# DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR ISOQUINOLONE AND ISOINDOLINONE DERIVATIVES

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

BY

BERK MÜJDE

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

JULY 2010

Approval of the thesis:

**DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR ISOQUINOLONE AND ISOINDOLINONE DERIVATIVES**

submitted by **BERK MÜJDE** in partial fulfillment of the requirements for the degree of **Master of Science in Department of Chemistry, Middle East Technical University** by,

Prof. Dr. Canan Özgen _____
Dean, Graduate School of **Natural and Applied Sciences**

Prof. Dr. İlker Özkan _____
Head of Department, **Chemistry Dept.**

Prof. Dr. Metin Balcı _____
Supervisor, **Chemistry Dept., METU**

**Examining Committee Members:**

Prof. Dr. Cihangir Tanyeli _____
Chemistry Dept., METU

Prof. Dr. Metin Balcı _____
Chemistry Dept., METU

Prof. Dr. Özdemir Doğan _____
Chemistry Dept., METU

Assist. Prof. Dr. Raşit Çalışkan _____
Chemistry Dept., S.Demirel University

Assist. Prof. Dr. Gani Koza _____
Chemistry Dept., Ahi Evran University

**Date:** 13.07.2010

**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: Berk Müjde

Signature:

# ABSTRACT

DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR ISOQUINOLONE AND ISOINDOLINONE DERIVATIVES

Müjde, Berk

M.Sc., Department of Chemistry

Supervisor: Prof. Dr. Metin Balcı

July 2010, 146 pages

Due to the wide range of physiological activities, heterocycles containing nitrogen and oxygen have always attracted the interest of chemists.

The objective of this research is to develop new synthetic routes to the synthesis of isoquinolone and isoindolinone derivatives starting from 2-(2-carboxyethyl)benzoic acid and homophthalic acid, respectively.

The half ester produced from 2-(2-carboxyethyl)benzoic acid was an important key compound for the synthesis of new isoquinolone derivatives which are expected to be biologically active. The corresponding acyl azides and isocyanates were generated

which might be used as a precursors to construct a variety of isoquinolone derivatives. Transformation of acyl azides into urea derivatives followed by ring-closure under the basic conditions provided isoquinolones.

Bromo- and methoxyhomophthalic acid derivatives were synthesized to increase in variety of isoindolinone derivative. Then corresponding anhydrides were generated to further reactions for synthesis of isoindolinone derivatives. Surprisingly, tetrazolinone derivatives are also formed by 1,3 dipolar cycloaddition. Whole products were conscientiously purified and characterized.

In addition, the similar methodology which was used for the synthesis of isoquinolone derivatives, was applied to 2-(carboxymethyl)furan-3-carboxylic acid to synthesize new nitrogen and oxygen containing heterocycles.

**Keywords:** Isoquinolone, isoindolinone, tetrazolinone, 1,3 dipolar cycloaddition.

# ÖZ

İZOKİNOLON VE İZOİNDOLİNON TÜREVLERİNİN SENTEZİ İÇİN YENİ SENTETİK YÖNTEMLERİNİN GELİŞTİRİMESİ

Müjde, Berk

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Balcı

Temmuz 2010, 146 sayfa

Azot ve oksijen içeren pek çok heterosiklik bileşik, fizyolojik aktivite gösterdiklerinden dolayı her zaman kimyacıların ilgisini çekmiştir.

Bu çalışmanın amacı, sırasıyla 2-(2-karboksietil)benzoik asit ve homofitalik asitten başlayarak izokinolon ve izoindolon türevlerinin sentezi için yeni sentetik yöntemlerin geliştirilmesidir.

2-(2-Karboksietil)benzoik asitten sentezlenen yarı ester, biyolojik aktivite göstermesi beklenen yeni izokinolon türevinin sentezinde önemli anahtar bileşik olmuştur. Bir çok

izokinolon türevlerinin oluşturulmasında öncül olabilecek açil azid ve izosiyanat türevleri sentezlendi. Üre türevlerinin sentezinden sonra, heterosiklik yapılar bazik şartlar altında halka kapanması reaksiyonu sonucu oluşturuldu.

Homofitalik asitten başlayarak, brom ve metoksihomofitalik asit türevleri, izoindolinon türevlerinin çeşitliliğini arttırmak için sentezlendi. Daha sonra ilgili anhidritlerin azid ile tepkimesinde 1,3-dipolar katılma sonucunda beklenmeyen tetrazolinon türevlerinin oluştuğu gözlendi. Ürünler saflaştırıldı ve karakterize edildi.

Bunlara ek olarak, izokinolon türevlerinin sentezinde kullanılan benzer metotlar, yeni azot ve oksijen içeren heterosiklik yapıların sentezi için 2-(karboksimetil)furan-3-karboksilik asite uygulandı.

**Anahtar kelimeler:** İzokinolon, izoindolinon, tetrazolinon, 1,3 dipolar katılma.

*To my family and lovely Senty…*

# ACKNOWLEDGEMENTS

I wish to express my sincere appreciation and thanks to my supervisor Prof. Dr. Metin Balcı for his guidance, valuable advices, moral support and for enlightening my professional and academic vision throughout my study.

I would like to express my sincere thanks to Dr. Sevil Özcan for her endless support, guidance, patience and motivation throughout this work.

I would like to express my sincere thanks to Assist. Prof. Dr. Gani Koza for his valuable guidance, discussion and support.

I would like to thank to NMR specialists Seda Karayılan and Zehra Uzunoglu for the NMR experiments.

I would like to express my great thanks to all the members of SYNTHOR Research Group especially to Burak, Alper, Melek, Merve, Çağatay, Kadir, Benan, Dilem, Zeynep and Yasemin for their friendship and helps.

I would like to thank to my friends Can Nebigil, Bahadır Doğan, Tamer Tezel, Cansel Işıklı for their precious friendship.

I wish to express my appreciation to the academic staff of METU Department of Chemistry for their professional support and guidance to the students of Department of Chemistry.

TUBITAK is gratefully acknowledged for the financial support via grant no 108M168.

Finally, I would like to give the biggest thanks to my family who have made everything possible for me with their love, affection, support and guidance throughout my whole life. The completion of this study would not have been possible without them.

# TABLE OF CONTENTS

# LIST OF TABLES

TABLES

# LIST OF FIGURES

FIGURES

# LIST OF ABBREVIATIONS

**Bzl**: Benzyl

**DBU**: 1,8-Diazabicyclo[5.4.0]undec-7-ene

**NBS**: *N*-Bromosuccinimide

**AIBN**: Azobisisobutyronitrile

**THF**: Tetrahydrofuran

**NMR**: Nuclear magnetic resonance

**IR**: Infrared

**J**: Coupling constant

**Hz**: Hertz

**ppm**: Parts per million

**mg**: miligram

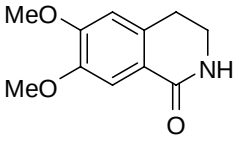
**mmol**: milimol

# CHAPTER 1

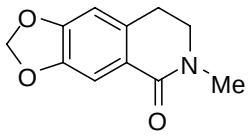
# INTRODUCTION

## 1.1 Isoquinolones

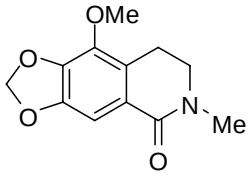
The isoquinolones are the member of alkaloids found in plants only in small amounts.[1] It is the structural backbone in naturally occurring alkaloids including dorianine **1**, coryaldine **2**, N-methylcoryaldine, and its 3,4-dihydro analog hydroxyhydrastinine, thalflavine **3**.[2-4] These alkaloids are principally isolated from *hernandiaceae, monimiaceae and ranunculaceae.*[5]




**dorianine (1)**




**N-methylcoryldine (2)**



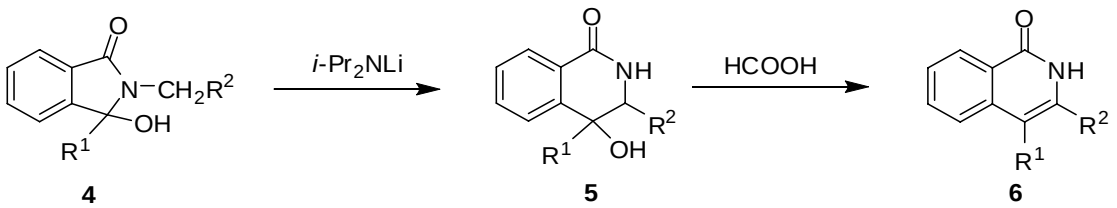

**thalflavine (3)**

The substituted isoquinolones are used as key structure in organic synthesis based on their stability and relative accessibility.[6] As a starting material in the total synthesis of natural alkoloids, isoquinolones are fascinating from the synthetic point of view.

The skeleton of isoquinolones which is biogenetically derived from the amino acid phenylalanine shows biomimetic characteristics.[8] It has been found that the substituted isoquinolones are the derivatives of highly effective antagonists of 5-HT3,[9] 5-6T$_3$,[10] glycoprotein IIb[11] and tachykinin[12] receptors. Antidepressant,[13] analgesic,[14] anti-inflammatory,[15] and hypolipidemic,[16] characteristics of substituted isocarbostyrils have also been found.

### 1.1.1 The Synthesis of Isoquinolones

In the beginnig of the century, Gabriel and Colman synthesized isoquinolone derivative **6** by ring enlargement process starting from phtalimide derivative **4** and following reaction with strong acid.[17] This rection is known as Gabriel-Colman Synthesis as shown in Scheme 1.

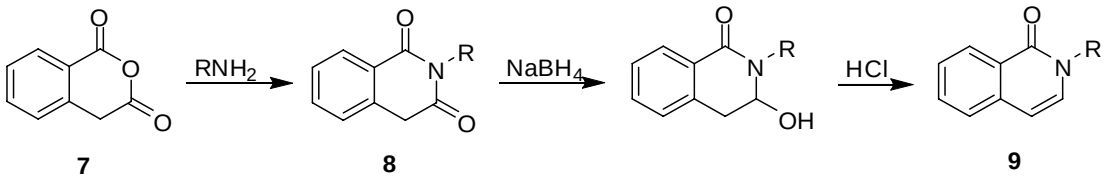



**4** **5** **6**

$R^1$= Ar, $R^2$= 4-$MeOC_6H_4$

**Scheme 1**

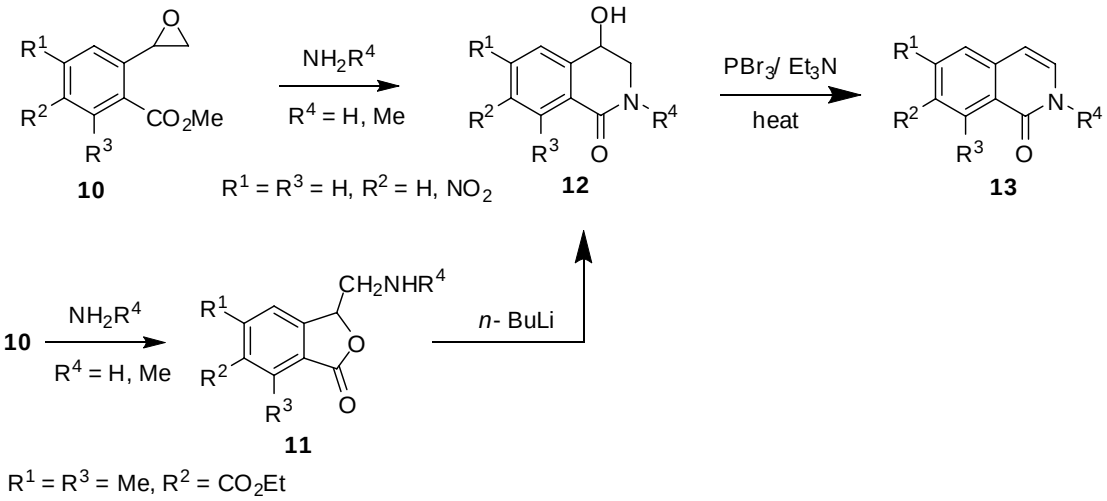
Substitution of heteroatom (oxygen to nitrogen) is one of the methods for the synthesis of isoquinolone derivatives. Gardner *et al.* have synthesized isoquinoline-1,3(*2H*,*4H*)-dione **8** by condensing homophthalic anhydride **7** with amine.[18] Reducing of **8** to 3-hydroxy derivatives followed by dehydration gave **9** as shown in Scheme 2.[19]




**7** **8** **9**

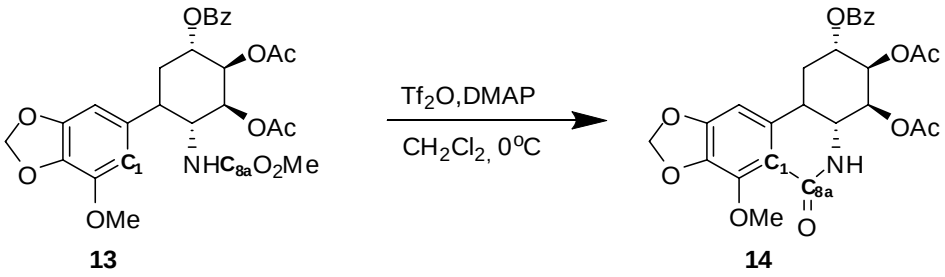
**Scheme 2**

For the substitution of heteroatom, another example from the literature has been reported by Ishikava *et al.*[20] based on the reaction of 2-methoxycarbonylstyrene oxide **10** with ammonia or methylamine to yield 4-hydroxy-1(2H)-isoquinolone **12**. This reaction is effected by electron-withdrawing substituents on the benzene ring. If $R^1 = R^3 = H$, $R^2 = H$, $NO_2$ reaction leads directly to isoquinolone **12**. However, in case of $R^1 = R^3 = Me$ and $R^2 = CO_2Et$, the intermediate **11** is formed. By treatment of intermediate with strong base, again 4-hydroxy-1(2H)-isoquinolone **12** can be synthesized. Dehydration process yields 1(2H)-isoquinolone **13** as shown in Scheme 3.[20]



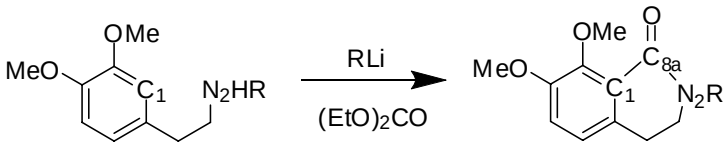

**Scheme 3**

An additional method for the synthesis of isoquinolone derivatives is the formation of $C_1$–$C_{8a}$ bond (Sheme 4). Hudlicky *et al.* have synthesized isoquinolone derivative **14** by modification of Bischler–Napieralski reaction which is reported by Banwell[21]. After synthesizing compound **13** in 6 steps, $C_1$–$C_{8a}$ bond has been formed as shown in Scheme 4. The yield has been reported as 40%.[22]




**Scheme 4**

The formation of $C_1$–$C_{8a}$ and $C_1$-$N_2$ bonds at the same which leads to isoquinolone derivatives has been described by Simig in 1990.[23] This reaction has common usage and the application of the ortho-lithiation-cyclization strategy to *N*-benzyl- and *N*-phenethylamine derivatives was published by Vicente *et al.*[24]

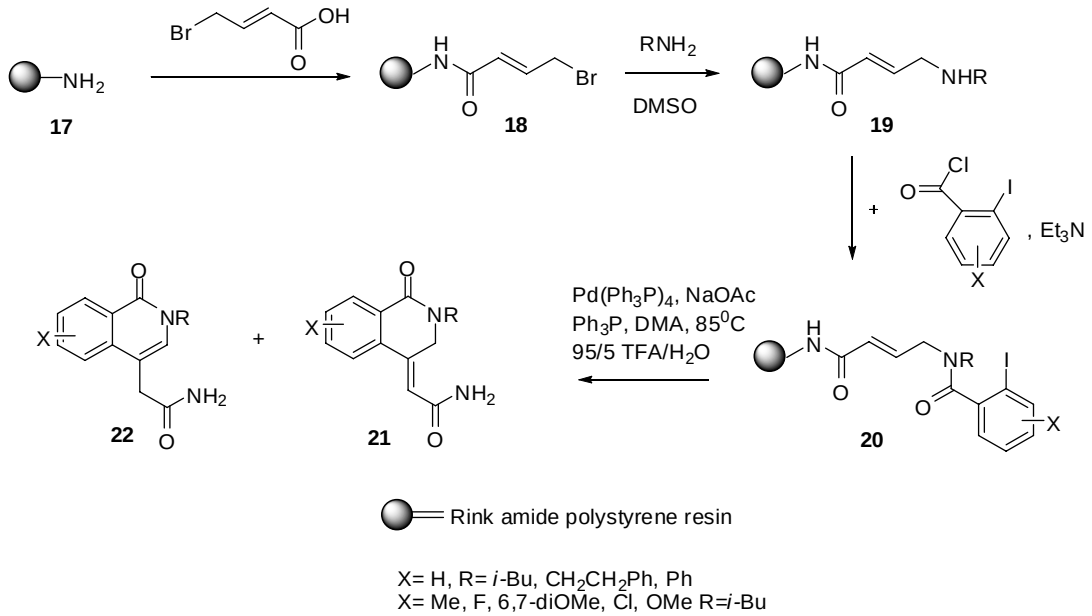



**15** **16**

**Scheme 5**

Isoquinolinone derivatives can easily be prepared by intramolecular Heck reaction. This type of reaction has numerous recent applications. Goff and Zuckermann have synthesized highly substituted isoquinolone derivative, by using this method as shown in Scheme 6.[25]

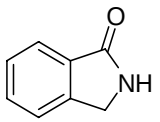
Acylation of the monopeptoid **19** with an *o*-iodo carboxylic acid chloride gives an intermediate **20** which later on undergoes a palladium(0)-catalyzed intramolecular Heck reaction to the peptoid backbone, which is facilitated by the electron withdrawing carboxamide group.



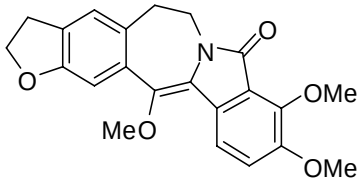

**Scheme 6**

## 1.2 Isoindolinones

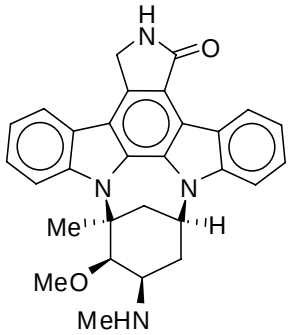
The isoindolinones, also known as 2,3-dihydro-1*H*-isoindol-l-one (phthalimidine) **23** are the structural backbones of many natural substances such as pictonamine **24**, isolated from the Chilean Barberis species,[26] staurosporine **25**, an alkaloid isolated from saccharothrise species.[27] Many compound which contain isoindolinone skeleton have clinical importance such as antiviral, antileukemic, antiinflammatory, antipsychotie and antiulcer properties.[28]




**Isoindolin-1-one 23**




**Pictonamine 24**

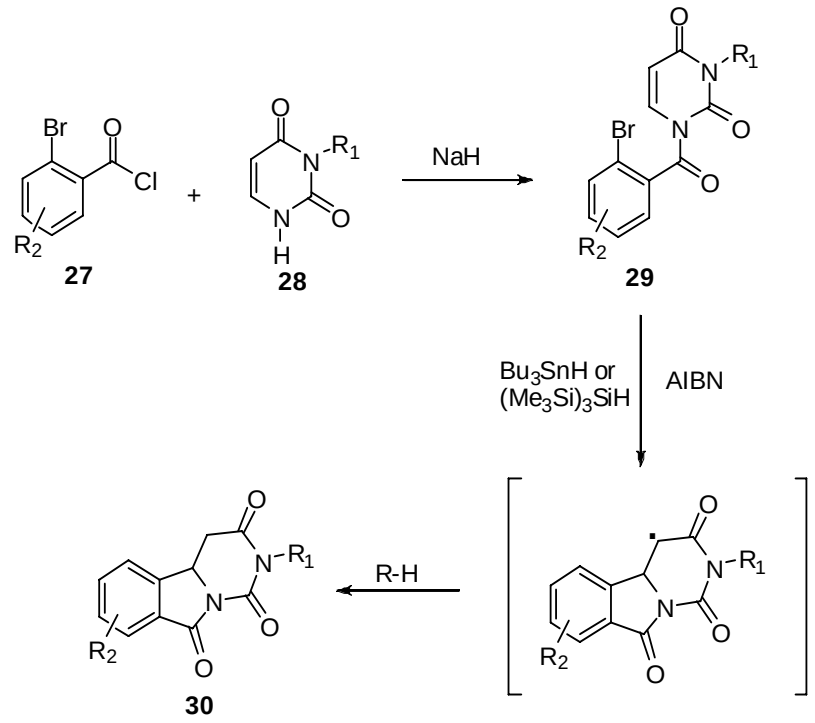



**Staurosporine 26**

Due to the structural similarities between isoindolinones and indoles, which are biologically important molecules,[29] isoindolinones have been a topic of science not only in medicinal chemistry but also in synthetic organic chemistry. For the synthesis of isoindolinone derivatives, several methods are available, which are based on the lithiation procedures, Grignard reactions, Diels-Alder reactions, reduction processes, rearrangement processes, Wittig reaction and photochemical reactions.[30]

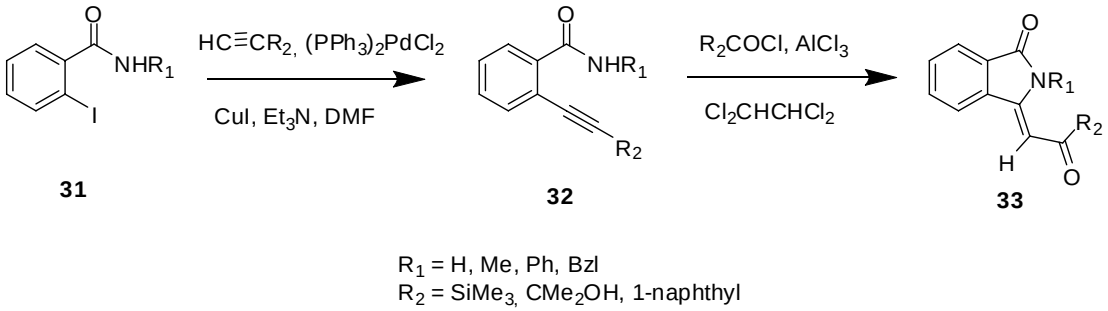
### 1.2.1 The Synthesis of Isoindolinones

There are several methods available for the synthesis of isoindolinones. The C-C bond formation method, based on the free radical or palladium-catalyzed ring closure reactions is one of the examples of these methods. Pugh *et al.*[31] have synthesized tri- and tetracyclic isoindolinones by free radical reactions. *N*-acylation of cyclic nitrogen compound **28** with 2-bromobenzoyl chloride **27** by NaH or pyridine leads to radical precursors. Further reactions of **28** with $Bu_3SnH$ or $(CH_3Si)_3SiH$ with catalytic amount of AIBN gives isoindolinone derivative **30** as shown in Scheme 7.[31]



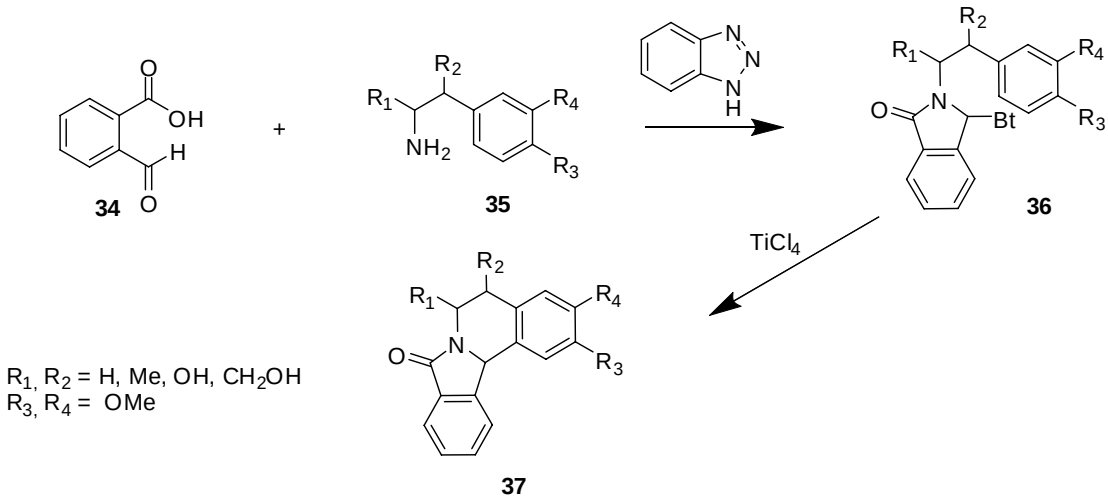

**Scheme 7**

Kundu *et al.* have synthesized isoindolinone derivatives by palladium-catalyzed ring closure reactions. Reaction between the *N*-substituted 2-iodobenzamides **31** and terminal alkynes in the presence of Pd or Cu catalysts and base gave (*Z*)-3-arylideneisoindolones **33** directly. Also, compound **31** underwent Pd-catalyzed reactions with (trimethylsilyl)acetylene to give compound **32** which cyclize to isoindolinone by Friedel-Crafts acylation as given in Scheme 8.[32]




**Scheme 8**

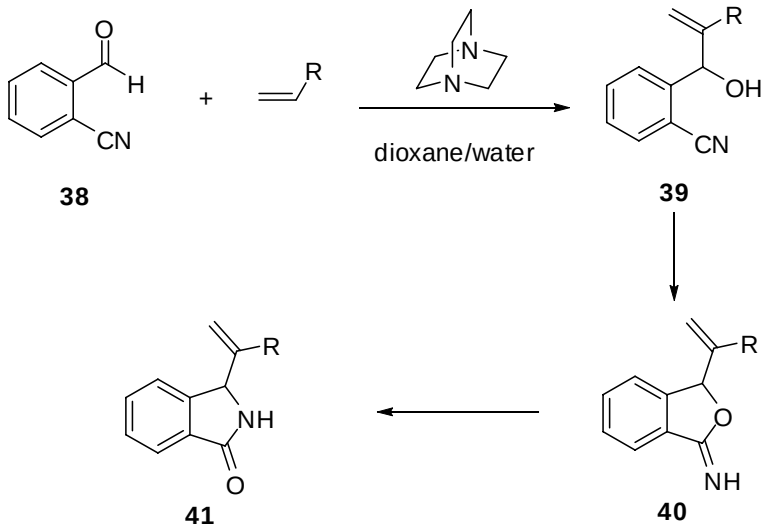
Katritzky *et al.* have reported that intramolecular condensation of chiral amine **35** with 2-carboxybenzaldehyde **34** in the presence of benzotriazole leads to isoindolinone derivative **36** in high stereoselectivity. Further reaction of **36** with $TiCl_4$ gives 5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-ones **37** (Scheme 9).[33]




**Scheme 9**

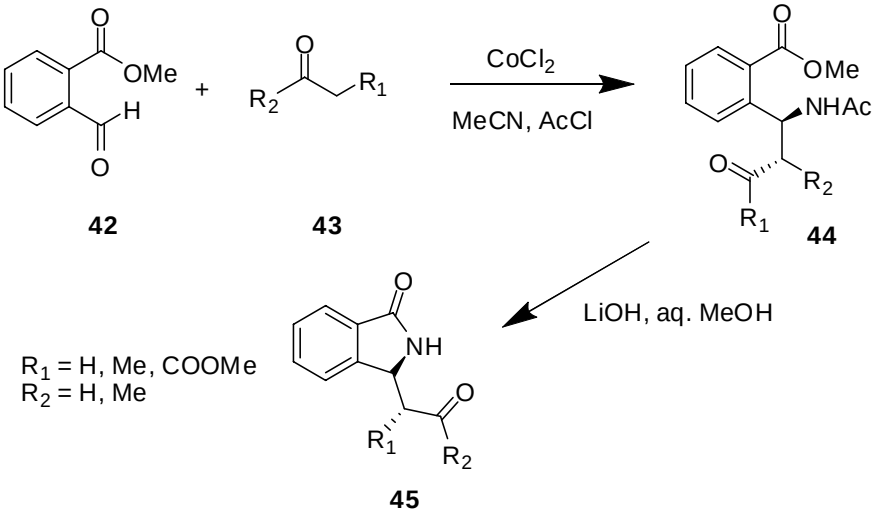
Baylis-Hillman reaction of 2-cyanobenzaldehyde **38** with activated alkenes **39** leads to 3-substituted-1-imino-1,3-dihydroisobenzofuran derivatives **40**. However, Lee *et al.*

have reported that 3-substituted-1-imino-1,3-dihydroisobenzofuran derivatives **40** transformed immediately into the isoindolinone derivatives **41** as shown in Scheme 10.[34] For the synthesis of **41**, 2-cyanobenzaldehyde **38** was reacted with methylacrylate in the presence of DABCO in dioxane/water (15:1) at room temperature.



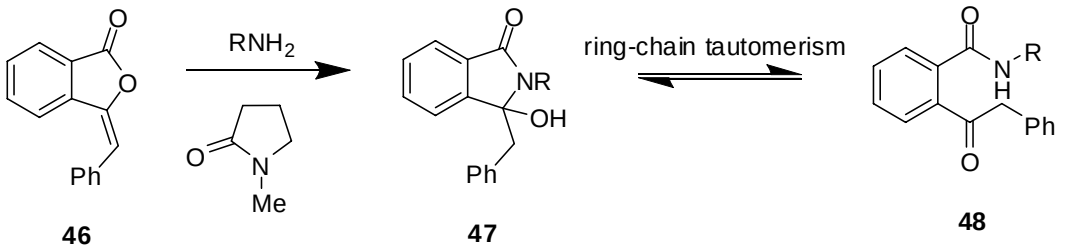

**Scheme 10**

1,2-Dicarbonyl compounds are also important starting materials to synthesize isoindolinone derivative. Iqbal and his coworkers have synthesized isoindolinone derivative starting from 2-carbomethoxybenzaldehyde **42**. A one-pot Co(II)-catalyzed three-component coupling process leads to compound **44** which is cyclized to 3-carbonylmethylisoindol-1-ones **45** as shown in Scheme 11.[35]




**Scheme 11**

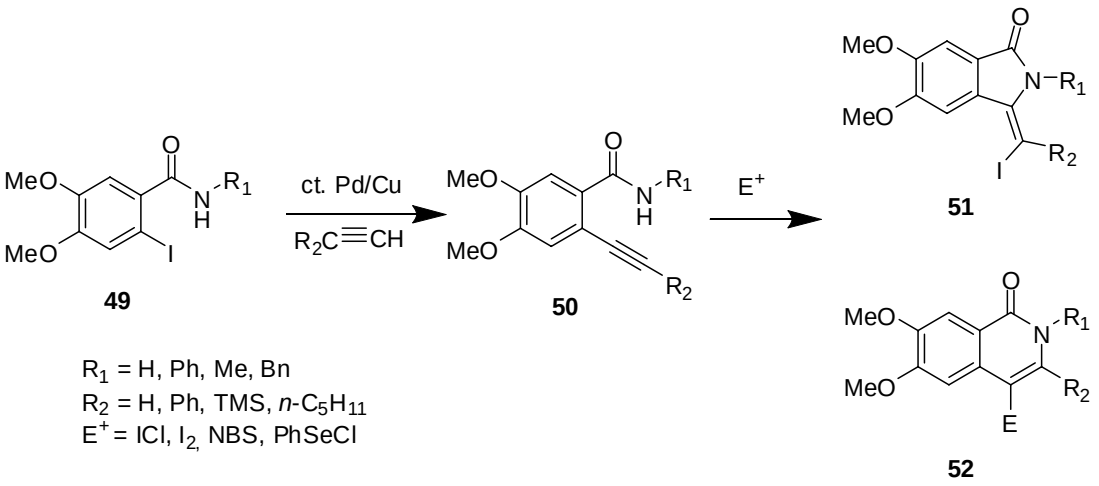
Yamamoto *et al.*[36] synthesized 3-hydroxyisoindolones **47** by ring-chain tautomerization. This synthesis is a distinct methodology which can be considered as the transformation of heterocycles to isoindoles. The reaction between butylamine and 3-benzalphthalide **46**, formed only isoindolinone **47**. But, if the reaction was carried out with *tert*-butylamine, isoindolinone **47** and chain products **48**, were formed. When R = Et, Bzl, adamantly, only product **48** was observed because of the ring-chain tautomerism as shown in Scheme 12.[37]




R = Bu, Bzl, *i*-Pr, Ph, $Ph_2CH$, cyclohexyl

**Scheme 12**

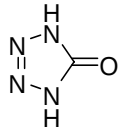
Another approach to isoindolinones has been reported by Larock and his co-workers in two steps which are preparation of *o*-(1-alkynyl)benzamides **50** by a Sonagashira coupling reaction and electrophilic cyclization, respectively. The required starting material **50** was prepared by Sonogashira coupling of the corresponding iodobenzamides with terminal alkynes in presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI using $Et_3N$ as solvent. Benzamide reacts with the stronger electrophile ICl as well as weaker electrophile $I_2$ for the electrophilic cyclization to give isoindolinone derivative **51** (Scheme 13). The weaker electrophile $I_2$ shows better regioselectivity, and also regioselectivity depends on the solvent used in this reaction. Using $CH_3CN$ as the solvent afforded better regioselectivity and a higher yield than using $CH_2Cl_2$.[38]




**Scheme 13**

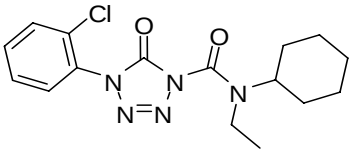
## 1.3 Tetrazolinones

Heterocyclic compounds, which have nitrogen atoms, display a broad spectrum of biological activities.[39] Tetrazolinones are the five-membered, unsaturated heterocyclic ketone having four nitrogen atoms and one double bond opposite to the carbonyl group.



**General structure of tetrazolinones**

Because of its encouraging herbicidal activity, tetrazolinone derivatives drew substantial attentions from pesticide chemists recently. The most known tetrazolinone derivative as a commercial herbicide is fentrazamide **53**, which is highly effective compound against many weeds and inhibits cell division.[40]

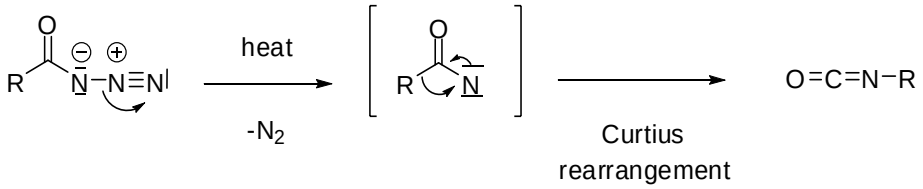


**fentrazamide 53**

## 1.4 Dipolar Cycloaddition with Azide

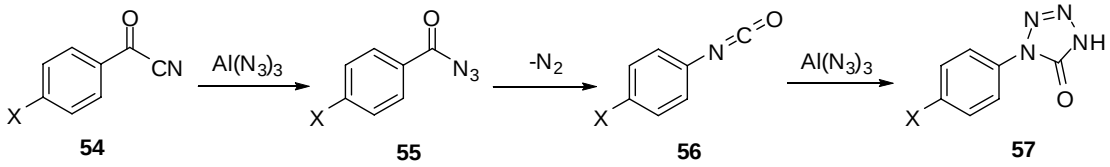
1,3-Dipolar cycloaddition reactions are substantial method for the formation of the five-membered ring which have more than one heteroatom. For 1,3-dipolar cycloadition with azide, isocyanates are the potential dipolarophilic parts of the reactions.[41]

By the Curtius rearrangement, alkyl and aryl isocyanates can be prepared from their corresponding acyl azides. It is possible to isolate isocyanates when the rection is performed by using aprotic solvent. Heat provides to leave $N_2$ gas from the acyl azide and and acyl nitrene is formed. Since acyl nitrenes have electron gap, the system rearranges in order to remove the electron gap. The non-bonding electrons on the nitrogen atom create a new bond between nitrogen and carbon of the carbonyl group and the R group migrates with its bonding electrons to the nitrogen, which has electron gap to complete the rearrangement.[42]



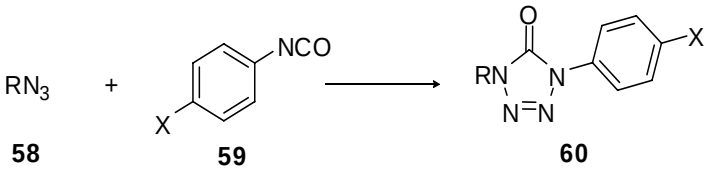

**Scheme 14**

In the early years, tetrazolinone derivatives have been synthesized by 1,3-dipolar cycloaddition reactions, starting from phenyl isocyanate **56** as a dipolarophile. In the synthesis of compound **57**, aluminum azide has been chosen as 1,3 dipole as shown in Scheme 15.[43]




**Scheme 15**

In 1973, L'abbė *et al.*[44] synthesized tetrazolinone derivative by 1,3-dipolar cycloaddition reaction. It was reported that aryl isocyanates did not react with aryl azides and tosyl azide but slow addition was observed with equimolar amounts of butyl azide and cyclohexyl azide as illustrated below in Scheme 16.[44]

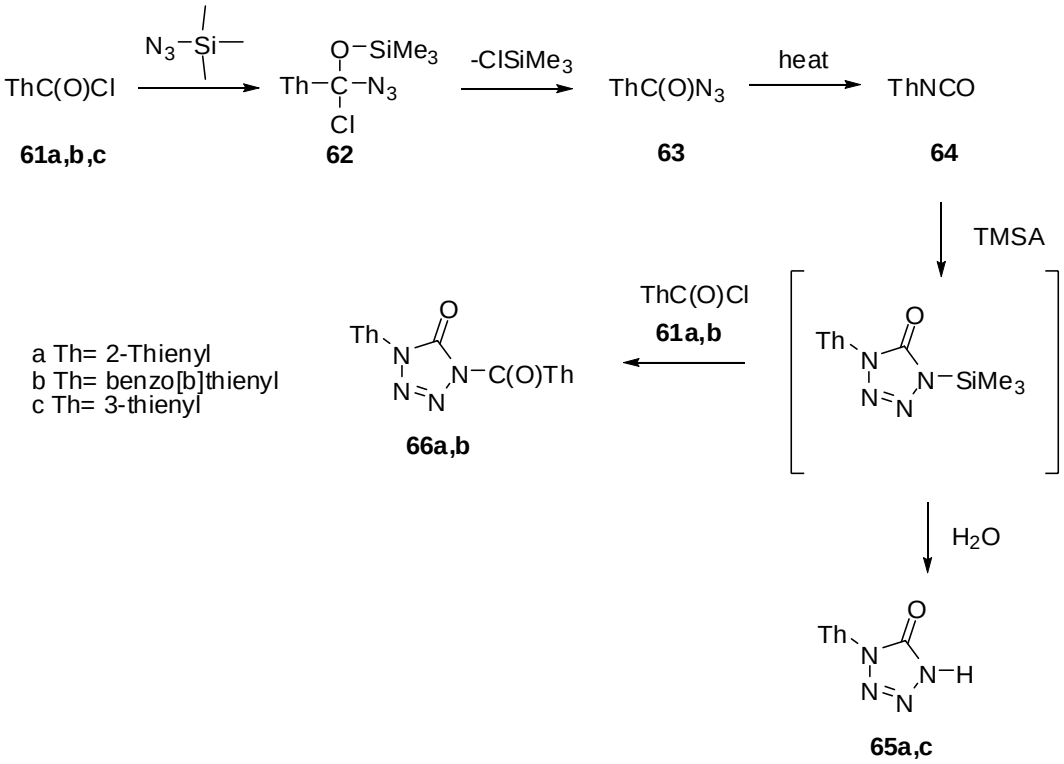



**58** **59** **60**

R= n-$C_4H_9$, o-$C_6H_{11}$, X= H, $NO_2$

**Scheme 16**

Zanirato and Toselli have described an efficient methodology for the synthesis of tetrazolinone derivative in a one pot reaction. It has been claimed that [2+3] cycloaddition of thienyl isocyanate with trimethylsilyl azide produced tetrazolinone derivative. As seen in Scheme 17, For the preparation of thienyl isocyanate, trimethysilyl azide (TMSA) and thenoyl chlorides have been chosen. It has been reported that thenoyl chlorides such as 2-thenoyl **61a**, benzo[b]thiophene-2-carbonyl **61b** and 3-thenoyl chloride **61c** gave different results depending on the reaction conditions and type of substrates.[45]

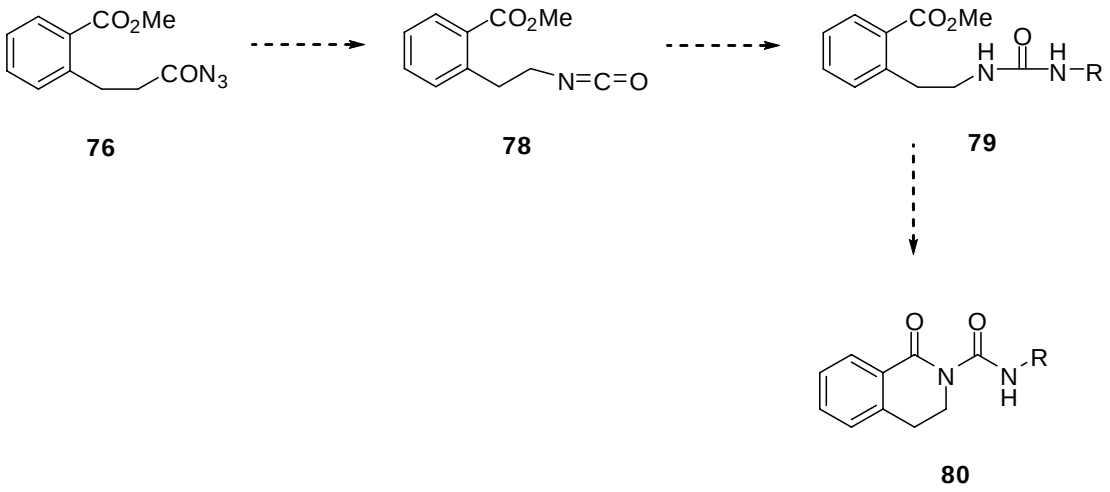



**Scheme 17**

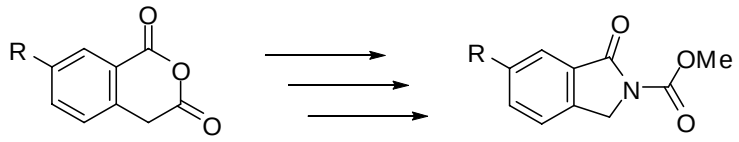
## 1.5 The Aim of the Thesis

The aim of this thesis is to develop a new methodology for the synthesis of isoquinolone and isoindolinone derivatives. This methodology will also be applied to 2-(carboxymethyl)furan-3-carboxylic acid to synthesize nitrogen and oxygen containing heterocycles.

In the first part of this study, by the generation of acyl azide **76,** the integration of nitrogen atom into the structure will be provided. The generated corresponding isocyanates **78** will be trapped to form the urea derivative **79** which will then undergo intramolecular cyclization reaction to produce isoquinolone derivative **80**.



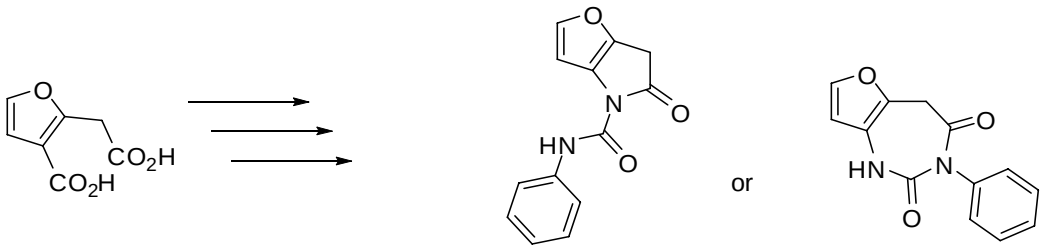

In the second part of the study, reactions of homophthalic anhydrides to synthesize isoindolinone derivative will be investigated.




R= H **97**
R= Br **98**
R= OMe **99**

R= H **101**
R= Br **102**
R= OMe **103**

Finally, the new heterocyles will be tried to synthesize by using the similar methodology which is used for the synthesis of isoquinolone derivative.




**122** **131** **132**

# CHAPTER 2

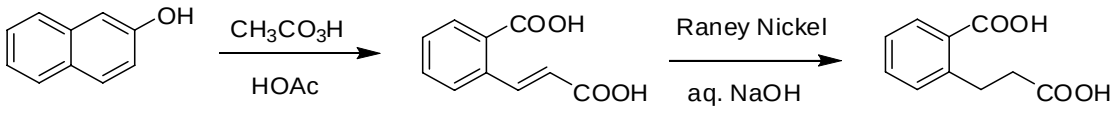
# RESULTS AND DISCUSSION

## 2.1 Synthesis of Isoquinolone Derivative

### 2.1.1 Synthesis of Starting Material: *β*-(*o*-Carboxyphenyl)propionic Acid (69)

*β*-(*o*-Carboxyphenyl)propionic acid **69** was chosen as the starting material which was already synthesized by Page and Tarbell in 1963.

As shown in Scheme 18, the reaction between peracetic acid and *β*-naphthol **67** in acetic acid leads to formation of *o*-carboxycinnamic acid **68**. Then *o*-carboxycinnamic acid was reacted with Raney nickel in aqueous solution of sodium hydroxide to give the starting material **69**.[46]

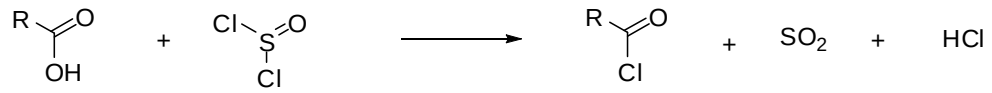



**67** **68** **69**

**Scheme 18**

### 2.1.2 Reaction of *β*-(*o*-Carboxyphenyl)propionic Acid (69) with Thionyl Choride: The Synthesis of Diester (73)

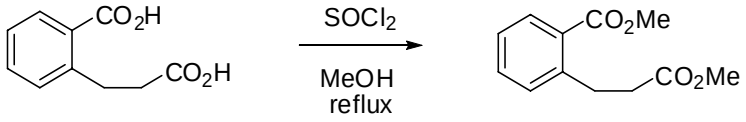
Thionyl choride is a well known inorganic compound due to its reactivity for the chlorination reactions. By using thionyl choride, carboxylic acid derivatives are converted into acyl choride derivatives (Scheme 19).[47]




**70** **71** **72**

**Scheme 19**

Thionyl chloride was reacted with β-(o-carboxyphenyl)propionic **69** in methanol to give dimethylester **73** (Scheme 20)**.**



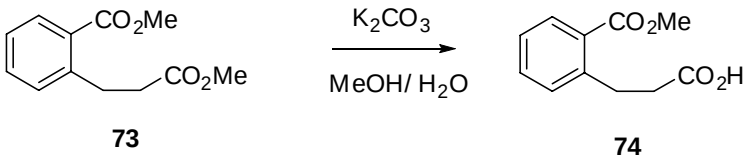

**69** **73**

**Scheme 20**

The formation of methyl 2-(3-methoxy-3-oxopropyl) benzoate **73** was proved by $^{1}$H-NMR and $^{13}$C-NMR spectra. Comparing the $^{1}$H-NMR and $^{13}$C-NMR spectra of carboxylic acid **69** and diester **73**, two new different methoxy peaks indicate the formation of compound **73**. Also comparing the IR spectra of these compounds, broad –OH stretching vanishes as a result of this reaction. By the light of this information, we can easily claim that chlorination takes places and acyl chlorides are converted to diester **73** by methanol.

### 2.1.3 Reaction of Di-ester 73 with Potassium Carbonate: The Formation of Halfester 74

For the formation of half-ester, compound **73** was treated with potassium carbonate to give half-ester **74**. Due to the conjugation between benzene ring and α-carbonyl group, γ-carbonyl group is more susceptible to reactions. Hence, hydrolysis took place regioselectively on the more reactive carbonyl group (Scheme 21).




**73** **74**

**Scheme 21**

As shown in Figure 1, $^{1}$H-NMR spectrum clearly shows the formation of half-ester **74** by the peaks of methoxy protons and –OH proton. Besides this, ratio of the integration values shows that one of the ester groups has been hydrolyzed. Also appearing of broad signal of –OH in IR spectrum proves the hydrolysis of ester to the compound **74**.

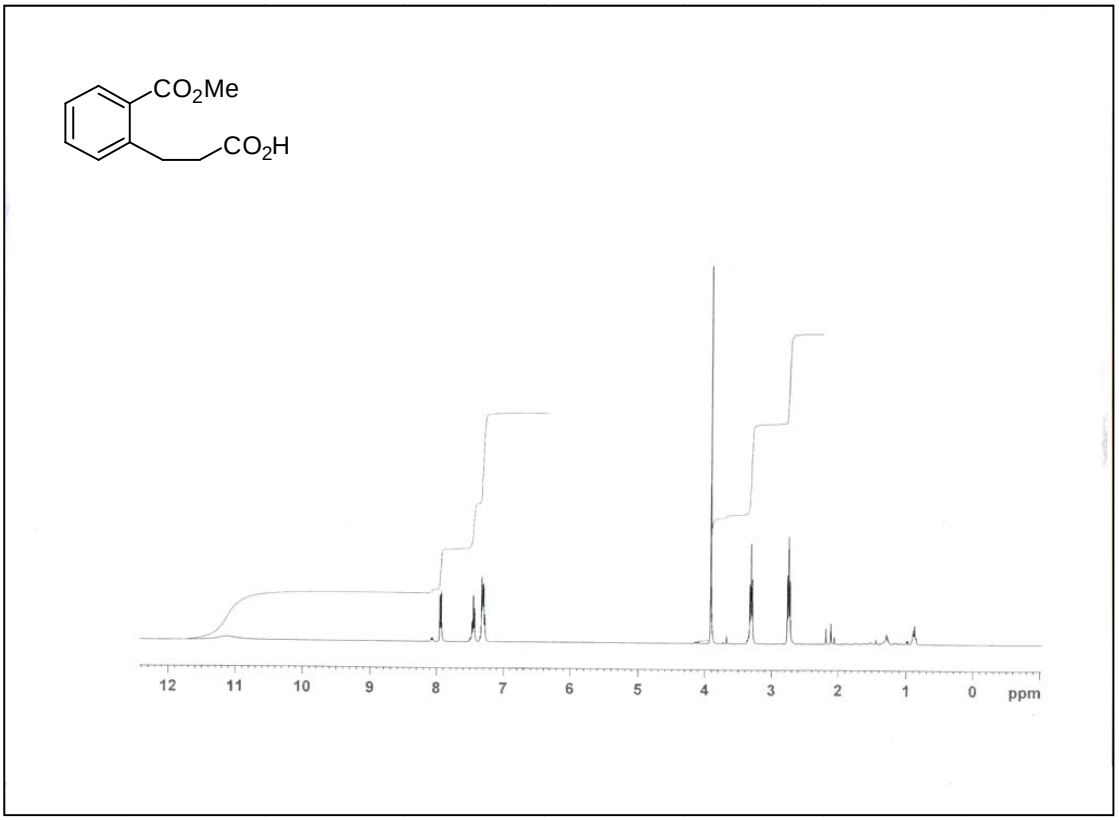
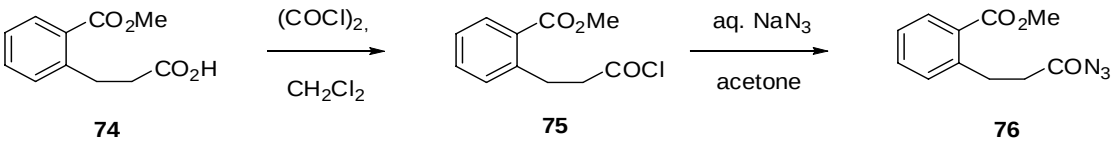



**Figure 1** $^{1}$H-NMR Spectrum of Compound **74**

### 2.1.4 The Synthesis of Acyl Azides

The azidination step is the most important step for the incorporation of a nitrogen atom into the structure. In order to achieve this, sodium azide was used for the conversion of carboxylic acids **74** into the corresponding acyl azides **76**. But firstly, carboxylic acid **74** was chlorinated by oxalyl chloride for the azidination process. Then, chlorinated compound **75** was reacted with sodium azide to form acyl azide **76** as shown in Scheme 22.




