

DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR FURAN FUSED
HETEROCYCLES

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SYSTEMS**

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ABSTRACT

DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES FOR FURAN FUSED HETEROCYCLES

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Fuopyranones and fuopyrrolones are furan-fused bicyclic heterocycles containing pyranone and pyrrolone framework respectively. Many natural products and pharmaceutical agents include these core structures. In this study, new synthetic methodologies were developed for the synthesis of fuopyranone and fuopyrrolone derivatives. In the first section of this thesis, methyl 2-(2-methoxy-2-oxoethyl)-3-furoate was hydrolyzed forming 2-(carboxymethyl)-3-furoic acid which underwent intramolecular cyclization reaction using two different methodologies forming fuopyranone derivatives. In the second part of the study, 2-(carboxymethyl)-3-furoic acid was regioselectively converted to acyl azide, which was accomplished by utilizing the reactivity differences between the two acid functionalities within the molecule. This acyl azide was then transformed into urea derivative to perform cyclization reaction yielding a new furan-fused heterocycle, fuopyrrolone. In both parts of this study, ring closure reactions were achieved benefiting from the reactivities of different carbonyl groups within the molecules.

Keywords: fuopyranone, fuopyrandione, fuopyrrolone, isocyanate, ring-closure reaction

ÖZ

FURANA KENETLENMİŞ HETEROSİKLİK YAPILARIN SENTEZİ İÇİN YENİ SENTETİK METOTLARIN GELİŞTİRİLMESİ

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Tez Yöneticisi: Prof. Dr. Metin Balcı

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Fuopiranonlar ve fuopiroolonlar, yapısında sırasıyla piranon ve pirolon iskeletleri bulunduran furana kenetlenmiş heterosiklik yapılardır. Bir çok doğal ürün ve farmasötik ajan yapısında bu çekirdek yapıyı bulundurur. Bu çalışmada, fuopiranon ve fuopiroolon sentezi için yeni sentetik metotlar geliştirildi. Bu tezin ilk kısmında, fuopiranon türevleri, metil 2-(2-metoksi-2-okzoetil)-3-furoat molekülünün hidrolizi sonucu oluşan 2-(karboksimetil)-3-furoik asit molekülünün, molekül içi siklizasyon reaksiyonu ile, iki farklı metot kullanılarak sentezlendi. Çalışmanın ikinci kısmında ise, 2-(2-(karboksimetil)-3-furoik asit, molekül içindeki iki asit fonksiyonel grubunun reaktivite farkından yararlanılarak, bölge seçici olarak açil azite dönüştürüldü. Bu açil azit daha sonra, yeni bir furana kenetlenmiş heterosiklik yapı olan fuopiroolon iskeletini oluşturmak için, siklizasyon reaksiyonunu gerçekleştirmek üzere üre türevine dönüştürüldü. Çalışmanın her iki kısmında da, halka kapatma reaksiyonları, moleküller içinde farklı karbonil gruplarının reaktivite farkından yararlanılarak yapıldı.

Anahtar Kelimeler: fuopiranon, fuopirandion, fuopiroolon, izosiyanat, halka kapatma reaksiyonu

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For the Love of Science...

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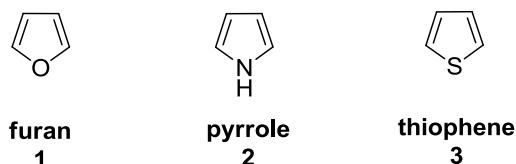
CHAPTER 1

INTRODUCTION

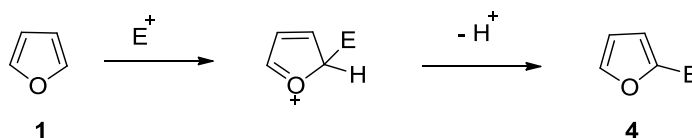
1.1. Furans

1.1.1 General properties of furan

Furan (**1**) is a five-membered, aromatic, heterocyclic organic compound. The aromaticity arises from delocalization of one of the lone pairs of the oxygen atom into the ring which is in agreement with the $4n+2$ Hückel's rule same as pyrrole (**2**) and thiophene (**3**) ring systems. The other lone pair of the oxygen atom attends perpendicular to the planar furan ring system. Furan (**1**) is the least aromatic ring system among the three kind of five-membered heteroaromatic systems; furan (**1**), pyrrole (**2**) and thiophene (**3**), that is why furan behaves as a good diene system.

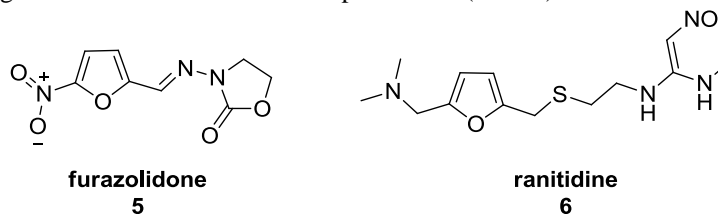


Furan undergoes regioselective electrophilic substitution reactions and it produce mostly α -substituted furans (**4**) by general addition-elimination mechanism (Scheme 1).¹



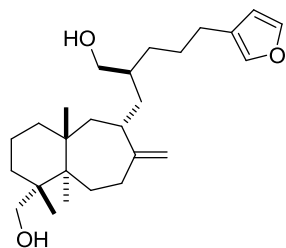
Scheme 1

Furan derivatives are used as flavors, functional polymers, and precursors in the synthesis of cyclic and acyclic compounds notably in Diels-Alder reactions. They have very wide range of usage on many commercially available products especially among pharmaceuticals such as; furazolidone (**5**) which is used in diarrhea and enteritis treatment (Furoxone)² and ranitidine (**6**) which is a histamine H_2 -receptor antagonist that blocks stomach acid production (Zantac)³.

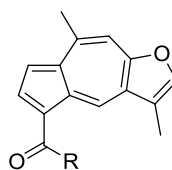


Apart from these; furan skeleton is found in many naturally occurring compounds and it has a very crucial role in heterocyclic chemistry field as they were reported to show promising biological activities.¹ One of the many publications about furan containing biologically active compounds is by Phuwapraisirisan *et al.*⁴ and it was reported that the isolation of a new furan containing compound named shinsonofuran (**7**) from the marine sponge *Stoebaextensa* possesses remarkable cytotoxicity. Moreover, Reddy *et al.*⁵ isolated and characterized two new furan derivatives, namely linderazulenes **8** and **9** and studied their cytotoxic activity and they found that both have moderate in vitro activity

against the P388 murine leukemia cell line and linderazulene **8** has moderate activity against PANC-1 pancreatic cell line.



shinsonefuran
7

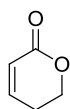


linderazulene
8 R = OMe
9 R = H

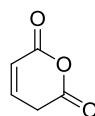
1.2 Pyranones and pyrandiones

1.2.1 General properties of pyranones and pyrandiones

Pyranone (**10**) and pyrandione (**11**) are six-membered heterocyclic compounds containing oxygen atom. They are of great importance because they exist in many fungal pigments which are isolated from many fungi and they are synthetically investigated.⁶ Additionally, they are found in many naturally occurring products that show various biological activities. Many scientists reported that compounds containing pyranone and pyrandione show antibacterial, anti-HIV, antifungal, antioxidant, anticancer and antidiabetic activities.⁷

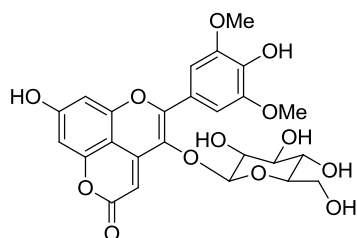


pyranone
10

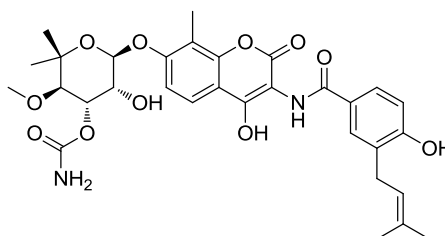


pyrandione
11

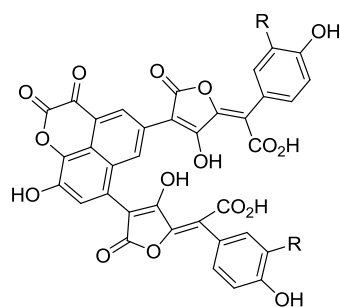
Recent studies showed that pyranoanthocyanins are the new class of anthocyanins which are pigments used in the red wine aging. A new stable yellowish pigment pyranone-anthocyanin A (**12**) was detected and purified and its formation mechanism in aged wines was investigated.⁸ There are clinically used examples of pyranone framework *e.g.* novobiocin (**13**) and these agents are considered to play a role in inhibiting the bacterial DNA gyrase enzyme.^{9,10} Also, badione A (**14**) and B (**15**) are pirandione containing pigments which are found in the bolete which is the fruit body of fungus and their formation were examined by Steglich *et al.*¹¹



pyranone anthocyanin A
12



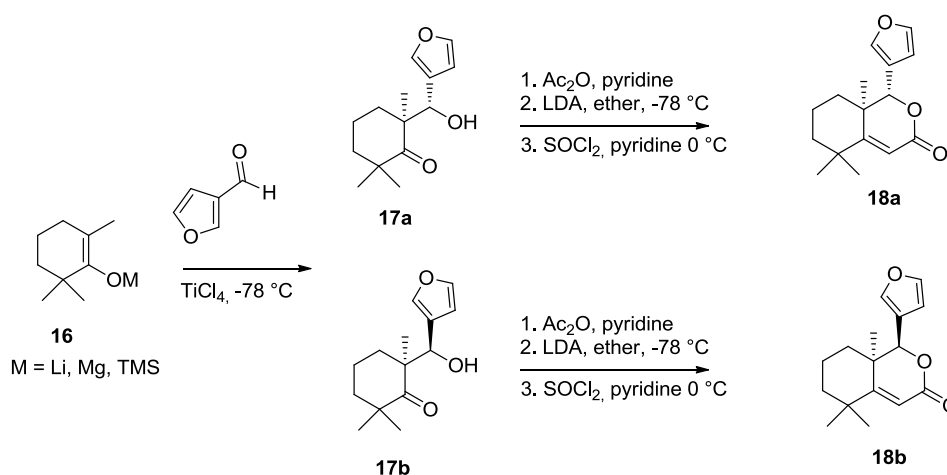
novobiocin
13



badion A, R = H
14
badion B, R: OH
15

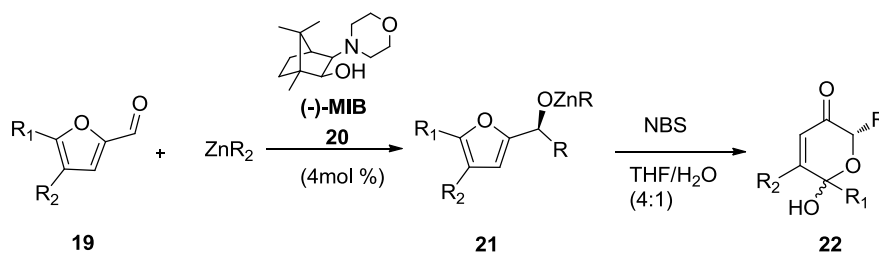
1.2.2. Synthesis of pyranones and pyrandiones

Pyranones and pyrandiones are precious building blocks among heterocyclic compounds as they have been widely found in natural products.¹² They are also used in diversity oriented syntheses.¹³ As an earlier example to pyranone (**18a, b**) synthesis, the study of Mateos *et al.* who had worked on preparing limonoid model compounds containing pyranone framework can be given.¹⁴ According to this study, Lewis acid catalyzed aldol condensation of metal enolate **16** was carried out yielding corresponding aldols **17a** and **17b**. After the acetylation from the alcohol functionality in **17a** and **17b**, the products were treated with LDA and SOCl₂ respectively to produce pyranones **18a** and **18b** (Scheme 2).



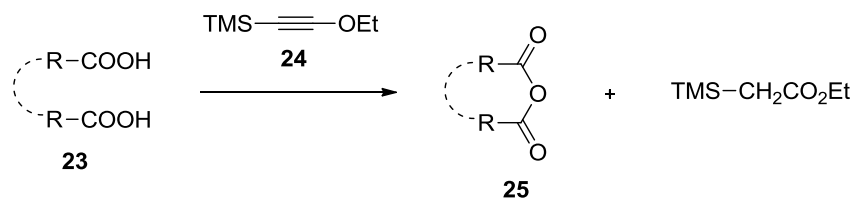
Scheme 2

Another method is published by Cheng *et al.* who studied one pot protocol to produce pyranones with enantioselectivities >90% starting with 2-furfurals (**19**). Nugent's¹⁵ enantioenriched amino alcohol was used as a catalyst which provides enantioselective addition. In this method, zinc furyl alkoxide intermediates **21** were obtained by asymmetric alkylation which was followed by oxidation with NBS via Achmatowicz reaction yielding pyranone derivatives **22** (Scheme 3).¹²



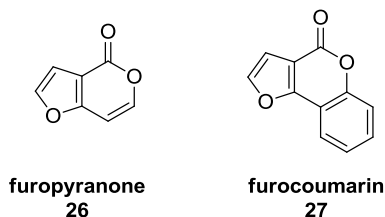
Scheme 3

Kita *et al.* reported a study on the synthesis of various pyrandione derivatives **25** using (trimethylsilyl)ethoxyacetylene (**24**) starting from diacid derivatives of many types of heterocyclic systems **23** including pyrrole, thiophene, benzene and indole (Scheme 4).¹⁶

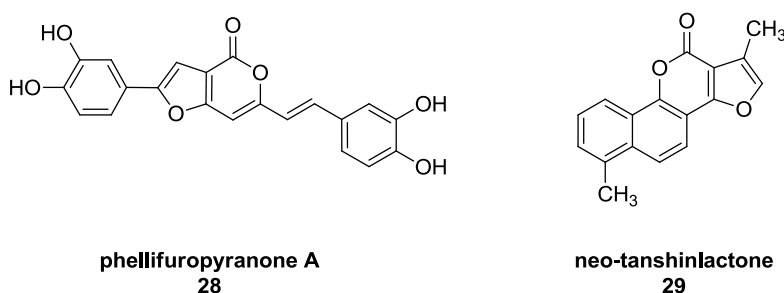


1.3 Furopyranones

Furopyranones (**26**) are heterocyclic systems containing a furan ring fused to a pyranone ring and furocoumarins (**27**) contain a furopyranone ring and an additional benzene ring. Those structures possess a crucial role due to their photosensitive properties which was found potential to be used in therapeutic purposes.¹⁷



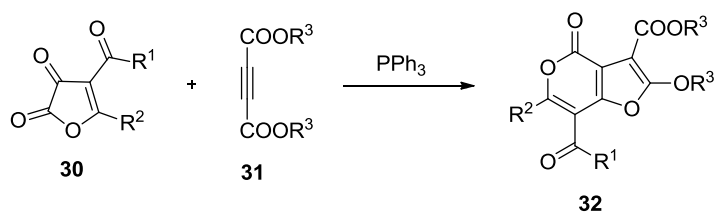
Nagatsu *et al.* worked on identifying the compounds in *Phellinus linteus*, which is a Basidiomycota fungus exhibiting anticancer activity. One new furopyranone derivative, phellifuropyranone A (**28**) was isolated and it was found that compound **28** has antiproliferative activity against melanoma cells and human lung cancer cells *in vitro*.¹⁸



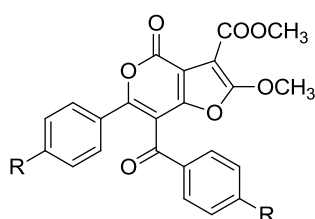
Neo-tanshinlactone (**29**) is one of the components of *Salvia miltiorrhiza* known as "Tanshen" which is a Chinese traditional medicine used in various types of diseases. Wang *et al.*¹⁹ isolated and synthesized compound **29** for the first time and investigated its anticancer activities against human cancer cells. It was reported that neo-tanshinlactone (**29**) was found to be 10 times more potent and 20 times more selective than antiestrogenic tomosifen citrate, which is clinically used in breast cancer therapies.

1.3.1 Synthesis of furopyranones

Recently, Koca *et al.* reported the synthesis of various new furopyranone derivatives **32**. In the published method, first triphenylphosphine was added to acetylenedicarboxylate **31**, followed by the intramolecular Wittig reaction between the formed adduct and furandione **30** took place to form furopyranone **32**.²⁰ In the further study, it was reported that two of those furopyranone derivatives (**33** and **34**) show antiproliferative and mitotic activity (Scheme 5).²¹

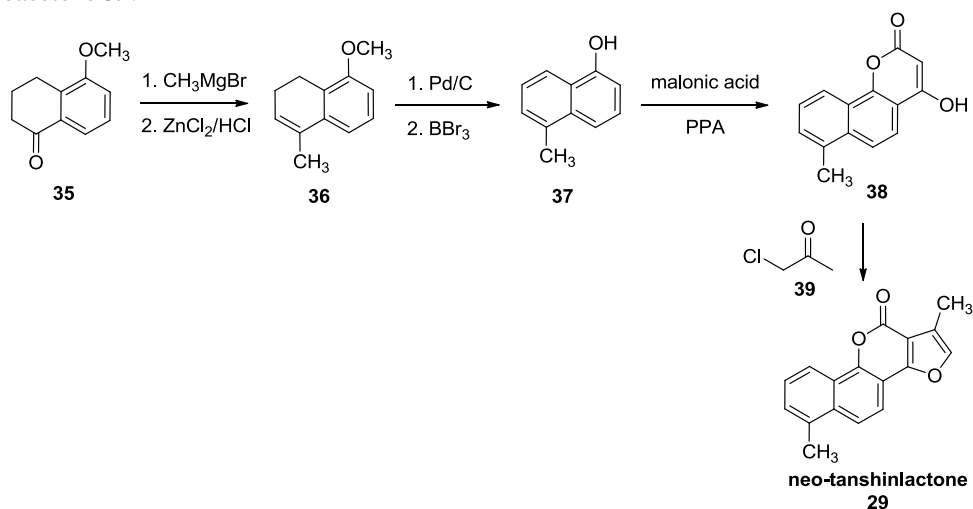


Scheme 5



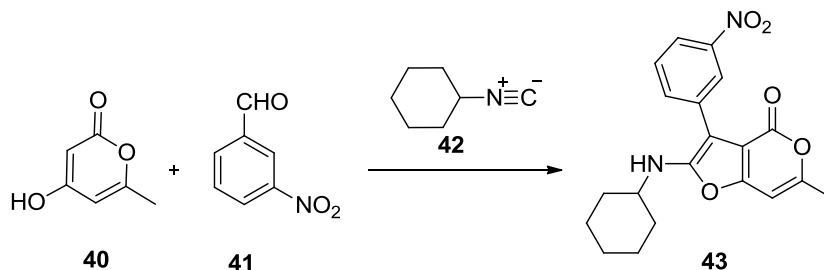
33 R = -CH₃
34 R = -OCH₃

Wang *et al.*¹⁹ synthesized neo-tanshinlactone (**29**), one of the most important furopyranone derivatives (Scheme 6). Their synthetic strategy starts with addition of a Grignard reagent to tetralone **35** followed by dehydration of resulting carbinol which yielded compound **36**. The aromatization was achieved after the dehydrogenation by palladium and methoxy group was converted to hydroxyl group by boron tribromide yielding compound **37**. After that, addition of malonic acid with PPA (phenylpropanolamine) to compound **37** gave the tricyclic product **38**. Finally, neo-tanshinlactone (**29**) was produced by condensing a furan ring system, which was achieved by the reaction of **38** with chloroacetone **39**.



Scheme 6

Lastly Nair *et al.*¹⁷ discovered a one-pot synthesis of various furan condensed heterocyclic systems using [4+1] cycloaddition reaction. The synthesis of furopyranone derivative **43** was achieved by the addition of 3-nitrobenzaldehyde (**41**) to pyranone derivative **40** followed by the [4+1] addition of cyclohexyl isocyanide (**42**) to the formed adduct (Scheme 7).

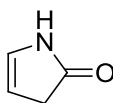


Scheme 7

1.4 Pyrrolones

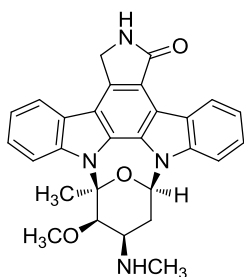
1.4.1 General properties of pyrrolones

Pyrrolones (**44**) are five-membered heterocyclic compounds containing nitrogen atom. Pyrrolones attract many chemists' attention due to their vast number of biological activities²² such as; antimicrobial, antibiotic and antimycobacterial, potential for treating various diseases²³ such as; cancer, inflammation, rheumatoid arthritis, multiple sclerosis, Parkinson's disease and cardiovascular disease, potential for applications in drug development²⁴ and agricultural industry.²⁵

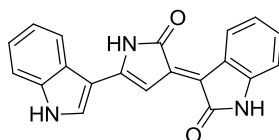


pyrrolone
44

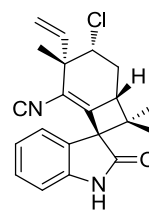
Funato *et al.*²⁶ studied absolute configuration of pyrrolone (**44**) containing natural product, staurosporine (**45**), which is a bacterial alkaloid having antimicrobial, hypertensive, cell cytotoxic, and platelet aggregation activity. In addition, staurosporine (**45**) is well known by its being most potent inhibitor of protein kinases.²⁷ Another example is violacein (**46**), a purple pigment isolated from *Chromobacterium violaceum* from Amazon river. Violacein (**46**) induces apoptosis in a variety of cancer cells including leukemia cell lines and showed trypanocidal, antibiotic and antitumor activities.^{28,29}



staurosporine
45



violacein
46

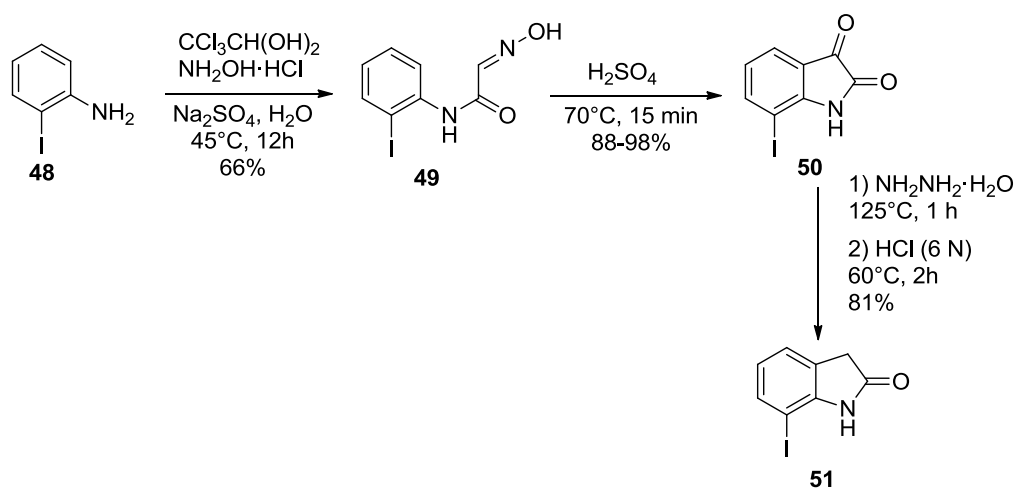


welwitindolinone A isonitrile
47

Welwitindolinone A isonitrile (**47**) is first isolated by Stratmann *et al.*³⁰ from cyanobacteria *Hapalosiphon welwischii* and *Westiella intricata*, which was then found to possess insecticidal, antimycotic, antifungal activity.³¹ It was also determined that welwitindolinone A isonitrile (**47**) exists potent anticancer activity against multiple drug-resistant ovarian cancer cell lines.^{32, 33}

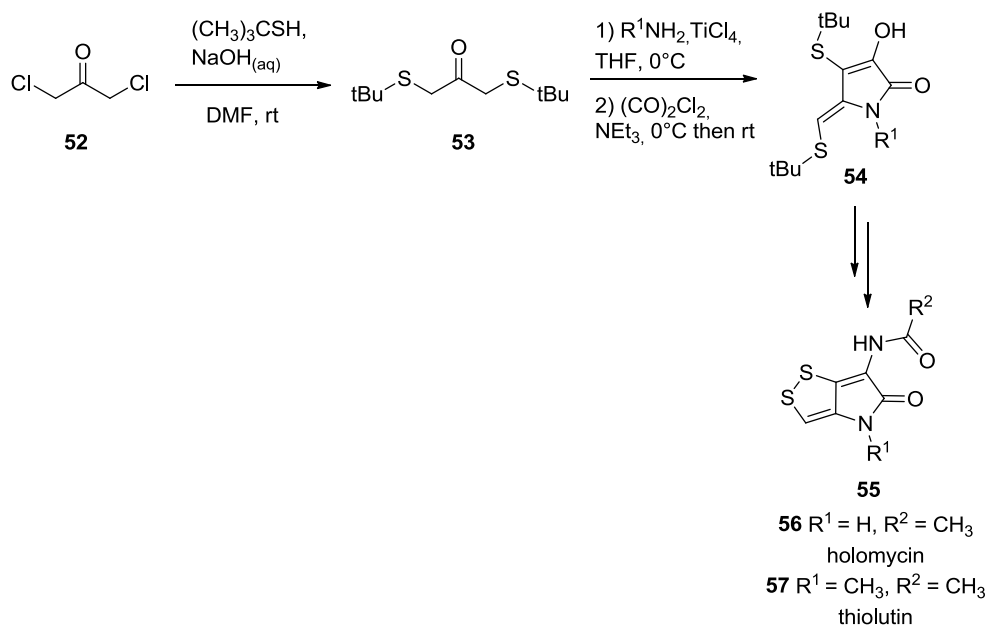
1.4.2 Synthesis of pyrrolones

Lin *et al.*³⁴ studied the synthesis of the core of a pyrrolone derivative, TMC-95A and B, which showed chymotrypsin-like, trypsin-like, and peptidoglutamyl-hydrolyzing activities of the 20S proteasome. In this study, Sandmeyer isonitrosoacetanilide Isatin Synthesis³⁵ was used in which 2-iodoaniline (**48**) was treated with chloral hydrate, hydroxylamine hydrochloride and sodium sulfate to give isonitrosoacetanilide **49**, followed by the addition of sulphuric acid to yield isatin **50**. Then isatin **50** was reacted with hydrazine hydrate and 6 N hydrochloric acid subsequently, which produced pyrrolone derivative **51** according to the Crestini's³⁶ method (Scheme 8).



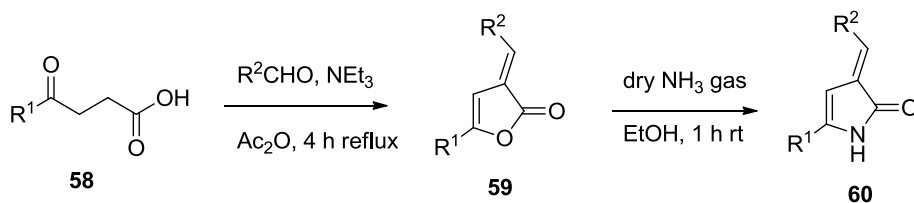
Scheme 8

Li *et al.*²² reported the synthesis, structure-activity relationship, and cytotoxic activity of substituted dithiopyrrolones **55** which are the derivatives of antibiotics holomycin (**56**) and thiolutin (**57**).³⁷ According to their synthetic pathway, commercially available 1,3-dichloroacetone **52** was reacted with two equivalents of *tert*-butylmercaptan and sodium hydroxide. Then obtained ketone **53** was treated with a variety of primary amines in the presence of titanium tetrachloride and triethylamine to give pyrrolone **54**, which was one of the core ring structures of the desired dithiopyrrolone **55** (Scheme 9).



Scheme 9

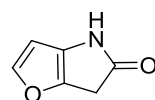
Husain *et al.*³⁸ have worked on the synthesis and biological activity of aryl-substituted butenolide **59** and pyrrolones **60**. In their synthetic route, prepared diketone **58** was reacted with a variety of aldehydes in the presence of triethylamine. Yielded butenolides **59** were further treated with dry ammonia gas to give pyrrolone derivatives **60** (Scheme 10).



Scheme 10

1.5 Fuopyrrolones

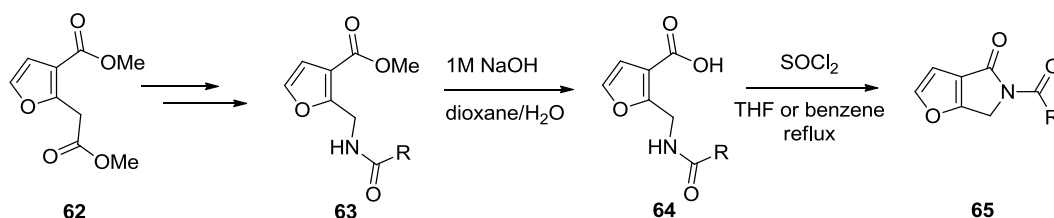
Many bicyclic alkaloids are considered as crucial compounds due to their common existence in natural products and their wide range of biological activities. Therefore, in the literature, there are many studies on their synthetic methodologies and also, their clinical utilities and drug developments are widely conducted by many scientists. For this reason, in the medicinal chemistry field, there is a continuous need in the heterocyclic analogues and fuopyrrolones **61** are one of the unexplored classes of heterocyclic compounds.



fuopyrrolone
61

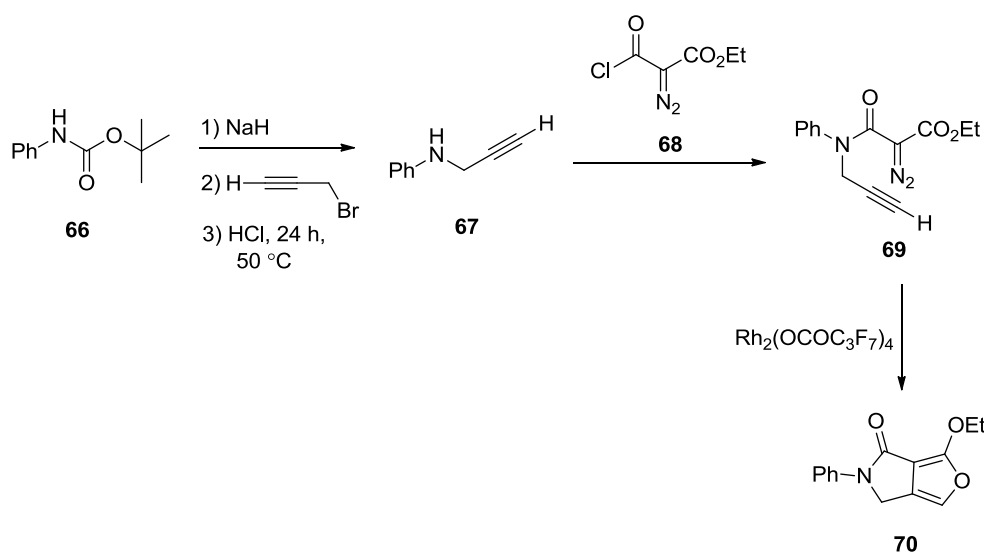
1.5.1 Synthesis of fuopyrrolones

Balcı *et al.*³⁹ reported the synthesis of one fuopyrrolone analogue **65**. In this methodology, compound **63**, which was obtained in 5 steps by starting from diester **62**, was hydrolyzed by 1 M of sodium hydroxide to yield compound **64**. Then, the cyclization was achieved by treating compound **64** with thionyl chloride that gave fuopyrrolone **65** (Scheme 11).



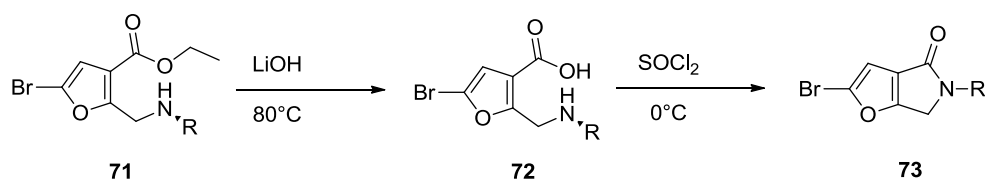
Scheme 11

Brown *et al.*⁴⁰ studied intramolecular C-H insertion using rodium(II) catalyst. According to their method, *t*-BOC aniline (**66**) was treated with sodium hydride and propargyl bromide subsequently to give *N*-propargyl aniline (**67**). Then, compound **67** was reacted with ethyl 2-diazomalonyl chloride to yield diazo ketone **69** which was then stirred in the presence of rodium(II) perfluorobutyrate to give fuopyrrolone **70** (Scheme 12).



Scheme 12

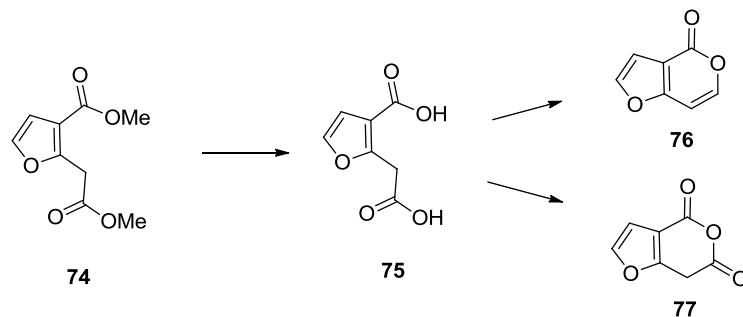
Another method for synthesizing fuopyrrolone derivatives was published by Chapdelaine and Herzog.⁴¹ In their method, prepared furoester **71** was hydrolyzed by lithium hydroxide to produce furoacid **72**, which was then treated with thionyl chloride to yield fuopyrrolone **73** (Scheme 13).



Scheme 13

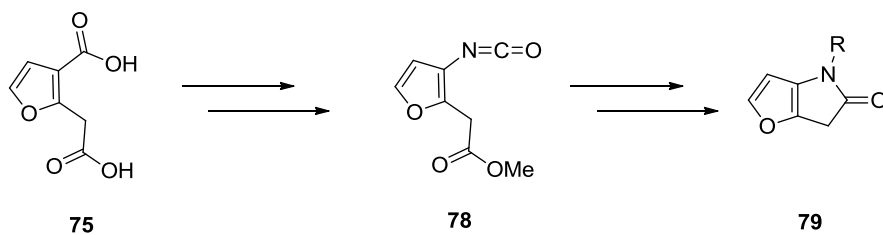
1.6 Aim of the study

The aim of this study was to develop new synthetic methodologies for furopyranone **76**, **77** and furopyrrolone derivatives **79** starting from diester **74** (Scheme 14).



Scheme 14

According to our synthetic strategy, first diacid **75** will be selectively converted to half-ester. The acid functionality connected to the methylene group will be protected as ester. The acid functionality connected to furan ring will be transferred to the corresponding isocyanate **78** via the corresponding acyl azide by application of Curtius rearrangement. The intramolecular cyclization reactions between the various functional groups attached to the furan ring will be studied (Scheme 15).



Scheme 15

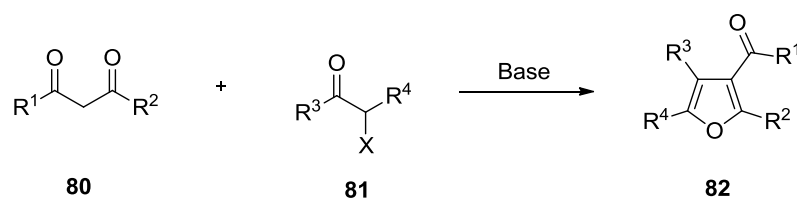
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of furopyranone derivatives

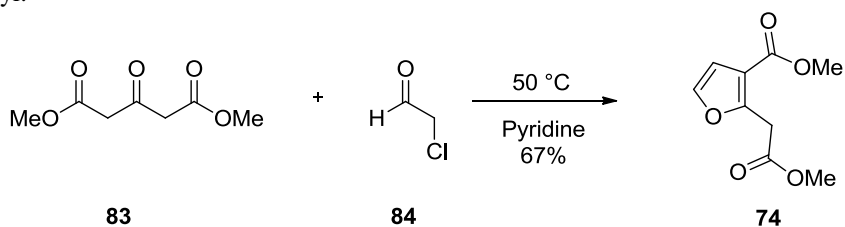
2.1.1 Synthesis of starting material: methyl 2-(2-methoxy-2-oxoethyl)-3-furoate

The synthesis of methyl 2-(2-methoxy-2-oxoethyl)-3-furoate (**74**) was published by Tada *et al.*⁴² which was a modified Feist-Binary^{43,44} furan synthesis (Scheme 16). According to this methodology, tetra-substituted furan derivative **82** was synthesized by the reaction of α -halocarbonyl compound **81** with β -diketoester **80** in the presence of a base.



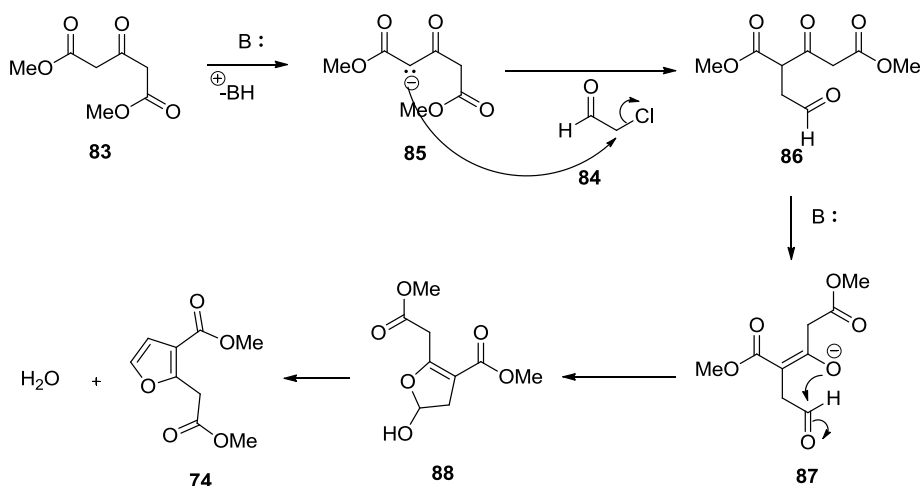
Scheme 16

As a variation of this substituted furan synthesis (Scheme 17), the furan diester **74** was synthesized using dimethyl 1,3-acetonedicarboxylate (**83**) as β -diketoester and chloroacetaldehyde (**84**) as α -halocarbonyl.^{39,45}



Scheme 17

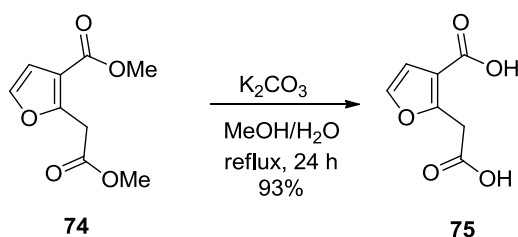
In the synthesis of furan diester **74**, firstly the acidic α -proton of dimethyl 1,3-acetonedicarboxylate (**83**) is captured by the pyridine to yield the carbanion **85** which is then reacted with chloroacetaldehyde (**84**). Then the formed intermediate **86** is converted to the enolate **87** which is then undergo intramolecular S_N2 reaction with the attack of the oxygen atom on the enolate group to the carbonyl unit. The cyclized product **88** then ejects water to yield the starting material **74** (Scheme 18).



Scheme 18

2.1.2 Synthesis of 2-(carboxymethyl)-3-furoic acid

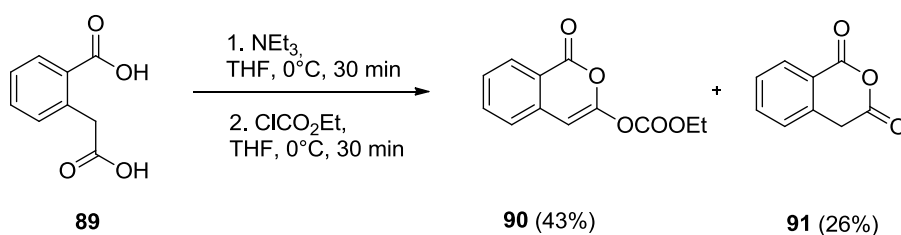
For the synthesis of furopyranone derivatives, the key compound was the furan diacid **75**. For the synthesis of the diacid **75**, hydrolysis reaction was performed. Treatment of furan diester **74** with potassium carbonate in methanol/water mixture at reflux temperature yielded furan diacid **75** in 93% yield (Scheme 19).



