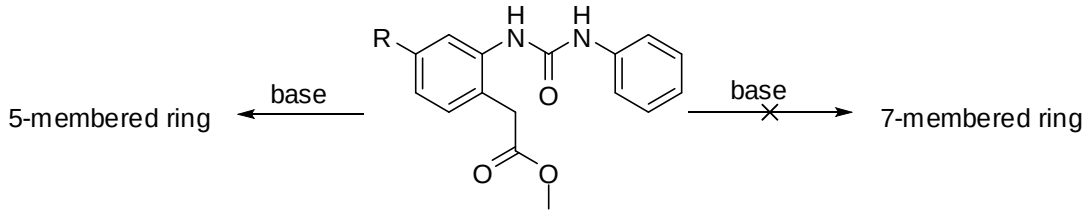
CONCLUSION

Ring-closure reaction is a very useful methodology in order to synthesize indole and indolinone derivatives starting from homophtalic acid derivatives **119**, **125**. Construction of the acyl azide **149**, **150** and isocyanate **152**, **153** precursors plays an important role throughout the synthetic route. Reaction of isocyanates with a diverse number of nucleophiles enables production of different amide **174**, urea **175** or urethane **176** derivatives which may lead to construct various five-membered ring substituted indole derivatives.



The urea derivatives have two probable ring closures leading to the five or seven-membered rings. This study showed that the homophthalic acid system prefers formation of the five membered rings under basic conditions. No any evidence was found about the formation of the seven-membered ring after the investigation of the

spectral data obtained from isaolated molecules. Besides the ^{1}H-NMR and ^{13}C-NMR spectra elemental analysis and HRMS data were supported the formation of final products.



R=Br **155**
R=OMe **156**

Furthermore, substituents attached to the benzene ring affected the ring closure reaction. Increasing base reactivity by the effect of the methoxy substituent led to further hydrolysis reactions and caused formation of some other side products. In addition to this bromium substituent did not change the reactivity of the bases.

On the other hand, controlling the positions and variety of the substitiuents by using relatively less harmless materials throughout the synthetic route is the common advantage of our methodology over most of the methodologies known in the literature. Substituents attached to either benzene or pyrolle rings can be modified. Changing the substituents attached to the homophthalic acids at the beginning of the synthetic route provides different substituents on the benzene ring of the indole structures at the end. Additionally strong nucleophilicity of the isocynates provides different urea, urethane or amide derivatives which may further lead to diversity at the C3 and N1 positions of the indole structures.