**74** **75** **76**

**Scheme 22**

Besides the $^{1}$H-NMR spectra, IR spectrum has important role for the characterization of acyl azide compound **76**. The characteristic frequency values of the azide appeared around 2270 and 2140 cm$^{-1}$ (Figure 2)

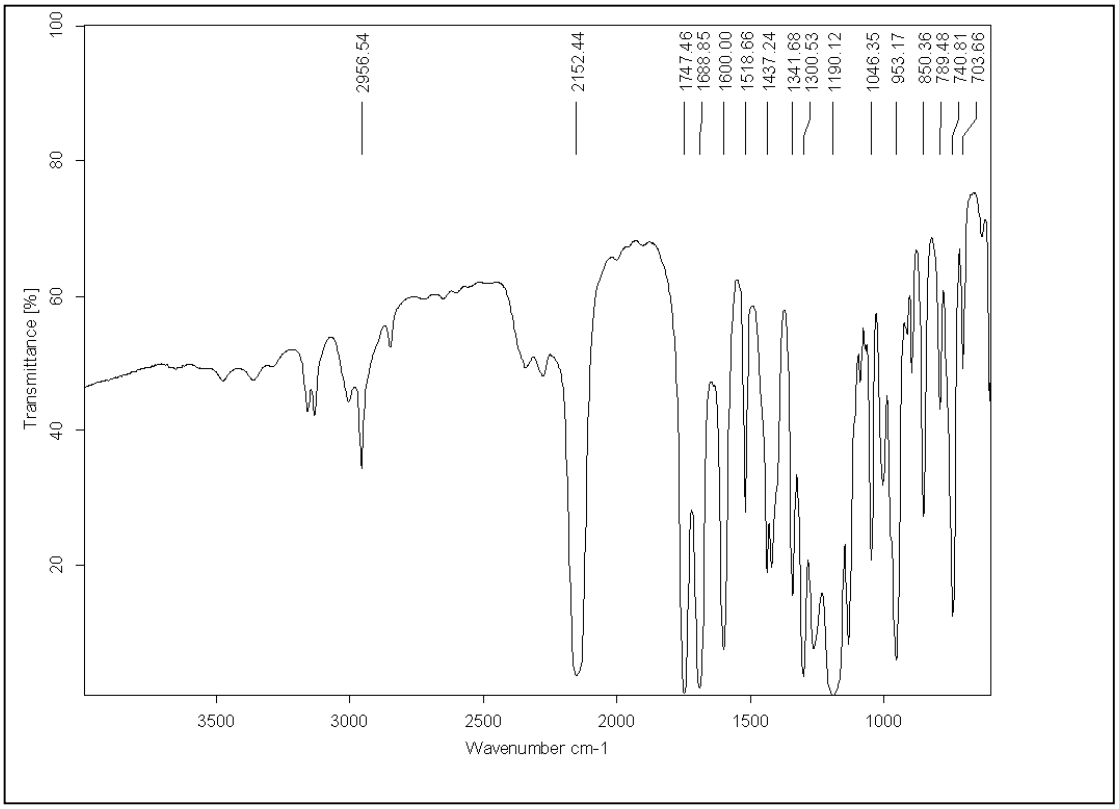
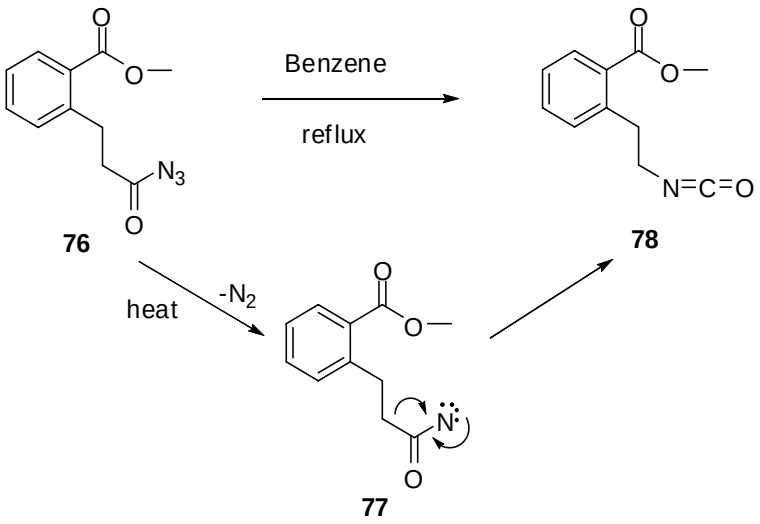



**Figure 2** IR Spectrum of Compound **76**

### 2.1.5 Reaction of Acyl Azide: Synthesis of Isocyanate

As much as azidination step, synthesis of isocyanates is also the key step for the synthesis of isoquinolone derivatives. Because of its strong electrophilicity, nucleophiles can easily be added to isocyanate and form the important precursors for the construction of isoquinolone derivatives.

Acyl azide **76** was transformed into acyl nitrene upon heating at reflux temperature of benzene. The formed intermediate **77** was rearranged immediately to the corresponding isocyanates **78** (Scheme 23).




**Scheme 23**

For the characterization of isocyanate, IR spectroscopy plays an important role because IR spectroscopy has characteristic frequency value for isocyanates which is around 2270-2280 $cm^{-1}$ (Figure 3). $^{1}$H-NMR and $^{13}$C-NMR support also the proposed structure of isocyanate **78.**

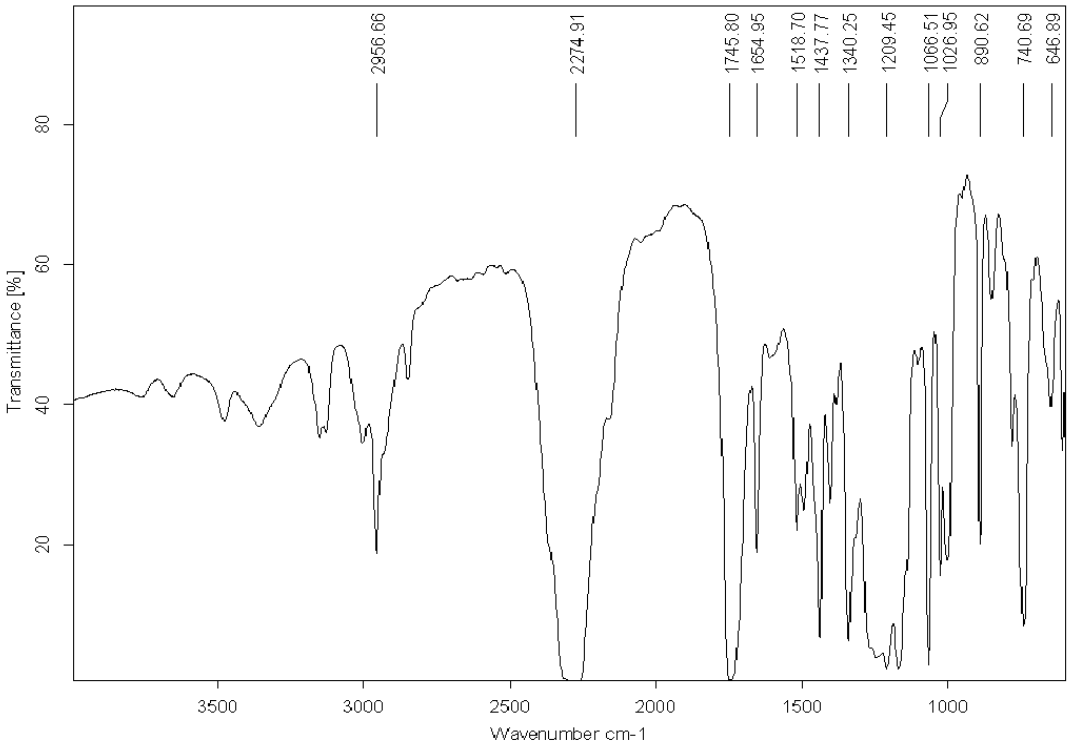
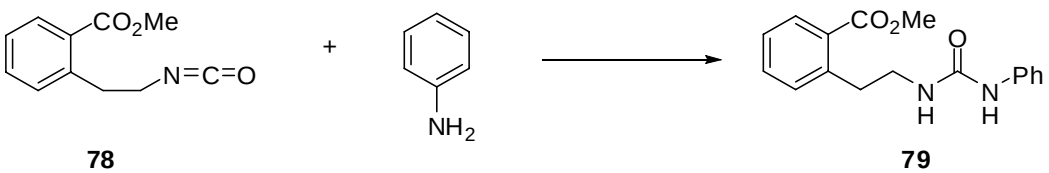



**Figure 3** IR Spectrum of compound **78**

### 2.1.6 Reaction of Isocyanate with Aniline: Synthesis of Urea Derivative

The isocyanates can be easily trapped by different nucleophiles due to its strong electrophilicity. If isocyanate group is reacted by the hydroxyl functional group, urethane derivatives are formed. But if they are reacted by amines, urea derivatives are formed.

Treatment of isocyanate **78** with aniline provided the urea derivative **79** (Scheme 24).



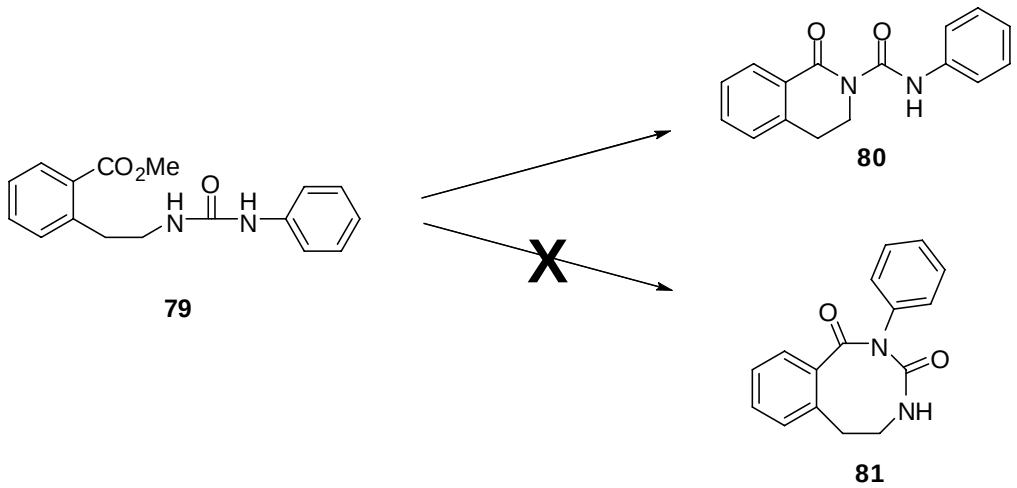

**78** **79**

**Scheme 24**

Characterization of the product is mostly based on $^{1}$H-NMR and $^{13}$C-NMR spectra. It was easy to determine from the $^{1}$H-NMR spectrum that the compound **79** contains two aromatic rings. Also two different -NH signals support the formation of compound **79**.

### 2.1.7 Synthesis of Isoquinolone Derivative

For the formation of isoquinolone derivative **80**, compound **79** was treated with a base, sodium hydride, which abstracted one of the acidic nitrogen protons and ring closure took place by the attack of the lone pair of nitrogen to the carbonyl carbon of ester group. Since the urea derivative **79** contains two different –NH protons, two different cyclization products can be formed. If NH-proton conjugated with the benzene ring is abstracted diazocine derivative (an eight-membered ring) **81** can be formed. In other case, isoquinolone derivatives (six-membered ring) **80** can be formed (Scheme 25). $^{1}$H-NMR and $^{13}$C-NMR spectra clearly proved that reaction of compound **79** with base yielded isoquinolone derivative **80**.




**Scheme 25**

The [1]H-NMR spectrum revealed three sets of proton signals matching with the product **80**; triplets at 3.05 ppm and 4.25 ppm indicating methylene protons, a broad singlet arising from -NH proton at 11.78 ppm and other aromatic protons centered between 8.14 and 7.10 ppm (Figure 4).

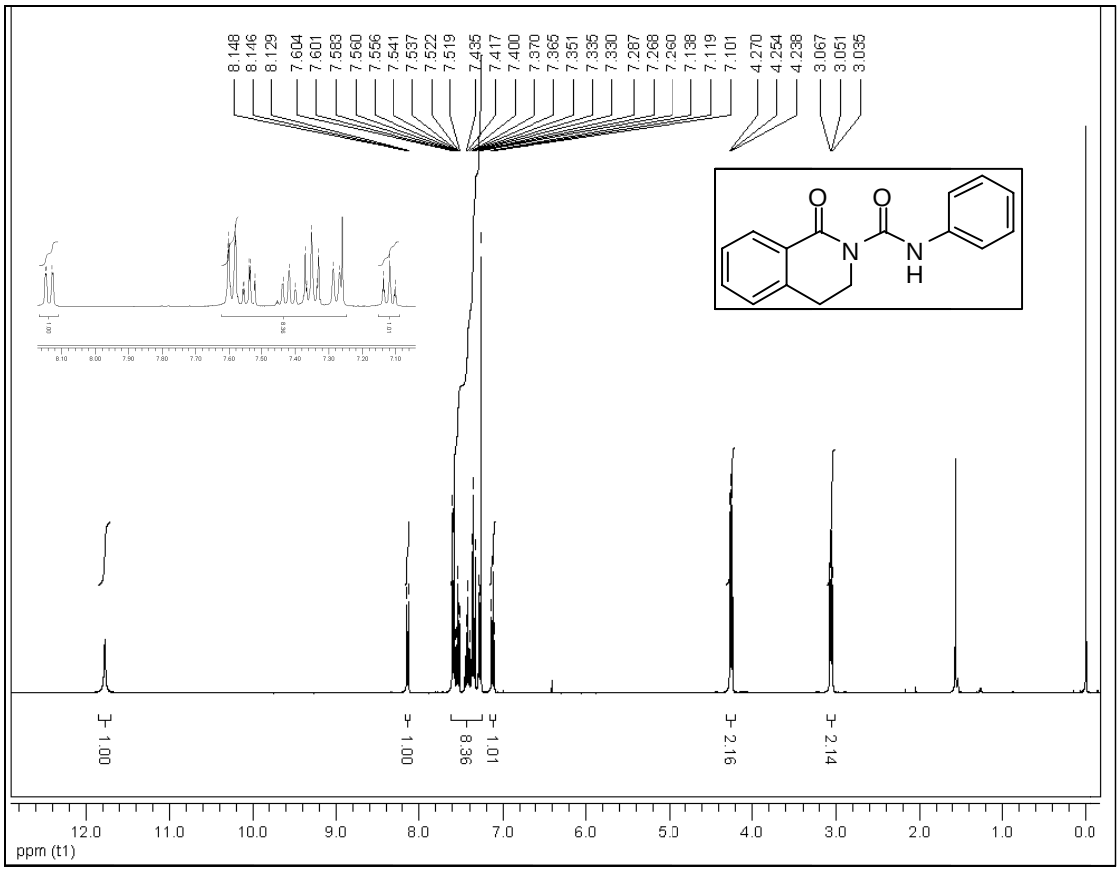
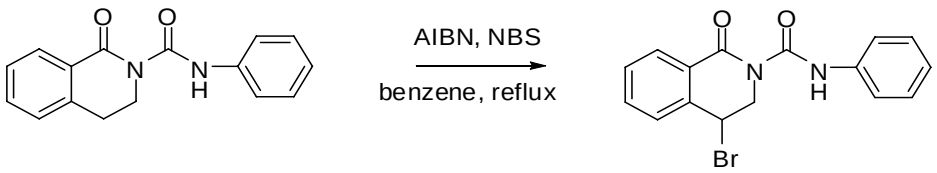



**Figure 4** [1]H-NMR Spectrum of Compound **80**

### 2.1.8 Benzylic Bromination of Isoquinolone Derivative 80

After successful synthesis of isoquinolone derivative **80**, the next step was the introduction of the double bond into the six-membered ring. In order to achieve this, benzylic carbon of isoquinolone derivative **80** was brominated by N-bromosuccinimide (NBS) for further elimination reaction.

The compound **80** was reacted by NBS in the presence of a radical initiator, AIBN, at reflux temperature of benzene. Brominated isoquinolone derivative **81** was isolated after column chromatography in 70% yield. $^{1}$H-NMR and $^{13}$C-NMR spectra clearly showed the formation of the mono brominated isoquinolone derivative **81** as shown in Scheme 26. With a radical initiator such as azobisisobutyronitrile (AIBN), NBS forms benzylic radical intermadiates, which is more stable than other carbon radicals, and the reaction yields benzylic bromides.[48]



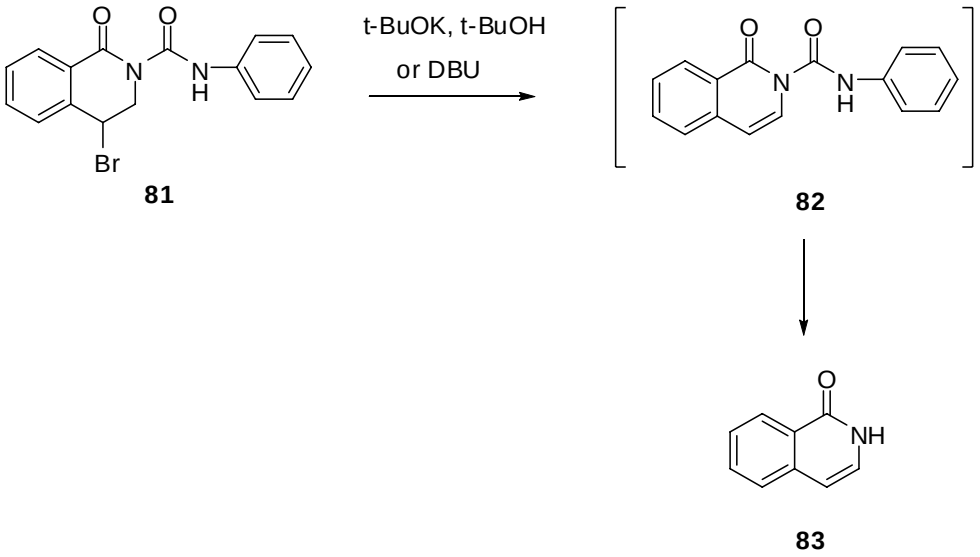

**80** **81**

**Scheme 26**

### 2.1.9 Elimination of Hydrogen Bromide: Formation of Fully Conjugated Isoquinolone Derivative 82

For the elimination step, the brominated isoquinolone derivative **81** was treated with potassium-*t*-butoxide (*t*-BuOK) or 1,8-diazabicycloundec-7-ene (DBU). Instead of the expected elimination product **82**, the compound **83** was isolated as the sole product.

After elimination of hydrogen bromide the compound **82** underwent further hydrolysis reaction to give compound **83** (Scheme 27)**.**




**Scheme 27**

$^{1}$H-NMR and $^{13}$C-NMR spectra were fully in agreement with the proposed structure of **83**. The $^{1}$H-NMR spectrum shows a broad triplet for H-1 proton due to the coupling with the adjacent olefinic proton H-2 and –NH. Moreover, doublet at 6.46 ppm belongs to H-2 and finally N-H proton appears at 9.19 ppm as a broad doublet. Aromatic protons lie in the range of 7.00-8.34 ppm (Figure 5).

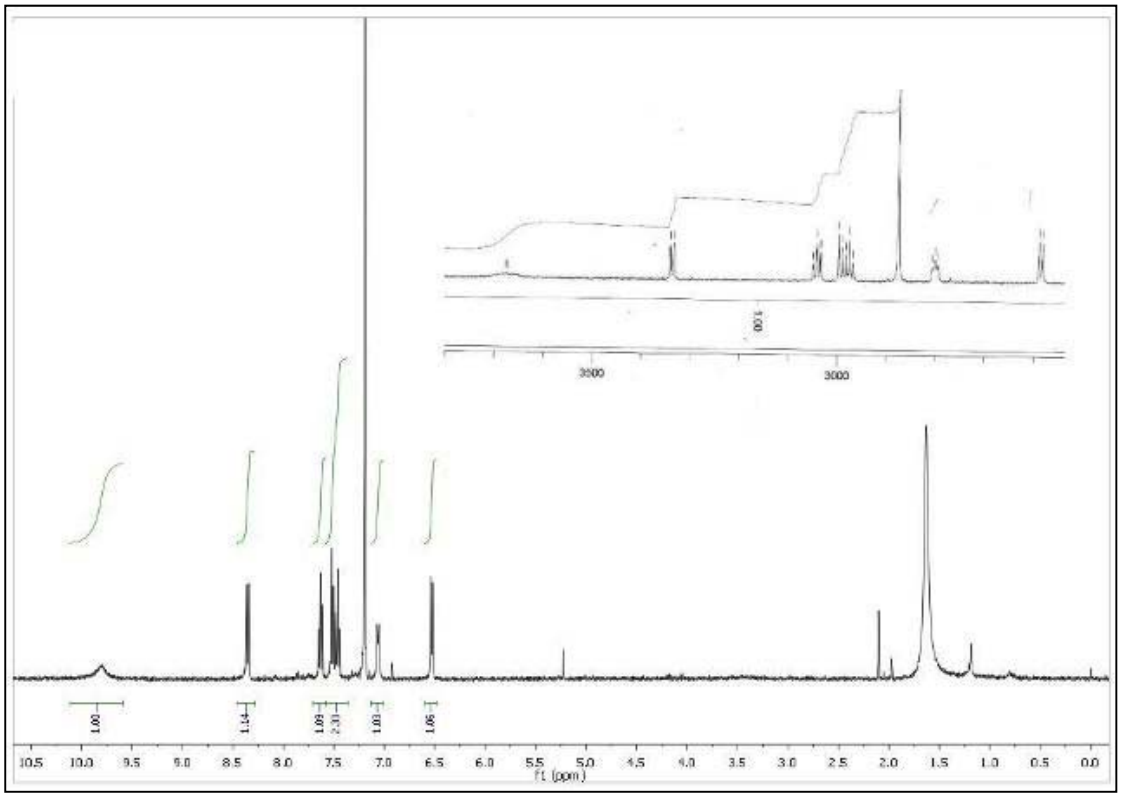
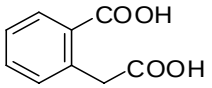


**Figure 5** $^{1}$H-NMR Spectrum of Compound **83**

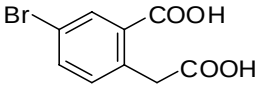
## 2.2 Synthesis of Isoindolinone Derivatives

### 2.2.1 Synthesis of Starting Materials

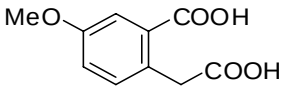
For the synthesis of isoindolinone derivatives, tree kind of homophthalic acid derivatives; homophthalic acid **90**, bromo-homophthalic acid **91** and methoxy-homophthalic acid **96** were chosen as starting materials.




**90**



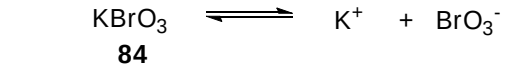

**91**



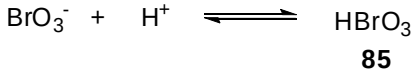

**96**

### 2.2.1.1 The Synthesis of 5-bromo-2-(2-hydroperoxy-2-oxoethyl)benzoperoxoic Acid

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 benzenes.[49] Aqueous solution of a strong acid, preferably sulphuric acid, leads to the production of active brominating species upon treatment with sodium or potassium bromates.[50] Potassium bromate **84** was used as bromine source. Initially participation of acidic proton generates bromic acid **85**.

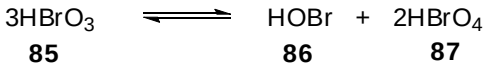



**84**




**85**

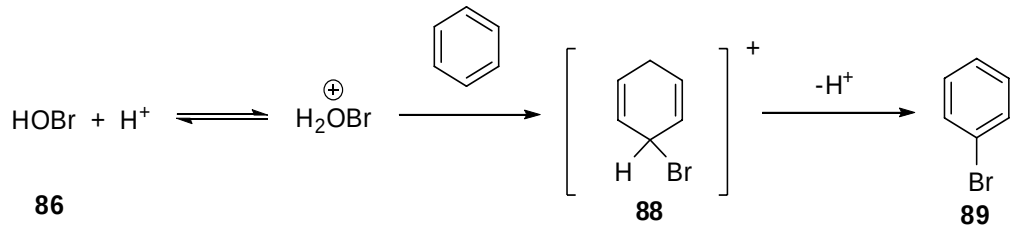
After the formation of the bromic acid a decomposition takes place to form hypobromous acid **86** and perbromic acid **87.**




**85** **86** **87**

Finally, hypobromous acid **86** 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 **88** yields the bromine substituted product **89** as shown in Scheme 28.

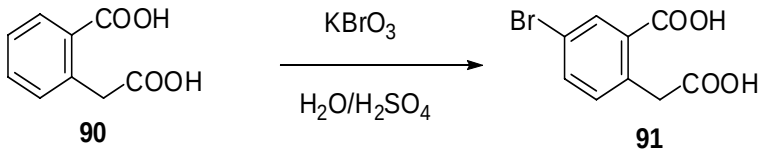



**86** **88** **89**

**Scheme 28**

Preparation of the desired bromo-homophthalic acid **90** was carried out by this method starting from the homophthalic acid **91** as given in Scheme 29. As the carboxylic acid behaves as meta director, substitution takes place at the meta position. Isolated yield was 44.4 % due to some possible side products which are soluble in water.

For the preparation of the desired bromo-homophthalic acid **91**, the same methodology was applied to homophthalic acid **90**.

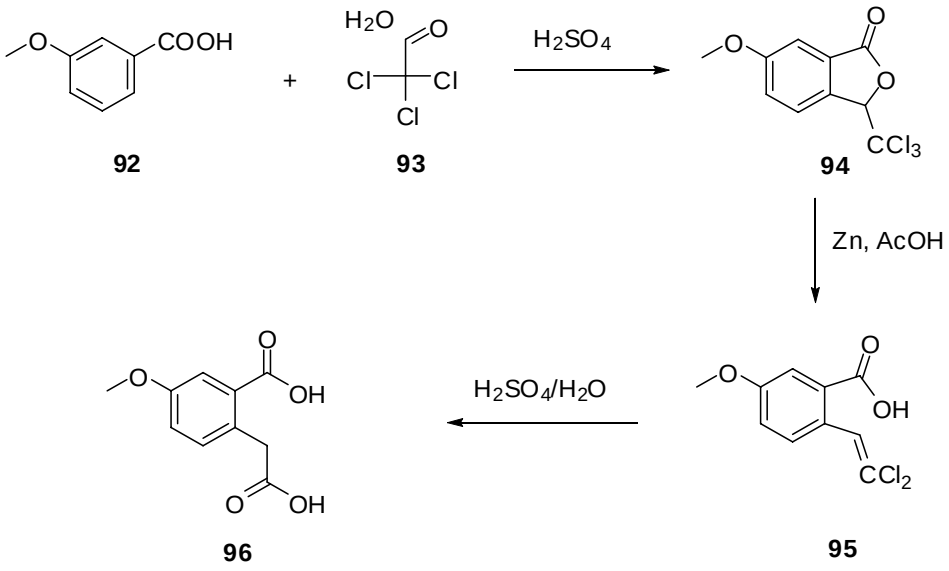



**90** **91**

**Scheme 29**

### 2.2.1.2 The Synthesis of Methoxy Substituted Homophthalic Acid: The reaction of 3-Methoxybenzoic Acid and Chloral Hydride

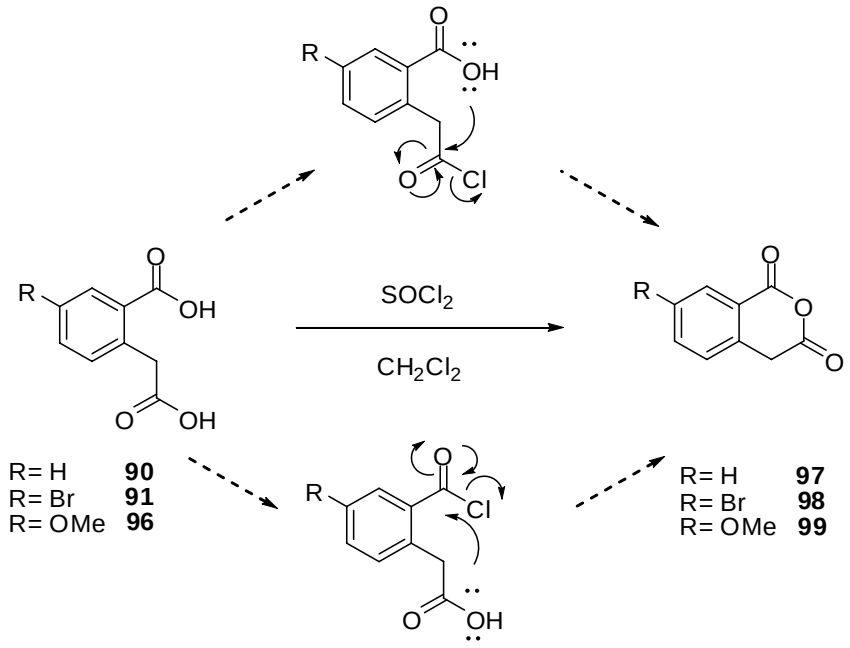
For the synthesis of methoxyhomophthalic acid **96**, an efficient procedure published in the literature was followed, which was modified.[51] The procedure consists of three steps. Initially 3-methoxybenzoic acid **92** and chloral hydrate **93** were subjected to a condensation reaction in the presence of sulphuric acid in order to obtain the corresponding lactone **94**. In the second step, the lactone derivative **94** was reduced by zinc in acetic acid to produce dichlorovinyl derivative **95**. Finally the desired compound **96** was synthesized by treatment of the dichlorovinyl derivative with sulphuric acid as shown in Scheme 30.




**Scheme 30**

### 2.2.2 Reaction of Homophthalic Acid Derivatives with Thionyl Chloride: The Synthesis of Homophthalic Anhyride Derivatives

In order to synthesize homophthalic anhyride derivatives **97-99**, homophthalic acid **90**, bromo-homophthalic acid **91** and methoxyhomophthalic acid **96** were treated with thionyl chloride in dichloromethane. First, one of the carboxylic acids underwent chorination reaction followed by cyclization by the attack of the hydroxyl group of the second acid function to give the corresponding anhydrides **97-99** (Scheme 31).

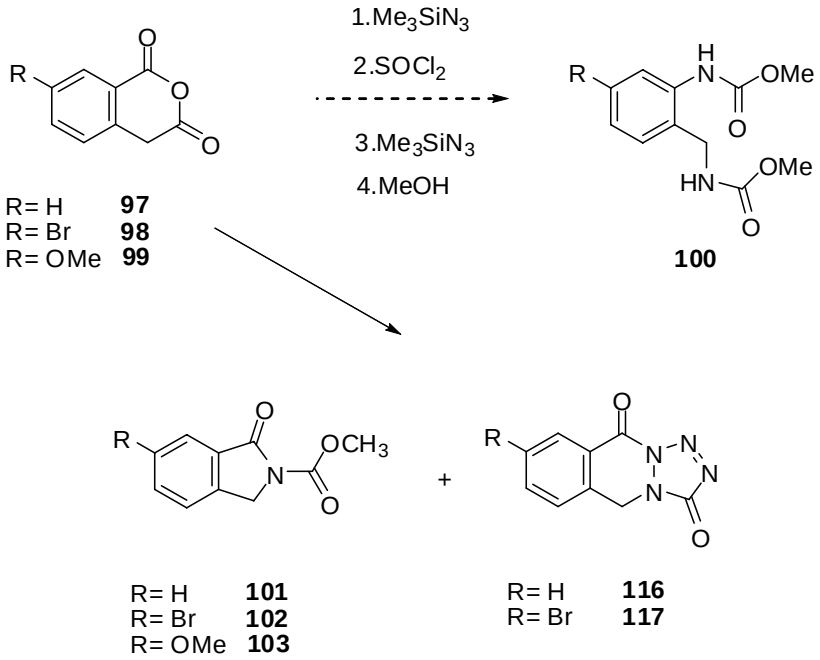



**Scheme 31**

Besides the $^{1}$H-NMR spectra, IR spectra confirmed also the formation of homophthalic anhydrides **97, 98, 99**. Disappearing of –OH peaks in IR spectrum proved that homophthalic acids were converted to corresponding anhydrides**.**

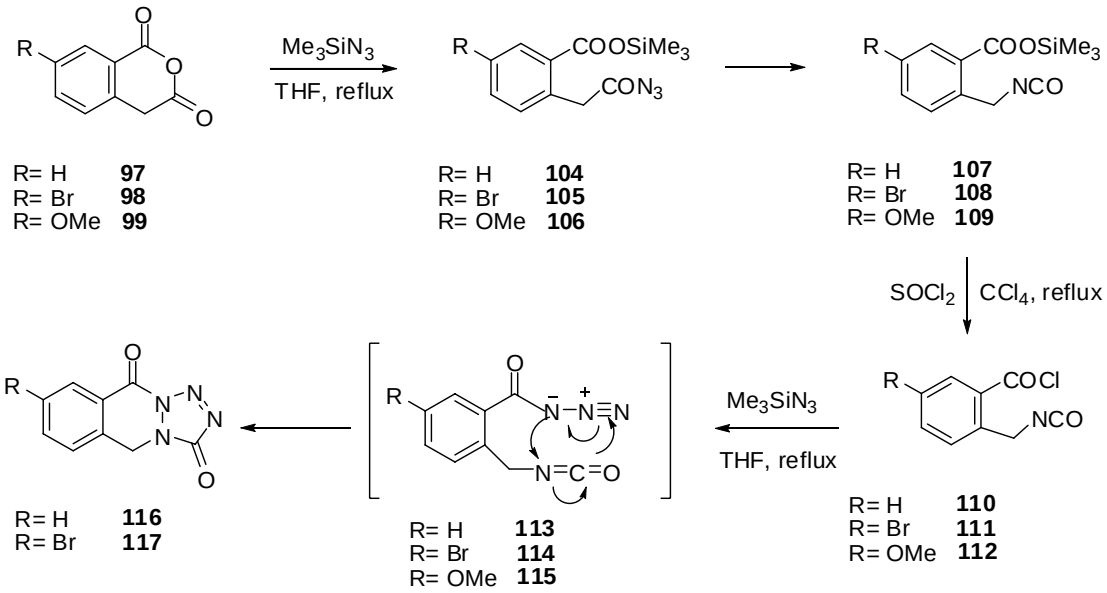
### 2.2.3 Reactions of Homophthalic Anhydrides: Formation of Isoindolinone Derivatives and Tetrazolinone Derivatives

Our primary goal was the synthesis of **100**, which is a important precursor for the further cyclization reactions. For the synthesis of **100**, we have reacted **97-99** with trimethylsilyl azide, thionyl chloride, followed by trimethylsilyl azide and methanol, respectively as shown in Scheme 32. Surprisingly, analysis of the products indicated the formation of isoindolinone (**101-103**) and tetrazolinone (**116**,**117**) instead of the expected product **100**.




**Scheme 32**

The products were separated by column chromatography and their structures were determined by spectral data. For the formation of those products, following mechanism was suggested as shown in Scheme 33. We assume, the first step is the opening of anhydride function by trimethylsilyl azide to furnish **104, 105,** and **106**. Acyl azide functions undergo Curtius rearrangement to form the isocyanates **107, 108** and **109**.




**Scheme 33**

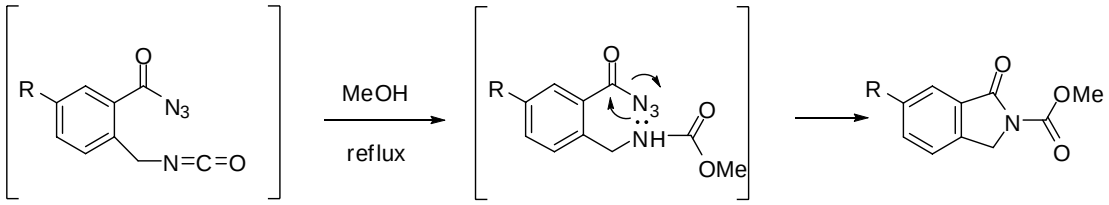
Under the reaction conditions, the protected acid group react with thionyl choride followed by trimethylsilyl azide to form the labile intermediates **113, 114, 115**. Acyl azide now can undergo 1,3 dipolar cycloaddition to isocyanate to give tetrazolinone derivatives **116**, **117**.

By 1,3-dipolar cycloaddition, intermediates **113, 114** were arranged to form tetrazolinone derivatives **116, 117**. Here, azides and isocyanates are 1,3-dipoles and dipolarophiles respectively. This addition forms simultaneously six- and five-membered rings.

It was reported that methoxy substituted intermediate **115** was not arranged to form tetrazolinone derivative.

The isocyanate functionality in **113-115** can also undergo an additional reaction with methanol beside a 1,3-dipolar cycloaddition reaction as described below.

Addition of methanol to isocyanates generates new intermediates **118, 119, 120**. At reflux temperature of methanol, lone pair electrons of nitrogen attack to the carbonyl group to form isoindolinone derivatives **101, 102, 103** as shown in Scheme 34.




R= H **113**
R= Br **114**
R= OMe **115**

R= H **118**
R= Br **119**
R= OMe **120**

R= H **101**
R= Br **102**
R= OMe **103**

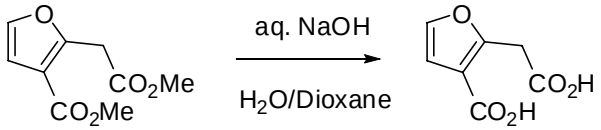
**Scheme 34**

## 2.3 Attempted Synthesis of Furopyrrolone Derivative

In this part we have tried to synthesize new heterocycles such as furopyrrolone derivative by applying of similar methodology which was applied to *β*-(*o*-carboxyphenyl)propionic acid **69**, by starting from 2-(carboxymethyl)furan-3-carboxylic acid **122**.

### 2.3.1 The Hydrolysis of Compound 121 and Formation of Half ester 126

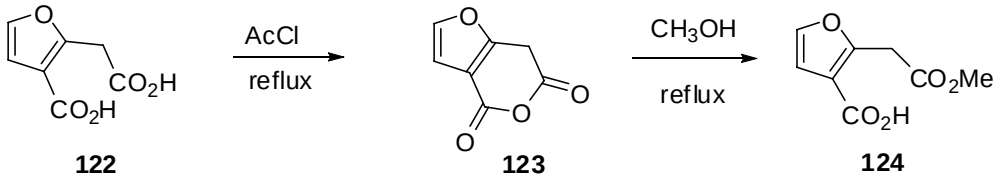
The hydrolysis of compound **121** with sodium hydroxide formed the carboxylic acid derivative **122** (Scheme 35). $^{1}$H-NMR and $^{13}$C-NMR spectra clearly showed the formation of compound **122** by the loss of methoxy groups.




**121** **122**

**Scheme 35**

For the synthesis of half-ester **124,** diacid **122** was treated with acetyl chloride to form anhydride **123**. Then it was reacted with methanol to give half-ester **124** (Scheme 36)**.**



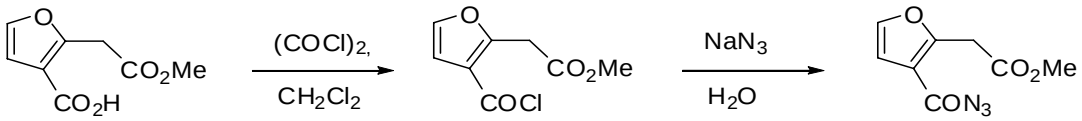

**122** **123** **124**

**Scheme 36**

$^{1}$H-NMR and $^{13}$C-NMR spectra clearly indicated the formation of anhydride **123** and as well as the half-ester **124.** IR spectrum also supported the proposed structure by newly formed –OH stretching peak.

### 2.3.2 The Synthesis of Acyl Azide 126

As it was mentioned in the synthesis of isoquinolone derivative, the azidination step is also an important step for incorporation of nitrogen atom into the structure. In order to achieve this goal, sodium azide was used for the conversion of carboxylic acids **124** into the corresponding acyl azide **126**. But firstly, carboxylic acid **124** was chlorinated by oxalyl chloride for the azidination process. Then, chlorinated compound **125** was reacted with sodium azide to form acyl azide **126** as shown in Scheme 37.




**124** **125** **126**

**Scheme 37**

Besides the $^{1}$H-NMR spectrum, IR spectrum plays an important role for the characterization of acyl azide **126**. The characteristic frequency values of the azide appeared around 2270 and 2140 $cm^{-1}$ (Figure 6).

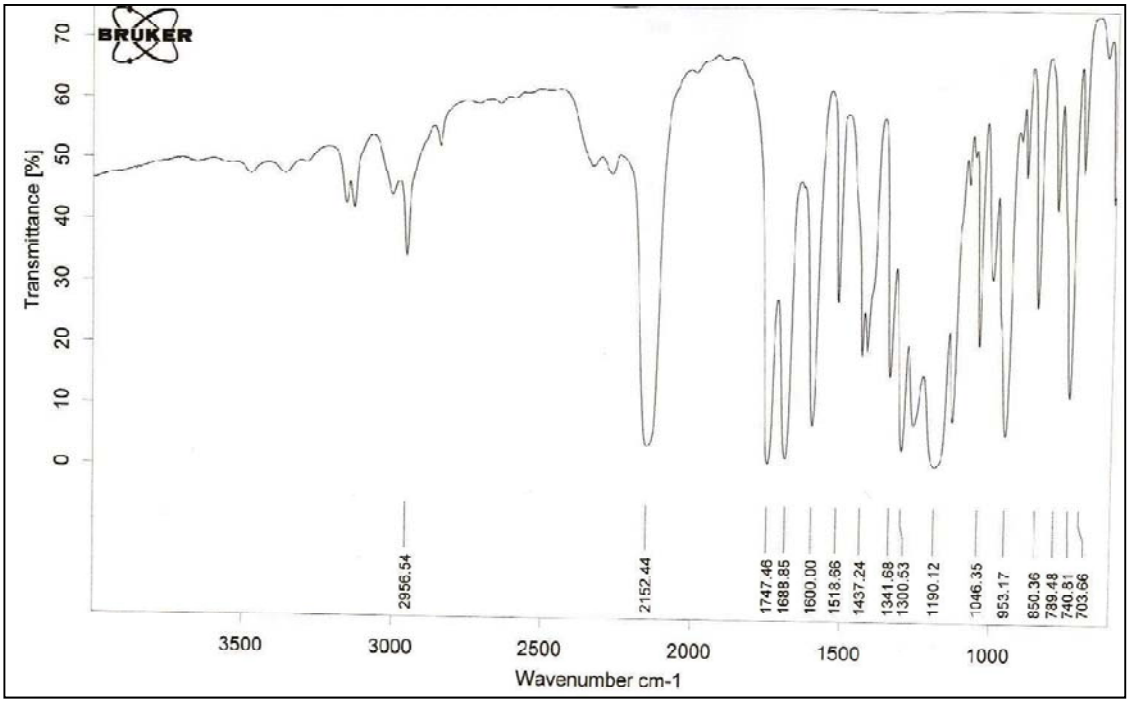
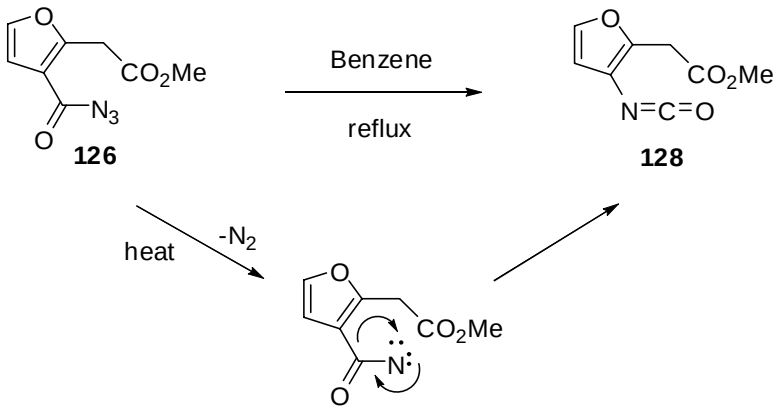



**Figure 6** IR Spectrum of Compound **126**

### 2.3.3 Synthesis of Isocyanate 130

Acyl azide **126** was transformed into acyl nitrene upon heating at reflux temperature of benzene. The formed intermediate **127** was rearranged immediately to the corresponding isocyanates **128** (Scheme 38).




**Scheme 38**

For the characterization of isocyanate **128**, IR spectroscopy plays an important role because IR spectroscopy has characteristic frequency value for isocyanates which is around 2270-2280 $cm^{-1}$ (Figure 7). Also $^{1}$H-NMR and $^{13}$C-NMR support the proposed structure of isocyanate **128.**

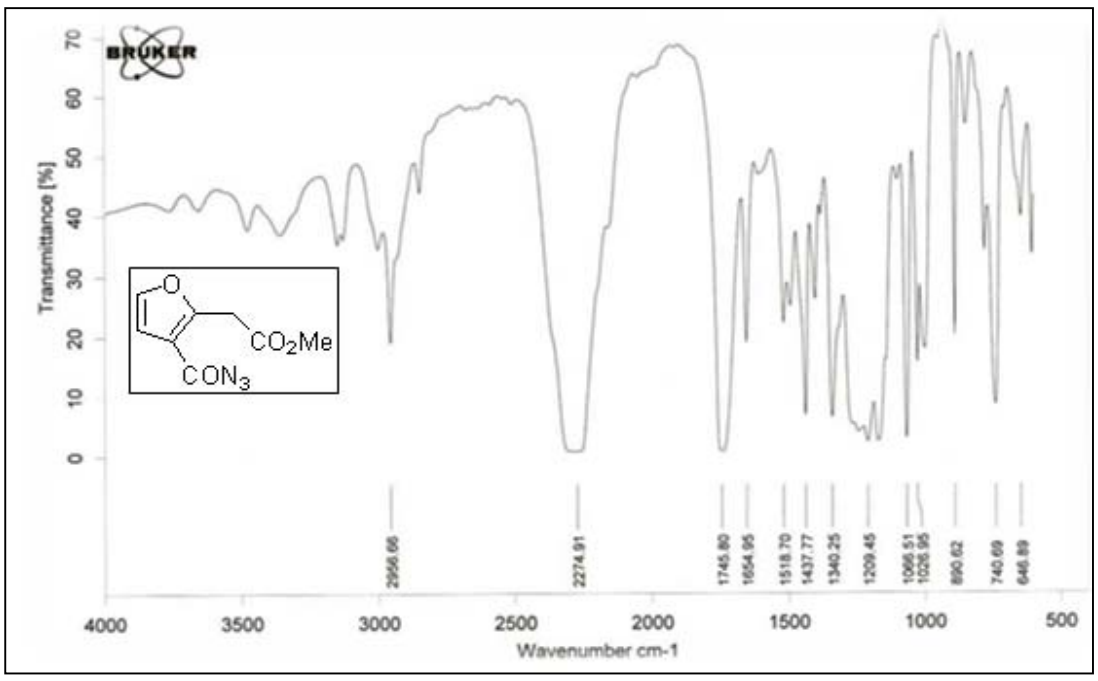
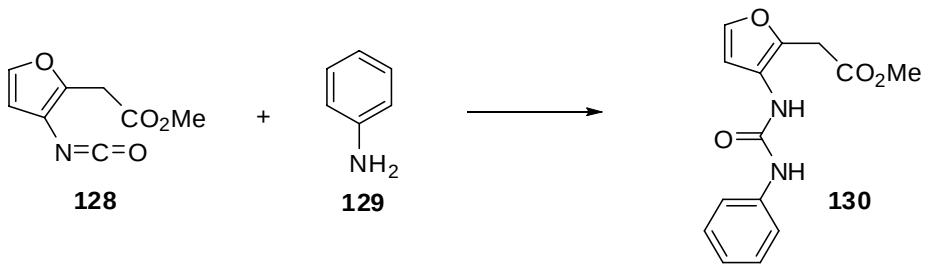



**Figure 7** IR Spectrum of Compound **128**

After synthesis of isocyanate **128,** it was reacted with aniline **129** to form urea derivative **130** as shown in Scheme 39.




**128** **129** **130**

**Scheme 39**

For the characterization of compound **130**, $^{1}$H-NMR spectrum gave useful information. We observed the characteristic peaks for the molecule. For instance, methyl and methylene protons resonate as sharp singlets at 3.59 ppm and 3.62 ppm, respectively. Two broad singlets at 6.88 ppm and 7.33 ppm belong to N-H protons. Aromatic protons appear in a range of 6.91-7.24 ppm (Figure 8).

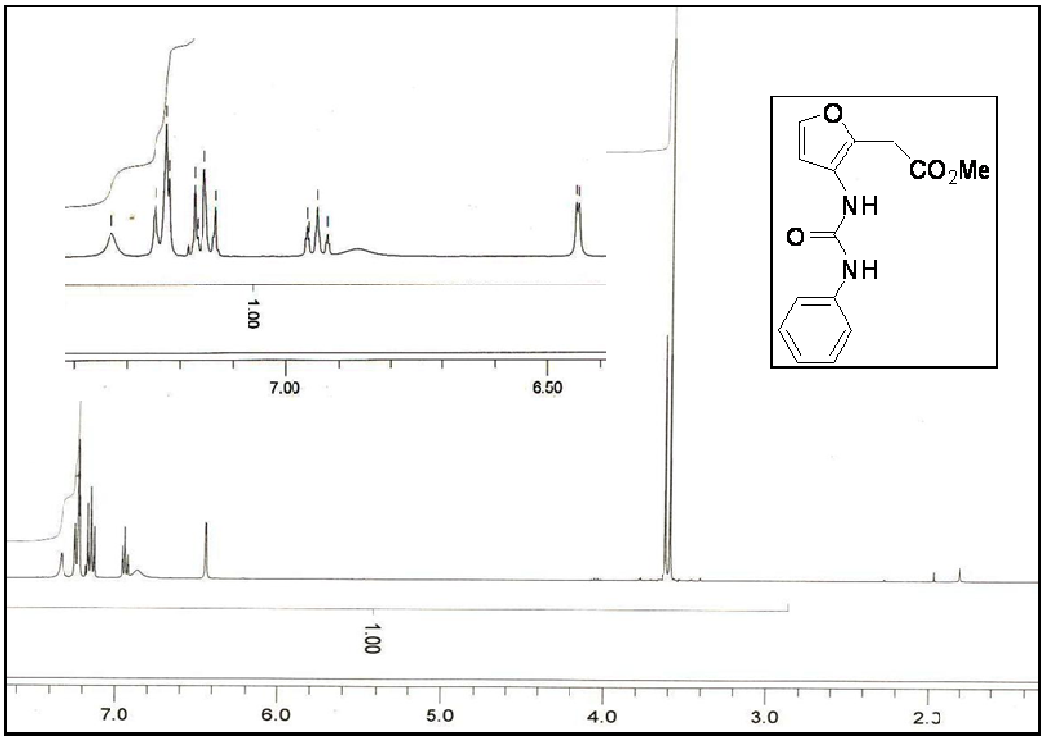
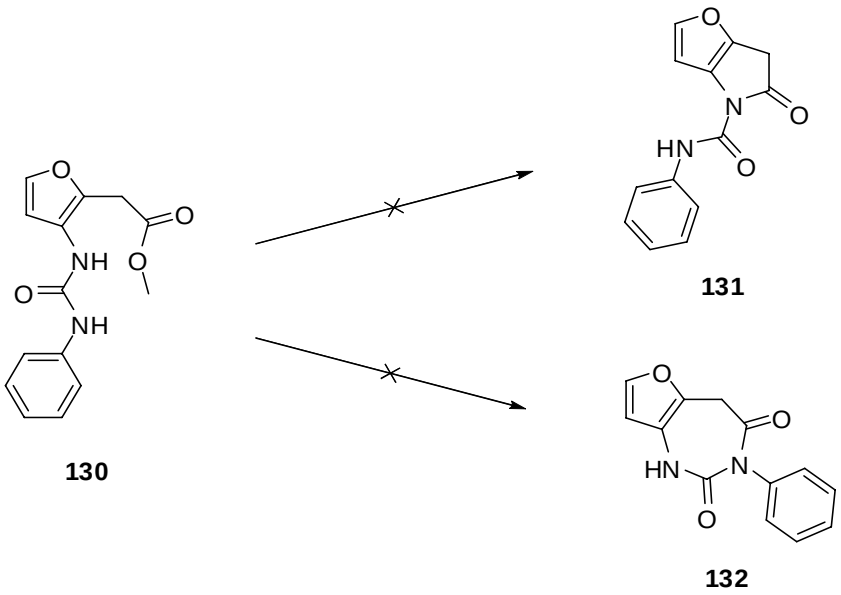



**Figure 8** $^{1}$H-NMR Spectrum of Compound **130**

### 2.3.4 Reaction of Urea Derivative 130 with Bases

The urea derivative **130** was reacted with potassium carbonate in acetonitrile at 60 ºC, for expecting a ring closure. It was expected that potassium carbonate would abstract one of the acidic nitrogen protons and ring closure would take place by attacking of lone pair of nitrogen to the carbonyl carbon of ester group. There were two possible ring closure paths, one of which producing a seven-membered ring **131** and the other producing a five-membered ring **132** (Scheme 40).




**Scheme 40**

Unfortunately, both products were not formed. It was observed that the reaction yielded only starting material **130**. Then, the reaction was repeated at temperatures which are reflux temperature of acetonitrile and at 150 $^{o}$C in a sealed tube. But, again ring closure did not occur.

At that point, it was decided to change the base. Firstly, cesium carbonate was used under the same conditions at three different temperatures (60 $^{o}$C, 82 $^{o}$C, the reflux temperature of acetonitrile, and 150 $^{o}$C). However, again no change on the starting material was observed.

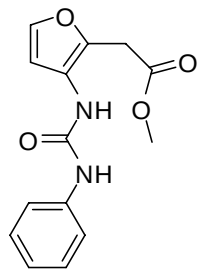
Secondly, lithium bis(trimethylsilyl)amide was chosen as a base. It is a strong non-nucleophilic base and generally used for the deprotonation reactions.[52] The reactions with lithium bis(trimethylsilyl)amide were carried out in THF at 66 $^{o}$C and 150 $^{o}$C (sealed tube). However, this base did not work for our reactions either.

Finially, sodium hydride was used as a base. Sodium hydride was reacted with compound **130** at 0 $^{o}$C in THF. After the reaction, it was observed that the reaction took place but yielded none of the expected products. It was observed that at the end of the

reaction, compound **130** was decomposed. Then, lower temperatures were tried for the reaction with NaH, however starting material **130** was isolated instead of expected products.

Bases and conditions for the ring closure reaction of compound **130** are summarized in Table 1.

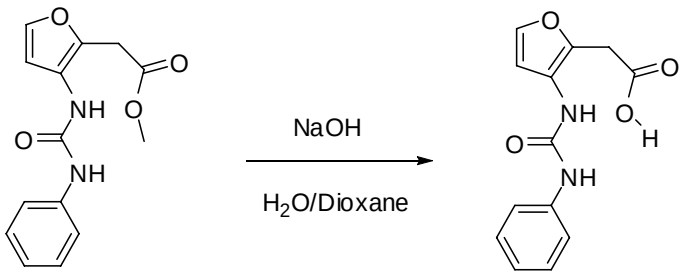
**Table 1** Reaction Conditions of Compound **130**

| | | | |
|---|---|---|---|
|  **130** | Potassium carbonate | 60°C, 82°C, 150°C | No reaction |
| | Cesium carbonate | 60°C, 82°C, 150°C | No reaction |
| | lithium bis(trimethylsilyl)amide | 66°C, 150°C | No reaction |
| | sodium hydride | -70°C, -10°C | No reaction |
| | | 0°C | Decomposition |

### 2.3.5 Ring Closure Reactions without Base

Since ring closure reaction of compound **130** with base could not be achieved, we decided to change the methoxy group attached to carbonyl with a better leaving group. Then, applying heat to the reaction medium would result in the closure of the compound to five or seven membered ring without any base.

In order to change the methoxy group of compound **130**, it was hydrolyzed by sodium hydroxide in water and dioxane mixture. This reaction yielded carboxylic acid **133** as shown in Scheme 41.




**130** **133**

**Scheme 41**

The $^{1}$H-NMR and $^{13}$C-NMR spectra of compound **133** clearly proved the formation of **135** since methoxy peak was disappeared.

We thought that chlorination of compound **133** would result in the formation of expected compounds **131** and **132**. However, chlorination process was also failed even after changing the temperatures. At the end of the chlorination reaction, a muddy black mixture was obtained. Since crude $^{1}$H-NMR did not contain any of the specific peaks that belong to the desired products, we did not proceed with the mixture for further reactions.

# CHAPTER 3

# EXPERIMENT

## 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 ($cm^{-1)}$.

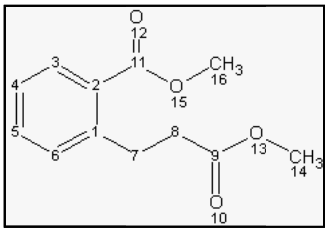
Column chromatographic separations were performed by using Fluka Silica Gel 60 plates with a particle size of 0.063–0.200 mm. Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Fluka.

