SYNTHESIS OF BRANCHED ALKYL SUBSTITUTED PHENYLENE DERIVATIVES AS POTENTIAL DRUG MOLECULES ACTIVE AGAINST PROSTATE CANCER

by

Turgay Yıldırım

B.S., Chemistry, Boğaziçi Üniversitesi, 2010

Submitted to the Institute for Graduate Studies in
Science and Engineering in partial fulfillment of
the requirements for the degree of
Master of Science

Graduate Program in Chemistry

Bogazici University

2012

To My Beloved Parents and Girlfriend

ACKNOWLEDGEMENTS

It would not have been possible to write this master thesis without the help and support of my advisor, committee members, colleagues, family and girlfriend.

First of all, I would like to express my deepest gratitude to my advisor, Assoc. Prof A. Ersin ACAR, for his guidance, patience, caring and encouragement during this study. I also feel very lucky for being a group member of Acar Research Goup and I would like to thank again Assoc. Prof. A. Ersin ACAR to believing and accepting me to his group.

I would like to thank my committee members Prof. Duygu Avcı Semiz and Assoc. Prof. Halil Kavaklı for spending their valuable times and reviewing my thesis.

I want to thank all of my lab friends; first of all Ahmet and Turhan for their support, enjoyable friendship and help to my study and Nurdan, Şükrü, Sezgin, Selda, Seda, Elif and Gökçe for their friendship. I also like to thank Nergiz, Aladdin, Özge for their friendship and especially Furkan for his support and enjoyable friendship.

I would like to thank Ayla Türkekul and Burcu Selen Çağlayan for the NMR analysis.

Finally, I want to thank to my family and girlfriend. Especially to my brothers Turgut and Kenan for always believing me and encouraging me. Last, but no means least, I like to thank my girlfriend for her unconditional love.

This research has been funded by Bogazici University Research Funds (BAP, Project No: 5085) and The Scientific and Technological Research Council of Turkey (TÜBİTAK, Project No: 109T431).

ABSTRACT

SYNTHESIS OF BRANCHED ALKYL SUBSTITUTED PHENYLENE DERIVATIVES AS POTENTIAL DRUG MOLECULES ACTIVE AGAINST PROSTATE CANCER

Prostate cancer is the most common cancer type among male all around the world. Androgens are steroid based hormones which control the maintenance of male sex characteristics. It was found that high levels of androgens increase the risk of getting prostate cancer in some men and also promote the prostate cell growth. Therefore, reducing androgen level could be successful to suppress tumor growth. The two most important androgens are testosterone (T) and dihydrotestosterone (DHT). Amount of testosterone and dihydrotestosterone in blood is proportional to the androgen biosynthesis. Therefore, suppression of these androgens have been become the target of many studies which deal with the PC. Androgens are synthesized in both testes and adrenal glands. Therefore, to stop androgen biosynthesis it is necessary to inhibit the androgen biosynthesis in both testes and adrenal glands. CYP17 catalyzes, in testes and adrenals, the synthesis of both testosterone and DHT. Because of that reason CYP17 is the main target enzyme for the treatment of prostate cancer. CYP-17 inhibitors can be classified as steroidal and non-steroidal inhibitors. Non-steroidal compounds have advantages to the steroidal compounds. In this respect researchers in Koc University screened computationally about 50000 molecules and a non-steroidal lead molecule was determined. In this project, variations on the lead compound were done where mainly branched alkyl substituted phenylene rings and their couplings with available naphtoic acid derivatives were targeted. For this purpose 9 compounds were synthesized successfully and sent to the Koc University for biological testing.

ÖZET

PROSTAT KANSERİNE KARŞI AKTİF, POTANSİYEL İLAÇ MOLEKÜLLERİ OLARAK DALLANMIŞ ALKİL FENİLEN TÜREVLERİNİN SENTEZİ

Prostat kanseri tüm dünya çapında erkekler arasında en yaygın kanser türüdür. Androjenler karakteristik erkeklik özelliklelerini kontrol eden steroid bazlı hormonlardır. Yüksek androjen seviyesinin bazı erkeklerde prostat kanserine yakalanma ihtimalini artırdığı ve kanserli hücreleri büyüttüğü kanıtlanmıştır. Bundan dolayı androjen seviyesinin düşürülmesiyle tümörlü hücrelerin büyümesi yavaşlatılabilir. Testosteron ve dihidrotestosteron en önemli iki androjendir. Kandaki testosteron ve dihidrotestosteron oranı androjen biyosentezi ile doğru orantılıdır. Bu sebepten dolayı testosteron ve dihidrotestosteron sentezini durdurmak prostat kanseri tedavisi için yürütülen birçok araştırmanın başlıca hedefi olmuştur. Androjenler testislerde ve böbrek üstü bezlerinde sentezlenir. Bundan dolayı androjen sentezinin durdurulması için testislerdeki ve böbrek üstü bezlerindeki androjen biyosentezin inhibe edilmesi gereklidir. CYP 17 testislerdeki ve böbrek üstü bezlerindeki testosteron ve dihidrotestosteron sentezini katalize eder. Bu sepele CYP 17 enzimi prostat kanseri tedavisinde hedef enzimdir. CYP 17 inhibitörleri steroid bazlı olanlar ve steroid bazlı olmayanlar olarak iki sınıfa ayrılabilir. Steroid bazlı olmayan moleküllerin steroid bazlı olanlara karşı avantajları vardır. Bu balgamda Koç üniversitesindeki araştırmacılar yaklaşık 50000 molekülü taradı ve steroid bazlı olmayan bir öncü bileşik bulundu. Bu projede dallanmış alkil takılı fenil bileşiklerinin sentezi ve bu bileşiklerin mevcut naftoik asit türevleriyle bağlama reaksiyonları amaçlanmıştır. Bu amaçla 9 molekül başarıyla sentezlendi ve biyolojik testler için Koç Üniversitesine gönderildi.

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LIST OF ACRONYMS/ABBREVIATIONS

ACS	American Cancer Society
ADMET	Adsorption, Distribution, Metabolism, Elimination and Toxicity
ADT	Androgen Deprivation Therapy
BE	Binding Energy
BPH	Benign Prostatic Hyperplasia
CADD	Computer Assisted Drug Design
$CDCl_3$	Deutorated chloroform
CH_2Cl_2	Dichloromethane
CYP	Cytochrome P-450
CYP 17	17 alpha-hydroxylase cytochrome P-450 (P-$450_{17\alpha}$)
DHT	5α-dihydrotestosterone
DE	Docking Energy
DNA	Deoxyribonucleic acid
DRE	Digital Rectal Exam
EtOAc	Ethyl acetate
IC_{50}	50% Inhibition of Concentration
LC-MS	Liquid Chromatography-Mass Spectroscopy
LH-RH	Luteinizing Hormone-Releasing Hormone
NMR	Nuclear Magnetic Resonance
PC	Prostate Cancer
PCF	Prostate Cancer Foundation
PDB	Protein Data Bank
PSA	Prostate-Specific Antigen
QSAR	Quantitative Structure Activity Relationship
SAR	Structure Activity Relationships
SBDD	Structure Based Drug Design
SEER	Surveillance Epidemiology and End Results
TEA	Triethylamine
THF	Tetrahydrofuran
TRUS	Transrectal Ultrasound

TLC	Thin Layer Chromatography
WHO	World Health Organization

1. INTRODUCTION

1.1. What is Cancer?

Cancer is a general name for more than 100 different diseases. The common point of these diseases is the uncontrolled growth of abnormal cells that grow beyond their usual boundaries and then spread over to other organs from adjoining parts of the body. This phenomena is named as metastasis which is the major cause of the death from cancer.

As reported by World Health Organization (WHO), cancer is the dominant cause of death around the globe. WHO also states that more than 11 million people are diagnosed with cancer every year and approximately 7.6 million people died from cancer in 2008. Furthermore, it is estimated that deaths from cancer will increase over 13.1 million in 2030 all around the world [1].

According to Surveillance Epidemiology and End Results (SEER), from 2003 to 2007 the average age at diagnosis for cancer of all sites was 66 years of age. Around 1.1% of the subjects were younger than 20; 2.7% were between 20 and 34; 5.6% were between 35 and 44; 14.1% were between 45 and 54; 22.7% were between 55 and 64; 24.7% were between 65 and 74; 21.4% were between 75 and 84; and 7.8% were 85+ years of age [2].

Although it has been scientifically proved that some factors increase the risk of getting cancer cells there is no obvious explanation why some people have cancer cells but others do not [3]. The main risk factors for cancer are:

- Growing older
- Tobacco
- Sunlight
- Ionizing radiation
- Certain chemicals
- Some viruses and bacteria

- Certain hormones
- Family history of cancer
- Alcohol

Treatment of cancer patients differs from type of the cancer that patients have but usually combination of therapies applied to the patients. Chemotherapy, hormone therapy, immunotherapy, gene therapy, radiation and surgery techniques are used for treatment of cancer [4].

1.2. Prostate cancer

Prostate cancer (PC) is the most common cancer type among male all around the world [5]. In fact apart from the lung cancer it is the second leading cause of death from cancer in the western world [6]. It is estimated that approximately 17% of men in US will be diagnosed with prostate cancer in their life and approximately 3% of them will die [7]. Several factors increase the developing prostate cancer [8]. The main factors are:

- Age
- Family history
- Race
- Living environment
- Changes in genome
- Changes in prostate glands

Although some PC types develop quickly, predominantly PC grows very slowly because of that it is difficult to see the symptoms of PC at the beginning stages. At later stages symptoms are more observable and common symptoms of PC can be stated as follows [9]:

- Urination problems
    (i) Often urination
    (ii) Difficulty at start and stop urination

(iii) Weak urinary flow

(iv) Hurtful sensation during urination

- Blood in urine or semen
- Pain in the hips
- Frequent low back pain
- Erection problems

1.3. Correlation between androgens and prostate cancer

Androgens are steroid based hormones which control the maintenance of male sex characteristics [10]. For normal development and maintenance of adrenal gland androgens have important role [11]. However, it was found that high levels of androgens increase the risk of getting prostate cancer in some men and also promote the prostate cell growth [12]. The two most important androgens are testosterone (T) and dihydrotestosterone (DHT) (Figure 1.1).