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APPENDIX A

SPECTRAL DATA

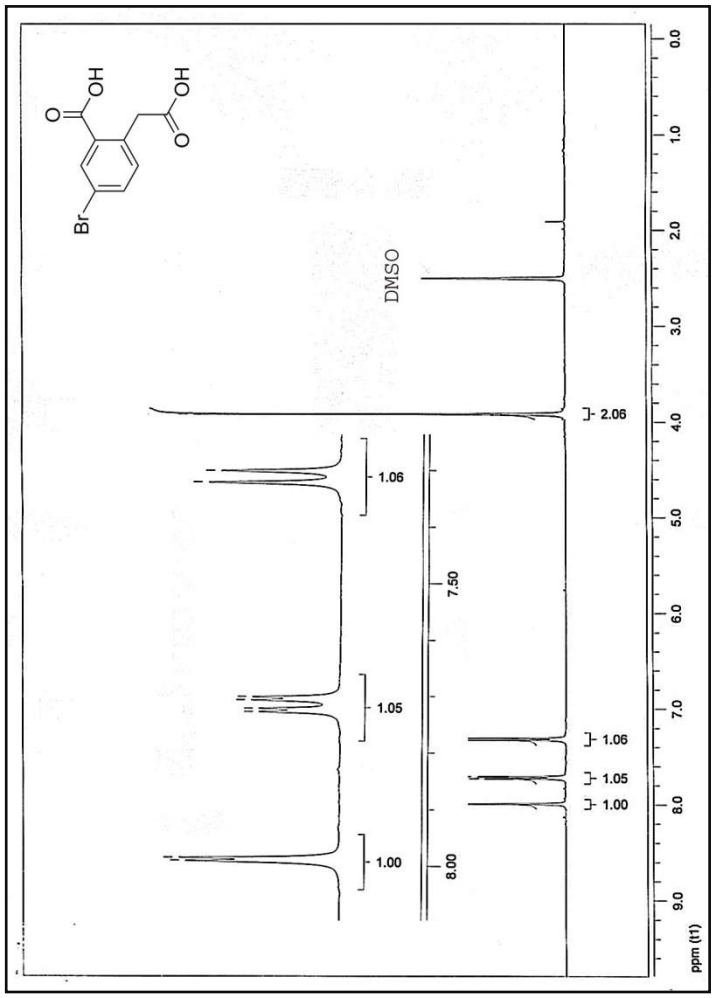

Figure A.1 ^{1}H-NMR spectrum of compound **119**

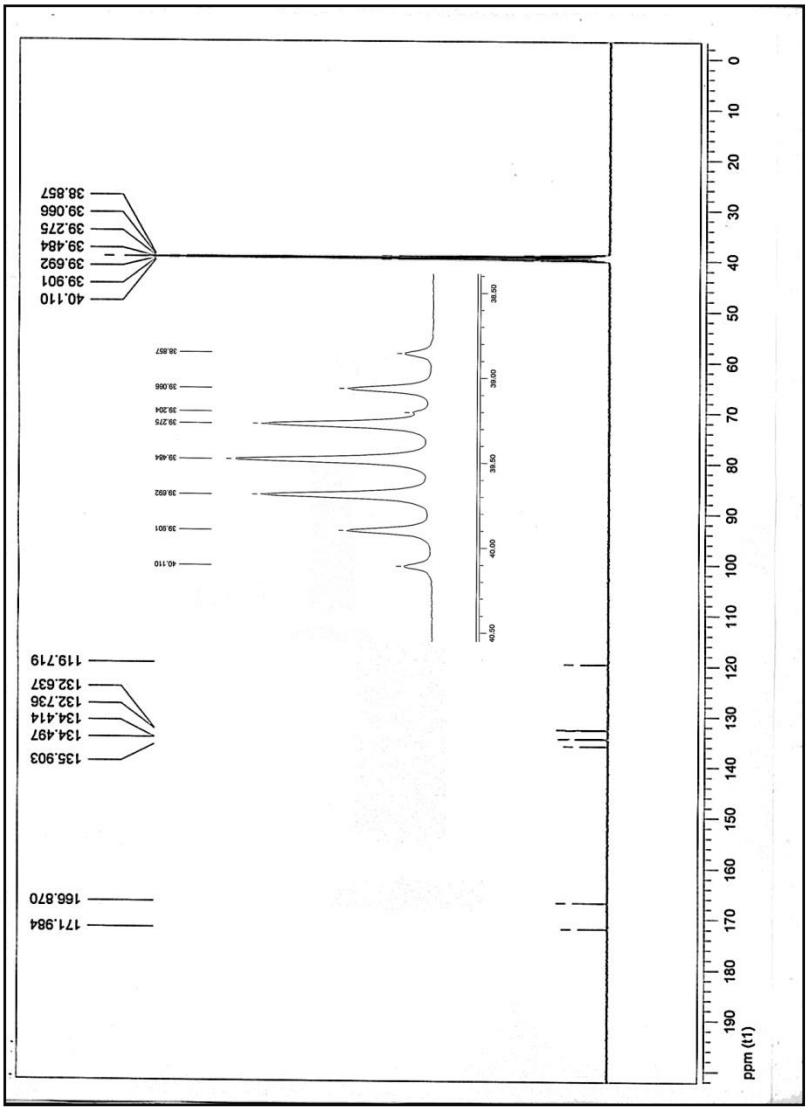

Figure A.2 ^{13}C-NMR spectrum of compound **119**

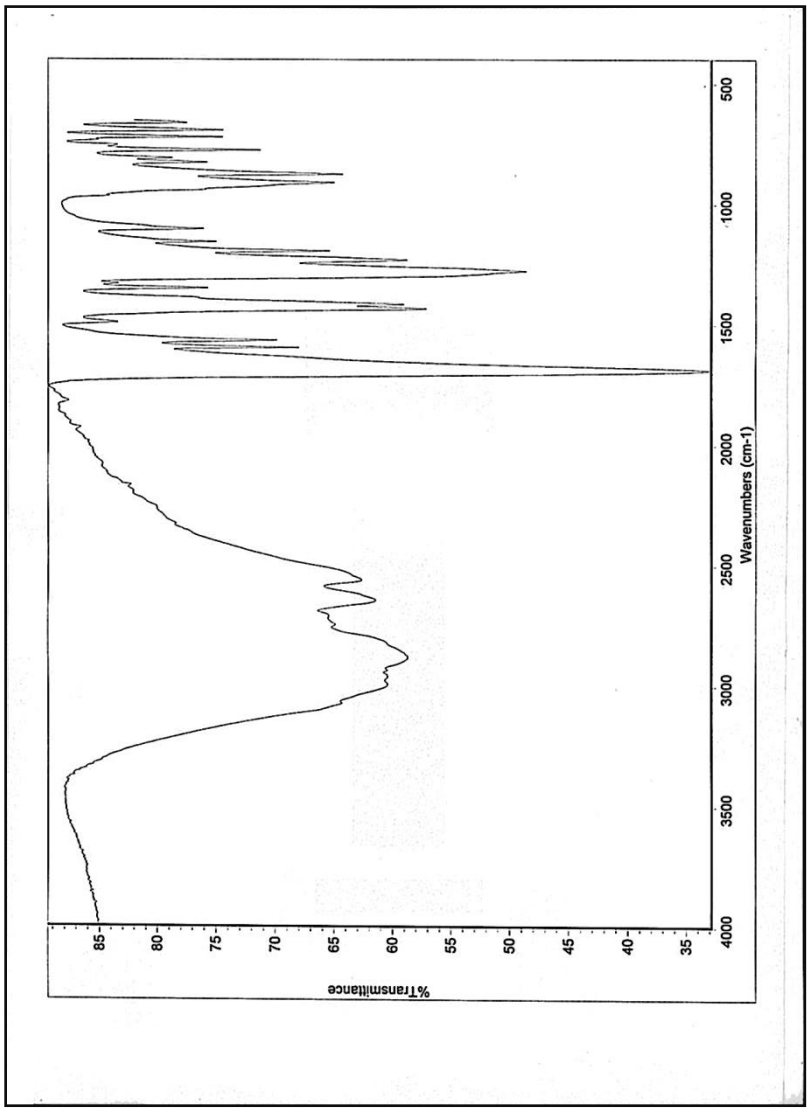

Figure A.3 IR spectrum of compound **119**

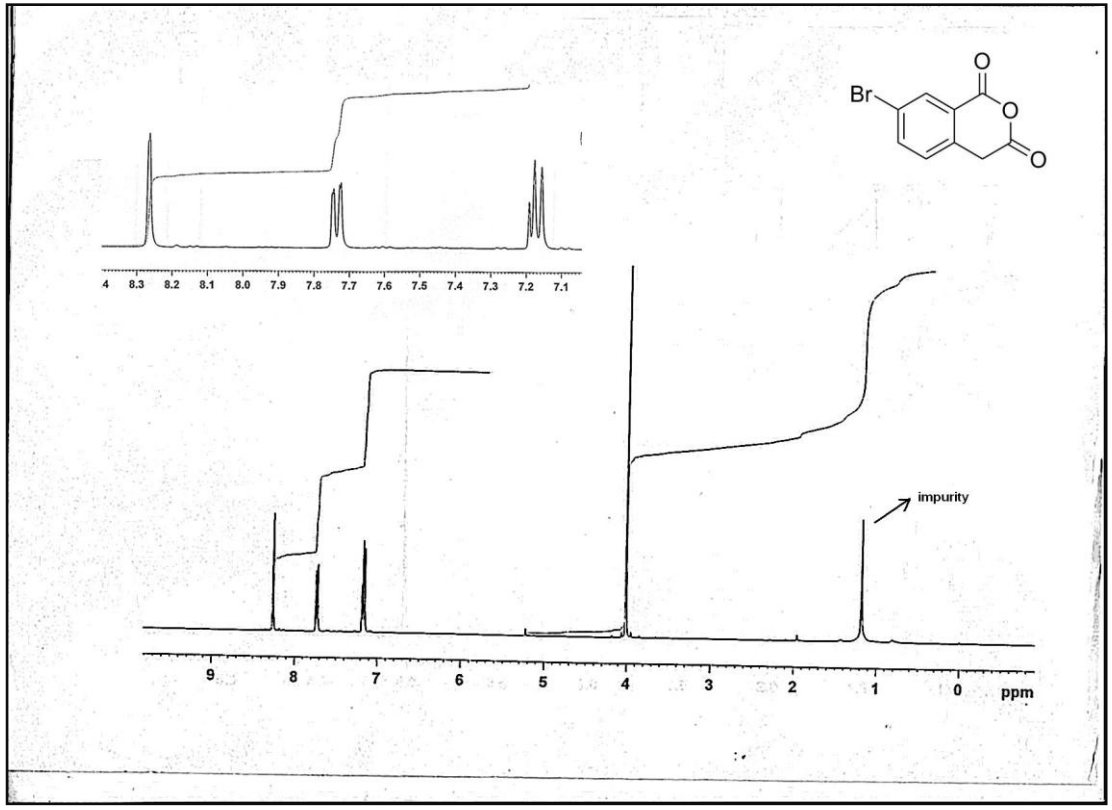

Figure A.4 ^{1}H-NMR spectrum of compound **132**

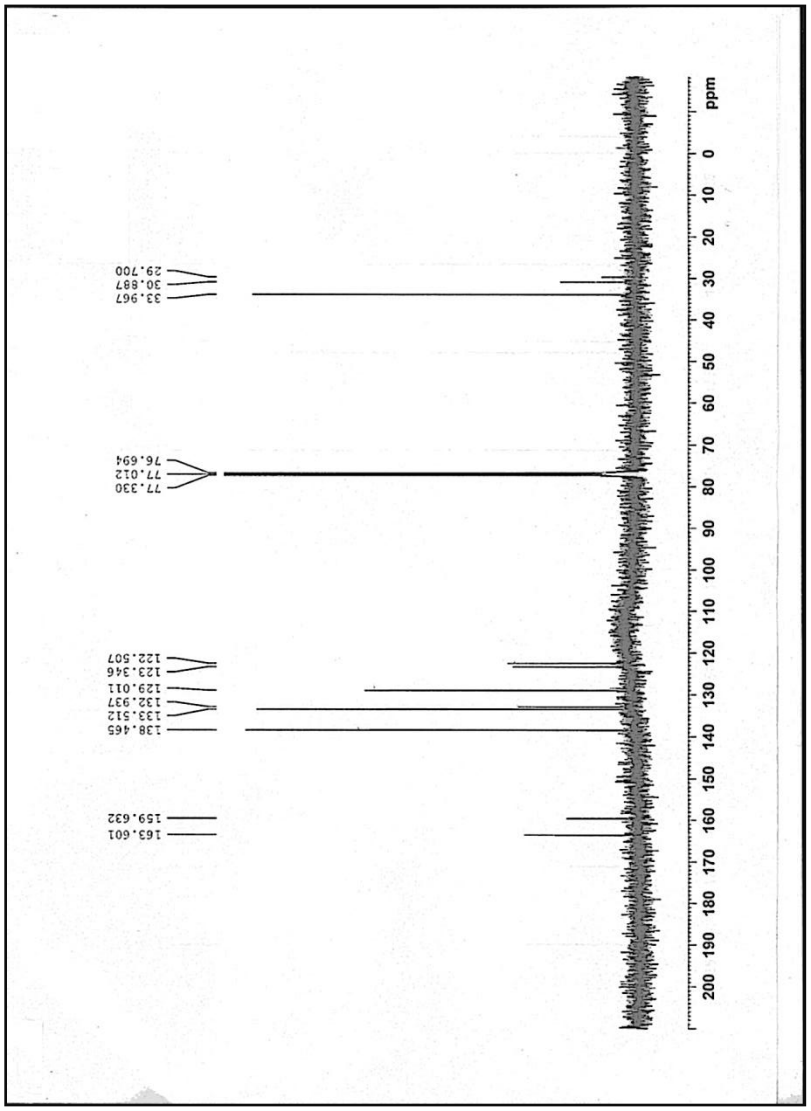

Figure A.5 ^{13}C-NMR spectrum of compound **132**

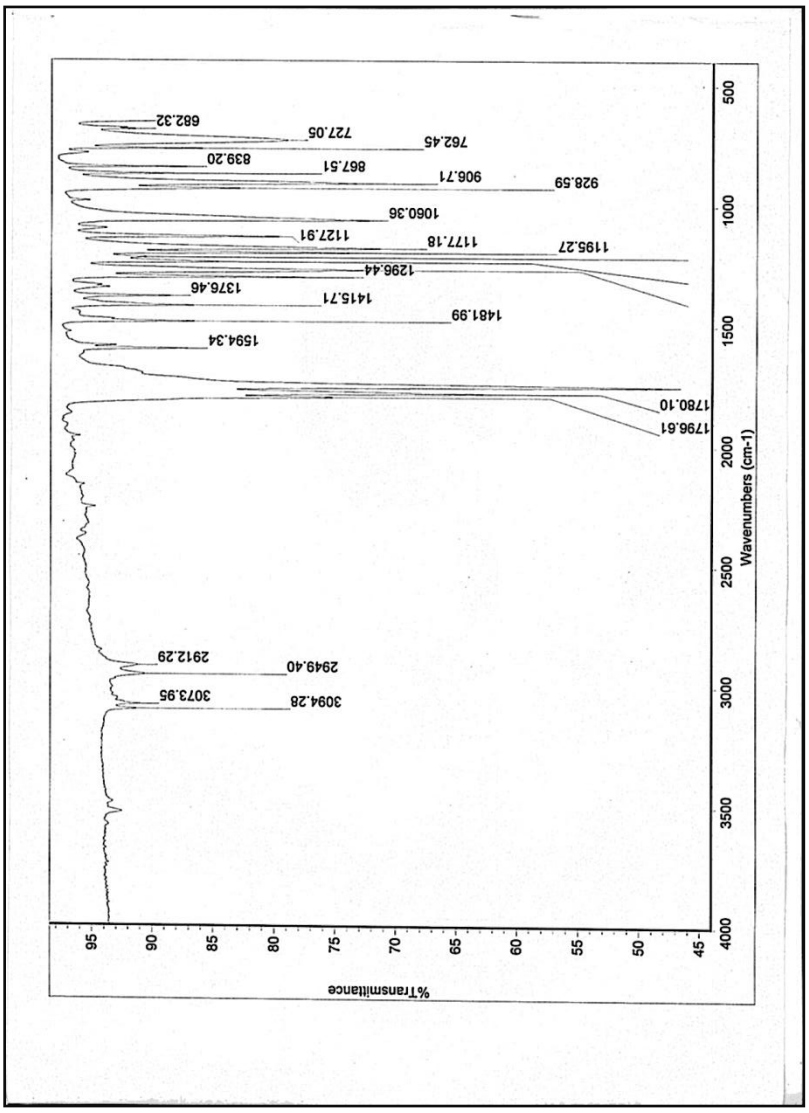

Figure A.6 IR spectrum of compound **132**

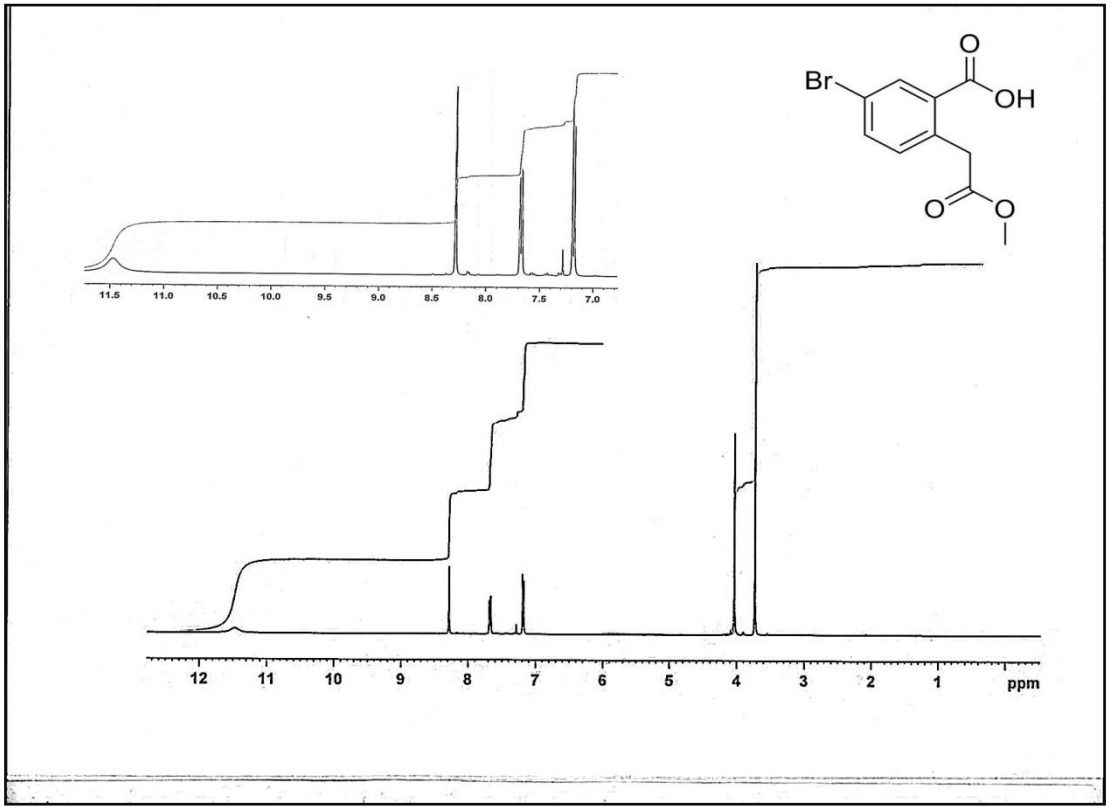

Figure A.7 ^{1}H-NMR spectrum of compound **136**

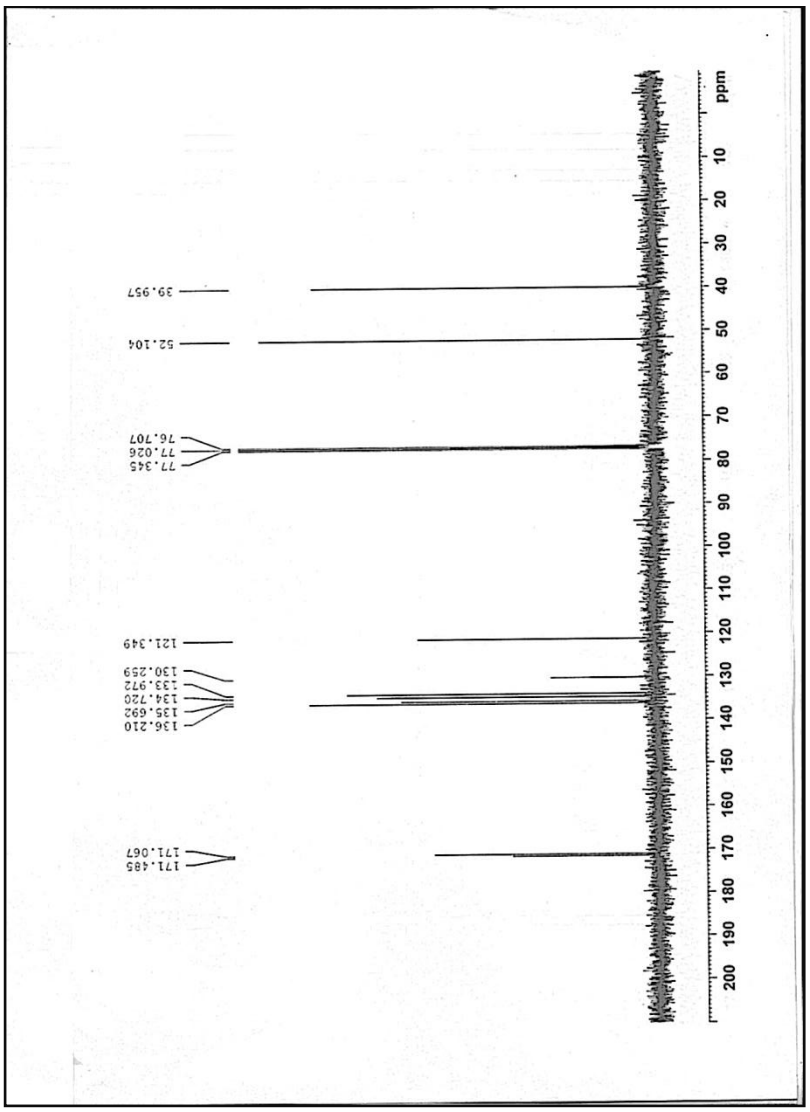

Figure A.8 ^{13}C-NMR spectrum of compound **136**

