SYNTHESIS OF 2-AMINOPYRROLE-3-CARBOXYLATES VIA ZINC PERCHLORATE MEDIATED ANNULATION OF α-CYANO-γ-KETOESTERS WITH AMINES

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SYNTHESIS OF 2-AMINOPYRROLE-3-CARBOXYLATES VIA ZINC PERCHLORATE MEDIATED ANNULATION OF α-CYANO-γ-KETOESTERS WITH AMINES

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ABSTRACT

SYNTHESIS OF 2-AMINOPYRROLE-3-CARBOXYLATES VIA ZINC PERCHLORATE MEDIATED ANNULATION OF α-CYANO-γ-KETOESTERS WITH AMINES

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2-Aminopyrrole-3-carboxylate derivatives are important starting materials for biologically active compounds like pyrrolotriazole, pyrrolotriazine so their synthese has great importance in the synthetic organic chemistry.

There are only two methods for the synthesis of 2-aminopyrrole-3-carboxylates in the literature. Therefore, there is a great need for the design and development of a new method for the synthesis of 2-aminopyrrole-3-carboxylates.

In this work, 2-aminopyrrole-3-carboxylate derivatives were synthesized starting from cyano acetic acid ethyl ester with a new method. In the first step, cyanoacetic acid ethyl ester was alkylated with bromo acetone in the presence of NaH. Then, obtained γ-ketoester was reacted with primary amines in the presence of catalytic amount of zincpechlorate ($Zn(ClO_4)_2$). As a result, 2-aminopyrrole-3-carboxylate derivatives were obtained. Cyanoacetic acid ethyl ester was also alkylated with various bromo acetophenone derivatives in the presence of DBU (1,8-Diazabicycloundec-7-ene). As a result of these reactions, different γ-ketoesters were obtained. The reaction of these γ-ketoesters with primary amines in the presence of catalytic

amount of $Zn(ClO_4)_2$ concluded with 2-aminopyrrole-3-carboxylate derivatives.

Keywords: 2-aminopyrrole-3-carboxylates, $Zn(ClO_4)_2$, Lewis acid, catalytic reaction

ÖZ

α-SİYANO-γ-KETOESTERLERİN ÇİNKO PERKLORAT KATALİZLİ
AMİNLEME-HALKALAŞTIRMA YOLUYLA
2-AMİNOPİROL-3-KARBOKSİLATLARIN SENTEZİ

AKCA, Nazmiye Bihter
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi : Prof. Dr. Ayhan S. DEMİR

Temmuz 2008, 78 sayfa

2-Aminopirol-3-karboksilat türevleri oldukça yüksek biyolojik aktivite gösteren pirolotriazol, pirolotriazin gibi bir çok bileşiğin sentezlenmesinde kullanılan yapıtaşlarıdır. Bu nedenle sentezleri literatürde büyük öneme sahiptir.

2-Aminopirol-3-karboksilat türevlerinin sentezlenmesi için literatürde sadece iki metod mevcuttur. Bu amaçla, 2-aminopirol-3-karboksilat yapıların dizaynına ve geliştirilmesine oldukça fazla ihtiyaç vardır.

Bu çalışmada, 2-aminopirol-3-karboksilat türevlerinin siyanoasetik asit etil esterden başlanarak sentezlenmesi için yeni bir yöntem geliştirilmiştir. Öncelikle siyanoasetik asit etil ester, bromo aseton ile NaH kullanılarak alkillenmiştir. Daha sonra, elde edilen γ-keto ester, primer aminler ve katalitik miktarda $Zn(ClO_4)_2$ ile reaksiyona konulmuş ve 2-aminopirol-3-karboksilat türevleri tek bir basamakta elde edilmiştir. Siyanoasetik asit etil ester, aynı zamanda DBU katalizörlüğünde de çeşitli bromo asetofenon türevleri kullanılarak alkillenmiştir. Bu reaksiyonun sonucunda farklı γ- keto ester türevleri elde edilmiştir. Elde edilen γ- keto esterler

ile katalitik miktarda $Zn(ClO_4)_2$ katalizörlüğünde primer aminler kullanarak, 2-aminopirol-3-karboksilat türevleri sentezlenmiştir.

Anahtar Kelimeler: 2-aminopirol-3-karboksilat, $Zn(ClO_4)_2$, katalitik reaksiyon

To my parents and friends

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LIST OF ABBREVIATIONS

$CHCl_3$	:	Chloroform
tert-$BuMe_2SiCl$	:	*tert*-buthylchlorodimethylsilane
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	:	Dichloroethane
DMAP	:	Dimethylaminopyridine
DMF	:	Dimethyl formamide
DMSO	:	Dimethyl sulfoxide
KOEt	:	Potassium ethoxide
$NaBH_4$	:	Sodium borahydride
NaH	:	Sodium hydride
NaOEt	:	Sodium ethoxide
NIS	:	*N*-iodosuccinimide
TBAF	:	Tetrabuthylammonium floride
TLC	:	Thin layer chromotography
$Zn(ClO_4)_2$	:	Zinc perchlorate
PTSA	:	*p*-Toluene sulfonic acid

CHAPTER 1

INTRODUCTION

1.1 Pyrroles in Chemistry and Biology

Pyrroles are important class of heterocyclic chemistry because many natural products, such as synthetic drugs, supramolecular compounds, electrochemical devices and many polymers have the pyrrole skeleton [1].

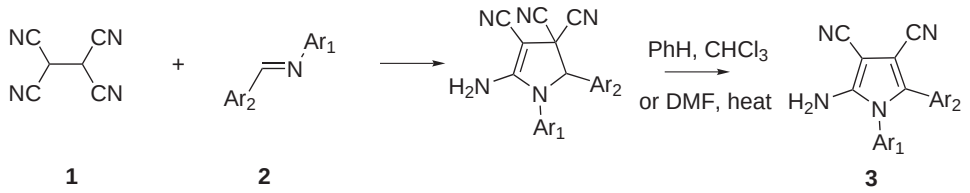
Especially, the derivatives with two aryl groups on adjacent positions include several classes of natural and unnatural compounds which show a variety of biological, pharmacological and biomedical properties [2]. Various kinds of substances isolated from natural sources (such as, lamellarins [3], lukianols [4], ningalins [5], storniamides [6], arcyriarubins [7], polycitones and polycitrins [8]) exhibit noteworthy biological properties such as hypolipidemic [9], antimicrobial [10], anti-inflammatory [11] and antitumour activity[12] and they are able to inhibit retroviral reverse transcriptases [i.e., human immunodeficiency virus type 1 (HIV-1)], cellular DNA polymerases [13] and protein kinases [14]. For example, Lamellarins O [3], P [3], Q [15] and R [3], are 3,4-diarylpyrrole-2-carboxylic acid esters, which is a part of a large group of DOPA-[1-amino-3-(30,40-dihydroxy-phenyl) propionic acid]-derived pyrrole alkaloids first isolated from the prosobranch mollusc *Lamellaria* sp. and later obtained from the ascidian *Didemnum* sp., the Australian sponge *Dendrilla cactus* [16] and an unidentified ascidian collected from the Arabiansea [2]. In addition, some of these compounds are functional intermediates in the synthesis of biologically influential naturally occurring alkaloids and unnatural heterocycle derivatives [17].

As a consequence of mentioned properties, pyrrole's usage increases day by day.

1.2 Methods for the Synthesis of 2-Aminopyrroles

Pyrroles are mainly synthesized by Hantzch, Knorr and Paal-Knoor reactions. The reaction of α-bromoketones with β-ketoesters and ammonia was reported by Hanthzch [18]. Moreover, synthesis of pyrroles with α-aminoketones, ammonia and β-ketoesters has been afforded by Knorr reaction [19]. Furthermore, the final and most frequently used reaction to yield pyrrole is Paal-Knorr method which is the reaction of 1,4-dicarbonyl compounds with primary amines (or ammonia) in the presence of various catalyts.

Although there have been many methods for various pyrroles, relatively few examples were published for the preparation of 2-aminopyrroles due to the unstability of aminopyrroles in air. For example, Nasakin and Korostova et al. has afforded pyrroles which contain amino and cyano groups, in 88-98% yield by the reaction of tetracyanoethane (**1**) with the Schiff bases **2** in ethanol or DMSO [20]. The tricyanodihydropyrroles has been produced as intermediates, which lose hydrogen cyanide on heating in benzene, $CHCl_3$ or DMF to give the required pyrroles **3** (Fig 1.1) [20].



1 **2** **3**

[Ar_1= Ph, 4-HOC_6H_4, 2-Pyridyl ;Ar_2=Ph, 4-HOC_6H_4, 2-furyl]

Figure 1.1: The synthesis of **3**

In 1987, Emilio et al. reported the syntheses of 2-amino-pyrrole-3-carboxylate derivatives. The reaction of ethoxycarbonylacetamidine (**4**), obtained in situ from hydrochloride and NaOEt, with α-bromoacetone **5** derivatives was carried out in absolute EtOH. Pure 2-amino-pyrrole-3-carboxylate derivatives **6** obtained in yields ranging 25%-64% (Figure 1.2) [21].

Moreover, De Rosa and colleagues described 1-substituted 2-aminopyrrole **11** (Figure 1.3). By an addition-elimination reaction, 1-substituted pyrrole and *N*-chlorophthalimide furnished *N*-(1-substituted-1*H*-pyrrol-2-yl)phthalimide **7** [22]. For removal of the phthaloyl group

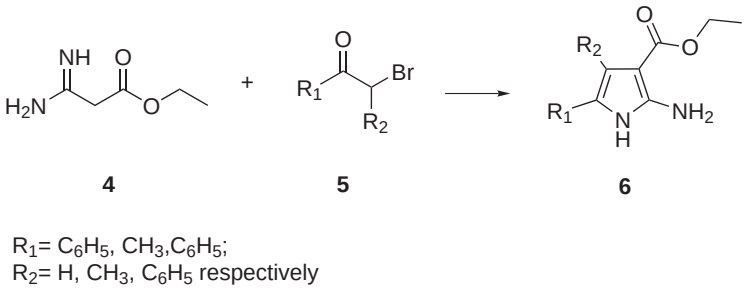


Figure 1.2: The synthesis of **6**

Ganem et al. method was carried out [23]. In the presence of $NaBH_4$, partial reduction of starting material **7** gave 2-(hydroxymethyl)-*N*-(1*H*-pyrrol-2-yl)benzamide (**8**). A solution of **8** in acetic acid at 80 °C for 2 h under a nitrogen atmosphere gave **9** and phthalide (**10**). Then, **9** was treated with NaOH and acetic acid and the reaction resulted with 2-aminopyrrole derivatives **11** [24].

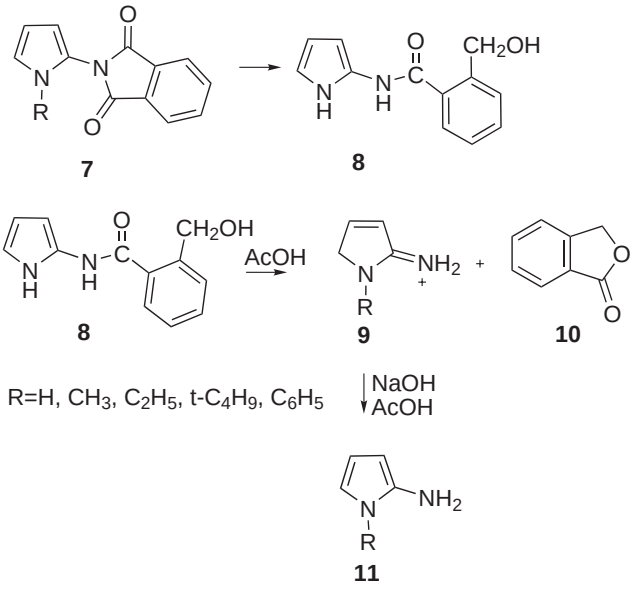


Figure 1.3: The synthesis of **11**

In 2004, Mohammed et al. synthesized 1,2-diaryl-1*H*-pyrroles **13**, containing amino and cyano groups, in 39-46% yield by the reaction of the corresponding phenacylmalononitrile derivatives **12** with aniline in absolute ethanol in the presence of catalytic amounts of con-

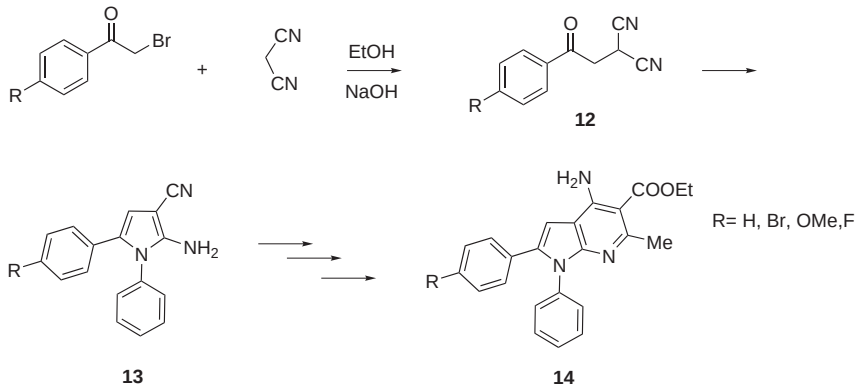


Figure 1.4: The synthesis of pyrrolo[2,3-b]pyridine derivatives

centrated HCl (Figure1.4) [25]. The 2-aminopyrrole derivatives have been used as precursors of new pyrrolo[2,3-*b*]pyridine derivatives **14** which are potent inhibitors of tumour necrosis factor [25].

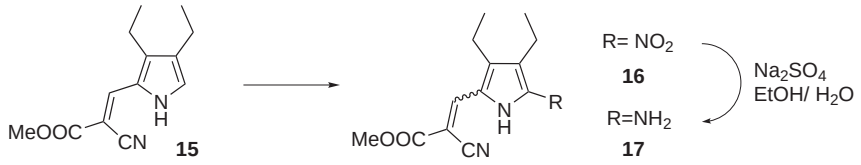


Figure 1.5: The synthesis of 3,4-diethyl-2-aminopyrrole

In addition, Pantoş et al. has reported 2-amino-3,4-diethyl pyrrole (**17**) which was new building blocks for coiled structures (Figure 1.5) [26]. Firstly, nitration reaction of (E)-methyl 3-(5-amino-3,4-diethyl-1H-pyrrol-2-yl)-2-cyanoacrylate (**15**) was afforded **16** in the presence of HNO_3 and acetic anhydride (Ac_2O). Then hydrogenation of nitro group in **16** furnished **17** by using Na_2SO_4 in EtOH/H_2O in 71% yield. Although, 5-amino-3,4-diethyl-pyrrole-2-carboxylate, 4-ethyl-3,5-dimethyl-2-amino-pyrrole, 3,4-diethyl-2-aminopyrrole have been reported to undergo appreciable decomposition in air within 5 min after their isolation, stability has been increased by storing these compounds at 24 °C under an argon blanket [26].

In 2006, Moore et al. published method of **21** (Figure 1.6) while synthesizing Distamycin A which is an inhibitor of human telomerase enzyme [27]. Nitration reaction of **18** resulted in **19** and then for the preparation of carboxylic acid, esterification of **19** with DMAP in EtOH

followed by hydrogenation of **20** under mild conditions yielded **21** [28].

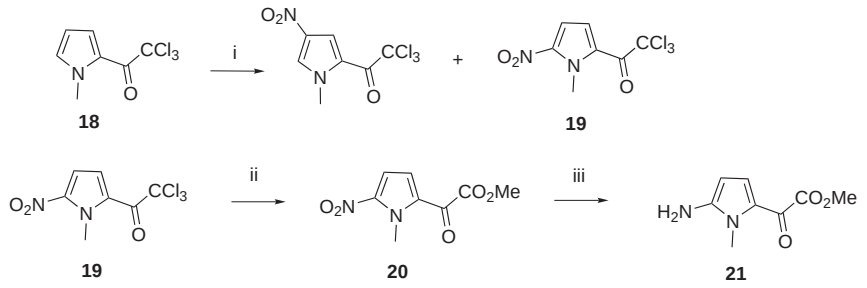


Figure 1.6: The synthesis method of **21** , i) HNO_3 dropwise, Ac_2O, -40°C-rt, $(CH_3)_2CHOH$, -40°C ii) 0.05 equiv. DMAP, MeOH, rt, N_2 iii) H_2 (30 psi), 10% Pd°C, THF

In 2007, Oda and colliques reported the synthesis of 5-acetyl-2-aminopyrrole C-deoxyribonucleoside (**32**) which may be used as an artifical base pair [29] (Figure1.7). Iodination of pyrrole **22** by *N*-iodosuccinimide afforded 2-acetyl-4-iodo-1*H*-pyrrole (**23**) [30]. Then, **24** was obtained by the treatment of **23** with nitric acid. The Heck coupling reaction took place when **24** and furanoid glycal reacted by using triphenylphosphine, triethylamine and DMF at microwave at 140 °C for 10 min., which concluded with **25** in low yield. Desilylation of **25** by TBAF resulted in 3′-keto nucleoside **26** in good yield. By diastereoselective reduction of 3′-keto group of **26**, 5-acetyl-2-nitro-1*H*-pyrrole C-deoxyribonucleoside **(27)** was obtained in high yield. The 3′ and 5′-hydroxyl groups of **27** were protected by the silyl group with retention of the stereochemistry in the presence of *tert*-$BuMe_2SiCl$, imidazole and DMF results in **28** with 97%. Then by the reduction of **28** in the presence of H_2, 10%-Pd-C, MeOH afforded **29** in 96% yield. Amide formation was achieved by introducing phenoxyacetyl group ($PhOCH_2COCl$) to **29** with trimethylamine in THF. **30**'s desilylation ended with the **31**. Removal of the phenoxyacetyl group with ethylene diamine gave the desired product 5-acetyl-2-amino-1*H*-pyrrole C-deoxyribonucleoside (**32**) [29].

Besides, Demir et al. introduced 2-aminopyrrole carboxylate derivatives **35** to the literature. The alkylated 1,3-diketone **33** was used as a starting material. After that, in the presence of primary amine and catalytic amount of *p*-TsOH, an enamine formation **34** was achived. Then, in the second step, enamine cyclized to yield pyrrole in the presence of KOEt. The reaction pathway can be seen in Figure 1.8 [31]. However, it is very important to synthesize pyrrole in one step under mild condition for atom economy and environment. In the light of this

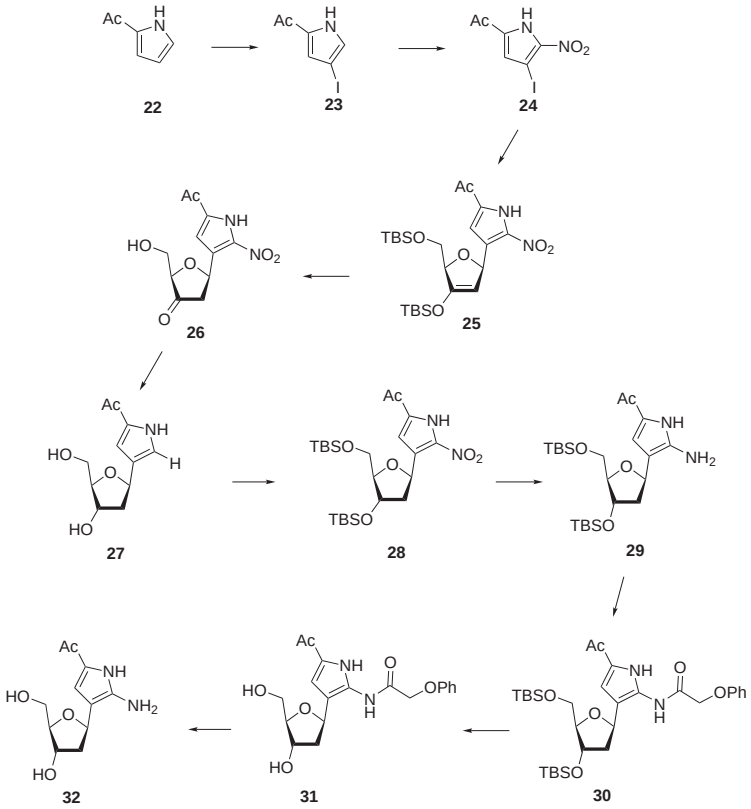


Figure 1.7: The synthesis of 5-acetyl-2-amino-1*H*-pyrrole *C*-deoxyribonucleoside

information further investigation was carried out to afford corresponding pyrroles **37** in one step. This aim was achieved by Demir et al. with the reaction of β-ketoester **36** and primary amine by using catalytic amount of $Zn(ClO_4)_2$ to obtain excellent yields (79-94%) (Figure 1.9) [32].

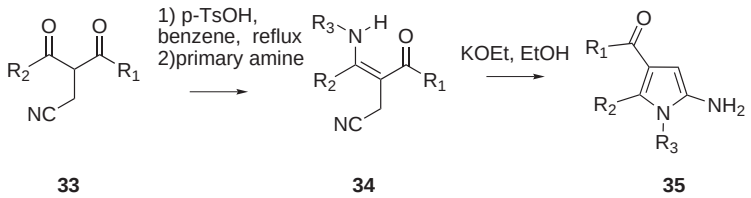


Figure 1.8: The synthesis of 2-aminopyrrole-4-carboxylate by enamine formation

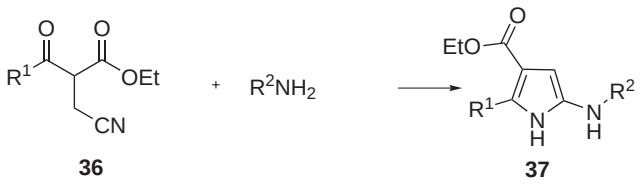


Figure 1.9: The synthesis method of 2-aminopyrrole-4-carboxylate derivatives in the presence of $Zn(ClO_4)_2$

1.3 The Importance of 2-Aminopyrrole Carboxlylates

Heterocycles with the functional groups in different positions has potential for further different structural modifications, making them useful for more complex compounds [33].

As known from researches many diseases have a relation with an abnormal gene expression and the ability to recreate transcription in a cell by small molecules could be vital in biology and human medicine [34]. A chemical approach to artificial gene regulation has been offered by minor-groove-binding polyamides, which bind predetermined DNA sequences, since aromatic five membered heterocycles have been used for DNA recognition which was reported by Marques [34]. As the result of Marques et al. research, 1-*H*-pyrrole **38** (Figure 1.10) containing polyamide showed high affinity to A·T sites and showed selectivity to G·C sites. For the synthesis of polyamides, 2-aminopyrrole carboxylates play a vital role.

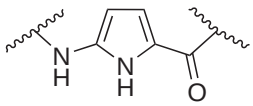


Figure 1.10: 1-*H*-pyrrole

Furthermore, **39** (Figure 1.11) derivatives were used as building blocks in a synthetic pathway to afford different *N*-bridgehead heterocycles (e.g. pyrrolotriazole and pyrrolotriazine) which are useful intermediates in drug discovery, agrochemicals, photographic materials and dyes [35].

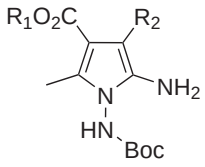


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Figure 1.11: 1-Boc-protected 1,2-diaminopyrrole derivative

In addition, 3-arylpiperazinylethyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4 (3*H*,7*H*)-dione (**40**) molecule showed high affinity for α_1- ARs in low nanomolar range and reduced development of benign prostatic hypertrophy was reported [36]. α_1- ARs regulate vascular tone and hypertropic growth of muscle and cardiac cells. The synthesis method of 3-arylpiperazinylethyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)- dione (**40**) is shown in Fig 1.12.

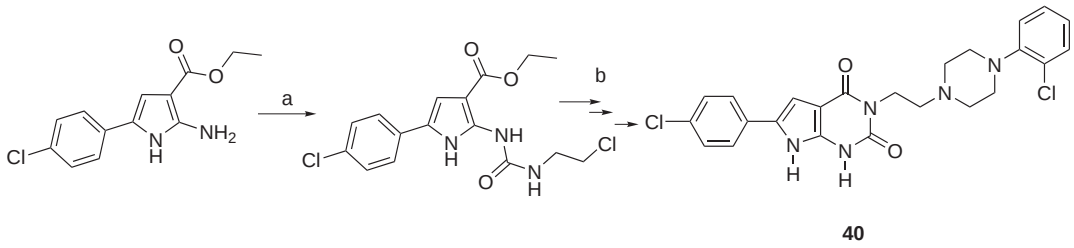

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Figure 1.12: Synthesis of **40**, (a) $ClCH_2CH_2NCO$, Toluene, reflux, (b) 1-(2-substituted phenyl)piperazine, $NaHCO_3$, NaI, THF, Reflux

Moreover, 2-aminopyrrole carboxylates are also used as anion binding receptor precursors due to the pyrrolic NH groups' good hydrogen bond donor property that are capable of interact with Lewis basic anions. Also, pyrrole functionalization as hydrogen bond acceptors (e.g. carbonyls) is easier than other structures such as amide and other functional groups [37]. The reported compound bispyrrole-2-yl-2,5 diamidopyrrole (**41**) has been used as an anion receptor [38]. Within the context of supramolecular chemistry, the anion receptor field is one of hot topics in that area due to wide range of applications in biomedical analysis and threaphy [38].

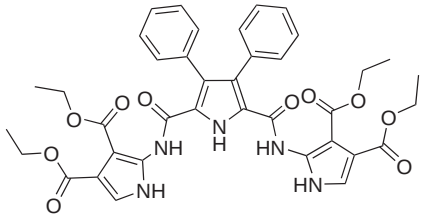

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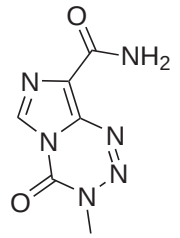
Figure 1.13: Bispyrrole-2-yl-2,5 diamidopyrrole (**41**) derivative



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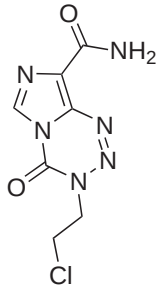
(a) Temozolomide



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(b) Mitozolomide

Figure 1.14: Imidazotetrazinone derivatives

As a consequence of great antineoplastic activity of two imidazotetrazinone derivatives, temozolomide (**42**) and mitozolomide (**43**), azolotetrazine systems aroused interest on themselves [39].

Mitozolomide showed antitumor activity on murine and xenograpth tumors [40]. However, during clinical trials, it was understood that it was too toxic [39]. The 3-methyl analogue, temozolomide, showed less potent but less toxic effect and has been used in the market under the name of Temodal [39]. Temodal shows activity aganist malignant melonoma, mycosis fungodies and brain tumors [39]. Then azolotetrazinone derivatives were reported by Diana and et al. Especially **44** in Figure 1.15 showed excellent response to inhibit breast cancer [39]. In the synthesis of azolotetrazinone **44**, 2-aminopyrrole-3-carboxylate was used as precursor shown in Figure 1.15.

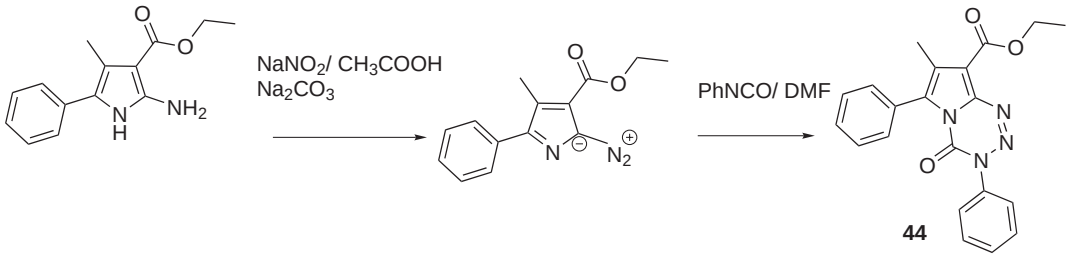


Figure 1.15: Synthesis of azolotetrazinone

Furthermore, 2-aminopyrroles-4-carboxlylate derivatives, which were synthesized by Demir et al. previously, were conformationally restricted GABA analogues 1.16 [31]. As known from literature, GABA receptor is one of two ligand-gated ion channels responsible for mediating the effects of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain [41].

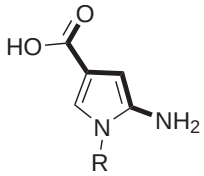


Figure 1.16: Restricted GABA analogue

As can be seen from the synthetic methods of biologically active compounds, 2-aminopyrrole carboxylates are used for the preparation of highly biologically active compounds.

1.4 Aim of the Work

The major aim of this research is to develop a simple and selective method for the syntheses of 2-aminopyrrole-3-carboxylate derivatives which are biologically important molecules since they are potential precursors of many drugs. They may show highly antineoplastic activity. Although they have great properties, only few synthesis methods exist in literature. The purpose of this work is shown retrosynthetically in Figure 1.17.

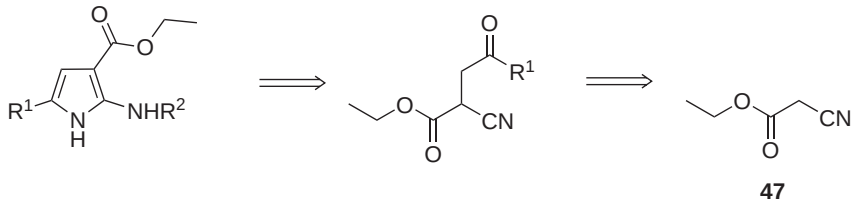


Figure 1.17: Retrosynthetic pathway of 2-aminopyrrole-3-carboxylate derivatives

Our first approach to 2-aminopyrrole-3-carboxylate derivatives was to synthesize them starting from cyanoacetic acid ethyl ester. Synthesis of 2-aminopyrrole-3-carboxylate derivatives was aimed by using alkylation of cyanoacetic acid ethyl ester, followed by $Zn(ClO_4)_2$ mediated cyclization of γ-ketoester compounds with primary amines. It was also aimed to find the optimum conditions in order to get 2-aminopyrrole-3-carboxylates in high yields.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of 2-aminopyrrole-3-carboxylates

Pyrrole core is one of the most prominent heterocycles since it is involved in crucial classes of natural products, synthetic pharmaceuticals, polypyrroles [42]. They have been proven to posses high biological activity as they exhibit antiinflammatory [43], antibacterial [44], antiviral [45] and antioxidant [46] activity.

