SYNTHETIC STUDIES DIRECTED TOWARDS CYCLOPENTANOIDS AND RELATED NATURAL PRODUCTS

A Thesis Submitted to

THE MAHARAJA SAYAJIRAO UNIVERSITY OF BARODA

For the Award of the Degree of

DOCTOR OF PHILOSOPHY
IN
APPLIED CHEMISTRY

By

DEEPAK SINGH

Research Supervisor

Prof. P. T. DEOTA

APPLIED CHEMISTRY DEPARTMENT
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Date: 03/10/2013

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CERTIFICATE

This is to certify that the work presented in the thesis entitled **"Synthetic studies directed towards cyclopentanoids and related natural products"** submitted by **Mr. Deepak Singh** for the award of the degree of **Doctor of Philosophy in Applied Chemistry** is the authentic and original research work carried out by him under my guidance and supervision in the Applied Chemistry Department, Faculty of Technology and Engineering, The Maharaja Sayajirao University of Baroda, Vadodara - 390001 India.

Prof. P. T. Deota
Research Supervisor

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Baroda.

DECLARATION

I hereby declare that all the information in the thesis entitled **"Synthetic studies directed towards cyclopentanoids and related natural products"** is my own research work conducted under the supervision of **Prof. Pradeep T. Deota** in **Applied Chemistry Department, Faculty of Technology and Engineering, The Maharaja Sayajirao University of Baroda, Vadodara (Gujarat)-390001 India**.

I further declare that to the best of my knowledge no part of this thesis has been submitted elsewhere for the award of any equivalent degree or Diploma.

Deepak Singh
03/10/2013

Deepak Singh

Research Scholar

DEDICATED
TO
MY PARENTS, BROTHER
&
SISTER

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One cannot forget the strength and support that one gets from their family. I feel a tremendous paucity of words to explicate my fortuity for unconditional love, sacrifices, invigorating inspiration and earnest care provided by my parents, **Mr. Sardar Singh** and **Mrs. Kantee Singh**, throughout the period of toil, turmoil and tribulations. I am enormously privileged to have parents that have given their all to and are as invested in my educational achievements as I am. They have been instrumental in my journey from infancy, and I know this is as much a victory for them as it is for me. I feel extremely proud to have achieved our dream. There are no suitable words to convey my regards to my uncle, **Dr. Ram Shankar Singh**, and aunt **Mrs. Deepti Singh** for their selfless affection, support, forever implicit and heartfelt well wishes and blessings. I also need to thank my younger brother **Mr. Rahul Singh** and younger sister **Ms. Neha Singh** for their encouragement, support and incessant help at the time of need. I also acknowledge and admire the love, confidence and moral support bequeathed to me by members in my family **Mr. Randhir Singh, Mr. Chandra Prakash Singh, Mr. Ajay Singh, Mr. Havaldar Singh, Mrs. Reetu Singh, Mrs. Gudia Singh, Mrs. Urmila Singh, Prince Singh, Maneesh Singh, Saurabh Singh, Prathmesh Singh, Utsav Singh, Madhu Singh, Ruchi Singh** without whose affection, the present endeavor would have remained an unrealized dream.

Deepak Singh

Contents

List of Abbreviations and Symbols

CCDC	Cambridge Crystallographic Data Centre
cm	Centimeter
EI-MS	Electron Impact Ionization Mass Spectrometry
ESI-MS	Electrospray Ionization Mass Spectrometry
FTIR	Fourier transform infrared spectroscopy
HRMS	High-resolution mass spectrometry
Mp.	Melting point
min	Minute
NMR	Nuclear magnetic resonance
RT	Room temperature
TLC	Thin layer chromatography
ORTEP	Oak Ridge thermal ellipsoid plot
CHN	Elemental analyzer
m/z	Mass-to-charge ratio
mmol	Millimoles
mL	Milliliters
α	Alpha
β	Beta
δ	Delta
°	Degree
ppm	parts per million
MHz	Mega hertz
θ	Theta
Å	Angstrom
°C	Degree Celsius
K	Kelvin
mg	Milligrams
g	Grams

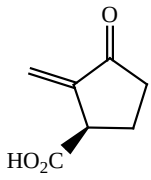
CHAPTER 1

General Introduction

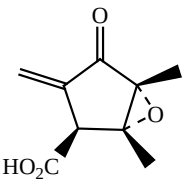
Organic chemistry is a branch of chemistry that governs the structure, properties and reactions of carbon containing compounds. It constitutes the building blocks of all living organisms such as lipids, peptides, proteins, enzymes, vitamins, carbohydrates, plants essential oils, alkaloids, flavoring compounds, perfumes and all other natural products. It also covers materials such as drugs, dyes, polymers, rubber, fuels, detergents etc.

Organic chemistry is a highly innovative part of science in which chemists can create new molecules having properties for the betterment of human life. The construction of organic compounds via organic reactions is a special branch of chemistry known as organic synthesis. Organic molecules possess very complex structures, so the synthesis of these compounds is one of the most important aspects of organic chemistry. In organic synthesis, there are two main areas of research: synthesis and methodology. The synthesis is a complete chemical production of complex organic molecules, natural products or their analogues from commercially available materials. However, the methodology involves the development of a new method for the synthesis of intermediates or products to give high yields and to be applicable for a wide range of substrates.

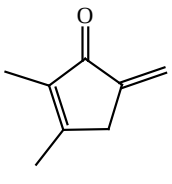
Cyclopentanoids are the carbocycles composed of five carbon atoms. The cyclopentanoid skeleton has been found as a core structure in many natural products and they exert a wide range of biological and pharmaceutical activities. Some examples are sarkomycin **1,** methylenomycins A **2**, methylenomycins B **3**, pentanomycin **4,** kjellmanianone **5,** plakevulin A **6**. These natural products show potent antibiotic and antitumor activities.[1] (**Figure 1.1**)



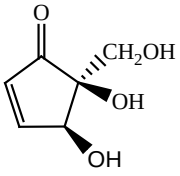
Sarkomycin **1**



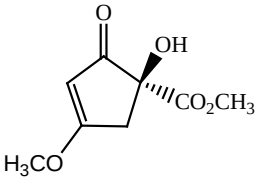
Methylenomycin A **2**



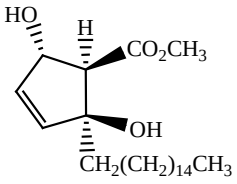
Methylenomycin B **3**



Pentanomycin **4**



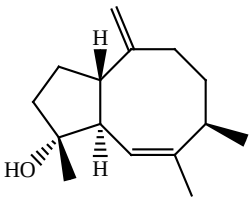
Kjellmanianone **5**



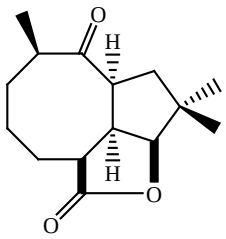
Plakevulin A **6**

Figure 1.1: Structures of cyclopentaniods natural products

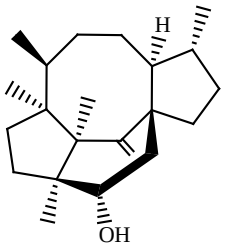
The cyclopentanoids are also present as basic structural units in monoterpenes, diterpenes, sesquiterpenes, triterpenes natural products as well as in complex molecular architectures such as fullerene C_{60} **14**. (**Figure 1.2**) Reports of carbocyclic skeletons in which cyclopentanoid form a part of the condensed or bridged polycyclic system have increased rapidly in recent years. Currently, more than 500 natural products constitute structurally diverse and interesting family of cyclopentanoids. These natural products are distributed in nature and have been isolated from terrestrial plants, marine organisms, fungi and insects. These compounds have received much attention from both structural and biological aspects due to their wide range of biological activities and structural complexities.[2] For example, dumortenol **7**,[2a] asteriscanolide **8**,[2b] longipenol **9**,[2c] progesterone **10**,[2d] endiandric acid B **11**,[2e] gurjunene **12**,[2f] phorbol **13**,[2g] etc. The potency of these cyclopentanoid derivatives has aroused considerable attention in chemistry and biochemistry.



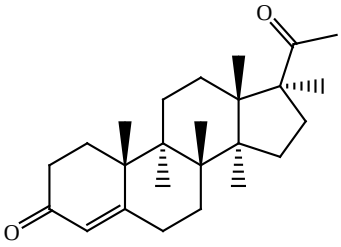
Dumortenol **7**



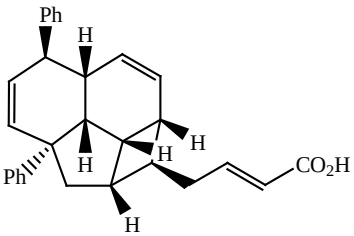
Asteriscanolide **8**



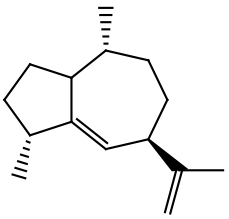
Longipenol **9**



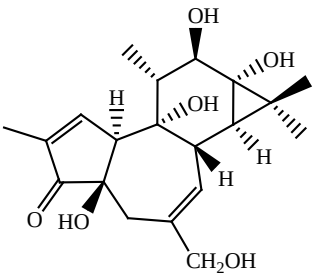
Progesterone **10**



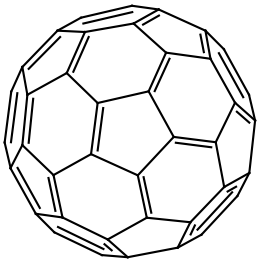
Endiandric acid B**11**



Gurjunene **12**



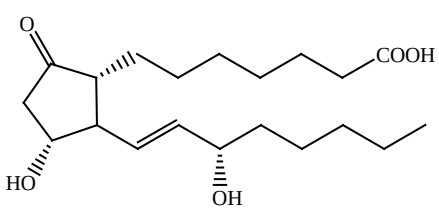
Phorbol **13**



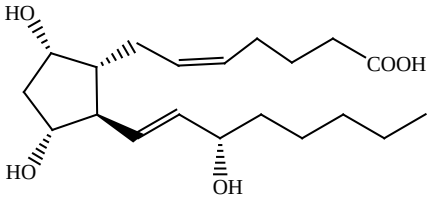
Fullerene **14**

Figure 1.2: Structures of compounds constitute cyclopentanoids as a structural unit

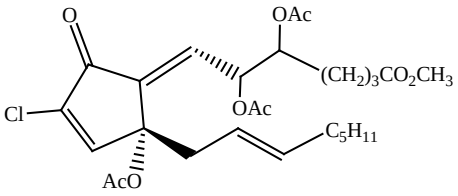
Cyclopentanoids are also present in prostaglandins (PGs) natural products. PGs form a class of natural products found in the reproductive system, the nervous system, the cardiovascular system and the immune system. Prostaglandins are medicinally important fatty hormones due to their wide range of biological and pharmacological activities that control many physiological processes. Kurzrok and Lieb first detected the prostaglandins natural products in 1930 due to their biological activities. The structures of first two members of prostaglandin family PGE_1 **15**, $PGF_{2\alpha}$ **16** were elucidated in 1960 by Bergstrom and Sjovall.[3a] It initiated new research in this area and other biologically interesting prostaglandins containing cyclopentanoids were discovered. Some examples are punaglandins **17** which exhibit anti-inflammatory and antitumor activities,[3b,c] halovulones **18** that possess antiproliferative activity.[3d] (**Figure 1.3**)



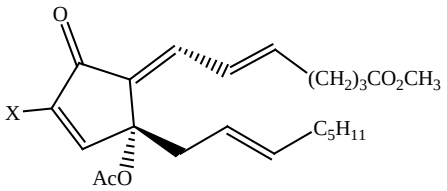
Prostagladin E_1 **15**



Prostagladin $F_{2\alpha}$ **16**



Punaglandins **17**

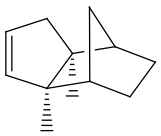


Halvulones **18**

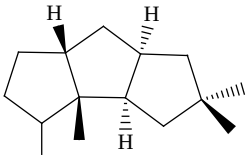
Figure 1.3: Structure of various cyclopentanoids natural products

Sesquiterpenoids are a class of biologically active natural products that have been identified in several plant marine and living organisms.[4] They have played an important role for a long time in treating and preventing diseases and continue to serve as important leads in modern drug discovery.[5] Polyquinanes are an important and rapidly growing subgroup of sesquiterpenoids that have generated worldwide interest due to their fascinating structures and potent biological activity.[6] In literature, around 300 of such natural products have been isolated having cyclopentanoid framework as a core structure. The polyquinanes natural products are composed of two or more fused cyclopentane rings with each other. Five different families of

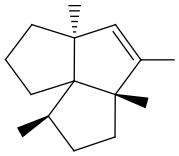
polyquinine based on cyclopentanoid skeleta are known. They are diquinane **19**,[7a] linear triquinane **20**,[7b] angular triquinane **21**,[7c] tetraquinane family **22**[7d] and bis-triquinane **23**.[7e]



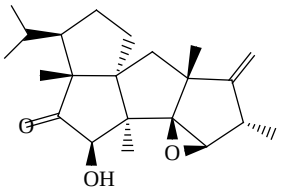
Albene **19**
Diquinane



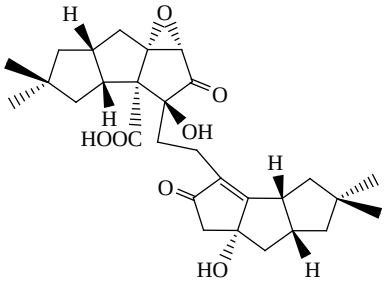
Capnellene **20**
Triquinane



α-Isocomene **21**
Angular triquinane



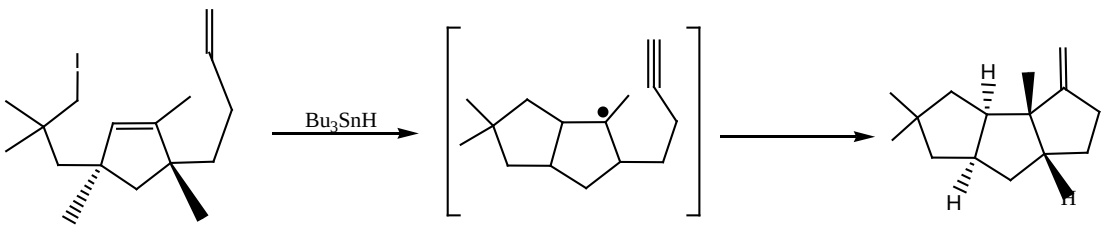
Dihydrocrinipellin-B **22**
Tetraquinane



Xeromphalinone F **23**
Bis-triquinane

Figure 1.4: Structures of polyquinane natural products

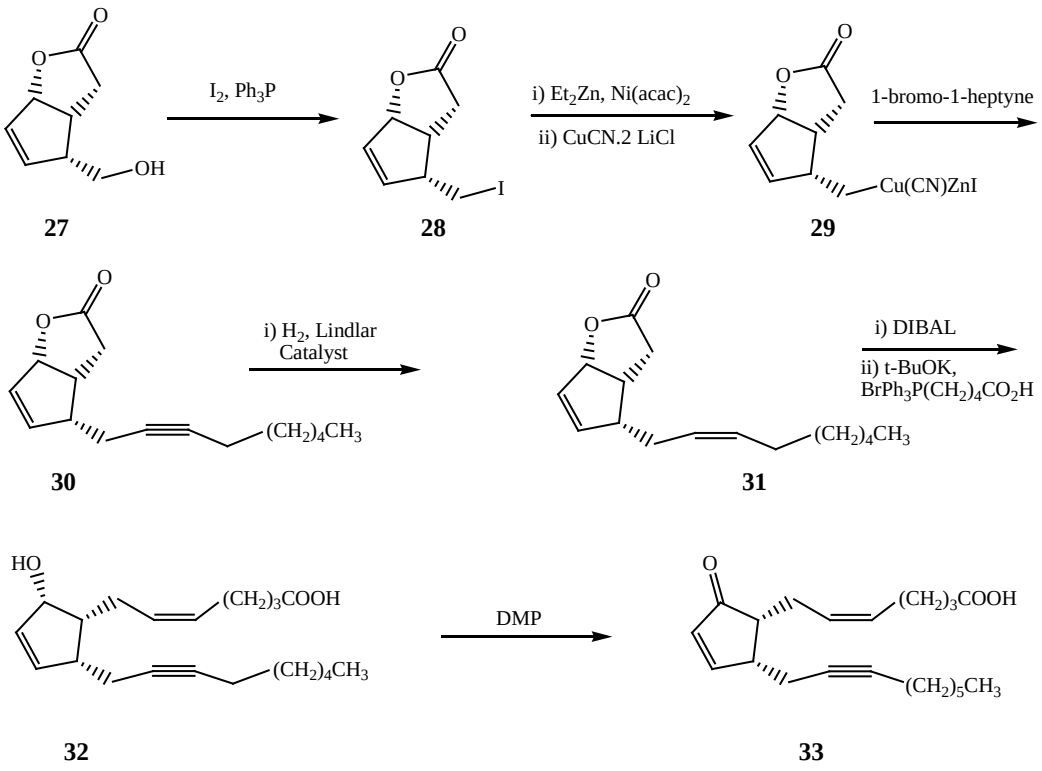
Cyclopentanoids are also present in a wide range of synthetic intermediates that are used as starting materials for the synthesis of many natural products and complex molecular architectures. The cyclopentanoids having iodoalkyl substituent are attractive starting materials in organic synthesis because iodine plays an important role to produce free radical species.[8a] Curran *et al* developed an efficient approach for the syntheses of hirsutene **26** via free radical cyclisation from iodoalkyl cyclopentanoid **24**.[8b,c] (**Scheme 1.1**)



24 **25** Hirsutene **26**

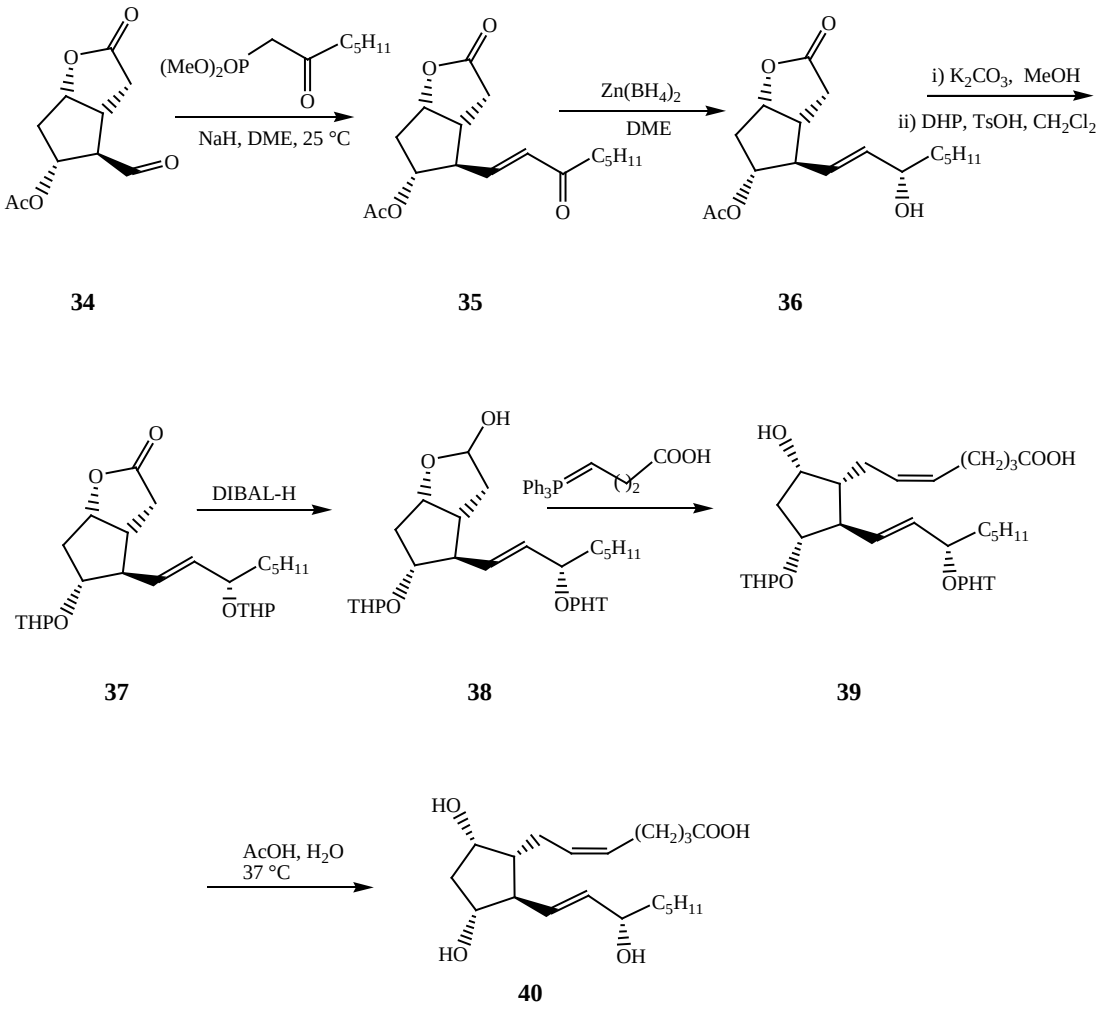
Scheme 1.1: Preparation of hirsutene **26** from iodoalkyl cyclopentanid **24**

The natural products like epi-jasmonates,[9a] isoprostanes,[9b] prostaglandins,[3c,9c] levuglandins[9d] have gained considerable interest for their biological and pharmaceutical activities. The challenging exercise in synthesis of these natural products is to install the two side chains on the cyclopentane ring having 1,2-*cis* or 1,2-*trans* configuration. The cyclopentanoid fused lactones such as **27**, **34** are synthetically useful intermediates to create the side chain at adjacent positions in a stereocontrolled manner. Vidari *et al* reported the synthesis of preclavulone A **33** having 1,2-*cis* configuration.[10] (**Scheme 1.2**) The hydroxyl lactone **27** was prepared by following the reported procedure.[11] The Mitsunobu reaction of **27** with iodine in presence of Ph_3P gave the corresponding iodide methyl lactone **28**. The lactone **28** gave copper-zinc complex **29** via formation of organozinc intermediate with Et_2Zn in the presence of $Ni(acac)_2$ followed by metallisation with CuCN.2LiCl. The treatment of copper-zinc complex **29** with 1-bromo-1-heptyne gave the corresponding coupling product **30**. Lindlar reduction of alkyne **30** afforded the corresponding alkene **31**. The reduction of lactone **31** with diisobutylaluminium hydride (DIBAL) gave its hemiacetal which on olefination by Wittig reaction afforded compound **32**. The Dess-Martin periodinane (DMP) oxidation of cyclopenyanol of **32** gave the precavulone A **33**.



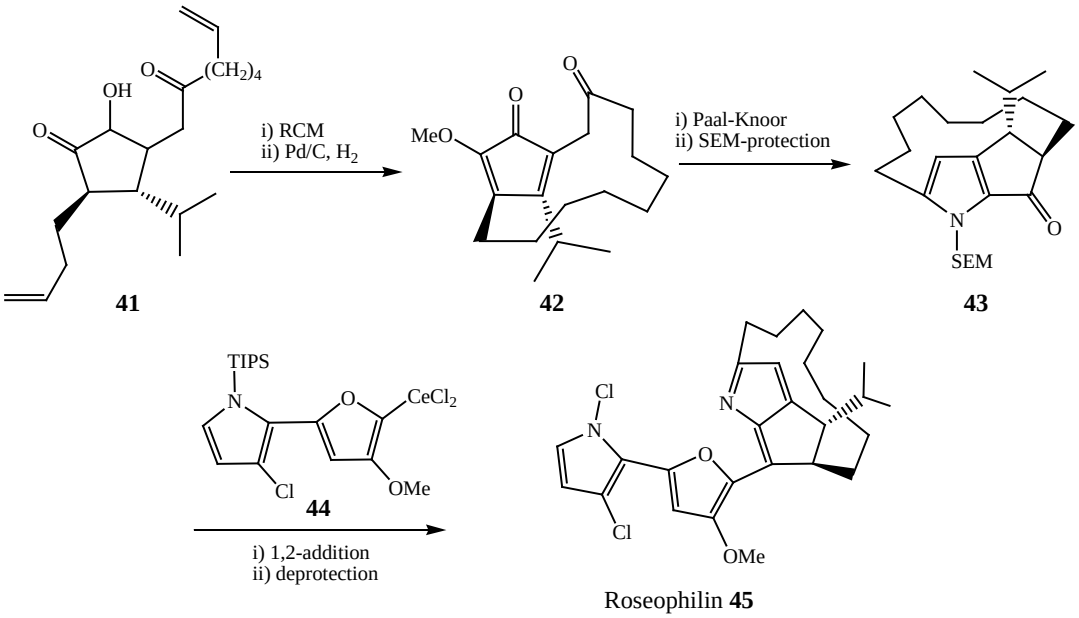
Scheme 1.2: Synthesis of preclavulone A from cyclopentanoid fused lactone

Corey *et al* also reported a unified approach towards the synthesis of prostaglandins $PGF_{2\alpha}$ **40** having 1,2-*trans* configuration via a series of steps from cyclopentanoid lactone **34**.[12] (**Scheme 1.3**) The bicyclic lactone **34** was prepared by following precursor reported by Corey *et al*.[12] The treatment of **34** with dimethyl-2-oxo-heptylphosphonate in di-methoxy ethane (DME) gave *trans*-enone lactone product **35** in a selective manner. The reduction of ketone **35** in DME with zinc borohydride afforded the hydroxyl lactone **36.** The deacetylation of **36** with potassium carbonate in water gave a diol, which was then converted into a bis-tetrahydropyranyl derivative **37** using dihydropyran in the presence of *p*-toluene sulphonic acid. The reduction of lactone **37** using diisobutylaluminium hydride (DIBAL) afforded the compound **38**. The witting olefination of **38** with 5-triphenylphosphoniopentanoic acid gave compounds **39**, which on hydrolysis using acetic acid water afforded prostaglandins $PGF_{2\alpha}$ **40**.



Scheme 1.3: Synthesis of prostaglandins $PGF_{2\alpha}$ form cyclopentanoid fused lactone

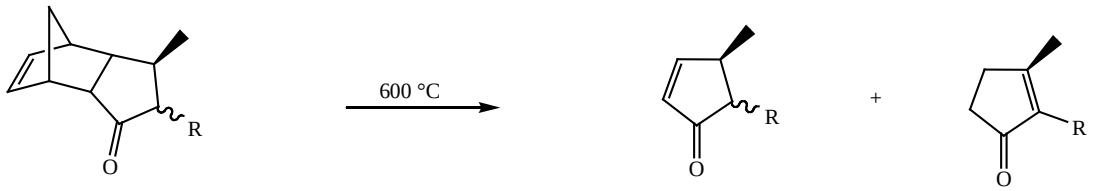
Roseophilin **45** is an anticancer drug isolated from *streptomyces griseoviridis* 1992.[13a] It inhibits the several phosphates, cdc25a, VHR and PTP1B, that play an important role in the growth of cancer cells.[13b] Flynn *et al* reported the synthesis of roseophilin **44** from the highly substituted cyclopentanoid **41**.[14] The cyclisation of **41** by ring closing metathesis and palladium-charcoal hydrogenation gave compound **42**. The pall-knoor reaction of **42** using NH_4OAc, $Ti(OiPr)_4$ and SEM protection afforded compound **43**. The 1,2 addition of **43** with the pyrrolylfuran **44** and elimination followed by deprotection of TOPS, SEM gave the desired product **45**. (**Scheme 1.4**)



Scheme 1.4: Synthesis of roseophilin **45** from cyclopentanoid precursor **41**

The versatility of cyclopentanoids as a structural unit in natural products as well as their presence in useful precursors has enhanced the interests of chemists in the synthesis of cylopentanoid skeletons. As a result, numerous methods have been developed for construction of cyclopentanoids involving the Aldol condensation, Nazarov cyclisation, Pauson-Khand reaction, Zimmerman rearrangement amongst many other methods.[15]

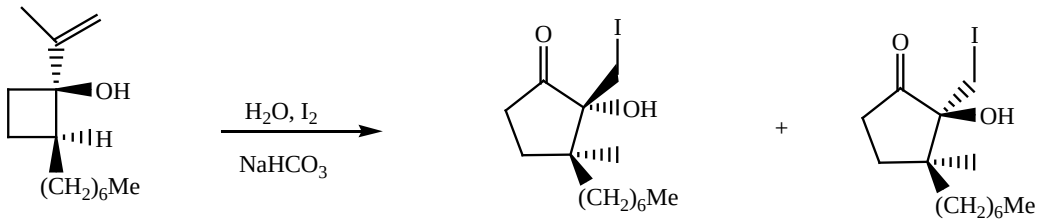
Stork *et al* had first reported the synthesis of cyclopentanoid in 1971 starting from the precursor **46**.[16a] The tricyclic ketone **46** was prepared by following the procedure reported by Sakan *et al*.[16b] Thermolysis of **46** under atmospheric pressure or in a sealed tube gave a mixture of cyclopentanoids **47** and **48**. (**Scheme 1.5**)



46 **47** **48**

Scheme 1.5: Synthesis of cyclopentanoids **47** and **48** by thermolysis of **46**

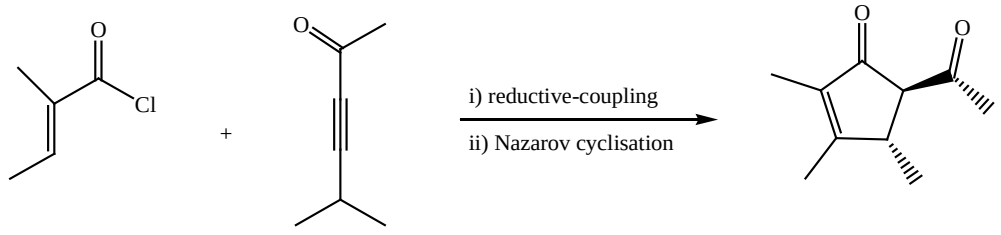
In the area of construction of cyclopentanoid skeleton Fukumoto *et al* reported the syntheses of iodoalkylated cyclopentanoid **50** and **51** by iodinium ion mediated ring expansion of olefinic cyclobutanols **49**.[17] (**Scheme 1.6**)



49 **50** **51**

Scheme 1.6: Syntheses of iodoalkylated cyclopentanoids

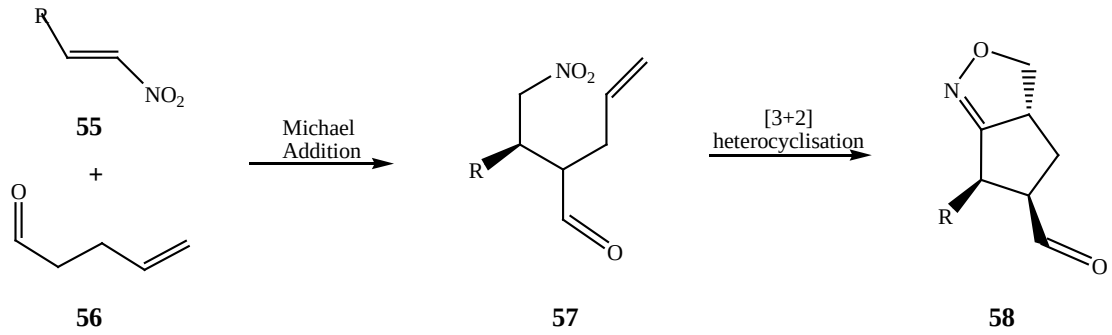
Flynn *et al* recently reported the two step protocol for the synthesis of highly substituted cyclopentanoid **54** by reductive coupling and Bronested acid catalyzed Nazarov cyclization reaction. [18] (**Scheme 1.7**)



52 **53** **54**

Scheme 1.7: Synthesis of cyclopentanoid **54** by Nazarov cyclisation

Michael addition is a cornerstone reaction in organic synthesis for the construction of various complex species in the synthesis of natural products and other biologically active compounds.[19] Further, in the area of construction of cyclopentanoid skeleta, Rodriguez *et al* developed a convenient and direct route for the synthesis of a functionalised cyclopentanoid skeleton by Michael addition reaction followed by [3+2]-heterocyclisation.[20] (**Scheme 1.8**)



Scheme 1.8: Syntheses of cyclopentanoid **58** by Michael addition and [3+2]-heterocyclisation

There is increasing evidence that the natural products and other pharmaceuticals containing cyclopentanoid as a structural unit possess a broad spectrum of biological and pharmaceutical activities. These natural products are also related with various biological processes. This thesis focuses on the synthesis of molecular architectures composed with cyclopentanoids framework. The synthetic studies explored in the thesis provide the development of new methods associated with photochemical transformations.

The second chapter describes the preface of prostaglandins (**PGs**) and their derivatives such as Levuglandins (**LGs**) and iso leuvglandins (**isoLGs)**. This chapter is focused on the design and development of a novel route towards synthesis of levugladin E_2 analogues.

Chapter three presents a novel method for the preparation of bisphenols and their oxidative acetylation studies for the syntheses of bis-cyclohexadienones. The photochemical behaviour of bis-cyclohexadienones is also investigated under UV irradiation.

Chapter four describes the synthetic exploration of the newly discovered chemistry in the construction of complex molecular architecture. We have presented the synthesis of a novel "bird shape" bis-triquinane and other novel carbocycles related to *cis-anti-cis* tricyclopentanoid framework starting from 2,6-dimethyl phenol.

Chapter five elaborates the development of a method for synthesis of bisphenols and calix[4]resorcinarenes using silica-supported perchloric acid as a heterogeneous catalyst under solvent free condition.

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CHAPTER 2

A novel approach towards syntheses of Levuglandins E_2 and D_2 analogues

2.1 Abstract

Design and development of a novel approach for the synthesis of Levuglandins **LGE_2** analogues **70** using the cheap and readily available starting materials isopropenyl acetate **61** and methyl oleate **62** has been reported. The reaction sequence involves photochemical [2+2] cycloaddition, hydrolysis, esterification, elimination and oxidative cleavage. All the intermediates were isolated using chromatographic techniques and characterized by their spectral and analytical analysis.

2.2 Introduction and objective

Lipids are essential components of cell membranes. They incorporate numerous polyunsaturated fatty acids (PUFAs) and are extremely important compounds in all organisms. PUFAs are the substrates for the various enzymatic and non enzymatic transformations that provide a variety of important signalling molecules, mediators, and other biologically active metabolites.[1] The main PUFAs in living organisms are α-linolenic acid (LA) **1**, arachidonic acid (AA) **2**, eicosapentaenoic acid (EPA) **3** and docosahexaanoic acid (DHA) **4**. (**Figure 2.1**)

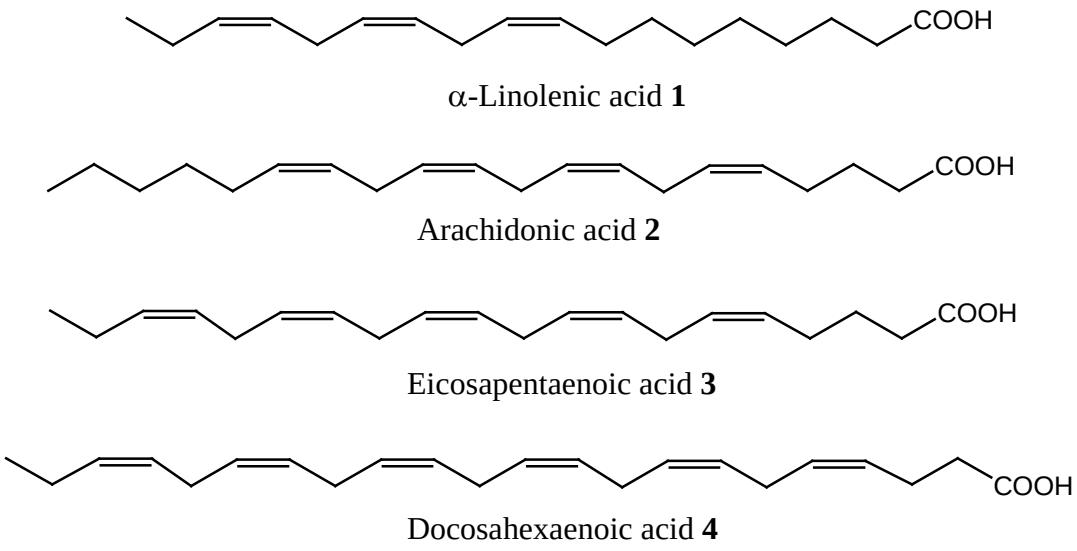
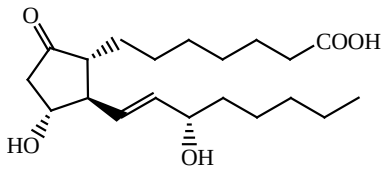


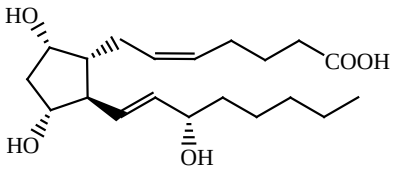
Figure 2.1: Structures of polyunsaturated fatty acids

Lipid oxidation in various biological systems contributes in normal physiological processes and is involved in the development of many chronic and inflammatory diseases such as antiphospholipid antibody syndrome, rheumatoid arthritis, multiple sclerosis and bowel diseases.[2] The presence of aerobic environment and readily oxidizable nature of polyunsaturated fatty acids plays a very important role in human health. The first observation of lipid oxidation problems was observed by the Swiss chemist Nicholas-Theodoro who noticed around 1800 that oil became viscous and had a bad smell when exposed to air. A systematic study on lipid auto oxidation was initiated around 1940 by Criegee *et al*. They proposed that hydroperoxides are the primary products of hydrocarbon oxidation.[3] The detailed study of auto oxidation of polyunsaturated fatty acid was initiated in 1970 by several research groups disclosing complex mixtures than those previously proposed.[4]

The most thoroughly studied enzymatic oxidation of a polyunsaturated fatty acid (PUFA) is the conversion of arachiodonic acid into prostaglandins (PGs).[5] Prostaglandins were first detected in 1930 by Kurzrok and Lieb due to their biological activity. They showed that the human semen could induce strong contractions or relaxations when applied to a human uterus.[6] A few years later, Von Euler and Goldblatt demonstrated independently the presence of a vasodepressor agent and a stimulating factor of muscles in human seminal plasma and sheep vesicular glands.[7] Von Euler indicated that the biological activity was due to a lipid-soluble material with acidic properties and named it as prostaglandin.[8] About 30 years after the discovery of the biological activity of prostaglandins, Bergstrom, Sjovall, and Samuelsson isolated the first two prostaglandins PGE_1 **5**, $PGF_{2\alpha}$ **6** and elucidated their structures in 1960.[9] (**Figure 2.2**)



PGE_1 **5**



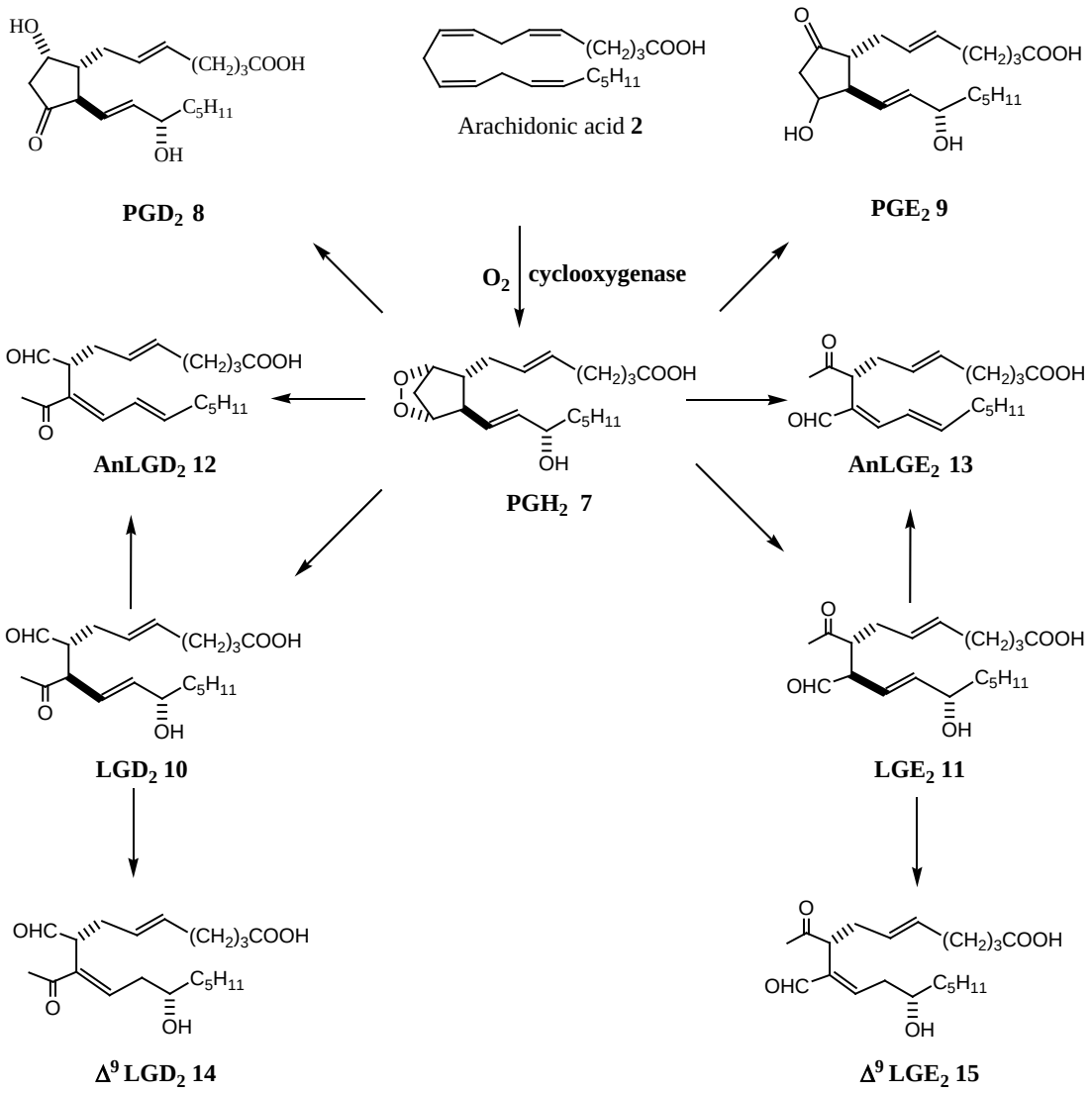
$PGF_{2\alpha}$ **6**

Figure 2.2: The structures of PGE_1, $PGF_{2\alpha}$

Levuglandins (LGs) and isolevuglandins (isoLGs) are the products of lipid peroxidation that are biologically active. The discovery of LGs was the result of an effort to elucidate the chemistry of prostaglandin endoperoxide PGH_2 **7**. PGH_2 **7** is the cyclooxygenase metabolite of the arachidonic acid (AA) **2**. It is a key intermediate in regulating the wide variety of cellular activities and undergoes various enzymatic and non-enzymatic rearrangements to provide physiologically active molecules. The spontaneous rearrangement of PGH_2 produces prostaglandins E_2 (PGE_2) **8** and prostaglandins D_2 (PGD_2) **9**.[10]

Salomon *et al* proposed that, rearrangement of PGH_2 **7** generates two levulinaldehyde derivatives termed as Levuglandins, LGE_2 **10** and LGD_2 **11,** because of their structural similarities with levulinaldehyde and their relation to Prostaglandins

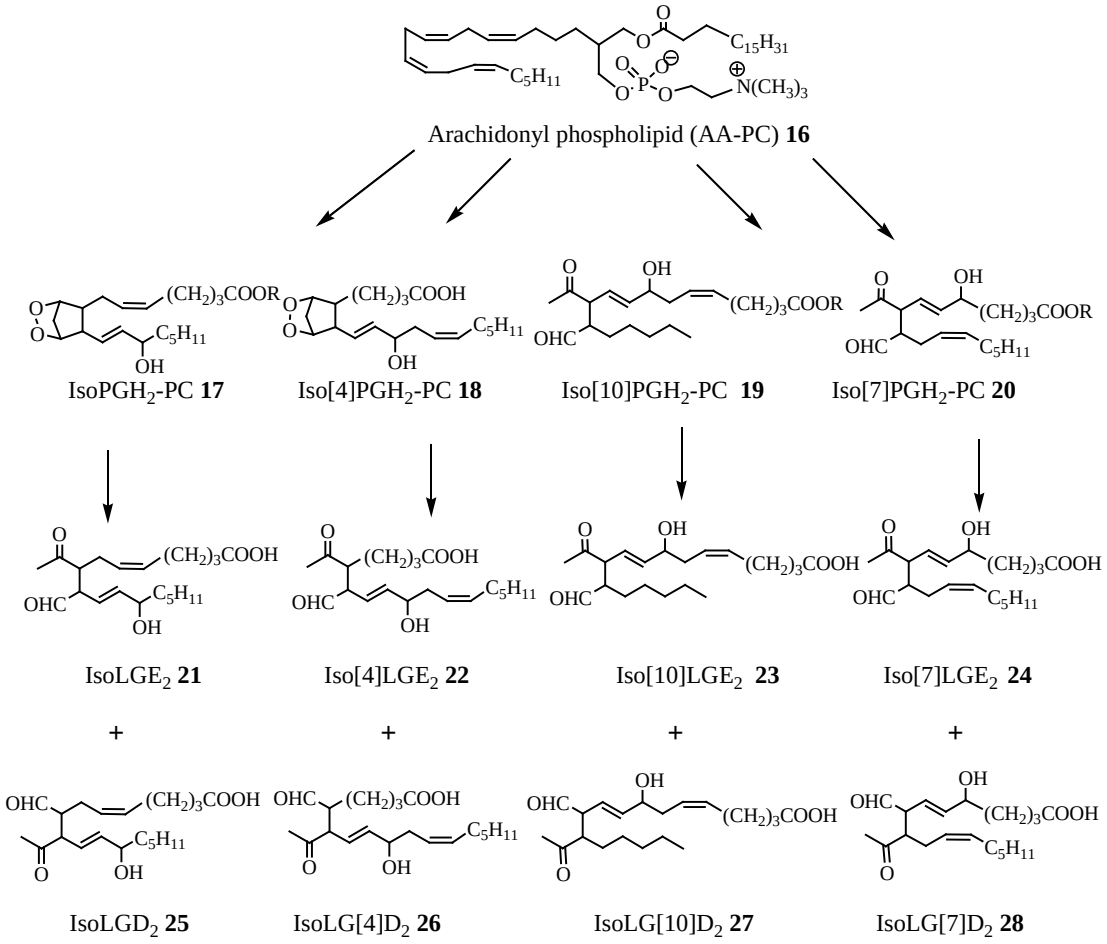
E_2 and D_2.[11] (**Scheme 2.1**) Both the levuglandins **10** and **11** are chemically sensitive compounds and are converted into anhydrolevuglandins, $AnLGE_2$ **12** and $AnLGD_2$ **13**, after losing a water molecule. They also produce Δ^9-LGD_2 **14** and Δ^9-LGD_2 **15** isomers by allylic rearrangement.[11,12]



Scheme 2.1: Rearrangement of PGH_2 generation of PGs and LGs

In addition to the rearrangement of AA **2** to PGH_2 **7** via the cyclooxygenase pathway Saloman *et al* reported the formation of other structurally different prostaglandin endoperoxide isomers by non-enzymatic free radical induced oxidation of arachidonic acid phospholipid (AA-PL) **16**.[13] They have discovered that the non-enzymatic free radical-induced oxidation of archidonic acid phospholipid (**AA-PL**) gave four structurally different phospholipid endoperoxide stereoisomers that are named as isoprostanes (isoPS) **17-20**. The rearrangement of these endoperoxide

intermediates produce four LGE_2 isomers **21-24**, that are $isoLGE_2$, $iso[4]LGE_2$, $iso[7]LGE_2$, $iso[10]LGE_2$ and four corresponding $isoLGD_2$ **25-28** isomers.[13] (**Scheme 2.2**)

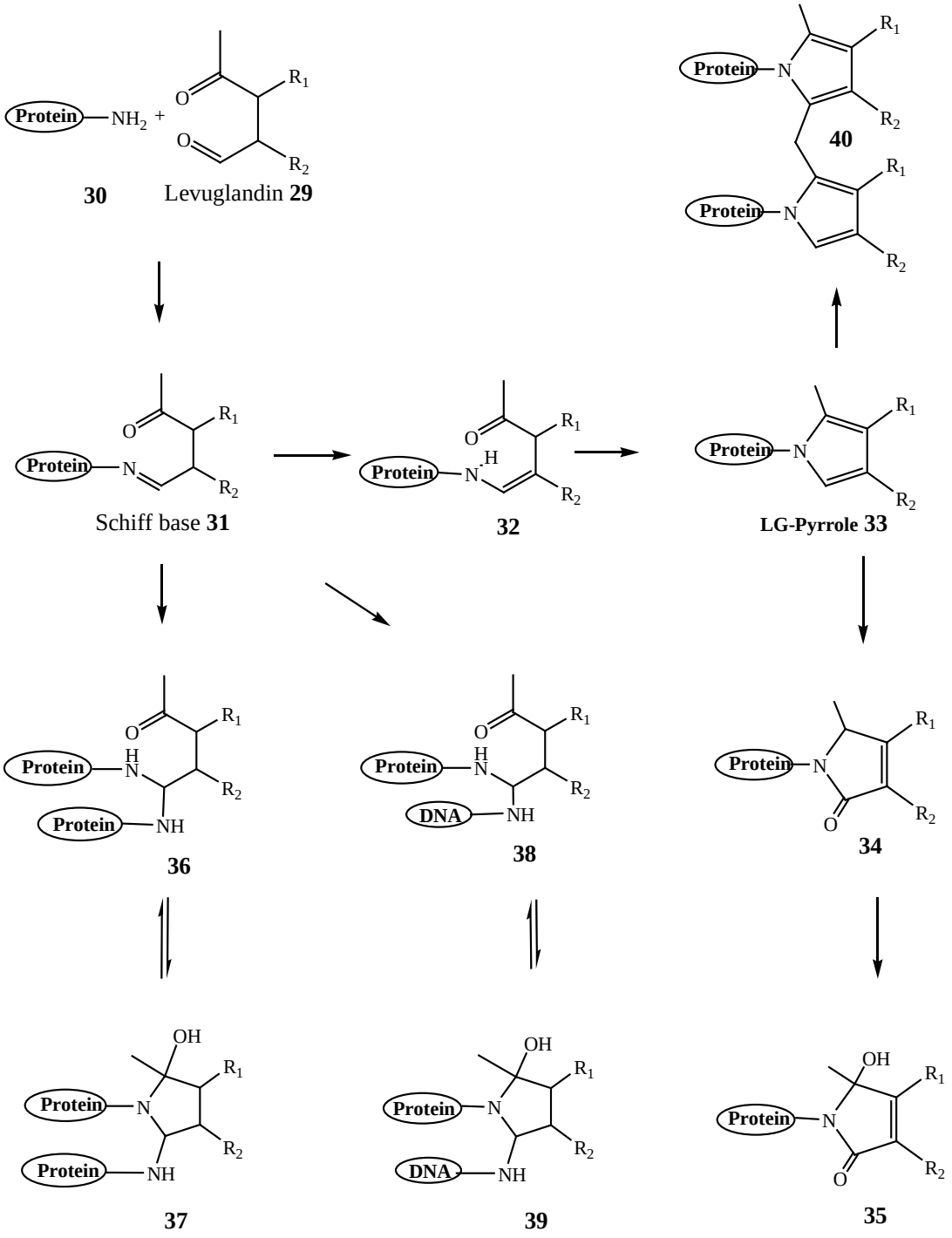


Scheme 2.2: Free radical-induced oxidation of arachidonic acid phospholipid (**AA-PC**) generation of isoLGs

LGs and isoLGs are highly cytotoxic, and bind covalently with the amino group in proteins to produce covalent adducts with greater avidity than the other lipid oxidation products.[14,15]

Salomon *et al* have proposed that the electrophilic γ-ketoaldehyde functionality in LGs has an extraordinary proclivity towards rapid covalent adduction with biomolecules.[16] The LGs **29** initially bind covalently with the amino group in proteins **30** via Paal-Knorr condensation to produce Schiff base adducts **31** which are transformed into pyrrole derivatives **33** by rapid cyclization and dehydration.[17,18] These highly alkylated pyrroles **33** are chemically sensitive compounds. In the

presence of oxygen they get oxidized to stable end products such as lactams **34** and hydroxy lactams **35**.[19] The LG-protein Schiff base adducts **31** also bind with primary amino group of other proteins leading to the formation of protein-protein crosslinks **36** and **37**. LGs also cause DNA-protein cross-links (DPCs) **38, 39** which are responsible for cell killing.[20] (**Scheme 2.3**)

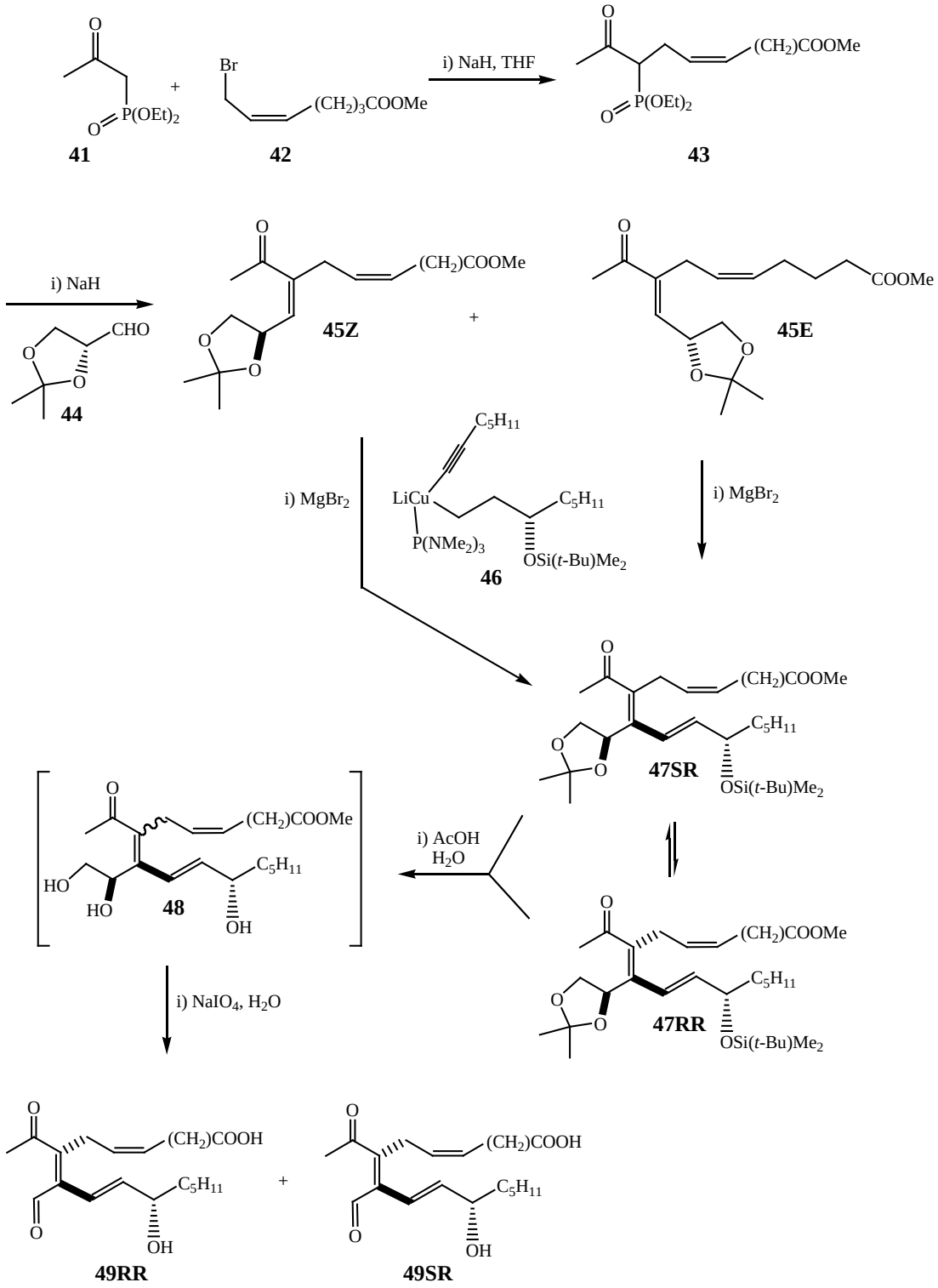


Scheme 2.3: Covalent adduction of LGs with protein

The protein-protein crosslink and protein polymerisation also occur in conjunction with the binding and are associated with various diseases such as alzheimer's diseases (AD), atherosclerosis, renal diseases etc.[21,22]

Levuglandin-protein adducts are detected *in vivo* by using polyclonal rabbit antibodies and are used as markers of oxidative injury.[19] The mean levels of isoLGs-protein adducts, as well as LGE_2-protein adducts, are elevated in the plasma of individuals with atherosclerosis and renal disease as compared to normal individuals.[22,23] Hence, the LG-protein adducts provide a quantitative assessment of oxidative stress.[24]

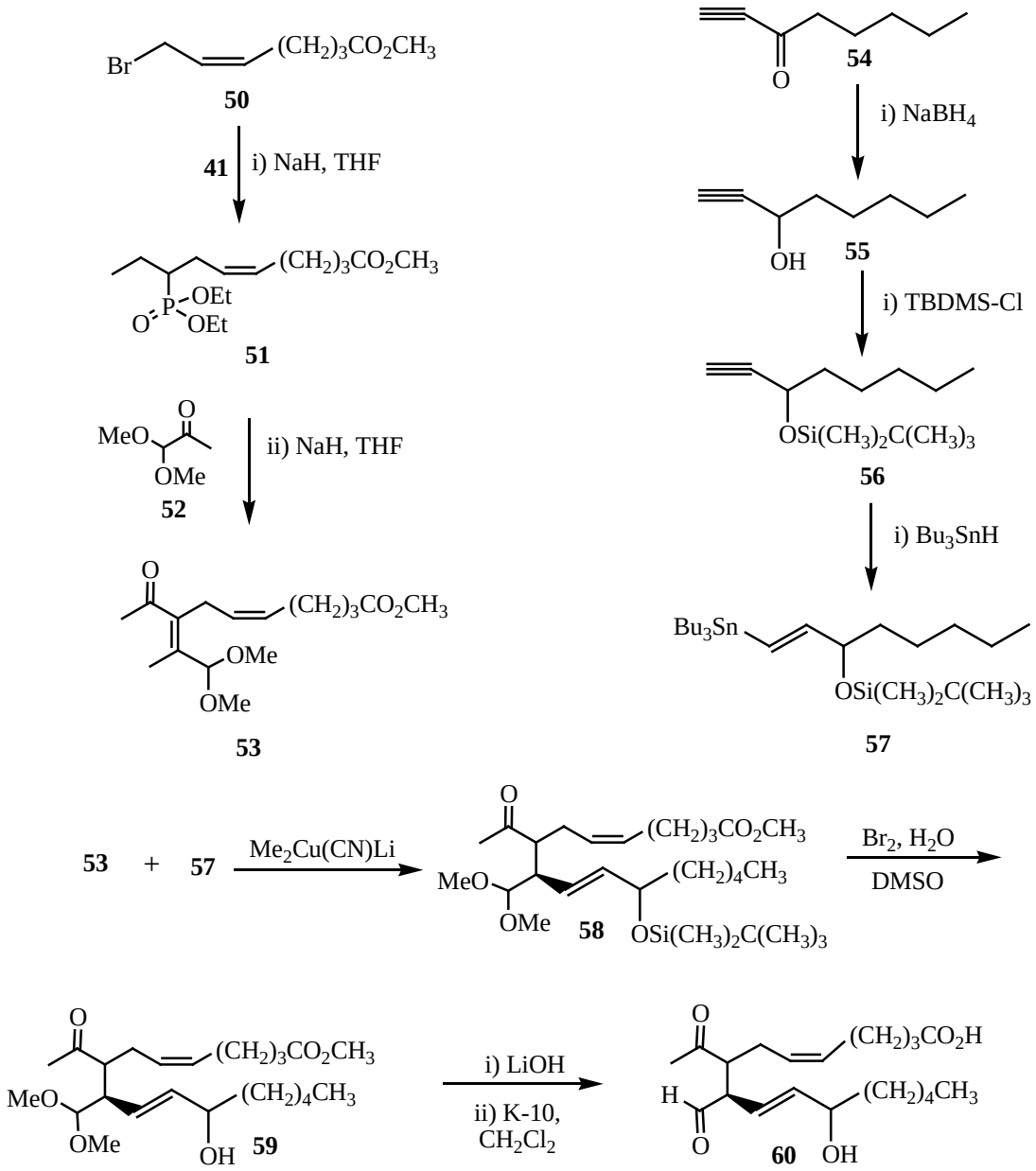
The synthesis of LGs constitutes a challenge for organic chemists due to their complicated structures. Only few methods for the syntheses of LGs have been developed by Salomon and co workers.[25] LGE_2 was the first member of levuglandin family synthesised by a chemist. Salomon *et al* has reported the synthesis of LGE_2 form ketophosphonoacetone **41** outlined in **scheme 2.4**. The alkylation of **41** with alkyl bromide **42** in the presence of NaH gave the corresponding ketophosphonate **43**. The Horner-Emmons condensation of sodium salt of **43** with isopropylidene glyceraldehydes **44** furnished nonracemic chiral enones **45E** and **45Z**. The magnesium bromide catalysed 1,4-addition of cuprate **46** with isomeric enone either **45E** or **45Z** afforded an identical mixture **47SR** and **47RR**. Deprotection of three hydroxy groups of **47SR** and **47RR** with acetic acid water followed by oxidative cleavage of triol **48** using $NaIO_4$ furnished the **LGE_2** mthyl ester **49RR** and **49SR**.[25a] (**Scheme 2.4**) Following similar procedure Salomon *et al* has also reported the synthesis of iso[4]LGE_2, iso[7]LGD_2 and 17-isoLGE_4 natural products.[25b-d]



Scheme 2.4: synthesis of LGE_2

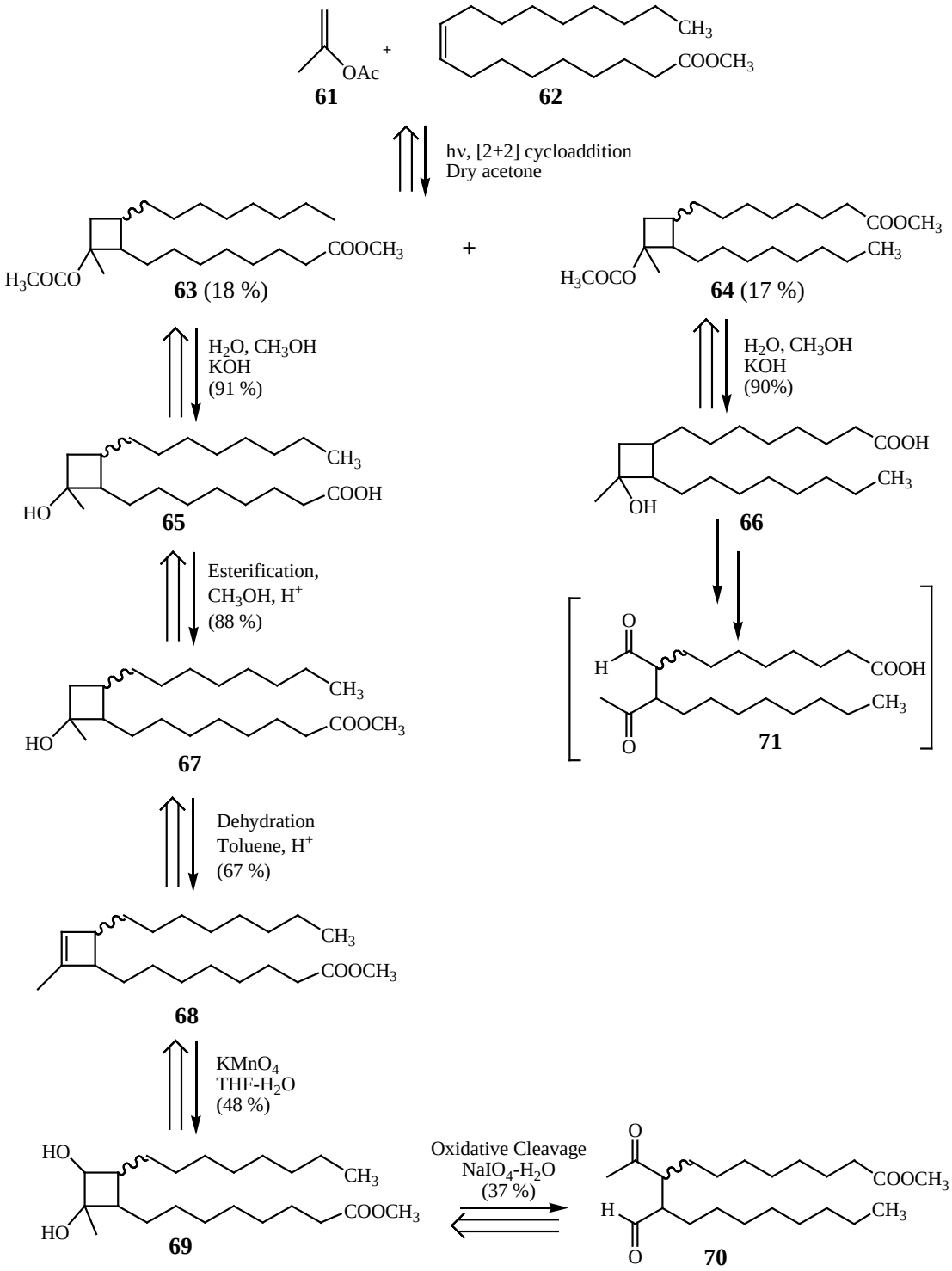
In the area of synthesis of LGs natural products the Amarnath *et al* reported the synthesis of LGE_2 from methyl-7-bromoheptanoate **50** and oct-1-yne-3-one **54**.[26] The condensation of **50** with ketophosphonoacetone **41** using sodiumhydride in THF

furnished **51**. The compound **51** gave the precursor **53** by condensation with **52** in presence sodium hydride. Similarly the stannane **57** was prepared from **54** in three steps. The reduction of **54** with sodium borohydride gave the hydroxy alkyne **55** which on treatment *tert*-butyldimethylsilyl chloride afforded corresponding silyl derivative **56.** The silyl derivative **56** converted to stannane **57** on heating in presence of tributyltin hydride. The treatment of enone **53** and stannane **57** with CuCN in presence of methyllethium in THF afforded the protected LGE_2 **58**. The removal of the silyl group using bromine walter followed by hydrolysis of ester group using lithium hydroxide and acetal by K-10 gave the LGE_2 **60**. (**Scheme 2.5**)



Scheme 2.5: Synthesis of Levuglandin E_2

In this chapter the design and development of a novel and general method for the construction of LGs analogues via a sequence [2+2] cycloaddition, hydrolysis, elimination and oxidative cleavage using cheap and readily available starting materials like isopropenyl acetate **61** and methyl oleate **62** has been reported. (**Scheme 2.6**)



Scheme 2.6: Synthesis of LGE_2 analogue **70**

2.3 Results and discussion

Photochemical reactions are most versatile tools in synthetic organic chemistry towards target oriented synthesis of the natural products and complex molecular architectures. [27] In photochemical reactions, the activation of substrate molecules and their transformation to the desired products takes place by absorption of electromagnetic radiation. The reactant molecule absorbs energy in the form of radiation and goes to an excited state. The excited states of molecules are rich in energy therefore reactions occurred in these states may be highly endothermic in the ground state. Numerous organic transformations can be achieved in sunlight or visible light with renewable energy sources. Thus a photochemical reaction provides the most significant way to access the exceptional molecular structures that cannot be achieved by other conventional methods. Photochemical transformation occurs without the use of any chemical reagents, thereby providing a greener pathway to the reactions.

Different types of photochemical transformations such as photo cycloaddition, photo rearrangement, photo electron-transfer, photo Friedel-Crafts, photo oxygenation and their use in assembling of highly functionalised structures and polycycles have been established from very simple and readily available materials.[27] Among all the photochemical reactions, the photo cycloaddition reaction in alkenes leading to cyclobutane is a valuable organic transformation to achieve the total syntheses of various natural products. [28]

Towards the synthesis of the LGs analogue **70,** a $\pi^{2s} + \pi^{2s}$ photocycloaddition reaction of **61** and methyl oleate **62** was performed under UV radiation in a quartz immersion well using a low pressure mercury lamp. Thus, a solution of **61** and **62** in acetone was irradiated with UV irradiation for 3.5h while maintaining temperature between 10-15 °C. After completion of the reaction the solvent was removed in a rotary evaporator under reduced pressure which gave a thick yellow liquid. This liquid was then chromatographed over a column of silica gel. The elution of column with a mixture of light petroleum and ethyl acetate furnished products **63** at R_f 7.5 and **64** at R_f 6.0 in almost equal amounts. (**Scheme 2.6**)

The structures of both the products **63** and **64** were readily discernible through their FTIR, ^{1}H and ^{13}C NMR and mass analysis data. FTIR spectrum of the

cycloadduct **63** showed a band at 1240 cm^{-1} for the C-O-C stretching of the acetate group along with bands at 1723, 1735 cm^{-1} for the characteristic carbonyl groups. Its ^{1}H NMR spectrum gave a triplet at δ 0.87, singlets at δ 2.05, 2.38, 3.66 for the protons of four methyl groups along with signals between δ 0.90-1.56 for the protons on methylene groups. It also displayed the multiplet between δ 2.10-2.12 for the methine protons. The ^{13}C NMR spectrum of **63** was also consistent with the proposed structure. It gave resonances at δ 13.52, 24.32, 27.60, 51.39 for the four methyl carbons and peaks at δ 28.98, 29.01, 29.04, 29.07, 29.25, 29.38, 29.50, 29.58, 29.73, 31.82, 31.85, 33.91, 33.98, 34.01, 38.30 (15C, CH_2) for the methylene carbons. Similarly the signals at δ 49.01, 50.01 for methine carbons, a signal at δ 81.68 for the carbon attached with acetate group and signals at δ 177.41, 177.45 for the two carbonyl carbons. The structure was further confirmed by its mass spectrum which gave a molecular ion peak at 396.21.

The FTIR spectrum of **64** showed a band at 1166 cm^{-1} for the C-O stretching of the acetate group along with 1730 and 1750 cm^{-1} for the characteristic carbonyl groups. Its ^{1}H NMR spectrum exhibited a triplet at δ 0.87, singlets at δ 1.61, 2.31 and 3.59 for the protons of four methyl groups. It also displayed multiplets between δ 0.97-1.62, 2.01-2.18 for the protons of the methylene groups along with multiplets between δ 1.86-1.98, 2.20-2.28 for the protons of methine groups. The ^{13}C NMR of compound **64** displayed signals at δ 14.23, 20.64, 22.27, 51.37 for the four methyl carbons and signals at δ 22.59, 24.65, 24.85, 26.39, 26.95, 27.83, 28.06, 28.86, 29.03, 29.16, 29.90, 31.63, 31.81, 32.51, 32.61, 33.98 for the carbons of methylene group. Similarly the signals at δ 33.98, 48.56 for two methine carbons along with a signal at δ 80.09 for the quaternary carbon attached to the acetate group. It also showed resonances at 174.24, 174.28 for the carbonyl carbons of acetate groups.

The presence of acetate groups in the cyclobutane ring in photocycloadduct **63** and **64** provide unique opportunities for their elaboration to the desired product **70**. Hence we attempted the next step of our strategy, which involved the hydrolysis of photo cycloadducts **63** and **64**. The photo cycloadduct **63** in methanol was treated with 10% aqueous solution of potassium hydroxide at room temperature for 2.5h. After usual work up followed by column chromatography, the crude product furnished the hydroxy acid **65** as a colourless liquid. (**Scheme 2.6**)

The structure of compound **65** was confirmed by its spectral analysis. Its FTIR spectrum showed a very strong broad band at 2450-3450 cm^{-1} which confirms the presence of carboxylic acid group. The ^{1}H NMR spectrum of compound **65** exhibited a broad singlet at δ 11.85 for the proton of acid group. The product has one OH group whose signal merged with the signals of aliphatic protons between δ 1.97 and 2.59. The presence of OH group was confirmed by D_2O exchange proton NMR spectrum, which showed the decrease in the peak area between δ 1.97 and 2.29. The ^{13}C NMR spectrum of compound **65** exhibited signals at δ 14.15, 23.04 for the carbons of two methyl groups and signals at δ 24.11, 27.08, 27.59, 28.46, 29.01, 29.23, 29.55, 30.56, 31.17, 31.86, 32.44, 32.71, 34.06, 35.59 represent the carbons of methylene groups. It also gave absorptions at δ 38.86, 50.08 for two methine carbons along with signals at δ 81.77, 179.50 for the carbon attached to OH group and one carbonyl carbon respectively.

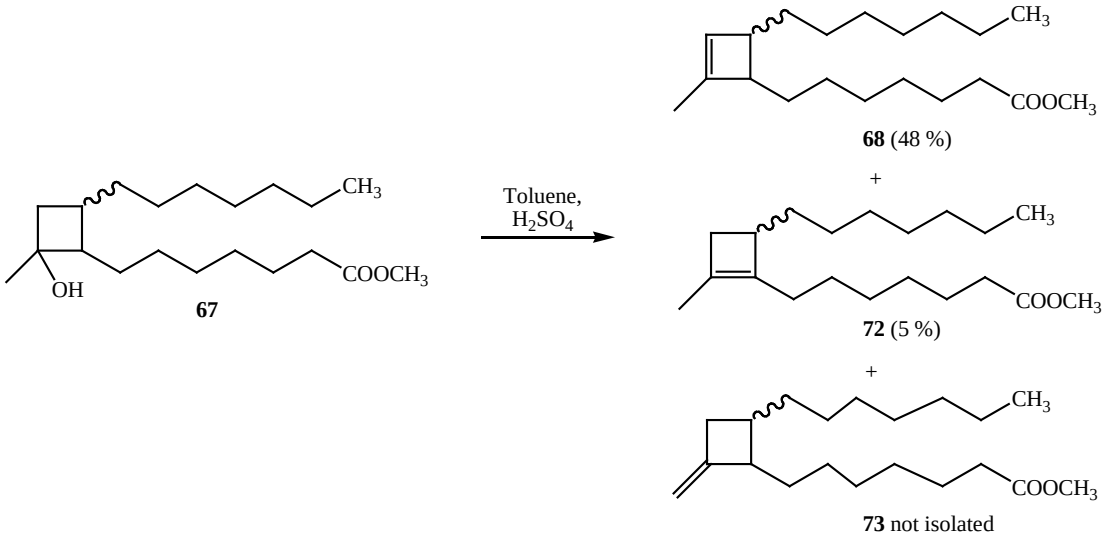
Similarly the hydrolysis of photocycloadduct **64** in methanol using an aqueous solution of KOH 10% under similar reaction conditions afforded hydroxy acid **66**. The structure of compound **66** was confirmed by its FTIR, ^{1}H, ^{13}C NMR and mass spectral analysis that were consistent with its structure.

To protect the acid functionality the hydroxy acid **65** converted into its corresponding methyl ester **67** by treatment with catalytic amount sulphuric acid in methanol. (**Scheme 2.6**)

The structure of the product **67** was confirmed by their spectral analysis. Its IR spectrum of showed an absorption band at 3380 cm^{-1} due to the presence of phenolic OH group, and strong bands at 1740 cm^{-1} for the presence of carbonyl groups. The ^{1}H NMR spectrum of compound **67** exhibited a sharp singlet at δ 3.66 which indicated the presence of methyl ester group along with signals at δ 0.95, 1.61 for two methyl groups. It also showed multiplets at δ 1.25-1.50, 2.19, 2.30 for the protons of methylene groups and a signal at δ 1.88 for the proton of OH group. Its ^{13}C NMR spectrum displayed signals at δ 13.92, 21.23 and 54.98 for carbons of methyl groups. It also displayed a signal at δ 71.94 for the carbon attached with OH group, along with a signal at δ 169.29 for the carbonyl carbon of acetate group.

We then attempted the next step involving the elimination of the hydroxy group of compound **67** to its corresponding cyclobutene derivative **68**, which is the key intermediate for the synthesis of the LG analogues **70**. However this process is tedious since there is a possibility for the formation of three different products **68, 71** and **72** by dehydration of compound **67**. (**Scheme 2.7**)

We attempted the catalytic dehydration of compound **67** in toluene using two different reagents; *p*-toluene sulphonic acid (*p*-TSA) and sulfuric acid (H_2SO_4). Thus a solution of **67** in toluene was heated in the presence of *p*-TSA at reflux temperature but the reaction did not show the formation of any product on TLC. So we attempted the sulphuric acid catalysed dehydration of **67.**



Scheme 2.7: Dehydration of hydroxy ester **67**

A mixture of H_2SO_4 and toluene was added to a stirred solution of hydroxy ester **67** in dry toluene at 0 °C. The stirring was further continued for 45 min with maintained temperature. The reaction mixture was then allowed to warm upto room temperature ~ 27 °C. The product was extracted in ethyl acetate and the solvent was removed in a rotatory evaporator under reduced pressure which gave a thick yellow liquid as a crude product. The column chromatography of the product over a column of silica gel using a mixture of light petroleum/ethyl acetate as eluents furnished an

inseparable mixture of two *regio* isomers **68** and **72** in the ratio **92.5:7.5**. However the product **73** was not obtained at all. (**Scheme 2.7, Figure 2.3**)

The ratio of both the products **68, 72** was calculated by the ratio of peak area of acetate methyl group in their ^{1}H NMR spectrum which gave singlets at δ 3.43, 3.67. (**Figure 2.3**) Based on the ratio of peak area it was found that the desired product **68** was formed in major amount.

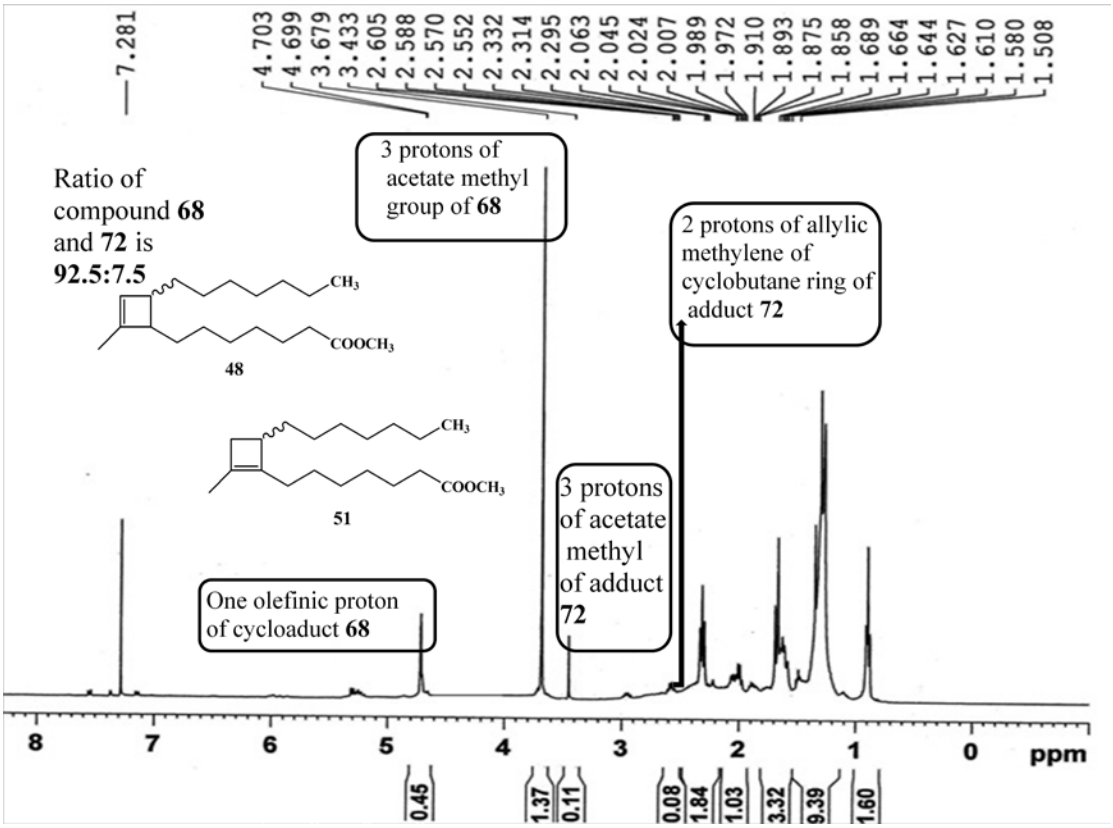
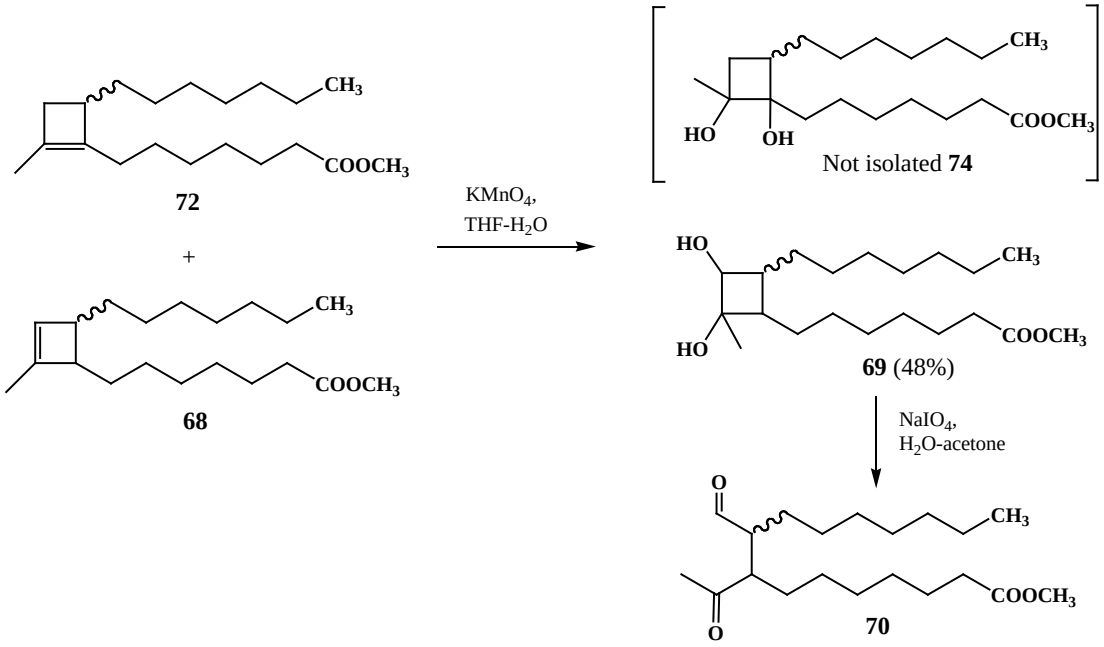


Figure 2.3: ^{1}H NMR of inseparable mixture of compound **68** and **72**

Towards the synthesis of LG analogue **70** it was necessary to cleave the alkene moiety of precursor **68** to corresponding γ-ketoaldehyde. Numerous methods have been reported in the literature for the cleavage of alkenes using various reagents such as $Pb(CH_3COO)_4$, HIO_4, O_SO_4-$KMnO_4$, O_3, MnO_2, PCC etc.[29] Use of most of these reagents converts alkene to diol and further diol to aldehyde or acid. Simandi *et al* in 1986 reported the selective cleavage of alkene to aldehyde using $KMnO_4$ in THF-water.[30] This method was applied to cleave the double bond in cyclobutene ring of precursor **68** for the synthesis of the desired product **70**.

Thus, to a stirred mixture of alkene **68**, **72** in THF, a solution of potassium permanganate in water was added over a period of 1h. Stirring was further continued for 3.5 h after which the reaction mixture was filtered on celite pad. THF was removed under reduced pressure and product was extracted with ethyl acetate (25 ml x 3). The combined extracts were washed with water, brine and dried over anhydrous sodium sulphate. Removal of solvent under reduced pressure followed by column chromatography furnished diol **69** (48%) as a colourless liquid. However, the diol **74** and desired γ-keto aldehyde **70** was not obtained. (**Scheme 2.8**)



Scheme 2.8: Synthesis of γ-keto aldehyde **70**

The structure of the diol **69** was fully discernible through its spectral analysis. Its IR spectrum showed a strong absorption band at 3284 cm^{-1} due to the presence of OH group, and a strong band at 1739 cm^{-1} for the carbonyl of acetate group. The ^{1}H NMR spectrum of diol **69** exhibited signals at δ 0.89, 1.54, 3.68 for the protons on methyl groups and signals at δ 1.21, 2.29 for protons of methylene groups. It also showed a singlet at δ 2.19 for the protons of two hydroxy group along with a signals at δ 2.45, 4.18 for the two methine protons. The ^{13}C NMR spectrum of **69** displayed signals at δ 14.12, 22.67 and 51.52 for carbons of three methyl groups and signals at δ 23.65, 24.78, 28.90, 29.01, 29.11, 29.32, 29.47, 30.98, 31.98, 31.85, 33.72, 33.77, 34.02, 34.05 for the methylene carbons. Similarly the signals at δ 74.33, 75.53 for

methine and quaternary carbons attached with OH group along with a signal at δ 174.33 for the carbonyl carbon of acetate group were obtained.

In order to synthesize the γ-keto aldehyde **70**, the diol **69** was subjected to oxidative cleavage. Thus, a solution of diol **69** in acetone-water (1:1) was added to a stirred solution of $NaIO_4$ in water-acetone (1:1) at 10 °C over a period of 15 min. The resulting mixture was stirred further for 1.5h, and then reaction was quenched by addition of ethylene glycol. The reaction mixture was extracted with ethyl acetate (25 ml x 3), washed with water, brine and dried over anhydrous sodium sulphate. Removal of solvent under reduced pressure gave a thick yellow liquid which was chromatographed over a column of silica gel. The elution of the column using a mixture of light petroleum/ethyl acetate afforded the keto aldehyde **70** as a colourless liquid. (**Scheme 2.8**)

The structure of **70** was confirmed by their spectral analysis. Its IR spectrum showed absorption bands at 1710, 1730 cm^{-1} due to the presence of the carbonyl groups. The ^{1}H NMR spectrum of compound **70** exhibited a sharp singlet at δ 9.37 which indicated the presence of aldehyde group along with signals at δ 0.89, 2.19 and 3.68 for three methyl groups. It also displayed cluster of multiplets between δ 0.96-1.71, 2.34 for the protons of methylene groups and a signal at δ 2.45 for the protons on methine groups. Its ^{13}C NMR spectrum gave resonances at δ 15.12, 19.24 and 51.52 for the carbons of three methyl groups. It also displayed signals at δ 35.75, 37.87 for the two methine carbons, along with signals at δ 174.33, 196.29, 198.93 for the three carbonyl carbons.

2.4 Experimental section

Ultraviolet spectra were recorded on a Perkin-Elmer Lambda-19 Spectrometer. Infrared spectra were recorded on a Perkin-Elmer PC-16 FTIR Spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 500/400 MHz NMR spectrometer (125/100 MHz for ^{13}C respectively) using $CDCl_3$ or DMSO-d_6 (TMS as an internal standard). Mass spectra were obtained on Thermo-Fisher DSQ II GCMS instrument.

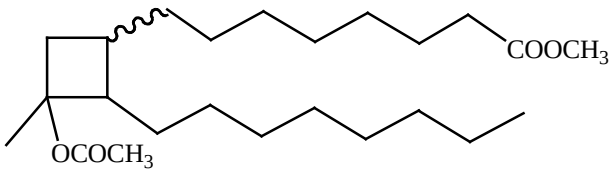
Column chromatography was performed using Acme's silica gel (60–120# mesh) and the elution was done using mixtures of light petroleum and ethyl acetate.

Yields (%) were reported based on the isolated material after column chromatography. Thin layer chromatography was performed using Acme's silica gel for TLC and the spots were visualized in iodine vapor.

Experimental procedures:

Synthesis of adducts (63) and (64):

A solution of methyl oleate (**62**) (1.00 g, 0.0034 mole) and isopropenyl acetate (**61**) (0.34 gm, 0.0034 mole) in acetone (~ 600 ml) was placed in an immersion well-type photoreactor and was irradiated for 6 h at 10-15 °C, with a 250 W low pressure mercury vapour lamp. After near completion of reaction (TLC), the solvent was removed under reduced pressure which gave a thick yellow liquid as a crude product. This product was then chromatographed over a column of silica gel. Elution of the column using a mixture of light petroleum/ethyl acetate (90:7) afforded the adduct (**64**) as a colourless liquid (0.23 gm, 17 % yield).



64

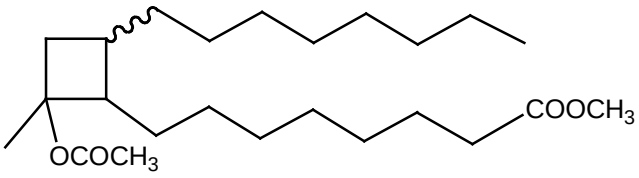
IR (KBr): 1160, 1730, 1750, 2838, 2875 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (3H, t, *J* = 6.75 Hz, CH_3), 0.97-1.62 (28H, m, $14CH_2$), 1.61 (3H, s, CH_3), 1.86-1.98 (1H, m, CH), 2.01-2.18 (2H, m, CH_2), 2.20-2.28 (1H, m, CH), 2.31 (3H, s, CH_3), 3.59 (3H, s, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.03, 20.64, 22.27 (3C, CH_3), 22.59, 24.65, 24.85, 26.39, 26.95, 27.83, 28.06, 28.86, 29.03, 29.16, 29.90, 31.63, 31.81, 32.51, 32.61 (15C, CH_2), 33.98, 48.56 (2C, CH), 51.37 (1C, CH_3), 80.09 (1C, Cq), 174.24, 174.28 (2C, CO).

MS (EI): m/z Calculated for $C_{24}H_{44}O_4$: 396.32; found 396.20 (M^+).

Further elution of the column with light petroleum / ethyl acetate (90:10) furnished adduct (**63**) (0.24 gm, 18 % yield).



63

IR (KBr): 1240, 1723, 1735, 2838, 2875 cm^{-1}.

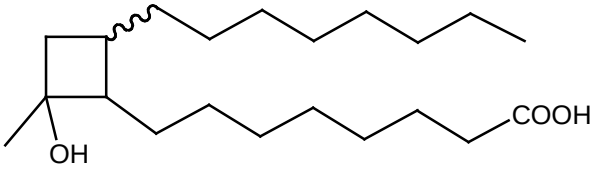
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (3H, t, *J* = 6.75 Hz, CH_3), 0.90-1.56 (28H, m, $14CH_2$), 1.62 (3H, s, CH_3), 2.05 (2H, m, CH_2), 2.10-2.32 (2H, m, 2CH), 2.38 (3H, s, CH_3), 3.66 (3H, s, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 13.52, 22.78, 24.32 (3C, CH_3), 27.60, 28.83, 29.01, 29.07, 29.25, 29.38, 29.50, 29.58, 29.73, 31.82, 31.85, 33.91, 33.98, 34.01, 38.30 (15C, CH_2), 39.84, 50.01 (2C, CH), 51.39 (1C, CH_3), 81.68 (1C, Cq) 177.41, 177.45 (2C, CO)

MS (EI): m/z calculated for $C_{24}H_{44}O_4$: 396.32; found 396.21 (M^+).

Synthesis of hydroxy acid (65):

To a stirred solution of cycloadduct (**63**) (4.00 gm, 0.012 mol) in methanol (50 ml) an aqueous solution of KOH (10%, 3.5 ml) was added over a period of 15 min at room temperature ~ 27 °C. The stirring was further continued for 2.5h. After completion of the reaction the reaction mixture was neutralised with aqueous HCl (1:4). The product was extracted in ethyl acetate (25 ml x 3). The combined organic extracts were washed with water, brine solution and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure furnishing a thick liquid which was then chromatographed over a column of silica gel. Elution of the column using a mixture of light petroleum ethyl acetate (90:30) furnished the hydroxy acid (**65**) a colourless liquid. (3.12 gm, 91 % yield)



65

IR (KBr): 1163, 1712, 2561-3255 cm^{-1}

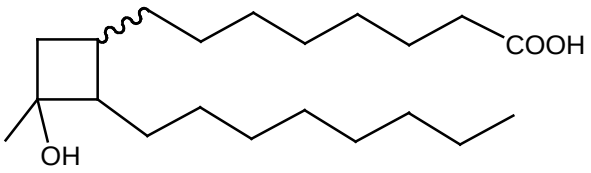
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.00 Hz, CH_3), 1.27-1.97 (28H, m, $14CH_2$), 2.17 (1H, s, OH superimposed with CH_2), 2.34 (2H, m, CH_2), 2.43 (2H, m, 2CH), 2.59 (3H, s, CH_3), 11.85 (1H, bs, COOH).

^{13}C NMR (100 MHz, $CDCl_3$): 14.15, 23.04 (2C, CH_3), 24.11, 27.08, 27.59, 28.46, 29.01, 29.23, 29.55, 30.56, 31.17, 31.86, 32.44, 32.71, 34.06, 35.59, 38.33, 38.86 (15C, CH_2), 45.93, 50.08 (2C, CH), 81.77(1C, Cq), 179.50 (1C, CO).

MS (ESI): m/z calculated for $C_{21}H_{40}O_3$: 340.54; found 340.8 (M^+).

Synthesis of hydroxy acid (66):

To a stirred solution of cycloadduct (**64**) (4.00 g, 0.012 mol) in methanol, an aqueous solution of NaOH (10%, 1.5 ml) was added over a period of 15 min at room temperature ~ 27 °C. The stirring was further continued for 2.5h. After completion of the reaction, the reaction mixture was neutralised with aqueous HCl (1:4). The product was extracted in ethyl acetate (25 ml x 3), the organic extracts were combined and washed with water, brine solution and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure furnishing a thick liquid which was chromatographed over a column of silica gel. Elution of column using a mixture of light petroleum ethyl acetate (90:30) furnished the hydroxy acid (**66**) a colour less liquid. (3.00 gm, 90 % yield)



66

IR (KBr): 1136, 1369, 1710, 3279 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, t, *J* = 6.00 Hz, CH_3), 1.14-1.62 (28H, m, $14CH_2$), 1.86-1.92 (2H, m, 2CH), 2.01 (1H, s, OH superimposed with CH_2), 2.03 (2H, m, CH_2), 2.30-2.35 (3H, t, CH_3), 10.86 (1H, bs, COOH).

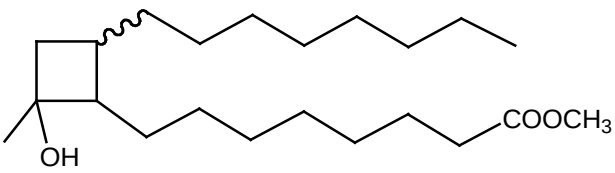
^{13}C NMR (100 MHz, $CDCl_3$): δ 14.01, 22.57 (2C, CH_3), 24.61, 25.38, 26.34, 26.81, 27.76, 27.94, 28.02, 28.97, 29.00, 29.64, 31.79, 32.48, 32.59, 33.97, 37.13 (15C, CH_2), 48.49, 54.82 (2C, CH), 73.21 (1C, Cq), 179.05 (1C, CO).

MS (ESI): m/z calculated for $C_{21}H_{40}O_3$: 340.54; found 340.3.

Synthesis of hydroxy ester (67):

To a stirred solution of hydroxy acid (**65)** (3 gm, 0.008 mole) in dry methanol (20 ml), concentrated sulphuric acid (0.01 ml) was added at room temperature ~27°C. The resulting mixture was further stirred for 1h. The reaction mixture was neutralised with a saturated solution of sodium bicarbonate and the product was extracted with ethyl acetate (25 ml x 3). The organic layers were combined, washed thoroughly with water, brine solution and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure which gave the crude product as a pale yellow liquid. This product was then chromatographed over a column of silica gel using light

petroleum and ethyl acetate afforded the hydroxy ester (**67)** as a colour less liquid. (2.63 gm, 88 % yield)



67

IR (KBr): 1150, 1742, 2891, 3380 cm^{-1}

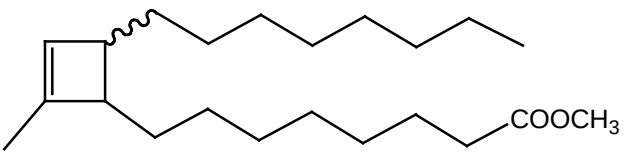
^{1}H NMR (400MHz, $CDCl_3$): δ 0.95 (3H, t, *J* = 7.00 Hz, CH_3), 1.10-1.50 (26H, s, $13CH_2$), 1.61 (3H, s, CH_3), 1.73 (2H, m, 2CH), 1.88 (1H, s, OH), 2.19 (2H, m, CH_2), 2.30 (2H, t, *J* = 10 Hz, CH_2), 3.66 (3H, s, CH_3).

^{13}C NMR (100MHz, $CDCl_3$): δ 13.92, 21.23 (2C, CH_3), 24. 21, 25.47, 27.50, 27.87, 28.08, 28.67, 28.87, 29.16, 29.35, 29.91, 30.01, 31.32, 32.62, 37.45, 48.65 (15C, CH_2), 51.34, 52.49 (2C, CH), 54.98 (1C, CH_3), 71.94 (1C, Cq), 174.19 (1C, CO)

MS (ESI): m/z calculated for $C_{22}H_{42}O_3$: 354.31; found 354.0 (M^+).

Synthesis of alkene (68):

A solution of H_2SO_4 in toluene (1 %) (5 ml) was added to a stirred solution of hydroxy ester (**67**) (2.50 g, 0.007 mol) in dry toluene (20 ml) at 0 °C. The stirring was further continued for 45 min with the maintained temperature 0 °C. The reaction mixture was allowed to warm upto room temperature and poured into a saturated solution of sodium bicarbonate to neutralise the excess acid. The products were extracted in ethyl acetate (25 ml x 3), washed successively with water, brine and dried over anhydrous sodium sulphate and concentrated in rotator evaporator under reduced pressure to give the crude product as a thick liquid. Column chromatography of the crude product over a column of silica gel using light petroleum ethyl acetate as eluents furnished an inseparable mixture of colourless liquid (**68**) (1.60 gm, 67 % yield) and (**72**) (0.12 gm, 5.00 % yield).



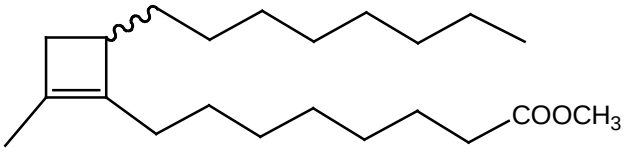
68

IR (KBr): 1435, 1458, 1743, 2924, 3005 cm^{-1}

^{1}H NMR (400 MHz $CDCl_3$): δ 0.89 (3H, t, *J* = 7.2 Hz, CH_3), 1.20-1.4 (20H, m, $10CH_2$), 1.50-1.68 (8H, m, $4CH_2$), 1.97-2.06 (2H, m, 2CH), 2.31 (3H, s, CH_3), 3.67 (3H, s, CH_3), 4.69 (1H, d, *J* = 2.6 Hz, olefinic).

^{13}C NMR (100 MHz): δ 14.00, 19.37 (2C, CH_3), 19.97-34.42 (14C, CH_2), 33.63, 34.12, (2C, CH), 50.30 (1C, CH_3), 130.56, 132.48 (2C, olefinic), 174.74 (1C, CO).

MS (EI): m/z calculated for $C_{22}H_{40}O_2$: 336.31; found 335.81 (M^+).



72

IR (KBr): 1435, 1458, 1743, 2924, 3005 cm^{-1}.

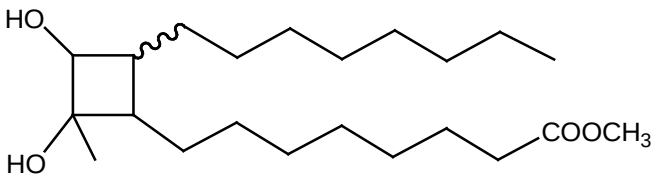
^{1}H NMR (400 MHz $CDCl_3$): δ 0.89 (3H, t, *J* = 7.2 Hz, CH_3), 1.20-1.4 (20H, m, $10CH_2$), 1.50-1.68 (8H, m, $4CH_2$), 1.97-2.06 (1H, m, CH), 2.31 (3H, s, CH_3), 2.58 (2H, m, CH_2), 3.43 (3H, s, CH_3).

^{13}C NMR (100 MHz): δ 14.00, 19.37 (2C, CH_3), 19.97-32.83 (15C, CH_2), 44.84 (1C, CH), 51.50 (1C, CH_3), 130.56, 132.48 (2C, olefinic), 174.74 (1C, CO).

MS (EI): m/z calculated for $C_{22}H_{40}O_2$: 336.31; found 335.81 (M^+).

Synthesis of diol (69):

To a stirred mixture of (**68, 72**) (1.70 gm, 0.005 mol) in THF-water (1:1, 10 ml), a solution of potassium permanganate (1gm, 0.006 mol) was added over a period of 1h. The stirring was further continued for 3.5 h after which the reaction mixture was filtered on a celite pad and THF was removed under reduced pressure. The product was extracted with ethyl acetate (25 ml x 3). The combined extracts were washed with water, brine solution and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure furnished the crude product as an oily liquid, which was purified by column chromatography over a column of silica gel using a mixture of light petroleum/ethyl acetate as eluents. This exercise afforded the diol (**69**) as a colourless liquid (0.84 gm, 48 % yield).



69

IR (KBr): 1739, 2851, 2918, 3284 cm^{-1}

^{1}H NMR (400 MHz $CDCl_3$): δ 0.89 (3H, t, *J* = 7.2 Hz CH_3), 1.2-1.61 (24H, m, $12CH_2$), 1.64 (3H, CH_3 merged with signal of methylene groups), 1.82 (2H, m, CH_2), 2.19 (2H, s,

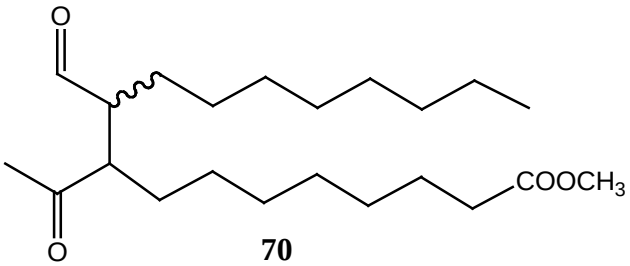
exchangeable OH), 2.29 (2H, t, J = 7.6 Hz, CH_2), 2.45 (2H, m, 2CH), 3.68 (2H, s, CH_3), 4.18 (1H, dd, J_1 = 7.2 Hz, J_2 = 3.20 Hz, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.12, 22.67 (2C, CH_3), 23.65, 24.78, 28.90, 29.01, 29.11, 29.32, 29.47, 30.98, 31.80, 31.85, 33.72, 33.77, 34.02, 34.05 (14C, CH_2), 37.79, 37.86 (2C, CH), 51.52 (1C, CH_3), 74.33 (1C, CH), 75.53 (1C, Cq), 174.33 (1C, CO).

MS (EI): m/z calculated for $C_{22}H_{42}O_4$: 370.31; found 370.22 (M^+).

Synthesis of γ-keto aldehyde (70):

A solution of $NaIO_4$ (0.43 gm, 0.002 mol) in acetone - water (10 ml, 1:1) was added to a stirred solution of diol (**69**) (0.80 gm, 0.004 mol) in acetone-water (15 ml, 1:3) at 10 °C over a period of 15 min. The resulting mixture was further stirred for 1.5 h and then the reaction was quenched by addition of ethyl glycol (1.00 gm, 0.016 mol). The product was then extracted with ethyl acetate (25 ml x 3), washed with water, brine and dried using anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave the crude product as a thick yellow liquid which was chromatographed over a column of silica gel. Elution of the column using light petroleum ethyl acetate (90:10) afforded the γ-keto aldehyde (**70**) as a colourless liquid. (0.29 gm, 37 % yield).



70

IR (KBr): 1710, 1750, 2935, 2964 cm^{-1}.

^{1}H NMR (400MHz $CDCl_3$): δ 0.89 (3H, t, J = 6.8 Hz, CH_3), 0.96-1.71 (26H, m, $13CH_2$), 2.19 (3H, s, CH_3), 2.34 (2H, m, CH_2), 2.45 (2H, m, 2CH), 3.68 (3H, s, CH_3), 9.37 (1H, s, CHO)

^{13}C NMR (100 MHz, $CDCl_3$): δ 15.12, 19.24 (2C, CH_3), 23.65, 24.70, 24.83, 28.90, 29.01, 29.23, 29.43, 29.72, 30.70, 31.80, 33.70, 33.76, 33.92, 34.06 (14C, CH_2), 35.75, 37.87 (2C, CH), 51.52 (1C, CH_3), 174.33, 196.23, 198.93 (3C, CO).

MS (EI): m/z calculated for $C_{22}H_{40}O_4$: 368.29; found 368.11 (M^+).

2.5 Conclusion

We have made an attempt to design and develop a synthetic route towards construction of Levuglandin skeleton, however no stereochemical separation is attempted at this stage. Depending upon the functionalities on two long side chains, the starting long chain alkene can be suitably modified for the synthesis of specific levuglandins.

2.6 References

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2.7 Spectral data of compounds