Scheme 19

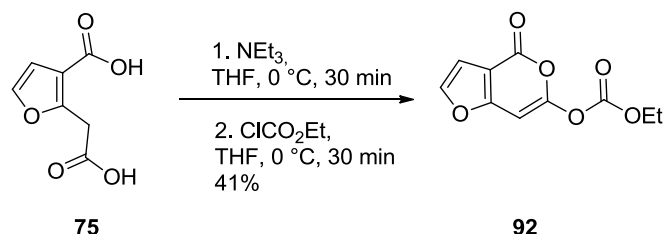
2.1.3 Synthesis of Ethyl 4-oxo-4H-furo[3,2-c]pyran-6-yl carbonate

After the synthesis of the key compound furan diacid **75**, our plan was to study cyclization reactions fused to the furan ring. Therefore, a previously published method by Balci *et al.*⁴⁶ was applied to the furan diacid **75**. In this published method, both isocoumarin **90** and anhydride **91** were observed (Scheme 20).



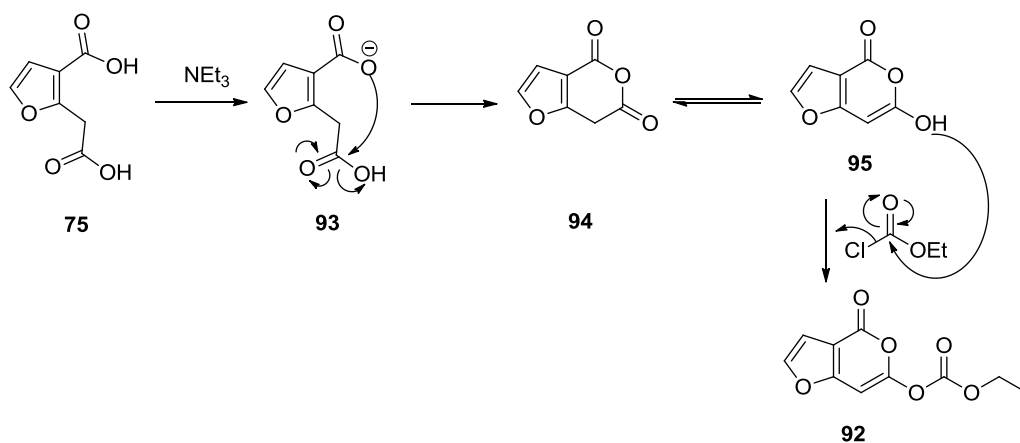
Scheme 20

Our attempt of the ring closure reaction was successful; however, starting with furan diacid **75**, only furopyranone **92** was produced. The starting compound **75** was treated with triethylamine at 0 °C. After 30 min, furopyranone **92** was yielded by adding ethyl chloroformate to the reaction mixture (Scheme 21).



Scheme 21

In the formation mechanism (Scheme 22), first the acidic proton on the carboxylic acid functionality is abstracted by triethylamine to form anion **93**. Then intramolecular cyclization takes place by the attack of the anion to the carbonyl group on the lower arm of the molecule producing furan anhydride **94**. The oxygen in the enol tautomer of the furan anhydride **95** attacks to the carbonyl unit of the ethyl chloroformate yielding furopyranone **92**.



Scheme 22

To confirm the structure, ^1H and ^{13}C -NMR spectra were used. In ^1H -NMR spectrum, furan protons resonate at 7.52 and 6.90 ppm as doublet and doublet of doublets, respectively. In addition, the CH proton in the pyranone ring resonates at 6.44 ppm as doublets with the coupling constant of 0.6 Hz, resulting from the long-range coupling (Figure 1).

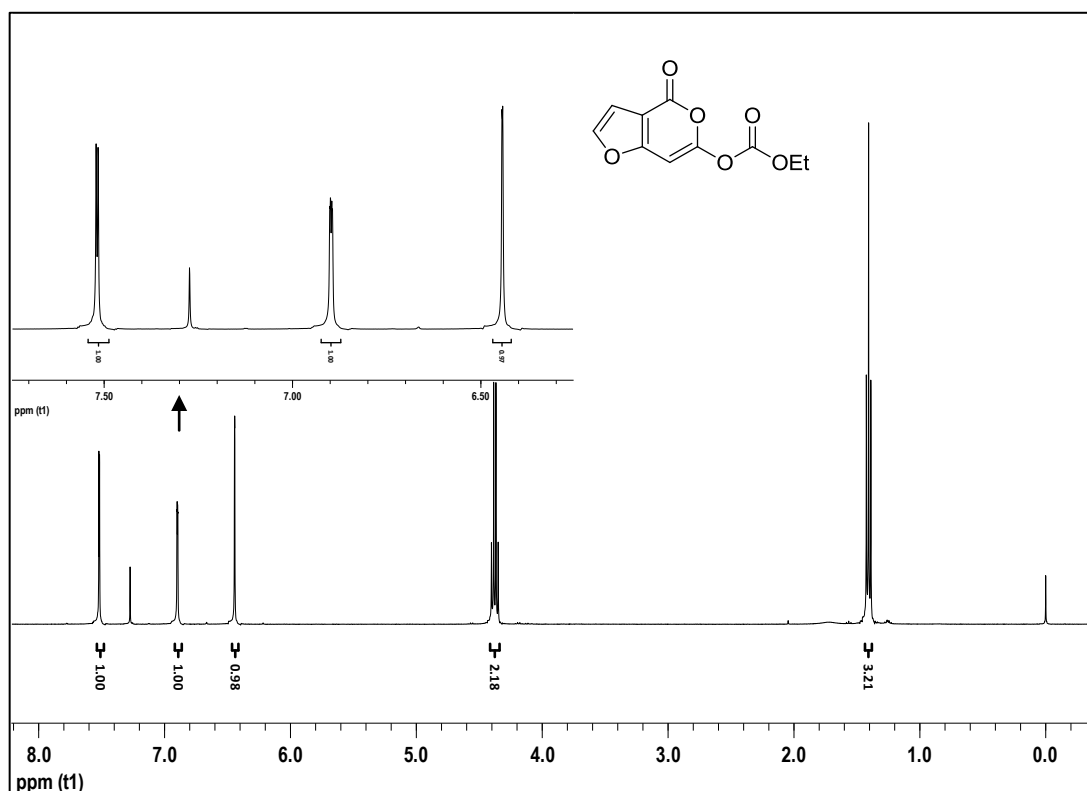
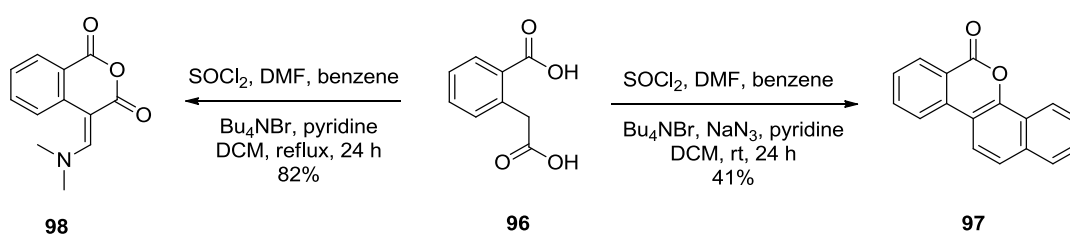


Figure 1 ¹H-NMR spectrum of furopyranone **92**

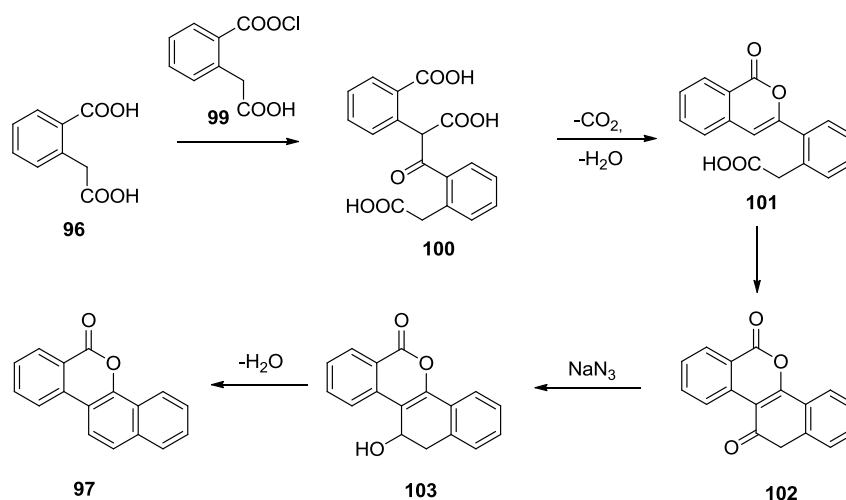
2.1.4 Synthesis of (7E)-7-[(dimethylamino)methylene]-4H-furo[3,2-c]pyran-4,6(7H)-dione

After the synthesis of the furopyranone **92**, another furopyranone framework construction was studied. In the study of Balci *et al.*⁴⁶, starting from homophthalic acid (**96**), dibenzochromenone **97** and anhydride **98** were synthesized (Scheme 23). With this inspiration, this method was performed using furan diacid **75** as the starting material.



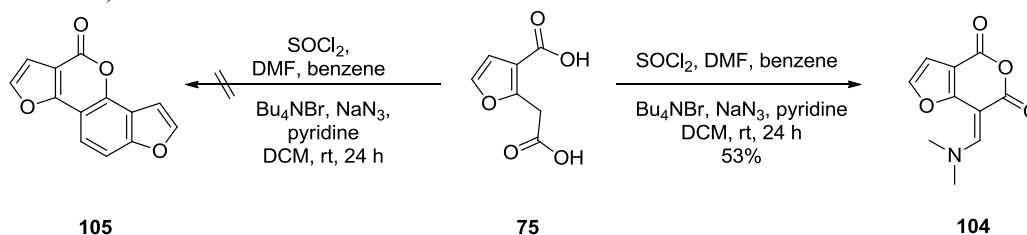
Scheme 23

According to their mechanism of the synthesis of dibenzochromenone **97** (Scheme 24), first the starting material **96** is chlorinated under the reaction condition then formed acyl chloride **99** and unreacted starting molecule forms the condensation product **100** which is then undergo decarboxylation followed by intramolecular cyclization to produce isocoumarine derivative **102**. In the presence of sodium azide in the reaction mixture, second ring closure and reduction takes place and aromatization is completed by H₂O elimination. Reduction by sodium azide is proposed due to the recent publication reported by Balci *et al.*⁴⁷ that sodium azide could reduce various carbonyl groups of quinones into hydroxyquinones. On the other hand, if the sodium azide is not present in the reaction mixture, anhydride **98** was formed instead of compound **97**, which is in agreement with the mechanism.



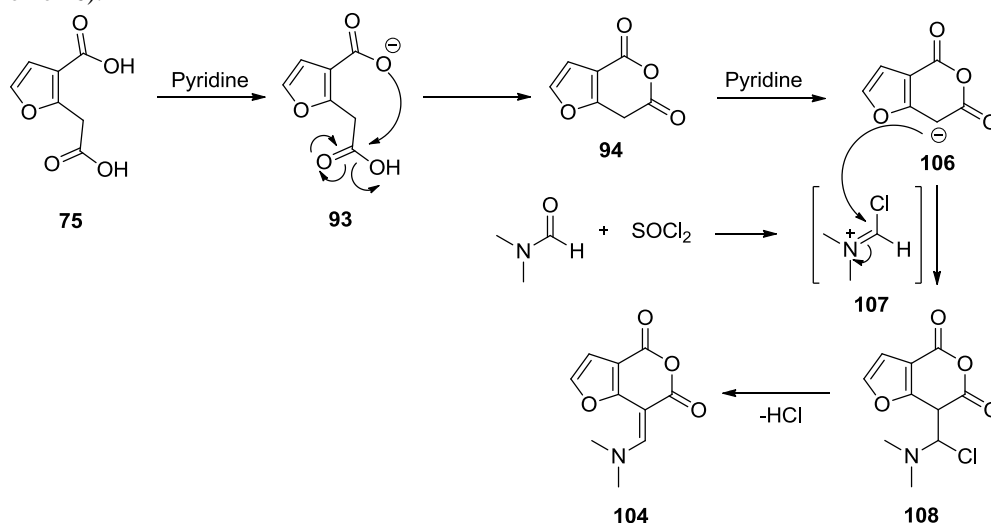
Scheme 24

With this information in mind, starting compound, furan diacid **75** was treated with sodium azide, thionyl chloride, dimethylformamide, pyridine, and tetrabutylammonium bromide as a catalyst in dichloromethane. Contrary to our expectations, furopyrandonone **104** was produced from the reaction (Scheme 25).



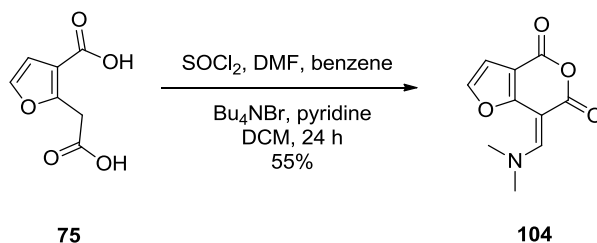
Scheme 25

According to the mechanism, first base removes an acidic proton from the lower arm of the molecule to form anion **93**. Then intramolecular cyclization takes place by the attack of the anion to the carbonyl group of the upper arm of the molecule yielding the anhydride **94**. Then a second molecule of base abstracts one of the acidic methylene protons to form anion **106**. This anion **106** attacks the formed Vilsmeier-Haack intermediate which is the chloroiminium ion **107** in the dropping funnel, producing the adduct **108**. Finally, HCl elimination from the molecule yields the furopyrandonone **104** (Scheme 26).



Scheme 26

Compared to the previously published methodology, we proposed that sodium azide has no role in this mechanism. Therefore, we conduct further experiments without sodium azide and found out that, the furopyrandione **104** was formed with approximately same yields even when sodium azide is not present in the reaction mixture (Scheme 27).



Scheme 27

Compound **104** was characterized using ^1H and ^{13}C NMR spectra. In the ^1H -NMR spectrum of the compound **104**, which is recorded in CD_3OD , the imine proton resonates at 7.97 ppm as singlet, and furan protons resonate at 7.40 and 6.66 ppm as doublets respectively.

In the ^1H -NMR spectrum of the compound **104**, which is recorded in CDCl_3 , we came across with two isomers in the ratio of (3:1). It is proposed that molecule is in equilibrium with its *Z* isomer in CDCl_3 (Figure 4); however, in CD_3OD (Figure 3), molecule is forced to be only in *E* form. The exact structure was confirmed by the single crystal X-ray analysis (Figure 2).

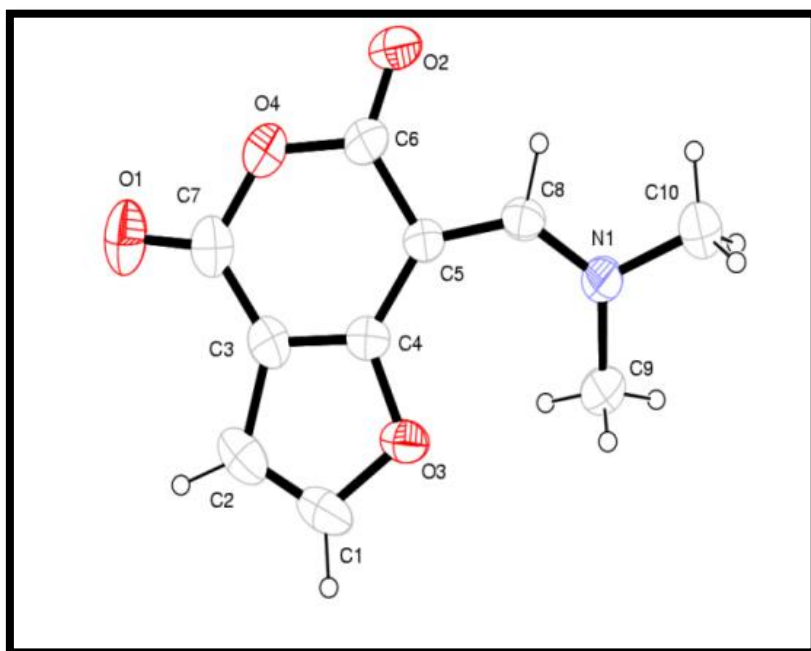


Figure 2 X-Ray analysis of furopyrandione **104**

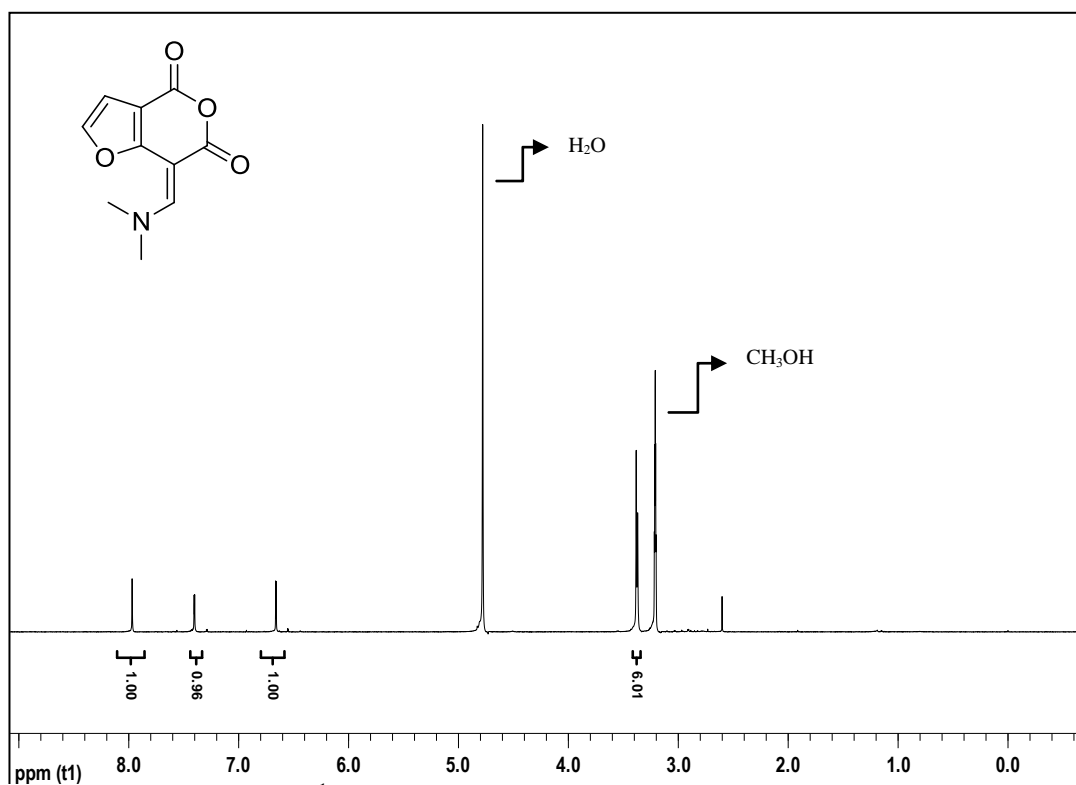


Figure 3 ¹H-NMR spectrum of furopyrandione **104** in CD₃OD

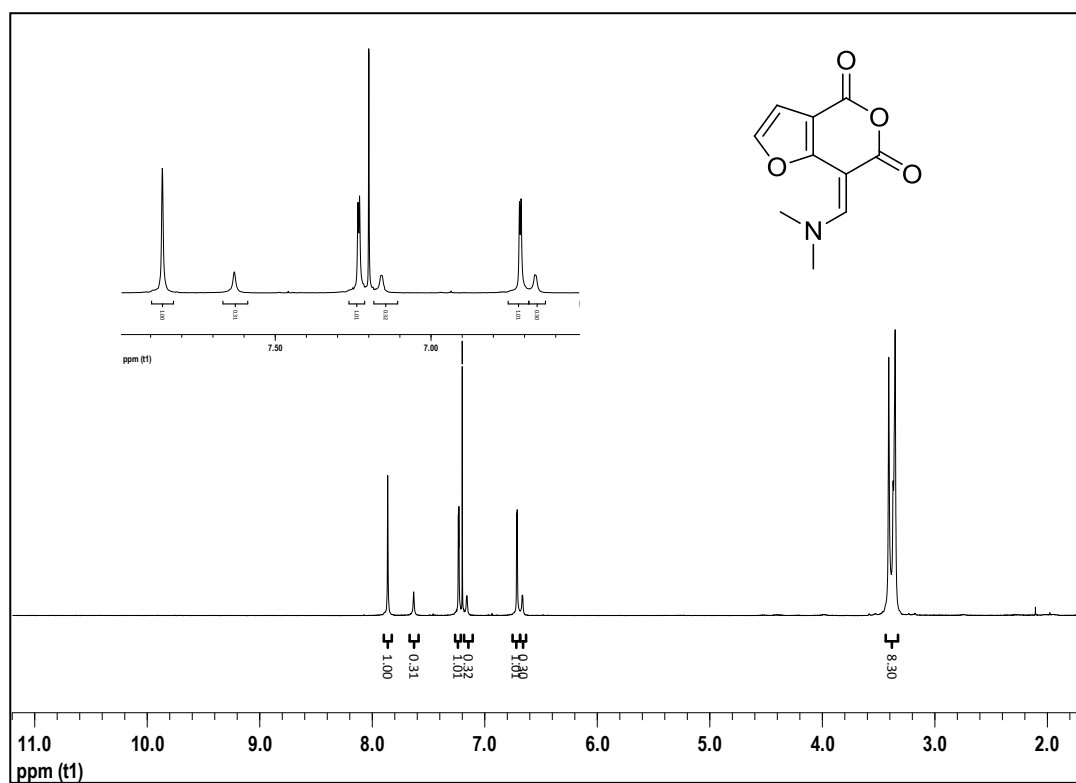
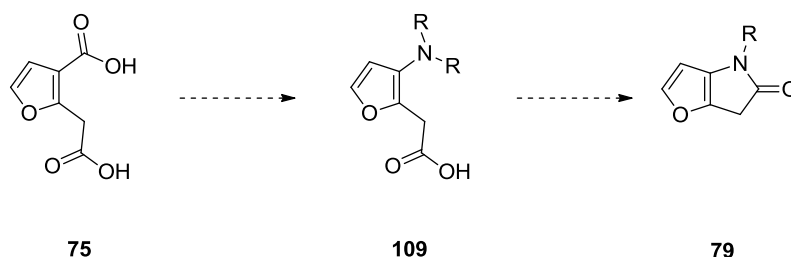


Figure 4 ¹H-NMR Spectrum of the Compound **104** in CDCl₃

2.2 Synthesis of furopyrrone derivatives

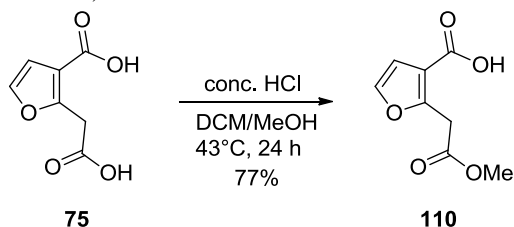
After the synthesis of furopyranone **92** and fuopyrandione **104**, we turned our attention to fuopyrrolone **79** framework construction, starting from diacid **75**, for which a nitrogen atom must be inserted into the molecule. Our aim was to introduce this nitrogen selectively to the upper arm of the molecule, which will be used as a nucleophile attacking to the electrophilic carbonyl group in the lower arm of the molecule, in order to perform the intramolecular cyclization reaction (Scheme 28). To introduce the nitrogen atom to the molecule, Curtius rearrangement⁴⁸, one of the most convenient methods to generate urea and urethane derivatives starting from acyl azides, can be used. Therefore, our synthetic pathway includes the formation of the corresponding acyl azide selectively in the upper arm of the molecule and to synthesize acyl azide, acyl chloride formation via half ester molecule can be used.



Scheme 28

2.2.1 Synthesis of 2-(2-methoxy-2-oxoethyl)-3-furoic acid

In order to proceed further on the upper arm of the molecule, we decided to protect the lower arm of the diacid **75** by esterification reaction. Furan diacid **75** in dichloromethane/methanol mixture (2:1) was treated with catalytic amount of concentrated hydrochloric acid. After 24 h, half ester **110** was produced in 77% yield (Scheme 29).



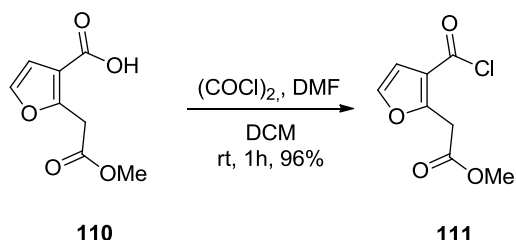
Scheme 29

In the molecule **75**, there are two carboxylic acid functionalities, which can be converted to ester groups; however, this reaction proceeds on esterification of only the lower arm of the molecule. This regioselectivity arises from the stability of the carbonyl group in the upper arm. The conjugation of the acid functionality with the furan framework decreases the electrophilic character of the carbonyl group for the nucleophilic attack of the methanol in the reaction mixture. That is why only the lower arm of the molecule is converted to ester group to yield half ester **110**.

The characterization of the molecule was conducted by IR, ¹H and ¹³C NMR spectra. In the ¹H-NMR, generation of a methyl peak compared with the starting compound **75** proves the structure of the molecule **110**.

2.2.2 Synthesis of methyl [3-(chlorocarbonyl)-2-furyl]acetate

After the protection of the lower arm of the molecule, we decided to convert the carboxylic acid functionality into an acyl chloride group since a leaving group is needed for the substitution with azide in the next step of our synthetic pathway (Scheme 30).

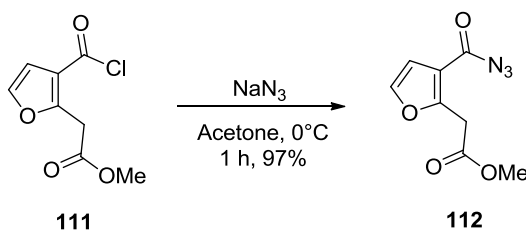


Scheme 30

To produce acyl chloride **111**, the half ester **110** was reacted with oxalyl chloride with catalytic amount of dimethylformamide in dichloromethane. Acyl chloride **111** was obtained in 96% yield after stirring the reaction mixture for 1 h at room temperature.

2.2.3 Synthesis of 1-[2-(2-methoxy-2-oxoethyl)-3-furoyl]triazol-1,2-dien-2-ium

With the leaving group attached, the molecule is ready for a substitution reaction with an azide group, which will be used to introduce a nitrogen atom into the molecule in the next step of the synthesis (Scheme 31).



Scheme 31

To generate the acyl azide **112**, molecule **111** was treated with NaN₃ in acetone at 0 °C for 1 h. The reaction was completed in 97% yield.

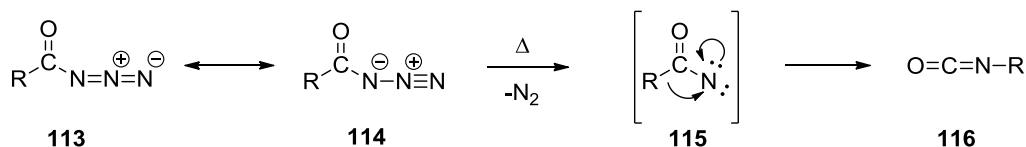
The IR spectrum was used to confirm the presence of the acyl azide group in the molecule which shows a characteristic peak around 2100 cm⁻¹.

2.2.4 Synthesis of methyl (3-isocyanato-2-furyl)acetate

After the introduction of the azide group into the molecule, Curtius rearrangement⁴⁸ was applied to obtain the corresponding isocyanates, which will be then attacked by the nucleophile. By this methodology, a nitrogen atom will be introduced to the molecule.

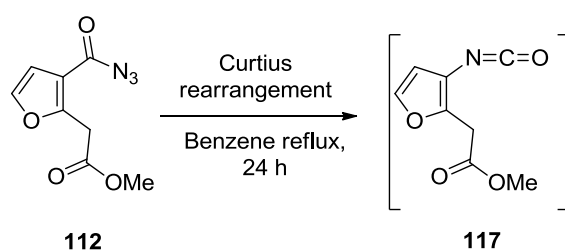
According to the mechanism of Curtius rearrangement (Scheme 32), nitrogen gas is evolved from the molecule forming acyl nitrene **115** as a reactive intermediate. The electron gap on the nitrogen in the nitrene **115** is the driving force of the rearrangement which is basically the formation of C-N double

bond by the nitrogen lone pairs and the movement of the -R group to nitrogen yielding isocyanate **116**.



Scheme 32

To the previously synthesized acyl azide **112** Curtius rearrangement was applied. The molecule **112** was stirred at reflux temperature in dry benzene for 24 h under N₂ atmosphere to yield isocyanate **117** (Scheme 33).



Scheme 33

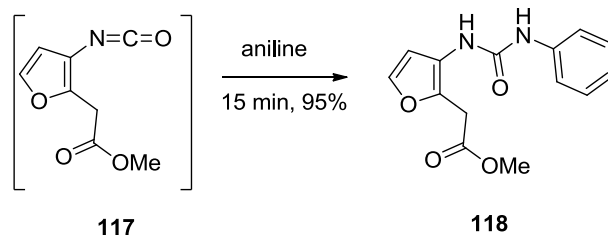
To confirm the structure of isocyanate **117**, IR spectrum was used since isocyanate group has a characteristic signal at around 2200 cm⁻¹.

2.2.5 Synthesis of methyl {3-[(anilincarbonyl)amino]-2-furyl}acetate

After the synthesis of isocyanate **117**, our aim was to use a nucleophile, which will attack to the electrophilic carbon on the isocyanate group. Since the nitrogen atom introduction will be completed by this reaction, the desired molecule to study ring closure reactions will be synthesized.

To obtain a urea derivative, aniline was chosen as a nucleophile to attack the electrophilic carbon on the isocyanate **117**. Having been chosen, aniline makes possible the intramolecular cyclization performed by two routes since the molecule contains two nucleophilic nitrogen atoms.

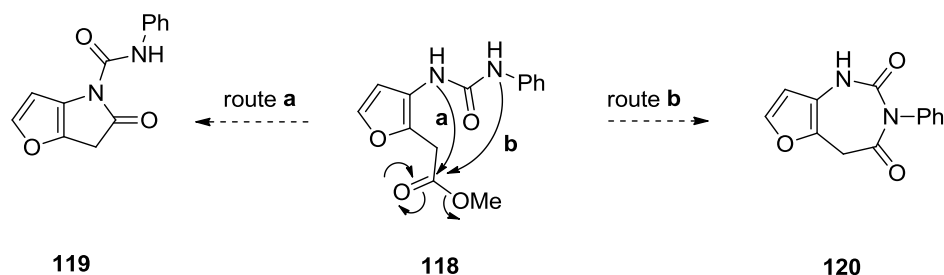
The refluxed solution of dry benzene and produced isocyanate was cooled to room temperature, then aniline was added to this solution. After 15 min of stirring, urea ester **118** was obtained in 95% yield (Scheme 34).



Scheme 34

To prove the structure of urea ester **118**, ^1H and ^{13}C -NMR spectra were used. Mono substituted benzene singals appeared in the ^1H -NMR spectrum indicating the addition of the aniline to the molecule.

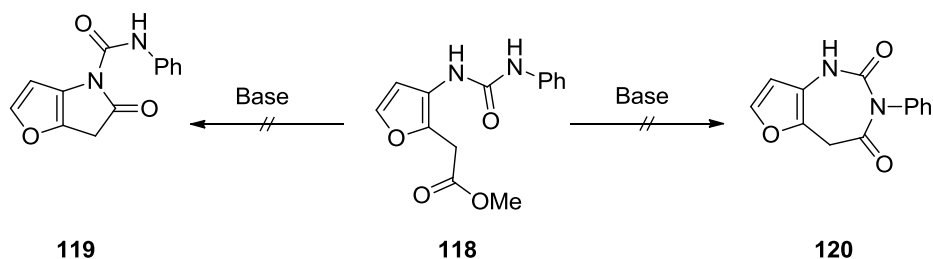
By the introduction of aniline, we completed the desired structure to study ring closure reactions. The idea was to conduct experiments that makes possible of the attack of nitrogen to the carbonyl group on the lower arm of the molecule followed by the departure of the methoxyl group. Since there are two -NH groups in the urea ester **118**, the production of both 5-membered (**119**) and 7-membered (**120**) rings is possible (Scheme 35).



Scheme 35

2.2.6 The ring closure attempts of methyl {3-[(anilino)amino]-2-furyl}acetate

For the ring closure reaction, we decided to use base for the cleavage of one of the acidic -NH protons in the molecule **118**. Therefore, urea ester **118** was reacted with various bases in different conditions to yield cyclization product. Unfortunately our attempts did not yield both of the possible ring closure products **119** and **120** (Scheme 36).



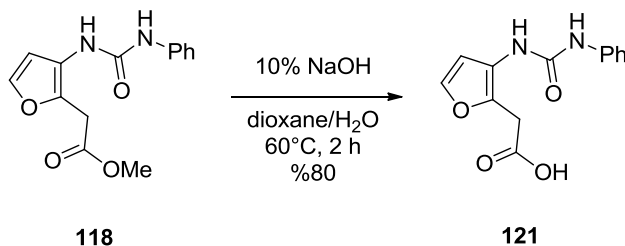
Scheme 36

The first attempt was performed using sodium hydride as a base at 0 °C in dry THF. Yet, the molecule **118** was decomposed and the desired molecules were not observed. Therefore, we decided to change the base into a weaker base than sodium hydride and LiHMDS (lithium bis(trimethylsilyl)amide) was used as a non-nucleophilic base to abstract one of the acidic -NH protons. The experiments were conducted at room temperature, 40 °C and reflux temperature in THF. At room temperature and 40 °C, the starting material was remained unreacted. Nevertheless, at reflux temperature, the peaks belong to the furan protons in the molecule **118** were disappeared in the ^1H -NMR spectrum indicating the furan ring was corrupted. Finally, potassium carbonate was used at reflux temperature in acetonitrile but the reaction did not proceed and starting material was recovered.

2.2.7 Synthesis of {3-[(anilinoacetyl)amino]-2-furyl}acetic acid

After the failed attempts of cyclization reactions, we decided to change the ester group in the lower arm of the molecule into a carboxylic acid group in which the -OH group will further transformed into a better leaving group than -OCH₃. This transformation would not only increase the electrophilic character of the carbonyl group but also provide a better leaving group attached to the carbonyl group, which will depart from the molecule after the intramolecular cyclization.

To obtain acid derivative **121** the urea ester **118** was hydrolyzed with 10% sodium hydroxide in dioxane/water (2:1) mixture at 60 °C. After 2 h, acid **121** was produced with 80% yield (Scheme 37).



Scheme 37

The characterization of compound **121** was achieved by ¹H and ¹³C-NMR spectra. In the ¹H-NMR spectrum (Figure 5), the broad -OH peak indicates the presence of carboxylic acid group and two -NH signals, mono substituted benzene signals and the methylene signal proves the structure.

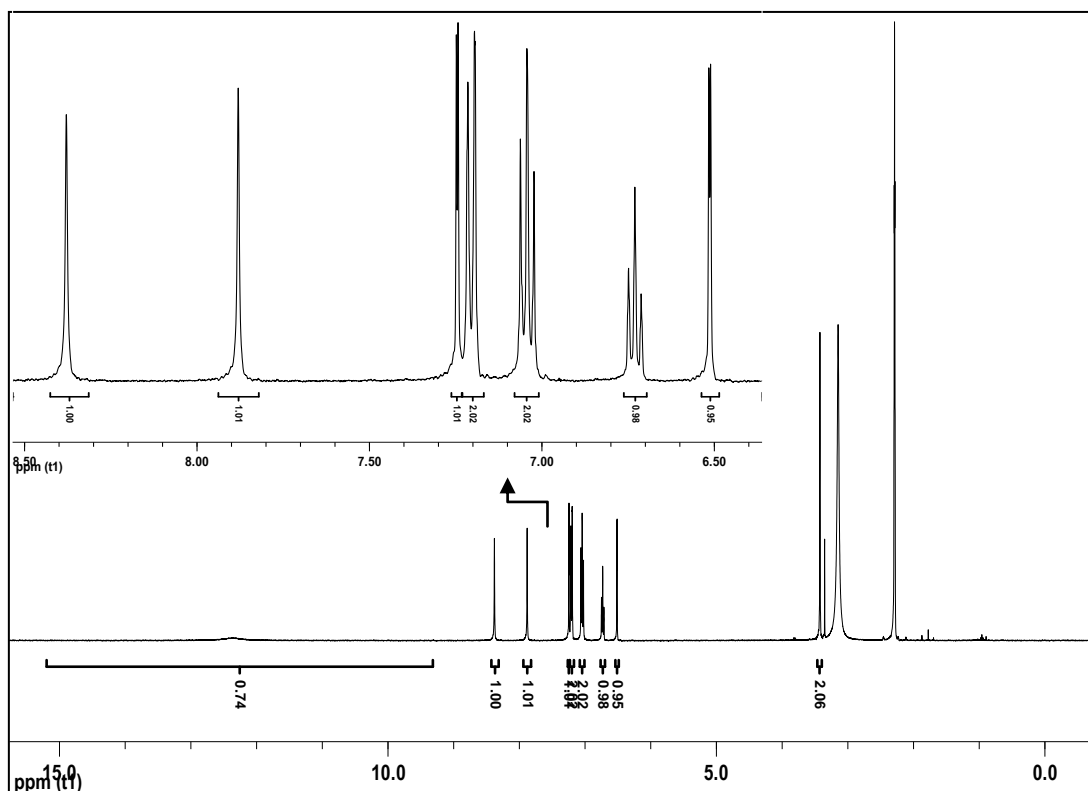
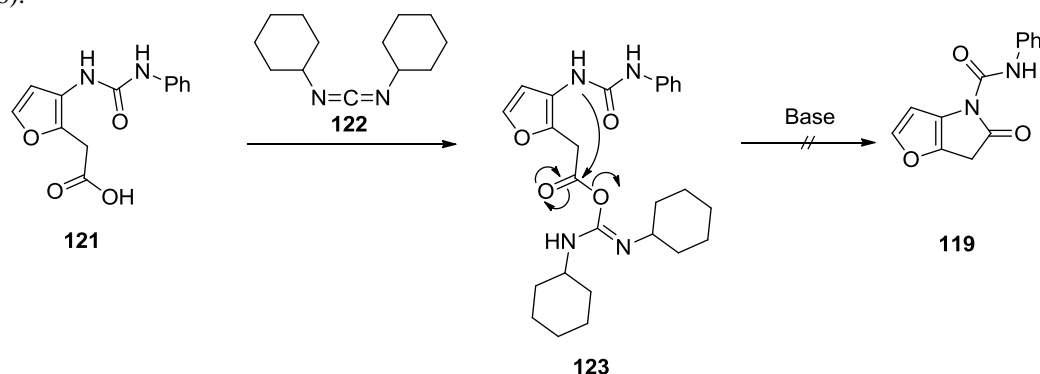


Figure 5 ¹H-NMR spectrum of the acid **123**

2.2.8 The ring closure attempts of {3-[(anilincarbonyl)amino]-2-furyl}acetic acid

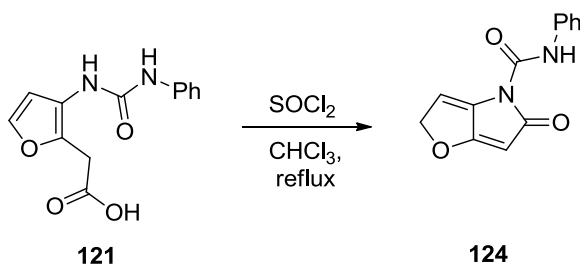
After the synthesis of acid **121**, we turned our attention to possible reagents that increase electrophilicity of the carbonyl group on the lower arm of the molecule. *N,N'*-Dicyclohexylcarbodiimide (DCC) (**122**) is an organic reagent widely used in the peptide synthesis and it is known for activating the carbonyl group for amine attack forming amides,⁴⁹ which is the same as our case. Acid **121** was reacted with DCC (**122**) in DCM at room temperature and the addition product was obtained. Nonetheless, the intramolecular cyclization was not achieved. Treating the molecule **123** with potassium carbonate in acetonitrile and triethylamine in toluene at reflux temperatures did not yield the desired cyclization product (Scheme 38).