2-Aminopyrrole-3-carboxylates are important structural motifs that are found particularly in pharmaceuticals displaying broad spectrum of biological activities ranging from antitumoral, antiviral or antibacterial activity. They constitute interesting starting materials for the syntheses of several important heterocyclic compounds such as pyrrolopyrimidine, pyrroloimidazotetrazinone, pyrrolopiperazine. So, the synthesis of 2-aminopyrrole-3-carboxylate has a great importance in literature since they are the key intermediates for more complicated structures which exhibit high biological activity.

However, until now, there are only two methods for the synthesis of 2-aminopyrrole-3-carboxylate derivatives which have been accomplished by Emilio et al. [21] and Duffy et al. [47]. The synthesis of 2-aminopyrrole-4-carboxylates has already been accomplished by Demir's group and their synthesis gave us an approach for the synthesis of 2-aminopyrrole-3-carboxylates [32].

Consequently, on this preliminary information from the previous work about the chemoselective and regioselective synthesis of 2-substituted aminopyrrole-4-carboxylate **50**, obtained as major product in the catalysis of $Zn(ClO_4)_2$ in high yields (Figure 2.1), gave us an idea to

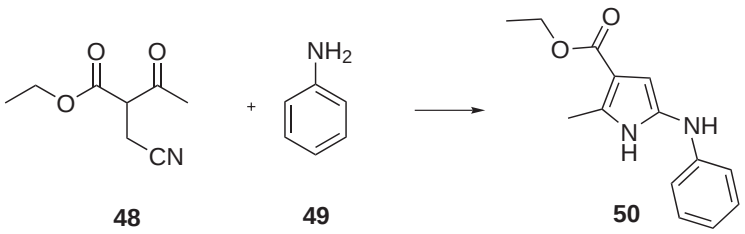


Figure 2.1: The synthesis of **50**

develop an approach for the synthesis of 2-substituted aminopyrrole-3-carboxylate **55**.

In Figure 2.2, the synthesis route of 2-aminopyrrole-3-carboxylate derivative from cyanoacetic acid ethyl ester via alkylation with α-bromoacetone which is followed by $Zn(ClO_4)_2$ mediated ring closure in the presence of 2,3-dimethyl aniline (**53**) is presented. In our reaction, 2-aminopyrrole-3-carboxylate **54** was obtained as the major product, on the other hand **55** was afforded as the minor product.

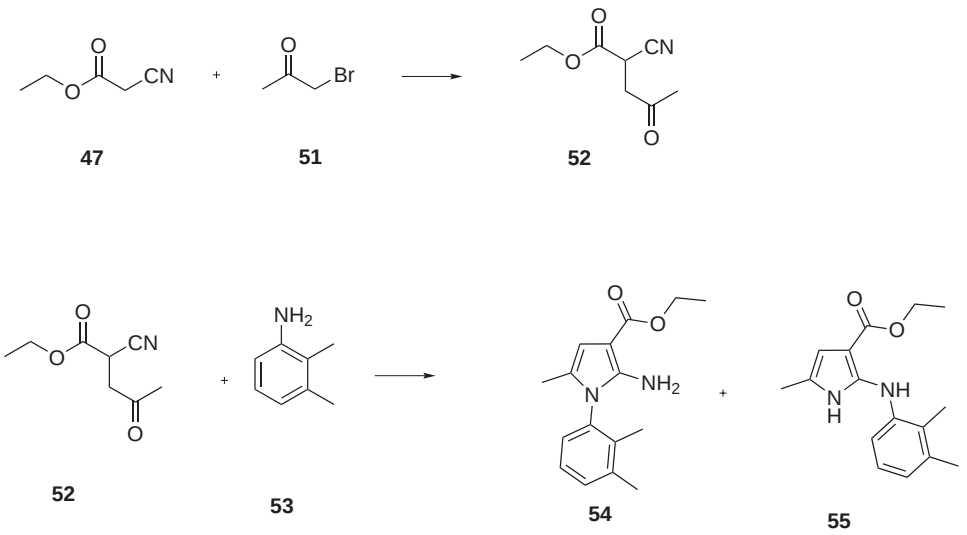
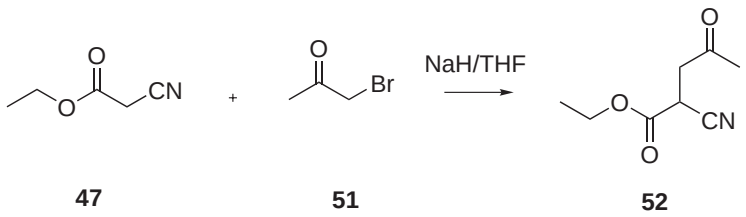


Figure 2.2: The synthesis of **54**

2.2 Alkylation of Cyanoacetic Acid Ethyl Esters

Several methods have been demostrated for the synthesis of α-alkylation of carbonyl carbon; using acid catalysts such as conc. H_2SO_4, P_2O_5, *p*-PTSA and basic reagents including NaH, DBU and K_2CO_3 [48]. Due to yields, the used reagent for the efficient synthesis of alkylated cyanoacetic acid ethyl ester was changed according to bromo acetone derivatives.



47 **51** **52**

Figure 2.3: Synthesis of γ-ketoester from cyanoacetic acid ethyl ester

Firstly, alkylation of cyanoacetic acid ethyl ester with bromoacetone was performed in the presence of NaH in THF as described in the literature (Figure 2.3) [49]. Cyanoacetic acid ethyl ester (**47**) was choosen as the starting material and it was allowed to react with bromoacetone in the presence of NaH at room temperature (25 °C) under argon atmosphere. The reaction was monitored by TLC (Silica gel, EtOAc/Hexane 1:3). After concentration of the reaction mixture, product was purified with column chromatography (Silica gel, EtOAc/Hexane 1:4). The desired product, γ-ketoester **52** was obtained as a white solid in 60 % yield. The reactions must be viewed with caution in order to prevent disubstitution on α-position of nitrile (-CN) and carbonyl group. The product of the reaction was identified by NMR spectrometry. We observed a quartet at 4.28 ppm (J= 7.2 Hz) for -CH_2 protons, a triplet at 3.92 ppm (J= 6.2 Hz) for -CH proton which was between -CN and carbonyl (-C=O) group, doublet of doublet between 3.19 and 2.96 ppm (J= 12.5 and 7.4 Hz) for -CH_2 protons which was on adjecent carbon of carbonyl group (-C=O). Furthermore, we observed a singlet at 2.18 ppm for -CH_3 protons near carbonyl group and a triplet at 1.18 ppm for -CH_3 group which is connected to -CH_2 for **52**.

On the other hand, when bromoacetophenone derivatives were used, there was an obvious decrease in yield after purification with flash column chromatography. We had difficulty in

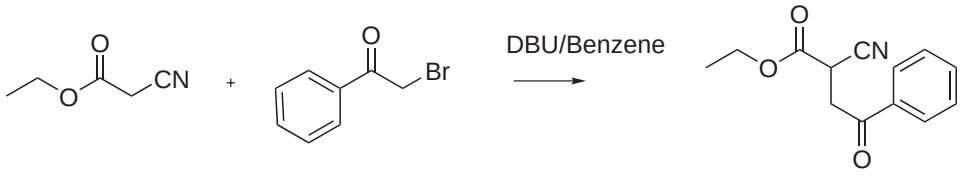


Figure 2.4: Synthesis of **57**

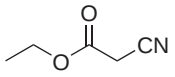
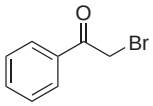
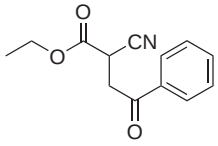
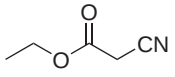
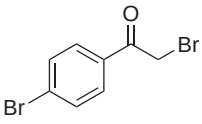
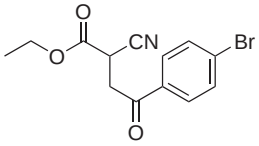
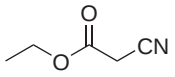
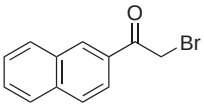
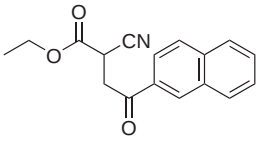
isolation step since Rf value of the desired product were close to the Rf value of cyanoacetic acid ethyl ester in all different eluent systems tested. Since, the consumption of cyanoacetic acid ethyl ester changed according to the base, for the efficient synthesis of γ-ketoesters, cyanoacetic acid ethyl ester was reacted with bromoacetophenone where DBU was used as base at room temperature in benzene under argon atmosphere according to literature [50]. The yield of the reaction was increased, this fact was proved with the yield of unreacted cyanoacetic acid ethyl ester purified via flash column chromatography. The reaction was monitored by TLC (Silica gel, EtOAc/Hexane 1:3). After concentration of the reaction mixture, product was purified with flash column chromatography (Silica gel, EtOAc/Hexane 1:6). The desired product, γ-ketoester derivative **57** was obtained as yellow solid (Figure 2.4). We additionally observed a multiplet between 7.19 and 7.98 ppm for phenyl protons in ^{1}H NMR spectra of **57**.

This reaction was used as reference and then alkylation reaction gave corresponding γ-ketoesters **59** and **61** at room temperature under argon in the pesence of DBU. The results were summarized in Table 2.1. The reactions must be handled carefully in order to prevent disubstitution on the carbon between nitrile (-CN) and carbonyl group (-C=O). The products of the reactions were identified by NMR spectroscopy.

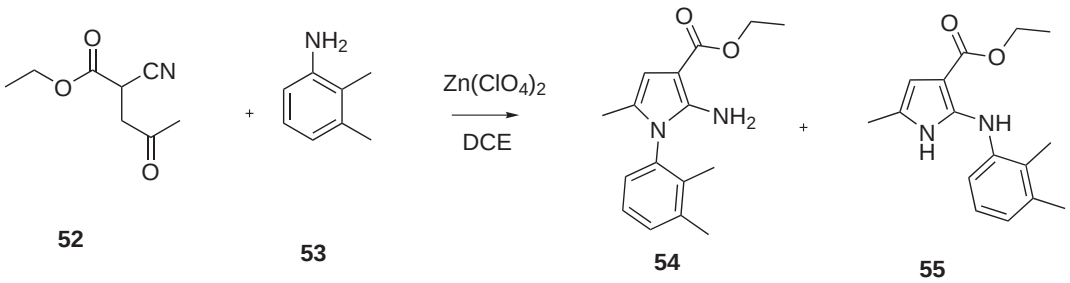
2.3 Zincperchlorate Mediated Reactions

Base catalyzed and acid catalyzed cyclizations to form pyrrole derivatives have been reported previously [31], [42]. Zinc perchlorates are known as strong Lewis acid and effective electrophilic activation catalysts for acylation [53], imine formation [54], thia-Micheal addition [55], acylal formation [56], esterification [57] and epoxide openning [58] reactions. To es-

Table 2.1: DBU catalyzed alkylation of cyanoacetic acid ethyl ester

Cynaoacetic acid ethyl ester	Substrate	γ-ketoester
 **47**	 **56**	 **57**
 **47**	 **58**	 **59**
 **47**	 **60**	 **61**

tablish generality of our previous work and by knowing importance of 2-aminopyrrole-3-carboxylate derivatives, we used $Zn(ClO_4)_2{\cdot}6H_2O$ as a catalyst which is known to be effective in many reactions besides being non-toxic, cheap, stable to air as well as moisture. Moreover, $Zn(ClO_4)_2{\cdot}6H_2O$ activates carbonyl group and nitrile group. For the formation of product, pK_a value of amine, steric and electronic factors play important roles.



52 **53** **54** **55**

Figure 2.5: $Zn(ClO_4)_2{\cdot}6H_2O$ mediated cyclization of γ-ketoester

For cyclization reaction, synthesized **52** was allowed to react with dimethyl aniline (**53**) in the presence of catalytic amount of $Zn(ClO_4)_2{\cdot}6H_2O$ in DCE at reflux to give desired aminopyrrole deriatives in 4 hours (Figure 2.5). The reaction was monitored by TLC (Silica gel,

EtOAc/Hexane 1:3). **54** and **55** were obtained as a major and minor product, respectively after purification with column chromatography (EtOAc/Hexane 1:4). The structural analysis was carried out by NMR spectroscopy. From the ^{1}H-NMR specturum of **54** which was white solid, we observed multiplet at 7.01-7.24 ppm for protons in 2,3-dimethylphenyl group, singlet at 6.06 ppm for aromatic proton that is the 4^{th} position on pyrrole ring, broad singlet at 4.64 ppm for -NH_2 protons, a quartet at 4.24 ppm (J=7.1 Hz) for -CH_2 protons. Beside, singlets at 2.35, 1.92 and 1.81 ppm for -CH_3 protons in pyrrole ring and in 2,3-dimethylphenyl group, and a triplet at 1.33 ppm for -CH_3 protons which was attached to -OCH_2- group were the evidences of **54**.

This reaction was used as a reference and the same reaction conditions were applied to other primary amine derivatives starting from ethyl 2-cyano-4-oxopentanoate (**52**) to obtain the corresponding 2-aminopyrrole-3-carboxylate derivatives. The reaction was monitored by TLC (Silica gel, EtOAc/Hexane 1:3). Purification was done with column chromatography (EtOAc/Hexane 1:4). The structural analysis were carried out by NMR spectroscopy. Different than **54** and **55**, -CH_3 protons at 1.92 and 1.81 ppm which belong to dimethyl aniline were not observed. Major and minor products and yields are given in Table 2.2. As can be seen from Table 2.2 , major products and minor products yields were between 41%-62% and 15%-35% respectively.

The importance of aryl functionality on pyrrole ring was reported since it increases the binding affinity which results in higher biological activity in molecule. To this end, we applied the same procedure to **57** in order to increase aryl functionality on pyrrole ring and to synthesize new, potentially highly biologically active 2-aminopyrrole-3-carboxylate derivative. For this purpose, **57** was allowed to react with **73** in presence of $Zn(ClO_4)_2{\cdot}6H_2O$ in DCE at reflux for 32 h. The reaction was monitored by TLC (Silica gel, EtOAc/Hexane 1:5). As a result, **75** was afforded as the only product in 20% yield after purification with column chromatography (EtOAc/Hexane 1:6). The structural analysis were carried out by NMR. Different than **54**, we observed integration increase in the aromatic region of ^{1}H-NMR specturum, because of increase in number of aryl group functionality on pyrrole ring. Additionally, we did not observe peaks due to -CH_3 protons on **53**. However, we observed a singlet at 4.90 ppm for -CH_2 protons of benzyl amine.

This reaction was used as reference and $Zn(ClO_4)_2$ catalyzed pyrrole formation when **57**, **59**

Table 2.2: $Zn(ClO_4)_2$ mediated pyrrole formation

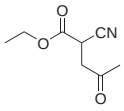
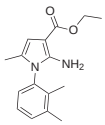
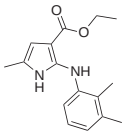
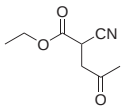
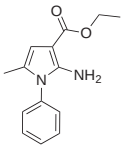
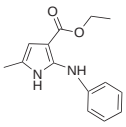
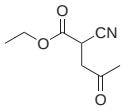
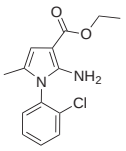
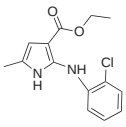
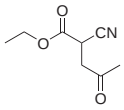
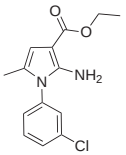
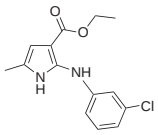
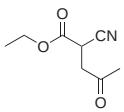
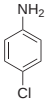
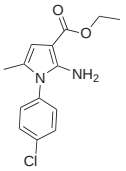
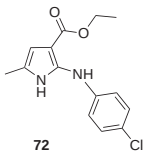
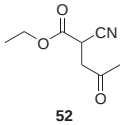
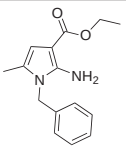
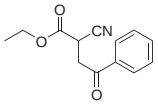
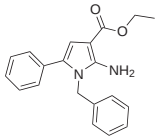
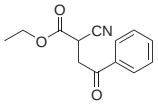
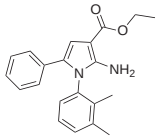
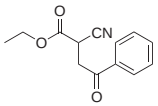
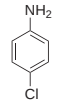
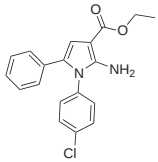
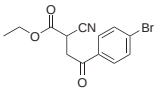
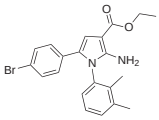
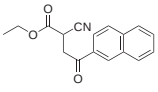
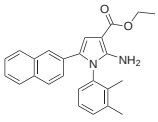
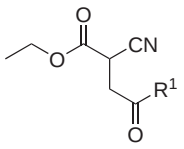
Entry	γ-keto ester	Amine	Major product	Yield (%)	Minor product	Yield(%)
1	 **52**	 **53**	 **54**	53%	 **55**	25%
2	 **52**	 **49**	 **62**	45%	 **63**	35%
3	 **52**	 **64**	 **65**	54%	 **66**	15%
4	 **52**	 **67**	 **68**	53%	 **69**	20%
5	 **52**	 **70**	 **71**	41%	 **72**	20%
6	 **52**	 **73**	 **74**	62%	-	-

Table 2.3: $Zn(ClO_4)_2$ mediated pyrrole formation when cyanoacetic acid was alkylated with bromo acetophenone derivatives

Entry	γ-keto ester	Amine	Major product	Yield (%)
1	 57	 73	 75	20%
2	 57	 53	 77	21%
3	 57	 70	 76	26%
4	 59	 53	 78	15%
5	 61	 53	 79	15%

and **61** was used as starting material were summarized in Table 2.3. **75**, **76**, **77**, **78** and **79** were obtained as the sole products after purification with column chromatography (EtOAc/Hexane 1:6). The structural analysis were carried out by NMR spectroscopy. The reaction yields were between 15% - 26%.



R^1 = -CH_3 **52** R^1 = -C_6H_5Br **59**

R^1 = -C_6H_5 **57** R^1 = -$C_{10}H_7$ **61**

Figure 2.6: γ-ketoesters

We observed differences during purification of the reaction products when we used aromatic and aliphatic amines. Although purification of the reactions by aromatic amines with flash column chromatography was facile, it was very problematic with aliphatic amines. As a consequence of the sensibility of reaction of **52** with **73**, we could not obtain the pure NMR spectrum of the minor product of reaction which was given in Table 2.2, entry 6. To increase the number of samples with aliphatic amine in addition to reaction of **73**, we also allowed phenyl ethyl amine to react with **52** under same conditions, however, we could not seperate major and minor products from each other with column chromatography.

In addition, although reaction conditions are the same except the starting materials and reflux temperature, the obvious differences in reaction rates, yields and obtained products can be seen from Table 2.2 and 2.3, when R^1 was alkyl group **52** and aromatic group **57**, **59**, **61** respectively (Table 2.3). The reaction time increased from 4 hours to 32 hours when **57**, **59**, **61** were used as starting materials. Beside, 2-aminopyrrole-3-carboxylate was obtained as a sole product and reaction yield decreased from 41-62% to 15- 26% when we started from one of the compounds; **57**, **59**, **61**.

To synthesize 2-aminopyrrole-3-carboxylate, we exploited our preliminary work which was reported by Demir et al. in 2006 can be seen in Figure 2.1 [32]. According to this work, 2-substituted aminopyrrole-4-carboxylate **50** was obtained as a major product in 91% yield regioselectively and chemoselectively. $Zn(ClO_4)_2$ is a strong Lewis acid and it is known that when $Zn(ClO_4)_2$ coordinates to the compound, it increases the electrophilicity of that atom.

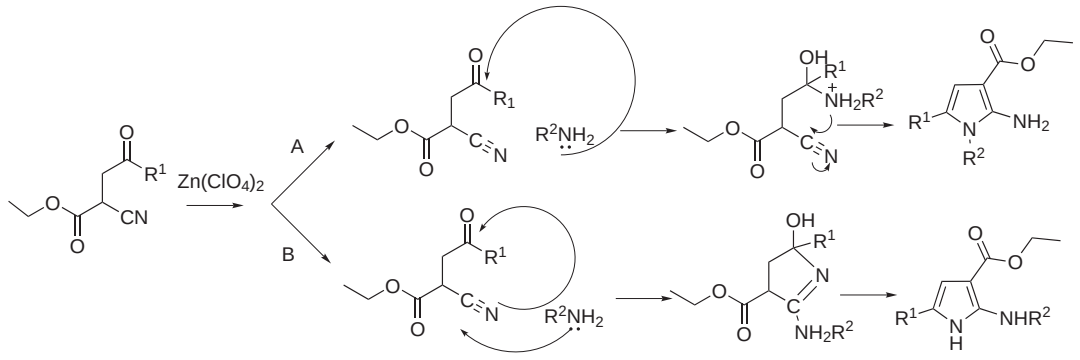
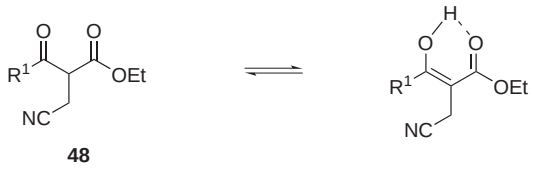


Figure 2.7: Reaction Mechanism

Thus, it polarizes both nitrile (-CN) and carbonyl group (-C=O) and carbonyl group reactivity is higher than the nitrile (-CN) group. As a result, one can expect to obtain 2-aminopyrrole-4-carboxylate as a major product, however, **48** forms a very stable enolate which diminish the reactivity of the carbonyl carbon(Figure 2.8). Thus, **50** is formed as a result of the attack of amine from the nitrile group regioselectively and chemoselectively (Figure 2.1). In complementary, since carbonyl carbon reactivity is higher than nitrile carbon, we expected to get 2-aminopyrrole-3-carboxylate as the major product and the N-substituted one as the minor product. As shown in Figure 2.7, major and minor products were formed according to proposed mechanism when R^1 was methyl.



48

Figure 2.8: Stable enolate formation

On the other hand, when R^1 was bulky, aromatic group, corresponding 2-aminopyrrole-3-carboxylate derivatives were obtained as a sole/major product in 15%- 26% yield (Figure 4.1). The reason for this difference can be explained by the role of $Zn(ClO_4)_2 \cdot 6H_2O$. The efficiency of method depends on oxophilicity of Zn cation which forms strong coordination bond with carbonyl oxygen and pK_a value of amine. $Zn(ClO_4)_2$ coordinates to carbonyl oxygen, primary amine and nitrile group and "2+" charge of complex is balanced by two perchlorate counter

anion. When R^1 was aromatic, activation of nitrile group became difficult because carbonyl carbon exhibited better electrophilic property. Steric hinderence and electronic factors also affected the yields.

For detailed examination, the role of $Zn(ClO_4)_2$ in catalyzing the cyclization reaction is depicted in Figure 2.9. The coordination of Zn^{2+} cation to cyanoacetic acid ethyl ester derivative generates the transition state **I**. The complexation via the oxygen atom increases the electrophilicity of carbonyl carbon. The nucleophilic attack by the lone pair of nitrogen atom of amine at the carbonyl carbon forms transition state **II**. An intramolecular proton shift takes place via transition state **III** as oxyanionic site forms hydrogen bond with one of the hydrogen atoms of the amine ($ArNH_2^+$) moiety. Hydrolysis of water molecule afforded in transition state **IV**. In transiton state **V**, an intramolecular attack by the lone pair of nitrogen atom to carbon of nitrile group (-CN) forms. An intramolecular proton shift takes place via transition state **VI** as anionic site of nitrogen atom at nitrile group forms hydrogen bond with the hydrogen atom of amine. After that $Zn(ClO_4)_2$ releases and by tautemerism 2-aminopyrrole-3-carboxylate is afforded as a major product. It was reported that the oxophilicity of the central metal cation is decreased by water molecules in metal perchlorate hydrates and in case of $Mg(ClO_4)_2$'s anhydrous form, the catalytic efficiency is diminished [59].

Because of the differences in chemical properties of substances, different reflux temperatures were also tried with the substrates **52** (reflux temperature 100 °C) and **57**, **59**, **61** (reflux temperature 150 °C). In addition, due to weaker acidic property of aliphatic amines, amino group could not generate proton transfer from itself to carbonyl oxygen in transition state **III**, thus require higher temperature (20 °C more) for reactions to take place.

To overcome the encountered problem in yields, firstly reaction temperature was increased which also caused an increase in the number of undefined side products. Additionally, using electron deficient γ-keto ester starting from cyanoacetic acid ethyl ester and 4-nitro bromo acetophenone were expected to increase the yields, however, we could not obtained corresponding γ-keto ester in sufficient yield.

Moreover, in the reactions, while R^1 was aromatic and the amines were aliphatic, we observed high amount (25%) of amino furan **80** which is found in many biologically active natural and synthetic compounds (Figure 2.10). To increase the yield of 2-aminopyrrole-3-carboxylate in

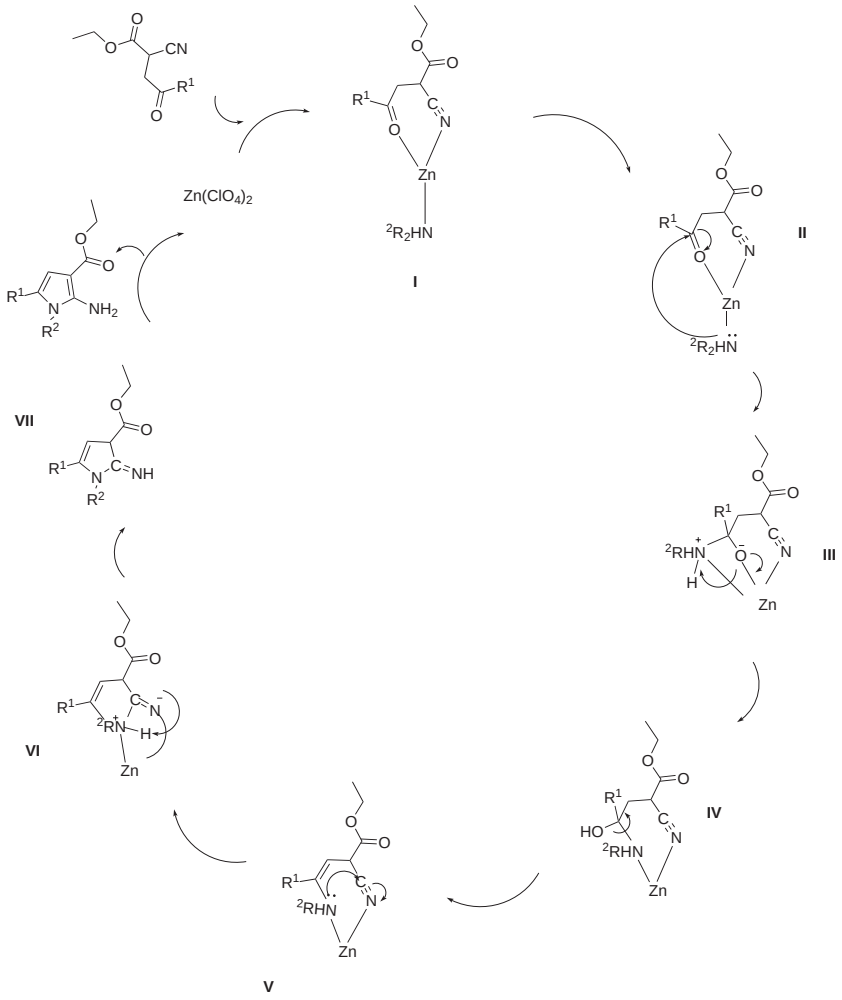


Figure 2.9: The role of $Zn(ClO_4)_2$ in the formation of 2-aminopyrrole

these reactions, we used 1 equivalent (eq.) of γ-ketoester **57**, 3 eq. of benzyl amine instead of 1.2 eq. however the yield of aminofuran and number of undefined side products increased again. Amino furan was obtained after column chromatography (EtOAc/Hexane 1:4). For the reaction of **59** with **73** in the presence of $Zn(ClO_4)_2$ at reflux we obtained ethyl 2-amino-5-(4-bromophenyl)furan-3-carboxylate (Figure 2.10 when R^1 was 4-bromophenyl). The reaction was monitored by TLC (Silica gel, EtOAc/Hexane 1:3). The structural analysis were carried out by NMR spectroscopy. In ^{1}H-NMR spectroscopy, doublet of doublet was observed for 4-bromophenyl protons between 7.36 - 7.24 ppm (J= 29.6 and 8.5 Hz), a singlet at 6.63 ppm for olefinic proton on furan ring, a singlet at 5.49 ppm for -NH_2 protons, a quartet at 4.2 ppm (J= 7.2 Hz) for CH_2 protons of ethoxy group, and a triplet at 1.27 ppm (J= 7.2 Hz) for CH_3 protons for the **80**.

Formation of the aminofuran derivative can be explained by the intramolecular nucleophilic attack of carbonyl oxygen to nitrile group since aliphatic amines are stronger bases than aromatic ones therefore they form a stronger complex with $Zn(ClO_4)_2$ that makes them sterically hindered and resulted in prevention of the intermolecular reaction when R^1 was aromatic (Figure 2.10).