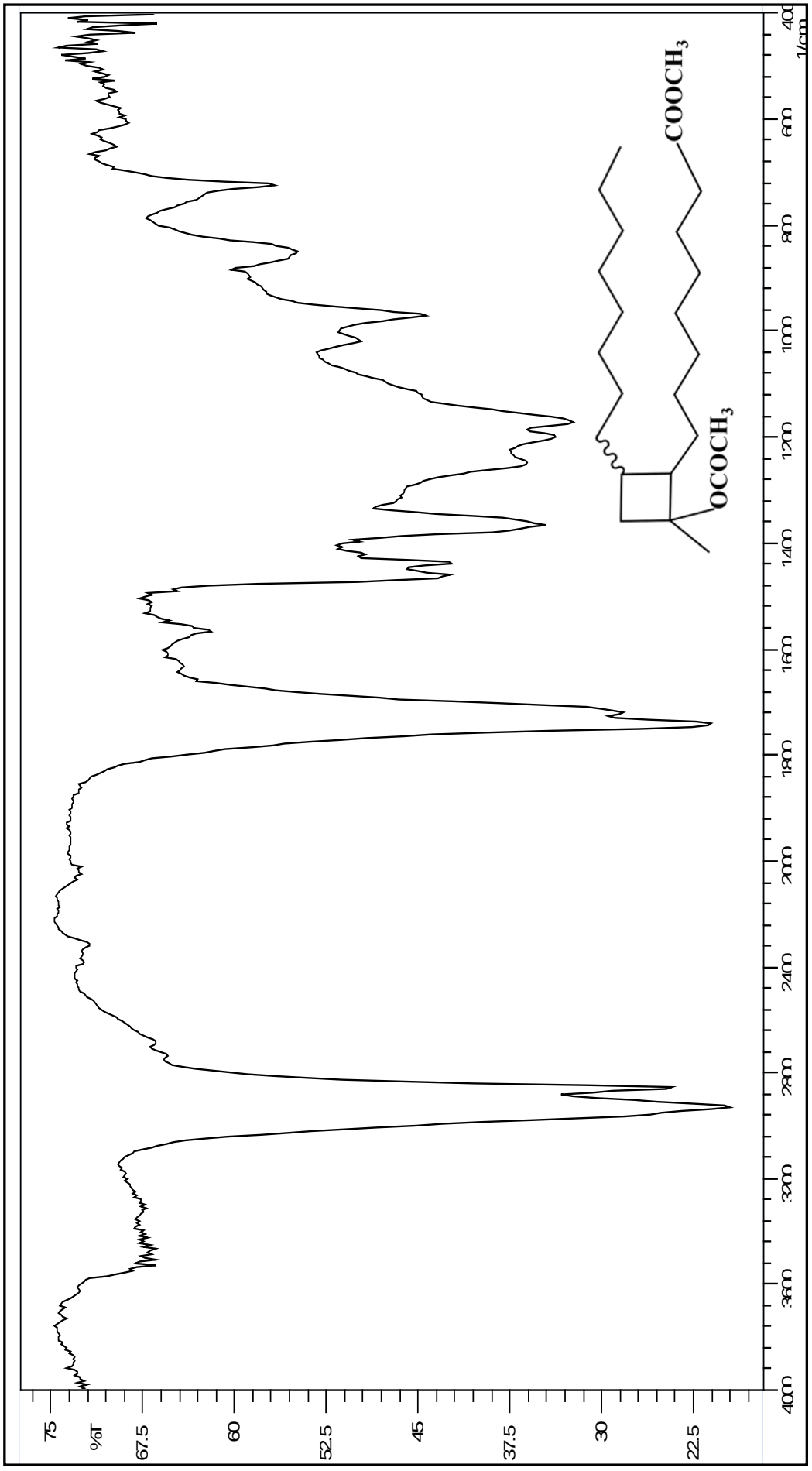


Figure 2.4: FTIR spectrum of compound **63**

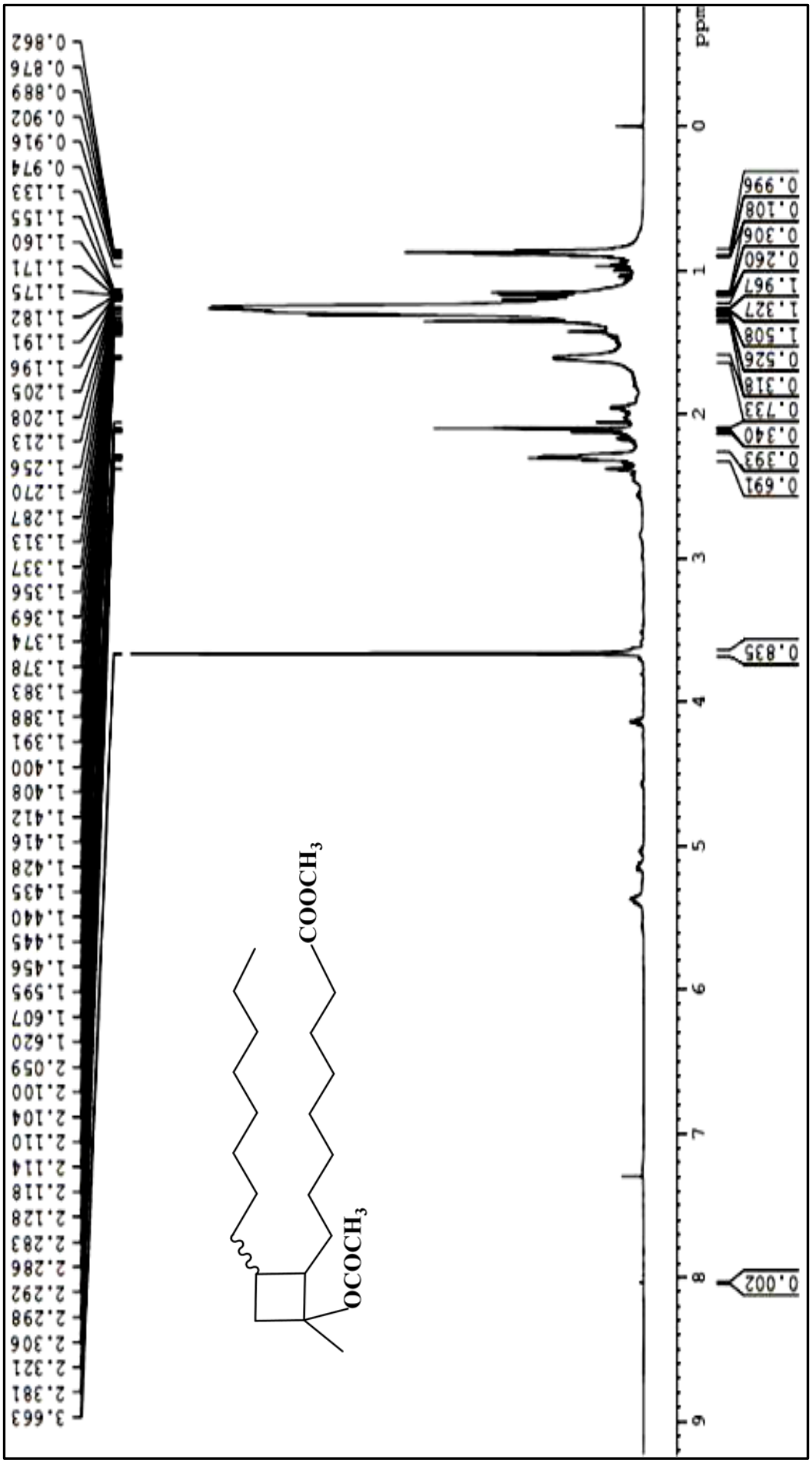


Figure 2.5: ^{1}H NMR spectrum of compound **63**

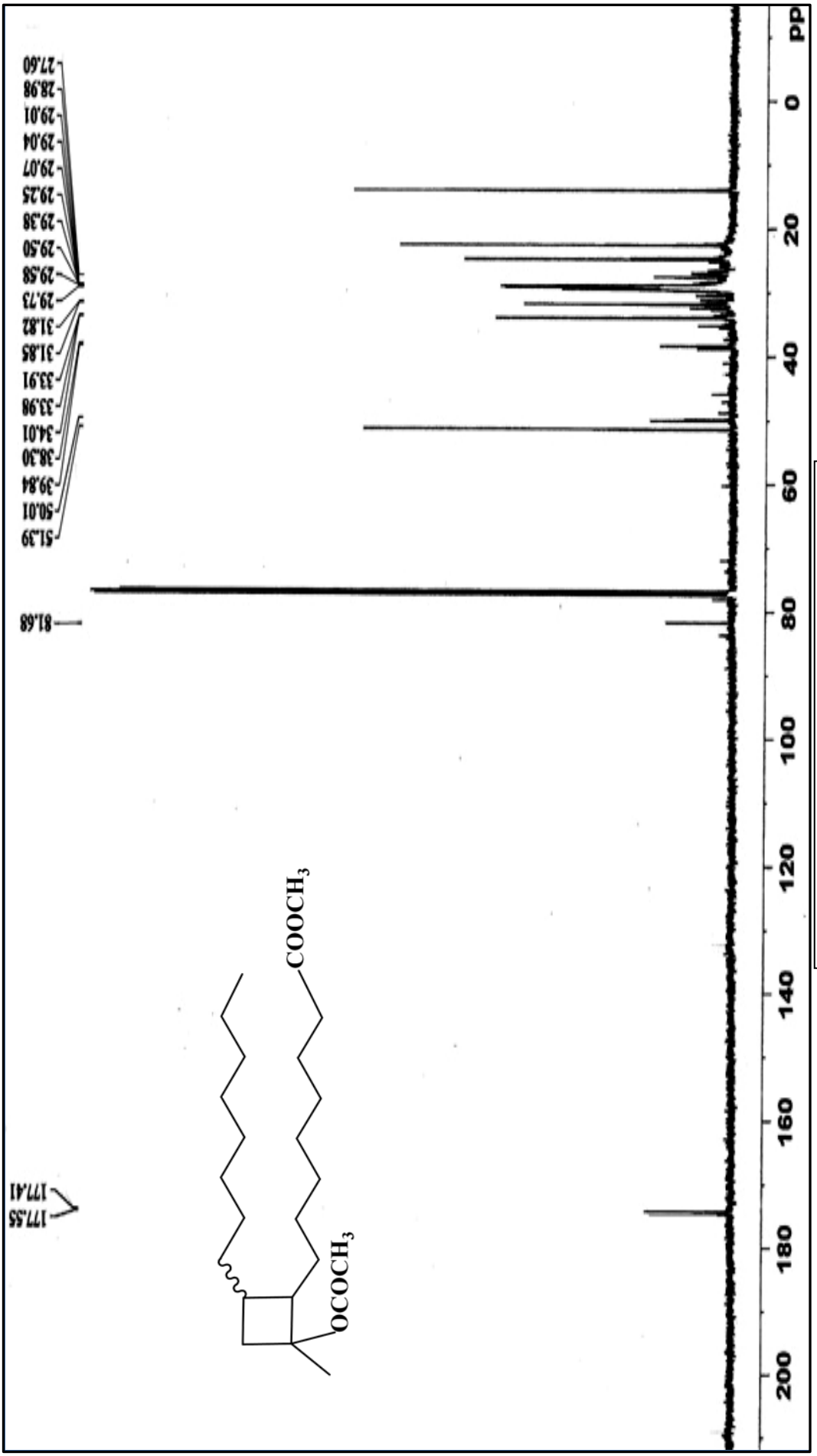


Figure 2.6: ^{13}C NMR spectrum of compound **63**

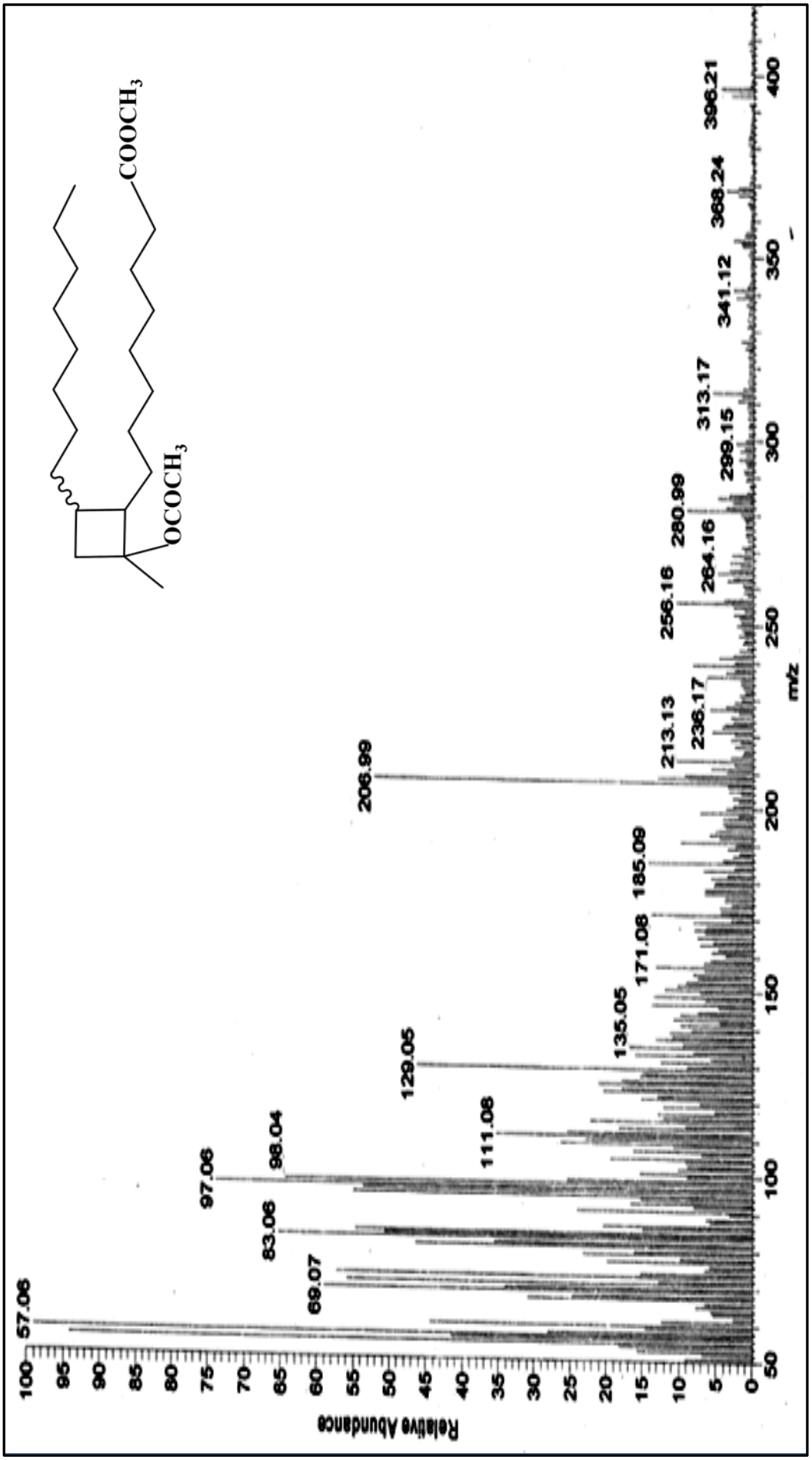


Figure 2.7: EI-MS spectrum of compound **63**

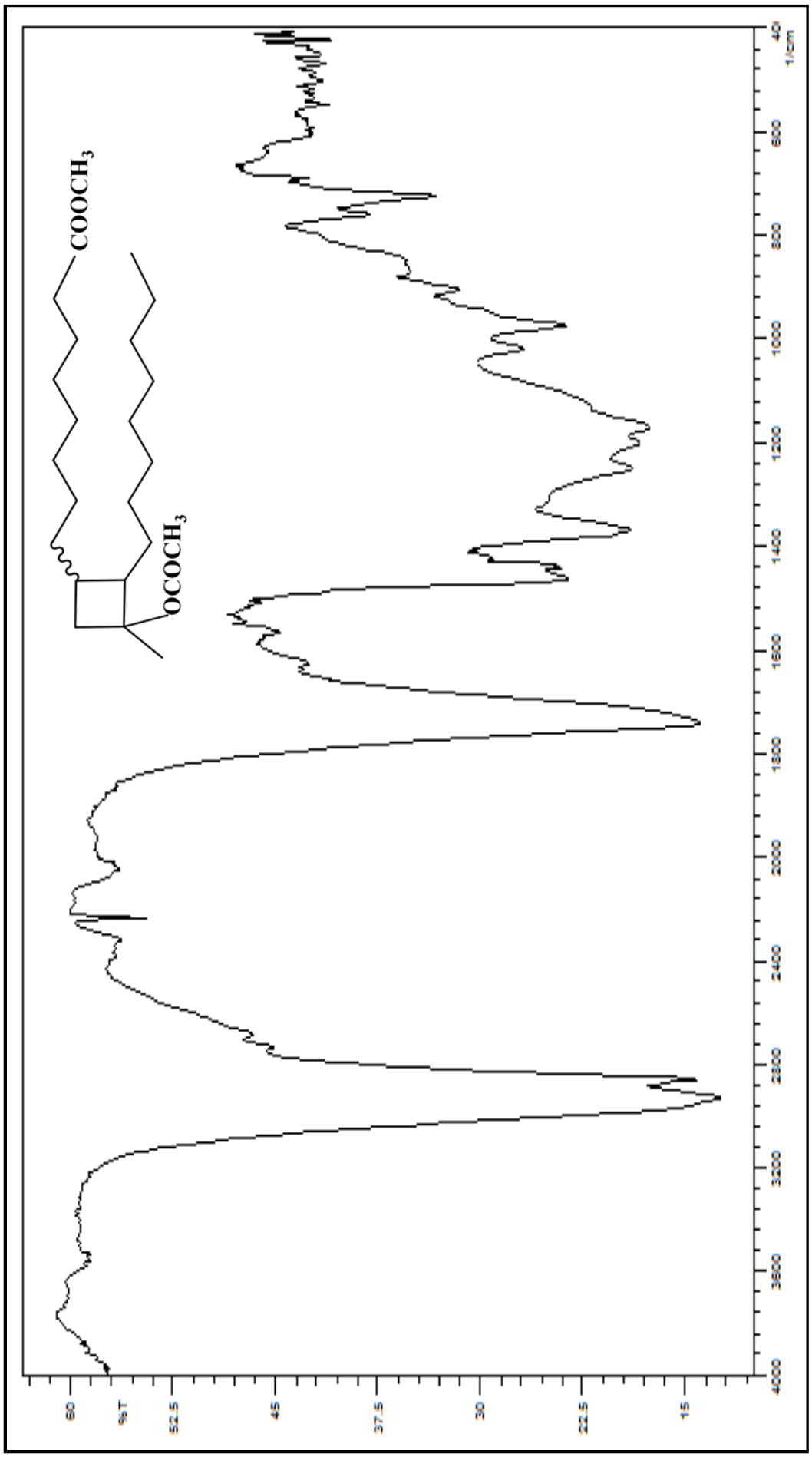


Figure 2.8: FTIR spectrum of compound **64**

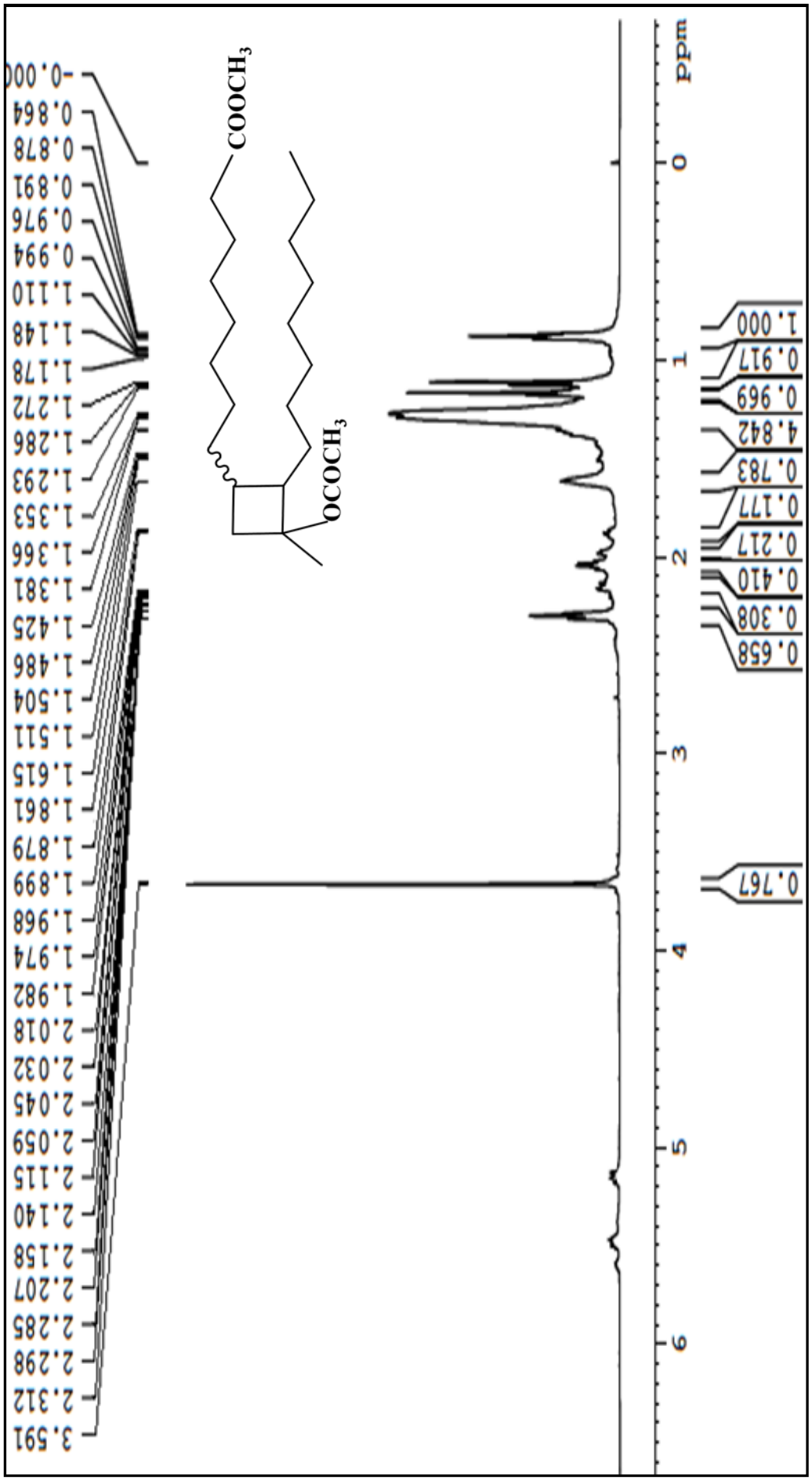


Figure 2.9: ^{1}H NMR spectrum of compound **64**

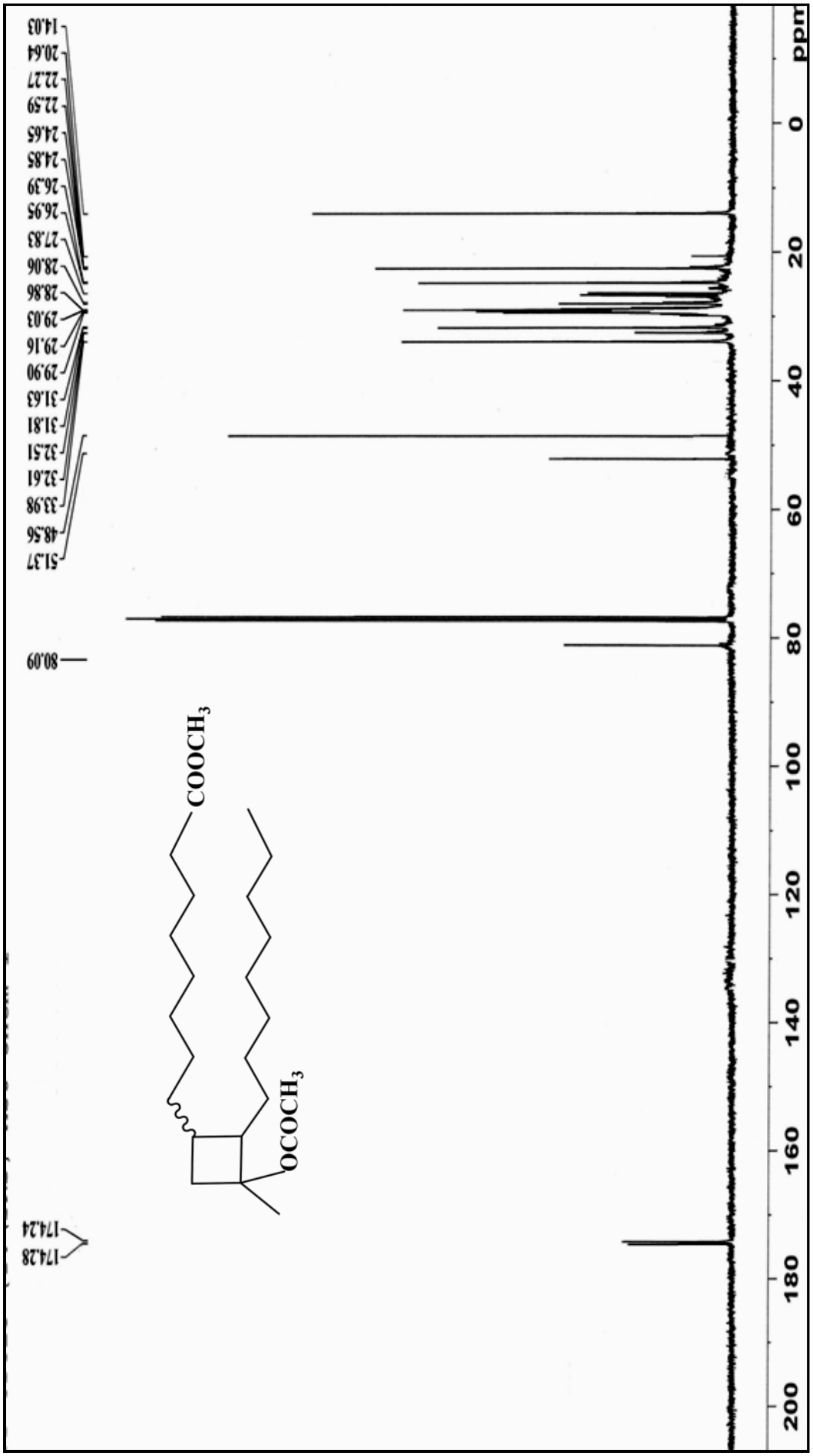


Figure 2.10: ^{13}C NMR spectrum of compound **64**

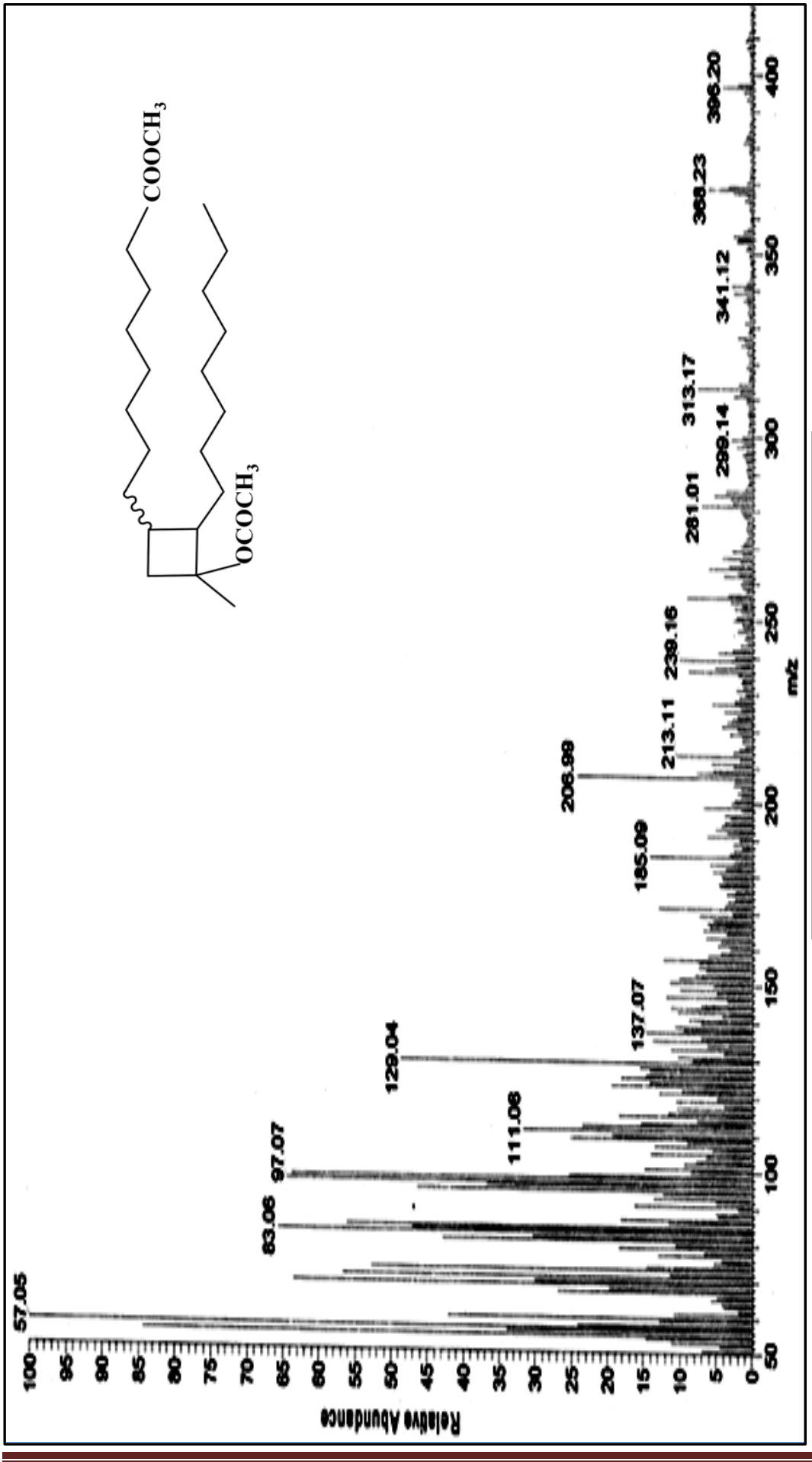


Figure 2.11: EI-MS spectrum of compound **64**

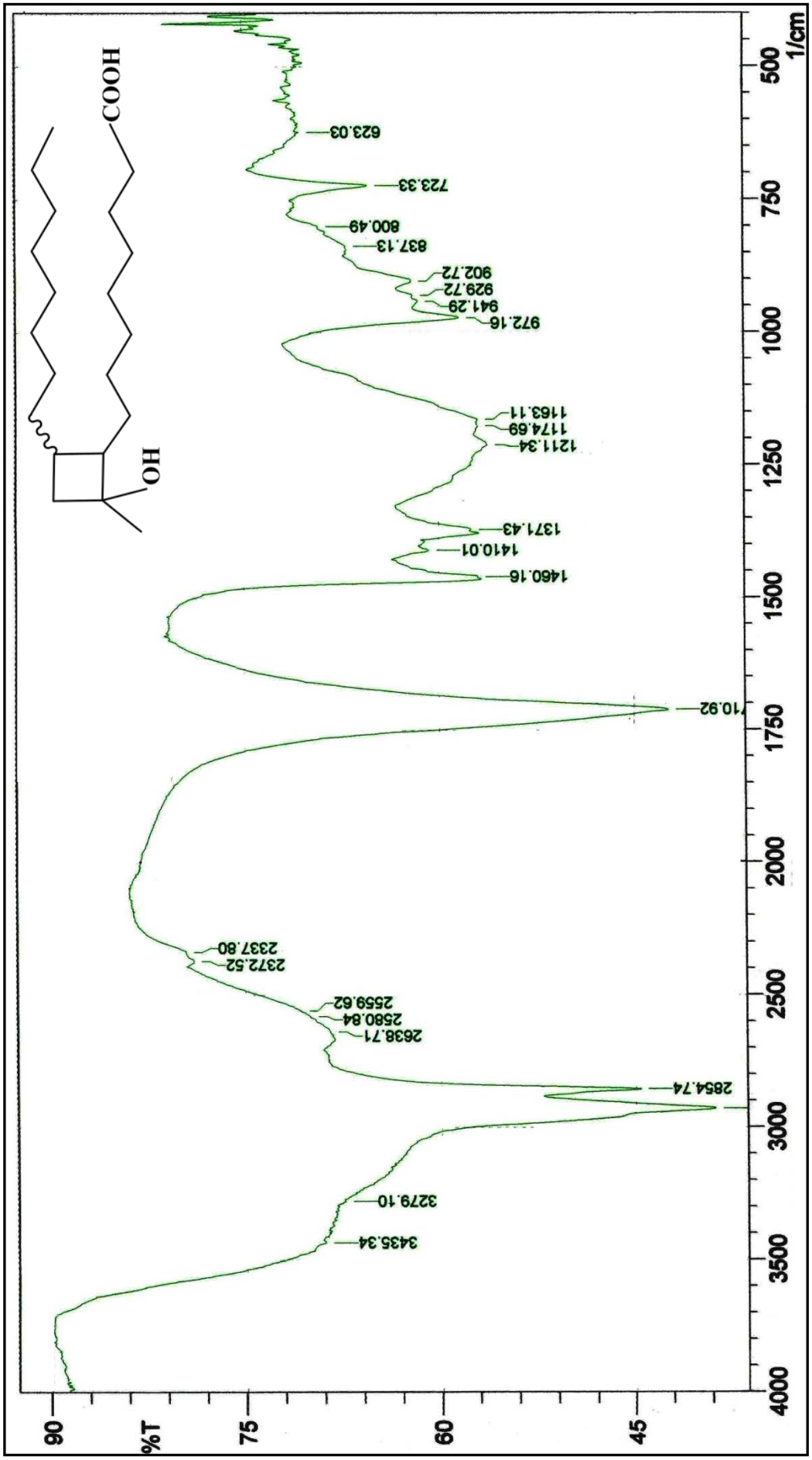


Figure 2.12: FTIR spectrum of compound **65**

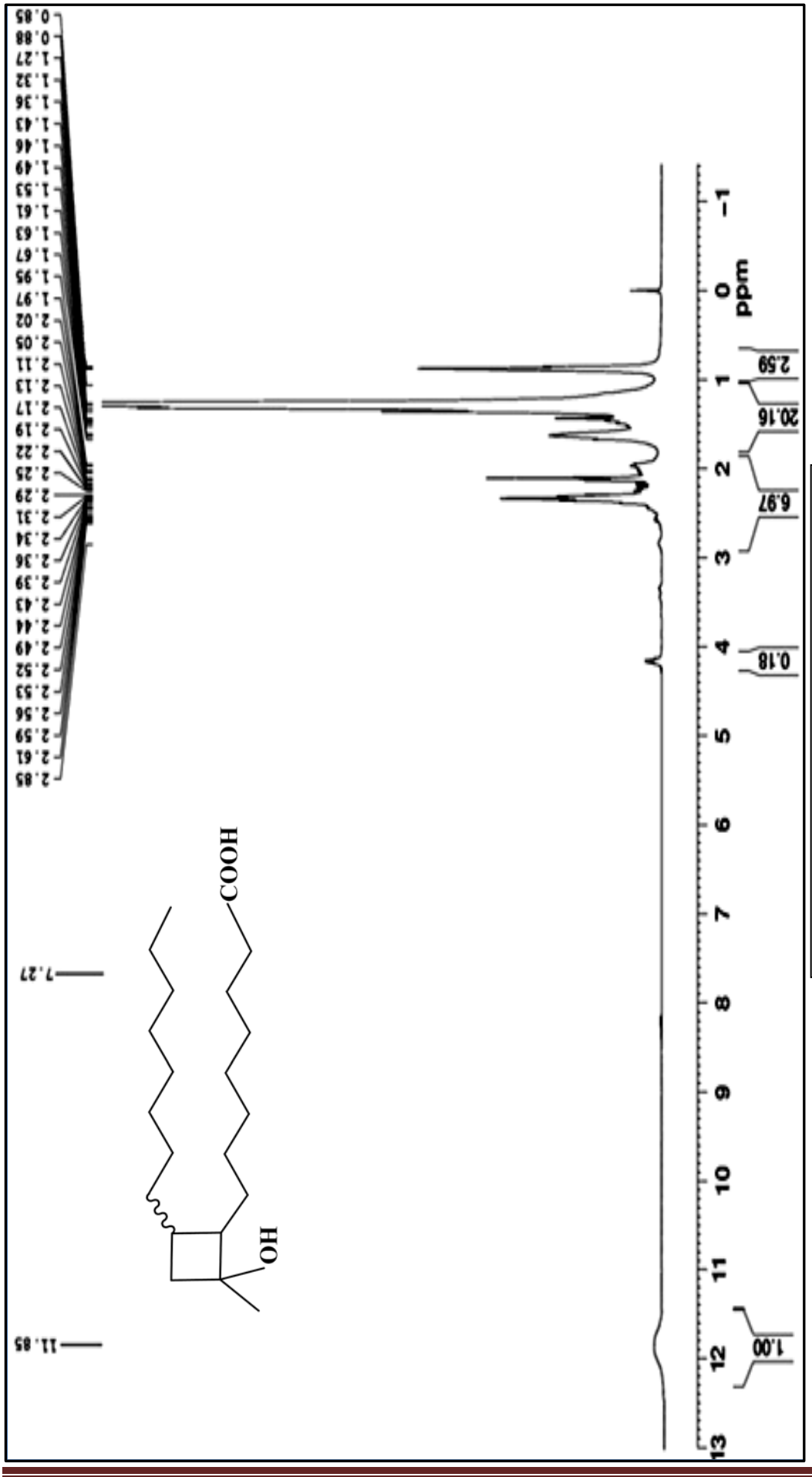


Figure 2.13: ^{1}H NMR spectrum of compound **65**

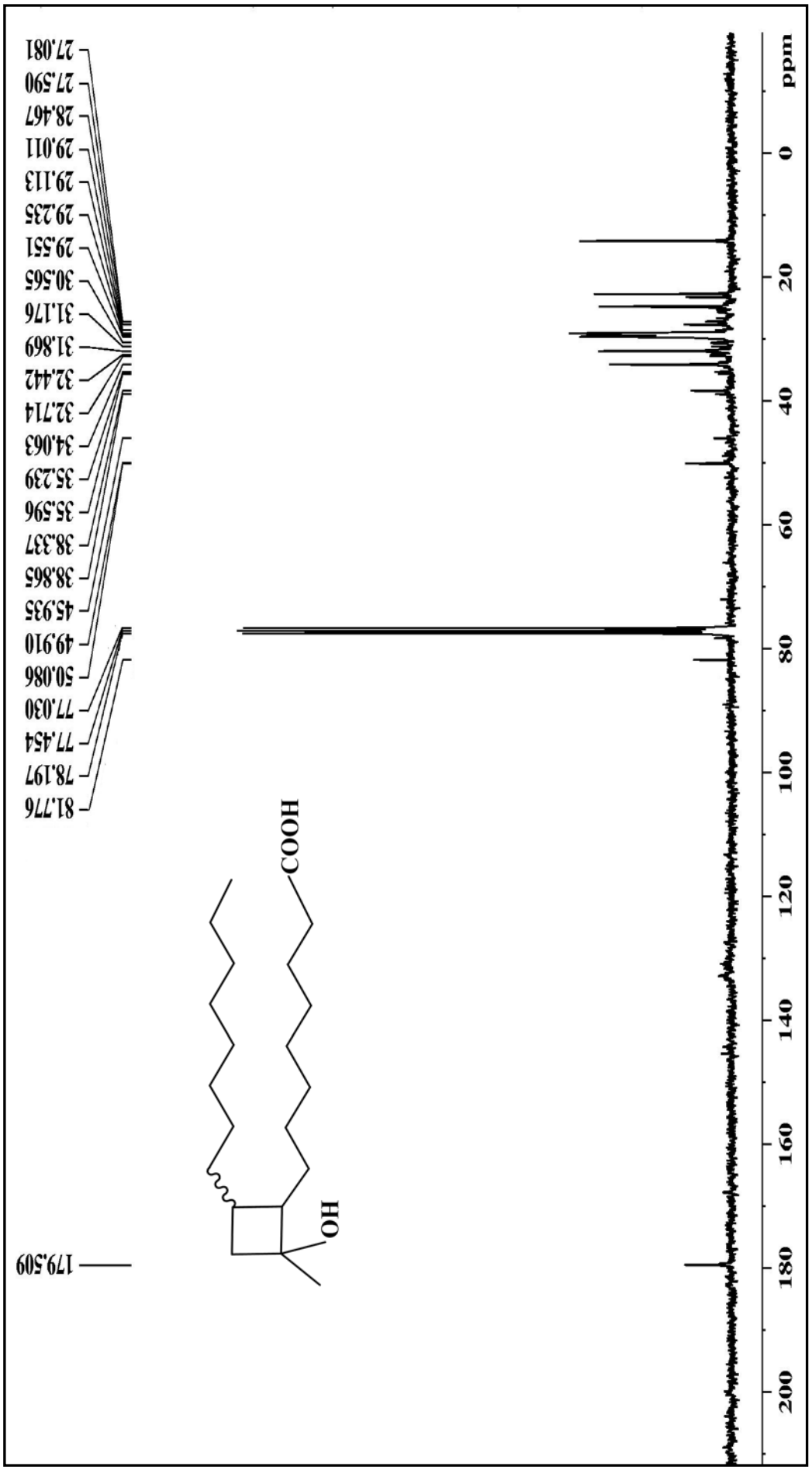


Figure 2.14: ^{13}C NMR spectrum of compound **65**

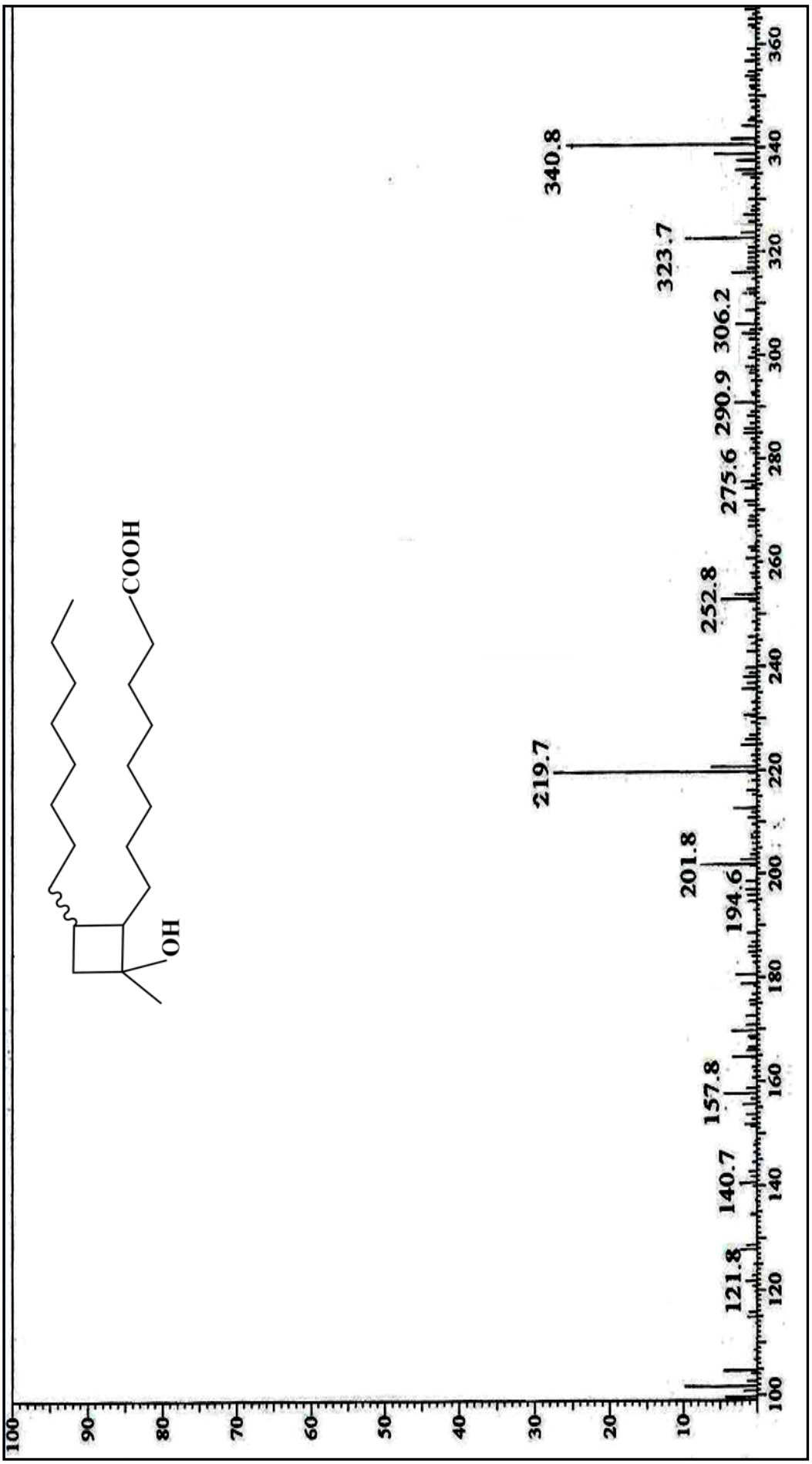


Figure 2.15: ESI-MS spectrum of compound **65**

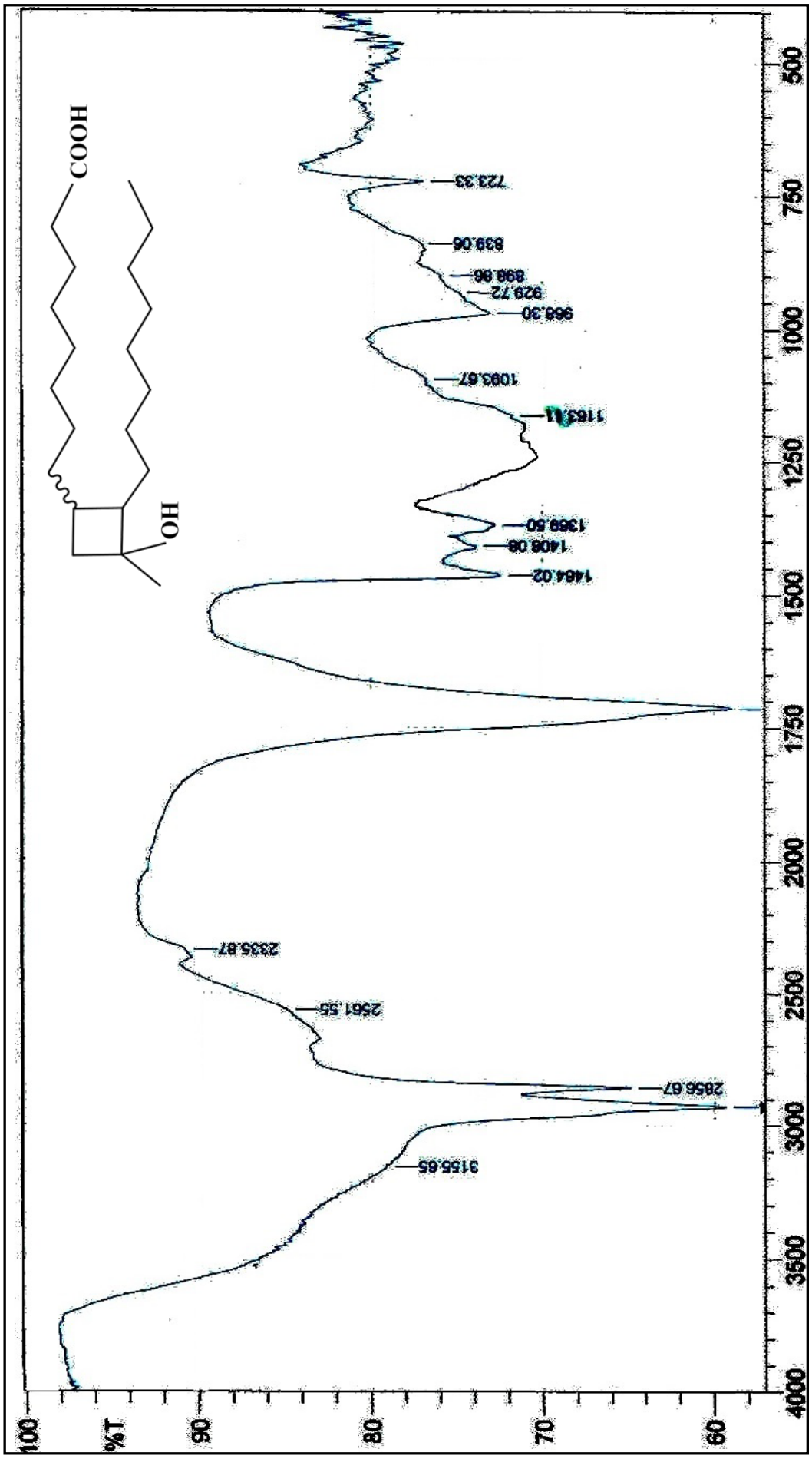


Figure 2.16: FTIR spectrum of compound **66**

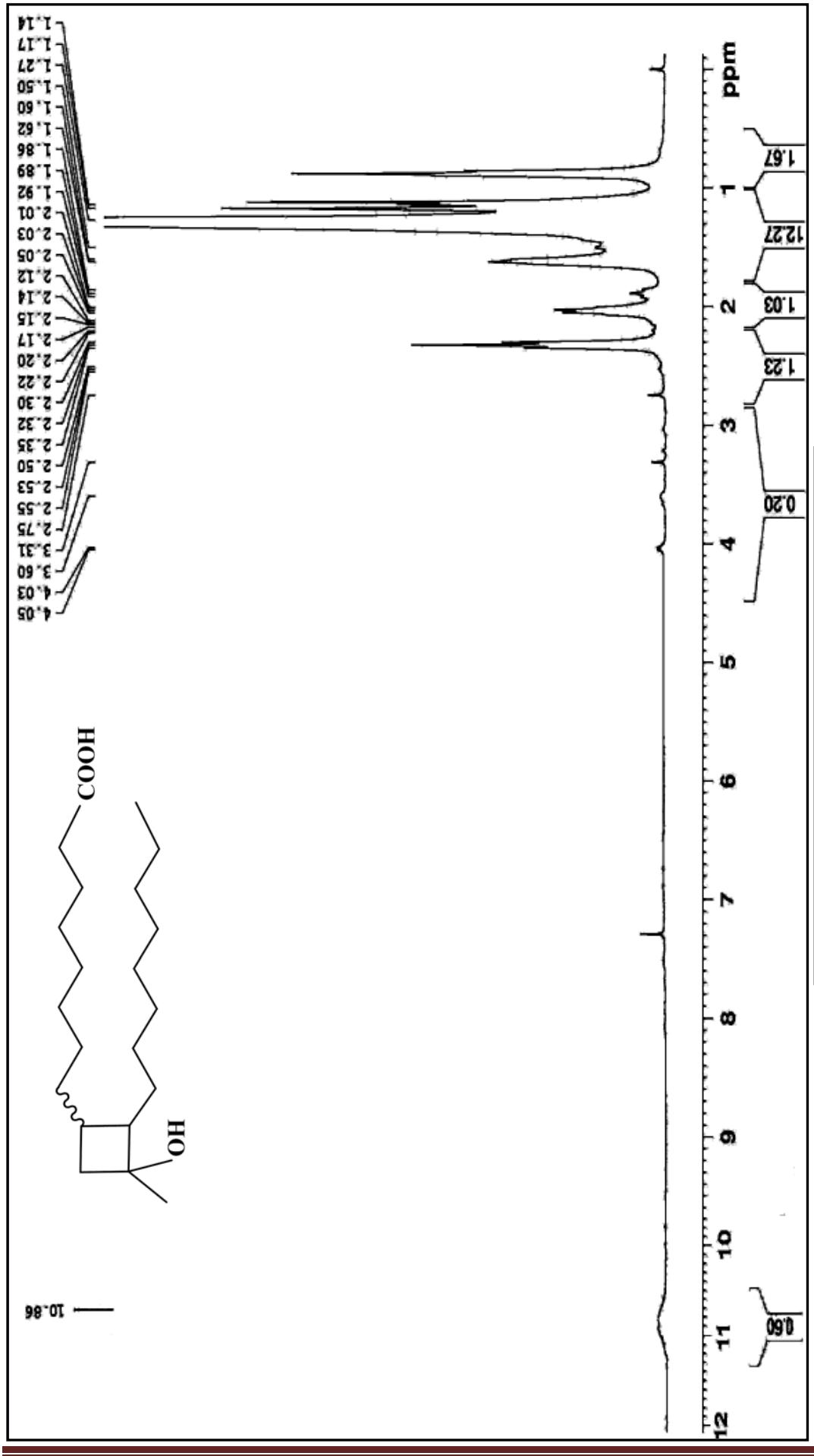


Figure 2.17: ^{1}H NMR spectrum of compound **66**

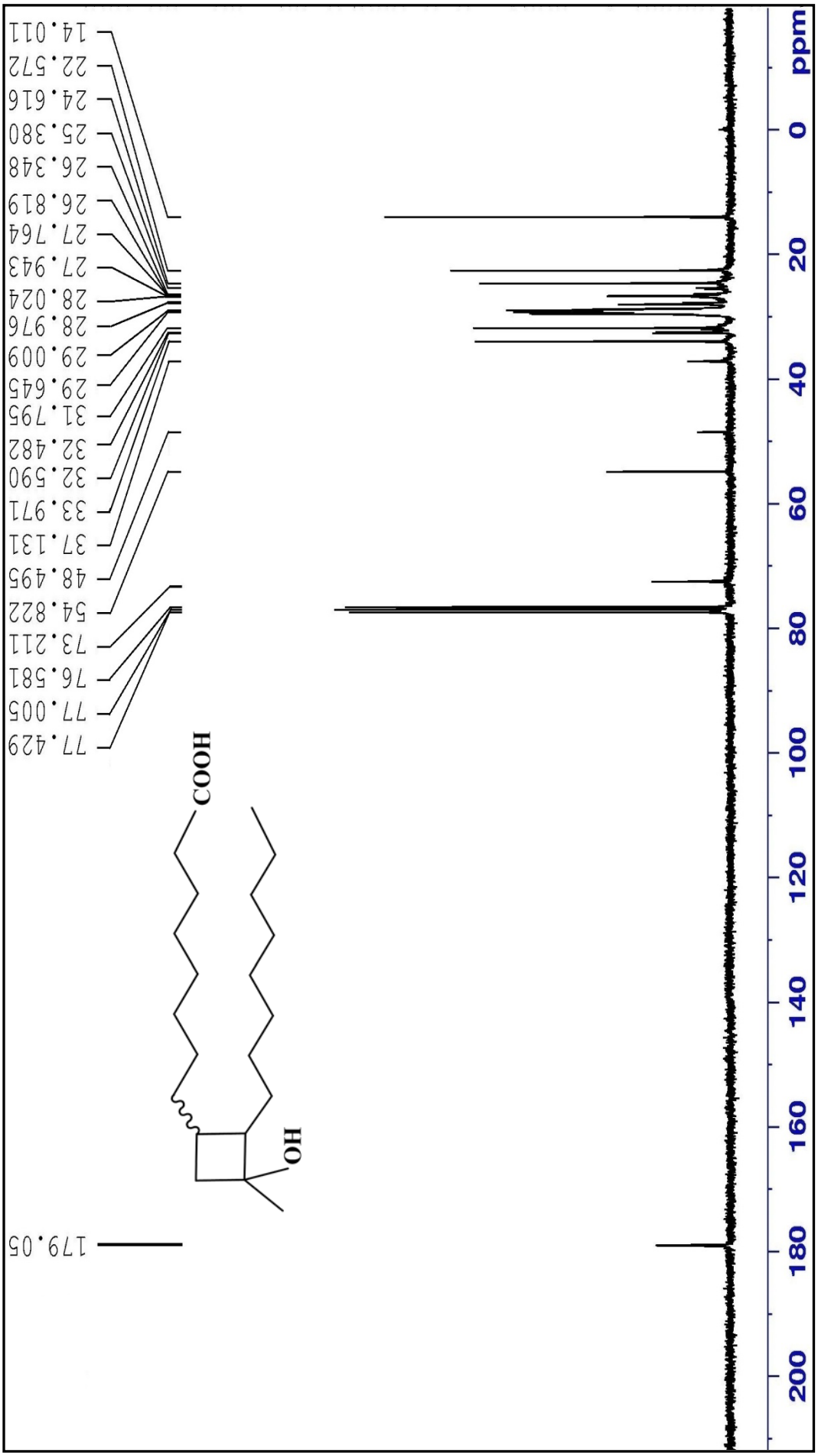


Figure 2.18: ^{13}C NMR spectrum of compound **66**

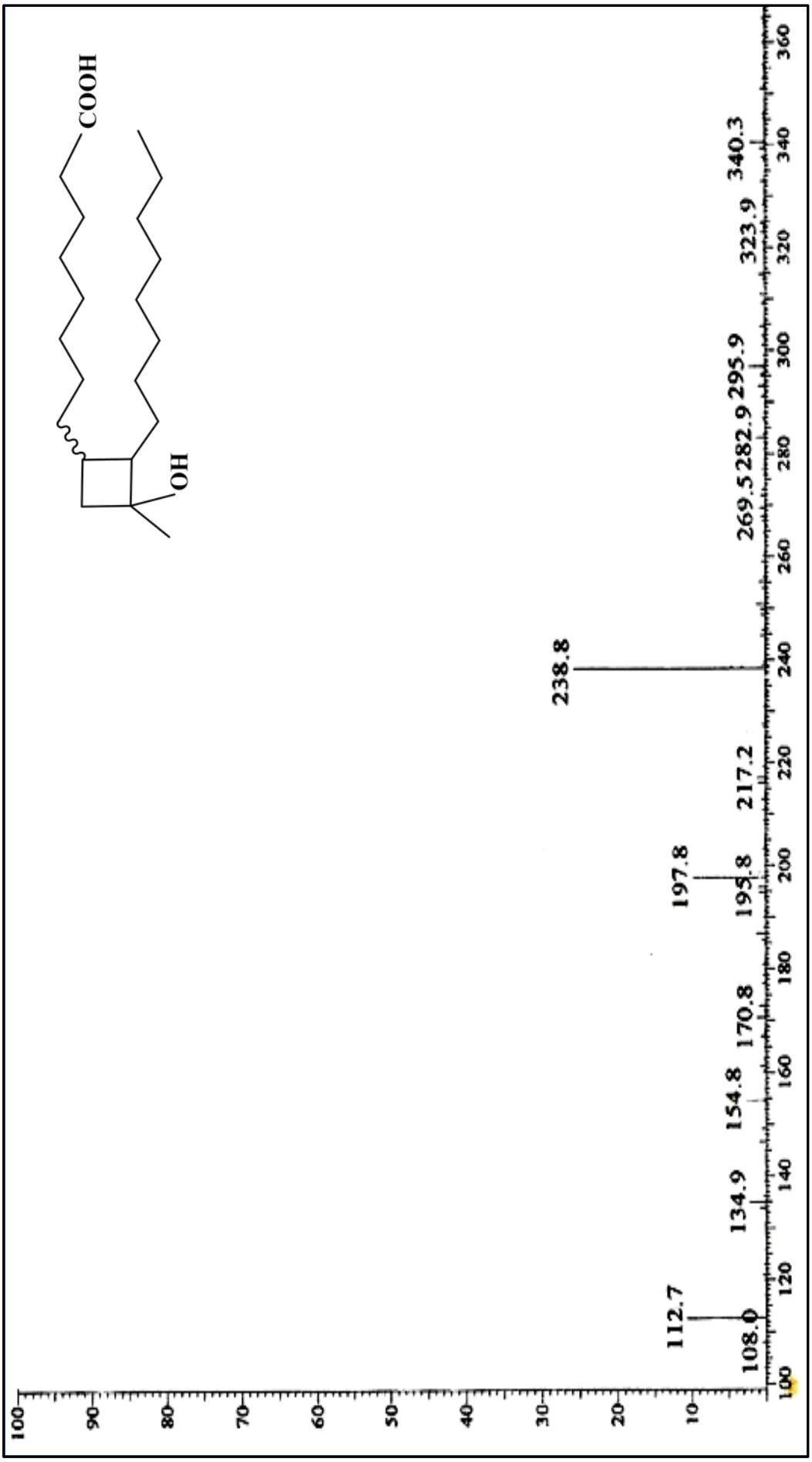


Figure 2.19: ESI-MS spectrum of compound **66**

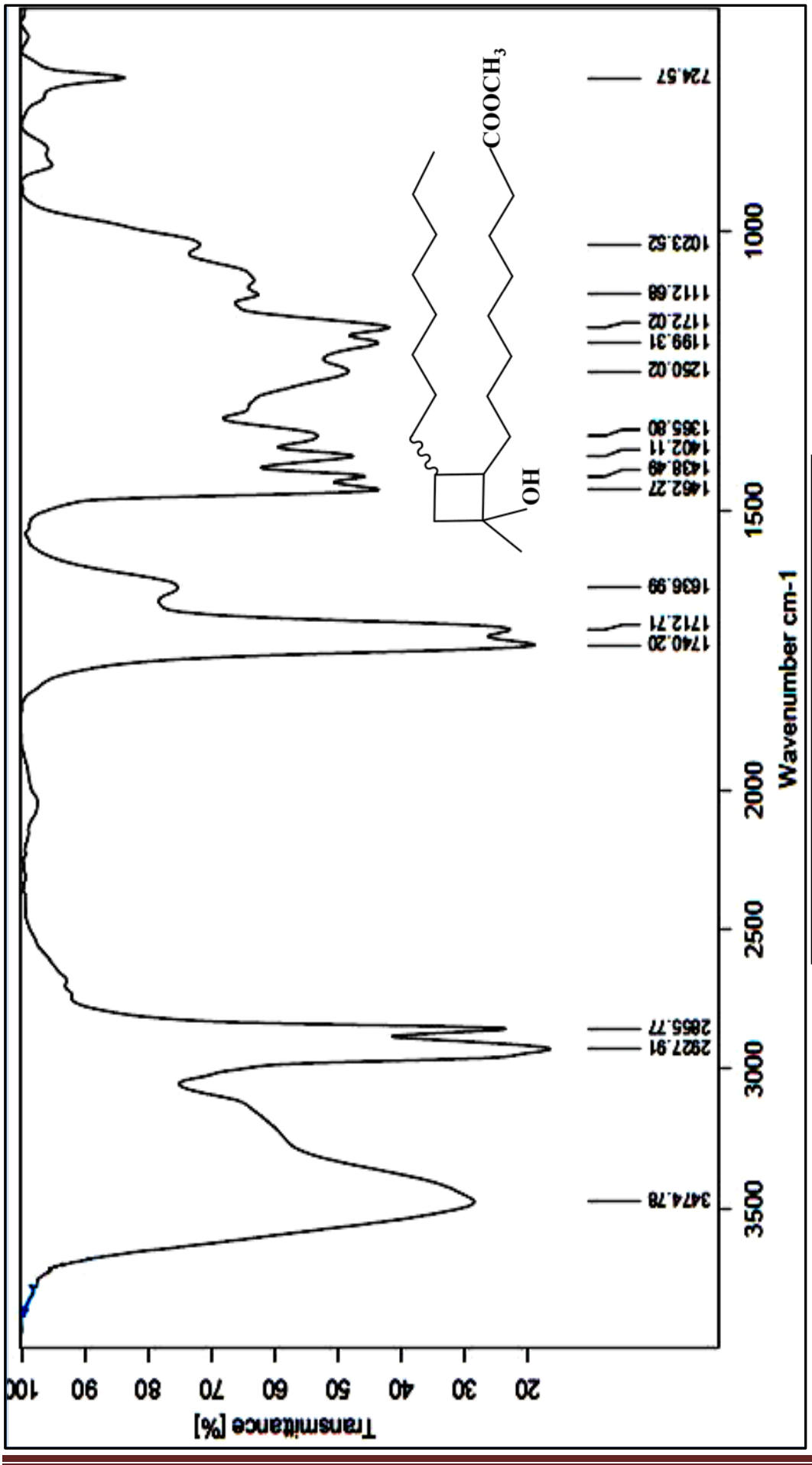


Figure 2.20: FTIR spectrum of compound **67**

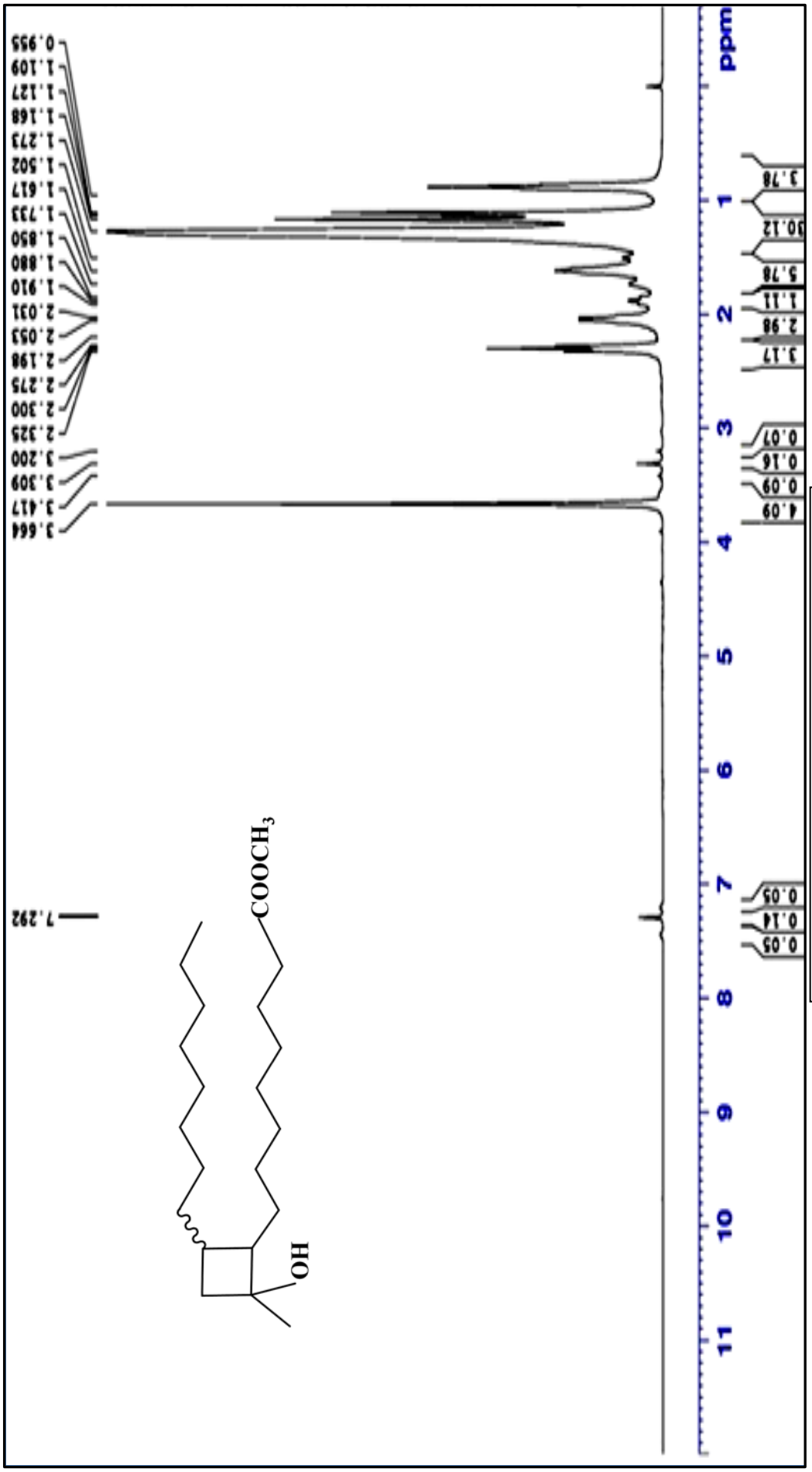


Figure 2.21: ^{1}H NMR spectrum of compound **67**

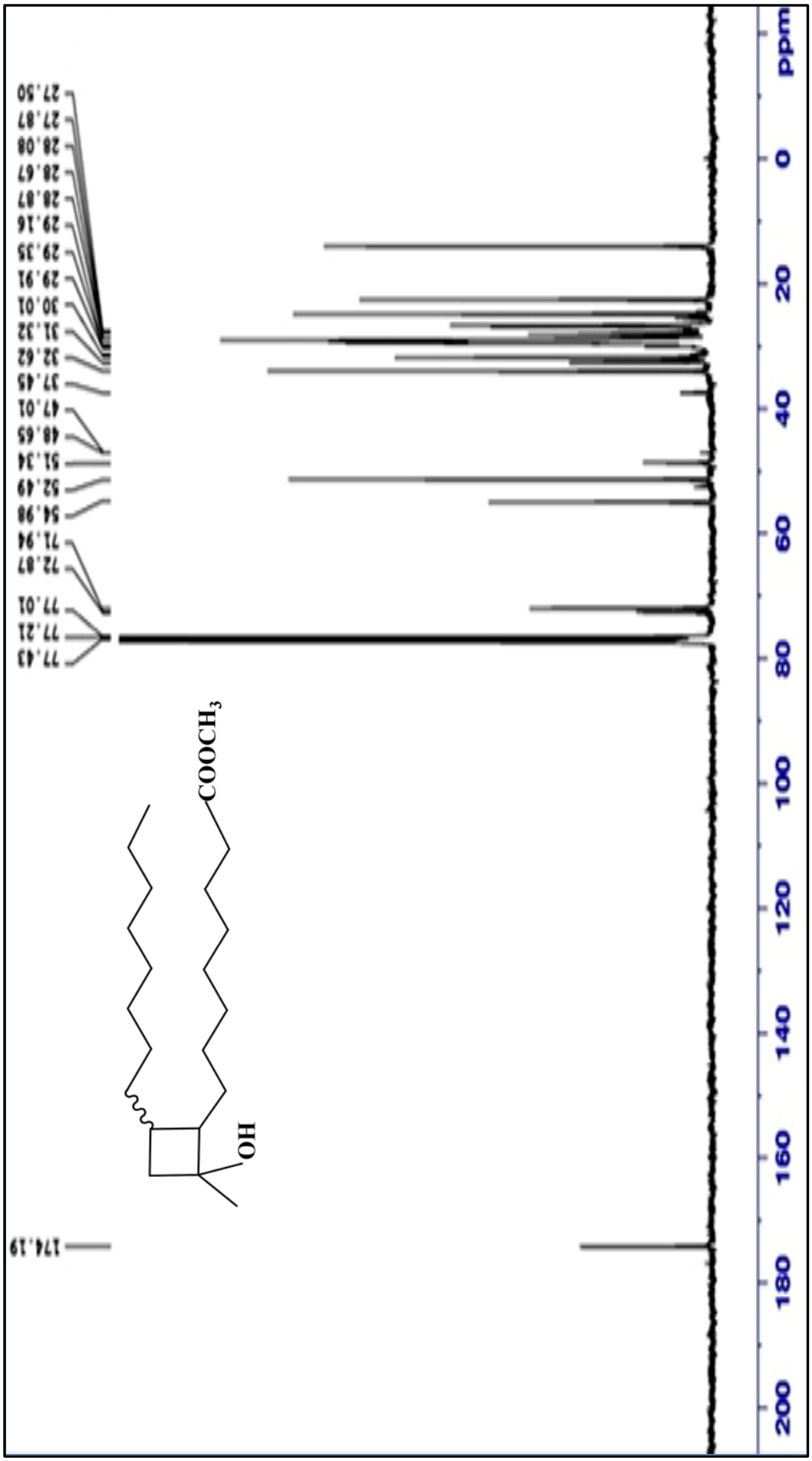


Figure 2.22: ^{13}C NMR spectrum of compound **67**

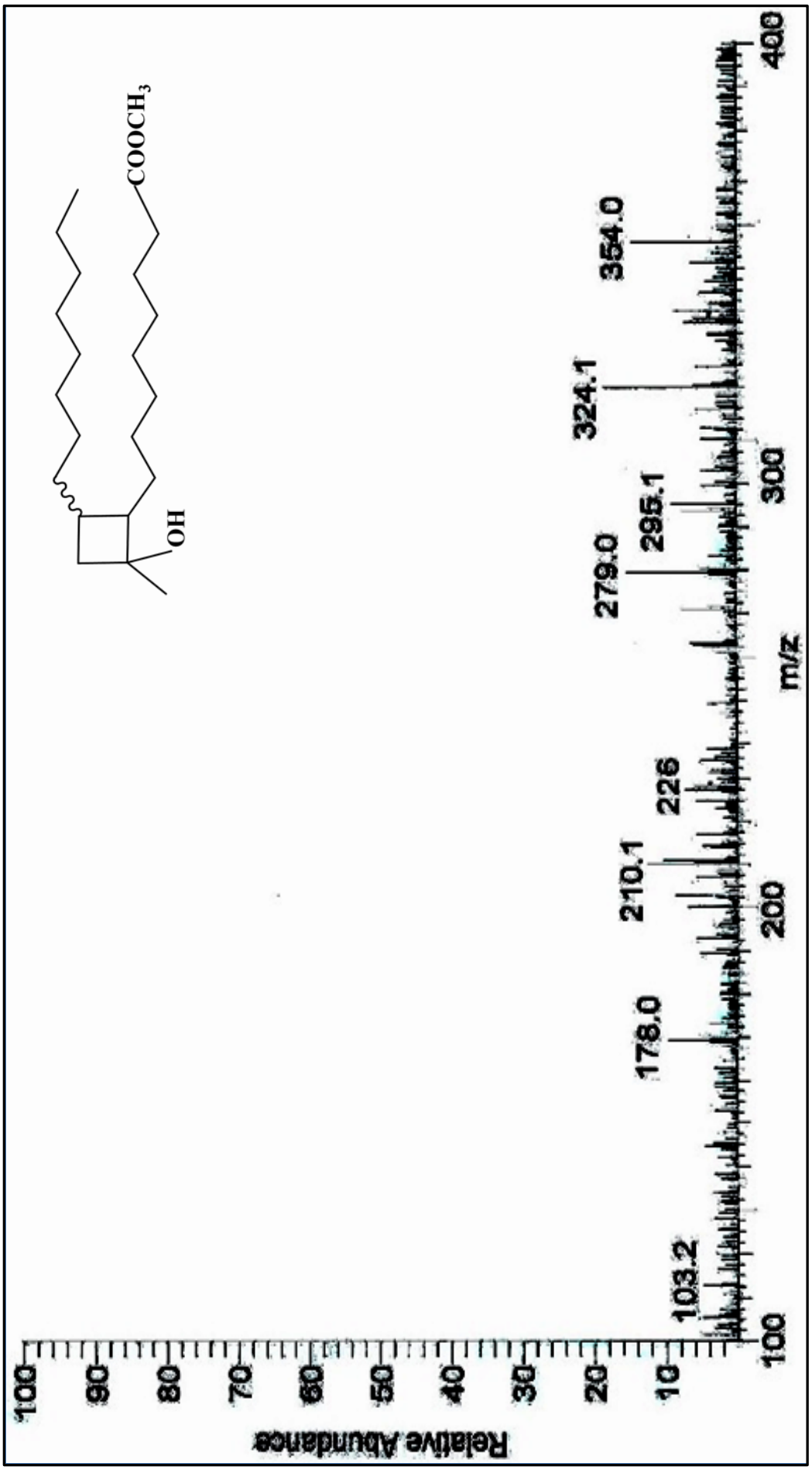


Figure 2.23: ESI-MS spectrum of compound **67**

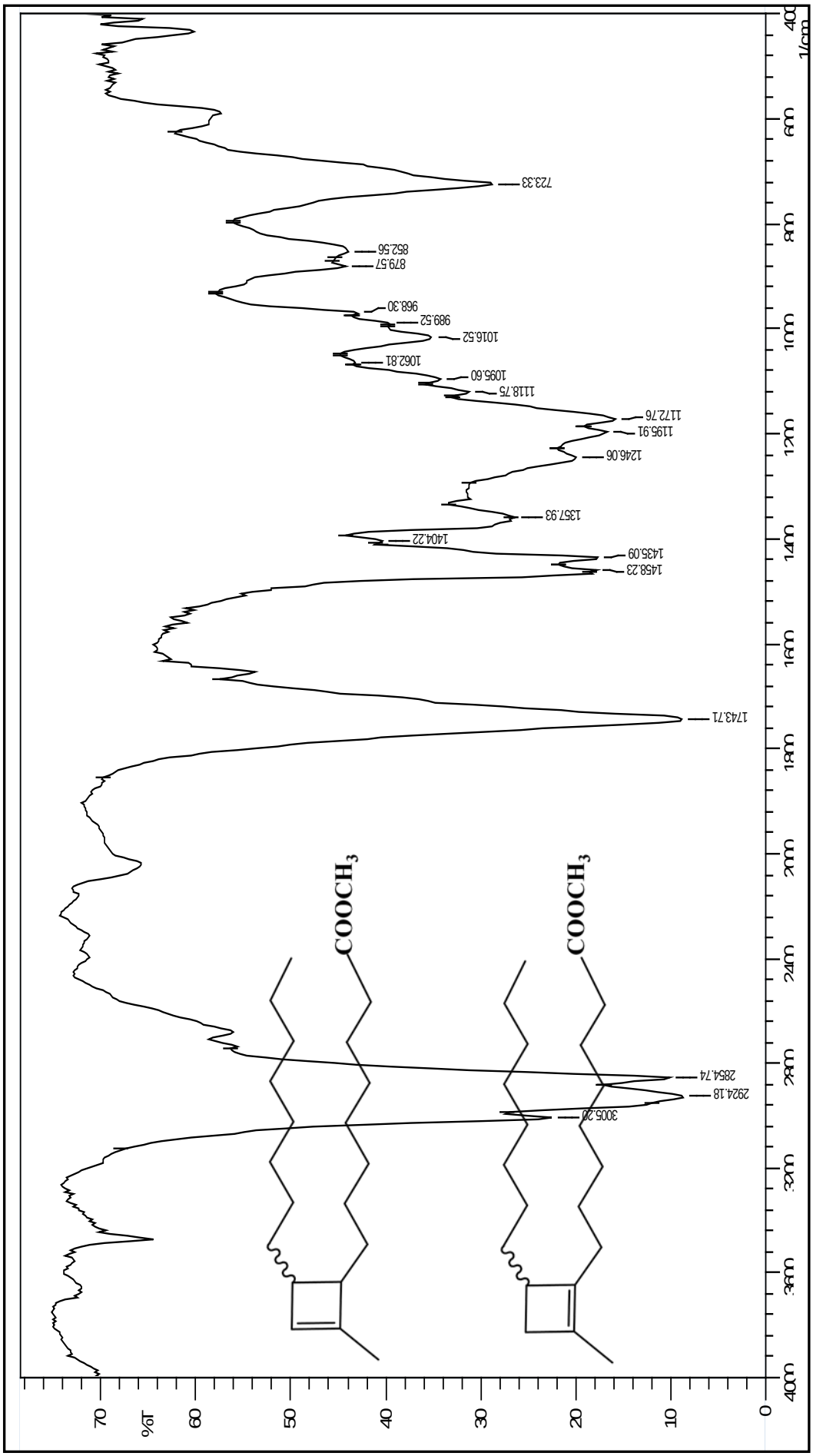


Figure 2.24: FTIR spectrum of compound **68** & **72**

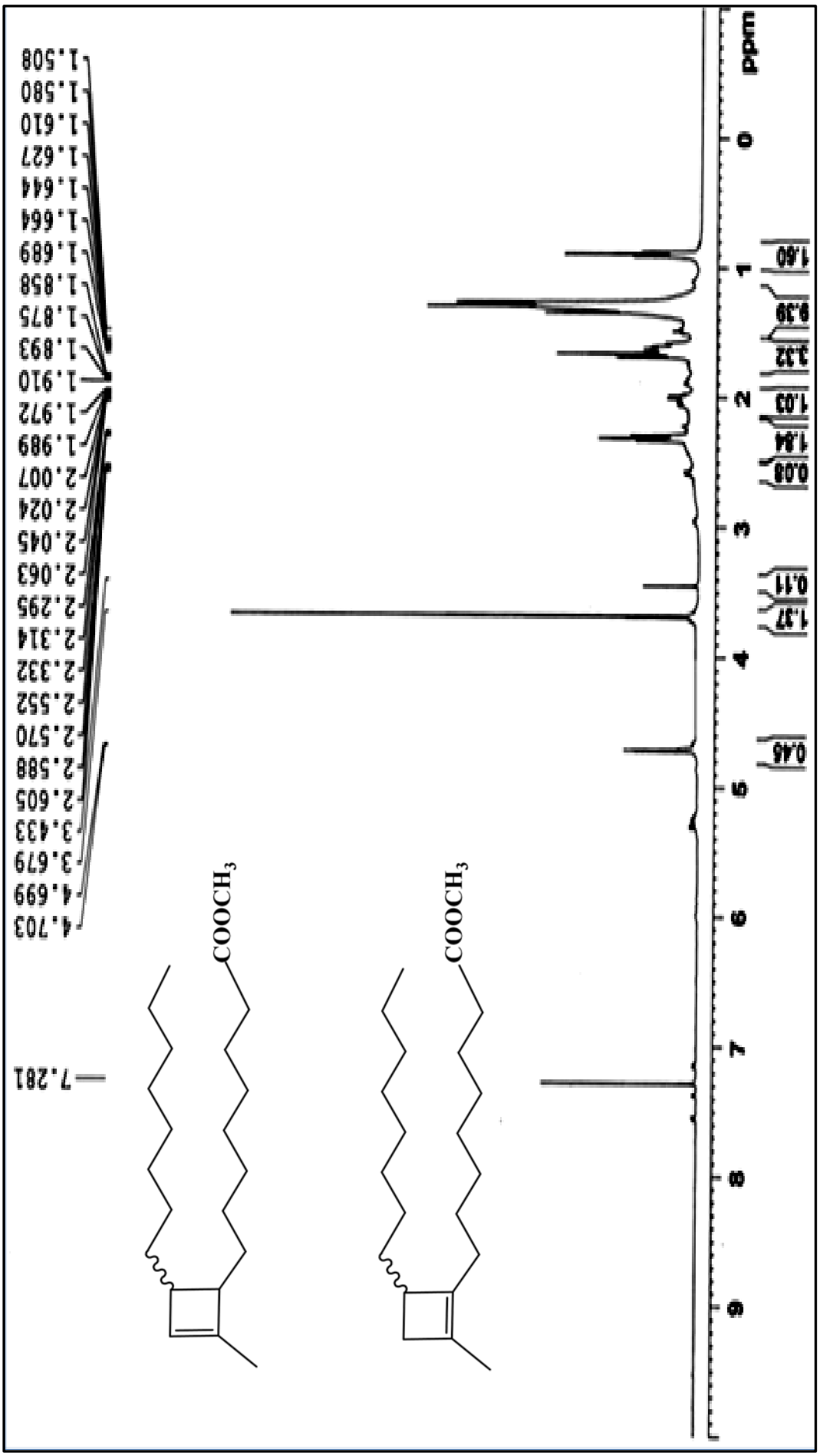


Figure 2.25: ^{1}H NMR spectrum of compound **68** & **72**

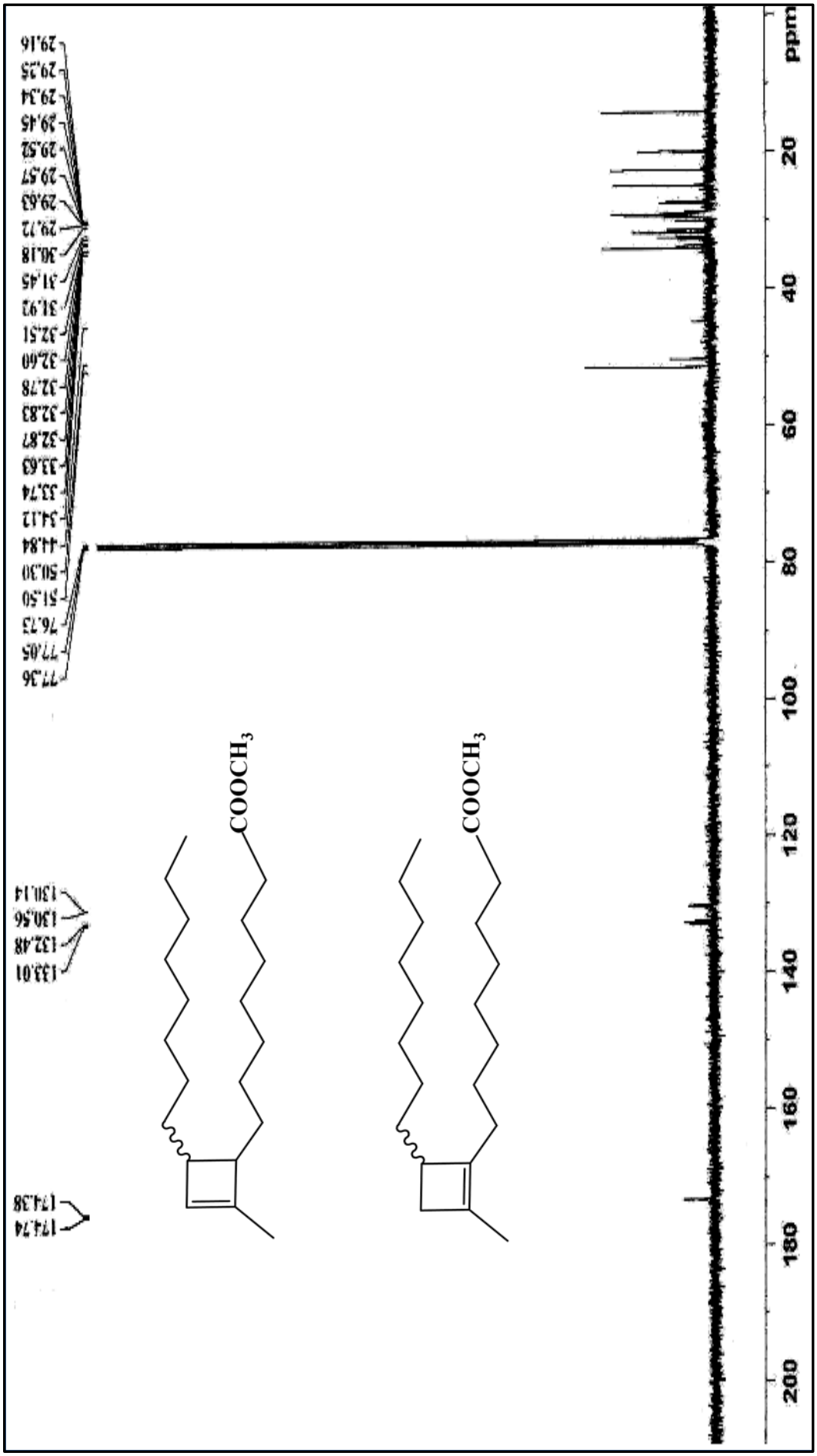


Figure 2.26: ^{13}C NMR spectrum of compound **68** & **72**

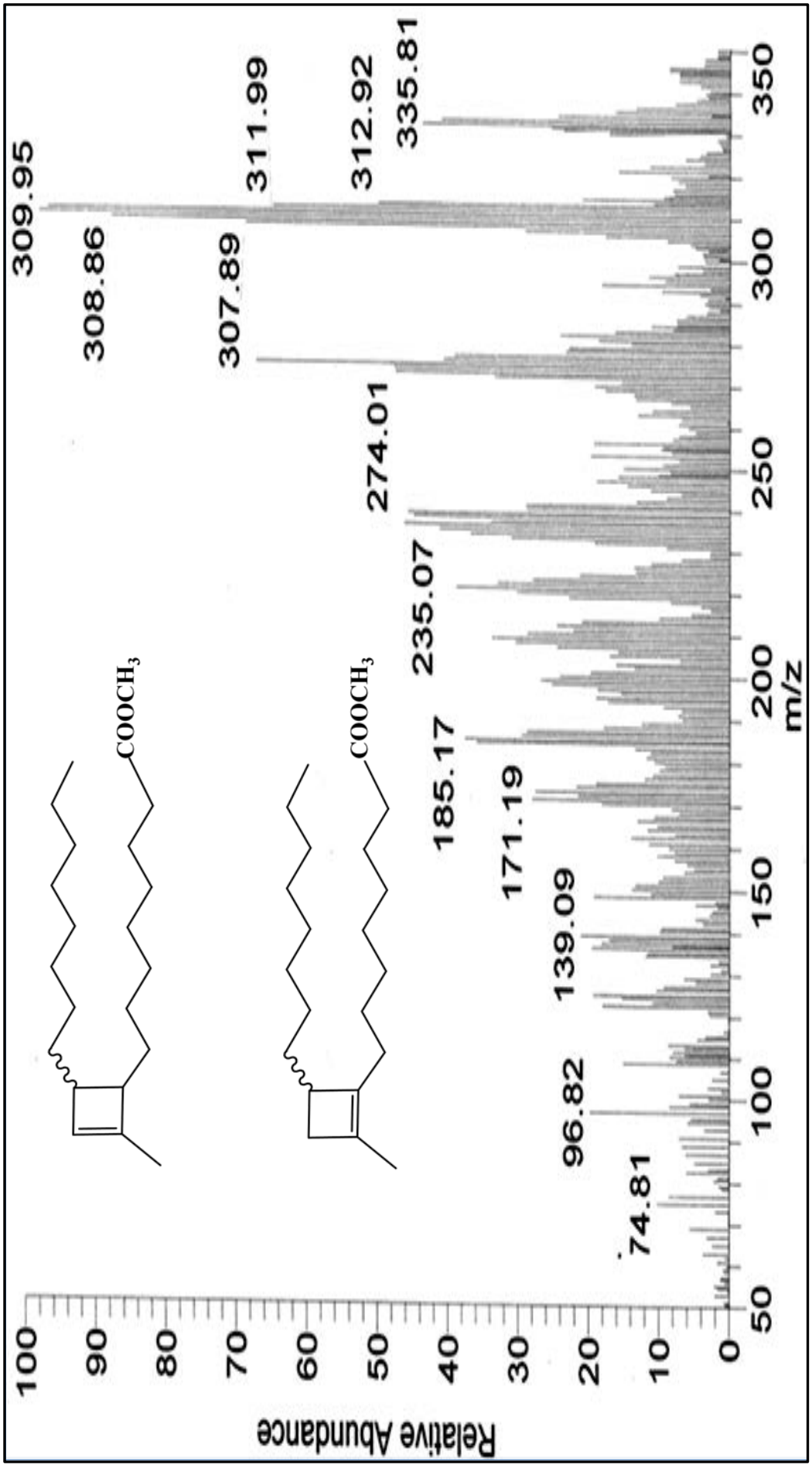


Figure 2.27: EI-MS spectrum of compound **68** & **72**

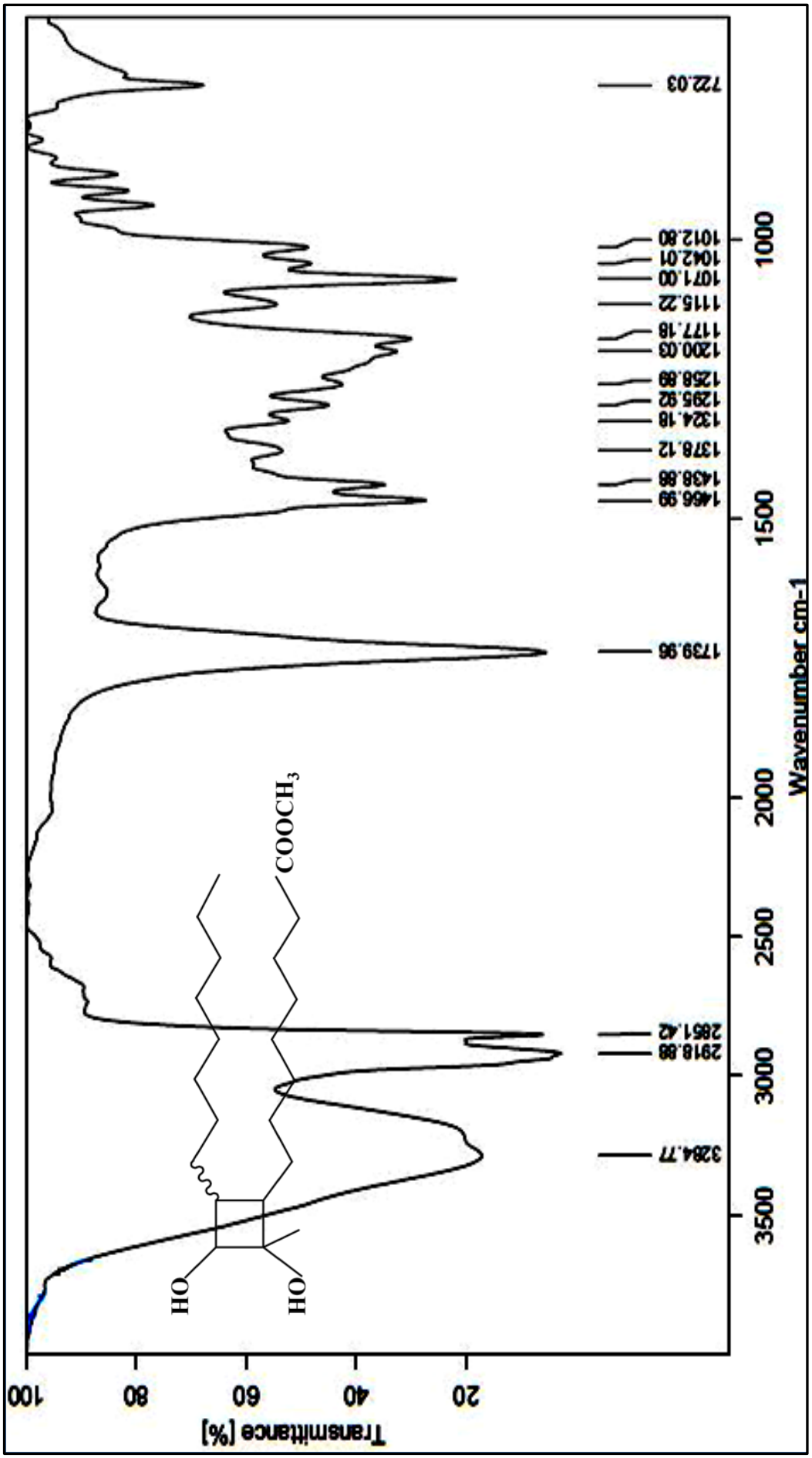


Figure 2.28: FTIR spectrum of compound **69**

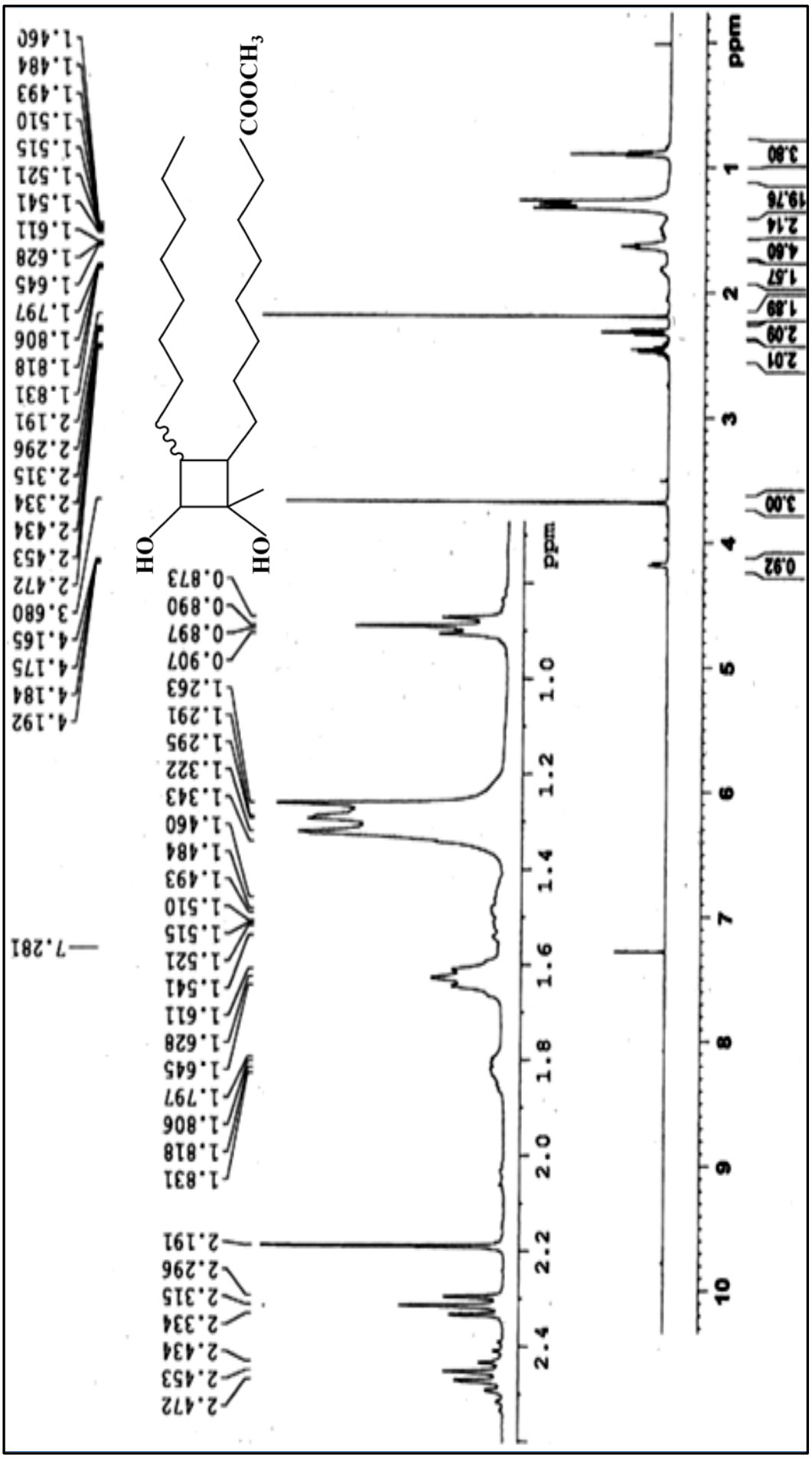


Figure 2.29: ^{1}H NMR spectrum of compound **69**

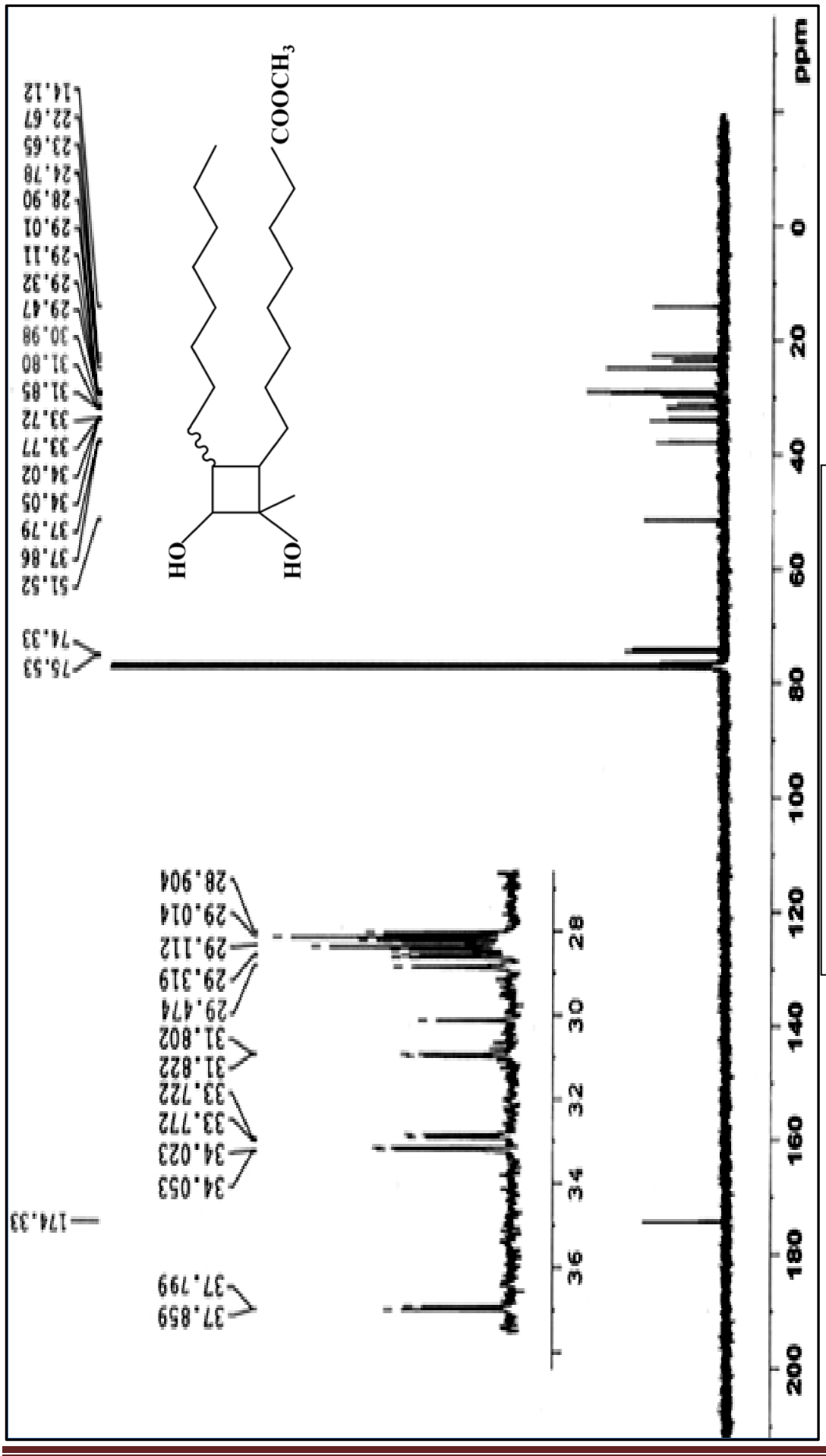


Figure 2.30: ^{13}C NMR spectrum of compound **69**

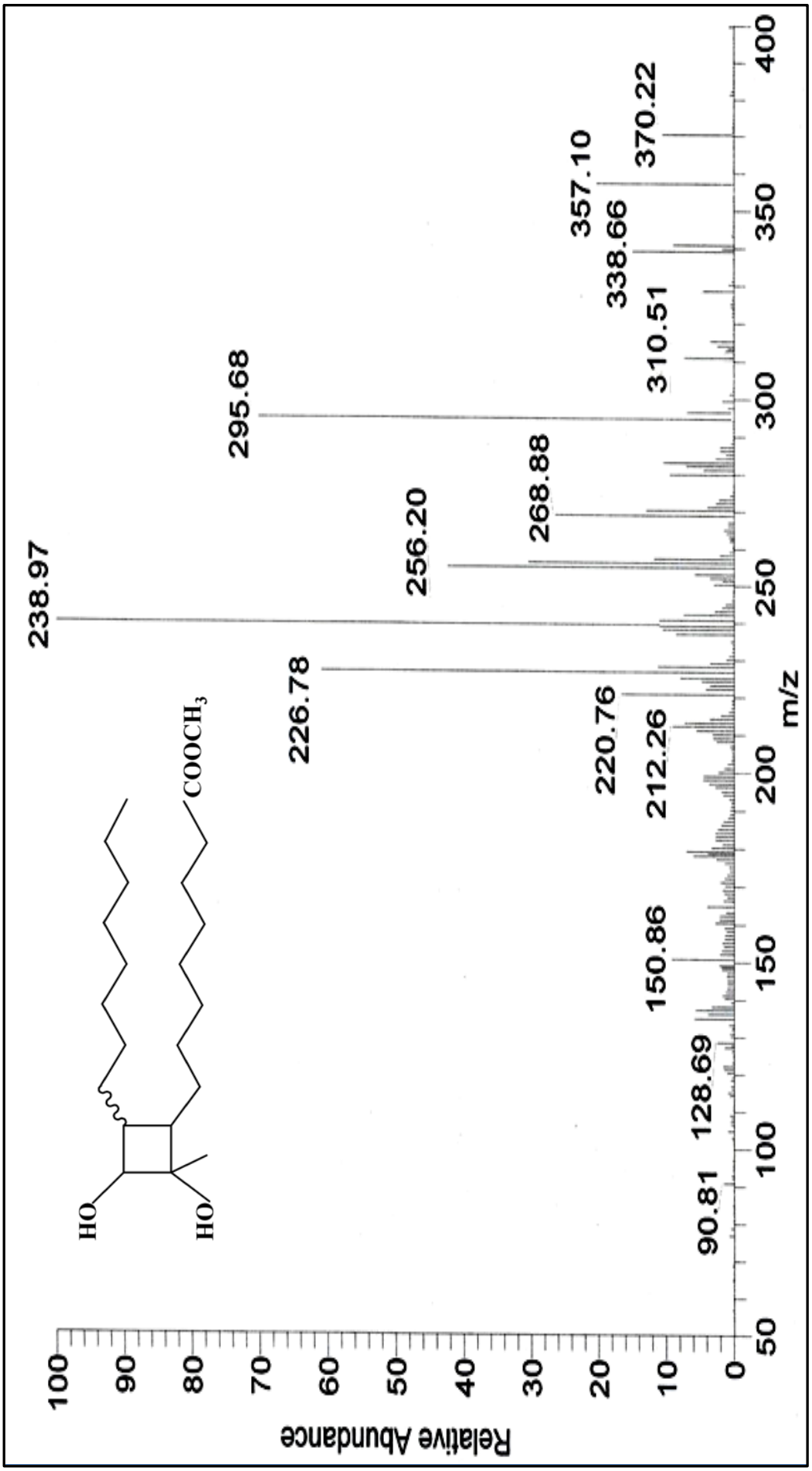


Figure 2.31: EI-MS spectrum of compound **69**

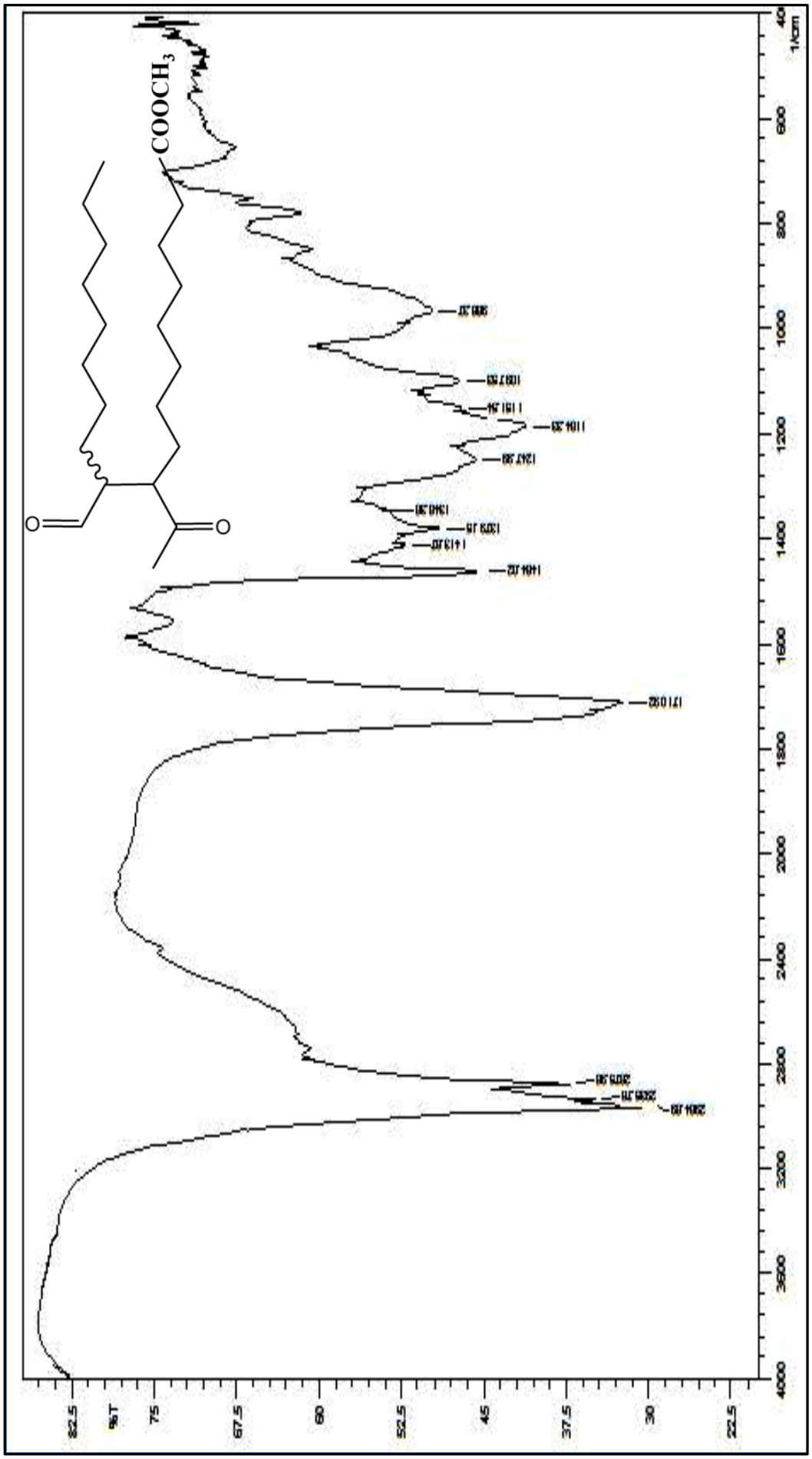


Figure 2.32: FTIR spectrum of compound **70**

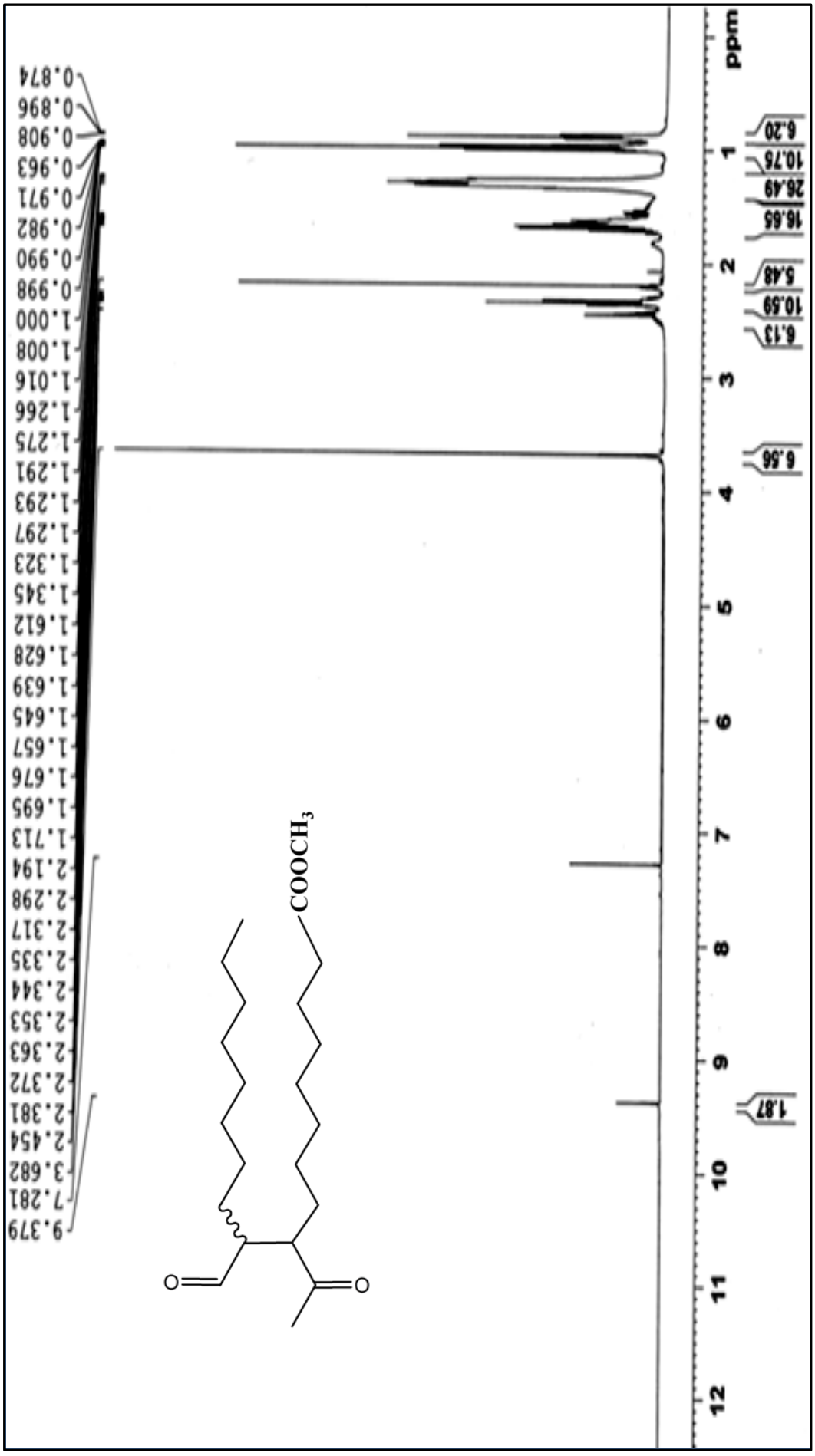


Figure 2.33: ^{1}H NMR spectrum of compound **70**

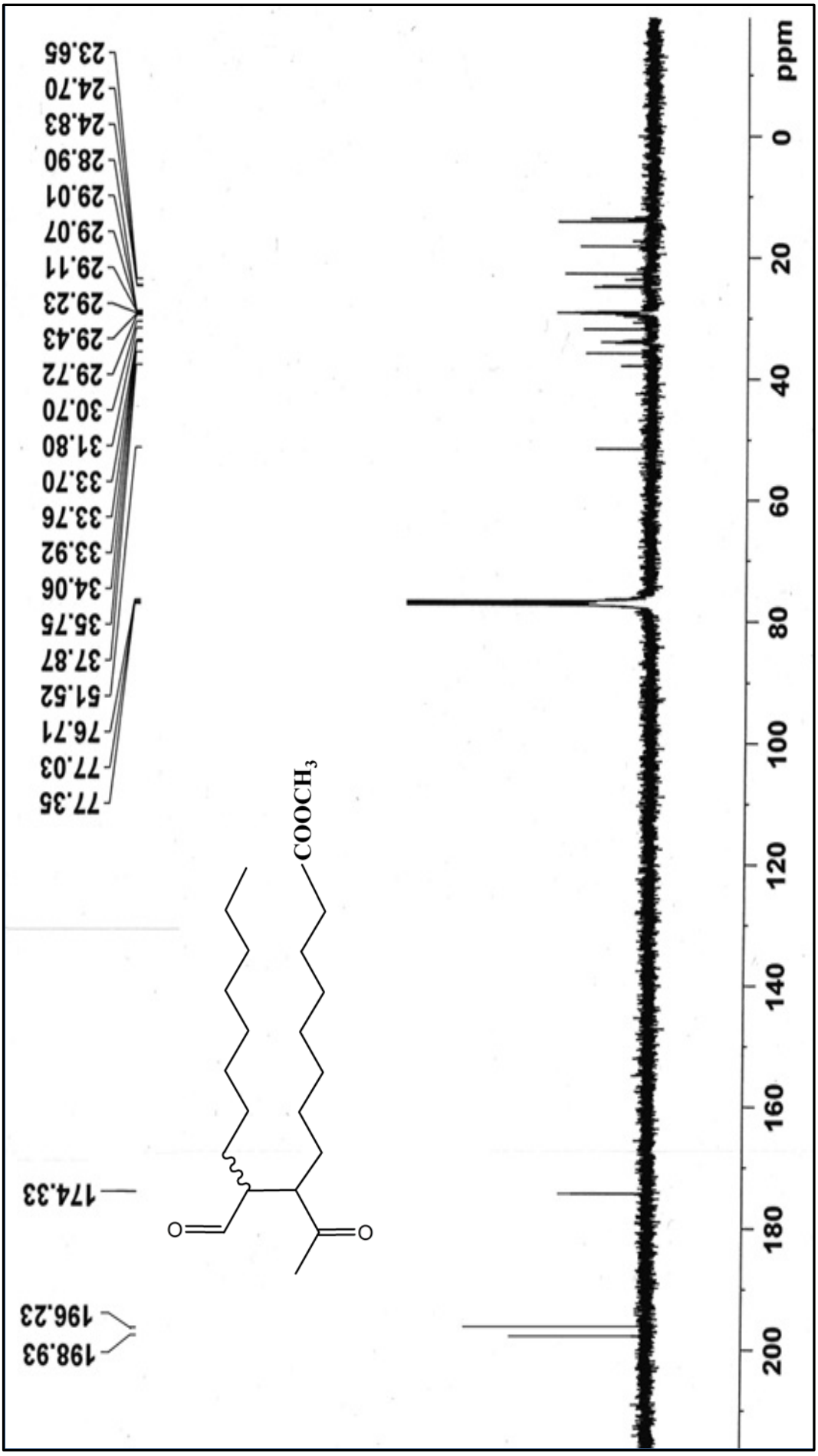


Figure 2.34: ^{13}C NMR spectrum of compound **70**

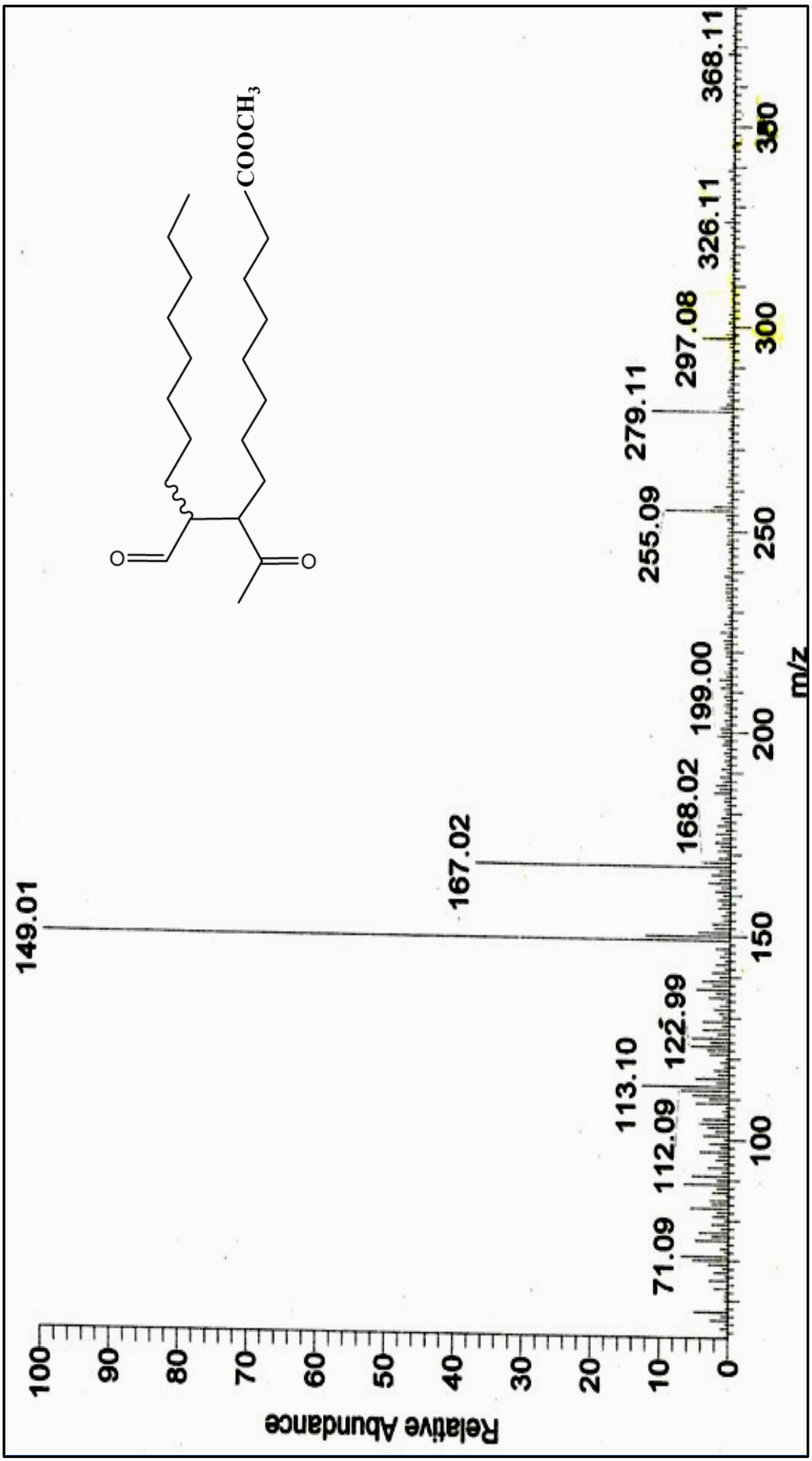


Figure 2.35: EI-MS spectrum of compound **70**

CHAPTER 3

Syntheses of novel bis-acetoxy cyclohexadienones and their photochemical studies

3.1 Abstract

Syntheses of bis-acetoxy cyclohexa dienones **52-57** by oxidative acetylation of bisphenols with Lead tetra acetate (LTA) and sodium meta periodate ($NaIO_4$) under different reaction conditions has been reported. The reaction of bisphenols **46-51** with LTA in ethyl acetate resulted in the formation of bis-acetoxy cyclohexadienones **52-57** which are stable towards inter and intra molecular cycloadditions. The treatment of bisphenols **47-51** with $NaIO_4$ in acetic anhydride resulted in the formation of novel diacetates **64-68**. The photochemical behaviour of bis-cyclohexadienone **52-57** has also been investigated under UV irradiation.

3.2 Introduction and objective

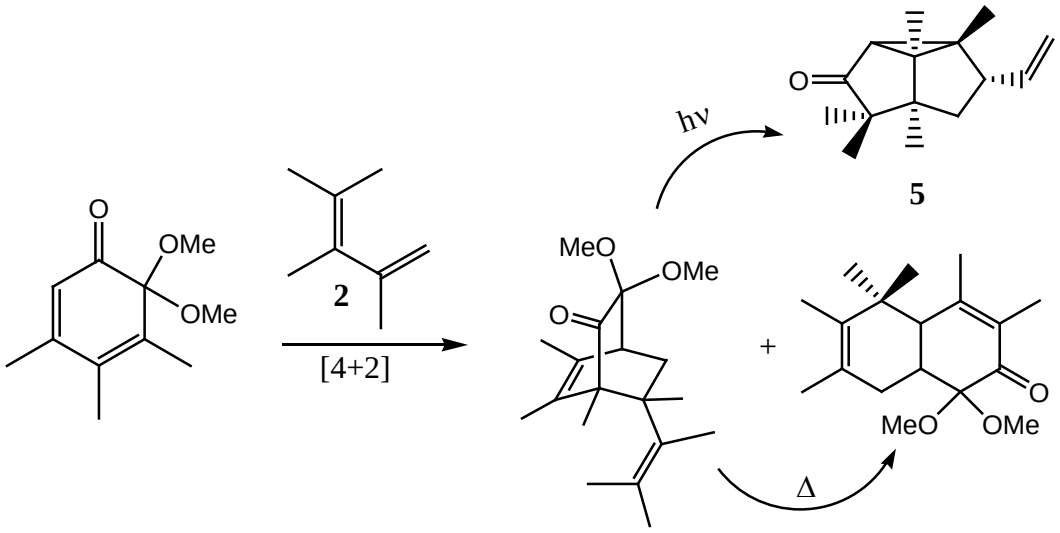
The development of simple and efficient method for rapid construction of complex organic molecules with stereochemical complexity from easily available materials is a challenging exercise in synthetic organic chemistry. The cyclohexadienone ketals, quinols and their congeners have enormous synthetic potential for creation of molecular complexity in stereo controlled manner.[1] The use of cyclohexadienones as starting materials has accelerated the development of new methods towards total syntheses of various natural products possessing diverse chemical behaviour and interesting biological profiles.[1,2]

The cyclohexadienone moiety is a conjugated diene in which both the double bonds are positioned between a carbonyl group and a stereogenic centre. The conjugated double bond and the carbonyl group in cyclohexadienone are a part of various chemical transformations and are employed in the total syntheses of several natural products. Despite their synthetic potential, the cyclohexadienones are underutilized due to their high reactivity resulting in great propensity towards dimerisation.[3] By virtue of their structure, cyclohexadienones behave both as a diene and a dienophile to produce corresponding dimers via Diels–Alder reaction in a highly stereoselective manner.[3]

Certain methods have also been developed to suppress this tendency and to explore its synthetic potential. The reactivity of cyclohexadienone towards dimerisation is less problematic, if it is intercepted in an intramolecular [4+2] cycloaddition.[4] The cyclohexadienones are stable with proper substitution to undergo a number of reactions such as 1,2- and 1,4-additions, both normal and inverse-demand Diels-Alder reactions, Michael reactions, sigmatropic shifts, electrocyclic rearrangements as well as bis-allylic displacements.[5]

The cyclohexadienone unit shows dual behaviour, i.e. it behaves as a diene as well as a dienophile in both inter and intramolecular mode of cycloadditon reactions.[6] For example, the intermolecular cycloaddition of cyclohexadienone **1** with 1,3-butadine **2** provided a mixture of two products, bicyclic compound **3** and *cis*-decalin **4.** (**Scheme 3.1**)

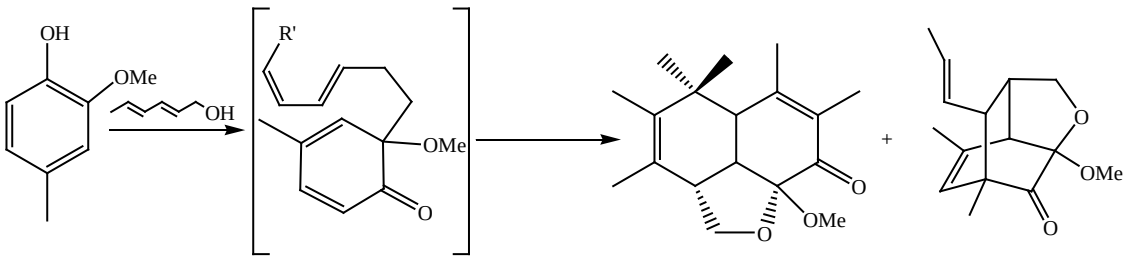
Formation of both the products **3** and **4** shows the dual character of cyclohexadienone as a diene and dienophile. The adduct **3** can also be transformed into **4** by heating upto 180 °C and into diquinane **5** by oxa di-π methane rearrangement.[6] (**Scheme 3.1**)



1 **3** **4**

Scheme 3.1: Cyclohexadienone as 4π and 2π intramolecular cycloaddition

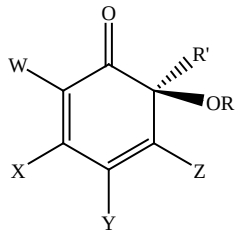
The intramolecular Diels-Alder reaction is also one of the most important protocols for rapid construction of highly substituted polycyclic carbon skeleton.[7] Owing to the dual behavioural nature of cyclohexadienone during the intramolecular cycloaddition, cyclohexadienone of type **7** when subjected to cycloaddition, gave a mixture of polycycles **8** and **9**.[8] (**Scheme 3.2**)



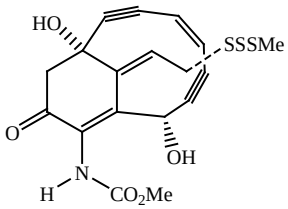
6 **7** **8** **9**

Scheme 3.2: Intramolecular Diels Alder cycloaddition of cyclohexadienone **7**

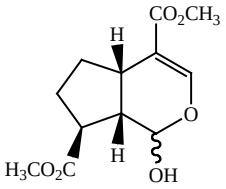
The cyclohexadienone building blocks **10** are key intermediates in the syntheses of various natural products. Magnus reported the use of cyclohexadienone in the synthesis of calicheamicinone **11**.[9] Liao *et al* have synthesized the forsythide derivative **12**,[10] Deslongchamp has reported the synthesis of ryanodol **13**[11] and Wood has implemented a more sophisticated tandem protocol towards the synthesis of natural product CP-263,114 **14**.[12] Singh *et al* have reported the syntheses of a group of triquinane natural products such as coriolin **15**.[13] In addition to these, the use of cyclohexadienones is also explored in syntheses of colchicine **16**,[14] lilifol B **17**, O-methyllliflodione **18**,[15] kadsurenone **19**,[15] xestoquinone **20**,[16] asatone **21,**[17] various diquinanes and propellanes[18] natural products. (**Figure 3.1**)



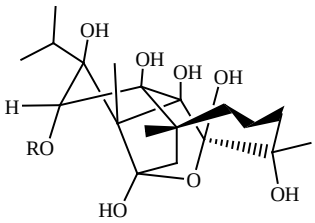
Cyclohexadienone **10**



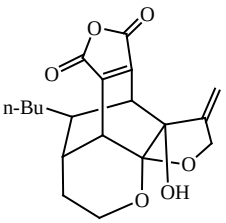
Calicheamicinone **11**



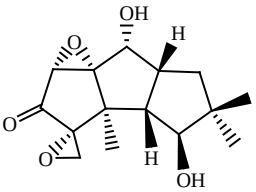
Forsythide **12**



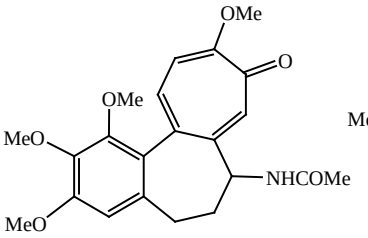
Ryanodol **13**



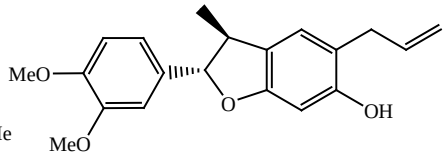
CP-263,114 **14**



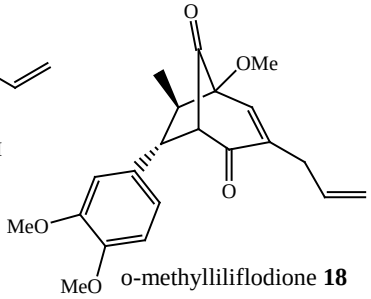
Coriolin **15**



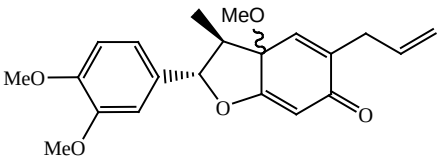
Colchicine **16**



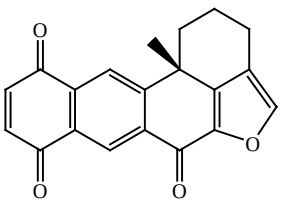
Lilifol B **17**



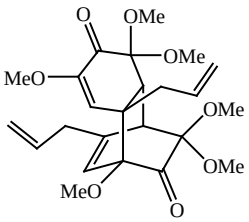
o-methyllliflodione **18**



Kadsurenone **19**



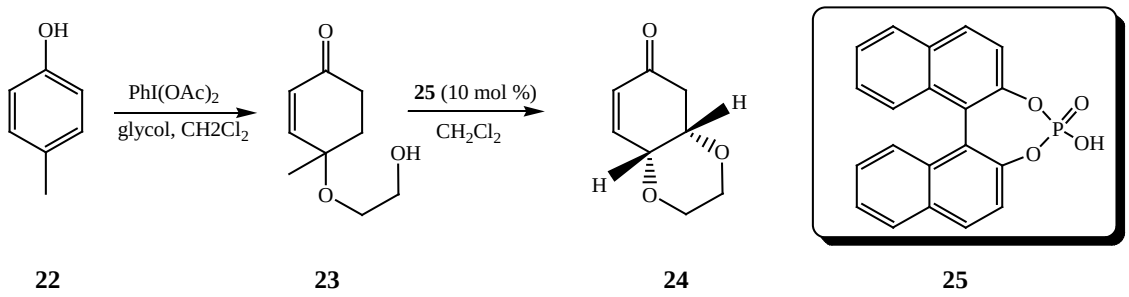
Xestoquinone **20**



Asatone **21**

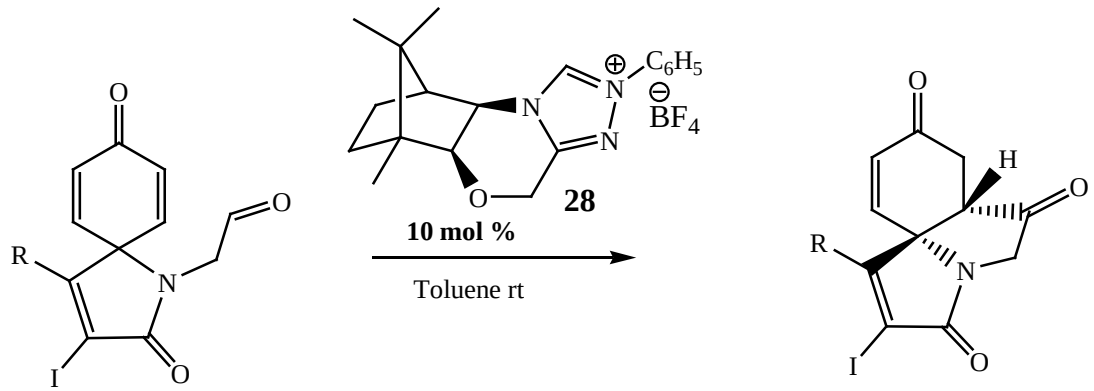
Figure 3.1: Potential of cyclohexadienones in syntheses of natural products

Cyclohexadienones also undergo desymmetrization reactions which are the most important and powerful methods for enantioselective syntheses of chiral molecules. You *et al* have reported the desymmetrisation of cyclohexadienone by oxa Michael reaction.[19] (**Scheme 3.3**) He also explored the distereoselective and enantioselective desymmetrisation of cyclohexadienones by Stetter reaction.[20] (**Scheme 3.4**)



22 **23** **24** **25**

Scheme 3.3: Desymmetrization of cyclohexadienone by oxa Michael reaction

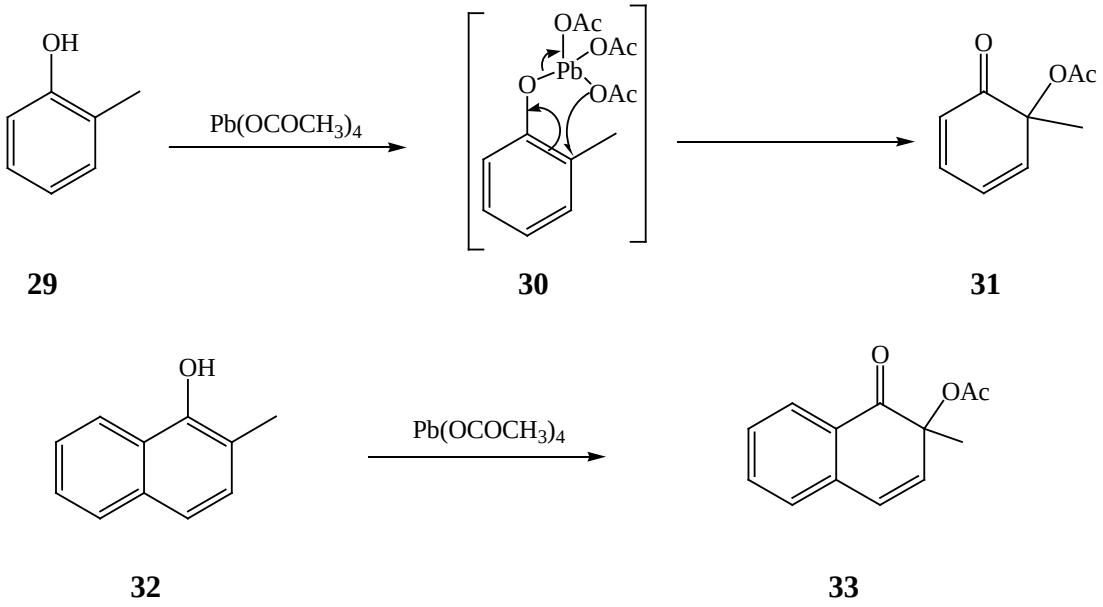


26 **27**

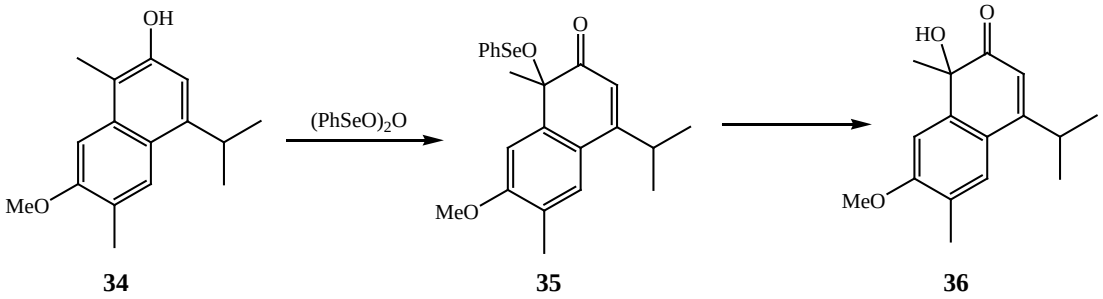
Scheme 3.4: Desymmetrization of cyclohexadienone by Stetter reaction

In general, the cyclohexadienones are generated by oxidation of phenols with a variety of reagents such as lead tetra acetate (LTA),[21] benzeneseleninic anhydride (BSA),[22] hypervalent iodide reagents,[23] sodium meta periodate,[24] diacyl peroxide,[25] trifluoro-peroxyacetic acid,[26] Pd-catalysed Friedel-Crafts reactions etc.[27]

The oxidation of phenols to cyclohexadienones with LTA is known as Wessely oxidation.[21] This reagent proved to be the most convenient one for oxidation of *o*-substituted phenols. The mechanism of the Wessely oxidation for *o*-alkylated phenols was investigated by Pinhey and Thomas.[28] They reported that the product formation occurs through an intramolecular oxidative delivery of acetate group from an intermediate $ArOPb(OAc)_3$ complex.[28] This method for oxidation of phenols to cyclohexadienones was further extensively investigated by Bhatt, Coleman, Hunter and Pinhey.[28,29] Bhatt *et al* reported the oxidation of napthol **32** with LTA for the synthesis of o-quinol acetate **33**.[30] (**Scheme 3.5**) LTA possesses a strong avidity for oxidation at the *ortho* position but the preference of delivery of the acetate group to the *ortho* side can be hindered by steric interaction and reaction conditions.[28]



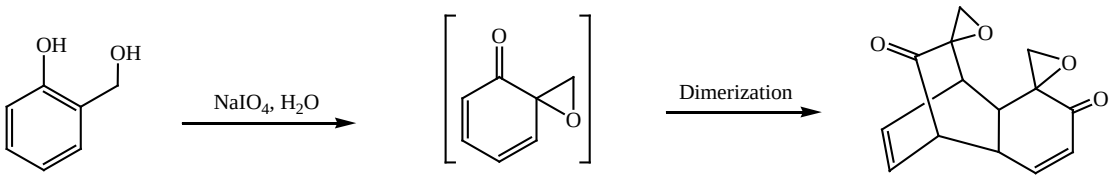
Scheme 3.5: Oxidation of phenol using LTA



Scheme 3.6: Synthesis of lacinilene **36** by oxidation of phenol **34** using BSA

Barton *et al* have studied the reactivity of phenols with benzeneseleninic anhydride (BSA) as an oxidising agent.[31] Meyers and Jeffs have used BSA for the synthesis of lacinilene **36** by oxidation of phenol of type **34.**[32] (**Scheme 3.6**)

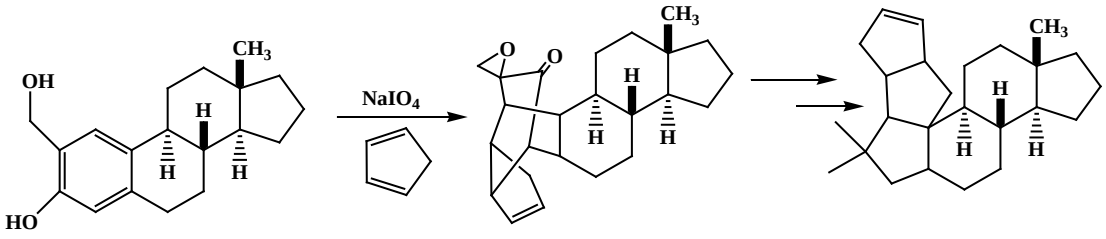
In addition to the above methods, Becker-Adler have reported the syntheses of various types of cyclohexadienones from a wide variety of phenols with sodium meta periodate ($NaIO_4$) in aqueous medium.[24] The spiroepoxy cyclohexadienone derivatives obtained from oxidation of *o*-hydroxy benzyl alcohol and substituted *o*-hydroxy benzyl alcohol by Adler method have proved to be of tremendous synthetic importance in the total syntheses of triquinanes, ovalicin, calicheamicinone natural products.[33] (**Scheme 3.7**)



37 **38** **39**

Scheme 3.7: Oxidation of phenol using $NaIO_4$

The Adler method for the preparation of cyclohexadienones is also applicable in the syntheses of hybrid molecules of two different classes of compounds. Singh *et al* reported the synthesis of steroid-polyquinane hybrid compound **42** starting from periodate oxidation of phenol **40**.[34] (**Scheme 3.8**)



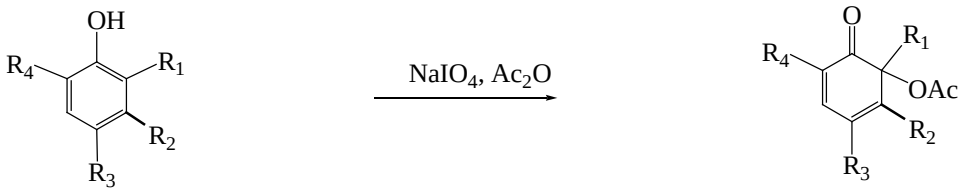
40 **41** **42**

Scheme 3.8: Syntheses of steroid-polyquinane hybrid compound **42**

Due to the presence of a reactive carbonyl group and conjugated double bonds, the cyclohexadienones are powerful intermediates in organic syntheses.[35] The iodine reagents such as phenyliodionium diacetate (PIDA), Phenyliodonium

bis(trifluoroacetate) (PIFA), iodoxybenzoic acid (IBX), Dess-Martin periodinane (DMP) are also used for the preparation of cyclohexadienones. Nicolau *et al* have developed a series of novel synthetic routes for the construction of complex polycycles, heterocycles, amino-sugars and unsaturated carbonyl compounds using iodine reagents.[36]

In the course of our efforts towards the syntheses of acetoxy cyclohexadienones earlier our group reported one-pot syntheses of acetoxy cyclohexadienones of type **44a-g** from corresponding phenols with $NaIO_4$ in acetic anhydride.[37] A general procedure for the syntheses of acetoxy cyclohexadienones from corresponding phenols was also established in good to moderate yields.[37] (**Scheme 3.9**)



43a-g **44a-g**

a) $R^1=R^4=CH_3$, $R^2=R^3=H$; b) $R^1=R^3=R^4=CH_3$, $R_2=H$; c) $R^1=R^2=CH_3$, $R^2=R^4=H$; d) $R^1= CH_2OH$, $R^2=R^3=R^4=H$; e) $R^1= CH_2OAc$, $R^2=R^3=R^4=H$; f) $R^1=OCH_3$, $R^2=R^3=H$, $R^4=CHO$; g) $R_1=R_2=H$, R^2-R^3= -OCO-CH-C(CH_3)-

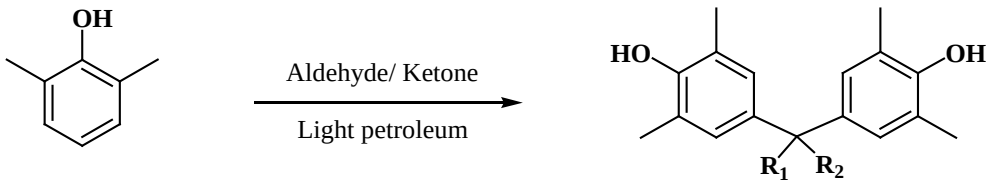
Scheme 3.9: Syntheses of acetoxy cyclohexadienones from phenols

Previously our group reported the base catalysed preparation of tetramethyl bisphenol-F and its oxidative acetylation towards the synthesis of corresponding bis-cyclohexadienone. The bisphenol–F on treatment with LTA in benzene gave bis-acetoxycyclohexadienone and on reaction with $NaIO_4$ in acetic anhydride produced acetylated bisphenol.[38]

In this chapter a novel method for the preparation of alkyl substituted bisphenols **46-51** from 2,6-dimethyl phenol **45** is reported. The bisphenols that were prepared were subjected to oxidative acetylation using two reagents, LTA and $NaIO_4$ under different reaction conditions towards syntheses of bis-cyclohexadienone **52-57**. The photochemical behavior of **52-57** under UV irradiation has also been investigated.

3.3 Results and discussion

Towards accomplishing the above objectives, we have developed a novel method for the preparation of bisphenols **46-51** by modifying the reported procedure of our group.[38] (**Scheme 3.10**) Thus, a mixture of phenol and aldehyde or ketone in light petroleum was stirred in the presence of a suitable acid (HCl in the case of aldehydes and H_2SO_4 in the case of ketones). After completion of the reaction (TLC), the reaction mixture was diluted five times of its volume and was further stirred for 15 minutes. The solid thus obtained was filtered on a Buchner funnel, washed thoroughly with water and dried at 85-90^oC under vacuum to give a solid which was purified by column chromatography over a column of silica gel using a mixture of light petroleum/ethyl acetate afforded bisphenol as a white crystalline solid in excellent yield. (**Scheme 3.10, Table 1**) The structures of the bisphenols were fully confirmed through their FTIR, ^1H and ^{13}C NMR and mass spectra.



45 **46-51**

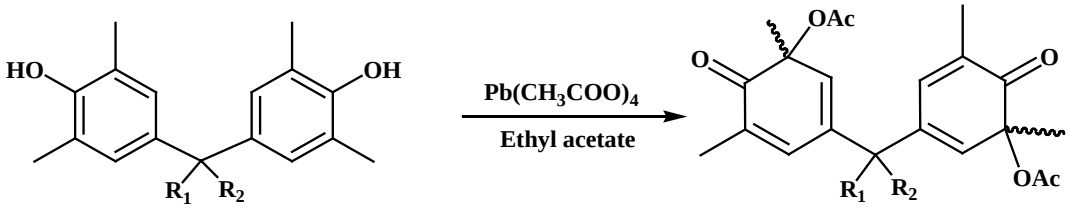
46) R_1=R_2=H; **47**) R_1=CH_3, R_2=H; **48**) R_1=CH_3CH_2, R_2=H **49**) R_1=$CH_3CH_2CH_2$, R_2=H; **50**) R_1=R_2=CH_3; **51**) R_1, R_2= -$(CH2)_4$-

Scheme 3.10: Preparation of bisphenol **46-51** from 2,6-dimethyl phenol **45**

Table 1: Preparation of bisphenols from 2,6-dimethyl phenol and aldehyde/ ketones

Entry	Aldehyde /ketone	Bisphenol	Time h	Yield (%)
1	HCHO	**46**	2.5	93
2	CH_3CHO	**47**	3.5	92
3	CH_3CH_2CHO	**48**	4	94
4	$CH_3(CH_2)_2CHO$	**49**	3	94
5	CH_3COCH_3	**50**	3.5	94
6	-$(CH_2)_2CO(CH_2)_2$-	**51**	4	91

Our group has earlier reported the oxidative acetylation of tetramethyl bisphenol-F **46** to bis-cyclohexadienone **52** using LTA in benzene. We have further investigated the oxidative acetylation of bisphenol-F **46** in different solvents due to the high carcinogenicity of benzene, and found that the reaction can also be accomplished in toluene with a maintained yield (52%) and in ethyl acetate with an improved yield (82%) at room temperature (27^0C) in a shorter reaction time. (**Entry 1, Table 2**)

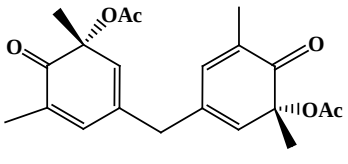


46-51 **52-57**

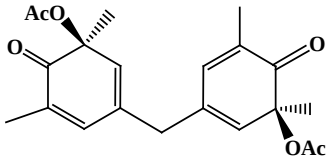
46) R_1=R_2=H; **47**) R_1=CH_3, R_2=H; **48**) R_1=CH_3CH_2, R_2=H **49**) R_1=$CH_3CH_2CH_2$, R_2=H; **50**) R_1=R_2=CH_3; **51**) R_1, R_2= -$(CH2)_4$-

Scheme 3.11: Oxidative acetylation of bisphenols **46-51**

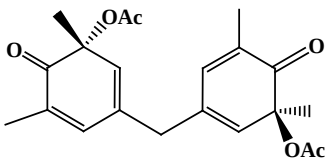
The bis-cyclohexadienone **52** has two chiral centres in its structure and hence there are four possible stereo isomers **52a-52d**. (**Figure 3.2**)



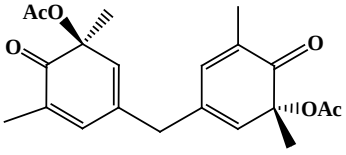
R,R- 52a



S,S- 52b



R,S- 52c



S,R- 52d

Figure 3.2: Possible stereoisomers of bis-cyclohexadienone

To establish the generality of the procedure for the syntheses of bis-cyclohexadienones we have also investigated the oxidative acetylation of bisphenols **47-51** using LTA in ethyl acetate. Thus, the bisphenols **47-51** were treated with LTA in ethyl acetate at room temperature ~ 27 C for an appropriate time (**Table 2**). The products were extracted in ethyl acetate and the solvent was removed under reduced pressure to give the crude product, which was chromatographed over a column of silica gel using a mixture of light petroleum and ethyl acetate as eluents furnished pure bis-cyclohexadienone **53-57**. (**Scheme 3.11, Table 2**)

Table 2: Synthesis of bis-cyclohexadienone by oxidative acetylation of bisphenols **46-51** with LTA

Entry	Bisphenol	Biscyclohexadienone	Time (min)	Yield (%)
1	**46**	**52**	45	82
2	**47**	**53**	45	76
3	**48**	**54**	40	84
4	**49**	**55**	50	84
5	**50**	**56**	35	78
6	**51**	**57**	40	64

The structures of bis-cyclohexadienones **52-57** were fully confirmed through their spectral and analytical data. The bis-dienones **52-57** showed a strong band around 1750 cm^{-1} in addition to the characteristic conjugate carbonyl absorption at around 1690 cm^{-1} in their IR spectrum. The ^{1}H NMR spectrum of all dienones exhibited signals at δ 3.5-3.8 indicating the presence of acetate methyl along with the signal of olefinic protons at δ 5.0 to 6.5 in addition to other characteristic signals of methyl, methylene and methine protons. The ^{13}C NMR and mass analysis data was also consistent with the structures of dienones.

The cyclohexadienone **58** of 2,6-dimethyl phenol **45** is a reactive intermediate which easily undergoes Diels-Alder cycloaddition to give its dimer **59**. (**Figure 3.3**) Similarly the oxidative acetylation of bisphenols **46-51** could lead to formation of several oxidation products by inter- and intra molecular mode of cycloaddition. The bis-cyclohexadienones **52** containing two cyclohexadienone moieties could be

expected to undergo intramolecular mode of cycloaddition ($\pi^{4s} + \pi^{2s}$) with either α,β- or γ,δ- double bonds to give two different products **60** and **61**. (**Figure 3.3**) Similarly, the structures **62** and **63** may also result from the inter molecular mode of cycloaddition of one bis-cyclohexadienone as 4π with the other as 2π involving the participation of α,β- or γ,δ- double bonds. (**Figure 3.3**) But the reactions only furnished a single product for each substrate. To study its possible intra- as well as inter- molecular cycloaddition reactions, the bis-dienones **52-57** were refluxed in *o*-xylene for 5h. We observed that the bis-dienones **52-57** were stable towards dimerisation under these reaction conditions even at higher temperatures.

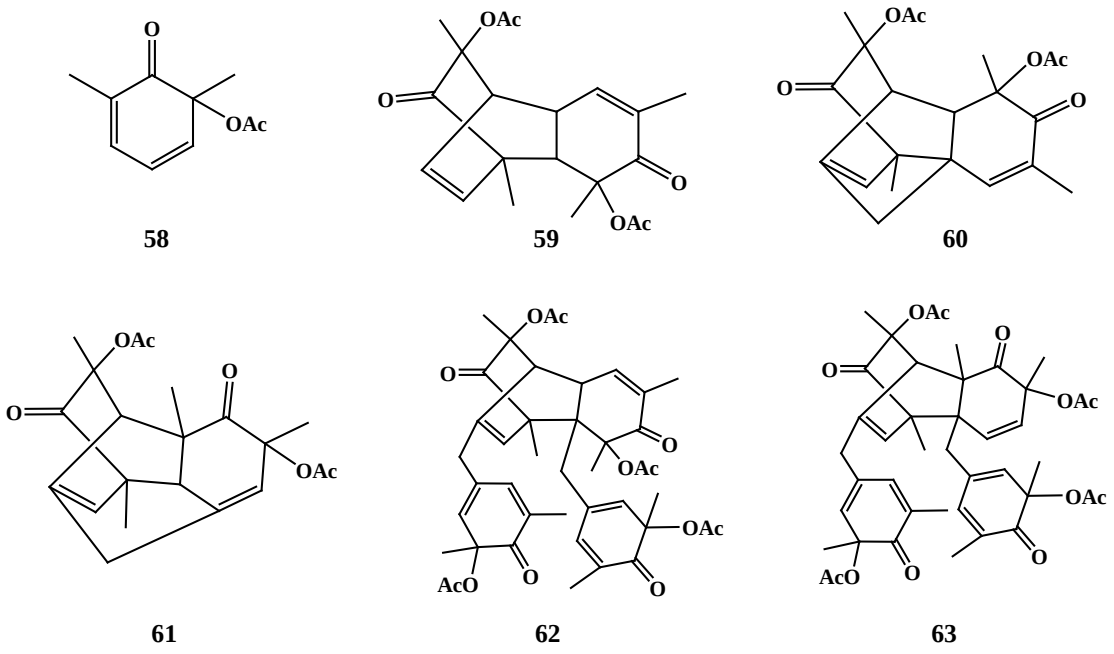
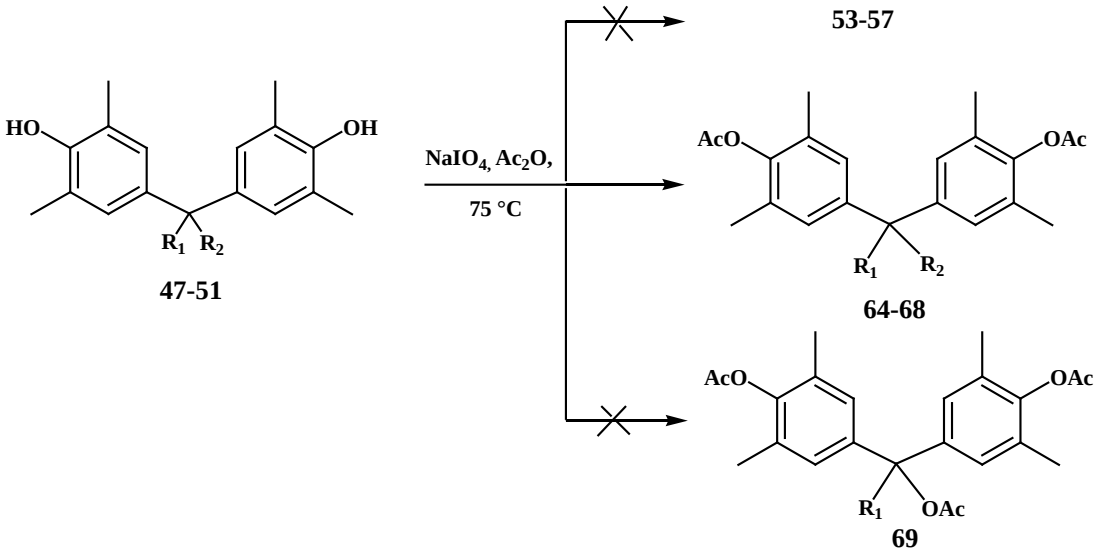


Figure 3.3: Possible products of oxidative acetylaion of bisphenol

The combination of the reagent $NaIO_4$ in acetic anhydride was also employed in the reaction of bisphenols towards syntheses of bis-acetoxy cyclohexadienones. In a previous work, our group have reported the reaction of bisphenol-F **46** with $NaIO_4$ in acetic anhydride at 75-80 ^oC for 5h resulting in the formation of a triacetate.[37] The formation of triacetate prompted us to extend the effect of $NaIO_4$ in acetic anhydride on other alkyl substituted bisphenols. Thus bisphenols **47-51** were treated with sodium meta periodate in acetic anhydride at 75-80 °C, which gave the novel diacetates **64-68** rather than the expected bis-acetoxy cyclohexadienone **53-57** or triacetate **69**.[38b] (**Scheme 3.12**)



47) R_1=CH_3, R_2=H; **48**) R_1=CH_3CH_2, R_2=H **49**) R_1=$CH_3CH_2CH_2$, R_2=H; **50**) R_1=R_2=CH_3; **51**) R_1, R_2= -$(CH_2)_4$-

Scheme 3.12: Reaction of bisphenols with $NaIO_4$ in acetic anhydride

Table 3: Acetylation of bisphenols **47-51** by $NaIO_4$ in Ac_2O

Entry	Bisphenol	Diacetates	Time (h)	Yield (%)
1	**47**	**64**	4	68
2	**48**	**65**	3.5	72
3	**49**	**66**	3.5	71
4	**50**	**67**	4	64
5	**51**	**68**	4.5	58

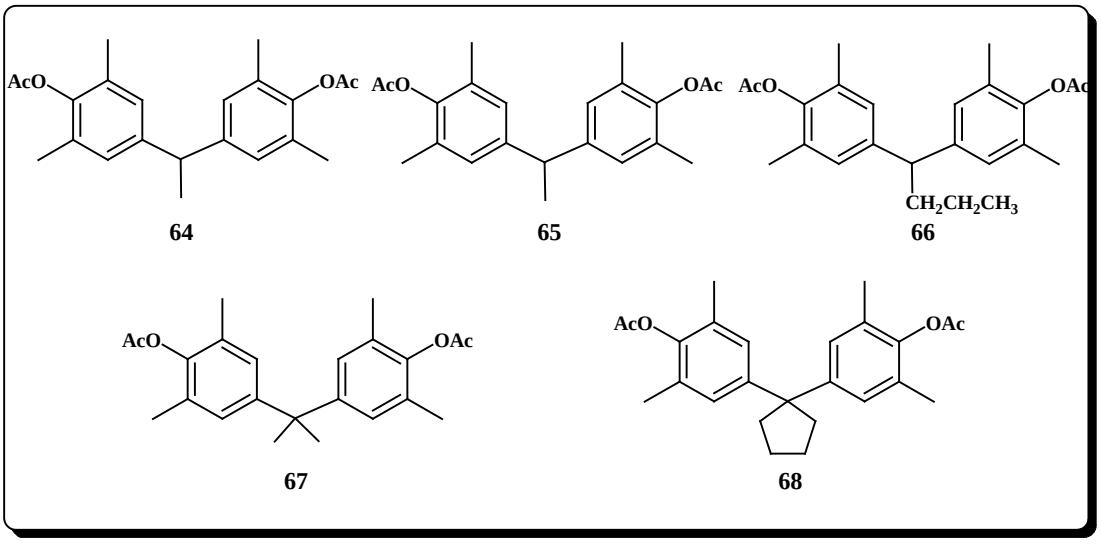
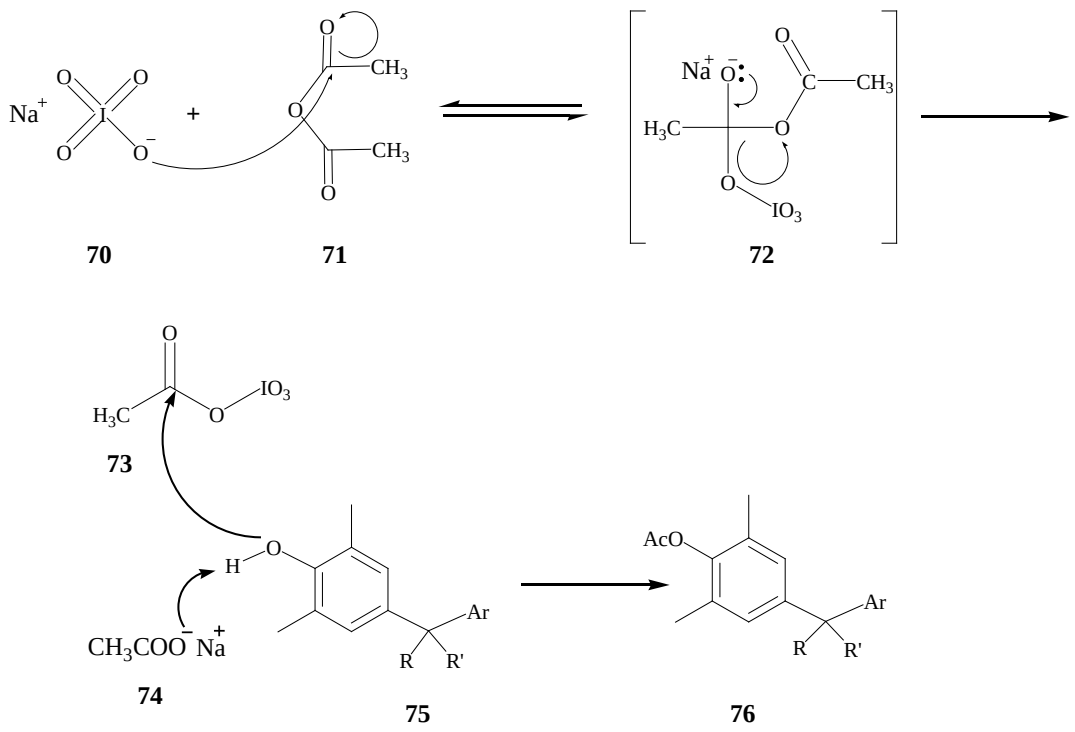


Figure 3.4: Structures of acylated products **64-68**

It was thought that the acetylation of phenols might be taking place due to nucleophilic attack of phenolic OH on a carbonyl of acetic anhydride without involvement of $NaIO_4$. To test this hypothesis bisphenol **47** was heated under reflux in Ac_2O however the formation of acetylated product was not observed. This indicated some role of $NaIO_4$ in acetyaltion of bisphenol.

We have proposed a plausible mechanism for the formation of the acetylated product of bisphenols.[38b] (**Scheme 3.13**) Periodate perhaps attacks on the carbonyl carbon of the anhydride **71** to generate sodium acetate **74** and ethanoylperiodate **73** via intermediate **72**. The sodium acetate thus formed is a conjugate base which initiates the nucleophilic substitution of bis-phenol **75** on carbonyl carbon of ethanoylperiodate **73** to give the acetylated product **76**. Acetylation of two hydroxyls in the bisphenol molecule may be synchronous or stepwise.



70 **71** **72** **73** **74** **75** **76**

Scheme 3.13: Acetylation of bisphenols using $NaIO_4$ in Ac_2O

In the support of the above proposed mechanism we have also studied the acetylation of bisphenol **5** in Ac_2O with KIO_4, CH_3COONa and CH_3COOH. (**Table 4**) It was found that the use of KIO_4 shortens the reaction time as compared to $NaIO_4$. This

may be due to the formation of conjugate base CH_3COOK that releases the acetate ion more easily than CH_3COONa. (**Table 4**) The reaction of **5** in Ac_2O with CH_3COONa requires higher temperature and longer reaction time than $NaIO_4$. This indicates the involvement of species **26** in acetylation during the reaction of bisphenols with $NaIO_4$ or KIO_4 in Ac_2O. We have also attempted the acetylation of **5** in Ac_2O in presence of CH_3COOH. The reaction with CH_3COOH not only required high temperature and longer time but did not reach on completion even under reflux.

Table 4: The acetylation of bisphenol **47** in Ac_2O using different reagents

Entry	reagent	Temp. (°C)	Time (h)	Yield %
1	$NaIO_4$	75	3	88
2	KIO_4	75	1.5	90
3	CH_3COONa	120	3.5	82
4	CH_3COOH	118	6	80[a]

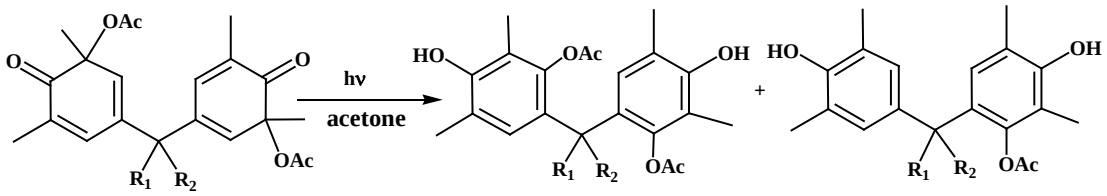
[a] the reaction did not reach completion, yield is based on the recovery of starting materials.

Photochemical reactions are one of the most commonly employed protocols in synthetic organic chemistry for the creation of various functionalities and simplification of multistep reactions in total syntheses.[39] In photochemistry, the reactions are induced by light as energy sources. The molecules reach electronically excited states by absorbing energy in the form of radiation. The distribution of electrons in the excited state of the molecule is different as compared to the ground state. As a result the chemical reactivity of the molecules increases and a transformation takes place in the reactants to give new products. The photochemical reactions have significant importance in organic chemistry to shorten the number of steps towards total syntheses of natural products, syntheses of polycyclic systems and highly functionalized structures etc.[39] In photochemical transformations, the activation of most of the reactants molecules occur without additional chemical reagents. Due to this tendency, photochemical reactions become interesting in the context of green chemistry.[40]

The photochemical reactions of cyclohexadienone systems have been reported in literature for a long time by different groups[41-43] but there is no report on

photochemical behavior of bis-cyclohexadienones. In this part of the work, the photochemical behavior of bis-acetoxy cyclohexadienones **52-56** was investigated under UV irradiation. Thus a solution of bis-cyclohexadienones **52** in acetone was irradiated with a mercury vapour lamp in a quartz immersion well for 1 hour, upon which a clean reaction occurred. Removal of solvent followed by column chromatography furnished two different aromatized products **77A** and **77B**. (**Scheme 3.14**) The compound **77A** was formed by migration of both the acetate groups followed by aromatisation of the cyclohexadienone ring, while the product **77B** was formed by migration of an acetate group in one cyclohexadienone unit followed by deacetylation from the other cyclohexadienone ring. (**Scheme 3.14**)

The aromatisation and acetate group migration in the cyclohexadienone ring system under these reaction conditions is unheard of in the existing literature.



52-57 **77A, 83A-87A** **77B, 83B-87B**

52) R_1=R_2=H; **53**) R_1=CH_3, R_2=H; **54**) R_1=CH_3CH_2, R_2=H; **55**) R_1=$CH_3CH_2CH_2$, R_2=H; **56**) R_1=R_2=CH_3; **57**) R_1, R_2= -$(CH_2)_4$-

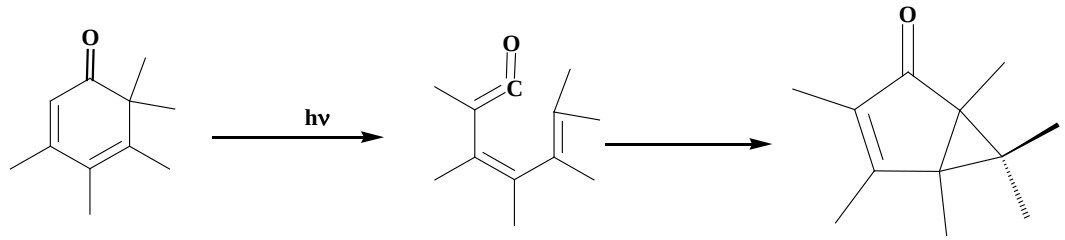
Scheme 3.14: Photochemical reaction of bis-cyclohexadienone **52-57**

The structures of the products **77A** and **77B** were confirmed by their spectral and analytical data. The IR spectrum of **77A** showed a strong absorption band at 3410 cm^{-1} due to the presence of phenolic OH group, a strong band at 1740 cm^{-1} owing the presence of a carbonyl group of the acetate and other characteristic absorptions at 1432 and 1482 denoting the aromatic ring. The ^{1}H NMR spectrum of compound **77A** exhibited singlets at δ 2.04, 2.15, 2.28 for the protons on methyl groups and a singlet at δ 3.53 for protons of the methylene group. It also showed a singlet at 4.72 for two phenolic OH along with a singlet at δ 6.67 for two aromatic protons. Its ^{13}C NMR

spectrum displayed signals at δ 9.66, 15.77 and 20.51 for the carbons of methyl groups. It also displayed signals at δ 29.81 for methylene carbons with δ 116.40, 120.79, 123.61, 129.14, 146.20, 151.07 for aromatic carbons, along with a signal at δ 169.29 for the carbonyl carbon of the acetate group. Its mass spectrum showed a molecular ion peak at 371.83 along with a base peak at 287.02.

The IR spectrum of compound **77B** displayed a characteristic band at 3572 cm^{-1} along with other signals confirming the conversion of the cyclohexadienone ring to the phenol derivative. Its ^{1}H NMR spectrum exhibited singlets at δ 2.04, 2.16, 2.21, 2.28 for methyl protons and a singlet at δ 3.63 for two protons of the methylene group along with a superimposed singlet for three aromatic protons at δ 6.77. The ^{13}C NMR spectrum of **77B** displayed signals at δ 9.70, 15.80, 15.96, 20.58 for methyl carbons and a signal at δ 35.23 for a methylene carbon. Similarly, signals at δ 116.53, 120.84, 122.90, 125.13, 128.91, 129.23, 131.84, 146.17, 150.44 and 151.01 for aromatic carbons confirms the aromatisation of cyclohexadienone ring. It also displayed a signal at δ 169.28 for the acetate carbonyl attached to the aromatic ring. The mass spectrum of **77B** showed a molecular ion peak at 313.88 and a base peak at 270.80 in addition to other diagnostic signals.

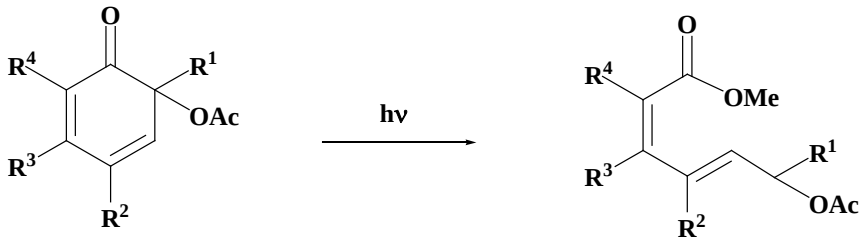
Hart *et al* have investigated the photochemistry of various types of cyclohexadienones. They reported that the photochemical transformation of 2,4-cyclohexadienone of type **78** in a reversible ring fission to give ketene **79** which thermally rearranges to a bicyclo[3.1.0] hexenone **80**.[42] (**Scheme 3.15**)



78 **79** **80**

Scheme 3.15: Photochemical reaction of cyclohexadienone **78**

Baldwin et al have also investigated the photochemical reaction of 6-acetoxycIohexa-2,4-dienones **81 (a-c)** and have proposed the formation of the open chain products **82 (a-c)**.[43] (**Scheme 3.16**)



81 (a-c) **82 (a-c)**

(a) R^1, $R^2 = CH_3$, R^3, R^4 = H, **(b)** R^1, R^2, $R^4 = CH_3$, R^3=H, **(c)** R^1, $R^3 = CH_3$, R^2,R^4 = H

Scheme 3.16: Photochemical reaction of acetoxy cyclohexadienone **81 (a-c)**

Encouraged by above results, we wanted to generalize this method of photochemical aromatization on other bis-cyclohexadienone **53-56**. Thus the cyclohexadienones **53-57** were irradiated in acetone at 15 $^{\circ}$C for different time intervals (**Table 5**). The reactions resulted in two different aromatized products for each substrate. It was observed that the reaction time increases with an increase of the alkyl substituents on the central carbon attached with both cyclohexadienone units. The structures of all the products were confirmed by its IR, ^{1}H and ^{13}C NMR and mass spectra. The acetoxy and alkyl substituted bisphenols that were prepared by the presented method are given in **Table 4 Figure 3.5**, summarizes the reaction time and yields % of products obtained from the photochemical reaction of acetoxy cyclohexadienones.

