

DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR THE
SYNTHESIS OF UNUSUAL ISOCOUMARIN AND INDOLE DERIVATIVES:
THE CHEMISTRY OF HOMOPHTHALIC ACID

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ABSTRACT

DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR THE SYNTHESIS OF UNUSUAL ISOCOUMARIN AND INDOLE DERIVATIVES: THE CHEMISTRY OF HOMOPHTHALIC ACID

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Many heterocyclic compounds containing nitrogen, oxygen and sulfur show wide range of physiological activities and their synthesis has always been attracted the interest of chemists.

The aim of this research is to develop new synthetic methodologies leading to the synthesis of new derivatives of isocoumarines, indoles, isoquinolines, benzodiazepinones and quinazolines, which have been found to show important biological activities.

Starting from homophthalic acid and bishomophthalic acid the corresponding acyl azides were proposed to be synthesized, which then would be used for the synthesis of various heterocycles. The proposed diazide from homophthalic was not formed due to the tendency of the ortho-positioned acid to undergo cyclization.

Instead, new unusual benzochromen and isocoumarin derivatives have been synthesized in a single step, for which reasonable mechanisms have been proposed.

The half ester produced from homophthalic acid was an important key compound for the synthesis of new highly substituted indole derivatives, which are expected to be biologically active.

The diisocyanate derived from was synthesized directly from ortho-bromo xylene was treated with alcohols and hydrazine to produce seven membered rings. Instead of the intramolecular cyclization reaction, they underwent polymerization to form new polymers.

Furthermore, new synthetic method for the synthesis of pyrazoles has been developed.

Key words: isocoumarin, isoquinoline, indole, benzodiazepinone, quinazoline, polyurethane, pyrazole.

ÖZ

İLGİNÇ İZOKUMARİN VE İNDOL TÜREVLERİNİN SENTEZİ İÇİN YENİ SENTETİK METODLARIN GELİŞTİRİLMESİ: HOMOFİTALİK ASİDİN KİMYASI

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Nitrojen, oksijen ve sulfur içeren pek çok heterosiklik bileşik geniş ölçüde fizyolojik aktivite gösterirler ve sentezleri her zaman kimyacıların ilgisini çekmiştir.

Bu tezin amacı önemli biyolojik aktiviteler göstermesi beklenen yeni izokumarin, indol, izokinolin, benzodiazepinon ve kinazolin türevlerinin sentezlerini hedefleyen yeni sentetik metotlar geliştirmektir.

Çeşitli heterosikliklerin sentezinde kullanılmak üzere homofitalik ve bishomofitalik asitten çıkarak ilgili açıl azidlerin sentezlenmesi tasarlanmıştır. Homofitalik asitten çıkılarak sentezi planlanan diazid, orto konumundaki asidin halka kapanması eğiliminden dolayı oluşmamıştır. Yapılan çeşitli azidasyon reaksiyonları ile yeni ilginç benzokromen ve izokumarin türevleri sentezlenip mekanizmaları tartışılmıştır.

Homofitalik asitten sentezlenen yarı ester, biyolojik aktivite göstermesi beklenen poli süstitüe indol türevlerin sentezinde önemli anahtar bileşik olmuştur.

Orto bromo ksilenden sentezlenen diizosiyanat yedili halka oluşturmak üzere alkol ve hidrazinle muamele edilmiştir. Intramoleküler halkalaşma reaksiyonu yerine yeni polimerler oluşturmak üzere polimerleşme reaksiyonu gerçekleşmiştir.

Ayrıca, pirazollerin sentezi için yeni bir sentetik metod geliştirilmiştir.

Anahtar kelimeler: izokumarin, izokinolin, indol, benzodiazepinon, kinazolin, poli uretan, pirazol.

To my parents, brother and little nephew CAN....

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LIST OF ABBREVIATIONS

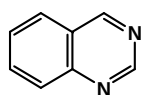
COSY	: Correlation spectroscopy
DEPT	: Distortionless enhancement by polarization transfer
DMF	: Dimethylformamide
DMSO	: Dimethylsulfoxide
HETCOR	: Heteronuclear Correlation Spectroscopy
HMBC	: Heteronuclear multi-bond coherence
HMQC	: Heteronuclear multiple quantum coherence
HRMS	: High Resolution Mass Spectrum
IR	: Infrared
J	: Coupling constant
MS	: Mass spectrum
NMR	: Nuclear magnetic resonance
ppm	: Parts per million
THF	: Tetrahydrofuran
HETCOR	: Heteronuclear Correlation Spectroscopy
UV	: Ultraviolet

CHAPTER 1

1. INTRODUCTION

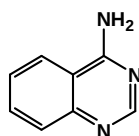
1.1. Quinazolines

Quinazoline (**1**) is a compound made up of two fused six-membered simple aromatic rings, a benzene ring and a pyrimidine ring.



quinazoline (**1**)

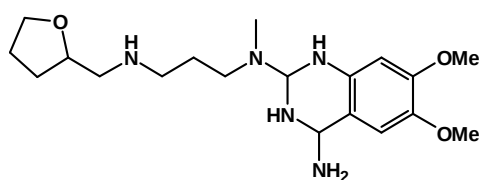
Quinazolines (**1**) are a wide family of compounds with well-known pharmacological properties such as analgesic, narcotic, anti-malarial and sedative.¹⁻⁵ Among the quinazoline derivatives, 4-amino quinazolines (**2**) are useful as fungicides⁶, anti-inflammatory⁷, anti-cancer⁸, anti-microbial and anti-hypertensive agents^{9,10}.



4-amino quinazoline (**2**)

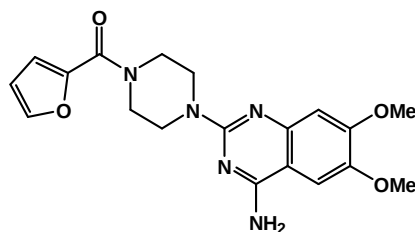
Alfuzosin (**3**) is used to treat symptoms of benign prostatic hyperplasia (BPH, enlarged prostate) such as frequent, urgent need to urinate during the day and at night, weak urine stream, and difficulty urinating. Alfuzosin (**3**) is in a class of medications called alpha-1 blockers.¹¹

It works by relaxing the muscles in the prostate and bladder neck to allow urine to flow more easily. Alfuzosin is used to treat the signs and symptoms of benign enlargement of the prostate. Benign enlargement of the prostate is a problem that can occur in men as they get older. The prostate gland is located below the bladder. As the prostate gland enlarges, certain muscles in the gland may become tight and get in the way of the tube that drains urine from the bladder. This can cause problems in urinating, such as a need to urinate often, a weak stream when urinating, or a feeling of not being able to empty the bladder completely. Alfuzosin helps to relax the muscles in the prostate and the opening of the bladder. This may help increase the flow of urine and/or decrease the symptoms.



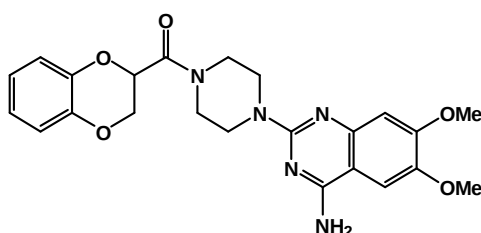
alfuzosin (3)

Prazosin (4), trade names Minipress® and Hypovase®, is a medication used to treat high blood pressure (hypertension). It belongs to the class of alpha-adrenergic blockers, which lower blood pressure by relaxing blood vessels. Specifically, prazosin is selective for the alpha-1 receptors on vascular smooth muscle. These receptors are responsible for the vasoconstrictive action of norepinephrine, which in turn raises blood pressure. By blocking these receptors, prazosin reduces blood pressure.¹²



prazosin (4)

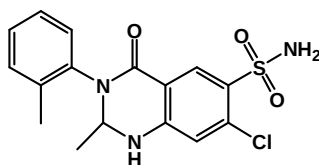
Like prazosin **(4)**, Doxazosin **(5)**, a quinazoline compound with the brand name Cardura®, is an alpha blocker used to treat high blood pressure and benign prostatic hyperplasia. It works by blocking the action of adrenaline on smooth muscle of the bladder and the blood vessel walls. Doxazosin is used to treat high blood pressure. It relaxes the muscle tissue of the blood vessels, which in turn lowers blood pressure. Doxazosin is also used to reduce urinary obstruction and relieve associated symptoms of benign prostatic hypertrophy (BPH).¹³



Doxazosin (5)

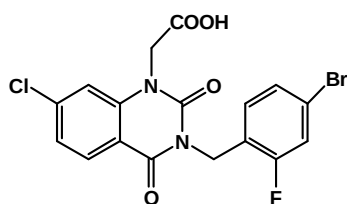
Metolazone **(6)** is an oral diuretic drug, commonly classified with the thiazide diuretics, and marketed under the brand names Zaroxolyn and Mykrox. It is primarily used to treat congestive heart failure and high blood pressure. Metolazone indirectly decreases the amount of water reabsorbed into the bloodstream by the kidney, so that blood volume decreases and urine volume increases. This lowers blood pressure and prevents excess fluid accumulation in heart failure. Metolazone is often used together with loop diuretics such as furosemide or bumetanide, but these

highly effective combinations can lead to dehydration and electrolyte abnormalities.¹⁴



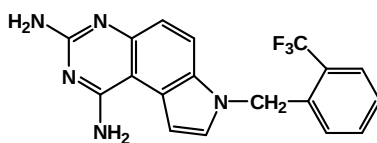
metalazone (6)

Zenarestat (**7**) was tested for prevention or controlling of diabetic complications.¹⁵



zenarestat (7)

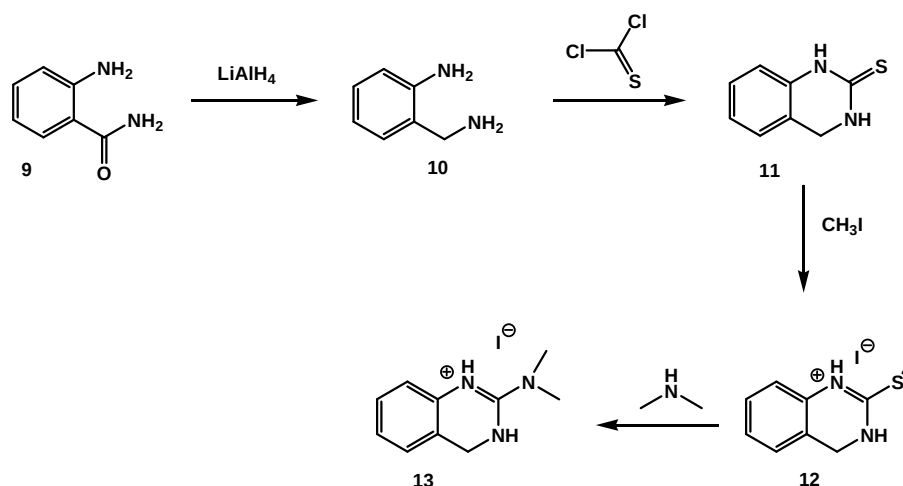
Pyrroloquinazolinediamine derivatives (**8**) were reported to possess anticancer, antimicrobial, and antimalarial activities.¹⁶



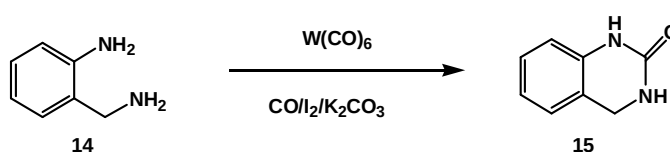
Pyrroloquinazolinediamine (8)

1.1.1. The Synthesis of Quinalizones

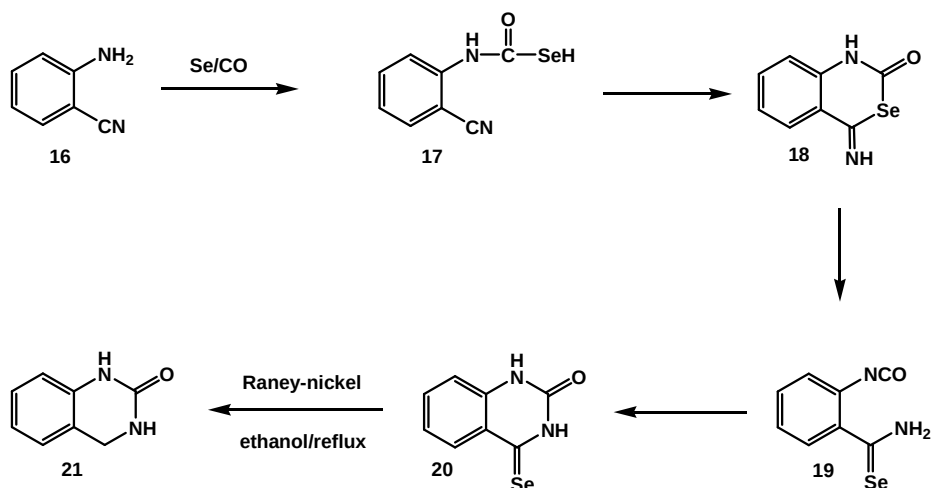
Based on the known biological activity of a variety of guanidine containing agents, Grosso and Nichols synthesized several N-substituted 3,4-dihydroquinolines (**13**). In the first step the benzamide (**9**) was reduced to the benzyl amine (**10**) with lithiumaluminium hydride, which then underwent into ring closure in the presence of thiophosgene to yield 3,4-dihydro-1H-quinazoline-2-thione (**11**). After methyl alkylation of (**11**), the quinazoline derivative (**13**) was obtained. This compound (**13**) can be considered to be rigid analog of phenylguanides, which has the activity of decreasing blood pressure. As expected, in anesthetized rats the compound (**13**) decreased blood pressure and were antagonists of the pressor response to norepinephrine.¹⁷



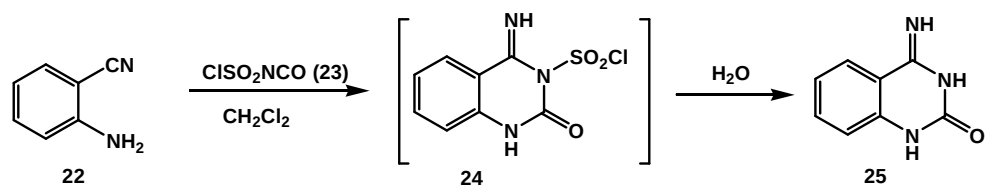
Direct conversion of o-aminobenzyl amine (**14**) to quinazoline derivative (**15**) has been performed using $\text{W}(\text{CO})_6$ as catalyst, I_2 as the oxidant and CO as the carbonyl source by McCusker *et al.*¹⁸



Carbonylation of o-substituted anilines (**16**) with carbon monoxide in the presence of selenium gives the selenium-containing heterocycle (**20**), which is then converted into the corresponding quinazoline derivative (**21**) by Raney-nickel reduction.¹⁹



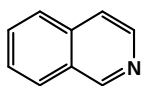
Reddy *et al.* have described an efficient one-pot convenient preparation of quinalizones (**25**) by the reaction of 2-aminobenzyl nitriles (**22**) with chlorosulfonyl isocyanate (**23**), affording ureidobenzonitriles (**24**), which on thermal cyclization gives (**25**).²⁰



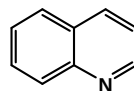
1.2. Isoquinolines

Isoquinoline (**26**), also known as benzo[c]pyridine or 2-benzaniline, is a heterocyclic aromatic organic compound. It is a structural isomer of quinoline. Isoquinoline (**26**) and quinoline (**27**) are benzopyridines, which are composed of a benzene ring fused

to a pyridine ring. Isoquinoline is the structural backbone in naturally occurring alkaloids including papaverine and morphine. The isoquinoline ring in these natural compounds derives from the aromatic amino acid tyrosine.



isoquinoline (26)

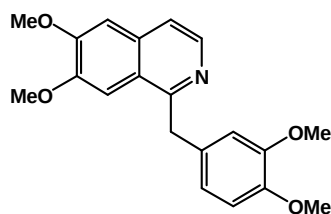


quinoline (27)

Isoquinoline was first isolated from coal tar in 1885 by Hoogewerf and van Dorp. They isolated it by fractional crystallization of the acid sulfate. Weissgerber developed a more rapid route in 1914 by selective extraction of coal tar, exploiting the fact that isoquinoline is more basic than quinoline. Isoquinoline can then be isolated from the mixture by fractional crystallization of the acid sulfate. Isoquinoline **(26)** is the structural backbone in naturally occurring alkaloids including papaverine **(28)** and morphine **(29)**. The isoquinoline ring in these natural compounds derives from the aromatic amino acid tyrosine.

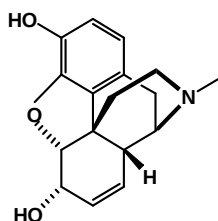
Papaverine **(28)** is an opium alkaloid used primarily in the treatment of visceral spasm, vasospasm (especially those involving the heart and the brain), and occasionally in the treatment of erectile dysfunction.²¹ While it is found in the opium poppy, **(28)** differs in both structure and pharmacological action from the other opium alkaloids.

Papaverine **(28)** is approved to treat spasms of the gastrointestinal tract, bile ducts and ureter and for use as a cerebral and coronary vasodilator²¹ in subarachnoid hemorrhage (combined with balloon angioplasty²² and coronary artery bypass surgery.²³ Papaverine may also be used as a smooth muscle relaxant in microsurgery where it is applied directly to blood vessels.



papaverine (28)

Morphine (**29**) is an extremely powerful opiate analgesic drug and is the principal active agent in opium. Like other opioids, e.g. heroin, morphine acts directly on the central nervous system (CNS) to relieve pain, and at synapses of the arcuate nucleus, in particular. Side effects include impairment of mental performance, euphoria, drowsiness, lethargy, and blurred vision. It also decreases hunger, inhibits the cough reflex, and produces constipation. Morphine (**29**) is highly addictive when compared to other substances and tolerance and physical and psychological dependence develop quickly. Patients on morphine often report insomnia, visual hallucinations and nightmares. Used in ACS "Chest Pain believed to be of cardiac origin" as an adjunct to nitroglycerine providing pain relief, decreasing patient anxiety and minimal coronary artery dilation, which helps oxygenate the heart.²⁴

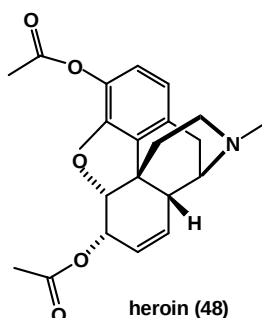


morphine (29)

Morphine (**29**) was first isolated in 1804 by the German pharmacist Friedrich Wilhelm Adam Sertürner (or Barnard Courtois), who named it "morphium" after Morpheus, the Greek god of dreams. But it was not until the development of the hypodermic needle (1853) that its use spread. It was used for pain relief, and as a "cure" for opium and alcohol addiction. Its extensive use during the American Civil

War allegedly resulted in over 400,000 sufferers from the "soldier's disease" of morphine addiction, although critics believe this to be a highly erroneous and misleading claim, pointing to the glaring lack of documented post-war cases.

Heroin (**48**) (diacetylmorphine) was derived from morphine in 1874. As with other drugs, its possession without a prescription was criminalized in the U.S. by the Harrison Narcotics Tax Act of 1914.



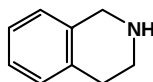
Morphine (**29**) was the most commonly abused narcotic analgesic in the world up until heroin (**48**) was synthesized and came into use. Even today, morphine (**29**) is one of the most sought after prescription narcotics by heroin addicts when heroin is scarce.

In a randomised double-blind study with crossover at an outpatient clinic in Bern, Switzerland, morphine was proven to have stronger side-effects than heroin at equianalgesic doses. Respiratory depression, miosis, sedation, itchiness, and euphoria were more pronounced with morphine.

High doses of morphine may be fatal due to respiratory depression. Nevertheless, patients in extreme pain are able to tolerate very high doses of morphine. This is because pain stimulates respiration, thus counteracting the respiratory depression.

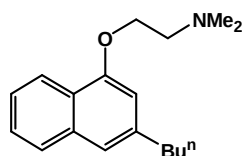
Parkinson's disease, a slowly progressing movement disorder, is thought to be caused by certain neurotoxins. A neurotoxin called MPTP (1[N]-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), the precursor to MPP⁺, was found and linked to Parkinson's disease in the 1980's. The active neurotoxins destroy dopaminergic neurons, leading to parkinsonism and Parkinson's disease. Several tetrahydroisoquinoline derivatives

(30) have been found to have the same neurochemical properties as MPTP. These derivatives may act as neurotoxin precursors to active neurotoxins.²⁵

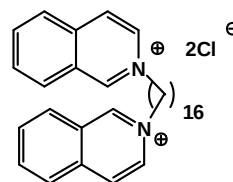


tetrahydroisoquinoline (30)

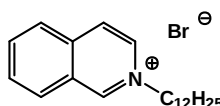
There are some other isoquinoline derivatives such as anesthetics, dimethisoquin (31); antifungal antiseptic agent, 2,2-methylenediisoquinolinium dichloride (32) and disinfectants, N-laurylisoquinolinium bromide (33).²⁶



dimethisoquin (31)



2,2-hexadecamethylenediisoquinolinium dichloride (32)

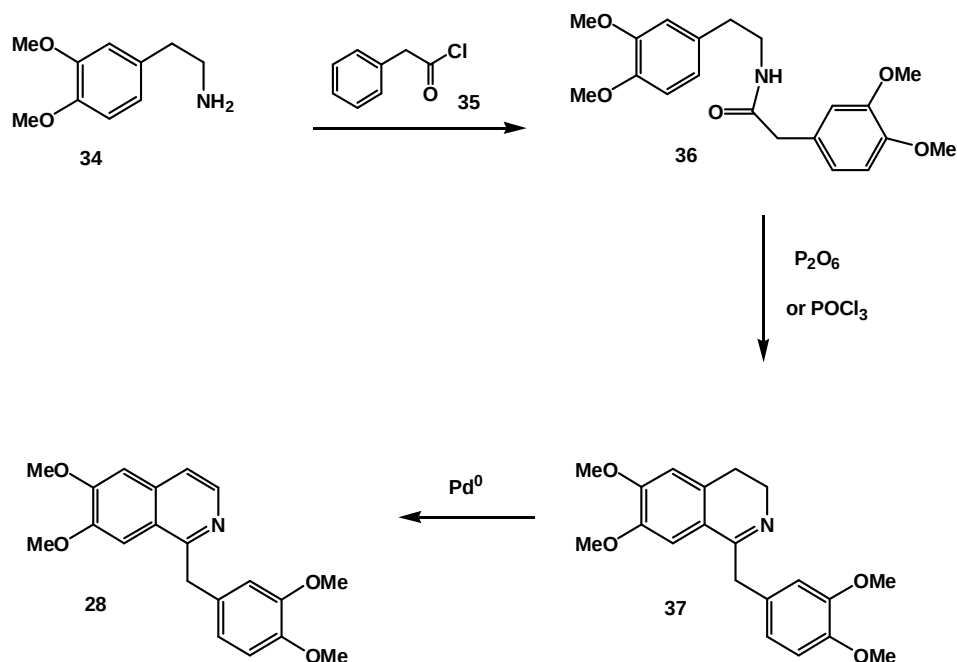


N-laurylisoquinolinium bromide (33)

1.2.1. The Synthesis of Isoquinolines

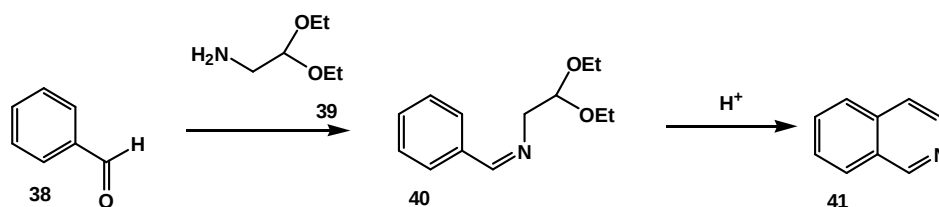
One of the earliest literatures for the synthesis of isoquinolines is Bischler Napieralski reaction by which the alkaloid papeverine (28) can be synthesised. In the first step β - ethyleneamine (34) is acylated and then cyclodehydrated by a Lewis acid, such as phosphoryl chloride or phosphorus pentoxide. The resulting 1-substituted-3,4-dihydroisoquinoline (37) can then be dehydrogenated using palladium.

The following Bischler-Napieralski reaction produces papaverine (**28**).²⁷



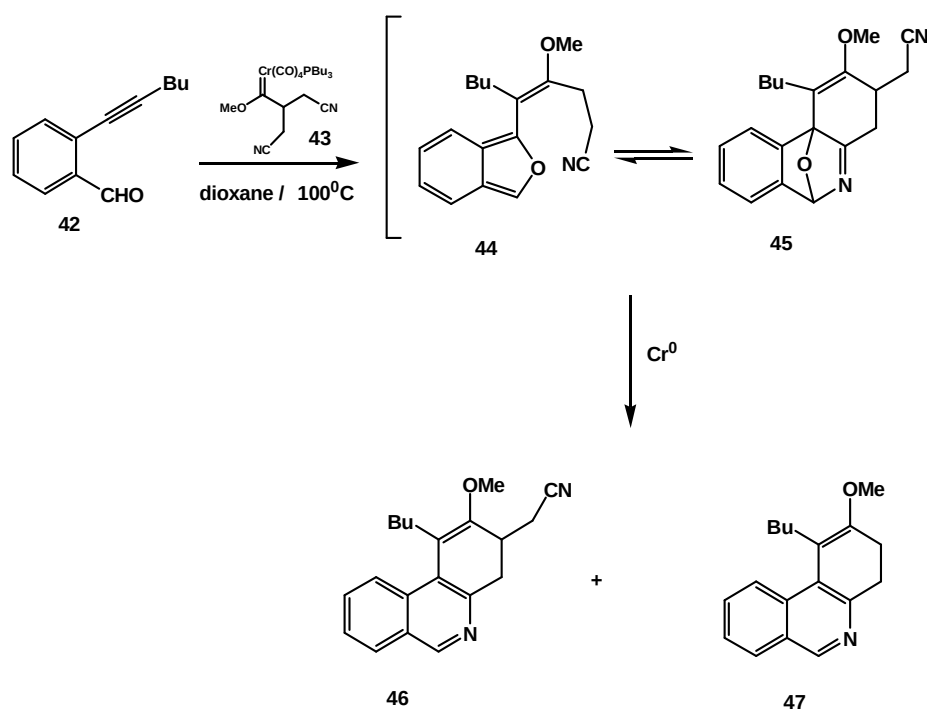
Pictet Gams reaction is also an early literature, which is the variation of Bischler Napieralski reaction. The Pictet-Gams reaction avoids the final dehydrogenation step of the Bischler-Napieralski reaction by constructing a β -phenylethylamine with a hydroxy group in the side chain.²⁸

One of the important earliest literatures is Pomeranz-Fritsch synthesis, in which arylaldehydes (**38**) with aminoacetaldehyde acetals (**39**) to give isoquinolines (**41**).²⁹

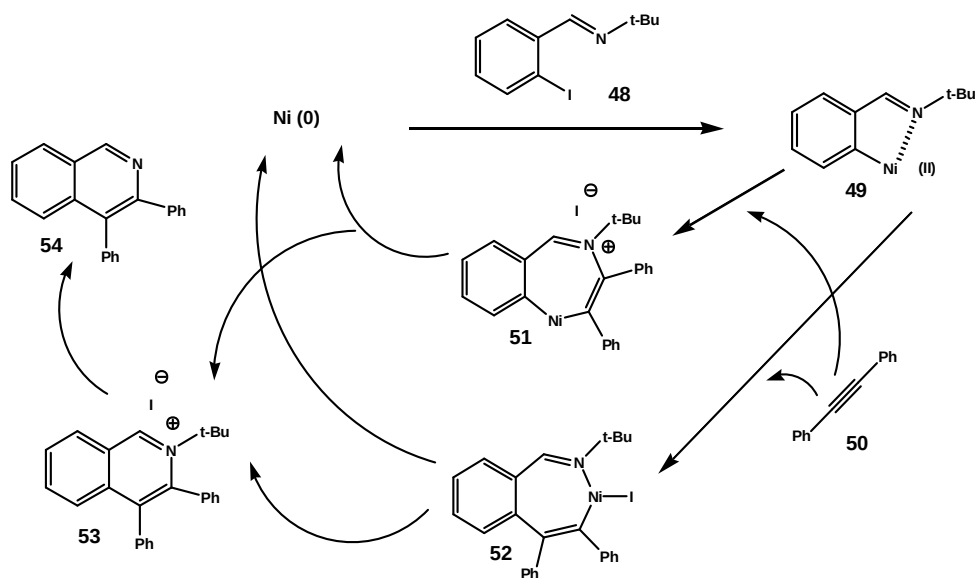


Since the methodologies in the early years needs harsh reaction conditions, in the recent years new synthetic methodologies have been improved for the synthesis of isoquinolines. One example from the recent years is the study of Heinden *et al.* which was succeeded with the coupling of 2-alkynylbenzaldehyde derivatives (**42**) β -cyanocarbene complexes (**43**).³⁰

The reaction involved the formation of an isobenzofuran followed by intramolecular Diels-Alder reaction with nitrile. The last step was the deoxygenation of (**45**) yielding the isoquinoline derivatives (**46**) and (**47**). They could not explain the formation of acetonitrile loss product (**47**).

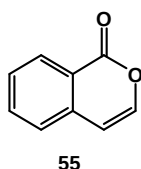


Another recent literature by Korivi *et al.* covers the highly efficient synthesis of isoquinolines (**54**) via nickel catalyzed annulation of tert-butyl imines of 2-iodobenzaldehydes (**48**) with various alkynes (**50**) under mild conditions; using refluxing acetonitrile.³¹ They explained the mechanism as follows:

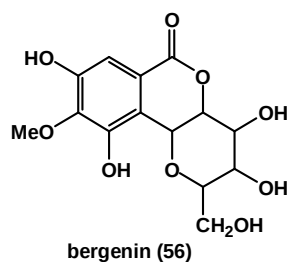


1.3. Isocoumarines

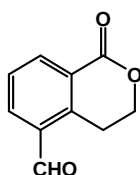
Isocoumarines (**55**) are the heterocyclic compounds, which include a lactone ring fused to benzene ring. They are natural structures found in many natural products that exhibit a broad range of biological activities including antiallergic and antimicrobial,^{32,33} immunomodulatory³⁴, cytotoxic³⁵, antifungal³⁶, antiinflammatory³⁷, antiangiogenic³⁸ and antimalaria³⁹. They can be isolated from plants, molds, bacteria and lichens.⁴⁰



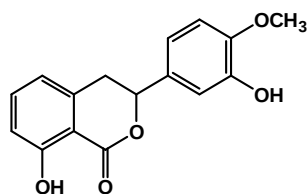
Bergenin (**56**), a naturally occurring isocoumarin is isolated from various medical plants. It shows mild anti-HIV activity⁴¹ and has anti-hepatotoxic activity⁴² and anti-ulcer activity.⁴³ Bergenin which was isolated from the aerial parts of *Fluggea Viraso* has been found to have good potential to treat cardiac arrhythmias.⁴⁴ The one, isolated from *Flueggea Microcarpa* shows antifungal activity against several plant pathogenic fungi.⁴⁵



Erythrocentaurin (**57**) is isolated from *Enicostema hyssopifolium*, which is widely distributed in Southern Pakistan. This plant is considered as medicinally important and used locally by the indigenous people as a remedy for malaria. In different regions of Pakistan, other species from the same family are used as digestive aids, stomachic tonics and for depurative, sedative and antipyretic effects. Erthocentaurin **57**, has also been found to be an active agent against serine proteases such as chymotrypsin and trypsin, these proteases are involved in the destruction of certain fibrous proteins.⁴⁶

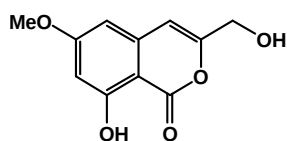


Phyllodulcin (**58**), which is extracted from the leaves of *Amacha* has been traditionally used as a sweet seasoning in Japan. Recently, several Japanese investigators have become interested in the pharmacological properties of the constituents of *Amacha*. They have found that a low dose of the extract potentiated cyclic AMP-induced steroidogenesis. Since phyllodulcin is the major constituent of *Amacha* extract, it acts as an inhibitor of adrenocortical phosphodiesterase.⁴⁷



phyllodulcin (58)

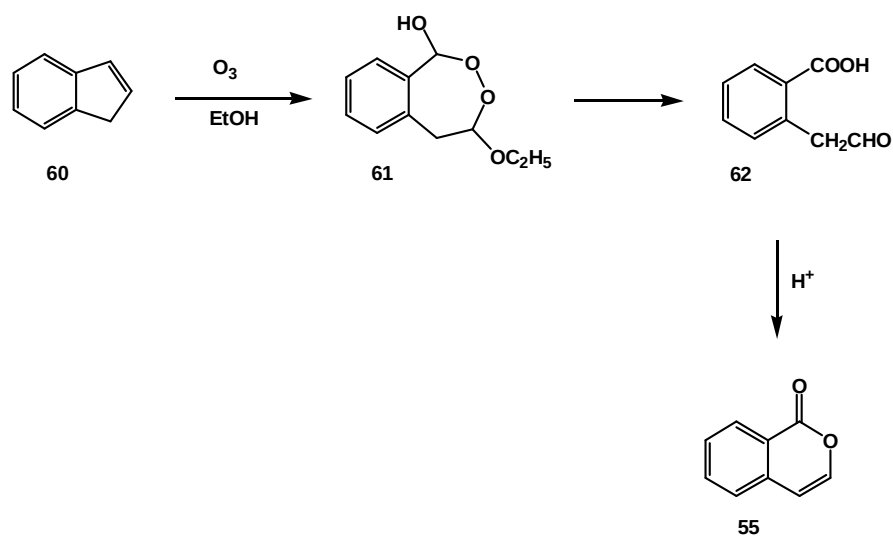
Cytogenin (**59**), a natural isocoumarin, which was extracted from a cultural broth of *Streptovercillium eurocidium* in 1990, was shown to possess potent antitumor activity against Ehrlich carcinoma in mice while exhibiting low cytotoxicity.⁴⁸ Studies have suggested that cytogenin exerts antitumor effects by activation or modulation of macrophages and T-cells.⁴⁹



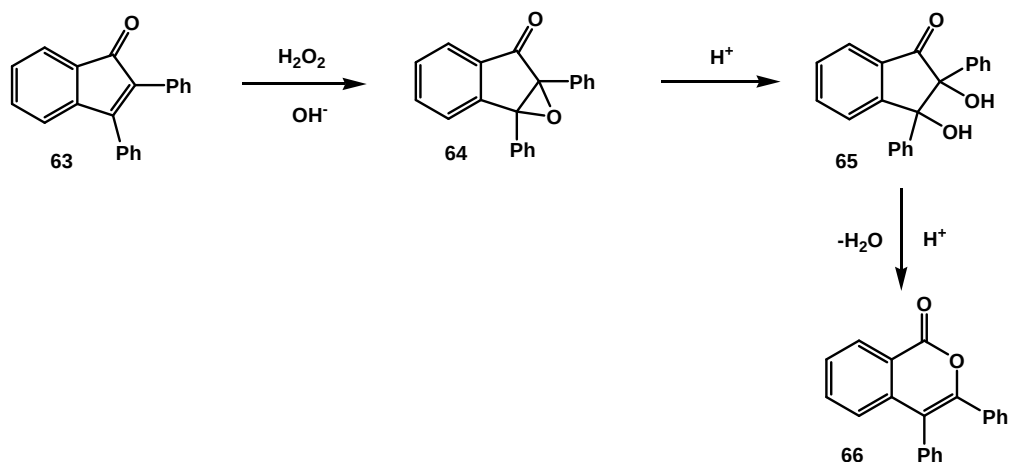
cytogenin (59)

1.3.1. The synthesis of Isocoumarines

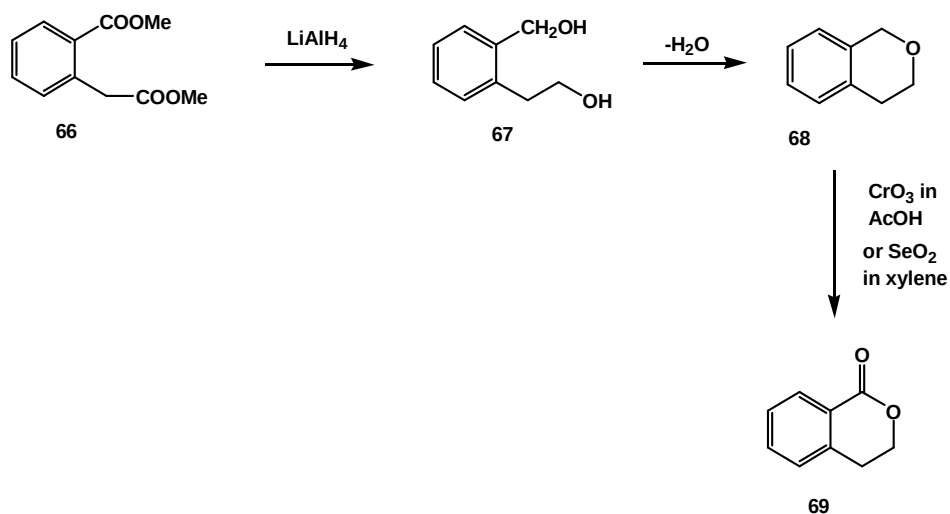
In the very early years, isocoumarines have been synthesized in high yield by ionization of indene (**60**) in ethyl alcohol, followed by decomposition of the intermediate cyclic perester (**61**). Treatment of the aldehyde (**62**) with the acid led to isocoumarin (**55**).⁵⁰



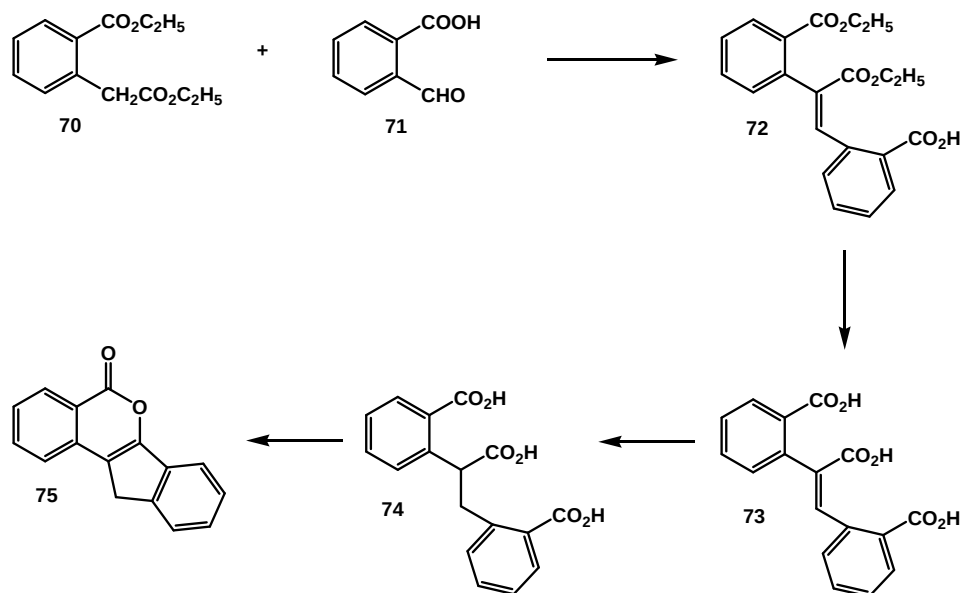
Oxidation of 2,3-diphenylindone (**63**) to 2,3-diphenyl-2,3-oxidoindanone (**64**), which then rearranged in the presence of acids to give 3,4-diphenylisocoumarin (**66**).⁵¹



Isochromans (**68**) have been important precursors in the synthesis of isocoumarines. They have been synthesised by the cyclization of the alcohol (**67**), which was the reduction product of homophthalic acid ester (**66**) with aluminium hydride. In the last step the isochroman was oxidized to isocoumarin (**69**) either by chromium trioxide or by selenium dioxide.^{52,53}



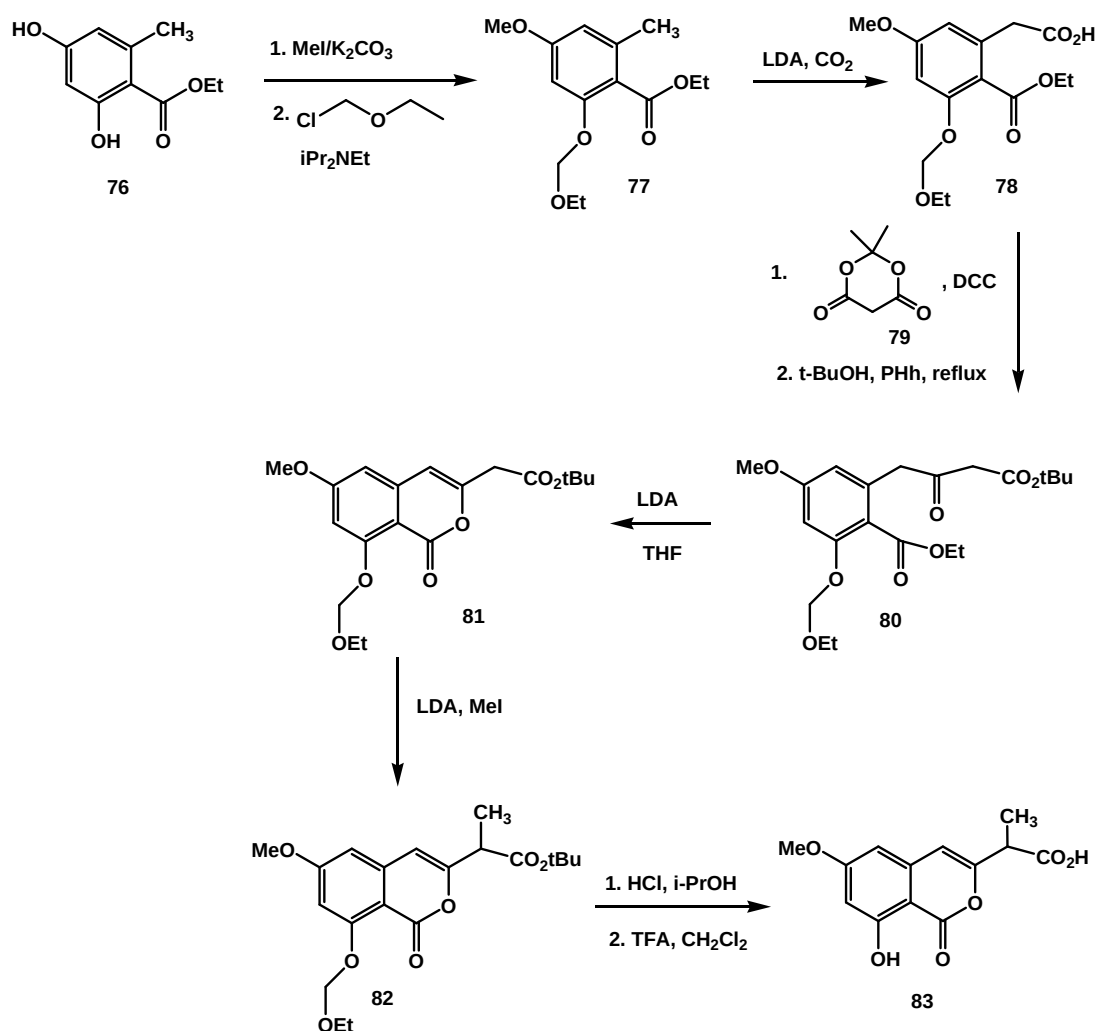
In the early years, condensation reactions have been used in the synthesis of isocoumarines (55). In one of the literature by Chatterja *et al.* the isocoumarin derivative (75) has been obtained from the condensation of phthaldehydic acid (71) with diethylhomophthalate (70).⁵⁴



Although the synthesis of isocoumarines was performed successfully in the early years, very little was known about their biological activity. In recent years, the activities of isocoumarines are known, so the synthesis of isocoumarines is based on their biological activity.

There is a growing interest on the total synthesis of natural isocoumarines and their synthetic analogs.

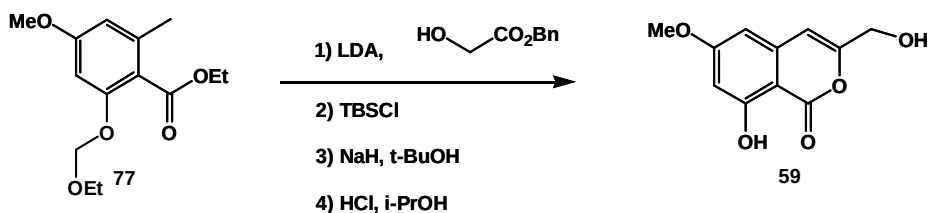
In 2004, Yuan *et al.* reported an efficient method for the synthesis of cytogenin, which was already known to be antitumor active and C(3) side chain modified analogue NM-3, a synthetic isocoumarin, which was previously reported to show similar biological activity with cytogenin.⁵⁵



Their synthetic approach began with ethyl orsellinate (**76**), which was followed with regioselective methylation to give the 4-methoxy derivative. The next step involved the protection of the other hydroxy group as the ethoxymethyl ether (**77**). Treatment

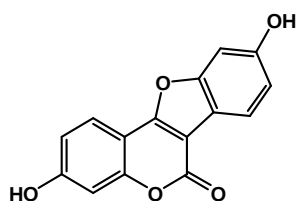
of **(77)** with LDA generated the benzylic anion which was quenched with carbondioxide to provide homophthalic acid ester **(78)**. Coupling with Meldrum's acid **(79)** in the presence of DCC gave the adduct which was difficult to purify and therefore the crude product was heated with t-butyl alcohol to give the desired β -ketoester functionality containing compound **(80)**. In the following step, lactonization was performed by exposure to LDA. Ester enolate alkylation with methyl iodide gave the compound **(82)**, which was then subjected to sequential t-butyl ester cleavage with hydrochloric acid and ethoxymethyl ether removal with trifluoroacetic acid yielded the desired isocoumarin, NM-3 **(83)**.

Cytogenin **(59)** was synthesised by a very similar method, which included onyl three steps. The benzylic anion, which was generated by the same way, was quenched with benzyl glycolate. Proton transfer was a competing reaction, and the condensation provided α -hydroxyketone. After protection of the primary hydroxyl as a TBS ether, lactonization was performed under basic conditions. The anti-angiogenic isocoumarin, cytogenin **(59)** was obtained after deprotection has been performed with hydrochloric acid.



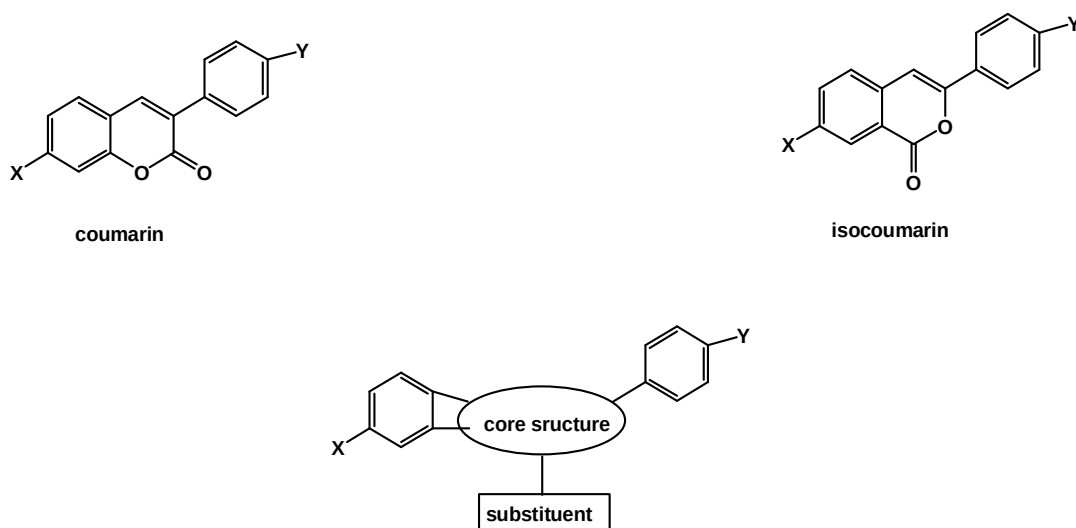
A recent literature by Angelis *et al.* in 2005 covers the synthesis of isocoumarins as estrogen beta selective ligands.⁵⁶ The estrogen receptors (ERs), members of the nuclear hormone receptor superfamily, mediate the activity of estrogens in many different organs, including the reproductive, skeletal, cardiovascular, and central nervous system.^{57,58,59} Two different types, the product of different genes, are known. ER α , the first discovered and ER β , which was only discovered in 1996.^{60,61} Both estrogen receptors bind 17 β -estradiol with high affinity and bind to classical estrogen elements in a similar way.

However, there are differences in their amino acid sequence, transcriptional activity and pattern of tissue distribution. Since ER β is mostly expressed in the prostate, ovary, colon, urinary tract, and some brain regions, a selective ER β agonist might maintain the beneficial effects of estrogen therapy in these ER β -rich tissues without increasing the risk of cancer in other organs that are ER α rich, such as breast and uterus. In addition, ER β has been shown to be antiproliferative when present along with ER α in breast cancer cells. For this reason, many researchers have focused their attention on the synthesis of compounds selective for ER β . The coumarine derivative coumestrol is long known to be an estrogenic compound with selective affinity for ER β .

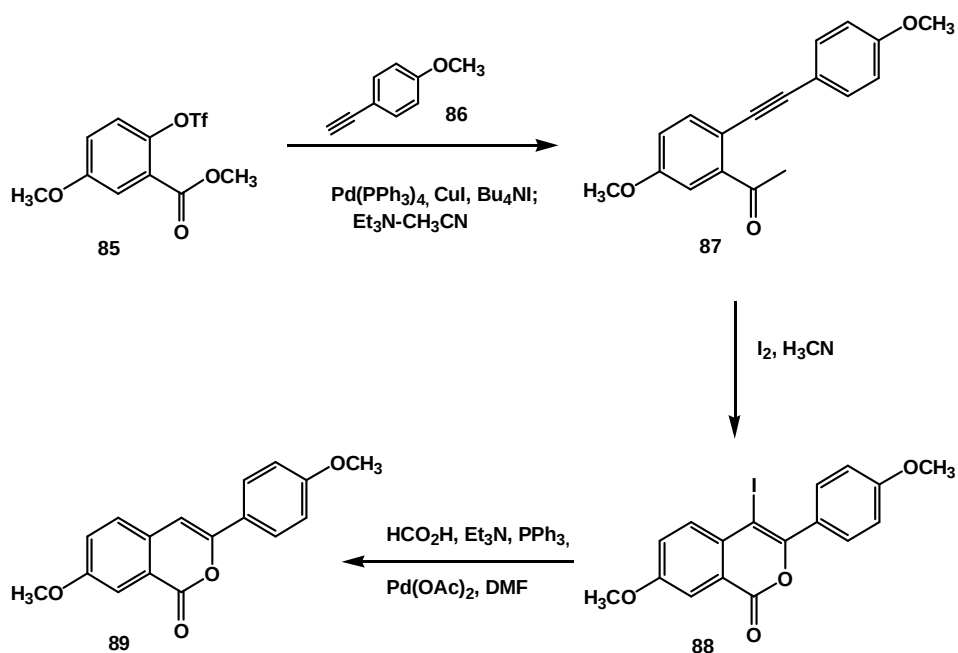


coumestrol (84)

According to the pharmacophore model, the core structure in coumarin is selective to the ER β . Since coumarines and isocoumarines have an isomeric arrangement of the central atoms of the heterocyclic core, isocoumarin core would also be ER β selective.

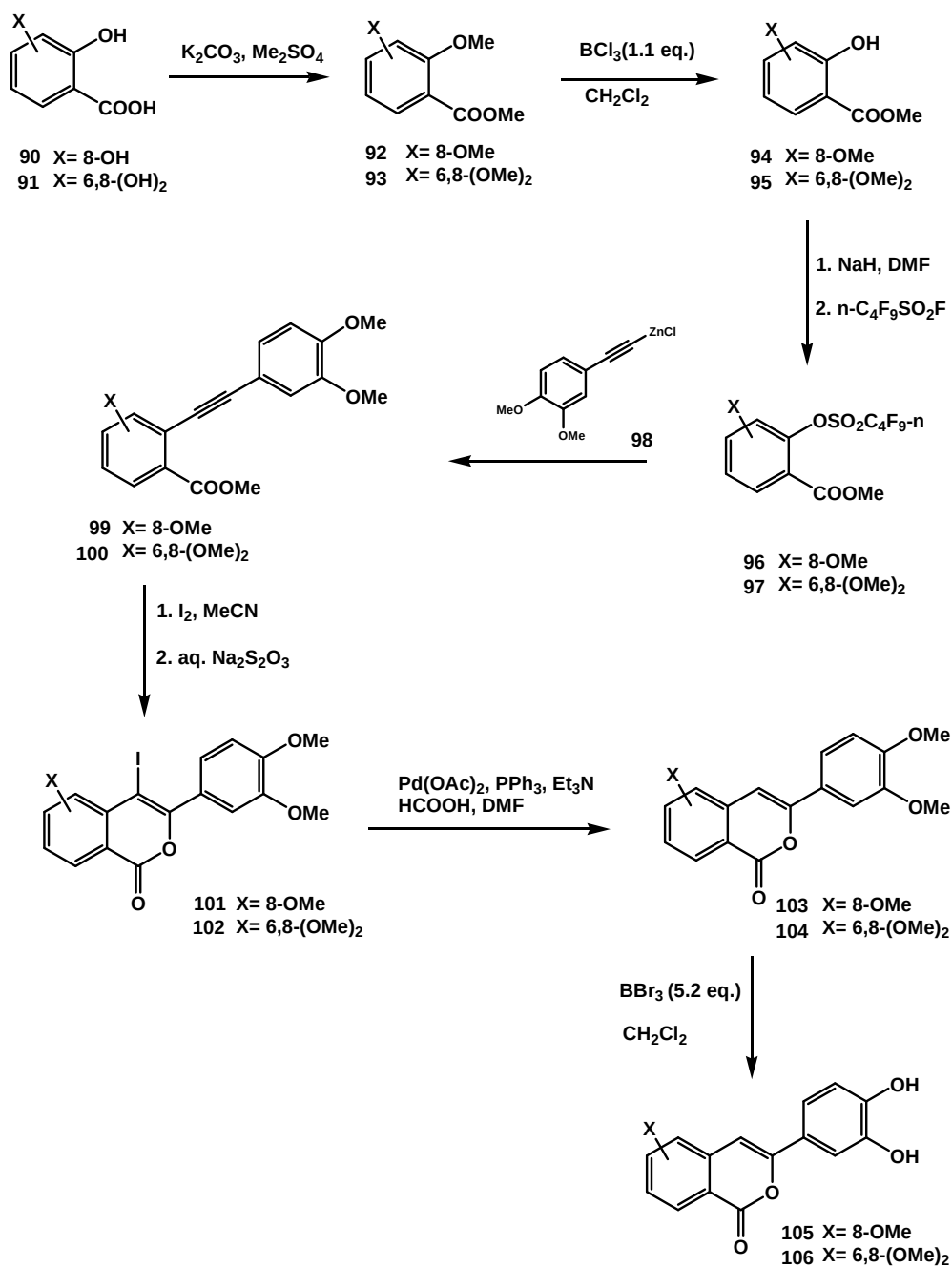


Under the influence of these suggestions, Angelis *et al.* have begun the synthesis of the desired isocoumarin with the palladium-catalyzed Sonogashira coupling reaction between the ester derivative (**85**) and 4-ethynylanisole (**86**), which gave the diarylacetylene (**87**). The acetylenic ester (**87**) could be easily converted to the isocoumarin by an iodo-lactonization reaction, yielding the iodoenol lactone (**88**), from which the iodine group can be removed readily by hydrogenolysis.



The final isocoumarin derivative (**89**) was found to show higher ER β selectivity than the coumarin derivative. The higher selectivity has been explained on the basis of the core structure. The two phenol rings in the isocoumarin structure is fused to form a heterocycle by reducing the size and increasing the core polarity. According to the pharmacophore model, the more the core size gets smaller, the more selectivity for ER β increases. That is the reason for isocoumarin derivative to have higher selectivity.

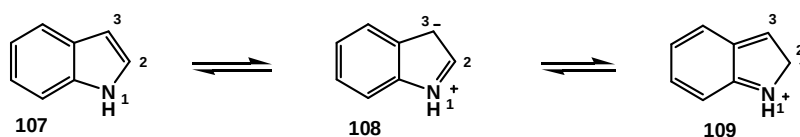
Thunberginol A (**103**) and B (**104**) are important antiallergic, antimicrobial and anticancer isocoumarines isolated from *Hydrangea Dulcis* Folium.^{62,63} Rossi *et al* designed a synthesis path for the synthesis of these two natural isocoumarines by iodolactonization of methyl 2-(arylethynyl)benzoic acids.⁶⁴ In the first step, the hydroxy groups were converted into methoxy groups giving the product **92** and **93**. In the second step o-hydroxy ester **94** and **95** was obtained by the usage of 1.1 equivalent of BCl₃. Reaction of **94** and **95** with NaH in DMF followed by treatment with perfluoro-1-butanesulfonyl fluoride provided **96** and **97** in high yield. This nonaflate **96, 97** was then reacted with a molar excess of 3,4-dimethylethynylzinc chloride **98** in the presence of Pd₂(dba)₃ and 1,1'-bis(diphenylphosphino)ferrocene to give the compound **99, 100**. Reaction of this ester with iodine in acetonitrile followed by the treatment with aqueous sodiumbisulfite yielded 4-aryl-3-iodoisocoumarin **101, 102**. In the following step iodine was replaced with hydrogen and nextly o-demethylation was performed with BBr₃ giving the isocoumarines thunberginol A (**103**) and B (**104**), which were found to be significantly active in the NCI 3-cell line, one dose primary anticancer.



1.4. Indoles

Indole (**107**) is an aromatic heterocyclic compound, which has a bicyclic structure, consisting of a six-membered benzene ring and pyrrole ring.

By participation of the nitrogen lone pair into the aromatic ring, indole is classified as a Π -excessive aromatic compound, which is isoelectronic with naphthalene.

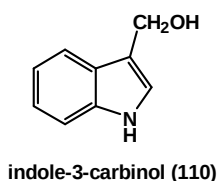


Like pyrrole, indole is a weak base and does not behave like a simple amine. As a result of being weak base, indole itself and its simple derivatives are quite reactive to strong acids. Due to the contribution of resonance structure (**108**), indole undergoes electrophilic substitution, mainly at position 3. Various molecular orbital calculations also find the highest electron density and highest concentration of HOMO at C-3. The C-2 position is the second most reactive site towards electrophiles. The indole nucleus, known to chemists as benzopyrrole, is the parent member of a broad spectrum of nitrogen heterocyclic biochemicals commonly found in nature. Indole derivatives occur in flower oils such as jasmine and orange blossom, and in less pleasant substances such as coal tar and fecal matter. Indoles also exist as melanin-related organics and indigoid pigments.

Experimental studies have shown that indoles have a protective effect against estrogen-related cancer such as breast cancers⁶⁵, colon and other types of cancer.^{66,67} They block the estrogen receptors, thus inhibiting the growth of tumors in the mammary gland and in other locations.

Among the indole derivatives, indole-3-carbinol (**110**) takes an important role because of being an important antitumor agent. It has achieved notoriety as a therapeutic phytochemical. The possible anticancer activity of substances such as (**110**) was recognized by the Roman statesman, Cato the Elder who in his treatise on

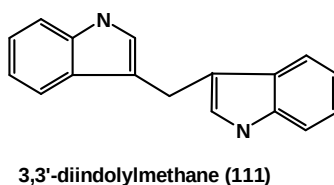
medicine wrote: "If a cancerous ulcer appears upon the breasts, apply a crushed cabbage leaf and it will make it well." Crushing a cabbage leaf would convert indole-3-glucosinolate to **(110)**, among other reactions. This recognition is not only because of the anticancer activity of indole-3-carbinol, but because the vegetables in which it occurs belong to the much maligned *Brassica* genus of cruciferous vegetables; the ever unpopular broccoli, brussel sprouts, cabbage, cauliflower, and kale. It would seem that indole-3-carbinol is partially responsible for the strong flavor that makes these vegetables so unpopular but healthy.



forms. It increases the ratio of 2-hydroxyestrone (good estrogen) to 16 alpha-hydroxyestrone (bad estrogen) and inhibits the 4-hydroxylation of estradiol. Indole-3-carbinol **(110)** is a highly effective anticancer agent⁶⁸, blocking carcinogenic substances before they reach their cellular targets and eliminating DNA damage in cell nuclei.

In animal models, **(110)** prevents the development of malignancies, including cervical cancer⁶⁹, breast cancer⁷⁰, prostate cancer⁷¹, endometrial cancer⁷² and skin cancer.⁷³ It is a strong antioxidant and stimulators of detoxifying enzymes, protecting the structure of DNA.

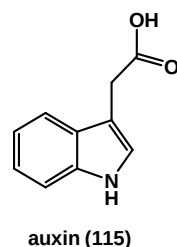
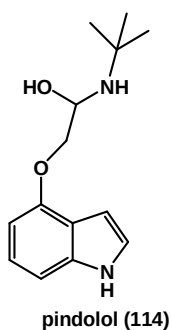
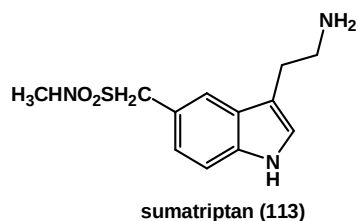
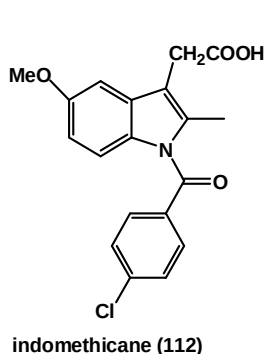
3,3'-Diindolylmethane (DIM) **(111)** is an also important indole derivative, which is derived from the digestion of indole-3-carbinol **(110)** in stomach or found naturally in several vegetables such as broccoli and cauliflower.



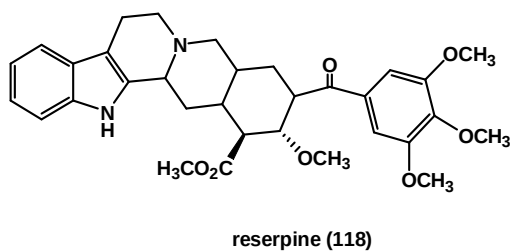
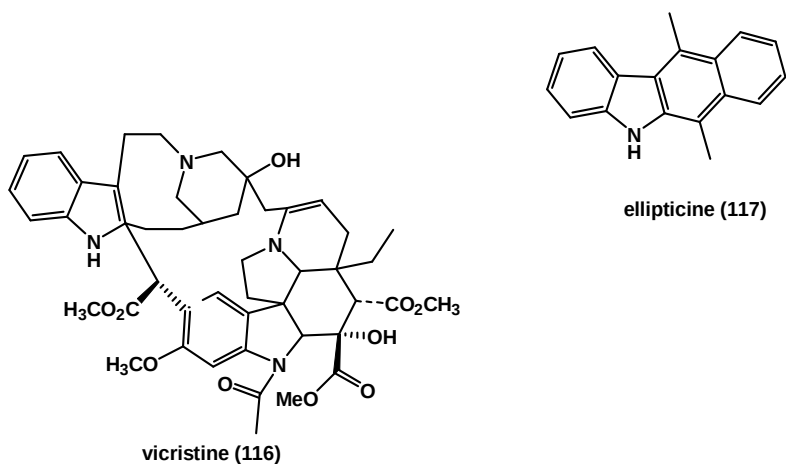
As a chemical compound, it is the dimeric major acid-catalyzed reaction product of **(110)**.

Super indole CVBTM is a nutritional dietary supplement designed to promote normal, healthy estrogen metabolism and reduce the risk of some diseases, including the cancer. The primary ingredients are a group of photochemicals extracted from the Brassica are; Indole-3-carbinol **(110)**, Diindonylmethane **(111)**, ascorbigen, sulporaphine, indoles, isothiocyanates and glucosinolates.

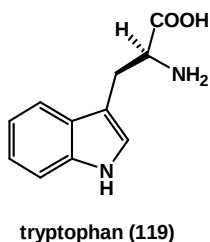
The other indole derivatives which have found use as drugs are indomethacin **(112)**, one of the first anti-inflammatory agent⁷⁶; sumatriptan **(113)**, which is used in the treatment of migraine headaches⁷⁷; pindolol **(114)**, one of the important beta blockers⁷⁸; and auxin (indole-3-acetic acid) **(115)**, acts as plant growth hormone.⁷⁹



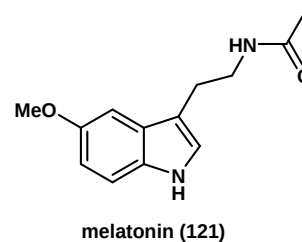
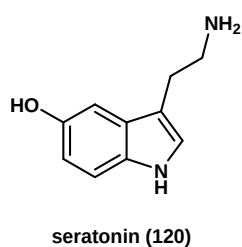
There are also some naturally occurring indoles which have clinical importance, such as alkaloid vincristine **(116)**; chemotherapeutic agent for cancer⁸⁰, derivatives of ellipticine **(117)**; anti-tumour active⁸¹, reserpine **(118)**; used in treatment of mental disorders⁸².



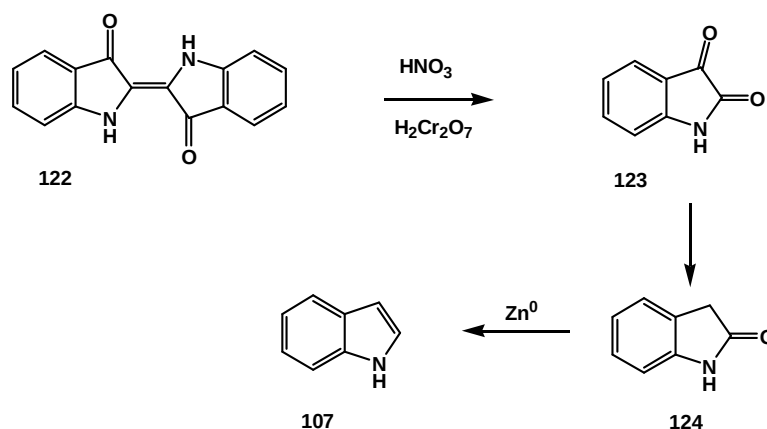
The indole structure is found in the amino acid tryptophan **(119)** and tryptophane containing proteins, which help to reduce depression and insomnia associated with hormonal fluctuations. Tryptophan-rich foods include banana, pineapple, plum, nuts, milk and cheese.



Tryptophan is the precursor to the neuro-transmitters serotonin **(120)** and melatonin **(121)**, which help to control appetite, body temperature, libido, and mood and to prevent depression.⁸³



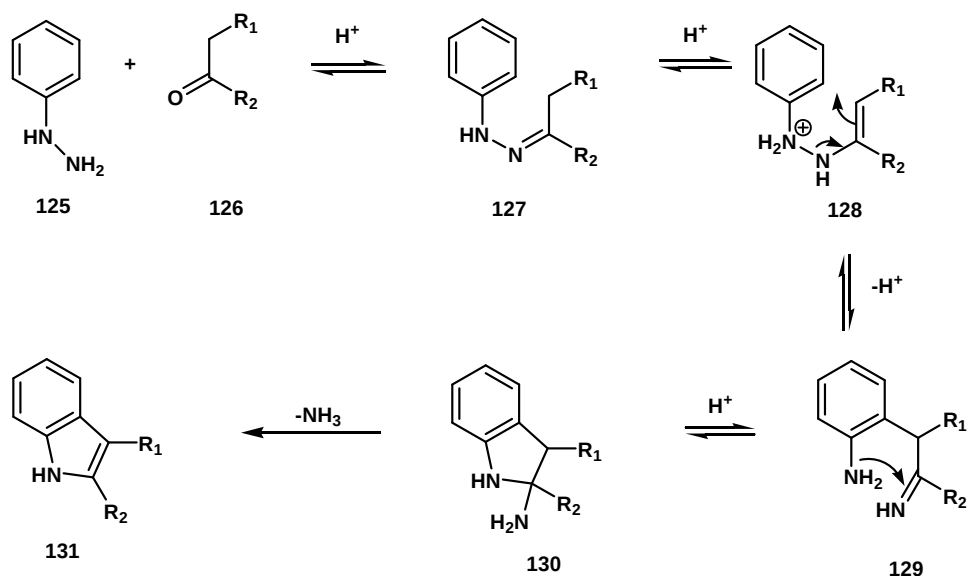
Because of having biological activity, synthesis of indole derivatives has been a topic of science not only in medical chemistry but also in synthetic organic chemistry. Indole chemistry began to develop with the study of the dye indigo (**122**), since it was first isolated by treatment of the indigo dye with oleum. Indigo (**122**) was first converted to 1H-indole-2,3-dione (isatin) (**123**) and then to oxindole (**124**). Then, in 1866, Adolf von Baeyer reduced oxindole (**124**) to indole (**107**) using zinc dust.⁸⁴



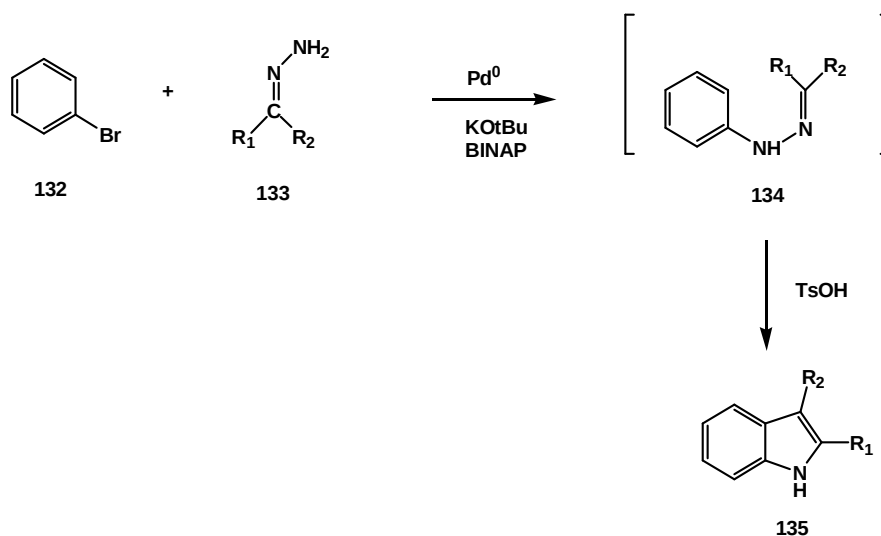
Certain indole derivatives were important dye stuffs until the end of 19th century. In the 1930s, interest in indole is intensified when it became known that the indole nucleus is present in many important alkaloids, as well as in tryptophan (**119**) and auxins (**115**), and it remains an active area of research.⁸⁵

1.4.1. The Synthesis of Indoles

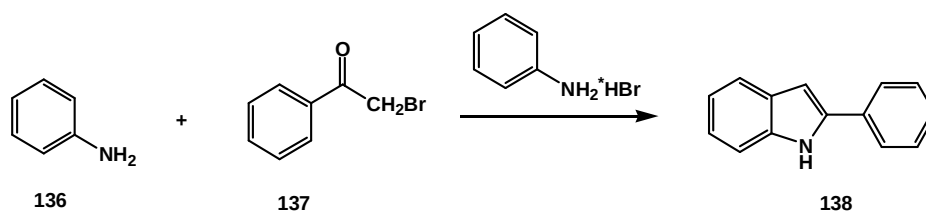
The Fischer indole synthesis, which remains the most versatile method for preparing indoles, was reported in 1883 by Fischer.⁸⁶ Today it is used in the synthesis of antimigraine drugs of the triptan class, which begins with the reaction of a (substituted) phenylhydrazine (**125**) with an aldehyde or ketone (**126**), initially forming a phenylhydrazone (**127**) which isomerizes to the respective enamine (**128**). After protonation, a cyclic [3,3]-sigmatropic rearrangement occurs producing an imine (**129**). The resulting imine forms a cyclic aminoacetal (**130**), which under acid catalysis that eliminates NH_3 , resulting in the energetically favorable aromatic indole (**131**).



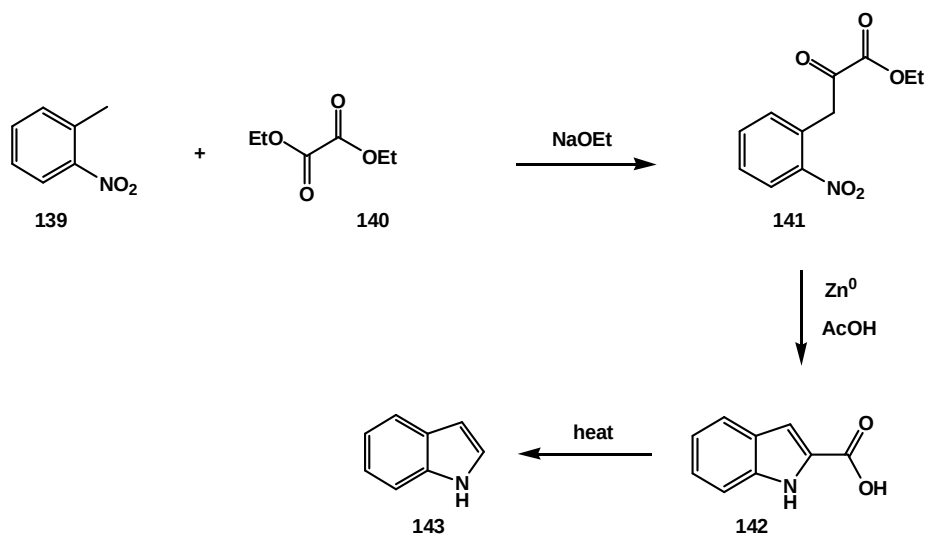
Using palladium chemistry, Buchwald has improved the Fischer indole synthesis.⁸⁵ They have utilized the palladium catalyzed coupling of hydrazones (**132**) with aryl bromides (**133**) as an entry to N-aryl hydrazones (**134**) for use in the Fischer indolization.



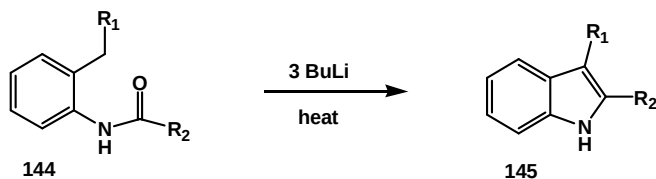
The Bischler-Möhlau indole synthesis is a chemical reaction that forms a 2-arylindole (**138**) from a α -bromo-acetophenone (**136**) and excess aniline (**137**).⁸⁶



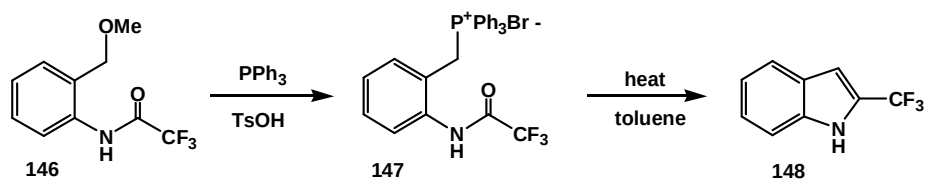
The Reissert indole synthesis is designed to synthesize indole (**142**) or substituted-indoles (**143**) from ortho-nitrotoluene (**139**) and diethyl oxalate (**141**) by reductive cyclization.⁸⁷



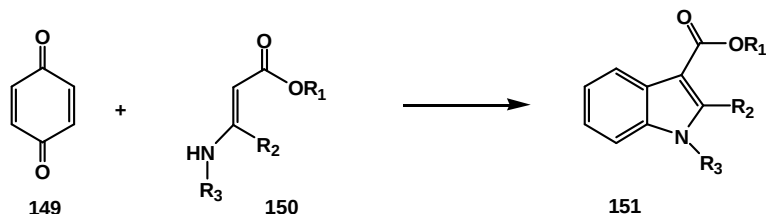
The Madelung synthesis is a chemical reaction that produces substituted or unsubstituted indoles (**145**) by the intramolecular cyclization of N-phenylamides (**144**) using strong base at high temperature.⁸⁸



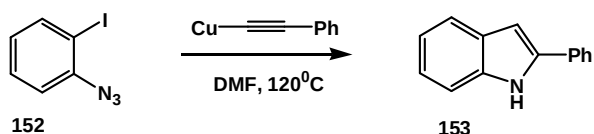
Since the Madelung synthesis has some harsh conditions such as strong bases, Holulihan *et al.* have modified this method by using milder conditions.⁸⁹ For example, benzylphosphonium salts (**147**), which can be generated in situ from the corresponding benzyl methyl ether (**146**) undergo facile cyclization to indoles (**148**) under thermal conditions.



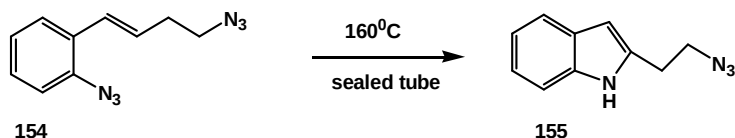
The Nenitzescu indole synthesis involves the formation of the key antitumor precursor 5-hydroxyindole (**151**) derivatives from benzoquinone (**149**) and β -aminocrotonic esters (**150**).⁹⁰



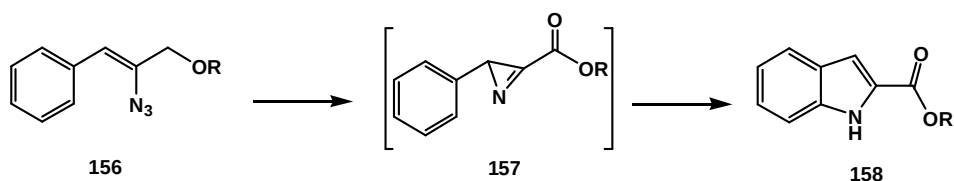
The Castro indole synthesis is the first discovered metal catalyzed cyclization of o-alkynylanilines (**152**) to indoles (**153**) using copper acetylene derivatives.⁹¹



The Sundberg indole synthesis, which involves the thermolysis of o-azidostyrenes (**154**) and cyclization of the resulting nitrene to form indoles has been modified by Molina *et al.* by performing the reaction in sealed tube.⁹²

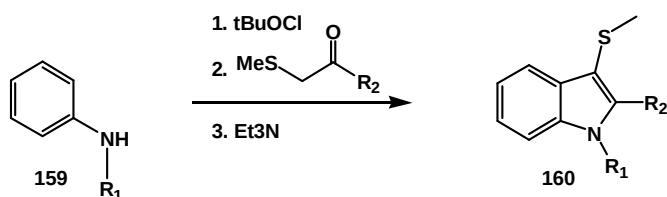


The Hemetsberger indole synthesis, which is also called the Hemetsberger-Knittel synthesis is related to the Sundberg indole synthesis except that the azido group is on the chain rather than on the benzene ring. This reaction involves the thermal decomposition of a 3-aryl-2-azido-propenoic ester (**156**) into an indole-2-carboxylic ester (**158**).⁹³



However, this is not a popular reaction, due to the lack of stability and difficulty in synthesizing the starting material.

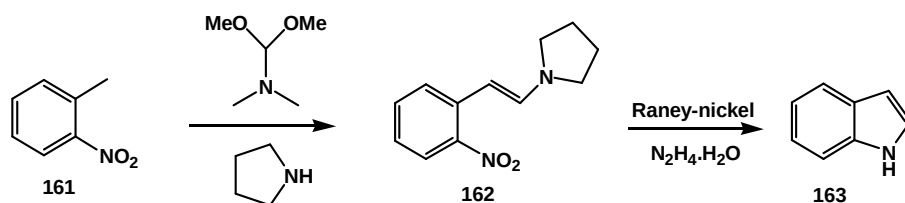
The Gassman indole synthesis is a one-pot chemical reaction used to synthesize substituted indoles (**160**) from aniline (**159**), in which none of the intermediates have been isolated.⁹⁴



R_1 can be hydrogen or alkyl, while R_2 works best with aryl, but can also be alkyl. Electron-rich anilines, such as 4-methoxyaniline, tend to fail in this reaction.

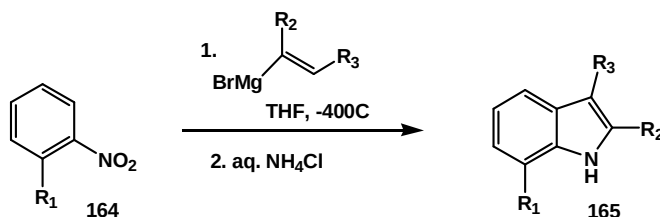
The 3-position thiomethyl group is often removed using Raney nickel to give the 3-H-indole.

The Leimgruber-Batcho indole synthesis produces indole (**56**) from *o*-nitrotoluenes (**161**).⁹⁵ The first step is the formation of an enamine (**162**) by using *N,N*-dimethylformamide dimethyl acetal and pyrrolidine. The desired indole (**163**) is then formed in a second step by reductive cyclization.

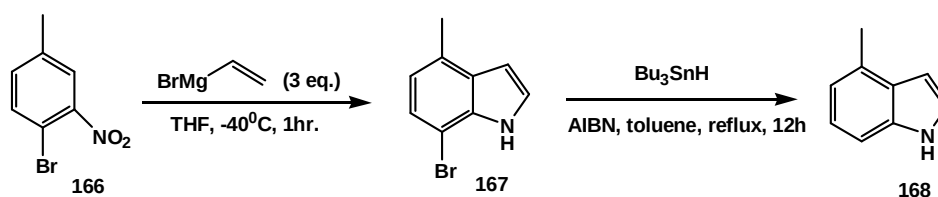


In the above scheme, the reductive cyclization is affected by Raney nickel and hydrazine. Palladium-on-carbon and hydrogen, stannous chloride, sodium dithionite⁹⁶ or iron in acetic acid⁹⁷ are also effective reducing agents.

The Bartoli indole synthesis is a [3,3]-sigmatropic rearrangement analogous to the Fischer indole synthesis, has been used to prepare substituted indoles **165** from ortho-substituted nitroarenes (**164**) with vinyl Grignard reagents.⁹⁸

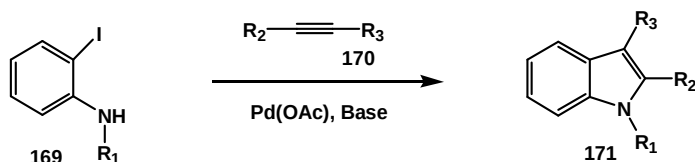


The reaction is unsuccessful without substitution ortho to the nitro group. Three equivalents of the vinyl Grignard reagent are also necessary for good yields. This method has become one of the shortest and most flexible routes to 7-substituted indoles.⁹⁹ The Leimgruber-Batcho indole synthesis gives similar flexibility and regioselectivity to indole derivatives. One advantage of the Bartoli indole synthesis is the ability to produce indoles substituted on both the carboxylic ring and the pyrrole ring, which is difficult to do with the Leimgruber-Batcho indole synthesis. Adrian Dobbs greatly enhanced the scope of the Bartoli indole synthesis by using an ortho-bromine as a directing group, which is subsequently removed by AIBN and tributyltin hydride.¹⁰⁰



The synthesis of 4-methylindole (**168**) highlights the ability of this technique to produce highly substituted indoles.

The Larock indole synthesis is a metal catalyzed reaction, which refers to the intramolecular Pd-catalyzed reaction of ortho-iodoanilines (**169**) and disubstituted alkynes **170** in a single step.¹⁰¹ The heteroannulation step is regioselective and almost gives 2,3-disubstituted indoles **171**, where the most sterically hindered group of the alkyne occupies the 2-position of the indole ring.

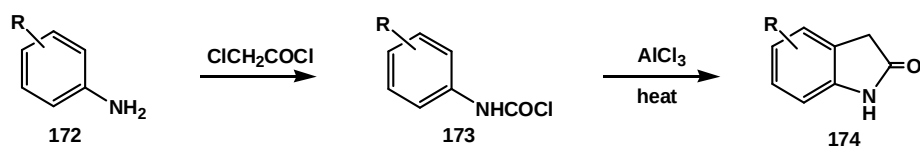


An excess of alkyne, using potassium carbonate or potassium acetate as the base, and adding one equivalent of lithium chloride tend to give the best yields. Many functional groups are tolerated on the aniline and the alkyne. Regarding the regioselectivity of the internal alkyne, the R-group with the largest steric bulk will end up in the R₂ position.

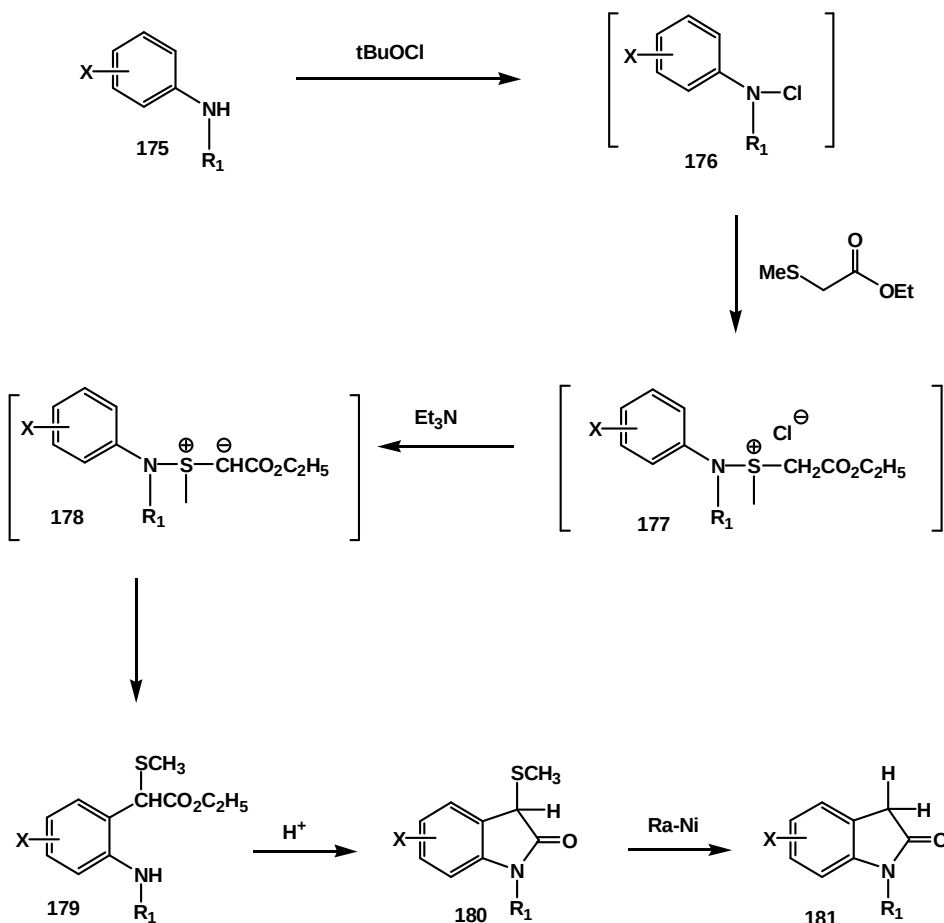
1.4.2. Oxindoles

Oxindoles (**124**) and their derivatives (**124**) are important class of indole family, which are used as synthetic intermediates of natural products and pharmaceutical reagents.¹⁰² They are also important precursors for the synthesis of indoles.

One of the oldest methods used in the synthesis of oxindoles is Friedel Crafts Alkylation. Substituted aniline **172** is firstly converted to **173** and then cyclization has been performed to yield the related oxindole **174**.¹⁰³ The Friedel Crafts reaction has a disadvantage, that it requires strongly acidic conditions.

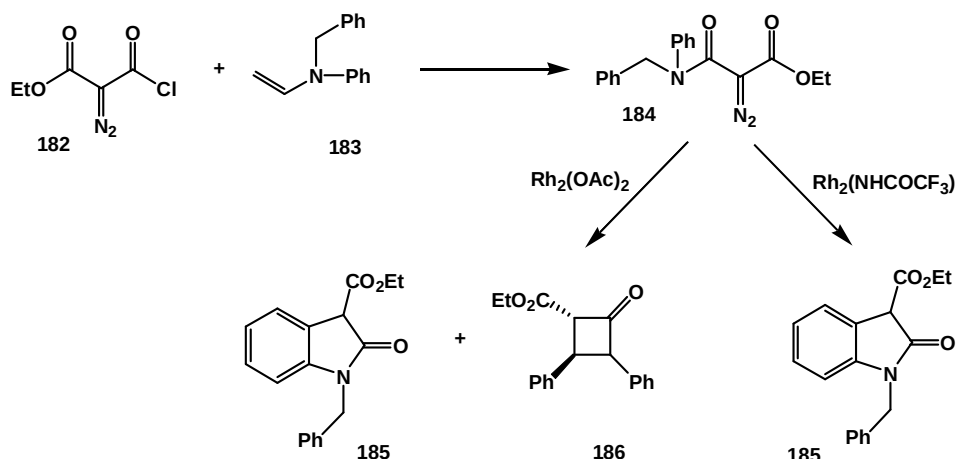


Gassman and his coworkers have synthesized oxindoles **178** from substituted anilines **175**) by using a more efficient way. They have used the same synthesis path as for indoles. When they have used α -carboxy sulfide instead of β -keto sulfide, the obtained product was oxindole derivative **181**.¹⁰⁴

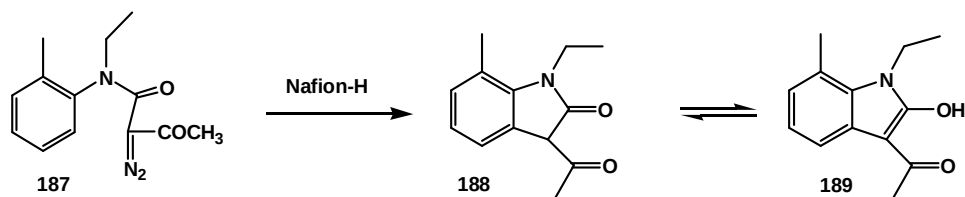


Brown *et al.* have synthesized oxindoles **185** by the Rh(II) catalysed decomposition of the corresponding diazoamides **183**, which were readily prepared from the corresponding diazo acid chlorides **182** and substituted amines **183**.¹⁰⁵ In case of rhodium(II) acetate usage as catalyst, besides the aromatic C-H insertion, intramolecular C-H insertion is also observed to give the corresponding lactam **186** as the major product.

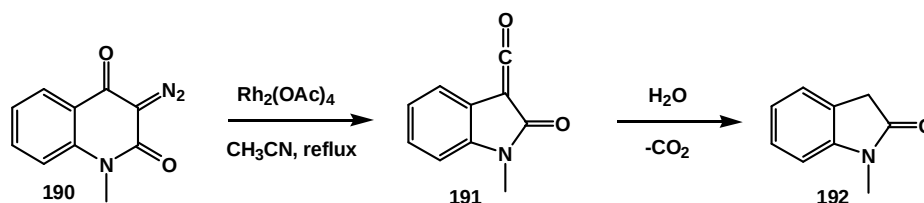
When the catalyst is changed to rhodium(II) trifluoroacetamide the reaction is promoted in the favor of the aromatic C-H insertion, yielding the only product oxindole **185**.



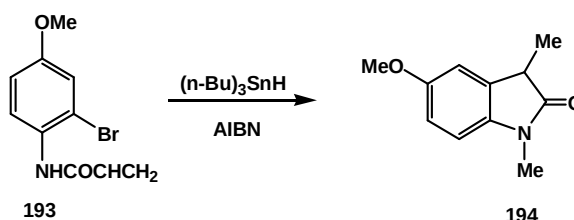
Nafion-H, the perfluorinated ion-exchange polymer is proved to be an exceptionally suitable alternative to $\text{Rh}_2(\text{OAc})_4$ for intramolecular aromatic substitution of diazoacetamides **187**. Doyle *et al.* have synthesized oxindoles **189** as the only product from the corresponding diazoacetamides **187** using Rh(II) acetate in trace amounts.¹⁰⁶ No products arising from the aliphatic C-H insertion is observed as in the case of previous literature from Brown *et al.* Then they have performed the reaction by using Nafion-H instead of rhodium (II) acetate, obtaining the same oxindole products with higher yields under faster reaction conditions. IR and NMR spectra demonstrate that 3-acyl-2-indalinones **188** exist in their tautomeric form **189**. Evidence for **189** consists of its hydroxyl stretching frequency, the absence of the methine proton at position 3 by ^1H NMR analysis and ^{13}C NMR spectra define the differences between the two tautomeric forms. Whereas **188** exhibits high field resonances at δ 172 and 171 for C-2 and acetyl carbonyl, the same signals are observed at 199 and 170, respectively, for **189**.



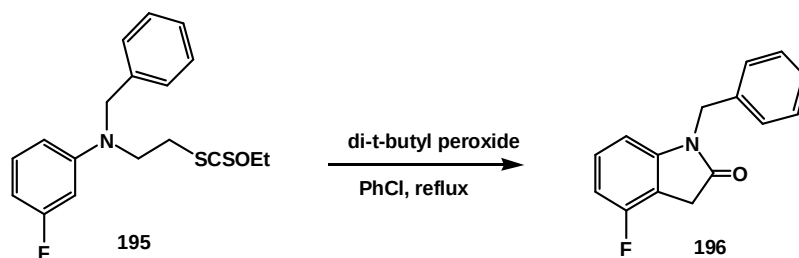
In a recent literature, a novel route to the synthesis of oxindoles (**192**) has been described by Lee *et al.* by using thermal and rhodium(II) catalysed Wolff rearrangements of diazoquinolinediones (**190**).¹⁰⁷



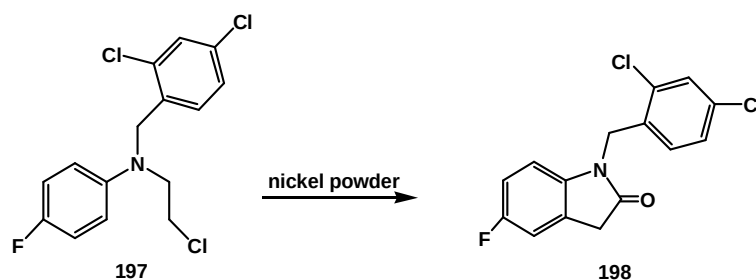
The synthesis of oxindoles is also possible by radical cyclization reactions. One of examples from the literature is given by Wrigth *et al.* based on the radicalic cyclization of N-acryloyl derivatives of 2-bromoaniline (**193**) with tri-*n*-butyltinhydride and AIBN to the 3-substituted oxindoles (**194**).¹⁰⁸



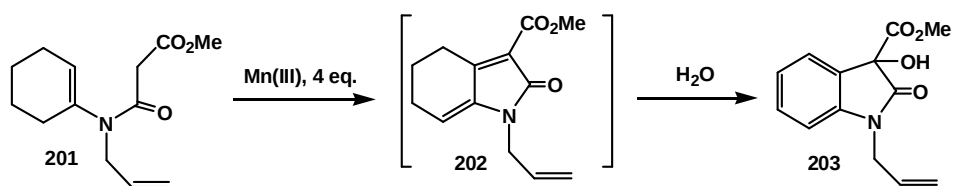
Another example from the literature by Axon *et al.* based on the radical chain reaction involving transfer of the xanthate group with anilides (**195**) to yield the corresponding oxindoles (**196**).¹⁰⁹



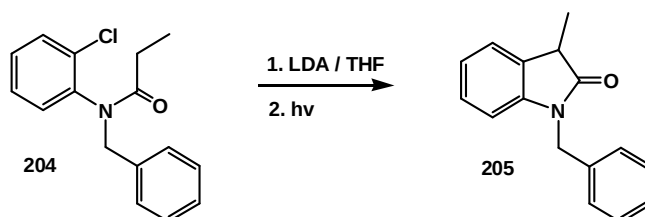
Although this method is efficient; so that xanthates have enough long time to undergo cyclization, it has some weaknesses, namely long heating periods, the need to keep initiating the relatively short chain radical and variable yields. So, this same research group a more practical alternative based on the particular reducing properties of nickel powder in combination with a weak organic acid such as acetic acid.¹¹⁰ The intermediate carbon radical derived from a haloanilide **197** is sufficiently long lived to undergo cyclization onto the aromatic ring to give finally an oxindole **198**.



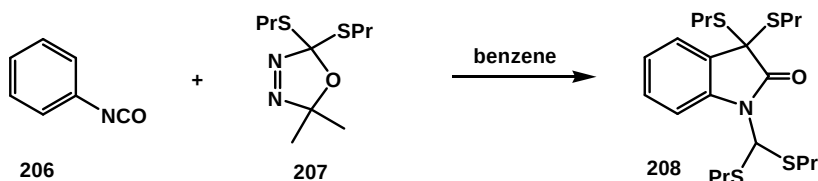
Manganese (III) based oxidative free radical based cyclizations have attracted considerable interest in recent years, most notably due to the work of Snider and co-workers.¹¹¹ This method has a number of advantages over alternative methods such as cost of the reagent, easy removal of by products and introduction of a functional group after carbon carbon bond formation. The most commonly used precursors for Mn (III) based cyclizations are β -keto esters **199** and malonic esters **200**, which undergo enolizations in the presence of Bu_3SnH and AIBN. Davies *et al.* used N-allyl amines **201** as starting material to yield the diene intermediate **202** by cyclization, which then oxidizes to oxindole **203** by Mn (III) acetate.¹¹²



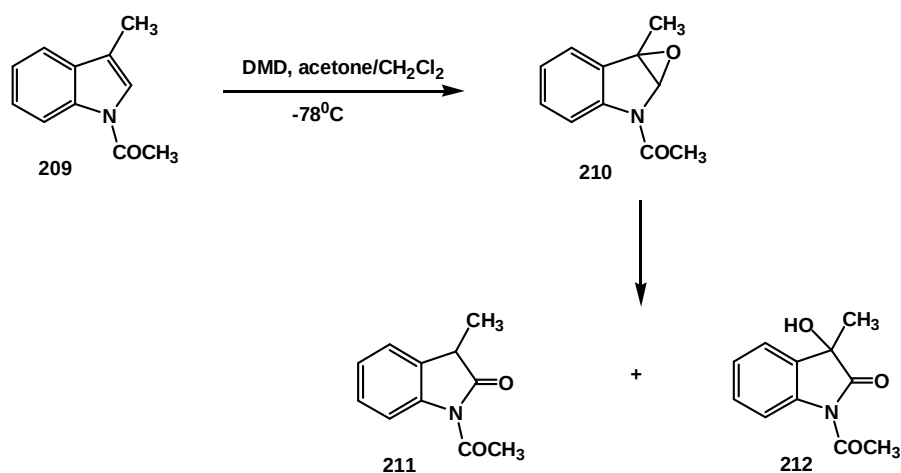
Oxindoles can also be synthesized by photocyclization going over monoanions, which can be exemplified from a literature by Goehring *et al.* in 1985.¹¹³ They have synthesised 1,3-dialkyloxindoles (**205**) with the monoanions of N-acyl N-alkyl-o-chloroanilines (**204**) by means of LDA in THF followed by irradiation with near-UV lights.



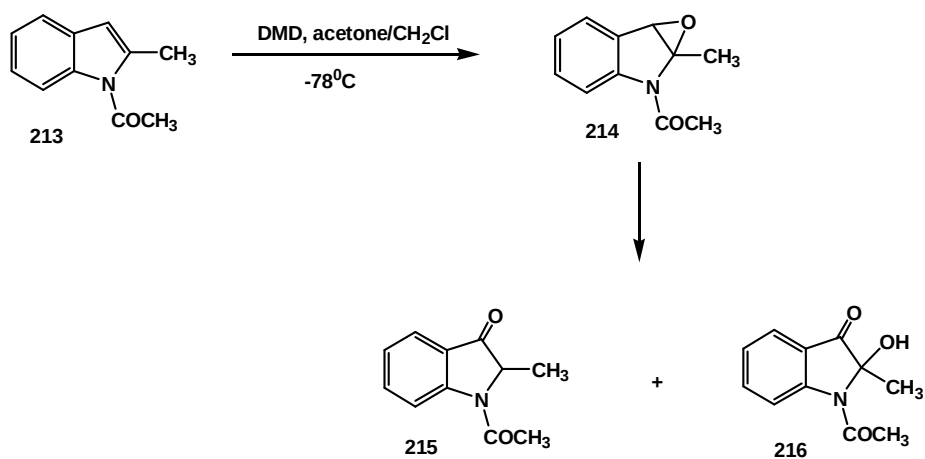
By using carben chemistry, isatin derivatives (**208**) have been synthesised with the thermally induced cyclization reaction of aryl isocyanates (**206**) and bis(alkylthio)carbenes (**207**).¹¹⁴



Zhang and Foote have described an efficient method for the synthesis of oxindoles by the oxidation of indoles (**209**) with dimethyldioxirane, in which the epoxide (**210**) opens via carbocation intermediate.¹¹⁵ In case of the indole (**209**) the carbocation develops exclusively at the benzylic position C-3 because of the conjugation with aromatic ring and by the alkyl group, leading to the pinacol-rearranged oxindole (**211**) as major product.



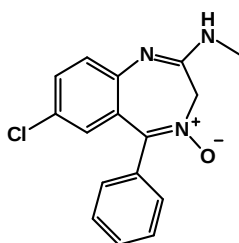
On the contrary, DMD oxidation of the indole (**213**) results in the formation of the epoxide **214**, which then opens to form the oxindole **215** as the major product due to the development of carbocation at C-2 by alkyl stabilization. Hydroxy indoles **212** and **216** are produced from further oxidations of major products.



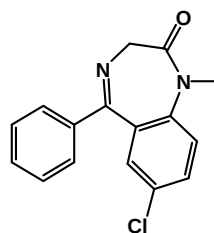
1.5. Benzodiazepinones

Benzodiazepinones are seven membered heterocycles consisting of a phenyl and diazpine group. In the literature, they are known to be a class of drugs with sedative, hypnotic, anxiolytic, anticonvulsant, amnestic and muscle relaxant properties. Benzodiazepinones are often used for short-term relief of severe, disabling anxiety or insomnia. Long-term use can be problematic due to the development of tolerance and psychological dependency.

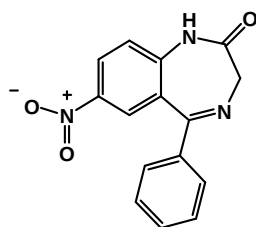
They are believed to act on the GABA receptor, the chief inhibitory neurotransmitter in the mammalian brain, GABA_A, the activation of which dampens higher neuronal activity.



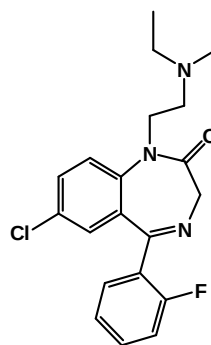
chlordiazepoxide (217)



diazepam (218)



nitrazepam (219)



flurazepam (220)

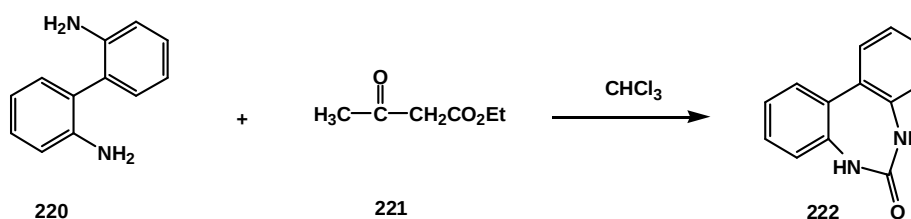
The first benzodiazepine, chlordiazepoxide (Librium®) **217** was discovered accidentally in 1954 by the Austrian scientist Dr Leo Sternbach . In 1963 approval for use was given to diazepam (Valium®) **218**, a simplified version of Librium

primarily to counteract anxiety symptoms. Sleep-related problems were treated with nitrazepam (Mogadon®) **219**, which was introduced in 1965 and flurazepam (Dalmane®) **220**, which was introduced in 1973.¹¹⁶

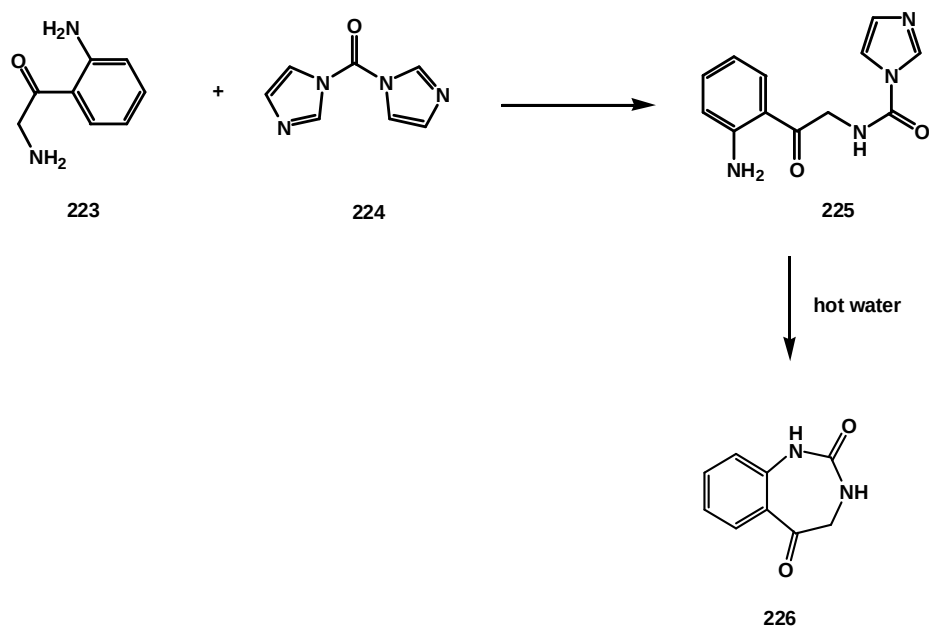
Benzodiazepinones can be generally classified as 1,3-, 1,4-, 1,5- and 2,4-benzodiazapinones which nearly show similar biological activities.

1.5.1. The Synthesis of 1,3-Benzodiazepinones

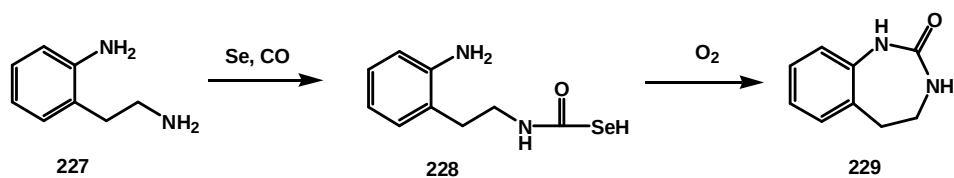
In the earliest years, 1,3-benzodiazapinones **222** have been synthesized by condensation reactions of biphenyl-2,2'-diamines **220** with either 3-oxo-butyric esters **221**.¹¹⁷



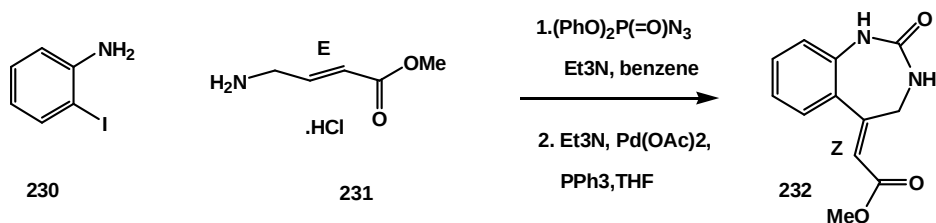
Taylor *et al.* have reacted 2,2'-diaminoacetophenone (**223**) with 1,1'-carbonyldiimidazole (**224**) to give N-(o-aminophenacylaminocarbonyl)imidazole (**225**) which then cyclized readily in hot water to give the benzodiazapinone **226**.¹¹⁸



N-carbonylation of o-positioned diamines **227** with carbon monoxide going through the amine derivative **228** is an alternative approach to the synthesis of 1,3-benzodiazapinones **229**.¹¹⁹

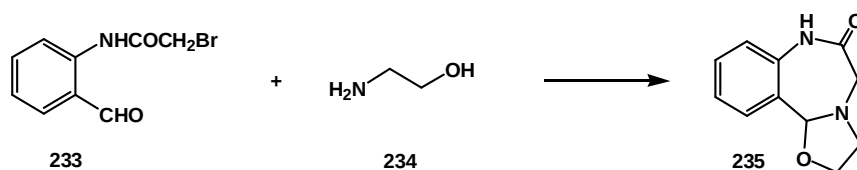


Another research group have succeeded the synthesis of analgesic and antihypertensive optically pure 1,3-benzodiazepine-2-ones **232** via intramolecular Heck reaction by using o-iodobenzoic acid **230** and methyl ester compound **231** as starting materials.¹²⁰

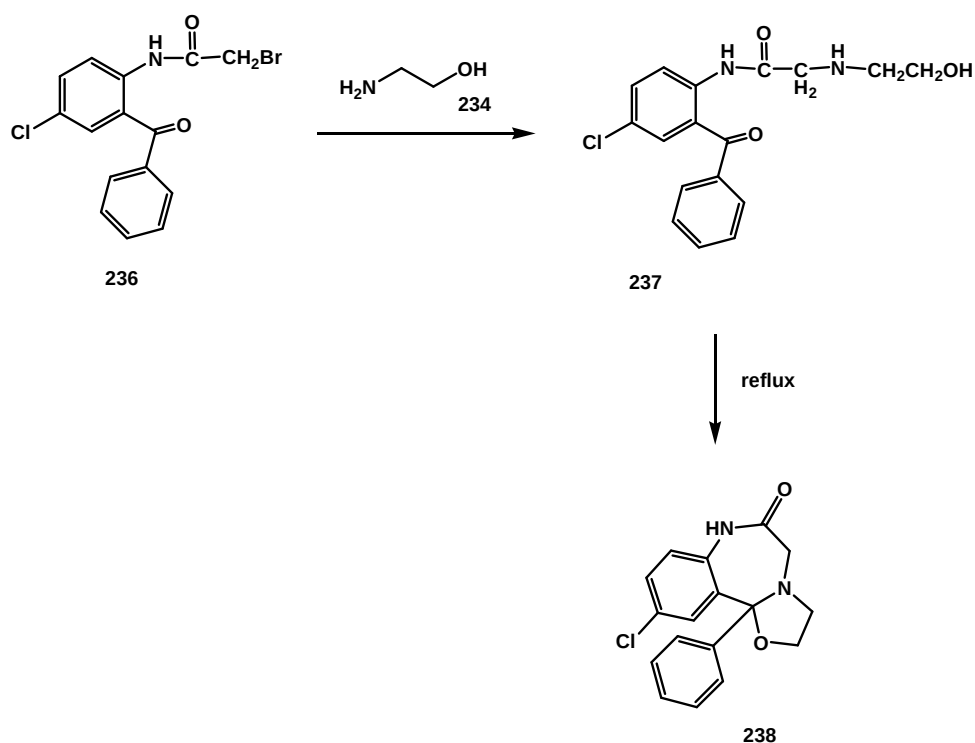


1.5.2. The synthesis of 1,4-benzodiazapinones

Considerable attention has also been directed towards the synthesis of 1,4-benzodiazapinones due to their important biological activity. In an earliest literature¹²¹, Miyadera *et al.* have synthesized anxiolytic sedatives 1,4-benzodiazapinones **238**. They have first performed the reaction of 2-bromoacetamidobenzaldehyde (**233**) with ethanolamine (**234**) expecting the tricyclic compound benzodiazapinone **235**.

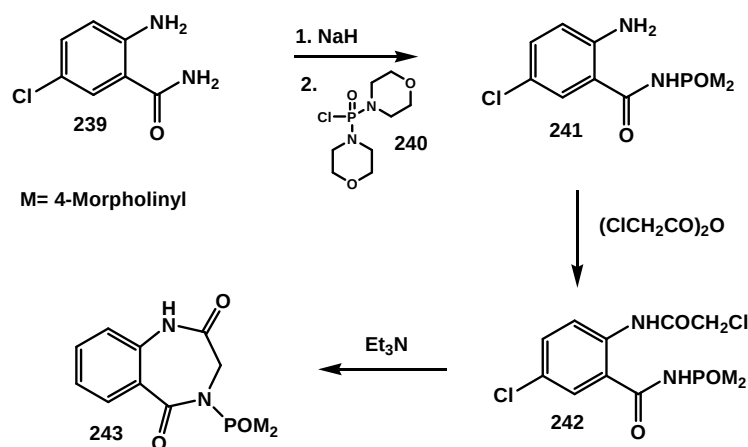


After the reaction was found to yield the expected product, they have designed a new reaction in which the reactants were a benzophenone derivative **236** and ethanolamine (**234**).

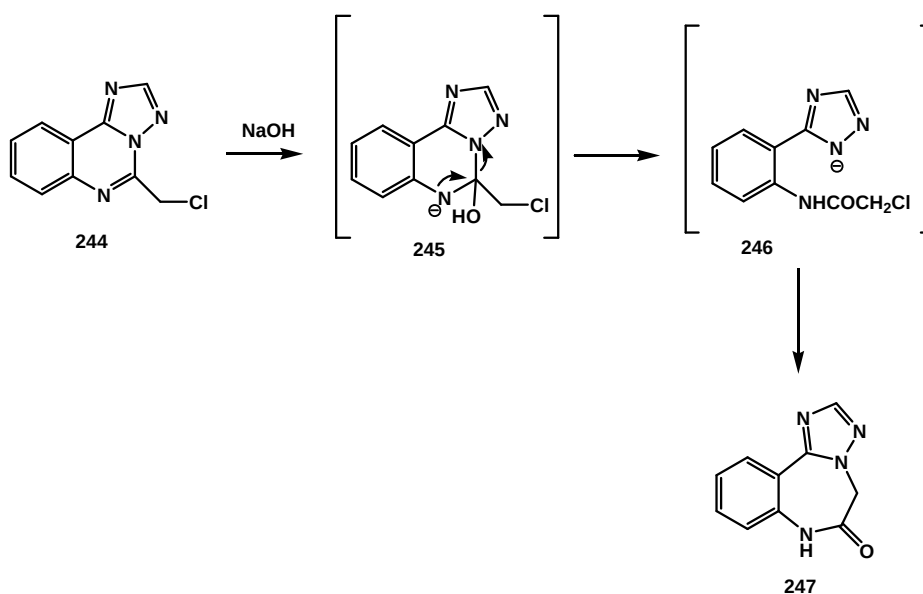


The isolated intermediate **237** underwent ring closure reaction by refluxing to yield the desired benzodiazepine derivative **238**, which was found to have excellent anxiolytic sedative activity.

Another literature for the synthesis of 1,4-benzodiazepinones is based on the reaction of ambident anions of anthranilamides **239** with di-4-morpholinylphosphinic chloride (**240**).¹²² N-phosphorylated product **241** was formed at the first step, which then was chloroacetylated to yield the product **242**. The last step was the cyclization of the compound **242** to the desired 1,4-benzodiazapinone **243**.

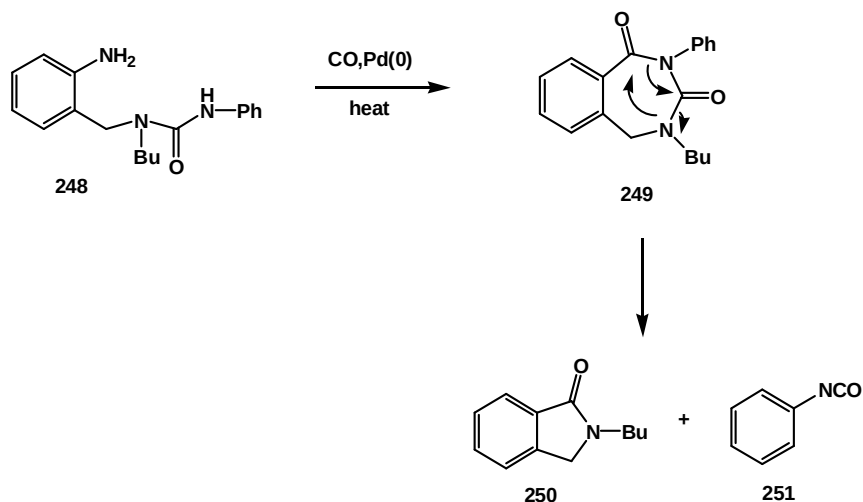


Six membered rings, quinazolines were found to undergo ring expansion reaction to give the corresponding benzodiazepines. Breuer has reacted chloromethylquinazoline (244) derivative with aqueous sodium hydroxide at room temperature to obtain the seven membered benzodiazepinone derivative 247 by the following mechanism.¹²³

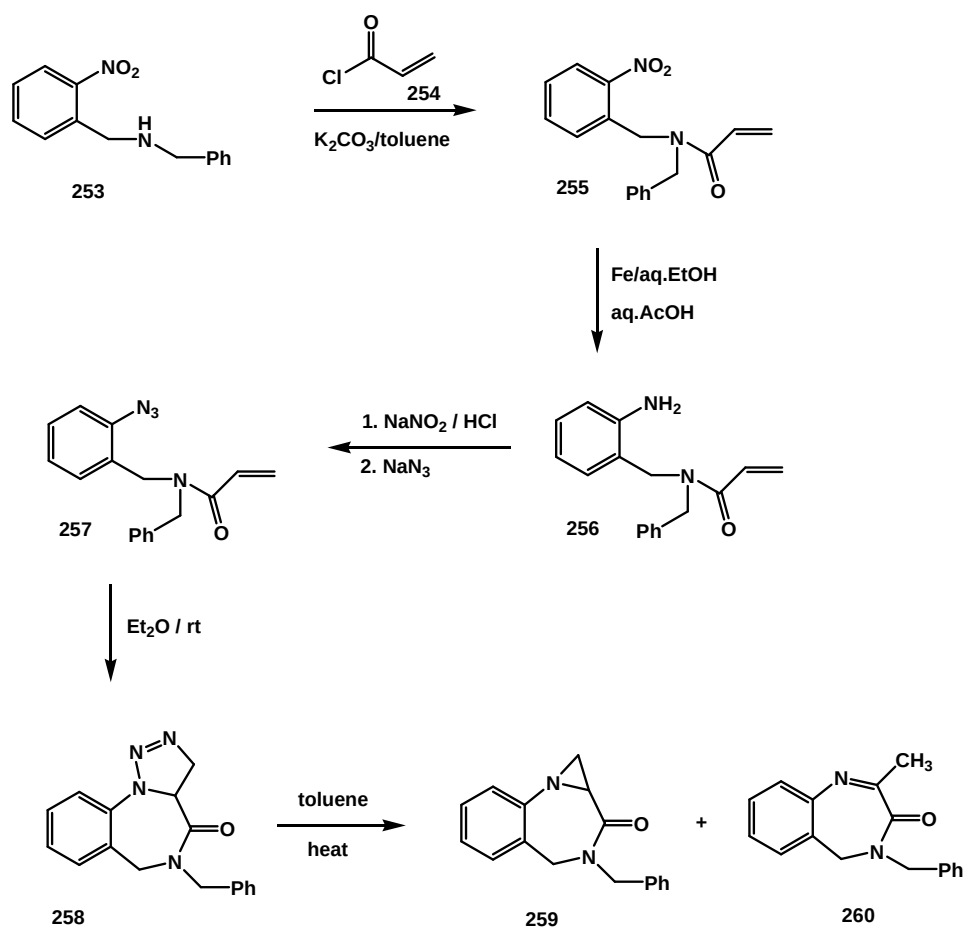


Palladium catalyzed ring formation leading to seven membered nitrogen containing heterocycles has recently proved to be a valuable technique, by which 1,4-benzodiazapinone derivatives 250 has been synthesized by Bocelli *et al.*¹²⁴ The urea 248, which was formed in two steps from iodobenzyl chloride, n-butyl amine (252)

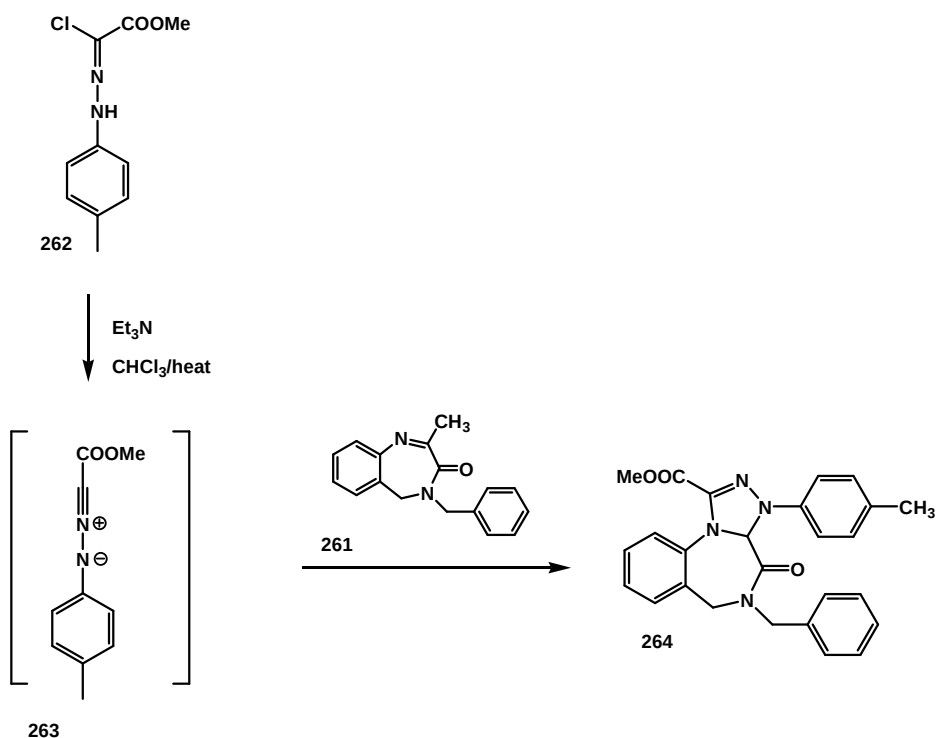
and phenylisocyanate (**251**) by heating with carbon monoxide in the presence of palladium as catalyst and potassium acetate as base. In this reaction the solvent choice is important for the distribution of products. Because the formed seven membered **249** ring undergoes ring contradiction unless polar solvent is used. Polar solvent, DMF stabilizes seven membered ring while prevents possible rearrangements and ring contradiction to five membered ring **250**.



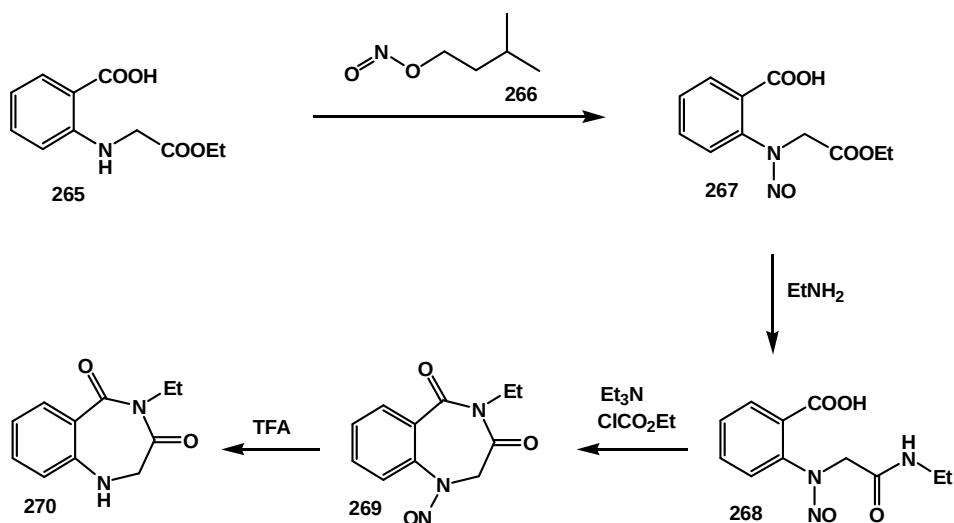
A recent literature describes the synthesis of 1,4-benzodiazapinones by the way based on the intramolecular cycloadditions of azide containing compounds.¹²⁵ The synthetic sequence starts with the akenoylation of N-benzyl-2-nitrobenzylamine **253**. Reduction of the aromatic nitro group of **255** gave N-alkenyl-2-amino-N-benzylamine **256** and diazotization of **256** was followed by treatment with sodium azide yielding azido compound **257**. An intermediate, which could not be isolated, underwent spontaneous intramolecular cycloaddition to the compound **258** during the work up. Thermal decomposition of the compound **258** gave a mixture of aziridine **259** and imine **260** as 1,4-benzodiazepinone derivatives.



The C=N double bond containing compound **261**, acted as a dipolarophile when reacted with the dipole **263**, which was generated from hydrazonyl chloride **262**. The resulting potential pharmacological active benzodiazapinone **264** was a result of the nitrilimine cycloaddition.

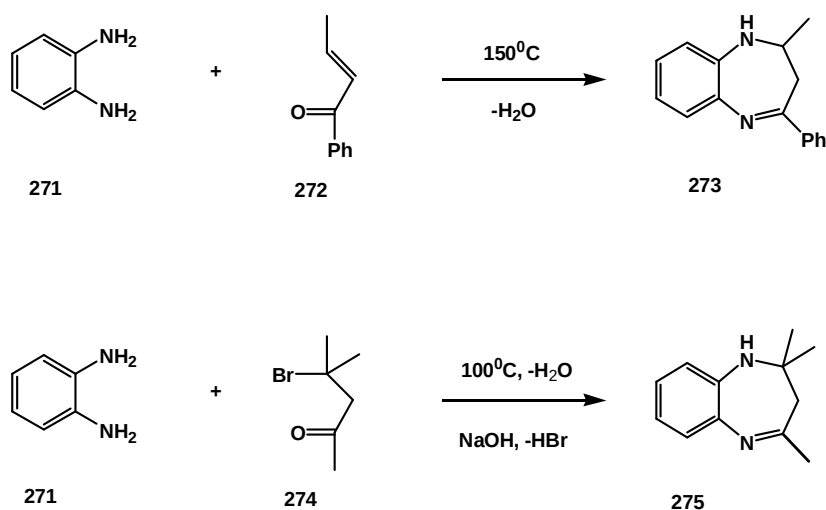


Wiklund *et al.* have followed a different strategy using 2-(carbamoylmethylamino)benzoic acid (**265**) as starting material.¹²⁶ The nucleophilicity of the carboxylate ion was increased by the electron donating amine functionality in the ortho position. The system was activated for ring closure by the introduction of a nitroso group onto the N-1. The compound **267** was converted to the ethyl amide **268** by aminolysis. Ring closure leading to the 1,4-benzodiazepinone **269** was then performed with ethyl chloroformate and triethylamine in acetonitrile. Due to its strongly electrong withdrawing character, the N-nitroso group functioned as a protective group. Deprotection of the nitrosamine to the free amine could be performed under acidic conditions yielding the product **270**.

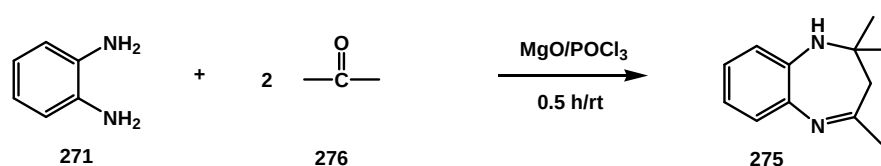


1.5.3. The synthesis of 1,5-Benzodiazapinones

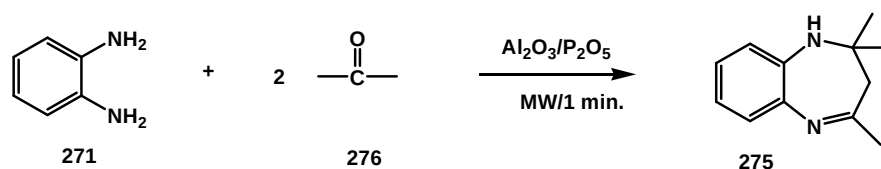
Including the earliest literatures, o-phenylenediamine **271** is used as the starting material for the synthesis of 1,5-benzodiazapinones **273**. Condensation reactions of o-phenylenediamine **271** either with α -, β -unsaturated carbonyl compounds¹²⁷ **272** or β -haloketones¹²⁸ **274** yielded 1,5-benzodiazapinones **273** and **275** at high temperatures.



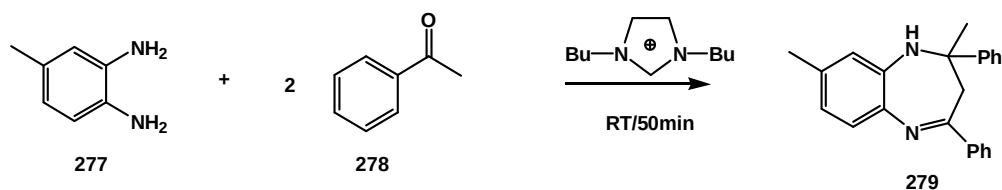
These condensation reactions suffer limitations, such as harsh reaction conditions, low-yields, tedious work up procedures and cooccurrence of several side reactions. Balakrishna *et al.* have performed the condensation reactions of o-phenylenediamine (**271**) with ketones **276** by surface-mediated reactions using a mixture of magnesium oxide and phosphorus oxychloride.¹²⁹ The advantage of surface-mediated reactions is their ease of execution and work up, mild reaction conditions, faster reaction rates, higher selectivity, solvent free conditions and cheaper conditions in comparison with their homogenous counterparts.



Nextly the same research group have found alumina-supported phosphorus pentoxide to give higher yields of 1,5-benzodiazepinones **275** under microwave irradiation when compared with the previous reaction conditions.¹³⁰



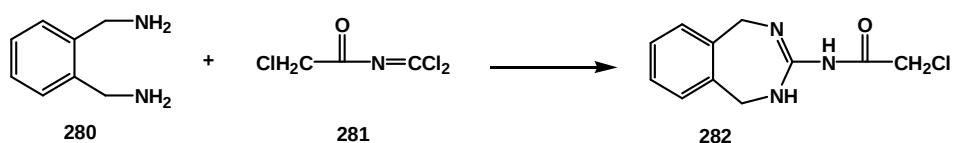
In recent years, the use of room temperature ionic liquids as ‘green’ solvents in organic synthetic processes has gained considerable importance due to their solvating ability, negligible vapor pressure, easy recyclability and reusability. Jarikote *et al.* have applied this green chemistry for the synthesis of 1,5-benzodiazapinones **279** using 1,3-n-dibutylimidazolium bromide as ionic liquid.¹³¹ The catalyst free reaction conditions gave rise to excellent isolated yields of the benzodiazepines **279** in a relatively short reaction time.



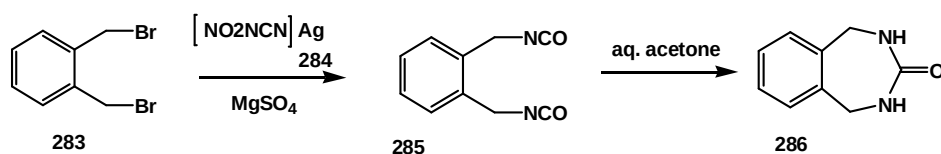
1.5.4. The synthesis of 2,4-benzodiazepinones

Among the benzodiazapinone derivatives the least studied type is the 2,4-benzodiazepinones. O-phenylenediamines (**280**) were found to be suitable starting materials for the synthesis of 2,4-benzodiazepines **282**. This condensation reaction was performed by Denis *et al.* using 2-chloro-N-dichloromethylene-acetamide (**281**).

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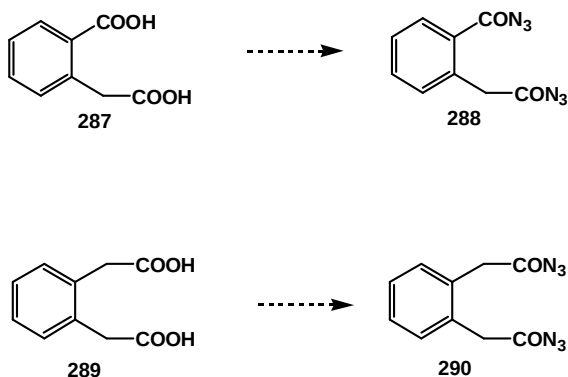


Starting from o-phenylenebromide **283** Boyer *et al.* have synthesised the corresponding diisocyanate **285** with silvernitrocyanoamide salt **284**, which then underwent ring cyclization with aqueous acetone to the corresponding 2,4-benzodiazepinone derivative **286**.¹³³

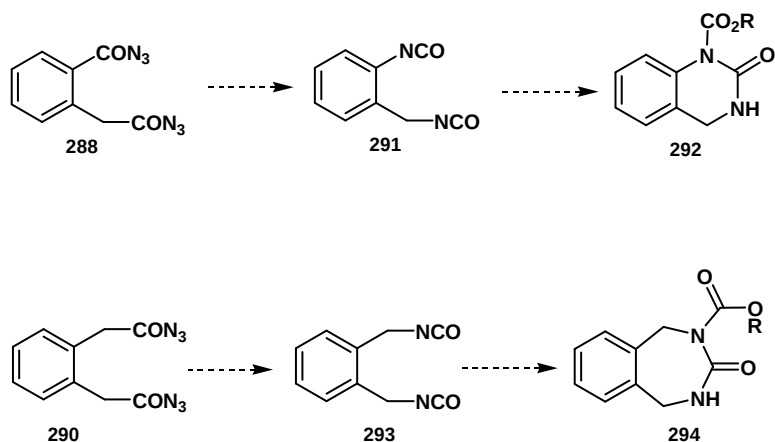


1.6. The Aim of the Thesis

The main aim of this thesis is the generation of diazides **288** and **290** derived from homophthalic acid **287** and bis homophthalic acid **289**, respectively.



In the second part of this work, the conversion of the formed azides **288** and **290** into quinazolines **292**, benzodiazepinones **294** and others will be studied. As intermediates, the corresponding isocyanates **291** and **293** will be generated in situ or isolated depending on their stabilities. The generated diisocyanates will be trapped with various nucleophiles to generate intramolecular cyclization reaction leading to various heterocyclic compounds.

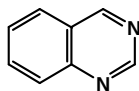


CHAPTER 2

2. RESULTS AND DISCUSSION

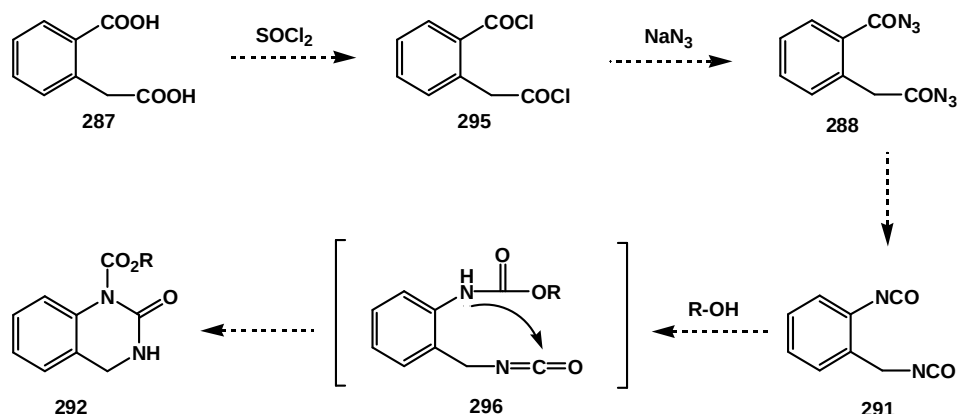
2.1. The Reaction of homophthalic acid (287) with thionyl chloride: The synthesis of lactone 298.

One of the aims of this thesis was to synthesize quinalizone **1** derivatives, which were found to show important biological activities.

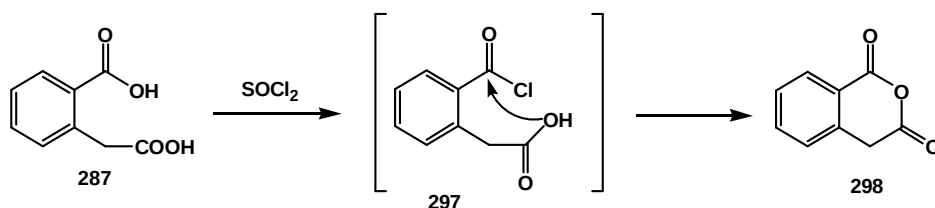


quinalizone (**1**)

Homophthalic acid (**287**) was chosen as the starting material. In the synthesis path, firstly the homophthalic acid (**287**) would be chlorinated to give the dichloride **295** and then the conversion of the chloride groups into diacyl azide **288** would be performed. If the diazide **288** could be obtained, it would transform into the diisocyanate derivative **291** by Curtius rearrangement. The diisocyanate **291** would be reacted with alcohols to give the corresponding quinalizone derivative **292**.

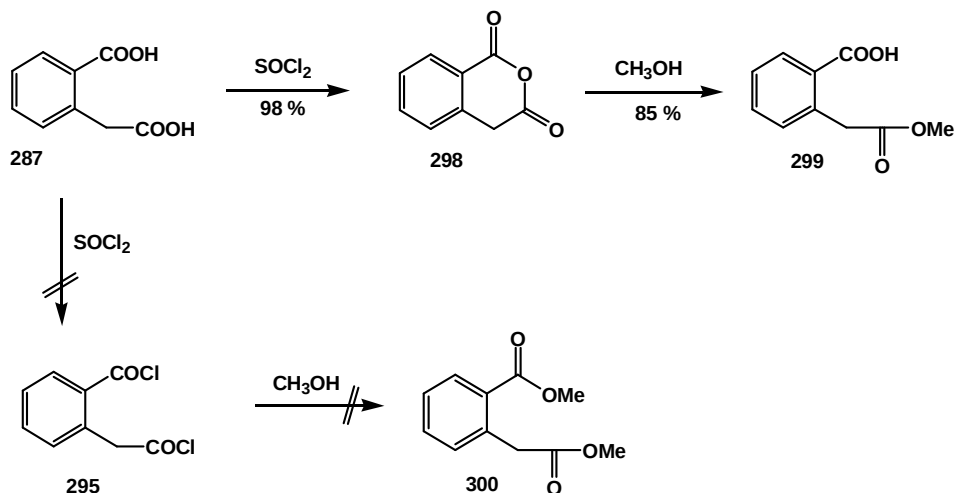


In the first step, the homophthalic acid (**287**) was reacted with thionyl chloride in refluxing dichloromethane. The formed product was characterized as the lactone **298** which was formed by ring closure. This result was reasonable due the ortho-positions of the acid groups. Because as soon as one the hydroxy groups was chlorinated, the attack of other hydroxy group was performed causing a ring closure.

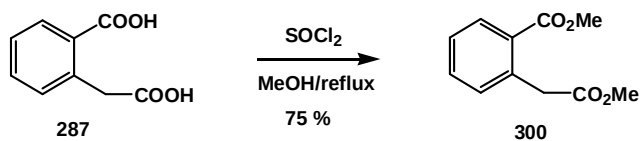


Scheme 1. Suggested mechanism for the formation of the compound **298**.

The product was refluxed with methanol and the formation of half ester **299** proved that the compound **298** was the lactone derivative. The ring opening reaction of **298** was a regioselective reaction yielding the half ester **299**, which was in agreement with the physical and spectral data that were already reported.¹³⁴ Additional signals of methoxy protons at 3.77 ppm and hydroxy proton at 11.0 ppm were the important points in the assignment of the half ester **299**. If the product was the dichloride, it would yield the diester **300**.



When the homophthalic acid (**287**) was refluxed with thionyl chloride in methanol, no ring closing was observed, the obtained product was the diester **300**. Because when the hydroxy group was chlorinated, it was replaced with methoxide group, which prevented the ring closure.¹³⁵

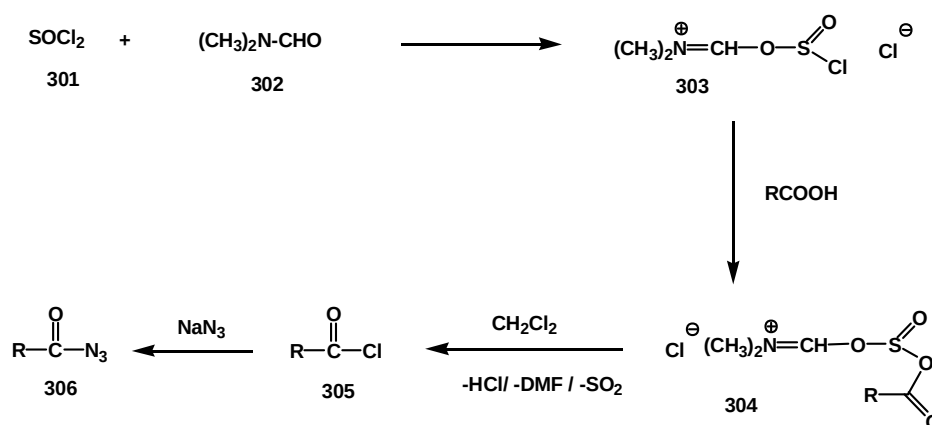


2.1.1. The Reaction of homophthalic acid with N,N-dimethylchloro sulfite methaniminium chloride (**303**) in the presence of sodium azide: The synthesis of 6H-dibenzo[c,h]chromen-6-one (**307**).

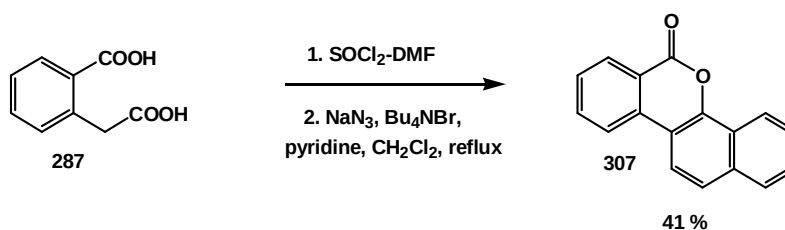
Since the dichloride **288** could not be obtained, the synthesis of the diazide **288** could not also be succeeded. In the literature, there are several methods for the direct conversion of the acid groups into azide groups.

So, we decided to apply these methods to our system in order to obtain the diazide **289** directly from the acid **287**.

Arrieta *et al.* have found an efficient reagent for the synthesis of acyl azides from carboxylic acids.¹³⁶ They have synthesized N,N-dimethylchlorosulfite methaniminium chloride (**303**) from thionyl chloride (**301**) and dimethylformamide (**302**), which have been used for the activation of carboxylic acids and for the formation of acyl chlorides **305**. Addition of sodium azide afforded the acyl azides **306**.



Therefore, this method was applied on the homophthalic acid (**287**) in order to obtain diacyl azide **288**. Unfortunately, at the end of the reaction the diazide **288** could not be detected. Instead, the isocoumarin derivative 6H-dibenzo[c,h]chromen-6-one (**307**) was formed in 41% yield which was characterized by comparison of its spectral data with those published in the literature.¹³⁷ The ^1H -NMR spectrum showed the presence of ten aromatic protons and carbonyl carbon at 161.2 ppm in the ^{13}C -NMR spectrum confirmed the presence of lactone ring.



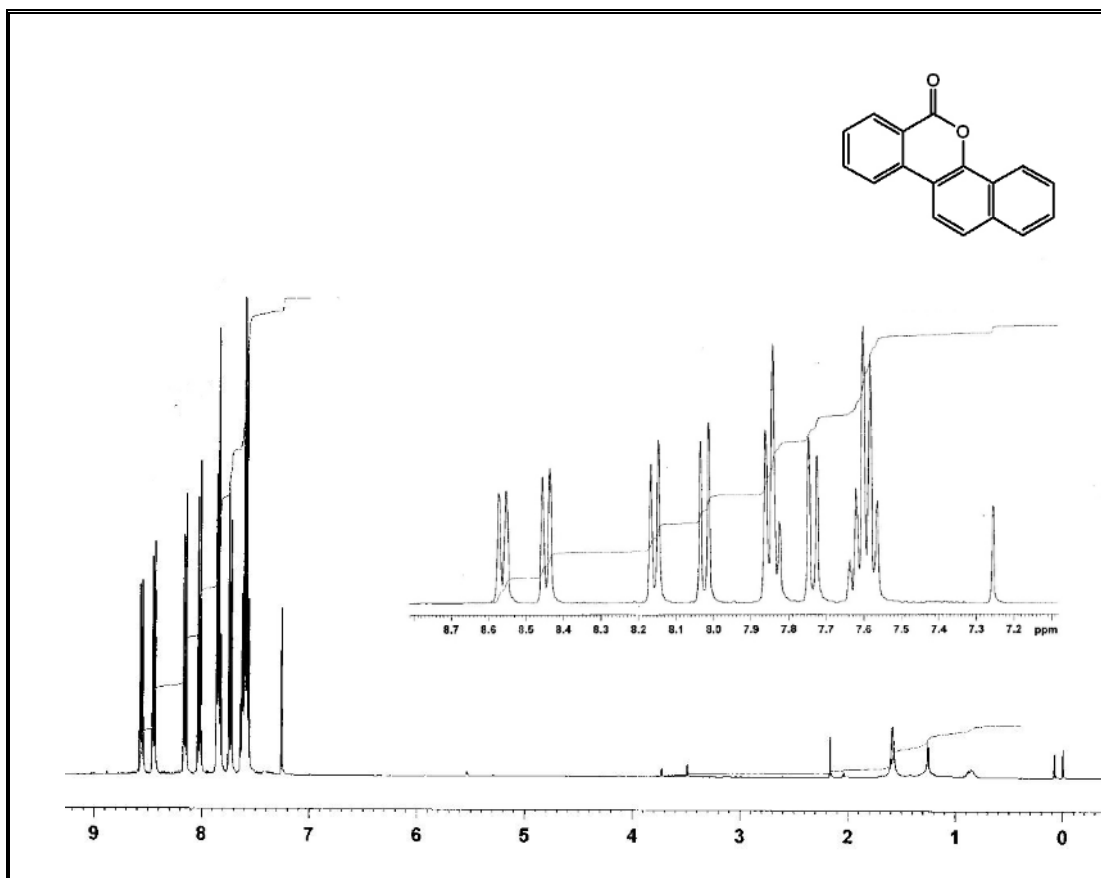
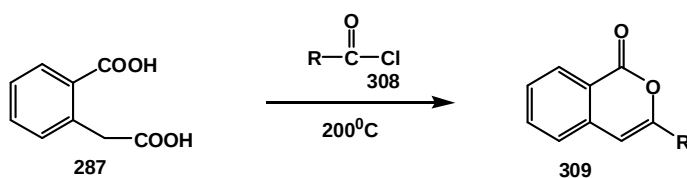


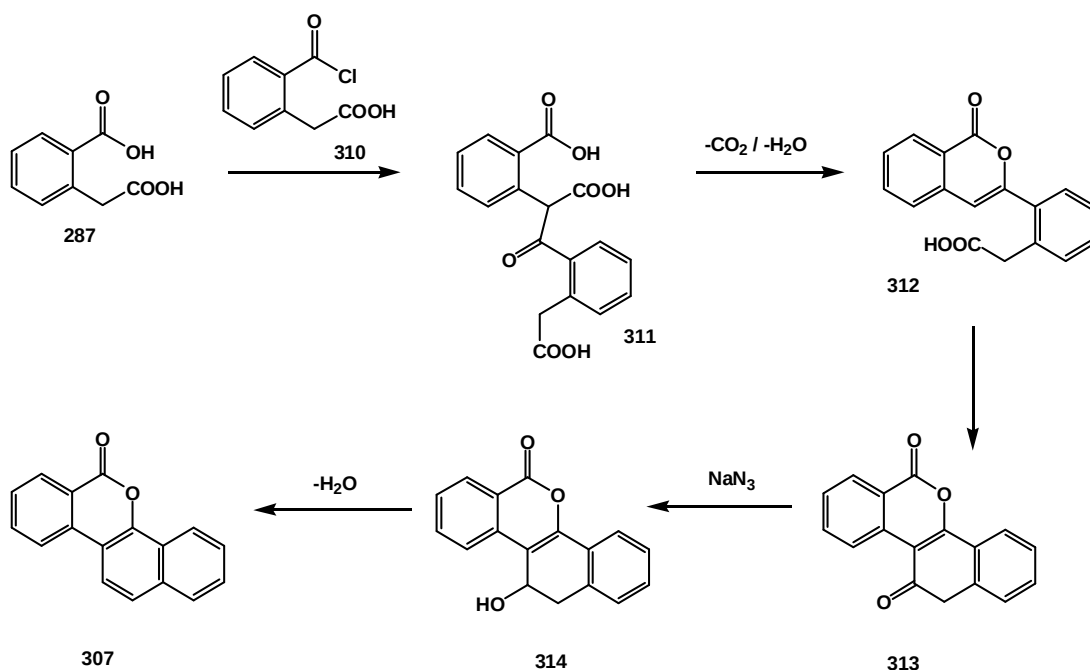
Figure 1. The ^1H -NMR spectrum of the compound **307**.

There are examples in the literature related with the ring closure of homophthalic acid **287** with acyl chlorides **308** at high temperatures to give the 3-substituted isocoumarines **309**.¹³⁸



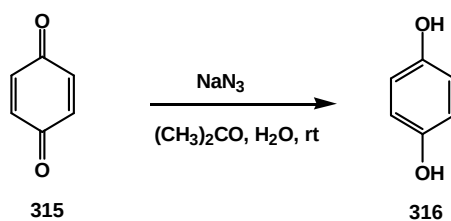
Considering this general reaction of homophthalic acid (**287**) with acylchlorides **308**, a tentative mechanism for the formation of **307** is outlined in Scheme 2. This reaction presumably occurs by initial attack of acid chloride **310**, formed under the

reaction condition, at methylene group of homophthalic acid (**298**) to form the condensation product. The intermediate **311** undergoes decarboxylation and cyclization to produce isocoumarine derivative **312**. Further cyclization and reduction of the carbonyl group with NaN_3 followed by H_2O elimination results in the formation of **307**.

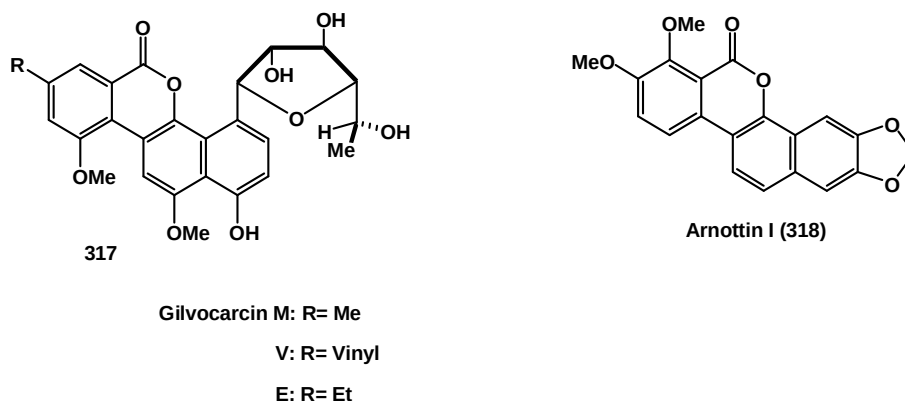


Scheme 2. Suggested mechanism for the formation of the compound **307**.

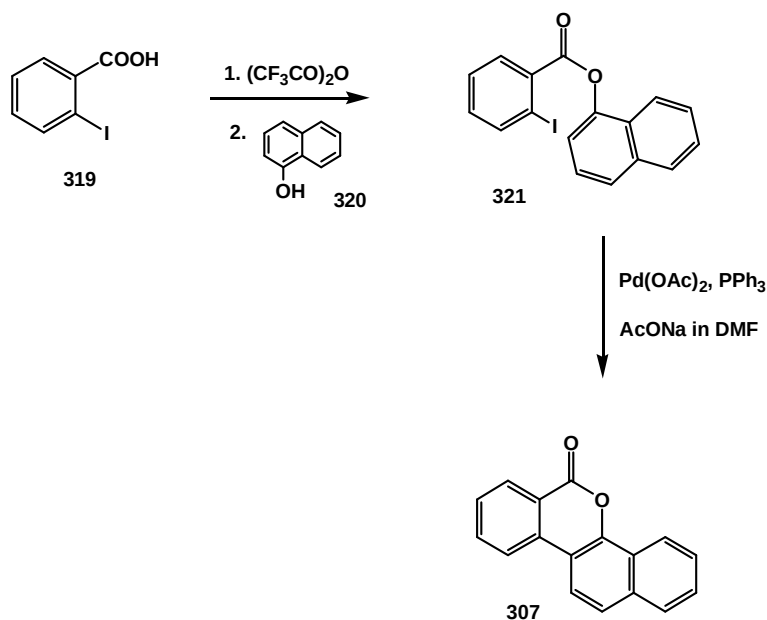
The reduction step was suggested to occur with sodium azide on the basis of a recent literature reported by Balci *et al.*¹³⁹ They discovered that NaN_3 could reduce the carbonyl groups in quinones **315** to the corresponding hydroxyl group **316** in high yield.