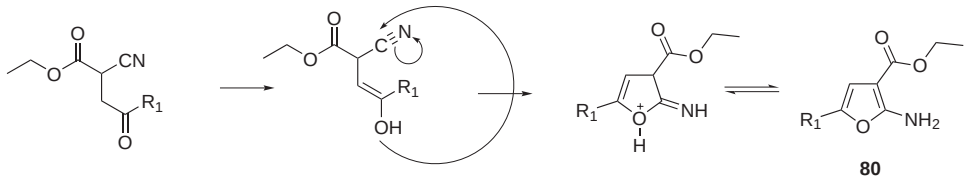


Figure 2.10: Formation mechanism of aminofuran

To find the most effective catalyst to obtain 2-aminopyrrole-3-carboxylate in higher yield, **57** was treated with **53** in the presence of catalytic quantities of various catalysts. Firstly, PTSA was added in catalytic amount in DCE at reflux. However, an increase in the yields was not observed. On the other hand, reaction time shortened by 50% (15-16 h). Furthermore, triflate salts ($Cu(OTf)_3$, $Sc(OTf)_3$, $Zn(OTf)_3$, $Co(OTf)_3$) were tried instead of $Zn(ClO_4)_2$ to increase yield since they are stronger Lewis acids than $Zn(ClO_4)_2$. **57** and **53** were reacted in the presence of catalytic amount of $Cu(OTf)_3$, $Sc(OTf)_3$, $Zn(OTf)_3$, $Co(OTf)_3$ under argon in acetonitrile and in dichoromethane (DCM) at reflux. However, we did not observe any conversion to product in the presence of catalytic amount of $Cu(OTf)_3$, $Sc(OTf)_3$, $Zn(OTf)_3$ after 28h. Although, after 30 min. in the presence of $Co(OTf)_3$,some product formation was observed, when reaction time was extended up to 32 hours pyrrole formation was not observed after column chromatography (EtOAc/Hexane 1:10). Moreover, K_2CO_3 was tried as a catalyst for the same reaction, neverthless, 1,2,3,4-substituted amino furan was obtained after column chromatography (EtOAc/Hexane 1:4). The structural analysis were carried out by NMR spectroscopy.

CHAPTER 3

EXPERIMENTAL

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ were reported in ppm relative to $CHCl_3$ (^{1}H: δ=7.27), $CDCl_3$ (^{13}C: δ=77.0) and CCl_4 (^{13}C: δ=96.4) as internal standards. IR spectra were recorded on a Perkin Elmer 1600 FTIR series instrument.

Column chromatography was conducted on silica gel 60 (40-63 μm). TLC was carried out on aluminum sheets precoated with silica gel 60 F_{254} (Merck), and the spots were visualized with UV light (l=254 nm and l=366 nm).

3.1 General Procedure for Alkylation of Cyanoacetic Acid Ethyl Ester

a. Cyanoacetic acid ethyl ester (2.5 mmol) was dissolved in THF (100 ml). NaH (3 mmol) was added slowly to the stirring mixture at 0 °C. The reaction was stirred at room temperature for 30 min. then α-bromoacetone (3 mmol) was added and continued stirring. Reaction was monitored by TLC (Silica gel, EtOAc/Hex 1:3). The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure and the crude pruduct was purified by flash column chromotography (EtOAc/Hexane 1:4).

b. Cyanoacetic acid ethyl ester (2.5 mmol) was dissolved in THF (100 ml). DBU (3 mmol) was added slowly to the stirring mixture at 0 °C. The reaction was stirred at room temperature for 30 min. then α-bromoacetophenone (3 mmol) was added and continued stirring. Reaction was monitored by TLC (Silica gel, EtOAc/Hexane 1:3). The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated

under reduced pressure and the crude pruduct was purified by flash column chromotography (EtOAc/Hexane 1:4).

3.1.1 Ethyl 2-cyano-4-oxopentanoate (52)

White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (3H, t, J=7.1 Hz), 2.18 (3H, s), 2.96-3.19 (2H, dd,J= 12.5 and 7.4 Hz), 3.92 (1H, t, J=7.1 Hz), 4.28 (2H,J= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 13.90, 29.29, 31.43, 41.97, 63.04, 96.13, 115.84, 165.13, 201.98.

3.1.2 Ethyl 2-cyano-4-oxo-4-phenylbutanoate (57)

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ; 1.18 (3H, t, J=7.1 Hz), 3,71 - 3.35 (2H, dd, J= 12.5 and 5.4 Hz), 4.08(1H, t, J= 7.2 Hz), 4.23 (2H, q, J= 7.2 Hz) ,7.19-7.98 (5H,m)^{13}C NMR (100 MHz, $CDCl_3$): 13.97, 31.71, 38.02, 63.09, 96.16, 116.16, 128.18, 128.82, 133.92, 135.41, 165.24, 193.70.

3.1.3 Ethyl 4-(4-bromophenyl)-2-cyano-4-oxobutanoate (59)

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (3H, t, J= 7.2 Hz), 3.76-3.41 (2H, dd, J= 10.6 and 7.2 Hz),4.12 (1H, t, J= 7.2 Hz), 4.31 (2H, q, J= 3.8 and 3.5 Hz), 7.83-7.63 (4H, dd, J= 64.2 and 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 13.96, 31.67, 37.96, 63.18, 96.15, 115.84, 129.61, 129.40, 132.21, 134.11, 165.11, 192.87.

3.1.4 Ethyl 2-cyano-4-(naphthalen-2-yl)-4-oxobutanoate (61)

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 ppm (3H, t, J= 7.1 Hz), 3.82-3.50 ppm (2H, dd, J= 10.5 and 7.1 Hz),4.12 ppm (1H, t, J= 7.1 Hz), 4.25 (2H, q, J= 7.1 Hz), 8.34-7.42 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 13.97, 14.24, 20.87, 31.81, 38.04, 60.12, 62.98, 96.16, 116.09, 123.51, 126.97, 127.81, 128.68, 128.84, 129.62, 130.10, 132.41, 132.74, 135.92, 165.29, 170.43, 193.63.

3.2 General Procedure for The Synthesis of Pyrroles

a. γ-Ketoester (1 mmol) was dissolved in DCE (5 ml). Corresponding amine (1.2 mmol) together with catalytic amount of $Zn(ClO_4)_2$ (5 mol%) was added to the stirring mixture and refluxed for 4 h. Reaction was monitored by TLC (Silica gel, EtOAc/Hex 1:3). The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure and the crude pruduct was purified by column chromotography (EtOAc/Hexane 1:4)).

b. γ-Ketoester (1 mmol) was dissolved in DCE (5 ml). Corresponding amine (1.2 mmol) together with catalytic amount of $Zn(ClO_4)_2$ (5 mol%) was added to the stirring mixture and refluxed for 32 h. Reaction was monitored by TLC (Silica gel, EtOAc/Hex 1:5). The reaction mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure and the crude pruduct was purified by column chromotography (EtOAc/Hexane 1:6)).

3.2.1 Ethyl 2-amino-5-methyl-1-(2,3-dimethylphenyl)-1*H*-pyrrole-3-carboxylate (54)

Yield: (54 mg, 53%), white solid (mp=89.2 ∘C), IR ($CHCl_3$): 3498, 3356, 2985, 1654, 1548 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (3H, t, J=7.1 Hz), 1.81 (3H, s), 1.92 (3H, s), 2.35 (3H, s), 4.24 (2H, q, J=7.1 Hz), 4.64 (2H, br.s, NH_2), 6.06 (1H, s), 7.01-7.24 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 12.11, 13.79, 14.79, 20.31, 58.63, 92.20, 103.77, 121.84, 125.28, 126.56, 128.97, 130.78, 136.09, 138.80, 145.46, 166.02. Anal. Calcd for $C_{16}H_20N_2O_2$ (272.2): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.52; H, 7.38; N,10.22.

3.2.2 Ethyl 2-(2,3-dimethylphenylamino) -5-methyl-1*H*-pyrrole-3-carboxylate (55)

Yield: (26 mg, 25%), pink oil, IR ($CHCl_3$): 3396, 3275, 2962, 1621, 1599 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (3H, t, J=7.1 Hz), 2.14 (3H, s), 2.22 (3H,s), 2.31 (3H, s), 4.24 (2H, q, J=7.1 Hz), 5.95 (1H, s), 6.89-7.11 (3H, m), 7.53 (1H, br.s), 7.97 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): 13.00, 13.62, 14.78, 20.76, 58.87, 93.61, 104.14, 117.62, 119.11, 125.53, 128.74, 138.48, 138.74, 143.29, 166.207. Anal. Calcd for $C1_6H_2N_2O_2$ (272.2): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.49; H, 7.36; N,10.20.

3.2.3 Ethyl 2-amino-5-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate (62)

Yield: (61 mg, 45%), brown oil, IR ($CHCl_3$): 3396, 3304, 2967, 1698, 1551 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (3H, t, J=7.1 Hz), 1.92 (3H, s), 4.25 (2H, q, J= 7.1 Hz), 4.79 (2H, bs, NH_2), 6.06 (1H, s), 7.10-7.51 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 12.49, 14.79, 58.71, 92.45, 104.38, 121.98, 128.15, 128.68, 129.82, 135.83, 146.35, 165.98. Anal. Calcd for $C1_4H_{16}N_2O_2$ (244.3): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.80; H, 6.53; N, 11.39.

3.2.4 Ethyl 5-methyl-2-(phenylamino)-1*H*-pyrrole-3-carboxylate (63)

Yield: (49 mg, 3%), brown oil, IR ($CHCl_3$): 3387, 3022, 2894, 1681, 1595 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (3H, t, J=7.1 Hz), 2.09 (3H, s), 4.16 (2H, q, J=7.1 Hz), 5.90 (1H, s), 6.89-7.24 (5H, m), 7.86 (1H, br s, NH), 8.03(1H, br s , NH); ^{13}C NMR (100 MHz, $CDCl_3$): 12.95, 14.69, 58.92, 94.99, 104.42, 118.62, 119.51, 122.47, 129.84, 140.97, 141.56, 166.02. Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.3): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.79; H, 6.55; N, 11.37.

3.2.5 Ethyl 2-amino-1-(2-chlorophenyl)-5-methyl-1*H*-pyrrole-3-carboxylate (65)

Yield: (150 mg, 54%), orange oil, IR ($CHCl_3$): 3318, 2925, 1697, 1592, 1453 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, t, J= 7.1 Hz), 1.83 (3H, s), 4.19 (2H, q, J=7.1 Hz), 4.63 (2H, br s, NH_2), 6.06 (1H, s), 7.19-7.53 (4H,m); ^{13}C NMR (100 MHz, $CDCl_3$): 11.97, 14.70, 58.93, 92.92, 96.12, 104.11, 122.46, 128.19, 130.82, 130.86, 133.47, 134.08, 145.42, 166.12. Anal. Calcd for $C_{14}H_{15}ClN_2O_2$ (278.08): C, 60.33; H, 5.42; N, 10.05. Found: C, 60.29; H, 5.40; N, 10.01.

3.2.6 Ethyl 2-(2-chlorophenylamino)-5-methyl-1*H*-pyrrole-3-carboxylate (66)

Yield: (42 mg, 15%), pink solid (mp= 82 ∘C), IR ($CHCl_3$): 3346, 2998, 2465, 1698, 1583 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, t, J= 7.1 Hz), 2.11 (3H, s), 4.12 (2H, q, J=7.1 Hz), 5.93 (1H, s), 6.72-7.27 (4H, m), 8.06 (1H, br s, NH), 8.23 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): 12.95, 14.59, 59.18, 98.14, 105.15, 115.49, 120.83, 121.57, 122.75, 127.71,

130.14, 138.27, 138.66, 165.54. Calcd for $C_{14}H_{15}ClN_2O_2$ (278.08): C, 60.33; H, 5.42; N, 10.05. Found: C, 60.30; H, 5.39; N, 10.02.

3.2.7 Ethyl 2-amino-1-(3-chlorophenyl)-5-methyl-1*H*-pyrrole-3-carboxylate (68)

Yield: (148 mg, 53%), orange oil, IR ($CHCl_3$): 3320, 2924, 1696, 1591, 1450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (3H, t, J= 7.1 Hz), 1.88 (3H, s), 4.16 (2H, q, J=7.1 Hz), 4.73 (2H, br s, NH_2), 5.98 (1H, s), 7.12-7.40 (4H,m); ^{13}C NMR (100 MHz, $CDCl_3$): 12.51, 14.77, 58.74, 92.86, 96.16, 105.01, 121.55, 126.30, 128.49, 128.94, 130.66, 135.55, 137.14, 145.26, 165.78. Anal. Calcd for $C_{14}H_{15}ClN_2O_2$ (278.08): C, 60.33; H, 5.42; N, 10.05. Found: C, 60.32; H, 5.41; N, 10.03.

3.2.8 Ethyl 2-(3-chlorophenylamino)-5-methyl-1*H*-pyrrole-3-carboxylate (69)

Yield: (33 mg, 20%), pink oil, IR ($CHCl_3$): 3486, 3453, 2998, 2468, 1695, 1587 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (3H, t, J=7.1 Hz), 2.19 (3H, s), 4.22 (2H, q, J=7.1 Hz), 5.97 (1H, s), 6.89-7.25 (4H, m), 7.91 (1H, br s, NH), 8.08 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): 12.91, 14.53, 59.07, 96.56, 104.75, 115.87, 117.52, 120.16, 121.96, 130.69, 135.58, 139.86, 142.64, 165.89. Calcd for $C_{14}H_{15}ClN_2O_2$ (278.08): C, 60.33; H, 5.42; N, 10.05. Found: C, 60.29; H, 5.38; N, 10.01.

3.2.9 Ethyl 2-amino-1-(4-chlorophenyl)-5-methyl-1*H*-pyrrole-3-carboxylate (71)

Yield: (31 mg, 41%), brown solid (mp=87.4 °C), IR ($CHCl_3$): 3419, 3302, 2980, 2359, 1651, 1539 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (3H, t, J=7.1 Hz), 1.85 (3H, s), 4.19 (4H, q, J=7.1 Hz), 4.72 (2H, br s, NH), 6.03 (1H, s), 7.19-7.43 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 12.41, 14.70, 58.93, 92.71, 104.48, 122.20, 129.44, 130.16, 134.18, 134.82, 145.40, 166.05. Calcd for $C1_4H_{15}ClN_2O_2$ (278.08): C, 60.33; H, 5.42; N, 10.05. Found: C, 60.31; H, 5.41; N, 10.04.

3.2.10 Ethyl 2-(4-chlorophenylamino)-5-methyl-1*H*-pyrrole-3-carboxylate (72)

Yield: (14 mg, 20%), brown solid(mp= 71.7 °C), IR ($CHCl_3$): 3373, 2979, 2338, 1660, 1597 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, J= 7.1 Hz), 2.06 (3H, s), 4.11 (2H, q. J=7.1 Hz), 5.91 (1H, s), 6.82-7.12 (4H, m), 7.84 (1H, br s, NH), 8.07 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$):12.87, 14.58, 59.24, 95.99, 104.40, 119.41, 120.68, 127.12, 129.73, 139.82, 140.62, 166.24. Calcd for $C1_4H_{15}ClN_2O_2$ (278.08): C, 60.33; H, 5.42; N, 10.05. Found: C, 60.32; H, 5.40; N, 10.03.

3.2.11 Ethyl 2-amino-1-benzyl-5-methyl-1*H*-pyrrole-3-carboxylate (74)

Yield: (46 mg, 60.2%), brown oil, IR ($CHCl_3$): 3426, 3324, 2978, 1648, 1531 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (3H, t, J=7.1 Hz), 2.11 (3H, s), 4.16 (2H, q, J=7.1 Hz), 4.63 (2H, br s, NH_2), 4.90 (2H, s), 6.02 (1H, s), 7.33-7.02 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 11.89, 14.64, 45.29, 58.52, 93.98, 104.12, 121.41, 125.69, 127.58, 128.98, 136.41, 144.96, 165.81. Anal. Calcd for $C1_5H_{18}N_2O_2$ (258.14): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.38; H, 6.98; N, 10.06.

3.2.12 Ethyl 2-amino-1-benzyl-5-phenyl-1*H*-pyrrole-3-carboxylate (75)

Yield: (28 mg, 20%), brown oil, IR: 3348, 3175, 2983, 2948, 2265, 1972, 1768, 1696, 1598 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (3H, t, J=7.1 Hz), 4.20 (2H, q, J=7.1 Hz), 4.70 (1H, br s, NH_2), 4.95 (2H, s), 6.36 (1H, s), 7.05-7.52 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 13.67, 45.76, 57.84, 94.24, 105.66, 121.50, 125.78, 126.53, 126.98, 127.24, 127.65, 128.19, 135.59, 131.48, 145.66, 166.05 . Anal. Calcd for $C_20H_20N_2O_2$ (320.15): C, 74.98; H, 6.29; N, 8.74. Found: C, 74.95; H, 6.23; N, 8.69.

3.2.13 Ethyl 2-amino-1-(4-chlorophenyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (76)

Yield: (31 mg, 21%), brown oil, IR ($CHCl_3$): 3375, 3190, 2973, 2921, 2879, 2275, 1898, 1750, 1678, 1575 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (3H, t, J=7.1 Hz), 4.22 (2H, q, J=7.1 Hz), 4.96 (2H, br s, NH_2), 6.48 (1H, s), 6.91-7.40 (9H, m) ; ^{13}C NMR (100 MHz, $CDCl_3$): 14.74, 59.08, 107.82, 114.06, 122.77, 126.087, 127.28, 128.18, 129.19, 130.01,

132.02, 134.36, 134.90, 146.36, 166.01. Anal. Calcd for $C_{19}H_{17}ClN_2O_2$ (340.8): C,66.96; H, 5.03; N, 8.22. Found: C,66.92; H, 5.01; N, 8.19.

3.2.14 Ethyl 2-amino-1-(2,3-dimethylphenyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (77)

Yield: (11 mg, 26%), brown oil, IR (neat): 3523, 3472, 3347, 2687, 2231, 2521, 2342, 1749, 1699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (3H, t, J=7.1 Hz), 1.87 (3H, s), 2.28 (3H, s), 4.27 (2H, q, J=7.1), 4.85 (2H, br s, NH2), 6.58 (1H, s), 6.98-7.27 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 14.00, 14.79, 20.34, 58.95, 93.81, 106.62, 125.72, 126.33, 126.56, 126.72, 127.51, 128.04, 130.72, 132.58, 135.25, 135.88 138.95, 146.97, 166.01. Anal. Calcd for $C_{21}H_{22}N_2O_2$ (334,17): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.32; H, 6.61; N, 8.33.

3.2.15 Ethyl 2-(2,3-dimethylphenylamino)-5-(4-bromophenyl)-1*H*-pyrrole-3-carboxylate (78)

Yield: (14 mg, 15%), brown oil, IR ($CHCl_3$): 3413, 3117, 3053, 2983, 2890, 2603, 2289, 1756, 1694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (3H, t, J=7.1 Hz), 1.79 (3H, s), 2.09 (3H, s), 4.21 (2H, q, J=7.1 Hz), 4.80 (1H,br s, NH_2), 6.51 (1H, s), 6.68-7.38 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 13.95, 14.76, 20.34, 20.46, 59.02, 93.43, 107.14, 113.53, 119.52, 123.97, 126.19, 127.56, 130.94, 131.74, 134.99, 135.86, 139.18, 147.16, 166.03. Anal. Calcd for $C_{21}H_{21}BrN_2O_2$ (413.08): C, 61.03; H, 5.12; N, 6.78. Found: C, 60.59; H, 5.09; N, 8.73.

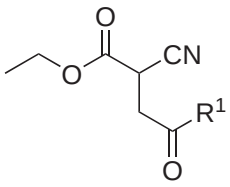
3.2.16 Ethyl 2-(2,3-dimethylphenylamino)-5-(naphthalen-2-yl)-1*H*-pyrrole-3-carboxylate (79)

Yield: (2 mg, 15%), brown oil, IR ($CHCl_3$): 3513, 3372, 3153, 2897, 2239, 2450, 2389, 1732, 1679 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (3H, t, J=7.1 Hz), 1.82 (3H, s), 2.21 (3H, s), 4.24 (2H, q, J=7.1 Hz), 4.84 (2H, br s, NH), 6.65 (1H, s), 7.14-7.58 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 14.03, 14.82, 20.34, 58.93, 107.38, 110.14, 116.49, 123.83, 125.11, 125.86, 126.61, 126.79, 126.95, 127.23, 127.39, 127.51, 127.74, 130.79, 131.69, 133.42, 135.45, 136.05, 139.04, 146.23, 166.47. Anal. Calcd for $C_{25}H_{24}N_2O_2$ (384.18): C, 78.10; H, 6.29; N, 7.29. Found: C, 78.03; H, 6.22; N, 7.21.

CHAPTER 4

CONCLUSION

2-Aminopyrrole-3-carboxylates constitute interesting intermediates for the syntheses of several important, highly biologically active heterocyclic compounds. These interesting and useful intermediates are used for several transformations like formation of pyrrolopyrimidine, pyrroloimidazotetrazinone, pyrrolopiperazine in synthetic organic chemistry. These complex structures have found exhibit biological activity against breast cancer, skin cancer, brain tumors, benign protatic hypertrophy and used as anion receptor upto now.



R^1 = -CH_3 **52** R^1 = -C_6H_4Br **59**

R^1 = -C_6H_5 **57** R^1 = -$C_{10}H_7$ **61**

Figure 4.1: γ-ketoesters

A new route has been developed in this work for the synthesis of 2-aminopyrrole-3-carboxylate derivatives. Cyanoacetic acid was alkylated in the presence of base. Obtained γ-ketoesters were allowed to react with different primary amines in the presence of $Zn(ClO_4)_2$ at reflux. Finaly, $Zn(ClO_4)_2 \cdot 6H_2O$ mediated cyclization of γ-ketoesters with primary amine derivatives gave the corresponding 2-aminopyrrole-3-carboxylate derivatives (Figure 4.2).

There were differences in reaction times, yields and obtained products, when R^1 were alkyl (**52**) and aromatic (**57**, **59**, **61**), respectively (Figure 4.1). The reaction time increased from 4 hours to 32 hours when aromatic substituted compounds were used as starting materials.

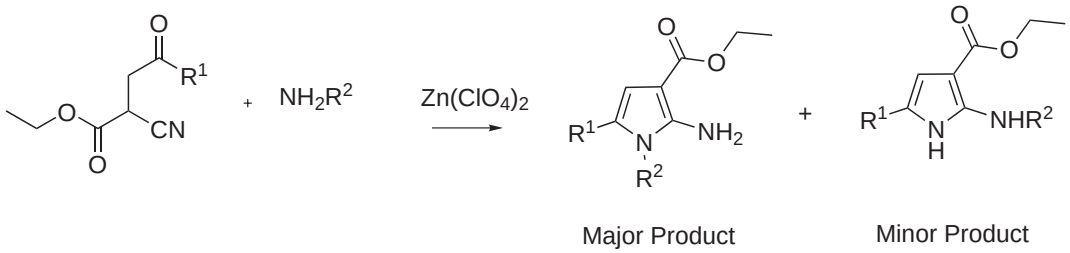


Figure 4.2: $Zn(ClO_4)_2{\cdot}6H_2O$ mediated cyclization of γ-ketoesters with primary amine derivatives

Beside, 2-aminopyrrole-3-carboxylate was obtained as a sole product and reaction yield decreased from 62-98% to 15- 26% when we started from one of **57**, **59**, **61**.

The role of $Zn(ClO_4)_2{\cdot}6H_2O$ was very crucial for the obtained result. Oxophilicity of Zn cation which forms strong coordination bond with carbonyl oxygen and pK_a value of amine affect the efficiency of method. Steric hindrance and electronic factors also play an important roles in the yields and obtained products. Due to importance of aryl functionality on pyrrole ring, to increase the yields of reactions, various catalysis were tried to obtain 2-aminopyrrole-3-carboxylate, however, it was understood that synthesizing 2-aminopyrrole-3-carboxylates in the presence of $Zn(ClO_4)_2{\cdot}6H_2O$ was the most efficient method. Although, it was reported that 2-amino pyrroles are very unstable in air, the obtained products are very stable on exposure to air.

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Appendix A

NMR DATA

NMR spectra were recorded on a Bruker DPX 400.

Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^1H: δ=7.27), $CDCl_3$ (^{13}C: δ=77.0) and CCl_4 (^{13}C: δ=96.4) as internal standards.

^1H and ^{13}C NMR spectra of products are given below.

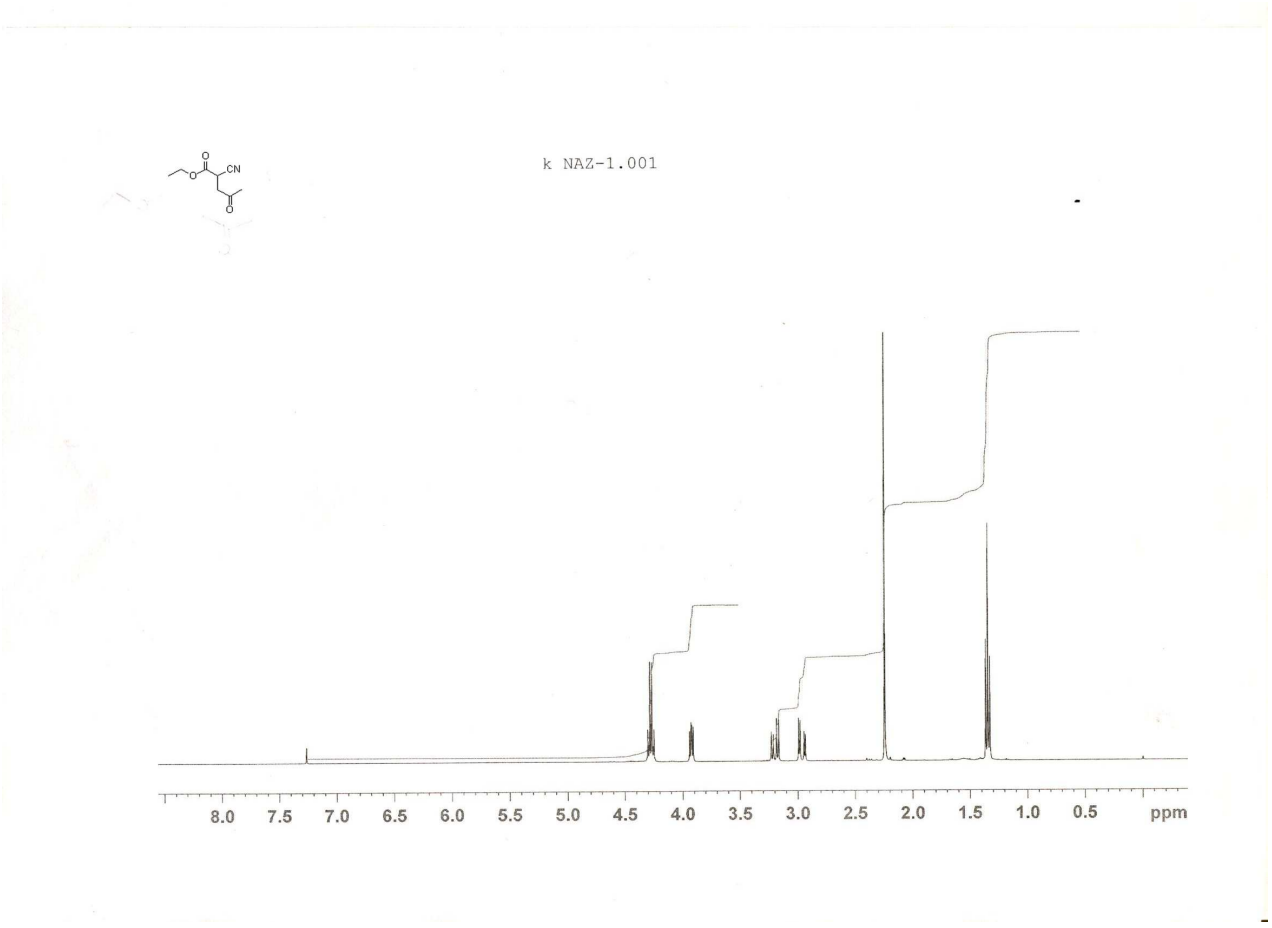

Figure A.1: Ethyl 2-cyano-4-oxopentanoate (**52**)