Table 5: Photochemical reaction of bis-acetoxy cyclohexadienones **52-57**

Entry	Cyclohexa dienone	Aromatised diacetate	Yield (%)	Aromatised Monoacetate	Yield (%)	Time (h)
1	**52**	**77A**	**64**	**77B**	8	1
2	**53**	**83A**	**58**	**83B**	6	1.25
3	**54**	**84A**	**62**	**84B**	4	2.5
4	**55**	**85A**	**66**	**85B**	6	3
5	**56**	**86A**	**66**	**86B**	8	2.45
6	**57**	**87A**	**68**	**87B**	4	3

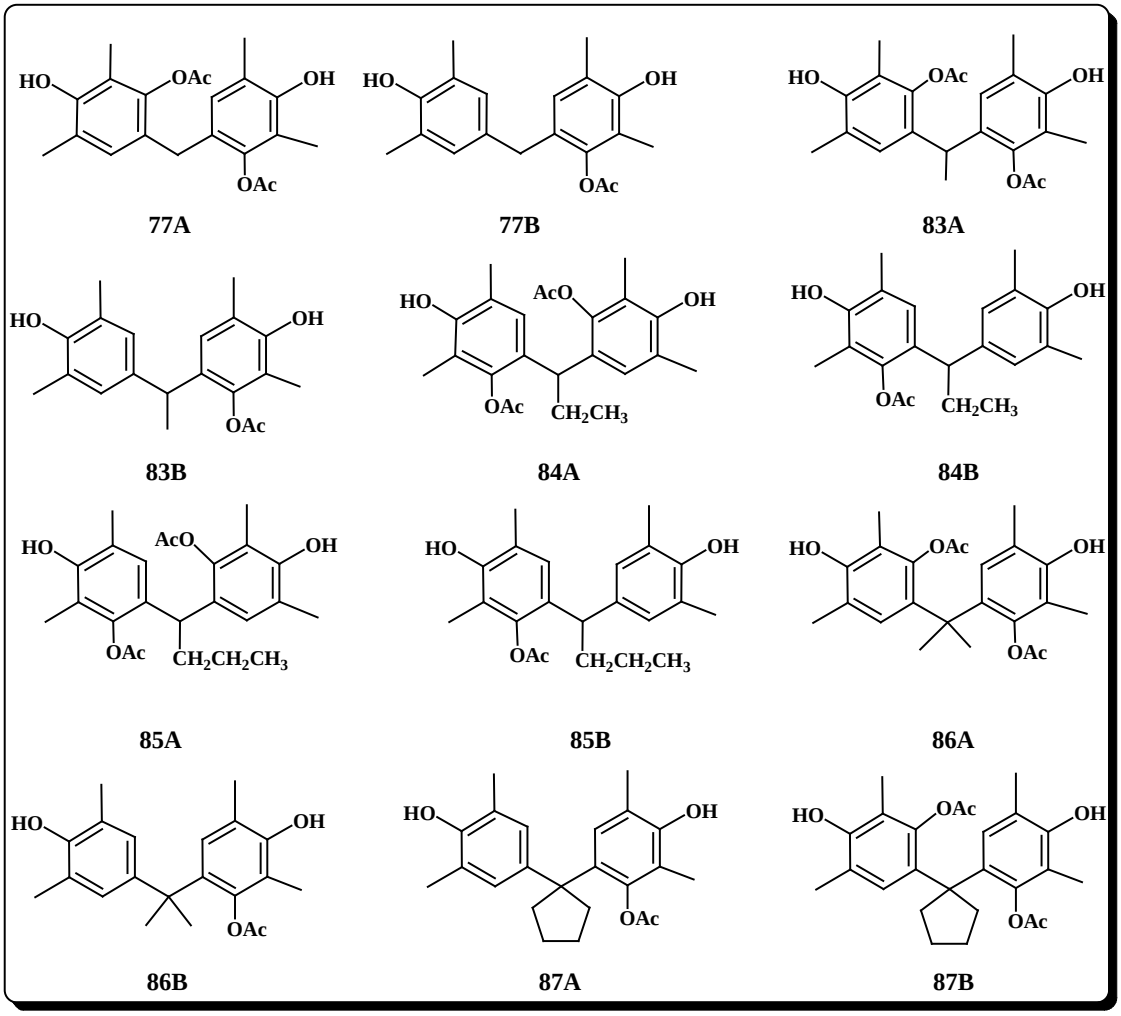


Figure 3.5: Structures of photochemical products of bis-cyclohexadienones **52-56**

3.4 Experimental section

Phenol, 2,6-dimethyl phenol, various aldehydes and ketones were purchased from Sigma Aldrich and used without further purification. Perchloric acid (70 % aq. Solution) was purchased from Merck and was used as such. All solvents were purchased as commercial grade and were distilled prior to use. Melting points were recorded in open capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer PC-16 FT IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300/400 MHz NMR spectrometer (75/100 MHz for ^{13}C respectively) using $CDCl_3$ or DMSO-d_6 (TMS as an internal standard). Mass spectra were obtained on Thermo-Fisher DSQ II GCMS instrument.

Purification of reaction products was carried out by column chromatography using silica gel (60-120 mesh size), using light petroleum and ethyl acetate mixtures as eluents. Thin layer chromatography was performed using Acme's Silica gel for TLC, and spots were visualized in iodine vapours.

Experimental procedures:

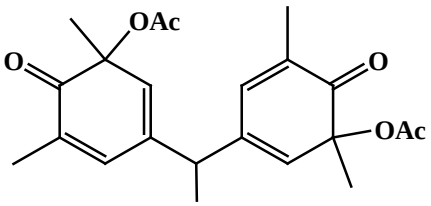
Typical experimental procedure for preparation of bisphenols 46-51:

To a stirred mixture of 2,6-dimethyl phenol **45** (5 g, 0.041 mol) and aldehyde/ketone (0.094 mol) in light petroleum (40 ml) hydrochloric acid (5 ml, 36 % w/v) was added in the case of aldehydes or H_2SO_4 (1.5 ml, 98%) in the case of ketones over a period of 15 minutes at room temperature (27^0C) and was further stirred for an appropriate time. (**Table 1**) The reaction mixture was then diluted ten times of its volume with water and was further stirred for 15 minutes. The solid thus obtained was filtered on a Buchner funnel, washed thoroughly with water and dried at 85-90^{o}C under vacuum to give a solid which was chromatographed over a column of silica gel. Elution of the column with light petroleum/ethyl acetate afforded bisphenol as a white crystalline solid. The structures of the products **46-51** were confirmed by completely matched mp, IR, ^{1}H and ^{13}C NMR and mass data are given in **chapter 5**.

Typical experimental procedure for syntheses of bis-acetoxy cyclohexadienones (52-57):

Lead tetra acetate (5.32 gm, 0.012 mol) was added to a solution of bisphenols (0.004 mol) in ethyl acetate (30 ml) in small portions with continuous stirring over a period of 15 minutes. The reaction mixture was stirred at room temperature (~27^{o}C) for an appropriate time (**Table 2)** after which it was diluted with ethyl acetate (150 ml) and stirred further for 15 minutes. Removal of the residue by filtration and concentration of the filtrate under reduced pressure furnished pale yellow liquids, which were chromatographed over a column of silica gel. Elution of the column with light petroleum and ethyl acetate gave pure product in good yield. Structure of the product was confirmed by its spectral and analytical analysis.

3-[1-(3-acetoxy-3,5-dimethyl-4-oxo-cyclohexa-1,5-dienyl)-ethyl]-1,5-dimethyl-6-oxo-cyclohexa-2,4-dienyl ester (53):



53

Mp. 149 °C

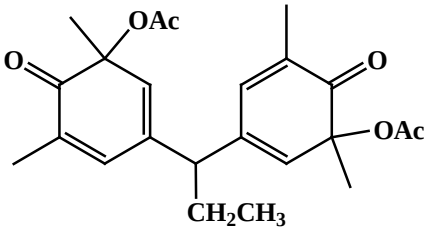
IR: (KBr): 1267, 1672, 1734, 3024 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (3H, d, *J=6.3 H_Z,* CH_3), 1.37 (6H, s, $2CH_3$), 1.90 (6H, s, $2CH_3$), 2.08 (6H, s, $2CH_3$), 3.11 (1H, q, *J* = 6.2 H_Z, CH), 5.91 (2H, s, olefinic), 6.60 (2H, s, olefinic).

^{13}C NMR (75 MHz $CDCl_3$): δ 13.91 (1C, CH_3), 15.19, 20.32, 28.83 (6C, CH_3), 42.30 (1C, CH), 78.32 (2C, carbon attached to $OCOCH_3$), 134.26, 134.97, 138.05, 138.72 (8C, olefinic), 168.99, 198.70 (4C, CO).

MS (EI): m/z Calculated for $C_{22}H_{26}O_2$ 386.44; found 386.04 (M^+).

3-[1-(3-acetoxy-3,5-dimethyl-4-oxo-cyclohexa-1,5-dienyl)-propyl]-1,5-dimethyl-6-oxo-cyclohexa-2,4-dienyl ester (54):



54

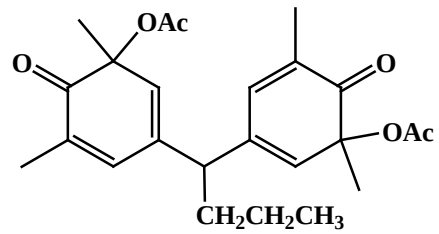
IR: (KBr): 1220, 1681, 1740, 3028 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (3H, t, *J* = 7.2 H_Z, CH_3), 1.61 (2H, m, CH_2), 1.85 (6H, s, $2CH_3$), 2.14 (6H, s, $2CH_3$), 2.32 (6H, s, $2CH_3$), 3.56 (1H, t, *J* = 7.2 H_Z, CH), 6.04 (2H, s, olefinic), 6.98 (2H, s, olefinic).

^{13}C NMR (100 MHz $CDCl_3$): δ 13.98 (1C, CH_3), 15.38 (1C, CH_2), 20.52, 24.14, 32.60 (6C, CH_3), 48.14 (1C, CH), 78.55 (2C, carbon attached to $OCOCH_3$), 133.73, 135.34, 138.27, 139.36 (8C, olefinic), 169.30, 199.07 (4C, CO).

MS (EI): m/z calculated for $C_{23}H_{28}O_6$ 400.19; found 399.82 (M^+).

3-[1-(3-acetoxy-3,5-dimethyl-4-oxo-cyclohexa-1,5-dienyl)-butyl]-1,5-dimethyl-6-oxo-cyclohexa-2,4-dienyl ester (55):



55

IR: (KBr): 1242, 1680, 1760, 3042 cm^{-1}.

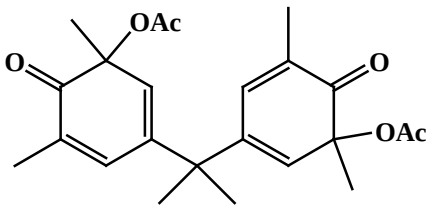
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, *J* = 7.5 Hz, CH_3), 1.24 (2H, m, CH_2), 1.44 (6H, s, $2CH_3$), 1.62 (2H, m, CH_2), 1.91 (6H, s, $2CH_3$), 2.09 (6H, s, $2CH_3$), 2.93 (1H, t, *J* = 7.0 Hz, CH),

5.91 (2H, s, olefinic), 6.55 (2H, s, olefinic).

^{13}C NMR (100 MHz $CDCl_3$): δ 14.12 (1C, CH_3), 15.35 (2C, CH_3), 20.27 (2C, CH_3), 24.05 (2C, CH_3), 31.93, 32.59 (2C, CH_2), 78.44 (2C, carbon attached to $OCOCH_3$), 133.70, 135.34, 138.24, 139.98 (8C, olefinic), 169.34, 199.03 (4C, CO).

MS (EI): m/z calculated for $C_{24}H_{30}O_6$ 414.20; found 414.36 (M^+).

3-[1-(3-acetoxy-3,5-dimethyl-4-oxo-cyclohexa-1,5-dienyl)-1-methyl-ethyl]-1,5-dimethyl-6-oxo-cyclohexa-2,4-dienylester (56):



56

Mp. 140 °C

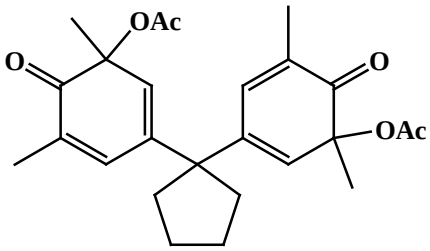
IR: (KBr): 1267, 1672, 1734, 3024 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (3H, s, $2CH_3$), 1.33 (6H, s, $2CH_3$), 1.88 (6H, s, $2CH_3$), 2.09 (6H, s, $2CH_3$), 5.95 (2H, s, olefinic), 6.58 (2H, s, olefinic).

^{13}C NMR (75 MHz $CDCl_3$): δ 15.44 (2C, CH_3), 20.55 (2C, CH_3), 24.05 (2C, CH_3), 25.77 (2C, CH_3), 41.25 (1C, Cq) 78.43 (2C, carbon attached to $OCOCH_3$), 133.29, 133.65, 138.09, 138.75 (8C, olefinic), 169.19, 198.84 (4C, CO).

MS (EI): m/z calculated for $C_{23}H_{26}O_2$ 400.05; found 400.46 (M^+).

3-[1-(3-acetoxy-3,5-dimethyl-4-oxo-cyclohexa-1,5-dienyl)-cyclopentyl]-1,5-di methyl-6-oxo-cyclohexa-2,4-dienylester (57):



57

IR: (KBr): 1240, 1674, 1730, 3010 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (6H, s, $2CH_3$), 1.66 (4H, m, $2CH_2$), 1.81 (4H, m, $2CH_2$), 1.90 (6H, s, $2CH_3$), 2.10 (6H, s, $2CH_3$), 5.97 (2H, s, olefinic), 6.58 (2H, s, olefinic).

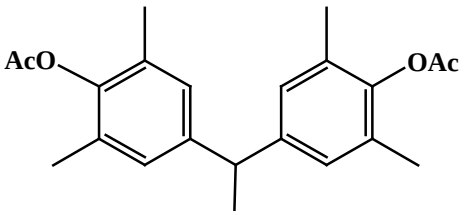
^{13}C NMR (75 MHz $CDCl_3$): δ 15.50 (2C, CH_3), 20.63 (2C, CH_3), 22.78, 24.21 (4C, CH_2), 34.01 (2C, CH_3), 54.21 (1C, Cq), 78.50 (2C, carbon attached to $OCOCH_3$), 133.68, 136.30, 138.56, 138.66 (8C, olefinic), 169.33, 198.97 (4C, CO).

MS (EI): m/z calculated for $C_{25}H_{30}O_2$ 426.5; found 426 (M^+).

Typical experimental procedure for syntheses of diacetates of bisphenol (64-68):

To a stirred solution of bisphenol (0.004 mol) in acetic anhydride (15 ml) sodium metaperiodate (1.28 gm, 0.006 mol) was added in small portions over a period of 15min. Stirring was further continued for of 5h while maintaining the reaction temperature 75 ^{0}C. The reaction mixture was allowed to cool down to room temperature and then poured into a vigorously stirred saturated solution of sodium bicarbonate (125ml) to neutralize the excess acid. The aqueous layer was then extracted with ethyl acetate (3 x 25 ml) and the organic extracts were successively washed with aqueous saturated bicarbonate (30 ml), water (20 ml), brine (20 ml) and was dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to furnish a dark brown residue, which was chromatographed over a column of silica gel using a mixture of light petroleum and ethyl acetate (85:15) furnished a white solid as acylated product. The structures of the products **64-68** were then confirmed by its physical properties and spectral data which are listed below.

Acetic acid 4-[1-(4-acetoxy-3,5-dimethyl-phenyl)-ethyl]-2,6-dimethyl-phenyl ester (64):



64

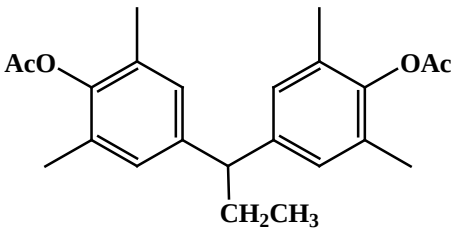
Mp. 112 °C

IR: (KBr): 1253, 1408, 1762, 3049 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.54 (3H, d, *J* = 7.2 H$_{Z,}$ CH$_3$), 2.12 (12H, s, 4CH$_3$), 2.31 (6H, s, 2CH$_3$), 3.96 (1H, q, *J* = 2.6 H$_{Z,}$ CH), 6.88 (4H, s, aromatic).

MS (EI) m/z: calculated for $C_{22}H_{26}O_4$ 354.18; found 354.08 (M^+).

Acetic acid 4-[1-(4-acetoxy-3,5-dimethyl-phenyl)-propyl]-2,6-dimethyl-phenyl ester (65):



65

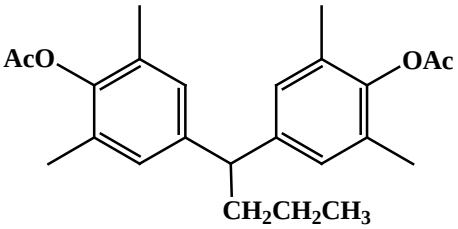
Mp. 96 °C

IR: (KBr): 1190, 1774, 2985, 3140 cm^{-1}.

^{1}H (400 MHz, CDCl$_3$): δ 0.82 (3H, t, *J* = 7.2 H$_Z$, CH$_3$), 1.976 (2H, m, CH$_2$), 2.105 (12H, s, 4CH$_3$), 2.30 (6H, s, 2CH$_3$), 3.50 (1H, t, *J* = 7.6 H$_{Z,}$ CH), 6.88 (4H, s, aromatic).

MS (EI) m/z: calculated for $C_{23}H_{26}O_4$ 368.47; found 368.11 (M^+).

Acetic acid 4-[1-(4-acetoxy-3,5-dimethyl-phenyl)-butyl]-2,6-dimethyl-phenyl ester 66:



66

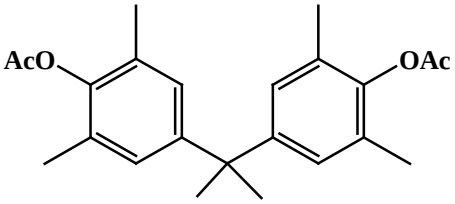
Mp. 118 °C

IR: (KBr): 1240, 1762, 2852, 3045 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, t, *J* = 7.4 H_Z, CH_3), 1.25 (2H, m, CH_2), 1.92 (2H, m, CH_2), 2.10 (12H, s, $4CH_3$), 2.29 (6H, s, $2CH_3$), 3.71 (1H, t, *J* = 7.8 H_Z, CH), 6.89 (4H, s, aromatic).

MS (EI) m/z: calculated for $C_{24}H_{28}O_4$ 382.49; found 382.12 (M^+).

Acetic acid 4-[1-(4-acetoxy-3,5-dimethyl-phenyl)-1-methyl-ethyl]-2,6-dimethyl-phenyl ester (67):



67

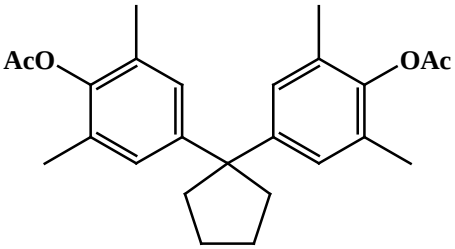
Mp. 138 °C

IR: (KBr): 1402, 1764, 3028 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (6H, s, $2CH_3$), 2.09 (12H, s, $4CH_3$), 2.31 (6H, s, $2CH_3$), 6.89 (4H, s, aromatic).

MS (EI) m/z: calculated for $C_{23}H_{28}O_4$ 368.2; found 368.10 (M^+).

Acetic acid 4-[1-(4-acetoxy-3,5-dimethyl-phenyl)-1-cyclopentyl]-2,6-dimethyl-phenyl ester (68):



68

Mp. 160 °C

IR: (KBr): 1402, 1764, 3028 cm^{-1}.

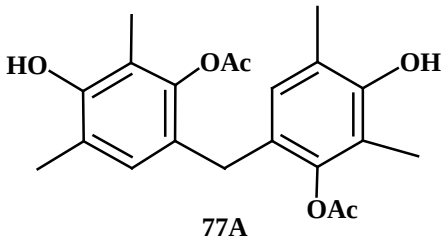
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71 (4H, m, $2CH_2$), 1.94 (4H, m, $2CH_2$), 2.14 (12H, s, $4CH_3$), 2.34 (6H, s, $2CH_3$), 6.49 (4H, s, aromatic).

MS (EI) m/z: calculated for $C_{25}H_{30}O_4$ 394.5; found 394.21 (M^+).

Typical experimental procedure for photochemical reaction of bis-acetoxy cyclohexadienone (52-57):

A solution of bis-acetoxy cyclohexadienone (0.003 mol) in acetone was irradiated with a mercury vapour lamp (125 W) in a quartz immersion well. After near completion of the reaction (TLC), acetone was removed under reduced pressure and the residue was purified by column chromatography over a column of silica gel. Elution of the column with light petroleum/ethyl acetate afforded two different products for each substrate. The structures of the products were then confirmed by their mp, FTIR, ^{1}H and ^{13}C NMR and mass spectral analysis.

Acetic acid 3-hydroxy -6-(4-hydroxy-3,5-dimethyl–benzyl)-2,4-dimethyl-phenyl ester (77A):



77A

Mp. 172 °C

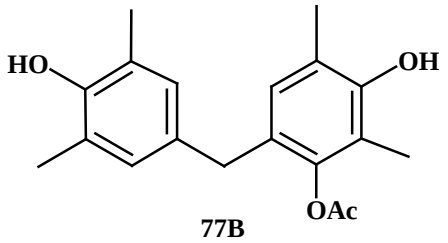
IR: (KBr): 1432, 1482, 1740, 3410 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (6H, s, $2CH_3$), 2.15 (6H, s, $2CH_3$), 2.28 (6H, s, $2CH_3$), 3.53 (2H, s, CH_2), 4.72 (2H, exchangeable OH), 6.67 (2H, s, aromatic).

^{13}C NMR (100 MHz $CDCl_3$): δ 9.66 (2C, CH_3), 15.77 (2C, CH_3), 20.51 (2C, CH_3), 29.81 (1C, CH_2), 116.40, 120.79, 123.61, 129.14, 146.20, 151.07 (12C, aromatic), 169.29 (2C, CO).

MS (EI) m/z: calculated for $C_{21}H_{24}O_6$ 372.16; found 371.83 (M^+).

Acetic acid 6-(2-acetoxy-4-hydroxy-3,5-dimethyl–benzyl)-3-hydroxy-2,4-dimethyl-phenyl ester (77B):



77B

Mp. 167 °C

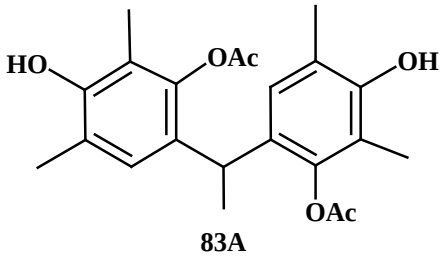
IR: (KBr): 1440, 1578, 1750, 3426 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (3H, s, CH_3), 2.16 (3H, s, CH_3), 2.21 (6H, s, $2CH_3$), 2.28 (3H, s, CH_3), 3.63 (2H, s, CH_2), 4.84 (2H, s, exchangeable OH), 6.77 (3H, s, aromatic).

^{13}C NMR (100 MHz $CDCl_3$): δ 9.70 (2C, CH_3), 15.80, 15.96 (2C, CH_3), 20.58 (1C, CH_3), 35.23 (1C, CH_2), 116.53, 120.84, 122.90, 125.13, 128.91, 129.23, 131.84, 146.17, 150.44, 151.01 (10C, aromatic), 169.28 (1C, CO).

MS (EI) m/z: calculated for $C_{19}H_{22}O_4$ 314.15; found 313.88 (M^+).

Acetic acid 3-hydroxy-6-[1-(4-hydroxy-3,5-dimethyl–phenyl)-ethyl]-2,4-dimethyl-phenyl ester (83A):



83A

Mp. 184 °C

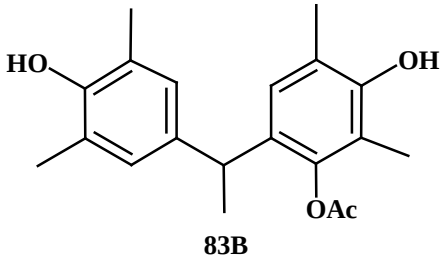
IR: (KBr): 1234, 1482, 1740, 2965, 3407 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (3H, d, *J* = 7.2 $H_{Z,}$ CH_3), 2.00 (6H, s, $2CH_3$), 2.18-2.34 (12H, m, $4CH_3$), 4.15 (1H, q, *J* = 7.2 Hz, CH), 4.70 (2H, s, exchangeable OH), 6.80 (2H, s, aromatic).

^{13}C NMR (50 MHz $CDCl_3$): δ 9.74 (1C, CH_3), 16.03 (2C, CH_3), 20.55 (2C, CH_3), 20.82 (2C, CH_3), 31.95 (1C, CH), 116.41, 120.73, 126.38, 129.20, 145.58, 150.86 (12C, aromatic), 171.28 (2C, CO).

MS (EI) m/z: calculated for $C_{22}H_{26}O_6$ 386.44; found 385.85 (M^+).

Acetic acid 6-[1-(2-acetoxy-4-hydroxy-3,5-dimethyl–phenyl)-ethyl]-3-hydroxy-2,4-dimethyl-phenyl ester (83B):



83B

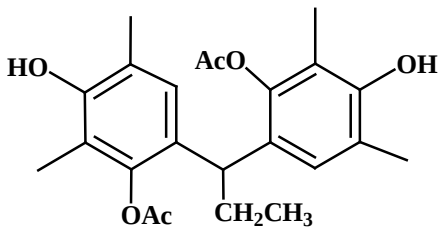
IR: (KBr): 1190, 1480, 1760, 2860, 3542 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (3H, d, *J* = 7.2 Hz, CH_3), 1.86 (3H, s, CH_3), 2.02 (3H, s, CH_3), 2.21 (6H, s, $2CH_3$), 2.34 (3H, s, CH_3), 3.78 (1H, q, *J* = 7.2 Hz, CH), 4.71 (2H, s, exchangeable OH), 6.78 (3H, s, aromatic).

^{13}C NMR (100 MHz $CDCl_3$): δ 9.83 (1C, CH_3), 15.26 (2C, CH_3), 16.07, 20.60, 29.72 (3C, CH_3), 37.54 (1C, CH), 116.48, 122.73, 126.68, 127.55, 132.70, 133.43, 140.46, 146.11, 150.33, 151.47 (10 C, aromatic), 169.41 (1C, CO).

MS (EI) m/z: calculated for $C_{20}H_{24}O_4$ 328.17; found 328.32(M^+).

Acetic acid 6-[1-(2-acetoxy-4-hydroxy-3,5-dimethyl–phenyl)-propyl]-3-hydroxy-2,4-dimethyl-phenyl ester (84A):



84A

Mp. 190 °C

IR: (KBr): 1226, 1482, 1745, 2955, 3445 cm^{-1}.

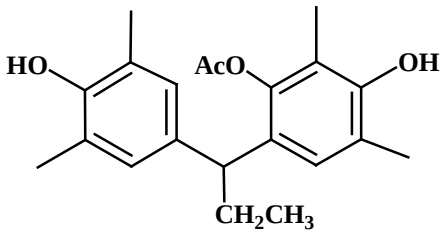
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (3H, t, *J* = 7.2 Hz, CH_3), 1.87 (2H, m, CH_2), 1.99 (6H, s,

$2CH_3$), 2.20 (6H, s, 2 CH_3), 2.33 (6H, s, $2CH_3$), 4.13 (1H, t, *J* = 7.2 Hz, CH), 4.65 (2H, s, exchangeable OH), 6.82 (2H, s, aromatic).

^{13}C NMR (100 MHz $CDCl_3$): δ 9.87 (1C, CH_3), 13.08 (2C, CH_3), 14.17 (2C, CH_3), 16.10 (2C, CH_3), 20.58 (1C, CH_2), 31.62 (1C, CH), 116.48, 120.59, 124.69, 126.83, 146.26, 150.79 (12C, aromatic), 169.56 (2C, CO).

MS (EI) m/z: calculated for $C_{23}H_{28}O6$ 400.46; found 400.48 (M^+).

Acetic acid 3-hydroxy-6-[1-(4-hydroxy-3,5-dimethyl–phenyl)-propyl]-2,4-dimethyl-phenyl ester (84B):



84B

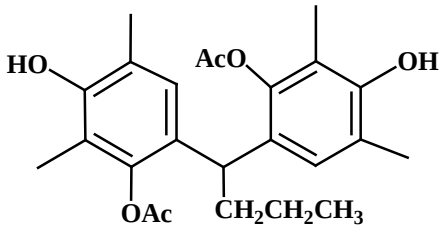
IR: (KBr): 1200, 1750, 2870, 3540 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, t, *J* = 7.2 Hz, CH_3), 1.27 (2H, m, CH_2), 2.00 (3H, s, CH_3), 2.22 (9H, superimposed s, $3CH_3$), 2.33 (3H, s, CH_3), 3.54 (1H, t, *J* = 7.2 Hz, CH), 4.50 (2H, s, exchangeable OH), 6.81 (1H, s, aromatic), 6.83 (2H, s, aromatic).

^{13}C NMR (100 MHz $CDCl_3$): δ 9.28 (1C, CH), 12.98 (2C, CH_3), 15.10, 16.11, 20.83 (3C, CH_3), 28.92 (1C, CH_2), 29.72 (1C, CH), 113.67, 120.64, 122.69, 127.78, 127.83, 128.09, 136.10, 137.42, 147.12, 150.24 (10C, aromatic), 170.44 (1C, CO).

MS (EI) m/z: calculated for $C_{21}H_{26}O_4$ 342.18; found 342.63 (M^+).

Acetic acid 6-[1-(2-acetoxy-4-hydroxy-3,5-dimethyl–phenyl)-butyl]-3-hydroxy-2,4-dimethyl-phenyl ester (85A):



85A

Mp. 142 °C

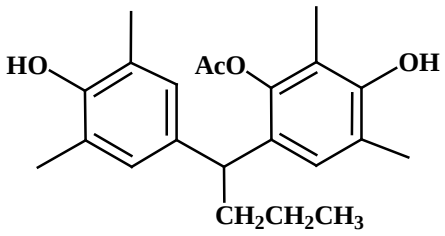
IR: (KBr): 1205, 1483, 1747, 2976, 3440 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, *J* = 7.2 Hz, CH_3), 1.27 (2H, m, CH_2), 1.83 (2H, m, CH_2), 1.99 (6H, s, $2CH_3$), 2.19 (6H, s, $2CH_3$), 2.33 (6H, s, $2CH_3$), 3.97 (1H, t, *J* = 7.2 Hz, CH), 4.72 (2H, s, phenolic OH), 6.82 (2H, s, aromatic).

^{13}C NMR (100 MHz $CDCl_3$): δ 9.87 (1C, CH_3), 17.45, 18.00, 19.46 (6C, CH_3), 29.07, 31.67 (2C, CH_2), 36.72 (1C, CH), 116.49, 120.65, 126.90, 145.98, 146.62, 150.79 (12C, aromatic), 169.16 (1C, CO).

MS (EI) m/z: calculated for $C_{24}H_{30}O_6$ 414.2; found 414.45 (M^+).

Acetic acid 3-hydroxy-6-[1-(4-hydroxy-3,5-dimethyl–phenyl)-butyl]-2,4-dimethyl-phenyl ester (85B):



85B

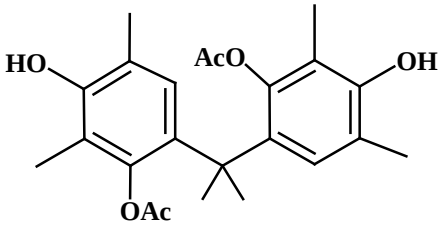
IR: (KBr): 1204, 1480, 1760, 2880, 3532 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, t, *J* = 7.2 Hz, CH_3), 1.26 (2H, m, CH_2), 1.96 (2H, m, CH_2), 2.11 (3H, s, CH_3), 2.25 (9H, s, CH_3), 2.33 (3H, s, CH_3), 3.66 (1H, t, *J* = 7.2 Hz, CH), 4.61 (2H, s, phenolic OH), 6.81 (2H, s, aromatic), 6.83 (1H, s, aromatic).

^{13}C NMR (100 MHz $CDCl_3$): δ 14.12 (1C, CH_3), 16.12 (2C, CH_3), 20.27, 21.30, 26.32 (3C, CH_3), 29.72, 32.69 (2C, CH_2), 39.73 (1C, CH), 112.77, 118.83, 122.69, 127.73, 130.57, 134.51, 138.01, 140.86, 146.52, 149.65 (10C, aromatic), 172.33 (1C, CO).

MS (EI) m/z: calculated for $C_{22}H_{28}O_4$ 356.2; found 355.95 (M^+).

Acetic acid 6-[1-(2-acetoxy-4-hydroxy-3,5-dimethyl–phenyl)-methyl-ethyl]-3-hydroxy-2,4-dimethyl-phenyl ester (86A):



86A

Mp. 202 °C

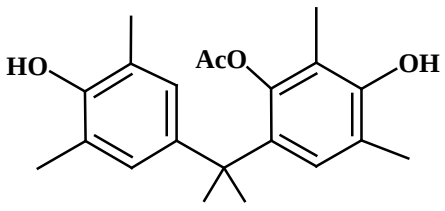
IR: (KBr): 1205, 1483, 1747, 2976, 3440 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (6H, s, $2CH_3$), 1.88 (12H, s, $4CH_3$), 2.26 (6H, s, $2CH_3$), 4.70 (2H, s, exchangeable OH), 7.08 (2H, s, aromatic).

^{13}C NMR (100 MHz $CDCl_3$): δ 16.19, 28.48, 30.98, 31.25 (8C, CH_3), 41.37 (1C, Cq), 122.16 126.96, 132.18, 136.47, 142.73, 149.89 (12C, aromatic), 170.16 (2C, CO).

MS (EI) m/z: calculated for $C_{23}H_{28}O_6$ 400.19; found 399.27 (M^+).

Acetic acid 3-hydroxy-6-[1-(4-hydroxy-3,5-dimethyl–phenyl)-1-methyl-ethyl]-2,4-dimethyl-phenyl ester (86B):



86B

Mp. 186 °C

IR: (KBr): 1204, 1480, 1580, 1760, 3540 cm^{-1}.

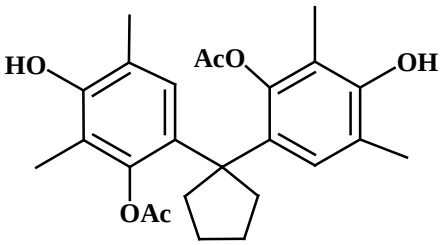
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (6H, s, $2CH_3$), 2.20 (3H, CH_3), 2.22 (12H, s, $4CH_3$),

4.54 (2H, s, exchangeable OH), 6.85 (3H, s, aromatic).

^{13}C NMR (100 MHz $CDCl_3$): δ 10.02 (2C, CH_3), 14.21, 16.06, 20.55, 29.79, 31.61 (5C, CH_3), 39.44 (1C, Cq), 117.58, 119.96, 125.24, 128.28, 132.57, 134.71, 143.54, 145.79, 150.65, 152.57 (10C, aromatic), 168.49 (2C, CO).

MS (EI) m/z: calculated for $C_{23}H_{28}O_6$ 342.43; found 342.63 (M^+).

Acetic acid 6-[1-(2-acetoxy-4-hydroxy-3,5-dimehyl-phenyl)-cyclopentyl]-3-hydroxy-2,4-dimethyl-phenyl ester (87A):



87A

Mp. 212 °C

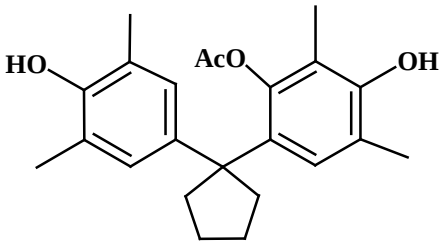
IR (KBr): 1226, 1482, 1603, 1741, 3493 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (4H, m, $2CH_2$), 1.93 (4H, s, $2CH_2$), 2.12 (6H, s, $2CH_3$), 2.14 (6H, s, $2CH_3$), 2.34 (3H, s, CH_3), 5.32 (2H, s, OH), 6.49 (2H, s, aromatic).

^{13}C NMR (100 MHz $CDCl_3$): δ 15.00, 20.14, 30.99 (6C, CH_3), 38.04, 55.22 (4C, CH_2), 58.77 (1C, Cq), 126.08, 129.24, 130.33, 132.74, 142.74, 147.46 (12C, aromatic), 165.44 (1C, CO).

MS (EI) m/z calculated for $C_{25}H_{30}O_6$ 426.2; found 426.00 (M^+).

Acetic acid 3-hydroxy-6-[1-(4-hydroxy-3,5-dimethyl-phenyl)-cyclopentyl]-2,4-dimethyl-phenyl ester (87B):



87B

IR (KBr): 1234, 1482, 1731, 3407 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (4H, m, CH_2), 1.56 (4H, m, CH_2), 1.61 (6H, s, $2CH_3$), 2.08 (6H, s, $2CH_3$), 2.10 (6H, s, $2CH_3$), 4.33 (2H, s, exchangeable OH), 5.83 (2H, s, aromatic), 5.94 (1H, s, aromatic)

^{13}C NMR (100 MHz $CDCl_3$): δ 14.97 (2C, CH_3), 18.24, 22.82, 28.16 (2C, CH_3), 30.99, 38.01 (4C, CH_2), 50.22 (1C, Cq), 120.88, 125.62, 126.55, 127.70, 129.37, 130.04, 134.40, 136.73, 137.59, 143.90 (10C, aromatic), 175.43 (1C, CO).

MS (EI) m/z calculated for $C_{25}H_{30}O_6$ 368.2; found 368.00 (M^+).

3.5 Conclusion

We have developed a novel method for the preparation of bisphenols **46-51**. The treatment of bisphenols **46-51** with LTA in ethyl acetate furnished bis-cyclohexadienones **52-57** while with $NaIO_4$ in acetic anhydride it resulted in the formation of acetylated products **64-68**. A probable mechanism for the acetylation of the bisphenol is also proposed. The photochemical behaviour of bis-cyclohexadienones was also investigated and it was found that cyclohexadienones on UV irradiation undergo photochemical aromatisation resulting in the formation of two different bis-phenols with migration of both the acetate groups followed by aromatisation and by migration of an acetate group in one cyclohexadienone unit followed by deacetylation from the other cyclohexadienone ring.

3.6 References

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3.7 Spectral data of compounds