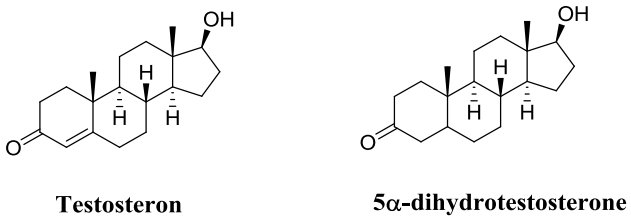


Figure 1.1. Structure of testosterone (T) and dihydrotestosterone (DHT).

Testosterone (T) is synthesized 90% in testes and 10% in adrenal glands then it is converted to dihydrotestosterone (DHT) which is more potent androgen by the enzyme 5α-reductase that is localized primarily in the prostate [13]. Amount of testosterone and dihydrotestosterone in blood is proportional to the androgen biosynthesis where high amounts increases the risk of getting prostate cancer [14, 16]. Therefore, reducing androgen level could be successful to inhibition of tumor growth [17].

1.4. Diagnosis of prostate cancer

Prostate specific antigen (PSA) is a physiologic product of normal epithelial cells and also it is known that men who have PS have relatively higher serum PSA compared to those who don't [18]. Therefore, at the early phases PSA level in blood which is determined by the PSA screening test can be used for the PC diagnosis [19].

Digital rectal examination (DRE) is another method to diagnose PC. To check the health of the internal organs DRE is used so it is an important method for early detection of tumors [20].

Transrectal ultrasound (TRUS) is a different method used for the diagnosis of prostate cancer. TRUS is a diagnostic and locator tool it is used by inserting an ultrasound probe into the rectum and releasing ultrasound waves and reflecting the image of the rectum on a screen [21].

If PSA level is very high and DRE is unsteady prostate biopsy is used to confirm the prostate cancer [22].

Progress of PC can be divided into 4 stages [23]:

- Stage A : Incidentally discovered and clinically undetectable
- Stage B : Detectable with DRE ; tumor spreads only in prostate
- Stage C : Locally invading tumor
- Stage D : Advanced stage; metastasis occurs and tumor invades the other parts of the body

1.5. Treatment of prostate cancer

Because of the age problems, expected lifetime, clinical stage, tumor grade, personal preferences and adverse effects it is difficult for doctors to choose the best treatment method for prostate cancer. The common treatment options can be stated as follows [24]:

- Prostatectomy (Surgery)
- Radiation therapy
- Hormone therapy
- Chemotherapy
- Cryosurgery
- Biological therapy
- High-Intensity Focused Ultrasound
- Proton Beamed Radiation Therapy

1.5.1. Androgen removal

About 80% of prostate cancers are androgen dependent. Androgens play an important role in the development, growth, and progression of the prostate cancer cells [25]. As stated before two main male hormones testosterone (T) and dihydrotestosterone (DHT) contribute to the progression of PC. Therefore, suppression of these androgens have been become the target of many studies which deal with the PC.

It has been found that androgen removal decreases the PSA level in the blood and also shrinks, stops growing of the cancerous cells [26]. Androgen removal used to be done with orchiectomy which is a surgery technique in which one or both of the testes are removed [27]. But orchiectomy cannot remove entire androgen biosynthesis because as stated earlier testes are not the only source of the androgens, adrenal glands also synthesize androgens.

1.5.2. Hormone therapy

Prostate cancer cells need androgens to survive and grow. In this respect the aim of the hormone therapy is to reduce the amount of androgens [28]. Hormone therapy can be applied in three ways [29]:

- Using anti-androgens to block androgen action

- Using luteinizing hormone-releasing hormone (LHRH) agonists ketoconazole and aminoglutethimide to interrupt testosterone production
- Taking estrogens

Nevertheless, none of these drugs are selective enough to inhibit the androgen formation. Also, all of these drugs have some significant side effects. For example ketoconazole, which is an imidazole antifungal agent, inhibits testicular and adrenal androgen synthesis by inhibiting cytochrome P-450-dependent 14-demethylation step in the steroid synthesis pathway [30] but ketoconazole also inhibit other cytochrome P-450 enzymes and causes dangerous hepatic dysfunction and gastrointestinal disturbances. Because of that, clinical use of ketoconazole is limited [31]. Like ketoconazole, anti-androgens have many side effects like liver problems, anemia and nausea. Also estrogens cause breast growth, tenderness and water retention.

Because of current treatment options' significant side effects which were mentioned above there is a need for new therapeutic methods which have minimum side effects.

1.6. New therapeutic approaches

In the last two decades researchers have focused their efforts on the development of new therapeutic methods because of the many crucial side effects of the standard treatment methods. Among these new methods androgen deprivation therapy (ADP) is the most promoting one which gives the best responses for the prostate patients [32].

It is believed that decreasing the biological androgen synthesis in both testes and adrenal glands could be useful in the treatment of the prostate cancer [33]. As stated before, androgens stimulate the prostate cancer. Hence, suppression of synthesis or release of androgenic hormones has become the major new therapeutic approach in the treatment of the prostate cancer [34]. Hence, mechanism of synthesis of testosterone (T) and dihydrotestosterone (DHT) has to be understood at first.

1.6.1. Biological Synthesis of Testosterone (T) and Dihydrotestosyerone (DHT)

P-450 (CYP) enzyme family takes has a crucial role as a catalyst in the biological synthesis of T and DHT. CYP enzyme system is a large family which consists of medium size proteins and a single iron prosthetic group [35]. CYP17 (P-450, 17α-hydroxylase-C17, C20 lyase) which is a member of P-450 enzyme family catalyzes the last step of the androgen biosynthesis in both testes and adrenals [36]. For the biosynthesis of androgens in both testes and adrenals cholesterol is the starting material [37]. As it can seen from Figure 1.2 [38], CYP17 is the key enzyme which catalyzes the two reactions firstly 17-α hydroxylation of pregnenolone and progesterone then 17,20-lyse reaction which cleaves C17-C20 bond to give 17-keto androgens androstendione and dehydroandrostendione (DHEA). These compounds are then converted to the testosterone (T).

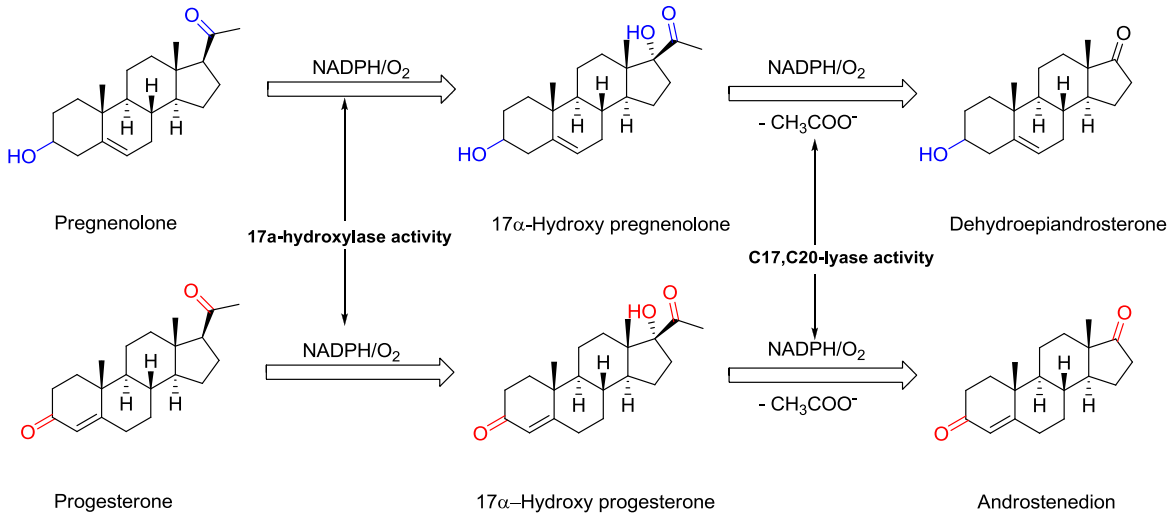


Figure 1.2. CYP17 catalyzed androgen biosynthesis.

1.6.2. Target enzyme: CYP-17

As mentioned before, androgens are synthesized in both testes and adrenal glands. Therefore, to stop androgen biosynthesis it is necessary to inhibit the androgen biosynthesis in both testes and adrenal glands [39].

Figure 1.3 shows the enzymatic pathway of androgen biosynthesis [40]. P-450, 17α-hydroxylase-C17, C20 lyase (CYP17) catalyzes, in testes and adrenals, the synthesis of both testosterone and DHT [36]. So, the inhibition of CYP17 should stop the biological androgen synthesis. Because of that reason CYP17 is the main target enzyme for the treatment of prostate cancer [41].