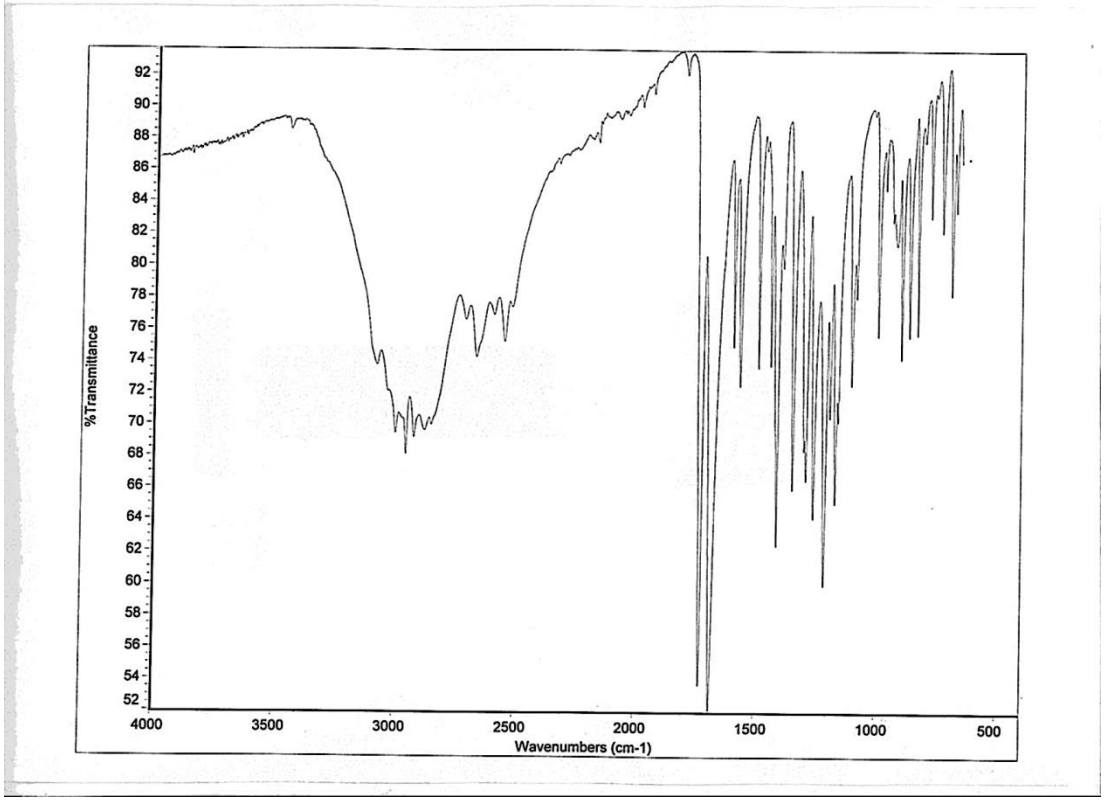

Figure A.9 IR spectrum of compound **136**

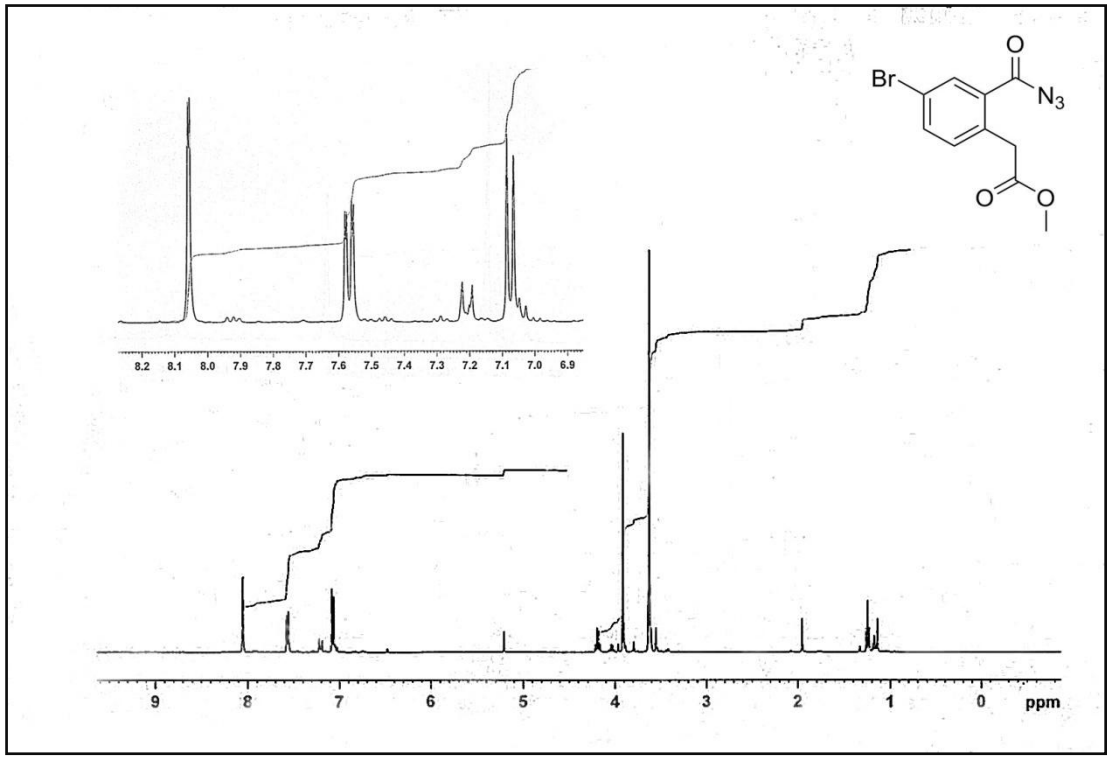

Figure A.10 ^{1}H-NMR spectrum of compound **149**

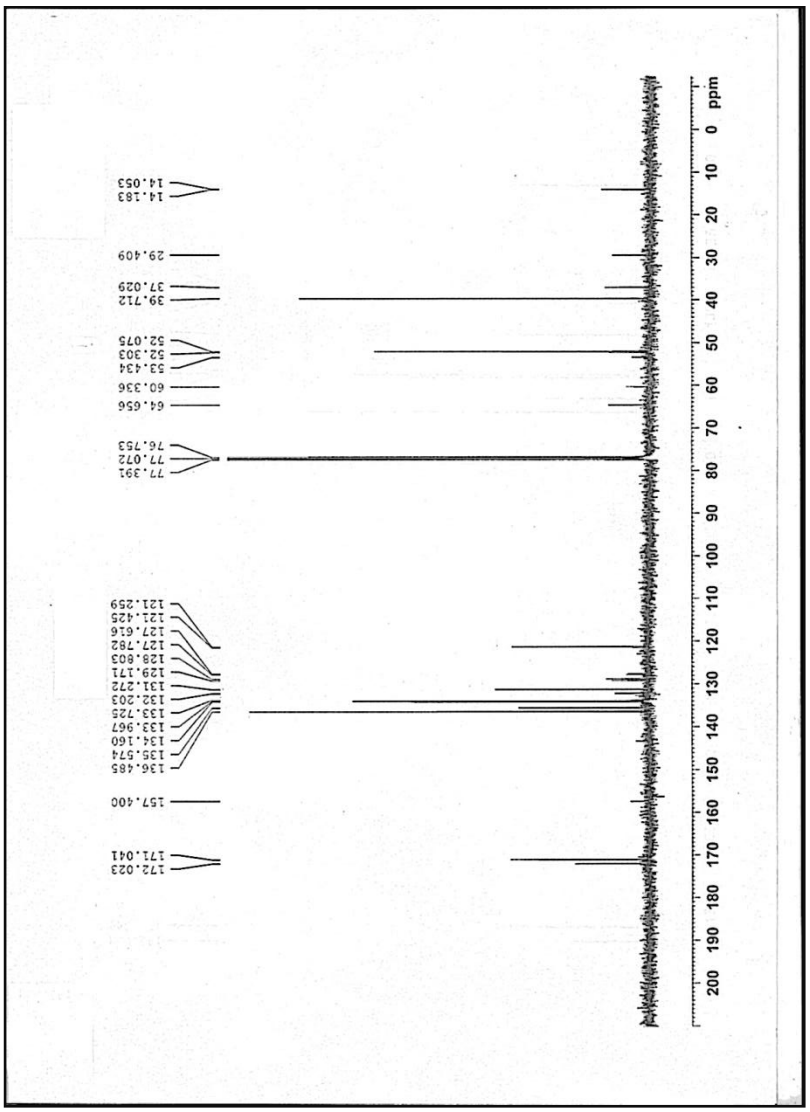

Figure A.11 ^{13}C-NMR spectrum of compound **149**

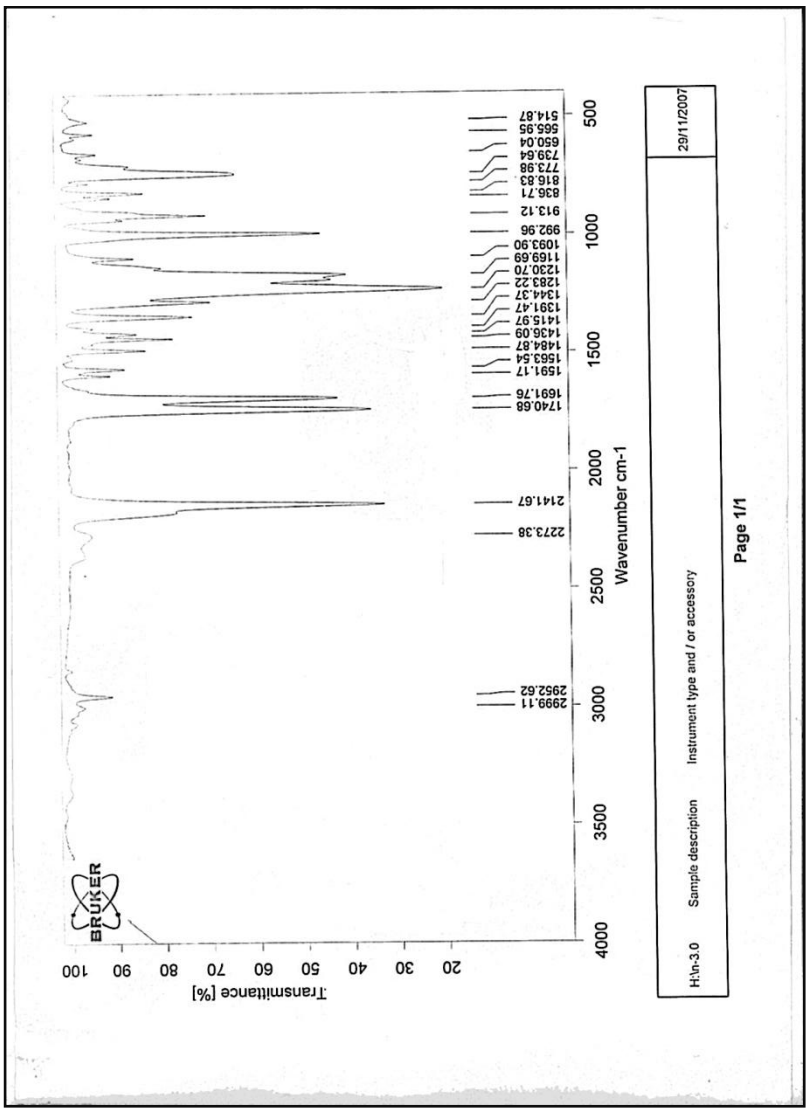

Figure A.12 IR spectrum of compound **149**

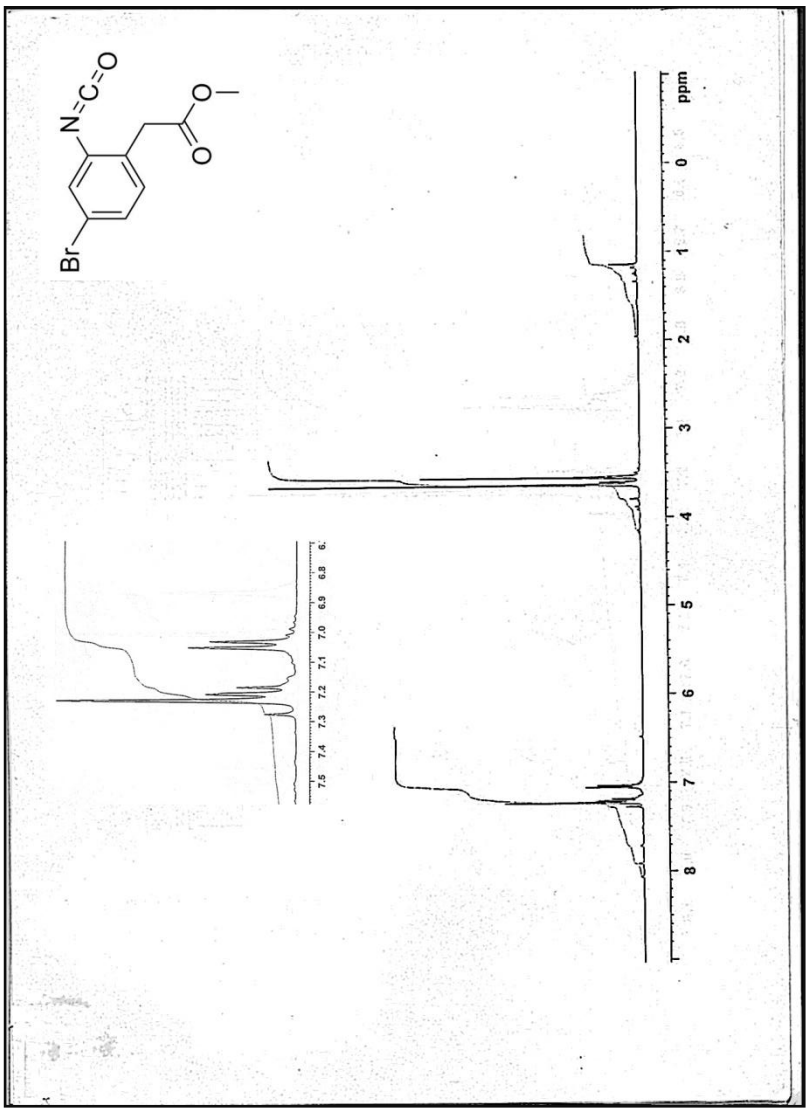

Figure A.13 ^{1}H-NMR spectrum of compound **152**

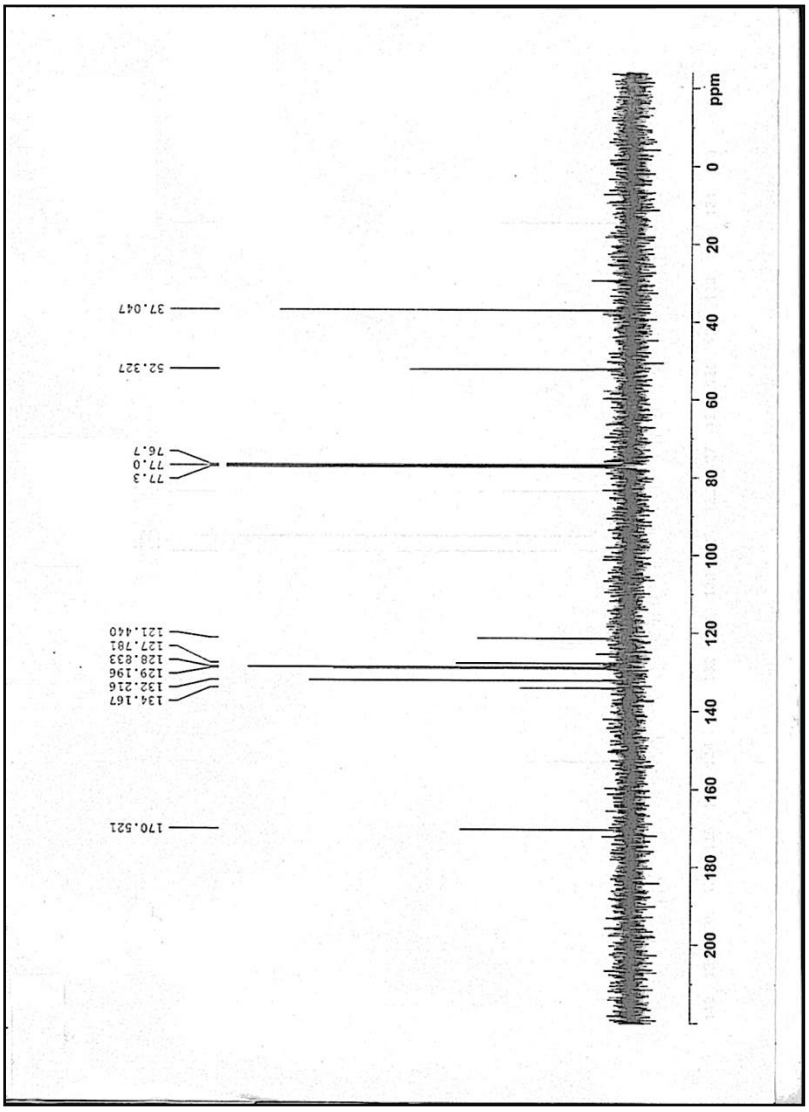

Figure A.14 ^{13}C-NMR spectrum of compound **152**

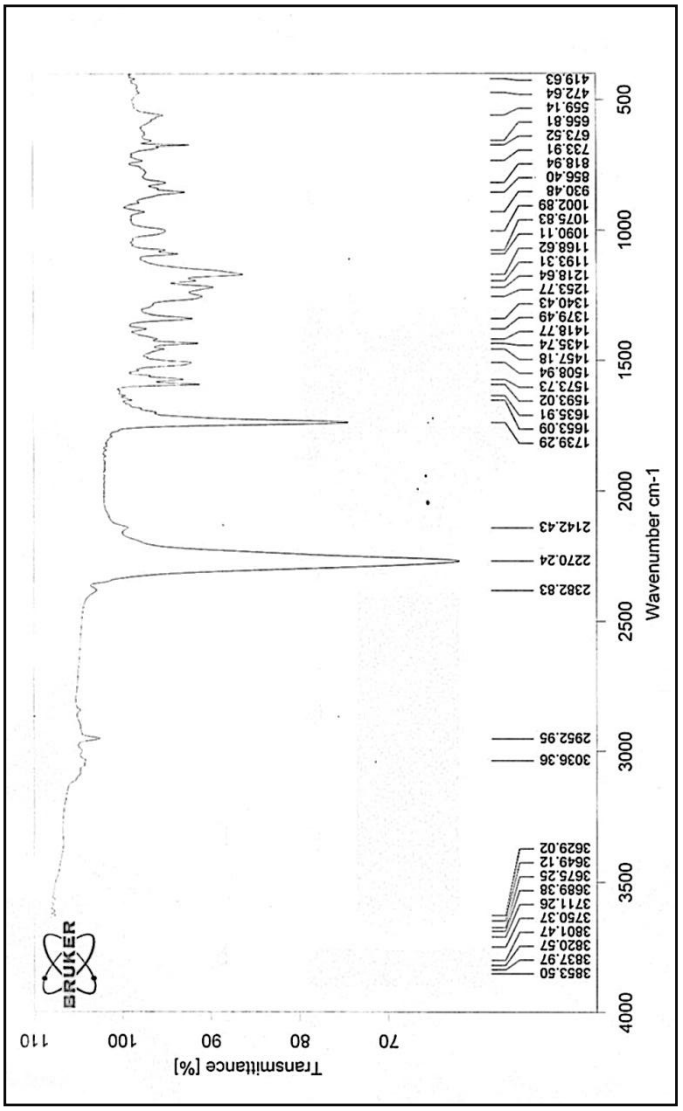

Figure A.15 IR spectrum of compound **152**

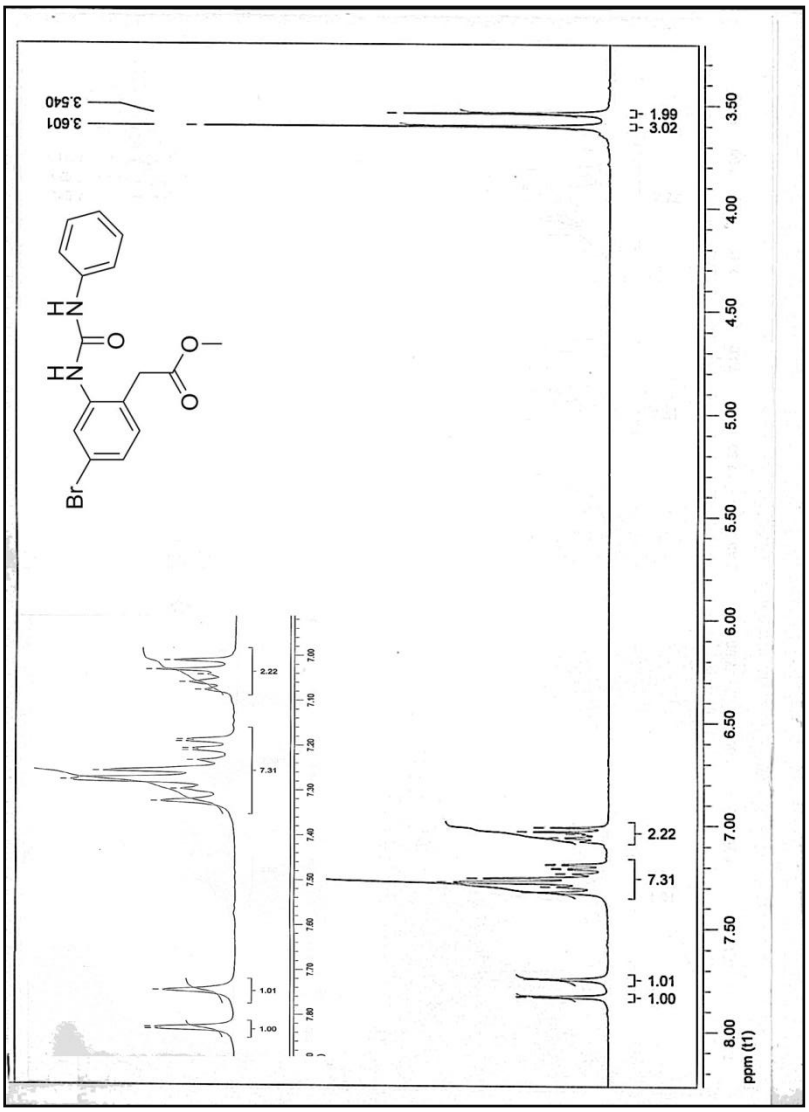

Figure A.16 ^{1}H-NMR spectrum of compound **155**

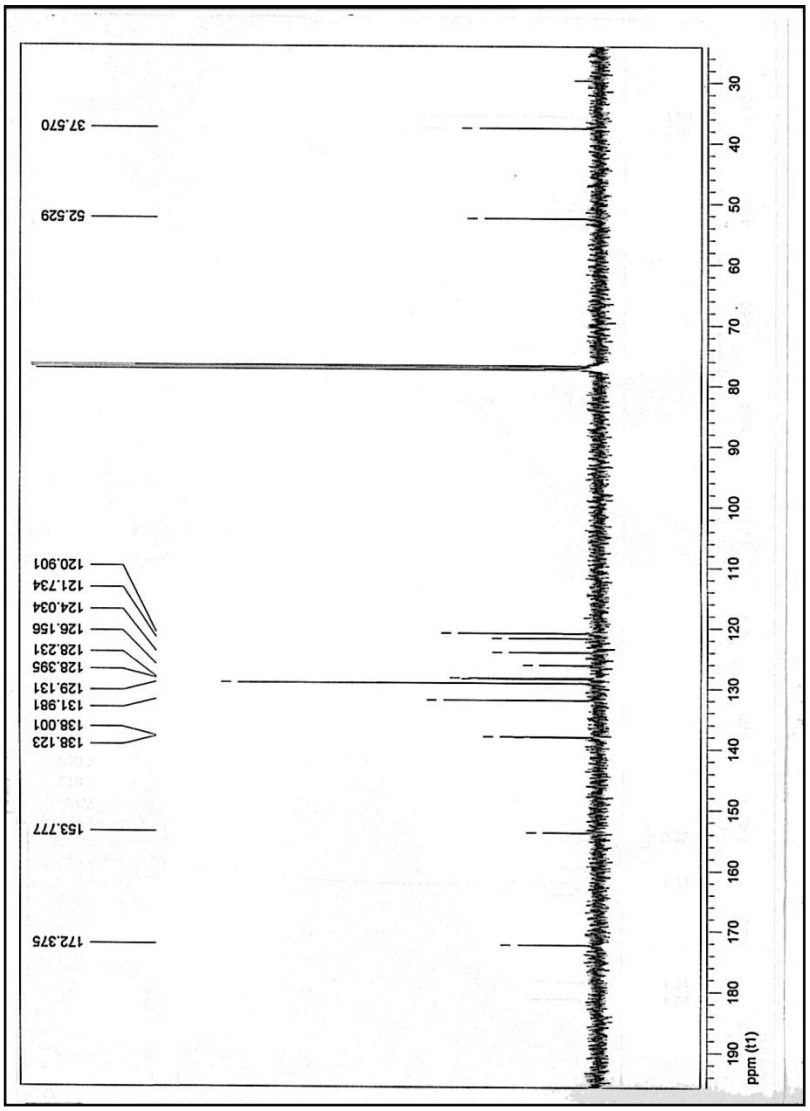

Figure A.17 ^{13}C-NMR spectrum of compound **155**

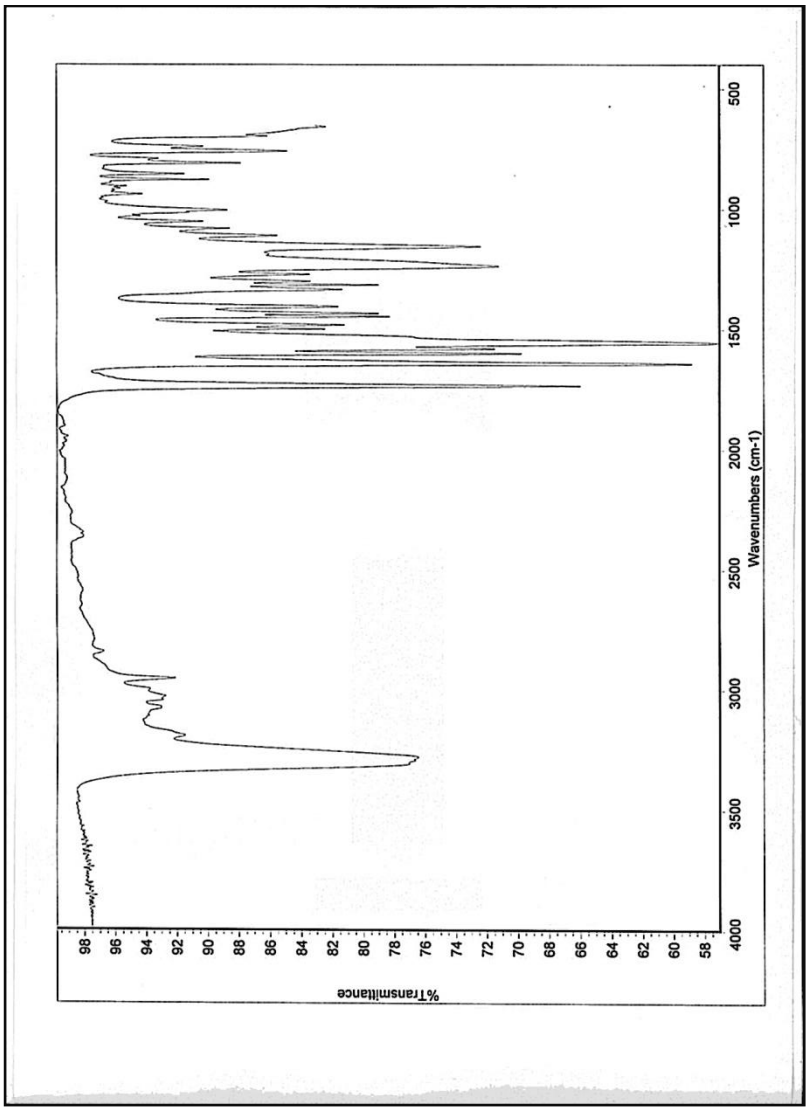