Scheme 38

Then we changed our course to chlorinating the lower arm of the acid **121** to perform the intramolecular cyclization. The acid **121** was reacted with thionyl chloride in benzene, THF and toluene at reflux temperatures and black polymerized muddy crude was obtained which did not show any peaks belonging to the desired product in ¹H-NMR in each case. Finally, a product was detected after chlorination using thionyl chloride in chloroform at reflux temperature (Scheme 39).

The ¹H-NMR, ¹³C-NMR, and full analysis (COSY, HMQC, HMBC, DEPT) were used to characterize the formed product. The molecule has lost one of the -NH protons which is in agreement with the cyclization product and in the DEPT-135 spectrum molecule shows a -CH₂ group resonating at 86.4 ppm. However, in ¹H-NMR spectrum these methylene protons resonate at 5.39 ppm which is much more lower field than expected (Figure 7). X-Ray analysis clarified the structure of the formed product (Figure 6), which is the rearranged furan system **124**. According to this framework, methylene protons are adjacent to the oxygen atom, which explains the shift of methylene protons to lower field in ¹H-NMR.



Scheme 39

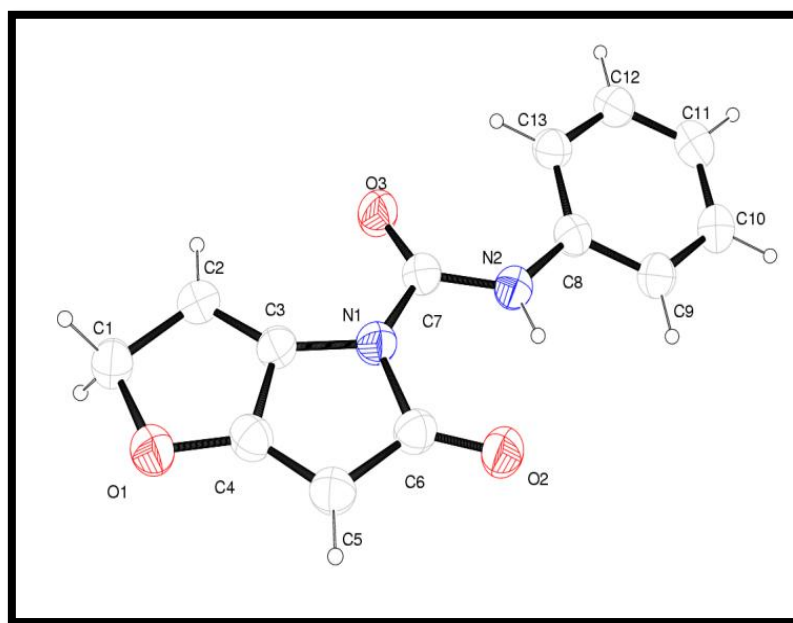


Figure 6 X-Ray Analysis of fuopyrrolone **124**

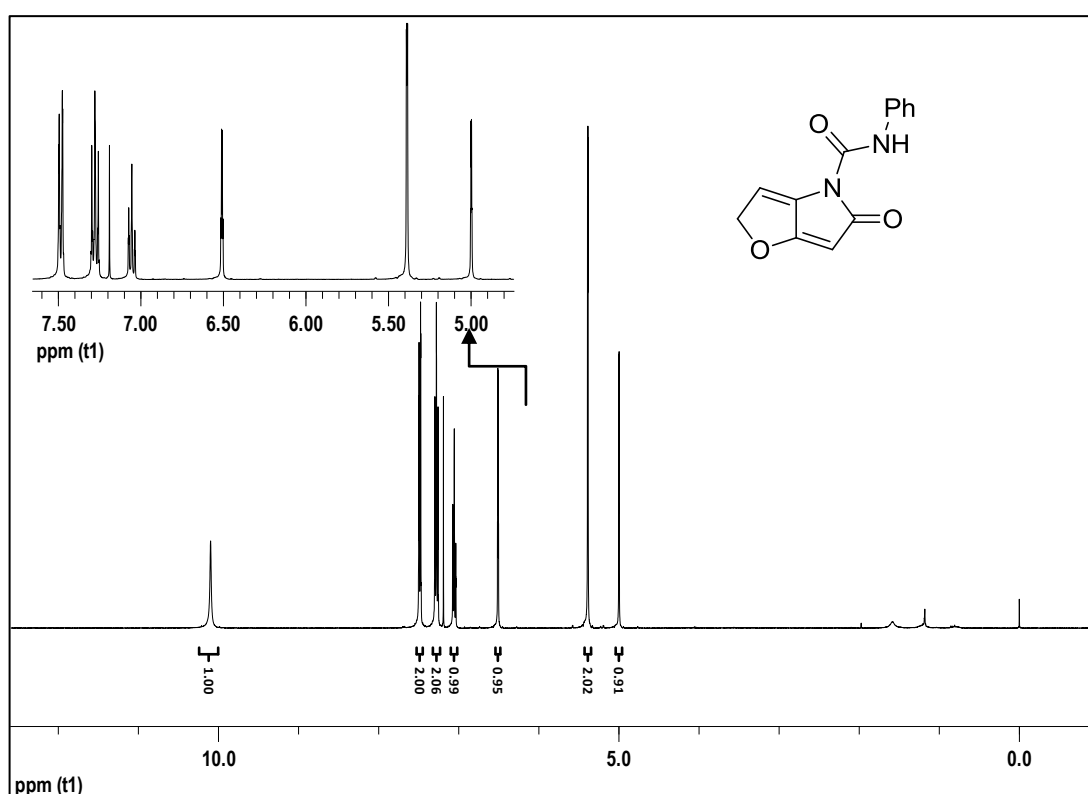
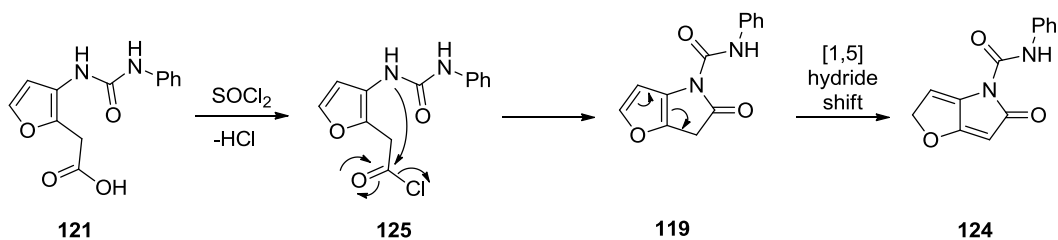


Figure 7 ^1H -NMR Spectrum of fuopyrrolone **124**

For this unexpected rearranged product, we proposed the following mechanism (Scheme 40). According to the proposed mechanism, first the carboxylic acid functionality on the lower arm of the molecule is chlorinated by thionyl chloride forming acyl chloride **125**. Then, intramolecular cyclization takes place yielding fuopyrrolone **119** which further undergoes a sigmatropic [1,5]

hydride shift. The hydride attached to the methylene on the furopyrrone **119** migrates to the carbon next to oxygen atom in the furan ring forming furopyrrone **124**.



Scheme 40

We also geometrically optimized the structures using DFT(B3LYP/6-31+G(d,p)) method (Figure 10). Single point solvation calculations with polarized continuum model (PCM) were carried out with chloroform since it was used in the experimental study. According to the calculations (Figure 8), it was found out that formed furopyrrone **124** is thermodynamically 4.53 kcal/mol more stable than the expected furopyrrone **119**, which is in agreement with the experimental result. We proposed that this energy difference arises from the extended conjugation of the rearranged furopyrrone **124**. Molecule prefers to possess this conjugation even if the aromatization of the furan ring is corrupted.

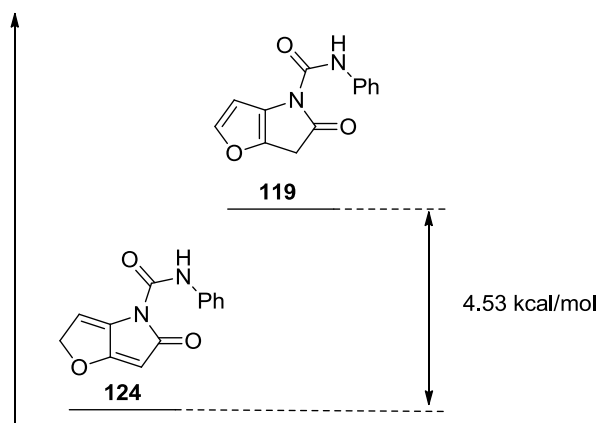


Figure 8 Relative energies of geometrically optimized compounds **124** and **119**

We also calculated relative energies of 7-membered rings **120** and **126** (Figure 9). 7-Membered rearranged cyclization product **126** was found out to be thermodynamically 4.61 kcal/mol less stable than molecule **120**. We propose that, in this case the extended conjugation is not contributing much stability as in the 5-membered ring closure product. The conjugation is not as effective as in the 5-membered ring. This can be explained by planarity of the structure of the 5-membered ring, which contributes to the efficiency of the conjugation.

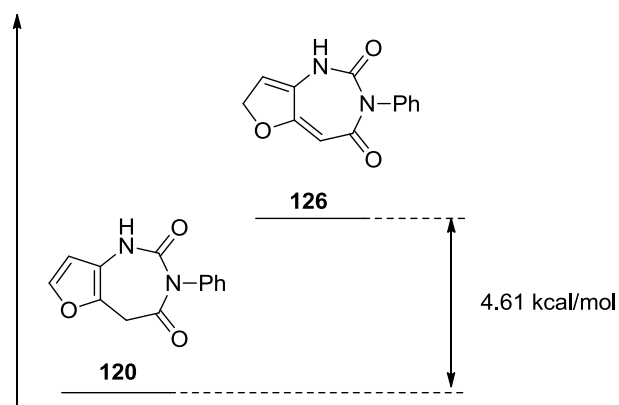


Figure 9 Relative energies of geometrically optimized compounds **120** and **126**

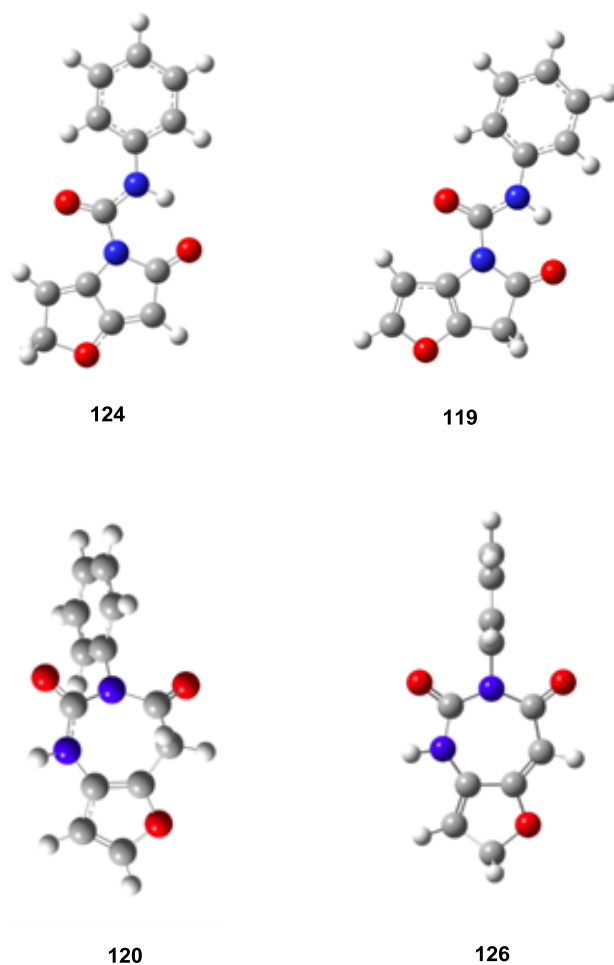
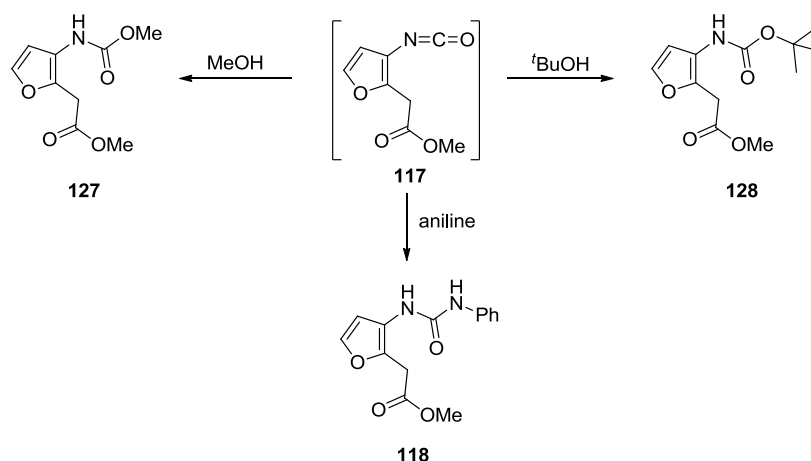


Figure 10 The optimized geometries of compounds **124**, **119**, **120** and **126**

2.2.9 Synthesis of urethane ester derivatives

After the synthesis of furopyrrolone **124**, we focused on the synthesis of urethane derivatives to experiment the same reaction, which was used in the synthesis of furopyrrolone **124**. To achieve this, we used Curtius rearrangement with different nucleophiles such as methanol and *tert*-butanol (Scheme 41).



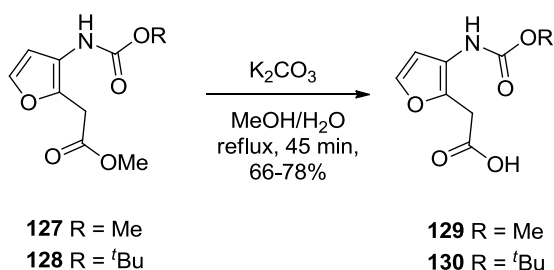
Scheme 41

In the synthesis of urea ester **118**, we have chosen aniline as a nucleophile to attack isocyanate **117**, however; in this case, we preferred methanol and *tert*-butanol as nucleophiles to yield the corresponding urethane esters **127** and **128** accordingly.

To confirm the structures of urethane derivatives **127** and **128**, ^1H and ^{13}C -NMR spectra were used. In the ^1H -NMR spectrum of urethane **127** an additional peak arising from $-\text{OCH}_3$ group, and in the ^1H -NMR spectrum of urethane **128** a singlet belonging to the $^t\text{BuOH}$ group were observed.

2.2.10 Synthesis of urethane acid derivatives

The ester functionality in the lower arm of the molecule was needed to be converted to corresponding carboxylic acids in order to be ready for the ring closure attempt, which was successful for the acid **121**. Therefore, the urethane ester derivatives **127** and **128** were hydrolyzed successively using a different method than the hydrolysis of urea ester **118** (Scheme 42). The reason of changing methodology arose from very low yields of urethane acids **129** and **130** when previous method was applied. Since sodium hydroxide is more basic than potassium carbonate, it may cause the hydrolysis of the urethanes forming carbamic acids, which are very unstable and they immediately undergo decarboxylation yielding corresponding amines. Separating amines and urethane acid derivatives cause difficulties during extraction and therefore result in low yields.



Scheme 42

Using potassium carbonate, however, eliminated this problem. In methanol water mixture, urethane ester derivatives **127** and **128** were reacted with potassium carbonate at reflux temperature for 45 min forming urethane acids **129** and **130** in 78% and 66% yields respectively.

Characterization of urethane acid derivatives was achieved using ^1H and ^{13}C -NMR spectra. The methoxy signals, which belong to the lower arm of the molecule, were disappeared.

The ring closure reactions of urethane acid derivatives **129** and **130** are still in progress.

CHAPTER 3

EXPERIMENTAL

3.1 General

Nuclear magnetic resonance ($^1\text{H-NMR}$ and $^{13}\text{C-NMR}$) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in CDCl_3 , CD_3OD and DMSO-d_6 with TMS as internal reference. Chemical shifts (δ) were expressed in units parts per million (ppm). Spin multiplicities were given as singlet (s), doublet (d), doublet of doublets (dd), triplet (t) and quartet (q) and coupling constants (J) were reported in Hertz (Hz).

Infrared spectra were recorded on a Thermo Smart Nicolet iS10 iTR and Bruker Platinum ATR FT-IR spectrometer. Band positions were reported in reciprocal of centimeters (cm^{-1}).

Melting points were obtained on Gallenkamp electronic melting point apparatus.

For the crystal structure determination, Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector) was used.

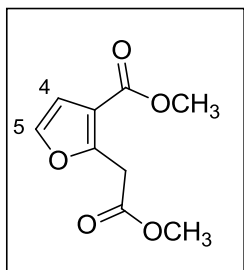
Column chromatographic separations were performed using Fluka Silica Gel 60 plates with a particle size of 0.063-0.200 mm. Thin layer chromatography (TLC) was performed using 0.25 mm silica gel plates purchased from Fluka.

Naming of the compounds were done by ACD NMR (Name generator).

Solvents were purified as reported in the literature.⁵⁰

3.2 Synthesis of methyl 2-(2-methoxy-2-oxoethyl)-3-furoate (74)

A solution of chloroacetaldehyde (**84**) (26.5 ml, 45%) in water was added dropwise to a solution of dimethyl 1,3-acetonedicarboxylate (**83**) (25 g, 143.5mmol) in pyridine (50 ml) with stirring. Stirring was continued for 24 h at 50 °C. Then the reaction mixture was extracted with water and ethyl acetate. The organic layer was washed successively with 2 M HCl, 5% NaHCO_3 , 10% NaOH and brine, and then dried over MgSO_4 . The solvent was evaporated and the product was purified by silica gel column chromatography eluting with hexane/ethyl acetate (3:1) to give product methyl 2-(2-methoxy-2-oxoethyl)-3-furoate (**74**) (19.2 g, 68%).



$^1\text{H-NMR}$: (400 MHz, CDCl_3) δ : 7.26 (d, $J_{5,4} = 1.9$ Hz, 1H, H-5), 6.62 (d, $J_{4,5} = 1.9$ Hz, 1H, H-4), 4.01 (s, 2H, $-\text{CH}_2$), 3.75 (s, 3H, $-\text{OCH}_3$), 3.65 (s, 3H, $-\text{OCH}_3$).

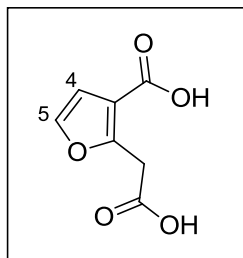
$^{13}\text{C-NMR}$: (100 MHz, CDCl_3) δ : 169.0, 163.8, 154.1, 141.8, 115.5, 110.7, 52.3, 51.5, and 33.4.

IR: 3000, 2954, 1742, 1713, 1611, 1341, 1309, 1173, 1153, 1134.

3.3 Synthesis of 2-(carboxymethyl)-3-furoic acid (75)

To a solution of diester **74** (5.0 g, 25.23 mmol) in 60 mL solution of 1:1 $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ was added K_2CO_3 (10.0 g, 72.36 mmol). The solution was refluxed for 24 h. Then the reaction mixture was

acidified with concentrated HCl (15 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was dried over MgSO₄ and concentrated under reduced pressure to give diacid **75** (3.97 g, 23.33 mmol) in 93% yield (mp 210-212 °C).



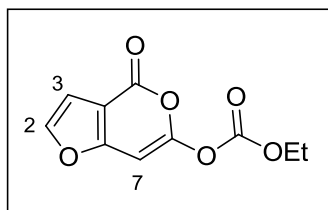
¹H-NMR: (400 MHz, DMSO-d₆) δ: 12.74 (br s, 2H, -OH), 7.72 (d, $J_{45} = 1.9$ Hz, 1H, H-5), 6.73 (d, $J_{54} = 1.9$ Hz, 1H, H-4), 4.04 (s, 2H, -CH₂).

¹³C-NMR: (100 MHz, DMSO-d₆) δ: 169.8, 164.3, 154.7, 142.2, 115.5, 110.7 and 33.3.

IR: 3130, 2929, 2683, 2618, 1683, 1461, 1314, 1216, 1185, 1169.

3.4 Synthesis of ethyl 4-oxo-4H-furo[3,2-c]pyran-6-yl carbonate (**92**)

To a solution of diacid **75** (1.50 g, 8.8 mmol) in 10 mL of THF at 0 °C, triethylamine (1.80 mL, 13.2 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 (1.65 mL, 17.6 mmol) in 6 mL THF and the reaction mixture was stirred at the same temperature for 30 min. The mixture was extracted with ethylacetate (2 × 15 mL) and water (20 mL) and the organic phase was washed with saturated NaHCO₃ solution (3 × 40 mL) and with water (2 × 25 mL). Then organic layer was dried over MgSO₄. After that, compound **92** (0.81 g, 3.1 mmol) was obtained and purified on silica gel column chromatography using hexane/ethylacetate as eluent (3:1) in 41% yield (mp 82-83 °C).



¹H-NMR: (400 MHz, CDCl₃) δ: 7.52 (d, $J_{23} = 2.0$ Hz, 1H, H-2), 6.90 (dd, $J_{32} = 2.0$ Hz, $J_{37} = 0.6$ Hz, 1H, H-3), 6.44 (d, $J_{73} = 0.6$ Hz, 1H, H-7), 4.38 (q, $J = 7.15$ Hz, 2H, -CH₂), 1.41 (t, $J = 7.15$ Hz, 3H, -CH₃).

¹³C-NMR: (100 MHz, CDCl₃) δ: 162.4, 155.9, 154.1, 150.4, 144.7, 108.4, 107.7, 86.1, 66.5 and 14.0.

IR: 1774, 1623, 1565, 1232, 1167, 1065.

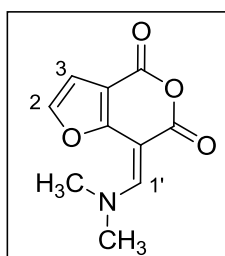
Elemental Analysis: Anal. Calcd. for C₁₀H₈O₆; C 53.58, H 3.60, O

42.82; Found: C 53.78, H 3.61.

HRMS calcd for C₁₀H₈O₆ (M+Na)⁺: 247.02131, found: 247.02467.

3.5 Synthesis of (7E)-7-[(dimethylamino)methylene]-4H-furo[3,2-c]pyran-4,6(7H)-dione (**104**)

Benzene (7 mL), dimethylformamide (2.8 mL) and thionyl chloride (2.3 mL) were mixed in a dropping funnel and two separate layers were formed in 5 min. The lower layer was added to a mixture of diacid **75** (2.36 g 13.9 mmol), tetrabutylammonium bromide (0.6 g, 2.3 mmol), and pyridine (3.2 mL) in 100 mL dichloromethane. The solution was kept stirring at room temperature overnight. Then the solution was washed with saturated NaHCO₃ solution (3 × 50 mL) and the organic extracts were washed with 1 M HCl solution (3 × 50 mL) and with water (2 × 25 mL). The organic layer was dried over MgSO₄ and the solvent was evaporated under vacuum. The residue was then purified by column chromatography (SiO₂, 120 g) eluting with ethylacetate to yield the compound **104** (1.53 g, 7.3 mmol). (Yield 53%, mp 154-155 °C)



¹H NMR: (400 MHz, CD₃OD) δ: 7.97 (s, 1H, H-1'), 7.40 (d, $J_{23} = 2.1$ Hz, 1H, H-2), 6.66 (d, $J_{32} = 2.1$ Hz, 1H, H-3), 3.38 (s, 3H, -CH₃), 3.37 (s, 3H, -CH₃).

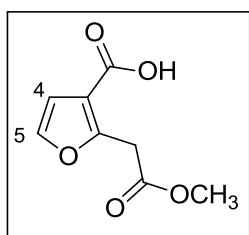
¹³C-NMR: (100 MHz, CDCl₃) δ: 164.8, 159.4, 157.8, 154.7, 141.8, 108.0, 103.9, 85.5, 49.0 and 42.9.

IR: 3126, 1752, 1694, 1608, 1529, 1476, 1432, 1391, 1312, 1271, 1116, 1082, 1051.

HRMS calcd for C₁₀H₉O₄N (M+H)⁺: 208.06043, found: 208.06348.

3.6 Synthesis of 2-(2-methoxy-2-oxoethyl)-3-furoic acid (**110**)

To a stirred solution of diacid **75** (3.5 g, 20.6 mmol) in 90 mL of dichloromethane/methanol (2:1) mixture, 15 drops of concentrated HCl were added. This mixture was kept stirring at 42 °C for 24 h. After the completion of the reaction, the solvent was evaporated to give the crude product which was then separated by column chromatography (160 g SiO₂, hexane/EtOAc, 3:1). The first fraction was identified as diester **74** (0.450 g, 2.27 mmol), and the second fraction was the half ester **110** (3.10 g, 15.8 mmol). (Yield 77%, mp 81-83 °C)



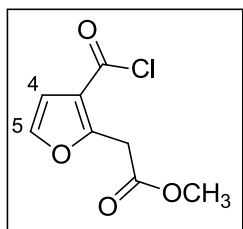
¹H-NMR: (400 MHz, CDCl₃) δ: 7.30 (d, *J*₅₄ = 2.0 Hz, 1H, H-5), 6.69 (d, *J*₄₅ = 2.0 Hz, 1H, H-4), 4.04 (s, 2H, -CH₂), 3.67 (s, 3H, -OCH₃).

¹³C-NMR: (100 MHz, CDCl₃) δ: 168.9, 168.8, 155.5, 142.1, 115.1, 111.0, 52.5 and 33.6.

IR: 3149, 3127, 2957, 2685, 2614, 1728, 1681, 1324, 1280, 1246, 1166.

3.7 Synthesis of methyl [3-(chlorocarbonyl)-2-furyl]acetate (**111**)

Oxalyl chloride (1.7 ml 20.6 mmol) was added to a stirred solution of half ester **110** (3.10 g, 15.8 mmol) in 40 mL dichloromethane, followed by addition of dimethylformamide (5 drops) as catalyst. After stirring this mixture for 1 h at room temperature, solvent was evaporated to give acyl chloride **111** (3.07 g, 15.1 mmol, 96%), which was used without purification for the next steps.



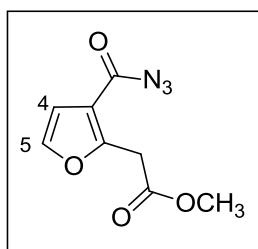
¹H-NMR: (400 MHz, CDCl₃) δ: 7.32 (d, *J*₅₄ = 2.1 Hz, 1H, H-5), 6.74 (d, *J*₄₅ = 2.1 Hz, 1H, H-4), 3.98 (s, 2H, -CH₂), 3.66 (s, 3H, -OCH₃).

¹³C-NMR: (100 MHz, CDCl₃) δ: 167.8, 162.0, 156.1, 142.4, 120.4, 112.6, 52.6 and 33.8.

IR: 3135, 2955, 1750, 1574, 1436, 1338, 1251, 1171.

3.8 Synthesis of 1-[2-(2-methoxy-2-oxoethyl)-3-furoyl]triazol-2-ium (**112**)

To a solution of acyl chloride **111** (3.07, 15.1 mmol) in 40 mL of acetone, NaN₃ (1.47 g, 22.6 mmol) in 8 mL of chilled water was added dropwise at 0 °C. This mixture was stirred for 1 h at 0 °C. Then, 100 mL water was added and the mixture was extracted with ethylacetate (2 × 100 mL). The combined organic extracts were dried over MgSO₄, and then concentrated to give the acyl azide **112** (3.05 g, 14.6 mmol, 97%) as colorless liquid.



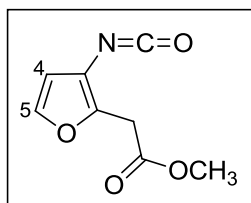
¹H-NMR: (400 MHz, CDCl₃) δ: 7.27 (d, *J*₅₄ = 2.0 Hz, 1H, H-5), 6.60 (d, *J*₄₅ = 2.0 Hz, 1H, H-4), 4.03 (s, 2H, -CH₂), 3.65 (s, 3H, -OCH₃).

¹³C-NMR: (100 MHz, CDCl₃) δ: 168.5, 168.1, 155.4, 142.2, 116.9, 110.5, 52.4 and 33.6.

IR: 2955, 2154, 2133, 1742, 1686, 1601, 1420, 1299, 1133.

3.9 Synthesis of methyl (3-isocyanato-2-furyl)acetate (**117**)

A solution of acyl azide **112** (3.05 g, 14.6 mmol) in 35 mL of dry benzene was stirred at reflux temperature for 24 h. Then, solvent was evaporated under vacuum to give the isocyanate **117** (2.51 g, 13.9 mmol).



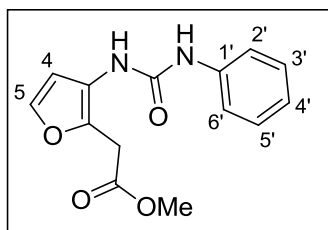
¹H-NMR: (400 MHz, CDCl₃) δ: 7.14 (d, $J_{54} = 2.0$ Hz, 1H, H-5), 6.18 (d, $J_{45} = 2.0$ Hz, 1H, H-4), 3.62 (s, 2H, -CH₂), 3.56 (s, 3H, -OCH₃).

¹³C-NMR: (100 MHz, CDCl₃) δ: 170.5, 143.2, 141.7, 127.2, 118.4, 110.9, 53.9 and 32.8.

IR: 2272, 1742, 907, 730.

3.10 Synthesis of methyl {3-[(anilincarbonyl)amino]-2-furyl}acetate (**118**)

To a solution of isocyanate **117** (2.51 g 13.9 mmol) in 40 mL dichloromethane, 1.5 mL (16.7 mmol) aniline was added at room temperature. Then this mixture was kept stirring at room temperature for 15 minutes. After dichloromethane was evaporated, the crude was purified by silica gel column chromatography (SiO₂, 90 g) eluting with hexane/ethyl acetate mixture (1:1) to give urea-ester **118** (3.81 g, 13.9 mmol, 100%, mp 142-143 °C).



¹H-NMR: (400 MHz, CD₃OD) δ: 7.41 (dd, $J_{2'3'} = J_{6'5'} = 8.6$ Hz, $J_{2'4'} = J_{6'4'} = 1.1$ Hz, 2H, H-2', 6'), 7.38 (d, $J_{54} = 2.0$ Hz, 1H, H-5), 7.29 (quasi t, $J_{3'2'} = J_{3'4'} = J_{5'6'} = J_{5'4'} = 7.4$ Hz, 2H, H-3', 5'), 7.02 (tt, $J_{4'3'} = J_{4'5'} = 7.4$ Hz, $J_{4'2'} = J_{4'6'} = 1.1$ Hz, 1H, H-4'), 6.64 (d, 1H, $J_{45} = 2.0$ Hz, H-4), 3.76 (s, 2H, -CH₂), 3.72 (s, 3H, -OCH₃).

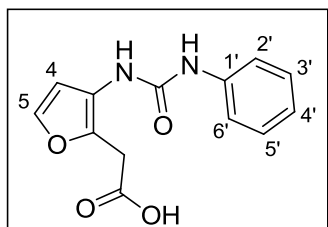
¹³C-NMR: (100 MHz, CDCl₃) δ: 170.5, 154.7, 141.8, 138.4, 128.9, 128.3, 123.4, 121.7, 120.1, 110.1, 52.6 and 31.6.

IR: 3288, 1739, 1557, 1495, 1340, 1221, 1163, 1095.

Elemental Analysis: Anal. Calcd. for C₁₄H₁₄N₂O₄; C 61.31, H 5.14, N 10.21; Found: C 61.59, H 5.03, N 10.06

3.11 Synthesis of {3-[(anilincarbonyl)amino]-2-furyl}acetic acid (**121**)

To a stirred solution of urea-ester **118** (3.81 g, 13.9 mmol) in 60 mL dioxane/water mixture (2:1) was added 4 mL of 10% NaOH solution at room temperature. Then this mixture was kept stirring at 60 °C for 2 h. Then, concentrated HCl (15 mL) was added dropwise to the reaction mixture. Then, the mixture was extracted with ethyl acetate (2 × 100 mL) and the organic layer was dried over MgSO₄. Finally, the acid **121** was obtained by evaporating the solvent under vacuum (2.89 g, 11.1 mmol) in 80% yield (mp 201-202 °C).



¹H-NMR: (400 MHz, DMSO-d₆) δ: 12.37 (br s, 1H, -COOH), 8.38 (s, 1H, -NH), 7.88 (s, 1H, -NH), 7.25 (d, $J_{54} = 2.0$ Hz, 1H, H-5), 7.21 (br d, $J_{2'3'} = J_{6'5'} = 7.6$ Hz, 2H, H-2', 6'), 7.04 (br t, $J_{3'2'} = J_{5'6'} = J_{3'4'} = J_{5'4'} = 7.9$ Hz, 2H, H-3', 5'), 6.73 (br t, $J_{4'3'} = J_{4'5'} = 7.3$ Hz, 1H, H-4')

6.51 (d, $J_{45} = 2.0$ Hz, 1H, H-4), 3.42 (s, 2H, -CH₂).

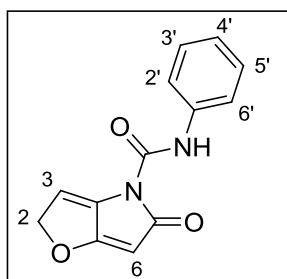
¹³C-NMR: (100 MHz, DMSO-d₆) δ: 170.6, 152.6, 140.6, 139.8, 136.0, 128.7, 122.3, 122.6, 118.0, 108.3 and 37.7.

IR: 3292, 3145, 1703, 1598, 1559, 1445, 1430, 1289, 1245.

HRMS calcd for C₁₃H₁₂N₂O₄ (M+H)⁺: 261.08698, found: 261.08817.

3.12 Synthesis of 5-oxo-N-phenyl-2,5-dihydro-4H-furo[3,2-b]pyrrole-4-carboxamide (124)

To a stirred solution of acid **121** (0.5 g, 1.92 mmol) in 20 mL CHCl₃ (ethanol free), 0.2 mL SOCl₂ was added at room temperature. Then this mixture was heated to reflux temperature and kept stirring for 24 h. The solvent was evaporated to give 0.21 g of the crude product (0.87 mmol, 45%) which was then purified by column chromatography (21 g SiO₂; hexane/ethyl acetate 3:1) compound **124**. (mp 115-117 °C)



¹H-NMR: (400 MHz, CDCl₃) δ: 10.10 (s, 1H, -NH), 7.49 (dd, $J_{2,3'} = J_{6,5'} = 8.5$ Hz, $J_{2,4'} = J_{6,4'} = 1.1$ Hz, 2H, H-2', 6'), 7.28 (br t, $J_{3,2'} = J_{5,6'} = 8.5$ Hz, $J_{3,4'} = J_{5,4'} = 7.4$ Hz 2H, H-3', 5'), 7.05 (tt, $J_{4,3'} = J_{4,5'} = 7.4$ Hz, $J_{4,2'} = J_{4,6'} = 1.1$ Hz, 1H, H-4'), 6.51 (dt, $J_{3,2} = 1.9$ Hz, $J_{3,6} = 1.4$ Hz, 1H, H-3), 5.39 (dd, $J_{2,3} = 1.9$ Hz, $J_{6,2} = 1.1$ Hz, 2H, H-2), 5.00 (dt, $J_{6,3} = 1.4$ Hz, $J_{6,2} = 1.1$ Hz, 1H, H-6).

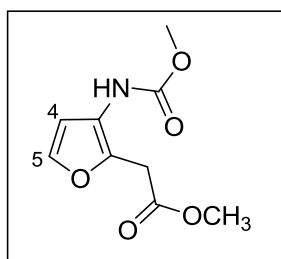
¹³C-NMR: (100 MHz, CDCl₃) δ: 176.0, 175.1, 148.3, 137.3, 133.4, 129.1, 124.3, 120.1, 112.5, 86.4 and 84.0.

IR: 3108, 1717, 1666, 1596, 1556, 1500, 1448, 1355, 1290, 1236, 1108, 1084.

HRMS calcd for C₁₃H₁₀N₂O₃ (M-H)⁻: 241.06187, found: 241.06241.

3.13 Synthesis of methyl {3-[(methoxycarbonyl)amino]-2-furyl}acetate (127)

The solution of acyl azide **112** (1.5 g, 7.17 mmol) in 30 mL dry methanol was stirred at reflux temperature overnight. Then the crude mixture was purified by column chromatography (80 g SiO₂; hexane/ethyl acetate 1:1) and 1.12 g (6.18 mmol, 86%) of urethane-ester **127** was isolated.



¹H-NMR: (400 MHz, CDCl₃) δ: 7.24 (d, $J_{5,4} = 2.0$ Hz, 1H, H-5), 7.12 (br s, 1H, -NH), 6.69 (br s, 1H, H-4), 3.74 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 3.70 (br s, 2H, -CH₂).

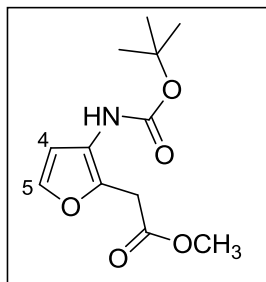
¹³C-NMR: (100 MHz, CDCl₃) δ: 170.4, 154.8, 140.8, 135.7, 122.0, 108.3, 52.4 and 32.3.

IR: 3120, 1706, 1508, 1437, 1239, 1100, 1060.

Elemental Analysis: Anal. Calcd. for C₉H₁₁NO₅; C 50.70, H 5.20, N 6.57; Found: C 50.77, H 5.045, N 6.482.

3.14 Synthesis of methyl {3-[(tert-butoxycarbonyl)amino]-2-furyl}acetate (128)

The solution of acyl azide **112** (1.5 g, 7.17 mmol) in 30 mL dry *tert*-butanol was stirred at reflux temperature for 2 d. Then the solvent was evaporated under vacuum conditions and the crude mixture was purified by column chromatography (65 g SiO₂; hexane/ethyl acetate 3:1) and 1.44 g (5.64 mmol, 79%) urethane-ester **128** was isolated.



¹H-NMR: (400 MHz, CDCl₃) δ: 7.22 (d, $J_{5,4} = 2.0$ Hz, 1H, H-5), 6.73 (br s, 1H, -NH), 6.69 (br s, 1H, H-4), 3.72 (s, 3H, -OCH₃), 3.70 (s, 2H, -CH₂), 1.49 (s, 9H, -CH₃).

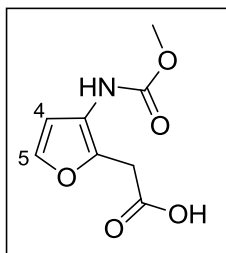
¹³C-NMR: (100 MHz, CDCl₃) δ: 168.9, 152.1, 139.3, 134.3, 121.0, 107.2, 51.0, 30.9 and 27.0.

IR: 3335, 2978, 1698, 1506, 1437, 1367, 1243, 1159, 1053, 1010.

HRMS calcd for C₁₂H₁₇NO₅ (M+Na)⁺: 278.09989, found: 278.10365.