The synthesis of 6H-dibenzo[c,h]chromen-6-one (**307**) was found to be important in the literature, because its skeleton is found in gilvocarcin type **317**, which has attracted much attention because of its high antitumor activity.¹⁴⁰ This skeleton is also found in some naturally occurring isocoumarines, such as arnottin (**318**).

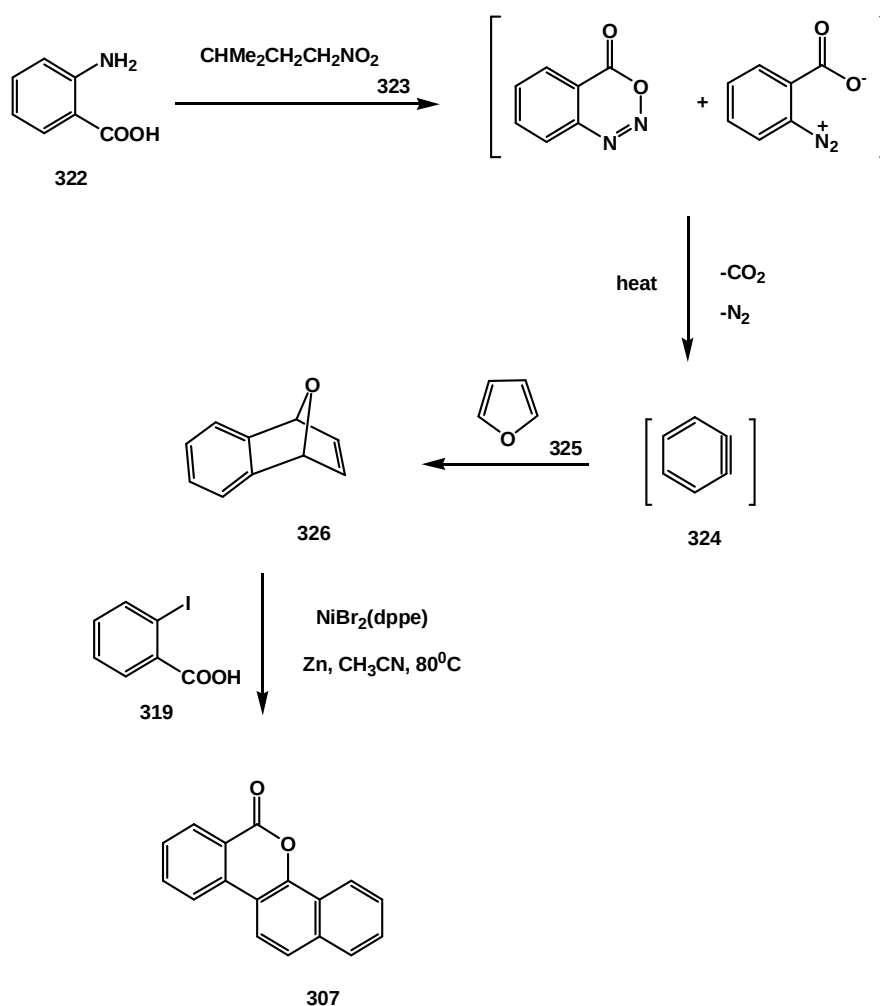


Harayami *et al.* have designed a synthetic plan for the synthesis of 6H-dibenzo[c,h]chromen-6-one (**307**) and its derivatives involving biaryl coupling reaction by palladium as a key reaction.¹⁴⁰



In the first step, the ester **321** was formed from 2-iodobenzoate (**319**) and 1-naphthol (**320**) and in the next step cyclization was performed.

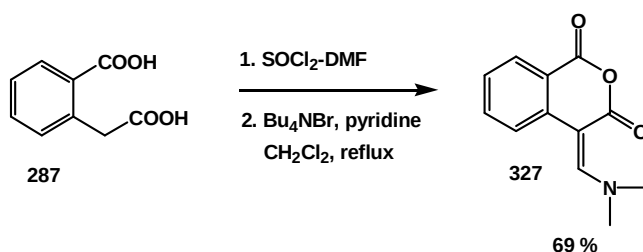
Rayabarapu *et al.* have also used 2-iodobenzoate (**319**) as starting material for the synthesis of 6H-dibenzo[c,h]chromen-6-one (**307**).¹⁴¹ In the presence of Ni catalyst and zinc metal powder, 2-iodobenzoate (**319**) underwent cyclization with 7-oxobenzonorbornadiene (**326**), which was synthesized from the cycloaddition reaction of furan (**325**) and benzyne (**324**), generated in situ from o-aminobenzoic acid (**322**) with isoamyl nitrite (**323**).



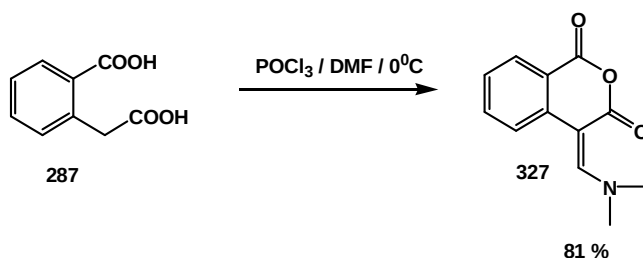
When we compare our synthesis path for 6H-dibenzo[c,h]chromen-6-one (**307**) with these literatures, it has the advantage of being single step starting with a simple compound, homophthalic acid (**287**) and low costing reagents. The literature methods needed more than one step.

2.1.2. Reaction of homophthalic acid with N,N-dimethylchlorosulfite methaniminium chloride (303) in the absence of sodium azide: The synthesis of (4Z)-4-[(dimethylamino)methylene]-1H-isochromene-1,3(4H)-dione (327).

In the synthesis of 6H-dibenzo[c,h]chromen-6-one (**307**), although sodium azide was used in the reaction medium, azide anion was not incorporated into the molecule and the role of sodium azide was under question. In order to investigate the behavior of sodium azide, the same reaction was run in the absence of sodium azide. Instead of the formation a dibenzochromen-6-one structure (**307**), aminomethylene compound **327** was formed as the sole product.

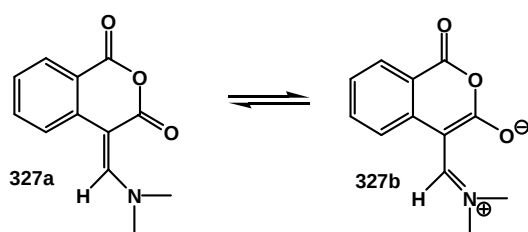


The intermediate **327** was identified by comparison of the spectral data with those reported in the literature which was obtained under the Vilsmeier condition (DMF/POCl_3) by Rodemann *et al.*¹⁴²



There was a special case in ^1H -NMR spectrum, which was not discussed by Rodemann *et al.*¹⁴² When the ^1H -NMR spectrum was run at room temperature, the methyl protons resonated as a broad singlet, which was under normal conditions expected to be a sharp singlet.

In the case of ^1H -NMR spectral measurements at 65°C , this broad singlet transformed into a sharp singlet. This case can be explained by the restricted rotation of the compound **327** at room temperature. Because of the conjugation of the lone pairs on nitrogen there is equilibrium in this molecule. Despite the equilibrium shown in Scheme 3, at room temperature the molecule exists exclusively in the form **327b**, where C-N bond shows partial double bond character and therefore rotation about the nitrogen atom slows down. Due to this slow rotation, the methyl groups cannot change their position and act as methyl groups bonded to double bond, which have slightly different chemical shifts. Because of that they resonate as a broad singlet. When the temperature is increased to 65°C , the equilibrium shifts to the form **327a**, a fast rotation about the C-N bond takes place so that NMR cannot distinguish between the methyl protons. As a result of that methyl protons resonate as a sharp singlet.



Scheme 3. The chemical equilibrium of compound **327**.

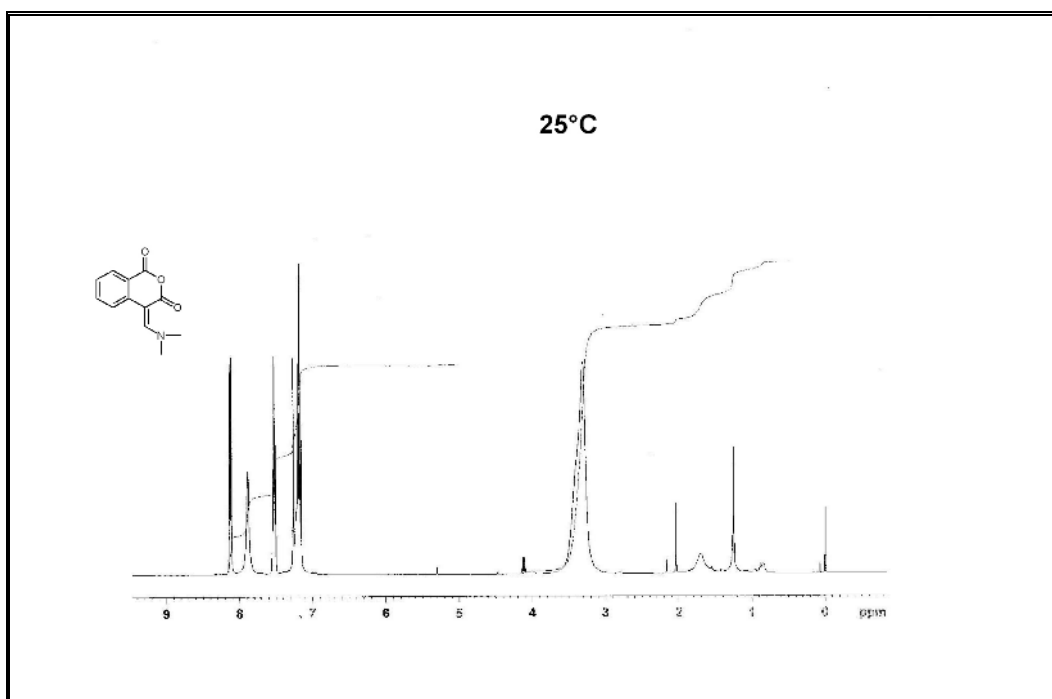


Figure 2. The ¹H-NMR spectrum of the compound **327** at 25°C.

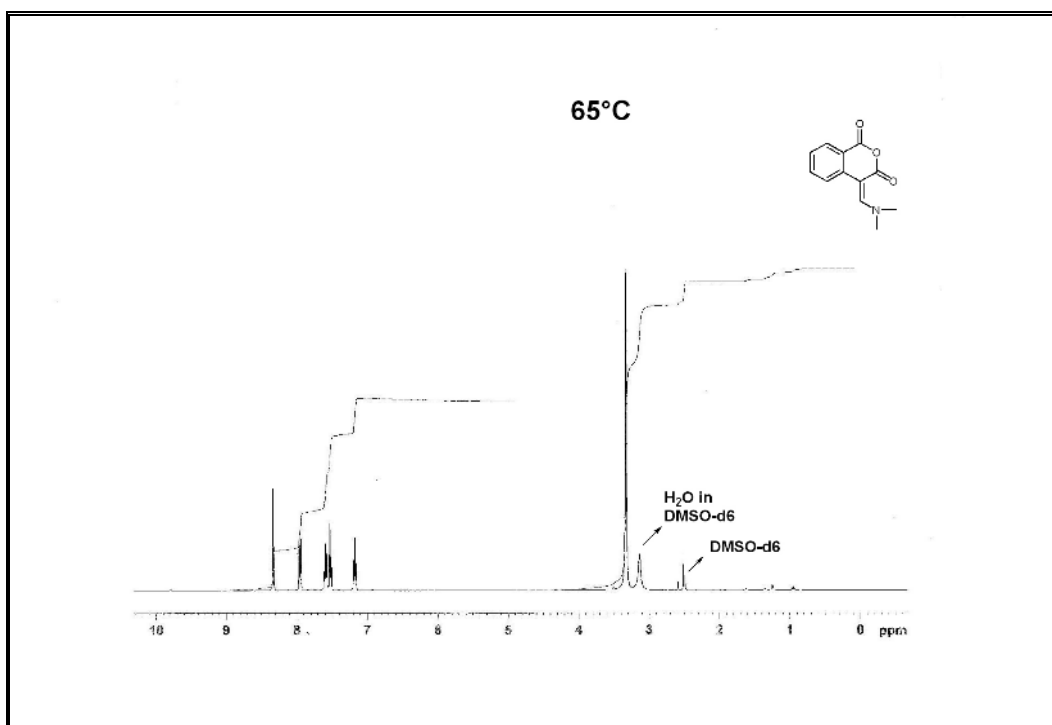
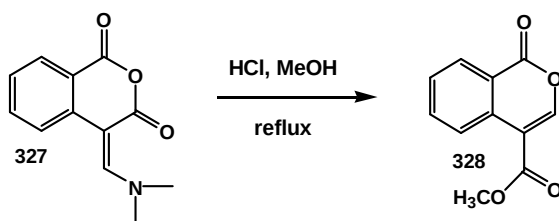


Figure 3. The ¹H-NMR spectrum of the compound **327** at 65°C.

The formation of **327** was proven by a chemical reaction, in which it was converted to the isocoumarine derivative **328** with methanol saturated with hydrogen chloride.

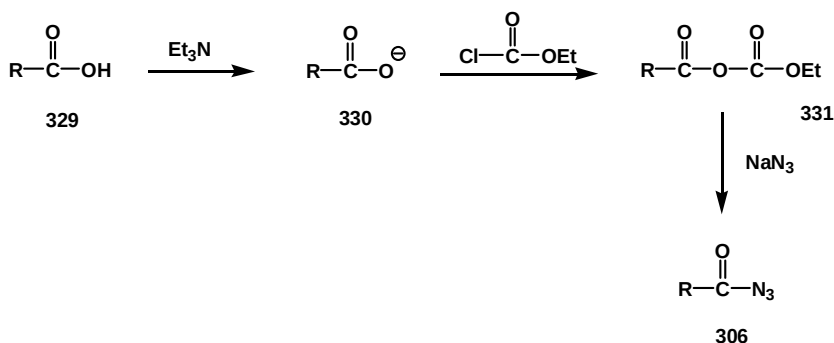


The ^1H -NMR and ^{13}C -NMR spectra of the compound are in agreement with those reported in the literature.¹⁴²

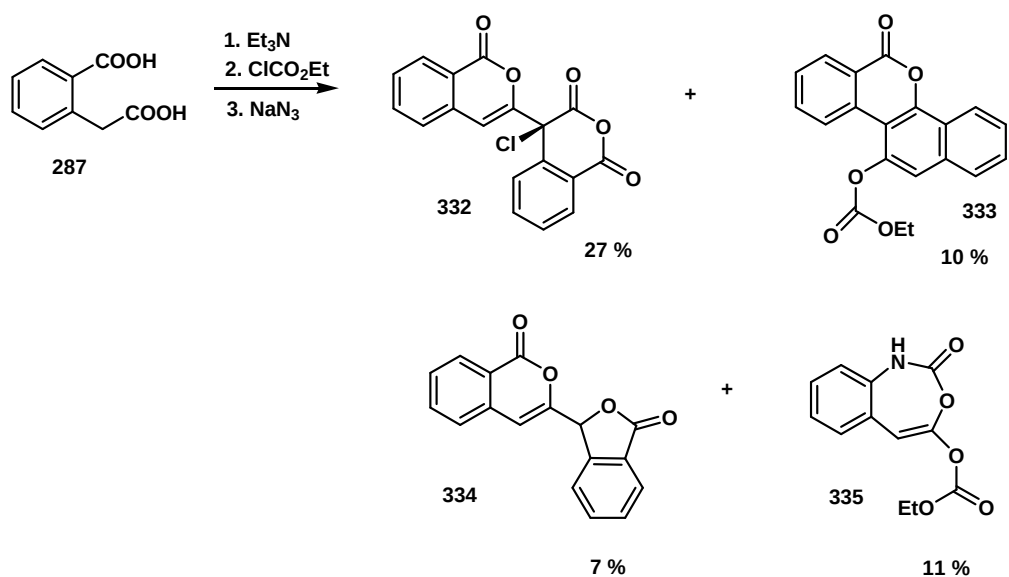
According to these results, it was understood that sodium azide in the reaction of homophthalic acid (**287**) with N,N-dimethylchloro sulfite methaniminium chloride (**303**) acted not as a source of azide, but as a reducing agent. Furthermore, it plays an important role in the formation of benzochromen **307** derivatives.

2.2. Reaction of homophthalic acid (**287**) with triethyl amine and ethyl chloroformate in the presence of sodium azide: The synthesis of unusual substituted isocoumarin derivatives.

Another literature method for the synthesis of acyl azides **306** involves the activation of acids **329** with ethyl chloroformate in the presence of triethyl amine followed by addition of a solution of sodium azide in water.¹⁴³



Homophthalic acid (**287**) was treated with triethyl amine, ethyl chloroformate and aqueous solution of sodium azide, respectively. The diacyl azide **288** could not be obtained again. Careful examination of the reaction mixture revealed the formation of the compounds **332**, **333**, **334** and **335**. The compound **332** precipitated from the reaction media. It was separated by vacuum filtration. The other isomers were separated on a silica gel column eluting with dichloromethane. COSY, HMQC and HMBC experiments allowed for the assignments of the structures of the four products.



2.2.1. Characterization of the compound 333.

The ^1H and ^{13}C NMR spectra of **333** was compared with those of 6H-dibenzo[c,h]chromen-6-one (**307**). The absence of one of the aromatic protons and the change of one of the aromatic signal resonances into singlet at 7.76 ppm and –OCH₂ protons at 4.38 ppm, carbon at 66.2 ppm and –CH₃ protons at 1.41 ppm and carbon at 14.6 ppm indicate the formation of the compound **333**.

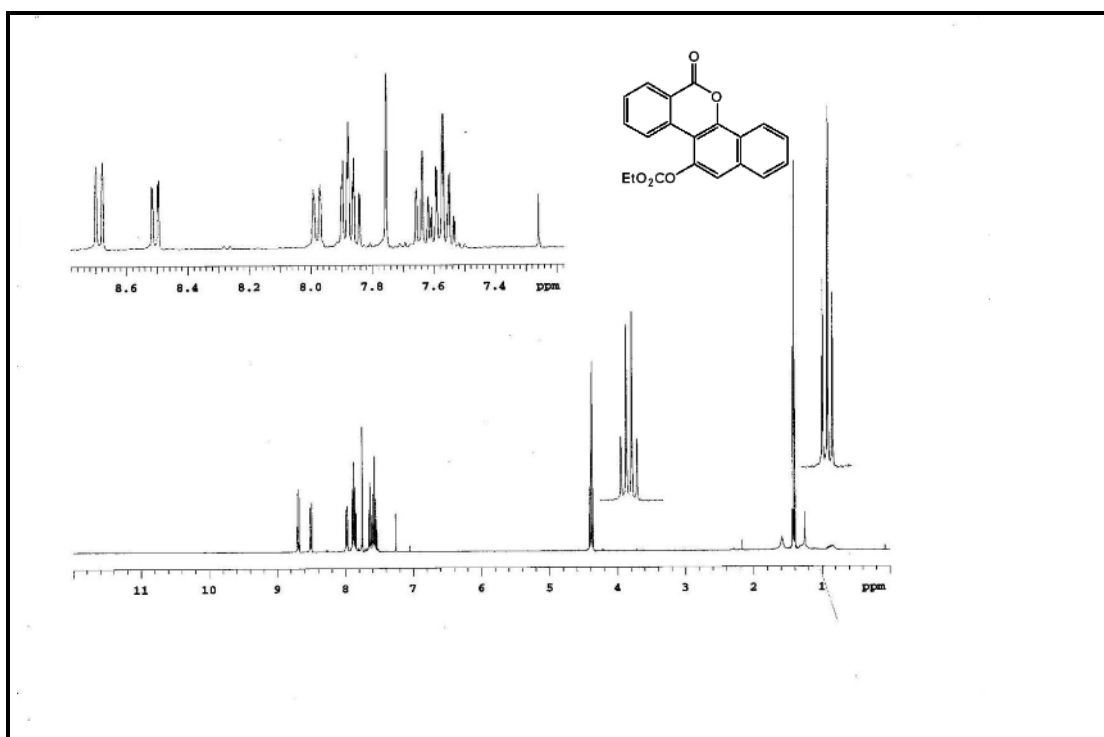
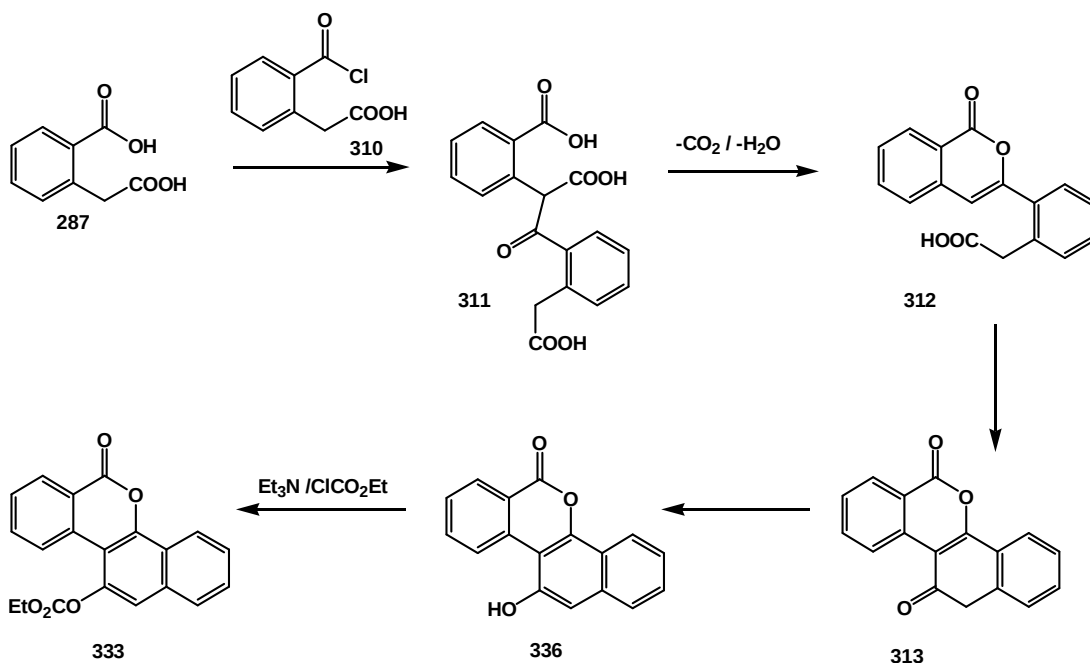


Figure 4. The ^1H -NMR spectrum of the compound **333**.

For the formation of **333** we suggest a similar mechanism as depicted in Scheme 4.



Scheme 4. Suggested mechanism for the formation of the compound **333**.

2.2.2. Characterization of the compound **332**

An HMBC experiment of **332** confirmed this structure especially by the correlation of the high field, at 80.2 ppm resonating carbon atom, C-4' bearing the chlorine atom with the double bond proton H-4 (at 6.89 ppm) located in the isocoumarine ring and the α -proton H-5' (at 7.41 ppm) of the other benzene ring. Furthermore the presence of four carbon resonances; the carbonyl carbons at 165.8, 163.6 and 160.6 and the double bond carbon C-4 at 103.8 supported the formation of an anhydride structure. The correct assignment of the carbonyl carbons were performed by the HMBC experiments. The two α -protons H-8 and H-8' (resonated at 8.03 ppm and 7.76 ppm, respectively) of the benzene rings correlated with each carbonyl carbons C_1 and $\text{C}_{1'}$, respectively.

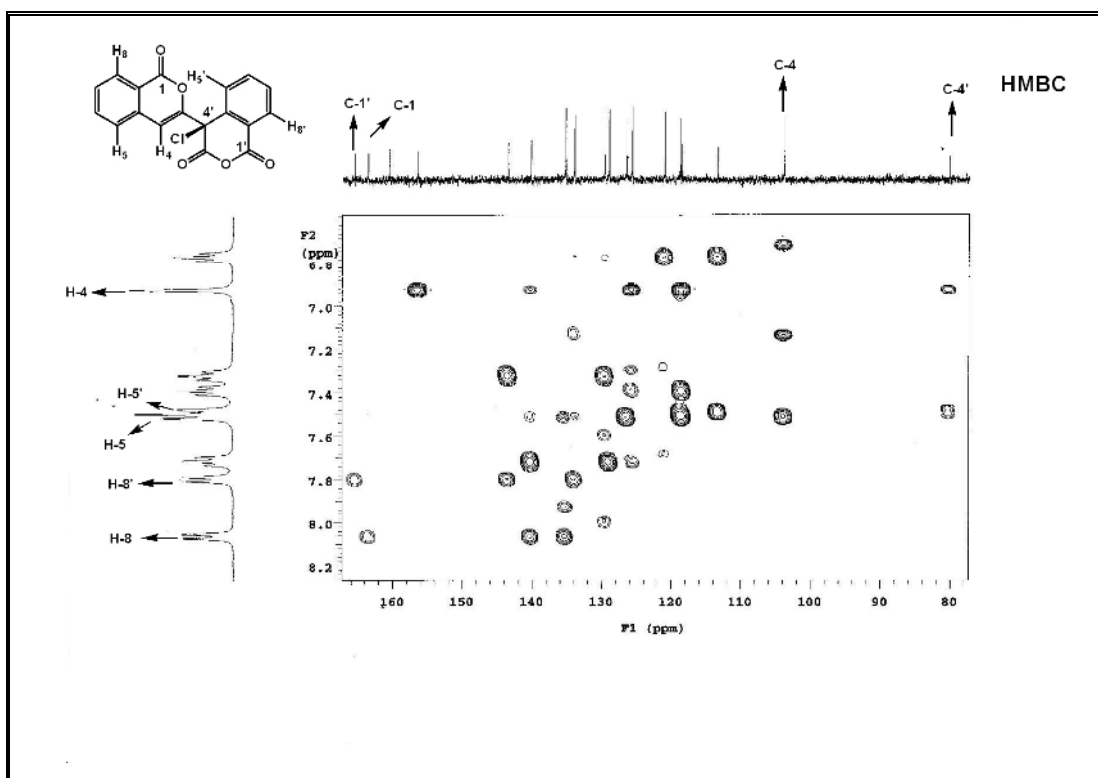
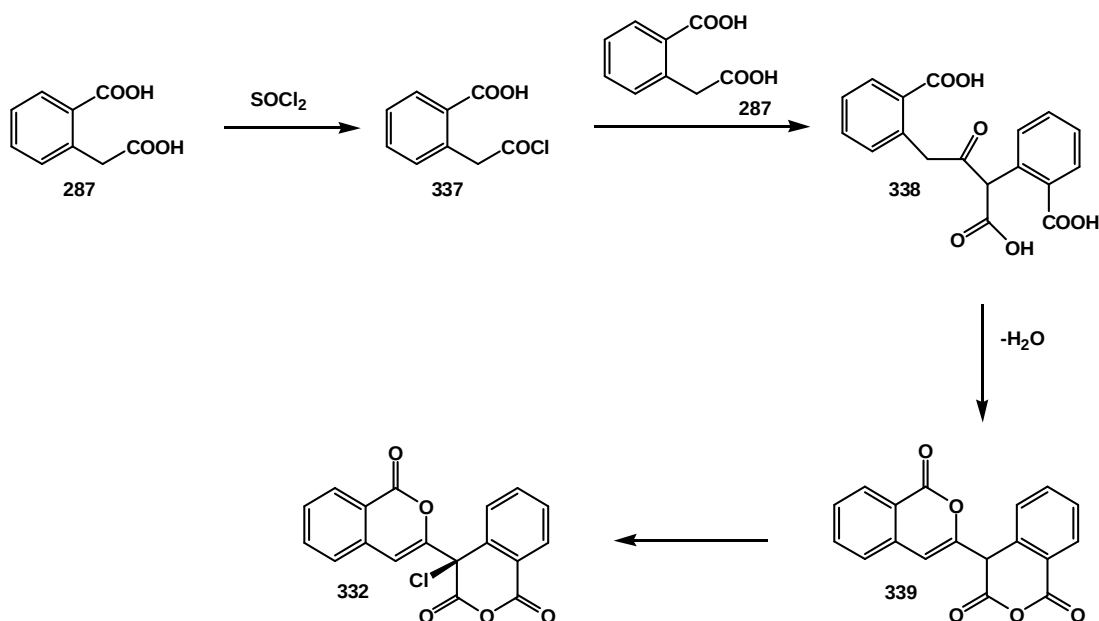


Figure 5. A part of HMBC experiment of the compound **332**.

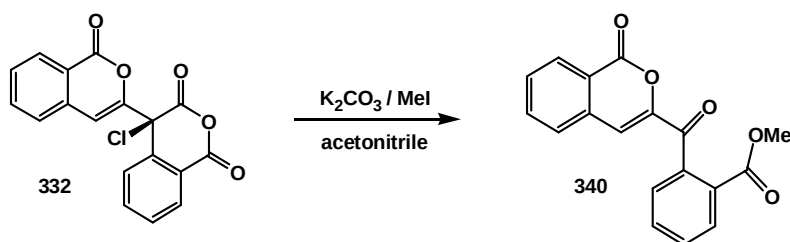
Our mechanistic approach for the formation of **332** is outlined in Scheme 5. The chlorinated product **337** condenses with the acid (**287**) to give the intermediate **338**, which then undergoes a ring closure to give the compound **339**. In the last step **339** is chlorinated under the reaction conditions.



Scheme 5. Suggested mechanism for the formation of the compound **332**.

2.2.3. Synthesis and characterization of the compound **340**

The chlorine compound **332** was treated with methyl iodide in the presence of potassium carbonate in acetonitrile to give the isocoumarine derivative **340** as a single compound.



Again COSY, HMQC and HMBC experiments allowed the correct assignment of the proposed structure. The presence of low field resonance at 189.3 ppm showed that there was a α,β -unsaturated ketone carbonyl in the structure. A strong correlation between the low field resonating carbonyl carbon and the double bond proton, H-4

and α -proton, H-3 of the benzene ring gave us information about the location of the ketone carbonyl. A strong correlation between H-4 and C-8a supported the position of double bond. The ester carbonyl and lactone carbonyl were assigned on the basis of the correlations with H-6 and H-8, respectively.

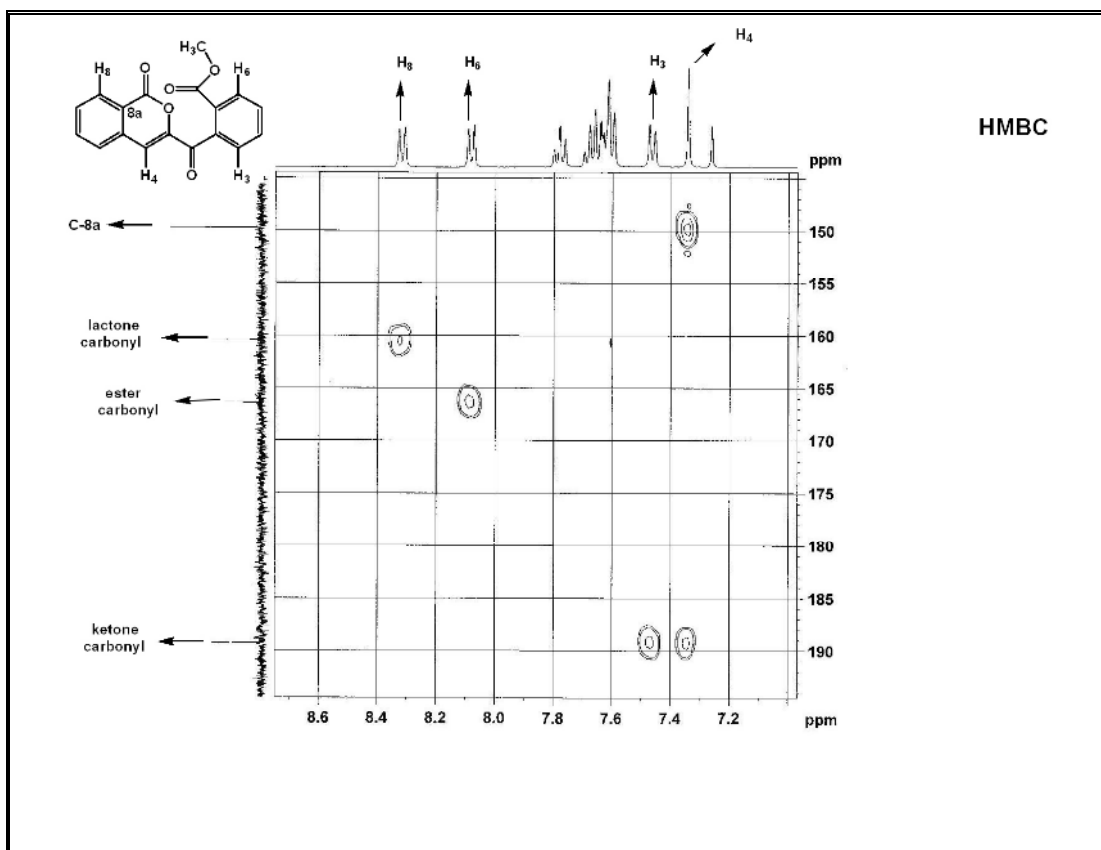


Figure 6. A part of HMBC experiment of **340**.

Finally, an X-Ray diffraction study of **340** was undertaken. The results of this study confirmed unambiguously the proposed structure.

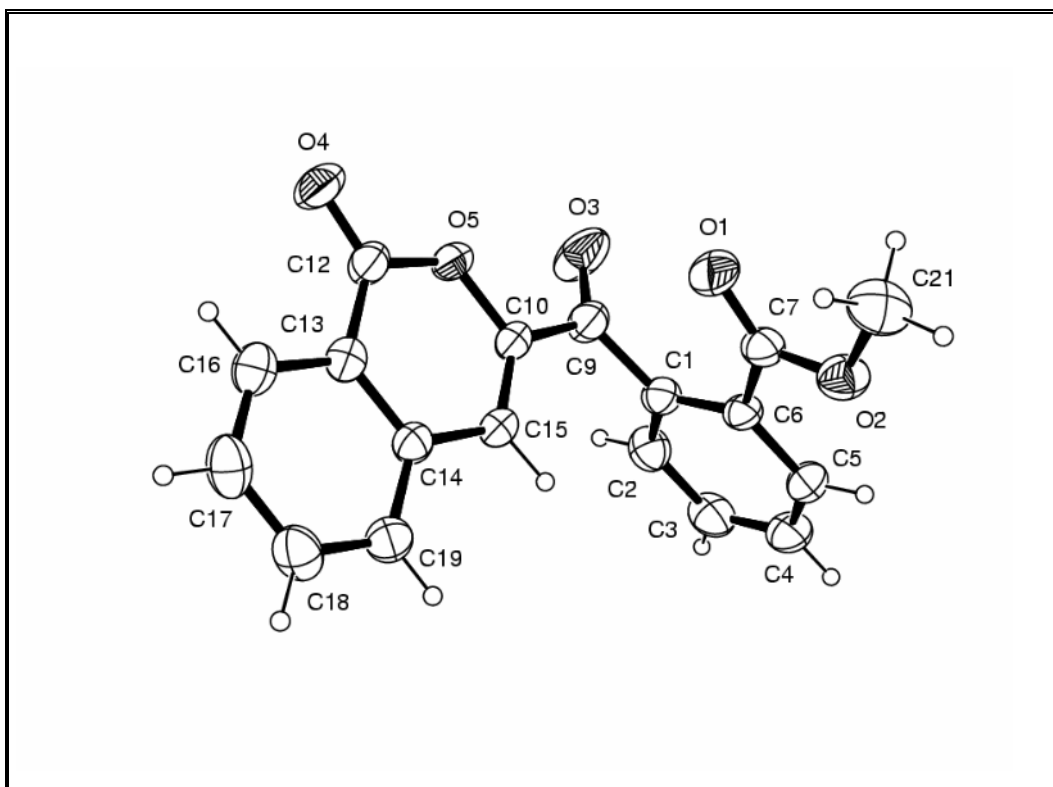
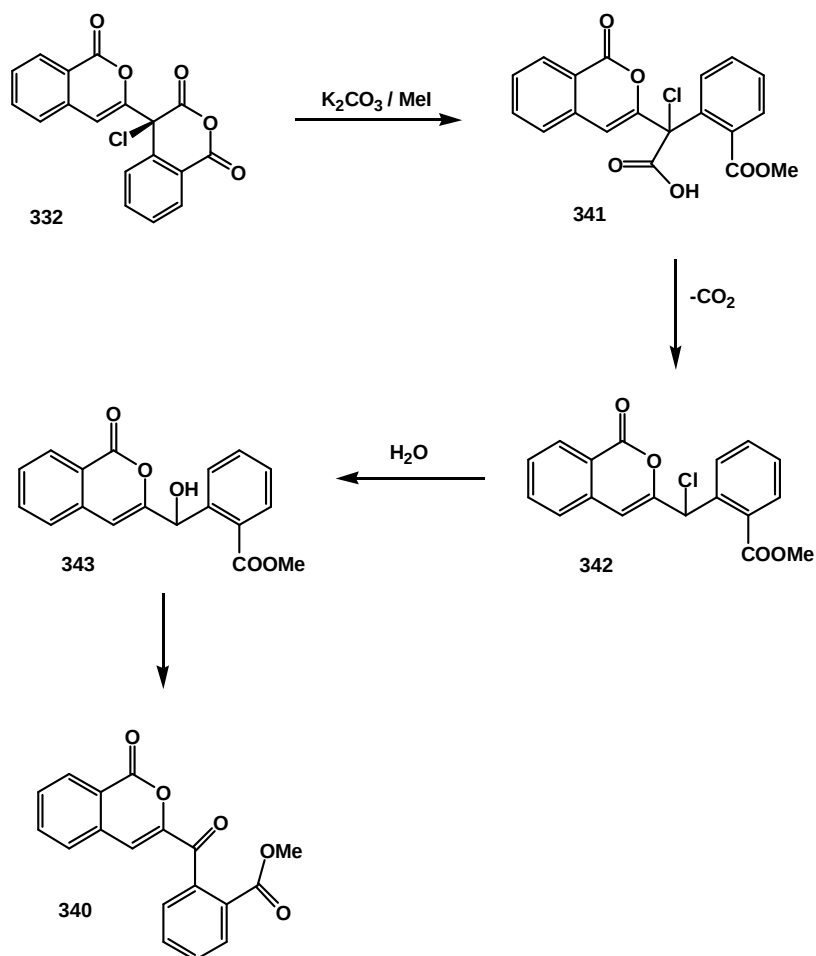


Figure 7. The X-ray crystal structure of the compound **340**.

The following mechanism is proposed for the formation of **340** shown in Scheme 6. Firstly the lactone ring was opened to half ester **341** and then decarboxylation occurred, followed by the substitution of chlorine group with hydroxy group and the last step was the oxidation step.



Scheme 6. Suggested mechanism for the formation of the compound **340**.

2.2.4. Characterization of the compound **334**.

The HMBC experiment of **334** revealed also a strong correlation between the carbon C-1 in the lactone ring with the double bond proton H-4 (at 7.14 ppm) as well as with the α -proton H-7 (at 7.64 ppm) of the second benzene ring. The carbon C-1 resonating at 78.9 ppm was a reasonable value for the sp^3 carbon and the two carbonyl carbons resonating at 161.5 and 170 ppm signaled the lactone rings. The assignment of each carbonyl carbon was done again with the correlation of α -protons

H-4' (at 7.76 ppm) and H-8 (at 8.13 ppm) of the benzene rings. Furthermore, the chemical shifts of all carbon atoms were in agreement with the expected values.

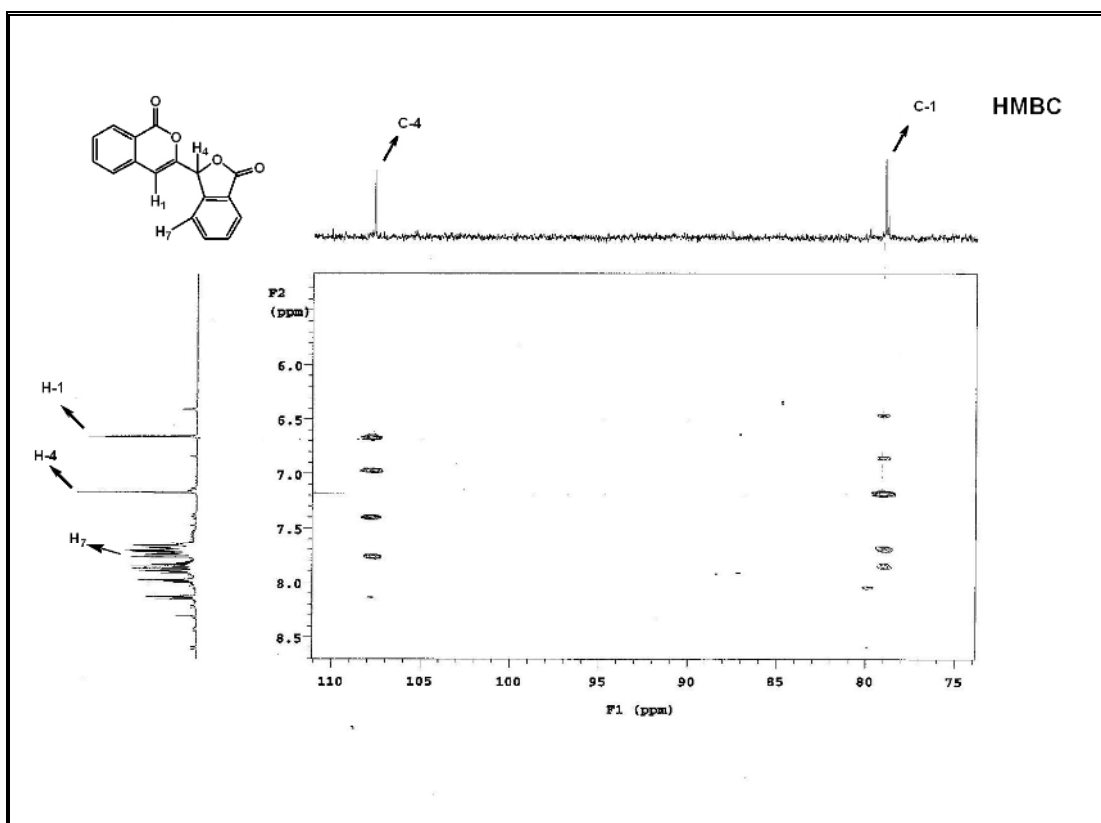
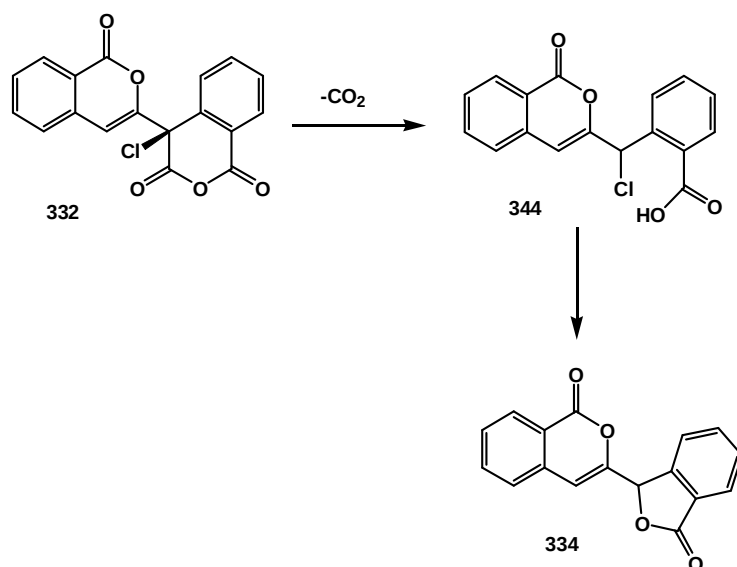


Figure 8. A part of HMBC experiment of the compound **334**.

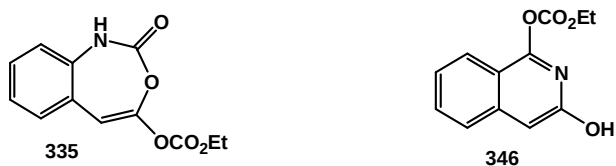
We assume that the compound **334** is a secondary product formed from the primary product **332** under the reaction conditions. Ring opening of **332** followed by decarboxylation and substitution of the chlorine atom by carboxylate ion would form the lactone **334**.



Scheme 7: Suggested mechanism for the formation of the compound **334**.

2.2.5. Characterization of the compound **335**.

The elemental analysis result showed the presence of one nitrogen atom in **335**. The proton resonating at 5.93 ppm indicated the presence of a double bond next to aromatic ring and the ethoxy protons as triplet and quartet at 4.26 ppm and 1.31 ppm, respectively showed the trapping of carboethoxyl group. There were two alternative compounds **335** and **346** responding to the ^1H and ^{13}C NMR spectra. In order to distinguish between these possible structures, a new experiment was performed to synthesize **346** on an independent way.



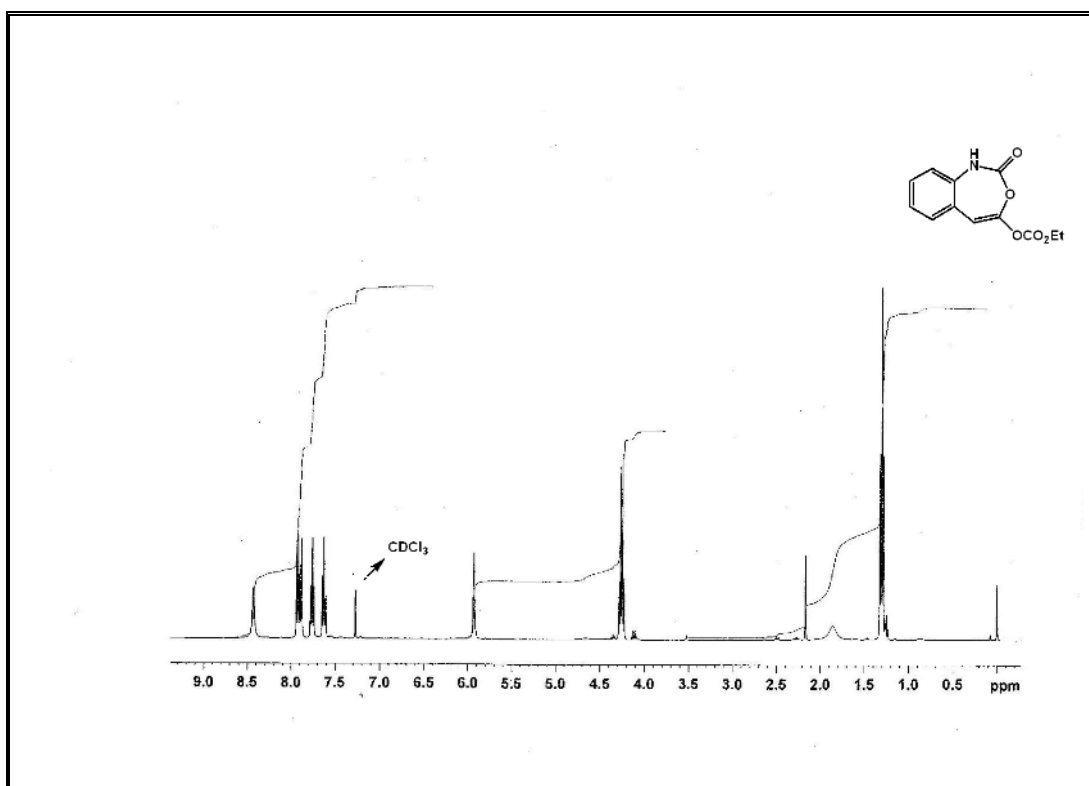
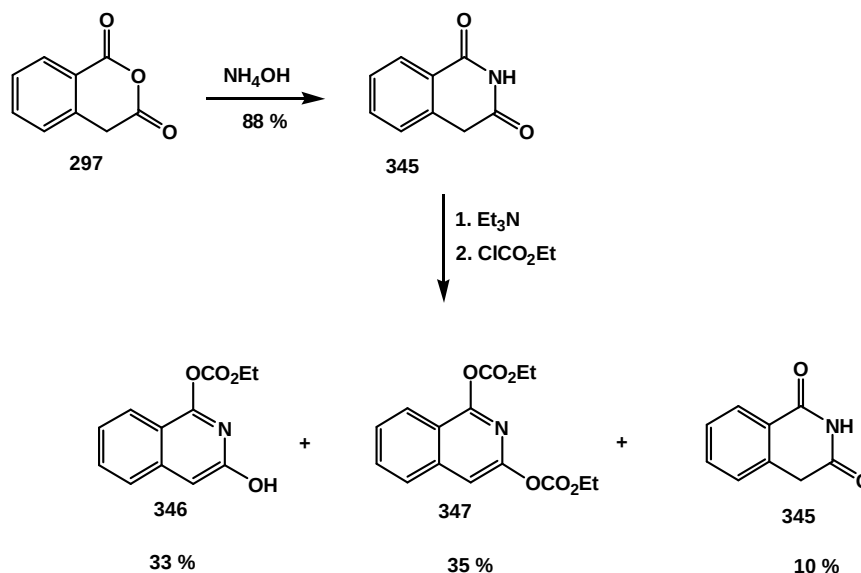


Figure 9. The ¹H-NMR spectrum of the compound 335.

2.2.5.1. Acetylation of tetrahydroisoquinoline (345): Synthesis of quinazoline derivatives 346 and 347.

The lactone **294** was firstly converted to the tetrahydroisoquinoline (**345**), which was then acetylated to give a mixture of three compounds **346**, **347** and recovered starting material **345**. These three compounds **346**, **347** and **345** were separated on a silicagel column eluting with chloroform:hexane (95 : 5).



The structure of **347** was confirmed by ^1H NMR and ^{13}C NMR, the resonance of the double bond proton at 7.46 ppm and the double bond carbon at 104.9 ppm were reasonable. The presence of two sets of protons at 4.38, 4.34, 1.39 and 1.37 ppm also indicated the presence of two ethoxy groups.

The structure of **346** was assigned by the double bond proton at 6.44 ppm and carbon at 95.2, ethoxy protons as triplet at 4.39 and as quartet at 1.44 ppm and carbons at 66.4 and 14.2 ppm.

Comparison of the spectral data of **346** with those of **335** clearly indicated that these compounds were different compounds, so we eliminated the structure of **346** and assigned the structure as **335**.

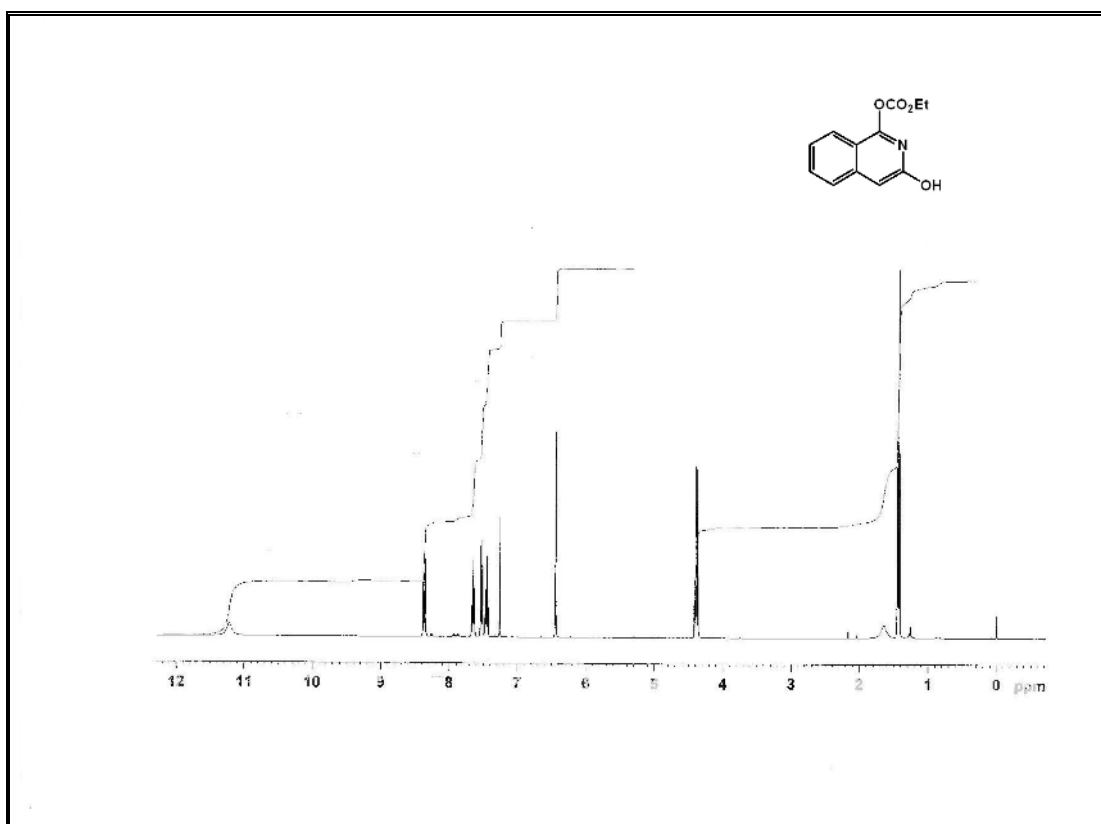
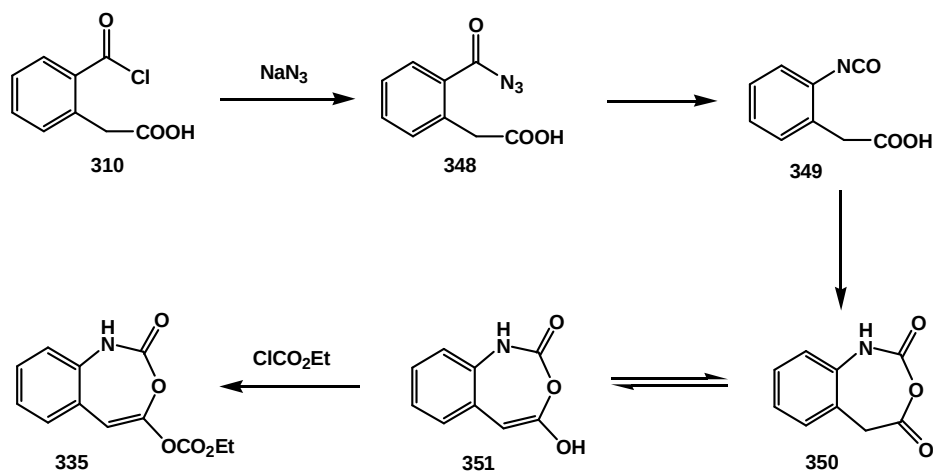


Figure 10. The ^1H -NMR spectrum of the compound **346**.

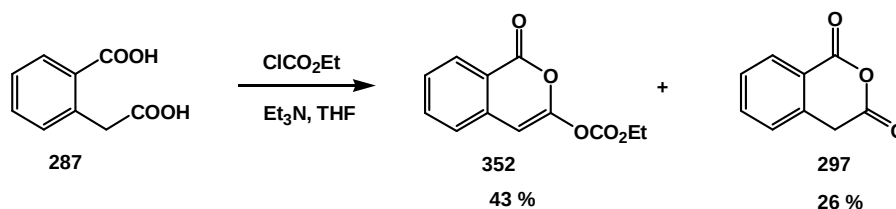
For the formation of the compound **335** the following mechanism is suggested in Scheme 8. The initially formed acyl chloride **310** can react with azide to give the acyl azide **348** which can then transform into the corresponding isocyanate **349** followed by trapping with the acid $-\text{OH}$ group under the reaction conditions. Enolization of the carbonyl group followed by trapping with ethylchloroformate can end up with the formation of **335**.



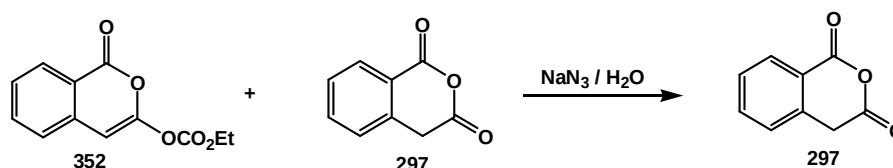
Scheme 8. Suggested mechanism for the formation of the compound 335.

2.3. The reaction of homophthalic acid (287) with triethyl amine and ethyl chloroformate in the absence of sodium azide: Synthesis of 352 and 297.

As mentioned in the previous chapter, reaction of **287** with triethyl amine and ethyl chloroformate in the presence of sodium azide gave unusual isocoumarin derivatives **302**, **303**, **304** and **305**. In order to check the mechanism of this reaction, homophthalic acid **287** was run under the same reaction conditions in the absence of sodium azide. The isocoumarine derivative **352** was formed as a major product (43 %) along with anhydride which was formed in 26 % yield. The structure of **352** was characterized by NMR spectral data. Especially, the double bond at 6.27 ppm and the ethyl protons resonating as a triplet and quartet at 1.41 ppm and 4.36 ppm, respectively clearly confirmed the structure.



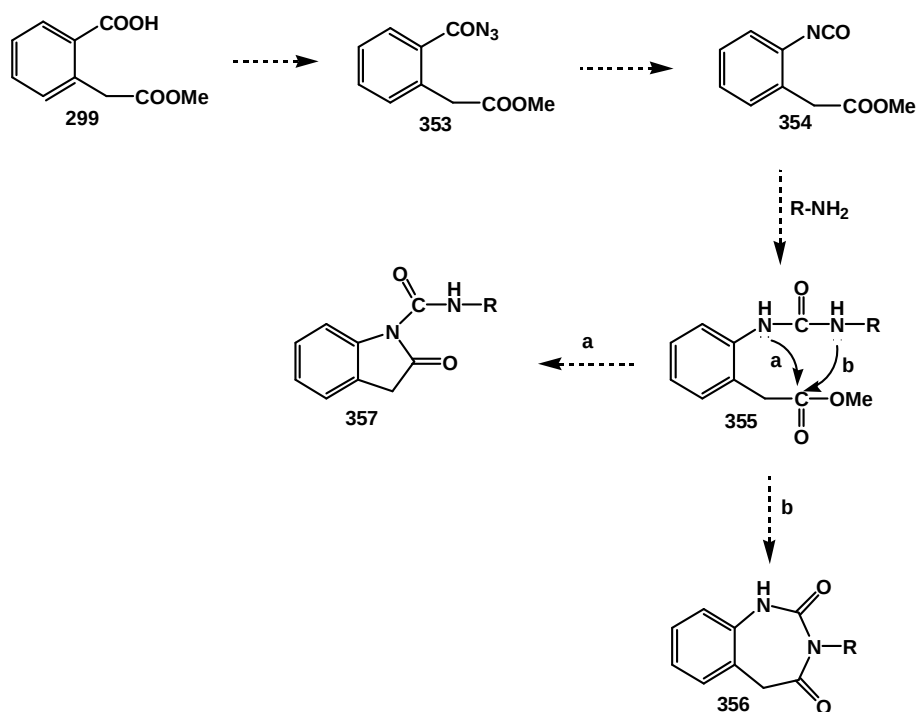
The reaction mixture was then reacted with aqueous solution of sodium azide to check whether the four compounds **332**, **333**, **334** and **335** would be obtained or not. Any traces of the compounds were not detected; instead the compound **352** was transformed into the lactone **297**.



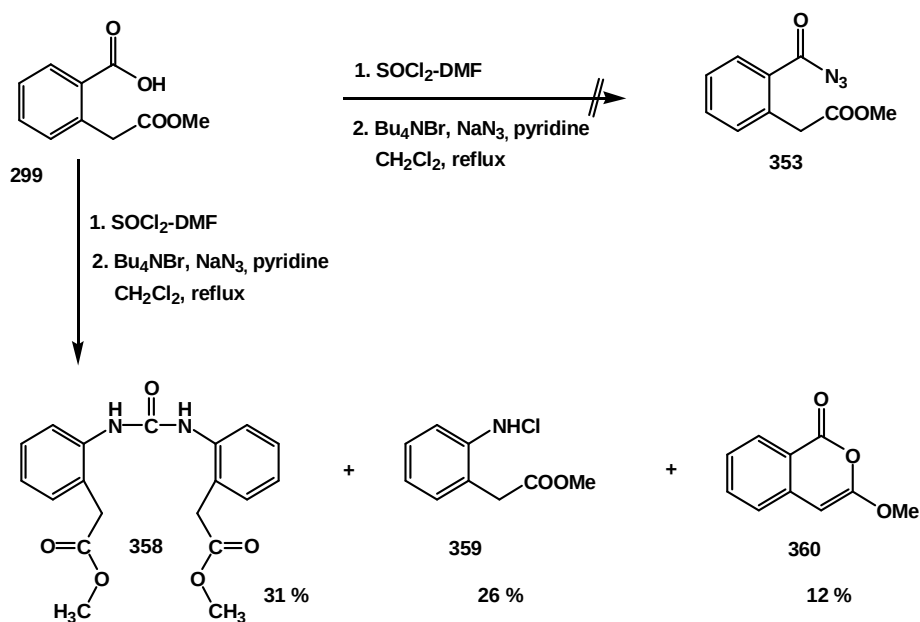
From the result of this reaction we can conclude that the reaction of homophthalic acid with ethyl chloroformate in the presence of triethyl amine and sodium azide yielded the products **332**, **333**, **334** and **335** in a single reaction.

2.4. The reaction of homophthalic acid monoester (299) with N,N-dimethylchloro sulfite methaniminium chloride (303) in the presence of sodium azide: Synthesis of the compounds 358, 359 and 360.

In this part of the thesis, the half ester (**299**) would be converted into the azide **353**, which then would be converted into the corresponding isocyanate **354**. The trapping of this isocyanate with amines would give such an intermediate **355**, on which there would be two possible attack paths to produce either a seven membered ring, benzodiazepinone derivative **356** or a five membered ring, indole derivative **357**.



So we started with the synthesis of the azide **353**. The half ester **299** was treated with N,N-dimethylchlorosulfite methaniminium chloride in the presence of sodium azide, pyridine and as phase transfer catalyst tetrabutyl ammonium bromide in refluxing dichloromethane was used.



Unfortunately, the expected azide **353** could not be isolated under the reaction products. Instead, a mixture of three compounds **358**, **359** and **360** was obtained. These compounds were separated on silica gel column eluting with chloroform:hexane (95:5). The products were characterized by using NMR spectral and physical data. The ^1H -NMR spectrum revealed four sets of proton signals matching with the major product **358**; a sharp singlet centered at 3.54 ppm indicating methyl protons, a singlet at 3.58 ppm indicating methylene protons, a broad singlet arising from nitrogen proton at 7.31 ppm and other aromatic protons centered between 7.06 and 7.63 ppm.

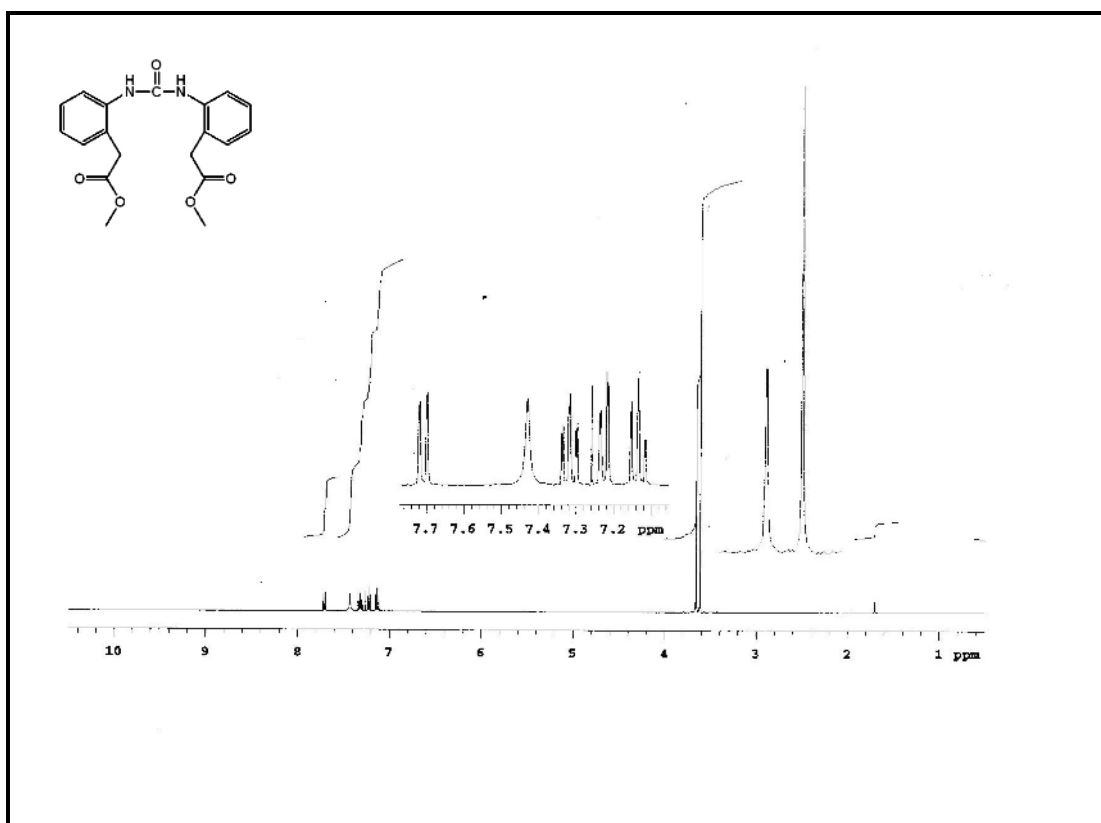
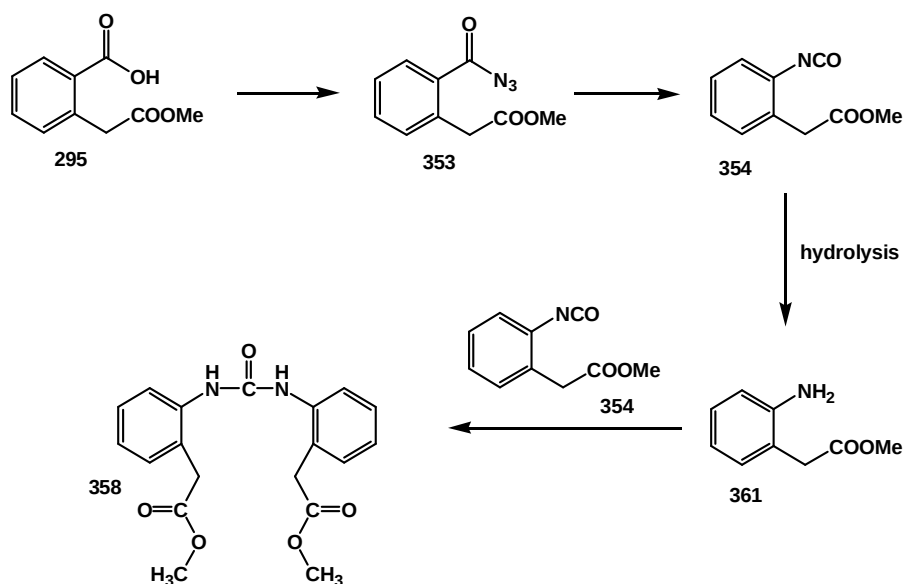


Figure 11. The ^1H -NMR spectrum of the compound **358**.

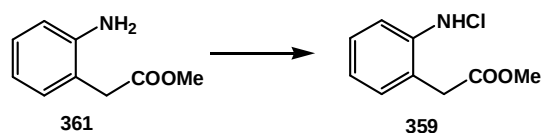
The High Resolution Mass spectrum clearly indicated the formation of the dimeric product. The found value (356.1363) was fully in agreement with the theoretical value (356.1372). The formation of the dimeric product **358** can be explained by very

reasonable mechanism depicted in Scheme 9. In the reaction medium, at first the azide compound **353** was formed and transformed into the isocyanate **354**. Partial hydrolysis of the isocyanate **354** formed the amine **361** and trapping of **354** with this amine **361** gave the dimeric product **358**.



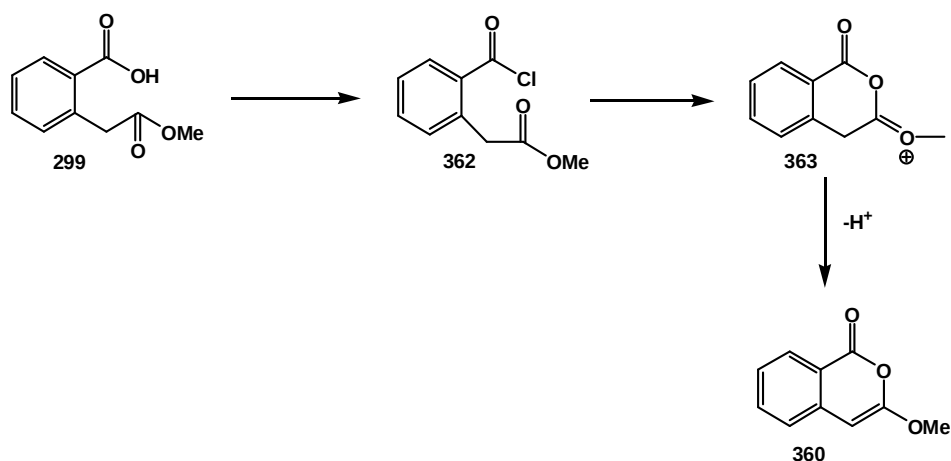
Scheme 9. Suggested mechanism for the formation of the compound **358**.

One of the products of the mixture was the chlorinated product **359**. The structure was in agreement with its ^1H -NMR spectrum, which revealed a singlet at 3.63 for methylene protons, a singlet at 3.73 for methoxy protons, four protons centered between 7.13 and 7.85 ppm for aromatic protons, one broad singlet for the acidic proton. One of the aromatic protons resonating at the lowest field, at 7.85 ppm was interesting. Due to the quadrupole effect of nitrogen atom it resonated almost as a broad singlet. We assume that some part of the amine **361** undergoes further chlorination reaction under reaction conditions.



Scheme 10. Formation of the compound **359**.

The other compound **360** was characterized on the basis of ^1H -NMR spectrum. The additional proton resonances of methoxy protons at 3.91 ppm and the double bond proton at 5.55 ppm indicated the formation of this compound **358**. Also, the ^1H -NMR spectrum and the melting point of the compound was in agreement with those reported in the literature.¹⁴⁴

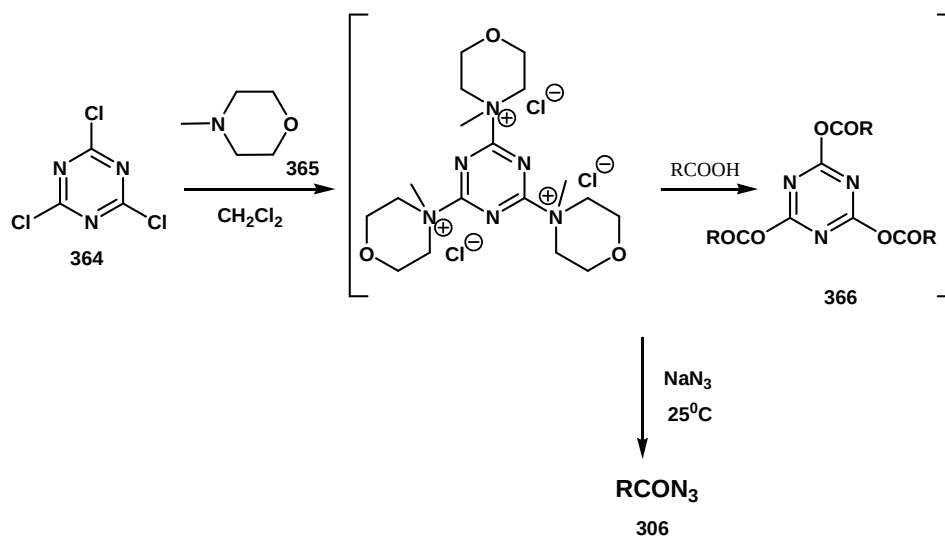


Scheme 11. Suggested mechanism for the formation of the compound **360**.

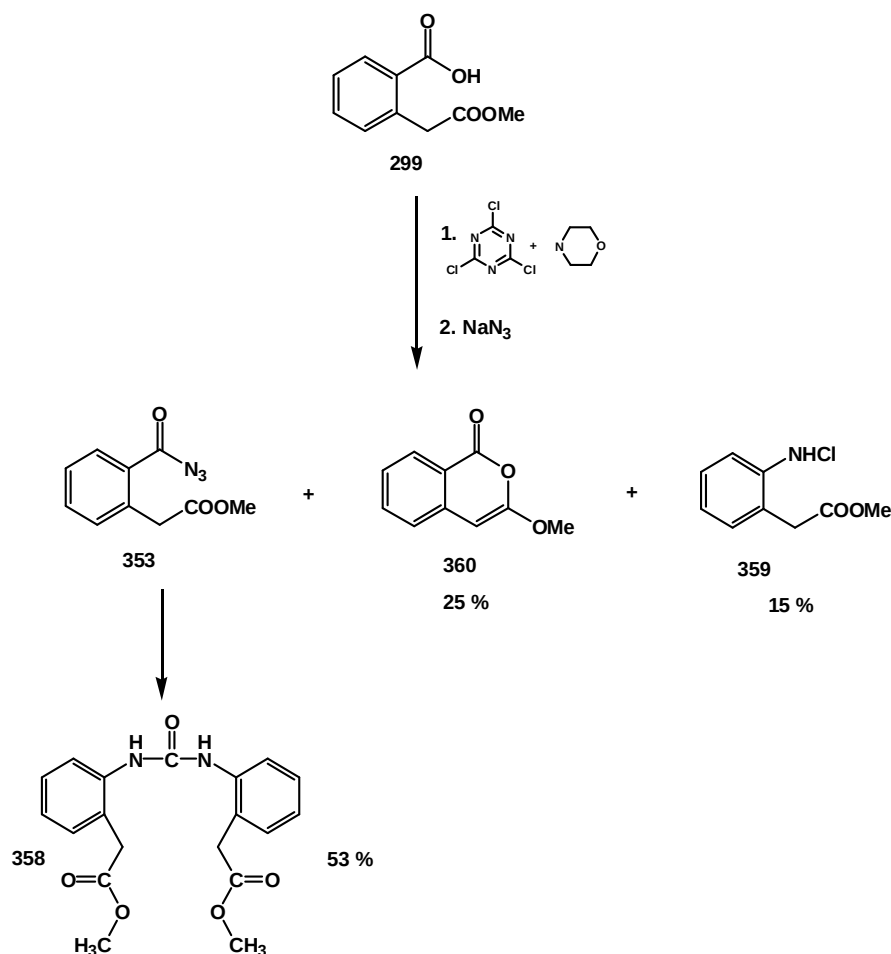
2.5. The reaction of homophthalic ester (**299**) with cyanuric chloride (**364**), N-methylmorpholine oxide (**365**) in the presence of sodium azide: Synthesis of the compounds **353**, **359** and **360**.

As a next trial for the conversion of acid group **299** into azide group **353**, we decided to follow another method in which cyanuric chloride **364** was used in the presence of

N-methyl morpholine oxide **365** for the activation of acid and sodium azide solution in water for the formation of azide **367**.¹⁴⁵



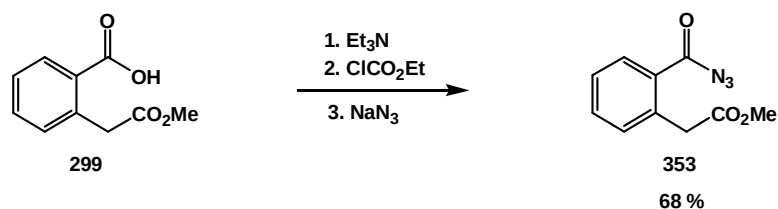
This azidation method was applied to the half ester **295**. Careful examination has revealed the formation of three products which were separated by column chromatography (SiO_2 , chloroform:hexane). The first fraction was the lactone **360**, the second was **359** and the last one was the dimeric product **358**. Unfortunately, the azide **367** was already converted to the dimeric product **358** on silica gel.



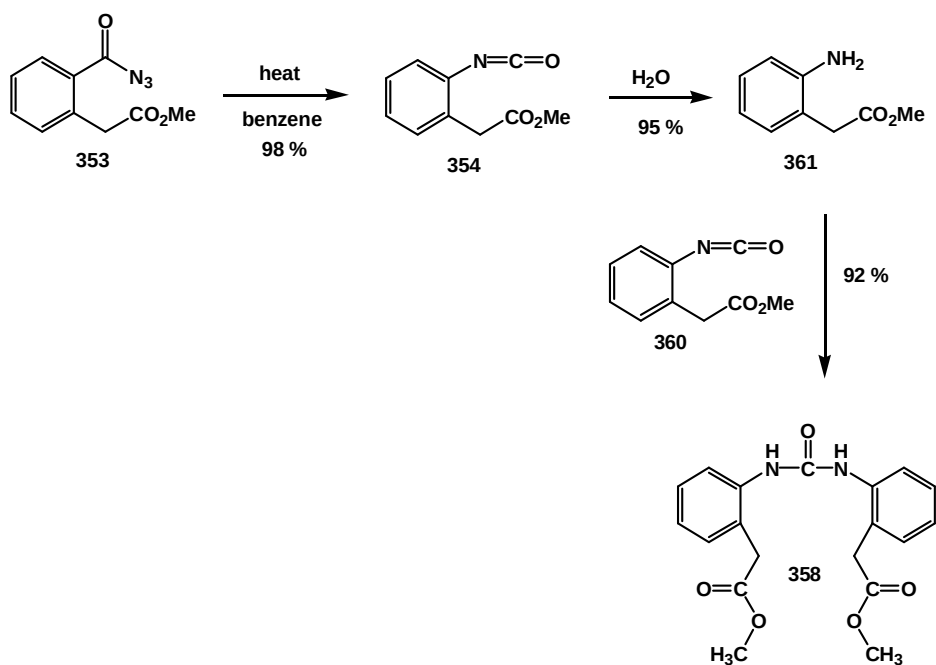
So, this method was also not efficient for the synthesis of the azide compound **353**.

2.6. The reaction of homophthalic acid with triethylamine, ethyl chloroformate in the presence of sodium azide: The synthesis and the chemistry of the azide **353**.

Next we decided to apply another procedure which we had already used for the diacid; triethyl amine, ethyl chloroformate and sodium azide at low temperatures. The azide **353** was obtained as the sole product. The formation of the azide **353** was proved by IR spectroscopy. The characteristic frequency values 2279 and 2138 cm^{-1} for the triple bond of the azide **353** were observed in the IR spectrum. Fortunately, during the work up procedure only a little amount of azide was converted into the dimeric product **358**.



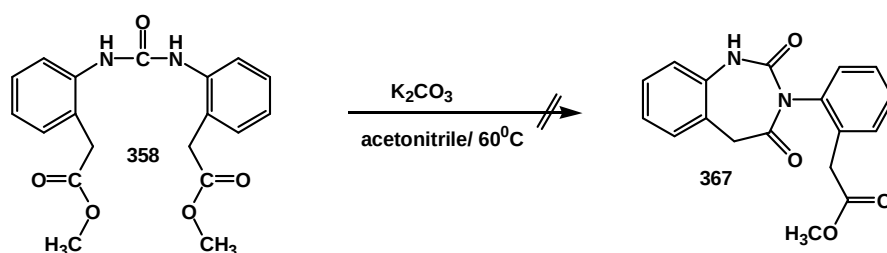
The azide **353** was immediately converted into the corresponding isocyanate **354** heating in benzene under nitrogen atmosphere, which was then reacted with its hydrolysis product **361** in order to check the formation of the dimeric compound chemically. The expected dimer **358** was formed. This observation also supports the suggested mechanism for the formation of **358**.



2.6.1. The chemistry of the symmetrical product 358: The synthesis of indole derivatives 368 and 369.

The symmetrical product **358** was reacted with potassium carbonate in acetonitrile at 60°C, expecting a ring closure.

There were two possible ring closing paths, one of which producing a seven membered ring **367** and the other a five membered ring **368**. According to NMR spectral data no trace of seven membered ring **367** was observed.



There were two products one of which **369** was soluble and the other **368** was insoluble in chloroform. The separation of the products was performed by solubility difference.

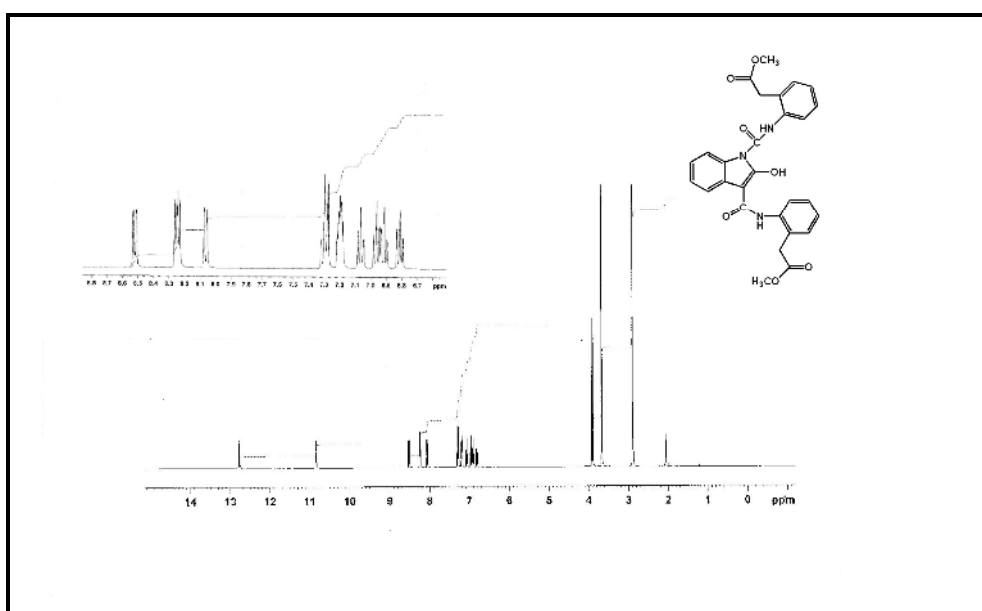
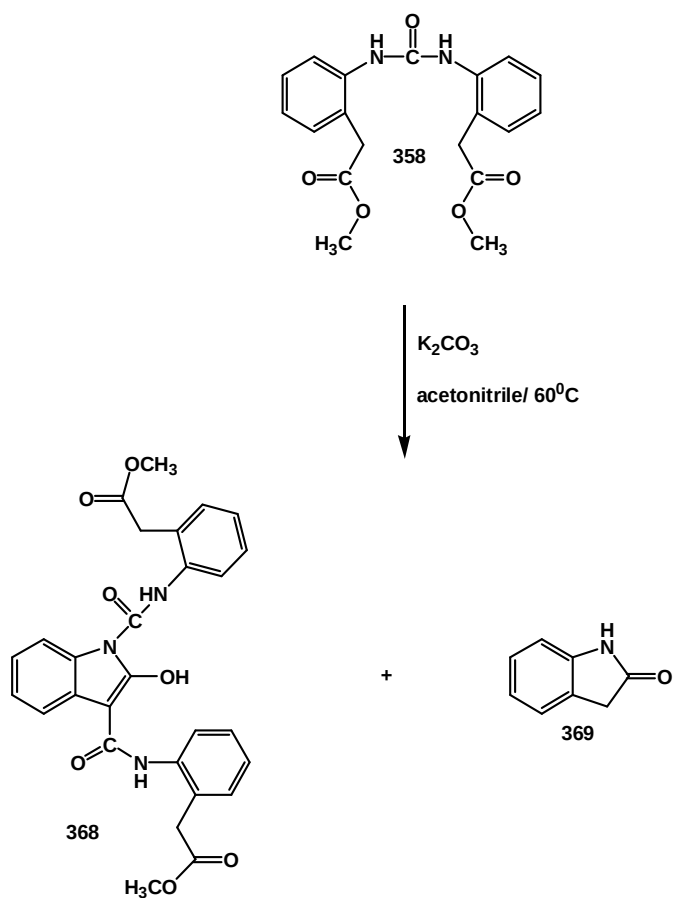


Figure 12. The ^1H -NMR spectrum of the compound **368**.

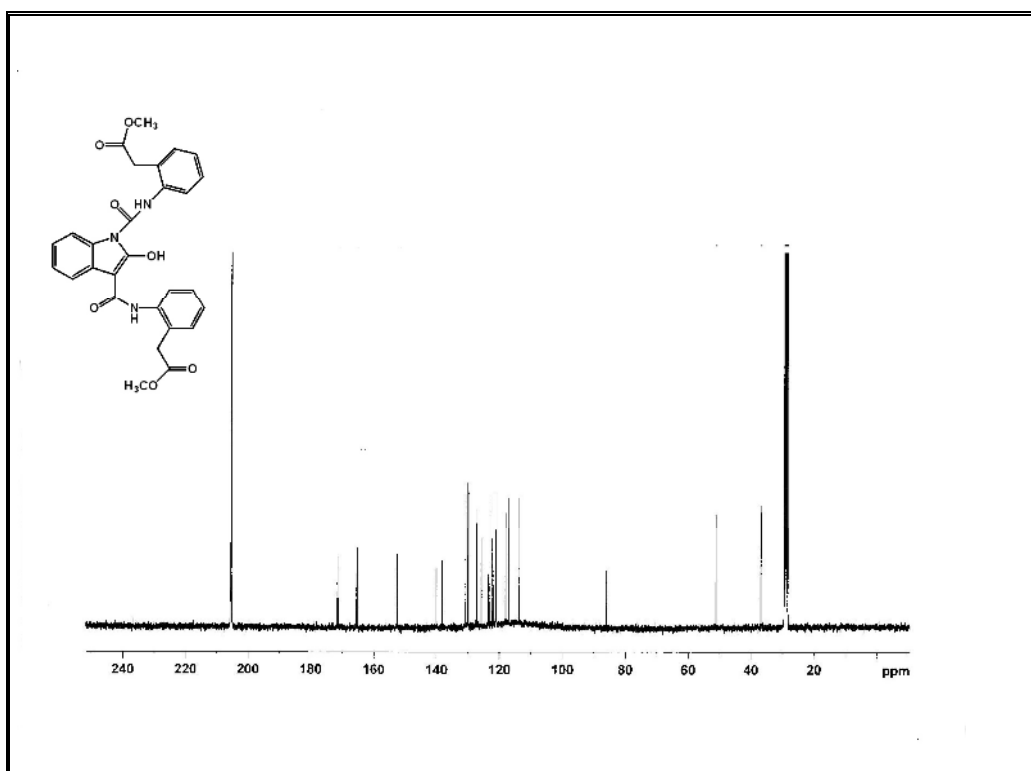
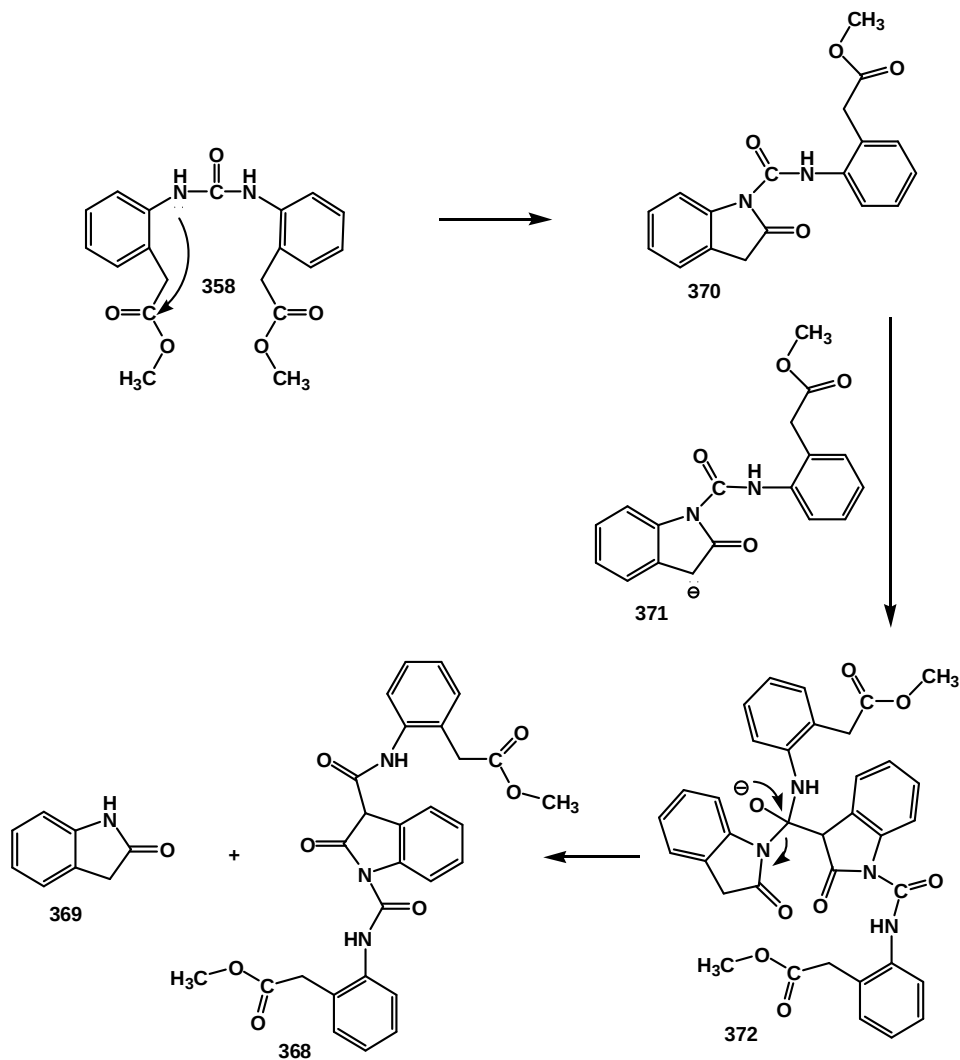


Figure 13. The ^{13}C -NMR spectrum of the compound **368**.

The indolinone **369** was consistent with the physical and spectral data of the one already reported in the literature.¹⁴⁶ The ^1H -NMR spectrum of **368** indicated the presence of three aromatic rings arising from the initial formation of dimeric product followed by the removal of one aromatic ring. The indole derivative **368** was characterized on the basis of NMR spectral data (^1H -NMR, ^{13}C -NMR, COSY, HMBC, HMQC, DEPT). All the carbons and protons resonate as expected. Especially the double bond carbon resonating around 85 ppm was an important hint for the assignment of the correct structures.

For the formation of indole derivative **368**, by taking the minor product **369** into account a general mechanism was suggested shown in Scheme 12.

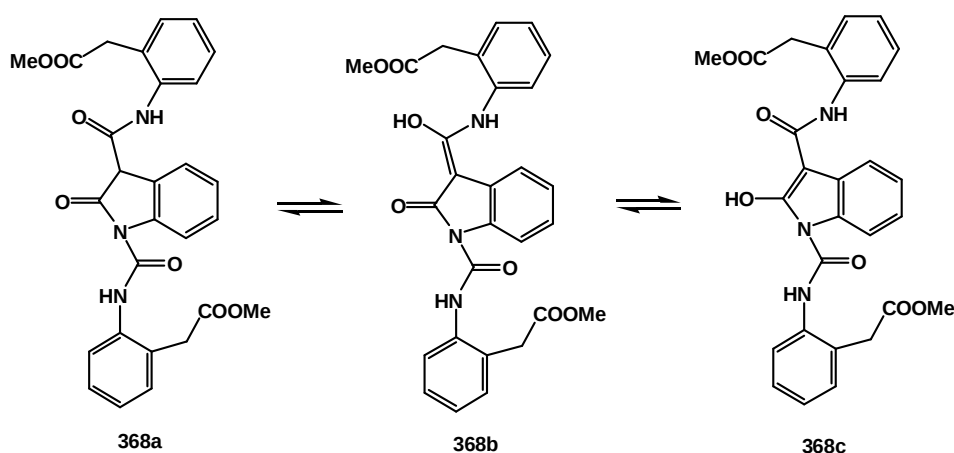


Scheme 12. Suggested mechanism for the formation of indole **368**.

Firstly the base abstracted the proton from the –NH forming the five membered ring **370**. The reaction did not stop at that step due to the excess base in the reaction medium the reaction went on by the abstraction of the acidic proton of some part of

the five membered ring and attack on the carbonyl of the other part of five membered ring forming the dimeric intermediate **372**. Removal of the the indalinone **369** yielded **385** which is in equilibrium with **386**.

The product **368** has three tautomeric forms. According to ^1H -NMR the absence of sp^3 carbon proton signal and ^{13}C -NMR and the presence of double bond carbon resonating around 85 ppm eliminates the possibility of the form **368a**. The left two forms **368b** and **368c** are in accordance with the NMR spectral data.



Scheme 13. Tautomeric forms of **368**.

Although the structure of **368** was characterized by NMR spectral data including COSY, HMBC and HMQC experiments and the formation of **368** was supported with mechanism the found elemental analysis was not in agreement with the theoretical one.

Anal. Calcd for $\text{C}_{28}\text{H}_{25}\text{N}_3\text{O}_7$: C, 65.24; H, 4.89; N, 8.15

Found: C, 54.16; H, 4.519; N, 7.025.

These results signaled the possible solvent incorporation. By using CHN calculator solvent correction was made. The purpose of this calculator is to determine possible solvent content in a sample that has been submitted for analysis that falls outside the acceptable error of $\pm 0.3\%$.

According to CHN calculation, 1.085 moles of chloroform was incorporated into **368**. In that case, the calculator result for elemental analysis shows the incorporation of 1.085 moles of chloroform.

Solvent corrected result: C, 54.16; 1H, 4.08; N, 6.51.

Solvent corrected elemental analysis result and found result are in agreement.

The structure of **368** was also confirmed by X-ray diffraction analysis.

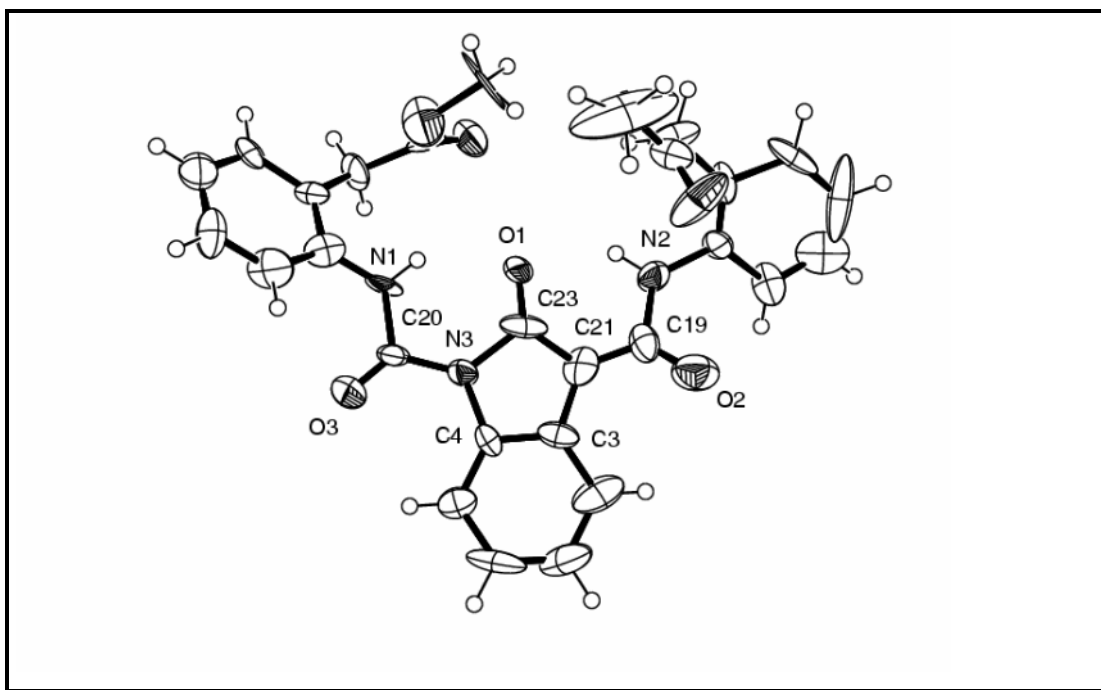
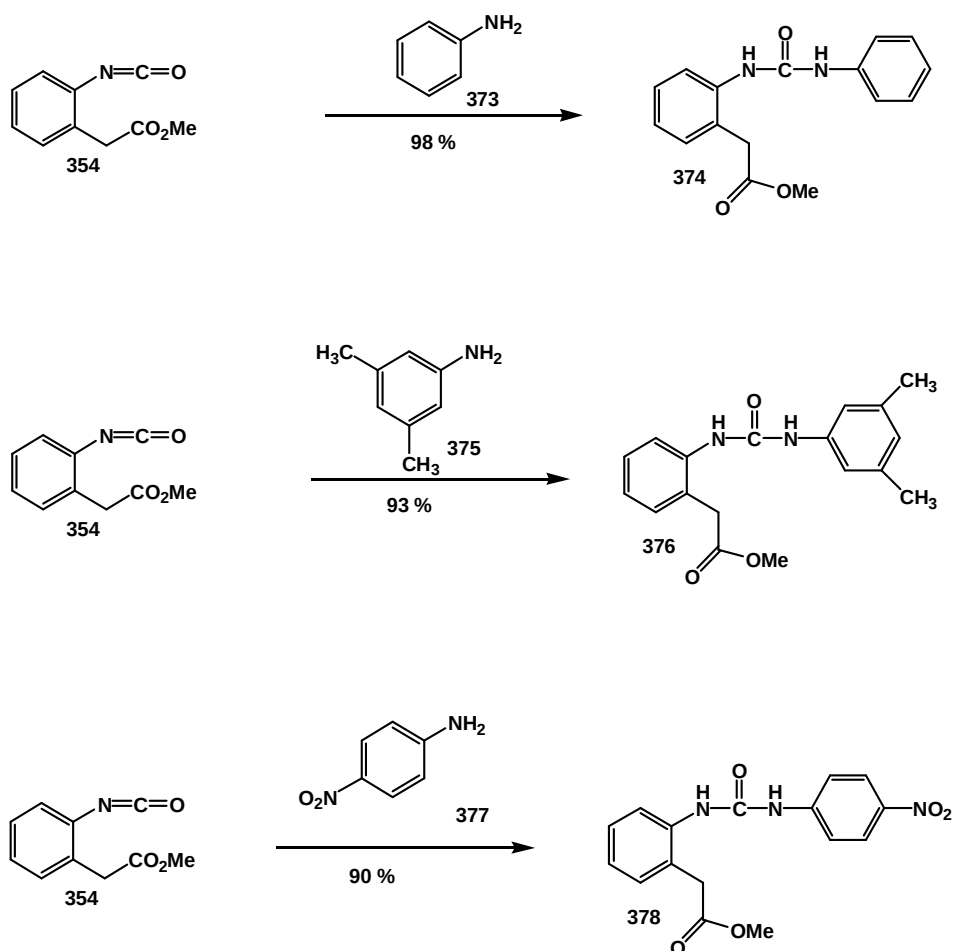


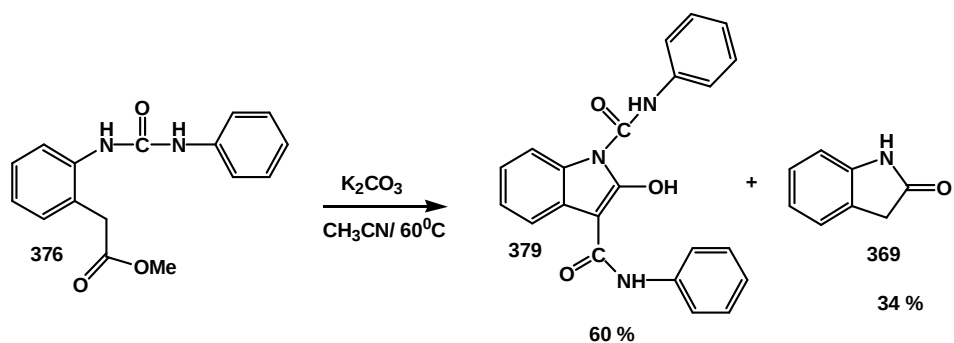
Figure 14. The X-ray crystal structure of the compound **368**.

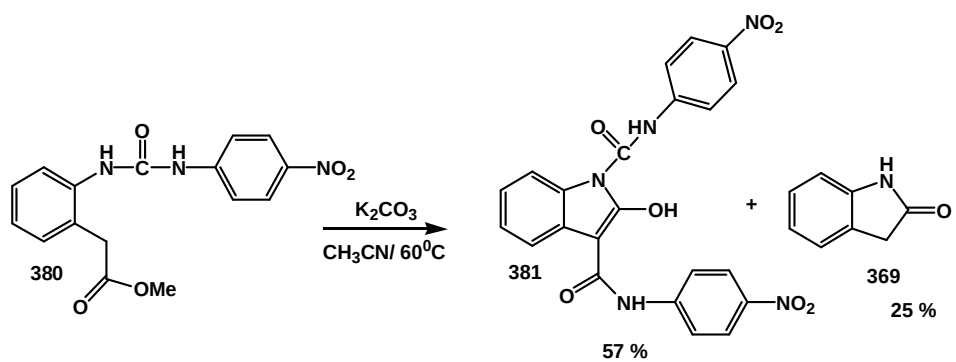
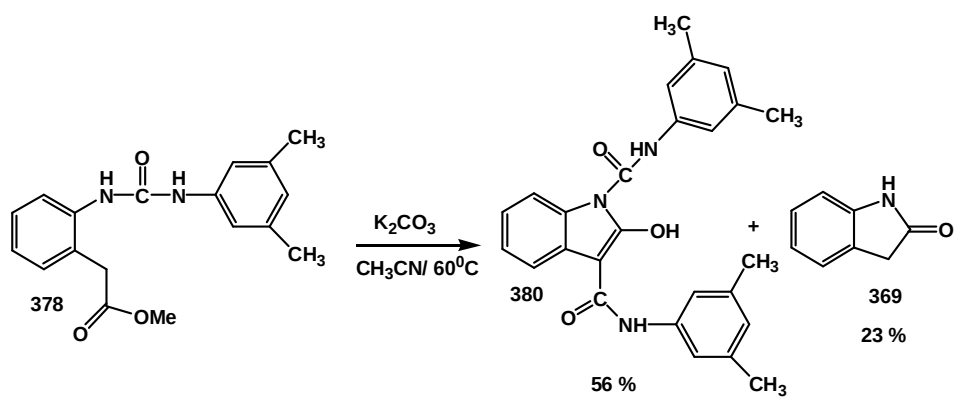
2.6.2. The chemistry of isocyanate **354**: Synthesis of indole derivatives

To test the scope and limitations of this reaction, the isocyanate **354** was reacted with aniline derivatives to give the corresponding urethane derivatives, which were characterized on the basis of physical and spectral data (^1H and ^{13}C -NMR, HMBC, HMQC, COSY, IR, elemental analysis.)



These urethanes **374**, **376** and **378** were then reacted with potassium carbonate under the same reaction conditions to give the derivatives of indoles **379**, **380**, **381** and the indolinone **369**.





The indole derivatives **379**, **380** and **381** were characterized on the basis of NMR spectral data (1H and ^{13}C -NMR, HMBC, HMQC, COSY, IR, elemental analysis).

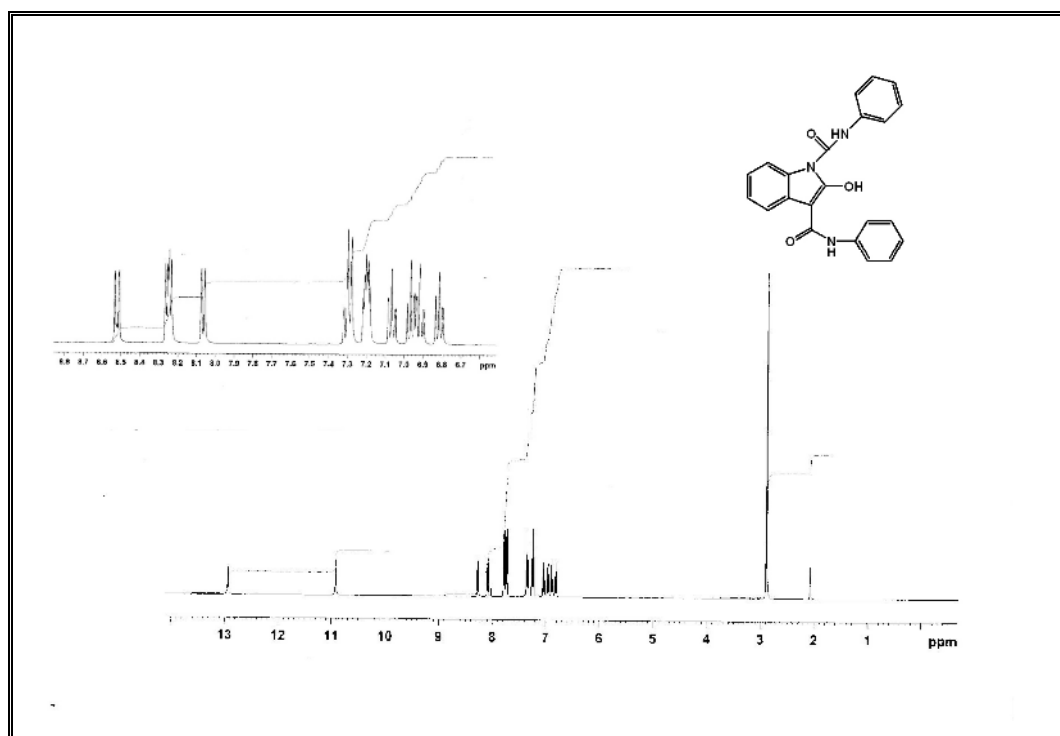


Figure 15. ^1H -NMR spectrum of the compound 379.

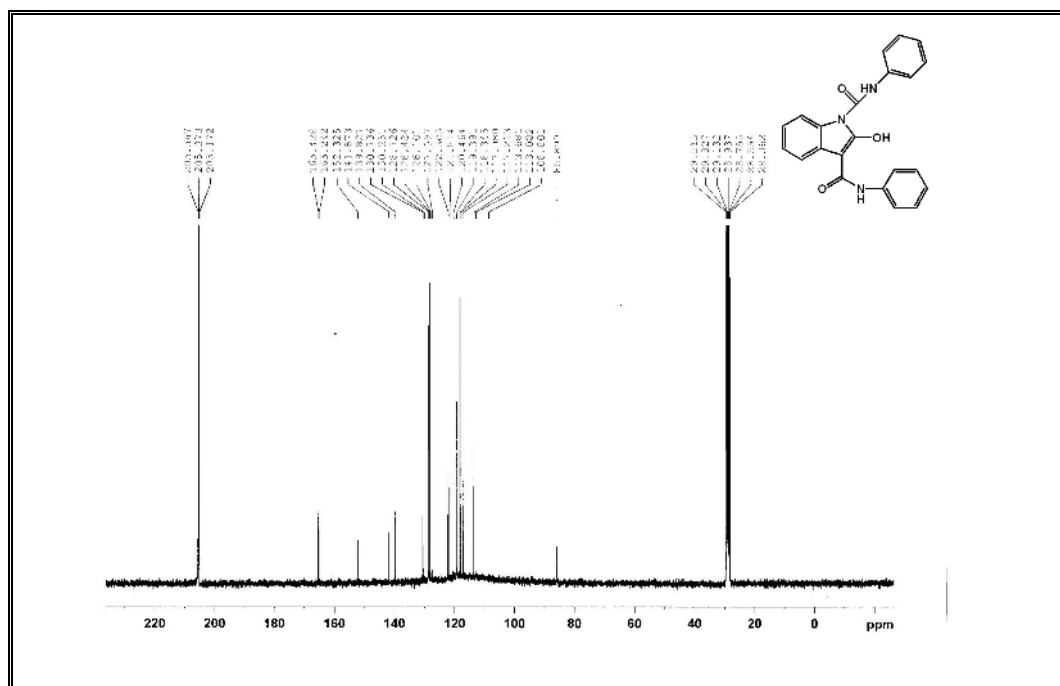
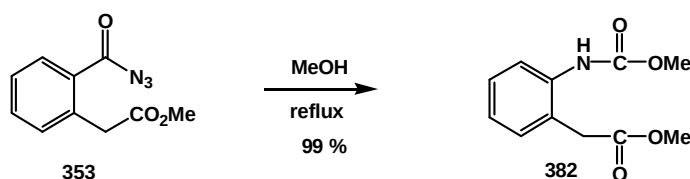


Figure 16. ^{13}C -NMR spectrum of the compound 379.

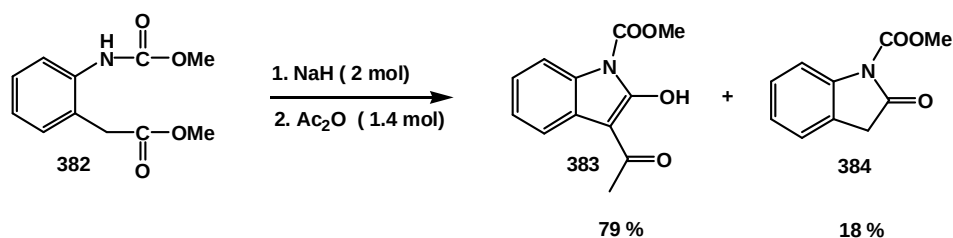
All the carbons and protons resonate as expected. Especially the double bond carbon resonating around 85 ppm was an important hint for the assignment of the correct structures. The elemental analysis results of the oxindoles are in agreement with the chloroform corrected results.

2.7. The chemistry of azide 353: The synthesis of indole derivatives.

As the next, the azide **353** was refluxed with methanol converting it into the urethane **382**, which was in agreement with the physical and spectral data with those published in the literature.¹⁴⁷



Reaction of **382** with sodium hydride and acetic anhydride yielded the indole derivative **383** and the oxindole derivative **384**.



The oxindole **384** was characterized on the basis of ^1H and ^{13}C - NMR spectra. The methoxy protons resonated as singlet at 3.82 ppm and methyl carbon at 53.0 ppm. The presence of methyl protons at 2.26 ppm as a singlet and carbon at 28.7 ppm confirmed the structure.

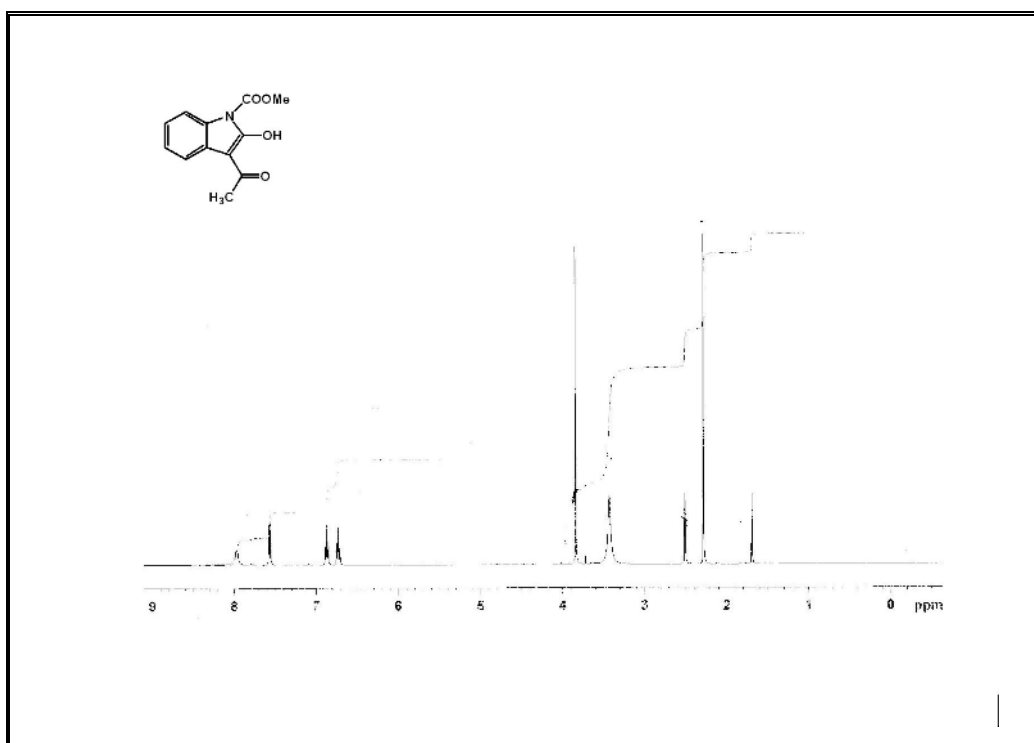


Figure 17. The ¹H-NMR spectrum of the compound **383**.

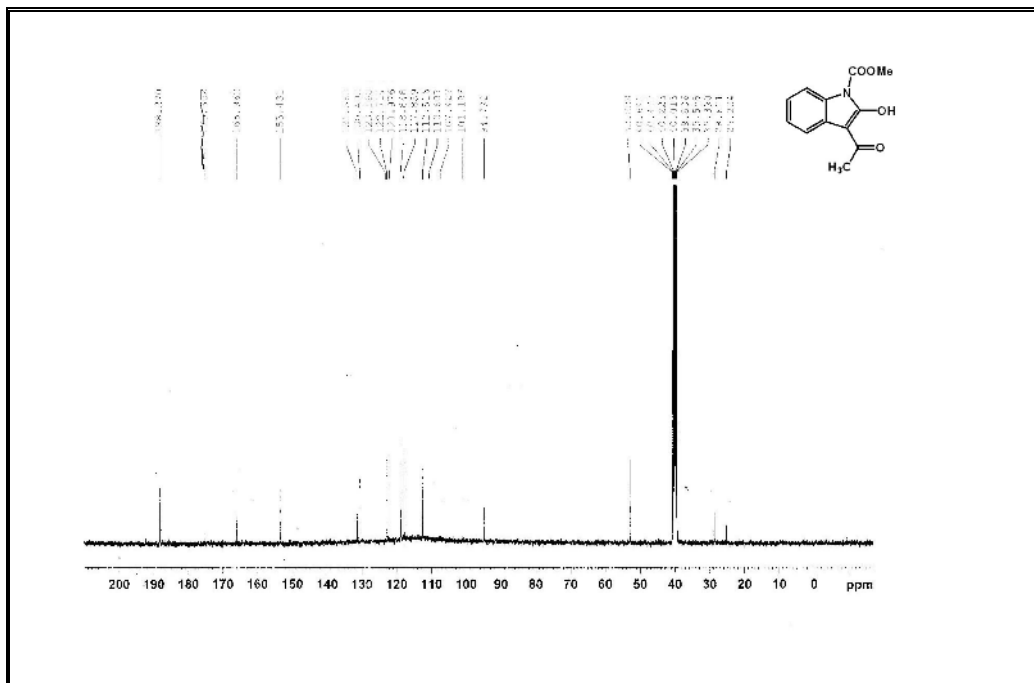
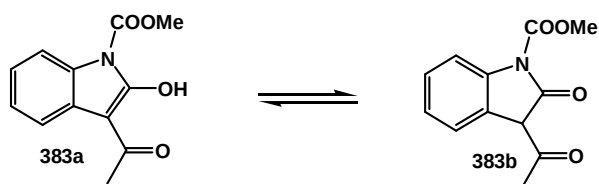


Figure 18. The ¹³C-NMR spectrum of the compound **383**.

The compound **383** can exist in two tautomeric forms **383a** and **383b**, which can be distinguished with the help of NMR and IR spectroscopy.



Scheme 14. Tautomeric forms of the compound **383**.

The comprehensive evidence for the structure **383** comes from ^{13}C -NMR spectrum of **387**, which includes the carbon attached to hydroxyl at 165.8 ppm and the 3-acetyl carbonyl carbon, which is a α,β -unsaturated carbonyl at 188.2 ppm, respectively. These two resonances clearly shows the existence of **383** in the form **383a**. Also the $-\text{OH}$ signal around 3500 cm^{-1} supports the form **383a**.

The elemental analysis results showed the incorporation of chloroform into **387**. We have three different analysis results from three different laboratories which are in accordance with the solvent corrected results. 0.845 moles of CHCl_3 incorporation was calculated.

Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{NO}_4$: C, 61.80; H, 4.75; N, 6.01

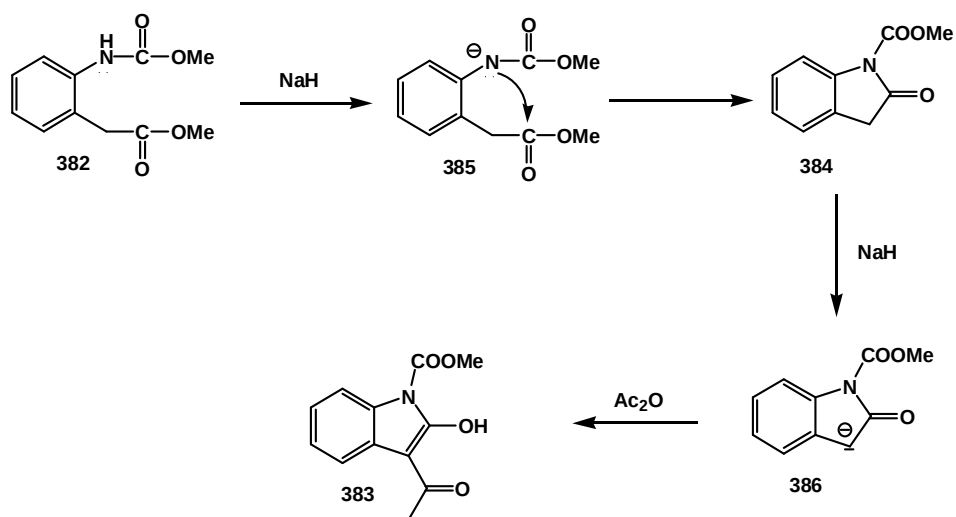
Found: C, 44.45; H, 3.74; N, 3.64. (Metu Central Laboratory)

Found: C, 46.67; H, 3.48; N, 3.72. (ATAL).

Found: C, 46.18; H, 3.83; N, 3.84. (Atatürk University)

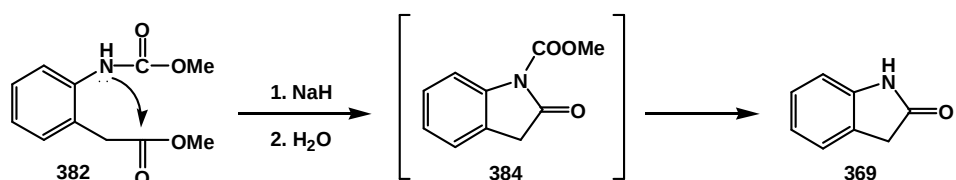
Solvent corrected result: C, 46.18; H, 3.57; N, 4.19

For the formation of the indole derivatives **383** and **384** the following mechanism is suggested. (Schem 15) The base, H^- anion first abstracts the $-\text{NH}$ proton forming the anion **389**, which attacks to the carbonyl carbon of the ester giving the oxindole **384**. Abstraction of the α -proton in **384** followed by the reaction of the carbanion **386** with acetic anhydride results in the formation of **383**.



Scheme 15. Suggested mechanism for the formation of **383**.

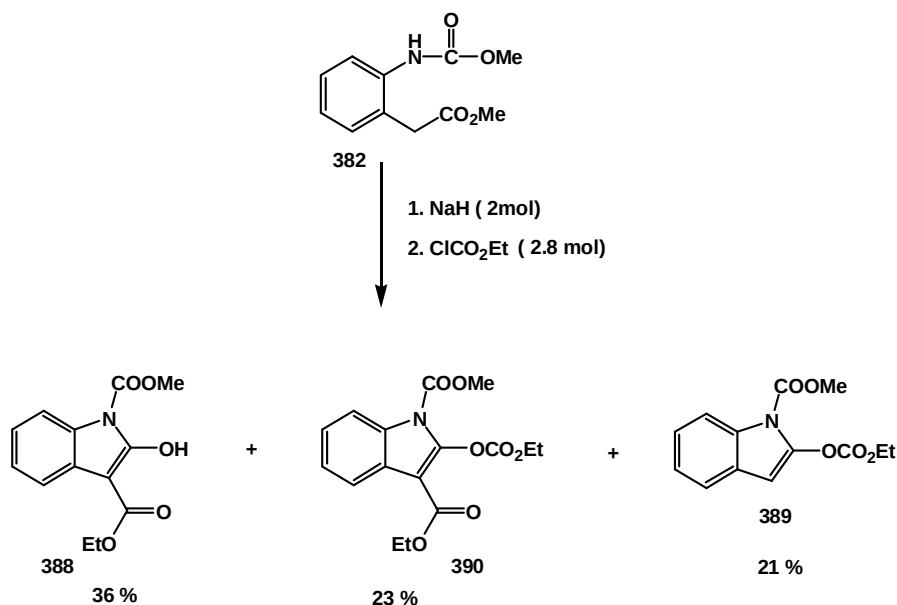
In order to shed light for the formation mechanism of **383** and **384**, the urethane **382** was reacted with sodium hydride in the absence of acetic anhydride. In that case, indalinone **369** was formed as the sole product. We assume that **369** is a secondary product and formed from the hydrolysis of the primarily formed product **384**.



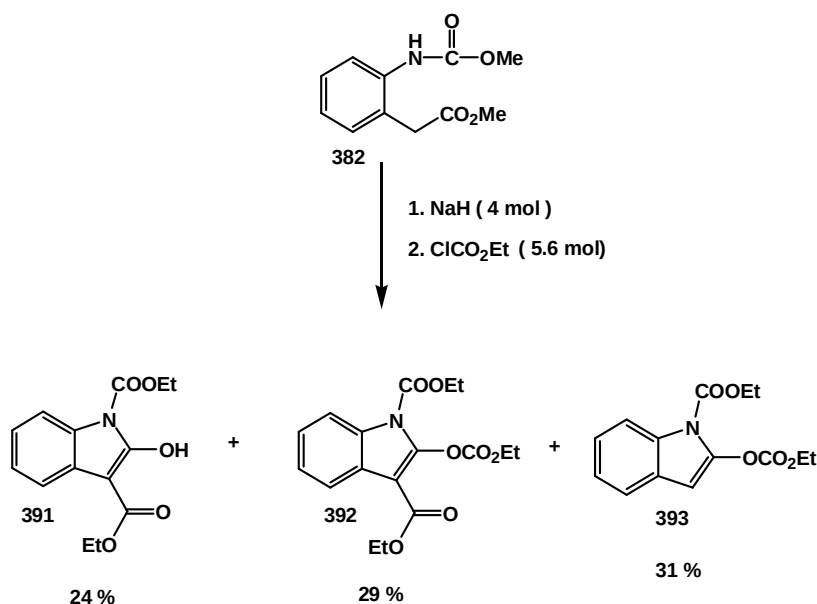
The presence of the hydroxyl group in **383** was also proved by a chemical reaction, in which **383** was treated with triethyl amine and ethyl chloroformate to give the acetylated product **387**. This product **387** was the chemical significance of **383** existing in the tautomeric form **383a**.



The compound **382** was then reacted with 2 moles of sodium hydride and 2.8 moles of ethyl chloroformate, changing the acetylation reagent to ethyl chloroformate and increasing the molar amount of acetylation agent twice. This time besides the carbon acetylated derivative **388**, two additional products were formed, oxygen acetylated **389** and diacetylated products **390**.

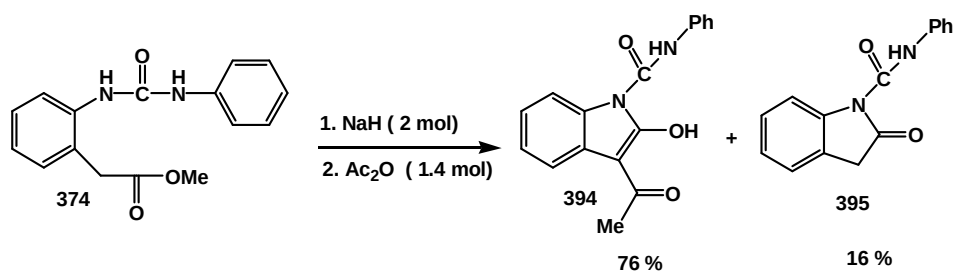


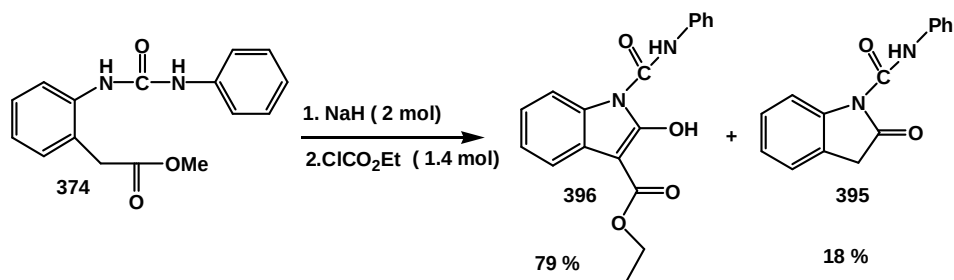
As a next trial, the molar amount of sodium hydride and ethyl chloroformate was doubled and the reaction was run under the same conditions. Because of additional base and ethylchloro formate, for the products **388**, **390** and **389** the methyl ester groups were changed into ethyl ester groups to give the products **391**, **392** and **393**, respectively. The excess base caused the removal of methyl ester and further attack of the lone pairs of nitrogen onto the ethyl chloroformate produced the detected compounds.



The products were easily characterized on the basis of ¹H and ¹³C-NMR, the methoxide protons and carbon were not observed any more. The additional ethyl groups gave rise to a triplet and quartet, whereas also methylene and methyl carbon were observed.

To test the scope and limitations of this method, the urethane **374** was subjected to the reaction in the presence of sodium hydride and acetylation reagents acetic anhydride or ethyl chloroformate under the same reaction conditions. The structures of the formed products were determined by means of spectral data. (¹H and ¹³C-NMR, IR, Mass, elemental analysis). They have been identified as indole **394** and **396** and indalinone derivative **395**.

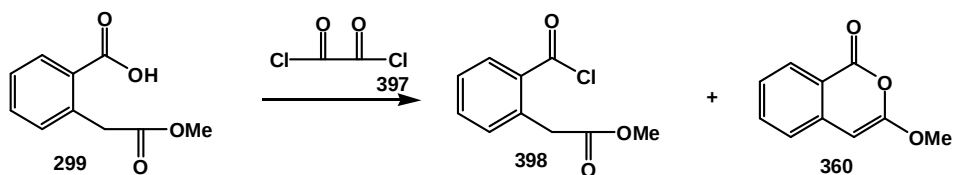




2.8. The synthesis of methyl [2-(chlorocarbonyl)phenyl]acetate (**398**) and its chemistry.

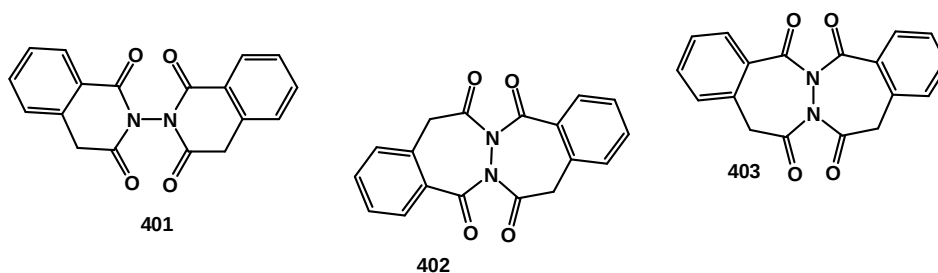
For the generation of nitrogen-containing seven-membered rings we turned our attention to the synthesis of acyl chloride **398** and its chemistry.

The half ester **299** was chlorinated with oxalyl chloride **397** following the way of Padwa *et al.*¹⁴⁸ The two products **398** and **360** were formed.

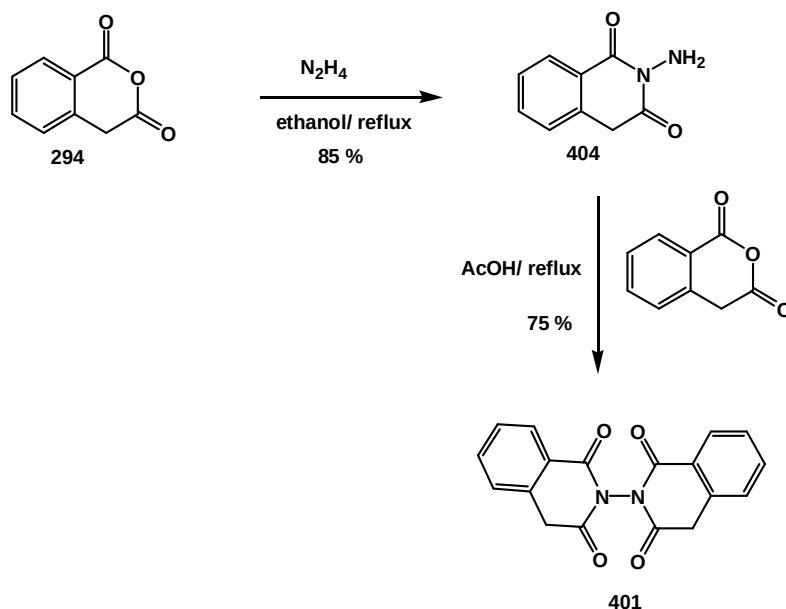


The formed compounds **398** and **360**, which were obtained in 3:2 molar ratio were not separated because of the possible hydrolysis of the acyl chloride **398** on any column material. Through the solution of the mixture ammonia gas was passed, the trapped amide **399** was separated in 54 % by crystallization of the reaction mixture from dichloromethane. The amide **399** was characterized on the basis of physical and spectral (¹H and ¹³C-NMR, IR, elemental analysis.) data. The methoxyl isocoumarine **360** was obtained in 38 % yield. After successful transformation of **398** from the mixture into the amide **399**, we reacted this mixture consisting of **398** and **360** with anhydrous hydrazine in dichloromethane at room temperature expecting a ring closure to give the seven membered benzodiazepine derivative **400**. According to the ¹H and ¹³C-NMR spectra the obtained product was not **400**, because no –NH protons

were detected in the ^1H -NMR spectrum. The mass spectrum of the formed product indicated the formation of a dimeric product. There were three possible dimerization products **401**, **402** and **403**, which cannot be distinguished from each other on the basis of spectral data.



Rosen *et al.* have already synthesized the dimeric product **401** from the reaction of homophthalic anhydride **294** and isoquinoline derivative **404** in refluxing ethanol.¹⁵⁰ The characterization of **400** was carried out by IR, elemental analysis and mass spectrum. Since it is an early literature, no NMR experiment was performed.

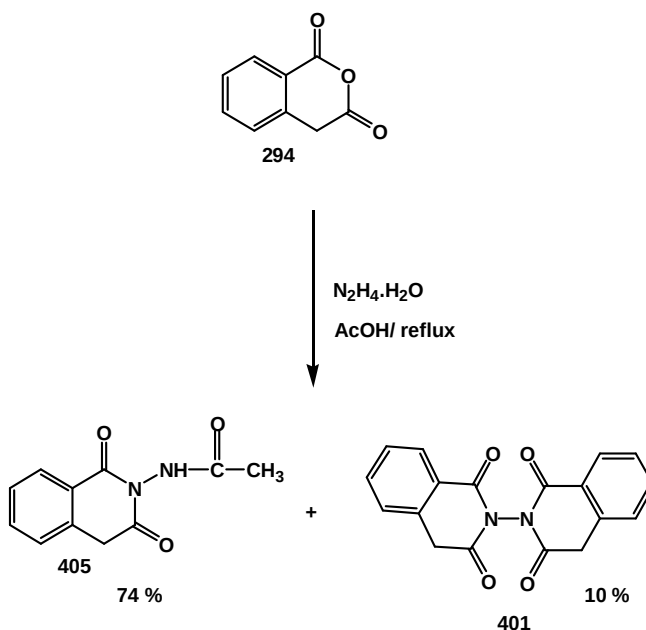


Due to the absence of the NMR spectral data, it was decided to react the isoquinoline derivative **404** and the lactone **294** under the same reaction conditions in order to see

whether the NMR spectra of the obtained product would match with the NMR spectra of our dimerization product **401** or not. Then we synthesized **404** from the lactone **294** by refluxing it with hydrazine in ethanol and reacted the isoquinoline **404** with the lactone **294** to obtain the dimeric product **401**. The ^1H -NMR spectrum of **401** was the same as the ^1H -NMR spectrum of the product that had already been obtained from the reaction of acyl chloride **398** with anhydrous hydrazine.

2.8.1. Synthesis of new isoquinoline derivative (406)

The lactone **294** was reacted with hydrazine monohydrate in refluxing acetic acid and yielded the products **405** as the major and **404** as the minor product



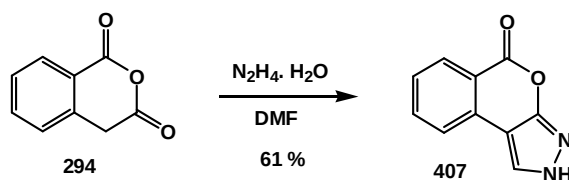
For further acetylation of **405**, it was submitted to a reaction with triethyl amine and ethyl chloroformate to yield the diacetylated product **406**.



The product **406** was characterized on the basis of ^1H and ^{13}C NMR spectra. The observation of two different ethyl protons and carbons indicated the presence of two different acetylated positions. The loss of acidic proton of **403** and formation of a new double bond proton at 6.65 ppm signaled the N-acetylation and O-acetylation, respectively.

2.8.2. Reaction of Homophthalic anhydride with hydrazine in refluxing DMF: Synthesis and characterization of the pyrazole derivative **407**.

After failure of the reaction of anhydride **294** with hydrazine to give a cyclization product of type **400**, we decided to change the reaction conditions. Therefore, homophthalic anhydride **294** was refluxed with hydrazine in dimethylformamide. A single product was formed. Unfortunately, the ^1H and ^{13}C - NMR spectral data did not indicate the formation of the expected cyclization products such as **400**, **402** or **403**. Detailed NMR analysis (COSY, DEPT, HMBC and HMQC) revealed the formation of a pyrazole derivative **407**.



The ^1H NMR spectrum consists of three sets of protons; four aromatic protons resonating as triplet at 7.49 ppm, triplet at 7.84 ppm, doublet at 7.92 ppm, doublet at 8.17 ppm, double bond proton as sharp singlet at 8.46 ppm and acidic proton as

broad singlet at 13.1 ppm. The low-field signal at 8.46 and increase in the number of carbon resonances strongly supported that dimethylformamide did not only act as solvent but also acted as a reaction reagent and was incorporated into the molecule. An HMBC experiment of **407** confirmed this structure especially by the strong correlation of the low field resonating proton H-1 with the quaternary carbons C-9b ($^2J_{CH}$) at 100 ppm and C-3a ($^3J_{CH}$) at 157.3 ppm. All the other proton and carbon signals are in accordance with the structure.

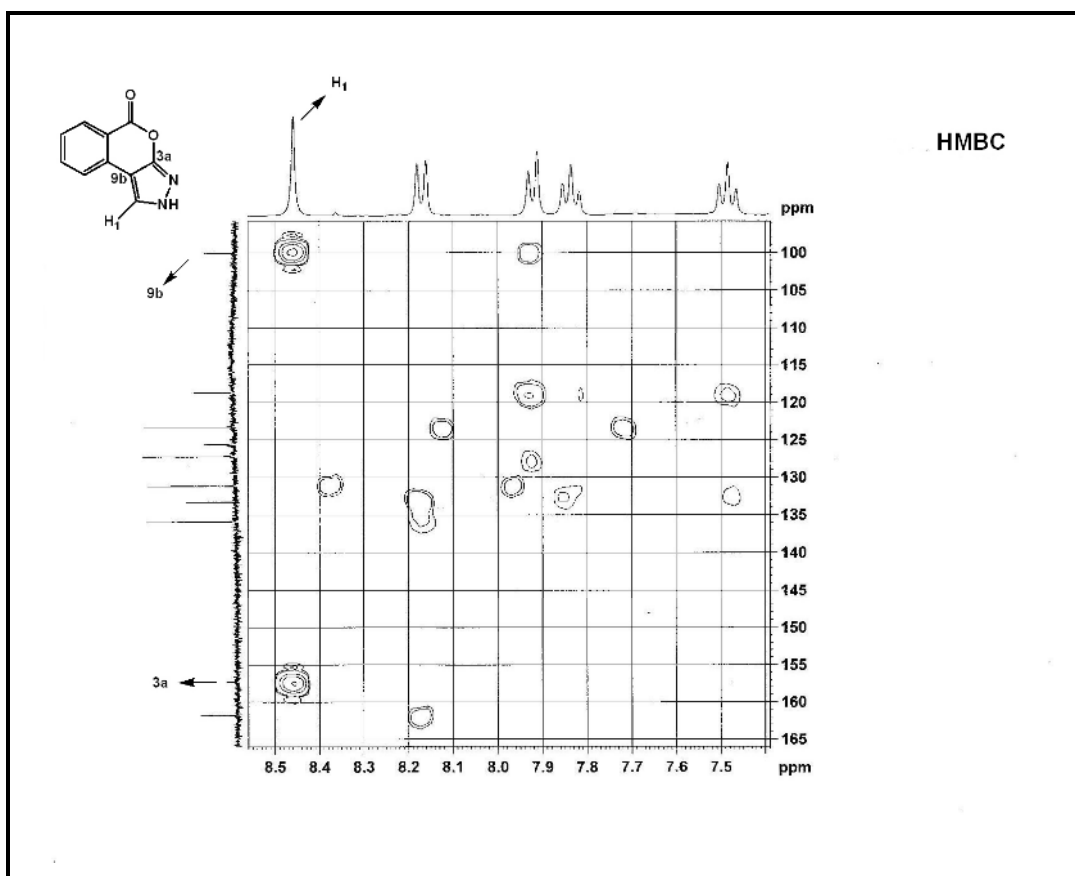
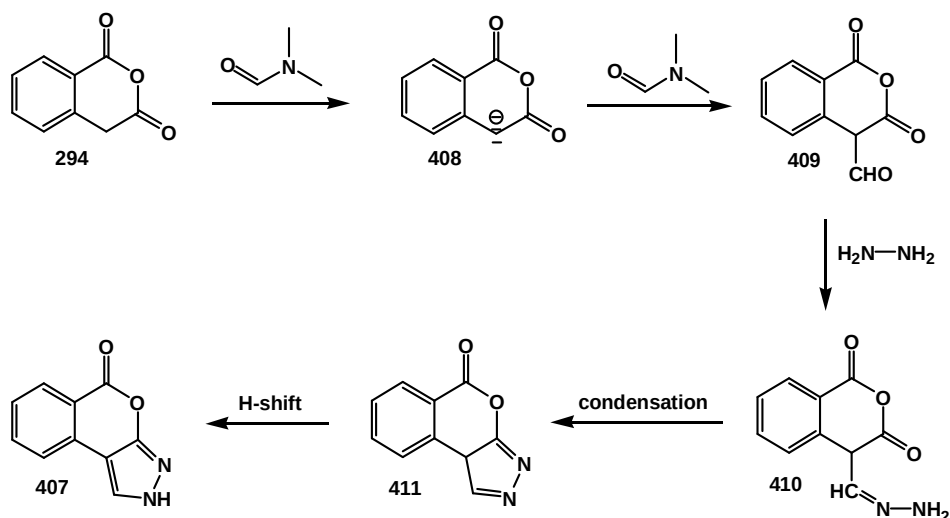


Figure 19: A part of HMBC experiment of the compound **407**.

Our suggested mechanism is shown in Scheme 16. According to this mechanism; firstly the generated carbanion **408** attacks the carbonyl group of dimethylformamide and forms the ketoaldehyde **409**. Reaction of **410** with hydrazine and further condensation followed by H-shift produces pyrazole **407**.

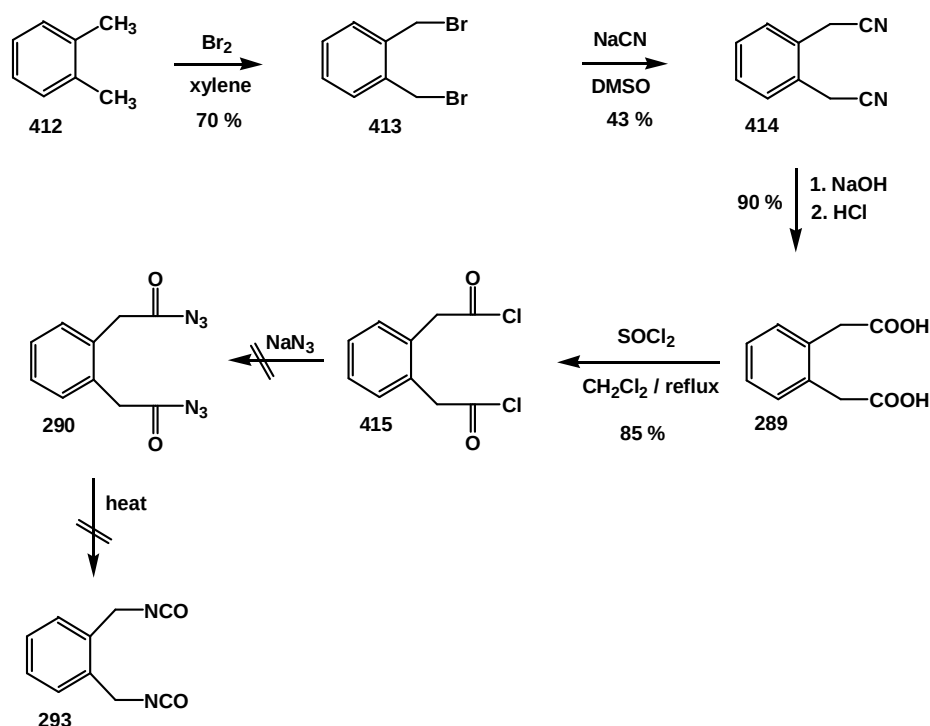


Scheme 16. Suggested mechanism for the formation of the compound **407**.

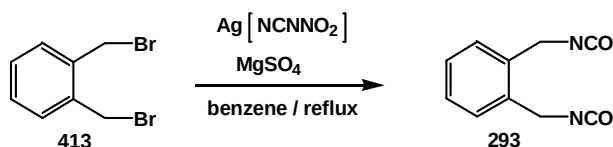
2.9. The chemistry of bishomophthalic acid (**289**)

In the last part of this thesis we decided to use bishomophthalic azide **290** to construct the benzodiazepinone skeleton. In our research for the synthesis of benzodiazapines a different method, going through the corresponding isocyanates, was followed. This synthesis path was started with high temperature bromination of *o*-xylene **412**, which was then followed by the transformation of the bromine groups **413** into cyanide groups with sodium cyanide in a polar solvent, dimethyl sulfoxide. Next, it was possible to synthesize the proposed diacid **289** by hydrolysis reaction from which the diacyl chloride **415** was obtained by refluxing with thionyl chloride in dichloromethane. In the next step it was proposed to synthesize the diacylazide **290** from this diacyl chloride **415** by using sodium azide, but this step failed. Because of the water used to dissolve sodium azide, the reaction underwent hydrolysis reaction, yielding back the diacid **289**. So, by using this path it was not possible to reach the corresponding diisocyanate, which would be used in the synthesis of benzodiazapines. Another disadvantage of this synthesis path was the

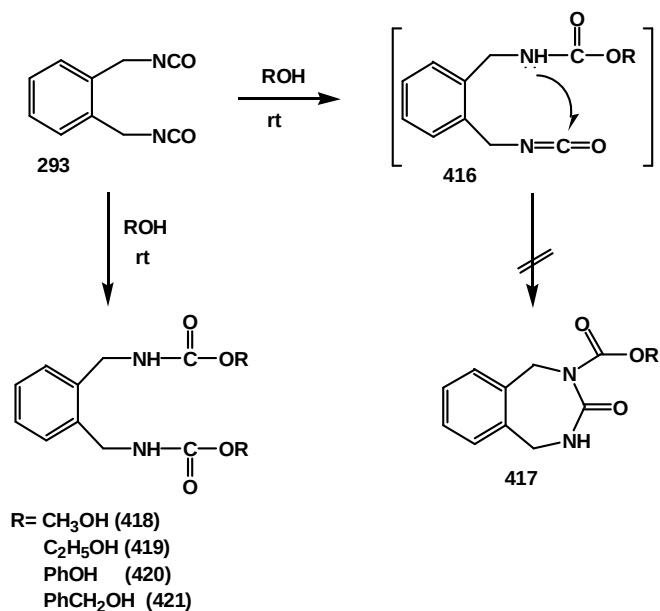
reasonable low yield synthesis of the cyanide compound **414**.



The diisocyanate **293** was obtained by a method from the literature by using silver salt in the presence of magnesium sulfate directly from the bromide **412**.¹³³

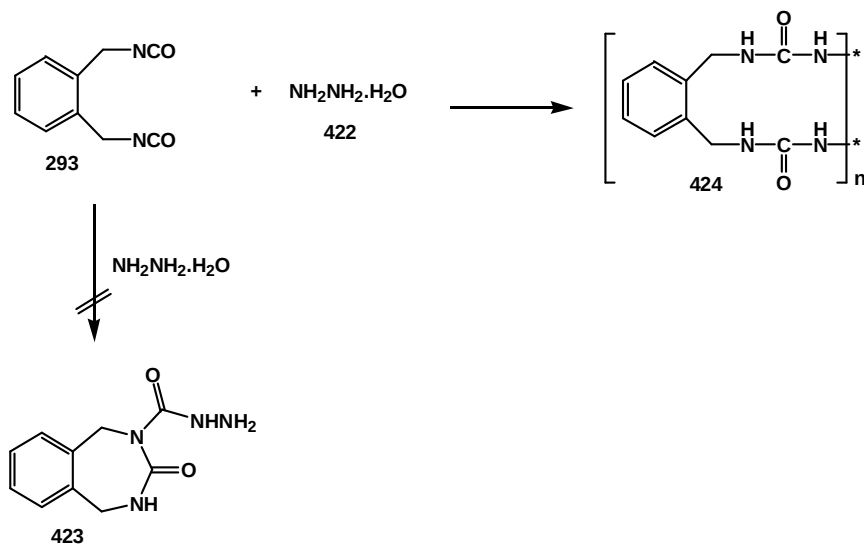


The diisocyanate **293** was then treated with equal mole of alcohols expecting the alcohol would transform one of the isocyanate groups into urethane **416** and then the lone pairs on the nitrogen would attack to the other isocyanate group, resulting a ring closure. But the reaction did not follow the expected route. Because both of the isocyanate groups showed the same reactivity, instead of a benzodiazapine derivative **417** a diurethane compounds **418**, **419**, **420** and **421** was obtained in good yield.



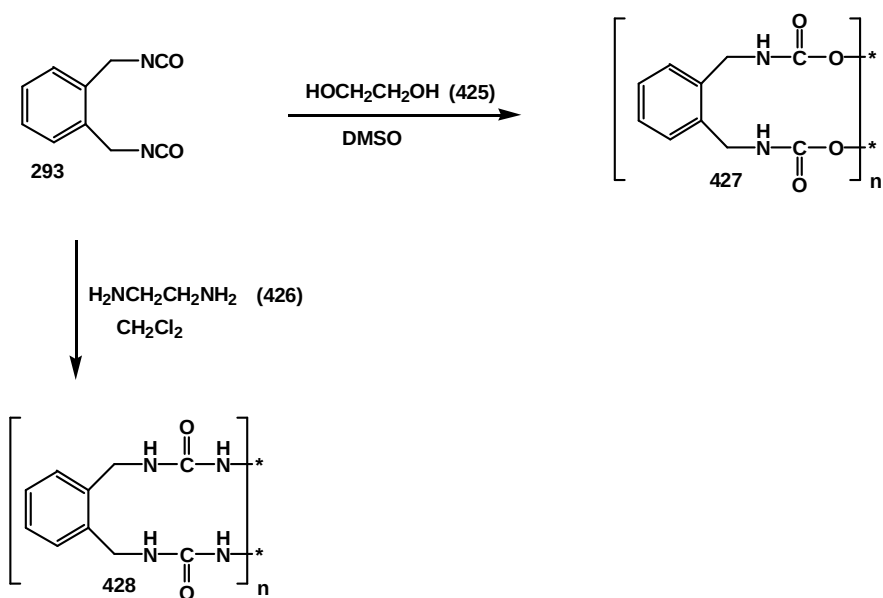
2.9.1. Synthesis of polyurethanes

Our attempts for the synthesis of benzodiazapines went on by trapping the diisocyanate **293** with hydrazine monohydrate **422** under the expectations of a ring closure. This reaction also failed, but the obtained product, **424** was characterized to be a polyurethane derivative and this case opened up a new entry for our research. We remarked that the isocyanate **293** could be used in the synthesis of polyurethanes.



The application of difunctional diisocyanates in the field of polymer chemistry led in the last decade to the successful preparation of many novel polymers. The search for new types of reaction of isocyanates as well as new isocyanates, can be used to synthesize polymers is a continuing challenge for chemists. The addition polymerization of diisocyanates with alcohols was first discovered by Boyer and coworkers in 1937.¹⁵⁰ There are a lot of literature concerning the synthesis of polyurethanes, which are used as coatings, adhesives, rubber vulcanizates. They are also used in the area of construction, otomobiles, liquid crystals and medicine.¹⁵¹

We nextly tried to conduct the polymerization reaction of diisocyanate **293** with ethylene glycol **425** and ethylenediamine **426** at room temperature. As expected, these two reagents **425** and **426** let the diisocyanate **293** to polymerize, yielding the polyurethanes **427** and **428**, respectively.



Further polymerization reactions are already planned for the future.

CHAPTER 3

3. EXPERIMENTAL

3.1. General Consideration

Nuclear Magnetic resonance (^1H -, ^{13}C - and 2D-) spectra were recorded on a Bruker Instruments Avance Series-Spectrospin DPX-400, Ultra Shield(400, 100 and 376.3 MHz for (^1H -, ^{13}C - nuclei), High Performance digital FT-NMR spectrometer with TMS and TFA ($\delta_{\text{CFCl}_3} = \delta_{\text{TFA}} -76.8$ ppm) as the internal and external standarts respectively, and the upfield as negative. Coupling constants (J values) are reported in Hertz (Hz), and spin multiplicities are indicated by following symbols; s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet).

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

UV spectra were recorded on a Hewlett-Packard 845-2A diodearray spectrometer.

Column chromatographic separations were performed by using Fluka Silikagel 60 (particle size 0.060-0.200 mm). The relative proportions of solvents refer to volume: volume ratio. Routine thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Fluka.

3.2. The synthesis of 1*H*- isochromene-1,3-(4*H*)-dione (298).

Homophthalic acid (9.3 g, 50mmol) was suspended in dichloromethane (150 ml) and thionyl chloride (14.5 ml, 200 mmol) was added into this suspension. The mixture was refluxed overnight and the solvent and excess thionyl chloride was evaporated under vacuum pressure to give **298**. (8.4g, 98 %).

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

¹H-NMR Spectrum: (400 MHz, CDCl₃) □ 8.22 (br d, $J_{87} = 7.8$ Hz, 1H, H-8), 7.70 (br dd, $J_{78} = 7.8$ Hz, $J_{76} = 7.6$ Hz, 1H, H-7), 7.52 (br t, $J_{67} = J_{65} = 7.6$ Hz, 1H, H-6), 7.35 (br d, $J_{56} = 7.6$ Hz, 1H, H-5), 4.14 (s, 2H, -CH₂).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) □ 165.0 (s, C-3), 161.3 (s, C-1), 135.9 (d, C-6), 134.7 (s, C-4a), 131.3 (d, C-8), 129.1 (d, C-7), 127.9 (d, C-5), 121.9 (s, C-8a), 34.7 (t, -CH₂).

Anal. Calcd for C₉H₆O₃ : C, 66.67; H, 3.73 Found: C, 66.48; H, 4.06.