Figure A.18 IR spectrum of compound **155**

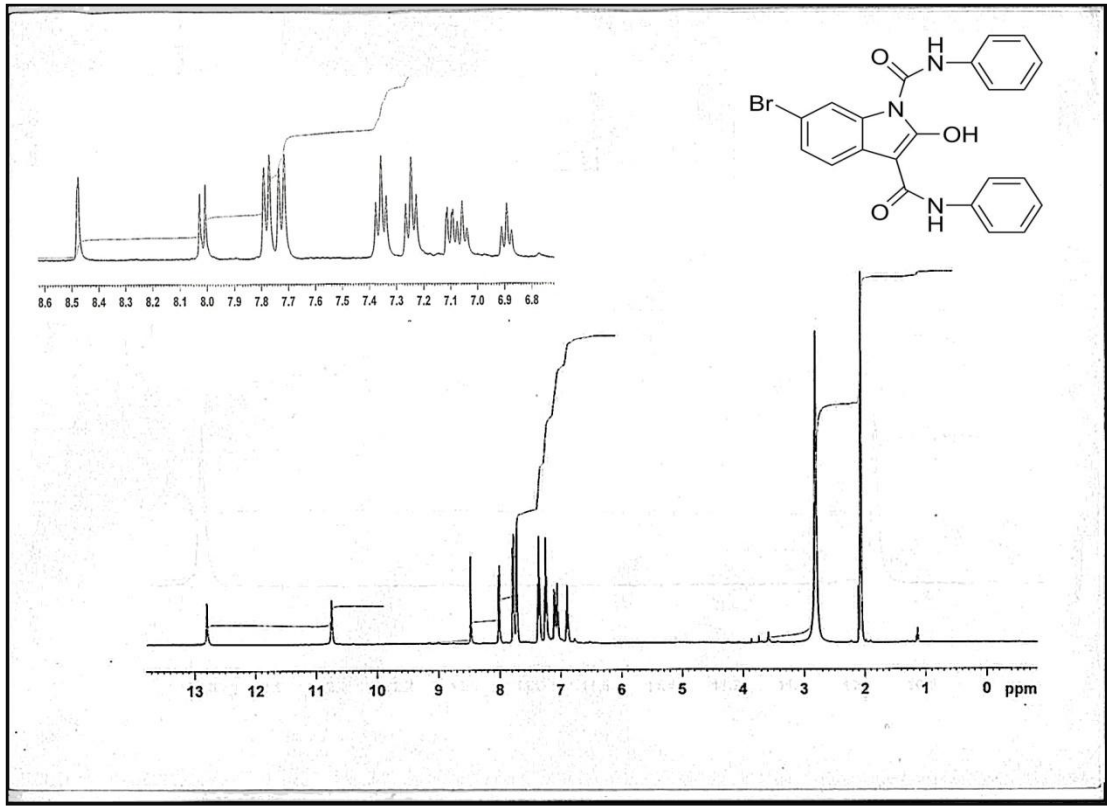

Figure A.19 ^{1}H-NMR spectrum of compound **159**

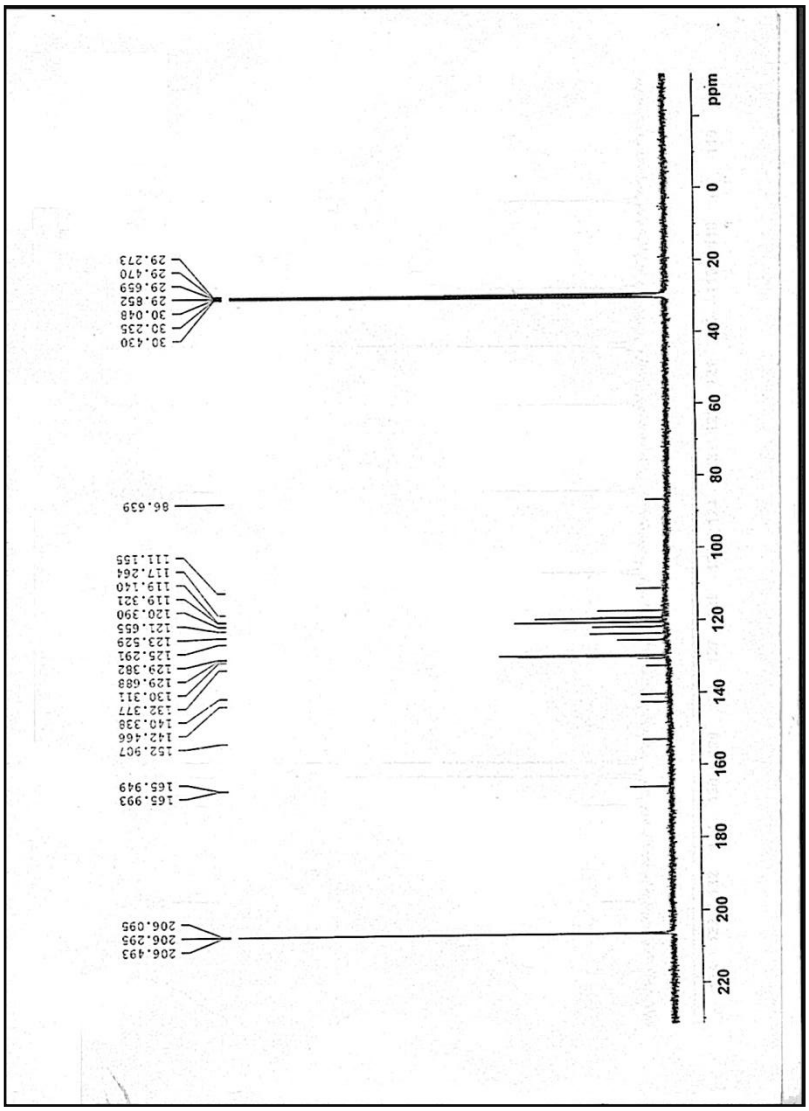

Figure A.20 ^{13}C-NMR spectrum of compound **159**

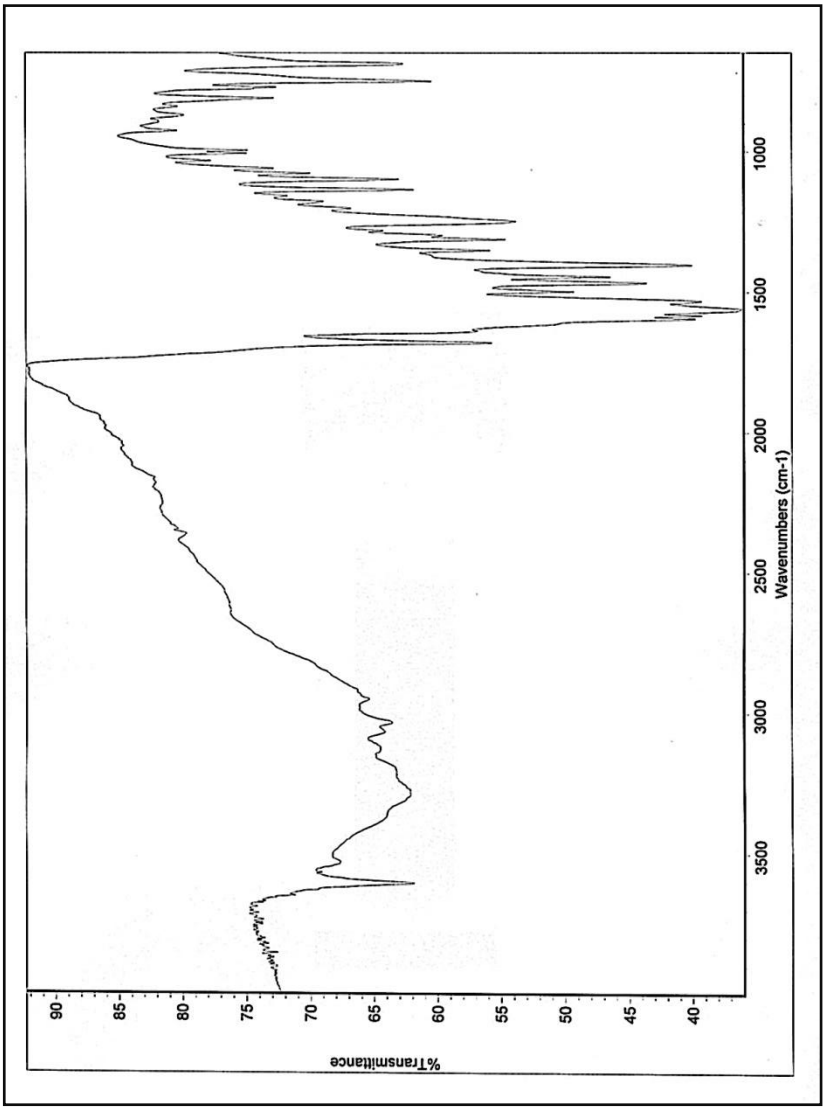

Figure A.21 IR spectrum of compound **159**

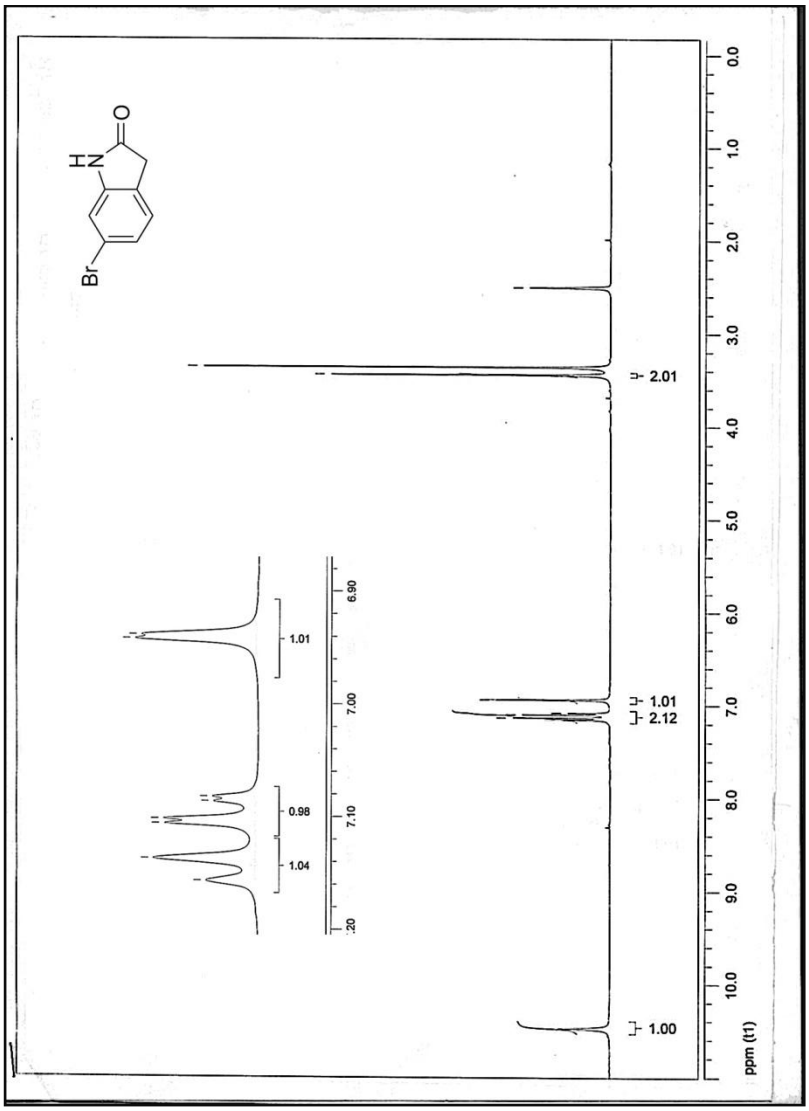

Figure A.22 ^{1}H-NMR spectrum of compound **160**

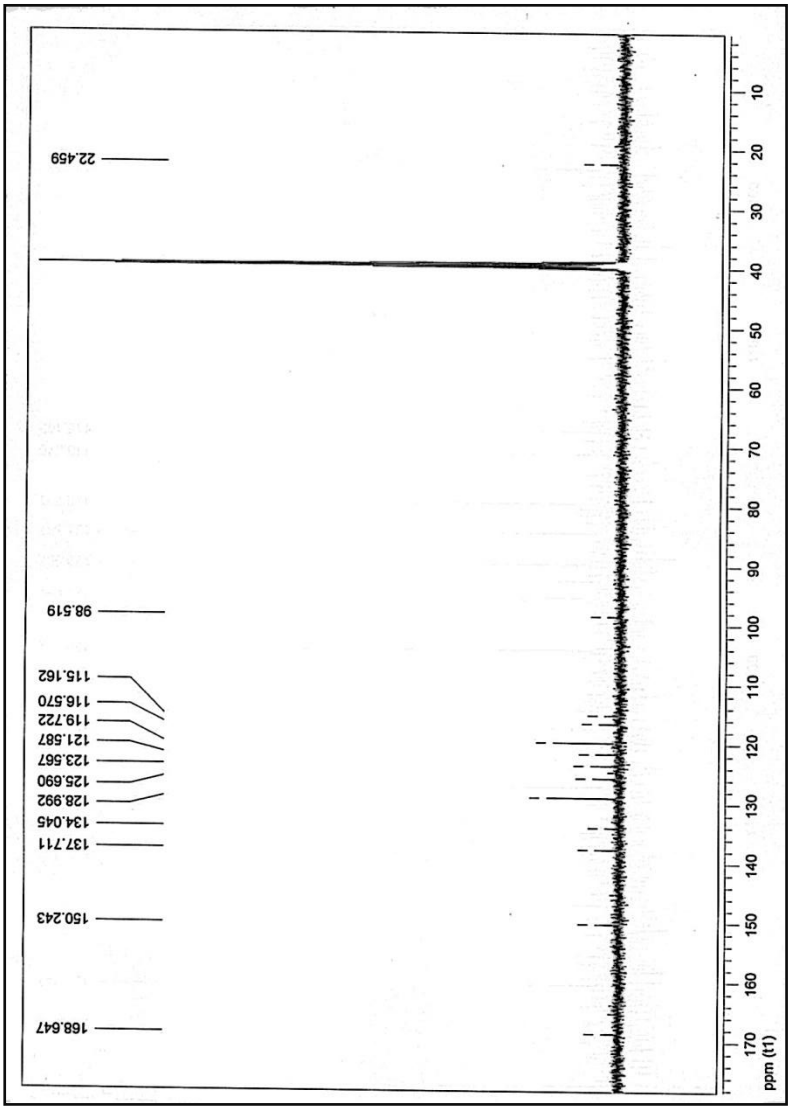

Figure A.23 ^{13}C-NMR spectrum of compound **160**

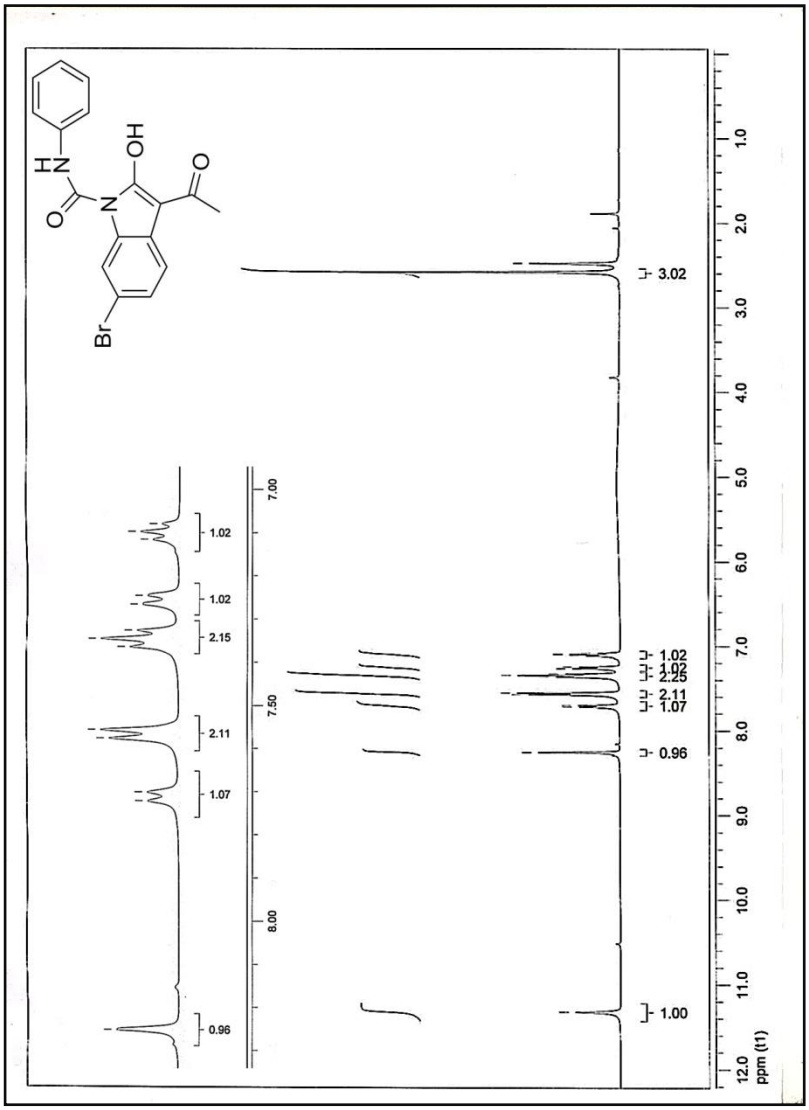

Figure A.24 ^{1}H-NMR spectrum of compound **163**

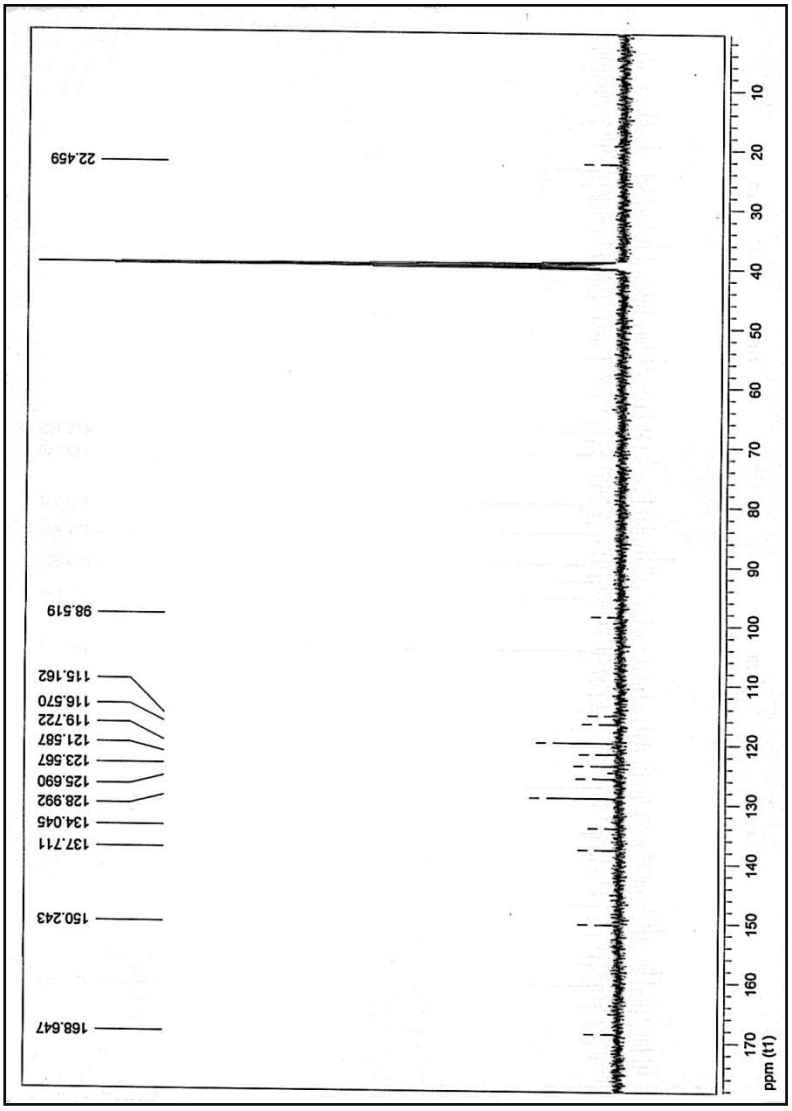

Figure A.25 ^{13}C-NMR spectrum of compound **163**

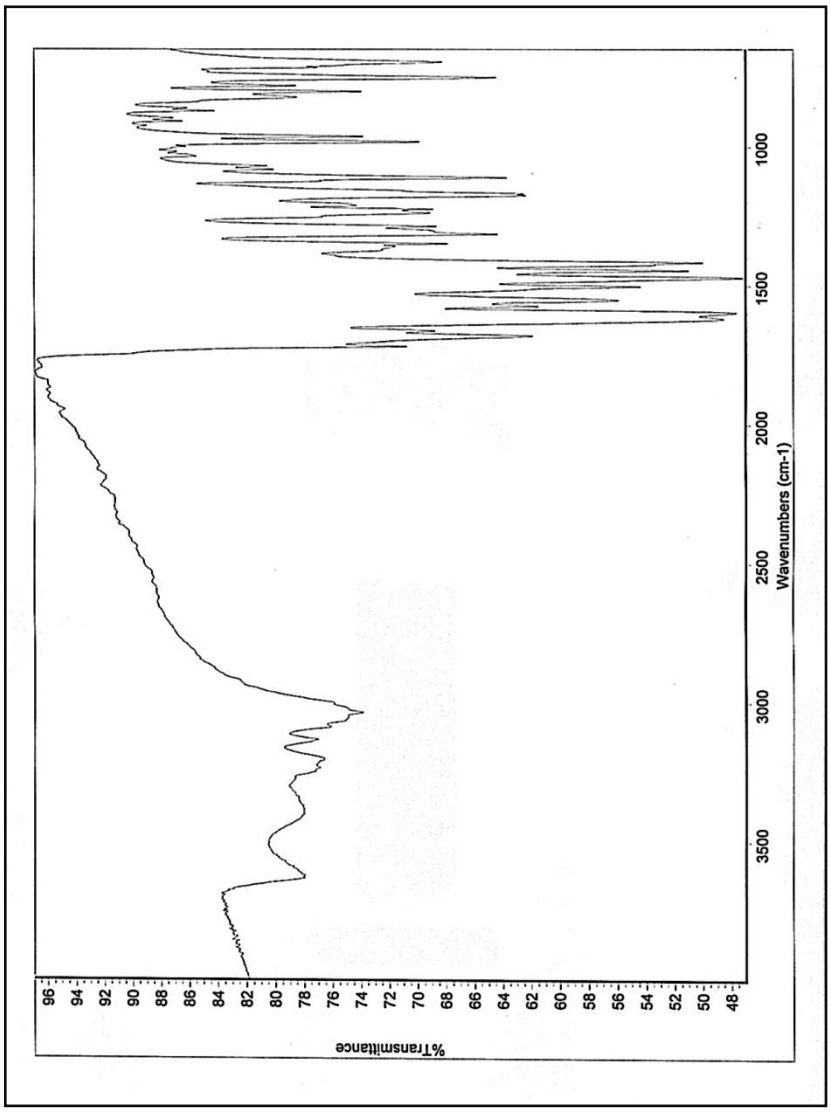

Figure A.26 IR spectrum of compound **163**

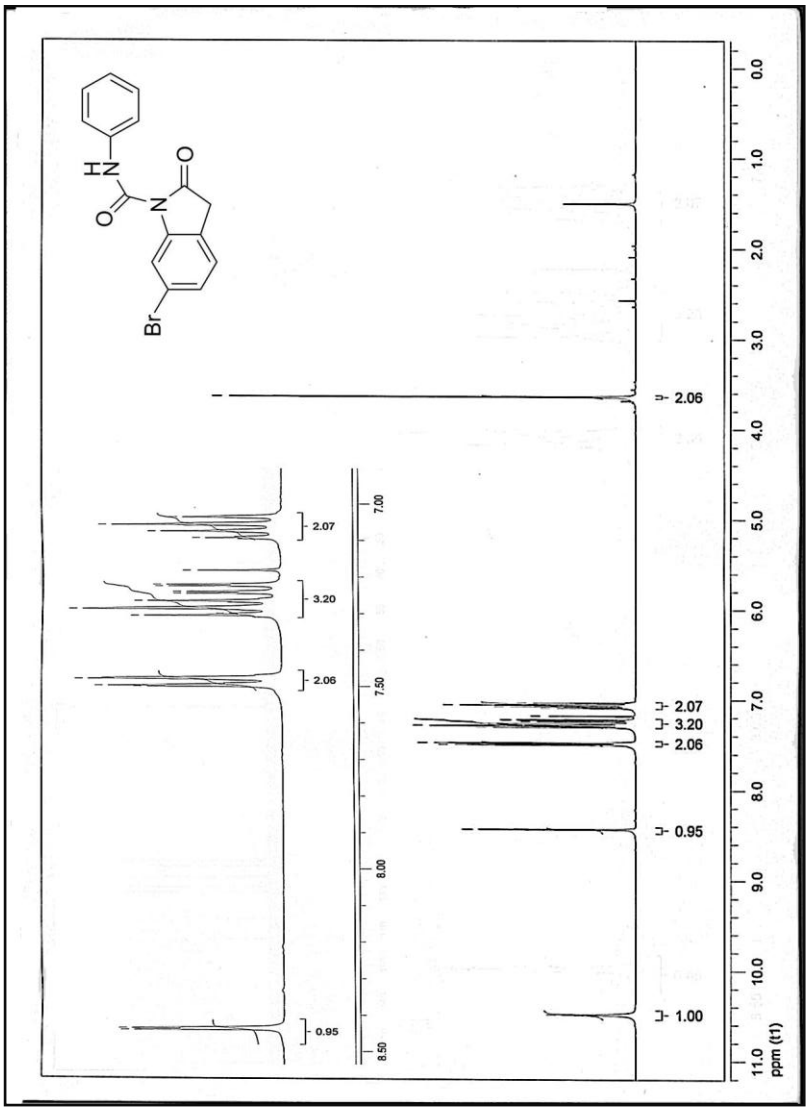