3.15 Synthesis of {3-[(methoxycarbonyl)amino]-2-furyl}acetic acid (**129**)

To a stirred solution of urethane-ester **127** (1.31 g, 6.15 mmol) in 40 mL of CH₃OH:H₂O (1:1) mixture, 1.02 g (7.38 mmol) of K₂CO₃ was added. Then the reaction mixture was refluxed for 45 min. After the completion of the reaction, the solution was acidified with 2 M of HCl (50 mL) and then extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over MgSO₄ and concentrated under vacuum conditions which gives 0.96 g (4.82 mmol, 78%) of urethane-acid **129**. (mp 134-136 °C)



¹H-NMR: (400 MHz, DMSO-d₆) δ: 12.40 (br s, 1H, -COOH), 9.13 (br s, 1H, -NH), 7.44 (d, *J*_{5,4} = 2.0 Hz, 1H, H-5), 6.64 (br s, 1H, H-4), 3.67 (br s, 2H, -CH₂), 3.62 (s, 3H, -OCH₃).

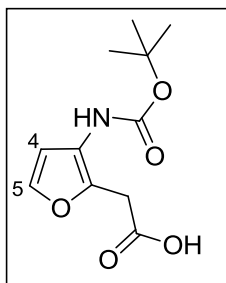
¹³C-NMR: (100 MHz, DMSO-d₆) δ: 170.6, 154.4, 140.7, 136.2, 121.9, 107.6, 51.6 and 31.4.

IR: 3285, 1696, 1509, 1264, 1215, 1060, 1036.

Elemental Analysis: Anal. Calcd. for C₈H₉NO₅; C 48.25, H 4.55, N 7.03; Found: C 48.49, H 4.508, N 6.920.

3.16 Synthesis of {3-[(tert-butoxycarbonyl)amino]-2-furyl}acetic acid (**130**)

To a stirred solution of urethane-ester derivative **128** (1.44 g, 5.64 mmol) in 40 mL of CH₃OH:H₂O (1:1) mixture, 0.94 g (6.80 mmol) of K₂CO₃ was added. Then the reaction mixture was refluxed for 2 h. After the completion of the reaction, the solution was acidified with 2 M of HCl (50 mL) and then extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over MgSO₄ and concentrated under vacuum conditions which gives 0.90 g (3.73 mmol, 66%) of the urethane-acid **130**. (mp 116-118 °C)



¹H-NMR: (400 MHz, DMSO-d₆) δ: 12.34 (br s, 1H, -COOH), 8.83 (br s, 1H, -NH), 7.41 (d, *J*_{5,4} = 2.0 Hz, 1H, H-5), 6.66 (br s, 1H, H-4), 3.67 (br s, 2H, -CH₂), 1.44 (s, 9H, -CH₃).

¹³C-NMR: (100 MHz, DMSO-d₆) δ: 170.7, 153.0, 140.5, 135.7, 122.1, 107.6, 78.7, 31.5 and 28.1.

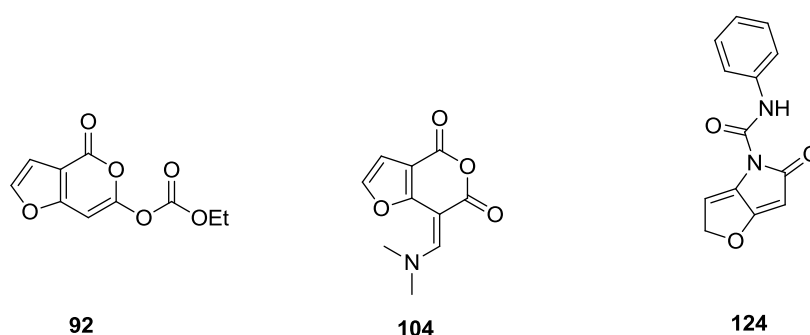
IR: 3114, 2976, 1694, 1366, 1228, 1158, 1097, 1062, 1009.

Elemental Analysis: Anal. Calcd. for C₁₁H₁₅NO₅; C 54.77, H 6.27, N 5.81; Found: C 54.35, H 6.459, N 5.759.

CHAPTER 4

CONCLUSION

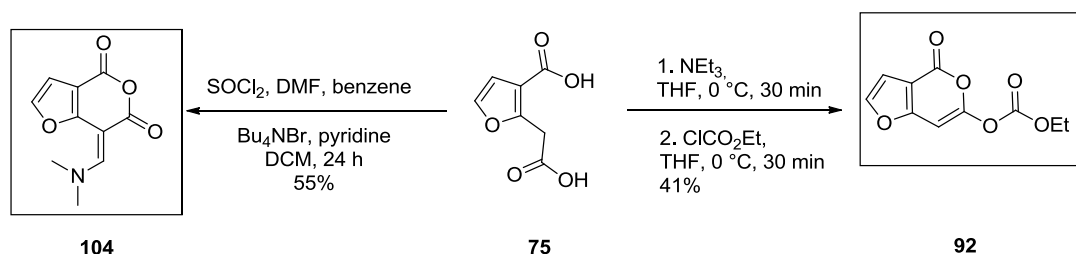
In this study, we developed new synthetic methodologies for the synthesis of furopyranone **92**, furopyrandione **104**, and furopyrrolone **126**. These compounds show potential for possessing biological activity since there are many biologically active compounds in the literature having the similar framework with these molecules.



Reactive intermediates such as chloroiminium ion and isocyanate were used in this work. In addition, regioselective esterification was performed using the reactivity difference of the corresponding carbonyl groups.

In the first part of this study, we focused on the synthesis of furopyranone derivatives. First, the starting material was synthesized using modified Fiest-Benary furan synthesis. Then furan diester **74** was hydrolyzed giving the furan diacid **75**, which was the starting molecule of the synthesis of furopyranone. Treating the furan diacid with triethylamine and ethylchloroformate gave the furopyranone **92**.

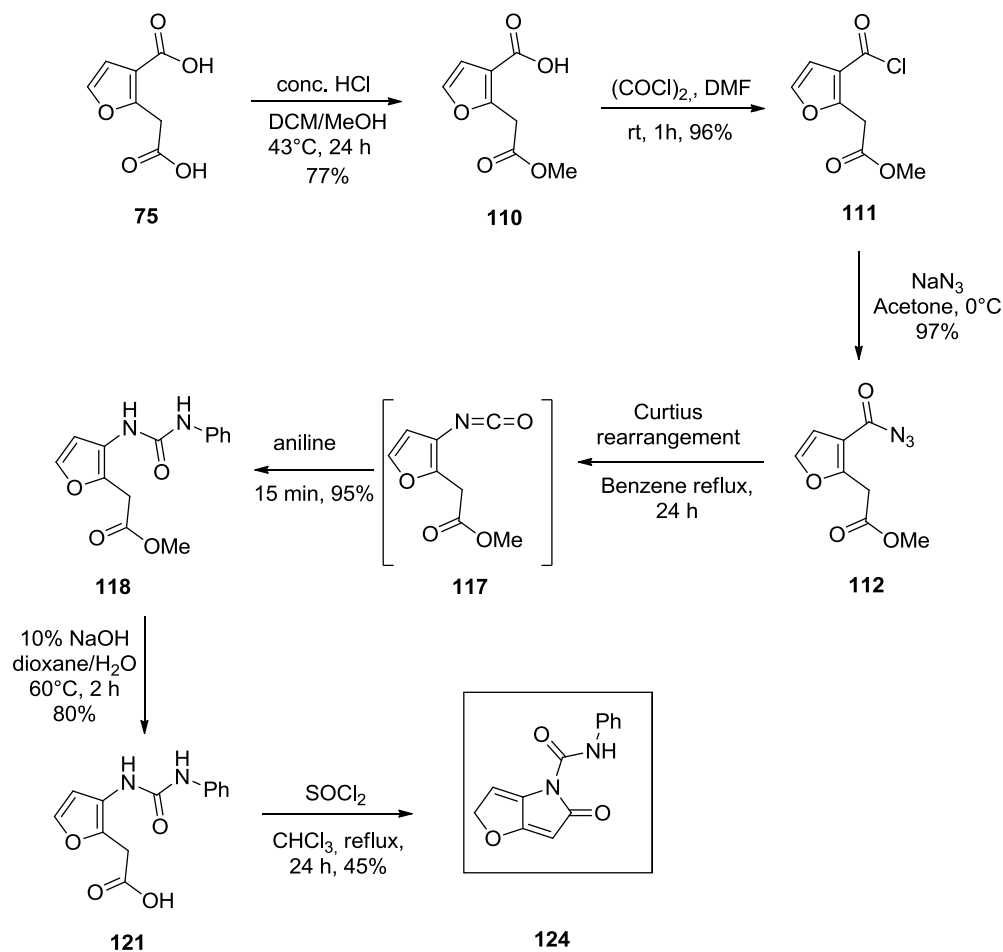
After the synthesis of furopyranone **92**, another method was developed in the synthesis of furopyranones. Furan diacid molecule was reacted with chloroiminium intermediate, which was generated from the *in situ* Vilsmeier-Haack reaction under basic conditions to yield furopyrandione **104**.



Scheme 43

In the second part of the work, the synthesis of furopyrrolone derivative was studied. To achieve this goal, the lower arm of the furan diacid molecule was protected by regioselective esterification so that

the nitrogen atom introduction can be performed on the upper arm of the molecule. Then the mono acid **110** was chlorinated to give acyl chloride **111** which was then further reacted with sodium azide to give corresponding acyl azide **112**. Formed acyl azide **112** was then converted to the isocyanate **117**, which was the key material of the synthetic pathway. In this step, the introduction of the nitrogen atom to the molecule was achieved. Then the reactive intermediate isocyanate was treated with aniline to give the urea ester derivative **118**. This molecule provided us two possible cyclization products due to the two -NH groups in the molecule. After the hydrolysis of the urea ester **118** to acid **121** we performed cyclization reaction yielding an unexpected rearranged furopyrrolone product **124**. Acid **121** was treated with thionyl chloride to produce this furopyrrolone **124**.