3.2.1. The synthesis of 2-(2-methoxy-2-oxoethyl)benzoic acid (299):

The lactone **298** (6g, 37mmol) was refluxed in methanol (50ml) for 2 hours. The solvent was concentrated to give the pure **299**. (6.1g, 85 %). Yellow crystalline compound mp. 98°C (lit.) 99-101° C (found).

299¹⁵³: **¹H-NMR Spectrum:** (400 MHz, CDCl₃) □ 11.0 (br s, 1H, -OH), 8.17 (dd, $J_{65} = 7.8$ Hz, $J_{64} = 1.3$ Hz, 1H, H-6), 7.56 (dt, $J_{45} = J_{43} = 7.6$ Hz, $J_{4,6} = 1.3$ Hz, 1H, H-4), 7.43, (dt, $J_{56} = 7.8$ Hz, $J_{54} = 7.6$ Hz, $J_{53} = 0.9$ Hz, 1H, H-5), 7.30 (d, $J_{34} = 7.6$ Hz, 1H, H-3).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) □ 172.3 (s, ester carbonyl), 171.9 (s, acid carbonyl), 136.8 (s, C-2), 133.3 (d, C-6), 132.4 (d, C-4), 131.9 (d, C-3), 128.6 (s, C-1), 127.6 (d, C-5), 51.9 (t, -OCH₃), 40.6 (t, -CH₂).

3.2.2. The synthesis of methyl 2-(2-methoxy-2-oxoethyl)benzoate (**300**).

Homophthalic acid (1.2g, 6.7mmol) was dissolved in methanol (25ml) and at 35°C thionyl chloride (1.8g, 15mmol) was added to this solution dropwise. The mixture was then let to reflux overnight. The solvent was concentrated under vacuo and the residue was dissolved in ether (50ml) and washed with water (2x50ml) and sodiumbicarbonate solution (2x50ml) and dried over calcium chloride. Ether was evaporated and yielded the viscos yellow liquid **300**. (1.1g, 80 %).

300¹⁵⁴ : **¹H-NMR Spectrum:** (400 MHz, CDCl₃) δ 7.93 (dd, $J_{65} = 7.8$ Hz, $J_{64} = 1.4$ Hz, 1H, H-6), 7.38 (dt, $J_{45} = J_{43} = 7.5$ Hz, $J_{46} = 1.5$ Hz, 1H, H-4), 7.26 (dt, $J_{56} = 7.8$ Hz, $J_{54} = 7.5$ Hz, $J_{53} = 1.3$ Hz, 1H, H-5), 7.16 (br d, $J_{34} = 7.5$ Hz, 1H, H-3), 3.94 (s, 2H, -CH₂), 3.77 (s, 3H, -OCH₃), 3.59 (s, 3H, -OCH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 170.9 (s, ester carbonyl), 166.5 (s, ester carbonyl), 134.9 (s, C-2), 131.4 (d, C-4), 131.3 (d, C-6), 130.0 (d, C-3), 128.7 (s, C-1), 126.4 (d, C-5), 51.0 (q, -OCH₃), 50.9 (q, -OCH₃), 39.5 (t, -CH₂).

3.3. The synthesis of 6H-dibenzo[*c,h*]chromen-6-one (**307**).

In a 25 ml dropping funnel, benzene (5 mL), dimethyl formamide (2 mL, 20.4 mmol) and thionyl chloride (1.6 mL, 22 mmol) were consecutively added, after 3-5 min two phases were separated and the lower layer was added to a suspension of the homophthalic acid **3** (1.8 g, 10 mmol), sodium azide (2.6g, 40 mmol), tetrabutylammonium bromide (0.6 g, 2 mmol) and pyridine (3.2 ml, 40 mmol) in dichloromethane (50ml). The mixture was then refluxed overnight and washed with saturated sodiumbicarbonate solution (3x50 mL) and water (2x25 mL). The organic phase was dried over magnesium sulfate and removed under reduced pressure. The residue was purified with column chromatography (Silca gel, CHCl₃) to give yellow crystals **8** (0.5 g, mp, 191.5-192.5, lit. mp. 179-180°C¹³⁷) in 41% yield. The product was crystallized from ethylacetate.

307¹³⁷: ¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.60 (dd, $J_{78}=7.9$ Hz, $J_{79}=1.2$ Hz, 1H, H-7), 8.49 (dd, $J_{43}=7.9$ Hz, $J_{42}=1.2$ Hz, 1H, H-4), 8.21 (br. d, $J_{12}=8.1$ Hz, 1H, H-1), 8.08 (d, $J_{12,11}=8.8$ Hz, 1H, H-12), 7.89 (ddd, $J_{23}=7.3$ Hz, $J_{21}=8.1$ Hz, $J_{24}=1.2$ Hz, 1H, H-2), 7.87 (dd, $J_{10,9}=8.1$ Hz, $J_{10,8}=1.4$ Hz, 1H, H-10), 7.78 (d, $J_{11,12}=8.8$ Hz, 1H, H-11), 7.65 (ddd, $J_{87}=7.9$ Hz, $J_{89}=6.9$ Hz, $J_{810}=1.4$ Hz, 1H, H-8), 7.63 (dd, $J_{98}=6.9$ Hz, $J_{9,10}=8.1$ Hz, 1H, H-9), 7.61 (dd, $J_{34}=7.9$ Hz, $J_{32}=7.3$ Hz, 1H, H-3).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 161.2 (s, carbonyl), 147.4 (s, C-4b), 135.5 (s, C-10a), 134.9 (d, C-9), 134.3 (s, C-12a), 130.7 (d, C-4), 128.6 (d, C-3), 127.9 (d, C-8), 127.7 (d, C-2), 127.2 (d, C-10), 124.5 (d, C-11), 123.9 (s, C-6a), 122.4 (d, C-7), 122.1 (d, C-1), 121.3 (s, C-10b), 119.2 (d, C-12), 113.1 (s, C-4a).

3.3.1. The synthesis of (4Z)-4-[(dimethylamino)methylene]-1H-isochromene-1,3(4H)-dione (327).

In a 25 ml dropping funnel, benzene (5mL), dimethyl formamide (2mL, 20.4mmol) and thionyl chloride (1.6mL, 22mmol), were consecutively added, after 3-5 min two phases were separated and the lower layer was added to a suspension of the homophthalic acid (1.8g, 10mmol), tetrabutylammonium bromide (0.6g, 2mmol) and pyridine (3.2mL, 40mmol) in dichloromethane (50mL). The mixture was then refluxed overnight and washed with aqueous HCl solution (2x50mL), water (2x50mL) and aqueous sodiumbicarbonate solution (2x50mL). The organic phase was dried over magnesium sulfate and removed by vacuo. The residue was chromatographed (Silica gel, ethyl acetate) to give the product **10** as yellow solid (1.5g) in 69% yield (mp.156-157°C, lit. mp. 144-145°C). The product was crystallized from ethylacetate:hexane (8:2).

327¹⁴²: ¹H-NMR Spectrum: (400 MHz, DMSO-d₆, 65°C) δ 8.34 (br s, 1H, H-1), 7.96 (br d, $J_{56}=7.8$ Hz, 1H, H-5), 7.59 (br dd, $J_{65}=7.8$ Hz, $J_{67}=7.4$ Hz, 1H, H-6), 7.53 (br d, $J_{87}=8.2$ Hz, 1H, H-8), 7.18 (br t, $J_{78}=8.2$ Hz, $J_{76}=7.4$ Hz, 1H, H-7), 3.34 (s, 6H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, DMSO-d₆, 65°C) δ 163.5 (d, C-1), 159.2 (s, C-1, carbonyl), 157.9 (s, C-3, carbonyl), 140.5 (s, C-4a), 135 (d, C-6), 129.9 (d, C-8), 123.7 (d, C-5), 120.7 (d, C-7), 116.4 (s, C-8a), 86.8 (s, C-4), 46.2 (q, -CH₃).

3.3.2. The synthesis of Methyl-1-Oxo-1*H*-isochromene-4-carboxylate (328).

The product **327** (0.7 g, 3 mmol) was dissolved in 20 mL methanol and dry HCl gas produced from sulfuric acid and sodium chloride was passed slowly through this solution. After the saturation was completed, it was refluxed for 2 hours. The solvent was removed and water was added to the residue which was then extracted with the chloroform (3x10 mL). The combined extracts were dried over magnesium sulfate and the solvent was removed at reduced pressure yielding the product **328** as a white solid which was crystallized from methanol (mp. 97-98°C, 0.5g, 76 %).

328¹⁴²: ¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.6 (br d, *J*₈₇ = 8.0 Hz, 1H, H-8), 8.33 (br d, *J*₅₆ = 7.9 Hz, 1H, H-5), 8.20 (s, 1H, -CH), 7.82 (ddd, *J*₆₅ = 7.9 Hz, *J*₆₇ = 7.5 Hz, *J*₆₈ = 1.2 Hz, 1H, H-6), 7.59 (br dd, *J*₇₈ = 8.0 Hz, *J*₇₆ = 7.5 Hz, 1H, H-7), 3.92 (s, 3H, -OCH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 164.5 (s, ester carbonyl), 160.7 (s, lactone carbonyl), 152.6 (d, C-3), 135.4 (d, C-6), 133.5 (s, C-4a), 130.0 (d, C-8), 129.0 (d, C-7), 125.4 (d, C-5), 120.5 (s, C-8a), 110.0 (s, C-4), 52.1 (q, -OCH₃).

3.4. The synthesis of the compounds 4'-Chloro-1*H*,1'*H*-3,4'-biisochromene-1,1',3'(4'*H*)-trione (332), Ethyl 6-oxo-6*H*-dibenzo[*c,h*]chromen-11-yl carbonate (333), 3-(3-oxo-1,3-dihydro-2-benzofuran-1-yl)-1*H*-isochromen-1-one (334) and Ethyl 2-oxo-1,2-dihydro-3,1-benzoxazepin-4-yl carbonate (335).

To a solution of homophthalic acid (10g, 56mmol) in 40mL THF at -5°C, a solution of triethylamine (12ml, 87mmol) in 25ml THF was added dropwise and the mixture was stirred for 30 min. This was followed by slow addition of a cooled solution of

ethylchloroformate (12ml, 130mmol) in 25ml THF and the reaction mixture was stirred at the same temperature for 30 min. A solution of sodium azide (14g, 215mmol) in 50mL water was then added dropwise and the mixture was let to stir at room temperature overnight. The product **332** (2.5g) which precipitated from the reaction medium was separated by filtration and the filtrate was extracted with two portions of ethyl acetate (50mL). The organic phase was then washed with saturated sodiumbicarbonate solution (3x75mL) and with water (2x50mL) and dried over magnesium sulfate. By the removal of ethyl acetate under reduced pressure a mixture of the products **333**, **334** and **335** (2.95g) was obtained. When the mixture was dissolved in CHCl_3 , the compound **334** precipitated and was filtered off. The filtrate was concentrated in vacuo and the mixture was chromatographed over silica gel eluting with CH_2Cl_2 . The first fraction **333** was identified as the dibenzochromen-6-one derivative **333**. As the second fraction **335** was isolated.

332: Green solid, 2.5g, decomposition at 227-228°C. The product is darkening at room temperature.

^1H -NMR Spectrum: (400 MHz, DMSO-d_6) δ 8.03 (br d, $J_{87} = 7.7$ Hz, 1H, H-8), 7.76 (dd, $J_{8'7'} = 7.8$ Hz, and $J_{8'6'} = 1.1$ Hz, 1H, H-8'), 7.70 (dt, $J_{67} = J_{65} = 8.0$ Hz, and $J_{68} = 1.1$ Hz, 1H, H-6), 7.48 (br d, $J_{56} = 8.0$ Hz, 1H, H-5), 7.41 (br d, $J_{5'6'} = 8.2$ Hz, 1H, H-5'), 7.36 (br dd, $J_{78} = 7.7$ Hz, $J_{76} = 8.0$ Hz, 1H, H-7), 7.29 (ddd, $J_{6'5'} = 8.2$ Hz, $J_{6'7'} = 7.8$ Hz, and $J_{6'8'} = 1.2$ Hz, 1H, H-6'), 6.89 (br s, 1H, H-4), 6.73 (br t, $J_{7'6'} = J_{7'8'} = 7.8$ Hz, 1H, H-7').

^{13}C -NMR Spectrum: (100 MHz, DMSO-d_6) δ 165.5 (s, C-1'), 163.6 (s, C-1), 160.6 (s, C-3'), 156.6 (s, C-3), 143.6 (s, C-4a'), 140.4 (s, C-4a), 135.4 (d, C-6), 134.1 (d, C-6'), 129.7 (d, C-8'), 129.1 (d, C-8), 126.5 (d, C-7), 125.8 (d, C-5), 121.1 (d, C-5'), 118.8 (d, C-7'), 118.6 (s, C-8a), 113.5 (s, C-8a'), 103.8 (d, C-4), 80.2 (s, C-4').

Anal. Calcd for $\text{C}_{18}\text{H}_9\text{ClO}_5$: C, 63.45; H, 2.66 Found: C, 62.43; H, 3.32.

IR (KBr, cm^{-1}): 2927, 1723, 1699, 1628, 1600, 1563, 1481, 1356, 1325, 1283, 1238, 1154, 1079, 1060, 1030, 970, 832, 757, 690, 670, 513.

333: 880 mg, 9.6% yellow solid, mp. 174-175°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.69 (dd, $J_{78} = 8.0$ Hz, $J_{79} = 0.7$ Hz, 1H, H-7), 8.5 (dd, $J_{10,9} = 8.1$ Hz, $J_{10,8} = 1.5$ Hz, 1H, H-10), 7.98 (dd, $J_{43} = 8.2$ Hz, $J_{42} = 0.9$ Hz, 1H, H-4), 7.89 (dd, $J_{12} = 7.0$ Hz and $J_{13} = 1.5$ Hz, 1H, H-1), 7.86 (ddd, $J_{87} = 8.0$ Hz, $J_{89} = 7.8$ Hz, and $J_{58} = 1.5$ Hz, 1H, H-8), 7.76 (s, 1H, H-12), 7.64 (dt, $J_{9,10} = J_{98} = 8.1$ Hz, and $J_{79} = 1.1$ Hz, 1H, H-9), 7.6 (dt, $J_{12} = J_{23} = 7.0$ Hz and $J_{24} = 1.5$ Hz, 1H, H-2), 7.56 (ddd, $J_{34} = 8.2$ Hz, $J_{32} = 7.0$ Hz, and $J_{31} = 1.5$ Hz, 1H, H-3), 4.38 (q, $J = 7.0$ Hz, 2H, H-1), 1.41 (t, $J = 7.0$ Hz, 3H, H-2).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 160.8 (s, C-6), 152.8 (s, C-13), 148.7 (s, C-11), 144.7 (s, C-4a), 135.5 (d, C-8), 133.7 (s, C-6a), 133.2 (s, C-12a) 131.3 (d, C10), 129.6 (d, C-9), 128.5 (d, C-2), 127.6 (d, C-1), 126.8 (d, C-3), 126.4 (d, C-7) 125.2 (s, C-4a), 122.5 (s, C-10a), 121.8 (d, C-4), 112.5 (d, C-12), 111.5 (s, C-10b), 66.2 (q, C-19), 14.6 (t, C-20).

MS: 70 eV, m/z; 334 (M⁺, 28%), 289 (25%), 262 (100%), 233 (76%), 204 (22%), 176 (27%).

Anal. Calcd for C₂₀H₁₄O₅ : C, 71.85; H, 4.59; N, 9.52. Found: C, 71.34; H, 4.59.

IR (KBr, cm⁻¹) 3284, 2973, 1753, 1633, 1604, 1488, 1464, 1320, 1266, 1247, 1233, 112.

334: Yellow-brown solid 550 mg (7.1%), mp. 256-257°C.

¹H-NMR Spectrum: (400 MHz, DMSO-d₆) δ 8.13 (br d, $J_{87} = 8.1$ Hz, 1H, H-8), 7.76 (br d, $J_{4'5'} = 7.7$ Hz, 1H, H-4), 7.87 (dd, $J_{67} = 7.2$ Hz, $J_{65} = 7.4$ Hz, $J_{68} = 1.1$ Hz, 1H, H-6), 7.83 (dd, $J_{6'7'} = 7.1$ Hz, $J_{6'5'} = 7.6$ Hz, and $J_{6'8'} = 1.1$ Hz, 1H, H-6'), 7.73 (br d, $J_{56} = 7.4$ Hz, 1H, H-5), 7.70 (br d, $J_{5'4'} = 7.7$ Hz, $J_{5'6'} = 7.6$ Hz, 1H, H-5'), 7.68 (br d, $J_{7'6'} = 7.1$ Hz, 1H, H-7'), 7.64 (dd, $J_{76} = 7.2$ Hz, $J_{78} = 8.1$ Hz, and $J_{75} = 1.1$ Hz, 1H, H-7), 7.14 (s, 1H, H-4), 6.63 (s, 1H, H-1).

¹³C-NMR Spectrum: (100 MHz, DMSO-d₆) δ 170.0 (s, C-3), 161.5 (s, C-1), 150.3 (s, C-3a), 146.6 (s, C-7a), 136.5 (s, C-4a), 135.8 (d, C-6), 131.0 (d, C-6'), 130.4 (d, C-5'), 129.7 (d, C-7), 127.6 (d, C-8), 126.0 (d, C-5), 125.8 (d, C-4), 125.6 (s, C-3), 124.0 (d, C-7'), 121.1 (s, C-8a), 107.7 (d, C-4), 79.0 (d, C-1).

MS: 70 eV, m/z; 279 (M+H⁺, 41%), 278 (100%), 249 (76%), 145 (60%), 117 (39%), 89 (74%).

HRMS: Found : 278.0585; Calculated: 278.0579

Anal. Calcd for C₁₇H₁₀O₄ : C, 73.38; H, 3.62 Found: C; 72.24; H, 3.67.

IR (KBr, cm⁻¹): 3010, 1770, 1727, 1661, 1603, 1487, 1462, 1381, 1346, 1296, 1219, 1187, 1147, 1099, 1053, 1011, 973, 873, 811, 757, 704.

335: Viscous yellow liquid, 750 mg, 10.8%.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.43 (br s, 1H, -NH), 7.93 (br d, *J*₆₇ = 7.6 Hz, 1H, H-6), 7.89 (br d, *J*₉₈ = 7.7 Hz, 1H, H-9), 7.76 (br dd, *J*₈₉ = 7.7 Hz, *J*₈₇ = 7.4 Hz, 1H, H-8), 7.63 (br dd, *J*₇₈ = 7.4 Hz, *J*₇₆ = 7.6 Hz, 1H, H-7), 5.93 (s, 1H, H-5), 4.26 (q, *J* = 7.1 Hz, 2H, -CH₂), 1.31 (t, *J* = 7.1 Hz, 3H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 168.9 (s, C-2), 165.2 (s, C-4), 149.9 (s, ester carbonyl), 143.9 (s, C-9a), 135.3 (d, C-8), 130.5 (d, C-7), 125.9 (d, C-6), 124 (s, C-5a), 123.9 (d, C-9), 77.9 (d, C-5), 62.9 (t, -OCH₂), 14.1 (q, -CH₃).

Anal. Calcd for C₁₂H₁₁NO₅ : C, 57.83; H, 4.45; N, 5.62 Found: C, 57.14; H, 4.39; N, 5.11.

MS Spectrum: 70 eV, m/z; 249 (M⁺, 5%), 145 (6%), 133 (100%), 105 (45%), 89 (10%).

IR (KBr, cm⁻¹): 3285, 2982, 1780, 1721, 1522, 1466, 1286, 11185, 1028, 9122, 749.

3.4.1. The synthesis of methyl 2-[(1-oxo-1*H*-isochromen-3-yl)carbonyl]benzoate (340).

To a suspension of compound **12** (0.48g, 1.4mmol) in acetonitrile (15mL) potassium carbonate (1g, 7.2mmol) and methyl iodide (0.2 g, 1.4mmol) were added. The suspension was stirred at 60°C and the reaction was completed in 1 hour, which was controlled by TLC. The residue was filtered off to remove the excess potassium carbonate. The filtrate was concentrated by vacuo to give the product **8** (0.3 g, 70 %) which was crystallized from methanol:chloroform (1:1).

340: Yellow crystals, mp. 140-141°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.33 (br d, $J_{87} = 7.8$ Hz, 1H, H-8), 8.08 (br d, $J_{6'5'} = 7.7$ Hz, 1H, H-6'), 7.79 (br t, $J_{67} = J_{65} = 7.8$ Hz, 1H, H-6), 7.68 (br t, $J_{4'3'} = J_{4'5'} = 7.4$ Hz, 1H, H-4'), 7.66 (br dd, $J_{5'6'} = 7.7$ Hz, $J_{5'4'} = 7.4$ Hz, 1H, H-5'), 7.62 (br t, $J_{78} = J_{76} = 7.8$ Hz, 1H, H-7), 7.61 (br d, $J_{56} = 7.8$ Hz, 1H, H-5), 7.47 (br d, $J_{3'4'} = 7.4$ Hz, 1H, H-3'), 7.34 (s, 1H, H-4), 3.80 (s, 3H, -OCH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 189.3 (s, ketone carbonyl), 166.4 (s, ester carbonyl), 160.5 (s, lactone carbonyl), 149.7 (s, C-8a), 139.5 (s, C-2'), 135.2 (s, C-1'), 135.1 (d, C-6), 132.8 (d, C-4'), 130.7 (C-5'), 130.5 (d, C-7), 130.06 (d, C-6'), 130.04 (d, C-8), 129.5 (s, C-3), 128.1 (d, C-3'), 127.9 (d, C-5), 122.8 (s, C-4a), 110.9 (d, C-4), 52.6 (q, -OCH₃).

Anal. Calcd for C₁₈H₁₂O₅: C, 70.13; H, 3.92 Found: C, 69.88; H, 3.96.

IR (KBr, cm⁻¹): 3075, 2955, 1733, 1681, 1625, 1606, 1453, 1434, 1308, 1284, 1203, 1141, 1033, 1050, 1026, 778, 715, 685.

3.4.2. The synthesis of isoquinoline-1,3(2*H*,4*H*)-dione (345).

Homophthalic acid (1g, 5.5 mmol) and ammonium hydroxide (5 ml) were placed in a flask. The mixture was heated on a heating mantle till water and ammonia were distilled, the compound solidified when sublimation started. (0.78 g, 87 %). Green-yellow solid, mp. 236-238°C (lit.) 236- 237°C (found).

345¹⁴⁴: Green-yellow solid, mp. 236-238°C (lit.) 236- 237°C (found).

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.35 (br s, 1H, -NH), 8.22 (br d, $J_{87} = 7.5$ Hz, 1H, H-8), 7.63 (br dd, $J_{78} = 7.5$ Hz, $J_{76} = 7.2$ Hz, 1H, H-7), 7.47 (br dd, $J_{67} = 7.2$ Hz, $J_{65} = 7.4$ Hz, 1H, H-6), 7.32 (br d, $J_{56} = 7.4$ Hz, 1H, H-5), 4.03 (s, -CH₂).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 170.3 (s, carbonyl), 164.9 (s, carbonyl), 138.1 (s, C-4a), 134.6 (d, C-6), 128.9 (d, C-8), 127.9 (d, C-5), 127.7 (d, C-7), 124.8 (s, C-8a), 36.3 (t, -CH₂).

3.4.3. The synthesis of carbonic acid ethyl ester 3-hydroxy-isoquinoline-1-yl ester (346) and carbonic acid 3-ethoxycarbonyloxyisoquinolin-1-yl ester ethyl ester (347).

The isoquinoline **345** (0.5g, 3mmol) was dissolved in freshly distilled THF (15ml). A solution of triethylamine (0.33g, 3.3 mmol) in 5 ml THF was added dropwise to the cooled solution of (at -5°C) and stirred for 30 min. Then a solution of ethyl chloroformate (0.4 g, 3.6 mmol) was added dropwise at the same temperature and stirred for 30 min. The mixture was extracted to remove ethyl acetate and washed with saturated sodium bicarbonate (3x25 ml) and water (3x25ml). The organic layer was dried over magnesium sulfate and concentrated under vacuum to give a mixture of the compounds **346** and **347** and the recovered starting material **345**. (0.75g) . These were separated on a silicagel column (50g) eluting with ethyl acetate:hexane (90%:10%). The viscos liquid diacetate **347** was obtained from the column (0.33g, 35 %) as the first fraction, the second was the recovered starting material **345** (0.07g, 10%), and the last one was **346** (0.24g, 33 %).

346: Light yellow solid mp. 142-143°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 11.2 (s, -OH), 8.37 (br d, $J_{87} = 8.0$ Hz, 1H, H-8), 7.65 (br dd, $J_{78} = 8.0$ Hz, $J_{76} = 7.3$ Hz, 1H, H-7), 7.53 (br d, $J_{56} = 7.9$ Hz, 1H, H-5), 7.46 (br dd, $J_{65} = 7.9$ Hz, $J_{67} = 7.3$ Hz, 1H, H-6), 6.44 (s, 1H, -CH, H-4), 4.39 (q, $J = 7.1$ Hz, 2H, -OCH₂), 1.44 (t, $J = 7.1$ Hz, 3H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 164.8 (s, C-1), 152.5 (s, C-3), 143.8 (s, ester carbonyl), 138.8 (s, C-4a), 133.9 (d, C-6), 128.4 (d, C-8), 127.3 (d, C-7), 127.1 (d, C-5), 121.7 (s, C-8a), 95.2 (d, C-4), 66.4 (t, -CH₂), 14.2 (q, -CH₃).

Anal. Calcd for C₁₂H₁₁NO₄ : C, 61.8; H, 4.75; N, 6.01. Found: C, 52.07; H, 4.5; N, 5.02. Solvent corrected: C, 52.11; H, 4.02; N, 4.88.

IR (KBr, cm⁻¹): 3500, 1774, 1657, 1607, 1553, 1302, 1268, 1160, 911, 774.

347: Yellow solid mp. 46-47°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.08 (br d, $J_{87} = 8.5$ Hz, 1H, H-8), 7.84 (br d, $J_{56} = 8.3$ Hz, 1H, H-5), 7.71 (br dd, $J_{76} = 7.3$ Hz, $J_{78} = 8.5$ Hz, 1H, H-7), 7.58 (br dd, $J_{65} = 8.3$ Hz, $J_{67} = 7.3$ Hz, 1H, H-6), 7.46 (s, 1H, -CH, H-4), 4.39 (q, $J = 7.1$ Hz, 2H, -OCH₂), 4.35 (q, $J = 7.2$ Hz, 2H, -OCH₂), 1.40 (t, $J = 7.2$ Hz, 3H, -CH₃), 1.38 (t, $J = 7.1$ Hz, 3H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 154.0 (s, C-1), 152.9 (s, C-3), 151.9 (s, ester carbonyl), 150.9 (s, ester carbonyl), 141.0 (s, C-4a), 131.8 (d, C-6), 127.7 (d, C-8), 126.7 (d, C-7), 123.7 (d, C-5), 119.9 (s, C-8a), 109.4 (d, C-4), 65.6 (t, -CH₂), 65.1 (t, -CH₂), 14.15 (q, -CH₃), 14.12 (q, -CH₃).

Anal. Calcd for C₁₅H₁₅NO₆ : C, 59.01; H, 4.95; N, 4.59. Found: C, 53.69; H, 4.60; N, 4.22. Solvent corrected: C, 53.72; H, 4.51; N, 4.09.

IR (KBr, cm⁻¹): 2986, 1770, 1633, 1596, 1367, 1218, 1152, 1069, 778.

3.4.4. The synthesis of carbonic acid 3-ethoxycarbonyloxyisoquinolin-1-yl ester ethyl ester (347).

The isoquinoline **345** (0.3g, 1.8mmol) was dissolved in freshly distilled THF (10ml). A solution of triethylamine (0.3g, 4.32mmol) in 3 ml THF was added dropwise to the cooled solution of (at -5°C) and stirred for 30 min. Then a solution of ethyl chloroformate (0.24g, 4.32 mmol) in 3ml THF was added dropwise at the same temperature and stirred for 30 min. The mixture was extracted to ethyl acetate and washed with saturated sodium bicarbonate (3x25ml) and water (3x25ml). The organic layer was dried over magnesium sulfate and concentrated under vacuum to give the sole product. (0.54g). It was purified on a silicagel column (20g) eluting with ethylacetate. (0.52g, 96 %).

3.4.5. The synthesis of ethyl 1-oxo-1H-isochromen-3-yl carbonate (352).

To a solution of homophthalic acid **287** (2.5g, 14mmol) in 10 mL THF at -5°C, triethylamine (3mL, 22mmol) in 6 mL THF was added dropwise and the mixture was stirred for 30 min. This was followed by slow addition of a cooled solution of ethylchloroformate (3 mL, 32mmol) in 6mL THF and the reaction mixture was stirred at the same temperature for 30 min. The mixture was extracted with two portions of ethylacetate (15mL) and the organic phase was washed with saturated sodiumbicarbonate (3x40mL) three times and with water (2x25mL) and dried over magnesium sulfate. After the concentration of ethyl acetate a mixture of the compounds **352** and **297** (2.2 g) (3:2) was obtained, which were separated on silica gel column chromatography using ethyl acetate/*n*-hexane (7:3). As the first fraction **297** was isolated (White crystals from chloroform 585 mg, 26%). The second fraction was identified as isocoumarin derivative **352** (1.4g, 43%).

352¹⁵⁵: White crystal mp. 93-94°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.27 (br d, $J_{87} = 8.3$ Hz, 1H, H-8), 7.72 (ddd, $J_{67} = 7.6$ Hz, $J_{65} = 7.9$ Hz and $J_{68} = 0.8$ Hz, 1H, H-6), 7.49 (br dd, $J_{76} = 7.6$ Hz, $J_{78} = 8.3$ Hz, 1H, H-7), 7.44 (br d, $J_{56} = 7.9$ Hz, 1H, H-5), 6.27 (s, 1H, -CH, H-4), 4.37 (t, $J = 7.1$ Hz, 2H, -OCH₂), 1.41 (q, $J = 7.1$ Hz, 3H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 160.6 (s, lactone carbonyl), 151.0 (s, C-3), 150.4 (s, ester carbonyl), 137.4 (s, C-4a), 135.3 (d, C-6), 130.0 (d, C-8), 127.9 (d, C-5), 126.0 (d, C-7), 119.5 (s, C-8a), 93.0 (d, C-4), 66.2 (t, -OCH₂), 14.0 (q, -CH₃).

To the mixture of the products **297** and **352** in THF (10 ml) a solution of sodium azide (3.5 g, 54 mmol) in water (12.5 ml) was added dropwise at 0°C and the mixture was stirred at room temperature overnight. After work up, the product **297** was obtained as the only product.

3.5. The synthesis of N,N'- bis (1-methyl phenyl acetato) urea (358), methyl {2-[(chloroamino)carbonyl]phenyl}acetate (359) and 3-methoxy-1*H*-isochromen-1-one (360).

In a 25 ml dropping funnel, benzene (6ml), dimethyl formamide (1.18ml, 11.8 mmol) and thionyl chloride (0.86ml, 22mmol), were consecutively added, after 3-5 min two phases were separated and the lower layer was added to a suspension of the half ester (2.3, 11.8mmol), sodium azide (1.5g, 23.6mmol), tetrabutylammonium bromide (0.35g, 1.18mmol) and pyridine (1.89 ml, 23.6 mmol) in dichloromethane (50ml). The mixture was then refluxed overnight and washed with saturated sodiumbicarbonate solution (3x50ml) and water (2x25ml). The organic phase was dried over magnesium sulfate and removed under reduced pressure to give 1.5 g of mixture. The compounds were separated on a silicagel column (40g) eluting with chloroform:hexane (95%:5%). The first compound coming from the column was **360** (0.24 g, 11.5 %), the second was the viscos liquid **359** (0.6g, 25.4%) and the last was **358** (0.65g, 30.95 %).

358: White solid as cotton form mp.177-178°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 7.71 (dd, J_{34} = 7.9 Hz, J_{35} = 1.2 Hz, 1H, H-3), 7.40 (br s, 1H, -NH), 7.31 (ddd, J_{43} = 7.9 Hz, J_{45} = 7.5 Hz, J_{46} = 1.5 Hz, 1H, H-4), 7.22 (dd, J_{65} = 7.4 Hz, J_{64} = 1.5 Hz, 1H, H-6), 7.13 (ddd, J_{54} = 7.5 Hz,, J_{56} = 7.4 Hz, J_{53} = 1.2 Hz, 1H, H-5), 3.58 (s, 2H, -CH₂), 3.54 (s, 3H, -OCH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 172.5 (s, ester carbonyl), 154.4 (s, amide carbonyl), 137.1 (s, C-2), 131.2 (d, C-6), 128.8 (d, C-4), 127.9 (s, C-1), 126.1 (d, C-5), 125.7 (d, C-3), 52.6 (q, -OCH₃), 38.5 (t, -CH₂).

Anal. Calcd for C₁₉H₂₀N₂O₅ : C, 64.04; H, 5.66; N, 7.86. Found: C, 64.31; H, 5.52; N, 7.84.

IR (KBr, cm⁻¹): 3332, 3268, 1740, 1638, 1613, 1599, 1573,1432, 1343,1220, 1168, 1008, 771,656.

HRMS: 356.1363 (found) 356.1372 (theoretical).

359: Viscos liquid.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.45 (br s, -NH), 7.85 (br d, $J_{65} = 7.6$ Hz, 1H, H-6), 7.33 (br dd, $J_{43} = 7.3$ Hz, $J_{45} = 8.0$ Hz, 1H, H-4), 7.20 (br d, $J_{34} = 7.3$ Hz, 1H, H-3), 7.13 (br dd, $J_{54} = 8.0$ Hz, $J_{56} = 7.6$ Hz, 1H, -H5), 3.73 (s, 3H, -CH₃), 3.63 (s, 2H, -CH₂).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 172.9 (s, ester carbonyl), 154.8 (s, C-2), 136 (s, C-1), 130.9 (d, C-6), 128.7 (d, C-4), 125.6 (d, C-5), 123.8 (d, C-3), 52.7 (t, CH₂), 38.5 (q, -OCH₃).

360¹⁴⁴: **Melting point:** 70-71°C (lit.) 67-68°C (found).

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.16 (d, $J_{87} = 8.2$ Hz, 1H, H-8), 7.60 (br dd, $J_{67} = 7.2$ Hz, $J_{65} = 8.1$ Hz, 1H, H-6), 7.30 (d, $J_{56} = 8.1$ Hz, 1H, H-5), 7.29 (br dd, $J_{76} = 7.2$ Hz, $J_{78} = 8.2$ Hz, 1H, H-7), 5.58 (s, 1H, H-4), 3.91 (s, 3H, -OCH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 161.1 (s, C-1), 159.8 (s, C-3), 139.9 (s, C-4a), 135.1 (d, C-6), 129.9 (d, C-8), 125.5 (d, C-5), 124.6 (d, C-7), 117.9 (s, C-8a), 79.1 (d, C-4), 56.0 (q, -OCH₃).

3.5.1. The synthesis of 1-[2-(2-methoxy-2-oxoethyl)benzoyl]triazol-1,2-dien-2-ium (353), methyl {2-[(chloroamino)carbonyl]phenyl}acetate (359) and 3-methoxy-1H-isochromen-1-one (360).

To a solution of cyanuric chloride (0.66 g, 3.6 mmol) in dichloromethane (20 ml) N-methyl morpholine (0.93g, 10.8 mmol) was added at 0°C-5°C with continuous stirring. A white suspension was formed to which a solution of 2-(2-methoxy-2-oxoethyl)benzoic acid (2.1g, 10.8 mmol) in dichloromethane (10 ml) was added and the stirring was continued at the same temperature for 3h. The mixture was filtered off and to this filtrate sodium azide (0.7 g, 10.8 mmol) in water (5ml) added dropwise and the stirring continued at room temperature overnight. The mixture was washed with a saturated solution of sodium bicarbonate (3x10 ml) and then with water (3x10 ml). The organic layer was dried over sodium sulfate and evaporated

under reduced pressure to give a mixture of 1.8 g. The compounds were separated on a silicagel column (40g) eluting with chloroform:hexane (95%:5%). The first compound coming from the column was **360** (0.47 g, 24.7 %), the second was **359** (0.33 g, 14.5 %) and the last was **358** (0.75 g, 52.4 %).

3.5.2. The synthesis of 1-[2-(2-methoxy-2-oxoethyl)benzoyl]triaz-1,2-dien-2-ium (**353**).

To a solution of half ester **299** (2.4g, 12 mmol) in 10 ml THF at -5°C , triethylamine (1.7ml, 12 mmol) in 6 ml THF was added dropwise and the mixture was stirred for 30 min. This was followed by slow addition of a cooled solution of ethyl chloroformate (1.6ml, 14.4 mmol) in 6 ml THF and the reaction mixture was stirred at the same temperature for 30 min. Then sodium azide (1.6g, 25mmol) in 10ml water was added dropwise at 0°C and was let to stir overnight. The mixture was extracted with two portions of ethylacetate (15ml) and the organic phase was washed with saturated sodiumbicarbonate (3x40ml) three times and with water (2x25ml) and dried over magnesium sulfate. After the concentration of ethyl acetate 1.8 g azide (**353**) was obtained.

353: Yellow solid mp. $71-73^{\circ}\text{C}$.

$^1\text{H-NMR}$ Spectrum: (400 MHz, CDCl_3) δ 8.02 (br d, $J_{65} = 7.9$ Hz, 1H, H-6), 7.55 (br dd, $J_{43} = 7.6$ Hz, $J_{45} = 7.5$ Hz, 1H, H-4), 7.37 (br dd, $J_{54} = 7.5$ Hz, $J_{56} = 7.9$ Hz, 1H, H-5), 7.27 (br d, $J_{34} = 7.6$ Hz, 1H, H-3), 4.05 (s, 2H, $-\text{OCH}_2$), 3.71 (s, 3H, $-\text{OCH}_3$).

$^{13}\text{C-NMR}$ Spectrum: (100 MHz, CDCl_3) δ 173.2 (s, azide carbonyl), 171.6 (s, ester carbonyl), 136.8 (s, C-2), 133.7 (d, C-4), 132.7 (d, C-6), 131.3 (d, C-5), 129.6 (s, C-1), 127.6 (d, C-3), 51.9 (q, $-\text{OCH}_3$), 40.3 (t, $-\text{CH}_2$).

IR (KBr , cm^{-1}): 2280, 2138, 1740, 1691, 1490, 1238, 1169, 985, 760.

3.6. The synthesis of 2-hydroxy-*N,N'*-methylphenylacetato -1*H*-indole-1,3-dicarboxamide **368** and 1,3-dihydro-2*H*-indol-2-one (**369**).

The compound **358** (0.6, 1.7mmol) was suspended in acetonitrile (20ml). The suspension was heated to 58°C-60°C and at that temperature excess potassium carbonate (1g, 7.2mmol) was added. The reaction was controlled by TLC and completed in one hour. Excess potassium carbonate was filtered and the solution was concentrated under reduced pressure. The residue was treated with chloroform, one of the compounds **369** was soluble in chloroform and the other **368** was insoluble. After concentration of chloroform, was purified on a silicagel (25g) eluting with ethyl acetate:hexane (70%:30%).

(0.08g, 35%). The other major compound was tried to be recrystallized with methanol/chloroform (3:1). Although any crystals could not be obtained, the compound was purified. (0.5g, 58 %).

368: Yellow crystal mp.205-206°C.

¹H-NMR Spectrum: (400 MHz, d-acetone) δ 12.48 (br s, -NH), 10.59 (br s, -NH), 8.38 (dd, $J_{6c5c} = 7.87$ Hz, $J_{6c4c} = 1.1$ Hz, 1H, H-6c), 8.08 (br d, $J_{76} = 7.7$ Hz, 1H, H-7), 8.04 (br d, $J_{6b5b} = 8.0$ Hz, 1H, H-6b), 7.88 (dd, $J_{45} = 7.7$ Hz, $J_{46} = 1.1$ Hz, 1H, H-4), 7.30 (dd, $J_{3b4b} = 8.4$ Hz, $J_{3b5b} = 1.5$ Hz, 1H, H-3a), 7.29 (dd, $J_{5a6a} = 8.1$ Hz, $J_{5a4a} = 7.7$ Hz, 1H, H-5a), 7.20 (dd, $J_{3c4c} = 7.3$ Hz, $J_{3c5c} = 1.5$ Hz, 1H, H-3b), 7.18 (ddd, $J_{5c4c} = 8.4$ Hz, $J_{5c6c} = 7.7$ Hz, $J_{5c3c} = 1.5$ Hz, 1H, H-5b), 7.07 (ddd, $J_{4b5b} = 7.7$ Hz, $J_{4b3b} = 8.4$ Hz, $J_{4b6b} = 1.1$ Hz), 6.96 (dt, $J_{54} = J_{56} = 7.7$ Hz, $J_{57} = 1.1$ Hz, 1H, H-5), 6.90 (ddd, $J_{4c3c} = 7.3$ Hz, $J_{4c5c} = 8.4$ Hz, $J_{4c6c} = 1.1$ Hz, 1H, H-4c), 6.79 (dt, $J_{65} = J_{67} = 7.7$ Hz, $J_{64} = 1.1$ Hz, 1H, H-6), 3.84 (s, 2H, -CH₂), 3.81 (s, 2H, -CH₂), 3.59 (s, 3H, -OCH₃), 3.58 (s, 3H, -OCH₃).

¹³C-NMR Spectrum: (100 MHz, d-acetone) δ 171.8 (s, ester carbonyl), 171.7 (s, ester carbonyl), 165.4 (s, carbonyl carbon), 165.1 (s, C-2), 140.1 (s, C-1b), 138.1 (s, C-1c), 131.5 (d, C-3b), 131.1 (d, C-3c), 130.6 (s, C-7a), 130.1 (s, C-3a), 128.3 (d, C-5b), 127.9 (d, C-5c), 126.5 (s, C-2b), 124.1 (d, C-4b), 123.7 (s, C-2c), 123.0 (d, C-

4b), 122.7 (d, C-5), 121.8 (d, C-4c), 121.1 (d, C-6c), 118.9 (d, C-6), 117.5 (d, C-4), 114.1 (d, C-7), 86.1 (s, C-3).

Anal. Calcd for $C_{28}H_{25}N_3O_7$: C, 65.24; H, 4.89; N, 8.15. Found: C, 54.16; H, 4.89; N, 7.02. Solvent corrected : C, 54.16; H, 4.08; N, 6.51.

IR (KBr, cm^{-1}): 3573, 3421, 1723, 1699, 1628, 1600, 1563, 1481, 1356, 1325, 1283, 1238, 1154, 1079, 1060, 1030, 970, 832, 757, 690, 670.

369¹⁴⁶: White solid mp. 124⁰C (lit.) 118-120⁰C (found).

¹H-NMR Spectrum: (400 MHz, $CDCl_3$) δ 9.10 (s, 1H, H-1) 7.25 (d, $J_{76} = 7.2$ Hz, 1H, H-7), 7.20 (dd, $J_{65} = 7.5$ Hz, $J_{67} = 7.2$ Hz, 1H, H-6), 7.0 (t, $J_{56} = 7.5$ Hz, $J_{54} = 7.8$ Hz, 1H, H-5), 6.9 (d, $J_{45} = 7.8$ Hz, 1H, H-4), 3.5 (s, 2H, H-3).

¹³C-NMR Spectrum: (100 MHz, $CDCl_3$) δ 178.3 (s, C-2), 142.6 (s, C-7a), 129.5 (d, C-6), 127.9 (s, C-3a), 125.3 (d, C-4), (122.4 (d, C-5) 109.9 (d, C-7), 36.34 (t, C-3).

3.7. The synthesis of methyl (2-isocyanatophenyl)acetate (354).

The azide compound (2g, 9mmol) was refluxed in benzene (25 ml) for 1.5 h and evaporated under vacuum to give the isocyanate (1.64 g, 99 %).

354¹⁵⁶: **¹H-NMR Spectrum:** (400 MHz, $CDCl_3$) δ 7.23 (br d, $J_{34} = 7.5$ Hz, 1H, H-3), 7.22 (br dd, $J_{43} = 7.5$ Hz, $J_{45} = 6.7$ Hz, 1H, H-4), 7.14 (br d, $J_{65} = 7.6$ Hz, 1H, H-6), 7.12 (br dd, $J_{56} = 7.6$ Hz, $J_{54} = 6.7$ Hz, 1H, H-5), 3.69 (s, 3H, -OCH₃), 3.66 (s, 2H, -CH₂).

¹³C-NMR Spectrum: (100 MHz, $CDCl_3$) δ 170.9 (s, ester carbonyl), 132.9 (s, C-1), 131.0 (d, C-3), 128.9 (s, C-2), 128.4 (d, C-6), 125.9 (d, C-5), 125.8 (s, C-4), 125.0 (s, isocyanate carbonyl), 52.0 (q, -OCH₃), 37.4 (t, -CH₂).

IR (KBr, cm^{-1}): 2954, 2280, 2145, 1737, 1591, 1523, 1455, 1437, 1341, 1223, 1164, 1006, 756.

3.7.1. The synthesis of methyl {2-[(anilincarbonyl)amino]phenyl}acetate (374).

To a solution of isocyanate (0.76 g, 4mmol) in dichloromethane (25ml) aniline (0.37 g, 4 mmol) was added and the mixture was stirred at room temperature for 2h. The solvent was removed yielding the urethane (1.13 g, 98 %).

374: White solid mp.157-158°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 7.64 (br d, $J_{34} = 7.9$ Hz, 1H, H-3), 7.4 (br s, 1H, -NH), 7.25-7.38 (m, 6H, aromat. protons), 7.16 (br dd, $J_{43} = 7.9$ Hz, $J_{45} = 7.5$ Hz, 1H, H-4), 7.1 (br t, $J_{54} = J_{56} = 7.3$ Hz, 1H, H-5), 6.78 (br s, 1H, -NH), 3.67 (s, 2H, -CH₂), 3.63 (s, 3H, -OCH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 172.7 (s, ester carbonyl), 153.9 (s, amide carbonyl), 138.3 (s, C-1a), 136.7 (s, C-2), 131.0 (d, C-6), 129.1 (d, C-3a and C-5a), 128.7 (d, C-3), 128.2 (s, C-1), 126.2 (d, C-4), 125.9 (d, C-5), 123.8 (d, C-2a and C-6a), 120.6 (d, C-4a), 52.4 (q, -OCH₃), 38.1 (t, -CH₂).

Anal. Calcd for C₁₆H₁₆N₂O₃ : C, 67.59; H, 5.67; N, 9.85. Found: C, 67.06; H, 5.70; N, 9.72.

IR (KBr, cm⁻¹): 3319, 3277, 1736, 1647, 1589, 1557, 1455, 1337, 1295, 1184, 1103, 965, 779.

3.7.2. The synthesis of methyl [2-({[(2,4-dimethylphenyl)amino]carbonyl}amino)phenyl]acetate (376).

To a solution of isocyanate (0.5 g, 2.6 mmol) in dichloromethane (25ml) 2,4 - dimethylaniline (0.32 g, 2.6 mmol) was added and the mixture was stirred at room temperature for 2h. The solvent was removed yielding the urethane (0.75 g, 93 %).

376: White solid mp. 180-181°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 7.61 (br d, $J_{34} = 8.0$ Hz, 1H, H-3), 7.30 (br d, $J_{6a5a} = 7.9$ Hz, H, H-6a), 7.23 (br dd, $J_{43} = 8.0$ Hz, $J_{45} = 7.3$ Hz, $J_{46} = 1.4$ Hz, 1H,

H-4), 7.12 (br d, $J_{5,6} = 6.9$ Hz, 1H, H-6), 7.04 (br dd, $J_{56} = J_{54} = 7.3$ Hz, 1H, H-5), 6.98 (s, 1H, H-3a), 6.95 (br d, $J_{5a6a} = 7.9$ Hz, 1H, H-5a), 3.49 (s, 2H, $-\text{CH}_2$), 2.23 (s, 3H, $-\text{CH}_3$), 2.16 (s, 3H, $-\text{CH}_3$).

^{13}C -NMR Spectrum: (100 MHz, CDCl_3) δ 172.0 (s, ester carbonyl), 155 (s, amide carbonyl), 136.9 (d, C-1a), 136 (s, C-2a), 132.9 (d, C-3a and C-5a), 131.6 (d, C-6), 130.8 (d, C-4), 128.4 (d, C-5), 127.6 (d, C-6a), 125.9 (s, C-1), 125.8 (s, C-2), 125.4 (d, C-3), 52.2 (q, $-\text{OCH}_3$), 37.9 (t, $-\text{CH}_2$), 20.9 (q, $-\text{CH}_3$), 17.7 (q, $-\text{CH}_3$).

Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.16; H, 6.41; N, 9.05.

IR (KBr, cm^{-1}): 3291, 1743, 1643, 1587, 1550, 1446, 1292, 1180, 1146, 1126, 1049, 930.

3.7.3. The Synthesis of methyl [2-({[(4-nitrophenyl)amino]carbonyl}amino)phenyl]acetate (378).

To a solution of isocyanate **354** (0.48g, 2.5mmol) in dichloromethane (25ml) 4-nitroaniline (**377**) (0.35g, 2.5mmol) was added and the mixture was stirred at 40°C for 3h. The solvent was removed yielding the urethane (0.74g, 90 %).

378: Yellow solid mp. $175\text{--}176^\circ\text{C}$.

^1H -NMR Spectrum: (400 MHz, CDCl_3) δ 8.14 (br d, $J_{3a2a} = J_{5a6a} = 8.3$ Hz, 2H, H-3a and H-5a), 7.67 (br s, $-\text{NH}$), 7.60 (br d, $J_{34} = 8.0$ Hz, 1H, H-3), 7.56 (br d, $J_{6a5a} = J_{2a3a} = 8.3$ Hz, 2H, H-2a and H-6a), 7.37 (br s, 1H, $-\text{NH}$), 7.34 (br dd, $J_{65} = 8.0$ Hz, $J_{64} = 1.6$ Hz, 1H, H-6), 7.27-7.21 (m, 2H, H-5 and H-6), 3.71 (s, 2H, $-\text{OCH}_2$), 3.69 (s, 3H, $-\text{OCH}_3$).

^{13}C -NMR Spectrum: (100 MHz, CDCl_3) δ 173.3 (s, ester carbonyl), 152.9 (s, amide carbonyl), 145.0 (s, C-1a), 142.6 (s, C-4a), 136.0 (s, C-2), 131.3 (d, C-6), 128.9 (d, C-4), 128.5 (s, C-1), 126.6 (d, C-3), 126.4 (d, C-5), 125.0 (d, C-3a and C-5a), 118.3 (d, C-2a and C-6a), 52.6 (q, $-\text{OCH}_3$), 38.0 (t, $-\text{CH}_2$).

Anal. Calcd for $\text{C}_{16}\text{H}_9\text{N}_3\text{O}_3$: C, 58.36; H, 4.59; N, 12.76. Found: C, 59.18; H, 4.86; N, 11.89.

IR (KBr, cm⁻¹): 3352, 1735, 1659, 1613, 1590, 1563, 1455, 1332, 1179, 852, 755.

3.7.4. The synthesis of 2-hydroxy-*N,N'*-diphenyl-1*H*-indole-1,3-dicarboxamide (379).

The compound **374** (2.47g, 8.7 mmol) was suspended in acetonitrile (20ml). The suspension was heated to 58°C-60°C and at that temperature excess potassium carbonate (4g, 29mmol) was added. The reaction was controlled by TLC and completed in one hour. Excess potassium carbonate was filtered and the solution was concentrated under reduced pressure. The residue was treated with chloroform, one of the compounds **371** was soluble in chloroform and the other **379** was insoluble. After concentration of chloroform, **379** was purified on a silicagel (25g) eluting with ethyl acetate:hexane (70%:30%). (0.39g, 33.5%). The other major compound was tried to be recrystallized with methanol/chloroform (3:1). Although any crystals could not be obtained, the compound was purified. (1.95g, 60 %).

379: Purple solid mp. 245-247°C.

¹H-NMR Spectrum: (400 MHz, d-acetone) δ 12.94 (br s, 1H, -NH), 10.93 (br s, 1H, -NH), 8.28 (br d, $J_{76} = 8.0$ Hz, 1H, H-7), 8.09 (br d, $J_{45} = 7.6$ Hz, 1H, H-4), 7.79 (br d, $J_{6c5c} = J_{2c3c} = 8.0$ Hz, 2H, H-6c and H-2c), 7.74 (br d, $J_{6b5b} = J_{2b3b} = 8.0$ Hz, 2H, H-6b and H-2b), 7.36 (br dd, $J_{5c4c} = J_{3c4c} = 7.7$ Hz, $J_{5c6c} = J_{3c2c} = 8.0$ Hz, 2H, H-5c and H-3c), 7.25 (br dd, $J_{5b4b} = J_{3b4b} = 7.7$ Hz, $J_{5b6b} = J_{3b2b} = 8.0$ Hz, 2H, H-5b and H-3b), 7.05 (br t, $J_{4c5c} = J_{4c3c} = 7.4$ Hz, 1H, H-4c), 6.96 (br t, $J_{54} = J_{56} = 7.5$ Hz, 1H, H-5), 6.89 (br dd, $J_{4b5b} = 7.7$ Hz, $J_{4b3b} = 7.7$ Hz, 1H, H-4b), 6.88 (br dd, $J_{65} = 7.6$ Hz, $J_{67} = 8.0$ Hz, 1H, H-6).

¹³C-NMR Spectrum: (100 MHz, d-acetone) δ 165.4 (s, C-2), 165.2 (s, double bond), 152.3 (s, amide carbonyl), 141.9 (s, C-1b), 139.8 (s, C-1c), 130.7 (s, C-7a), 130.3 (s, C-3a), 128.7 (d, C-3b and C-5b), 128.4 (d, C-3c and C-5c), 122.3 (d, C-6), 121.8 (d, C-5), 120.5 (d, C-4b), 119.4 (d, C-4c), 118.3 (d, C-6b and C-2b), 117.9 (d, C-2c and C-6c), 117.2 (d, C-4), 113.6 (d, C-7), 85.9 (s, C-3).

Anal. Calcd for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31. Found: C, 61.41; H, 4.23; N, 9.98. Solvent corrected: C, 61.41; H, 4.01; N, 9.51.

IR (KBr, cm^{-1}): 3027, 1691, 1635, 1595, 1469, 1437, 1455, 1353, 1244, 1134, 1027, 1011, 988, 897.

3.7.5. The synthesis of 2-hydroxy-*N,N'*-(2,4-dimethylphenyl)-1*H*-indole-1,3-dicarboxamide (**380**).

The compound **376** (1.2g, 3.8mmol) was suspended in acetonitrile (15ml). The suspension was heated to 58°C-60°C and at that temperature excess potassium carbonate (2g, 14mmol) was added. The reaction was controlled by TLC and completed in one hour. Excess potassium carbonate was filtered and the solution was concentrated under reduced pressure. The residue was treated with chloroform, one of the compounds **371** was soluble in chloroform and the other **380** was insoluble. After concentration of chloroform, was purified on a silicagel (25 g) eluting with ethyl acetate:hexane (70%:30%). (0.1g, 23.3 %). The other major compound was tried to be recrystallized with methanol/chloroform (3:1). Although any crystals could not be obtained, the compound was purified. (0.9g, 56 %).

380: White solid dec.p. 272-274°C.

1H -NMR Spectrum: (400 MHz, d-acetone) δ 12.79 (br s, 1H, -NH), 10.81 (br s, 1H, -NH), 8.32 (br d, $J_{76} = 8.2$ Hz, 1H, H-7), 8.29 (br d, $J_{45} = 8.0$ Hz, 1H, H-4), 8.21 (br d, $J_{6b5b} = 8.1$ Hz, 1H, H-6b), 8.10 (br d, $J_{6c5c} = 7.6$ Hz, 1H, H-6c), 7.03 (br s, 1H, H-3b), 7.00 (br d, $J_{5b6b} = 8.1$ Hz, 1H, H-5b), 6.93 (br s, 1H, H-3c), 6.91 (br d, $J_{5c6c} = 7.6$ Hz, 1H, H-5c), 6.91 (br dd, $J_{67} = 8.2$ Hz, $J_{65} = 7.4$ Hz, 1H, H-6), 6.80 (br dd, $J_{54} = 8.0$ Hz, $J_{56} = 7.4$ Hz, 1H, H-5), 2.42 (s, -CH₃), 2.38 (s, -CH₃), 2.28 (s, -CH₃), 2.23 (s, -CH₃).

^{13}C -NMR Spectrum: (100 MHz, d-acetone) δ 165.5 (s, C-2), 165.4 (s, double bond), 152.5 (s, amide carbonyl), 137.8 (s, C-1c), 135.8 (s, C-1b), 131.3 (s, C-4b), 130.8 (s, C-7a), 130.7 (d, C-5c), 130.4 (s, C-4c), 130.3 (d, C-5b), 128.9 (s, C-3a), 127.3 (s, C-2c), 126.6 (s, C-3c), 126.4 (s, C-3b), 124.9 (s, C-2b), 121.6 (d, C-6),

120.6 (d, C-6b), 119.3 (d, C-4), 117.7 (d, C-5), 117.1 (d, C-6c), 113.6 (d, C-7), 86.2 (s, C-3), 19.9 (q, -CH₃), 17.63 (q, -CH₃), 17.59 (q, -CH₃).

Anal. Calcd for C₂₆H₂₅N₃O₃ : C, 73.05; H, 5.89; N, 9.83. Found: C, 65.52; H, 5.21; N, 8.97. Solvent corrected: C, 65.67; H, 5.30; N, 8.68.

IR (KBr, cm⁻¹): 2916, 1678, 1620, 1598, 1579, 1557, 1528, 1471, 1357, 1304, 1266, 1227, 1204, 1177, 1138, 1119, 1120, 1016, 1004, 913, 867, 780, 763, 754, 734, 717, 682.

3.7.6. The synthesis of 2-hydroxy-N,N'-bis(4-nitrophenyl)-1H-indole-1,3-dicarboxamide (381).

The compound **378** (0.3, 0.9mmol) was suspended in acetonitrile (10ml). The suspension was heated to 58°C-60°C and at that temperature excess potassium carbonate (1g, 7.2mmol) was added. The reaction was controlled by TLC and completed in one hour. Excess potassium carbonate was filtered and the solution was concentrated under reduced pressure. The residue was treated with chloroform, one of the compounds **371** was soluble in chloroform and the other **381** was insoluble. After concentration of chloroform, was purified on a silicagel (25g) eluting with ethyl acetate:hexane (70%:30%). (0.03g, 25 %). The other major compound was tried to be recrystallized with methanol/chloroform (3:1). Although any crystals could not be obtained, the compound was purified. (0.24g, 57 %).

381: Red-brown solid mp. 266-267°C.

¹H-NMR Spectrum: (400 MHz, d-acetone) δ 13.76 (br s, -NH), 11.49 (br s, -NH) 8.30 (br d, $J_{3b2b} = J_{5b6b} = 8.3$ Hz, 2H, H-3b and H-5b), 8.25 (br d, $J_{76} = 8.0$ Hz, 1H, H-7), 8.20 (br d, $J_{3c2c} = J_{5c6c} = 8.3$ Hz, 1H, H-3c and H-5c), 8.1 (br d, $J_{45} = 7.1$ Hz, 1H, H-5), 7.99 (m, 4H, H-4b, H-6b, H-4c and H-6c), 7.05 (br dd, $J_{54} = 7.1$ Hz, $J_{56} = 7.6$ Hz, 1H, H-5), 6.99 (br dd, $J_{65} = 7.6$ Hz, $J_{67} = 8.0$ Hz, 1H, H-5b).

¹³C-NMR Spectrum: (100 MHz, d-acetone) δ 166.4 (s, carbonyl), 165.5 (s, double

bond), 152.7 (s, amide carbonyl), 148.9 (s, C-4c), 146.8 (s, C-1c), 143.3 (s, C-4b), 141.6 (s, C-1b), 131.6 (s, C-6), 130.6 (s, C-7a), 126.9 (s, C-3a), 125.9 (d, C-3c and C-5c), 123.5 (d, C-2c and C-6c), 119.9 (d, C-5), 119.8 (d, C-3b and C-5b), 118.5 (d, C-4), 118.3 (d, C-2b and C-6b), 114.8 (d, C-7), 87.3 (s, C-3).

IR (KBr, cm^{-1}): 3326, 2909, 1693, 1649, 1595, 1504, 1462, 1406, 1328, 1263, 1176, 1112, 1088, 847, 751.

3.8. The synthesis of methyl {2-[(methoxycarbonyl)amino]phenyl}acetate (**382**).

1.5 g azide was refluxed in dry benzene (20ml) under nitrogen atmosphere for 1.5h to give the urethane (1.48g, 97 %). No purification was needed.

382¹⁵⁷: White solid mp.58-59°C.

^1H -NMR Spectrum: (400 MHz, CDCl_3) δ 7.87 (br s, 1H, -NH), 7.76 (br d, $J_{34} = 7.9$ Hz, 1H, H-3), 7.29 (br dd, $J_{45} = 7.4$ Hz, $J_{43} = 7.9$ Hz, 1H, H-4), 7.18 (br d, $J_{65} = 7.4$ Hz, 1H, H-6), 7.07 (br t, $J_{54} = J_{56} = 7.4$ Hz, 1H, H-5), 3.77 (s, 3H, -CH₃), 3.70 (s, 3H, -CH₃), 3.62 (s, 2H, -CH₂).

^{13}C -NMR Spectrum: (100 MHz, CDCl_3) δ 172.7 (s, ester carbonyl), 154.8 (s, amide carbonyl), 136.9 (s, C-2), 130.8 (d, C-4 and C-6), 128.5 (d, C-5 and C-3), 124.7 (s, C-1), 52.5 (q, -OMe), 52.3 (q, -OMe), 38.4 (t, -CH₂).

3.8.1. The synthesis of methyl 3-acetyl-2-hydroxy-1*H*-indole-1-carboxylate (**383**) and methyl 2-oxoindoline-1-carboxylate (**384**).

To a solution of urethane **382** (0.4g, 1.8mmol) in freshly distilled THF (15 ml) at 0°C sodium hydride (0.086g, 3.6mmol) was added and stirred at the temperature for 30 min. Then acetic anhydride (0.26g, 2.5mmol) was added to this solution and stirred at room temperature overnight. The product **383** precipitated in the reaction medium, was filtered off and purified by washing with chloroform. (0.33g, 79 %). The filtrate was concentrated under vacuum to give the crude **384**, which was recrystallized from

chloroform: hexane (5:1). (0.06g, 17.6 %).

382: Pale pink solid mp. 245-246°C.

¹H-NMR Spectrum: (400 MHz, DMSO-d₆) δ 7.97 (br. s, 1H, H-7), 7.57 (d, $J_{45} = 7.9$ Hz, 1H, H-4), 6.88 (t, $J_{67} = J_{65} = 7.4$ Hz, 1H, H-6), 6.73 (t, $J_{56} = J_{45} = 7.4$ Hz, 1H, H-5), 3.84 (s, 3H, -OCH₃), 2.29 (s, 3H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, DMSO-d₆) δ 188.4 (s, C-10), 166.0 (s, C-2), 153.4 (s, C-8), 131.4 (s, 7a), 130.5 (s, 3 a), 122.7 (d, C-6), 118.8 (d, C-5), 117.9 (d, C-7), 112.5 (d, C-4), 94.8 (s, C-3), 52.8 (q, C-9), 28.6 (q, C-11).

Anal. Calcd for C₁₂H₁₁NO₄ : C, 61.80; H, 4.75; N, 6.01

Found: C, 44.45; H, 3.74; N, 3.64. (Metu Central Laboratory)

Found: C, 46.67; H, 3.48; N, 3.72. (ATAL).

Found: C, 46.18; H, 3.83; N, 3.84. (Atatürk University)

Solvent corrected result: C, 46.18; H, 3.57; N, 4.19

IR (KBr, cm⁻¹) : 3450, 3053, 1758, 1638, 1586, 1524, 1481, 1442, 1428, 1337, 1217, 1184, 1117, 1007, 940, 782, 720.

384: Pale yellow crystalline compound mp. 92-93°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 7.88 (br d, $J_{76} = 8.2$ Hz, 1H, H-7), 7.33 (br dd, $J_{65} = 7.4$ Hz, $J_{67} = 8.2$ Hz, 1H, H-6), 7.26 (br d, $J_{45} = 7.4$ Hz, 1H, H-4), 7.17 (br t, $J_{56} = J_{54} = 7.4$ Hz, 1H, H-5), 4.02 (s, 3H, -CH₃), 3.64 (s, 2H, -CH₂).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 172.7 (s, amide carbonyl), 151.5 (s, ester carbonyl), 140.6 (s, C-7a), 128.3 (d, C-6), 124.6 (d, C-4), 124.2 (d, C-5), 123.3 (s, C-3a), 115.3 (d, C-7), 53.9 (q, -OCH₃), 36.5 (t, -CH₂).

Anal. Calcd for C₁₀H₉NO₃ : C, 62.82; H, 4.74; N, 7.33. Found: C, 62.27; H, 4.78; N, 7.55.

IR (KBr, cm⁻¹): 1776, 1721, 1446, 1352, 1296, 1244, 1149, 1055, 787.

3.8.2. The synthesis of methyl 3-acetyl-2-[(ethoxycarbonyl)oxy]-1H-indole-1-carboxylate (**387**).

The indole **383** (0.6g, 2.6 mmol) was suspended in freshly distilled THF (20 ml) and triethyl amine (0.37g, 3.6 mmol) in 5 ml THF was added to this suspension at -5°C and stirred at the same temperature for 30 min. Next, ethyl chloroformate (5g, 4.6 mmol) was added dropwise at -5°C and stirred 30 min. The solution was extracted with ethyl acetate (2x25 ml) and washed with saturated sodium bicarbonate solution (3x25 ml) and with water (3x25 ml). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure to give the crude **387**. (0.71g). It was purified on a silicagel (35 g) eluting with ethyl acetate. (0.65g, 82.8 %).

387: Pink crystalline compound mp. 84-85°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 7.95 (d, $J_{45} = 8.4$ Hz, 1H, H-4) 7.69 (d, $J_{76} = 7.7$ Hz, 1H, H-4), 7.32 (dd, $J_{67} = 7.7$ Hz, $J_{65} = 7.6$ Hz, 1H, H-6), 7.18 (dd, $J_{56} = 7.6$ Hz, $J_{54} = 8.4$ Hz, 1H, H-5), 4.36 (q, $J = 7.2$ Hz, 2H, -OCH₂), 4.03 (s, 3H, -OCH₃), 2.73 (s, 3H, -CH₃), 1.41 (t, $J = 7.2$ Hz, 3H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 165.9 (s, C-2), 161.2 (s, ketone carbonyl), 151.8 (s, ester carbonyl), 151.2 (s, ester carbonyl), 137.3 (s, C-7a), 129.4 (d, C-6), 124.9 (d, C-5), 124.1 (d, C-4), 121.5 (s, C-3a), 115.6 (s, C-3), 115 (d, C-7), 65.9 (t, -OCH₂), 54.1 (q, -OCH₃), 18.6 (q, -CH₃), 14.4 (q, -CH₃).

MS: 70 eV, m/z; 306 (M⁺, 2%), 234 (32%), 202 (25%), 160(100%), 129 (30%), **118 (42%)**.

Anal. Calcd for C₁₀H₁₁NO₃ : C, 59.01; H, 4.95 ; N, 4.59. Found: C, 59.01; H, 4.83 ; N, 4.69.

IR (KBr, cm⁻¹) 1777, 1755, 1736, 1660, 1470, 1444, 1380, 1358, 1267, 1244, 1177, 1100, 1046.

3.8.3. The synthesis of 3-ethyl 1-methyl 2-hydroxy-1*H*-indole-1,3-dicarboxylate (388), 2-[(ethoxycarbonyl)oxy]-1*H*-indole-1,3-dicarboxylate (390) and methyl 2-[(ethoxycarbonyl)oxy]-1*H*-indole-1-carboxylate (391).

To a solution of urethane **382** (0.4g, 1.8mmol) in freshly distilled THF (15 ml) at 0°C sodium hydride (0.086g, 3.6 mmol) was added and stirred at the temperature for 30 min. Then ethyl chloroformate (0.5g, 5 mmol) was added to this solution and stirred at room temperature overnight. The product **388** precipitated in the reaction medium, was filtered off and purified by washing with chloroform. (0.17g, 36.2 %). The filtrate was concentrated under vacuum to give a mixture of **390** and **389** (0.28 g) which separated on a silicagel (30 g) eluting with chloroform to give **390** (0.14 g, 23.3 %) and **389** (0.1 g, 21.3 %).

389: Viscous pale yellow liquid.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.05 (br d, $J_{76} = 8.3$ Hz, 1H, H-7), 7.50 (br d, $J_{45} = 7.5$ Hz, 1H, H-4), 7.33 (ddd, $J_{67} = 8.3$ Hz, $J_{65} = 7.3$ Hz, $J_{64} = 1.1$ Hz, 1H, H-6), 7.25 (dd, $J_{56} = 7.3$ Hz, $J_{54} = 7.5$ Hz, 1H, H-5), 4.38 (q, $J = 7.0$ Hz, 2H, OCH₂), 4.03 (s, 3H, -OCH₃), 1.41 (t, $J = 7.0$ Hz, 3H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 152.5 (s, C-2), 150.7 (s, ester carbonyl), 141.6 (s, amide carbonyl), 132.6 (s, C-7a), 126.6 (s, C-3a), 124.5 (d, C-6), 123.6 (d, C-5), 120.8 (s, C-4), 115.4 (s, C-7), 97.4 (s, C-3), 65.9 (t, -CH₂), 53.9 (q, -OCH₃), 14.2 (q, -CH₃).

Anal. Calcd for C₁₃H₁₃NO₅ : C, 59.31; H, 4.98; N, 5.32. Found: C, 58.35; H, 5.69; N, 4.61.

IR (KBr, cm⁻¹): 2925, 1779, 1745, 1614, 1464, 1374, 1326, 1269, 1236, 1209, 917, 748.

390: Yellow crystalline compound mp. 75-76°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.15 (br d, $J_{76} = 6.9$ Hz, 1H, H-7), 8.07 (br d, $J_{45} = 6.9$ Hz, 1H, H-4), 7.36-7.40 (m, 2H, H-5 and H-6), 7.18 (br dd, $J_{78} = 7.4$

Hz, $J_{76} = 6.9$ Hz, 1H, H-7), 4.43 (q, $J = 7.2$ Hz, $-\text{OCH}_2$), 4.39 (q, $J = 7.1$ Hz, $-\text{OCH}_2$), 1.46 (t, $J = 7.2$ Hz, $-\text{CH}_3$), 1.42 (t, $J = 7.1$ Hz, $-\text{CH}_3$).

^{13}C -NMR Spectrum: (100 MHz, CDCl_3) δ 162.7 (s, double bond carbon, C-2), 151.2 (s, carbonyl), 150.2 (s, carbonyl), 145.0 (s, carbonyl), 131.5 (s, C-7a), 125.4 (d, C-7), 124.6 (d, C-6), 124.5 (s, C-3a), 121.8 (d, C-5), 115.2 (d, C-4), 101.7 (s, C-3), 66.2 (t, $-\text{OCH}_2$), 60.5 (t, $-\text{OCH}_2$), 54.5 (q, OCH_3), 14.28 (q, $-\text{CH}_3$), 14.20 (q, $-\text{CH}_3$).

Anal. Calcd for $\text{C}_{16}\text{H}_9\text{N}_3\text{O}_3$: C, 54.70; H, 4.88; N, 3.99. Found: C, 54.53; H, 4.92; N, 3.98.

IR (KBr, cm^{-1}): 2985, 1760, 1712, 1606, 1543, 1453, 1362, 1315, 1266, 1114, 1031, 876, 756.

3.8.4. The synthesis of diethyl 2-hydroxy-1*H*-indole-1,3-dicarboxylate (**391**), diethyl 2-[(ethoxycarbonyl)oxy]-1*H*-indole-1,3-dicarboxylate (**392**), ethyl 2-[(ethoxycarbonyl)oxy]-1*H*-indole-1-carboxylate (**393**).

To a solution of urethane **382** (0.77g, 3.5mmol) in freshly distilled THF (20 ml) at 0°C sodium hydride (0.34g, 14mmol) was added and stirred at the temperature for 30 min. Then ethyl chloroformate (2g, 19.6 mmol) was added to this solution and stirred at room temperature overnight. The product **391** precipitated in the reaction medium, was filtered off and purified by washing with chloroform. (0.23g, 23.7 %). The filtrate was concentrated under vacuum to give a mixture of **392** and **393**, (0.7g) which separated on a silicagel (30g) eluting with chloroform to give **392** (0.35g, 28.7 %) and **393** (0.3g, 30.9 %).

391: Pink solid dec. point 171-172°C.

^1H -NMR Spectrum: (400 MHz, $\text{DMSO}-d_6$) δ 7.60 (br d, $J_{76} = 8.0$ Hz, 1H, H-7), 7.52 (br d, $J_{45} = 7.7$ Hz, 1H, H-4), 6.95 (br dd, $J_{54} = 7.7$ Hz, $J_{56} = 7.5$ Hz, 1H, H-5), 6.78 (br dd, $J_{65} = 7.5$ Hz, $J_{67} = 8.0$, 1H, H-6), 4.38 (q, $J = 7.0$ Hz, 2H, $-\text{OCH}_2$), 4.17 (q, $J = 7.0$ Hz, 2H, $-\text{OCH}_2$), 1.37 (t, $J = 7.0$ Hz, 3H, $-\text{CH}_3$), 1.31 (t, $J = 7.0$ Hz, 3H, $-\text{CH}_3$).

¹³C-NMR Spectrum: (100 MHz, DMSO-d₆) δ 166.6 (s, carbonyl), 165.5 (s, C-2), 152.0 (s, carbonyl), 129.2 (s, C-7a), 128.9 (s, C-3a), 122.6 (d, C-6), 118.4 (d, C-5), 117.2 (d, C-4), 112.9 (d, C-7), 81.4 (s, C-3), 61.7 (t, -OCH₂), 57.4 (t, -OCH₂), 14.8 (q, -CH₃), 14.2 (q, -CH₃).

IR (KBr, cm⁻¹): 3443, 3044, 2979, 1731, 1668, 1605, 1591, 1555, 1487, 1416, 1383, 1329, 1227, 1096, 1049, 1005, 923, 788, 771.

392: Pink crystalline compound mp. 66-67°C

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.16 (br d, *J*₇₆ = 7.8 Hz, 1H, H-7), 8.11 (br d, *J*₄₅ = 7.9 Hz, 1H, H-4), 7.35-7.40 (m, 2H, H-5 and H-6), 4.52 (q, *J* = 7.2 Hz, 2H, -CH₂), 4.41 (q, *J* = 7.2 Hz, 2H, -CH₂), 4.39 (q, *J* = 7.2 Hz, 2H, -CH₂), 1.45 (t, *J* = 7.1 Hz, 3H, -CH₃), 1.40 (m, 9H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 162.7 (s, C-2), 160.5 (s, carbonyl), 153.7 (s, carbonyl), 151.1 (s, carbonyl), 144.9 (s, C-3a), 131.6 (s, C-7a), 125.3 (d, C-7), 124.5 (d, C-6), 121.6 (d, C-8), 115.0 (d, C-5), 101.6 (s, C-3), 66.1 (t, -OCH₂), 64.2 (t, -OCH₂), 60.5 (t, -OCH₂), 14.3 (q, -CH₃), 14.2 (q, -CH₃), 14.0 (q, -CH₃).

Anal. Calcd for C₁₇H₁₉NO₇ : C, 58.45; H, 5.48; N, 4.01. Found: C, 60.46; H, 6.26; N, 3.4.

IR (KBr, cm⁻¹): 2982, 2923, 1783, 1755, 1712, 1600, 1581, 1458, 1423, 1374, 1268, 1194, 1034, 764.

393: Pink-white solid mp. 57-58°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.08 (br d, *J*₇₆ = 8.3 Hz, 1H, H-7), 7.50 (br d, *J*₄₅ = 7.5 Hz, 1H, H-4), 7.32 (br dd, *J*₅₄ = 7.5 Hz, *J*₅₆ = 7.3 Hz, 1H, H-5), 7.26 (br dd, *J*₆₅ = 7.3 Hz, *J*₆₇ = 8.3 Hz, 1H, H-6), 6.31 (s, 1H, H-3), 4.48 (q, *J* = 7.1 Hz, 2H, -CH₂), 4.37 (q, *J* = 7.1 Hz, 2H, -CH₂), 1.45 (t, *J* = 7.1 Hz, 3H, -CH₃), 1.42 (t, *J* = 7.1 Hz, 3H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 152.5 (s, C-2), 150.3 (s, ester carbonyl), 141.6 (s, amide carbonyl), 132.7 (s, C-7a), 126.8 (s, C-3a), 125.2 (d, C-6), 124.4 (d, C-5), 123.7 (s, C-4), 115.4 (s, C-7), 97.2 (s, C-3), 65.9 (t, -CH₂), 63.9 (t, -CH₂), 14.2 (q, -CH₃), 13.6 (q, -CH₃).

Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.54; H, 5.45; N, 5.05. Found: C, 60.21; H, 5.45; N, 5.15.

IR (KBr, cm^{-1}): 2989, 2929, 1782, 1749, 1614, 1453, 1400, 1374, 1329, 1269, 1247, 1213, 1127, 1105, 917, 745.

3.9. The synthesis of 3-acetyl-2-hydroxy-*N*-phenyl-1*H*-indole-1-carboxamide (394) and 2-oxo-*N*-phenylindoline-1-carboxamide (395).

To a solution of urethane **374** (0.5g, 1.8mmol) in freshly distilled THF (15 ml) at 0°C sodium hydride (0.086g, 3.6 mmol) was added and stirred at the same temperature for 30 min. Then acetic anhydride (0.26g, 2.5 mmol) was added to this solution and stirred at room temperature overnight. The product **394** precipitated in the reaction medium, was filtered off and purified by washing with chloroform. (0.4g, 75.5 %). The filtrate was concentrated under vacuum to give the crude **395**, which was recrystallized from ethylacetate: hexane (5:2). (0.07g, 15.5 %).

394: White solid mp. 168-169°C.

1H -NMR Spectrum: (400 MHz, DMSO- d_6) δ 11.30 (s, 1H, NH), 8.12 (dd, $J_{45} = 8.0$ Hz, $J_{46} = 1.5$ Hz, 1H, H-4), 7.83 (br d, $J_{67} = 6.6$ Hz, 1H, H-7), 7.59 (d, $J_{1011} = J_{1413} = 7.3$ Hz, 2H, H-10 and H-14), 7.35 (br. t, $J_{1011} = J_{1112} = 7.3$ Hz, 2H, H-11 and H-14), 7.17 (dt, $J_{67} = J_{56} = 7.3$ Hz, $J_{46} = 1.5$ Hz, 1H, H-6), 7.15 (dt, $J_{45} = J_{56} = 7.3$ Hz, $J_{57} = 1.4$ Hz, 1H, H-5), 7.10 (t, $J_{67} = 7.3$ Hz, 1H, H-12), 2.65 (s, 3H, -CH₃).

^{13}C -NMR Spectrum: (100 MHz, DMSO- d_6) $\square$ 176.3 (s, C-15), 170.6 (s, C-2), 150.6 (s, C-8), 138.3 (s, C-9), 135.0 (s, 7a), 129.7 (d, C-11 and C-13), 125.8 (d, C-6), 124.5 (d, C-12), 124.4 (d, C-5), 124.3, (d, C-6), 122.3, (s, 3a), 120.5 (C-10 and C-14), 115.1 (d, H-4), 101.6 (s, C-3), 20.4 (q, C-16).

MS Spectrum: 70 eV, m/z; 294 (M^+ , 15%), 175 (100%), 157 (49%), 133 (24%), 119 (38%), 91 (25%), 77 (26%).

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 68.49; H, 4.71; N, 9.84.

IR (KBr, cm⁻¹): 3202, 3144, 3096, 1720, 1662, 1589, 1560, 1495, 1461, 1375, 1294, 1227, 1175, 1112, 969, 835, 782, 759, 706.

395: ¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 10.59 (br s, 1H, H—NH), 8.24 (br d, $J_{76} = 8.2$ Hz, 1H, H-7), 7.51 (br d, $J_{2b3b} = J_{6b5b} = 8.1$ Hz, 2H, H-2b and H-6b), 7.28 (m, 3H, H-5, H-3b and H-5b), 7.22 (br d, $J_{45} = 8.1$ Hz, 1H, H-4), 7.18 (m, 2H, H-6 and H-4b) 3.7 (s, 2H, -CH₂).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 177.7 (s, C-2), 149.5 (s, carbonyl), 141.6 (s, C-7a), 137.1 (s, 1b), 129.1 (d, C-3b and C-5b), 128.5 (d, C-4), 124.7 (d, C-5), 124.5 (d, C-6), 123.9 (d, C-7), 122.9 (s, C-3a), 120.6 (d, C-2b and C-6b), 116.8 (d, C-4b), 37.1 (t, -CH₂).

3.9.1. The synthesis of ethyl 1-(anilincarbonyl)-2-hydroxy-1*H*-indole-3-carboxylate (**396**) and 2-oxo-*N*-phenylindoline-1-carboxamide (**395**).

To a solution of urethane **373** (0.5g, 1.8mmol) in freshly distilled THF (15 ml) at 0°C sodium hydride (0.086g, 3.6mmol) was added and stirred at the temperature for 30 min. Then ethyl chloroformate (0.27g, 2.5mmol) was added to this solution and stirred at room temperature overnight. The product **396** precipitated in the reaction medium, was filtered off and purified by washing with chloroform. (0.46g, 79.3 %). The filtrate was concentrated under vacuum to give the crude **395**, which was from ethylacetate: hexane (5:2). (0.08g, 17.8 %).

396: ¹H-NMR Spectrum: (400 MHz, DMSO-d₆) δ 12.88 (br s, 1H, -NH), 8.13 (br d, $J_{76} = 8.0$ Hz, 1H, H-7), 7.65 (br d, $J_{2b3b} = J_{5b6b} = 7.9$ Hz, 2H, H-2b and H-6b), 7.59 (br d, $J_{45} = 7.6$ Hz, 1H, H-4), 7.35 (br dd, $J_{3b2b} = J_{5b6b} = 7.9$ Hz, $J_{3b4b} = J_{5b4b} = 7.4$ Hz, 1H, H-3b and H-5b), 7.06 (br dd, $J_{54} = 7.6$ Hz, $J_{56} = 7.4$ Hz, 1H, H-5), 6.98 (br dd, $J_{65} = 7.4$ Hz, $J_{67} = 8.0$ Hz, 1H, H-6), 6.82 (br dd, $J_{4b3b} = 7.4$ Hz, $J_{4b5b} = 7.4$ Hz, 1H, H-4b), 4.2 (q, $J = 7.0$ Hz, -OCH₂), 1.33 (t, $J = 7.0$ Hz, -CH₃).

¹³C-NMR Spectrum: (100 MHz, DMSO-d₆) δ 166.3 (s, carbonyl), 166.2 (s, C-2), 151.6 (s, carbonyl), 138.8 (s, C-1b), 130.0 (s, 7a), 129.0 (d, C-3b), 128.9 (d, C-6b), 128.2 (s, C-3a), 122.7 (d, C-7), 122.1 (d, C-6), 119.2 (d, C-2b and C-6b), 118.6 (d, C-5), 117.1 (d, C-4), 113.5 (s, C-4b), 82.2 (s, C-3), 57.4 (t, -OCH₂), 14.8 (q, -CH₃).

IR (KBr, cm⁻¹): 3456, 1677, 1655, 1625, 1558, 1528, 1490, 1385, 1254, 1134, 1087, 790, 748.

3.10. The synthesis of methyl [2-(chlorocarbonyl)phenyl]acetate (**398**) and 3-methoxy-1*H*-isochromen-1-one (**360**).

To a solution of half ester **299** (1g, 5.2 mmol) in dichloromethane (20 ml) oxalyl chloride (1.4 ml, 16.2 mmol) and dimethylformamide (1 drop) was added and the mixture was stirred at room temperature for 2 hours. Then the solvent and excess oxalyl chloride were removed under reduced pressure to give a mixture of **398** and **360** (1 g) in 3:2 ratio, respectively.

3.10.1. The synthesis of methyl [2-(aminocarbonyl)phenyl]acetate (**399**).

The mixture of the compounds **398** and **360** (0.88g) was dissolved in dichloromethane (20 ml) and ammonia gas was passed through the solution for 1 hour. The precipitate was filtered and the residue was concentrated under reduced pressure to give a mixture of **399** and **360** (0.88g). The amide **399** was separated by recrystallization with dichloromethane. (0.45g, 49 %). The isochromen **360** was obtained. (0.32g, 36 %).

399: Yellow crystal mp. 155-157°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 7.60 (dd, $J_{34} = 7.6$ Hz, $J_{56} = 1.3$ Hz, 1H, H-3) 7.42 (dt, $J_{43} = J_{45} = 7.6$ Hz, $J_{46} = 1.5$ Hz, 1H, H-4), 7.35 (dt, $J_{54} = J_{56} = 7.6$ Hz, $J_{53} = 1.3$ Hz, 1H, H-4), 7.29 (dd, $J_{65} = 7.6$ Hz, $J_{64} = 1.5$ Hz, 1H, H-6), 6.63 (s, -NH), 5.95 (s, -NH), 3.93 (s, 2H, -CH₂), 3.75 (s, 3H, -OCH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 172.7 (s, ester carbonyl), 171.4 (s, amide carbonyl), 135.5 (s, C-2), 132.4 (s, C-1), 131.3 (d, C-5), 130.7 (d, C-6), 128.2 (d, C-3), 127.6 (d, C-4), 52.2 (q, -OCH₃), 38.9 (t, -CH₂) .

Anal. Calcd for C₁₀H₁₁NO₃ : C, 62.17; H, 5.74 ; N, 7.25. Found: C, 63.36; H, 5.75; N, 7.28.

IR (KBr, cm⁻¹) 3373, 3169, 1723, 1669, 1615, 1593, 1577, 1495, 1232, 1196, 1130, 1046.

3.10.2. The synthesis of 1*H*,1'*H*-2,2'-biisoquinoline-1,1',3,3'(4*H*,4'*H*)-tetrone (401).

The mixture of the compounds **398** and **360** (0.88g) was dissolved in dichloromethane (20 ml) and anhydrous hydrazine (5 ml) was added into it at rt. The precipitate was **398** and filtered off, washed with chloroform. (0.21g, 44 %). The residue was concentrated under reduced pressure (0.3g, 35 %).

401¹⁴⁹: ¹H-NMR Spectrum: (400 MHz, DMSO-d₆) δ 8.11 (br d, *J*₈₇ = 7.8 Hz, 1H, H-8), 7.83 (br dd, *J*₇₈ = 7.8 Hz, *J*₇₆ = 7.5 Hz, 1H, H-7), 7.59 (br dd, *J*₆₇ = 7.5 Hz, *J*₆₅ = 7.8 Hz, 1H, H-6), 7.54 (br d, *J*₅₆ = 7.8 Hz, 1H, H-5), 4.63 (s, -CH₂).

¹³C-NMR Spectrum: (100 MHz, DMSO-d₆) δ 166.9 (s, C-1), 161.6 (s, C-3), 135.6 (s, C-4a), 135.4 (d, C-6), 128.9 (d, C-5), 128.9 (d, C-8), 1278.4 (d, C-7), 123.9 (s, C-8a), 36.8 (t, -CH₂).

IR (KBr, cm⁻¹) 2974, 1953, 1725, 1607, 1555, 1504, 1488, 1392, 1261, 1182, 983, 871, 738.

3.10.3. The synthesis of 2-aminoisoquinoline-1,3(2*H*,4*H*)-dione (404).

Homophthalic anhydride was added (1g, 6.2 mmol) was added to a solution of hydrazine monohydrate (0.36 ml, 6.2 mmol) in ethanol (15 ml) and refluxed overnight. The precipitate formed was filtered off, washed with dilute acetic acid and dried. (0.85 g, 80 %).

404: Yellow solid mp. 151-153°C (lit). 143-145°C (found).

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.21 (br d, $J_{87}=7.9$ Hz, 1H, H-8) 7.60 (br dd, $J_{78}=7.9$ Hz, $J_{76}=7.4$ Hz, 1H, H-7), 7.48 (br dd, $J_{67}=7.4$ Hz, $J_{65}=7.7$ Hz, 1H, H-6), 7.30 (br d, $J_{56}=7.7$ Hz, 1H, H-5), 5.29 (br s, 2H, -NH₂), 4.12 (s, -CH₂).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 166.3 (s, ester carbonyl), 161.9 (s, amide carbonyl), 133.8 (d, C-6), 133.3 (s, C-4a), 128.9 (d, C-7), 127.9 (d, C-5), 127.3 (d, C-8), 124.6 (s, C-8a), 36.0 (t, -CH₂).

3.10.4. The synthesis of N-(1,3-dioxo-3,4-dihydroisoquinolin-2(1H)-yl)acetamide (405) and synthesis of 1*H*,1'*H*-2,2'-biisoquinoline-1,1',3,3'(4*H*,4'*H*)-tetrone (401).

Homophthalic anhydride (0.8 g, 4.9 mmol) was dissolved in hot glacial acetic acid (5ml) and hydrazine monohydrate (0.3 ml) was added into it dropwise and refluxed overnight. The precipitate was filtered off and washed with water to give a mixture of the products **405** and **401**. The mixture was dissolved in hot ethanol and **405** precipitated immediately and filtered to give the pure compound **405**. (0.85g, 74 %). The dimeric product **401** was obtained as the minor product.(0.16 g, 10 %).

405¹⁴⁹: White solid mp. 233.5-234.5°C.

¹H-NMR Spectrum: (400 MHz, DMSO-*d*₆) δ 10.4 (br s, 1H, -NH), 8.06 (br dd, $J_{87}=7.8$ Hz, 1H, H-8) 7.72 (br dd, $J_{67}=7.4$ Hz, $J_{65}=7.7$ Hz, 1H, H-6), 7.52 (br dd, $J_{78}=7.8$ Hz, $J_{76}=7.4$ Hz, 1H, H-7), 7.44 (br d, $J_{56}=7.7$ Hz, 1H, H-5), 4.35 (d, $J=6.3$ Hz, 2H, -CH₂), 3.33 (s, 3H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, DMSO-*d*₆) δ 168.0 (s, C-1), 167.5 (s, C-1), 134.9 (d, C-6), 134.0 (d, C-7), 128.2 (d, C-5), 127.8 (d, C-8), 127.5 (s, C-4a), 124.4 (s, C-8a), 36.4 (t, -CH₂), 20.3 (q, -CH₃).

3.10.5. The synthesis of 2-[acetyl(ethoxycarbonyl)amino]-1-oxo-1,2-dihydro-isoquinolin-3-yl ethyl carbonate (406).

The acetamide **405** (1g, 4.6mmol) was dissolved in THF (20ml) and cooled to -5°C. A solution of triethylamine (0.15 ml, 1.1 mmol) in 3 ml THF was added into it dropwise. Then ethylchloroformate (0.1 ml, 1.1 mmol) in 3ml THF was added dropwise at the same temperature. After the additon was completed, ethyl acetate (20 ml) was added to the mixture and washed with saturated sodiumbicarbonate (3x10ml) and with water (3x10ml). The organic layer was dried over magnesium chloride and the residue (1.35 g) was purified by column chromatography eluting with ethyl acetate/ hexane (7:3). The product (1.25 g) was obtained in 75 % yield.

406: ¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 8.32 (br d, $J_{87} = 8.1$ Hz, 1H, H-8), 7.65 (br dd, $J_{65} = 7.9$ Hz, $J_{67} = 7.5$ Hz, 1H, H-6), 7.51 (br d, $J_{56} = 7.9$ Hz, 1H, H-5), 7.44 (br dd, $J_{78} = 8.1$ Hz, $J_{76} = 7.5$ Hz, 1H, H-7), 6.53 (s, 1H, H-4), 4.32 (q, $J = 7.1$ Hz, 2H, -OCH₂), 4.24 (q, $J = 7.1$ Hz, 2H, -OCH₂), 2.69 (s, 3H, -CH₃), 1.36 (q, $J = 7.1$ Hz, 3H, -CH₃), 1.2 (q, $J = 7.1$ Hz, 3H, -CH₃),

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 168.7 (s, carbonyl), 159.6 (s, carbonyl), 151.8 (s, carbonyl), 150.8 (s, carbonyl), 142.1 (s, C-4), 135.7 (s, C-4a), 134.5 (d, C-6), 129.7 (d, C-8), 128.0 (d, C-5), 127.6 (d, C-7), 124.1 (s, C-8a), 96.3 (s, C-4a), 66.1 (t, -OCH₂), 64.3 (t, -OCH₂), 24.9 (q, -CH₃), 14.2 (q, -CH₃), 14.0 (q, -CH₃).

IR (KBr, cm⁻¹): 2991, 1785, 1761, 1693, 1371, 1303, 1220, 1178, 1096.

3.11. The synthesis of isochromeno[3,4-c]pyrazol-5(2H)-one (407).

To a solution of homophthalic anhydride (0.6g, 3.7mmol) in 5ml DMF hydrazine (1ml) was added and refluxed overnight. During the work-up procedure by the addition of water **407** precipitated and filtered off. (0.42g, 61 %).

407: Brown solid mp. 263-264°C.

¹H-NMR Spectrum: (400 MHz, DMSO-d₆) δ 13.14 (br s, 1H, -NH), 8.46 (br s, 1H, H-1), 8.17 (br d, $J_{67} = 7.9$ Hz, 1H, H-6), 7.92 (br d, $J_{98} = 7.7$ Hz, 1H, H-9), 7.92 (br dd, $J_{89} = 7.7$ Hz, $J_{87} = 7.5$ Hz, 1H, H-8), 7.49 (br dd, $J_{78} = 7.5$ Hz, $J_{76} = 7.9$ Hz, 1H, H-7), 4.52 (q, $J = 7.2$ Hz, 2H, -CH₂), 4.41 (q, $J = 7.2$ Hz, 2H, -CH₂), 4.39 (q, $J = 7.2$ Hz, 2H, -CH₂), 1.45 (t, $J = 7.1$ Hz, 3H, -CH₃), 1.40 (m, 9H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, DMSO-d₆) δ 161.8 (s, C-5), 157.3 (s, C-3a), 135.9 (d, C-8), 133.3 (s, C-9a), 131.2 (d, C-6), 127.2 (d, C-7), 125.6 (d, C-1), 123.7 (s, C-8), 118.7 (s, C-5a), 100.0 (s, C-9b).

Anal. Calcd for C₁₇H₁₉NO₇ : C, 64.52; H, 3.25; N, 15.05. Found: C, 63.25; H, 3.45; N, 16.03.

IR (KBr, cm⁻¹): 3218, 2958, 1733, 1705, 1685, 1625, 1590, 1496, 1434, 1318, 1242, 1187, 1076, 1053, 942, 871, 757.

3.12. The synthesis of 1,2-bis(bromomethyl)benzene (413).

At constant 125-130°C bromine (16g) was added into o-xylene (5g, 47mmol) dropwise. After the addition was completed, the mixture was cooled and let to mix overnight. The brominated product was precipitated and filtered off. (8.7g, 70 %).

413¹⁵⁸: White solid mp. 98°C (found) 96-97°C (lit.)

¹H-NMR Spectrum: (400 MHz, CDCl₃) □ 7.36-7.30 (m, 4H, aromatic protons), 4.66 (br s, 2H, -CH₂).

3.12.1. The synthesis of 1,2-bis(cyanomethyl)benzene (414).

Ortho-bromoxylene **413** (1.16g, 4.4mmol) was dissolved in 7 ml DMSO at 45°C, then sodium cyanide (0.86g, 17.6mmol) into it slowly. The mixture was stirred for 5 hours, then cooled, diluted with water and extracted with ether. The ether layer was dried over calcium chloride and evaporated to give yellow crystalline compound **414**. (0.3g, 43 %).

414¹⁵⁹: Yellow solid mp. 57-58°C (found) 59-60°C (lit.).

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 7.18 (s, 4H, aromatic protons), 3.58 (br s, 2H, -CH₂).

3.12.2. The synthesis of 1,2-bishomophthalic acid (289).

The nitrile **414** (1g, 6.4 mmol) was refluxed with 15 ml NaOH solution (10 %) for 4 hours. 2 ml ethanol was added in order to accelerate the reaction. After the reaction finished, ammonia was let to leave from the reaction medium and concentrated hydrochloric acid was added. The acid **289** precipitated and filtered off by washing with water. (1.12g, 90 %).

289¹⁶⁰: Yellow solid mp. 151°C (found) 150-152°C (lit.).

¹H-NMR Spectrum: (400 MHz, DMSO-d₆) δ 7.03 (s, 4H, aromatic protons), 3.46 (br s, 2H, -CH₂).

¹³C-NMR Spectrum: (100 MHz, D₂O) δ 173.1 (s, carbonyl), 133.6 (s, quaternary), 129.6 (d, aromatic carbons), 40.7 (t, -CH₂).

3.12.3. The synthesis of 2-chlorocarbonylmethyl-phenyl)-acetyl chloride (415).

Bishomophthalic acid (5g, 26 mmol) was suspended in dichloromethane and thionylchloride (7ml) was added into it and the mixture was refluxed till a clear solution was formed. The solvent and the excess thionyl chloride was evaporated to give the dichloride (5.1 g, 85 %).

415¹⁶¹: **¹H-NMR Spectrum:** (400 MHz, CDCl₃) δ 7.20 (s, 4H, aromatic protons), 4.00 (br s, 2H, -CH₂).

3.12.4. The synthesis of 1,2-bis-isocyanatomethylbenzene (293).

Silver nitrocyuanamide (3.5g) and anhydrous magnesium sulfate (0.35g) were suspended in anhydrous benzene (20ml) and stirred under nitrogen. Ortho-bromo xylene (2g, 7.6mmol) was added into the suspension and refluxed for 3 hours. The solvent was concentrated under vacuum to give the diisocyanate (1.3g, 90 %).

293¹³³: ¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 7.34 (s, 2H, aromatic protons), 7.28 (s, 2H, aromatic protons), 4.43 (br s, 2H, -CH₂).

3.12.5. The synthesis of methyl 2-((methoxycarbonyl)amino)methylbenzyl carbamate (418).

The diisocyanate (0.4g, 2.1mmol) was dissolved in methanol (5ml) and in 15 min the urethane precipitated and filtered off. (0.45g, 85 %).

418: White solid mp. 168-169°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 7.28 (s, 4H, aromatic protons), 4.94 (br s, 2H, -NH), 4.37 (br d, *J* = 5.8 Hz, 4H, -CH₂), 3.72 (s, 6H, -OCH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 157.5 (s, carbonyl), 138.3 (s, quaternary carbons), 128.2 (d, aromatic protons), 52.6 (t, -CH₂), 45.2 (q, -OCH₃).

Anal. Calcd for C₁₂H₁₆N₂O₄ : C, 57.13; H, 6.39; N, 11.1. Found: C, 58.94; H, 5.73; N, 11.2.

IR (KBr, cm⁻¹): 3321, 2991, 1696, 1571, 1250, 1071, 875, 714.

3.12.6. The synthesis of ethyl 2-{{(ethoxycarbonyl)amino}methyl}benzyl carbamate (419).

The diisocyanate (0.4g, 2.1mmol) was dissolved in ethanol (5ml) and in 15 min the urethane precipitated and filtered off. (0.52g, 88 %).

419: White solid mp. 115-116°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 7.28 (s, 4H, aromatic protons), 4.97 (br s, 2H, -NH), 4.36 (br d, *J* = 5.5 Hz, 4H, -CH₂), 4.17 (q, *J* = 7.1 Hz, 4H, -OCH₂), 1.27 (t, *J* = 7.1 Hz, 6H, -CH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 157.1 (s, carbonyl), 138.3 (s, quaternary carbons), 128.2 (d, aromatic protons), 61.4 (t, -OCH₂), 45.1 (t, -CH₂), 15.0 (q, -CH₃).

Anal. Calcd for C₁₄H₂₀N₂O₄ : C, 59.99; H, 7.19; N, 9.99. Found: C, 60.16; H, 6.78; N, 10.28.

IR (KBr, cm⁻¹): 3311, 2993, 1686, 1539, 1254, 1054, 876, 712.

3.12.7. The synthesis of phenyl 2-{{[phenoxy carbonyl]amino}methyl}benzyl carbamate (420).

The diisocyanate (0.4g, 2.1mmol) was dissolved in dichloromethane (10 ml) and phenol (0.2g, 2.1 mmol) was added into the solution dropwise and in 1 hour the reaction was completed. The solvent was evaporated to give the urethane (0.68g, 86%).

420: White-yellow solid mp. 112-113°C.

¹H-NMR Spectrum: (400 MHz, CDCl₃) δ 7.34 (s, 4H, aromatic protons), 4.94 (br s, 2H, -NH), 4.37 (br d, *J* = 5.8 Hz, 4H, -CH₂), 3.72 (s, 6H, -OCH₃).

¹³C-NMR Spectrum: (100 MHz, CDCl₃) δ 157.5 (s, carbonyl), 138.3 (s, quaternary carbons), 128.2 (d, aromatic protons), 52.6 (t, -CH₂), 45.2 (q, -OCH₃).

Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.1. Found: C, 58.94; H, 5.73; N, 11.2.

IR (KBr, cm^{-1}): 3318, 3061, 2924, 1690, 1554, 1454, 1362, 1248, 1159, 985, 912, 757.

3.12.8. The synthesis of benzyl 2-((benzoxycarbonyl)amino)methyl}benzyl carbamate (421).

The diisocyanate (0.4g, 2.1mmol) was dissolved in dichloromethane (10 ml) and benzyl alcohol (0.23g, 2.1 mmol) was added into the solution dropwise and in 1 hour the reaction was completed. The solvent was evaporated to give the urethane (0.75 g, 88 %).

421: White crystalline compound mp. 151-152°C.

1H -NMR Spectrum: (400 MHz, $CDCl_3$) δ 7.28 (s, 4H, aromatic protons), 7.18 (br dd, $J_{32} = 8.0$ Hz, $J_{34} = 7.2$ Hz, 4H, H-3), 6.89 (br t, $J_{43} = J_{45} = 7.2$ Hz, 4H, H-4), 6.81 (br d, $J_{23} = 8.0$ Hz, 4H, H-2), 5.71 (br s, 2H, -NH), 4.53 (s, 4H, -CH₂).

^{13}C -NMR Spectrum: (100 MHz, $CDCl_3$) δ 155.7 (s, carbonyl), 134.3 (s, quarternary carbons), 130.6 (d, aromatic protons), 129.7 (d, C-3), 129.7 (d, C-4), 128.9 (d, aromatic carbons), 120.8 (s, C-1), 115.4 (d, C-2), 44.0 (t, -CH₂).

IR (KBr, cm^{-1}): 3333, 3060, 2923, 1689, 1537, 1455, 1355, 1276, 1141, 976, 838, 750.

3.12.9. The synthesis of polyurethane (424).

To a solution of the diisocyanate (0.5g, 2.66mmol) in 15 ml dichloromethane hydrazine (0.13g, 2.66 mmol) was added. As soon as the hydrazine was added, a precipitate was formed and filtered off to give the polyurethane **424**.

3.12.10. The synthesis of polyurethane (427).

To a solution of the diisocyanate (0.5g, 2.66mmol) in 10 ml dimethylsulfoxide ethylene glycol (0.16g, 2.66 mmol) was added. It was let to stir overnight and by the addition of water the polyurethane **427** precipitated and was filtered.

3.12.11. The synthesis of polyurethane (428).

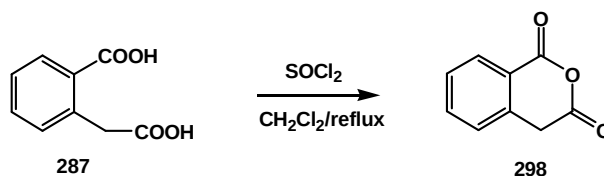
To a solution of the diisocyanate (0.6g, 3.2mmol) in 15 ml dichloromethane ethylenediamine (0.19g, 3.2 mmol) was added. As soon as the hydrazine was added, a precipitate was formed and filtered off to give the polyurethane **428**.

CHAPTER 4

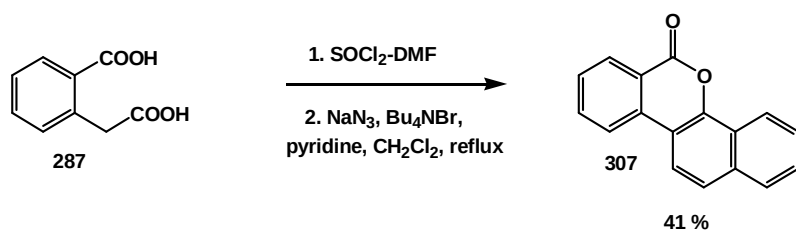
4. CONCLUSION

The aim of this thesis was the development of new synthetic methodologies starting from diazides leading to the synthesis of quinazoline **1** and benzodiazepinone **294** derivatives by a different methodology. The azidation reactions did not form the corresponding azides. However, by interesting mechanisms, unusual isocoumarine and indole derivatives were synthesized.

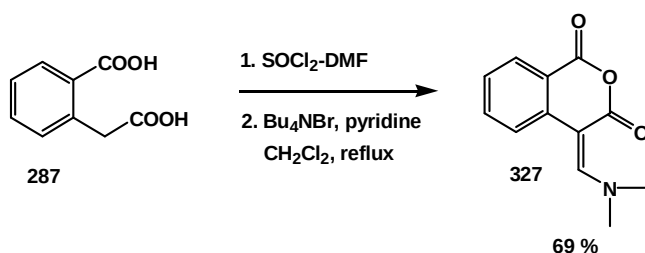
Homophthalic acid underwent chlorination reaction to give the lactone derivative instead of the dichloride. This case showed the great tendency of the acid to undergo cyclization.



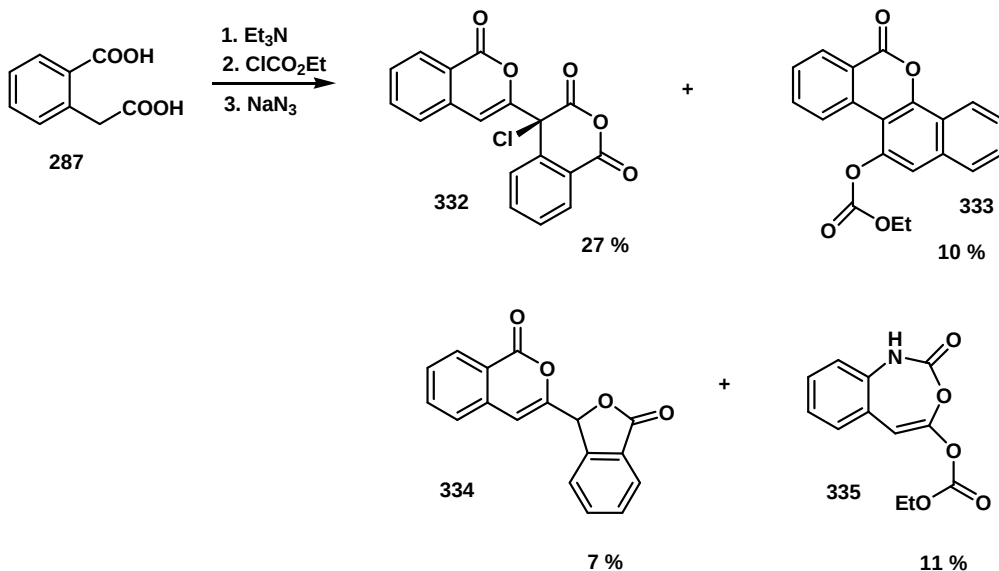
In the direct conversion of the acid groups into azide groups, the diacid was reacted with N,N-dimethylchloro sulfitemethaniminium chloride in the presence of sodium azide. Instead of the diazide, the obtained product was a benzochromen derivative **307**. Although sodium azide was used, incorporation of nitrogen atom was not observed. The obtained product was a benzochromen derivative **307**. This reaction allowed a new efficient synthetic method for the synthesis of benzochromen skeleton, which is found in important biological active compounds. The developed method is the shortest one compared with other published in the literature.



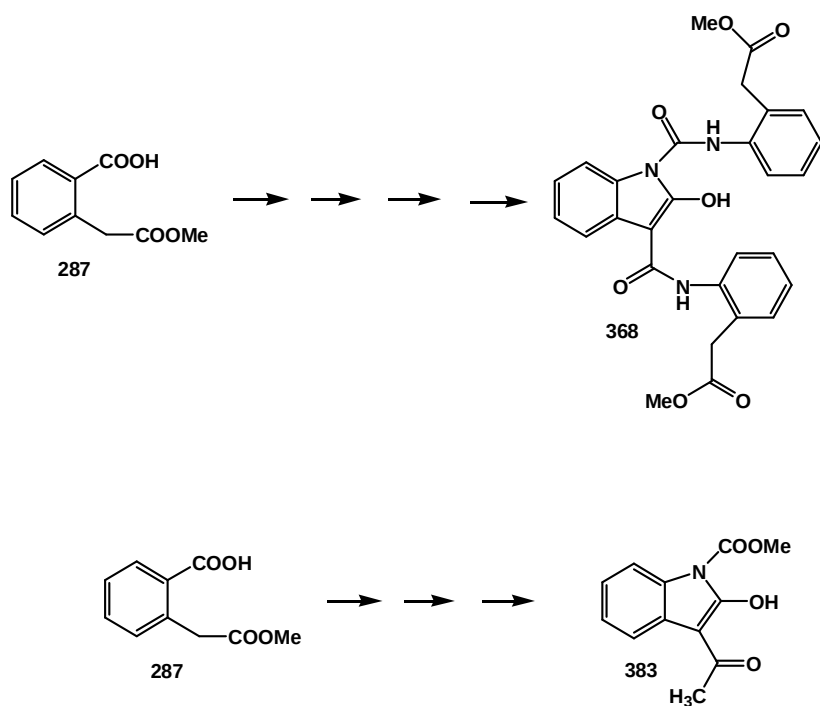
The reaction was run in the absence of sodium azide in order to determine the role of sodium azide. Instead of benzochromen derivative **307** amino methylene compound was formed and that underlined the role of sodium azide to act as a reducing agent.



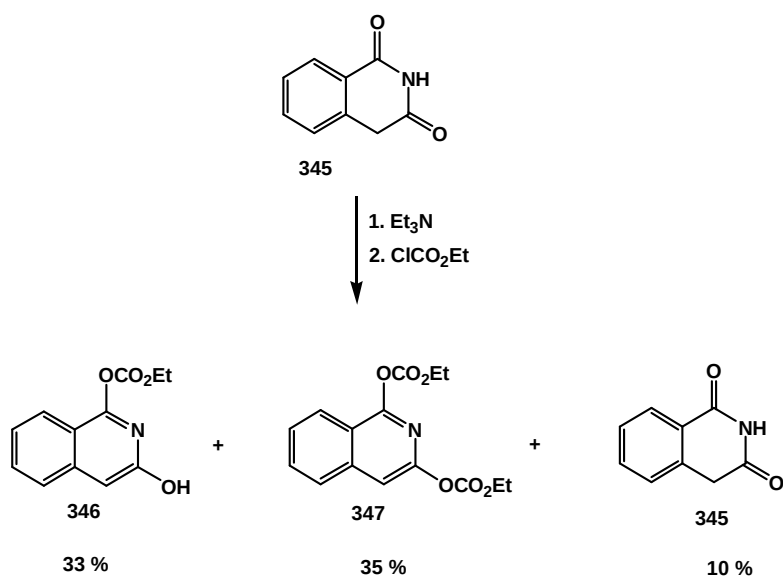
Another azidation reaction in the presence of triethyl amine, ethyl chloroformate and sodium azide yielded four different new unusual compounds **332**, **333**, **334** and **335**, among which only benzazapine derivative **335** has incorporated nitrogen atom.



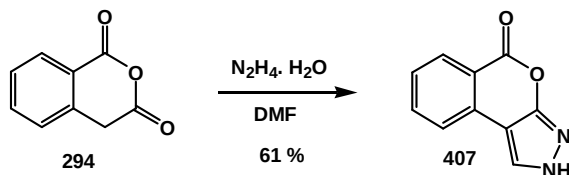
The azidation of half ester **287** generated new highly substituted indole derivatives such as **368** and **383**, which are expected to show biological activities.



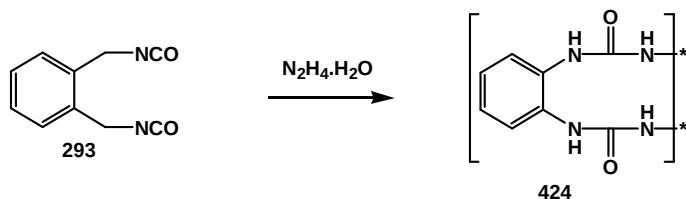
Furthermore, acetylation of isoquinoline derivative led to new quinazoline derivatives **346** and **347**.



The reaction of the lactone **294** with dimethylformamide led to a new synthetic method for the synthesis of pyrazole derivative **407**. This method will be used for the synthesis of new pyrazole derivatives.



In the synthesis of benzodiazepines, although the target compound was not formed, new polyurethane derivatives have been obtained. The diisocyanate was found to have the property of polymerization to give the corresponding polyurethanes. In the future, more polymerization reactions are going to be performed to yield new polyurethane derivatives.



REFERENCES

1. Petersen S.; Herlinger H.; Tietze.; Siefken W., *Angew. Chem.*, **1962**, 74, 855.
2. Bogentoft C.; Kronenberg L.; Daniellson C., *Acta Pharm. Suec.*, **1969**, 6, 489.
3. John S.; Jung B., *Pharmazie*, **1978**, 33, 299.
4. John S., *Pharmazie*, **1981**, 36, 583.
5. Shaban M.A.; Taha M.A.M.; Sharahira E.M., *Adv. Heterocycl. Chem.*, **1991**, 52, 1.
6. a) Nakagami K.; Yokoi S.; Nishumura K.; Nagai S.; Honda T.; Oda K.; Fujii K.; Kobayashi R.; Kojima M., *US Pat.* **1982**, 4323680. b) Haley G.J. *US Pat.* **1994**, 5373011.
7. Palanki M.S.S.; Suto M.J. *US Pat.* **1999**, 5939421.
8. Barker A.J. *US Pat.* **1999**, 5942514 and **1999**, 5932574.
9. Nauta W.T., *US Pat.* **1976**, 3980650.
10. Mizogami S.; Hiranuma H.; Sekiya T.; Hanuzuka M., *US Pat.* **1986**, 4607034.
11. a) Debruyne F.M.; Jardin A.; Colloi D.; Geffriaud R.C., *Eur. Urol.*, **1998**, 34, 169. b) Mckeage K.; Plosker G.L., *Drugs*, **2002**, 62, 633.
12. a) Jaillon P., *Clin. Pharmacokinet.*, **1980**, 5, 365. b) Punekar S.V.; Kelkar A.R.; Gavande P.M.; Rao N.R.; Date J.A.; Prem A.R., *J. Postgrad Med.*, **1995**, 41, 1999.
13. a) Andersen M.; Dahlstrand C.; Hqye K., *Eur. Urol.*, **2000**, 38, 485. b) Satar S.; Sebe A.; Avci A.; Yesilagac H.; Gokel Y., *Human and Experimental Toxicology*, **2005**, 24, 337. c) Evans M., Perara P.W.; Donoghue J., *Br. Med. J.*, 1997, 314, 1869. d) Graham R.M.; Pettinger W.A., *New Engl. J. Med.*, **1979**, 300, 232.

14. a) Naik S.R.; Sheth U.K., *Indian J. Exp. Biol.*, **1975**, 13, 27. b) Kiyangi A.; Field M.J.; Pawsey C.C., *Lancet*, **1990**, 335, 29.
15. Takayoshi K.; Hiroshi M.; Takashi F.; Shoji T.; Toshio G., *Biol. Chyrst.*, **2002**, 58, 622.
16. Ledig K.W., *US Pat.* **1978**, 4, 118, 561.
17. Grosso, J.; Nichols, D. *J. Med. Chem.* **1980**, 23, 1261.
18. McCusker J.E.; Main D.A.; Johnson, K.S.; Grasso, A.C.; McElwee-White, L. *J. Org. Chem* **2000**, 65, 5216.
19. Yoshida, T.; Kamde, N.; Murai, S.; Sonoda, N. *J. Org. Chem.* **1987**, 52, 1611.
20. Reddy N.A.V.; Kamal A.; Sattur P.B. *Synth. Comm.* **1988**, 18, 525.
21. Koch H.J.; Raschka C.; Speich R.; Jeuni R.; Opravil M.; Jaccard R., *Swiss Med. Weekly*, **2002**, 132, 105.
22. Liu J.K.; Couldwell W.T., *Neuro. Care*, **2005**, 2, 124.
23. Takeuchi K.; Sakamoto S.; Nagayashi Y.; Nishizowa H.; Matsubara J., *Euro. J. Cardio-Thoracic Surg.*, **2004**, 26, 956.
24. Gilran I.; Bailey J.; Tu D.; Holden R.R.; Weaver D.F.; Houlden R.L., *New Engl. J. Med.*, **2005**, 352, 1324.
25. a) Dostert P.; Benedetti M.S.; Della V.F.; Allievi C.; La Croix R.; Dordain G.; Vernoy D.; Durif F., *Advan. in Neuro.*, **1993**, 60, 218. b) Antkiewioz-Michaluk L., *Pol. J. Pharmacol.*, **2002**, 54, 567. c) Pagel P.; Schubert R.; Wolf H.U., *J. Chromatography B: Biomed. Sci. App.*, **2000**, 746, 283. d) Jenner P., *Journal of Neurology*, 1992, 239, 1432.
26. a) Gentry L.C.; Lukas R.J., *Pharmacology*, **2001**, 29, 1038. b) Krodel E.K.; Beckman R.A.; Cohen J.B., *Molecular Pharmacology*, **1979**, 15, 294.
27. Bischler, A.; Napieralski, B., *Ber.* 1893, **1903**, 26, 1891.
28. Pictet A.; Gams A., *Ber.*, **1910**, 43, 2384 .
29. a) Pomeranz C., *Monatsch*, **1893**, 14, 116. b) Fritsch P., *Ber.*, **1893**, 26, 419.
30. Ghorai B.K.; Jiang D.; Herndon J.W., *Org. Lett.*, **2003**, 5, 4261.
31. Korivi P.R.; Cheng C.H., *Org. Lett.*, **2005**, 7, 5179.
32. Matsuda H.; Shimoda H.; Yoshikawa M., *Bioorg. Med. Chem.*, **1999**, 7, 1445.

33. Yoshikawa M.; Harada E.; Naitoh Y.; Inoue K.; Matsuda H.; Shimoda H.; Yamahara J.; Murakami N., *Chem. Pharm. Bull.*, **1994**, 42, 2225.
34. Matsuda H.; Shimoda H.; Yamahara J.; Yoshikawa M.; *Bioorg. Med. Chem. Lett.*, **1998**, 8, 215.
35. Whyte A.C.; Gloer J.B.; Scoot J.A.; Mallock D.; *J. Nat. Prod.*, **1996**, 59, 765.
36. Nozawa K.; Yamada M.; Tsuda Y.; Kawai K.; Nakajima S., *Chem. Pharm. Bull.*, **1981**, 29, 2689.
37. Furuta T.; Fukuyama Y.; Asakawa Y., *Phytochemistry*, **1986**, 25, 517.
38. Lee J.H., Park Y.J., Kim H.S., Hong Y.S., Kim K.W., Lee J.J., *Antibiot.*, **2001**, 54, 463.
39. Chinworungsee M.; Kittakoop P.; Isaka M.; Chanphen R.; Tanticharoen M.; Thebtaranonth Y.J., *J. Chem. Soc. Perkin Trans. 1*, **2002**, 2473.
40. Barry R.D.; *Chem. Rev.*, 1964, 64, 229.
41. Piacente S.; Pizza C.; De Tommasi N.; Mahmood N., *J. Nat. Prod.*, **1996**, 59, 565.
42. H.S. Kim, et al.; *J. Ethnopharmacol.*, **2000**, 69, 79.
43. Goel R.K.; Maiti R.N.; Manickam M.; Ray A.B., *Indian. J. Exp. Biol.*, **1997**, 35, 1080.
44. Pu HL; Huang X; Zhao J.H.; Hong A., *Planta Med.*, **2002**, 68 , 372.
45. Prithiviraj B.; Singh U.P.; Manickam M.; Srivastava J.S.; Ray A.B., *Plant Pathol.*, **1997**, 46, 224.
46. Zamarrud; Viqor U. A.; Shazia A.; Qaiser M., *Acta Crystall.*, **2006**, 62, 405.
47. Masahiro K.; Miyuki K.; Eiji M.; Haruhisa N., *Pharmaco. and Toxicol.*, **2002**, 90, 106-108.
48. Haiqing Y.; Bernd J.; Paul H.; Richar E. T., *Curr. Org. Synt.*, **2004**, 1.
49. Kumagai H.; Masuda T.; Ishizuka M.; Takeuchi T.J., *Antibiotics*, **1995**, 48, 175.
50. Warnell J.L.; Shriner R.L., *J.Am.Chem.Soc.*, **1957**, 79, 3165.
51. Allen C.F.H.; Van Allan J.A., *J.Am. Chem. Soc.*, **1943**, 65, 1230.
52. Prasad D.; Chaudhury D.N., *J. Indian Chem. Soc.*, **1962**, 39, 672.

53. Maitte P., *Ann. Chim.*, **1954**, 9, 431.
54. Chatterjea J.N.; Mucherjee H., *J. Indian Chem. Soc.*, **1960**, 37, 443.
55. Haiqing Y.; Bernd J.; Paul H.; Richard E.T., *Curr. Org. Synth.*, **2004**, 1,9.
56. Angelis M.D.; Stossi F.; Waibel M.; Katznellenbogen B.S.; Katznellenbogen J.A., *Bioor. Med. Chem.*, **2005**, 13, 6529.
57. Turner R.T.; Rickard D.; Spelsberg T.C.; Sibonga J.D., *In Osteoporosis; Humana Press.*, **2002**, 309.
58. Mendelsohn M.E., *Am. J. Cardiol.*, **2002**, 89, 12E.
59. Behl C., *Nat. Rev. Neurosci.*, **2002**, 3, 442.
60. Mosselman S.; Polman J.; Dijkema R., *FEBS Lett.*, **1996**, 392, 49.
61. Kuiper G.G.; Enmark E.; Pelto H.M.; Nilsson S.; Gustafsson J.A., *Proc. Natl. Acad. Sci. U.S.A.*, **1996**, 93, 5925.
62. Ohta S.; Kamata Y.; Inagaki T.; Masuda Y.; Yamashita M.; Kawasaki I., *Chem. Pharm. Bull.*, **1993**, 41, 1118.
63. Yoshikawa M.; Shimada H.; Yagi N.; Murakami N.; Shimoda H.; Yamahara J.; Matsuda H., *Chem. Pharm. Bull.*, **1996**, 44, 1890.
64. Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L., *Tetrahedron.*, **2003**, 59, 2067.
65. Srivastava B.; Shukla Y. *Cancer Lett.*, **1998**, 134, 91.
66. Qi M.; Anderson A.E.; Chen D.Z.; Sun S.; Auborn K.J., *Mol. Med.*, **2005**, 11, 59.
67. Jin L.; Qi M.; Chen D.Z.; Anderson A.; Yong G.Y.; Arbeit J.M.; Auborn K.J., *Cancer Res.*, **1999**, 59, 3991.
68. Grubbs C.J.; Steele V.E.; Casebolt T.; Juliana M.M.; Eto I.; Whitaker IM; Dragnev K.H.; Kelloff G.J.; Lubet L.R., *Anticancer Res.*, **1995**, 15, 709.
69. Garikapaty V.P.; Ashok B.T.; Chen Y.G.; Mittelman A.; Iatrapoulus M.; Tiwari R.K.; *Oncol Rep.*, **2005**, 13, 89. Sarkar F.H.; Li Y., *J. Nutr.*, **2004**, 134, 3493S.
70. Kojima T.; Tanaka T.; Mori H., *Cancer Res.*, **1994**, 54, 1446.
71. Srivastava B.; Shukla Y., *Cancer Lett.*, **1998**, 134, 191.

72. a) Carter T.H.; Liu K.; Ralph W.J.; Chen D.Z.; Qi M.; Fan S.; Yuan F.; Rosen E.M.; Auburn K.J.; *J. Nutr.*, **2002**, 132, 3314. b) Chen I.; McDougal A.; Wang F.; Safe S.; *Carcinogenesis*, **1998**, 45, 1129.
73. Chang X.; Tou J.C.; Hong C.; Kim H.A.; Riby J.E.; Firestone G.L.; Bjeldones L.F., *Carcinogenesis*, **2005**, 26, 771.
74. Shen T.Y.; Winter C.A., *Adv. Drug Res.*, **1987**, 12, 89.
75. Fenuk W.; Humphrey PRA, *Drug Der. Res.*, **1992**, 26, 235.
76. Frishman W.H., *J.Med.*, **1983**, 308, 940.
77. Schneider E.A.; Wrigthman F., *Rel. Comp. Compr. Treatise*, **1978**, 1, 29.
78. Brossi A.; Suffness M., *The Alkoloids* , **1990**, 37, 1990.
79. Gribble G.W., *The Alkoloids*, **1990**, 39, 239. Bisagni E., *Act. Chem. Ther.*, **1990**, 17, 33.
80. Schlittler E., *The Alkoloids*, **1965**, 8, 287.
81. Osborne N.N., *Biology of Serotonergic Transmission*, John Wiley, Chichester, UK, **1982**.
82. Baeyer A., *Ann.*, **1866**, 140, 295.
83. Van Order R.B., Lindwall H.G., **1942**, 30, 69.
84. Fischer E., Jourdan F., *Ber.*, **1883**, 16, 241.
85. Buchwald S. L.; Wagaw S.; Yang B.H., *J. Am. Chem. Soc.*, **1998**, 120, 6621.
86. a) Bischer A. *et al*, *Ber.*, **1892**, 25, 2860. b) Bischer A., *Ber.*, **1893**, 26, 1336. c) Möhlau R., *Ber.*, **1881**, 14, 171. d) Möhlau R., *Ber.*, **1882**, 15, 2480. e) Nelson R.; Seefeld R.L., *Ber.*, **1958**, 80, 5957.
87. a) Reissert A., *Ber.*, **1897**, 30, 1030. b) Noland W.E., Banda R.J., *Org. Synt.*, **1973**, 5, 567. c) Noland W.E., Banda R.J., *Synth.*, **1963**, 4, 40. d) J.P., Brue W.J., *J. Am. Chem. Soc.*, **1945**, 67, 423.
88. Madelung W., *Ber.*, **1912**, 45, 1128.
89. Houlihan W.J.; Parrino V.A.; Uike Y., *J. Org. Chem.*, **1981**, 46, 4511.
90. a) Nenitzescu C.D., *Bull. Soc. Chim. Rom.*, **1929**, 11, 37. b) Allen J.R.; Pidacks C.J.; Weiss M.J., *J. Am. Chem. Soc.*, **1966**, 88, 2536. c) Allen J.R., *Org. React.*, **1973**, 20, 337. d) Pawlak J.M.; Khau V.V.; Hutchison D.R.; Mortinelli M.J., *J. Org. Chem.*, **1996**, 61, 9055.

91. a) Castro C.E.; Stephens R.D., *J. Org. Chem.*, **1963**, 28, 2163. b) Castro C.E.; Stephens R.D., *J. Org. Chem.*, **1963**, 28, 3313.
92. Molina P.; Alcantara J.; Lopez Leonardo C., *Tetrahedron Lett.*, **1995**, 36, 953.
93. a) Hemetsberger H.; Knittel D.; *Monatsch. Chem.*, **1972**, 103, 194. b) Knittel D., *Synt.*, **1985**, 186.
94. a) Gassman P.G.; Gruetzmacher G.; Van Bergen T.J., *J. Am. Chem. Soc.*, **1973**, 95,6508. b) Gassman, P. G.; Van Bergen, T. J., *J. Am. Chem. Soc.*, **1974**, 96, 5508. c) Gassman, P. G.; Gruetzmacher, G.; Van Bergen, T. J., *J. Am. Chem. Soc.*, **1974**, 96, 5512.
95. a) Batcho, A. D.; Leimgruber, W. *U.S. Patent* 3,732,245 and *U.S. Patent* 3,976,639. b) Smallheer, J. M. *J. Org. Chem.* **1981**, 46, 1753. c) Clark, R. D.; Repke, D. B., *Heterocycles*, **1984**, 22, 195-221. d) Batcho, A. D.; Leimgruber W., *Org. Synth.*, **1985**, 63, 214.
96. Garcia, E. E.; Fryer, R. I., *J. Heterocycl. Chem.*, **1974**, 11, 219.
97. Ponticello, G. S.; Baldwin J. J., *J. Org. Chem.*, **1979**, 44, 4003.
98. a) Bartoli G.; Palmieri, G.; Bosco M.; Dalpozzo R., *Tetrahedron Lett.*, **1989**, 30, 2129. b) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Palmieri, G.; Marcantoni, E.; *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2757. c) Dobbs, A. P.; Voyle, M.; Whitall, N., *Syn.*, **1999**, 1594. d) Dalpozzo, R.; Bartoli, G., *Curr. Org. Chem.*, **2005**, 9, 163.
99. a) Dobson D.; Todd A.; Gilmore J., *Synth. Commun.*, **1991**, 21, 611. b) Dobson, D. R.; Gilmore, J.; Long, D. A., *Synth.*, **1992**, 79.
100. Dobbs, A., *J. Org. Chem.*, **2001**, 66, 638.
101. Larock, R.C.; Yum, E. K.; Refvik, M. D., *J. Org. Chem.*, **1998**, 63, 7652.
102. Deak G. et al, *J. Med. Chem.*, **1977**, 20, 1384.
103. Beckett A.H.; Daisley R.W.; Walter J., *Tetrahedron*, **1968**, 24, 6093.
104. Gassman P.G.; Gruetzmacher G.; Van Bergen T.J., *J. Am. Chem. Soc.*, **1974**, 96, 5508.

105. Brown D.S.; Elliot M.C.; Moddy C.J.; Mowlem T.J.; Marino J.P.; Padwa A., *J. Org. Chem.*, **1994**, 59, 2447.
106. Doyle Michael P.; Shanklin Michael S.; Pho Hoan Q.; Mahapatro N., *J. Org. Chem.*, **1988**, 53, 1017.
107. Lee Y. R.; Jung Y. S.; Byung S. K., *Tetrahedron Lett.*, **1999**, 40, 8219.
108. Wright C.; Shulkind M.; Jones K.; Thompson M., *Tetrahedron Lett.*, **1987**, 28, 6389.
109. Axon J.; Boiteau L.; Boivin J.; Forbes J.; Zard S., *Tetrahedron Lett.*, **1994**, 35, 1719.
110. Boivin J.; Yousfi M.; Zard S., *Tetrahedron Lett.*, **1994**, 35, 9553.
111. Snider B.B, *Chem. Rev.*, **1996**, 96, 339.
112. Davies T.; Kapur N.; Parsons A., *Tetrahedron Lett.*, **1998**, 39, 4397.
113. Goehring R.; Sachdeva Y.; Pisipati S.; Sleevi M.; Wolfe J., *J. Am. Chem. Soc.*, **1985**, 107, 435.
114. Rigby J.; Danca D., *Tet. Lett.*, **1999**, 40, 6891.
115. Zhang X.; Foote S., *J. Am. Chem. Soc.*, **1993**, 115, 8867.
116. Sternbach L.H. *The discovery of librium*. Agents Actions 1972, 2,193.
117. Michler W.; Zimmermann A., Zurich S., *Ber. Deutsc. Chem. Gesell.*, 1881,14, 2177.
118. Taylor, J.B., Tully, W. R., *J. Chem. Soc., Perkin Trans. 1*,1976, 12, 1331.
119. Yoshida T., *Bull.Chem. Soc. Jpn.*, 1987, 60, 1793.
120. Hayashi *et al*, *Heterocycles*, 1998, 48, 1331.
121. Miyedera *et al*, *J. Med. Chem.*, 1971, 14, 520.
122. Ning *et al*, *J. Org. Chem.*, 1976, 41, 2720.
123. Breuer H., *Tetrahedron Lett.*, 1976, 23, 1935.
124. Bocelli *et al*, *Tetrahedron Lett.*, 1999, 40, 2623.
125. Garanti L., Molteni G., Broggin G., *J. Chem. Soc., Perkin Trans. 1*, 2001, 1816.
126. Wiklund P., Rogers-Evans M., Bergman J., *J. Org. Chem.*, 2004, 69, 6371.
127. Walter R., Stahlofen P., *Chem. Ber.*, 1957, 90,815.

128. Ried W., Torinus E., *Chem. Ber.*, 1959, 92, 2902.
129. Balakrishna M.S., Kaboudin B., *Tet. Lett.*, 2001, 42, 1127.
130. Kaboudin B., Navaee K., *Heterocyc.*, 2001, 55, 1443.
131. Jarikato D.V., *Tetrahedron Lett.*, 2003, 44, 1835.
132. Descours, D., Festal, D., *Synth.*, 1983, 12, 1033.
133. Boyer, J. H., Manimaran T., Wolford L. T., *J. Chem. Soc., Perkin Trans. 1*, 1988, 8, 2137.
134. a) Sheehan J.C.; O'Neill R.C. *J. Am. Chem. Soc.* **1950**, 72, 4614. b) Amalendu B.; Mohan M.A.; Santa B.; Saumitra D. *Indian J. Chem.* **1987**, 64, 34.
135. Michael G.; Hutchings A.; Chippalande M.; Ferguson I. *Tetrahedron* **1988**, 44, 3727.
136. Arrieta A.; Aizpurua J.M.; Palomo C. *Tetrahedron Lett.* **1984**, 25, 3365.
137. Balanika M.; Hussain N.; Amin S.; Hecht S.S., *J. Org. Chem.* **1998**, 53, 1017.
138. a) Nozawa K.; Yamada M.; Tsuda Y.; Kawai K.; Nakajami S. *Chem. Pharm. Bull.* **1981**, 29, 2491. b) Kaji H.; Yamada M.; Nozawa K.; Nakajima S. *Org. Prep. Proced. Int.* **1986**, 18, 253. c) Hussain M.; Hussain M.T.; Rama N.H.; Hameed S.; Malik A.; Khan K.M. *Nat. Prod. Res.* **2003**, 17, 207. d) Hussain M.; Rama N.H.; Hameed S.; Malik A.; Khan K. *Nat. Prod. Res.* **2005**, 19, 41. e) Zamani K.; Faghihi K.; Ebrahimi S. *Turk. J. Chem.* **2005**, 29, 171.
139. Algi F.; Balci M. *Synthetic Commun.* **2006**, 36, 2293.
140. Harayami T.; Yasuda H. *Heterocycles* **1997**, 46, 61.
141. Rayaparabu D.K.; Shukla P.; Cheng C.H. *Org. Lett.* **2003**, 5, 4903.
142. a) Belgaonkar V.; Usgaonkar R.N. *Tetrahedron Lett.* **1975**, 3849. b) Deady L.W.; Rodemann T. *Heterocyclic Chem.* **2001**, 38, 1185.
143. Barikani M.; Yeganeh H.; Ataei S.M. *Polym. Int.* **1999**, 48, 1264.
144. Spangler R.J. *J. Org. Chem.* **1977**, 42, 1697.
145. Nanded V.; India M. *Tetrahedron Lett.* **2002**, 43, 3413.

146. La Monica G.; Ardizzora G.; Maddinelli G.; Tollari S. *J. Mol. Cat.* **1986**, 38, 327.
147. a) Goehring R.R. *J. Am. Chem. Soc.* **1985**, 107, 435. b) Kawase M. *Synthetic Commun.* **1990**, 20, 887.
148. Padwa A.; Beall S.L.; Eidell C.K.; Worsencroft K.J. *J. Org. Chem.* **2001**, 66, 2414.
149. Rosen G.; Popp F.D. *J. Heterocyclic Chem.* **1969**, 6, 9.
150. a) Bodwell G.J.; Houghton T.J.; Miller D. *Tetrahedron Lett.* **1997**, 38, 1469. b) Boyer O. *Mod. Plast* **1937**, 24, 149.
151. a) Barikani M.; Yeganeh H.; Ataei M.S. *Polym. Int.* **1999**, 48, 1264. b) Mallakpour S.; Shahmohammadi M.H. *Polym. Int.* **2004**, 53, 184. c) Ioan S.; Lupu M.; Macocinschi D. *High Per. Polym.* **2005**, 17, 533.
152. Kita Y.; Akai S.; Yashgi M.; Nakajima Y.; Yasuda H.; Tamura Y. *Tetrahedron Lett.* **1984**, 25, 6027.
153. Banerjee A.; Adak M.M.; Das S.; Banerjee s.; Sengupta S. *J. Ind. Chem. Soc.* **1987**, 64, 34.
154. Sheehan J.C.; O'Neill R.C. *J. Am. Chem. Soc.* **1950**, 72, 4614.
155. Schnekenburger J. *Ach. Pharm.* **1965**, 298, 405.
156. Niki T.; Mizukoshi T.; Takahashi H.; Satow J.; Ogura T.; Yamagishi K.; Suzuki H.; Hayasaka F. *PCT Int. App.* **2001**, 350.
157. La Monica G.; Maddinelli G.; Tollari S. *J. Mol. Cataly.* **1986**, 38, 327.
158. Long Y.Q.; Jiang X.H.; Dayam R.; Raveendra S.T.; Shoemaker R.S.; Shizuko N.N. *J. Med. Chem.* **2004**, 47, 2561.
159. Kobler H.; Schusker K.H.; Simchen G. *Just. Lieb. Ann. Chem.* **1978**, 12, 1946.
160. Grossert J.S.; fang D.D.; White R.L. *Can. J. Chem.* **2005**, 83, 1878.
161. Aubert T.; Farnier M.; Guillard R. *Synth.* **1990**, 2,149.

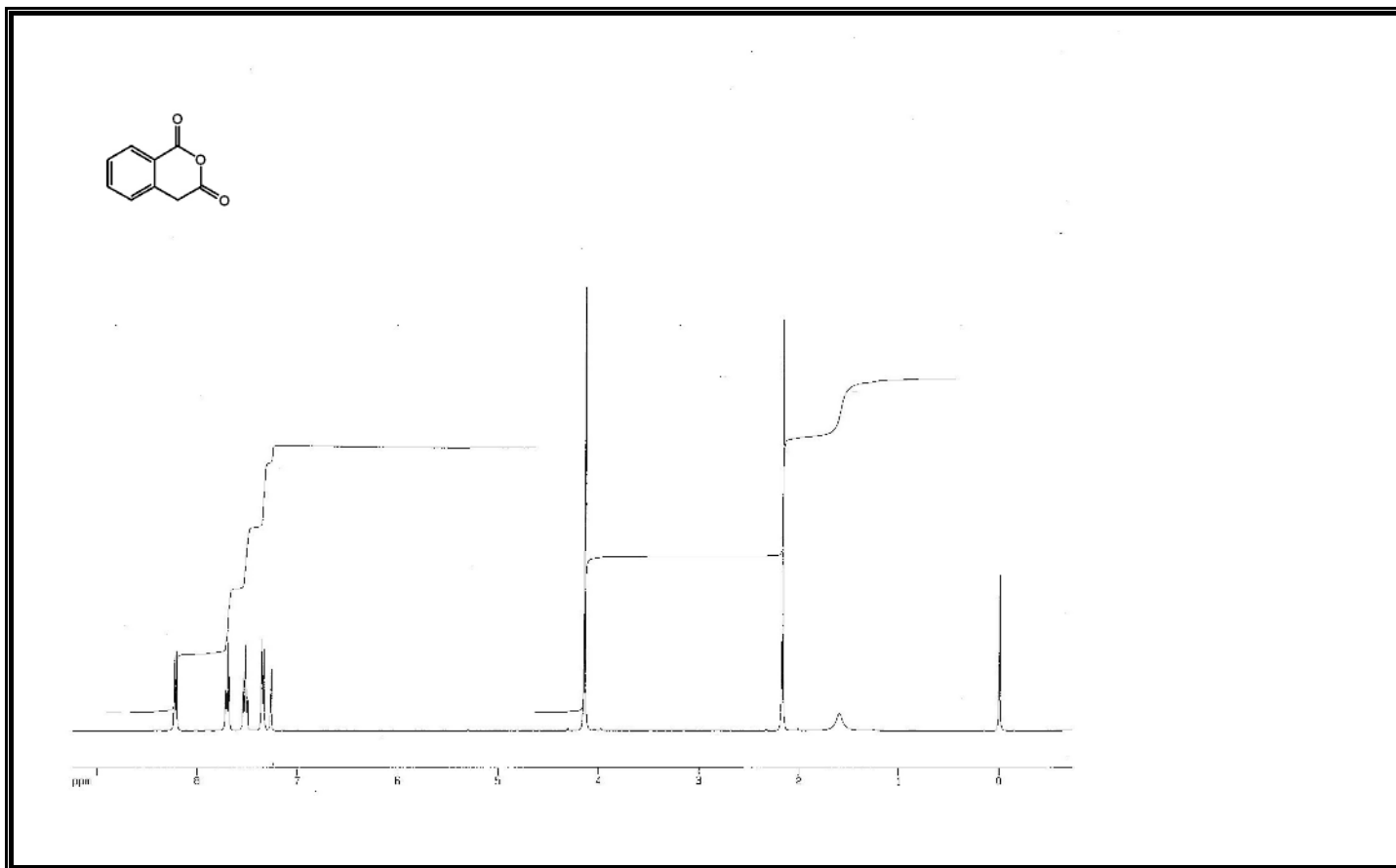


Figure A1 ^1H -NMR Spectrum of Compound 298.

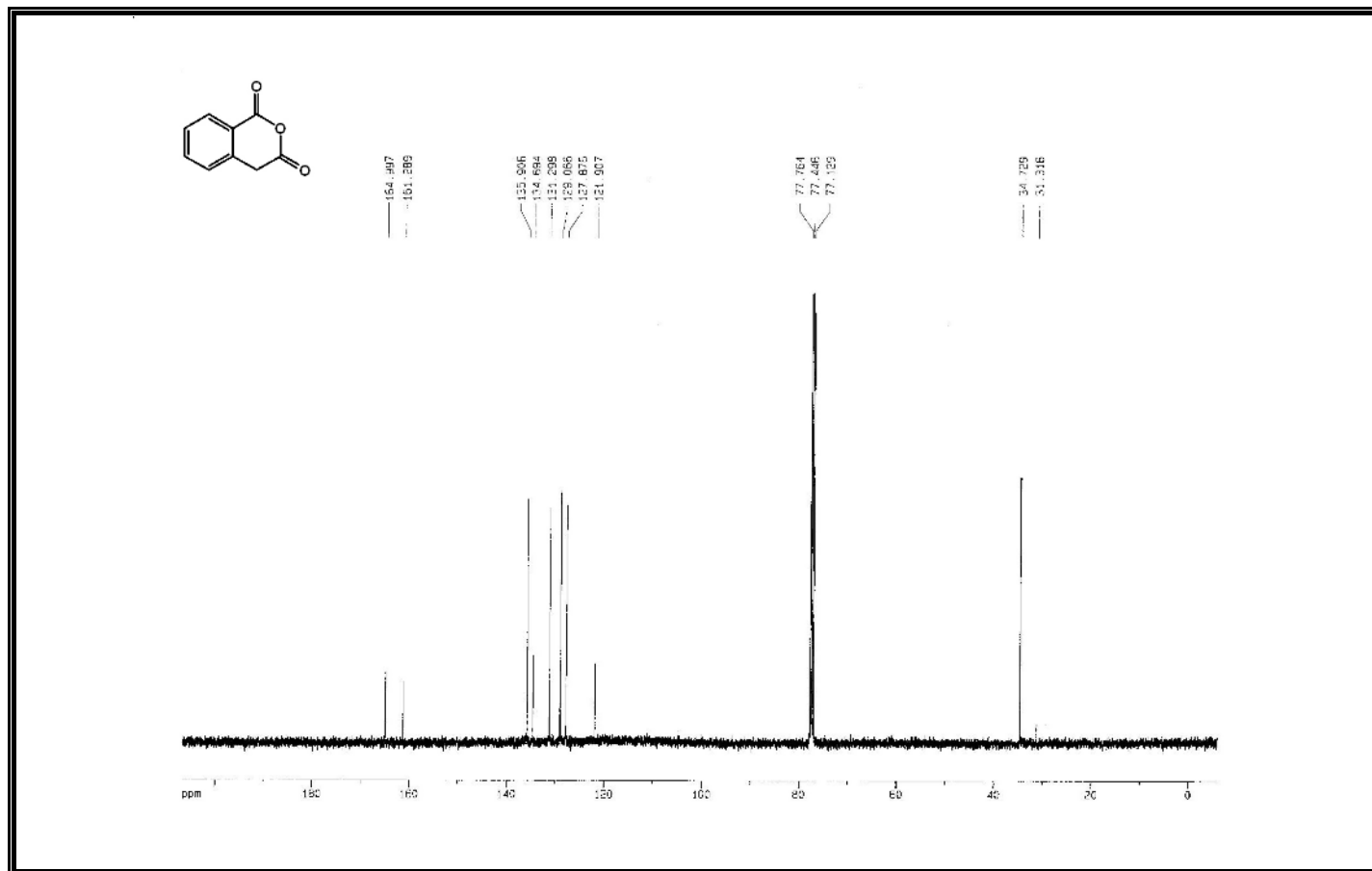


Figure A2 ¹³C-NMR Spectrum of Compound 298.

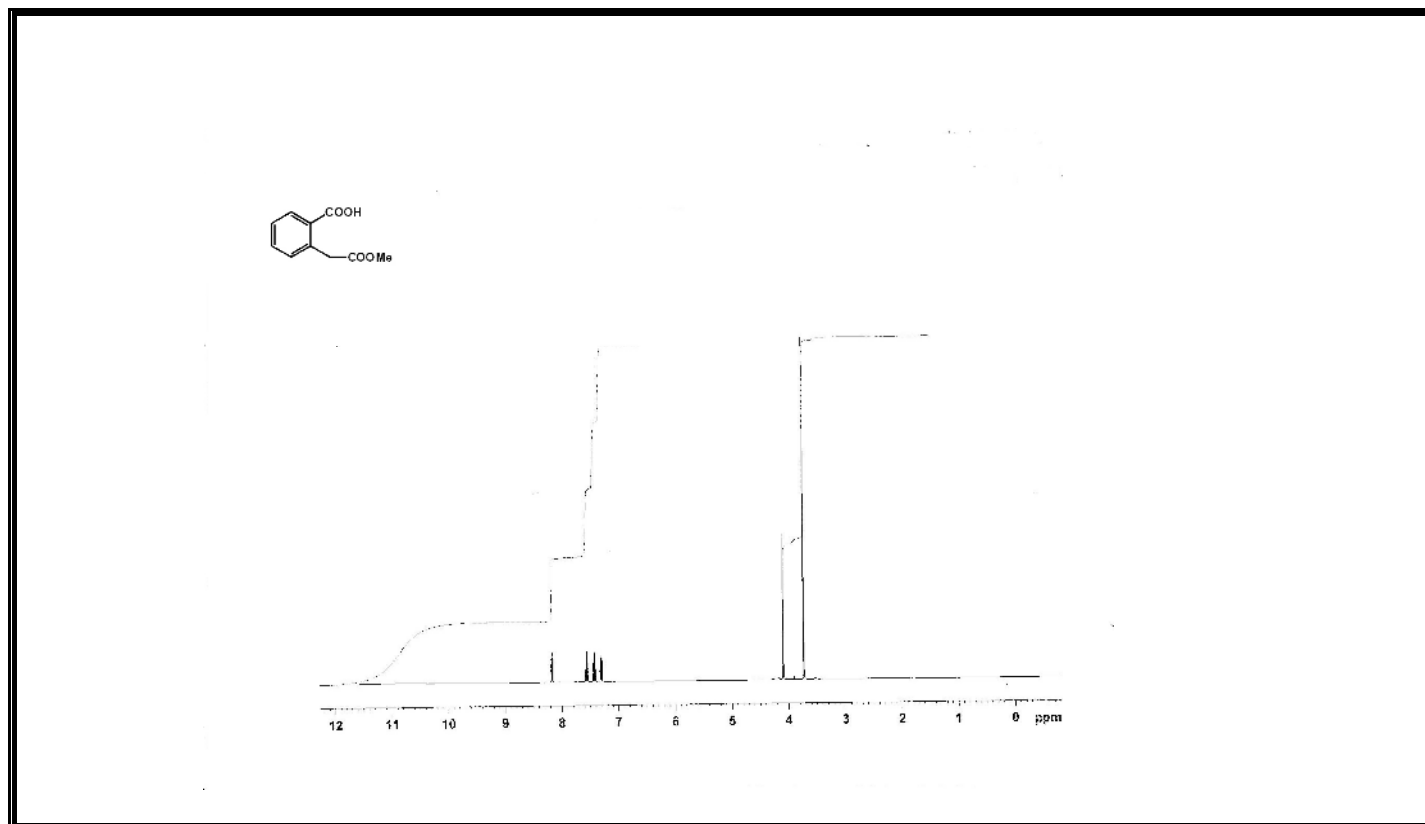


Figure A3 ^1H -NMR Spectrum of Compound 299.

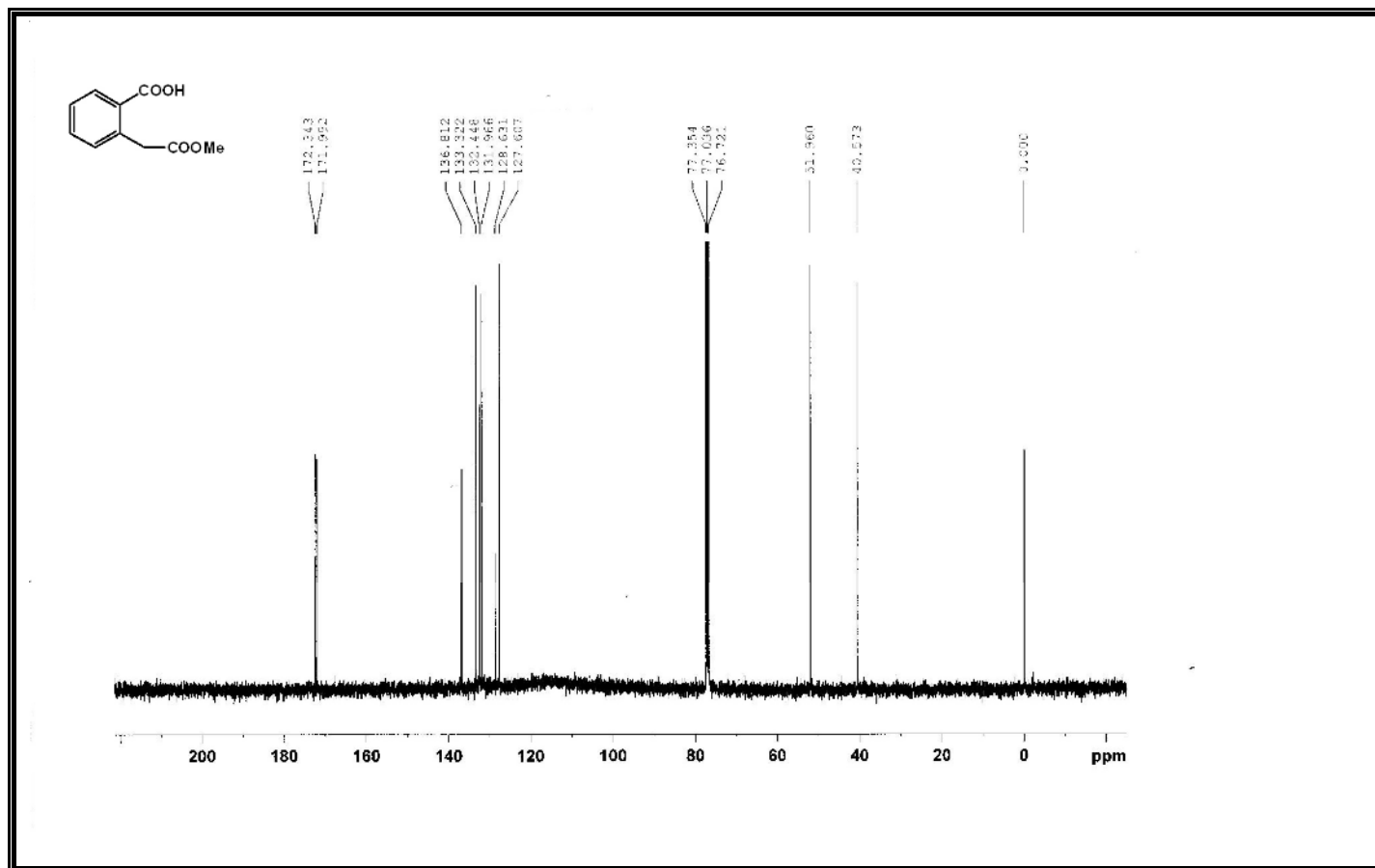


Figure A4 ^{13}C -NMR Spectrum of Compound 299.