Compounds were named by using ChemDraw Ultra 10.0.

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

## 3.1 Synthesis of methyl 2-(3-methoxy-3-oxopropyl)benzoate (73)

2-(2-carboxyethyl)benzoic acid **69** (2.0 g, 10.3, mmol) was dissolved in 30 mL of methanol. To this mixture was added thionyl chloride (1.02 ml, 12.36 mmol) and solution was heated up to the reflux temperature (70-80 $^{o}$C). The reaction was monitored by TLC. After the completion of the reaction, methanol and excess thionyl chloride was evaporated to produce product **73** (2.14 g, 9.6 mmol, 94%, pale yellow viscous liquid)




**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ: 7.88 (d, $J_{3,4}$ =8.0 Hz, 1H, H-3 ), 7.40 (t, $J_{4,5}$= $J_{5,6}$=6.5 Hz, 1H, H-5), 7.25 (d, $J_{5,6}$=6.5 Hz, 1H, H-6), 7.25 (t, $J_{3,4}$ = $J_{4,5}$ = 6.5 Hz, 1H, H-4) 3.86 (s, 3H, -$OCH_3$), 3.63 (s, 3H, -$OCH_3$), 3.25 (t, $J_{8a,b,7a}$= $J_{8a,b,7b}$ =7.02 Hz, 2H, H-8a,b) 2.65 (t, $J_{8a\ ,7a,b}$= $J_{8b,7a,b}$ =6.98 Hz, 2H-7a.b);

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ: 173.2, 167.4, 142.4, 132.9, 131.0, 130.8, 129.3, 126.3, 51.9, 51.4, 35.4, 29.8.

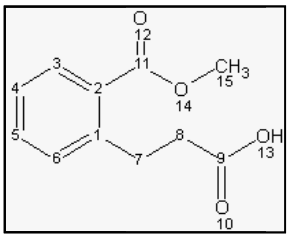
**IR** (KBr, $cm^{-1}$) 3726.4, 2952.1, 2256.3, 1718.9, 1601.7, 1576.8, 1489.6, 1366.3, 1257.8, 1131.3, 907.5, 648.1.

## 3.2 Synthesis of 3-(2-(methoxycarbonyl)phenyl)propanoic acid (74)

Methyl 2-(3-methoxy-3-oxopropyl)benzoate **73** (2.14 g, 9.6 mmol) was dissolved in 25 ml of methanol and 25 ml of water. To this mixture was added excess potassium carbonate (3 g, 21 mmol) and solution was heated up to 60 $^{o}$C for 2 hours. After 2 hours, the mixture was cooled to the room temperature. To this mixture was added dropwise hydrochloric acid solution to obtain acidic medium. 3-(2-(methoxycarbonyl)phenyl)propanoic acid **74** and unreacted methyl 2-(3-methoxy-3-oxopropyl)benzoate **73** was separated with ethyl acetate (50 ml) by extraction. Further

extraction of this mixture with %10 sodium hydroxide solution provided the separation of 3-(2-(methoxycarbonyl)phenyl)propanoic acid **74** and unreacted methyl 2-(3-methoxy-3-oxopropyl)benzoate **73** from each other. These steps were performed on unreacted methyl 2-(3-methoxy-3-oxopropyl)benzoate **73** till it was converted to compound **74**. The aqueous phase, which contains compound **74**, was extracted with ethyl acetate (50 mL). The combined organic extracts were dried over $Mg_2SO_4$. Ethyl acetate was evaporated to give product **74**.

White solid, mp. 69.3 – 69.6 $^oC$.



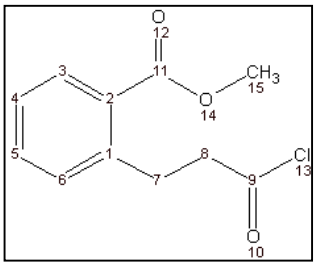

**$^1$H-NMR** (400 MHz, $CDCl_3$) δ : 11.12 (br. s., 1H, -OH), 7.95 (d, $J_{3,4}$ = 7.6 Hz, 1H, H-3 ), 7.45 (t, $J_{4,5}$= $J_{5,6}$ = 7.6 Hz, 1H, H-5), 7.31 (d, $J_{5,6}$=7.6 Hz, 1H, H-6), 7.31 (t, $J_{3,4}$ = $J_{4,5}$ = 7.6 Hz, 1H, H-4) 3.91 (s, 3H, -$OCH_3$), 3.31 (t, $J_{8a,b,7a}$= $J_{8a,b,7b}$ =7.7 Hz, 2H, H-8a,b) 2.66 (t, $J_{8a\ ,7a,b}$= $J_{8b,7a,b}$ = 7.8 Hz, 2H-7a.b);

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ: 173.2, 167.4, 142.4, 132.9, 131.0, 130.8, 129.3, 126.3, 51.2, 35.4, 29.8.

**IR** (KBr, $cm^{-1}$) 2812.9, 2650.4, 1678.2, 1599.5, 1492.2, 1308.1, 1214.8, 1150.1, 809.2, 680.1, 536.1.

## 3.3 Synthesis of Methyl 2-(3-chloro-3-oxopropyl)benzoate (75)

3-(2-(Methoxycarbonyl)phenyl)propanoic acid **74** (1,0 g, 4,8 mmol) was dissolved in 25 ml of dichloromethane. To this mixture was added oxalyl chloride (0.5 ml, 5.76 mmol) and solution was kept at room temperature for 1 hour. After the reaction was completed dichloromethane was evaporated to give product **75** (0.97 gr, 4.27 mmol, 89%).

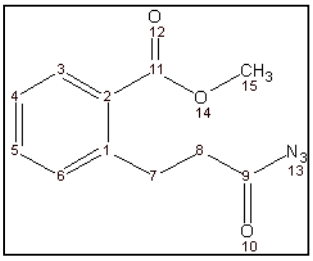


**$^{1}$H-NMR** (400 MHz, $CDCl_3$) *δ:* 7.96 (d, $J_{3,4}$=7.8 Hz, 1H, H-3 ), 7.41 (td, $J_{4,5}$= $J_{5,6}$ = 7.7 Hz, $J_{3,5}$ = 1.5 Hz, 1H, H-5), 7.30 (td, $J_{3,4}$ = $J_{4,5}$ = 7.7 Hz, $J_{4,6}$ = 1.3 Hz, 1H, H-4), 7.28 (d, $J_{5,6}$=7.5 Hz, 1H, H-6), 3.29 (m, 4H, H-8a,b, H-7a,b), 3.88 (s, 3H, -$OCH_3$).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$)*δ:* 173.2, 167.4, 140.7, 132.6, 131.4, 131.2, 129.0, 127.0, 52.1, 48.4, 30.2.

## 3.4 Synthesis of Methyl 2-(3-azido-3-oxopropyl)benzoate (76)

Methyl 2-(3-chloro-3-oxopropyl)benzoate **75** (0.97 g, 4.27 mmol) was dissolved in 25 ml of acetone. To this mixture was added dropwise sodium azide (1,5 g, 23 mmol) in 25 ml of water at 0 $^{o}$C and solution was kept at 0 $^{o}$C for 1 hour. After the reaction was completed, methyl 2-(3-azido-3-oxopropyl)benzoate **76** was separated with ethyl acetate (50 ml) by extraction with water (50 ml). The combined organic extracts were dried over $Mg_2SO_4$. Ethyl acetate was evaporated to give product **76** (0.84 g, 3.57 mmol, 83%, pale yellow viscous liquid).



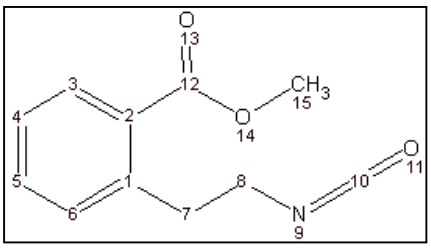
**$^{1}$H-NMR** (400 MHz, $CDCl_3$) *δ:* 7.96 (d, $J_{3,4}$=7.8 Hz, 1H, H-3 ), 7.41 (td, $J_{4,5}$= $J_{5,6}$ = 7.7 Hz, $J_{3,5}$ = 1.5 Hz, 1H, H-5), 7.30 (td, $J_{3,4}$ = $J_{4,5}$ = 7.7 Hz, $J_{4,6}$ = 1.3 Hz, 1H, H-4), 7.28 (d, $J_{5,6}$=7.5 Hz, 1H, H-6), 3.88 (s, 3H, -$OCH_3$), 3.58 (t, $J_{7a,b,8a}$= $J_{7a,b,8b}$ =6.8 Hz, 2H, H-7a,b) 2.71 (t, $J_{7a\ ,8a,b}$= $J_{7b,8a,b}$ = 6.8 Hz, 2H-8a.b);

**$^{13}$C-NMR** (100 MHz, $CDCl_3$)*δ:* 179.7, 167.4, 141.9, 139.7, 131.0, 130.8, 129.3, 126.3, 52.1, 43.8, 38.3.

**IR** (KBr, $cm^{-1}$) 2956.5, 2152.4 ($N_3$), 1742.4, 1688.9, 1600.3, 1437.2, 1300.1, 1046.4, 850.4, 740.9.

## 3.5 Synthesis of Methyl 2-(3-isocyanato-3-oxopropyl)benzoate (78)

Methyl 2-(3-azido-3-oxopropyl)benzoate **76** (0.84 g, 3.6 mmol) was dissolved in 25 ml of benzene and heated to reflux temperature (75-80 $^0$C). After the rearrangement was complete, benzene was evaporated to give product **78** (0.82g, 3.52 mmol, 98%, pale yellow viscous liquid).




**$^1$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.89 (d, $J_{3,4}$=7.8 Hz, 1H, H-3 ), 7.39 (t, $J_{4,5}$= $J_{5,6}$ = 7.5 Hz, 1H, H-5), 7.27 (d, $J_{5,6}$=5.3 Hz, 1H, H-6), 7.27 (t, $J_{3,4}$ = $J_{4,5}$ = 6.1 Hz, 1H, H-4) 3.82 (s, 3H, -$OCH_3$), 3.53 (t, $J_{7a,b,8a}$= $J_{7a,b,8b}$ =6.7 Hz, 2H, H-7a,b) 2.66 (t, $J_{7a\ ,8a,b}$= $J_{7b,8a,b}$ =6. 8 Hz, 2H-8a.b);

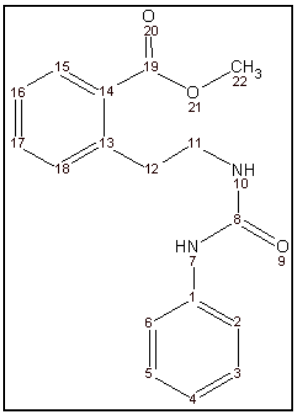
**$^{13}$C-NMR** (100 MHz, $CDCl_3$)$\delta$: 167.4, 139.4, 132.5, 131.0, 130.8, 129.8, 128.3, 122.2, 52.1, 43.8, 36.3.

**IR** (KBr, cm$^{-1}$) 2953.2, 2271.4 (NCO), 1715.9, 1489.7, 1353.5, 1264.6, 1085.8, 966.1, 751.8, 582.3.

## 3.6 Synthesis of Methyl 2-(2-(3-phenylureido)ethyl)benzoate (79)

Methyl 2-(3-isocyanato-3-oxopropyl)benzoate **78** (0.82 g, 3.52 mmol) was dissolved in 25 ml of dichloromethane. To this mixture was added aniline and kept for 2 hours at room temperature. After 2 hours, mixture was washed with 2 molar of hydrochloric acid (25 ml) solution in order to get rid of excess aniline. The combined organic extracts were dried over $Mg_2SO_4$. Dichloromethane was evaporated. The crude product was chromatographed on silica gel (20 g) eluting with hexane/ethyl acetate (1:1) by column chromatography to give product **79** (0.68 g, 2.28 mmol, 65%).

White solid, mp. 131-144$^{o}$C




**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ : 7.84 (d, 7.2 Hz, H-15), 6.94 – 7.41 (m, 8H, H-2,3,4,5,6,16,17,18) 7.29 (br s, NH, H-7), 5.4 (br. s, NH, H-10) 3.81 (s, 3H, -$OCH_3$), 3.42 (dt, $J_{11a,b,10}$ = 6.5 Hz, $J_{11a\ b,12a}$ = $J_{11a,b,12b}$ = 7.2 Hz, 2H, H-11a,b) 3.09 (t, $J_{12a\ b,11a}$ = $J_{12a,b,11b}$ = 7.5 Hz, 2H - 12a.b);

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ : 168.2, 156.3, 149.9, 139.2, 132.4, 131.6, 130.8, 129.4, 128.9 (C-3, C-5), 126.6, 123.0, 120.4 (C-2, C-6), 42.0, 34.9.

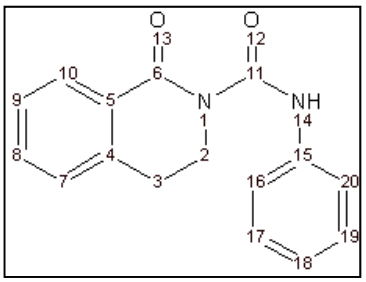
**IR** (KBr, cm-1) 3354, 3316, 3022, 2947, 1721, 1629, 1593, 1557, 1443, 1314, 1247, 1108, 1087, 1028, 968.

**Anal. Calcd. for** $C_{17}H_{18}N_2O_3$; C, 68.44; H, 6.08; N, 9.39; O, 16.09. Found: C, 68.53; H, 5.82; N, 9.74.

## 3.7 Synthesis of 1-oxo-N-phenyl-3,4-dihydroisoquinoline-2(*1H*)-carboxamide (80)

Methyl 2-(2-(3-phenylureido)ethyl)benzoate **79** (0.68 g, 2.28 mmol) was dissolved in 25 ml of THF. To this mixture was added sodium (0.063 g, 2.74 mmol) hydride and kept for half an hour at 0 $^{0}$C. After reaction completed, water was added dropwise to neuturalize unreacted sodium hydride. After, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3x50 ml). The combined organic extracts were dried over $MgSO_4$. Removal of the solvent gave the crude product, which chromatographed on silica gel (20 g) eluting with hexane/ethyl acetate (3:2). The obtained product was crystallized from ethyl acetate/hexane (5:1) to give white solid **80** (0.41g, 1.54mmol**,** 68%)

White solid, mp. 162-165 $^0$C




**$^1$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 11.78 (br.s., -NH, H-14), 8.13 (dd, $J_{9,10}$ =6.8 Hz, $J_{8,10}$ =1.0 Hz 1H, H-10 ), 7.58 (dd, $J_{16,17}$= $J_{19,20}$ = 7.5 Hz, $J_{16,18}$= $J_{18,20}$ = 1.2 Hz, 2H, H-16, H-20), 7.54 (td, $J_{7,8}$= $J_{8,9}$= 7.5 Hz, $J_{8,10}$= 1.3 Hz, 1H, H-8), 7.41 (t, $J_{9,10}$ = $J_{8,9}$ = 6.8 Hz, 1H, H-9), 7.35 (t, $J_{17,18}$= $J_{16,17}$=$J_{18,19}$ = $J_{19,20}$ = 7.5 Hz, 2H, H-17, H-19), 7.27 (d, $J_{7,8}$= 7.5 Hz, 1H, H-7), 7.12 (t, $J_{17,18}$ = $J_{18,19}$ = 7.5 Hz, 1H, H-18), 4.25 (t, $J_{2a,b,3a}$= $J_{2a,b,3b}$ =6.4 Hz, 2H, H-7a,b) 3.05 (t, $J_{2a\ ,3a,b}$= $J_{2b,3a,b}$ =6.4 Hz, 2H-8a.b).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$)$\delta$ : 168.1, 152.6, 140.2, 138.2, 133.8, 129.6, 129.4(C-17, C-19), 129.2, 127.7, 127.4, 124.4, 120.8(C-16, C-20), 41.9, 28.2.

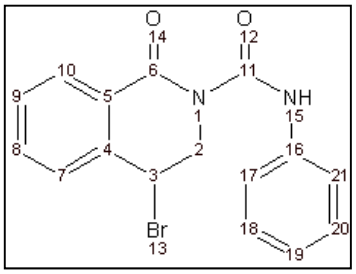
**IR** (KBr, cm-1) : 2924, 1703, 1653, 1596, 1556, 1445, 1392, 1318, 1225, 1151, 898, 737

**Anal. Calcd. for** $C_{16}H_{14}N_2O_2$; C, 72.16; H, 5.30; N, 10.52; O, 12.02. Found: C, 72.16; H, 5.19; N, 10.55.

## 3.8 Synthesis of 4-bromo-1-oxo-N-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxamide (81)

1-Oxo-N-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxamide **80** (0.41 g, 1.54 mmol) was dissolved in 10 ml of benzene. To this mixture was added NBS (0.27 g, 1.54 mmol) and AIBN (0.05 g, 0.03 mmol) and heated up to the reflux temperature (75-80 $^0$C) for 5 hours. After the reaction completed, the mixture was filtered. Removal of the solvent gave the crude product, which chromatographed on silica gel (20 g) eluting with hexane/ethyl acetate (3:2). The obtained product was crystallized from ethyl acetate/hexane (5:1) to give white solid **81** (0.35g, 1.02mmol, 70%)**.**

White solid, mp. 151- 154 $^0$C




**$^1$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 11.69 (br.s., -NH, H-15), 8.21 (dd, $J_{9,10}$ =7.8 Hz, $J_{8,10}$ =1.2 Hz 1H, H-10 ), 7.62 (dd, $J_{17,18}$= $J_{20,21}$ = 7.5 Hz, $J_{17,19}$= $J_{19,21}$ = 1.2 Hz, 2H, H-17, H-21), 7.63 (td, $J_{9,10}$ = $J_{8,9}$ = 7.6 Hz, $J_{7,9}$= 1.3 Hz, 1H, H-9), 7.54 (td, $J_{7,8}$= $J_{8,9}$= 7.6 Hz, $J_{8,10}$= 1.3 Hz, 1H, H-8), 7.45 (dd, $J_{7,8}$= 7.6 Hz, $J_{7,9}$= 1.3 Hz, 1H, H-7), 7.36 (t, $J_{18,19}$= $J_{17,18}$=$J_{19,20}$ = $J_{20,21}$ = 7.5 Hz, 2H, H-18, H-20), 7.12 (tt, $J_{17,18}$ = $J_{18,19}$ = 7.5 Hz, $J_{17,19}$= $J_{19,21}$ = 1.2 Hz, 1H, H-19), 5.44 (t, $J_{2a,b,3}$ = 2.9 Hz, 1H, H-3) 5.20 (dd, $J_{2a\ ,2b}$ = *14.9,* $J_{2a,3}$ = 3.1 Hz, 1H, H–2a), 3.93 (dd, $J_{2a\ ,2b}$ = *14.9,* $J_{2b,3}$ = 2.8 Hz, 1H, H–2b).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$)$\delta$ *:* 166.3, 151.8, 139.6, 136.8, 134.3, 132.0(C-18, C-20), 129.9, 129.8, 127.7, 126.9, 122.0(C-17, C-21), 116.9, 48.5, 43.1.

**IR** (KBr, cm$^{-1}$) 3129, 3033, 1701, 1657, 1592, 1546, 1500, 1486, 1440, 1389, 1292, 1176, 1149, 1014, 958.

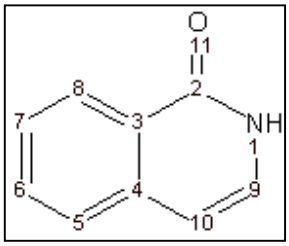
**Anal. Calcd. for** $C_{16}H_{13}BrN_2O_2$; C, 55.67; H, 3.80; Br, 23.15; N, 8.12; O, 9.27. Found: C, 55.45; H, 3.68; N, 8.13.

## 3.9 Synthesis of isoquinolin-1(2H)-one (83)

4-Bromo-1-oxo-N-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxamide **81** (0.353 g, 1.023 mmol) was dissolved in 10 ml of t-BUOH. To this mixture was added t-BuOK (0.113 g, 1.023 mmol) and heated up to the reflux temperature (70-85 $^0$C) for 15 minutes. Removal of the solvent gave the crude product, which chromatographed on silica gel (15 g) eluting with hexane/ethyl acetate (3:2). The obtained product was

crystallized from ethyl acetate/hexane (5:1) to give white solid **83** (0.103 g, 0.7 mmol, 70%)

White solid, mp. 210-212 $^{o}C$[54]




**$^{1}$H-NMR** (400 MHz, $CDCl_3$) *δ:* 9.19 (br.d., $J_{1,9}$ = 3.0 Hz, -NH, H-1), 8.34 (d, $J_{7,8}$ =7.9 Hz, 1H, H-8 ), 7.63 (td, $J_{7,8}$= $J_{6,7}$ = 7.9 Hz, $J_{5,7}$= 1.3 Hz, 1H, H-7), 7.60 (td, $J_{6,7}$ = $J_{5,6}$ = 7.6 Hz, $J_{6,8}$= 1.3 Hz, 1H, H-6), 7.59 (dd, $J_{5,6}$= 7.9 Hz, $J_{5,7}$= 1.2 Hz, 1H, H-5), 7.00 (dd, $J_{1,9}$=3.0 Hz, $J_{9,10}$ = 7.3 Hz, 1H, H-9), 6.44 (d, $J_{9,10}$ = 7.3 Hz, 1H, H-10)

**$^{13}$C-NMR** (100 MHz, $CDCl_3$)*δ:* 162.7, 138.1, 133.0, 127.5, 127.2, 127.1, 126.3, 107.5, 99.9.

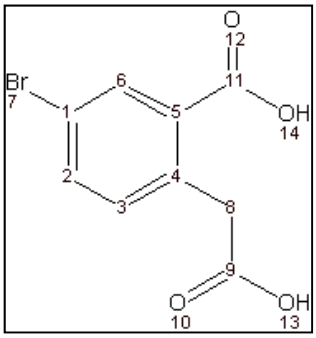
**IR** (KBr, $cm^{-1}$) 3517, 3205, 3004, 2253, 1735, 1534, 1476, 1437, 1370, 1335, 1216, 1163, 1111, 1074, 937.

**Anal. Calcd. for** $C_9H_7NO$; C, 74.47; H, 4.86; N, 9.65; O, 11.02. Found: C, 71.22; H, 4.55; N, 9.19.

## 3.10 Synthesis of 5-bromo-2-(carboxymethyl)benzoic acid (91)

Homophtalic acid **90** (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 drop wise 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 **91** (3.2 g, 12 mmol, 44.4 %). The product was crystallized from EtOAc/hexane (4/1).

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, H-8a,b)

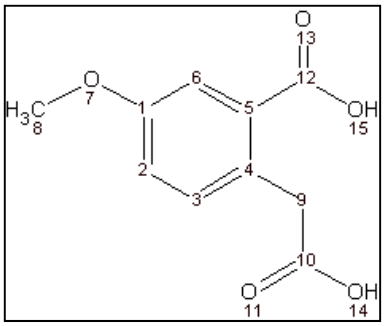
**$^{13}$C-NMR** (100 MHz, DMSO-$_{d6}$) δ 172.0, 166.9, 135.9, 134.5, 134.4, 132.7, 132.6, 119.7, 39.2

**IR** (KBr, cm$^{-1}$) 2874, 2641, 1592, 1431, 1274, 1228, 1191, 1153, 907, 772, 718.

**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.

## 3.11 Synthesis of 2-(carboxymethyl)-5-methoxybenzoic acid (96)

3-Methoxybenzoic acid **92** (12.5 g, 82 mmol), chloral hydride **93** (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 **94** (21 g, 74 mmol, 90.2 %.). To (19 g, 67 mmol) **94** 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 **95** (14 g, 56 mmol, 83.5 %.). To 20 ml 90% sulphuric acid, **95** (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 **96** (4.5 g, 21 mmol, 91.3 %).



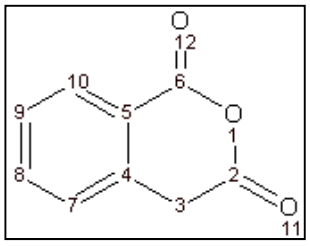
**$^{1}$H-NMR** (400 MHz, DMSO-$_{d6}$) δ 7.40 (d, $J_{6,2}$ = 2.8 Hz, 1H, H-6), 7.23 (br d, $J_{3,2}$ = 8.4 Hz, 1H, H-3), 7.07 (br dd, $J_{2,3}$ = 8.4 Hz, $J_{2,6}$= 2.8 Hz, 1H, H-2), 3.85 (s, 2H, H-9a,b), 3.78 (s, 3H, -OCH$_3$)

**$^{13}$C-NMR** (100 MHz, DMSO-$_{d6}$) δ 172.7, 168.0, 157.8, 133.4, 131.5, 128.5, 117.4, 115.3, 55.2, 38.9

## 3.12 Synthesis of Isochroman-1,3-dione (97)

Homophthalic acid **90** (5 g, 27.8 mmol) was dissolved in dicholoromethane (100 ml). To this mixture was added an excess amount of thionyl chloride (5 ml, 68 mmol) at refux temperature. Than the reaction was left stirring until all the homophthalic acid was dissolved in the mixture. After the completion of the reaction solvent and excess thionyl chloride was evaporated under vacuum pressure to get **97** (4.4 g, 26.9 mmol, 97 %)

Yellow solid mp. 144-145°C (lit.) 143ºC (found).



**$^{1}$H-NMR** (400 MHz, CDCl$_3$) δ: 8.22 (br d, $J_{9,10}$ = 7.8 Hz, 1H, H-10), 7.70 (br dd, $J_{9,10}$ = 7.8 Hz, $J_{8,9}$ = 7.6 Hz, 1H, H-9), 7.52 (br t, $J_{8,9}$ = $J_{7,8}$= 7.6 Hz, 1H, H-8), 7.35 (br d, $J_{7,8}$ = 7.6 Hz, 1H, H-7), 4.14 (s, 2H, H-3a,b).

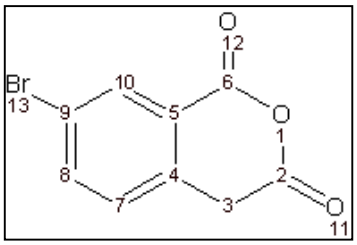
**$^{13}$C-NMR** (100 MHz, CDCl$_3$) δ: 165.0, 161.3, 135.9, 134.7, 131.3, 129.1, 127.9, 121.9, 34.7.

**Anal. Calcd for $C_9H_6O_3$ :** C, 66.67; H, 3.73 Found: C, 66.48; H, 4.06.

## 3.13 Synthesis of 7-bromoisochroman-1,3-dione (98)

Bromine substituted homophthalic acid **91** (5 g, 19 mmol) was dissolved in dicholoromethane (100 ml). To this mixture was added an excess amount of thionyl chloride (5 ml, 68 mmol) at refux temperature. Than the reaction was left stirring until all the bromine substituted homophthalic acid was dissolved in the mixture. After the completion of the reaction solvent and excess thionyl chloride was evaporated under vacuum pressure to get **98** (4.5 g, 18.6 mmol, 97.8 %)

Pale 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, H-3a,b)

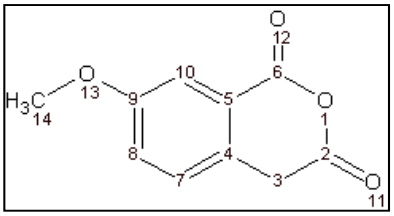
**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ: 161.2, 157.2, 136.0, 131.1, 130.5, 126.6, 120.9, 120.1, 31.6

**IR** (KBr, $cm^{-1}$) 3094, 2949, 1796, 1780, 1296, 1195, 1177, 1060, 906, 762, 727.

**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

## 3.14 Synthesis of 7-methoxyisochroman-1,3-dione (99)

Methoxy substituted homophthalic acid **96** (5 g, 23.7 mmol) was dissolved in dicholoromethane (100 ml). To this mixture was added an excess amount of thionyl chloride (5 ml, 68 mmol) at refux temperature. Than the reaction was left stirring until all the methoxy substituted homophthalic acid was dissolved in the mixture. After the completion of the reaction solvent and excess thionyl chloride was evaporated under vacuum pressure to get **99** (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, H-3a,b), 3.82 (s, 3H, -OCH3);

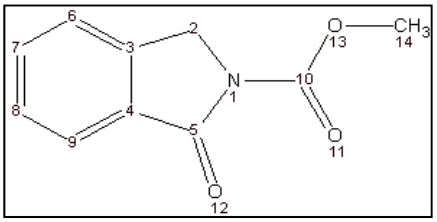
**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ: 164.9, 161.2, 159.9, 128.8, 126.6, 124.2, 122.7, 113.2, 56.0, 34.0

## 3.15 Synthesis of Methyl 1-oxoisoindoline-2-carboxylate (101) and 3H-tetrazolo[2,1-b]phthalazine-3,10(*5H*)-dione (116)

Homophthalic anhydride **97** (3.16 g, 19.5 mmol) was dissolved in THF (25 mL). To this mixture was added 1.2 equivalent of trimethylsilyly azide (3.06 mL, 23.4 mmol) and kept at reflux temperature (66$^{o}$C) for 3 hours. At the end of the reaction, THF was removed under vacuum. The residue was collected and dissolved in $CCl_4$ (25 mL) and to this mixture was added thionyl chloride (1.6 mL, 23.4 mmol). After 3 hours of stirring at reflux temperature (77$^{o}$C), the solvent was removed. The remaining residue was dissolved in THF (25 mL) and was added TMSA (3.06 mL, 23.4 mmol). After 3 hours of stirring at reflux temperature (66$^{o}$C) the solvent was removed and the residue was dissolved in methanol (25 mL). Stirring 3 hours at reflux temperature, methanol was evaporated. The residue was chromatographed on silica gel (50 g) (3:2 Ethyl Acetate/Hexane) to get compounds **101** and **116** with yields 40 % and 38 %. The obtained products were crystallized from ethyl acetate/hexane (5:1) to give white solid **101**, **116**.

**Methyl 1-oxoisoindoline-2-carboxylate (101)**

White solid m.p. 143-147 °C



**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ: 7.78 (d, $J_{8,9}$ = 7.5 Hz, 1H, H-9), 7.57 (t, $J_{7,8} = J_{8,9}$ = 7.5 Hz, 1H, H-8), 7.46 (d, $J_{6,7}$ = 7.5 Hz, 1H, H-6) 7.42 (t, $J_{6,7} = J_{7,8}$ = 7.5 Hz, 1H, H-7), 4.72 (s, 2H, H-2a,b), 3.85 (s, 3H, -OCH3).

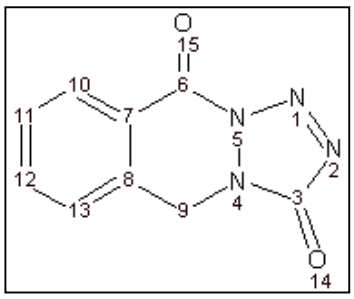
**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ: 171.4, 157.4, 146.4, 138.9, 136.1, 133.7, 129.9, 128.5, 58.5, 54.3.

**IR** (KBr, $cm^{-1}$) 2956, 2251, 1785, 1598, 1469, 1263, 1190, 1103, 1019, 999, 884, 771, 681, 581, 479.

**Anal. Calcd. For** $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33; O, 25.11. Found: C, 62.51; H, 4.48; N, 7.70.

**3H-Tetrazolo[2,1-b]phthalazine-3,10(5H)-dione (116)**

Pale yellow solid m.p. 281-283 °C



**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ: 7.86 (d, $J_{10,11}$ = 7.5 Hz, 1H, H-10), 7.63 (t, $J_{10,11} = J_{11,12}$ = 7.5 Hz, 1H, H-11), 7.46 (m, 2H, H-12, H-13), 4.39 (s, 2H, H-9a,b).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ: 165.6, 154.4, 140.7, 134.3, 130.4, 128.9, 125.5, 123.3, 49.2.

**IR** (KBr, $cm^{-1}$) 2251, 1744, 1695, 1363, 1337, 1282, 1213, 1194, 1158, 722, 554.

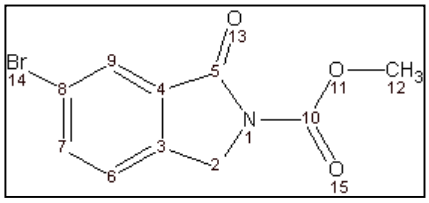
**Anal. Calcd. For** $C_9H_6N_4O_2$: C, 53.47; H, 2.99; N, 27.71; O, 15.83. Found: C, 53.21; H, 3.38; N, 27.49

## 3.16 Synthesis of Methyl 6-bromo-1-oxoisoindoline-2-carboxylate (102) and 7-bromo-3H-tetrazolo[2,1-b]phthalazine-3,10(*5H*)-dione (117)

Bromine substituted homophthalic anhydride **98** (4.68 g, 19.5 mmol) was dissolved in THF (25 mL). To this mixture was added 1.2 equivalent of TMSA (3.06 mL, 23.4 mmol) and kept at reflux temperature (66 $^{o}$C) for 3 hours. At the end of the reaction, THF was removed under vacuum. The residue was collected and dissolved in $CCl_4$ (25 mL) and to this mixture was added thionyl chloride (1.6 mL, 23.4 mmol). After 3 hours of stirring at reflux temperature (77 $^{o}$C), the solvent was removed. The remaining residue was dissolved in THF (25 mL) and was added TMSA (3.06 mL, 23.4 mmol). After 3 hours of stirring at reflux temperature (66$^{o}$C) the solvent was removed and the residue was dissolved in methanol (25 mL). Stirring 3 hours at reflux temperature, methanol was evaporated. The residue was chromatographed on silica gel (50 g) (3:2 Ethyl Acetate/Hexane) to get compounds **102** and **117** with yields of 32 % and 36 %.

**Methyl 6-bromo-1-oxoisoindoline-2-carboxylate (102)**

Pale yellow solid m.p. 186-188 °C

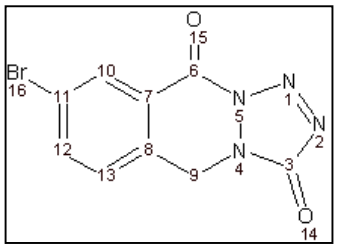



**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ: 8.1 (d, $J_{7,9}$ = 2.0 Hz, 1H, H-9), 7.77 (dd, $J_{7,9}$ = 2.0 Hz, $J_{6,7}$ = 6.2 Hz, 1H, H-7), 7.38 (d, $J_{6,7}$ = 6.2 Hz, 1H, H-6), 4.80 (s, 2H, H-2a,b), 3.99 (s, 3H, -OCH3).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ: 165.0, 153.6, 139.6, 137.1, 133.3, 128.6, 125.1, 123.6, 54.2, 49.2.

**IR** (KBr, $cm^{-1}$) 3058, 3007, 2949, 2848, 1767, 1695, 1438, 1363, 1320, 1256, 1208, 1139, 1005, 886, 848.

**7-Bromo-3H-tetrazolo[2,1-b]phthalazine-3,10(5H)-dione (117)**



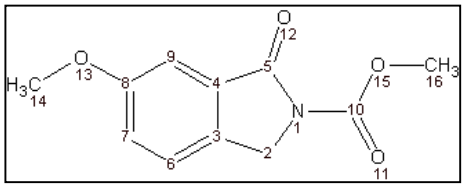

**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ: 8.0 (d, $J_{7,9}$ = 2.0 Hz, 1H, H-9), 7.73 (dd, $J_{7,9}$ = 2.0 Hz, $J_{6,7}$ = 6.2 Hz, 1H, H-7), 7.33 (d, *J*6,7 = 6.2 Hz, 1H, H-6), 4.74 (s, 2H, H-2a,b).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ: 164.5, 154.7, 139.5, 137.7, 132.7, 128.8, 135.3, 132.2, 49.3.

**IR** (KBr, $cm^{-1}$) 2957, 2260, 2160, 1799, 1758, 1757, 1325, 1251, 1145, 1057, 1026, 913, 842, 736.

## 3.17 Synthesis of Methyl 6-methoxy-1-oxoisoindoline-2-carboxylate (103)

Methoxy substituted homophthalic anhydride **99** (3.75 g, 19.5 mmol) was dissolved in THF (25 mL). To this mixture was added 1.2 equivalent of TMSA (3.06 mL, 23.4 mmol) and kept at reflux temperature (66 $^{o}$C) for 3 hours. At the end of the reaction, THF was removed under vacuum. The residue was collected and dissolved in $CCl_4$ (25 mL) and to this mixture was added thionyl chloride (1.6 mL, 23.4 mmol). After 3 hours of stirring at reflux temperature (77 $^{o}$C), the solvent was removed. The remaining residue was dissolved in THF (25 mL) and was added TMSA (3.06 mL, 23.4 mmol). After 3 hours of stirring at reflux temperature (66$^{o}$C) the solvent was removed and the residue was dissolved in methanol (25 mL). Stirring 3 hours at reflux temperature, methanol was evaporated. The residue was chromatographed on silica gel (50 g) (3:2 Ethyl Acetate/Hexane) to get compound **103** (2.28 g, 10.3 mmol, 53 %).

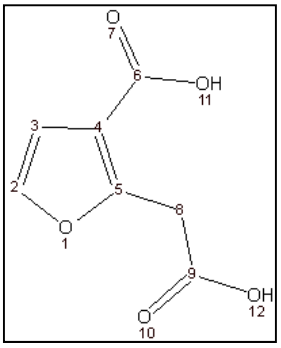


**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ: 7.63 (d, $J_{7,9}$ = 2.8 Hz, 1H, H-9), 7.19 (d, $J_{6,7}$ = 8.4 Hz, A-part of AB-system, 1H, H-6), 7.07 (dd, $J_{6,7}$ = 8.4 Hz, $J_{7,9}$ = 2.8 Hz, B-part of AB-system, 1H, H-7), 3.99 (s, 2H, H-2a,b), 3.86 (s, 3H, -$OCH_3$), 3.70 (s, 3H, -$OCH_3$).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$) δ: 164.8, 158.7, 139.4, 133.5, 128.8, 125.1, 119.7 116.5, 55.5, 51.9, 39.8.

## 3.19 Synthesis of 2-(carboxymethyl)furan-3-carboxylic acid (122)

To a mixture of water/methanol (30 mL/30 mL) was added methyl 2-(2-methoxy-2-oxoethyl)furan-3-carboxylate **121** (5 g, 25.3 mmol) and excess amount of $K_2CO_3$ ( 5.3 g, 37.9 mmol). The mixture was left for stirring at 60$^{o}$C. The reaction was monitored on TLC. After the completion of the reaction, excess HCl was added to the mixture to obtain acidic medium. Then, the mixture was extracted with ethyl acetate (40 mL). The combined organic extracts were dried over $Mg_2SO_4$. Ethyl acetate was evaporated and gave product **122** (4.17 g, 24.5 mmol, 97 %).

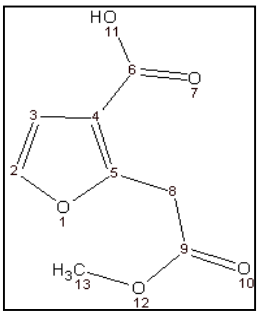


**$^{1}$H-NMR** (400 MHz, DMSO-$_{d6}$) δ: 12.60 (br. s, 2H, H-11,12), 7.40 (d, $J_{2,3}$ = 1.5 Hz, 1H, H-2), 6.60 (d, $J_{2,3}$ = 1.5 Hz, 1H, H-3), 3.90 (s, 2H, H-8a,b).

**$^{13}$C-NMR** (100 MHz, DMSO-$_{d6}$) δ: 169.7, 164.3, 154.7, 142.2, 115.5, 110.8, 33.3.

## 3.20 Synthesis of 2-(2-methoxy-2-oxoethyl)furan-3-carboxylic acid (124)

A mixture of 2-(carboxymethyl)furan-3-carboxylic acid **122** (4.17 g, 24.5 mmol) and acetyl chloride (30 mL) was left for stirring at reflux temperature (52 $^{o}$C) until obtaining clear solution. After the completion of the reaction, acetyl chloride was evaporated and the residue was dissolved in methanol (30 mL). The mixture was left for stirring at reflux temperature (65 $^{o}$C) for three hours. Removal of the solvent gave the crude product, which chromatographed on silica gel (200 g) eluting with hexane/ethyl acetate (3:1). The obtained product was crystallized from ethyl acetate/hexane (3:1) to give white solid **124** (3.16 g, 17.2 mmol, 70 %).




**$^{1}$H-NMR** (400 MHz, DMSO-$_{d6}$) δ: 10.80 (br. s, 1H, H-11), 7.39 (d, $J_{2,3}$ = 1.5 Hz, 1H, H-2), 6.75 (d, $J_{2,3}$ = 1.5 Hz, 1H, H-3), 4.15 (s, 2H, H-8a,b), 3.72 (s, 3H, -$OCH_3$).

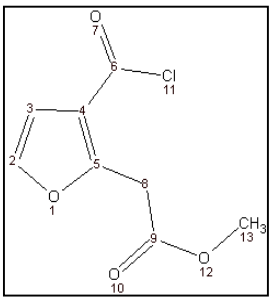
**$^{13}$C-NMR** (100 MHz, DMSO-$_{d6}$) δ: 168.9, 155.4, 142.1, 141.8, 115.2, 111.0, 52.4, 33.5.

**IR** (KBr, cm$^{-1}$) 3127, 2933, 2681, 2611, 1728, 1676, 1600, 1346, 1207, 1131, 1035, 926, 855, 701.

## 3.21 Synthesis of Methyl 2-(3-(chlorocarbonyl)furan-2-yl)acetate (125)

2-(2-methoxy-2-oxoethyl)furan-3-carboxylic acid **124** (3,16 g, 17,2 mmol) was dissolved in 40 ml of dichloromathane. To this mixture was added oxalyl chloride (1.7 ml, 20.6 mmol) and solution was kept at room temperature for 1 hour. After the reaction

was completed, dichloromethane was evaporated and gave product **125** (3.27 gr, 16.2 mmol, 94%).

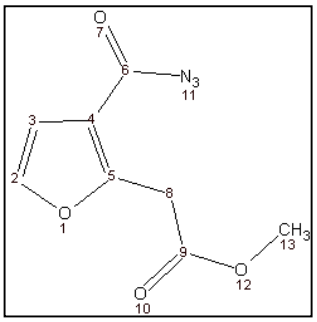


**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ: 7.39 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 6.83 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-3), 4.12 (s, 2H, H-8a,b), 3.71 (s, 3H, -$OCH_3$).

**$^{13}$C-NMR** (100 MHz, DMSO-$_{d6}$) δ: 167.8, 162.0, 156.1, 142.3, 120.4, 112.7, 52.6, 33.8.

## 3.22 Synthesis of Methyl 2-(3-(azidocarbonyl)furan-2-yl)acetate (126)

Methyl 2-(3-(chlorocarbonyl)furan-2-yl)acetate **125** (3.27 g, 16.2 mmol) was dissolved in 40 ml of acetone. To this mixture was added dropwise sodium azide (1,58 g, 24.3 mmol) in 40 ml of water at 0 $^{o}$C and solution was kept at 0 $^{o}$C for 1 hour. After the reaction was completed, Methyl 2-(3-(azidocarbonyl)furan-2-yl)acetate **126** was separated with ethyl acetate (50 ml) by extraction with water (50 ml). The combined organic extracts were dried over $Mg_2SO_4$. Ethyl acetate was evaporated and gave product **126** (2.78 g, 13.3 mmol, 82%).



**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ: 7.28 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 6.61 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-3), 4.04 (s, 2H, H-8a,b), 3.66 (s, 3H, -$OCH_3$).

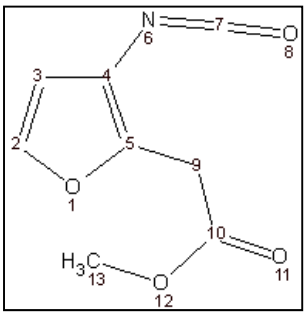
**$^{13}$C-NMR** (100 MHz, DMSO-$_{d6}$) δ: 169.1, 169.4, 155.1, 142.0, 118.8, 111.2, 53.4, 34.5.

**IR** (KBr, $cm^{-1}$) 2956, 2152, 1747, 1688, 1600, 1518, 1437,

1341, 1190, 953, 850, 740, 703.

## 3.23 Synthesis of Methyl 2-(3-isocyanatofuran-2-yl)acetate (128)

Methyl 2-(3-(azidocarbonyl)furan-2-yl)acetate **126** (2.78 g, 13.3 mmol) was dissolved in 35 ml of benzene and heated to reflux temperature (75-80 $^0$C). After the rearrangement was completed, benzene was evaporated and gave product **128** (2.36g, 13.03 mmol, 98%).




**$^1$H-NMR** (400 MHz, $CDCl_3$) δ: 7.17 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 6.21 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-3), 3.65 (s, 2H, H-8a,b), 3.58 (s, 3H, -$OCH_3$).

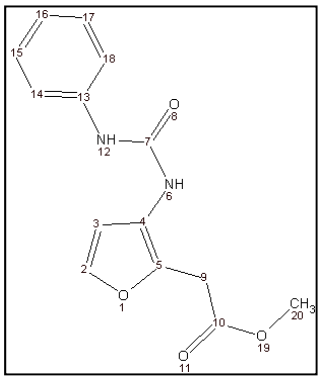
**$^{13}$C-NMR** (100 MHz, DMSO-$_{d6}$) δ: 168.1, 142.4, 139.1, 125.0, 110.8, 109.2, 51.4, 31.5.

**IR** (KBr, cm$^{-1}$) 2956, 2274, 1745, 1654, 1518, 1437, 1340, 1209, 1190, 1066, 1026, 890, 740, 646.

## 3.24 Synthesis of Methyl 2-(3-(3-phenylureido)furan-2-yl)acetate (130)

Methyl 2-(3-isocyanatofuran-2-yl)acetate **128** (2.36g, 13.03 mmol) was dissolved in 40 ml of dichloromethane. To this mixture was added aniline **129** and kept for 2 hours at room temperature. After 2 hours, mixture was washed with 2 molar of hydrochloric acid (25 ml) solution in order to get rid of excess aniline. The combined organic extracts were dried over $Mg_2SO_4$. Dichloromethane was evaporated. The crude product was

purified with hexane/ethyl acetate (1:1) by column chromatography and gave product **130** (2.57 g, 9.38 mmol, 72%).

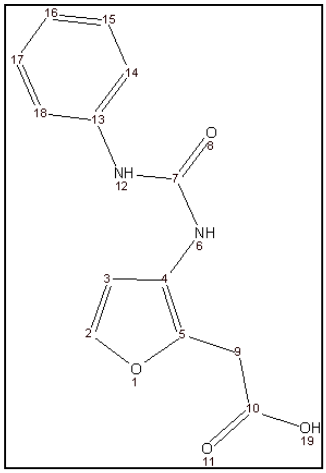


**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ: 7.33 (br. s, 1H, -NH-6) 7.22 (dd, $J_{17,18}$ = $J_{14,15}$ = 8.4 Hz, $J_{16,18}$ = $J_{14,16}$ = 1.2 Hz, 2H, H-14,16), 7.22 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 7.15 (t, $J_{14,15}$ = $J_{15,16}$ = $J_{16,17}$ = $J_{17,18}$ = 8.4 Hz, 2H, H-15,17) 6.94 (tt, $J_{15,16}$ = $J_{15,17}$ = 8.4 Hz, $J_{14,16}$ = $J_{16,18}$ = 1.2 Hz, 1H, H-16), 6.87 (br s., 1H, -NH-12), 6.44 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-3), 3.62 (s, 2H, H-9a,b), 3.59 (s, 3H, -$OCH_3$).

**$^{13}$C-NMR** (100 MHz, DMSO-$_{d6}$) δ: 169.1, 153.3, 141.4, 138.1, 129.0, 123.7, 121.8, 119.2, 100.5, 53.4, 31.5.

## 3.25 Synthesis of 2-(3-(3-phenylureido)furan-2-yl)acetic acid (133)

Methyl 2-(3-(3-phenylureido)furan-2-yl)acetate **130** (1g, 3.64 mmol) was dissolved in 40 ml of dioxane and 20 ml of water mixture. To this mixture was added 10% NaOH solution (4.0 ml) and kept stirring at 60 $^{o}$C for 2 hours. The reaction was monitored on TLC. After the completion of the reaction, excess HCl was added to the mixture to obtain acidic medium. Then, the mixture was extracted with ethyl acetate (40 mL). The combined organic extracts were dried over $Mg_2SO_4$. Ethyl acetate was evaporated and gave product **133** (0.92 g, 3.53 mmol, 97 %).




**$^{1}$H-NMR** (400 MHz, DMSO-$_{d6}$) δ: 12.48 (br. s, 1H, -OH, H-6), 7.33 (br. s, 1H, -NH-6) 7.22 (dd, $J_{17,18} = J_{14,15} = 8.4$ Hz, $J_{16,18} = J_{14,16} = 1.2$ Hz, 2H, H-14,16), 7.22 (d, $J_{2,3} = 2.0$ Hz, 1H, H-2), 7.15 (t, $J_{14,15} = J_{15,16} = J_{16,17} = J_{17,18} = 8.4$ Hz, 2H, H-15,17) 6.94 (tt, $J_{15,16} = J_{15,17} = 8.4$ Hz, $J_{14,16} = J_{16,18} = 1.2$ Hz, 1H, H-16), 6.87 (br s., 1H, -NH-12), 6.44 (d, $J_{2,3} = 2.0$ Hz, 1H, H-3), 3.62 (s, 2H, H-9a,b), 3.59 (s, 3H, -$OCH_3$).

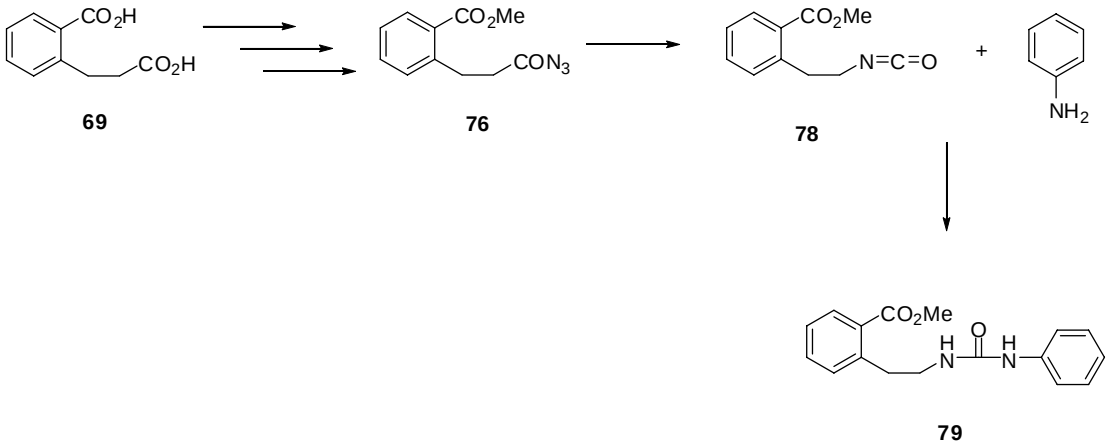
**$^{13}$C-NMR** (100 MHz, DMSO-$_{d6}$) δ: 174.1, 153.6, 143.4, 138.1, 127.2, 124.7, 121.6, 119.4, 100.5, 32.7.

# CHAPTER 4

# CONCLUSION

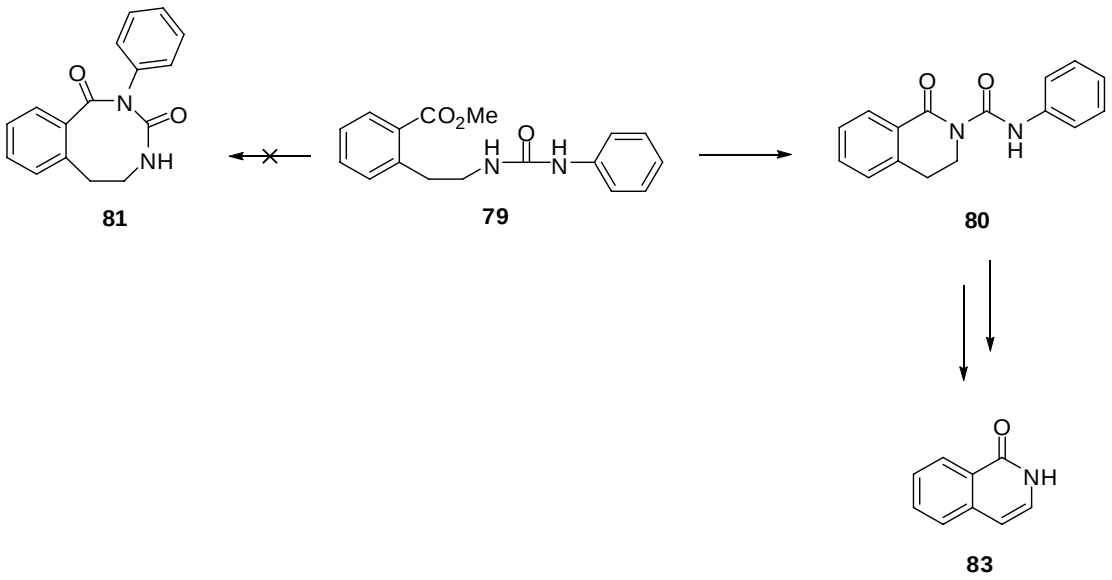
The aim of this thesis was the development of new methodologies to synthesize isoquinolone and isoindolinone derivatives. The methodology, which was appropriate pathway for the synthesis of isoquinolone derivatives, was also be applied to 2-(carboxymethyl)furan-3-carboxylic acid to synthesize nitrogen and oxygen containing heterocycles.

In the first part of the study, incorporation of nitrogen atom into the structure was achieved by the formation of acyl azide **76** which was the key step for the synthesis of isoquinolone derivatives. Transformation of acyl azide to the isocyanate **78** and further reaction with amine led to formation of urea derivative which was the precursor of isoquinolone derivative **79** (Scheme 42).