Scheme 44

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APPENDIX A

SPECTRAL DATA

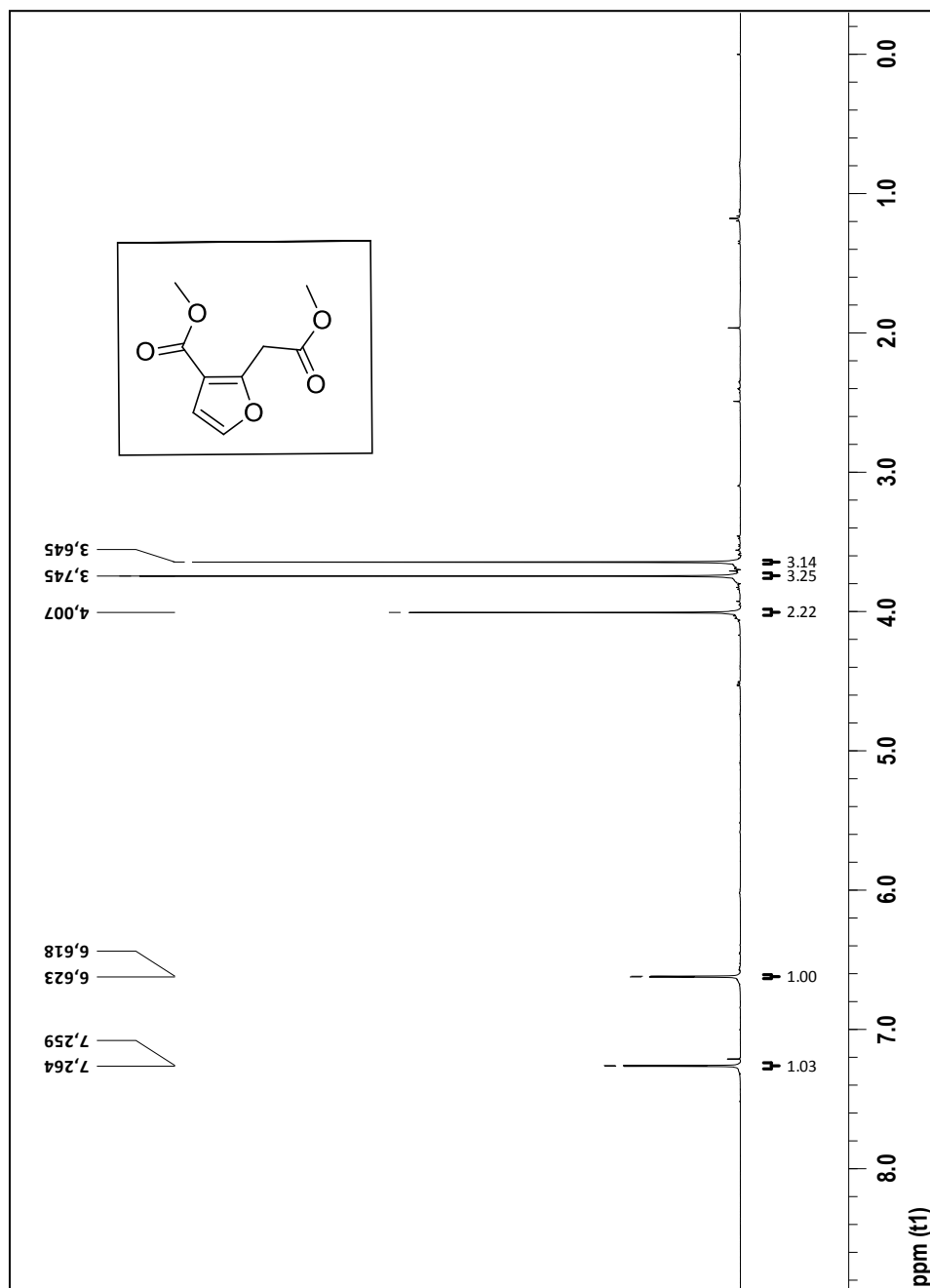


Figure 11 ¹H-NMR Spectrum of Compound 74

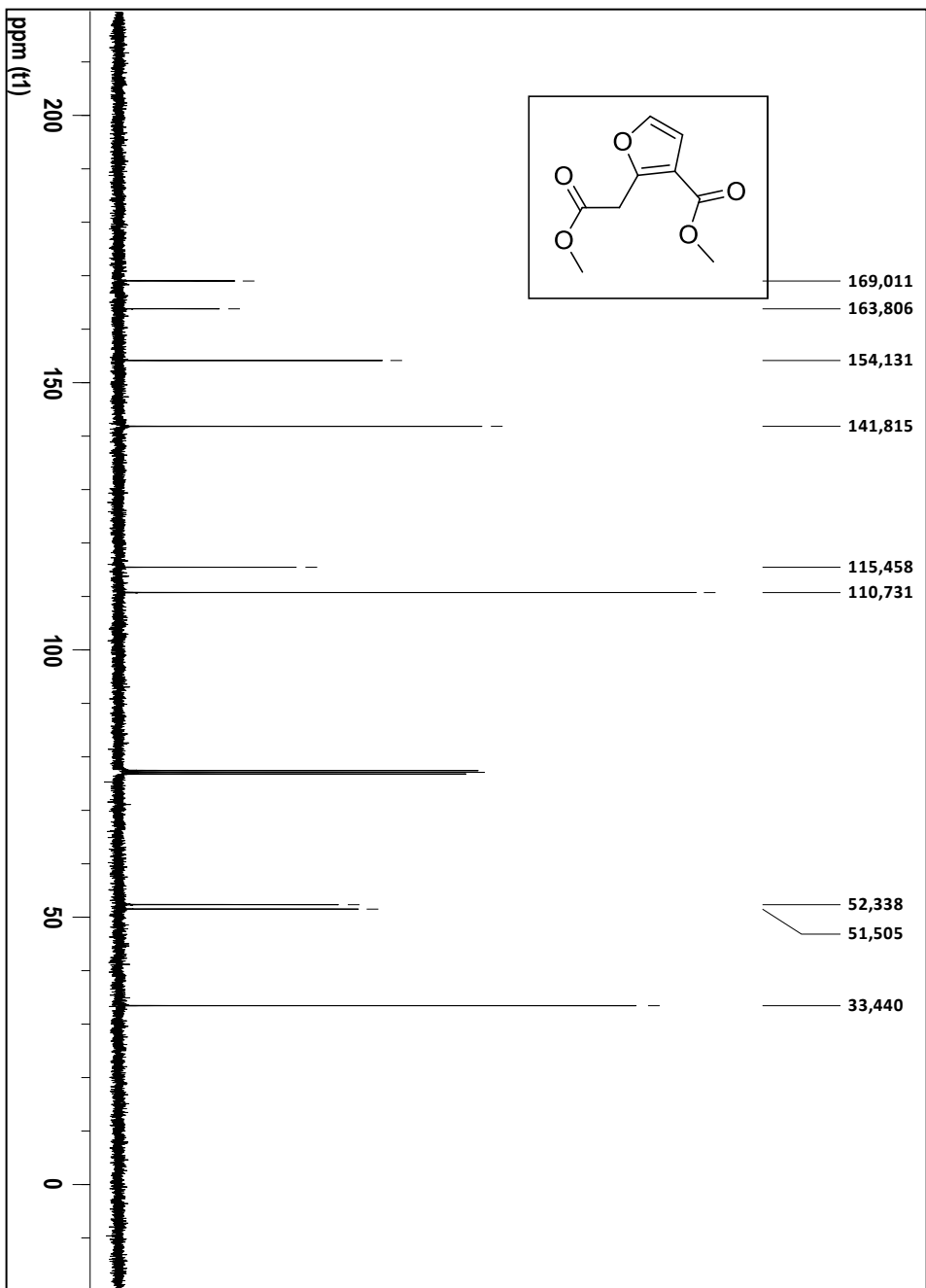


Figure 12 ^{13}C -NMR Spectrum of Compound 74

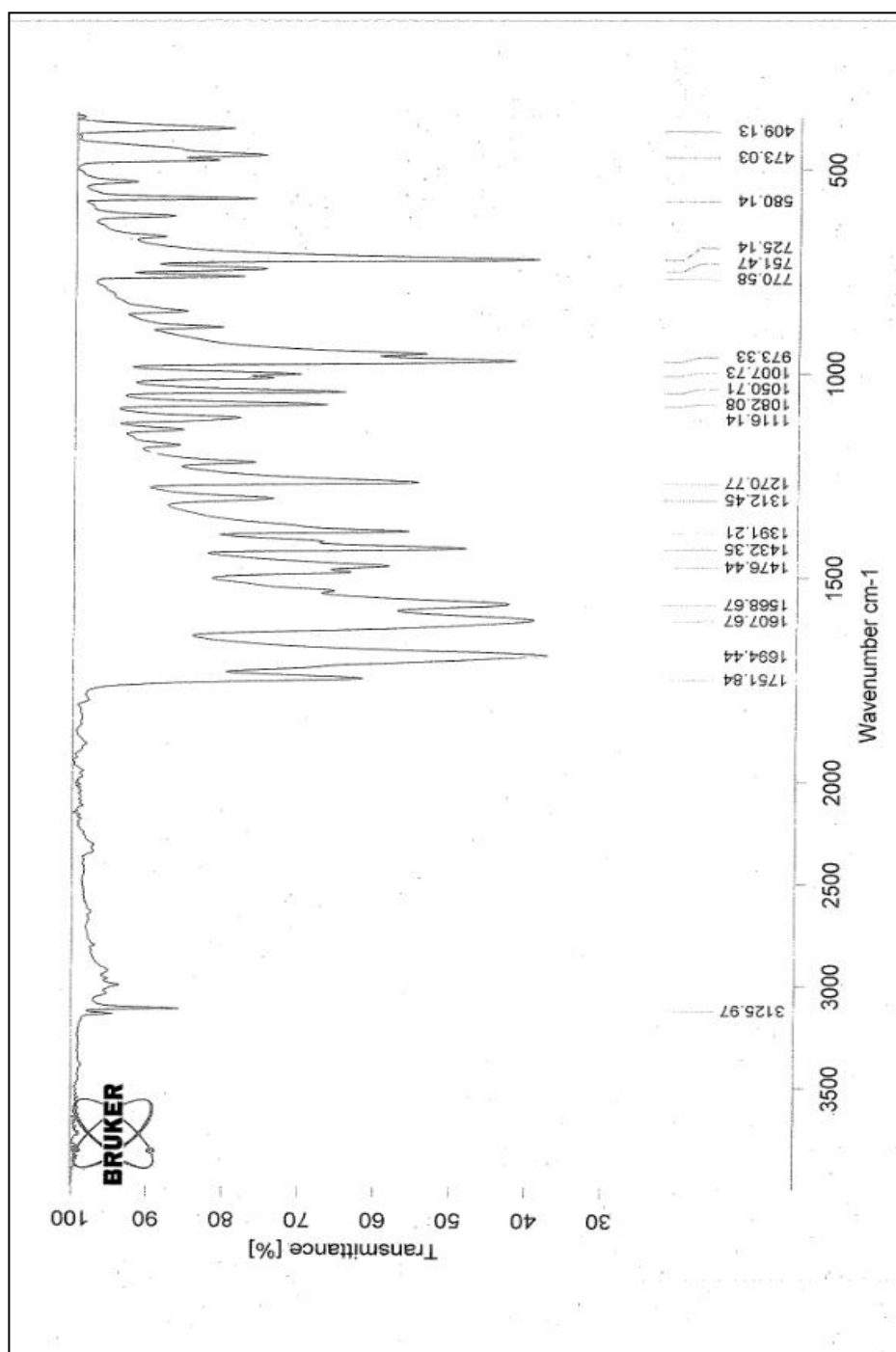


Figure 13 IR Spectrum of Compound 74

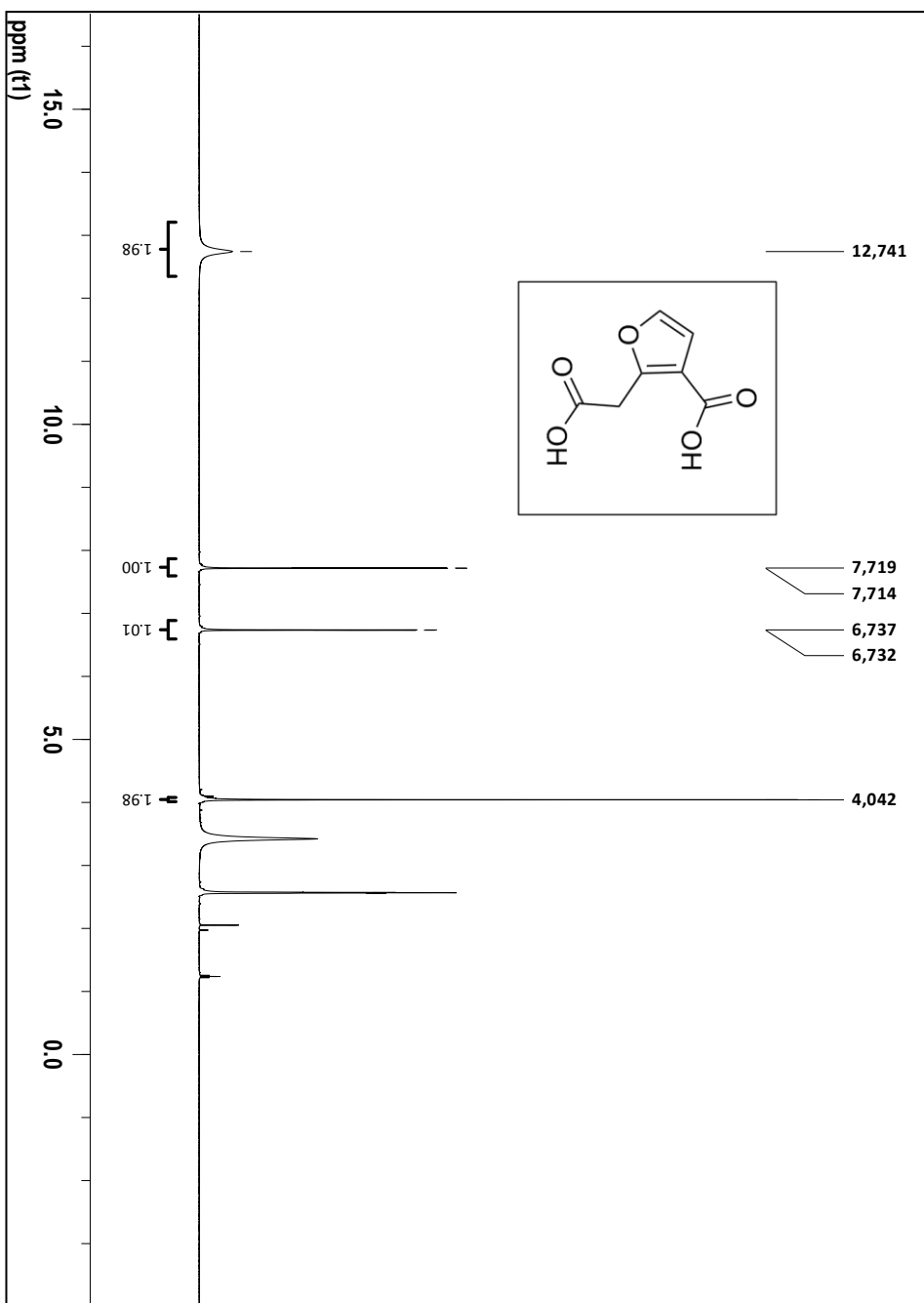


Figure 14 ¹H-NMR spectrum of compound 75

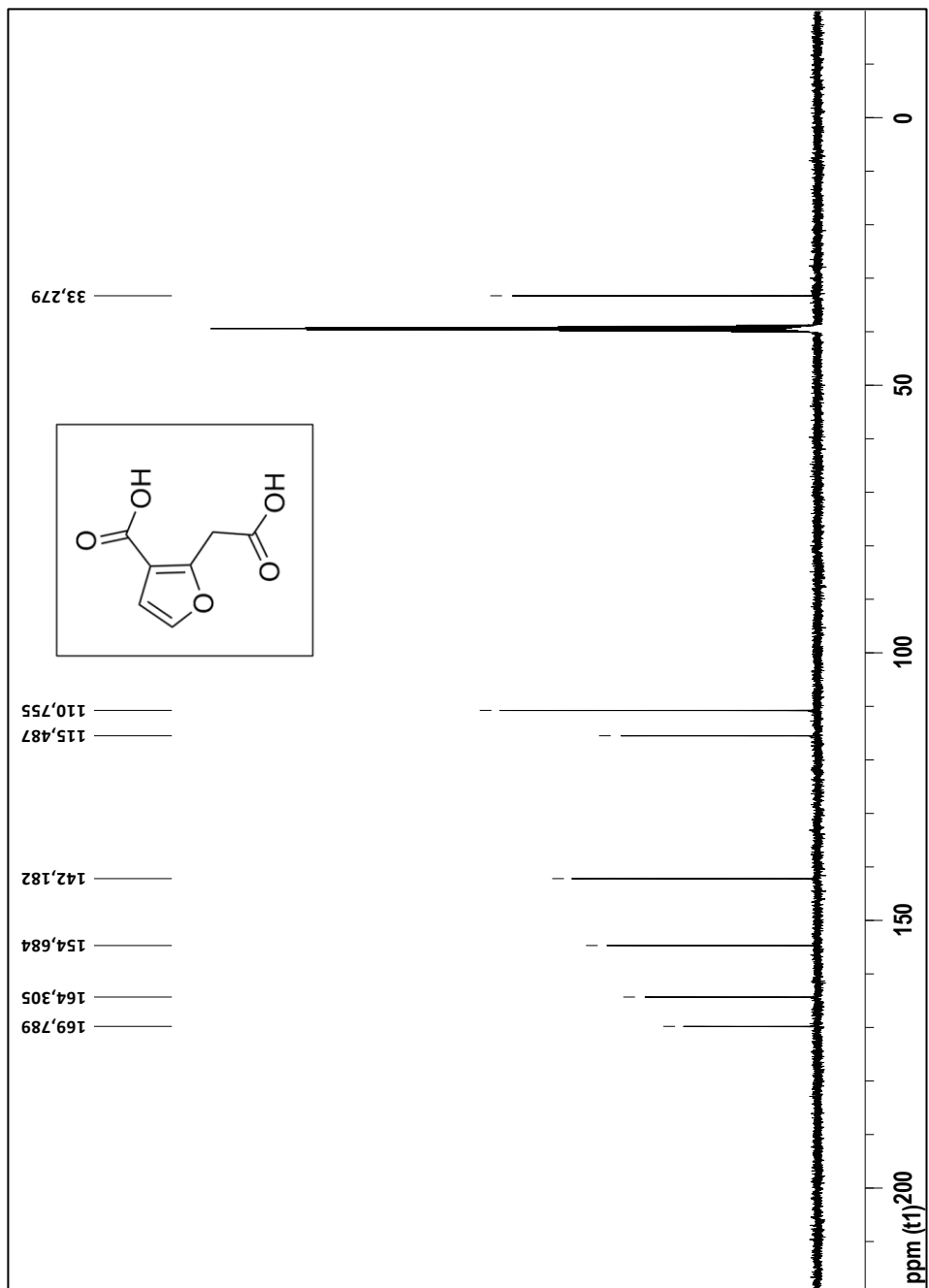


Figure 15 ¹³C-NMR Spectrum of compound 75

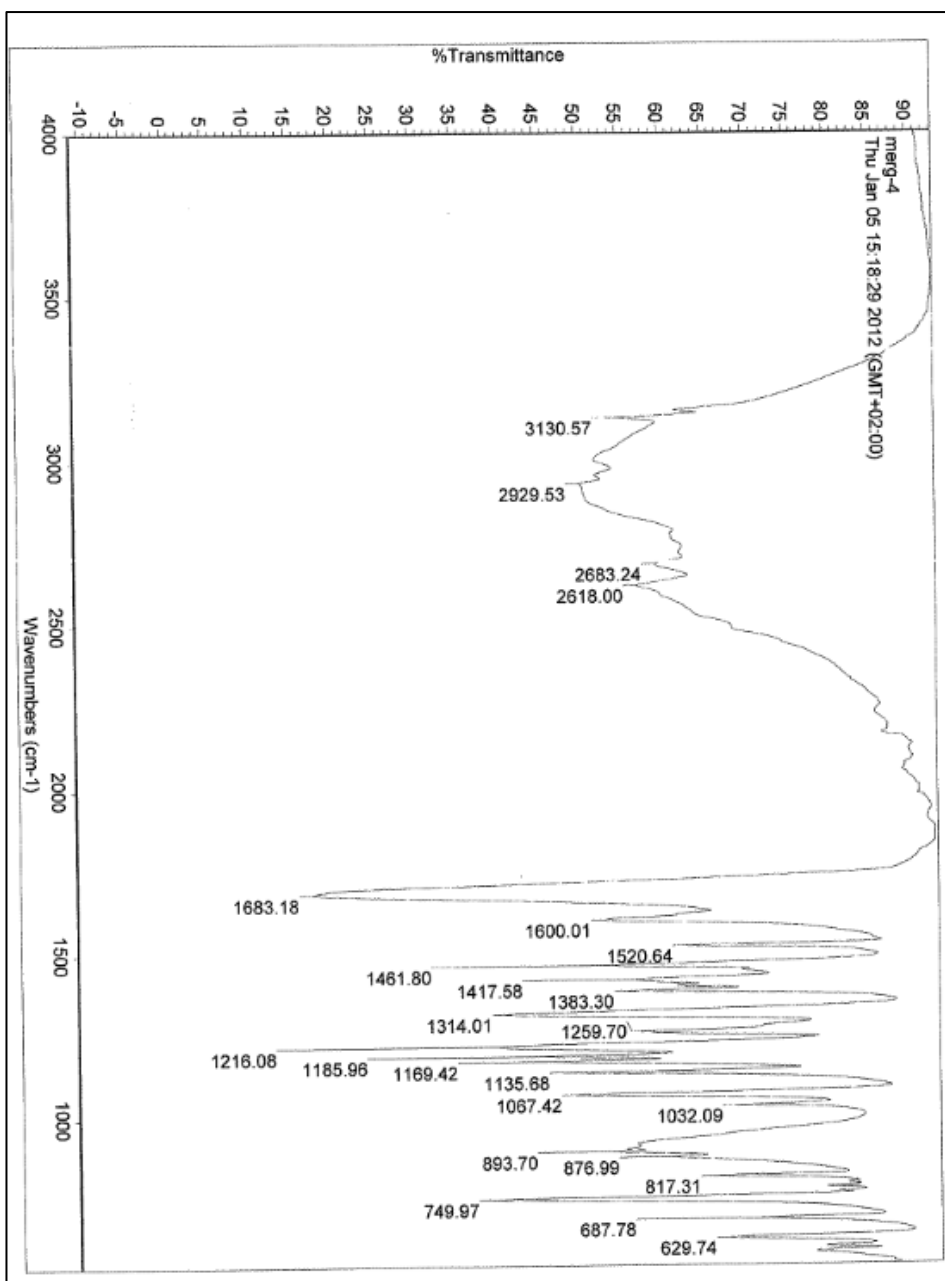


Figure 16 IR Spectrum of compound 75

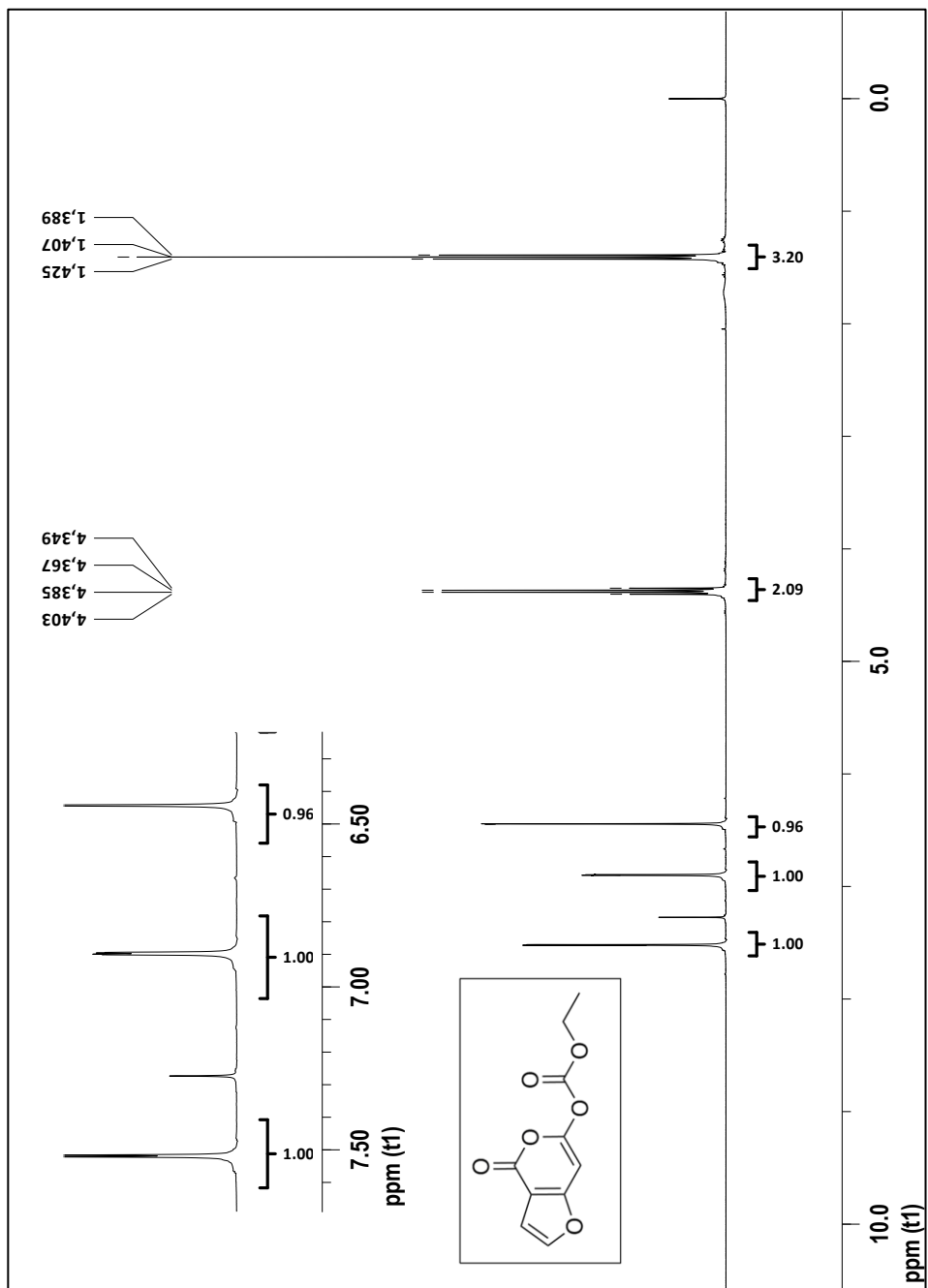


Figure 17 $^1\text{H-NMR}$ Spectrum of Compound 92

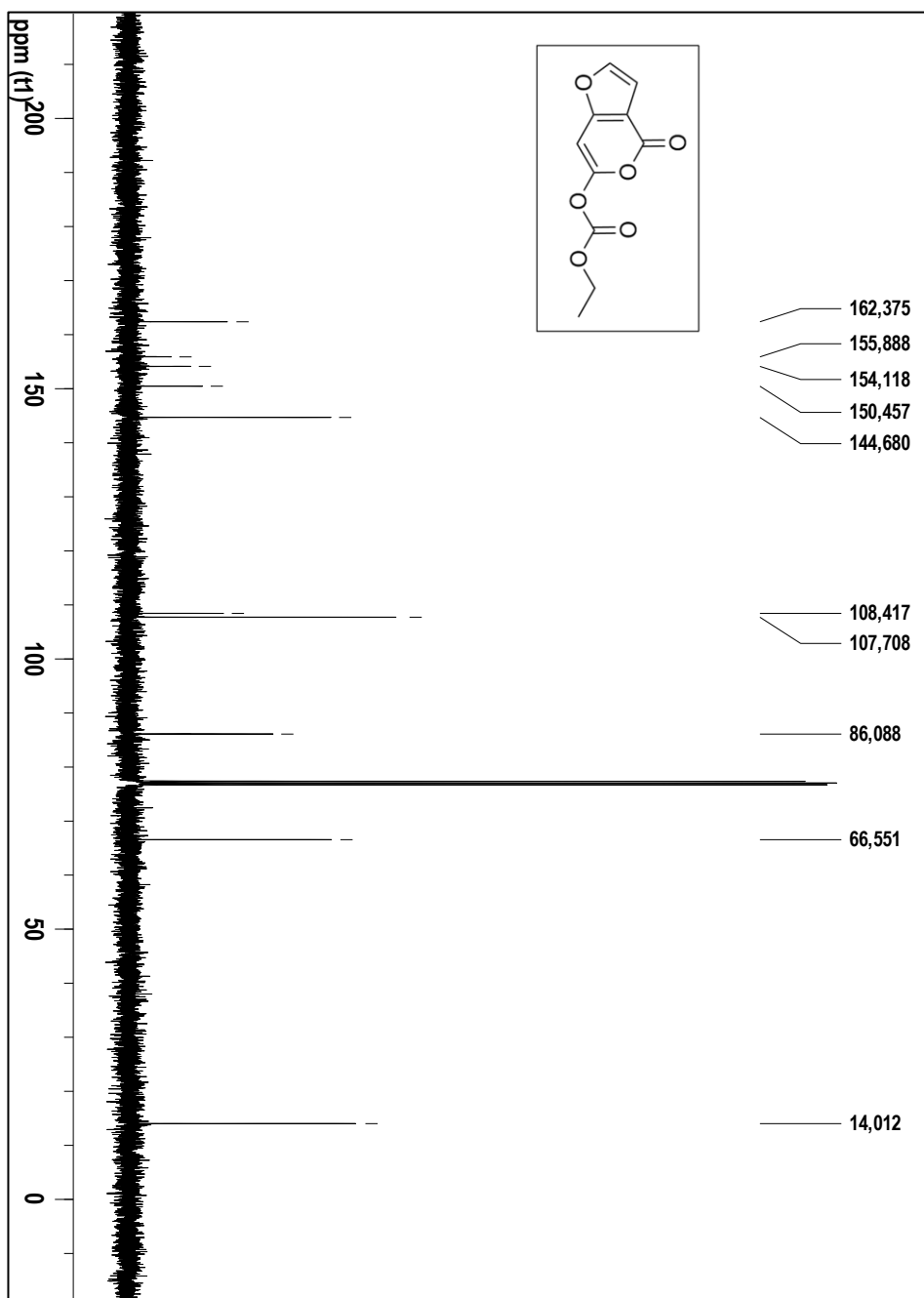


Figure 18 ^{13}C -NMR Spectrum of Compound 92

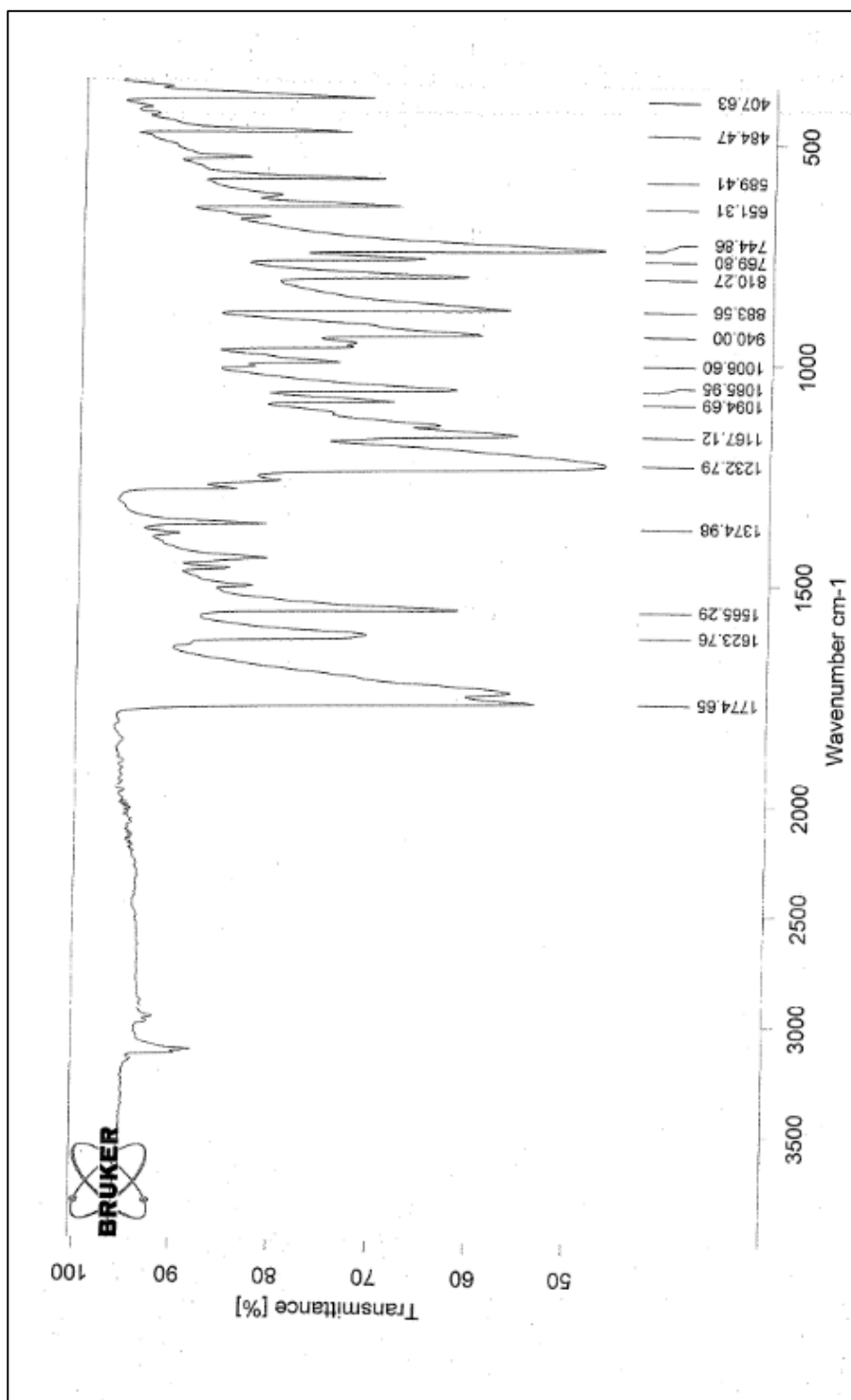


Figure 19 IR Spectrum of Compound 92

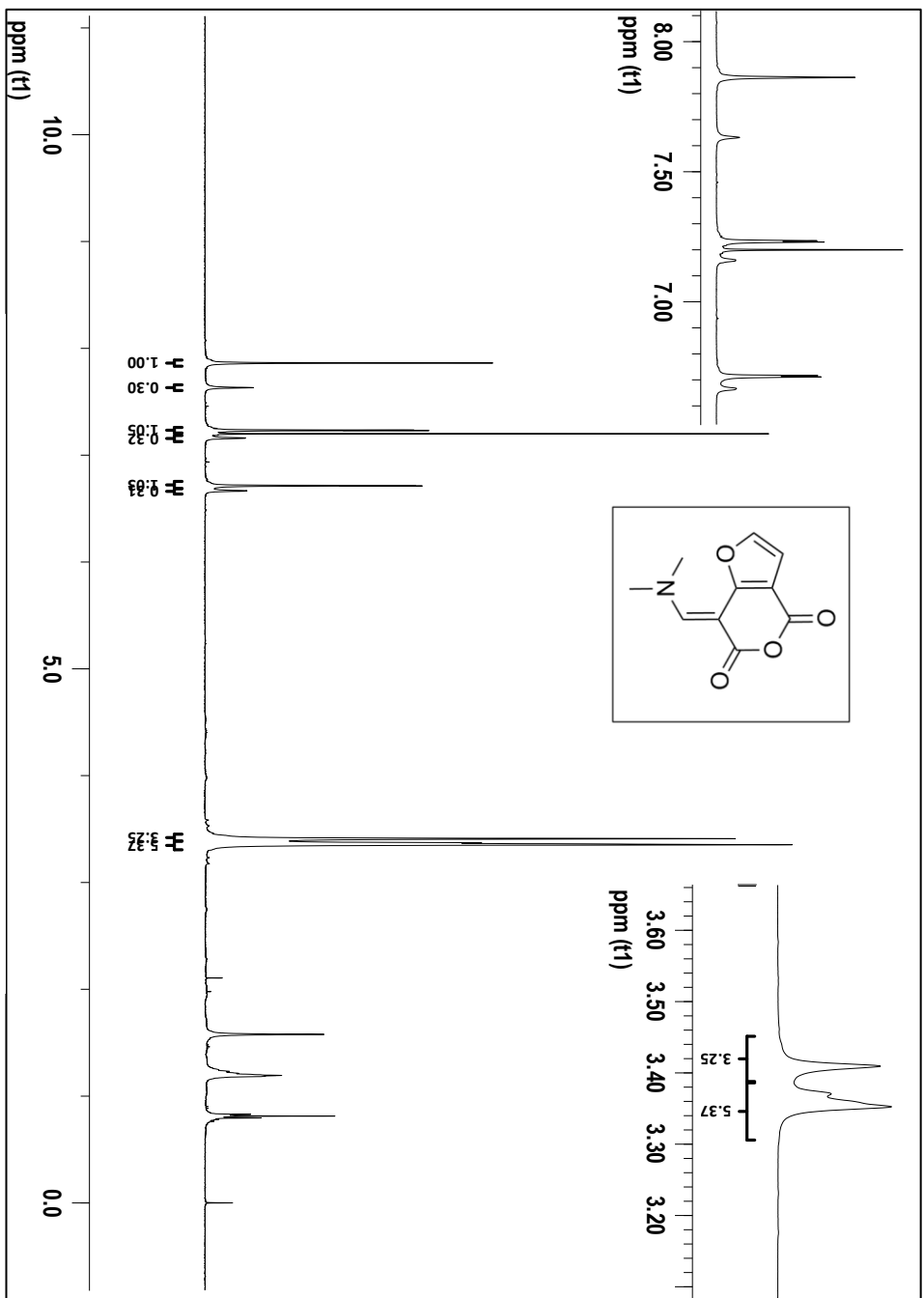


Figure 20 ¹H-NMR Spectrum of Compound 104 in CDCl₃

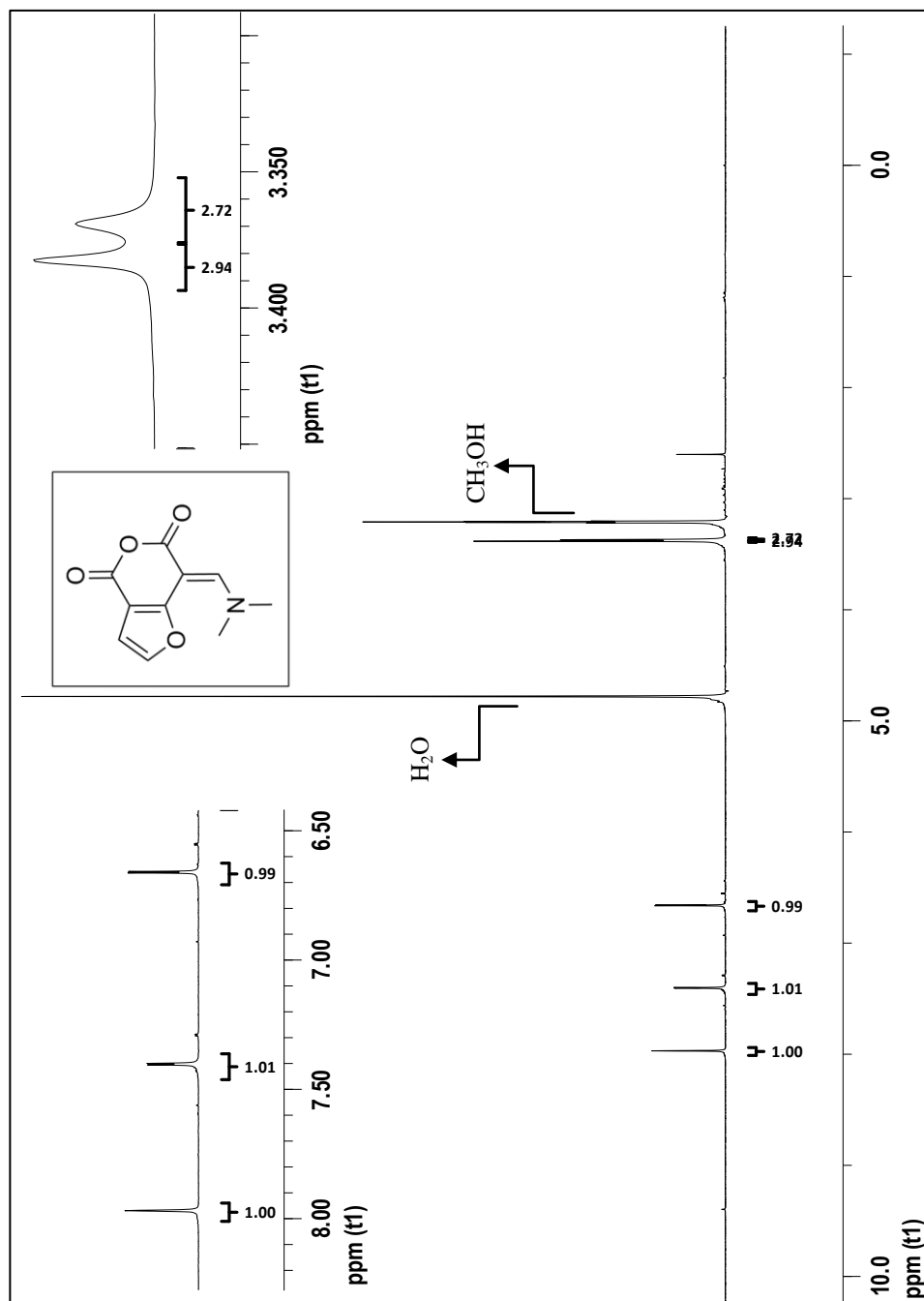


Figure 21 $^1\text{H-NMR}$ Spectrum of Compound **104** in CD_3OD

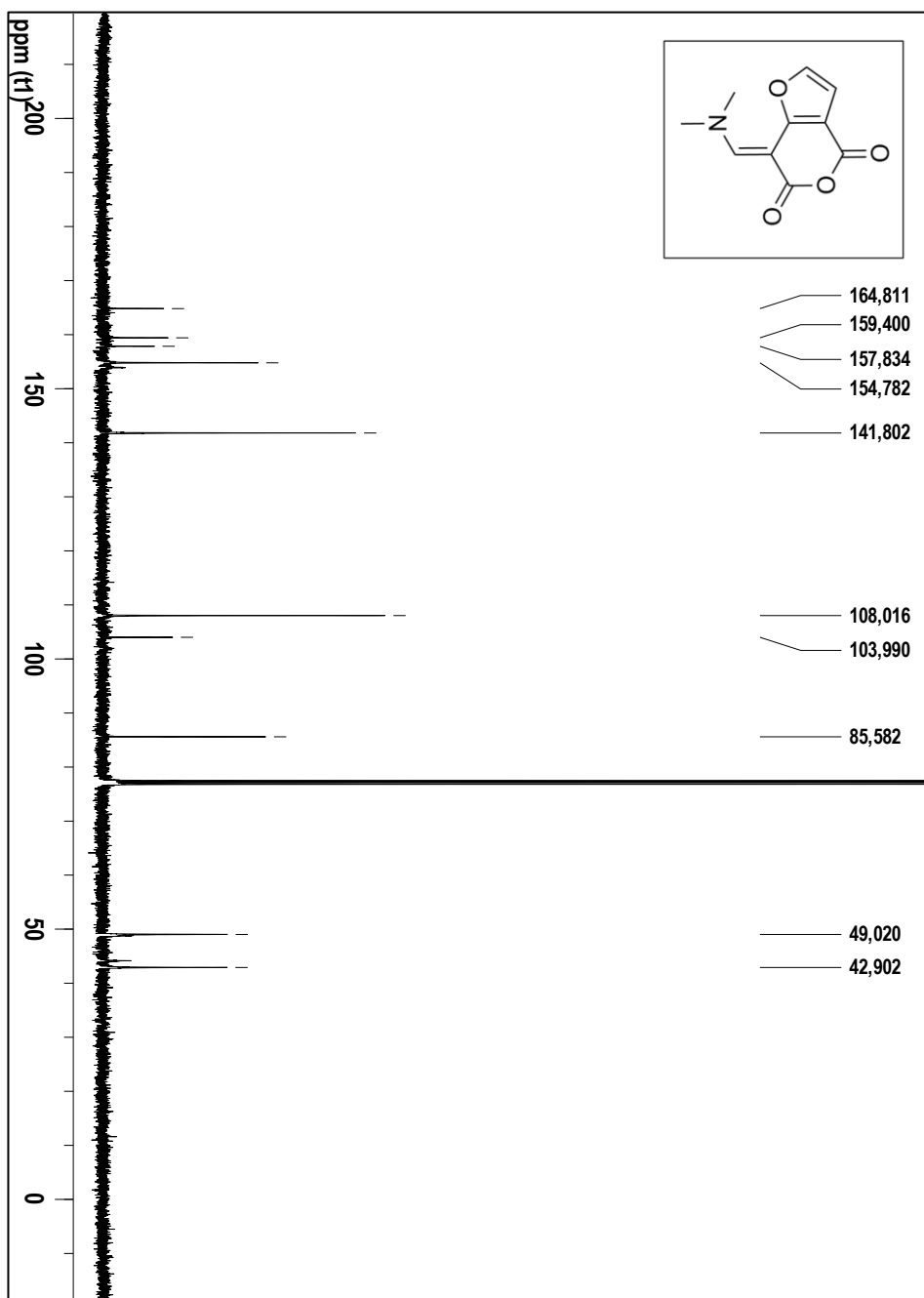