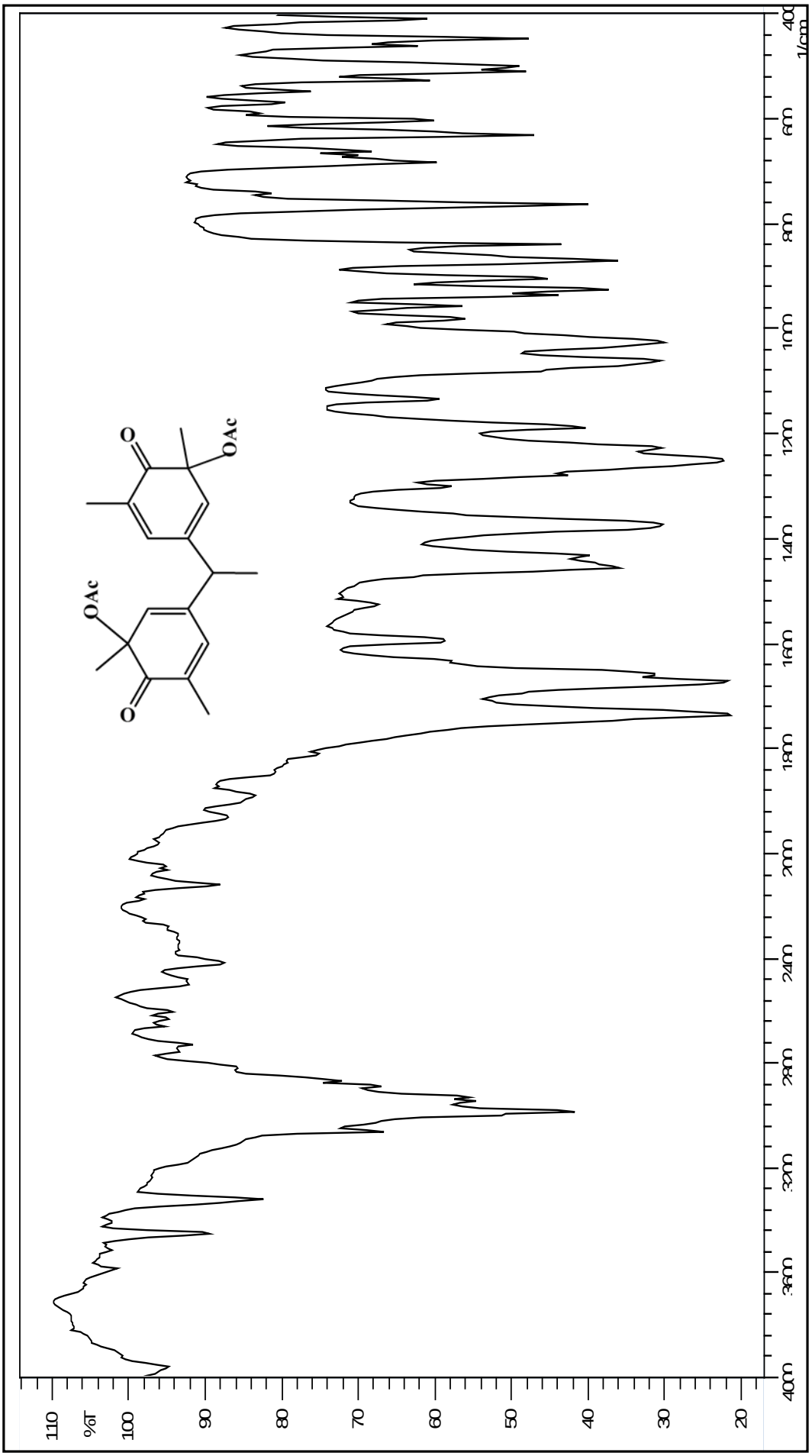


Figure 3.6: FTIR spectrum of compound **53**

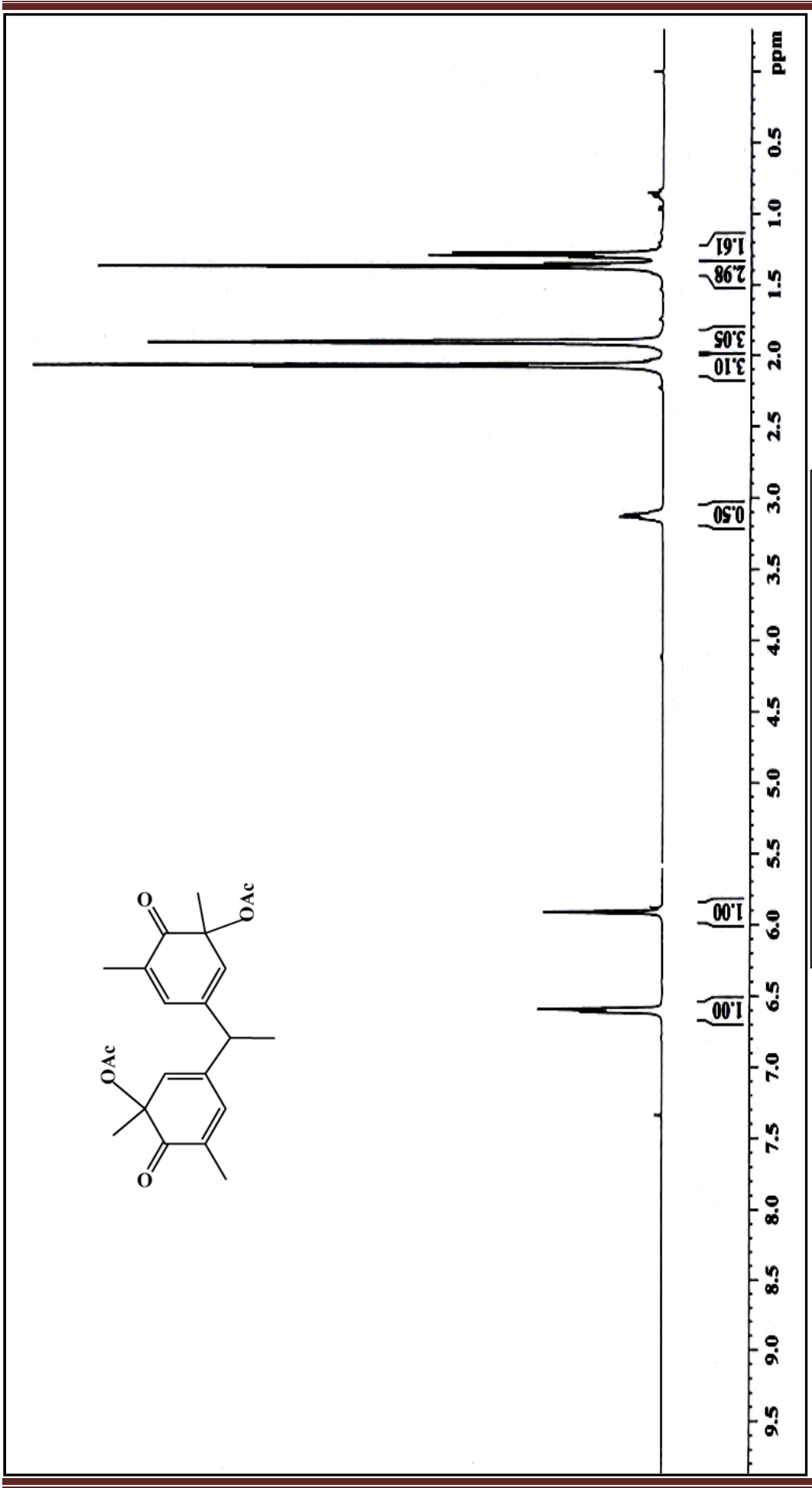


Figure 3.7: ^{1}H NMR spectrum of compound 53

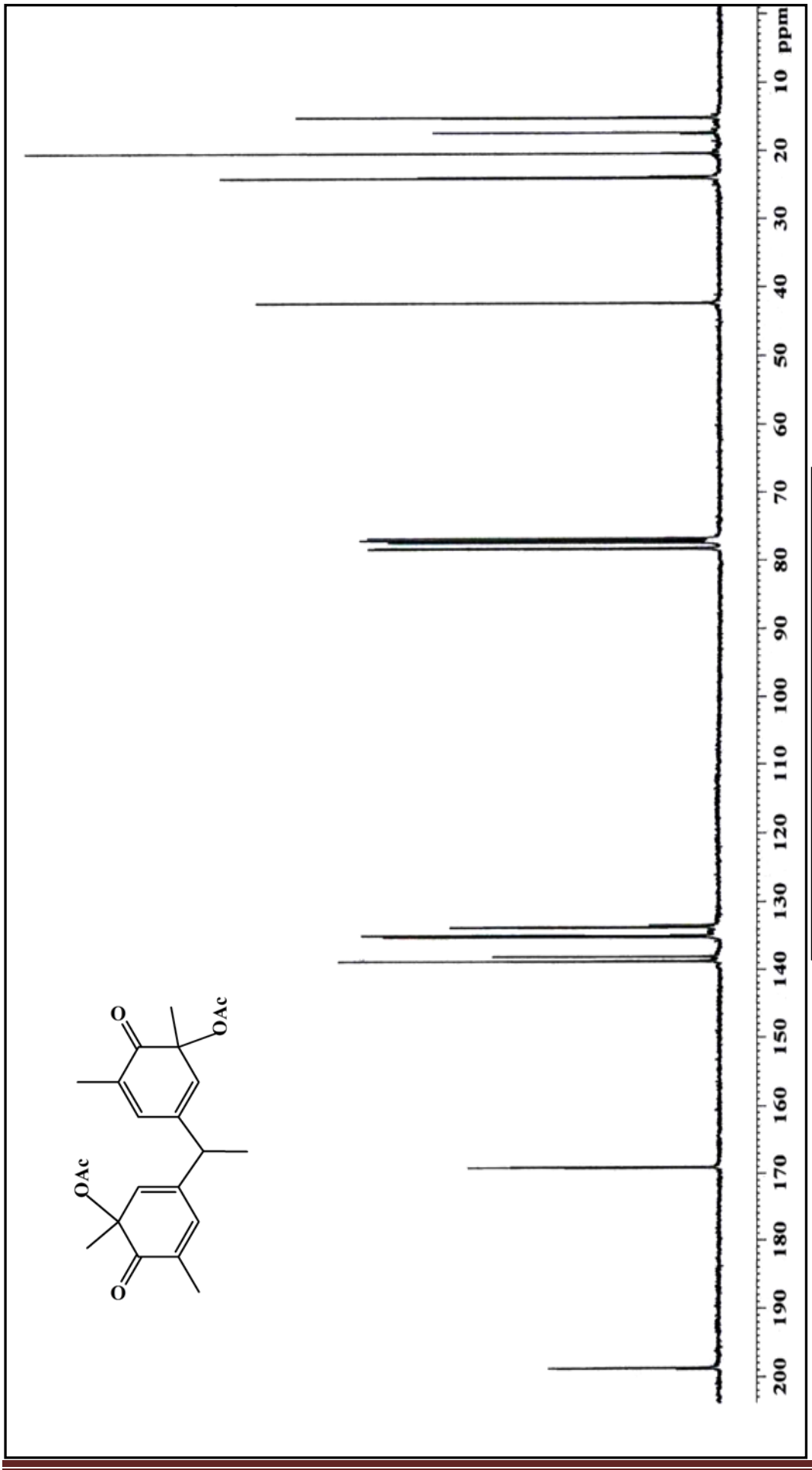


Figure 3.8: ^{13}C NMR spectrum of compound **53**

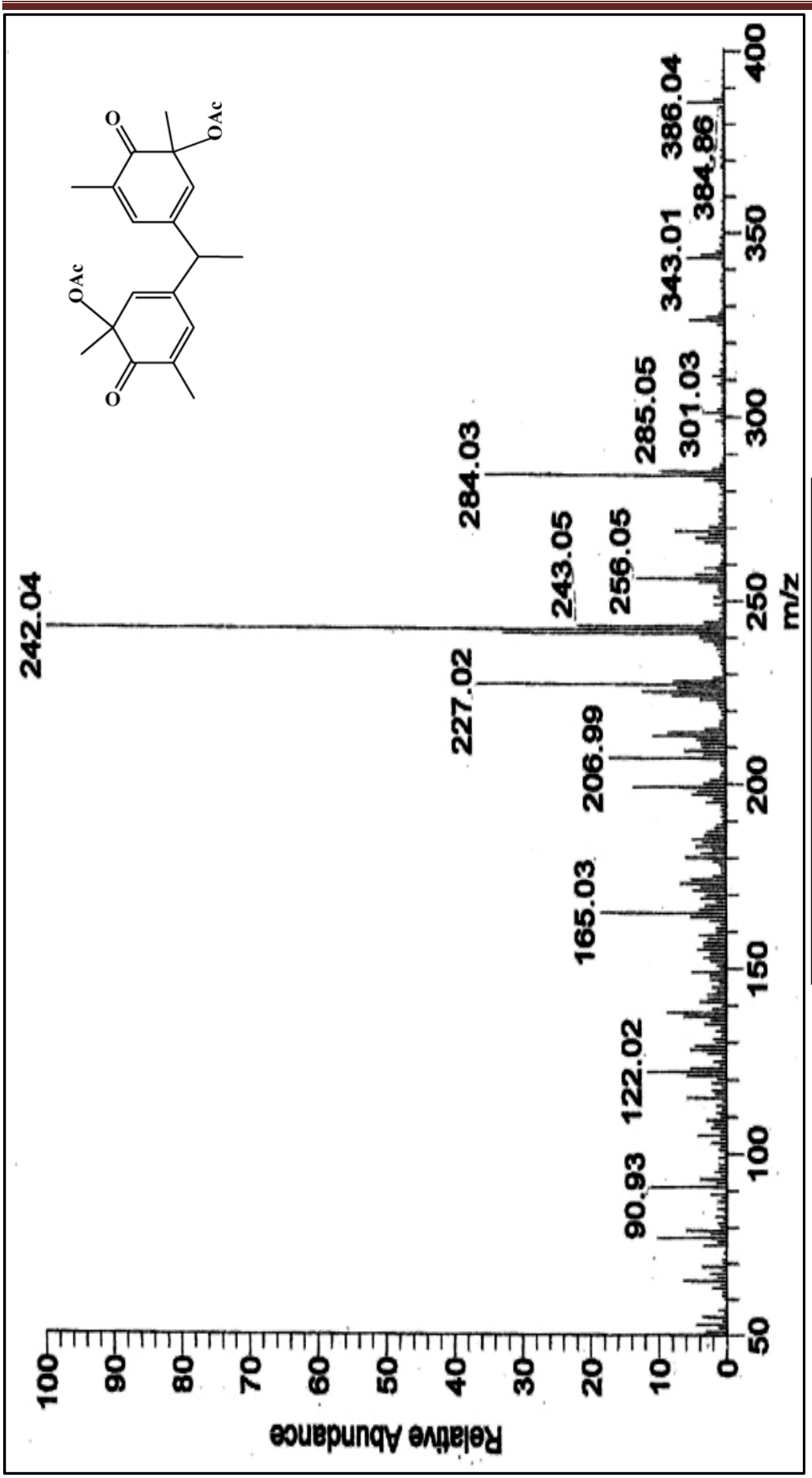


Figure 3.9: EI-MS spectrum of compound **53**

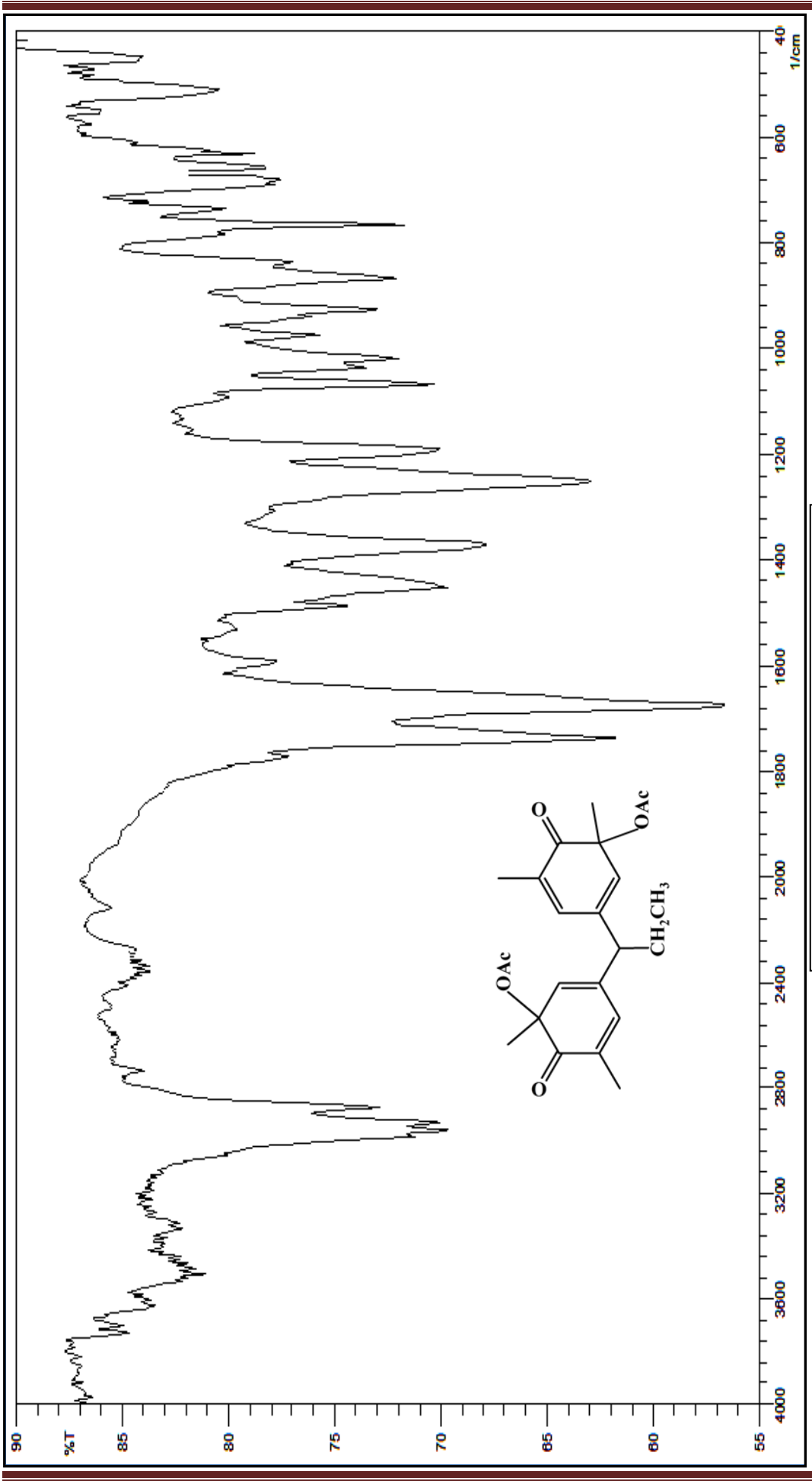


Figure 3.10: FTIR spectrum of compound **54**

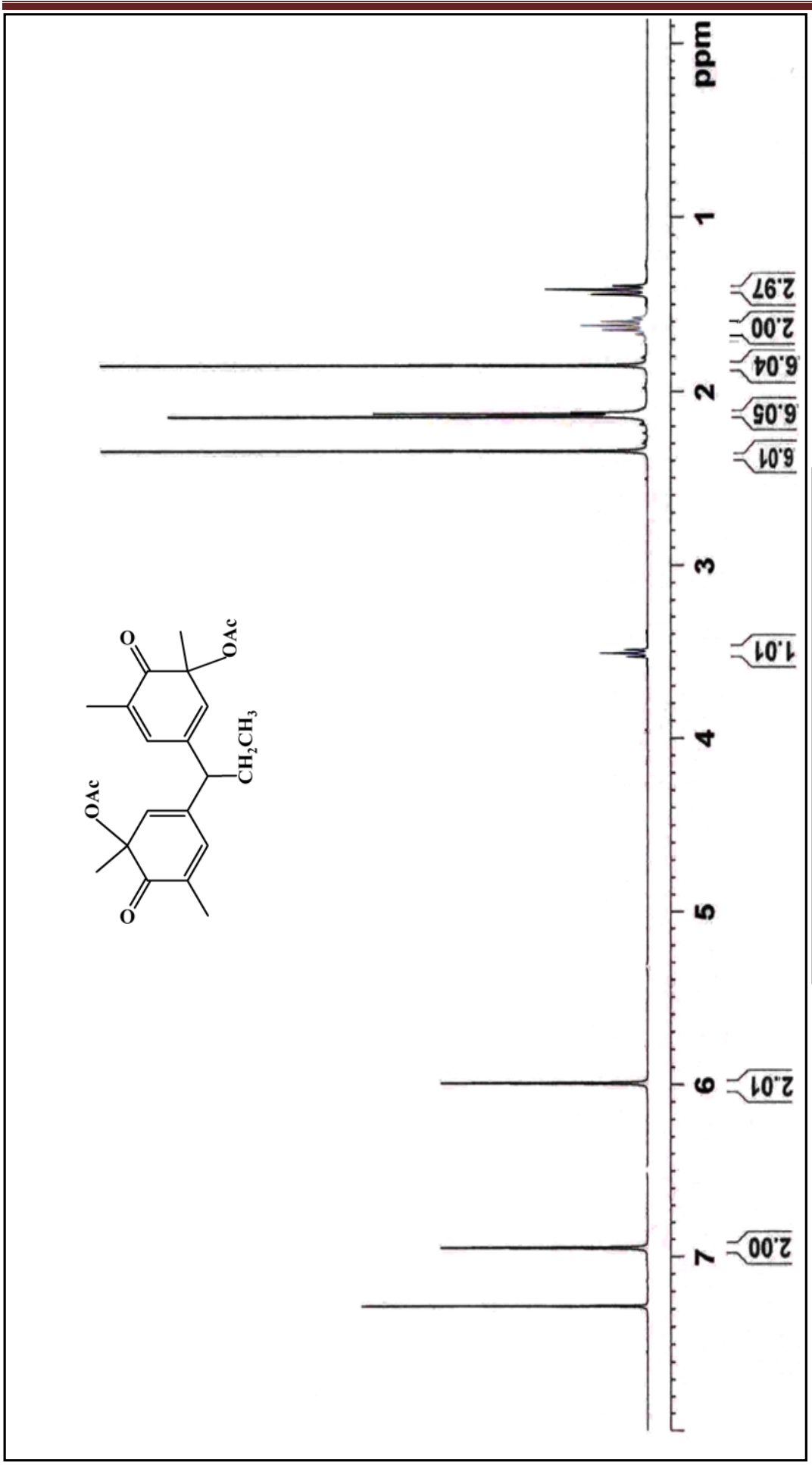


Figure 3.11: ^{1}H NMR spectrum of compound **54**

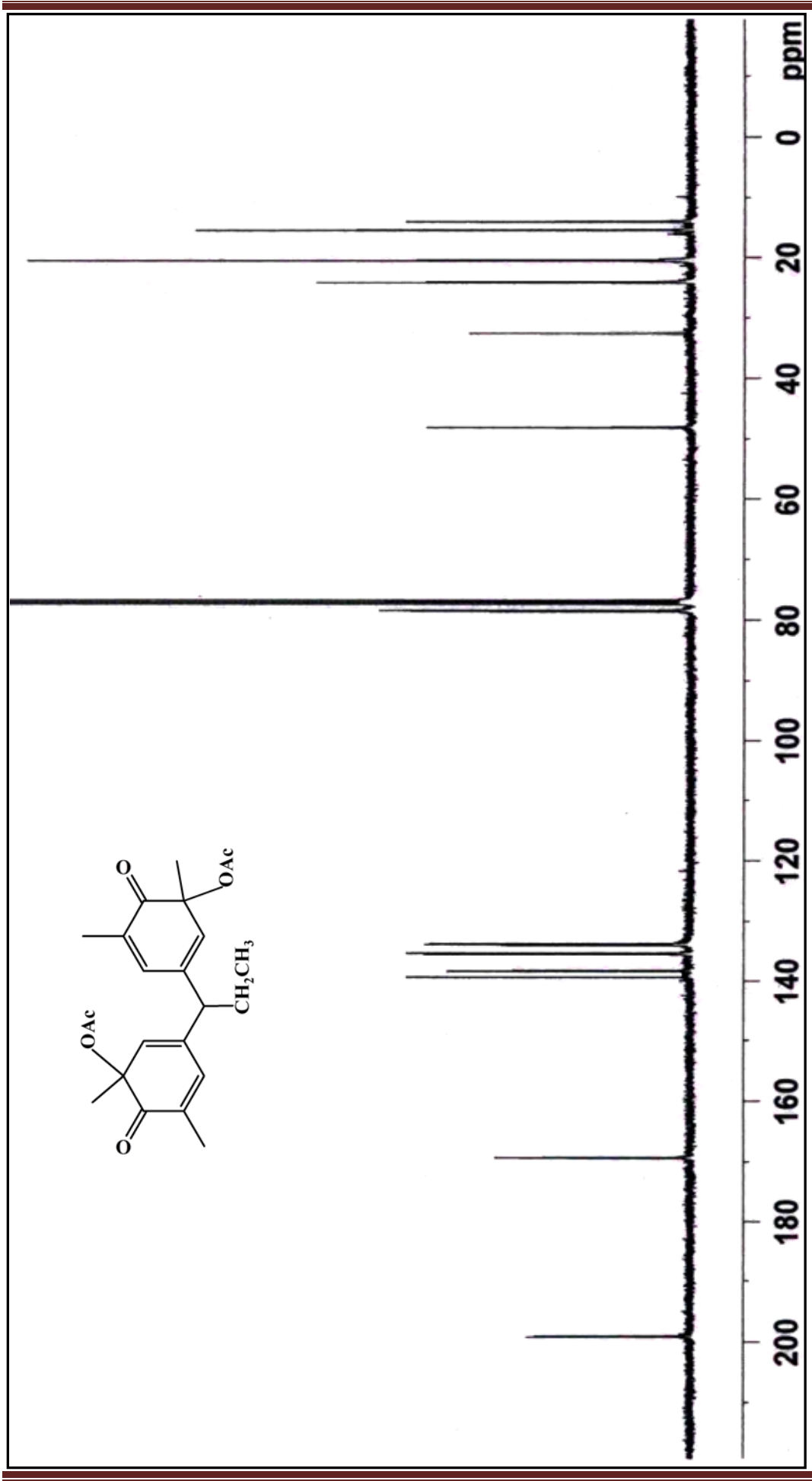


Figure 3.12: ^{13}C NMR spectrum of compound **54**

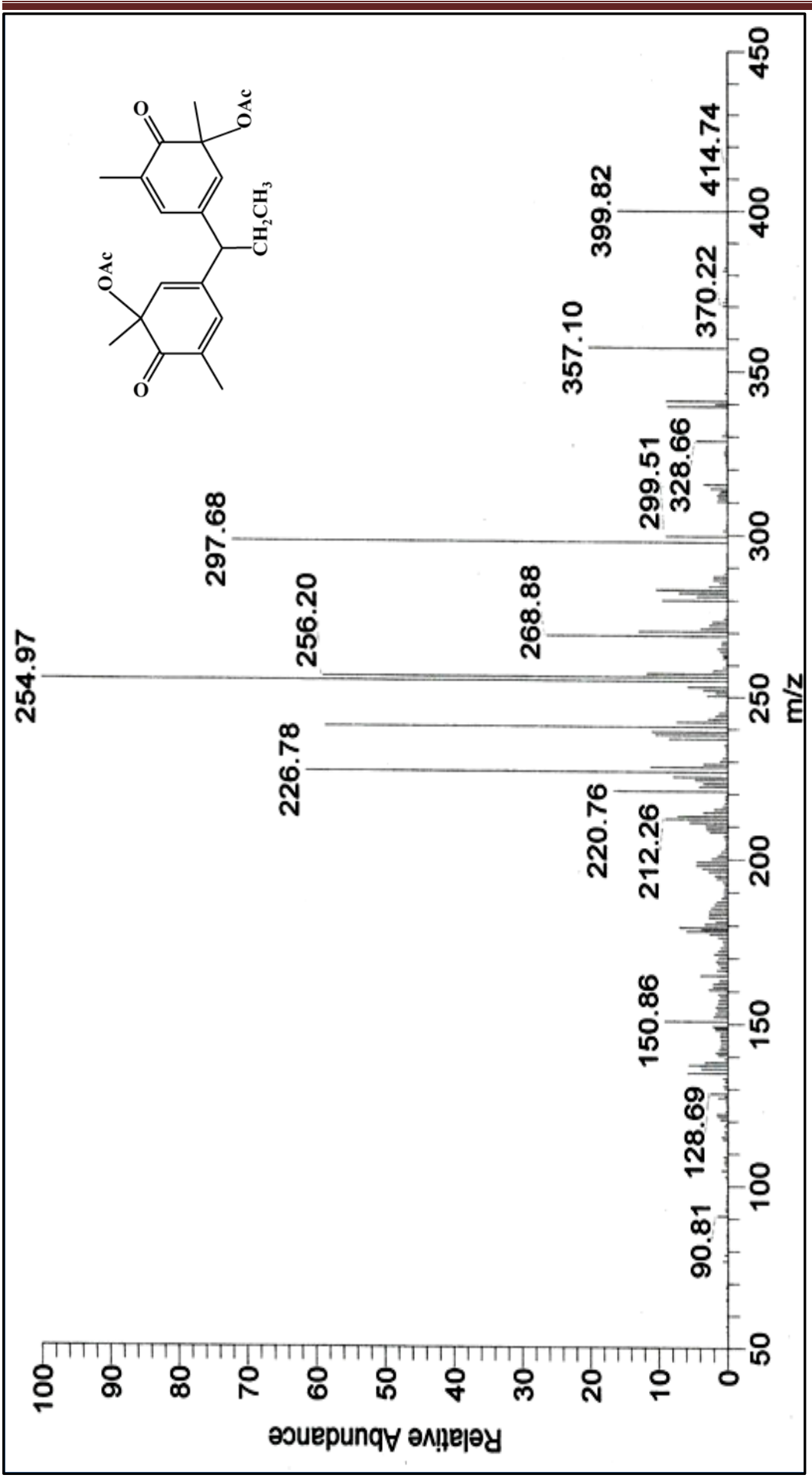


Figure 3.13: EI-MS spectrum of compound **54**

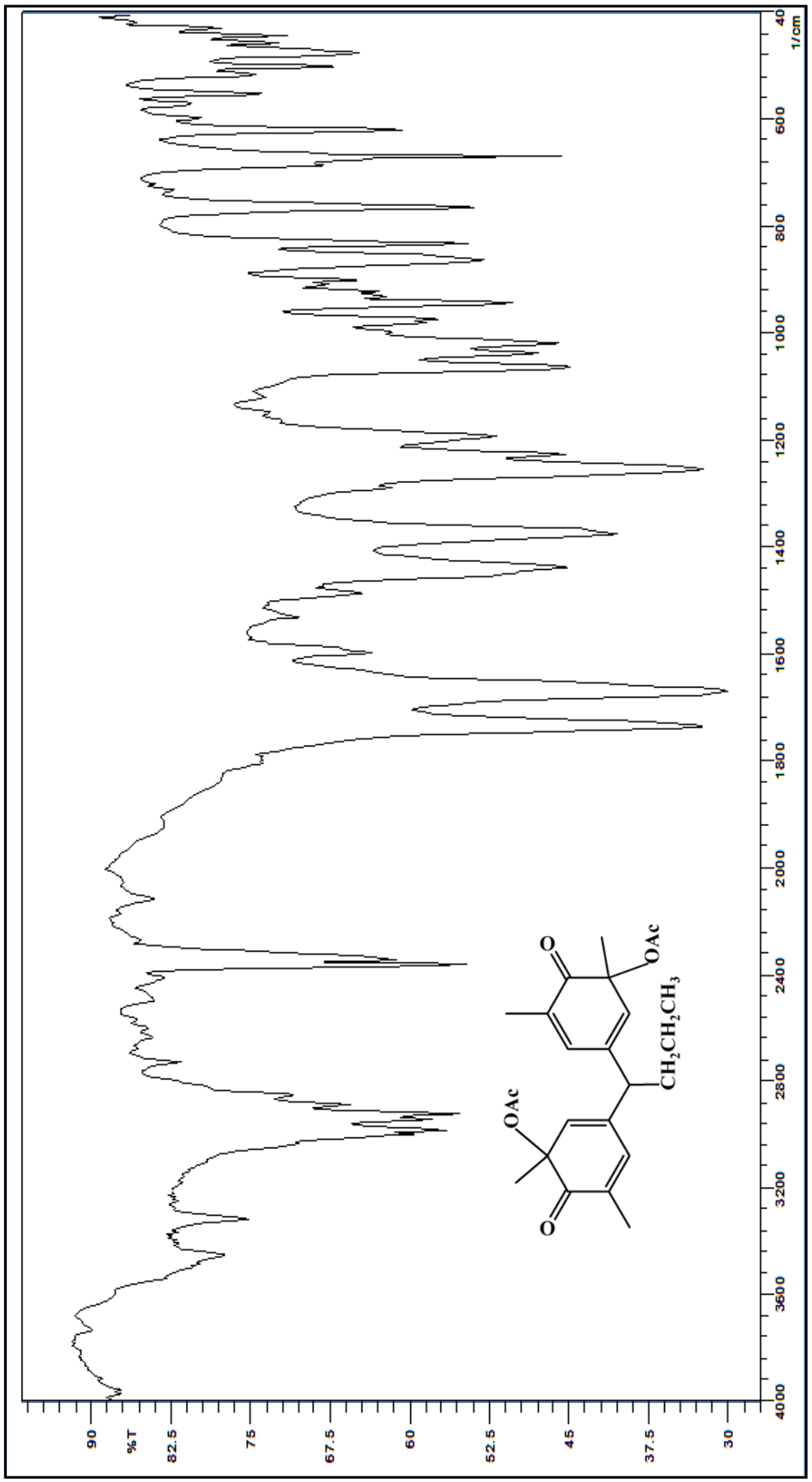


Figure 3.14: FTIR spectrum of compound **55**

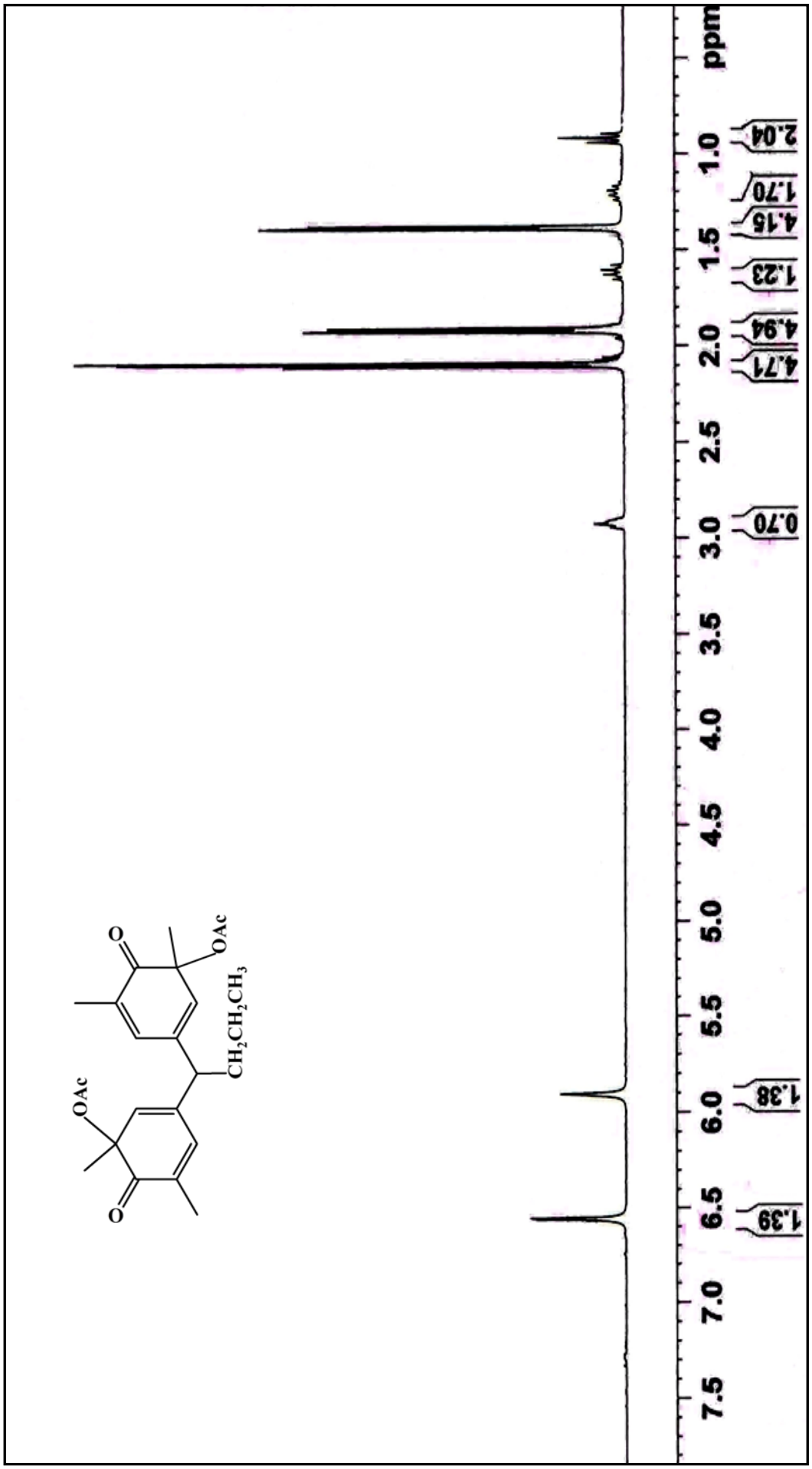


Figure 3.15: ^{1}H NMR spectrum of compound **55**

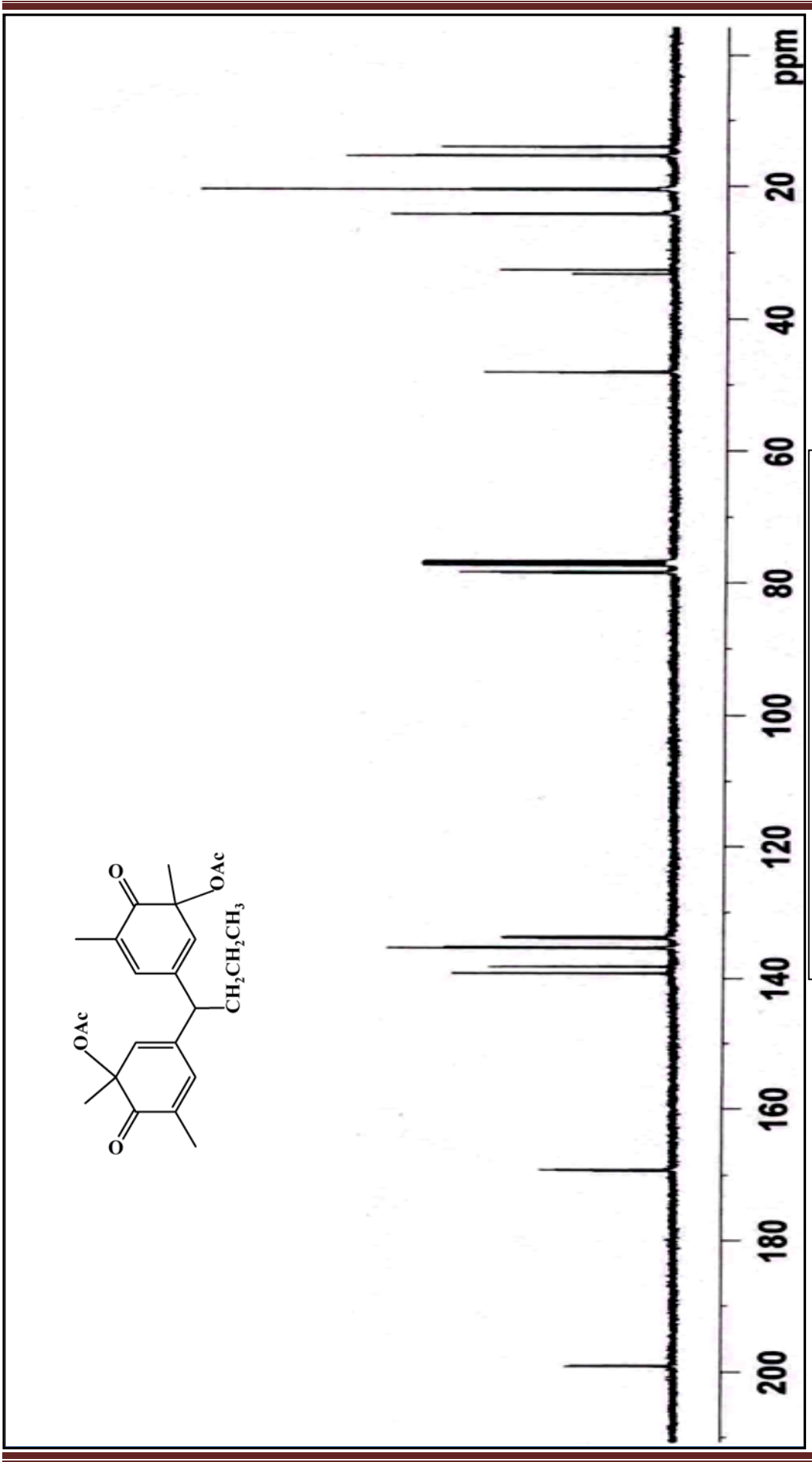


Figure 3.16: ^{13}C NMR spectrum of compound **55**

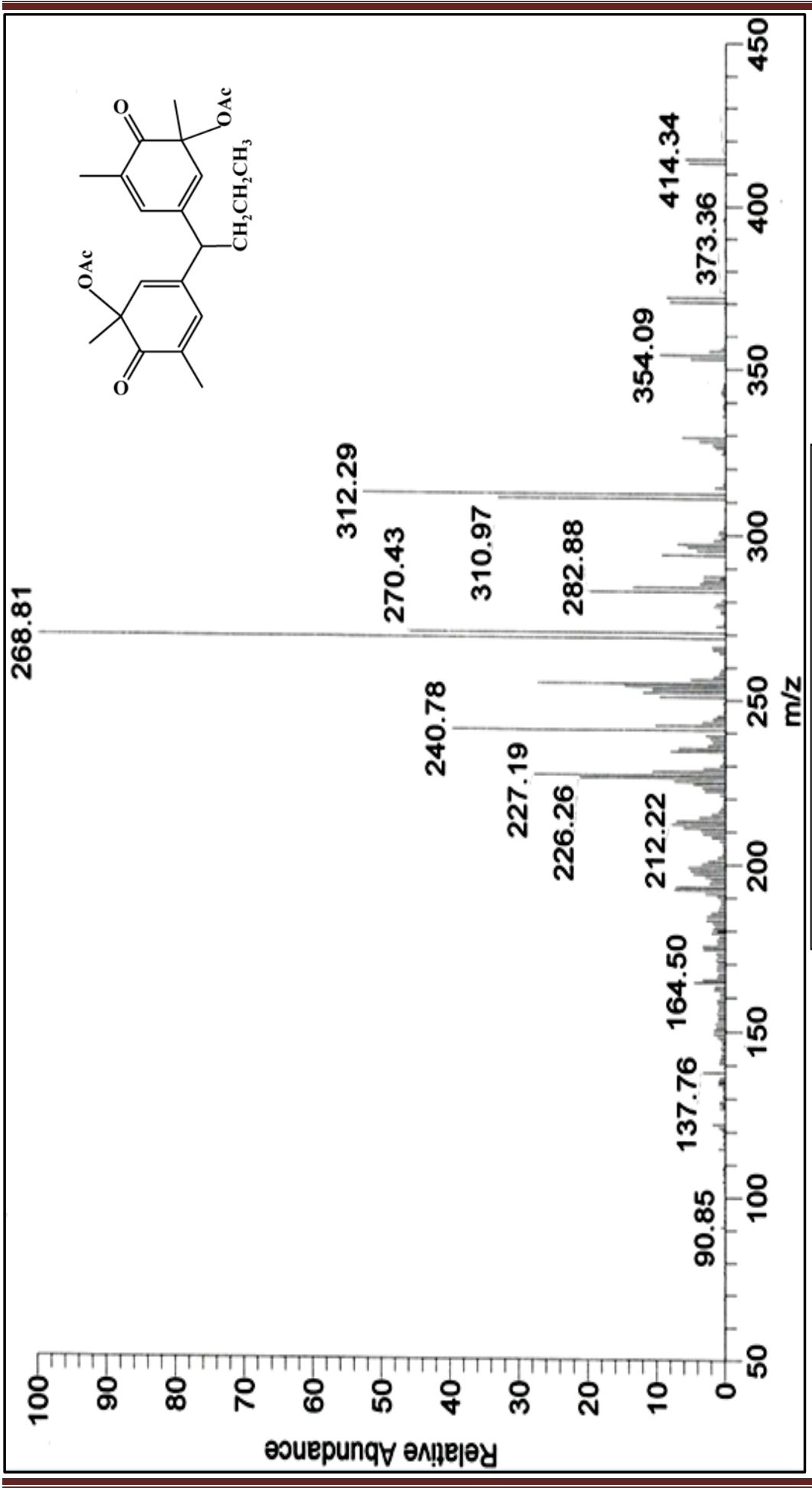


Figure 3.17: EI-MS spectrum of compound 55

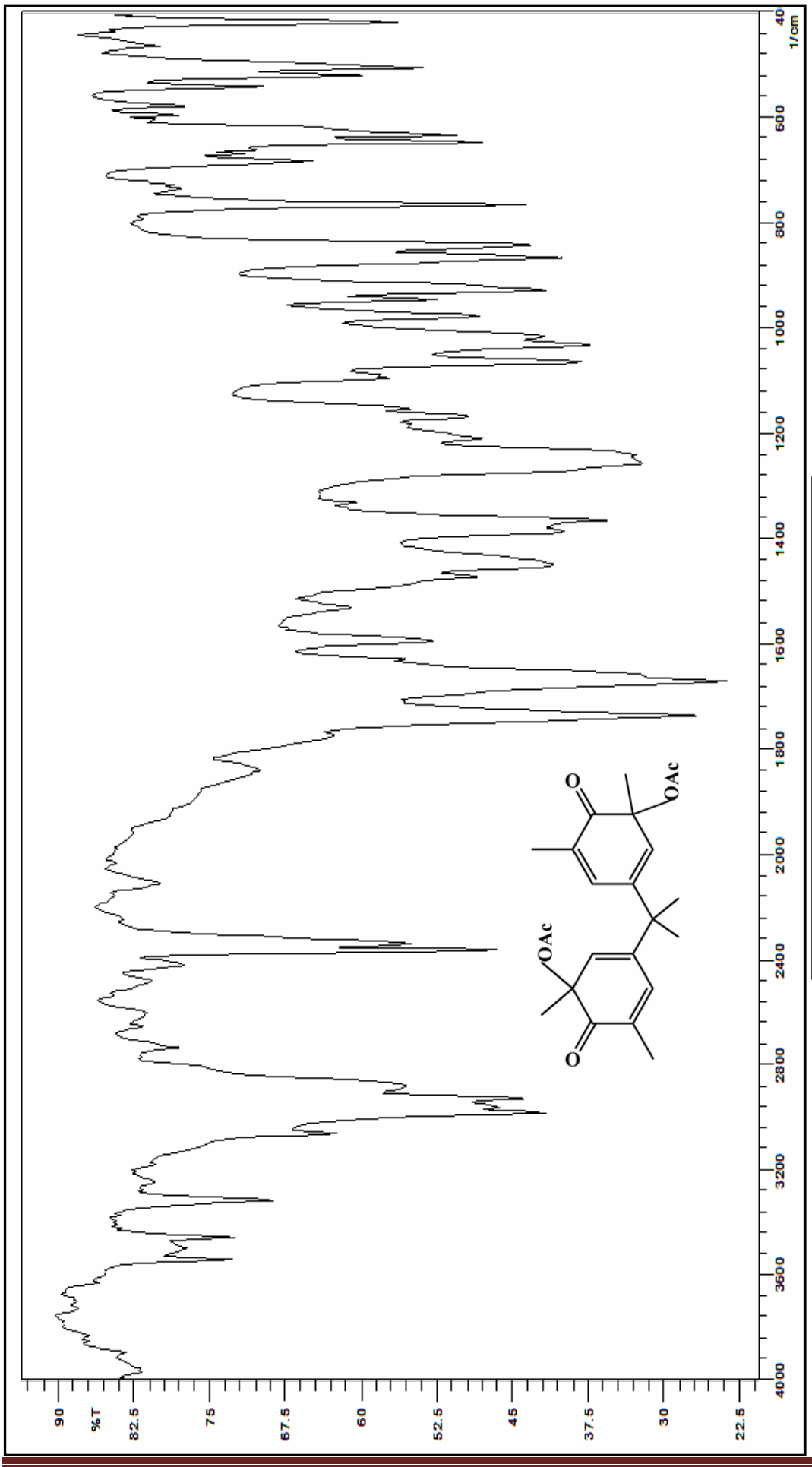


Figure 3.18: FTIR spectrum of compound **56**

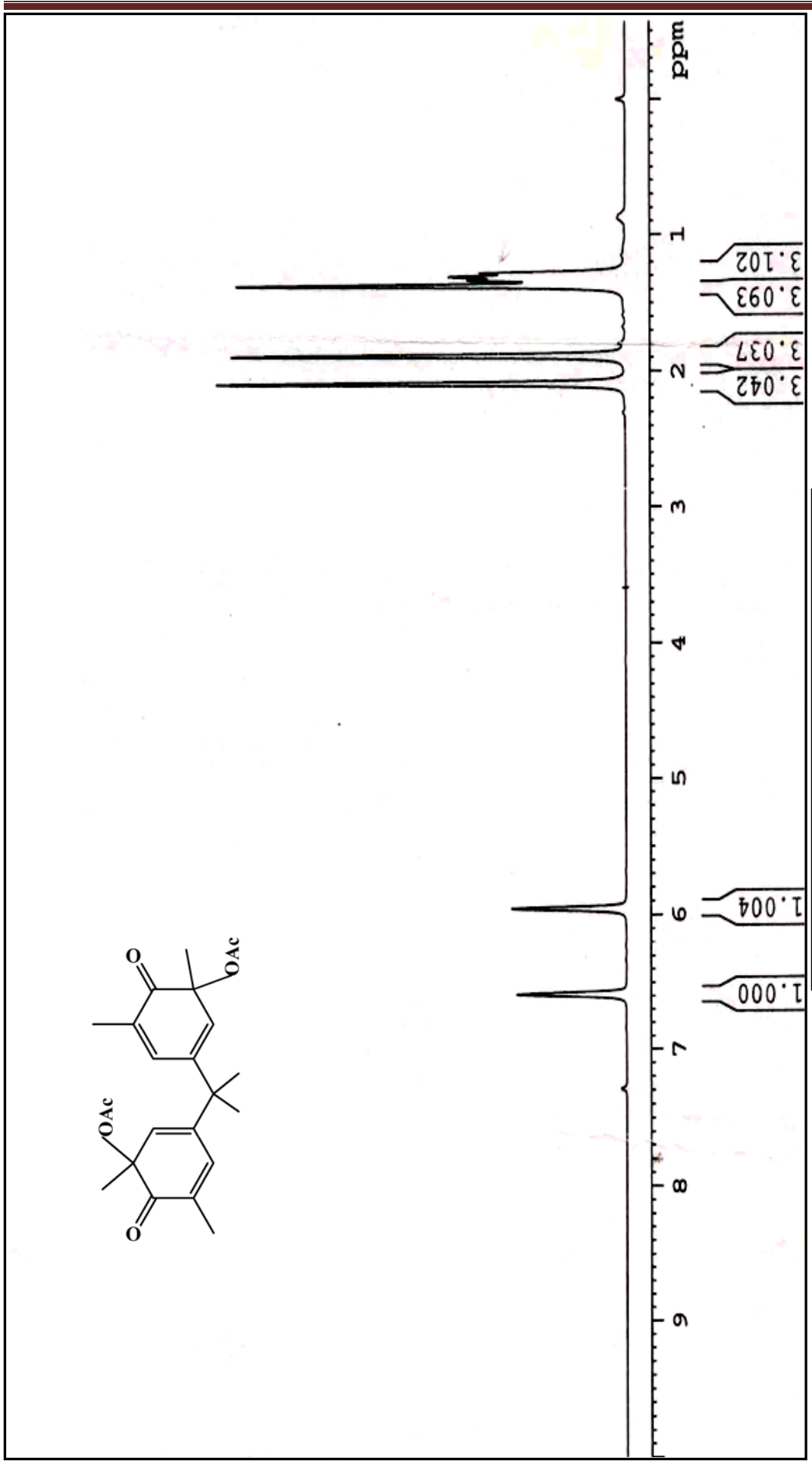


Figure 3.19: ^{1}H NMR spectrum of compound **56**

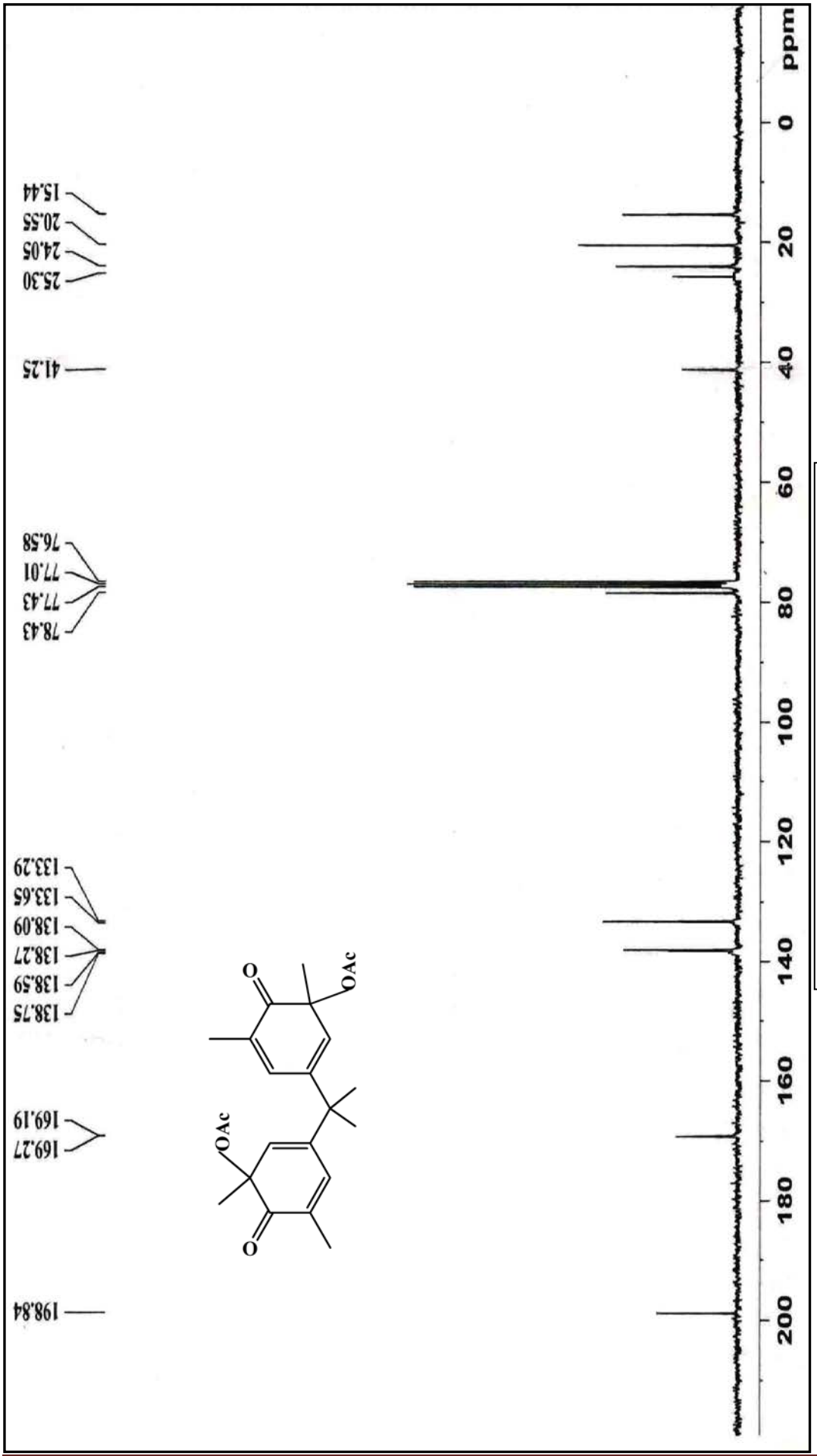


Figure 3.20: ^{13}C NMR spectrum of compound **56**

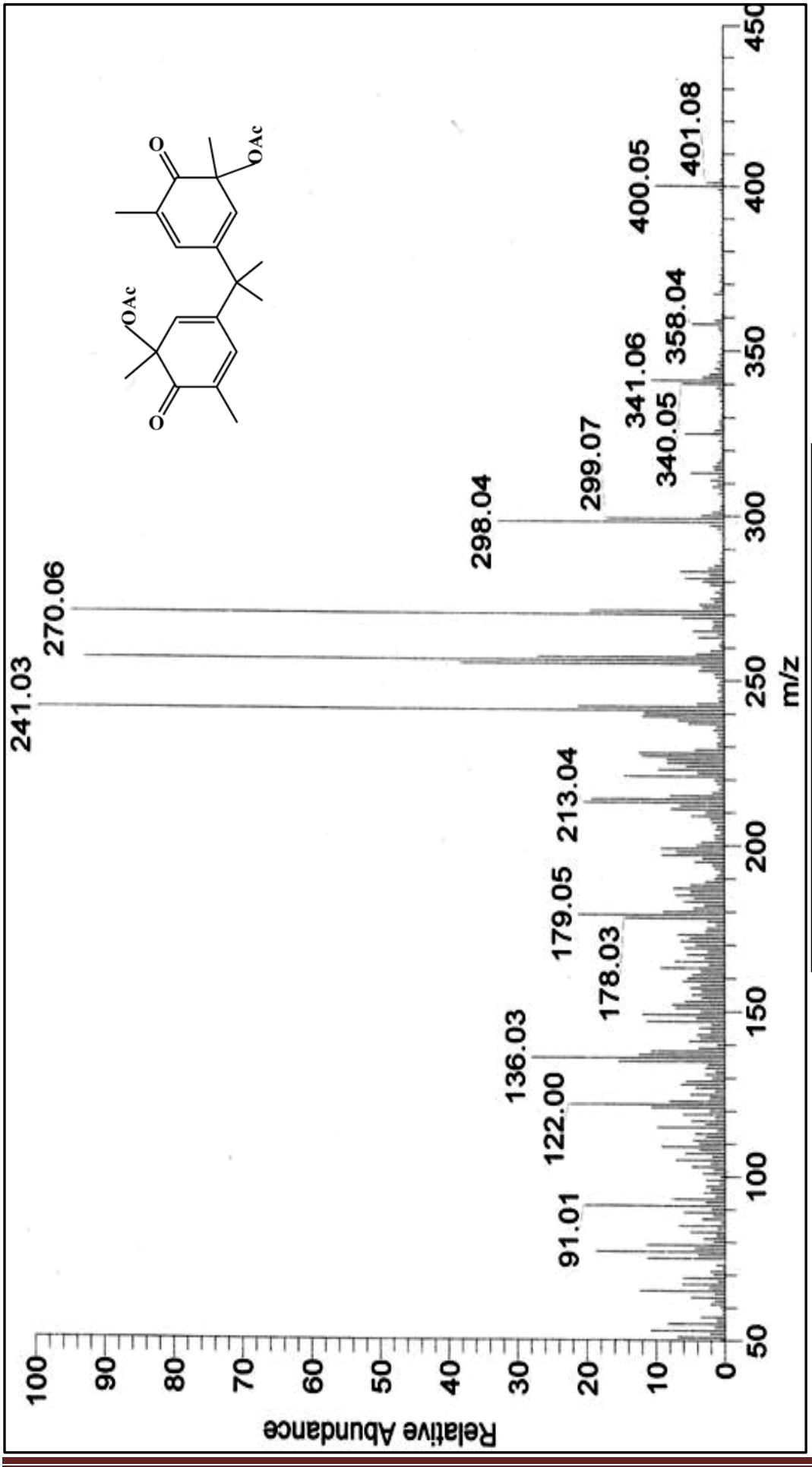


Figure 3.21: EI-MS spectrum of compound **56**

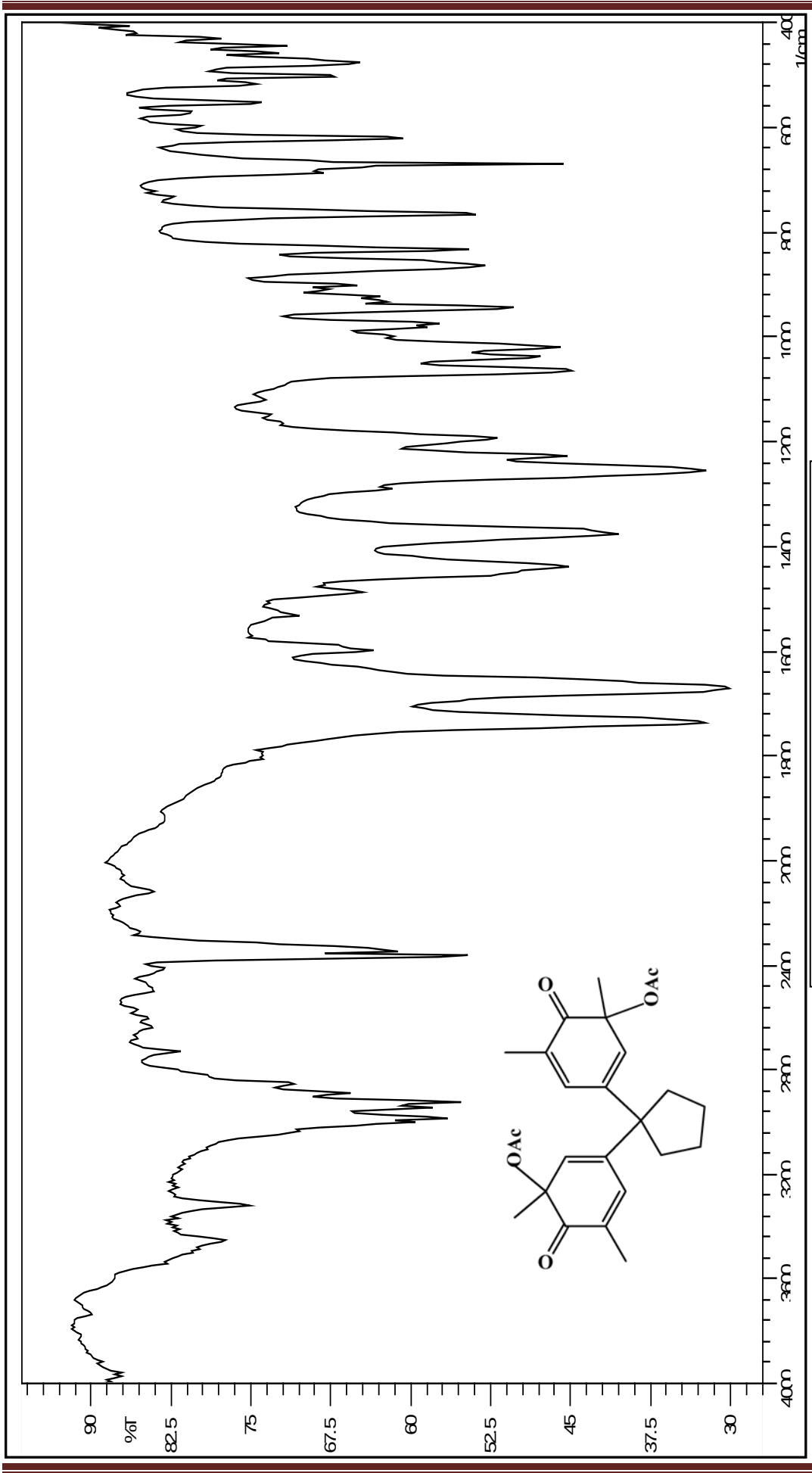


Figure 3.22: FTIR spectrum of compound **57**

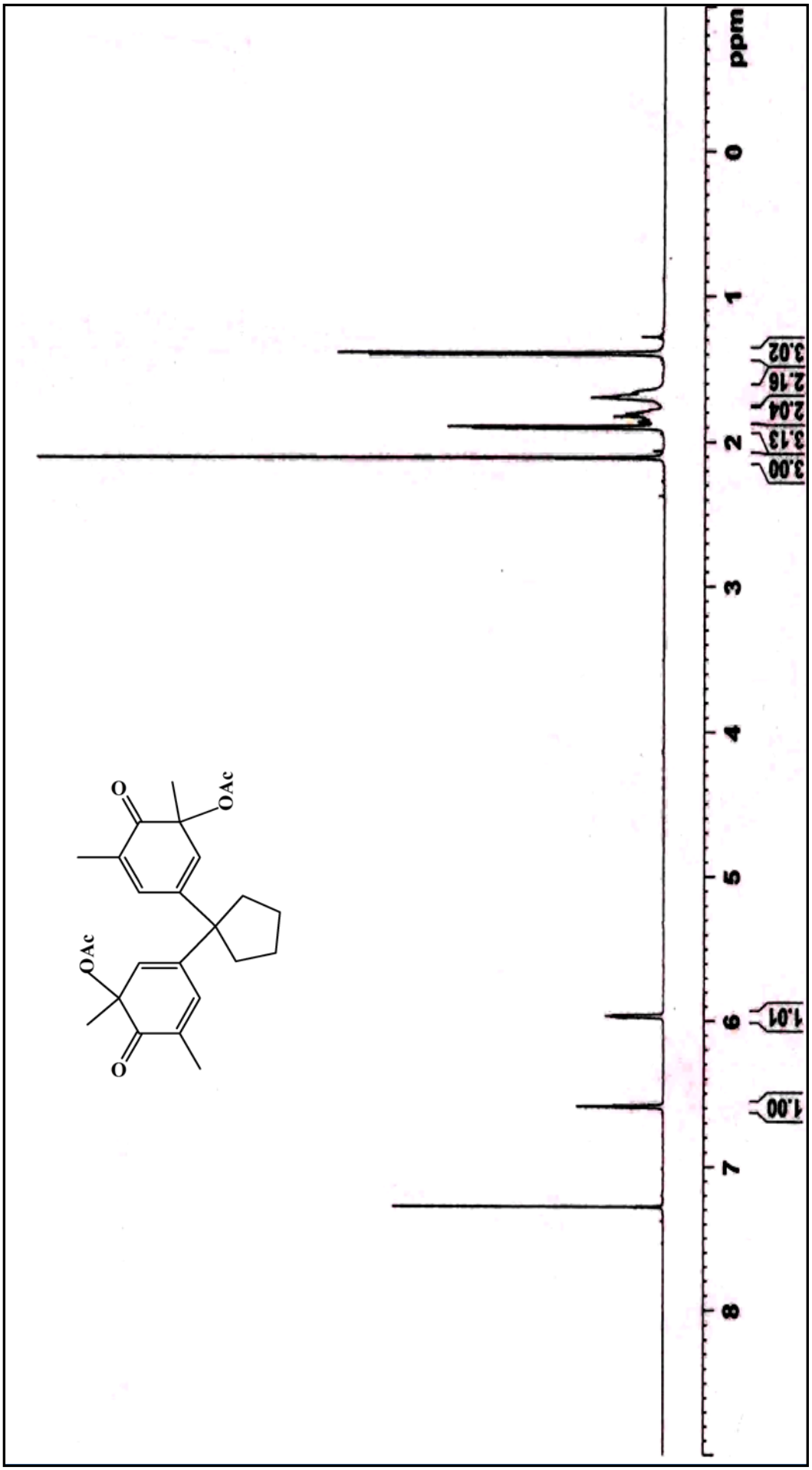


Figure 3.23: ^{1}H NMR spectrum of compound **57**

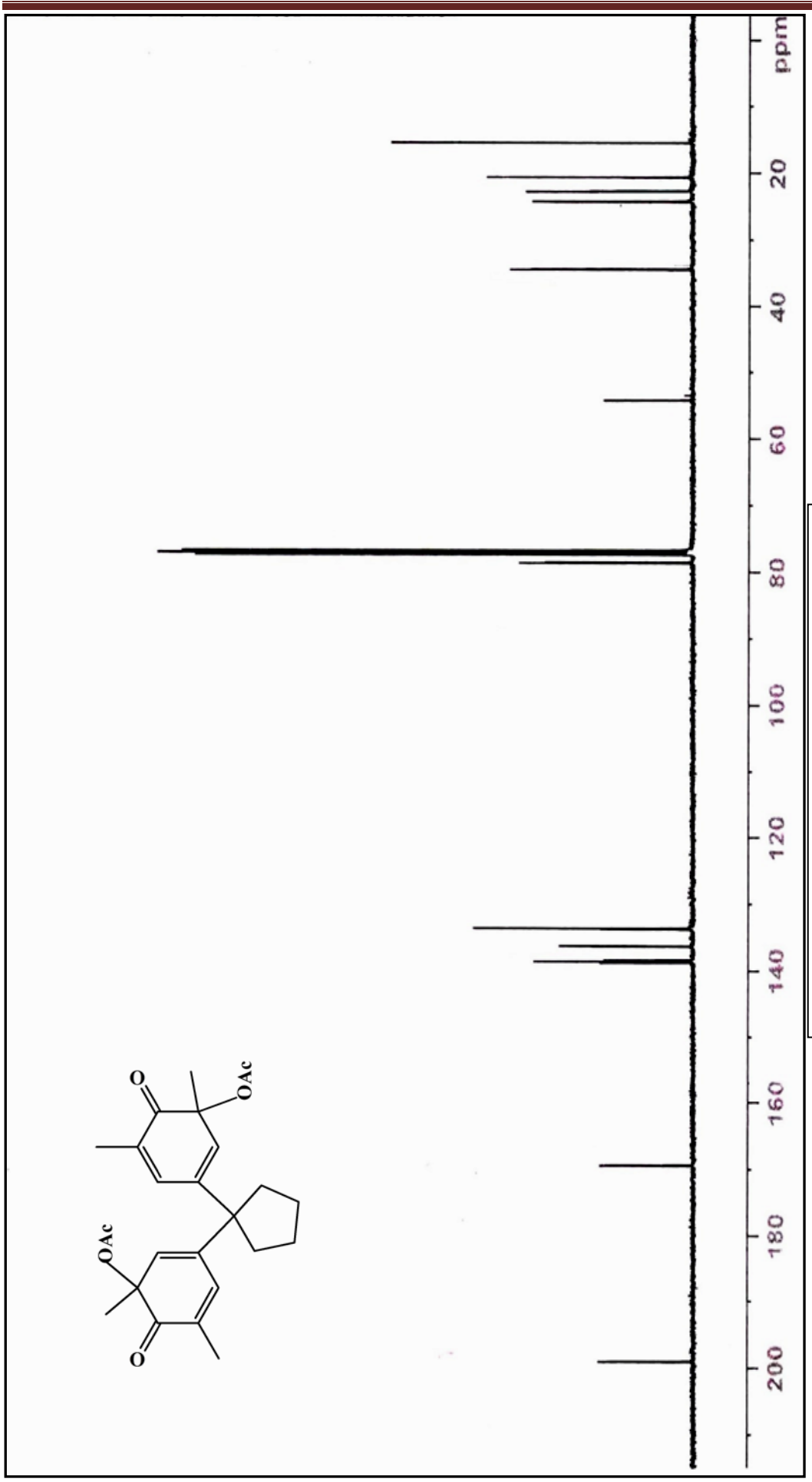


Figure 3.24: ^{13}C NMR spectrum of compound **57**

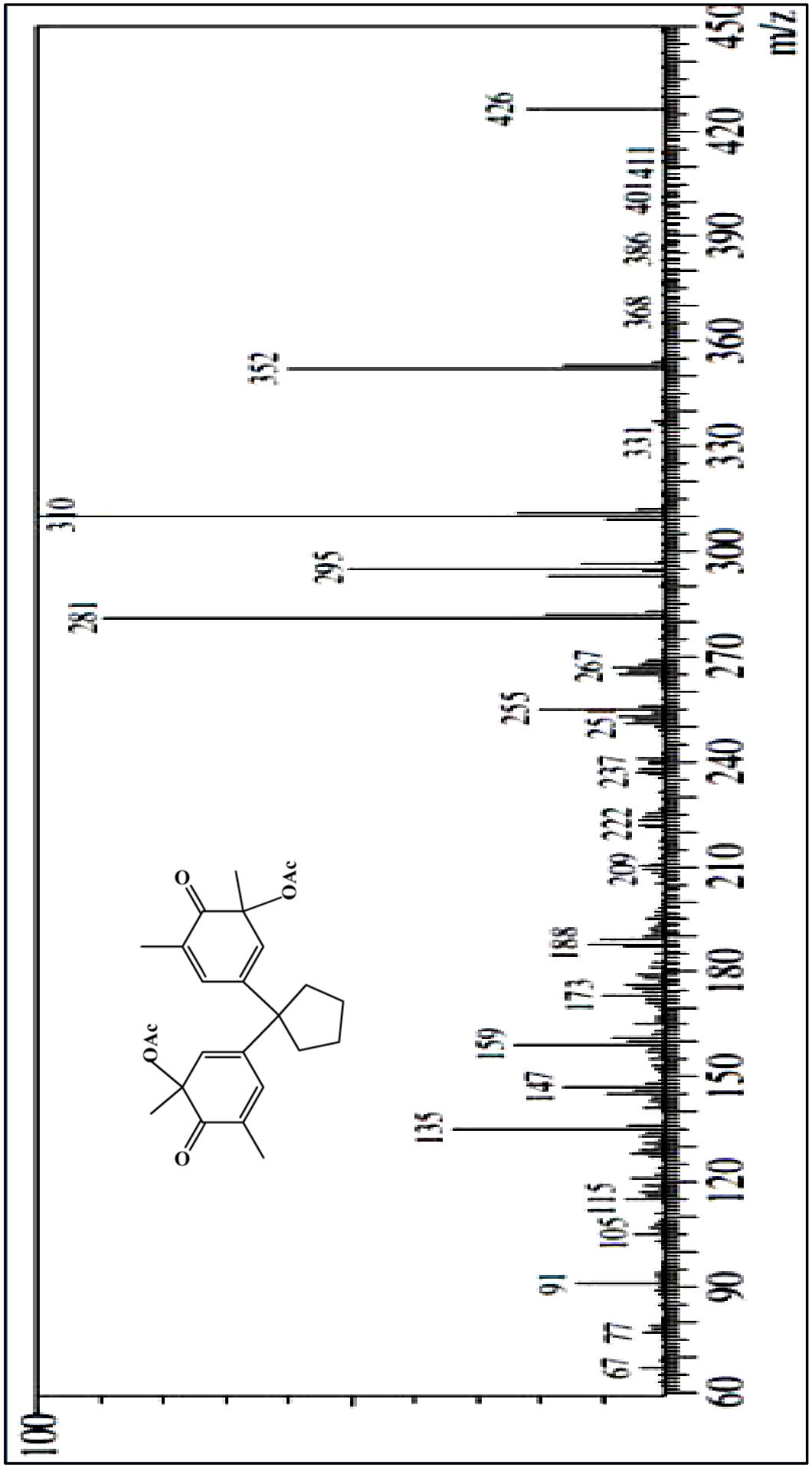


Figure 3.25: EI-MS spectrum of compound **57**

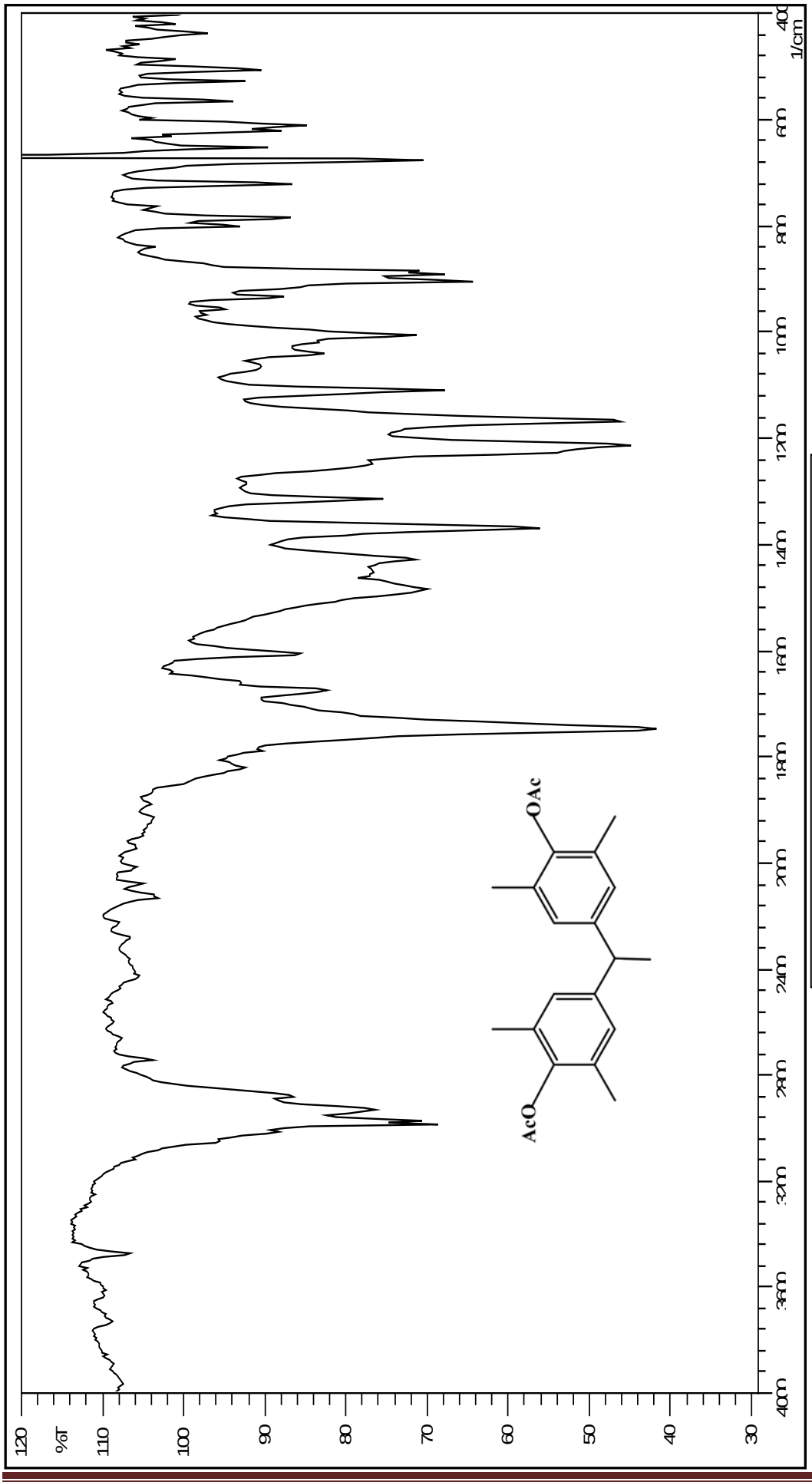


Figure 3.26: FTIR spectrum of compound **64**

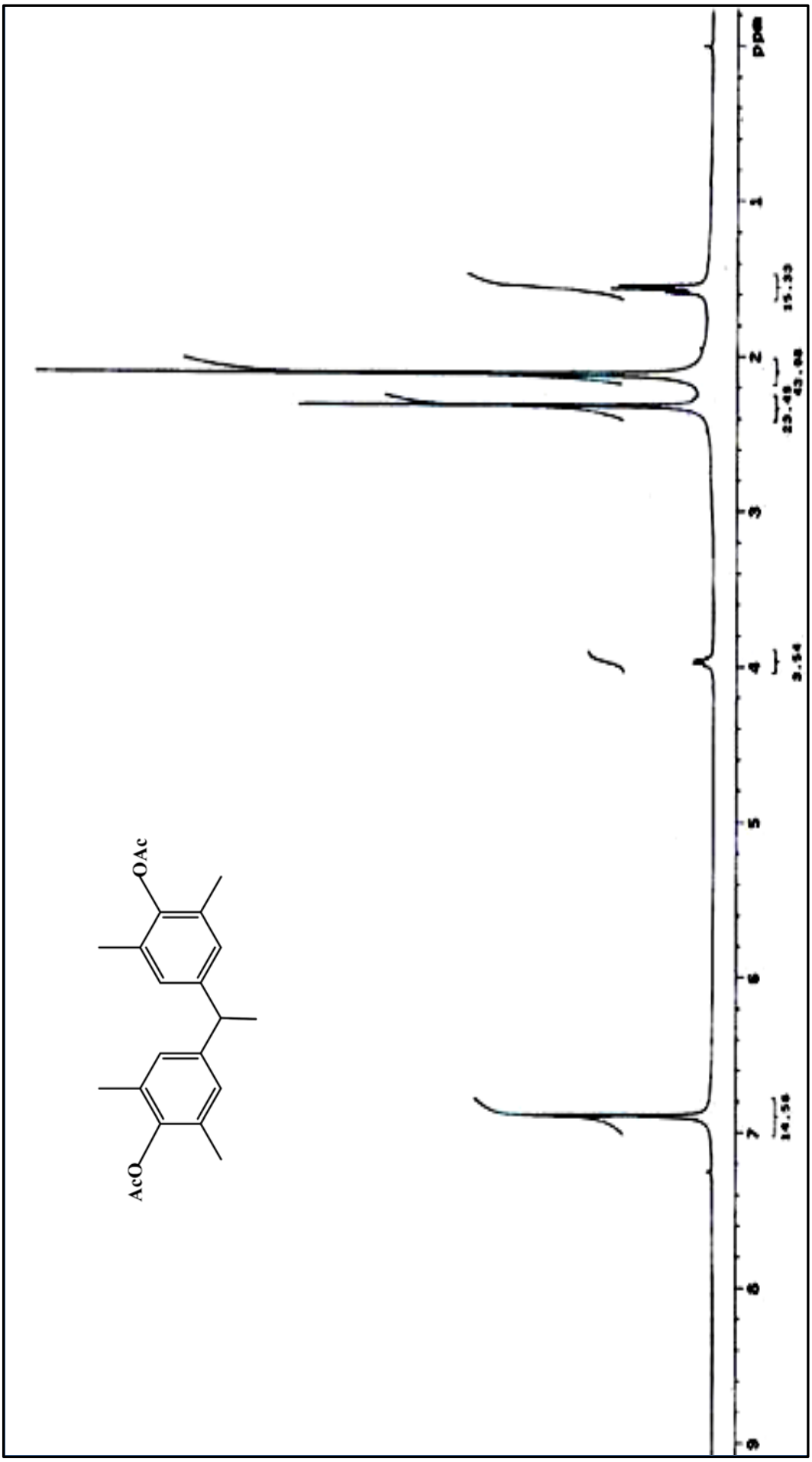


Figure 3.27: ^{1}H NMR spectrum of compound **64**

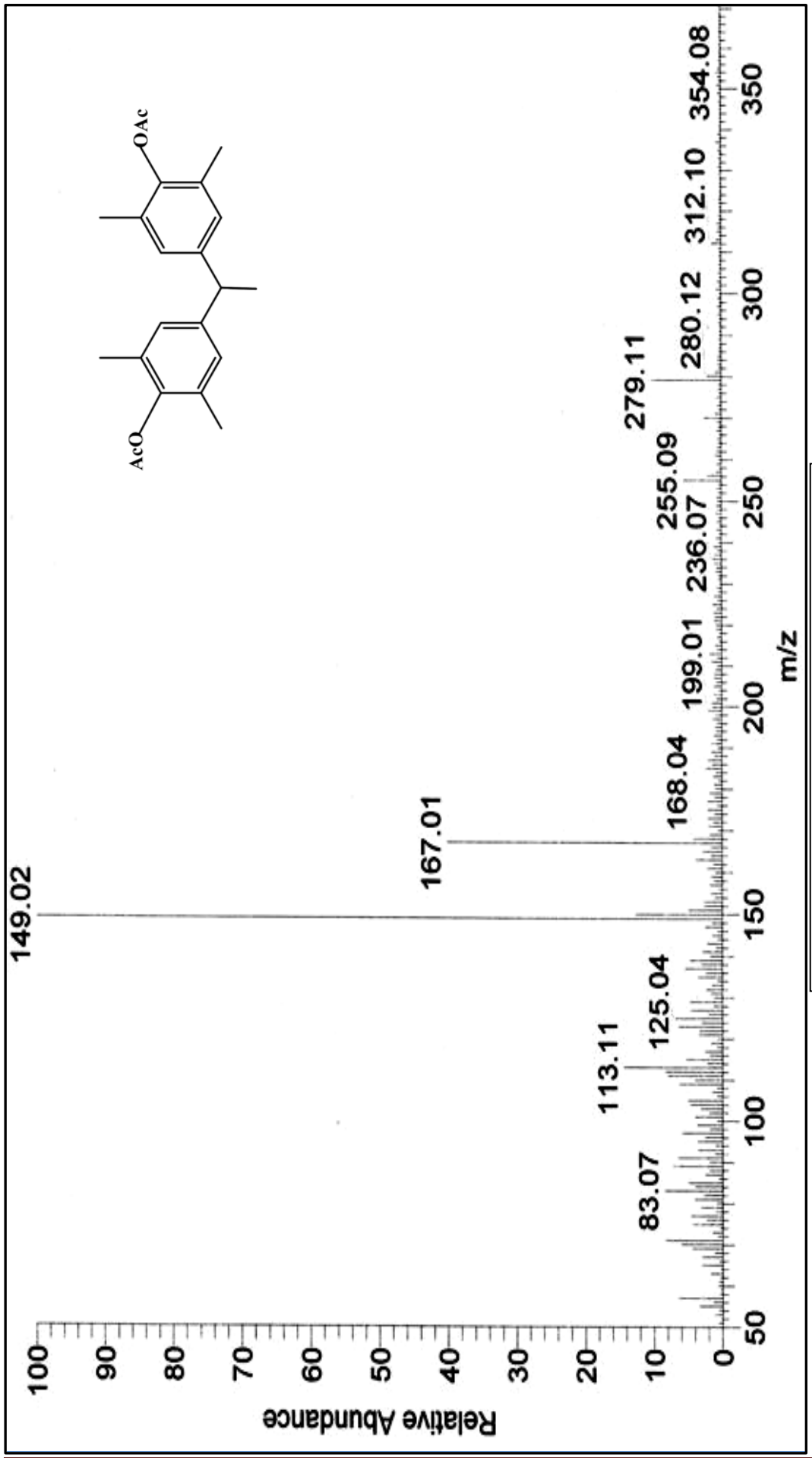


Figure 3.28: EI-MS spectrum of compound **64**

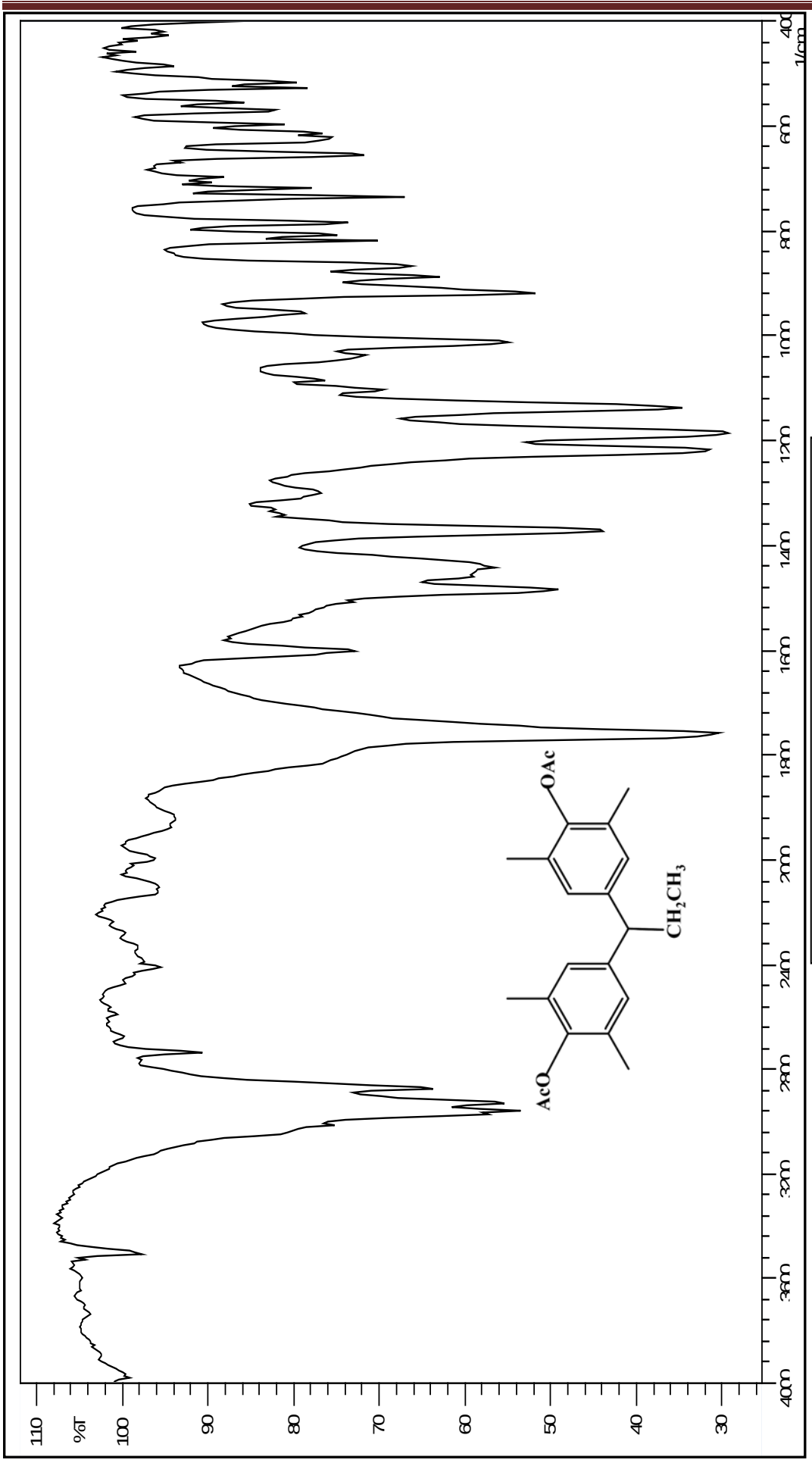


Figure 3.29: FTIR spectrum of compound **65**

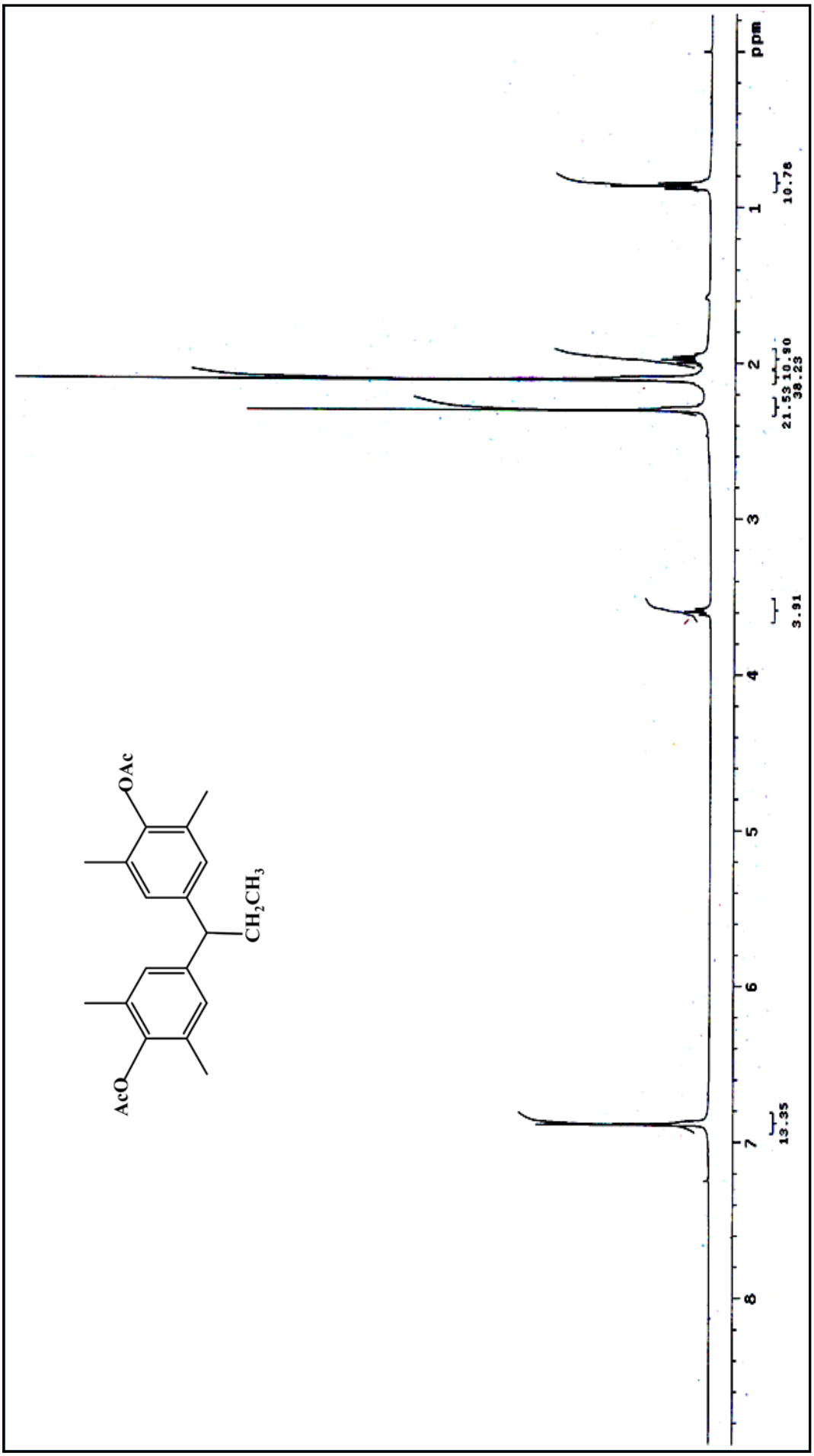


Figure 3.30: ^{1}H NMR spectrum of compound **65**

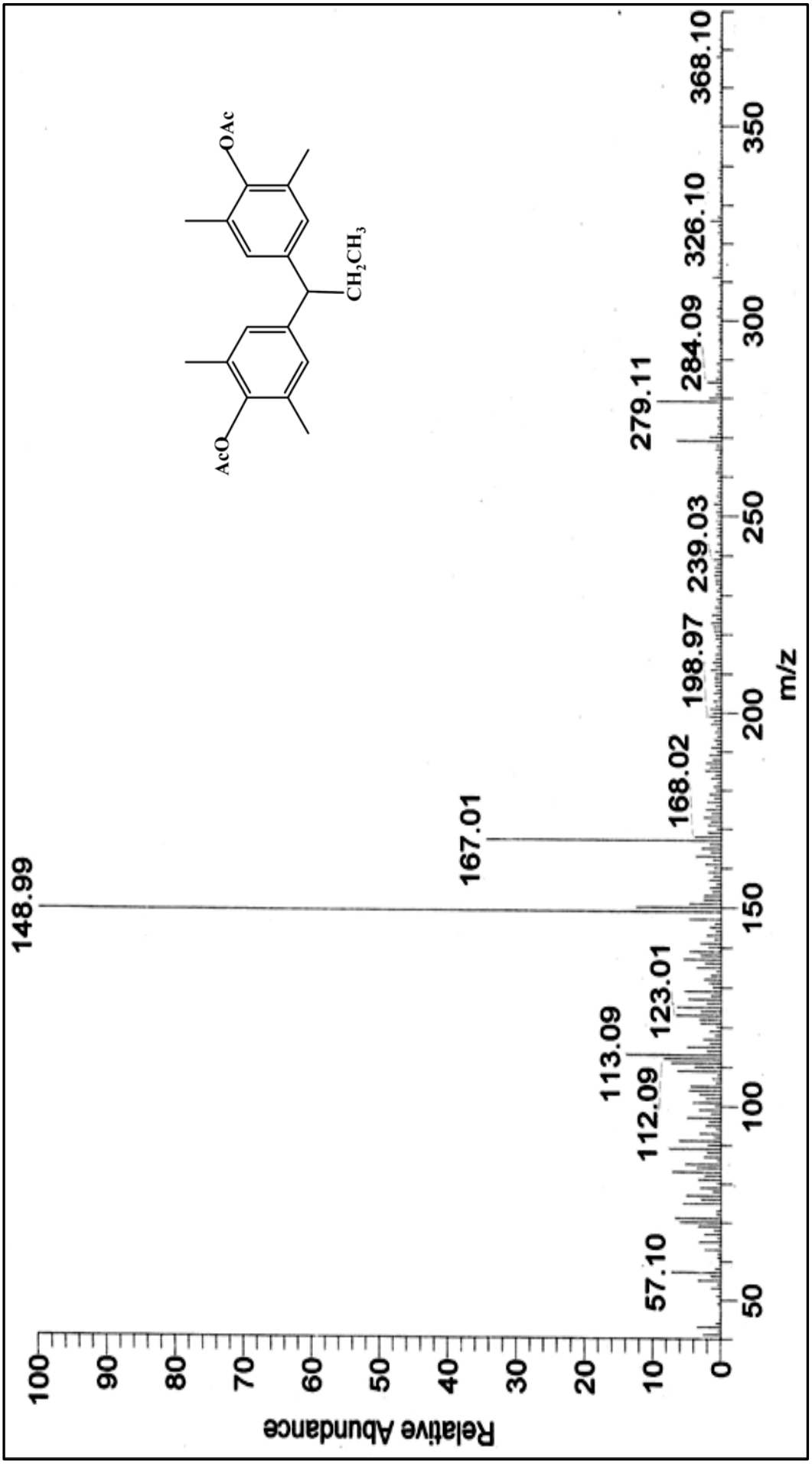


Figure 3.31: EI-MS spectrum of compound **65**

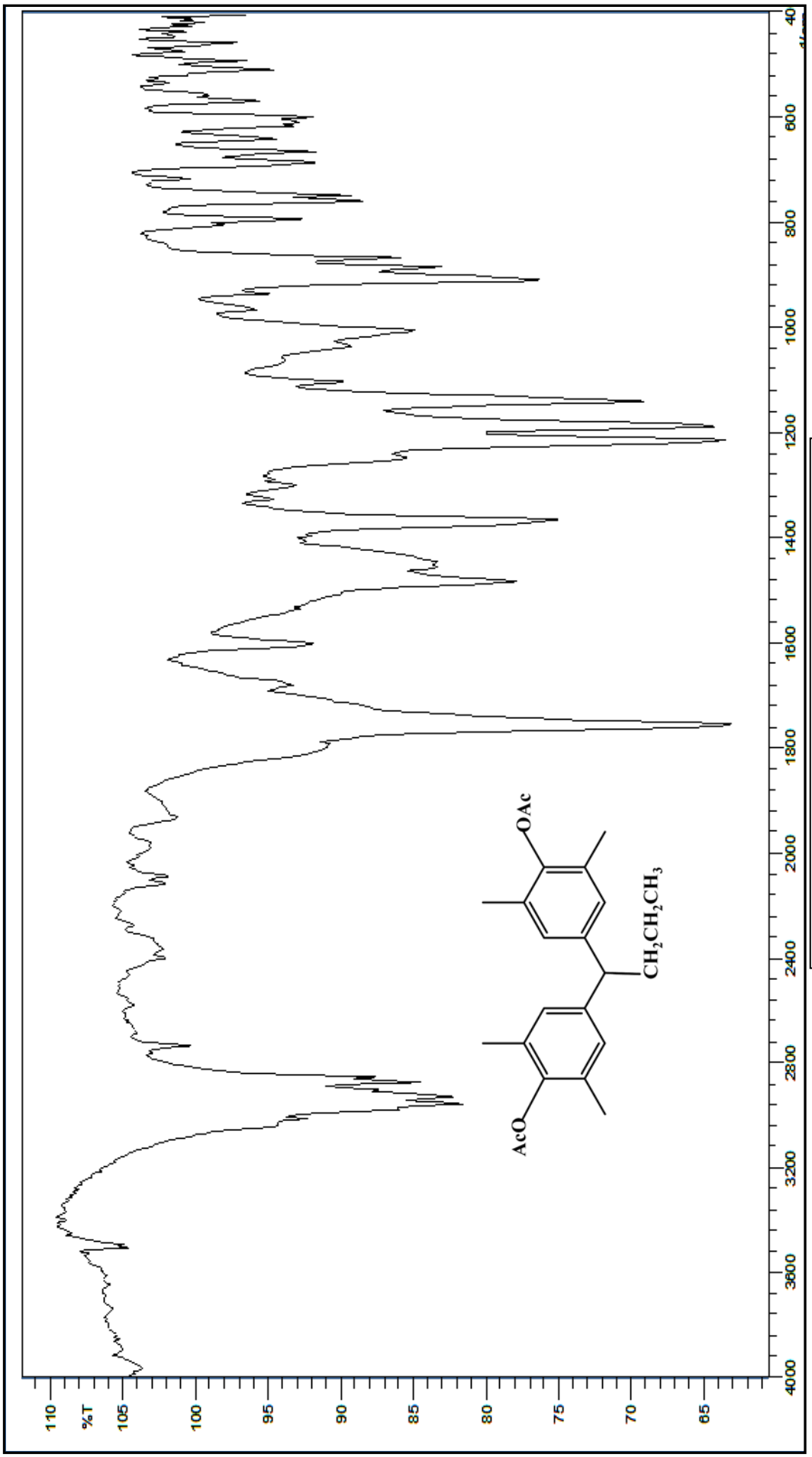


Figure 3.32: FTIR spectrum of compound **66**

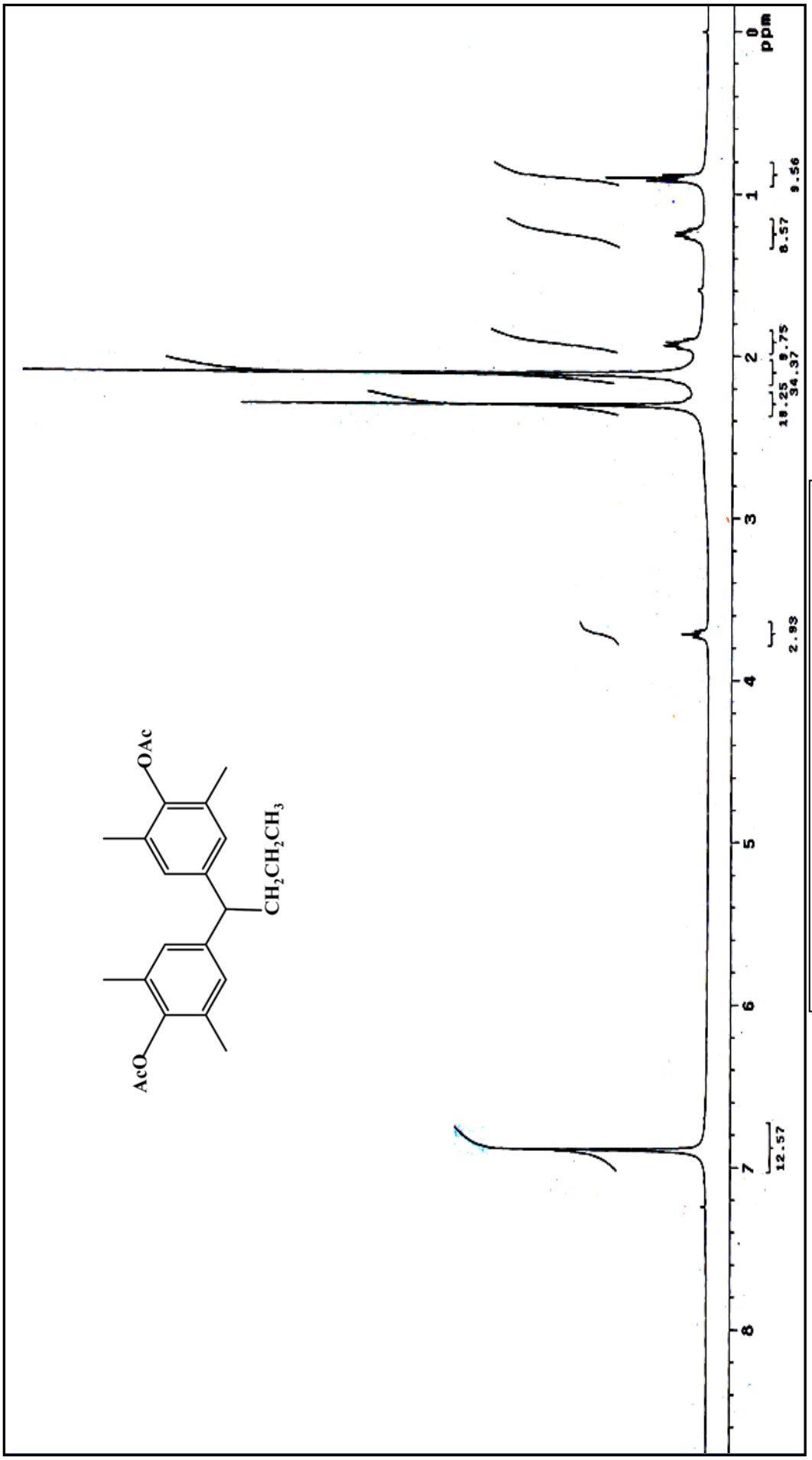


Figure 3.33: ^{1}H NMR spectrum of compound **66**

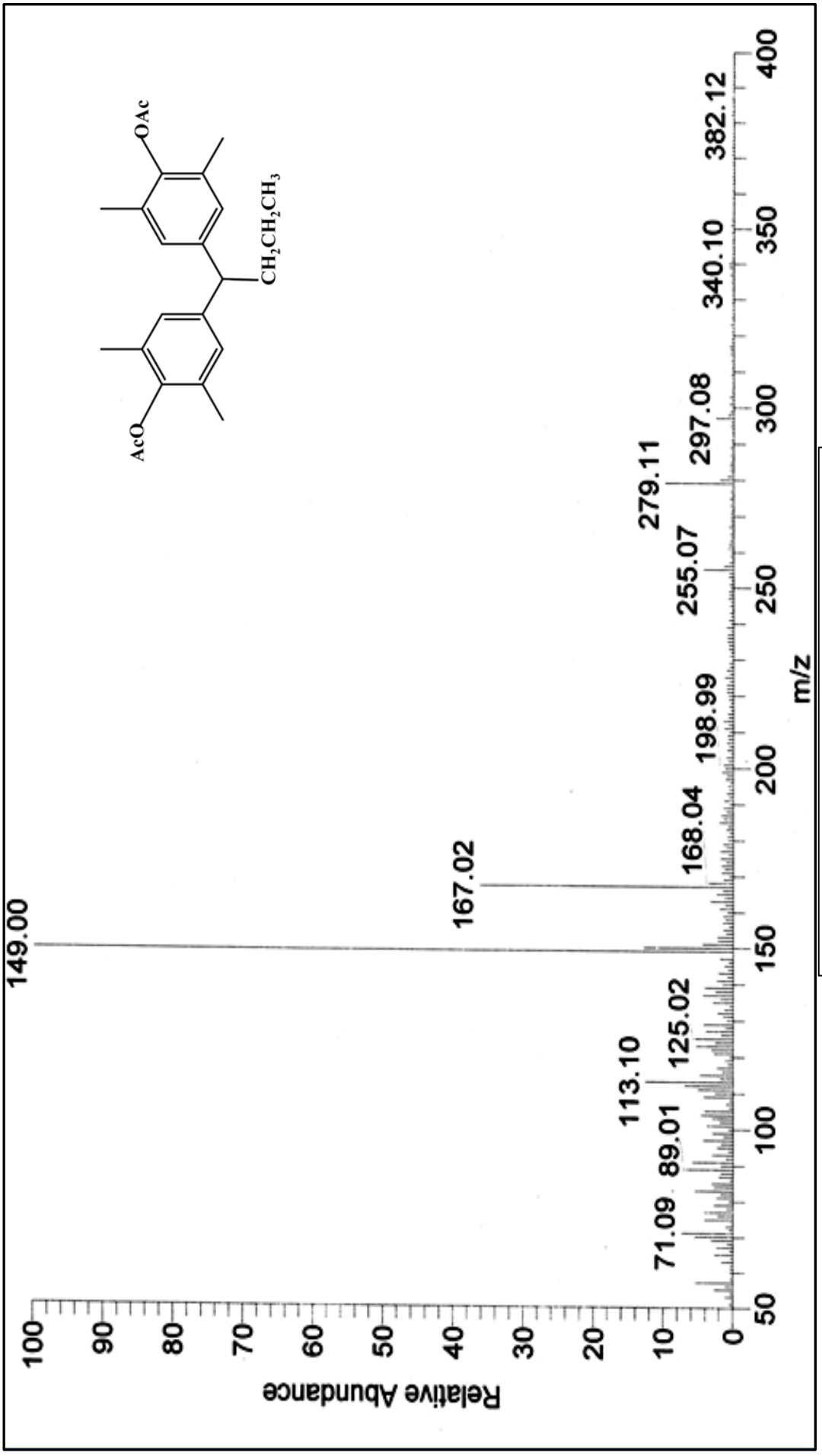


Figure 3.34: EI-MS spectrum of compound **66**

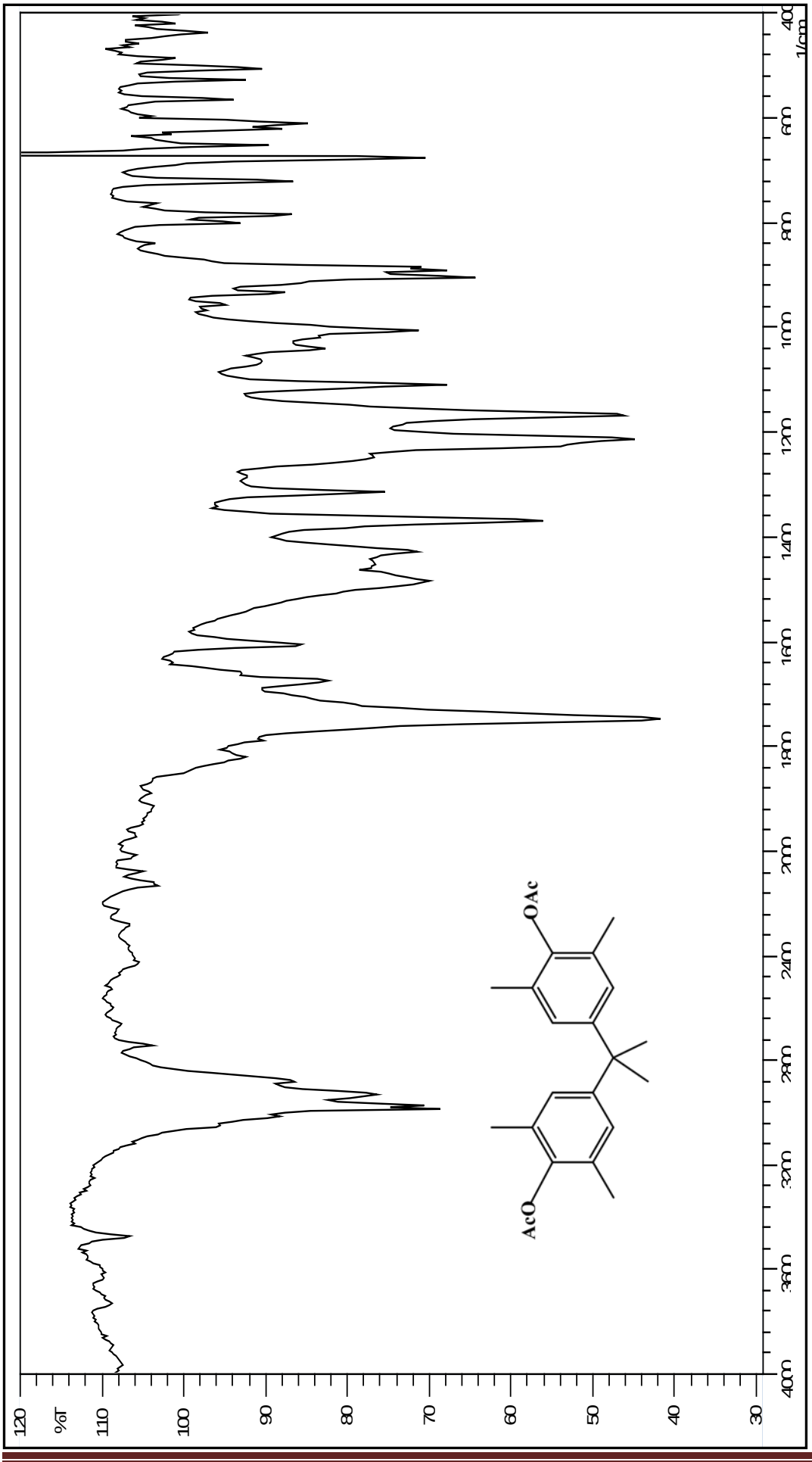


Figure 3.35: FTIR spectrum of compound **67**

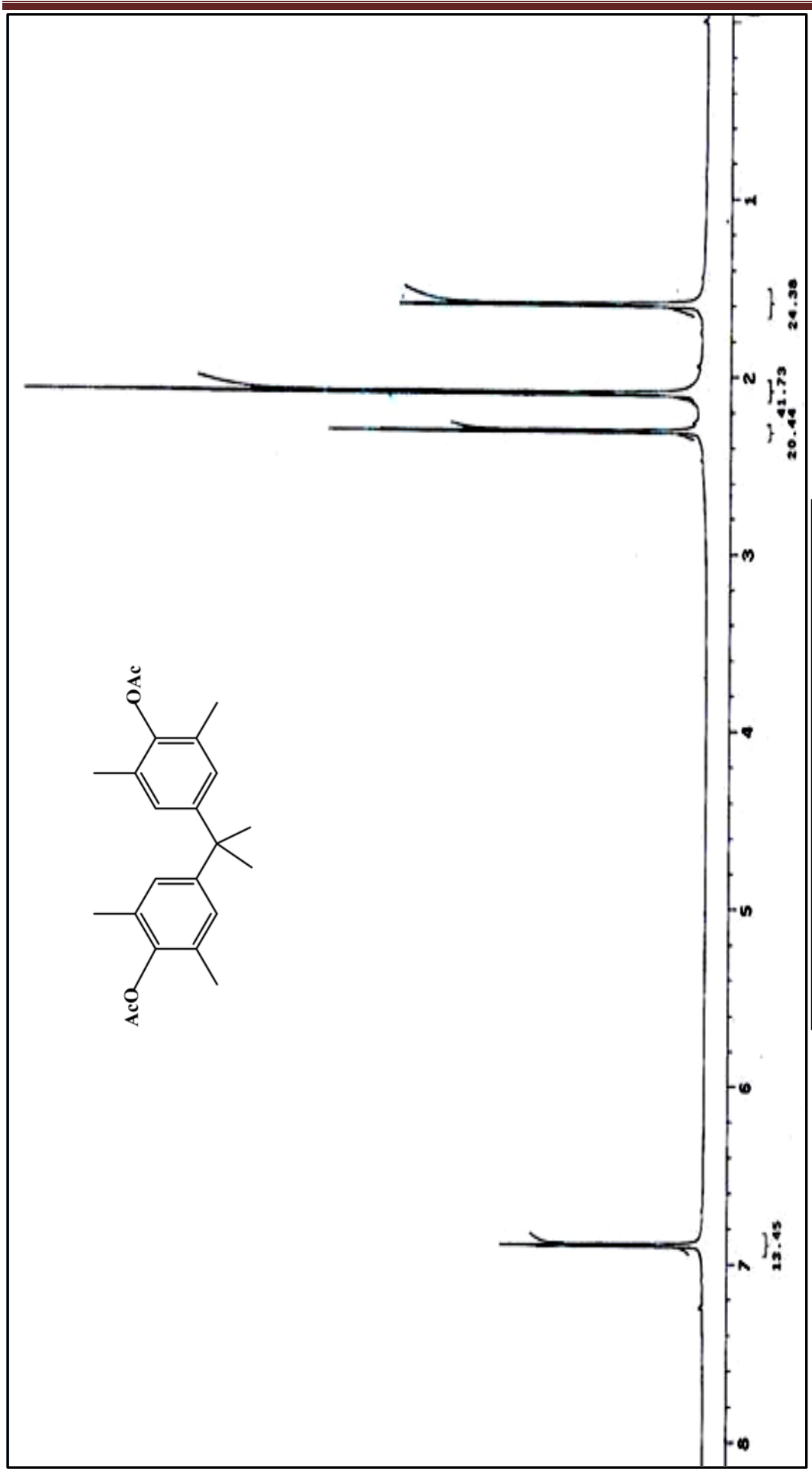


Figure 3.36: ^{1}H NMR spectrum of compound **67**

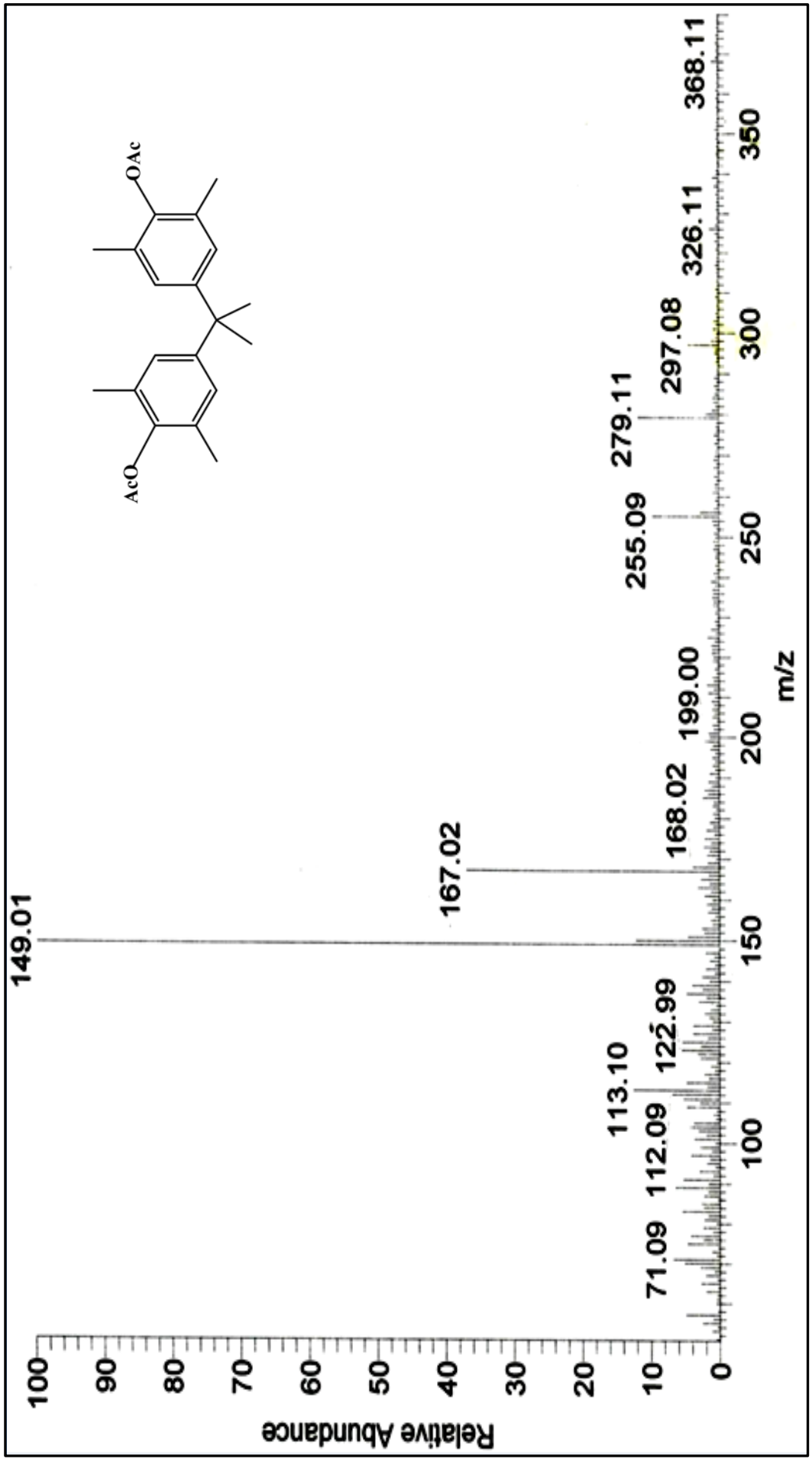


Figure 3.37: EI-MS spectrum of compound **67**

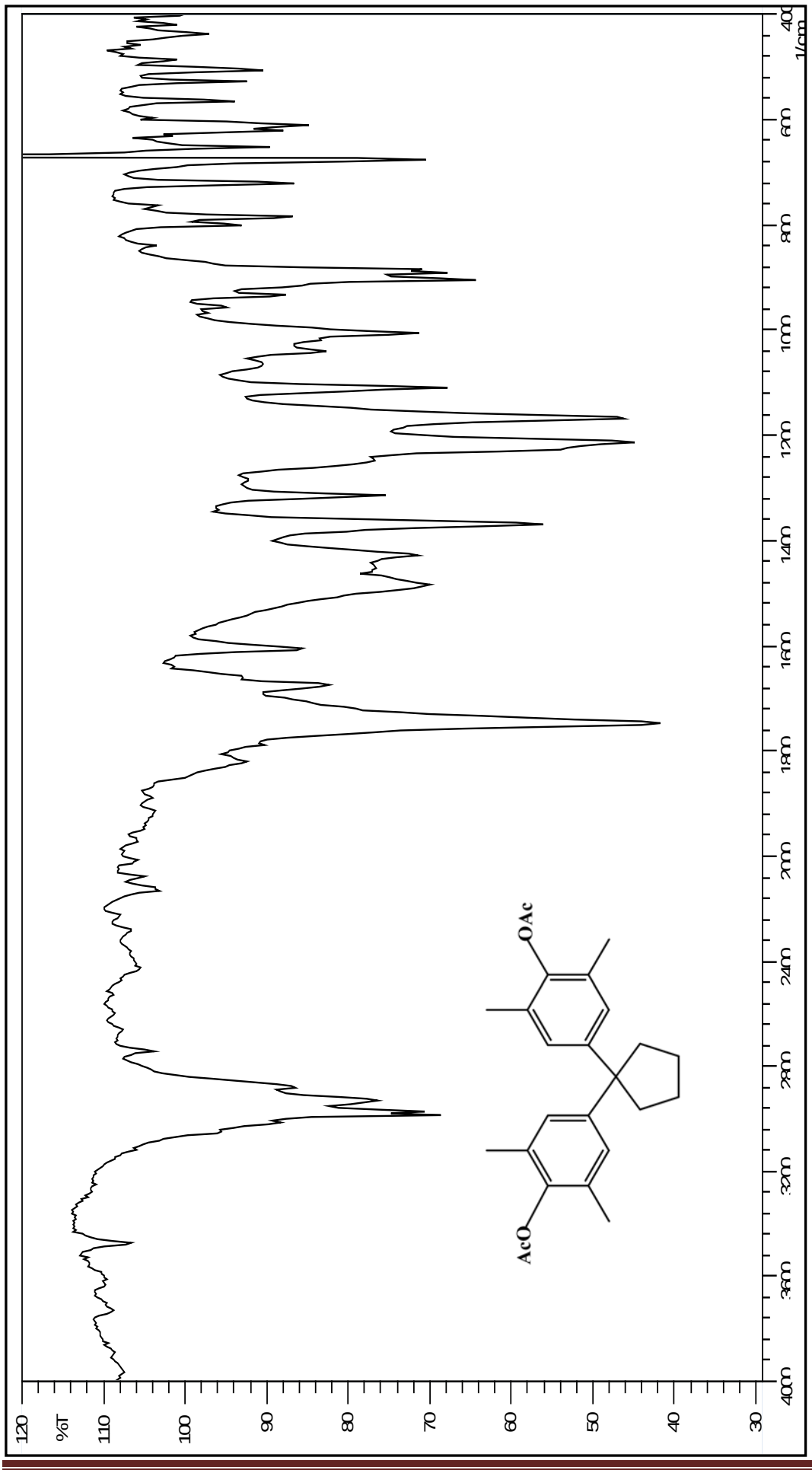


Figure 3.38: FTIR spectrum of compound **68**

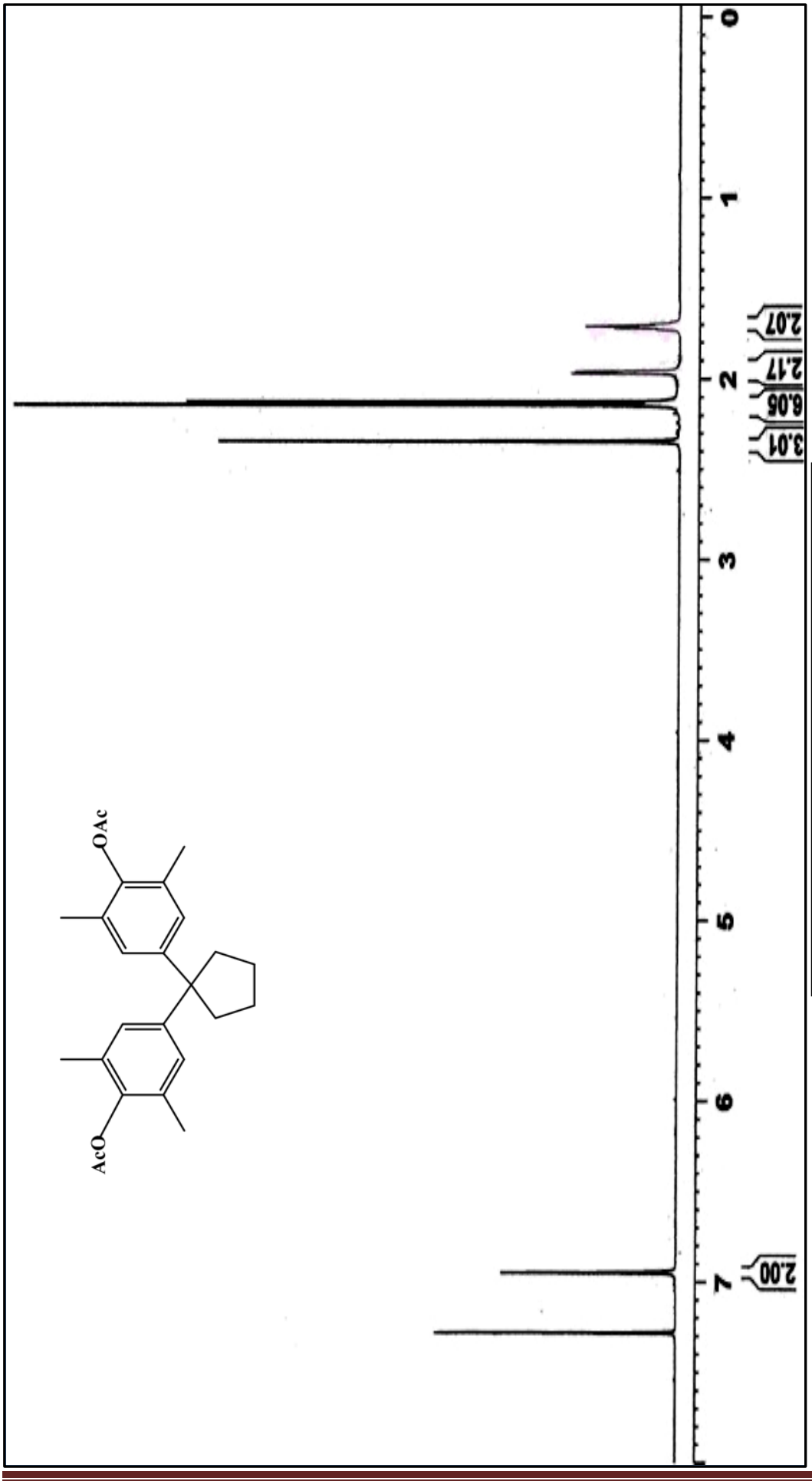


Figure 3.39: ^{1}H NMR spectrum of compound **68**

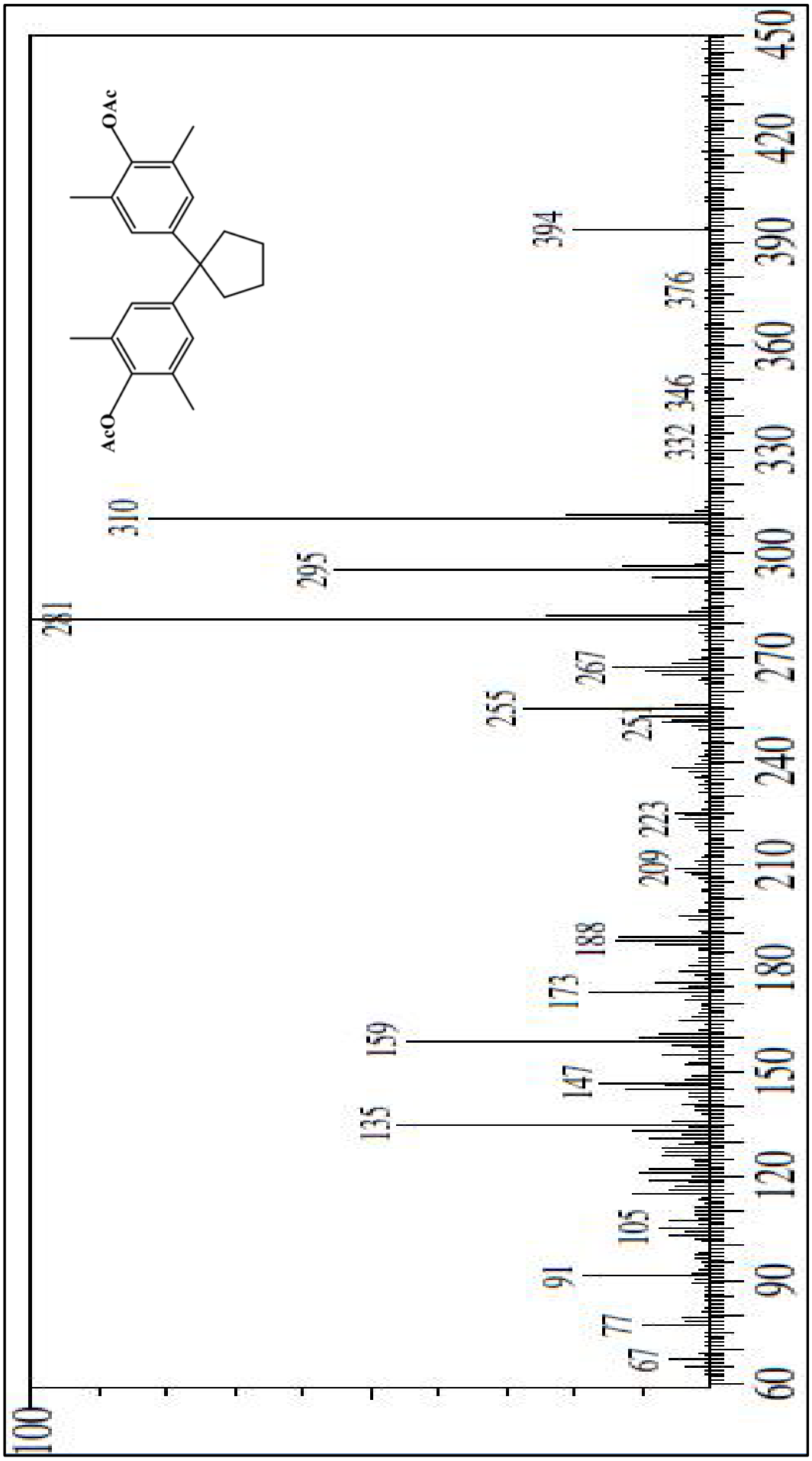


Figure 3.40: EI-MS spectrum of compound **68**

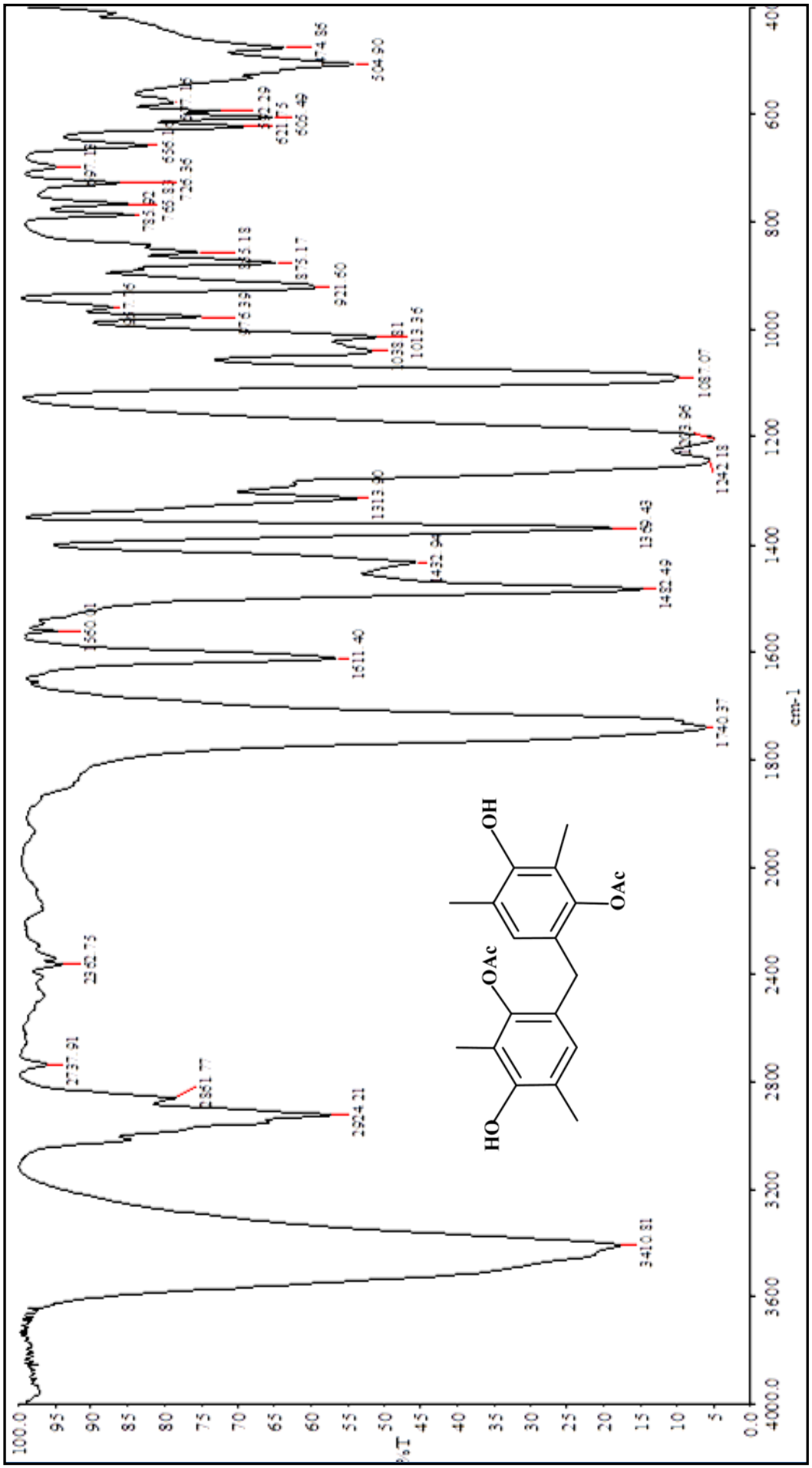


Figure 3.41: FTIR spectrum of compound **77A**

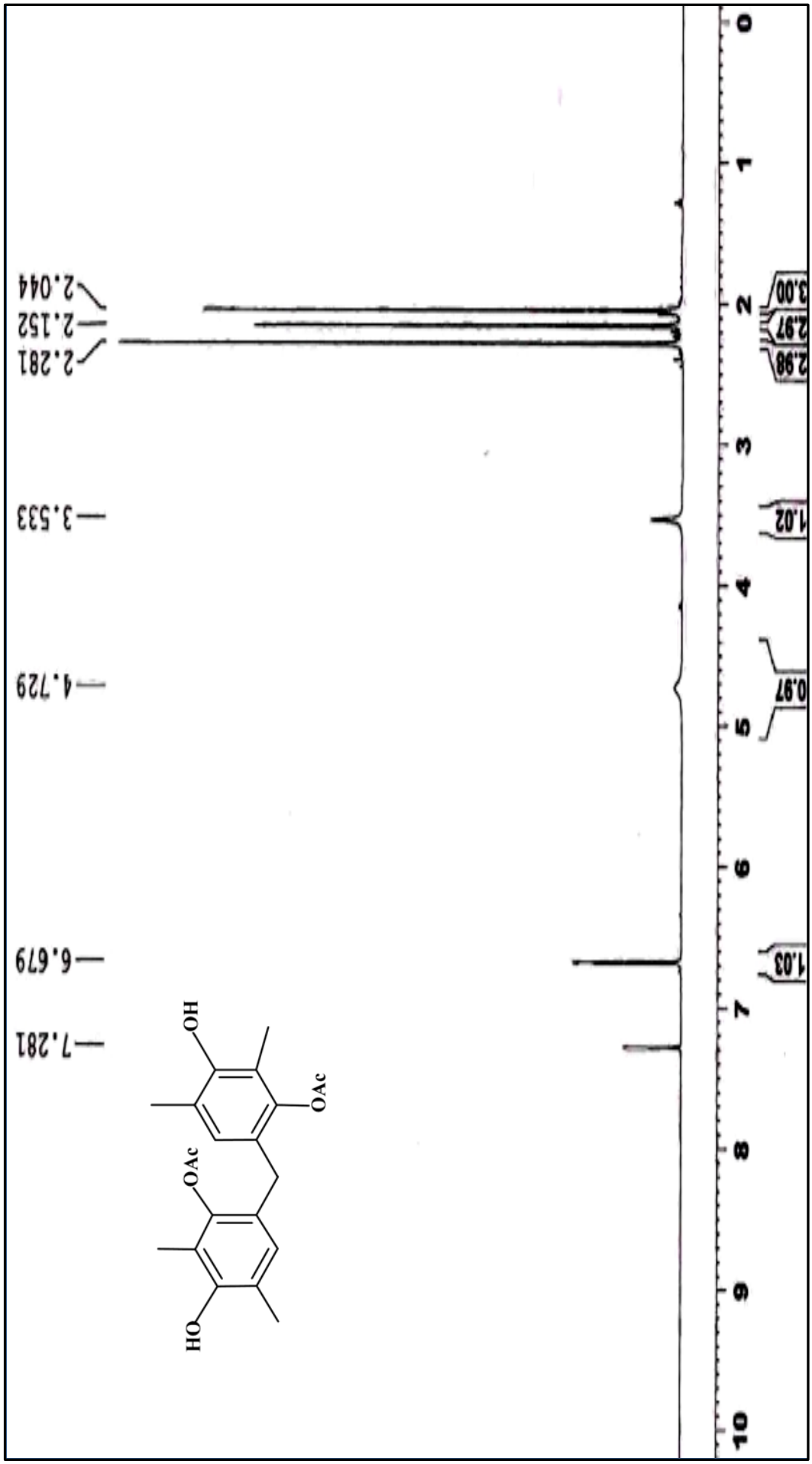


Figure 3.42: ^{1}H NMR spectrum of compound **77A**

Figure 3.43: ^{13}C NMR spectrum of compound **77A**

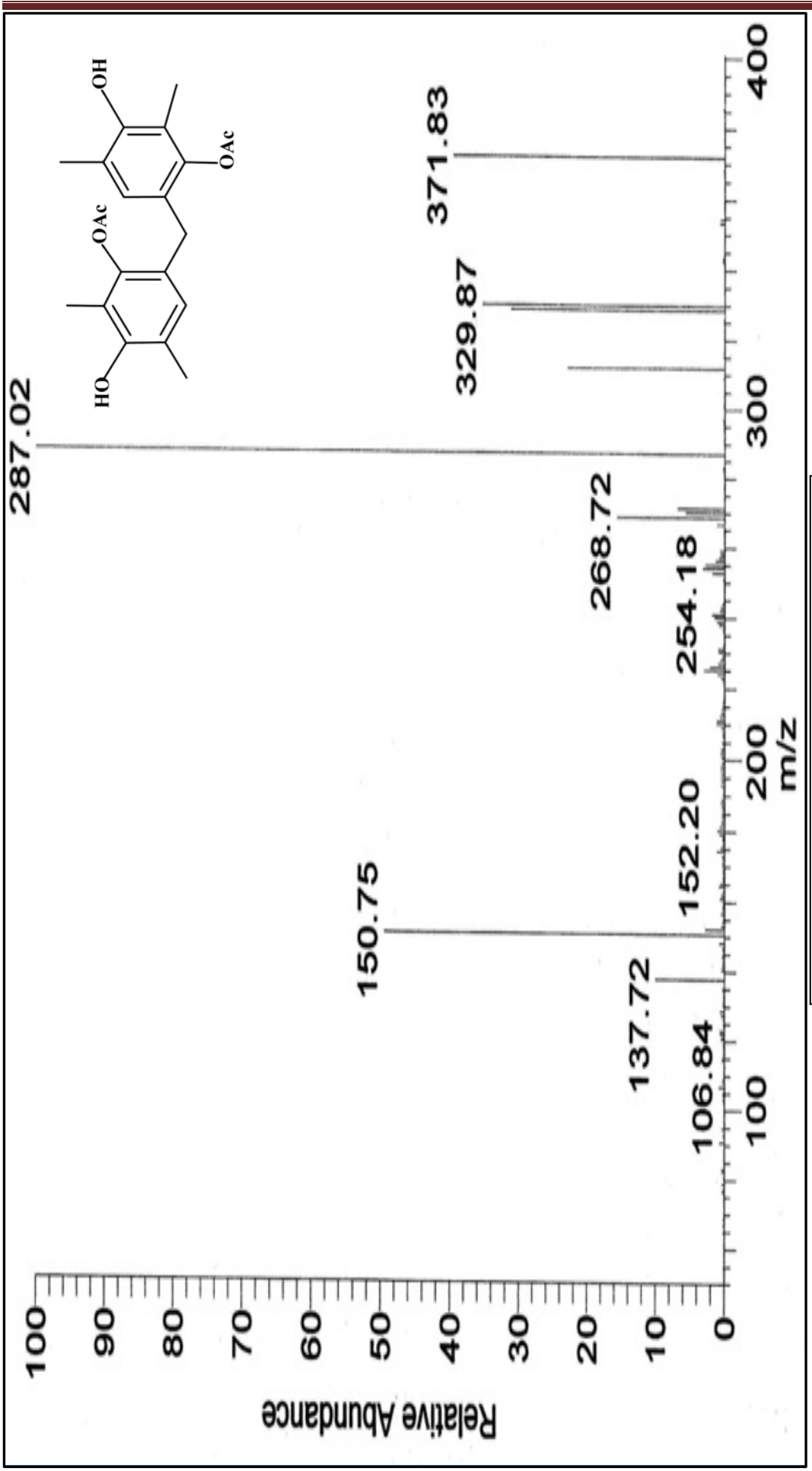


Figure 3.44: EI-MS spectrum of compound **77A**

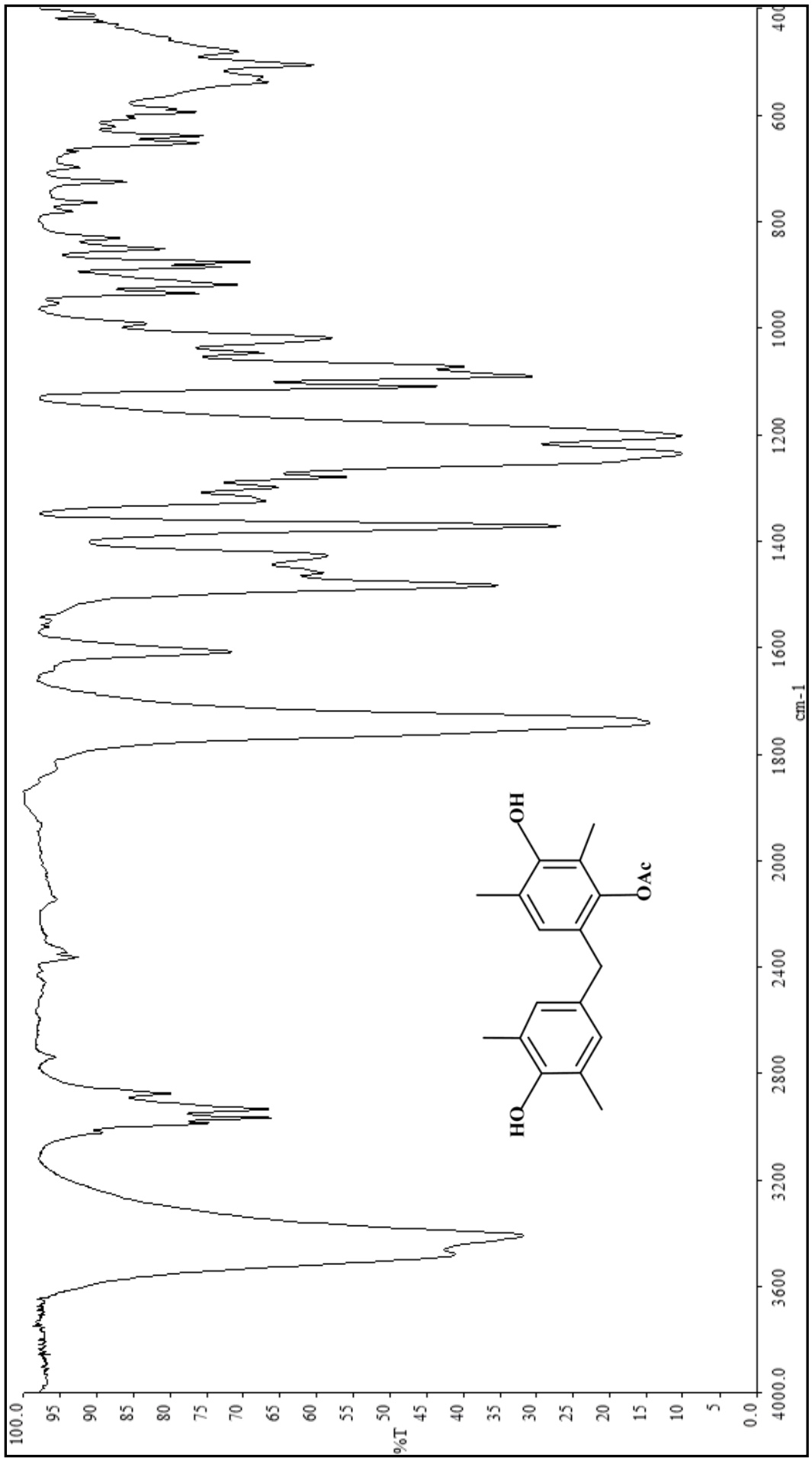


Figure 3.45: FTIR spectrum of compound **77B**

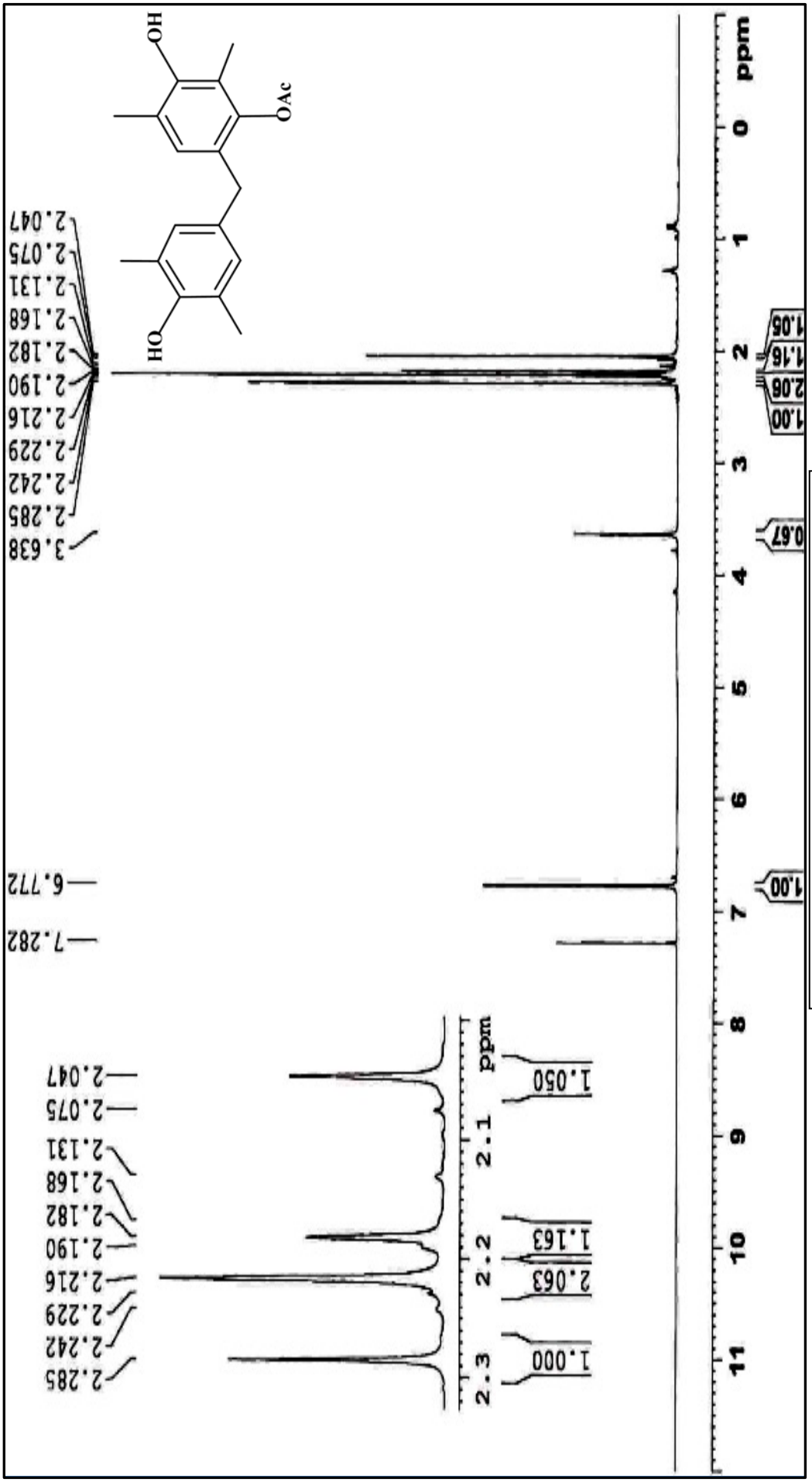


Figure 3.46: ^{1}H NMR spectrum of compound **77B**

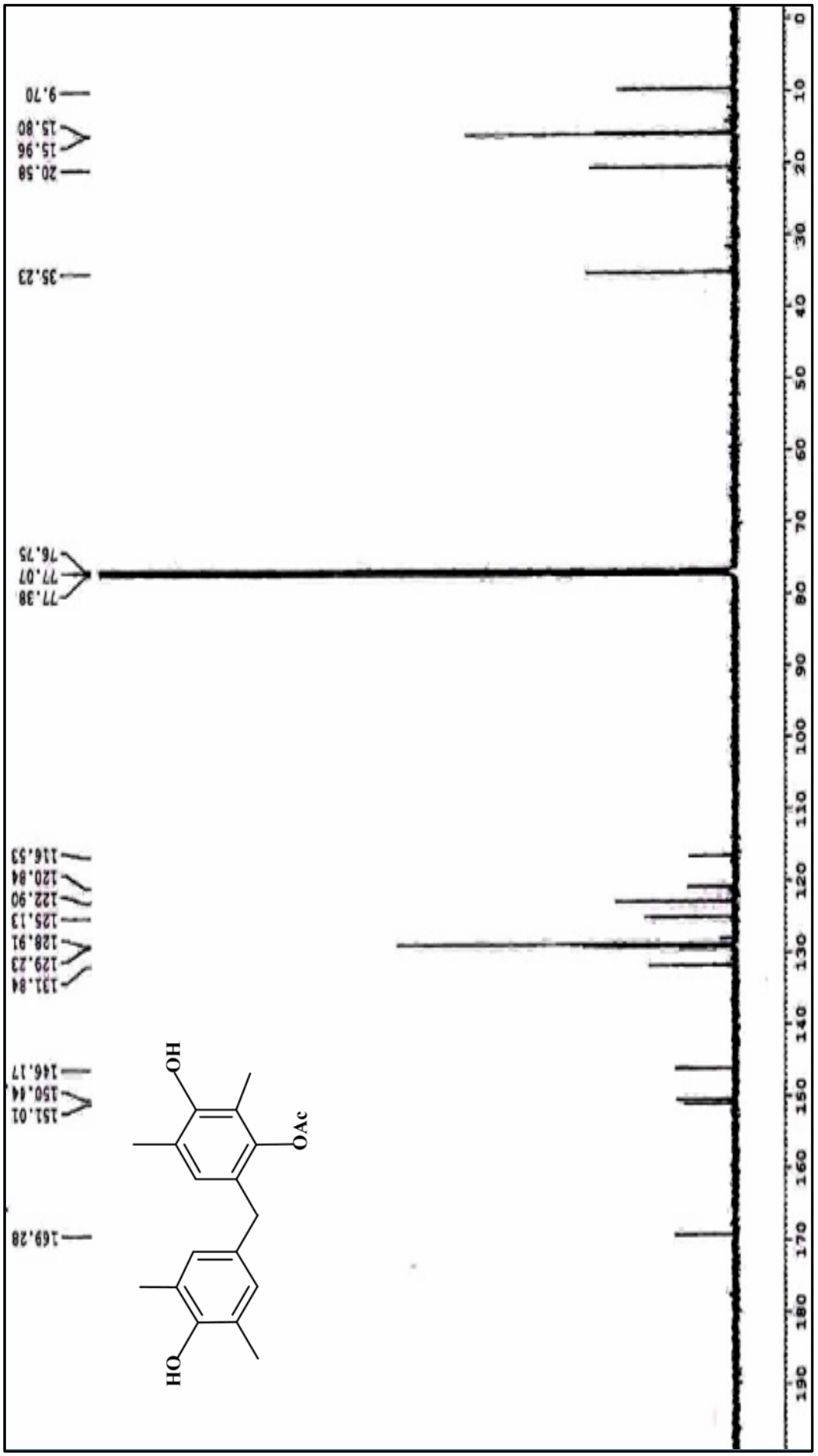


Figure 3.47: ^{13}C NMR spectrum of compound **77B**

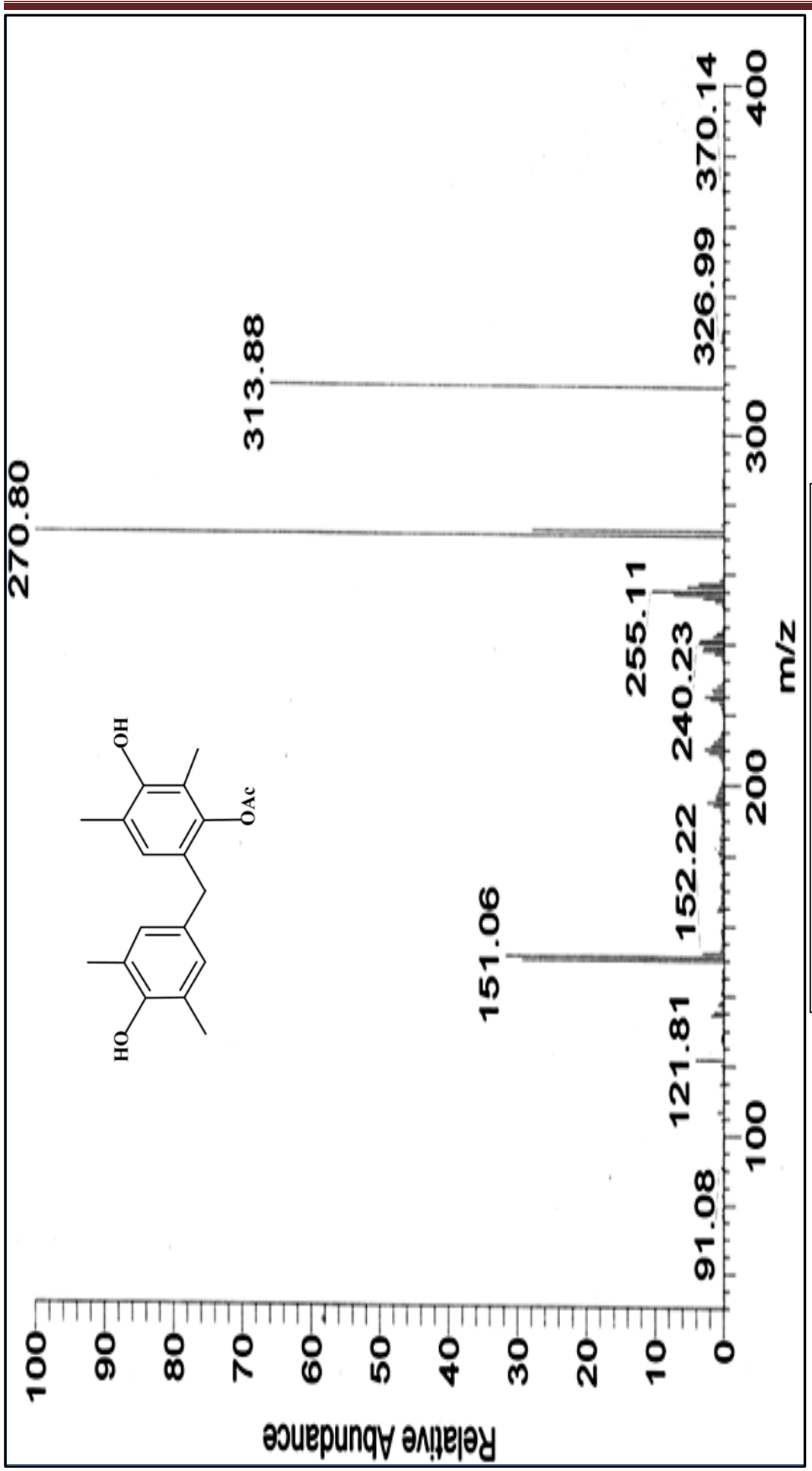


Figure 3.48: EI-MS spectrum of compound **77B**

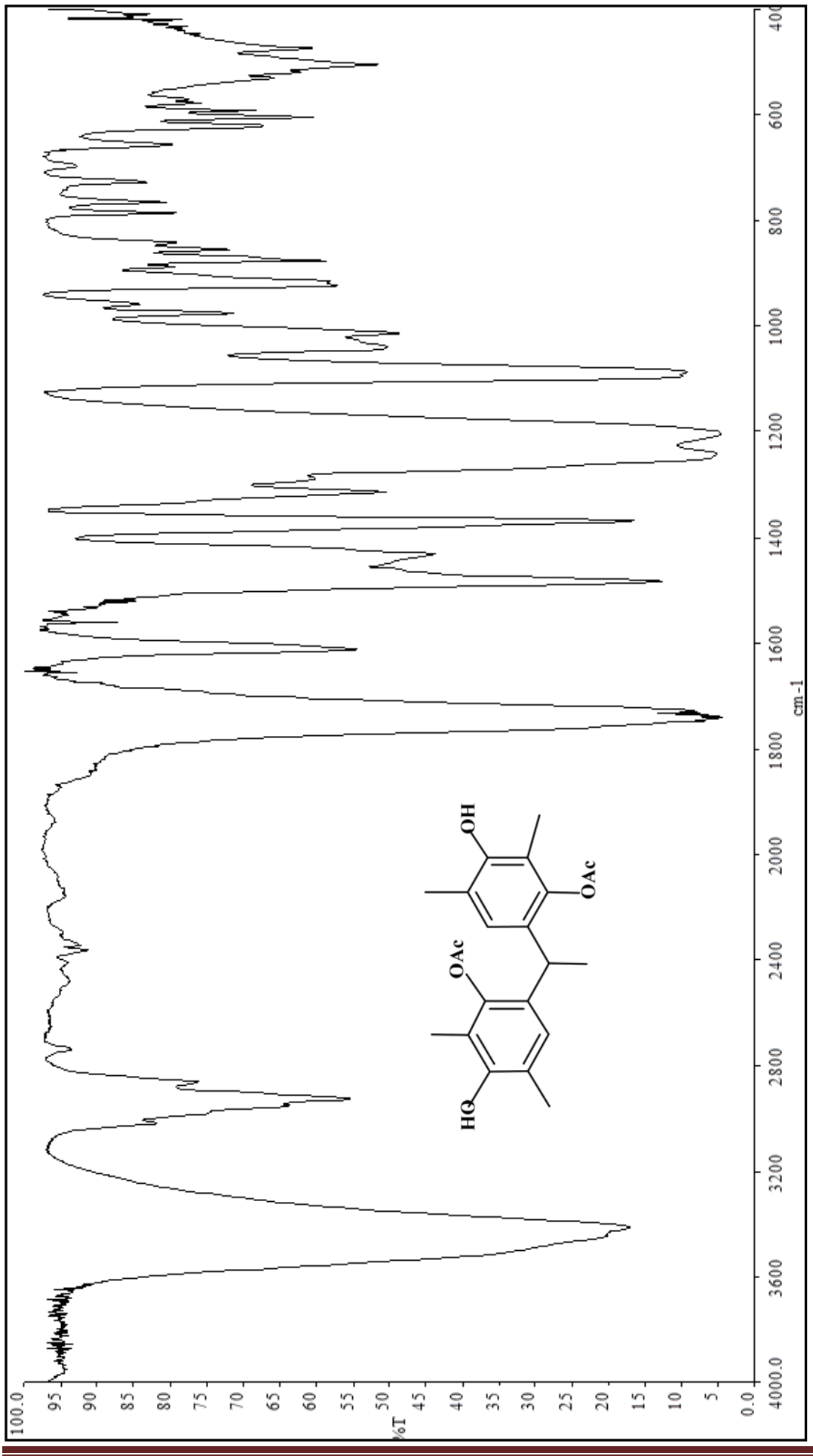


Figure 3.49: FTIR spectrum of compound **83A**

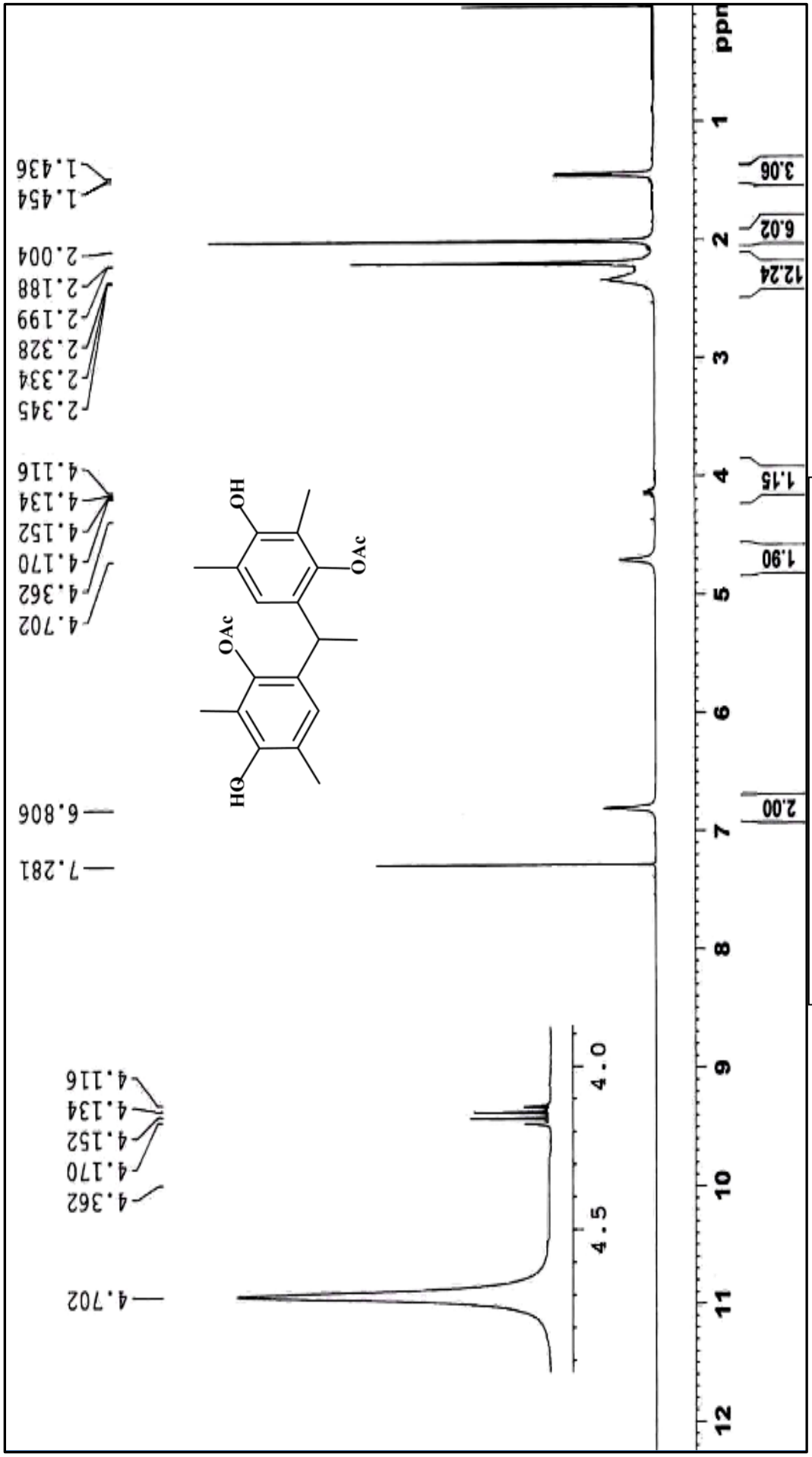


Figure 3.50: ^{1}H NMR spectrum of compound **83A**

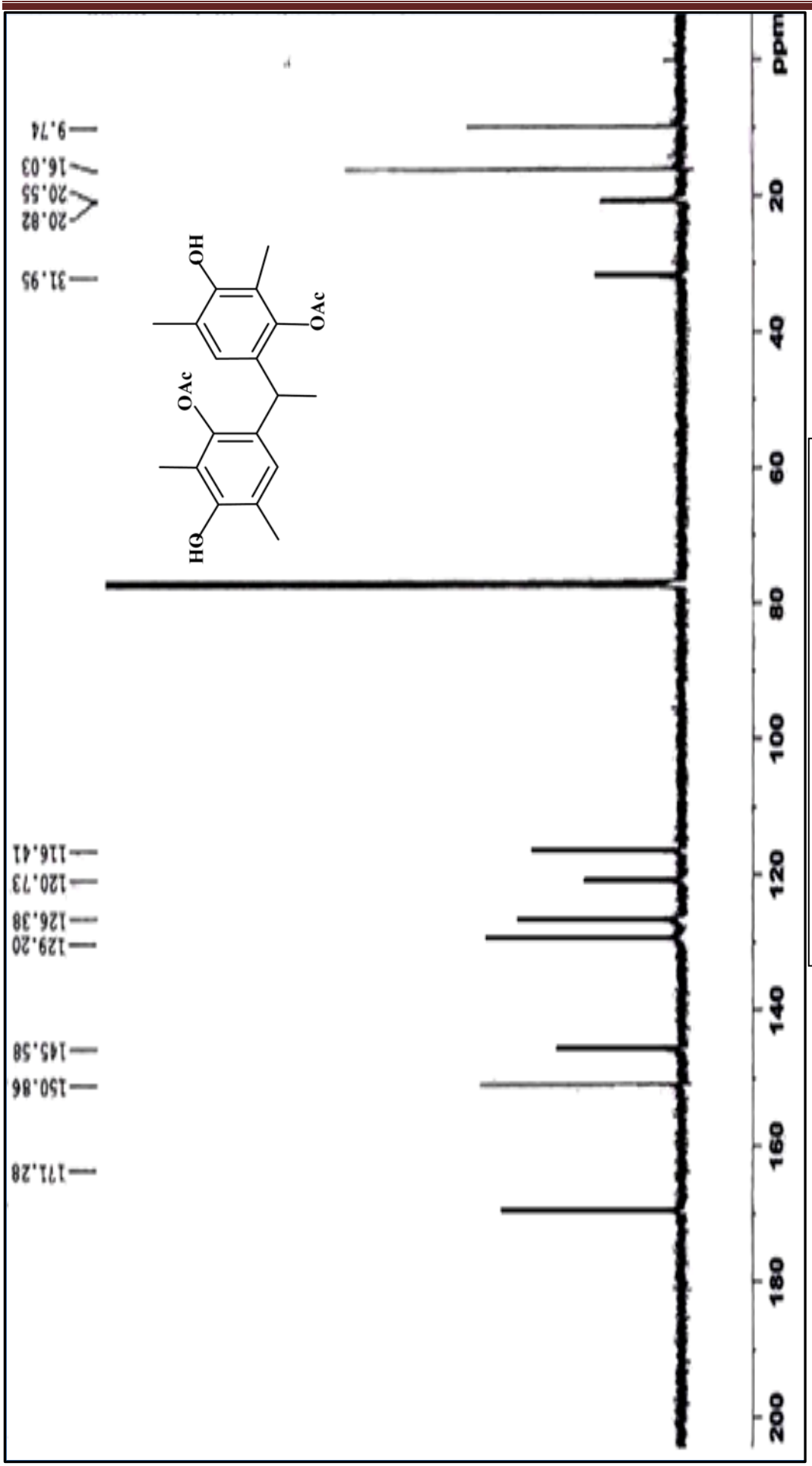


Figure 3.51: ^{13}C NMR spectrum of compound **83A**

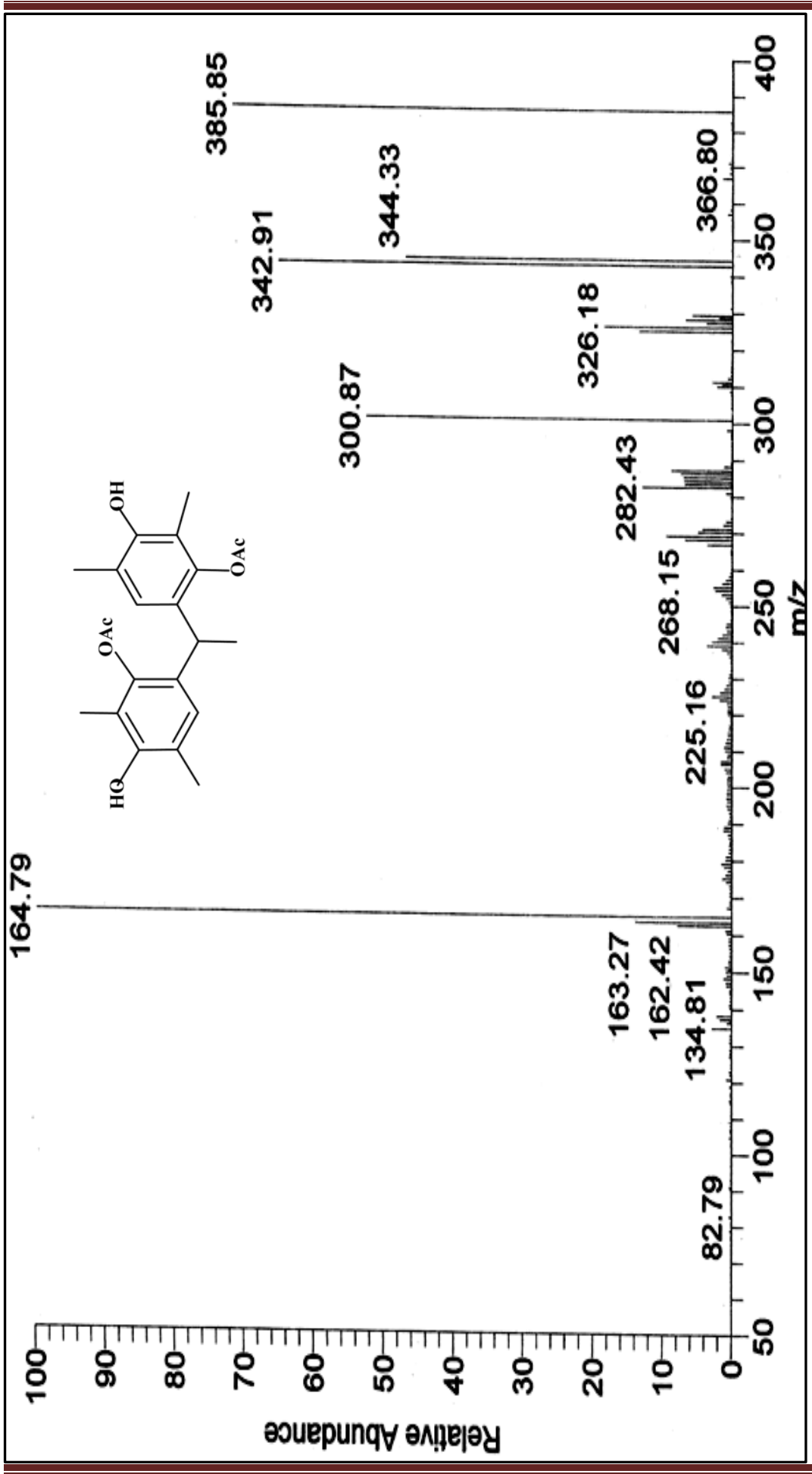


Figure 3.52: EI-MS spectrum of compound **83A**

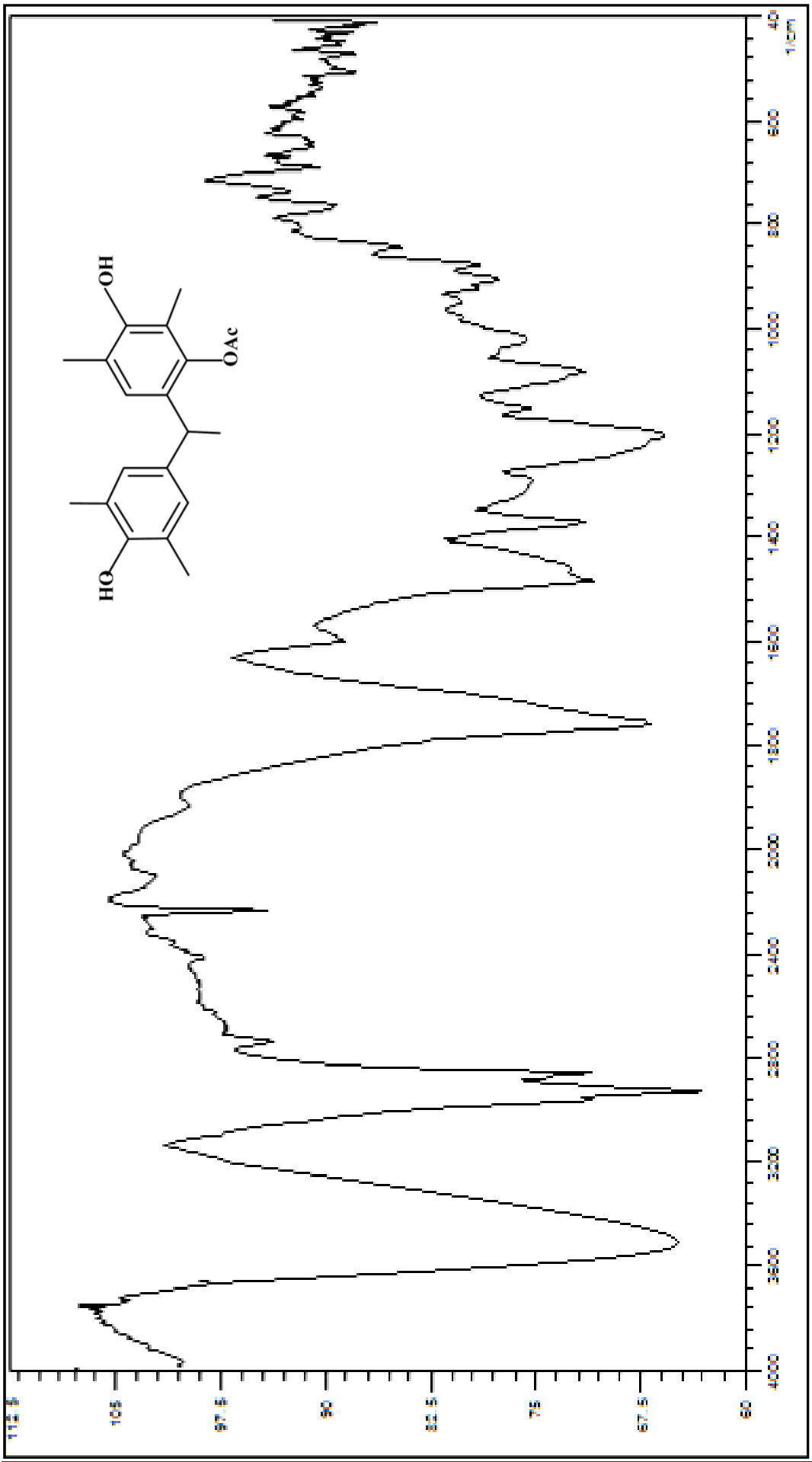


Figure 3.53: FTIR spectrum of compound **83B**

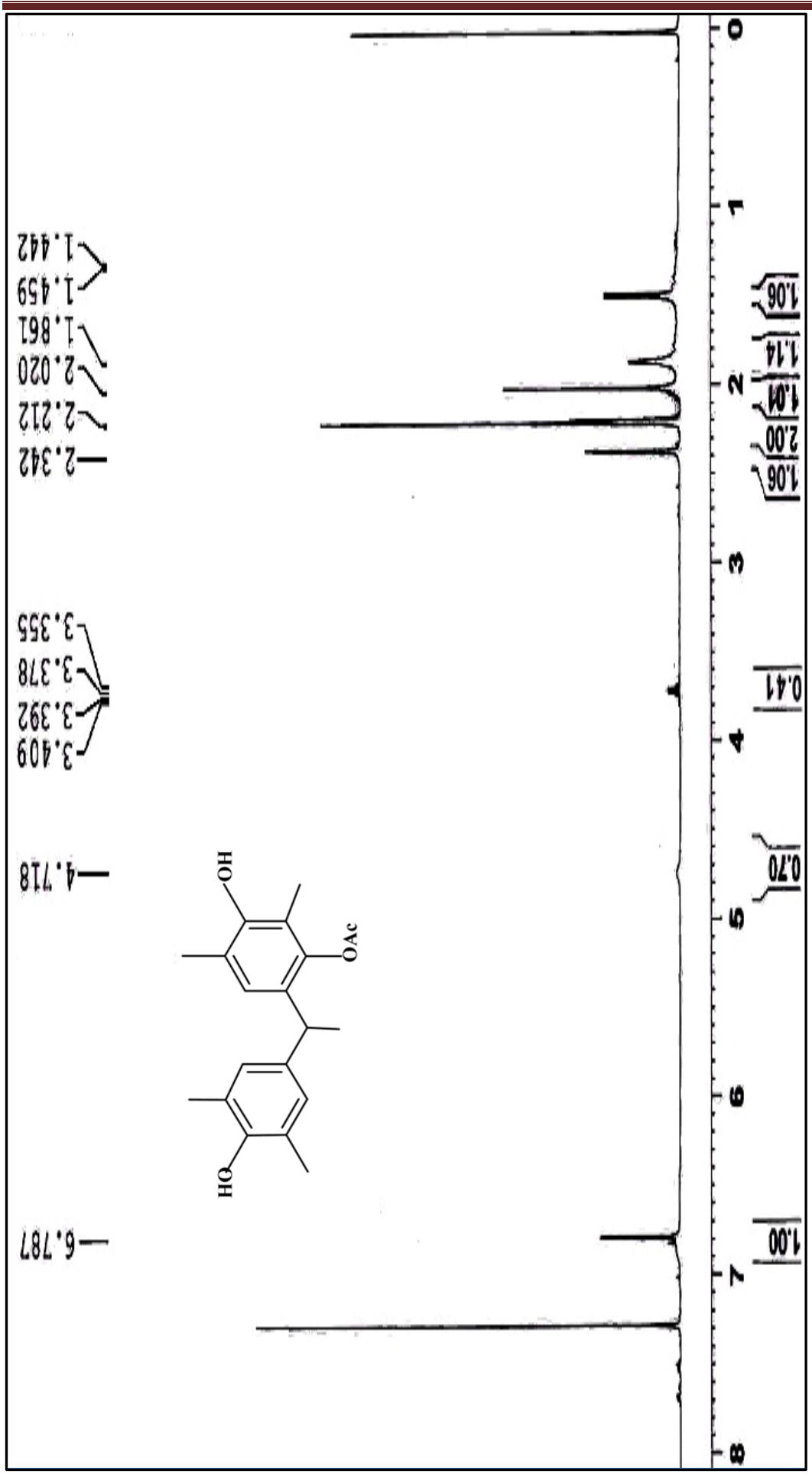


Figure 3.54: ^{1}H NMR spectrum of compound **83B**

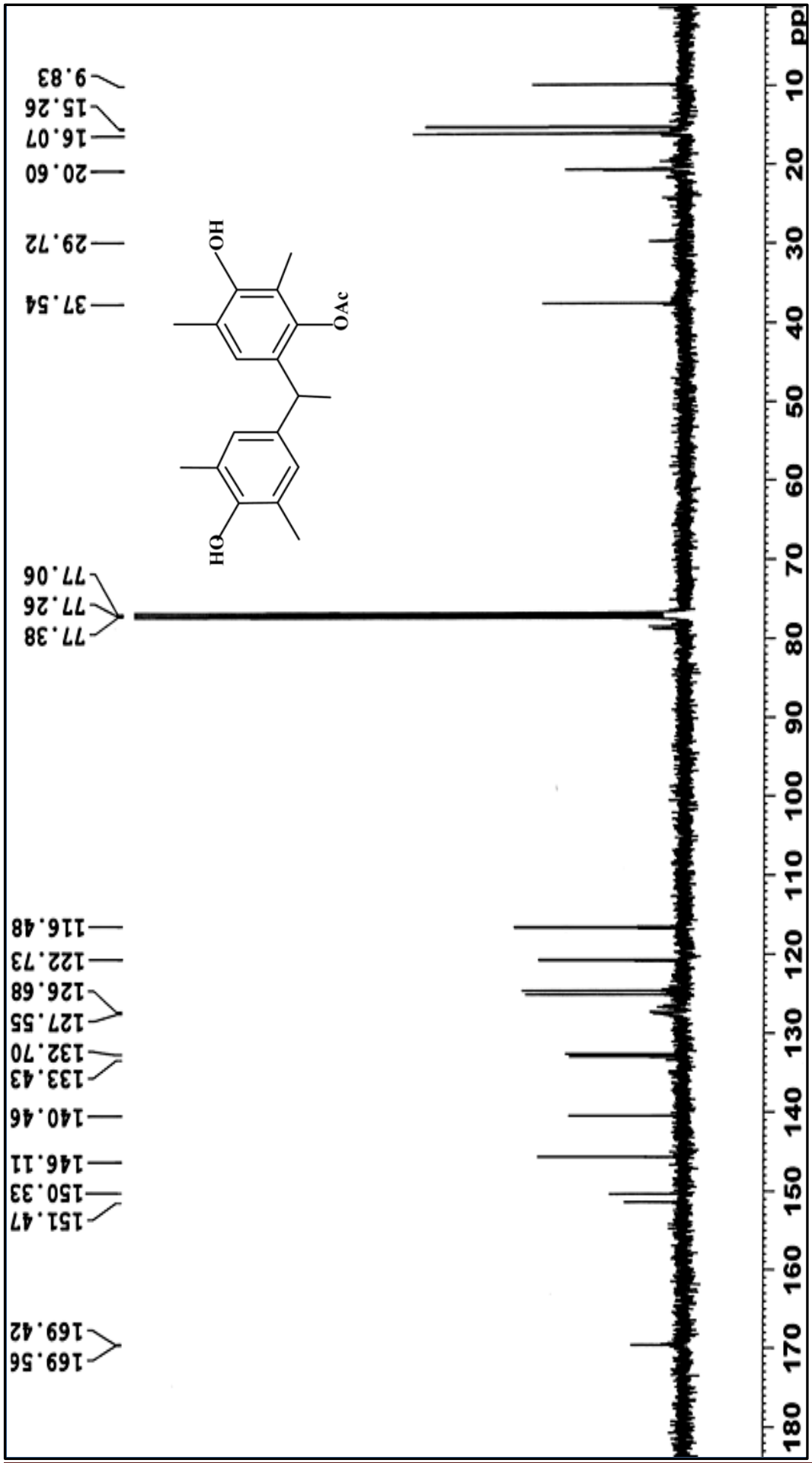


Figure 3.55: ^{13}C NMR spectrum of compound **83B**

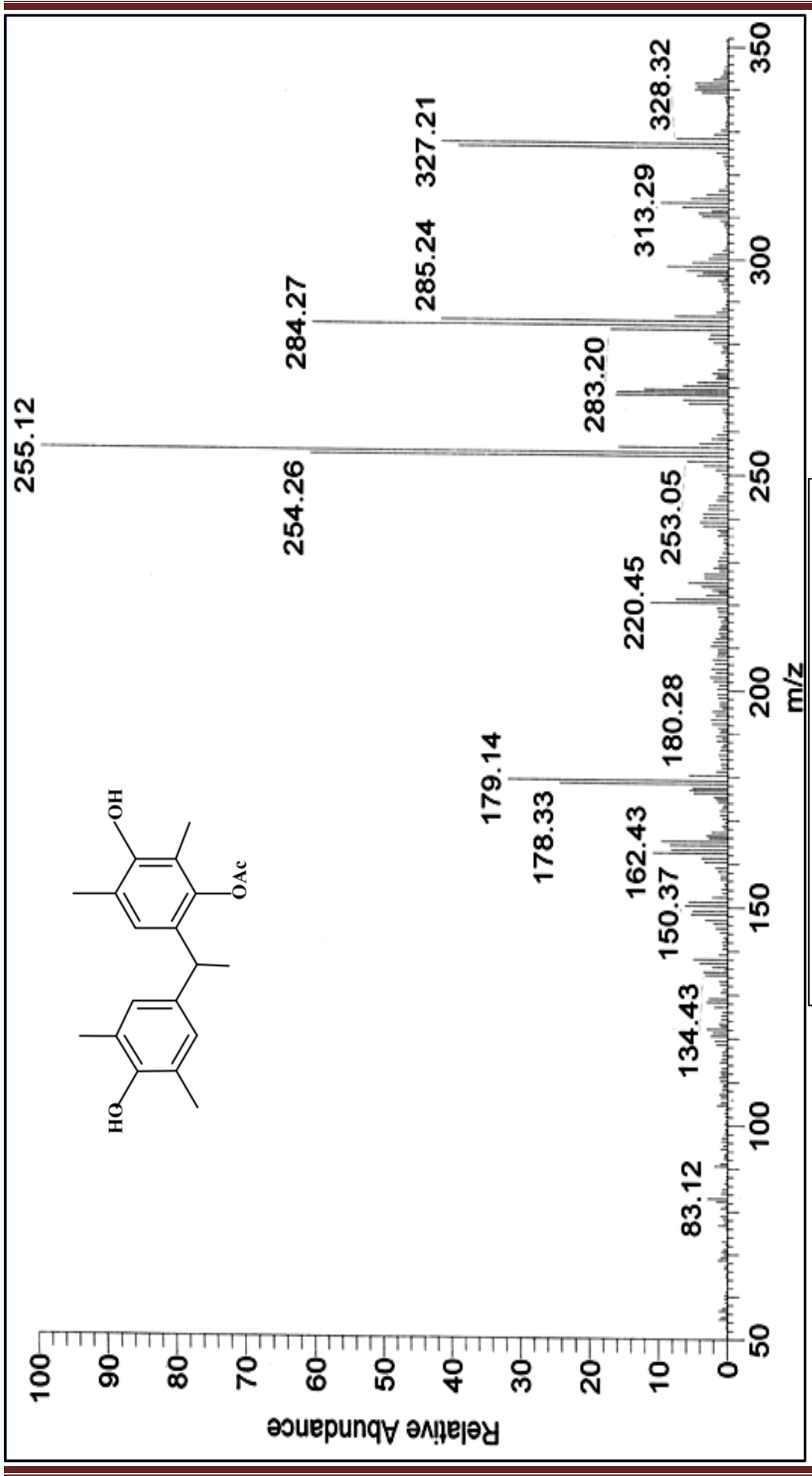


Figure 3.56: EI-MS spectrum of compound **84B**

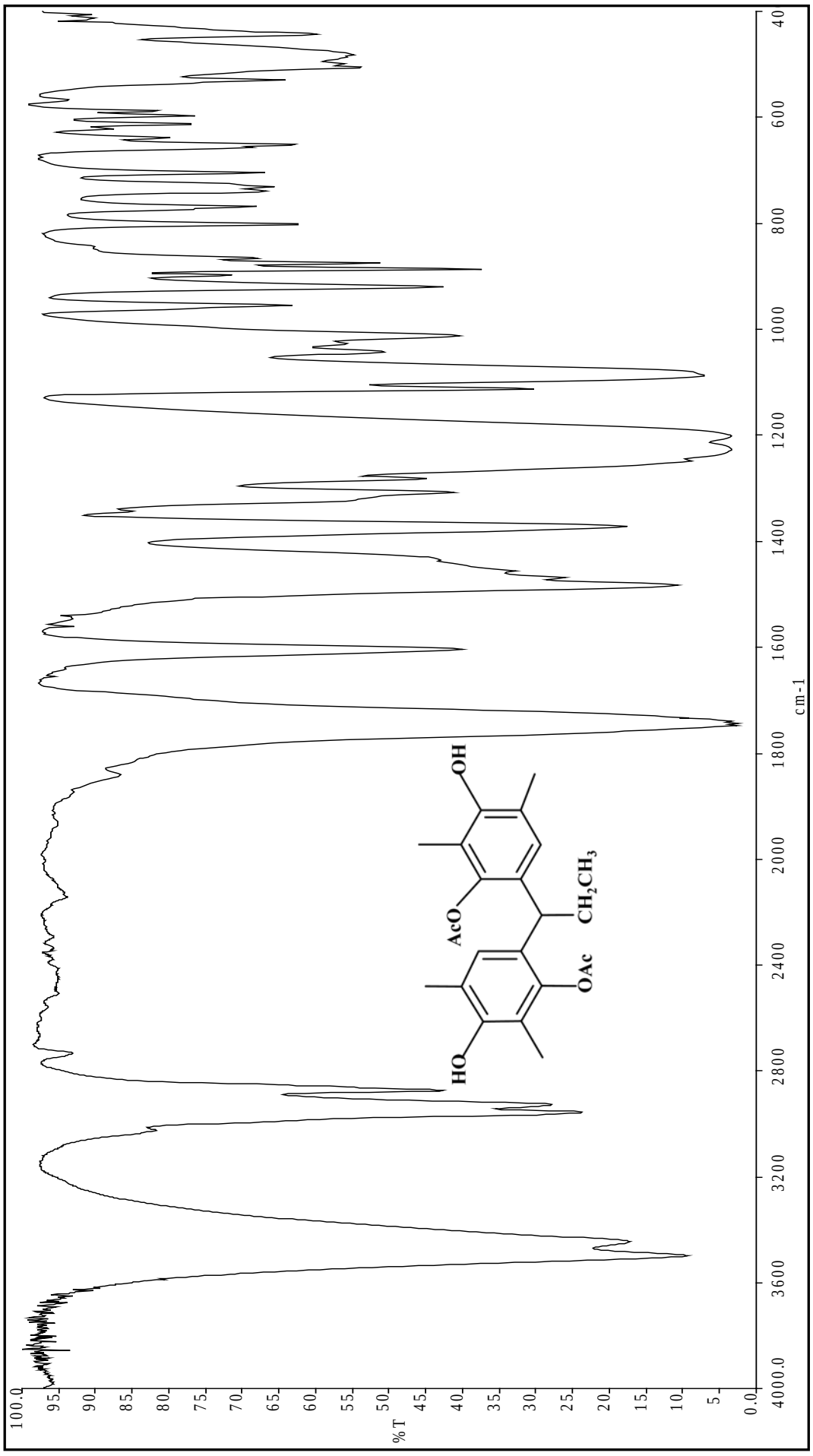


Figure 3.57: FTIR spectrum of compound **84A**

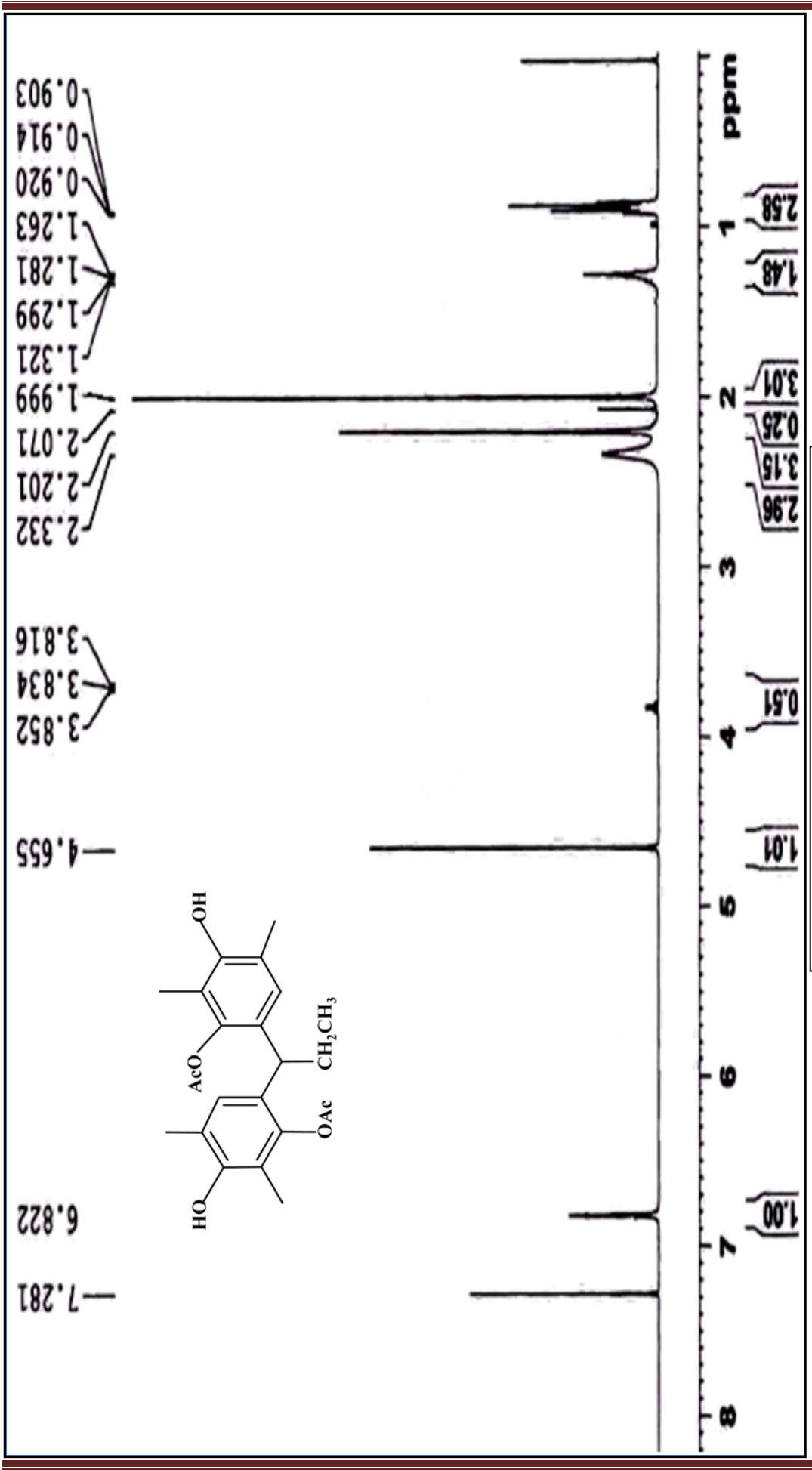


Figure 3.58: ^{1}H NMR spectrum of compound **84A**

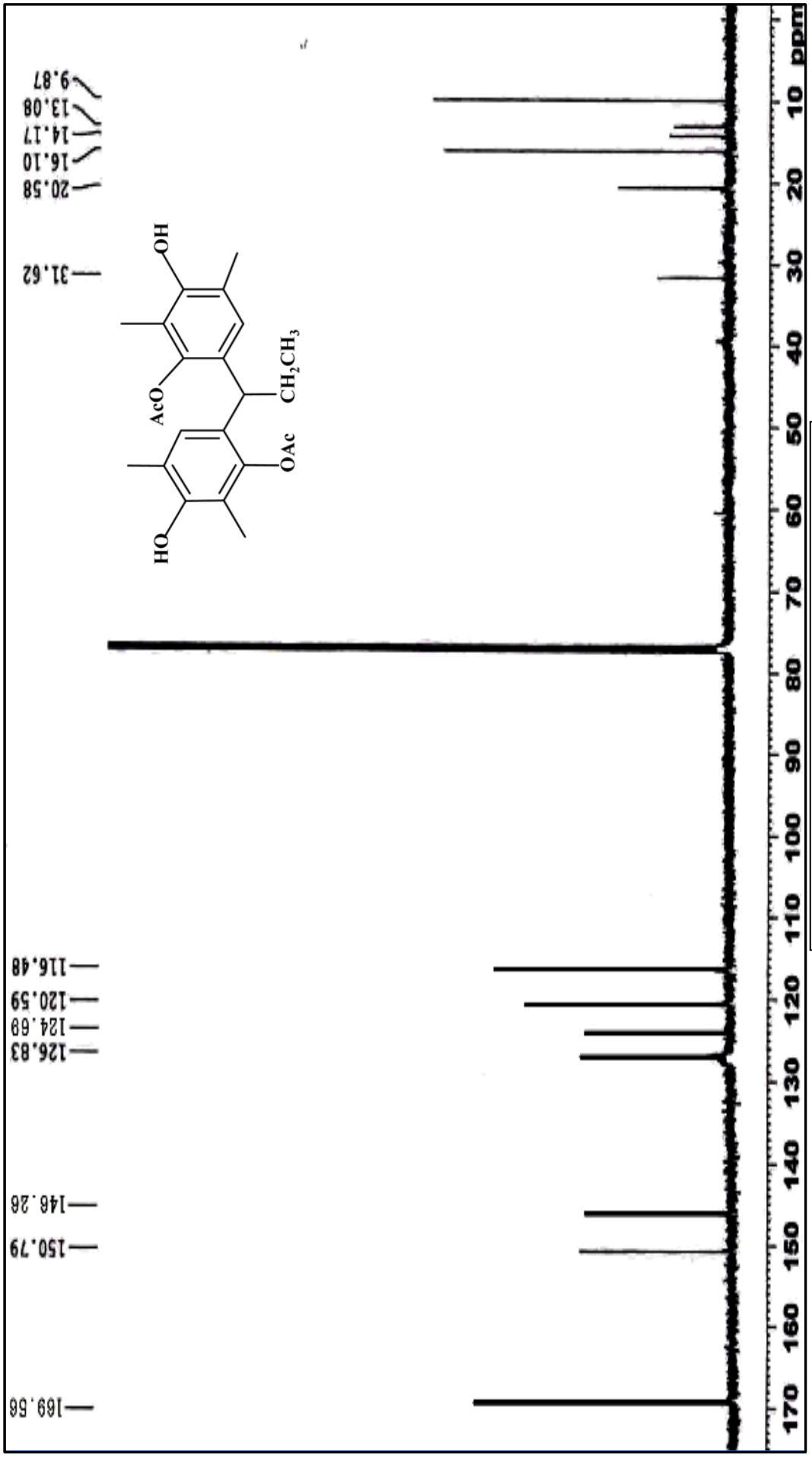


Figure 3.59: ^{13}C NMR spectrum of compound **84A**

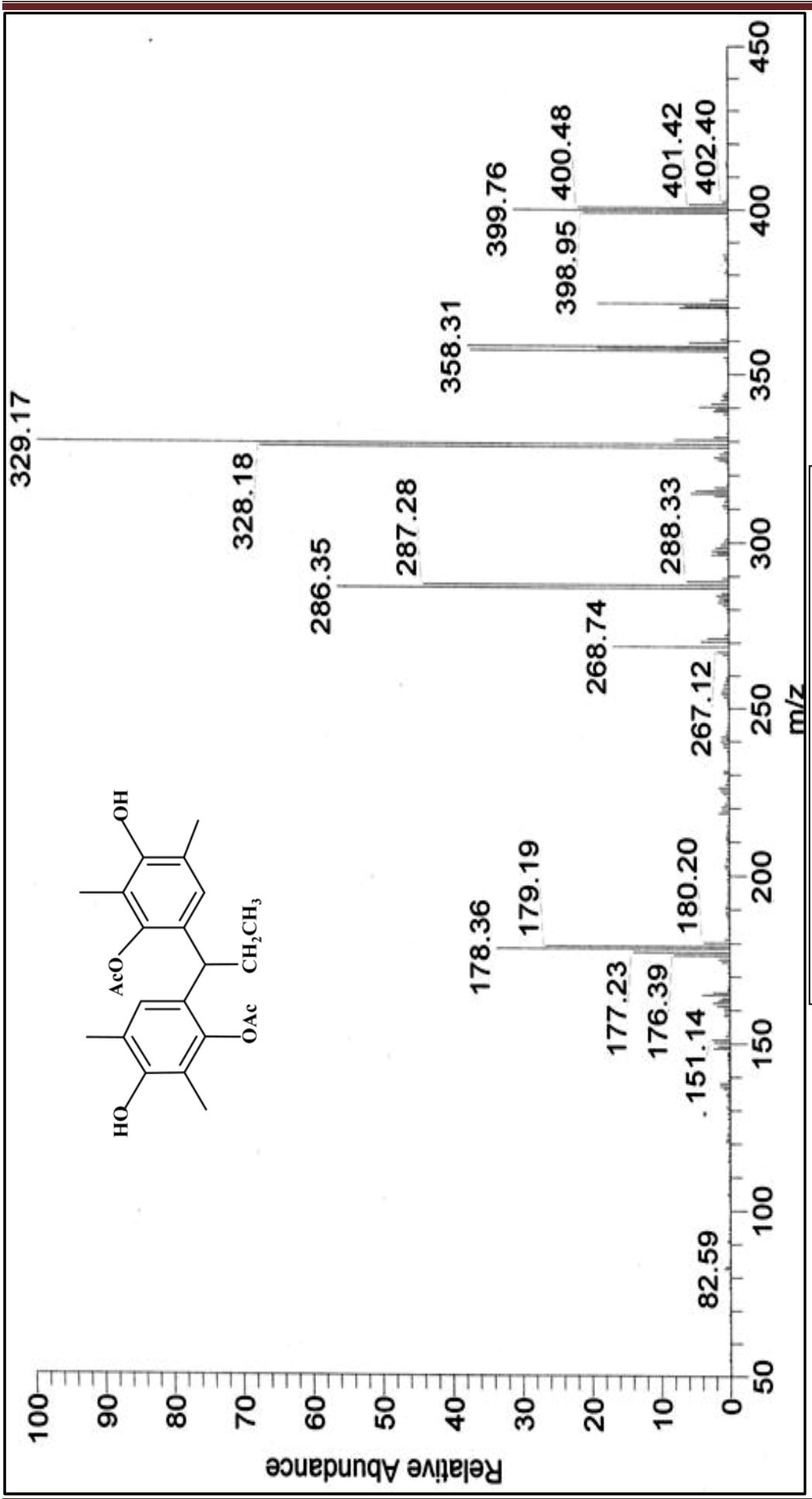


Figure 3.60: EI-MS spectrum of compound **84A**

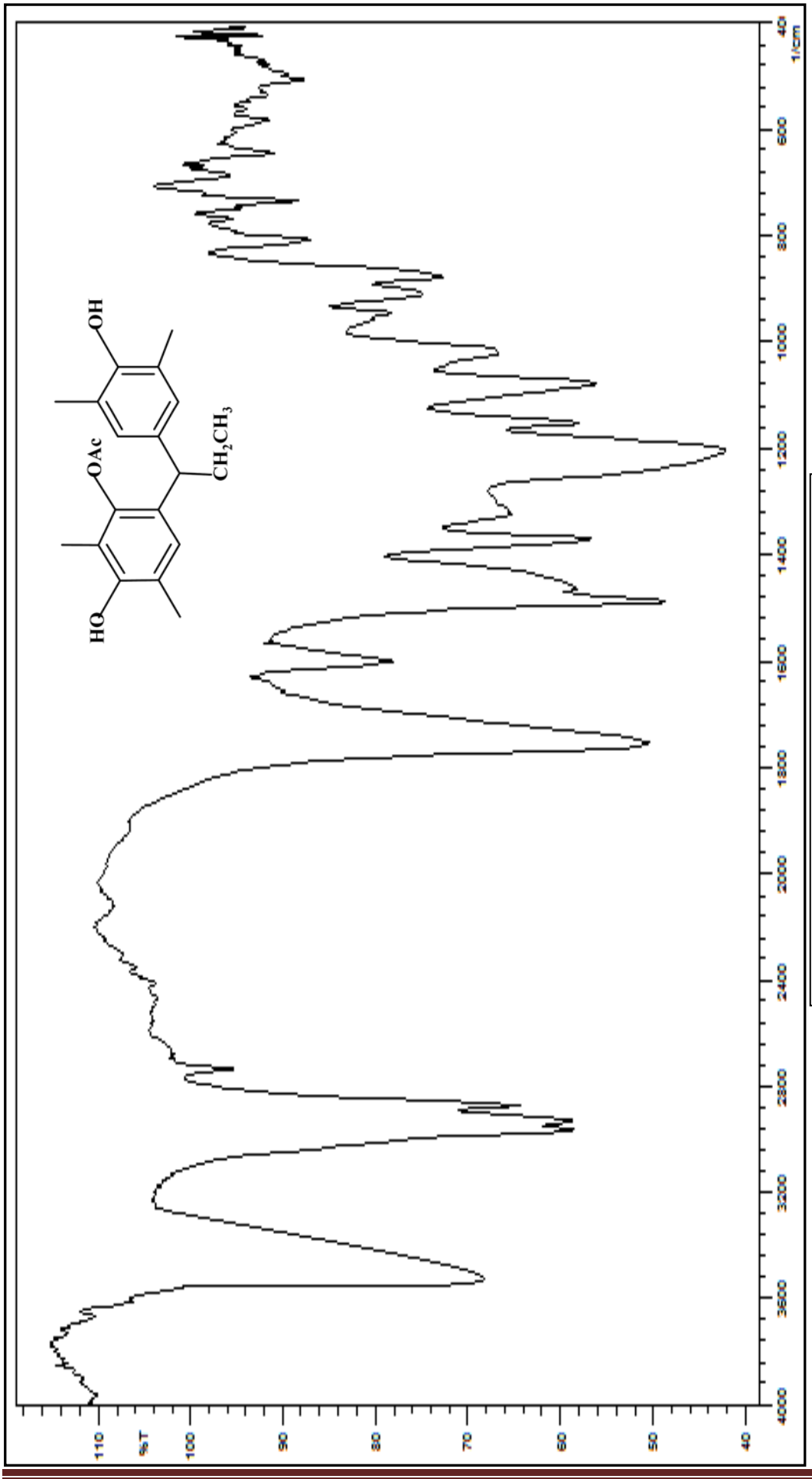


Figure 3.61: FTIR spectrum of compound **84B**

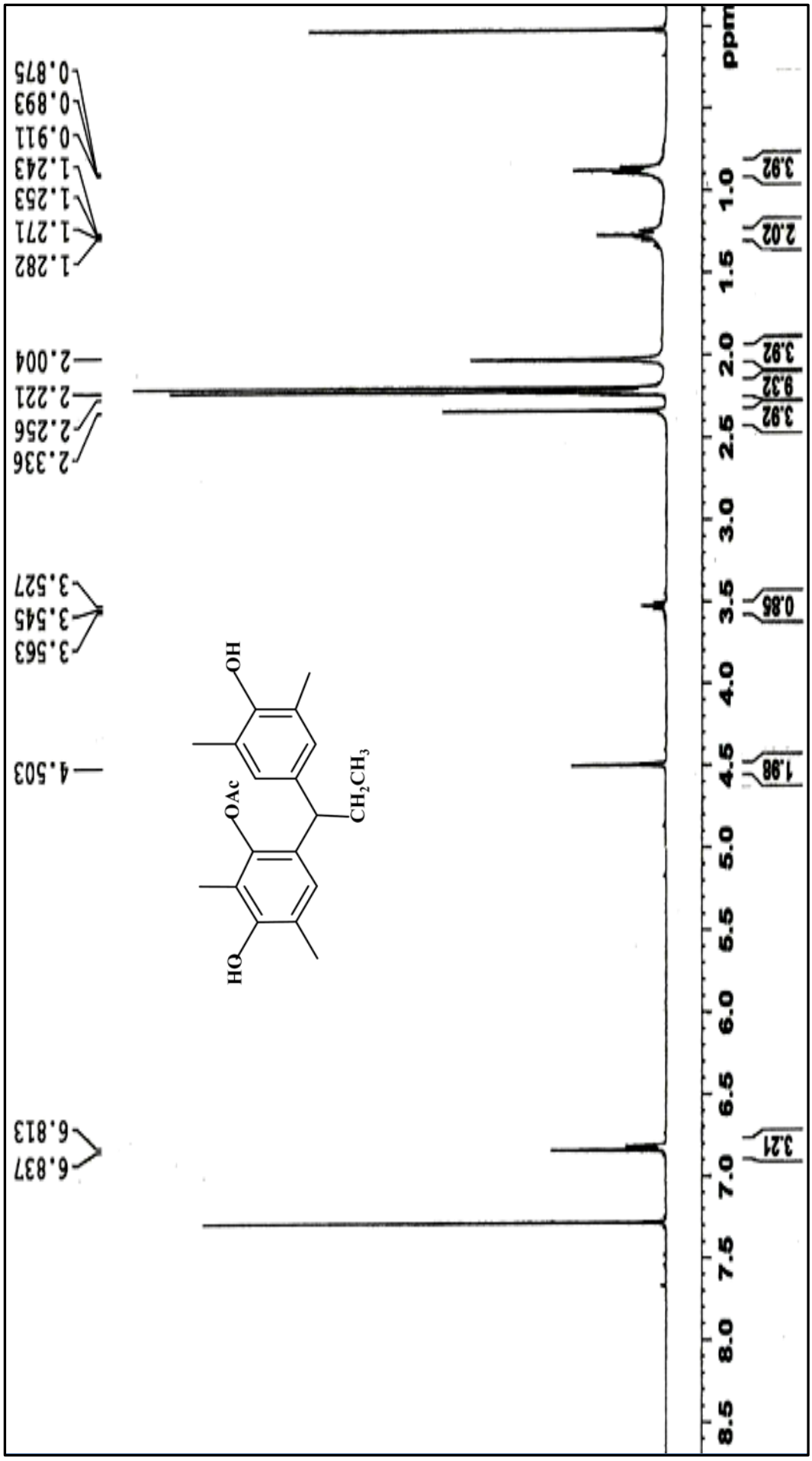


Figure 3.62: ^{1}H NMR spectrum of compound **84B**

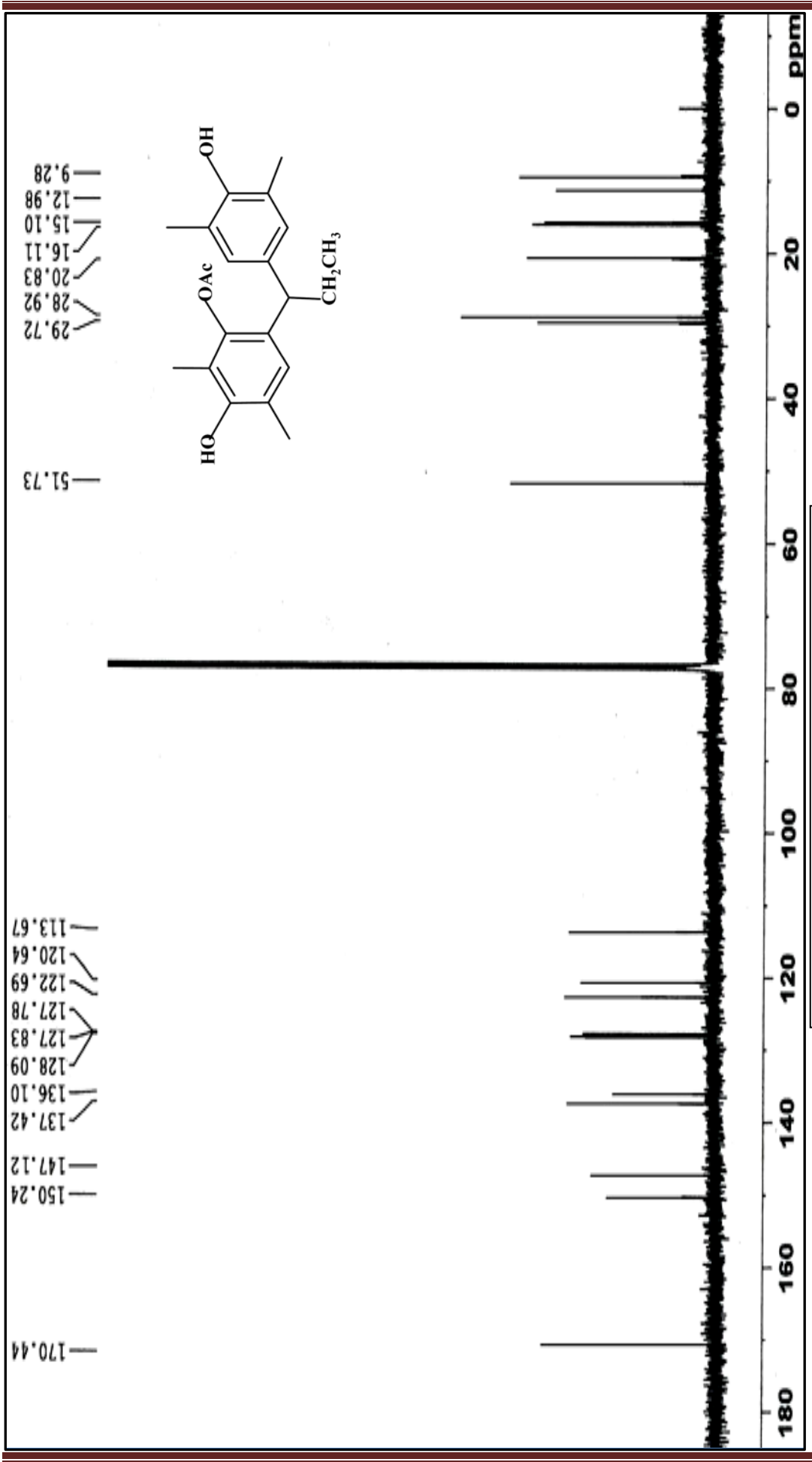


Figure 3.63: ^{13}C NMR spectrum of compound **84B**

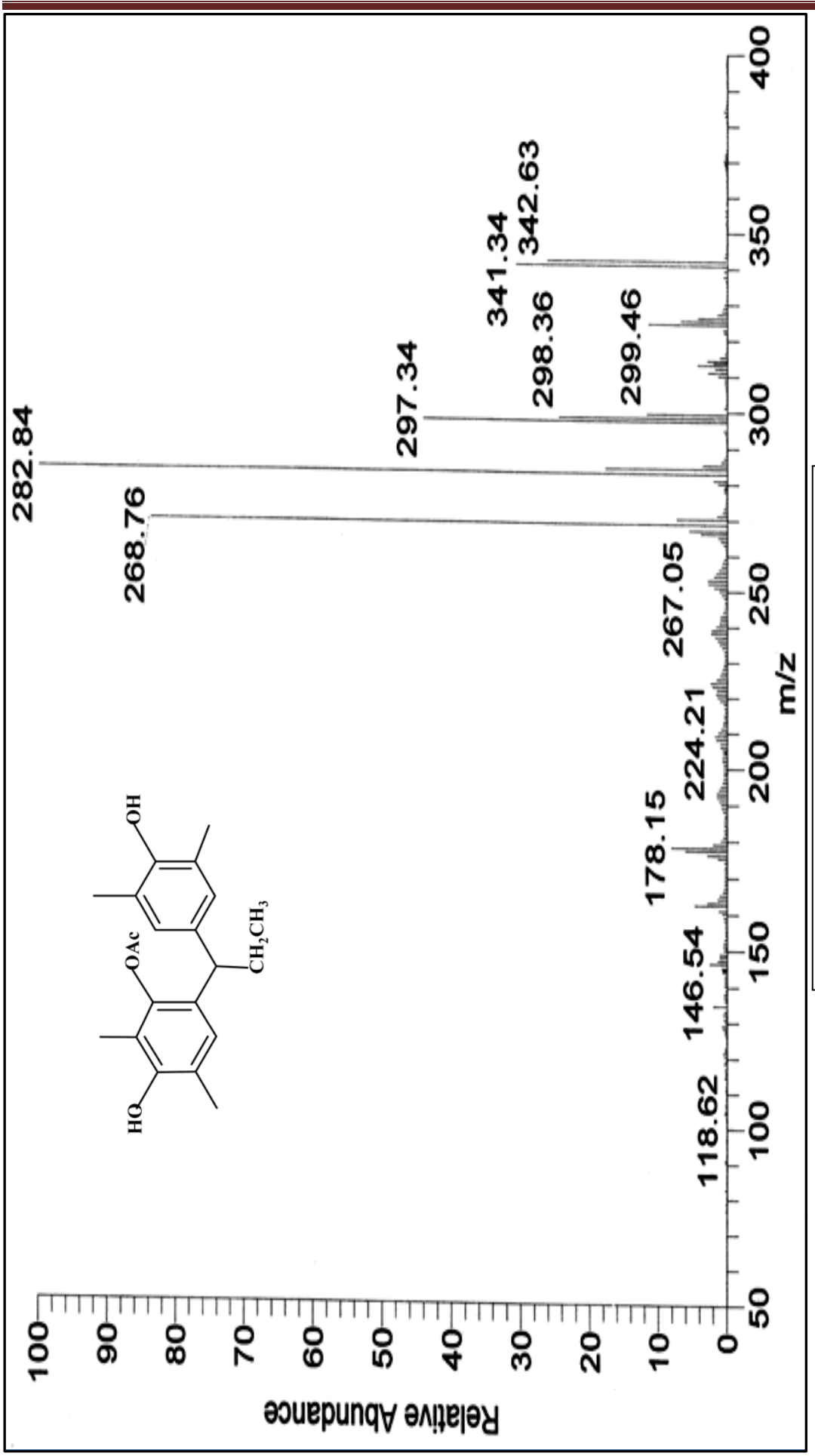


Figure 3.64: EI-MS spectrum of compound **84B**

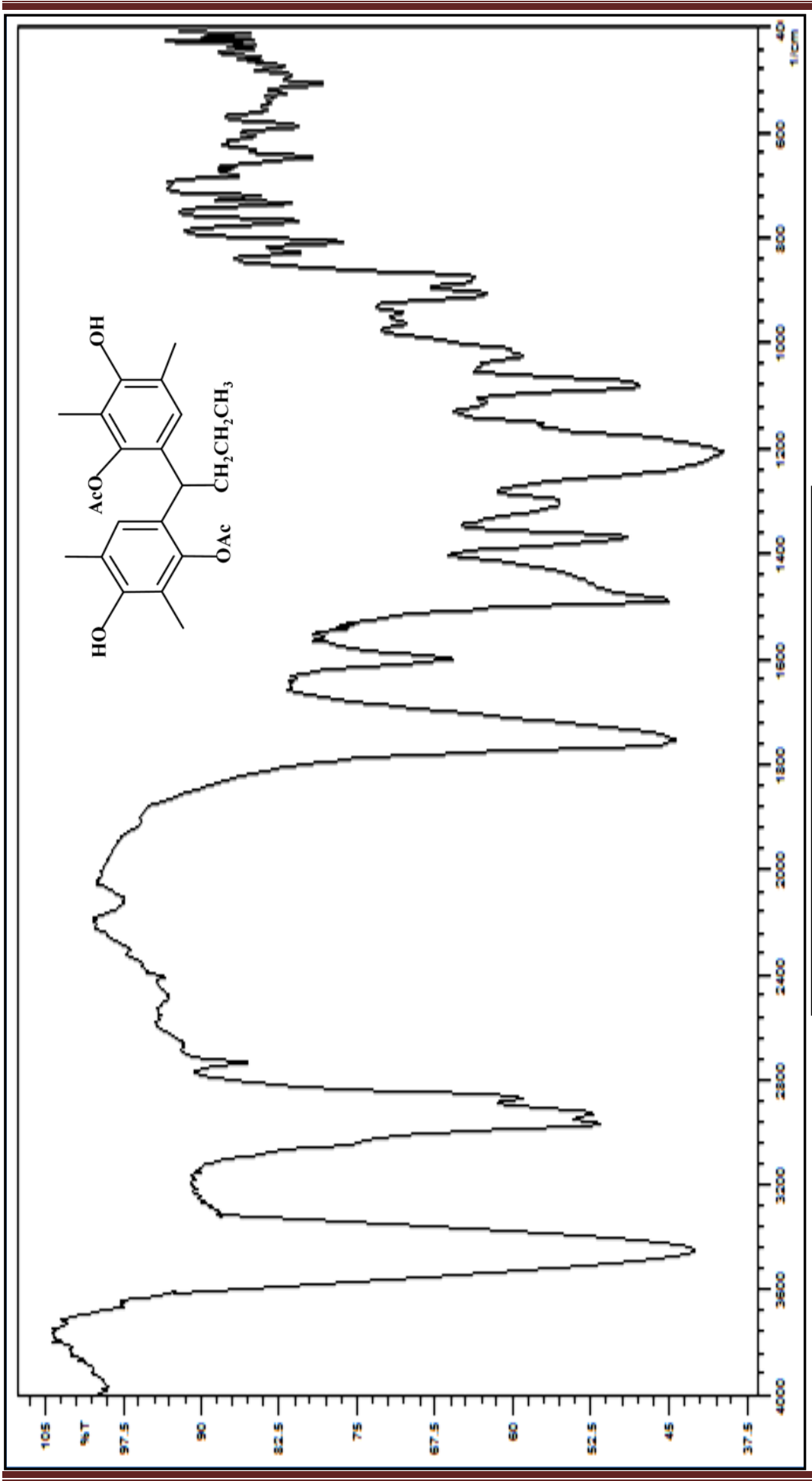


Figure 3.65: FTIR spectrum of compound **85A**

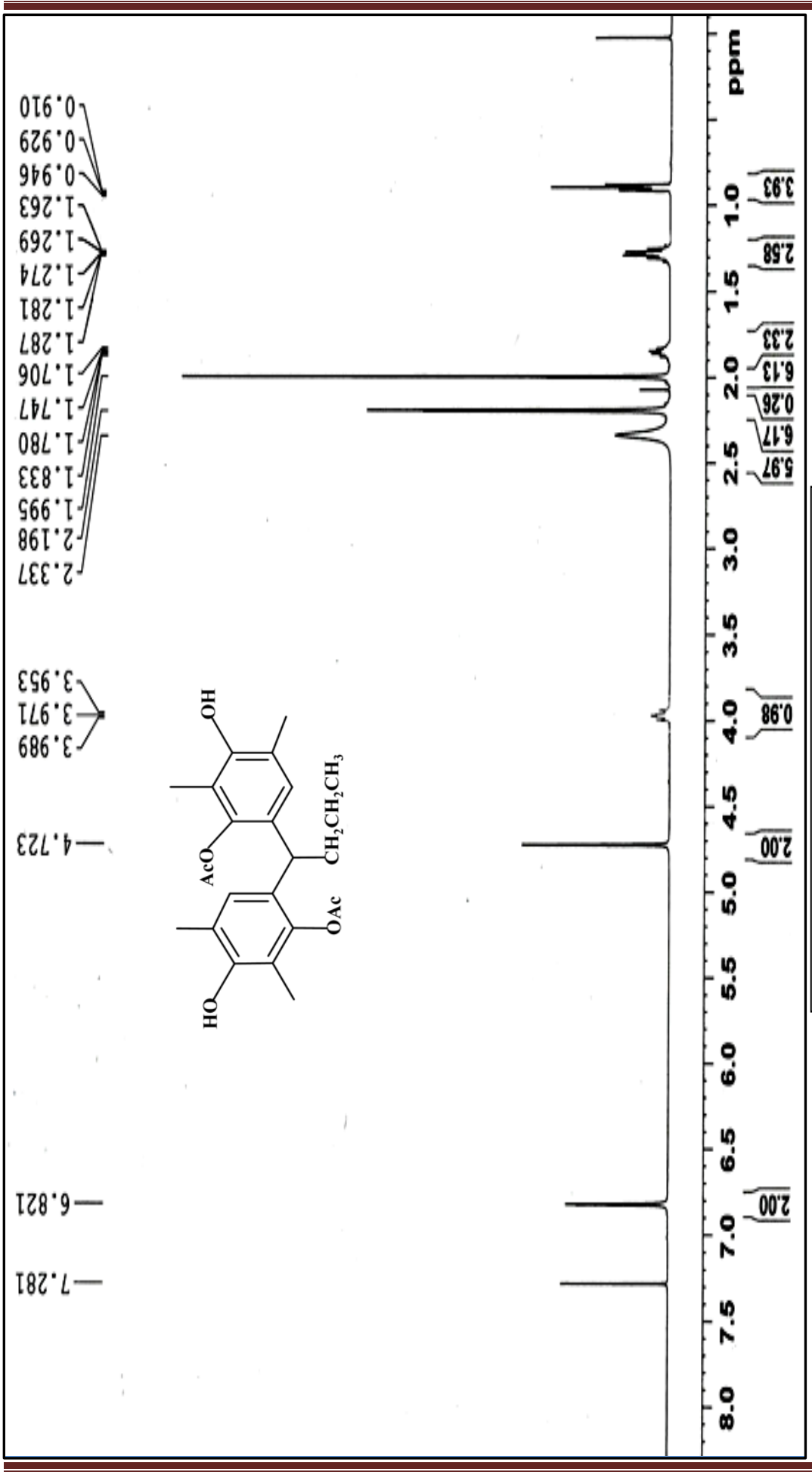


Figure 3.66: ^{1}H NMR spectrum of compound **85A**

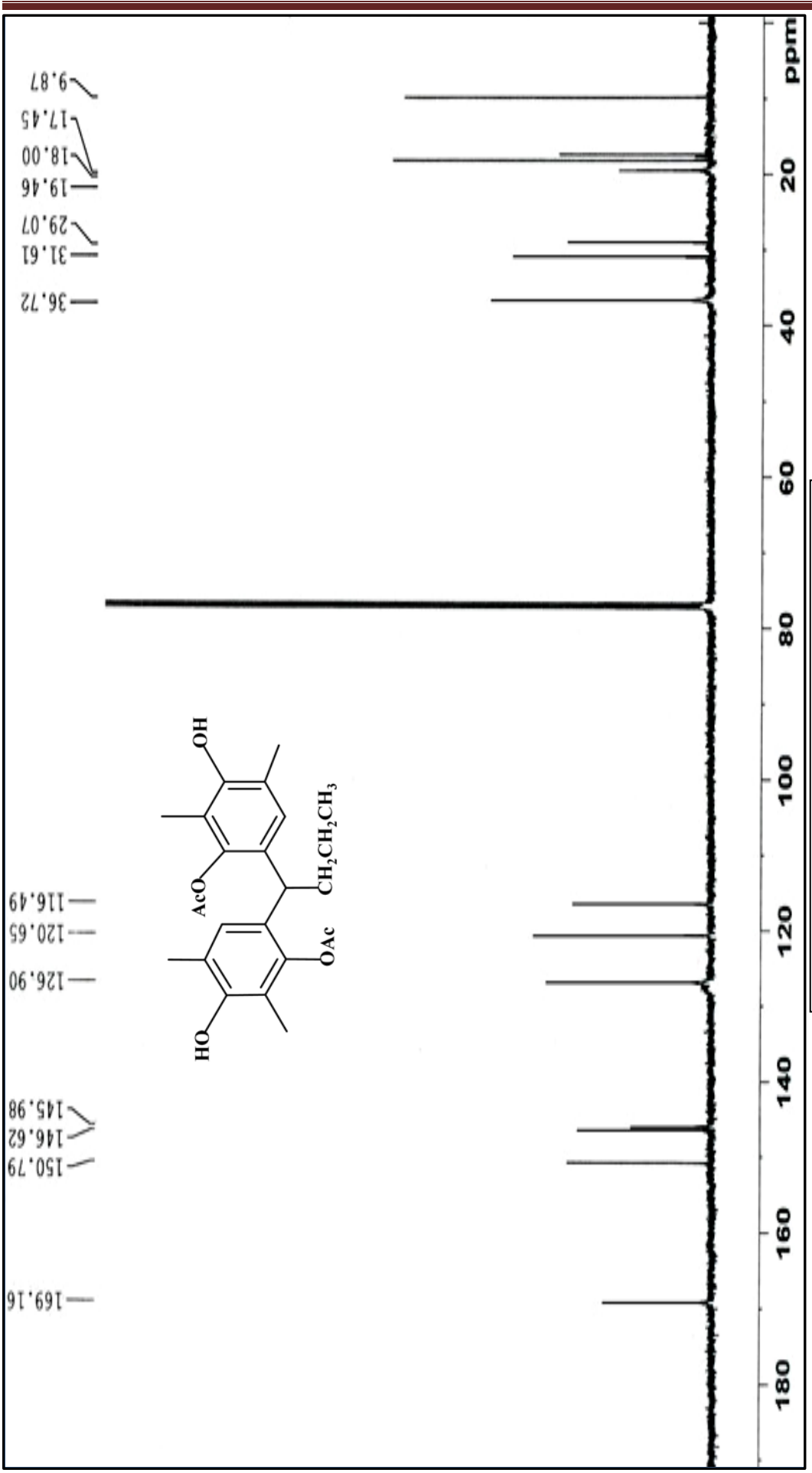


Figure 3.67: ^{13}C NMR spectrum of compound **85A**

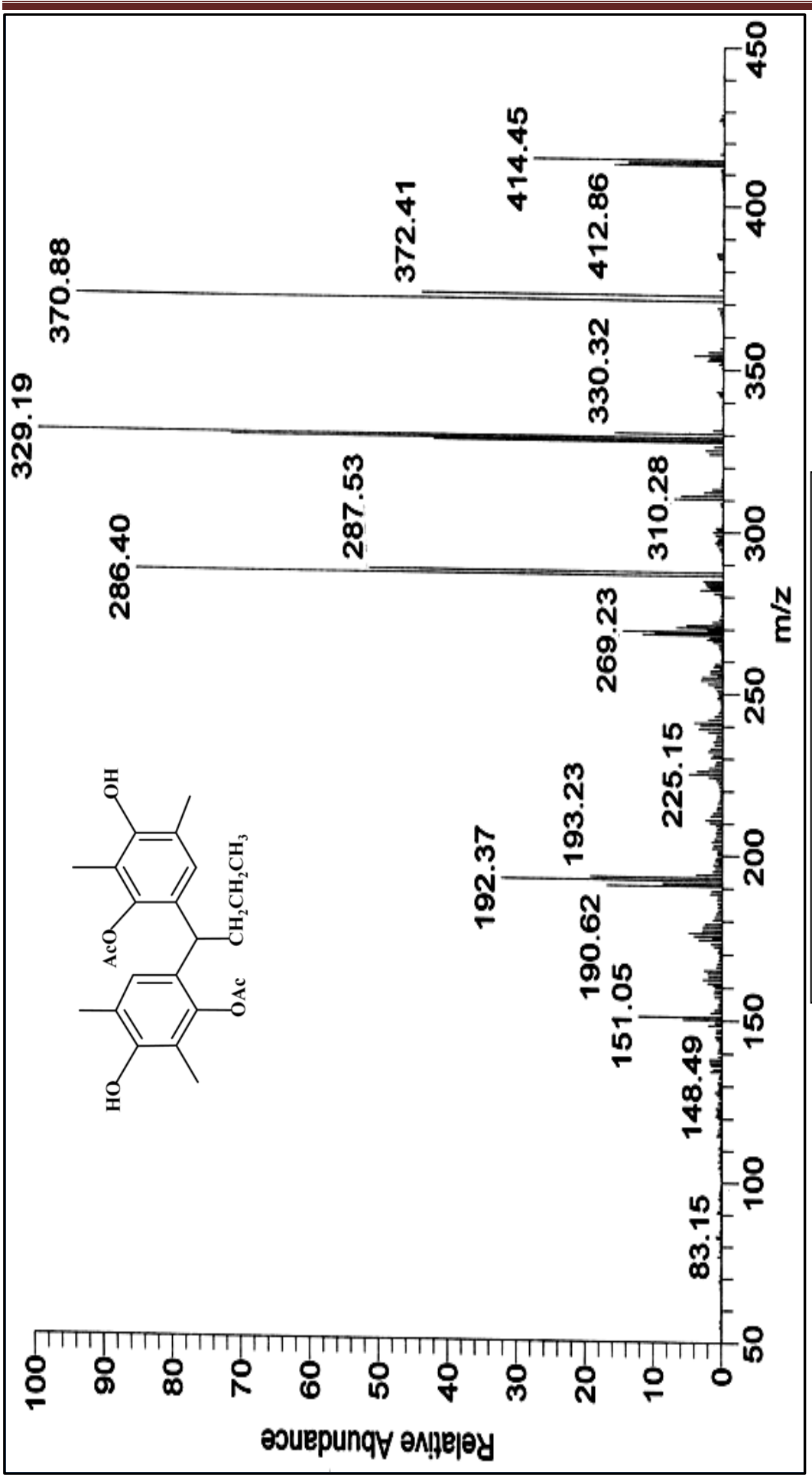


Figure 3.68: EI-MS spectrum of compound **85A**

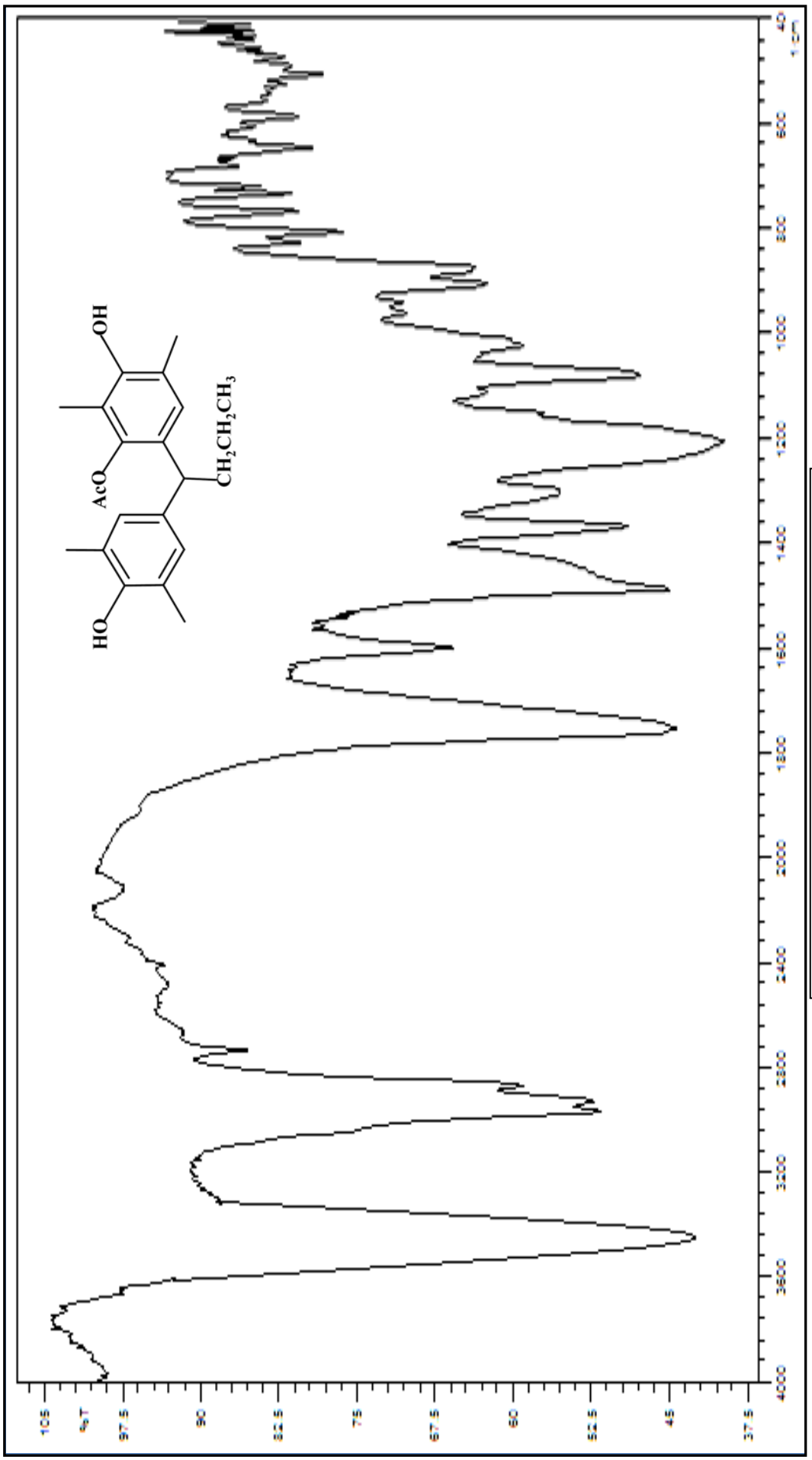


Figure 3.69: FTIR spectrum of compound **85B**

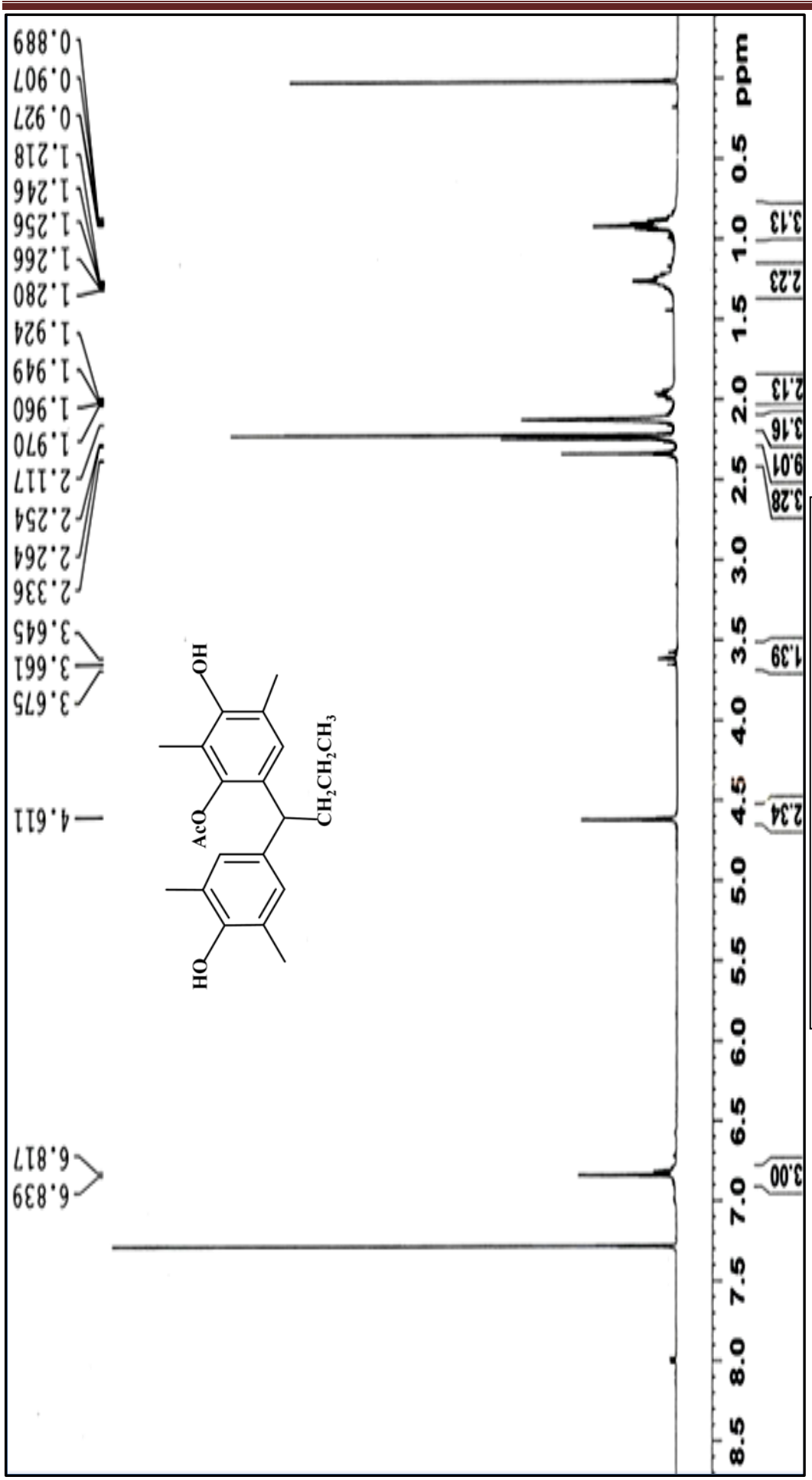


Figure 3.70: ^{1}H NMR spectrum of compound **85B**

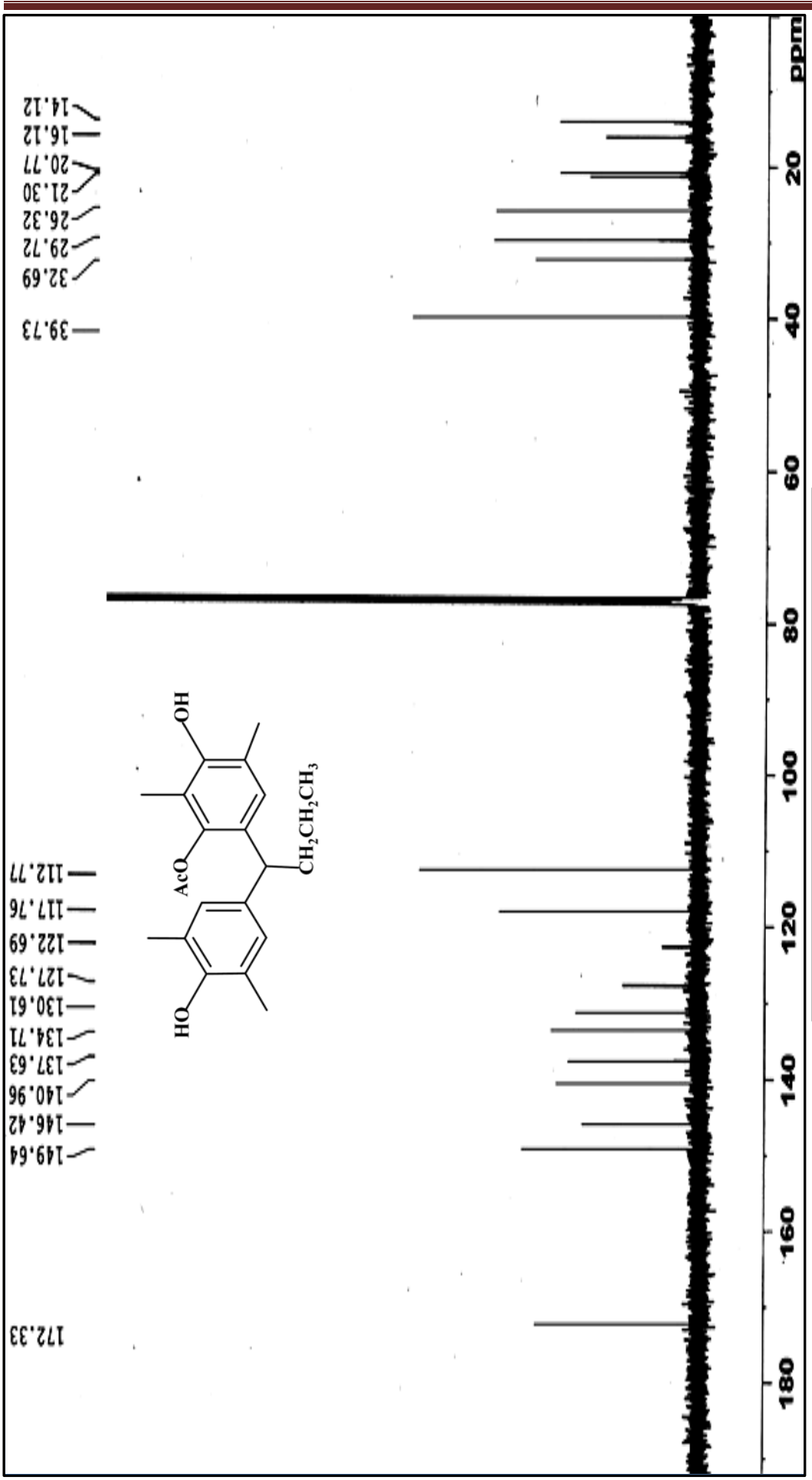


Figure 3.71: ^{13}C NMR spectrum of compound **85B**

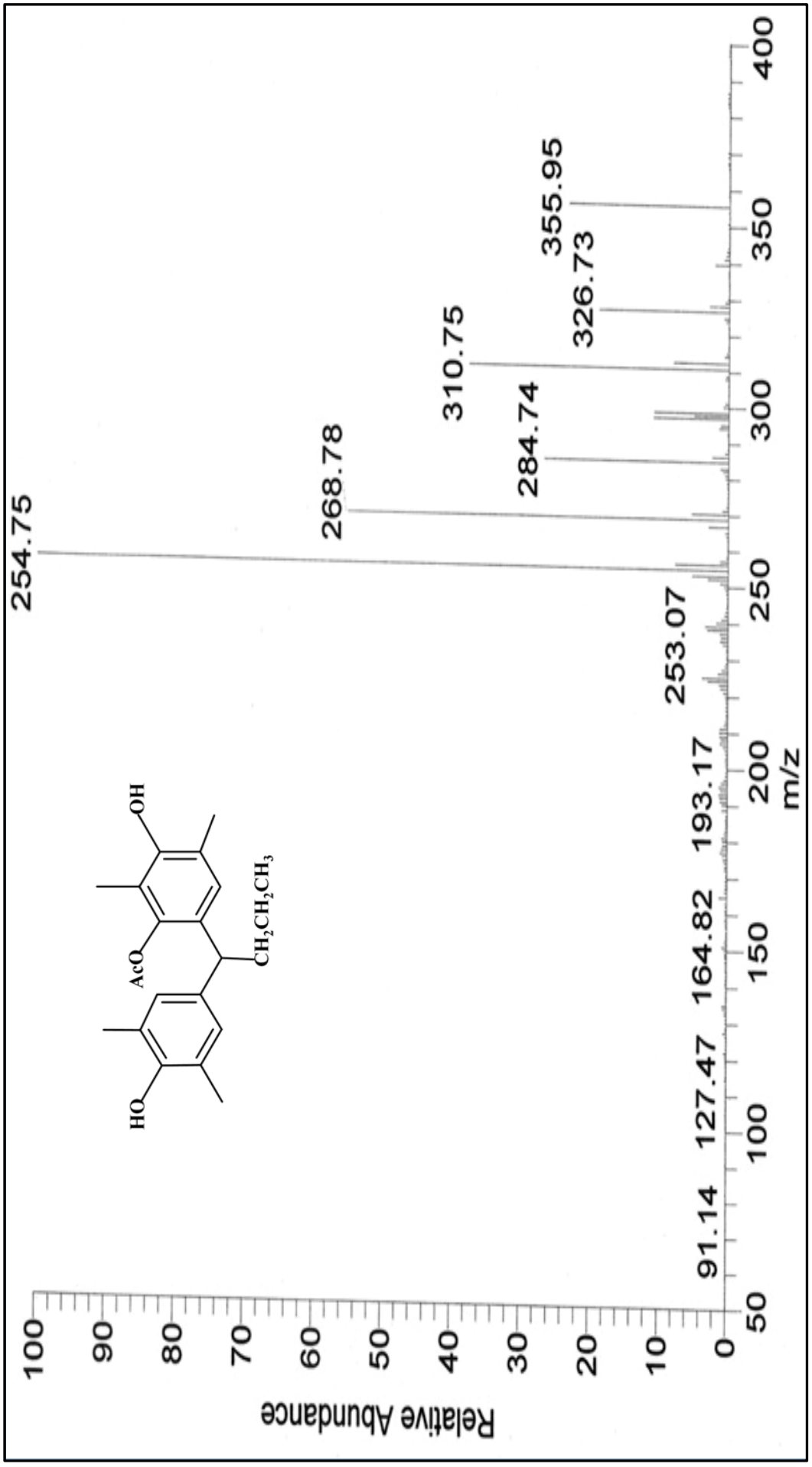


Figure 3.72: EI-MS spectrum of compound **85B**

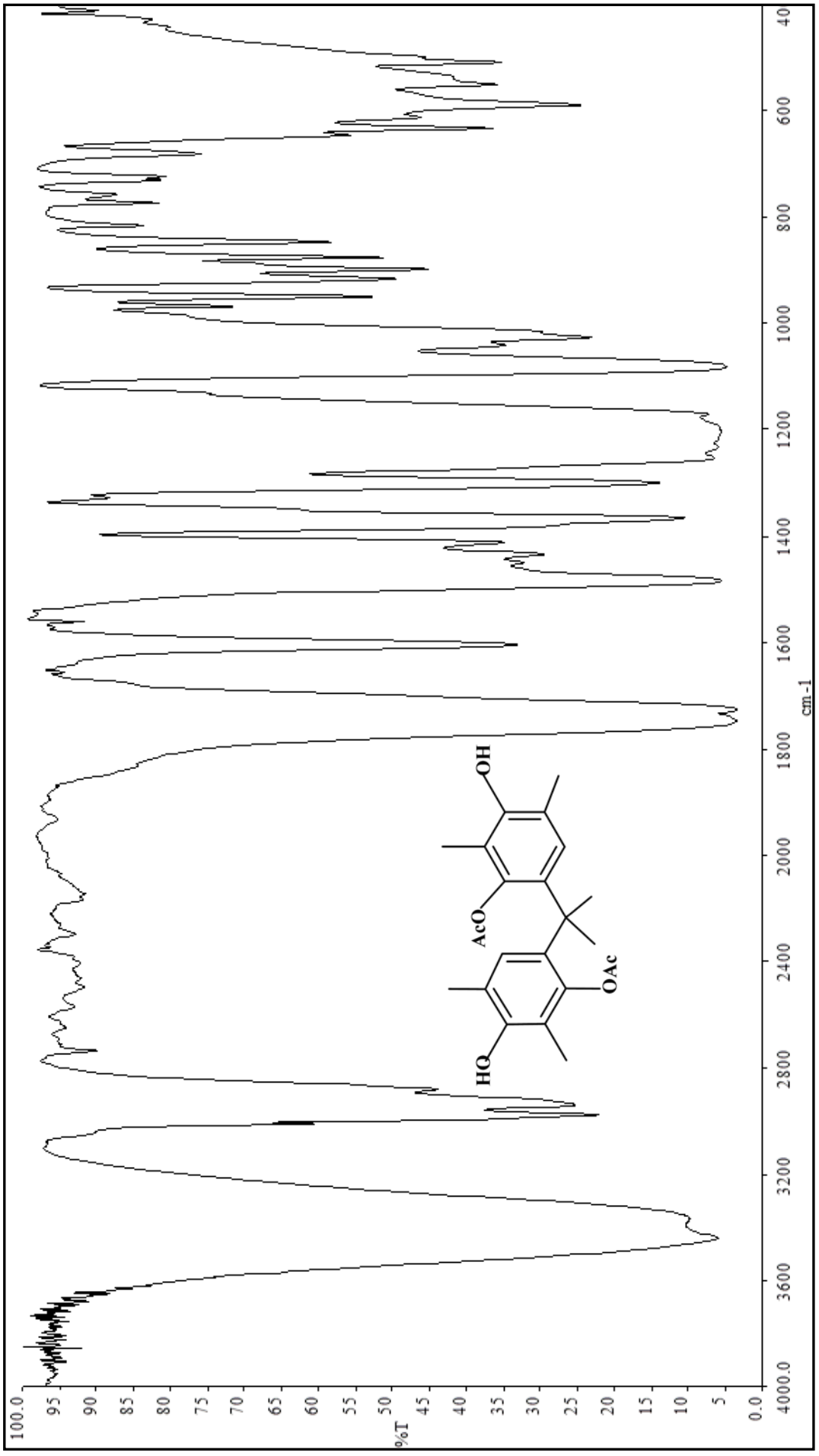


Figure 3.73: FTIR spectrum of compound **86A**

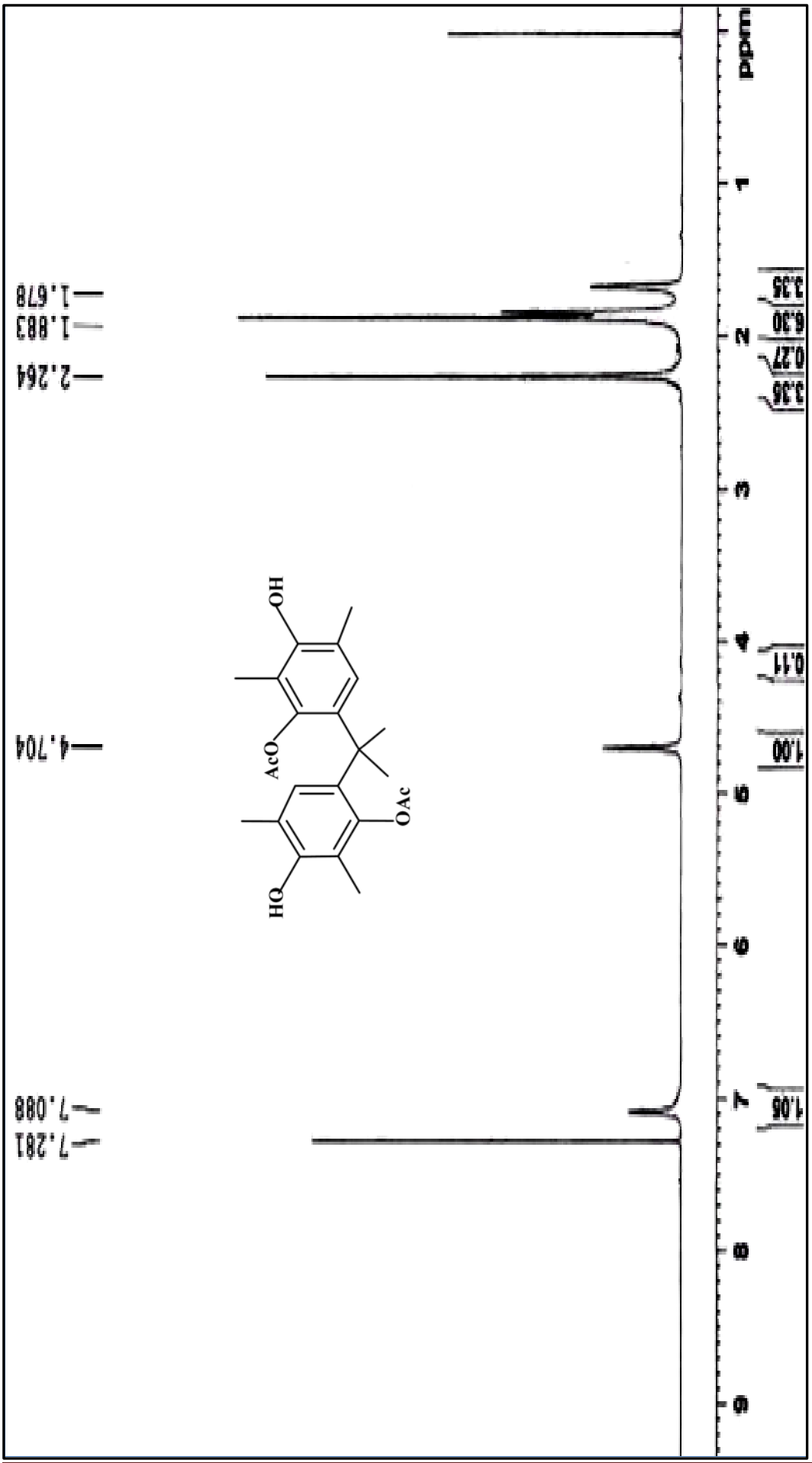


Figure 3.74: ^{1}H NMR spectrum of compound **86A**

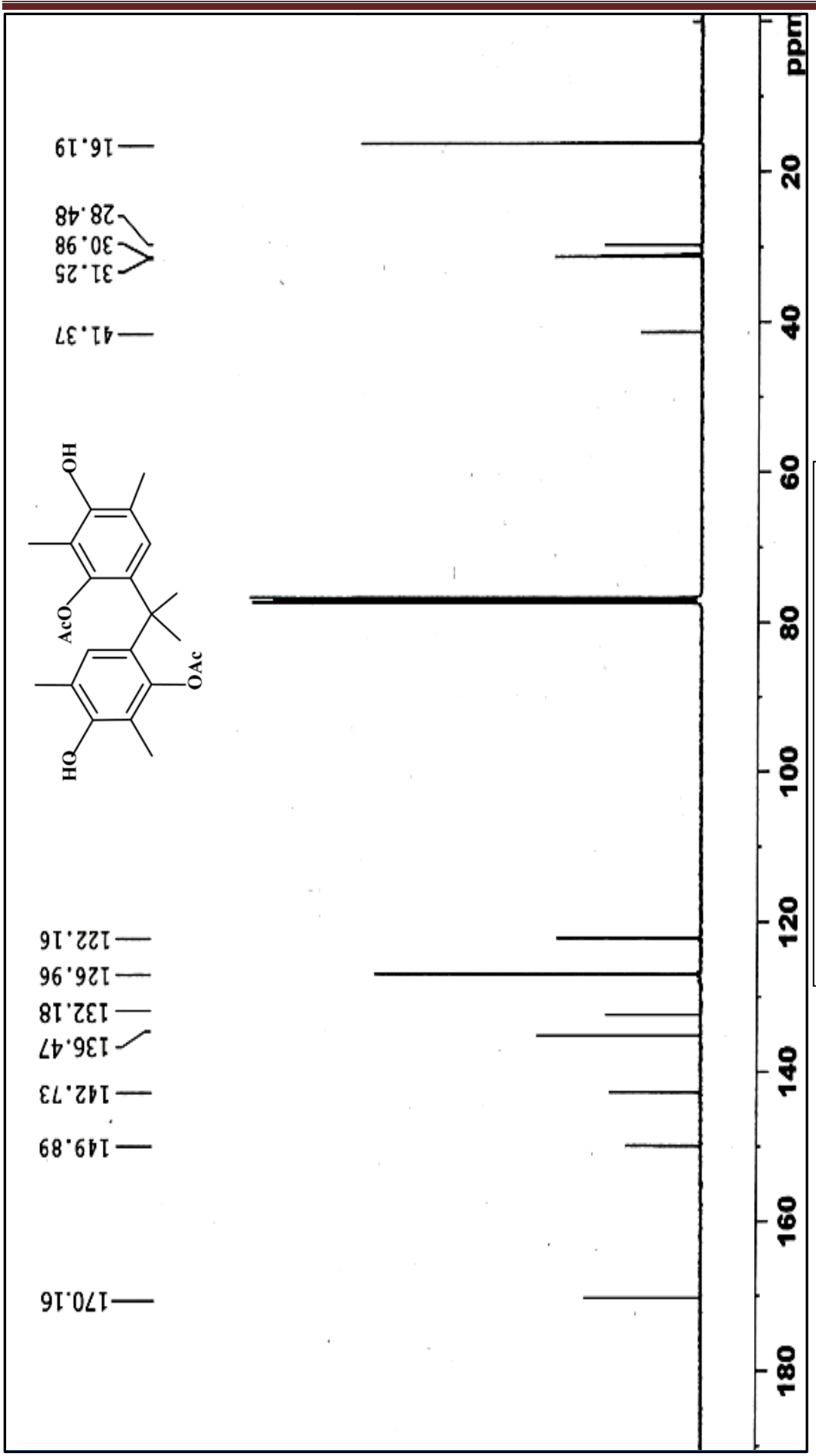


Figure 3.75: ^{13}C NMR spectrum of compound **86A**

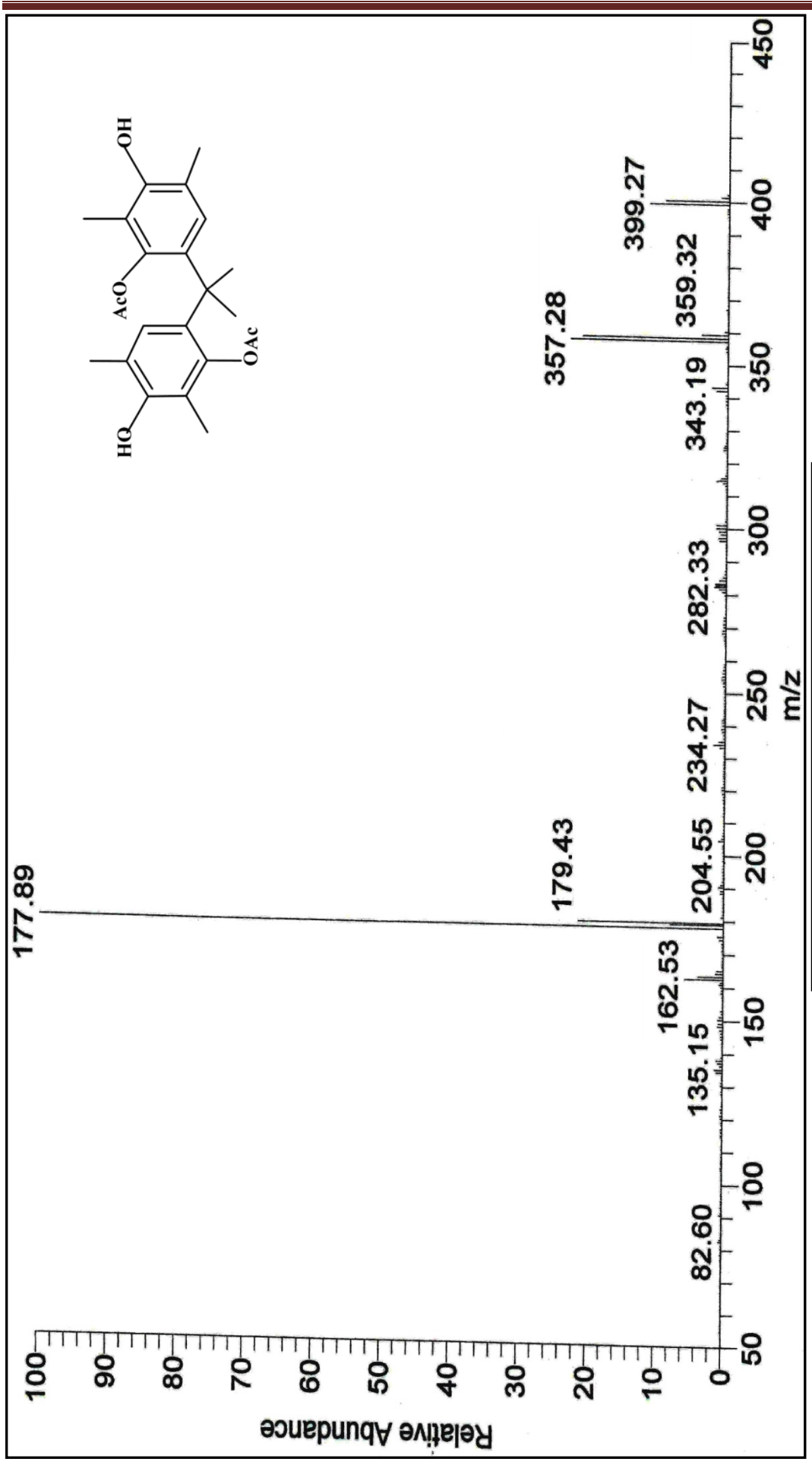


Figure 3.76: EI-MS spectrum of compound **86A**

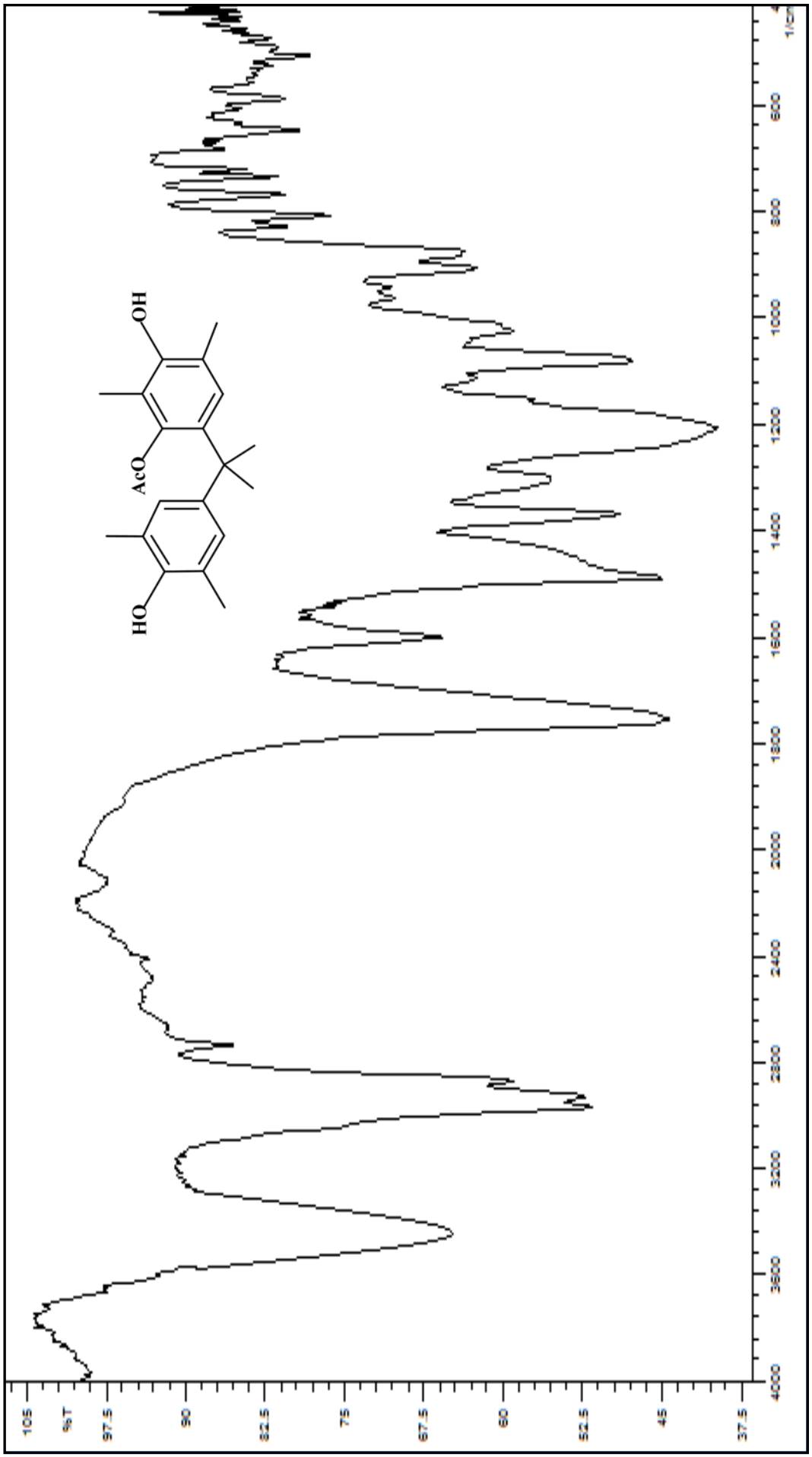


Figure 3.77: FTIR spectrum of compound **86B**

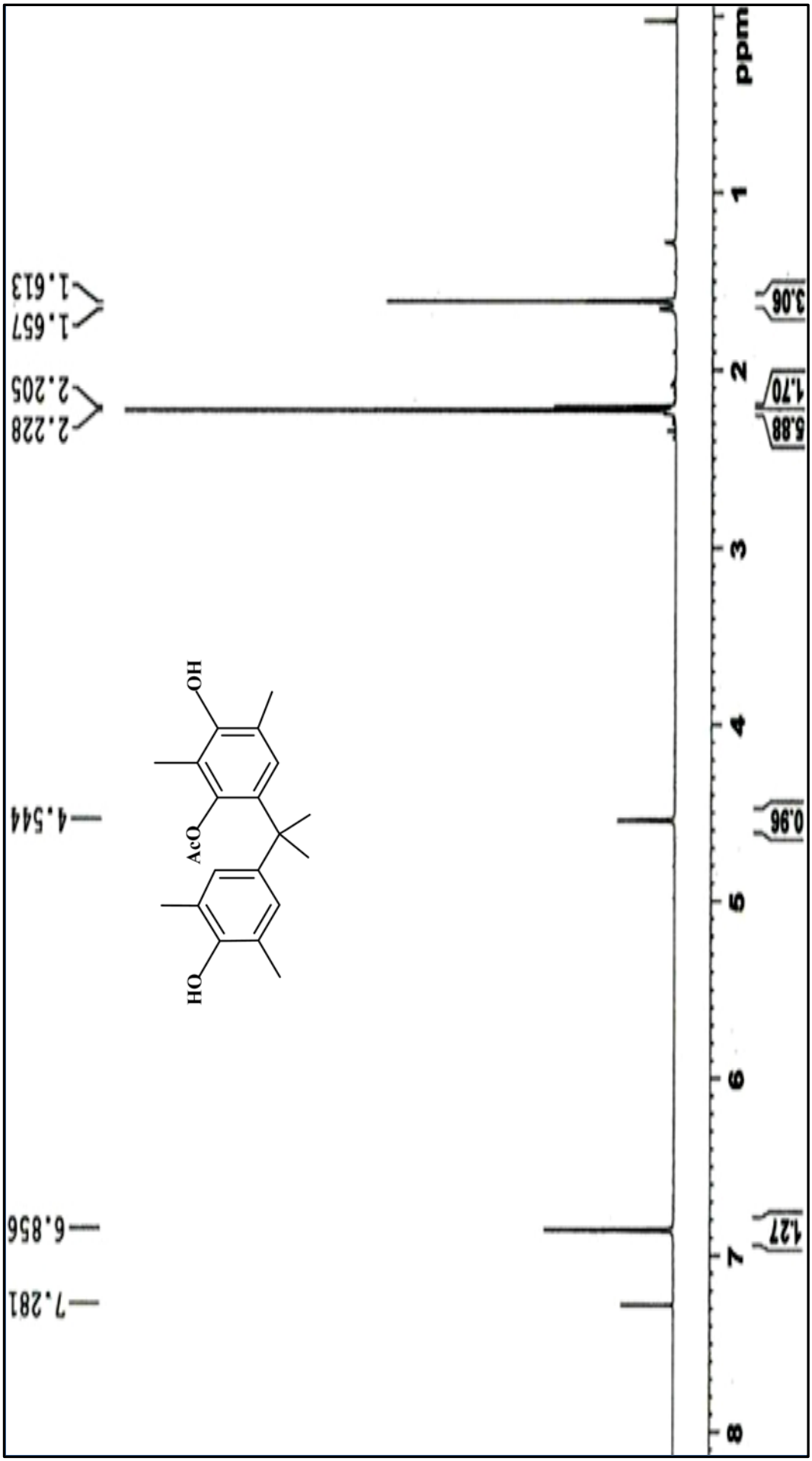


Figure 3.78: ^{1}H NMR spectrum of compound **86B**

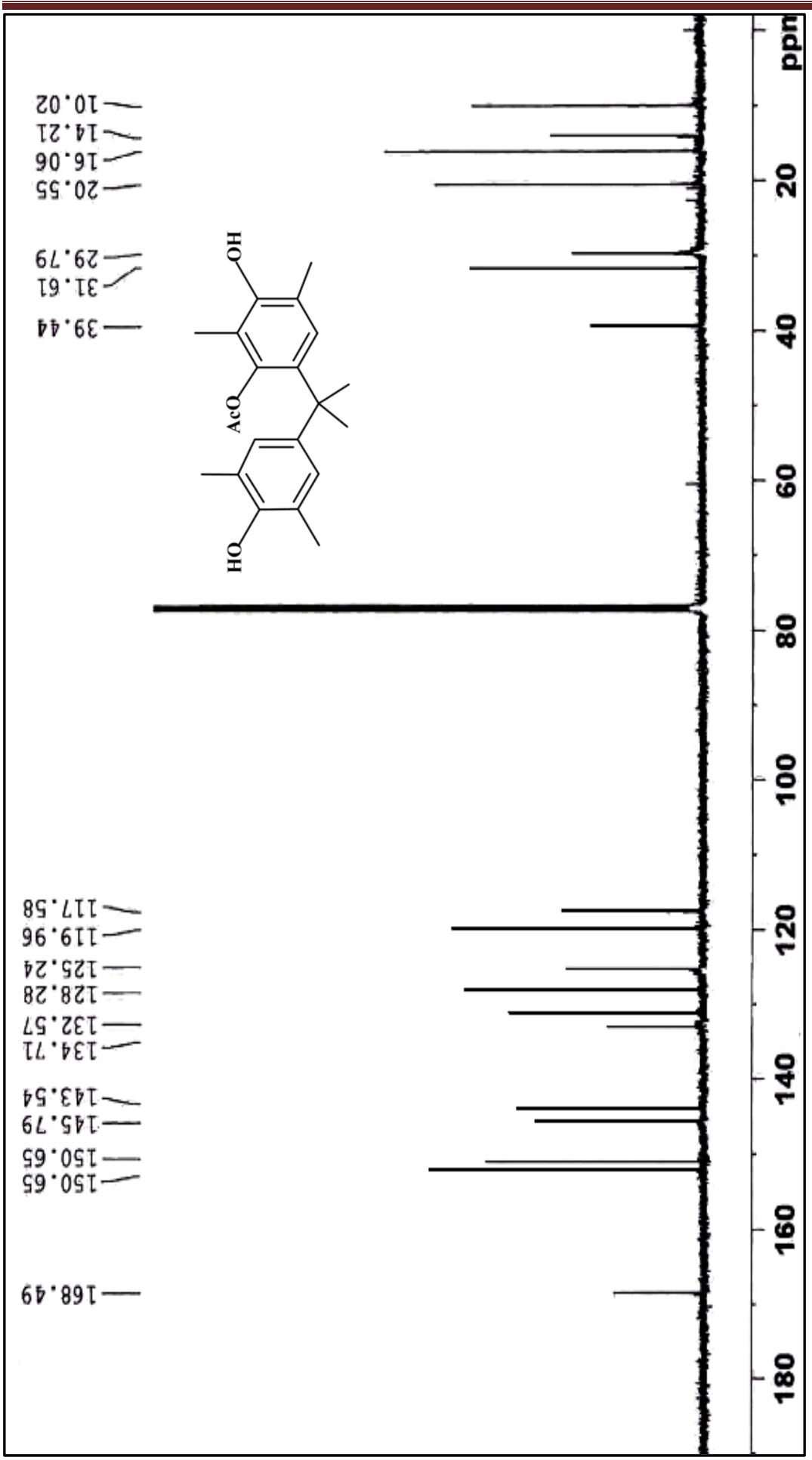


Figure 3.79: ^{13}C NMR spectrum of compound **86B**

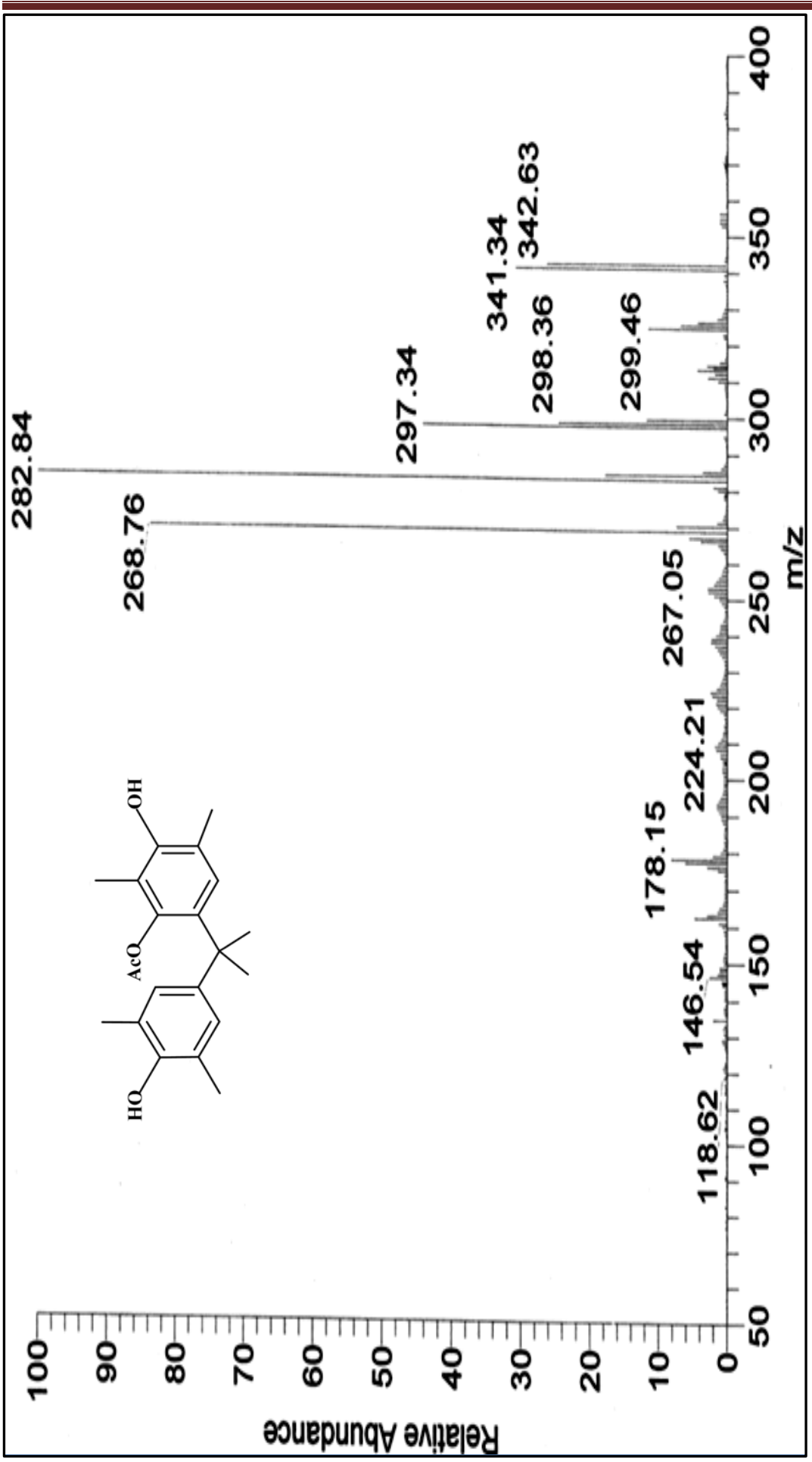


Figure 3.80: EI-MS spectrum of compound **86B**

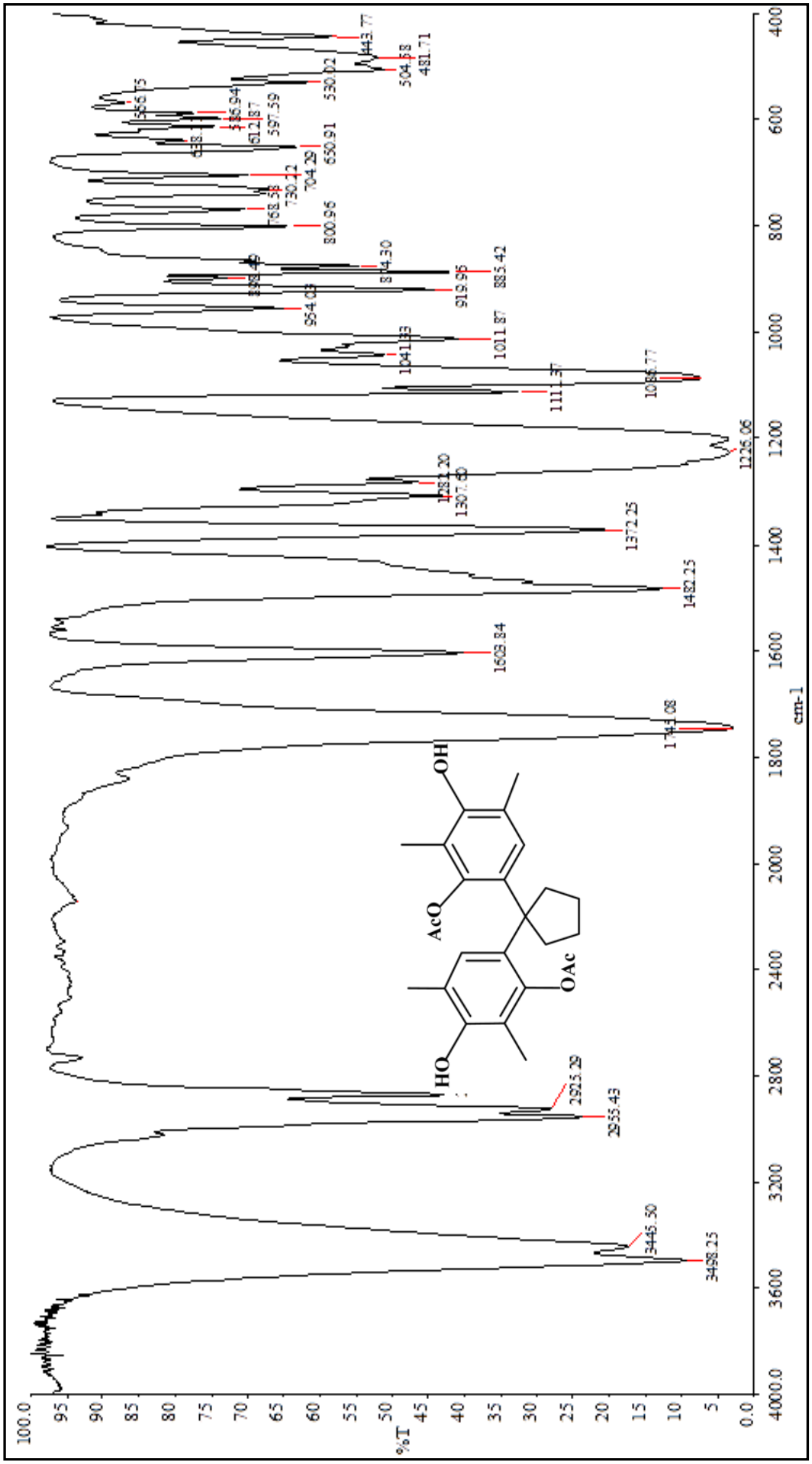


Figure 3.81: FTIR spectrum of compound **87A**

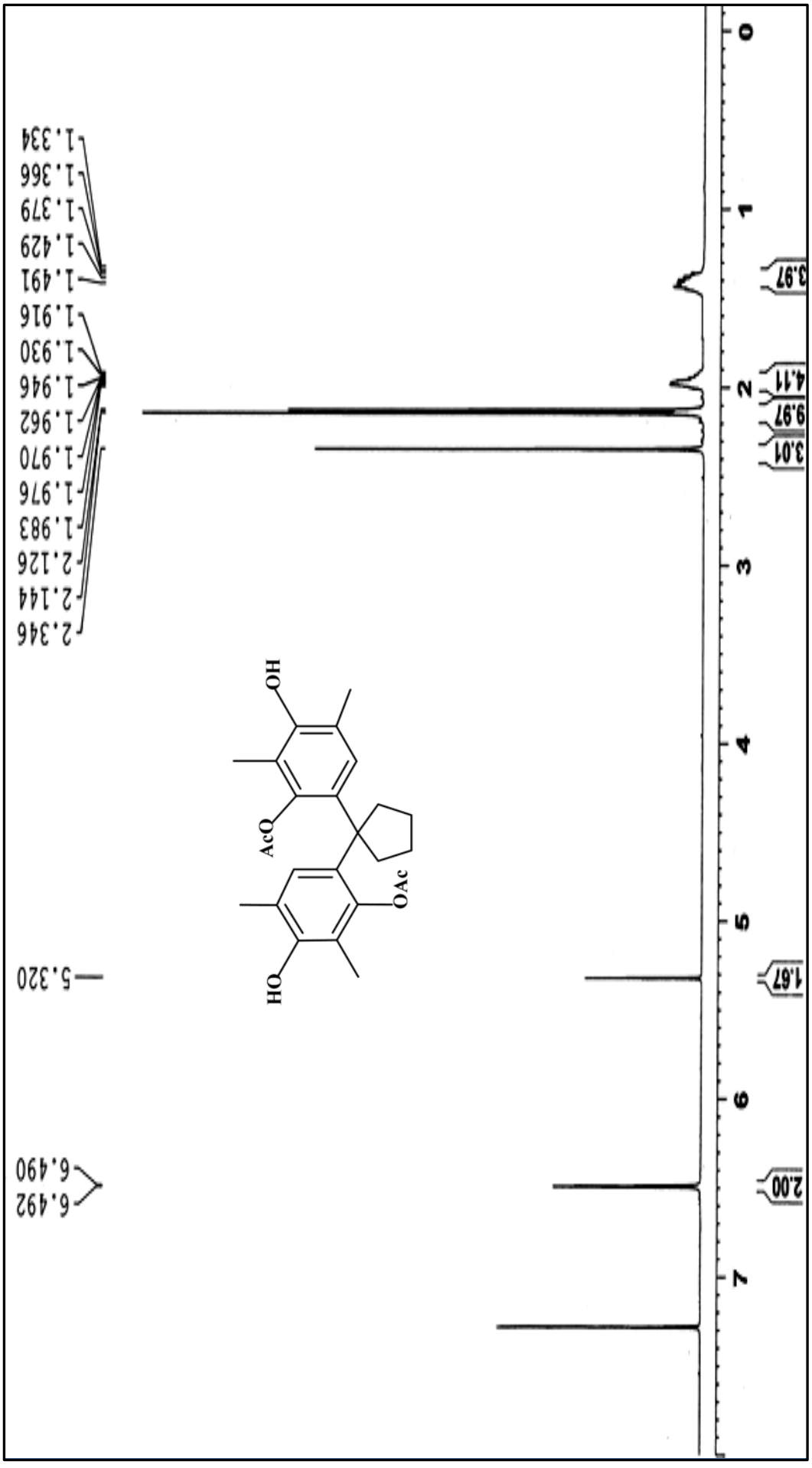


Figure 3.82: ^{1}H NMR spectrum of compound **87A**

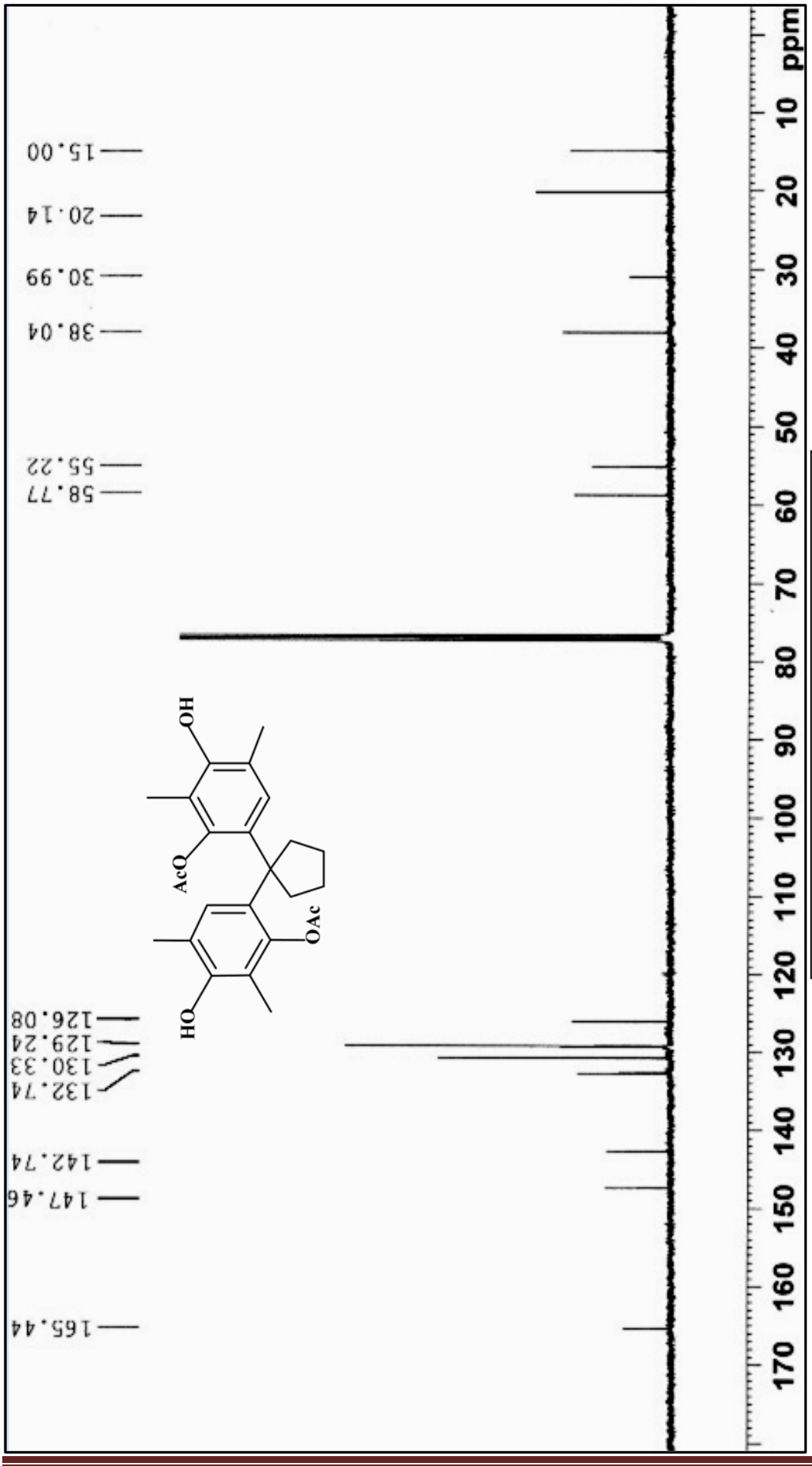


Figure 3.83: ^{13}C NMR spectrum of compound **87A**

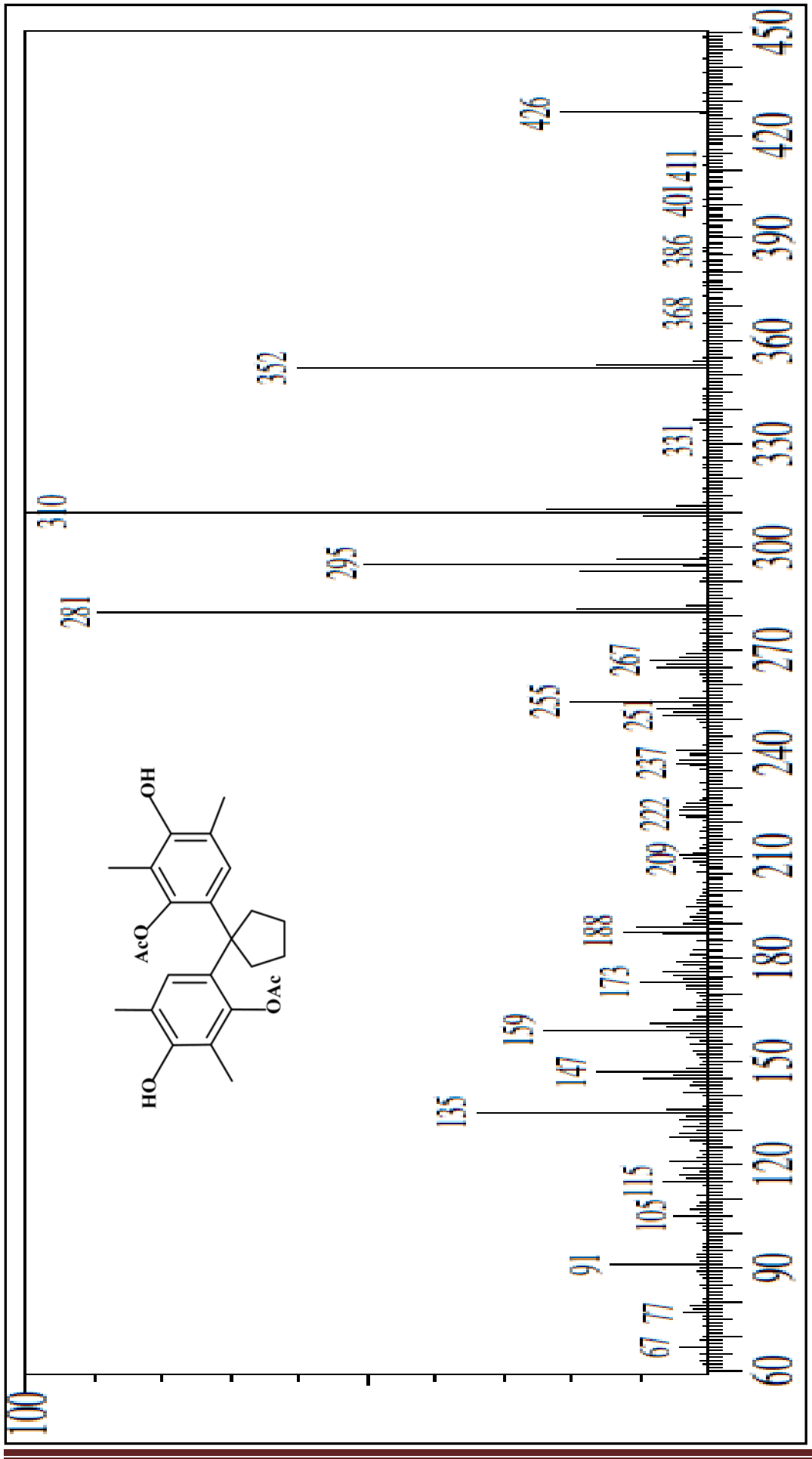


Figure 3.84: EI-MS spectrum of compound **87A**

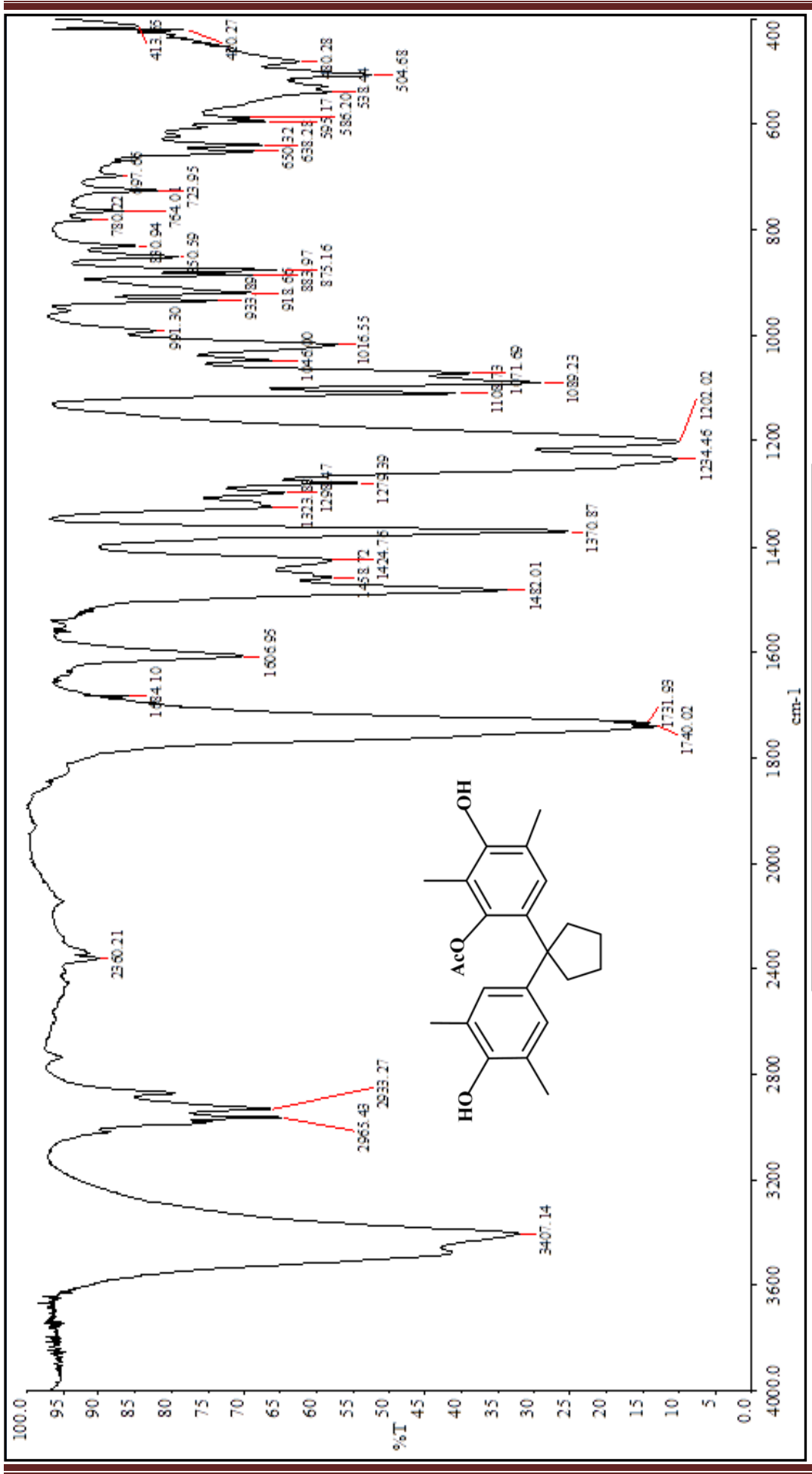


Figure 3.85: FTIR spectrum of compound **87B**

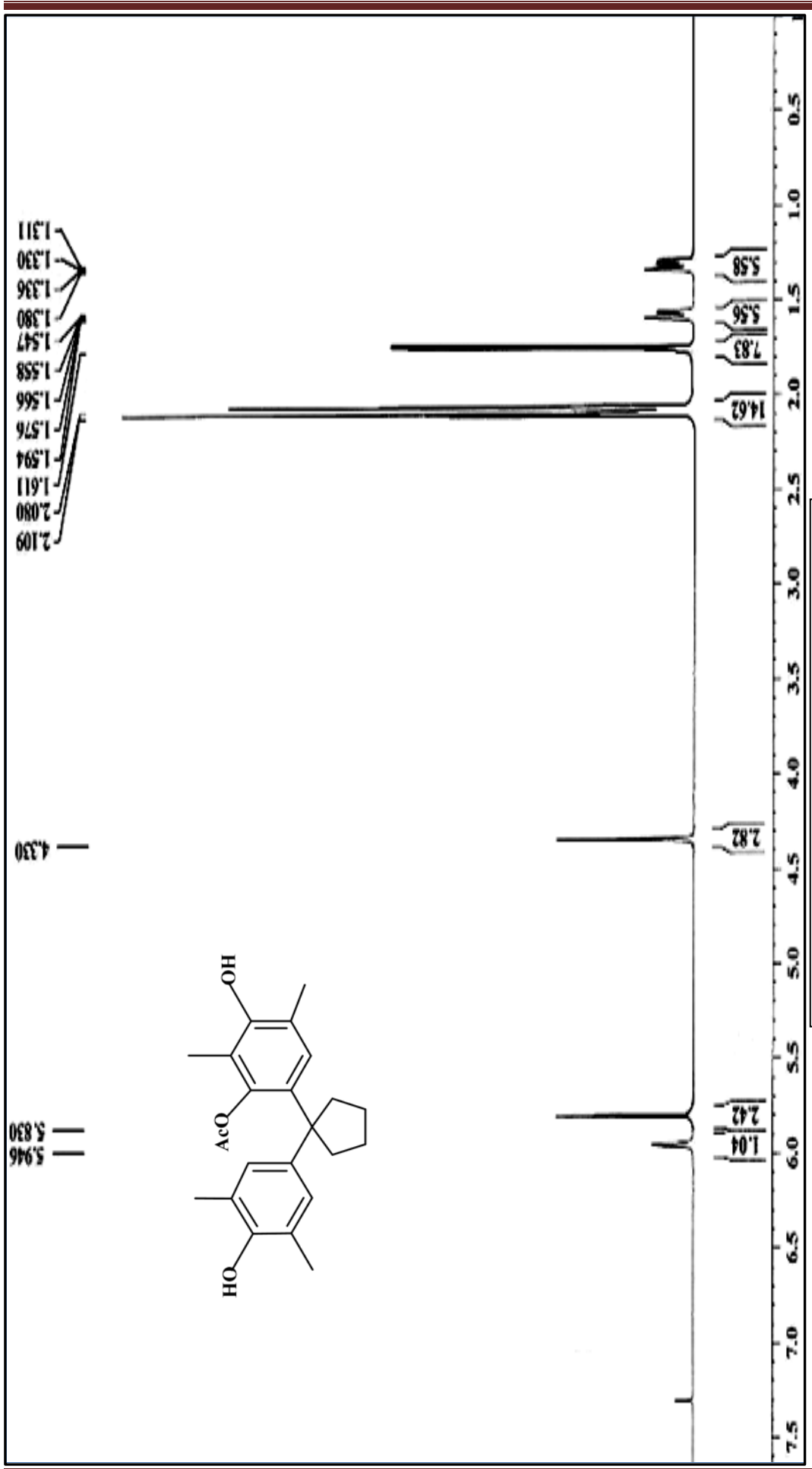


Figure 3.86: ^{1}H NMR spectrum of compound **87B**

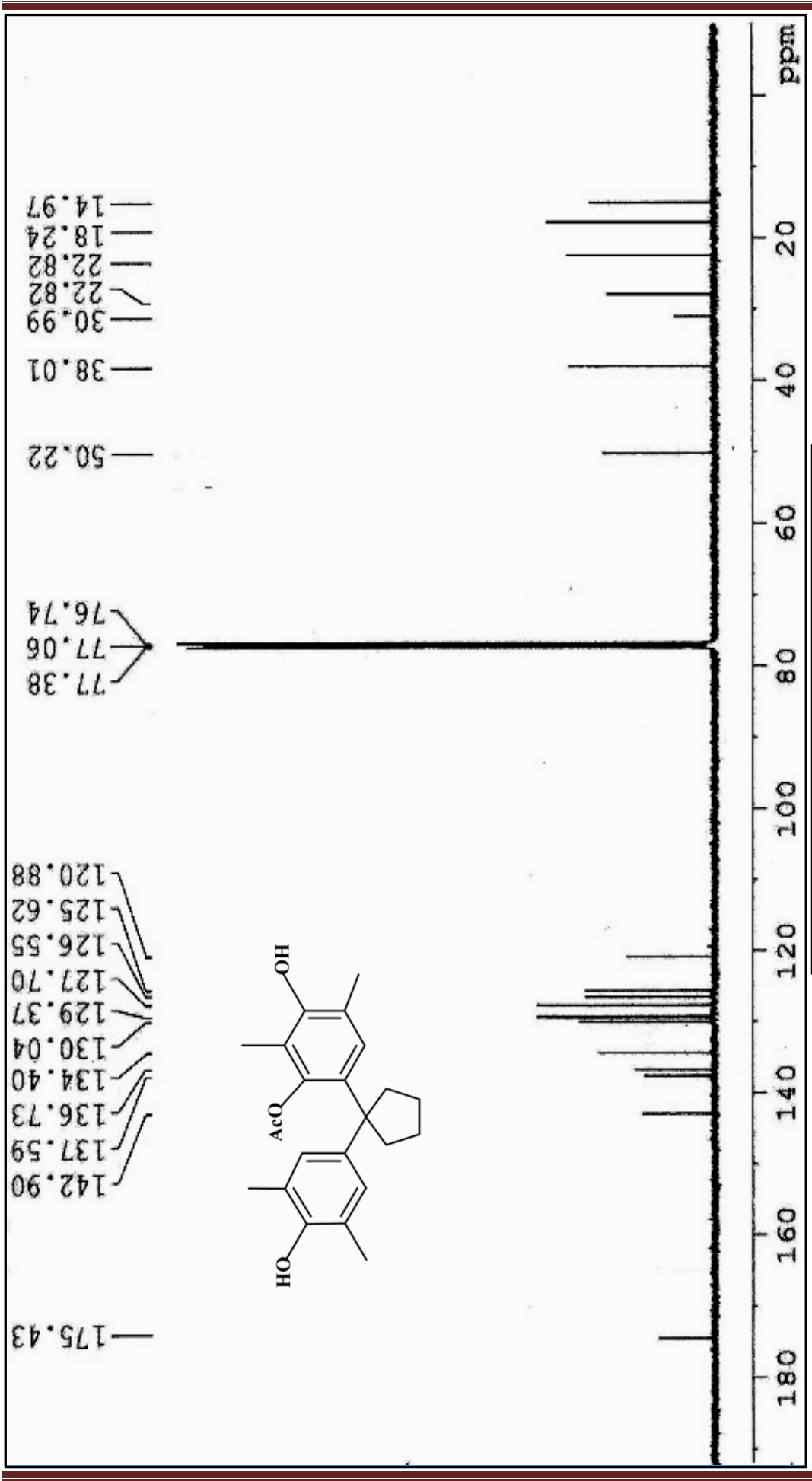


Figure 3.87: ^{13}C NMR spectrum of compound **87B**

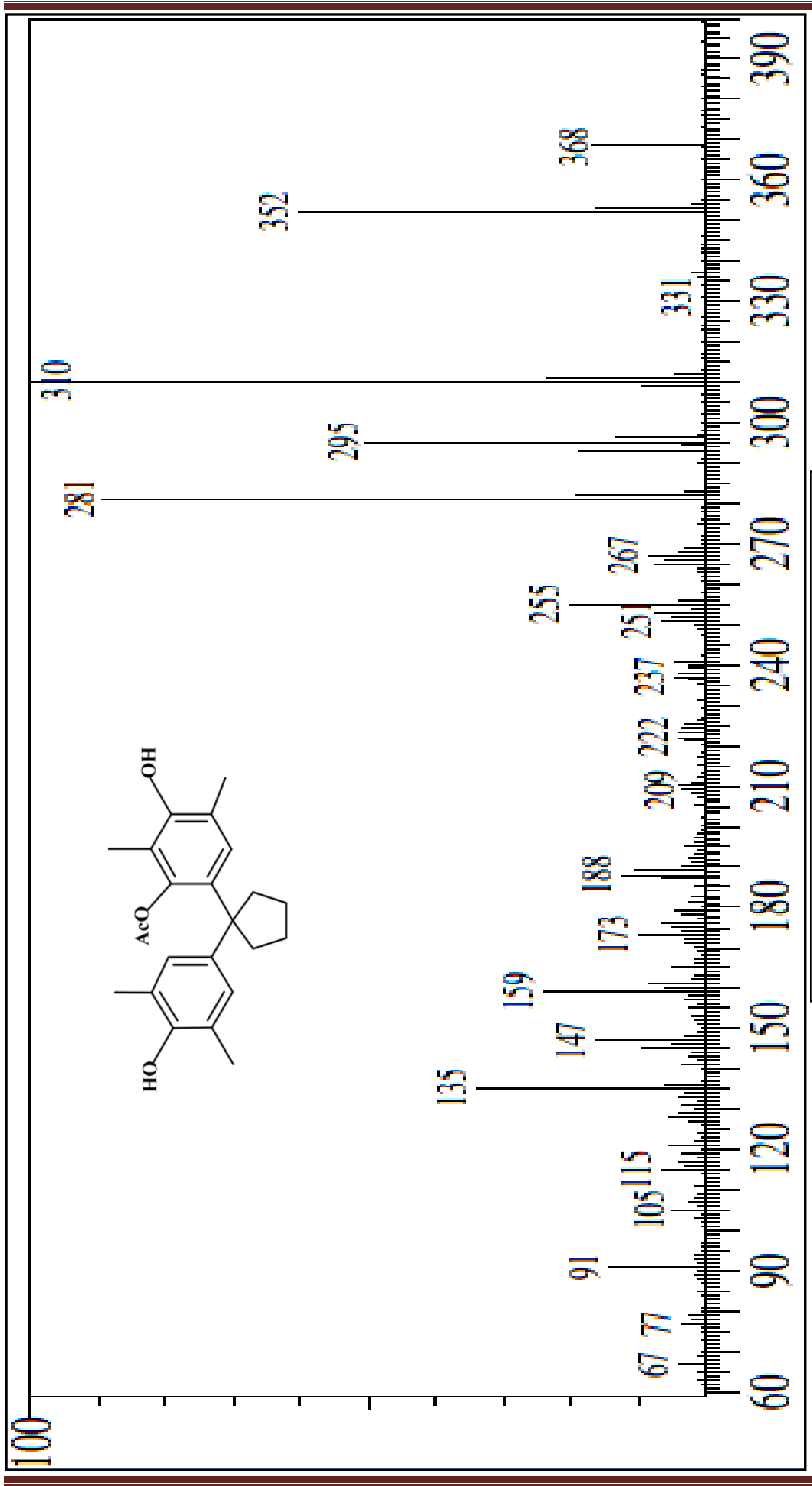


Figure 3.88: EI-MS spectrum of compound **87B**

CHAPTER 4

Studies in synthesis of bis-triquinanes: cycloaddition of bis-cyclohexadienone and photochemical rearrangements of annulated bis-tricyclic[5,2,2,$0^{2,6}$]undecadienone

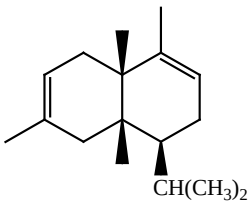
4.1 Abstract

A novel approach for the synthesis of novel “bird shape” bis-triquinane **61** and other novel carbocycles related to *cis-anti-cis* tricyclopentanoid frame work from simple precursors such as 2,6-dimethyl phenol **56** and cyclopentadiene have been reported. The cycloaddition of bis-cyclohexadienone **58** with cyclopentadiene gives carbocycles **59** and **60**. The photochemical oxa di-π methane ODPM rearrangement in carbocycles **60** gives bis-triquinane **61**, possessing a fascinating molecular architecture and a triquinane linked with bridged tetracyclic system **88**. Pentasubstituted phenols **90** and **91** have also been synthesised during attempted photochemical oxa di-π methane rearrangement of carbocycle **59** a tricyclic system connected with a 2,4-cyclohexadienone unit. A probable mechanism is proposed for the photochemical aromatisation of cyclohexadienone ring.

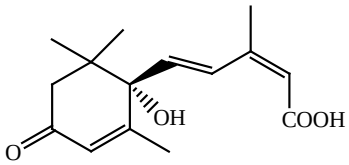
4.2 Introduction and objective

Terpenes are the most widely distributed and structurally diverse class of naturally occurring organic compounds. Nature has composed terpenes with an unusual arrangement of carbocyclic framework containing a wide array of ring and functionalities. They play an important role in both nature and human applications. The terpenes are composed from five carbon isoprene units, which can assemble itself in thousands of ways.[1]

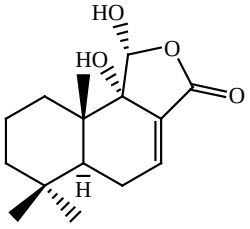
The compounds containing three isoprene units are recognized as sesquiterpenes. The family of biochemically transformed products of sesquiterpene by oxidation or rearrangement is known as sesquiterpenoids. Sesquiterpenoids are a class of biologically active natural products that have been identified in several plants such as Acanthaceae, Anacardiaceae, Apiaceae, Euphorbiaceae, Lauraceae, Magnoliaceae, Rutaceae, Winteraceae and Hepatideae etc.[2] They are known to possess a wide variety of biological and pharmacological activities such as antimicrobial, cytotoxic, antiinflammatory, antiviral, antibacterial, antifungal as well as allergenic potency.[2] They have played a significant role over the last 200 years in treating and preventing diseases and continue to serve as important leads in modern drug discovery.[3] The sesquiterpenoids are classified into various categories such as acylic, monocyclic, bicyclic, tricyclic etc. depending upon the number of rings present in the molecule. Some important classes of sesquiterpenoids are given in **Figure 4.1**.[4]



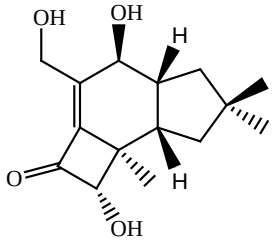
β-Cadinene **1**



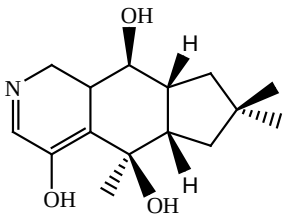
Abscisic acid **2**



Ugandenial A **3**



Tsugicolline A **4**



Divaricatine C **5**

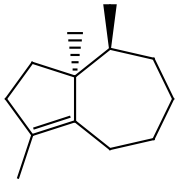

Clavukerin A **6**

Figure 4.1: Structures of some important sesquiterpenoids

Among all classes of sesquterpinoids a small and important subgroup is known as polyquinanes. The word polyquinane, *poly+quin+ane" quin (five),* is the common name given to the carbocyclic frames which contain five membered rings of carbon atoms fused to each other. (**Figure 4.2**) Polyquinanes are a rapidly growing subgroup of sesquiterpenoids that have generated worldwide interest since their discovery among organic chemists due to their fascinating molecular architecture and potent biological activity. In the literature, approximately three hundred of these natural products are isolated from plants, marine organisms, fungi and insects. The polyquinane skeleton has been found among sesquiterpenes, di-sesterpenes and in steroids also.

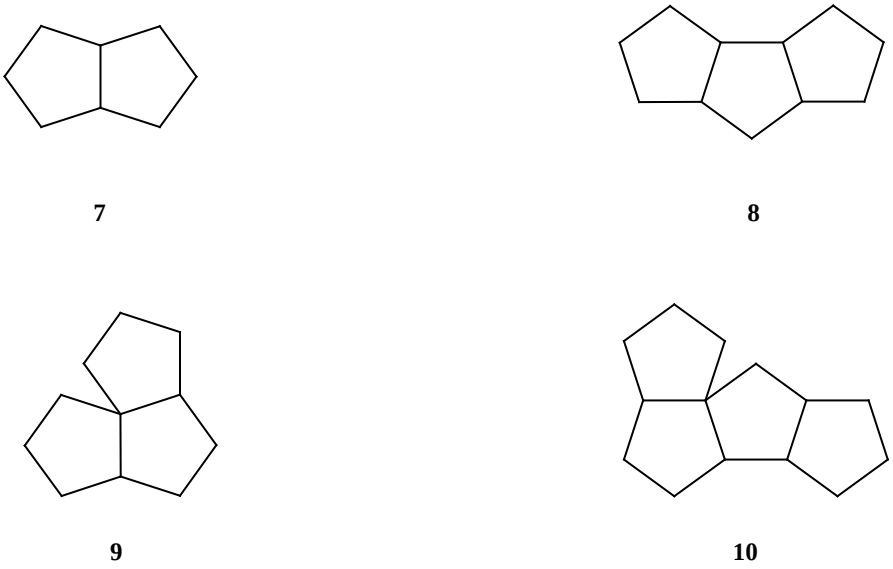
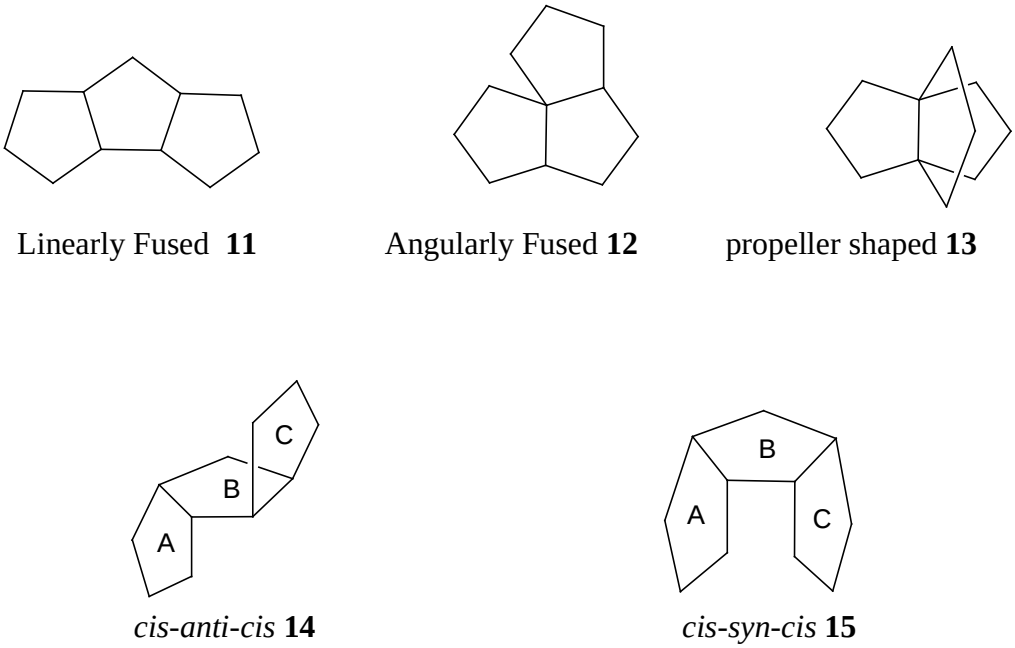


Figure 4.2: Basic skeleton of polyquinanes

Polyquinane natural products originating from three cyclopentane rings are termed as "triquinanes." Amongst the natural polyquinanes, triquinanes are most abundant. The triquinanes constitute a large and diverse group of biologically active natural products used in traditional medicines for the treatment of inflammatory diseases.[5] The triquinanes have been present in nature for a long time, but the definitive structure of the first member (Hirsutic acid-C) wasn't confirmed until 1966.[6]



Linearly Fused **11** Angularly Fused **12** propeller shaped **13**

cis-anti-cis **14** *cis-syn-cis* **15**

Figure 4.3: Arrangement of cyclopentane ring in triquinane skeleton

The triquinane natural products embody three C_{11} tricyclopentanoid skeleta incorporating a system of linearly fused rings **11**, angularly fused rings **12** and propeller shaped propellenes **13**. (**Figure 4.3**)

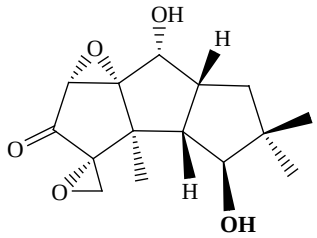
Four different families of C_{11}-carbocyclic skeleta based on linearly fused cyclopentane rings **11** are known. They are (1) Hirsutane family, (2) Capnellane family (3) Pleurotellane family and (4) Ceratopicane family.[7] Whereas, six families based on angularly fused five membered rings **12** are known, namely (1) Isocomene family, (2) Pentalenene family, (3) Silphinene family, (4) Silphiperfolene (5) Laurenene (6) Retigeranic acid family[8] while Propeller shaped triquinane **13** has only one family known as Modhephene.[9]

The class of linearly fused tricyclopentanoids **11** is further divided into two categories depending upon the mode of fusion of the third cyclopentane ring "C". Two different isomers as shown in **Figure 4.3** are *cis-anti-cis* **14** and *cis-syn-cis* **15**.

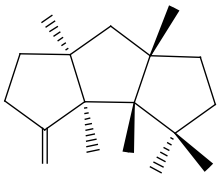
Osawa and co-workers[10] reported that the *cis-anti-cis* **14** is more stable compared to the hindered folded form, *cis-syn-cis* isomer **15** due to its chair like

conformation.[10] The *cis-anti-cis* isomer has received greater attention because it constitutes the basic carbocyclic framework of biologically important triquinanes natural products. (**Figure 4.3**)

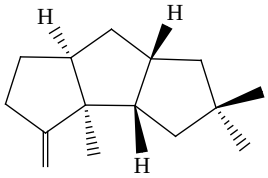
Among all classes of triquinanes, linear ones have been attracting continuous attention from synthetic chemists due to their promising biological activity and their role as building blocks for exotic molecular architecture.[11,12] For example, Coriolin **16** shows antitumour and antibacterial activitiy,[13] capnellene **17** and its congeners have been suggested to act as a chemical defense agent to inhibit the growth of microorganisms and to prevent larval settlement,[14] Hirsutene **18,** hirsutic acid **19**, have antibiotic and antitumor properties.[15] Isohirsutic acid **20**, cucumin **21** possess cytotoxic and antimalerial activity[16], Ceratopicanol **22**,[17] Pleurotellic acid **23,** pleurotellol **24** possesses antibiotic properties[18] etc. (**Figure 4.4**)



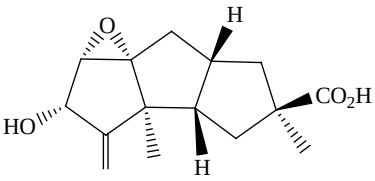
Coriolin **16**



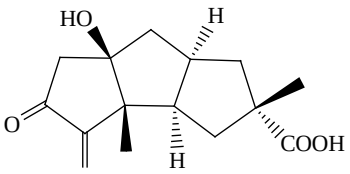
Capnellene **17**



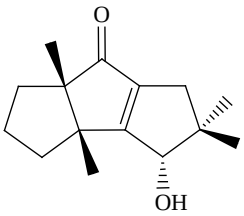
Hirsutene **18**



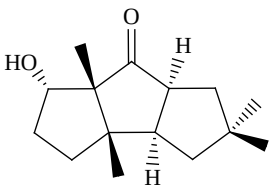
Hirsutic acid **19**



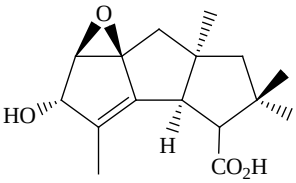
Isohirsutic acid **20**



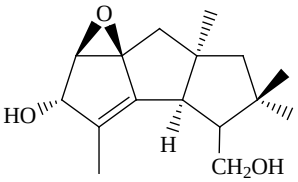
Cucumin H **21**



Ceratopicanol **22**



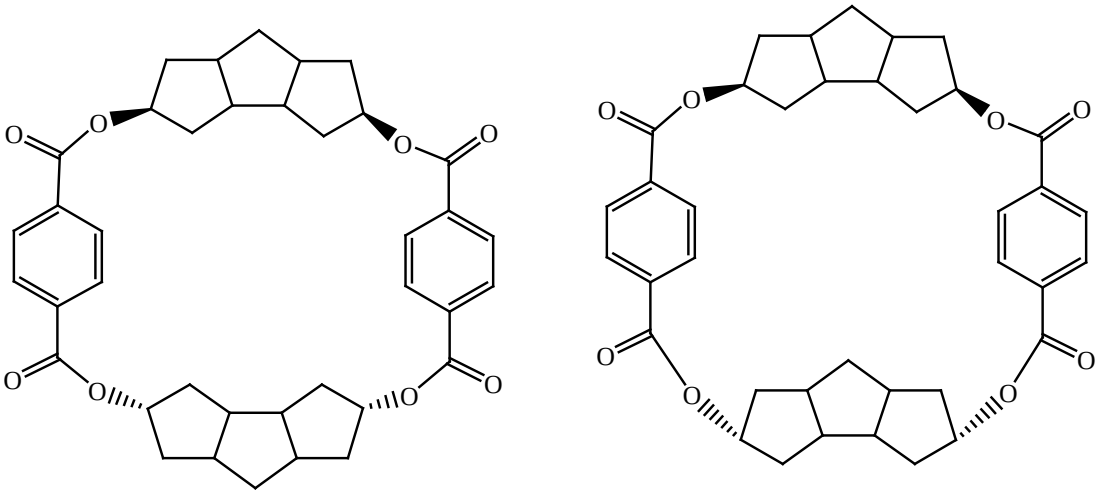
Pleurotellic acid **23**



Pleurotellol **24**

Figure 4.4: Structure of some potent triquinane natural products

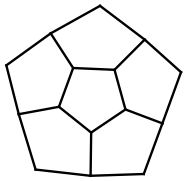
Macrocyclic systems having binding sites likes ethers, lactones and amides have aroused considerable interest in recent years, in the area of supramolecular chemistry.[19] Linear triquinanes having *cis-syn-cis* configuration are employed as building blocks in designing of the various macrocyclic systems. *Mehta et al* reported the syntheses of various types of macrocyclic rings as dimer, trimer tetramer of basic triquinane skeleton by the reaction of *cis-syn-cis* triquinane diol with terephthaloyl chloride.[20] The stereoisomeric structure of macrocyclic rings having two *cis- syn-cis* triquinane moities pointing in the opposite direction that is up-down isomer **25** and in the same direction down-down isomer **26** are given in **Figure 4.5**.



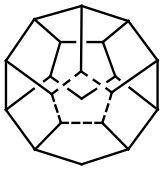
up-down isomer **25** up-up isomer **26**

Figure 4.5: Macrocyclic system as dimer of triquinane skeleton

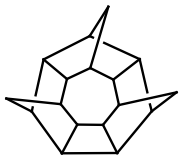
The synthesis of polycyclic hydrocarbon molecules like peristylane **27**, dodecahedrane **28**, prismane **29,** and roof shaped molecules **30** and **31** is a major synthetic challenge in organic chemistry. Having *cis-syn-cis* stereochemistry, the tricyclopentanoid skeleton also plays an important role as a building block in the assembling of some exotic, complex molecular architectures.[21] (**Figure 4.6**)



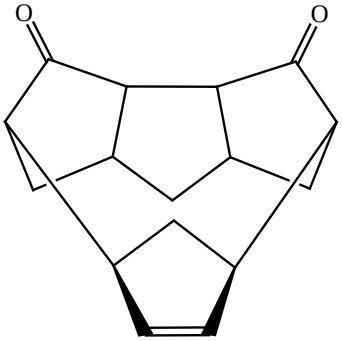
Peristylane **27**



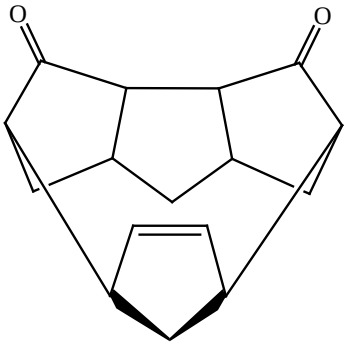
Pentagonal dodecahedrane **28**



Heptacyclic prismane **29**



30



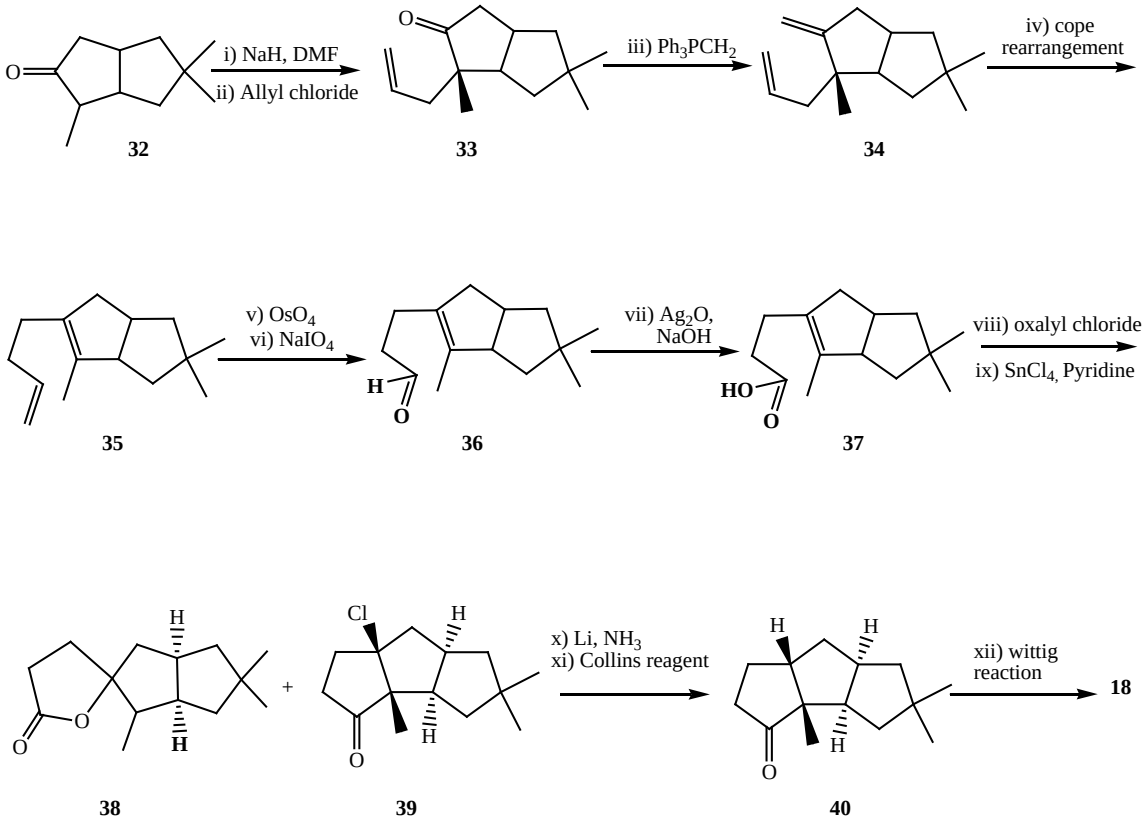
31

Figure 4.6: Exotic molecular architecture having triquinane ring system

The complicated carbocyclic frame work with the presence of various functionalities in triquinanes as well as their value in the construction of polycyclic hydrocarbons have enhanced the interest of chemists in the synthesis of tricyclopentanoids skeleton. As a result, numerous synthetic roots have been developed for the construction of both *cis-anti-cis* and *cis-syn-cis* type triquinane frame works by different methodologies.[22]

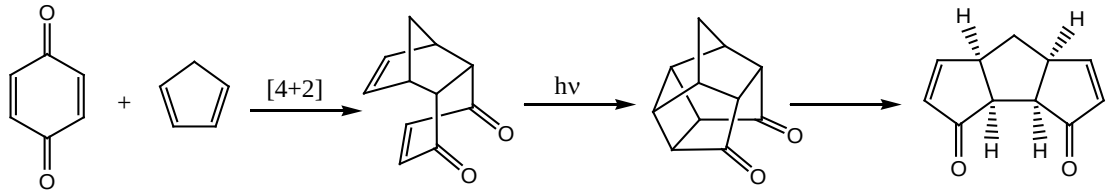
Hirsutene was the first member of the triquinane family synthesised by a chemist. *Shigeo Nozoe et al*. had first reported its synthesis in 1975 starting form precursor **32**.[23] The bicyclic ketone **32** was prepared by following the procedure reported by matsumoto *et al*.[24] The treatment of the enolate anion of **32** with allyl chloride gives alkylated product **33** in a selective manner. The Wittig reaction of the ketone **33** afforded the hydrocarbon **34**. The hydrocarbon **34** underwent cope rearrangement and gave the diene compound **35** which by treatment with OsO_4 followed by oxidative cleavage using $NaIO_4$ afforded the aldehyde **36**. The oxidation of **36** using Ag_2O-NaOH in aqueous THF gave the carboxylic acid **37**. The intramolecular cyclisation of acid chloride of **37** with $SnCl_4$ in carbon disulfide gave

the desired product **38** and a spiro lactone **39**. The treatment of chloro ketone **39** with lithium metal in liquid ammonia and ether containing t-BuOH followed by oxidation of a reduced ketone with Collins reagent afforded the nor ketone **40**. The nor ketone **40** was converted to Hirsutene **18** by treatment with excess of Wittig reagent in DMSO. (**Scheme 4.1**)



Scheme 4.1: Synthesis of hirsutene **18** from bicyclic ketone **32**

In the area of construction of triquinane, Mehta *et al* reported the synthesis of linearly fused *cis-syn-cis* triquinane skeleton **45** and their further isomerisation into *cis-anti-cis* triquinane skeleton from simple and readily available precursors hydroquinone **41** and cyclopentadiene **42**. The Diels-Alder cyclo addition of **41** with **42** gave product **43**. The intermolecular [2+2] photochemical cyclo addition of **43** results in the formation of product **44** which on cleavage of the σ-bond furnished *cis-syn-cis* triquinane skeleton **45.** (**Scheme 4.2)** He also explored potent of the skeleton **45** in total synthesis of triquinane natural products such as coriolin **16** , capnellene **17**, hirsutene **18**, that have *cis-anti-cis* configurations in their molecular framework.[25]