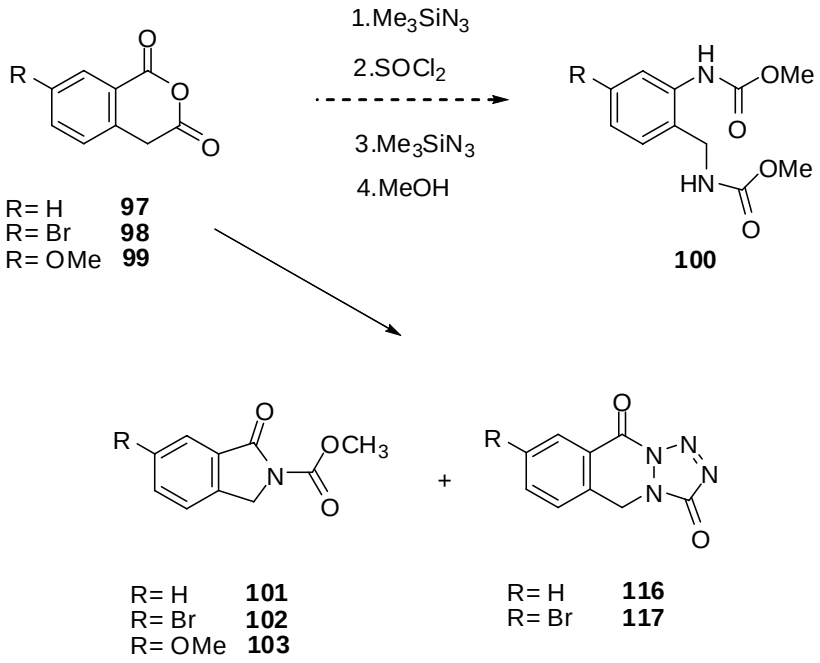

**Scheme 42**

The urea derivative has two possible ring closures leading to the six or eight-membered rings. This study showed that only six-membered ring **80** was formed under basic conditions. We assume that, abstraction of N-H proton, which is conjugated with benzene ring was not preferred. Instead, N-H proton which is attached to the methylene unit was abstracted to form isoquinolone derivative. Further reactions for the introduction of the double bond in the six-membered ring, led to formation of isoquinolin-1(2H)-one **83** (Scheme 43).



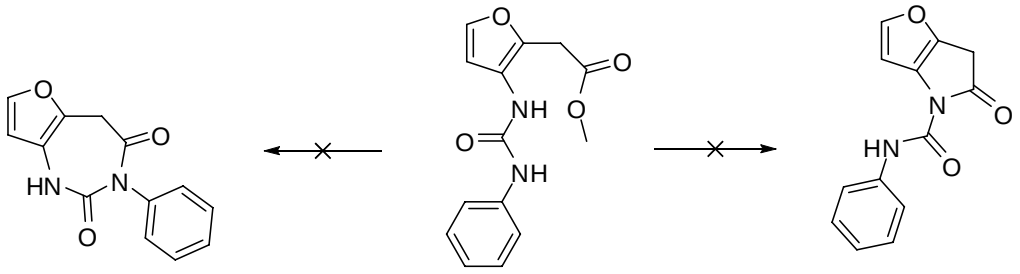

**Scheme 43**

In the second part of the study, our primarily goal was the synthesis of **100** starting from homophthalic anhydrides. Surprisingly, analysis of the products indicated the formation of isoindolinone **101-103** and tetrazolinone derivatives **116** and **117** (Scheme 44).




**Scheme 44**

Finally, we have tried to synthesize new heterocycles such as furopyrrolone derivative by applying of similar methodology which was applied to β-(o-carboxyphenyl)propionic acid **69**, by starting from 2-(carboxymethyl)furan-3-carboxylic acid **122**. After synthesis of the urea derivative **130**, ring closure reaction was applied under basic conditions. However, the reaction produced neither five nor seven-membered rings (Scheme 45).




**132** **130** **131**

**Scheme 45**

# REFERENCES


1. Shamma, M. The Isoquinoline Alkaloids, Chemistry and Pharmacology, Academic Press, New York, **1972**, p. 90.

2. Southon, I. W. Buckingham, J. *Dictionary of Alkaloids*, Chapman and Hall, Vol. 1, New York, **1989**, p. 347.

3. Shamma, M., Moniot, J. L. *Isoquinoline Alkaloids Research*, Plenum Press, New York, London, **1978**, p. 57

4. Shamma, M. The *Isoquinoline Alkaloids, Chemistry and Pharmacology* Academic Press, New York, **1972**, p. 90

5. Lee, A. W. M., Chan, W. H. *J. Chem. Soc. Perkin Trans*., **1992**, *1(3)*, 309.

6. Glushkov, V. A., Shklyaev, Yu. V. *Chem Heterocycl Comp*, **2001**, *37*, 6.

7. Dmitriev, A. S., Abaev, V. T. *Tetrahedron* **2007**, *63(38)*, 9437.

8. Fisher, M. J., Gunn, B. P., Um, S., Jakubowski, J. A. *Tetrahedron. Lett*., **1997**, *38*, 5747.

9. Berger, J., Clark, R. D. *Chem. Abstr*., **1996**, *124*, 317007.

10. Okegawa, N., Kawamura, M. *Chem. Abstr*., **1991**, *114*, 228918.

11. Hutchinson, J. H., Cook, J. J., Brashear, K. M., Breslin, M. J., Glass, J. D., Gould, R. J., Halczenko, W., Holahan, M. A., Lynch, R. J., Sitko, G. R., Stranieri, M. T., Hartman, G. D. *J. Med. Chem*., **1996**, *39*, 4583.

12. Natsugari, H., Shirafuji, H., Doi, T. *Chem. Abstr*., **1994**, *120*, 134310.

13. Sulkovski, T. S., Wille, M. A. *Chem. Abstr*., **1969**, *71*, 112830.

14. Senda, O., Ohtani, O., Katho, E., Miyake, H., Fujiwara, K. *Chem. Abstr*., **1981**, *95*, 132692.

15. Kubo, K., Ito, N., Souzu, I., Isomura, Y., Homma, H. *Chem. Abstr*. **1979**, *90*, 168468.

16. Hasegava, M., Shirai, K., Matsumoto, K., Suzuki, Y., Takahasi, I. *Chem. Abstr*. **1994**, *121*, 912.

17. Gabriel, S., Colman, J. *Chem. Ber*. **1900**, *33*, 980.

18. Semple, J. E., Rydzewski, R. M., Gardner, G. *J. Org. Chem*. **1996**, *61*, 7967.

19. Cheng, C.-Y., Tsai, H.-B., Lin, M.-S. *J. Heterocycl. Chem*. **1995**, *32*, 73.

20. Sugimoto, A., Shinba-Tanaka, H., Ishikava, M. *Synthesis*, **1995,** 431.

21. Banwell, M. G., Bissett, B. D., Busato, S., Cowden, C. J., Hockless, D. C. R., Holman, J. W., Read, R. W., Wu, A. W. E. *J. Chem. Soc., Chem. Commun*. **1995**, 2551.

22. Gonzalez, D., Martinot, T., Hudlicky, T. *Tetrahedron Lett*. **1999**, *40*, 3077.

23. Simig, G. *Synlett*, **1990**, 425.

24. Lete, E., Collado, M. I., Sotomayor, N., Vicente, T. *J. Heterocycl. Chem*. **1995**, *32*, 1751.

25. Goff, D. A., Zuckermann, R. N. *J. Org. Chem*. **1995**, *60*, 5748.

26. Valencia, E., Fajardo, V., Firdous, S., Freyer, A. J., Shamma, M. *Terahedron Lett*. **1985**, *26*, 993.

27. Tamaoki, T., Nomoto, H., Takahashi, I., Kato, Y., Morimoto, M., Tomita, F. *Biochem. Biophys. Res. Commun*. **1986**, *135*, 397.

28. Kundu, N. G., Khan, M. W., Mukhopadhyay, R. *Tetrahedron*, **1999**, *55*, 12361.

29. Sundberg, R. J. *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, **1984**, *4*, 370-376.

30. Kundu, N. G., Khan, M. W. Mukhopadhyay, R. *Tetrahedron*, **1999**, *55*, 12361.

31. Zhang, W., Pugh. G. *Tetrahedron Lett*. **1999**, *40*, 7591.

32. Khan, M. W., Kundu, N. G. *Synlett*, **1997**, 1435.

33. Katritzky, A. R., Mehta, S., He, H .-Y. *J. Org. Chem*. **2001**, *66*, 148.

34. Song, Y. S., Lee, C. H., Lee, K. -J. *J. Heterocycl. Chem*. **2003**, *40*, 939.

35. Rao, I. N., Prabhakaran, E. N., Das, S. K., Iqbal, J. *J. Org. Chem.* **2003**, *68*, 4079.

36. Stajer, G., Csende, F. *Curr. Org. Chem.* **2005**, *9*, 1277.

37. Nishio, T., Yamamoto, H. *J. Heterocycl. Chem*. **1995**, *32*, 883.

38. Tuanli Y., Richard C. L. *J. Org. Chem*., **2005**, *70*, 1432-1437.

39. Yan-Ping, L., Long, L., Guang-Fu, Y. *J. Heterocycl. Chem*. **2007**, *44*, 937.

40. Yan-Ping, L., Guang-Fu. Y. *Bioorg. Med. Chem.* **2007**, *15(4)*, 1716.

41. Gilchrist, T. L. *Heterocyclic Chemistry*, Addison Weasley Longman Limited, Third Edition, **1997**, 91-106.

42. Balci, M. *Reaction Mechanisms*, TUBA press, First Edition, **2008**, 336.

43. Horwitz, J. P. Fisher B. E., Tomazevski, A. J. *J. Am. Chem. Soc*. **1959**, *81*, 3076.

44. Vandensavel, J-M., Smets G., L'abbe, G. *J. Org. Chem*. **1973**, *38*, 675.

45. Toselli, M., Zanirato, P. *J. Chem. Soc*. *Perkin Trans.,* **1992**, *1(9)*, 1101.

46. Page G. A., Tarbell, D. S. *Org. Syn.,* **1963**,. *4,*136.

47. http://en.wikipedia.org/wiki/Thionyl_chloride Last visited on 10.06.2010.

48. Djerassi, C. *Chem. Rev.* **1948**, *43*, 271.

49. Groweiss, A. *Org. Process Res. Dev.* **2000**, *4*, 30.

50. Furuya, Y., Morita, A., Urasaki, I. *B. Chem. Soc. Jpn*. **1968,** *41*, 997.

51. Andlooa, A., Roane, D. S., Rudra, S., Peng, B., Hill, R.A. *Bioorgan. Med. Chem*. **2003,** *11*, 2099.

52. http://en.wikipedia.org/wiki/Lithium_bis(trimethylsilyl)amide Last visited on 10.06.2010.

53. Furniss, B. S., Hannaford, A. C., Smith G. S. W., Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*. 5th ed.; Wiley and Sons: 1994.