Figure 22 $^{13}\text{C-NMR}$ Spectrum of Compound 104

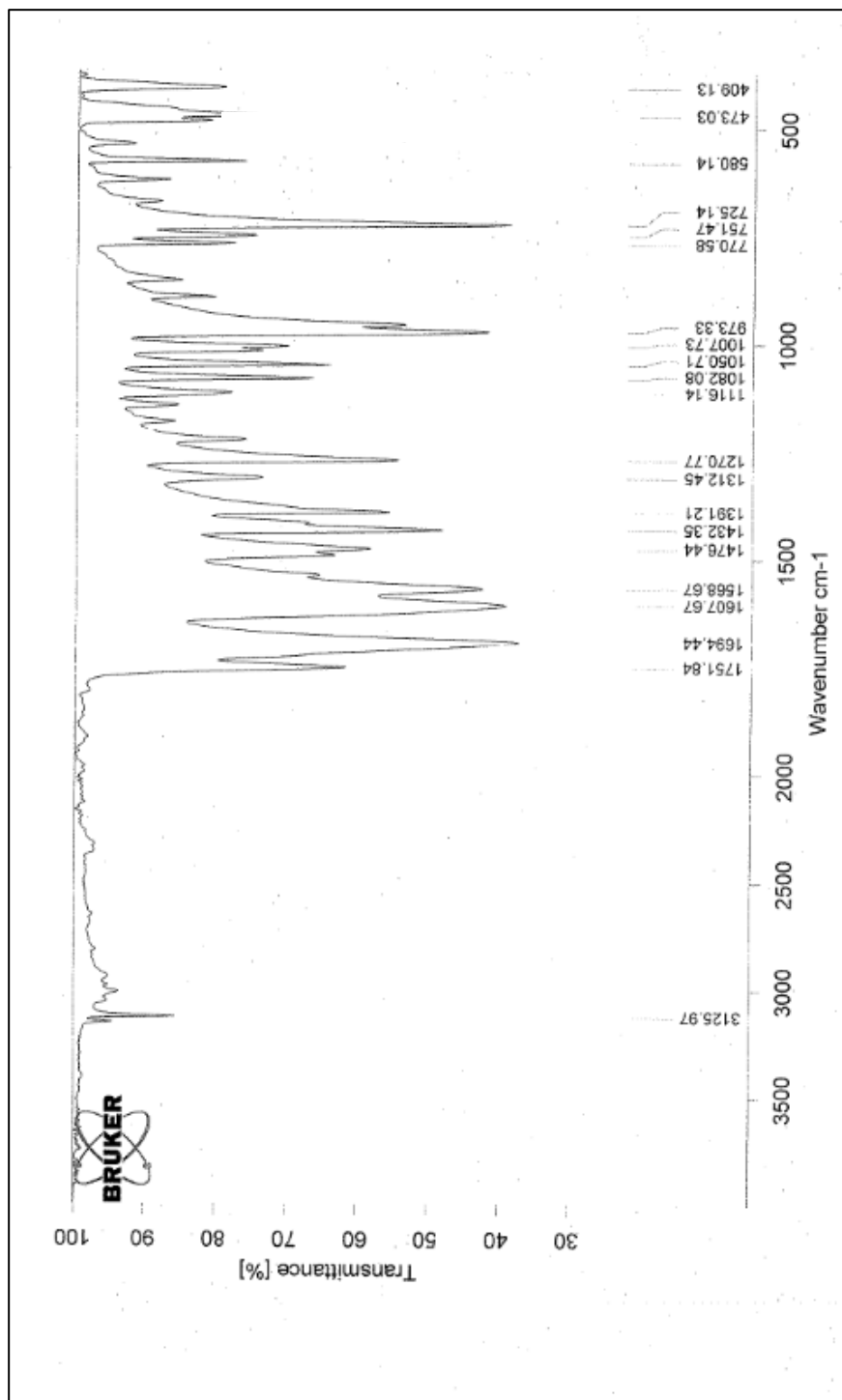


Figure 23 IR Spectrum of Compound 104

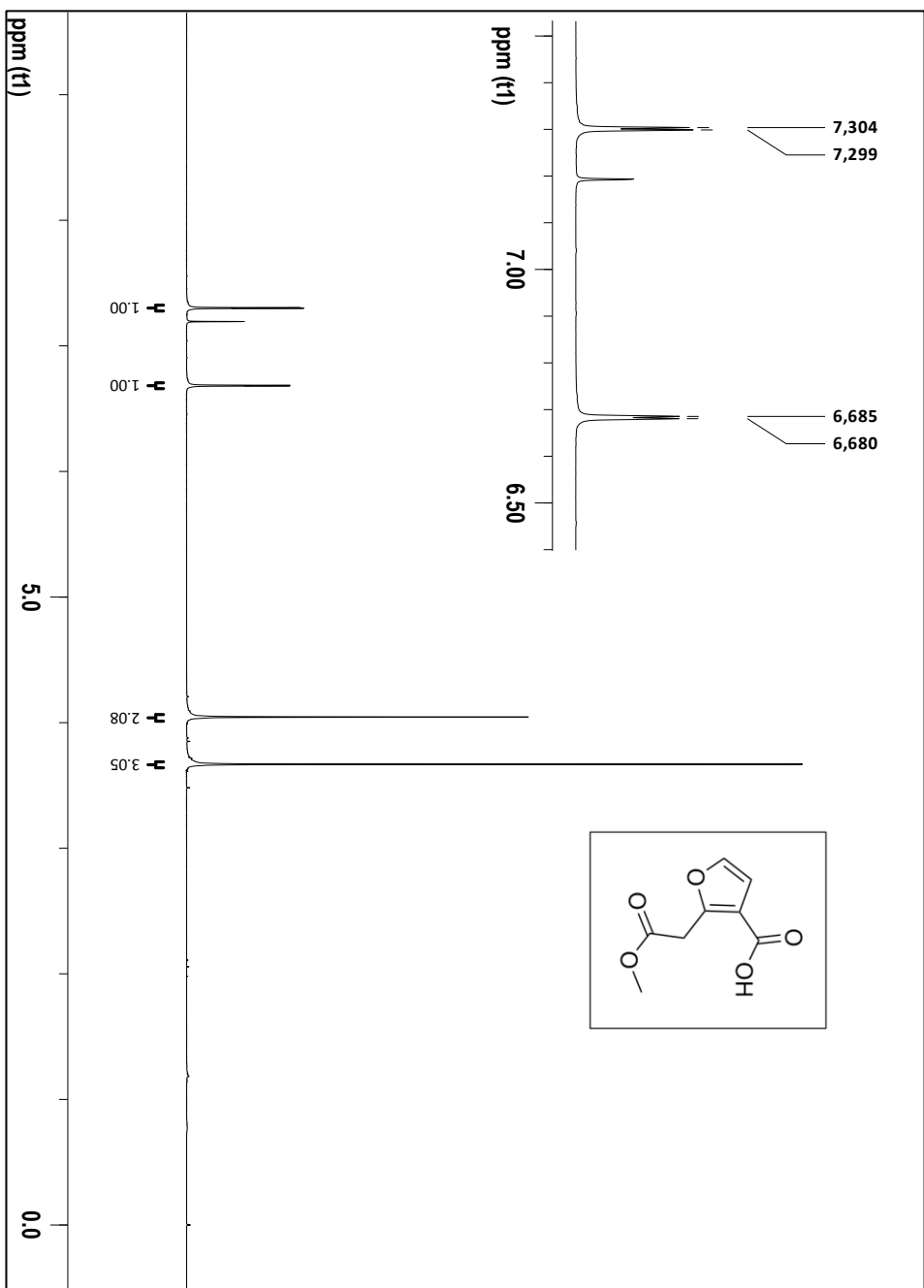


Figure 24 ¹H-NMR Spectrum of Compound 110

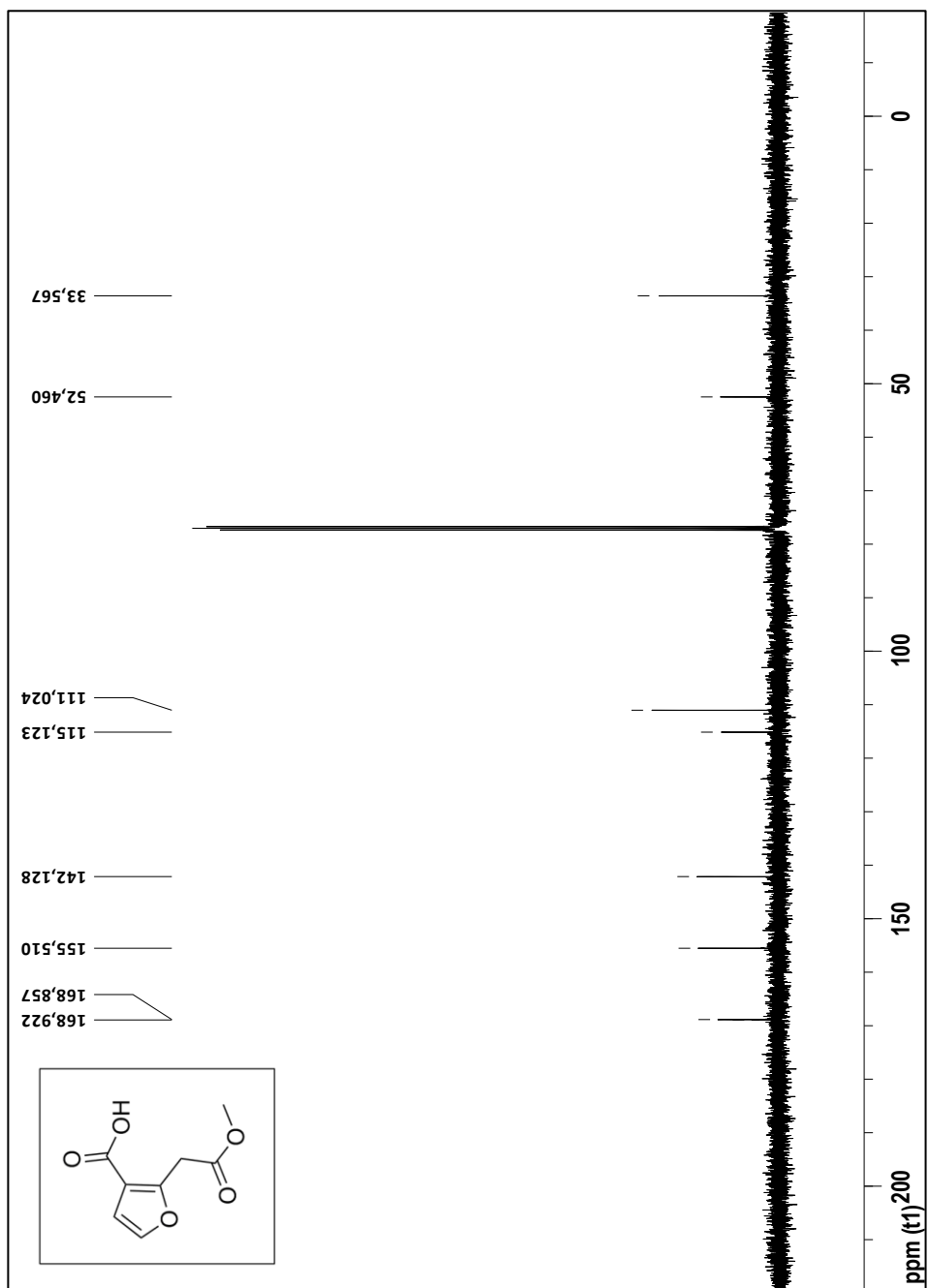


Figure 25 ¹³C-NMR Spectrum of Compound 110

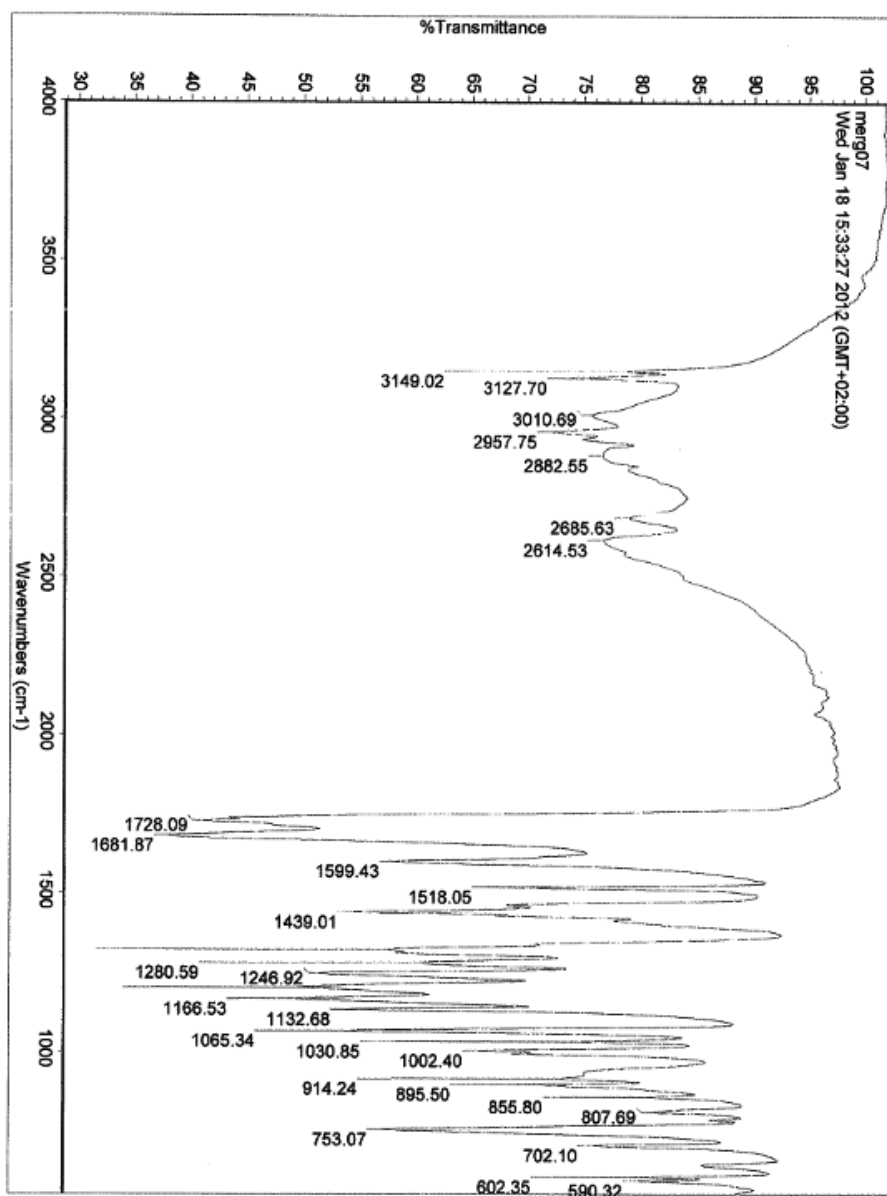


Figure 26 IR Spectrum of Compound 110

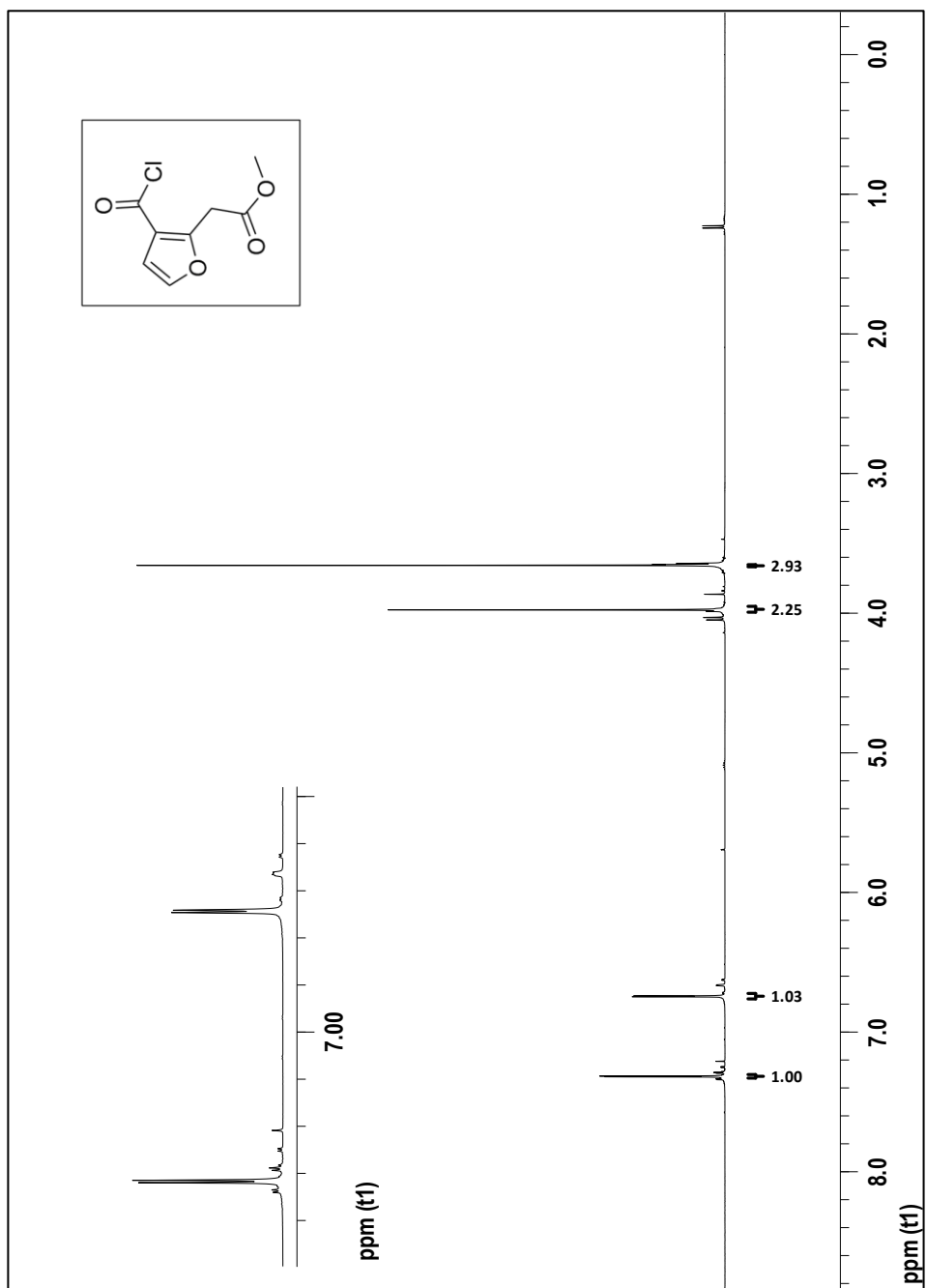


Figure 27 ¹H-NMR Spectrum of Compound 111

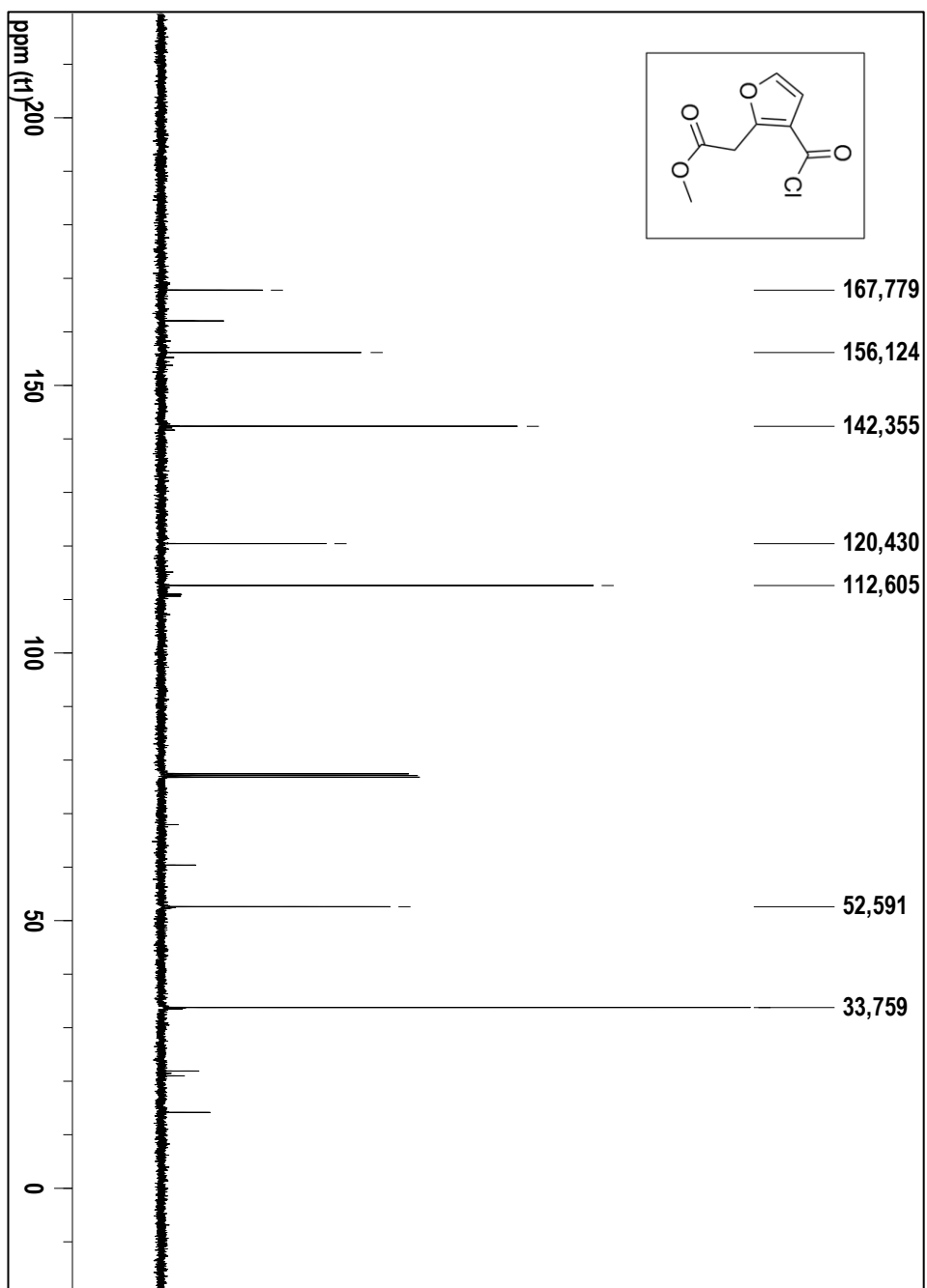


Figure 28 ^{13}C -NMR Spectrum of Compound III

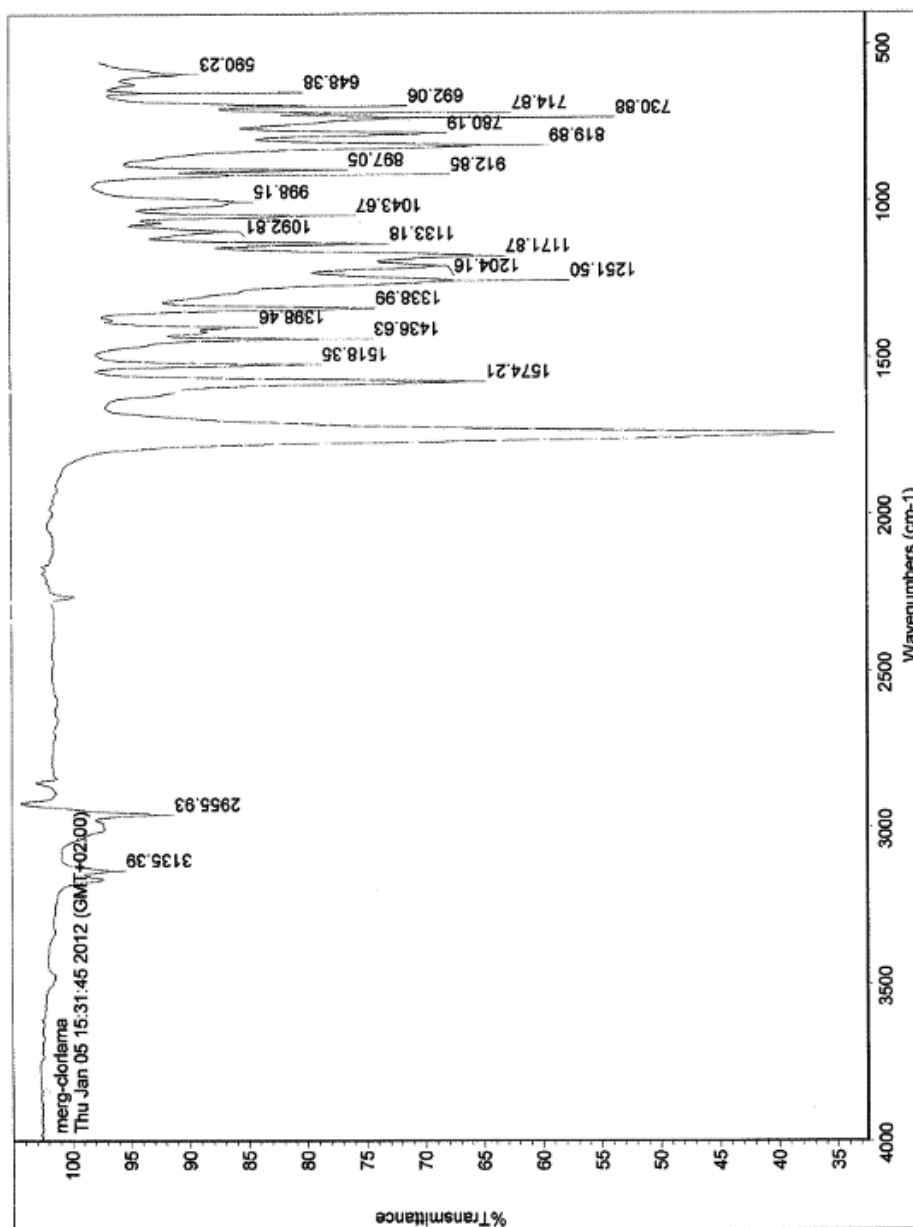


Figure 29 IR Spectrum of Compound 111

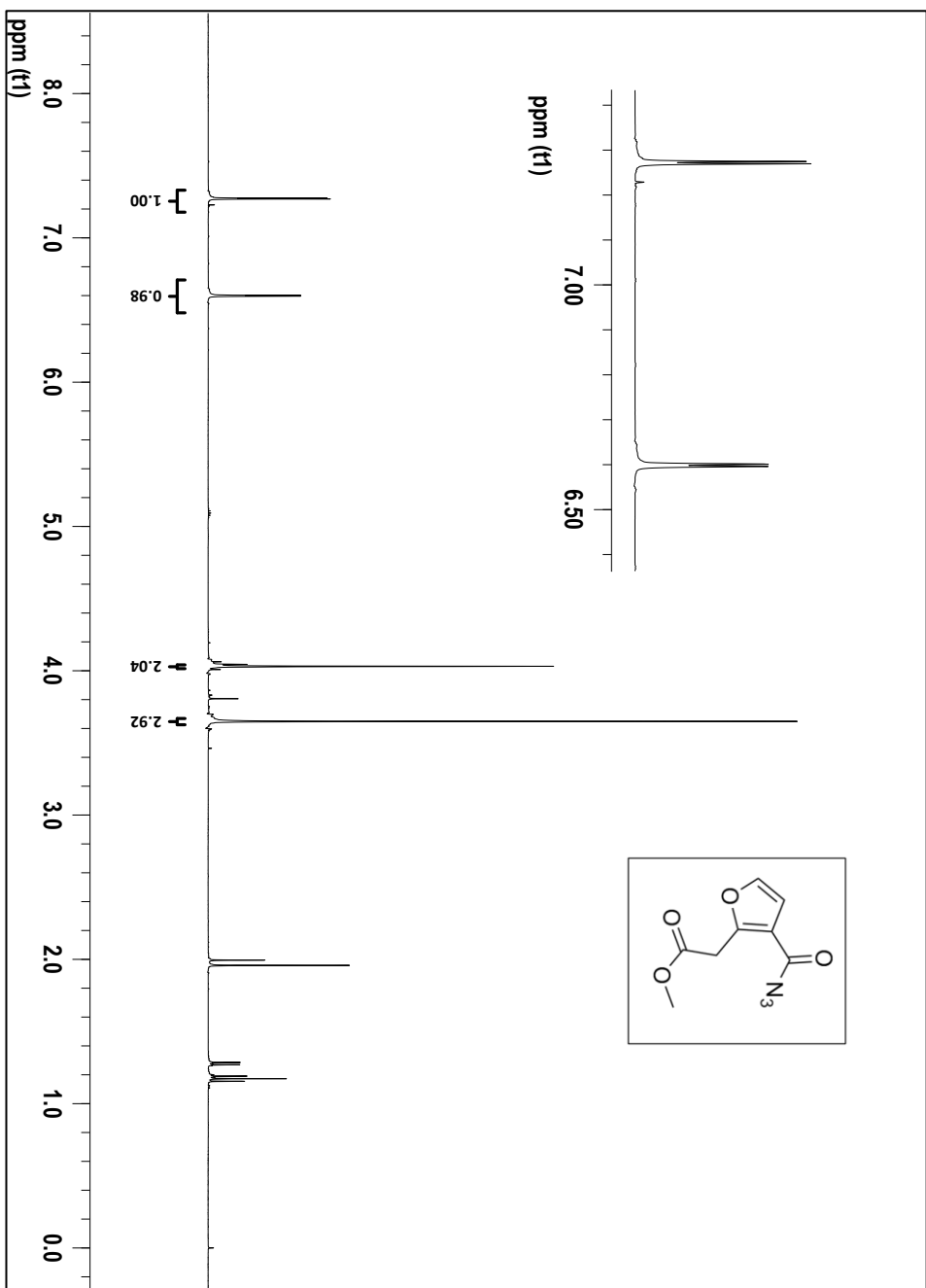


Figure 30 ¹H-NMR Spectrum of Compound 112

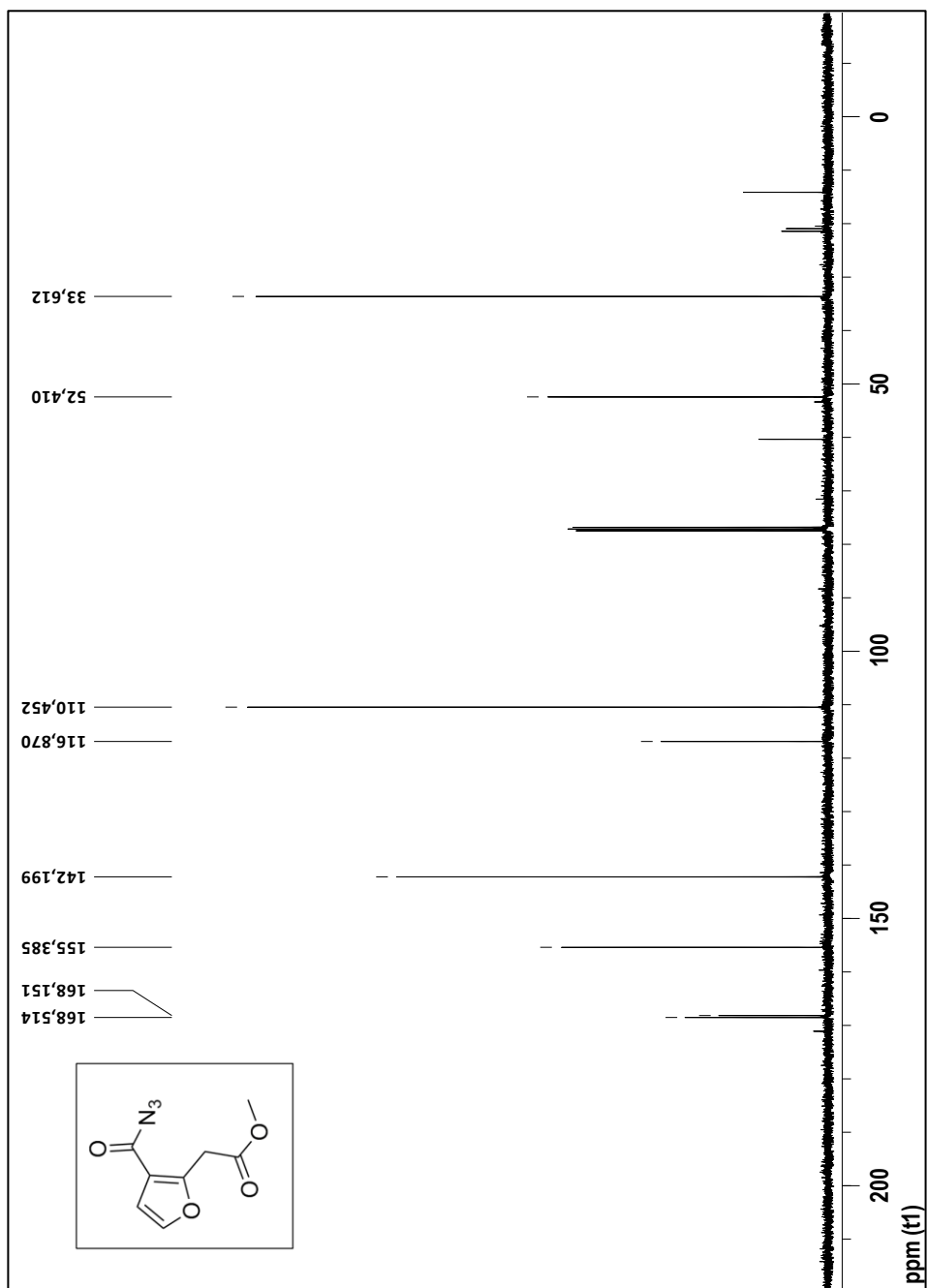


Figure 31 ¹³C-NMR Spectrum of Compound 112

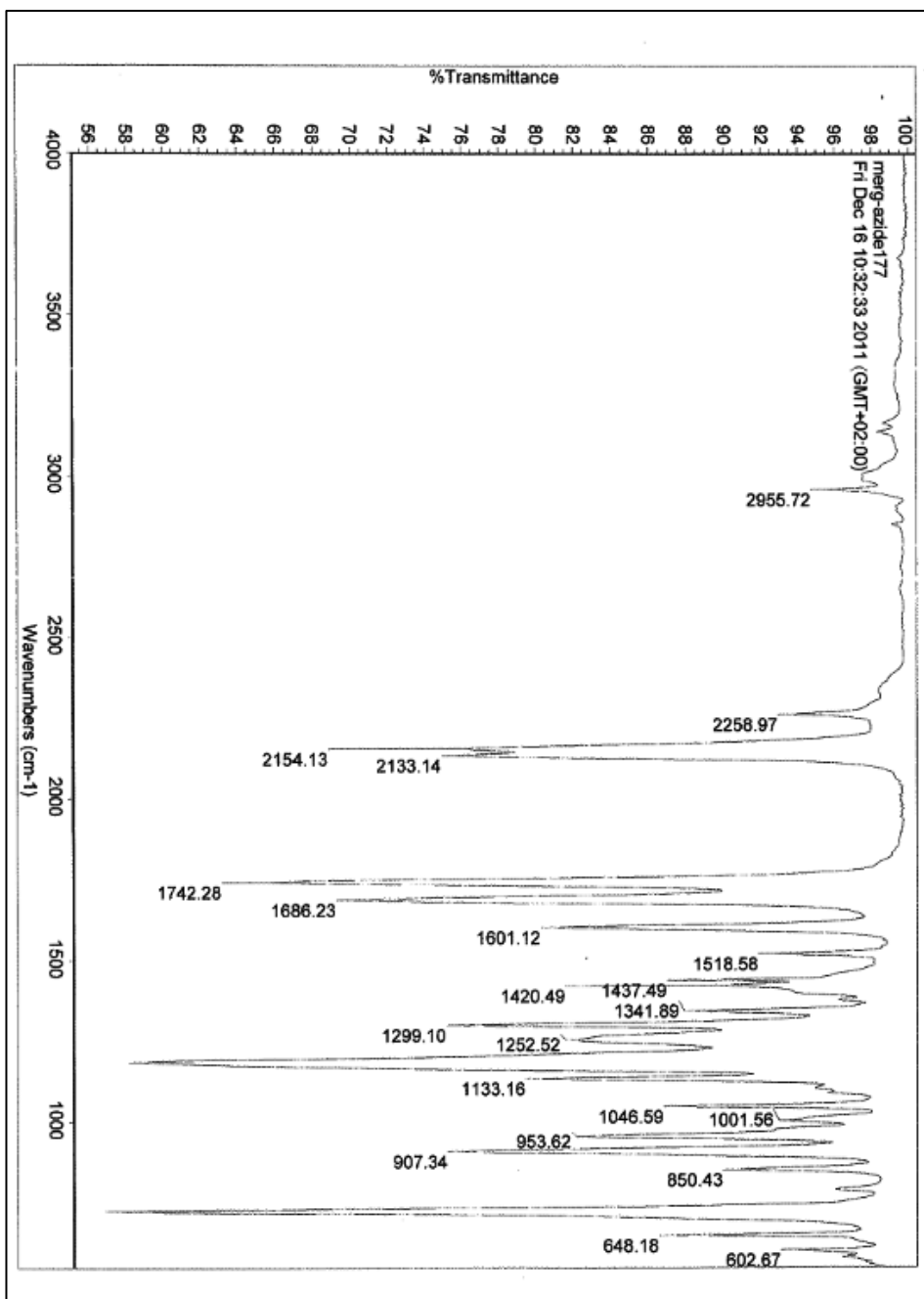


Figure 32 IR Spectrum of Compound II2

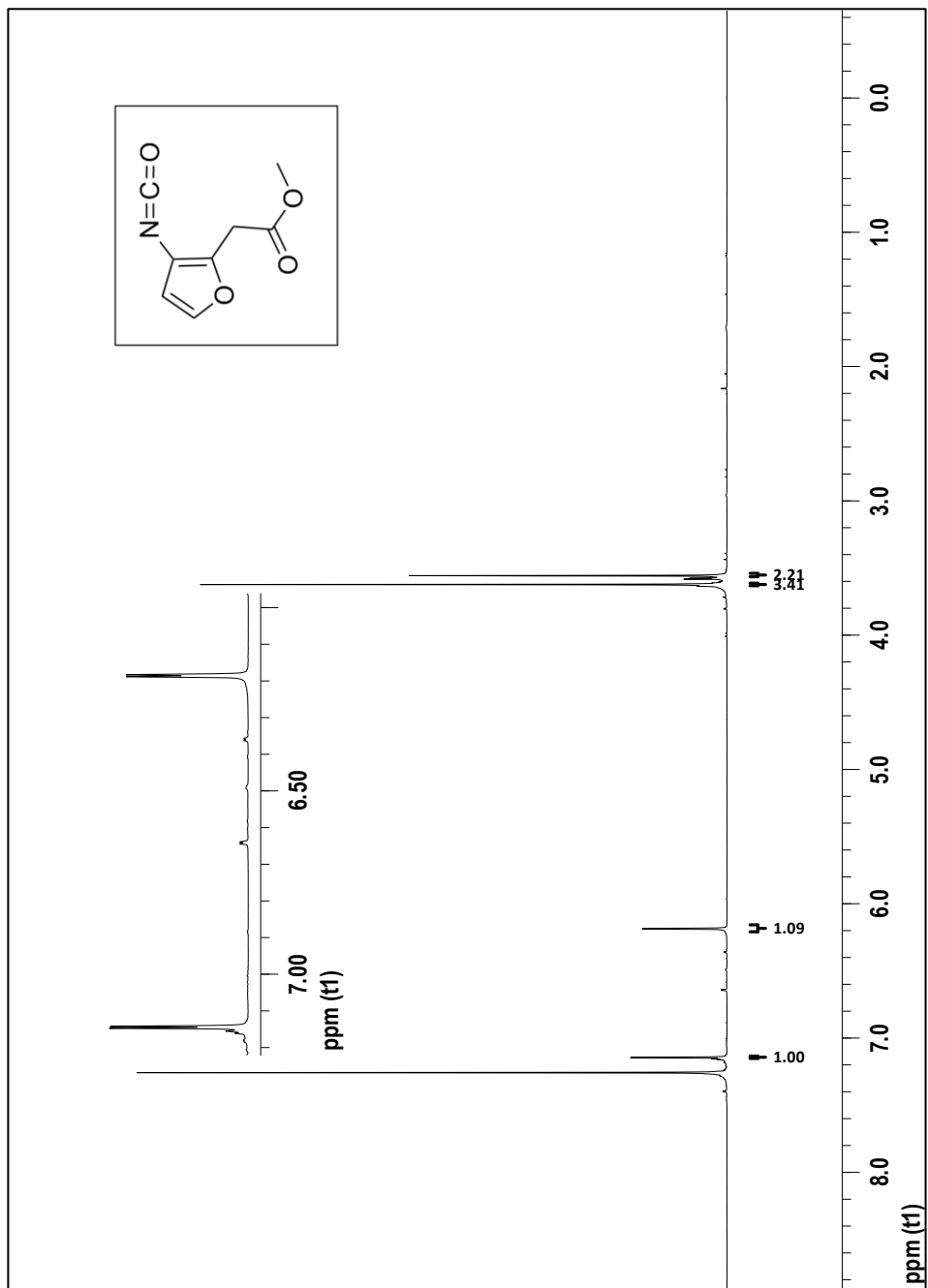


Figure 33 ¹H-NMR Spectrum of Compound 117

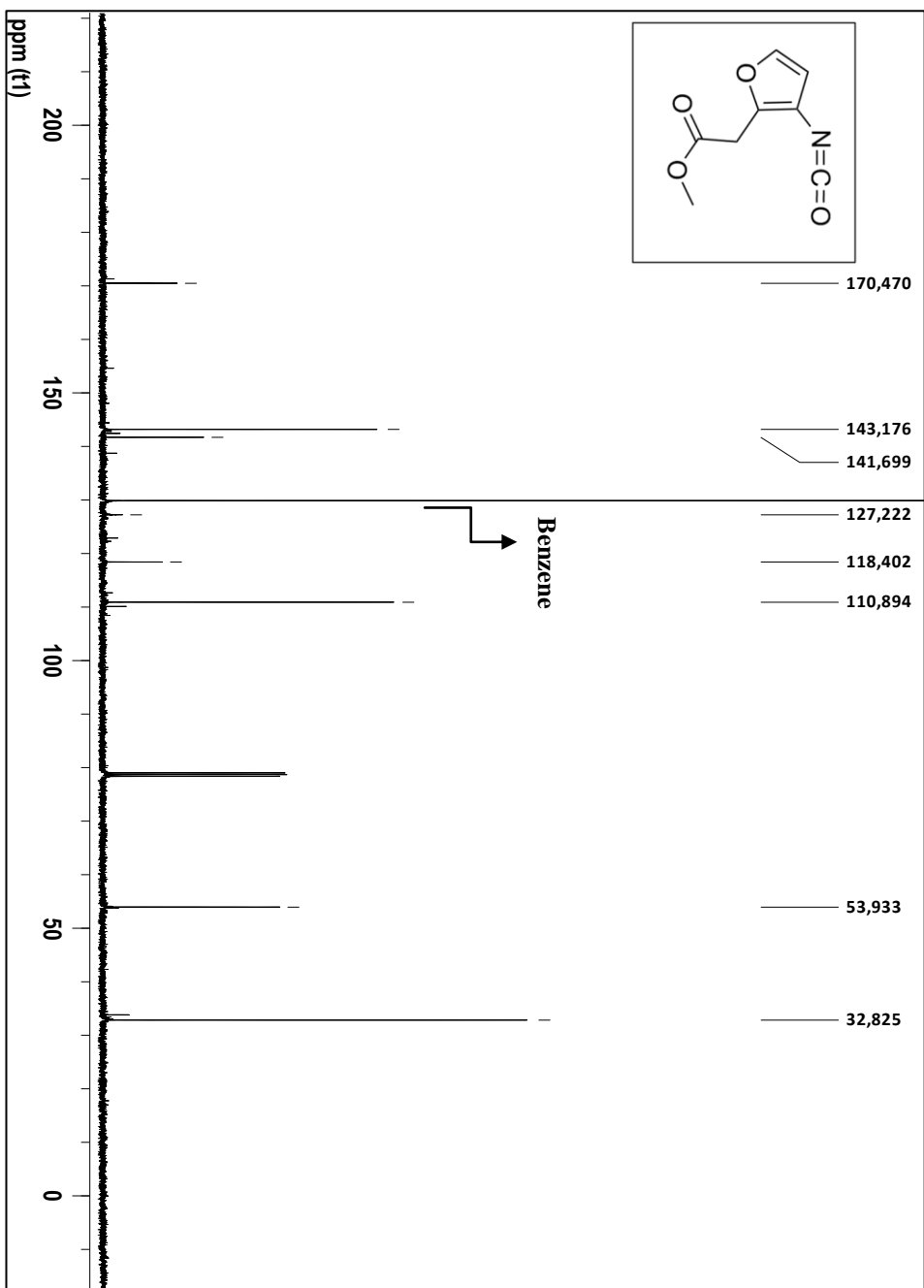


Figure 34 ^{13}C -NMR Spectrum of Compound 117