Figure A.27 ^{1}H-NMR spectrum of compound **161**

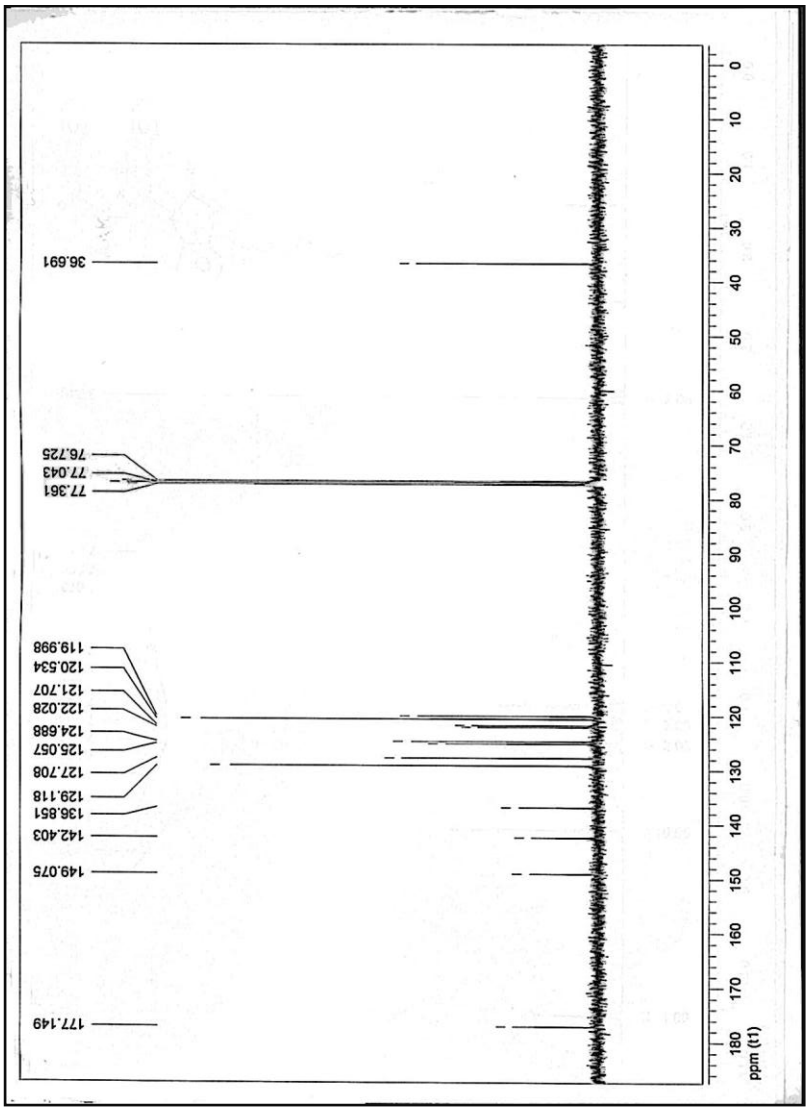

Figure A.28 ^{13}C-NMR spectrum of compound **161**

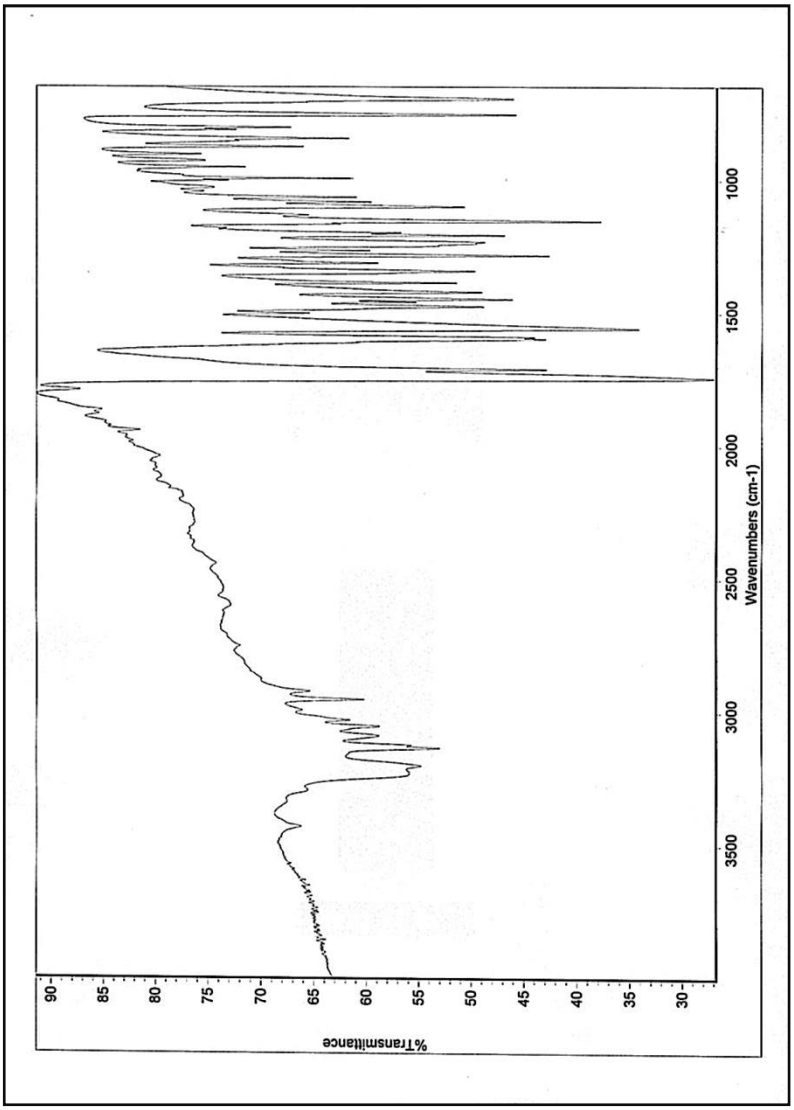

Figure A.29 IR spectrum of compound **161**

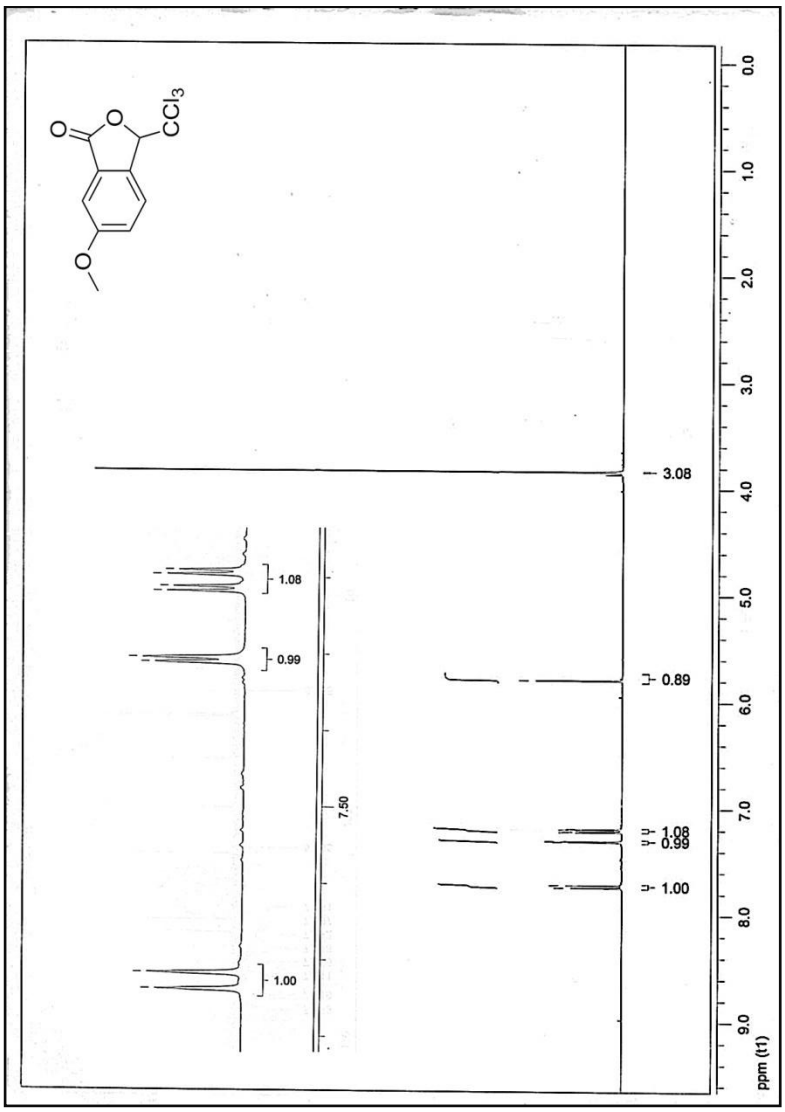

Figure A.30 ^{1}H-NMR spectrum of compound **122**

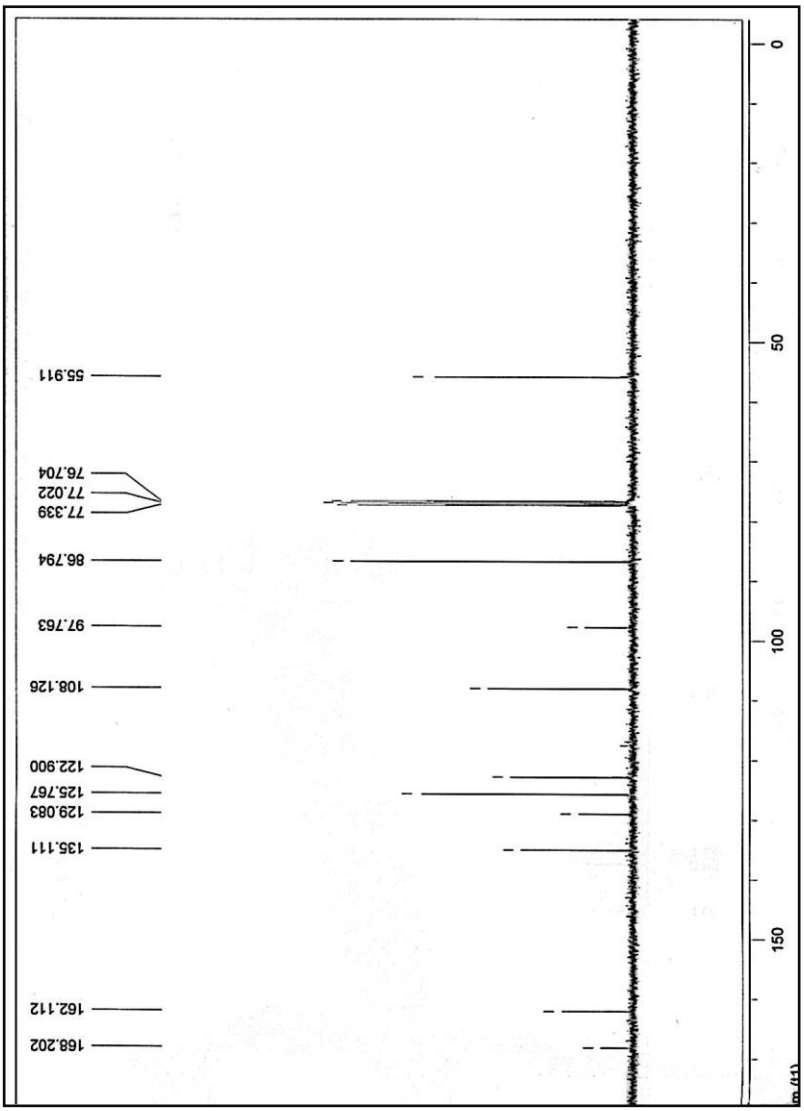

Figure A.31 ^{13}C-NMR spectrum of compound **122**

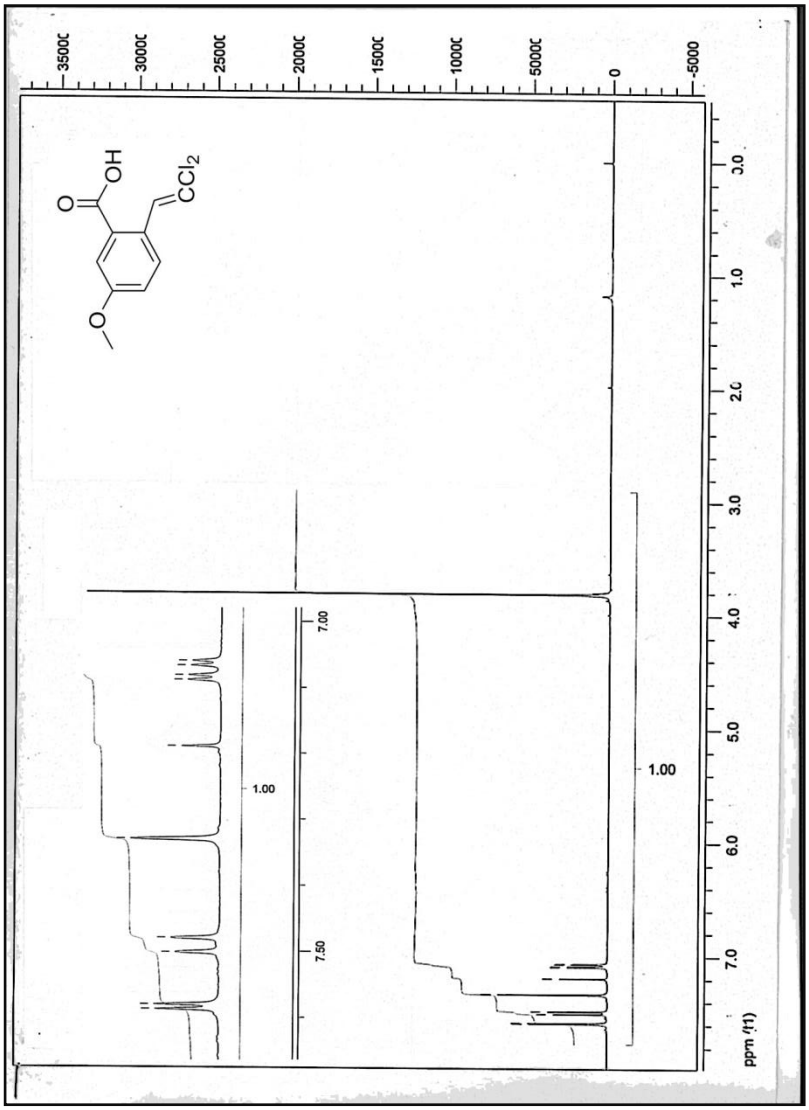

Figure A.32 ^{1}H-NMR spectrum of compound **123**

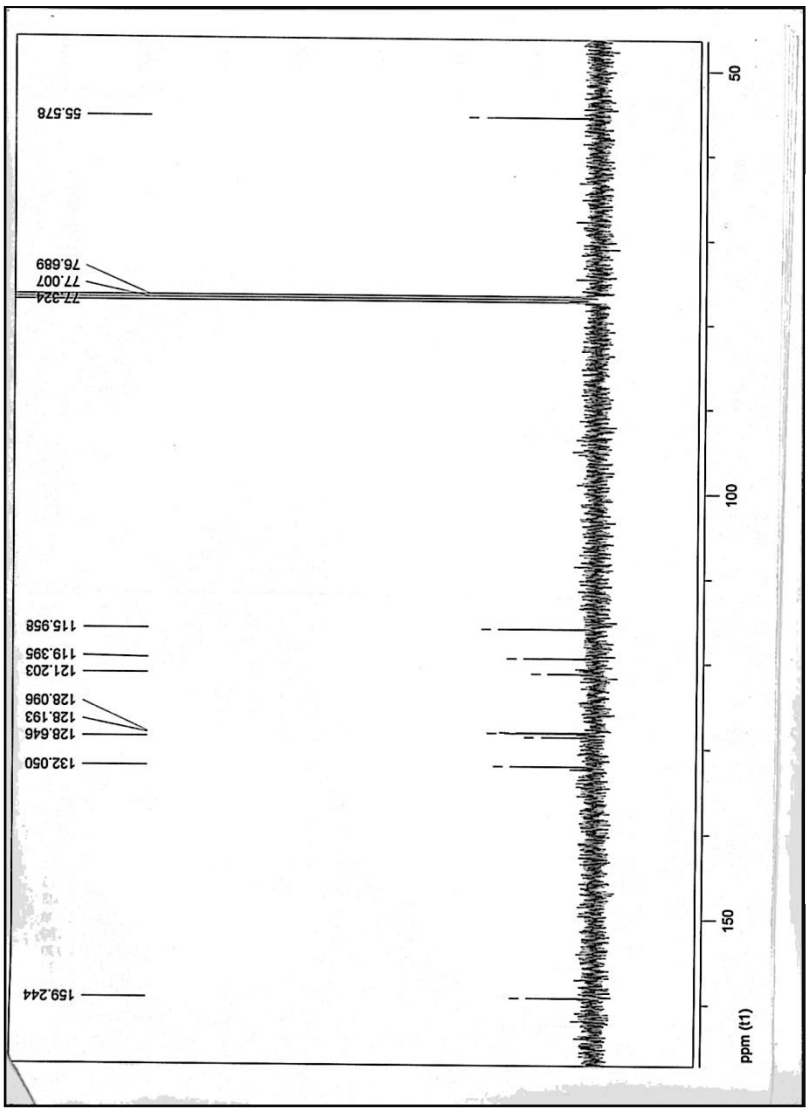

Figure A.33 ^{13}C-NMR spectrum of compound **123**

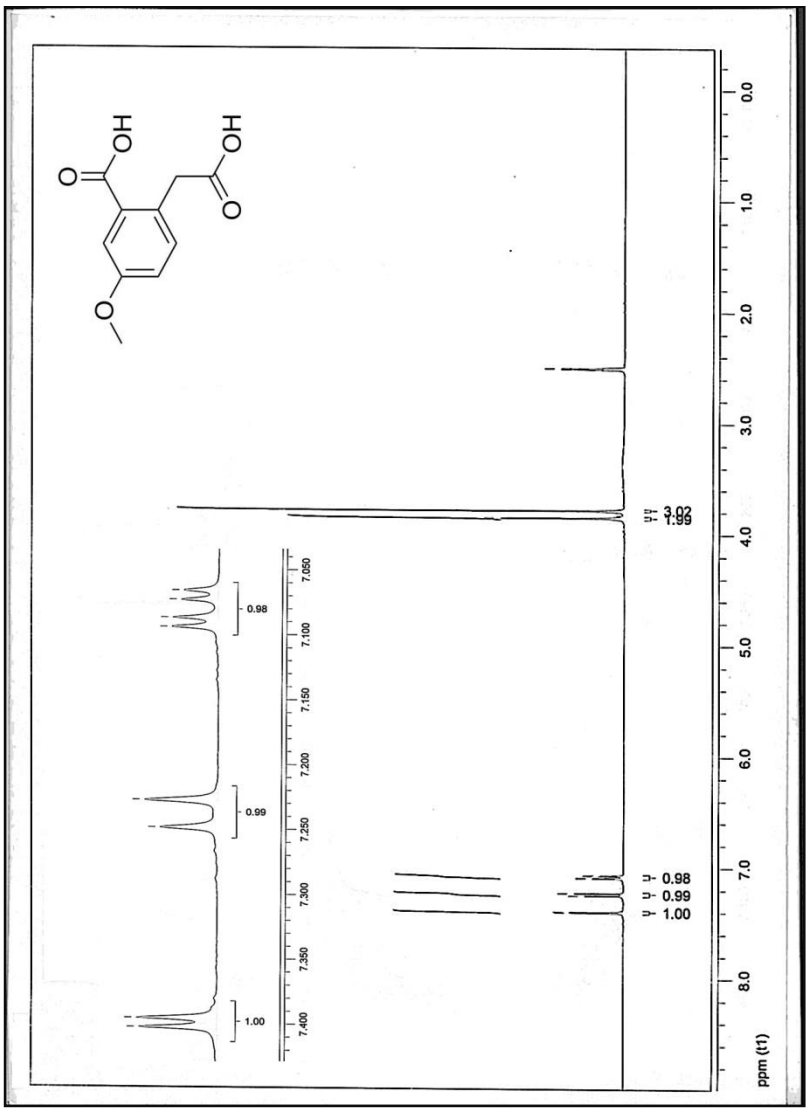

Figure A.34 ^{1}H-NMR spectrum of compound **125**

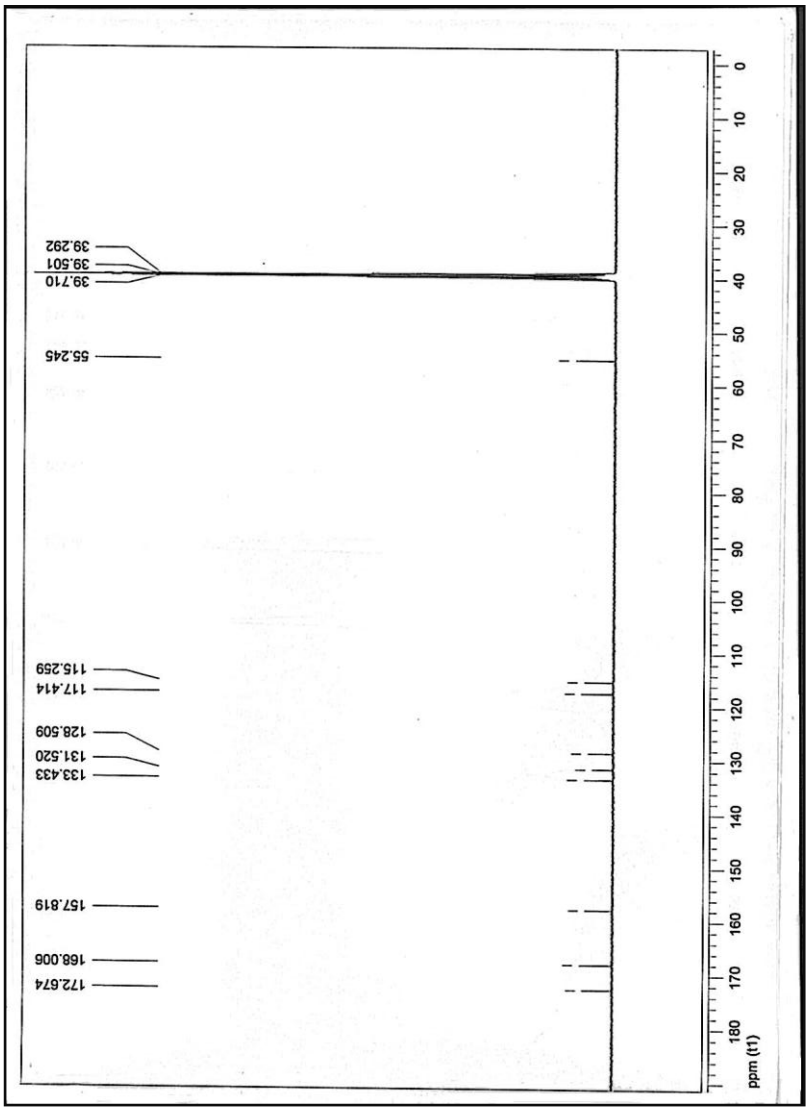

Figure A.35 ^{13}C-NMR spectrum of compound **125**