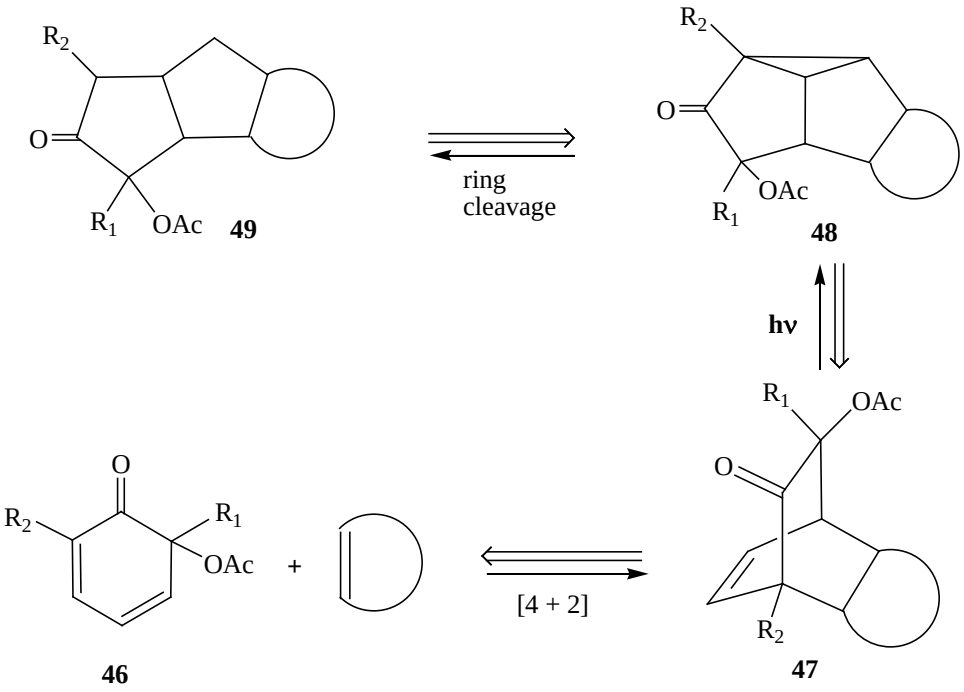


41 **42** **43** **44** **45**

Scheme 4.2

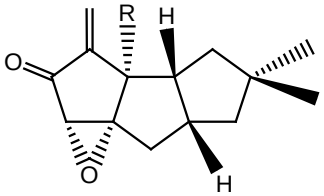
Triquinane framework of type **45** is also employed as intermediate in synthesis of complex molecular architecture like roof shape molecule **30, 31**.[21c]

In this context, Singh *et al* also reported a unified approach towards the synthesis of linearly fused triquinanes[26] of the type **49** via a peripheral ring cleavage of the tetracyclic intermediate **48**, which is easily obtainable from the key intermediate **47** via photochemical oxa-di-π-methane rearrangement.[27] The chromophoric system **47** was assembled via an inverse electron demand [4+2] cycloaddition between a cyclohexa-2,4-dienone of the type **46** and a suitable dienophile. (**Scheme 4.3)**

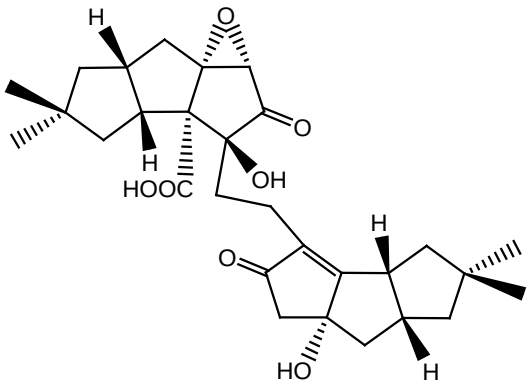


Scheme 4.3

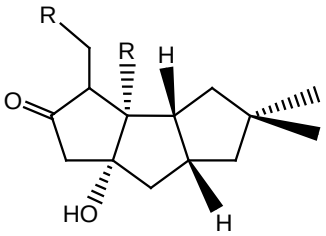
In continued research in the area of triquinanes natural products, both "extraction and synthesis" recently in 2010 Opatz *et al* have encountered six new linear triquinane sesquterpenoids from *Xeromphalina sp.*, named Xeromphalinone (A-F) **50**-**55**.[28] Out of six four molecules of Xeromphalinone A-D **50**, **51**, **53**, **54** belong to the linearly fused *cis-anti-cis* triquinane family while Xeromphalinone E **52** and F **55** have a totally different type of molecular architecture composed with two triquinane skeletons attached with a carbon–carbon bond or ester linkage. They are recognised as bis-triquinanes. (**Figure 4.7**) The presence of two tricyclic frameworks with different functional groups and stereochemical complexity have further enhanced the interest in this family of compounds.[28]



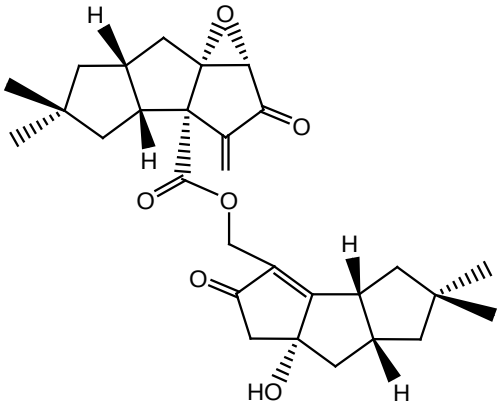
R= CH_2OH Xeromphalinone A **50**
R= CHO Xeromphalinone B **51**



Xeromphalinone E **52**



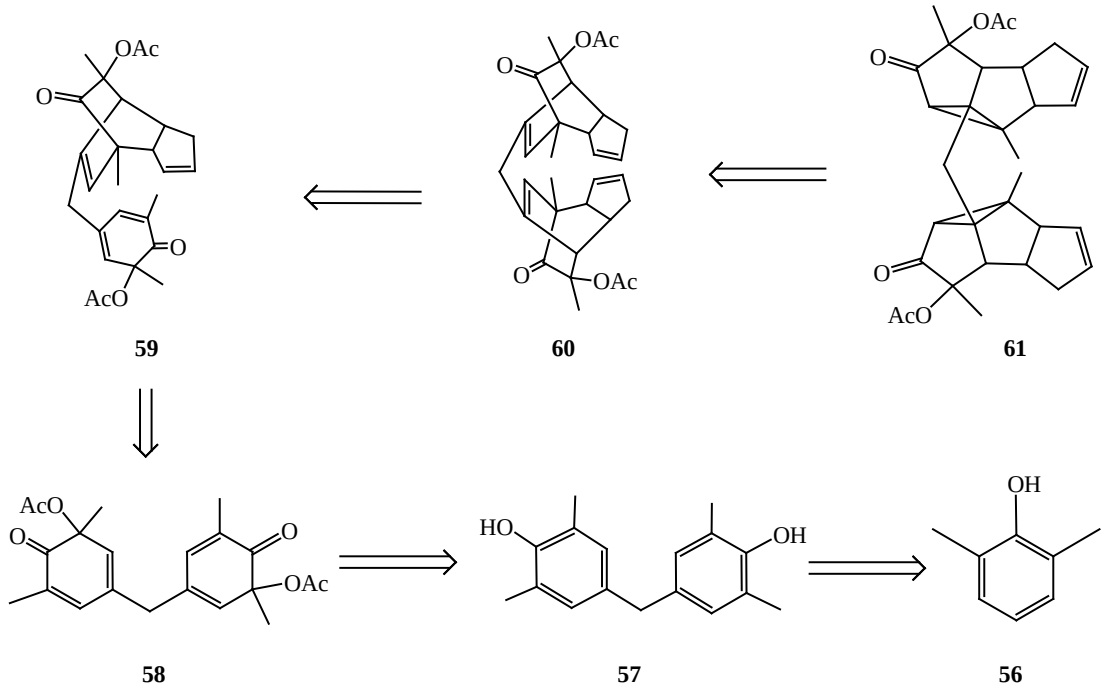
R = H Xeromphalinone C **53**
R =Me Xeromphalinone D **54**



Xeromphalinone F **55**

Figure 4.7: Structures of some triquinanes and bistriquinine natural products extracted from Xeromphalina sp.

In the present work, synthesis of a "bird-shaped" bis-triquinane molecule $C_{31}H_{36}O_6$ **61** possessing a fascinating molecular architecture from readily available materials 2,6-dimethyl phenol **56** and cyclopentadiene is reported. The bis-triquinane **61** is assembled through the union of two triquinane skeletons connected by a methylene group with an inner carbon of peripheral cyclopropane ring to generate an array of a bird. (**Scheme 4.4**)



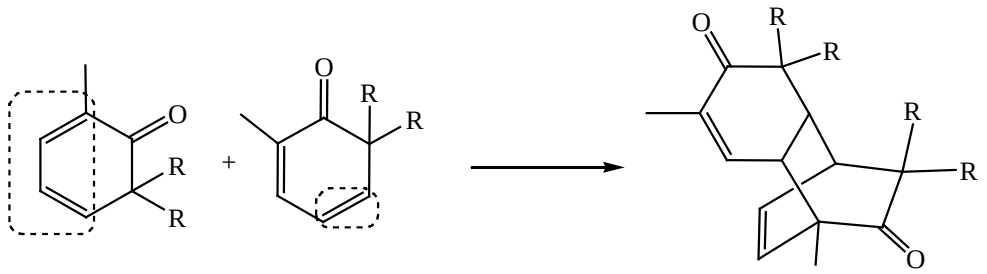
59 **60** **61**

58 **57** **56**

Scheme 4.4: Retro synthetic plan for synthesis of bistriquinane **61** from 2,6-dimethyl phenol **56**

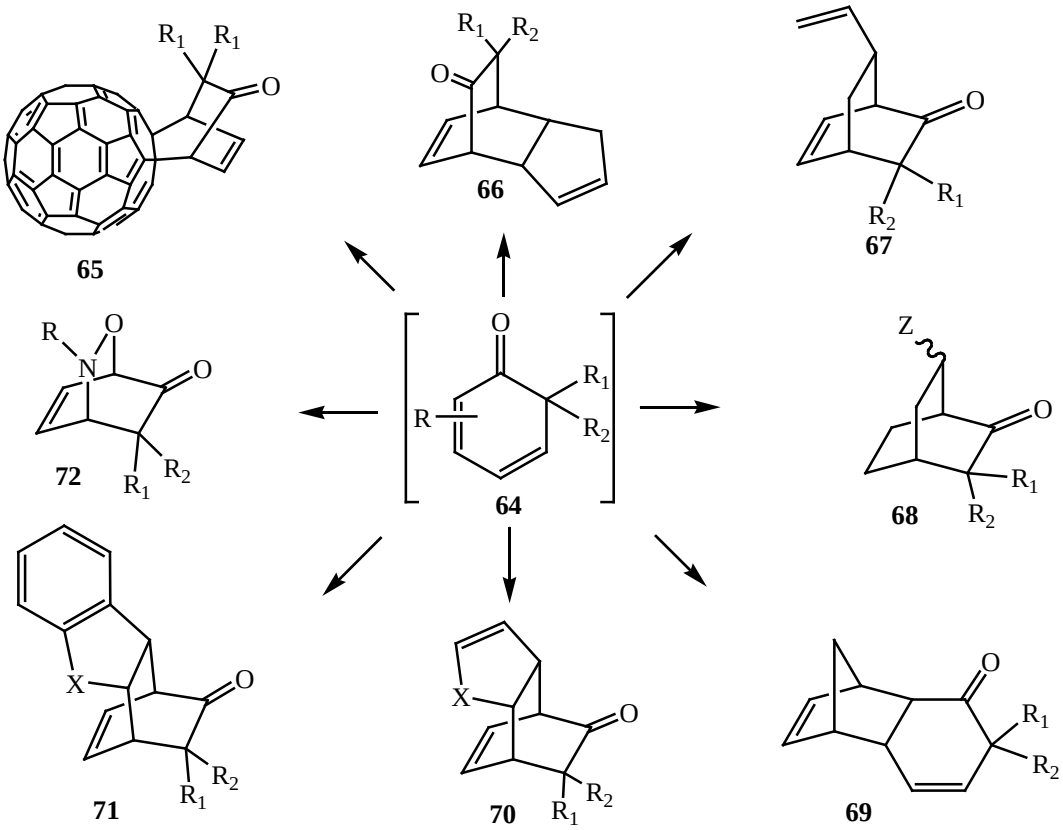
4.3 Results and discussion

In the previous chapter various methods for the syntheses of bis-cycohexadienones using different reagents and reaction conditions have been discussed. Cyclohexadienones of type **62** are reactive intermediates which easily undergo Diels-Alder reaction to produce corresponding dimers of type **63** (**Scheme 4.5),** while bis-cyclohexadienones are stable towards inter and intramolecular mode of cycloaddition even at higher temperature.[29]



Diene **62** Dienophile **62** Diels -Alder Dimer **63**

Scheme 4.5: Dimerisation of cyclohexadienone



Scheme 4.6: Products from cycloaddition of 2,4-cyclohexadienone

The Diels-Alder reactions have considerable interest in synthetic organic chemistry for their role in ability towards various organic transformations in accomplishing the synthesis of various natural products and complex molecular architectures.[30] In organic syntheses stereogenic centres are created by the transformation of a sp^2 hybrid carbon to a tetrahedral sp^3 hybrid carbon. Commonly

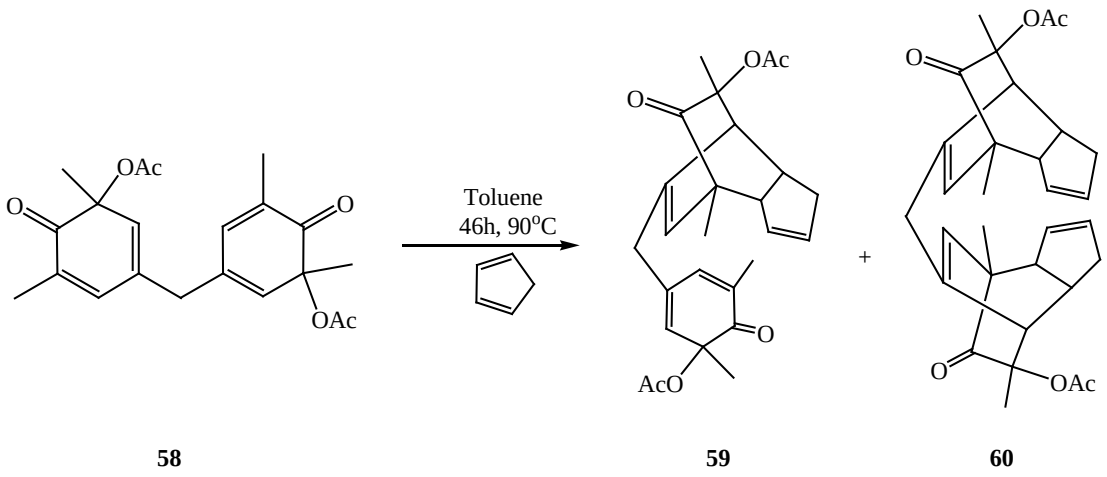
these are generated by nucleophilic reactions at the carbonyl group, electrophilic reactions on olefinics and by pericyclic reactions. Among all types of pericyclic reactions, Diels Alder cycloadition reactions are the most versatile and useful reactions in which four stereogenic centres are generated by a single experiment.[30] The Diels–Alder reaction in cyclohexadienone enjoys widespread use in organic syntheses owing to its ability of forming two bonds in a cyclohexadiene system in a highly stereoselective and predictable manner.[31] Many synthetic routes are previously reported for the oxidation of phenols to corresponding cyclohexadienone and their normal and inverse demand Diels Alder cycloaddition with highly reactive dienophiles such as malaic anhydride, dimethyl acetylene dicarboxylate, as well as with olefins and dienes etc.[32] (**Scheme 4.6**)

The adducts from such cycloadditions have been exploited for the development of new routes towards the syntheses of natural products such as polyquinane, cis-decalins, magellanine, calicheamicinone, forsthide, ryanodol, phomactin etc. that possess interesting biological profiles.[32]

Diels-Alder cycloaddition of bis-cyclohexadienone of type **58** with cyclopentadiene access novel molecular architectures **59**, **60**. Our efforts for syntheses of these novel carbocycles **59**, **60** are described here.

The precursor bis-cyclohexadienone **58** was prepared from 2,6-dimethyl phenol **56** in two steps. The condensation of **56** with formaldehyde gave tetramethyl bisphenol-F **57** which on oxidative acetylation with Lead tetra acetate in ethyl acetate gave bis-cyclohexadienone **58.**

The bis-cyclohexadienone **58** was heated in toluene at 90 °C while circulating cooled water (10-15 °C) and freshly cracked cyclopentadiene was added in to portions at every two hours. The reaction was continued for 46h, the solvent was removed under reduced pressure to furnish a thick yellow liquid which was chromatographed over a column of silica gel gives product **59** and **60**.[29] (**Scheme 4.7**)



58 **59** **60**

Scheme 4.7: Cycloaddition in bis-cyclohexadienone **58**

The reaction of cyclopentadiene and bis-cyclohexadienone **58** on cycloaddition could give rise to eleven major isomers **73-78** (**Figure 4.9**), **59** and **60** (**Scheme 4.7**) in addition to their corresponding stereoisomers.

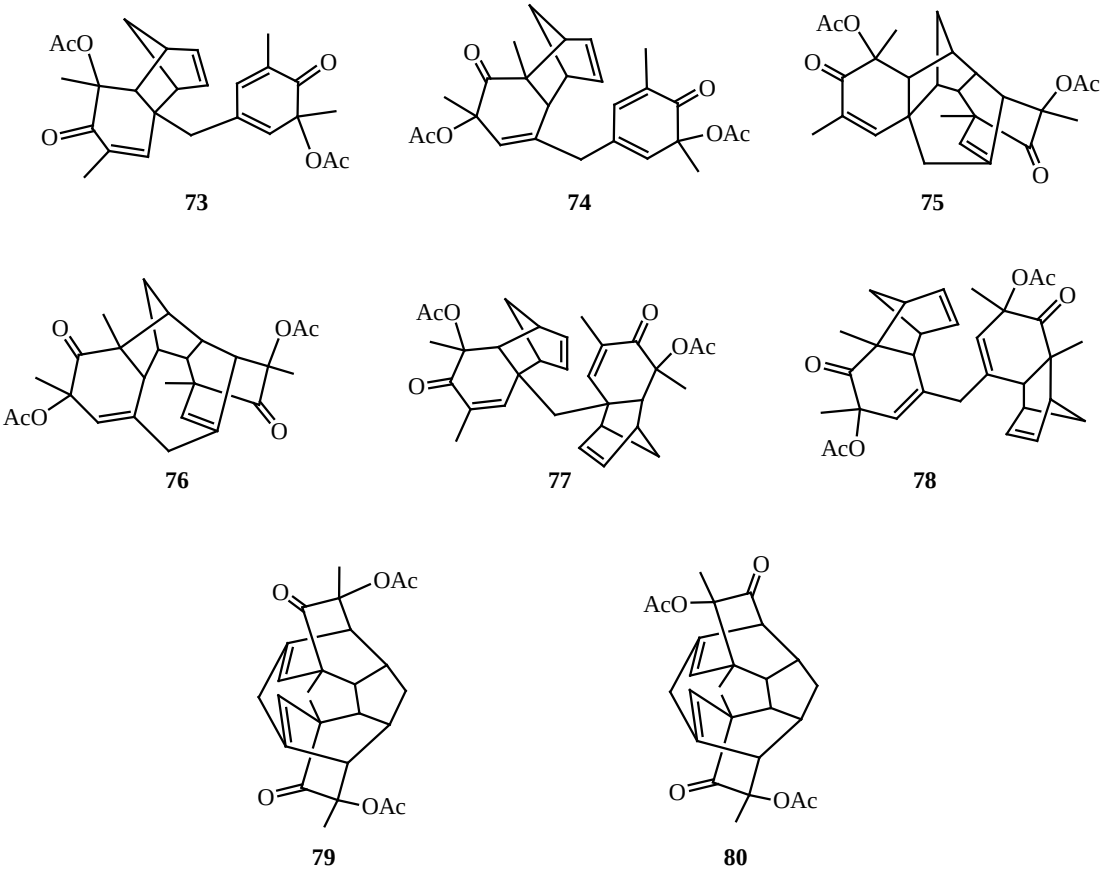
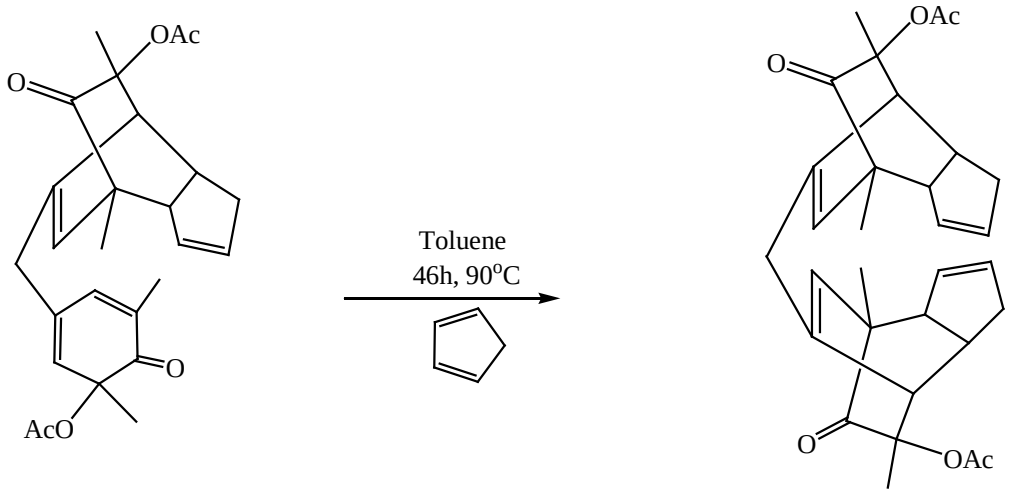


Figure 4.8: Structures of possible products resulting from cycloaddition of **58** with cyclopentadiene

Structures **73** and **74** may result from the cycloaddition of cyclopentadiene as 4π and **58** as 2π partner. Similarly **73** and **74** could undergo subsequent intramolecular cycloaddition to generate **75** and **76** respectively. On the other hand, the two cyclohexadienone units in **58** could also participate independently in cycloaddition with cyclopentadiene to form **77** and **78** involving the participation of α,β- or γ,δ-double bonds. While **59** and **60** could be formed from cycloaddition of **58** behaving as a 4π component and cyclopentadiene as 2π component with the addition of respectively one and two molecules of cyclopentadiene, the structure **59** could also give rise to **79** and **80** via an intramolecular mode of cycloaddition of the remaining cyclohexadienone unit with the double bond in the cyclopentene ring.

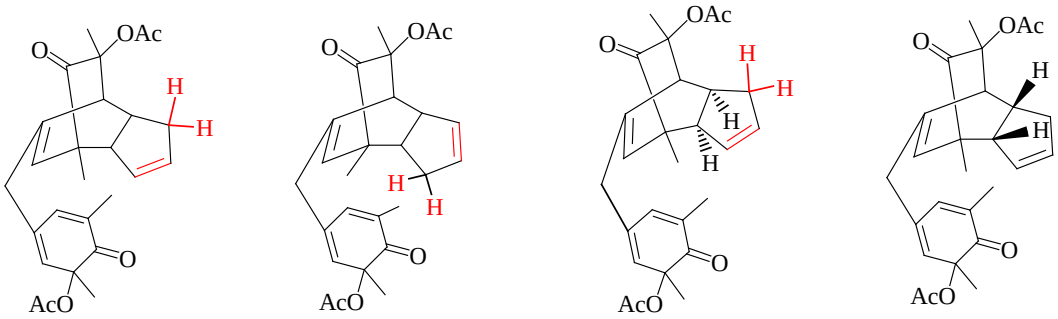
Thus the reaction of bis-cyclohexadienone **58** and cyclopentadiene could in principle give rise to a number of products. However, only two products **59** and **60** were isolated from the reaction. During the cycloaddition the bis-cyclohexadienone part behaved as a diene (π^4 -component) and cyclopentadiene as a dienophile (π^2-component). It was envisioned that diadduct **60** could also be accessed from mono adduct **59** by cycloaddition with cyclopentadiene. Thus, the mono adduct **59** was heated at 90 °C in toluene with cyclopetadiene for 28h. Removal of the solvent followed by column chromatography furnished a white crystalline product **60** as expected. (**Scheme 4.8**)



59 **60**

Scheme 4.8: Synthesis of bis-adduct **60** from mono-adduct **59**

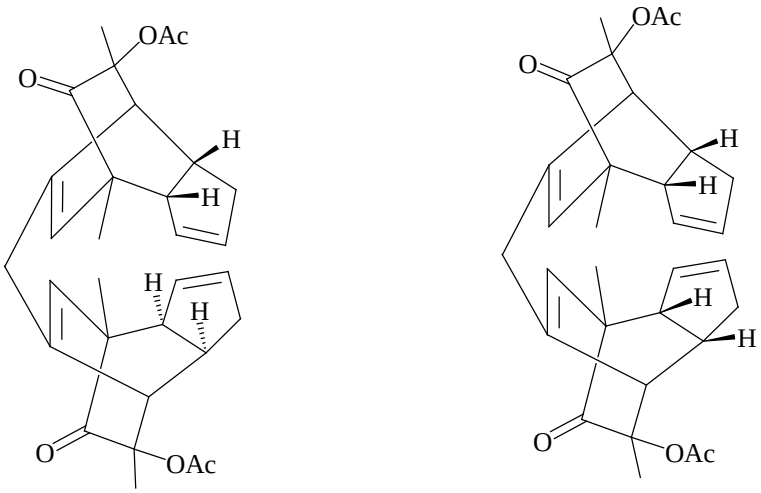
The product **59** formed by 1:1 cycloaddition of **58** and cyclopentadiene may have two different *regio* isomers **59a** and **59b** depending on the mode of approach of **58** with cyclopentadiene in transition state. While only product **59b** was isolated from the reaction. The product **59b** may also have two stereo isomers **59c** and **59d** depeding on *exo* and *endo* mode of cycloaddition. (**Figure 4.9**) However, the formation of a single *stereo specific endo* product **59d** was observed.



59a **59b** **59c** **59d**

Figure 4.9: Possible regio isomers and stereo isomers of monoadduct **59**

Similarly the bis-adduct **60** may also have two different stereoisomers **60a** and **60b** depending on the *exo* or *endo* mode of cycloaddition of a second mole of cyclopentadiene with mono adduct **59**. (**Figure 4.10**) However, only a single *stereo* specific product **60b** was isolated from the reaction.



60a **60b**

Figure 4.10: Stereo isomers of bis -adduct **60**

The structures of **59** and **60** were readily discernible through their spectral and analytical data. The ^{1}H NMR spectrum of adduct **59** exhibited singlets at δ 1.30, 1.53, 1.73, 1.98 for protons on methyl groups and singlet at δ 2.07 for protons on acetate methyl groups. It also showed a doublet at δ 2.00, a multiplet at δ 2.51, a doublet of doublet at δ 3.66 for protons on methine group along with two multiplets at δ 2.76, 2.91 and a singlet at δ 3.02 for protons on methylene groups in addition to singlets at δ 5.26, 5.49, 6.52, a multiplet at δ 5.72, a doublet of doublet at δ 5.89 for olefinic protons. Its ^{13}C NMR spectrum displayed signals at δ 15.38, 15.80, 20.04, 20.06, 22.74, 24.26 for six methyl carbons and signals at δ 35.27, 38.39, 43.32 for three methine carbons with δ 48.92, 51.90 for two methylene carbons, δ 53.96 a quaternary carbon and δ 78.19, 80.75 for two carbons attached with acetate group. Similarly signals at δ 127.71, 128.55, 129.96, 133.68, 134.18, 136.56, 139.7, 142.75 for eight olefinic carbons in addition to characteristic signals at δ 169.34, 170.28, 198.61, 206.85 for acetate and ketonic carbonyl carbons were also observed. The mass spectrum of **59** displayed a molecular ion peak at M^{+} 438.20.

The structure of **59** was further proved by its single-crystal X-ray analysis **Figure 12**, which clearly displays the *endo* stereochemistry of the products with a free cyclohexadienone unit.

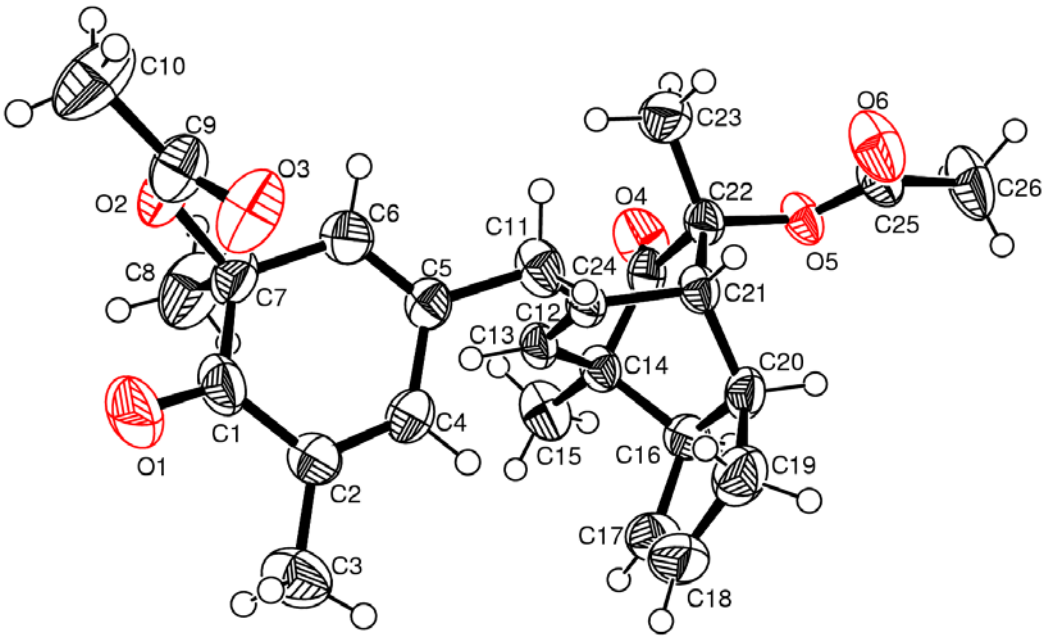


Figure 4.11: ORTEP presentation of carbocycle **59**

The detail of X-ray structure of compound **59** is given below.

Table 1: Crystal data of compound **59**

Empirical formula	$C_{26}H_{30}O_6$
Formula weight	438.50
Temperature	292(2) K
Wavelength	0.71073
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	a = 8.1113(5) Å b = 11.4403(7) Å c = 13.5633(9) Å α = 77.46° β = 77.19° γ = 89.61°
Volume	1196.94(13) Å
Z	2
Density (Calculated)	1.217 Mg / m^3
Absorption coefficient (μ)	0.086 mm^{-1}
F(000)	468
Crystal Size	0.33 x 0.28 x 0.21 mm
θ range for data collection	1.69-28.28°
Reflections collected	8603
Independent Reflections	4194 [R (int) = 0.0325]
Max. and Min. transmission	0.9822 and 0.9723
Refinement Method	Full-matrix least-square on F^2
Data / restraints / parameters	4194 / 0 / 295
Goodness of fit on F^2	0.900
Final R indices [I>2 sigma(I)]	R1 = 0.0450 wR2 = 0.0985
Final R indices (all data)	R1 = 0.0873 wR2 = 0.1079
Largest difference peak and hole	0.172 and -0.156 e/ $Å^3$

The structure of the adduct **60** is highly symmetrical, its ^{1}H, ^{13}C, 2D ^{1}H ^{1}H COSY, ^{1}H ^{13}C HSQC NMR spectrum showed only half number of signals of total protons and carbons. Thus the ^{1}H NMR spectrum of (4) exhibited singlets at δ 1.29, 1.51, 2.05 for protons on methyl groups and a doublet at δ 1.98, a multiplet at δ 2.52, a doublet of doublet at δ 3.64 for protons on methine groups along with multiplets at δ 2.72, 2.88, a singlet at δ 3.16 for protons of methylene groups. It also showed a singlet at δ 5.35, a doublet of doublet at δ 5.51, a multiplet δ 5.69 for olefinic protons.

The ^{13}C NMR spectrum was also consistent with the proposed structure which exhibited resonances at δ 15.96, 20.56, 22.76 for methyl carbons and signals at δ 35.34, 38.36, 52.29 for three methine carbons with δ 43.61, 53.76 for two methylene carbons. It also displayed resonances at δ 51.39, 88.68 for a quaternary carbon and a carbon attached with acetate group respectively. Similarly, there were signals at 126.68, 128.69, 134.59, 141.27 for olefinic carbons and characteristic signals at δ 170.27, 206.70 for acetate and ketonic carbonyl carbons. The structure deduced from ^{1}H and ^{13}C NMR was further proved by 2D ^{1}H ^{1}H COSY and ^{1}H ^{13}C HSQC NMR.

The ^{1}H ^{1}H COSY NMR spectrum of adduct **60** exhibited signals at δ 1.29, 1.51, 2.05 having no corresponding off diagonal peaks represent the three methyl groups. Other diagonal peaks at δ 1.98, 2.52, 3.64 having one, four and two corresponding off diagonal peaks represent three protons of methine groups. It also exhibited diagonal peaks at δ 2.72, 2.88 with three corresponding off diagonal peaks for each for the two protons of methylene group of cyclopentadiene moiety. The diagonal peak at δ 3.16 having no off diagonal peak represents the central methylene group. The diagonal peak at δ 5.35 having no corresponding off diagonal peak and diagonal peaks peaks at δ 5.51, 5.69 having two, three corresponding off diagonal peaks displays three olefinic protons. (**Figure 4.12**)

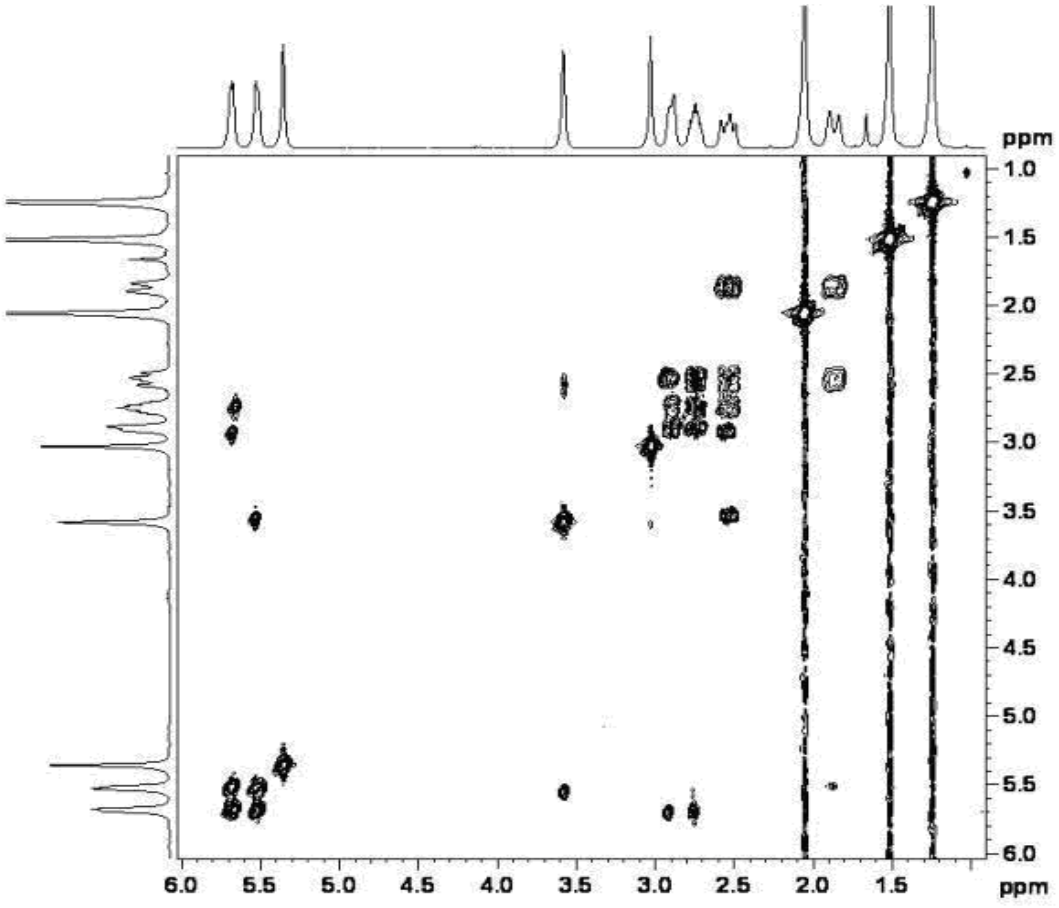


Figure 4.12: ^{1}H-^{1}H COSY NMR spectrum of bis-adduct **60**

The ^{1}H ^{13}C HSQC NMR spectrum displayed cross peaks for proton and carbon at δ (1.29, 15.96), (1.51, 20.56), (2.05, 22.76) for three methyl groups and δ (1.98, 35.34), (2.52, 38.36), (3.64, 52.29) for three methine groups with δ (2.72, 53.76), (2.88, 53.76) for methylene group of cyclopentene ring. It also showed resonance at δ (3.16, 43.61) for central methylene group along with characteristic resonance at δ (5.35, 126.68), (5.51, 128.69) and (5.69, 134.59) for olefinics. The quaternary carbon, the carbon attached to the acetate group, acetate carbonyl, and the keto carbon did not display any signal because they have no protons on corresponding carbon atoms. (**Figure 4.13**)

The mass spectrum of **60** displayed a molecular ion peak at M^{+} 504.25. Elemental analyses were in good agreement with the required for the $C_{31}H_{36}O_6$ was found C, 73.86 %; H, 7.14 %, and calculated C, 73.80 %; H, 7.34 % for $C_{31}H_{36}O_6$.

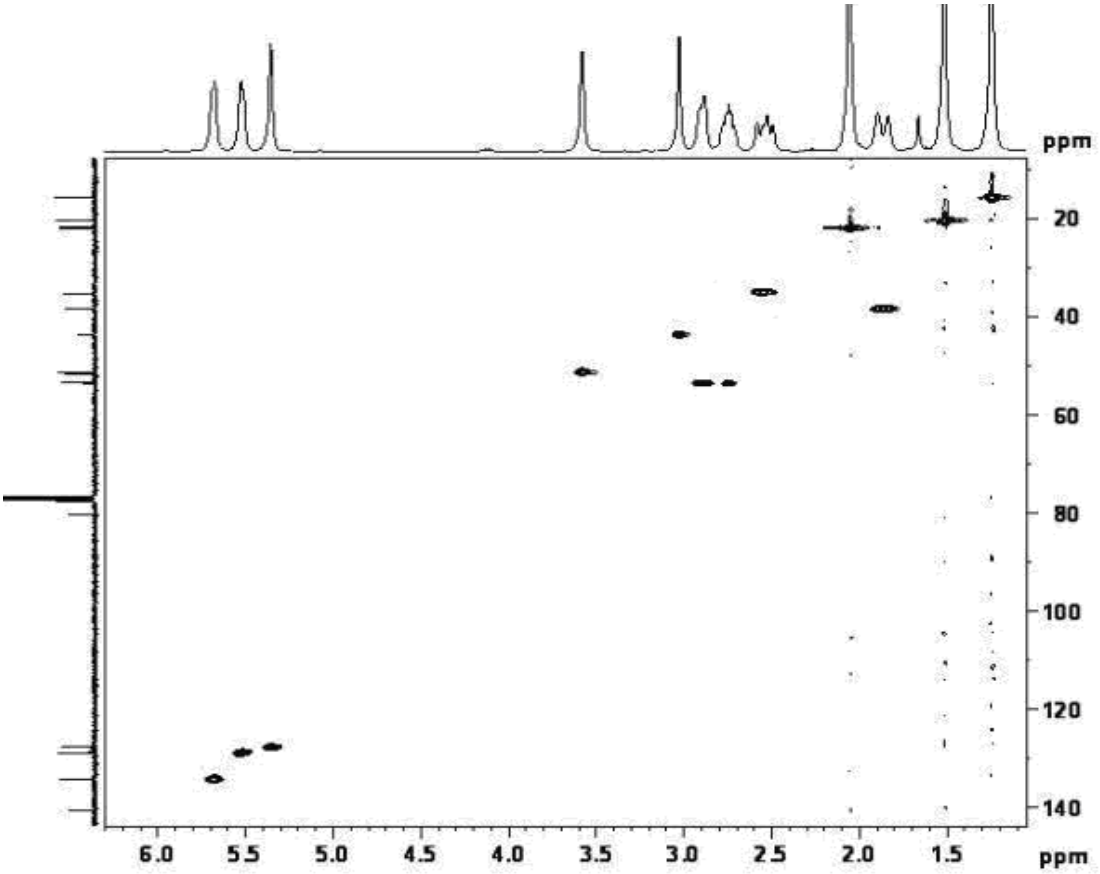


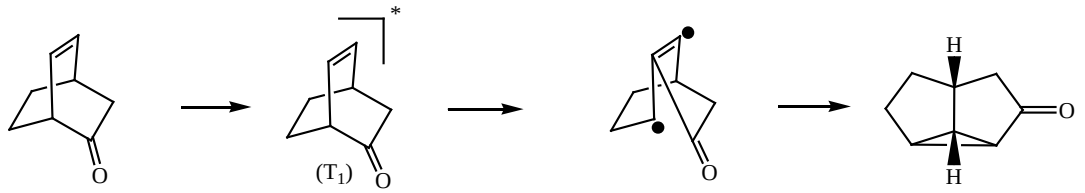
Figure 4.13: ^{1}H ^{13}C HSQC NMR of bis-adduct **60**

The photochemical reactions have attracted significant interest for their ability to act as a key step in the creation of complex molecular architecture and in various natural products syntheses.[33] In photochemical reactions the substrate activation and transformation towards the desired molecule takes place without using any chemical reagents. Therefore the photochemical reactions are also interesting in the area of green chemistry. Different types of photochemical transformations and their use in total syntheses, synthesis of highly functionalised structure, polycyclics have been established from very simple and readily available substrates. Some of these reaction can be carried out in sun light or visible light with renewable energy sources.[33]

In organic chemistry various type of photochemical reactions such as photo cycloaddition,[34] photochemical rearrangements,[35] photochemical electron transfer,[36] photo oxygenation[37] and photo Friedel-crafts reaction have been employed to design specific targeted molecules with considerable structural and stereochemical complexity.[38] Amongst the photochemical reactions the photochemical oxa-di-π

methane ODPM rearrangement is the one most commonly used rearrangement to achieve the complexity in syntheses of the many polycyclic complex molecules with controlled stereochemistry for a long time.[39]

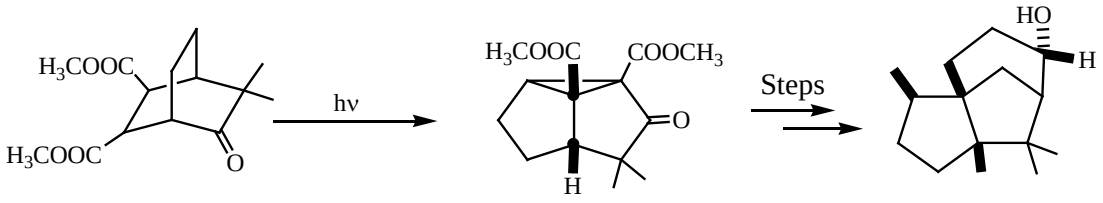
A mechanism for the ODPM rearrangement in bicyclo[2,2,2]octanone **81** having rigid β,γ-enones chromophoric system is presented below.



81 **82** **83** **84**

Scheme 4.9: Mechanism of the ODPM rearrangement

Yates and Stevens first employed the ODPM rearrangement in compound **85** for the formal total synthesis of (+)-cedrol **87**[40] **Scheme 4.10.** The substrate **85** was prepared by Diels-Alder cycloaddition, and was subjected to irradiation in the presence of acetophenone as a sensitizer afforded the product **86**. The linear triquinanes such as capnellene, phellodonic acid, hirsutene, complicatic acid, and hirsutic acid have also been synthesised by odpm rearrangement as a key step.[41]

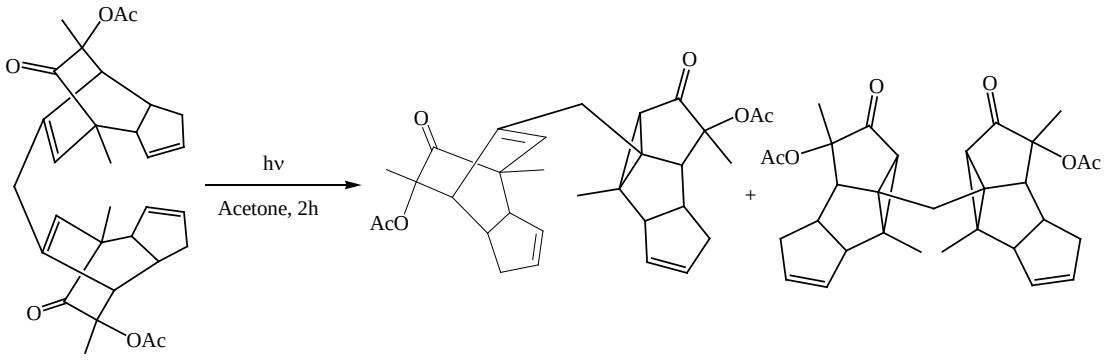


85 **86** **87**

Scheme 4.10: ODPM rearrangement in compound **85**

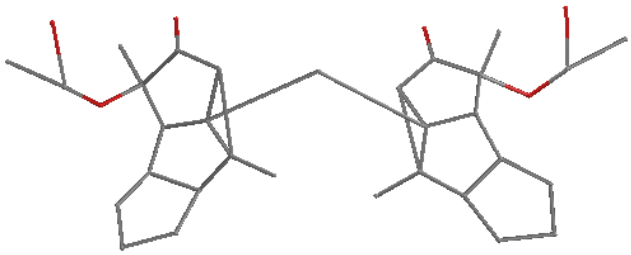
In this part of the work we explore the photochemical ODPM rearrangement of mono-adduct **59** and bis-adduct **60** having β,γ-unsaturated carbonyl systems for the synthesis of novel bis-triquinane **61**.[42] Thus, a solution of **60** in acetone both as a solvent and as a triplet sensitizer was irradiated with mercury vapour lamp (125 W) in

a quartz immersion well for 2 h. The products **88** and **61** were isolated after the removal of solvent under reduced pressure followed by column chromatography. (**Scheme 4.11)**



60 **88** **61**

Scheme 4.11: ODPM rearrangement of di-adduct **60** syntheses of mono-triquinane **88** and bis-triquinane **61**



61

Figure 4.14: Energy minimised 'bird shape' skeleton of bis-triquinane **61**

The structures of the compounds **88** and **61** were readily discernible through their FTIR, ^{1}H, ^{13}C, DEPT-90, DEPT-135 NMR and mass analysis data. It was interesting to observe half the number of signals in the NMR spectrum of **61** due to its highly symmetrical structure. Its ^{1}H NMR spectrum exhibited singlets at δ 1.25, 1.53, 2.07 for protons on methyl groups and a singlet at δ 1.90, a multiplet at δ 2.77, a superimposed doublet of doublet at δ 2.91, a singlet at δ 3.04 for protons on methine groups along with multiplets at δ 2.54, a singlet at δ 3.36 for protons of methylene groups. It also showed a doublet of double at δ 5.54, a multiplet 5.68 for olefinic protons.

The ^{13}C NMR spectrum of **61** was also consistent with the proposed structure which exhibited resonances at δ 15.72, 20.43, 21.98 for three methyl carbons and signals at δ 35.30, 51.20, 53.46, 58.58 for four methine carbons with δ 38.40, 43.61 for two methylene carbons. It also displayed resonances at δ 51.73, 64.26 for two quaternary carbon and δ 88.47 for a carbon attached with acetate group. Similarly signals at δ 127.55, 128.77 for two olefinic carbons and characteristic signals at δ 170.22, 206.78 for acetate and keto carbonyl carbons were observed. The structure of **61** deduced from ^{1}H and ^{13}C NMR was further proved by DEPT-90 and DEPT-135 NMR.