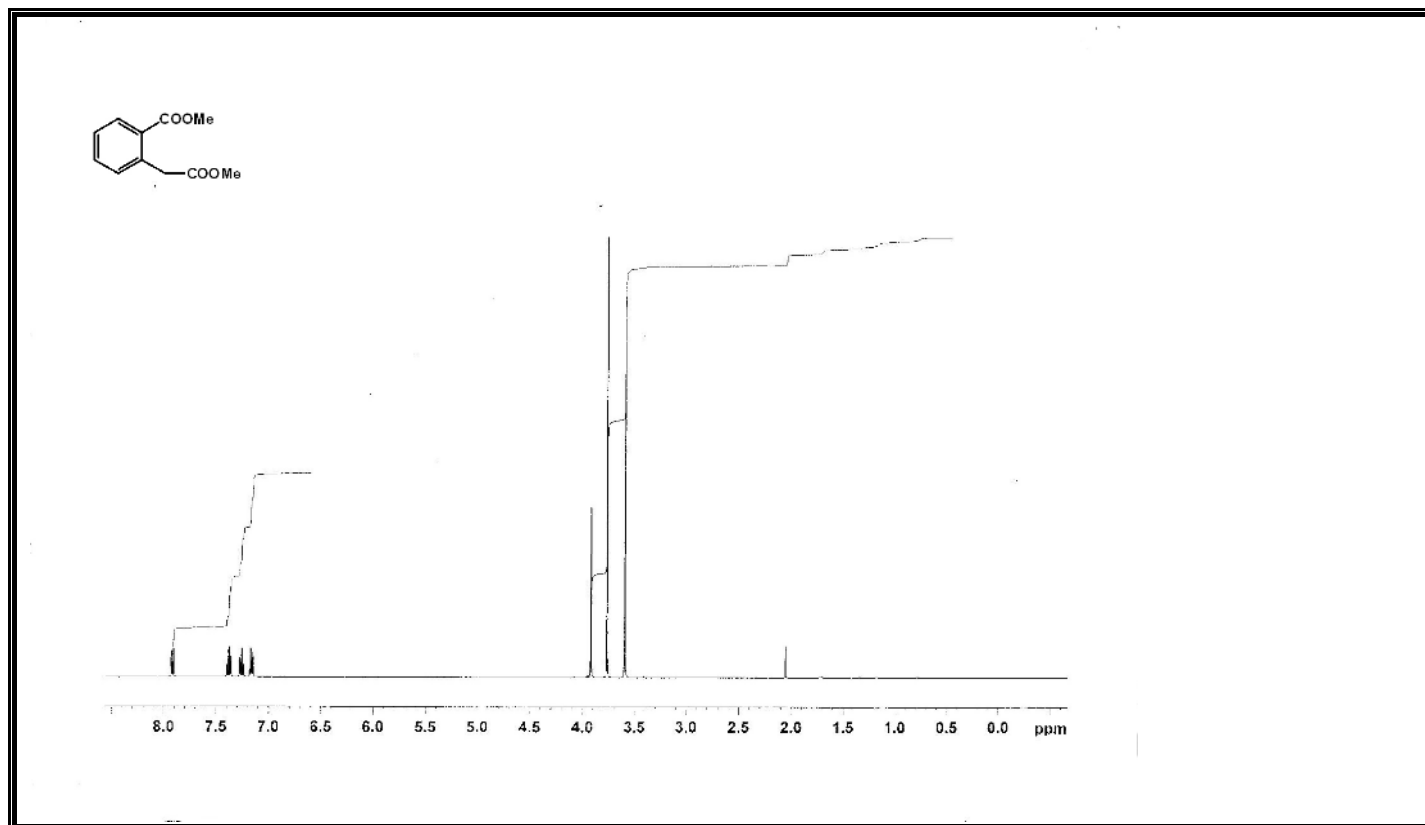


Figure A5 ^1H -NMR Spectrum of Compound 300.

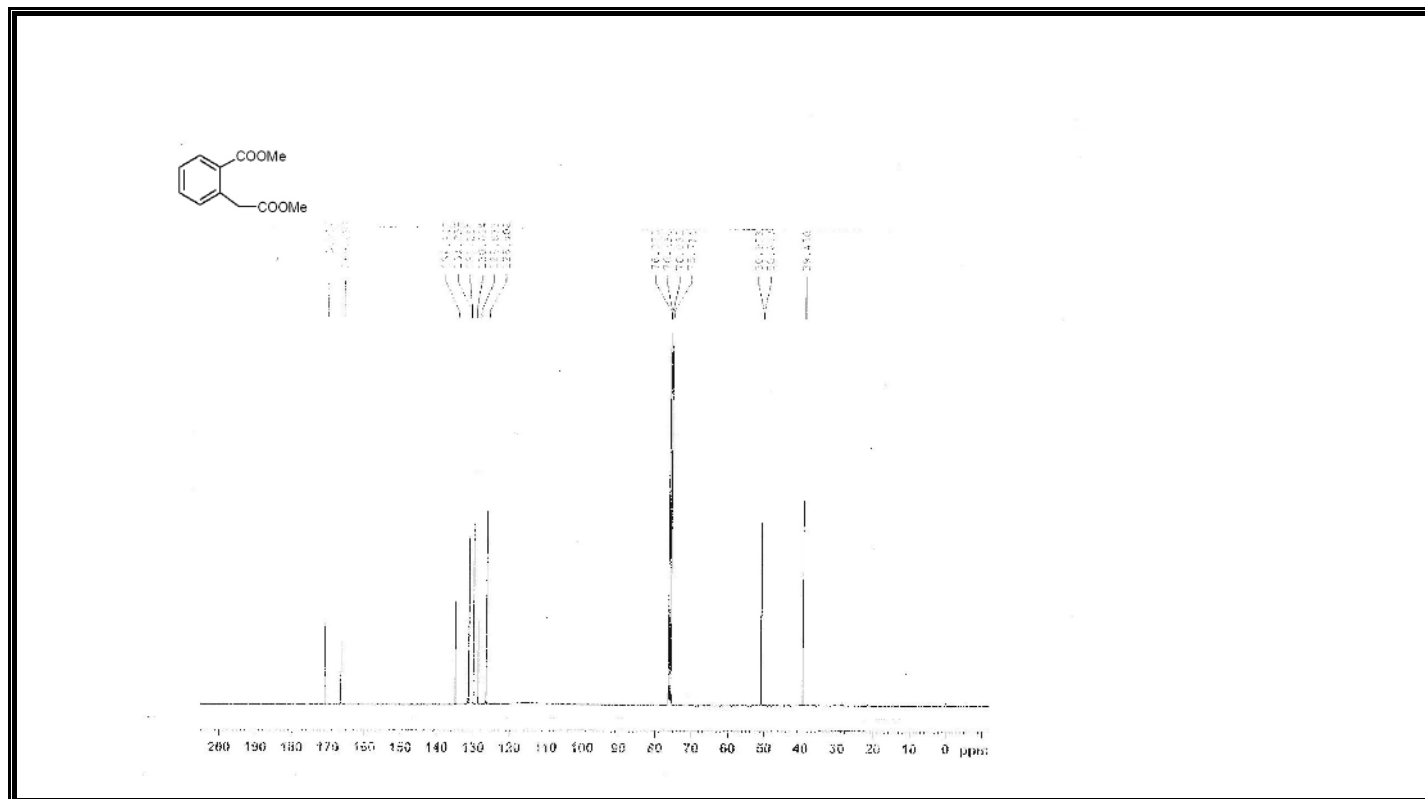


Figure A6 ^1H -NMR Spectrum of Compound **300**.

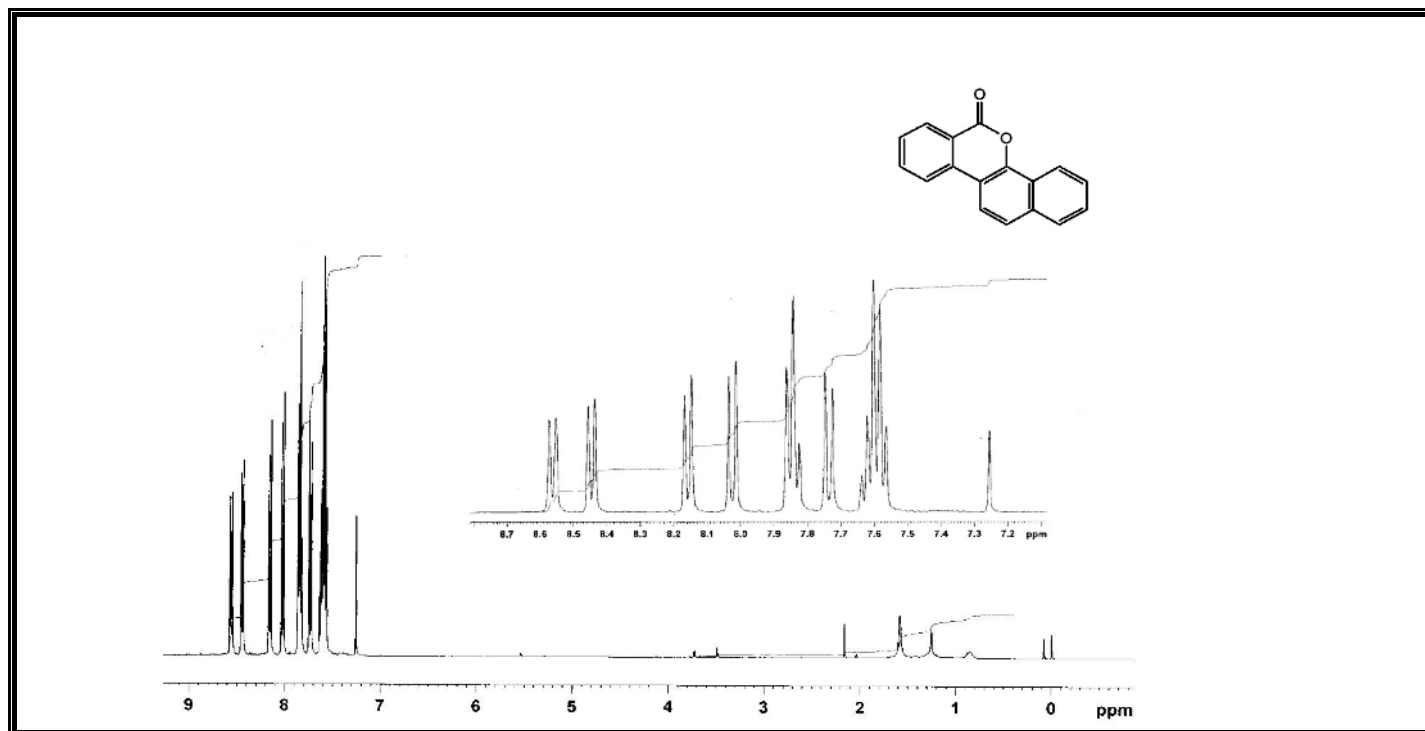


Figure A7 ^1H -NMR Spectrum of Compound 307

Figure A8 ^{13}C -NMR Spectrum of Compound **307**.

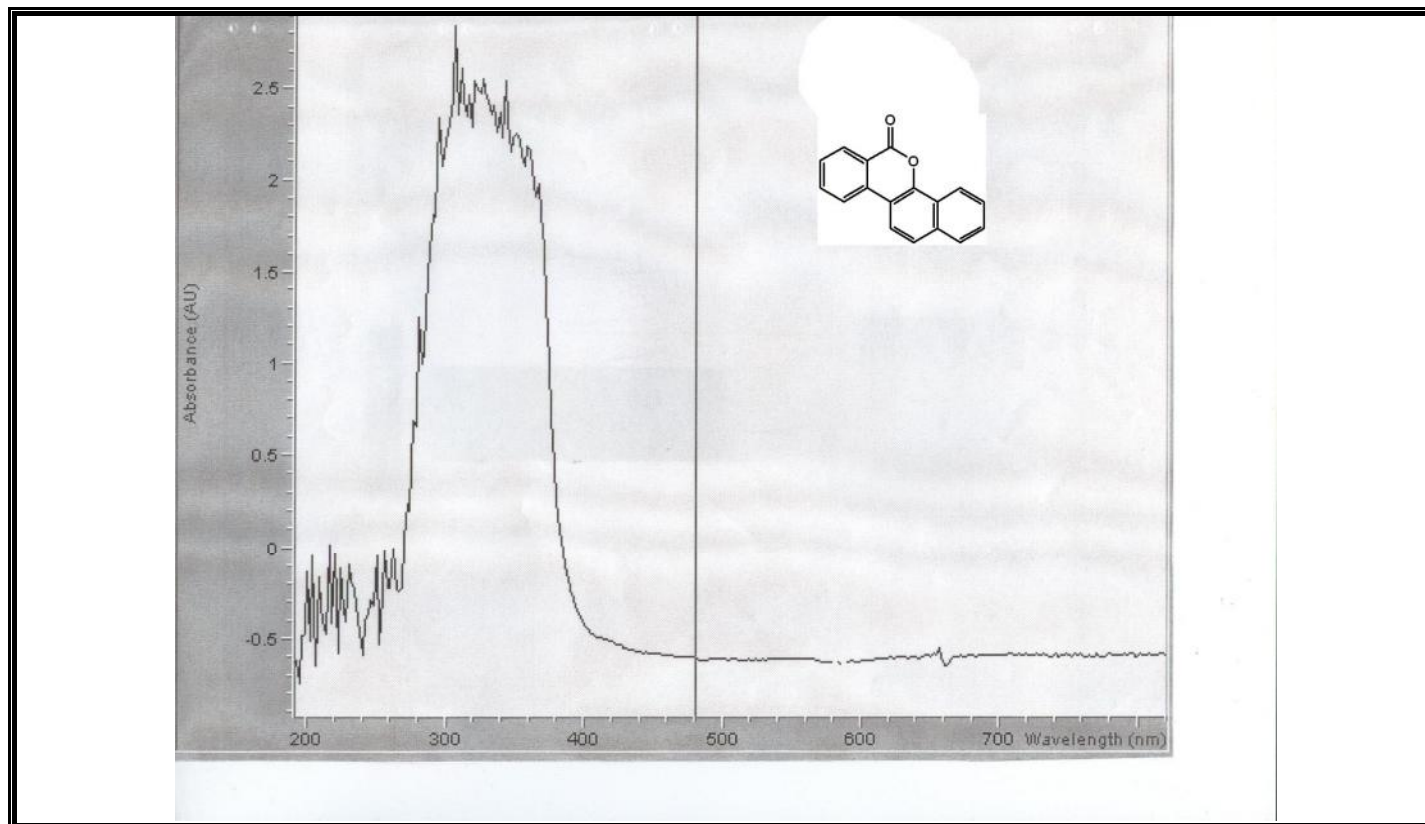


Figure A9 Uv-Spectrum of 307.

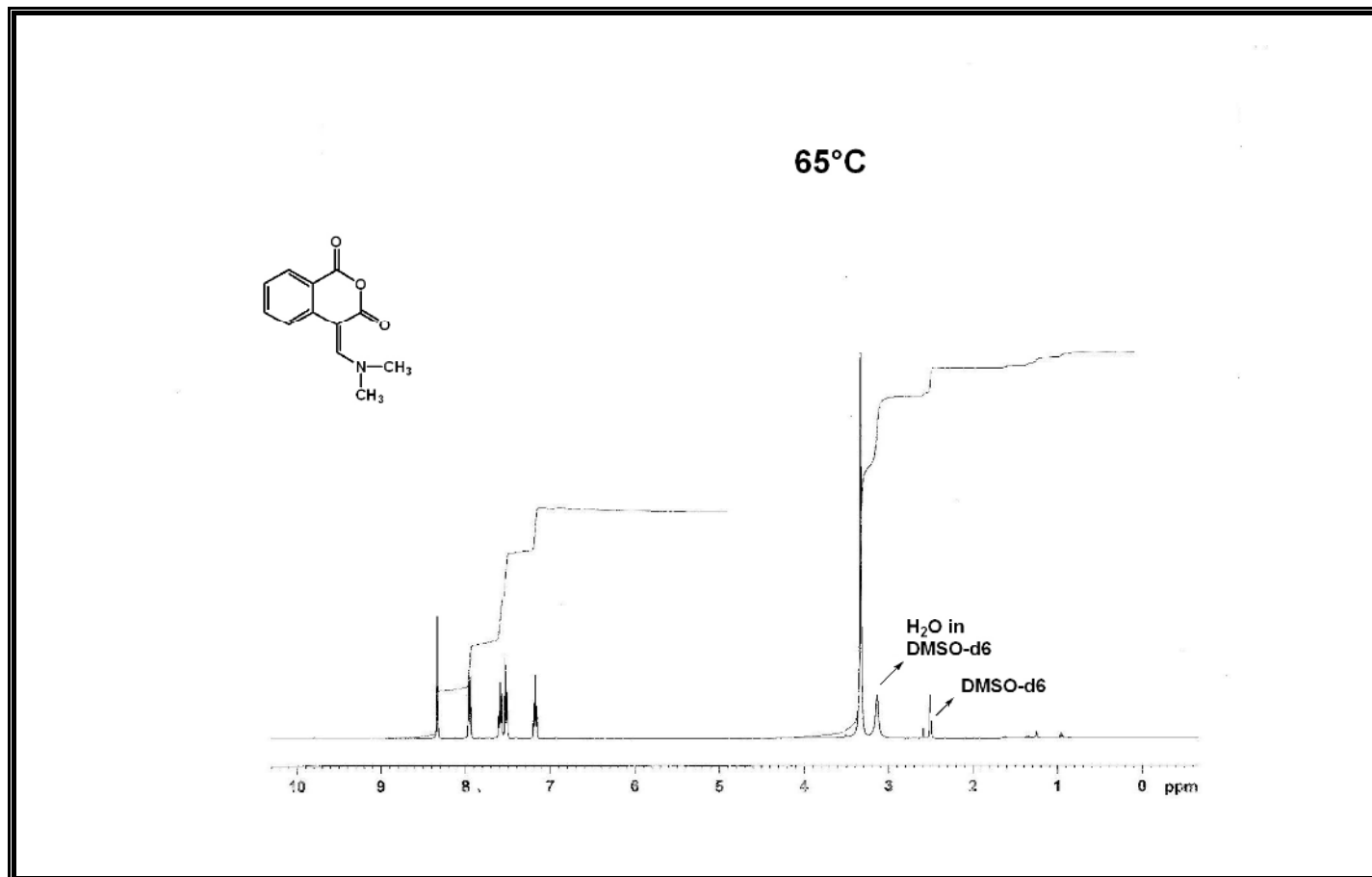


Figure A10 ¹H-NMR Spectrum of Compound 327.

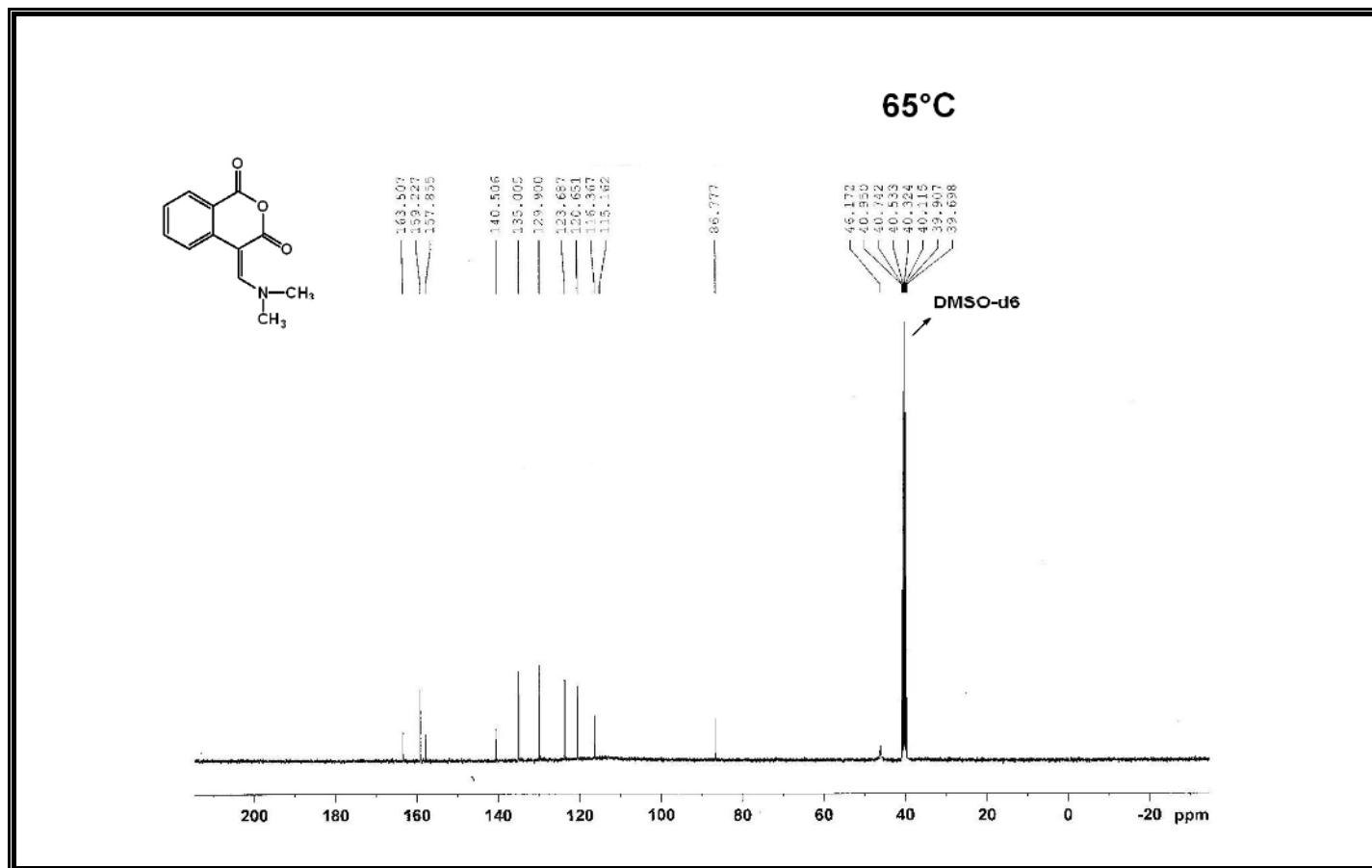


Figure A11 ^{13}C -NMR Spectrum of Compound 327.

Figure A12 ^1H -NMR Spectrum of Compound **328**.

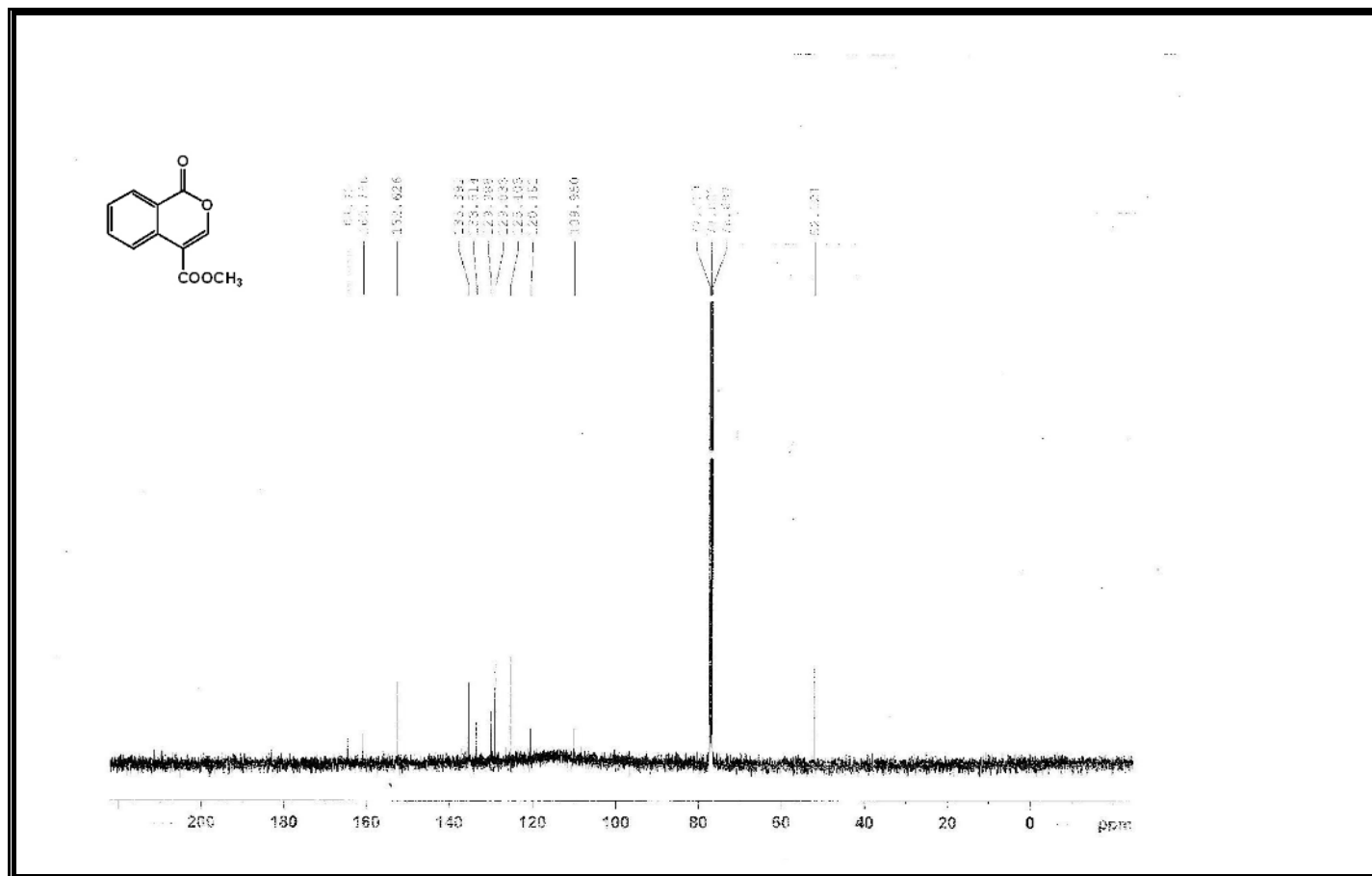


Figure A13 ¹³C-NMR Spectrum of Compound 328.

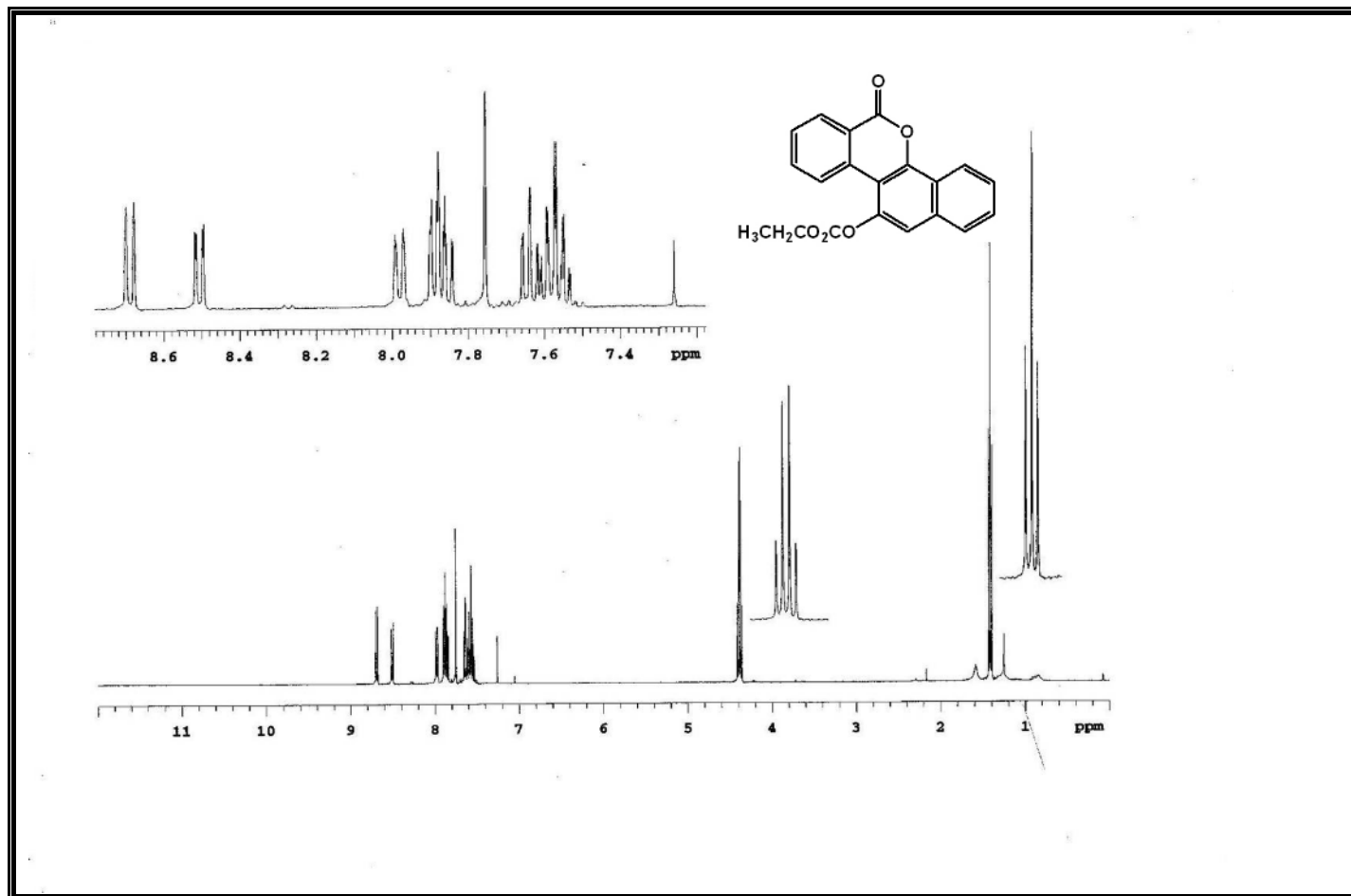


Figure A14 ^1H -NMR Spectrum of Compound 333.

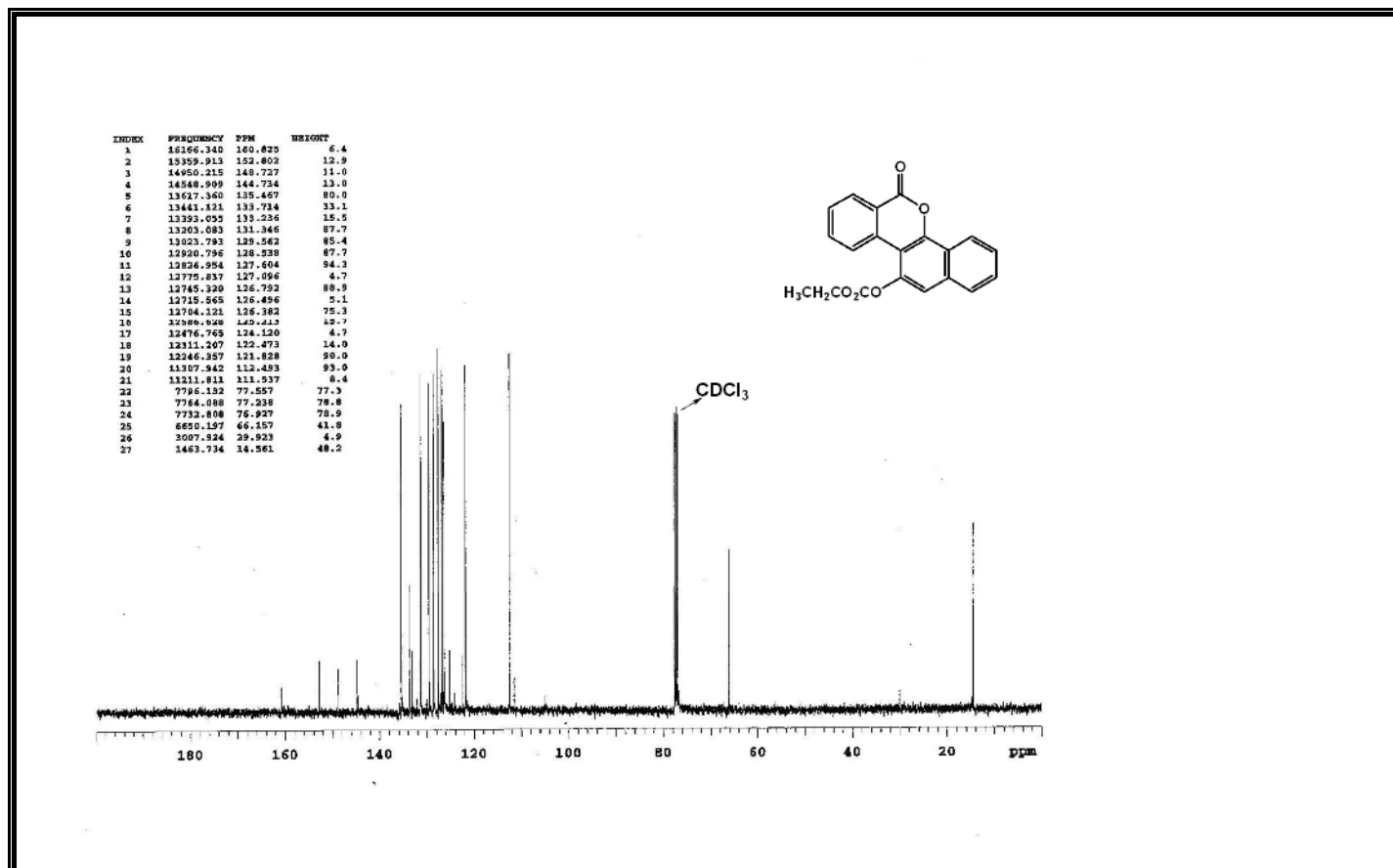


Figure A15 ¹³C-NMR Spectrum of Compound 333.

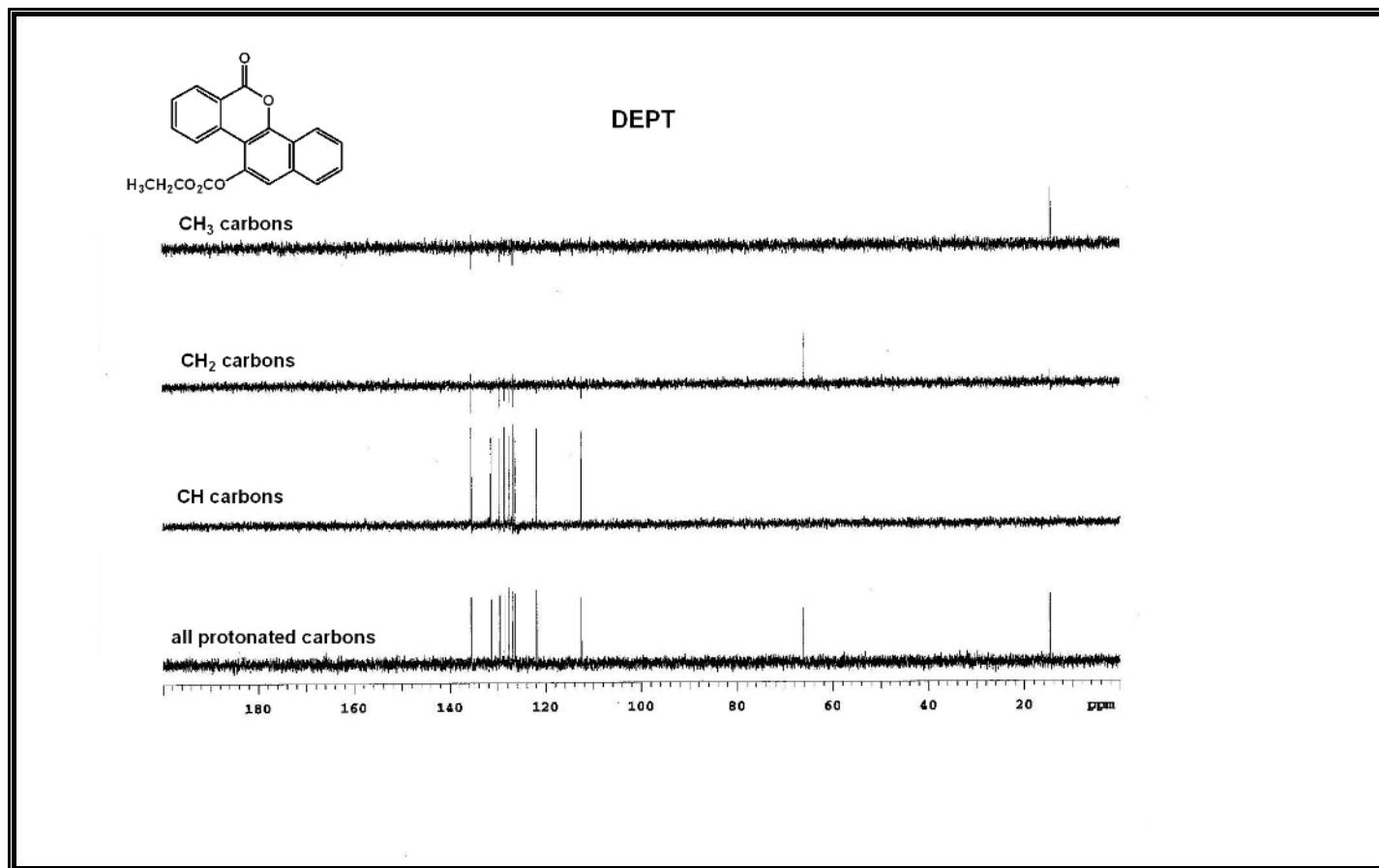


Figure A16 DEPT Spectrum of Compound 333.

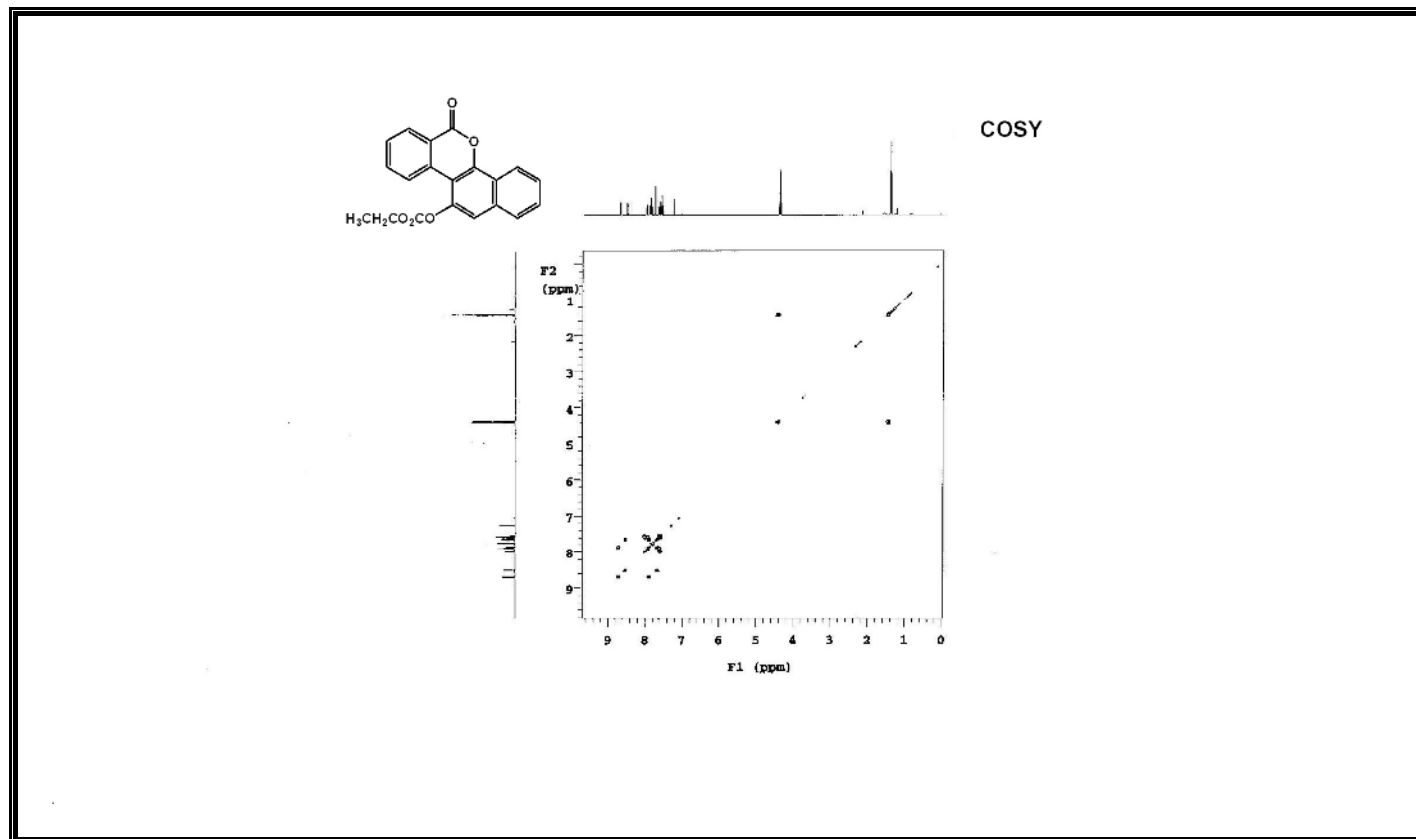


Figure A17 COSY Spectrum of Compound 333.

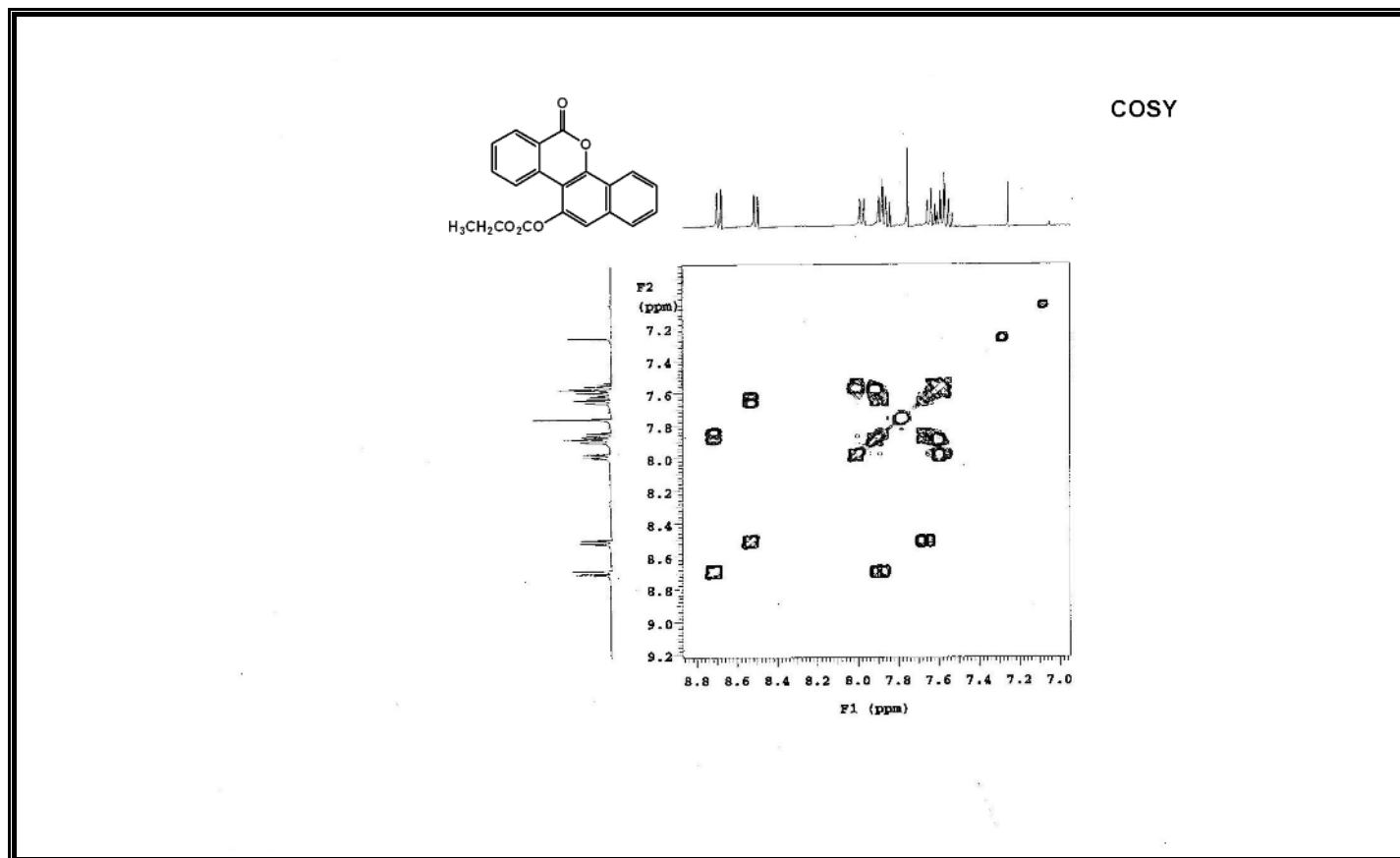


Figure A18 Expanded COSY Spectrum of Compound 333.

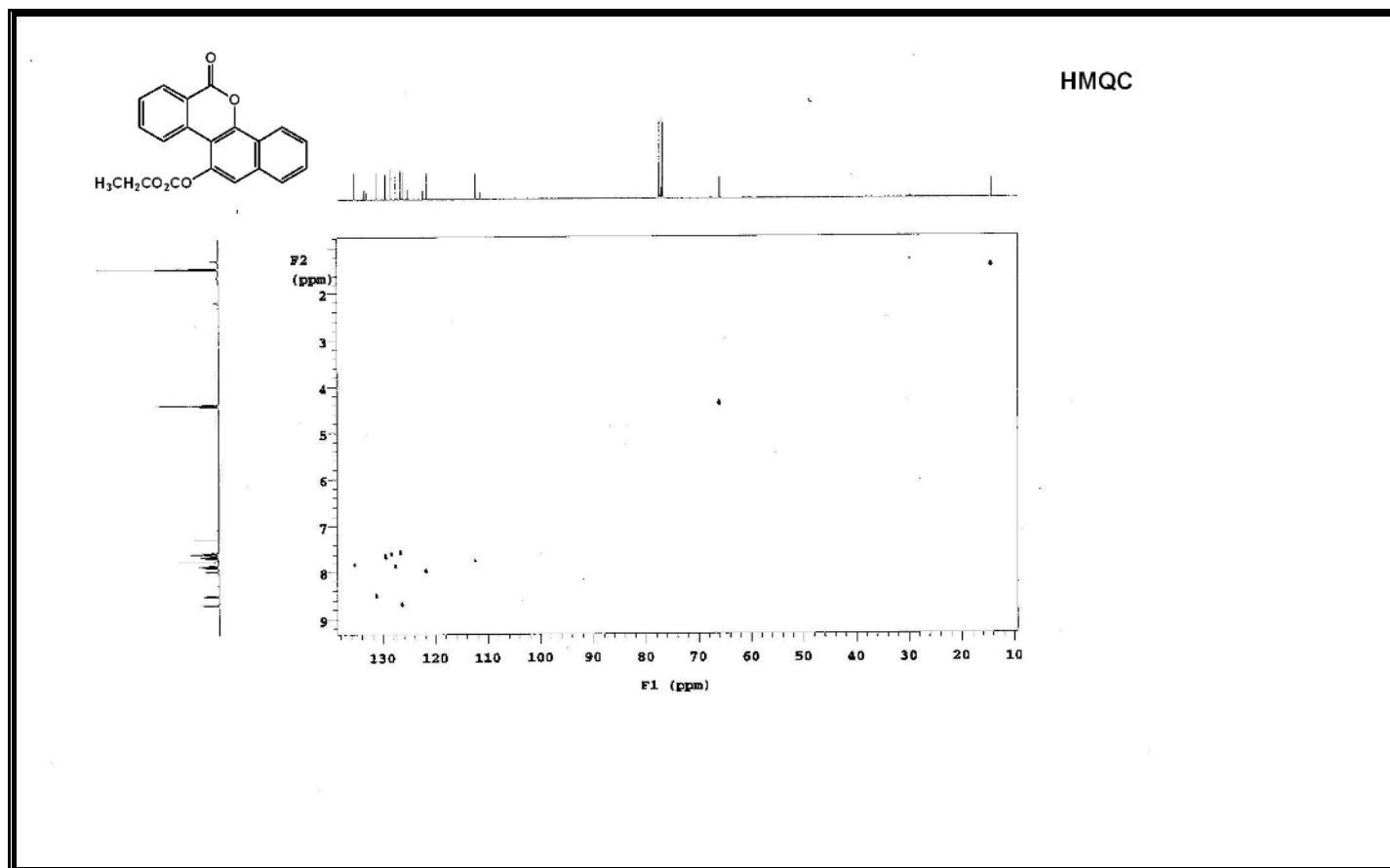


Figure A19 HMQC Spectrum of Compound 333.

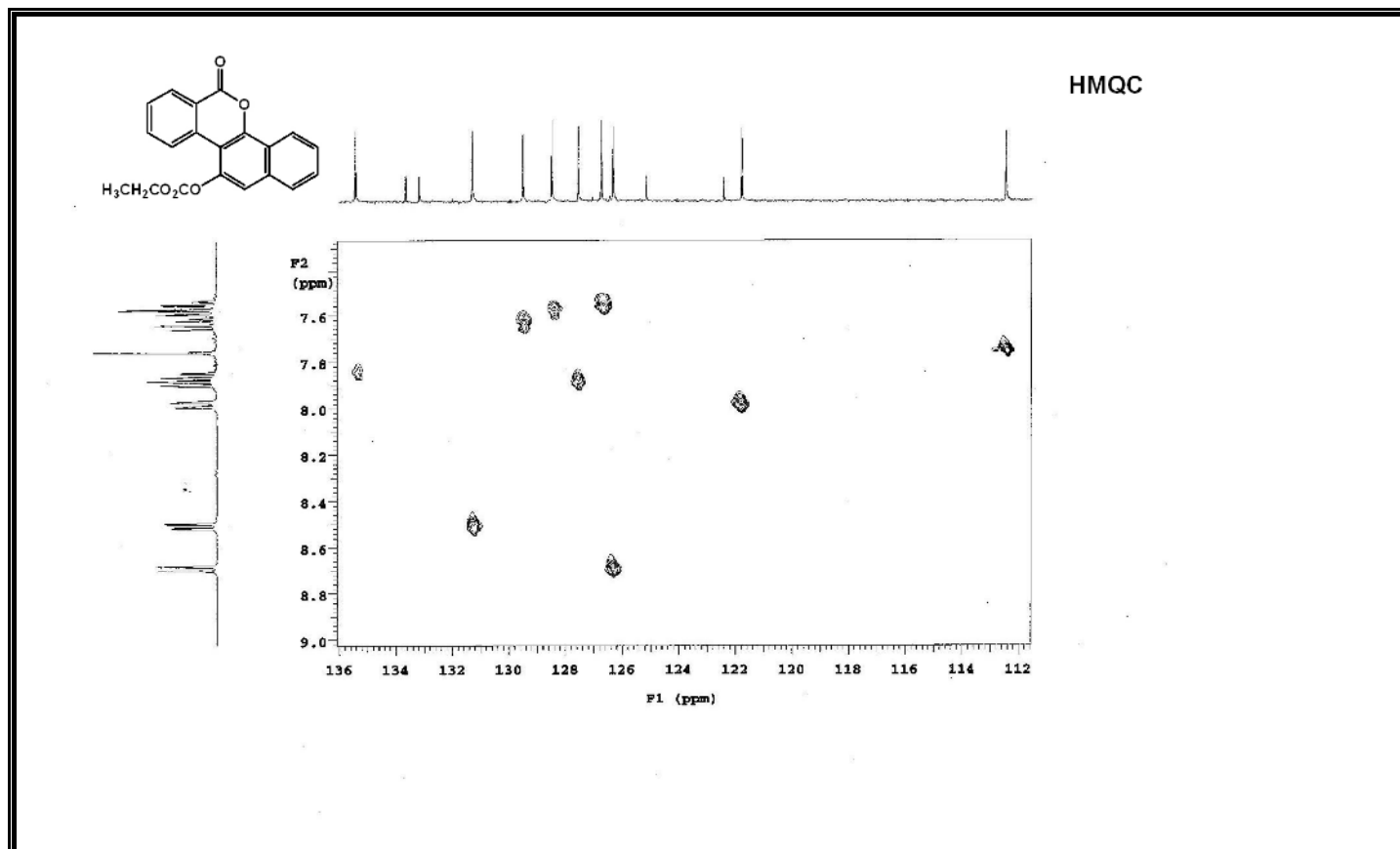


Figure A20 Expanded HMQC Spectrum of Compound 333.

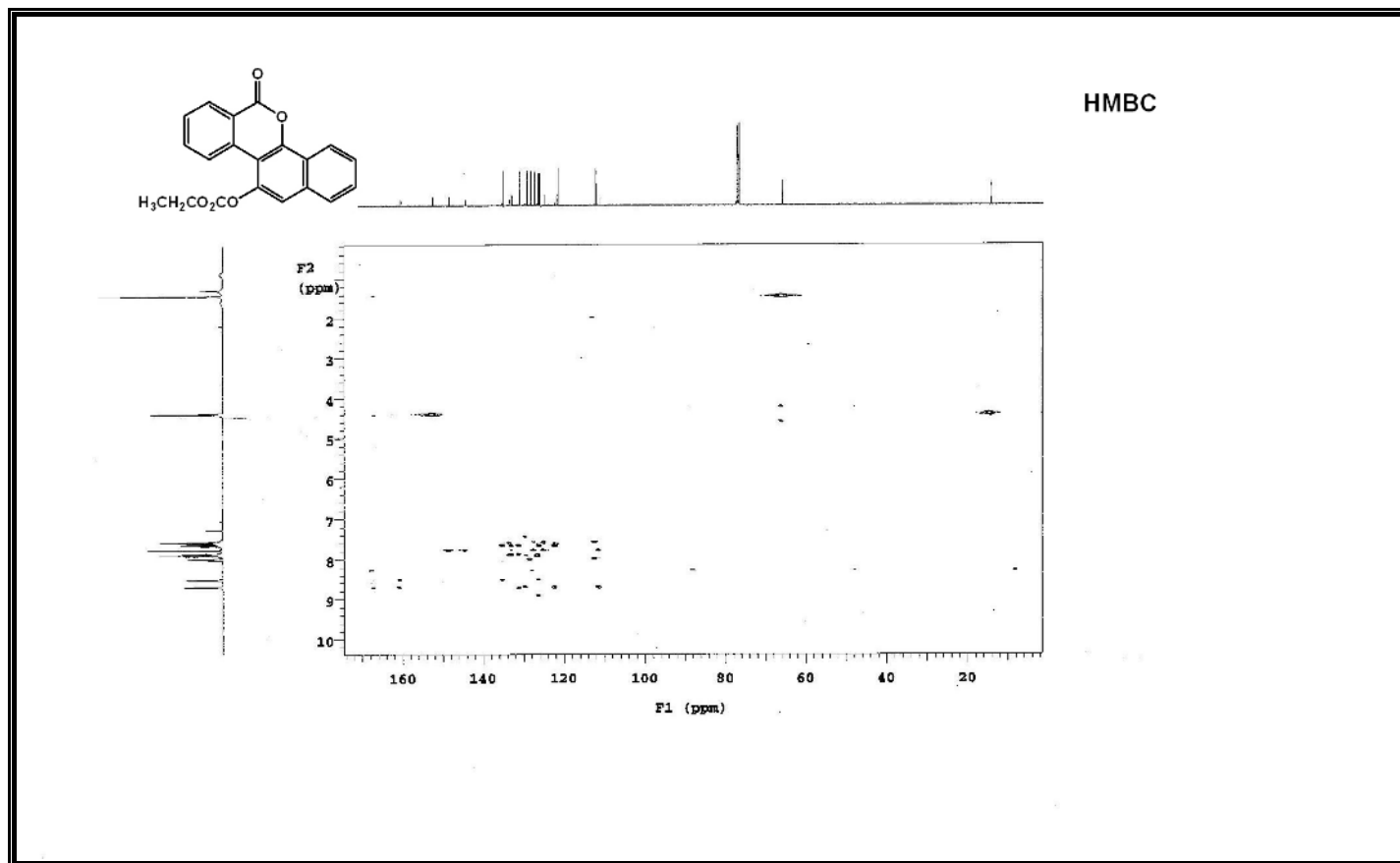


Figure A21 HMBC Spectrum of Compounds 333.

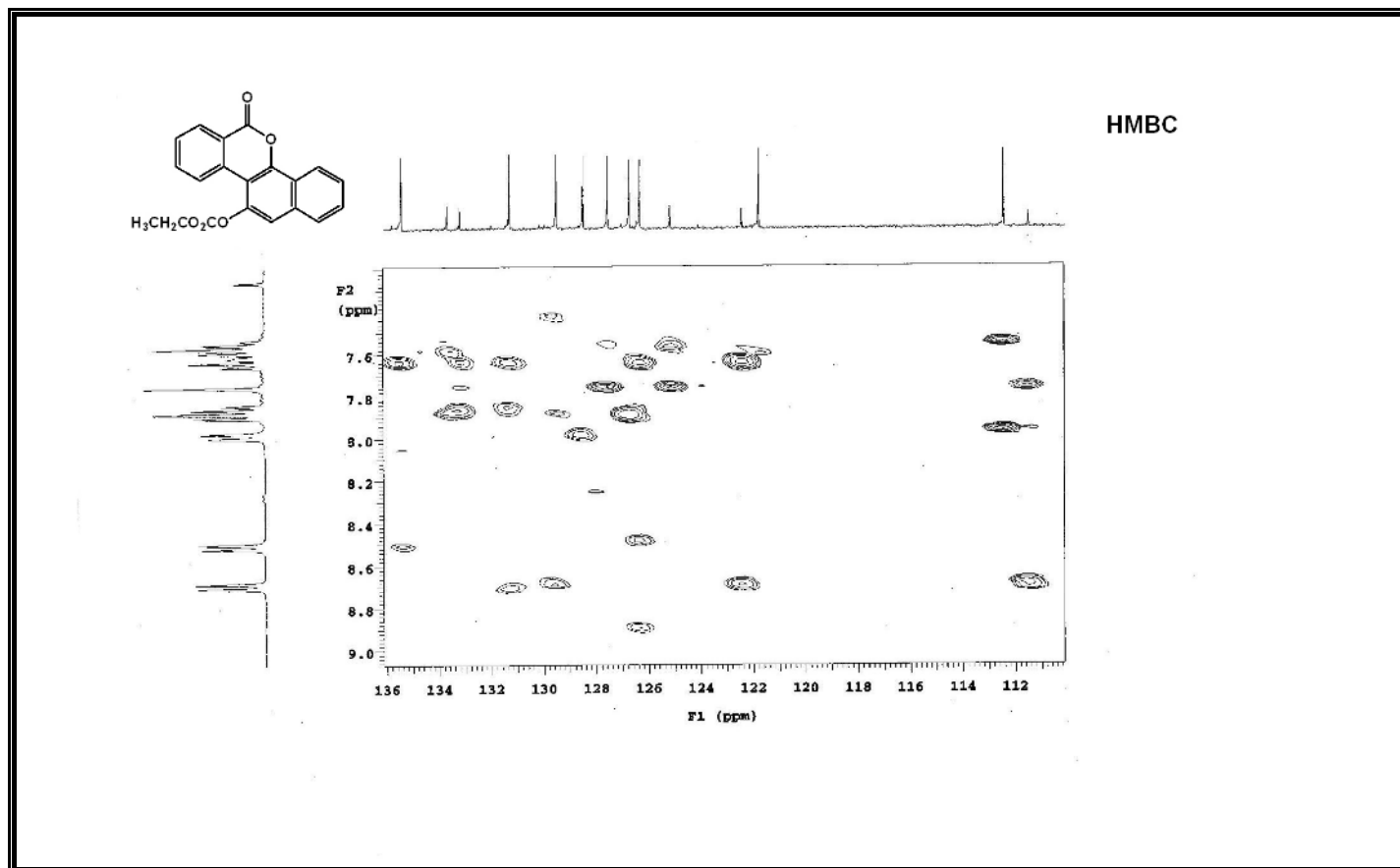


Figure A22 Expanded HMBC Spectrum of Compound 333.

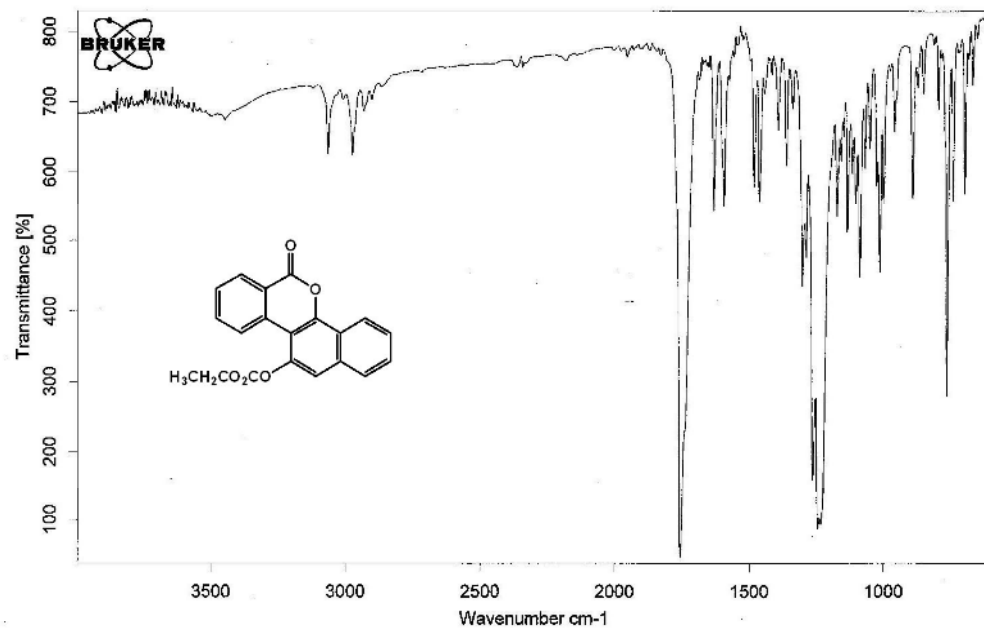


Figure A23 IR Spectrum of Compound 333.

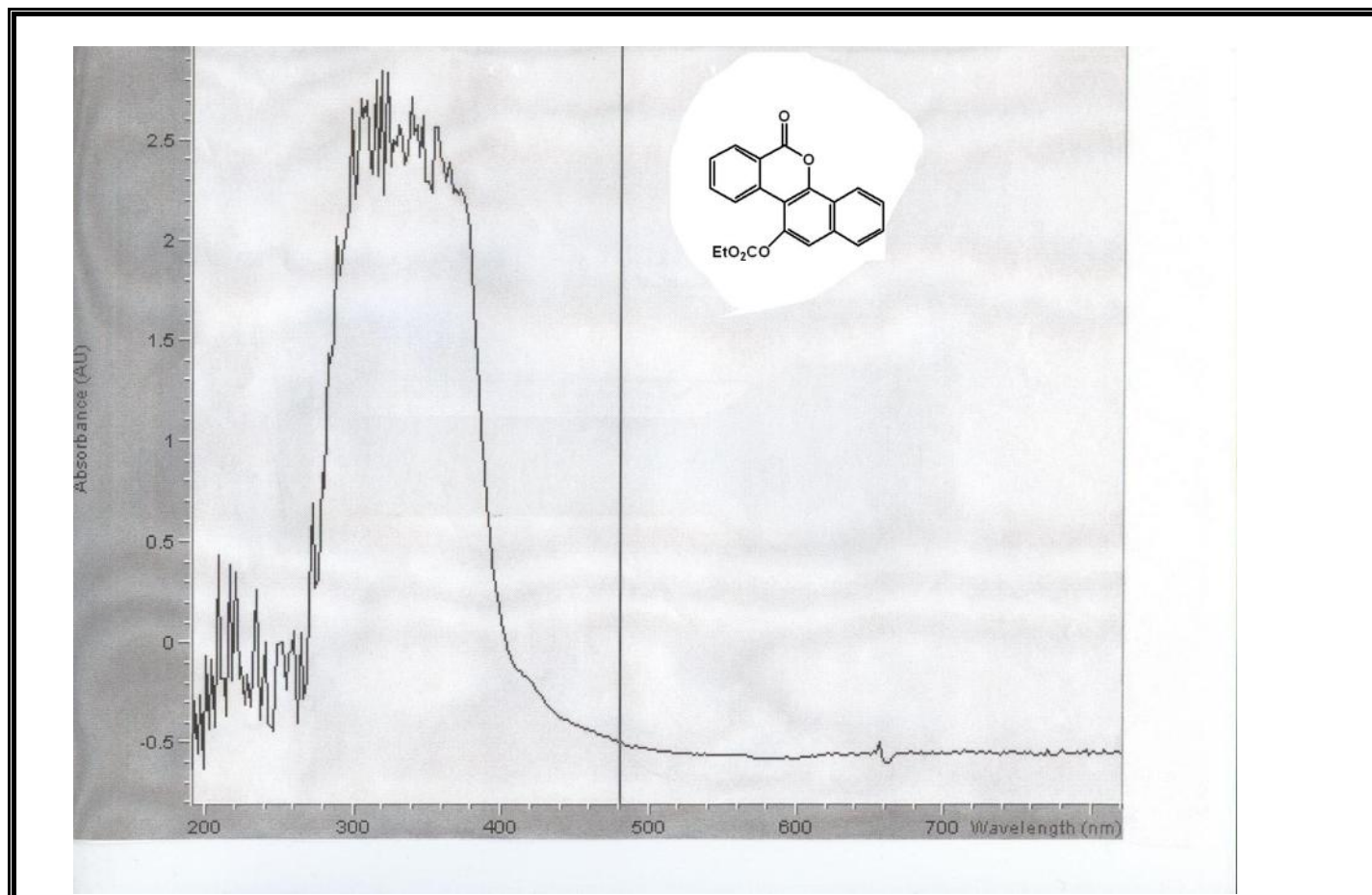


Figure A24 UV Spectrum of Compound 333.

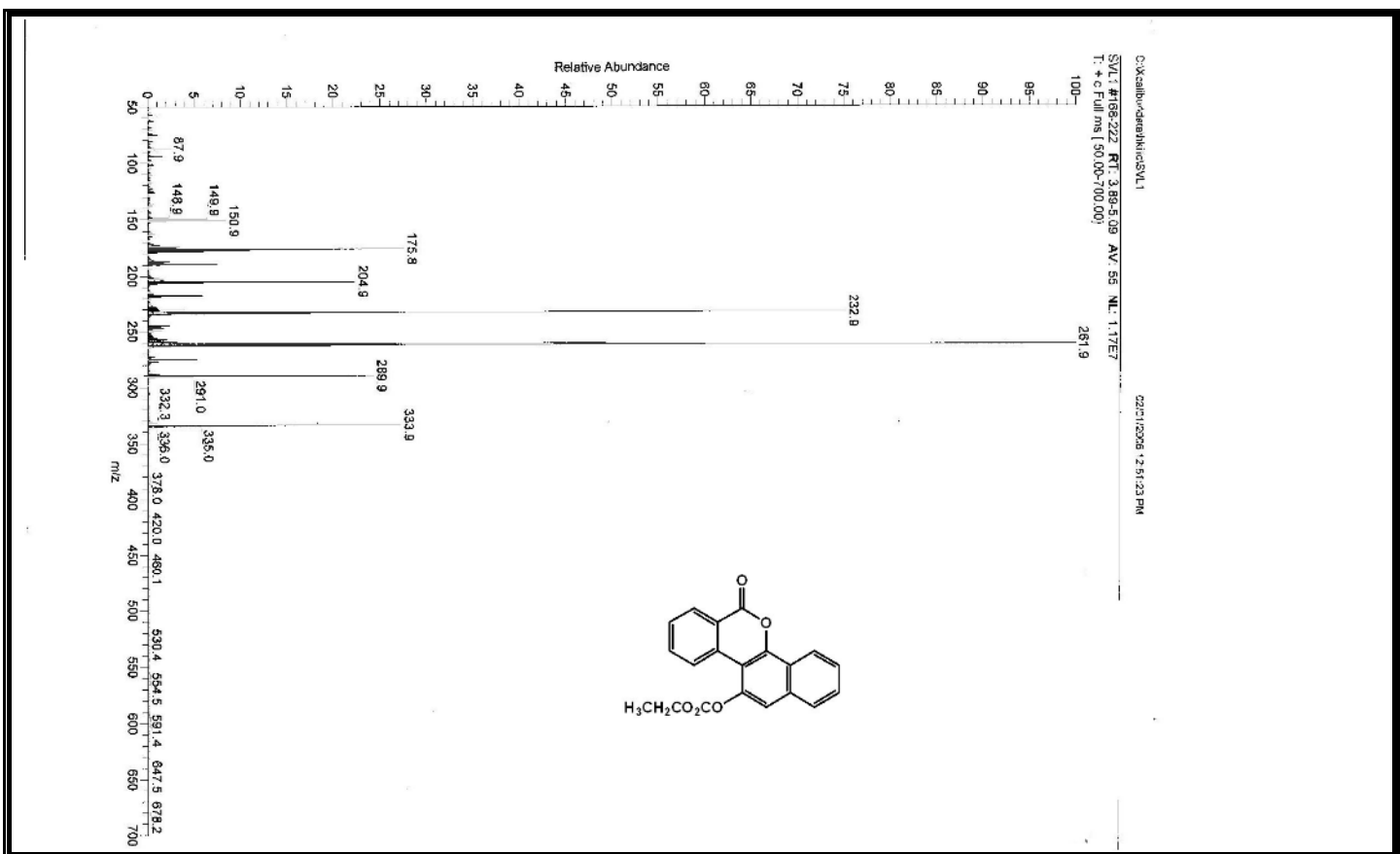


Figure A25 Mass Spectrum of Compound 134.

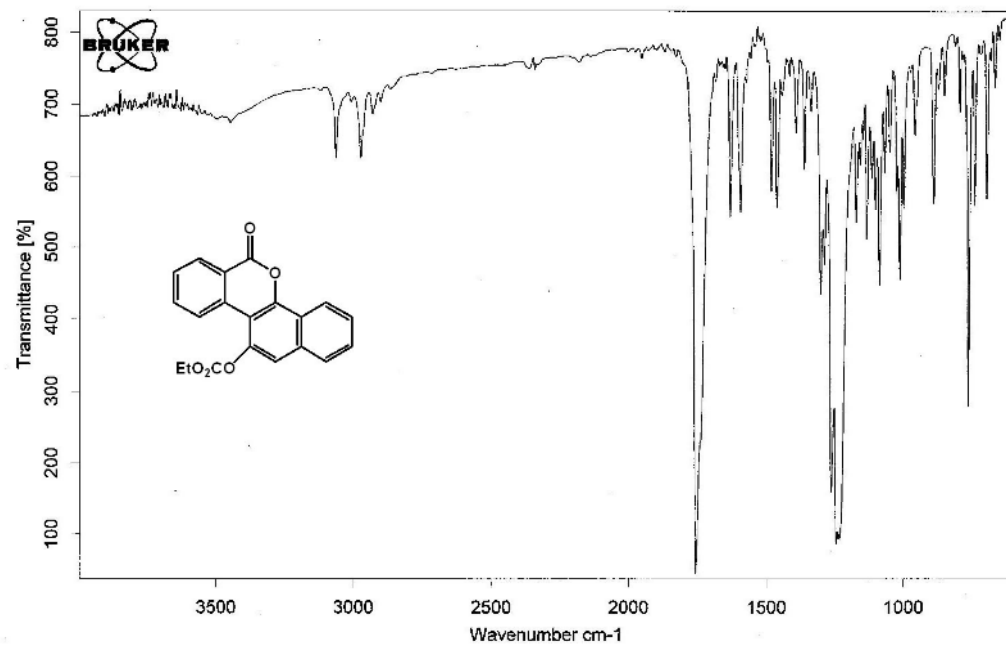


Figure A26 IR Spectrum of Compound 333.

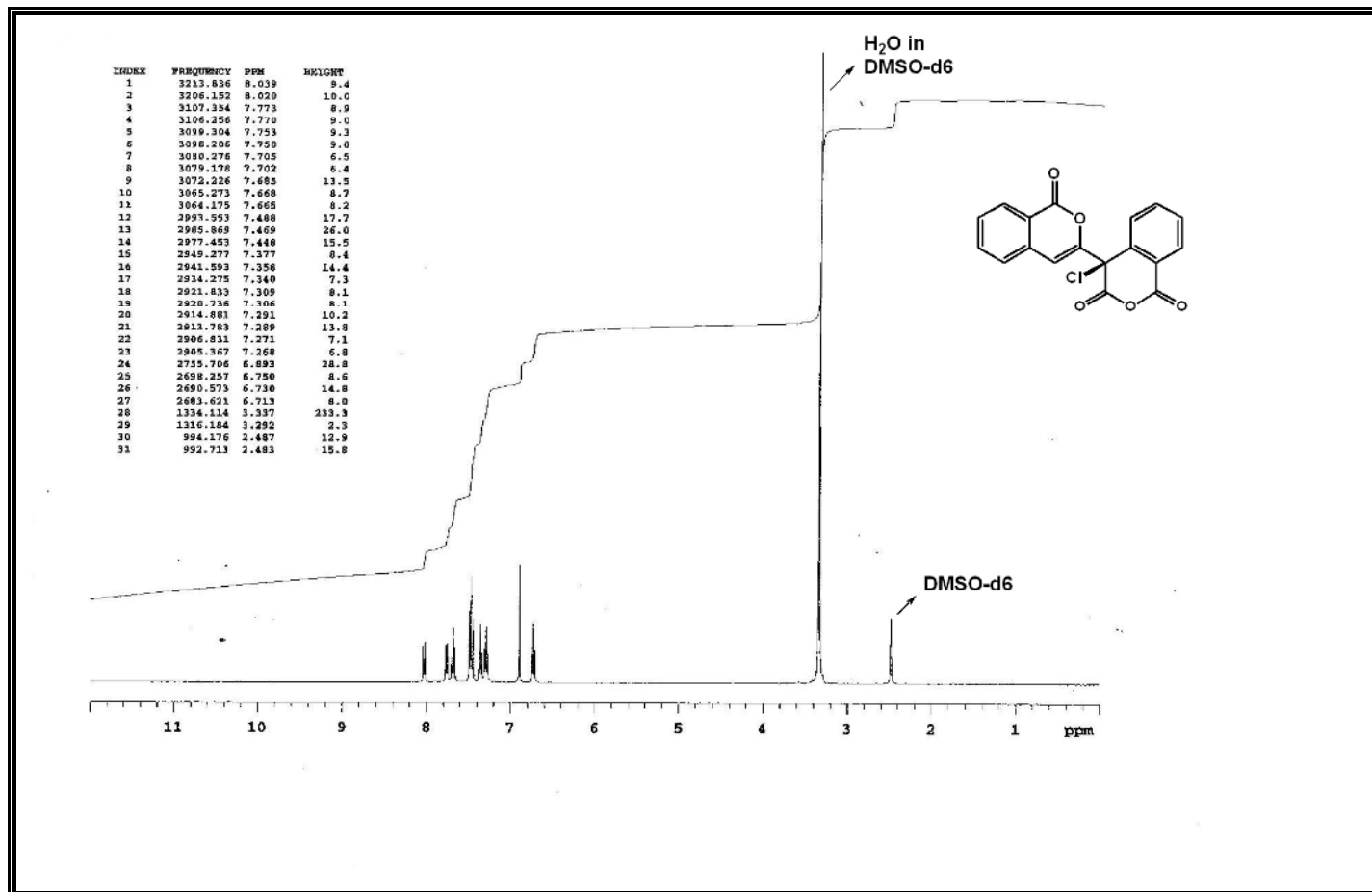
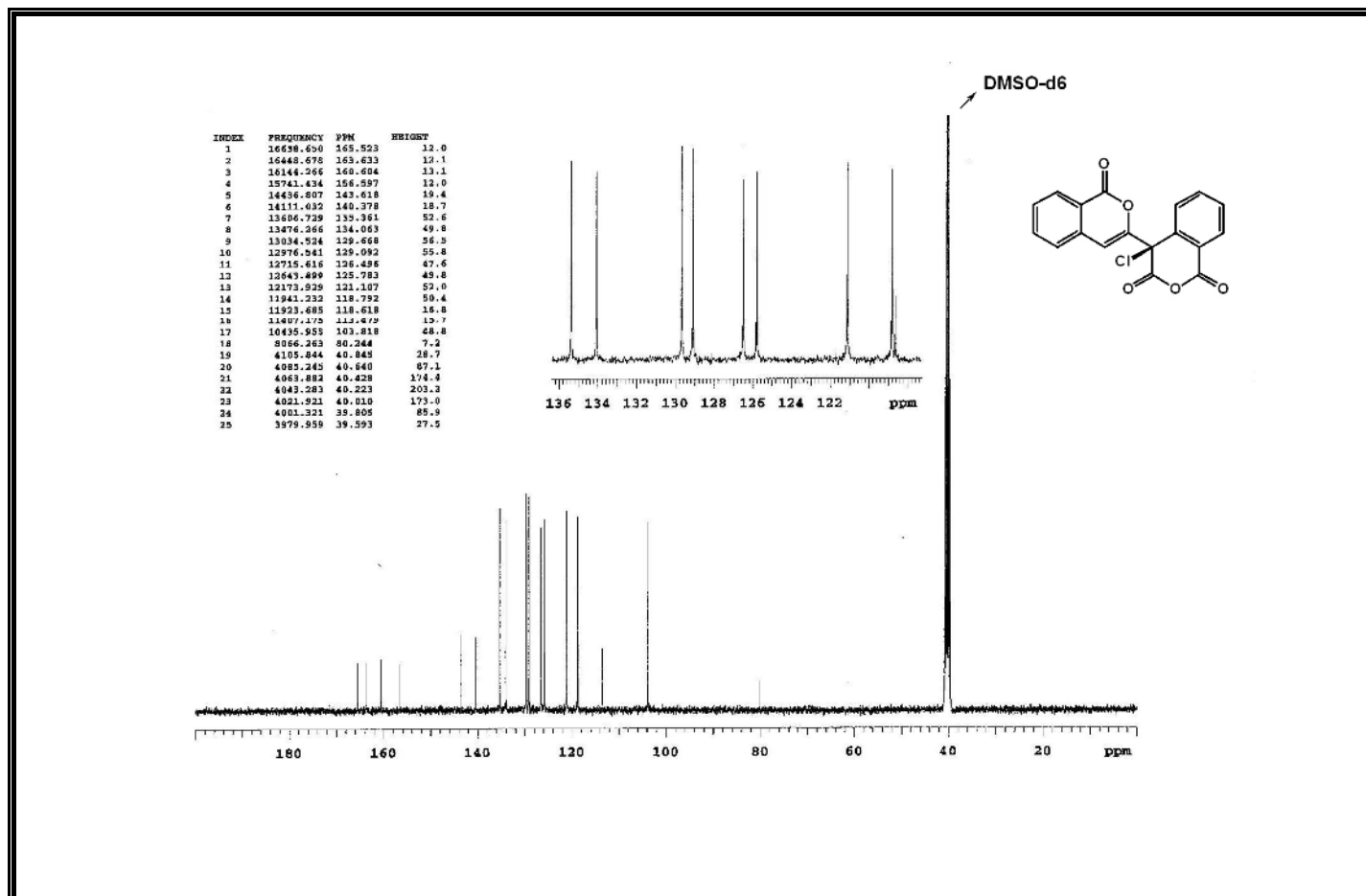


Figure A27 ¹H-NMR Spectrum of Compound 332.



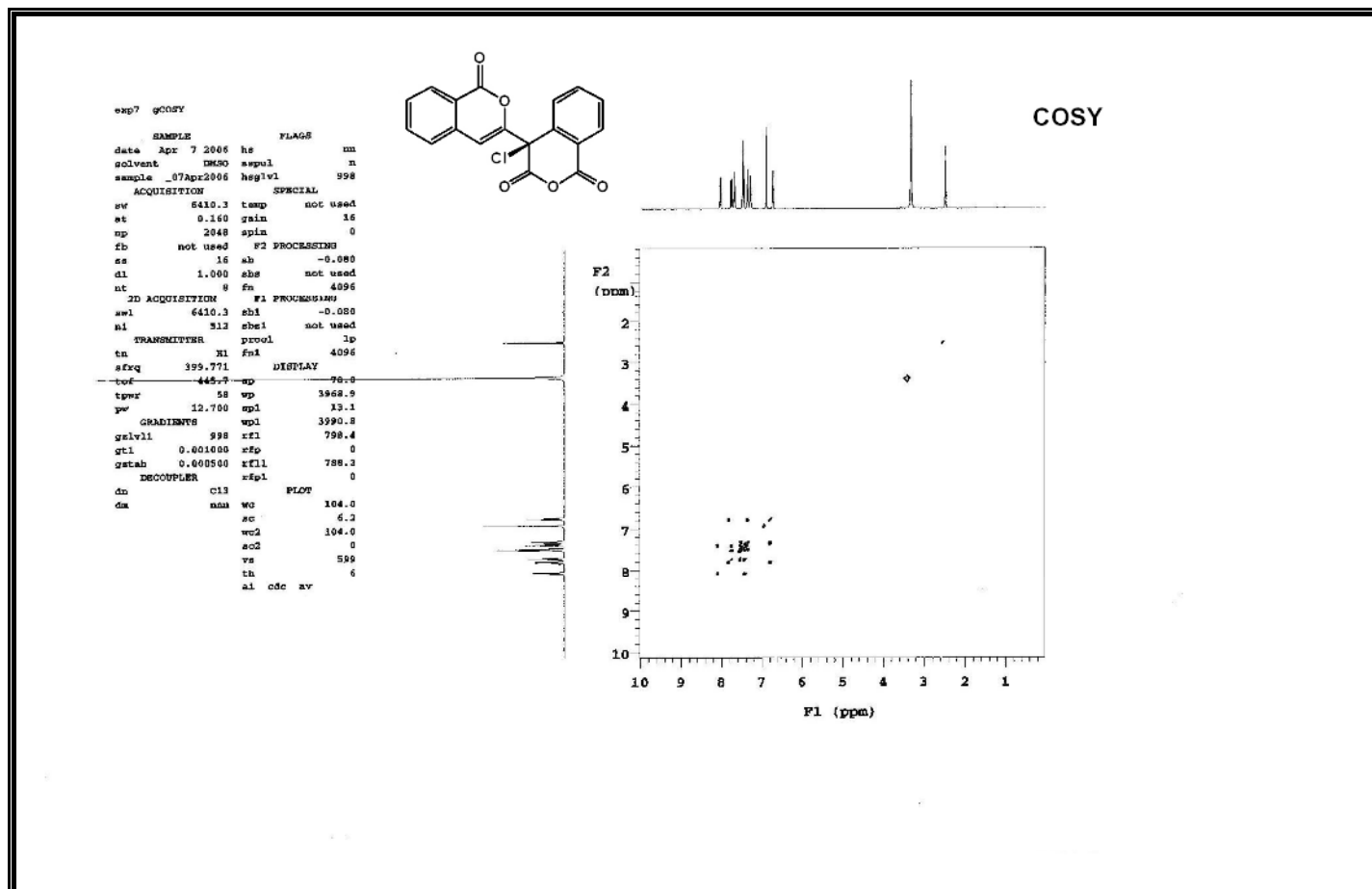


Figure A29 COSY Spectrum of Compound 332.

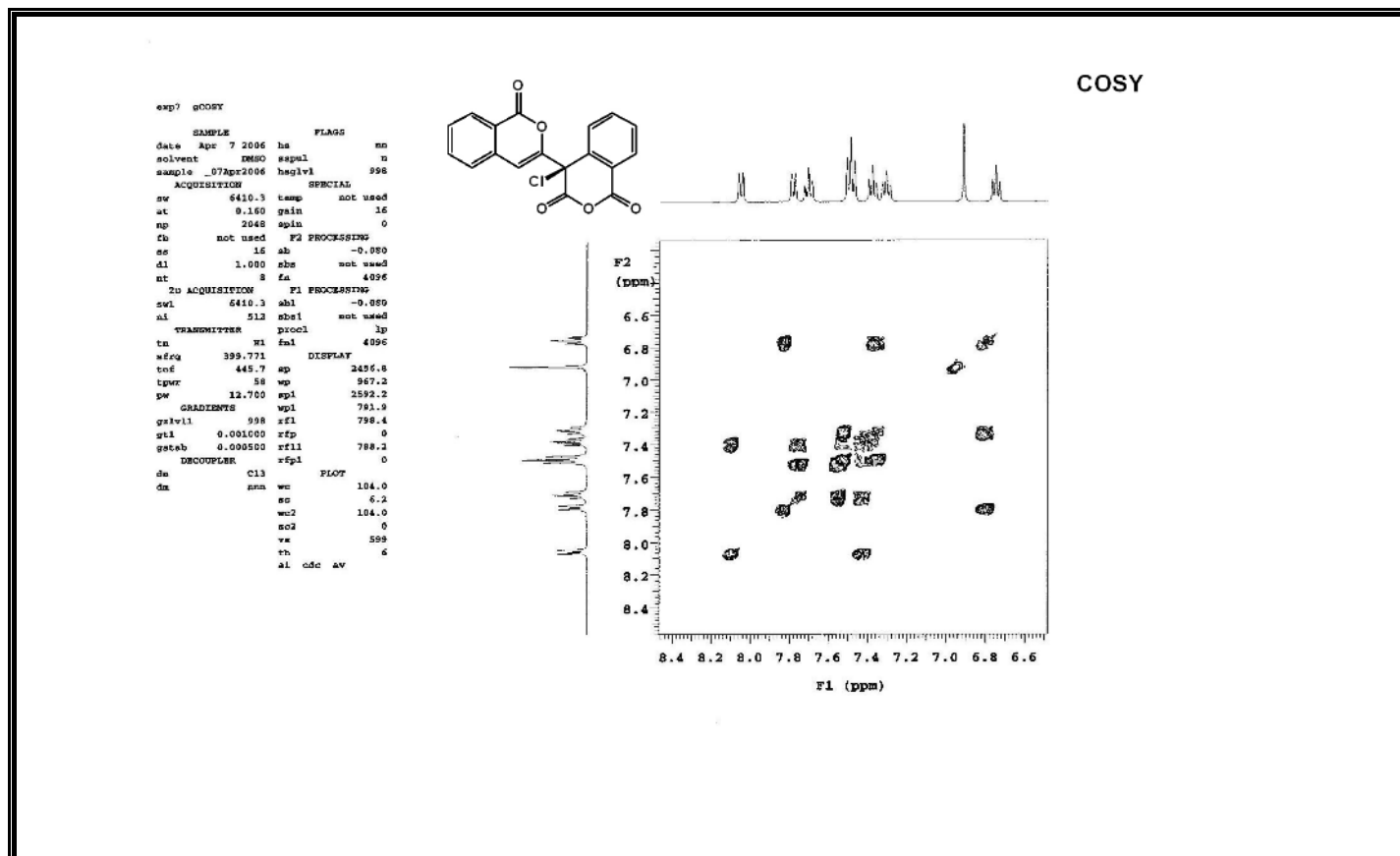


Figure A30 Expanded COSY Spectrum of Compound 332.

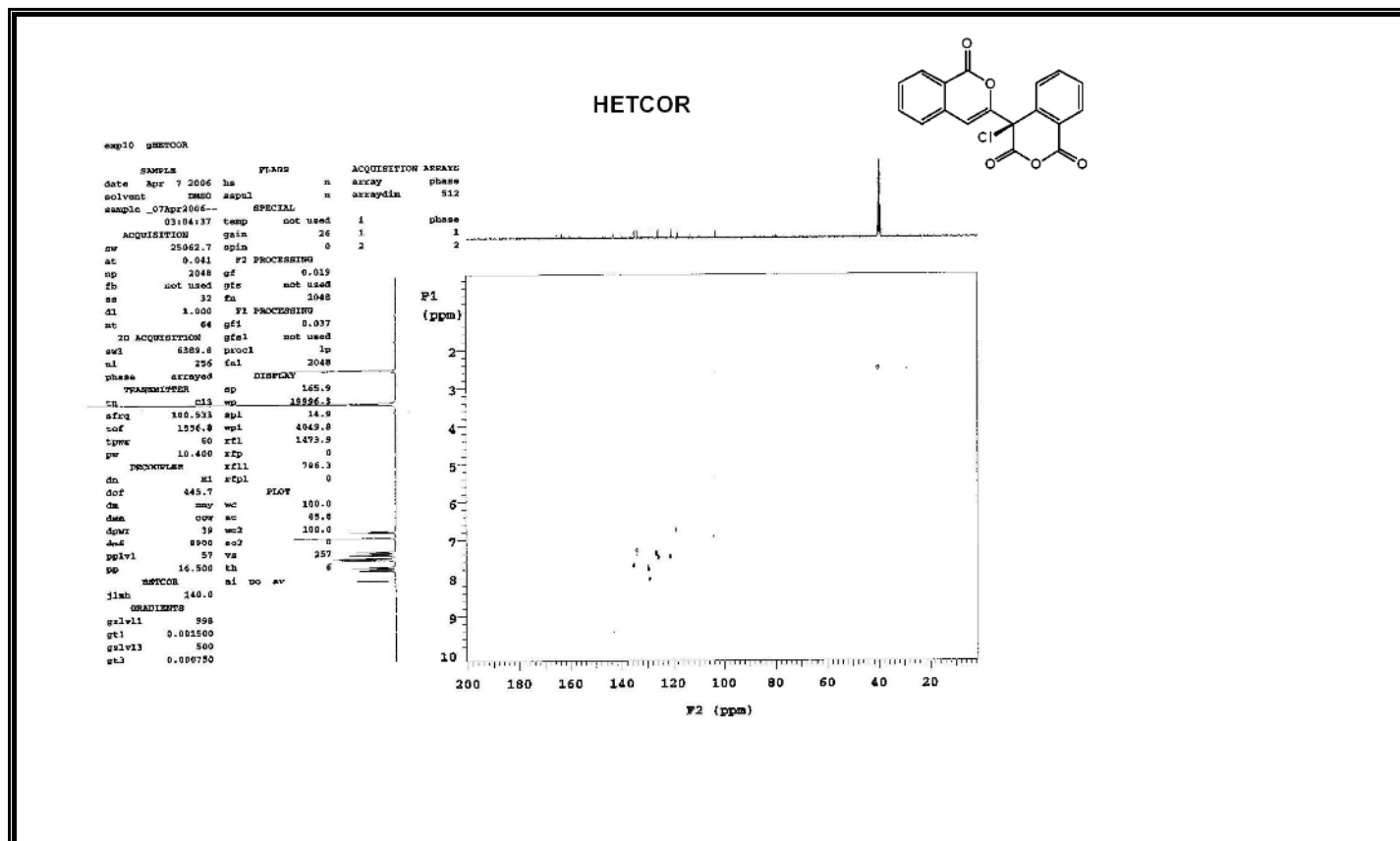


Figure A31 HETCOR Spectrum of Compound 332.

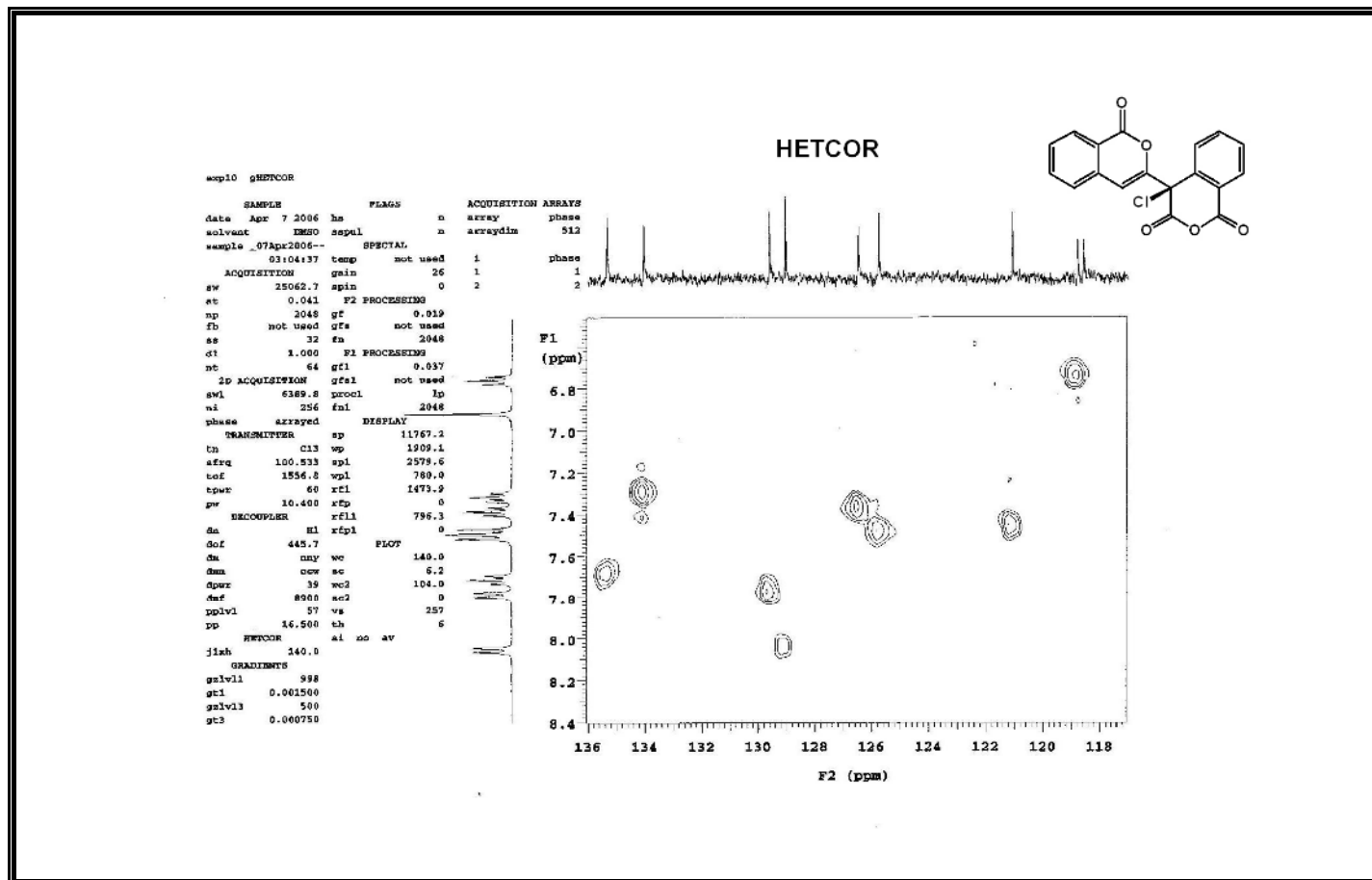


Figure A32 Expanded HETCOR Spectrum of Compound 332.

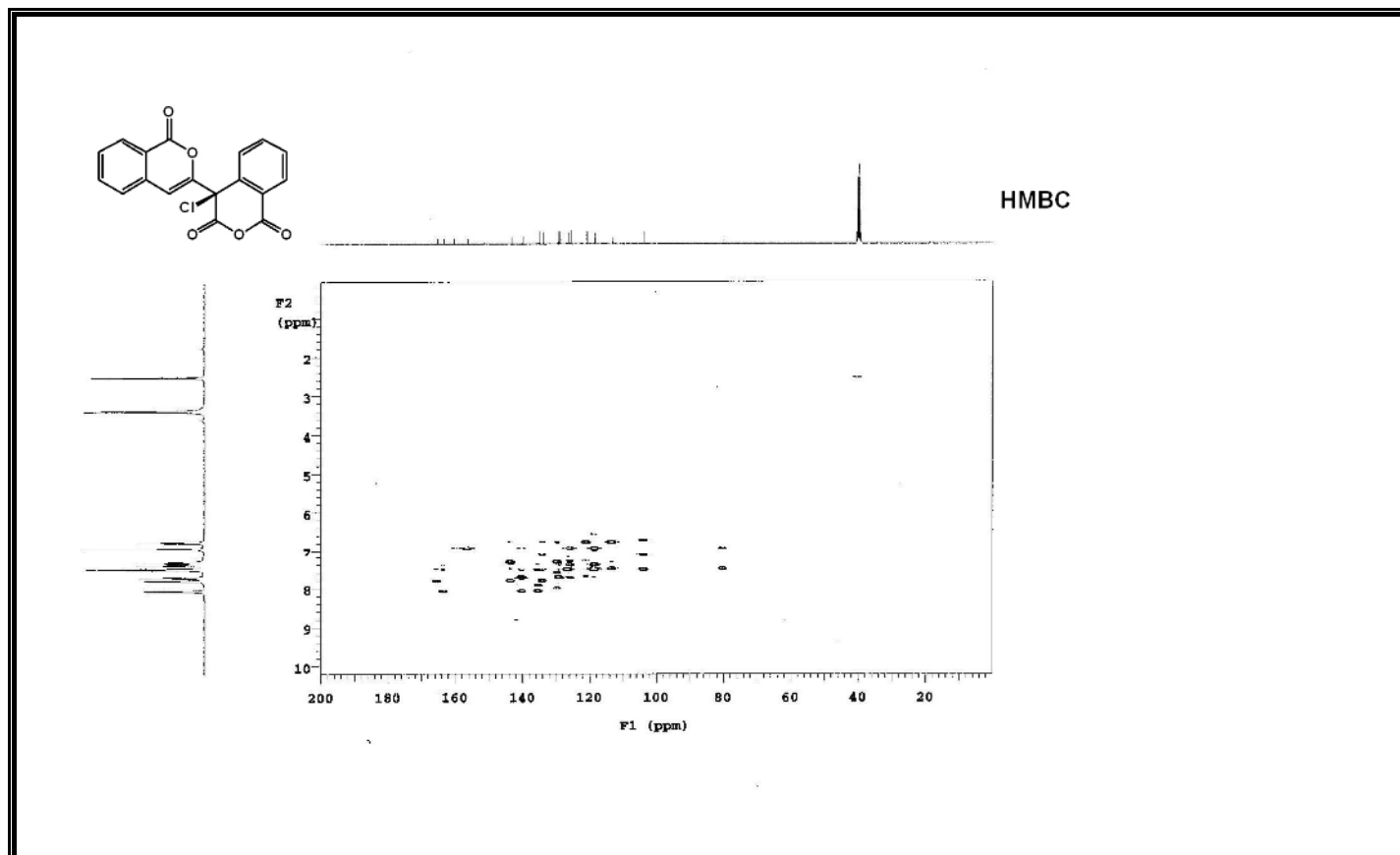


Figure A33 HMBC Spectrum of Compound 332.

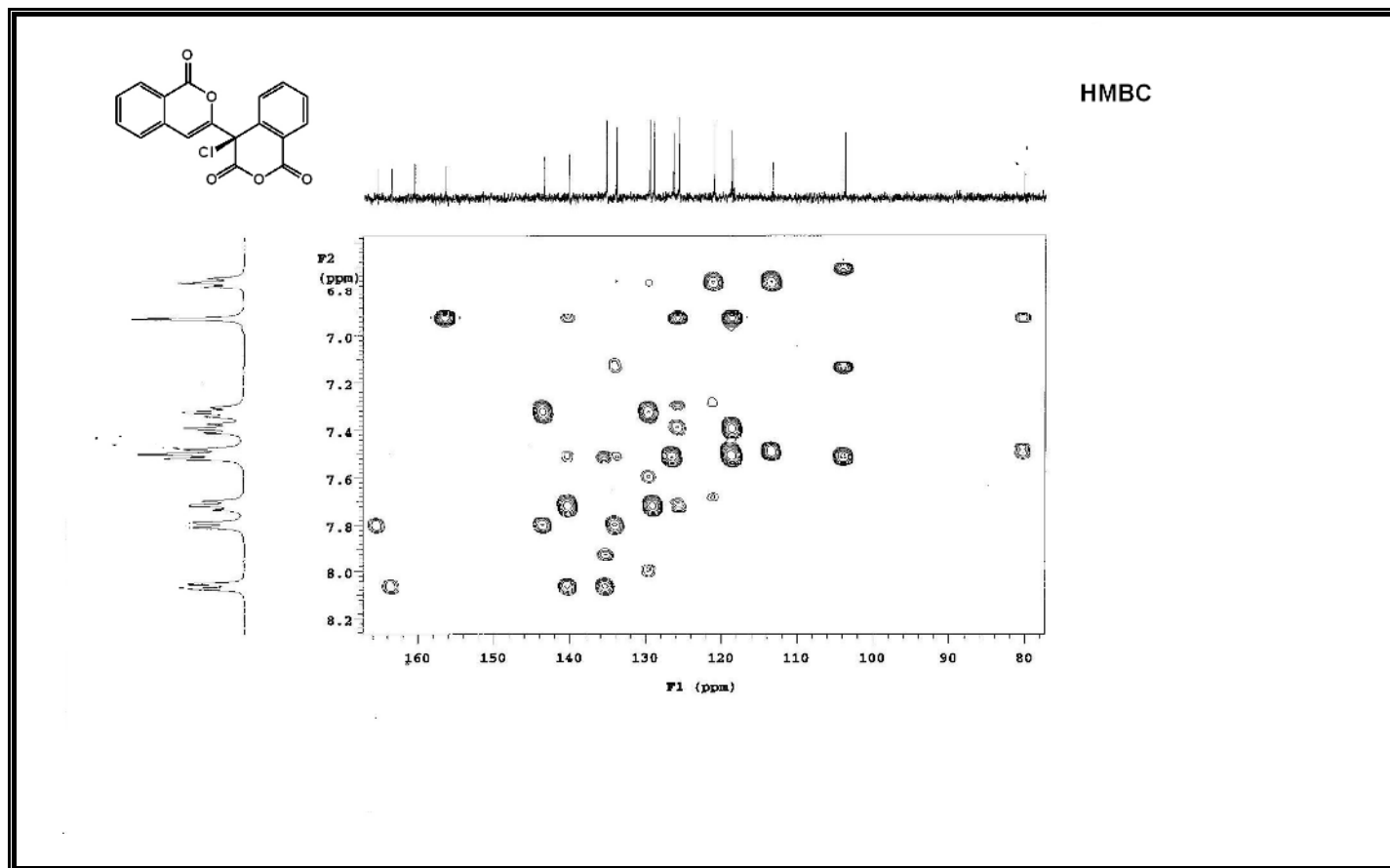


Figure A34 Expanded HMBC Spectrum of Compound 332.

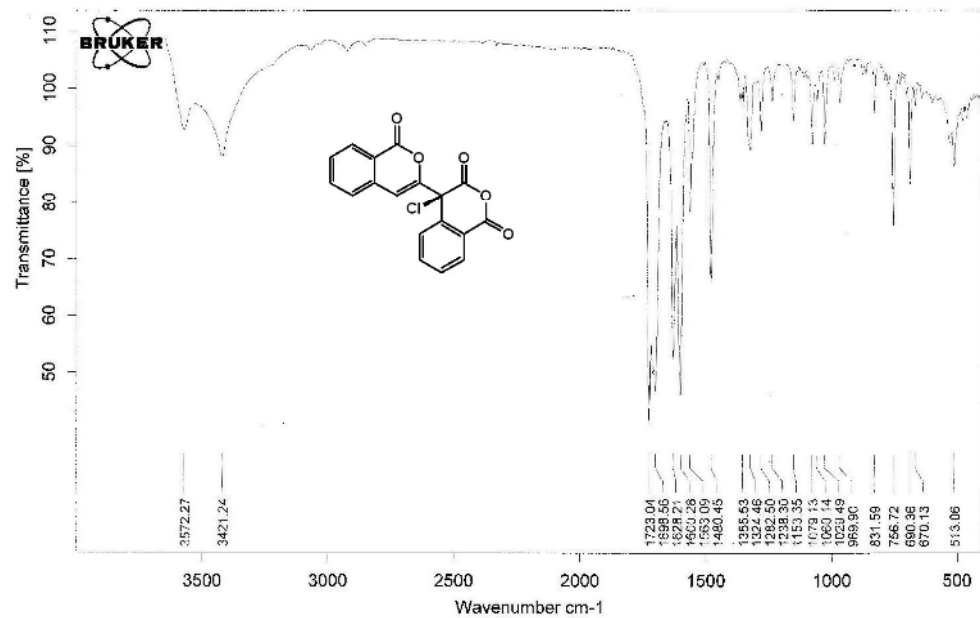


Figure A35 IR Spectrum of Compound 332.

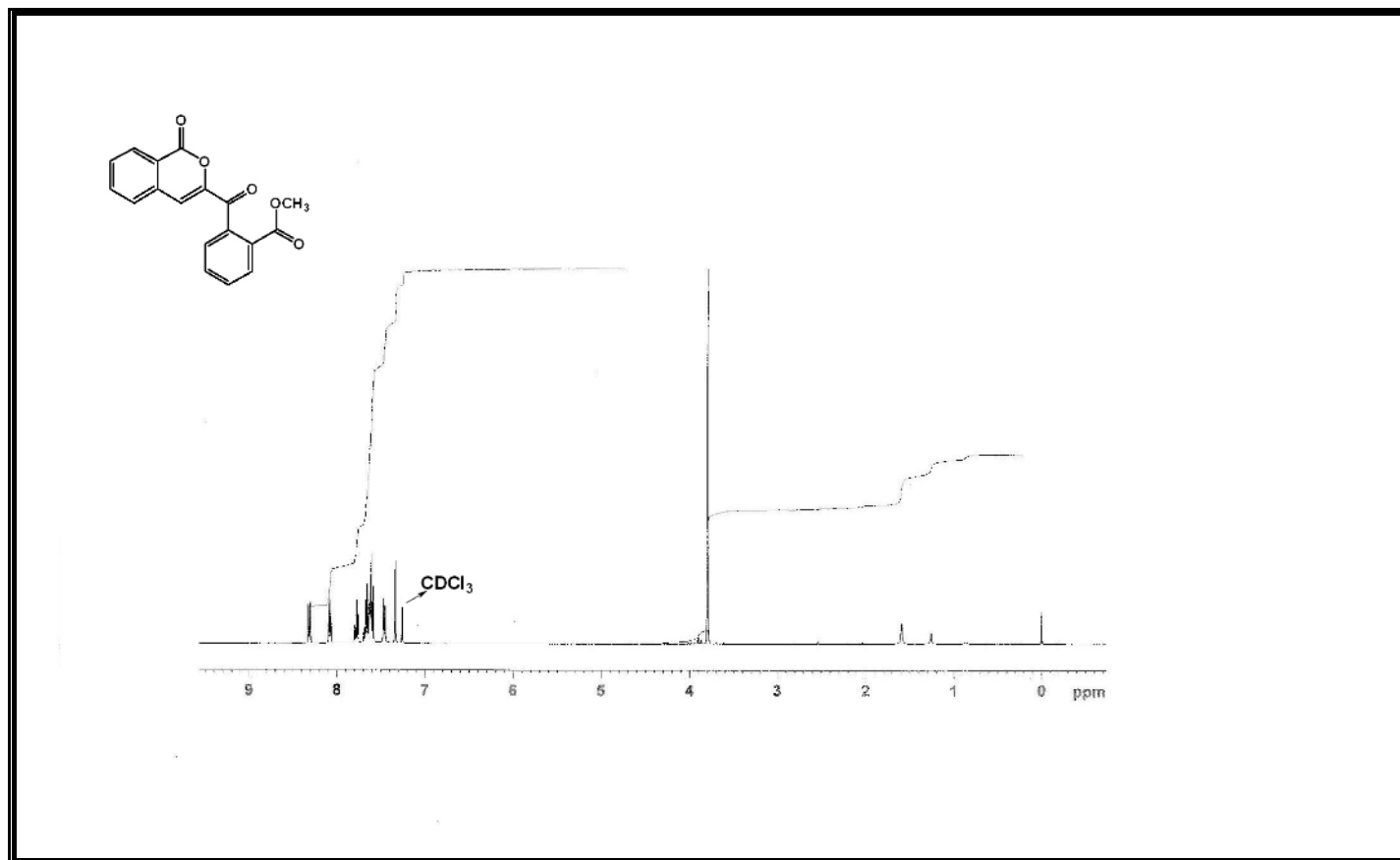


Figure A36 ^1H -NMR Spectrum of Compound 340.

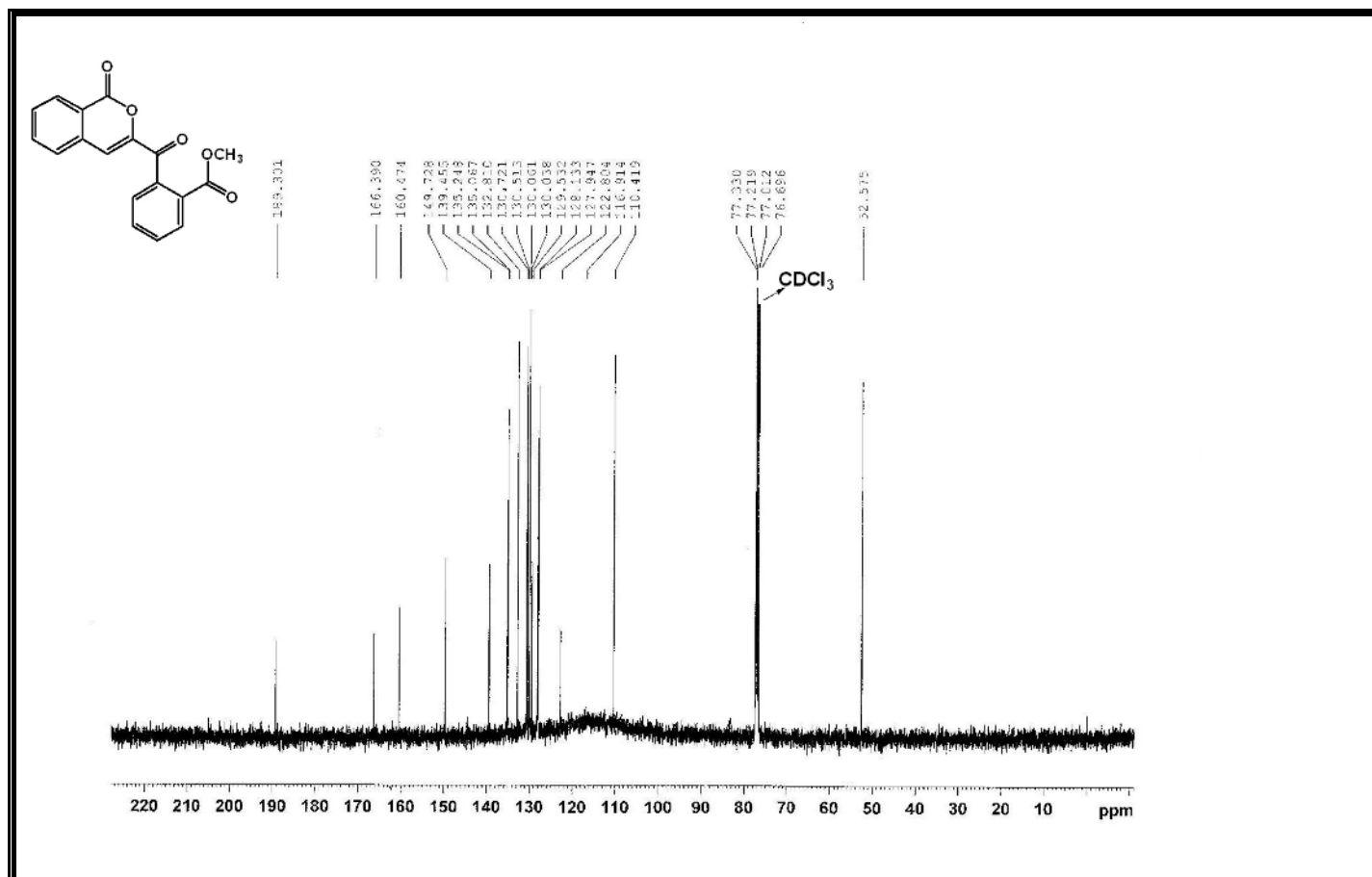


Figure A37 ¹³C-NMR Spectrum of Compound 340.

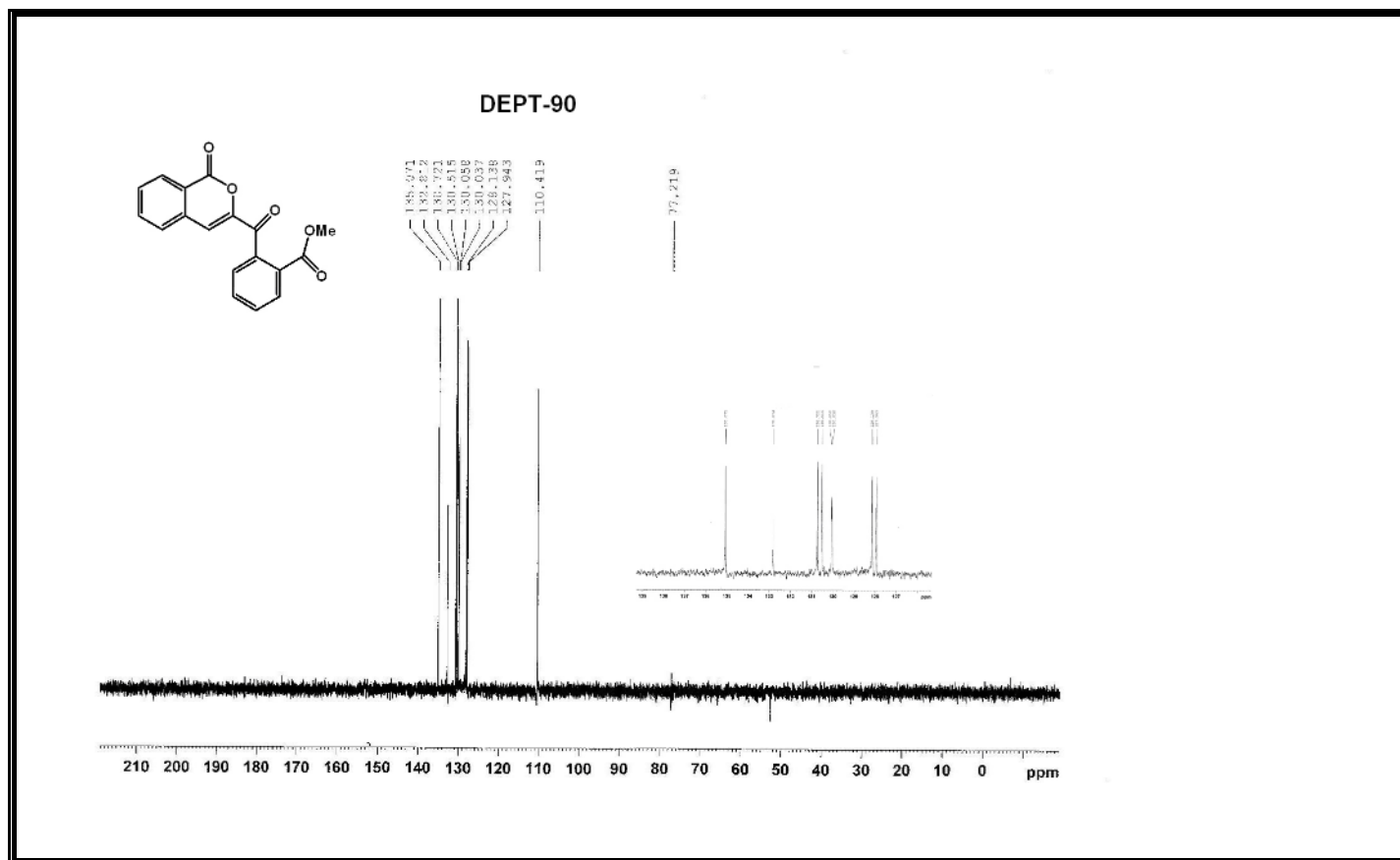


Figure A38 DEPT-90 Spectrum of Compound 340.

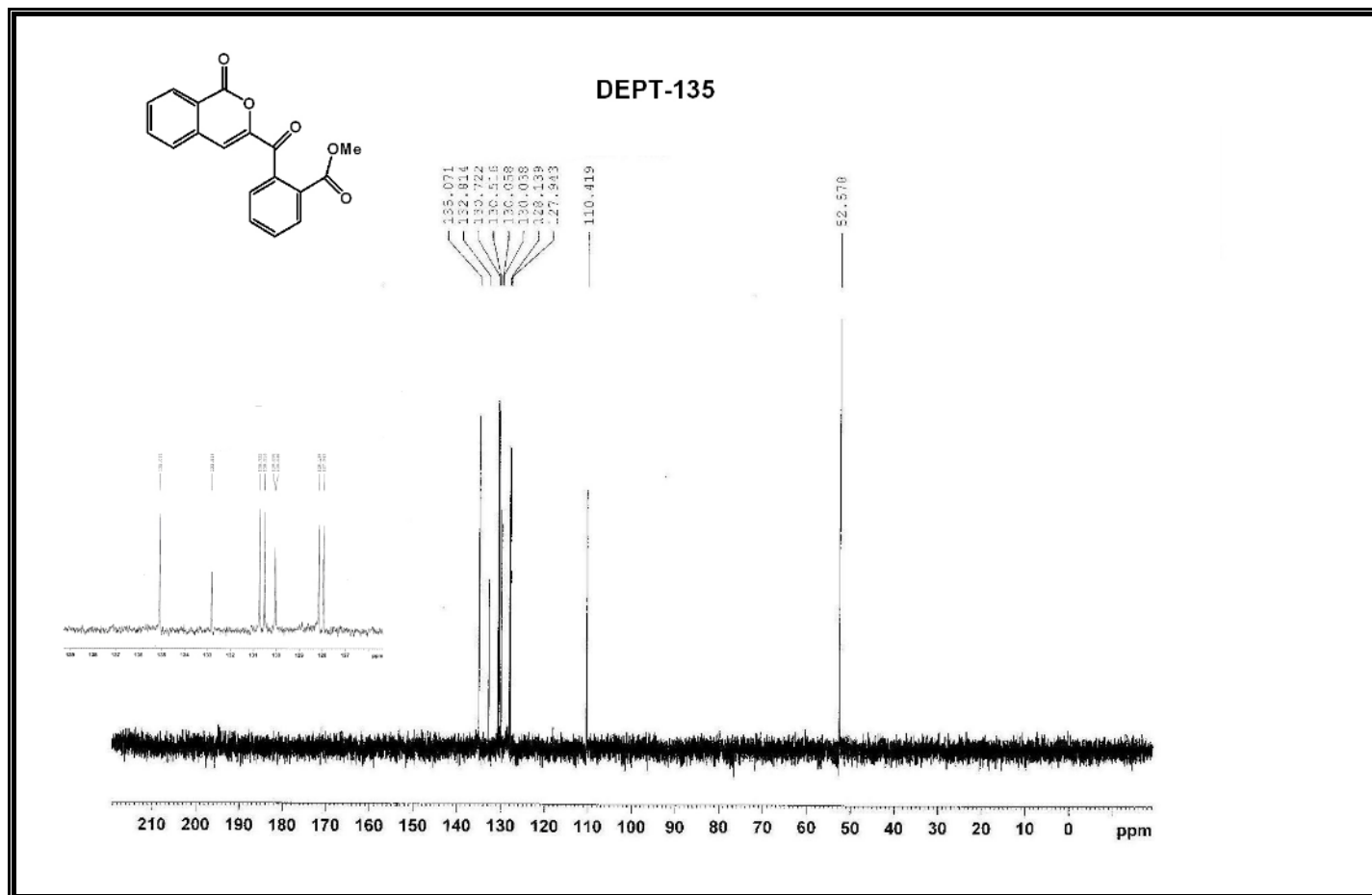


Figure A39 DEPT-135 Spectrum of Compound 340.

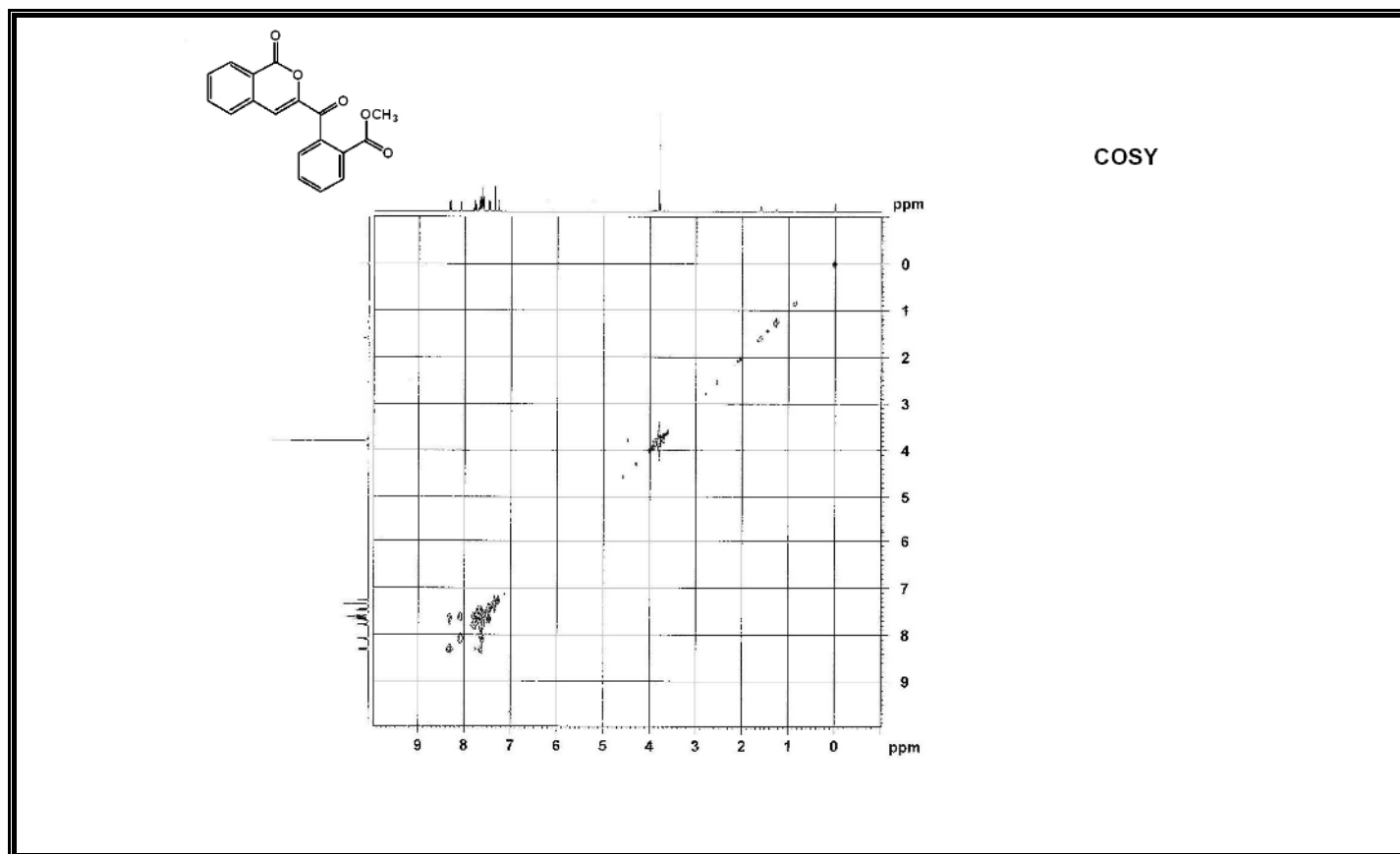


Figure A40 COSY Spectrum of Compound 340.

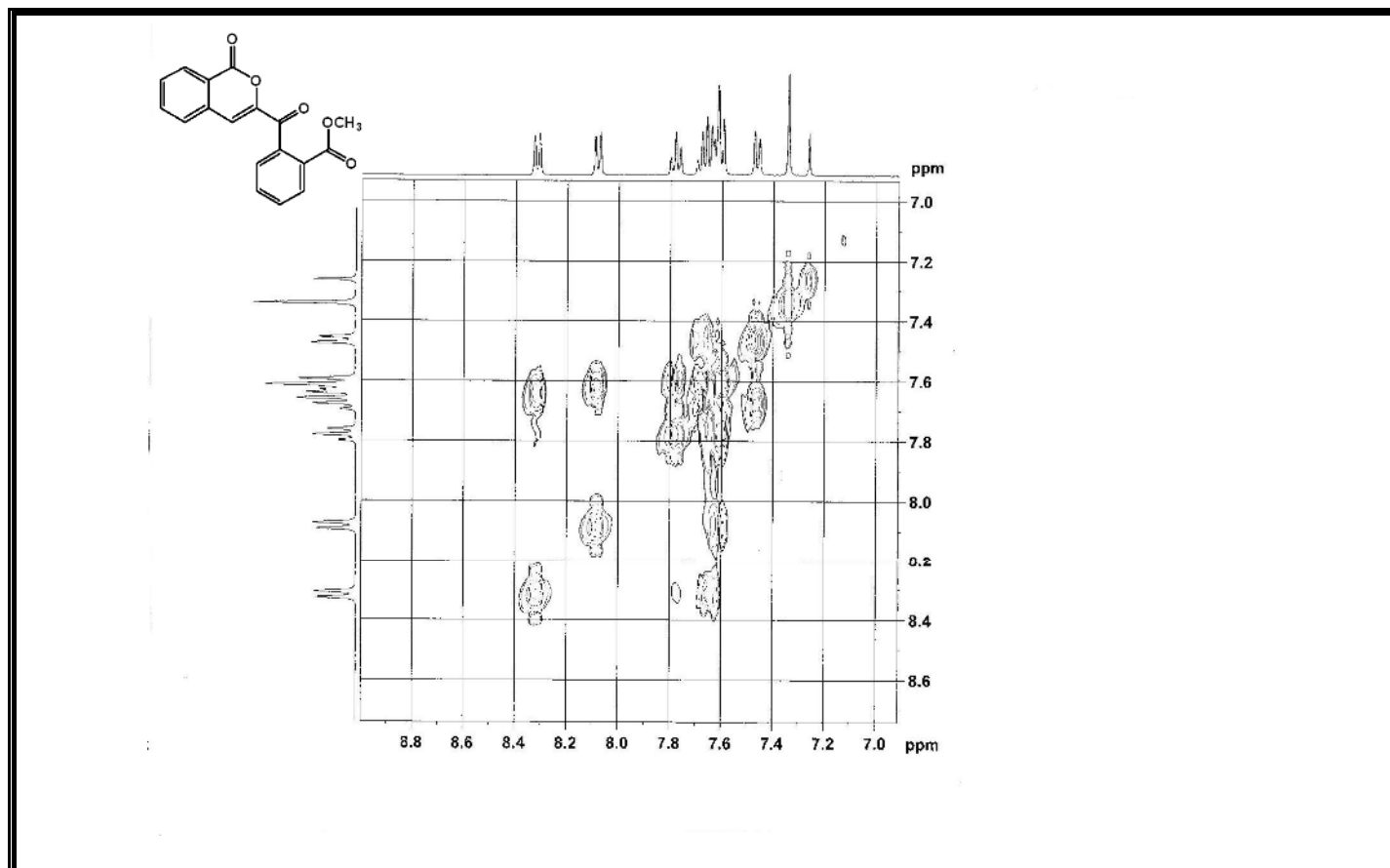


Figure A41 Expanded COSY Spectrum of Compound 340.

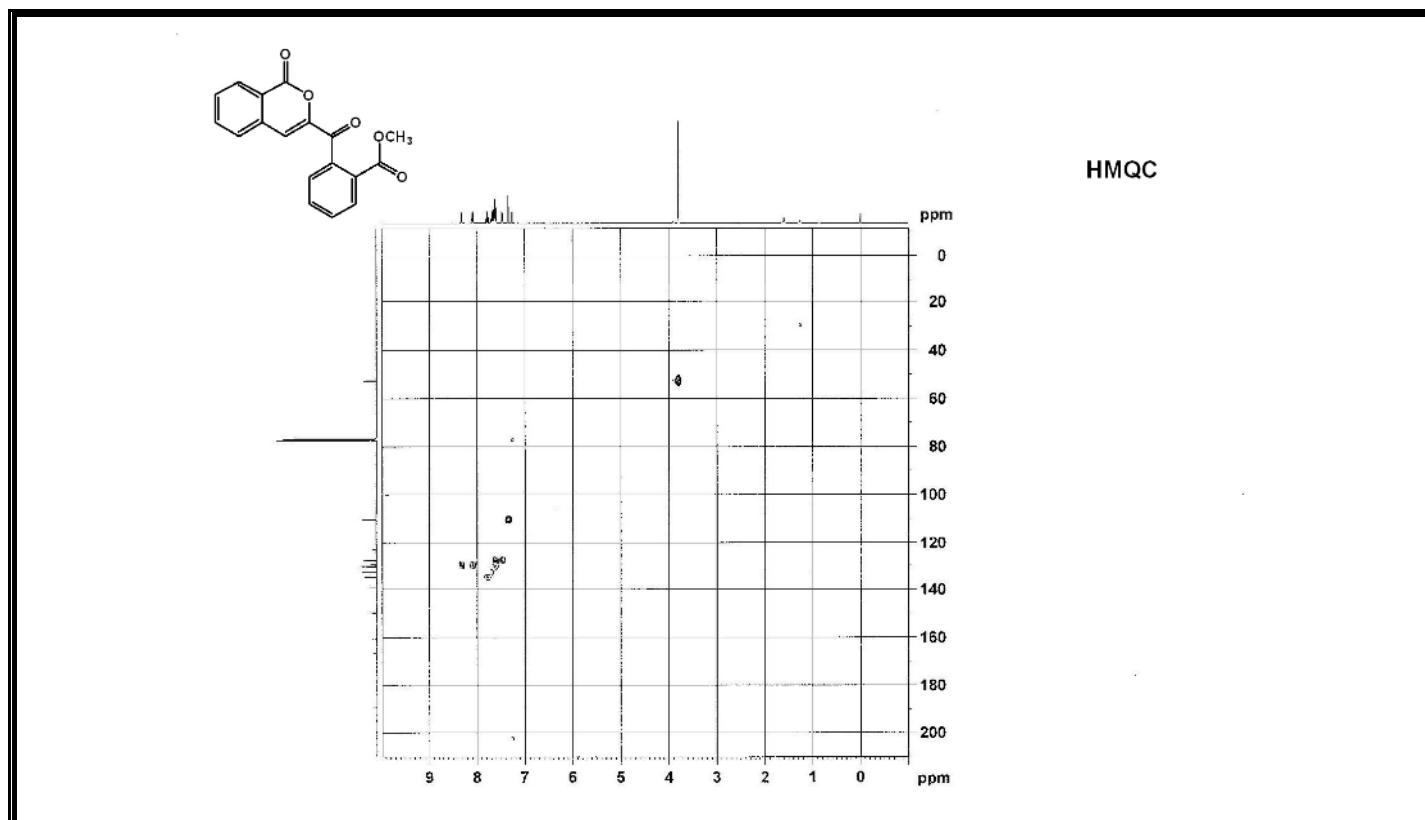


Figure A42 HMQC Spectrum of Compound 340.

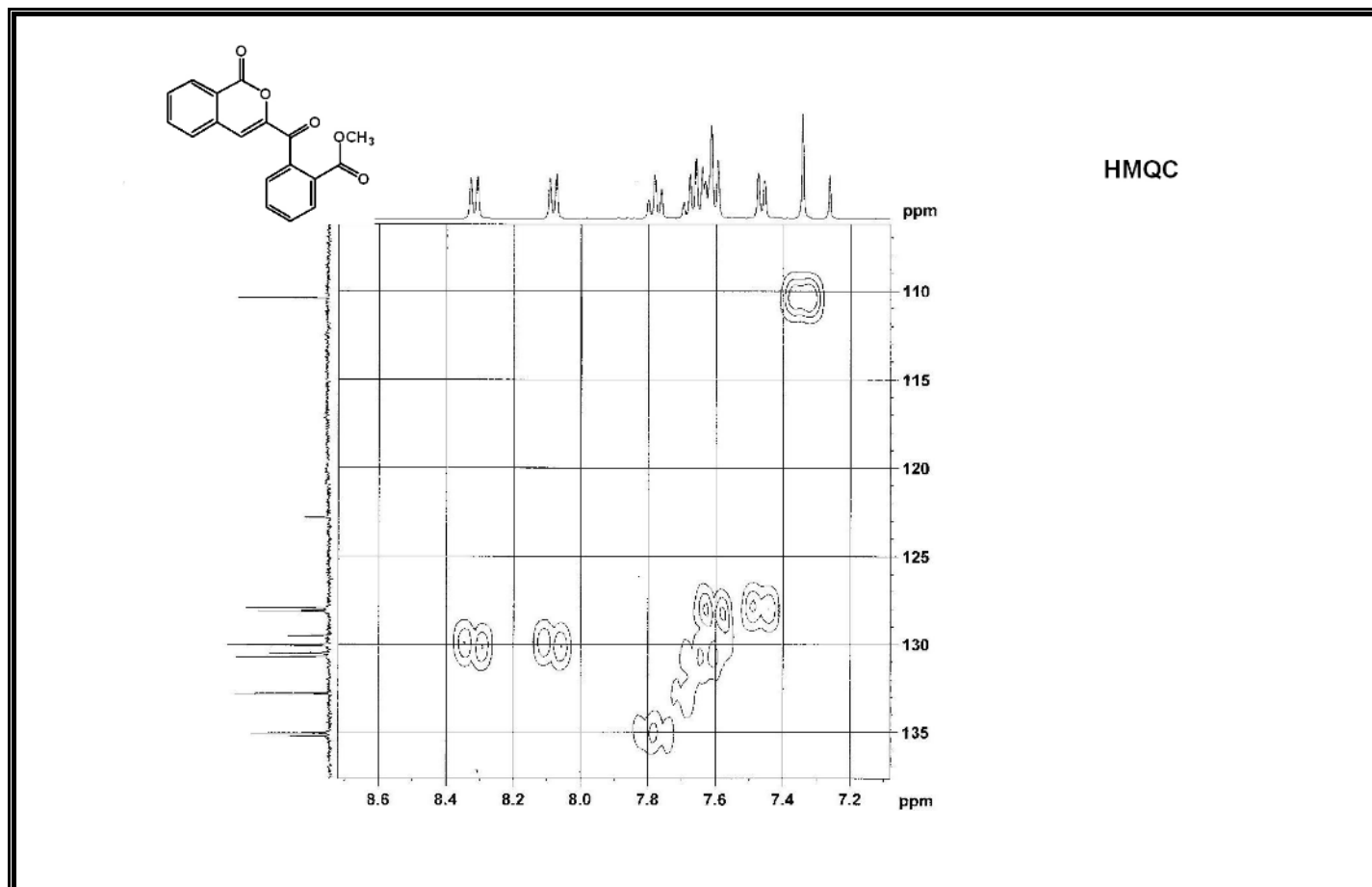


Figure A43 Expanded HMQC Spectrum of Compound 340.

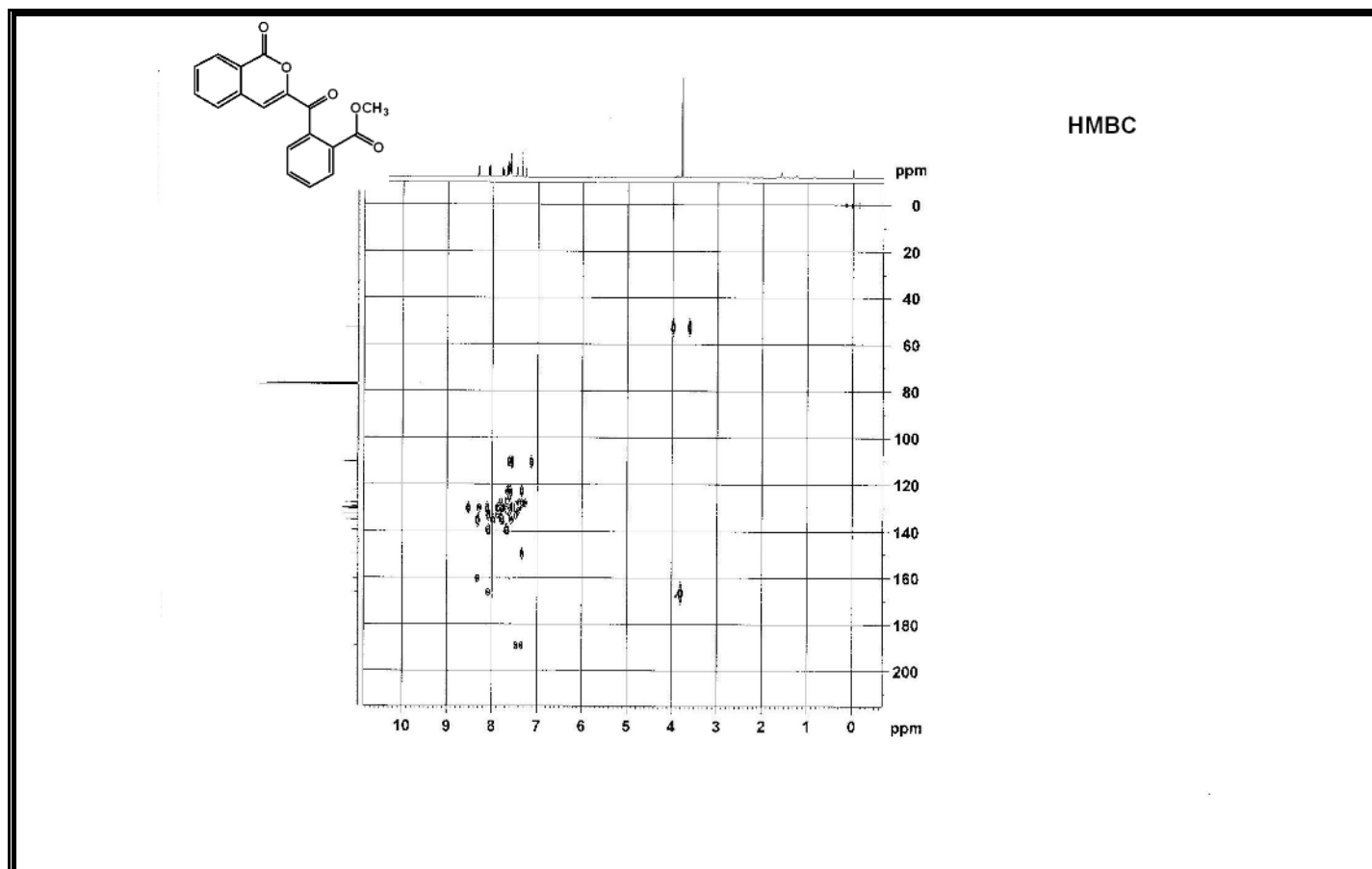


Figure A44 HMBC Spectrum of Compound 340.

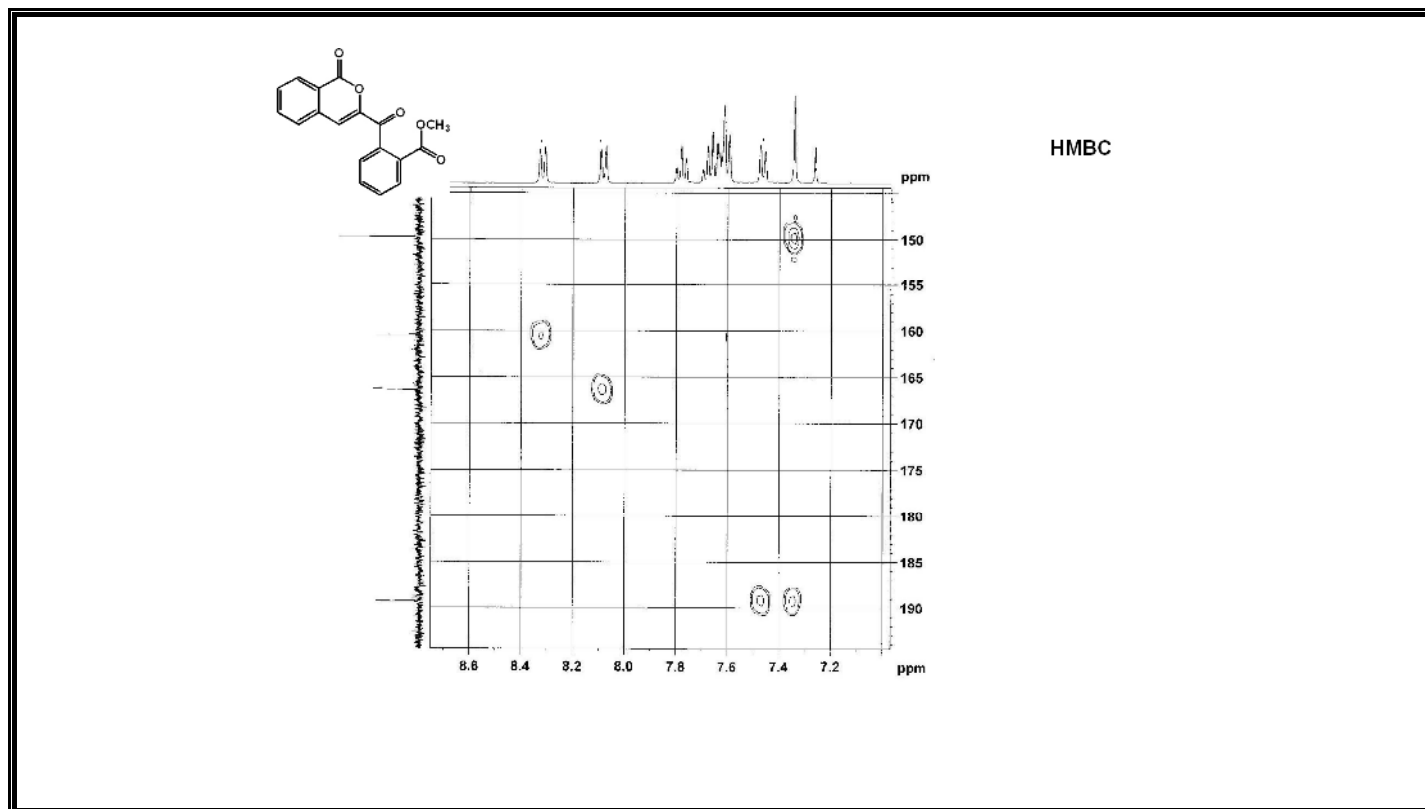


Figure A45 Expanded HMBC Spectrum of Compound **340**.

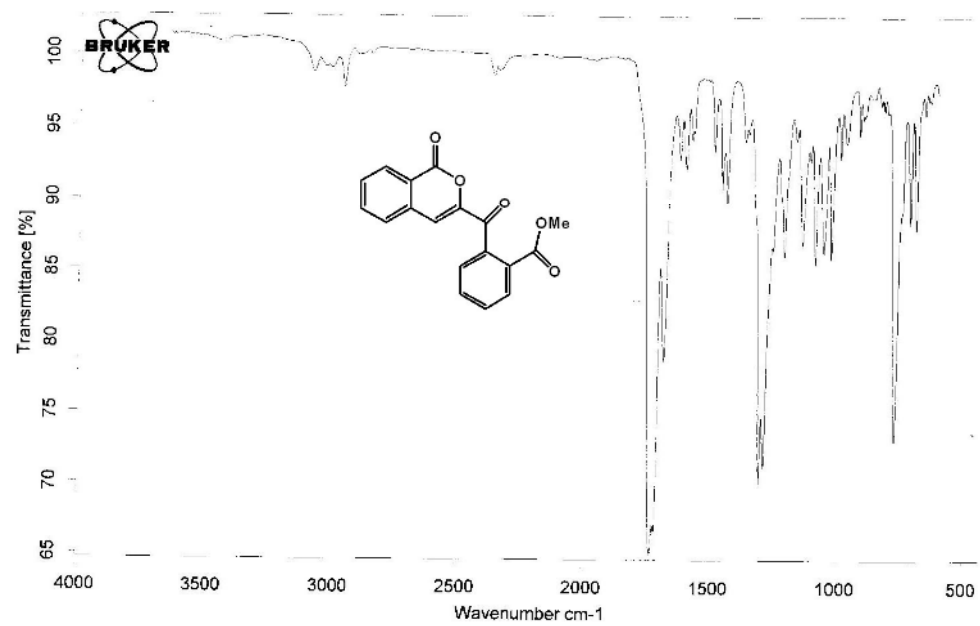


Figure A46 IR Spectrum of Compound 340.

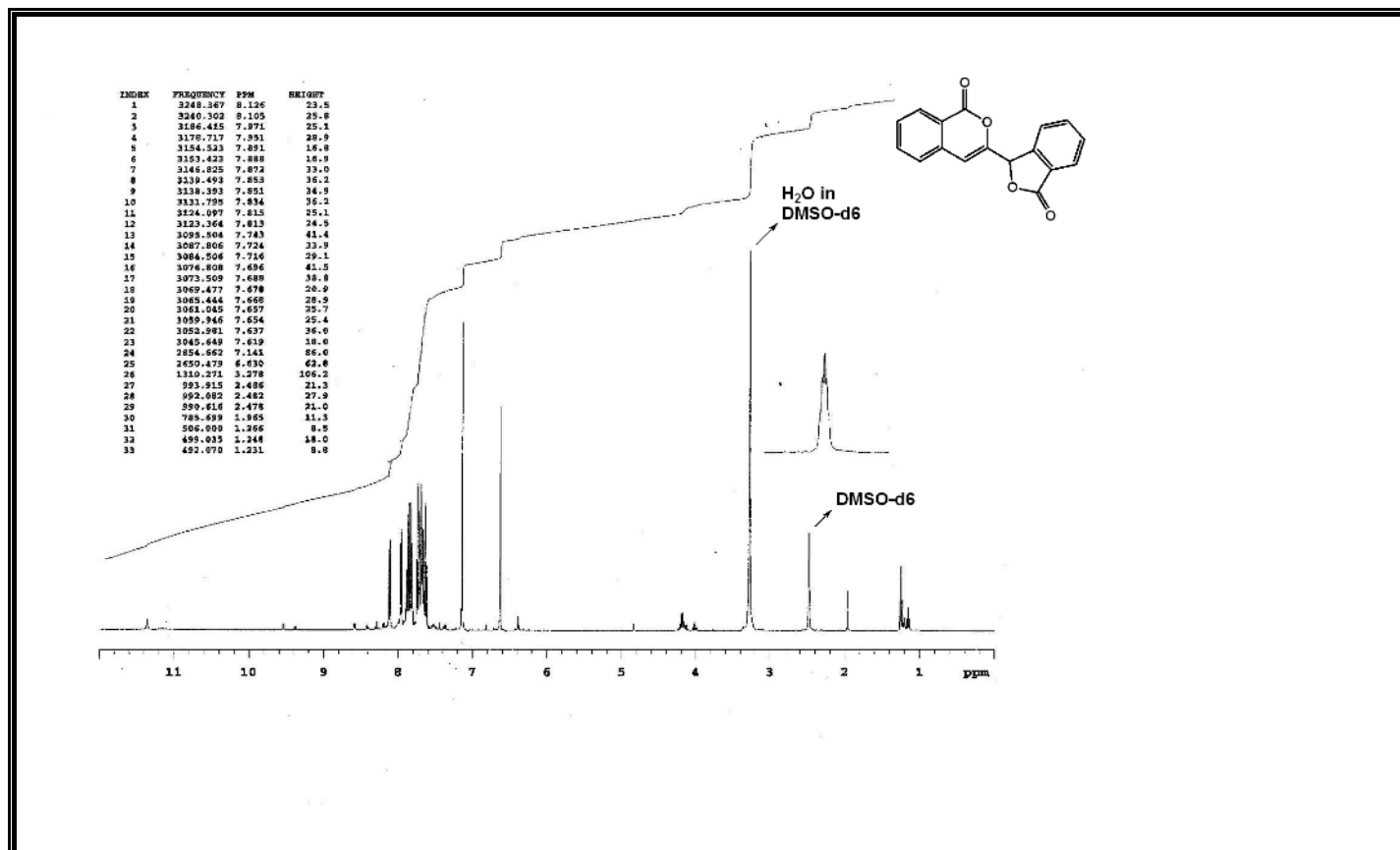


Figure A47 ¹H-NMR Spectrum of Compound 334.

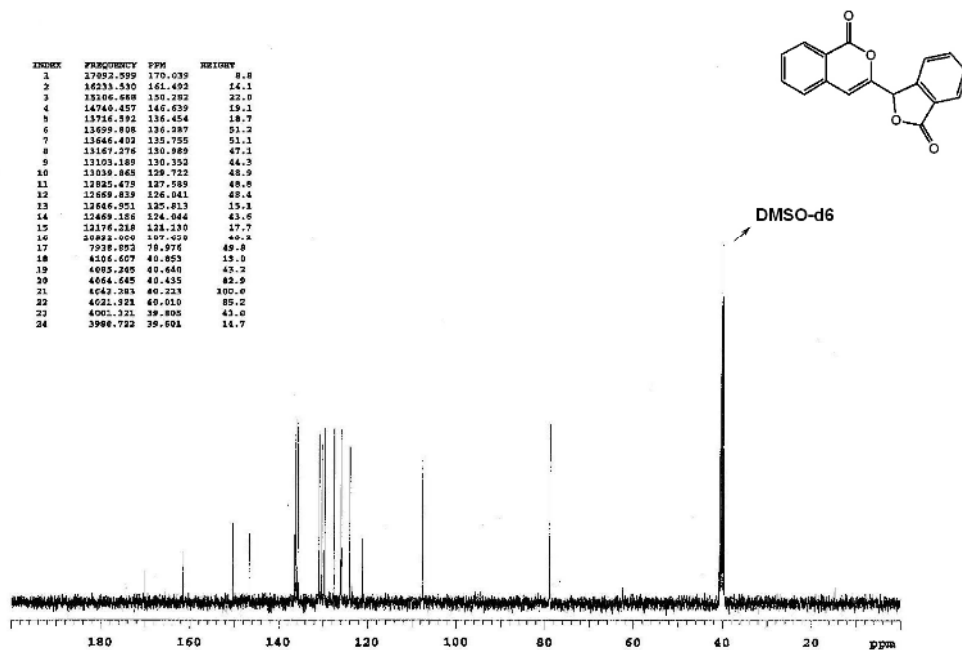


Figure A48 ¹³C-NMR Spectrum of Compound 334.