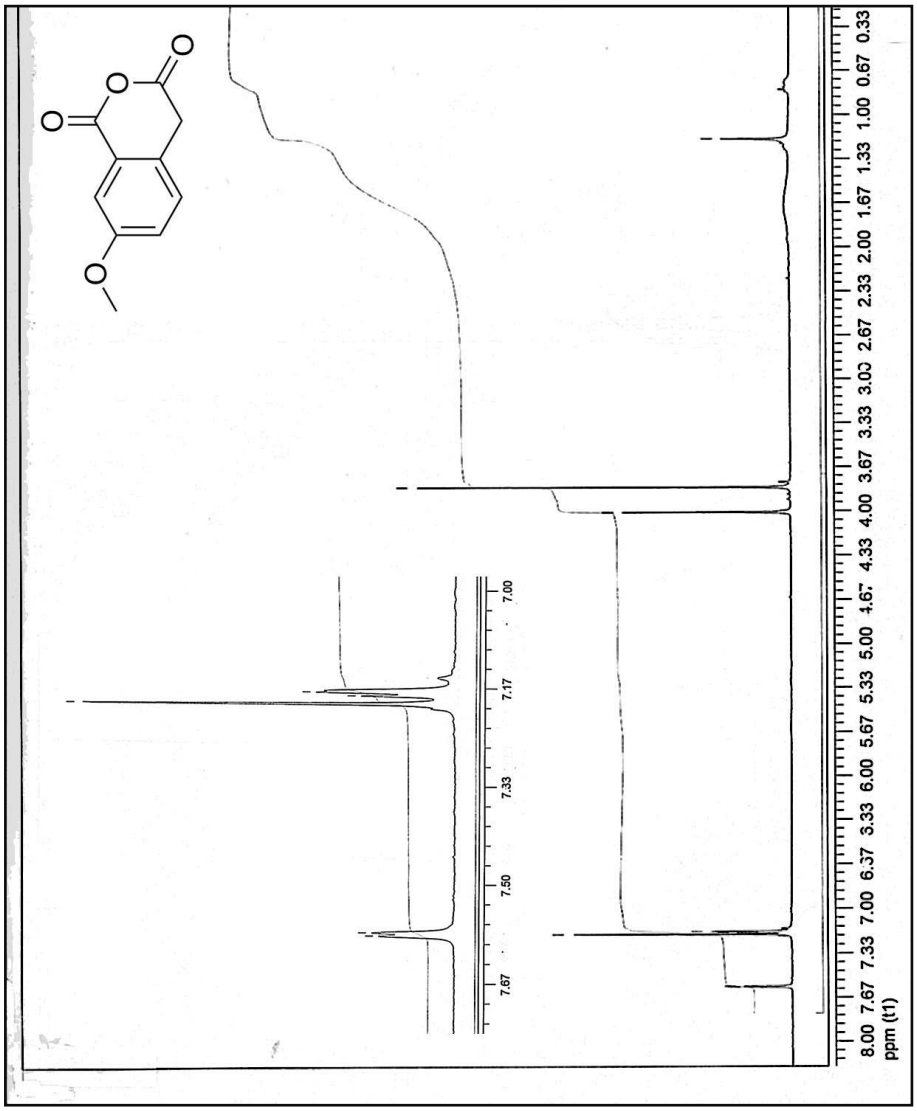

Figure A.36 ^{1}H-NMR spectrum of compound **133**

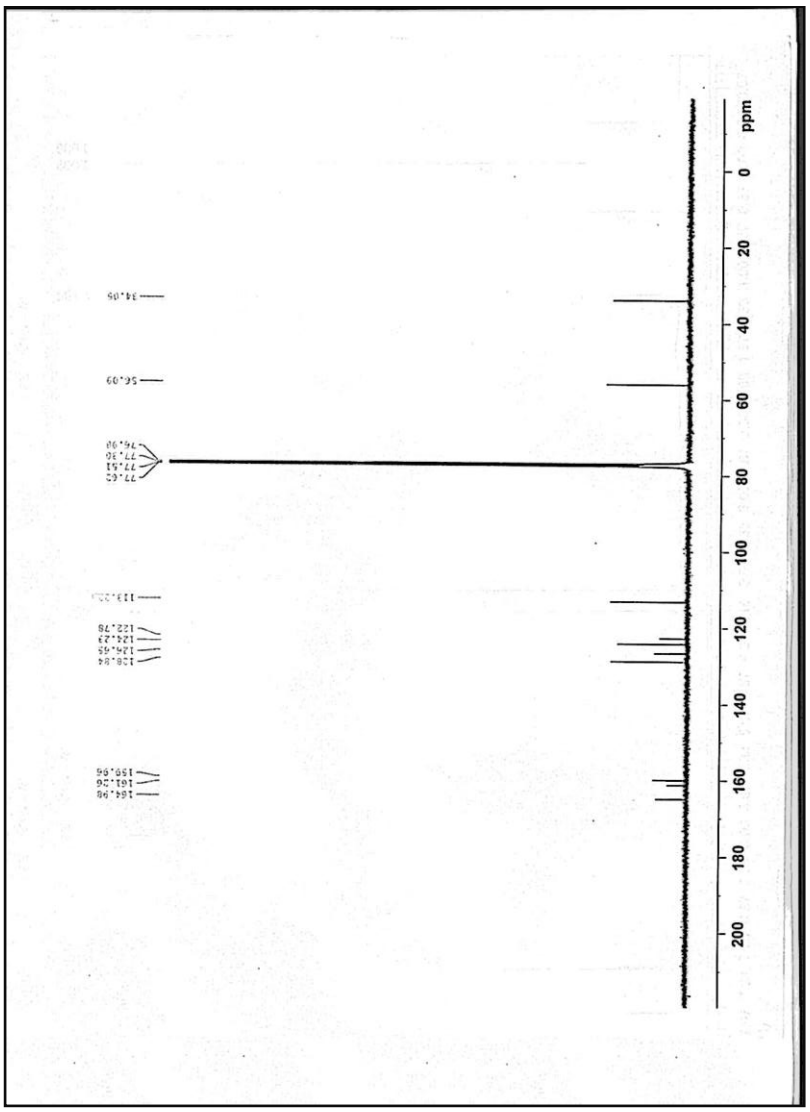

Figure A.37 ^{13}C-NMR spectrum of compound **133**

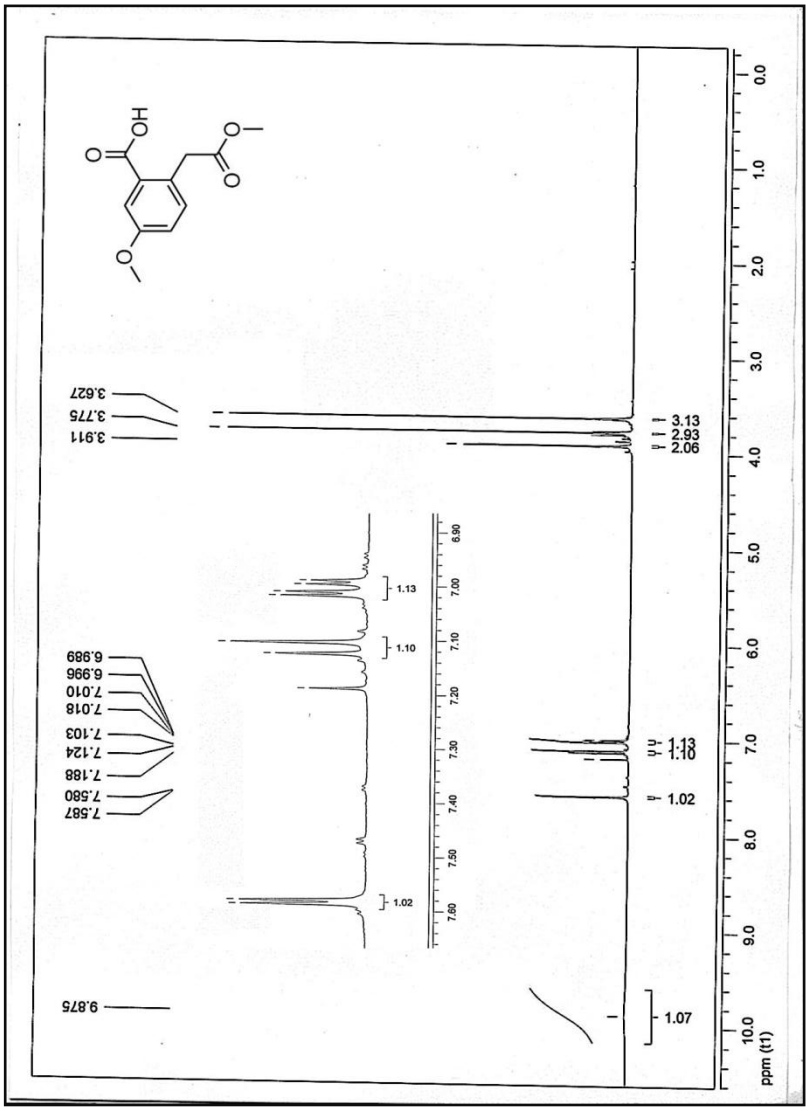

Figure A.38 ^{1}H-NMR spectrum of compound **137**

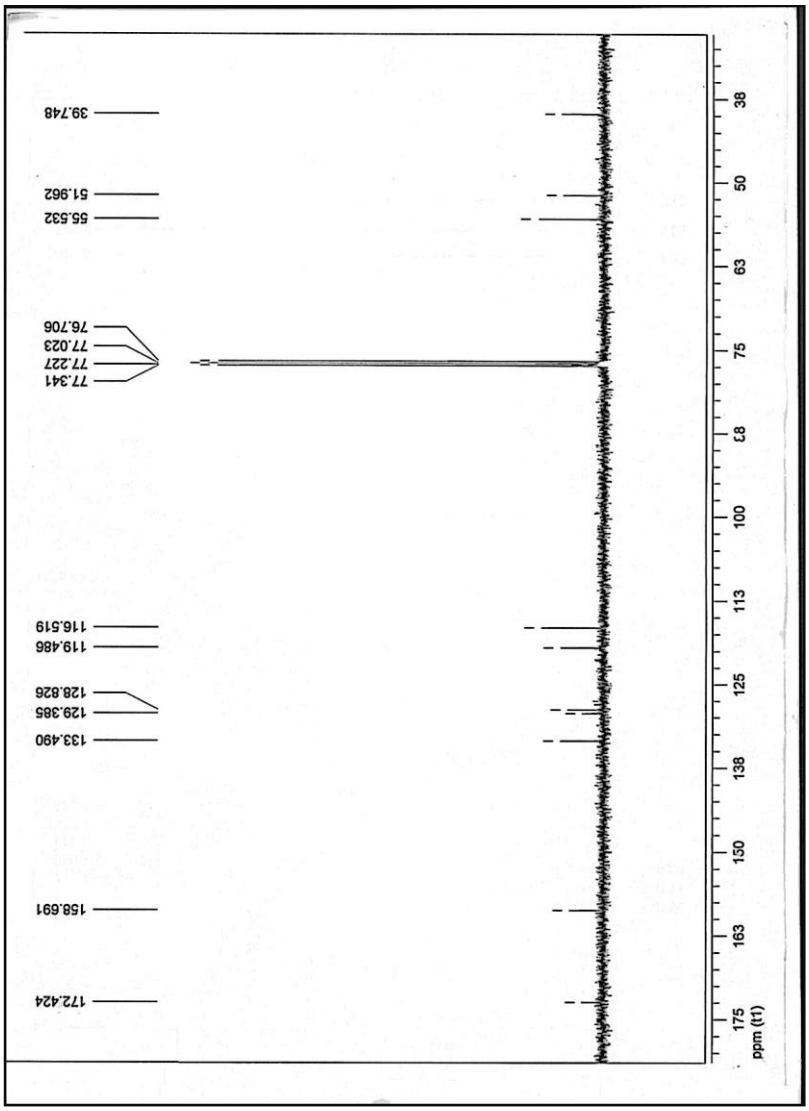

Figure A.39 ^{13}C-NMR spectrum of compound **137**

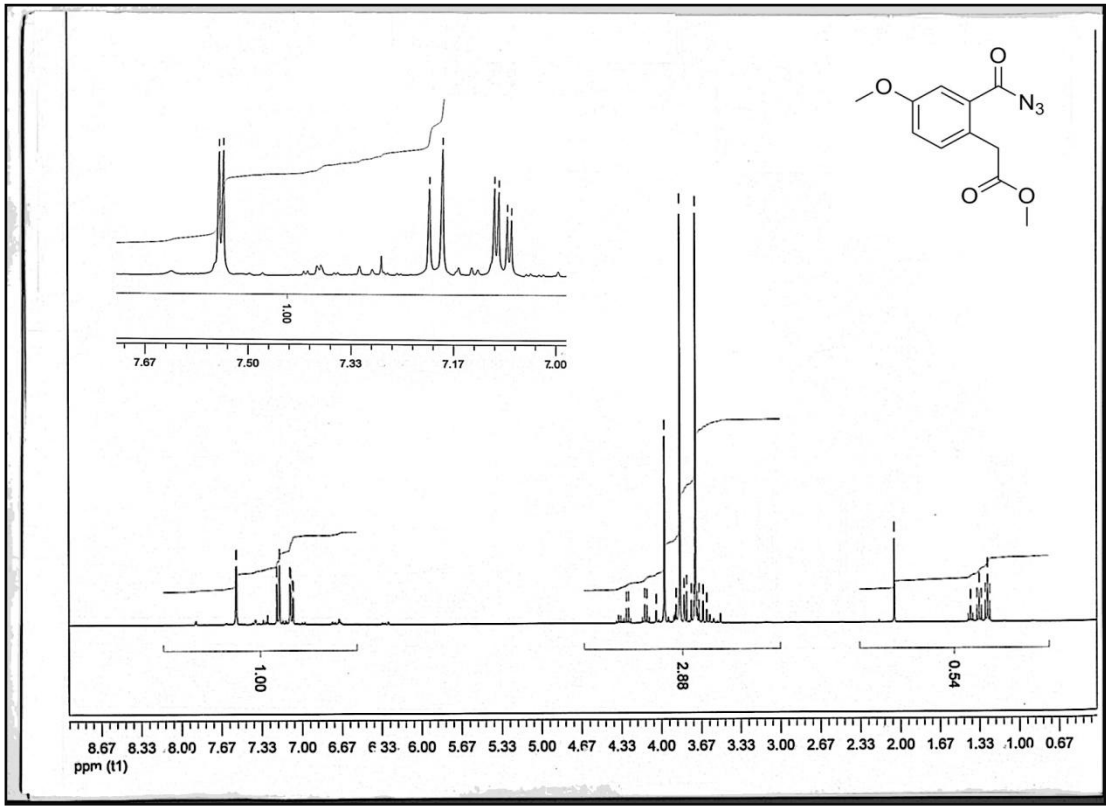

Figure A.40 ^{1}H-NMR spectrum of compound **150**

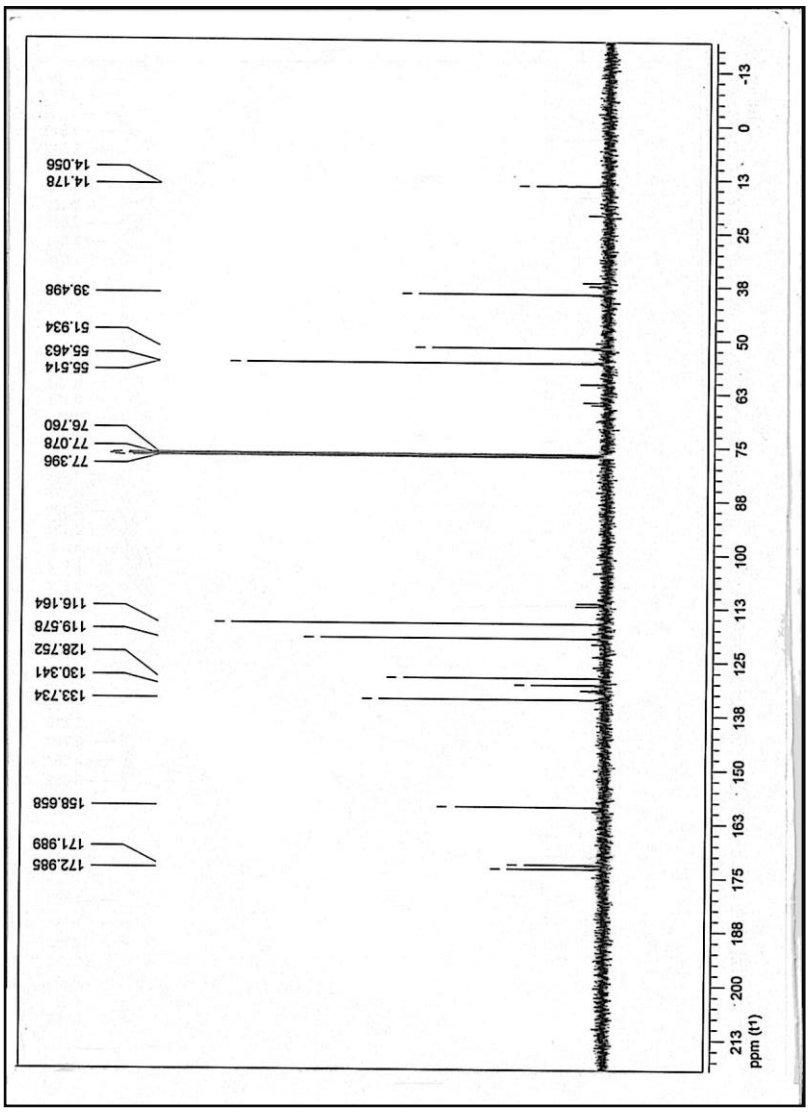

Figure A.41 ^{13}C-NMR spectrum of compound **150**

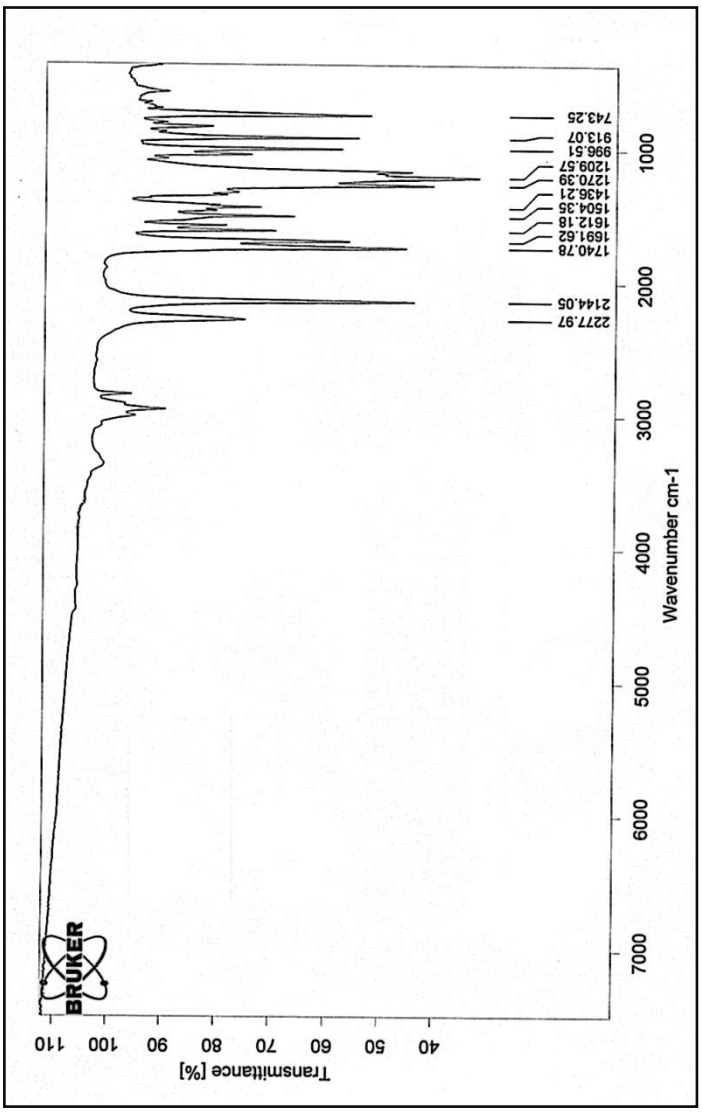

Figure A.42 IR spectrum of compound **150**

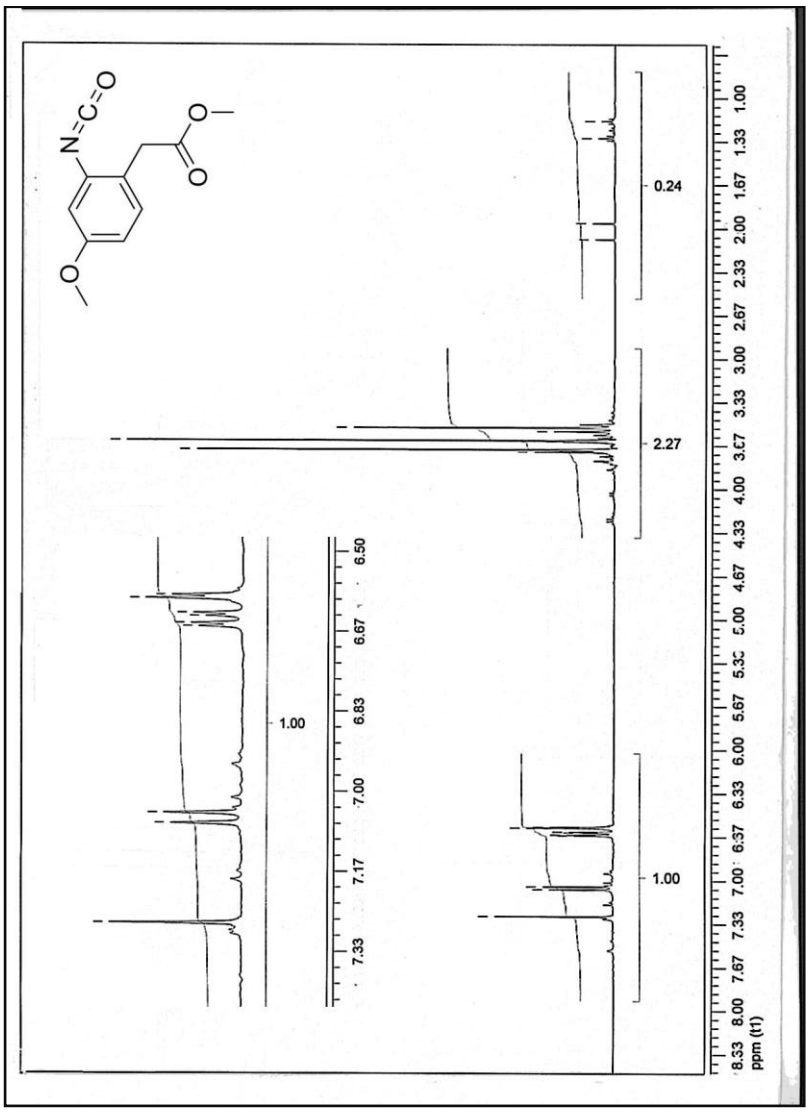

Figure A.43 ^{1}H-NMR spectrum of compound **153**

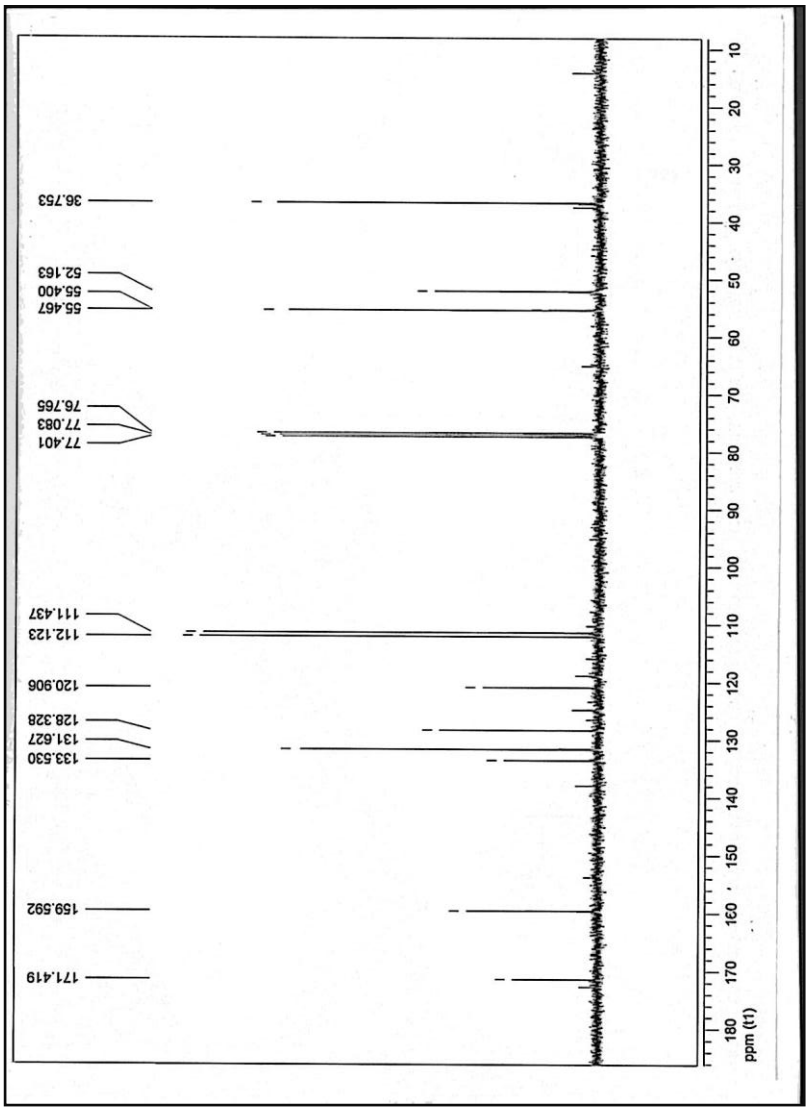

Figure A.44 ^{13}C-NMR spectrum of compound **153**