The DEPT-90 spectrum of compound **61** exhibited only positive signals at δ 35.30, 51.20, 53.46, and 58.58 for carbons of four aliphatic methine groups and signal at δ 127.55, 128.77 representing the carbons of olefinic methine groups. Its DEPT-135 NMR spectrum exhibited two negative signals at 38.40, 43.61 represent the carbons of two methylene groups. It also gave positive peaks at δ 15.72, 20.43, 21.98 for carbons of three methyl groups along with signals at δ 35.30, 51.20, 53.46, 58.58, 127.55 and 128.77 for carbons of four aliphatic and two olefinic methine groups.

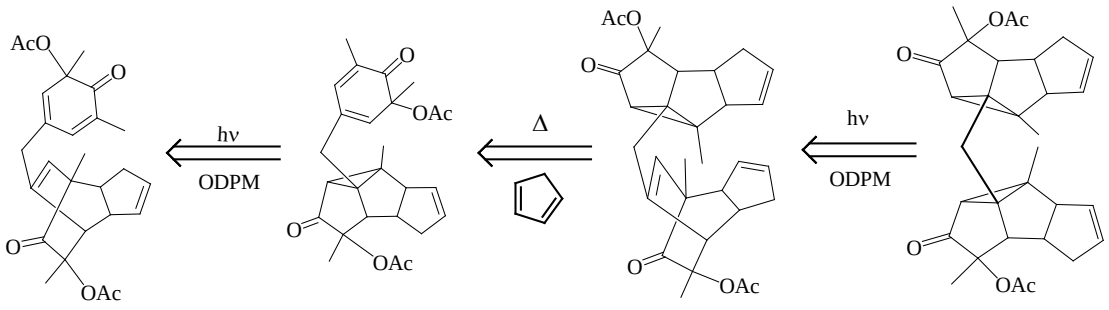
The structure of mono-triquinane **88** was also confirmed by its spectral and analytical analysis. Its ^{1}H NMR spectrum of **88** exhibited singlets at δ 1.08, 1.24, 1.51, 1.58, 2.07 for protons on methyl groups and two multiplets at δ 1.71-1.83, 2.12-2.35, a singlet δ 2.93 for the protons of methylene groups. It also showed two singlets at δ 1.43, 3.52, a multiplet at δ 2.99, a cluster of multiplets between δ 2.76-2.39 in addition to other characterstic signals.

The ^{13}C NMR spectrum of **88** displayed signals at δ 15.04, 17.11, 20.39, 21.57, 21.97, 22.17 for six methyl carbons and signals at δ 35.31, 41.97, 42.16, 50.26, 53.59, 57.58, 58.06 for seven methine carbons with δ 37.95, 38.23, 40.48 for three methylene carbons, δ 45.08, 48.62, 51.42 quaternary carbons and δ 80.50, 88.87 for two carbons attached with acetate group. Similarly signals at δ 124.76, 128.49, 131.06, 132.93, 133.76 and 141.92 for six olefinic carbons in addition to characteristic signals at δ 169.42, 170.20, 206.57, 207.86 for acetate and keto carbonyl carbons were also observed. The structure of **88** was further proved by its DEPT-90 and

DEPT-135 NMR spectral analysis. The DEPT-90 NMR of **88** gave only positive signals at δ 35.31, 41.97, 42.16, 50.26, 53.59, 57.58 and 58.06 for seven methine carbons. Its DEPT-135 NMR spectrum gave negative signals at δ 37.95, 38.23, 40.48 for carbons of methylene groups along with characteristic signals of carbons of methine and methyl groups.

The cascade reactions are one of the most important branch in organic chemistry which constitutes the major area of research in organic syntheses during the last two decades.[43] The cascade reactions have several benefits such as atom economy, economies of time, manual work, resource management and waste generation because several transformations are carried out in one step.[44] The cascade reaction also covers the area of green chemistry. For example a single solvent, workup procedure, and purification step are required to achieve the product that otherwise would have to be prepared over the course of several individual steps.[45]

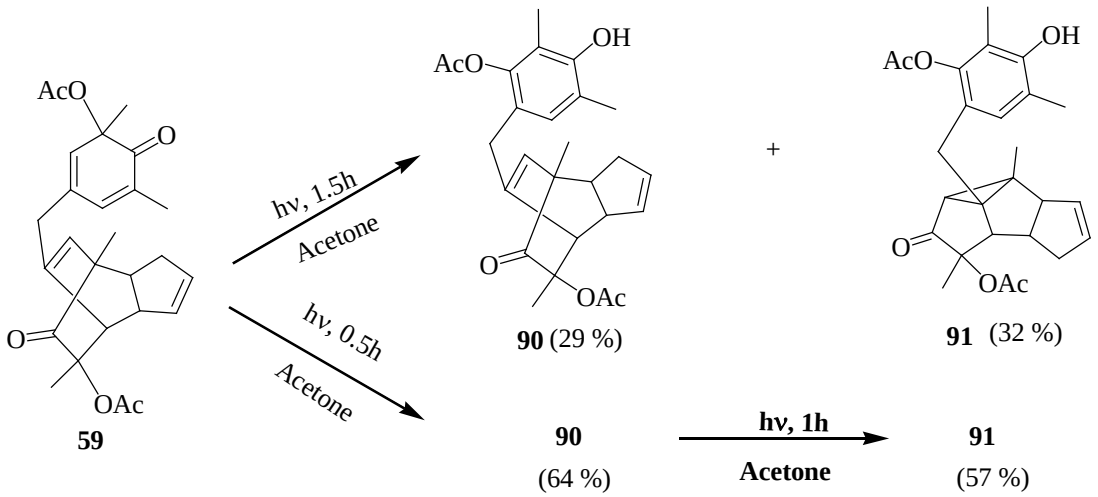
In the present strategy it was envisioned that the bis-triquinane **61** could also be accessed through tandem photochemical-thermal-photochemical protocol from precursor **59** as shown in **Scheme 4.12**.



59 **89** **88** **61**

Scheme 4.12

Attempted photoreaction of chromophore **59** afforded the product **90** as a result of the aromatisation of cyclohexadienone moiety with the migration of an acetate group however compound **89** was not obtained at all. (**Scheme 4.13)**



Scheme 4.13: Photochemical rearrangement in mono adduct **59**

It was interesting to note that when the same reaction of compound **59** was continued for 1.5 h, an aryl substituted tetracycle **91** was additionally isolated. The photochemical aromatisation of cyclohexadienone moiety under these reaction conditions is hitherto unknown in the literature to the best of our knowledge.

The structure of **90** was established through its spectral data and by its single crystal X-ray analysis. Its ORTEP picture is shown in **Figure 4.15**.

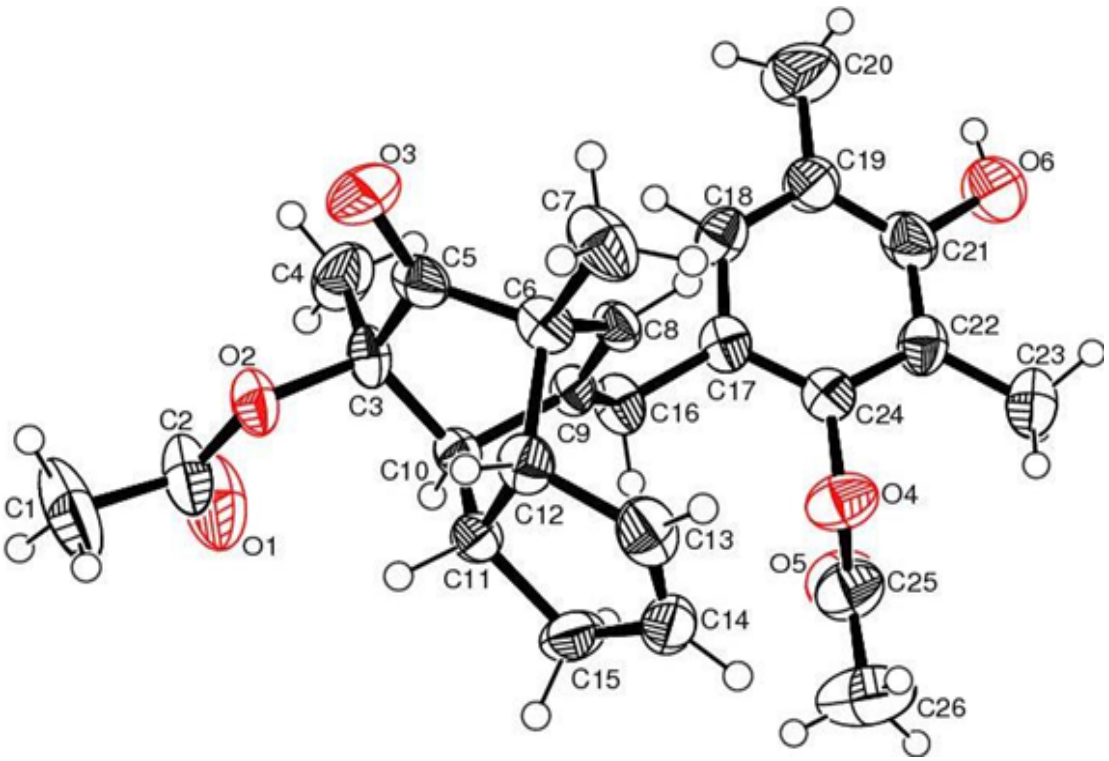


Figure 4.15: ORTEP diagram of **90**

The X-ray structure is deposited at the Cambridge crystallographic data centre for compound **92 (CCDC – 892381).** The detail of compound **92** is given below.

Table 2: Crystal data of compound **90**

Empirical formula	$C_{26}H_{30}O_6$
Formula weight	438.50
Temperature	292(2) K
Wavelength	0.71073
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	a = 8.7851 (9) Å b = 9.5997 (7) Å c = 14.4976 (9) Å α = 104.917° β = 92.442° γ = 100.885°
Volume	1154.8(2) Å
Z	2
Density (Calculated)	1.261 Mg / m^3
Absorption coefficient (μ)	0.089 mm^{-1}
F(000)	468
Crystal Size	0.33 x 0.26 x 0.21 mm
θ range for data collection	2.99-25°
Reflections collected	9054
Independent Reflections	4057 [R (int) = 0.0510]
Max. and Min. transmission	0.9816 and 0.9713
Refinement Method	Full-matrix least-square on F^2
Data / restraints / parameters	4057 / 0 / 295
Goodness of fit on F^2	1.098
Final R indices [I>2 sigma(I)]	R1 = 0.1525 wR2 = 0.4579
Final R indices (all data)	R1 = 0.1663 wR2 = 0.4650
Largest difference peak and hole	0.536 and -0.508 e/ $Å^3$

The FTIR spectrum of compound **90** showed a characteristic band at 3572 cm^{-1} along with other signals confirming the conversion of the cyclohexadienone ring into a phenol derivative. In its ^{1}H NMR spectrum the methyl protons exhibited singlets at δ 1.18, 1.50, 2.00, 2.05, 2.16, 2.27 and two multiplets at δ 2.73, 2.86 and a singlet at δ 3.20 for methylene groups. Similarly a superimposed doublet of a doublet at δ 1.78, a multiplet at δ 2.86, a singlet at δ 3.71 for four methine protons in addition to a singlet at δ 4.93, two multiplets at δ 5.46, 5.70 for three olefinic protons, a broad singlet at 5.19 for proton of exchangeable phenolic OH, along with a characteristic singnal of aromatic proton at δ 6.70.

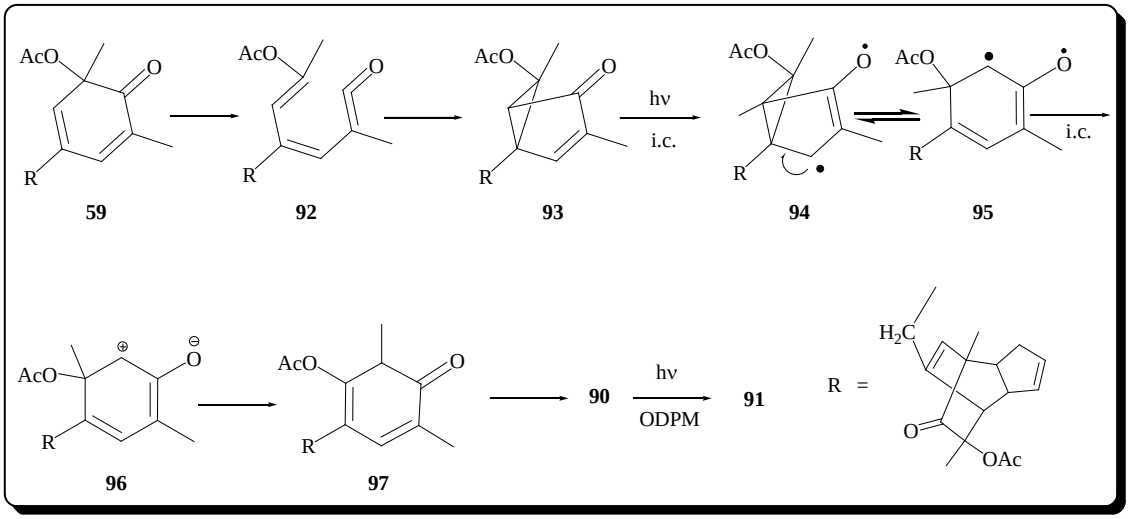
The ^{13}C NMR spectrum of **90** displayed signals at δ 9.76, 15.55, 15.74, 19.88, 20.47, 21.88 for six methyl carbons and signals at δ 35.71, 37.71 for two methylene carbons with δ 38.27, 48.67, 51.34, 53.61 for three methine carbons, δ 53.61 for a quaternary carbon and δ 80.78 for one carbon attached with acetate group. Similarly signals at δ 116.65, 120.49, 121.24, 125.45 for four olefinic carbons, signals at δ 128.27, 129.78, 133.82, 144.97, 146.40, 151.61 for six carbons confirmed the aromatisation of cyclohexanone ring. The signals at δ 168.98, 170.21 and 207.12 for carbonyls of acetates and ketone carbons were also observed.

The structure of aromatised triquinane **91** was also confirmed by its FTIR, ^{1}H, ^{13}C NMR and mass spectral data. It showed a strong band of phenolic OH at 3282 cm^{-1} in addition to the characteristic carbonyl absorptions at 1757 cm^{-1} and 1716 cm^{-1} in its IR spectrum. Its ^{1}H NMR spectrum exhibited singlets at δ 1.28, 2.06, 2.19, 2.36 indicating the presence of six methyl groups, singlet at δ 1.72, a multiplet at δ 2.31 for protons of two methylene groups, a doublet at δ 1.63, a multiplet at δ 3.04, a singlet at 3.14 for protons of methine groups.

The ^{13}C NMR of **91** was also consistent with the proposed structure, which exhibited resonance at δ 9.88, 15.74, 17.53, 18.41, 20.69, 21.67 for methyl carbons and signals at δ 28.67, 38.02 for two methylene carbons with δ 42.54, 45.91, 47.82 and 49.90 for four methine carbons. Similarly it showed signals at δ 54.82, 55.15 for two quaternary carbons, a signal at δ 88.06 for carbon attached to $OCOCH_3$ group, signals at δ 116.70, 121.35, for two olefinic carbons and signals at δ 122.48, 129.36,

130.83, 132.59, 146.26, 151.67 for six aromatic carbons. It also displayed signals at 169.10, 169.90, 209.48 for acetate and keto carbonyl carbons.

A probable mechanism for the formation of **90** and **91** via photochemical aromatisation of cyclohexadienone is proposed in **scheme 4.14**. Photolytic ring cleavage converts cyclohexadienone **59** into **92** which perhaps rearranges to **93**.[46] The bicyclic ketone **93** may further give **90** via a series of steps.[47] (**Scheme 4.14**)



Scheme 4.14: Suggested mechanism of formation of **90** and **91**

4.4 Experimental Section

2,6-Dimethyl phenol, dicyclopentadiene were purchased from Sigma Aldrich. Freshly cracked cyclopentadiene was used. Hydrochloric acid (36 % w/v) was purchased from Merck. All other solvents were purchased from Merck and distilled prior to use.Column Chromatography was performed using Acme's silica gel (60-120 mesh size) and the elution was done using light petroleum and ethyl acetate mixtures. Thin layer chromatography was performed using Acme's silica gel for TLC, and spots were visualized in iodine vapor. The yields (%) are reported based the recovery of the starting material after column chromatography. IR spectra were recorded on a Perkin–Elmer PC-16 FT IR spectrometer as KBr pallets. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 FT NMR (100 MHz for ^{13}C respectively) spectrometer using $CDCl_3$ as solvent containing tetramethylsilane as an internal

standard. Mass spectra were recorded on Thermo-Fisher DSQ II GCMS instrument. obtained on a Shimadzu QP-5050 mass spectrometer.

Experimental Procedures:

Preparation of tetramethyl bis-phenol-F (57):

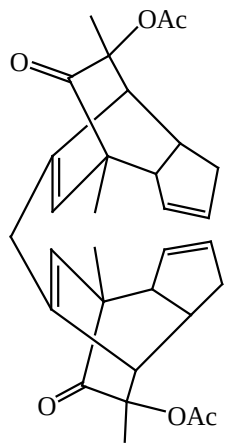
Bishenol-F was prepared by condensation of 2,6-dimethyl phenol **56** with formaldehyde by following the procedure reported in **Chapter 3.**

Preparation of bis-acetoxy cyclohexadienone (58):

The bisacetoxy cyclohexadienone **58** was synthesised by oxidative acetyaltion of tetramethyl bisphenol-F using Lead tetra acetate in ethyl acetate following the procedure reported in **Chapter 3.**

Syntheses of monoadduct (59) and bis-adduct (60):

A solution of bis-cyclohexadienone (**58**) (4.0 g, 0.010 mol) in dry toluene (40 ml) was heated to 90^{o}C in an oil bath while circulating cooled water (10-15^{o}C) and freshly cracked cyclopentadiene (23 ml) was added to it in portions (1ml every two hours). The reaction was continued for 46 hours after which it was allowed to cool to room temperature (~27 ^{0}C). The solvent was removed under reduced pressure to furnish a thick yellow liquid which was chromatographed over a column of silica gel. Elution of the column with light petroleum / ethyl acetate (90:10) afforded the bis-adduct (**60**) as a white solid (0.5 g, 21%).



60

Mp. = 240 °C.

IR (KBr): , 1234, 1367, 1440, 1637, 1732 and 1739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.29 (6H, s, 2CH_3), 1.51 (6H, s, 2CH_3), 1.98 (2H, d, J = 4.8 Hz, 2CH), 2.05 (6H, s, 2CH_3), 2.52 (2H, m, 2CH), 2.72 (2H, m, CH_2), 2.88 (2H, m, CH_2), 3.16 (2H, s, CH_2), 3.64 (2H, dd, J_1 = 6.0 Hz, J_2 = 2.0 Hz, 2CH), 5.35 (2H, s, olefinic), 5.51 (2H, dd, J_1 = 5.6 Hz, J_2 = 2.4 Hz, olefinic), 5.69 (m, 2H, olefinic).

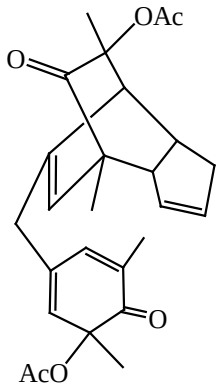
^{13}C NMR (100 MHz; $CDCl_3$): 15.96, 20.56, 22.76 (3C, CH_3), 35.34, 38.36, 52.29 (3C, CH), 43.61, 53.76 (2C, CH_2), 51.86,

(2C, Cq), 80.86 (2C, carbon attached to $OCOCH_3$), 126.68, 128.89, 134.59, 141.27 (4C, olefinic) 170.27, 206.65 (4C, CO).

HRMS (ESI): m/z calculated for $C_{31}H_{36}O_6$: 504.61; found 504.250 (M^+).

Elemental analysis calculated for $C_{31}H_{36}O_6$ (504): C, 73.80; H, 7.14 %. Found: C, 73.86; H, 7.34 %.

Further elution of the column with light petroleum / ethyl acetate (85:15) afforded the monoadduct (**59**) as a white crystalline solid (1.5 g, 51%).



59

Mp. = 178 °C.

IR (KBr): 1260, 1447, 1685, 1732, 1739, and 3040 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.30 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.73 (3H, s, CH_3), 1.98 (3H, s, CH_3), 2.00 (1H, d, J = 3.6 Hz, CH), 2.07 (6H, s, $2CH_3$), 2.51 (1H, m, CH), 2.76 (1H, m, CH_2), 2.91 (1H, m, CH_2), 3.02 (2H, s, CH_2), 3.66 (1H, dd, J_1 = 4.4 Hz, J_2 = 2.0 Hz, CH), 5.26 (1H, s, olefinic), 5.49 (1H, s, olefinic), 5.72 (1H, m, olefinic), 5.89 (1H, m, olefinic), 6.52 (1H, s, olefinic).

^{13}C NMR (100 MHz $CDCl_3$): 15.38, 15.80, 20.04, 20.06 (4C, CH_3) 22.74, 24.26 (2C, CH_3), 35.27, 38.39, 43.32 (3C, CH), 48.92 (1C, Cq) 51.90, 53.96 (2C, CH_2) 78.28, 80.75 (2C, carbon attached to $OCOCH_3$), 127.71, 128.55, 129.96, 133.68, 134.18, 136.56, 139.7, 142.75 (8C, olefinic) 169.34, 170.28, 198.61, 206.85 (2C, CO).

HRMS (EI): m/z calculated for $C_{26}H_{30}O_6$ 438.51; found 438.20 (M^+).

Elemental analysis calculated for $C_{26}H_{30}O_6$ (438): C, 71.23; H, 6.84 %. Found: C, 71.61; H, 7.02 %.

ORTEP diagram of single crystal analysis of mono adduct (**59**) is shown in Fig. **4.11**.

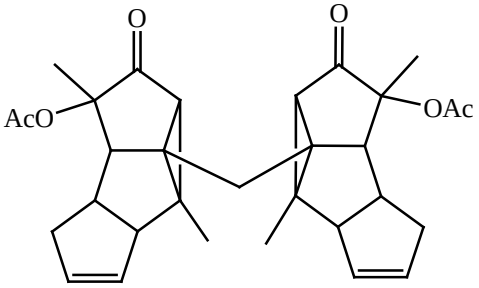
Synthesis of bis-adduct (60) from monoadduct (59):

A solution of the adduct (**59)** (2 gm, 0.004 mol) in dry toluene (20 ml) was heated to 90^{o}C in an oil bath while circulating cooled water (10-15^{o}C) and freshly cracked cyclopentadiene (14 ml) was added to it in portions (1ml every two hours). The reaction was continued for 28 hours after which it was allowed to cool to room temperature. The solvent was removed under reduced pressure to give a thick yellow liquid which was chromatographed over a column of silica gel. Elution with light petroleum / ethyl acetate (90:10) afforded adduct (4) (0.5 g, 37 %). Its identity was

confirmed by comparing mp, IR, ^{1}H and ^{13}C NMR data with the compound **(60)** mentioned above.

Synthesis of monotriquinane (88) and bis-triquinane (61):

A solution of precursor (**60)** (0.5g 0.0009 mol) in acetone (600 ml) solvent as well as sensitizer was irradiated for 2 h with a mercury vapour lamp 125 W in a quartz photochemical reactor. After the completion of reaction (TLC) acetone was removed under reduced pressure to furnish a yellow solid which was chromatographed over a column of silica gel. Elution of column with petroleum ether/ethyl acetate (90:10) afforded compound **(61)** (0.146g, 20%). It was interesting to observe half the number of signals in the NMR spectrum due to its highly symmetrical structure.



61

Mp. = 252 ^{0}C

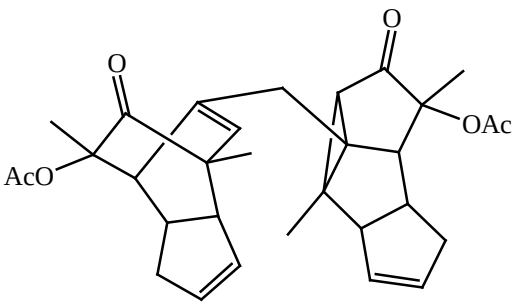
IR (KBr): 1234, 1728, 2931, 3039 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (6H, s, $2CH_3$), 1.53 (6H, s, $2CH_3$), 1.90 (2H, s, CH_2), 2.07 (6H, s, $2CH_3$), 2.54 (4H, m, $2CH_2$), 2.77 (2H, m, 2CH), 2.91(2H, super- imposed dd, J = 7.6 H_Z, 2CH), 3.04 (2H, s, 2CH-α to carbonyl), 3.36 (2H, t, J = 2.4 Hz, 2CH), 5.54 (2H, dd, J_1 = 5.5 Hz, J_2 = 2.0 Hz, olefinic), 5.69 (2H, m, olefinic).

^{13}C NMR (100 MHz $CDCl_3$): δ 15.72, 20.43, 21.98 (6C, CH_3), 35.30 (2C, CH), 38.40, 43.61, (2C, CH_2), 51.20 (2C, CH), 51.73 (2C, Cq), 53.46, 58.58 (4C, CH), 64.26 (2C, Cq), 80.47 (2C, attached to $OCOCH_3$), 127.55, 128.77 (4C, olefinic), 170.22, 206.78 (4C, CO).

MS (EI): m/z calculated for $C_{31}H_{36}O_6$ 504.61; found 504.14 M^+, 443 (60.73%), 401 (100%), 228.14 (59.15%), 202 (88.30%).

Further elution of the column with petroleum ether/ ethyl acetate (85:15) furnished the compound **(88)** (0.164g, 32 %).



88

Mp. = 236 ^{0}C

IR (KBr): 1586, 1754, 2950, 3126 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.43 (1H, s, α-CH), 1.51 (3H, s, CH_3), 1.58 (3H, s, CH_3),

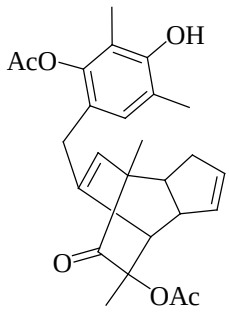
1.71-1.83 (2H, m, CH_2), 2.07 (s, 6H, CH_3), 2.12-2.35 (2H, m, CH_2), 2.76-2.39 (cluster of multiplets, 3H, CH), 2.99 (1H, m, CH superimposed with signal of CH_2), 2.93 (2H, m, CH_2), 3.26 (1H, d, *J* = 8 Hz, CH), 3.52 (1H, s, CH bridgehead), 5.48 (2H, m), 5.70 (1H, s, β-H of enone group), 5.71 (2H, m).

^{13}C NMR (75 MHz $CDCl_3$): δ 15.04, 17.11, 20.39, 21.57, 21.97, 22.17 (6C, CH_3), 35.31 (1C, CH), 37.95, 38.23, 40.48 (3C, CH_2), 41.97, 42.16 (2C, CH), 45.08, 48.62 (2C, Cq), 50.26 (1C, CH), 51.42 (1C, CH), 53.59, 57.58, 58.06, (3C, CH), 80.50, 88.87 (2C, attached to $OCOCH_3$), 124.76, 128.49, 131.06, 132.93, 133.76, 141.92 (6C, olefinic), 169.42, 170.20, 206.57, 207.86 (4C, CO).

MS (EI): m/z calculated for $C_{31}H_{36}O_6$ 504.61; found 503.66 M^+, 401.13 (22%), 269.78 (33.74%), 201 (90.73%), 186.18 (100%).

Synthesis of aromatised product (90):

A solution of precursor **(59)** (0.5g 0.0011mol) in acetone (600 mL) was irradiated for 0.5 h with a mercury vapour lamp in a quartz photochemical reactor. The solvent was removed under reduced pressure to give crude yellow solid which was purified over a column of silica gel. (The elution of the column with petroleum ether/ethyl acetate 90:10 furnished pure compound (**90)** (0.32g, 64 %).



90

Mp. = 194 ^{0}C.

IR: (KBr): 1486, 1757, 2944, 3572 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.78 (2H, superimposed dd, *J* = 3.9 Hz, 2CH), 2.00 (3H, s, CH_3), 2.05 (3H, s, CH_3), 2.16 (3H, s, CH_3), 2.27 (3H, s, CH_3), 2.47 (1H, m, CH), 2.73 (1H, m, CH_2), 2.86 (1H, m, CH_2), 3.20 (2H, s, CH_2), 3.71 (1H, s, CH bridgehead), 4.93 (1H, s, olefinic), 5.19 (1H, bs, phenolic OH), 5.46 (1H, m, olefinic), 5.70 (1H, m, olefinic), 6.70 (1H, s, CH).

^{13}C NMR (75 MHz $CDCl_3$): δ 9.76, 15.55, 15.74, 19.88, 20.47, 21.88 (6C, CH_3), 37.84, 35.71 (2C, CH_2), 38.27, 48.67, 51.34 (3C, CH), 53.61 (1C, Cq), 116.65, 120.49, 121.24, 125.45, (4C, olefinic), 80.78 (1C, attach to $OCOCH_3$), 128.27, 129.78, 133.82, 144.97, 146.40, 151.61 (6C, aromatic), 168.98, 170.21, 207.12 (3C, CO).

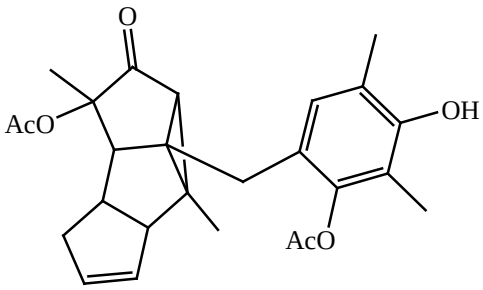
Mass (EI): m/z calculated for $C_{26}H_{30}O_6$ 438.51; found 438.16 M^+, 279.12 (10.65%), 149 (100%).

ORTEP diagram of single crystal analysis of aromatised product (**90**) is shown in Fig. **4.15**.

Syntheses of compound (90) and (91):

Precursor **(59)** (0.5g 0.0011mol) was dissolved in acetone (600 ml) in a quartz photochemical reactor and irradiated for 1.5 h. The solvent was removed under reduced pressure to furnish a yellow solid which was chromatographed over a column of silica gel. Elution of the column with petroleum ether/ethyl acetate (90:10) afforded compound (**90)** (0.146g, 29%). Its identity was confirmed by completely matched mp, IR, ^1H and ^{13}C NMR data with the compound (**90)** mentioned above.

Further elution of column with petroleum ether/ ethyl acetate (85:15) afforded compound **(91)** (0.164g, 32%).



91

Mp. = 186 ^{0}C.

IR: (KBr): 1444, 1481, 1757, 2976, 3282 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (6H, s, $2CH_3$), 1.63 (1H, d, *J* = 4.8 Hz, CH), 1.72 (2H, s, CH_2), 2.06 (6H, s, $2CH_3$), 2.19 (3H, s, CH_3), 2.31 (2H, m, CH_2), 2.36 (3H, s, CH_3), 3.04 (2H, m, CH), 3.14 (1H, s, CH), 4.84 (1H, s, phenolic OH), 5.68 (2H, m, olefinic), 6.81 (1H, s, aromatic).

^{13}C NMR (100 MHz $CDCl_3$): δ 9.88, 15.74, 17.53, 18.41, 20.69, 21.67 (6C, CH_3), 28.67, 38.02 (2C, CH_2), 42.54, 45.91, 47.82, 49.90 (4 x C, CH), 54.82, 55.15 (2C, Cq), 88.06 (1C, attach to $OCOCH_3$), 116.70, 121.35 (2C, olefinic), 122.48, 129.36, 130.83, 132.59, 146.26, 151.67 (6C, aromatic), 169.10, 169.90, 209.48 (3C, carbonyl).

Mass (EI): m/z calculated for $C_{26}H_{30}O_6$ 438.51; found 438.34 (M^+).

4.5 Conclusion

We have reported an efficient synthesis of mono and bis-adducts **59** and **60** having β,γ-unsaturated carbonyl chromophore, through an inverse electron demand $\pi^{4s}{}_+ \pi^{2s}$ cycloaddition reaction. The photochemical ODPM rearrangement of both the

chromophoric systems **59** and **60** was explored towards the synthesis of *cis-anti-cis* bis-triquinane skeleton **61**. The photochemical reaction in **60** led to the formation of monotriquinane connected with tricycle[5,2,2,$0^{2,6}$]undecanones **88** and bis-triquinane **61** while, UV irradiation in mono adduct resulted in the formation of two different products pentasubstituted phenol connected with tricycle[5,2,2,$0^{2,6}$]undecadienone **90** and pentasubstituted phenol jointed with a triquinane skeleton **91**.

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4.7 Spectral Data of compounds

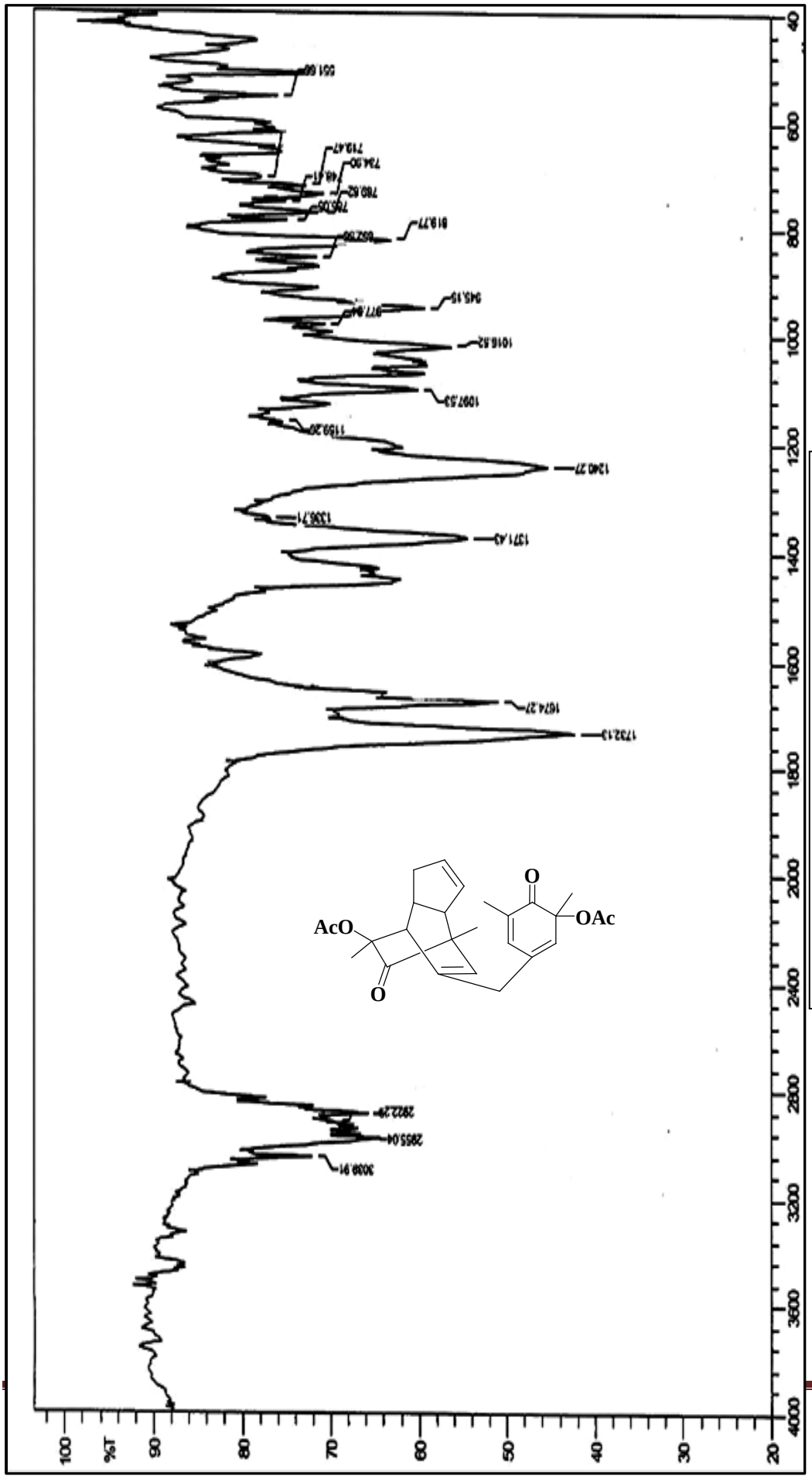


Figure 4.16: FTIR Spectrum of Compound **59**

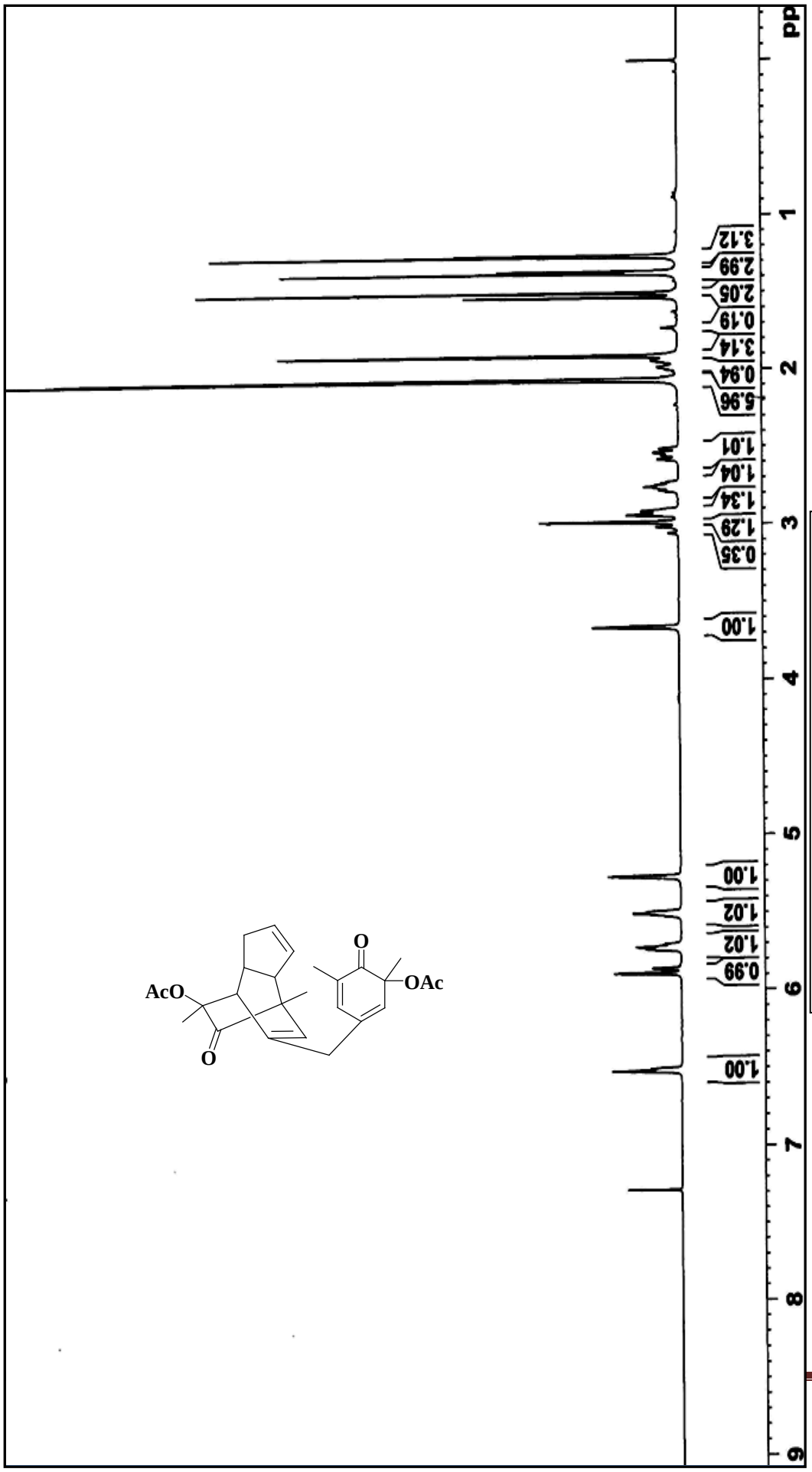


Figure 4.17: ^{1}H NMR spectrum of compound **59**

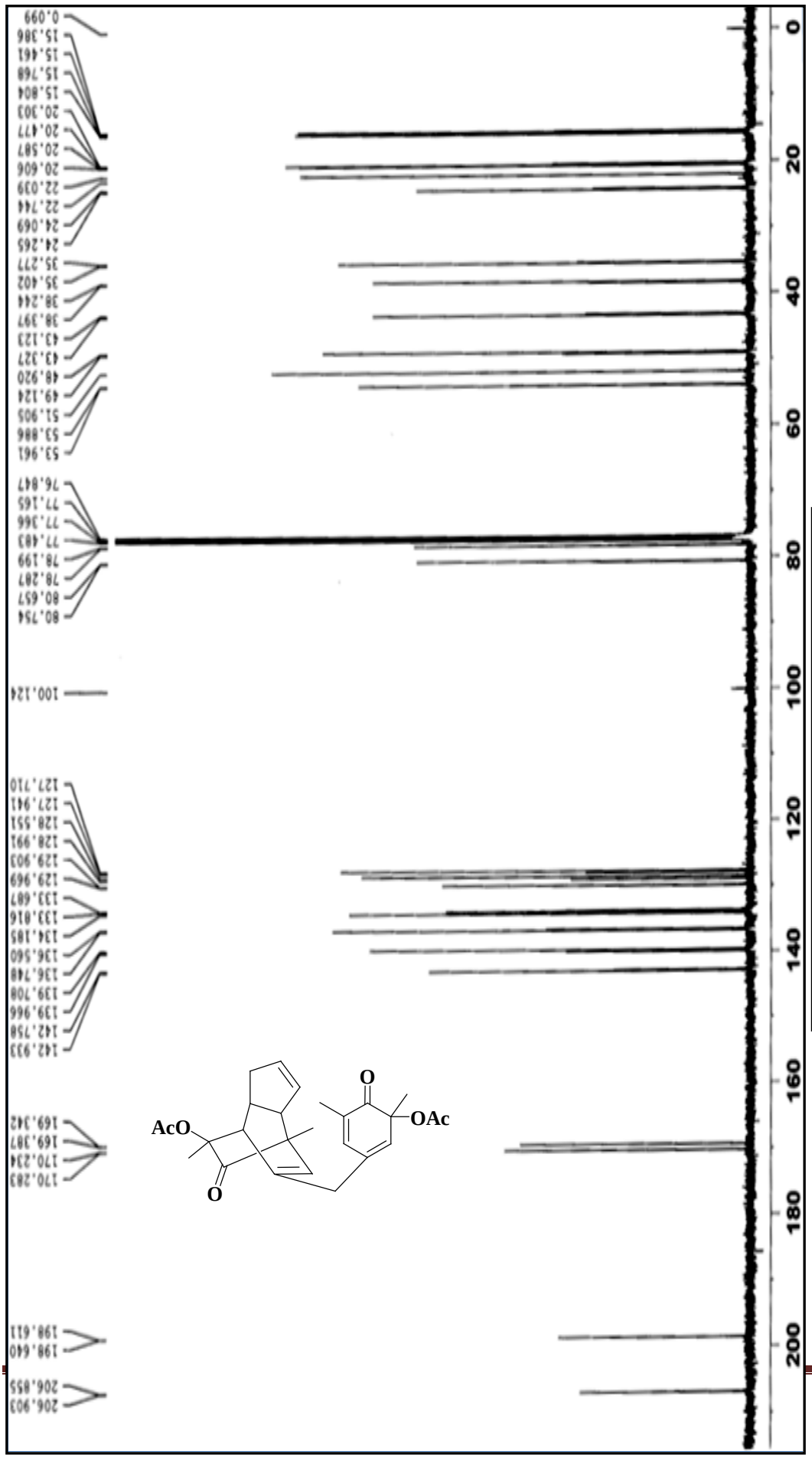


Figure 4.18: ^{13}C NMR spectrum of compound **59**

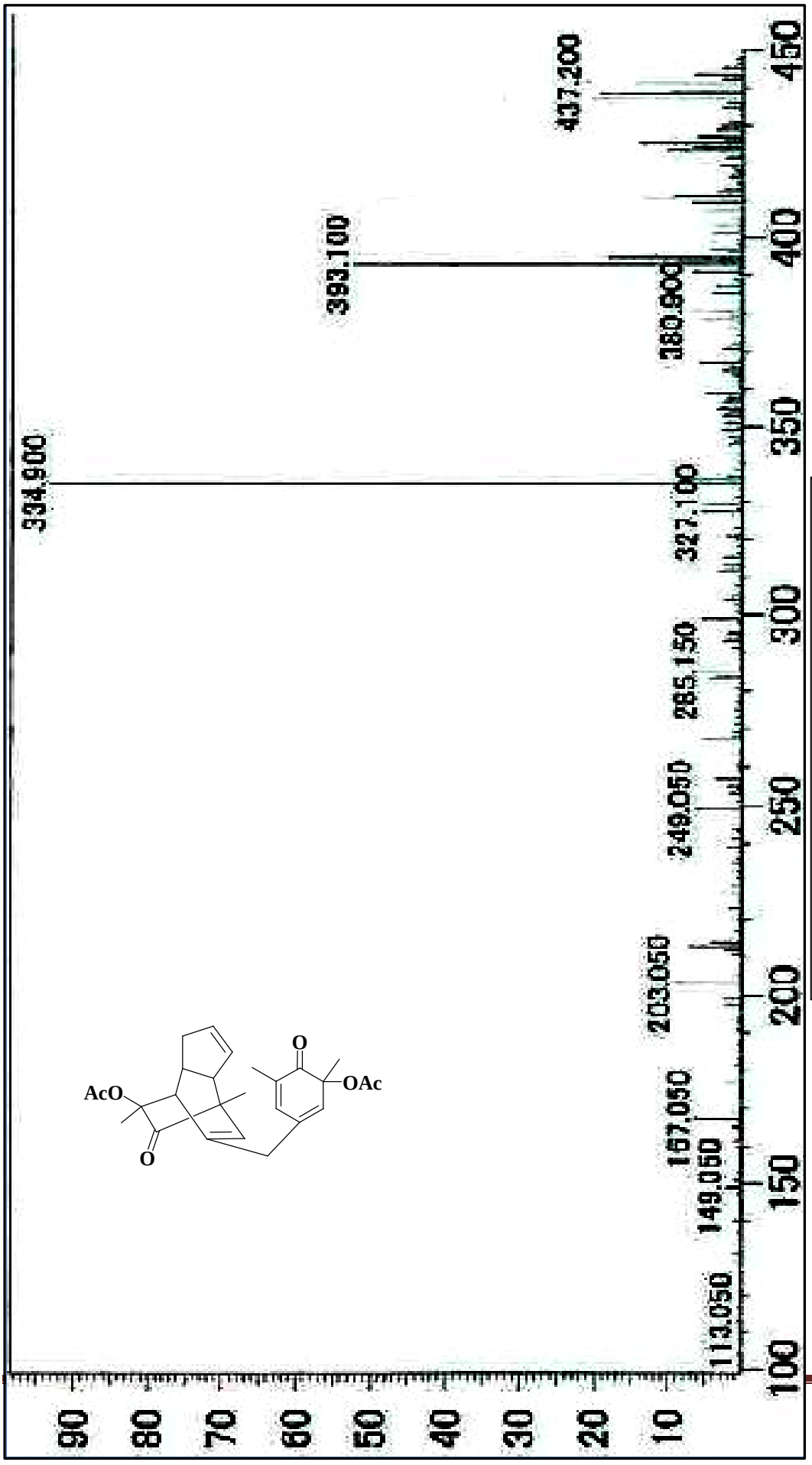


Figure 4.18: HRMS spectrum of compound **59**

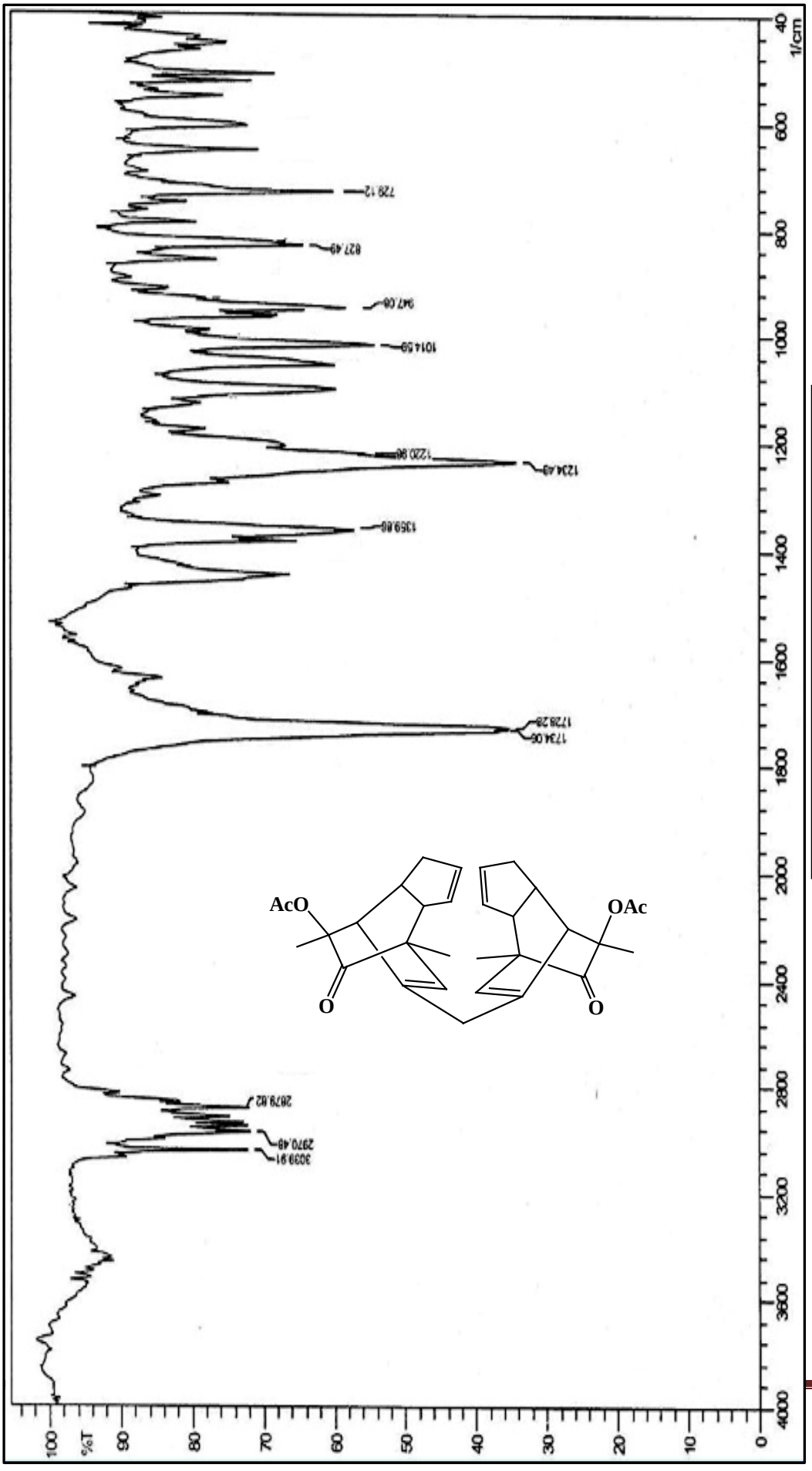


Figure 4.20: FTIR Spectrum of Compound **60**

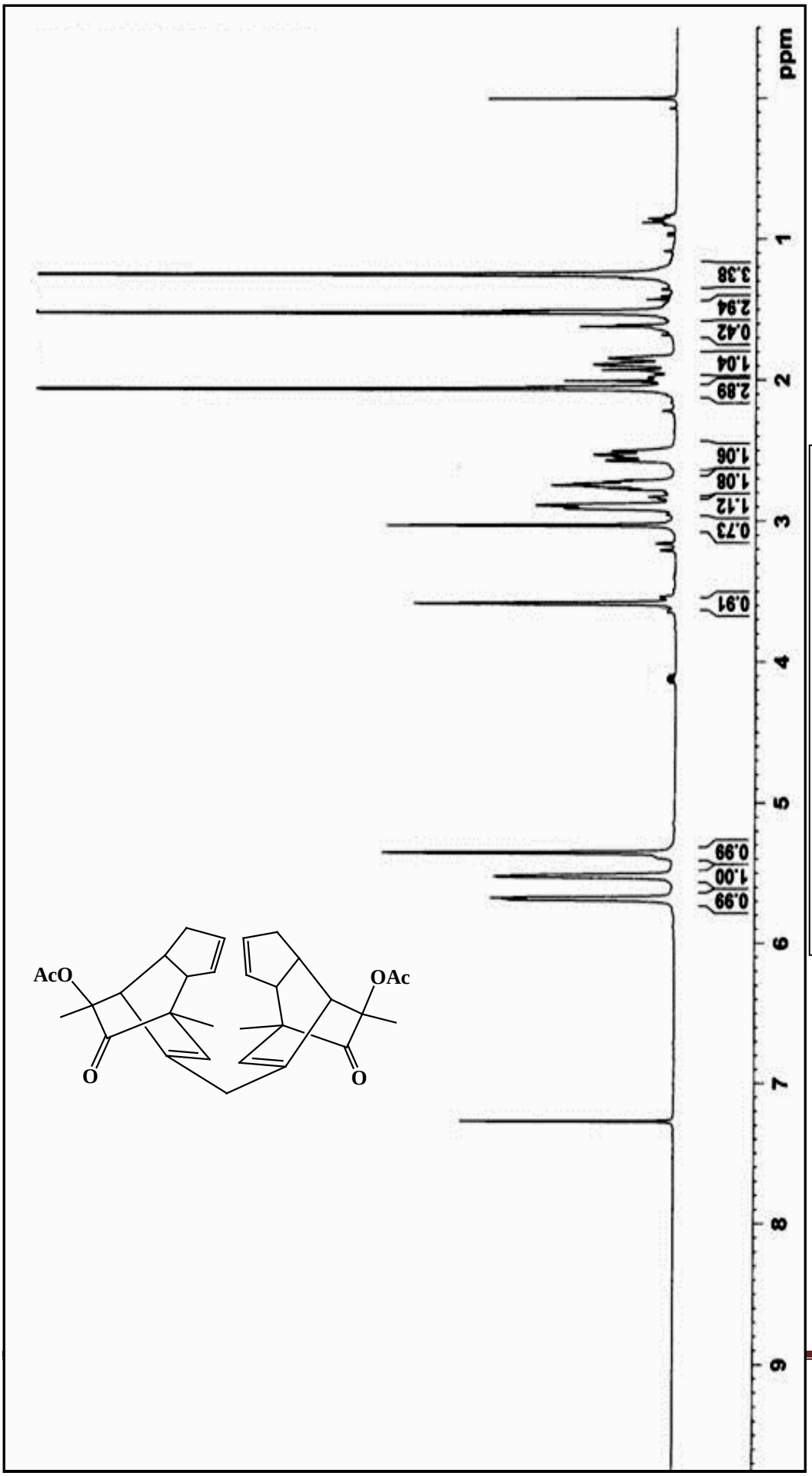


Figure 4.21: ^{1}H NMR of spectrum compound **60**

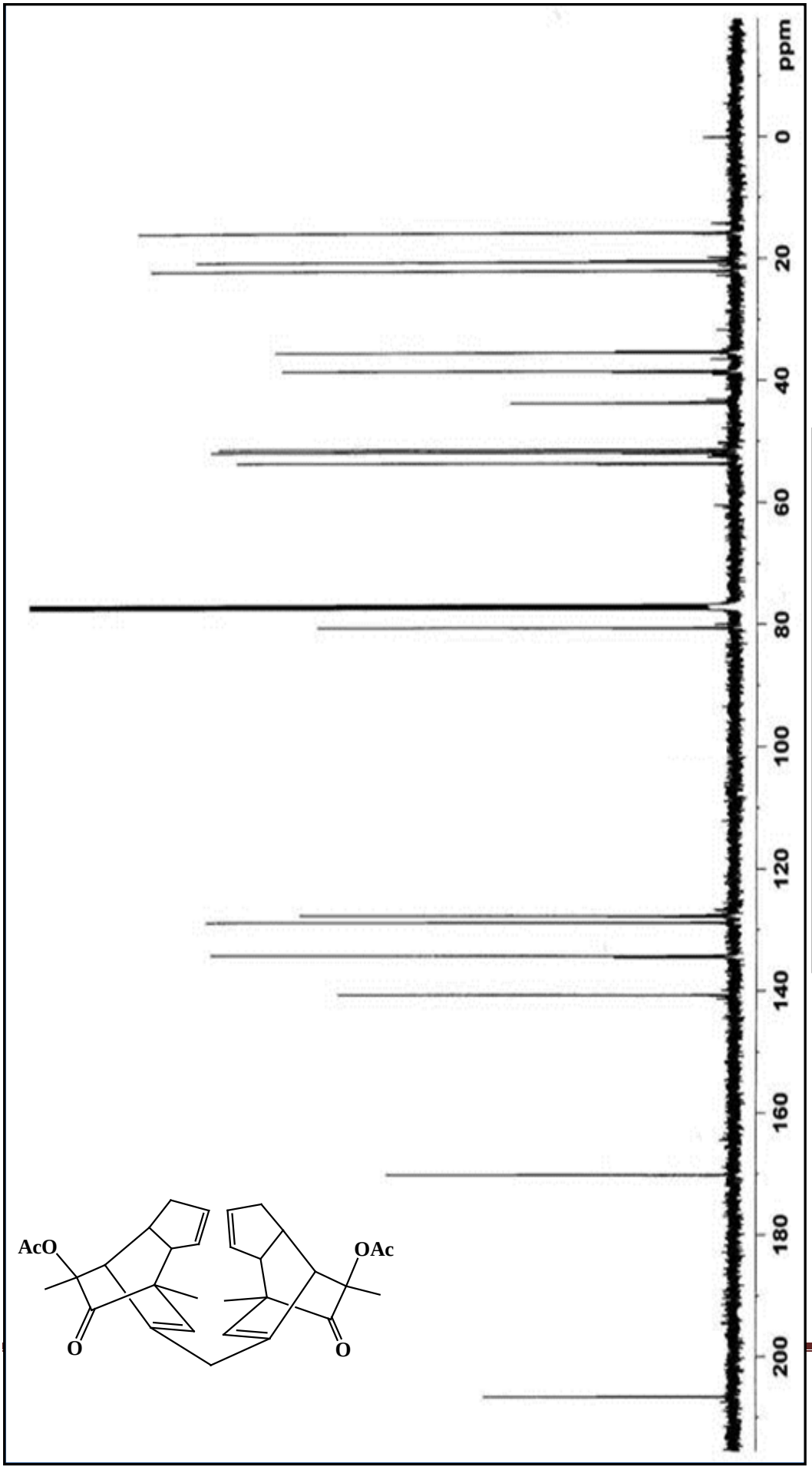


Figure 4.22: ^{13}C NMR of spectrum compound **60**

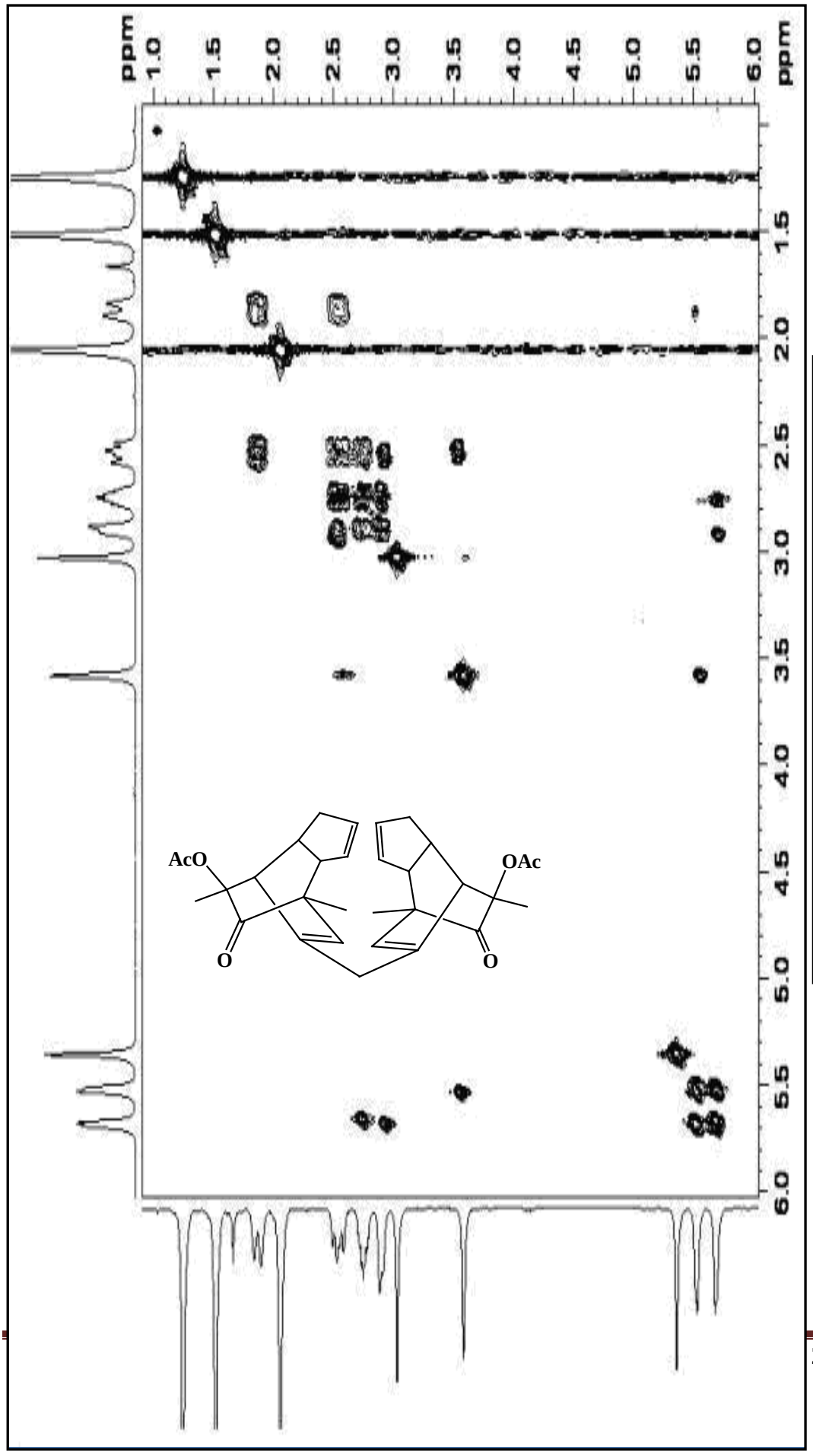


Figure 4.23: ^{1}H-^{1}H COSY NMR spectrum of compound **60**

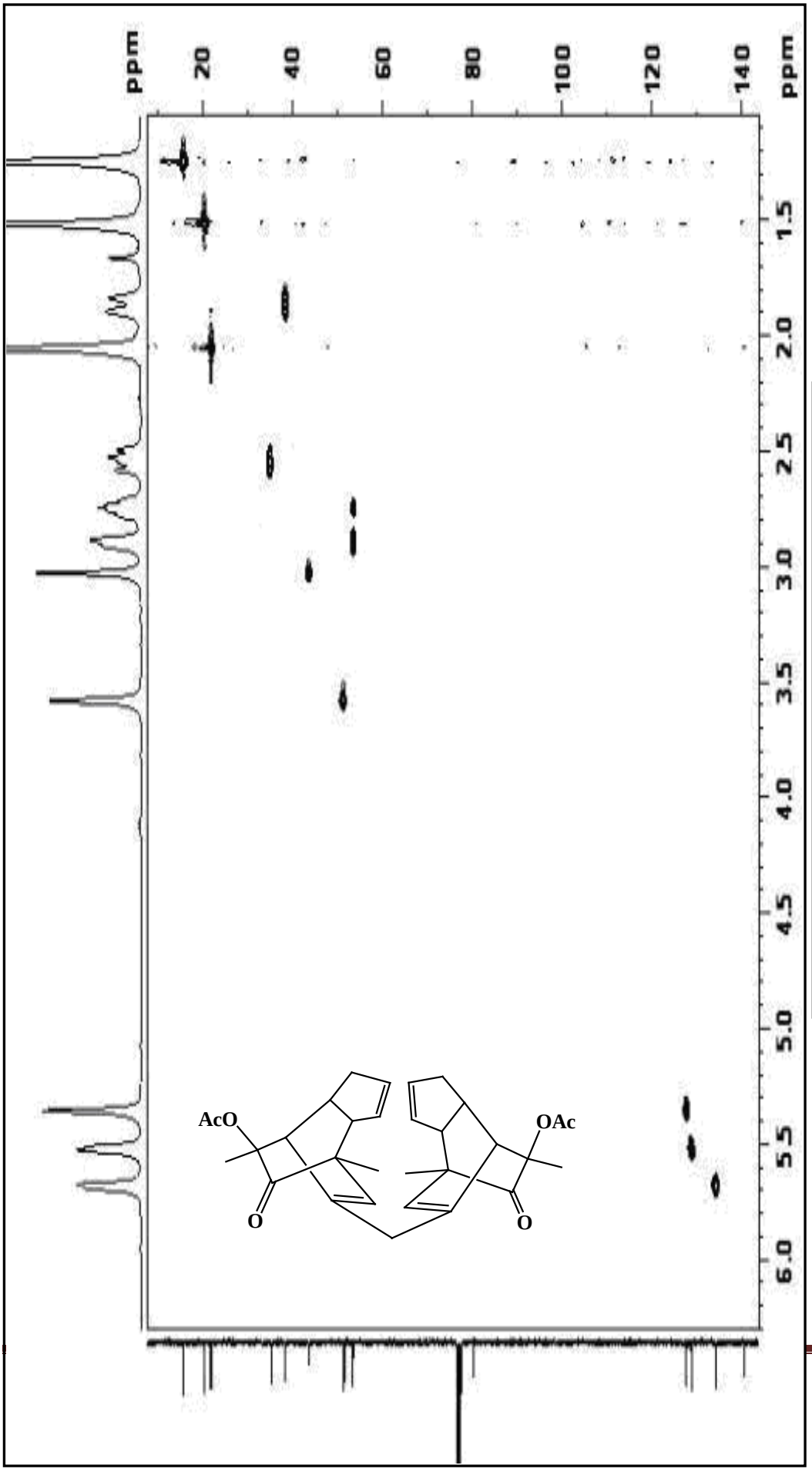


Figure 4.24: ^{1}H-^{13}C HSQC NMR spectrum of compound **60**

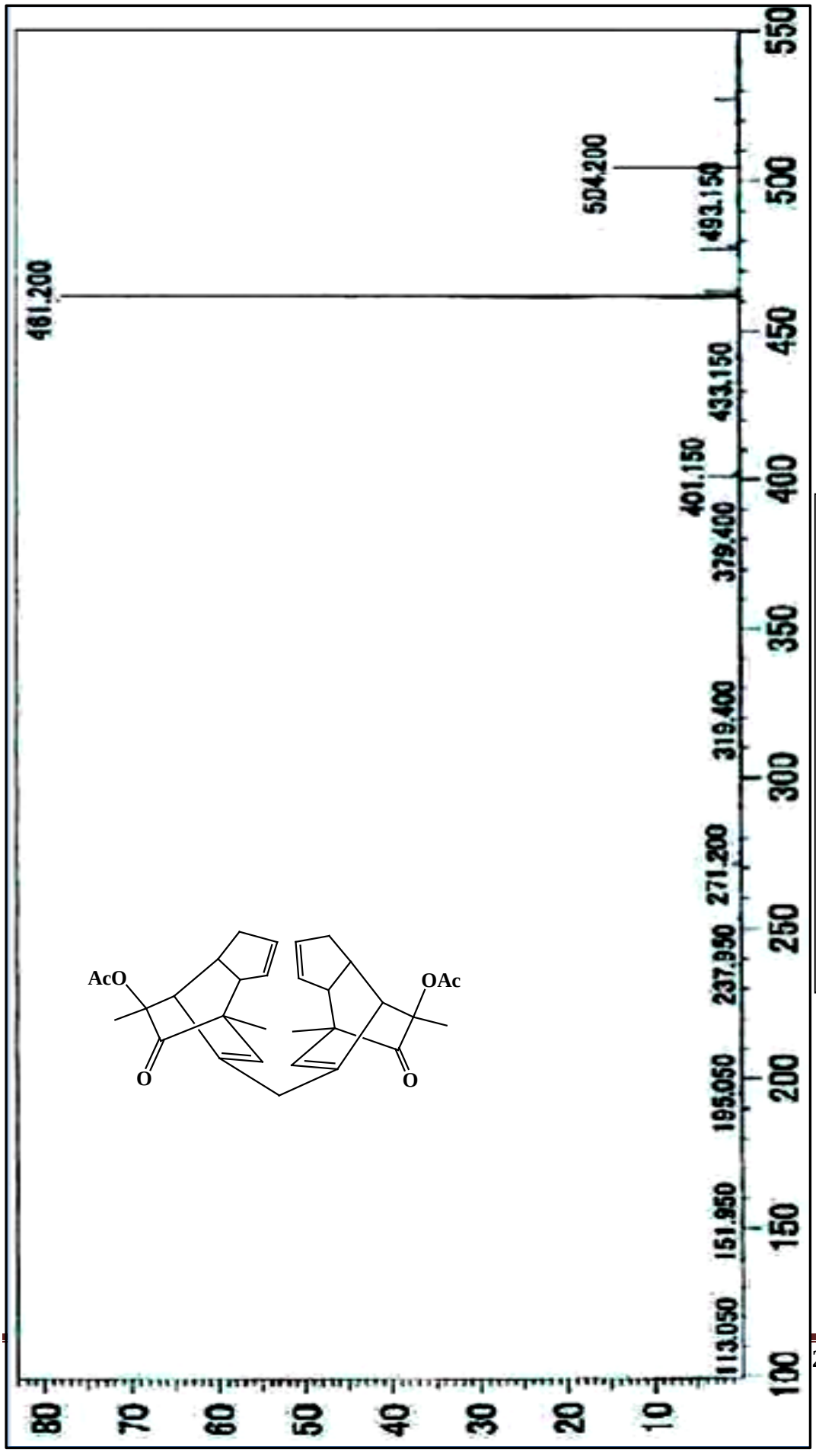


Figure 4.25: HRMS spectrum of compound **60**

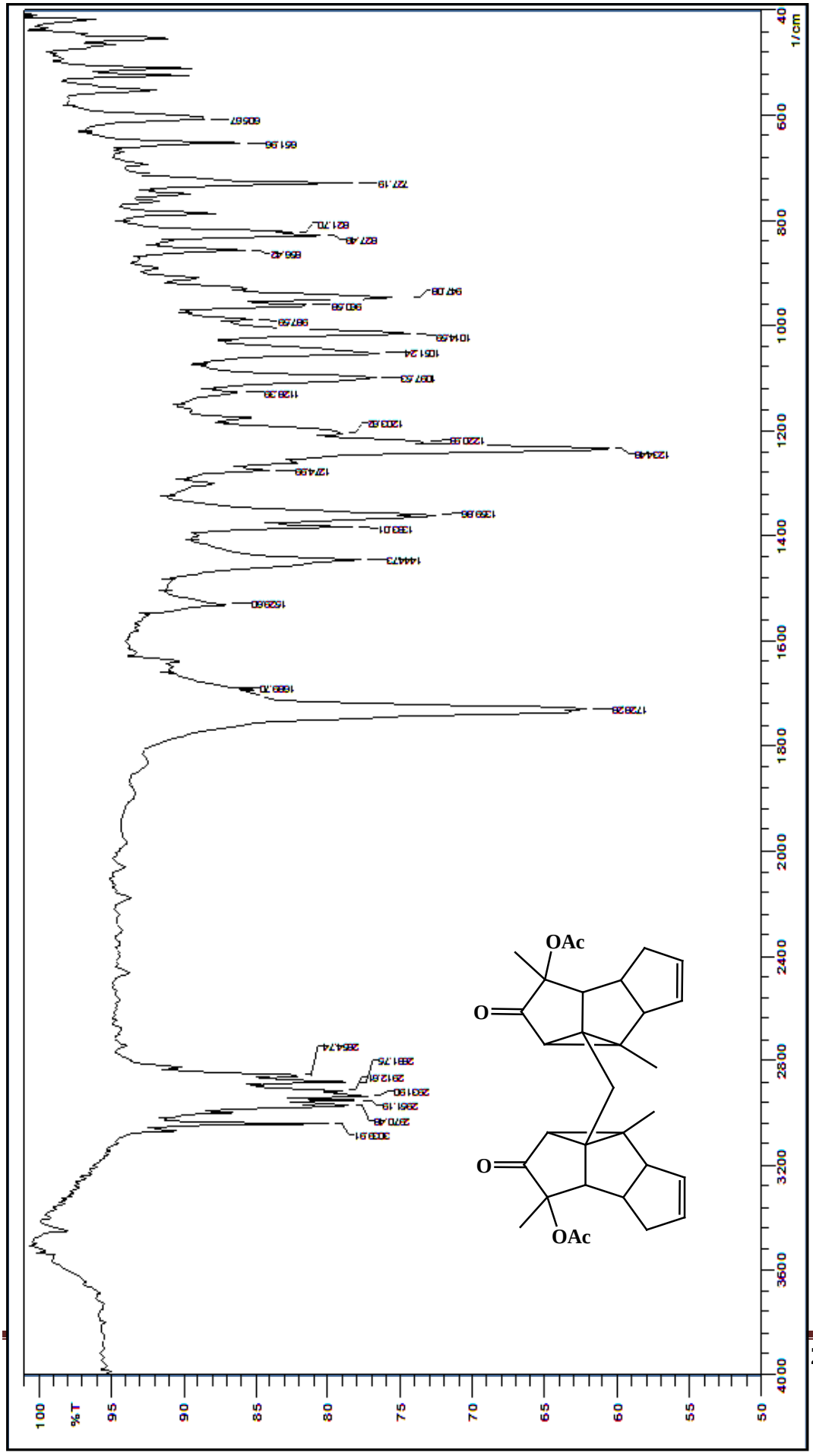


Figure 4.26: FTIR spectrum of compound **61**

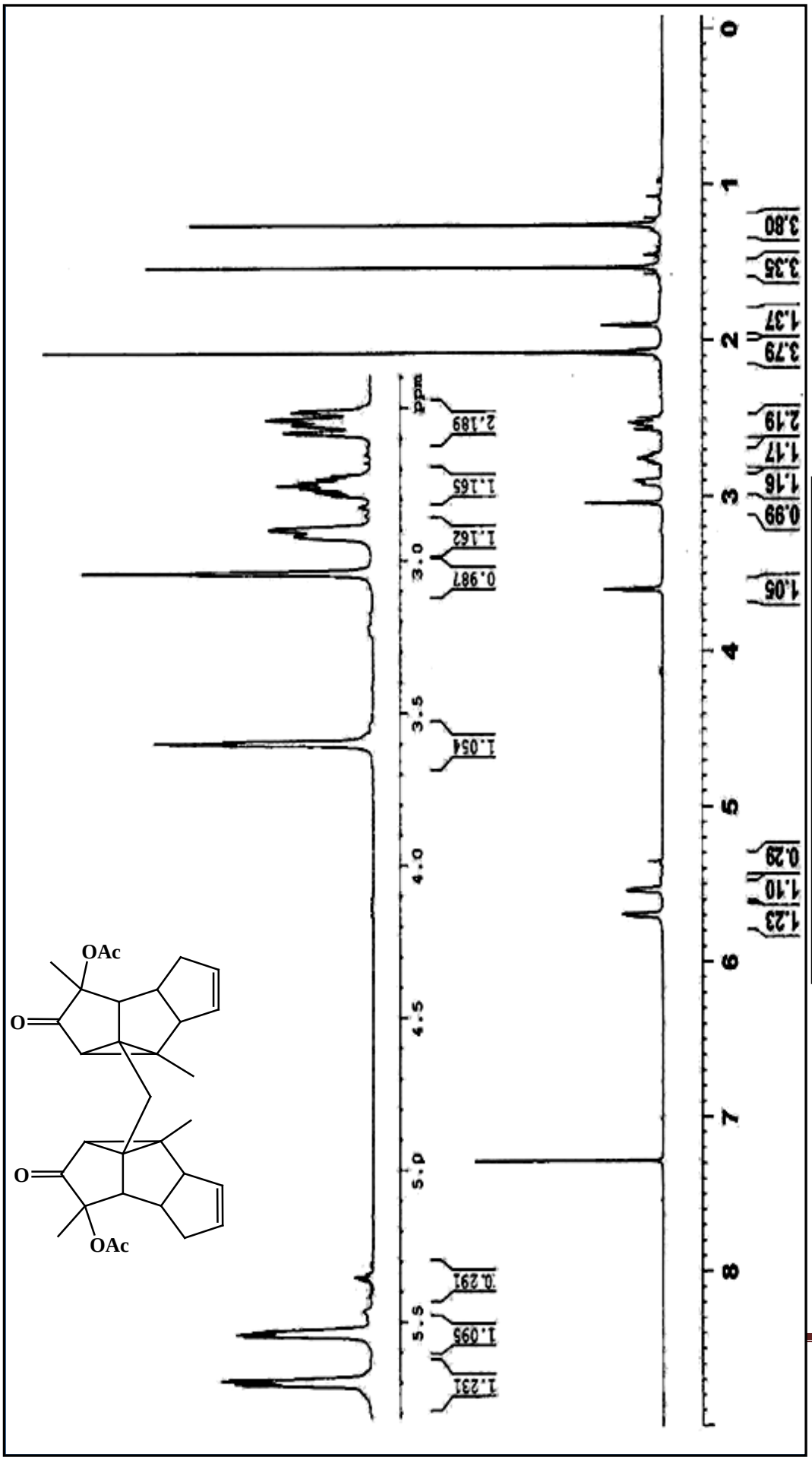


Figure 4.27: ^{1}H NMR spectrum of compound **61**

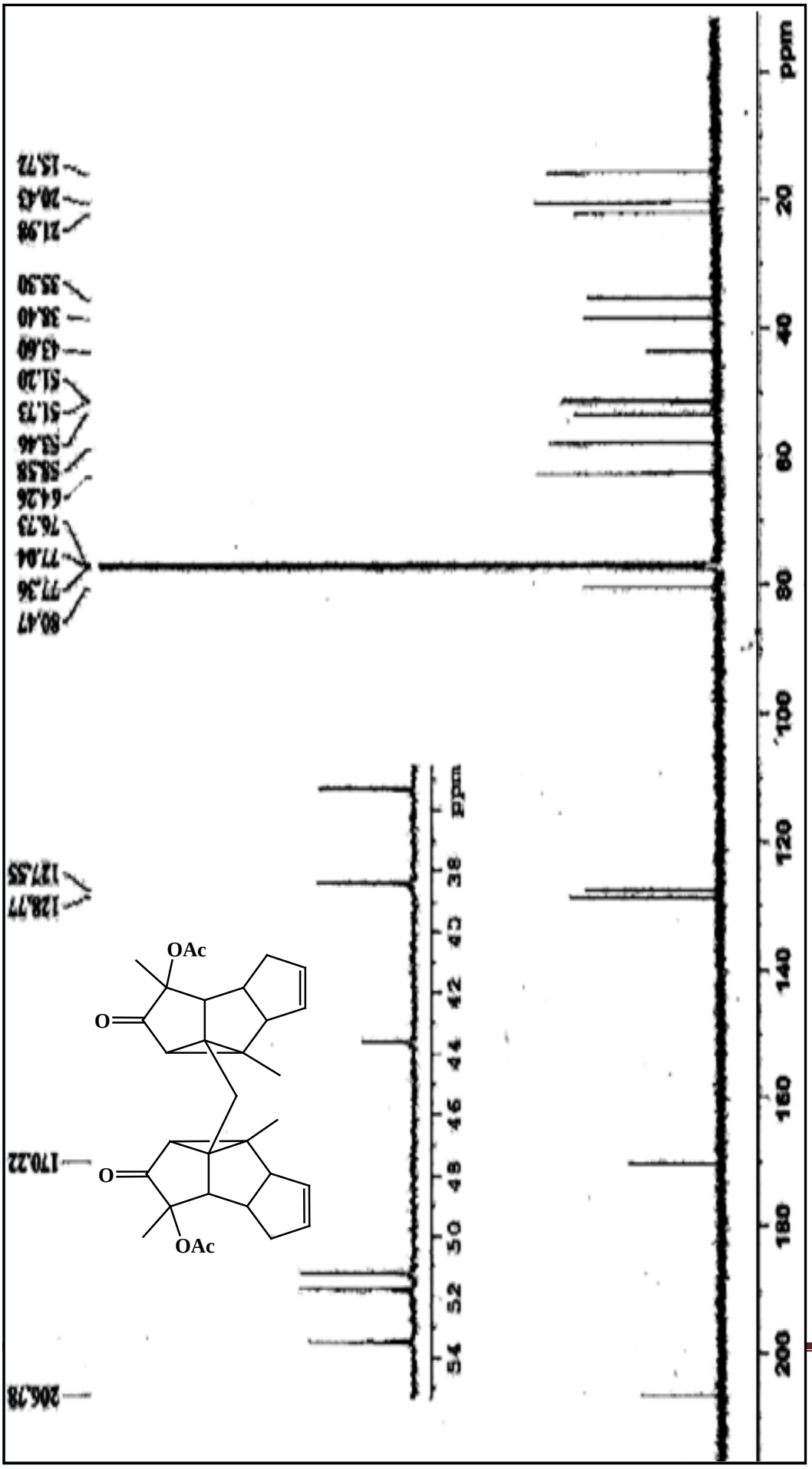


Figure 4.28: ^{13}C NMR spectrum of compound **61**

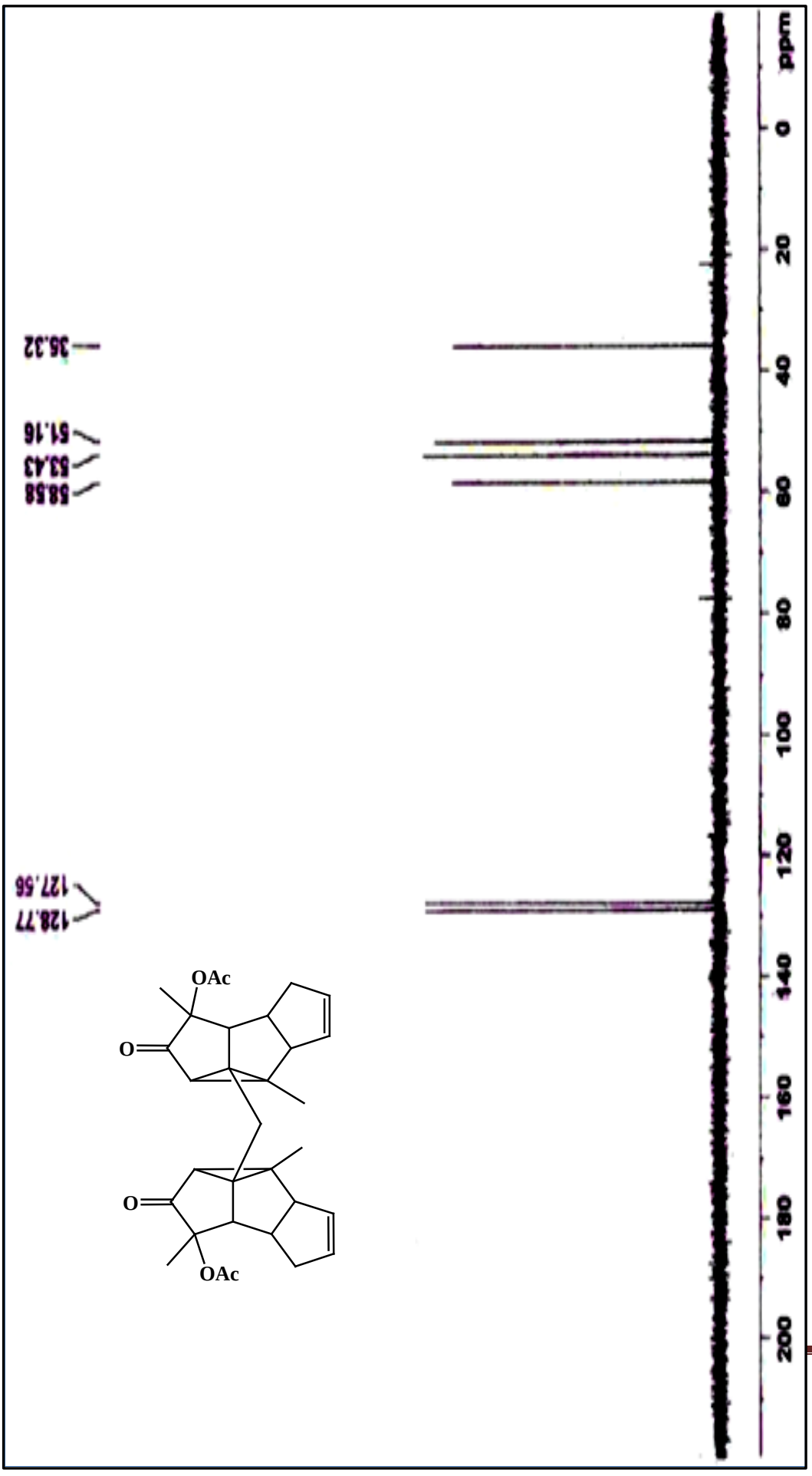


Figure 4.29: DEPT-90 NMR spectrum of compound **61**

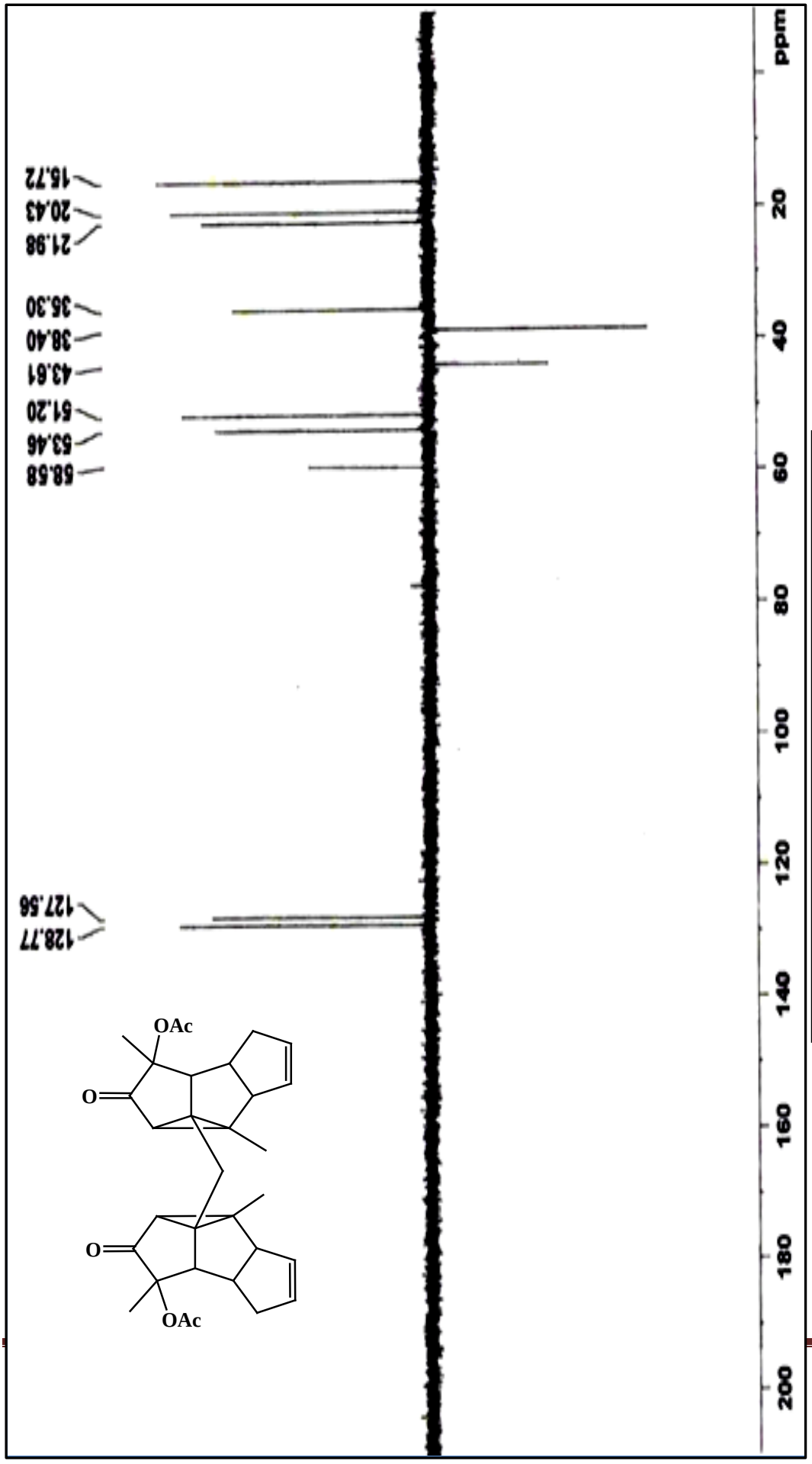


Figure 4.30: DEPT-135 NMR spectrum of compound **61**

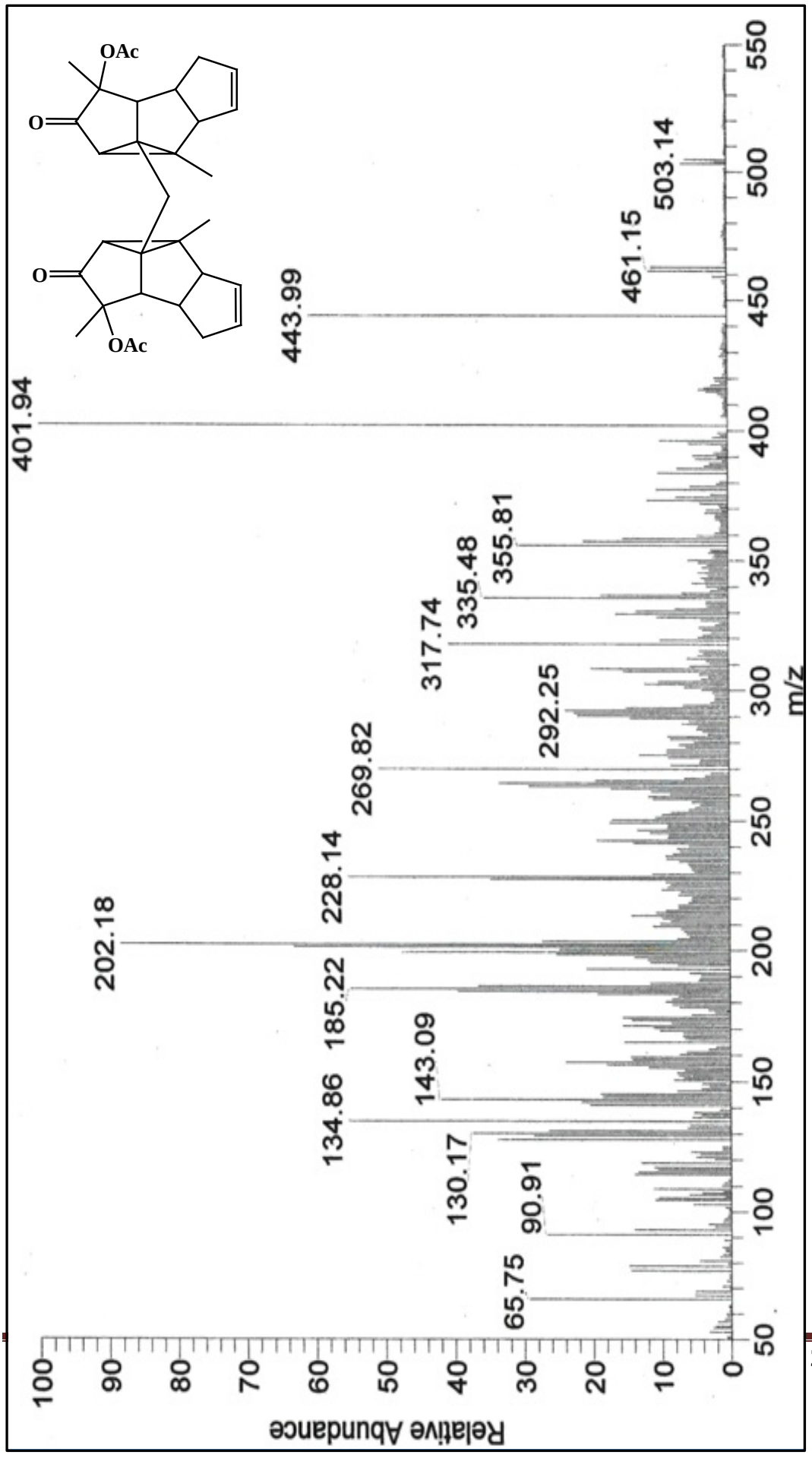


Figure 4.31: EI-MS spectrum of compound **61**

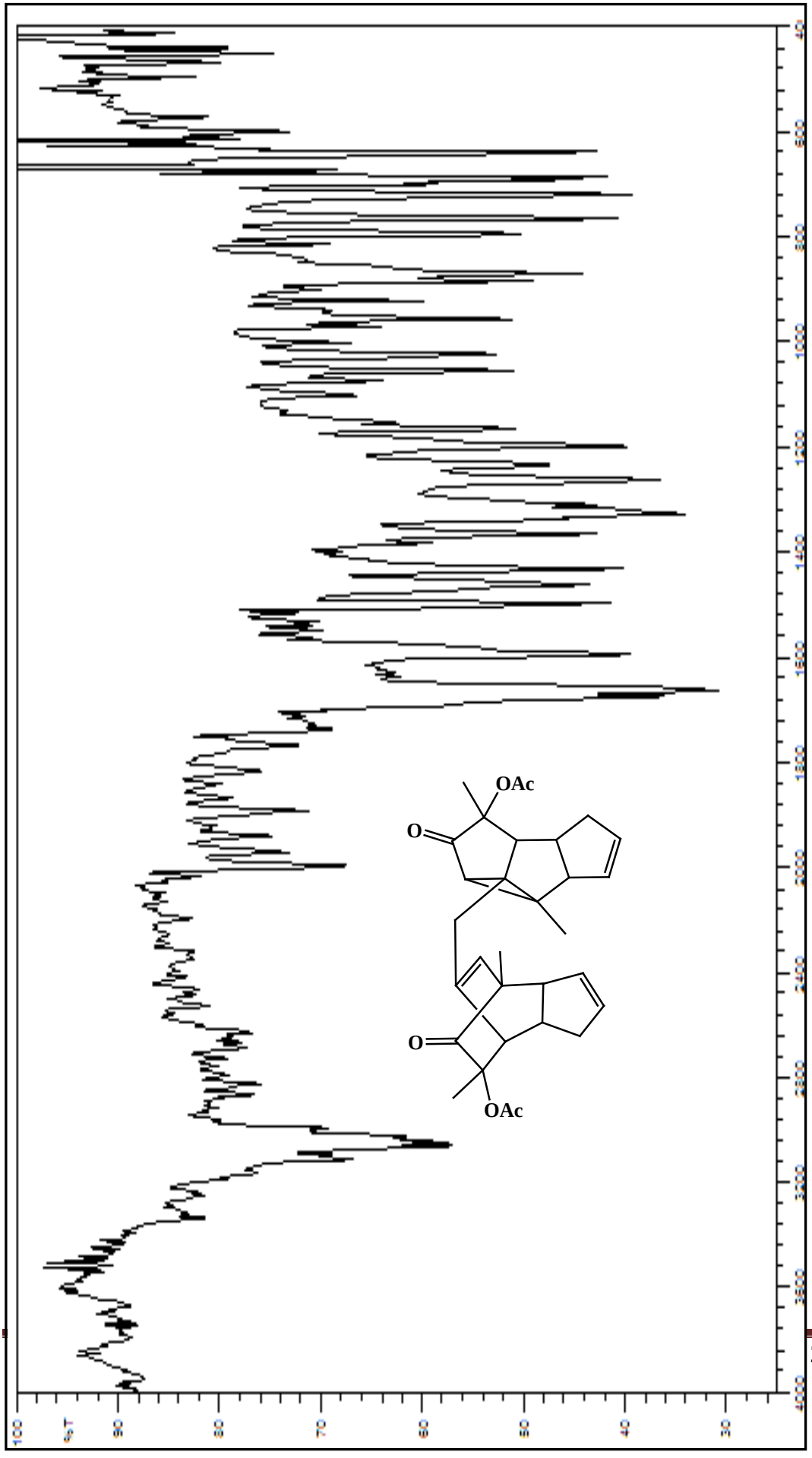


Figure 4.32: FTIR spectrum of compound **88**

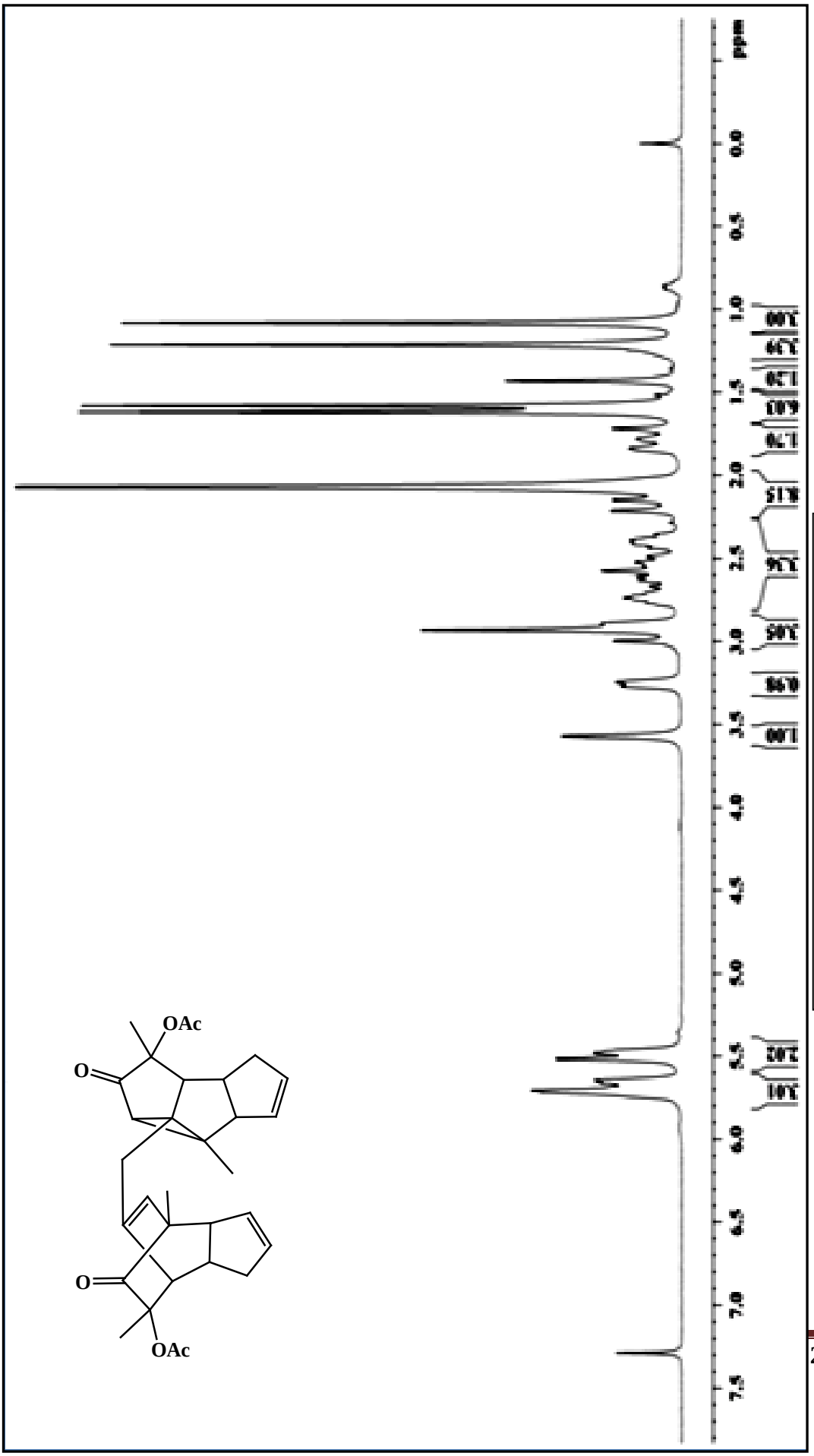


Figure 4.33: ^{1}H NMR spectrum of compound **88**

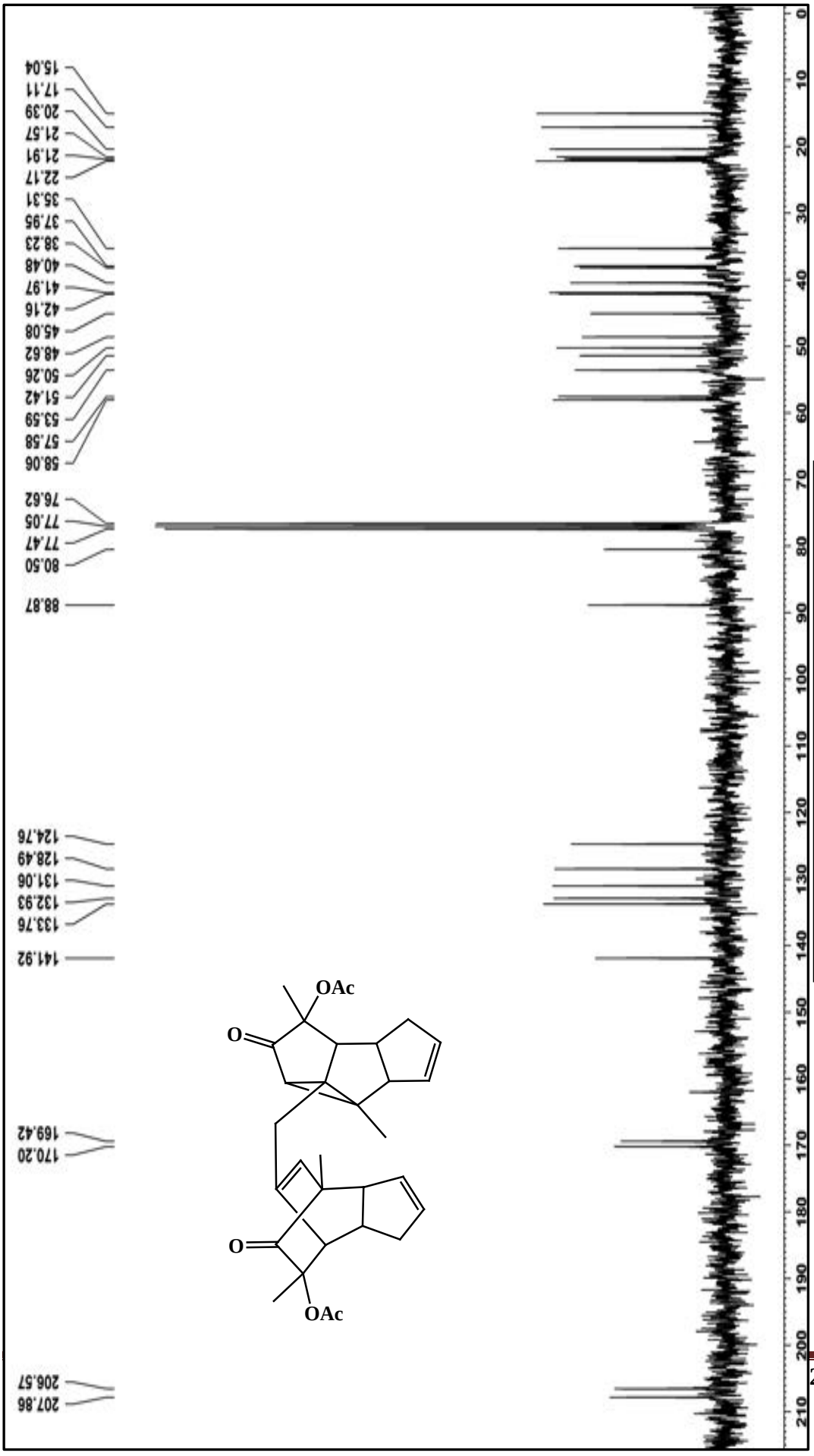


Figure 4.34: ^{13}C NMR spectrum of compound **88**

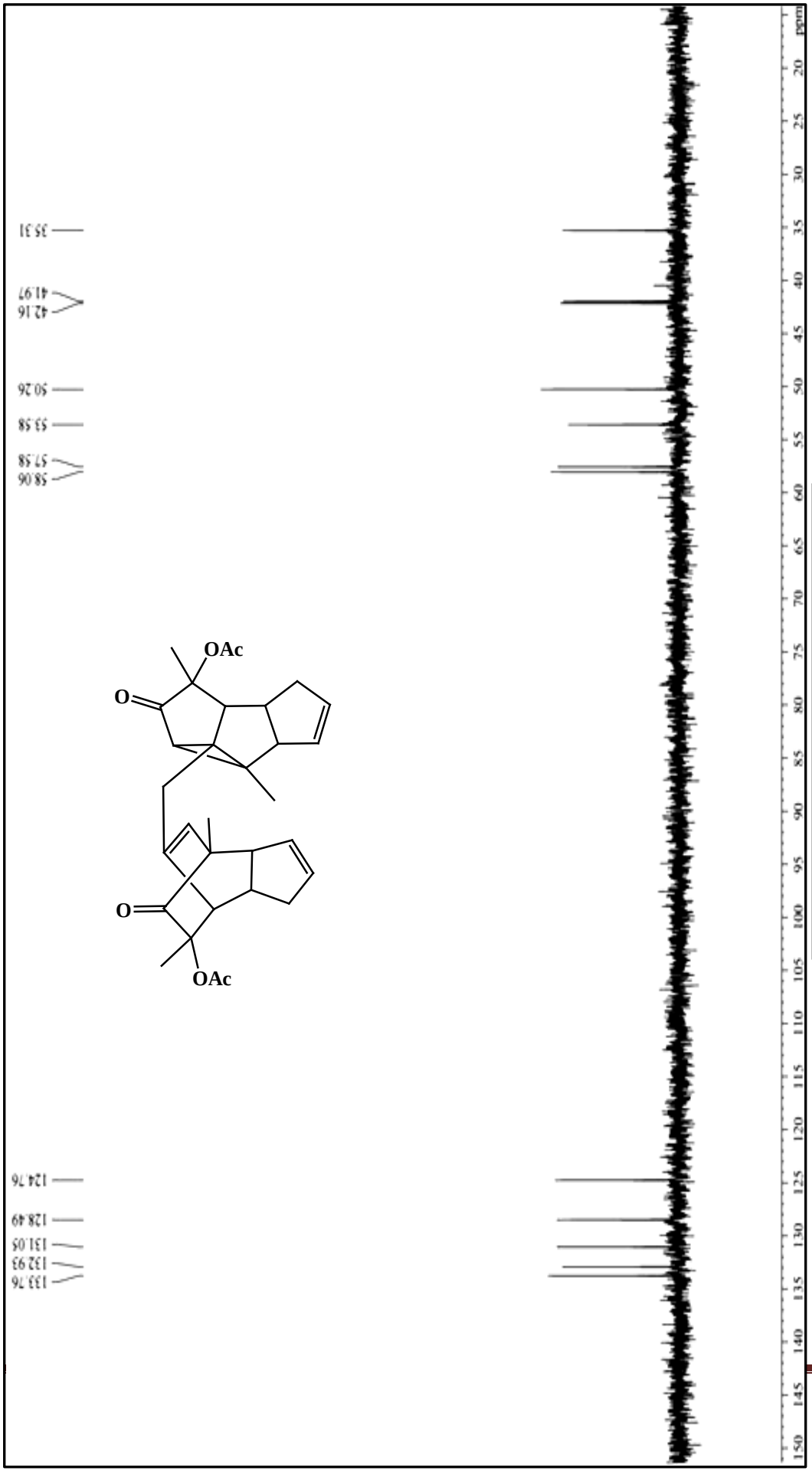


Figure 4.35: DEPT-90 NMR of compound **88**

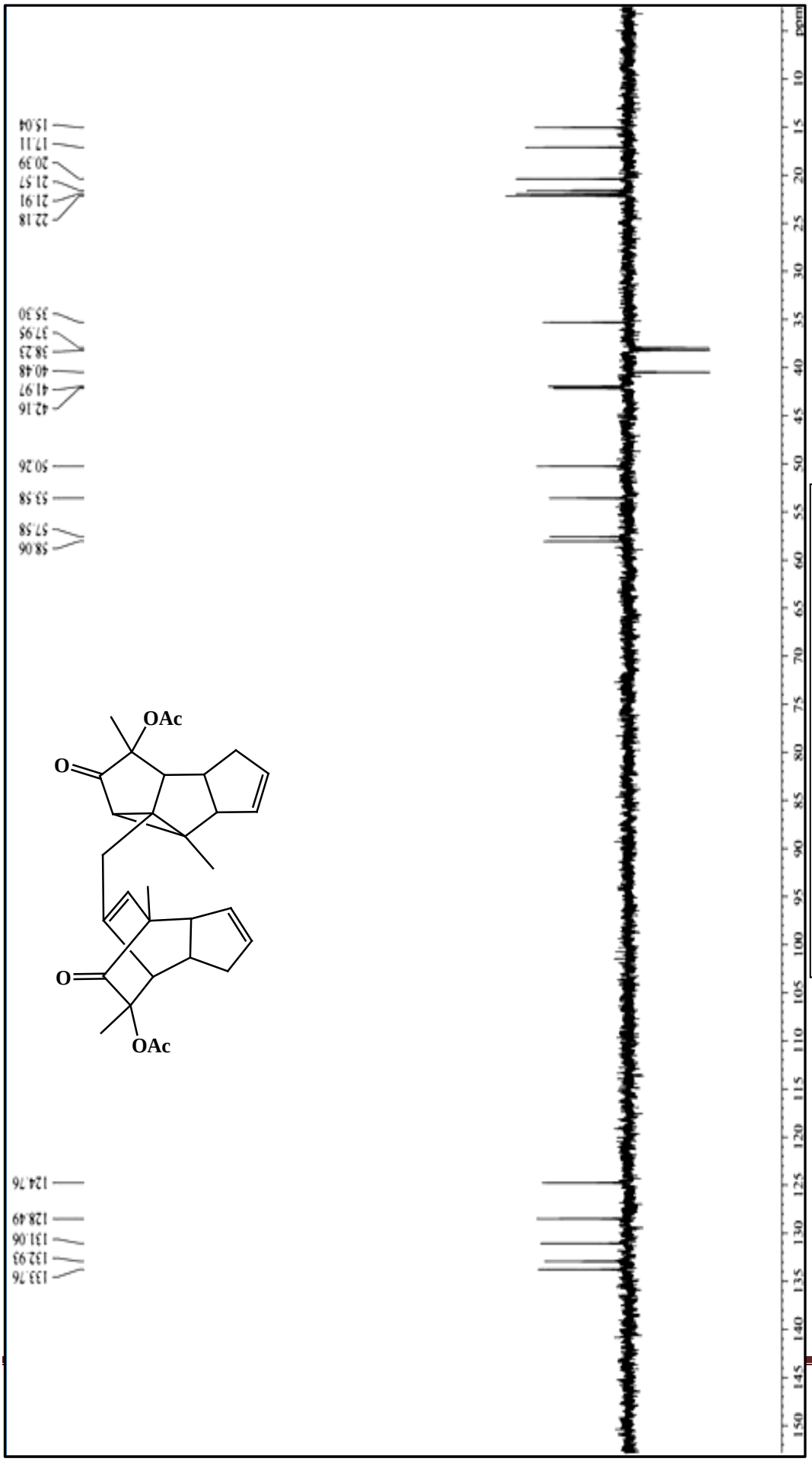


Figure 4.36: DEPT-135 NMR of compound **88**

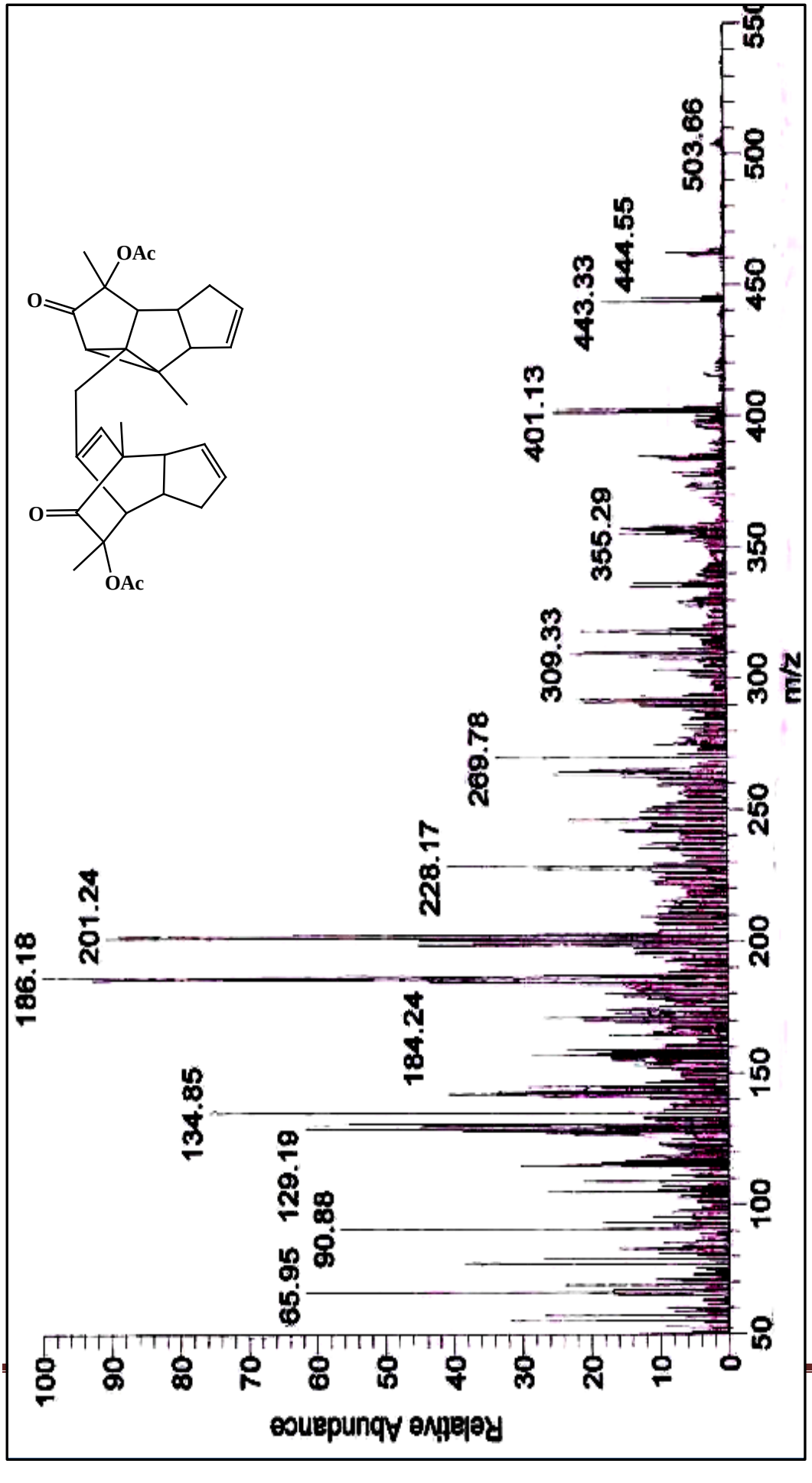


Figure 4.37: EI-MS spectrum of compound **88**

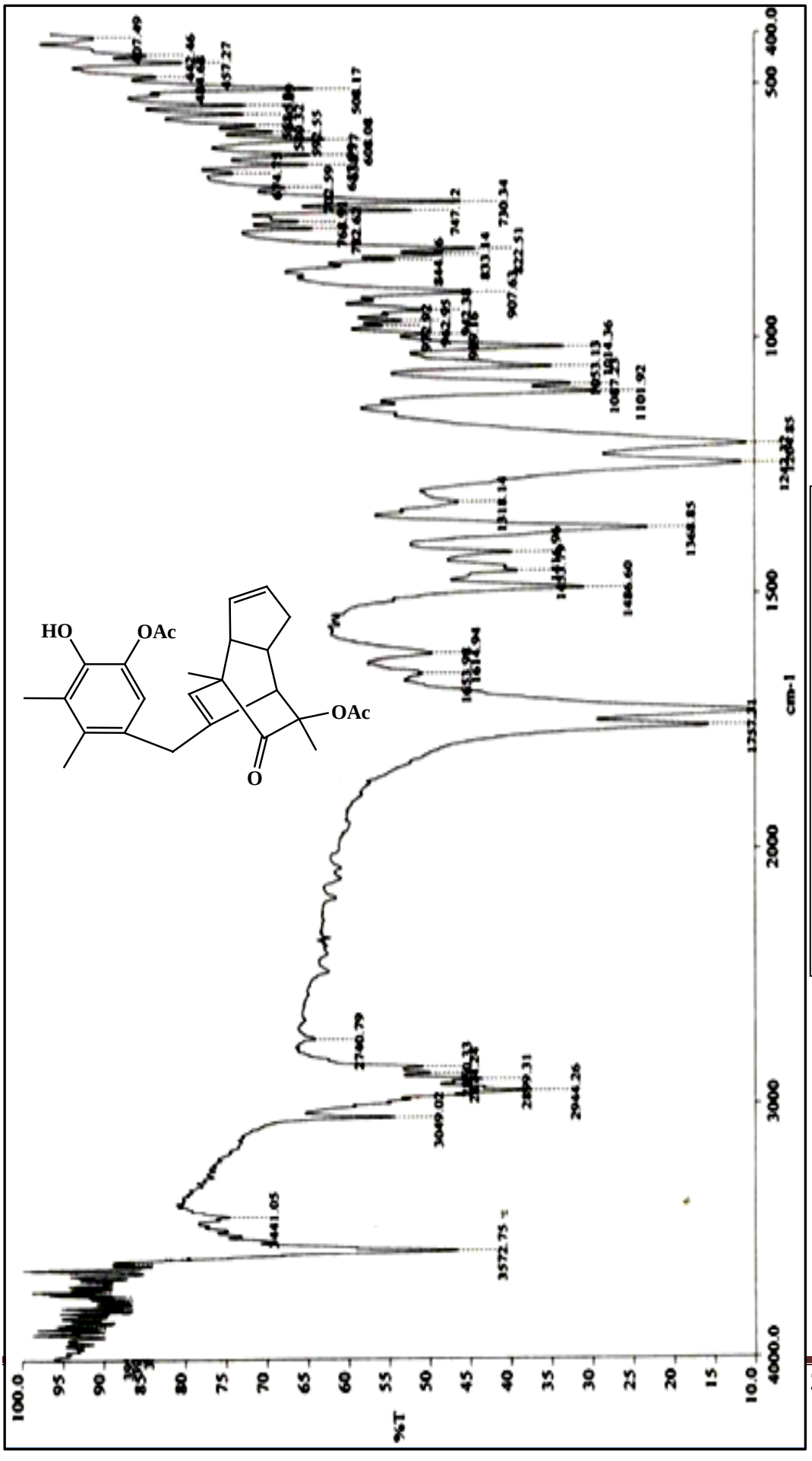


Figure 4.38: FTIR spectrum of compound **90**

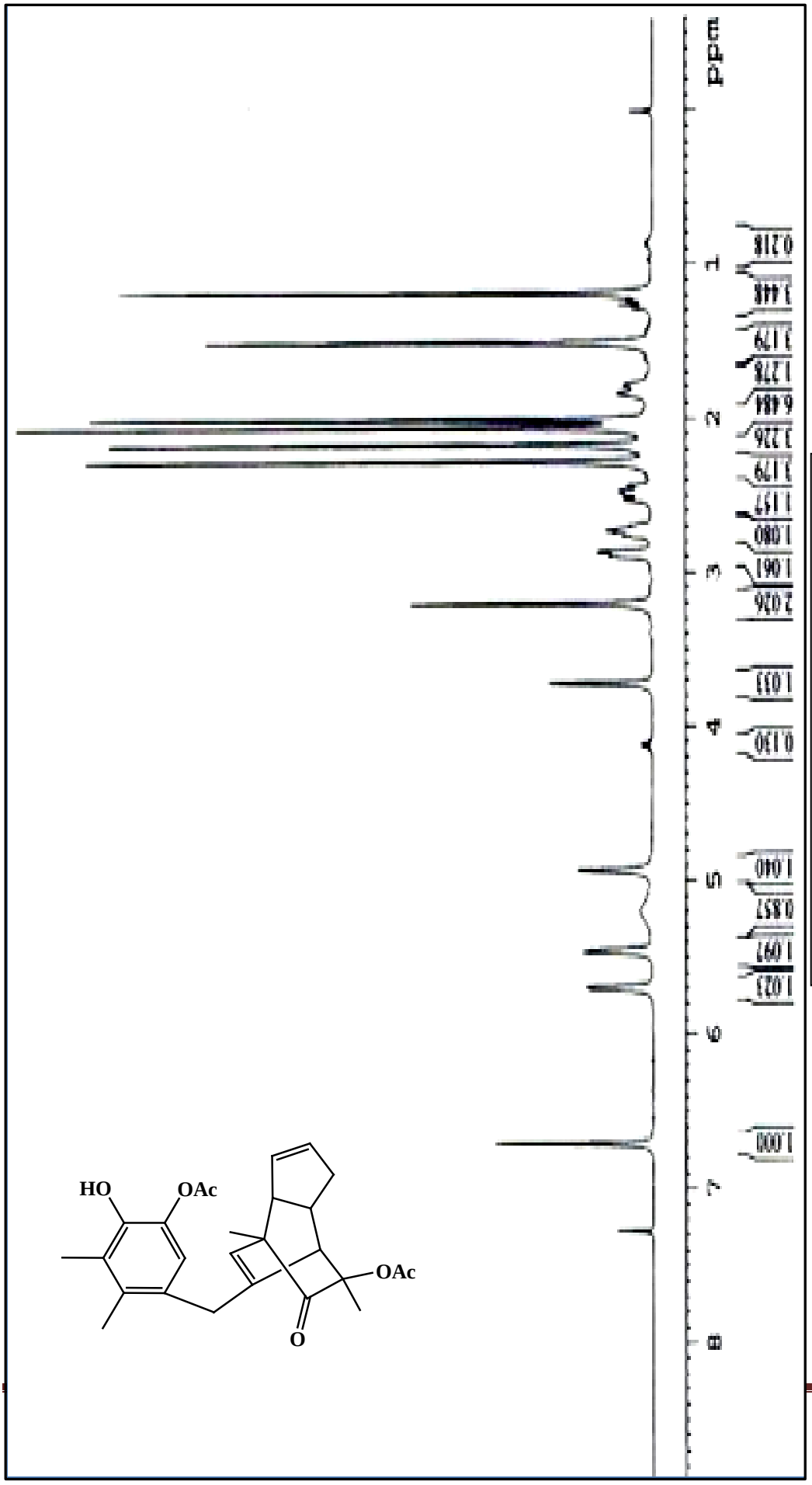


Figure 4.39: ^{1}H NMR spectrum of compound **90**

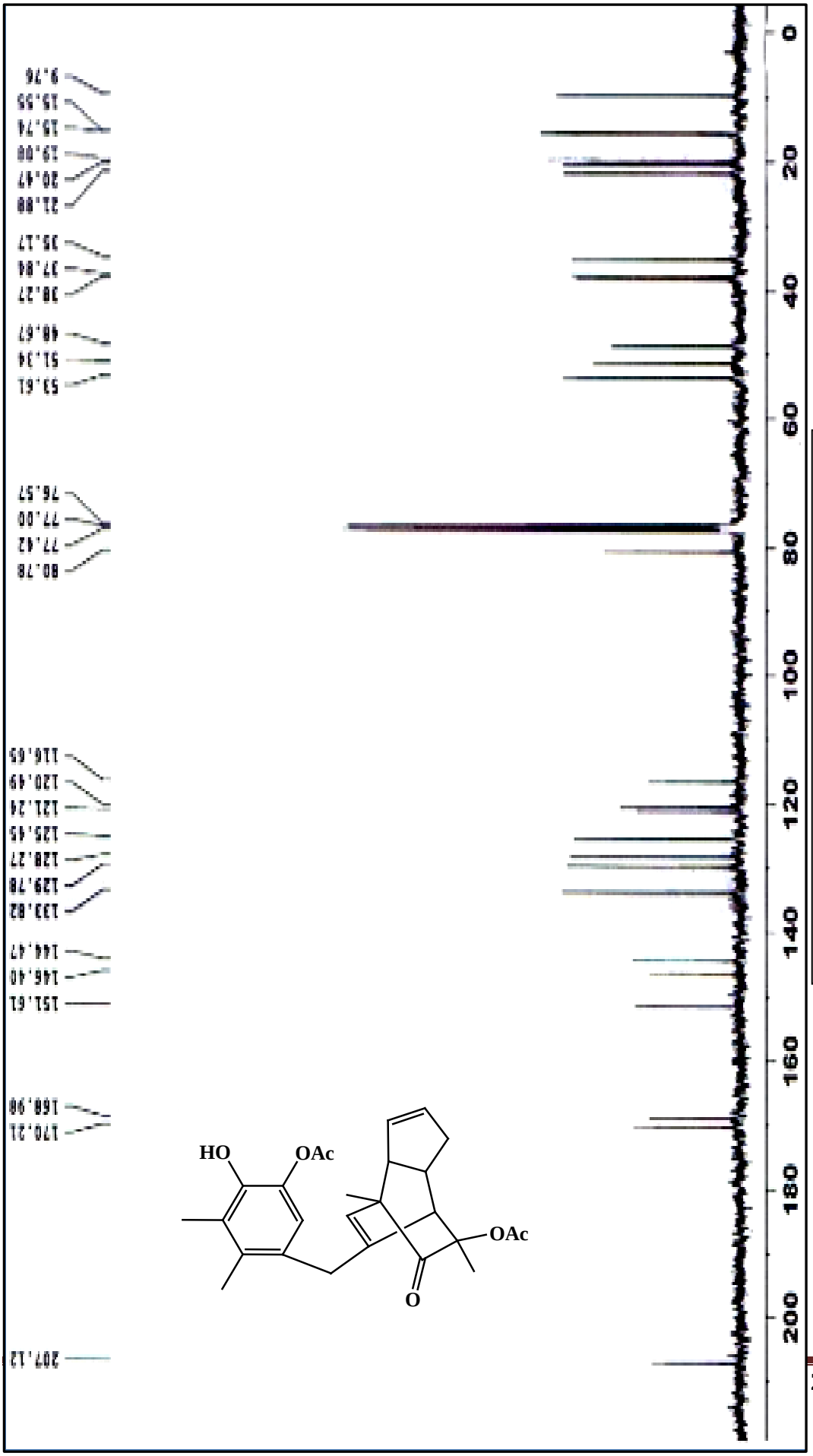


Figure 4.40: ^{13}C NMR spectrum of compound **90**

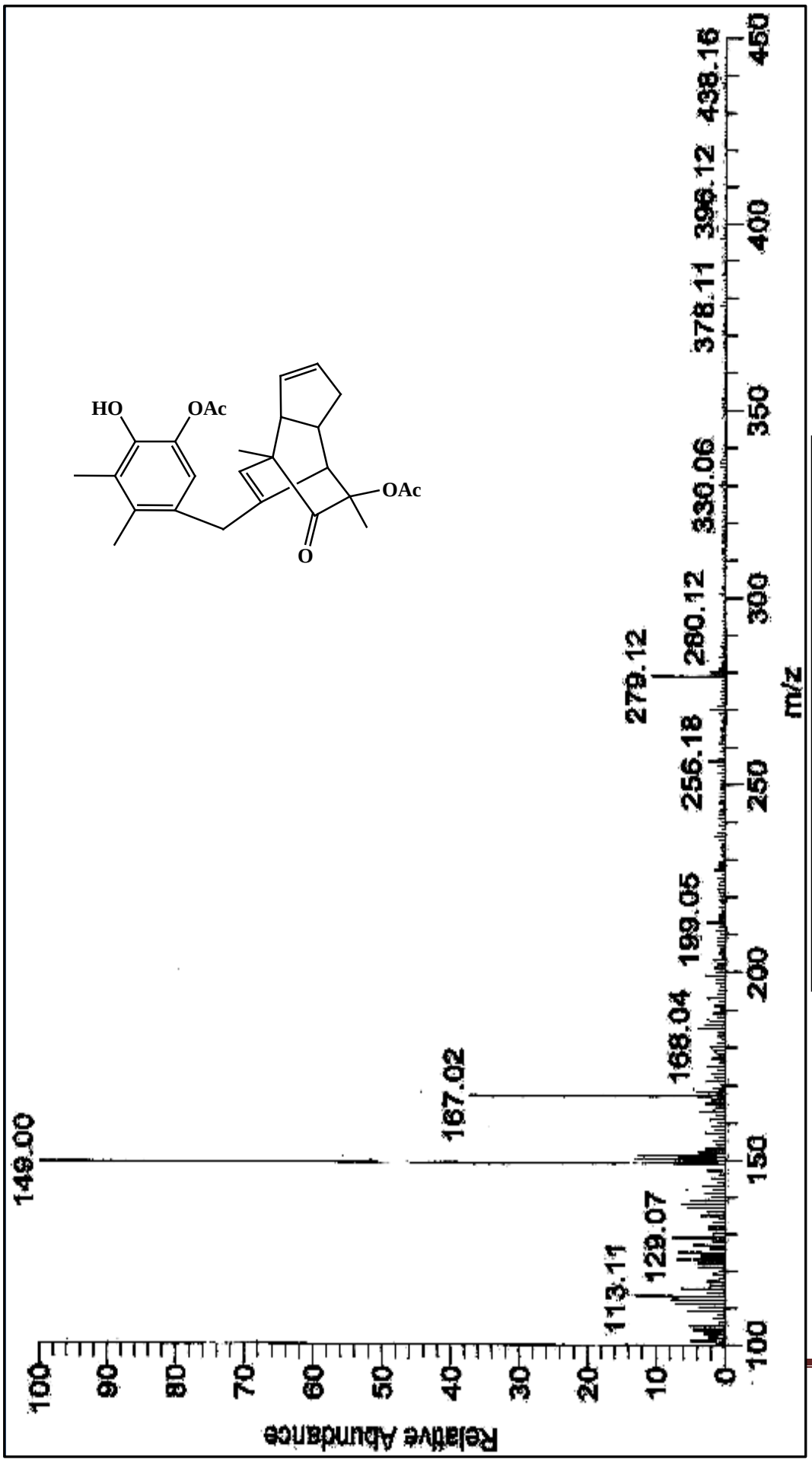


Figure 4.41: EI-MS spectrum of compound **90**

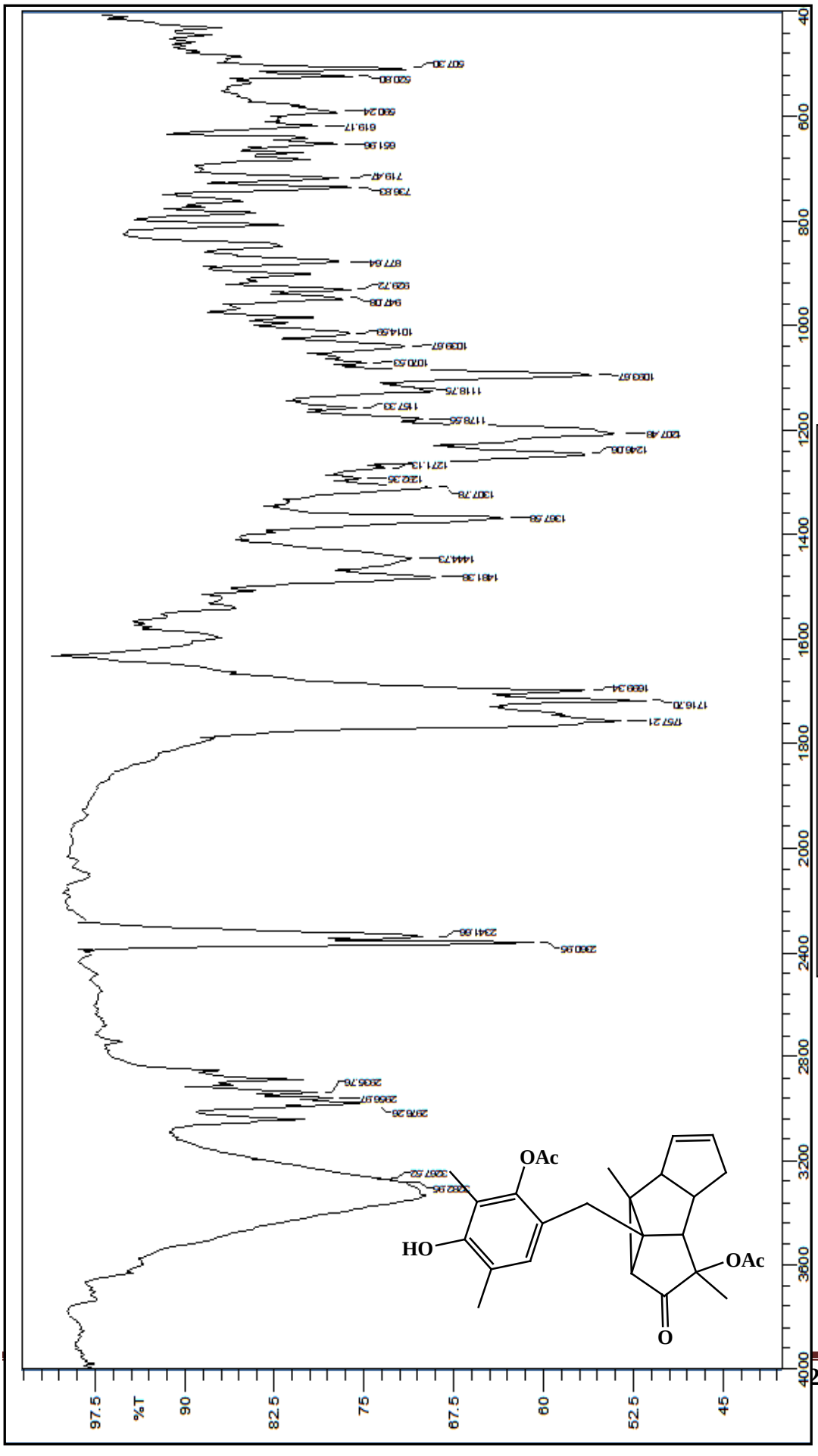


Figure 4.42: FTIR spectrum of compound **91**

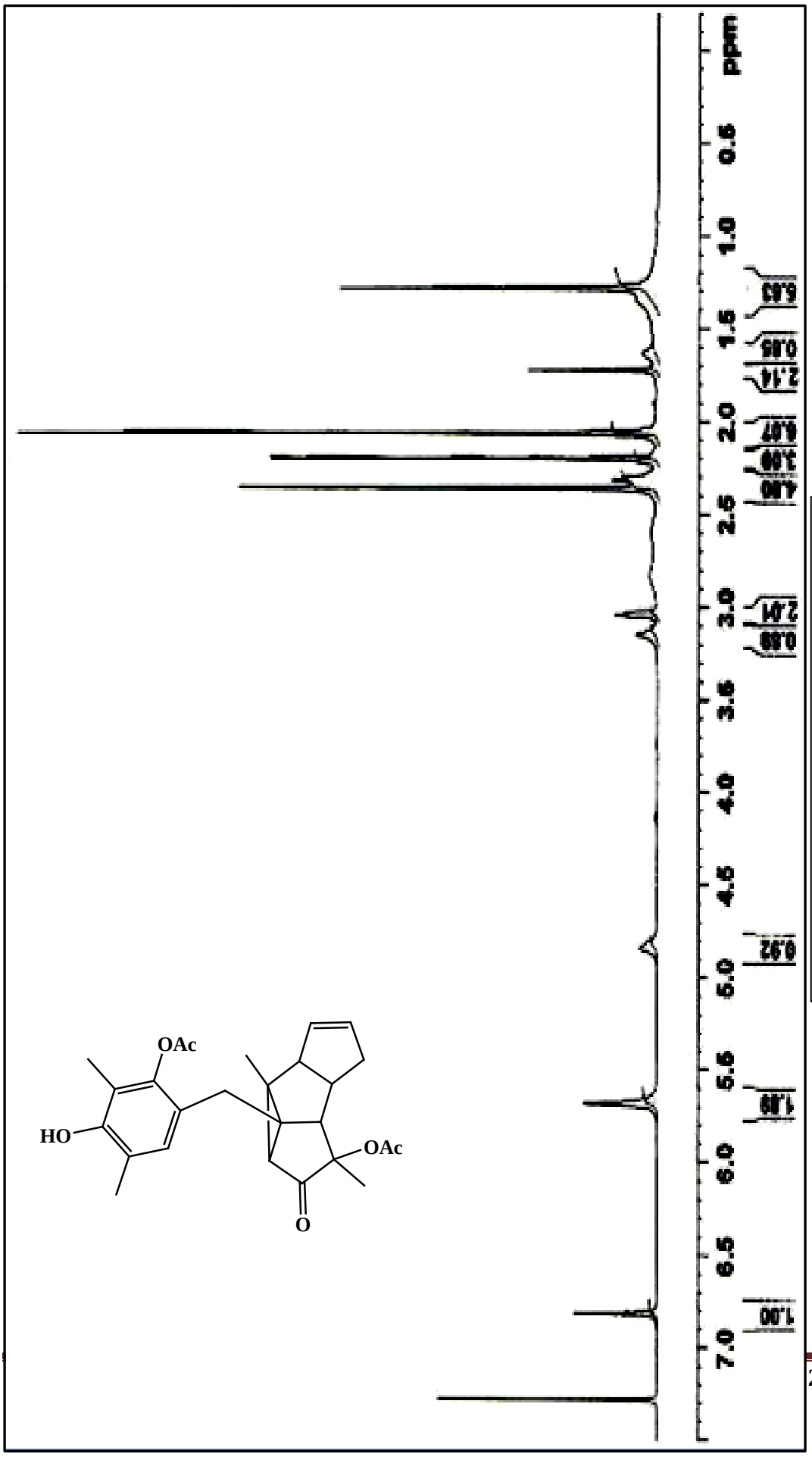


Figure 4.43: ^{1}H NMR spectrum of compound **91**

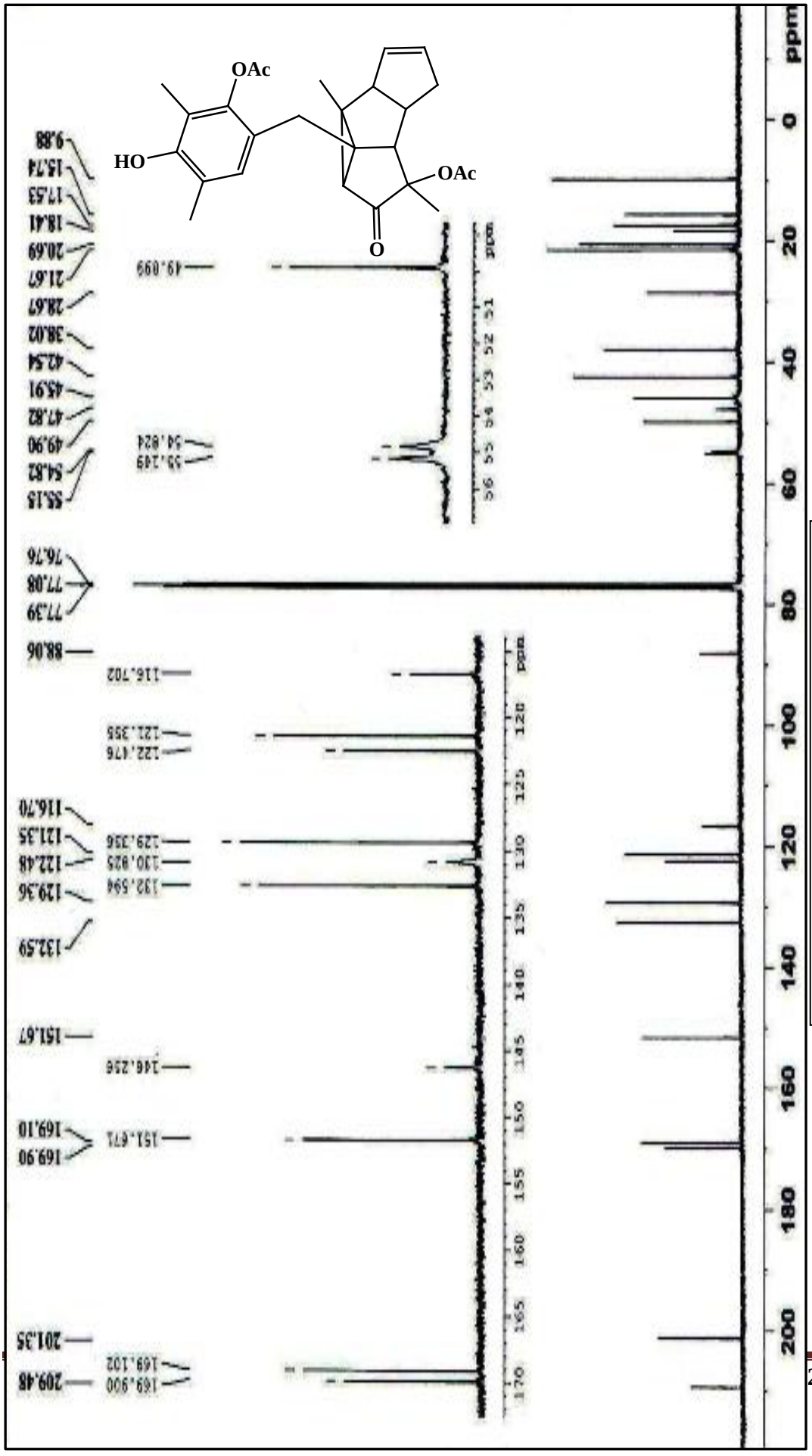


Figure 4.44: ^{13}C NMR spectrum of compound **91**

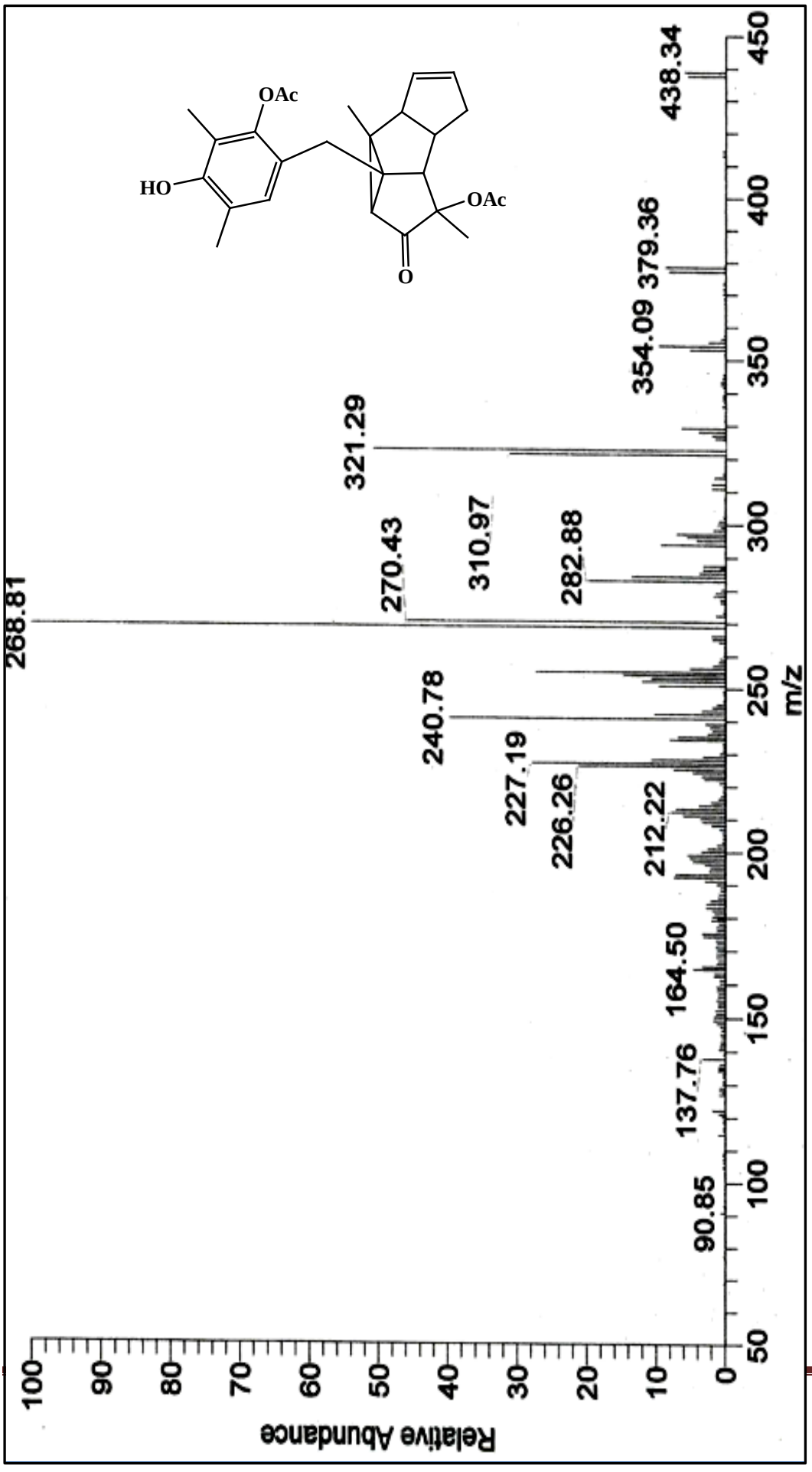


Figure 4.45: EI-MS spectrum of compound **91**

CHAPTER 5

Silica supported perchloric acid as a heterogenous catalyst for synthesis of bisphenols and calix[4]resorcinarene

5.1 Abstract

Preparation of various alkyl substituted bisphenols by condensation of phenols with aldehydes or ketones using silica supported by perchloric acid $HClO_4$- SiO_2 as a heterogeneous catalyst has been described. The use of $HClO_4$-SiO_2 for preparation of calix[4]resorcinarene from resorcinol and aromatic aldehydes is also reported. The catalyst is easily recovered and reused for three cycles without loss of activity. The structures of all the compounds are deduced by analytical and spectral analysis.