54 Singh, Harjit, *Synthesis*, **1983**, *10*, 791.

# APPENDIX

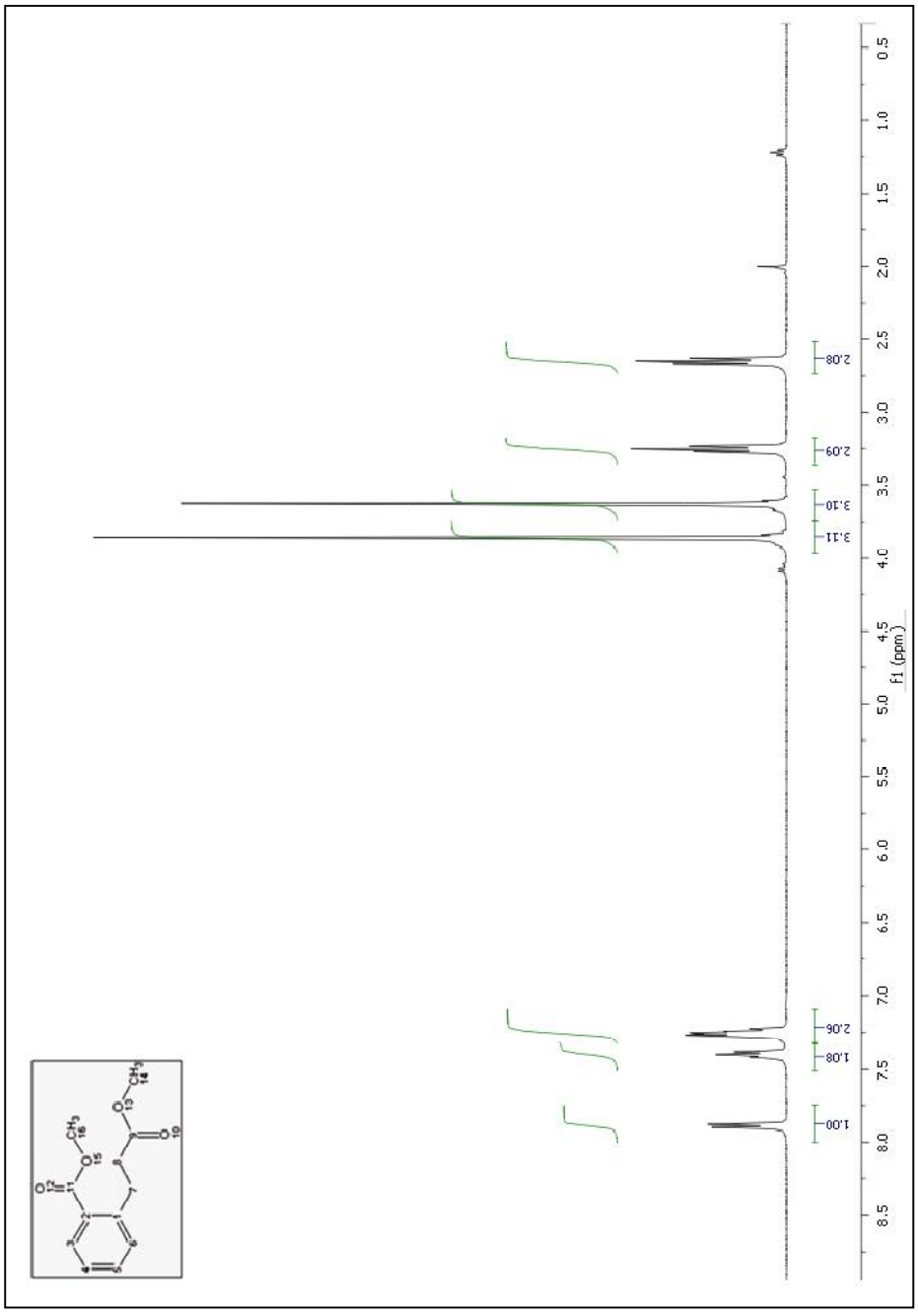



**Figure 9** 1H-NMR Spectrum of Compound **73**

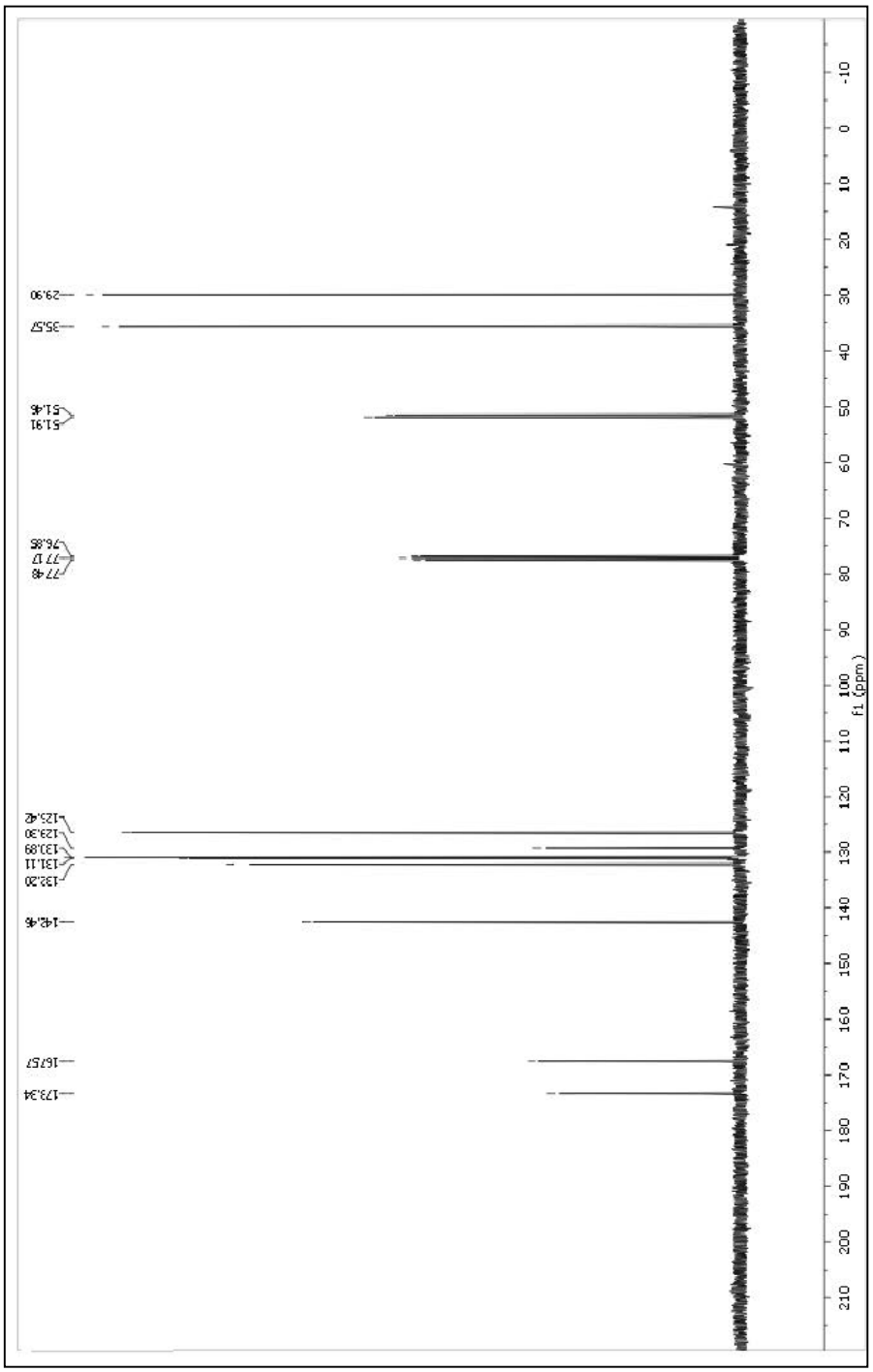



**Figure 10** $^{13}$C -NMR Spectrum of Compound **73**

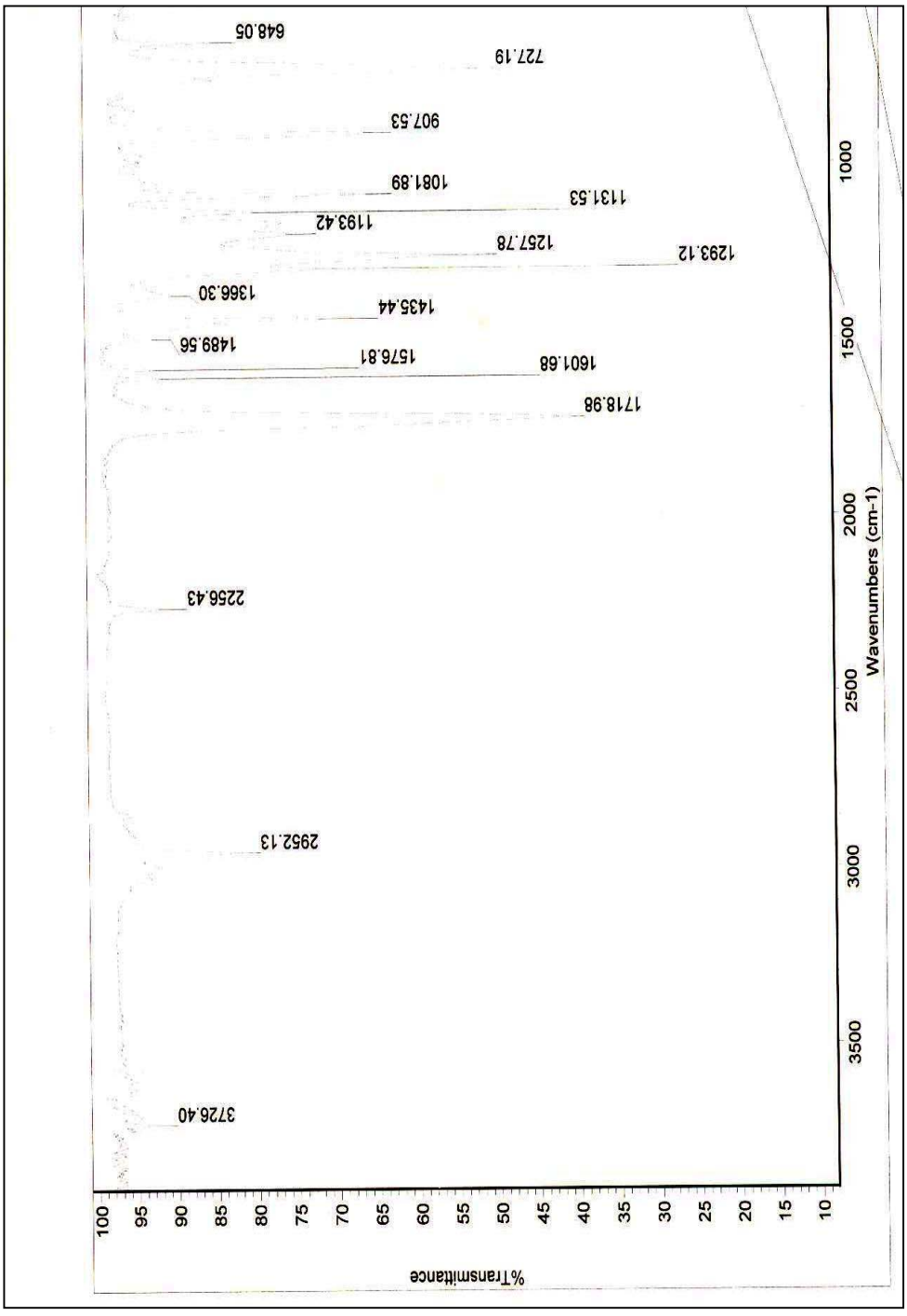



**Figure 11** IR Spectrum of Compound **73**

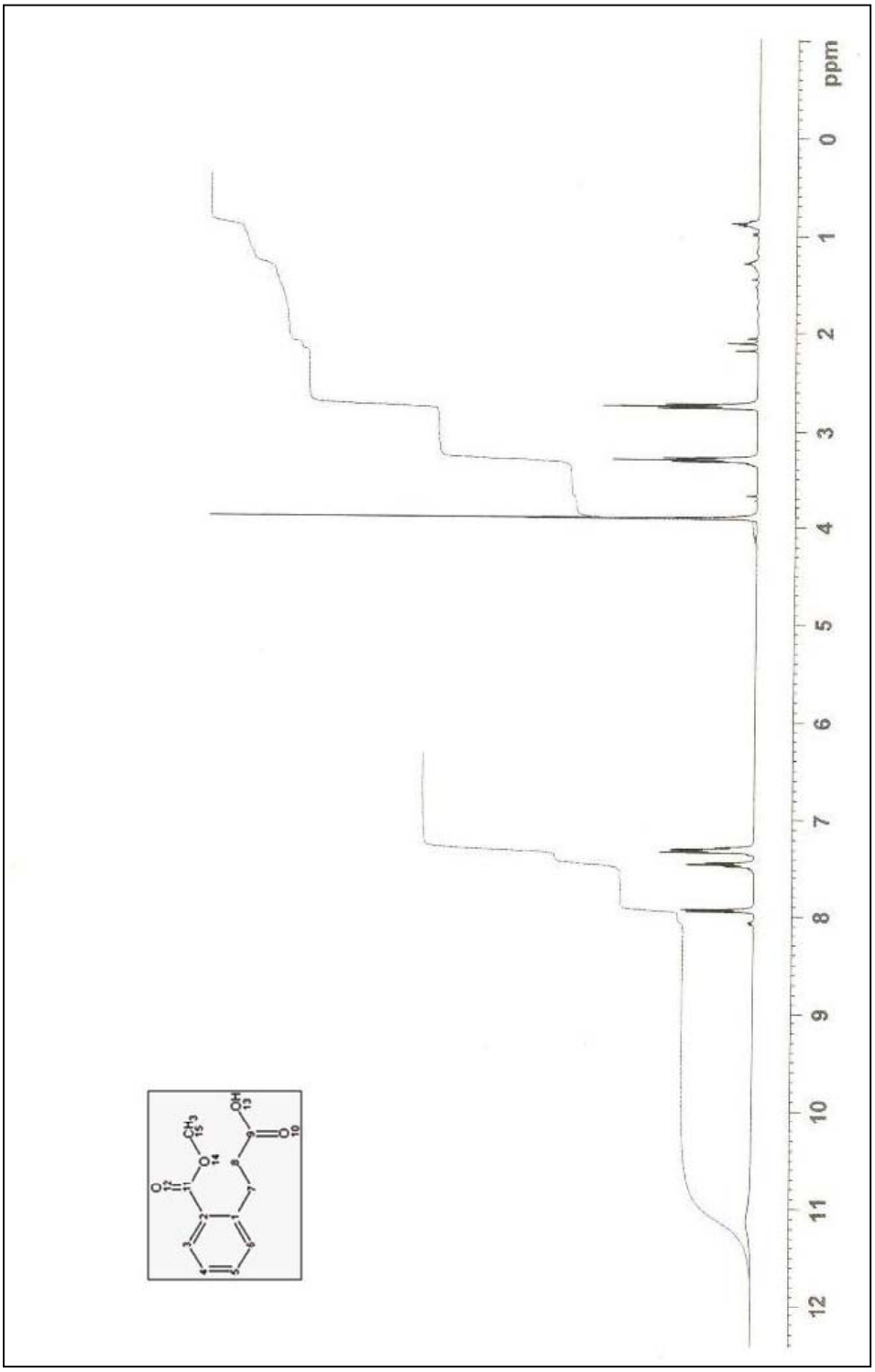



**Figure 12** $^{1}$H-NMR Spectrum of Compound **74**

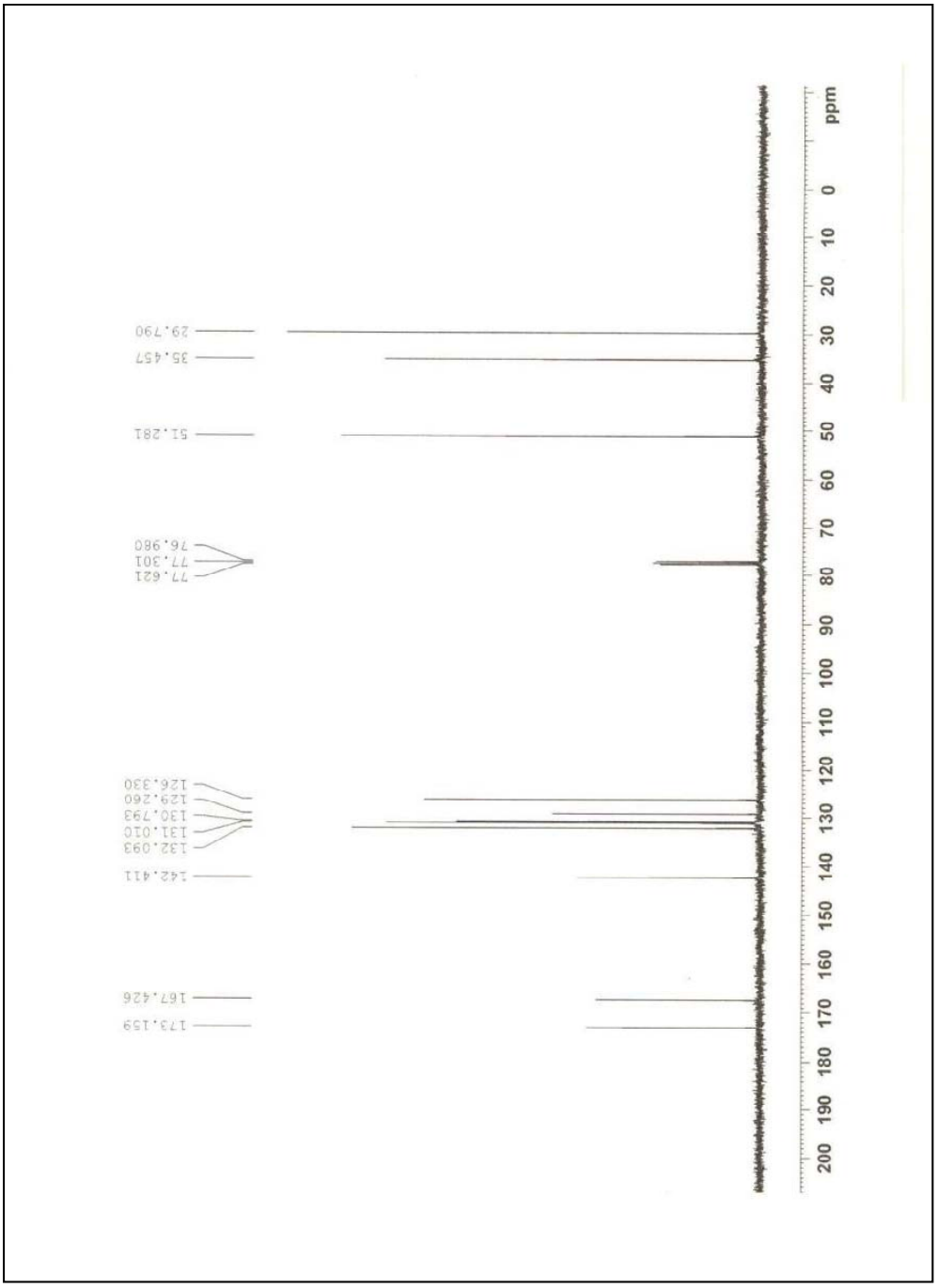



**Figure 13** $^{13}C$ -NMR Spectrum of Compound **74**

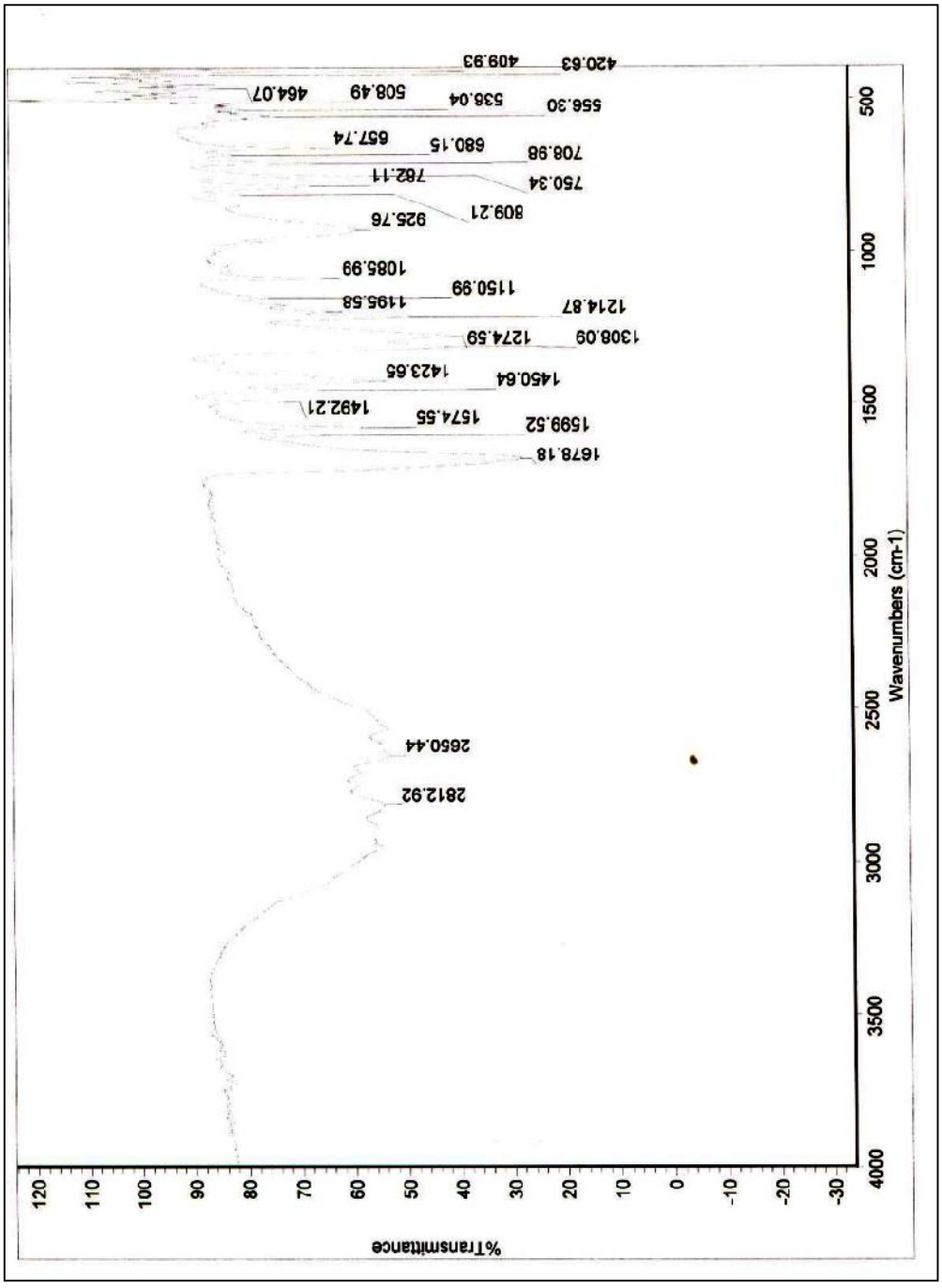



**Figure 14** IR Spectrum of Compound **74**

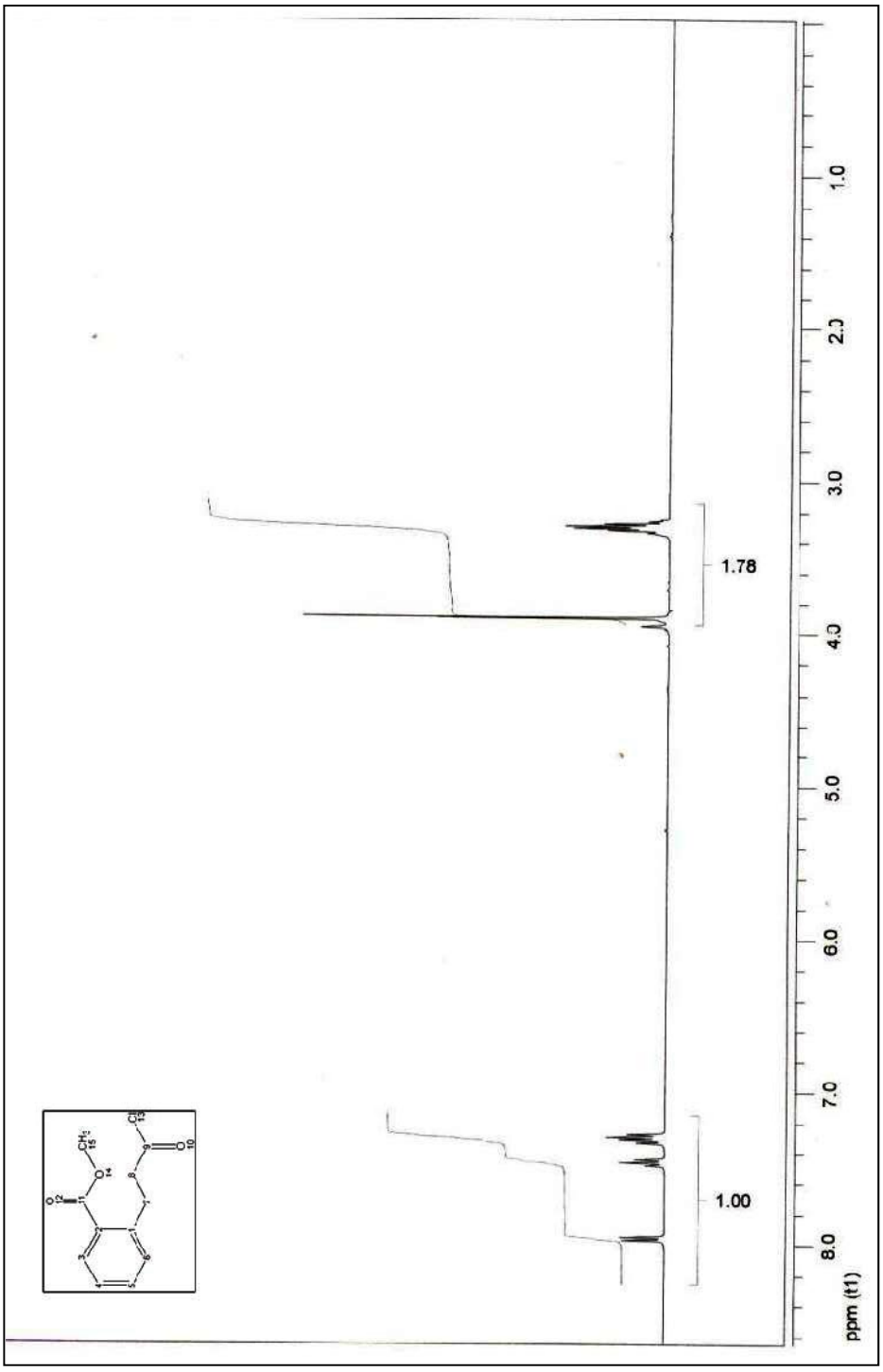



**Figure 15** $^{13}$H -NMR Spectrum of Compound **75**

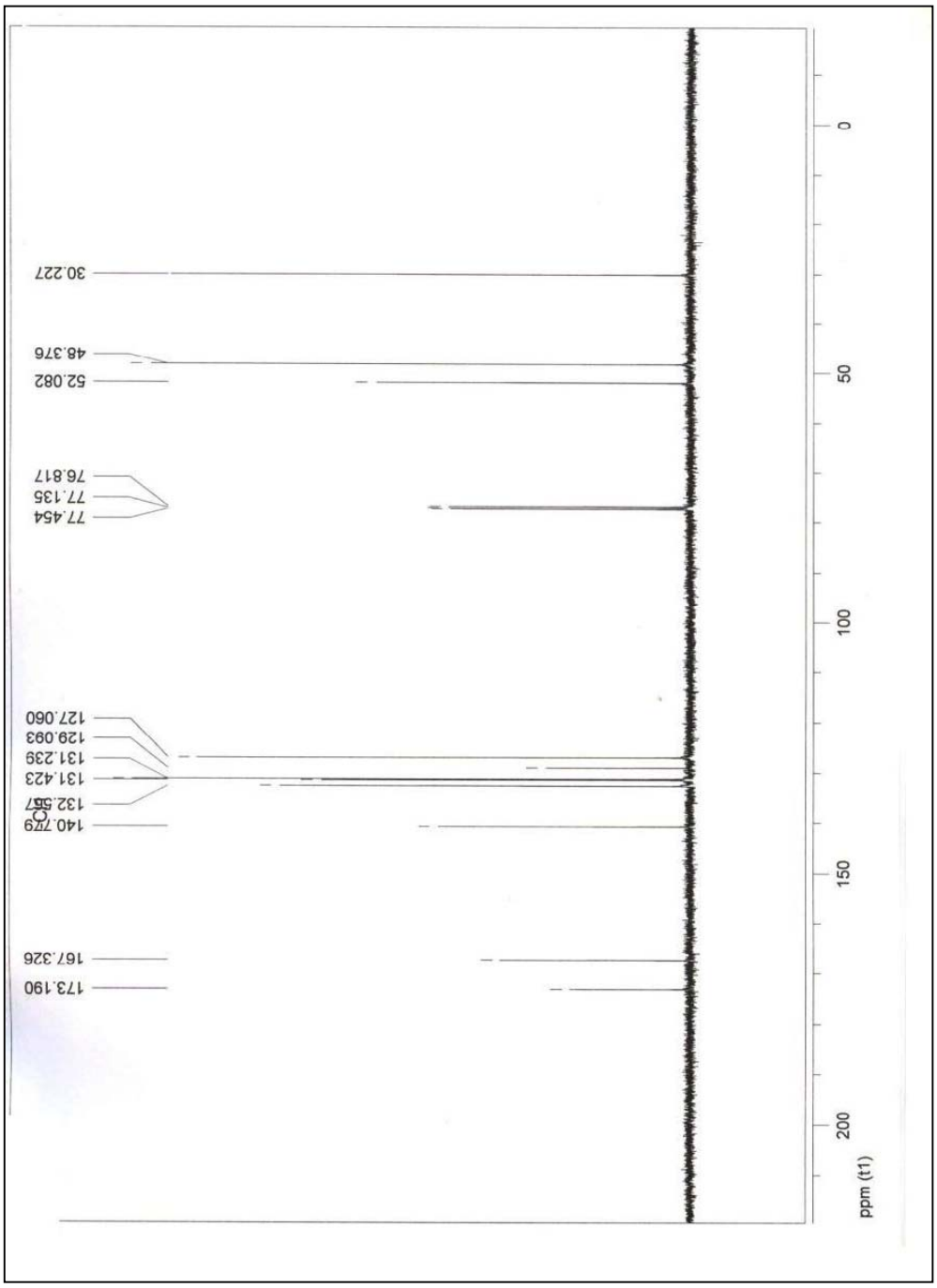



**Figure 16** $^{13}$C -NMR Spectrum of Compound **75**

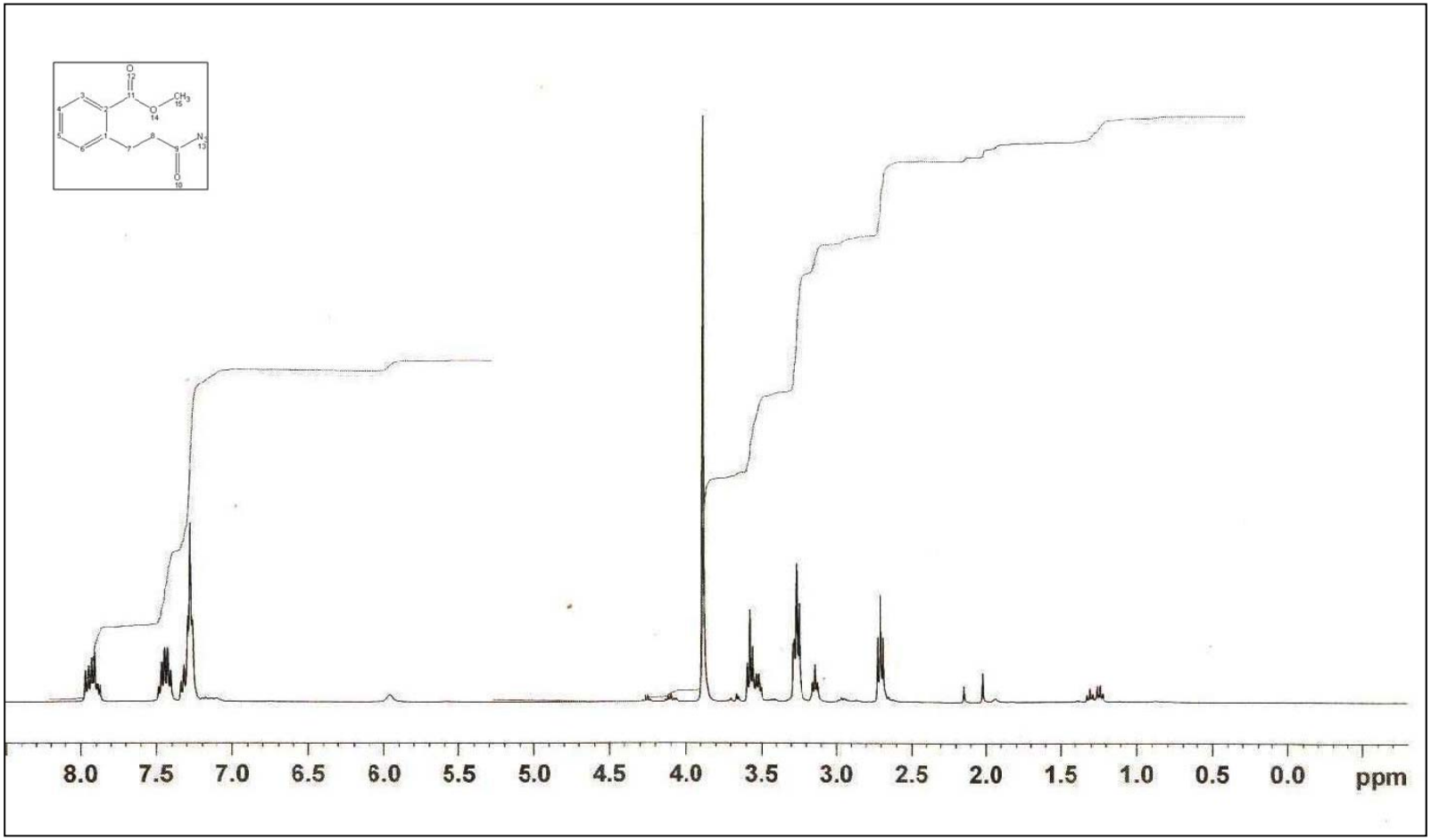



**Figure 17** $^{1}$H -NMR Spectrum of Compound **76**

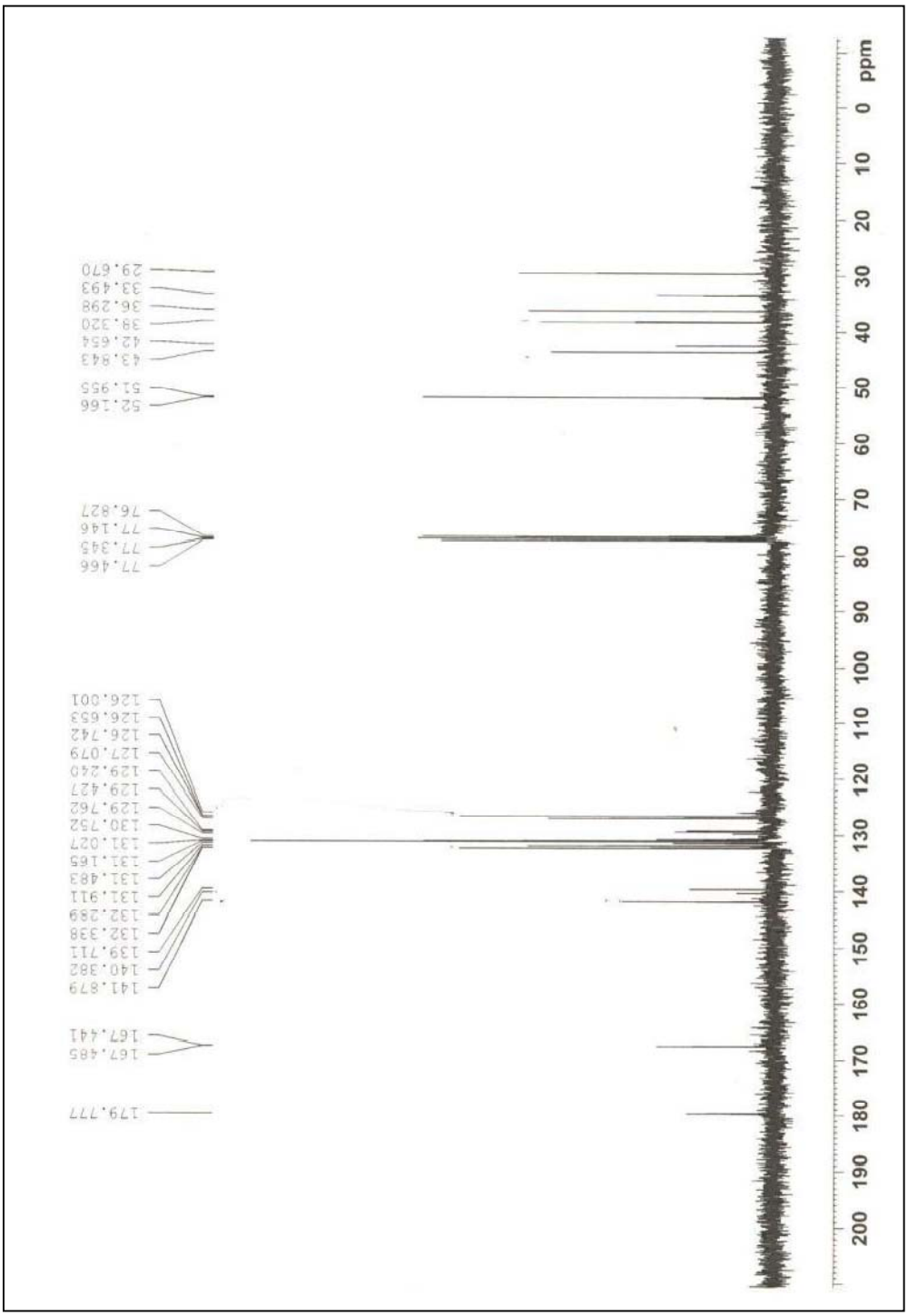



**Figure 18** $^{13}C$ -NMR Spectrum of Compound **76**

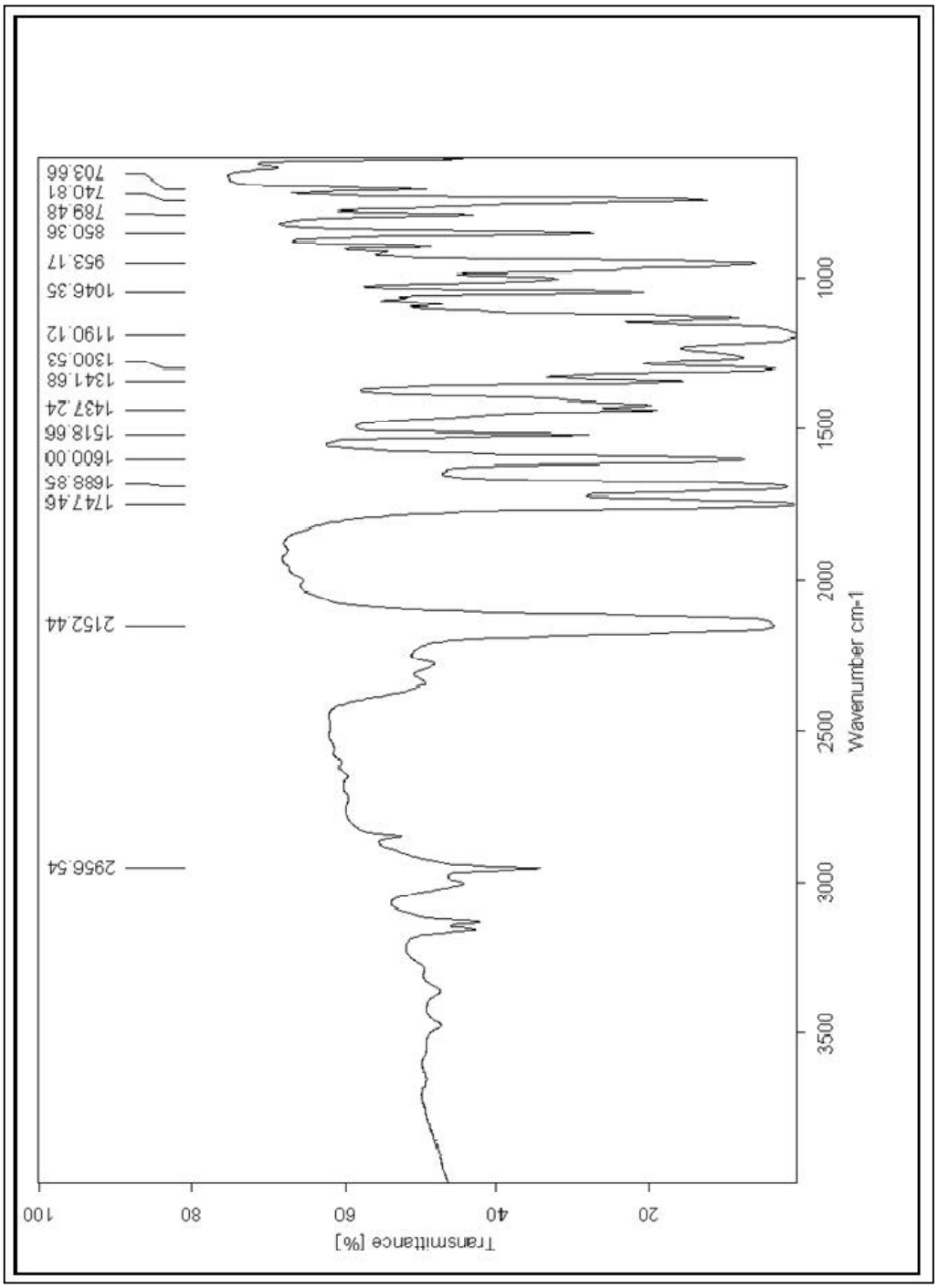



**Figure 19** IR Spectrum of Compound **76**

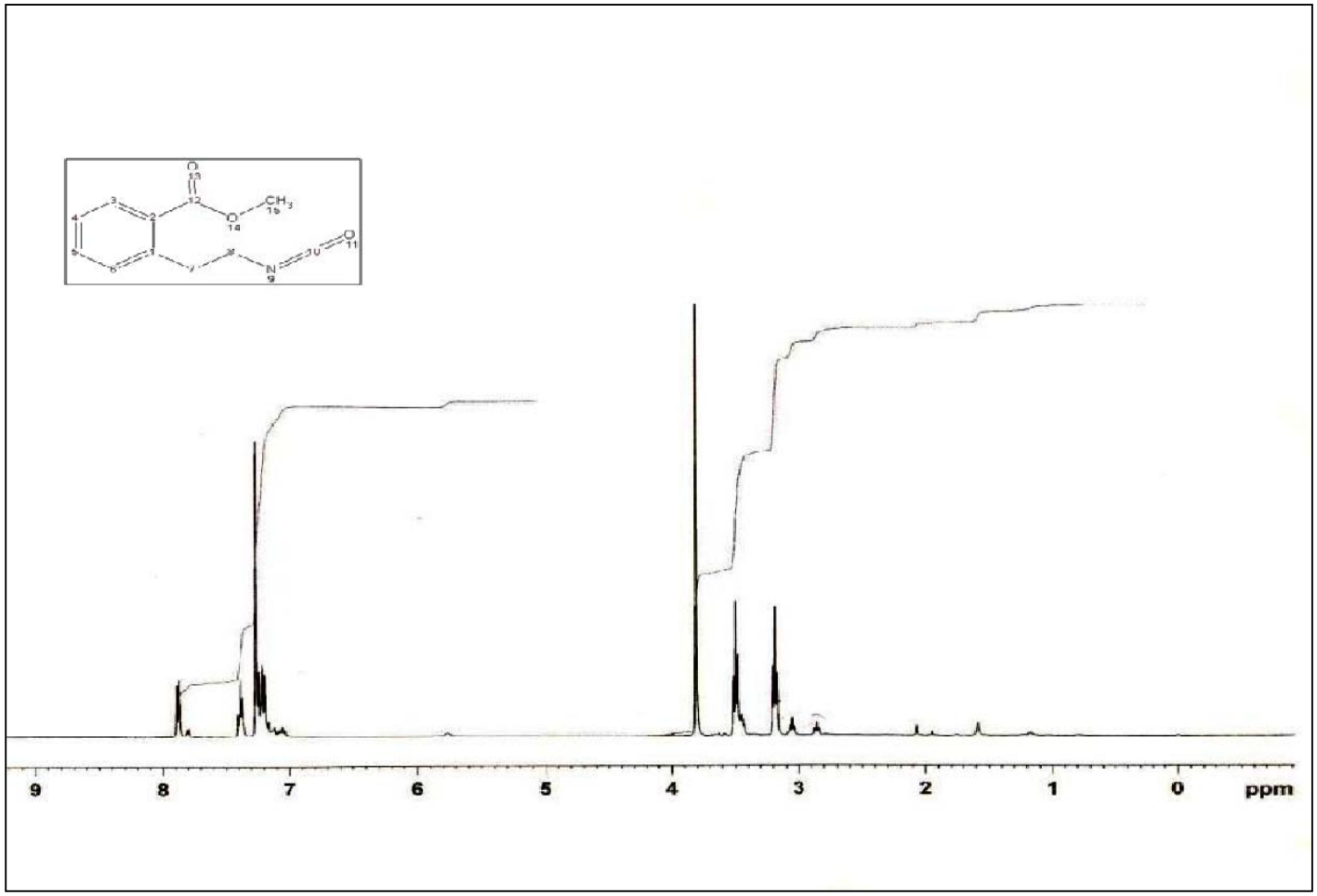



**Figure 20** $^{1}$H -NMR Spectrum of Compound **78**

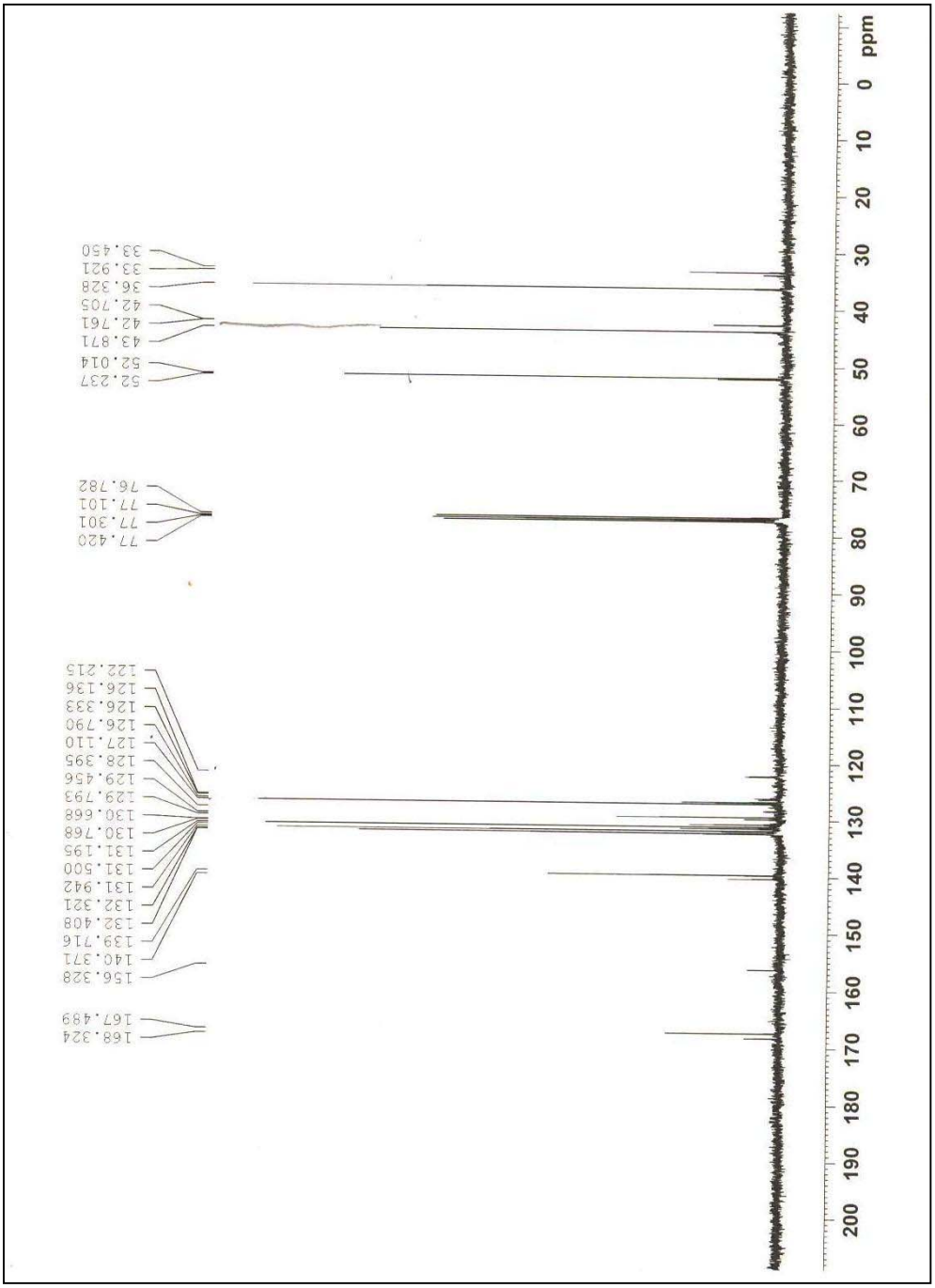



**Figure 21** $^{13}$C -NMR Spectrum of Compound **78**

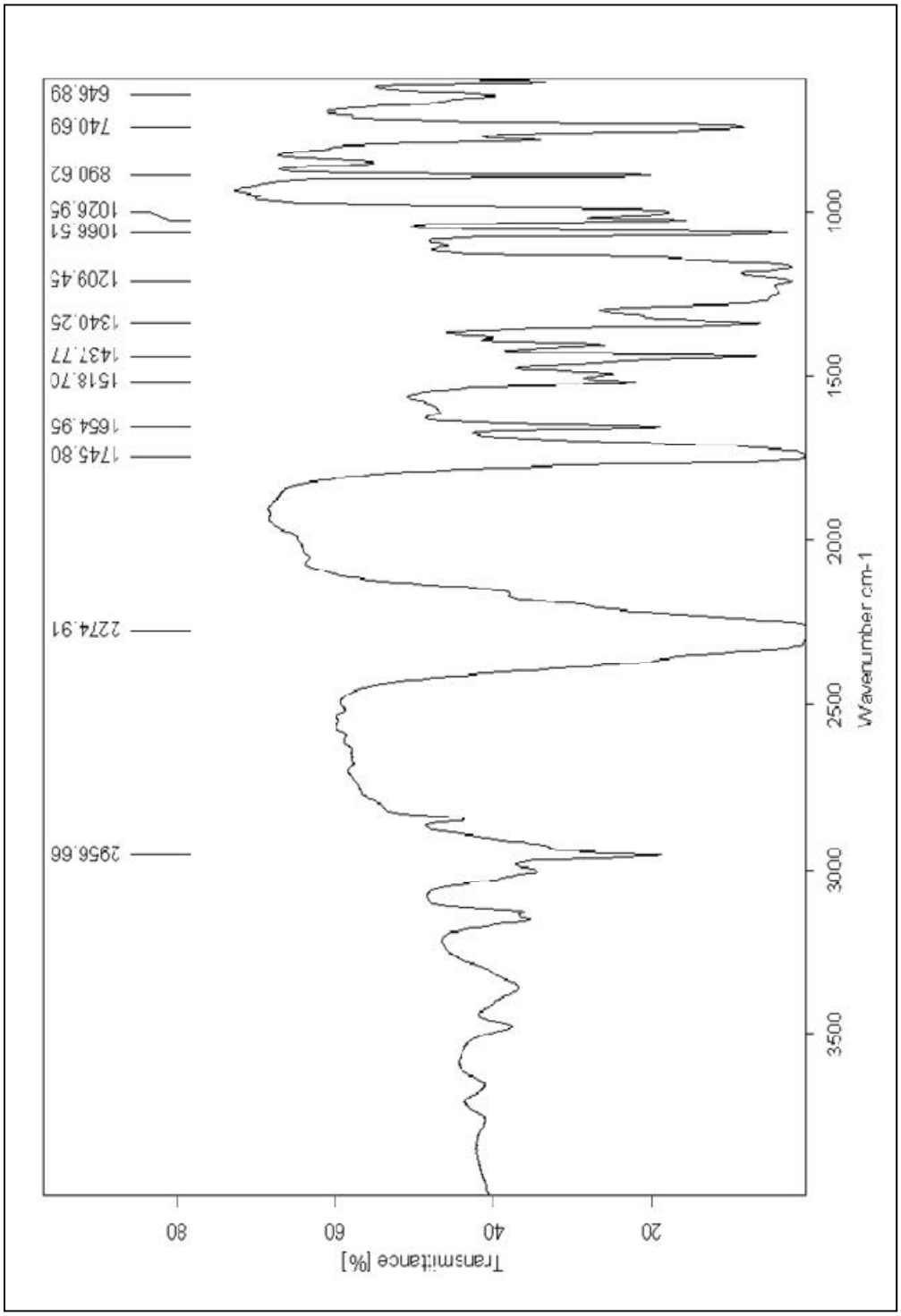



**Figure 22** IR Spectrum of Compound **78**

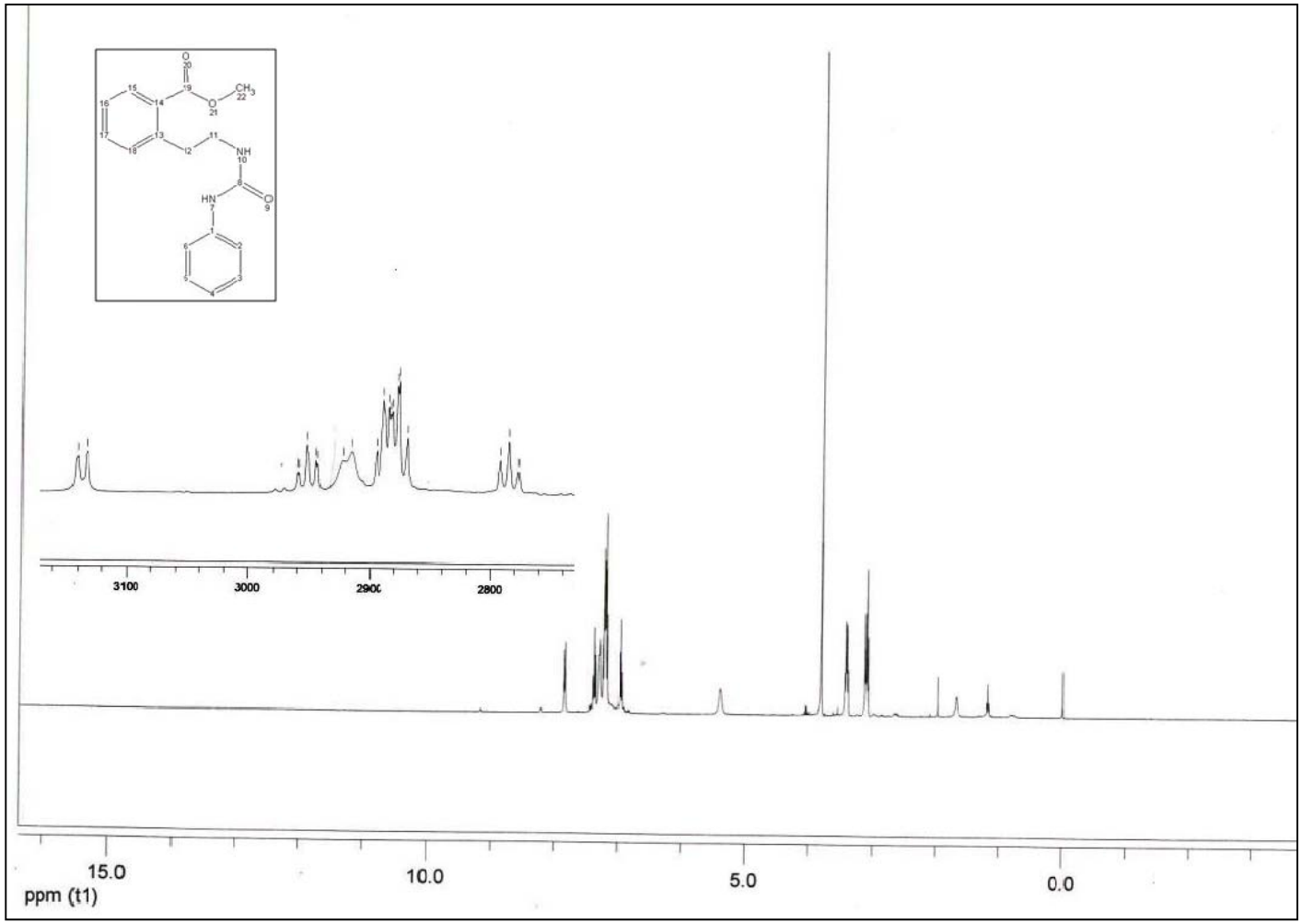



**Figure 23** $^{1}$H -NMR Spectrum of Compound **79**

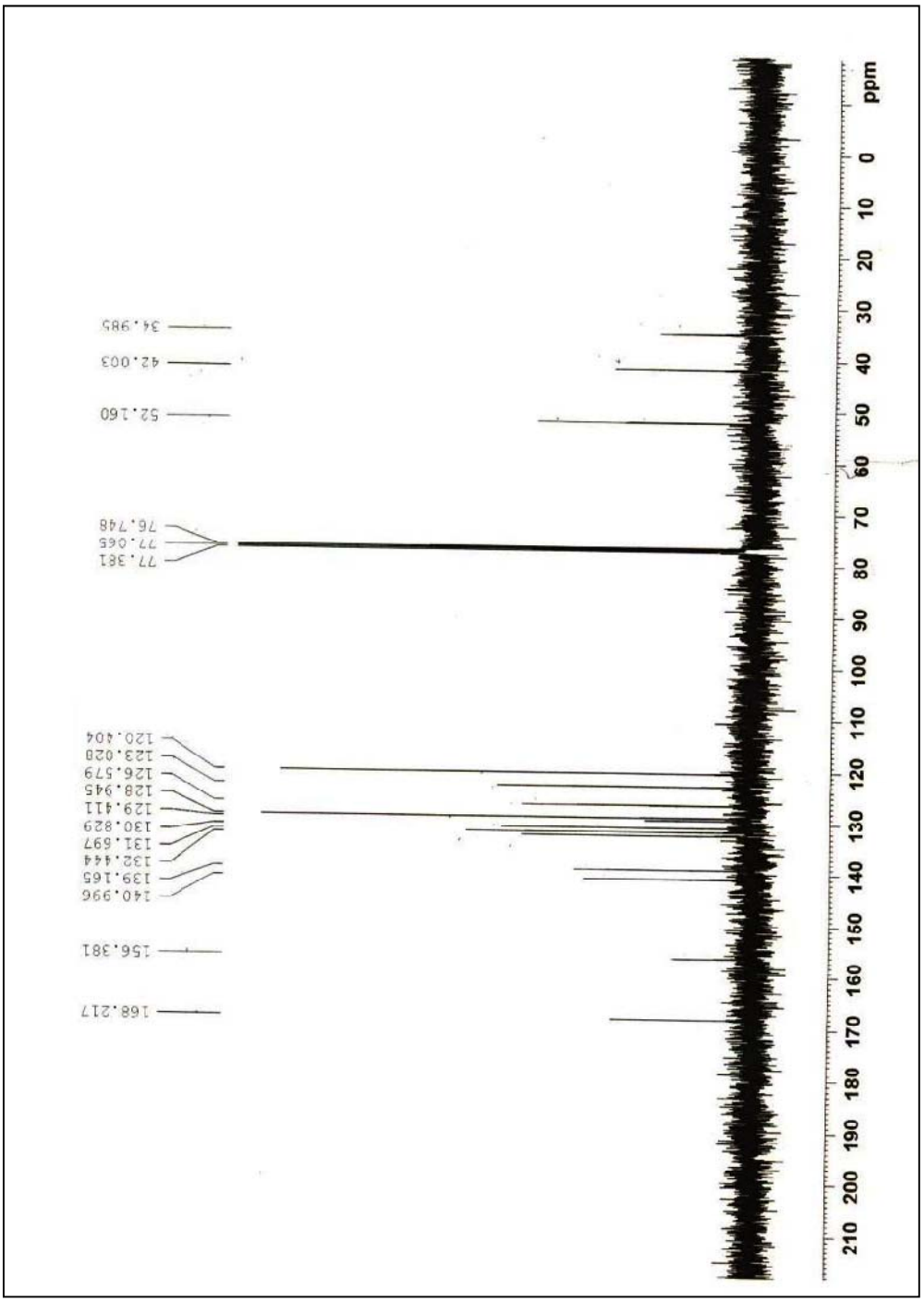



**Figure 24** $^{1}$C -NMR Spectrum of Compound **79**

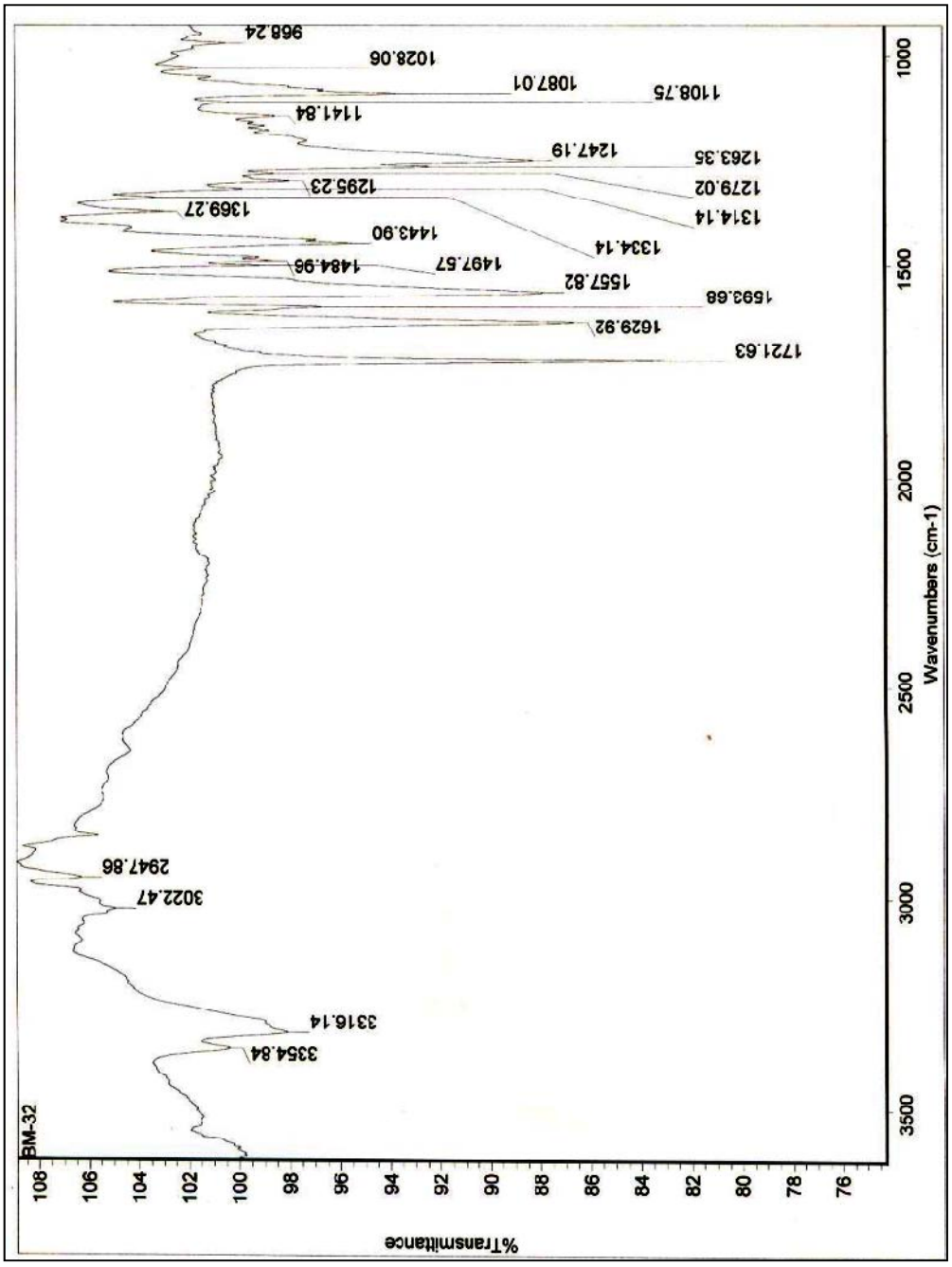



**Figure 25** IR Spectrum of Compound **79**

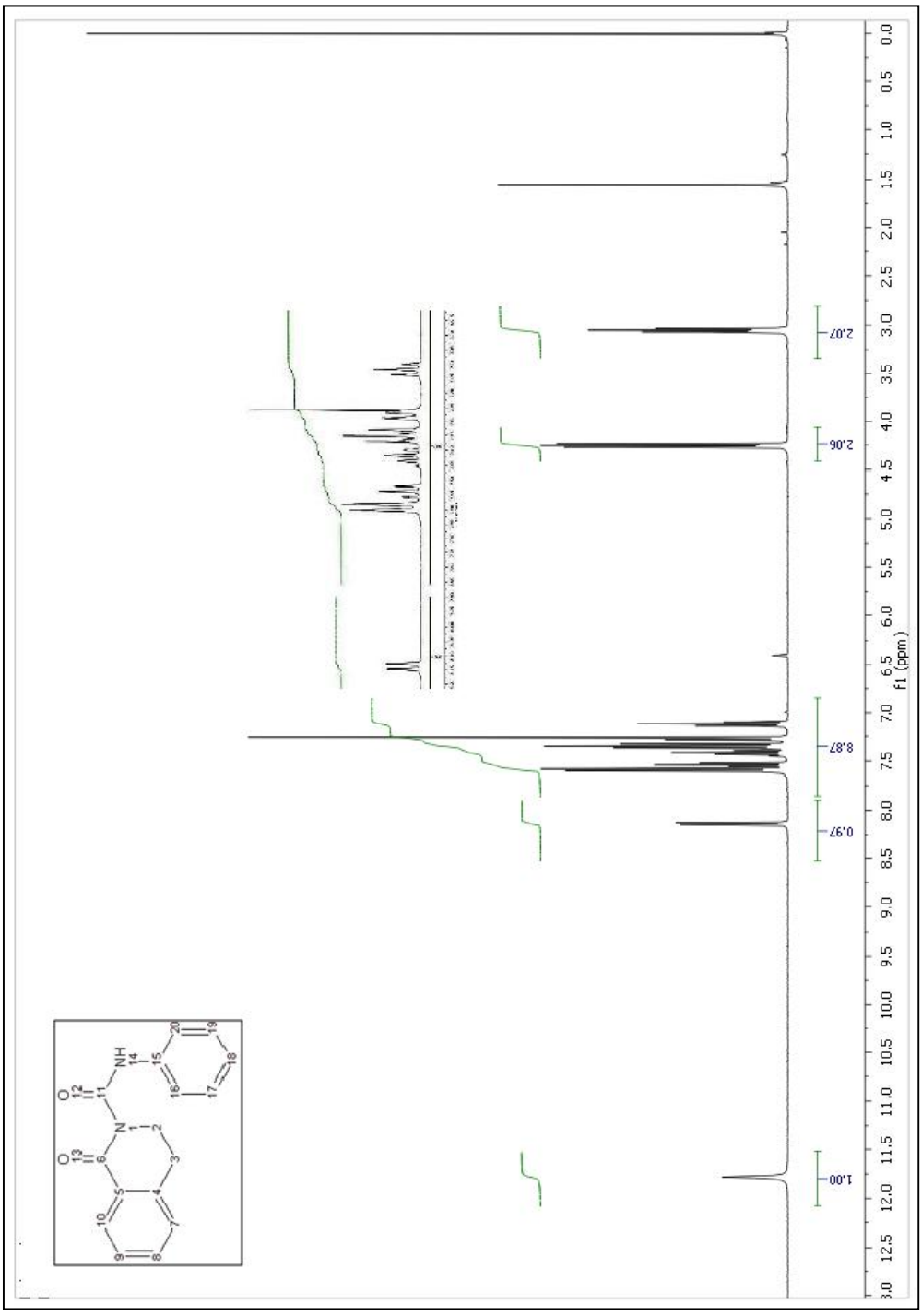