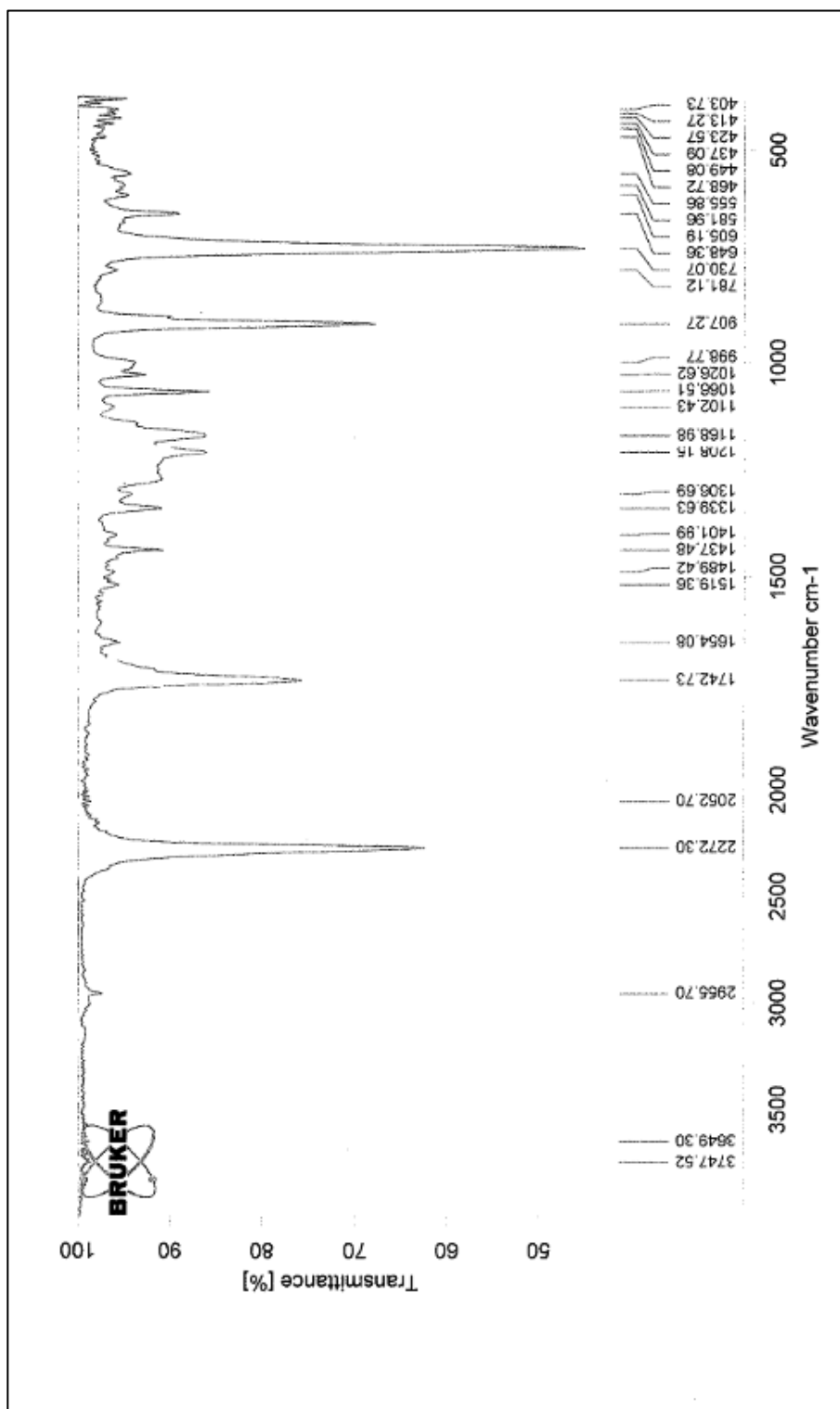


Figure 35 IR Spectrum of Compound 117

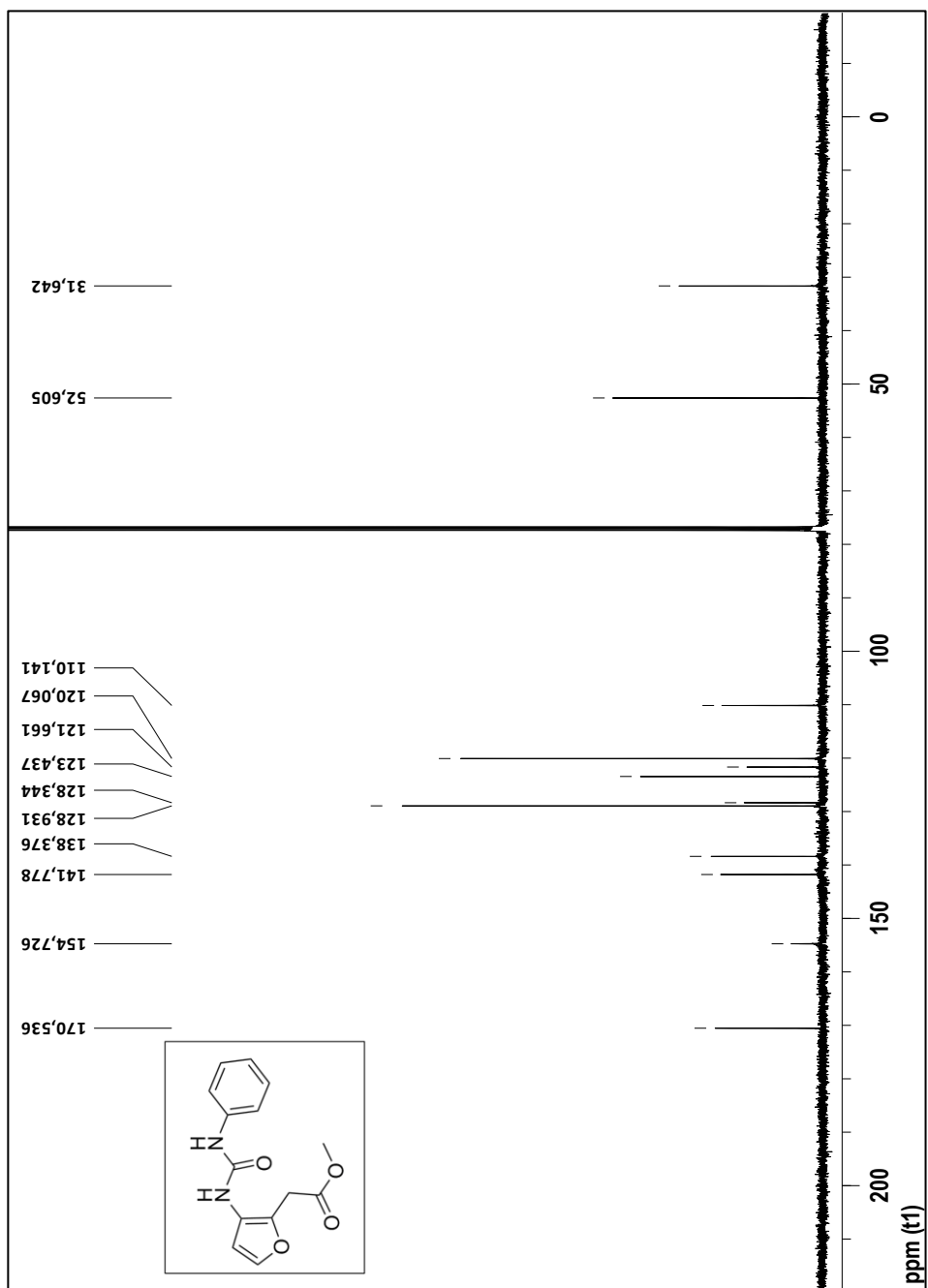


Figure 37 ¹³C-NMR Spectrum of Compound 118

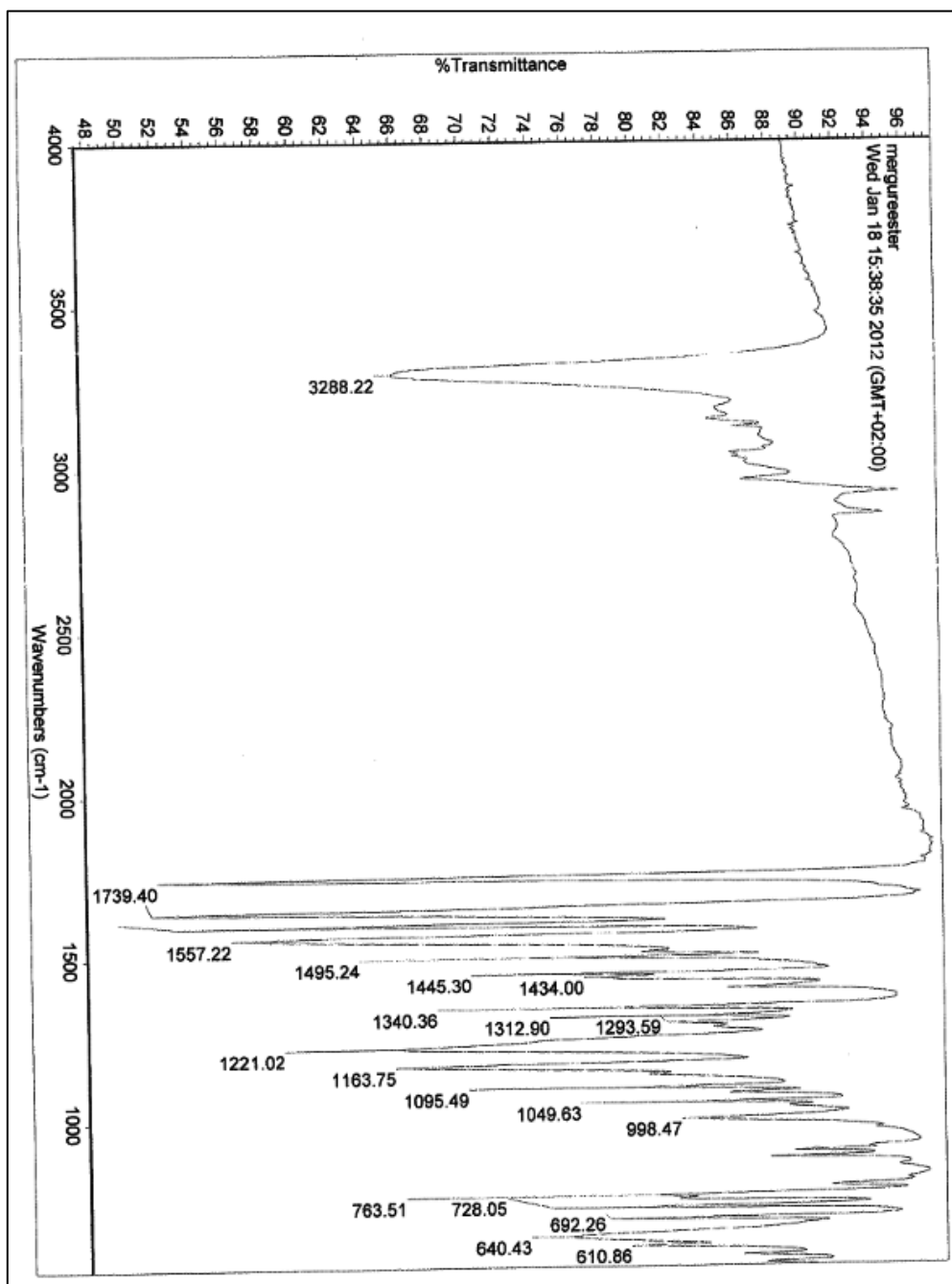


Figure 38 IR Spectrum of Compound 118

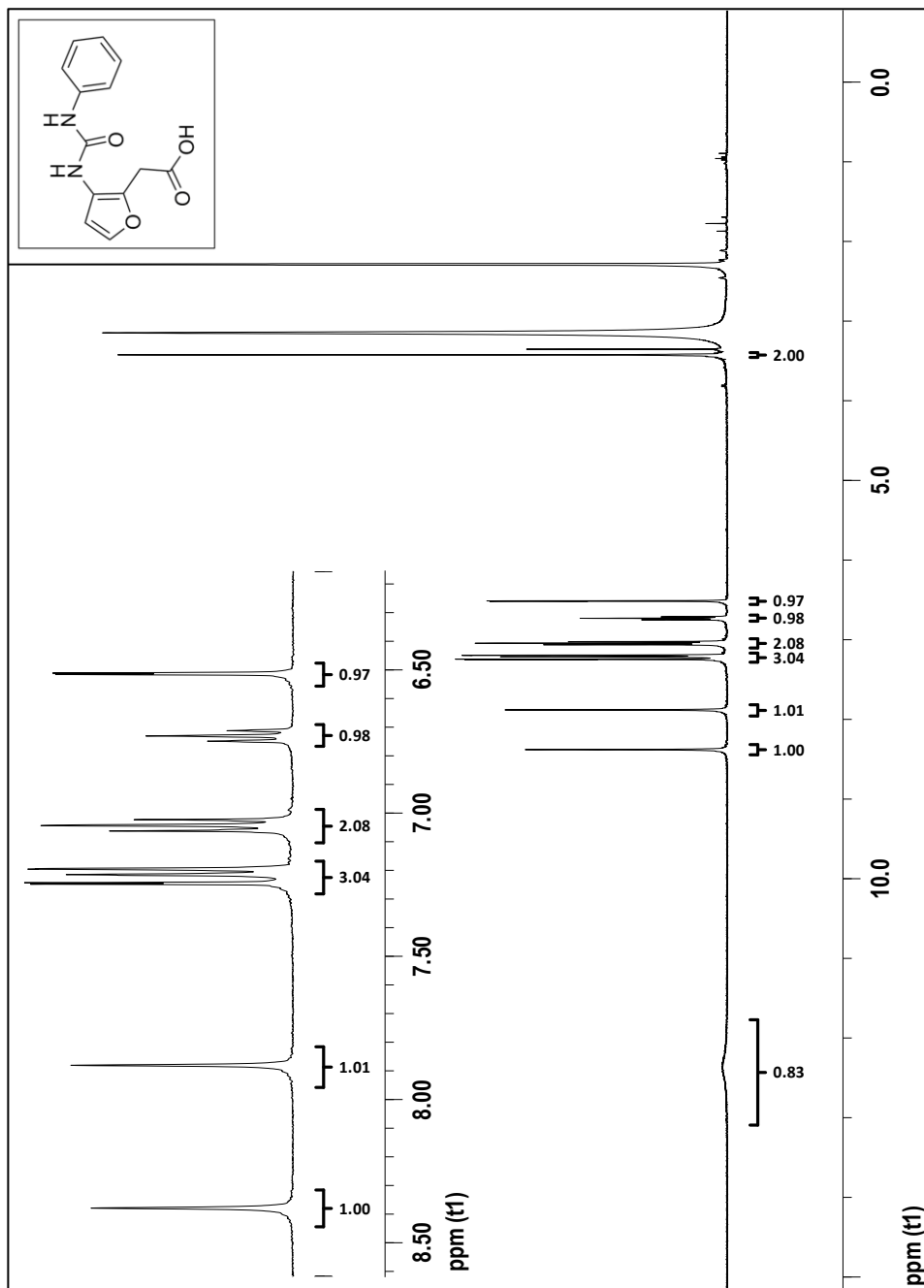


Figure 39 ¹H-NMR Spectrum of Compound 121

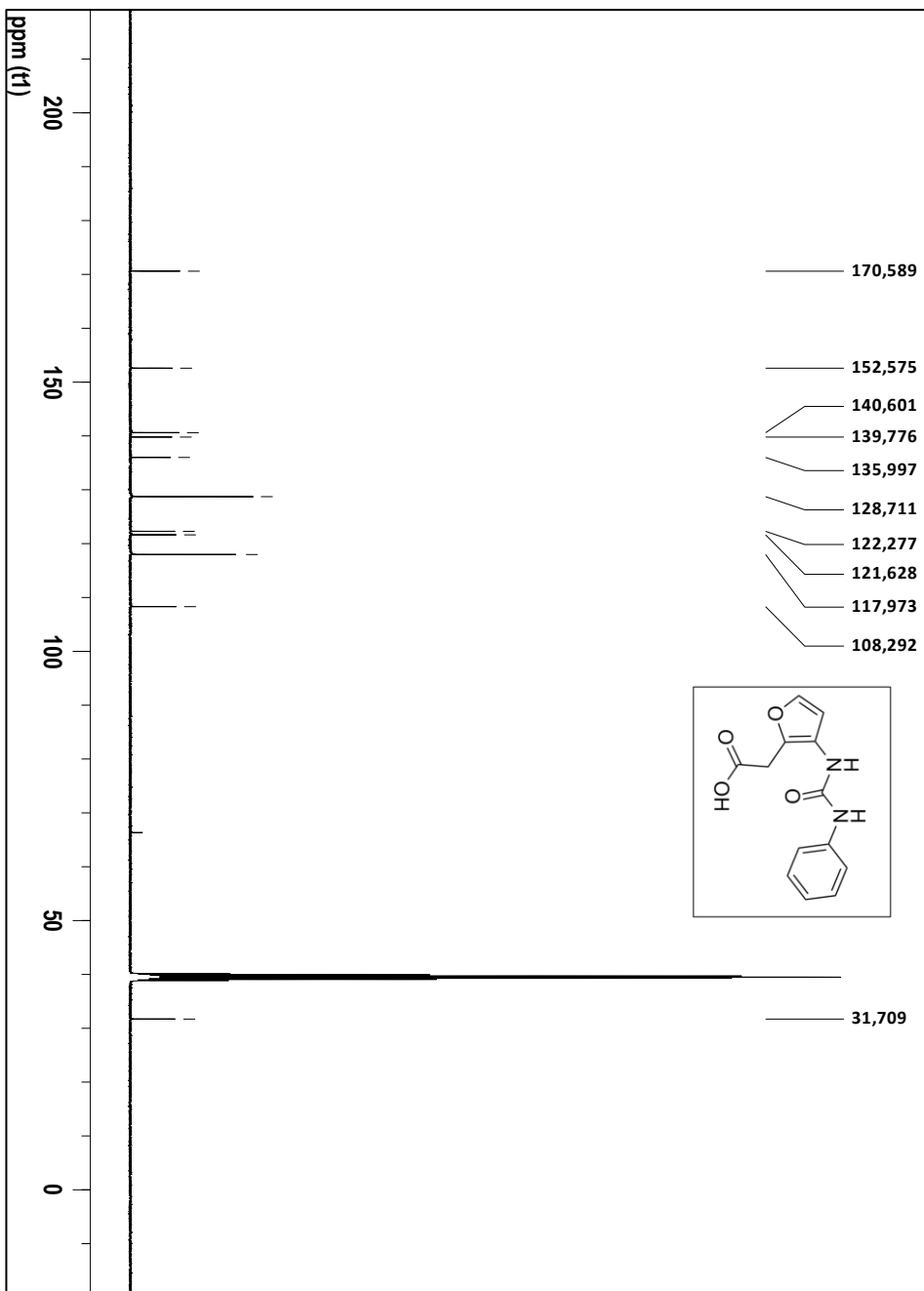


Figure 40 ¹³C-NMR Spectrum of Compound 121

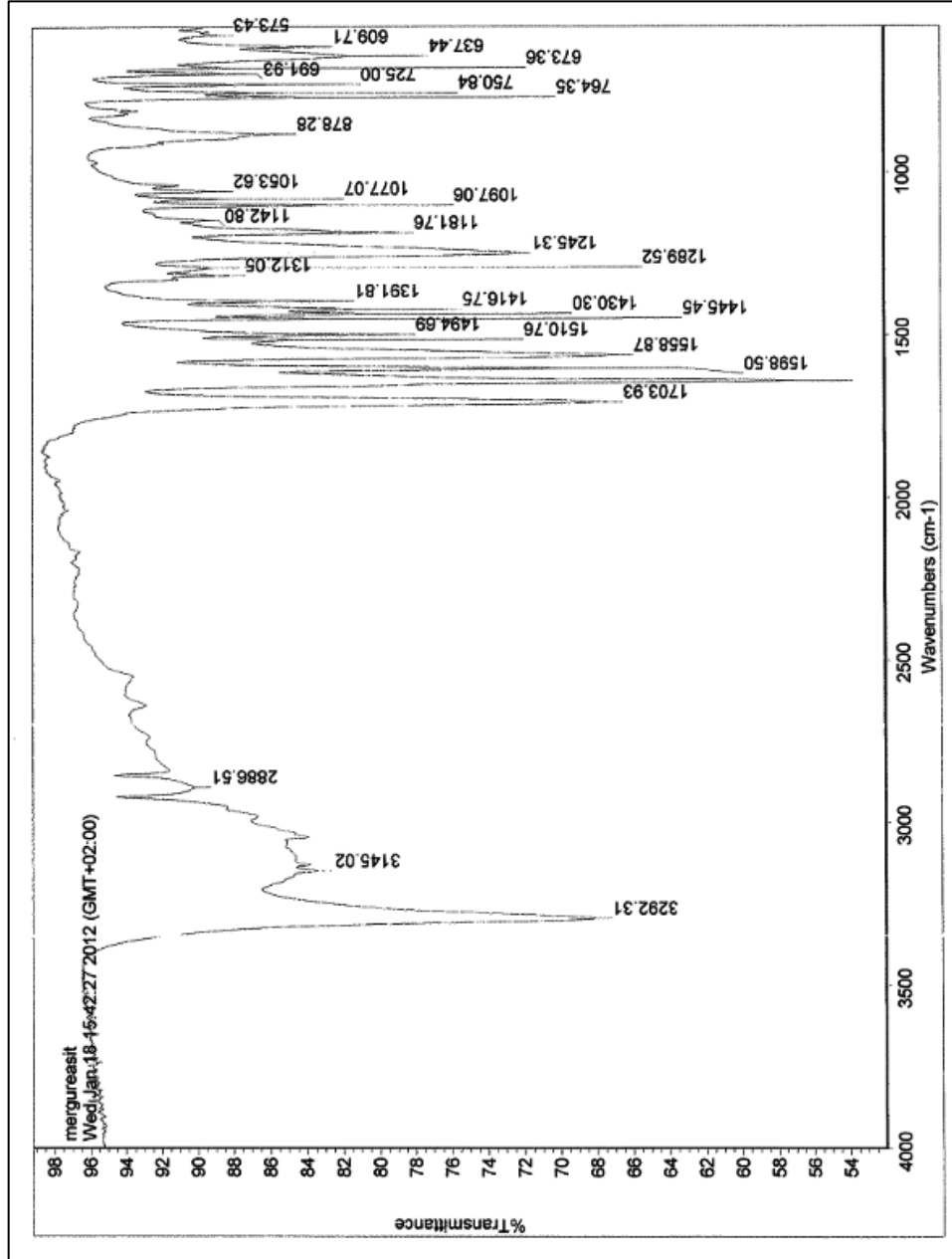


Figure 41 IR Spectrum of Compound 121

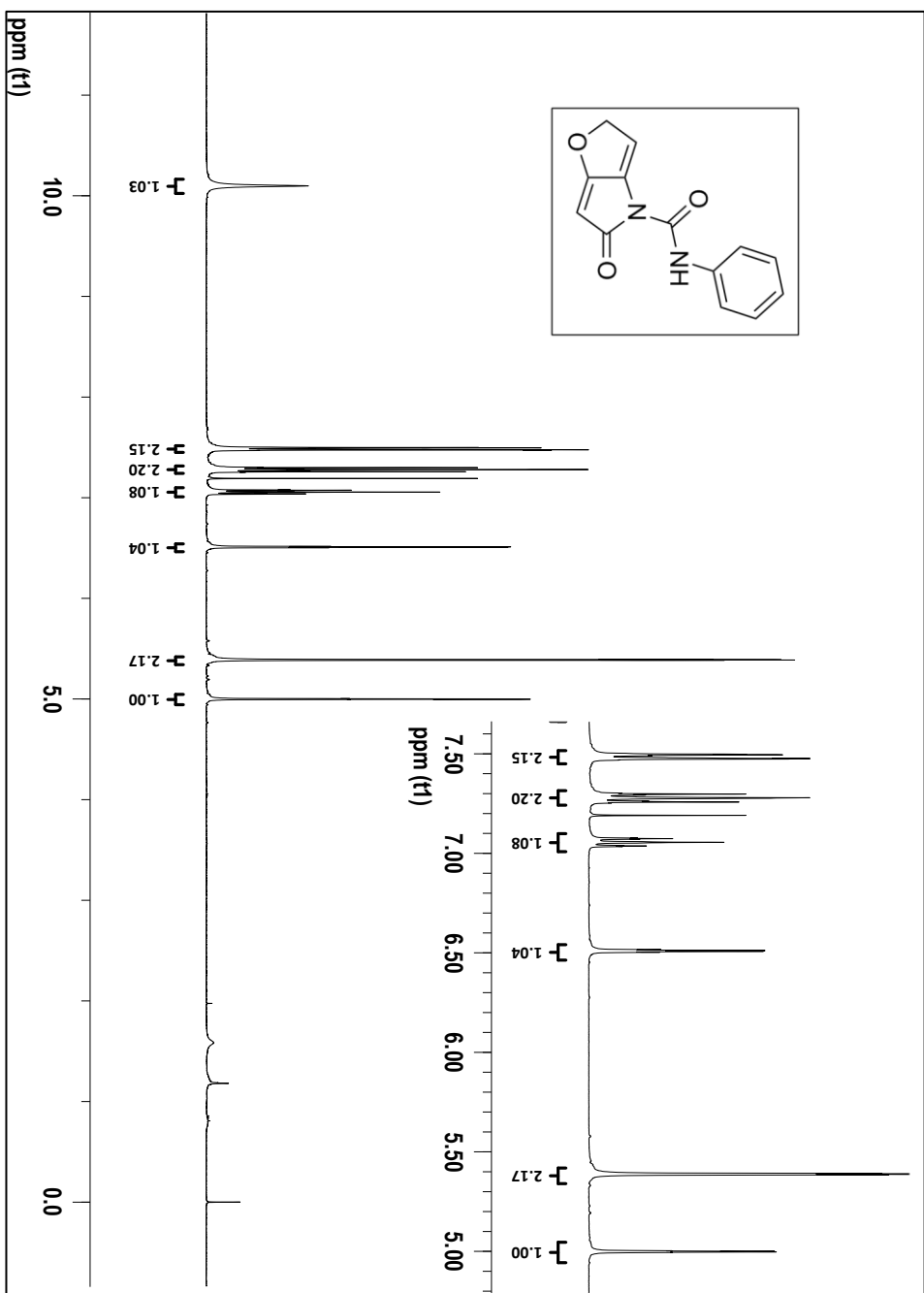


Figure 42 ¹H-NMR Spectrum of Compound 124

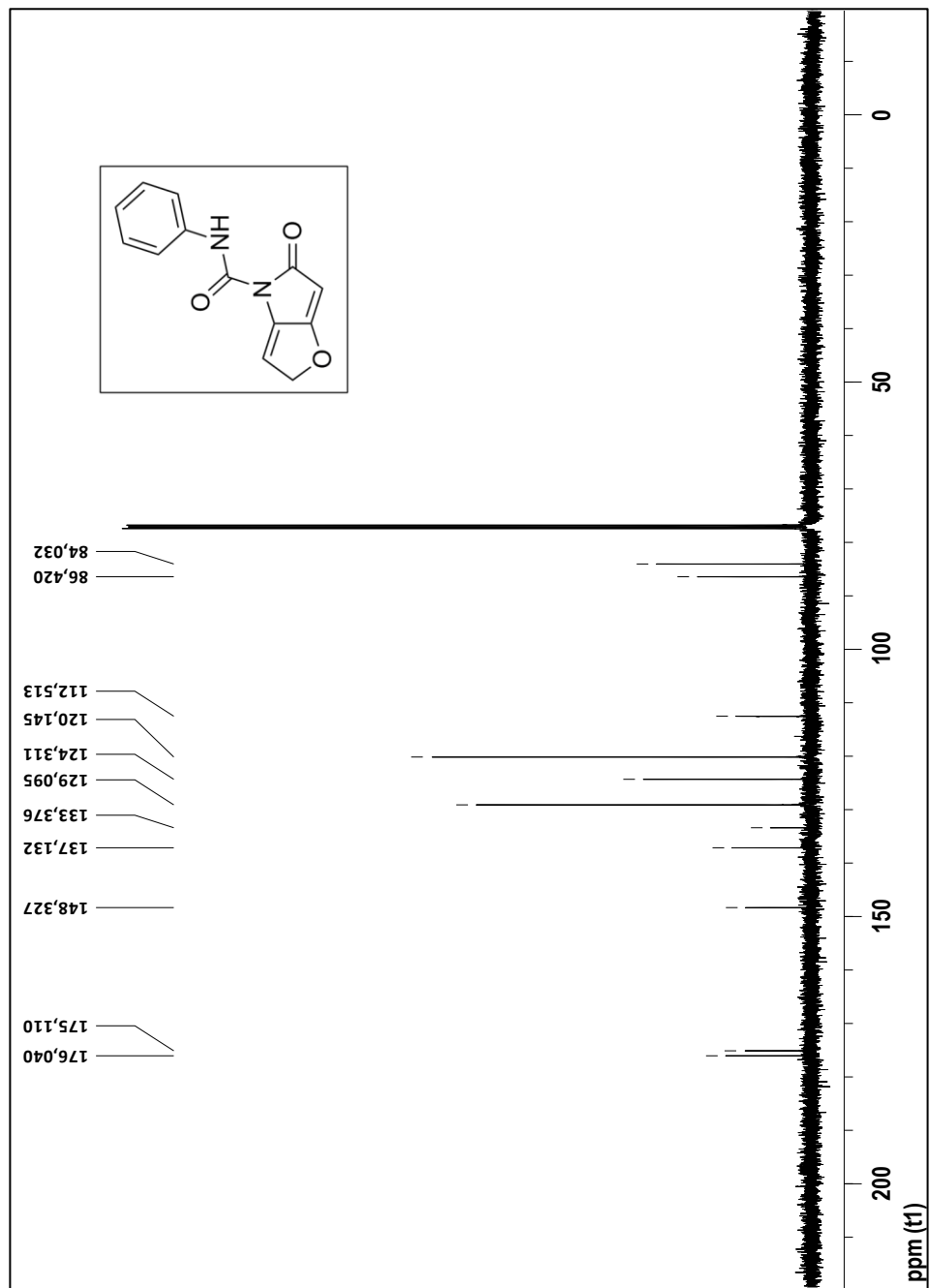


Figure 43 ¹³C-NMR Spectrum of Compound 124

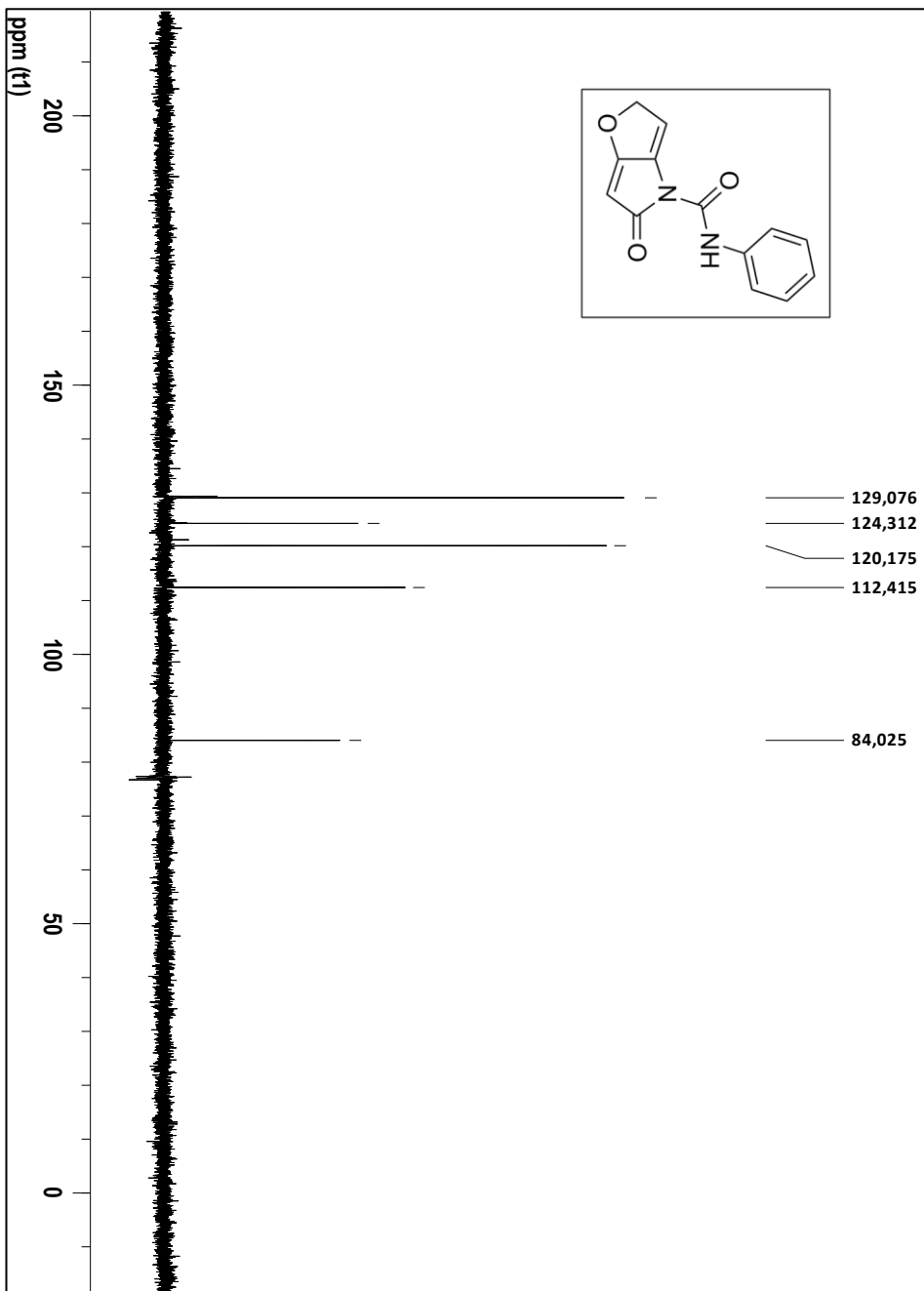


Figure 44 DEPT 90 Spectrum of Compound 124

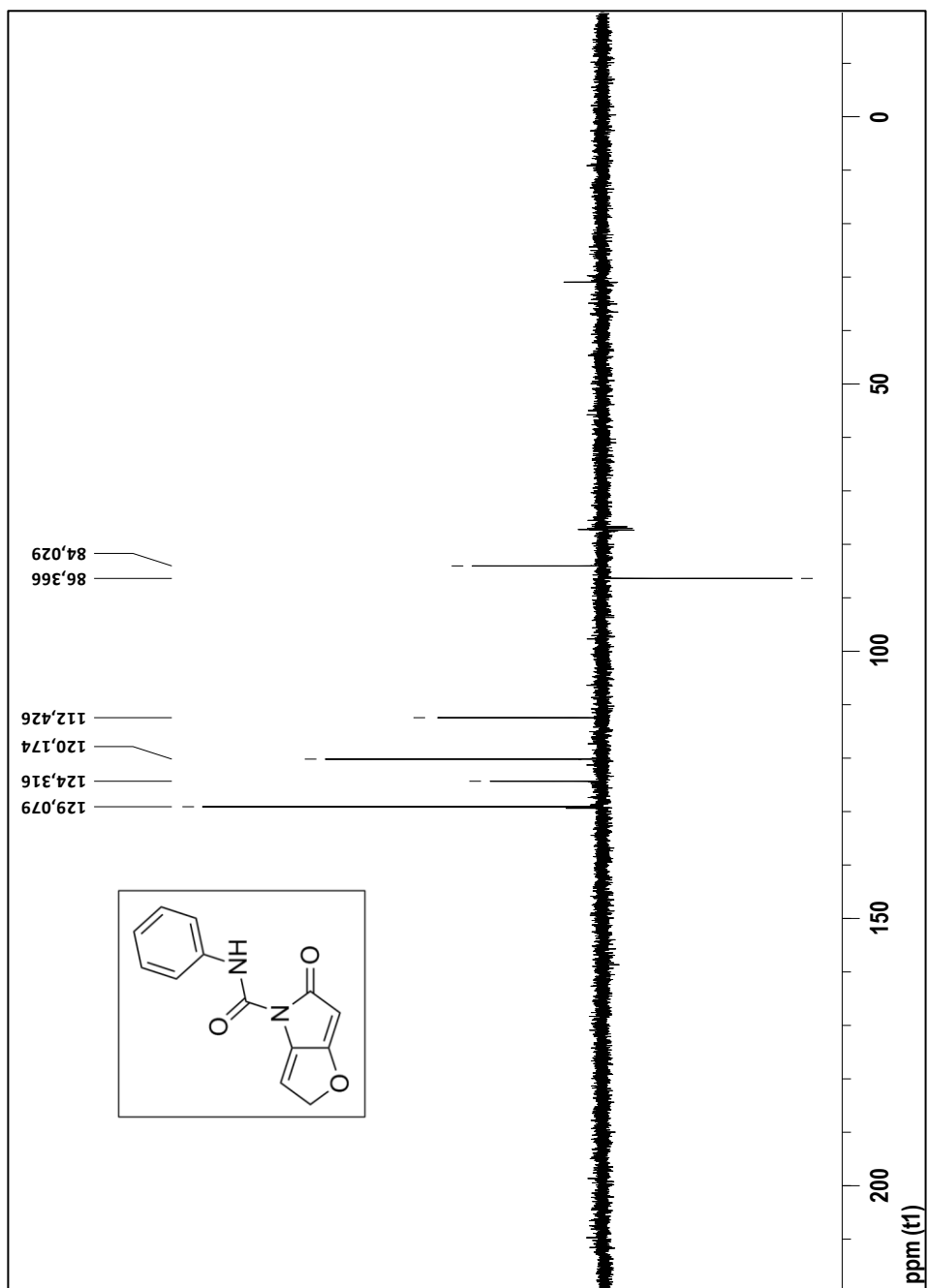


Figure 45 DEPT 135 Spectrum of Compound 124

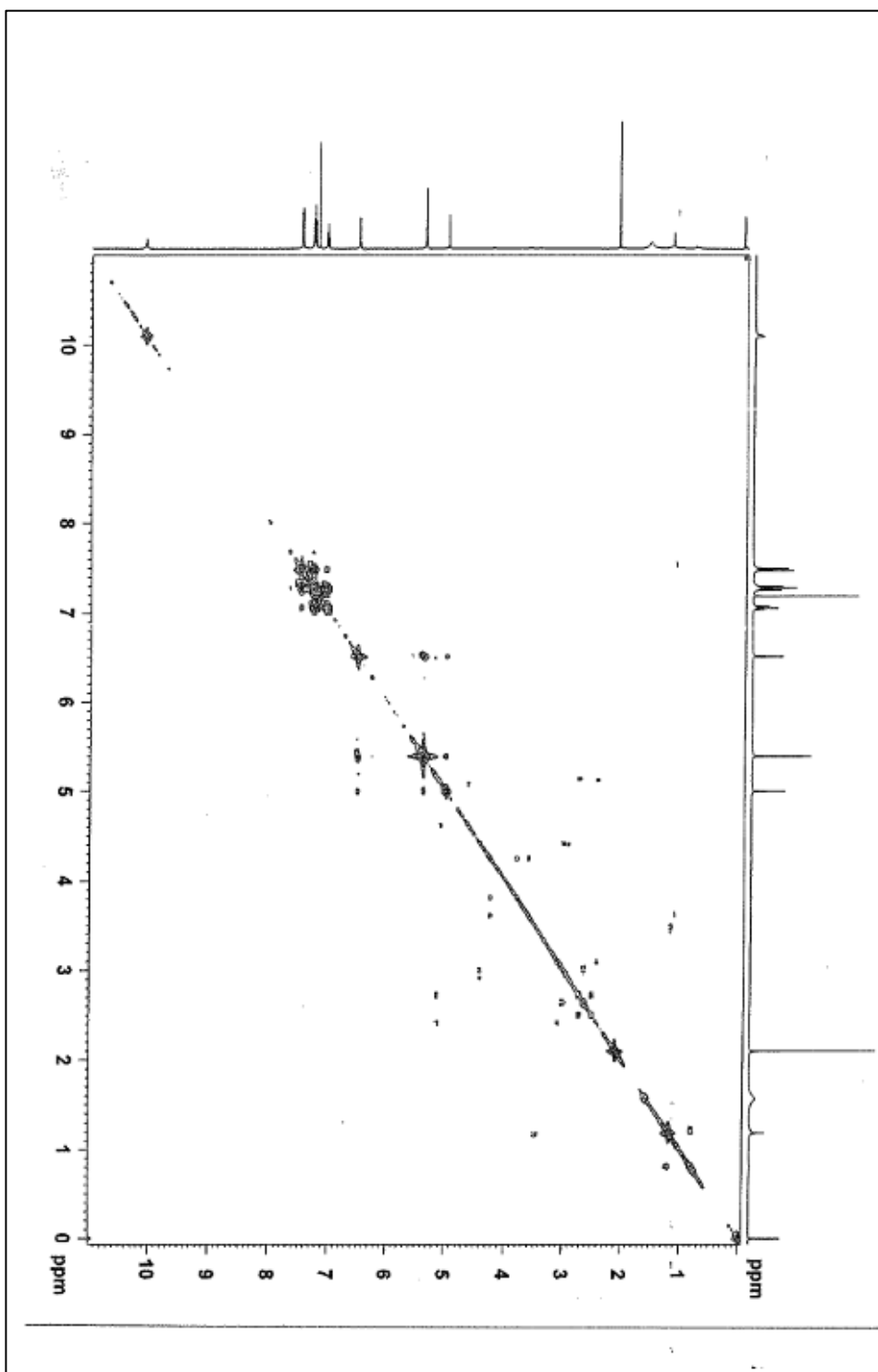


Figure 46 COSY Spectrum of Compound 124

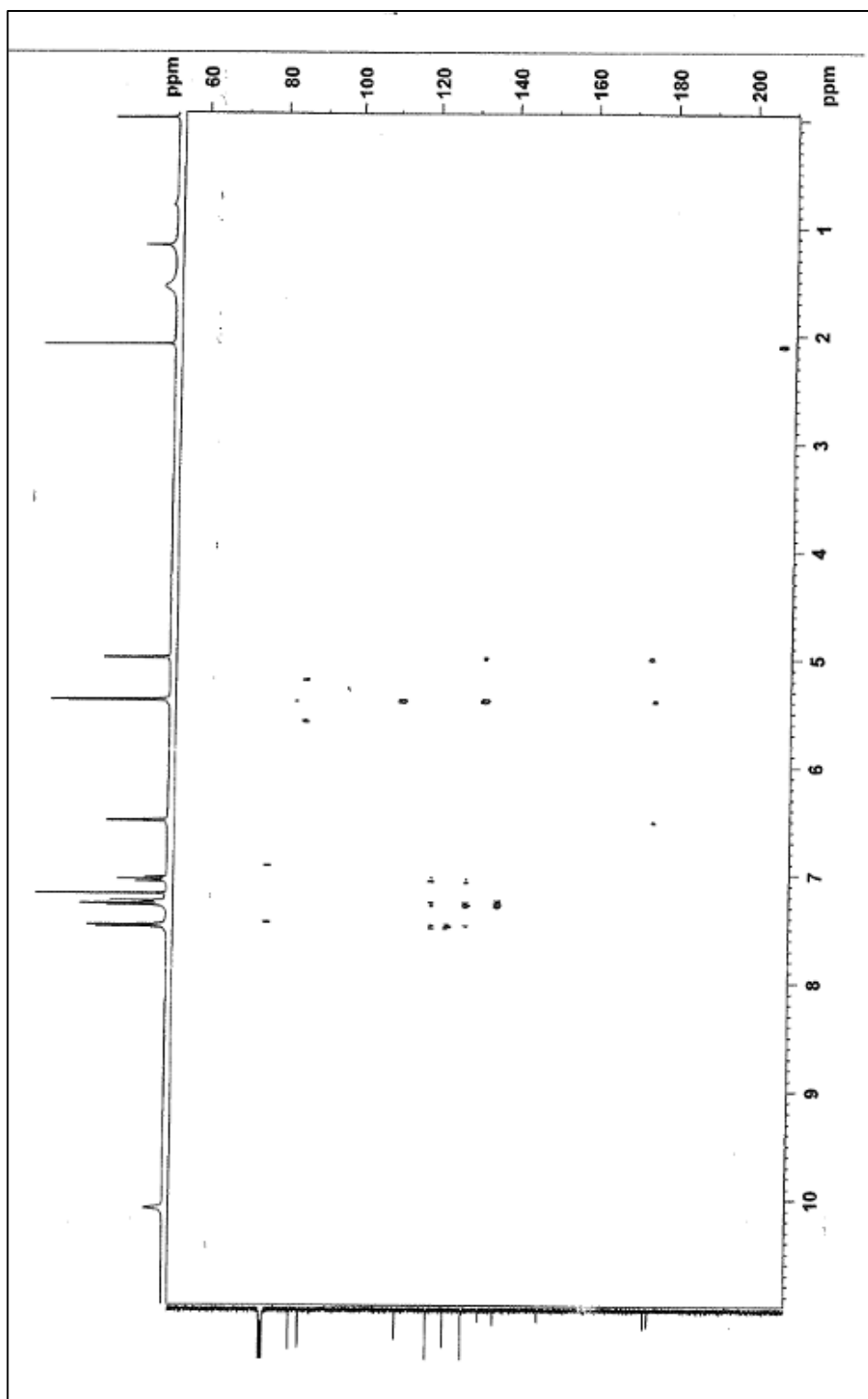


Figure 47 HMBC Spectrum of Compound 124

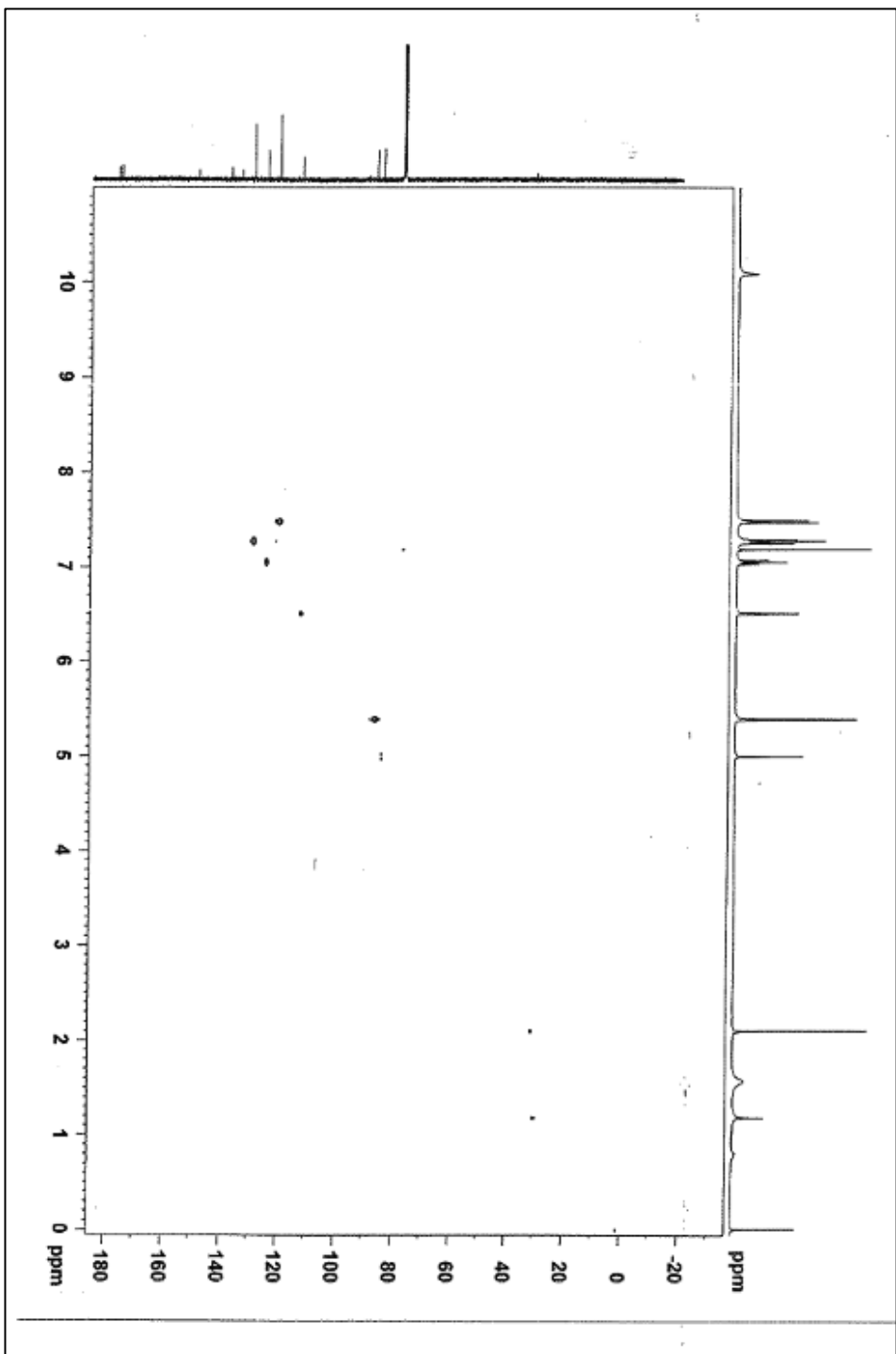


Figure 48 HSQC Spectrum of Compound 124