5.2 Introduction and objective

The term catalysis was first employed by Berzelius in 1836. He stated that several substances have the ability to exercise a force on other substances and are able to bring a transformation in reactants to give new products without undergoing a chemical change themselves. Such types of substances are called catalysts. The force was termed as catalytic force, and the transformation brought by this force was termed as catalysis.

In 1895, Ostwald applied the principles of thermodynamics to show that a catalyst modifies the rate at which chemical transformation takes place. He stated that catalysis is a kinetic phenomenon and defined catalysts as being the substances that alter the rate of a chemical reaction and remain unchanged during the course of reaction.[1]

Catalysts have been successfully used in the chemical industries for more than 100 years. For example, the production of sulphuric acid by lead chamber process, the conversion of ammonia to nitric acid, the catalytic hydrogenation etc. Later development in this area included new highly selective catalysts, multi component reactions, zeolites and transition metal complexes that are used in chemical industries.[2]

Catalysts play a critical role in the development of chemical industries on more economic and sound footing. It was estimated that around 80% of the existing chemical processes are catalytic and newly developed processes are 90% catalyst based. Besides applications in fine chemicals, catalysts also have extensive applications in pharmaceutical, automobile, petrochemical, food and many other industries. Catalysts not only reduce the cost of production but also improve the quality of products. The suitability of a catalyst for an industrial process depends on properties such as activity, selectivity, stability and environmental compability.[3]

Activity:

The activity of a catalyst is defined as the rate at which the catalyst causes the reaction to proceed. Activity of a catalyst arises due to active sites present on the

surface of the catalyst which induces the catalytic action. The rate of a catalytic reaction depends on the catalytic sites present on the surface of the catalyst and can be increased by increasing surface area of the catalyst. It is believed that the higher the surface area of a catalyst higher will be the activity. It is notable, that only the catalytic surface (active sites) is active during the reaction. However, the nature of the activity of the catalyst differs under different reaction conditions. Hence it is important to distinguish the active behaviour of a catalyst under different reaction conditions.

Selectivity:

It is the efficiency with which a catalyst causes the reaction to proceed in the direction to give a desire product. A chemical reaction leads to the formation of several feasible products. A catalyst facilitates the formation of a desire product, while inhibiting the formation of other molecules. The efficiency of the catalyst causes the reaction to proceed in the direction of the desired product.

Stability:

A catalyst alters the reaction rate, without being consumed in the process. Since it was not consumed in the process, each catalyst molecule participated in many consecutive cycles and a small amount of catalyst is required relative to the substrate for the completion of reaction. The catalyst can be recovered and reused consecutive times for further reactions. The catalyst loses its stability by poisoning, fouling and thermal degradation and attrition. The deactivation of a catalyst can be observed by measuring its activity or selectivity as a function of time. Catalyst that loses their activity during the process can be regenerated before they ultimately have to be replaced. The stability of a catalyst determines the life time of reactors.

Environmental compatibility:

The catalytic processes should produce zero or minimum emission of waste products that do not pollute the environment. It is focused towards development of non-toxic, eco-friendly, recyclable catalysts which give high selectivity of desire products. To achieve these challenges the industry requires the development of simple, efficient and innovative catalytic technologies that offer high yield and improved selectivity as well as low solvent requirements.

Present Trends in catalyst:

In past few years, there has been an increasing concern for pollution prevention and the approach to solve these problems by development of processes and technologies that produce minimum or zero waste. This new approach is known as Green Chemistry. It involves the synthesis, processing and use of chemicals so as to reduce the potential risk for human health and environment. This new approach is also familiar by the names of environmentally benign chemistry and clean chemistry. Today green chemistry is a frontier area of research and is receiving considerable attention.

Green chemistry and catalysis:

Green chemistry is critical need in the present era of globalization and rapid industrialization. The world has come to face the hard realities of environmental degradation caused by the unscrupulous measures of targeting maximum industrial production and ignoring the consequence of environmental hazards. Green chemistry holds the key to the future survival of humanity and plants. The specific purpose of green chemistry is to devise methods, strategies and processes that minimise the risks to the environment and human health. This provides the best opportunity for chemists, manufactures and processers to use chemicals safely and to carry out their work under safe conditions. The main focus of green chemistry is to increase production efficiency and at the same time, eliminate or minimize the waste.

Catalysts play an important role to achieve the goals of green chemistry. The catalysts such as asymmetric catalysis, bio catalysis, heterogeneous catalysis, phase transfer catalysis, enzyme catalysis and solid acid catalysis are few examples that have a direct and significant impact on accomplishing the goals of green chemistry. Amongst the various catalytic systems used, the solid acid catalysts have attracted great attention due to their special surface structure or active sites which provide a pathway to perform better. The activity and selectivity of a reagent dispersed on the surface of a support are improved as the effective surface area of a reagent is increased. As a result, they are expected to be performed better than the individual reagents.

Solid acid catalyst –An alternative Approach to liquid acid catalyst:

The liquid acids such as H_2SO_4, HF, and H_3PO_4 have been extensively used as homogenous catalysts in the variety of organic transformations. These liquid acid catalysts are potential environmentally hazardous chemicals and become a major area of concern due to operational difficulties such as toxicity, corrosiveness, effluent disposal, product separation, storage and handling. The recovery and reusability of these catalysts is also difficult. Owing to increased environmental awareness and a quest for zero emission technologies, much attention has been given to developing alternatives to these existing catalysts. The solid acids are the safe and more convenient alternatives to liquid acid catalysts that are used in synthetic organic chemistry in petroleum industries, fine chemicals syntheses, pharmaceuticals etc.[4]

Advantages of solid acid catalyst:

The solid acid catalysts are very effective and some of them are known to exceed the acidity of mineral acids. They also hold their acidity internally and are thus easy to handle and do not corrode the reaction vessels or reactors. They can allay concern about safety and environmentally hazardous emission as they are non toxic and non volatile. Being heterogeneous in nature separation from reaction mixture is easy and the catalyst can be regenerated and reused. The disposal of used solid acid is less problematic as compared to the disposal of liquid acids that requires much money and efforts towards treatment and effluent neutralisation.

Therefore in the last few years, solid supported reagents have gained worldwide attention as unique acid catalysts.[5] The efficiency of a reagent dispersed on the surface of the support is improved, as the effective surface area (active sites) of the reagents is increased. Solvent-free clean synthetic technology, safety, high yields, low toxicity, recyclability, moisture resistance, air tolerance and inexpensive nature are other common features that make the use of solid supported reagents as attractive alternatives to conventional acids.[7]

Among all mineral acids, perchloric acid finds significant applications in acid-catalysed various organic transformations such as esterification, cationic polymerisation, isomerisation and rearrangements. Perchloric acid is a colourless, odourless, oily and one of the strongest and most corrosive mineral acid that is very

hygroscopic. It is an explosive compound, when heated and on contact with combustible materials.[8]

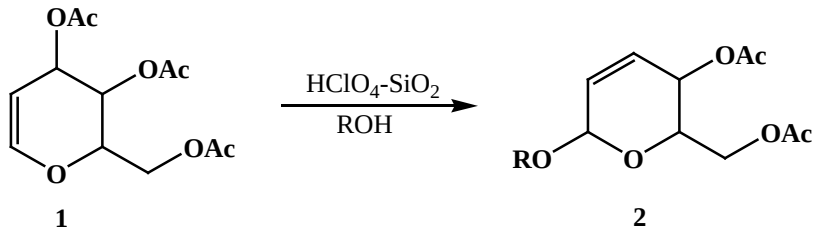
The application of perchloric acid has been found to be more useful synthetically when its intrinsic hazardousness is reduced by adsorbing it on silica gel.[8] $HClO_4$-SiO_2 being a heterogeneous catalyst has received considerable attention as an inexpensive, non-toxic, recyclable, affording the corresponding products in excellent yields with high selectivity in variety of organic transformations.

Protection and deprotection reaction:[9]

In building complex molecules, a great obstacle is the presence of many functional groups that are either highly reactive or stubbornly inert. Therefore during multistep syntheses of the natural products the synthetic protocol depends largely on protection and deprotection reactions. Esterification and trans esterification are very important reactions in synthetic organic chemistry for the synthesis of drugs and pharmaceuticals. Esters also act as protecting group for both alcohols and acids. $HClO_4$-SiO_2 is used for protection of phenols, thiols, alcohols and amines by acylation with acetic anhydrides using solvent free condition.[9a] $HClO_4$-SiO_2 is also found to be a heterogeneous catalyst for the synthesis of acylals from aldehydes, β-keto enol esters from ketones under very mild condition.[9b]

Application in carbohydrate chemistry:[10]

2,3-unsaturared-*O*-glycosides obtained by Ferrier rearrangement are useful intermediates in syntheses of biologically active compounds such as glycopeptides building blocks, oligosaccharides etc. $HClO_4$-SiO_2 is the most widely and recently used catalyst for performing Ferrier rearrangement. There are several advantages to using this catalyst such as high yield, simplicity of operation, cleaner reaction profiles, short reaction time, no stringent condition and no need for special precaution.[10] (**Scheme 5.1**)

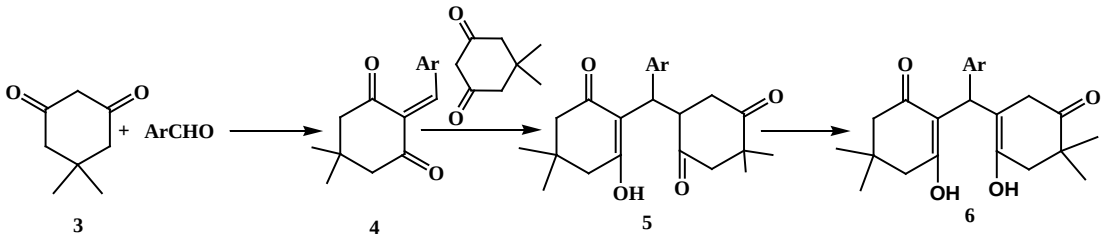


1 **2**

Scheme 5.1: Synthesis of 2,3-unsaturated –o-glucosides by ferrier rearrangement.

Conjugate addition:[11]

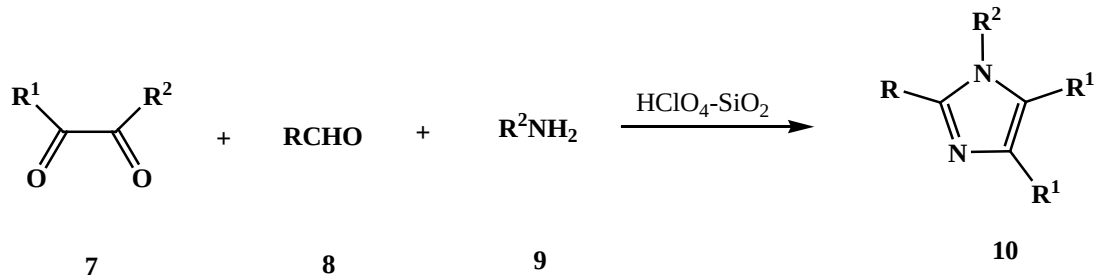
Conjugate reaction of nucleophiles to α,β-unsaturated carbonyl compounds are acid catalysed reaction. One pot Knoevenagel condensation, Michal addition and cyclodehydration can be catalysed by Perchloric-silica in acetonitrile, water and solvent-free condition with better yields (Scheme 2).[11a] The addition of thiols to α,β-carbonyls thia-Michal is a very important reaction in carbon-sulphur bond formation. Among catalysts exploited for this reaction $HClO_4$-SiO_2 is efficient and valuable for addition to α,β-unsaturated ketones, carboxylic esters, nitriles and amides.[11b] (**Scheme 5.2**)



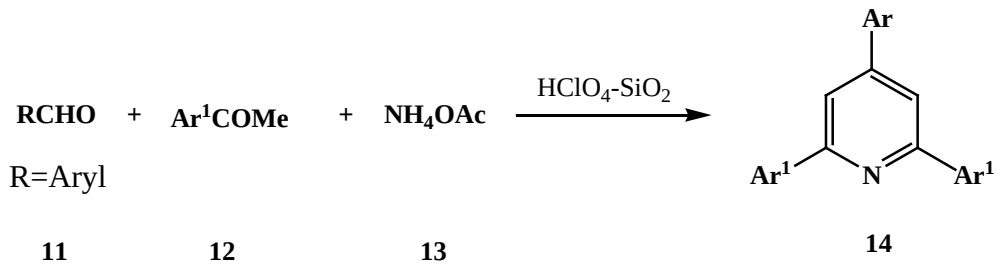
Scheme 5.2: Knoevenagel condensation and Michal addition

Ring synthesis:[12]

Imidazole ring is the core molecule in many biological systems such as histidine, histamine and biotin. Among the various synthetic routes towards synthesis of imidazoles, an interesting synthesis involves a multicomponent reaction catalysed by $HClO_4$-SiO_2 (Scheme 3).[12a] The pyridine derivative can also be synthesised by a three component reaction of aldehydes, ammonium acetate and acetophenone catalysed by Perchloric acid supported on Silica gel as an efficient catalyst (**Scheme 5.3, 5.4**).[12b]



Scheme 5.3: Preparation of five membered imidazole ring **10**



Scheme 5.4: Preparation of six membered pyridine derivative **14**

Further application of $HClO_4$-SiO_2 is in the N-t-butoxycarbonylation of amines, tetrahydropyranylation, synthesis of amidoalkyl naphthols, cleavage of ketals and benzylidene acetals, Hantzsch condensation, β-aminoketones, homoallylic amines, poly-substituted quinolines, coumarins, synthesis of enaminones and enamino esters etc.[13]

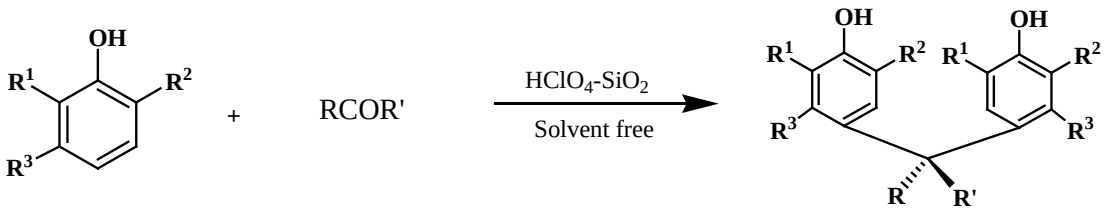
Bisphenols are a group of chemicals with two hydroxyl phenyl functionalities. It is a colourless solid and soluble in organic solvents but less soluble in water. Bisphenols both from natural and unnatural origin represent an important family of antioxidants.[14] Having two phenol functional groups these are used as important industrial chemicals for the production of polycarbonate plastic and epoxy resins, in which polycarbonate is used in eyeglass lenses, medical equipments, digital media, cell phones, electrical equipments, house hold applications, safety equipments, and automobiles. The epoxy resins are also used in industrial floorings, adhesives, industrial protective coatings, powder coatings, automotive primers, can coatings and printed circuit boards.[15] Bisphenols have also been employed in the design of supramolecular hosts.[16] There is evidence that derivatives of bisphenols have also been used for the evaluation of many biological processes such as enhancing cell cation transport, measurement of renal tubular function, estimation of kidney blood flow, lipid and hydrogen peroxide formation, pH indicator in tissue culture media.[17] Interestingly, these compounds also act as estrogen receptor ligand agonists.[18]

Literature records a number of methods for their synthesis from phenols, using a variety of catalysts such as, mineral acids, bases, mesoporous silica, solid acid catalysts, zeolites, non-zeolite molecular sieves, acid pretreated montmorillonite clays, cation-exchange resins, collision fluid segment etc.[19] However, some of these

reagents are hygroscopic and difficult to handle. Occasionally these methods involve the use of corrosive reagents, nitrogen atmosphere or harsh conditions.

Objective of the present work:

In view of its inherent properties like environmental compatibility, greater selectivity, operational simplicity, moisture-insensitive, and less corrosive nature, it was interesting to find out the behaviour of $HClO_4$-SiO_2 as a solid acid catalyst for the synthesis of bisphenols. We have found that $HClO_4$-SiO_2 allows the reaction of several alkyl substituted phenols and aldehydes or ketones to bisphenols by direct condensation reaction in good to excellent yields in shorter reaction times.



15 **16** **17 - 30**

17-22) R_1=R_2=CH_3, R_3=H; **23-28)** R_1=R_2=R_3=H; **29-30)** R_1=H, R_2=CH_3CHCH_3, R_3= CH_3

R, R' = Alkyl/H/benzyl/-(CH_2)n-

Scheme 5.5: preparation of bisphenols from phenols

5.3 Results and discussion

The use of eco-friendly, inexpensive and safe catalysts having high efficiency under mild conditions has gained much importance in synthetic chemistry. In continuation of our earlier studies on synthesis of bisphenols[19a,b] we have reported a new, simple, mild and effective procedure for the synthesis of bisphenol. (**Scheme 5.5**)

The reagent system $HClO_4$-SiO_2 was prepared by following the reported procedure and used for the synthesis of bisphenols.[9] To evaluate the better catalytic activity of this supported reagent over the aqueous $HClO_4$ a model study was carried out with 2,6-dimethyl phenol and formaldehyde without catalyst, with silica alone

treated under similar condition as the catalyst, with aqueous $HClO_4$ and in the presence of catalyst under solvent free condition at 60 °C. (**Table 1**) The reaction using aqueous $HClO_4$ gave 89% yield while no reaction was observed in the presence of silica alone. However, the use of $HClO_4$-SiO_2 afforded 94% yield under solvent free condition. From the study, it is clearly demonstrated that the silica supported perchloric acid is indeed an effective catalyst in term of reaction time and yields.

Table 1: Comparison of results of 2,6-dimethyl phenol with formaldehyde under different catalytic conditions.

Entry	Catalyst	Time (h)	Yield [%][a]
1.	No catalyst	14	0
2.	Silica(pre-treated as catalyst)	12	89
3.	$HClO_4$-SiO_2(2mol-%)	4	94
4.	Aqueous $HClO_4$(2mol-%)	12	89

[a] Isolated yield

In order to determine the optimum quantity of the catalyst, a reaction of 2,6-dimethyl phenol and formaldehyde was carried out under varying amounts of the catalyst at 60 °C. After some experiments, it was found that the use of 40 mg of catalyst (0.02 mmol of $HClO_4$) per 1.0 mmol of phenol gives corresponding bisphenols in excellent yields. The use of larger amounts of the catalyst did not improve the results. (**Table 2**)

Table 2: Optimization of amount of silica supported perchloric acid on the reaction of 1 mmol of phenol under solvent free condition

Entry	Catalyst (Mol %)	Time (h)	Yield (%)
1	1.0	8	64
2	1.5	12	90
3	**2.0**	**4**	**94**
4	3.0	8	88
5	4.0	10	80

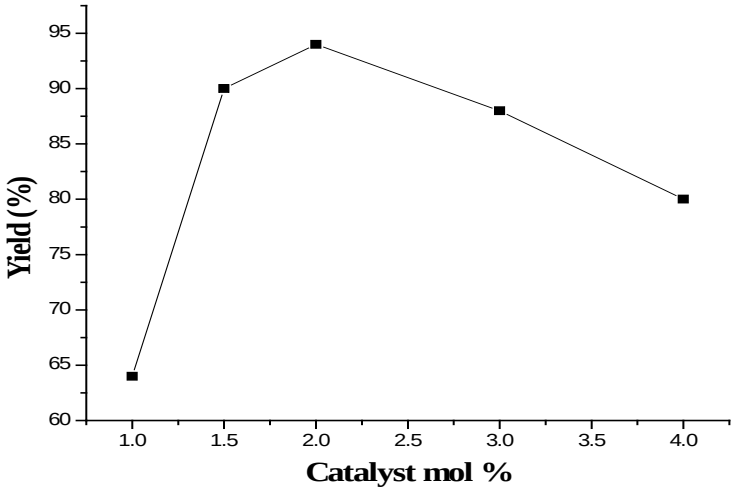


Figure 5.1

The product formation in organic reactions also depends upon the nature of the solvent. A model study was also carried out in different solvents (**Table 3**) for the preparation of **4a** (**Scheme 5.5**).

Table 3: Solvent effect in synthesis of 3a using $HClO_4$-SiO_2 catalyst

Entry	Solvent	Time (h)	Yield %
1	Methanol	10	84
2	Ethanol	10	88
3	Water	12	82
4	Chloroform	10	85
5	Dichloroethane	10	72
6	**Solvent-free**	**4**	**94**

The results obtained from the above studies (**Tables 1, 2, 3**) it is clear that silica supported perchloric acid is an efficient catalyst in terms of time and yield under solvent free condition. To generalize the procedure, 2,6-dimethyl phenol was treated with various aldehydes and ketones under optimised condition, which gave products with maintained yields.

We have also studied the reaction of phenol with carbonyls in the presence of same the catalyst under identical condition. The phenol has free *ortho* and *para* positions so the condensation with carbonyls may occur at both positions to give different products (**Figure 5.2**). But during the reaction only *para* product **19** was isolated for each. The structures of products were confirmed by comparing their analytical and spectral data with reported in literature.

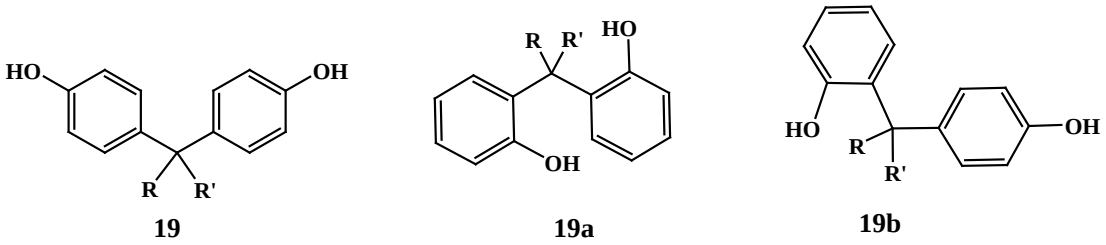


Figure 5.2

Thymol is extracted from various plants such as Monarda didyma, Monarda fistulosa, Trachyspermum ammi, Origanum compactum, Origanum dictamnus, Origanum onites, Origanum vulgare, and Thymus zygis as a white crystalline solid with a pleasant smell.

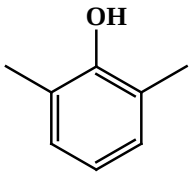
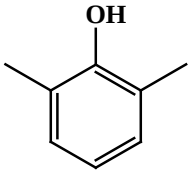
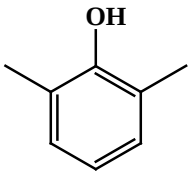
Thymol possesses microbial activity and antibacterial activity.[20a] Thymol has been used in alcohol solution and in dusting powders for treatment of tinea or ring worm infection.[20b] Thymol is also used as a rapidly degrading, non-persisting pesticide.[20c] It is also employed as an antiseptic in mouth wash and tooth paste as Euthymol.

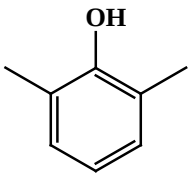
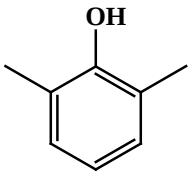
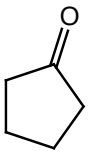
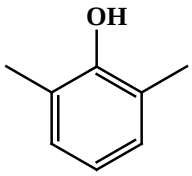
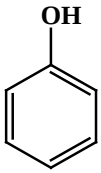
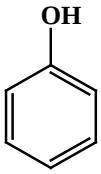
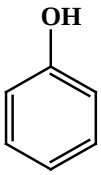
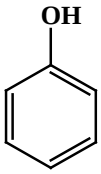
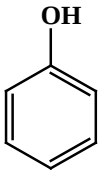
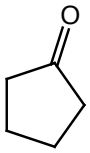
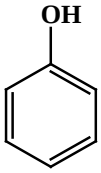
In view of the above inherent applications, it was interesting to syntheses the bisphenols of thymol which is unreported in the literature. We have also attempted the above optimised method for syntheses of bisphenol of thymol. Thymol was treated under similar conditions with benzaldehyde for 4h, which gave product **29**. The structure of the compound was fully discernible from its FTIR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. Its IR spectrum showed a strong band at 3489 cm^{-1} for OH group in addition to 1508, 1454, 1408 cm^{-1} characteristic absorptions for aromatic rings. Its ^{1}H NMR exhibited singlet at δ 1.06 for four aliphatic methyl groups and singlet at δ 2.09 represents the presence of two aromatic methyl groups. It also

showed multiplet at δ 3.10 for two protons of methine groups, singlet at δ 4.52 for two exchangeable phenolic OH group, singlet at δ 5.55 one proton of methine group, along with singlet at δ 6.56, 7.04 and multiplet at δ 7.20-7.29 for ten aromatic protons. Its ^{13}C NMR spectrum displayed signals at δ 19.09, 22.47, 22.72 for three methyl carbons and signals at δ 26.80, 49.24 for two methine carbons. Similarly signals at δ 117.01, 125.92, 127.48, 128.10, 129.49, 130.90, 134.54, 134.77, 143.79 and 150.56 for ten aromatic carbons. Similarly the reaction of thymol with butraldehyde was also performed and product **30** was isolated in good yield and fully characterised by spectral and analytic data.

The reaction of α-napthol, β-napthol, 2-hydroxybenzaldehyde, o-aminophenol, 2-hydroxy benzoic acid, o-nitrophenol was also attempted with carbonyls under similar conditions. The reaction does not show the formation of any type of bisphenol. Thus preparation of bis-amino phenol, bis-nitro phenol, bis-salicylic acid phenol was unsuccessful by this catalyst.

Table 4: $HClO_4$-SiO_2 catalyzed preparation of bisphenols **17-30** under solvent-free condition

Entry	Phenol	aldehyde	Bisphenol	Time (h)	Yield (%)
1		HCHO	**17**	4	93
2		CH_3CHO	**18**	5	91
3		CH_3CH_2CHO	**19**	3.5	92

4		$CH_3(CH_2)_2CHO$	**20**	4	94
5			**21**	4.5	86
6		CH_3COCH_3	**22**	5	94
7		CH_3COCH_3	**23**	4	84
8		CH_3CHO	**24**	5	92
9		CH_3CH_2CHO	**25**	5	84
10		$CH_3CH_2CH_2CHO$	**26**	4	86
11			**27**	4	87
12		CH_3COCH_3	**28**	3.5	88

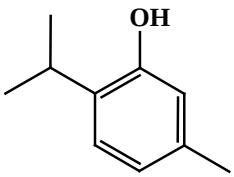
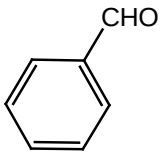
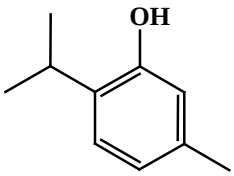
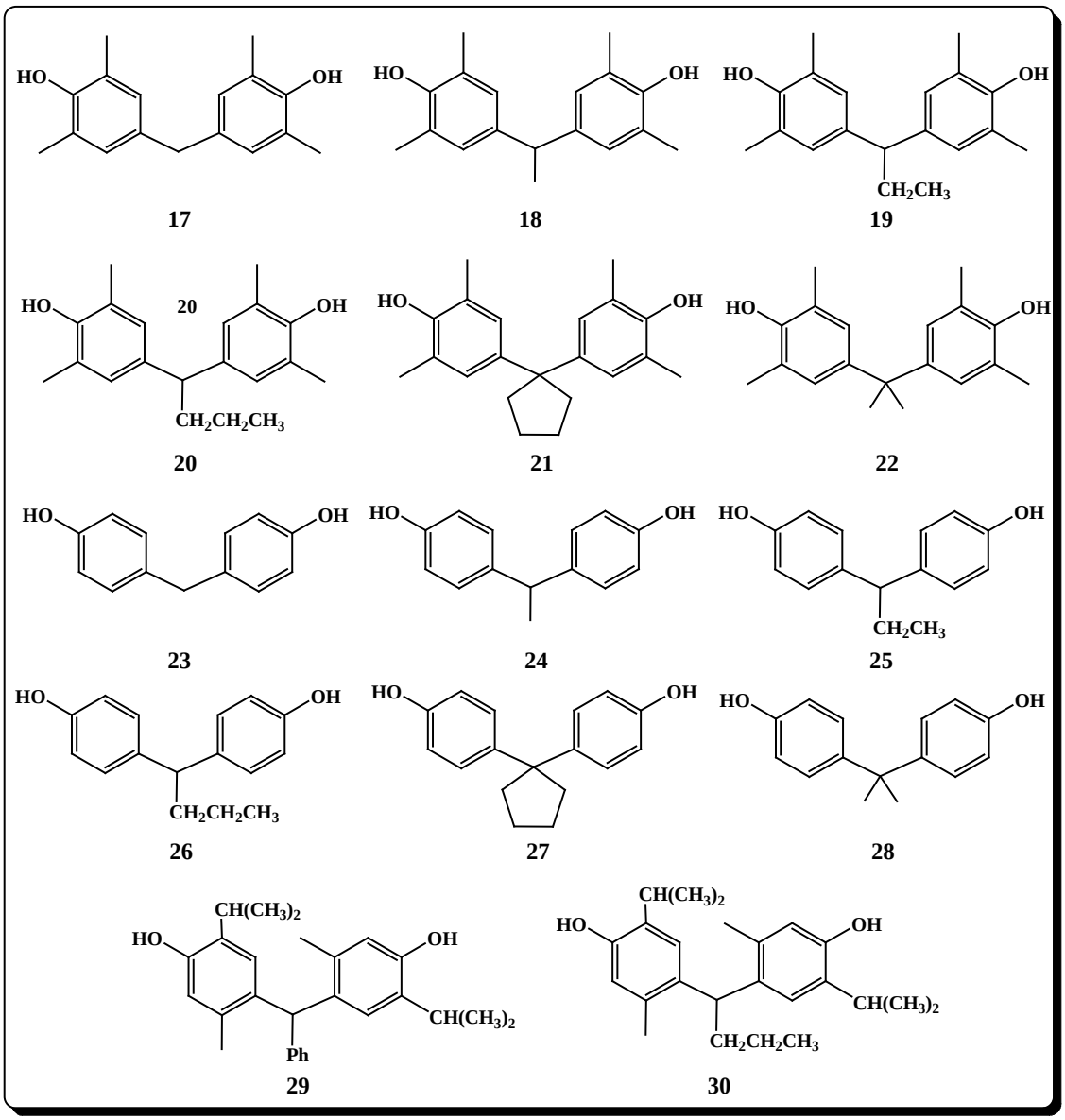
13			**29**	5	92
14		$CH_3CH_2CH_2CHO$	**30**	6	94

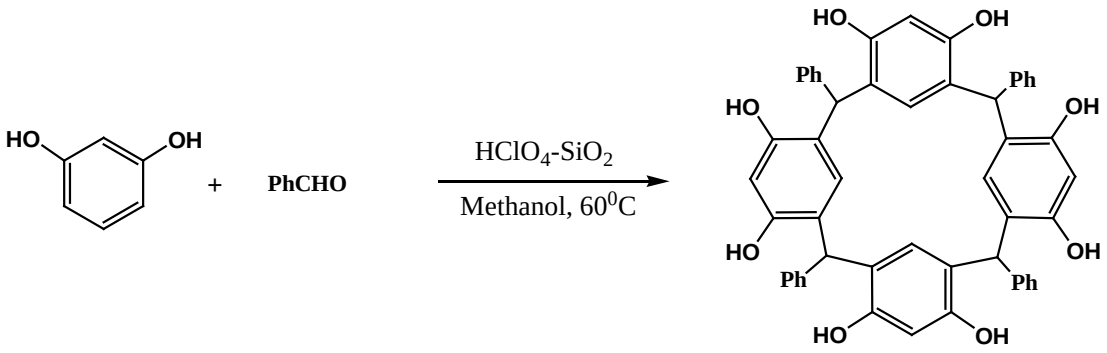
Figure 5.3: Structures of bisphenols **17-30**



In order to widen the scope of the reagent, we also investigated the reaction of resorcinol with aromatic aldehyde to furnish calix[4]resorcinarene. Synthesis of calix[4]resorcinarenes is an important and useful exercise in synthetic organic chemistry due to its various applications such as host compounds for the extraction of metal ions, sugars and organic molecules. They have also been used as a component in stationary phases in HPLC, photoresists and membranes preparation. Interestingly they have also been employed in liquid crystals by the appropriate choice of alkyl groups.[21]

Resorcinarenes are commonly prepared by mineral acid catalyzed condensation of resorcinol with aldehydes or ketones. However this procedure requires the use of large quantities of acid, leading to excessive waste extreme that are environmentally unfriendly and expensive. Some conventional Lewis acids like $BF_3.OEt_2$, $AlCl_3$, and $SnCl_4$ have been reported for the synthesis of aromatic aldehydes derived resorcinarenes. These Lewis acids have several drawbacks such as they need to be used in stoichiometric amounts, easily deactivated by water and cannot be recycled and reused.[22]

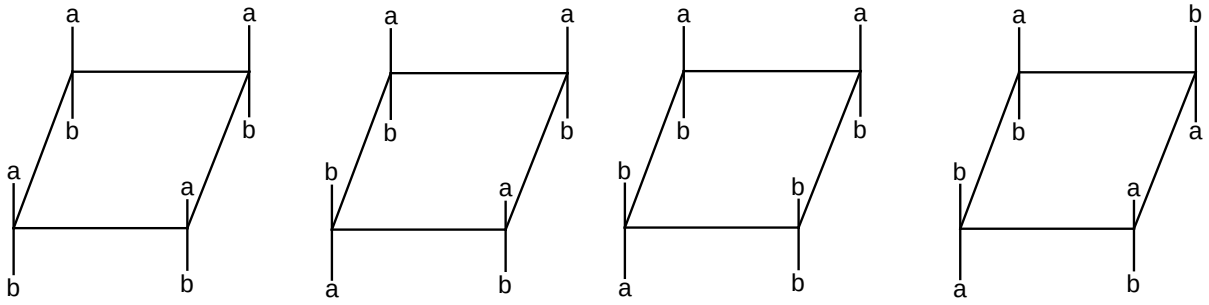
Here we are reporting the synthesis of calix[4]resorcinarene using $HClO_4$-SiO_2 as a recyclable catalyst from benzaldehyde with resorcinol. Thus in a mixture of resorcinol and catalyst in methanol at 60^0C the benzaldehyde was added drop wise over period of 10 minutes. The reaction was further continued for 3h. The catalyst was separated by filtration and can be reused up to three times without substantially losing its activity. The filtrate was concentrated in rotatory evaporator and let to stand for recrystalisation. After 12h good crystals of compound are obtained.



31 **32** **33**

Scheme 5.6: Preparation of calix[4]resorcinarenes

The cyclic tetrameric oligomers **33** derived from condensation of resorcinol with aldehyde can exists in four possible configuration *cis-cis-cis* (ccc), *cis-cis-trans* (cct), *cis-trans-trans* (ctt) and *trans-cis-trans* (tct).



Where (a) Methine (b) R of aldehyde RCHO

Figure 5.4: Possible configuration of calix[4]resorcinarenes.

Stereoselectivity in cyclooligomerisation:

In four possible stereoisomers (**Figure 5.4**) Hogberg proposed that the *cct* and *tct* are not formed during the reaction of resorcinol with aromatic aldehydes. He demonstrated that *ctt* isomer from faster than the *ccc* isomer but the *ctt* isomer isomerised to *ccc* isomer.[22a,b]

In our reaction conditions the reaction of resorcinol with benzaldehyde gives only single *ctt* isomer having C_{2v} symmetry. Two structures having symmetry C_{4v} and C_{2v} (**Figure 5.5**) are distinguishable by their ^{1}H NMR shifting of *o*- hydrogen of resorcinol. In ^{1}H NMR spectrum of compound **33** exhibit singlet at 5.52 δ for four protons of methine Ar_3CH and a singlet at 5.54 δ for two protons of *ortho* to OH group. It also showed singlet at 6.11 δ value for two other protons of *ortho* to OH group. The two different signals at 5.54 and 6.11of four protons *ortho* to hydroxyl group confirm the C_{2v} stereochemistry of the products. The singlet at 6.33 δ value for four protons of *meta* to hydroxyl group along with multiplet at 6.60 δ for eight aromatic protons in addition to a multiplet at 6.85 δ for 12 aromatic protons. The eight hydroxyl protons give signals at two different δ values, singlet at 8.48 for 4H, 8.60 for other 4H. This spectrum proves the formation of only C_{2v} isomer during the reaction of resorcinol with benzaldehyde.

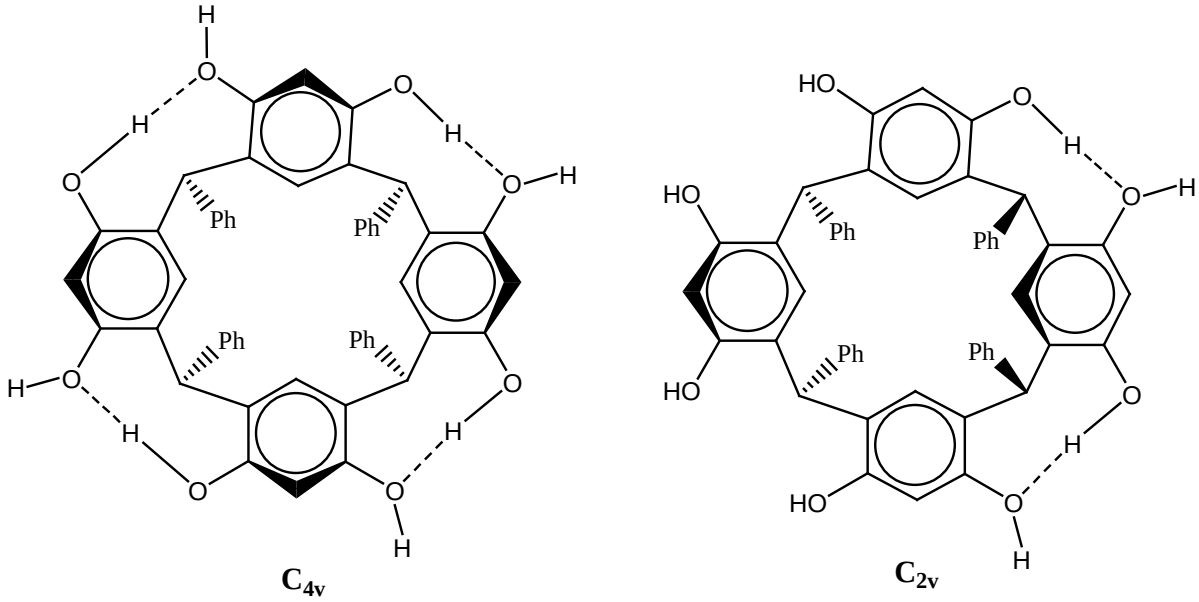


Figure 5.5: Configuration of calix[4]resorcinarenes **33**.

5.4 Experimental Section

Melting points were recorded in open capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer PC-16 FT IR spectrometer. ^{1}H NMR spectra were recorded on Bruker 200/300/400 MHz NMR spectrometer using $CDCl_3$ or DMSO-d_6 (TMS as an internal standard). Mass spectra were obtained on Thermo-Fisher DSQ II GCMS instrument. Phenol, 2,6-dimethyl phenol, various aldehydes and ketones were purchased from Sigma Aldrich and used without further purification. Perchloric acid (70 % aq. solution) was purchased from Merck and was used as such. All other solvents were purchased as commercial grade and distilled prior to use.

Purification of reaction products was carried out by column chromatography using silica gel (60-120 mesh size), using light petroleum and ethyl acetate mixtures as eluents. Thin layer chromatography was performed using Acme's Silica gel for TLC, and spots were visualized in iodine vapours.

Experimental Procedures:

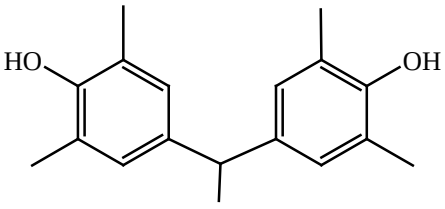
Preparation of $HClO_4$-SiO_2 catalyst.[7]

$HClO_4$ (6.0 g, 42 mmol as a 70% aq. solution) was added to a suspension of SiO_2 (18 g) in Et_2O (50 ml) under stirring. The mixture was concentrated and residue was heated at 100°C for 72 h under vacuum, to obtain $HClO_4$-SiO_2 (2.20 mmol/g) as free flowing powder. (100 mg = 0.233 mmol of $HClO_4$).

Typical experimental procedure for the preparation of Bisphenols (17-30):

To a stirred mixture of phenol (0.016 mol) and aldehyde or ketone (0.042 mol) was added $HClO_4$-SiO_2 (540 mg) over a period of 15 minutes and was further stirred for appropriate time at given temperature (Table 5). After completion of the reaction (TLC), ethyl acetate (50ml) was added and the catalyst was removed by filtration. The filtrate was washed with aqueous saturated $NaHCO_3$, saturated brine and was dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel to furnish bispenols (**Table 1**). The physical and spectral data of the products were identical with those reported in the literature.

4,4′-Ethylidenebis(2,6-dimethyl phenol) (18):[23a]



18

Mp. 141 °C, (Reported lit. 143 C°)

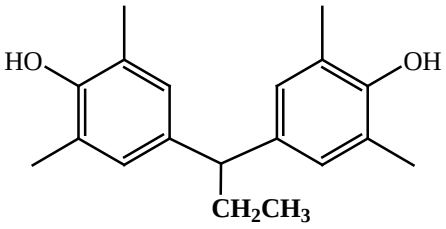
IR (KBr): 869, 1604, 3016, 3385 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): 1.51 (3H, d J = 7 H_Z, CH_3), 2.10 (12H, s, 4CH_3, aromatic), 3.84 (1H, q, J = 7 H_Z, CH), 4.49 (2H, s, exchangeable OH), 6.81 (4H, s, aromatic).

^{13}C NMR (50 MHz $CDCl_3$): 16.68 (4C, CH_3), 23.02 (1C, CH_3), 43.88 (1C, CH), 123.40, 128.20, 139.30, 150.89 (4C, aromatic).

MS (EI): m/z calculated for $C_{18}H_{22}O_2$ 270.16; found 270. 20 (M^+).

4,4'-Propylidenebis(2,6-dimethyl phenol) (19):[23b]



19

Mp. 138-140 °C (Reported literature 140.7 °C)

IR (KBr): 1290, 1604, 2960, 3398 cm^{-1}.

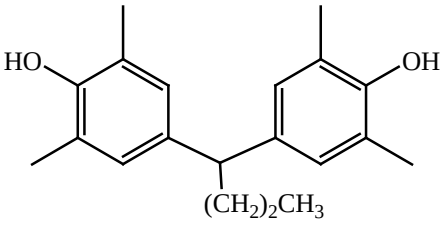
^{1}H NMR (200 MHz, $CDCl_3$): 0.81 (3H, t, J = 7.5 H_Z, CH_3), 1.90 (2H, m, CH_2) 2.19 (12H, s,

4CH_3), 3.50 (1H, t, *J* = 7.5 H_Z, CH), 4.44 (2H, s, exchangeable OH), 6.81 (4H, s, aromatic).

^{13}C NMR (50 MHz $CDCl_3$): 13.63 (1C, CH_3), 16.74 (4C, CH_3), 29.59 (1C, CH_2), 52.42 (1C, CH), 123.37, 128.47, 138.12, 150.90 (4C, aromatic).

MS (EI): m/z calculated for $C_{19}H_{24}O_2$ 284.18; found 284.21 (M^+).

4,4′-butylidenebis(2,6-dimethyl phenol) (20):[23c]



20

Mp. 112 °C, (Reported Lit. 176-177 °C).

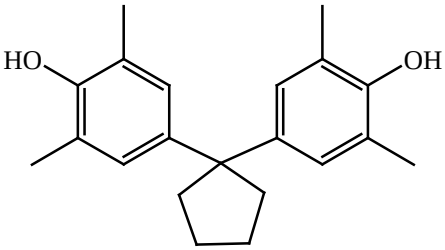
IR (KBr): 1220, 1465, 1604, 3583 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): 0.85 (3H, t, *J* = 7.5 Hz, CH_3), 1.2 (2H, m, CH_2), 1.90 (2H, m, CH_2), 2.19 (12H, s, 4CH_3), 3.50 (1H, t, *J* = 7.5 H_Z, CH), 4.44 (2H, s, phenolic OH), 6.81 (4H, s, aromatic).

^{13}C NMR (50 MHz $CDCl_3$): 14.77 (1C, CH_3), 16.72 (4C, CH_3), 21.94 (1C, CH_2), 38.98 (1C, CH_2), 50.17 (1C, CH), 123.41, 128.40, 138.30, 150.86 (4C, aromatic).

MS (EI): m/z calculated for $C_{.}H_{26}O_2$ 298.19; found 298.22 (M^+).

4,4'-Cyclopentanebis(2,6-dimethyl phenol) (21):[23d]



21

Mp. 181-182 °C

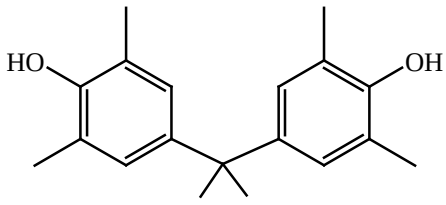
IR (KBr): 1305, 1600, 3049, 3504 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): 1.65 (8H, m, 2CH_2), 2.17 (12H, s, 4CH_3, aromatic), 4.44 (2H, s, exchangeable OH), 6.85 (4H, s, aromatic).

^{13}C NMR (50 MHz $CDCl_3$): 16.84 (4C, CH_3), 23.62 (2C, CH_2), 39.53 (2C, CH_2), 54.84 (1C, Cq), 122.58, 127.71, 141.64, 150.45 (4C, aromatic).

MS (EI): m/z calculated for $C_{21}H_{26}O_2$ 310.19; found 310.21 (M^+).

4,4′-Isopropylidenebis(2,6-dimethyl phenol) (22):[23e]



22

Mp. 159-160 °C, (Reported Lit. 161-162 °C)

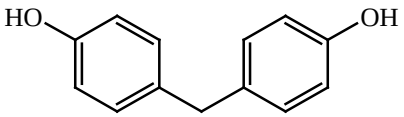
IR (KBr): 1220, 1465, 1485, 1604, 2956, 3335 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): 1.58 (6H, s, $2CH_3$), 2.18 (12H, s, $4CH_3$), 4.49 (2H, s, exchangeable OH), 6.82 (4H, s, aromatic).

^{13}C NMR (75 MHz $CDCl_3$): 16.10 (2C, CH_3), 31.20 (4C, CH_3), 41.32 (1C, Cq), 122.16, 126.91, 142.72, 149.83(4C, aromatic).

MS (EI): m/z calculated for $C_{19}H_{24}O_2$ 284.18; found 284.03 (M^+), 242.04.

4,4′-Methylenebisphenol (23):[23f]



23

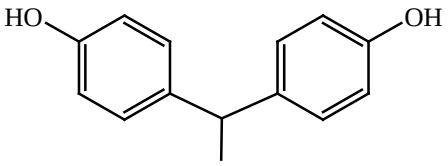
Mp. 159-160 °C, (Reported lit. 158 °C)

IR (KBr): 1169, 1455, 1599, 3260 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): 3.67 (2H, s, CH_2), 6.72 (4H, d, *J* = 7.5 Hz, 4CH), 6.91 (4H, d, *J* = 7.5 Hz, 4CH), 9.18 (2H, s, exchangable OH).

MS (EI): m/z, calculated for $C_{13}H_{12}O_2$ 200.08; found 200.03 (M^+).

4,4′-Ethylidenebisphenol (24):[23f]



24

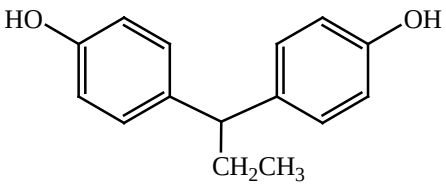
Mp. 123-124 °C (Reported lit. 122 °C)

IR (KBr): 1238, 1508, 1614, 2978, 3421 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.59 (3H, d, *J* = 7.5 H_Z, CH_3), 4.04 (1H, q, *J* = 7.5 H_Z, CH), 6.75 (4H, d, *J* = 8 H_Z, 4CH aromatic), 7.07 (d, 4H, *J* = 8 H_Z, 4CH aromatic), 7.95 (s, 2H, exchangeable OH).

MS (EI): m/z calculated for $C_{14}H_{14}O_2$ 214.10; found 214.04 (M^+).

4,4'-Propylidenebisphenol (25):[23f]



25

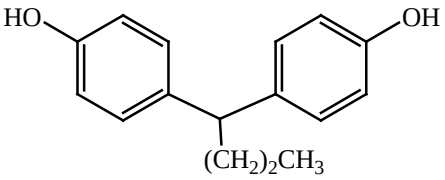
Mp. 132-133 °C. (Reported lit. 129 °C).

IR (KBr): 1172, 1508, 1612, 2951, 3301 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): 0.77 (3H, t, *J* = 7 $Hz_,$ CH_3), 1.94 (2H, m, CH_2), 3.77 (1H, t, *J* = 8 H_Z), 5.10 (2H, s, exchangeable OH), 6.75 (4H, d, *J* = 8 H_Z, 4CH), 7.08 (4H, d, *J* = 8 H_Z, 4CH).

MS (EI): m/z calculated for $C_{15}H_{16}O_2$ 228.12; found 228.09 (M^+).

4,4′-butylidenebisphenol (**26**)**:**[23f]



26

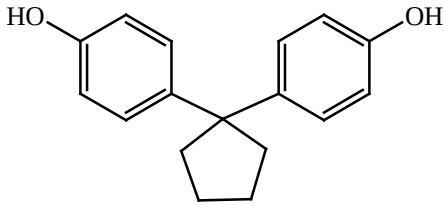
Mp. 139-140 °C, (Reported Lit. 137 °C)

IR (KBr): 1120, 1425, 1614, 3512 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): 0.90 (3H, t, *J* = 7 Hz, CH_3), 1.23 (2H, m, CH_2), 1.90 (2H, m, CH_2), 3.77 (1H, t, *J* = 8 H_Z, CH), 4.77 (2H, s, exchangeable OH), 6.71 (4H, d, *J* = 7.5 H_Z, 4CH), 7.05 (4H, d, *J* = 7.5 H_Z, 4CH).

MS (EI): m/z calculated for $C_{16}H_{18}O_2$ 242.13; found 242.05 (M^+).

4,4'-Cyclopentanebisphenol (**27**)**:**[23g]



27

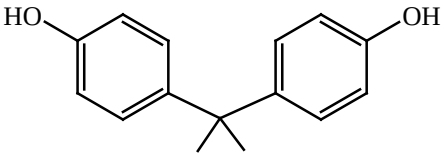
Mp. 158-160 °C, (Reported lit. 156 °C)

IR (KBr): 1177, 1444, 1612, 2869, 3242 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.70 (4H, m, $2CH_2$), 2.23 (4H, m, CH_2), 4.74 (2H, s, exchangeable OH), 6.72 (4H, d, *J* = 8.4 H_Z, 4CH), 7.12 (4H, d, *J* = 8.4 H_Z, 4CH).

MS (EI): m/z calculated for $C_{17}H_{18}O_2$ 254.13; found 254.19 (M^+).

4,4′-Isopropylidenebisphenol (**28**)**:**[23h]



28

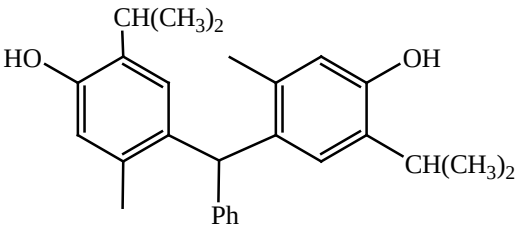
Mp. 158-159 °C, (Reported lit. 151 °C).

IR (KBr): 1218, 1445, 1597, 2964, 3342 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): 1.63 (6H, s CH_3), 6.75 (4H, d, *J* = 8.4 H_Z, 4CH), 7.12 (4H, d, *J* = 8.4 H_Z, 4CH), 9.12 (2H, s, exchangeable OH).

MS (EI): m/z calculated for $C_{15}H_{16}O_2$ 228.12; found 228.09 (M^+).

4-((4-hydroxy-5-isopropyl-2-methylphenyl)(Phenyl)methyl)-2-isopropyl-5-methyl phenol (**29**)**:**



29

Mp. 172 °C

IR (KBr): 1460, 1506, 2960, 3481 cm^{-1}.

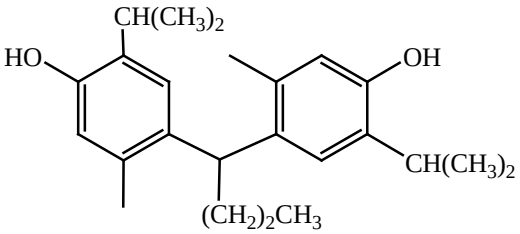
^{1}H NMR (400 MHz, $CDCl_3$): 1.06 (12H, d, *J* = 6.8 H_Z, $4CH_3$), 2.09 (6H, s, $2CH_3$), 3.10 (2H, m, CH), 4.52 (2H, s,

exchangeable OH), 5.55 (1H, s, CH), 6.56 (4H, s, 4CH), 7.02-7.29 (5H, m, 5CH).

^{13}C NMR (100 MHz, $CDCl_3$): 19.09 (1C, CH_3), 22.47, 22.72 (2C, $2CH_3$), 26.80 (1C, CH), 49.24 (1C, CH), 117.01, 125.92, 127.48, 128.10, 129.49, 130.90, 134.54, 134.77, 143.79, 150.56 (10C, aromatic).

MS (EI): m/z calculated for $C_{27}H_{32}O_2$ 388.54; found 388.02 (M^+).

4-(1-(4-hydroxy-5-isopropyl-2-methyl phenyl) butyl) -2-isopropyl-5-methyl phenol (**30**)**:**



30

Mp. 165-166 °C

IR (KBr): 1454, 1508, 2962, 3489 cm^{-1}.

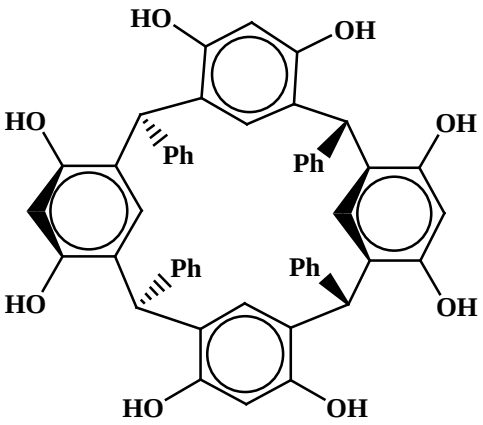
^{1}H NMR (400 MHz, $CDCl_3$): 0.96 (3H, t, J = 3.6 H_Z, CH_3), 1.23 (6H, d, J = 6.8 H_Z, $2CH_3$), 1.33 (6H, d, J = 6.8 H_Z, $2CH_3$), 1.37 (2H, m, CH_2), 1.86 (2H, m, CH_2), 2.20 (6H, s, $2CH_3$), 3.12 (2H, m, 2CH), 4.11 (1H, t, J = 7.6 H_Z), 4.53 (2H, s, exchangeable OH), 6.52 (2H, s, 2CH), 6.99 (2H, s, 2CH).

^{13}C NMR (100 MHz, $CDCl_3$): 14.17, 19.06, 21.20 (3C, CH_3), 22.77, 26.78 (2C, CH_2), 38.62, 41.11 (2C, CH), 116.89, 125.18, 131.14, 134.27, 135.41, 150.05 (6C, aromatic).

MS (EI): m/z calculated for $C_{24}H_{32}O_2$ 352.51; found 3353.95 (M^+).

Experimental procedure for synthesis of Calix[4]resorcinarenes (**33**)**:**

To a stirred mixture of resorcinol **31** (1.00g, 0.009 mol) in 15 mL methanol and $HClO_4$-SiO_2 (300 mg) was added benzaldehyde **32** (0.009 mol) over a period of 15 min at 60 ^{0}C and was further stirred for 3 hrs. After completion of the reaction, 150 ml of methanol was added in reaction mixture and stirred for 10 minutes. The catalyst was then separated by hot filtration. The filtrate was concentrated in a rotary evaporator and allowed to stand for recrystallisation to furnish a pure product. The structure of the product was confirmed by its physical and spectral analysis.



33

Mp. 238-240 °C, (Reported Lit. 240 °C).

IR (KBr): 1218, 1445, 1597, 2964, 3342 cm^{-1}

^{1}H NMR (400 MHz, DMSO-d_6): 5.52 (4H, s, CH), 5.54 (2H, s, ArH, *ortho* to OH), 6.11 (2H, s, ArH, *ortho* to OH), 6.33 (4H, s, *meta* to OH), 6.59 (8H, m, ArH), 6.85 (12H, m, ArH), 8.48 (4H, s, ArOH), 8.60 (4H, s, ArOH).

MS (ESI): m/z calculated for $C_{52}H_{40}O_8$ 792.82; found 793.2 (M^+).

5.5 Conclusion

We have demonstrated the use of perchloric acid silica gel ($HClO_4$-SiO_2) as an efficient catalyst for the synthesis of bisphenols by the condensation of various alkyl substituted phenols with carbonyl compounds. The synthesis of calix[4]resorcinarenes under the same catalytic condition was also described via condensation of resorcinol with aromatic aldehyde. Furthermore this method does not have disadvantages such as involvement of toxic solvent. We also attempted the syntheses of bisphenol of α-napthol, β-napthol, 2-hydroxybenzaldehyde, o-aminophenol, 2-hydroxy benzoic acid, o-nitrophenol with carbonyls under similar conditions. The reaction does not show the formation of bisphenol. Thus the preparation of bis-amino phenol, bisnitrophenol phenol, bis-salicylic acid phenol was unsuccessful by this catalyst.

5.6 References

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5.7 Spectral data of compounds