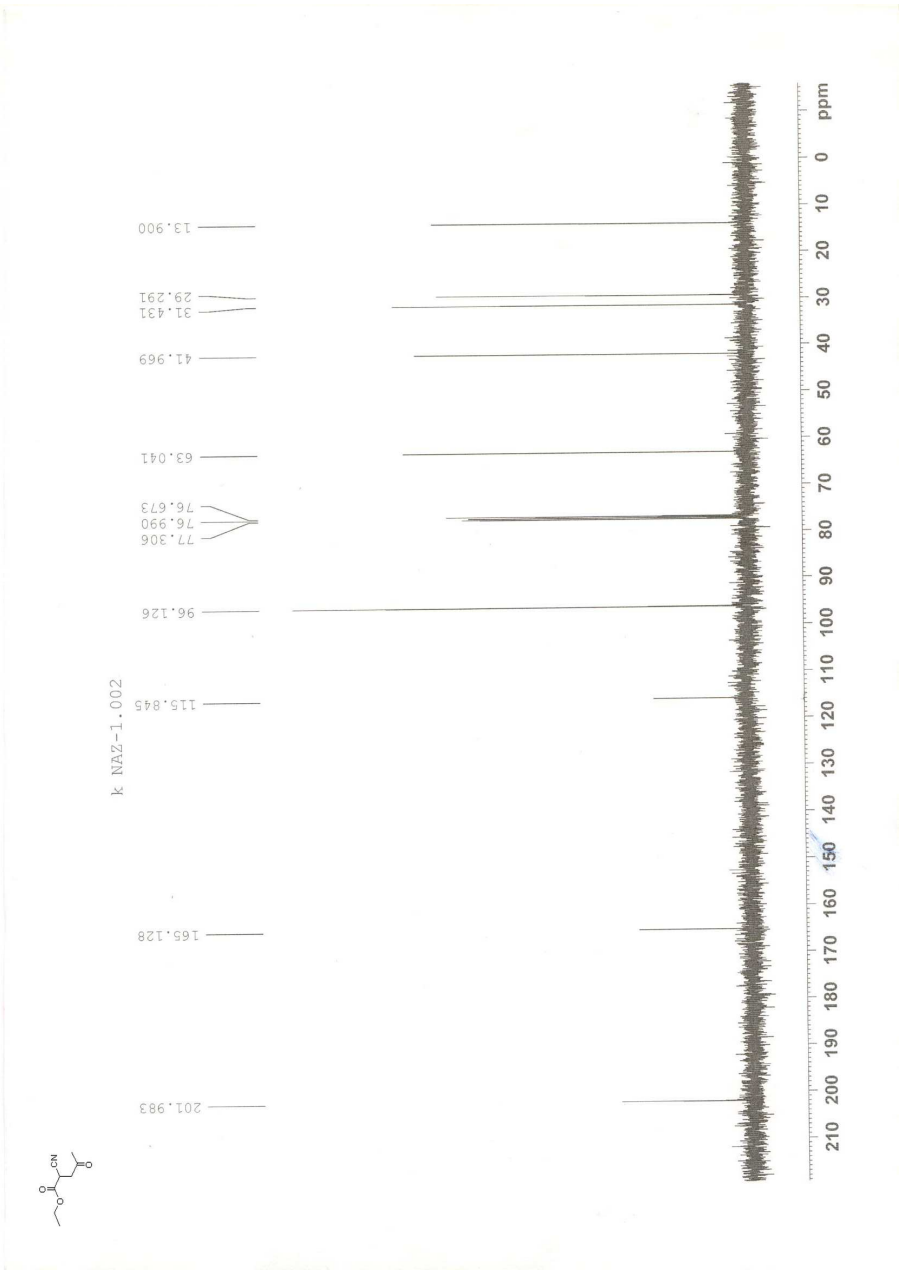

Figure A.2: Ethyl 2-cyano-4-oxopentanoate (**52**)

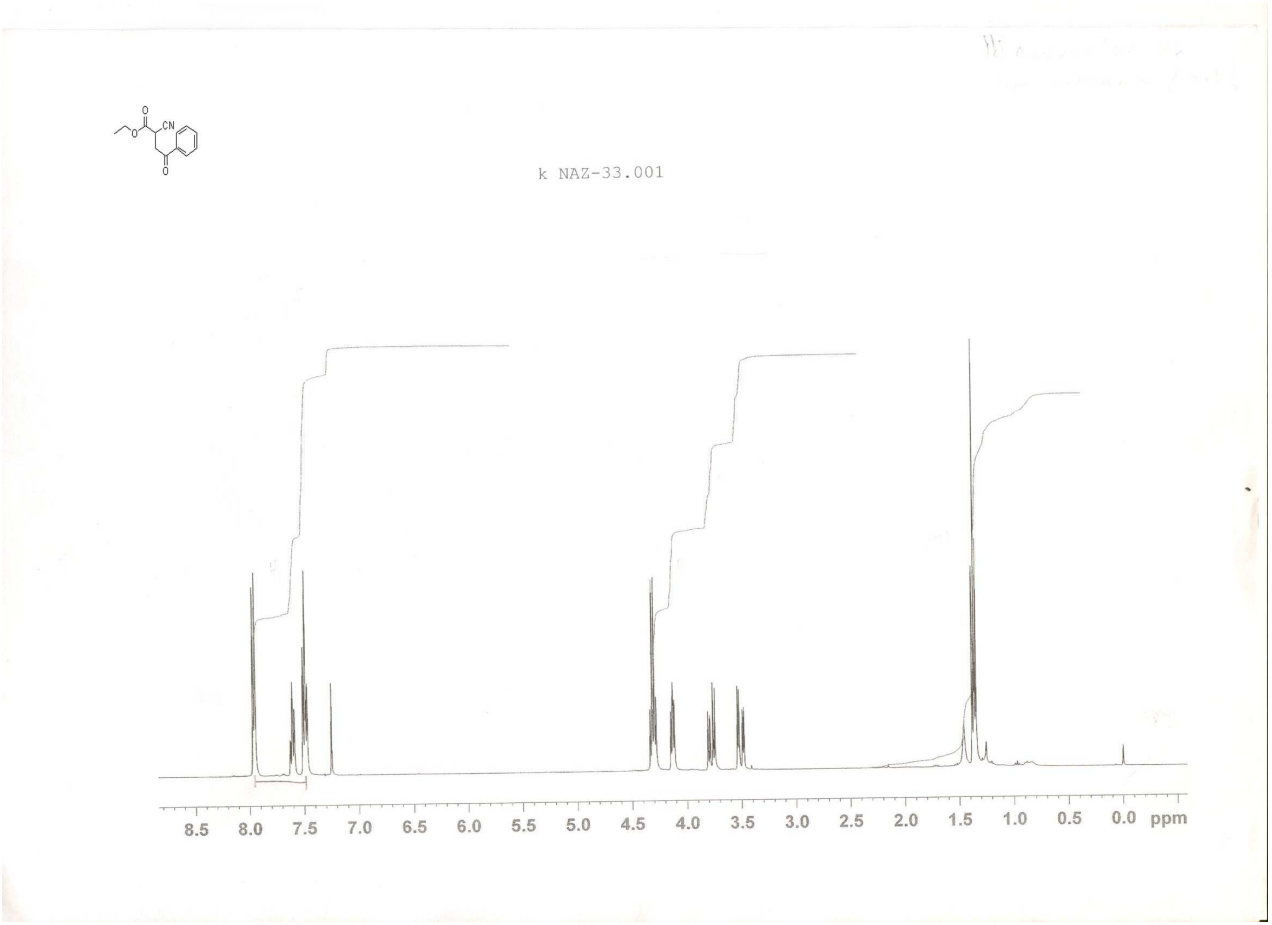

Figure A.3: Ethyl 2-cyano-4-oxo-4-phenylbutanoate (**57**)

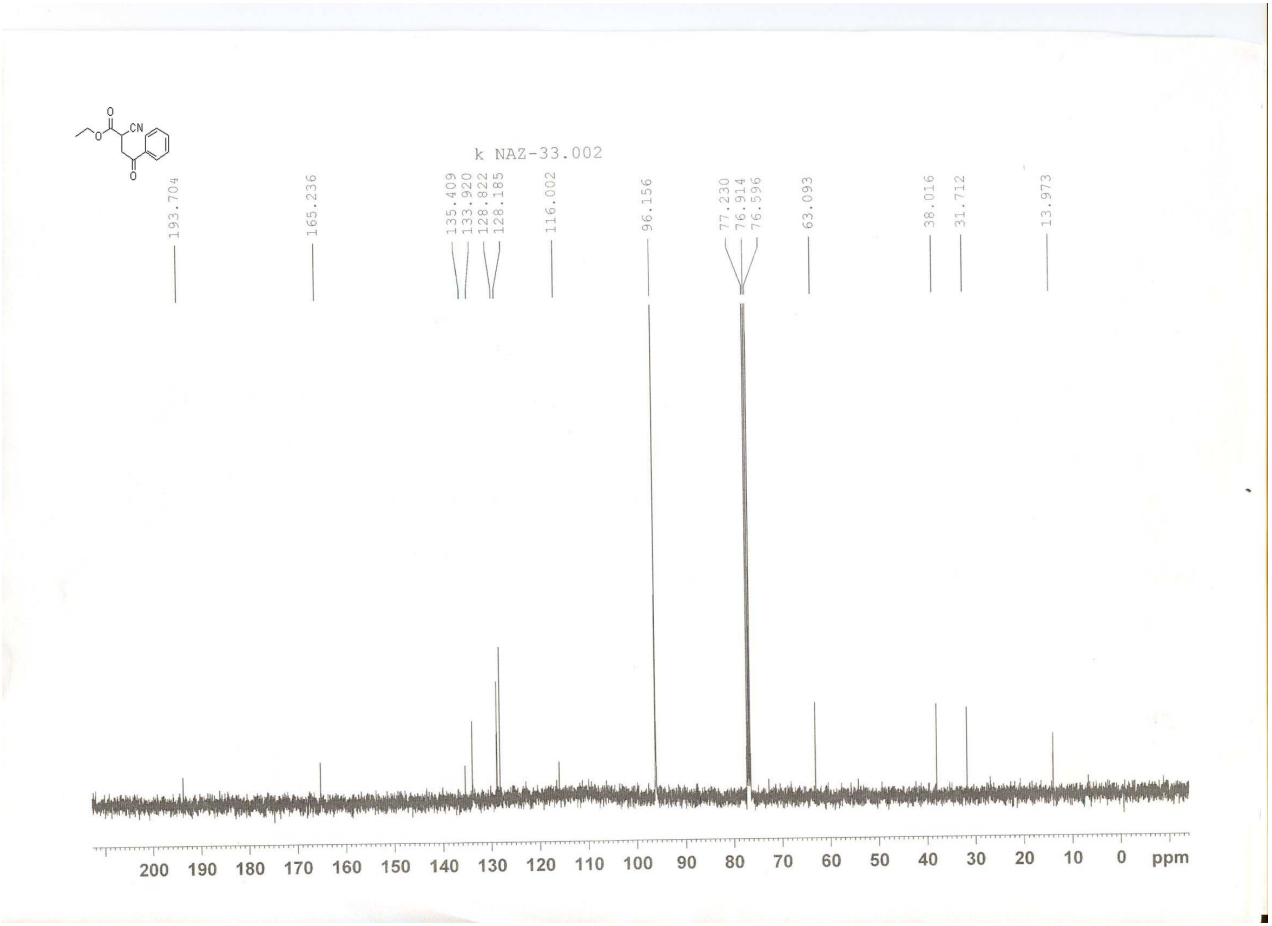

Figure A.4: Ethyl 2-cyano-4-oxo-4-phenylbutanoate (**57**)

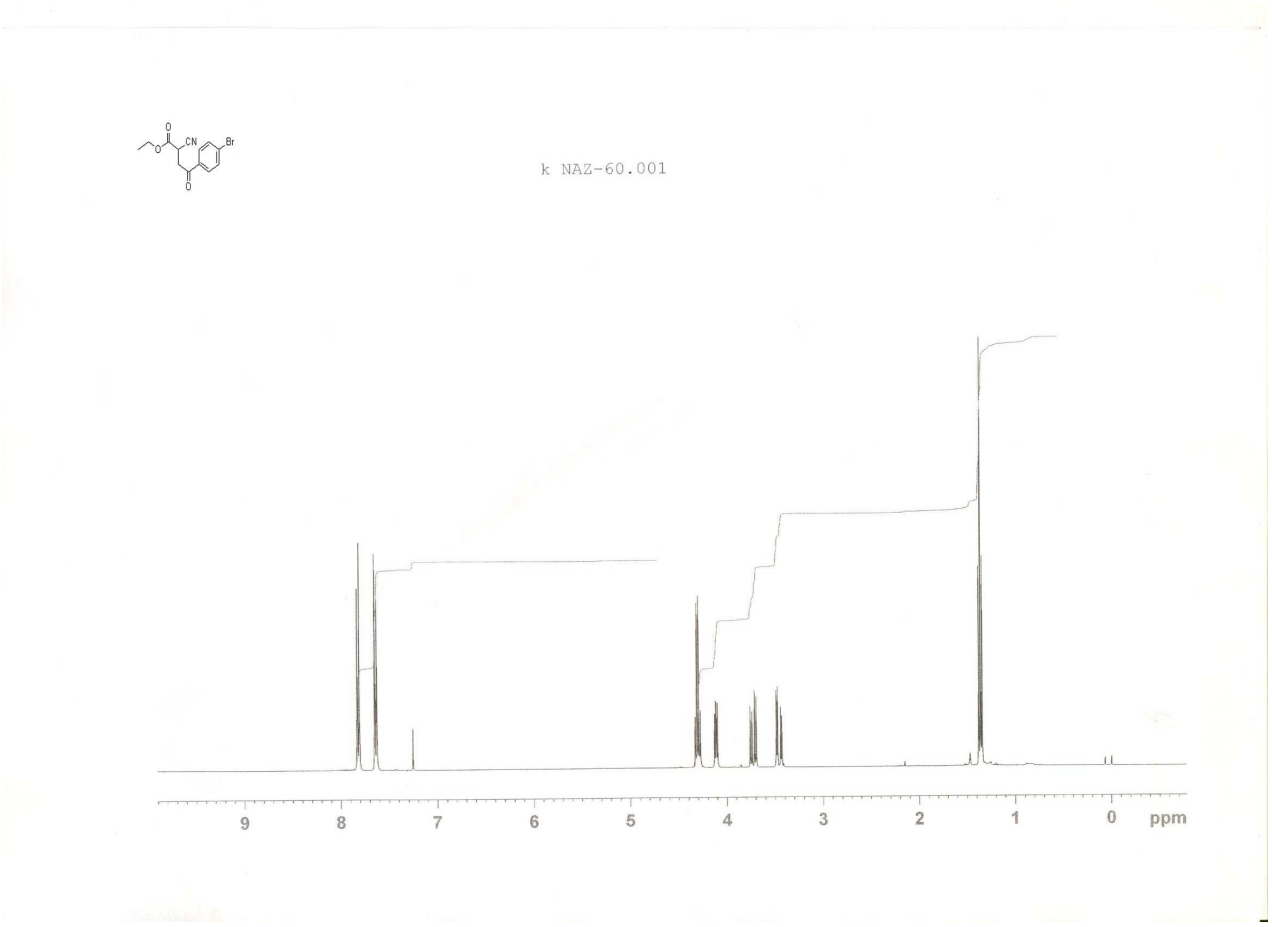

Figure A.5: Ethyl 4-(4-bromophenyl)-2-cyano-4-oxobutanoate (**59**)

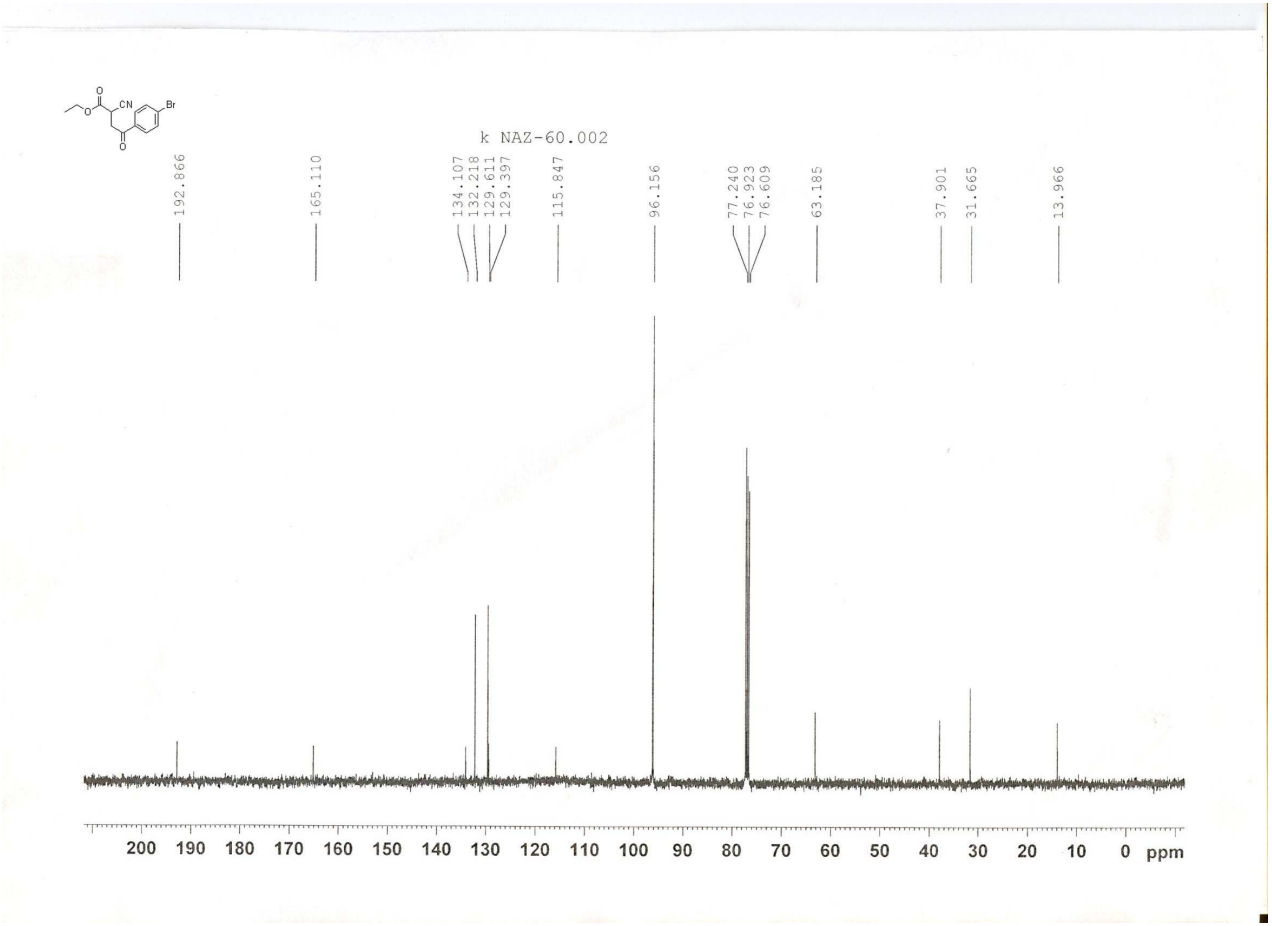

Figure A.6: Ethyl 4-(4-bromophenyl)-2-cyano-4-oxobutanoate (**59**)

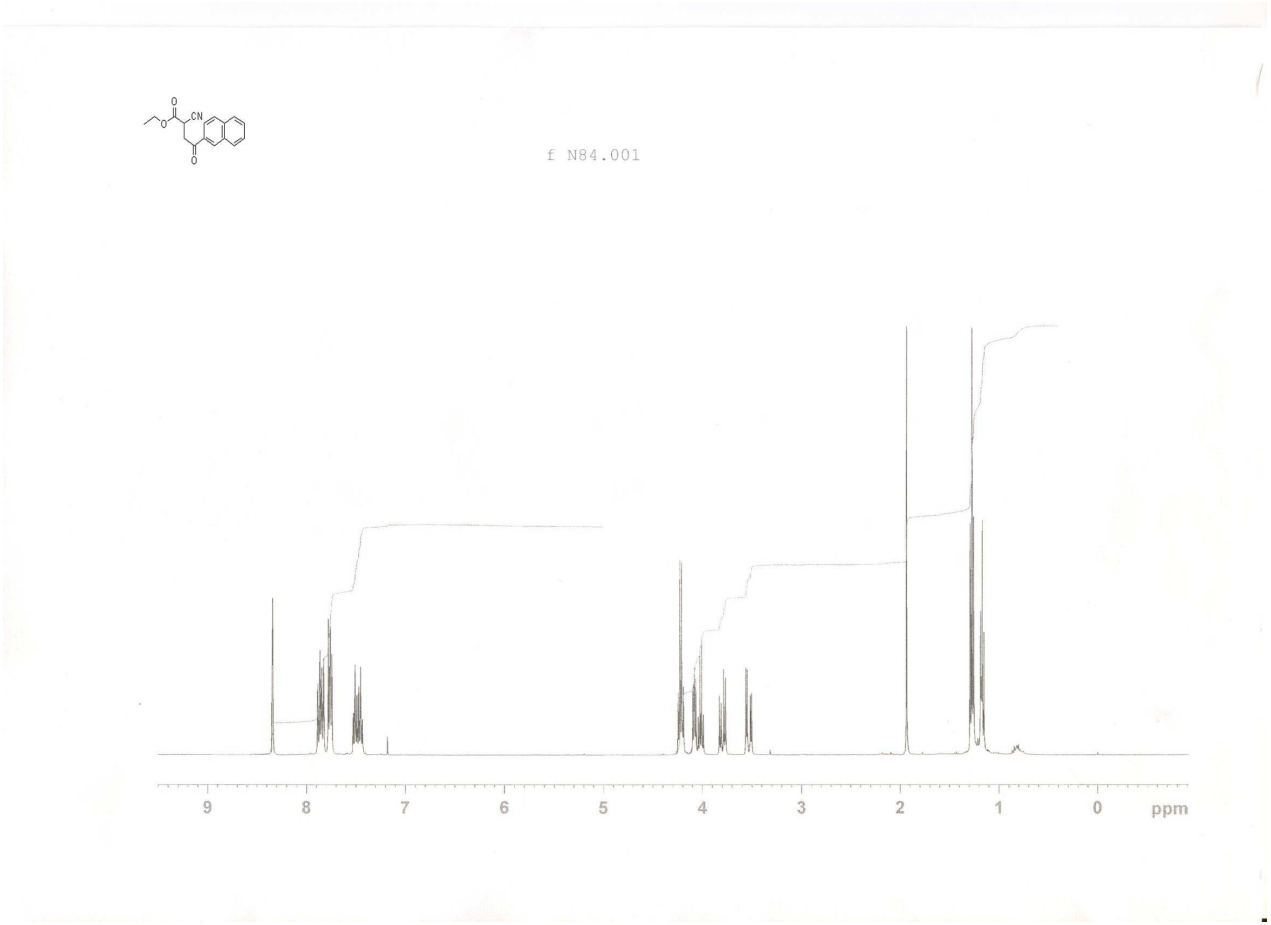

Figure A.7: Ethyl 2-cyano-4-(naphthalen-2-yl)-4-oxobutanoate (**61**)

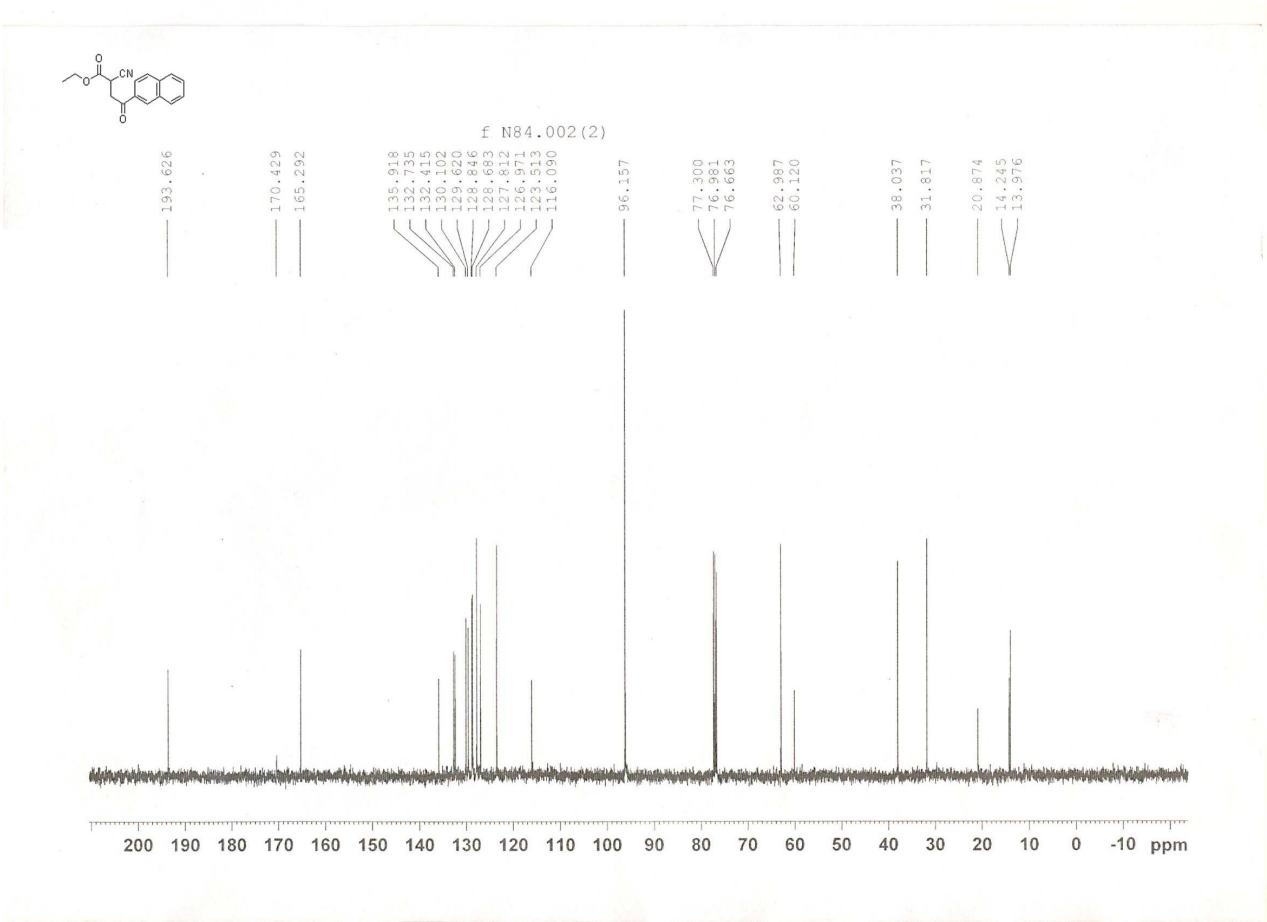

Figure A.8: Ethyl 2-cyano-4-(naphthalen-2-yl)-4-oxobutanoate (**61**)

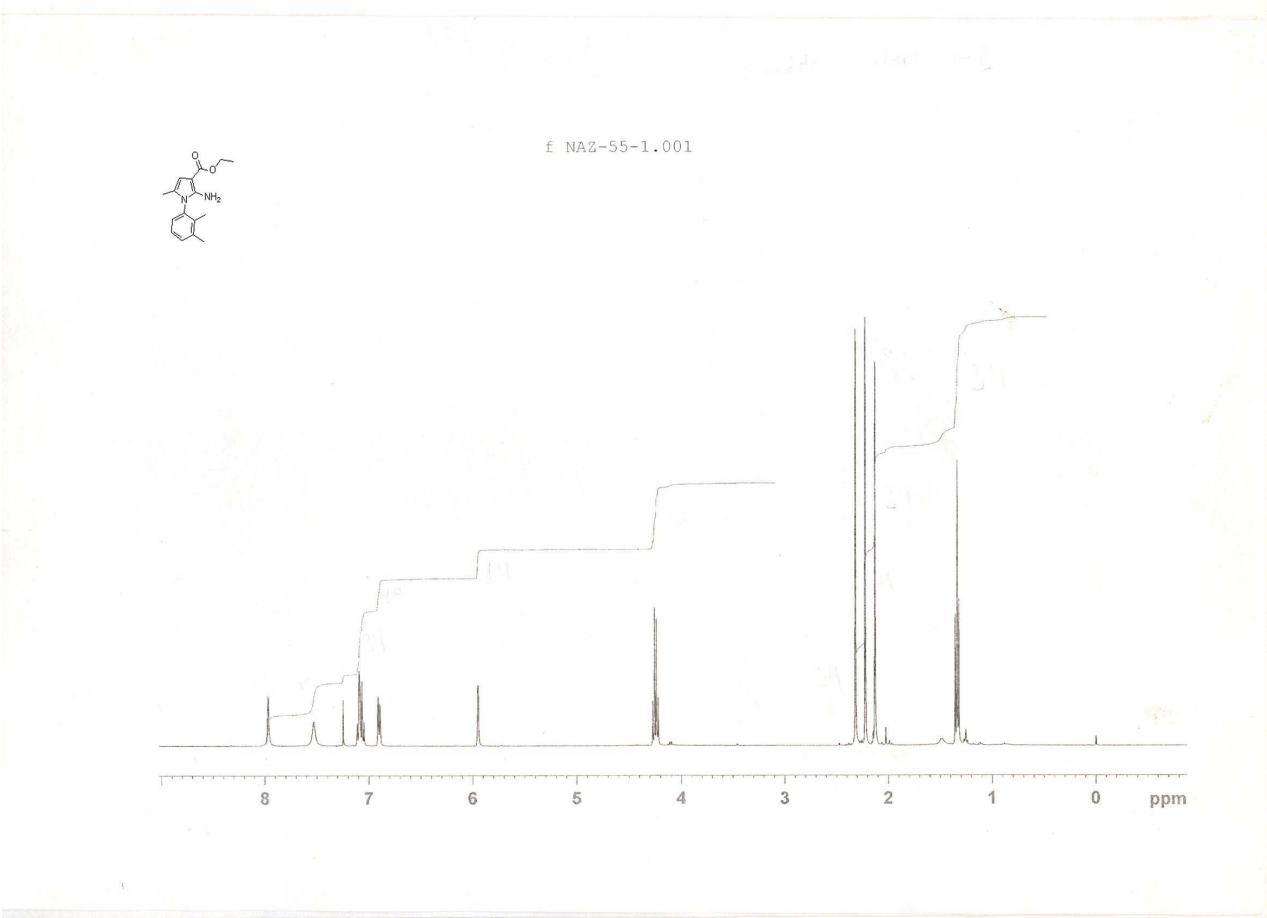

Figure A.9: Ethyl 2-amino-5-methyl-1-(2,3-dimethylphenyl)-1*H*-pyrrole-3-carboxylate (**54**)