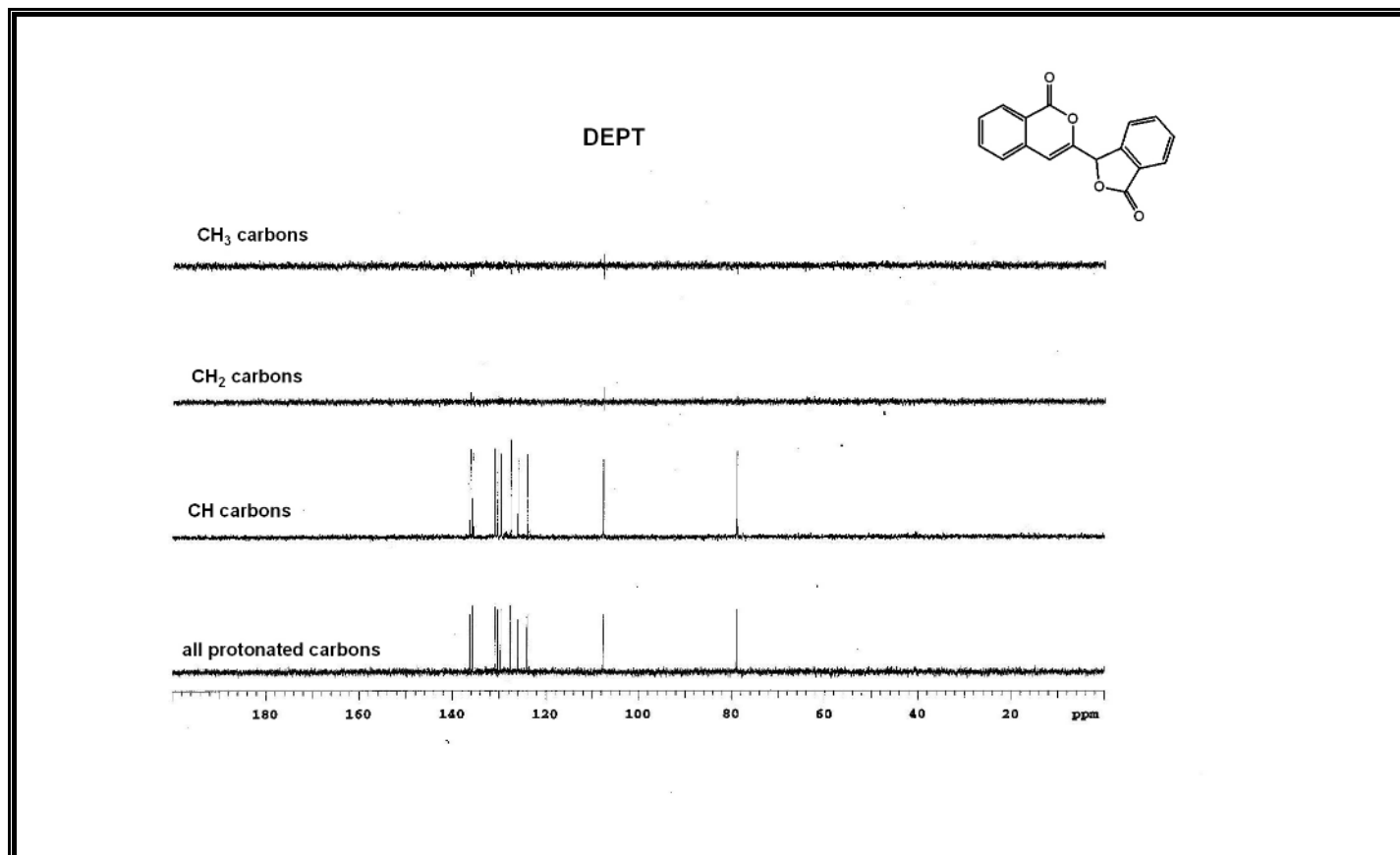


Figure A49 DEPT Spectrum of Compound 334.

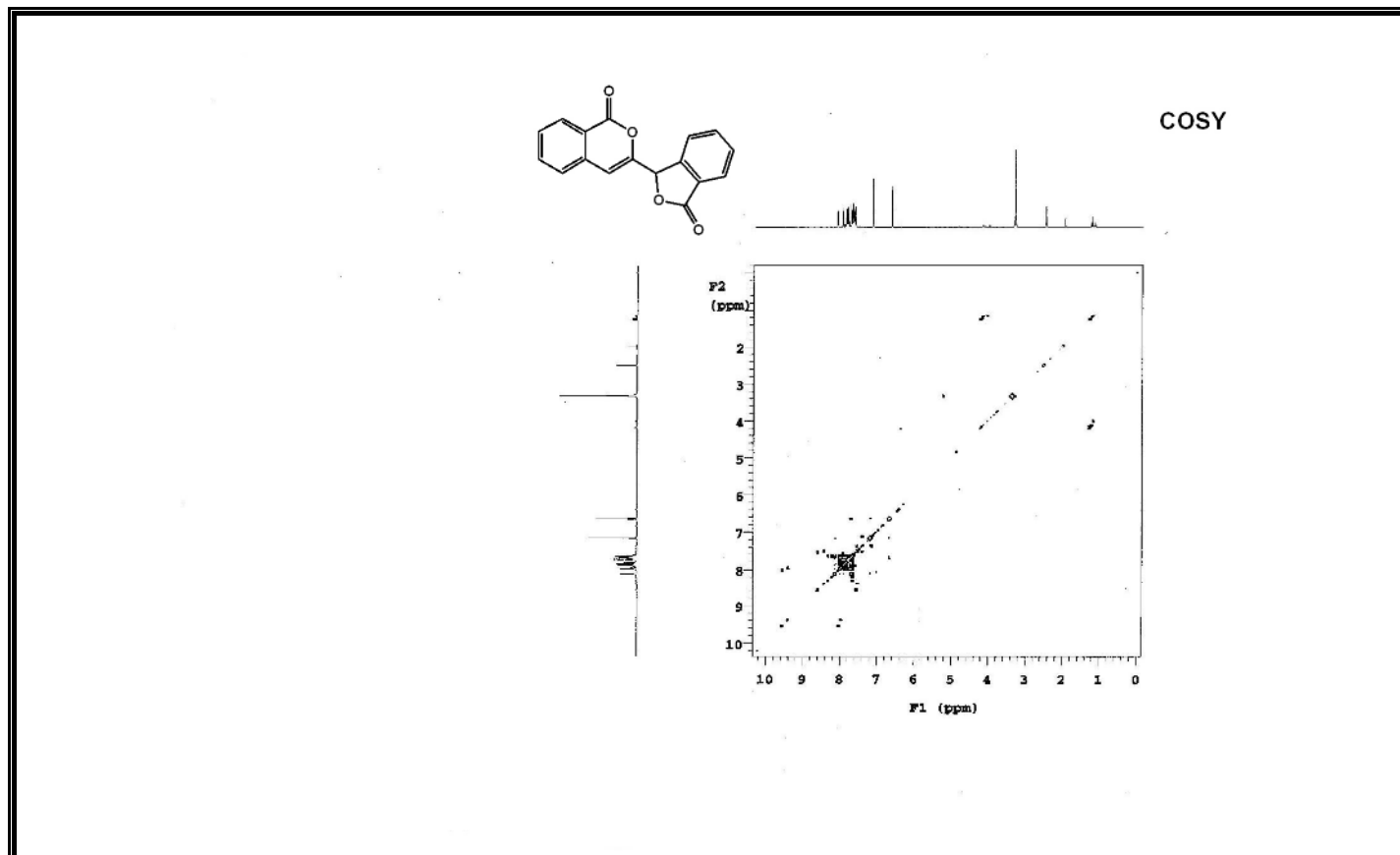


Figure A50 COSY Spectrum of Compound 334.

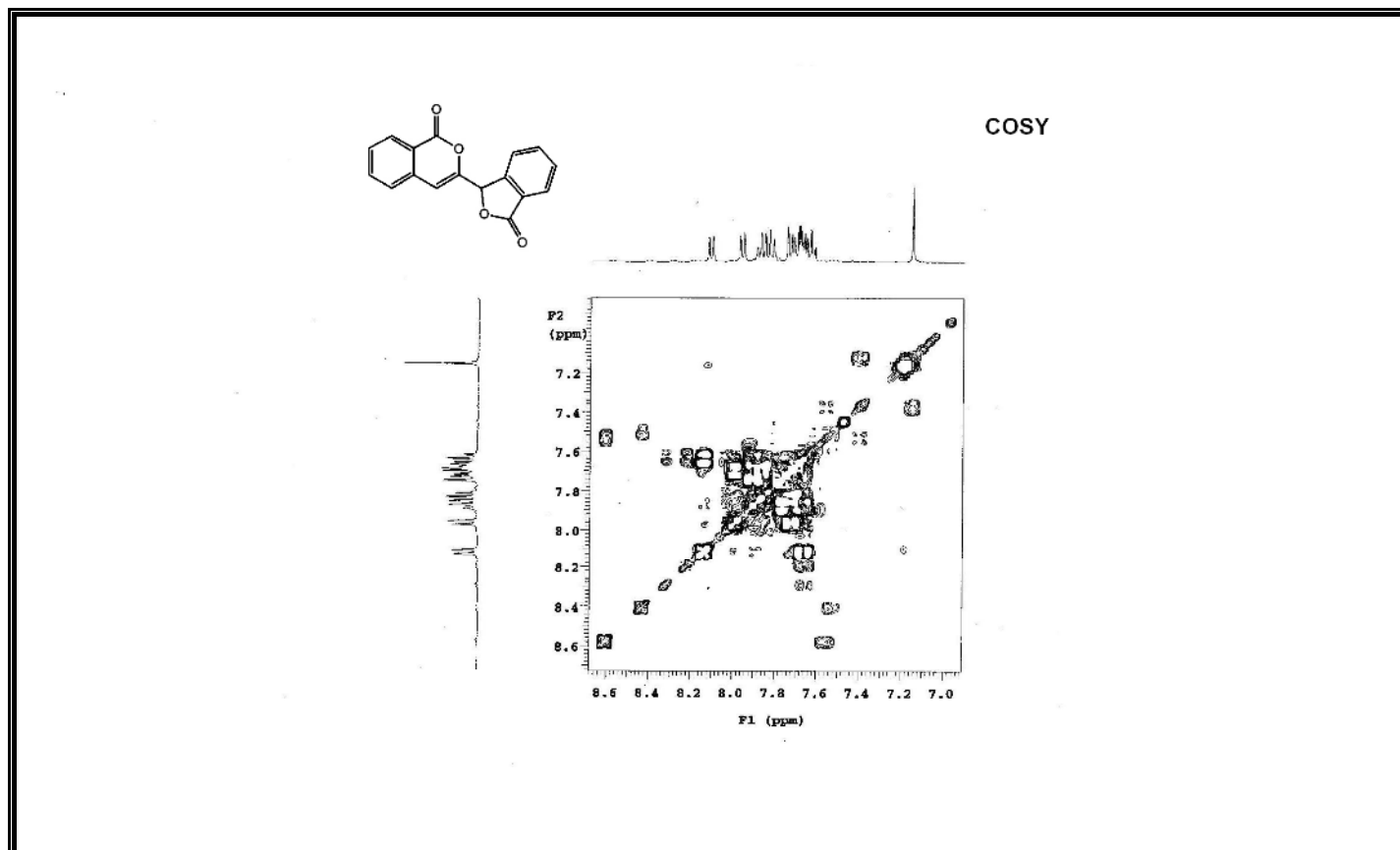


Figure A51 Expanded COSY Spectrum of Compound 334.

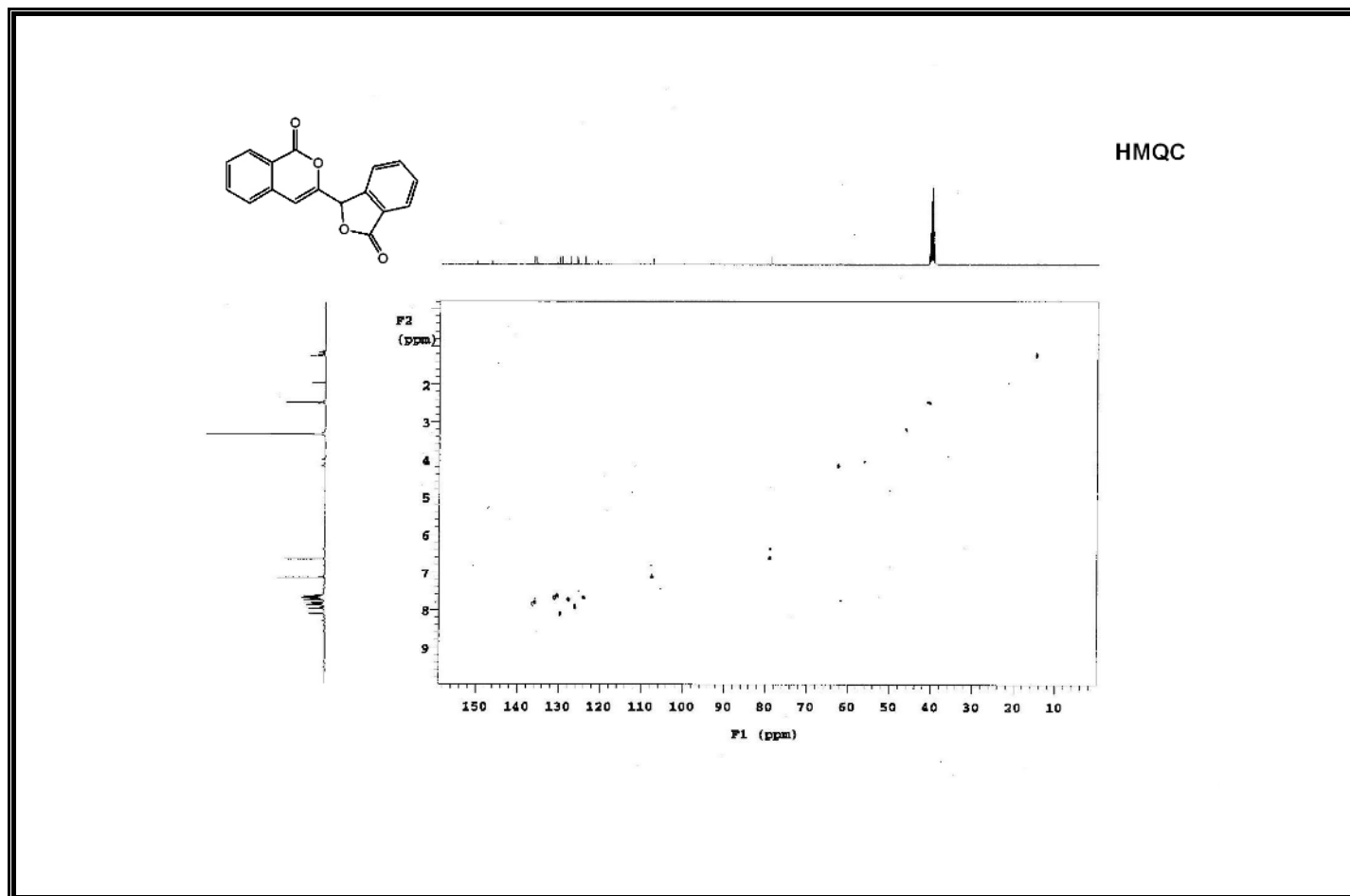


Figure A52 HMQC Spectrum of Compound 334.

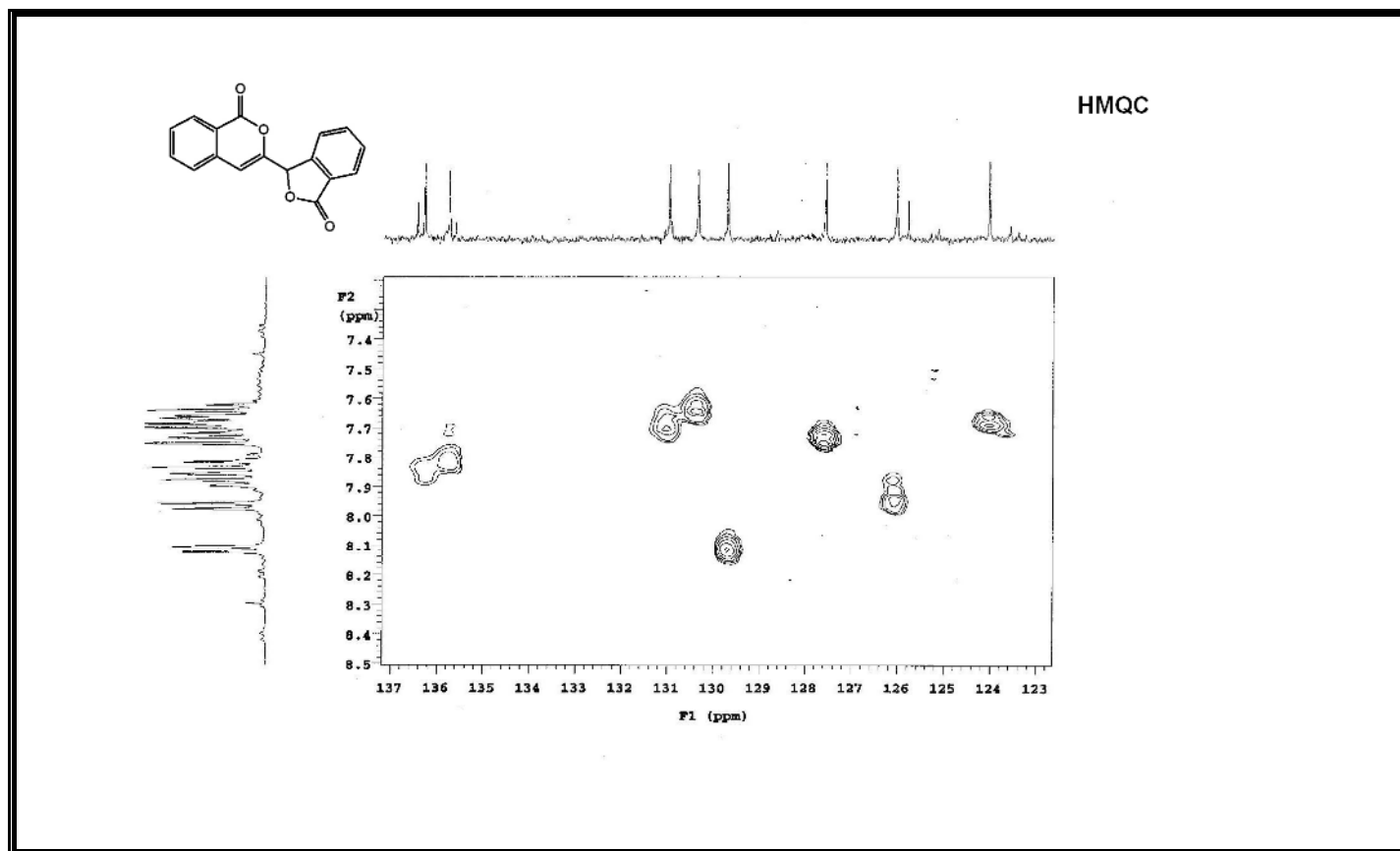


Figure A53 Expanded HMQC Spectrum of Compound 334.

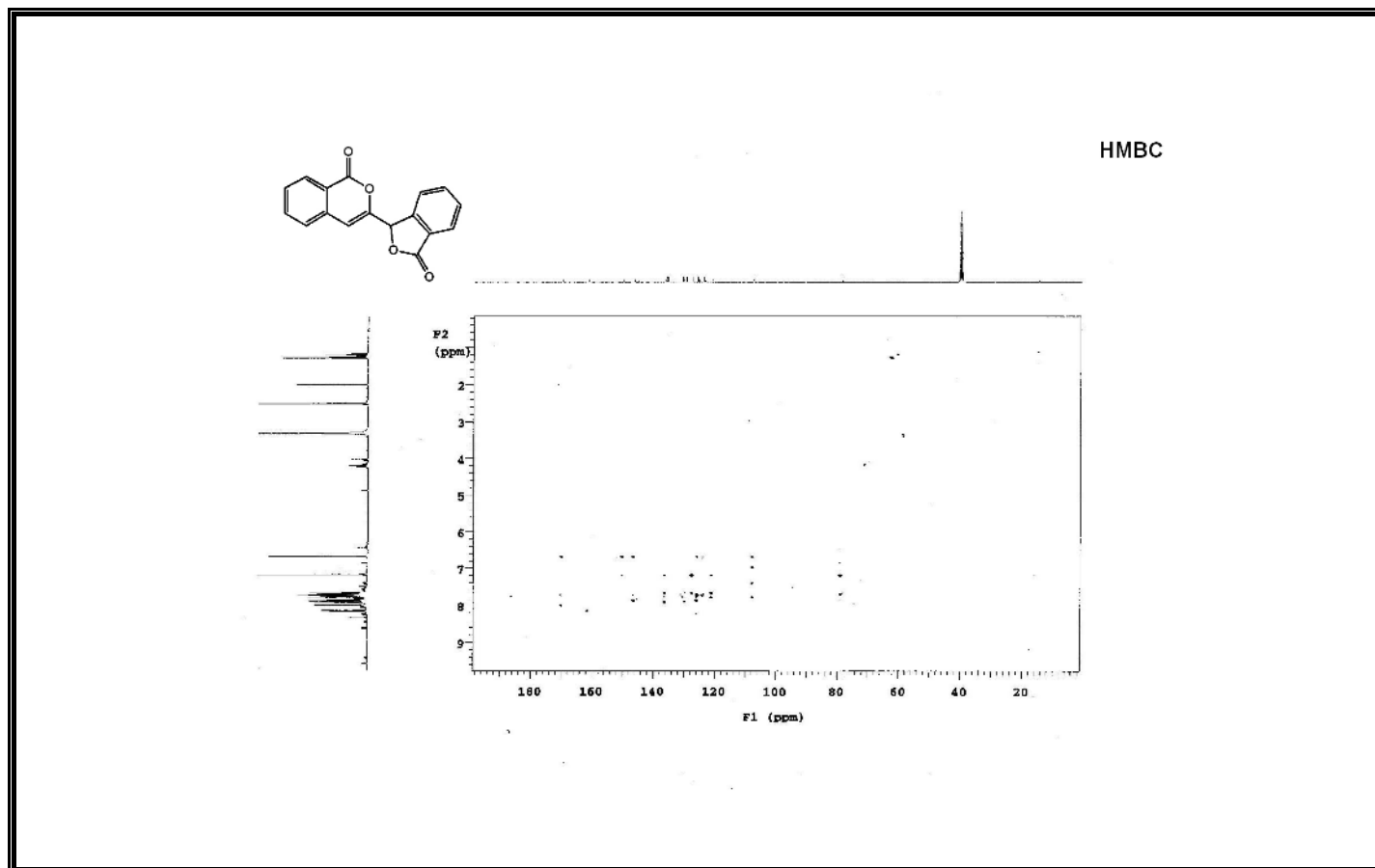


Figure A54 HMBC Spectrum of Compound 334.

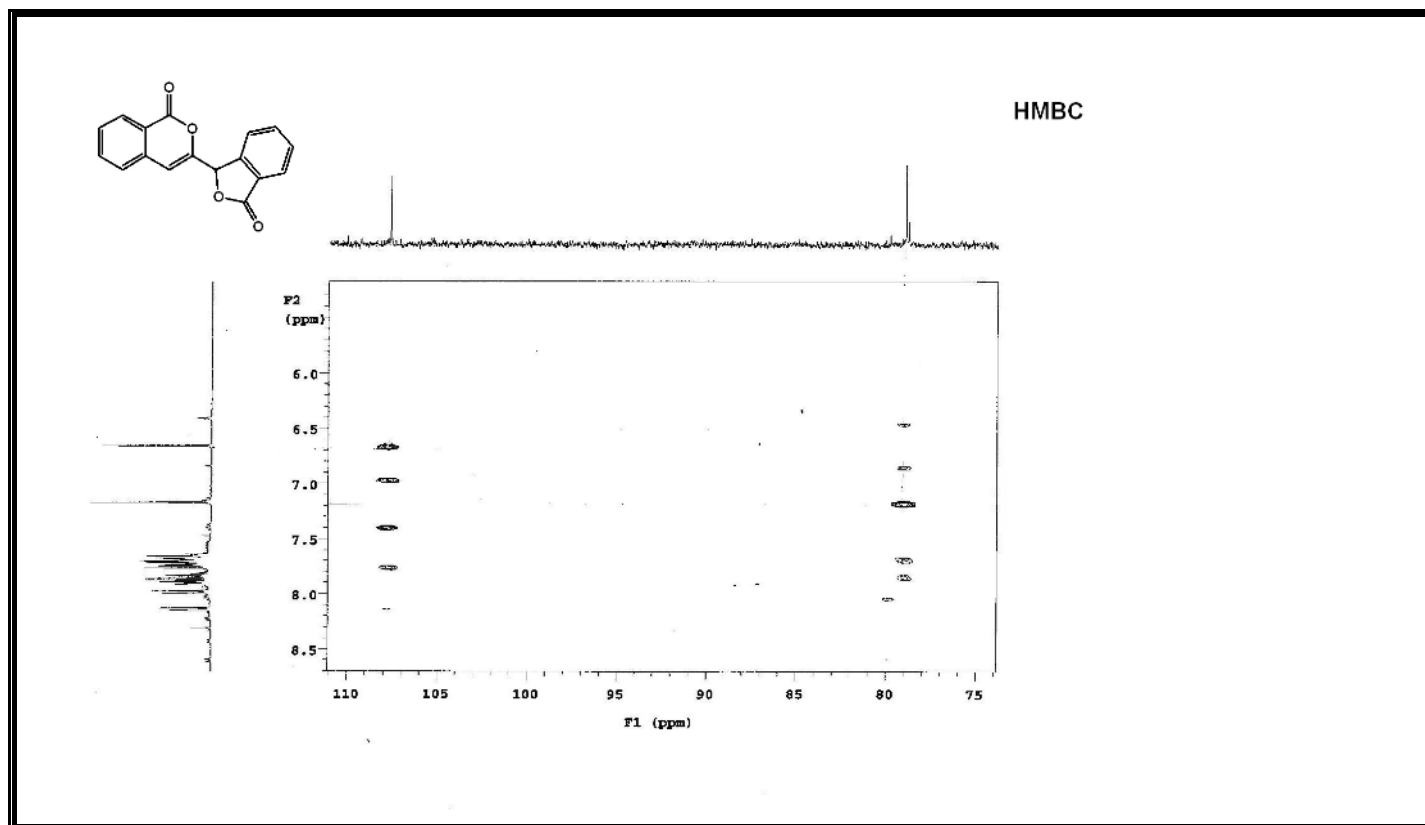


Figure A55 Expanded HMBC Spectrum of Compound 334.

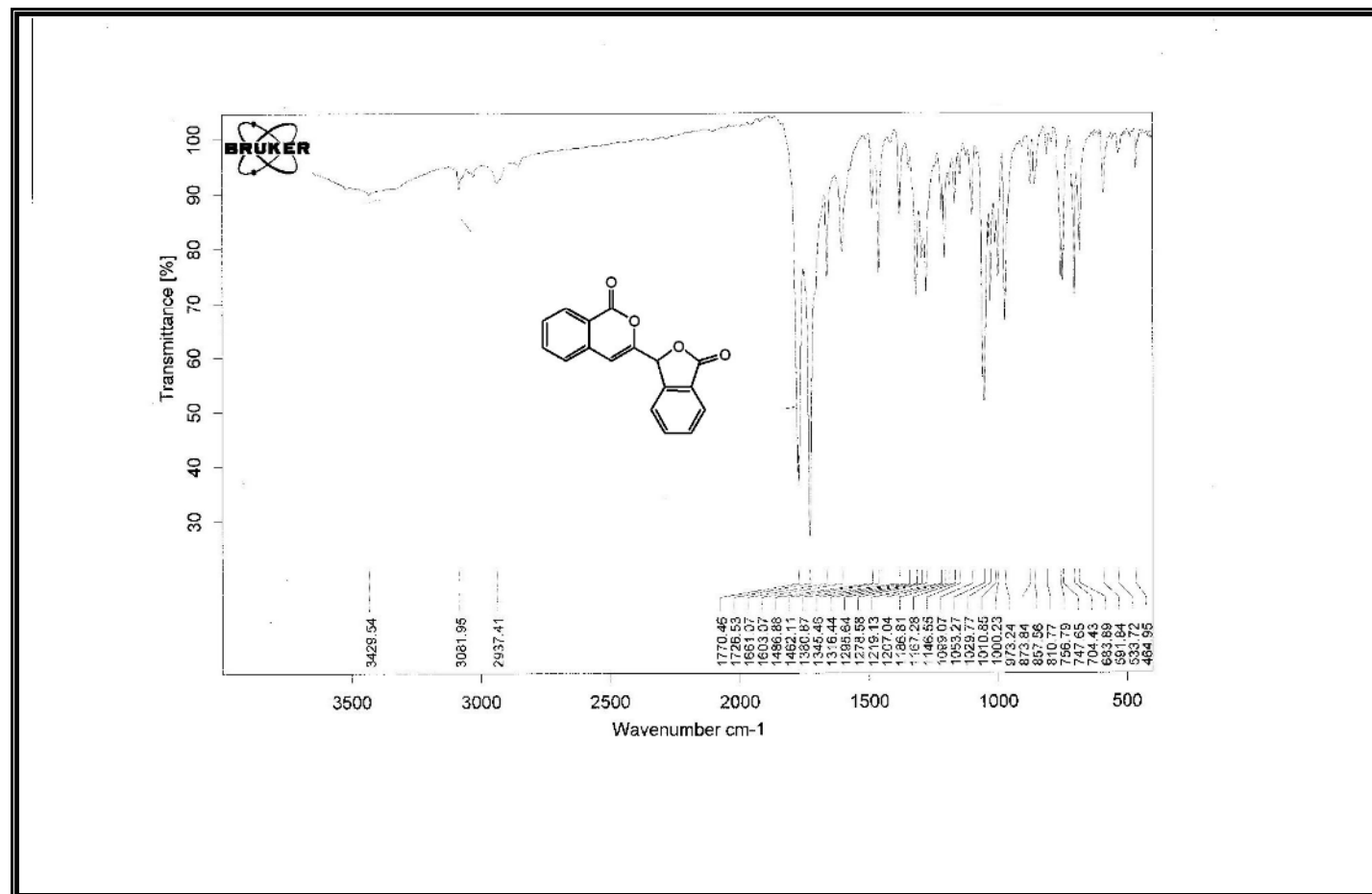


Figure A56 IR Spectrum of Compound 334.

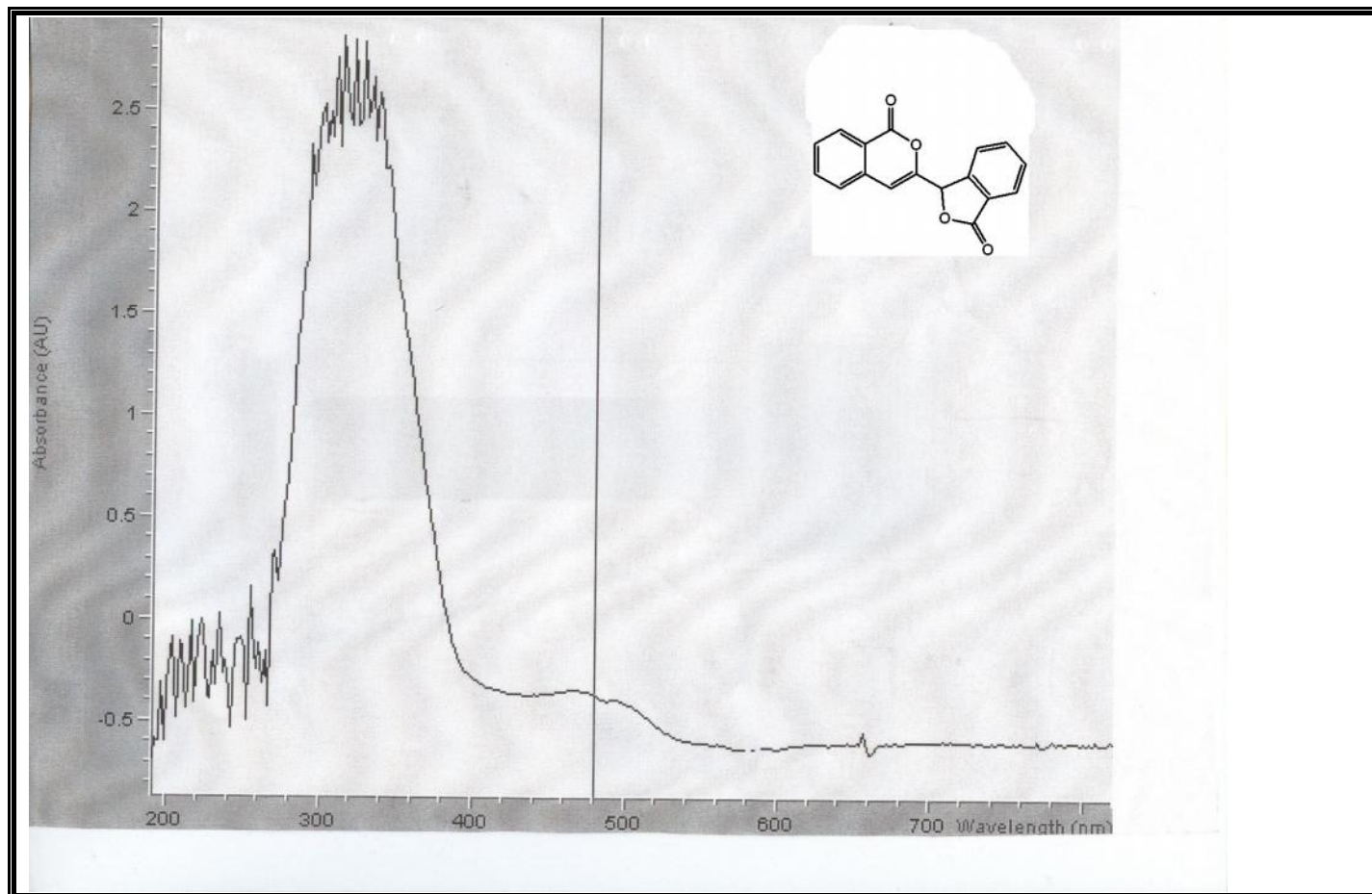


Figure A57 UV Spectrum of Compound **334**.

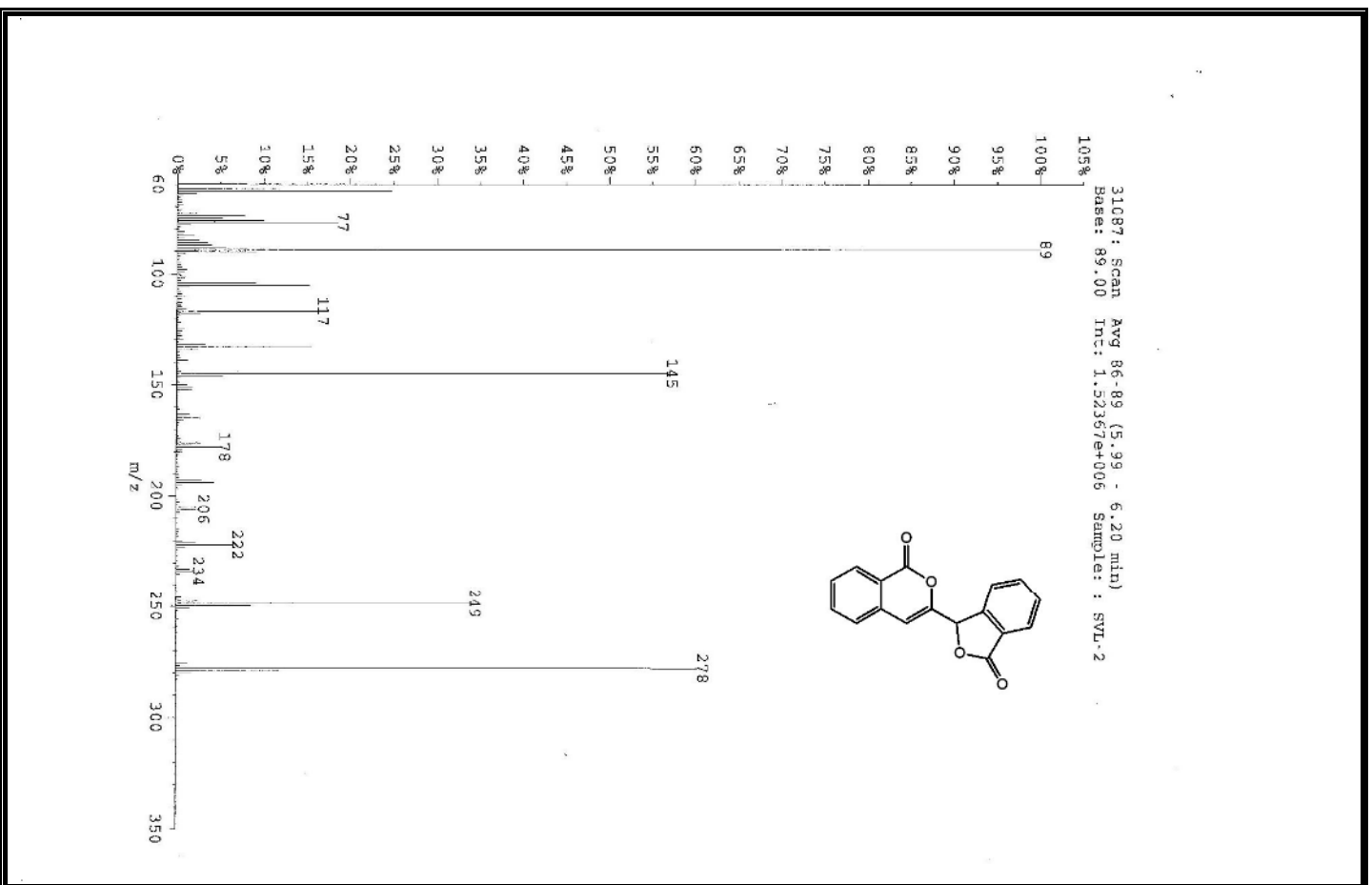


Figure A58 High Resolution Mass Spectrum of Compound **334**.

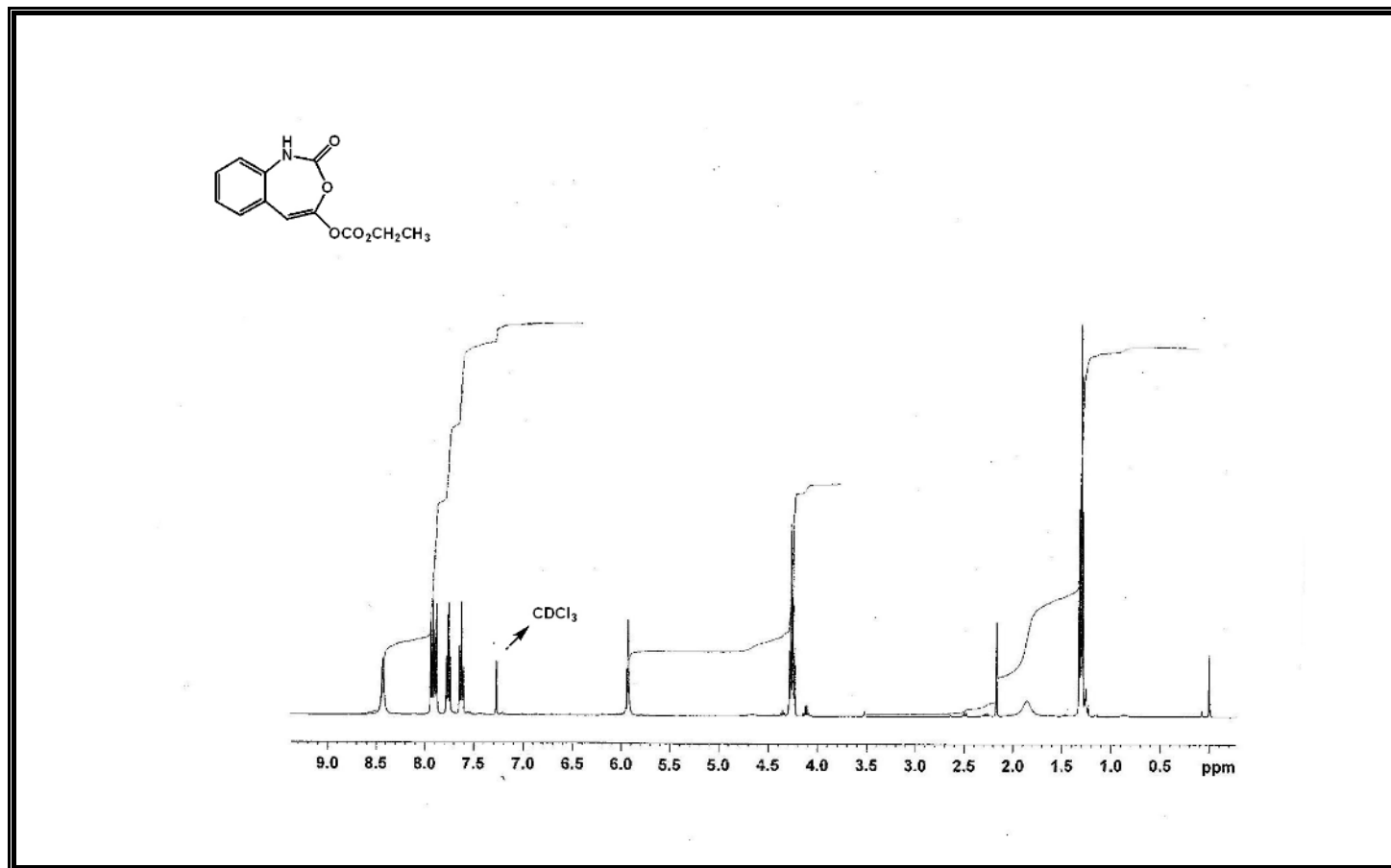


Figure A59 ^1H -NMR Spectrum of Compound 335.

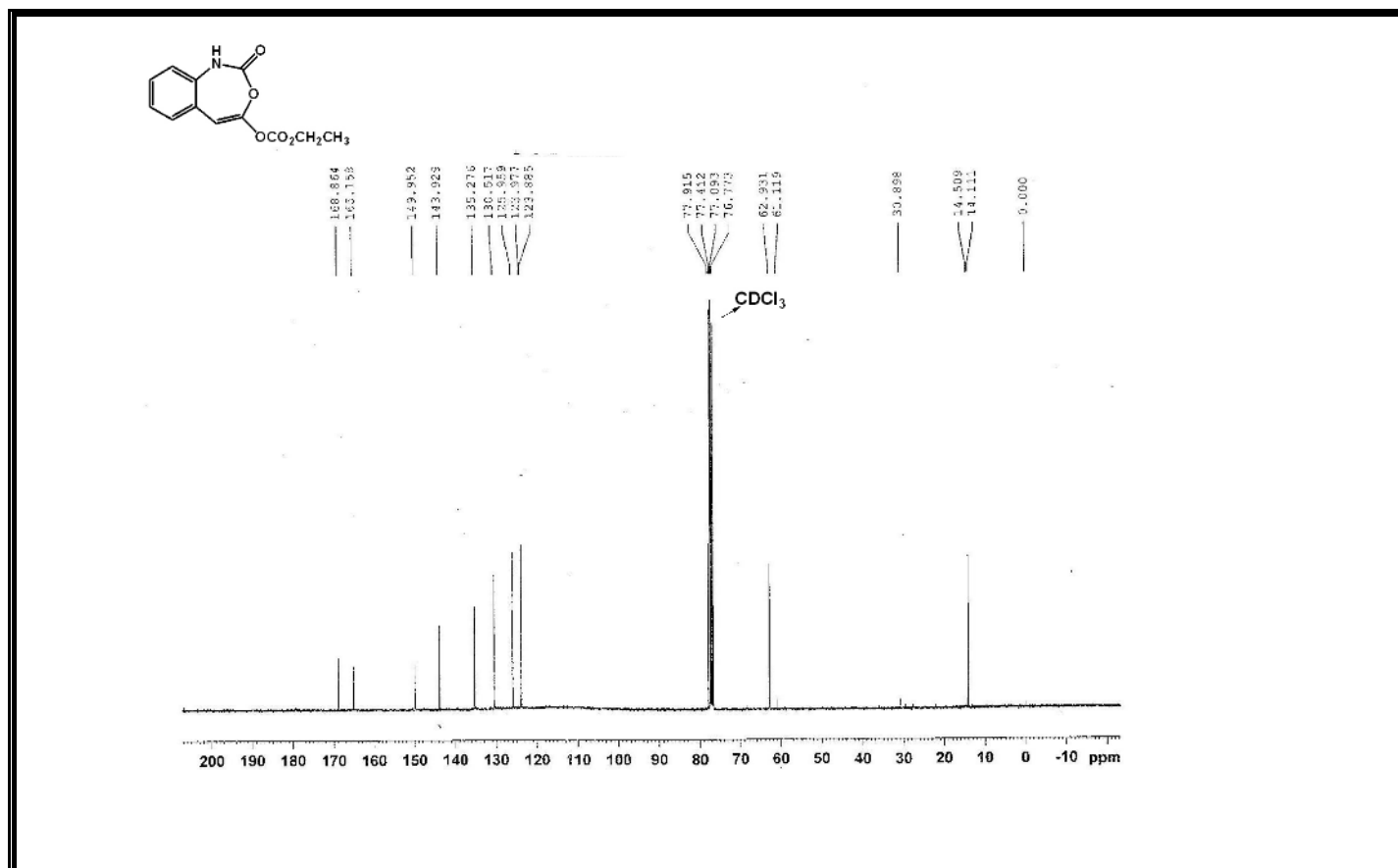


Figure A60 ¹³C-NMR Spectrum of Compound 335.

DEPT-90

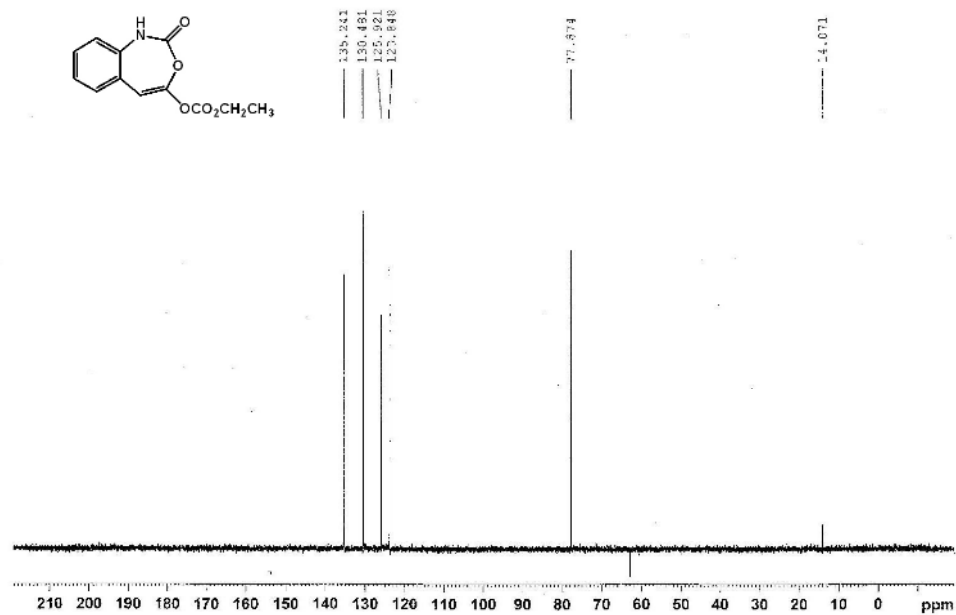


Figure A61 DEPT-90 Spectrum of Compound 335.

DEPT-135

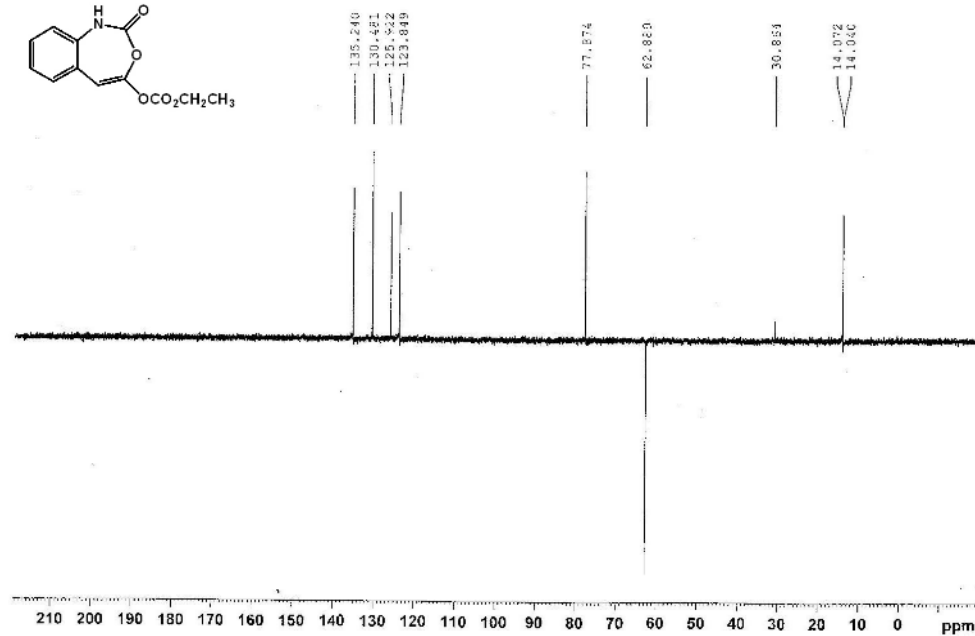
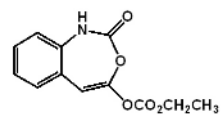


Figure A62 DEPT-135 Spectrum of Compound 335.

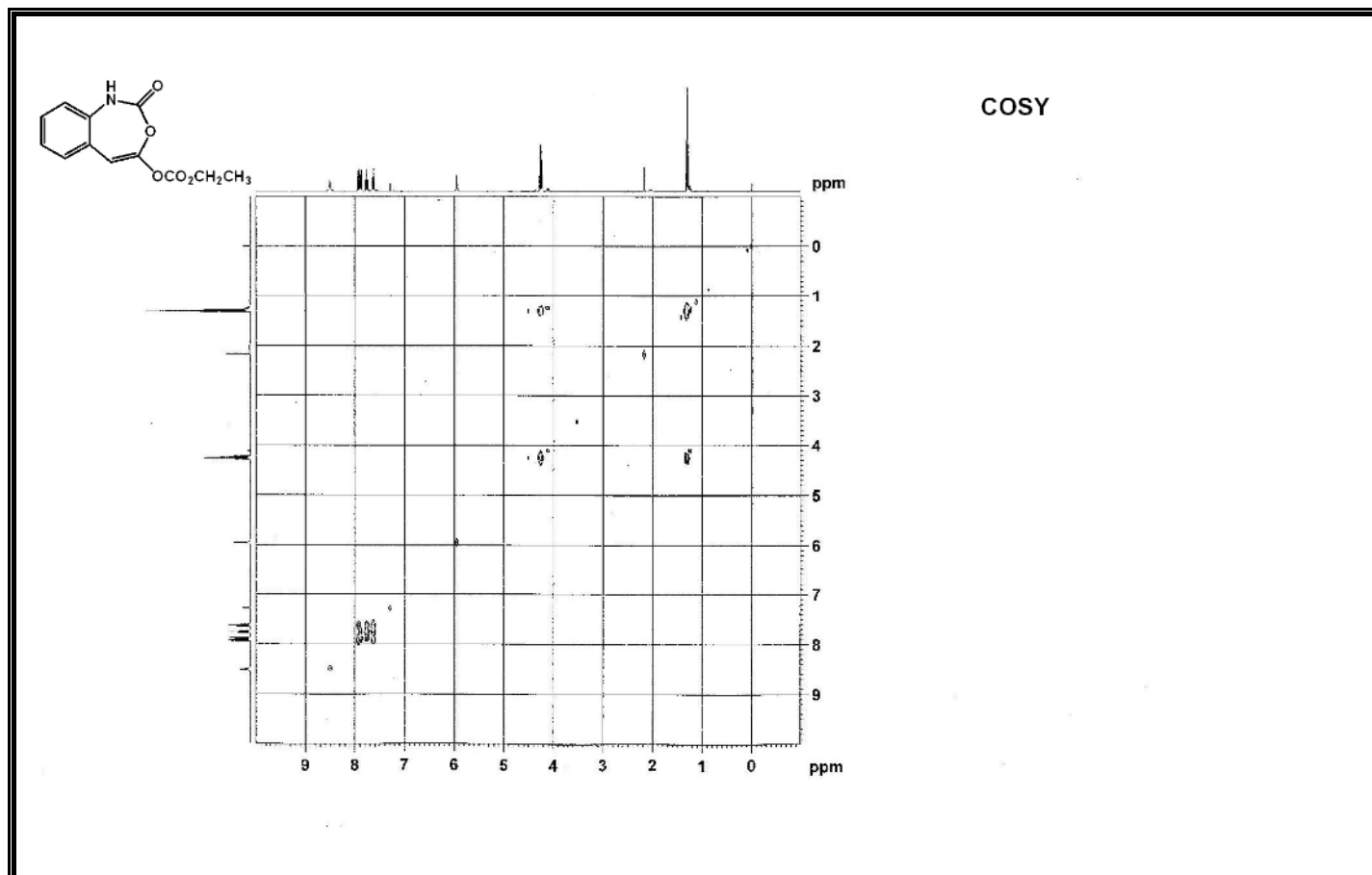


Figure A63 COSY Srectrum of Compound 335.

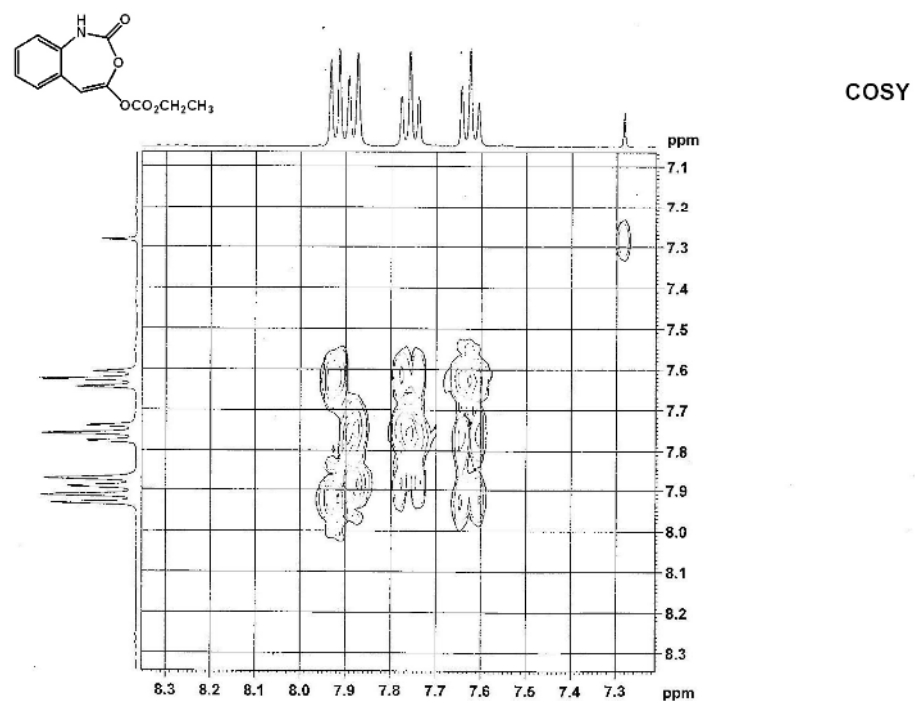


Figure A64 Expanded COSY Spectrum of Compound 335.

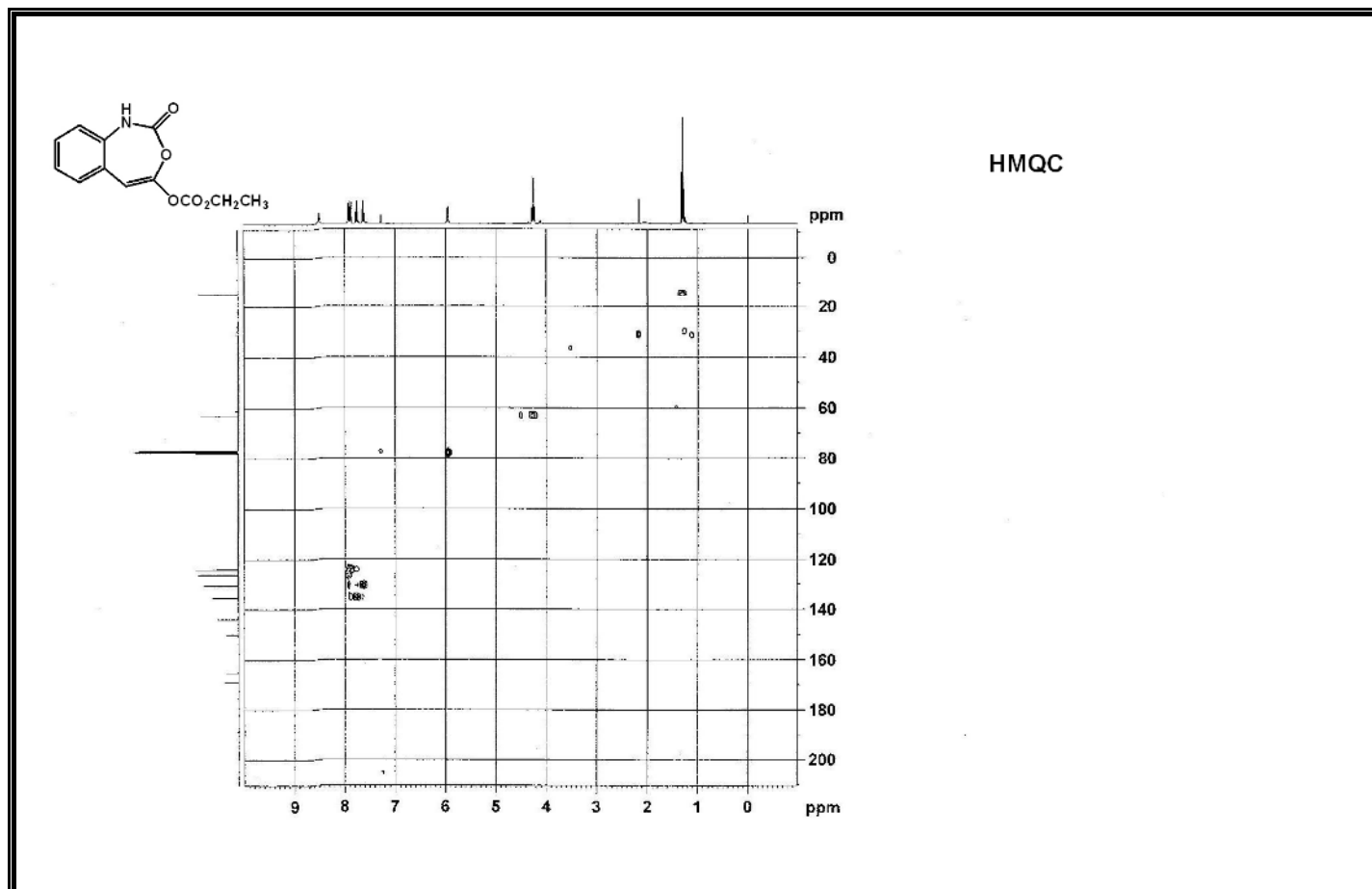


Figure A65 HMQC Spectrum of Compound 335.

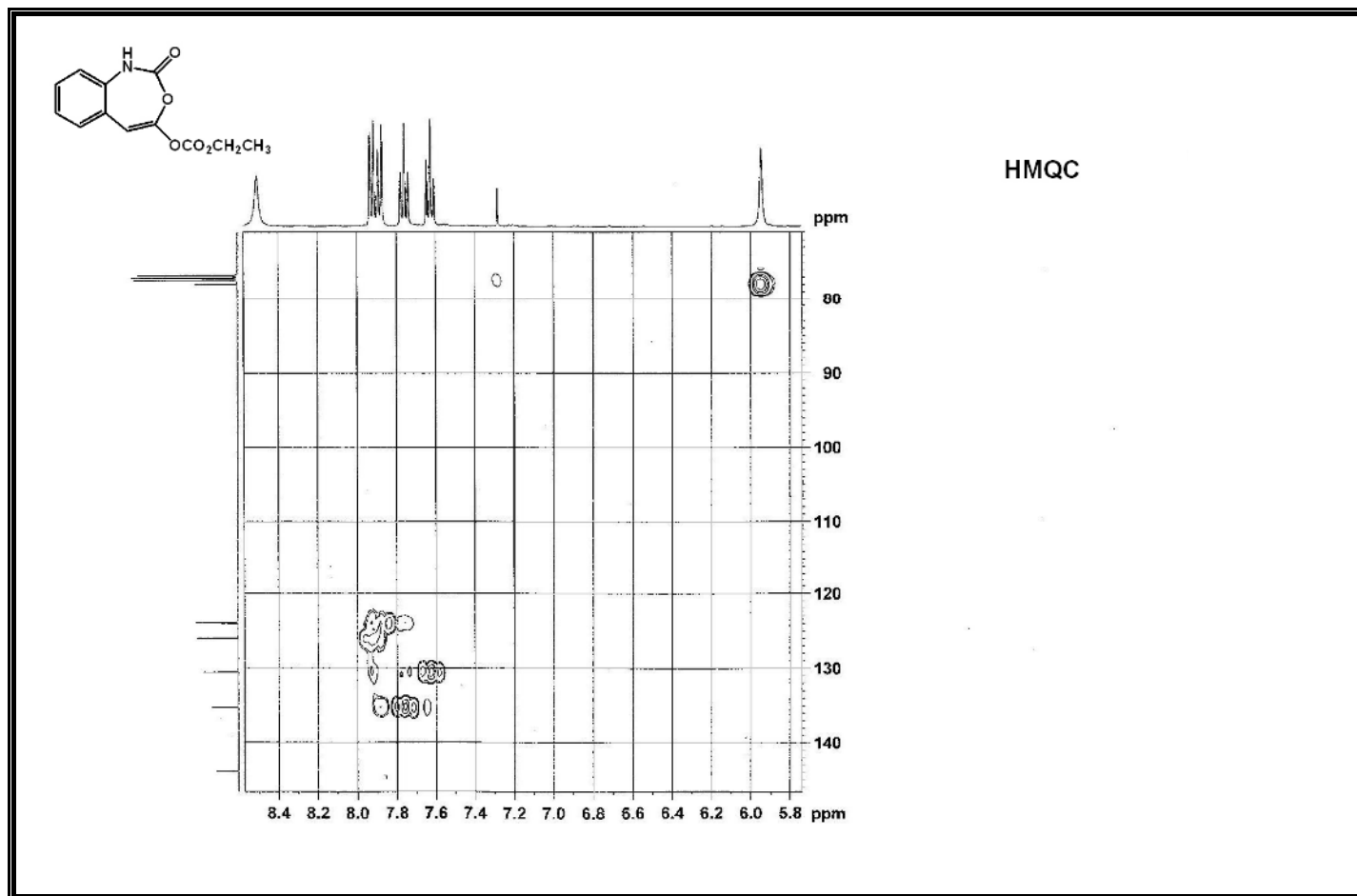


Figure A66 Expanded HMQC Spectrum of Compound 335.

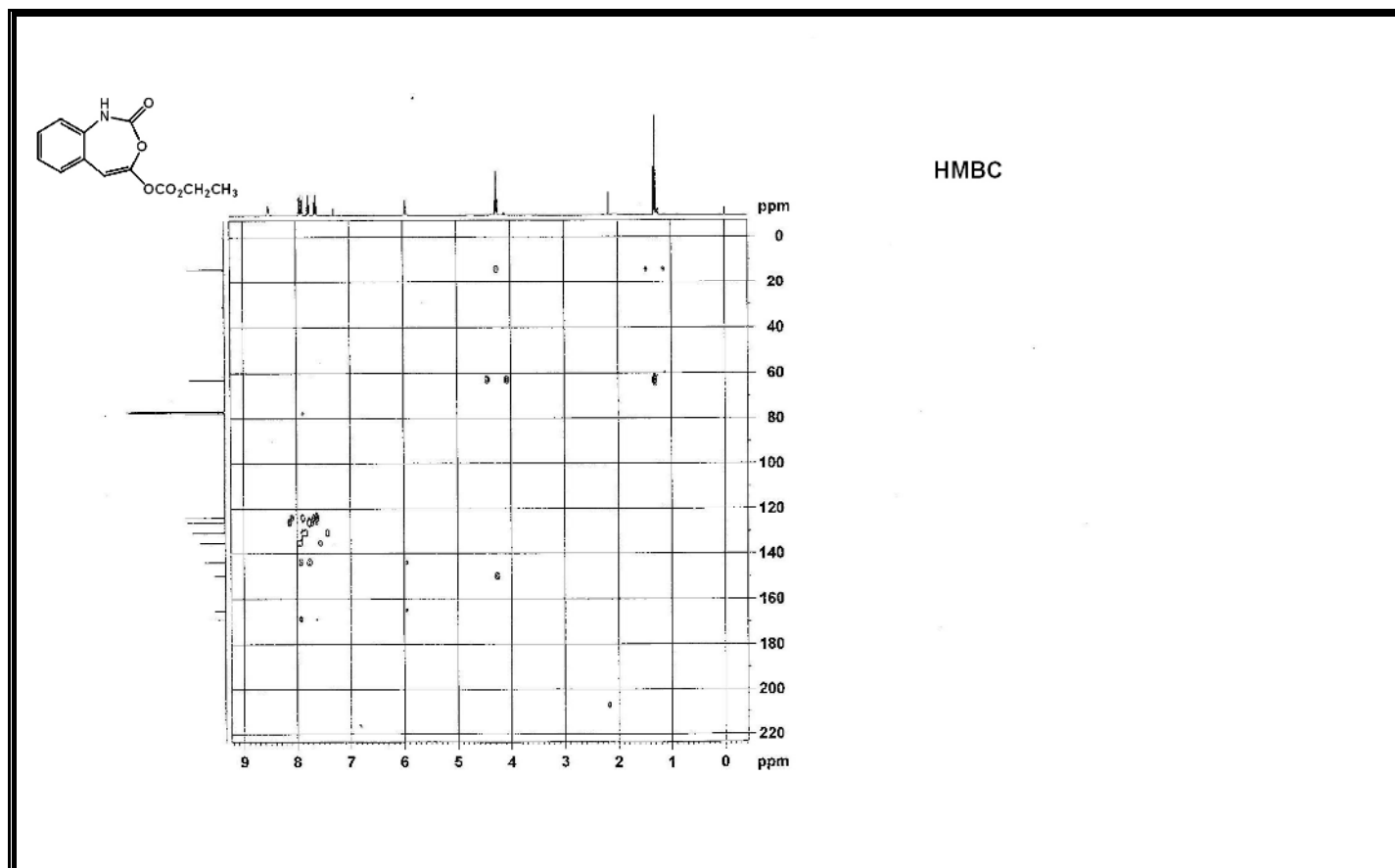


Figure A67 HMBC Spectrum of Compound 335.

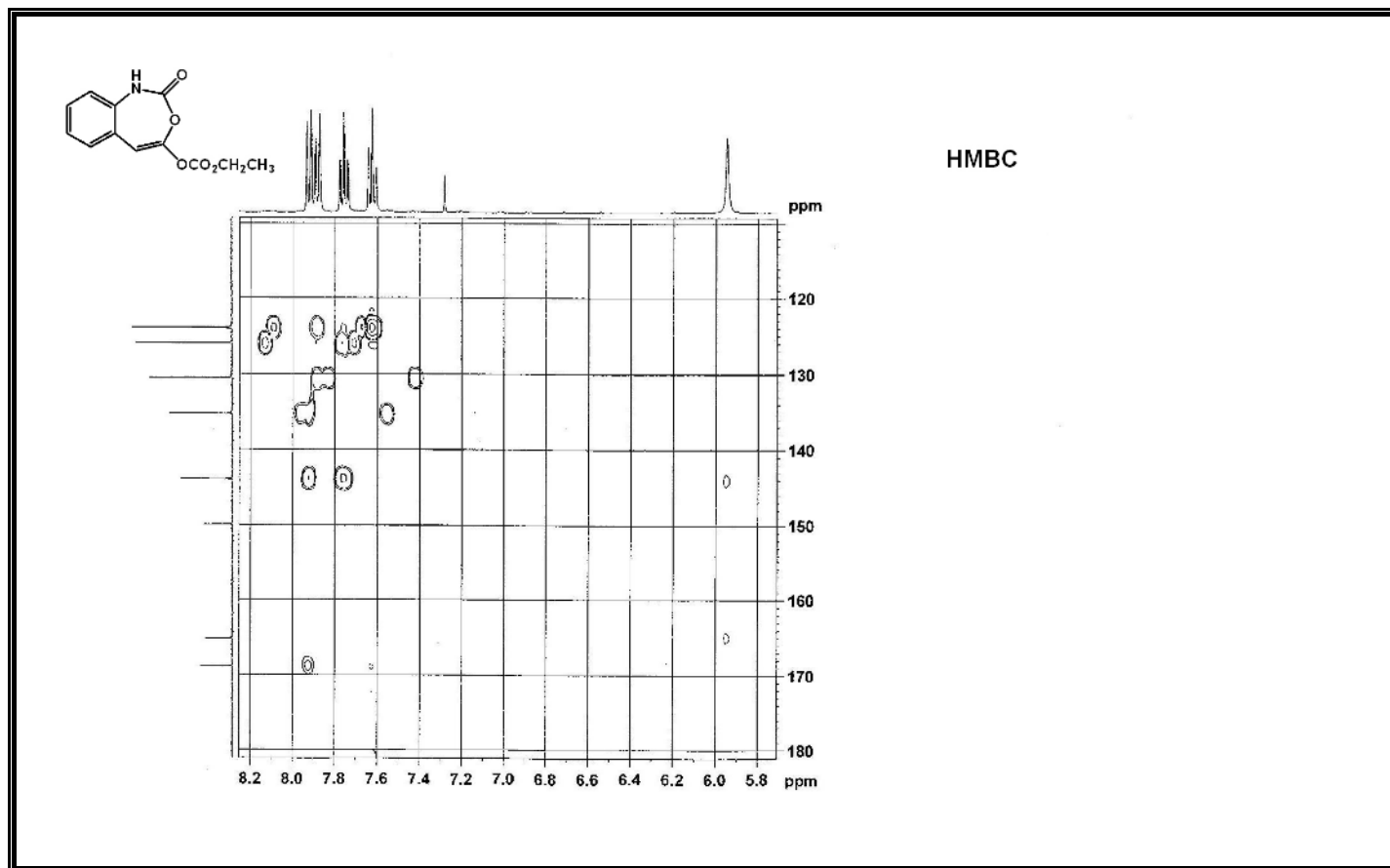


Figure A68 Expanded HMBC Spectrum of Compound 335.

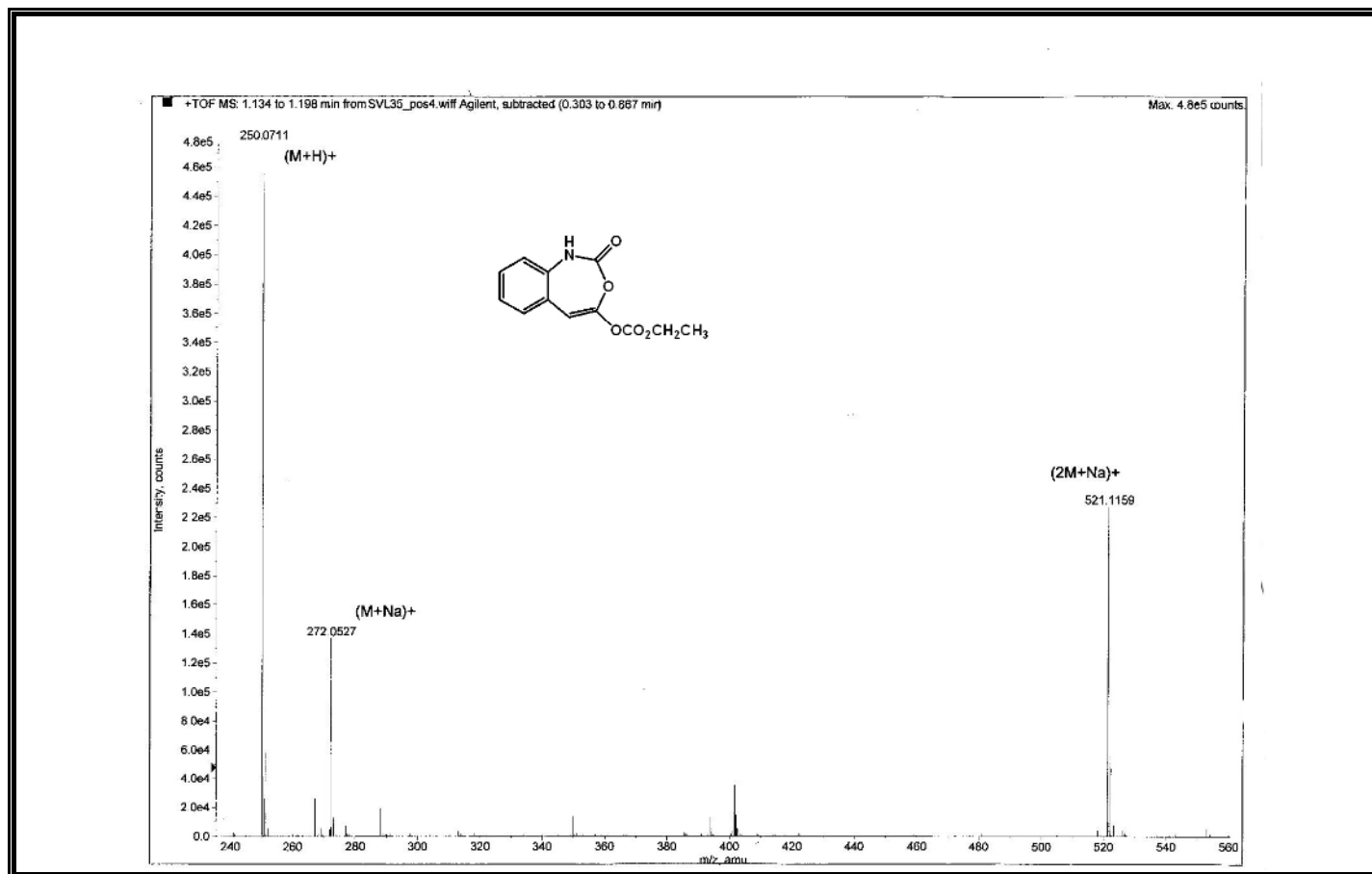


Figure A69 Mass Spectrum of Compound 335.

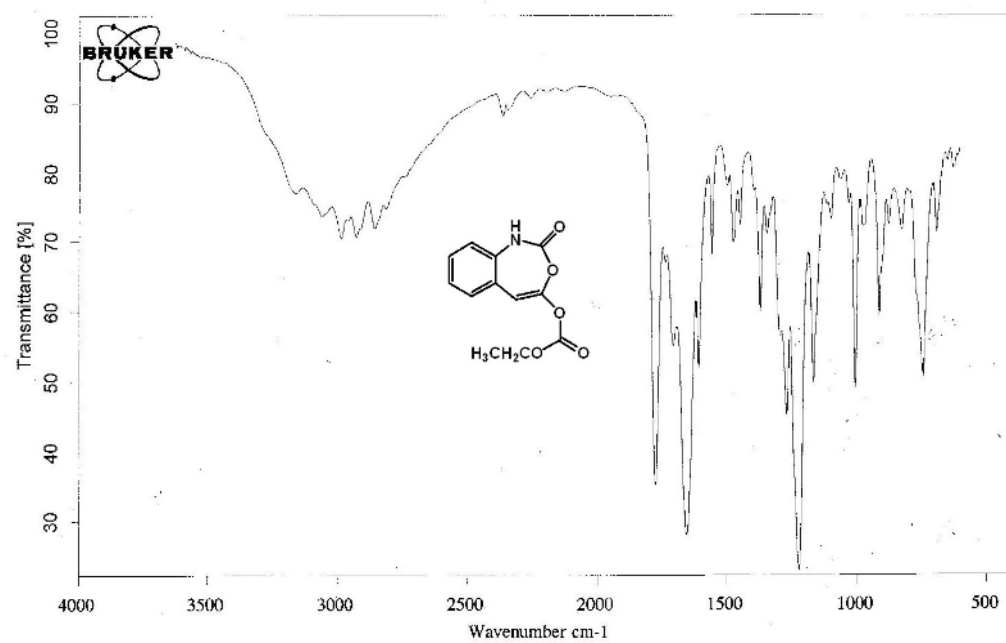


Figure A70 IR Spectrum of Compound 335.

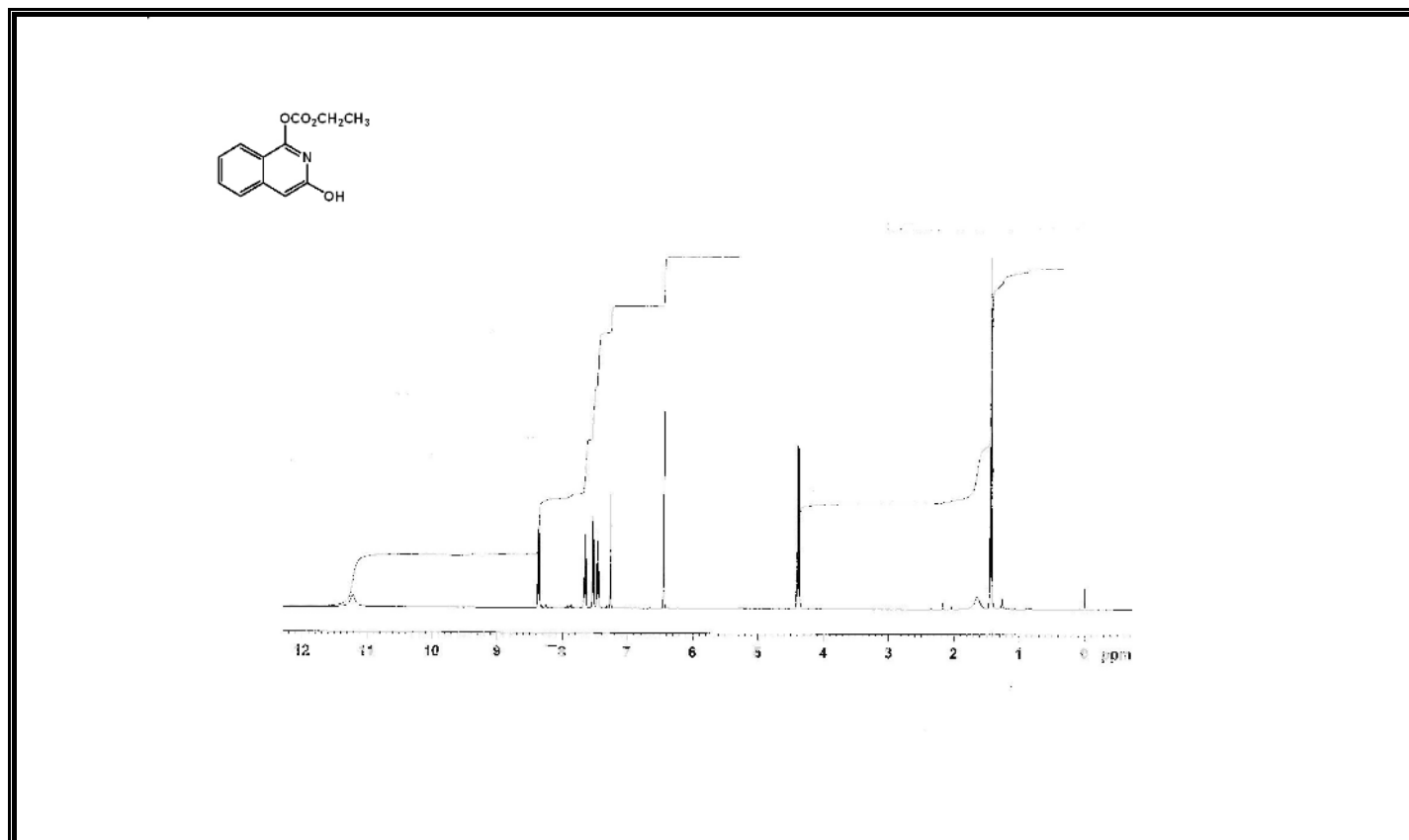
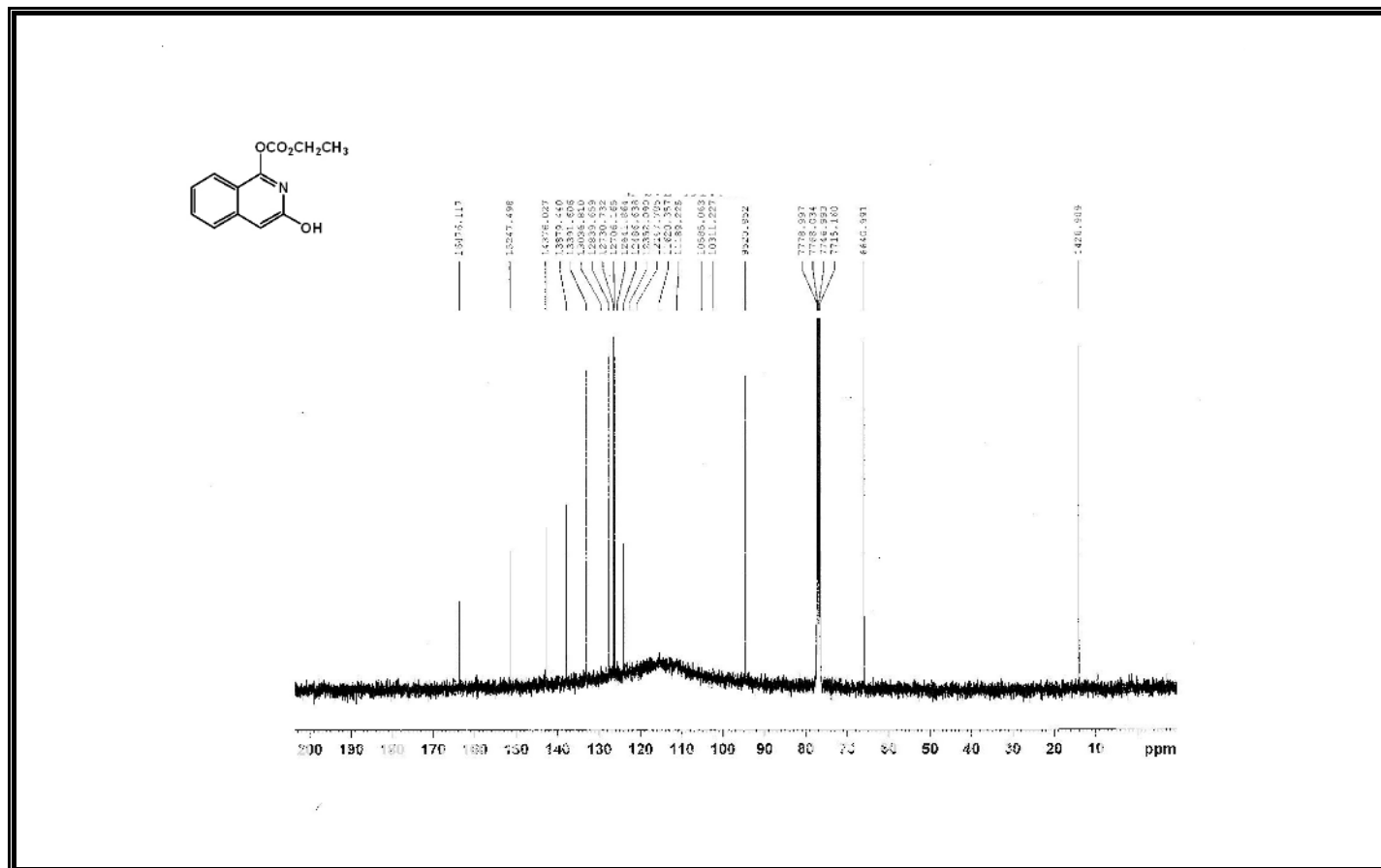


Figure A71 ^1H -MNR Spectrum of Compound **346**.



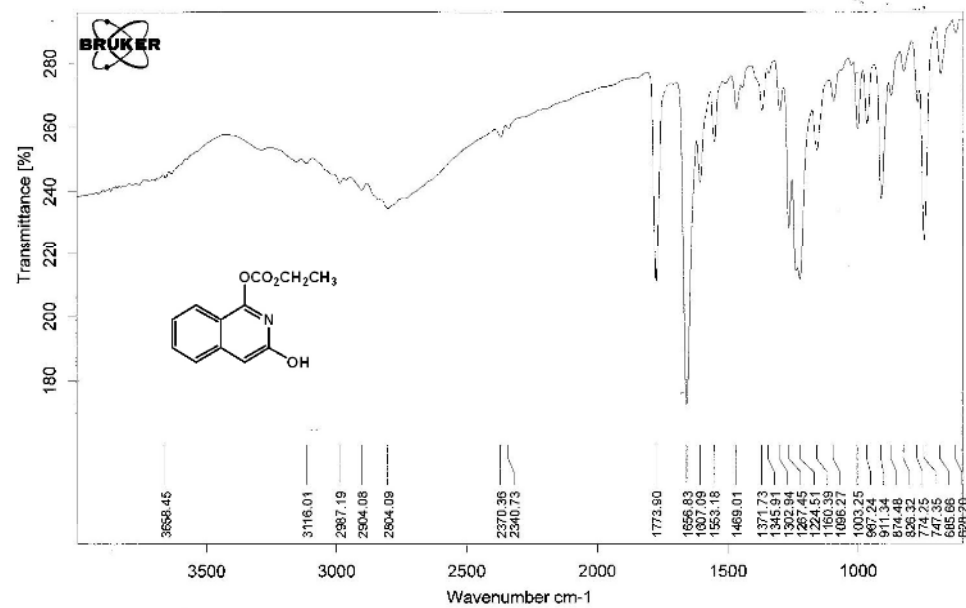


Figure A73 IR Spectrum of Compound 346.

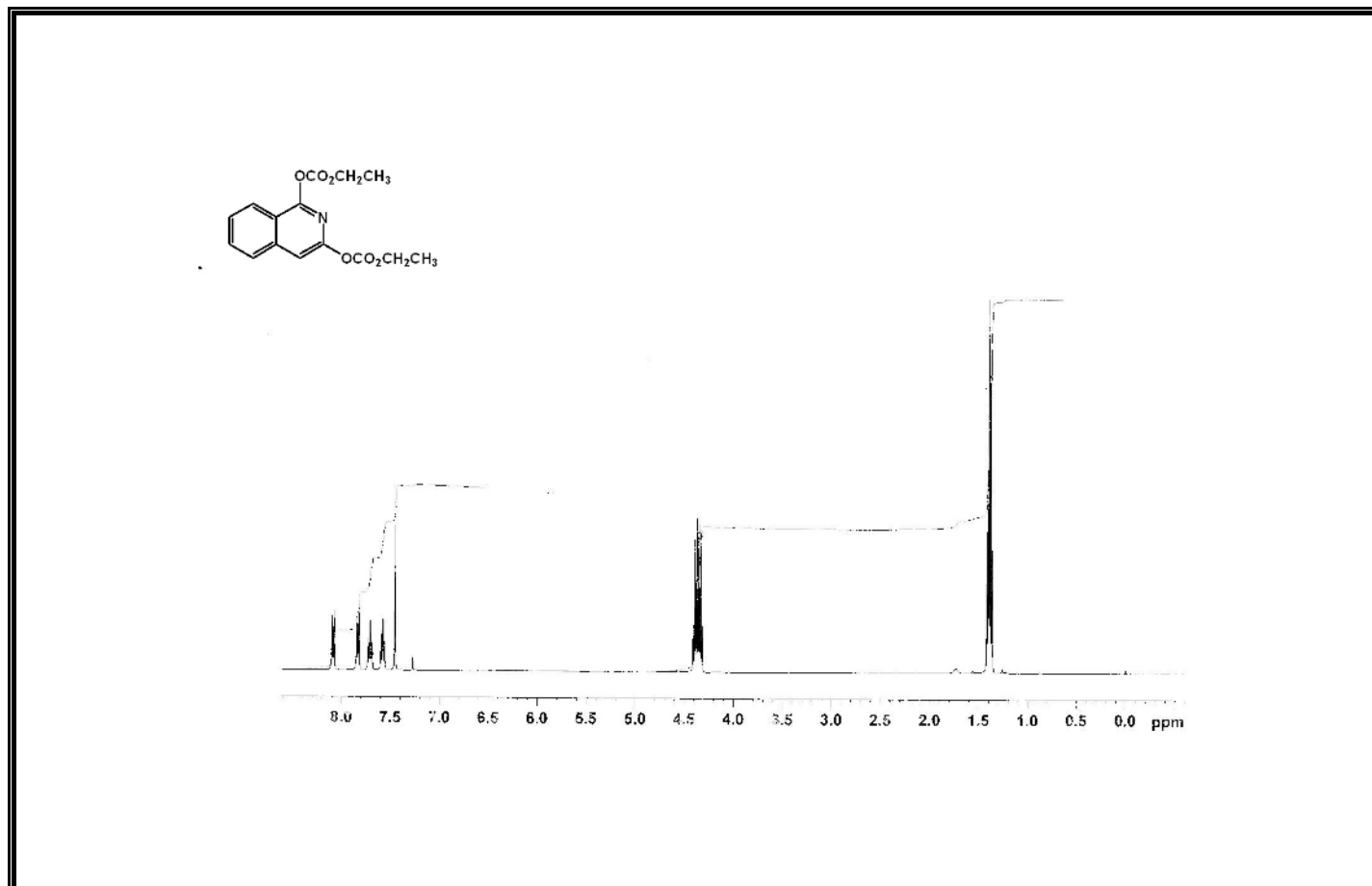
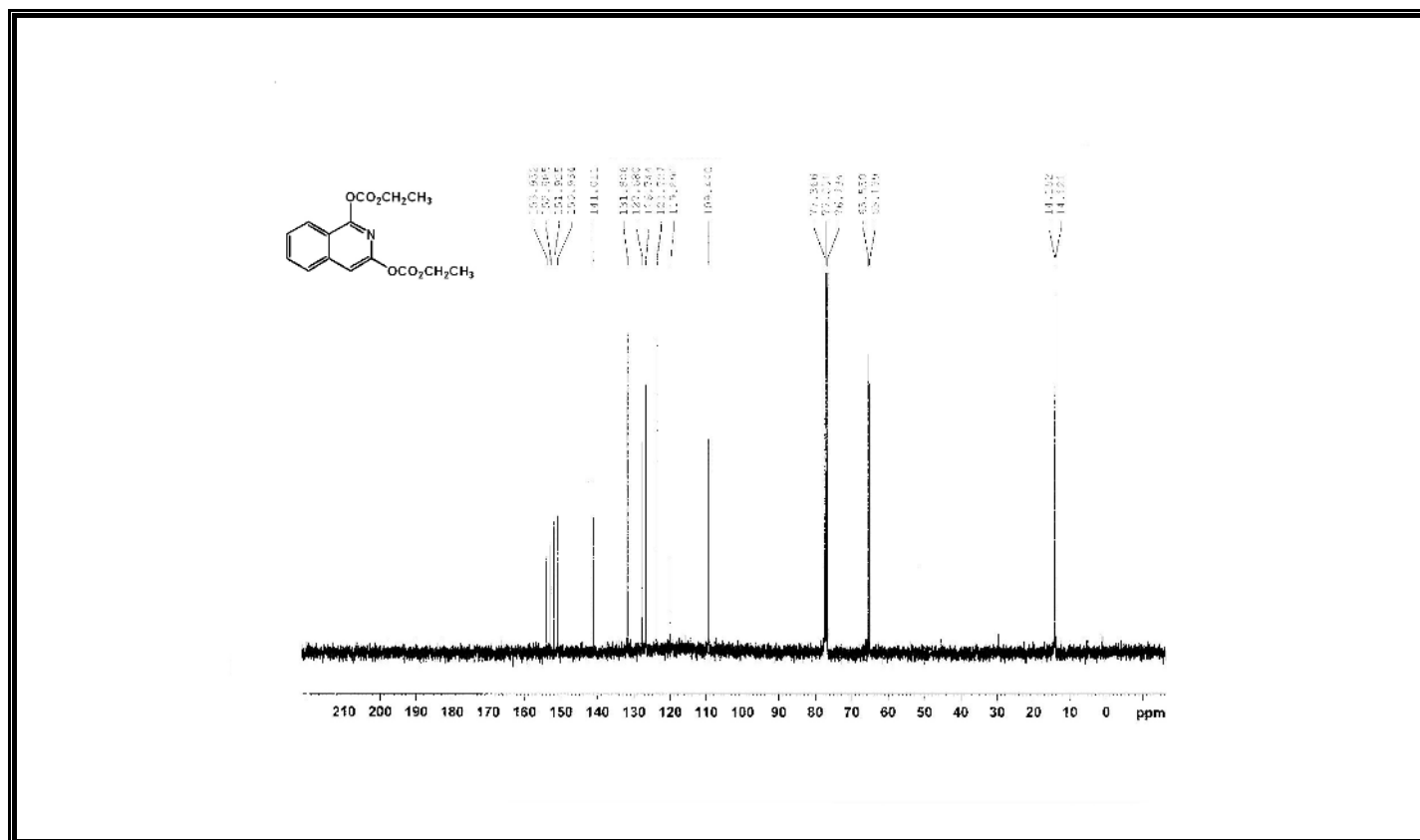


Figure A74 ^1H -NMR Spectrum of Compound 347.



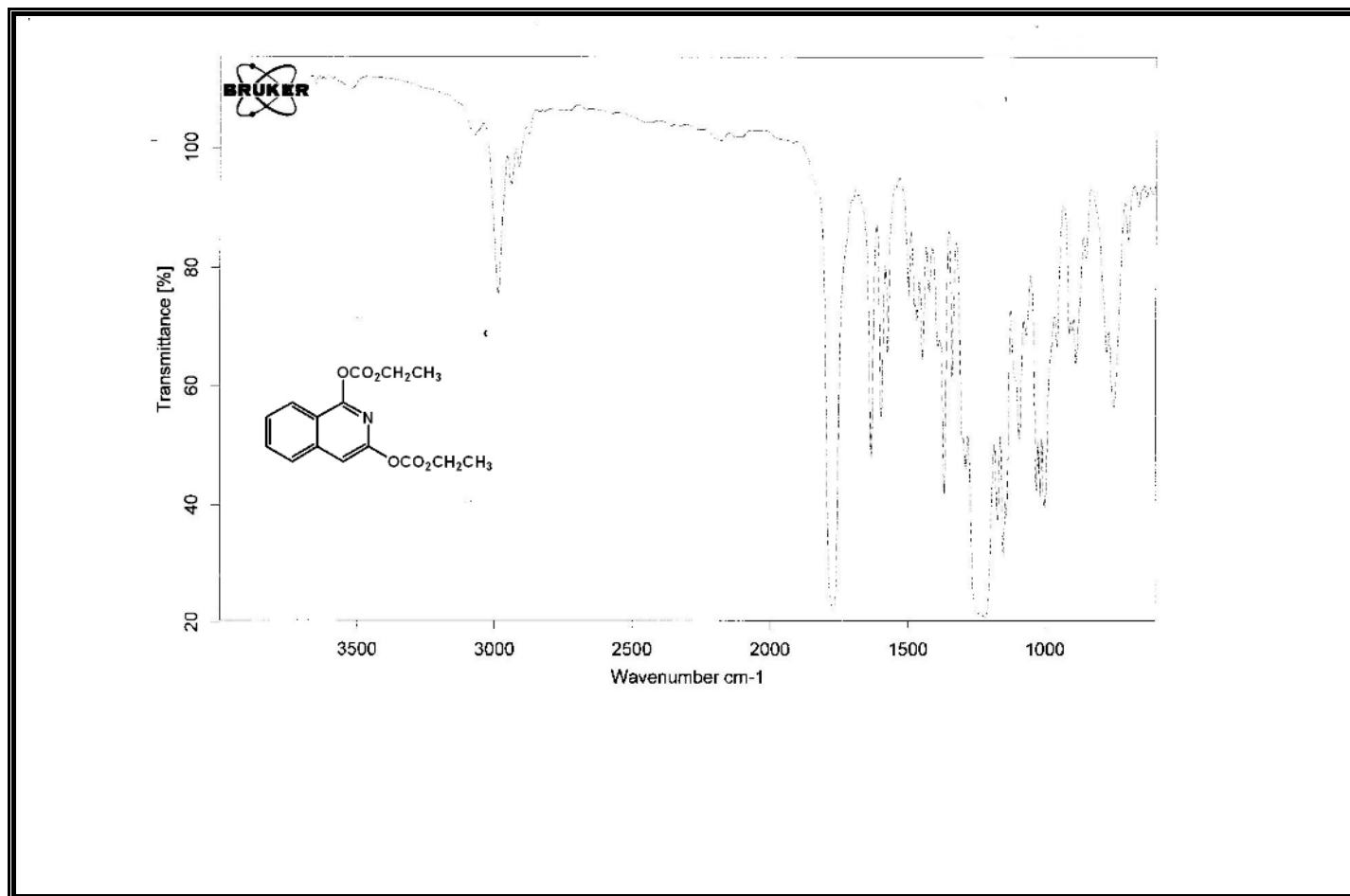


Figure A76 IR Spectrum of Compound 347.

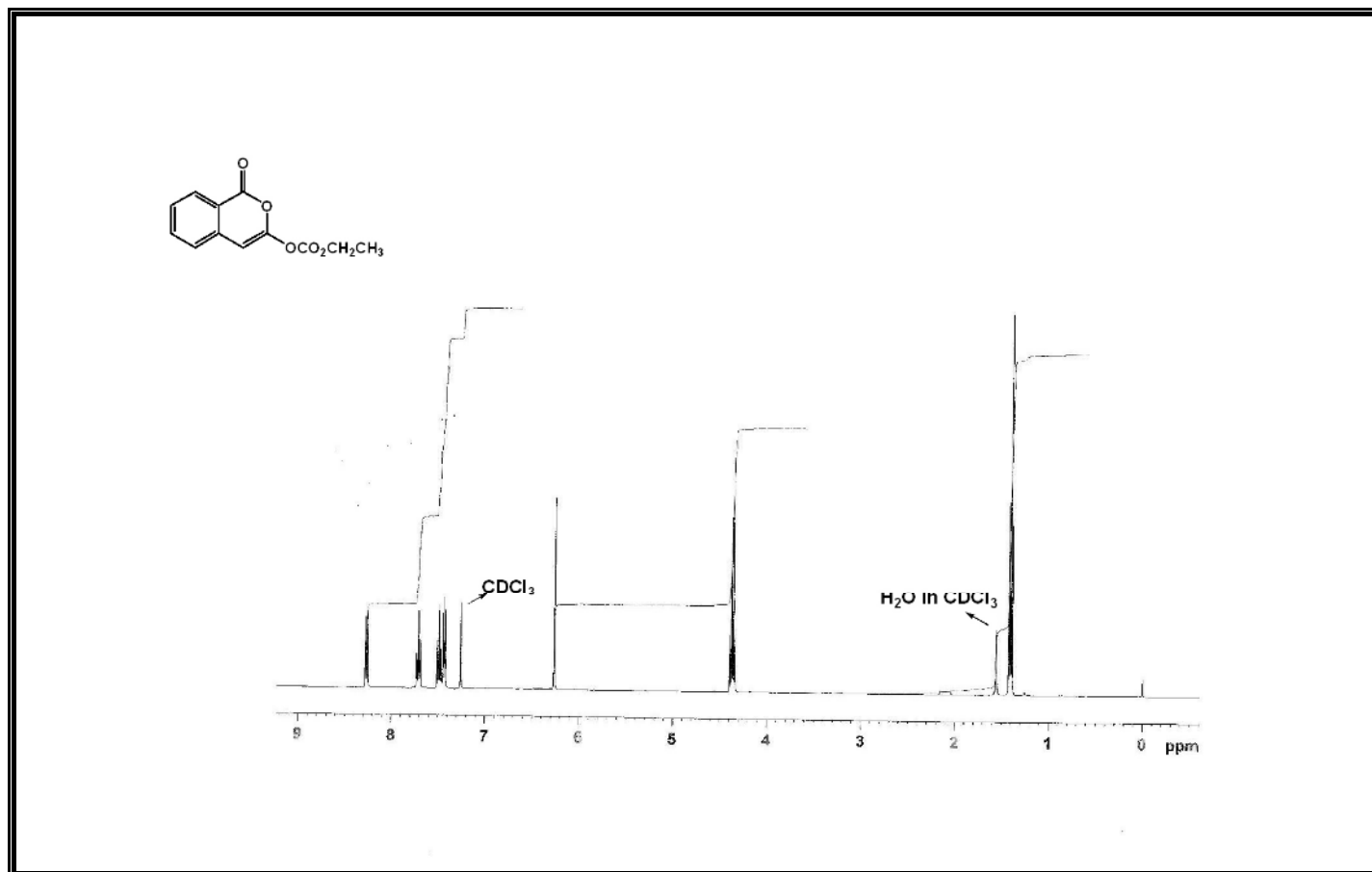


Figure A77 ¹H-NMR Spectrum of Compound 352.

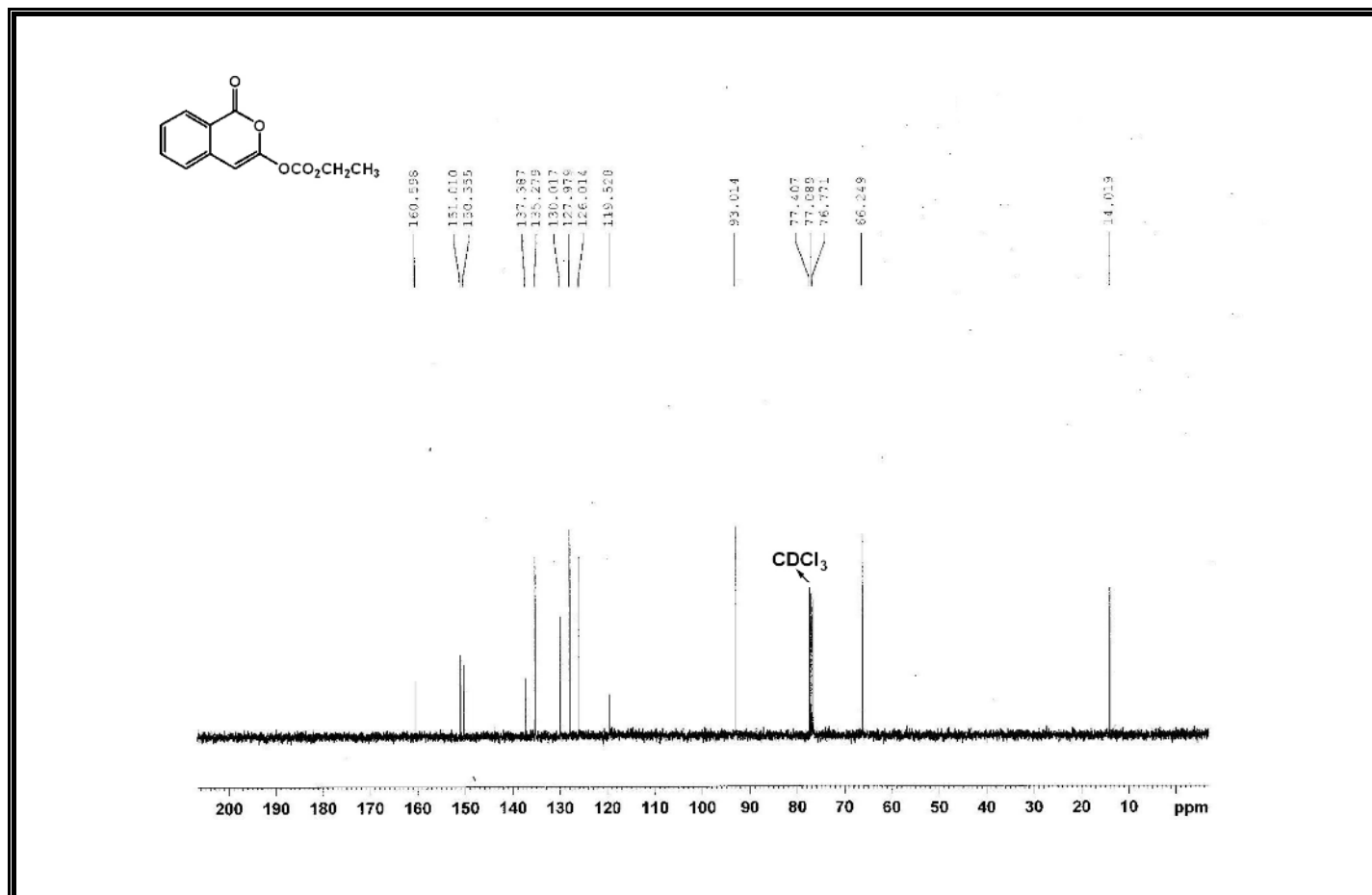


Figure A78 ^{13}C -NMR Spectrum of Compound 352.

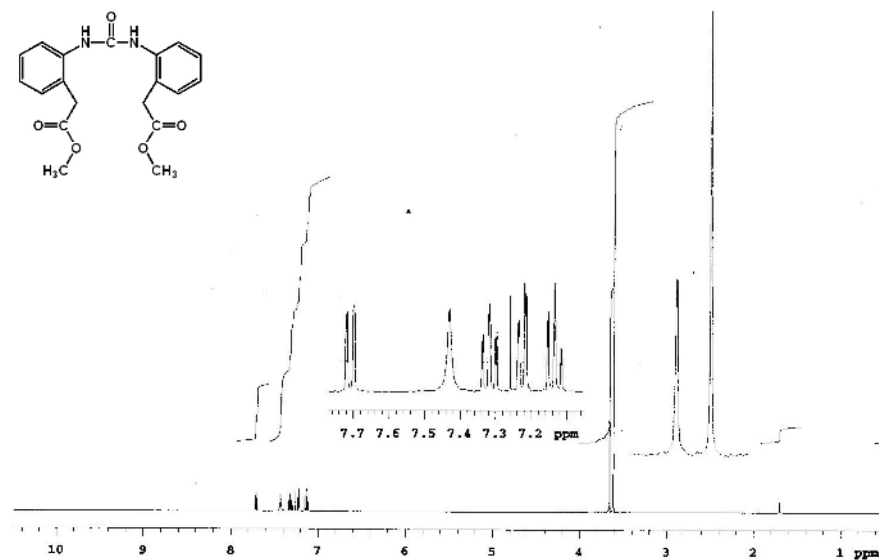


Figure A79 ^1H -NMR Spectrum of Compound 358.

INDEX	FREQUENCY	PPM	INTENSITY
1	17341.267	172.533	678
2	15517.079	154.366	5.8
3	13779.666	137.084	8.8
4	13304.010	131.156	48.6
5	12947.499	128.803	48.9
6	12855.946	127.893	4.8
7	12670.552	126.048	37.1
8	12638.508	125.722	39.8
9	7797.657	77.572	25.1
10	7766.614	77.253	25.7
11	7733.571	76.935	26.7
12	5289.875	52.624	20.2
13	3866.230	38.462	53.9

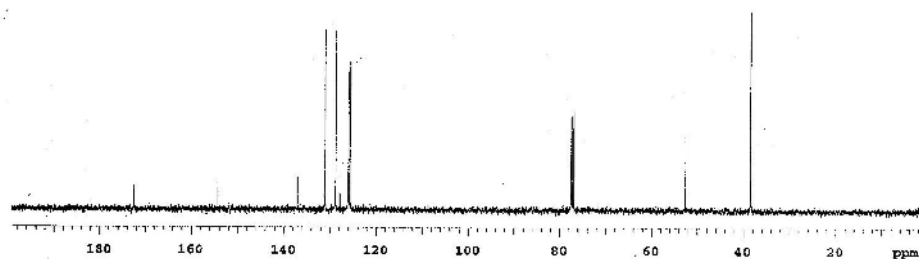
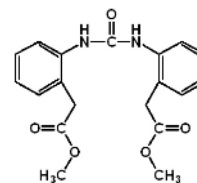


Figure A80 ^{13}C -NMR Spectrum of Compound 358.

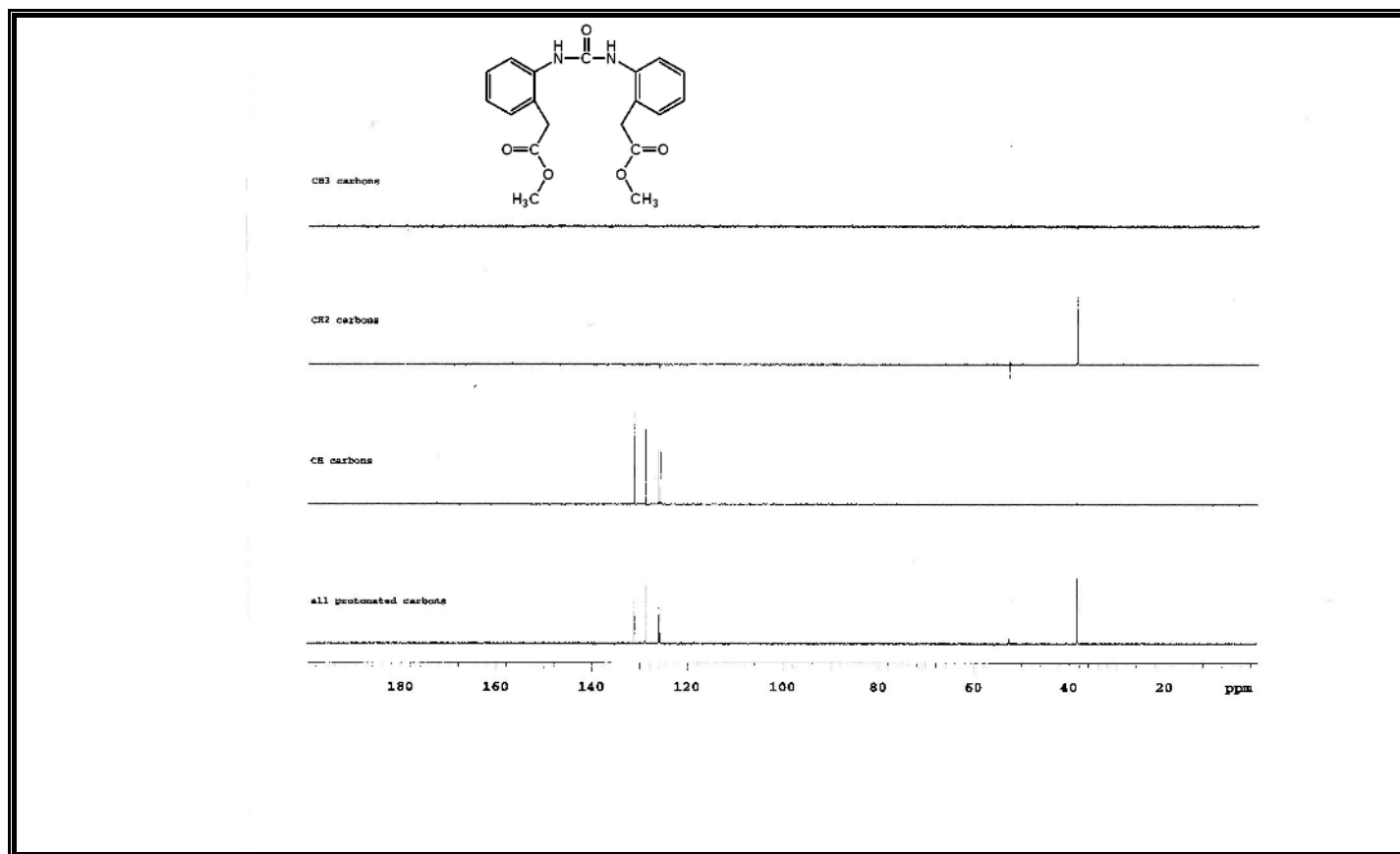


Figure A81 DEPT Spectrum of Compound 358.

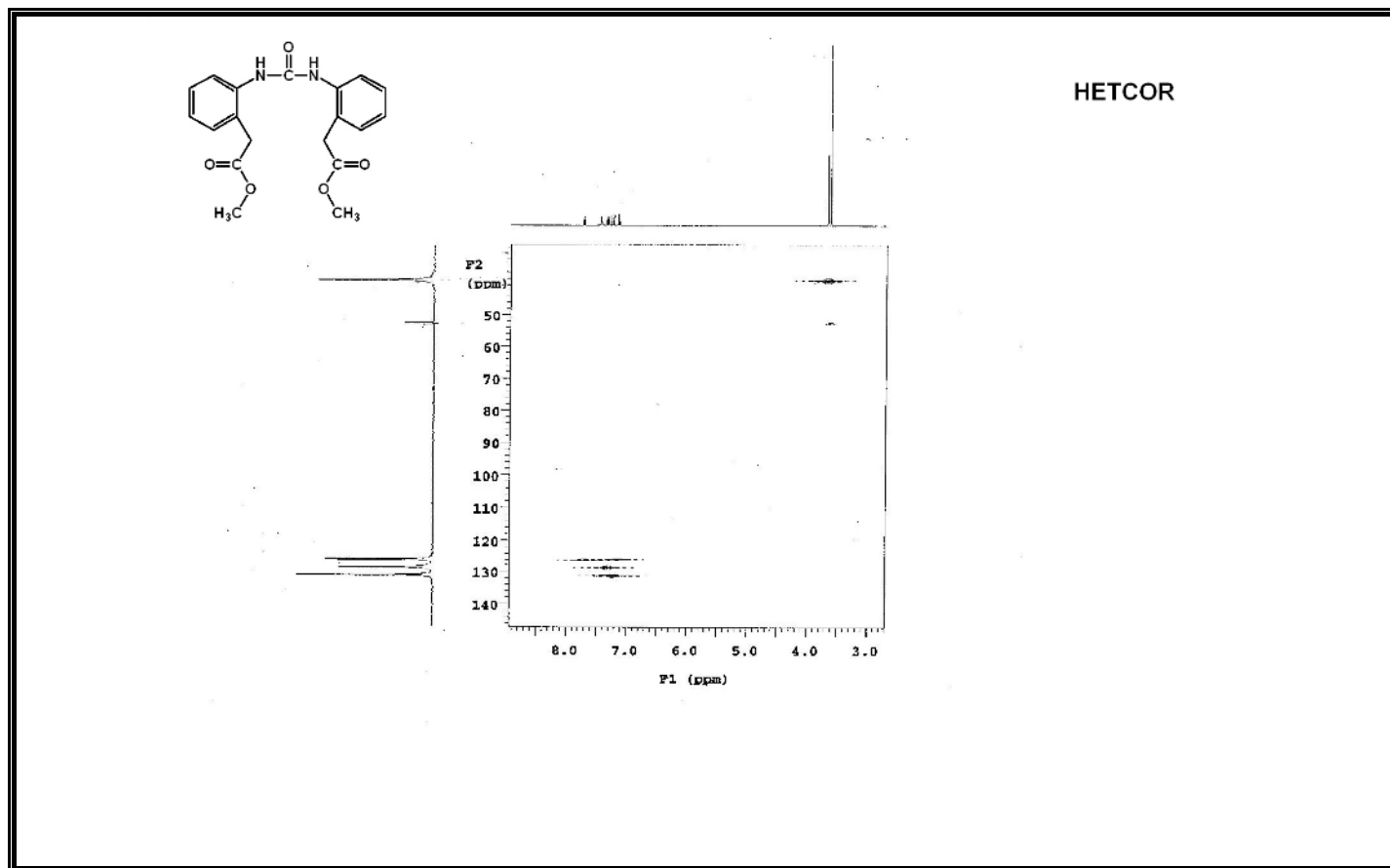


Figure A82 HETCOR Spectrum of Compound 358.

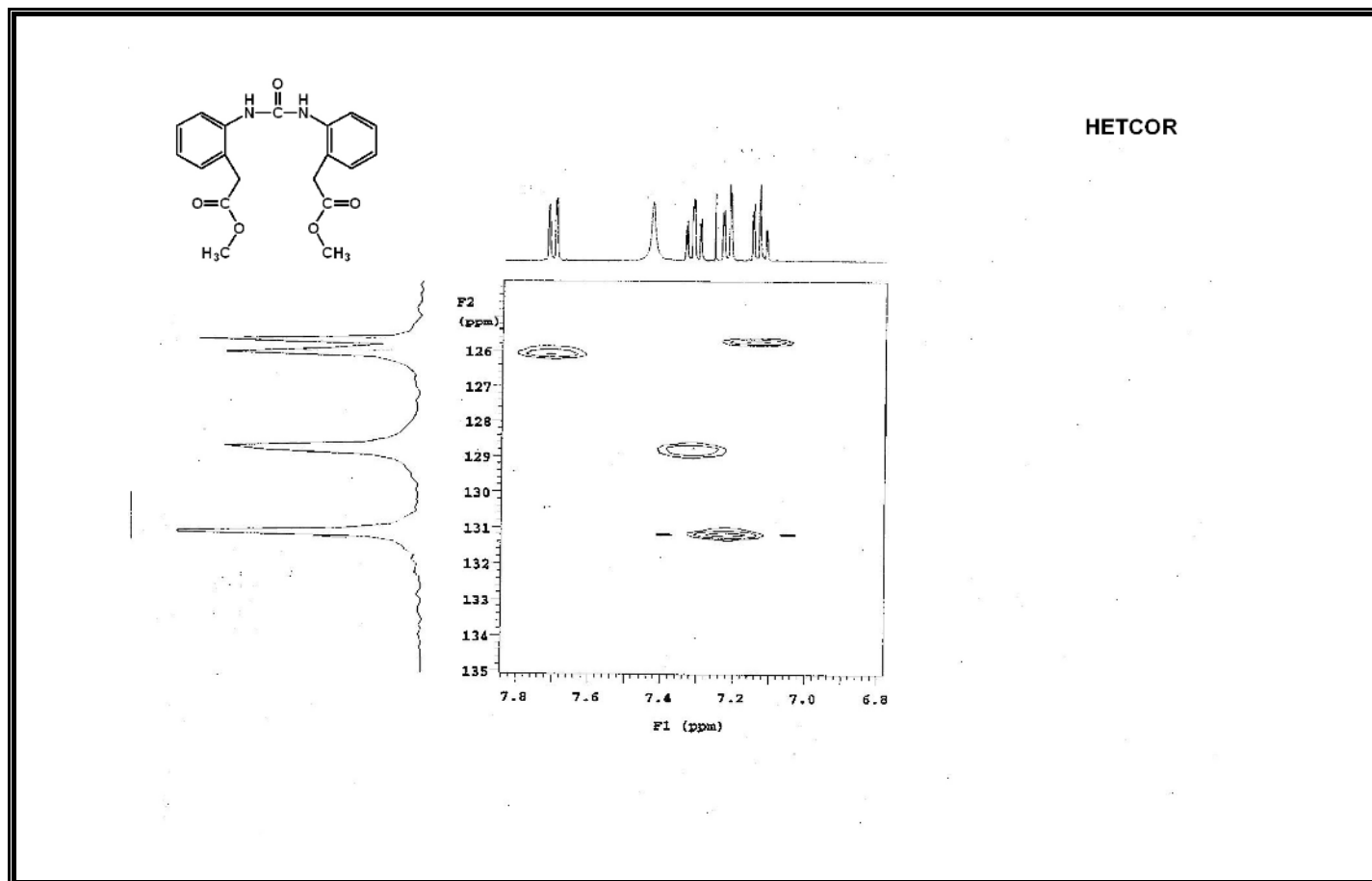


Figure A83 HETCOR Spectrum of Compound 358.

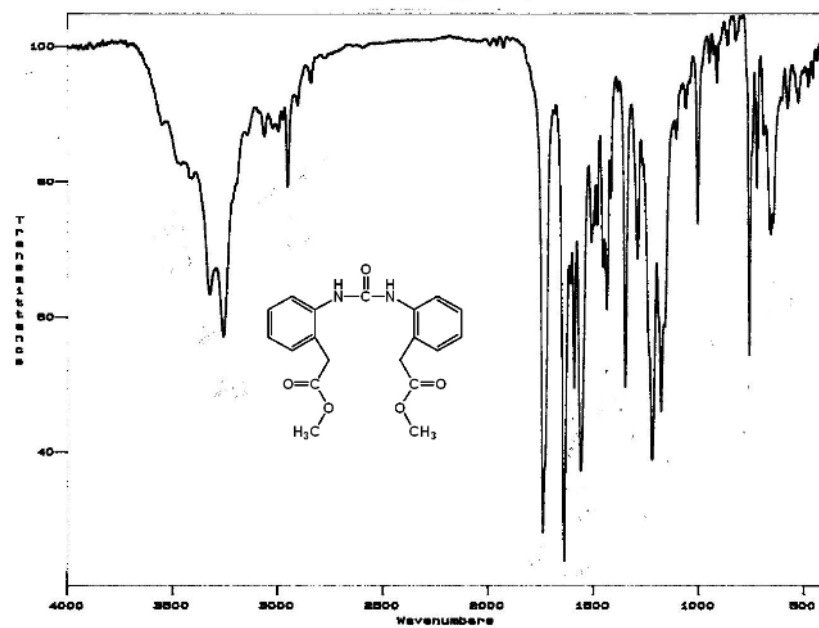


Figure A84 IR Spectrum of Compound 358.

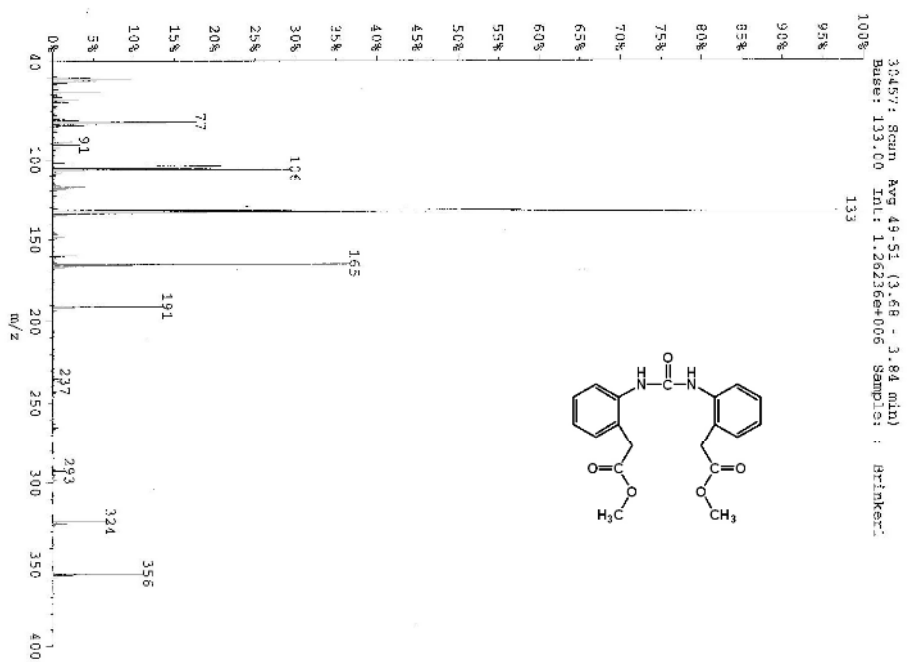


Figure A85 High Resolution Mass Spectrum of Compound **358**.

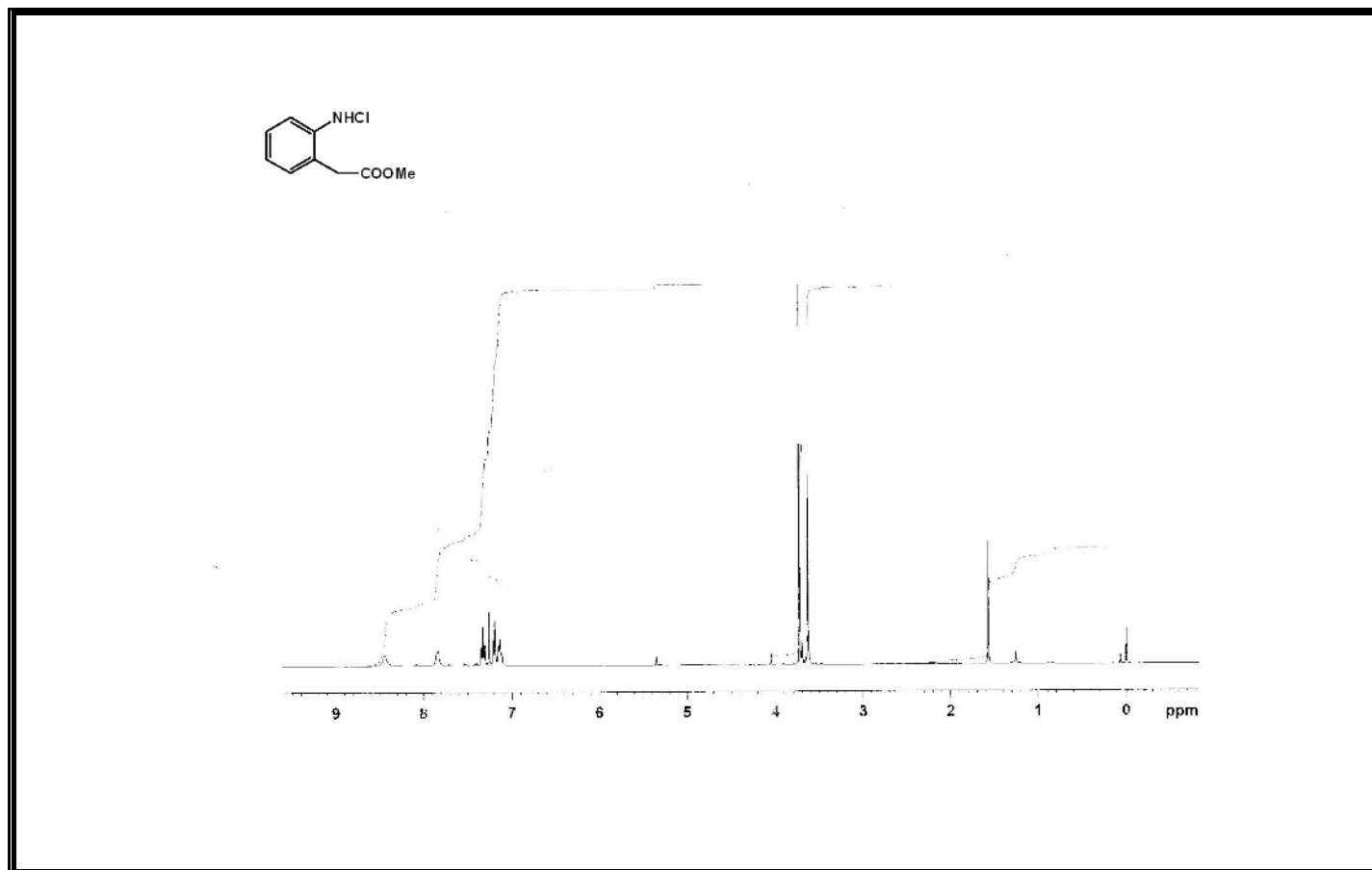


Figure A86 ^1H -NMR Spectrum of Compound 359.

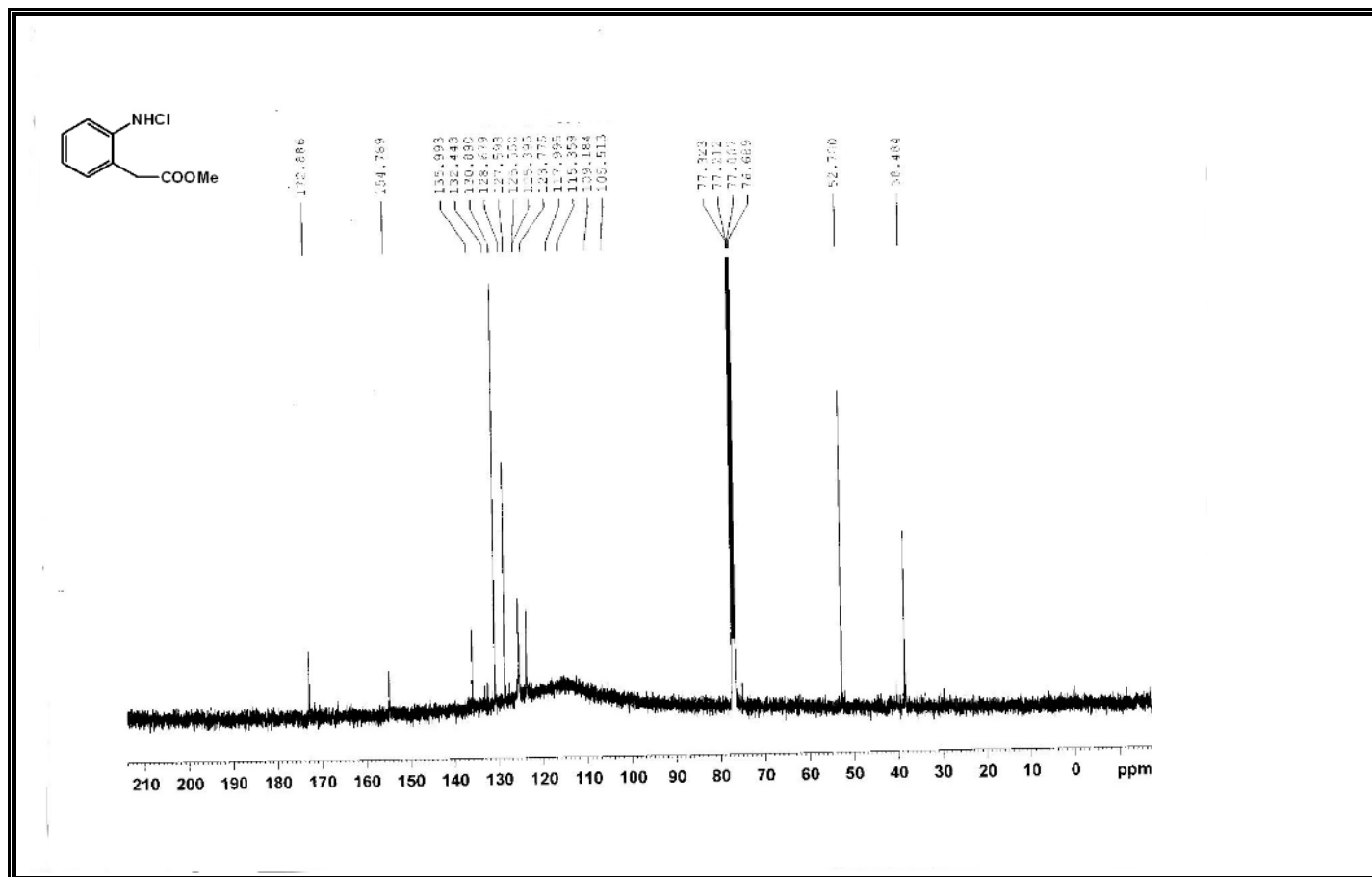


Figure A87 ^{13}C -NMR Spectrum of Compound 359.

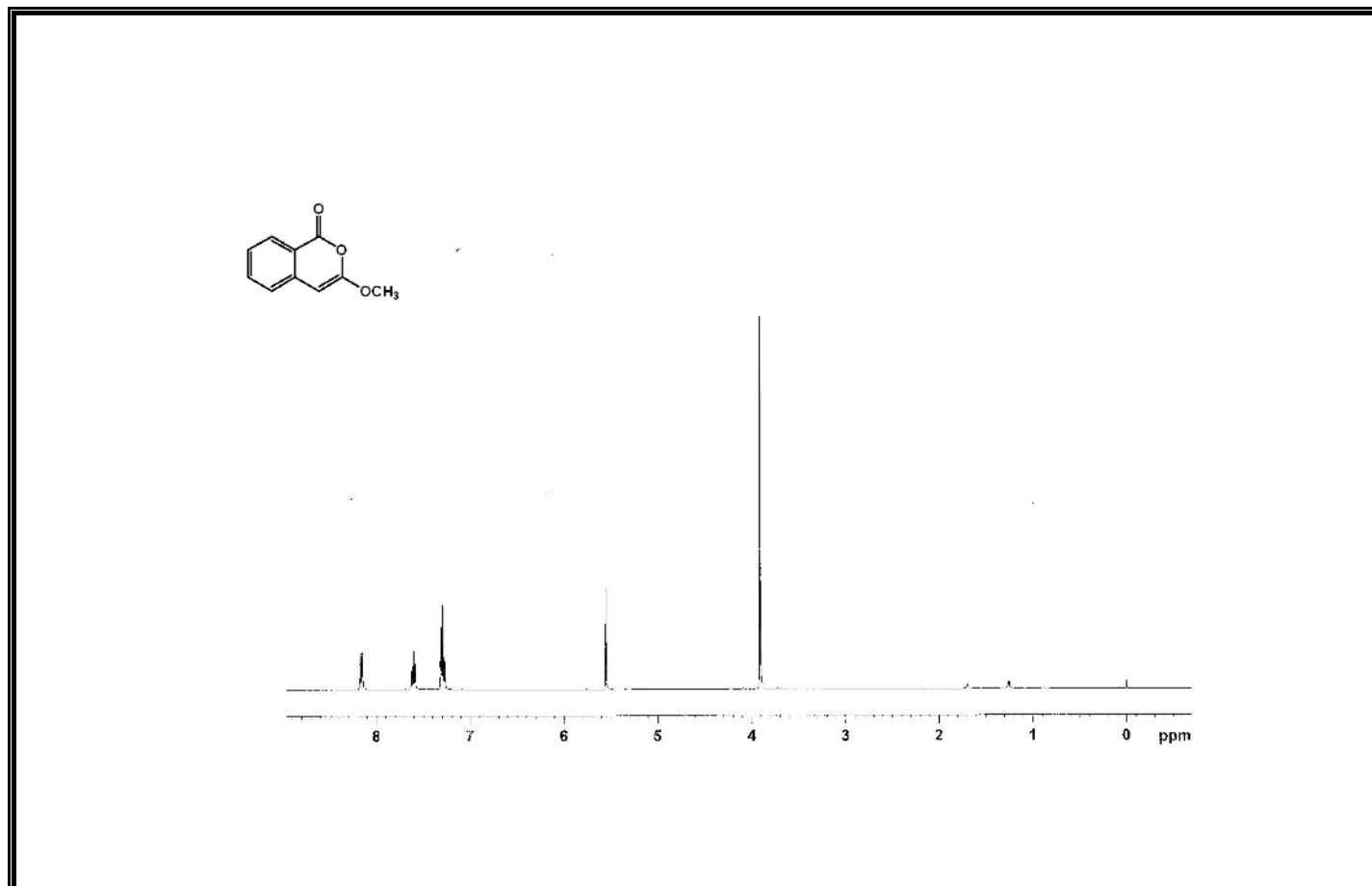


Figure A88 ^1H -NMR Spectrum of Compound 360.

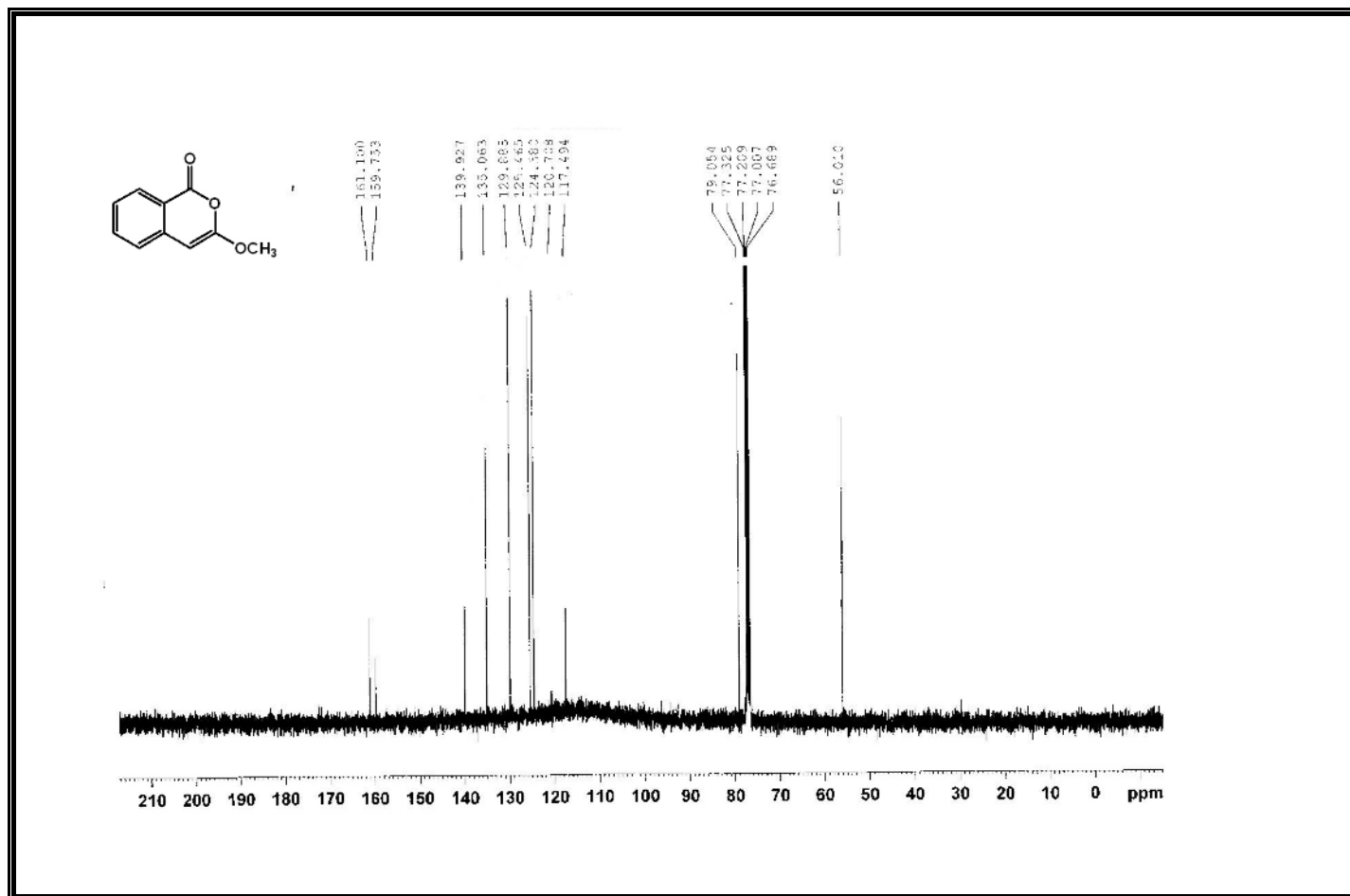


Figure A89 ^{13}C -NMR Spectrum of Compound 360.

Figure A90 ^1H -NMR Spectrum of Compound **368**.

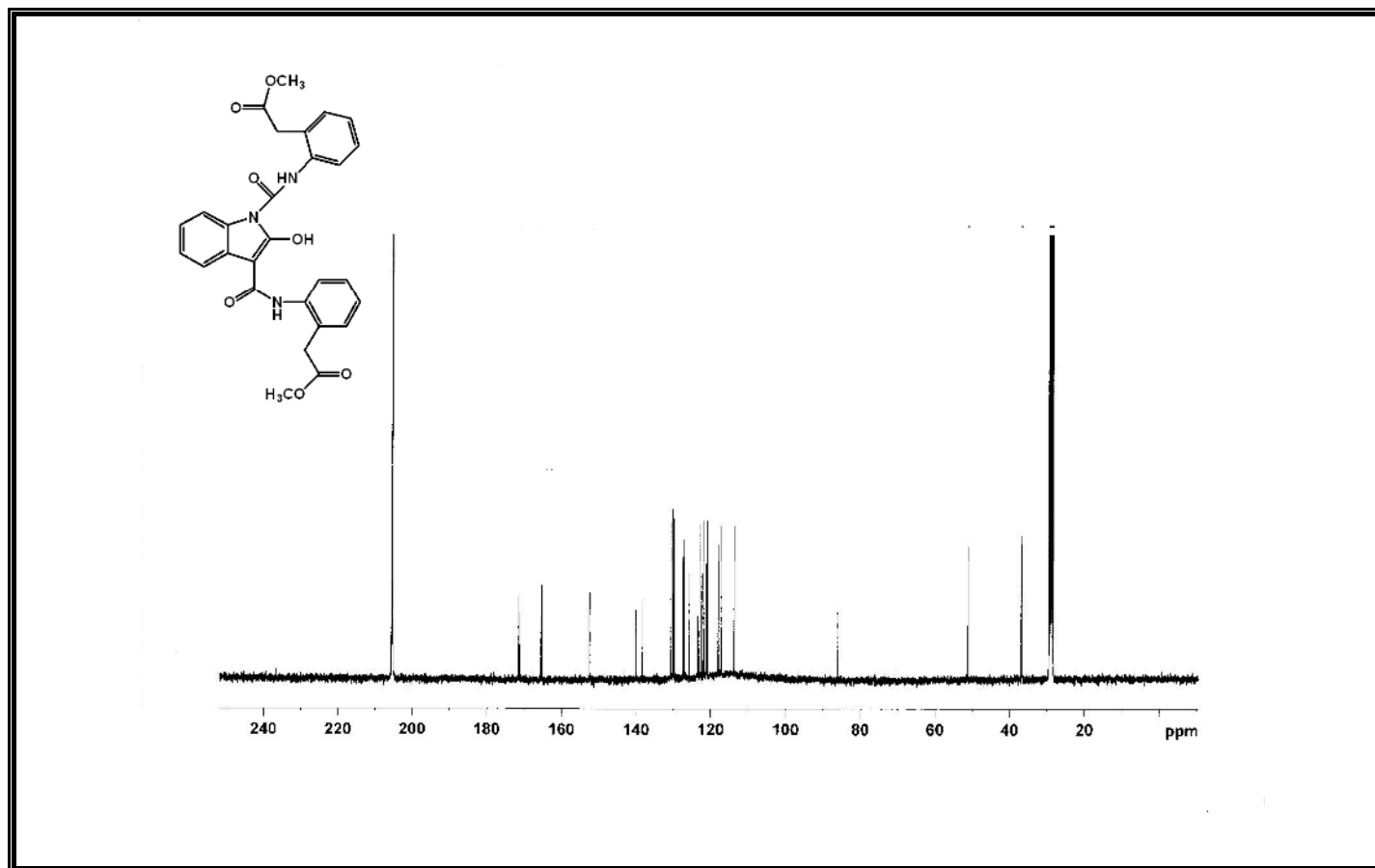


Figure A91 ^{13}C -NMR Spectrum of Compound **368**.

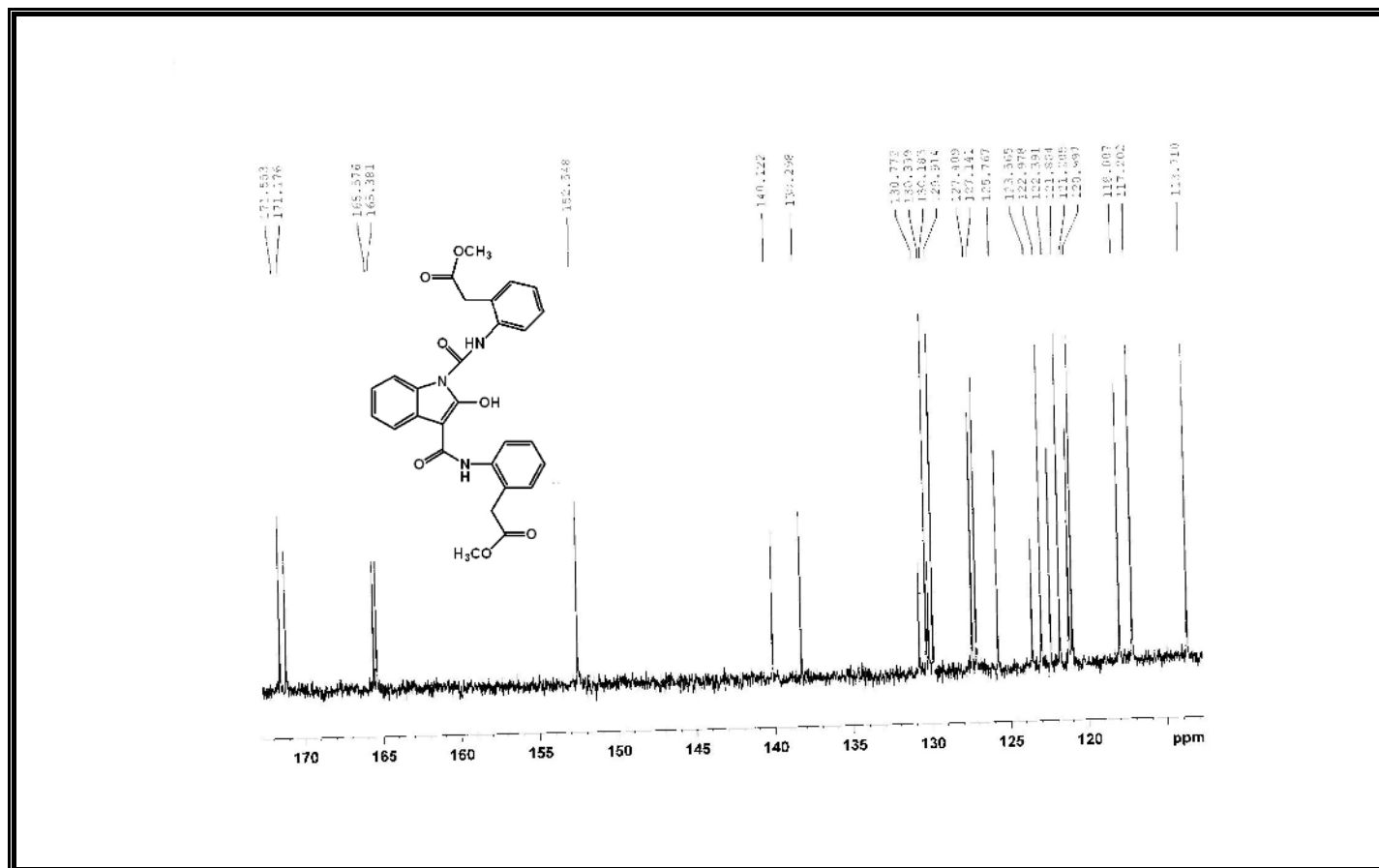


Figure A92 Expanded ¹³C-NMR Spectrum of Compound 368.

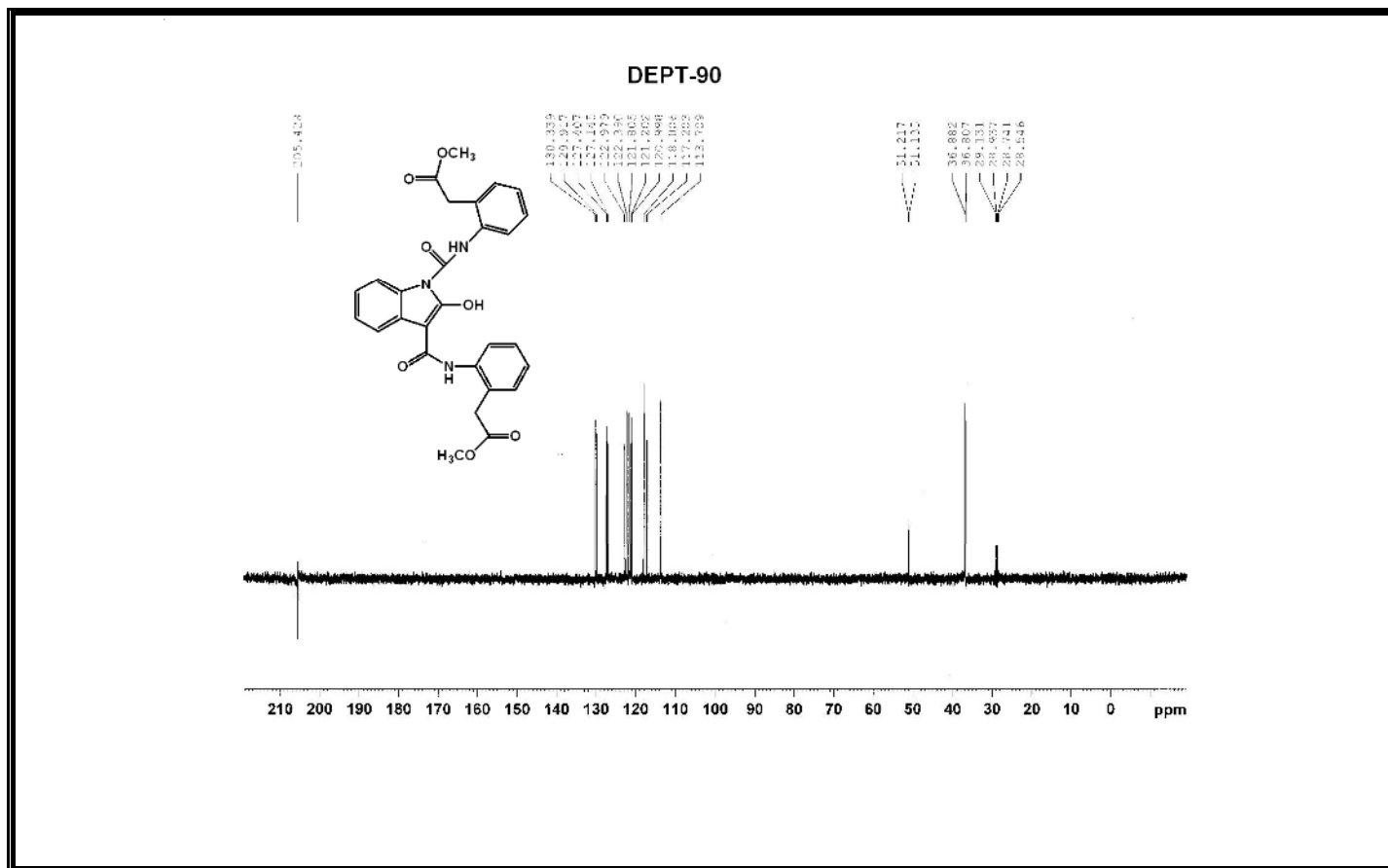


Figure A93 DEPT-90 Spectrum of Compound **368**.

Figure A94 DEPT-135 Spectrum of Compound **368**.

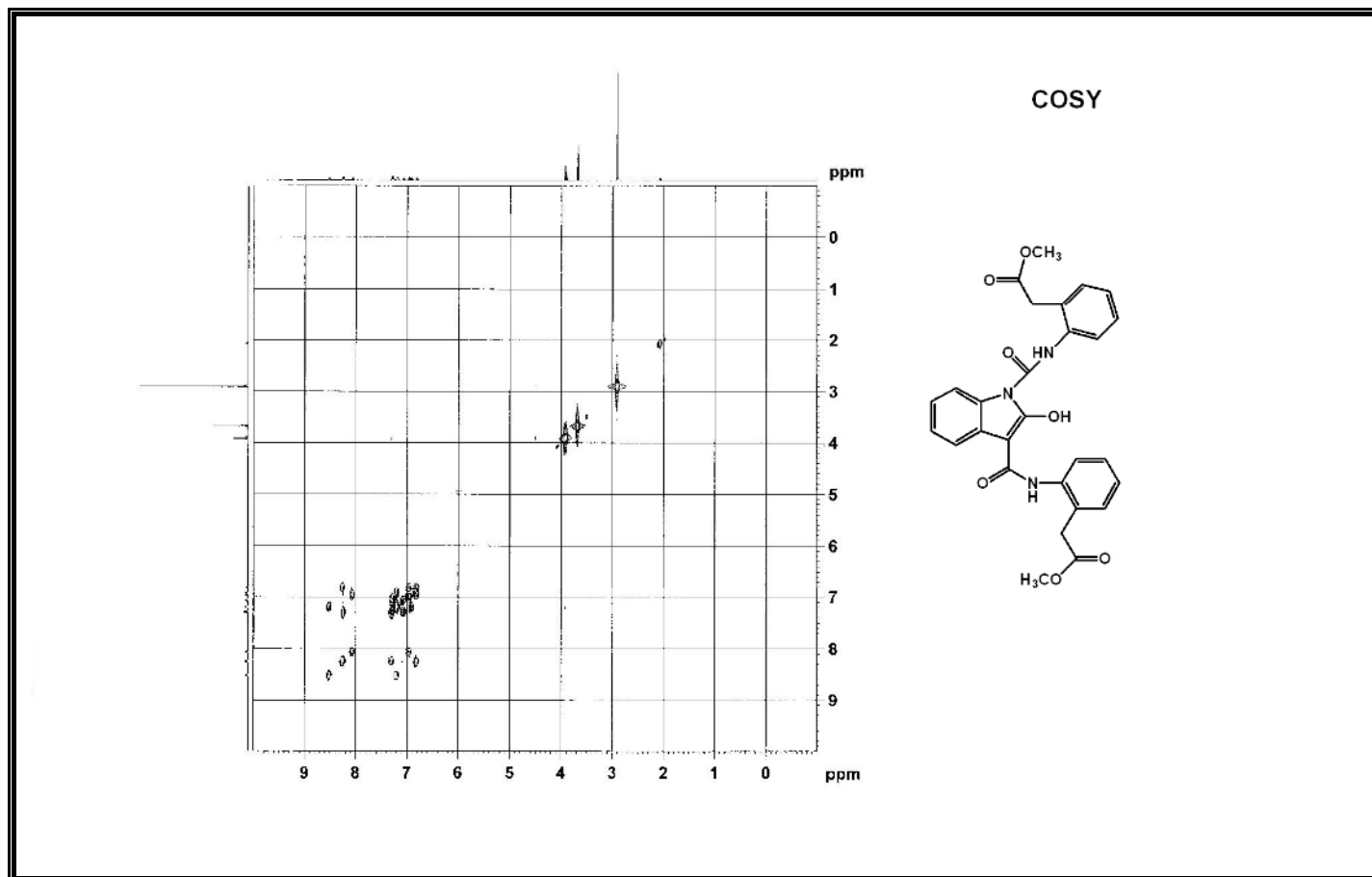


Figure A95 COSY Spectrum of Compound 368.