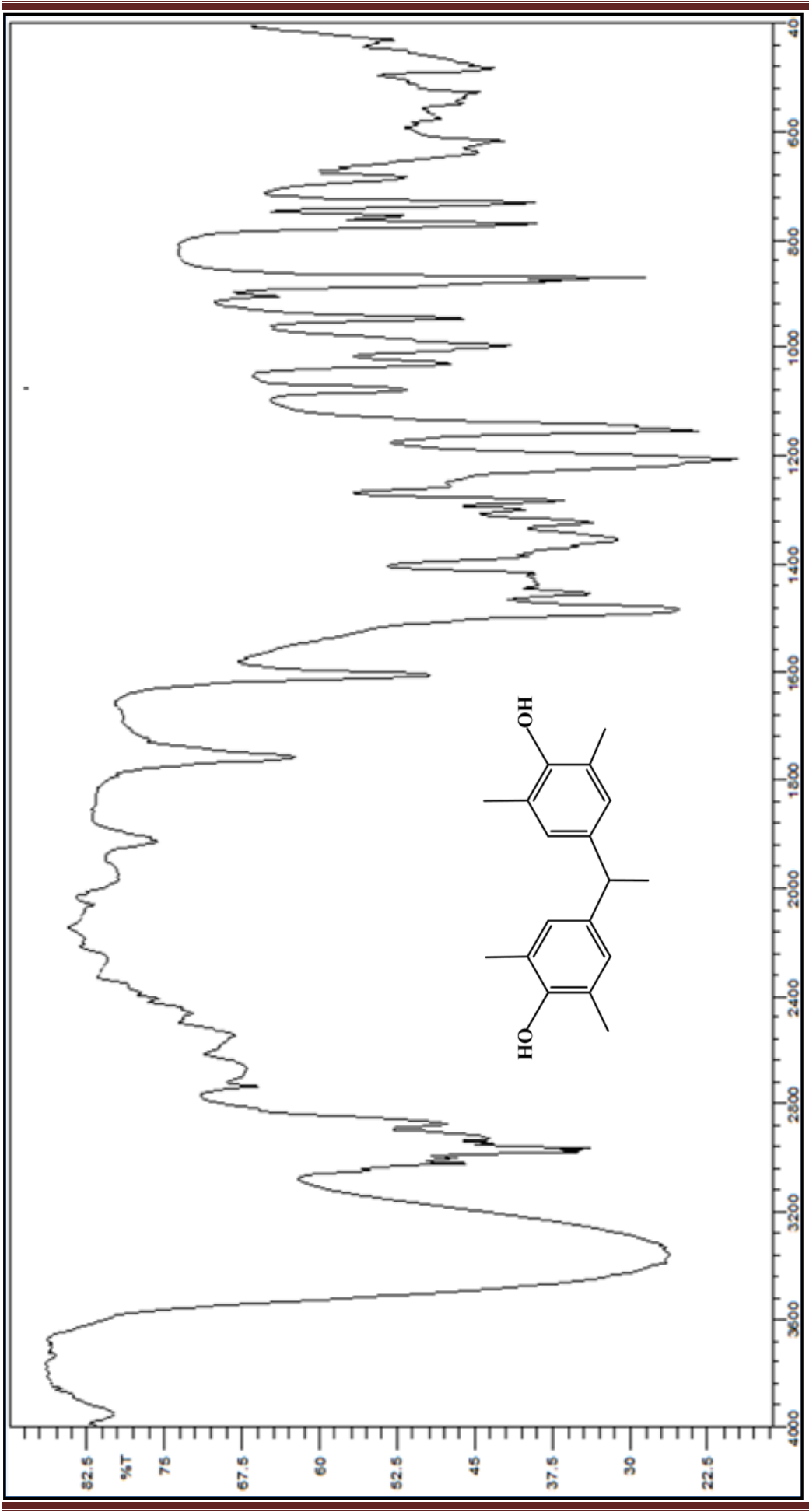


Figure 5.6: FTIR spectrum of compound **18**

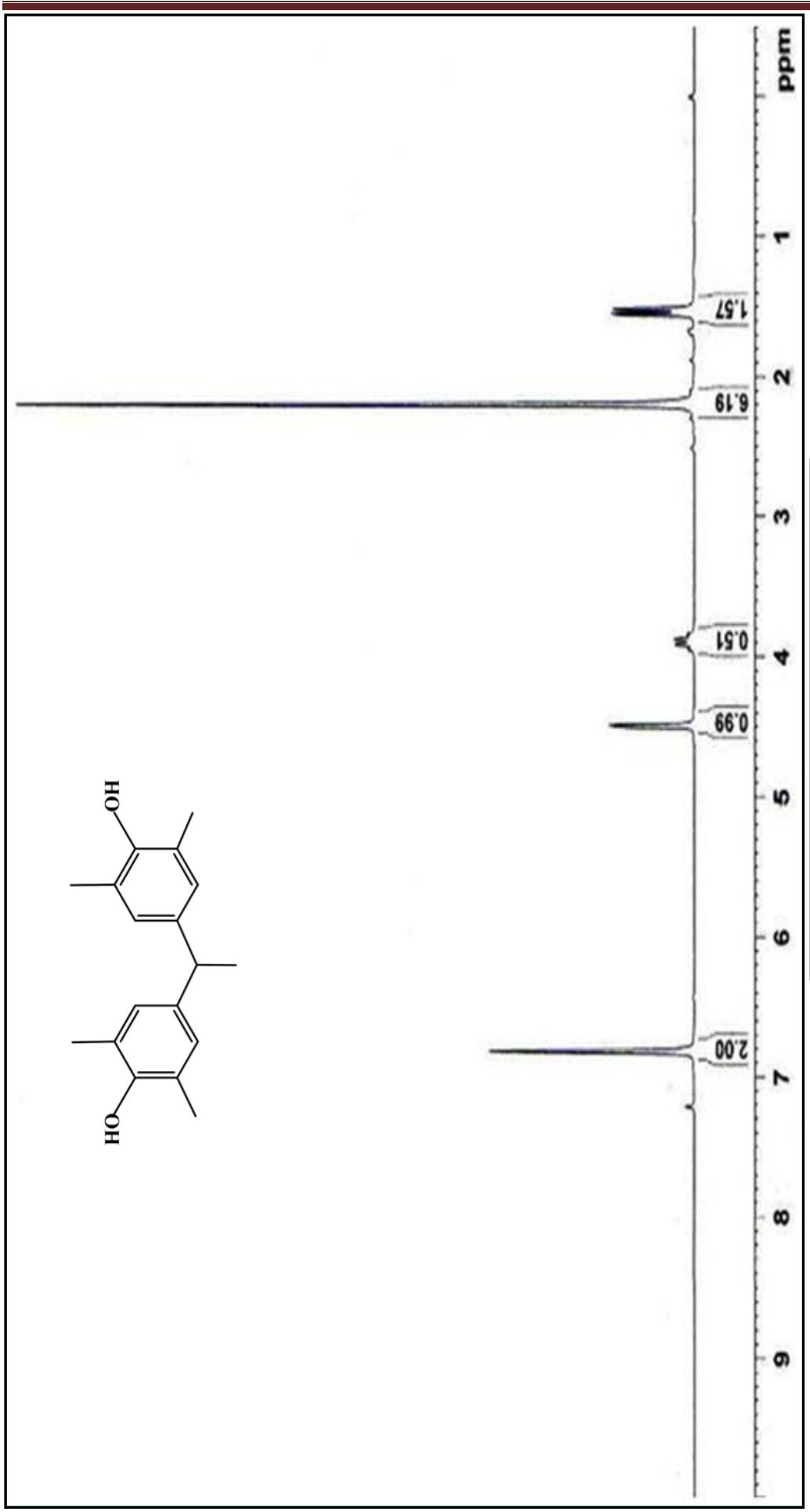


Figure 5.7: ^{1}H NMR spectrum of compound **18**

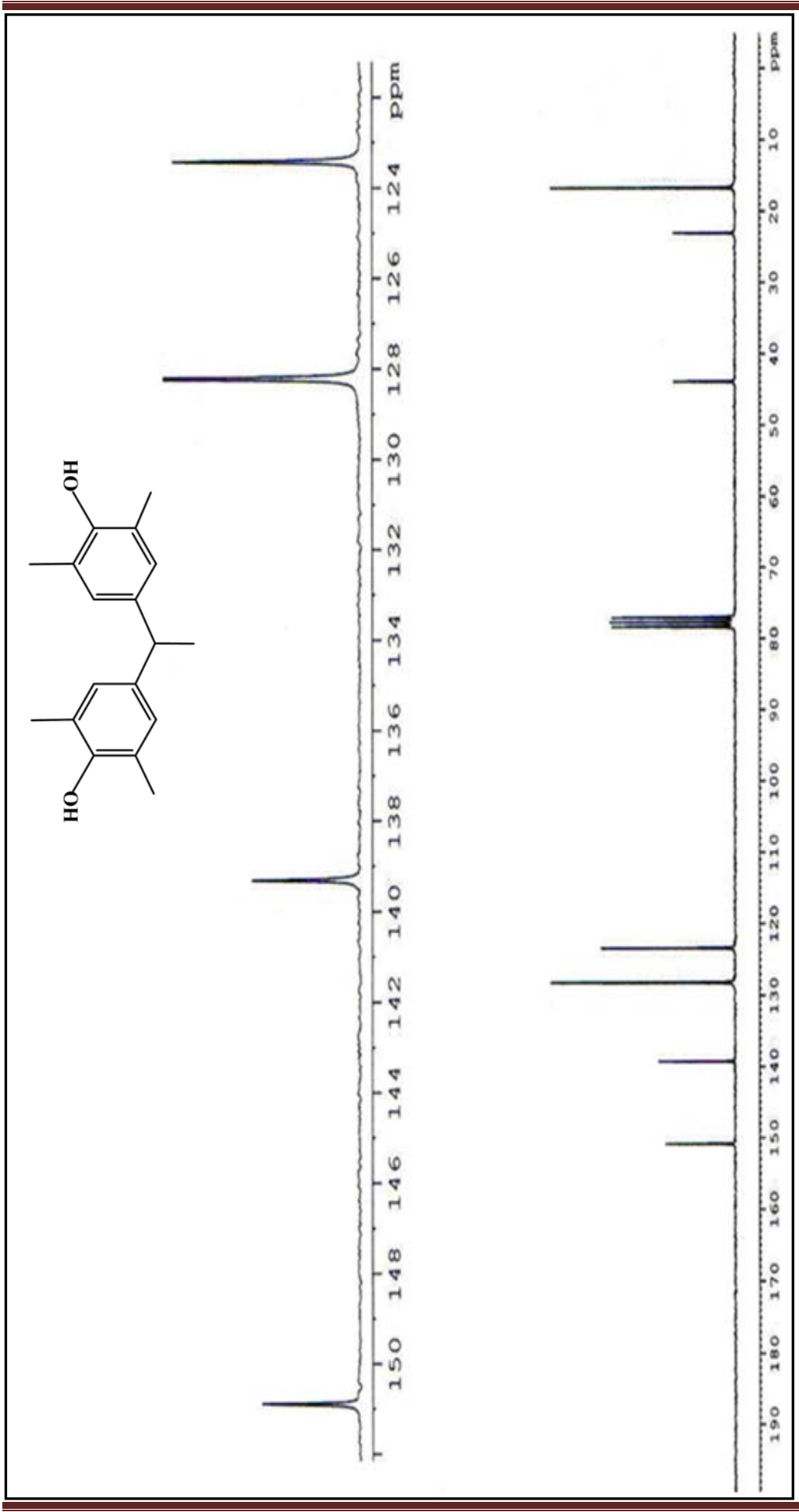


Figure 5.8: ^{13}C NMR spectrum of compound **18**

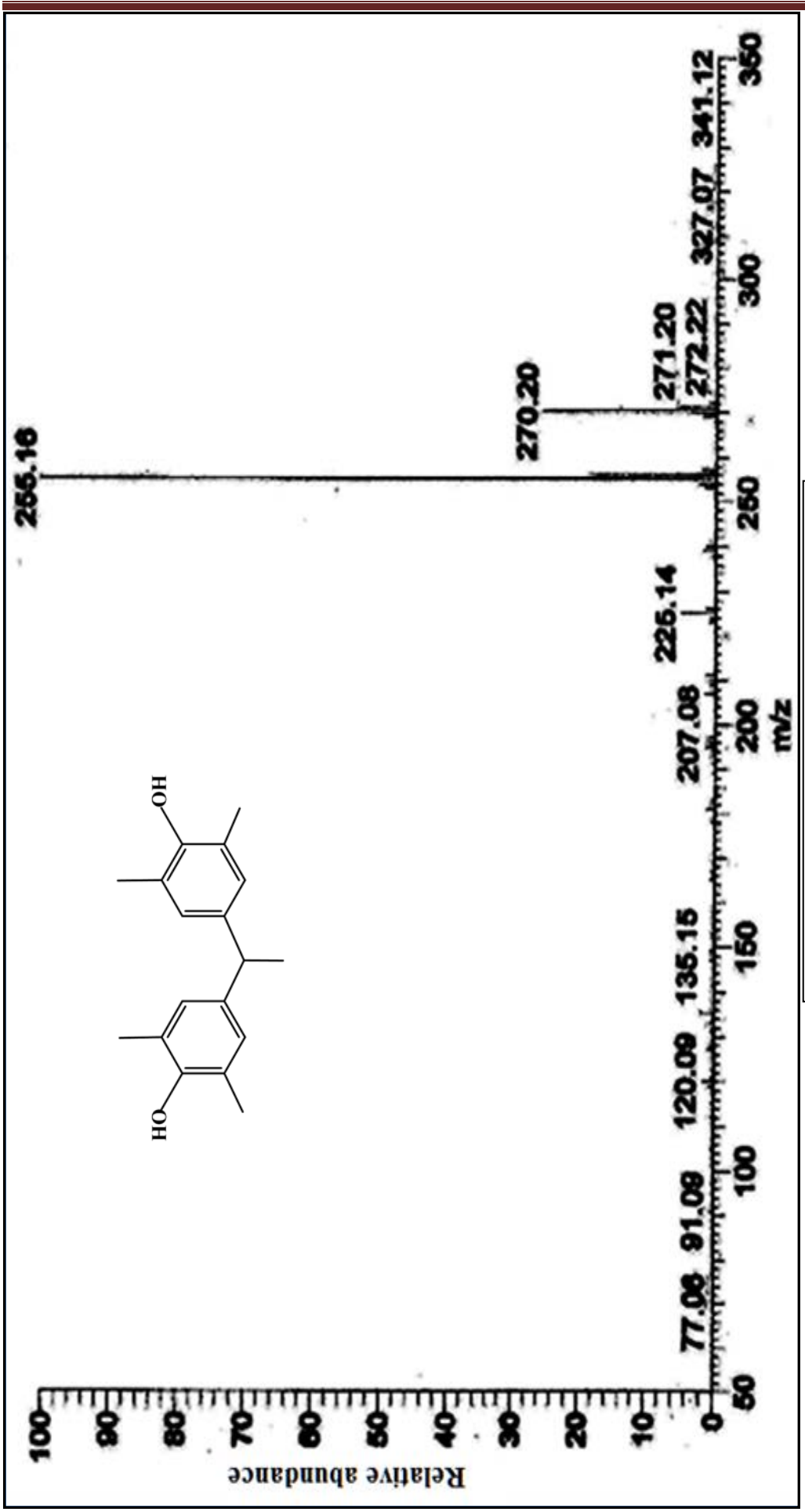


Figure 5.9: EI-MS spectrum of compound **18**

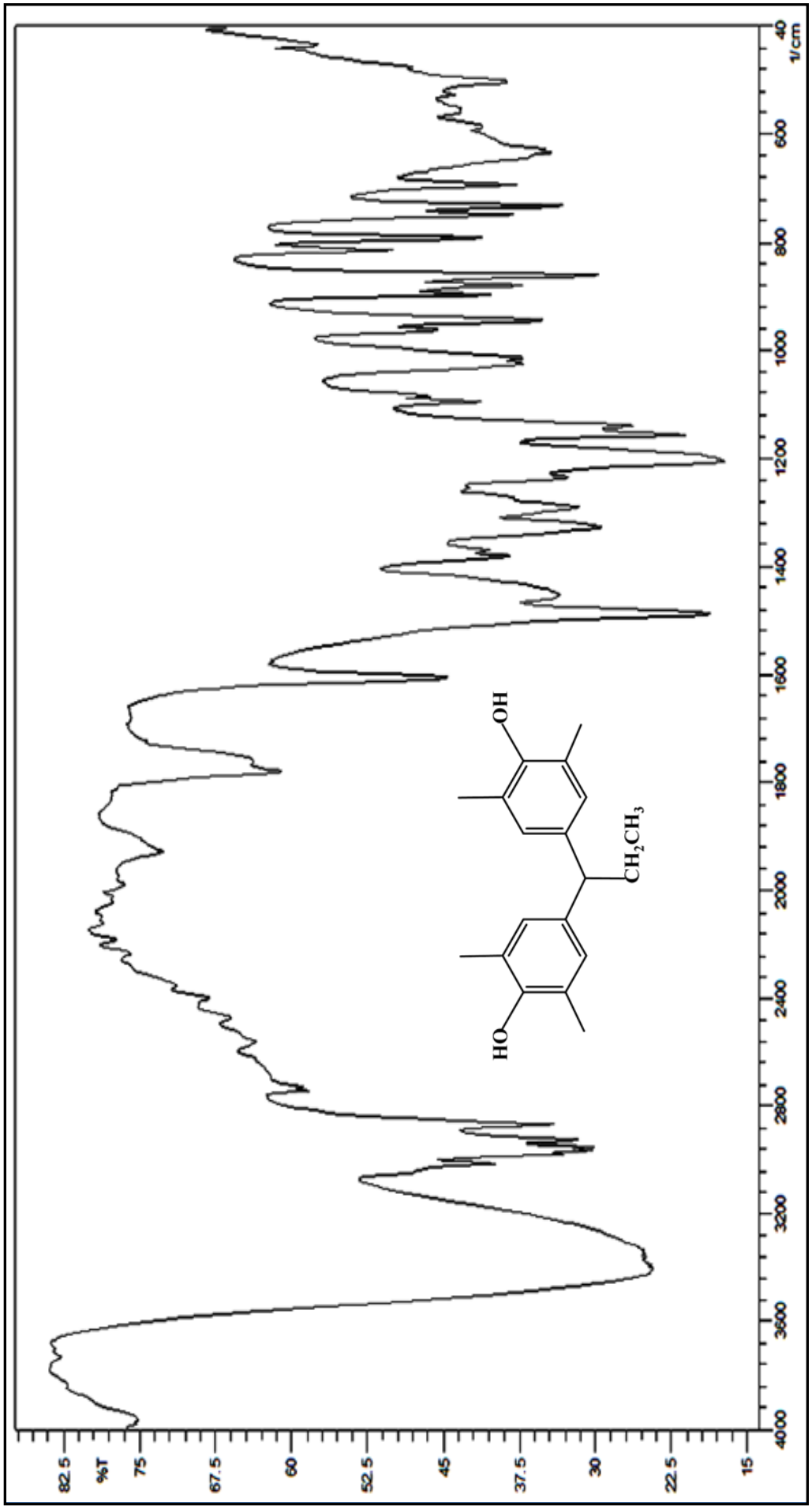


Figure 5.10: FTIR spectrum of compound **19**

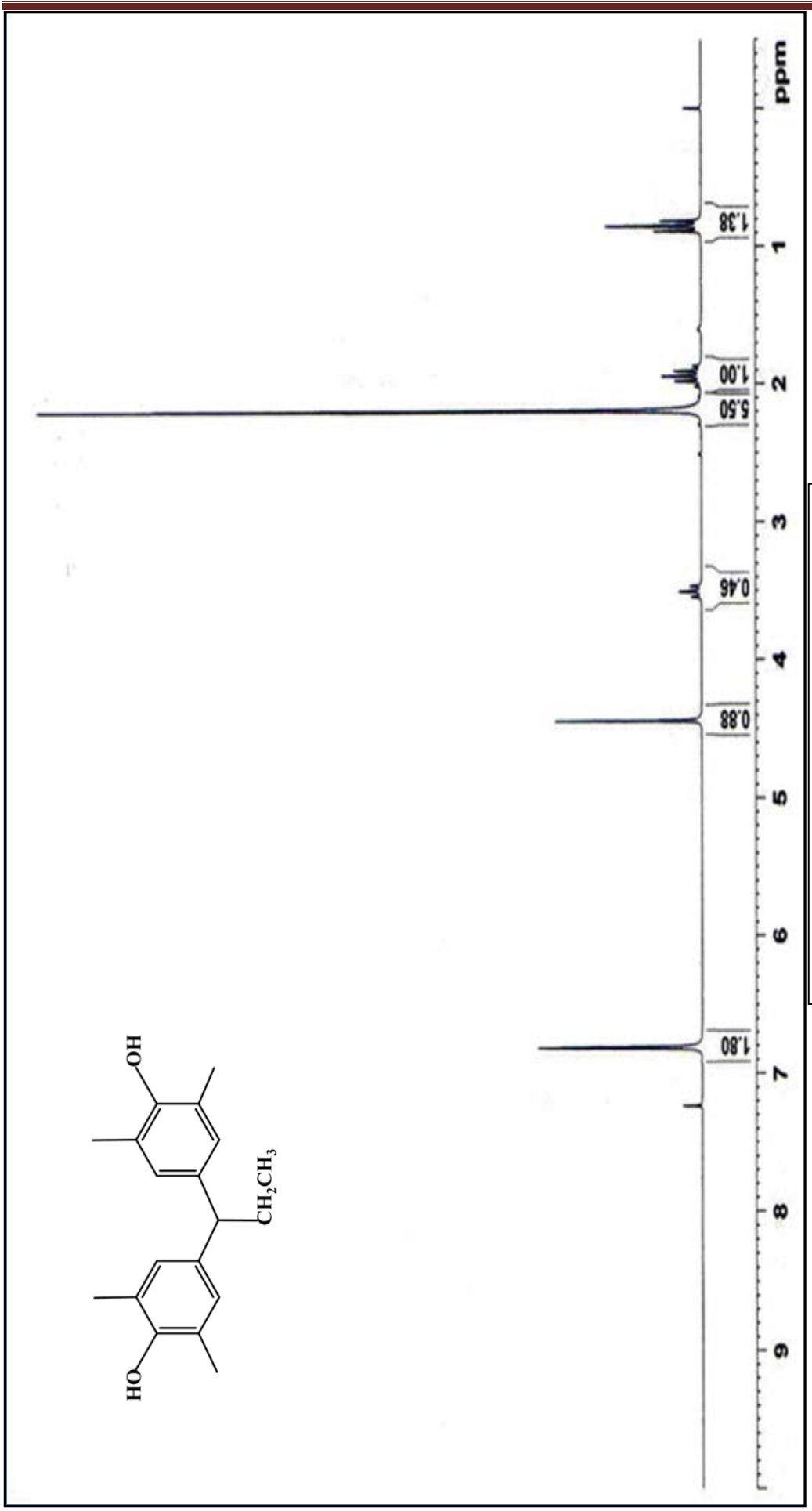


Figure 5.11: ^{1}H NMR spectrum of compound **19**

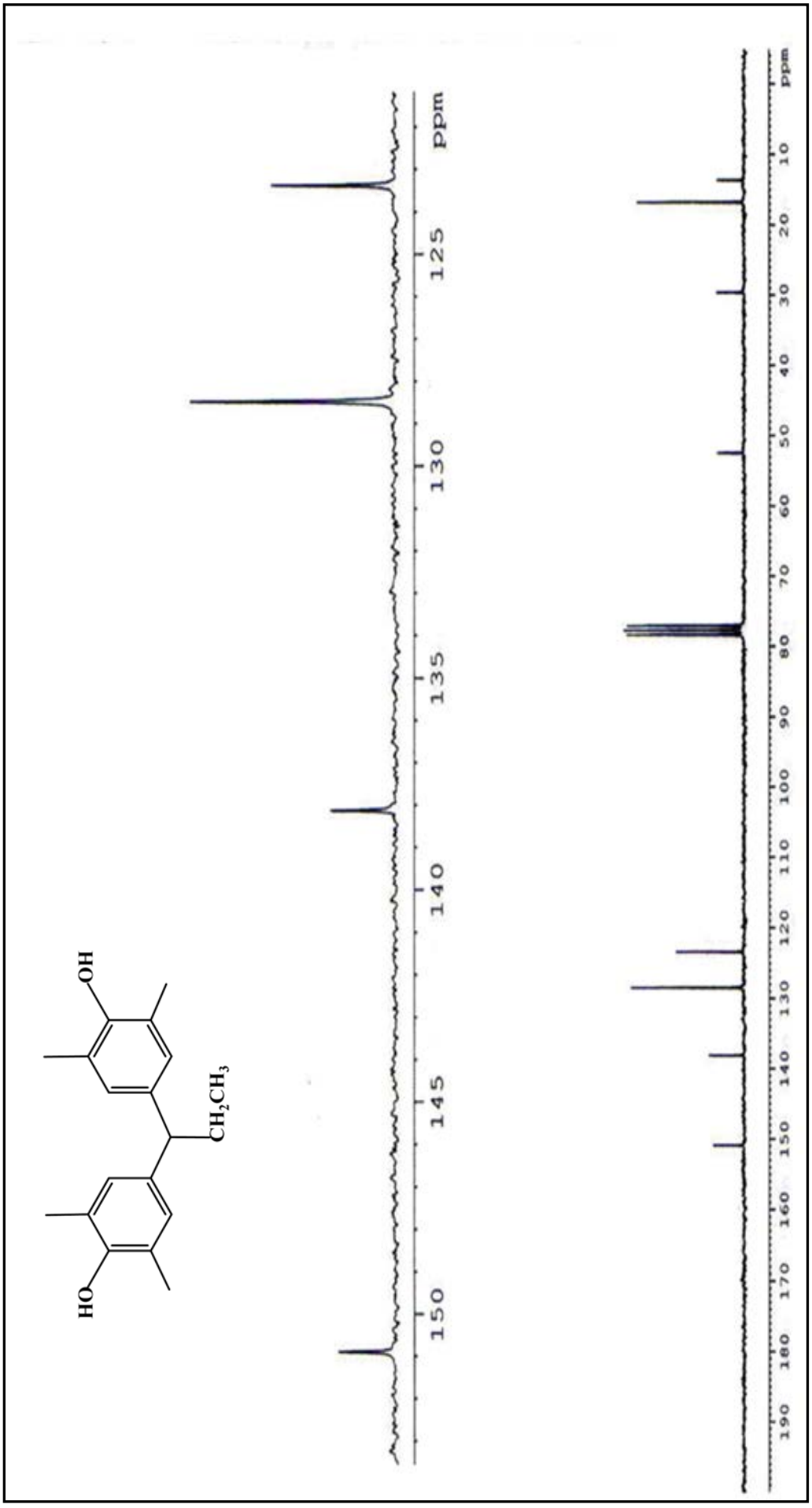


Figure 5.12: ^{13}C NMR spectrum of compound **19**

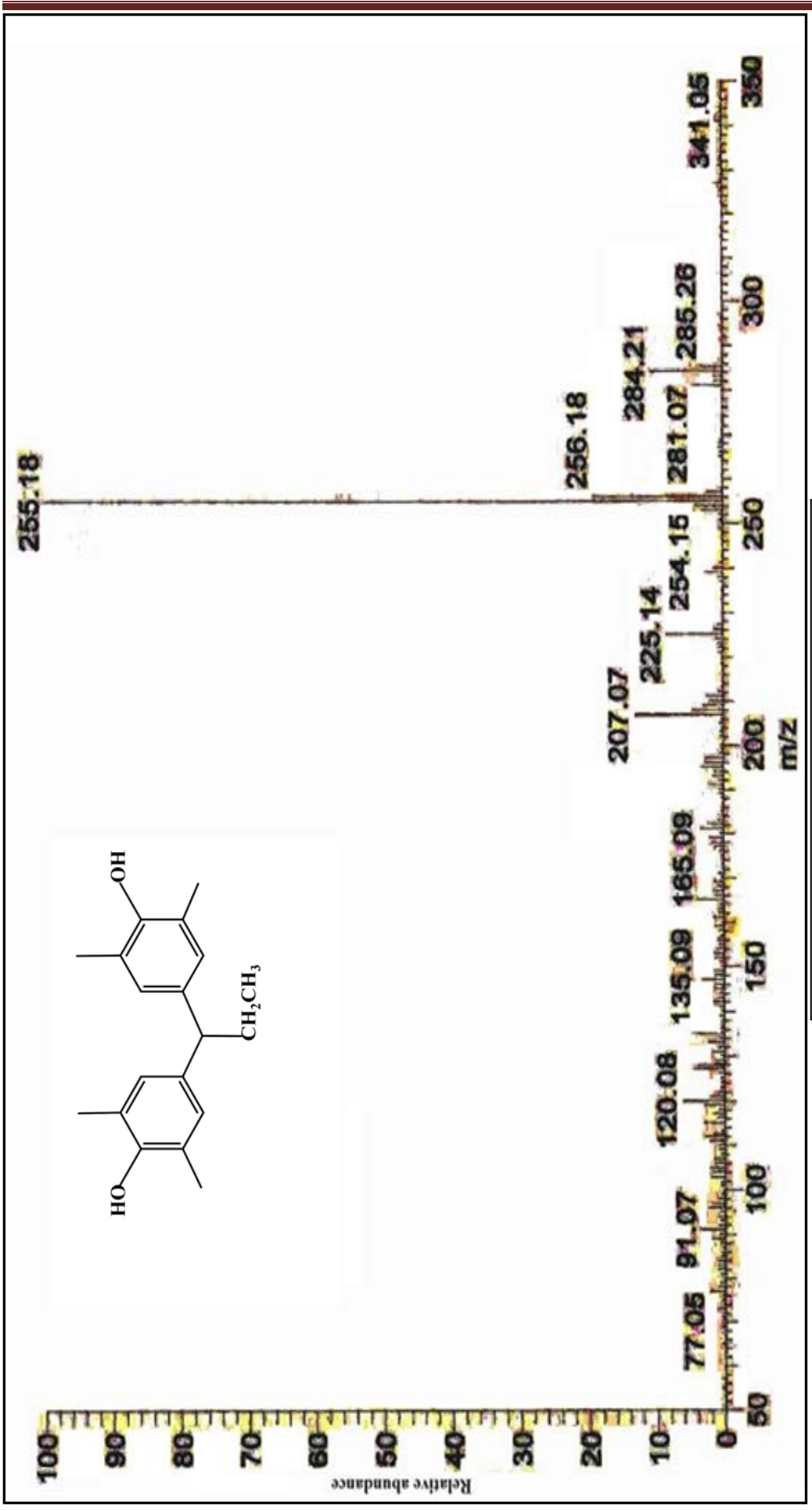


Figure 5.13: EI-MS spectrum of compound **19**

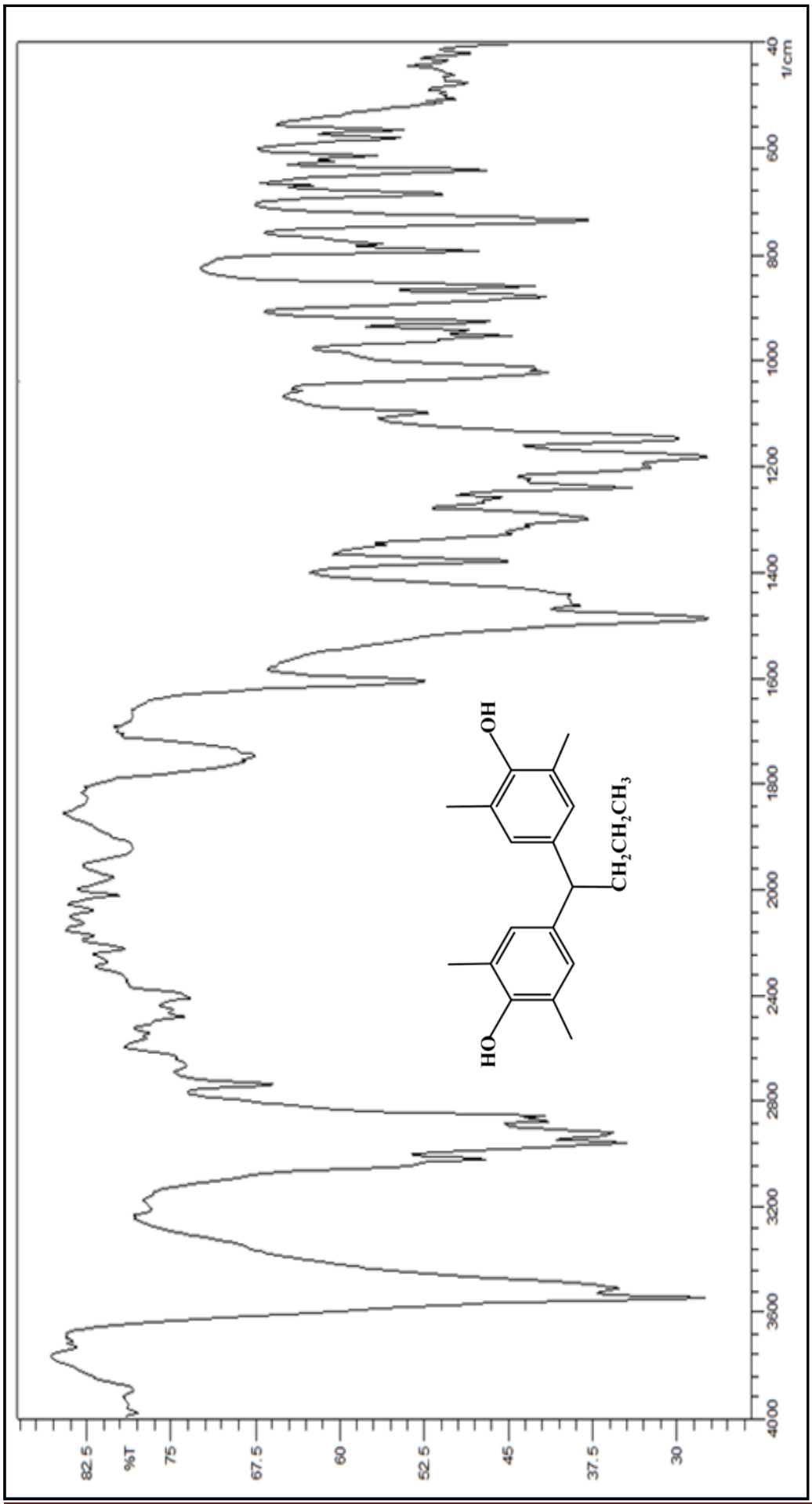


Figure 5.14: FTIR spectrum of compound **20**

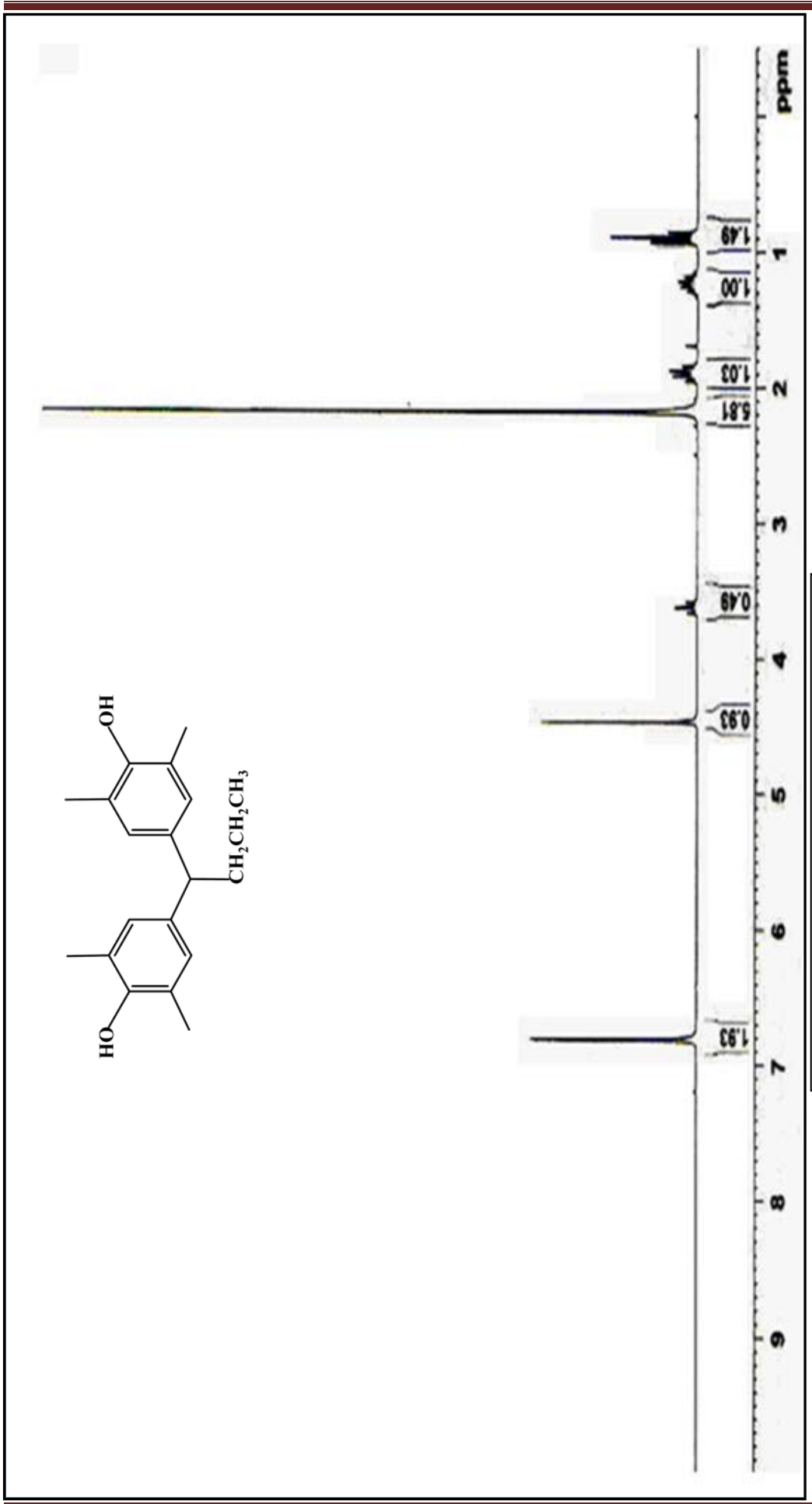


Figure 5.15: ^{1}H NMR spectrum of compound **20**

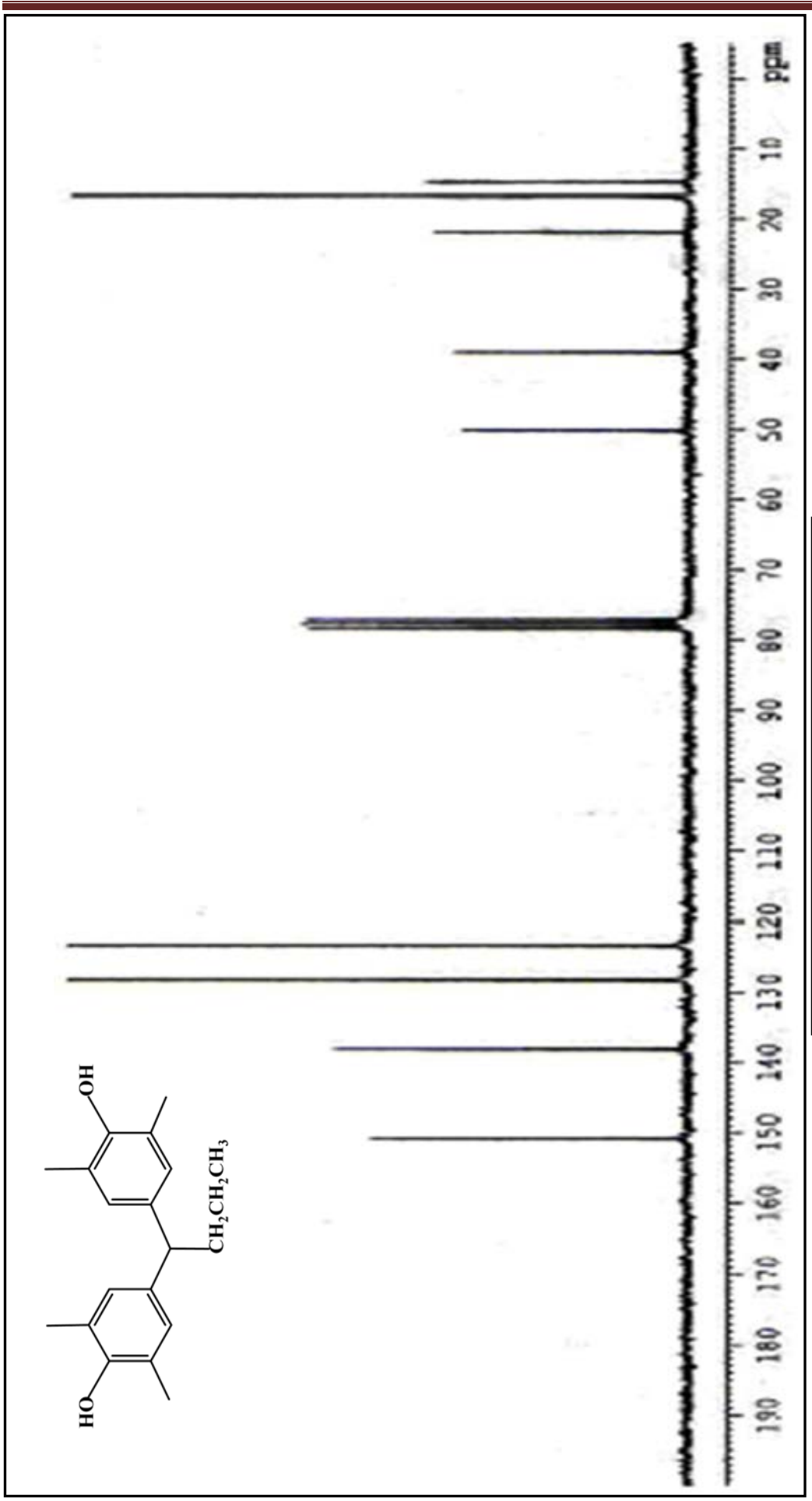


Figure 5.16: ^{13}C NMR spectrum of compound **20**

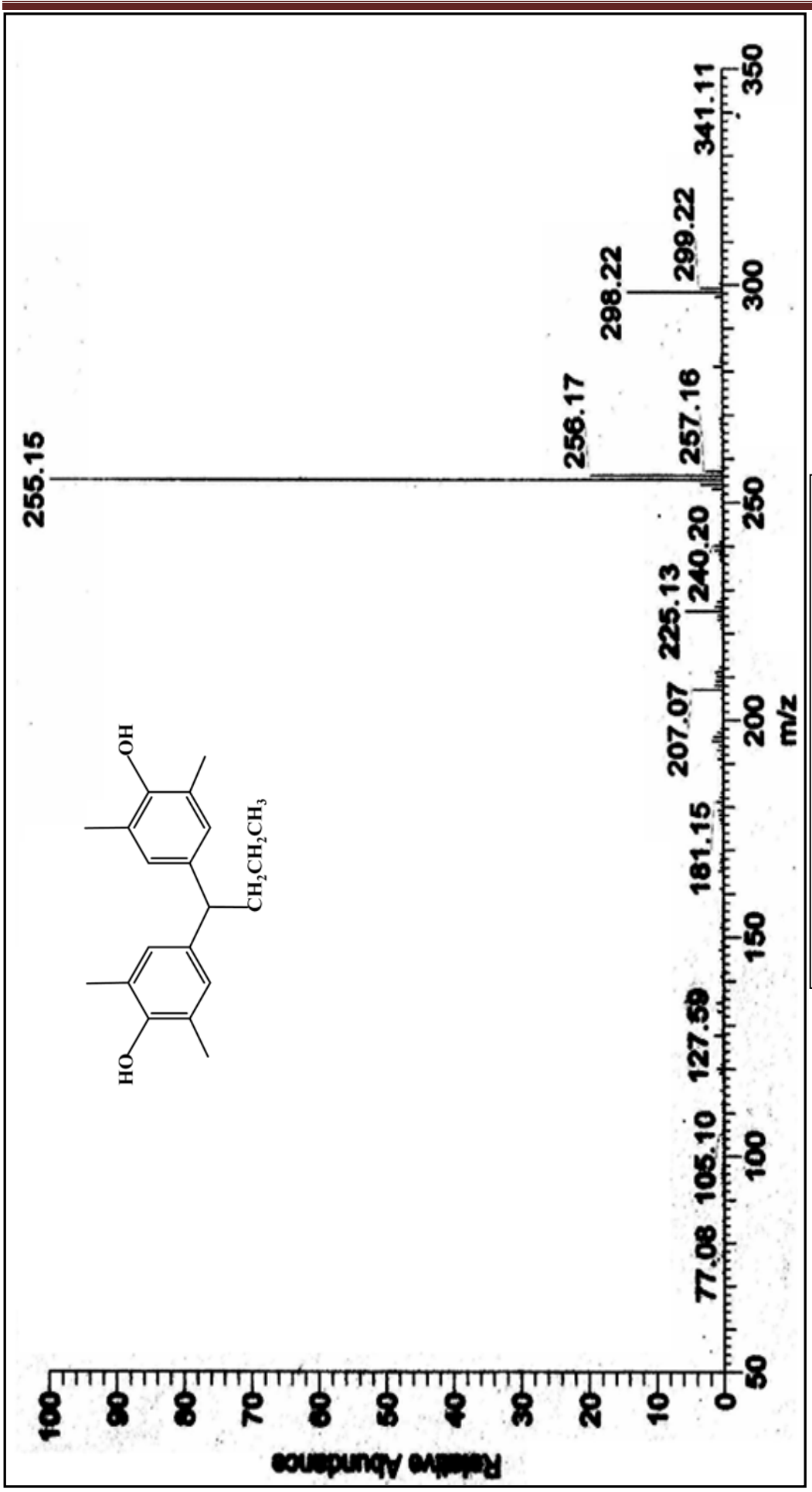


Figure 5.17: EI-MS spectrum of compound **20**

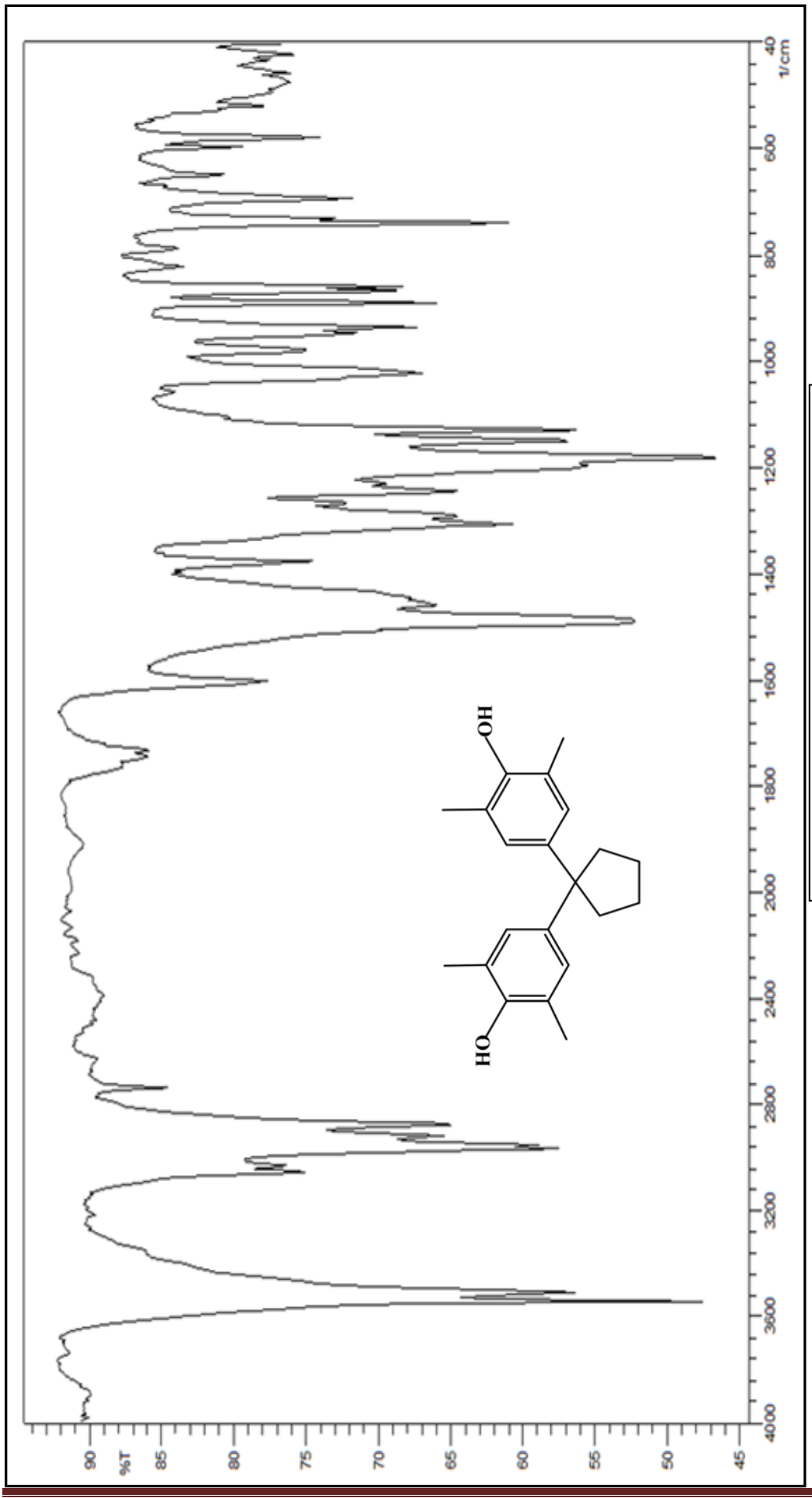


Figure 5.18: FTIR spectrum of compound **21**

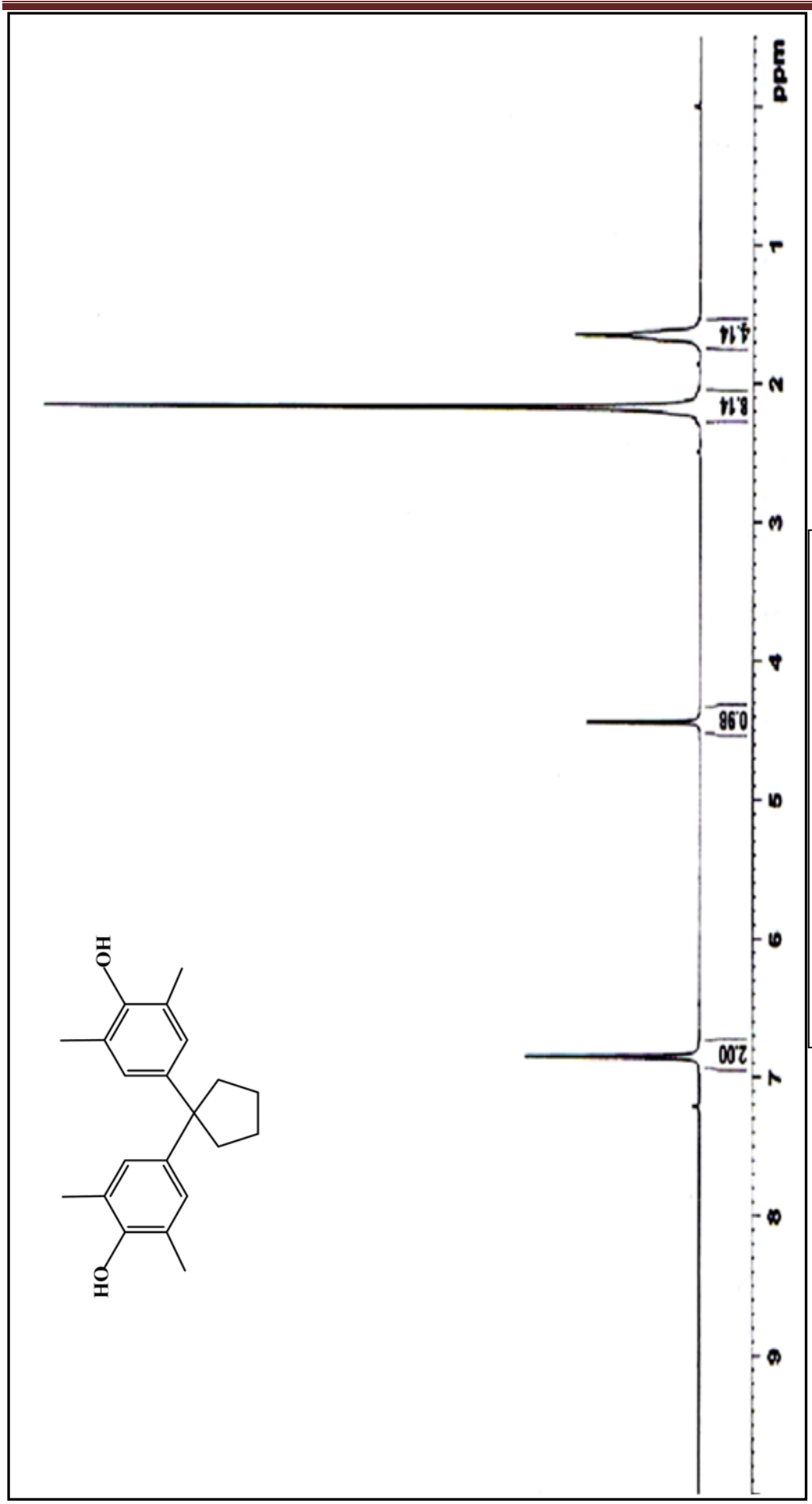


Figure 5.19: ^{1}H NMR spectrum of compound **21**

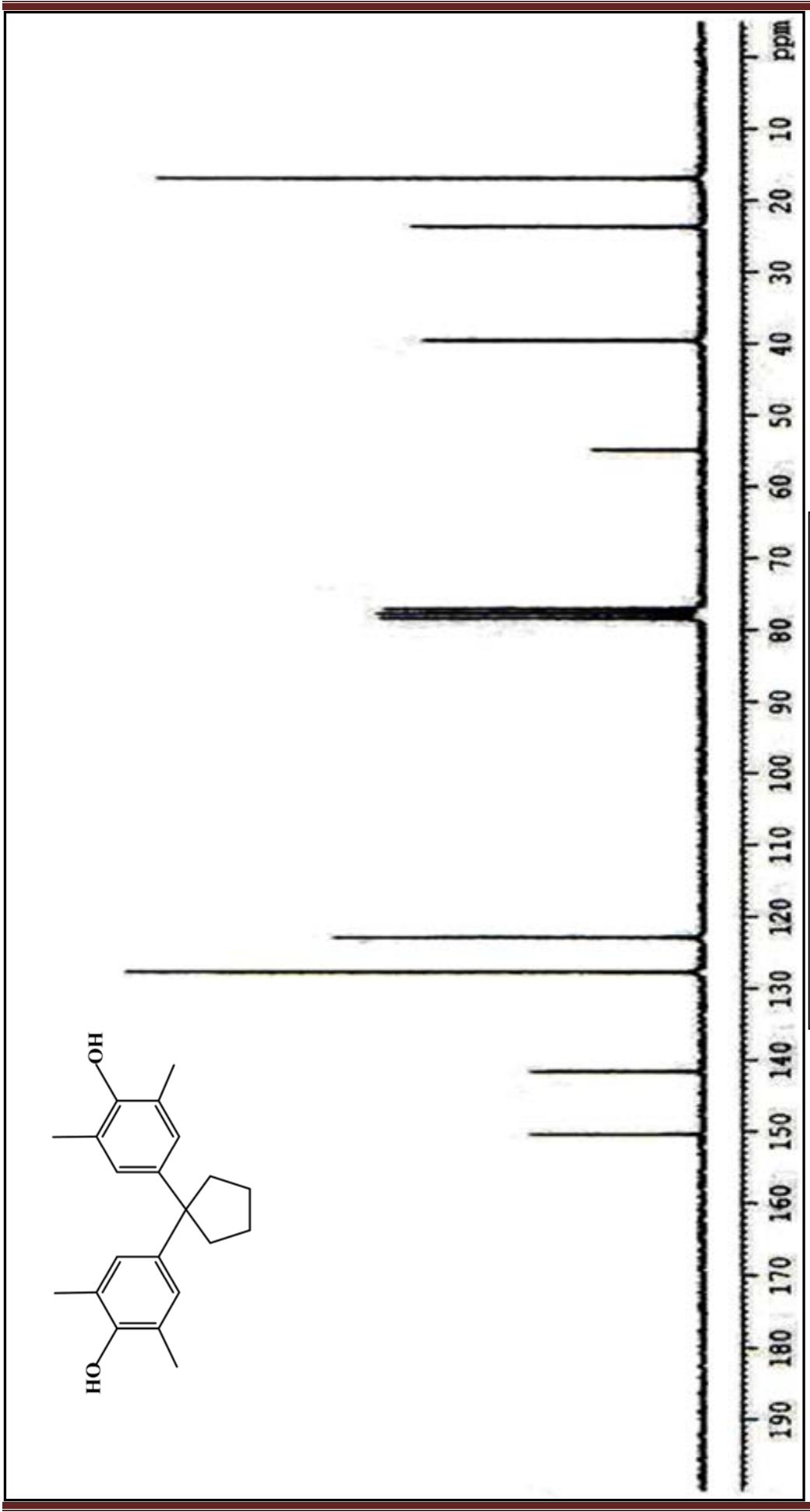


Figure 5.20: ^{13}C NMR spectrum of compound **21**

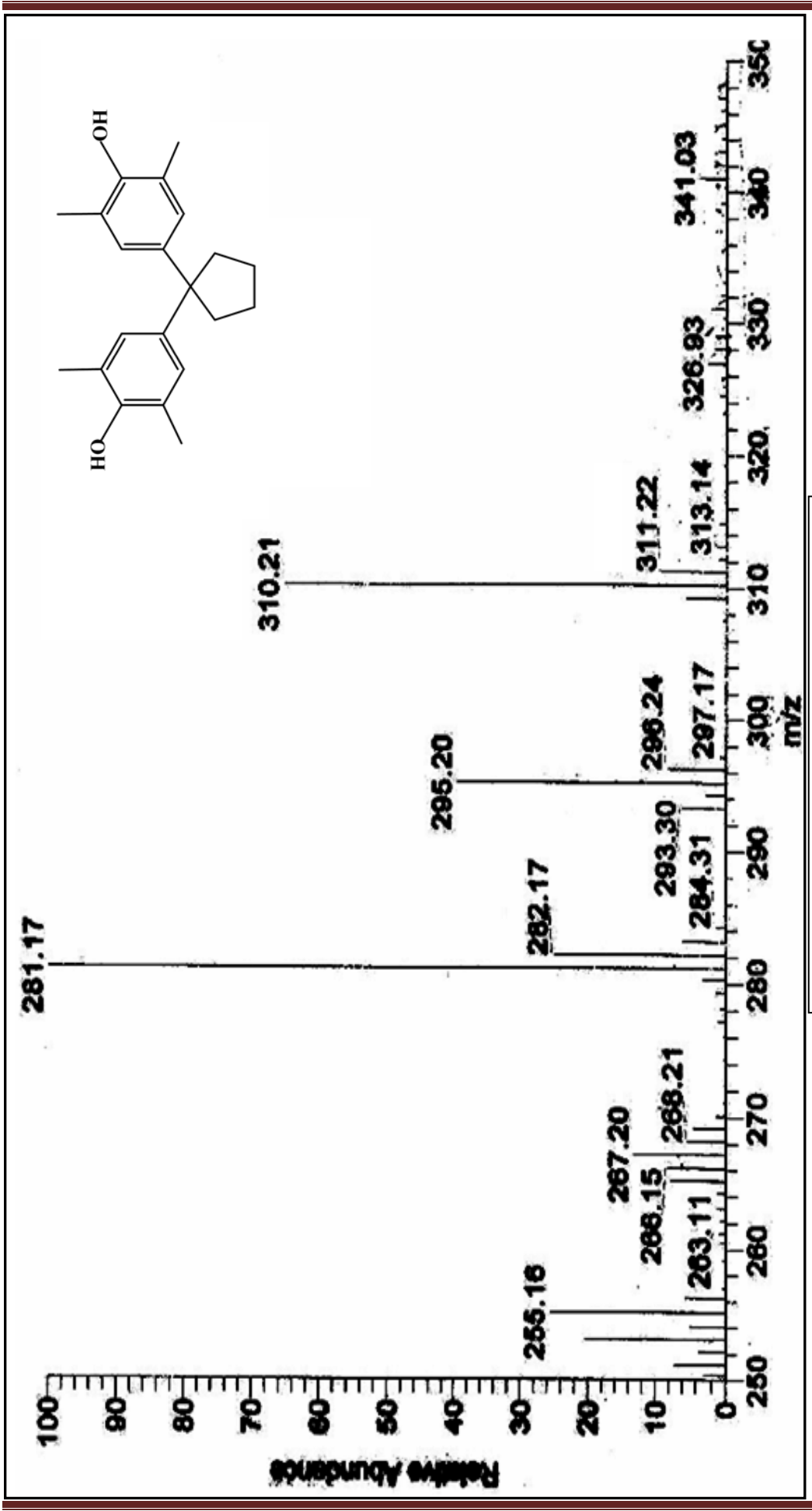


Figure 5.21: EI-MS spectrum of compound **21**

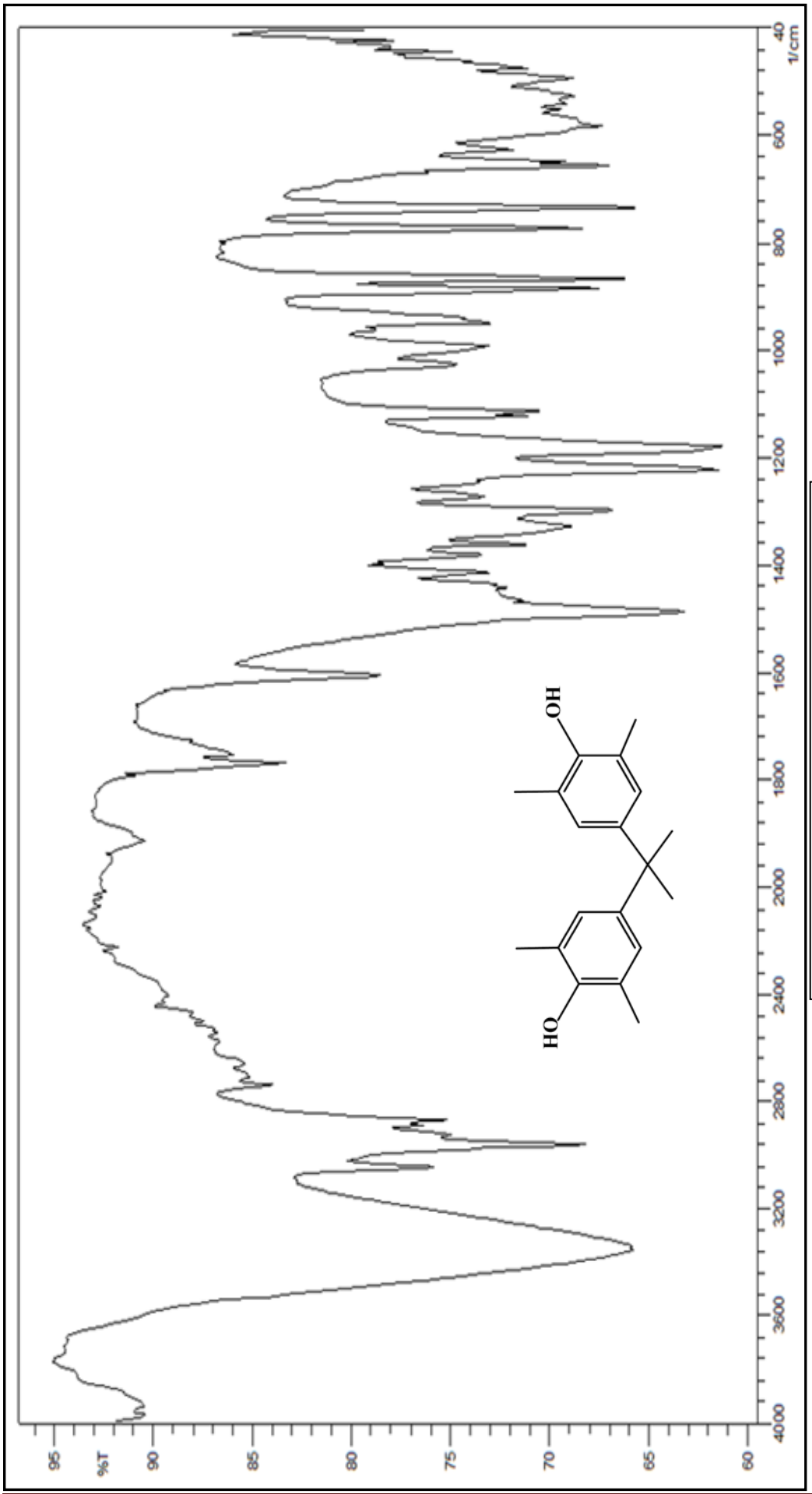


Figure 5.22: FTIR spectrum of compound **22**

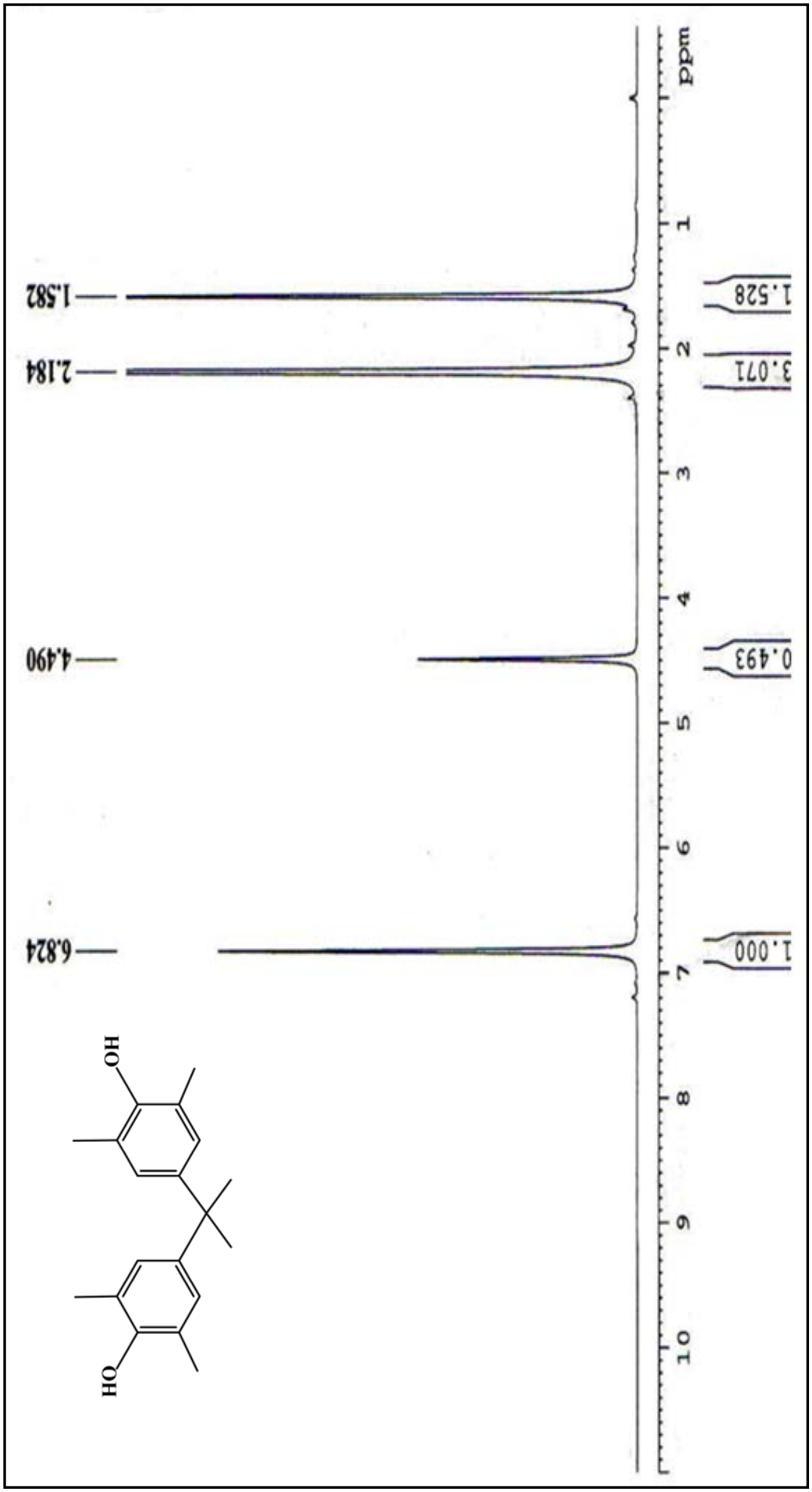


Figure 5.23: ^{1}H NMR spectrum of compound **22**

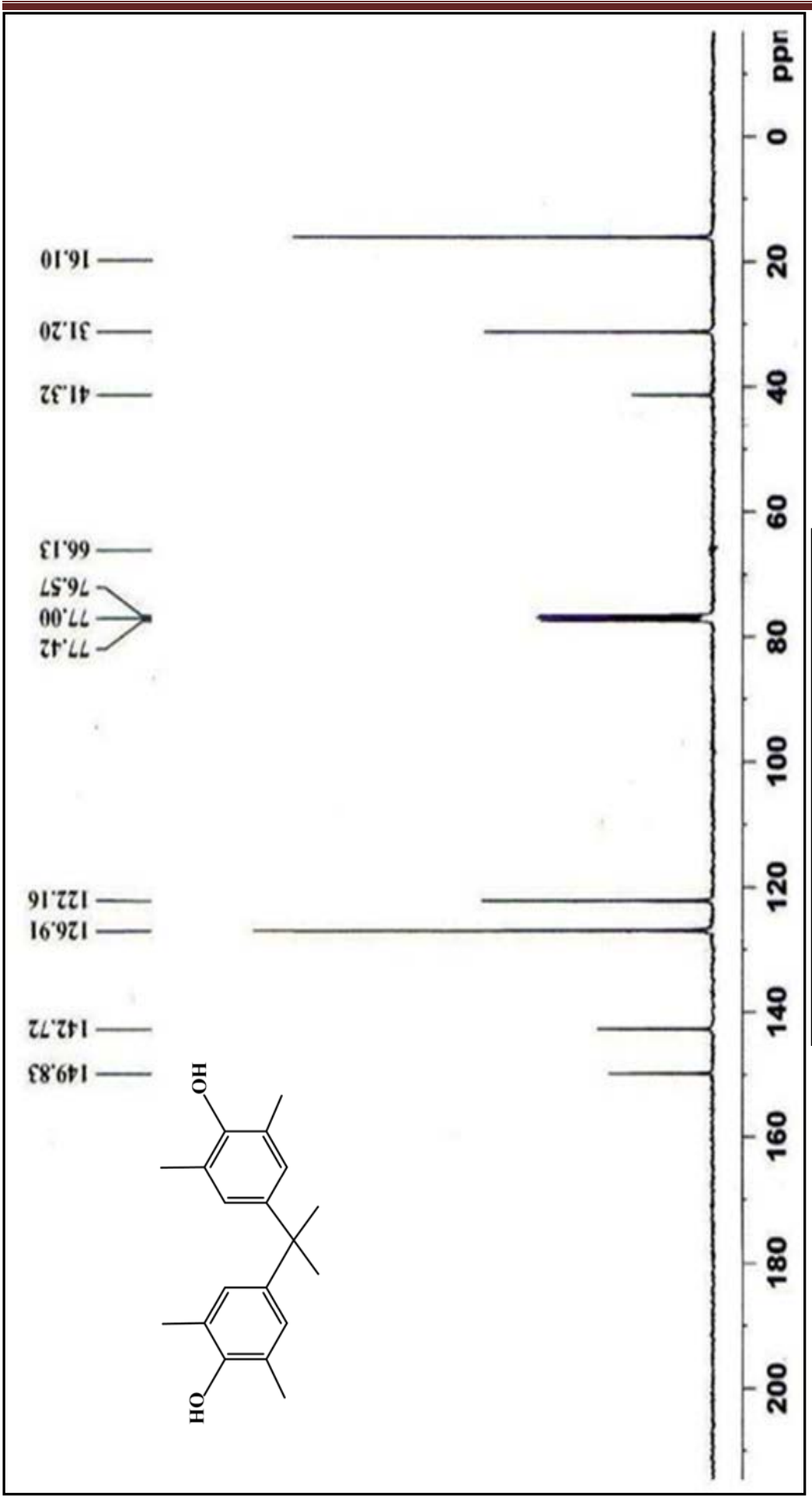


Figure 5.24: ^{13}C NMR spectrum of compound **22**

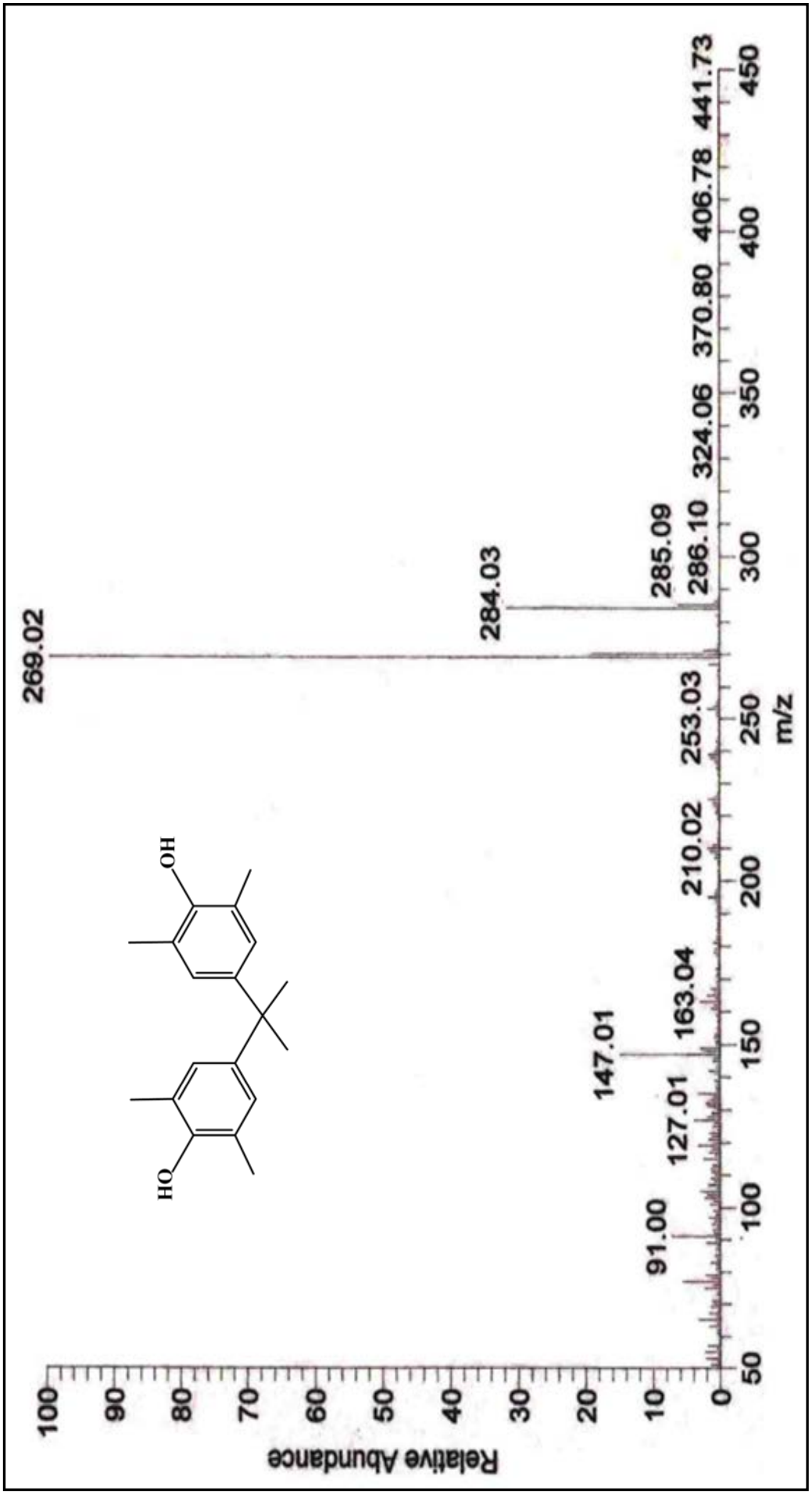


Figure 5.25: EI-MS spectrum of compound 22

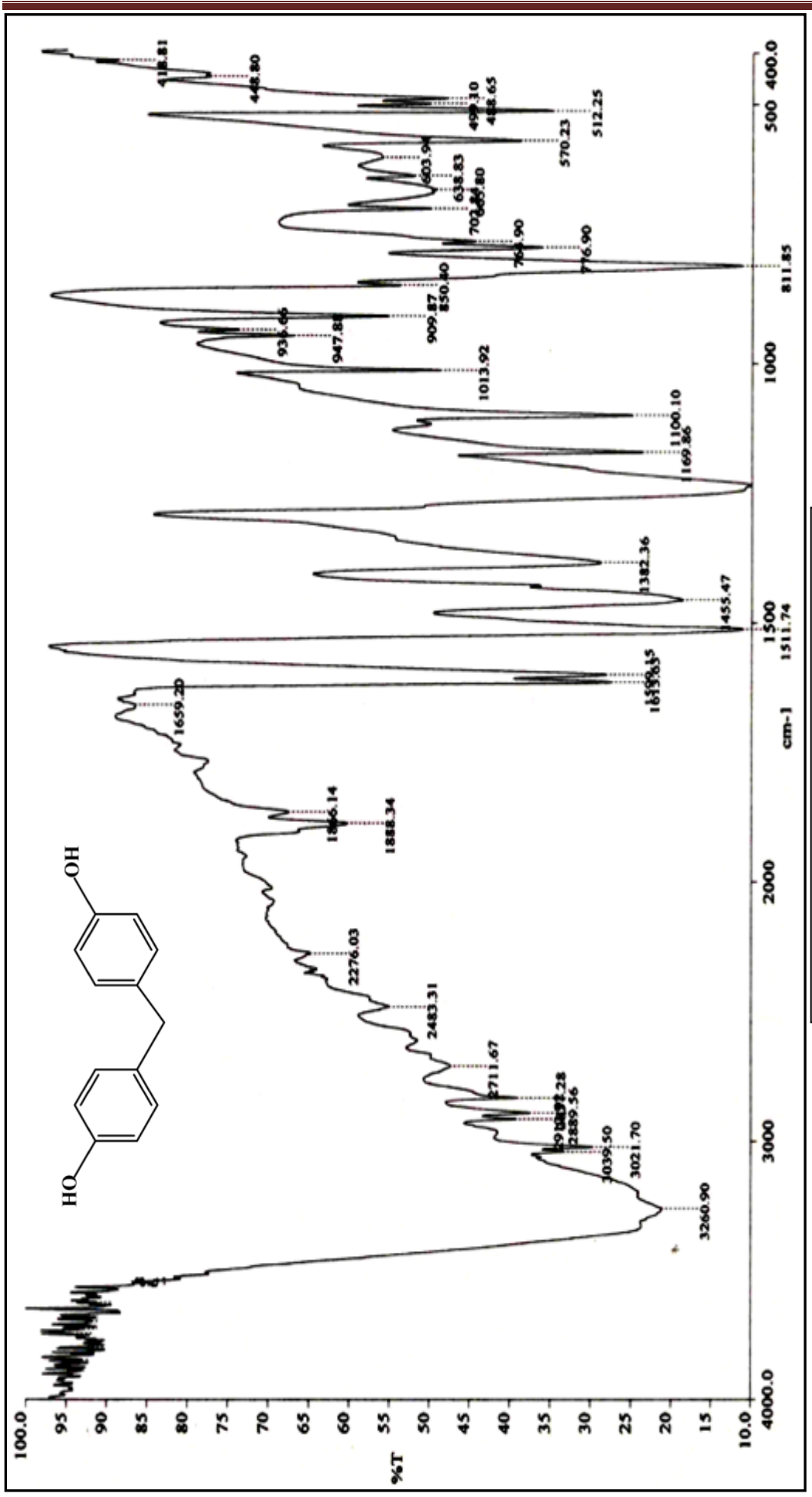


Figure 5.26: FTIR spectrum of compound **23**

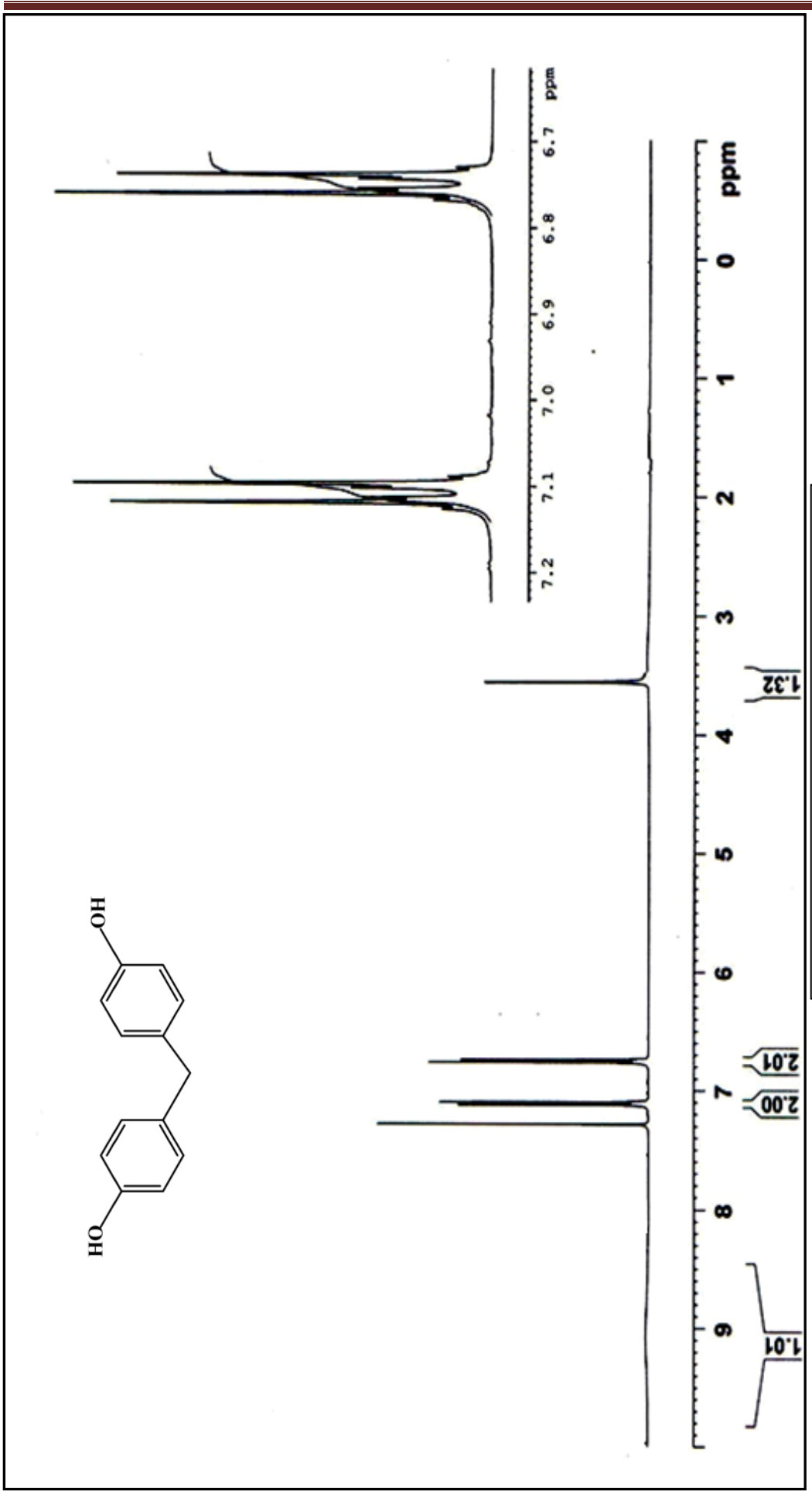


Figure 5.27: ^{1}H NMR spectrum of compound **23**

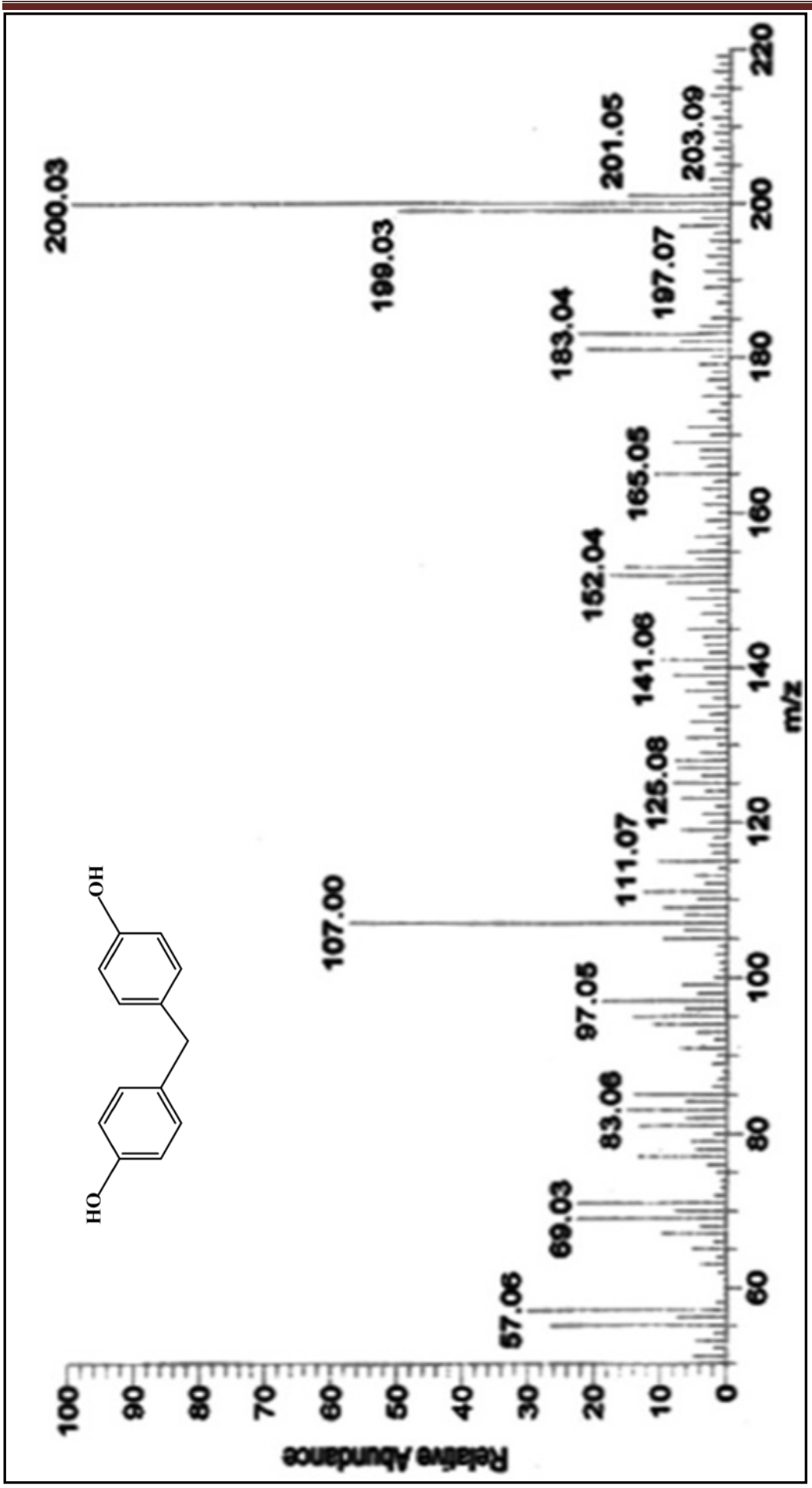


Figure 5.28: EI-MS spectrum of compound **23**

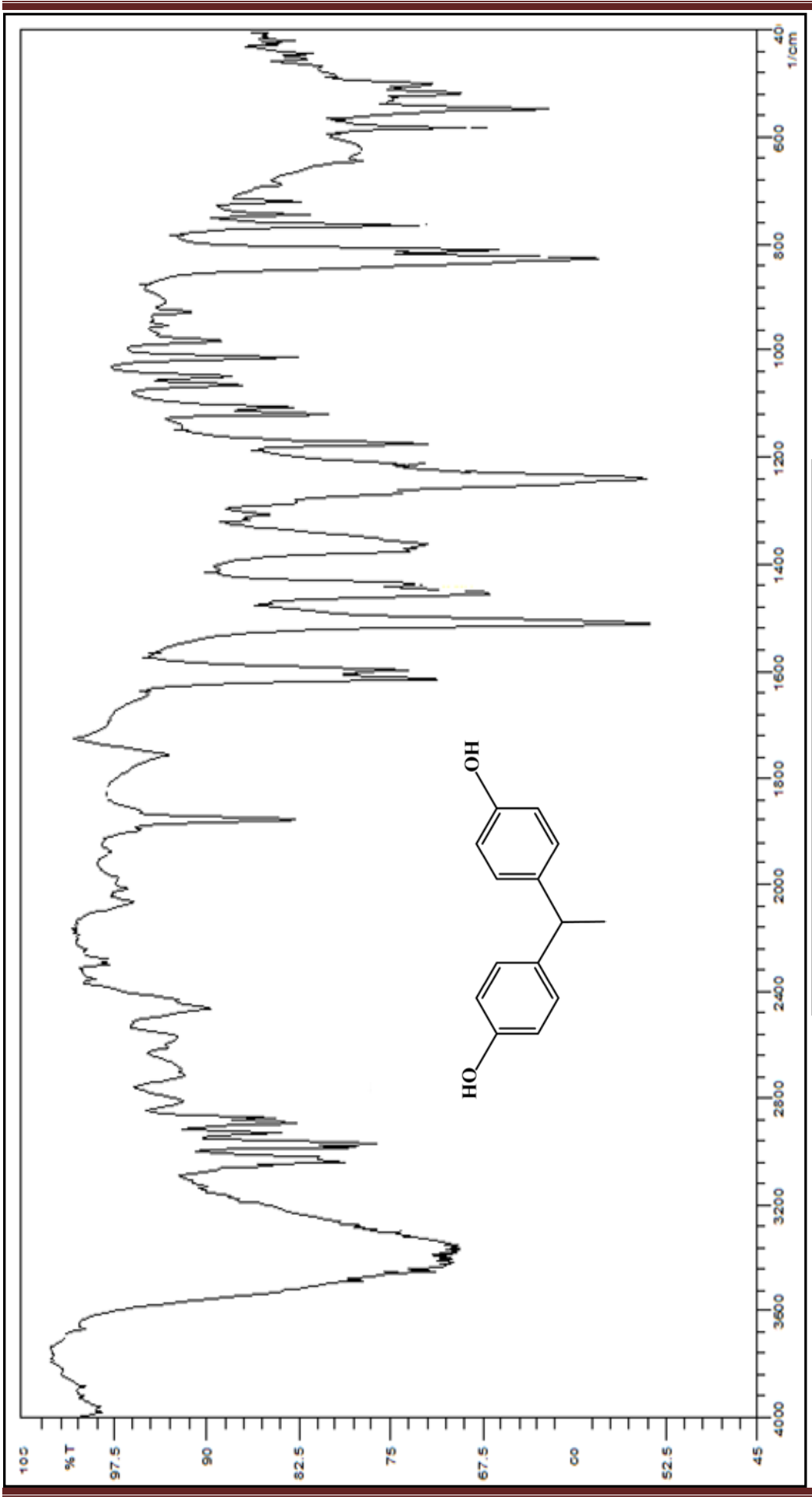


Figure 5.29: FTIR spectrum of compound **24**

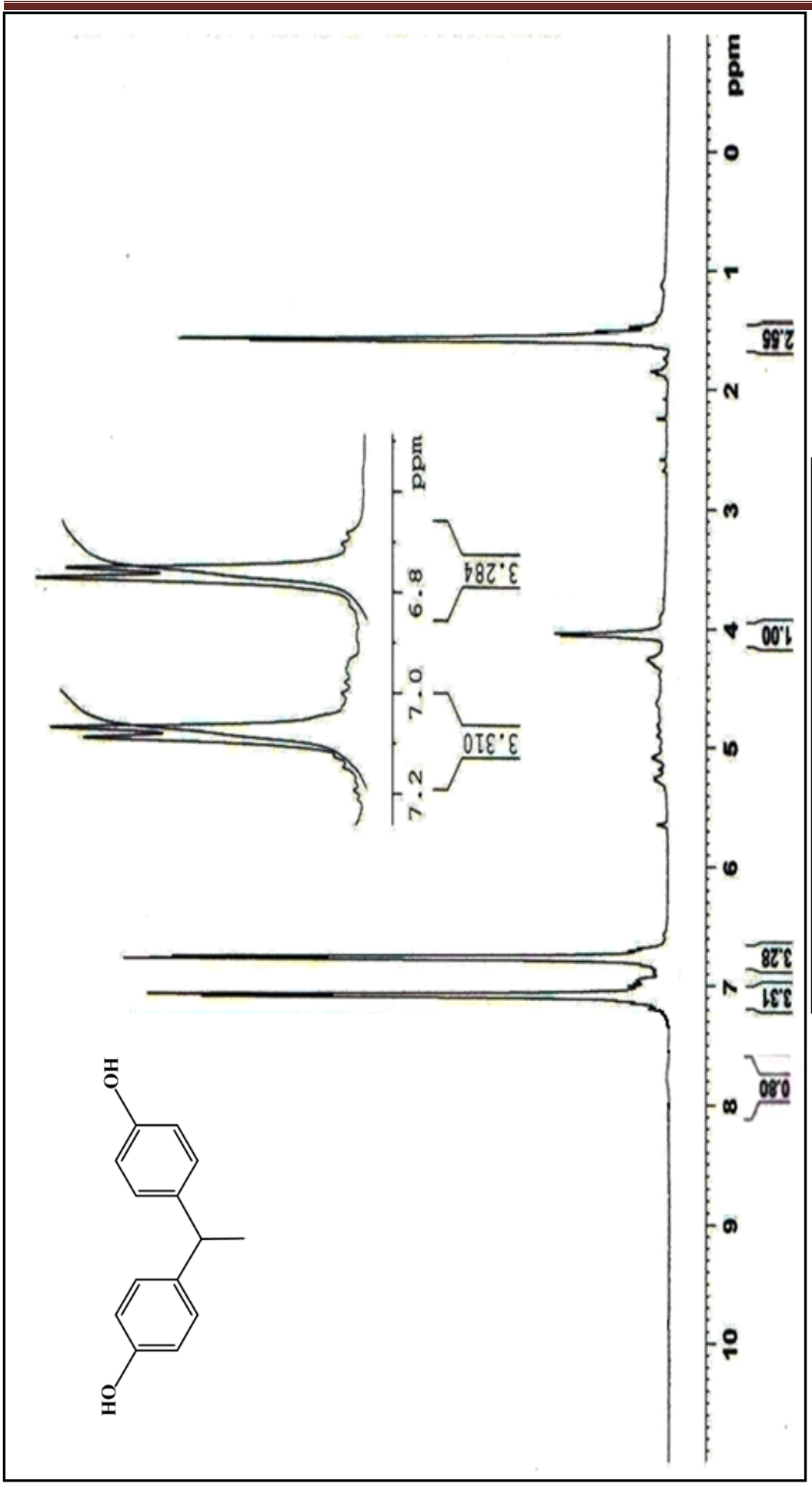


Figure 5.30: ^{1}H NMR spectrum of compound **24**

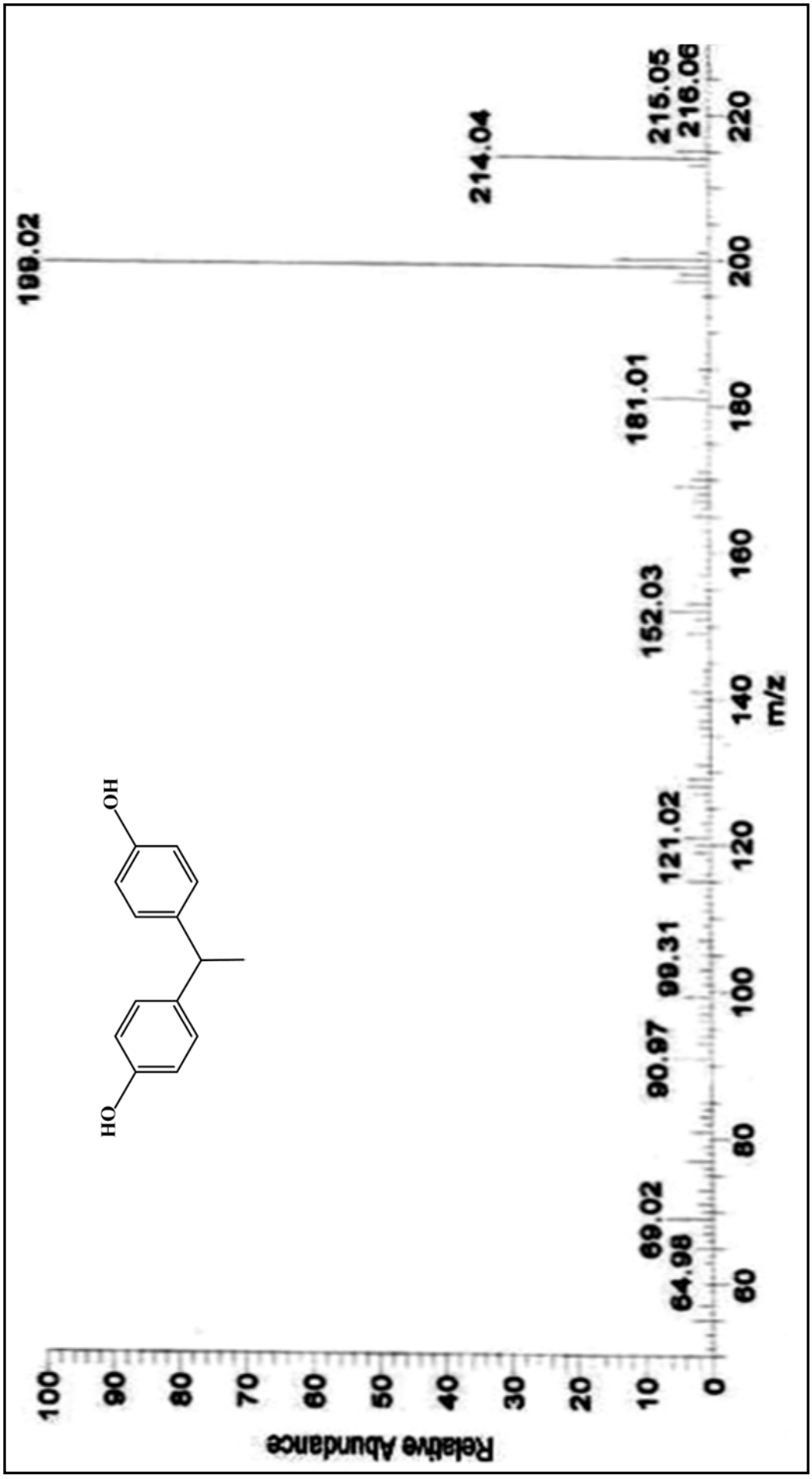


Figure 5.31: EI-MS spectrum of compound **24**

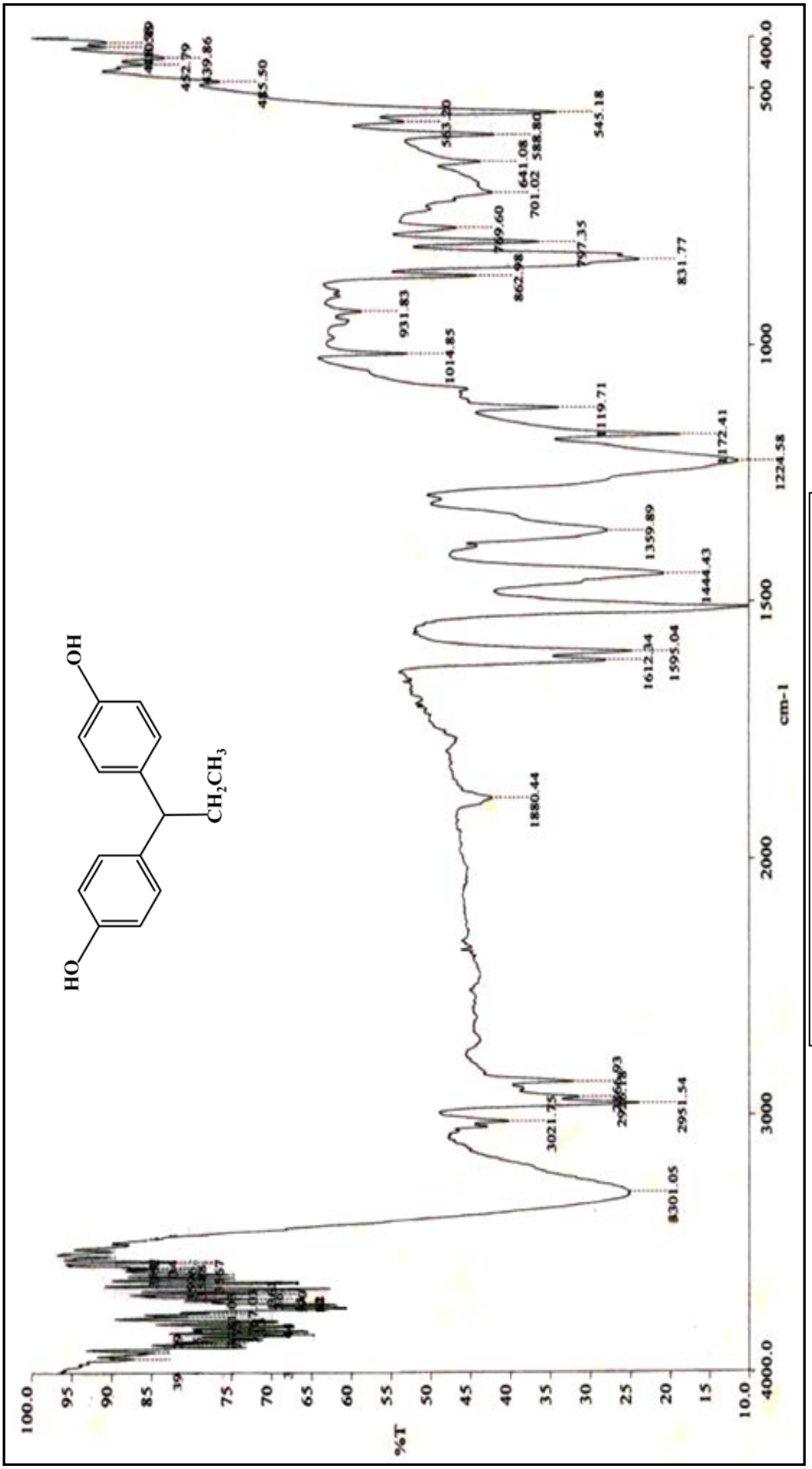


Figure 5.32: FTIR spectrum of compound **25**

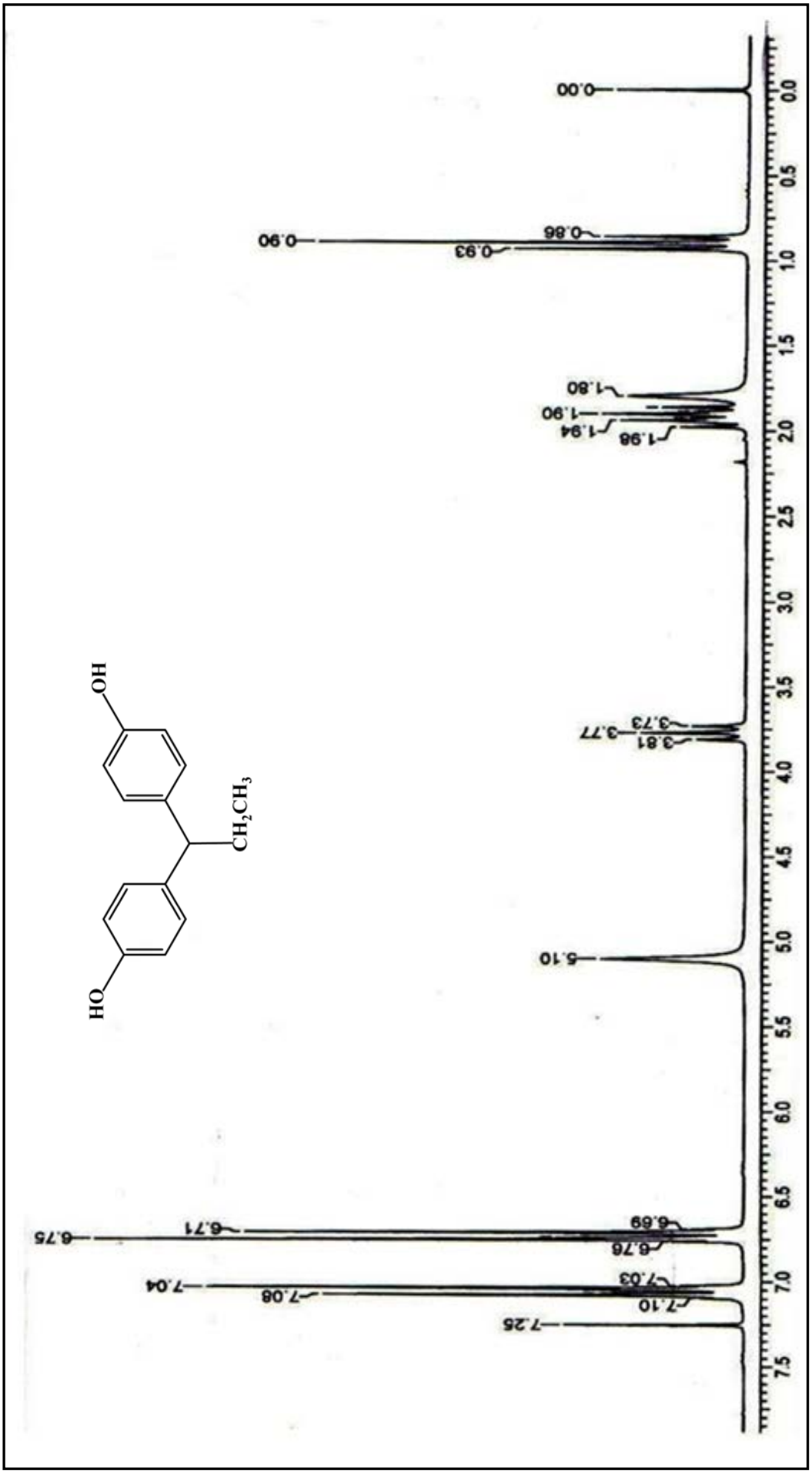


Figure 5.33: ^{1}H NMR spectrum of compound **25**

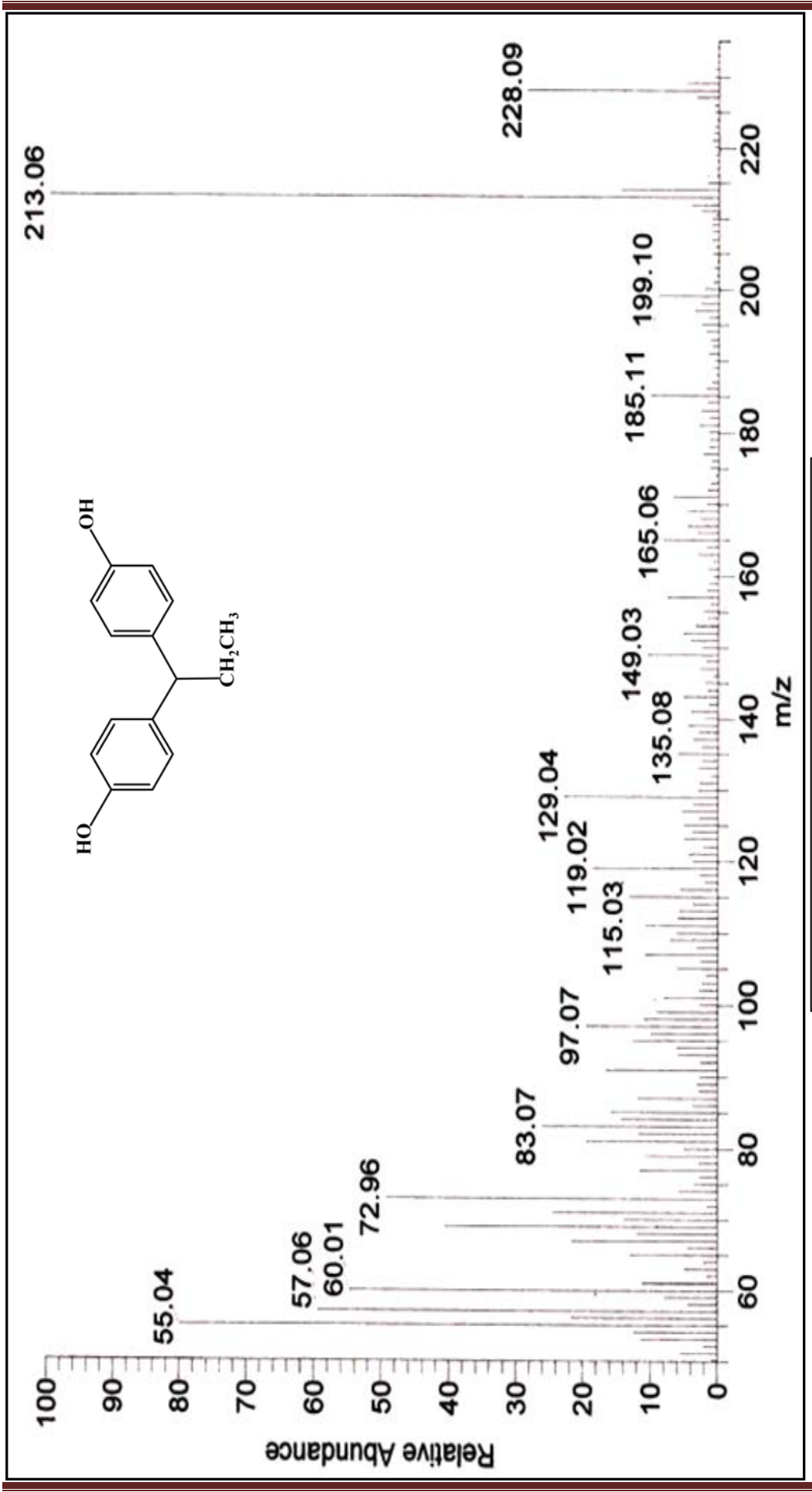


Figure 5.34: EI-MS spectrum of compound **25**

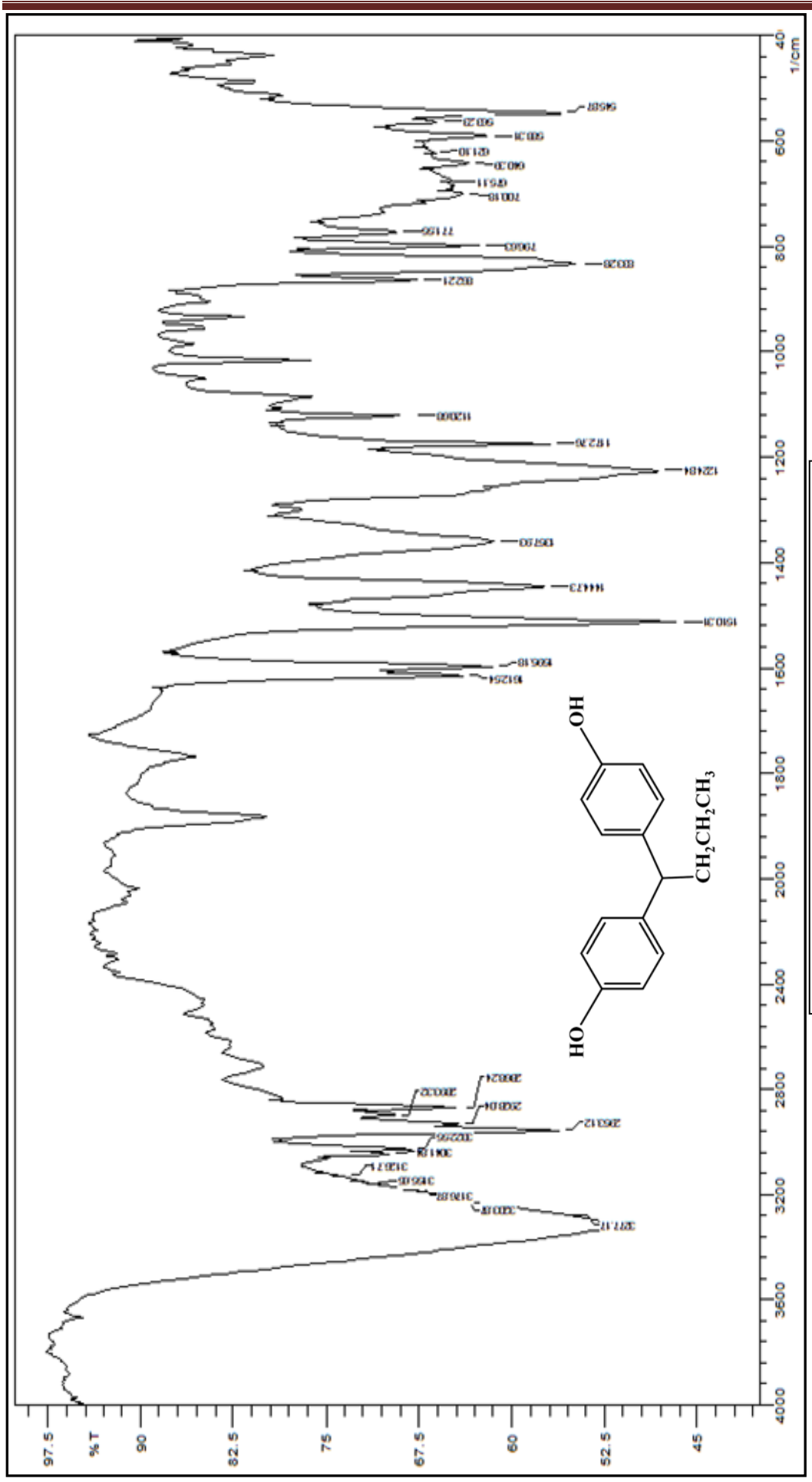


Figure 5.35: FTIR spectrum of compound **26**

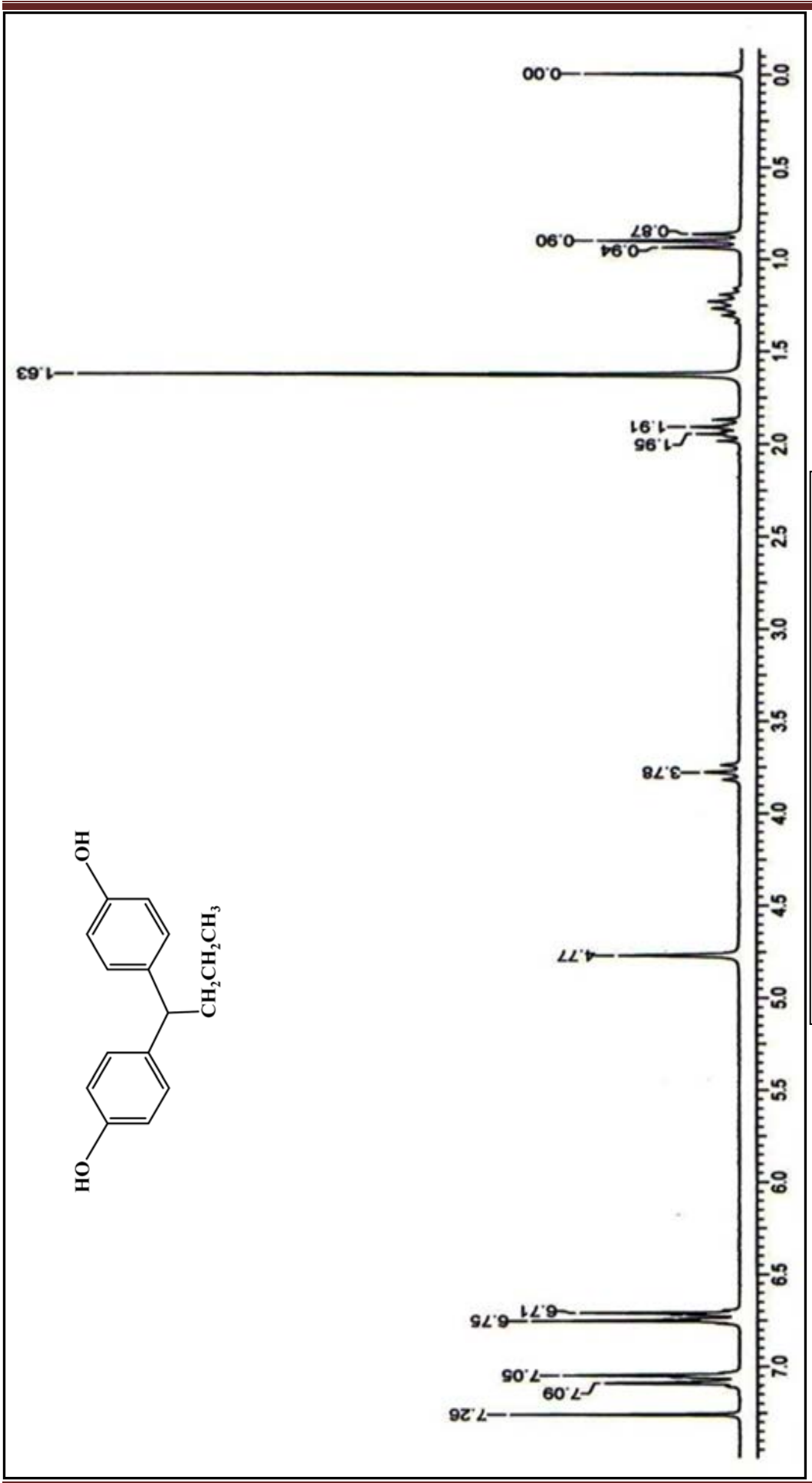


Figure 5.36: ^{1}H NMR spectrum of compound **26**

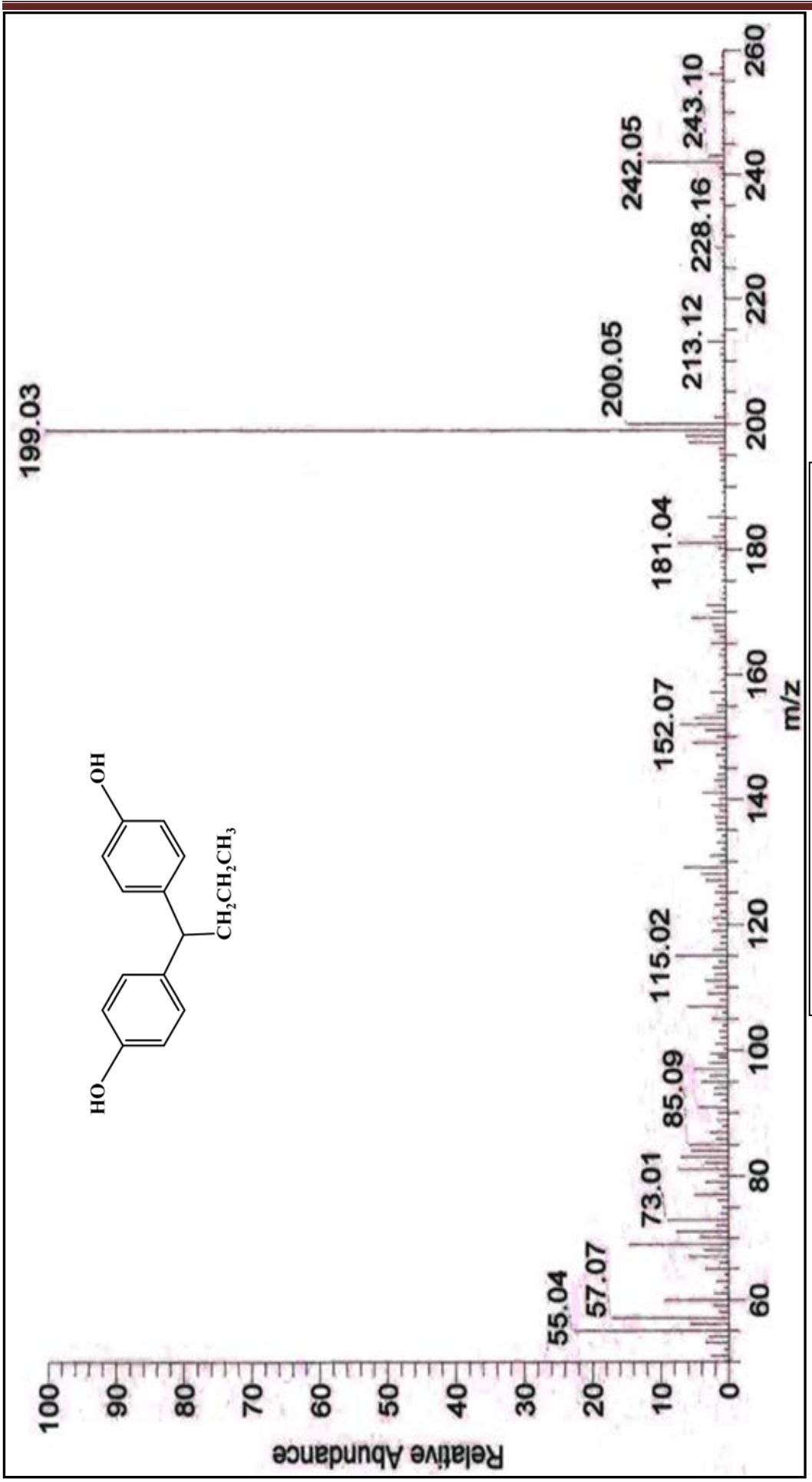


Figure 5.37: EI-MS spectrum of compound **26**

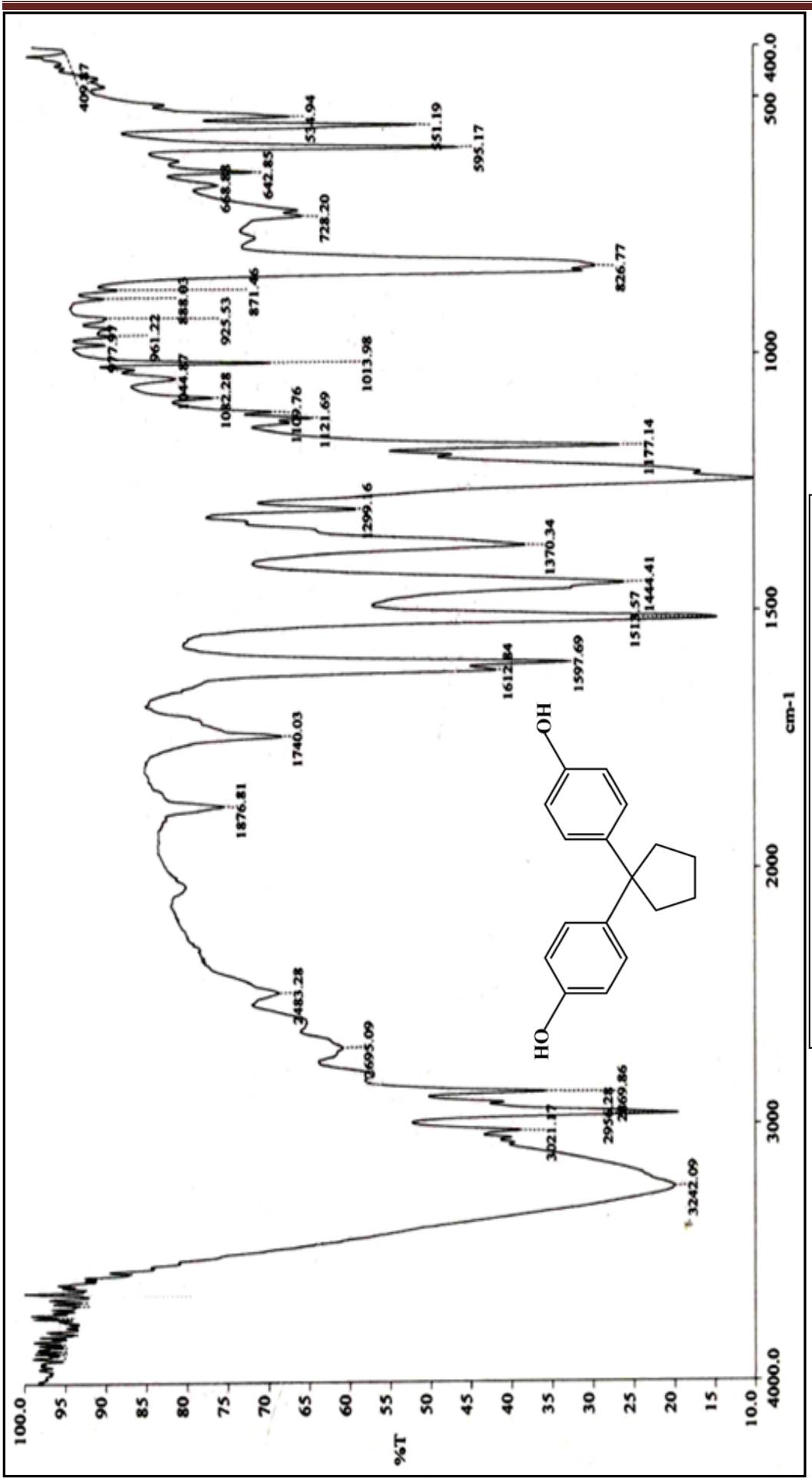


Figure 5.38: FTIR spectrum of compound **27**

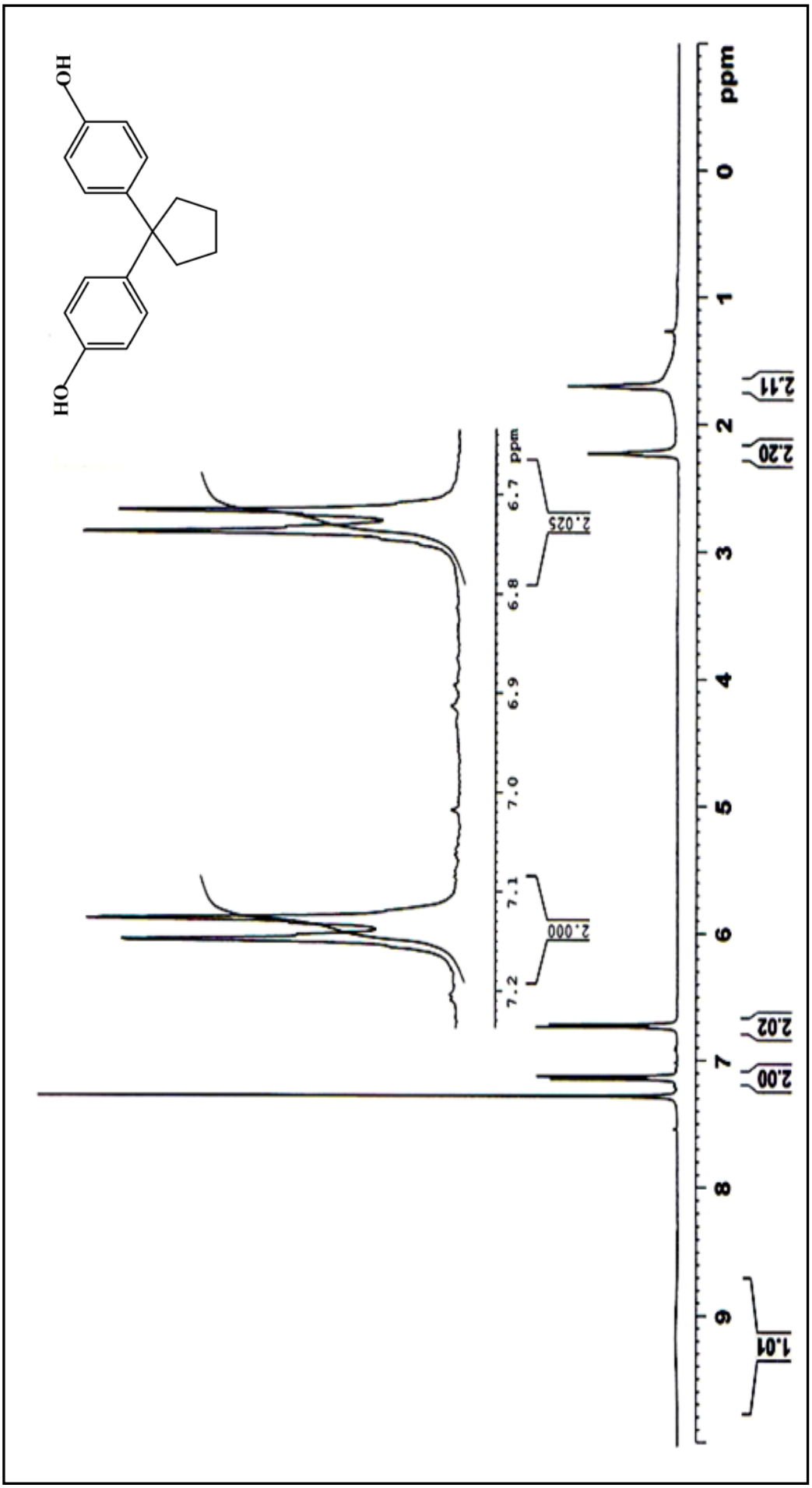


Figure 5.39: ^{1}H NMR spectrum of compound **27**

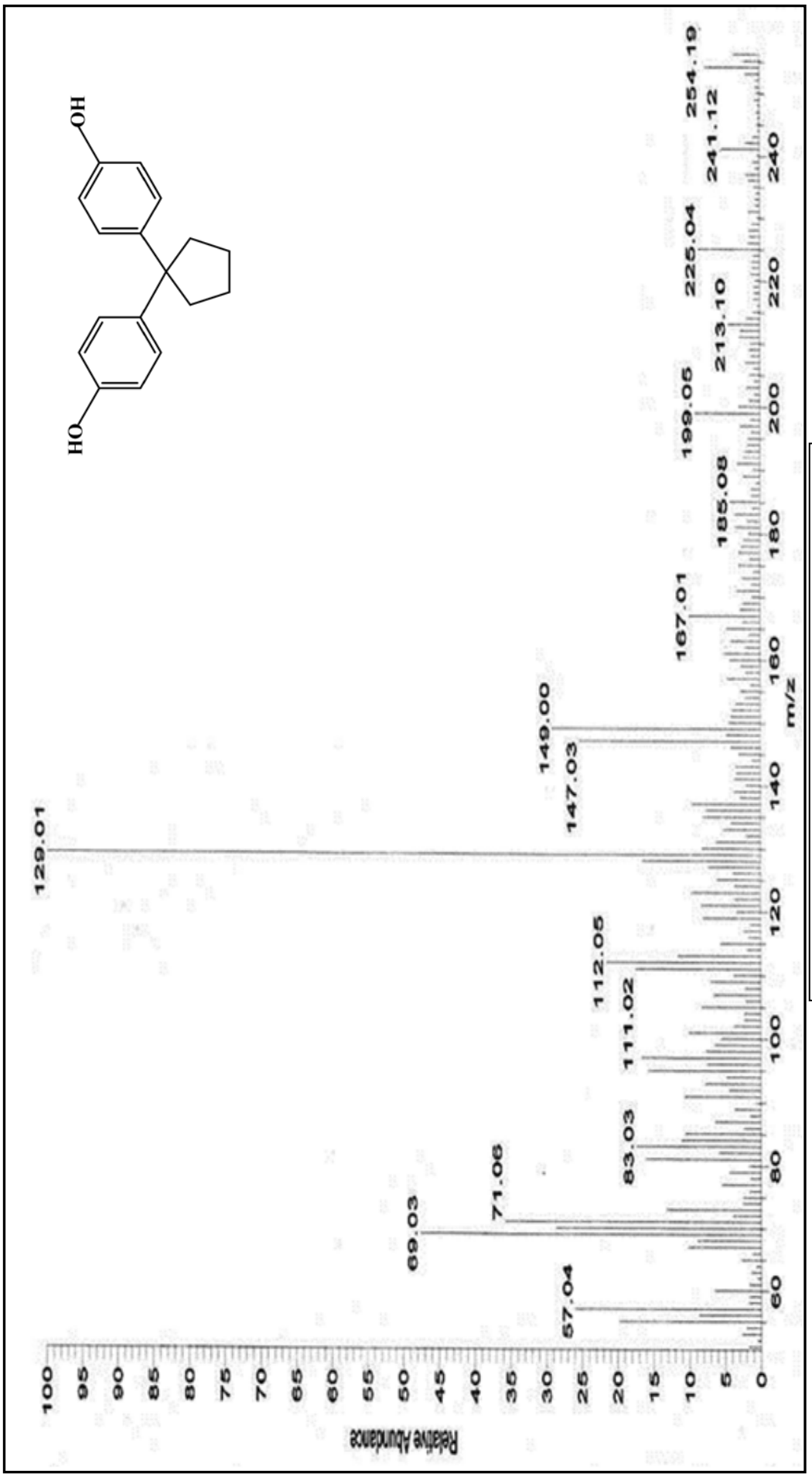


Figure 5.40: EI-MS spectrum of compound **27**

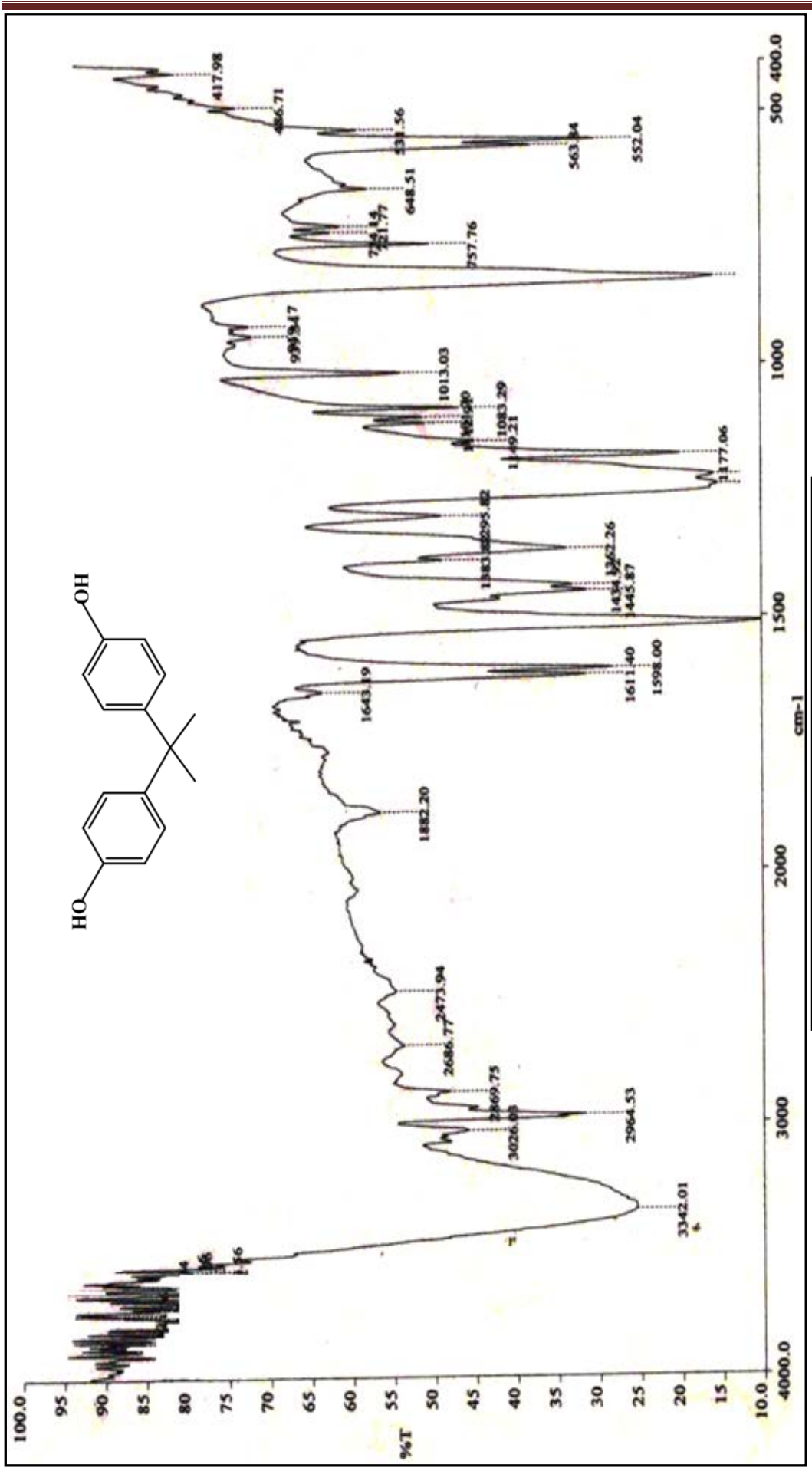


Figure 5.41: FTIR spectrum of compound **28**

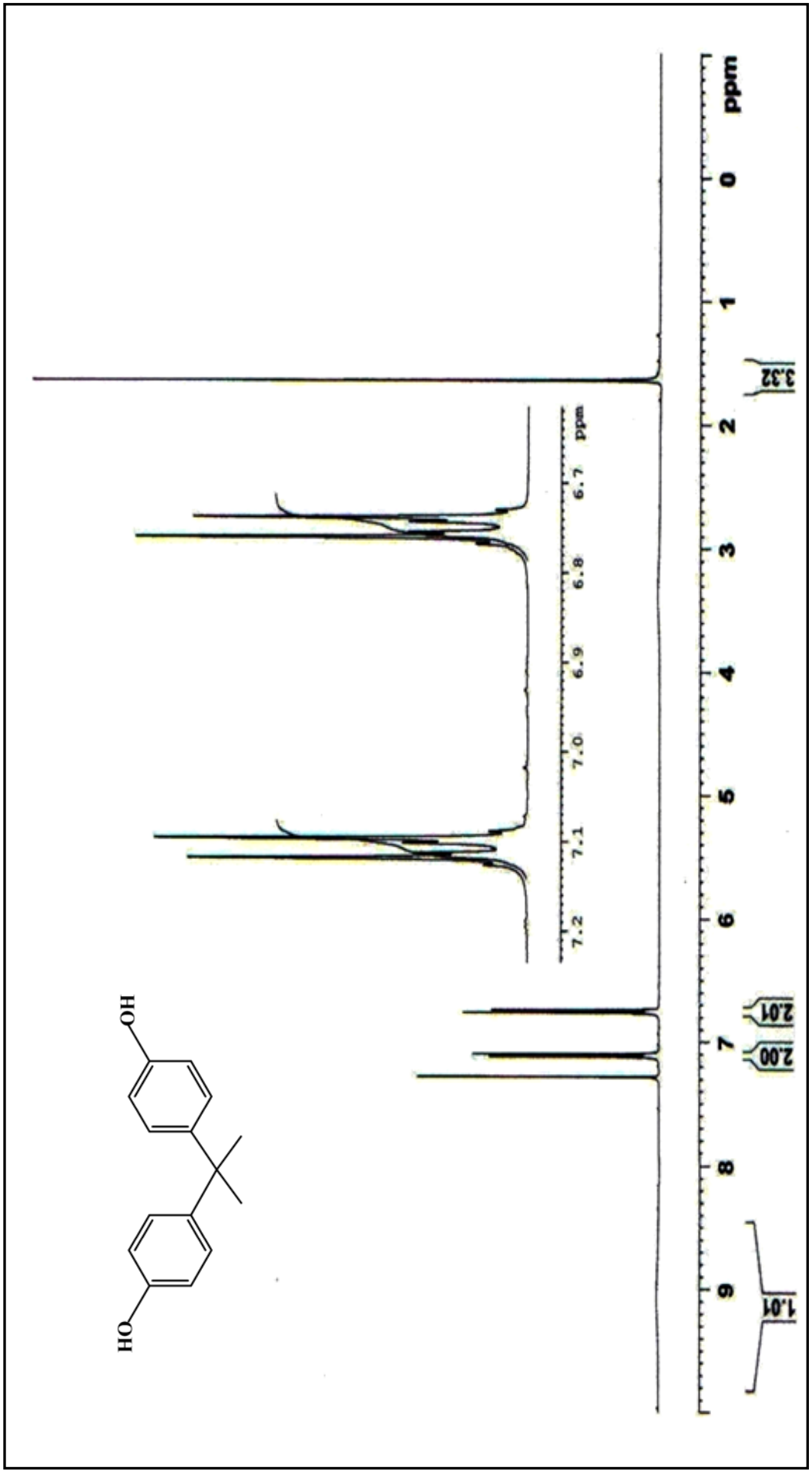


Figure 5.42: ^{1}H NMR spectrum of compound **28**

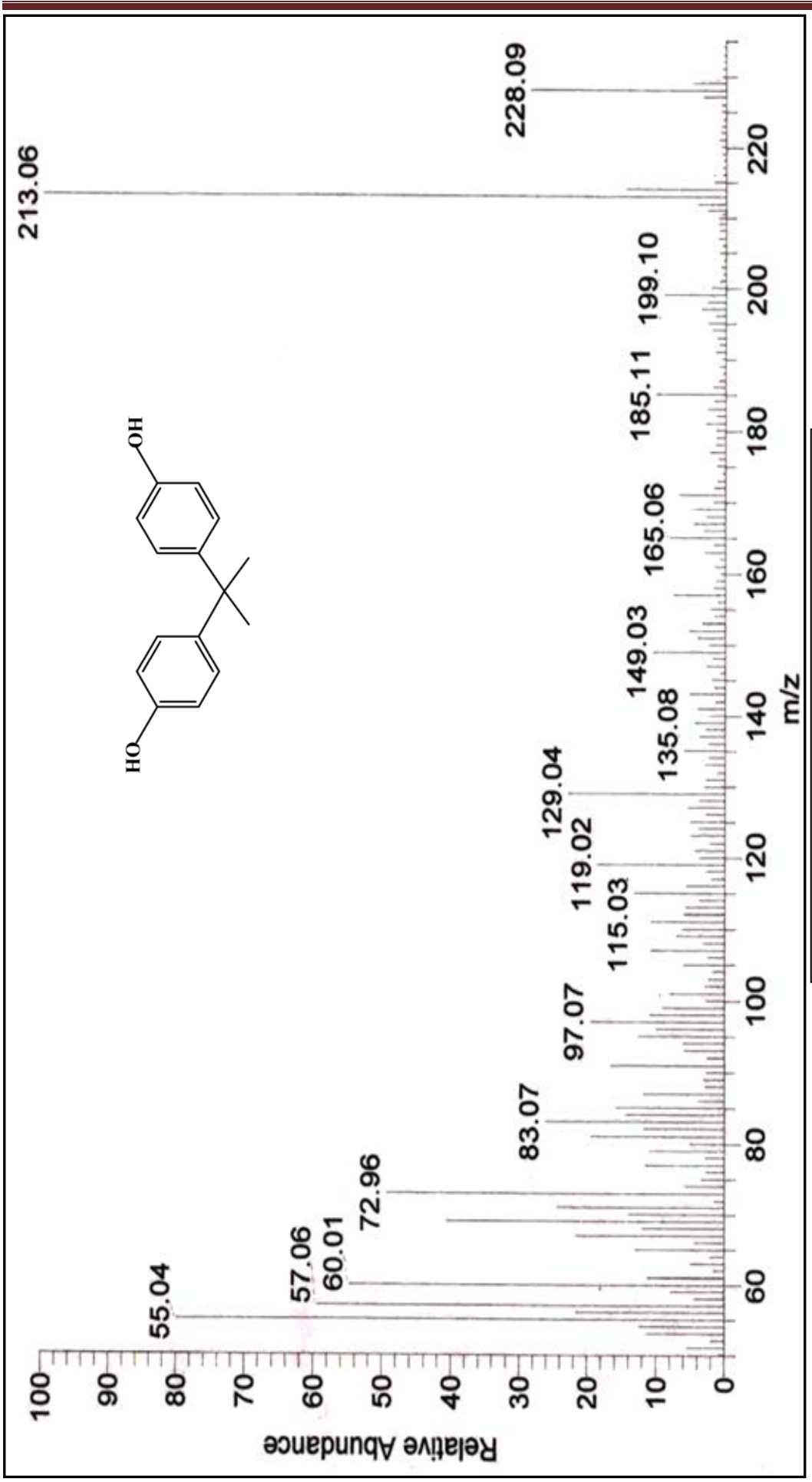


Figure 5.43: EI-MS spectrum of compound **28**

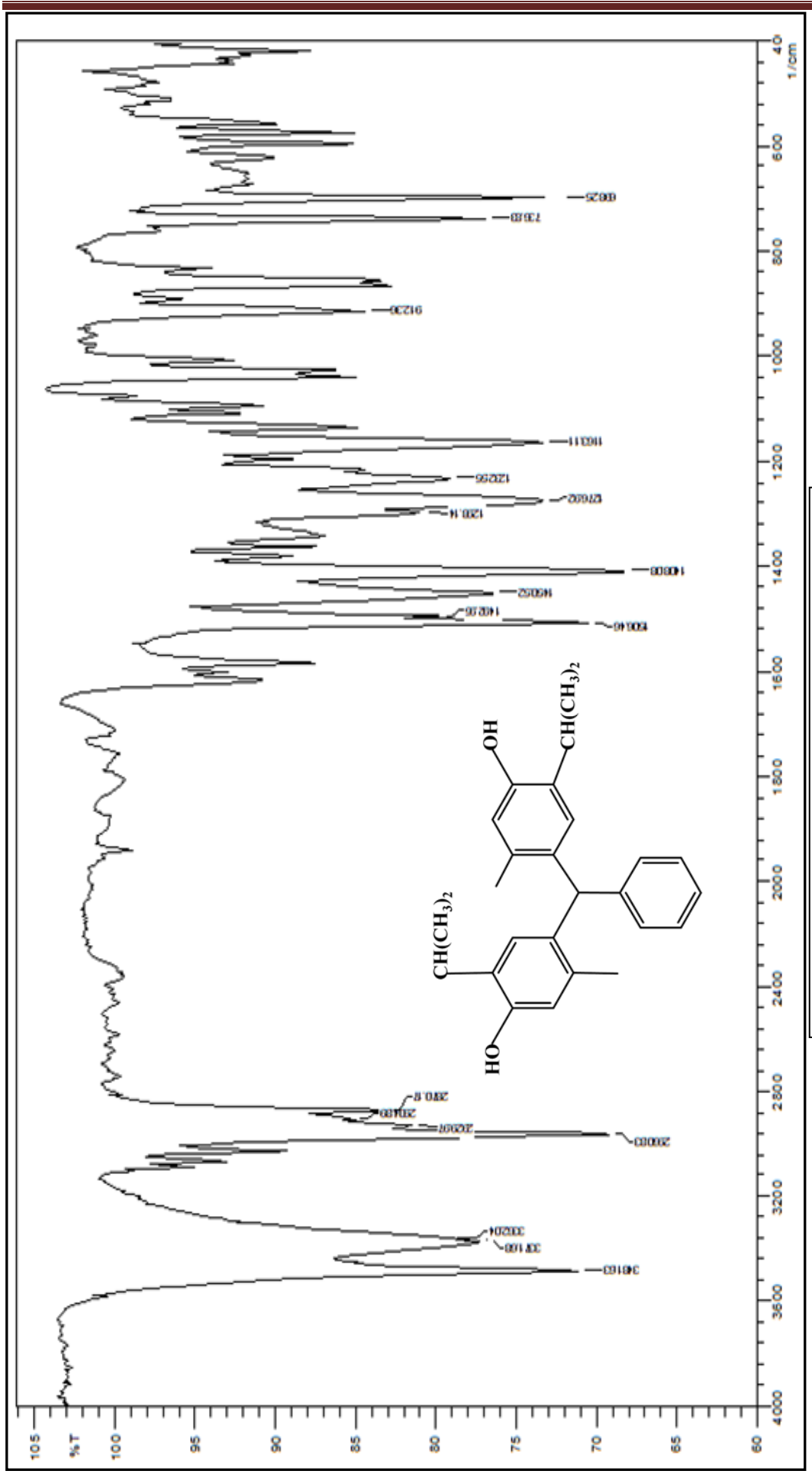


Figure 5.44: FTIR spectrum of compound **29**

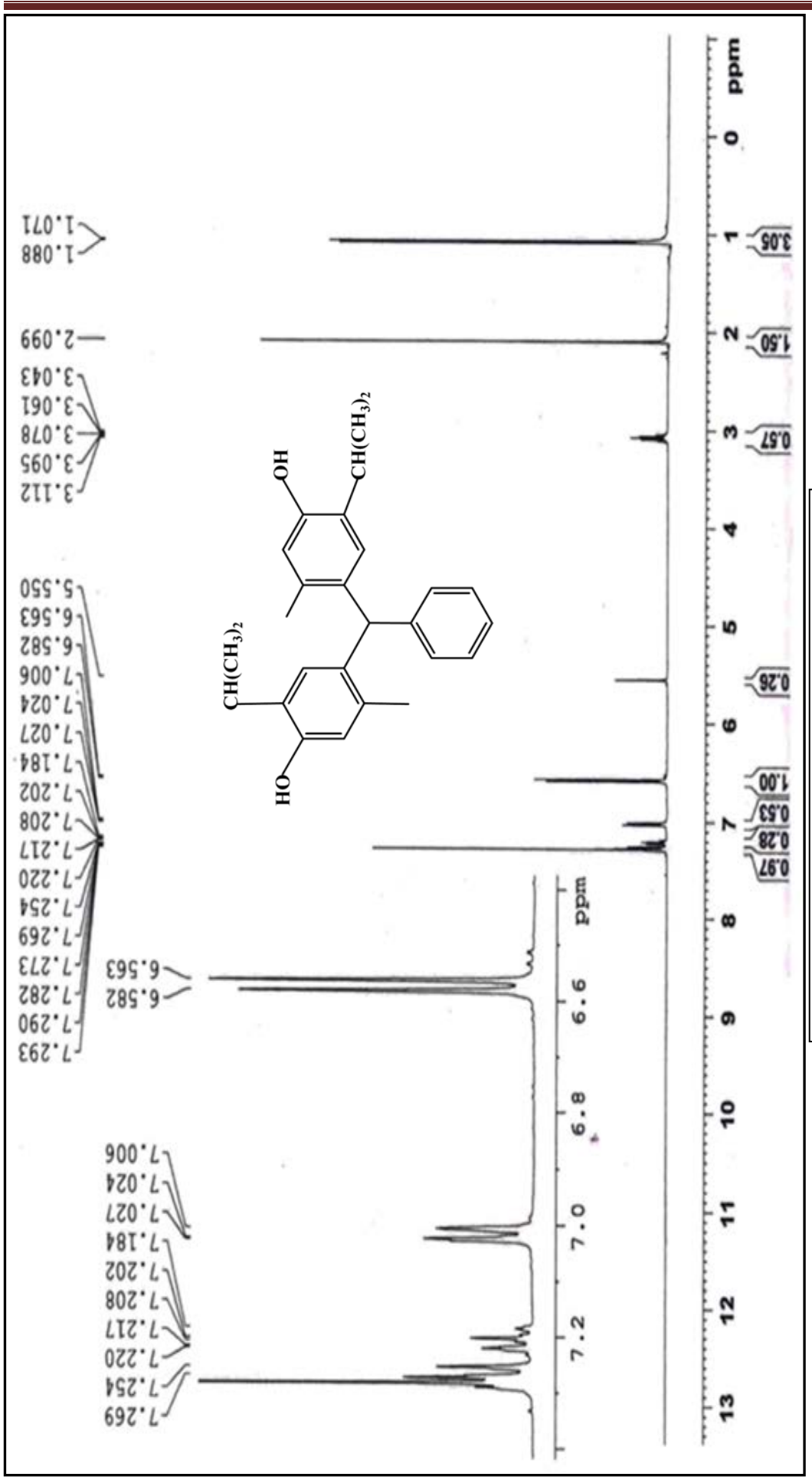


Figure 5.45: ^{1}H NMR spectrum of compound **29**

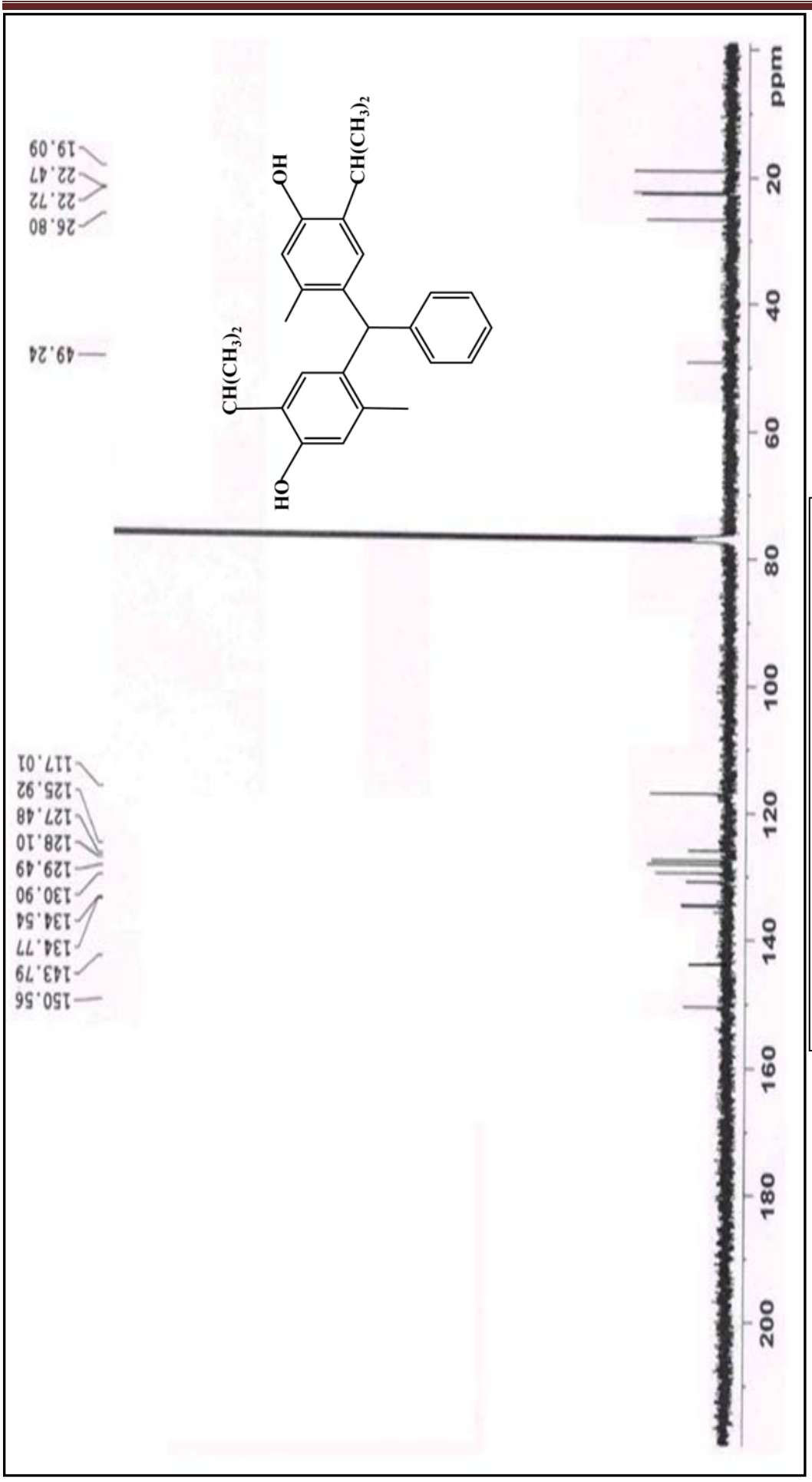


Figure 5.46: ^{13}C NMR spectrum of compound **29**

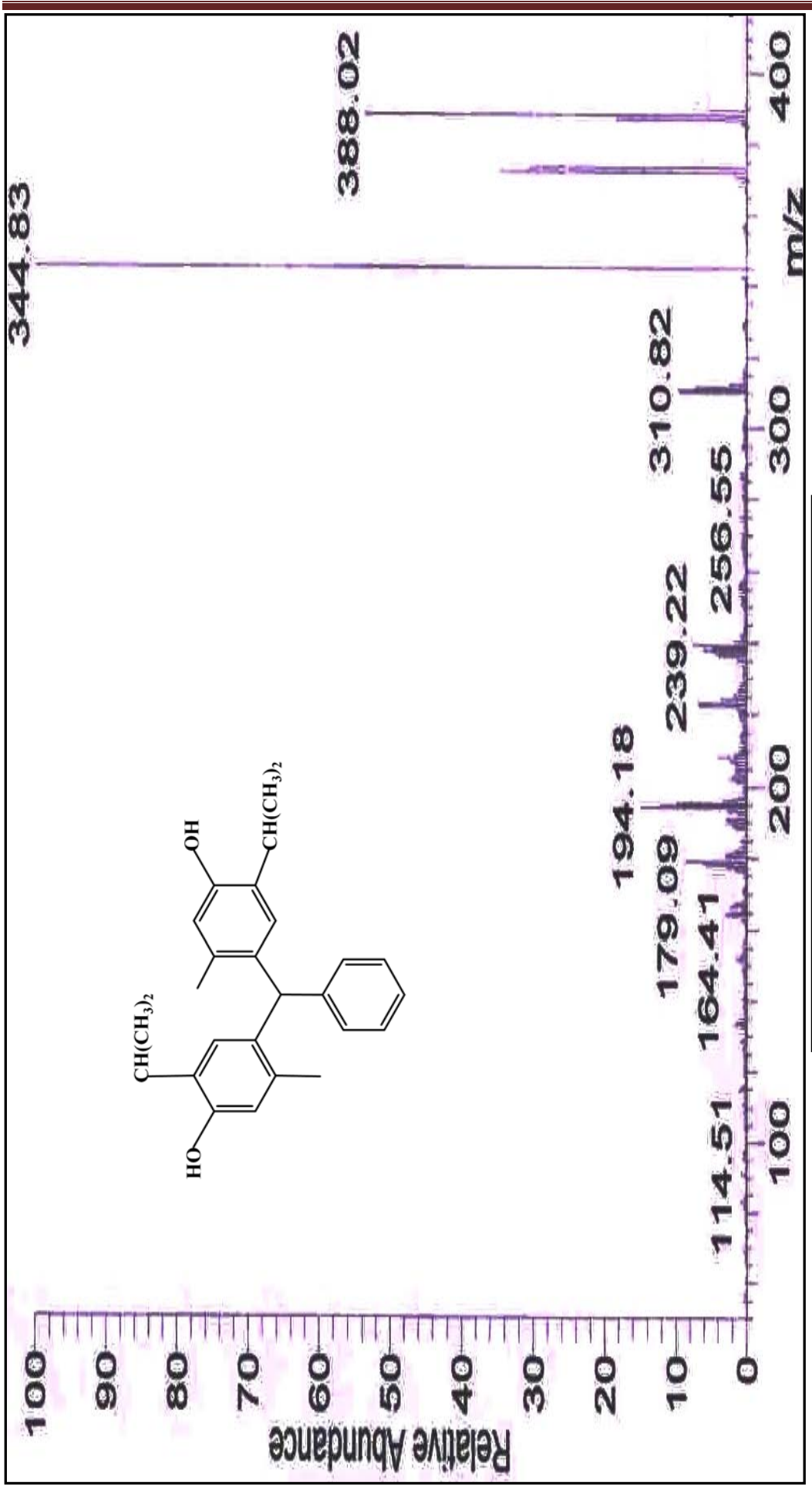


Figure 5.47: EI-MS spectrum of compound **29**

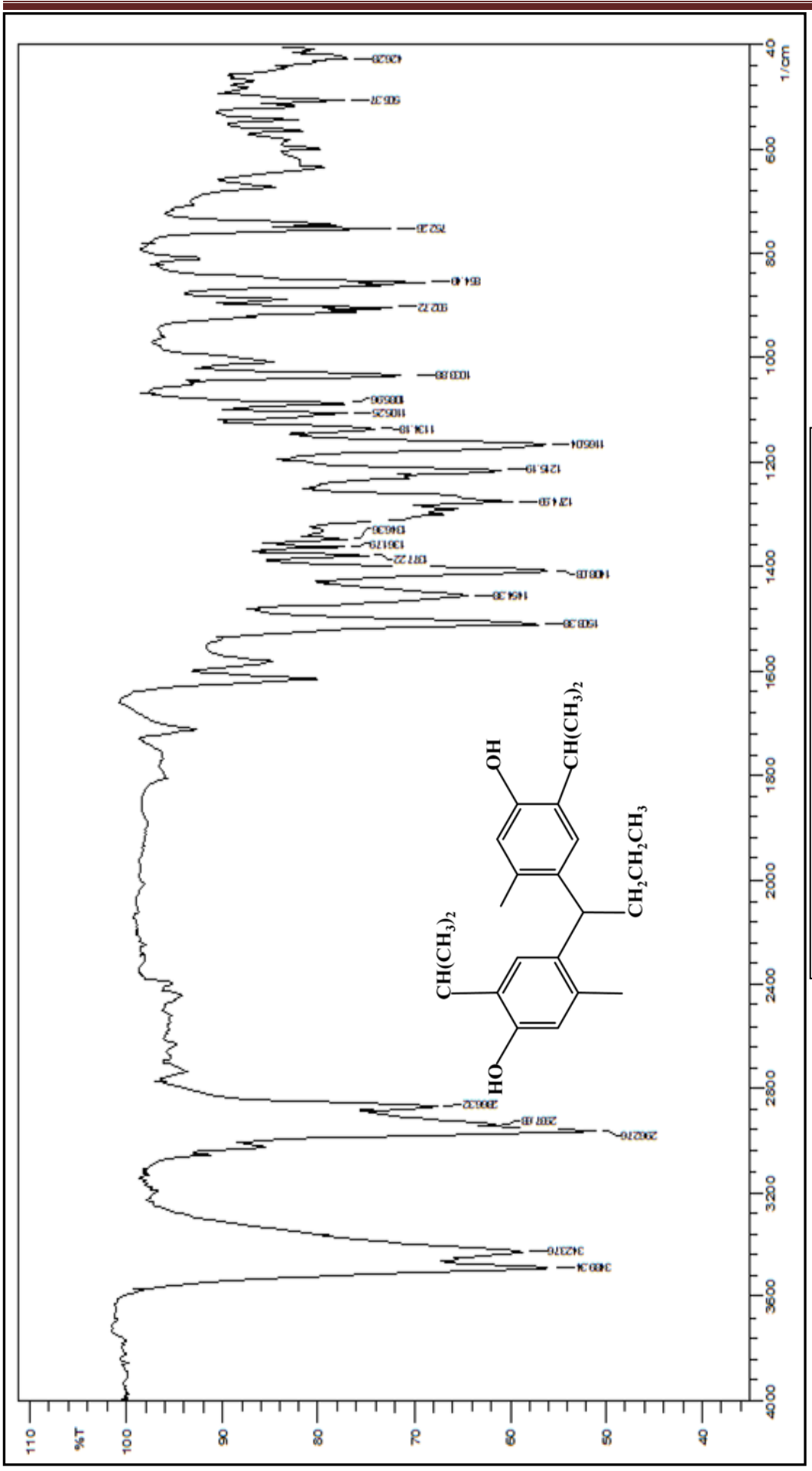


Figure 5.48: FTIR spectrum of compound **30**

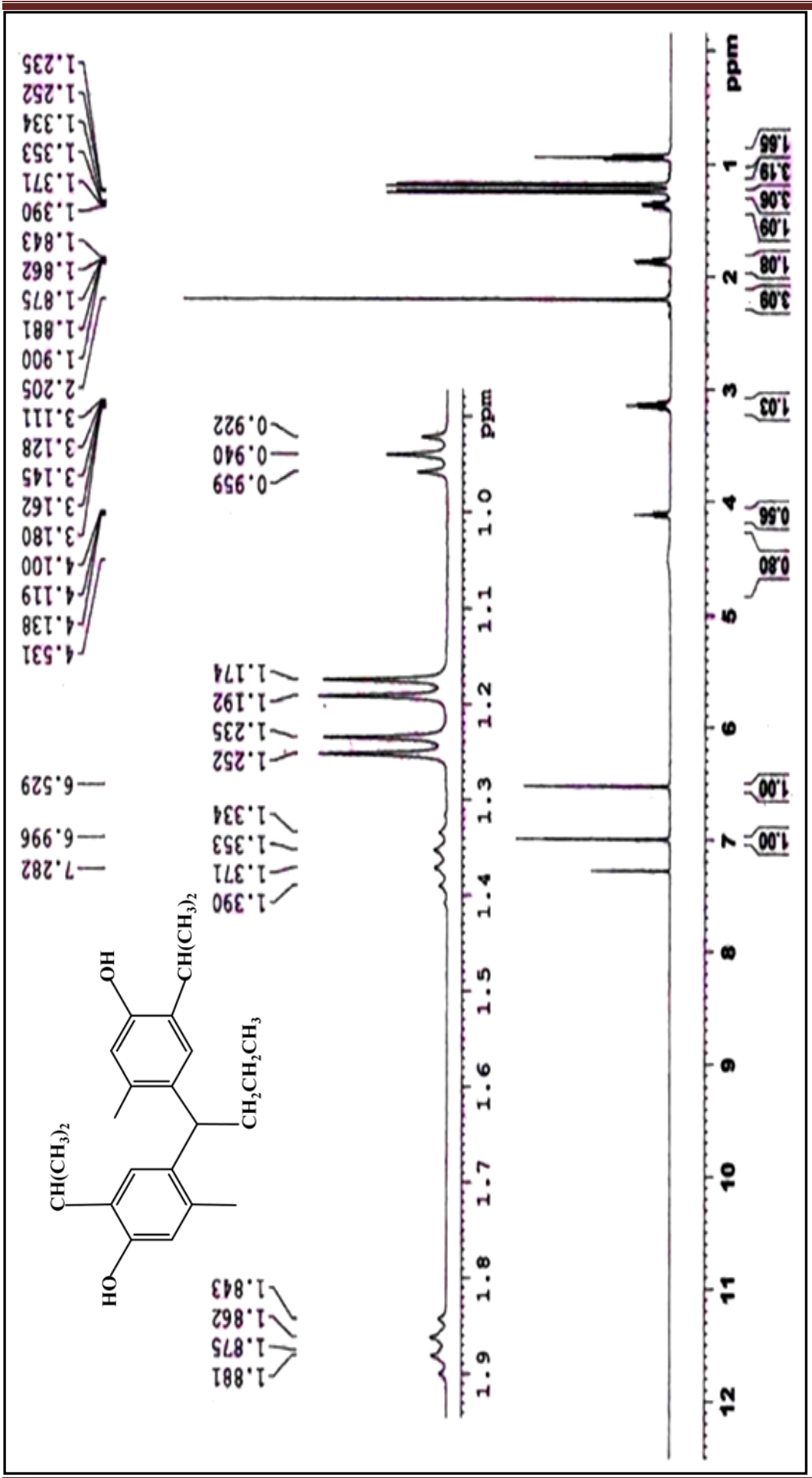


Figure 5.49: ^{1}H NMR spectrum of compound **30**

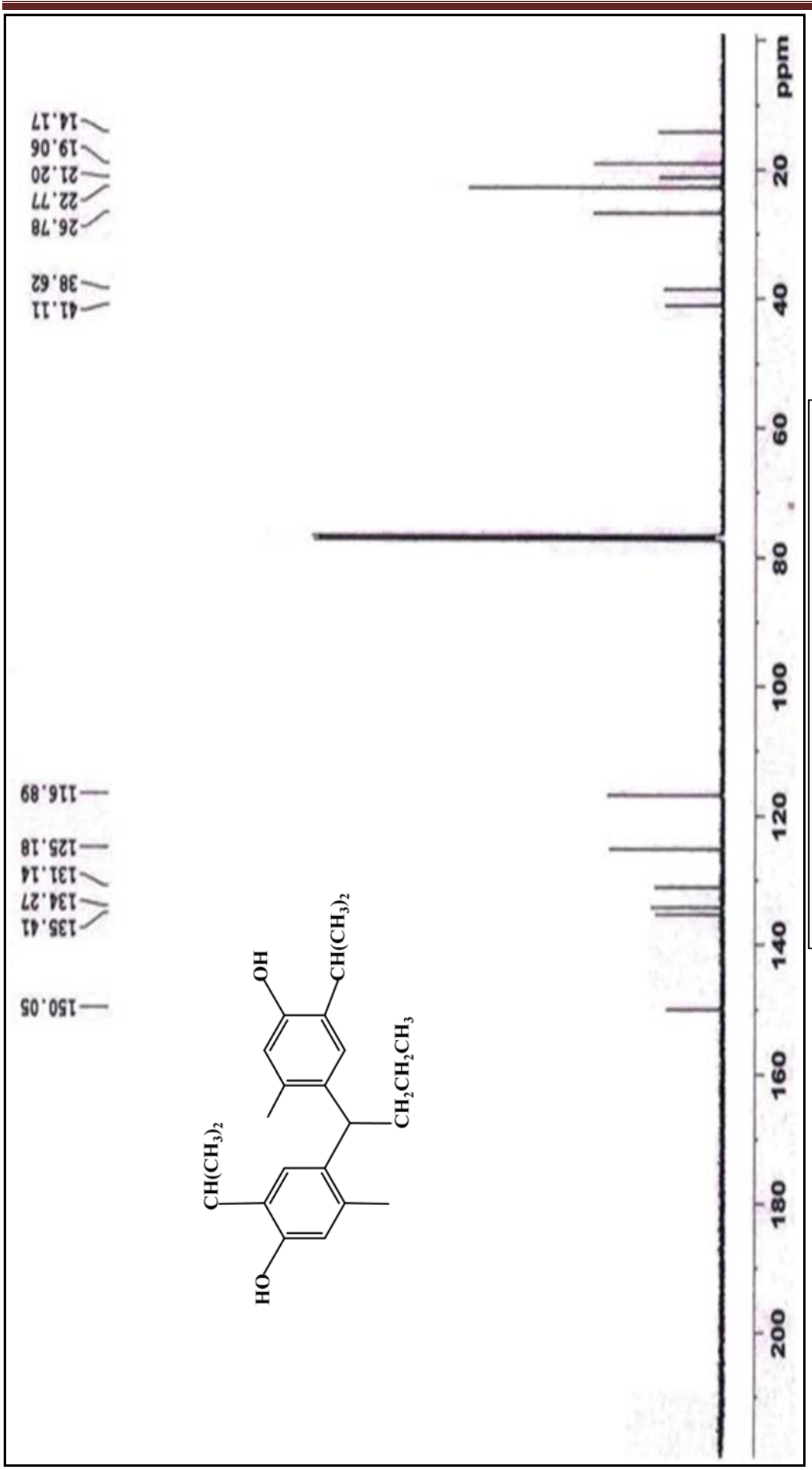


Figure 5.50: ^{13}C NMR spectrum of compound **30**

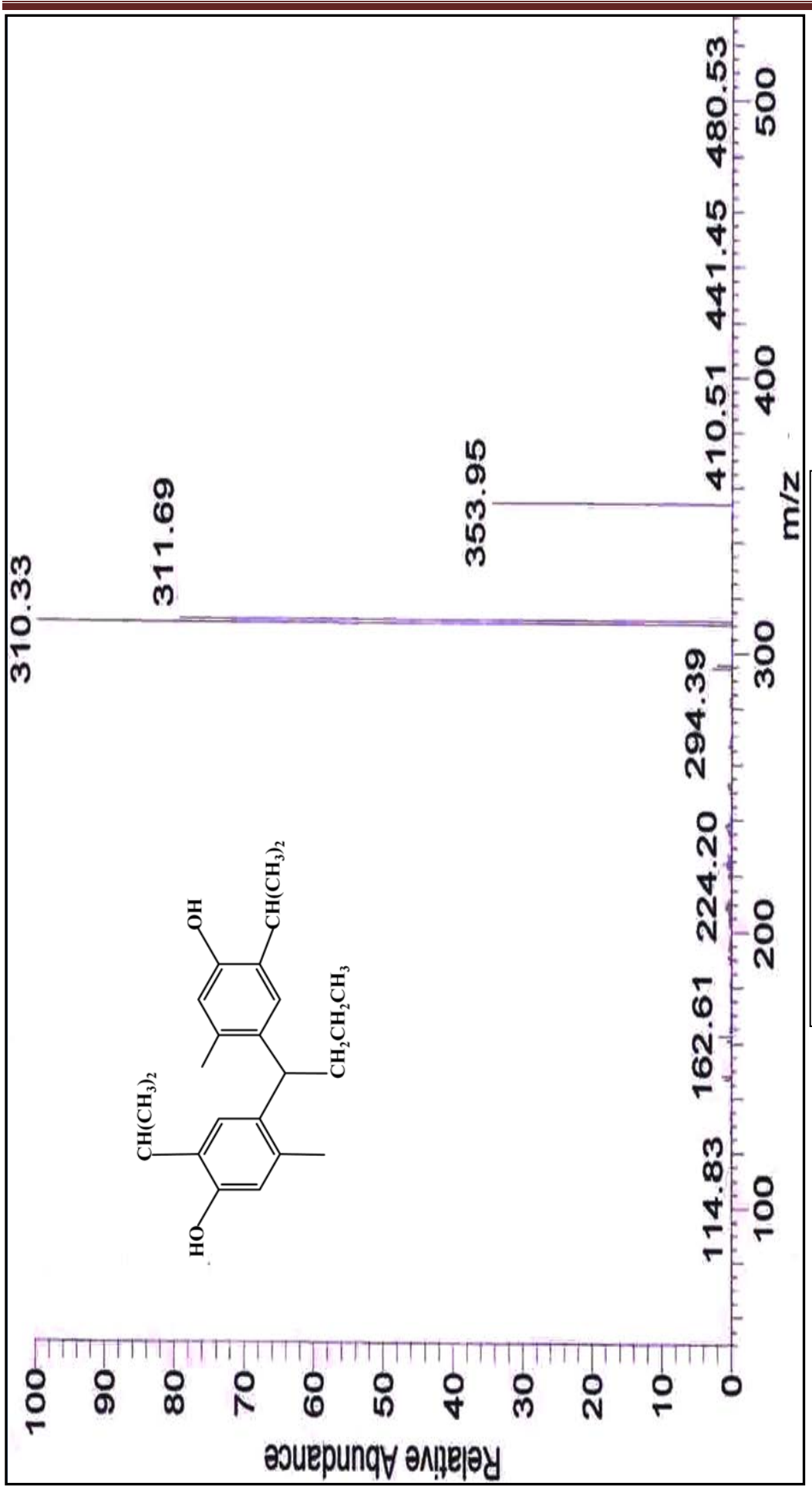


Figure 5.51: EI-MS spectrum of compound **30**

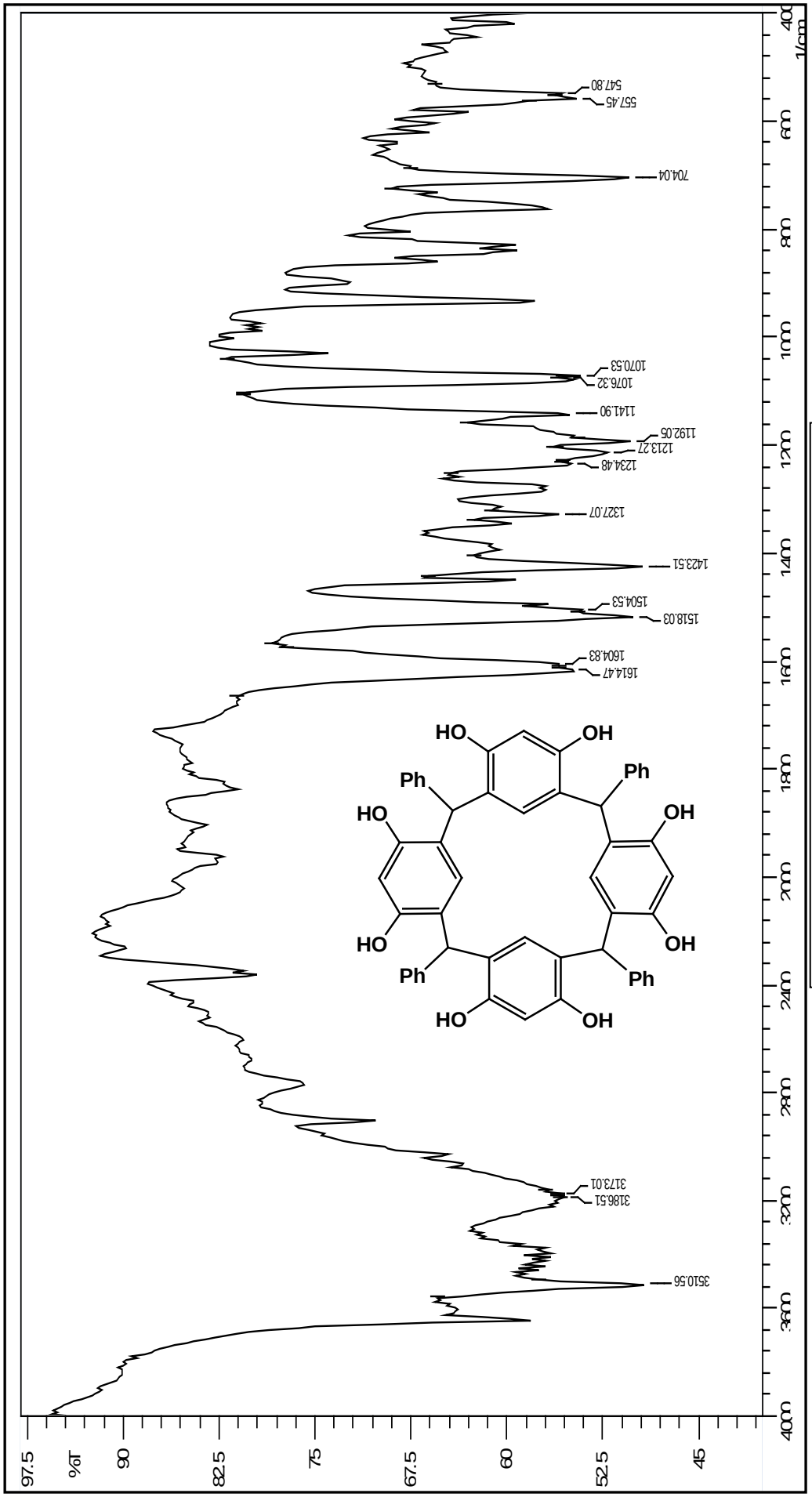


Figure 5.52: FTIR spectrum of compound **33**

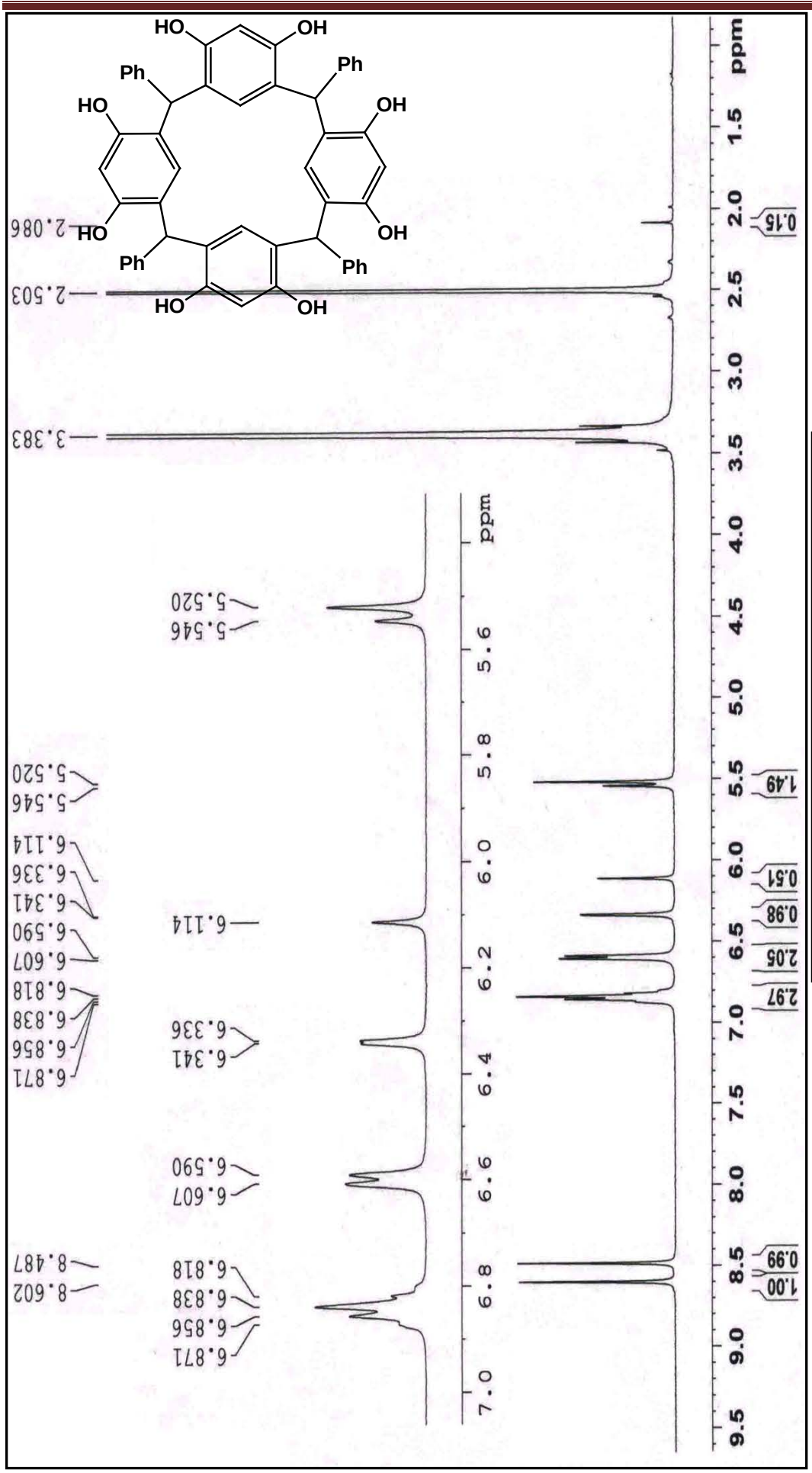


Figure 5.53: ^{1}H NMR spectrum of compound **33**

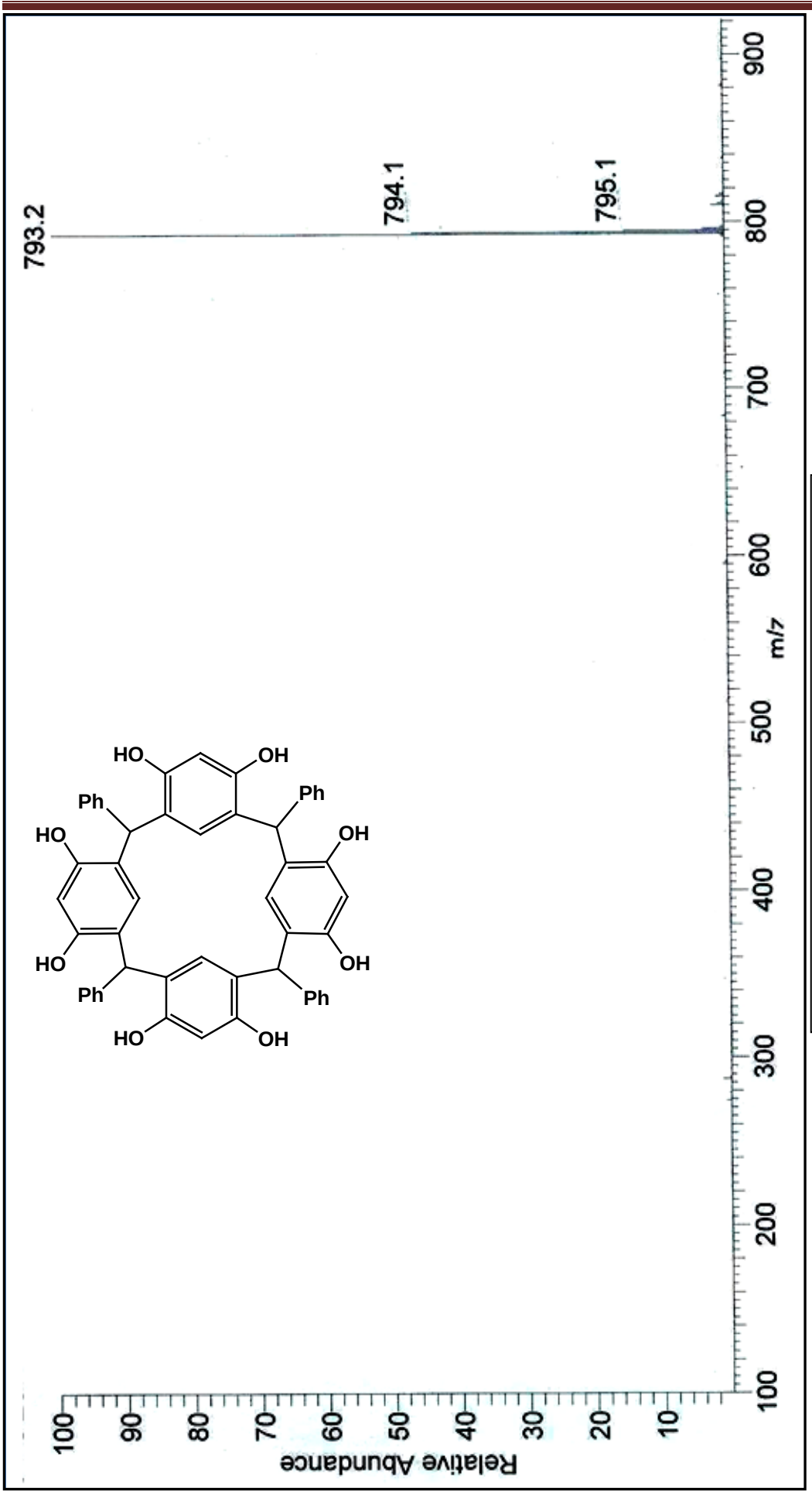


Figure 5.54: ESI-MS spectrum of compound **33**

Summary

Thesis Title

SYNTHETIC STUDIES DIRECTED TOWARDS CYCLOPENTANOIDS AND RELATED NATURAL PRODUCTS

Submitted to

THE MAHARAJA SAYAJIRAO UNIVERSITY OF BARODA

By

DEEPAK SINGH

Research Supervisor

Prof. P. T. DEOTA

APPLIED CHEMISTRY DEPARTMENT

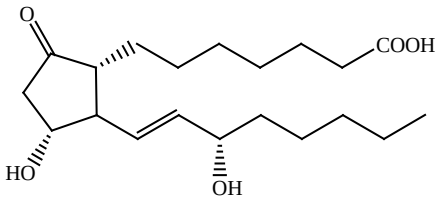
THE MAHARAJA SAYAJIRAO UNIVERSITY OF BARADA, VADODARA (GUJARAT) - 390001, INDIA

October-2013

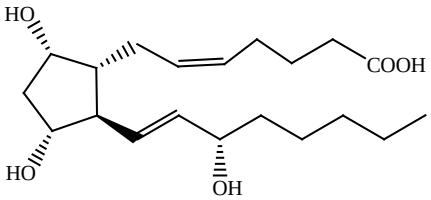
Organic chemistry is a branch of chemistry that governs the structural properties and reaction of carbon containing compounds. Organic chemistry is a highly innovative part of science in which chemists can create new molecules having properties for the betterment of human life. The construction of organic compounds via organic reactions is a special branch of chemistry known as organic synthesis. Organic molecules posses very complex structures and hence the synthesis of these compounds is one of the most important aspects in organic chemistry.

Cyclopentanoids are carbocycles composed of five carbon atoms. Cyclopentanoids are valuable building blocks for the synthesis of many natural products and complex molecular architectures. The major class of biologically interesting compounds constitute structurally diverse and interesting family of cyclopentanoids.[1]

Cyclopentanoids are also present in prostaglandins (PGs) natural products Prostaglandins are medicinally important fatty hormones due to their wide range of biological and pharmacological activities that control many physiological processes. Kurzrok and Lieb first detected the prostaglandins natural products in 1930 due to their biological activities. The structures of first two members of prostaglandin family PGE_1 **1**, $PGF_{2\alpha}$ **2** were elucidated in 1960 by Bergstrom and Sjovall. It initiated new research in this area and other biologically interesting prostaglandins containing cyclopentanoids were discovered.[2] (**Figure 1**)



Prostagladin E_1 **1**



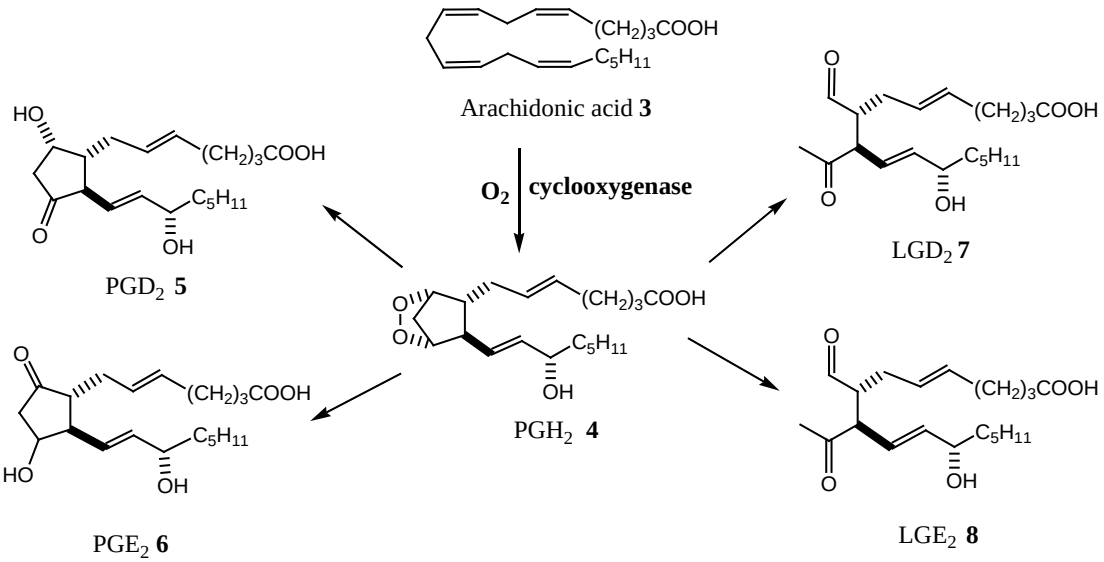
Prostagladin $F_{2\alpha}$ **2**

Figure 1: Structure of various cyclopentanoids natural products

The **First chapter** of this thesis covers a detailed introduction of cyclopentanoids, stereochemistry, methodology for their preparation and application towards synthesis of natural products as well as complex molecular architectures containing cyclopentanoids as building blocks.

The **Second chapter** describes the preface of prostaglandins PGs and their derivatives such as levuglandin LDE_2 and levuglandin LGD_2. It essentially focuses on design and development of a novel route towards synthesis of levuglandin analogue.

Lipids are essential components of the cell membrane. They incorporate numerous polyunsaturated fatty acids. Lipid oxidation in various biological systems contributes to normal physiological process and is involved in the development of many chronic diseases.[3] Levuglandins (LGs) are the products of lipid peroxidation that are biologically active. The discovery of LGs was the result of an effort to elucidate the chemistry of prostaglandin endoperoxide PGH_2 **4**. PGH_2 **4** is the cyclooxygenase metabolite of arachidonic acid **3**. Spontaneous rearrangement of PGH_2 **4** generates PGD_2 **5** and PGE_2 **6**. Salomon *et al* proposed that the rearrangement of PGH_2 **4** also generates two levulinaldehyde derivative with prostanoid side chain namely Levuglandins LGD_2 **7** and LGE_2 **8** respectively.[3] (**Scheme 1**)

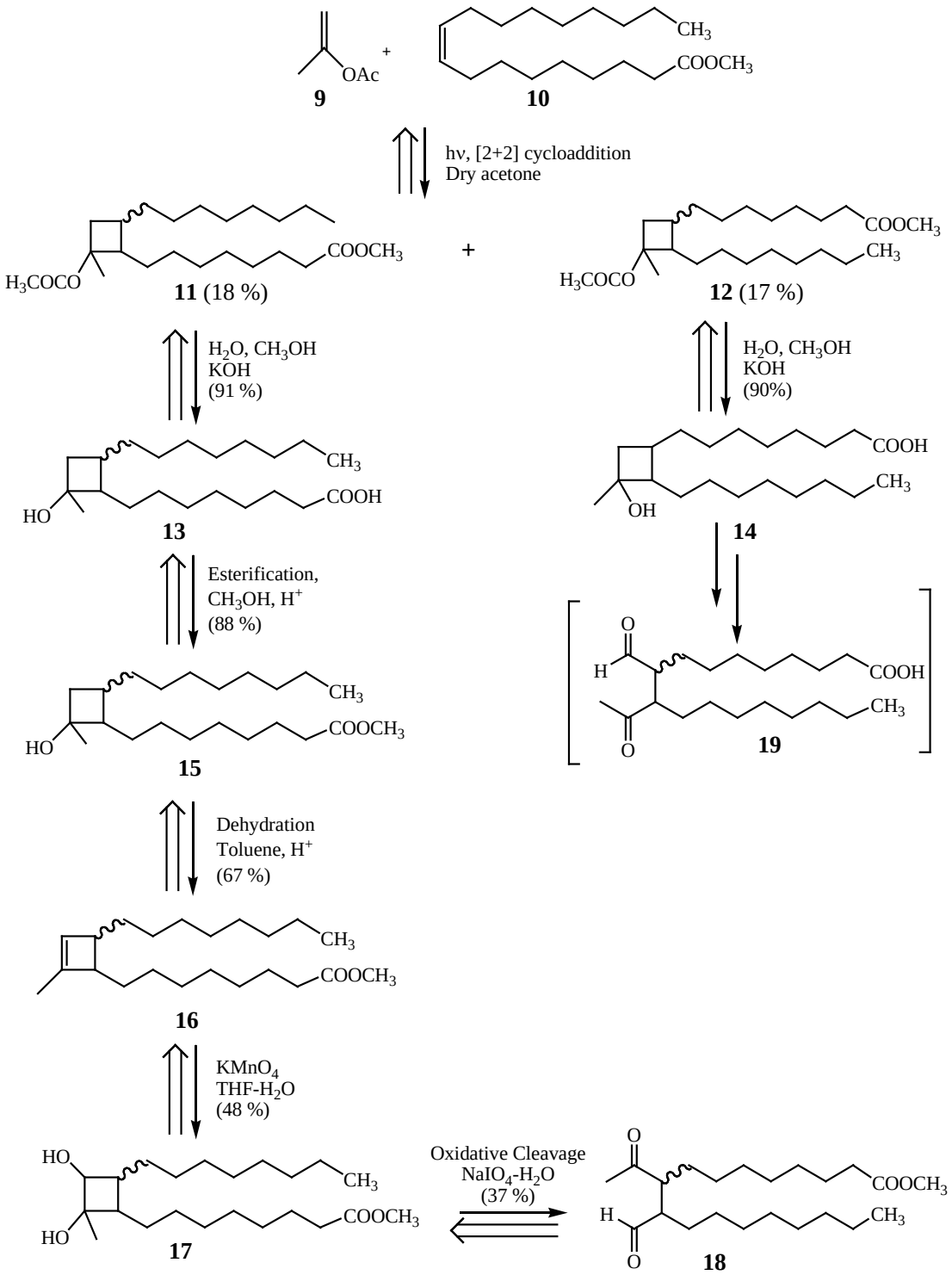


Scheme 1: Rearrangement of PGH_2 generation of PGs and LGs

LGs bind covalently with the amino group in proteins due to their reactive electrophilic γ-ketoaldehyde functionality and are associated with various diseases such as alzheimer's diseases (AD), atherosclerosis, renal diseases etc.[3] The synthesis

of LGs constitutes a challenge for organic chemists due to their complicated structure. Only few methods have been developed for their synthesis.[4]

We initiated a research to design and develop a general method for the construction of LGs framework via a sequence involving [2+2] cycloaddition, hydrolysis, elimination and oxidative cleavage using cheap and easily available starting materials like isopropenyl acetate **9** and methyl oleate **10** (**Scheme 2**).

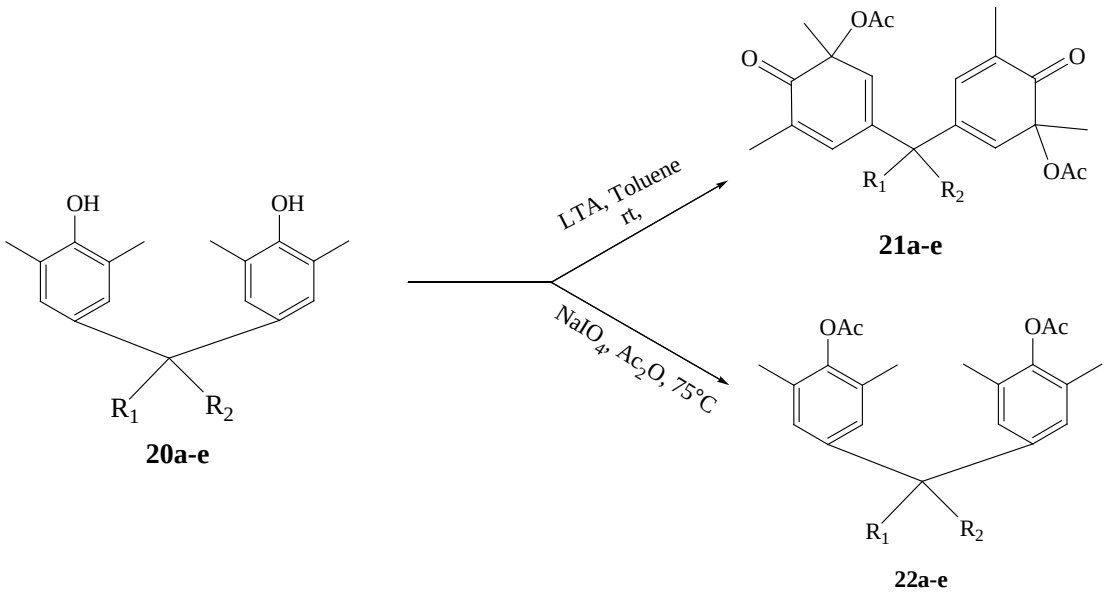


Scheme 2: Synthesis of LGE_2 analogue **18**

Chapter three explores a novel method for the preparation of bisphenols and their oxidative acetylation studies for syntheses of bis-cyclohexadienonens. The

photochemical behaviour of bis-cyclohexadienones has also been investigated under UV irradiation.

Cyclohexadienones are useful starting intermediates for the development of novel molecular architecture and new methods towards efficient synthesis of various natural products.[5] Here, in this part of work, we have described our investigation towards synthesis of bis-cyclo hexadienone by oxidative acetylation of bisphenols under different reaction conditions.[6] (**Scheme 3**)

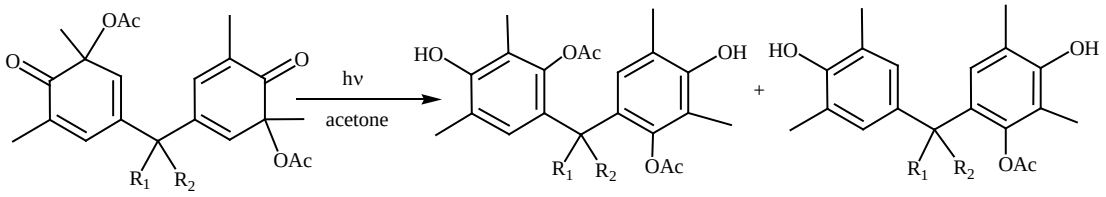


(a) R_1=CH_3, R_2=H; (b) R_1=CH_3CH_2, R_2=H; (c) R_1=$CH_3CH_2CH_2$, R_2=H; (d) R_1=R_2=CH_3; (e) R_1, R_2= -$(CH_2)_4$-;

Scheme 3: Oxidative acetylation of bisphenol **20a-e**

The treatment of bisphenols **20a-e** with LTA in ethyl acetate furnished bis-cyclohexadienones **21a-e** whereas treating them with $NaIO_4$ in acetic anhydride resulted in the formation of acetylated products **22a-e**.[6a] The photochemical behaviour of bis-cyclohexadienones was also investigated and it was found that cyclohexadienones on UV irradiation undergo photochemical aromatisation resulting in the formation of two different bis-phenols with migration of both the acetate groups followed by aromatisation and by migration of an acetate group in one

cyclohexadienone unit followed by deacetylation from the other cyclohexadienone ring. (**Scheme 4**)



21a-e **23A-27A** **23B-27B**

Scheme 4: Photochemical reaction of bis-cyclohexadienone **21a-e**

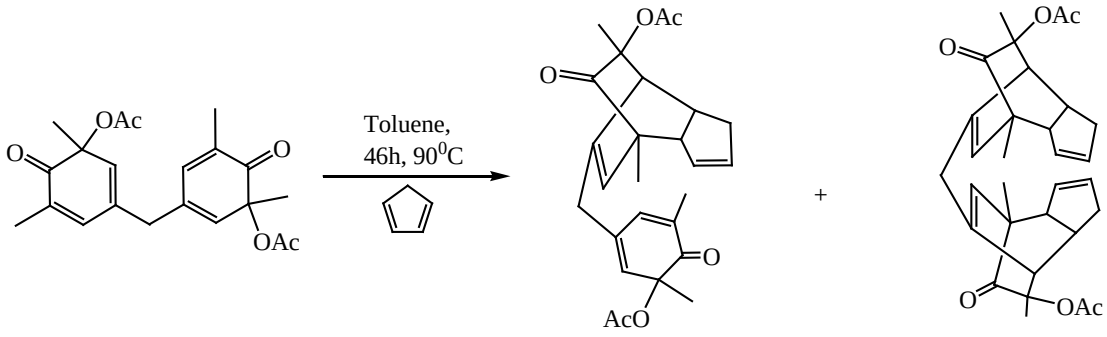
Chapter four is devoted to the cycloaddition of biscyclohexadienone and their photochemical rerrangement towards synthesis of bistriquinane.

Natural products are compounds derived from plants and other living organisms that usually have pharmacological or biological activity, for the use of drug discovery and drug design.

Polyquinane is a common name for carbocyclic frames composed of fused five membered rings. Polyquinanes, an important class of sesquiterpenoids, have generated a worldwide interest since their discovery among organic chemists due to their unique and fascinating molecular architecture and promising biological activity.[7]

Compounds containing three cyclopentane rings fused together are known as “triquinanes” and among all the polyquinanes, they are the most abundant. Triquinane natural products are a subset of polyquinanes. They have been attracting continuous attention from synthetic chemists due to their promising biological activity and their role as building blocks for the syntheses of exotic molecular architecture.[7]

In the synthetic exploration of the newly discovered chemistry in the construction of complex molecular architecture, we initiated a plan directed towards synthesis of bird-shaped bis-triquinane molecule **32** starting from bis-cyclohexadienone **28**.

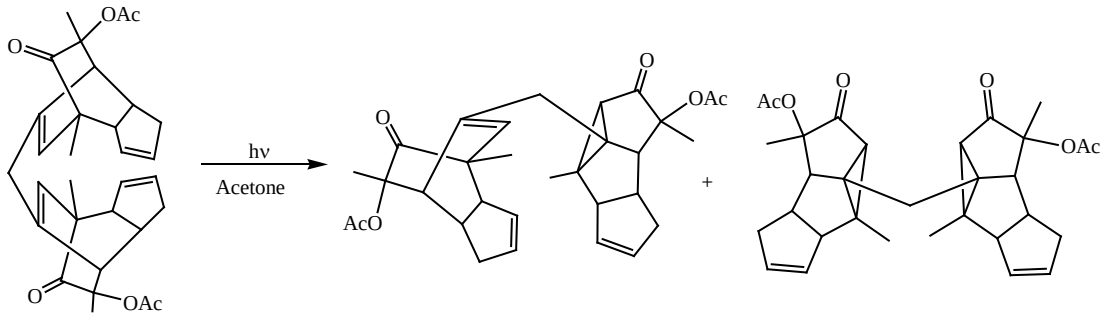


28 **29** **30**

Scheme 5: Cycloaddition in bis-cyclohexadienone **28**

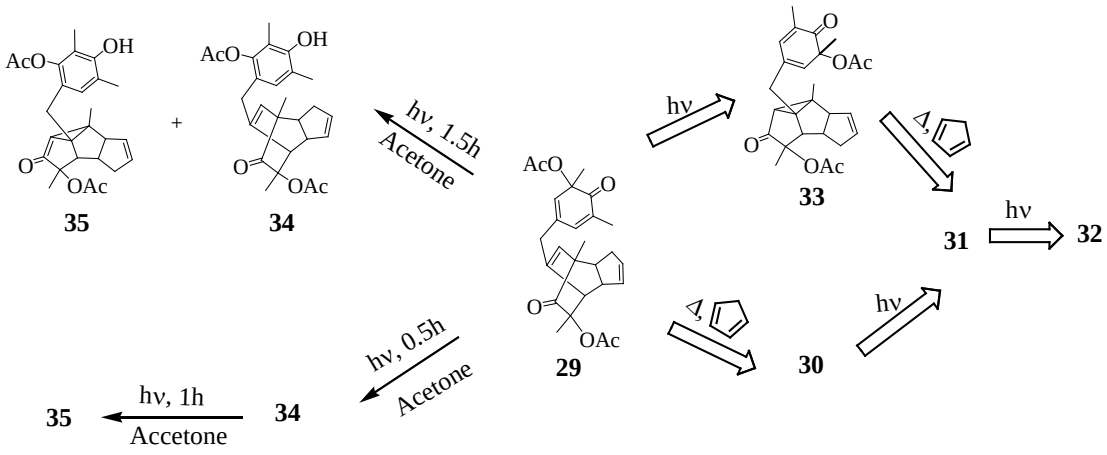
The Diels-Alder cycloaddition of bis-cyclohexadienone **28** with cyclopentadiene gave a mixture of two products mono-adduct **29** and bis-adduct **30**.[6b] (**Scheme 5**)

The photochemical reactions have attracted significant interest for their ability to act as a key step in the creation of complex molecular architecture and in various natural products syntheses.[8] Compounds containing β,γ-enones undergo two unique reactions that are characteristic of their excited states. The triplet sensitized irradiation leads to 1,2-acyl shift while direct excitation induces a 1,3-acyl shift. Thus, when a solution of **30** in acetone, both as solvent and as a triplet sensitizer, was irradiated with mercury vapour lamp (125 W) in a quartz immersion well for 2h, the products **31** and **32** were isolated.[6c] (**Scheme 6**)



30 **31** **32**

Scheme 6: ODPM rearrangement of bis-adduct **30**



Scheme 7: Photochemical reaction of mono-adduct **29**

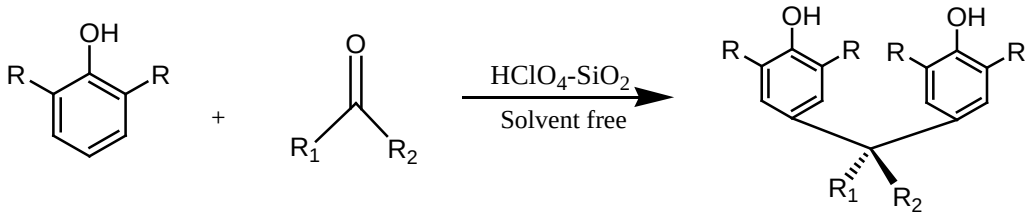
Alternatively it was envisioned that the bis-triquinane **32** could also be accessed through tandem photochemical-thermal-photochemical process from precursor **29**. **(Scheme 7**) However attempted photochemical reaction of **29** resulted in the formation of **34** and **35** and did not furnish product **33**. The photochemical reaction of **29** in acetone for 0.5h furnished product **34**.[6c] It was interesting to note that when the same reaction was continued for 1.5h, additionally aryl substituted tetracycle **35** was also isolated however compound **33** was not obtained at all. The photochemical aromatisation of cyclohexadienone moiety under these reaction conditions is hitherto unknown in the literature to the best of our knowledge.

Chapter five deals with the development of a method for synthesis of bisphenols using silica supported perchloric acid as a heterogeneous catalyst under solvent free condition**.**

Solid supported reagents are unique acid catalysts that have gained much importance over last two decades due to their economical and environmental benefits.[9] Among all mineral acids, perchloric acid finds significant application in acid-catalysed various organic transformations such as esterification, cationic polymerisation, isomerisation and rearrangements. Application of perchloric acid has been found to be more useful synthetically when its intrinsic hazardousness is reduced by adsorbing it on silica gel. $HClO_4$-SiO_2 being a heterogeneous catalyst has received considerable attention as an inexpensive, non-toxic catalyst for a variety of organic transformations such as glycosylation, Ferrier rearrangement, Michael addition, Friedel-Crafts reactions,

protection and de-protection reactions of alcohols, phenols, thiols, amines and carbonyls.[9]

We have found that perchloric acid on silica gel ($HClO_4$-SiO_2) functions as a catalyst for the preparation of alkyl substituted bisphenols by condensation of various phenols with aldehydes / ketones. (**Scheme 8**)

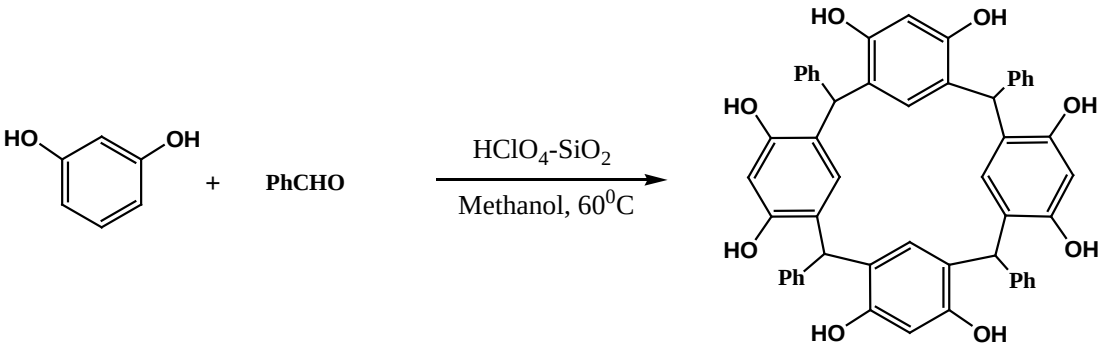


36 **37** **38**

R, R_1, R_2 = alkyl, H, benzyl, -$(CH)_n$-

Scheme 8: Preparation of bisphenols

We also investigated the reaction of resorcinol with aromatic aldehyde for the synthesis of calix[4]resorcinarene. Synthesis of calix[4]resorcinarines is an important and useful exercise in synthetic organic chemistry due to their various applications such as host compounds for the extraction of metal ions, sugars and organic molecules.[10] Resorcinarenes are commonly prepared by mineral acid catalyzed condensation of resorcinol with aldehydes or ketones. However this procedure requires the use of large quantities of acid, leading to its excessive waste that can be environmentally unfriendly and expensive. Here we are reporting the synthesis of calix[4]resorcinarene using $HClO_4$-SiO_2 as a recyclable catalyst from benzaldehyde with resorcinol. (**Scheme 9**)



39 **40** **41**

Scheme 9: Preparation of calix[4]resorcinarenes

Structures of all the compounds were established through their spectral and analytical data. Melting points were recorded in open capillary tubes and are uncorrected. Ultraviolet spectra were recorded on a Perkin-Elmer Lambda-19 Spectrometer. Infrared spectra were recorded on a Perkin-Elmer PC-16 FTIR Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 200 or 300 or on 400 FT NMR (50/75/100 MHz for ^{13}C respectively) spectrometer using. Mass spectra were recorded on a Thermo-Fischer DSQ II GCMS instrument. Column chromatography was performed using Acme's silica gel (60–120 mesh size) or neutral alumina (200-400 mesh size). Thin layer chromatography was performed using Acme's silica gel for TLC or on Merck 60 F254 aluminium coated pates. Spots were visualized under UV light or in iodine vapour.

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LIST OF PUBLICATION:

1. Deepak Singh, Pradeep T. Deota "**Synthesis of a novel bis-triquinane: a photochemical rearrangement in cyclohexadienone moiety resulting in aromatisation"** *Tetrahedron Letters*, **2012**, *53*, 6527
2. Deepak Singh, Pradeep T. Deota "**Cycloaddition of bis-cyclohexa-2,4-dienones: Synthesis of novel carbocycles"** *Synthetic Communication*, **2013**, *43*, 292.
3. Deepak Singh, Pradeep T. Deota "**An unusual involvement of $NaIO_4$ in the acetylation of bisphenol during attempted oxidative acetylation"** *Tetrahedron Letters*, 2013, (accepted)
4. Deepak Singh, Pradeep T. Deota "**Bisphenols and Calix[4]resorcinarenes using silica supported perchloric acid as an efficient and reusable heterogeneous catalyst"** *Journal of Chemical Sciences* (Submitted)
5. Deepak Singh, Pradeep T. Deota "**Syntheses of novel bis-acetoxy cyclohexadienones and their photochemical studies" (***Manuscript under preparation***)**
6. Deepak Singh, Pradeep T. Deota "**A novel approach towards syntheses of Levuglandins E_2 analogues" (***Manuscript under preparation***)**

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3. **Regional Science Congress "Science for Shaping the Future of India"** 15-16 September 2012 The M. S. University of Baroda.
4. **19th meeting of the Nuclear Magnetic Resonance Society, India** 3-6 February 2013 IIT Mumbai.

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2. **Second prize, *Poster Competition "International Year of Chemistry-2011"*** The M. S. University of Baroda