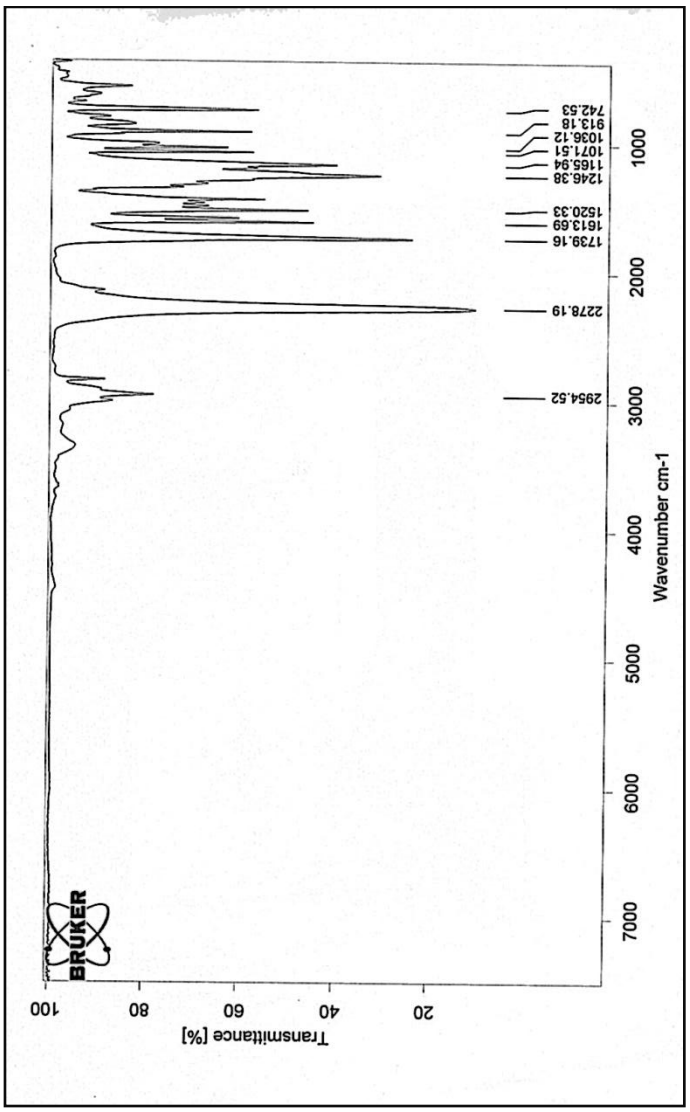

Figure A.45 IR spectrum of compound **153**

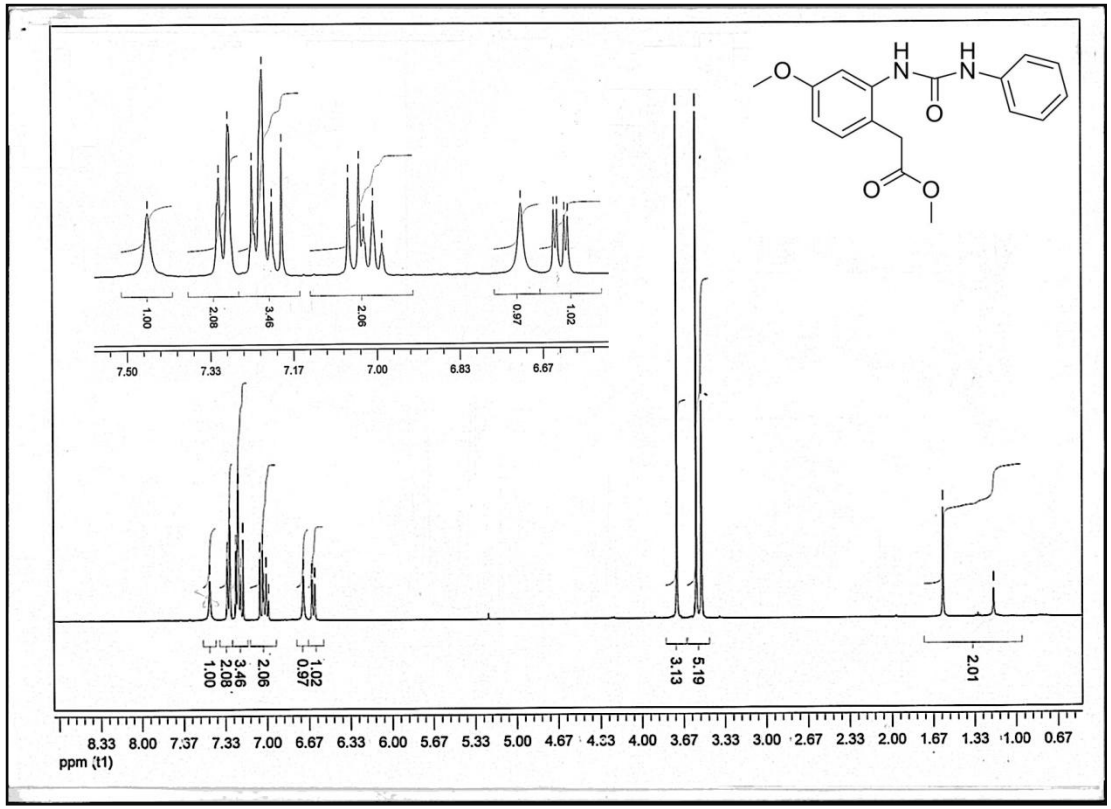

Figure A.46 ^{1}H-NMR spectrum of compound **156**

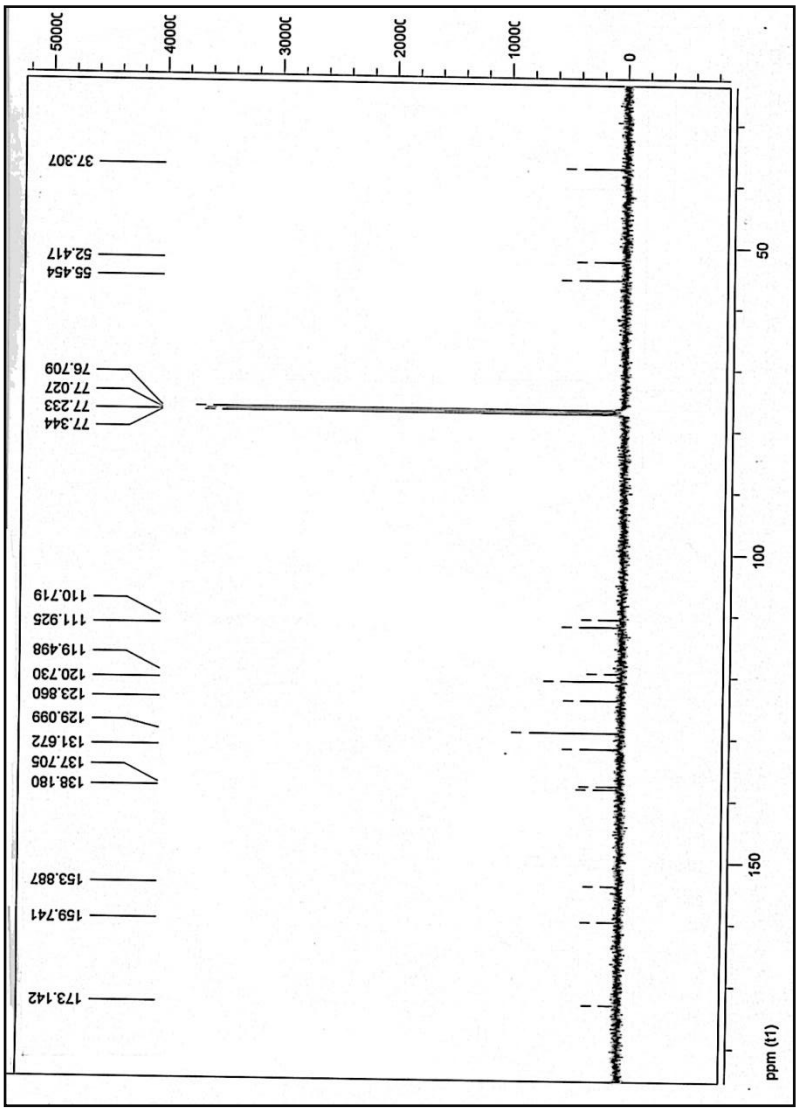

Figure A.47 ^{13}C-NMR spectrum of compound **156**

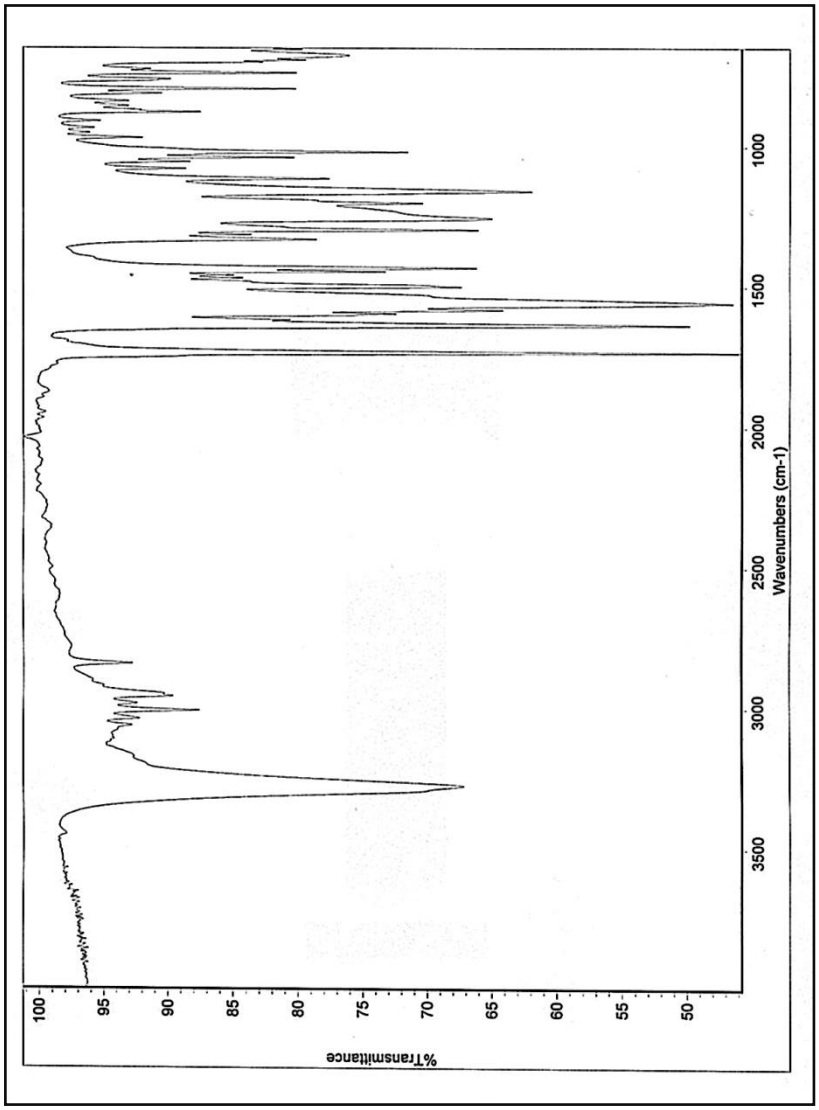

Figure A.48 IR spectrum of compound **156**

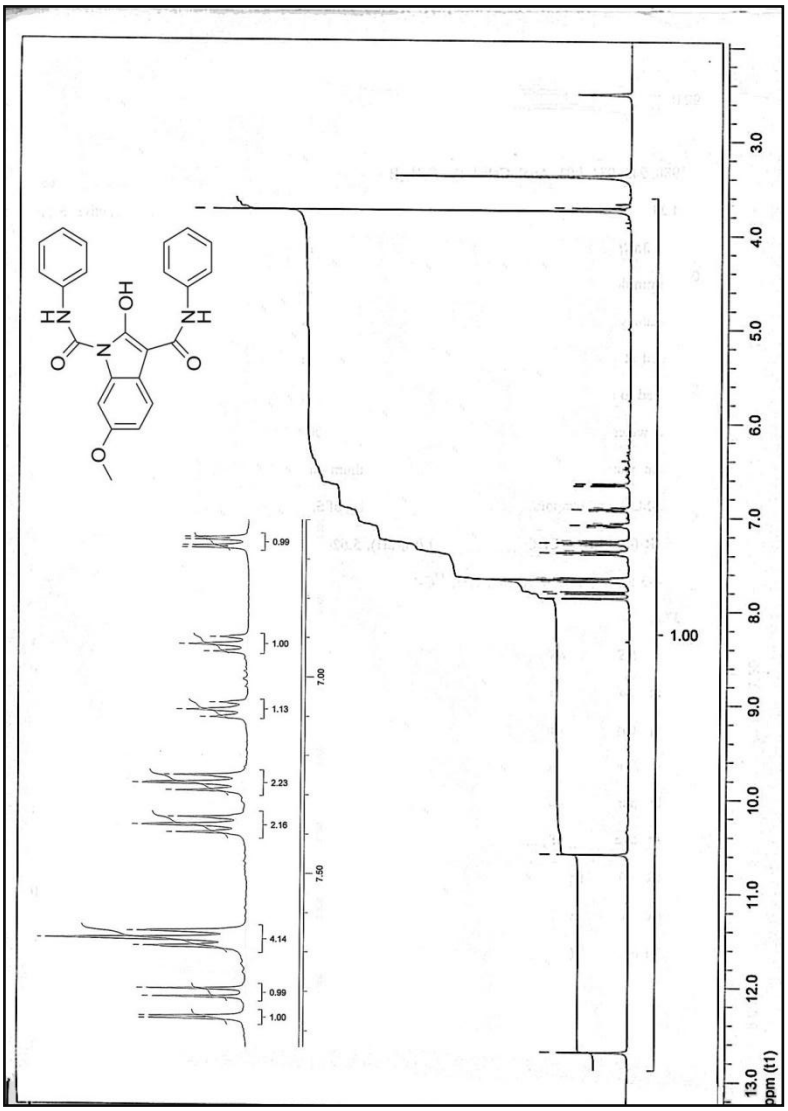

Figure A.49 ^{1}H-NMR spectrum of compound **166**

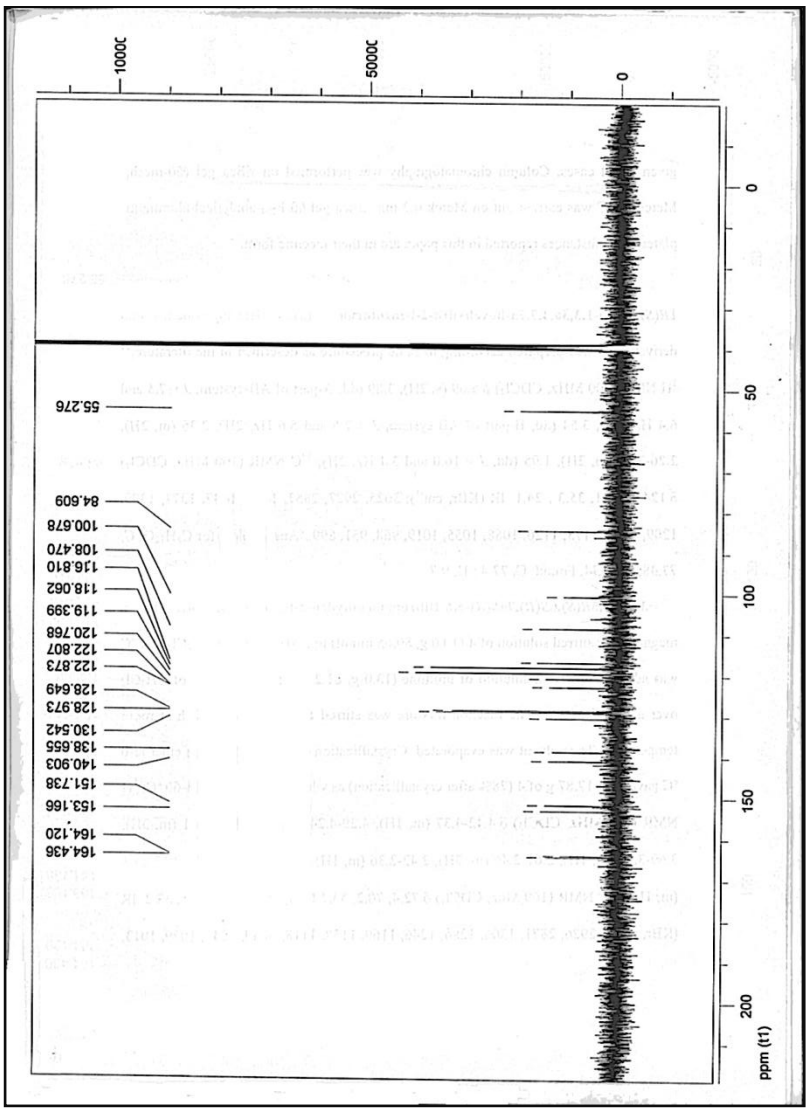

Figure A.50 ^{13}C-NMR spectrum of compound **166**

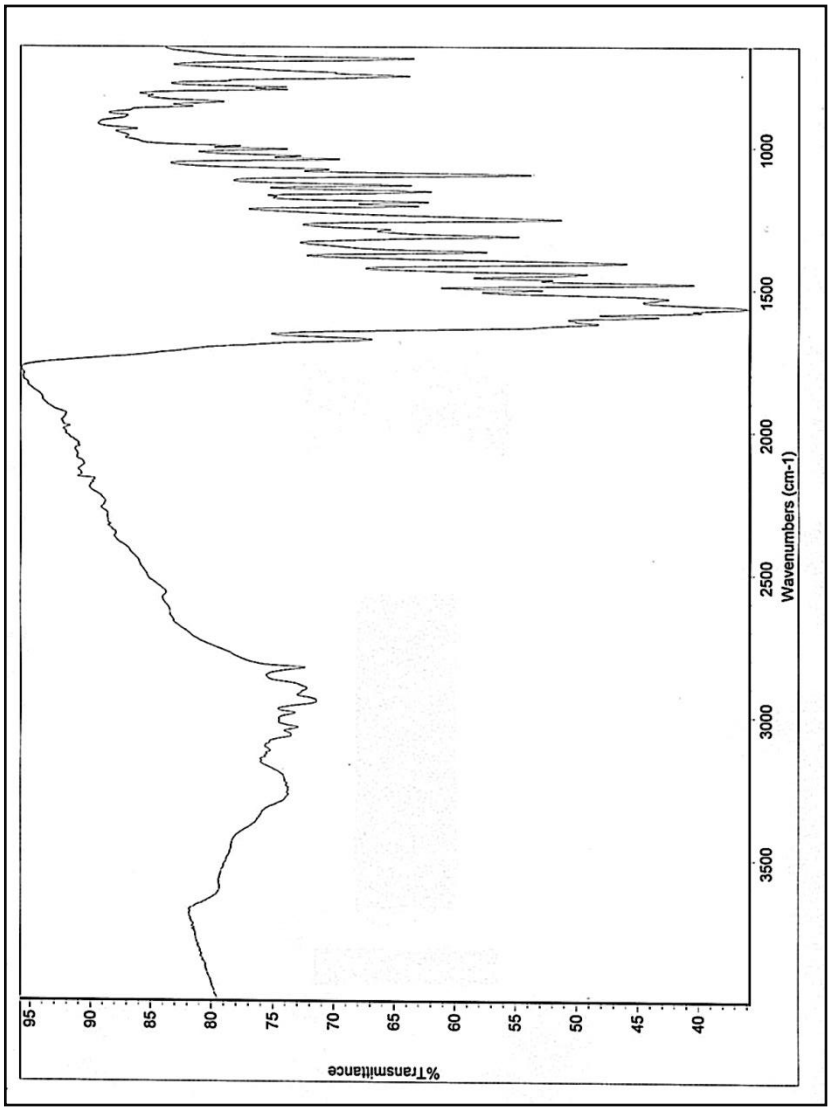

Figure A.51 IR spectrum of compound **166**

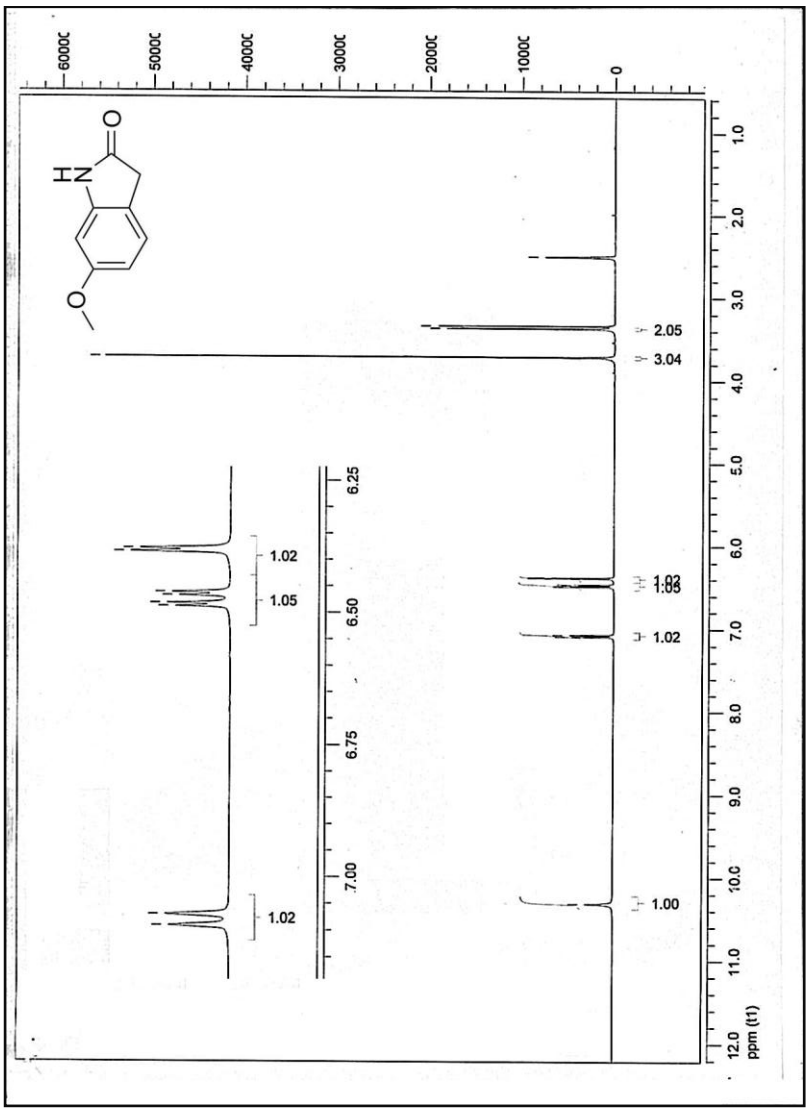

Figure A.52 ^{1}H-NMR spectrum of compound **167**

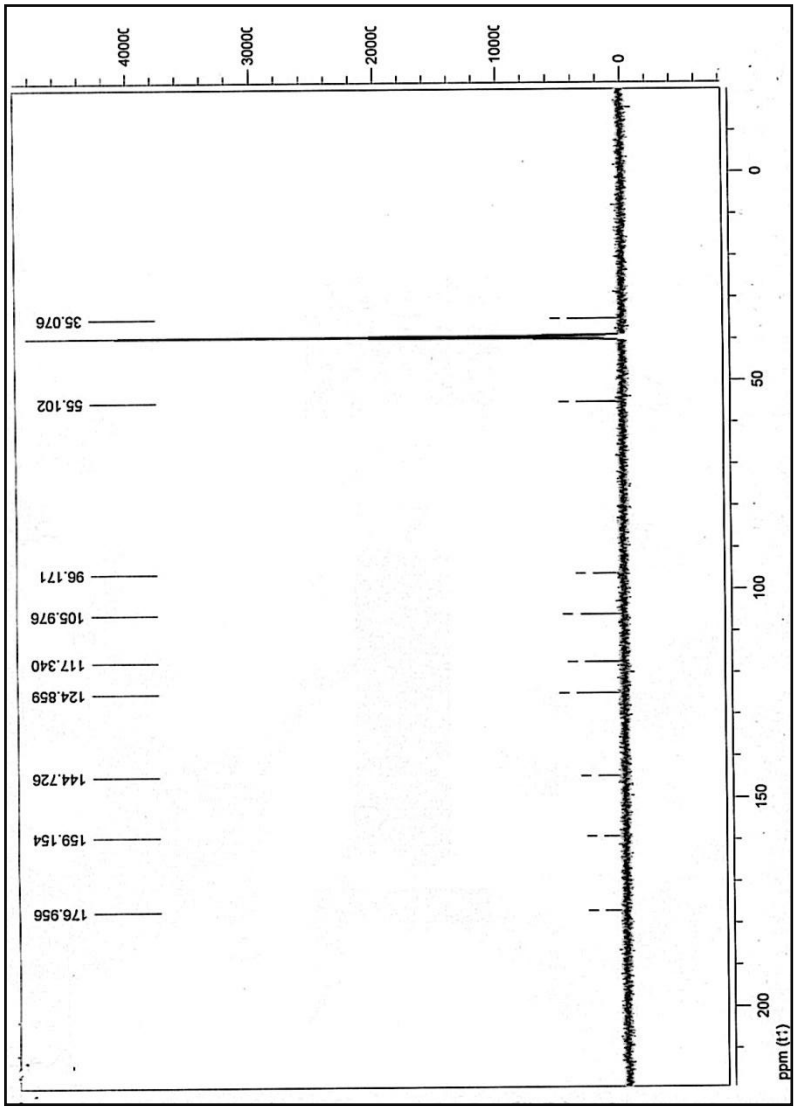

Figure A.53 ^{13}C-NMR spectrum of compound **167**