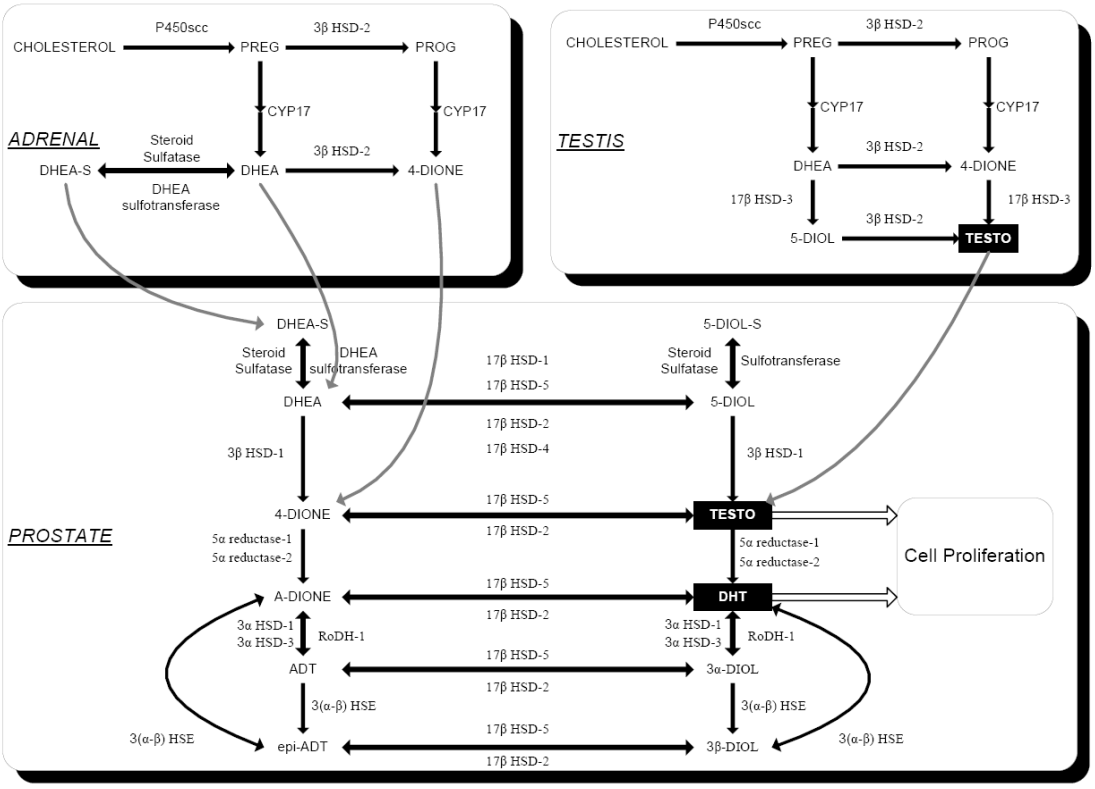


Figure 1.3. Enzymatic synthesis of androgens in testes and adrenals.

1.7. Drug Discovery, Design and Optimization

1.7.1. Drug Discovery

Initial step for the drug discovery is to decide on the disease which will be tried to cure. Second step is to determine the important bio-macromolecules which are involved in the disease [42]. After choosing the target bio-macromolecules, lead compound selection is crucial. Lead compounds which are the starting materials for drug design can be defined as

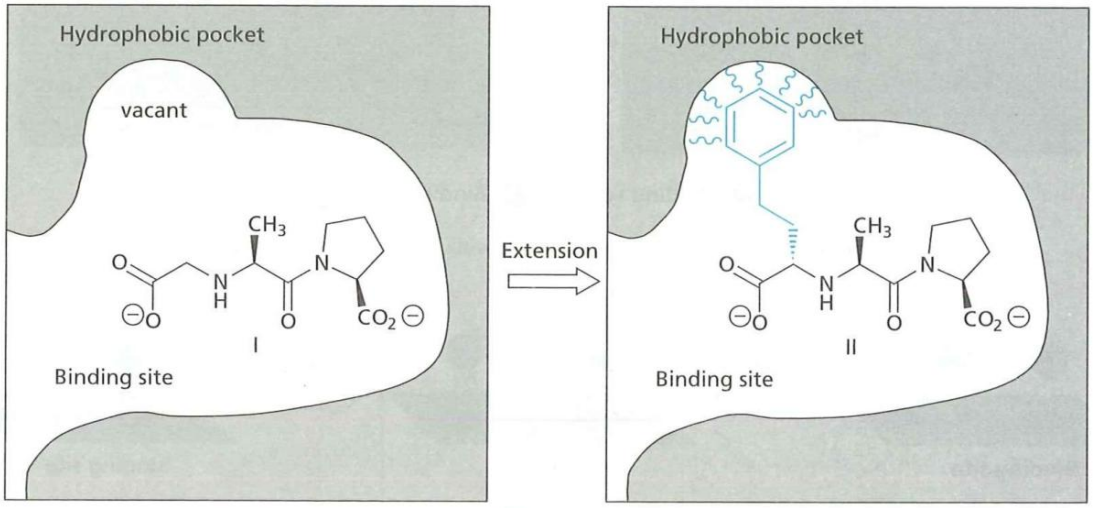
chemical substances that show pharmacological activity to the target bio-macromolecules [42].

1.7.2. Drug design

For a drug molecule to have enough activity, selectivity and have less side effects it is very important that it is complementary to its bio-molecular target in terms of shape and charge [43]. In this respect, drug design is a repeated process where the structure of the target molecules is altered to find the best fits [44].

1.7.3. Drug optimization

After finding the lead compound usually it is necessary to optimize the structure of the lead compound for higher efficiency. Indeed a drug molecule should fit the target bio-macromolecule very tightly. For example, in the inhibition of the angiotensin-converting enzyme (ACE), introducing a phenyl alkyl group to the lead compound, Figure 1.4 [45] increased the inhibition by a factor of 1000 more. In this case, binding an extra aromatic ring to the lead compound increased the hydrophobic interaction between the lead compound and target enzyme so drug molecule fit the enzyme more tightly [46]. Apart from adding new functional groups to the lead compound like amines, amides, aldehydes, ketones and alcohols, chain extension and ring expansion can be also used.



ACE inhibitors.

Figure 1.4. Extension of ACE lead compound.

Additionally, as can be seen in the Figure 1.5 [47] modification of lead compound can also enhance the IC_{50} value of the drug molecule.

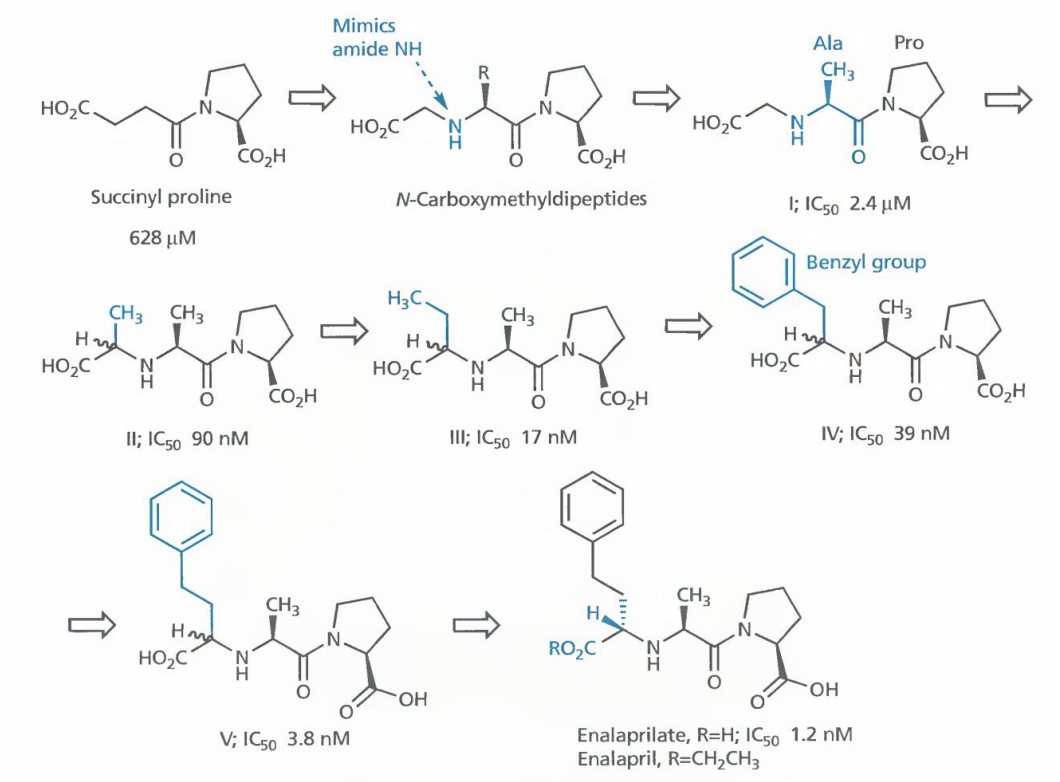


Figure 1.5. Development of enalaprilate.

Ligand based drug design and structure based drug design are two main drug design approaches. In this study structure based drug design is used [48].

1.7.4. Structure based drug design

Structure-based drug design (SBDD) which is used in this study has been accepted as a well organized and feasible approach in pharmaceutical industry and academia [49]. SBDD consists of following steps [50]:

- Determine the target protein
- Construction of 3-D structure of the target protein
- Implementation of high-throughput screening assay
- Identification of lead compound
- Determination of computer assisted methods for estimating the relationship of new compounds
- Planning the synthetic route to synthesize the desired compounds

1.8. Computational Studies

1.8.1. Computational Modeling of CYP-17

To understand the catalytic activities, substrate and reaction selectivity enzyme structure has to be determined [51]. Otherwise, it is not possible to design a specific drug to inhibit the target enzyme. Up to now there was no crystal structure of CYP-17 in the literature but there is a computer model as can be seen in Figure 1.6 with PDB ID code 2c17. Like all P450 enzymes CYP-17 has a heme group and a hydrophobic environment [52].