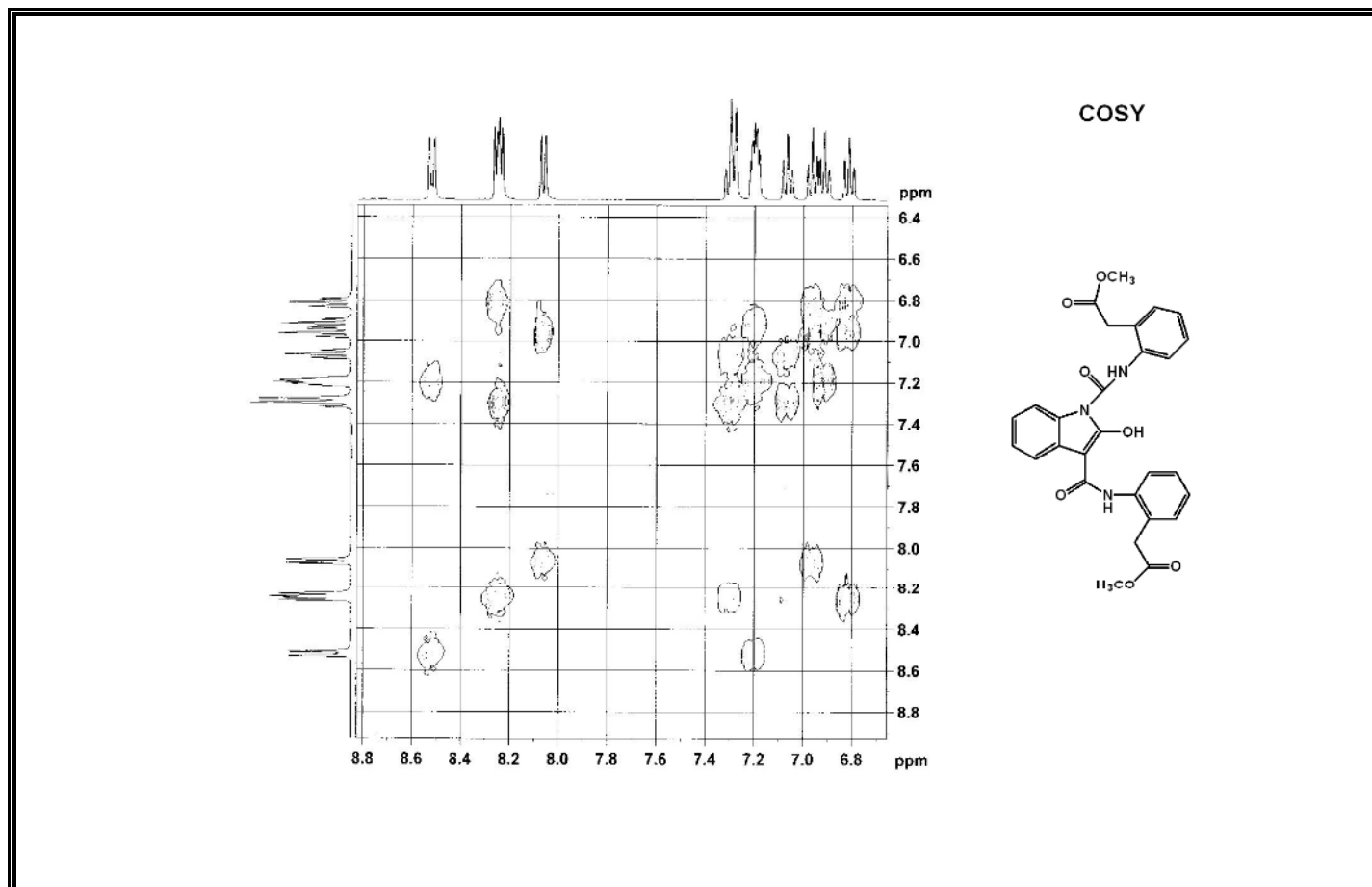


Figure A96 Expanded COSY Spectrum of Compound 368.

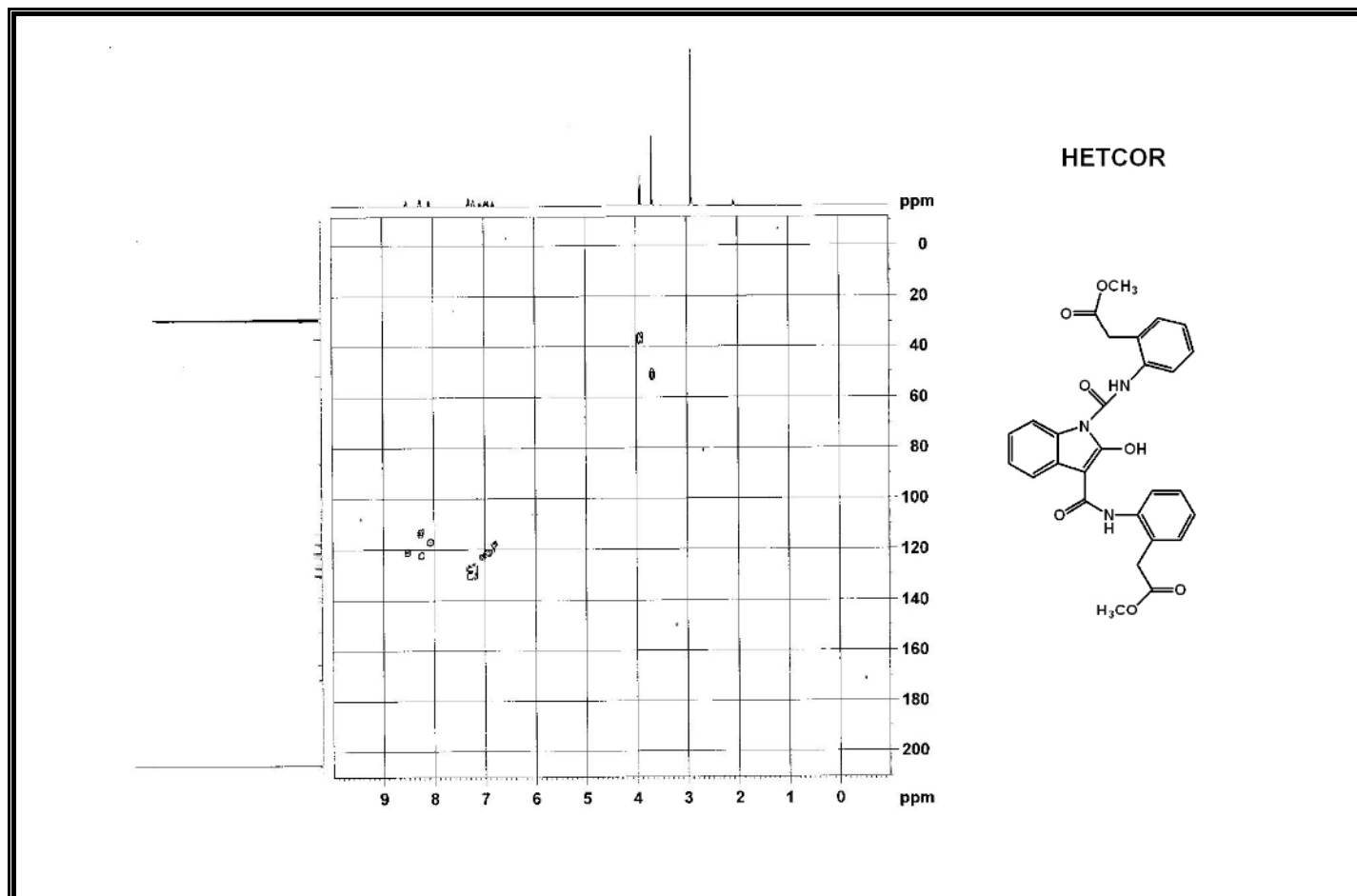


Figure A97 HETCOR Spectrum of Compound 368.

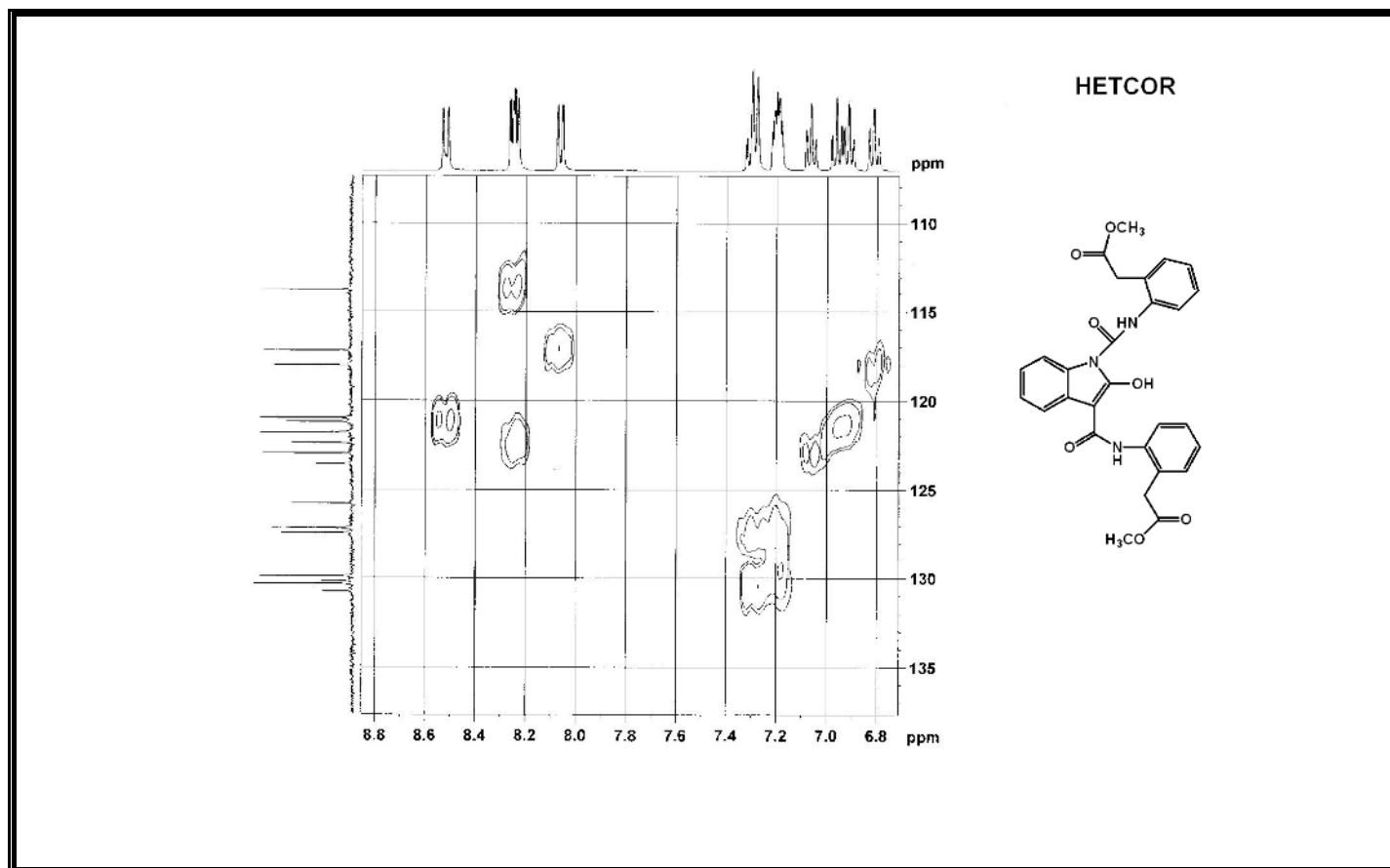


Figure A98 Expanded HETCOR Spectrum of Compound 368.

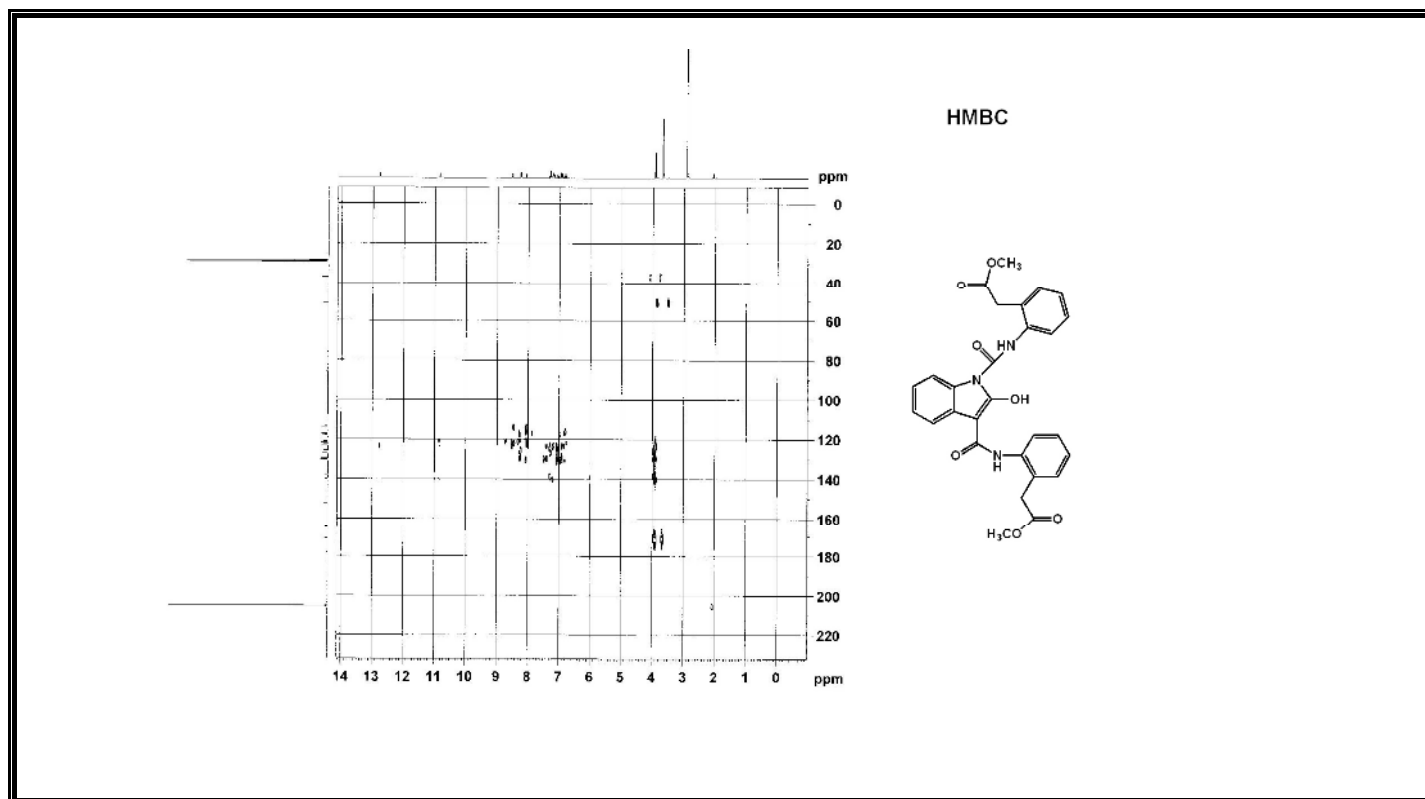


Figure A99 HMBC Spectrum of Compound **368**.

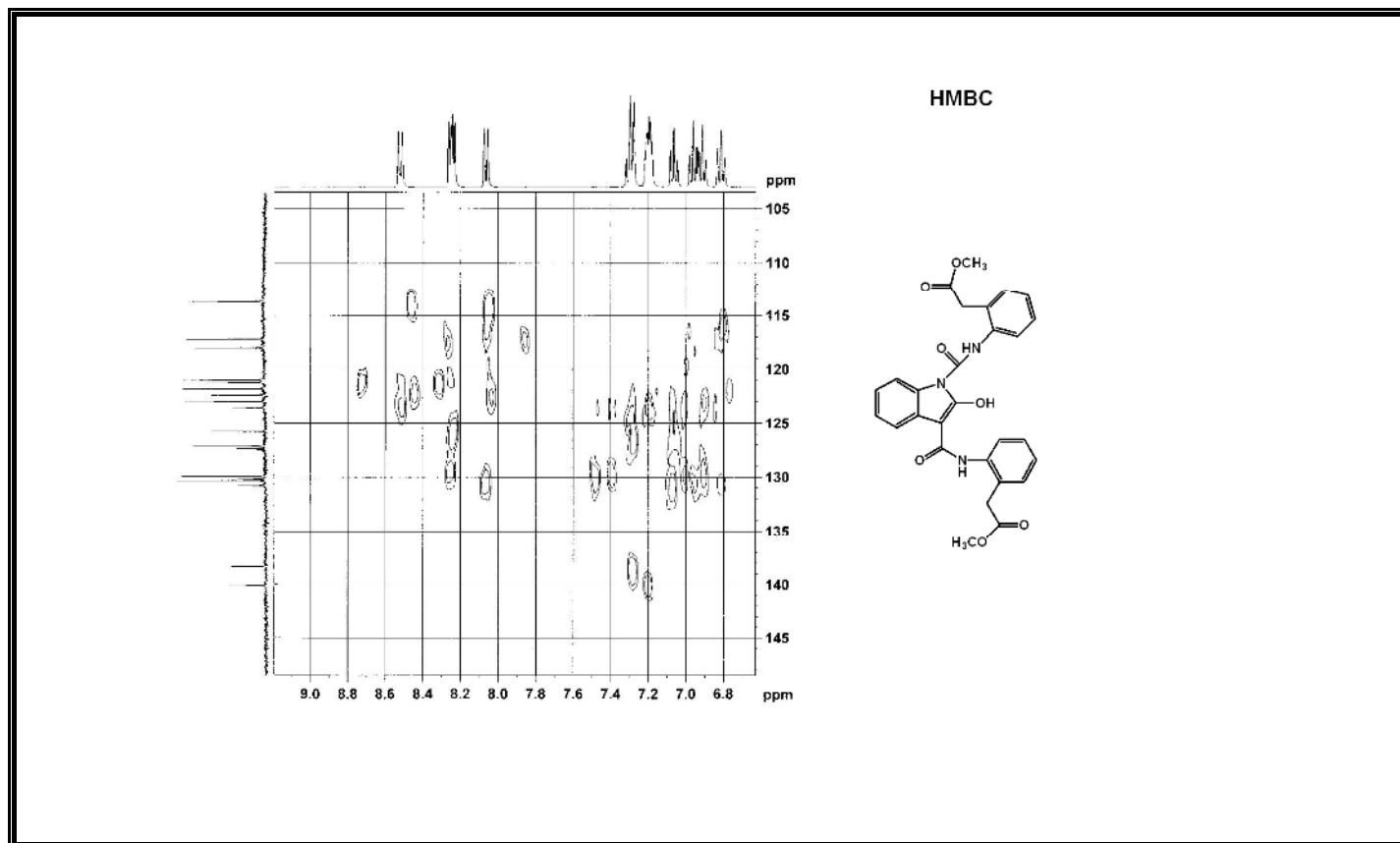


Figure A100 Expanded HMBC Spectrum of Compound **386**.

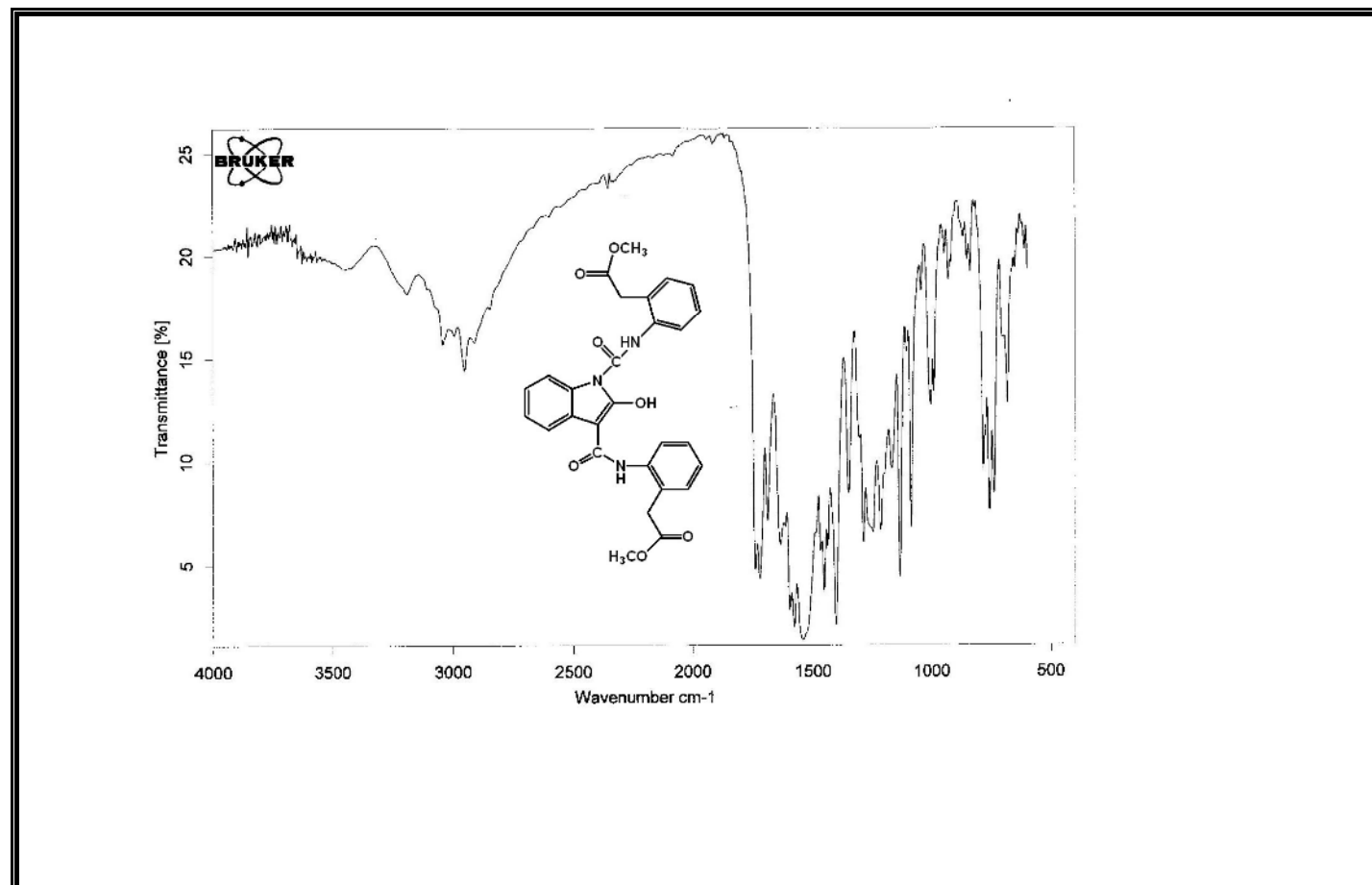


Figure A101 IR Spectrum of Compound 368.

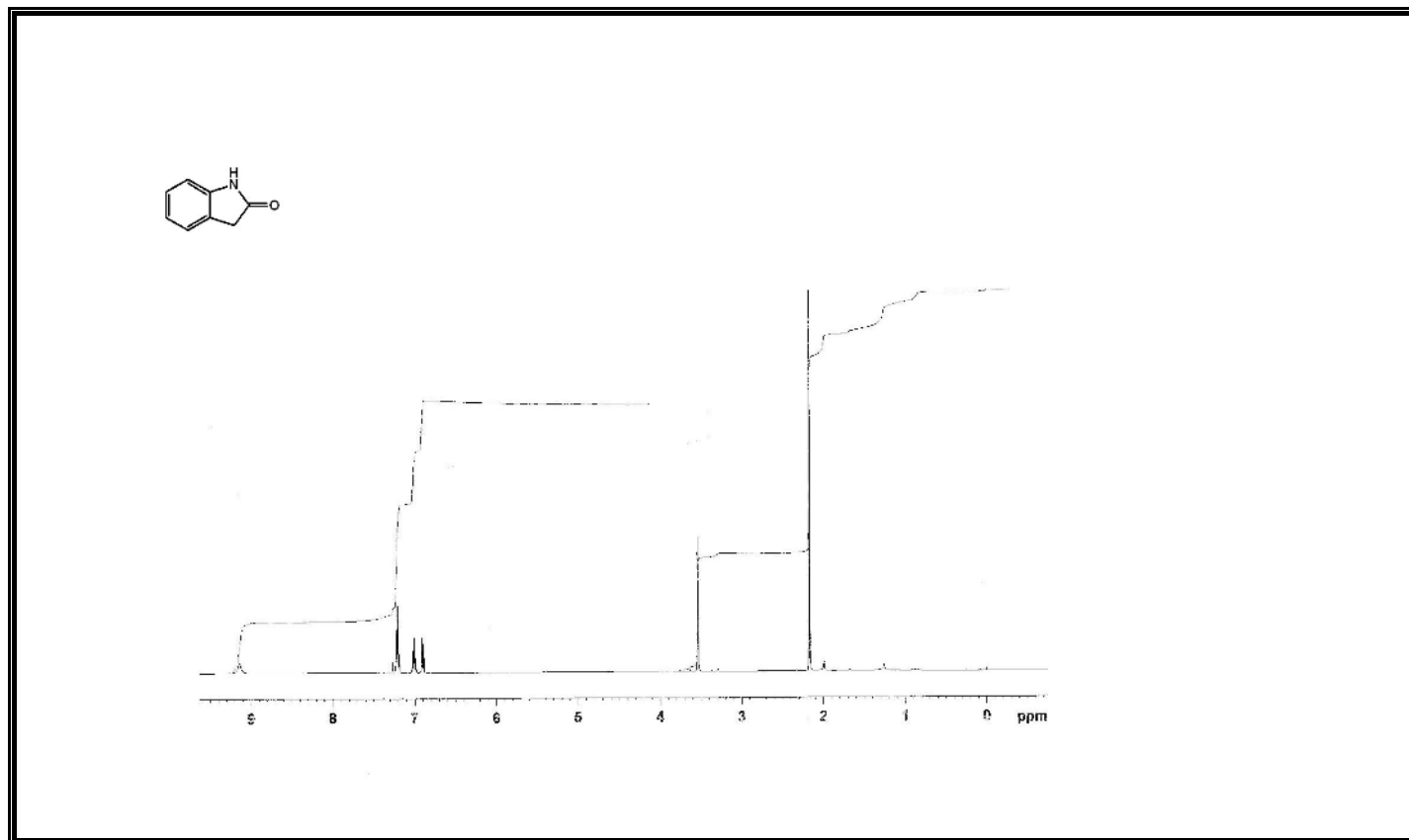
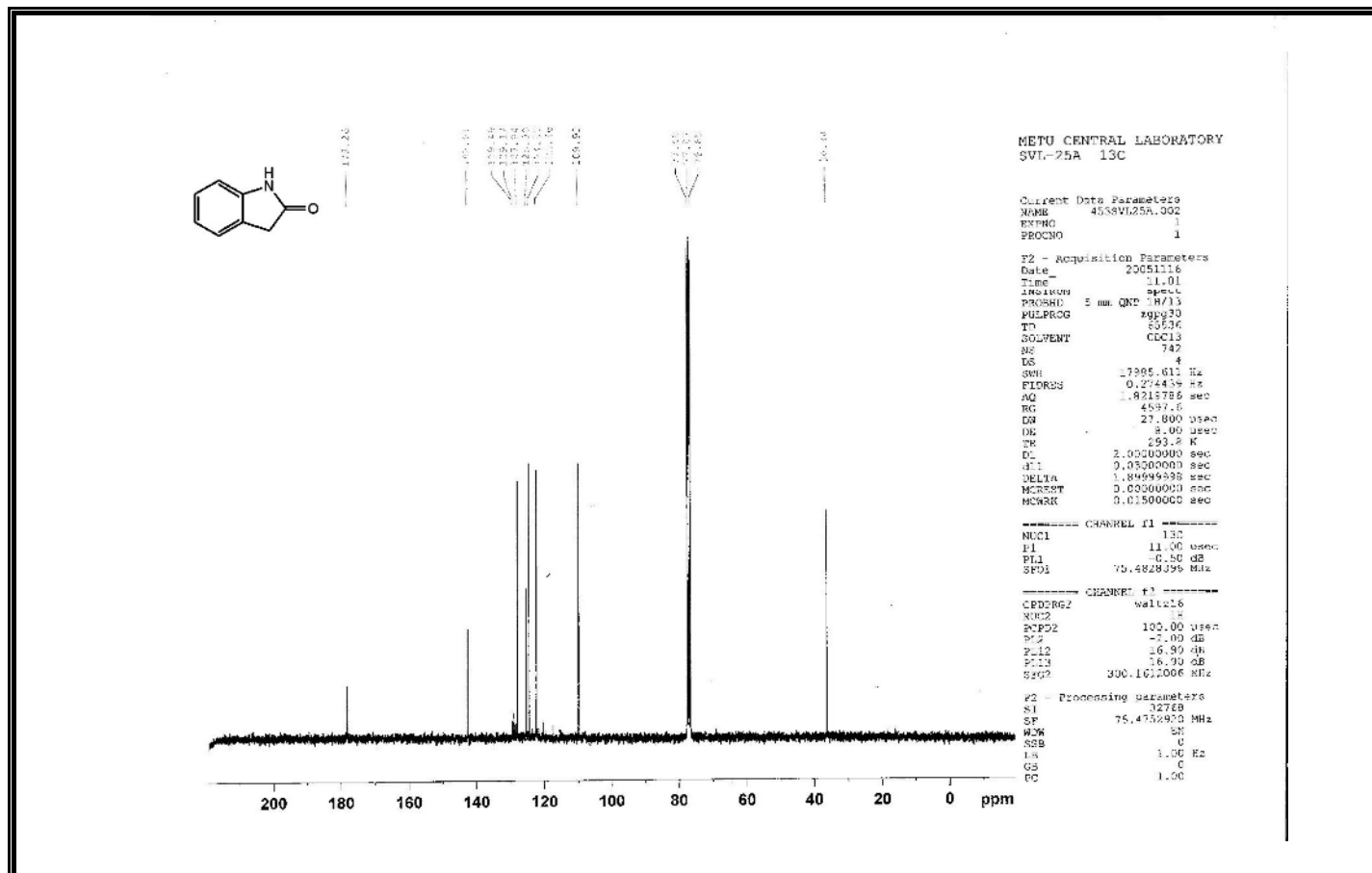


Figure A102 ^1H -NMR Spectrum of Compound **369**.

Figure A103 ^{13}C -NMR Spectrum of Compound 369.

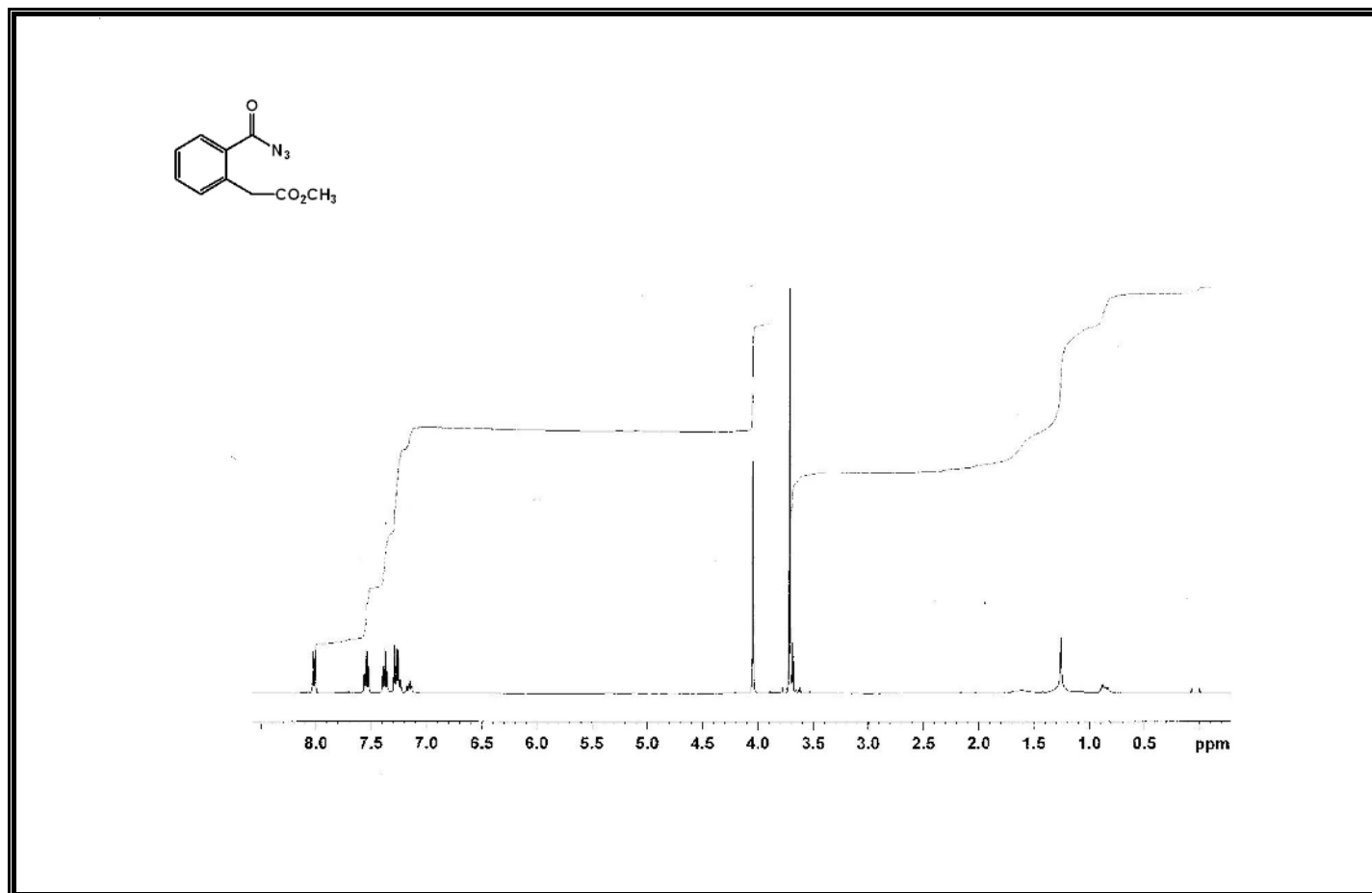


Figure A104 ^1H -NMR Spectrum of Compound 353.

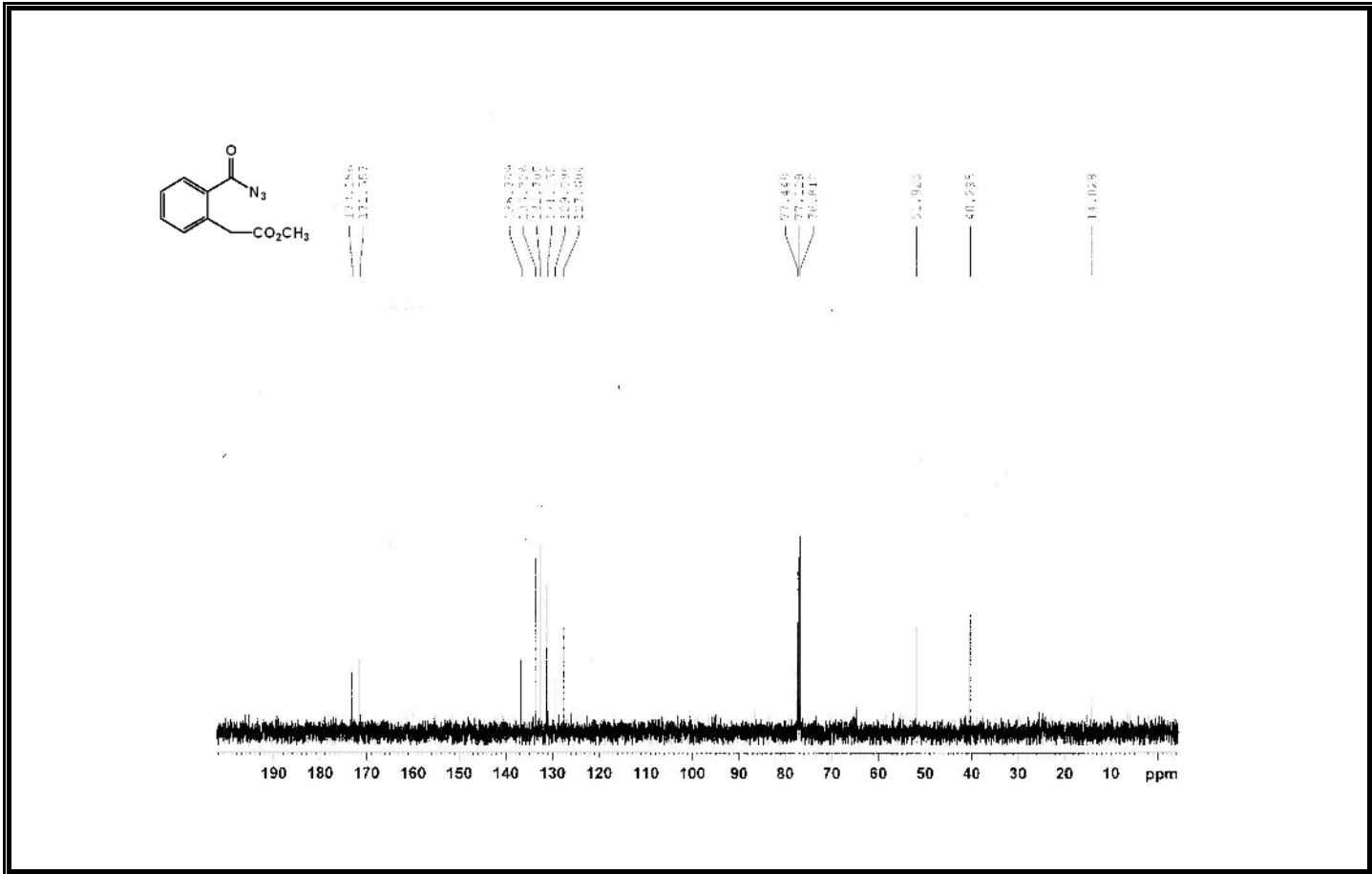


Figure A105 ^{13}C -NMR Spectrum of Compound **353**.

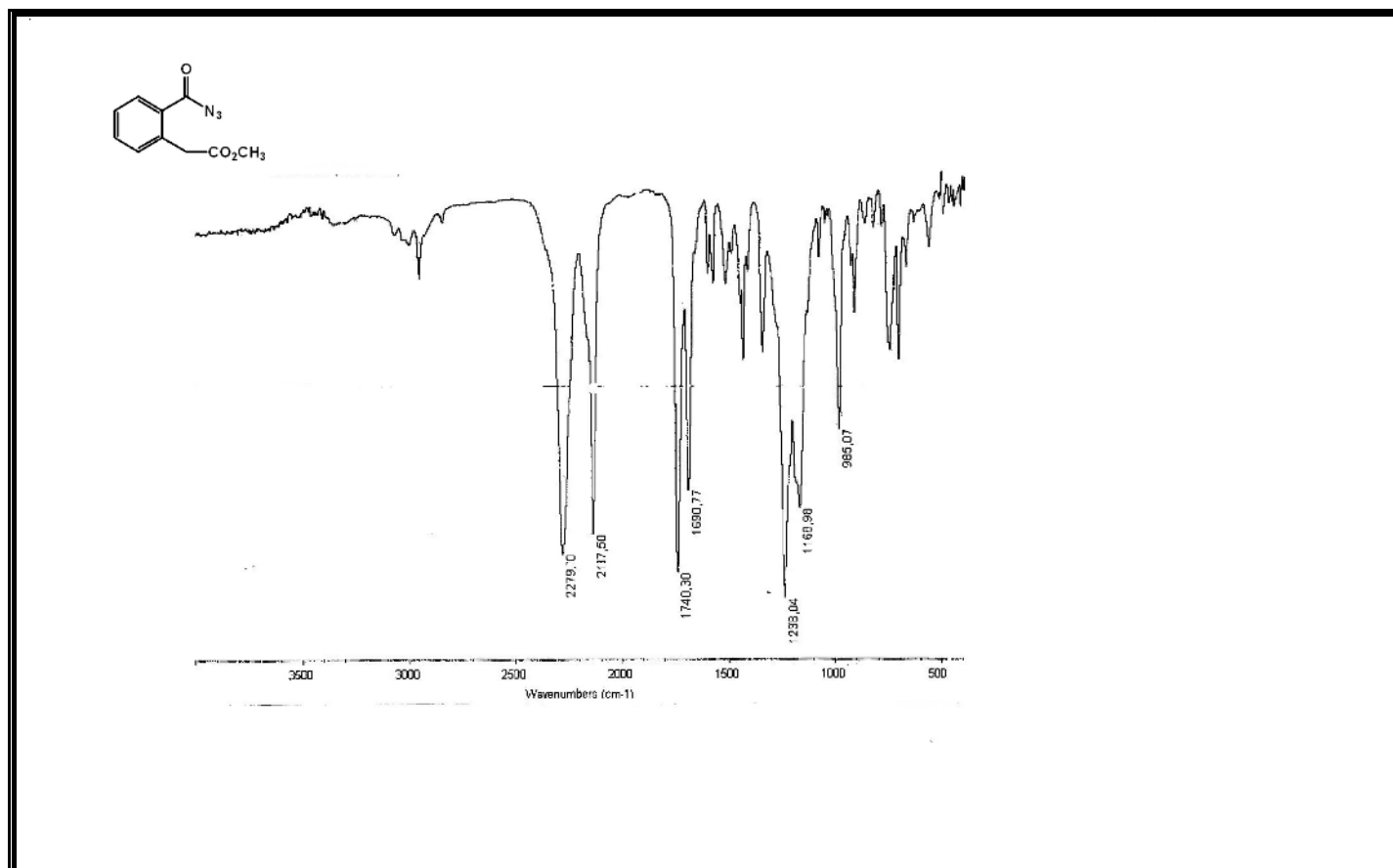


Figure A106 IR Spectrum of Compound 353.

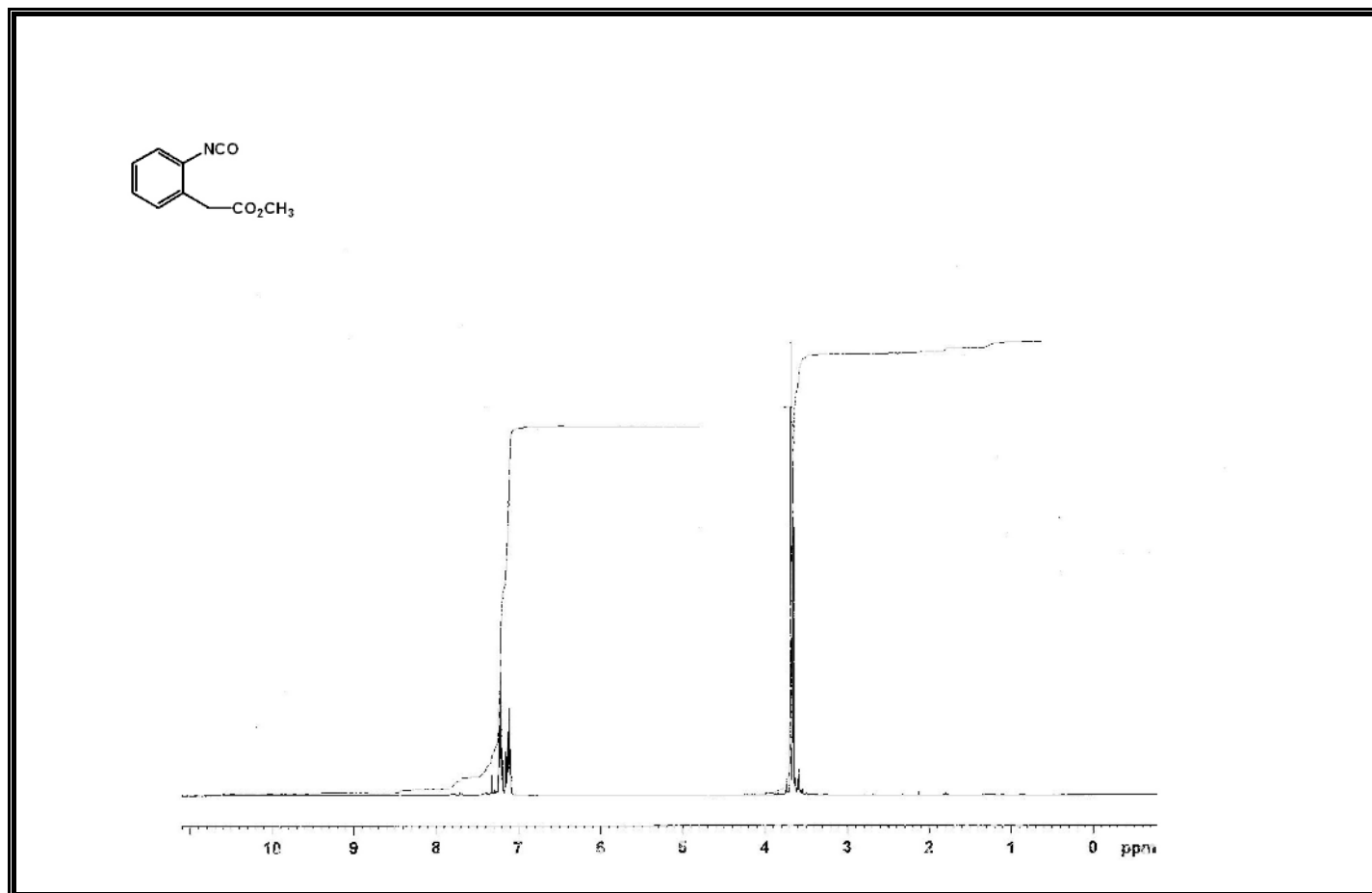


Figure A107 ^1H -NMR Spectrum of Compound 354.

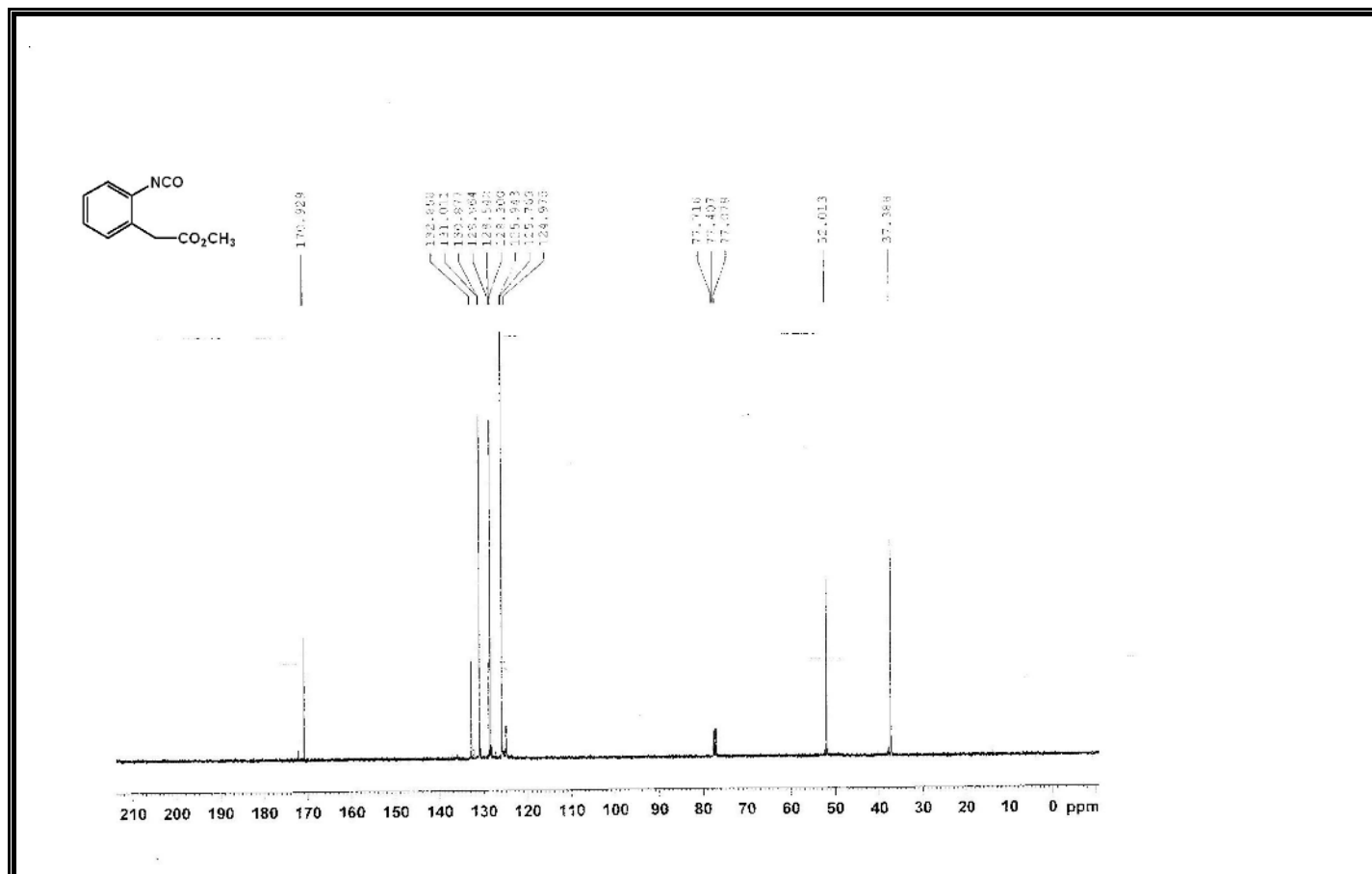


Figure A108 ^{13}C -NMR Spectrum of Compound 354.

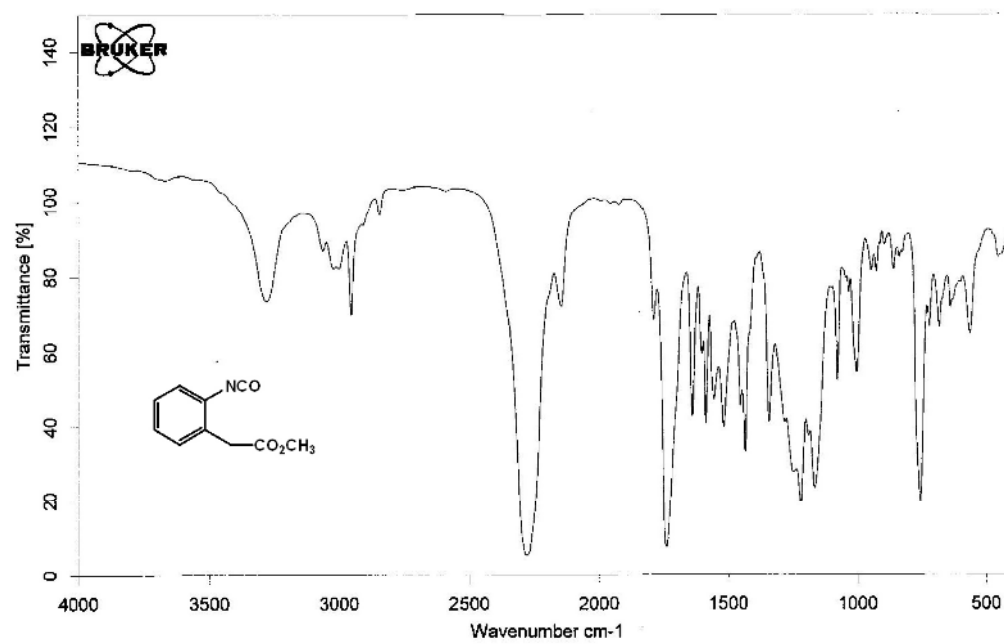


Figure A109 IR Spectrum of Compound 354.

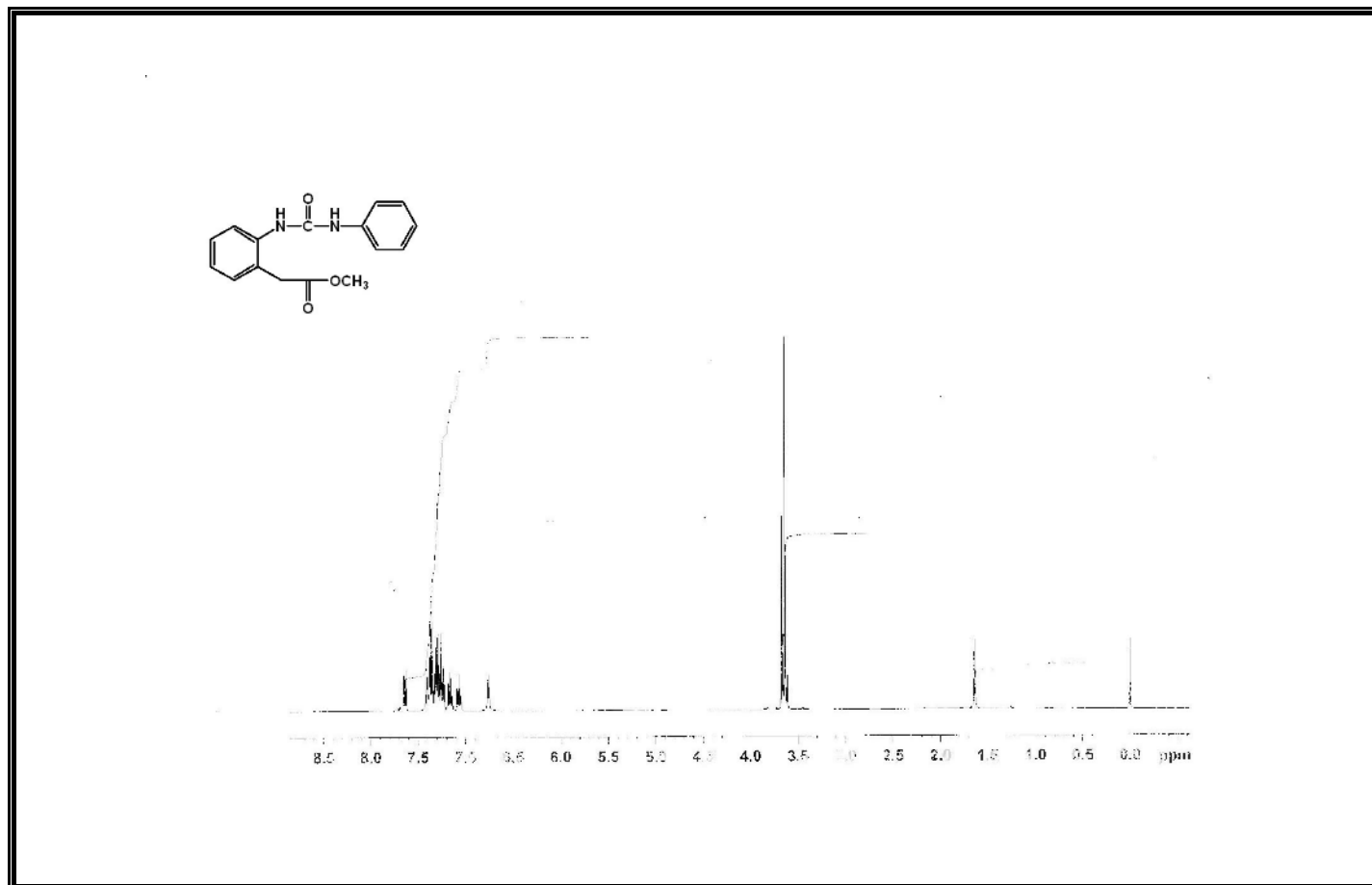


Figure A110 ^1H -NMR Spectrum of Compound 374.

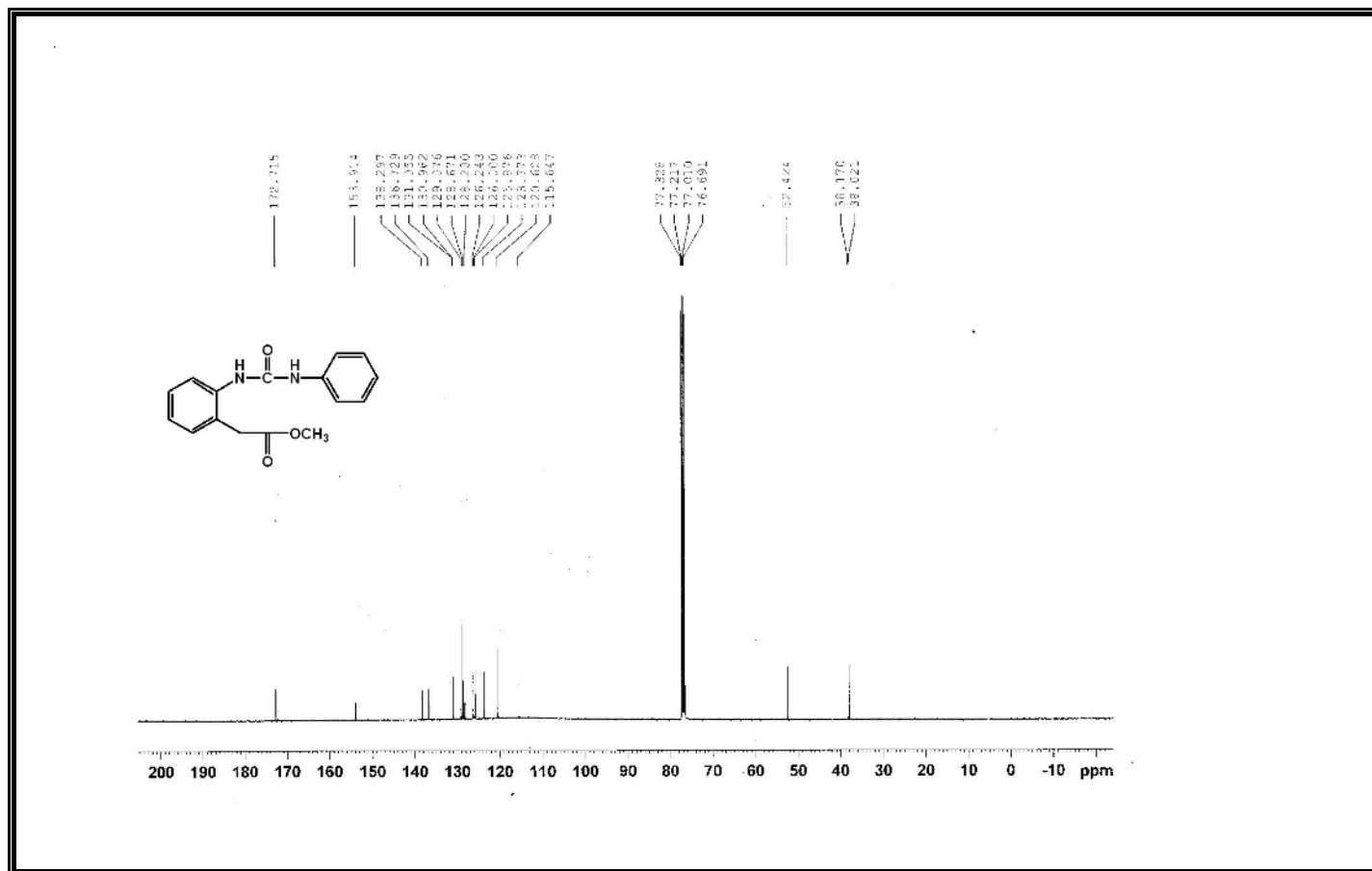


Figure A111 ^{13}C -NMR Spectrum of Compound 374.

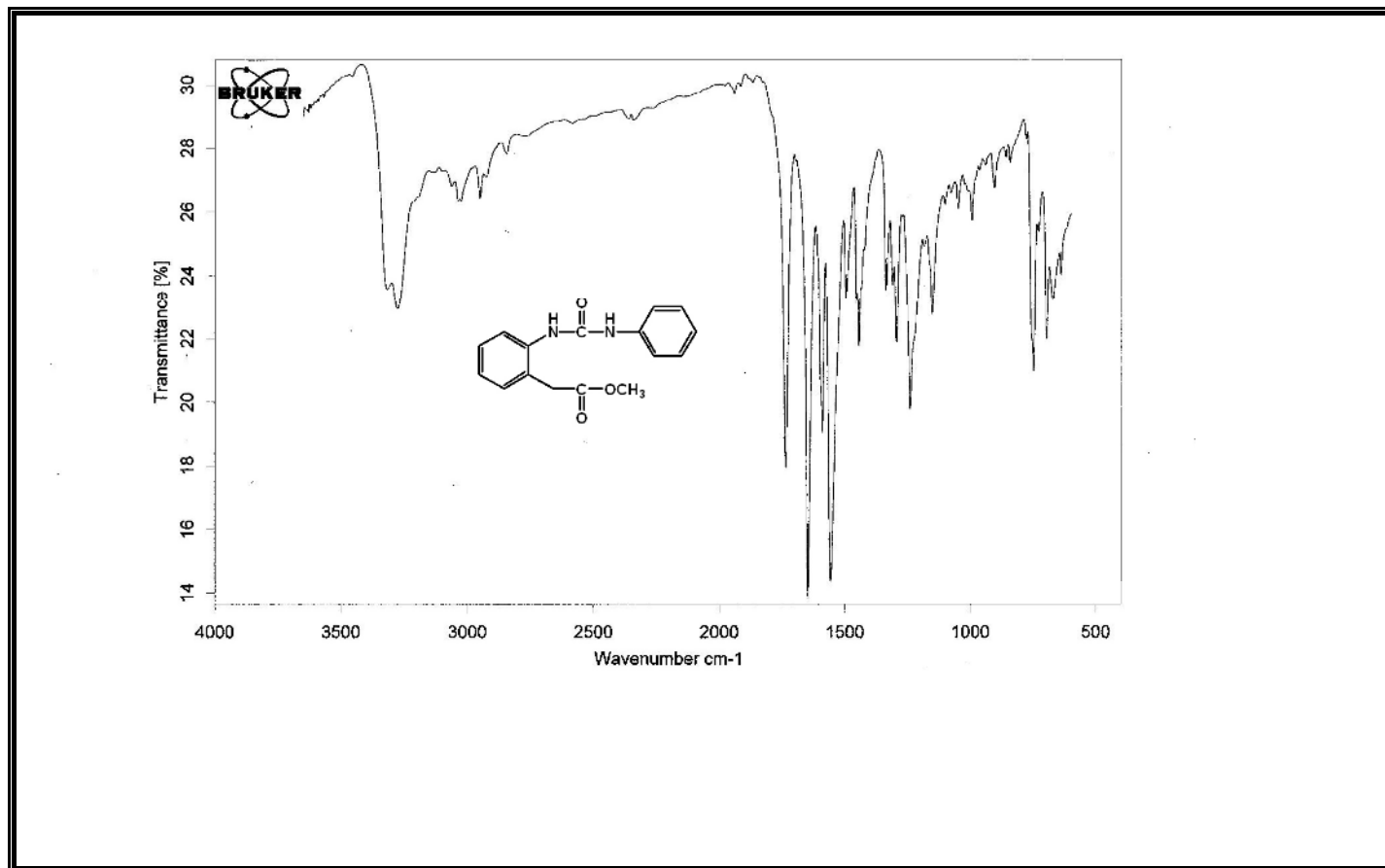


Figure A112 IR Spectrum of Compound 374.

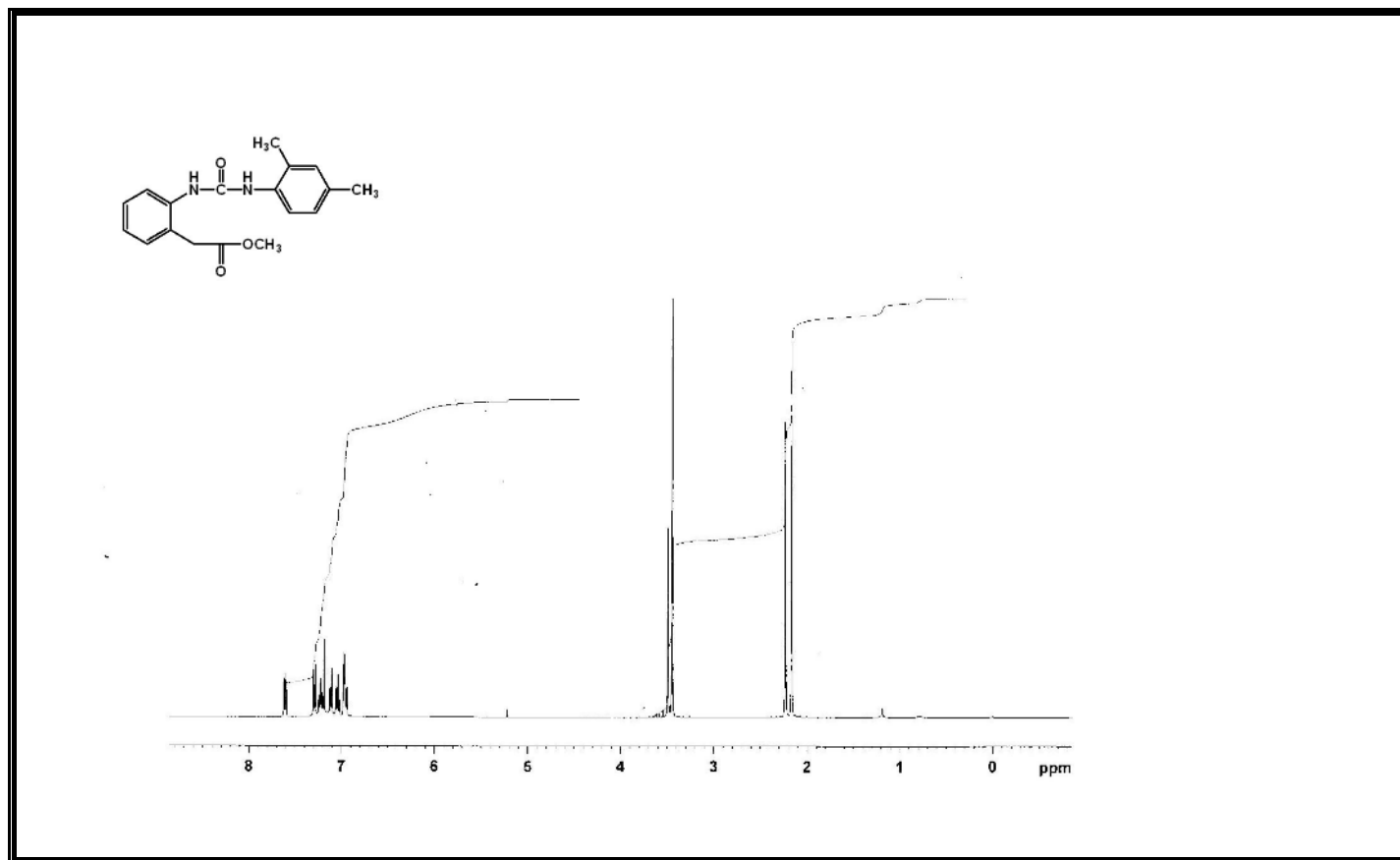


Figure A113 ^1H -NMR Spectrum of Compound 376.

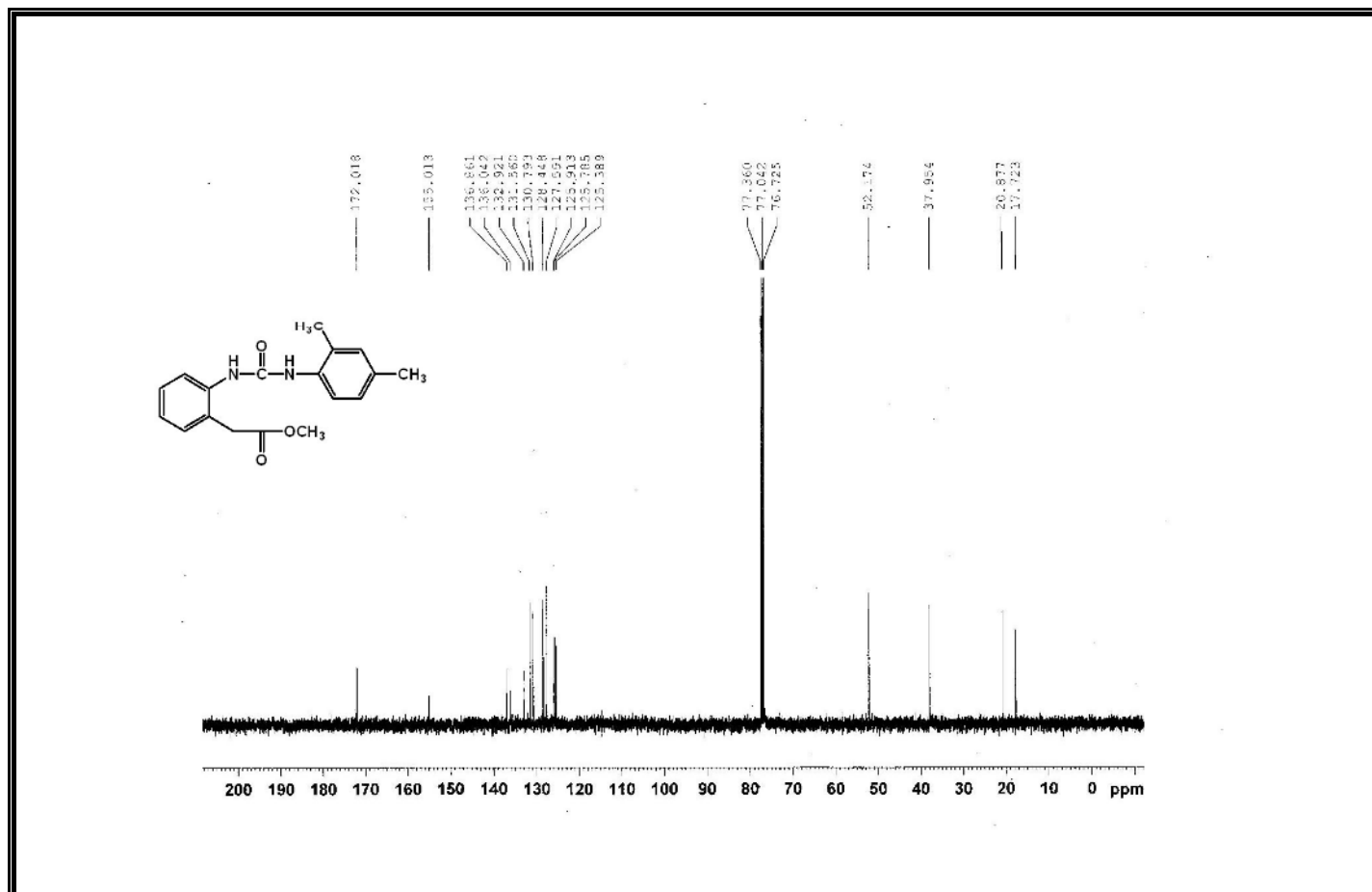


Figure A114 ¹³C-NMR Spectrum of Compound 376.

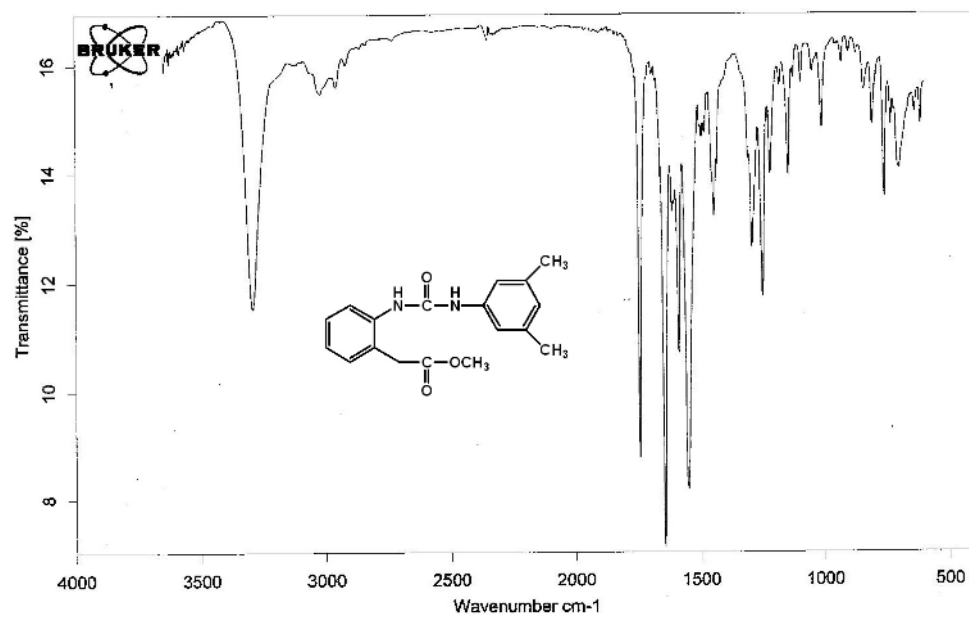


Figure A115 IR Spectrum of Compound 376.

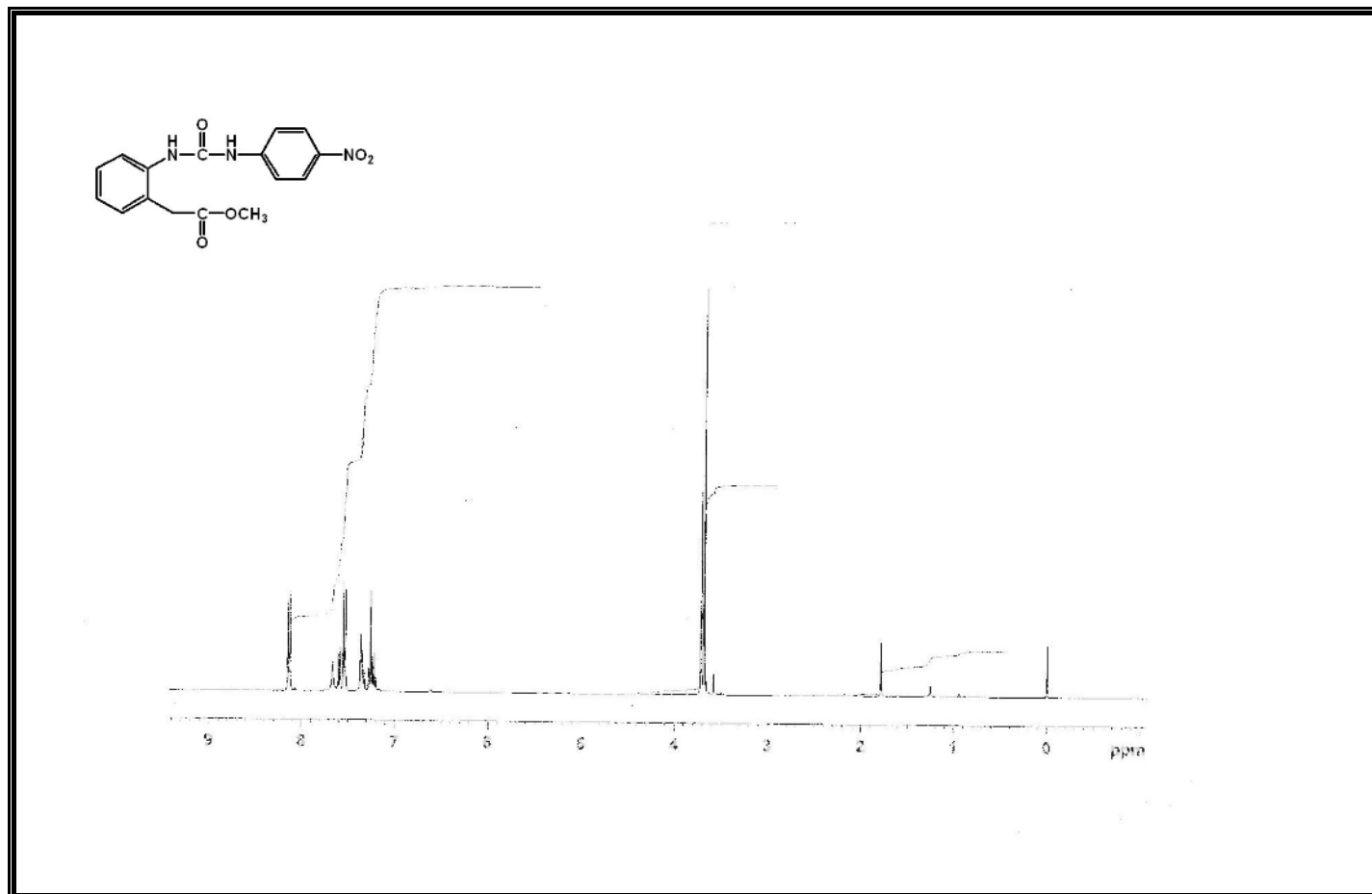


Figure A116 ¹H-NMR Spectrum of Compound 378.

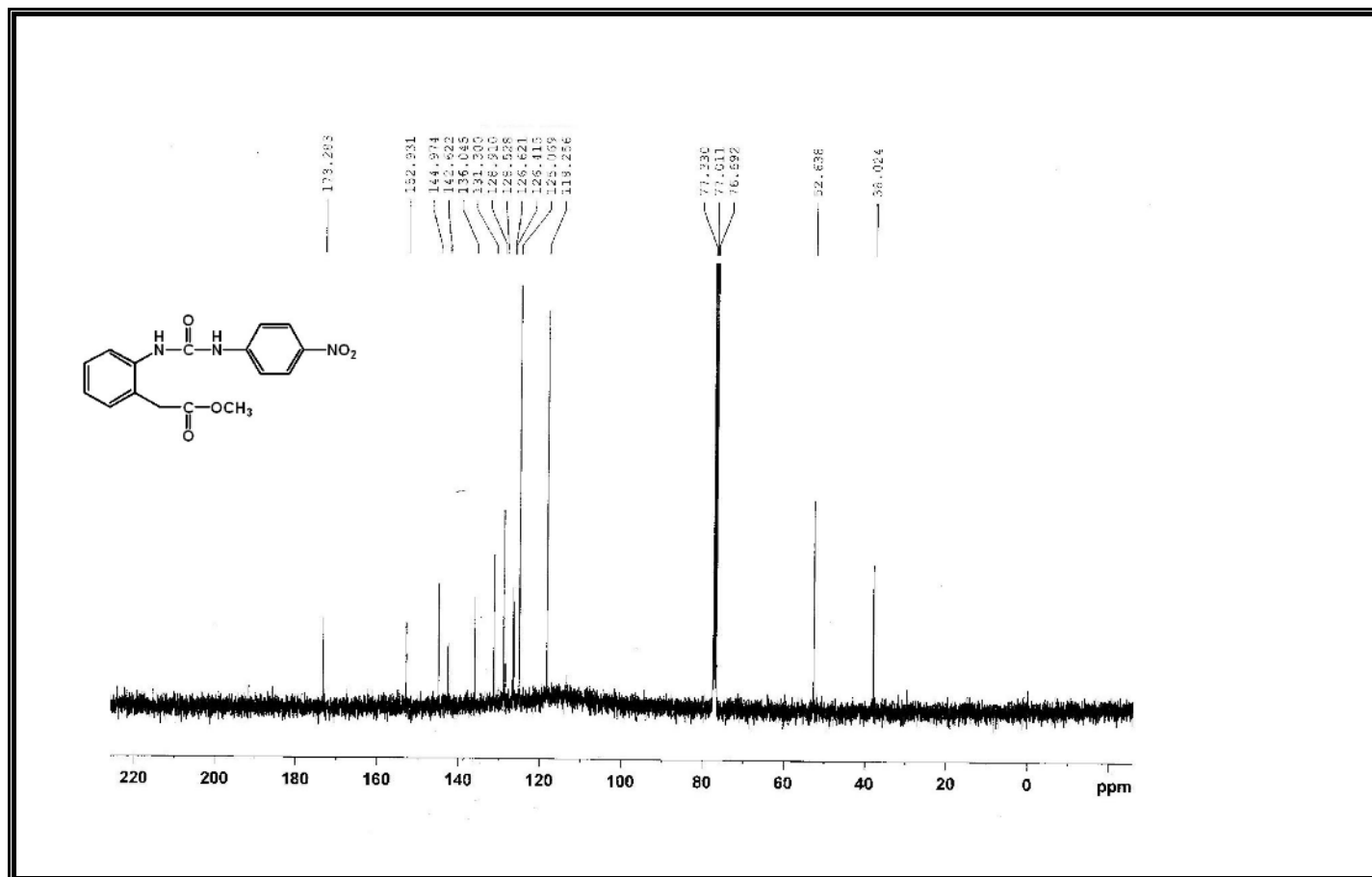


Figure A117 ¹³C-NMR Spectrum of Compound 378.

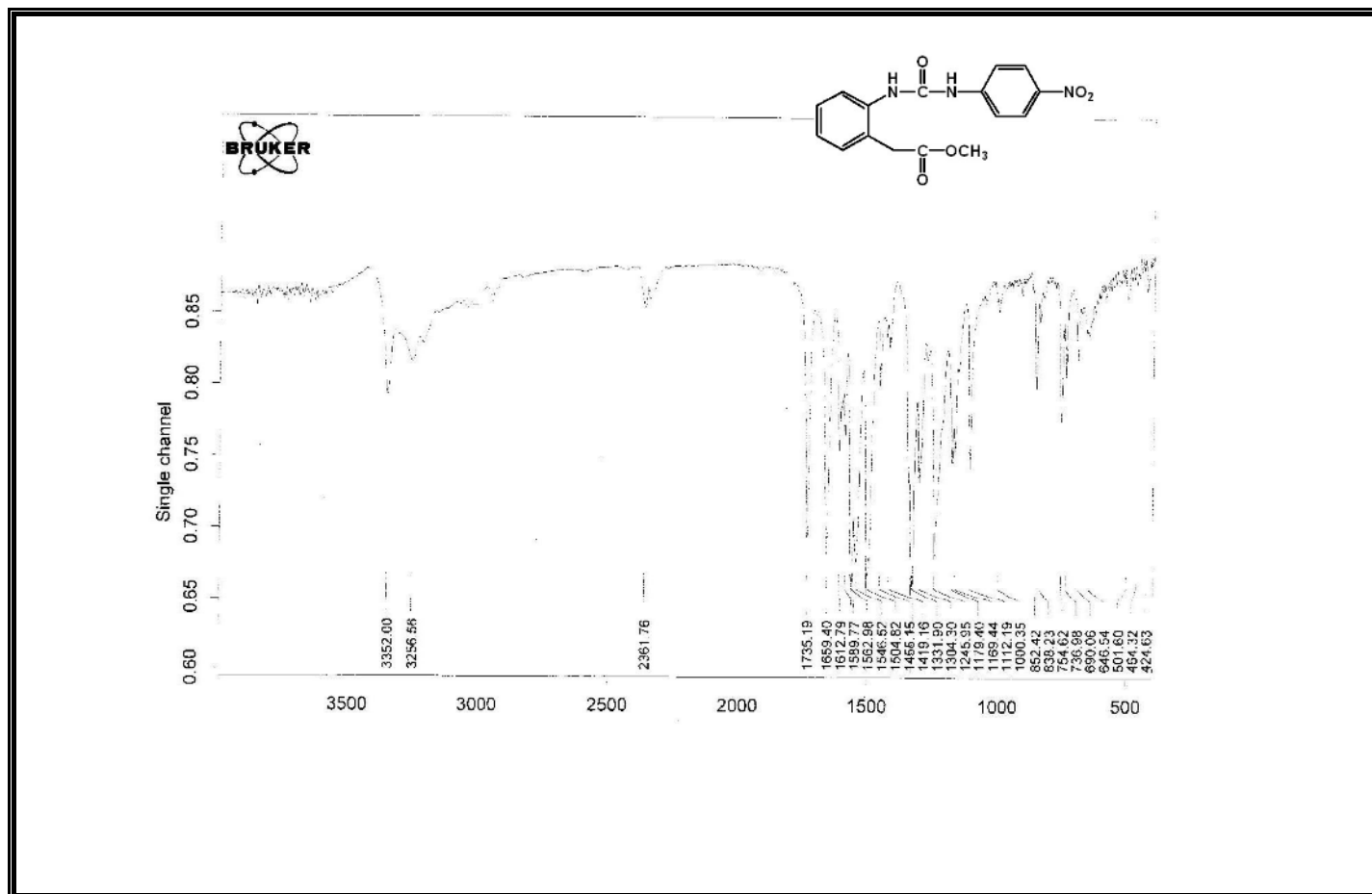


Figure A118 IR Spectrum of Compound 378.

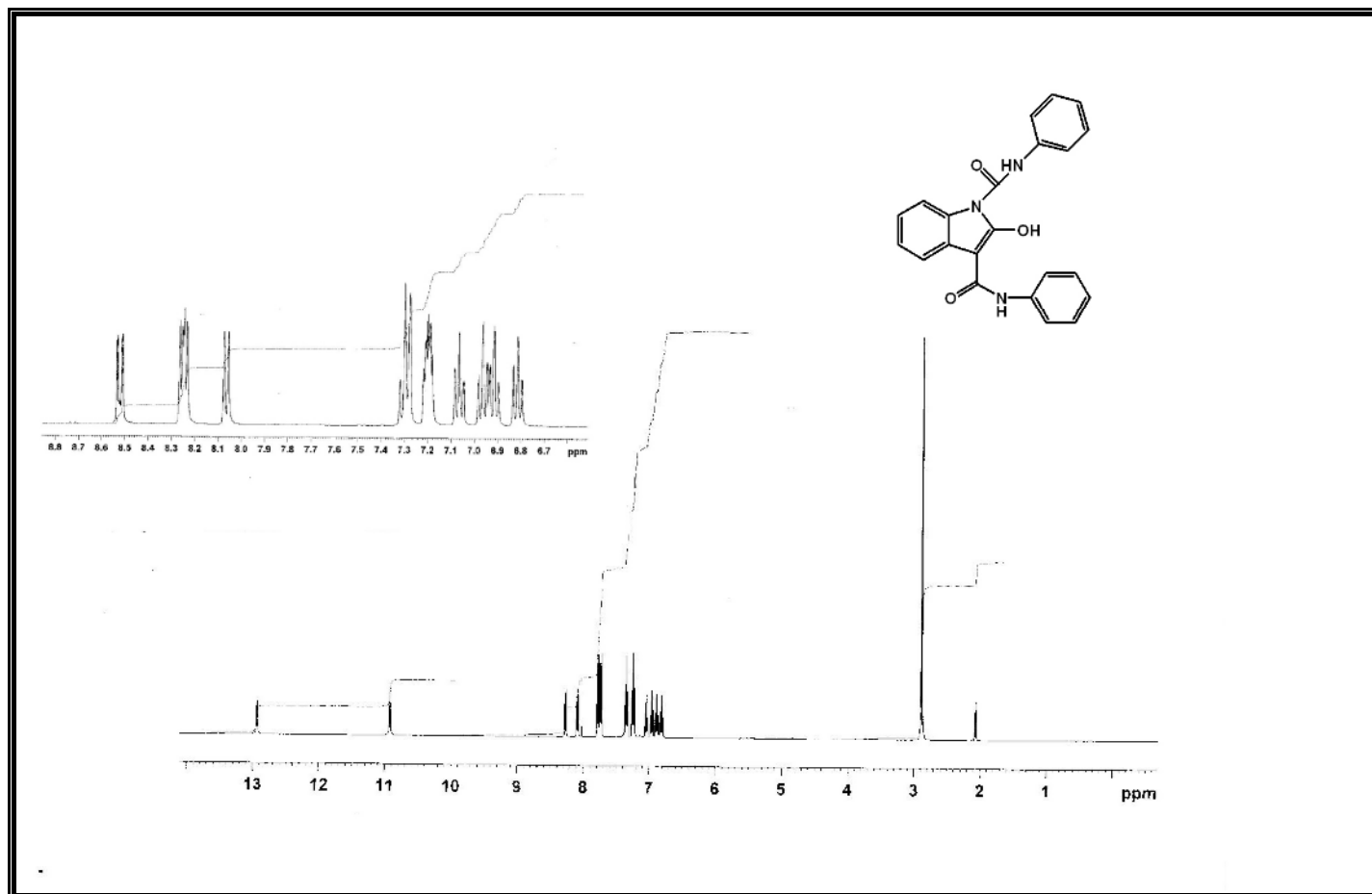


Figure A119 ^1H -NMR Spectrum of Compound 379.

Figure A120 ^{13}C -NMR Spectrum of Compound **369**.

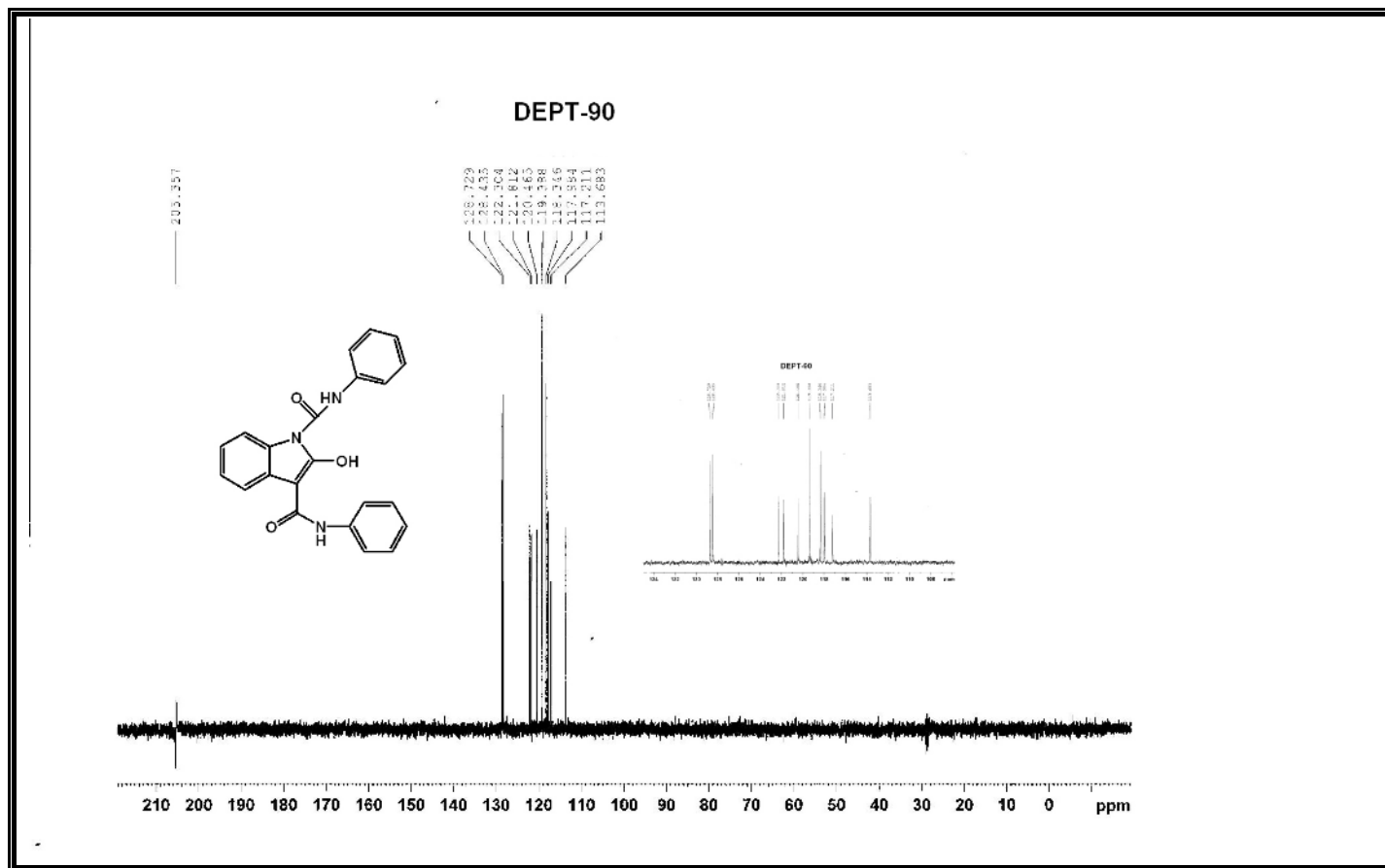


Figure A121 DEPT-90 Spectrum of Compound 379.

Figure A122 DEPT-135 Spectrum of Compound **379**.

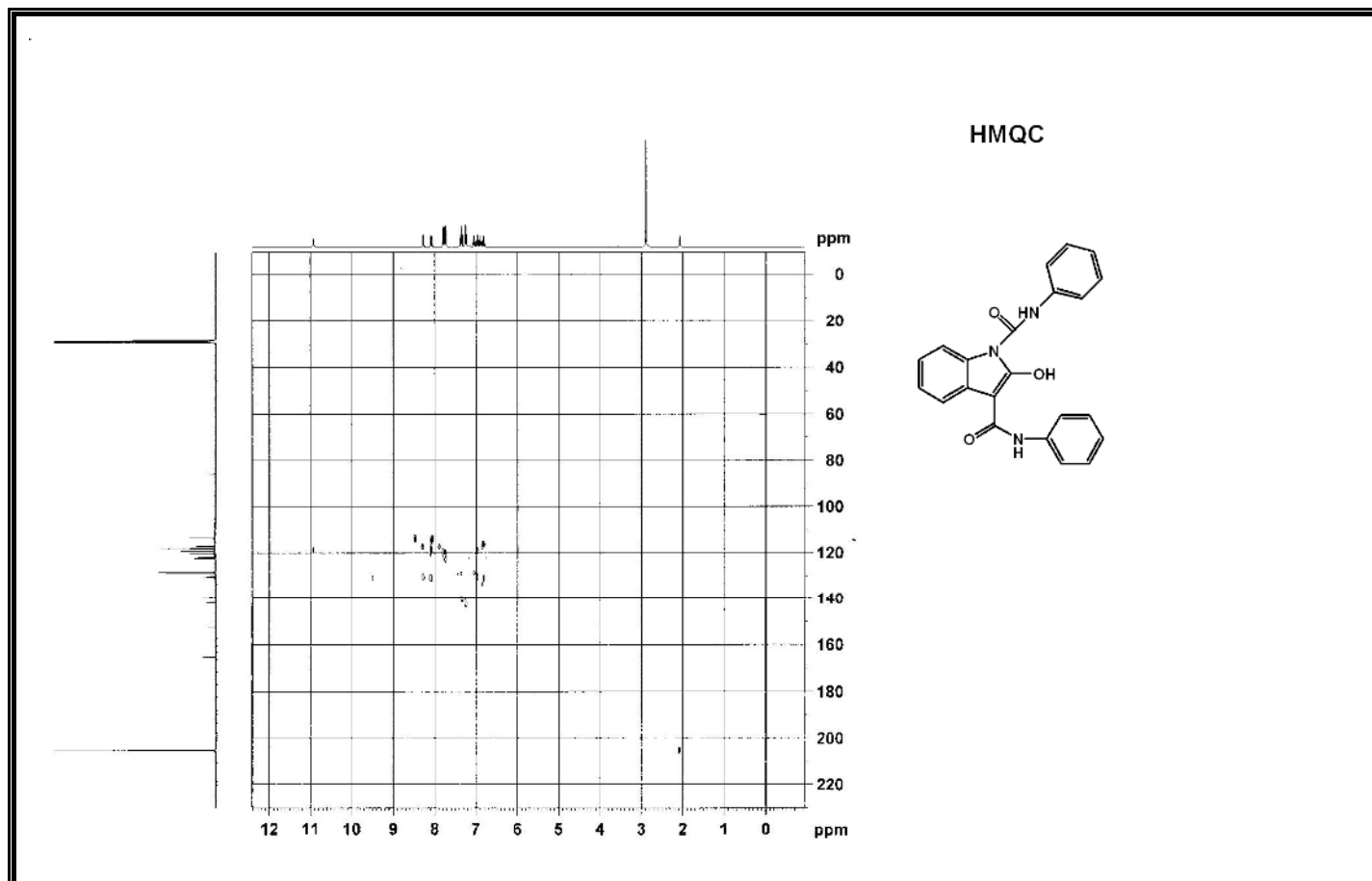


Figure A123 HMQC Spectrum of Compound 379.

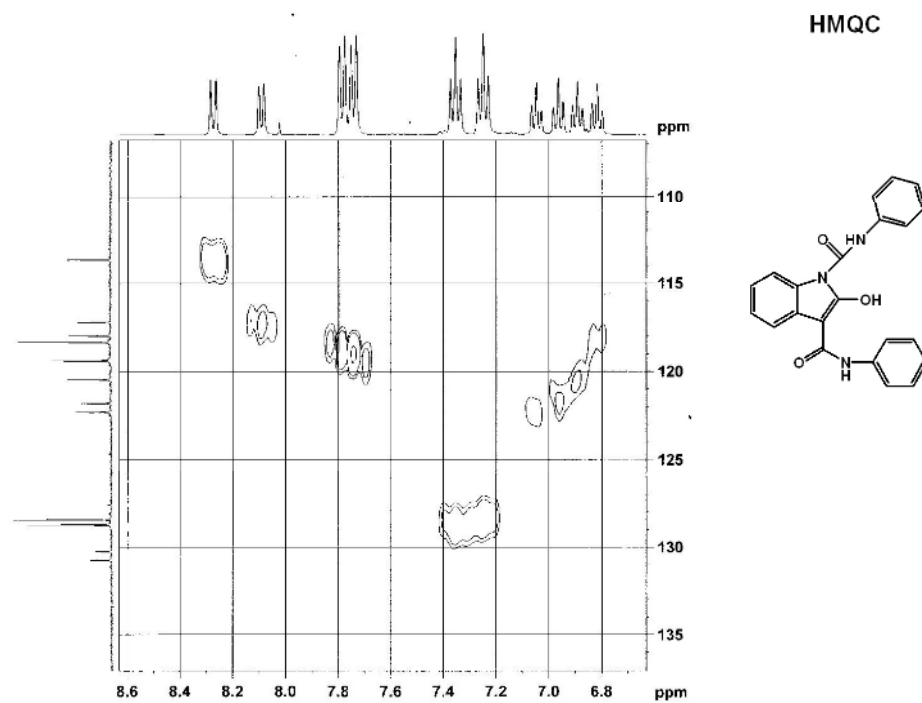


Figure A124 Expanded HMQC Spectrum of Compound 379.

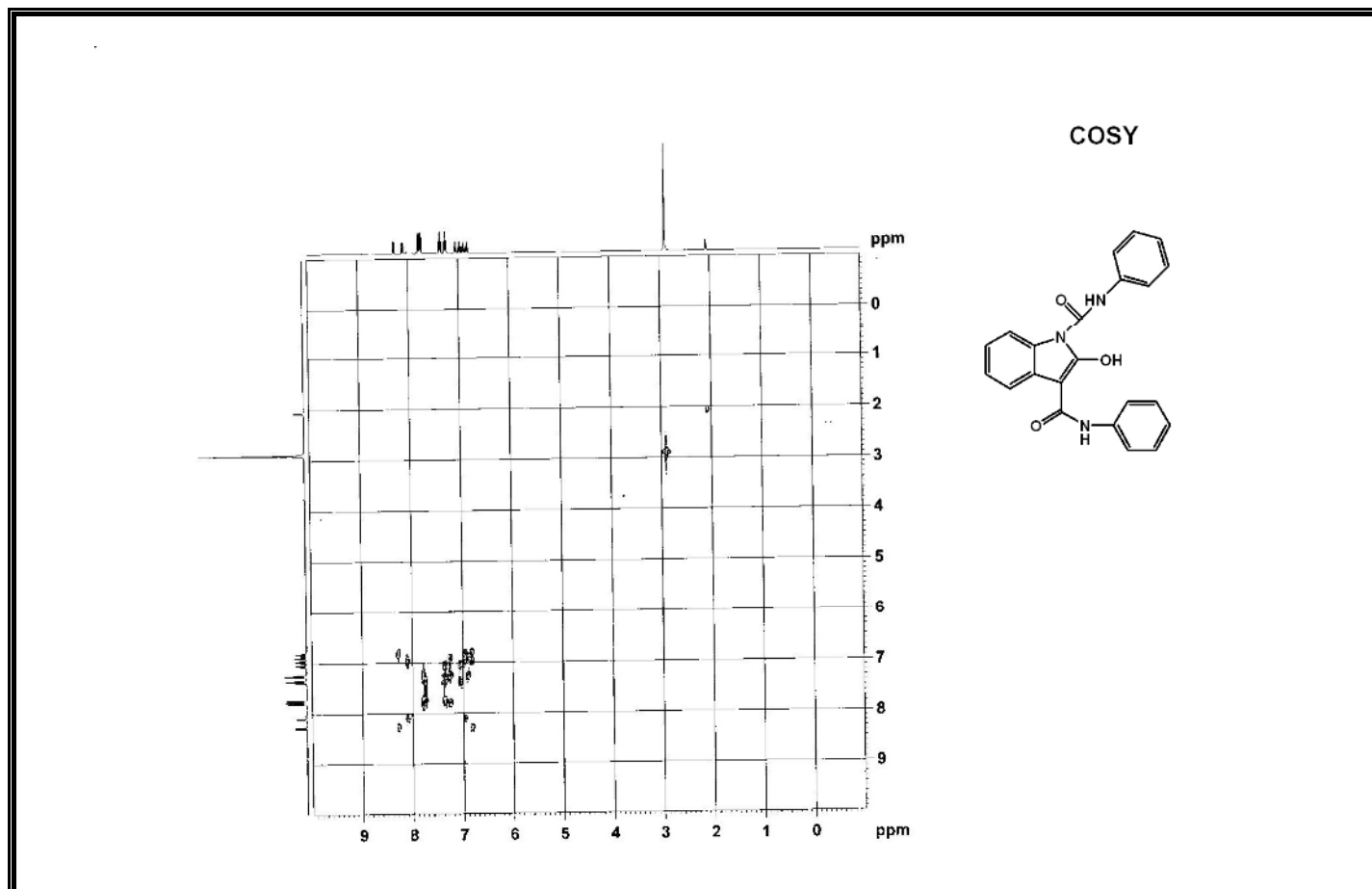


Figure A125 COSY Spectrum of Compound 379.

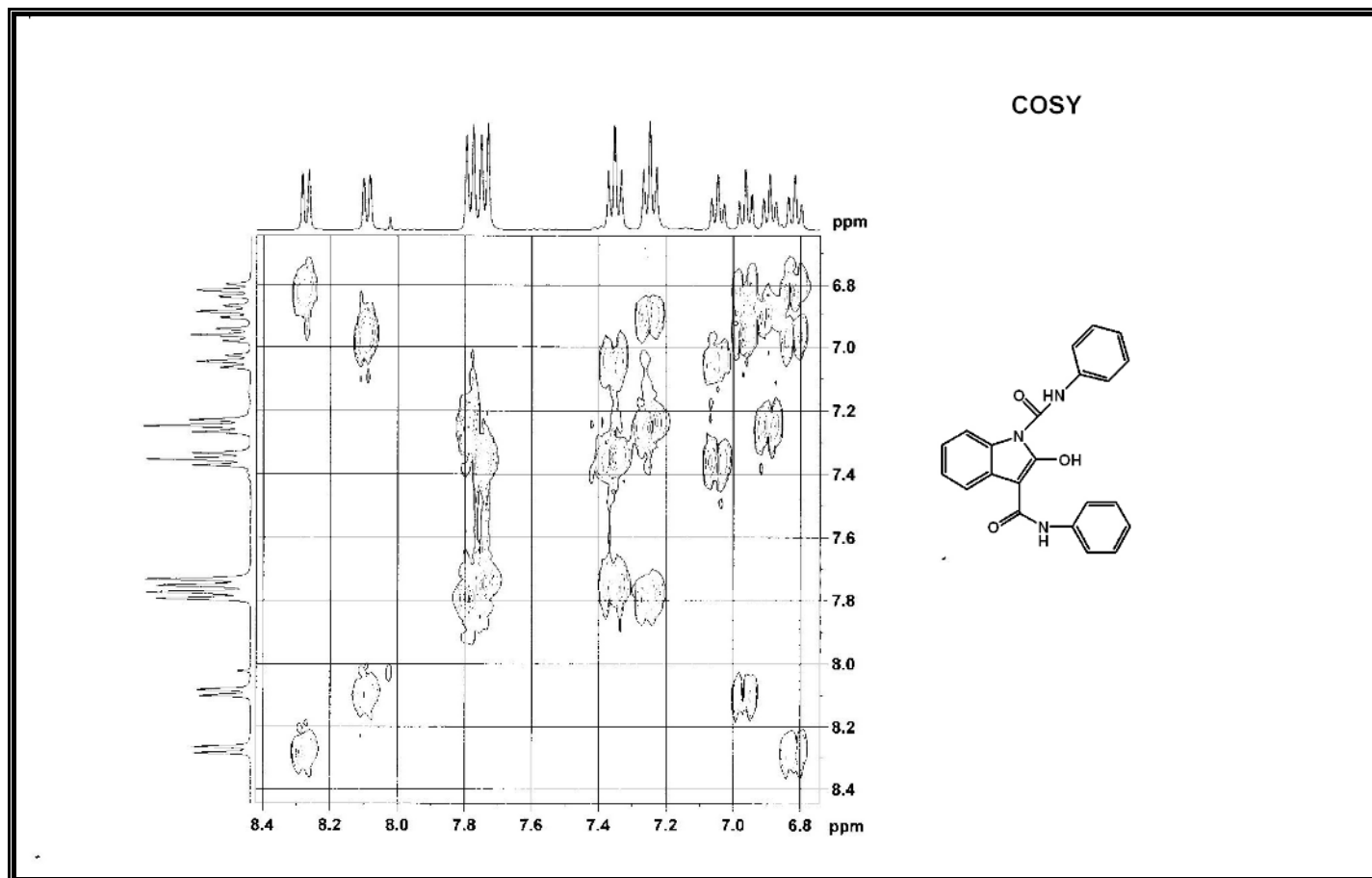


Figure A126 Expanded COSY Spectrum of Compound 379.

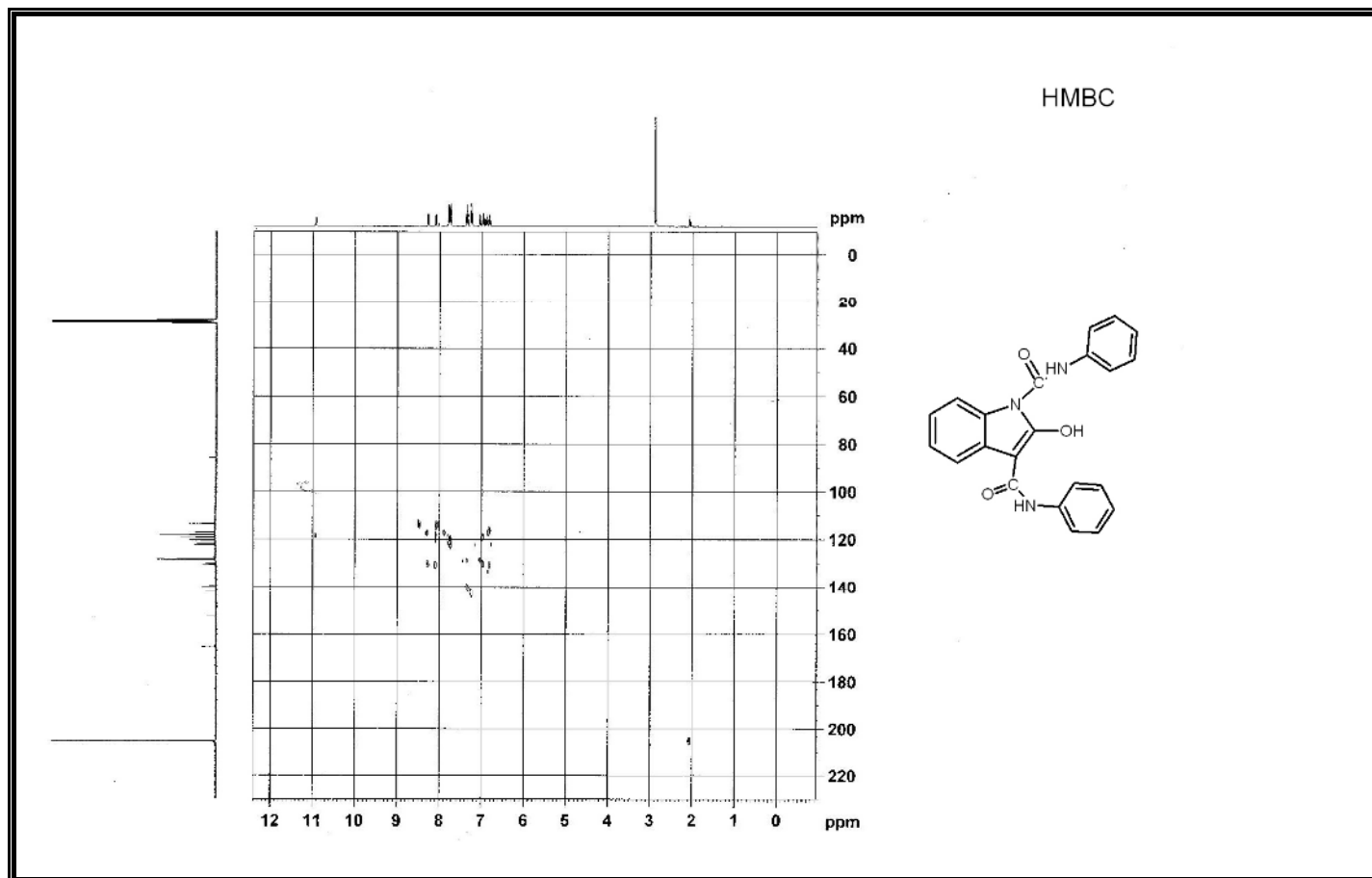


Figure A127 HMBC Spectrum of Compound 379.

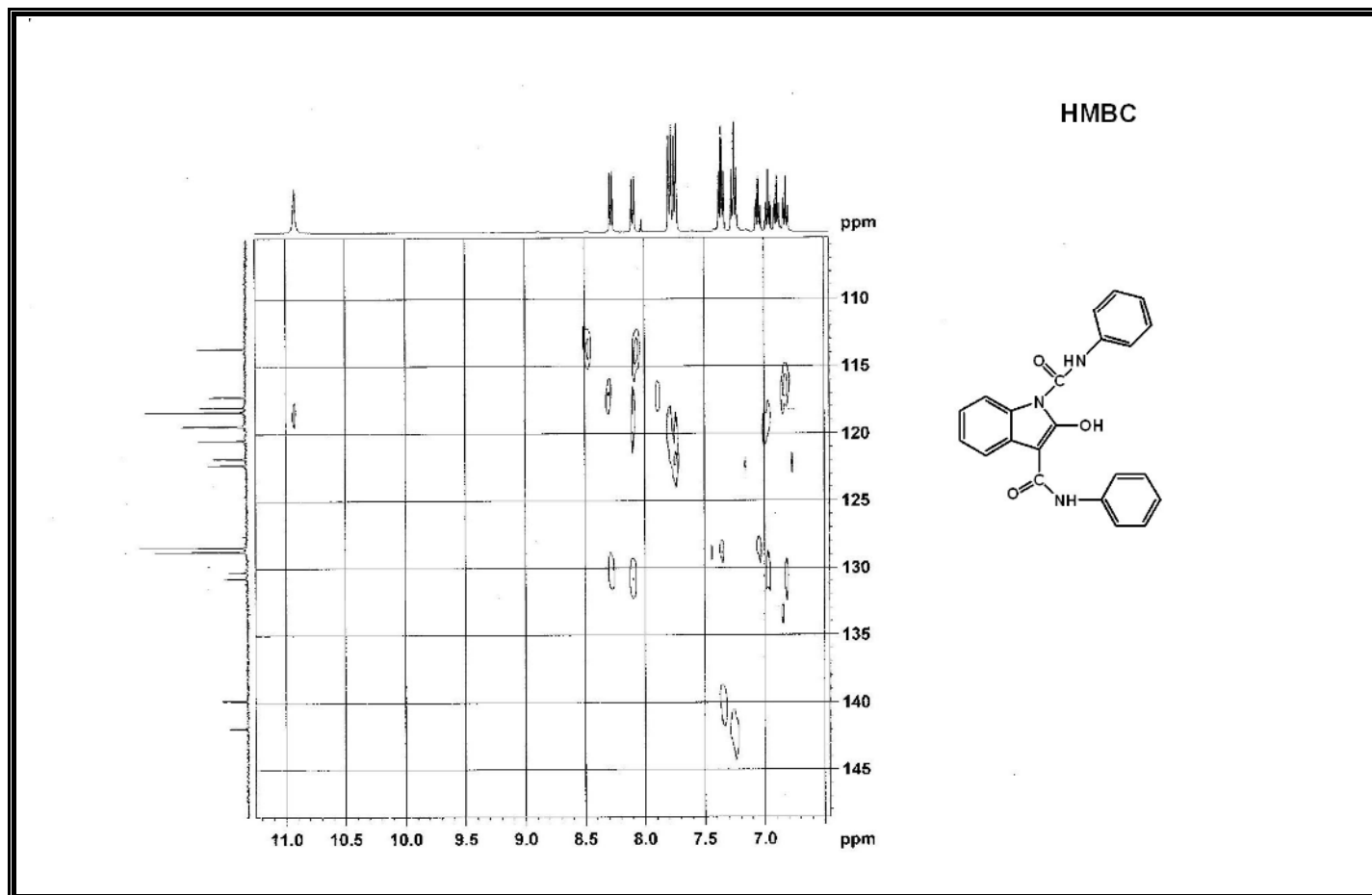


Figure A128 Expanded HMBC Spectrum of Compound **379**.

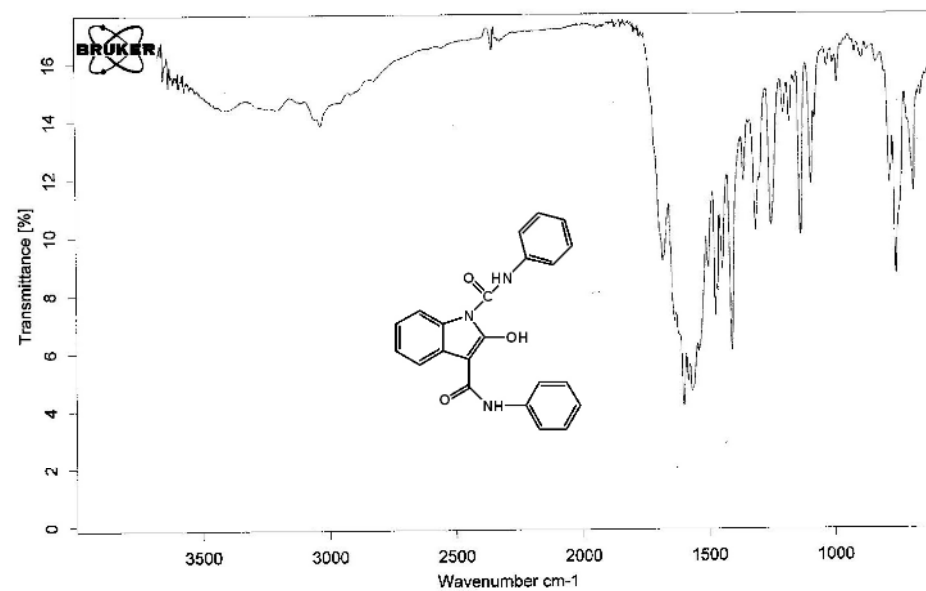


Figure A129 IR Spectrum of Compound 379.

Figure A130 ^1H -NMR Spectrum of Compound **380**.

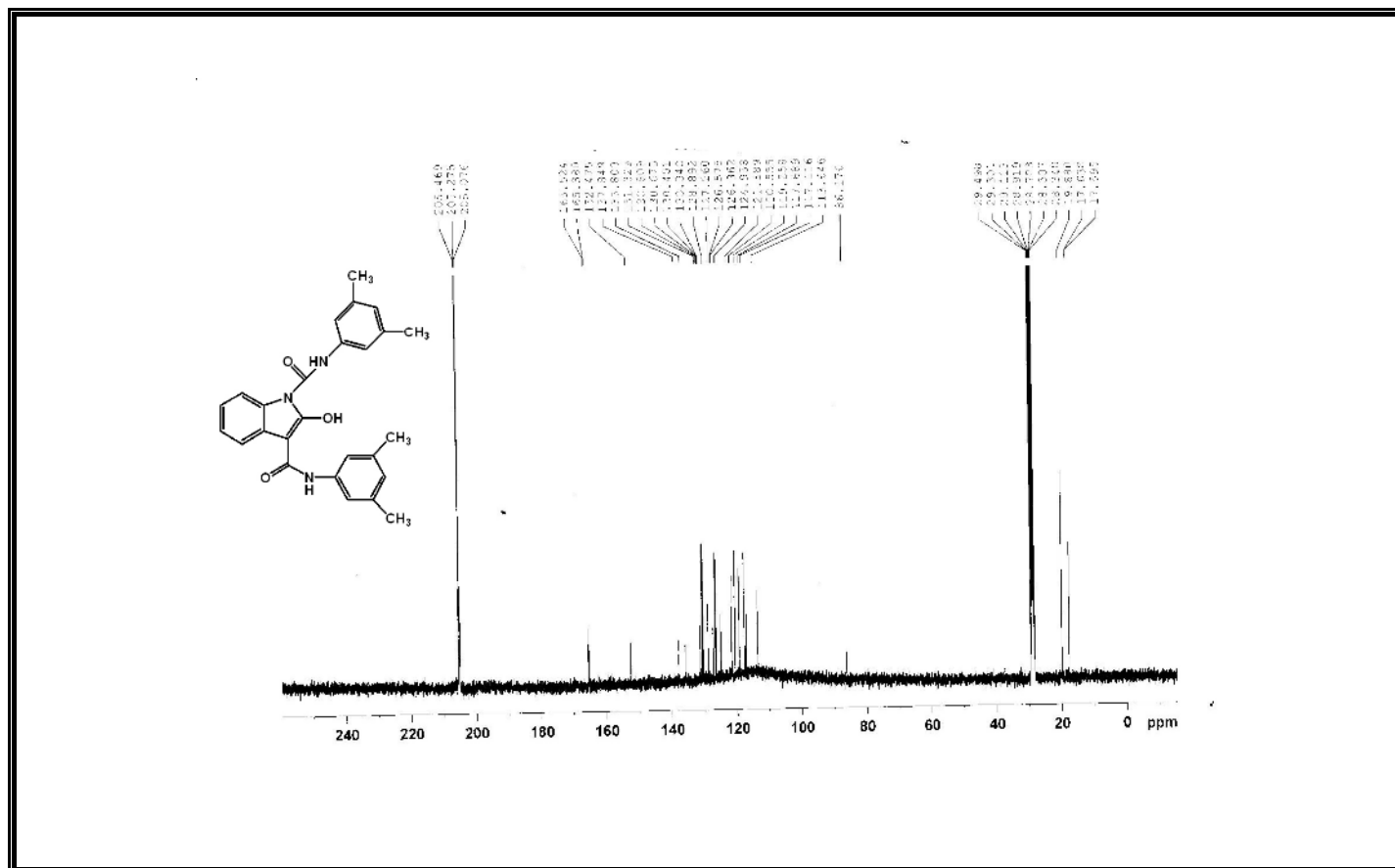


Figure A131 ^{13}C -NMR Spectrum of Compound 380.

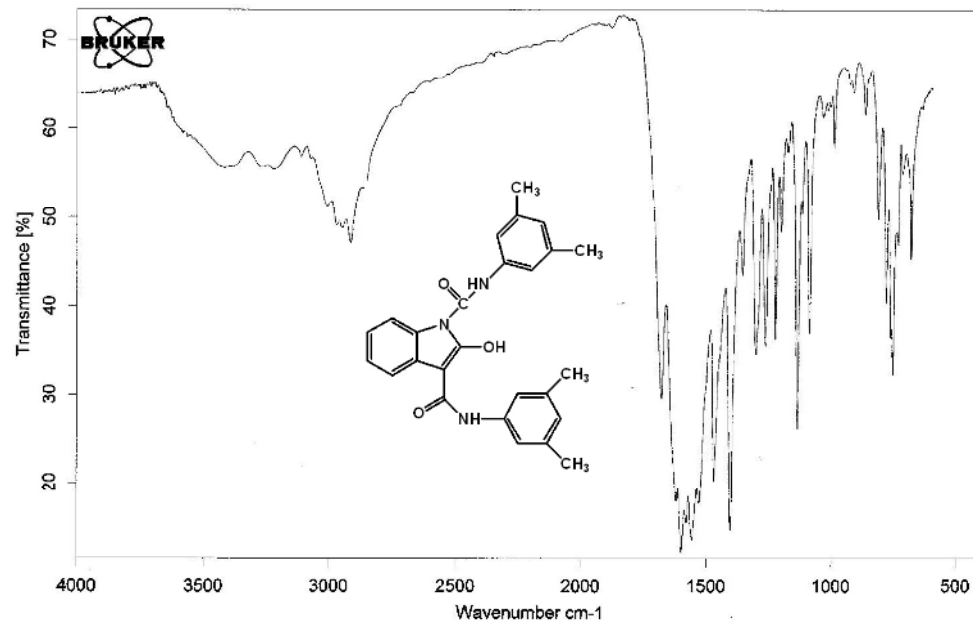


Figure A132 IR Spectrum of Compound 380.

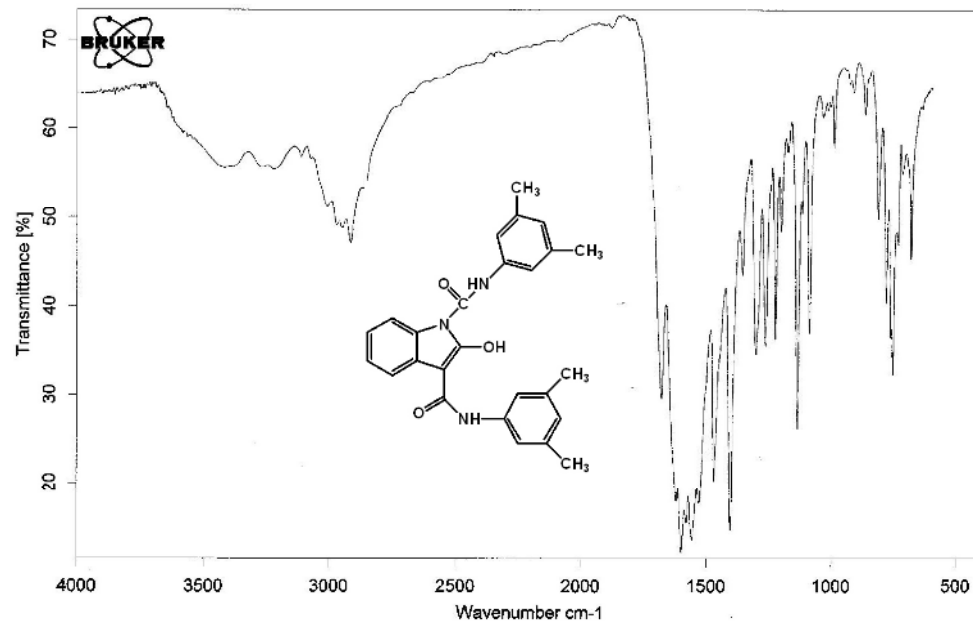


Figure A132 IR Spectrum of Compound 380.

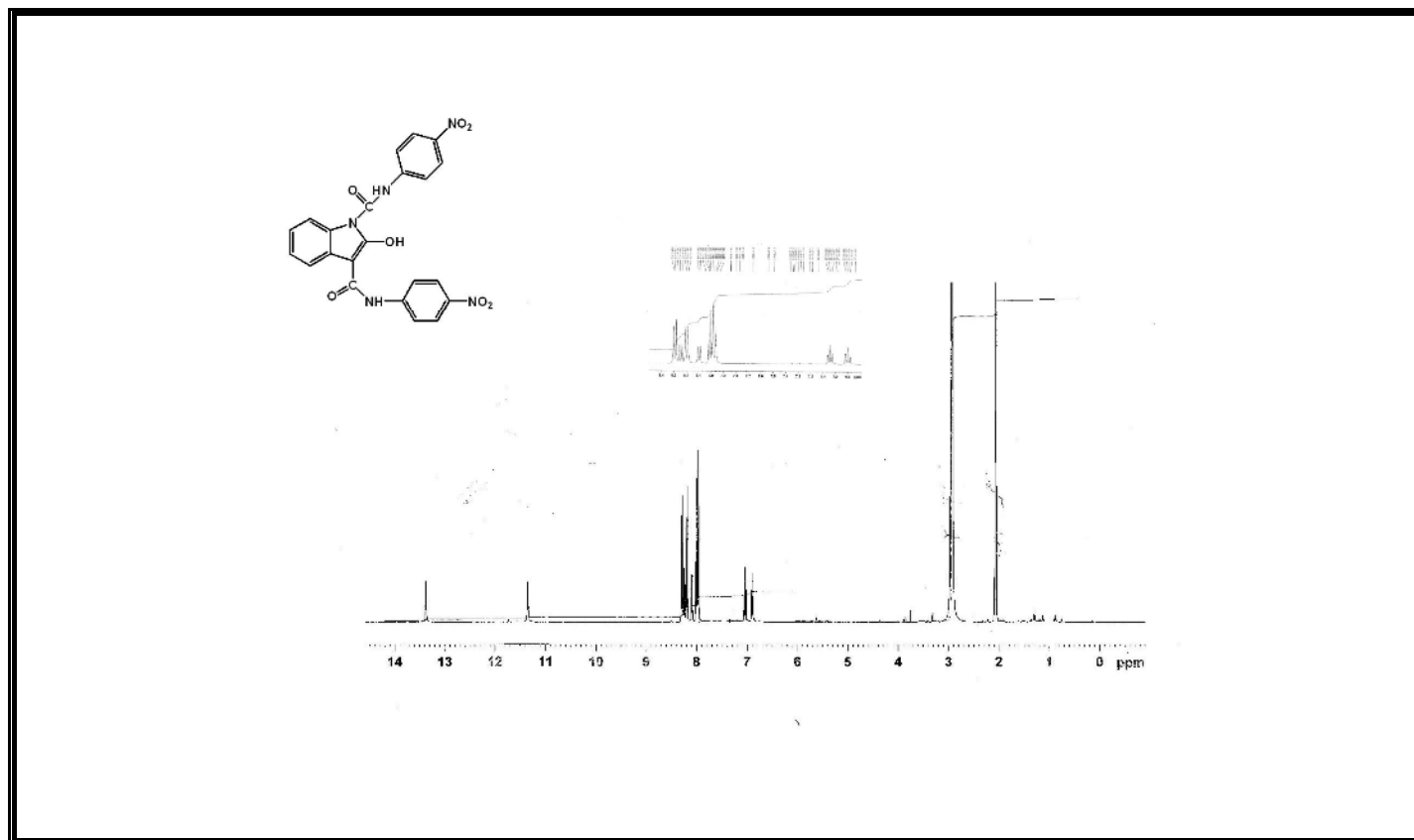


Figure A133 ^1H -NMR Spectrum of Compound 381.

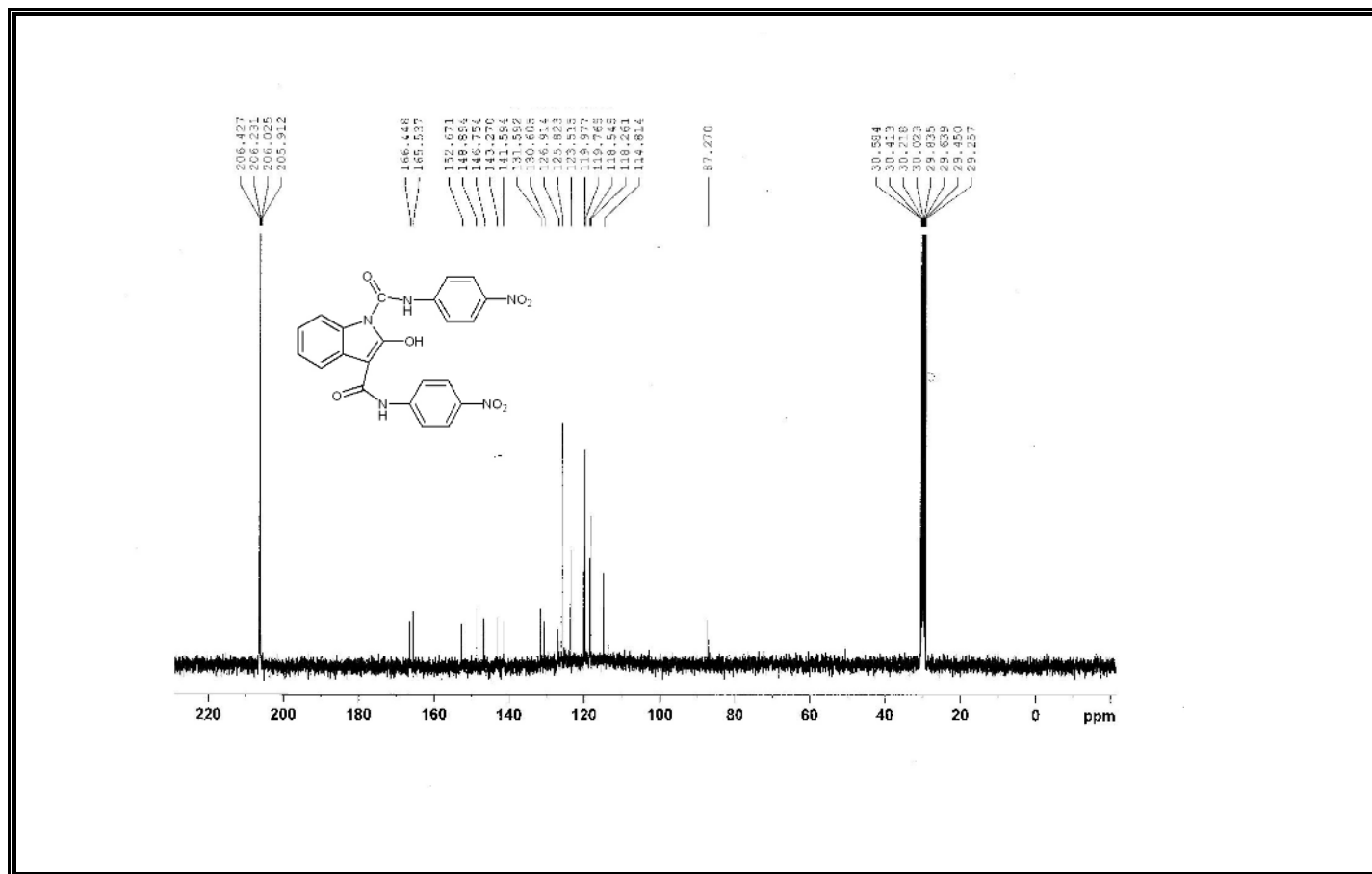


Figure A134 ^{13}C -NMR Spectrum of Compound 381.

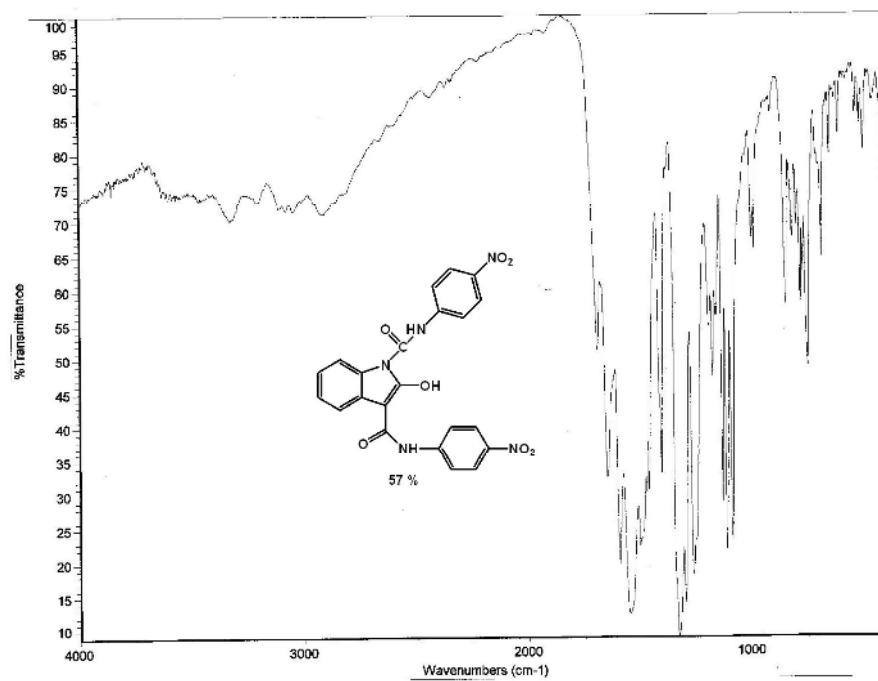


Figure A135 IR Spectrum of Compound 381.

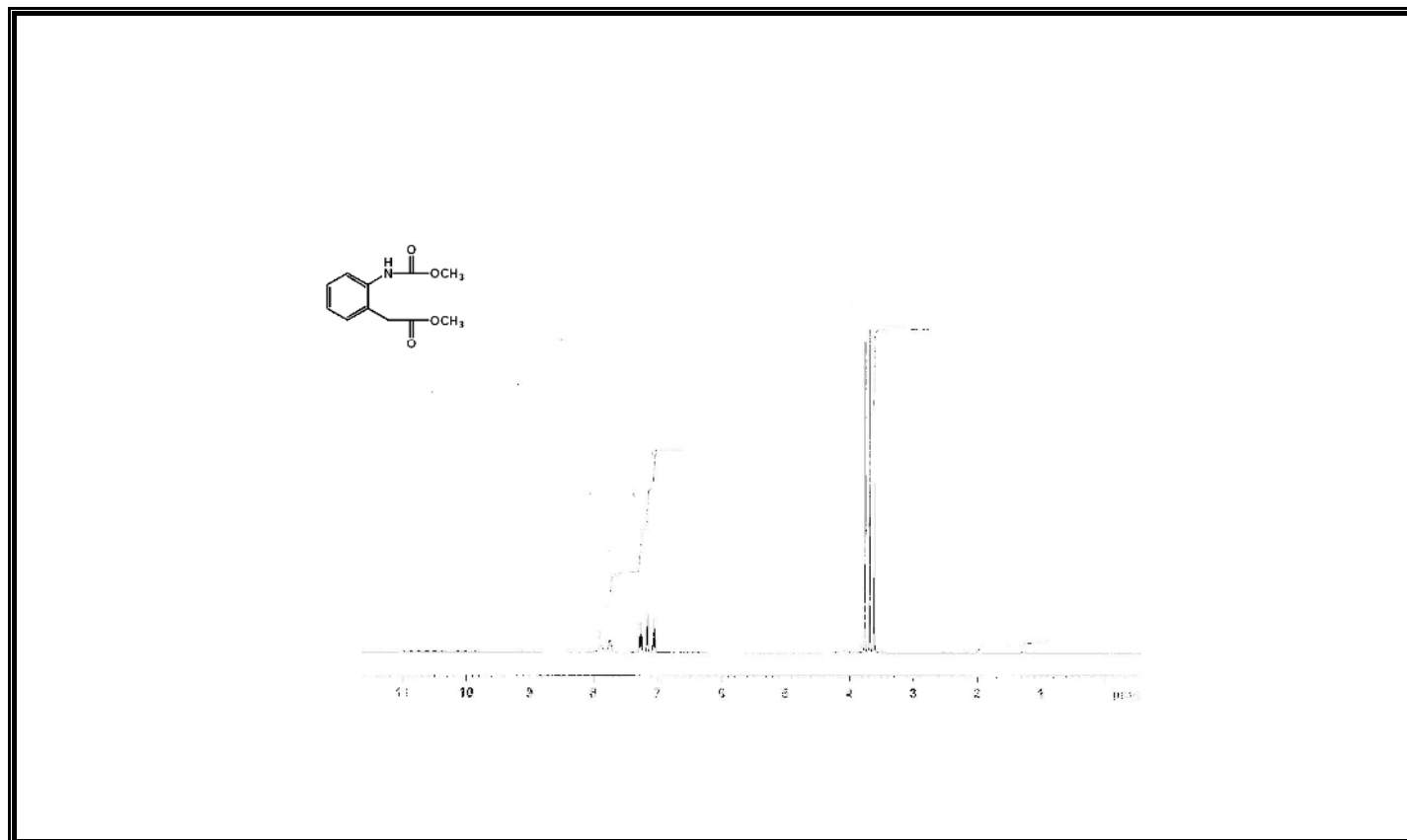


Figure A136 ^1H -NMR Spectrum of Compound 382.

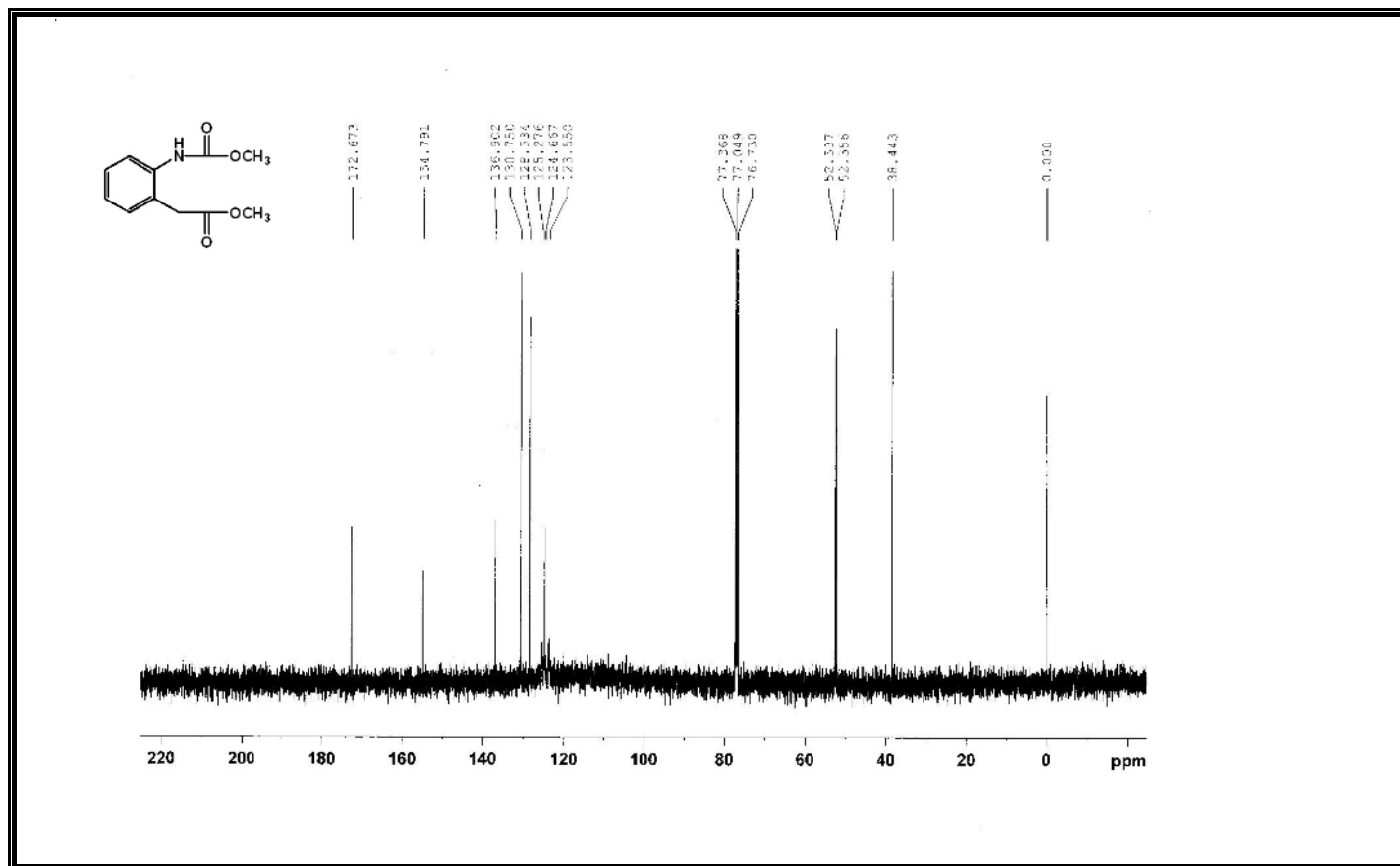


Figure A137 ¹³C-NMR Spectrum of Compound 133.

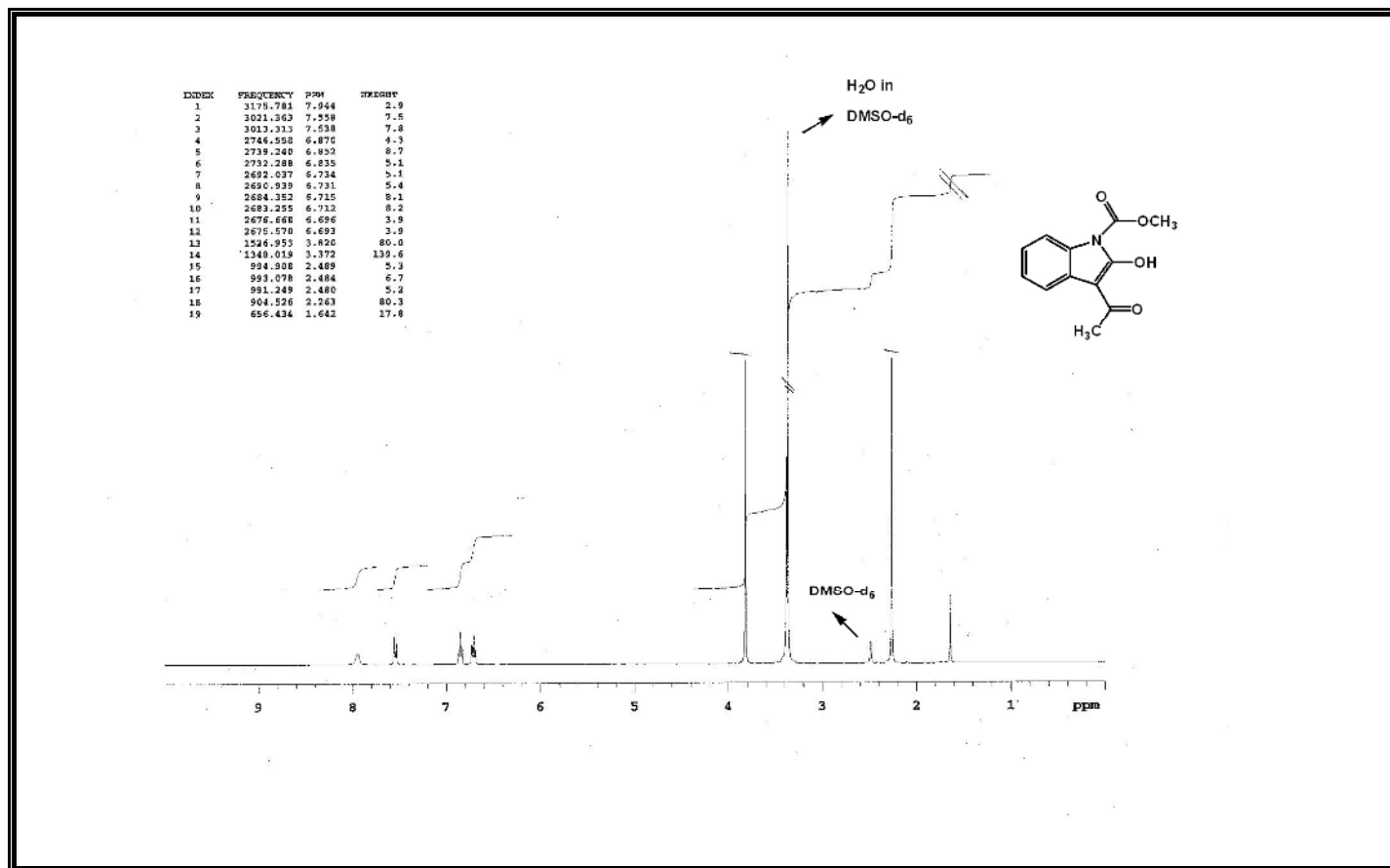


Figure A138 ¹H-NMR Spectrum of Compound 383.

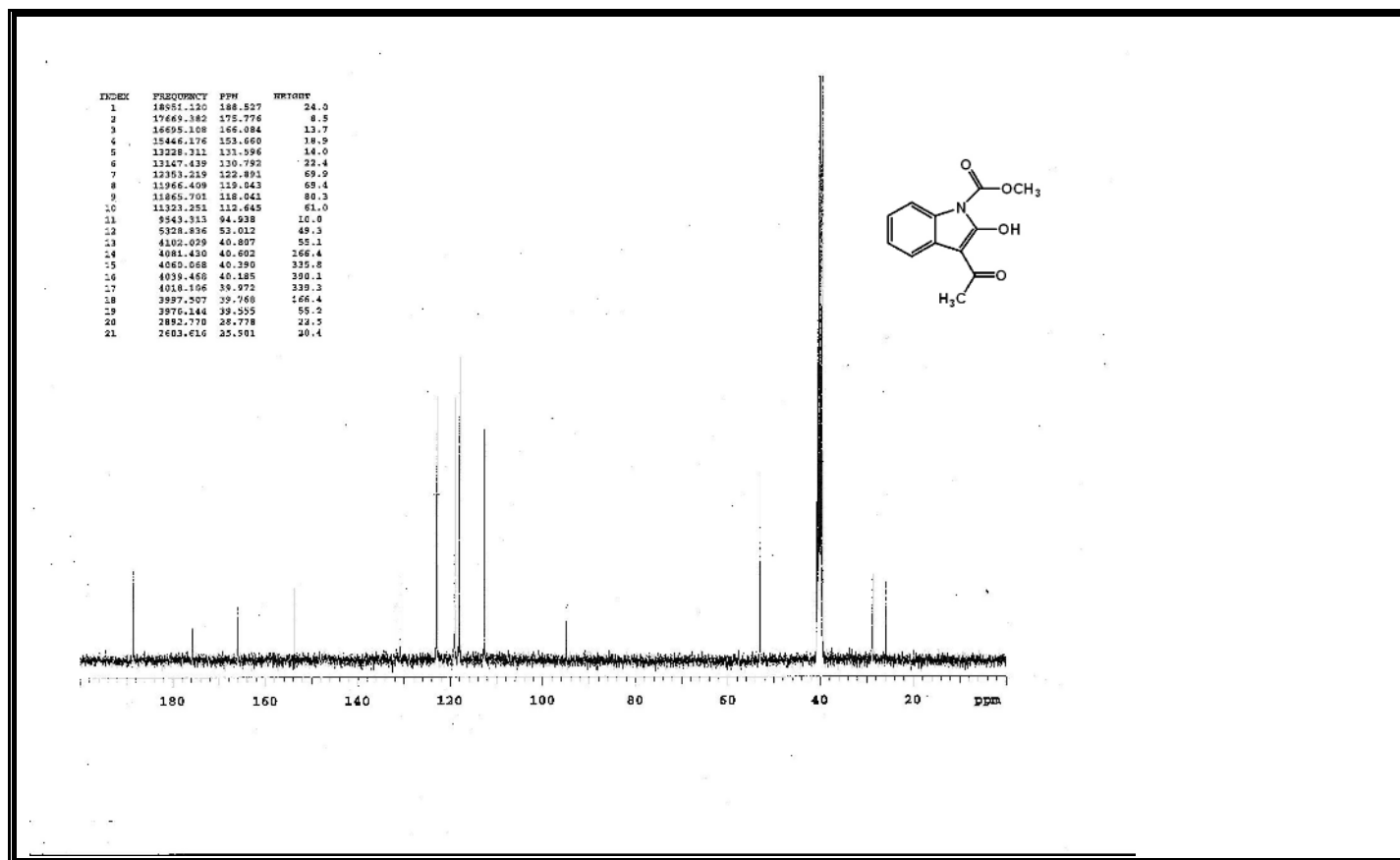


Figure A139 ^{13}C -NMR Spectrum of Compound 383.

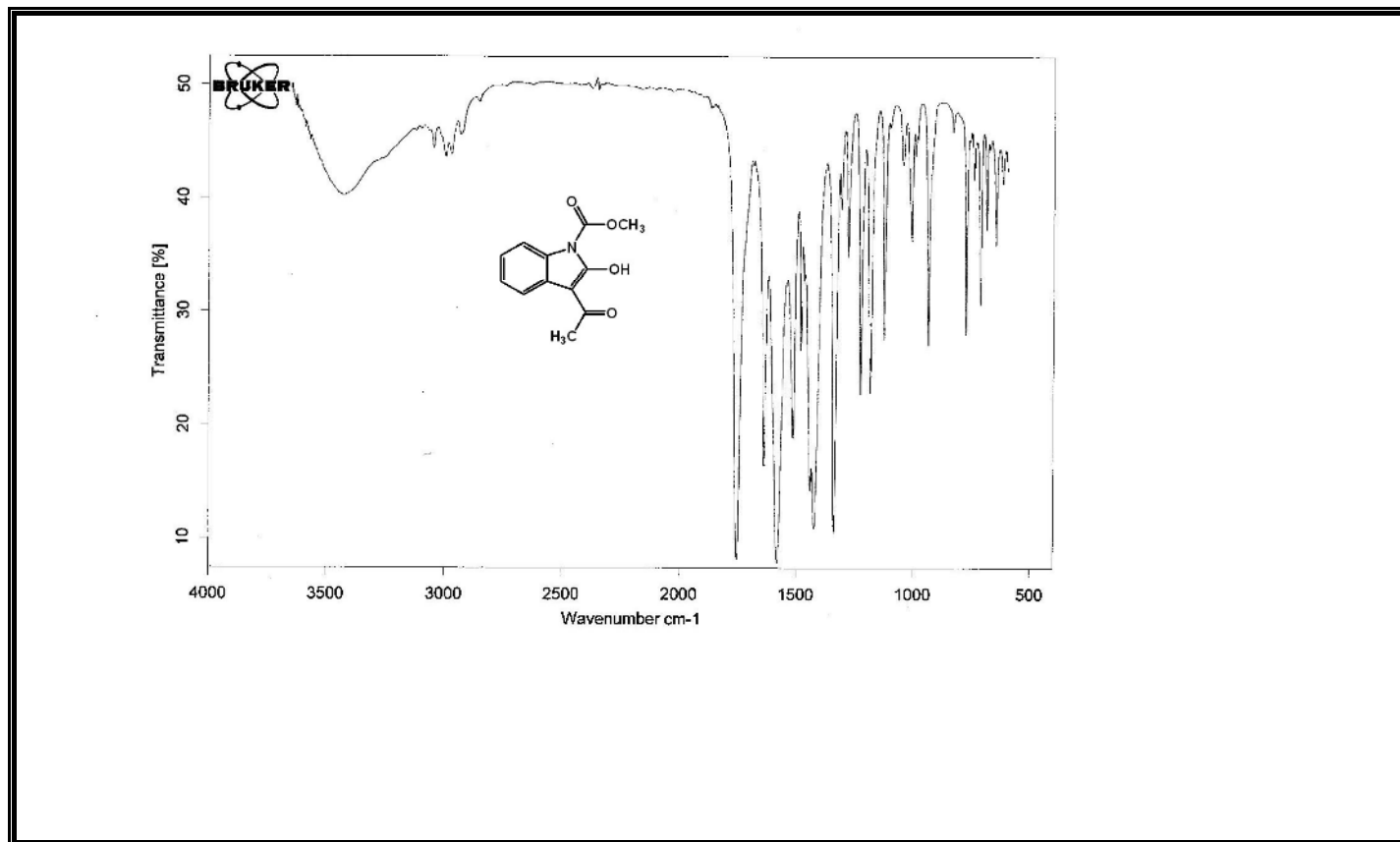


Figure A140 ¹³C-NMR Spectrum of Compound 383.