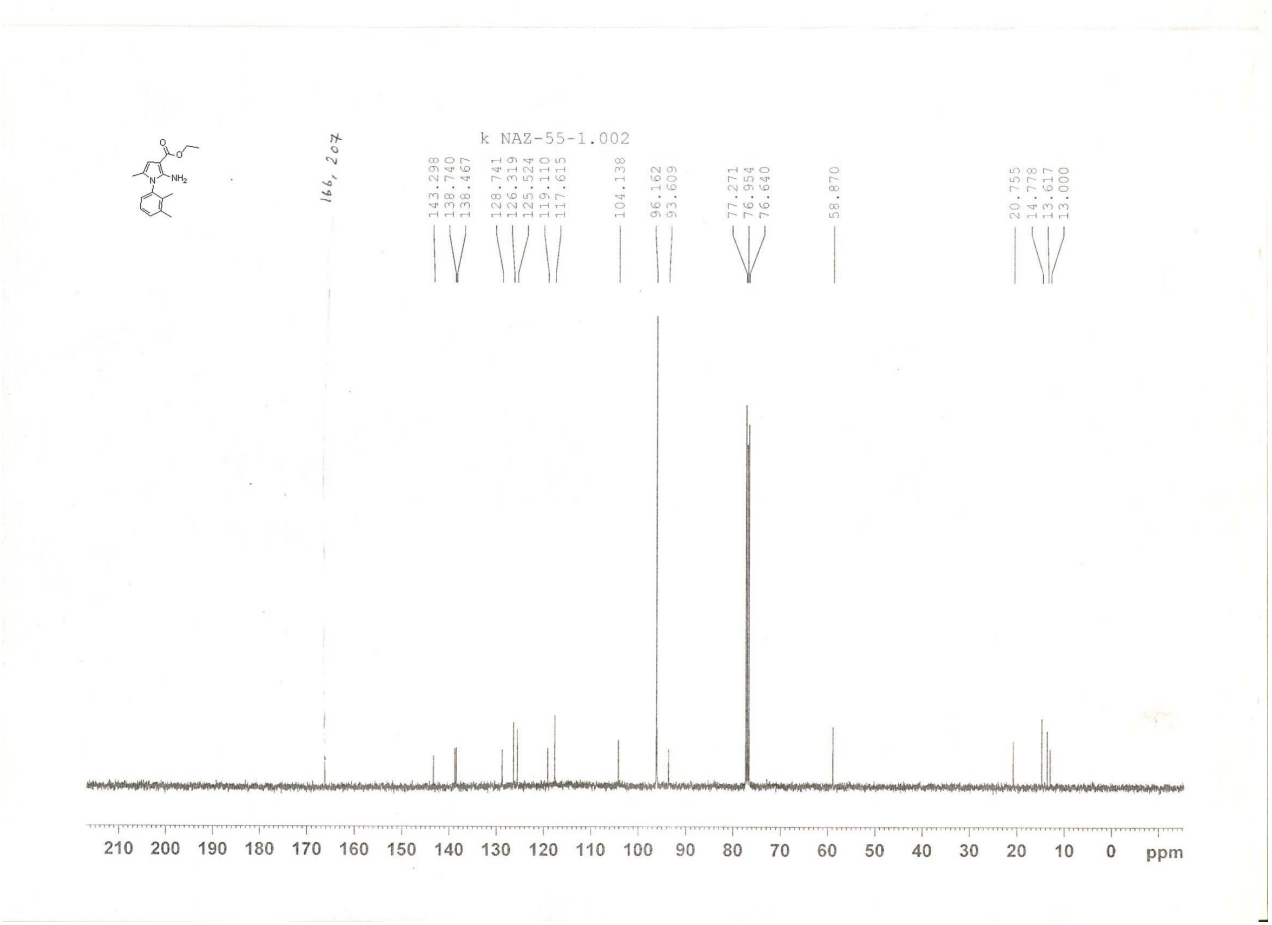

Figure A.10: Ethyl 2-amino-5-methyl-1-(2,3-dimethylphenyl)-1*H*-pyrrole-3-carboxylate (**54**)

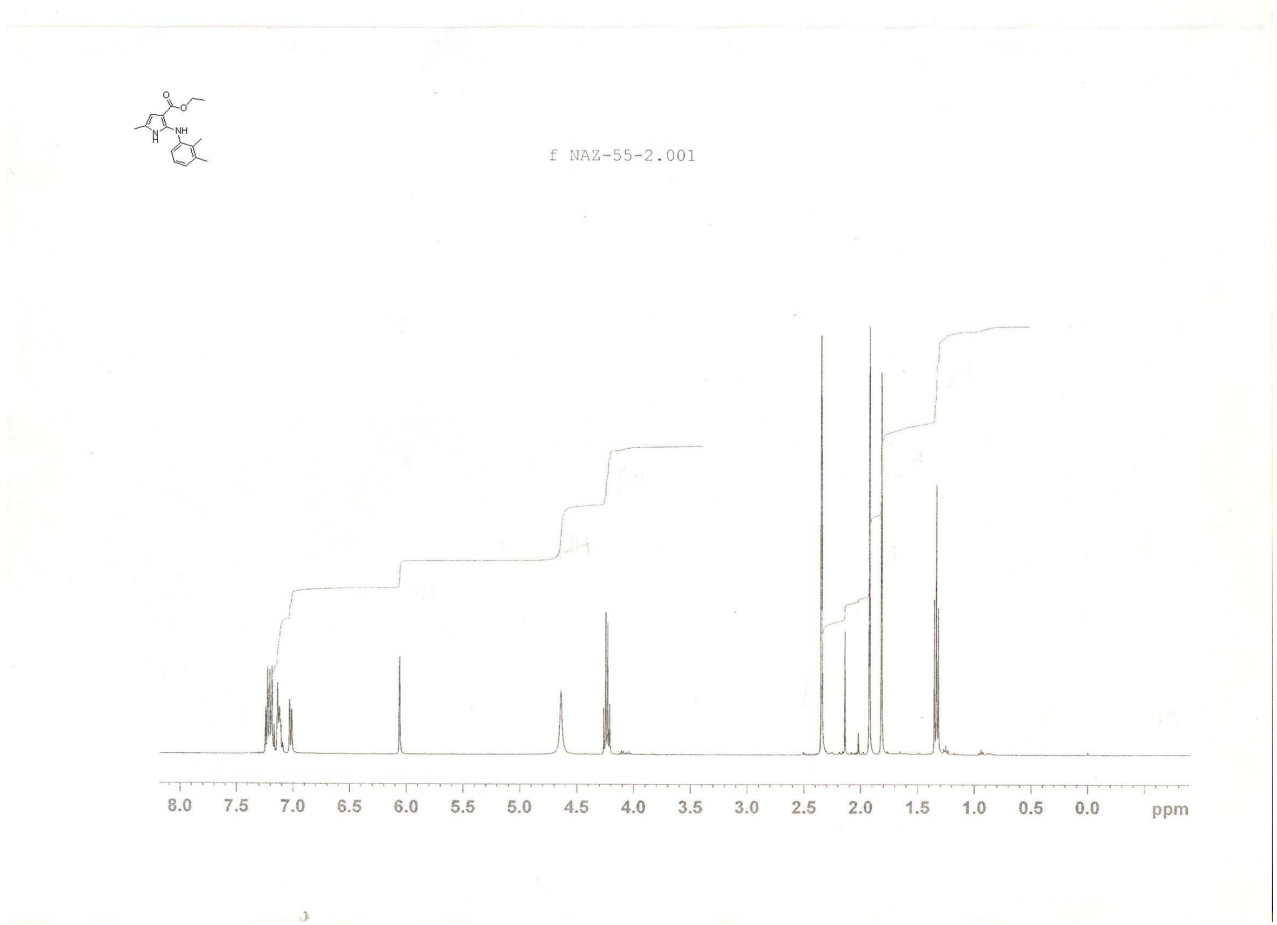

Figure A.11: Ethyl 2-(2,3-dimethylphenylamino)-5-methyl-1*H*-pyrrole-3-carboxylate (**55**)

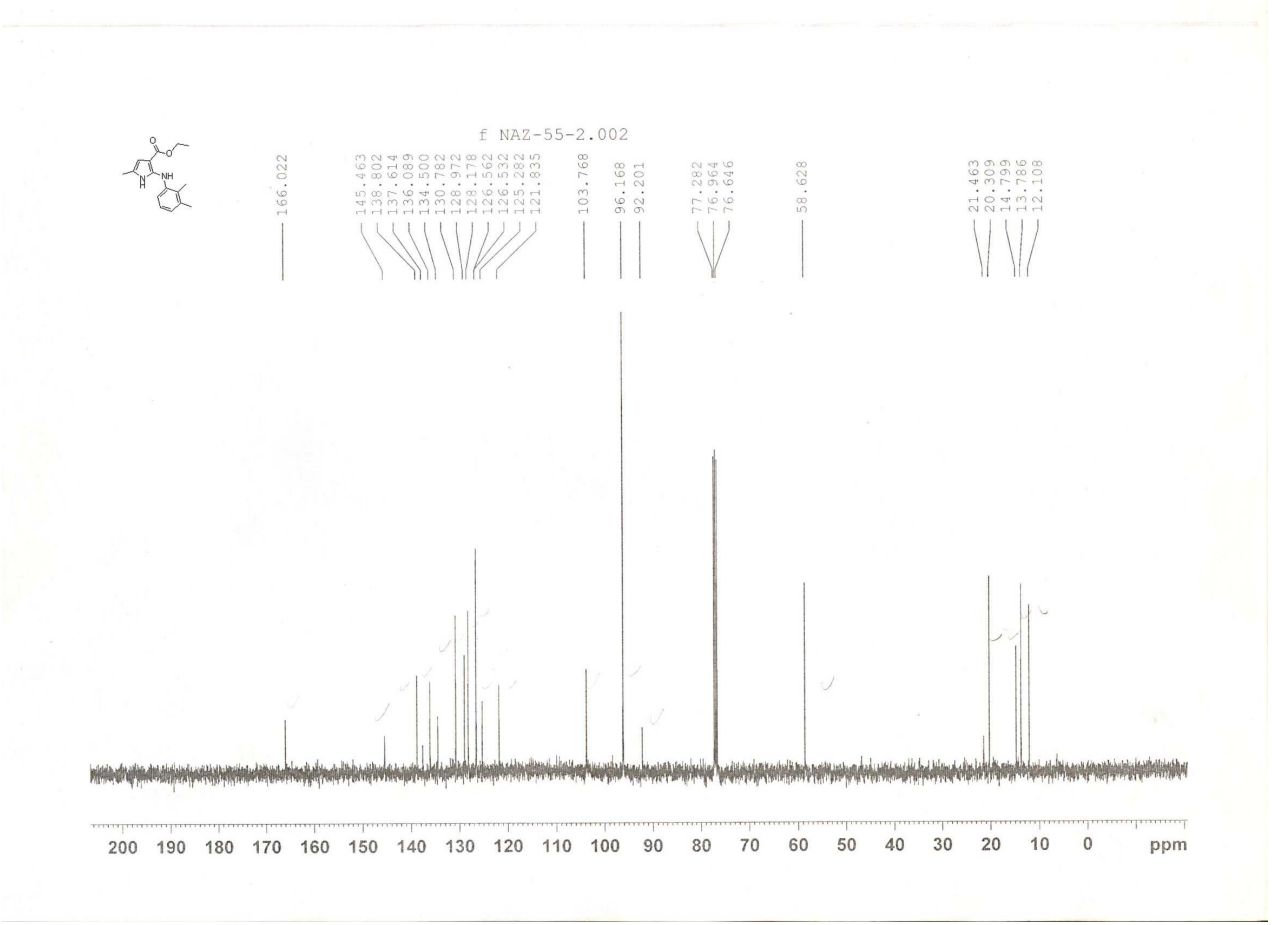

Figure A.12: Ethyl 2-(2,3-dimethylphenylamino)-5-methyl-1*H*-pyrrole-3-carboxylate (**55**)

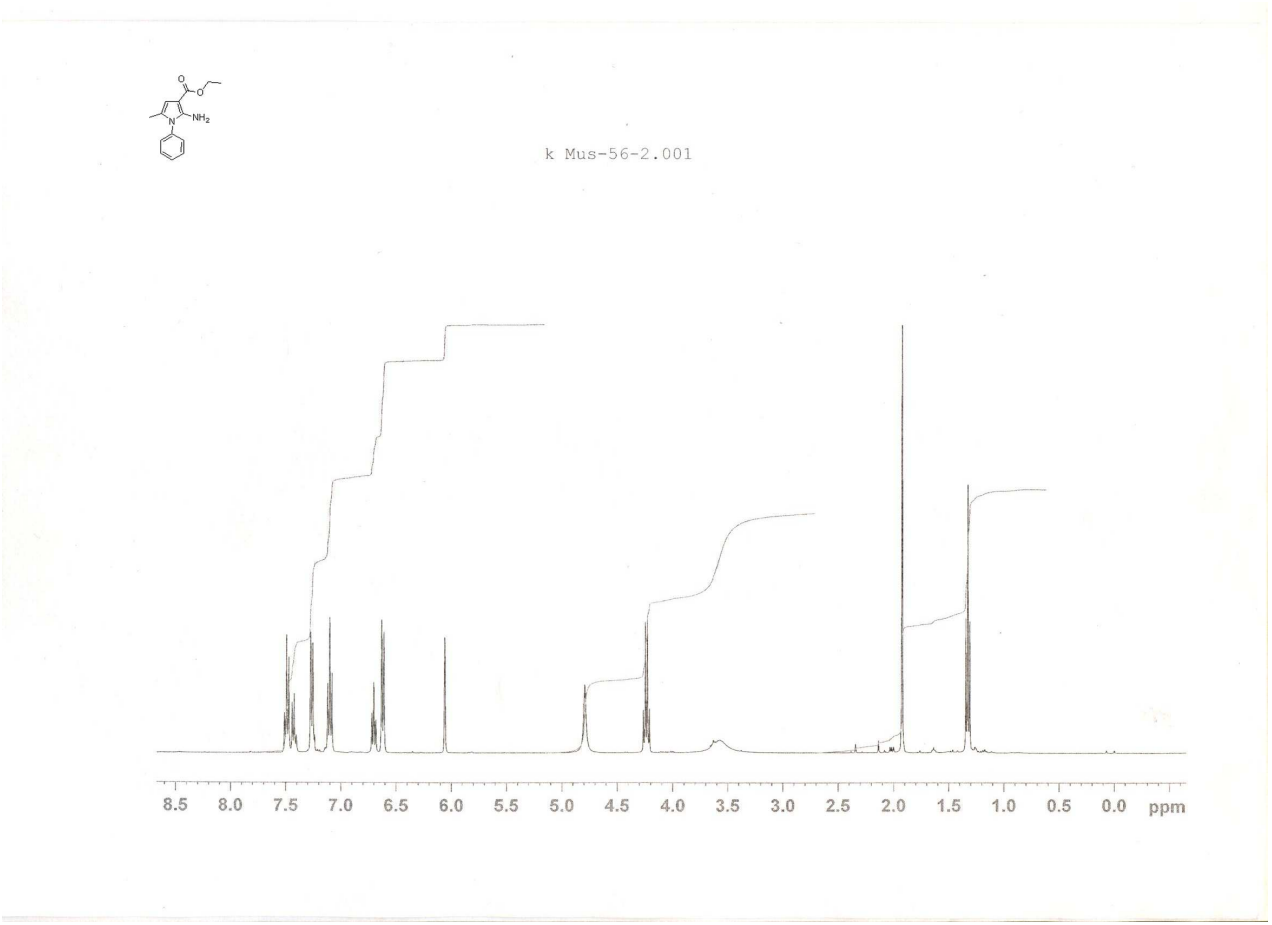

Figure A.13: Ethyl 2-amino-5-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate (**62**)

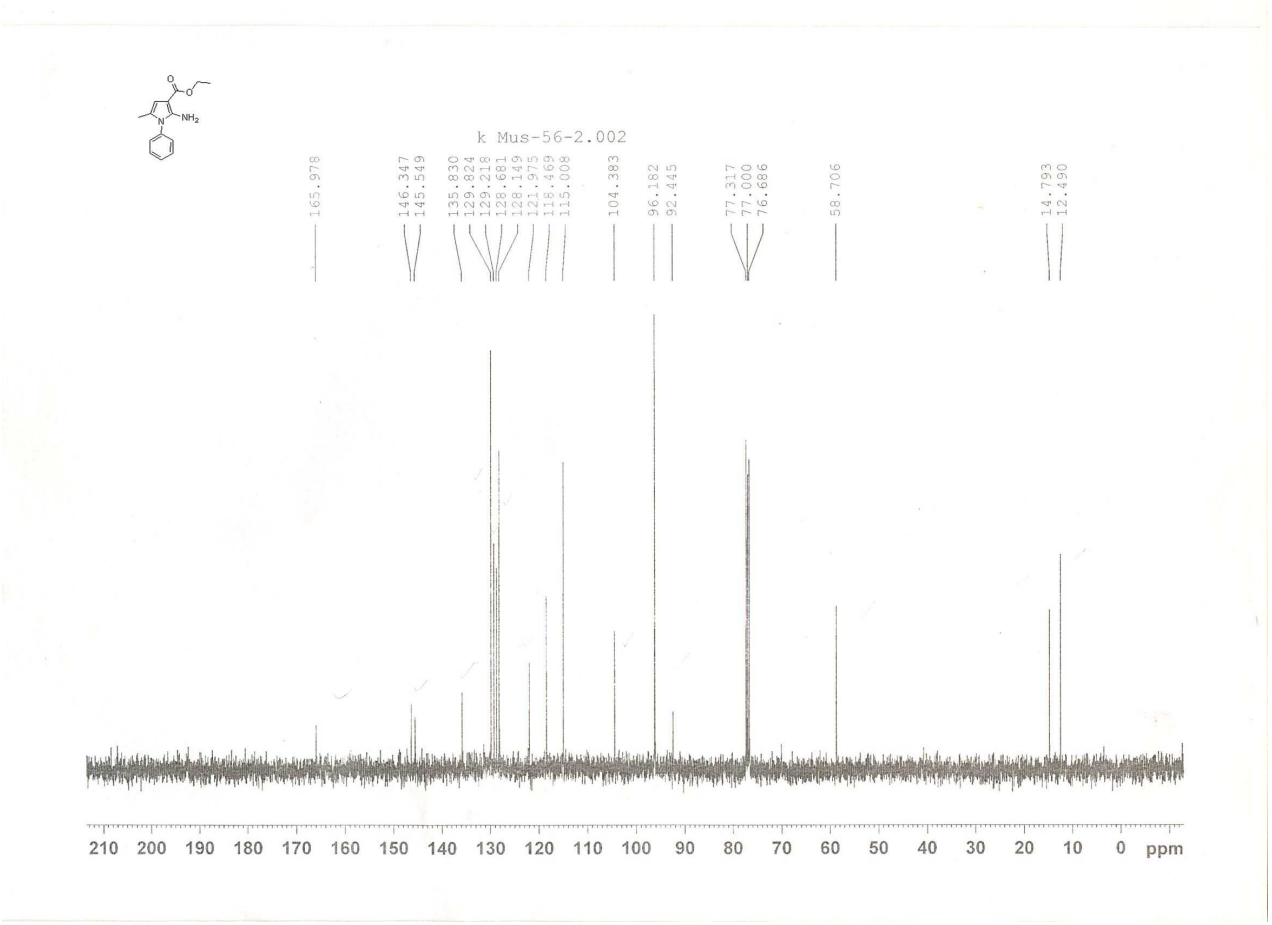

Figure A.14: Ethyl 2-amino-5-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate (**62**)

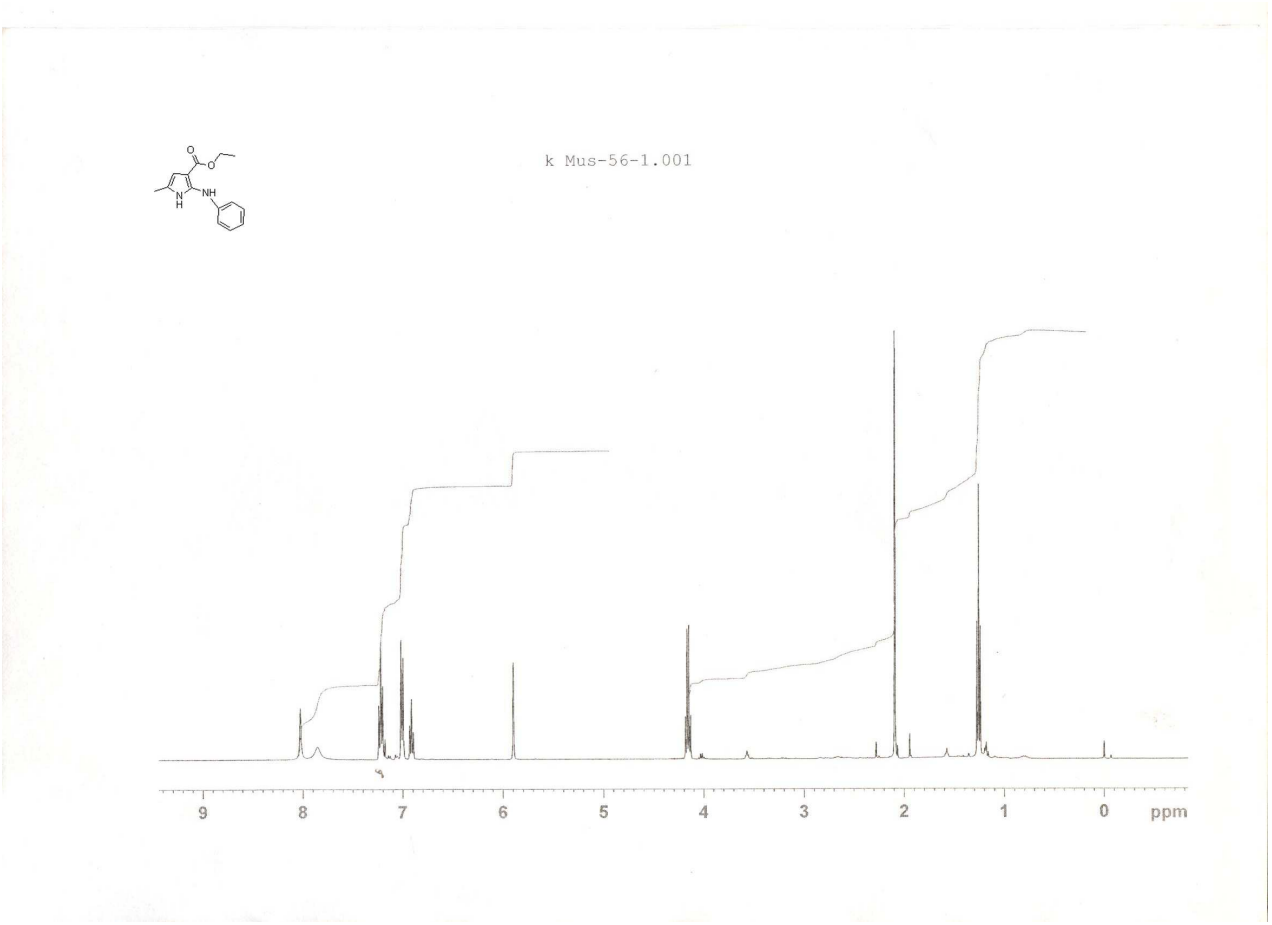

Figure A.15: Ethyl 5-methyl-2-(phenylamino)-1*H*-pyrrole-3-carboxylate (**63**)

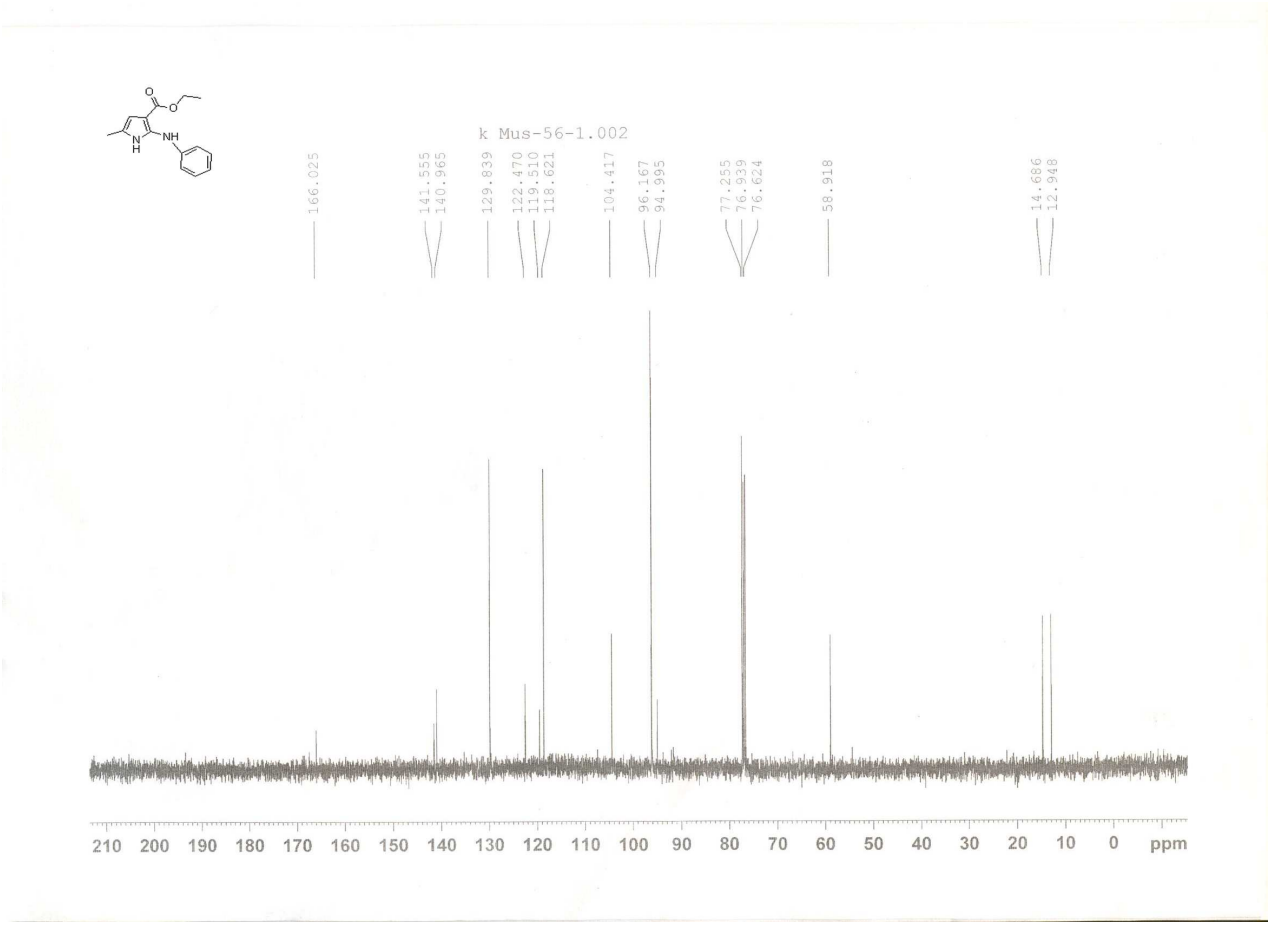

Figure A.16: Ethyl 5-methyl-2-(phenylamino)-1*H*-pyrrole-3-carboxylate (**63**)

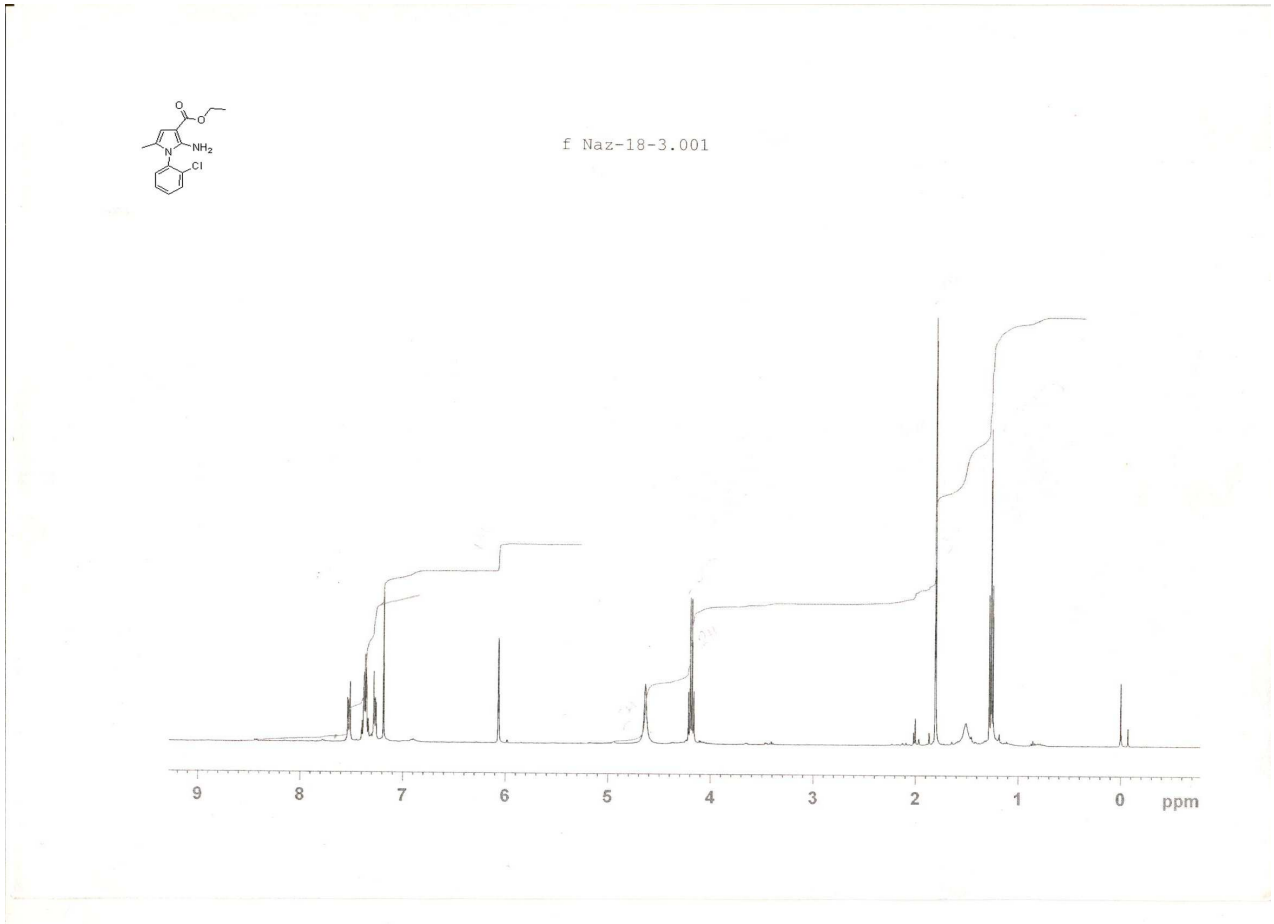

Figure A.17: Ethyl 2-amino-1-(2-chlorophenyl)-5-methyl-1*H*-pyrrole-3-carboxylate (**65**)