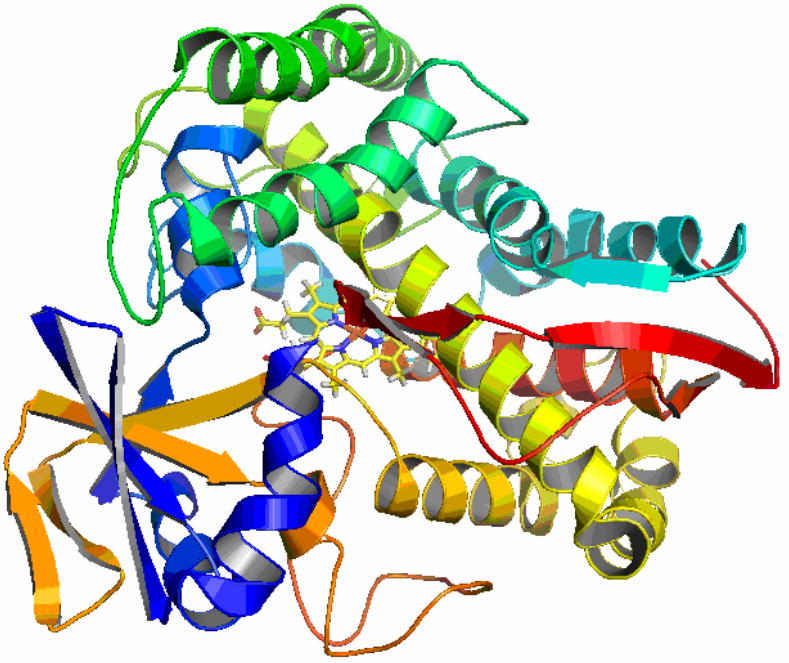


Figure 1.6. Computer generated model of CYP-17.

Computational modeling of CYP-17 is constructed in Koc University by Prof. Metin Türkay and Assoc. Prof. Halil Kavaklı. 3D model of CYP-17 was done based on class II P450 crystal structure, namely P450BMP. They estimated that CYP-17 has smaller pocket than the previous models where the substrate binds and they concluded that only planer substrates accommodate in this pocket [52].

1.8.2. CYP-17 Inhibitors

In enzyme catalyzed reactions an enzyme provides a specific area (active site of the enzyme) to the substrates where these substrates can bind. If an inhibitor binds to the active site of the enzyme reversibly it prevents the approach of the natural substrate to the active site of the enzyme so it stops the enzyme catalyzed reaction as long as it stays there. Therefore, there is a competition between the substrate and inhibitor for binding the active site of the enzyme.

As mentioned earlier, active site of the CYP-17 has a heme moity which has a porphyrin ring with a central iron (Figure 1.8). The role of this iron is to activate molecular

oxygen which is needed for the subsequent conversion of natural substrate. Therefore a CYP-17 inhibitor candidate should make complex with the heme iron.

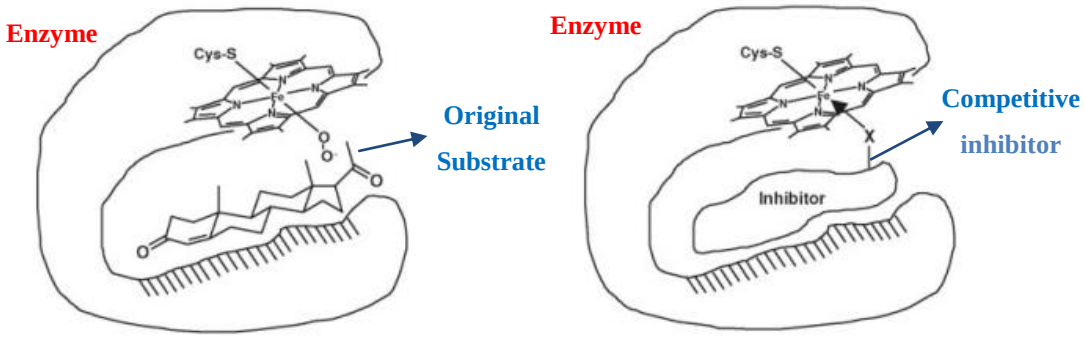


Figure 1.7. Progesterone vs Inhibitor binding to the active site of CYP-17.

1.8.3. Selection of Inhibitors for CYP-17

CYP-17 inhibitors can be classified as steroidal and non-steroidal inhibitors. Figure 1.9 shows some of the steroidal and non-steroidal inhibitors of CYP-17.

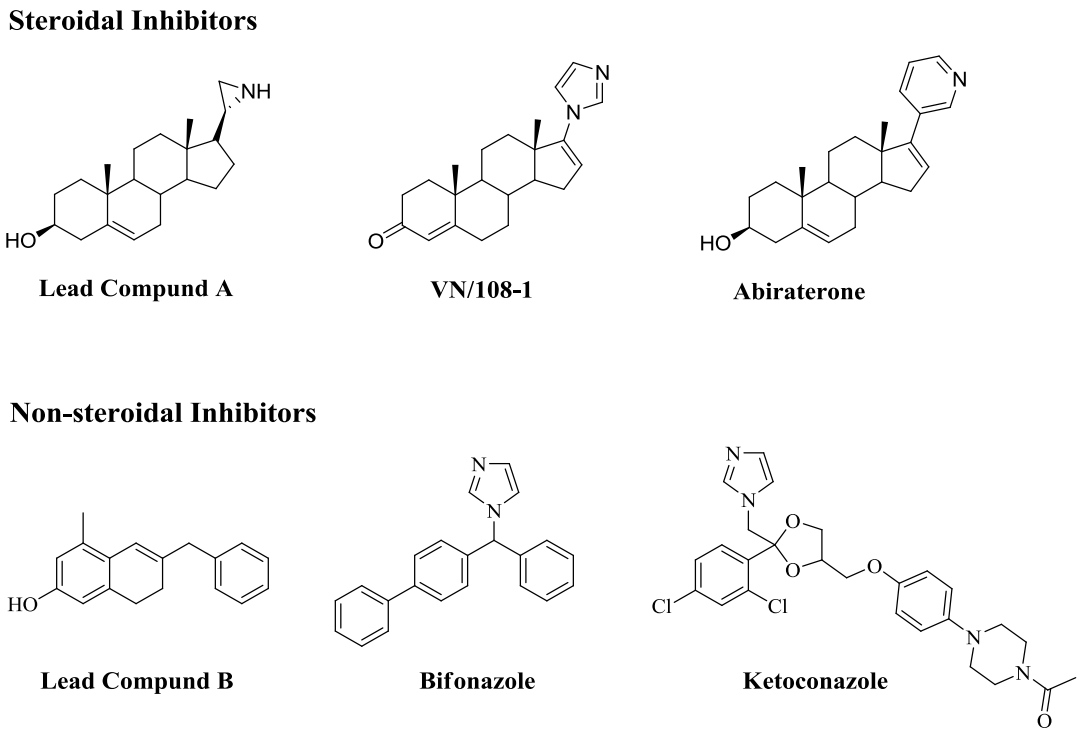
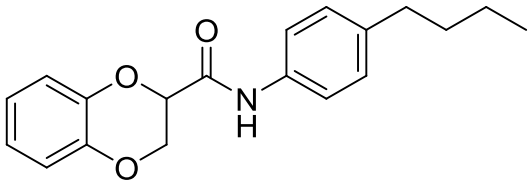


Figure 1.8. Literature examples of CYP-17 inhibitors.

Although some steroidal compounds developed in recent years like abiraterone which is the only steroidal compound in the clinical trial, there are good reasons to replace the steroidal drugs by non-steroidal drugs because of their high affinity towards the steroid receptors which causes crucial side effects.

Among the non-steroidal compounds ketoconazole can be stated. Ketoconazole is originally an antimycotic compound which later was proved to be active against prostate cancer [49]. However, for the treatment of prostate cancer it has not enough selectivity.

As stated above, non-steroidal compounds have advantages to the steroidal compounds. In this respect researchers in Koc University screened about 50000 molecules and 23 non-steroidal drug candidates were found. Between these 23 candidates a lead molecule was determined (Figure 1.10) which gave best results in docking and binding energy, ADMET (adsorption, distribution, metabolism, elimination and toxicity), Quantitative Structure Activity Relationship (QSAR) studies and IC_{50} measurements.



Docking Energy: -9.38kcal/mol
Binding Energy: -7.45 kcal/mol
IC_{50} : 35μM

Figure 1.9. Structure of the Lead Molecule.

1.8.4. Substituents on the Lead Molecule and Their Functions

To find the best molecule for inhibition of the target enzyme some changes on the lead molecule should be done, because modifying the lead compound could increase the therapeutic effect of the lead molecule. In Figure 1.11 substituents and their estimated functions in the inhibition of the CYP-17 can be seen.

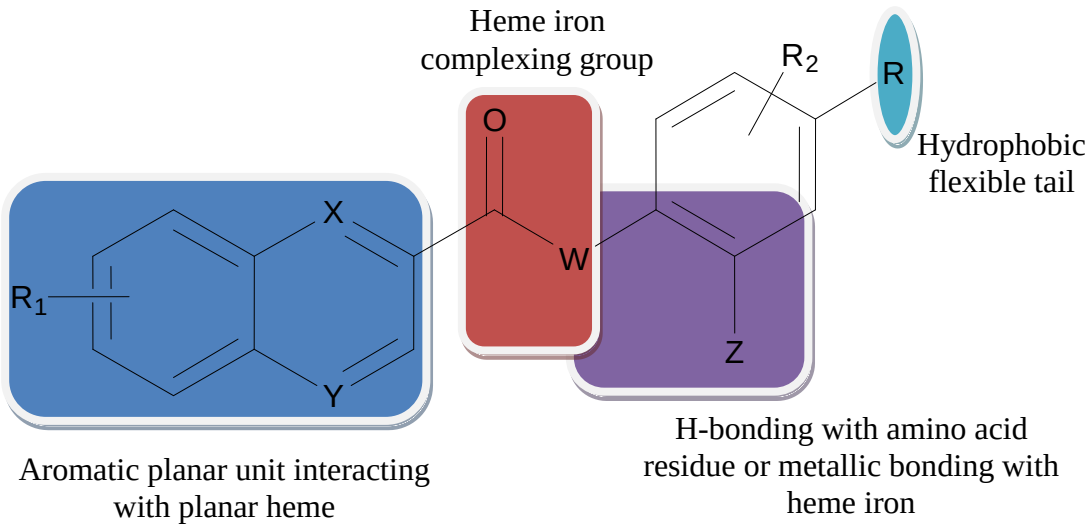


Figure 1.10. Functional groups on the lead compound and their possible functions.

Additionally, Table 1.1 shows the possible modifications on the lead copound.