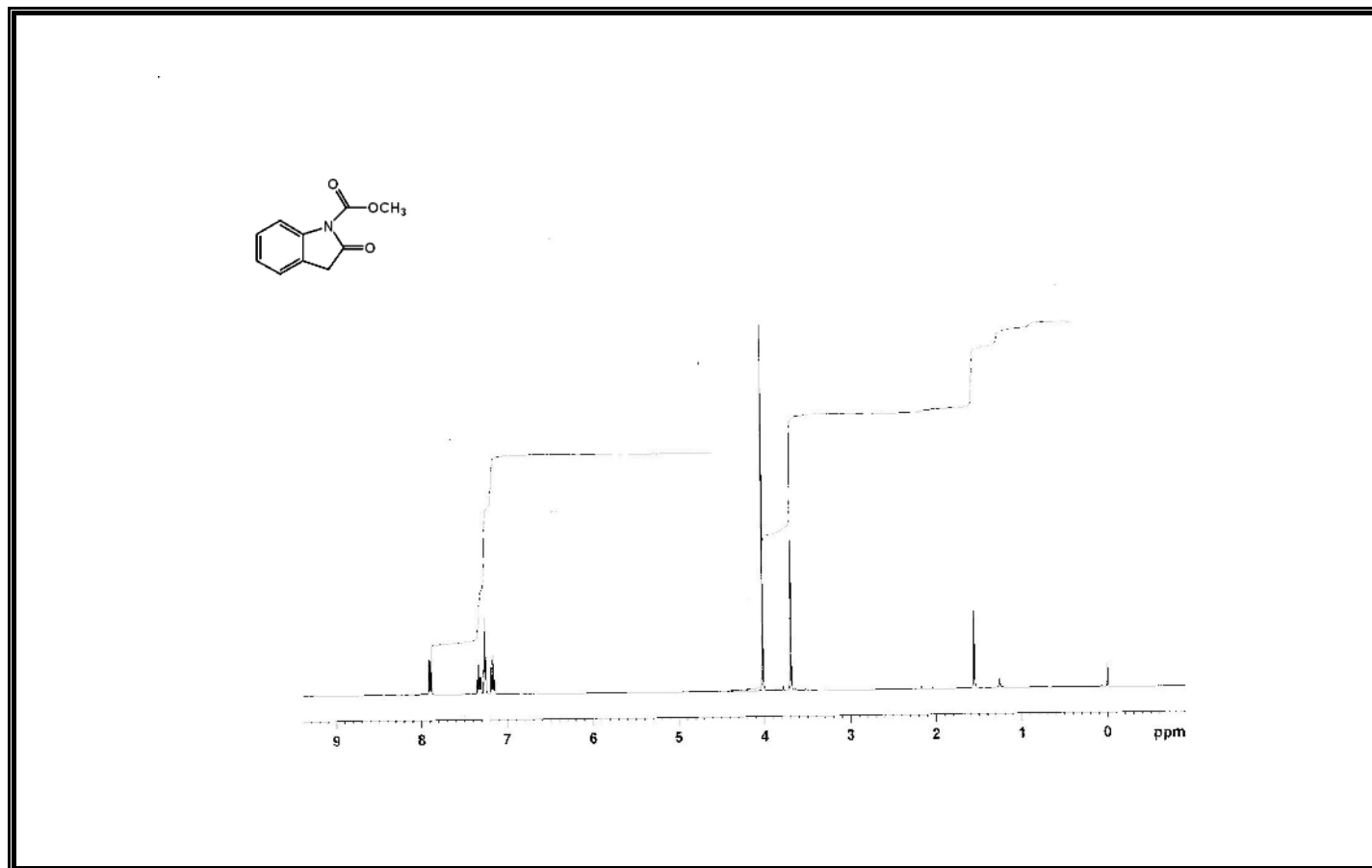


Figure A141 ^1H -NMR Spectrum of Compound **384**.

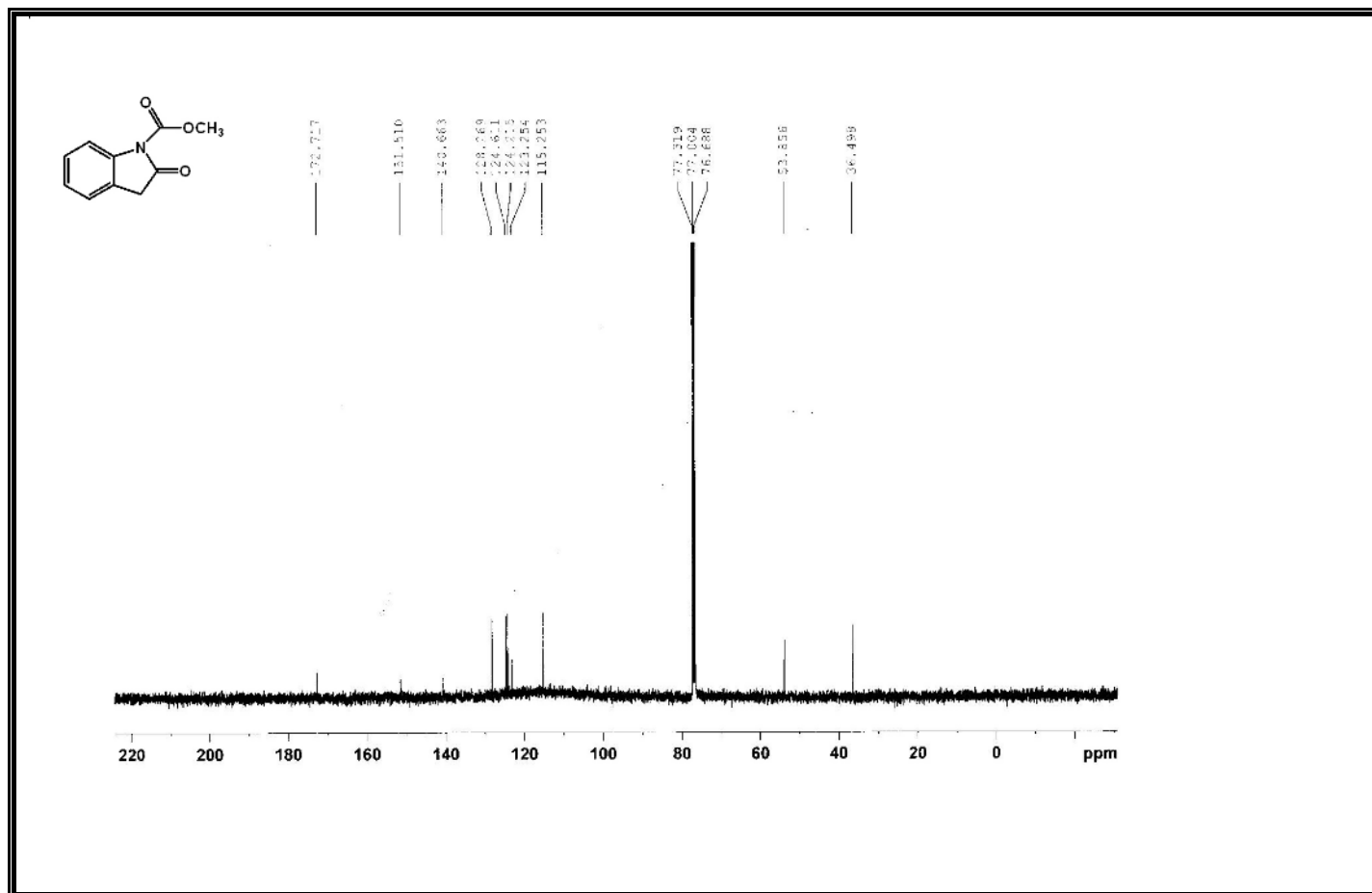


Figure A142 ¹³C-NMR Spectrum of Compound 384.

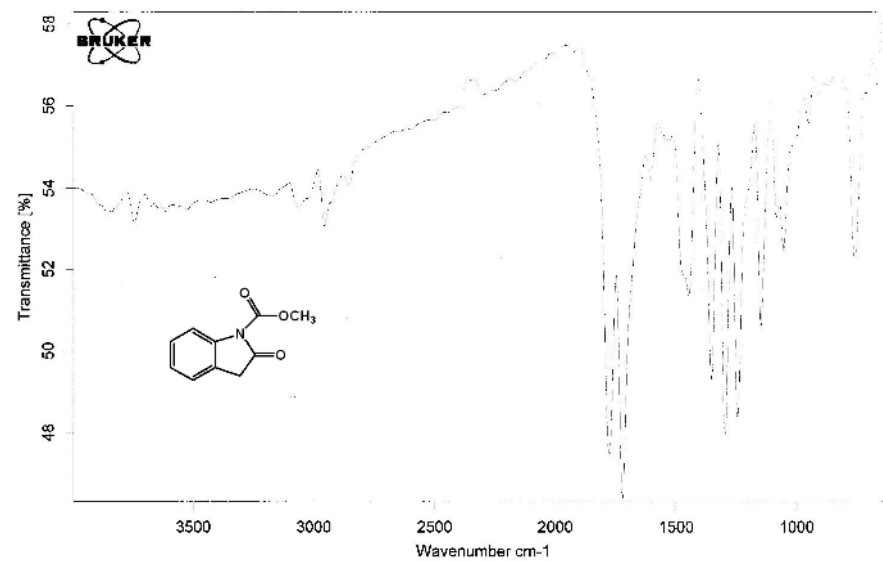


Figure A143 IR Spectrum of Compound 384.

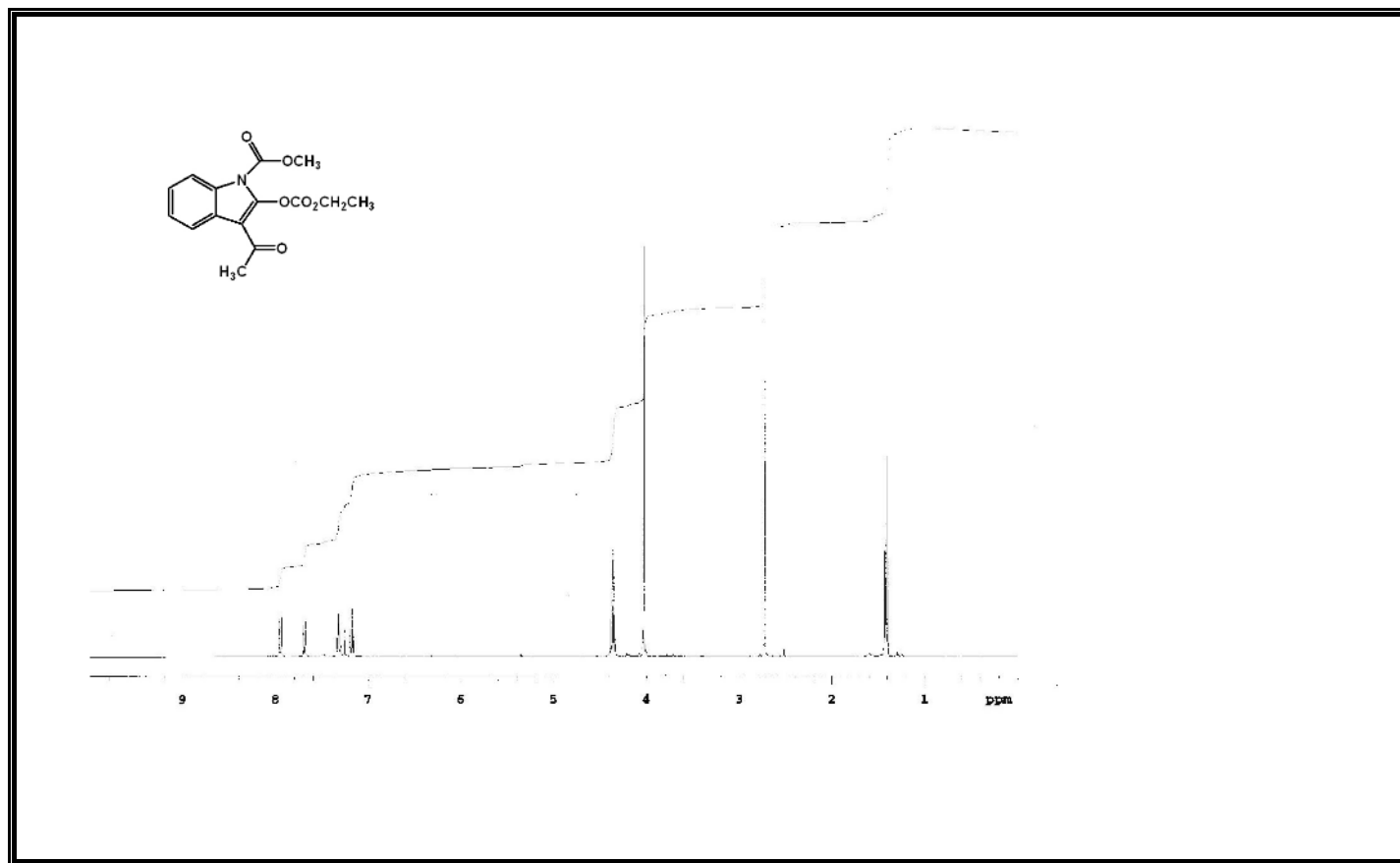


Figure A144 ^1H -NMR Spectrum of Compound 387.

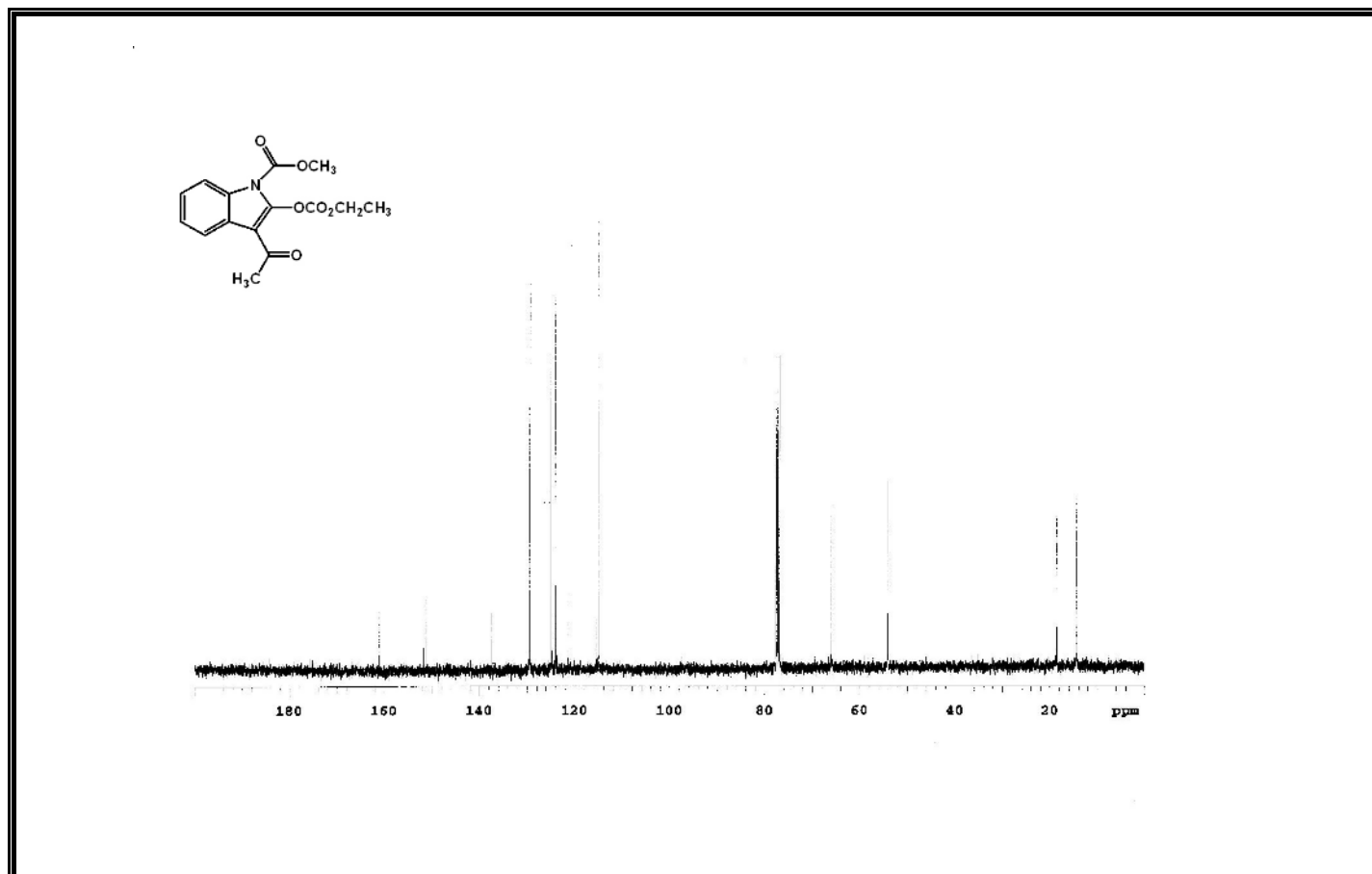


Figure A145 ^{13}C -NMR Spectrum of Compound 387.

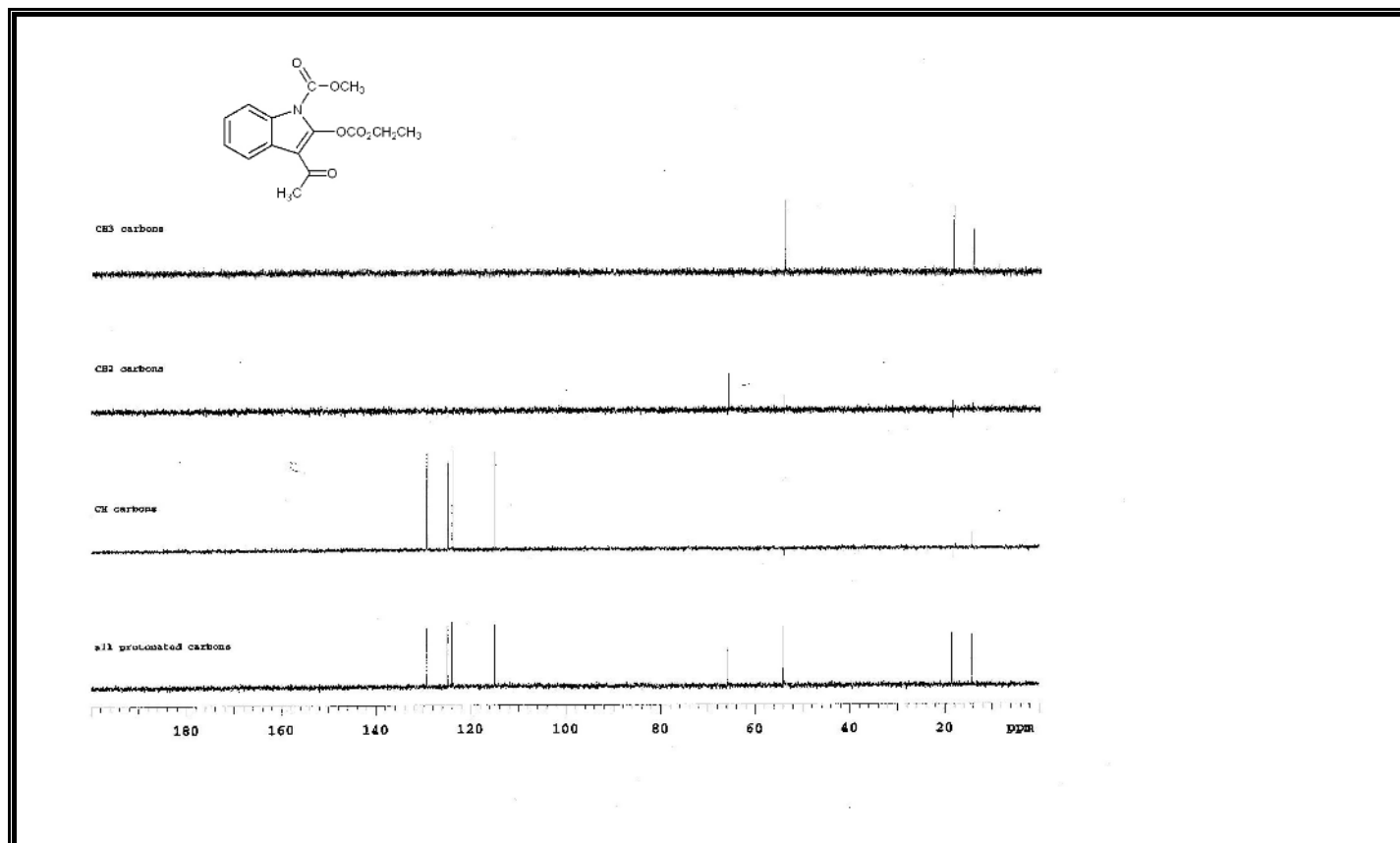


Figure A146 DEPT Spectrum of Compound 387.

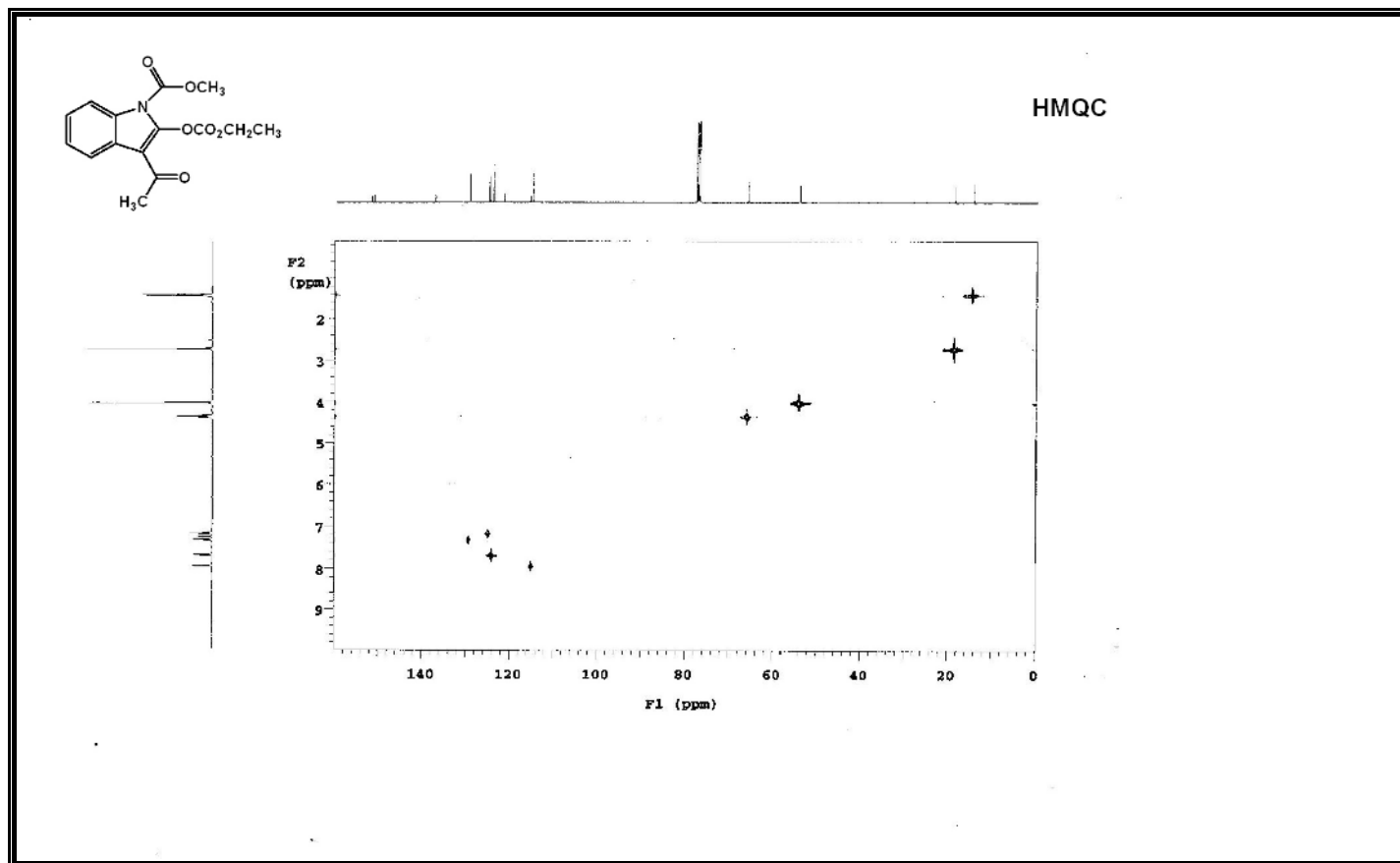


Figure A147 HMQC Spectrum of Compound 387.

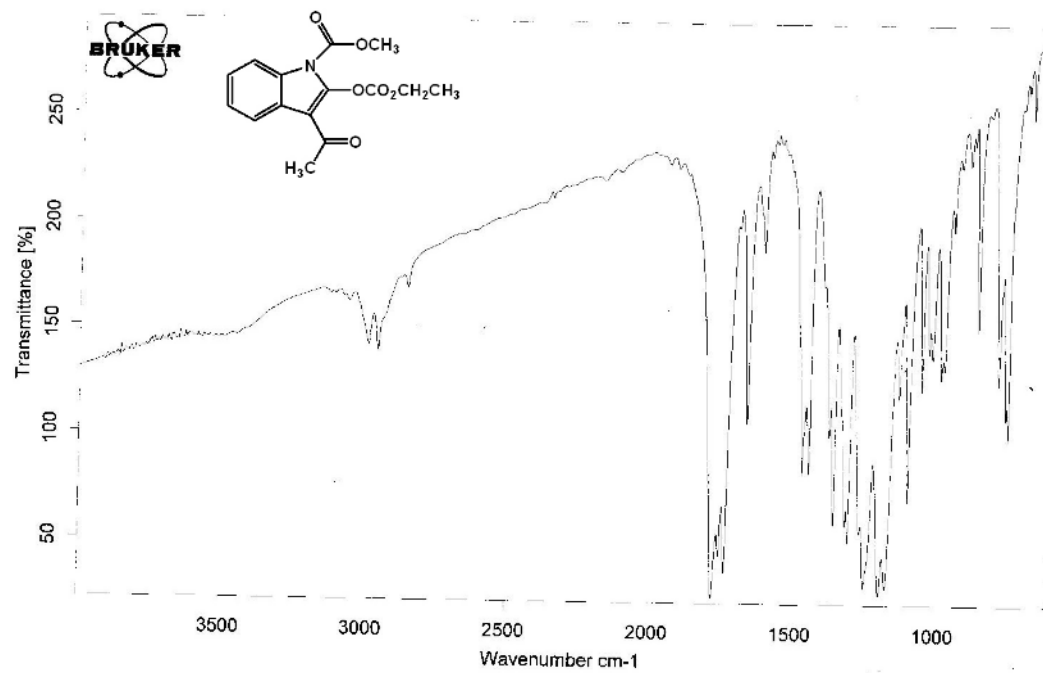


Figure A148 IR Spectrum of Compound 387.

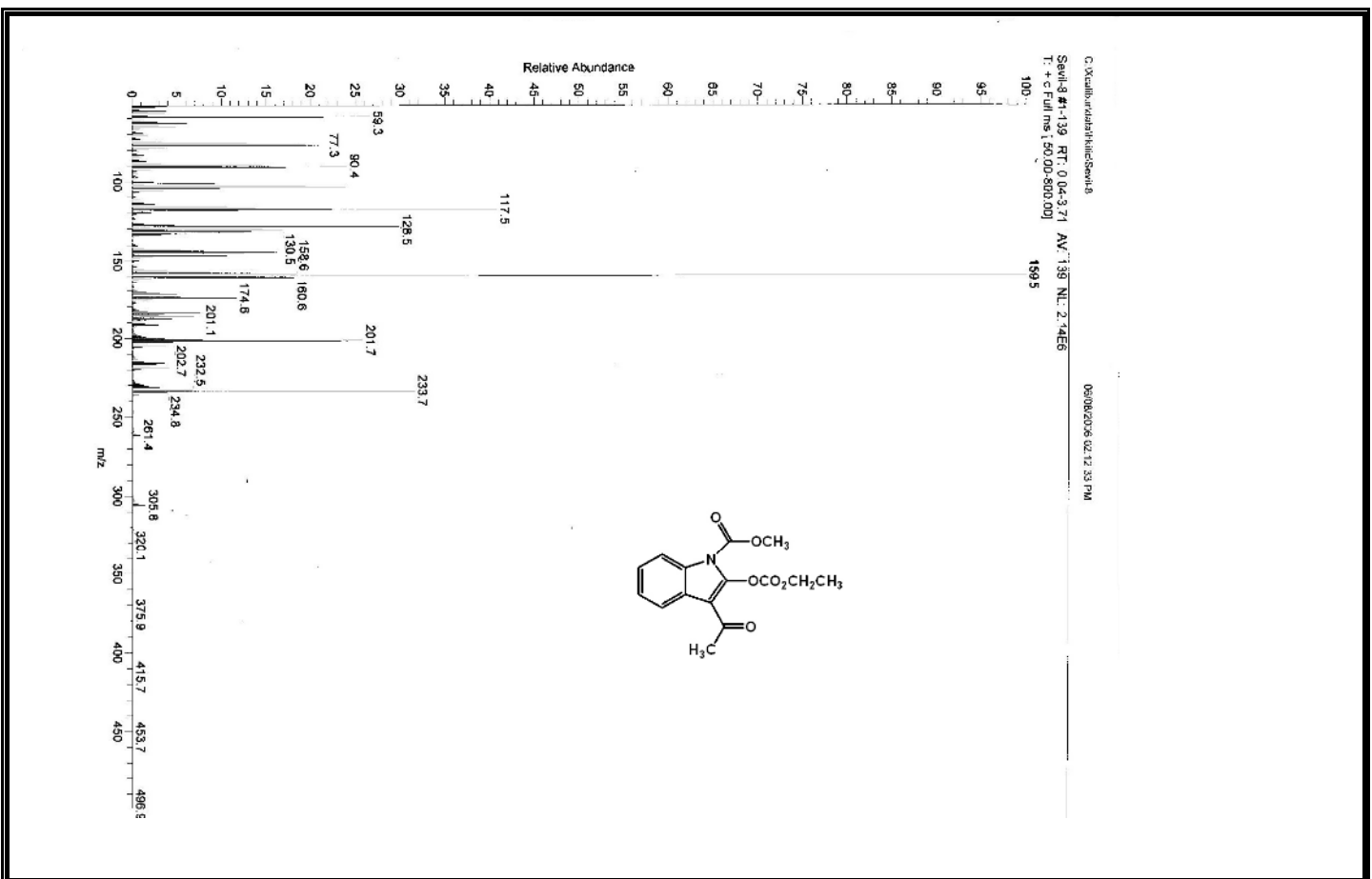


Figure A149 Mass Spectrum of Compound 387.

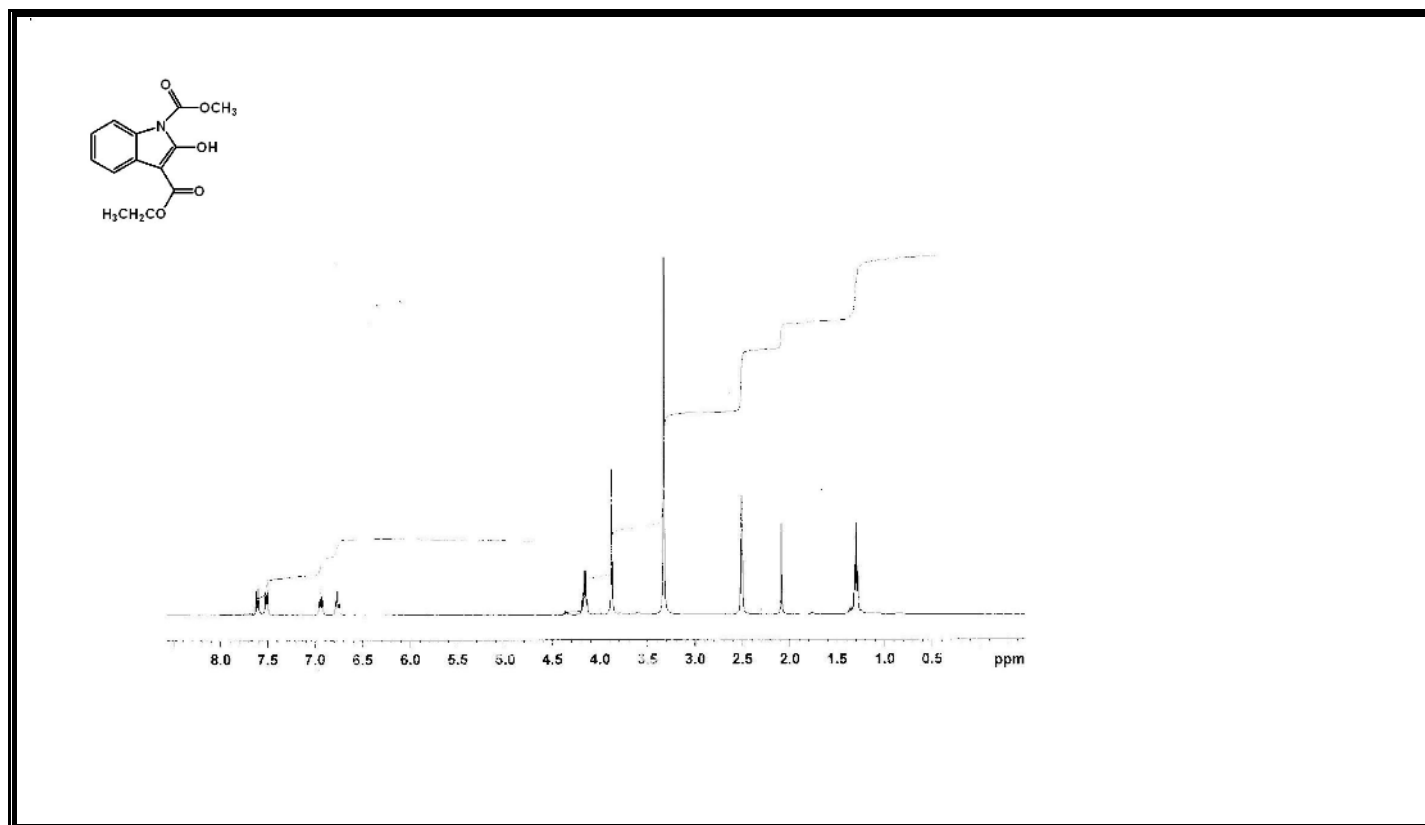


Figure A150 ^1H -NMR Spectrum of Compound 388.

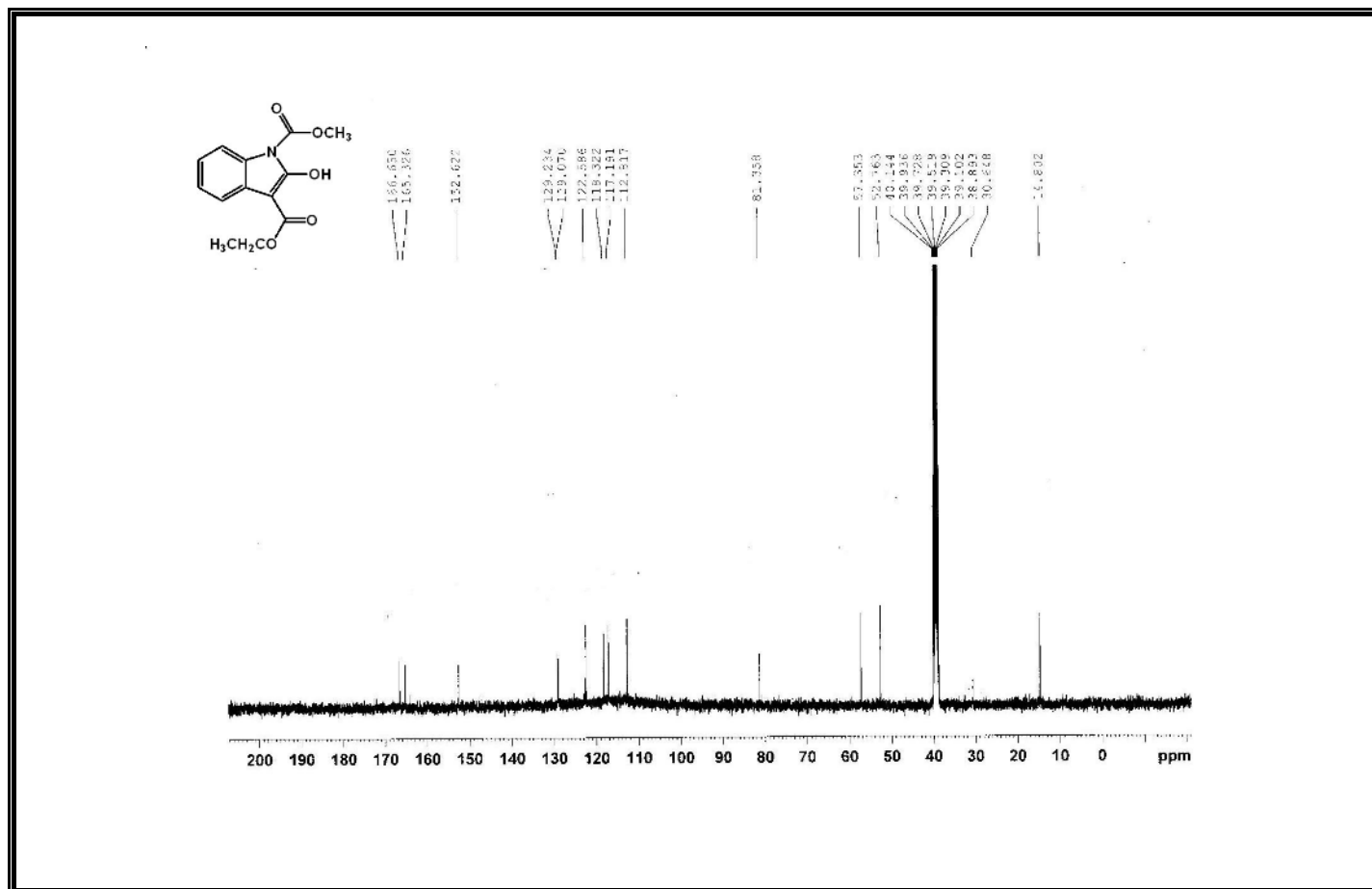


Figure A151 ^{13}C -NMR Spectrum of Compound 388

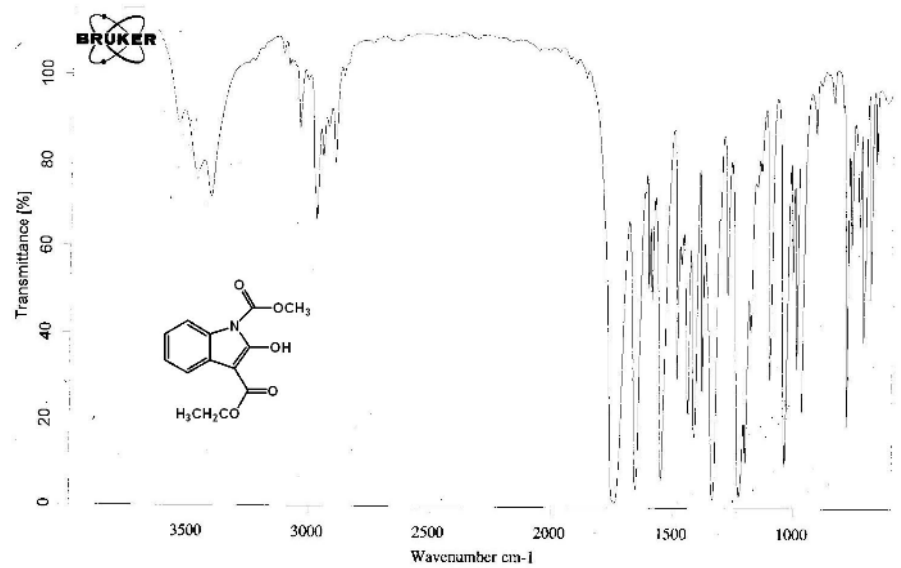


Figure A152 IR Spectrum of Compound 388.

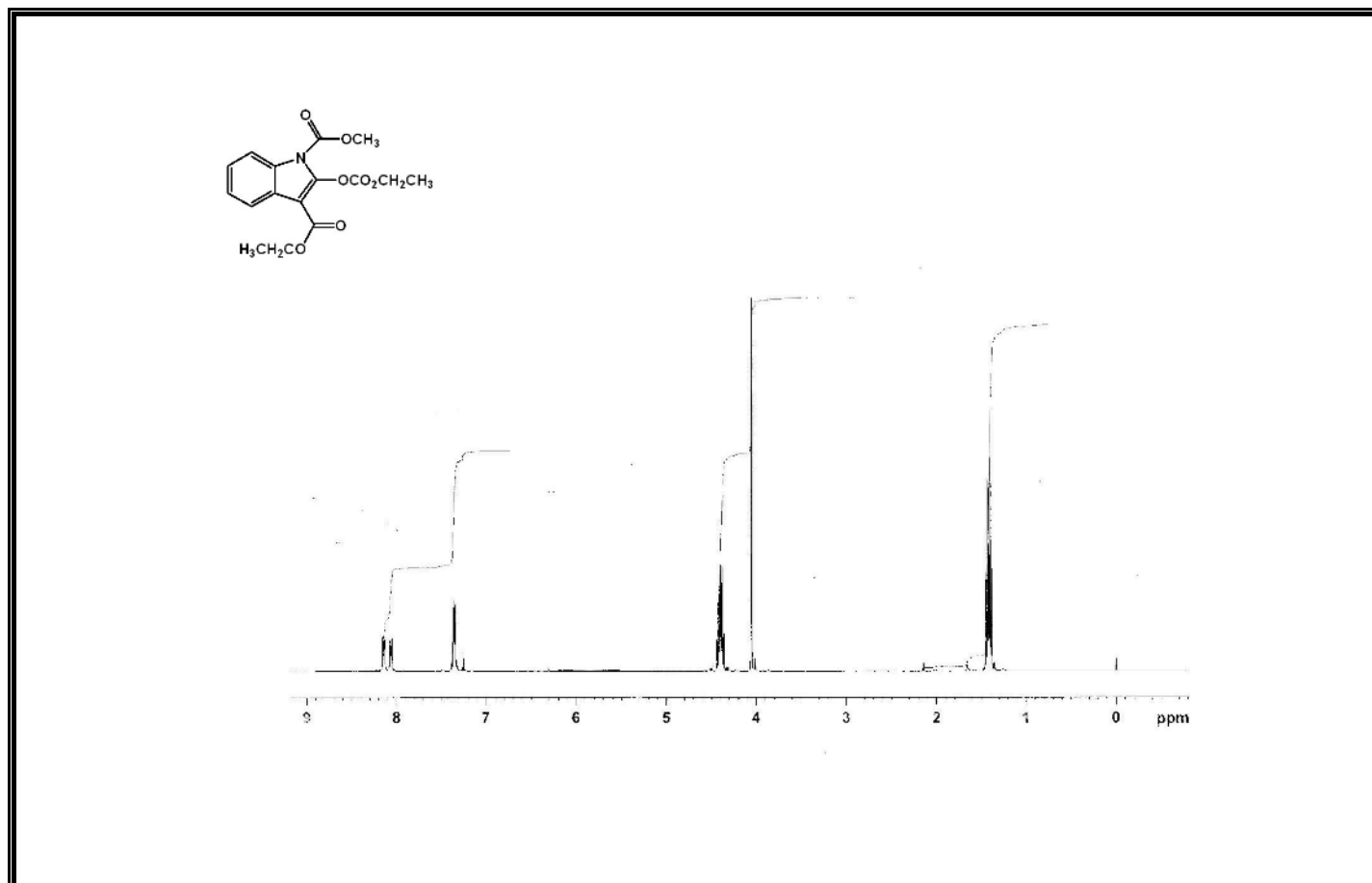


Figure A153 ^1H Spectrum of Compound 390.

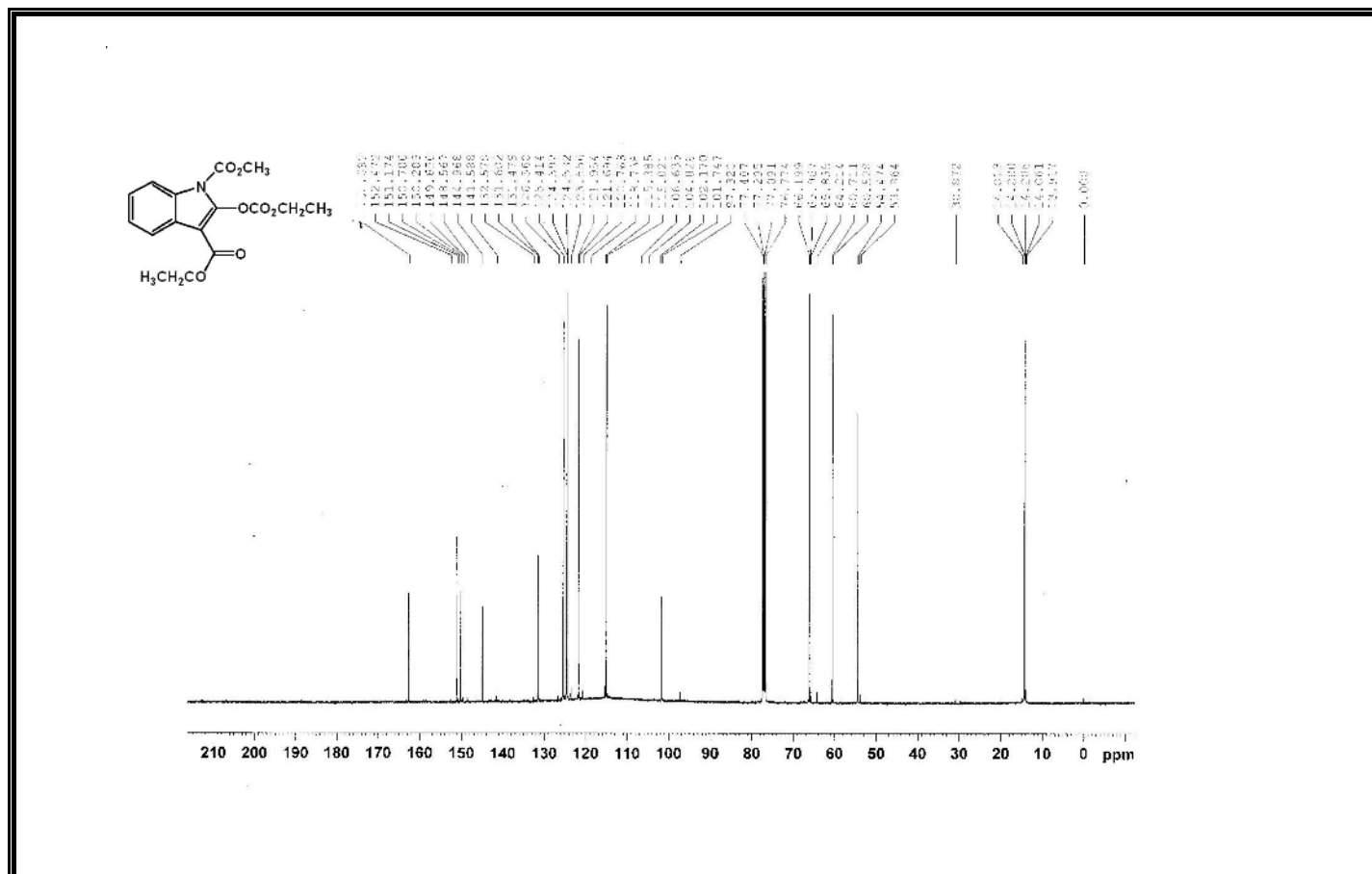


Figure A154 ¹³C-NMR spectrum of Compound 390.

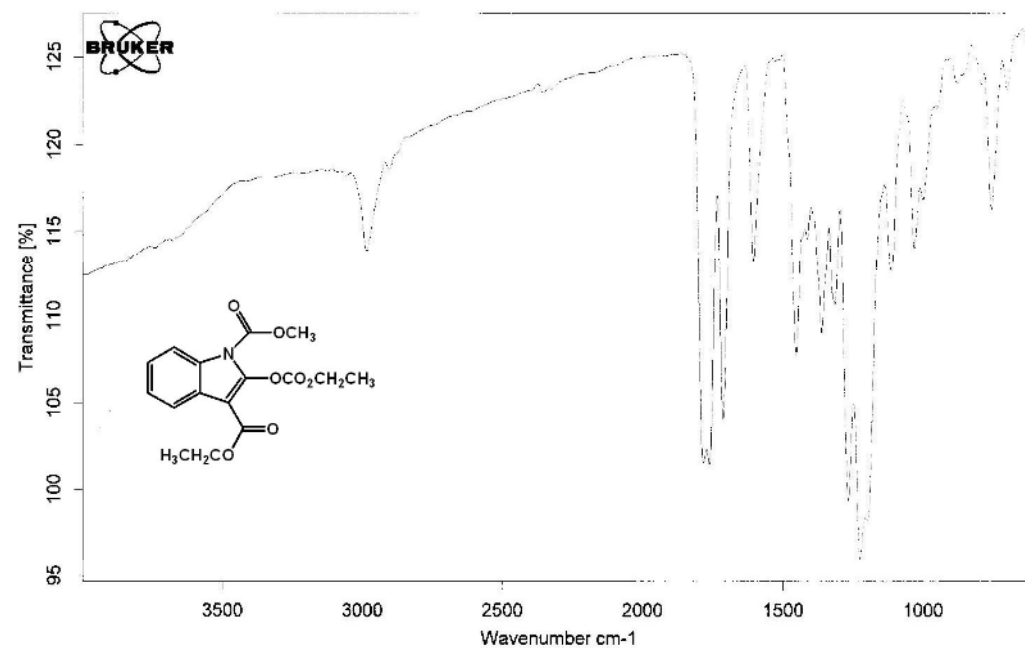


Figure A155 IR Spectrum of Compound 390.

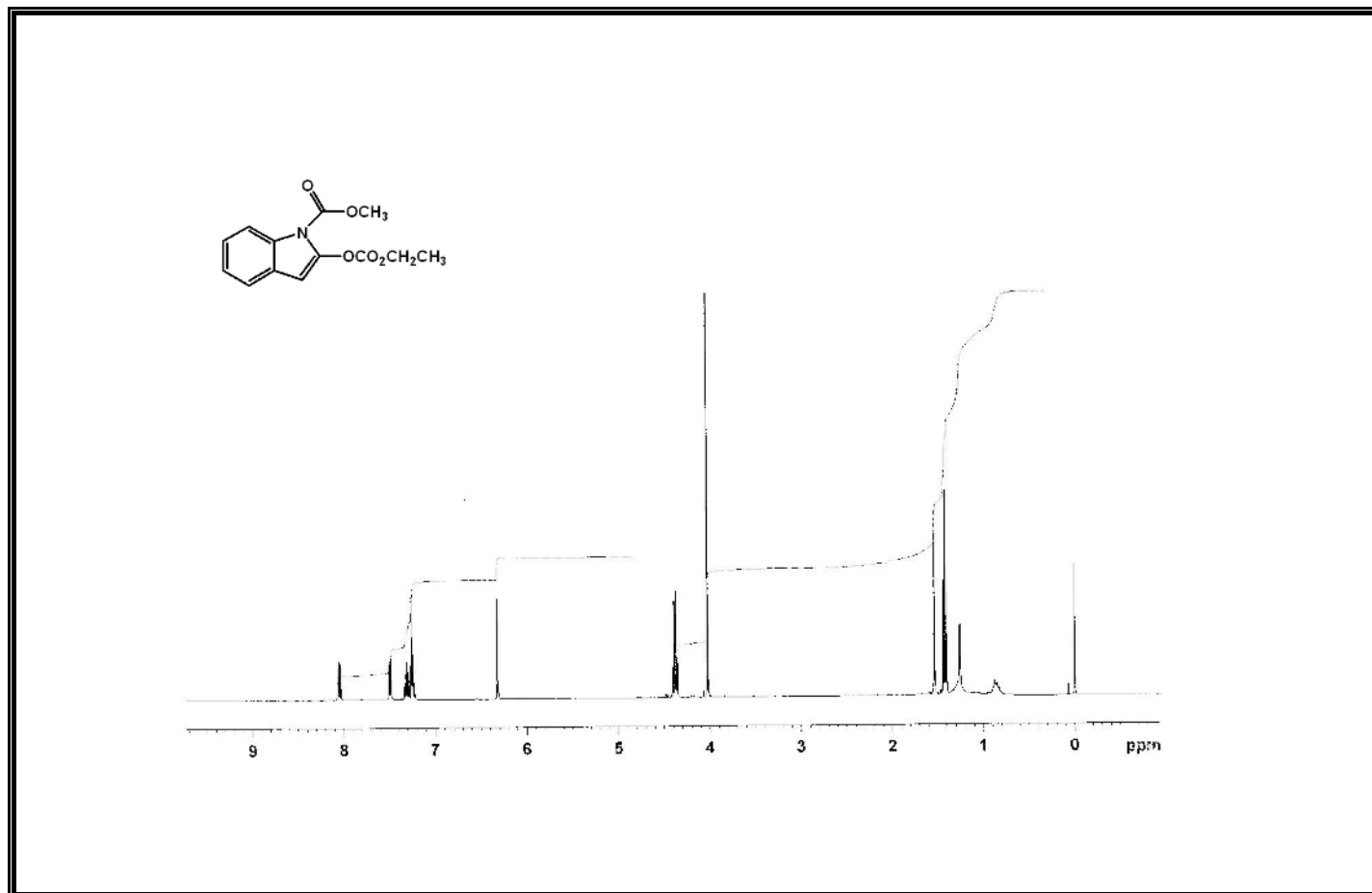


Figure A156 ^1H -NMR Spectrum of Compound **389**.

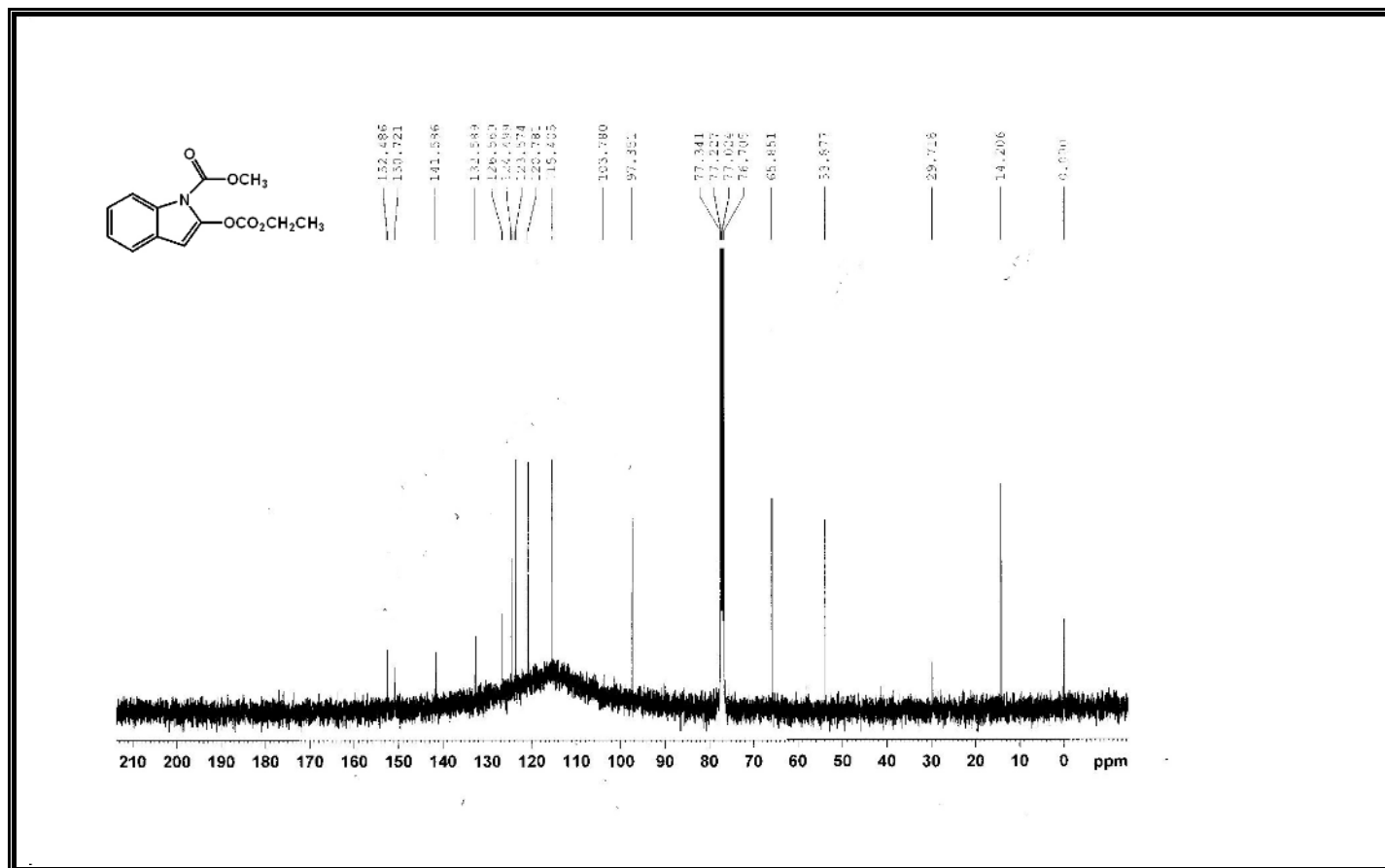


Figure A157 ¹³C-NMR Spectrum of Compound 389.

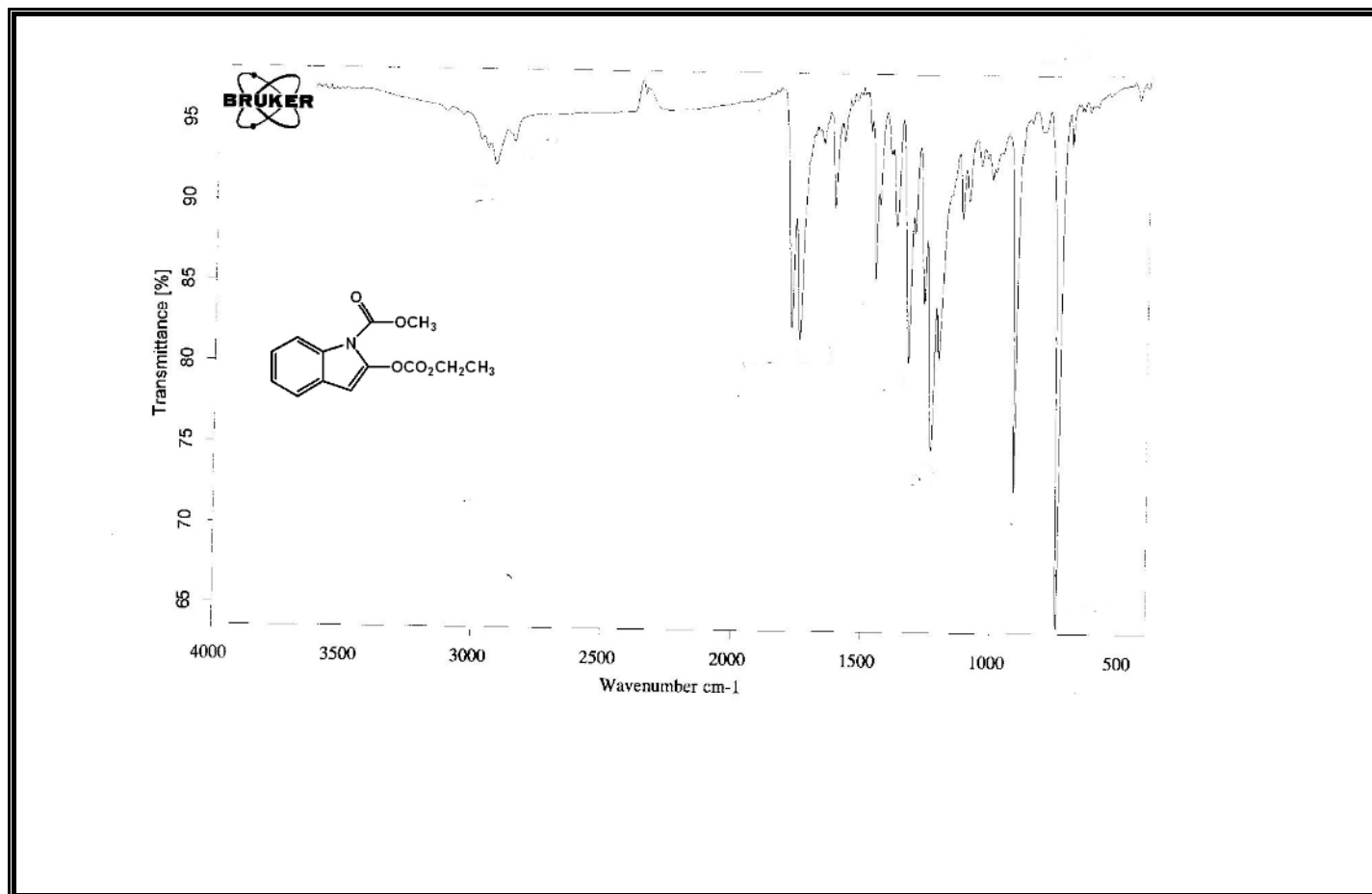


Figure A158 IR Spectrum of Compound 389.

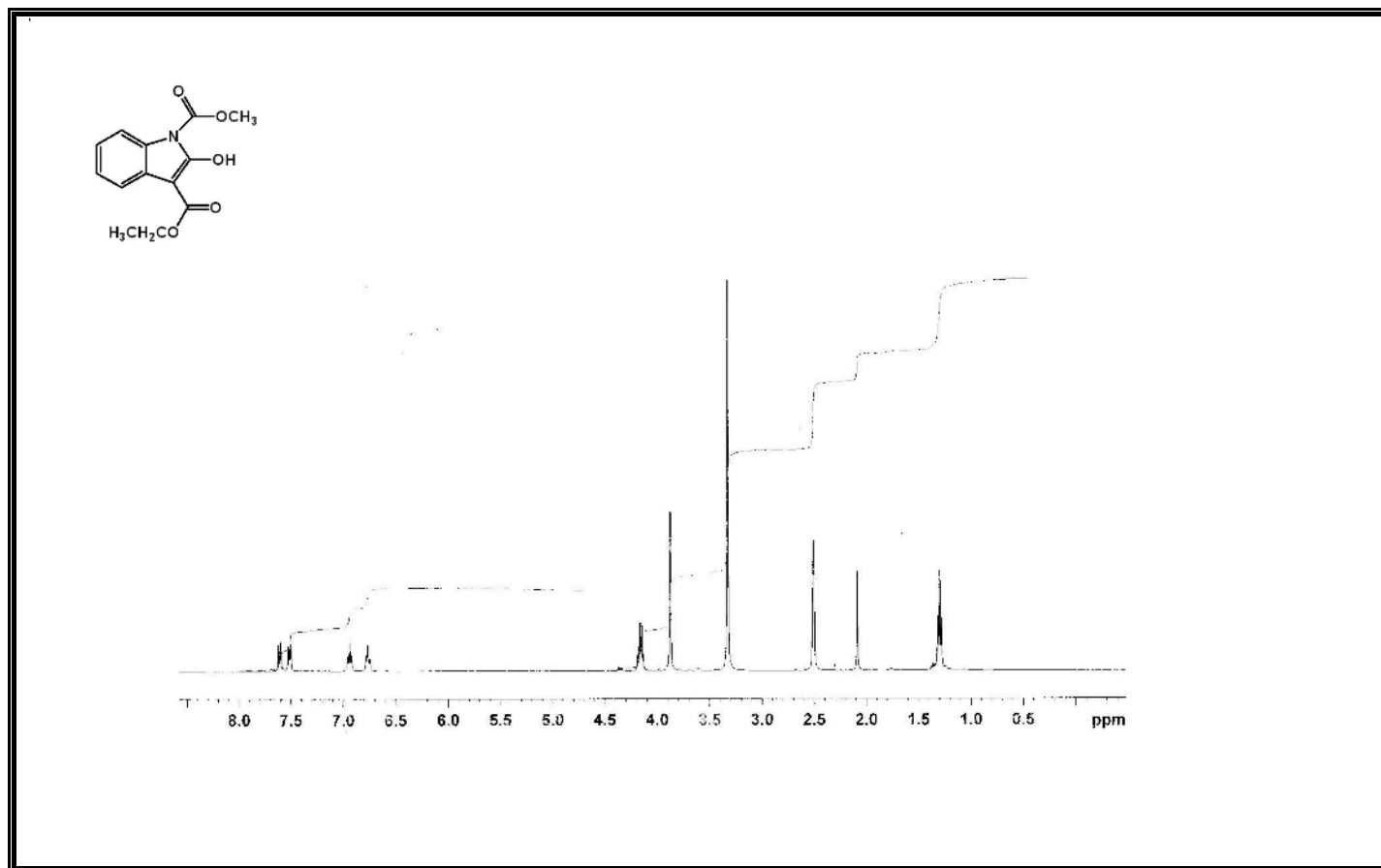


Figure A159 ^1H -NMR Spectrum of Compound **388**.

Figure A160 ^{13}C -NMR Spectrum of Compound **388**.

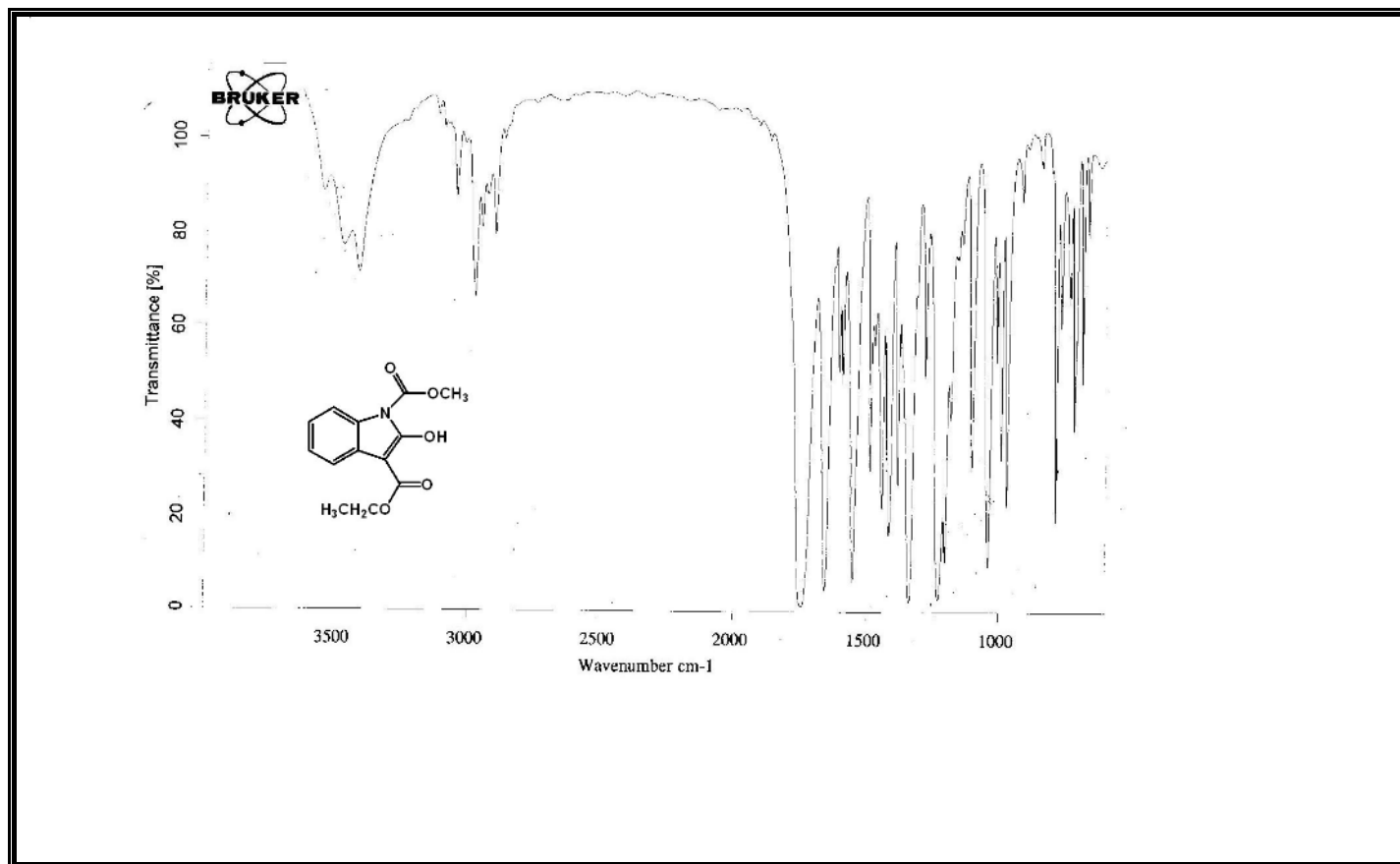


Figure A161 IR Spectrum of Compound 388.

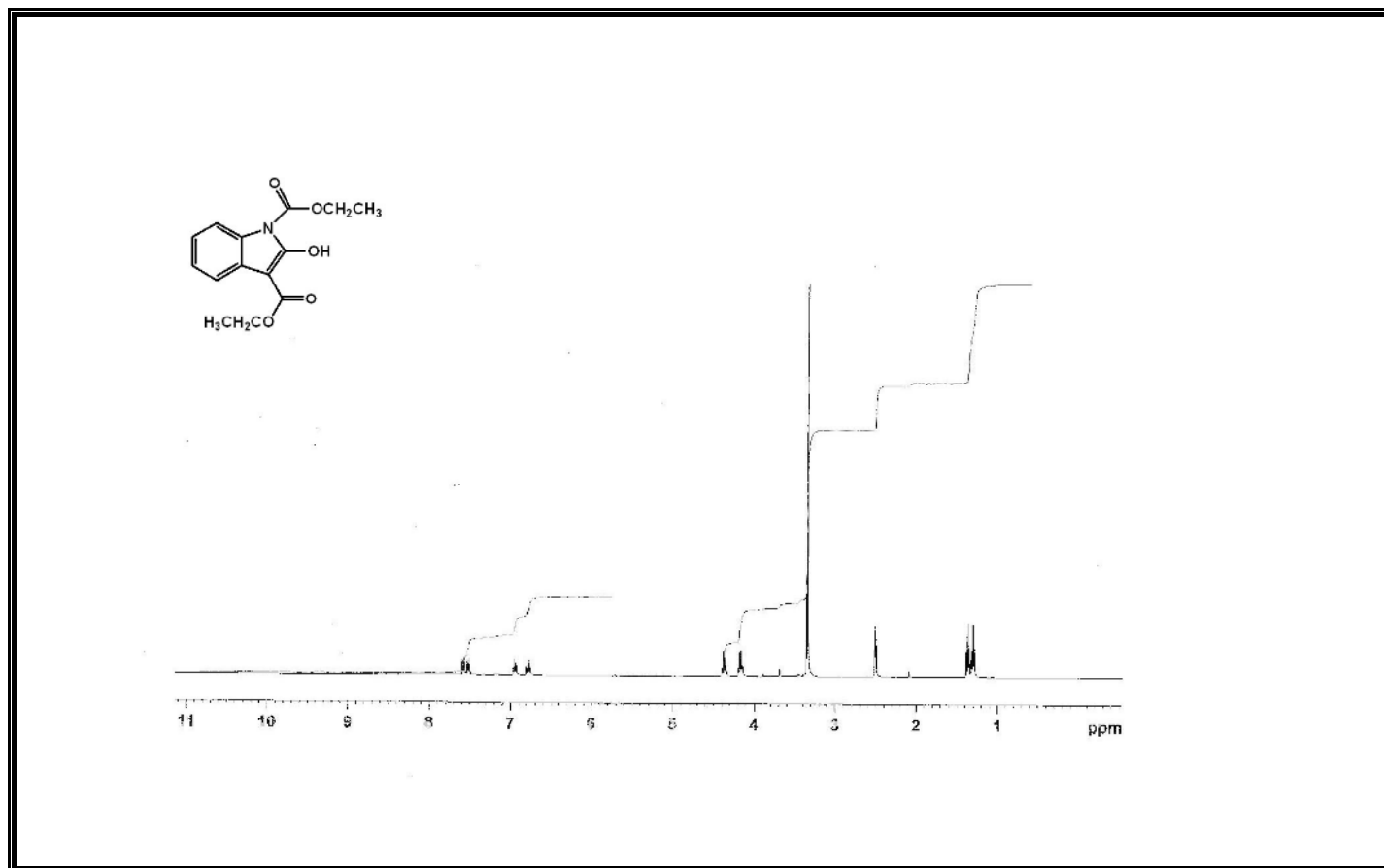


Figure A162 ^1H -NMR Spectrum of Compound **391**.

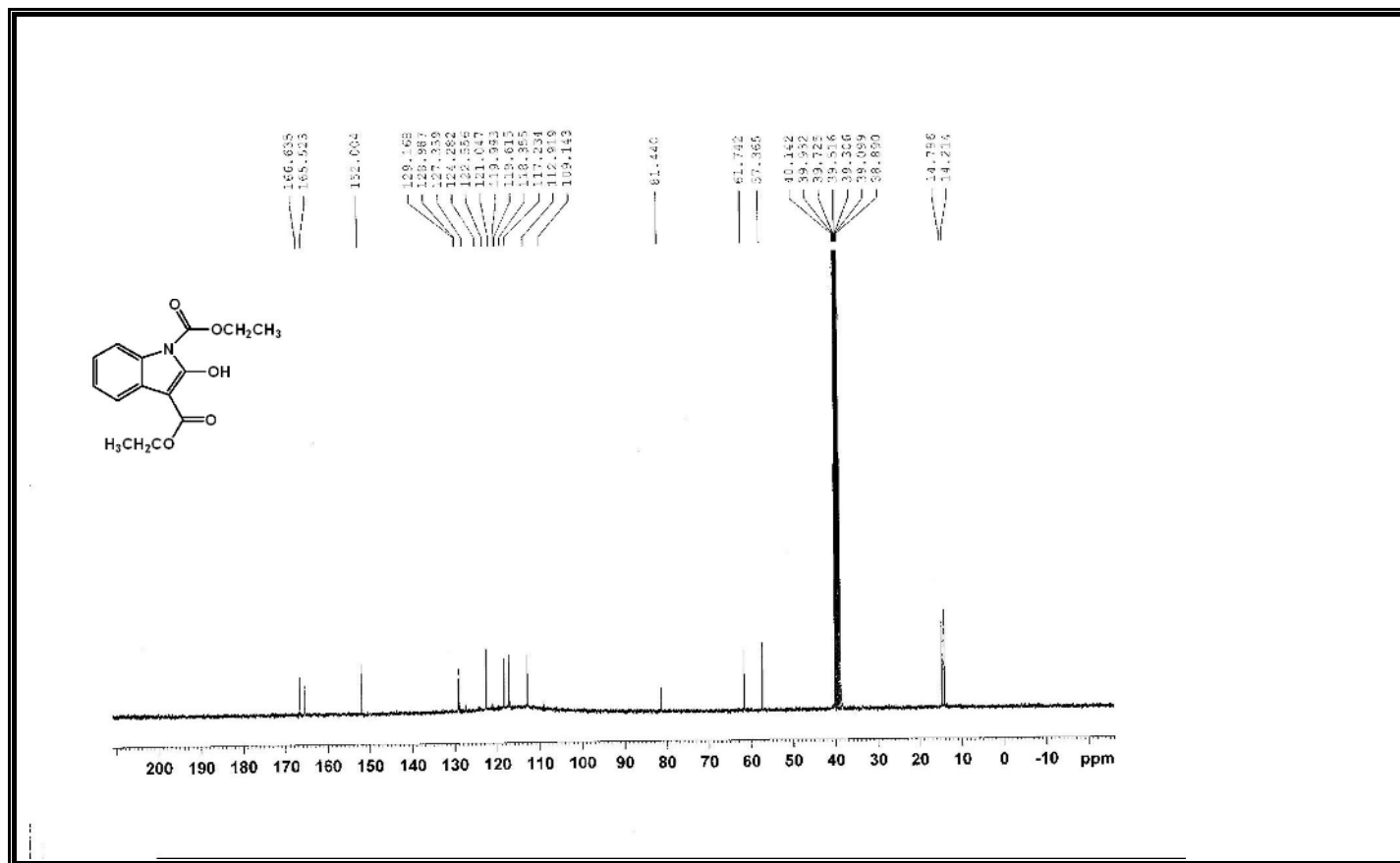
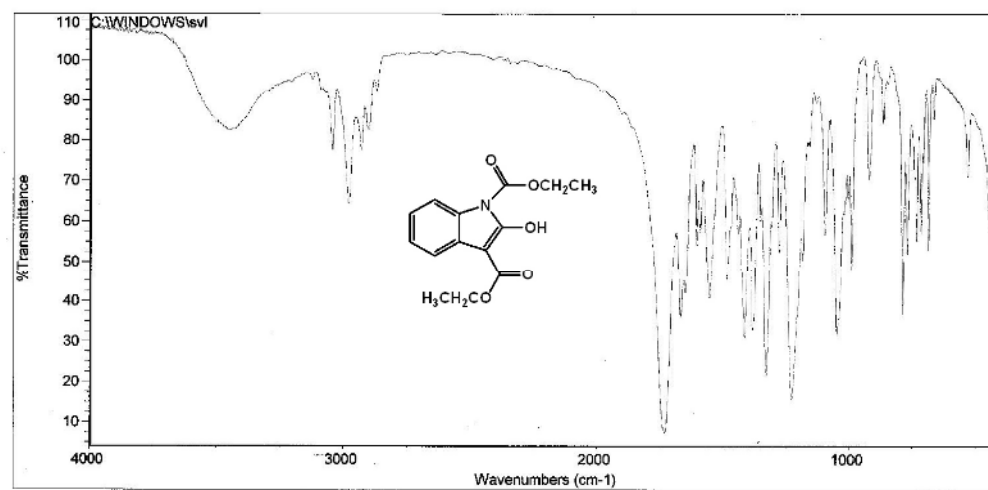


Figure A163 ¹³C-NMR Spectrum of Compound 391.



Sun Dec 31 19:58:06 2006

FIND PEAKS:

Spectrum: C:\WINDOWS\svl
Region: 4000.00 400.00
Absolute threshold: 3.003
Sensitivity: 50

Peak list:

No peaks were found.

Figure A164 IR Spectrum of Compound 391.

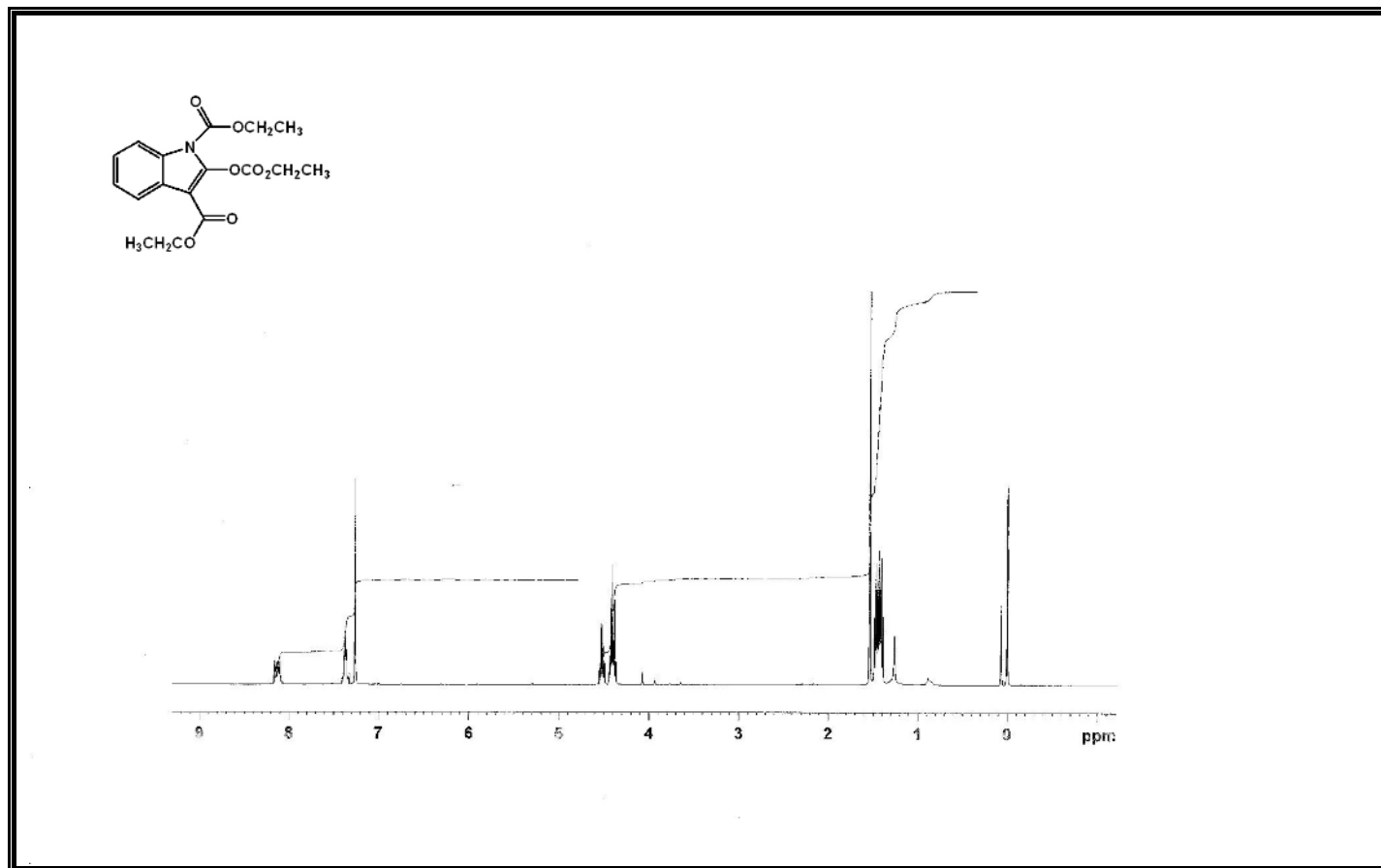


Figure A165 ^1H -NMR Spectrum of Compound 392.

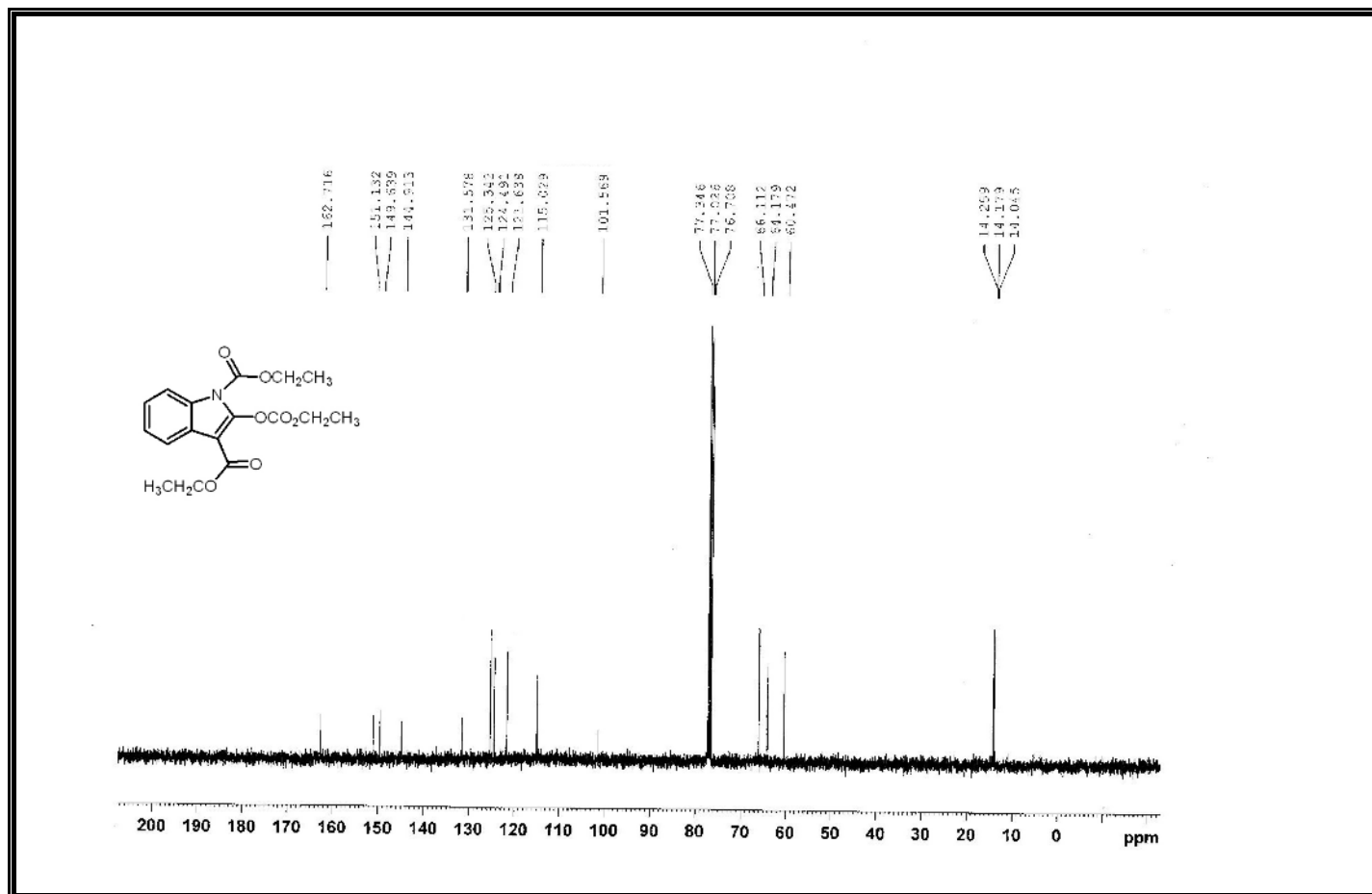


Figure A166 ¹³C-NMR Spectrum of Compound 392.

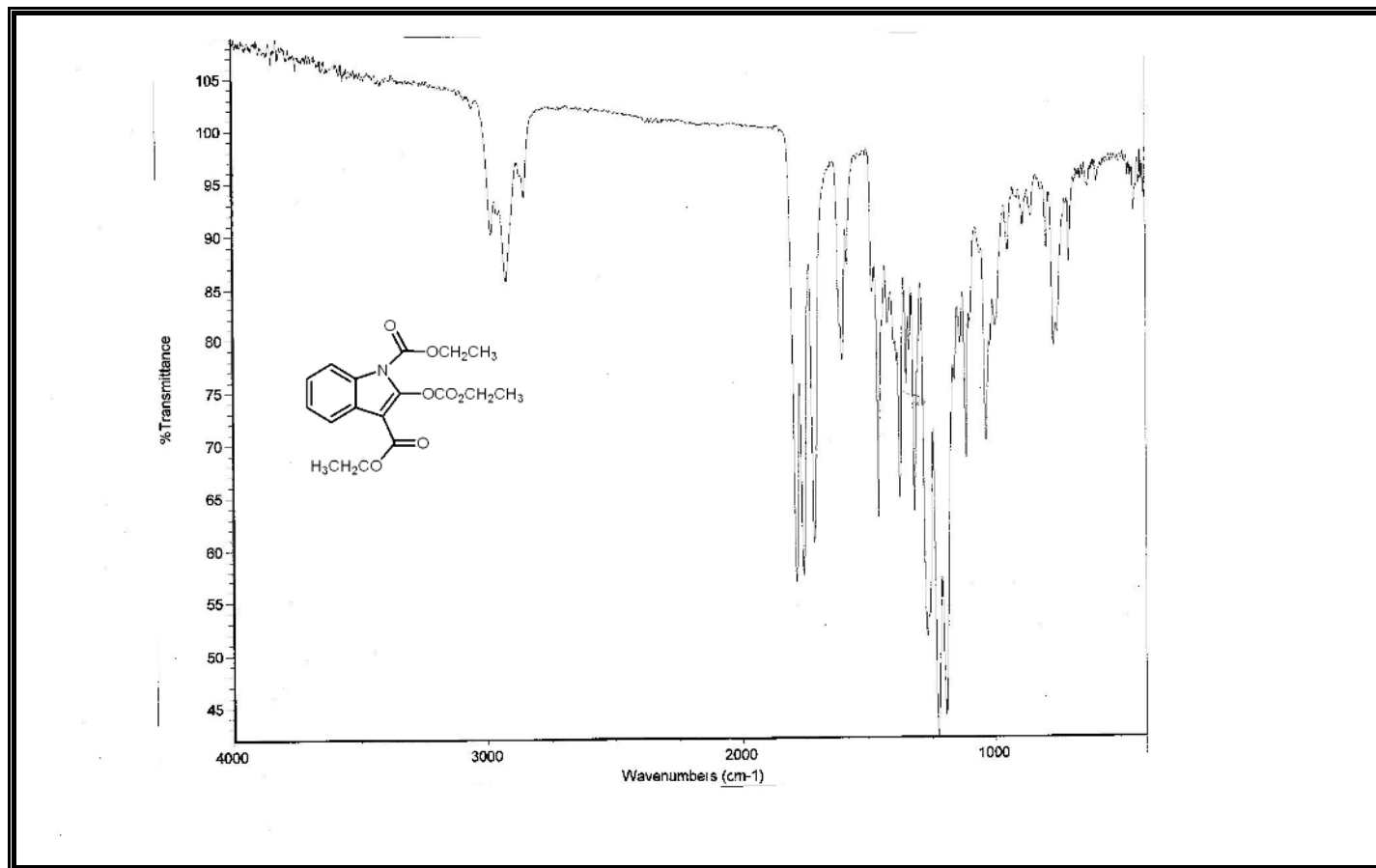


Figure A167 IR Spectrum of Compound 392.

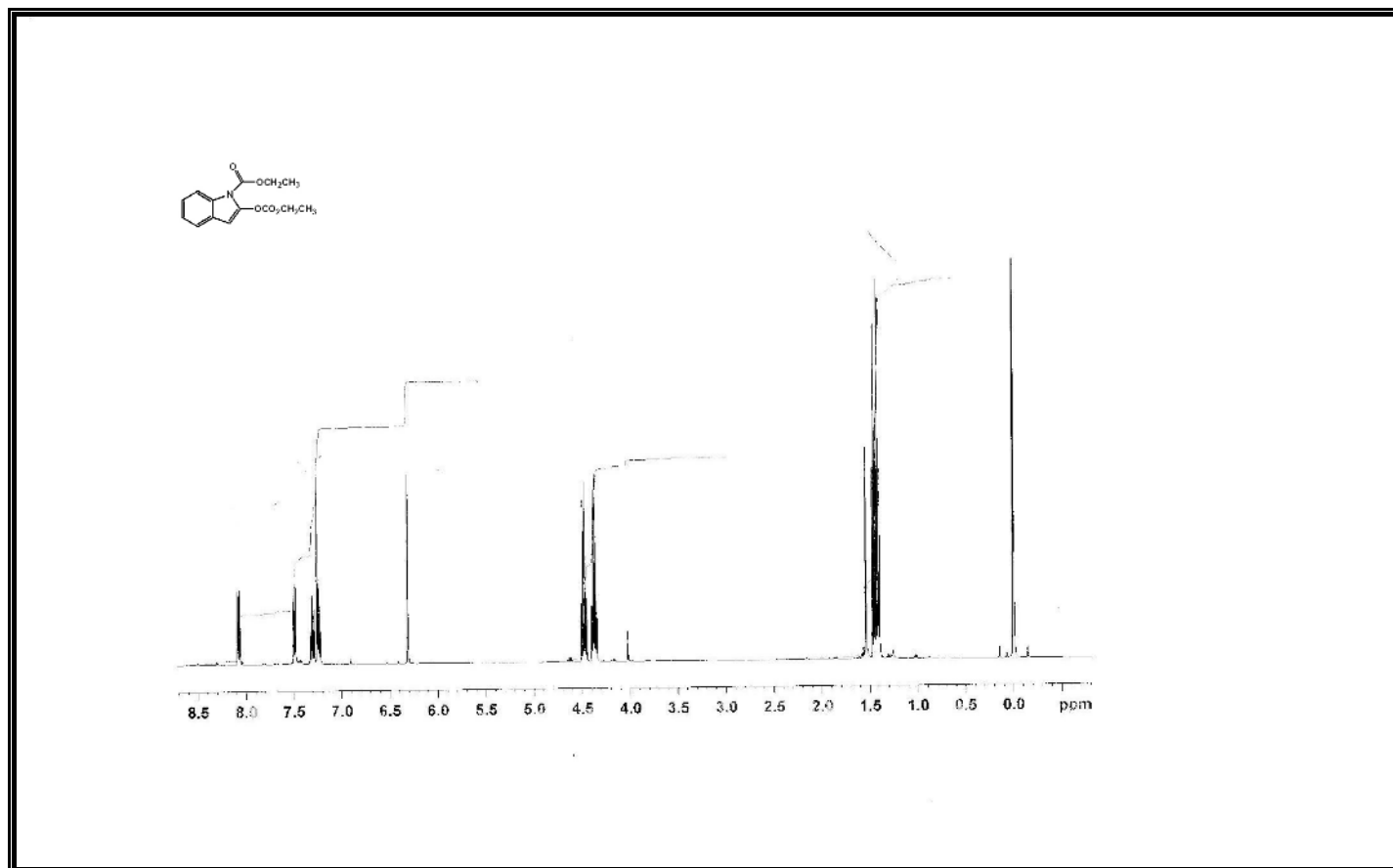


Figure A168 ¹H-NMR Spectrum of Compound 393.

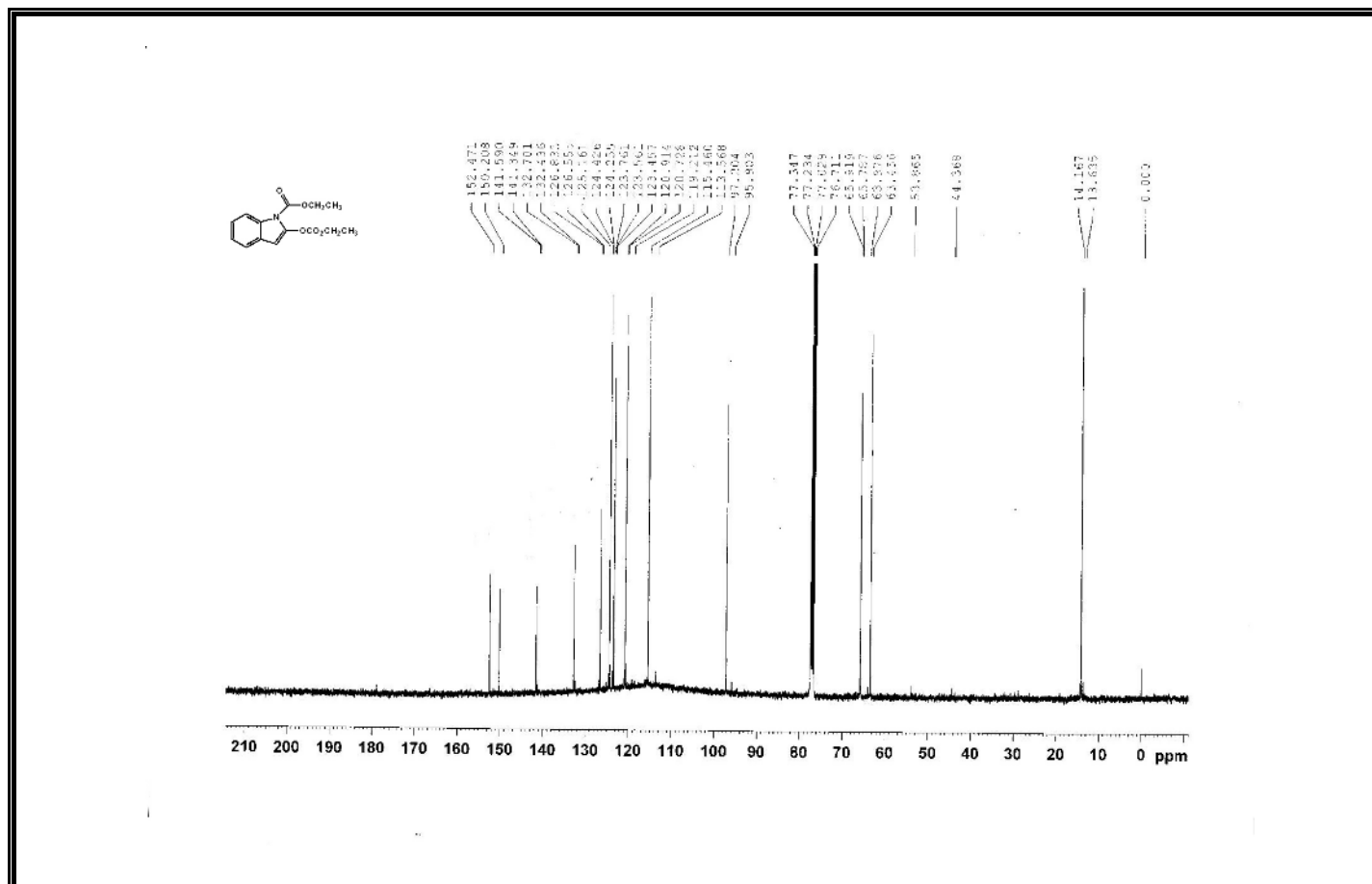


Figure A169 ¹³C-NMR Spectrum of Compound 393.

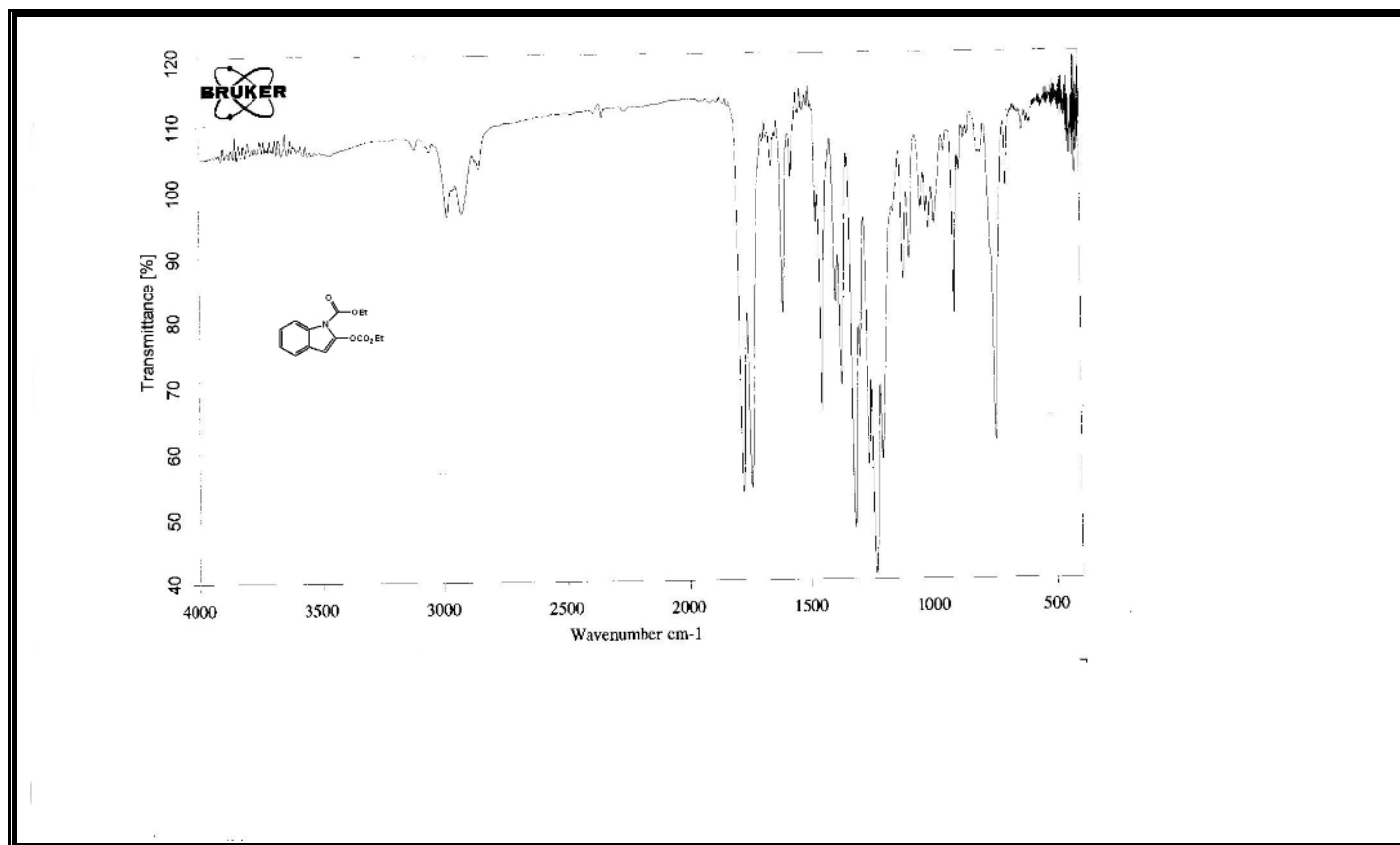
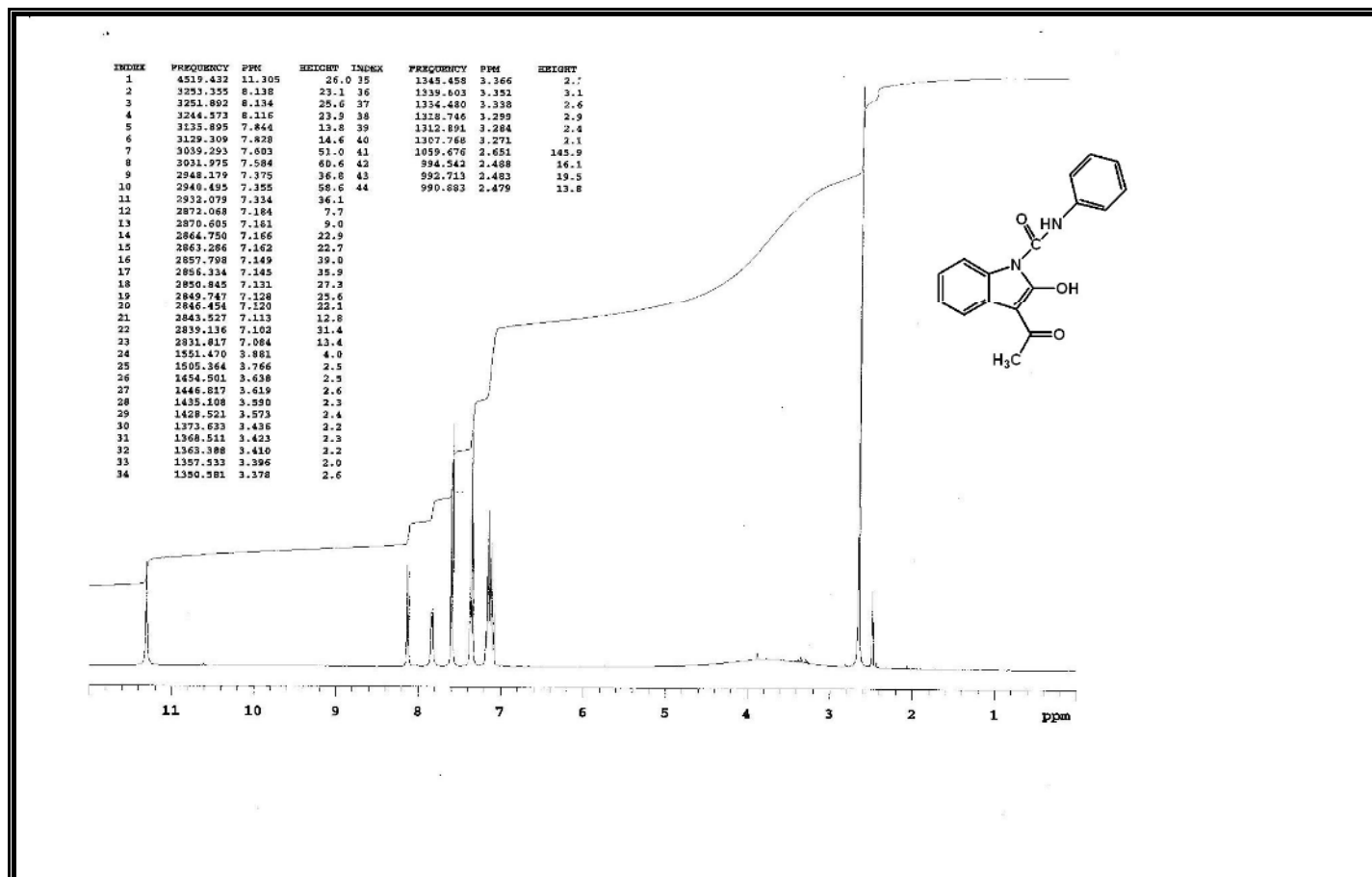


Figure A170 IR Spectrum of Compound 393.

Figure A171 ¹H-NMR Spectrum of Compound 394.

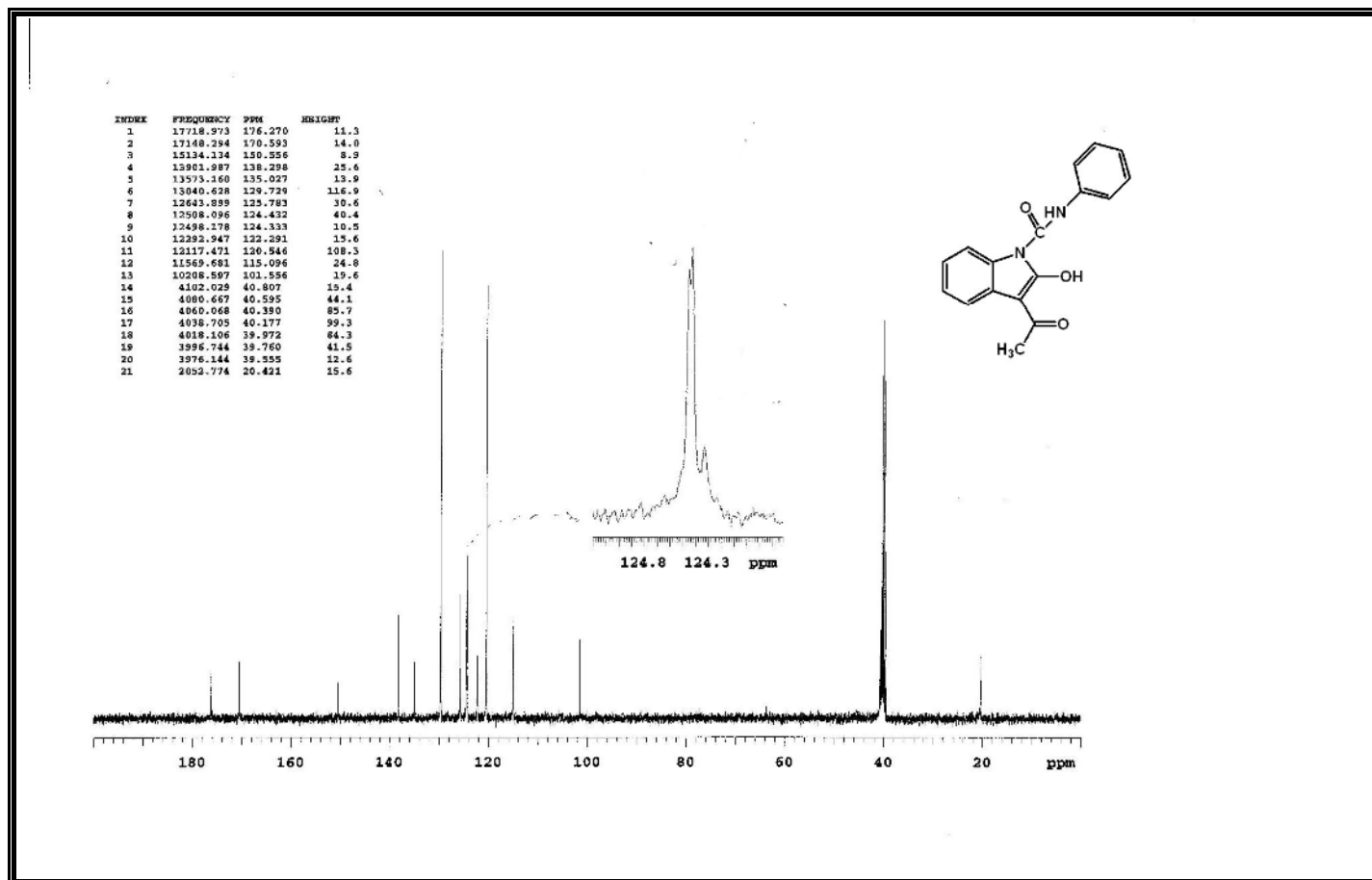


Figure A172 ¹³C-NMR Spectrum of Compound 394.

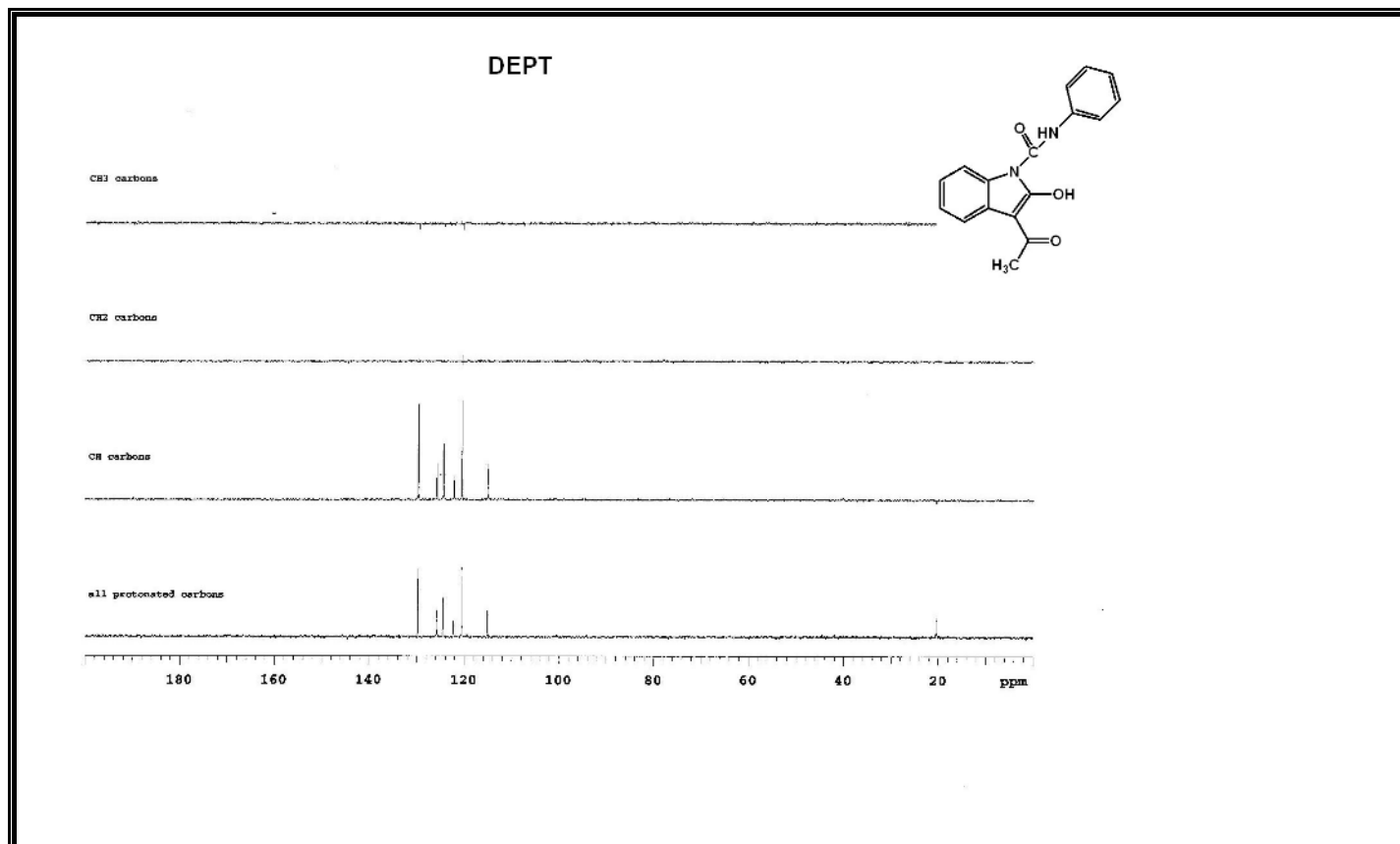


Figure A173 DEPT Spectrum of Compound **394**.

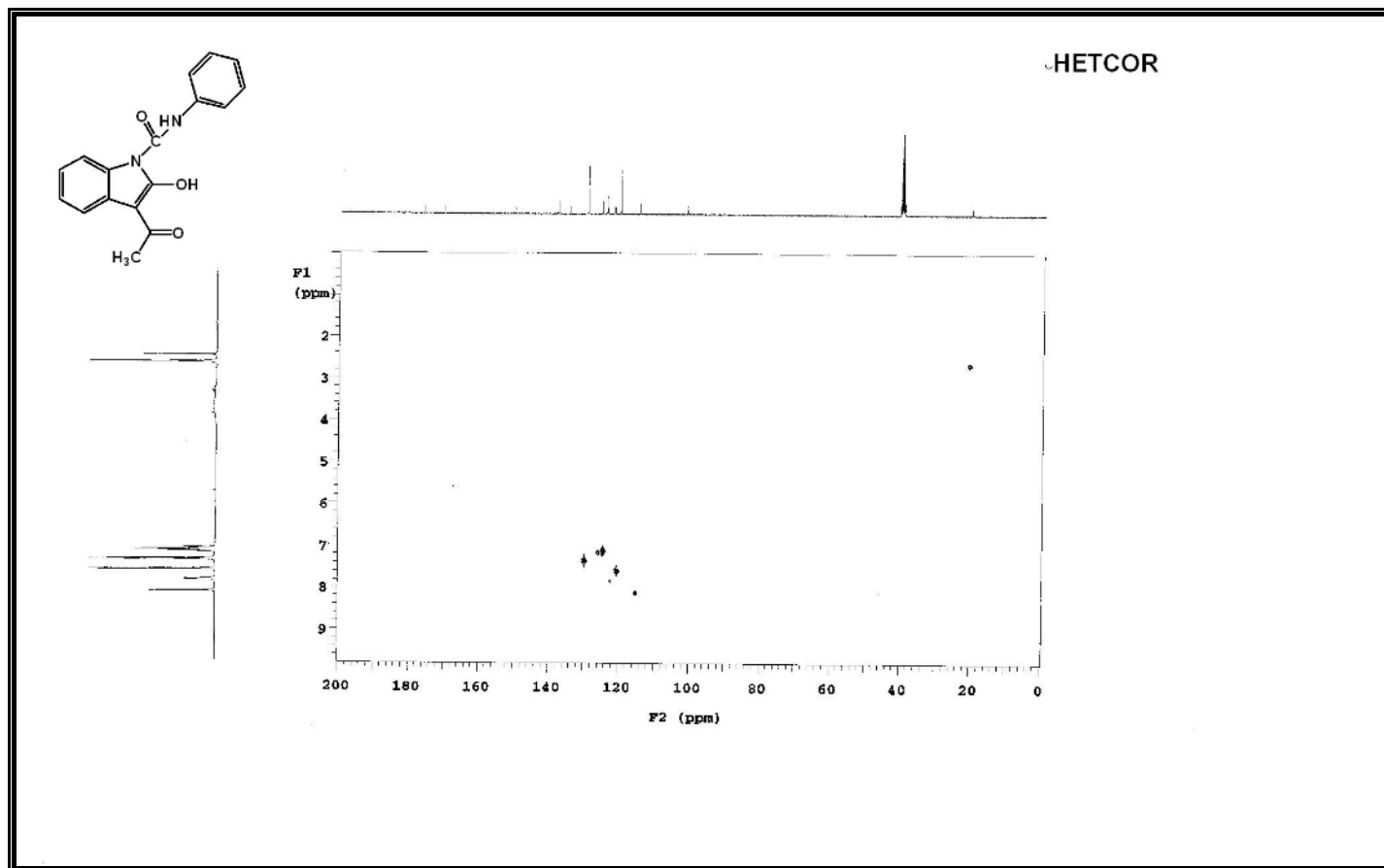


Figure A174 HETCOR Spectrum of Compound 394.

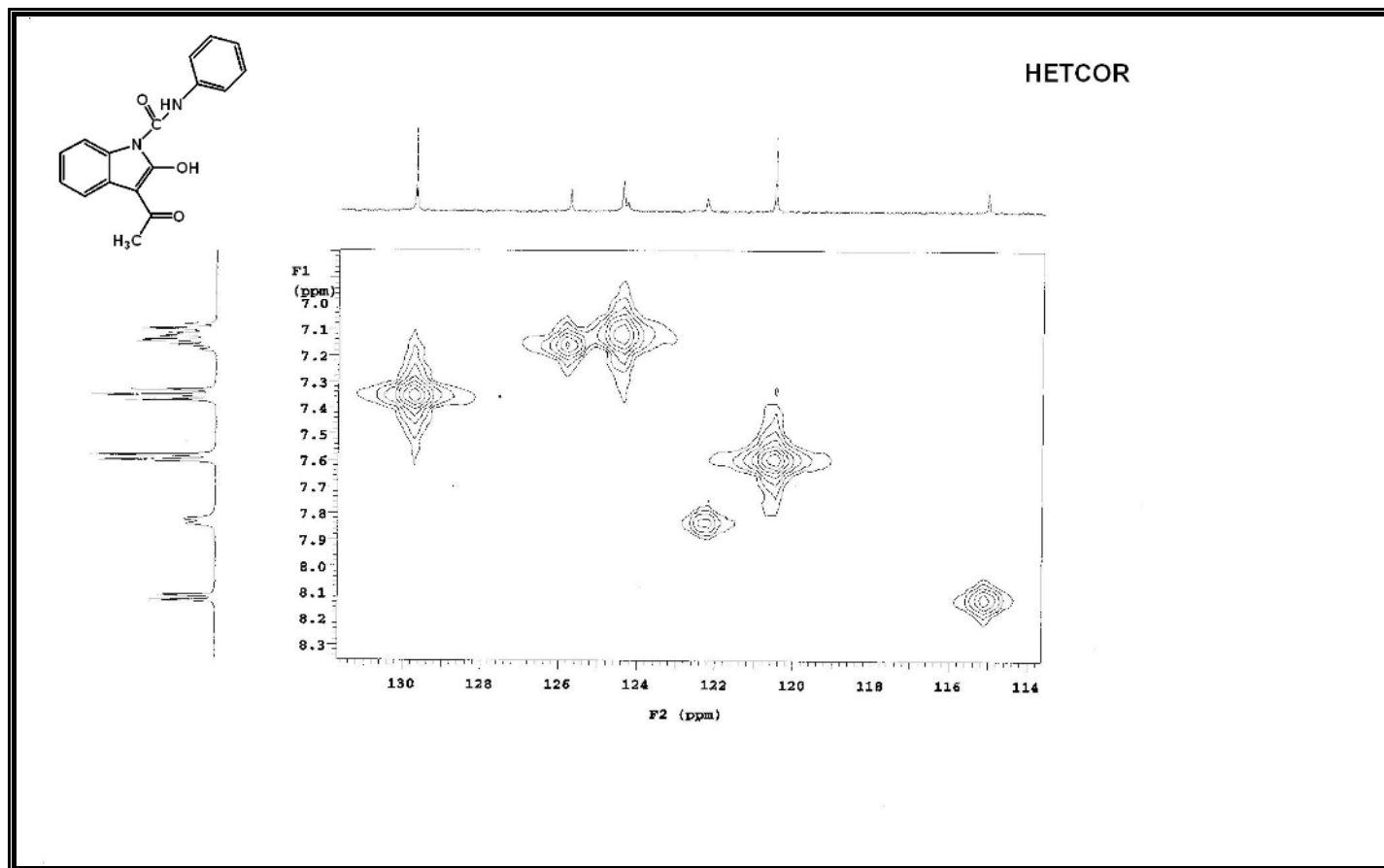


Figure A175 Expanded HETCOR Spectrum of Compound **394**.

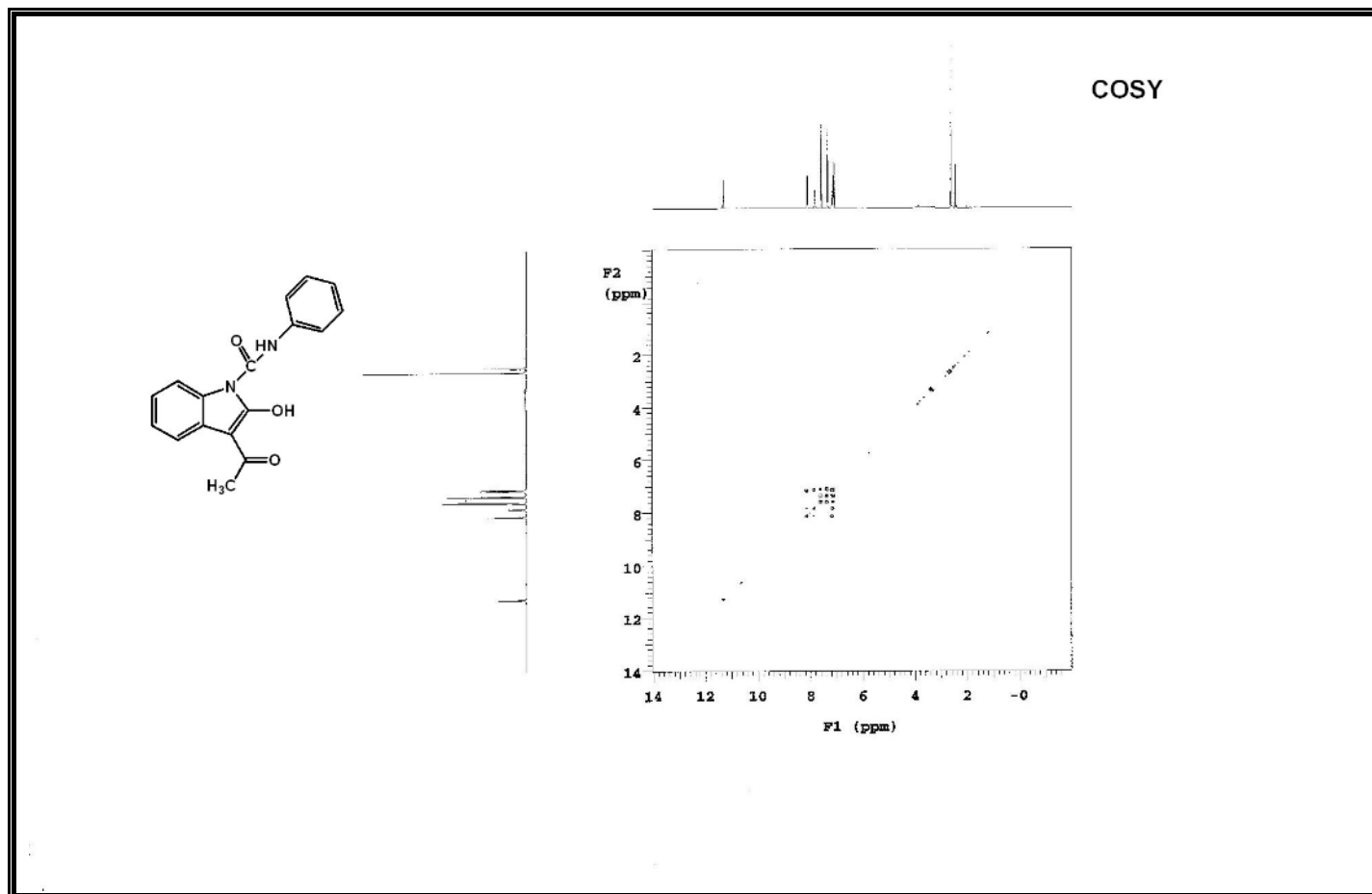


Figure A176 COSY Spectrum of Compound 394.

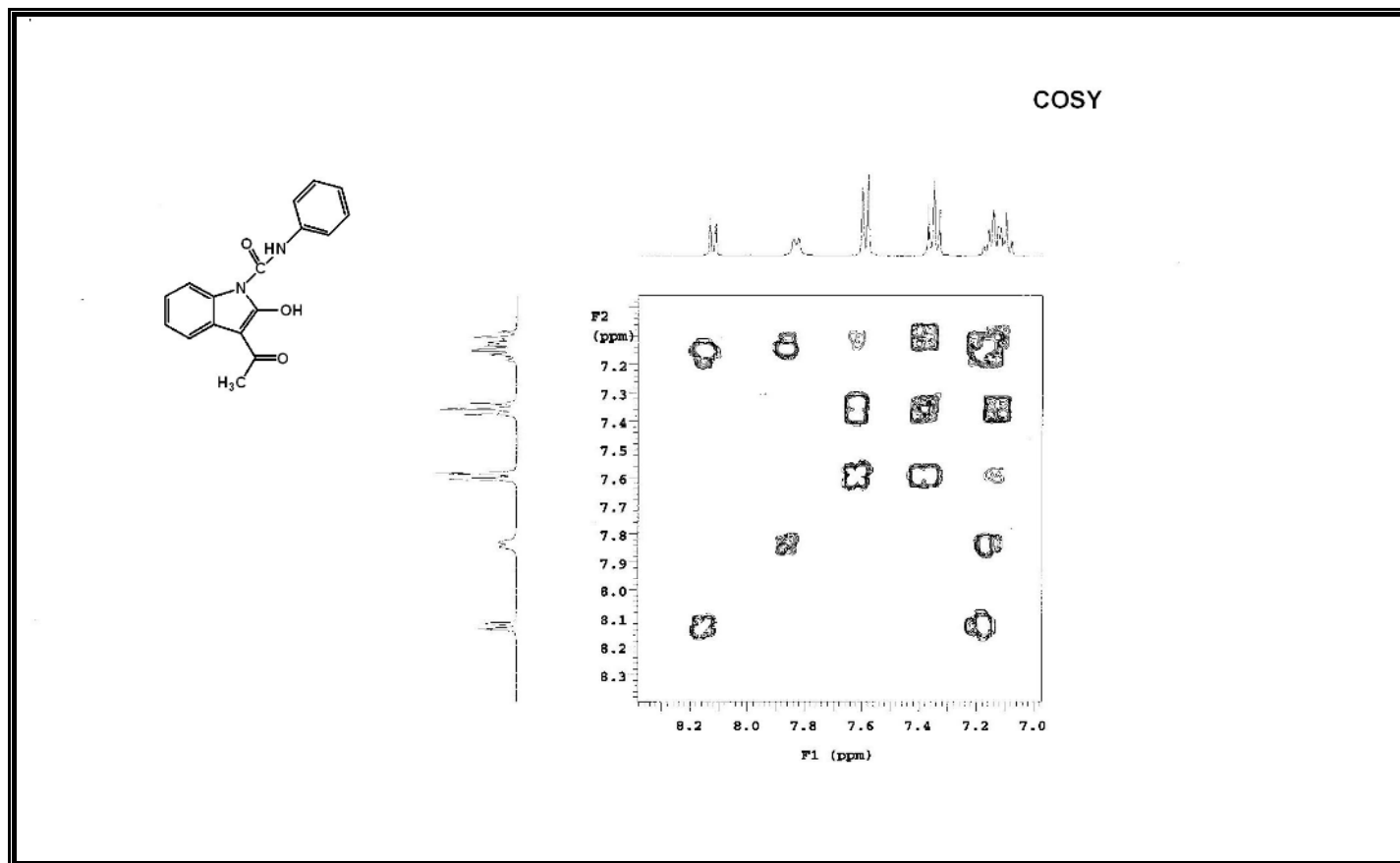


Figure A177 Expanded COSY Spectrum of Compound 394.

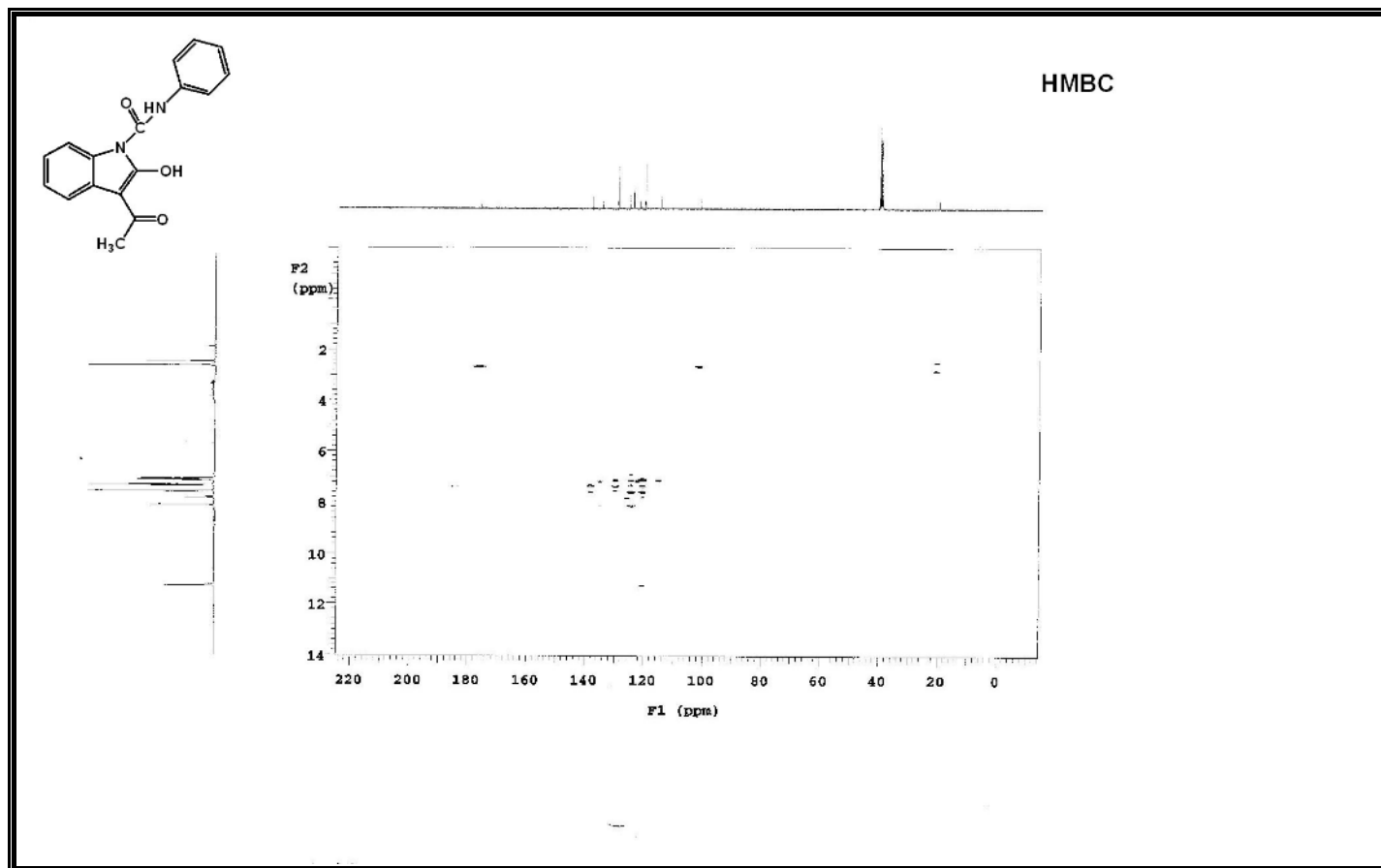


Figure A178 HMBC Spectrum of Compound 394.

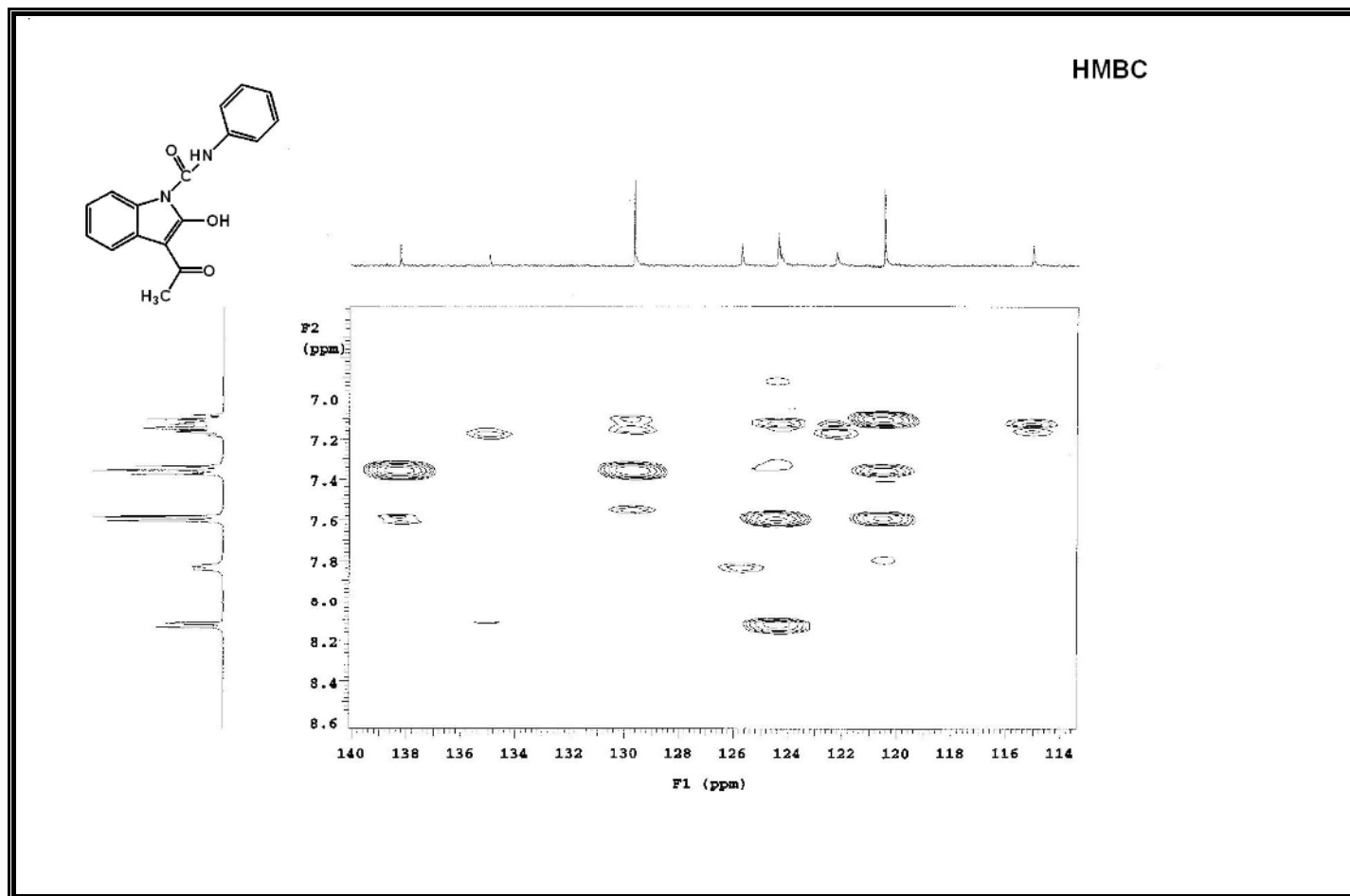


Figure A179 Expanded HMBC Spectrum of Compound 394.

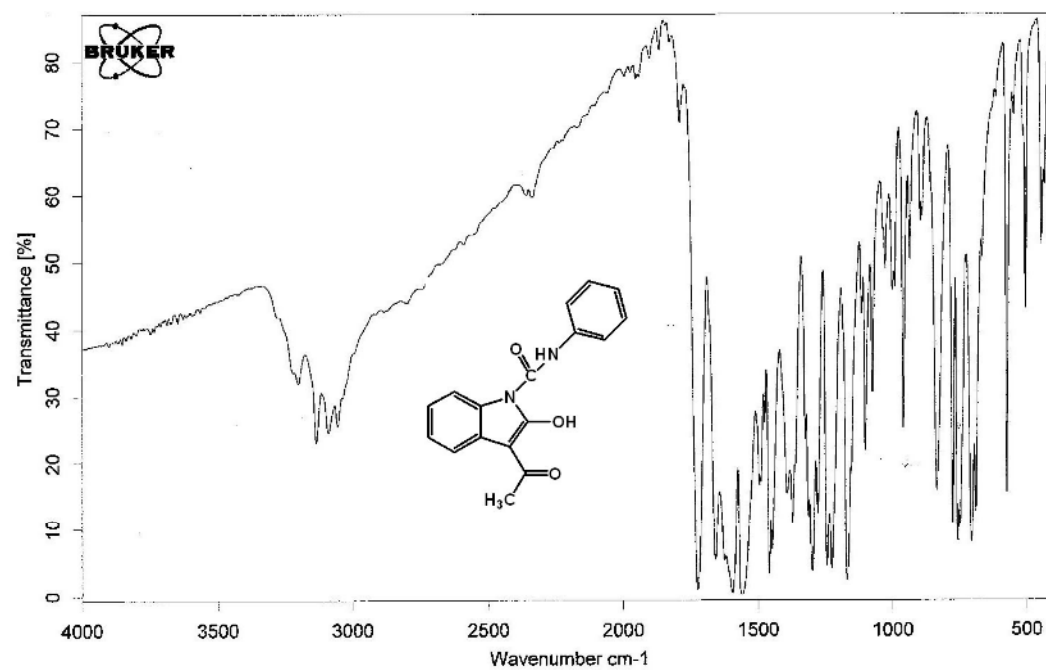


Figure A180 IR Spectrum of Compound 394.

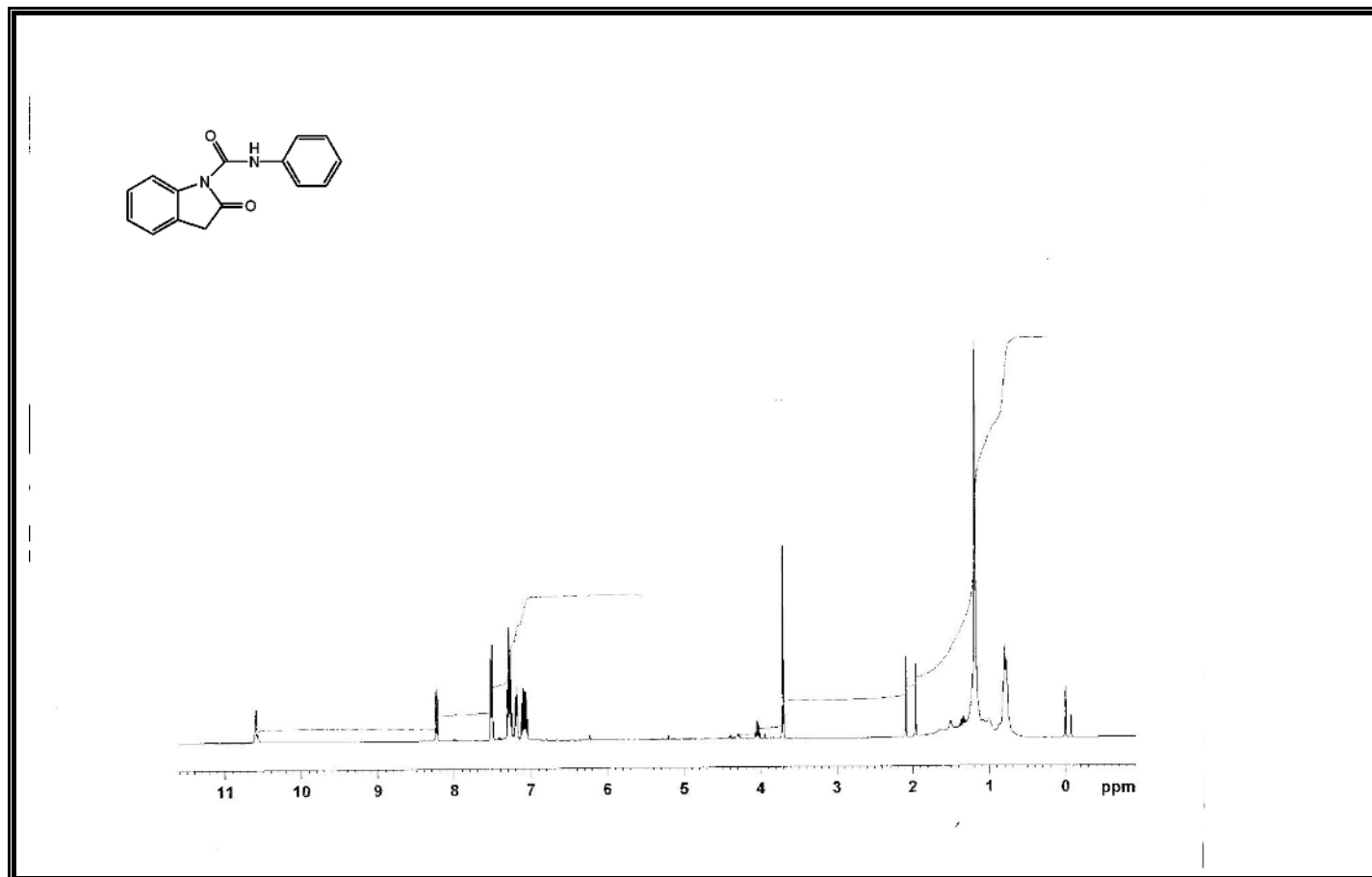


Figure A181 ^1H -NMR Spectrum of Compound 395.

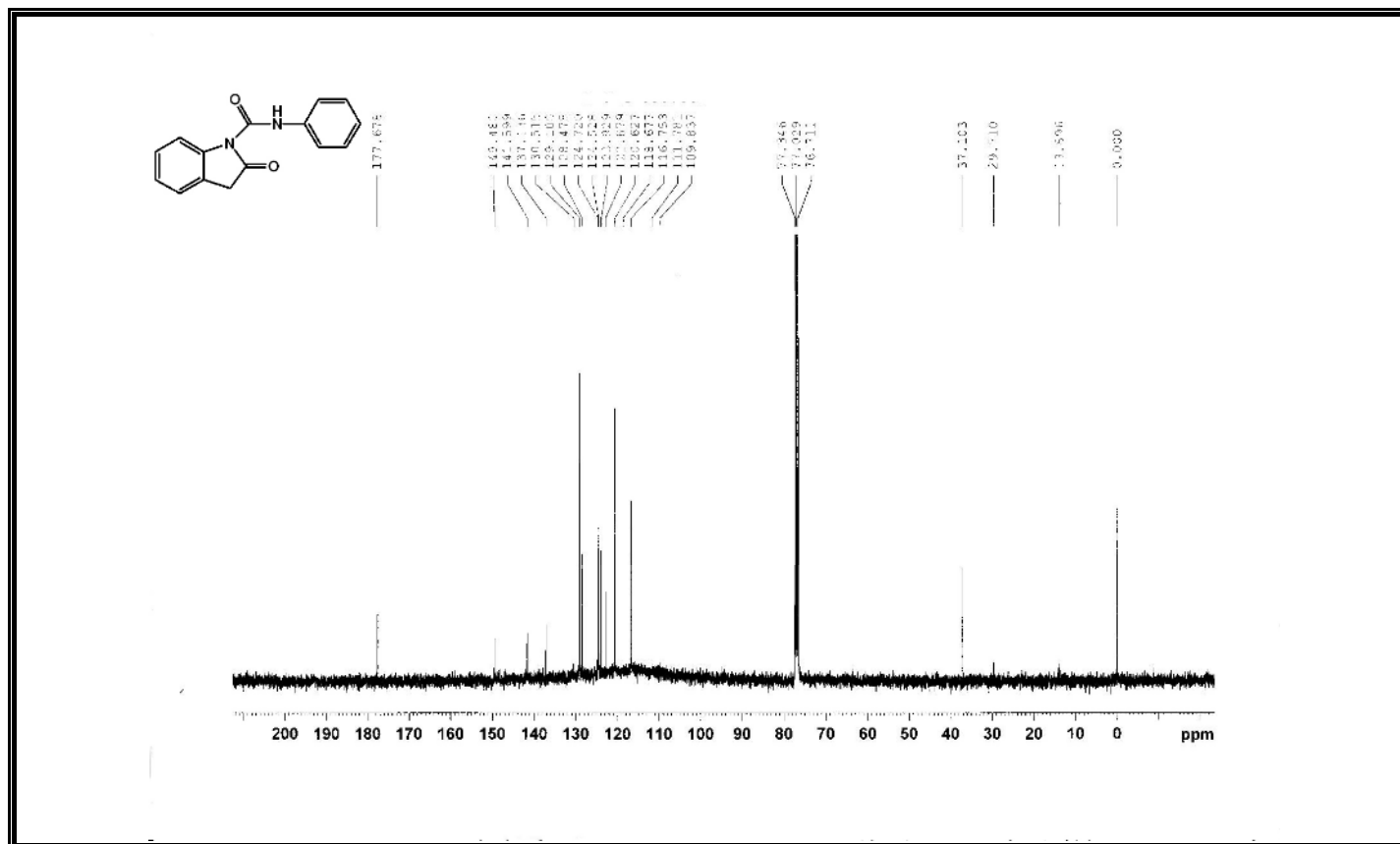


Figure A182 ^{13}C -NMR Spectrum of Compound 395.

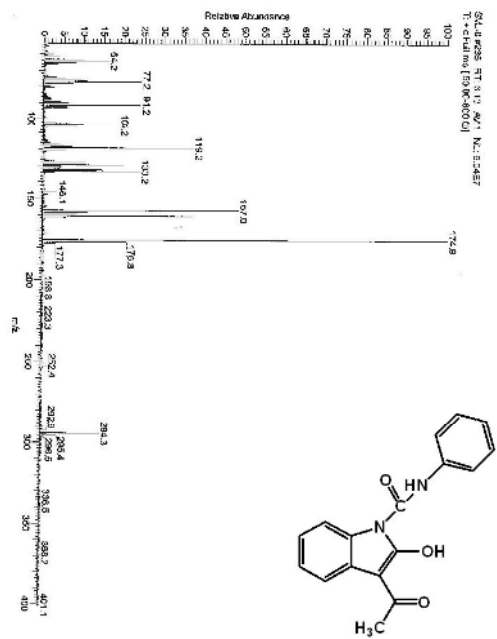


Figure A183 Mass Spectrum of Compound 394.

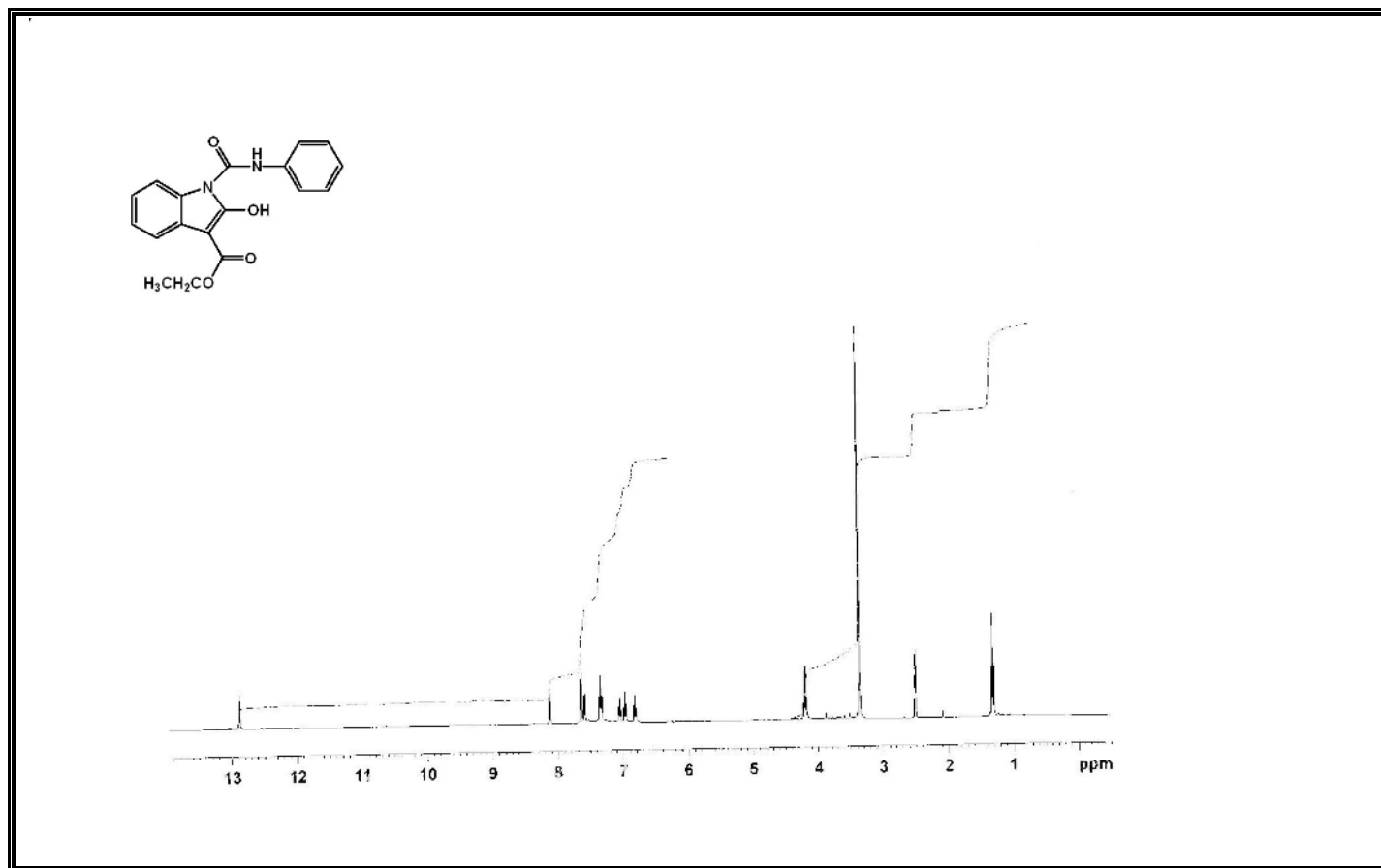


Figure A184 ¹H-NMR Spectrum of Compound **396**.

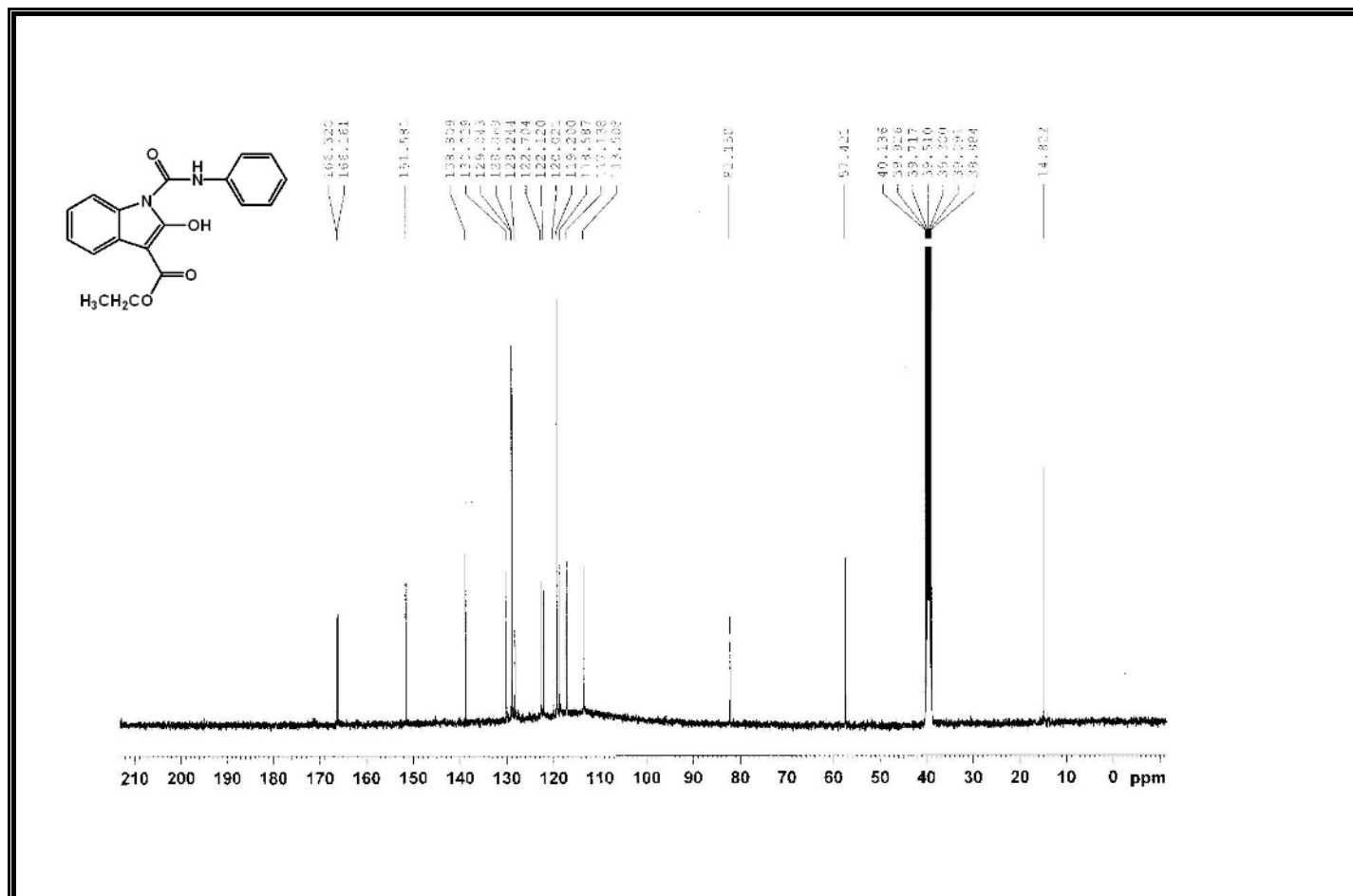


Figure A185 ¹³C-NMR Spectrum of Compound 396.