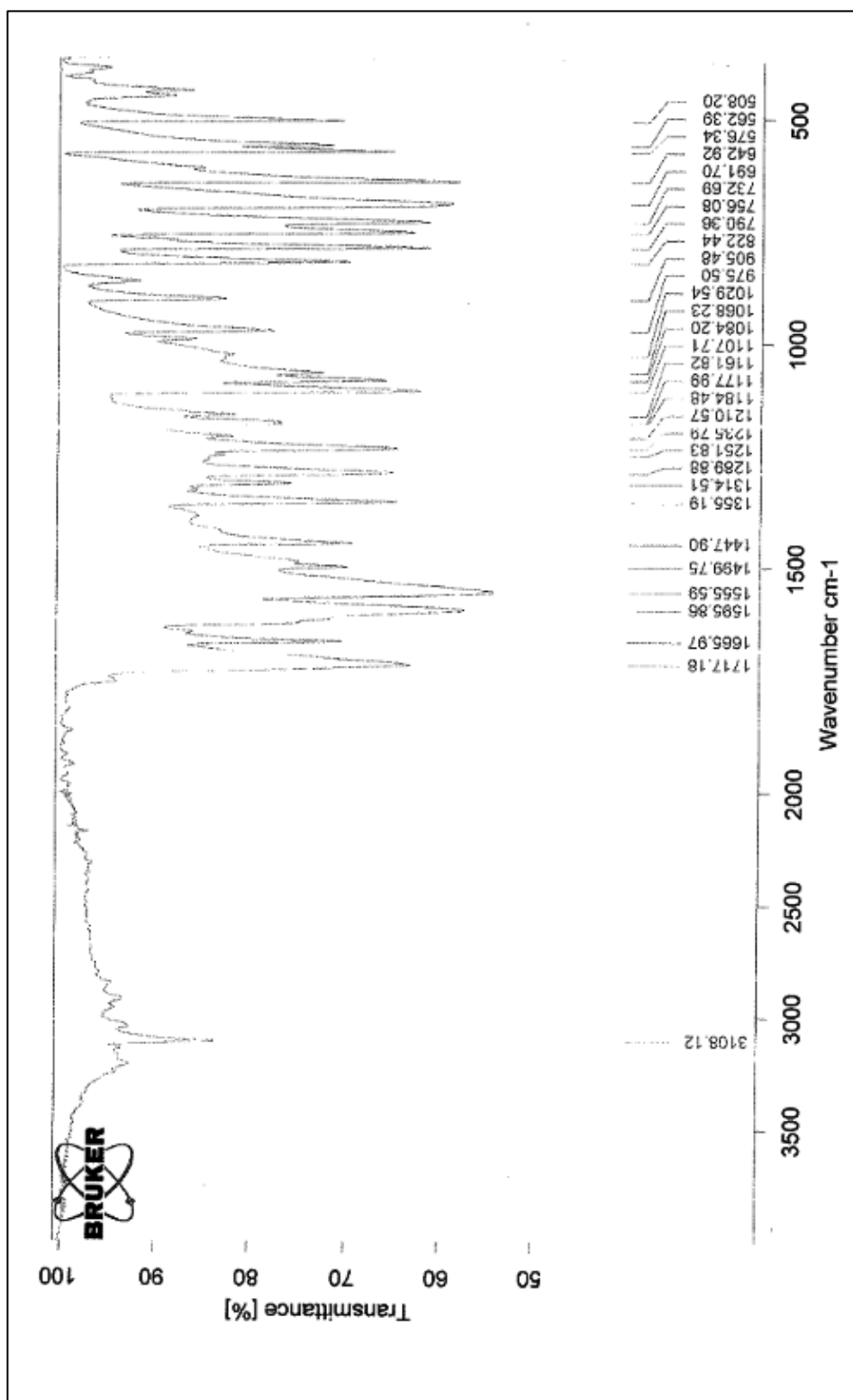


Figure 49 IR Spectrum of Compound 124

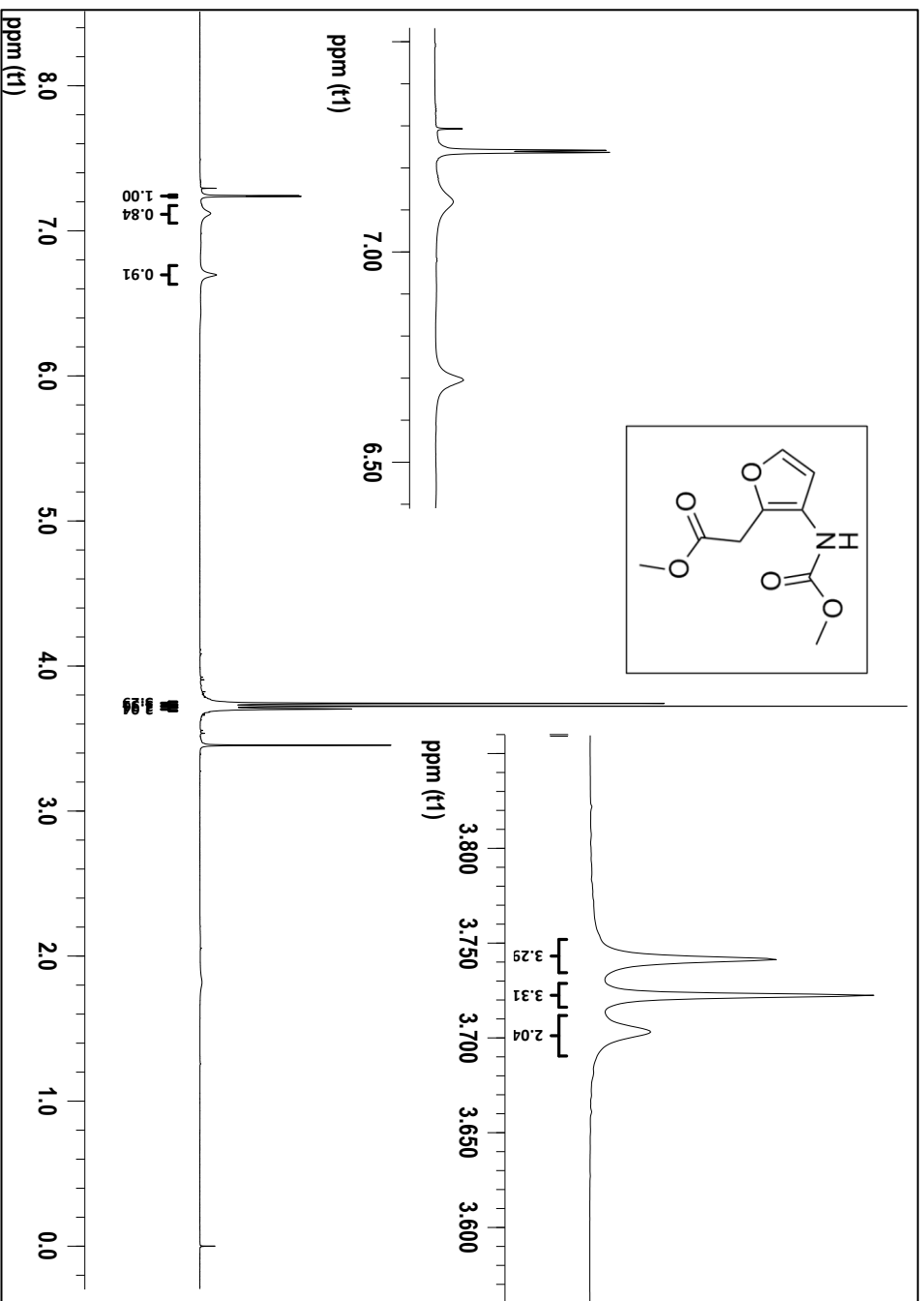


Figure 50 $^1\text{H-NMR}$ Spectrum of Compound 127

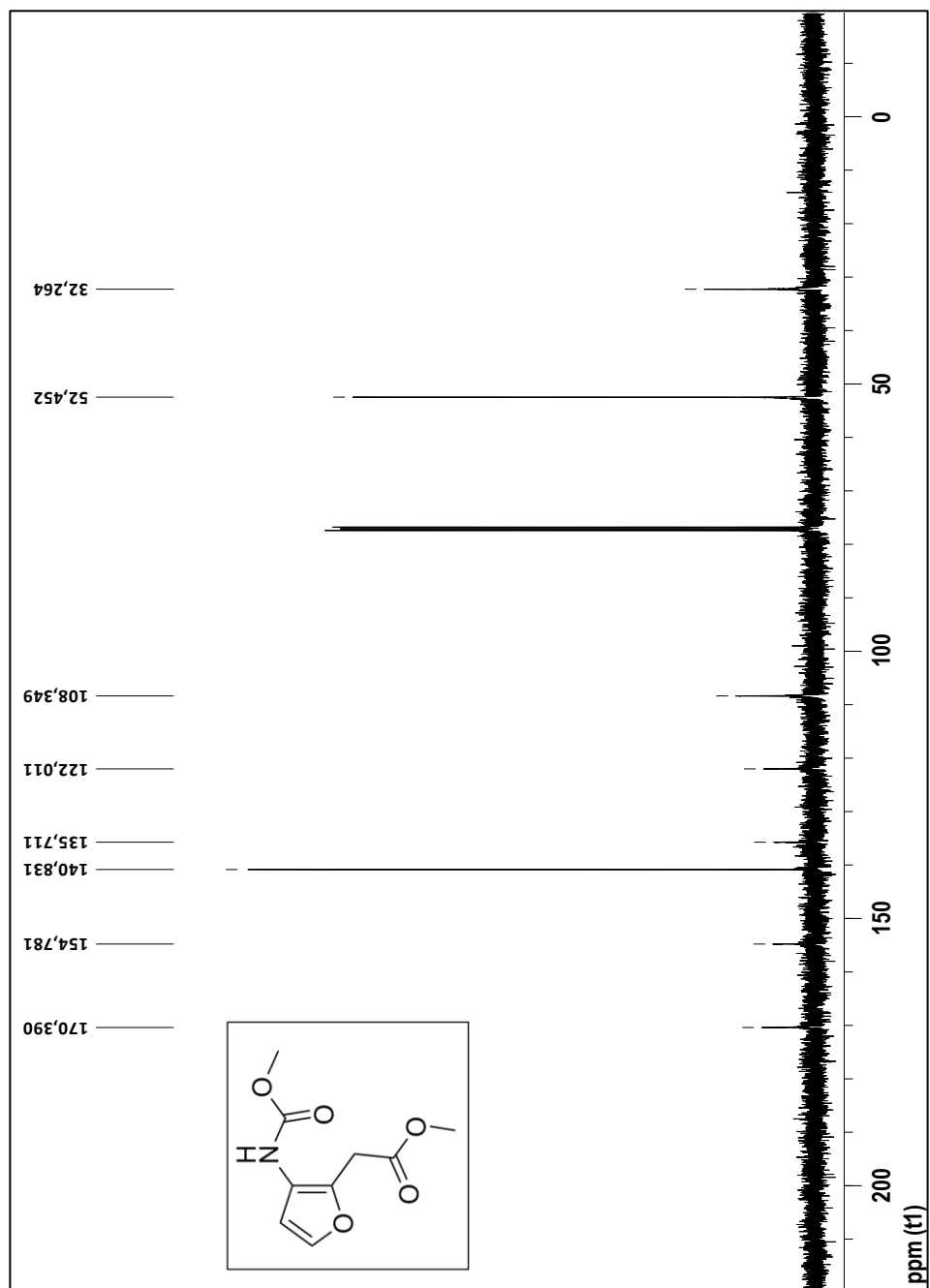


Figure 51 ¹³C-NMR Spectrum of Compound 127

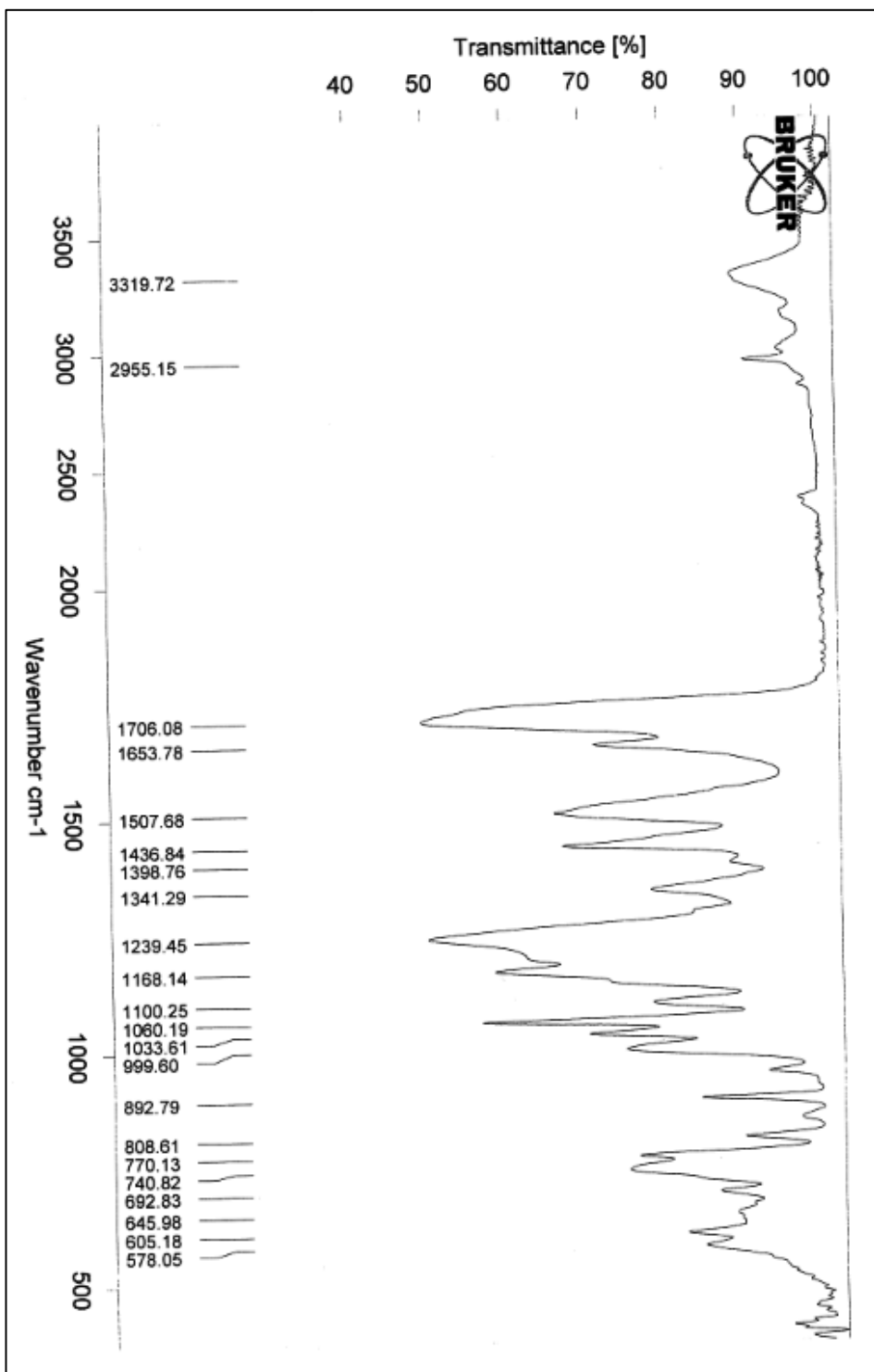


Figure S2 IR Spectrum of Compound 127

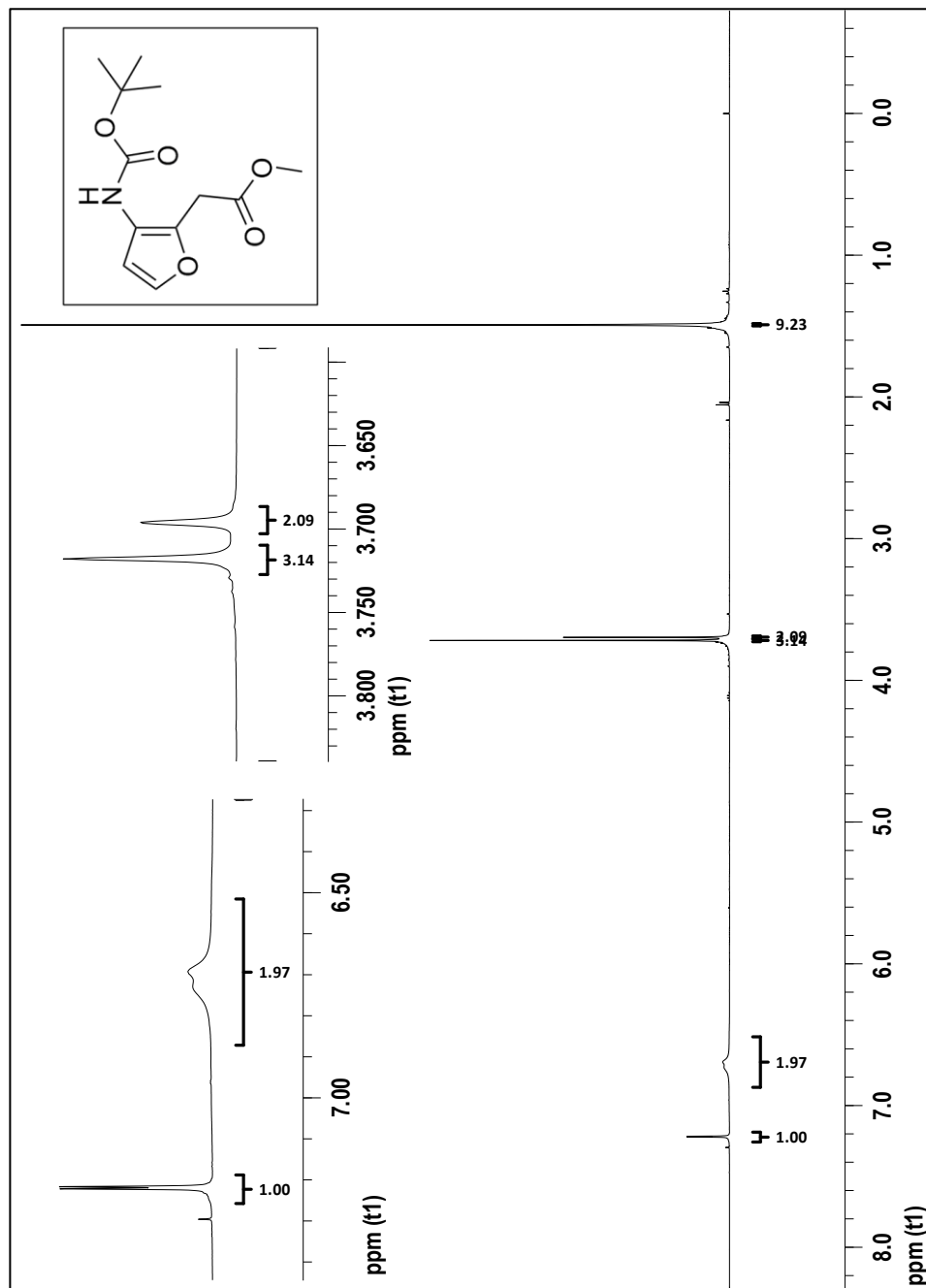


Figure 53 ¹H-NMR Spectrum of Compound 128

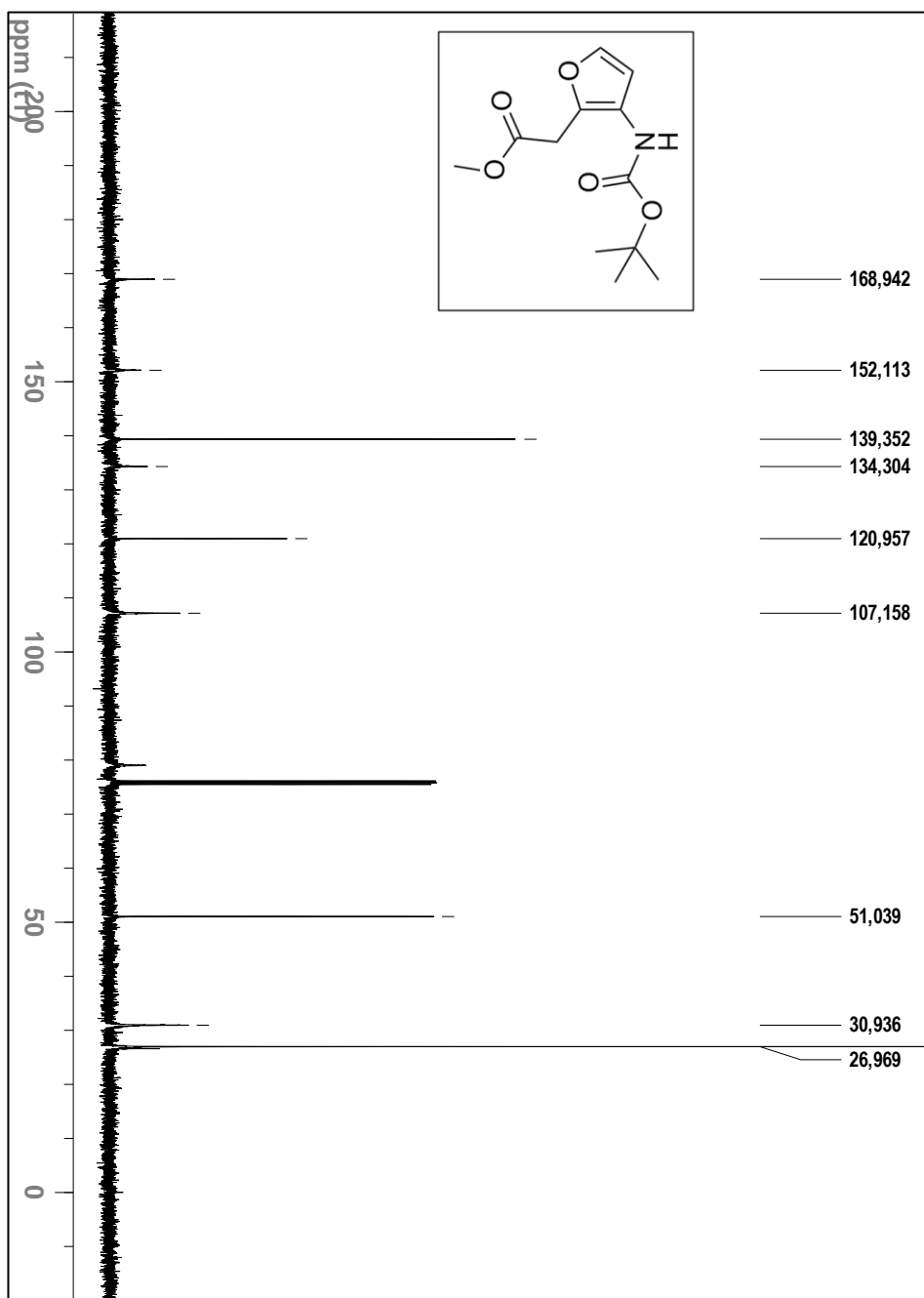


Figure S4 ^{13}C -NMR Spectrum of Compound 128

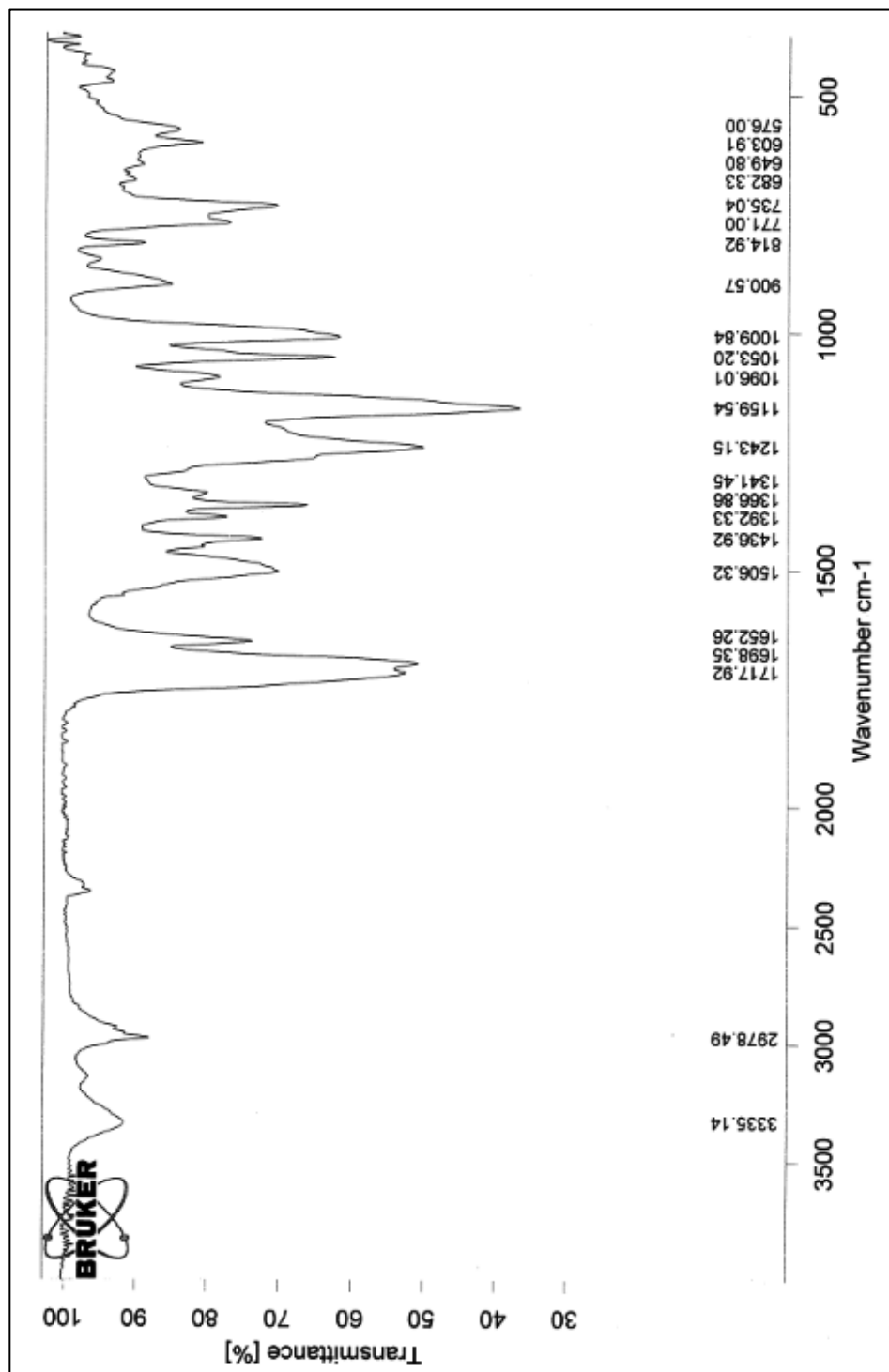


Figure 55 IR Spectrum of Compound 128

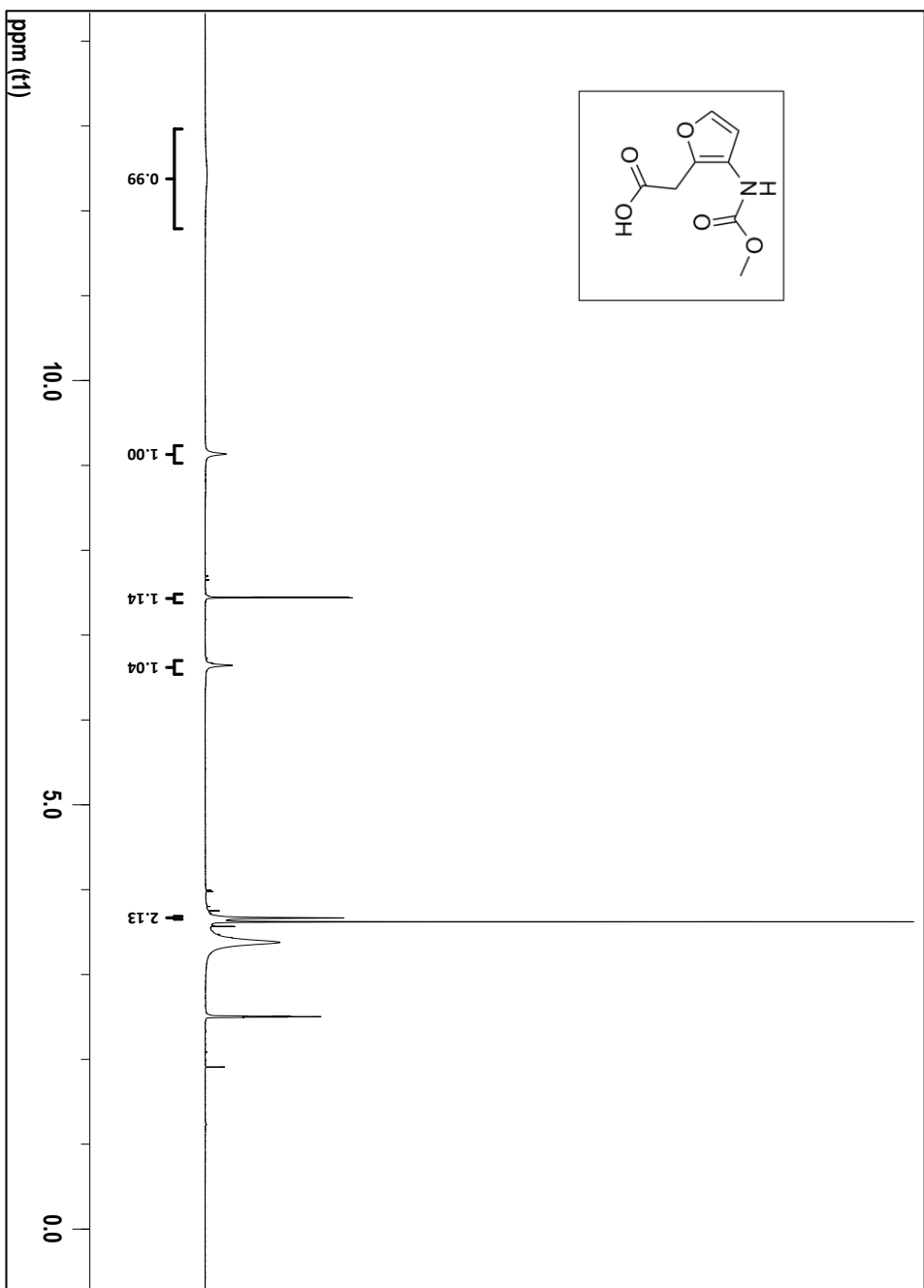


Figure 56 ¹H-NMR Spectrum of Compound 129

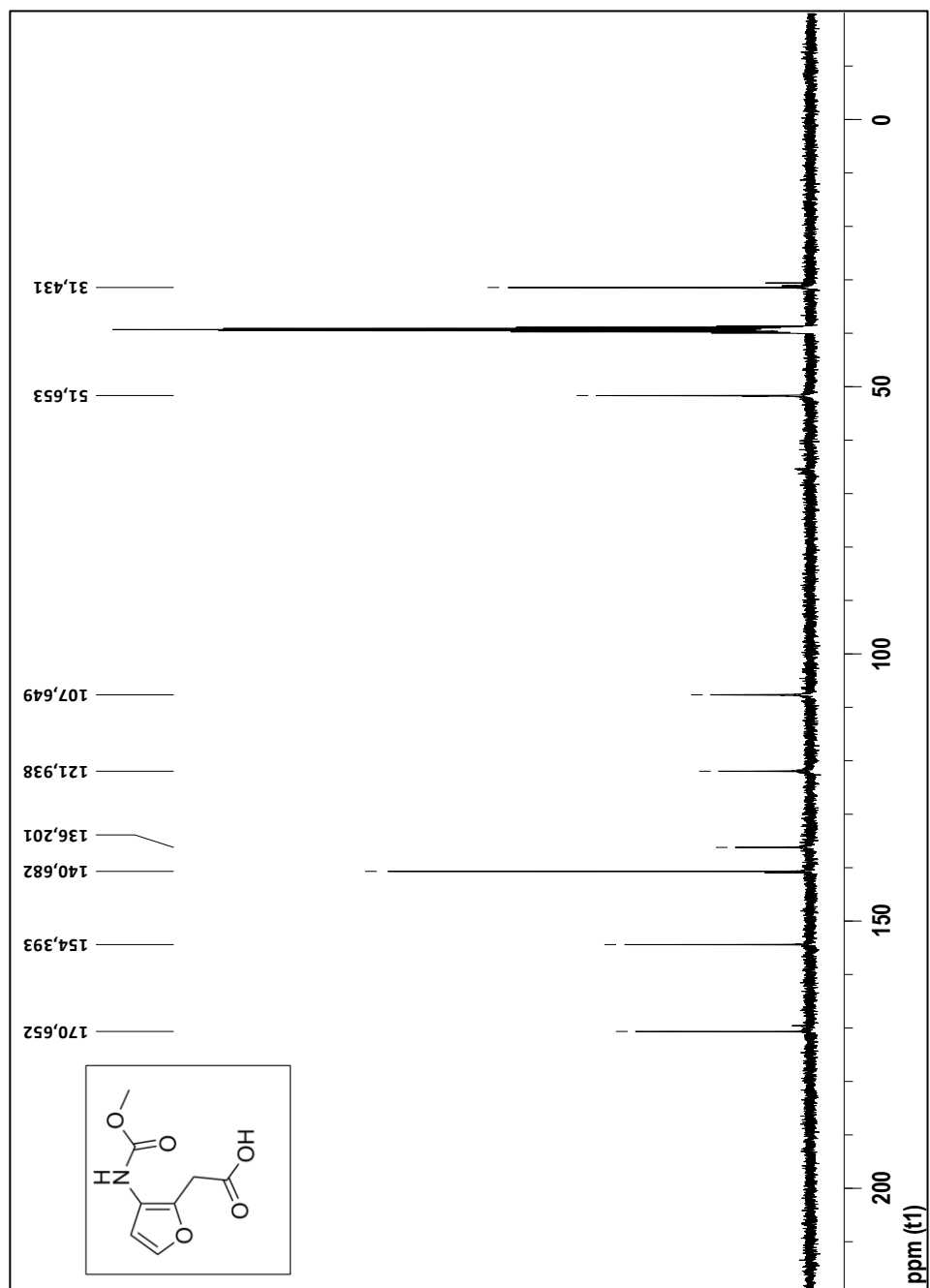


Figure 57 ¹³C-NMR Spectrum of Compound 129

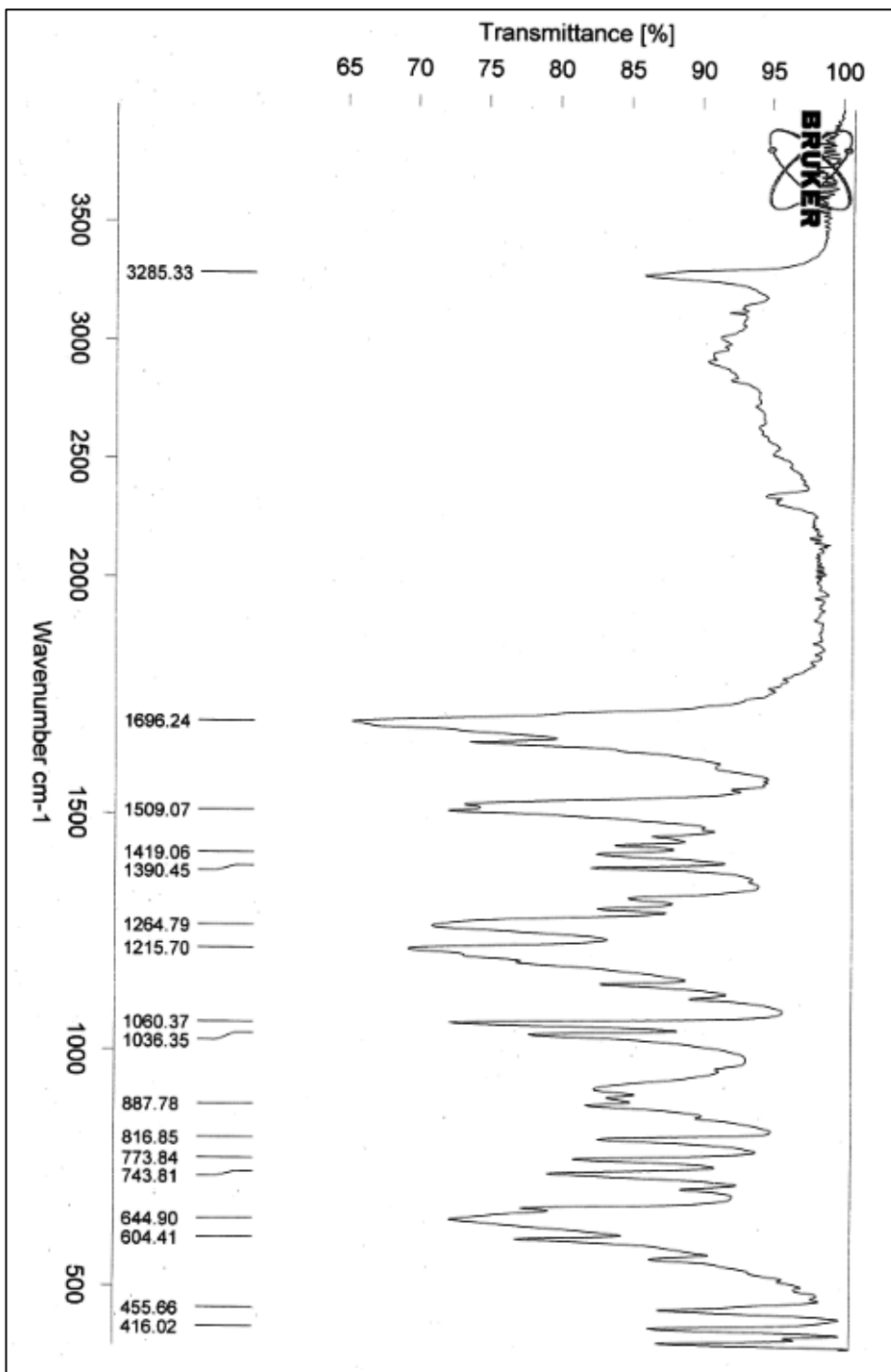


Figure S8 IR Spectrum of Compound 129

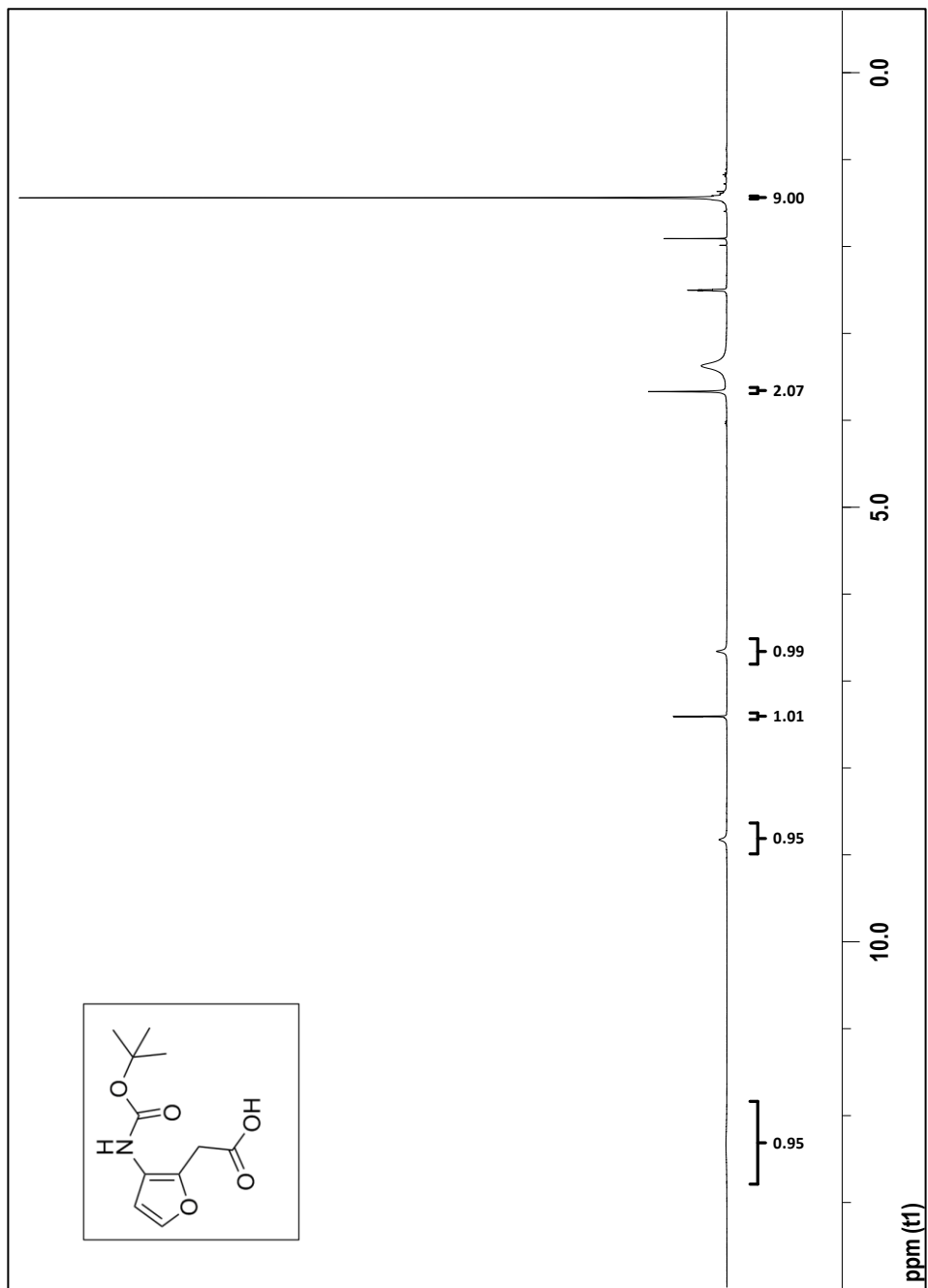


Figure 59 ¹H-NMR Spectrum of Compound 130

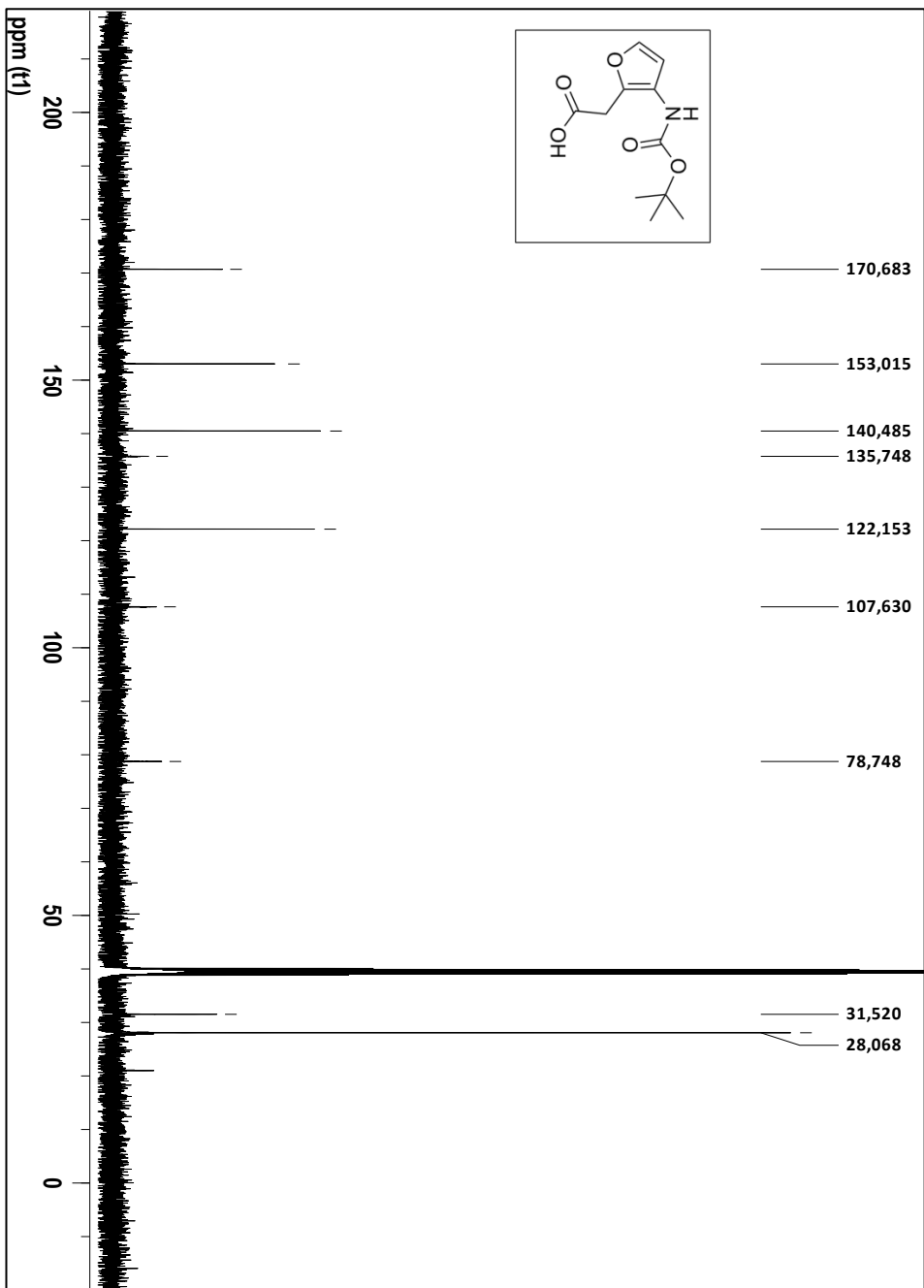


Figure 60 ¹³C-NMR Spectrum of Compound 130

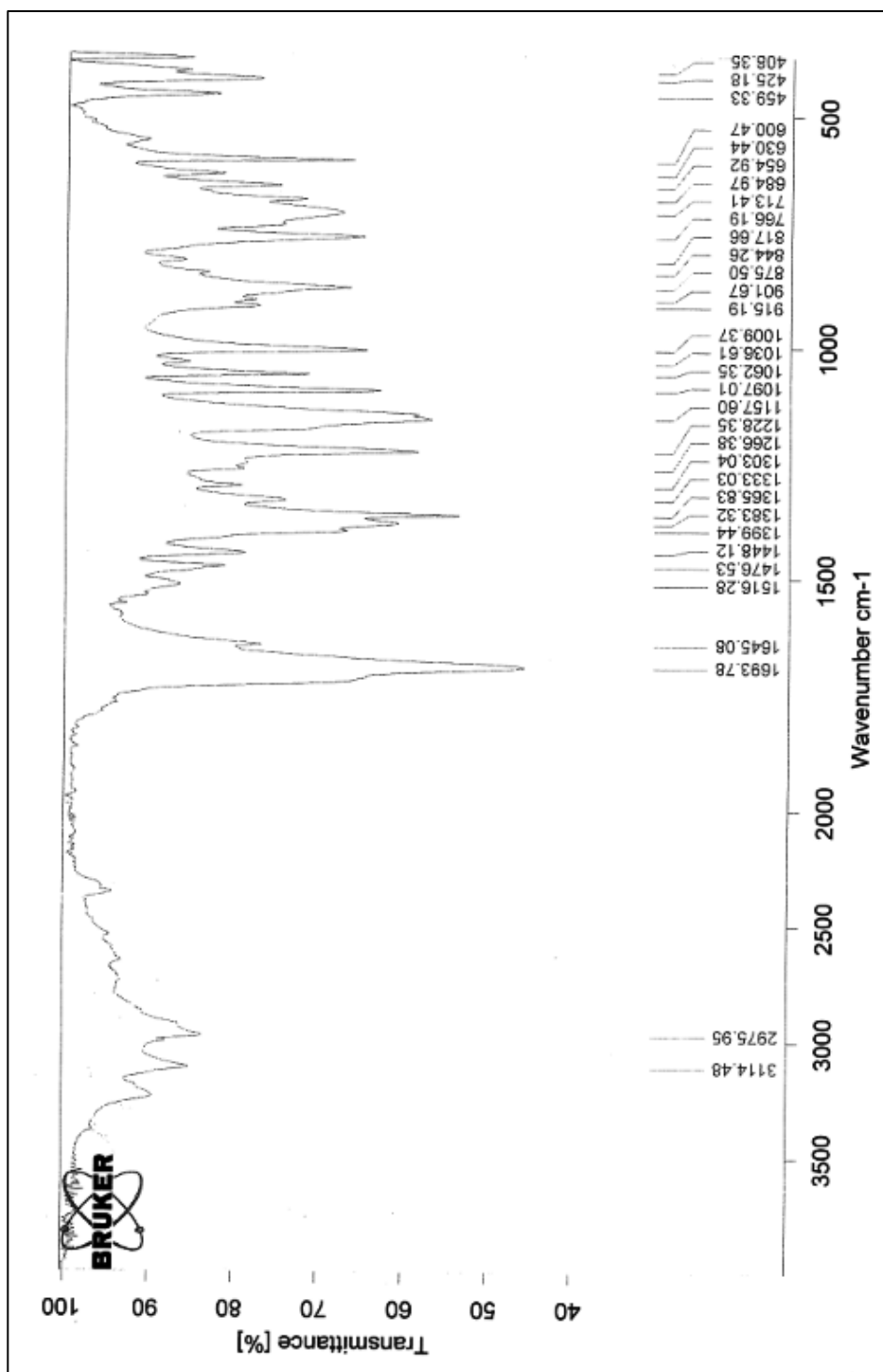


Figure 61 IR Spectrum of Compound 130