**Figure 26** $^{1}$H -NMR Spectrum of Compound **80**

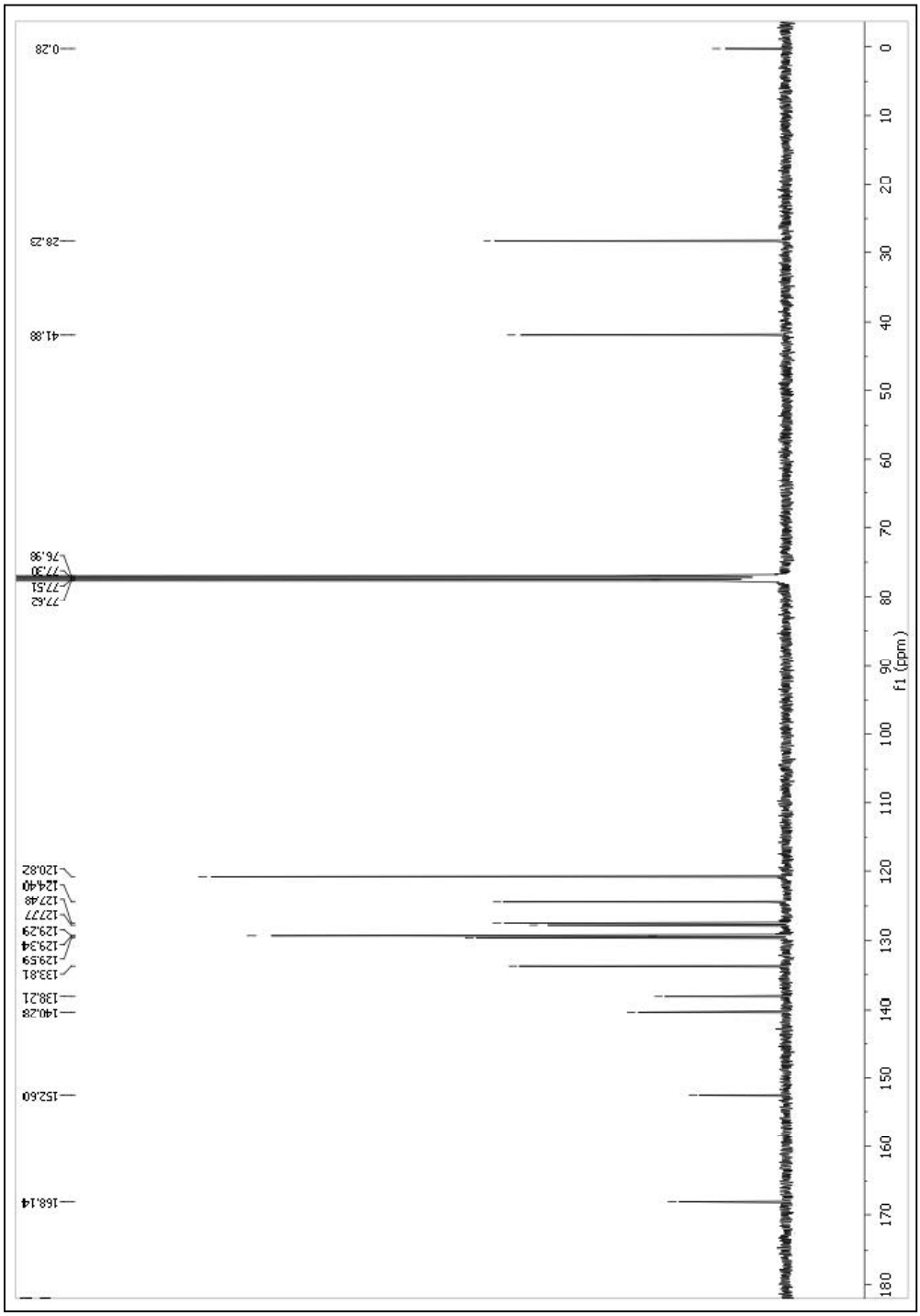



**Figure 27** $^{13}$C -NMR Spectrum of Compound **80**

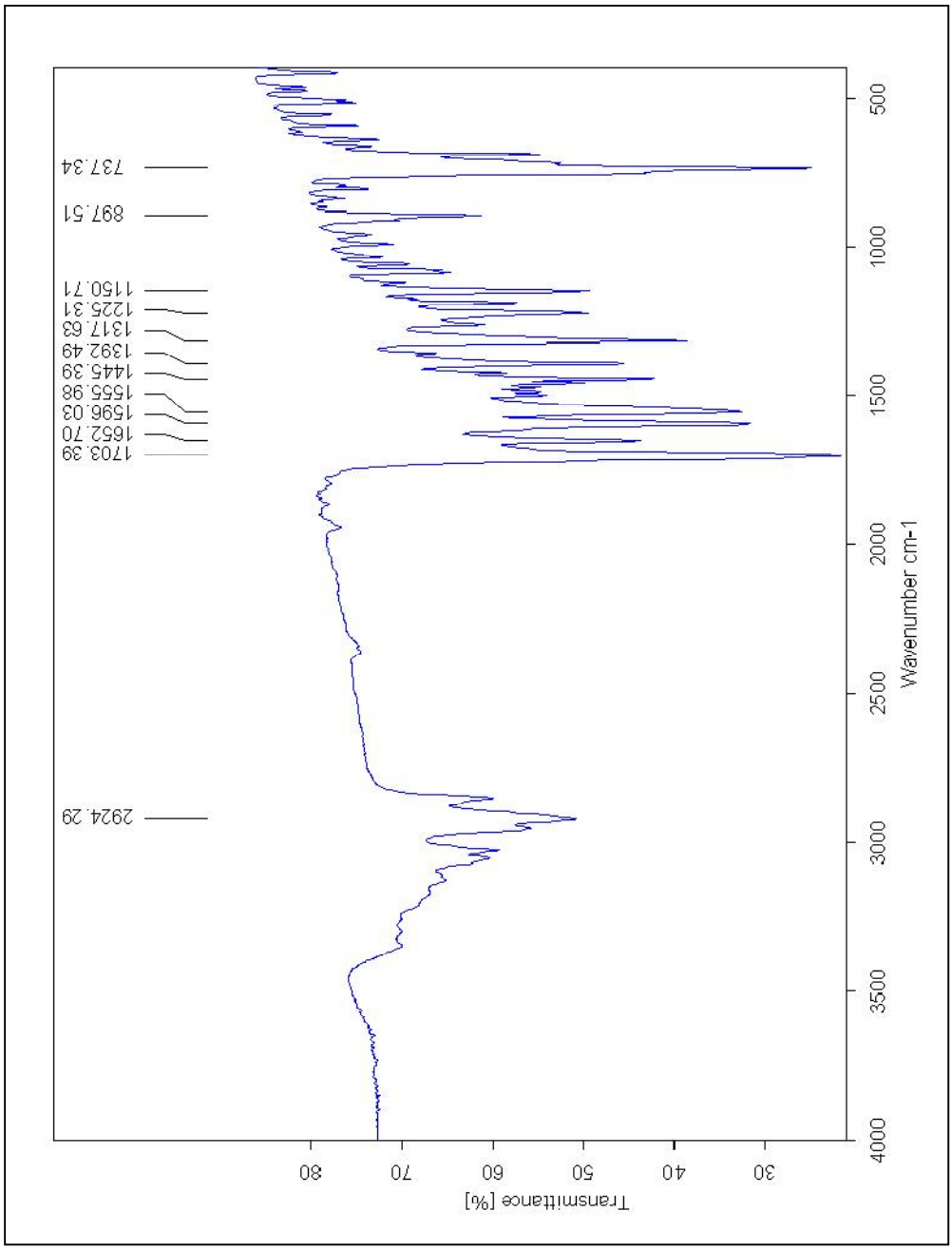



**Figure 28** IR Spectrum of Compound **80**

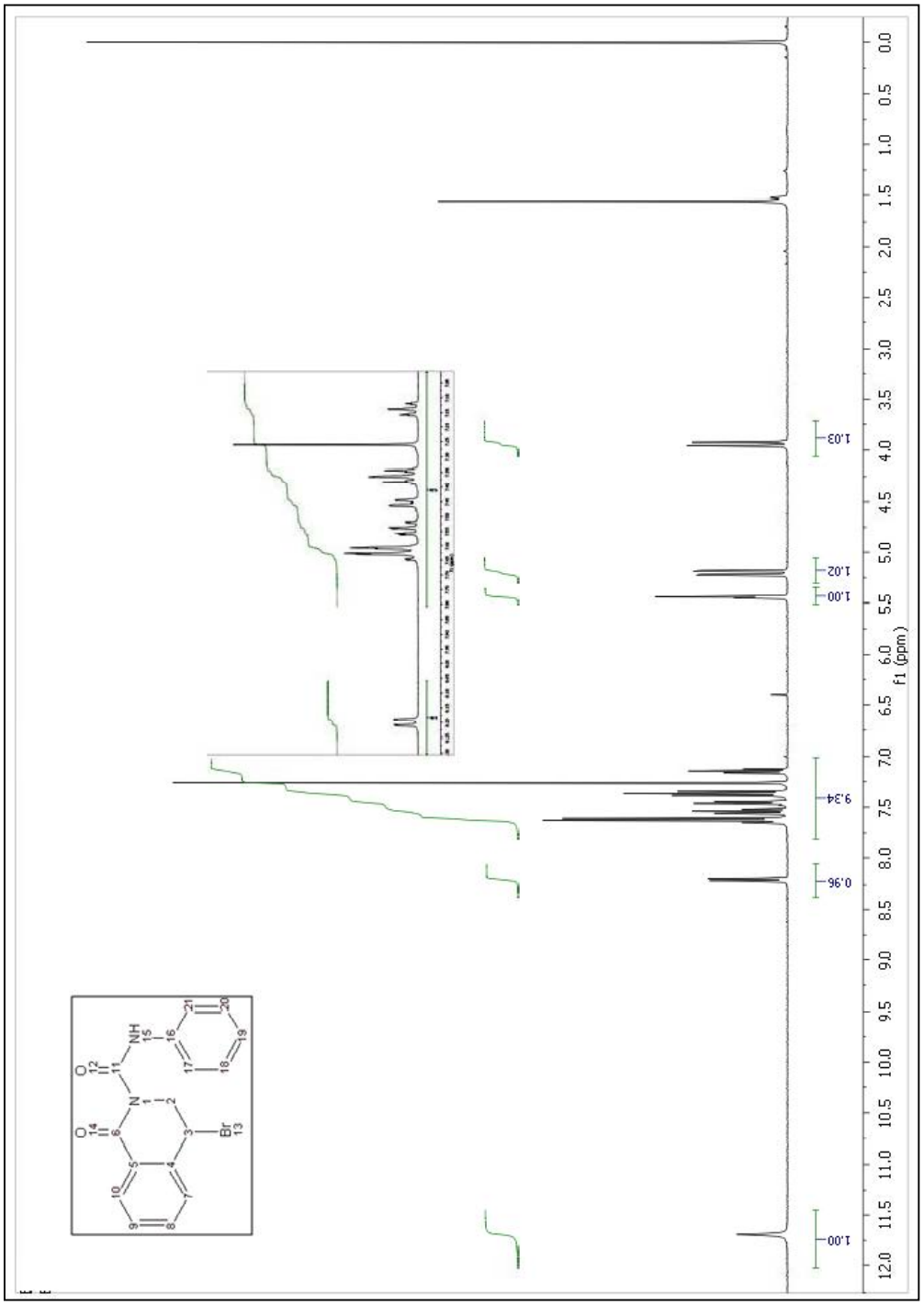



**Figure 29** $^{1}$H -NMR Spectrum of Compound **81**

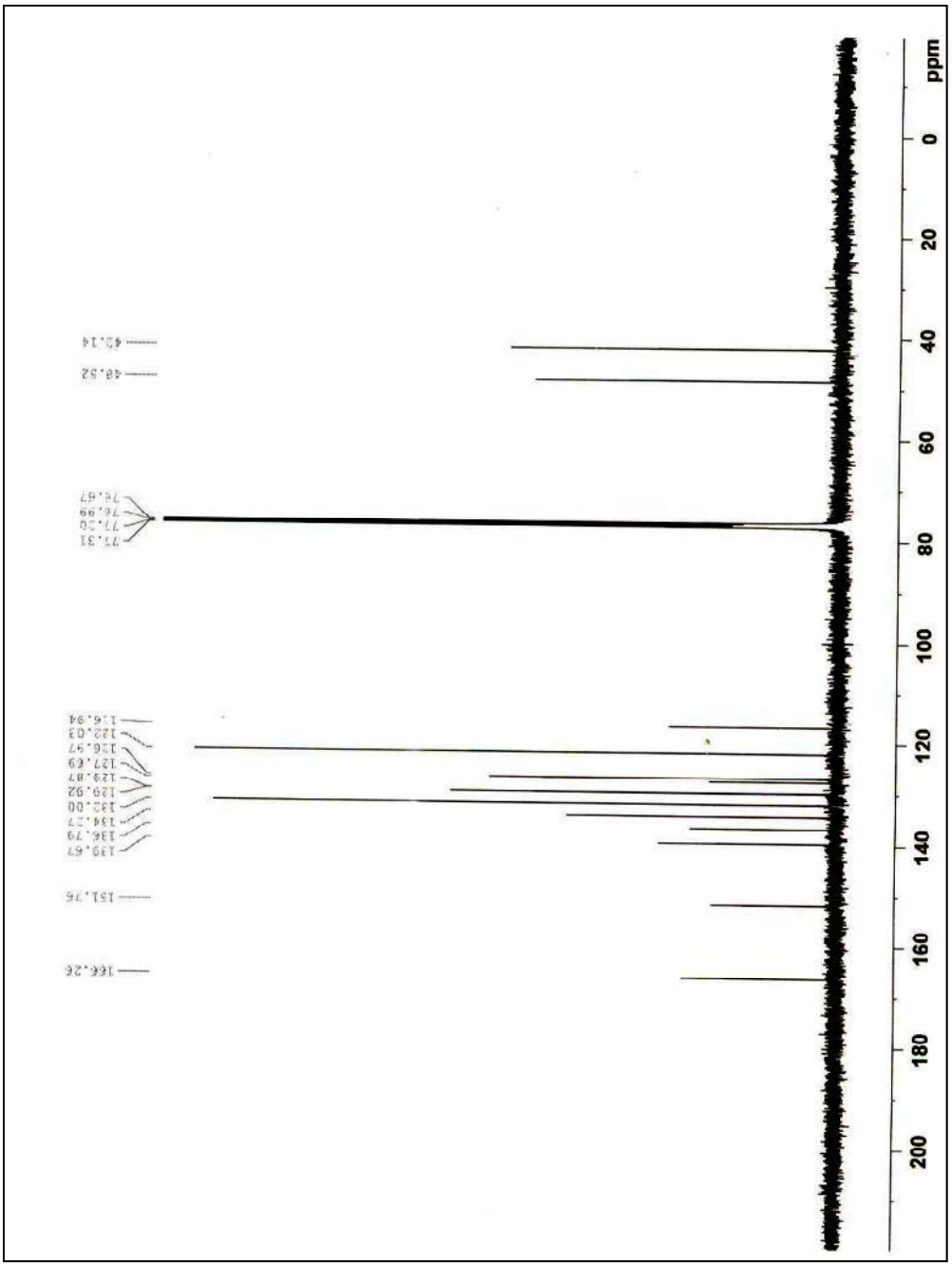



**Figure 30** $^{13}$C -NMR Spectrum of Compound **81**

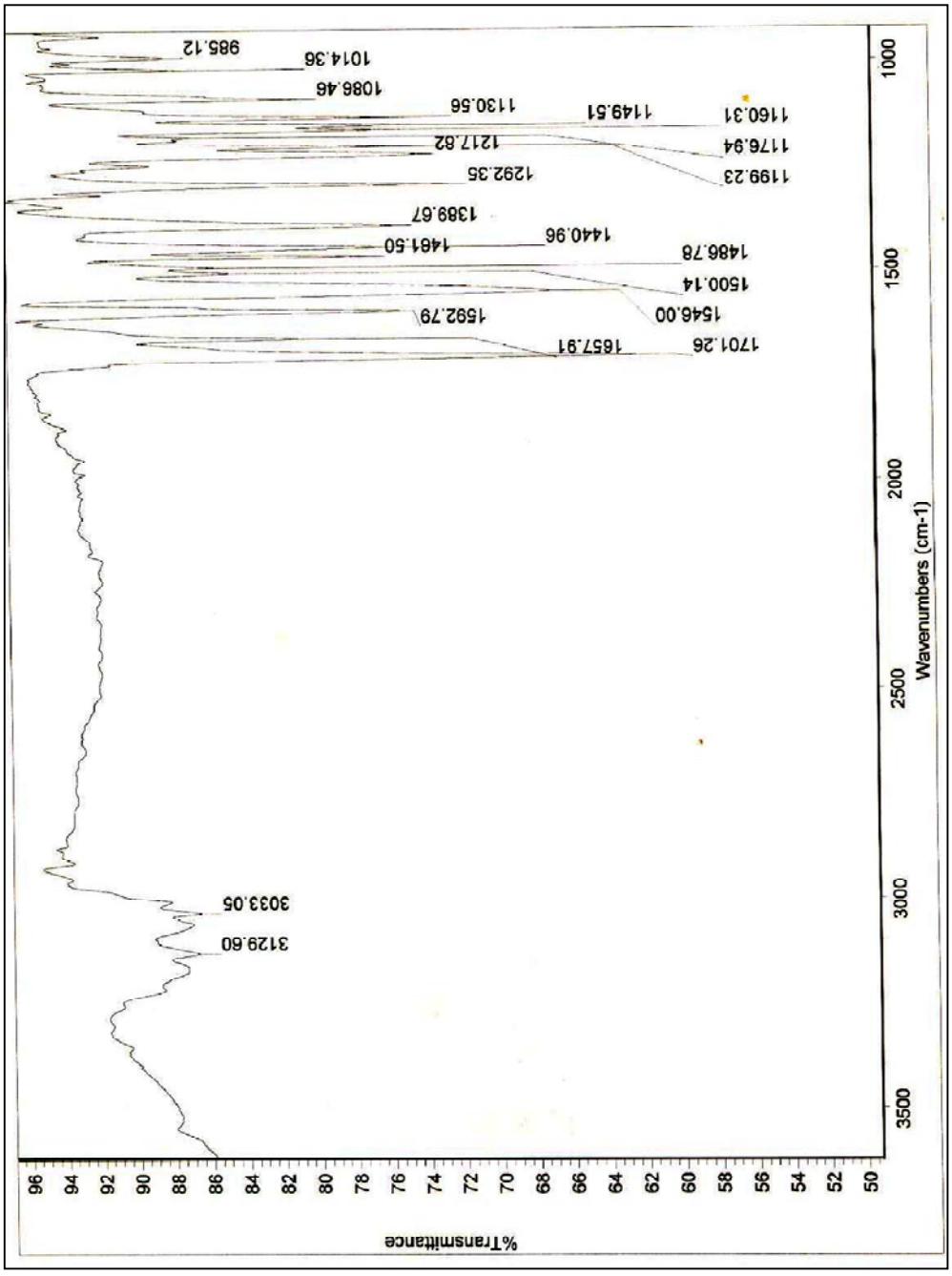



**Figure 31** IR Spectrum of Compound **81**

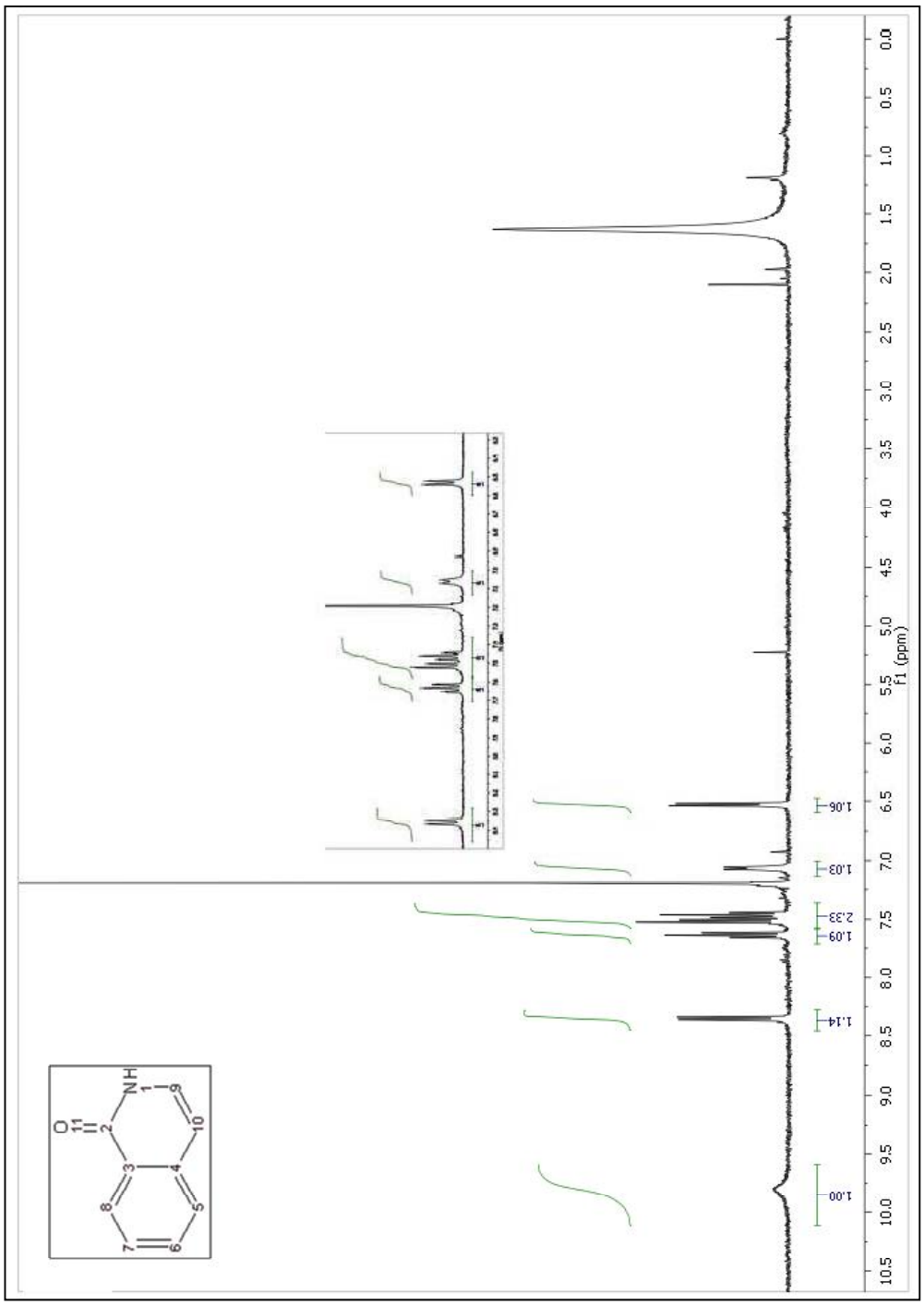



**Figure 32** $^{1}$H -NMR Spectrum of Compound **83**

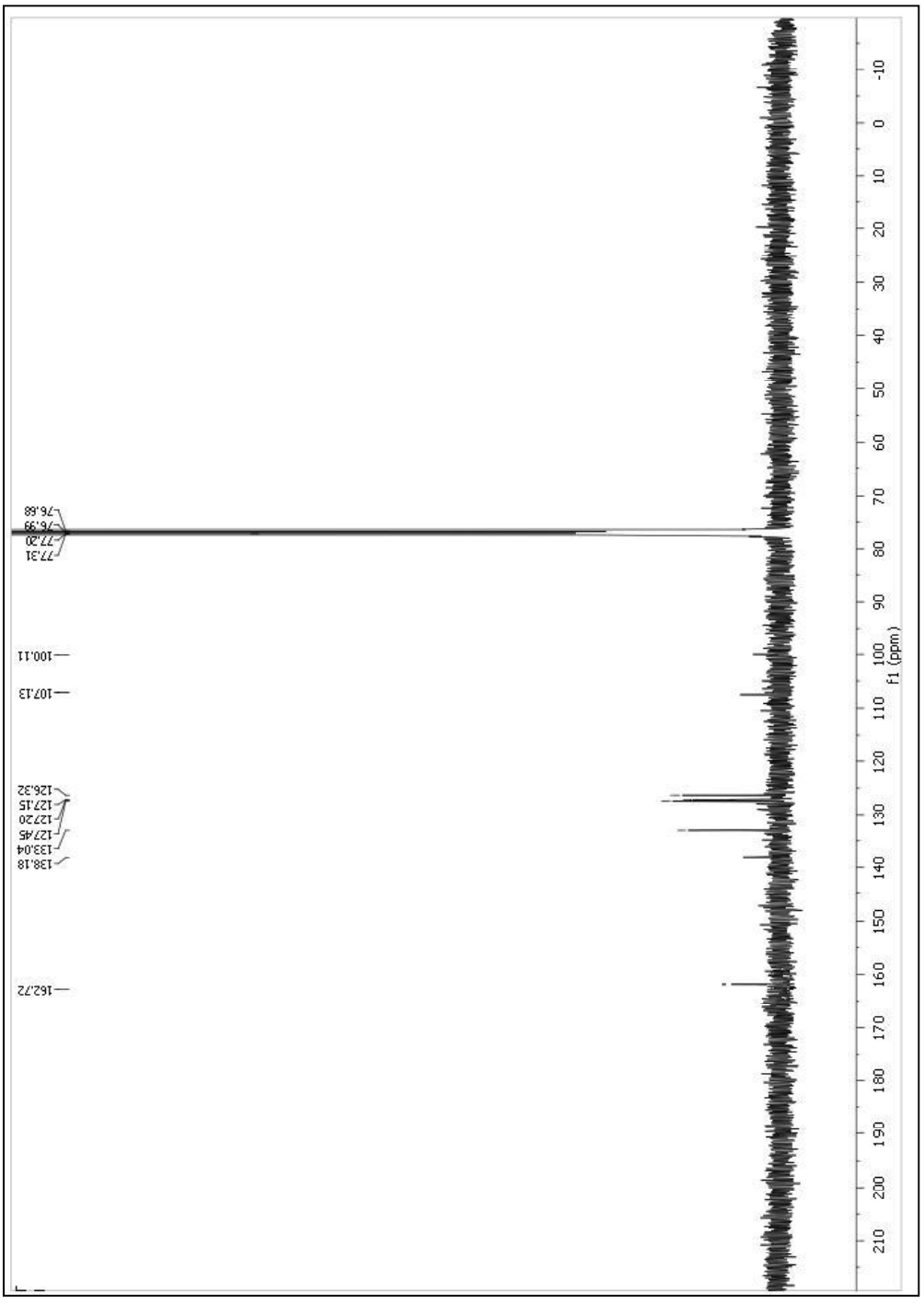



**Figure 33** $^{13}C$ -NMR Spectrum of Compound **83**

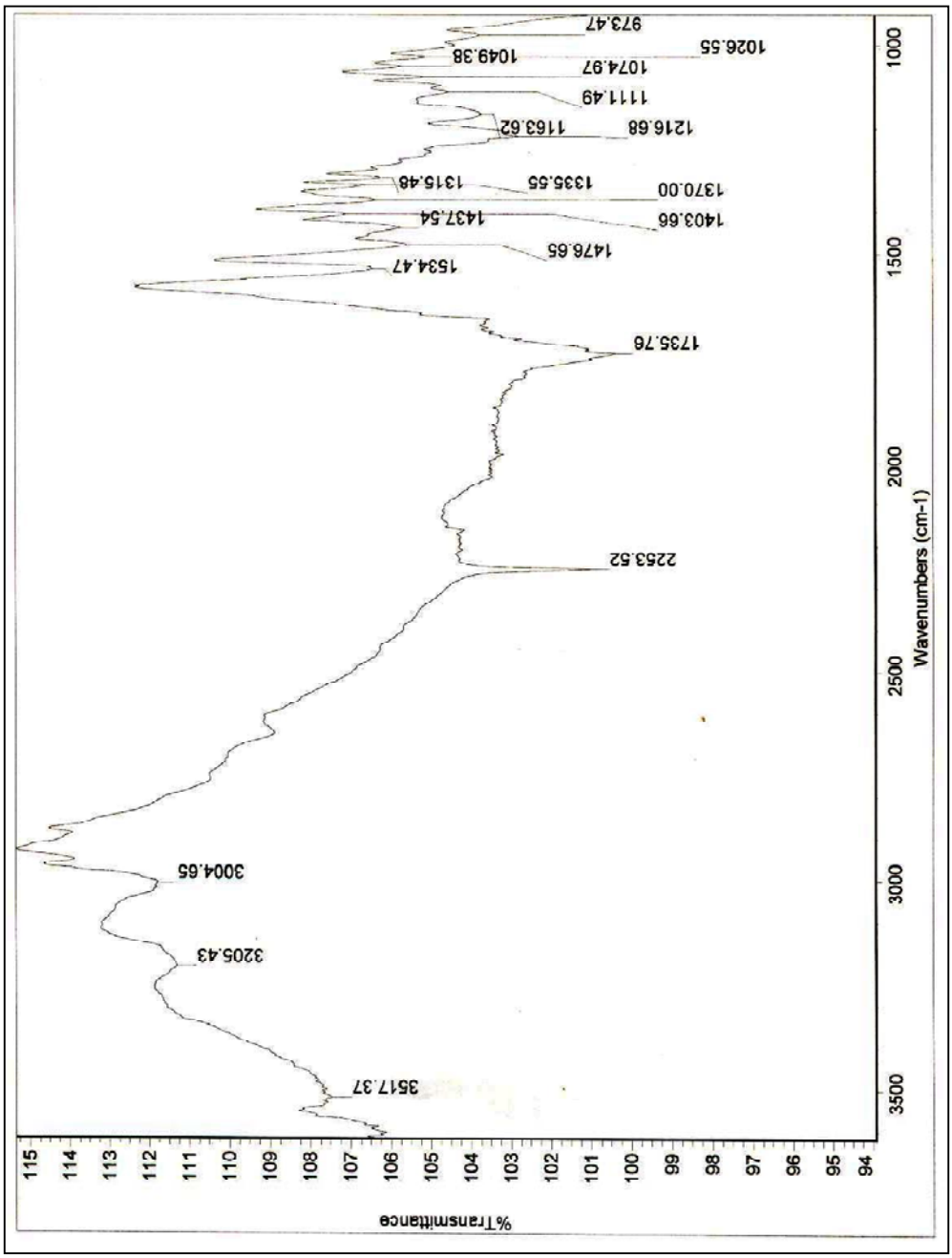



**Figure 34** IR Spectrum of Compound **83**

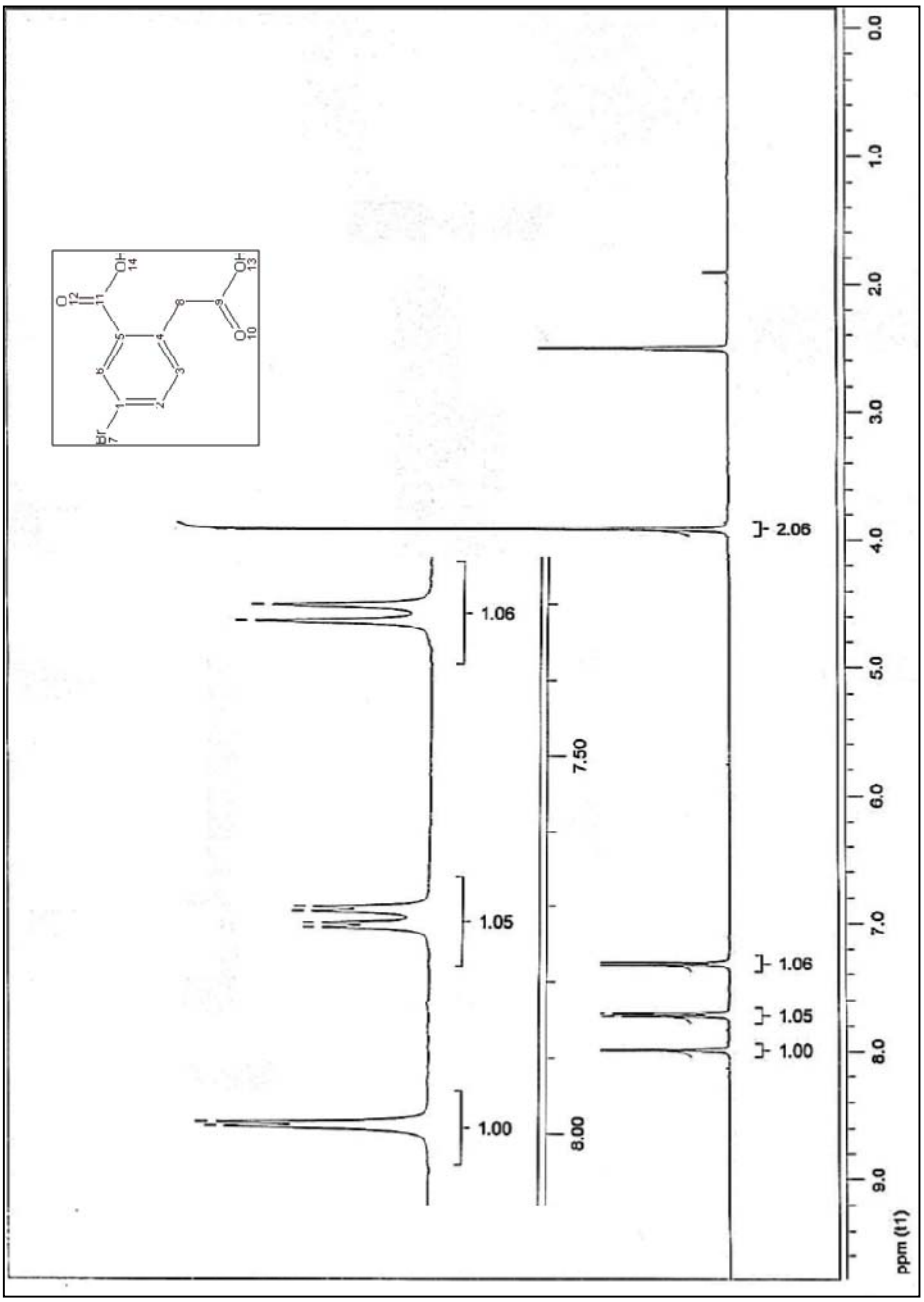



**Figure 35** $^{1}$H -NMR Spectrum of Compound **91**

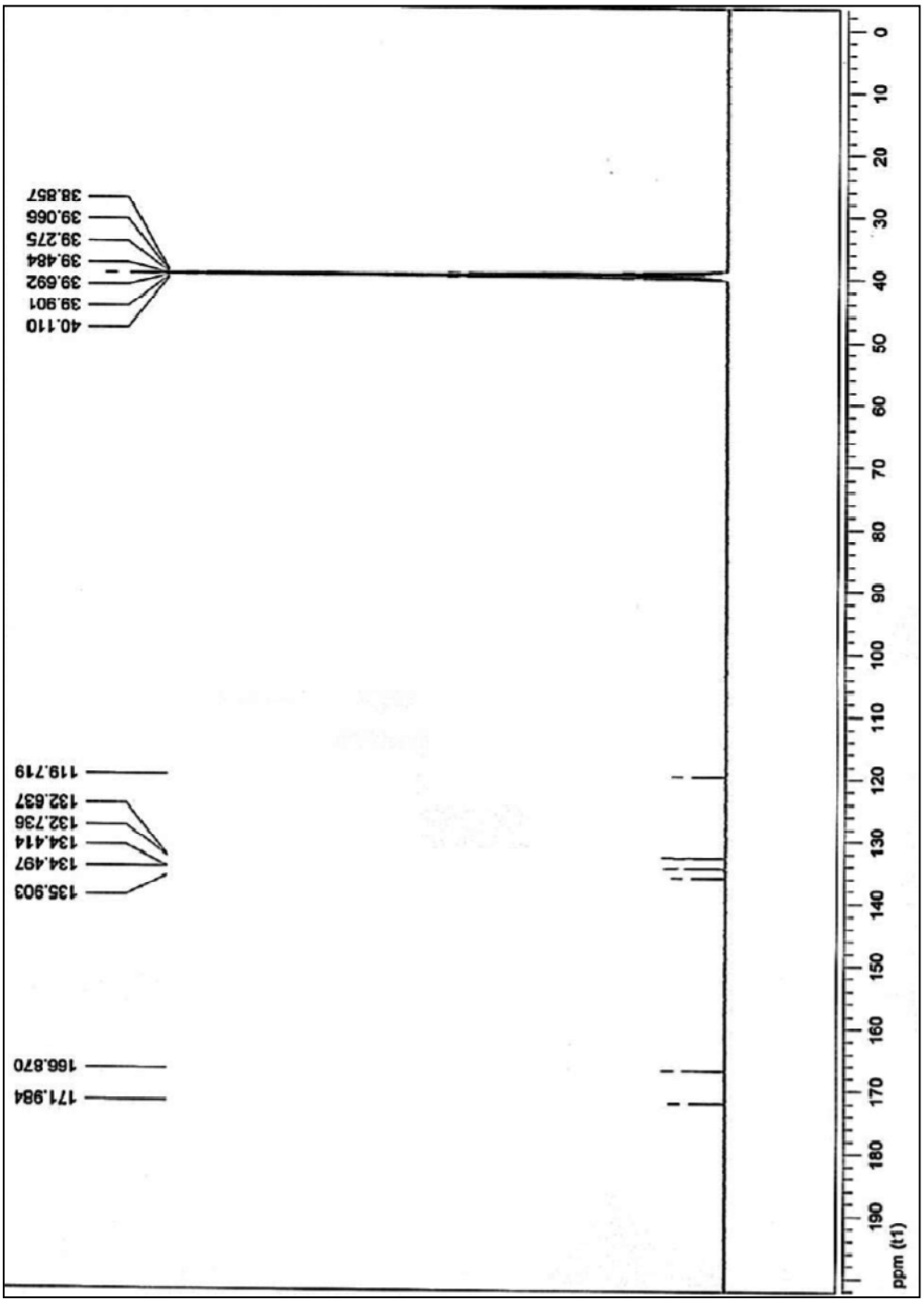



**Figure 36** $^{13}$C -NMR Spectrum of Compound **91**

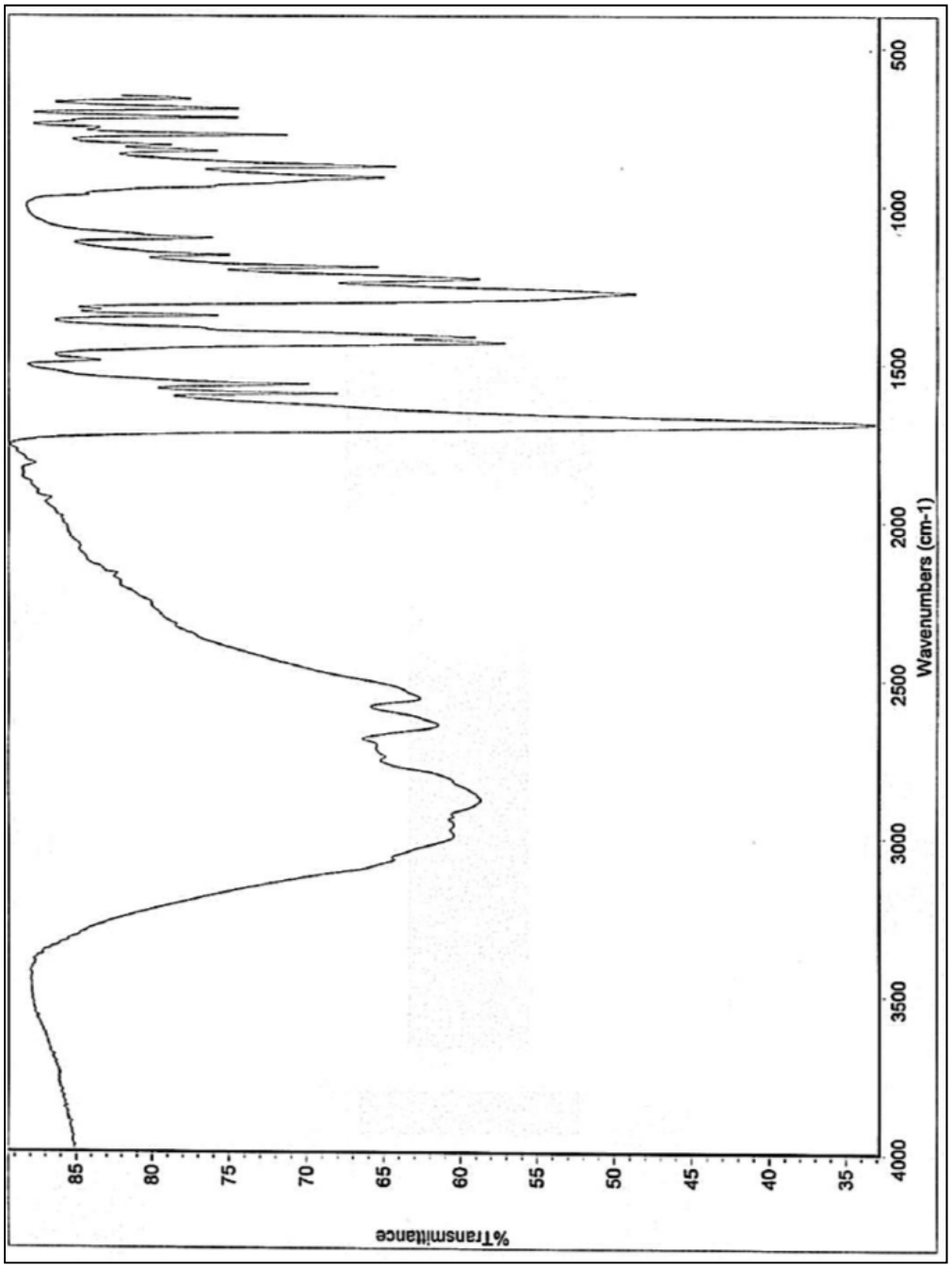



**Figure 37** IR Spectrum of Compound **91**

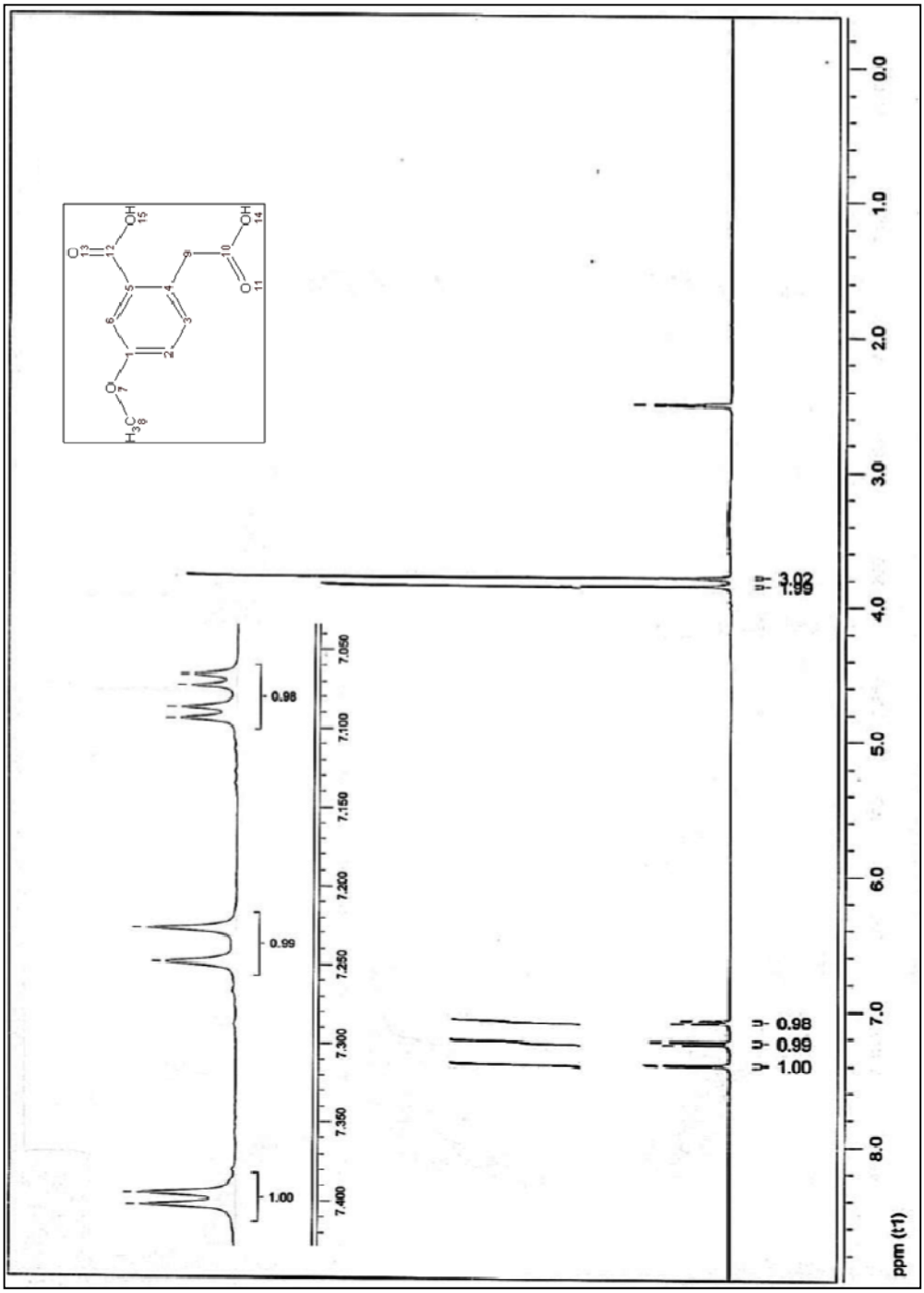



**Figure 38** $^{1}$H -NMR Spectrum of Compound **96**

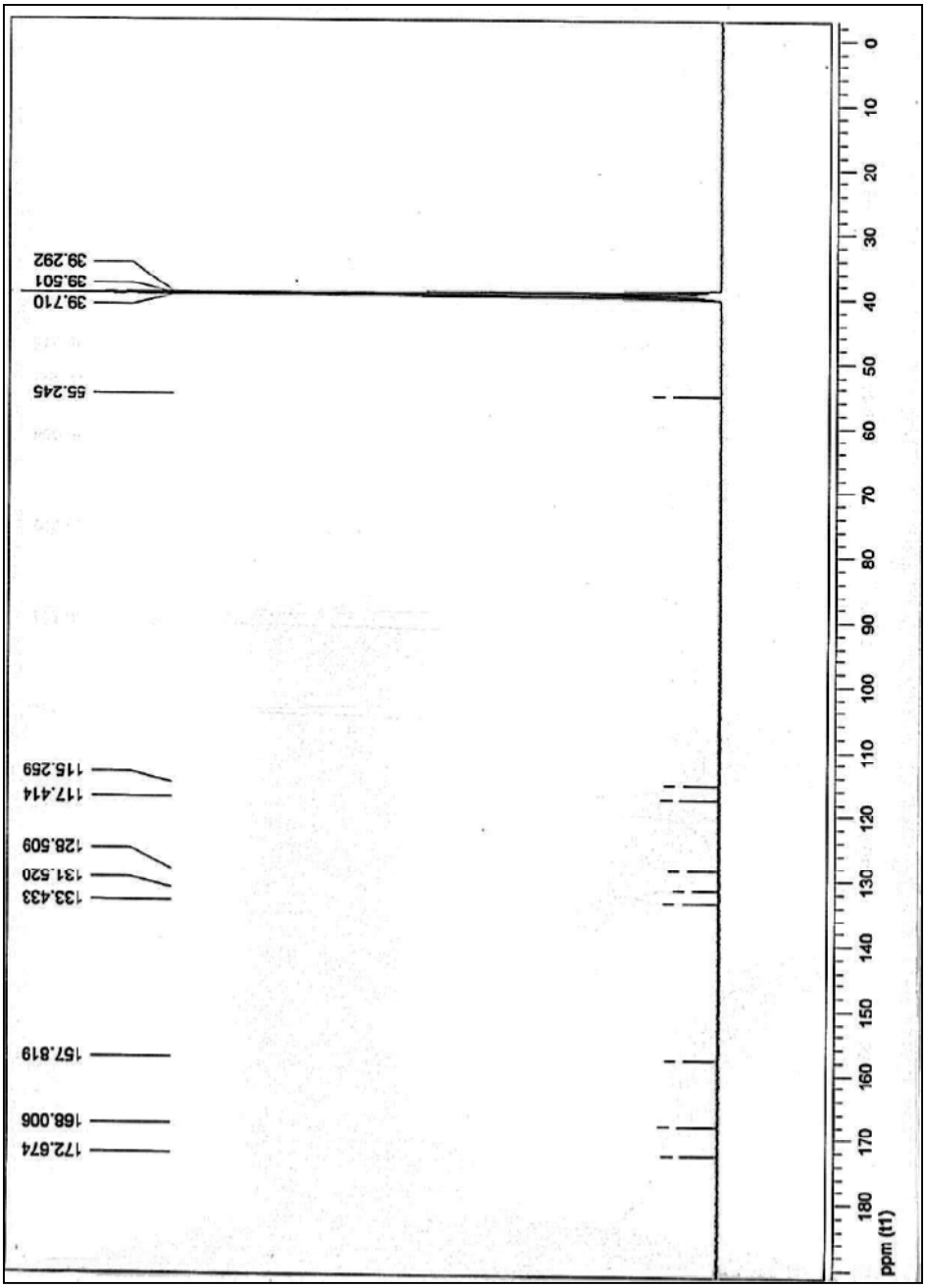



**Figure 39** $^{13}$C -NMR Spectrum of Compound **96**

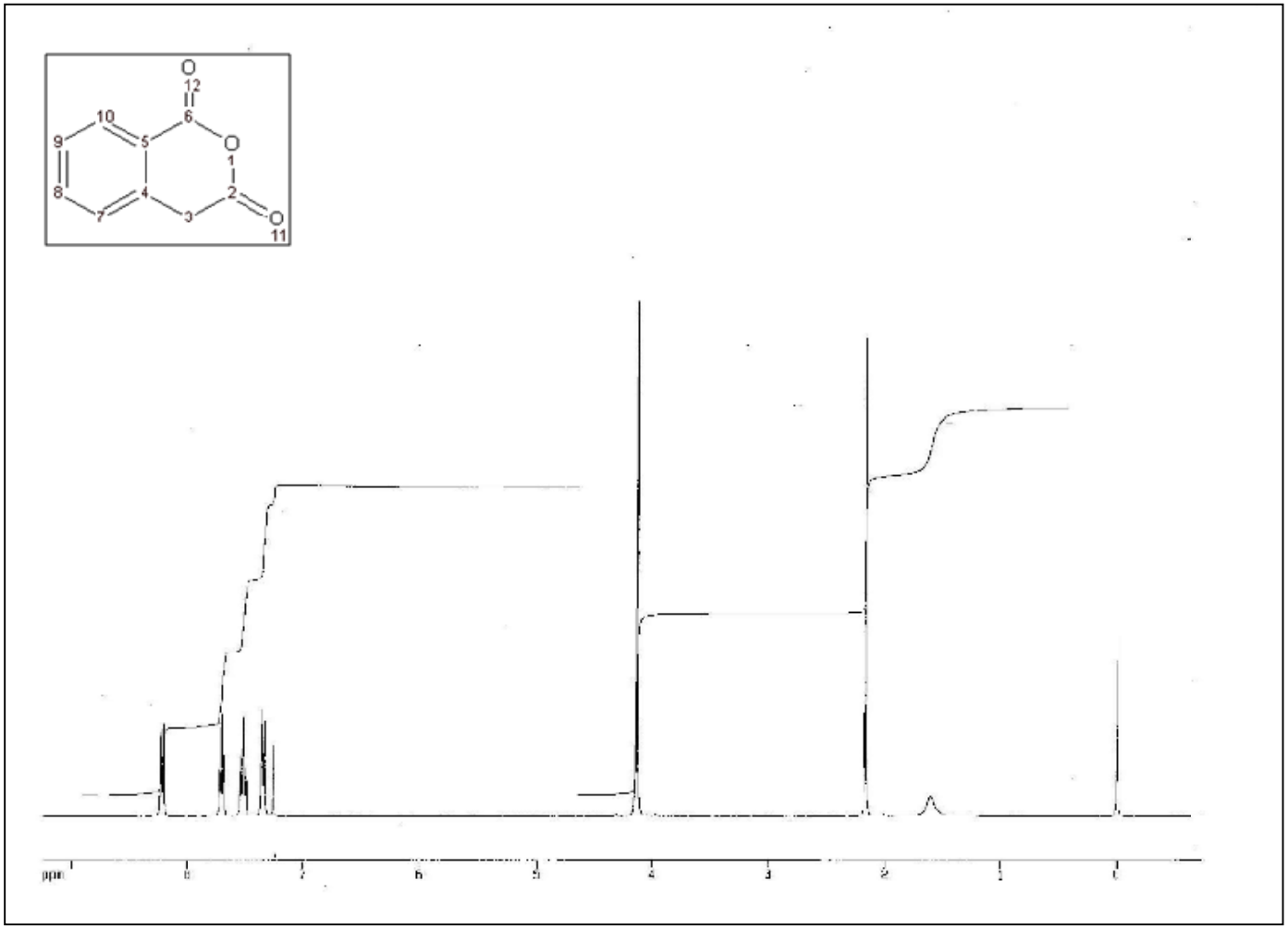



**Figure 40** $^{1}$H -NMR Spectrum of Compound **97**

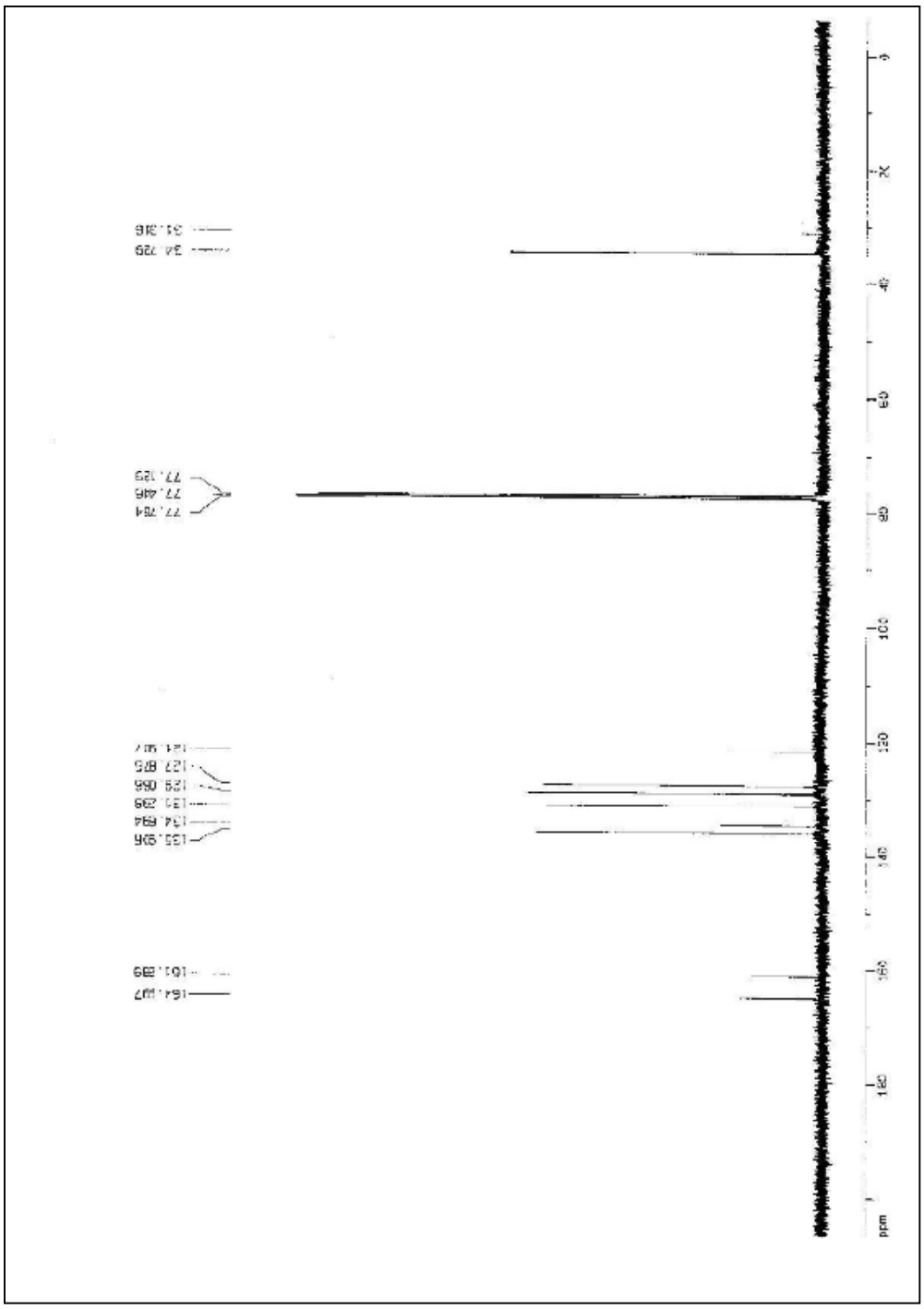


**Figure 41** $^{13}$C -NMR Spectrum of Compound **97**

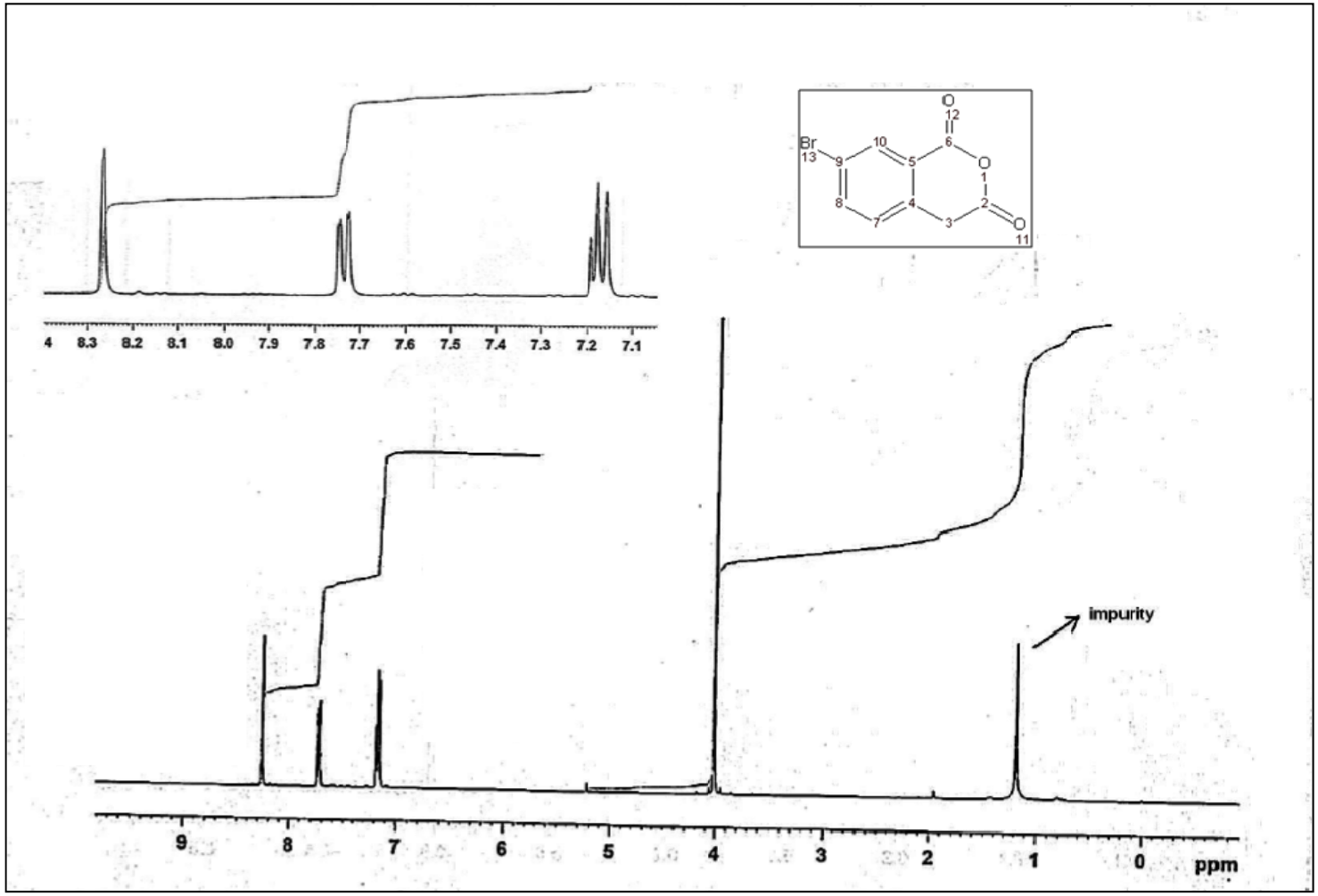



**Figure 42** $^{1}$H -NMR Spectrum of Compound **98**

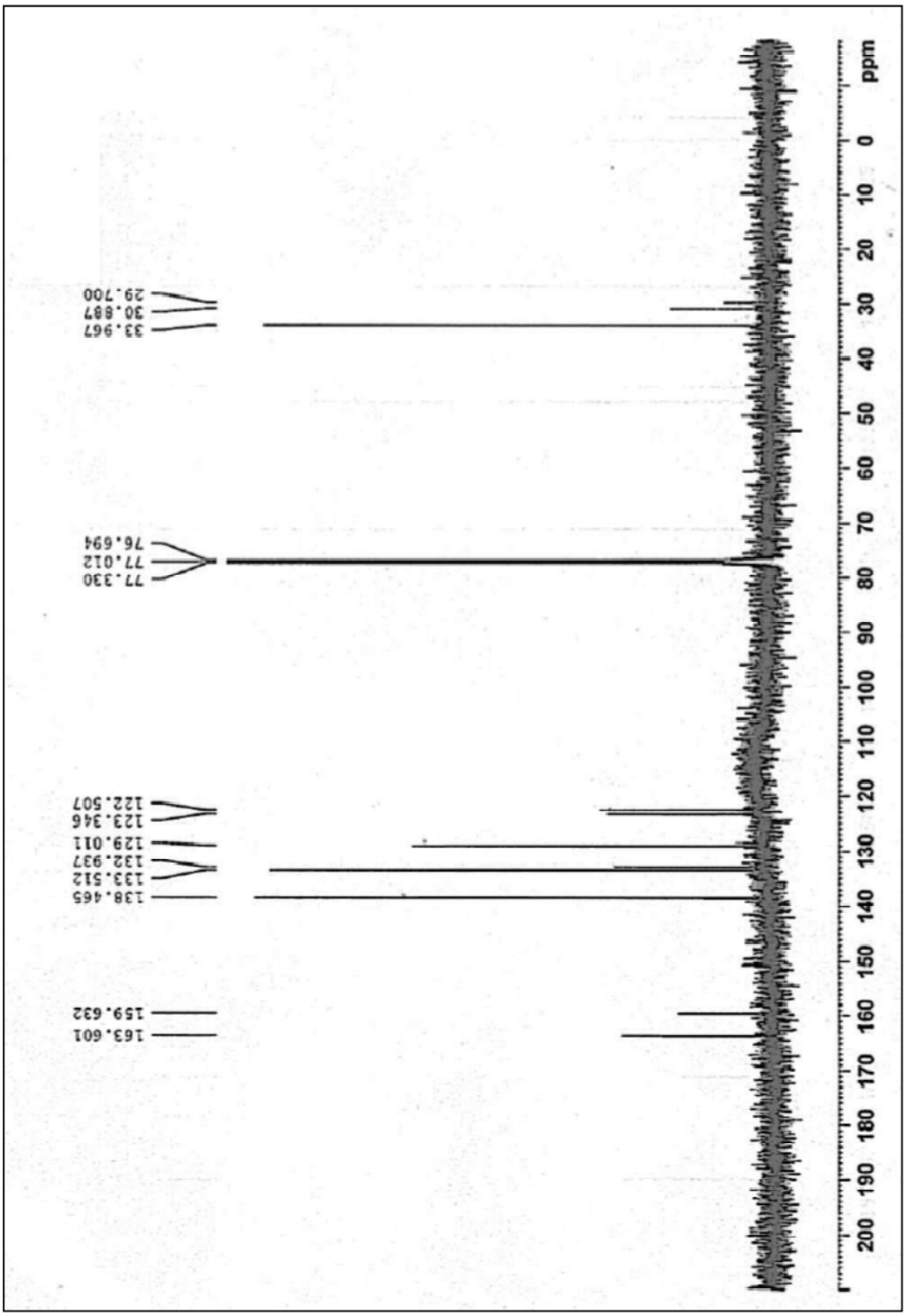