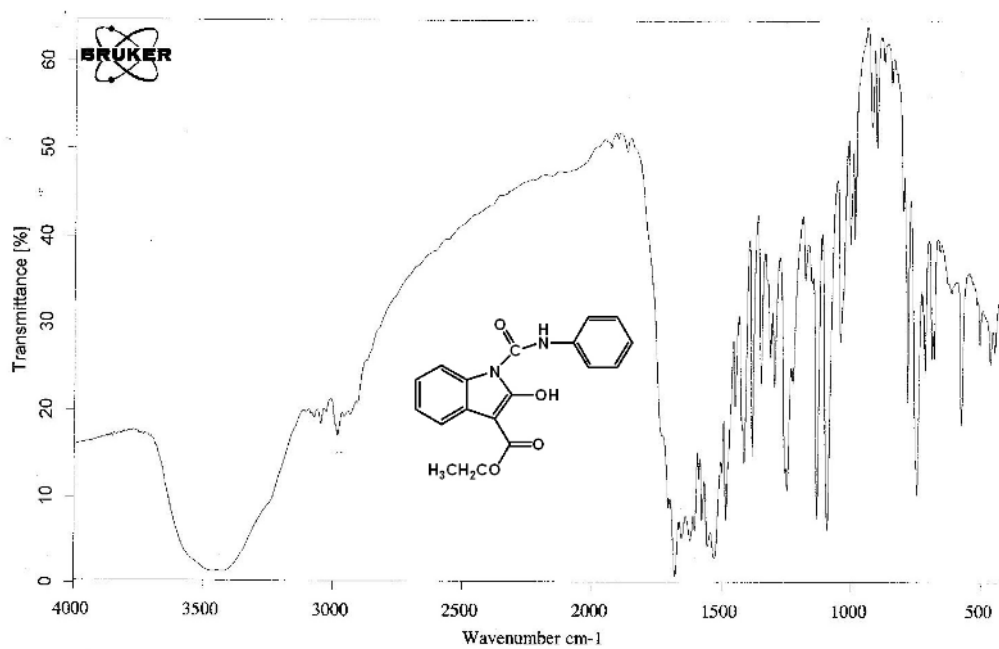


Figure A186 IR Spectrum of Compound 396.

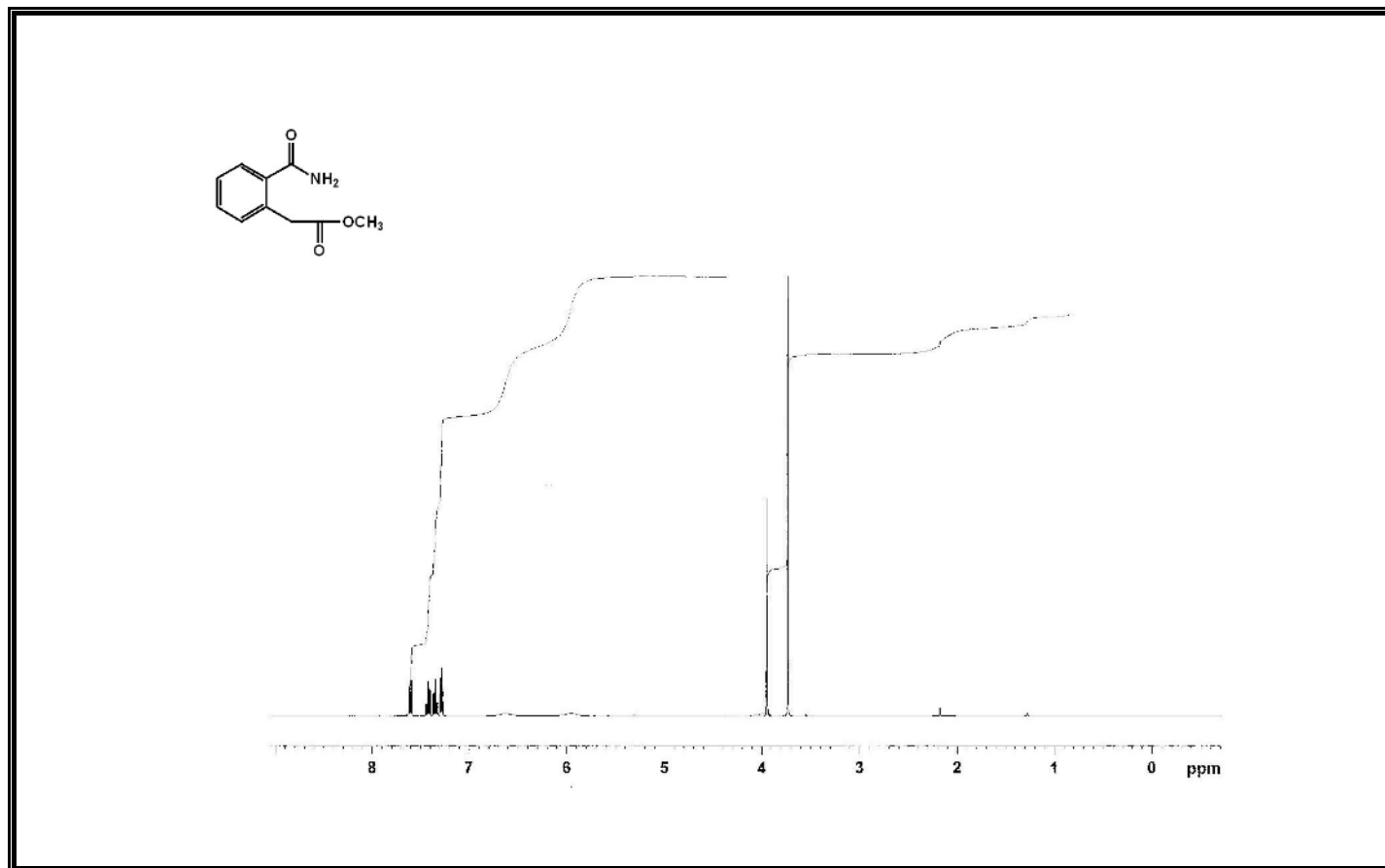


Figure A187 ^1H -NMR Spectrum of Compound 399.

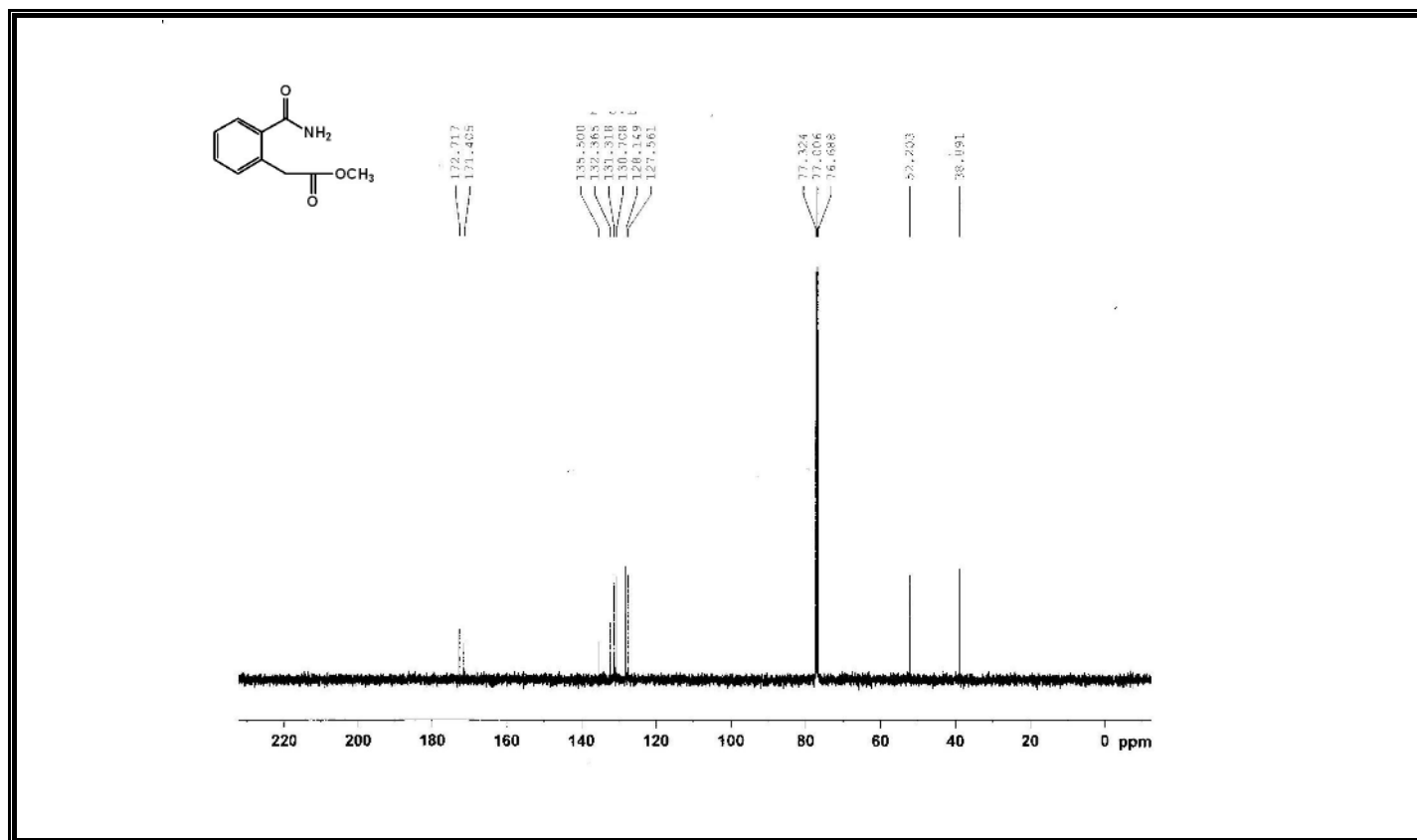


Figure A188 ¹³C-NMR Spectrum of Compound 399.

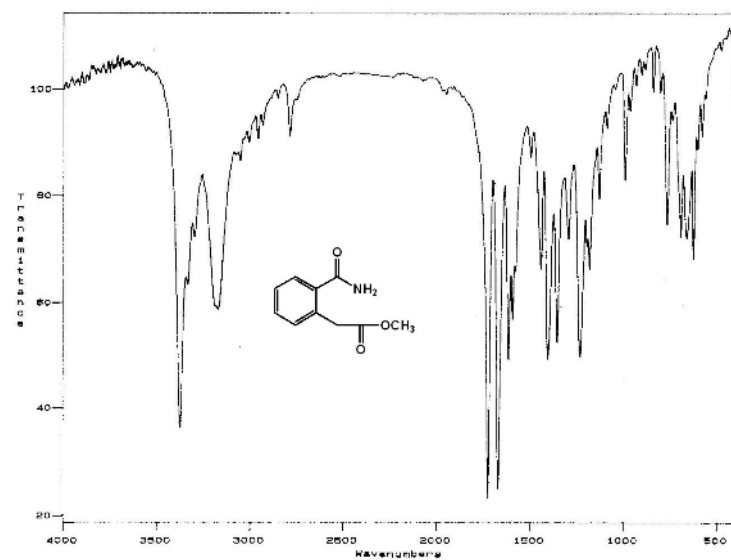


Figure A189 IR Srectrum of Compound **399**.

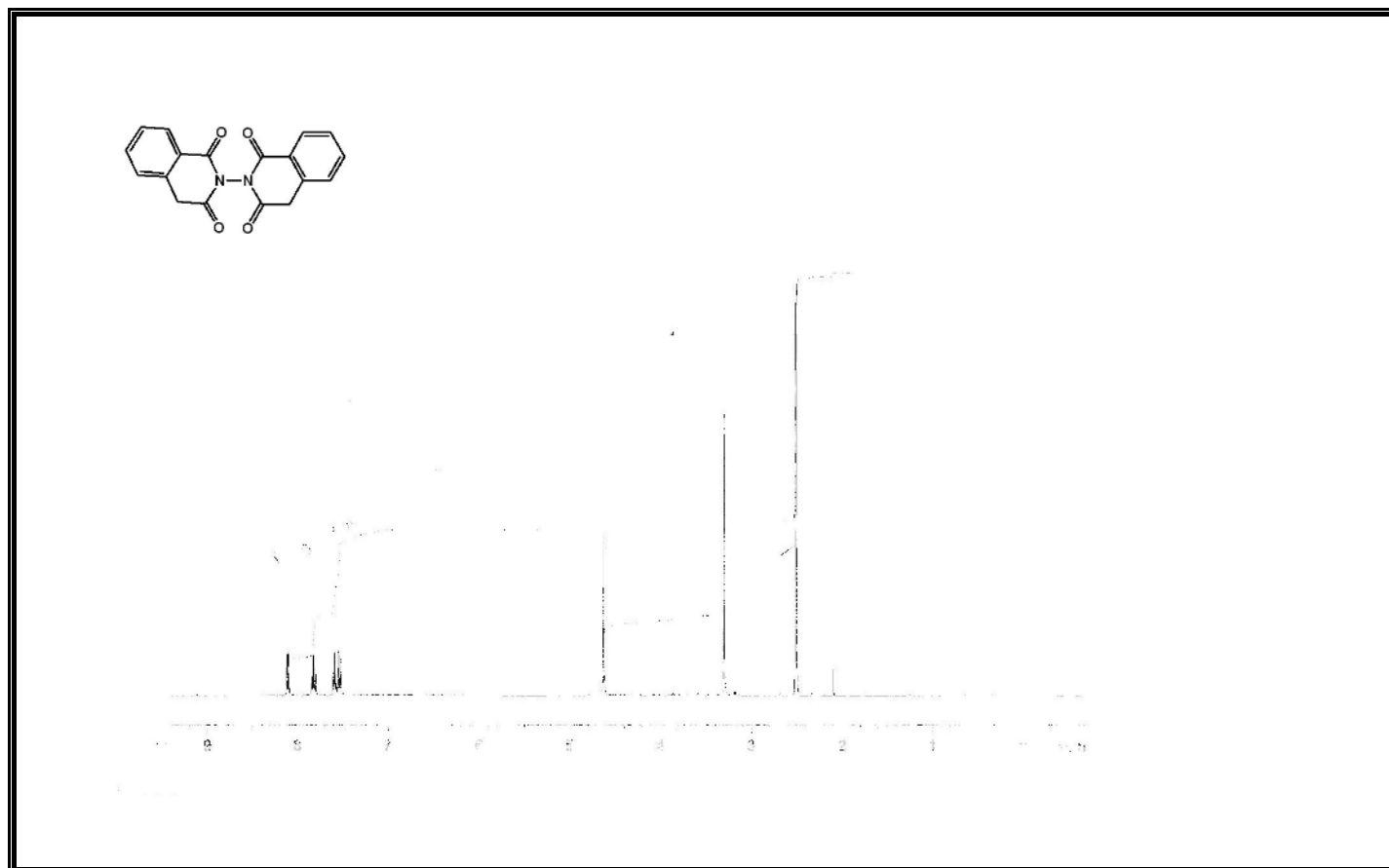


Figure A190 ^1H -NMR Spectrum of Compound **401**.

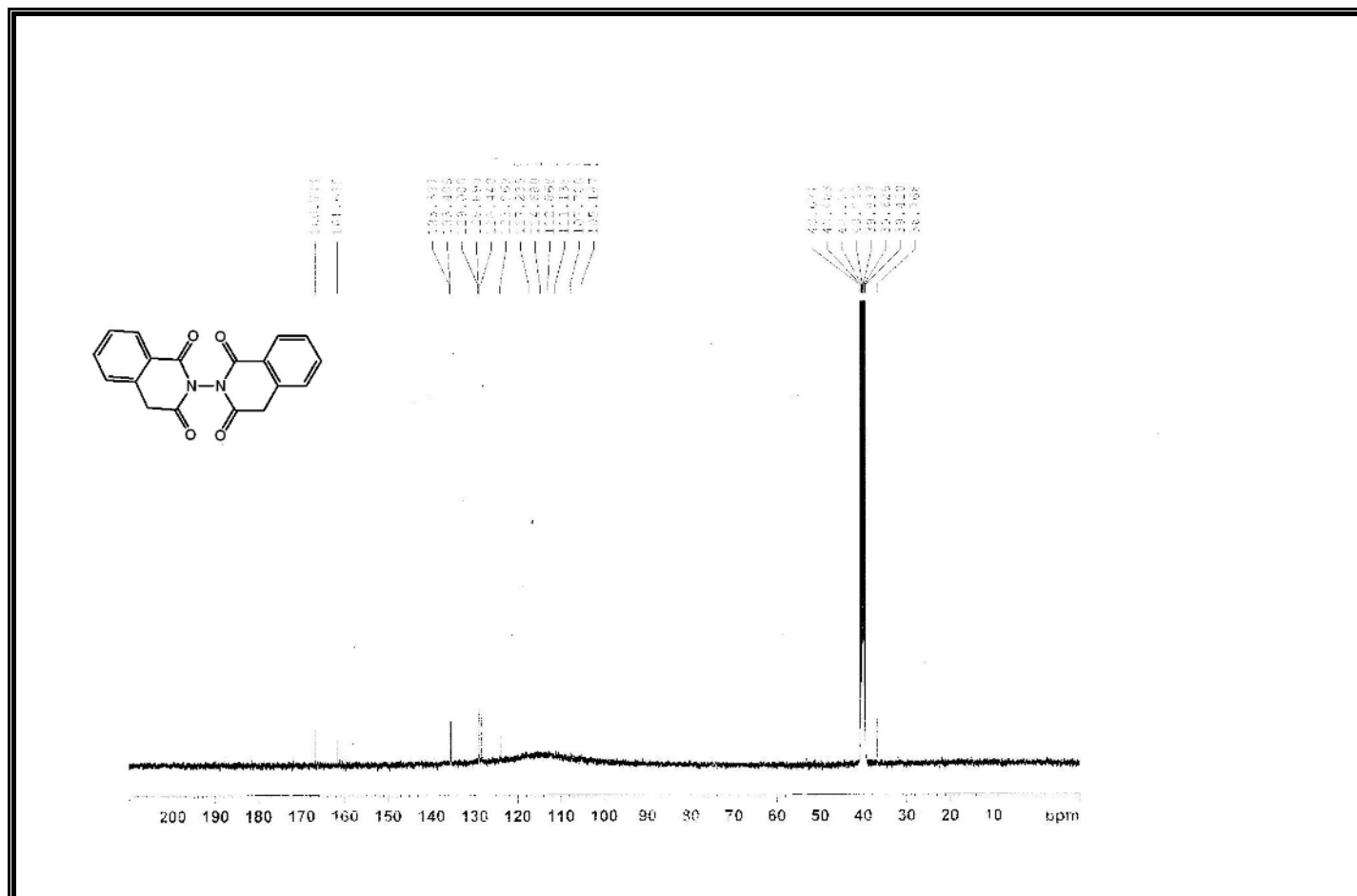


Figure A191 ¹³C-NMR Spectrum of Compound 401.

Figure A192 DEPT-135 Spectrum of Compound **401**.

Figure A193 IR Spectrum of Compound **401**.

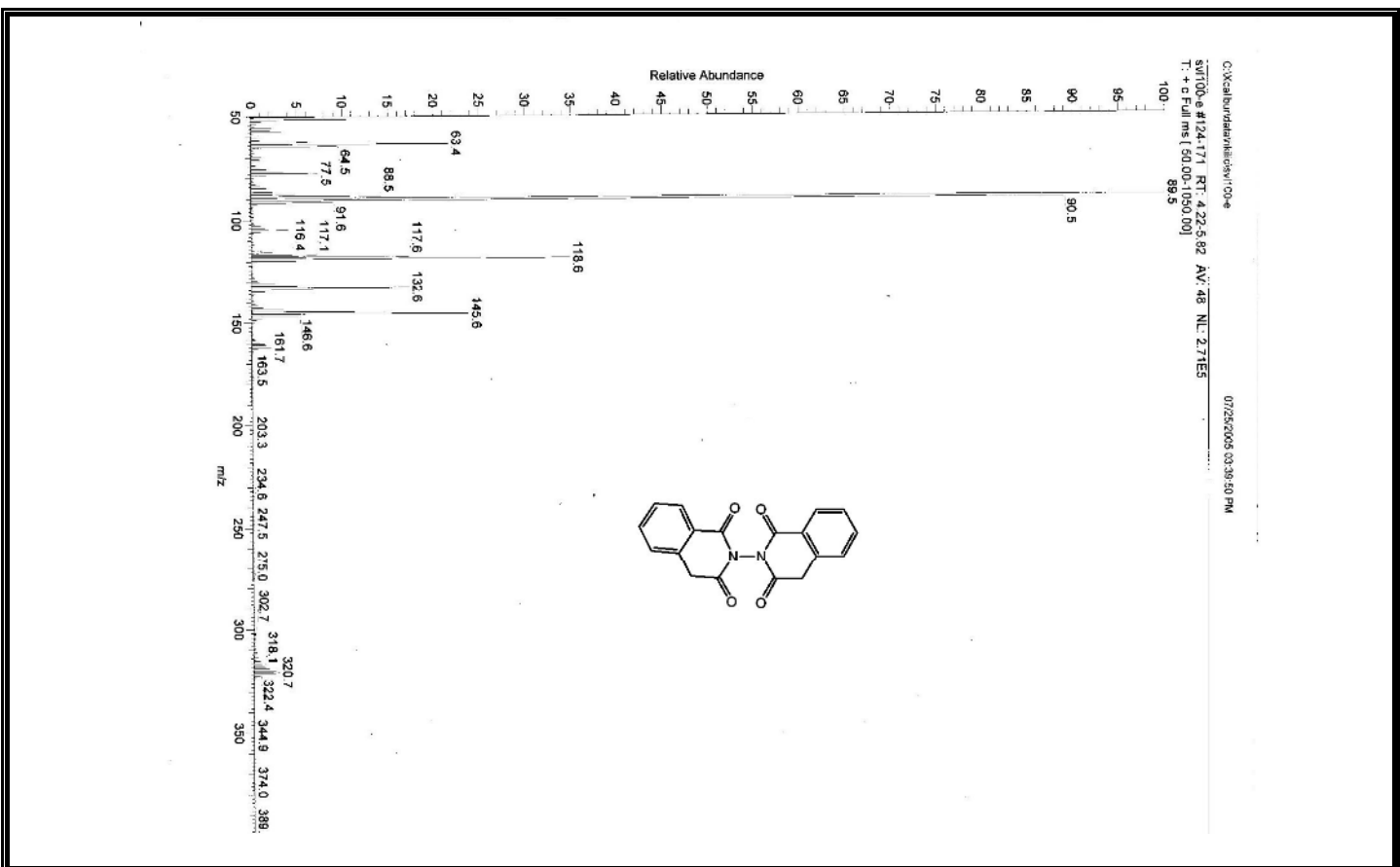


Figure A194 Mass Spectrum of Compound **401**.

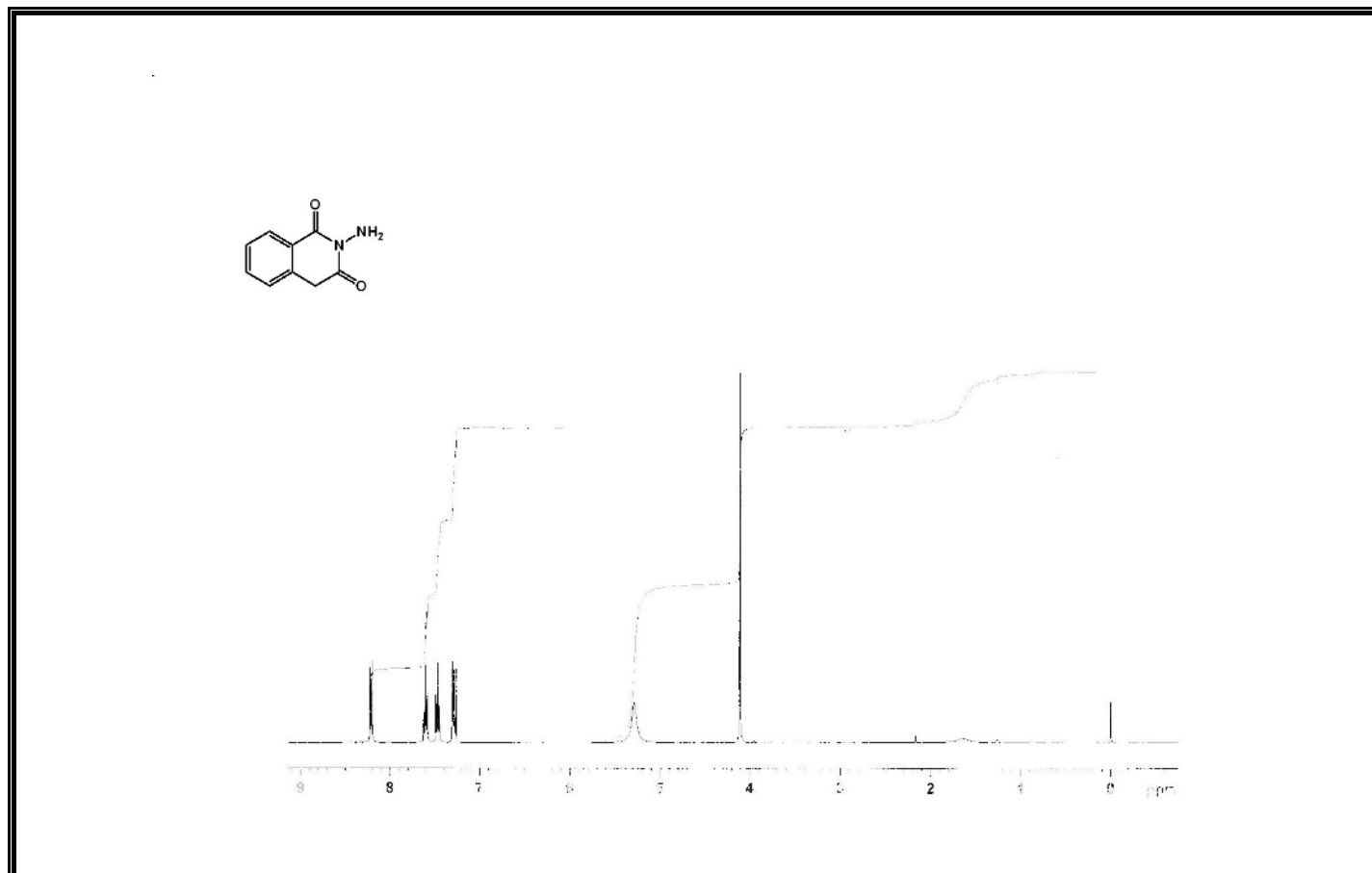


Figure A195 ^1H -NMR Spectrum of Compound 404.

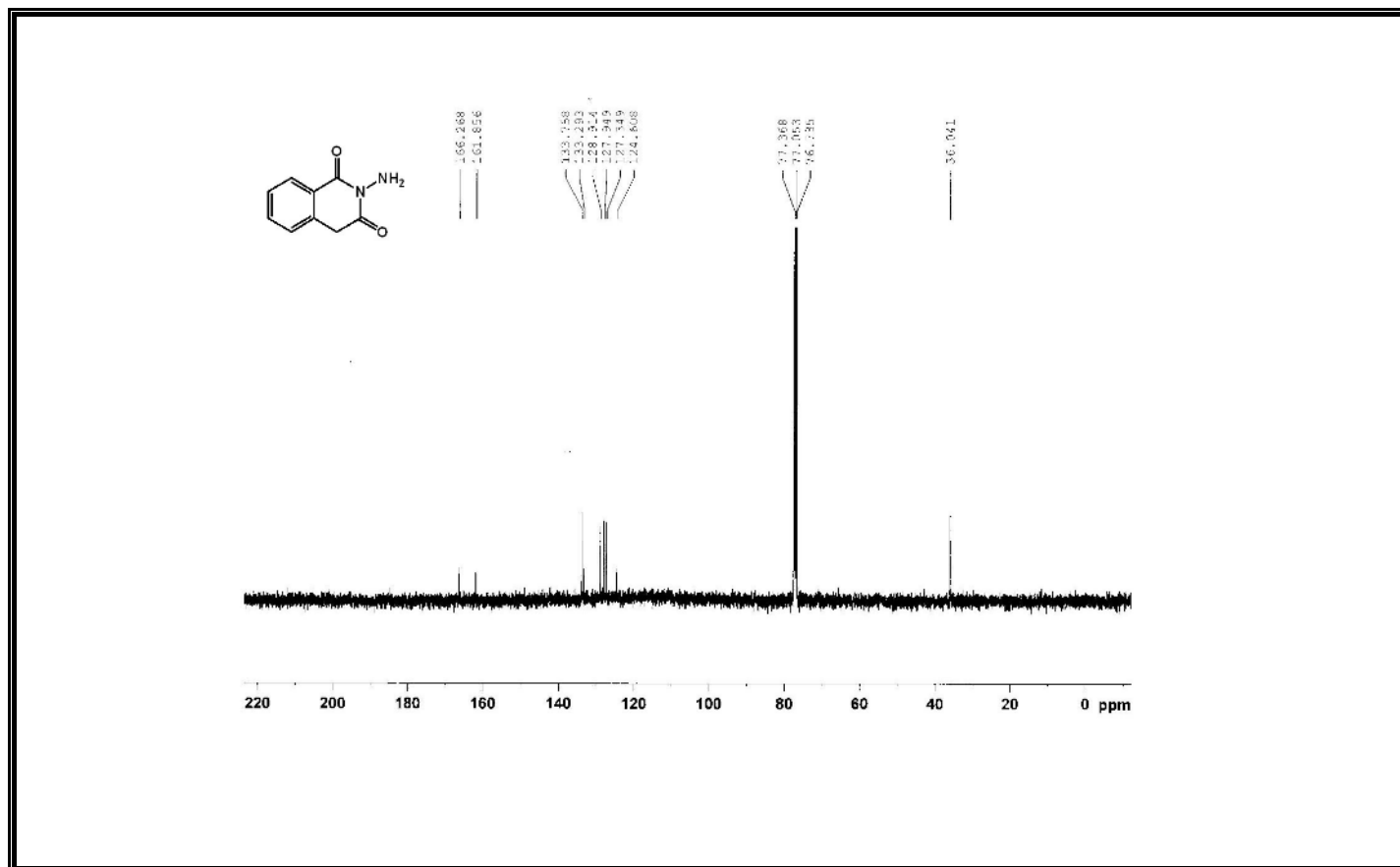


Figure A196 ¹³C-NMR Spectrum of Compound 404.

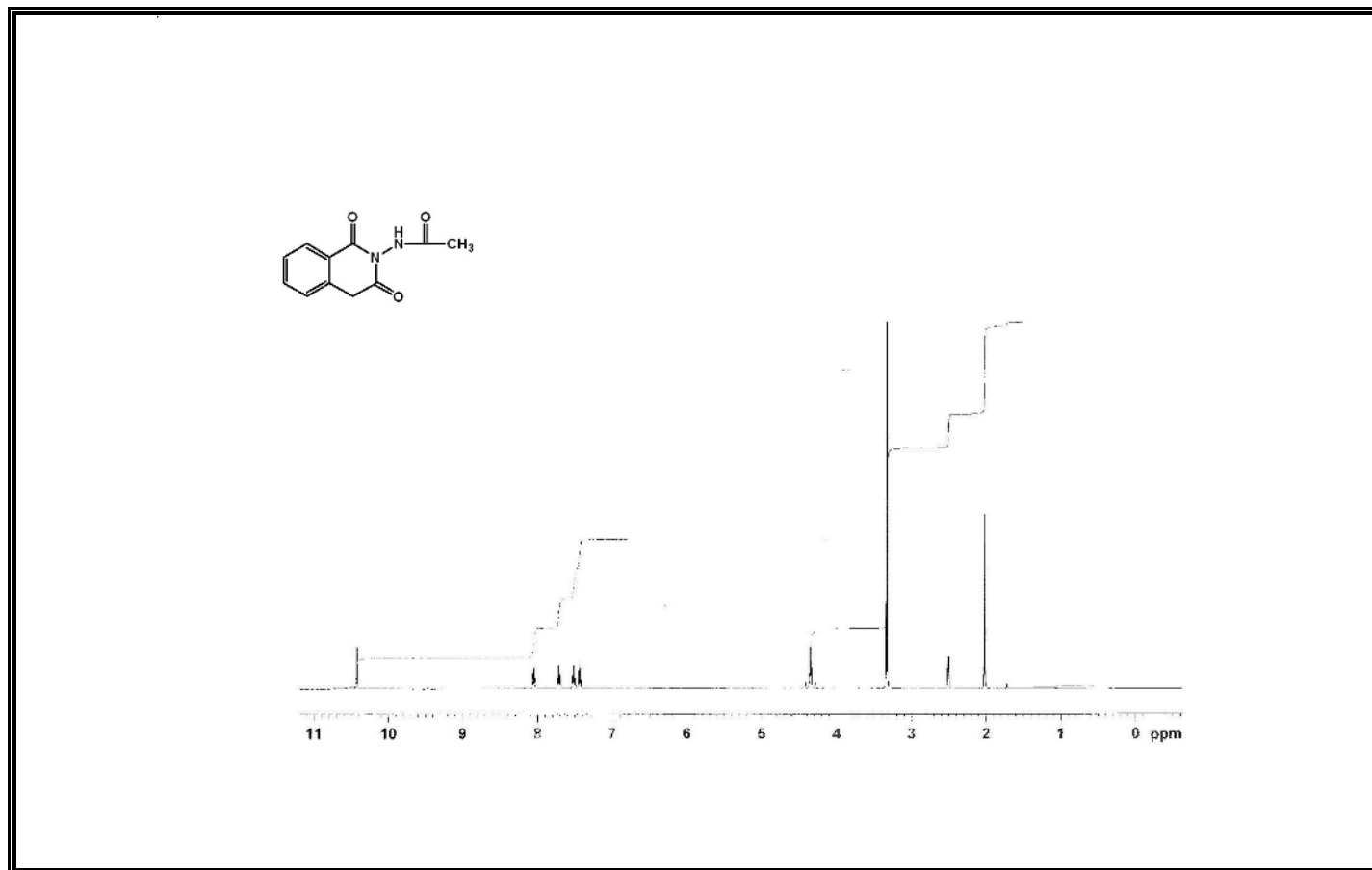


Figure A197 ^1H -NMR Spectrum of Compound 405.

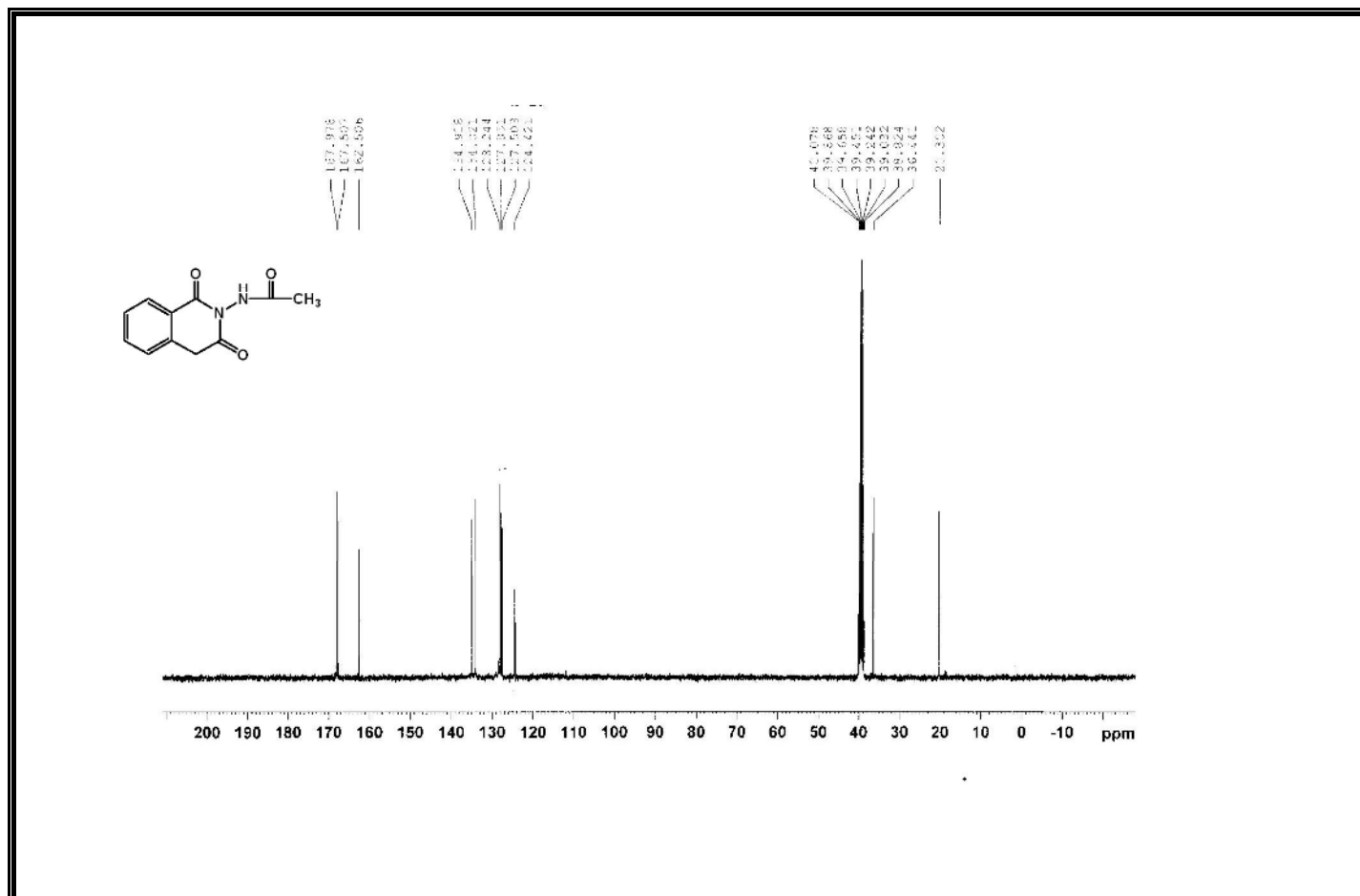


Figure A198 ¹³C-NMR Spectrum of Compound 405.

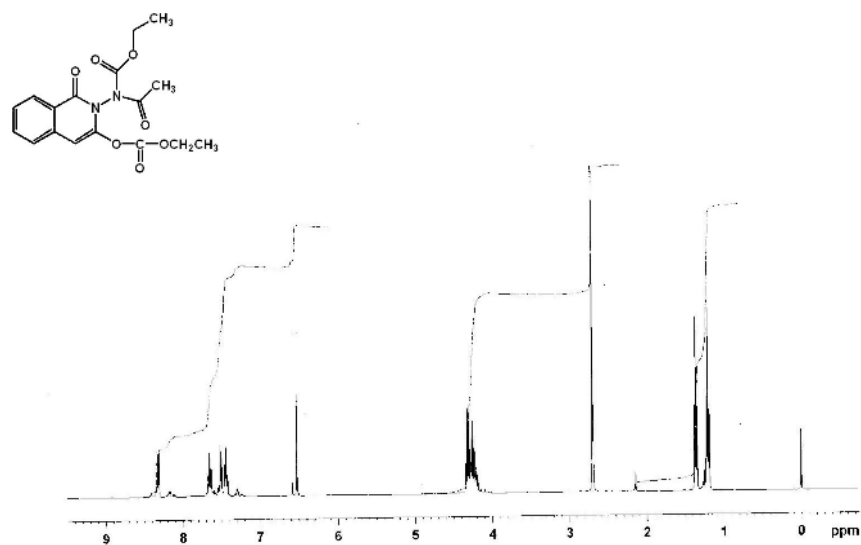


Figure A199 ^1H -NMR Spectrum of Compound **406**.

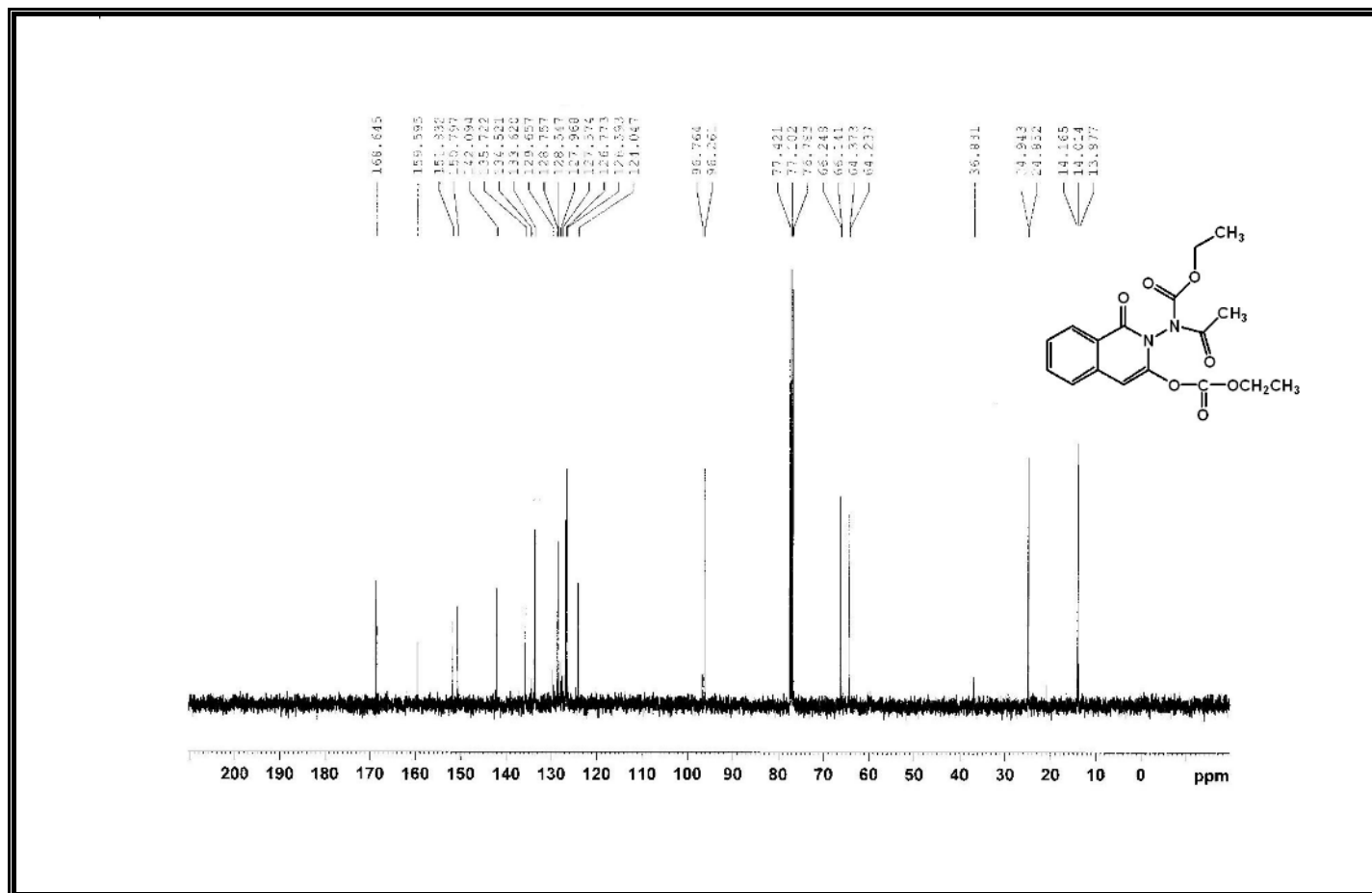


Figure A200 ^{13}C -NMR Spectrum of Compound 406.

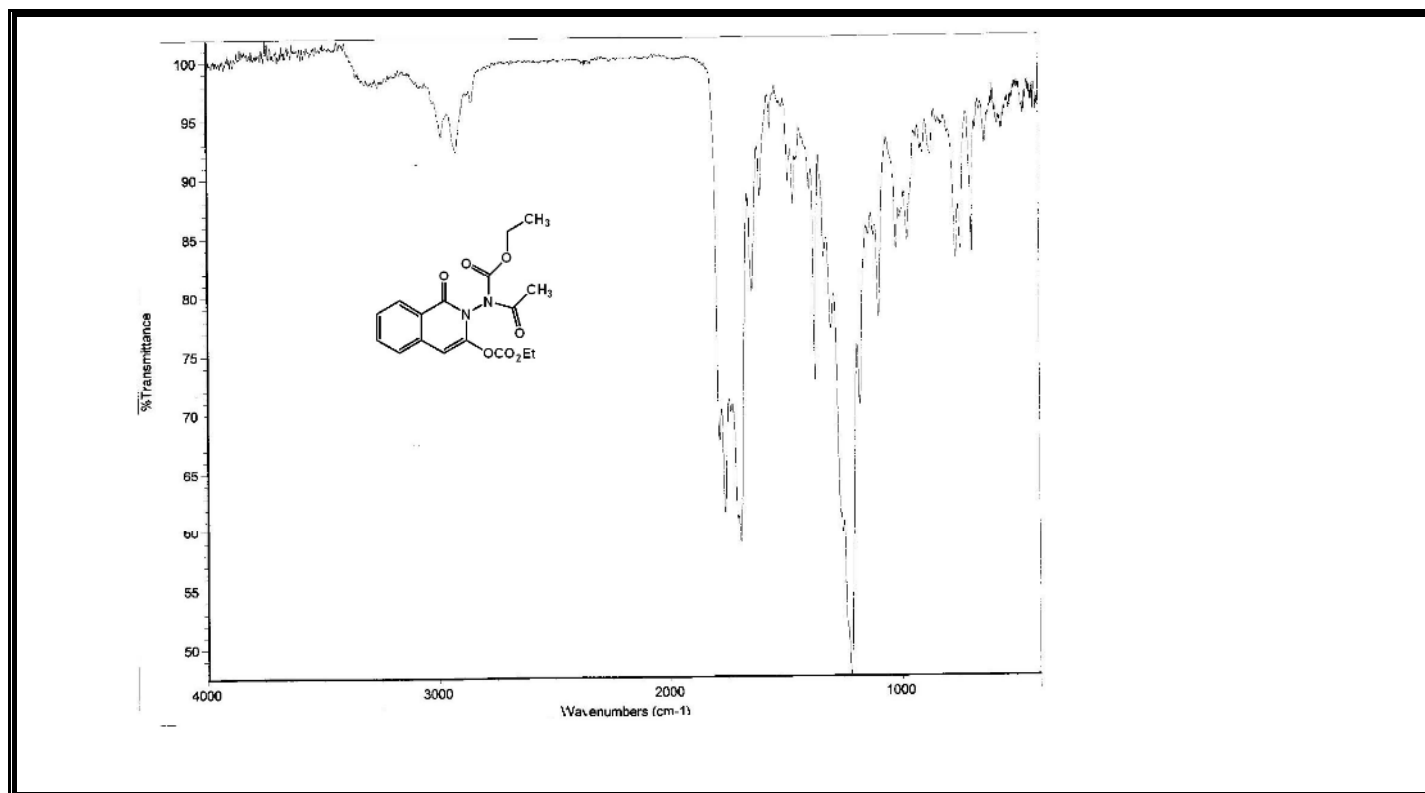


Figure A201 IR Spectrum of Compound 406.

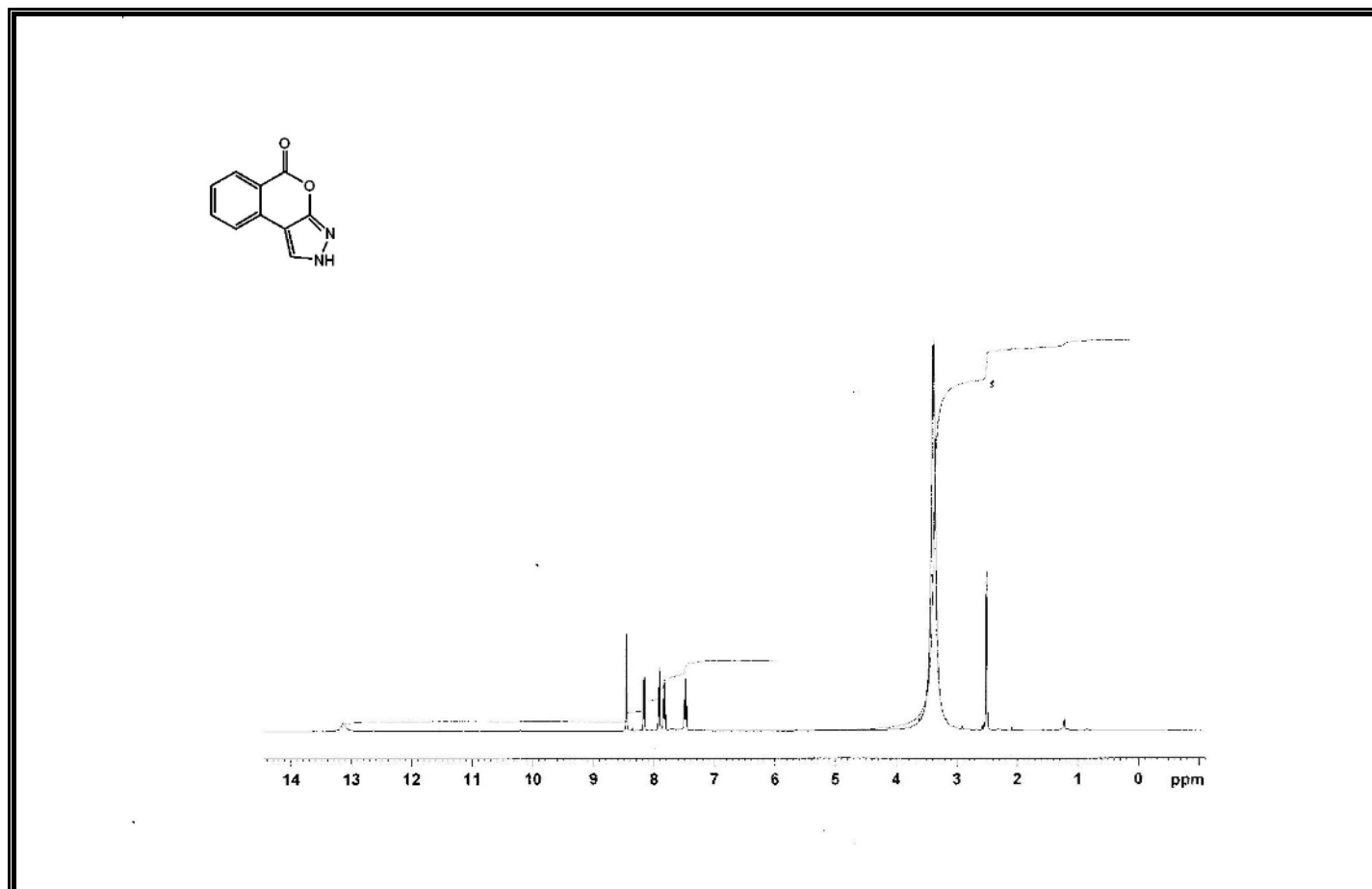


Figure A202 ^1H -NMR Spectrum of Compound 407.

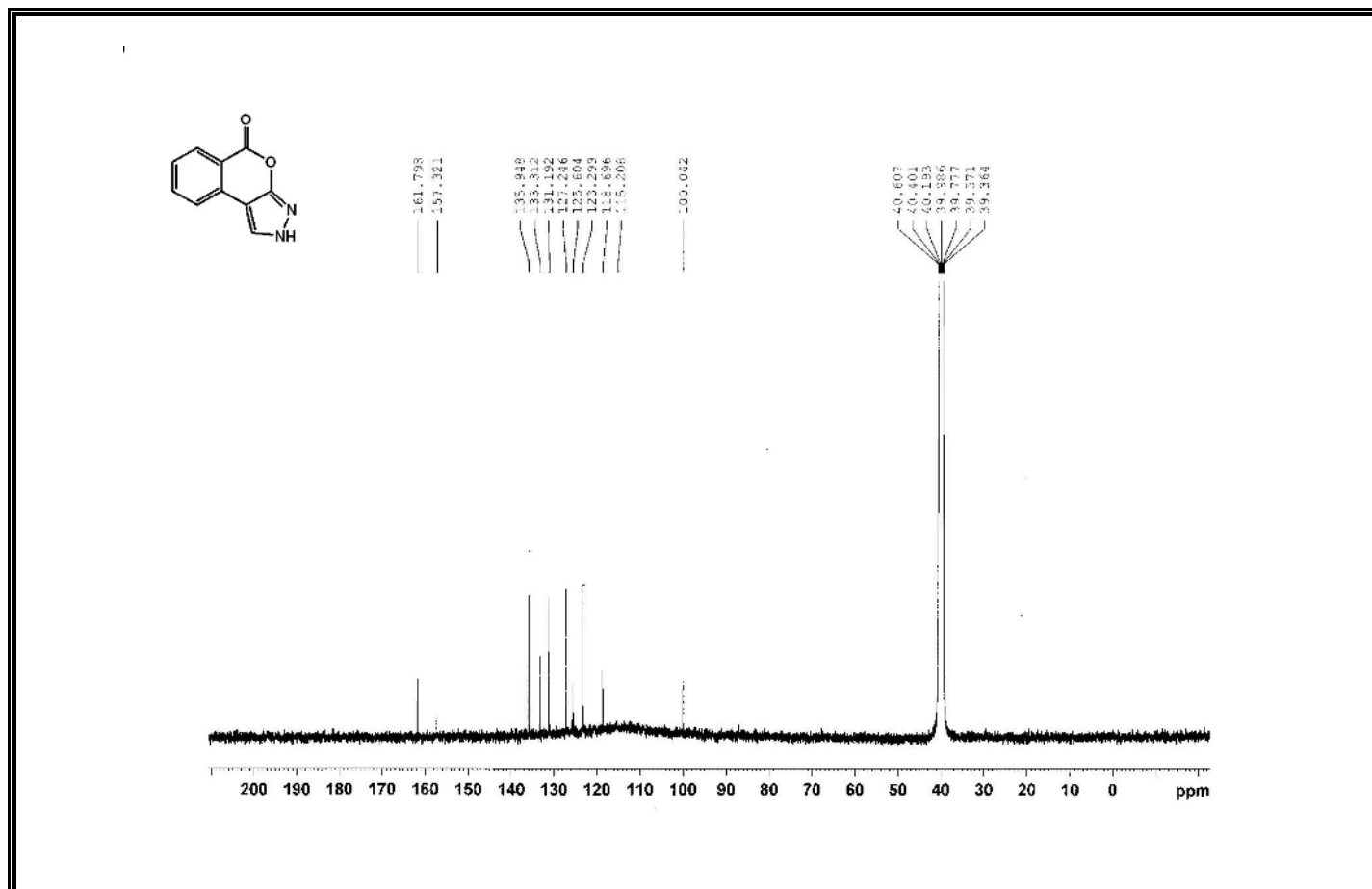


Figure A203 ^{13}C -NMR Spectrum of Compound 407.

DEPT-90

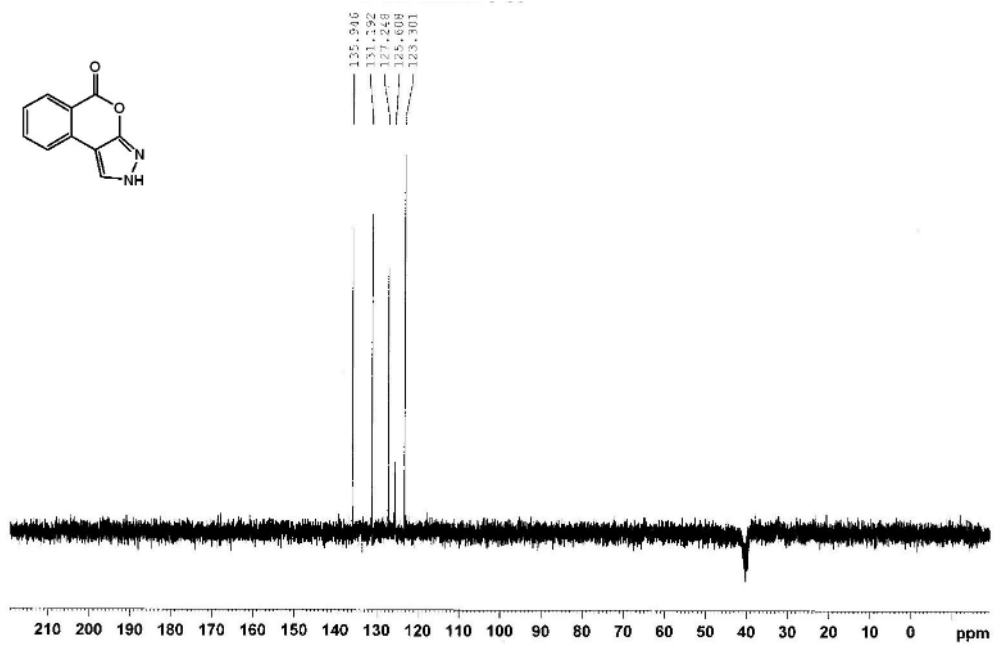


Figure A204 DEPT-90 Spectrum of Compound 407.

Figure A205 DEPT-135 Spectrum of Compound **407**.

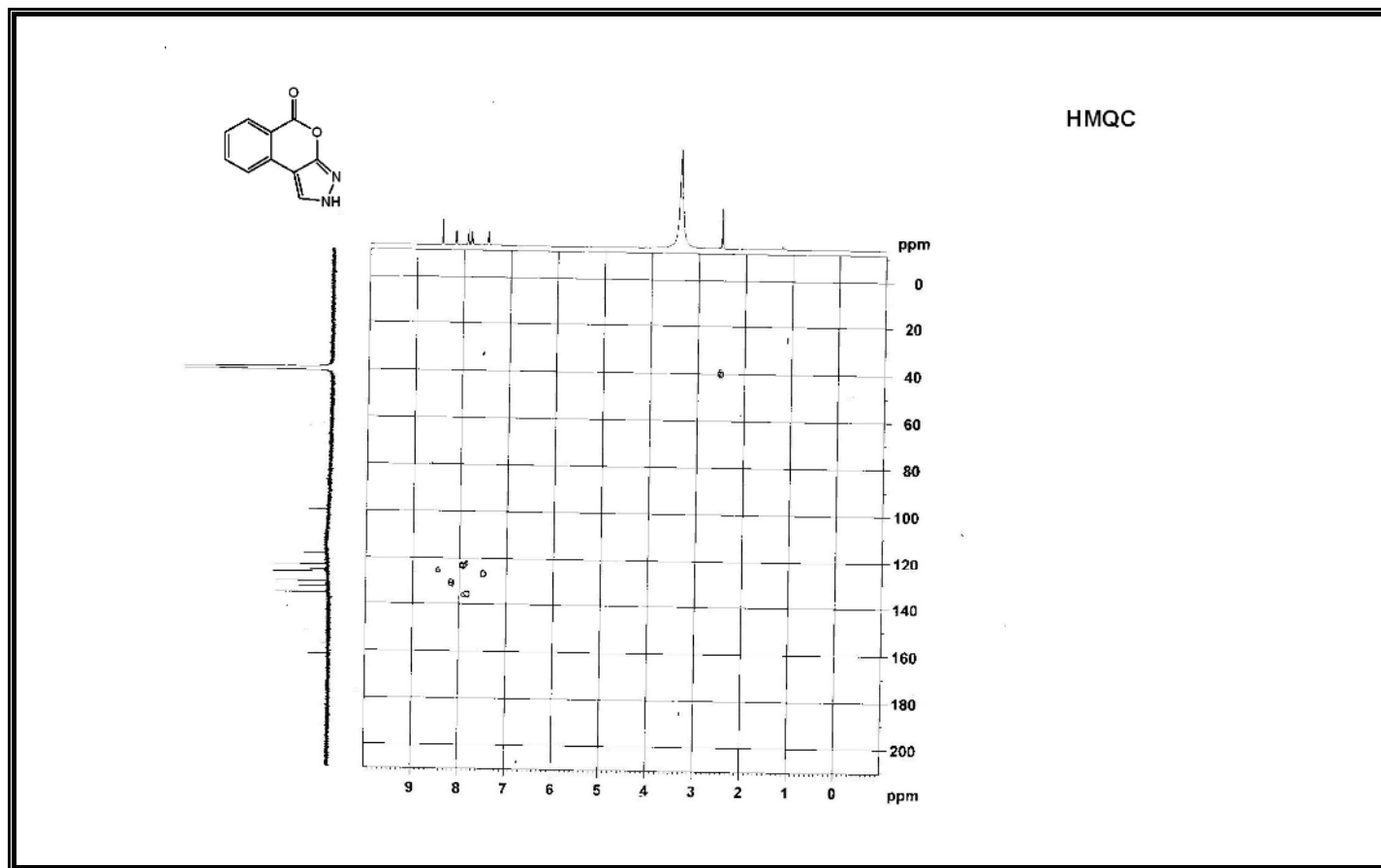


Figure A206 HMQC Spectrum of Compound 407.

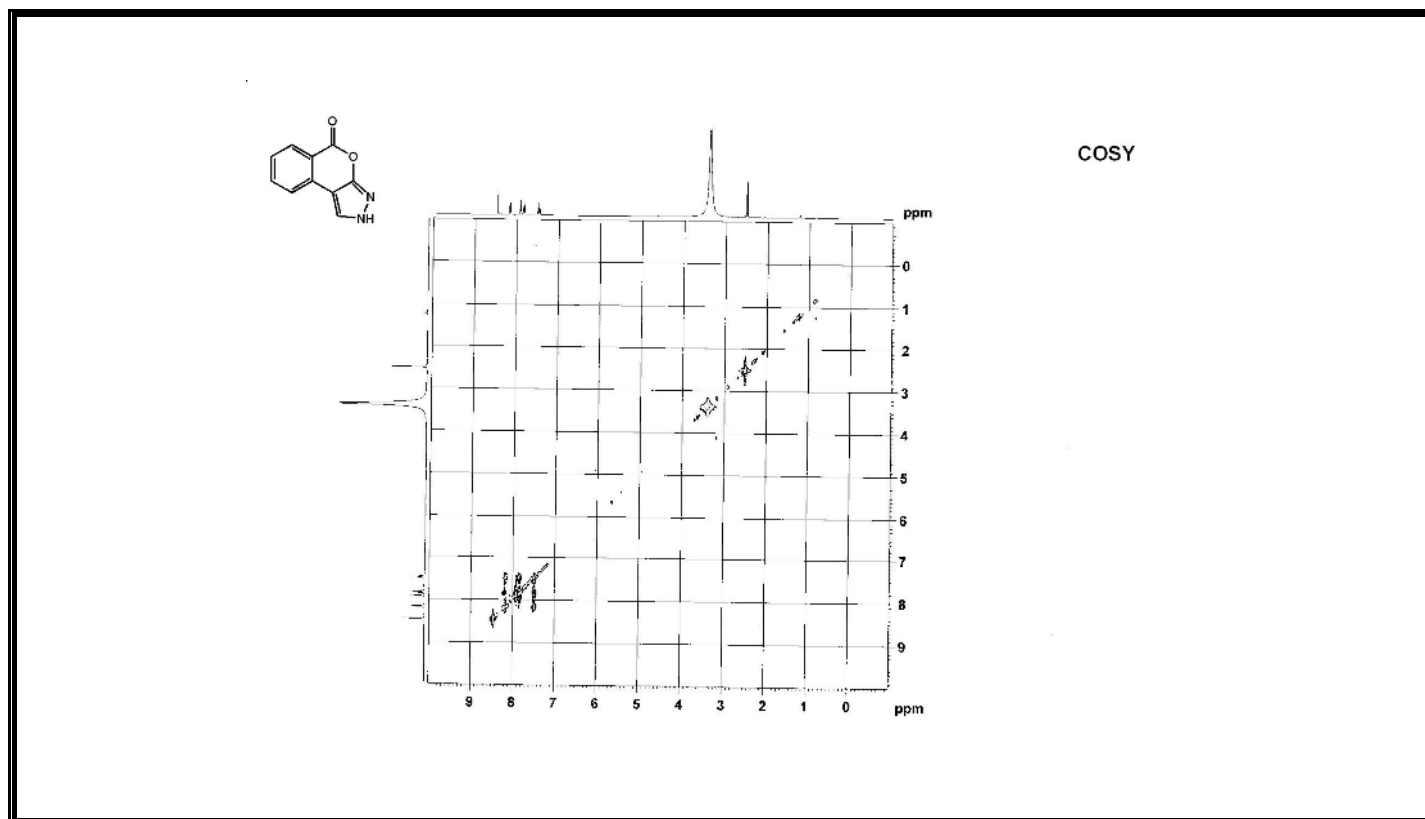


Figure A207 COSY Spectrum of Compound 407.

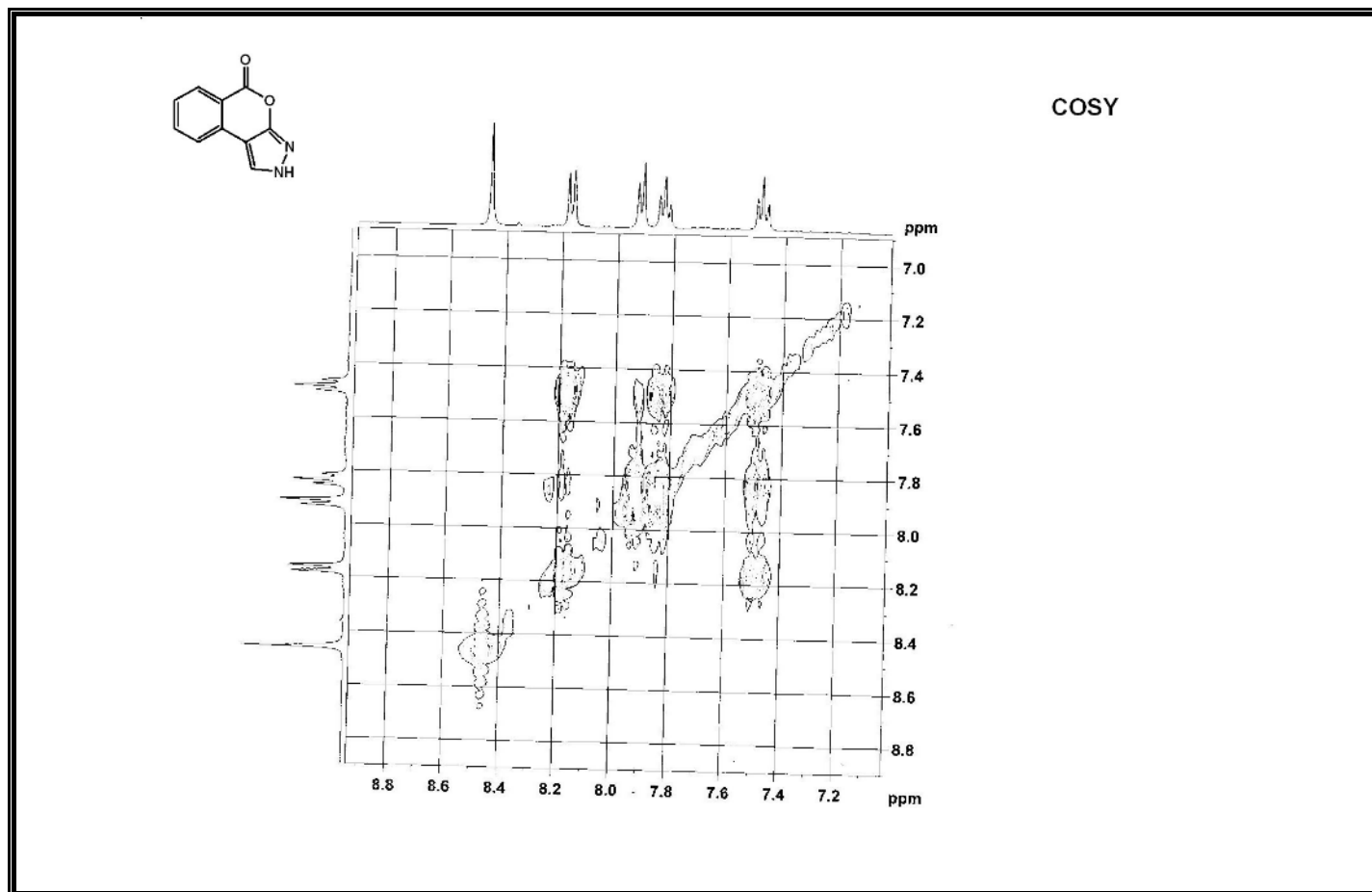


Figure A208 Expanded COSY Spectrum of Compound **407**.

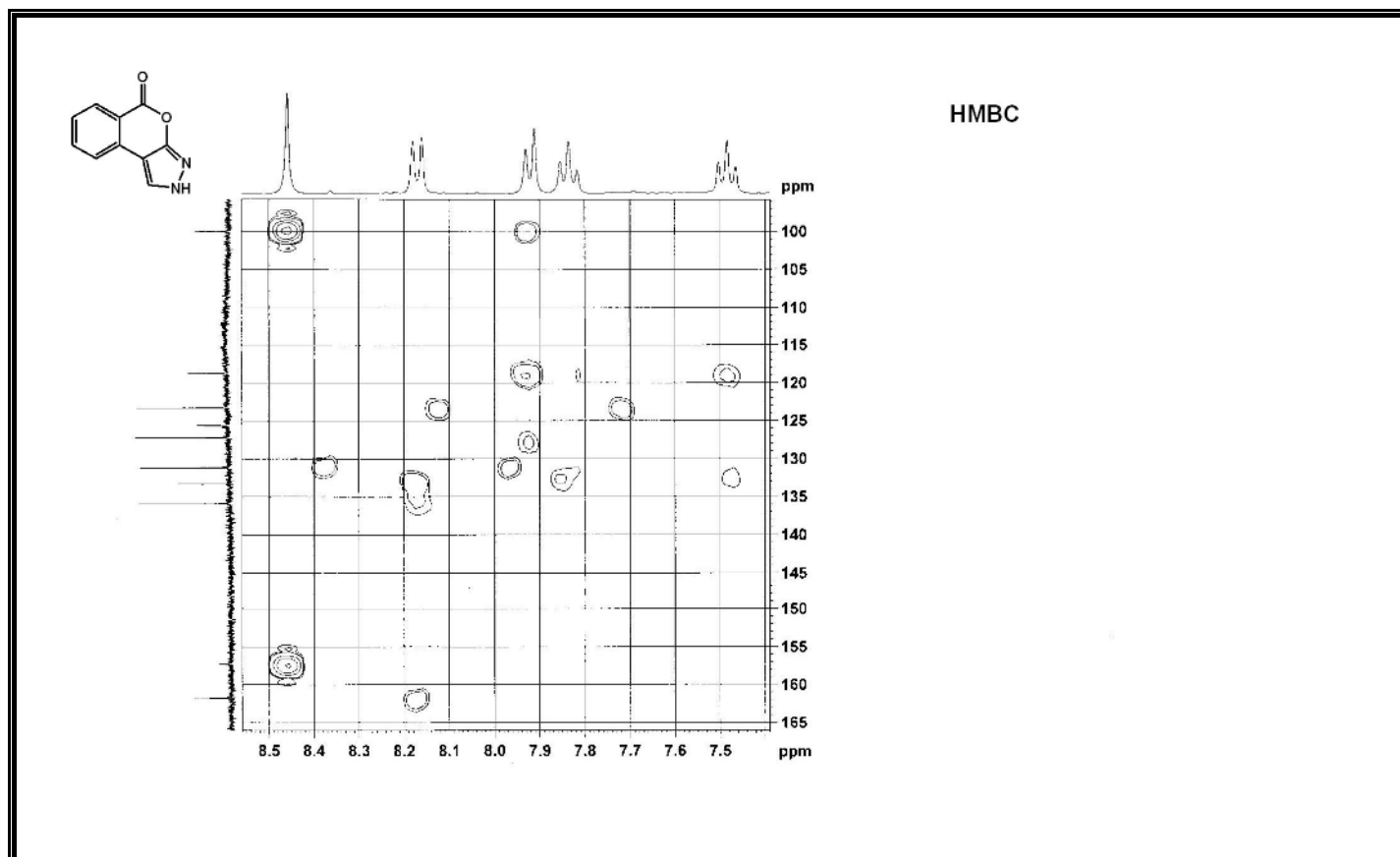


Figure A209 A part of HMBC Spectrum of Compound **407**.

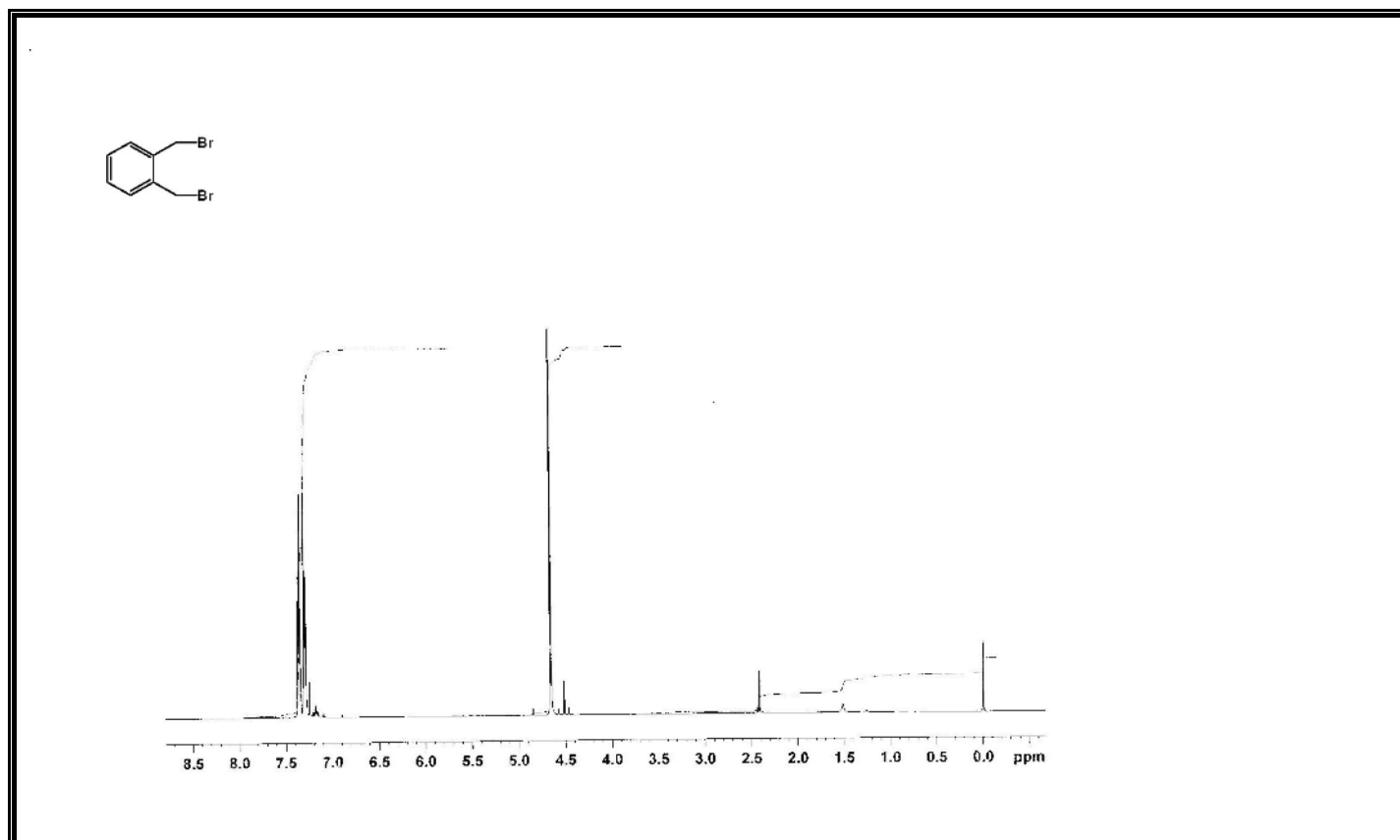


Figure A210 ^1H -NMR Spectrum of Compound 413.

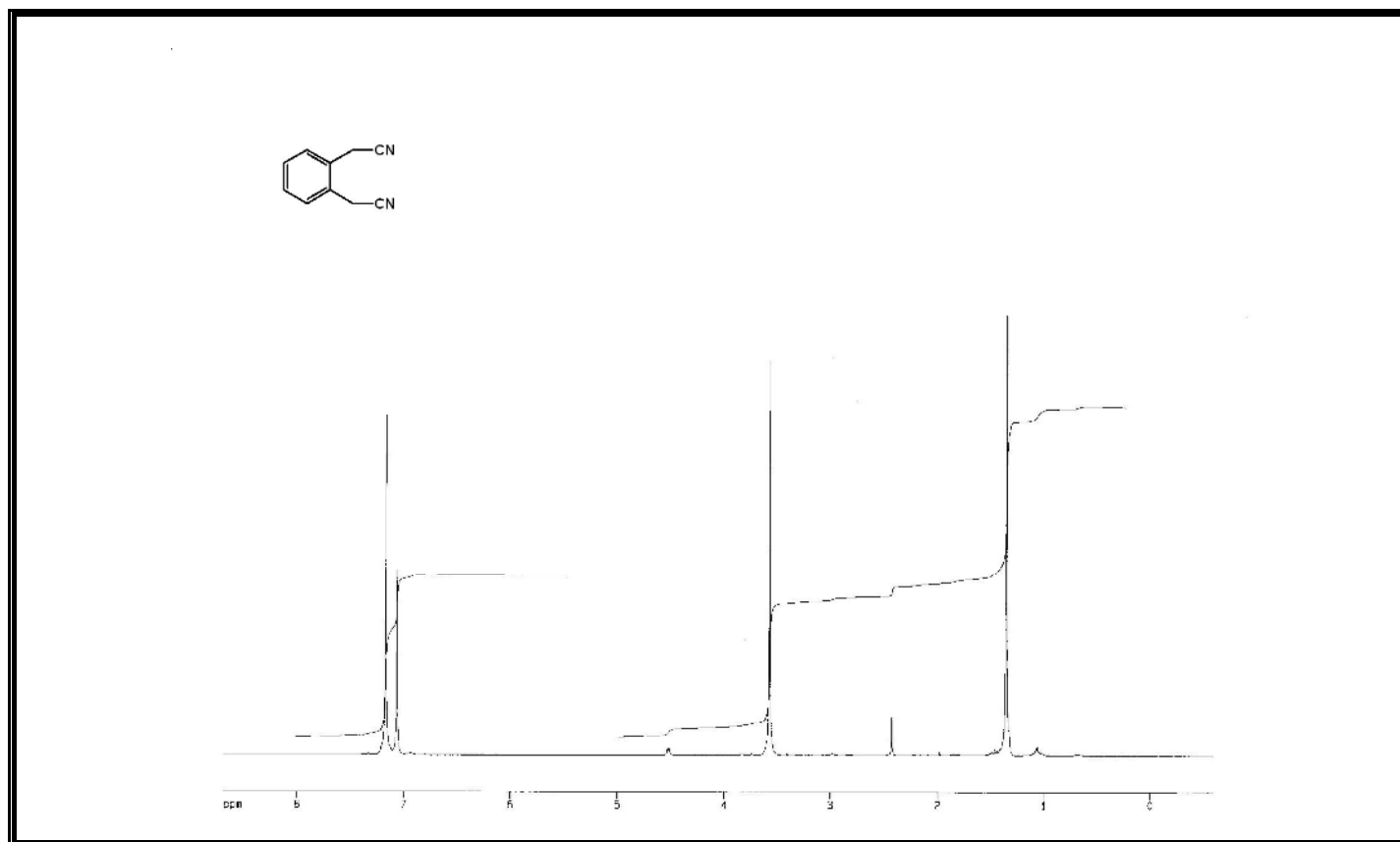


Figure A211 ^1H -NMR Spectrum of Compound **414**.

Figure A212 ^1H -NMR Spectrum of Compound **289**.

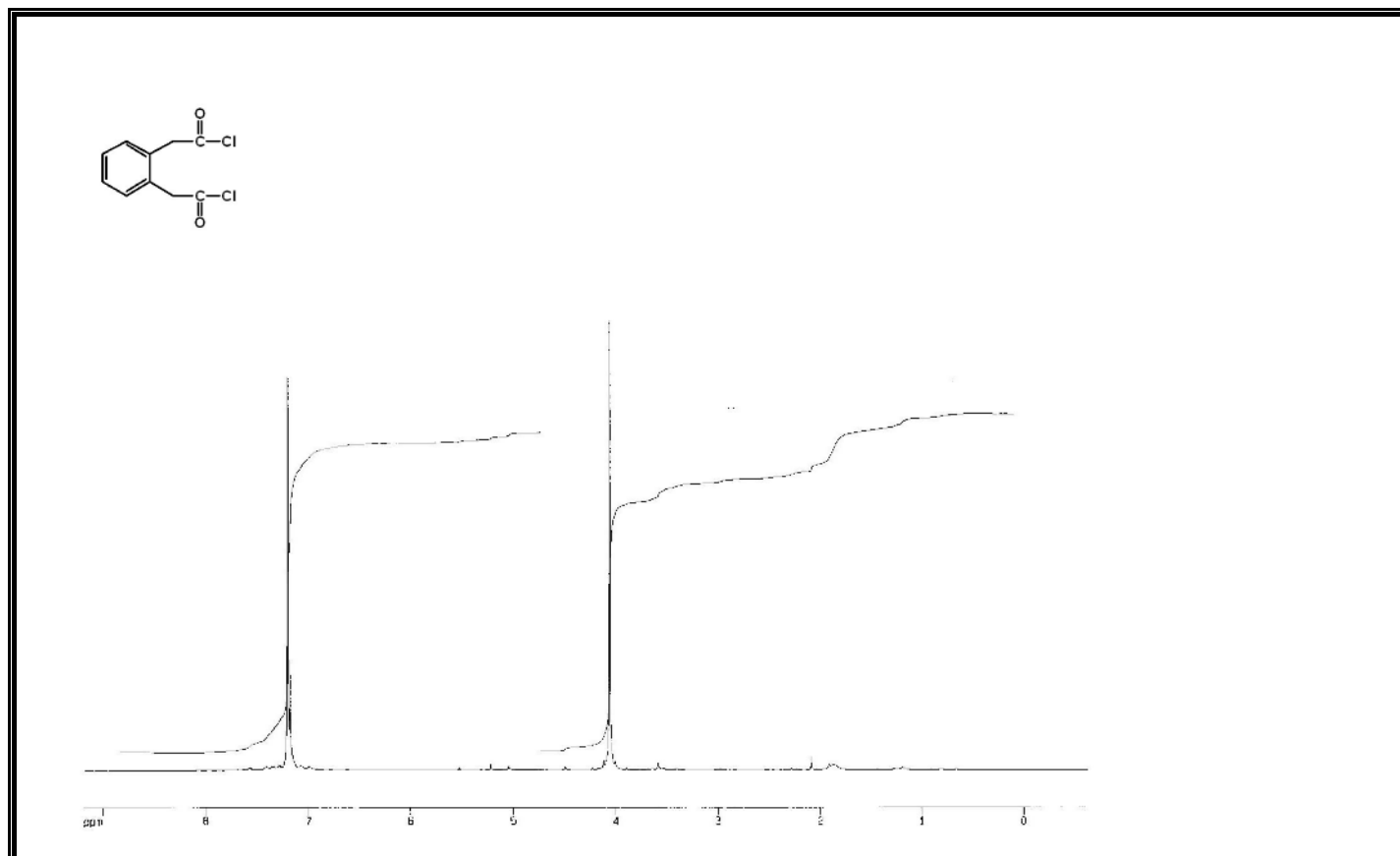


Figure A213 ^1H -NMR Spectrum of Compound 415.

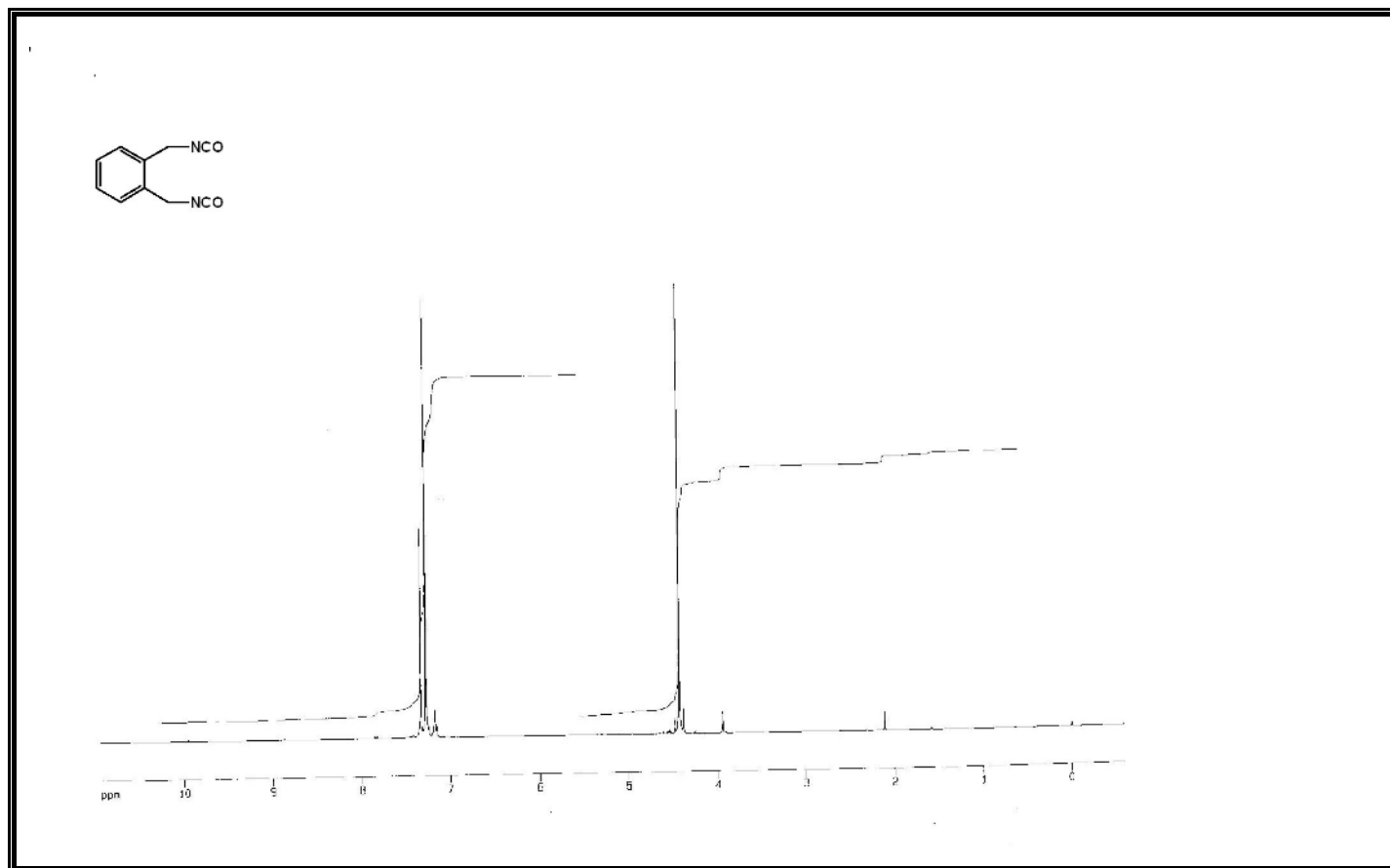


Figure A214 ^1H -NMR Spectrum of Compound 293

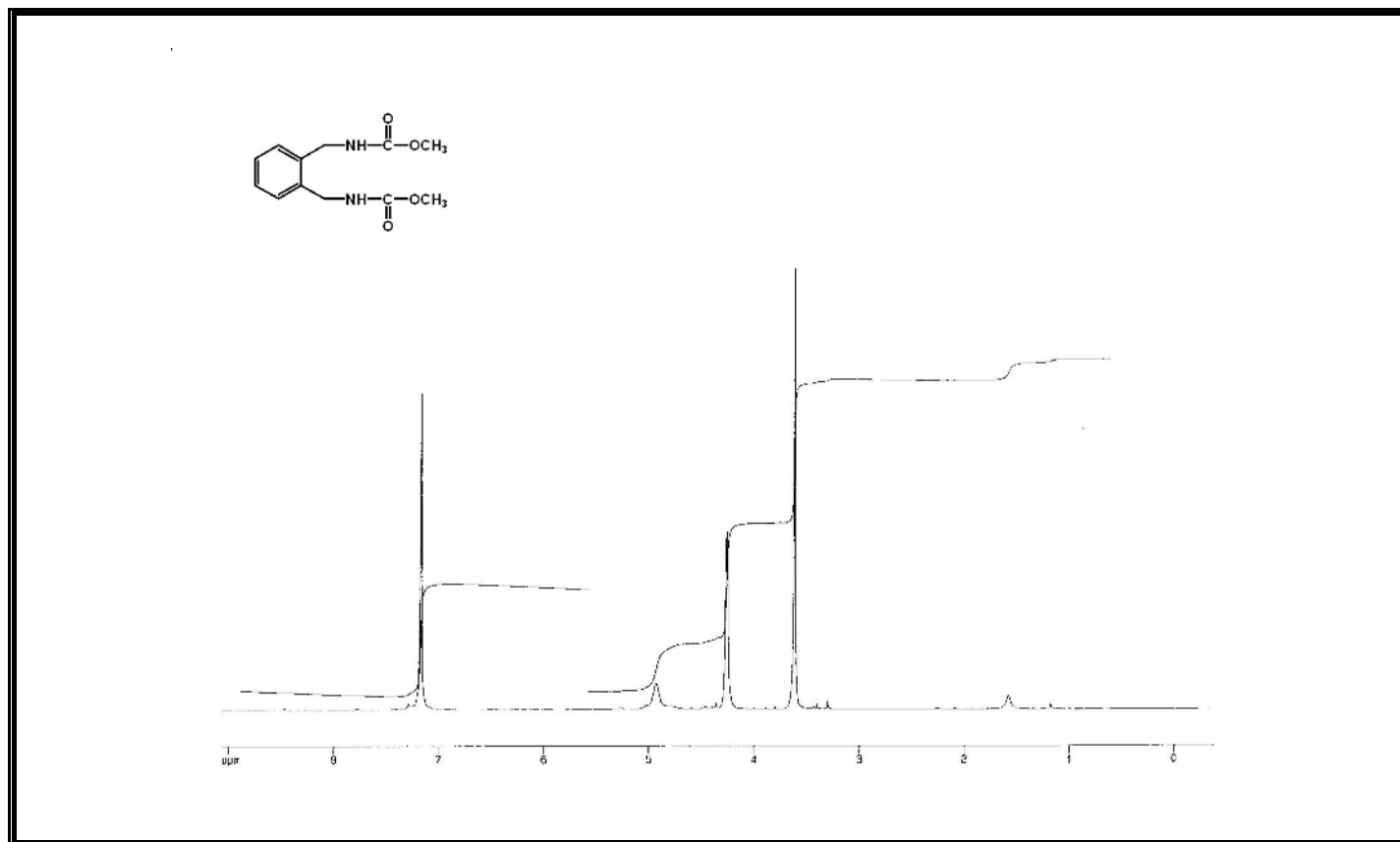


Figure A215 ^1H -NMR Spectrum of Compound 418.

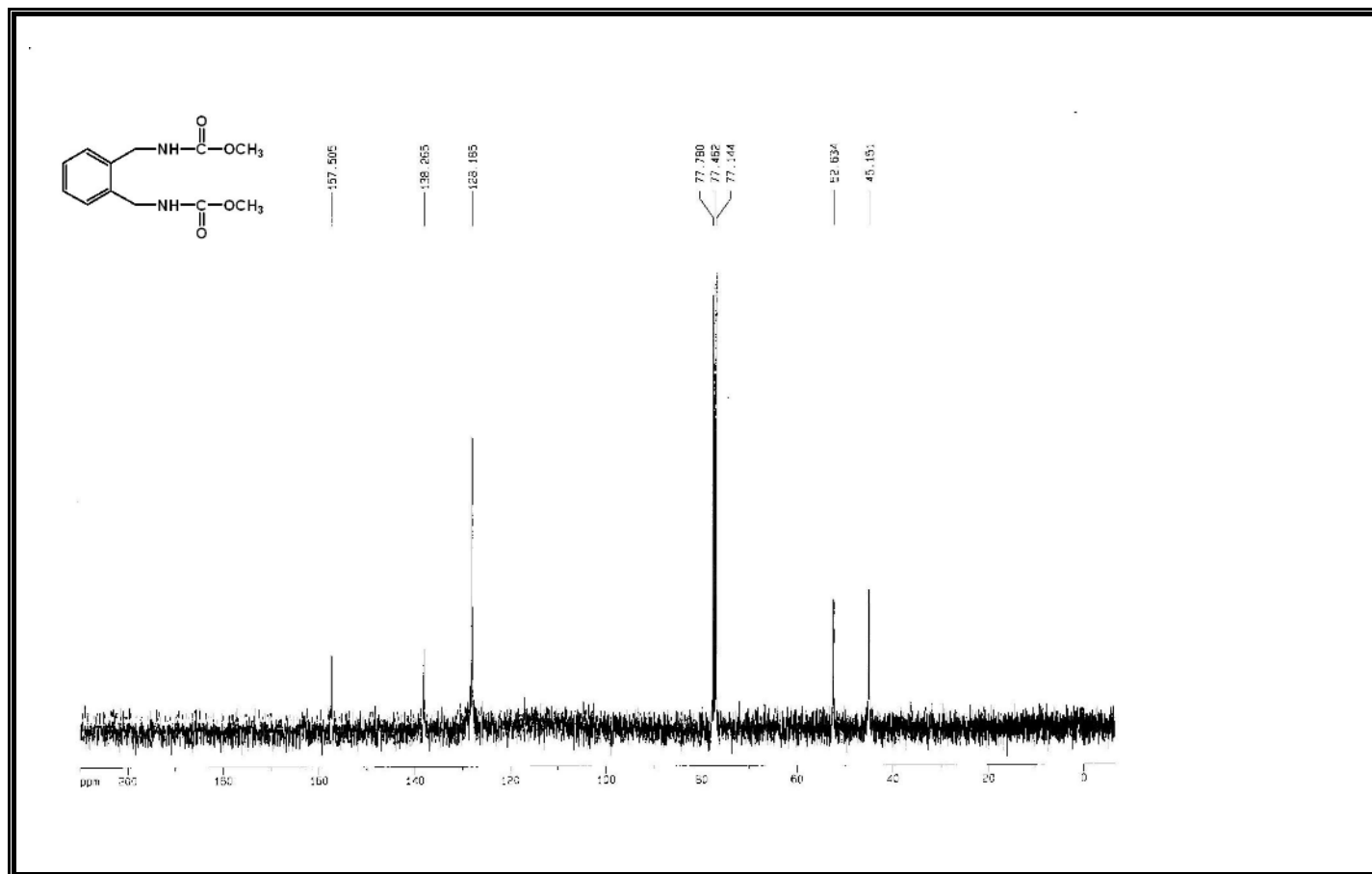


Figure A216 ^{13}C -NMR Spectrum of Compound 418.

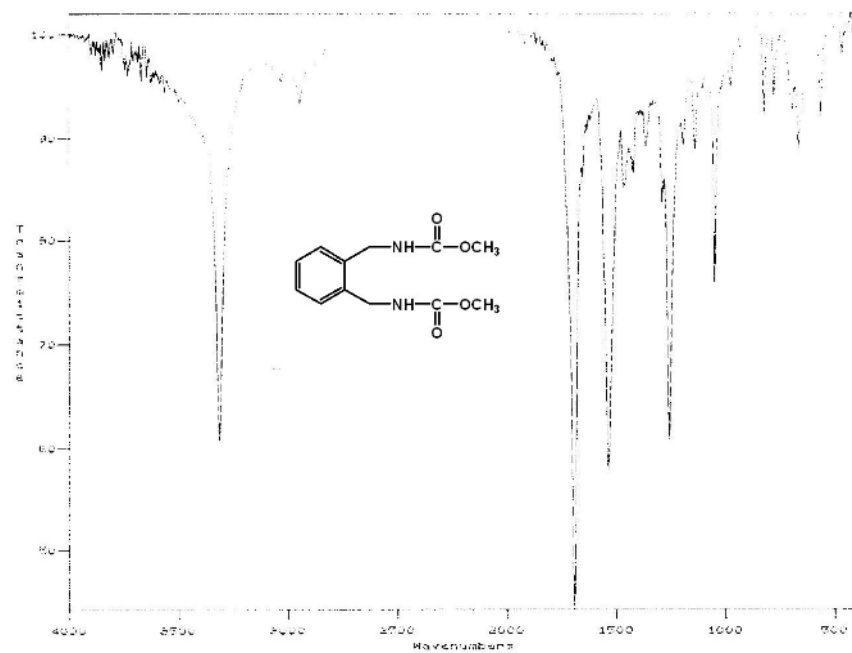


Figure A217 IR Spectrum of Compound 418.

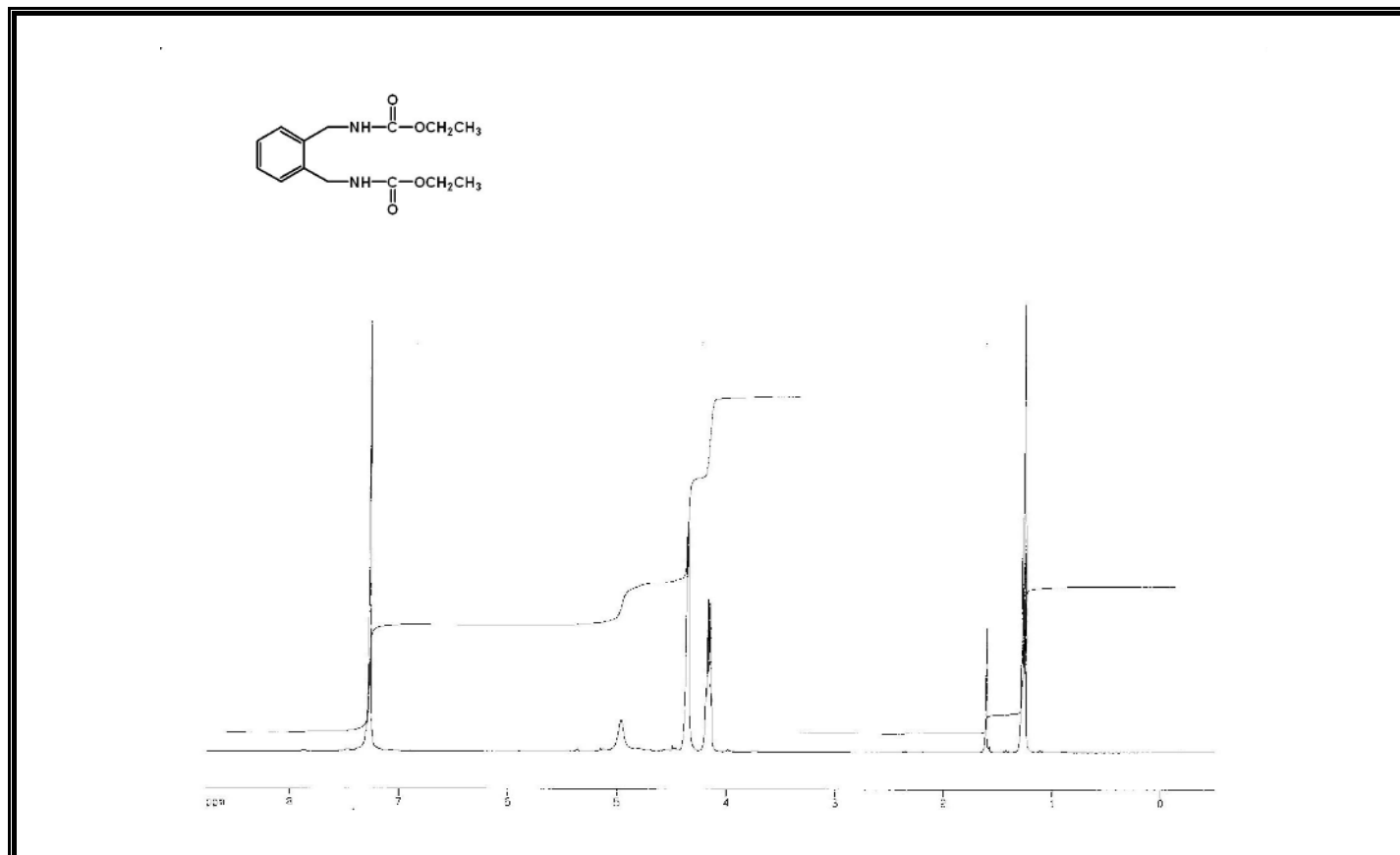


Figure A218 ^1H -NMR Spectrum of Compound **419**.

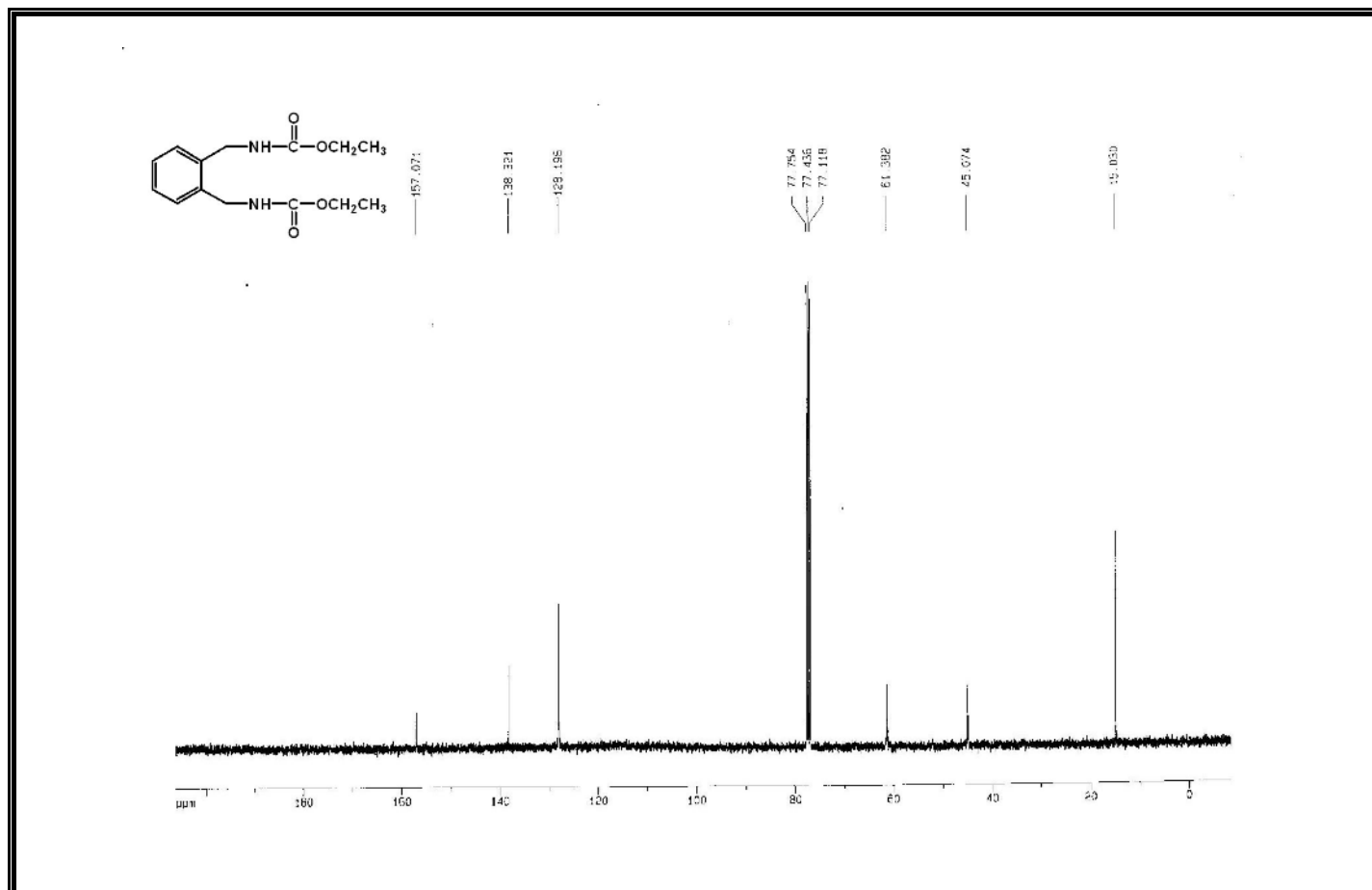


Figure A219 ^{13}C -NMR Spectrum of Compound 419.

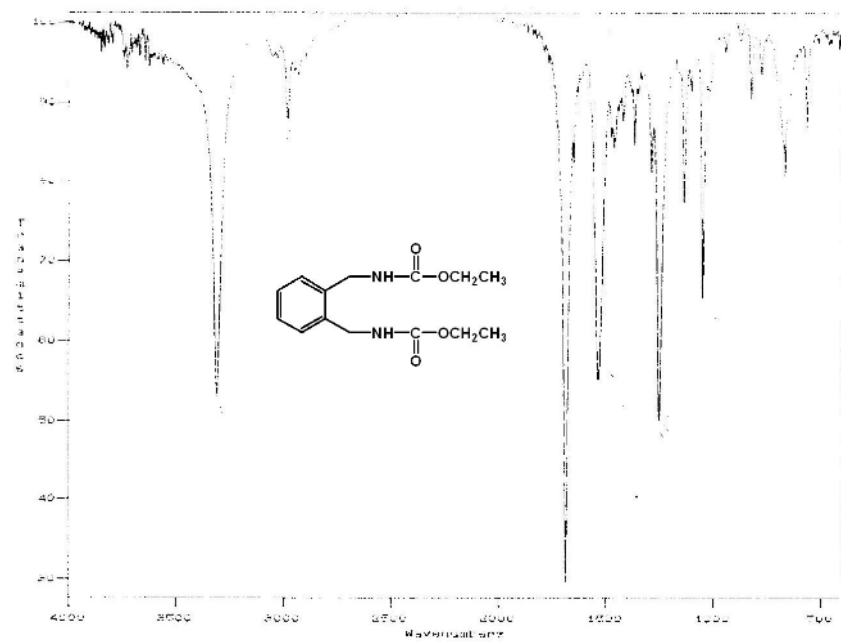


Figure A220 IR Spectrum of Compound 419.

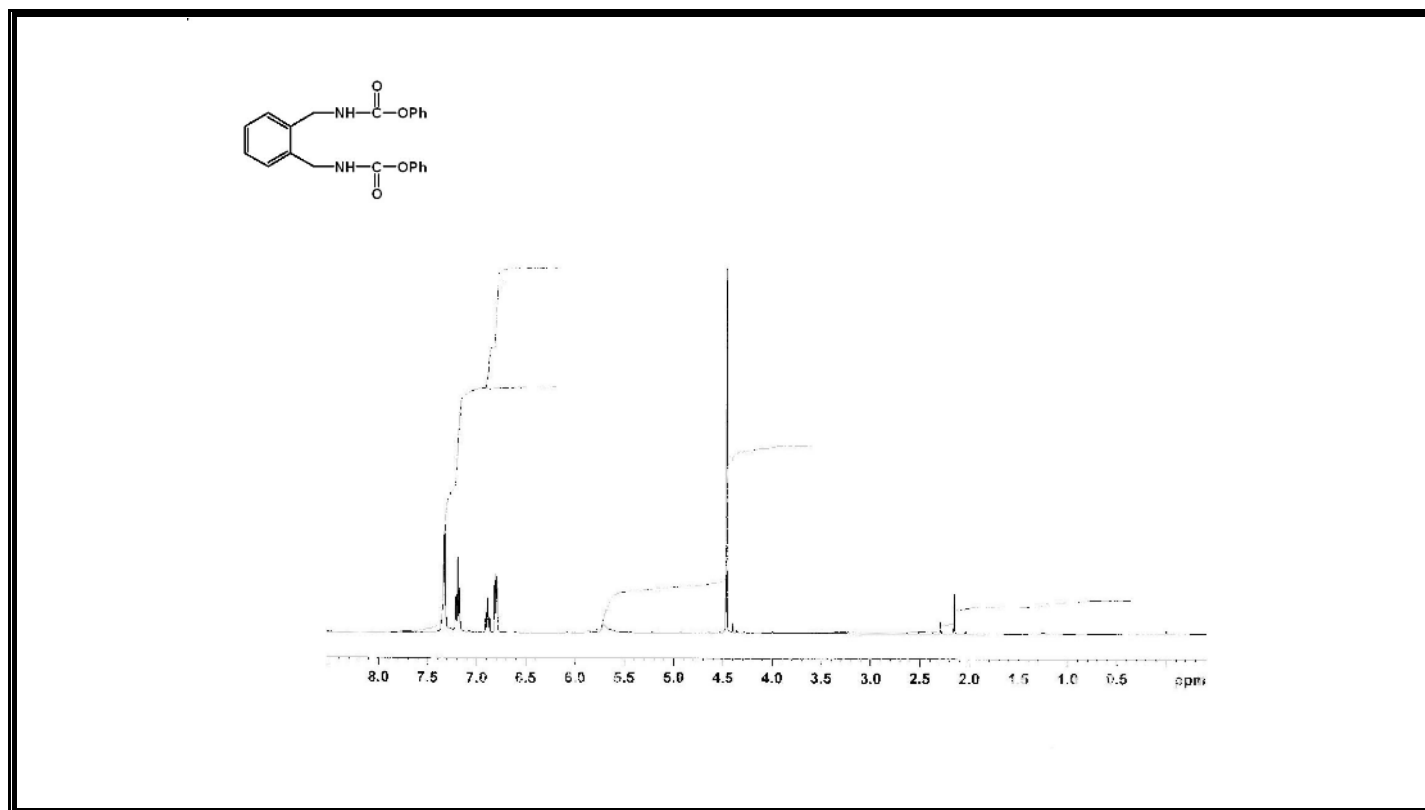


Figure A221 ^1H -NMR Spectrum of Compound 420.

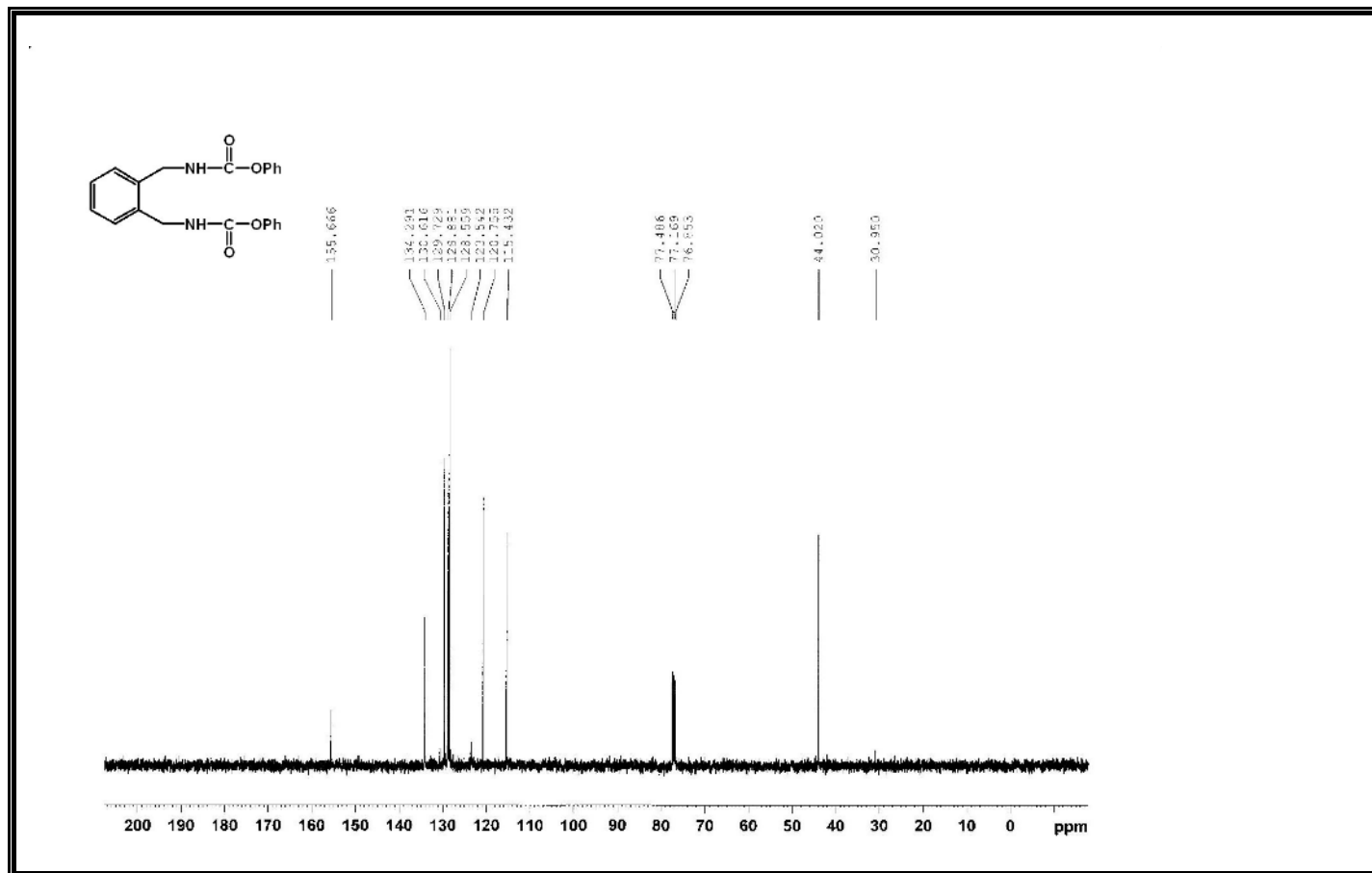


Figure A222 ¹³C-NMR Spectrum of Compound 420.

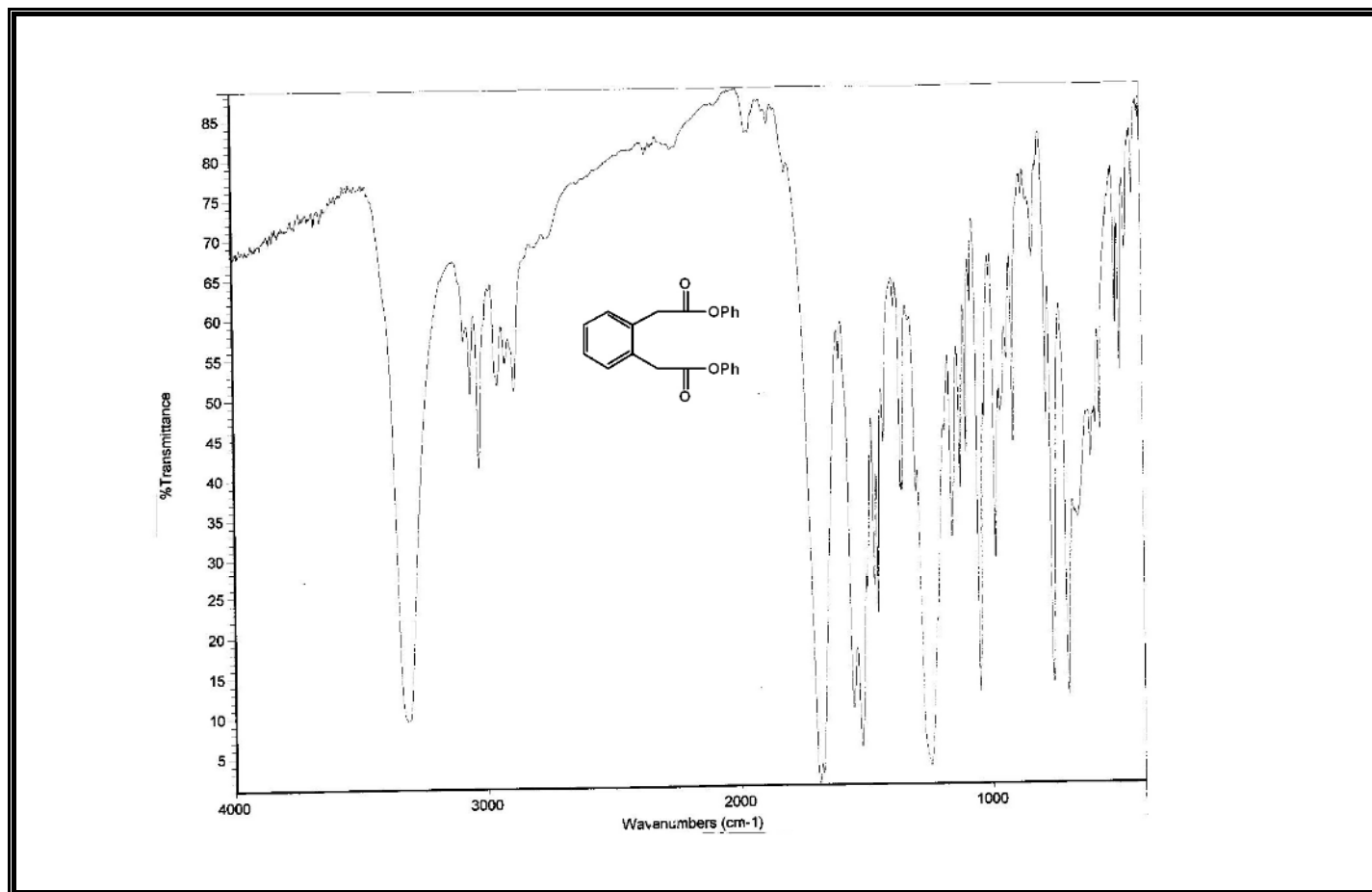


Figure A223 IR Spectrum of Compound 420.

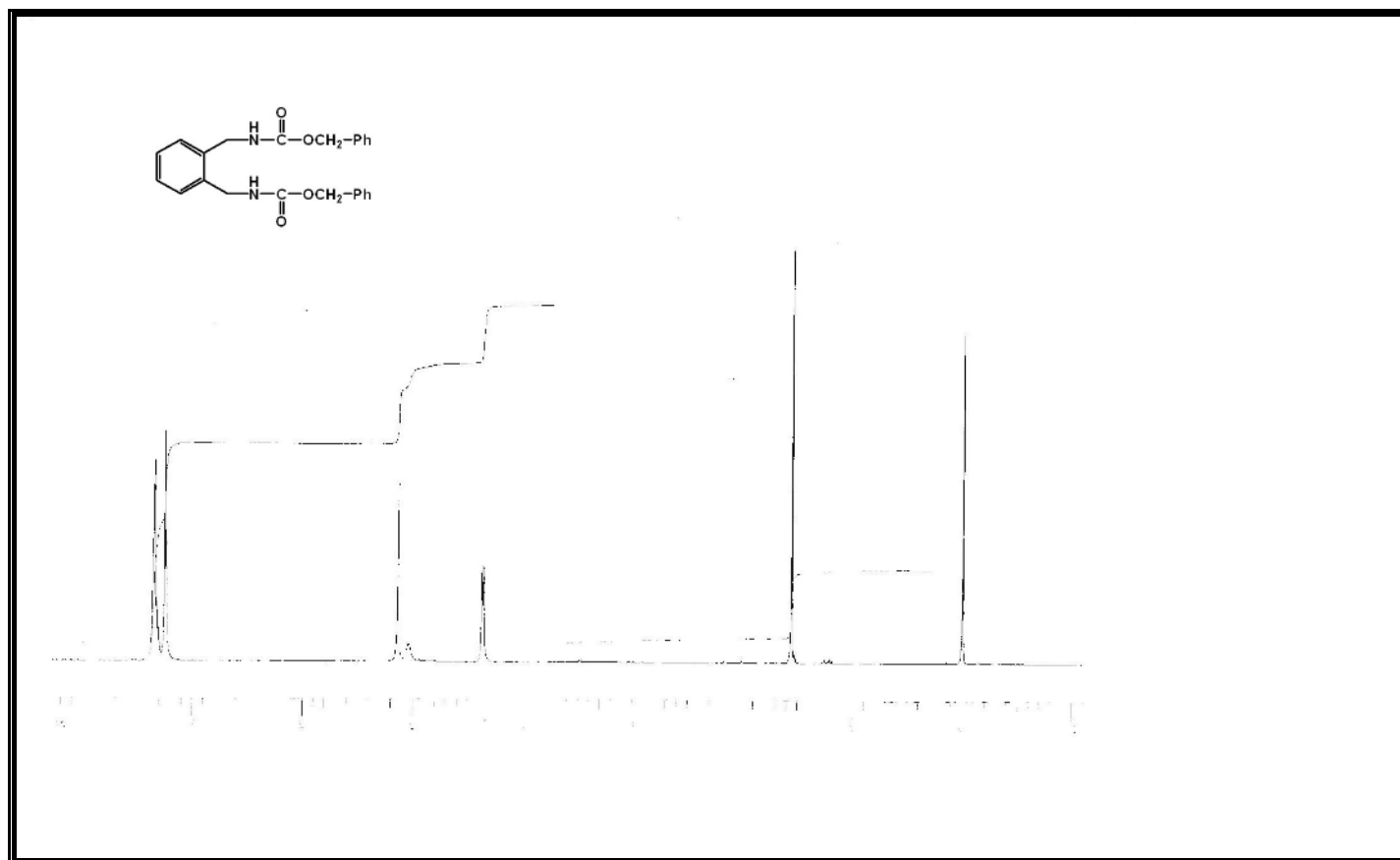


Figure A224 ^1H -NMR Spectrum of Compound 421.

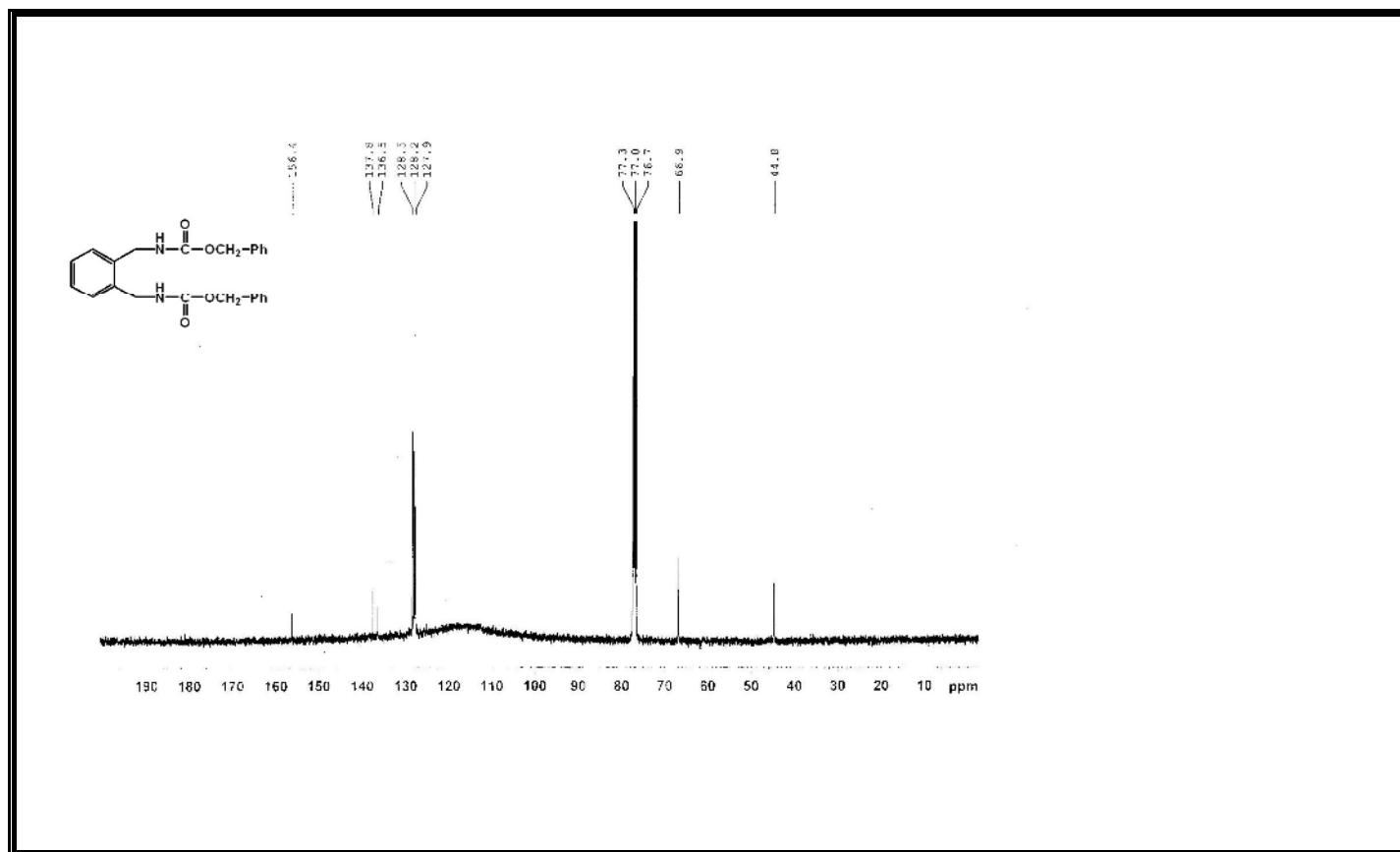


Figure A225 ^{13}C -NMR Spectrum of Compound 422.

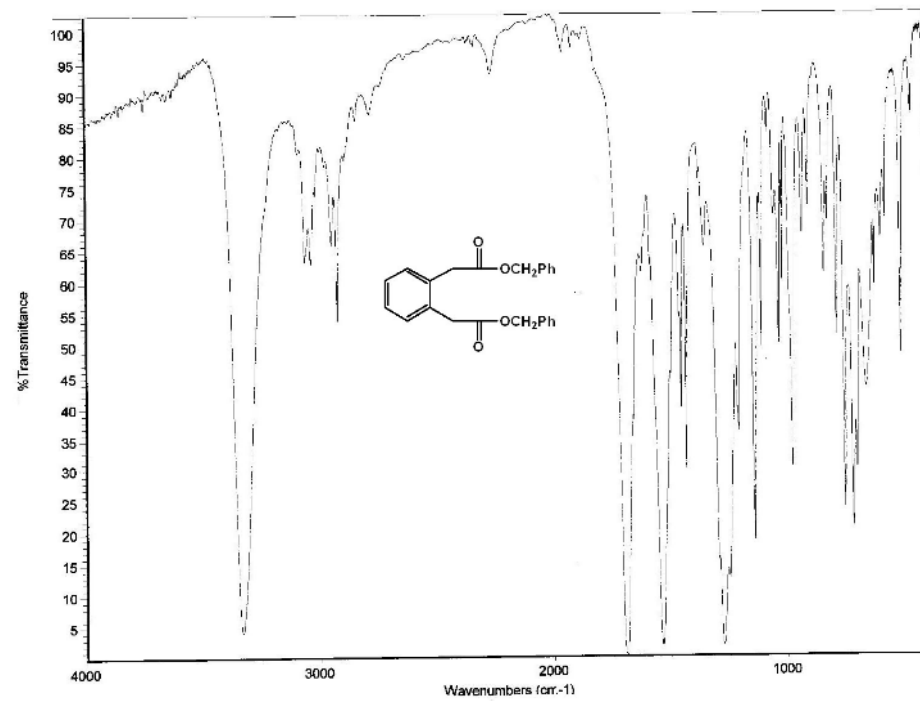


Figure A226 IR Spectrum of Compound 421.

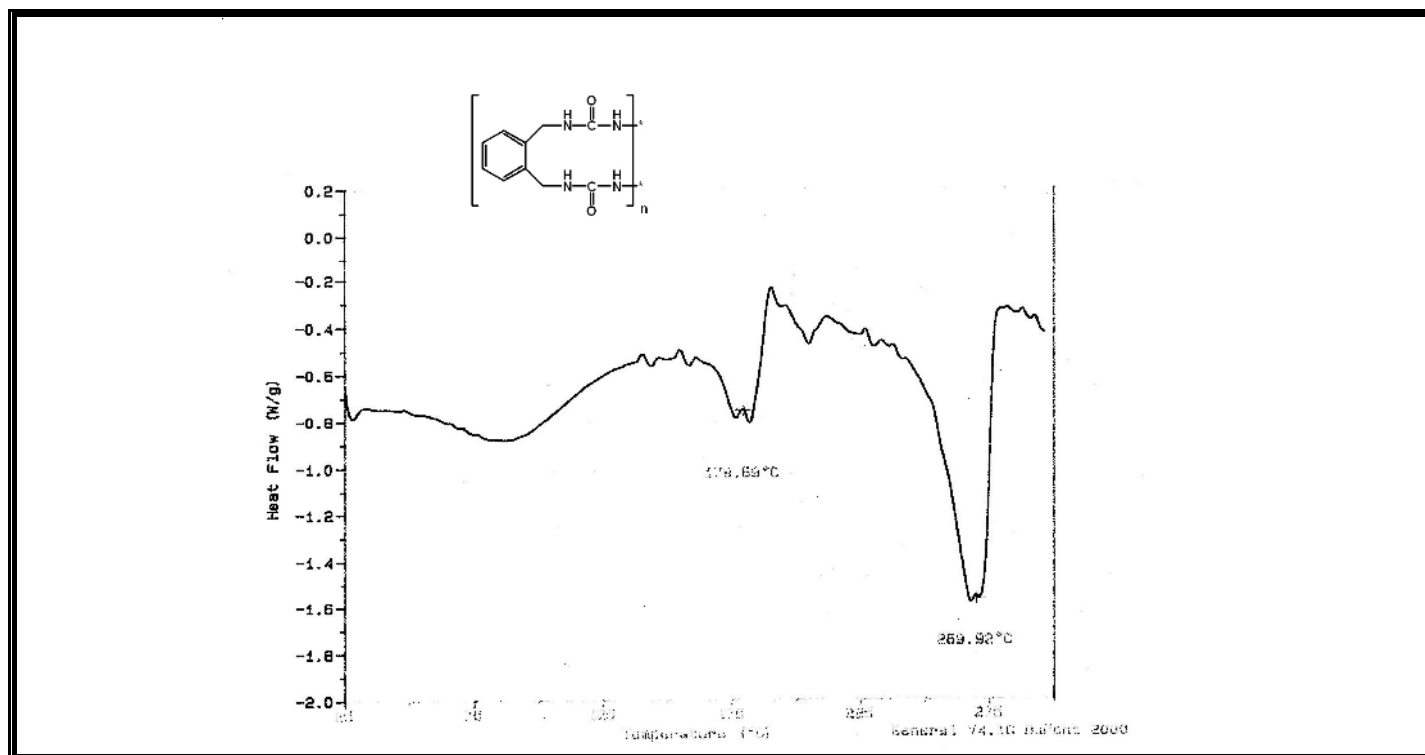


Figure A227 DSC Spectrum of Compound 424.

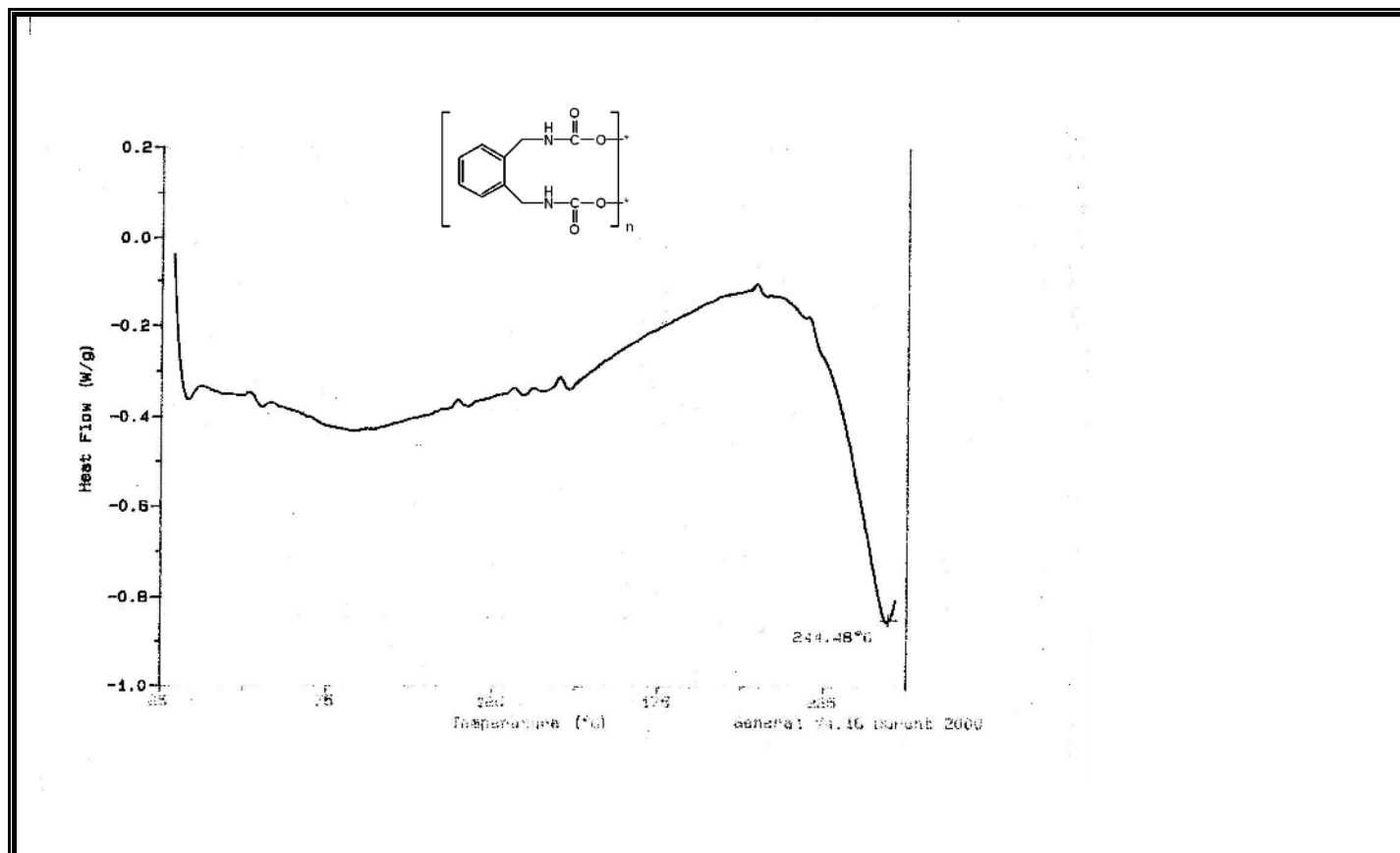


Figure A228 DSC Spectrum of Compound 427.

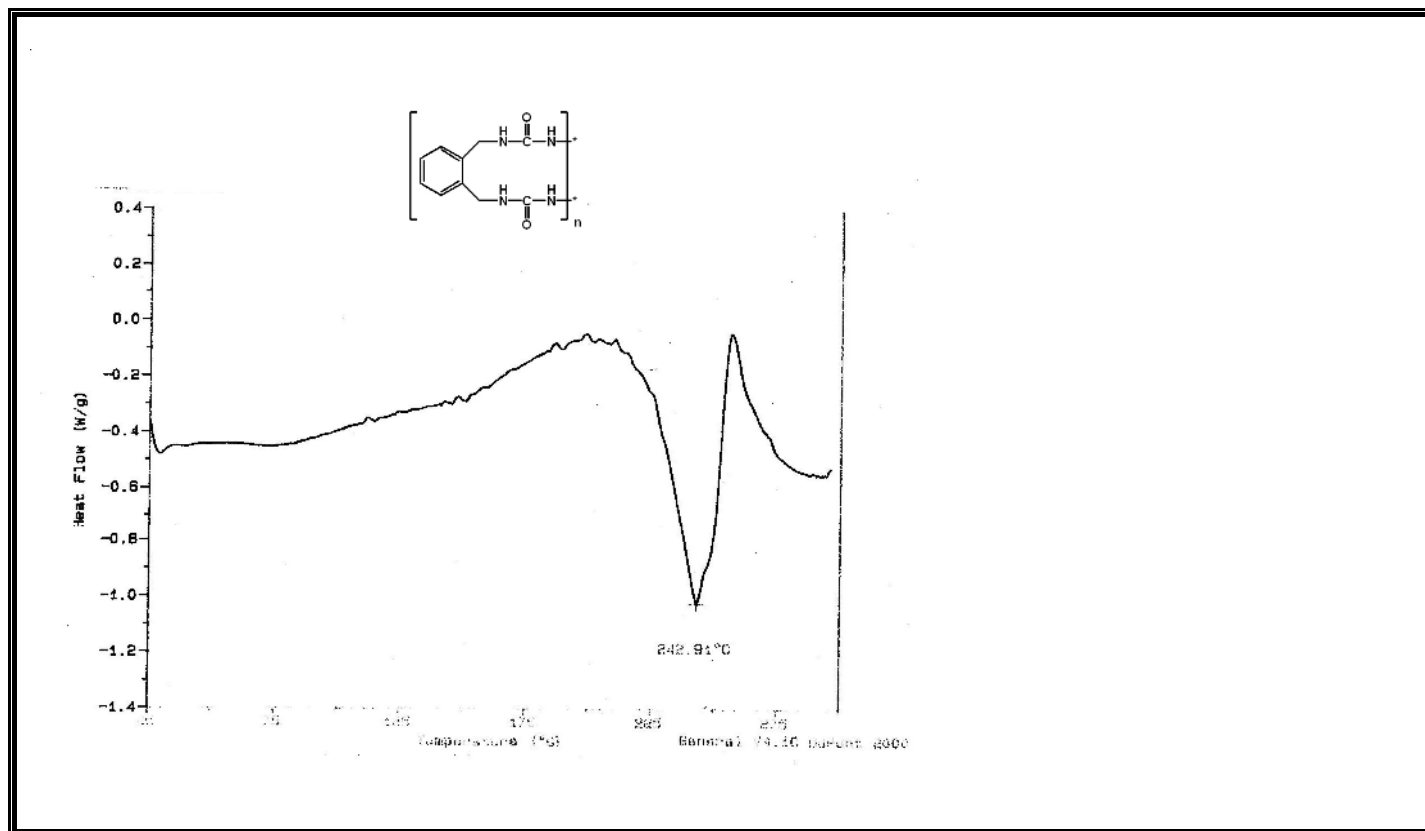


Figure A229 DSC Spectrum of Compound **428**.

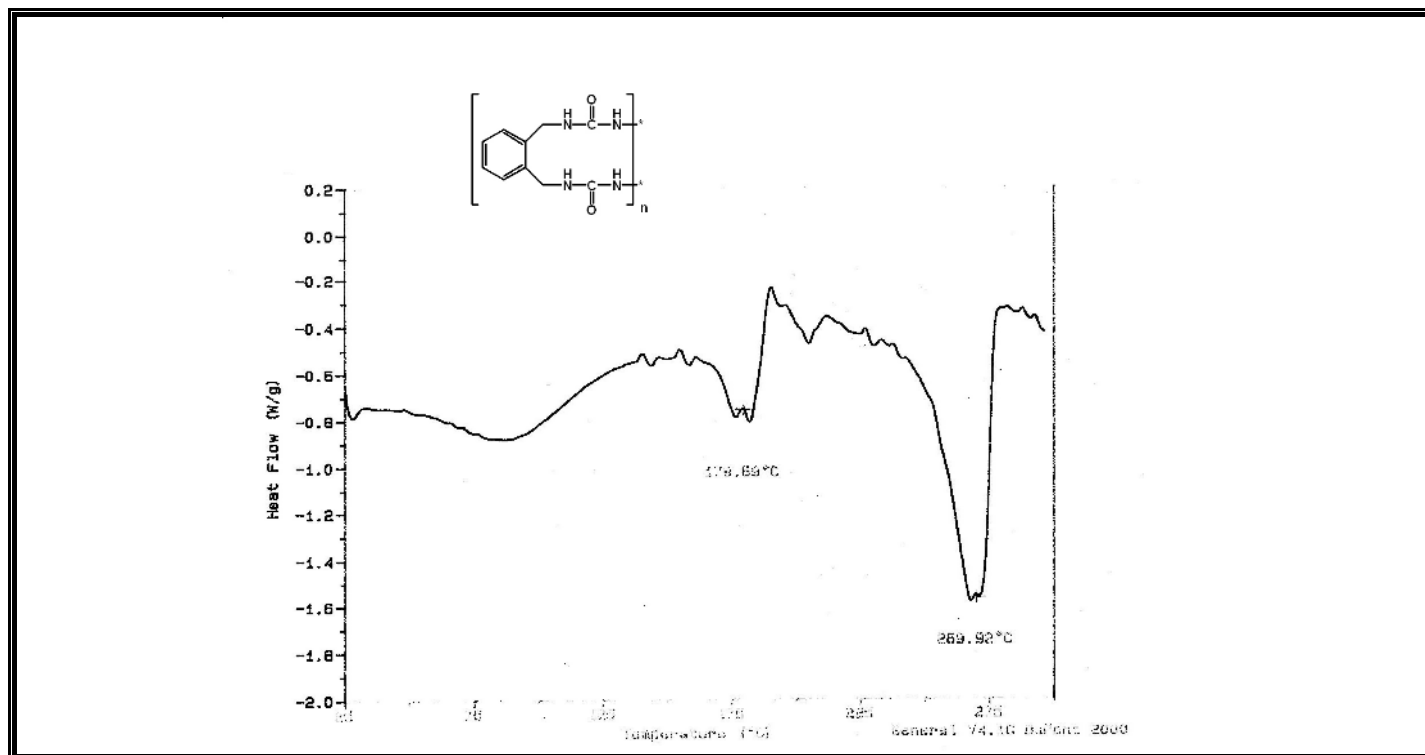


Figure A230 DSC Spectrum of Compound 424.

APPENDIX B

SUPPLEMENTARY TABLES FOR compound no. 1

Table 1
Fractional atomic coordinates and isotropic temperature factors (Angstrom squared), with standard deviations in the least significant digits in parentheses. For anisotropic atoms, the equivalent isotropic temperature factors are shown.

	x/a	y/b	z/c	U
C(8)	0.3481(13)	0.1158(3)	0.3169(12)	0.099
H(22A)	0.3686	0.2199	0.3014	0.145
H(22B)	0.3632	0.0348	0.2463	0.145
H(22C)	0.41616	0.0468	0.3594	0.145
O(4)	0.3453(2)	0.2056(2)	0.5238(1)	0.093(3)
H(15)	-0.06629	0.03260	0.75810	0.063(3)
O(3)	0.13644(17)	0.2653(15)	0.4235(11)	0.069
C(13)	0.2271(2)	-0.0159(2)	0.593(1)	0.059
C(11)	0.0197(2)	0.0724(2)	0.7763(1)	0.059
C(12)	0.1129(2)	-0.0311(2)	0.6379(1)	0.057
C(2)	0.15043(18)	0.14471(18)	0.38274(2)	0.077
C(10)	0.0409(2)	0.2263(2)	0.773(1)	0.059
C(6)	-0.1010(2)	0.2703(2)	0.5393(2)	0.053
C(14)	0.2501(3)	0.1334(2)	0.6831(2)	0.066
C(7)	0.0581(3)	0.2293(2)	0.4827(2)	0.066
C(1)	-0.1726(2)	0.3422(2)	0.5504(2)	0.062
C(9)	-0.0587(3)	0.3737(2)	0.7169(2)	0.073
C(5)	-0.2181(3)	0.2486(3)	0.4823(2)	0.070
N(5)	-0.17107	0.2031	0.40506	0.077
C(18)	0.0918(3)	-0.2159(2)	0.8434(2)	0.072
N(49)	0.01538	-0.24857	0.81383	0.090
C(16)	0.2293(3)	-0.2951(3)	0.5615(2)	0.081
C(17)	0.35887	-0.37539	1.00284	0.094
C(15)	0.3201(3)	-0.1359(3)	0.5525(2)	0.073
H(16)	0.39686	-0.10879	0.58750	0.083
O(1)	0.20107(19)	0.26784(23)	0.52273(13)	0.095
C(3)	-0.4741(2)	0.3867(3)	0.6428(2)	0.084
H(3)	-0.59939	0.39793	0.67763	0.095
O(2)	-0.0611(3)	0.3151(2)	0.7402(2)	0.075
C(2)	-0.3862(3)	0.3803(3)	0.7007(2)	0.075
H(2)	-0.40933	0.43923	0.71939	0.086
C(4)	-0.4034(3)	0.2992(3)	0.5318(2)	0.084
H(4)	-0.48056	0.27912	0.49526	0.091
C(17)	0.1838(3)	-0.3368(3)	0.5026(2)	0.081
H(18)	0.16963	-0.44477	0.51629	0.092

Table 2
Vibration parameters (Angstrom squared) in the expression:
-2(p_{ij} squared) U_{ij}[(h.a_i squared) + 022:(k.b_j squared) +
033:(l.c_j squared) + 2.012:h.k.a_i.b_j + 2.013:h.l.a_i.c_j +
2.023:k.l.b_j.c_j)

	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
C(8)	0.065(1)	0.099(2)	0.106(2)	-0.021(1)	0.001(1)	-0.006(1)
O(4)	0.039(1)	0.091(2)	0.108(1)	-0.042(1)	-0.065(2)	0.013(1)
O(3)	0.073(8)	0.0637(7)	0.0685(8)	-0.0284(5)	-0.0358(6)	0.0008(6)
C(13)	0.056(1)	0.066(1)	0.051(1)	-0.013(1)	-0.017(1)	0.000(1)

Table B1 X-Ray Spectrum data of Compound 368.

C(7) - C(6) - C(5) - H(5)	3.0
C(9) - C(6) - C(7) - C(1)	169.3
C(7) - C(6) - C(5) - C(4)	-177.0
C(9) - C(6) - C(1) - C(9)	-179.2
C(3) - C(6) - C(5) - H(5)	179.9
C(5) - C(6) - C(1) - C(2)	-0.5
C(1) - C(6) - C(5) - C(4)	-0.1
C(6) - C(1) - C(9) - C(10)	-77.2
C(6) - C(1) - C(9) - C(3)	109.7
C(6) - C(1) - C(2) - C(3)	6.9
C(2) - C(1) - C(9) - H(2)	-179.1
C(9) - C(1) - C(2) - C(10)	104.0
C(2) - C(1) - C(9) - C(3)	179.7
C(9) - C(1) - C(2) - H(2)	-69.0
C(5) - C(6) - C(1) - C(2)	-0.3
C(6) - C(5) - C(4) - C(3)	0.5
C(6) - C(5) - C(4) - H(4)	-179.5
H(5) - C(5) - C(4) - C(3)	-179.5
H(5) - C(5) - C(4) - H(4)	0.5
C(12) - C(18) - C(17) - C(18)	0.1
C(12) - C(18) - C(17) - H(18)	-179.9
H(19) - C(18) - C(17) - C(18)	-179.9
H(19) - C(18) - C(17) - H(18)	0.1
H(17) - C(16) - C(15) - C(13)	-179.8
H(17) - C(16) - C(15) - H(16)	0.1
H(17) - C(16) - C(17) - C(18)	179.9
H(17) - C(16) - C(17) - H(18)	-0.1
C(17) - C(16) - C(17) - C(18)	0.2
C(15) - C(16) - C(17) - C(18)	0.2
C(17) - C(16) - C(17) - H(18)	-179.9
C(15) - C(16) - C(17) - H(18)	179.9
C(15) - C(16) - C(17) - C(13)	-0.1
C(15) - C(16) - C(17) - H(10)	179.4
H(3) - C(3) - C(2) - C(1)	179.4
H(3) - C(3) - C(2) - H(2)	-0.6
H(3) - C(3) - C(4) - C(5)	179.9
H(3) - C(3) - C(4) - H(4)	-0.1
C(3) - C(3) - C(2) - C(1)	-0.6
C(3) - C(3) - C(4) - C(5)	-0.1
C(3) - C(3) - C(2) - H(2)	179.4
C(3) - C(3) - C(4) - H(4)	179.9

Table 3
Complete listing of bond distances (Angstroms)

C(8) - H(21A)	0.960(3)	C(0) - H(21D)	0.960(3)
C(8) - H(21C)	0.960(3)	O(4) - C(14)	1.203(3)
H(15) - C(11)	0.990(2)	O(5) - C(10)	1.374(3)
O(5) - C(11)	1.374(3)	C(13) - C(12)	1.399(3)
C(13) - C(14)	1.459(3)	C(13) - C(18)	1.389(3)
C(11) - C(12)	1.439(3)	C(11) - C(10)	1.390(3)
C(12) - C(10)	1.401(3)	O(2) - C(7)	1.329(3)
C(6) - C(9)	1.481(3)	C(6) - C(7)	1.484(3)
C(6) - C(1)	1.394(3)	C(6) - C(5)	1.385(3)
C(7) - O(1)	1.202(3)	C(1) - C(9)	1.436(3)
C(7) - C(12)	1.390(3)	C(9) - O(3)	1.204(3)
C(8) - H(5)	0.930(2)	C(5) - C(4)	1.373(3)
C(18) - H(19)	0.930(2)	C(18) - C(17)	1.377(3)
C(16) - H(17)	0.930(3)	C(16) - C(15)	1.377(3)
C(16) - C(17)	1.383(3)	C(15) - H(16)	0.950(2)
C(3) - H(3)	0.930(3)	C(3) - C(2)	1.376(3)

Table B2 X-Ray Spectrum data of Compound 368.

C(3) - C(4)	1.365(4)	C(2) - H(2)	0.930(3)
C(4) - H(4)	0.930(3)	C(17) - H(18)	0.930(3)
Table 4			
Complete listing of bond angles (degrees)			
H(21A)-C(8)-H(21B)	109.5(3)	H(21A)-C(8) -	
H(21C)	109.5(3)	C(10)-C(5) -	
H(21B)-C(8)-H(21C)	109.5(3)	C(10)-C(5) -	
C(4)	121.8(2)	C(12)-C(13)-C(15)	
C(12)-C(13)-C(14)	120.4(2)	C(12)-C(13)-C(15)	
120.1(2)		F(15)-C(11)-C(12)	
C(14)-C(13)-C(15)	119.5(2)	C(12)-C(11)-C(10)	
121.9(2)			
H(15)-C(11)-C(10)	117.5(2)	C(13)-C(12)-C(18)	
120.6(2)			
C(13)-C(12)-C(14)	117.8(2)	C(13)-C(12) -	
119.2(2)		C(5)-C(10) -	
C(11)-C(12)-C(18)	123.0(2)	C(5)-C(10) -	
C(14)	123.2(2)	C(11)-C(10) -	
C(5)-C(10)-C(19)	125.7(2)	C(11)-C(10) -	
C(8)	125.7(2)	C(7)-C(6) -	
C(7)-C(6)-C(1)	121.5(2)	C(4)-C(14)-C(15)	
C(5)			
C(11)-C(6)-C(5)	118.1(2)		
118.1(2)			
C(14)-C(14)-C(13)	117.3(2)		
C(13)			
C(12)-C(7)-C(6)	123.6(2)	C(12)-C(7) -	
C(11)		C(6)-C(11) -	
C(6)-C(7)-O(1)	123.6(2)	C(6)-C(11) -	
C(9)		C(9)-C(1) -	
C(6)-C(1)-C(2)	119.0(2)	C(10)-C(9)-O(3)	
C(12)			
C(10)-C(9)-C(1)	117.4(2)		
120.7(2)			
C(11)-C(9)-O(3)	121.4(2)	C(6)-C(5) -	
H(5)		H(5)-C(5) -	
C(6)-C(5)-C(4)	120.7(2)	C(12)-C(13)-C(17)	
C(4)		F(17)-C(13)-C(15)	
C(12)-C(13)-H(13)	120.0(2)	C(15)-C(13)-C(17)	
120.0(2)			
H(13)-C(13)-C(17)	118.7(3)		
120.6(2)			
C(13)-C(15)-C(16)	119.7(2)		
120.2(2)			
C(16)-C(15)-H(16)	120.0(3)		
C(2)			
H(3)-C(3)-C(4)	120.0(2)		
C(4)			
C(11)-C(12)-C(18)	120.8(2)		
119.7(3)			
H(12)-C(12)-C(13)	119.6(3)		
120.2(2)			
C(3)-C(4)-H(4)	119.9(3)		
H(4)			
C(18)-C(17)-C(15)	120.5(2)		

Table B3 X-Ray Spectrum data of Compound 368.

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