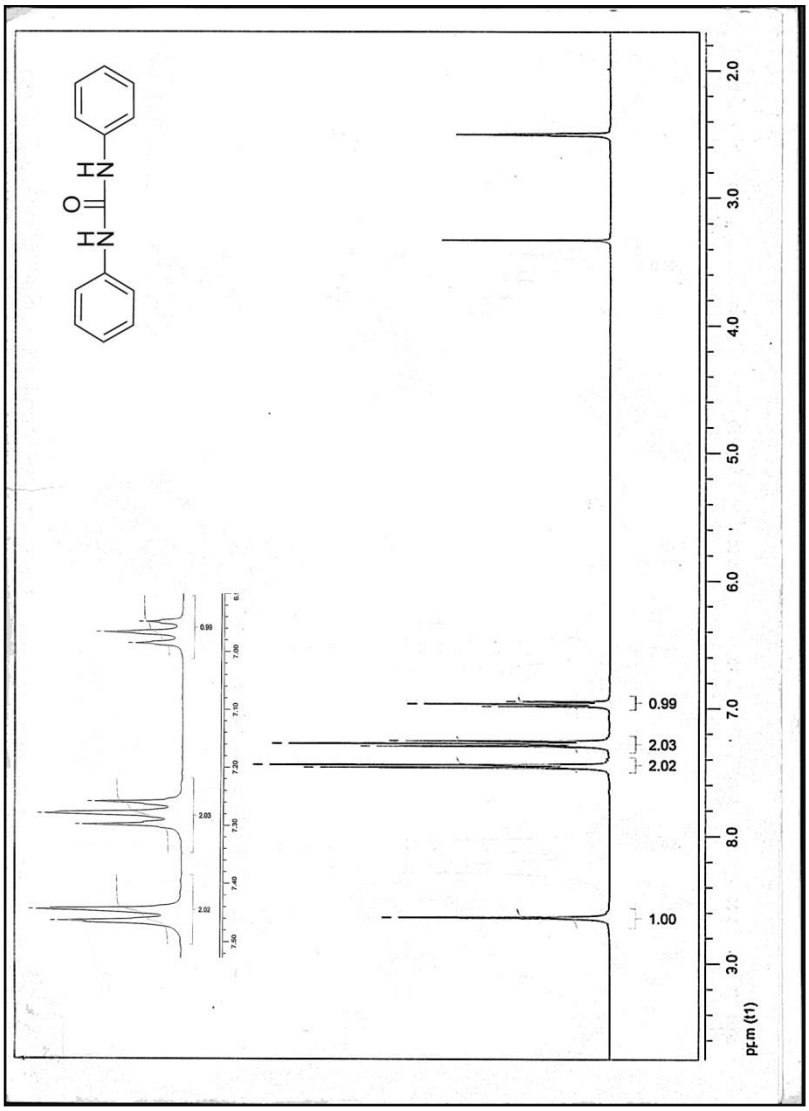

Figure A.54 ^{1}H-NMR spectrum of compound **169**

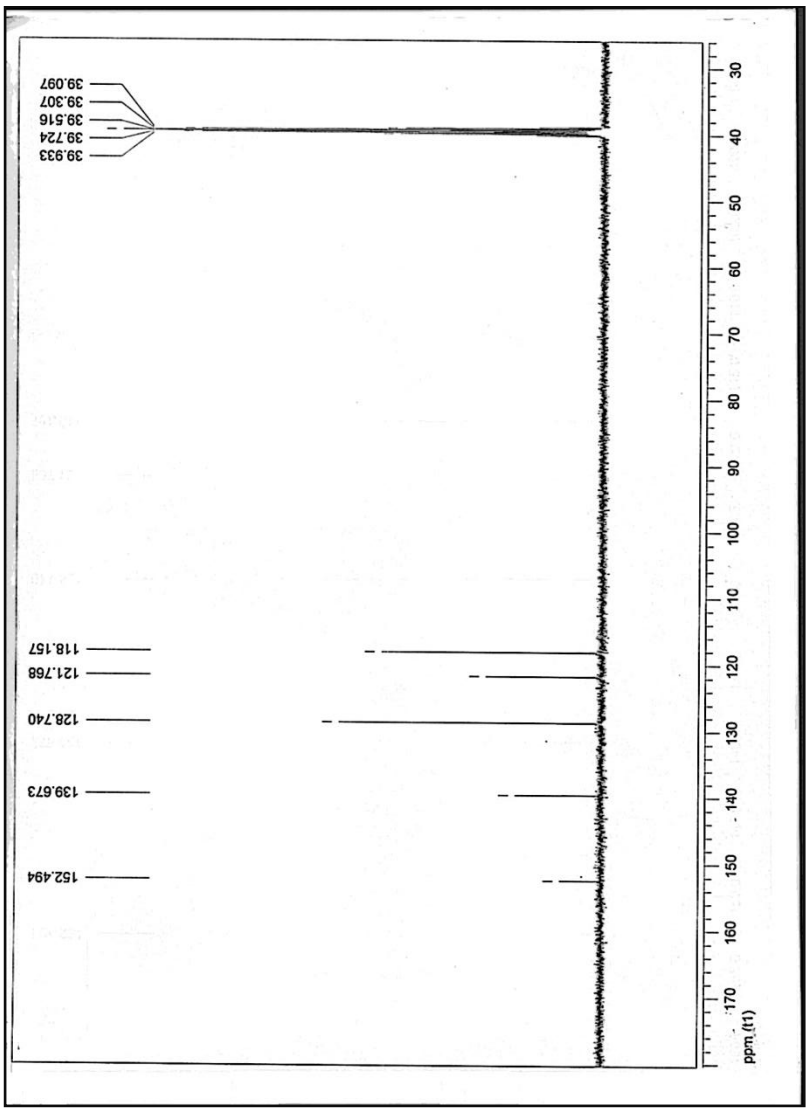

Figure A.55 ^{13}C-NMR spectrum of compound **169**

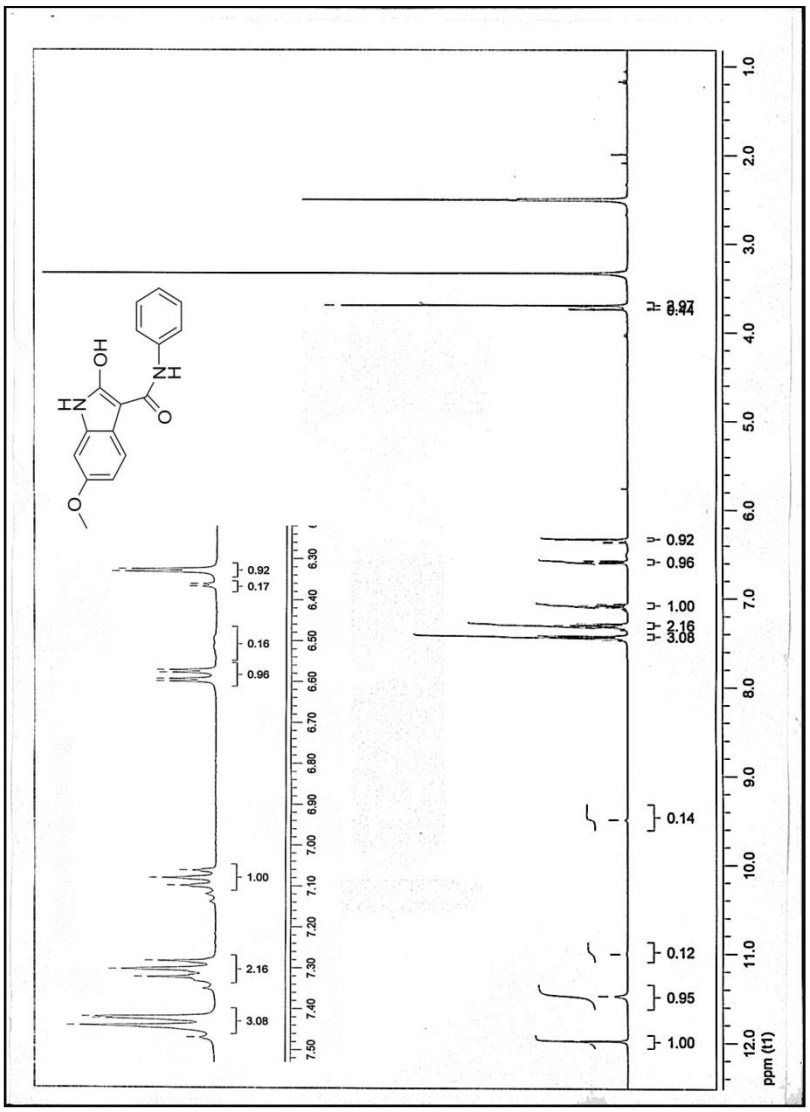

Figure A.56 ^{1}H-NMR spectrum of compound **168**

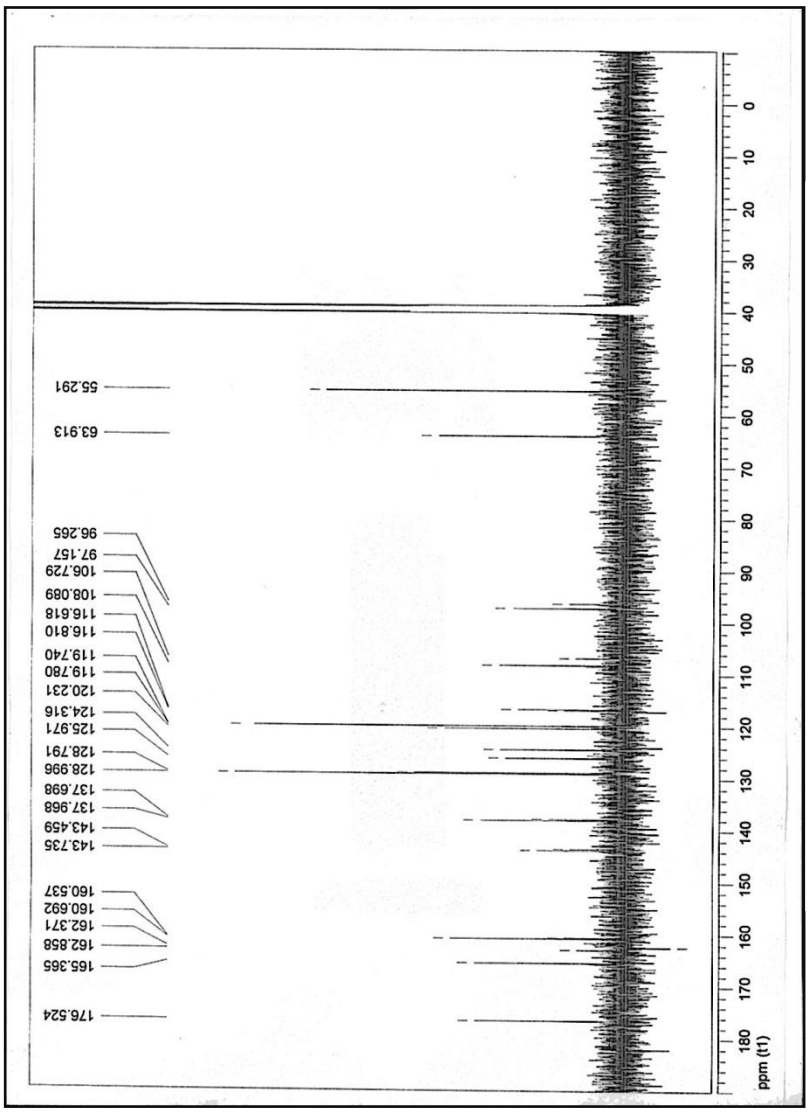

Figure A.57 ^{13}C-NMR spectrum of compound **168**

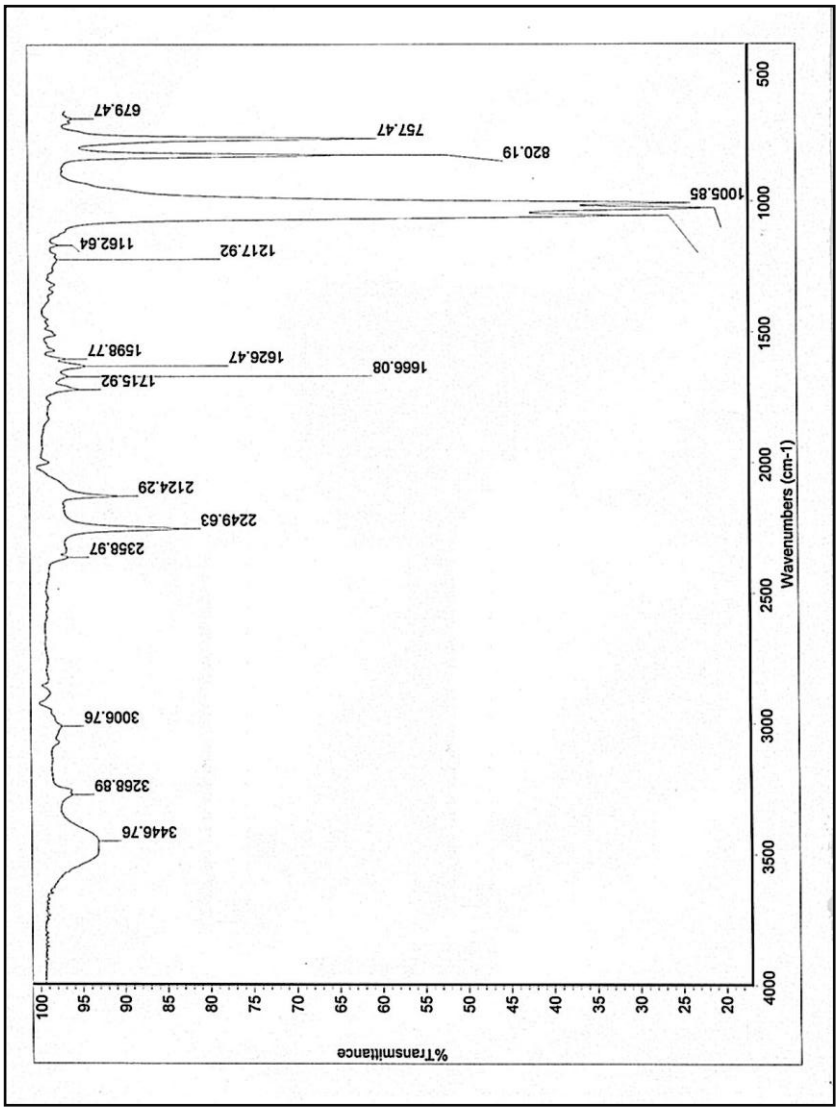

Figure A.58 IR spectrum of compound **168**

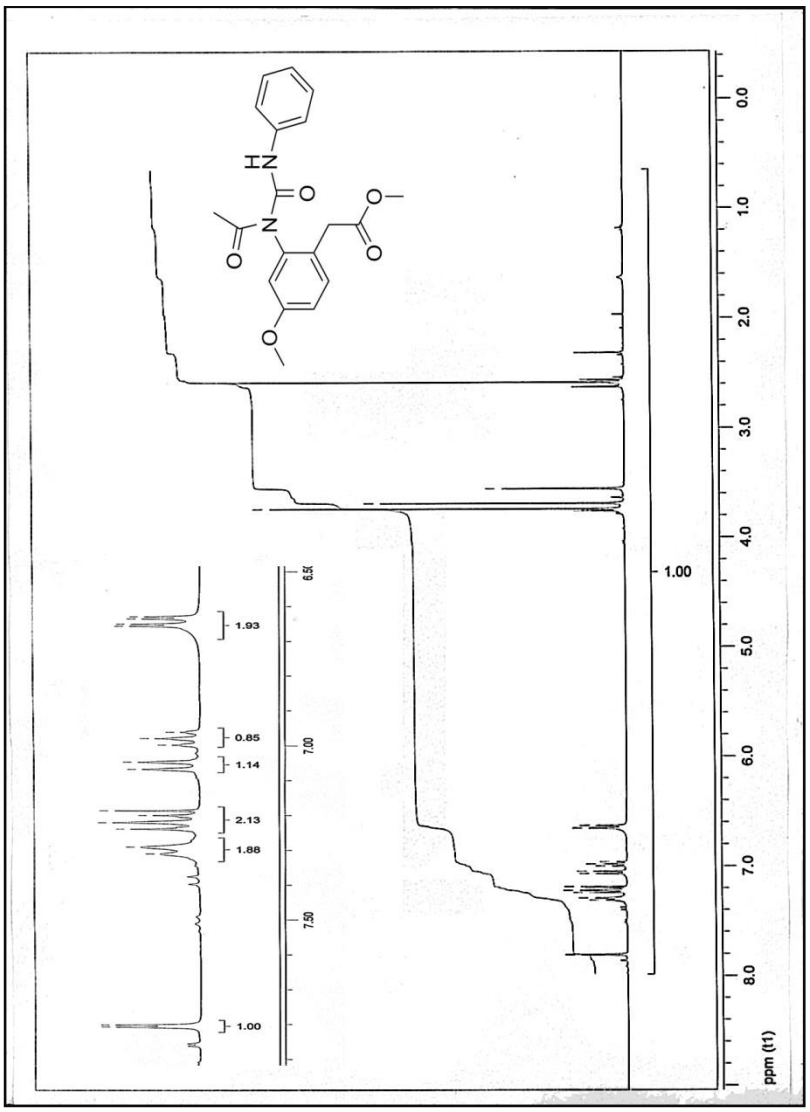

Figure A.59 ^{1}H-NMR spectrum of compound **172**

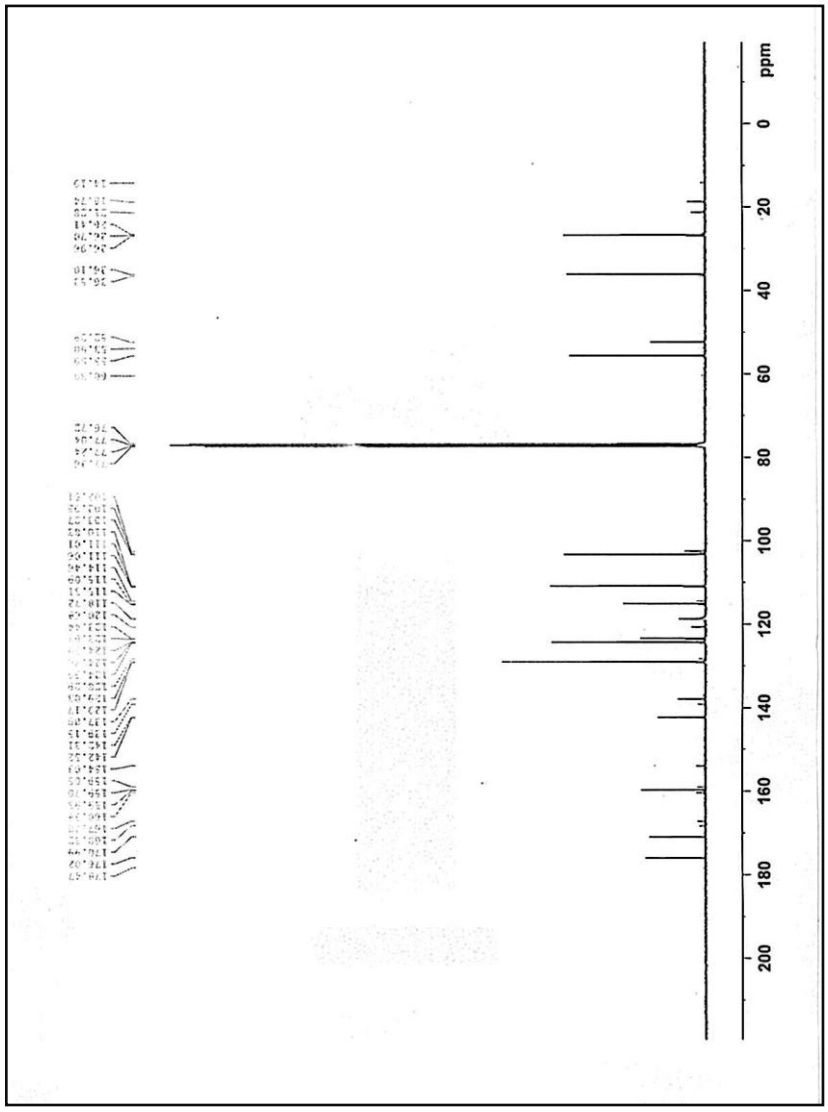

Figure A.60 ^{13}C-NMR spectrum of compound **172**

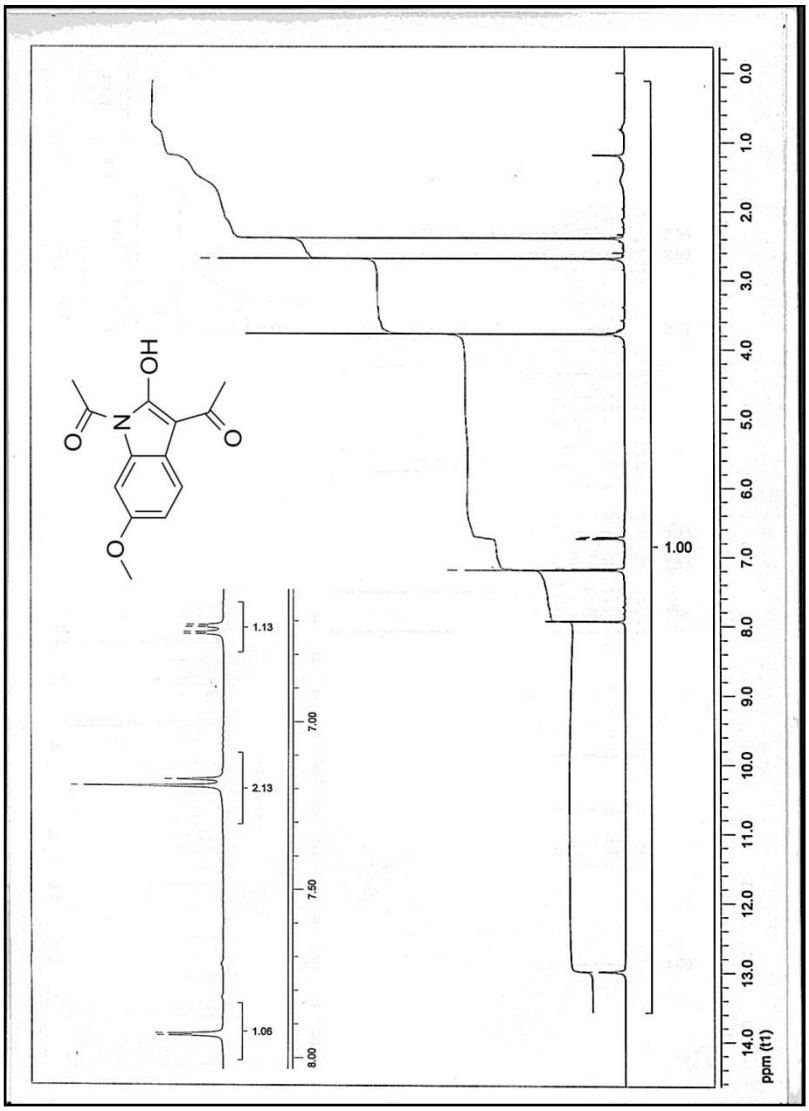

Figure A.61 ^{1}H-NMR spectrum of compound **173**

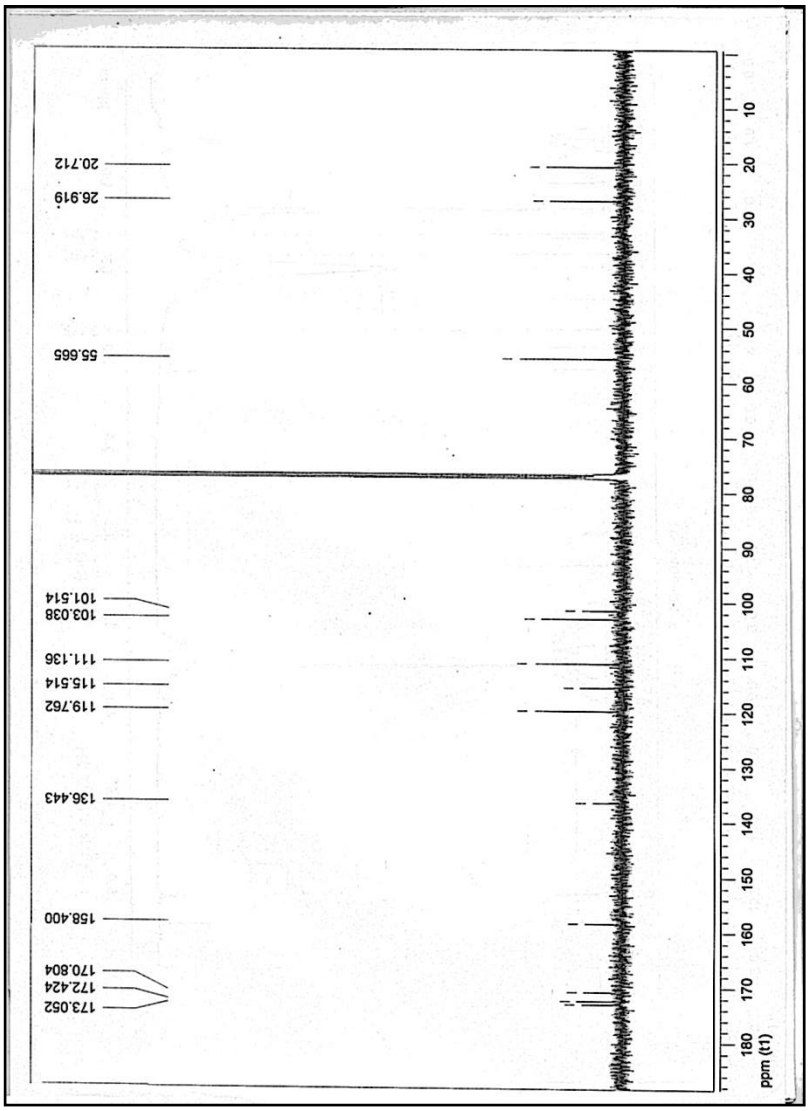

Figure A.62 ^{13}C-NMR spectrum of compound **173**