**Figure 43** $^{13}$C -NMR Spectrum of Compound **98**

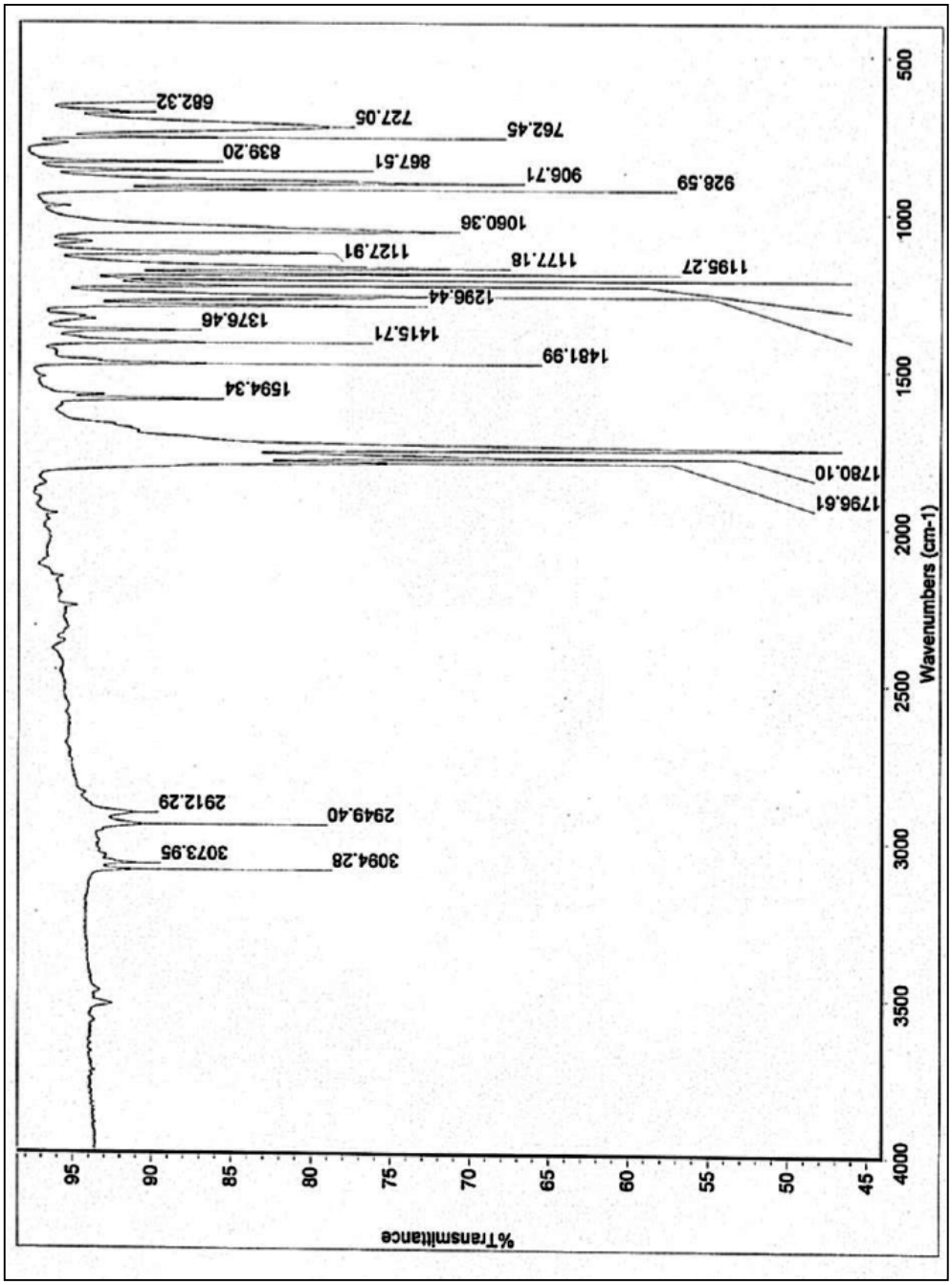



**Figure 44** IR Spectrum of Compound **98**

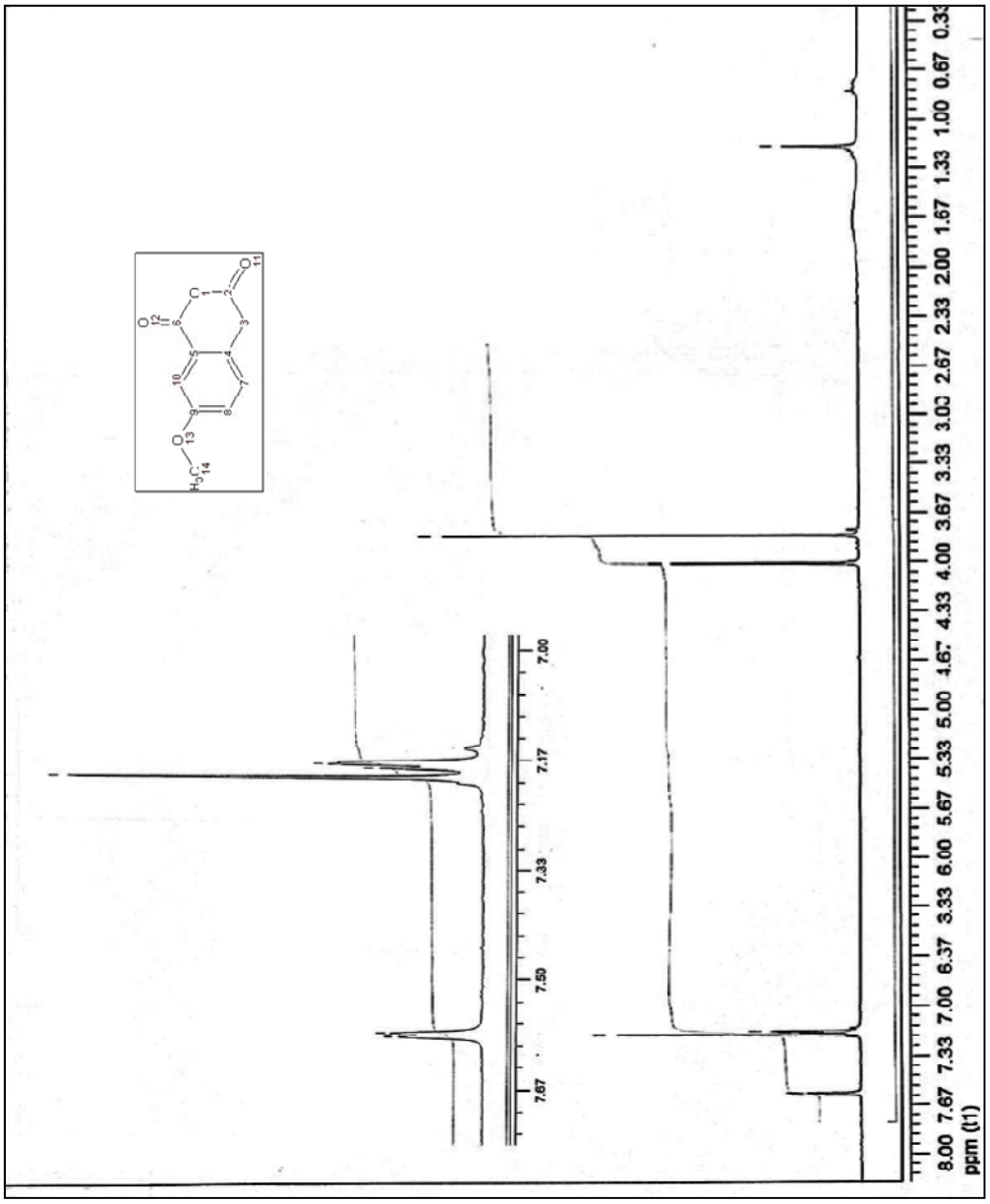



**Figure 45** $^{1}$H -NMR Spectrum of Compound **99**

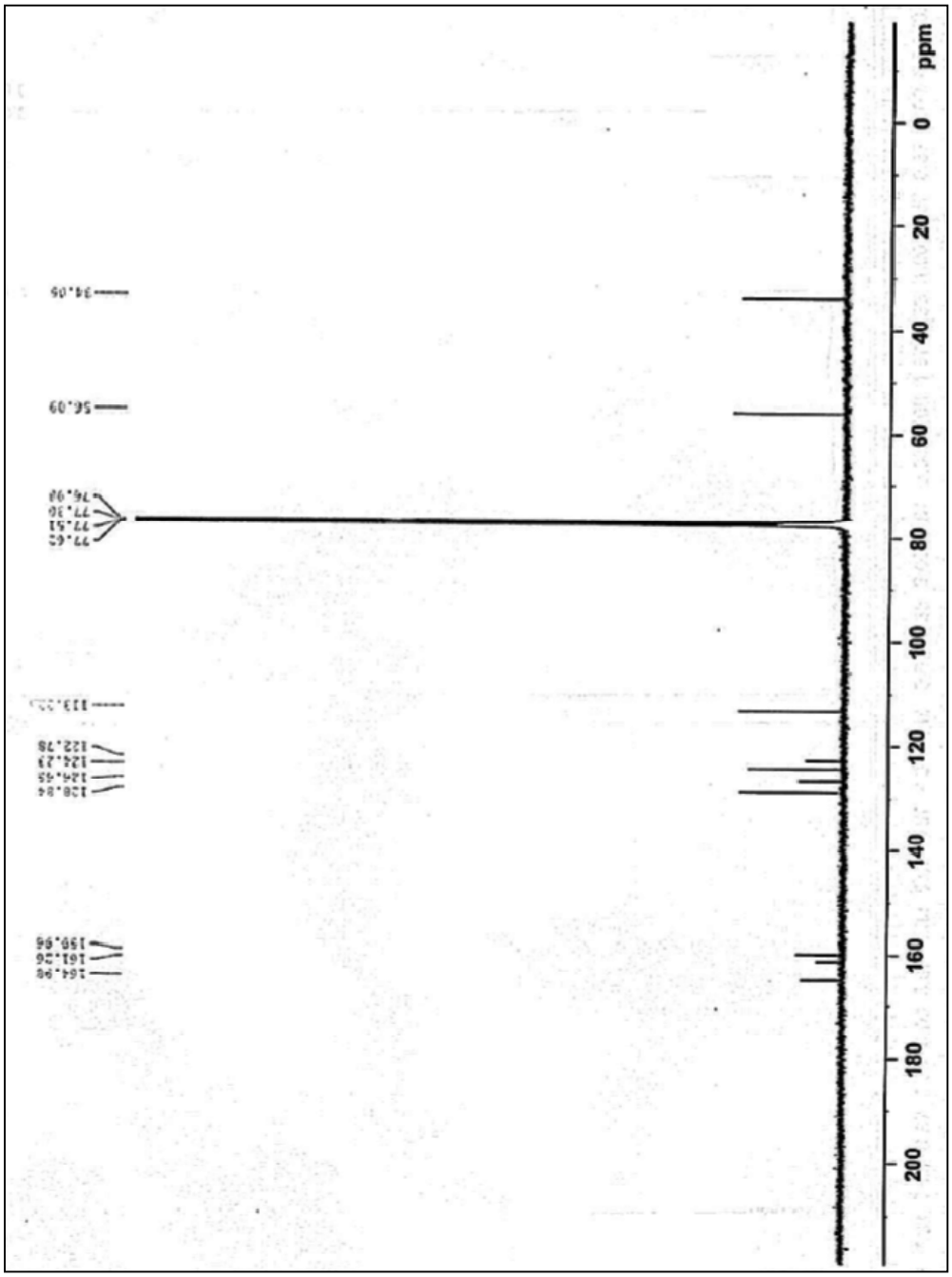



**Figure 46** $^{13}$C -NMR Spectrum of Compound **99**

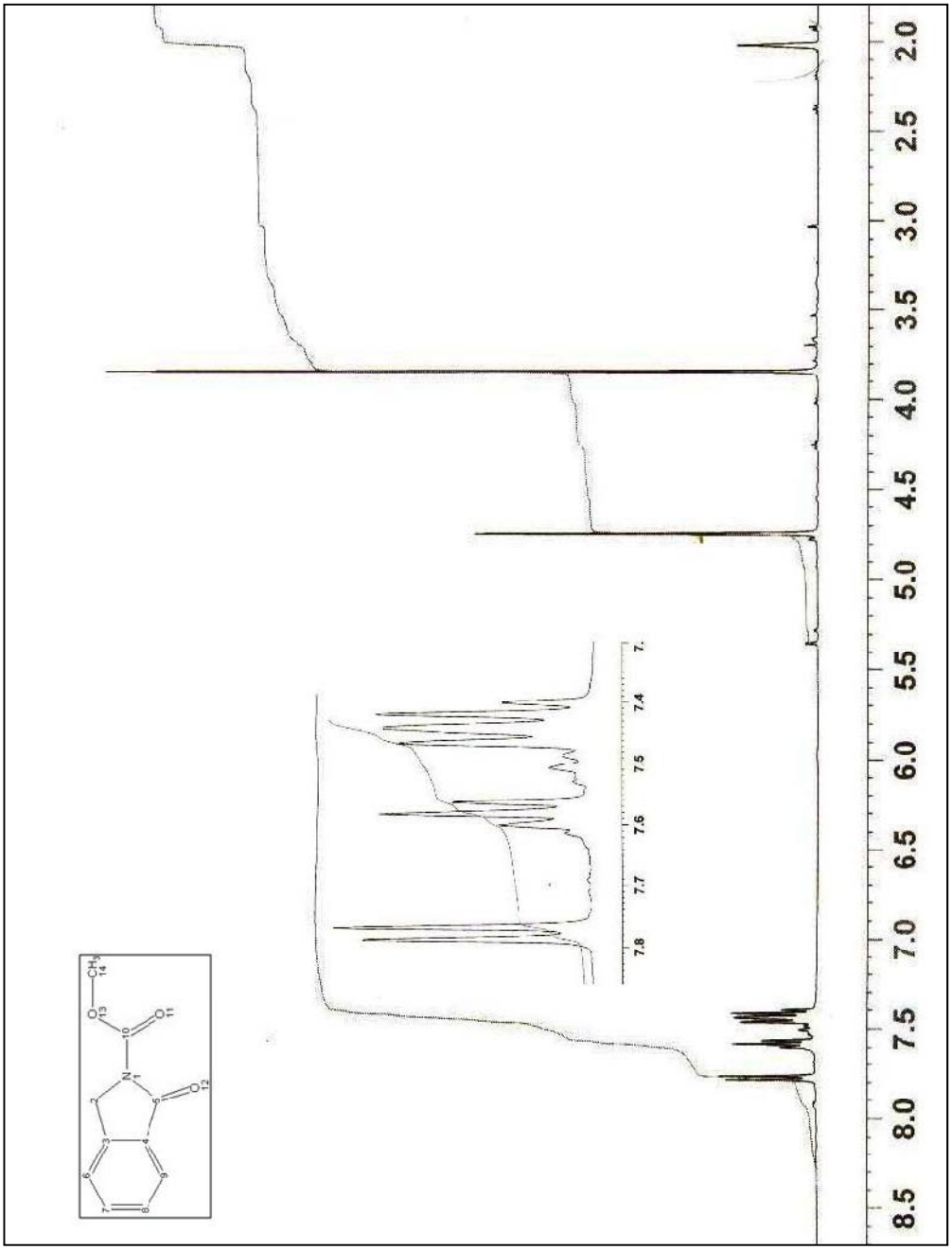



**Figure 47** $^{1}$H -NMR Spectrum of Compound **101**

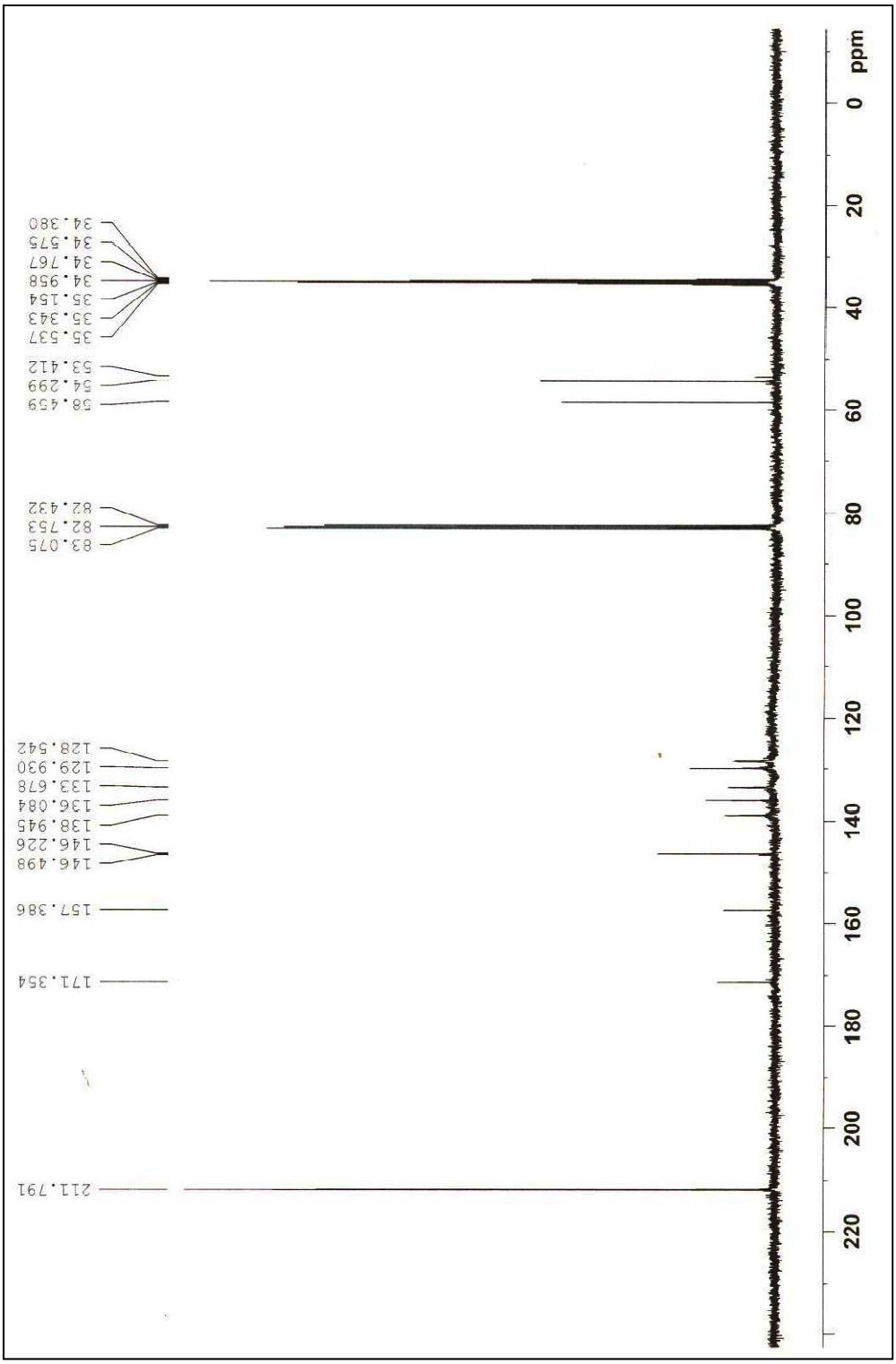



**Figure 48** $^{13}$C -NMR Spectrum of Compound **101**

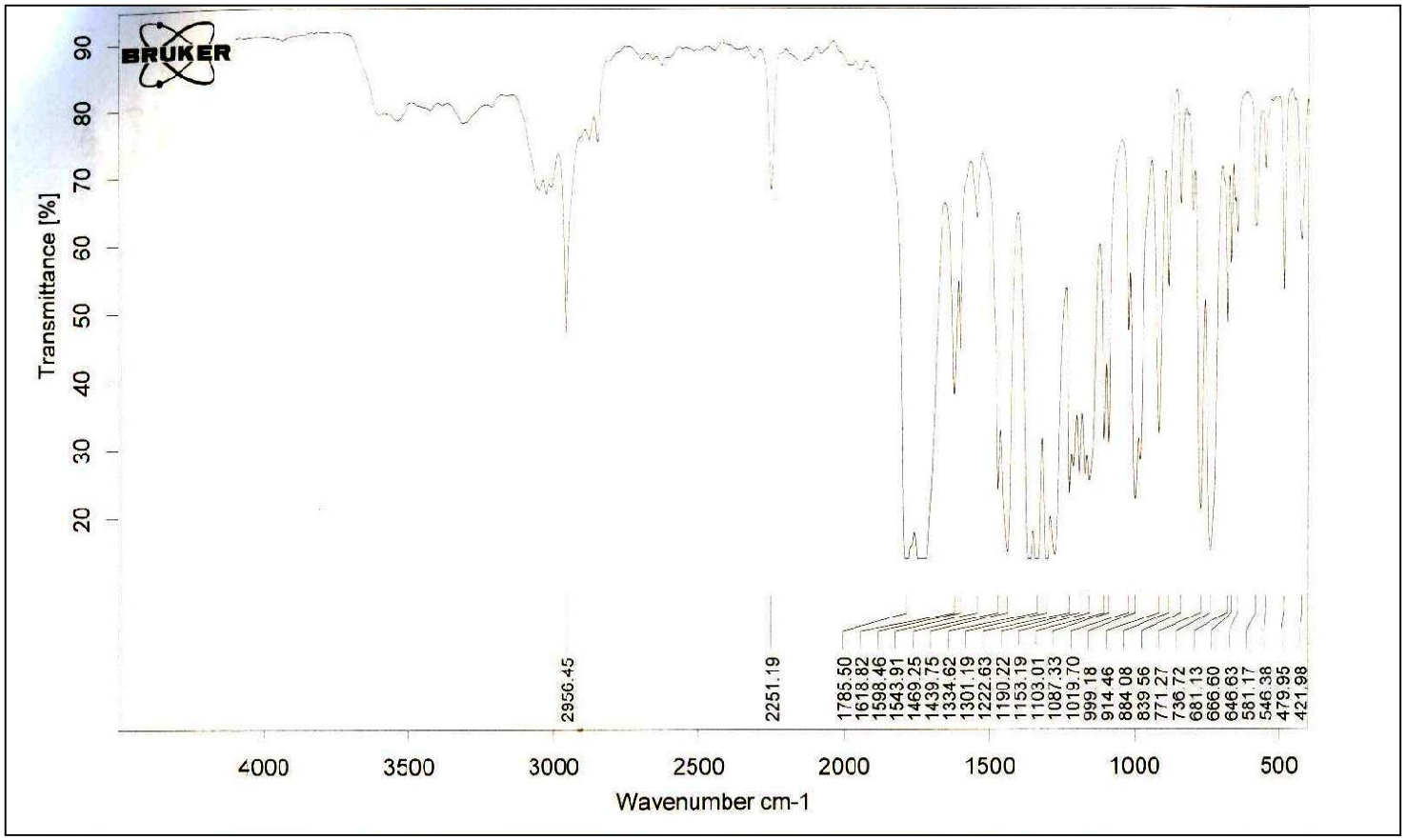



**Figure 49** IR -NMR Spectrum of Compound **101**

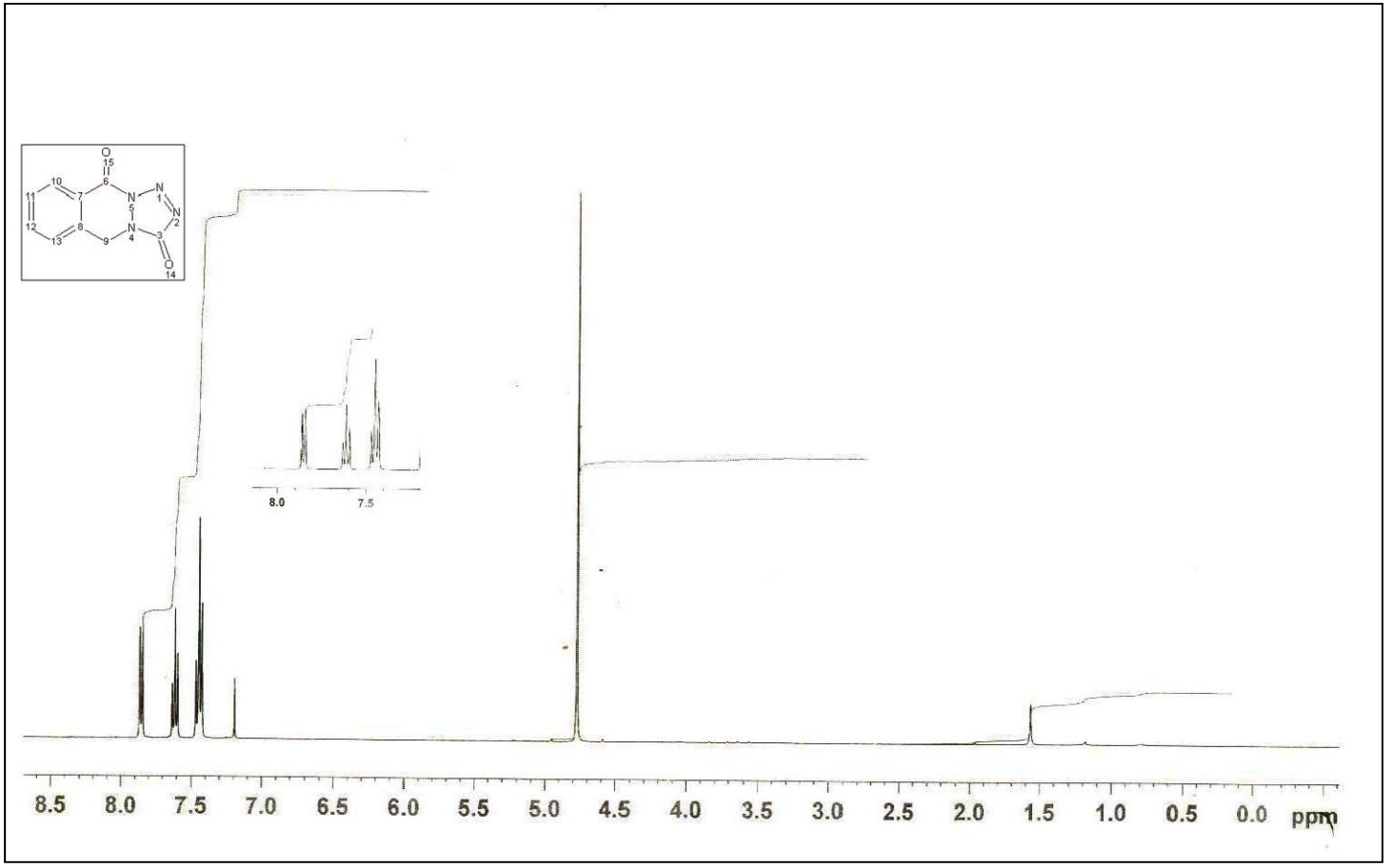



**Figure 50** $^{1}$H -NMR Spectrum of Compound **116**

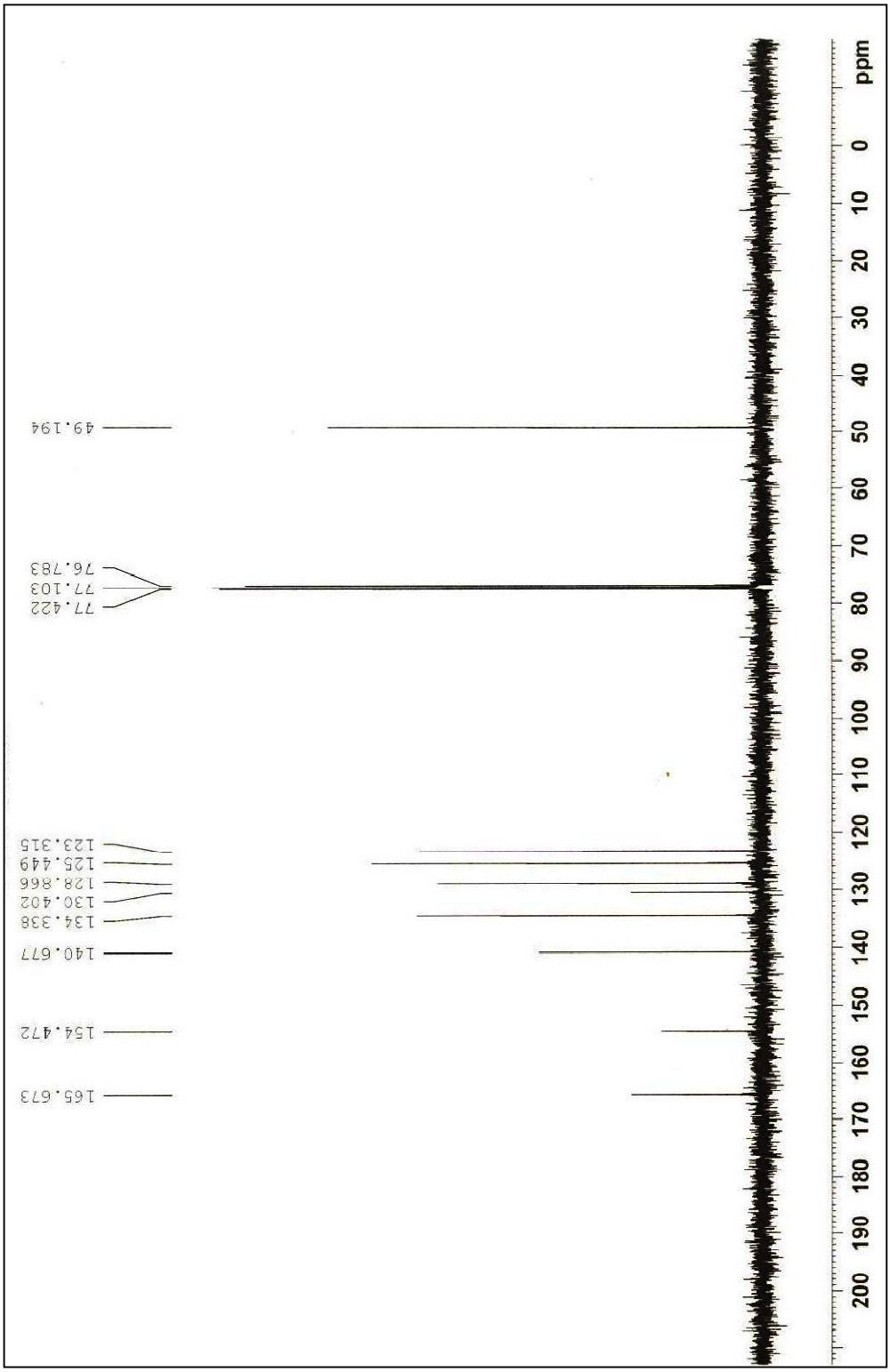



**Figure 51** $^{13}C$ -NMR Spectrum of Compound **116**

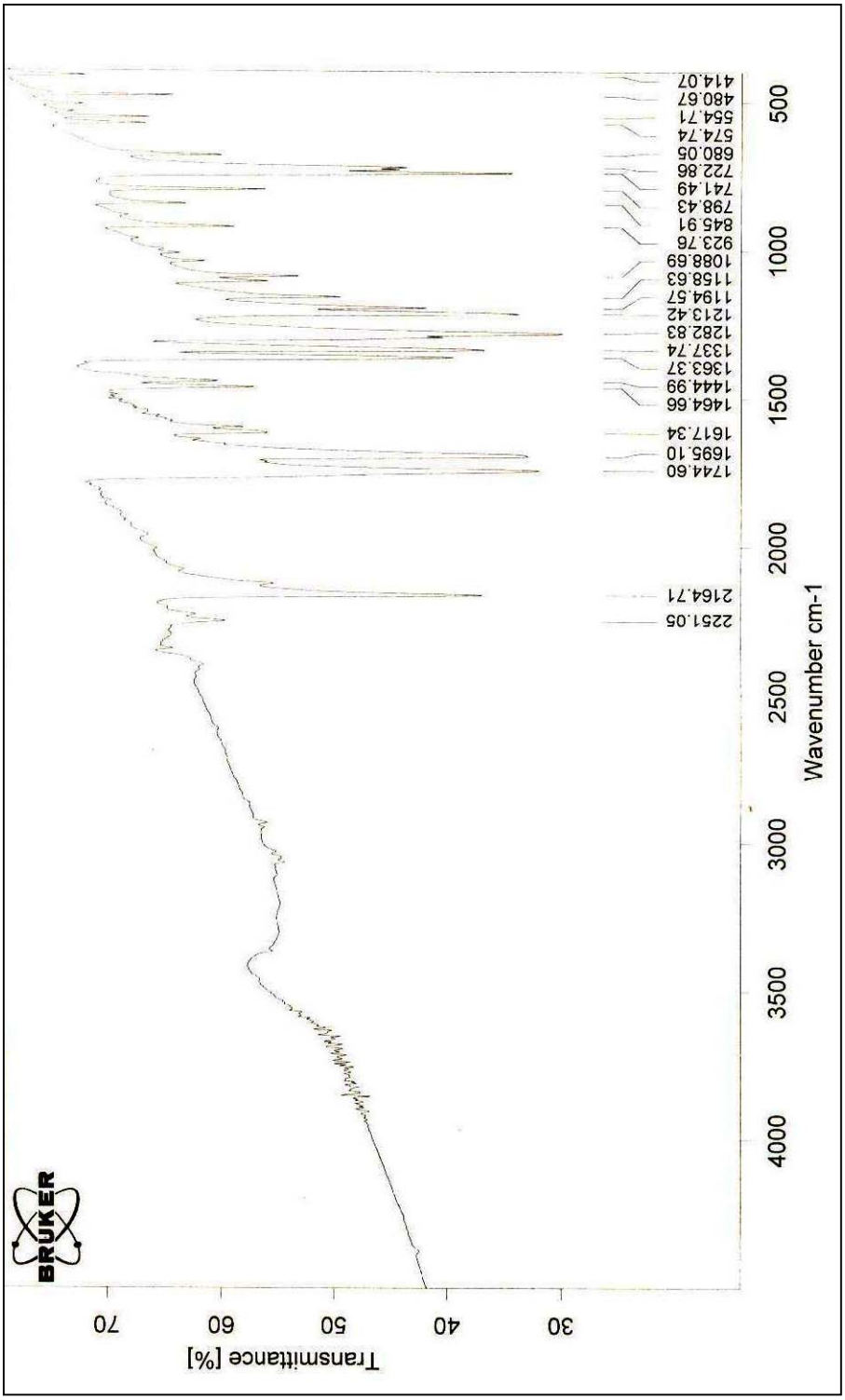



**Figure 52** IR -NMR Spectrum of Compound **116**

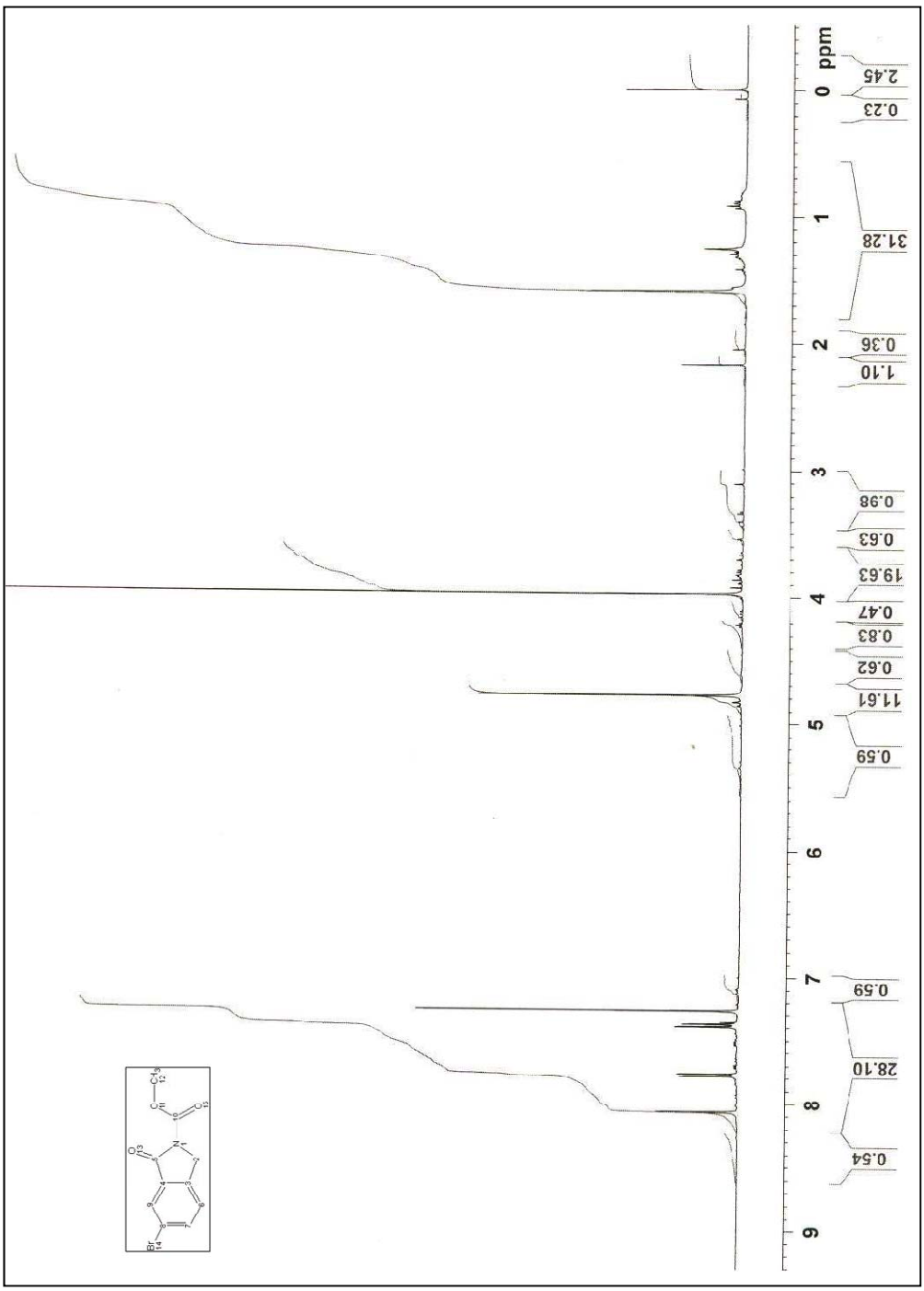



**Figure 53** $^{1}$H -NMR Spectrum of Compound **102**

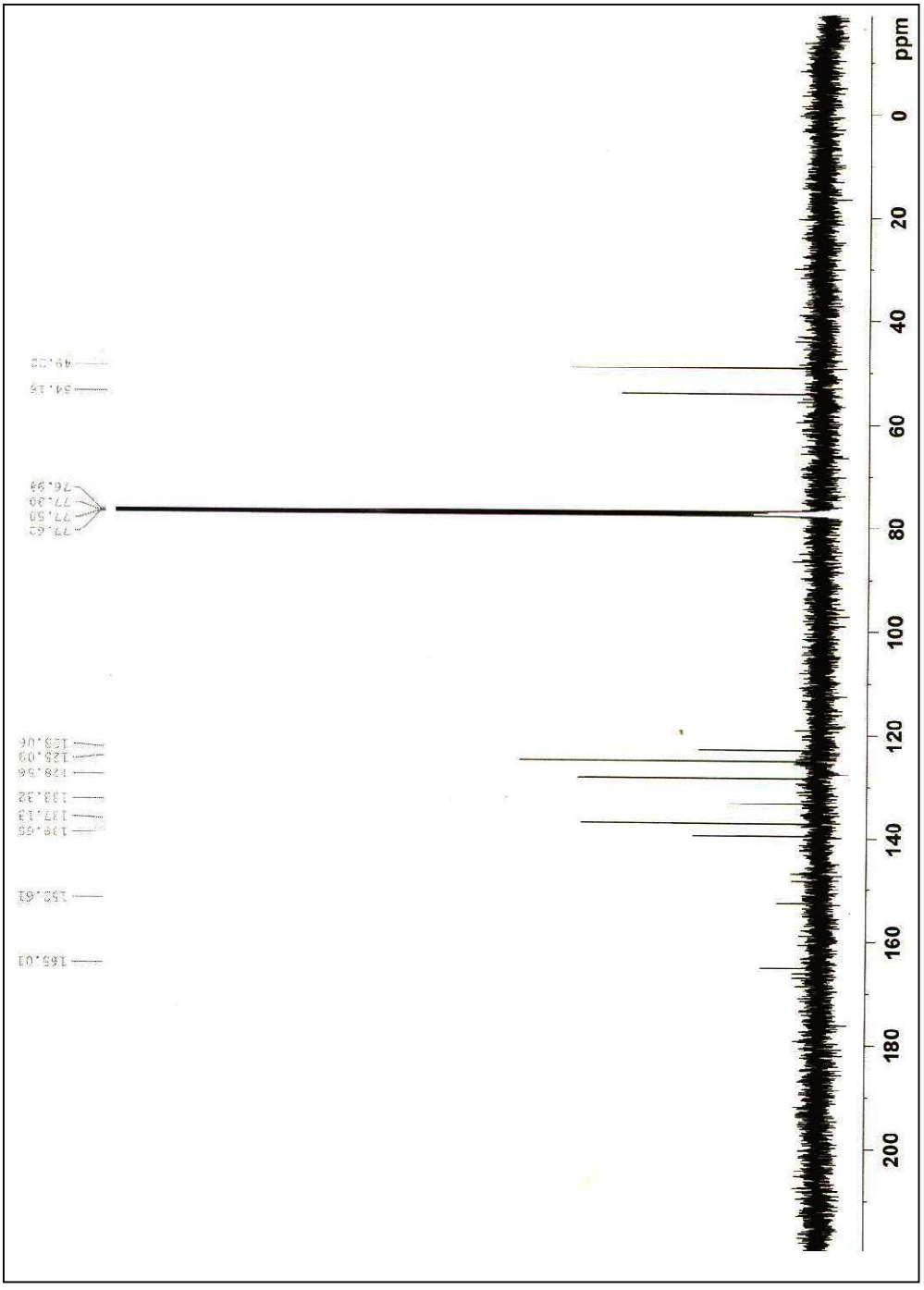



**Figure 54** $^{13}$C -NMR Spectrum of Compound **102**

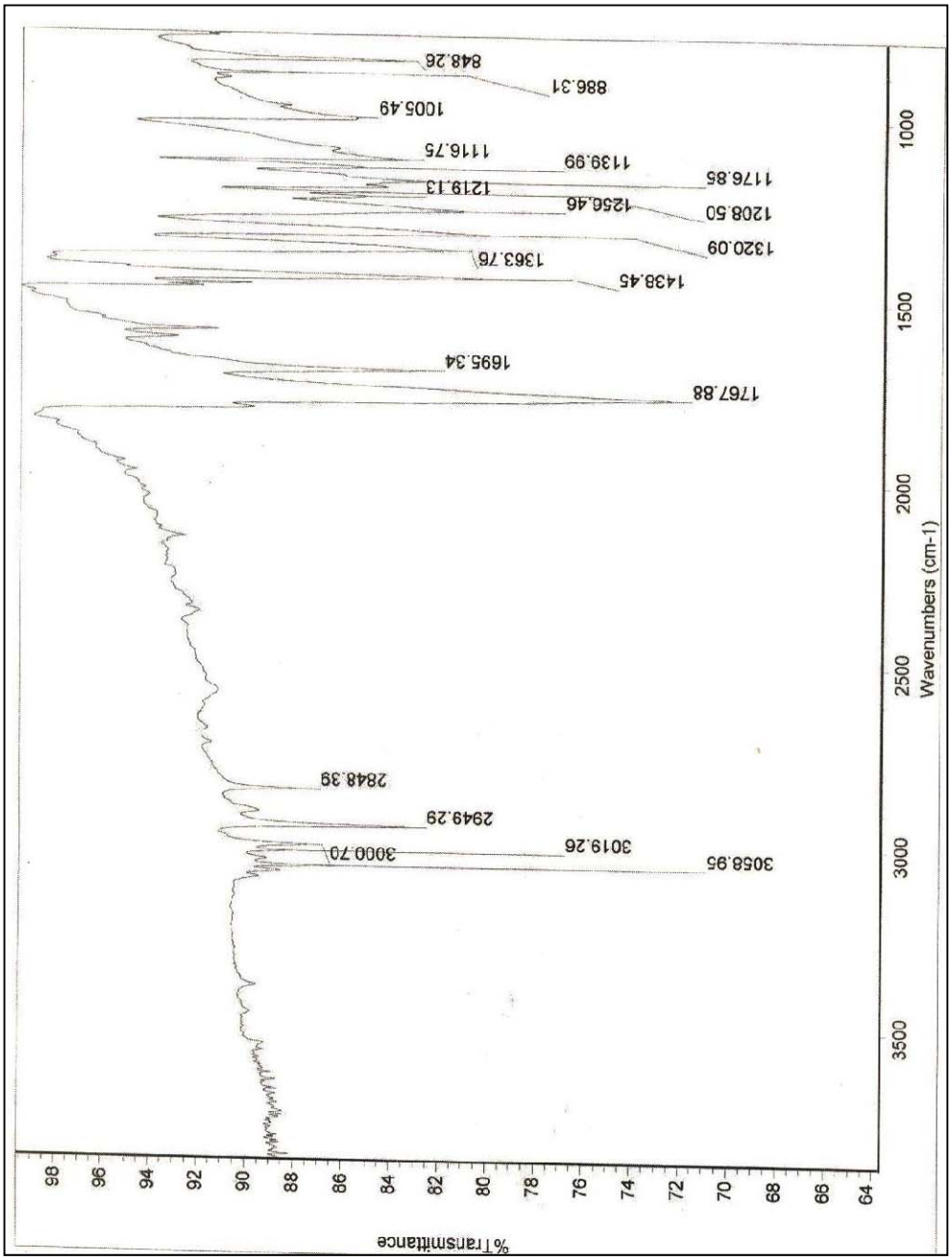



**Figure 55** IR Spectrum of Compound **102**

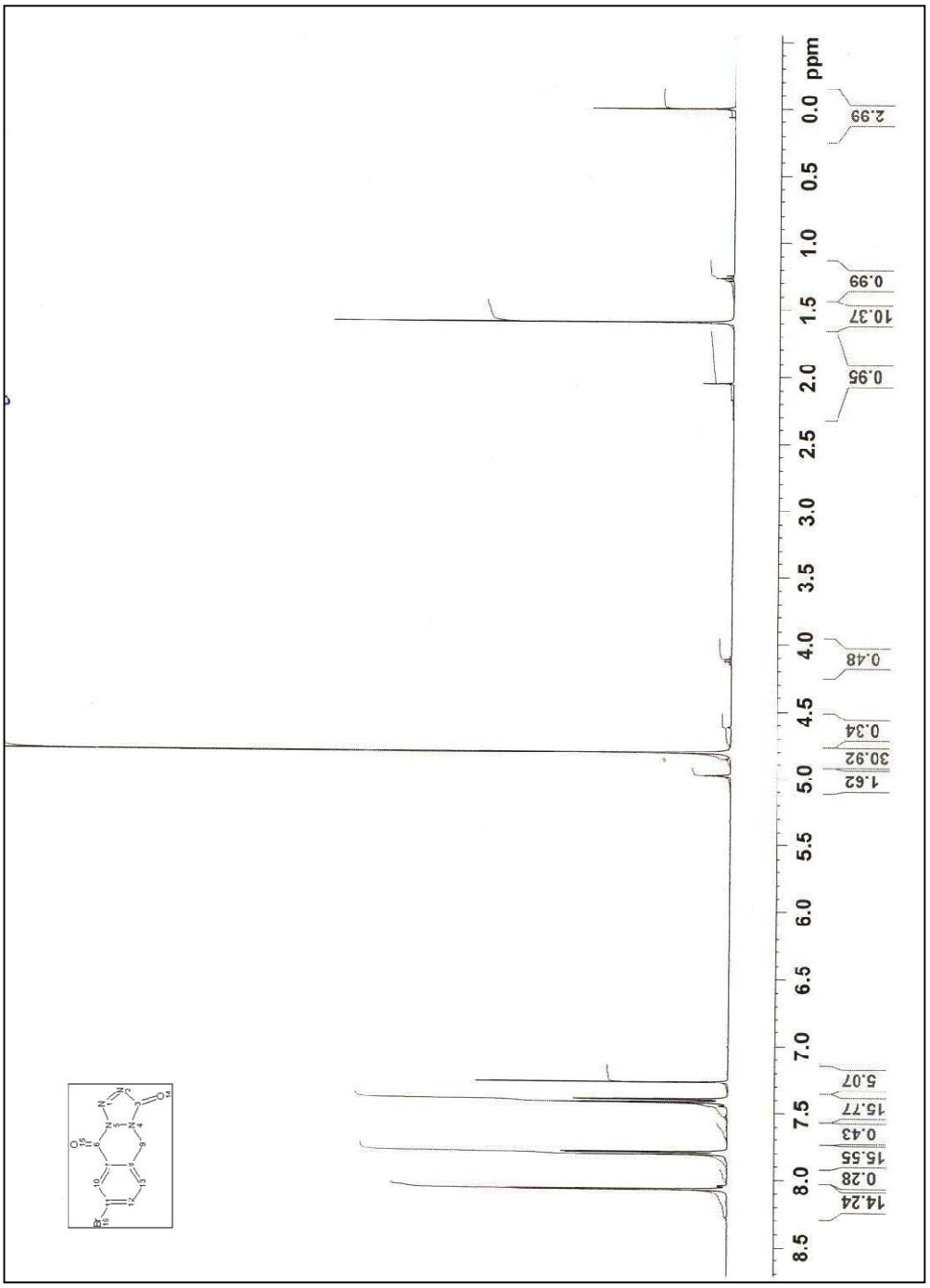



**Figure 56** $^{1}$H -NMR Spectrum of Compound **117**

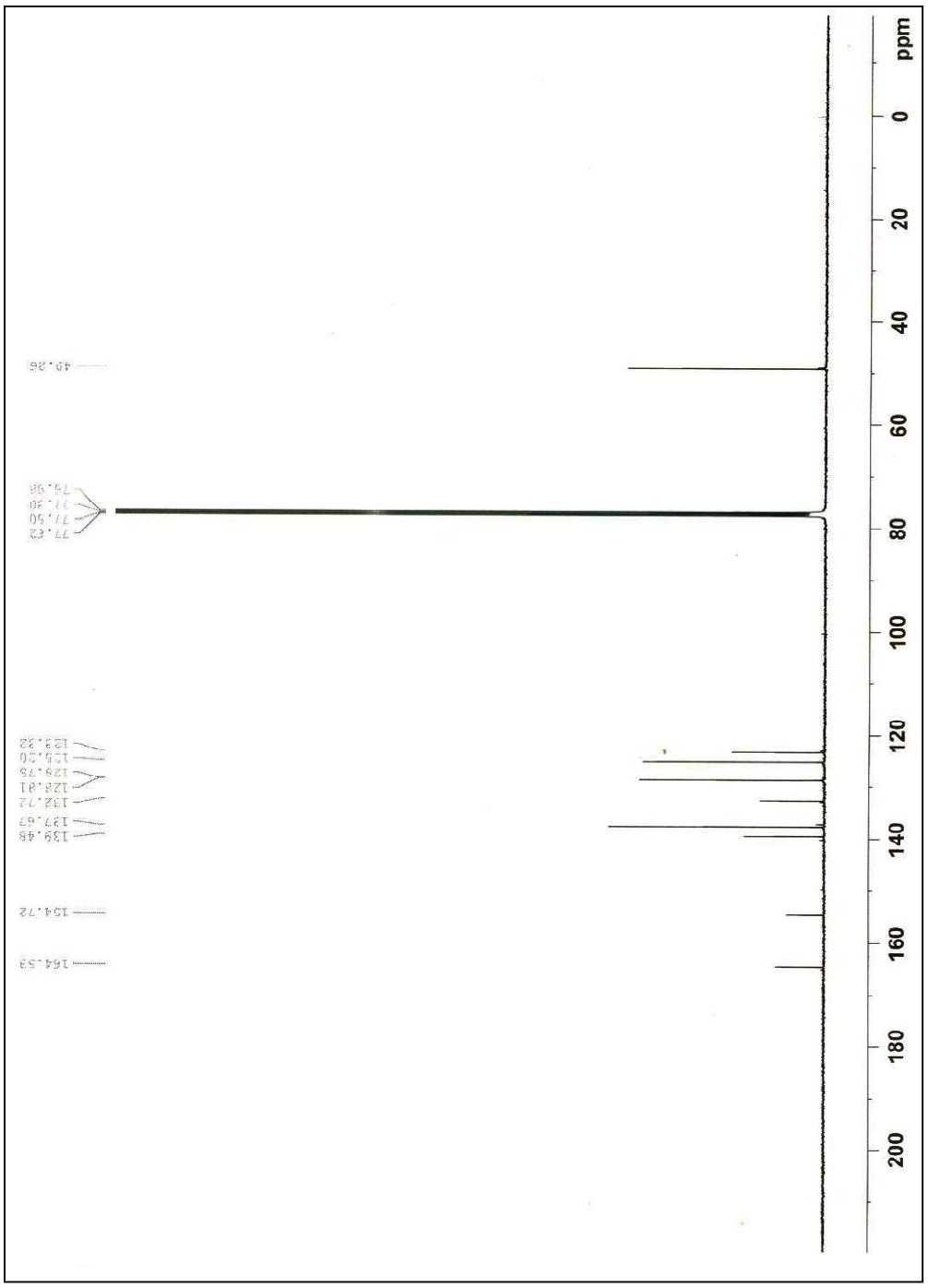



**Figure 57** $^{13}$C -NMR Spectrum of Compound **117**

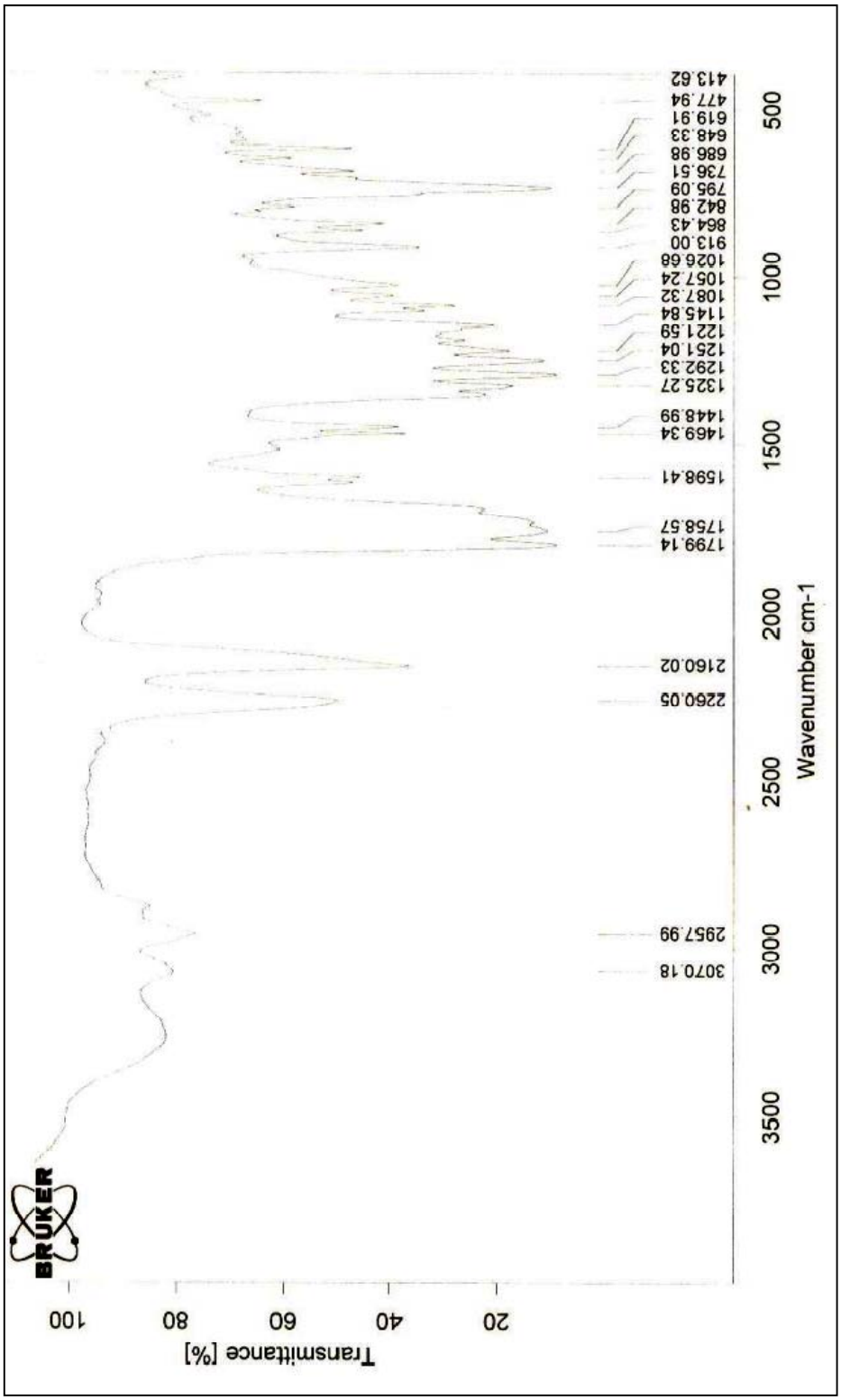



**Figure 58** IR Spectrum of Compound **117**

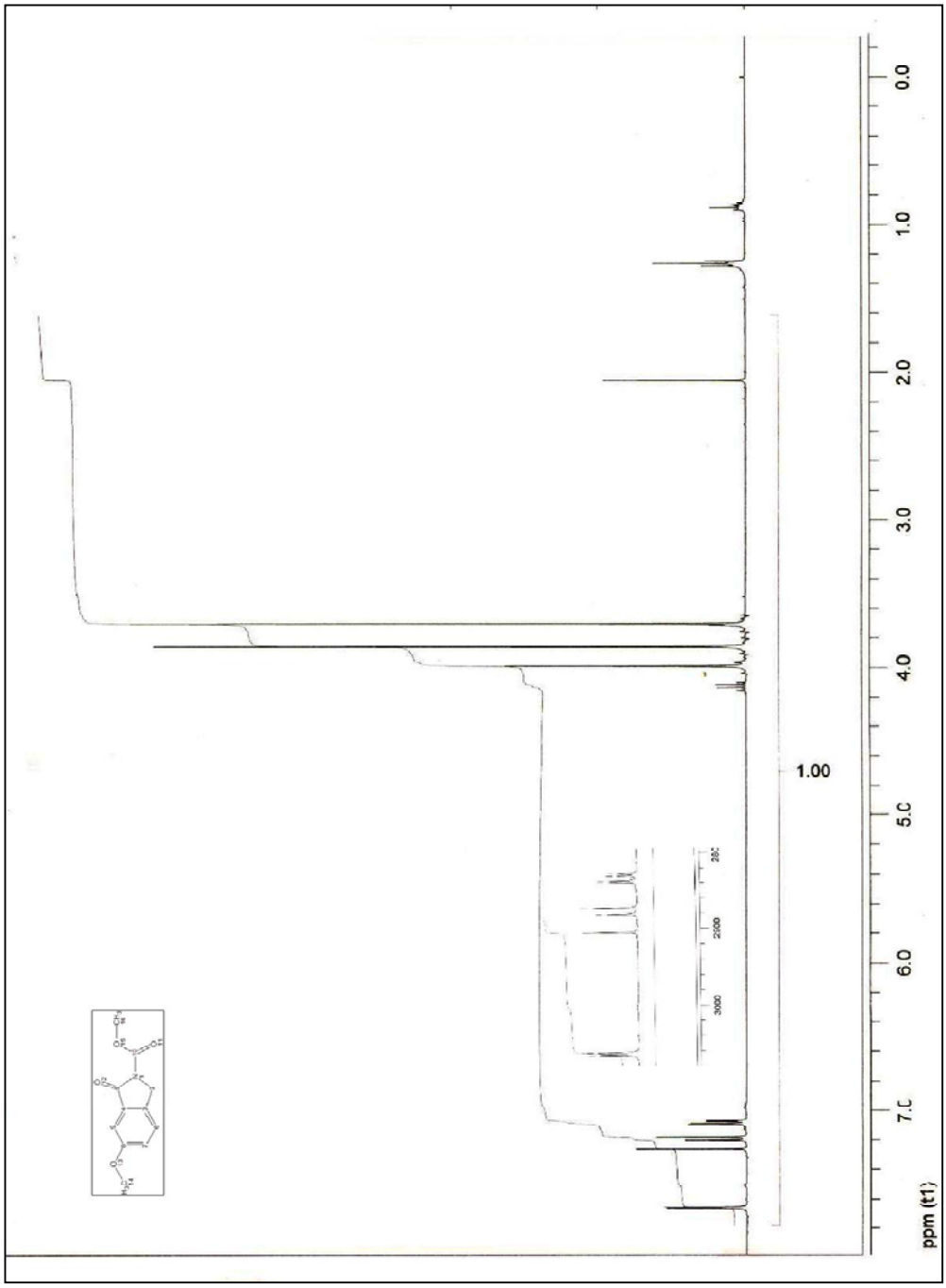



**Figure 59** $^{1}$H -NMR Spectrum of Compound **103**

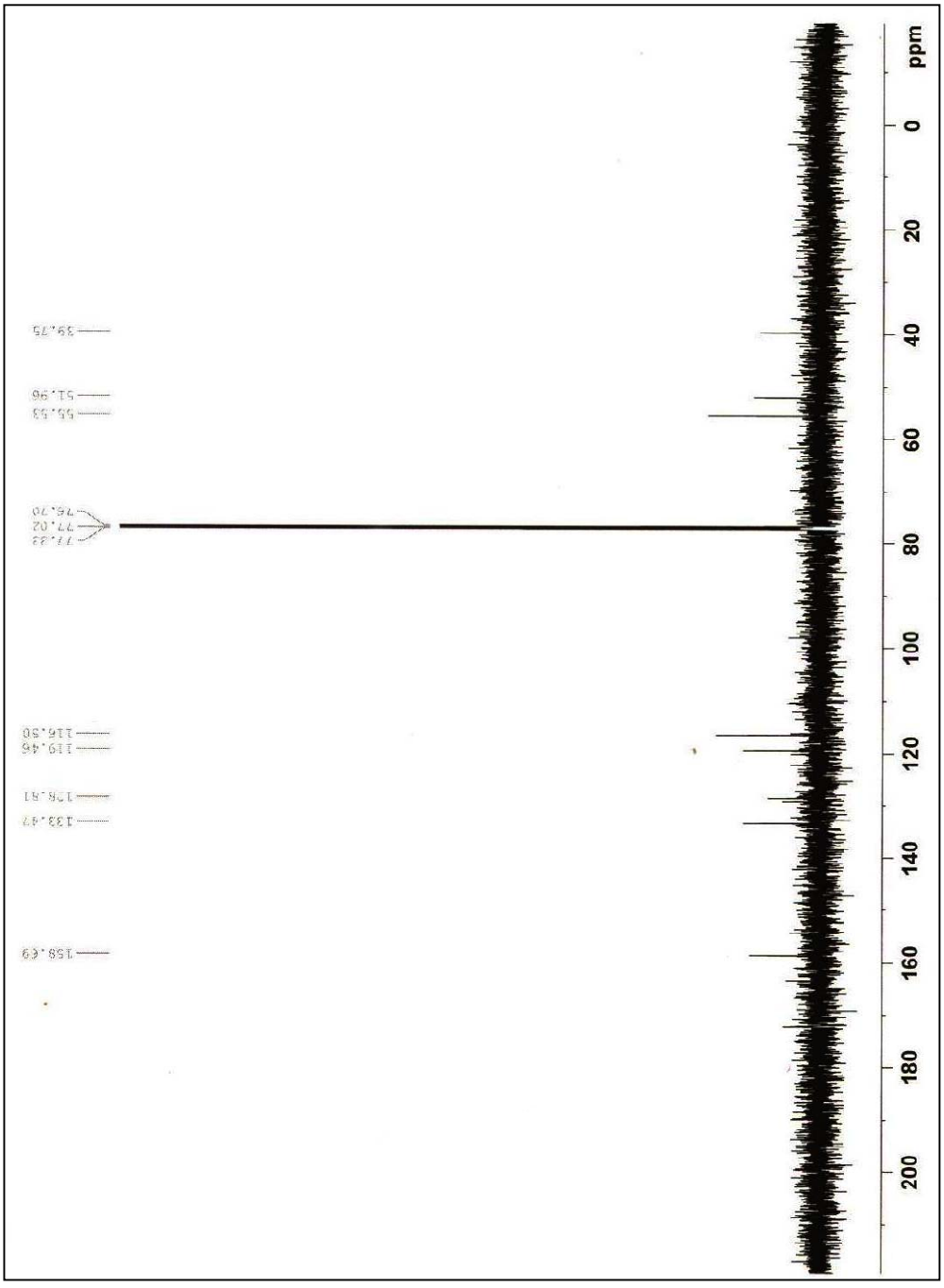