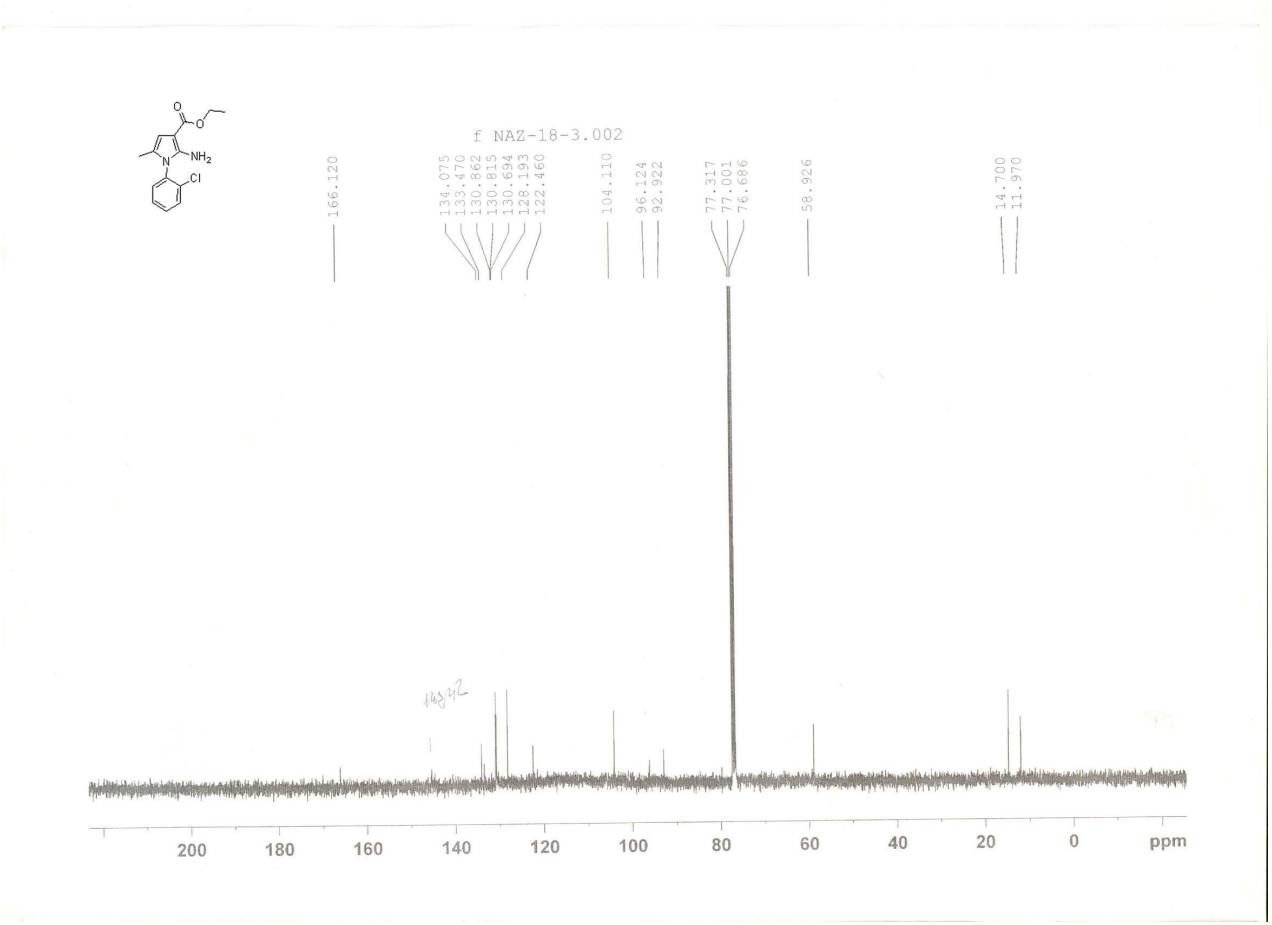

Figure A.18: Ethyl 2-amino-1-(2-chlorophenyl)-5-methyl-1*H*-pyrrole-3-carboxylate (**65**)

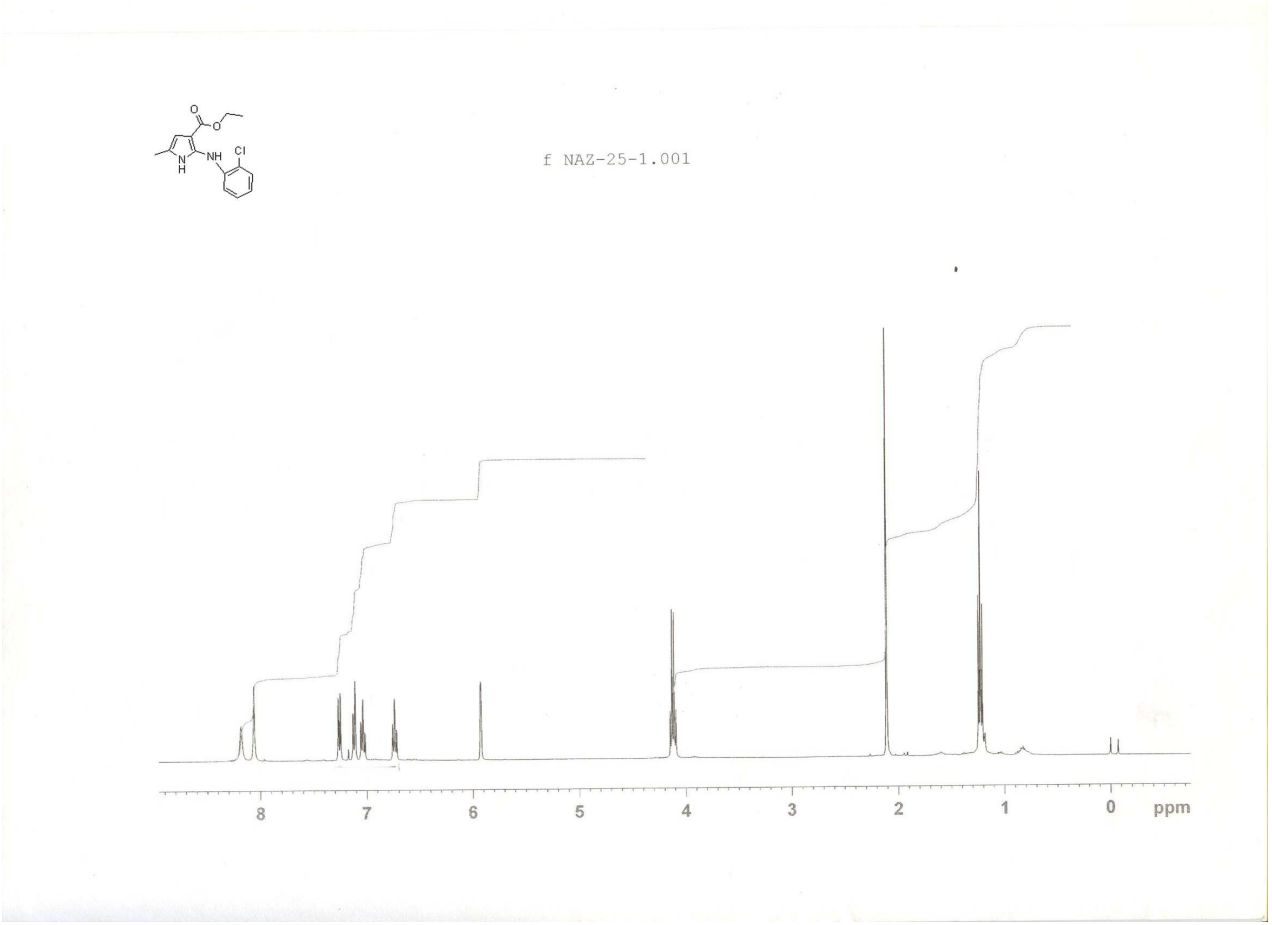

Figure A.19: Ethyl 2-(2-chlorophenylamino)-5-methyl-1*H*-pyrrole-3-carboxylate (**66**)

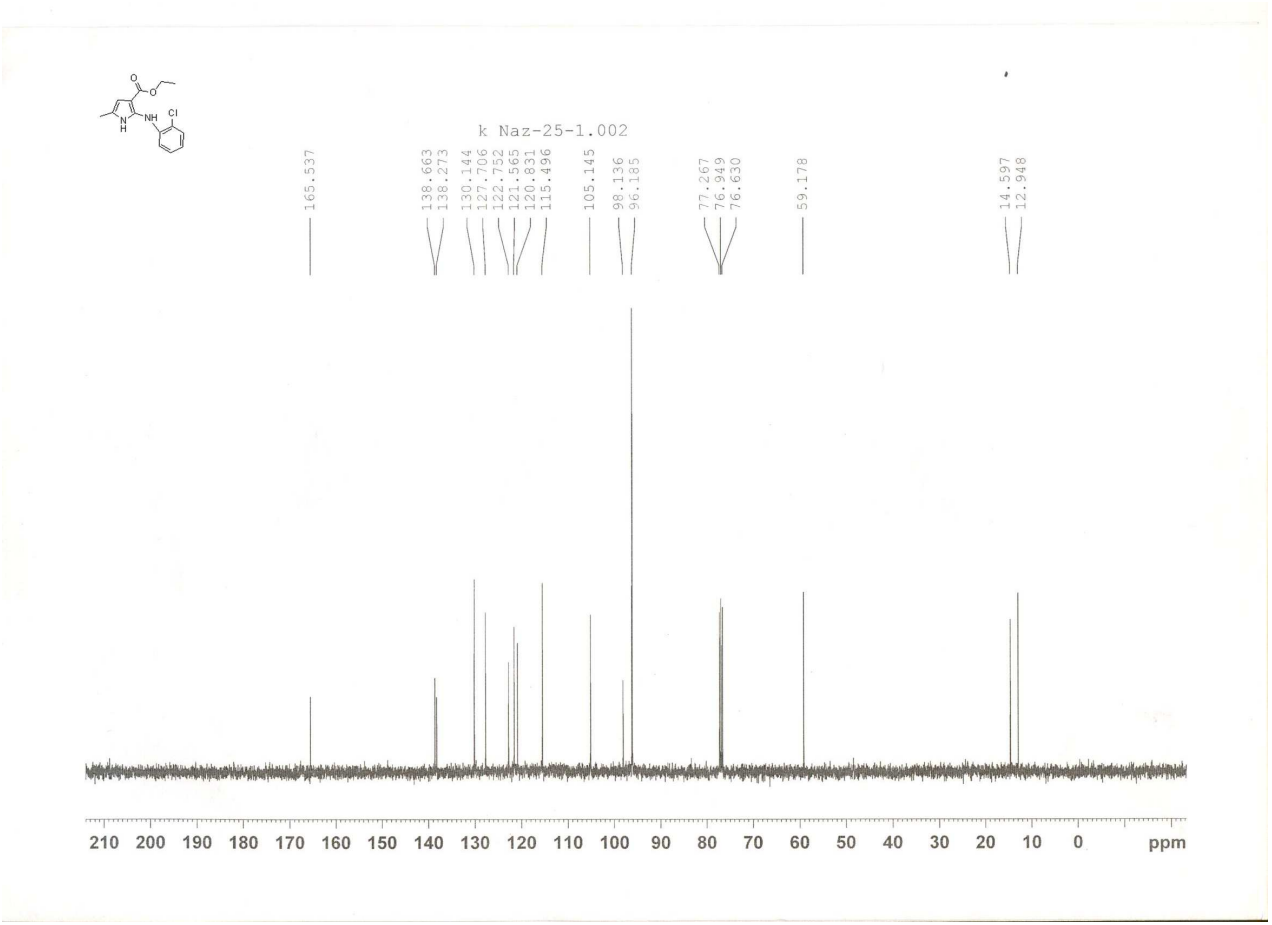

Figure A.20: Ethyl 2-(2-chlorophenylamino)-5-methyl-1*H*-pyrrole-3-carboxylate (**66**)

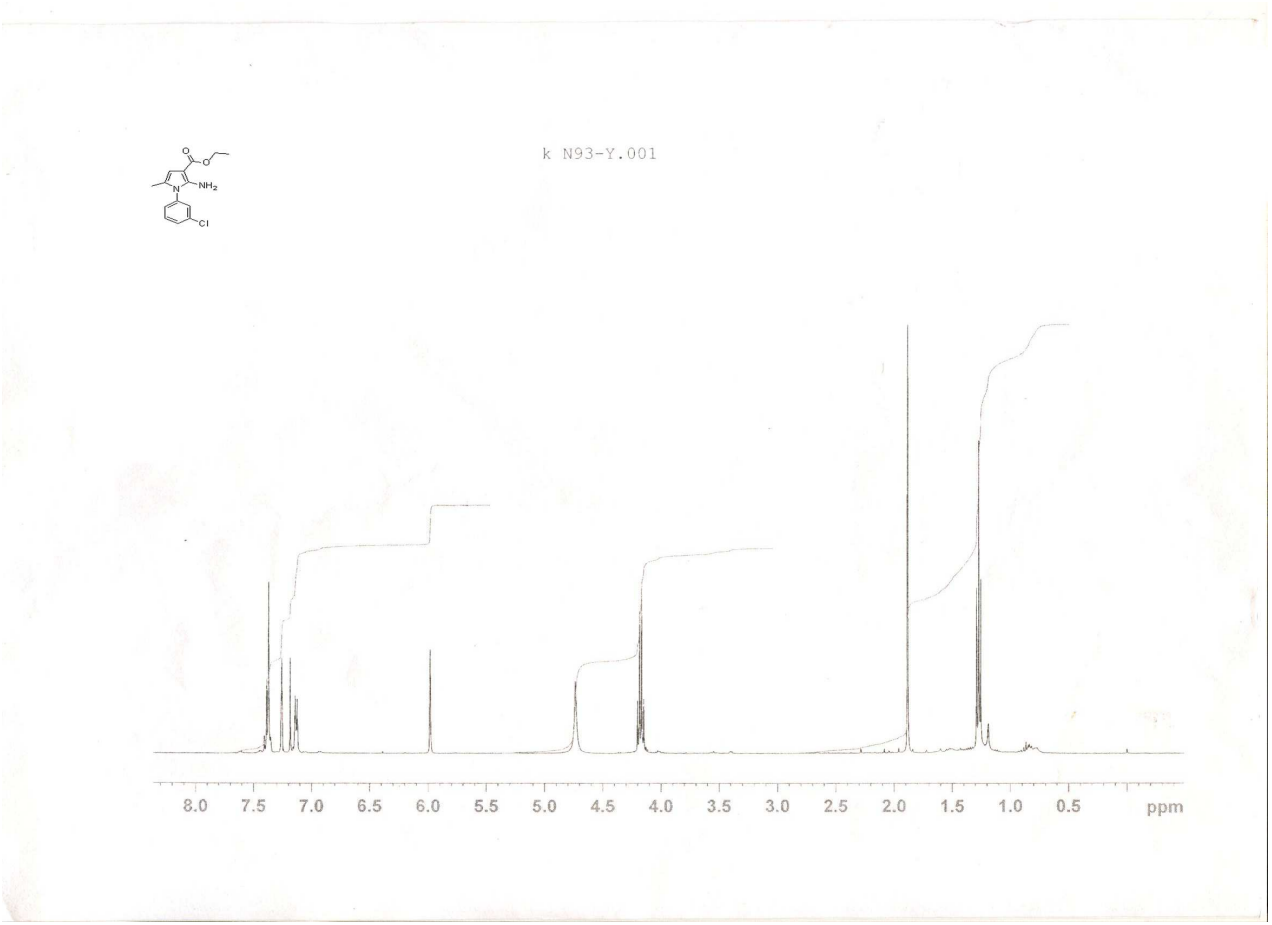

Figure A.21: Ethyl 2-amino-1-(3-chlorophenyl)-5-methyl-1*H*-pyrrole-3-carboxylate (**68**)

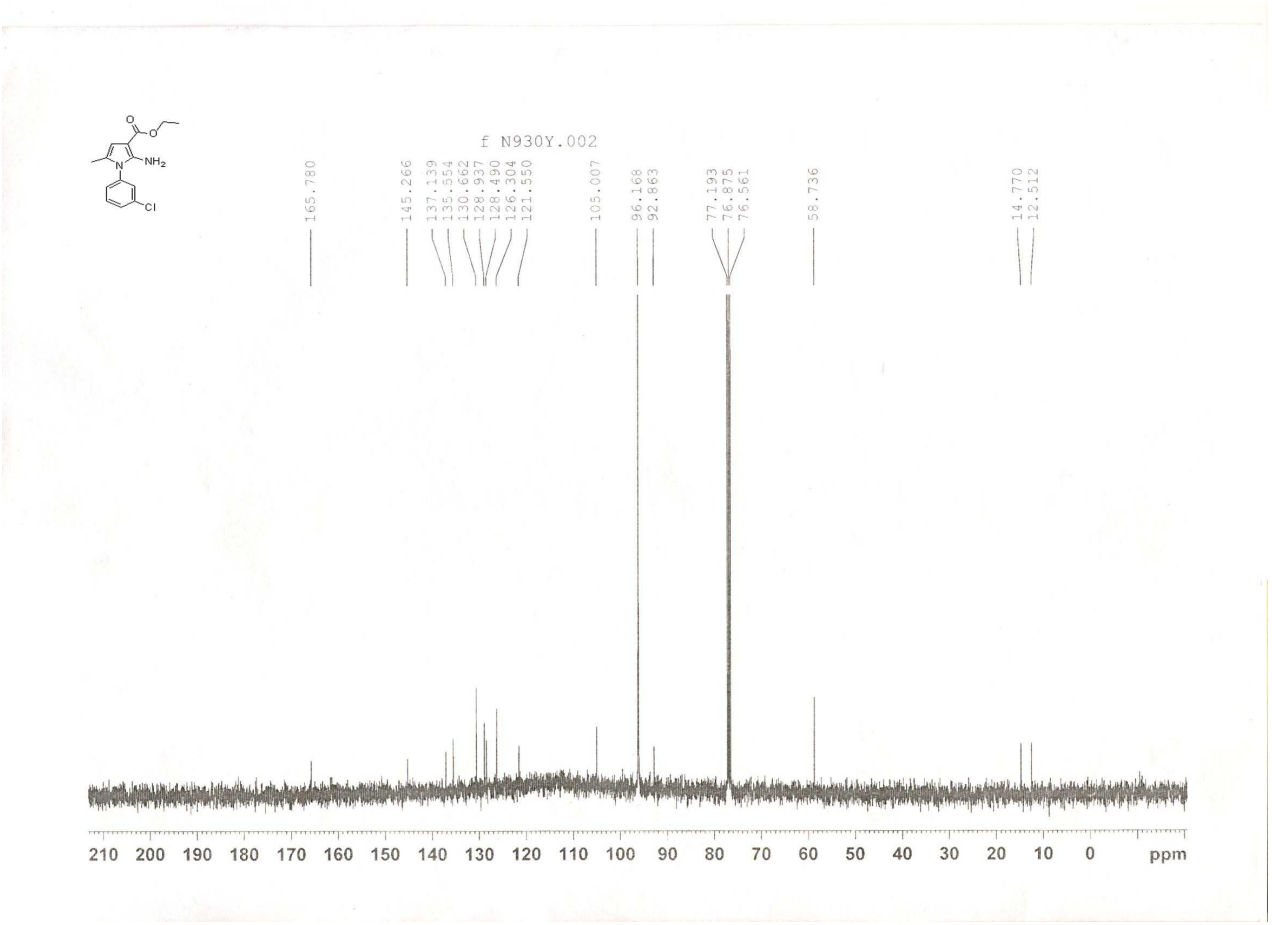

Figure A.22: Ethyl 2-amino-1-(3-chlorophenyl)-5-methyl-1*H*-pyrrole-3-carboxylate (**68**)

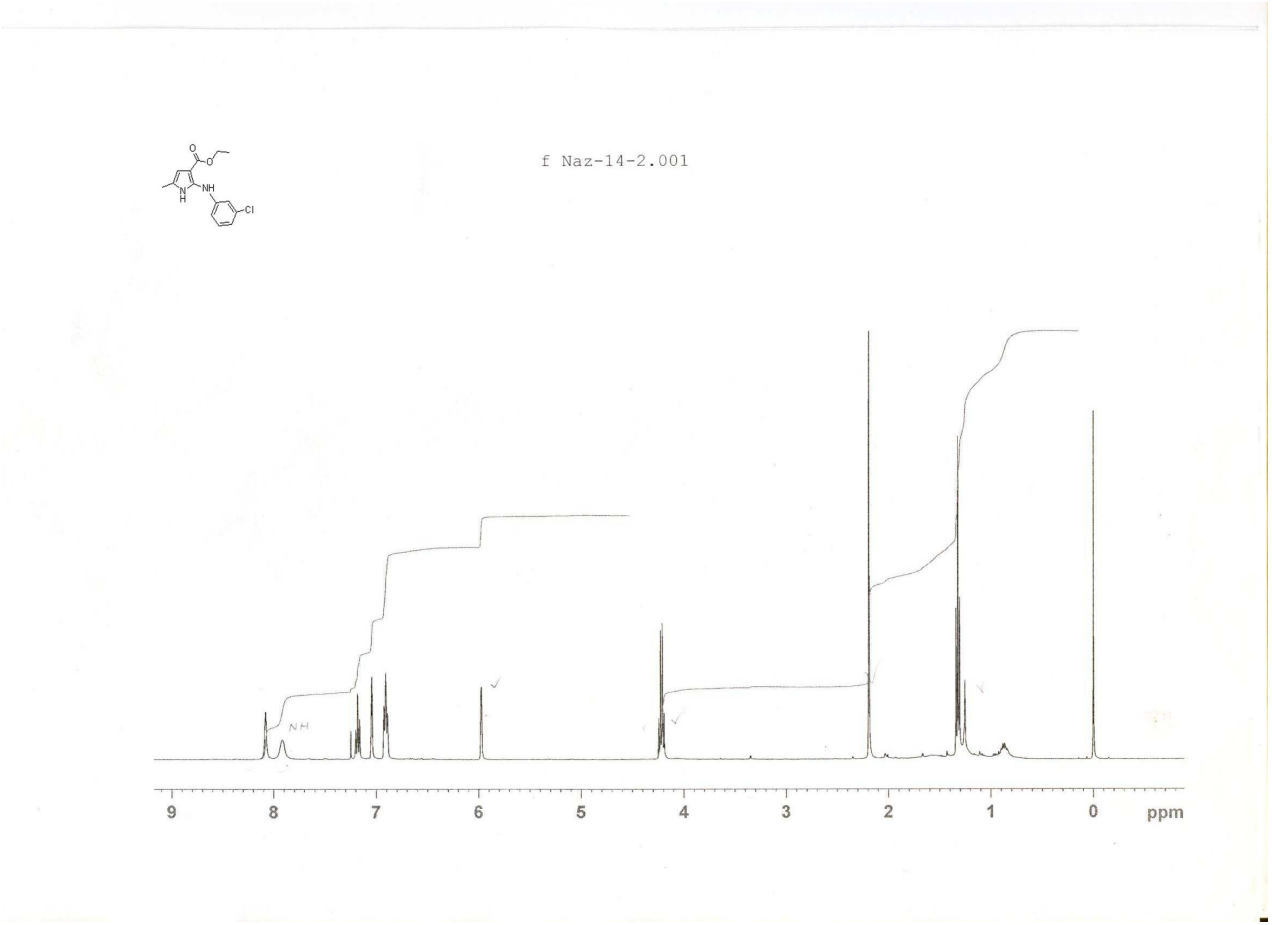

Figure A.23: Ethyl 2-(3-chlorophenylamino)-5-methyl-1*H*-pyrrole-3- carboxylate (**69**)

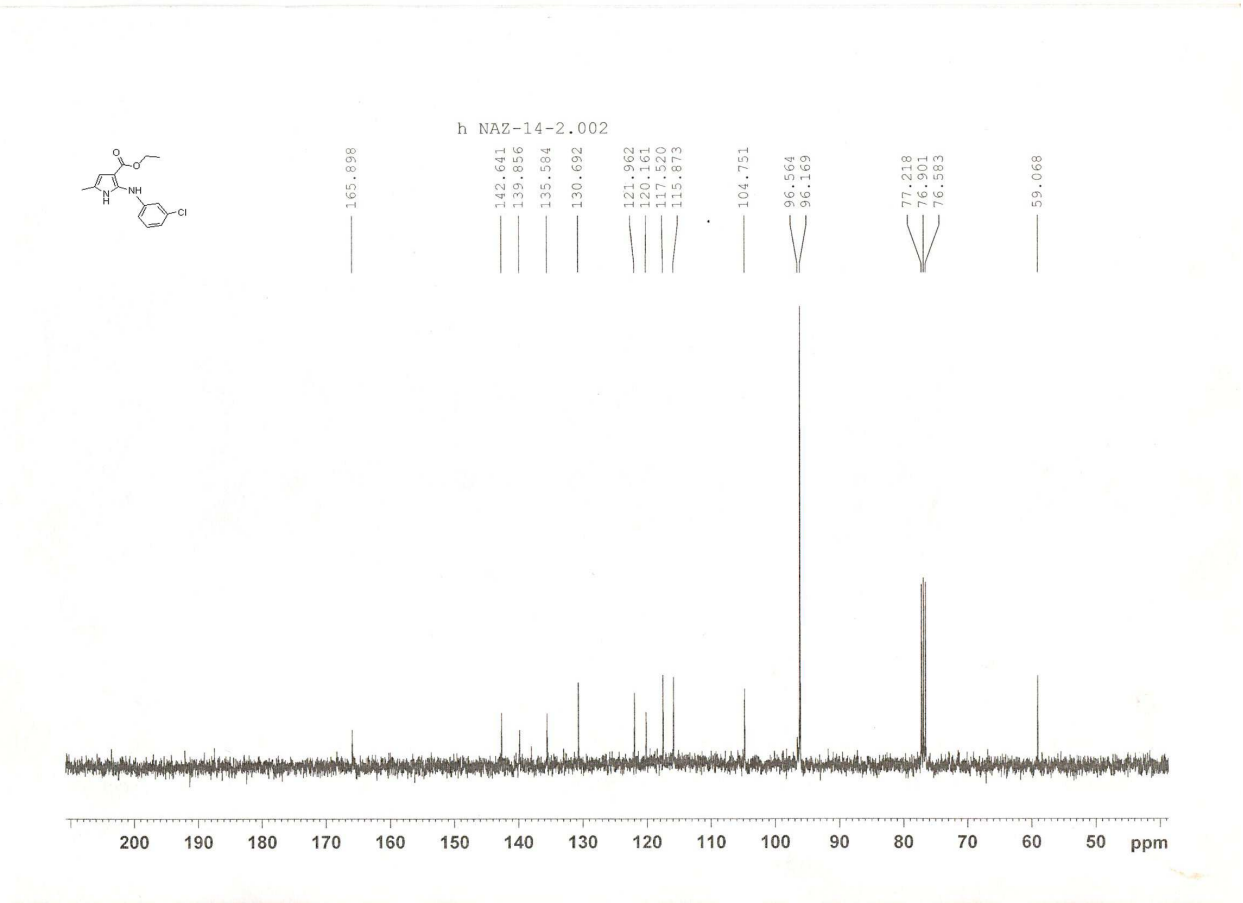

Figure A.24: Ethyl 2-(3-chlorophenylamino)-5-methyl-1*H*-pyrrole-3- carboxylate (**69**)

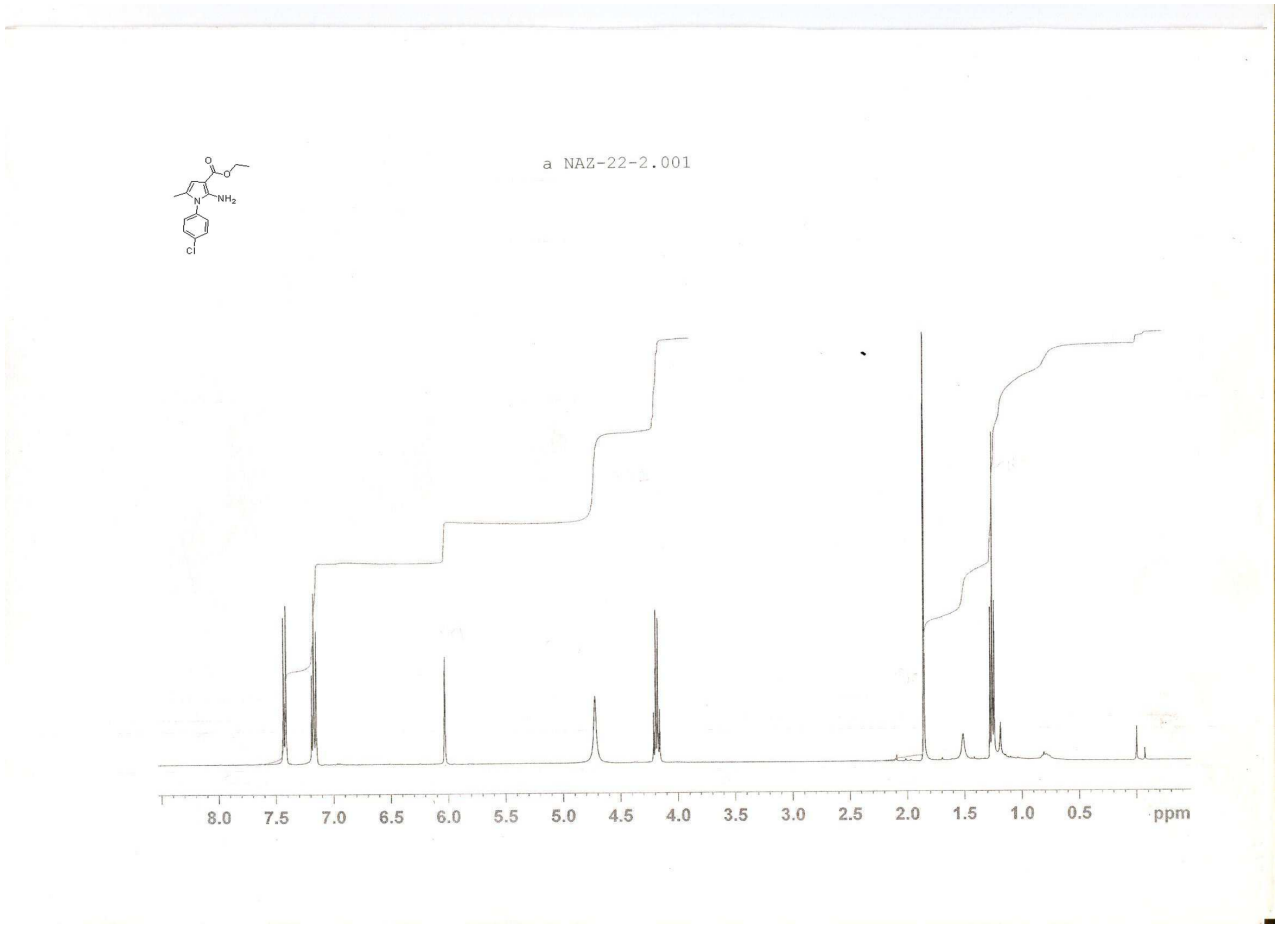

Figure A.25: Ethyl 2-amino-1-(4-chlorophenyl)-5-methyl-1*H*-pyrrole-3-carboxylate (**71**)