Table 1.1. Possible modifications on the lead compound.

X and Y atoms	C, O
W atom	N, O, C
Z group	-OR, -NR_2 (R= -H, Alkyl)
R	C_2 - C_6 alkyl or alkoxy, Branching alkyl
R_1	-OMe, -H, -F (at different positions)

1.8.5. Docking and Binding Energy Studies

Binding energy is the strength of the interaction between the enzyme and the candidate drug molecule. Docking energy is related to the approach of the candidate drug molecule to the enzyme. Docking and binding energy calculations were conducted at Koc University with the help of AutoDock computational program. Table 1.2 and Table 1.3 show the docking and binding energies of the lead molecule and lead molecule's derivatives.

Table 1.2. Docking and Binding Energies of Lead Compound.

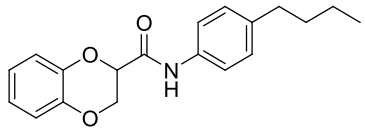
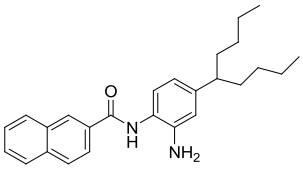
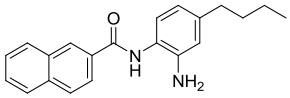
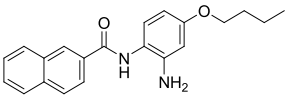
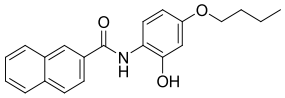
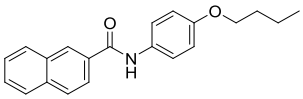
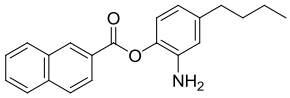
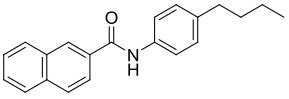
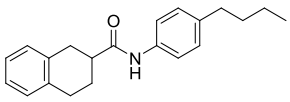
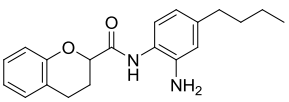
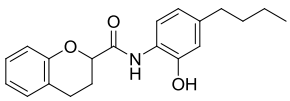
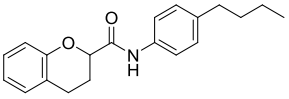
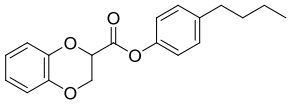
Lead Compound	**Docking Energy (D.E.) (kcal/mol**	**Binding Energy (B.E.) (kcal/mol)**
	**-9.38**	**-7.45**

Table 1.3. Docking and Binding Energies of some Lead Compound Derivatives.

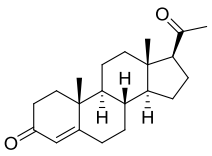
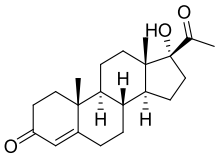
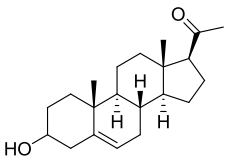
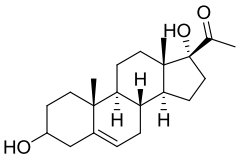
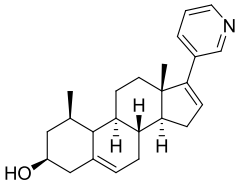
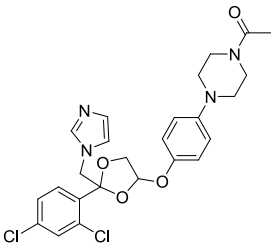
Compounds	**D.E.**	**B.E.**	**Compounds**	**D.E.**	**B.E.**
	-11.85	-9.44		-10.56	-8.47
	-10.66	-8.39		-10.38	-8.10
	-9.85	-7.63		-10.14	-8.26
	-9.89	-7.77		-9.50	-7.85
	-9.31	-7.33		-9.23	-7.30
	-9.43	-7.61		-8.54	-6.67

As it can be seen from Table 1.2 and Table 1.3 some lead compound derivatives have better docking and binding energy values than the lead compound.

1.8.6. Docking and Binding Energy Calculations of Natural Substrates

To compare the docking and binding energies of the lead compound derivatives same calculations was done for the natural substrates and current drug molecules for prostate cancer. (Table1.5)

Table 1.4. Docking and Binding Energies of Natural Substrates and Current Drugs.

Compounds	**Docking (kcal/mol)**	**Binding (kcal/mol)**	**Compounds**	**Docking (kcal/mol)**	**Binding (kcal/mol)**
 Progesterone	-10.04	-9.73	 17hydroxyprogesterone	-9.61	-9.68
 Pregnenolone	-9.71	-9.44	 17hydroxypregnenolone	-10.15	-10.10
 Abiraterone	-9.30	-9.33	 Ketoconazole	-11.13	-9.33

2. AIM OF THE STUDY

The lead compound in this project can be divided in two parts, as can be seen in Figure 2.1, as right and left hand side.

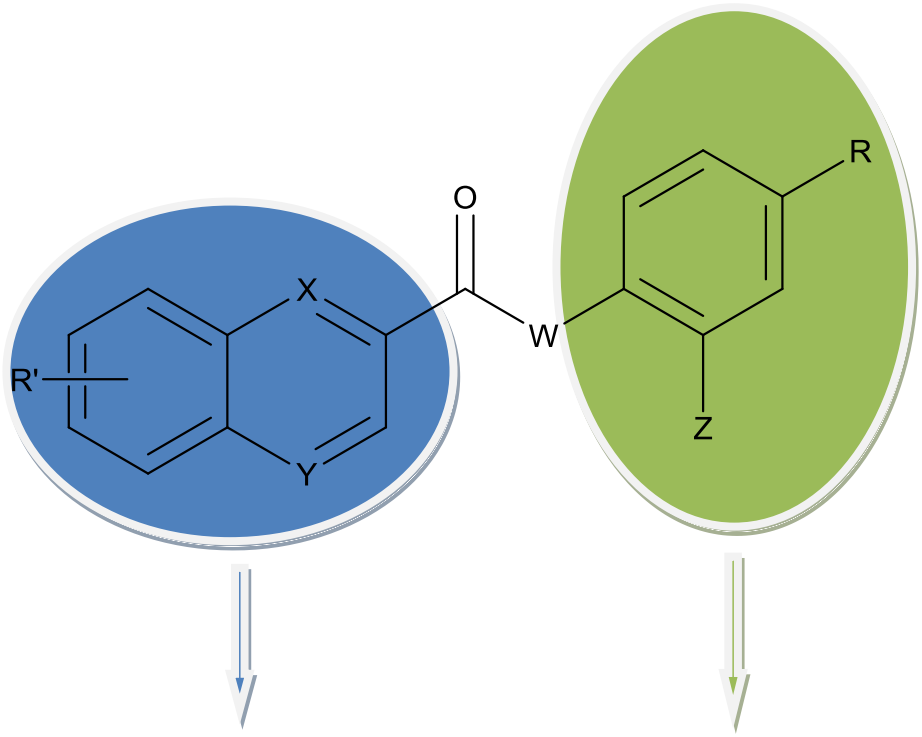


Figure 2.1. Parts of the Lead Compound.

In this project X and Y atoms were chosen as C atoms therefore napthoic acid derivatives were used at the left hand side. For the right hand side of the lead molecule W was determined as N and Z as H.

The main target of this project is to synthesize alkyl and branched alkyl substituted phenyl groups at the R position. Figure 2.2 summarizes the targeted lead molecule optimizations.

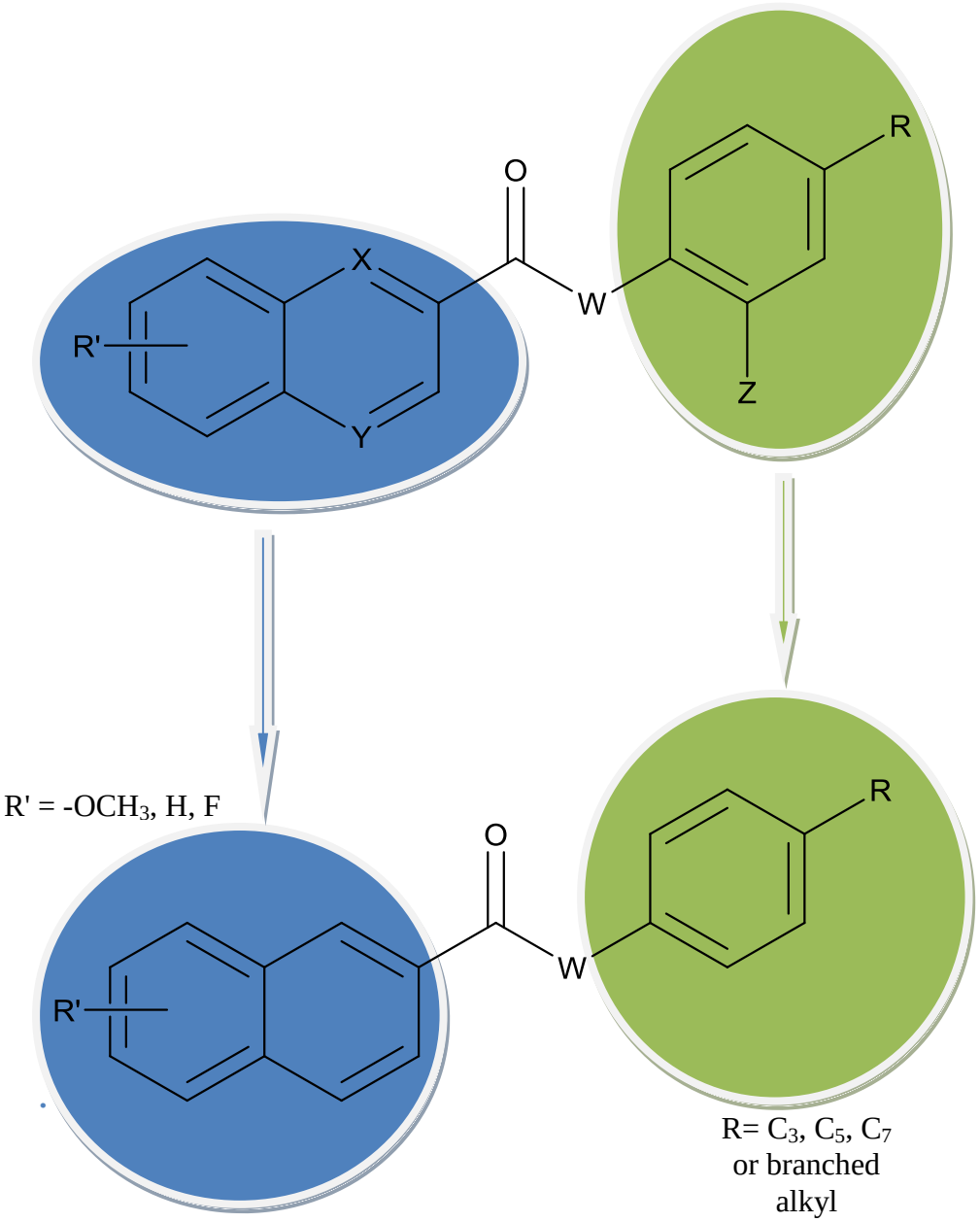
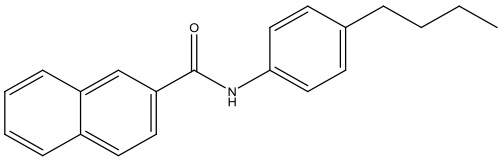