**Figure 60** $^{13}$C -NMR Spectrum of Compound **103**

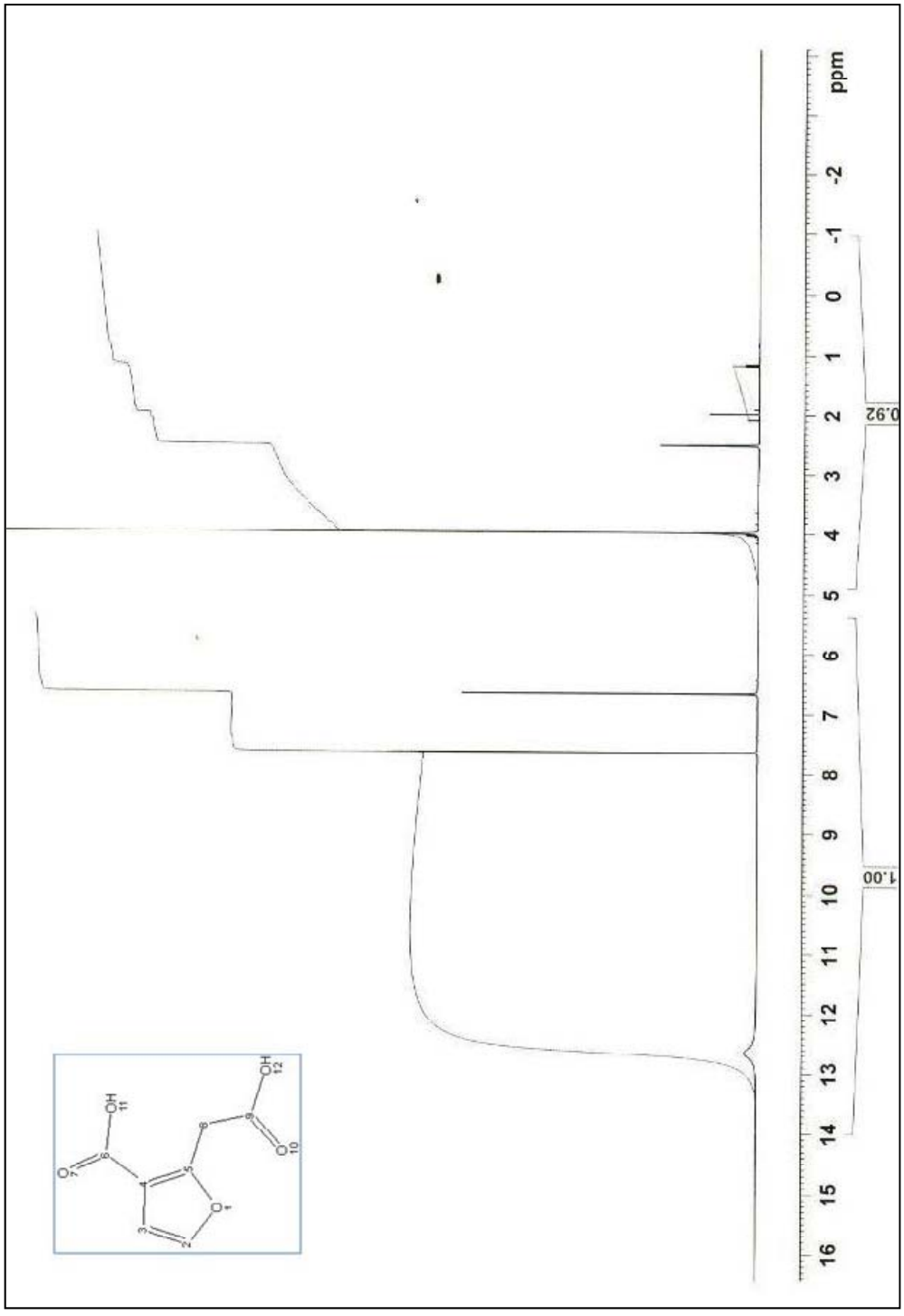



**Figure 61** $^{1}$H -NMR Spectrum of Compound **122**

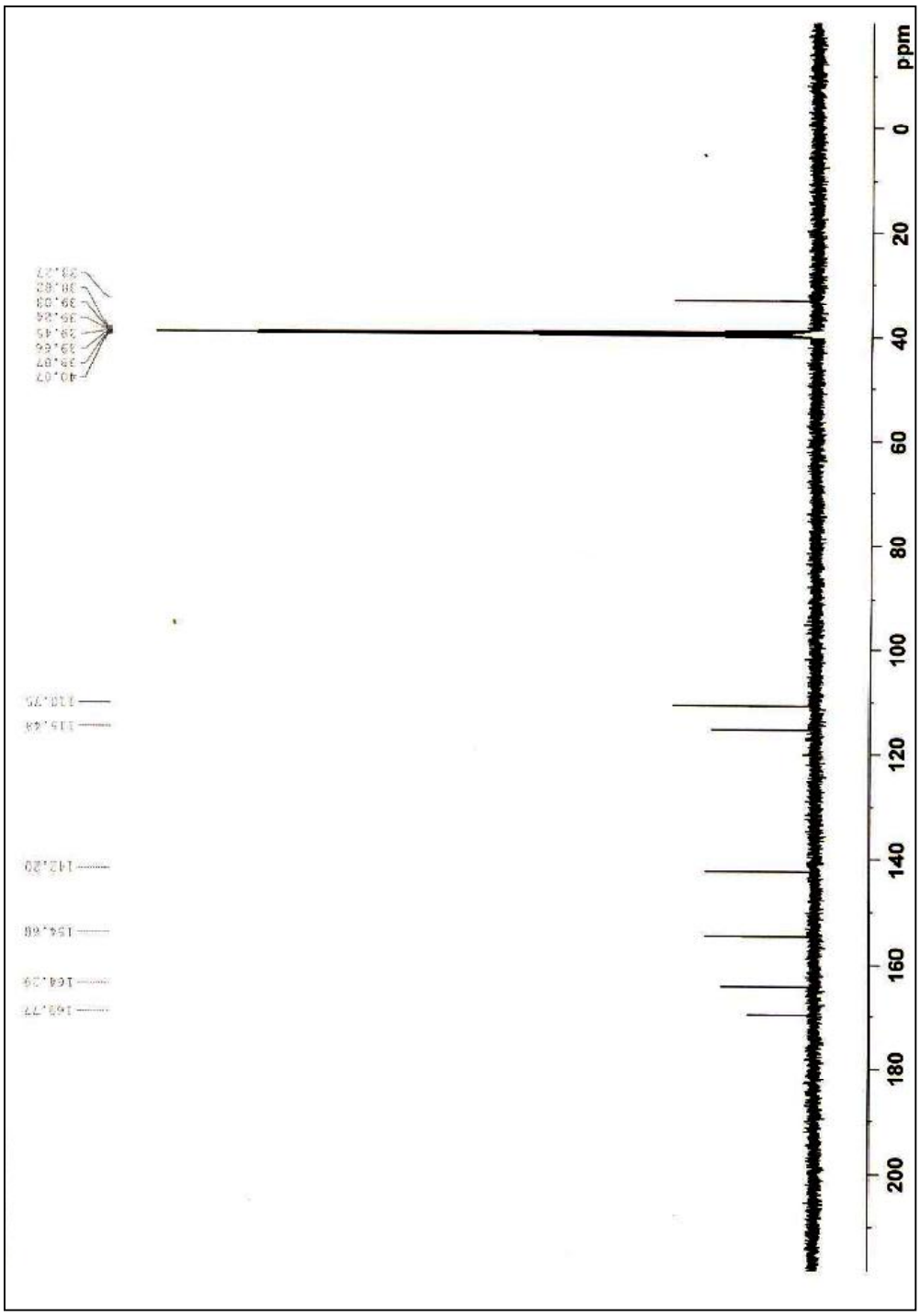



**Figure 62** $^{13}$C -NMR Spectrum of Compound **122**

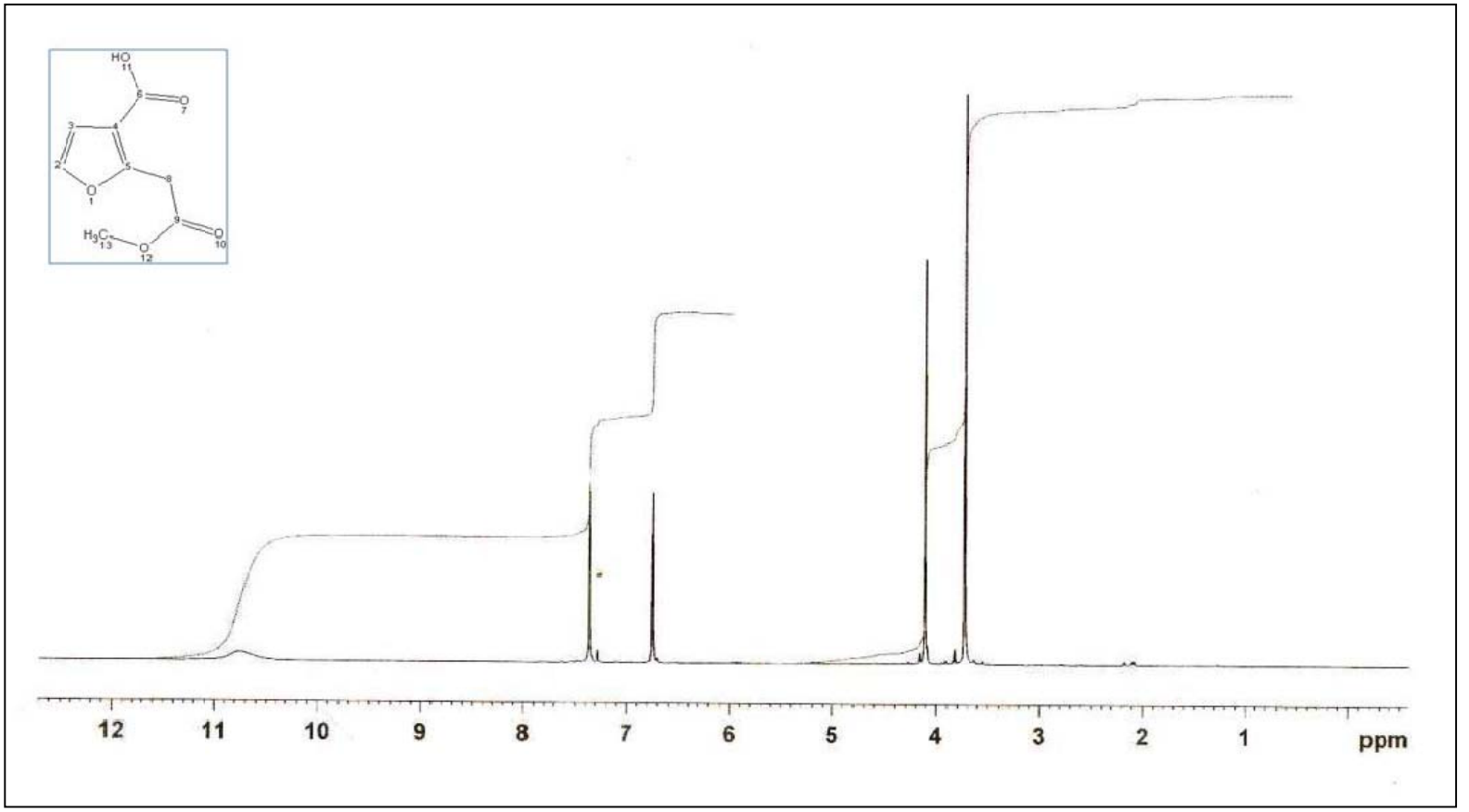



**Figure 63** $^{1}$H -NMR Spectrum of Compound **124**

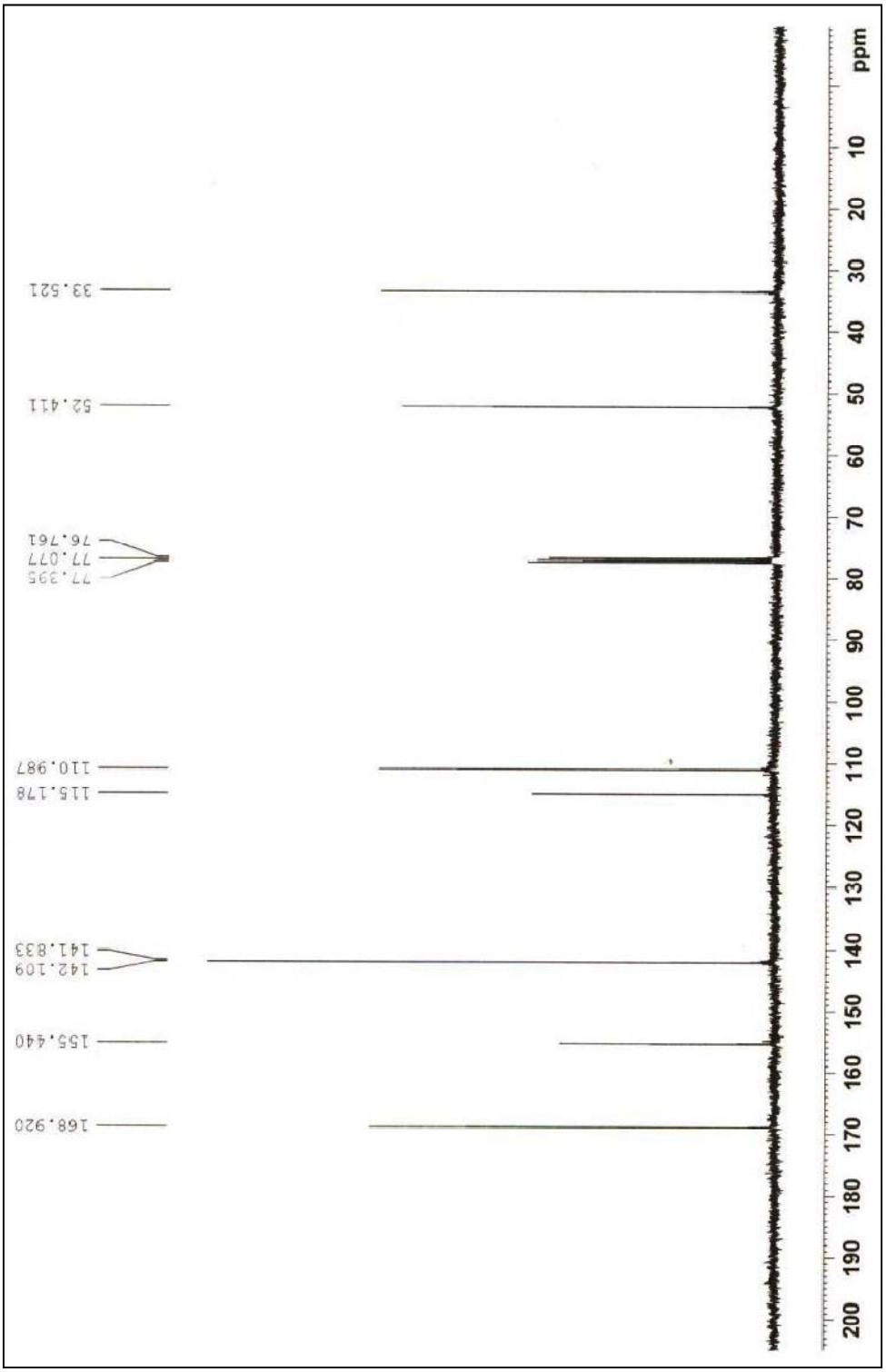



**Figure 64** $^{13}$C -NMR Spectrum of Compound **124**

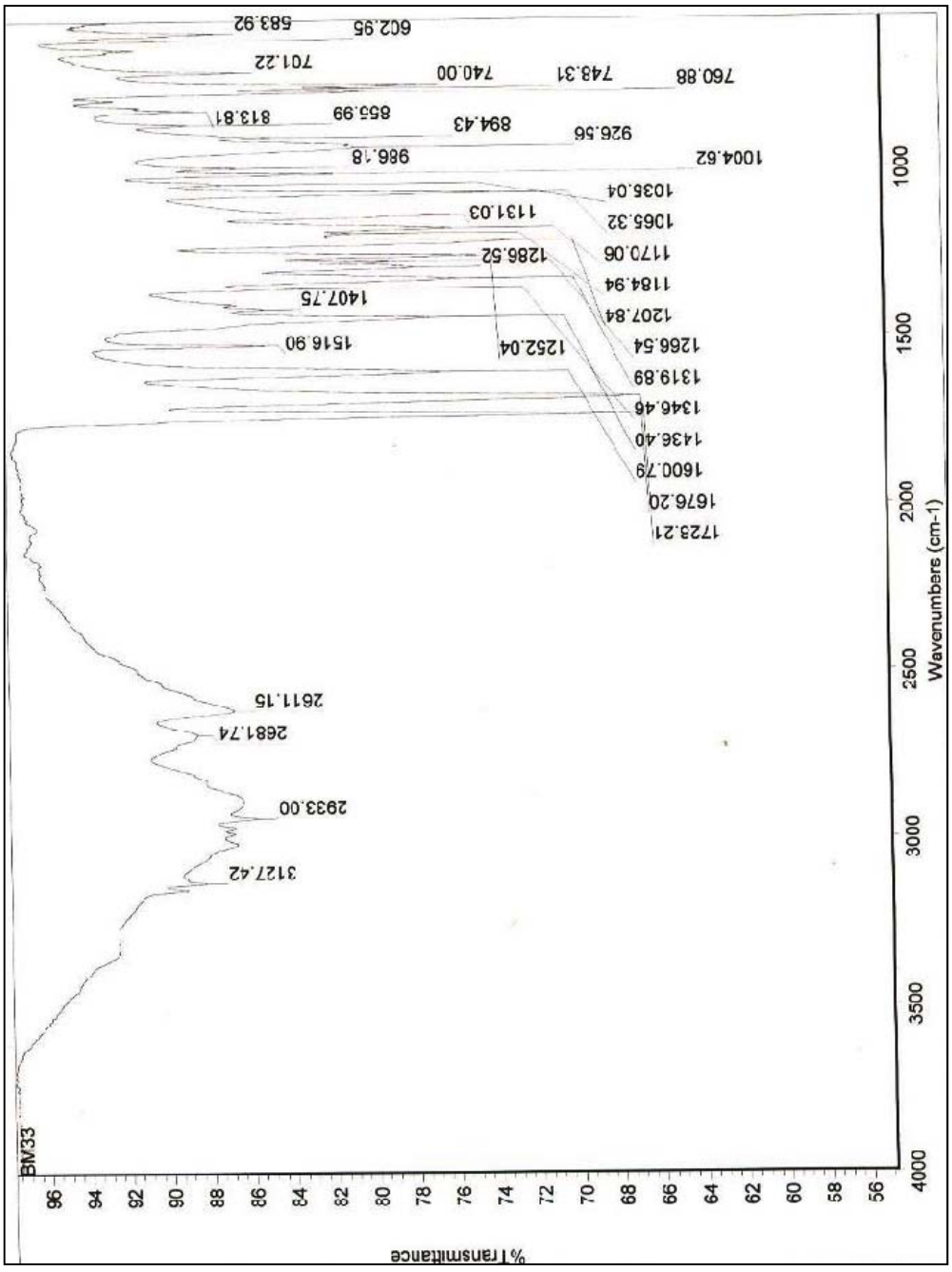



**Figure 65** IR - Spectrum of Compound **124**

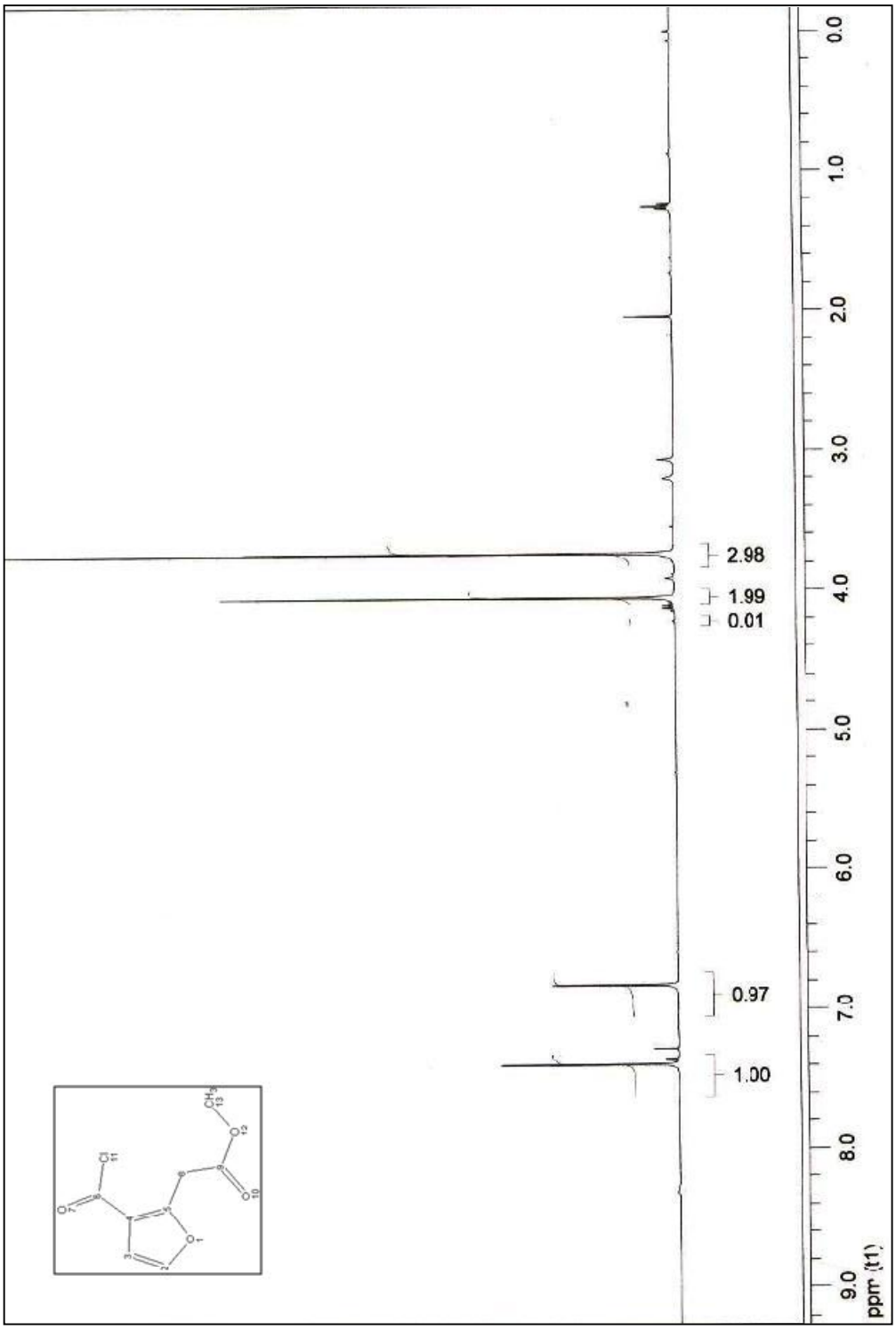



**Figure 66** $^{1}$H -NMR Spectrum of Compound **125**

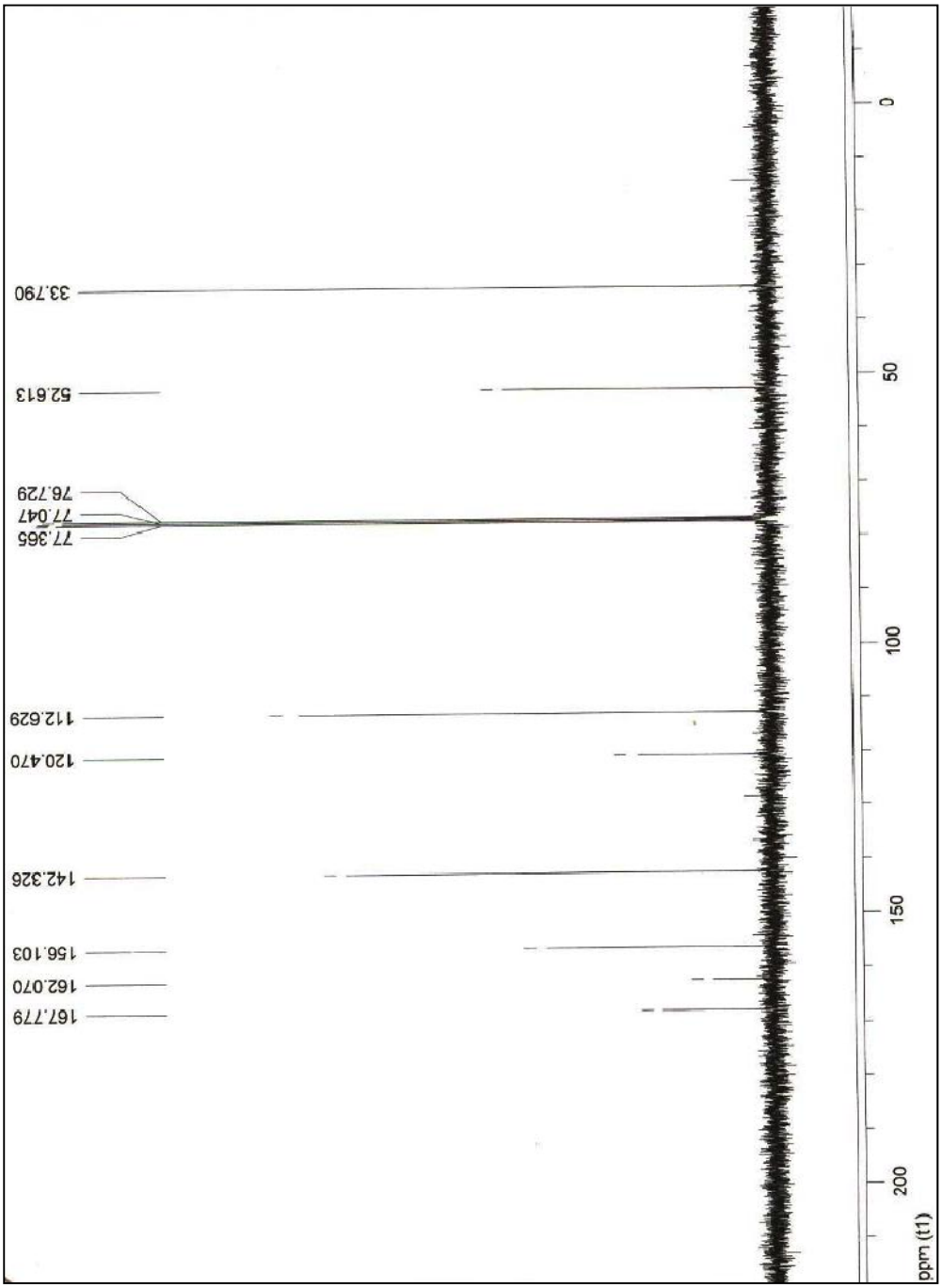



**Figure 67** $^{13}$C -NMR Spectrum of Compound **125**

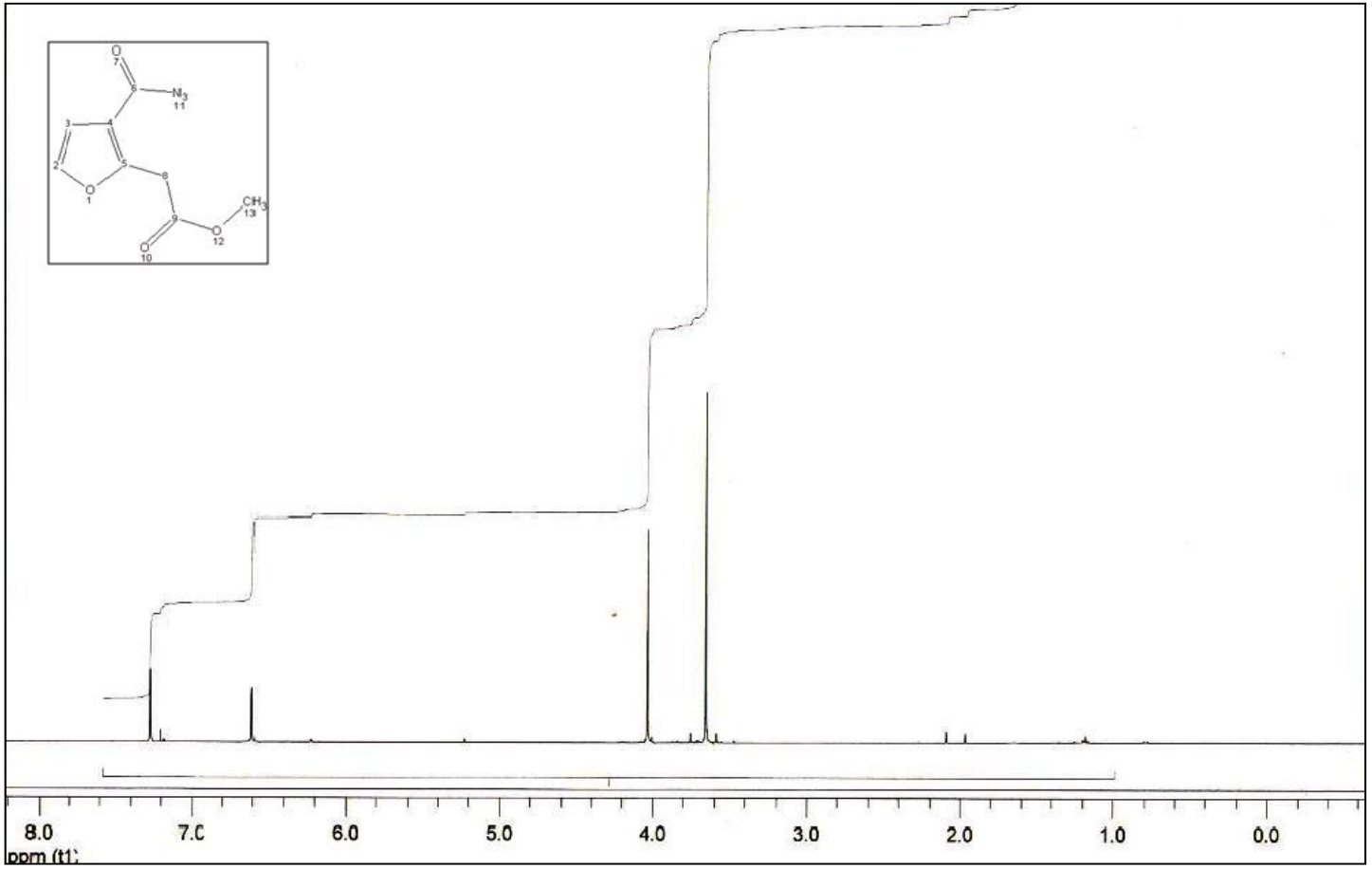



**Figure 68** $^{1}$H -NMR Spectrum of Compound **126**

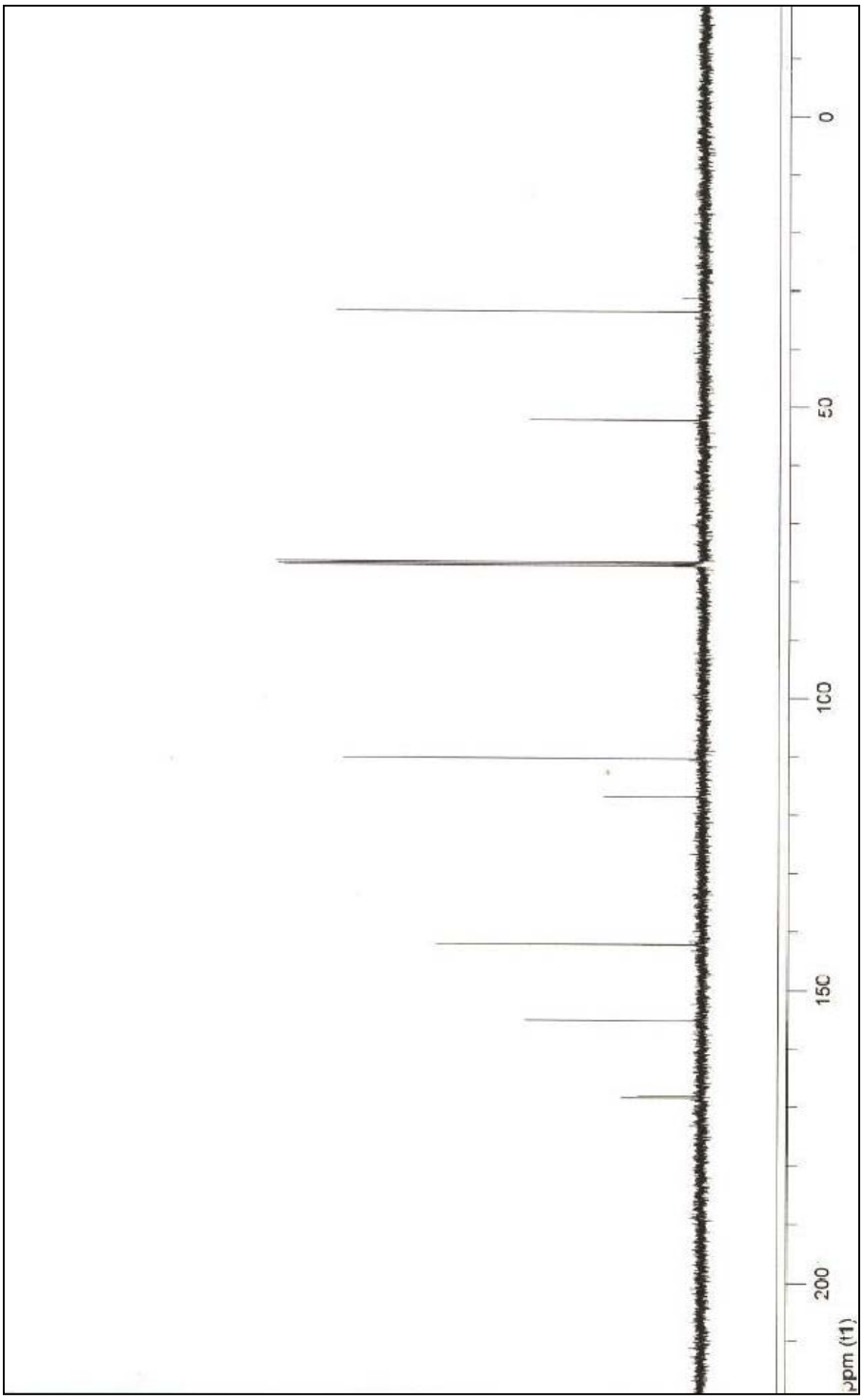



**Figure 69** $^{13}$C -NMR Spectrum of Compound **126**

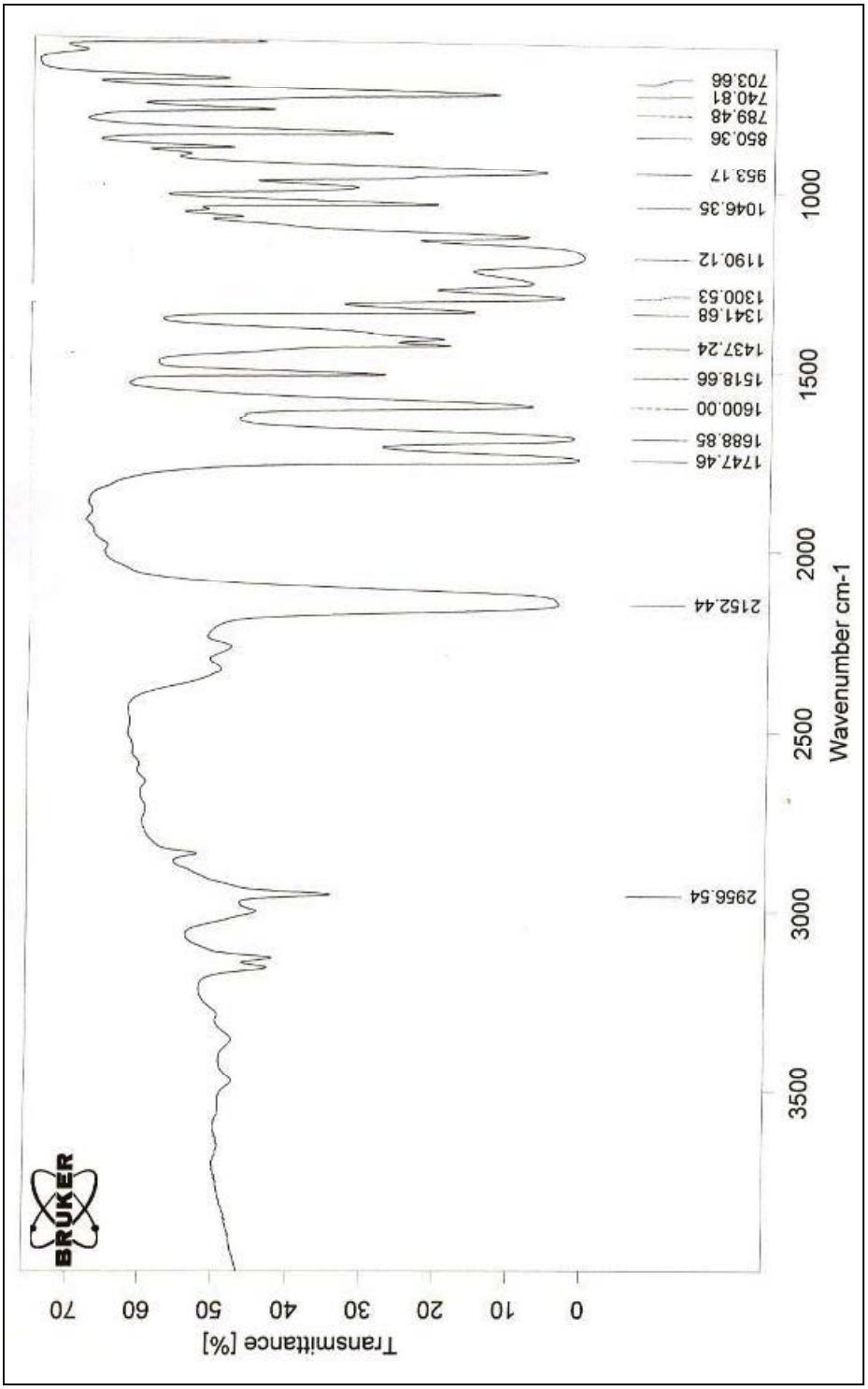



**Figure 70** IR Spectrum of Compound **126**

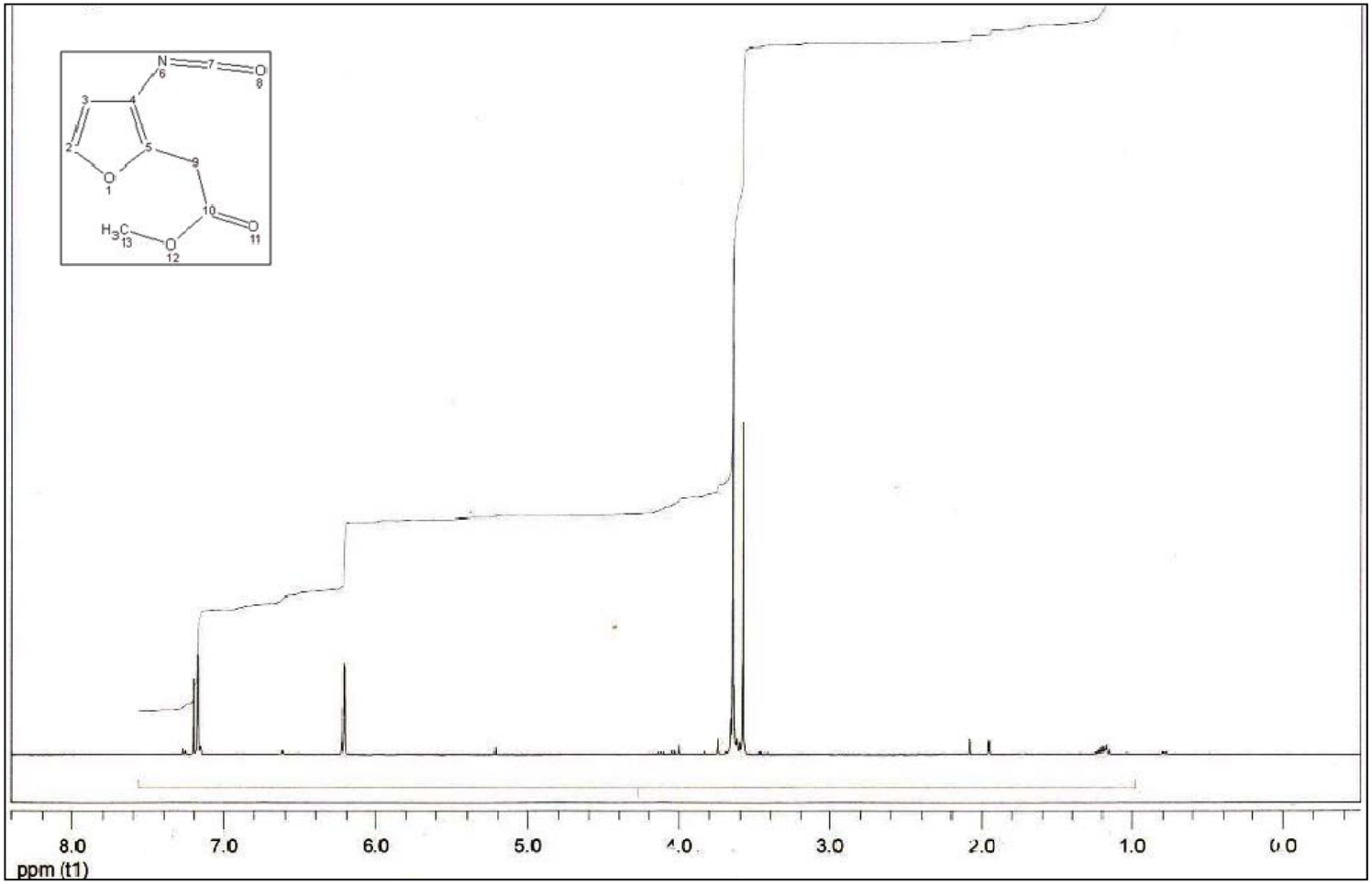



**Figure 71** $^{1}$H -NMR Spectrum of Compound **128**

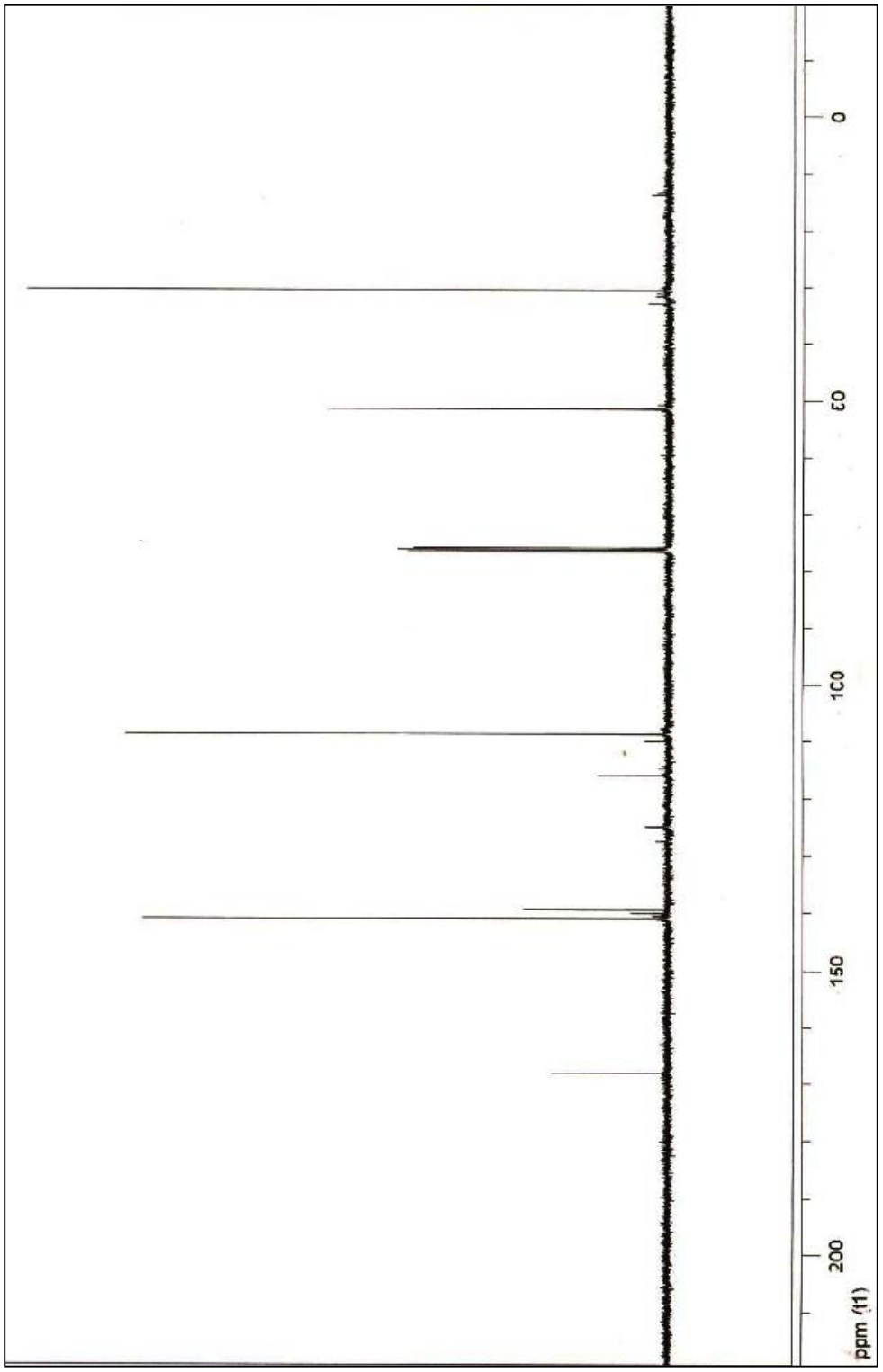



**Figure 72** $^{13}C$ -NMR Spectrum of Compound **128**

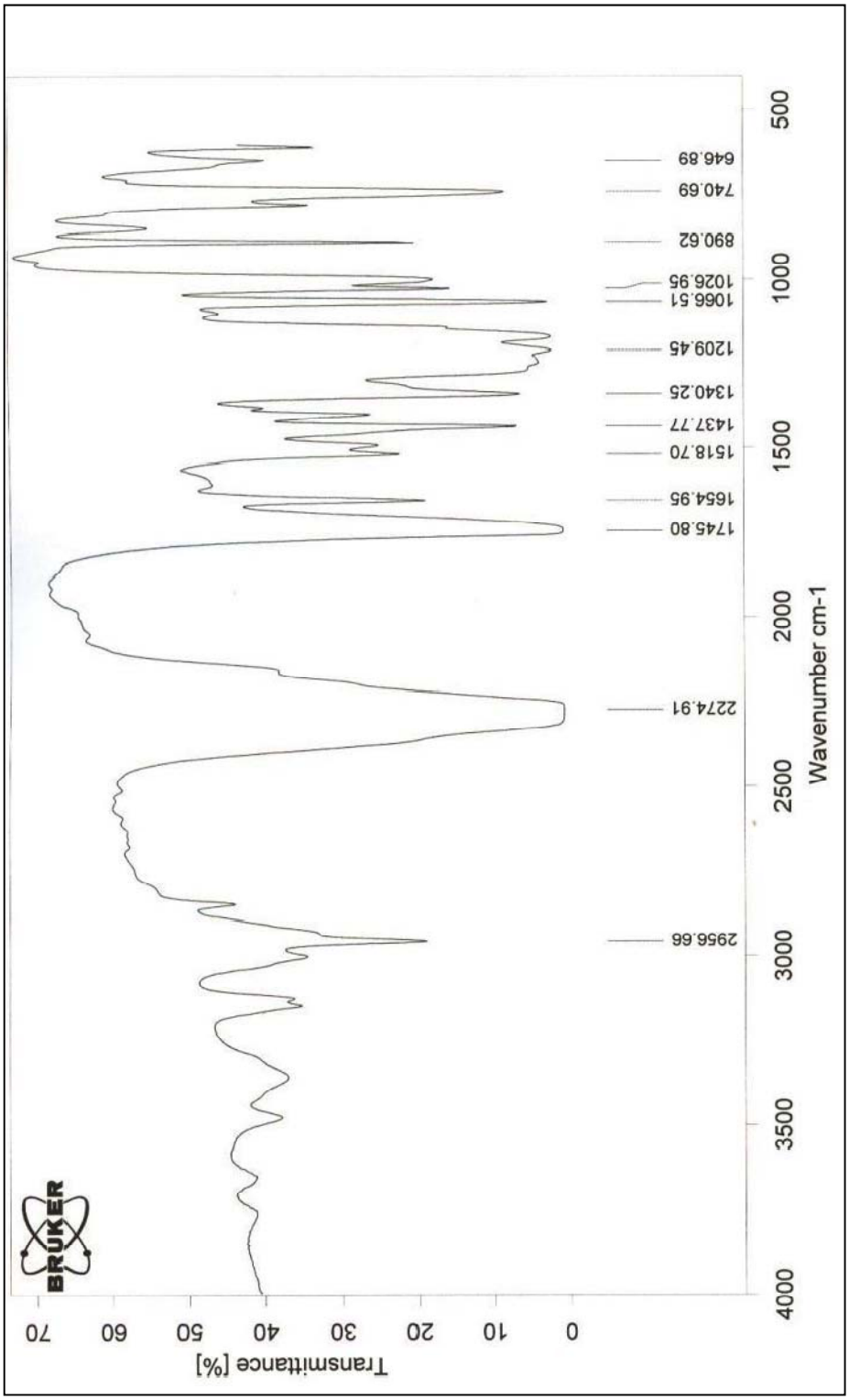



**Figure 73** IR Spectrum of Compound **128**

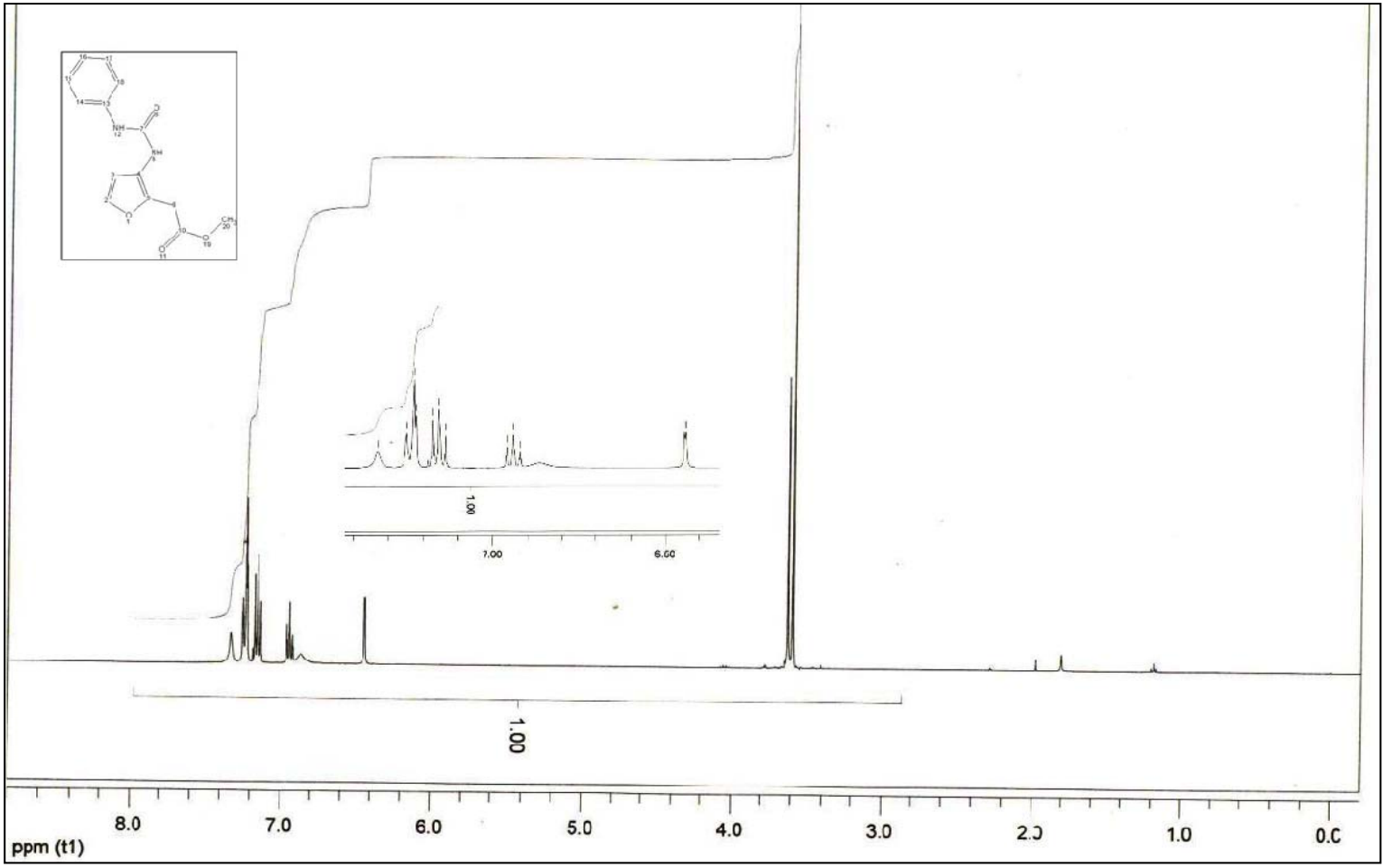



**Figure 74** $^{1}$H -NMR Spectrum of Compound **130**

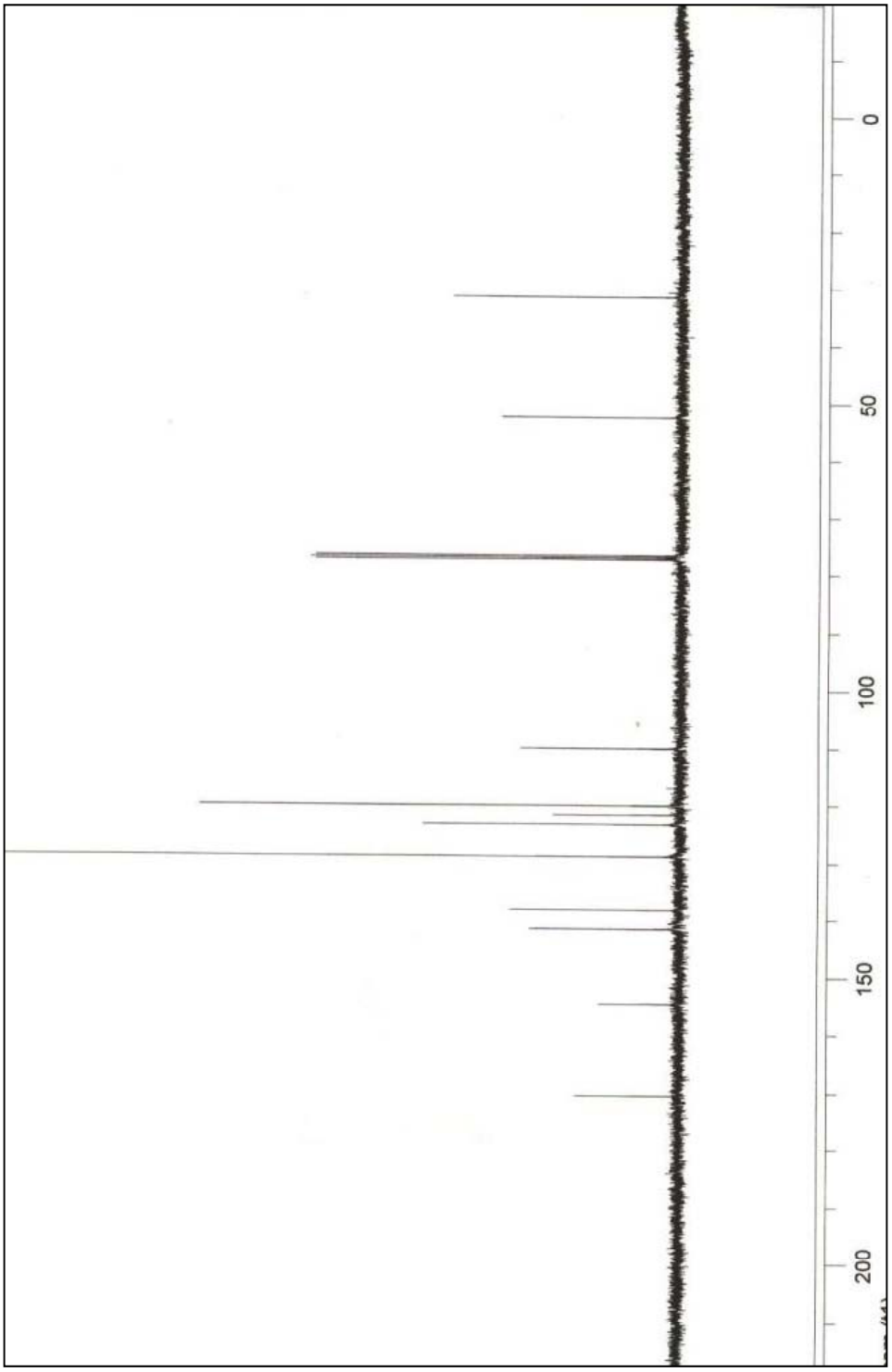



**Figure 75** $^{13}$C -NMR Spectrum of Compound **130**

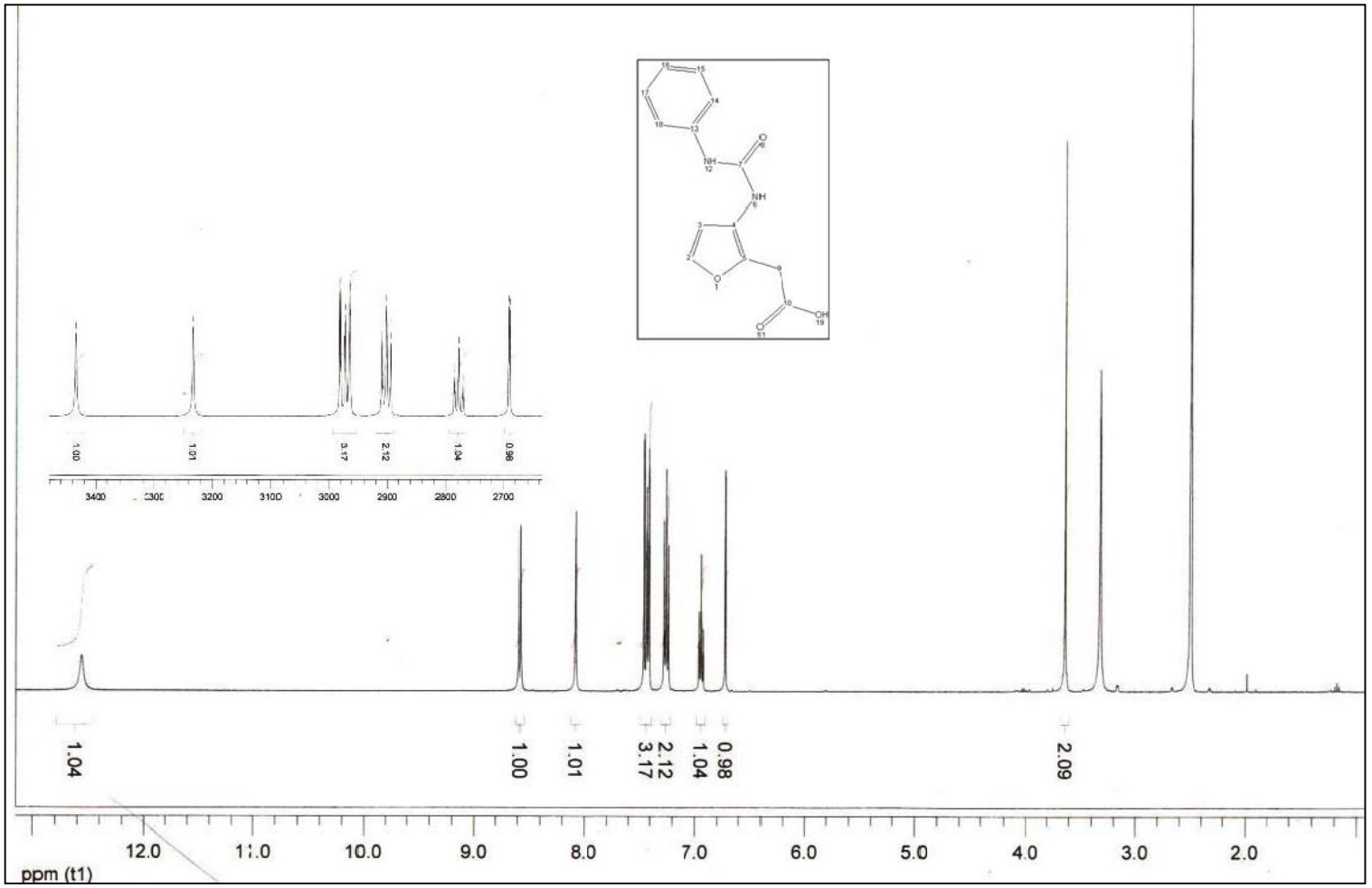



**Figure 76** $^{1}$H -NMR Spectrum of Compound **133**

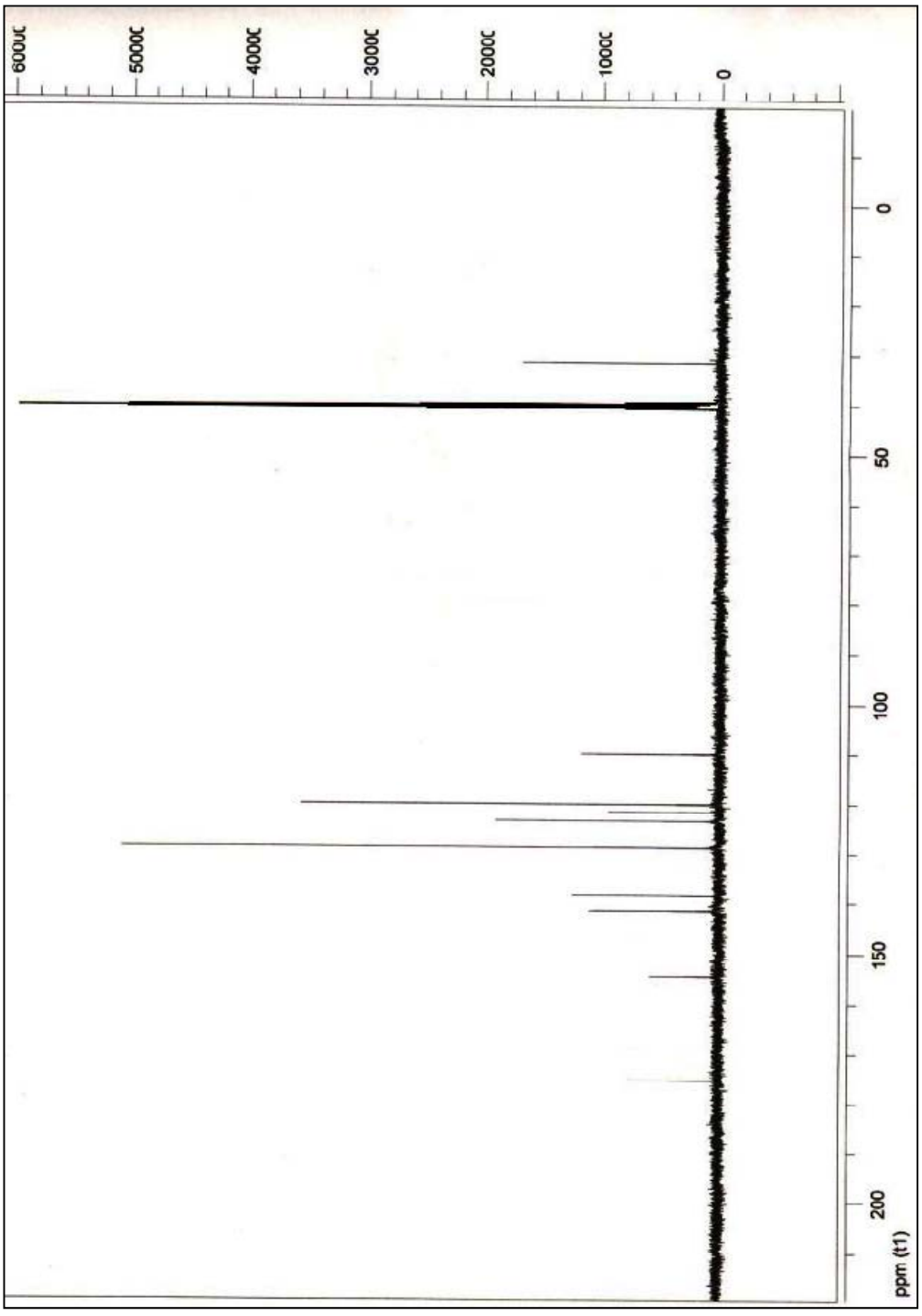



**Figure 77** $^{13}$C -NMR Spectrum of Compound **133**