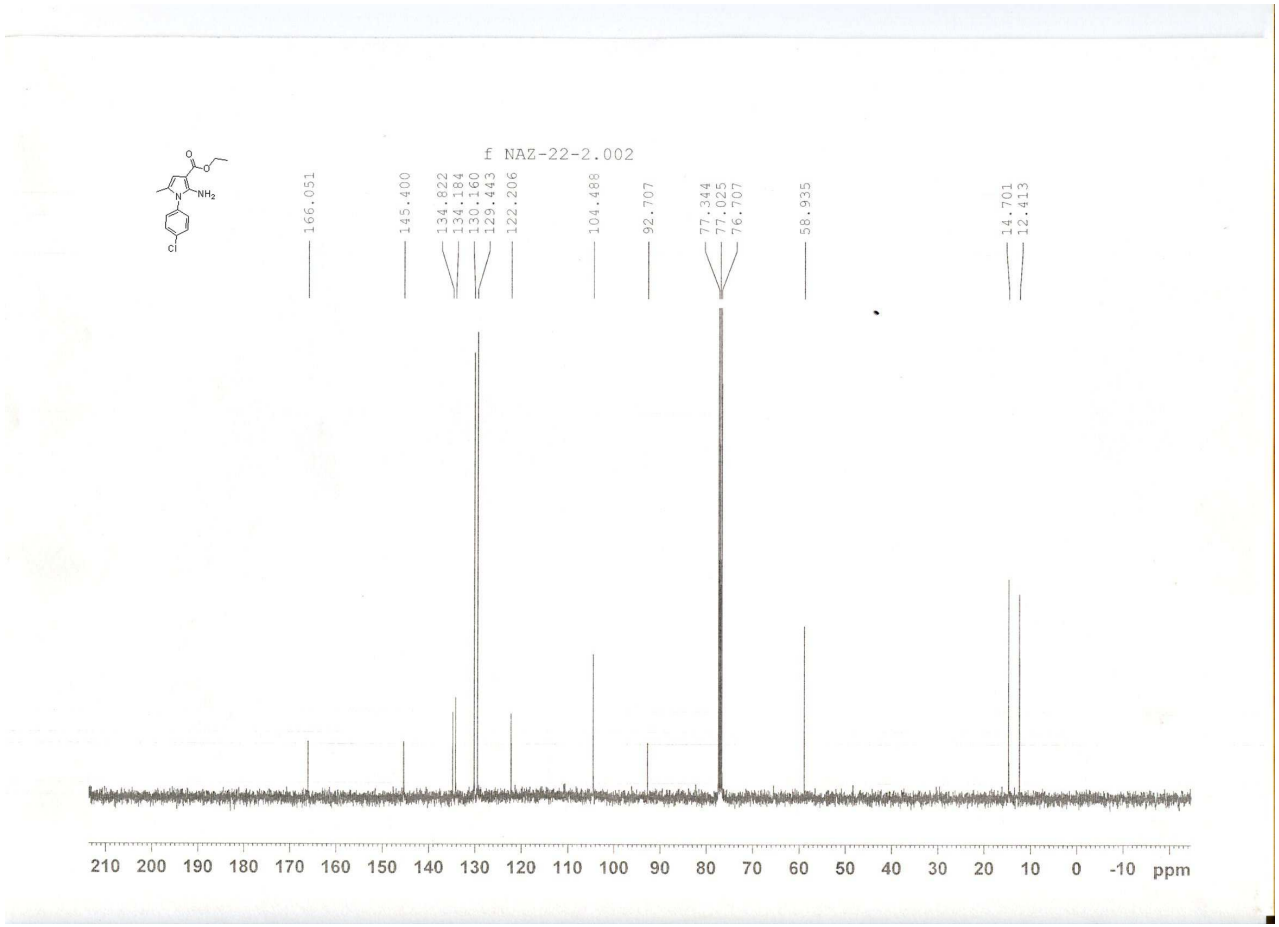

Figure A.26: Ethyl 2-amino-1-(4-chlorophenyl)-5-methyl-1*H*-pyrrole-3-carboxylate (**71**)

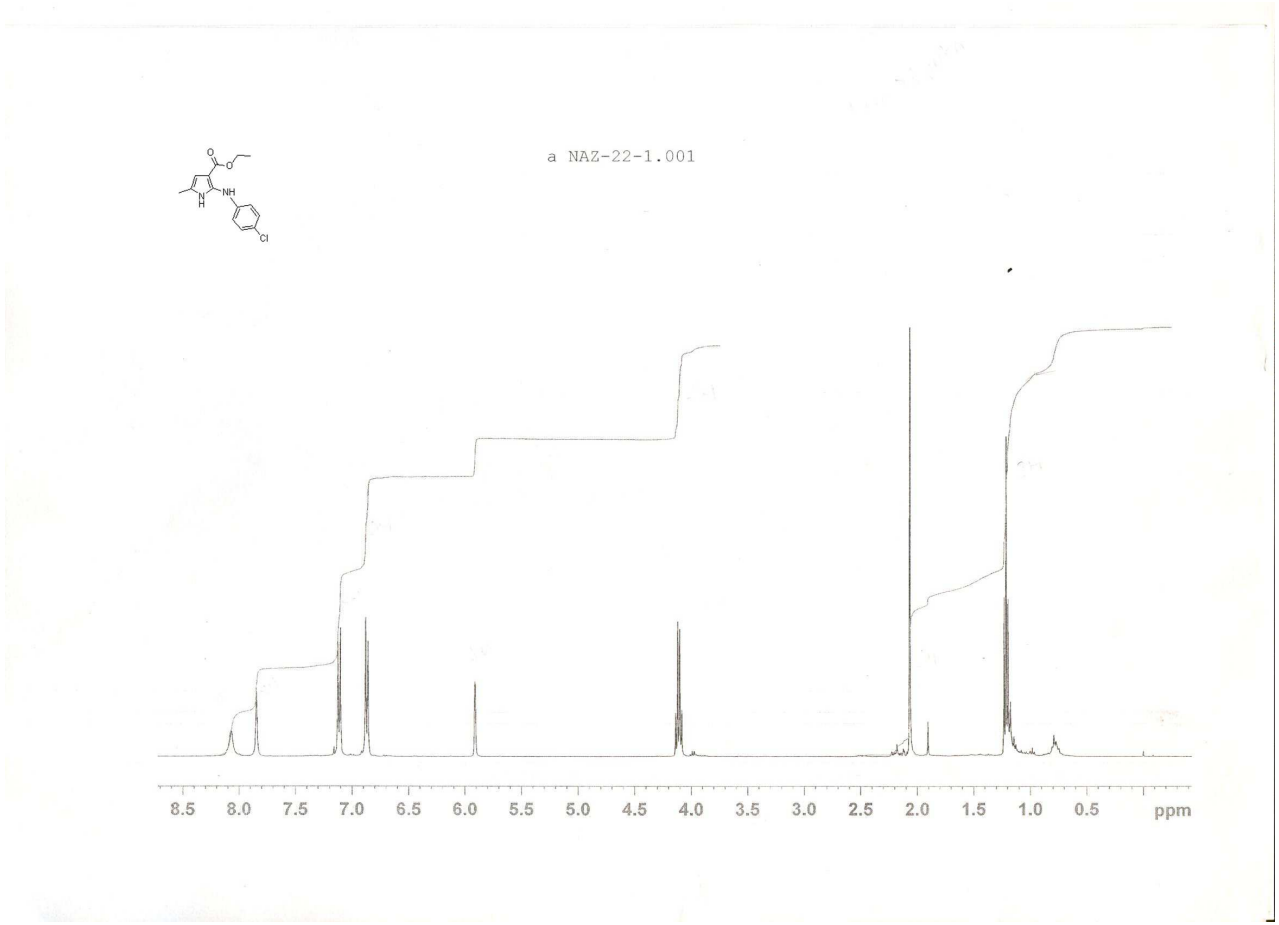

Figure A.27: Ethyl 2-(4-chlorophenylamino)-5-methyl-1*H*-pyrrole-3- carboxylate (**72**)

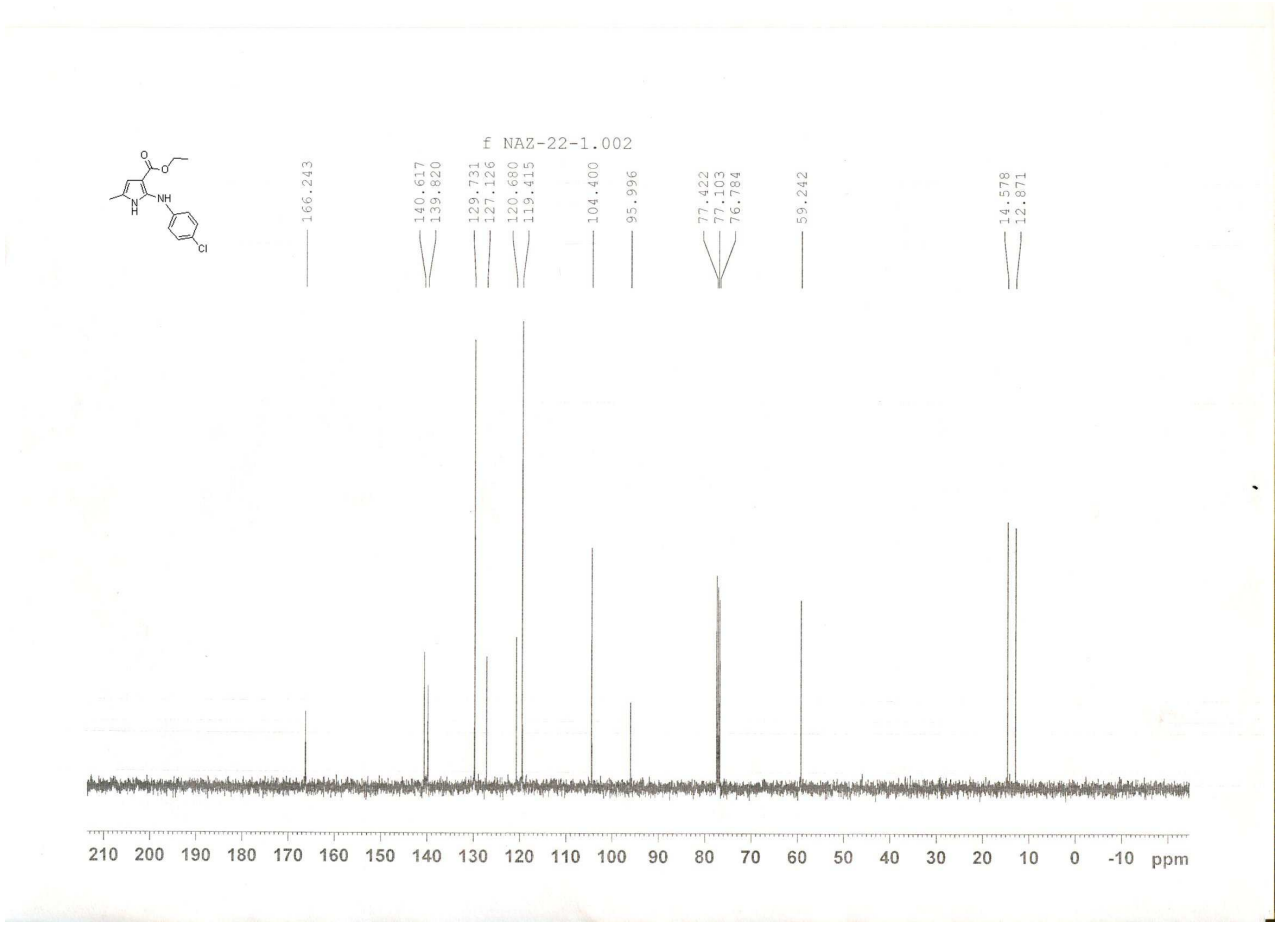

Figure A.28: Ethyl 2-(4-chlorophenylamino)-5-methyl-1*H*-pyrrole-3- carboxylate (**72**)

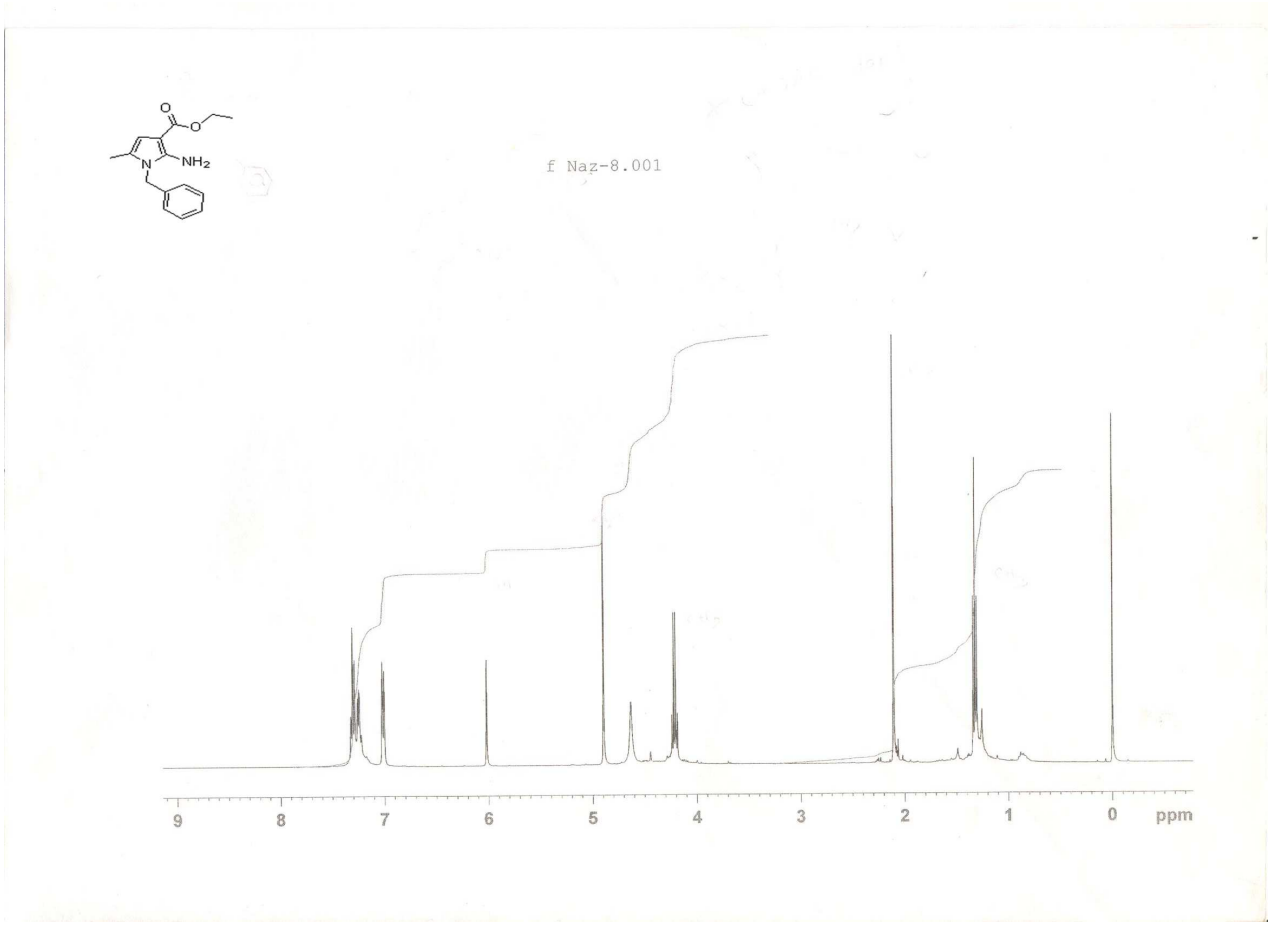

Figure A.29: Ethyl 2-amino-1-benzyl-5-methyl-1*H*-pyrrole-3-carboxylate (**74**)

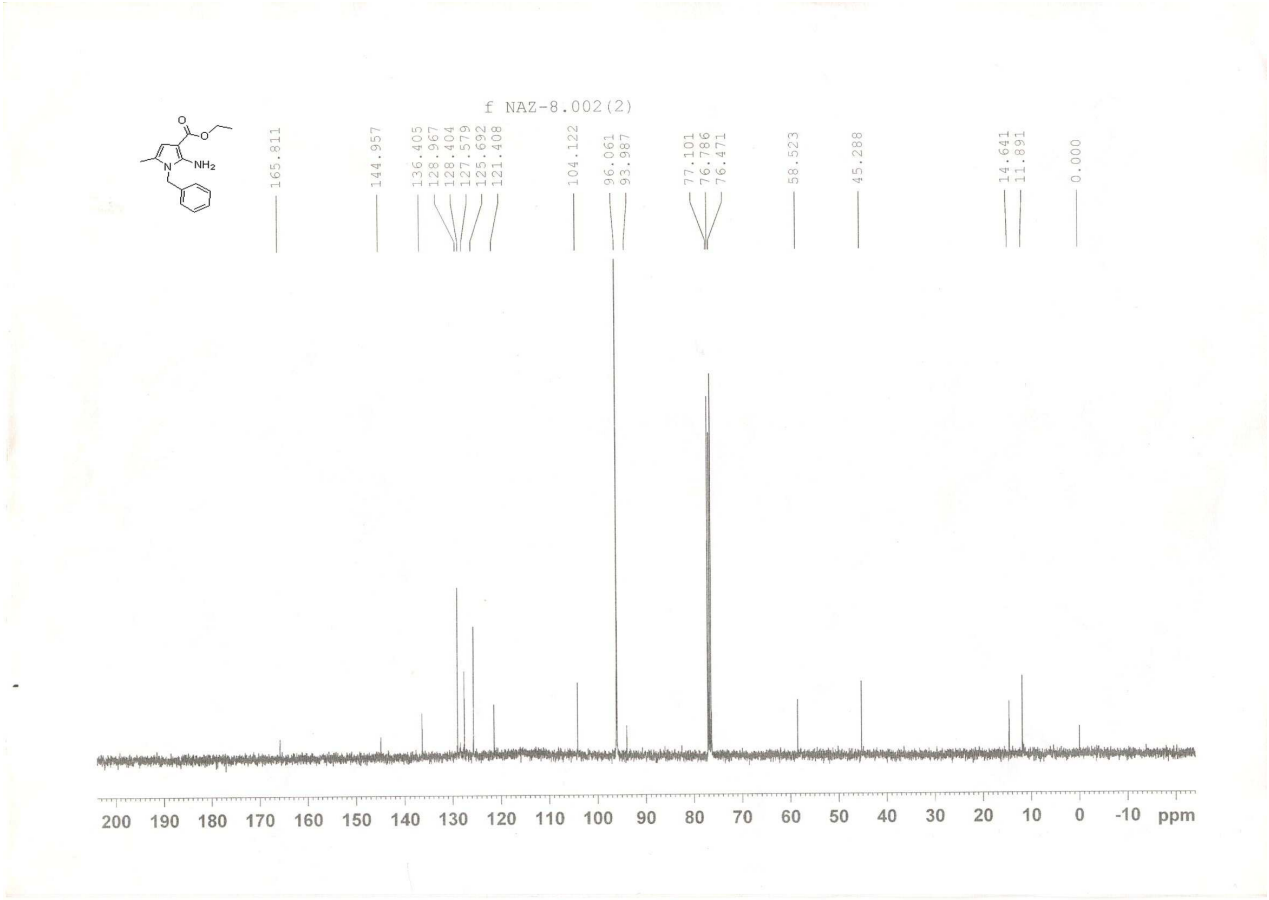

Figure A.30: Ethyl 2-amino-1-benzyl-5-methyl-1*H*-pyrrole-3-carboxylate (**74**)

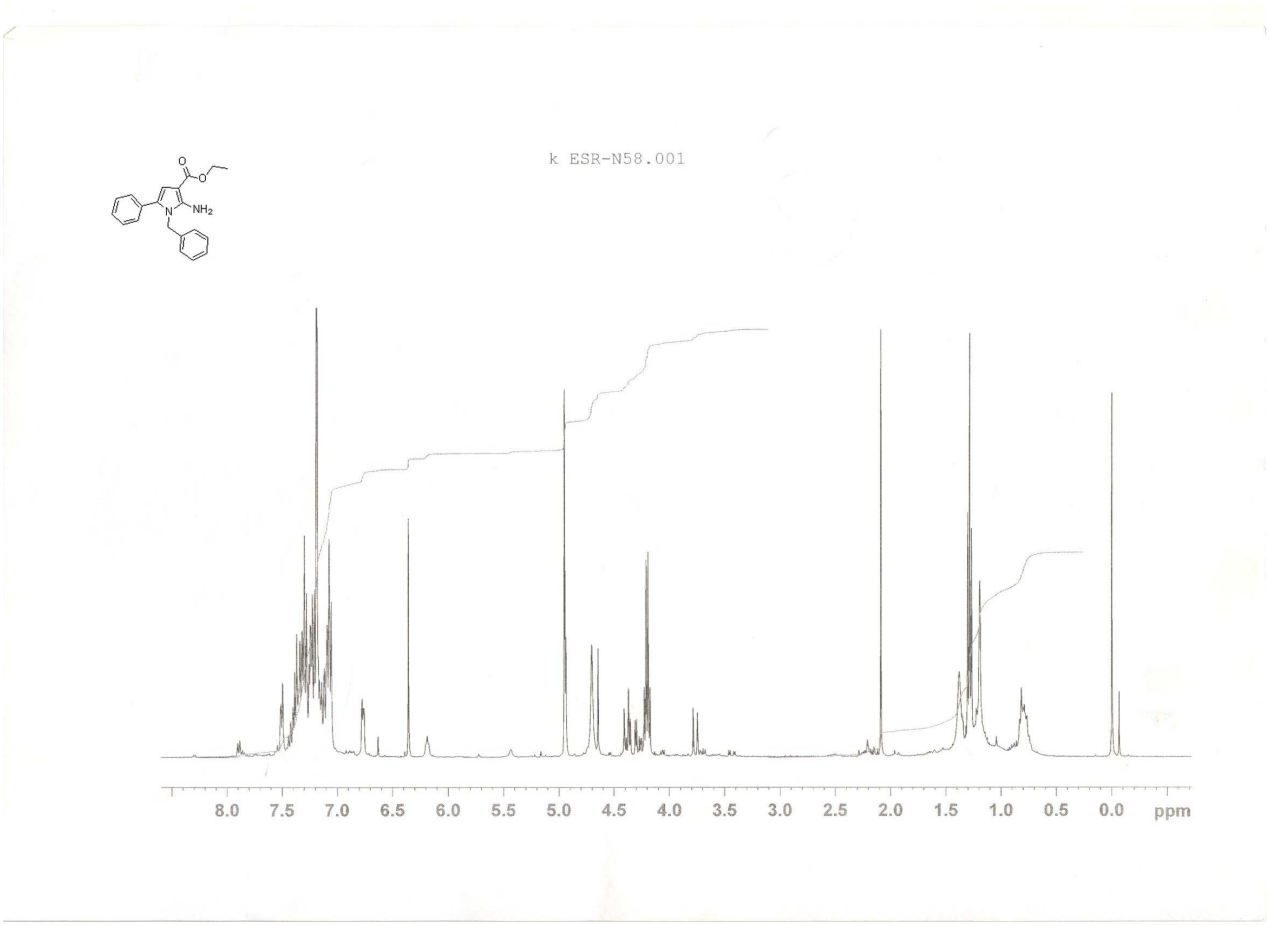

Figure A.31: Ethyl 2-amino-1-benzyl-5-phenyl-1*H*-pyrrole-3-carboxylate (**75**)

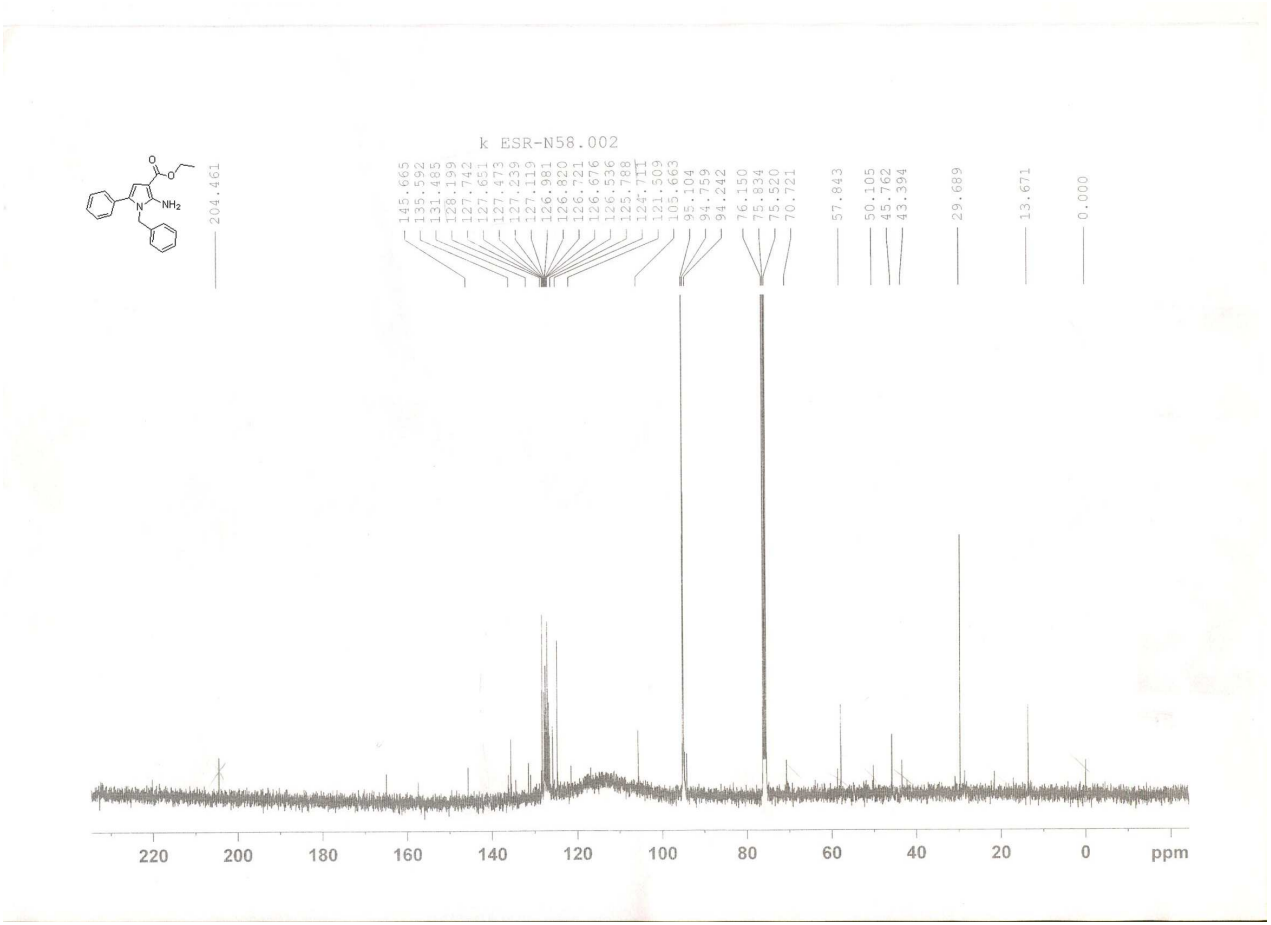

Figure A.32: Ethyl 2-amino-1-benzyl-5-phenyl-1*H*-pyrrole-3-carboxylate (**75**)