Figure 2.2. Lead Molecule' Optimization.

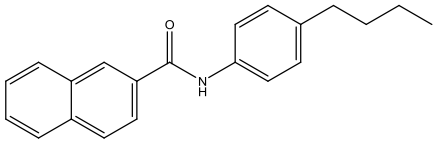
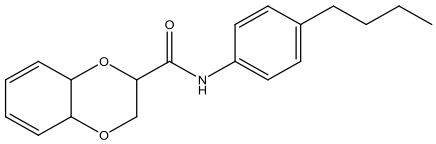
The logic behind making the lead optimization this way is to understand the effect of chain length and the effect of branching on the activity. Earlier compound SE 6 (Figure 2.3) which was synthesized by Selda Erkoc and showed 79% inhibition at 5µM and an IC_{50} value of 2.3µM which is fifteen times more active than the lead compound (Table 2.1).



SE6

Figure 2.3. Structure of the SE6.

Table 2.1. Comparison of SE6 via Lead Molecule.

Compounds	**% Inhibition At 5 µM**	**IC50 (Nm)[α]**
 **SE6**	79	2300
 **Lead Compound**	-	35650

Additionally, before synthesizing these targeted compounds their docking and binding energy calculations were made and it was found that they have better values compared to the lead molecule. (Table 2.2, Table 2.3)

Table 2.2. Docking and Binding Energy of the Lead Molecule.

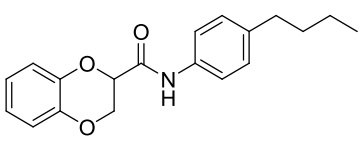
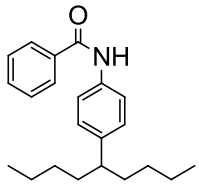
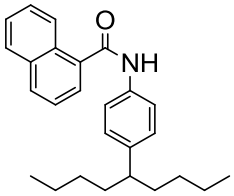
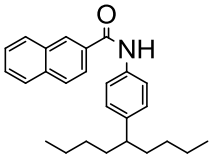
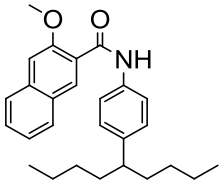
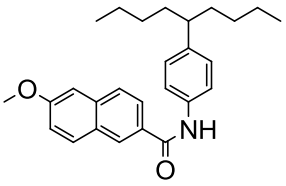
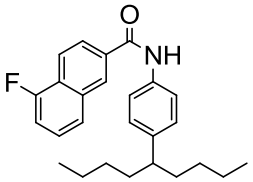
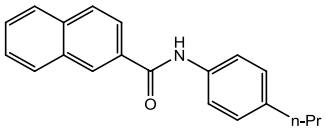
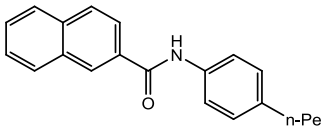
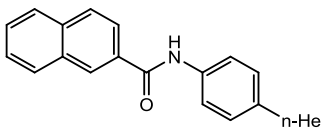
Lead Compound	**Docking Energy (D.E.) (kcal/mol**	**Binding Energy (B.E.) (kcal/mol)**
	**-9.38**	**-7.45**

Table 2.3. Docking and Binding Energy Results of Targeted Molecules.

Final Product	D.E	B.E	Final Product	D.E	B.E
	-11.72	-8.25		-11.39	-7.88
	-11.08	-7.62		-8.49	-7.28
	-9.94	-6.49		-10.54	-7.85
	-8.49	-6.89		-9.71	-7.45
	-10.20	-7.30			

3. RESULTS AND DISCUSSION

In this project mainly alkyl substituted and branched alkyl substituted phenyl rings and their couplings with available naphthoic acid derivatives were targeted to understand the effect of chain length and branching on the alkyl substituted phenyl ring.

The general strategy followed in the synthesis of branched alkyl substituted phenyl rings was as follows; ethyl 4-aminobenzoate was used as the starting material. First, aromatic amine protection was done to prevent the side reactions in the next step. Protection of amine was done with Ac_2O in water. Then n-Butyl lithium (n-BuLi) used as a nucleophile which attacks the carbonyl of the ethyl ester to make branching on the phenyl ring. n-BuLi is also a strong base therefore THF was used as solvent and reaction was carried out -78^oC to prevent side reactions. n-BuLi amount used in this reaction was more than twofold of ethyl ester due to the possibility of hydrogen abstraction from the amide. After the double addition of n-BuLi to the ethyl ester a tertiary benzylic alcohol obtained. Then reduction of alcohol was carried out by Et_3SiH and $Et_2O.BF_3$ in dry dichloromethane (DCM) as solvent. In the next stage deprotection reaction was carried out by refluxing at 70 ^oC with 30% sulfuric acid and methanol. Finally obtained product was coupled with naphtoic acid derivatives.

To confirm these reactions ^{1}H-NMR Spectroscopy, ^{13}C-NMR Spectroscopy and Mass Spectroscopy were used.

3.1. Synthetic Approaches to Synthesize 4-(nonan-5-yl)aniline

Figure 3.1 shows the synthetic approach used to synthesize 4-(nonan-5-yl)aniline.

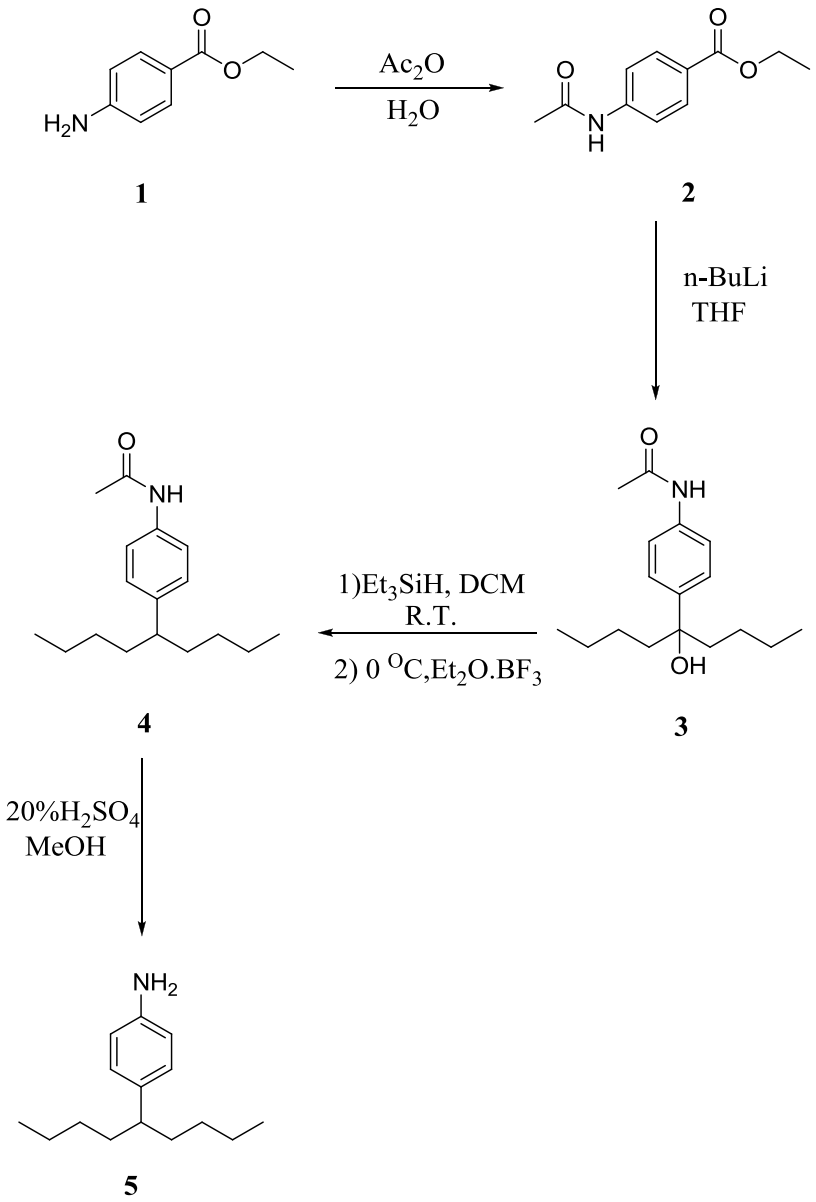


Figure 3.1. The synthetic approach to synthesize 4-(nonan-5-yl)aniline.

For the synthesis of 4-(nonan-5-yl)aniline compound **1** , 4-aminobenzoate, was used as the starting material. Firstly amine protection was done, Ac_2O in water used and white colored product was obtained in 91% yield by pouring reactant in icy water and precipitating.

Then n-BuLi was added to the compound **2** at -78^oC in dry THF to obtain yhe branched alkyl substituted compound **3**. In this reaction THF was used as solvent because of its coordination ability with Li^+ ion. Moreover, this reaction was done under nitrogen to prevent the flame caused by interaction of n-BuLi with air. When the reaction was

complete to get rid of the unreacted n-BuLi small portion of MeOH was added to the reaction mixture. Yield of this reaction was 69% it is low when compared to the other reactions in this synthetic pathway, the reason to have such a low yield could be the hydrogen abstraction of Bu^- from the amide part of the compound **2**.

Next implementation was to convert the tertiary benzyl alcohol on the compound **3** to the corresponding alkane **4**. In this reaction, firs compound **3** was dissolved together with Et_3SiH in dry DCM at room temperature then temperature of the reaction mixture was decreased to the 0^0C and $Et_2O.BF_3$ all at once. When the reaction was complete $NaHCO_3$ added to the reaction mixture to get rid of the unreacted $Et_2O.BF_3$. This reaction was carried out under nitrogen and yield of this reaction was 84%.

Finally to obtain 4-(nonan-5-yl)aniline, compound **5**, deprotection of the amide which is on the compound **4** was done. For this reaction compound **4** was refluxed with 30% sulfuric acid and methanol at 70 ^0C. Yield of this reaction was 89%.

3.2. Synthetic Approaches for Coupling of 4-(nonan-5-yl)aniline with Naphtoic Acid Derivatives

To synthesize different drug candidates against prostate cancer compound **5** was coupled with benzoic acid and naphthoic acid derivatives. Figure 3.2 shows all acids involved in the coupling reactions.

3.3. Synthetic Approaches for Coupling of 4-propylaniline, 4-pentylaniline and 4-heptylaniline with 2-naphtoic acid

Same coupling technique was applied to the 4-propylaniline, 4-pentylaniline and 4-heptylaniline that are commercially available for coupling with 2-naphtoic acid. Figure 3.3 indicates the amines which were involved in coupling reaction with 2-naphtoic acid.

In these *in-situ* coupling reactions firstly PBr_3 was used as the brominating reagent in dry DCM and under the nitrogen to convert the benzoic acid and naphthoic acid derivatives

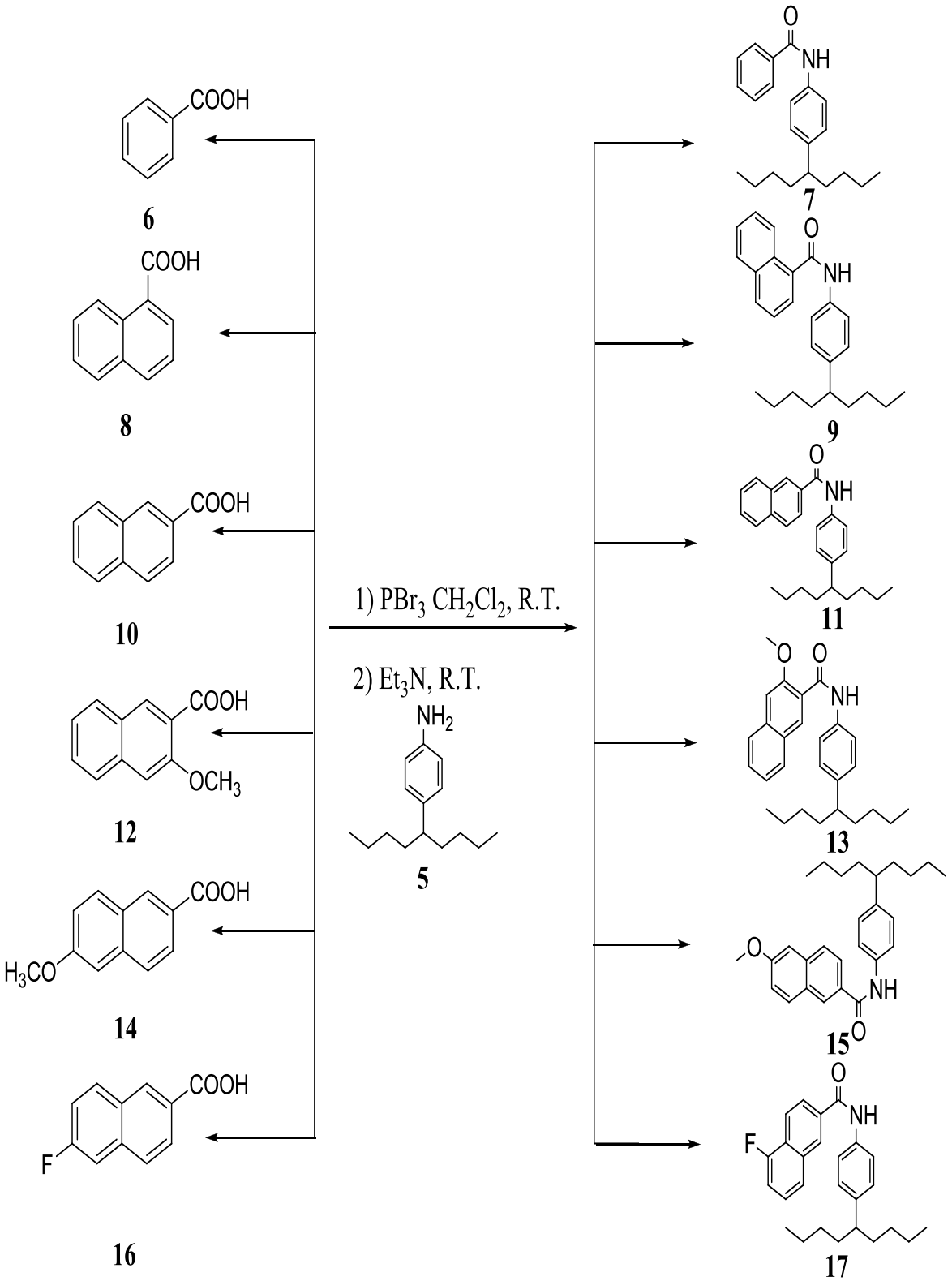


Figure 3.2. Coupling of 4-(nonan-5-yl)aniline with benzoic acid and naphthoic acid derivatives.

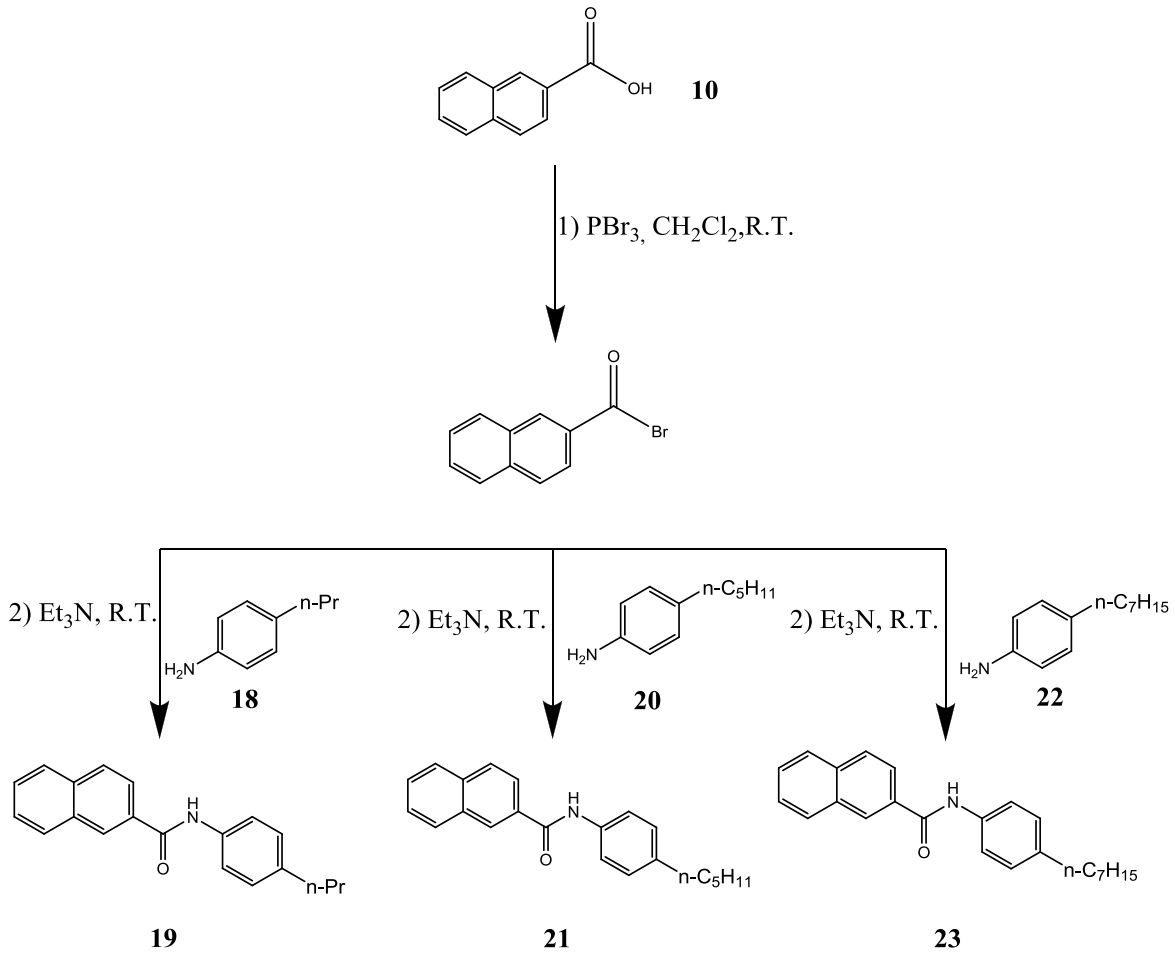


Figure 3.3. Amines which were involved in coupling reaction with 2-naphtoic acid.

to the corresponding acid bromides. Since the reaction is an *in-situ* coupling reaction acid bromides were not isolated. Three hours later, triethylamine (TEA) was added to the reation mixture to neutralize the HBr which evolves through the reaction and then 4-(nonan-5-yl)aniline (**5**) was added. Reaction was stirred at room temperature over-night and final products obtained after concentration and purification.