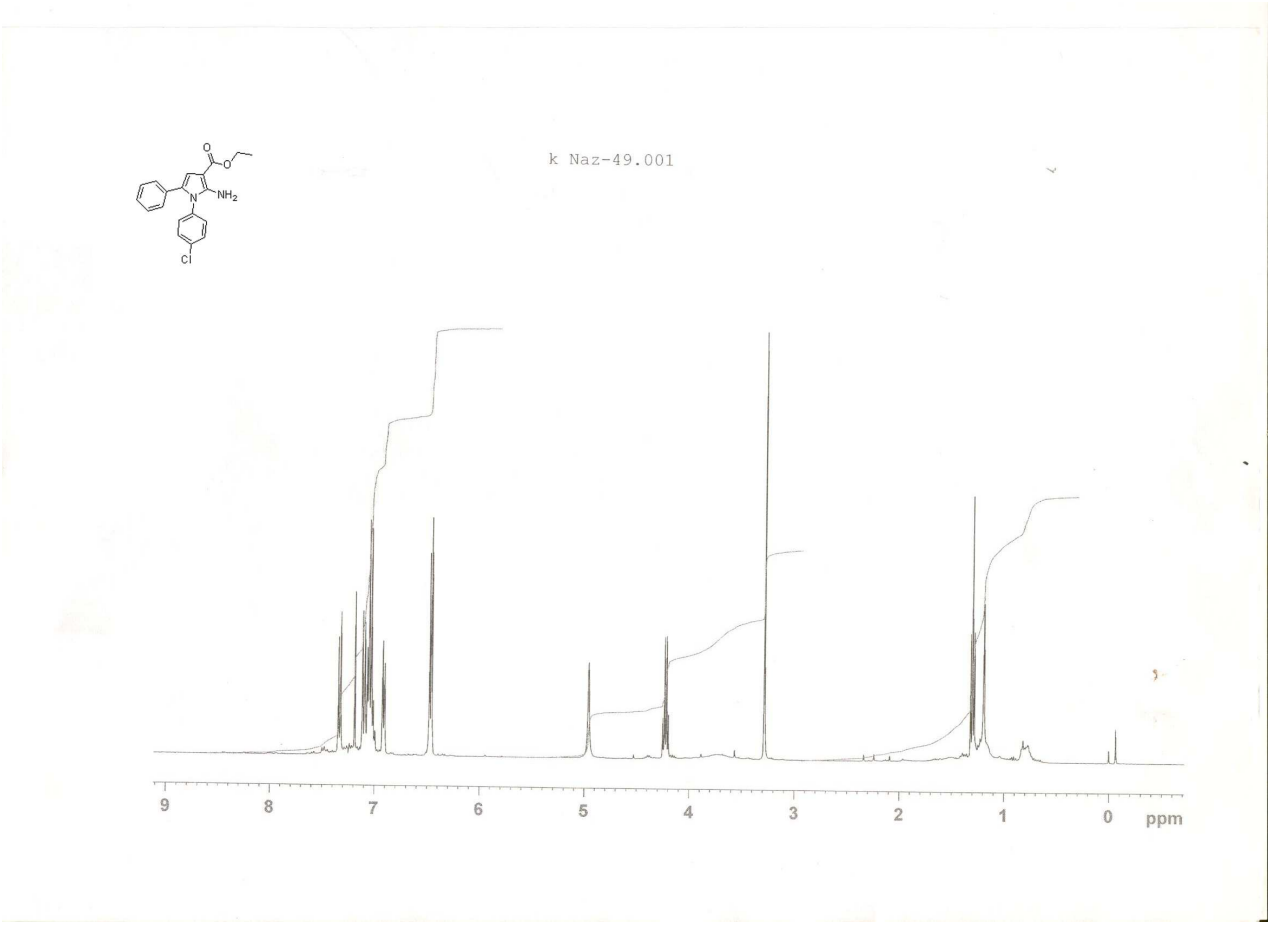

Figure A.33: Ethyl 2-amino-1-(4-chlorophenyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (**76**)

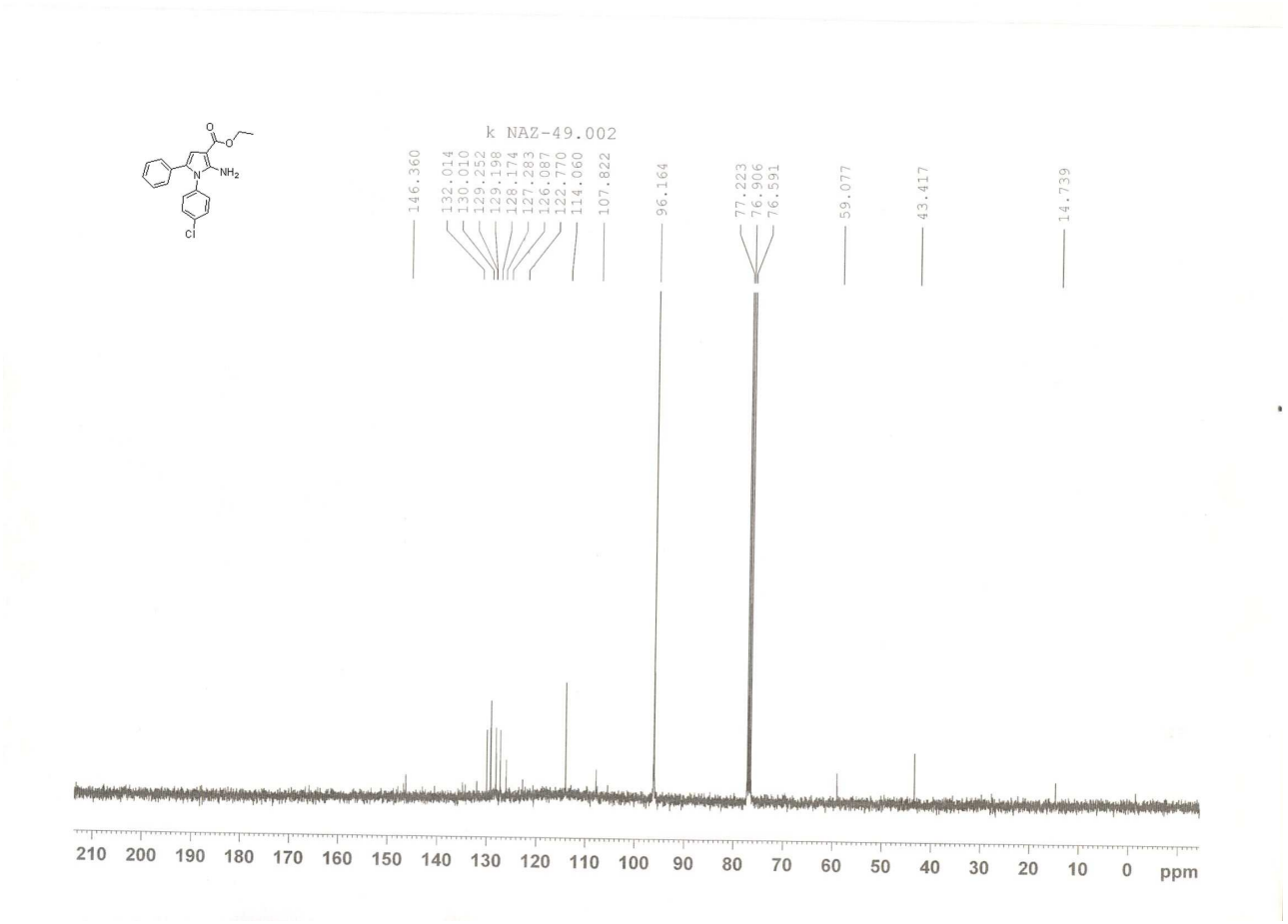

Figure A.34: Ethyl 2-amino-1-(4-chlorophenyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (**76**)

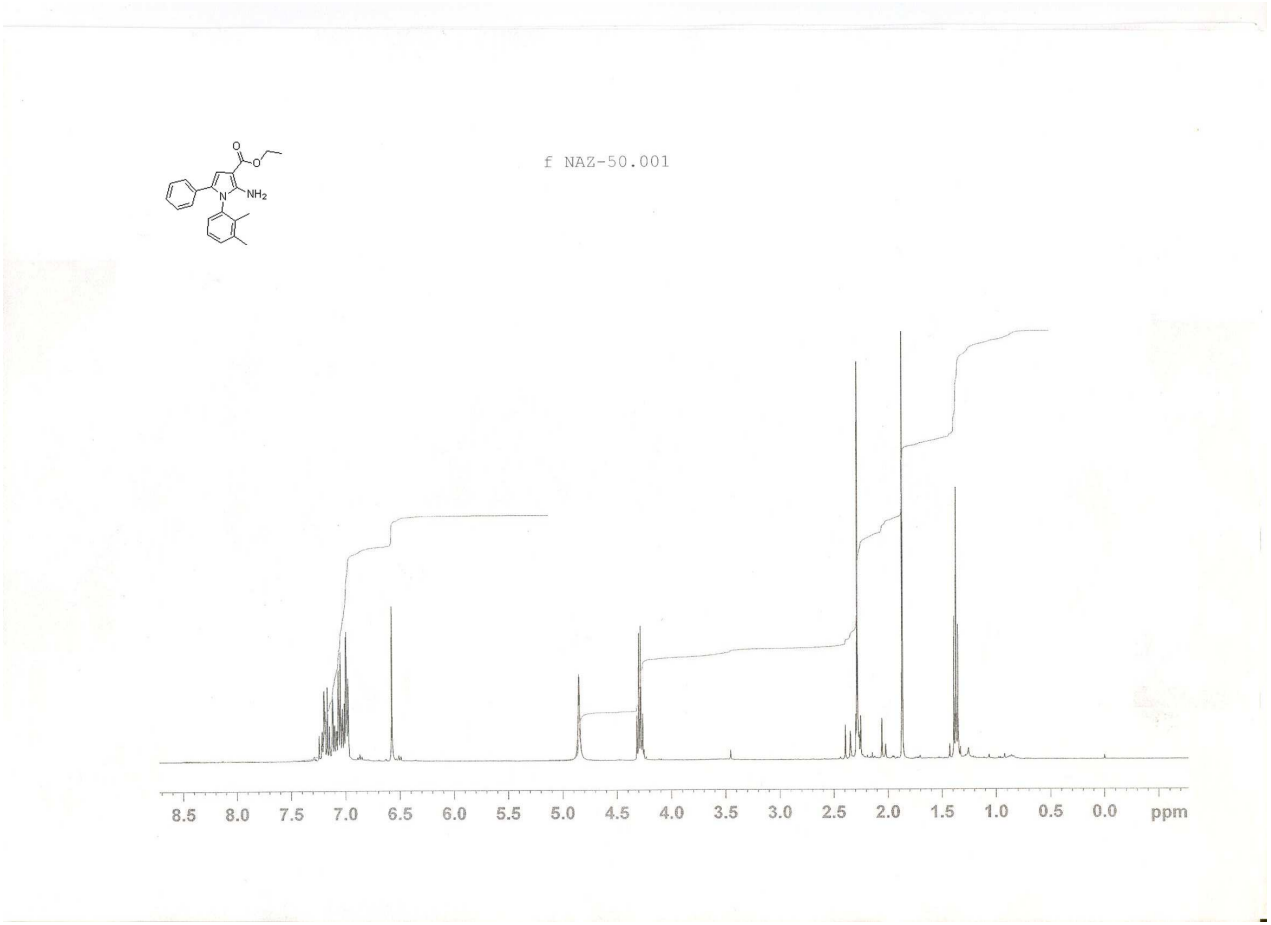

Figure A.35: Ethyl 2-amino-1-(2,3-dimethylphenyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (**77**)

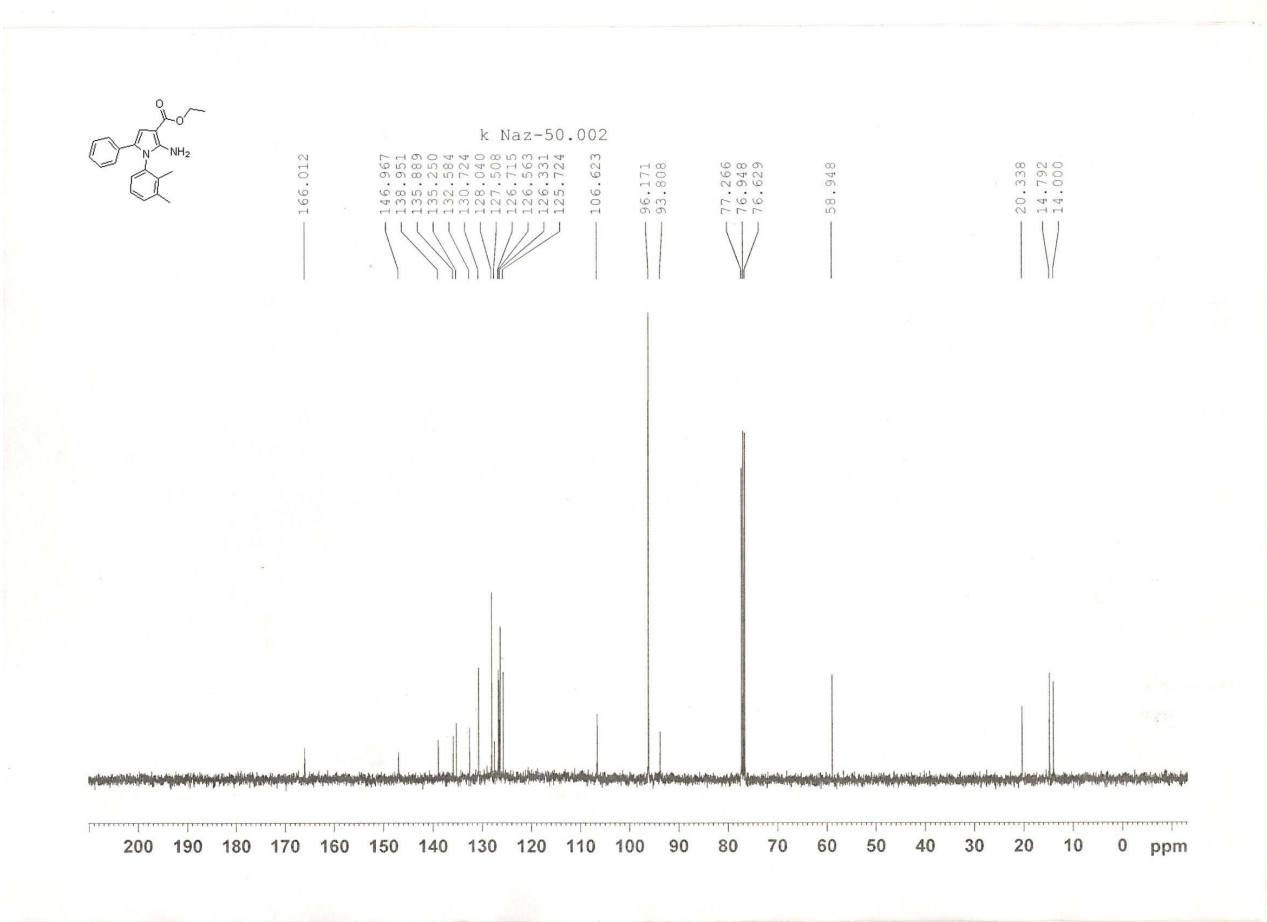

Figure A.36: Ethyl 2-amino-1-(2,3-dimethylphenyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (**77**)

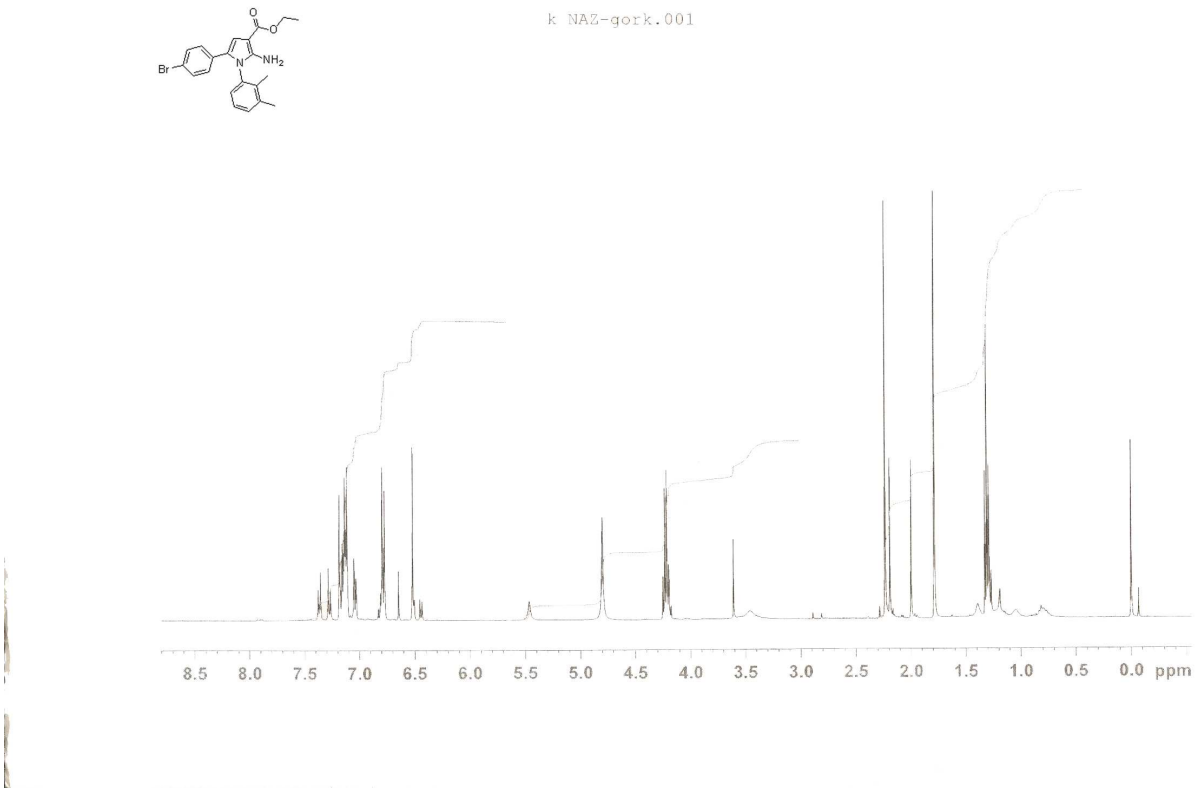

Figure A.37: Ethyl 2-(2,3-dimethylphenylamino)-5-(4-bromophenyl)-1*H*-pyrrole-3-carboxylate (**78**)

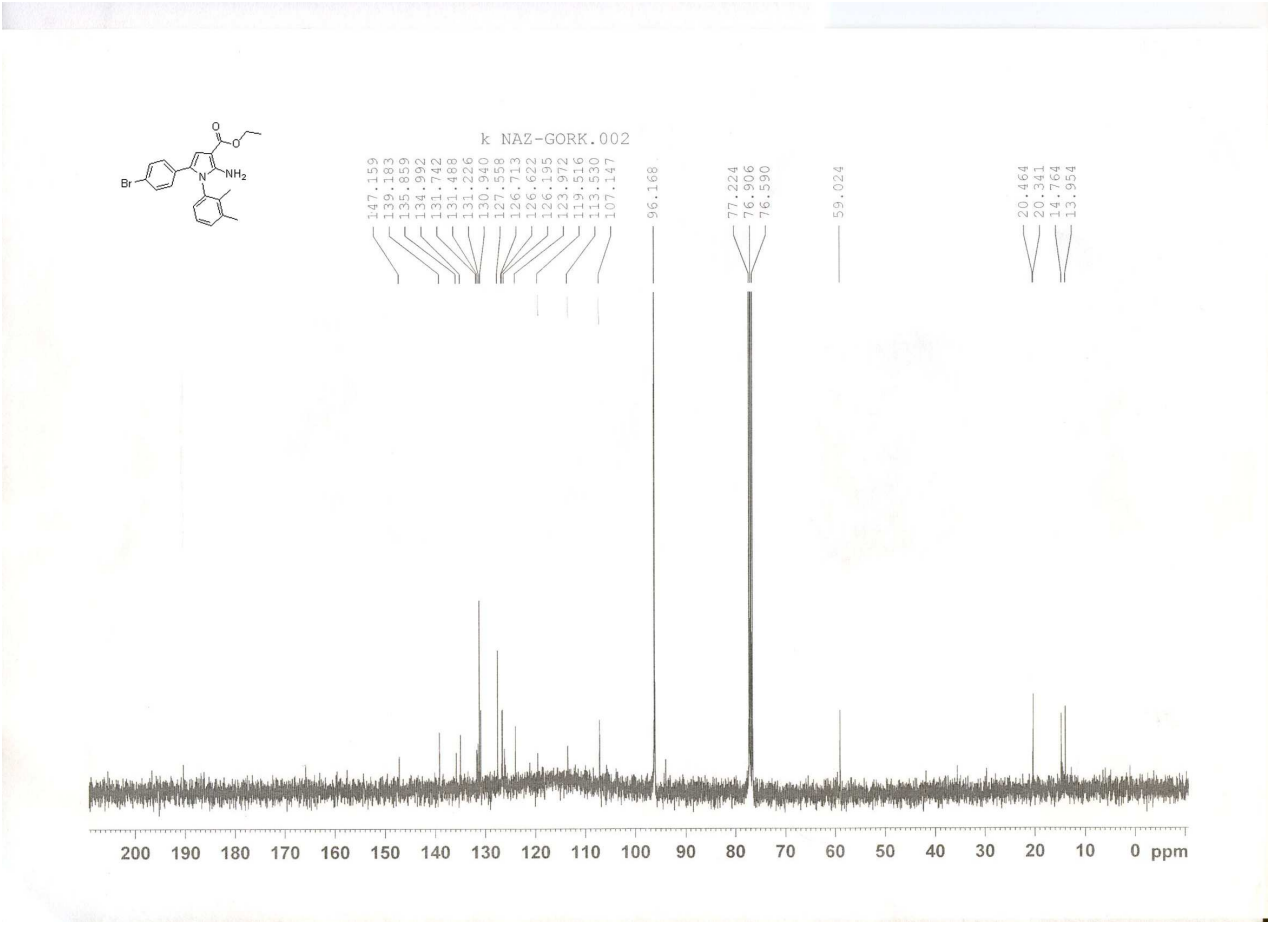

Figure A.38: Ethyl 2-(2,3-dimethylphenylamino)-5-(4-bromophenyl)-1*H*-pyrrole-3-carboxylate (**78**)

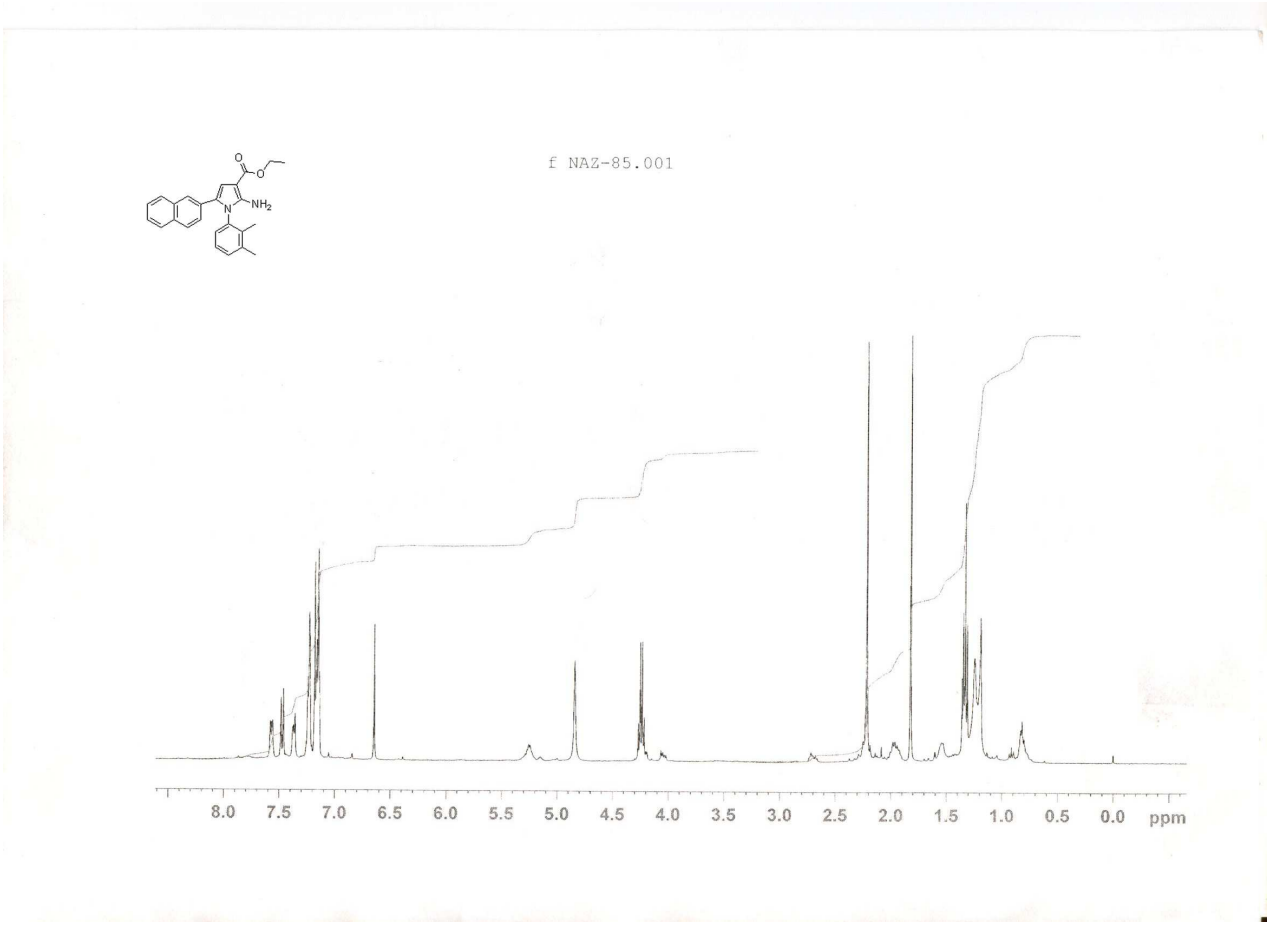

Figure A.39: Ethyl 2-(2,3-dimethylphenylamino)-5-(naphthalen-2-yl)-1*H*-pyrrole-3-carboxylate (**79**)

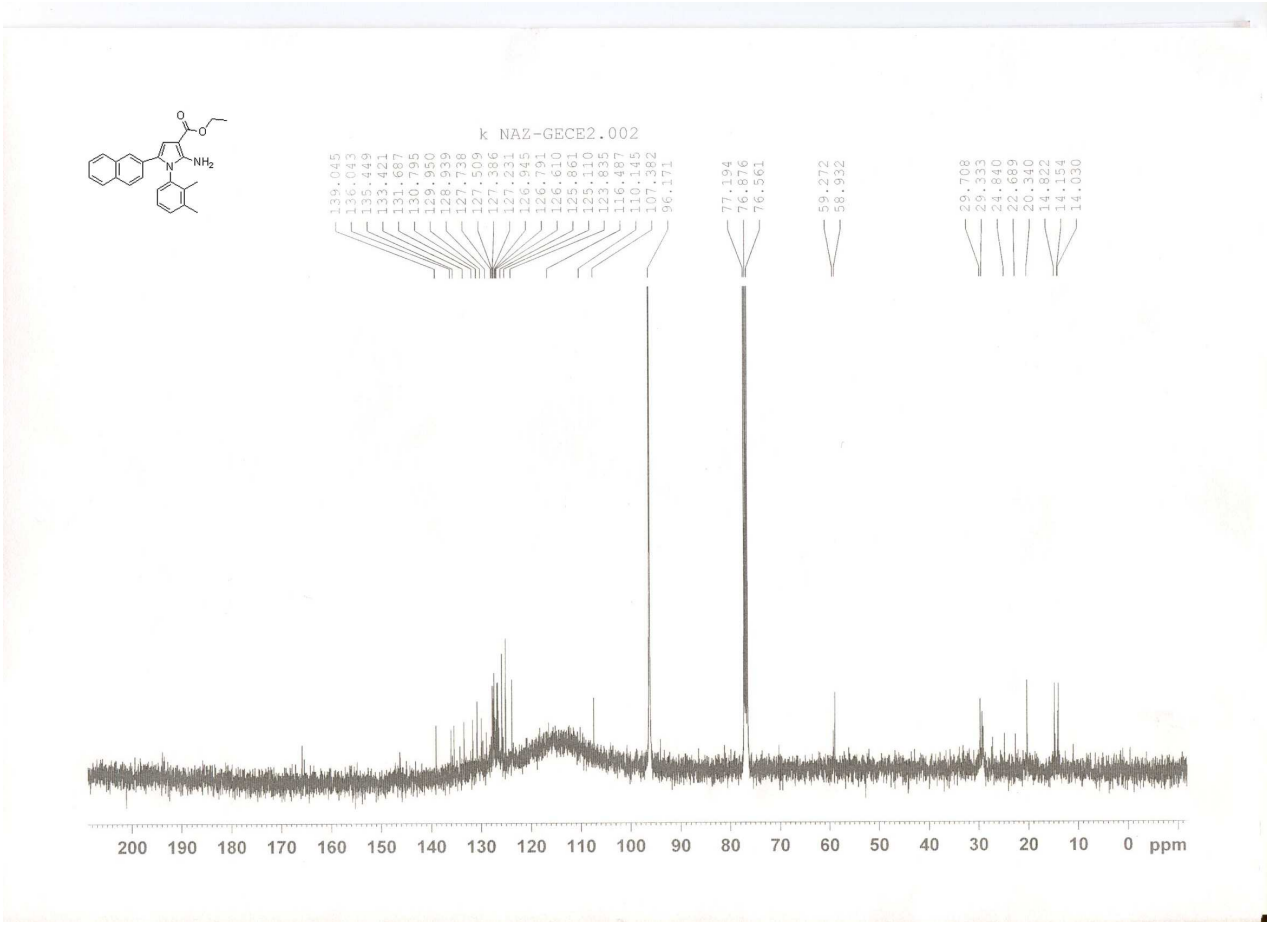

Figure A.40: Ethyl 2-(2,3-dimethylphenylamino)-5-(naphthalen-2-yl)-1*H*-pyrrole-3-carboxylate (**79**)