These *in-situ* coupling reactions have very short reaction times at room temperature. However, these reactions have very low yields (30-40 %).

4. EXPERIMENTAL

4.1. Methods and Materials

All chemicals were used as received from the manufacturer (Merck, Aldrich, Alfa Aesar, and Riedel de Haen). Dry solvents (CH_2Cl_2, THF and Toluene) were obtained from ScimatCo Purification System; other solvents were dried with molecular sieves. Cooling to -78°C was carried out using a Cryostat. Column chromatography was performed using silicagel-60 (43-60 nm). Thin layer chromatography was performed using silica gel plates (Kiesel gel 60 F254, 0,2mm, Merck) and aluminum oxide plates.

4.2. Instrumentation

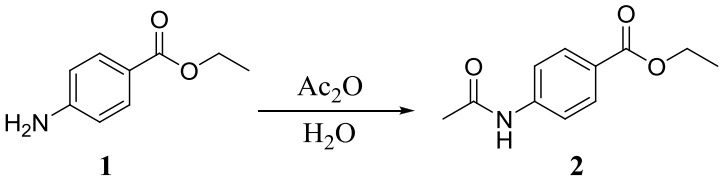
Thin layer chromatography plates were viewed under 254 nm UV lamp. ^{1}H-NMR, ^{13}C-NMR spectra were recorded by using a Varian Gemini 400 MHz spectrometer Varian Associates, Palo Alto, CA) in $CDCl_3$ as solvent at the Advanced Technologies Research and Development Center at Bogazici University.

4.3. Synthesis of Lead Compound Derivatives

4.3.1. Synthesis of ethyl 4-acetamidobenzoate (2)

The reaction was done according to literature procedure [52]. The compound **1** (15g, 91mmol) and 25 ml H20 was added into the two necked round bottom flask fitted with a magnetic stirrer and compound **1** was dissolved. Then, Ac_2O (18.6g, 182mmol) was added to the solution in the round bottom flask. After stirring 4 hours at room temperature, white precipitation was observed. The reaction was monitored by using TLC silica plates and CH_2CL_2 as the eluent phase. One spot on silica gel plate was observed as the only product. The reaction was poured into stirring icy water beaker in order to precipitate all products that weren't precipitated. Suction filtration was next step to remove the water and the

remaining Ac_2O. Product was dried in desiccators and 17.160g product was obtained in 91% yield. **^{1}H-NMR** ($CDCl_3$), δ: 1.33 (t, 3H, CH_2CH_3), 2.16 (s, 3H, CH_3), 4.3 (q, 2H, OCH_2CH_3), 7.63 (dd, 2H, Ar*H*), 7.91 (dd, 2H, Ar*H*), 9.04 (s, 1H, N*H*), ppm. **^{13}C-NMR** ($CDCl_3$), δ: 14.65 (OCH_2CH_3), 24.87 (CH_3), 61.32 (OCH_2), 119.43 (2C, Ar*C*), 125.90 (Ar*C*), 130.96 (2C, Ar*C*), 143.01 (Ar*C*), 166.84 (*C*=*O*), 170.04 (*C*=*O*) ppm.

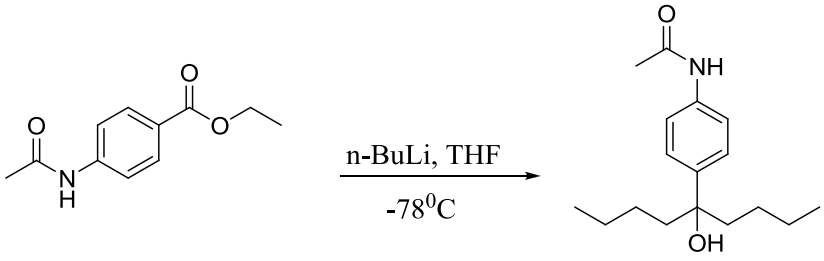


1 **2**

Figure 4.1. Synthesis of ethyl 4-acetamidobenzoate (2).

4.3.2. Synthesis of N-(4-(5-hydroxynonan-5-yl)phenyl)acetamide (3)

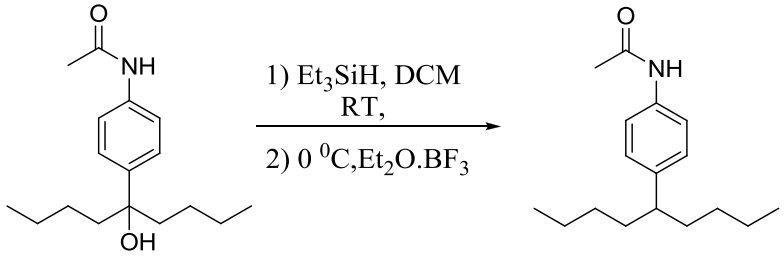
The reaction was done according to the literature procedure [53]. The experiment was carried out under nitrogen and at -78^{0}C in cryostat. The compound **2** (3g, 14.5mmol) and 80 ml dry THF was added into a two necked round bottom flask fitted with a magnetic stirrer. n-BuLi (43.5mmol, 21.75mL) was transferred to the flask via a deoxygenated syringe in a dropwise manner at seven times in 3 ml portions. After stirring 5 hours at -78^{0}C, reaction color turned from colorless to yellow. The reaction progress was monitored by TLC using silica gel plates and 3:1 dichloromethane ethyl acetate as the eluent phase. When the reaction was complete MeOH (50ml) was added to get rid of the unreacted n-BuLi. Then 150ml H_2O was added to the flask and the mixture was extracted 3 times with 100mL of dichloromethane portions. The extracts were collected and the organic layer was dried over anhydrous Na_2SO_4 by overnight. Then product was concentrated and the crude product was impure. In order to purify the product column chromatography was done by using silica gel and 3:1 dichloromethane ethyl acetate as the eluent phase. 2.8g white colored solid product was obtained in 69% yield. **^{1}H-NMR** ($CDCl_3$), δ: 0.82 (t, 6H, CH_2CH_3), 1.01 (m, 2H, $CH_2CH_2CH_3$), 1.22 (m, 6H, $CH_2CH_2CH_2$), 1.75 (m, 4H, $CH_2CH_2CH_2$), 1.95 (b, 1H, O*H*), 7.28 (d, 2H, Ar*H*), 7.46 (d, 2H, Ar*H*), 7.95 (s, 1H, N*H*) ppm.



2 **3**

Figure 4.2. Synthesis of N-(4-(5-hydroxynonan-5-yl)phenyl)acetamide (3).

4.3.3. Synthesis of N-(4-(nonan-5-yl)phenyl)acetamide (4)



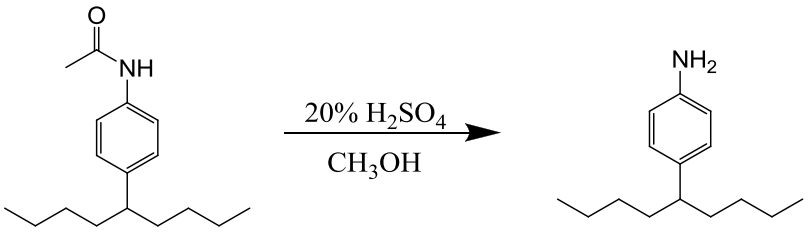
3 **4**

Figure 4.3. Synthesis of N-(4-(nonan-5-yl)phenyl)acetamide.

The reaction was done according to literature procedure [54]. Firstly, compound **3** (2.40g, 8.66mmol) was dissolved in dry CH_2CI_2 (20ml), together with triethylsilane (2.01g, 17.32mmol). After the reaction mixture was cooled at 0^0C, etherated boron trifluoride was added all at once (2.34g, 17.32mmol). The reaction progress was monitored by TLC using silica oxide gel plates and dichloromethane as the eluent phase. After 45 minutes, the reaction was quenched with the addition of aqueous saturated Na_2CO_3 (5ml). Following the addition of CH_2CI_2 (60ml), the organic layer washed with brine, dried over Na_2SO_4 by leaving overnight, and purified by column chromatography by using silica gel and 3:1 hexane ethyl acetate as eluent phase. 1.9 g white solid product was obtained in 84% yield. **^{1}H-NMR** ($CDCl_3$), δ: 0.74 (t, 6H, CH_2CH_3), 1.08 (m, 8H, $CH_2CH_2CH_3$), 1.44 (m, 4H, $CH_2CH_2CH_2$), 2.06 (s, 3H, CH_3), 2.35 (m, 1H, ArC*H*), 6.98 (d, 2H, Ar*H*), 7.35 (d, 2H, Ar*H*), 7.82 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.01 (2C, CH_3), 21.75 (2C, CH_2), 28.80 (2C, CH_2), 35.67 (2C, CH_2), 44.43 (*C*H), 118.99 (2C, Ar*C*), 126.99 (2C, Ar*C*), 134.68 (Ar*C*), 141.44 (Ar*C*), 167.61 (C=O) ppm.

4.3.4. Synthesis of 4-(nonan-5-yl)aniline (5)

Deprotection was done by the hydrolysis of the amide group to amine by using 20% H_2SO_4. Compound **4** (2.11g, 8.07mmol) was dissolved in 40 mL of CH_3OH in a two-necked round bottom flask fitted with a reflux condenser and a magnetic stirrer. 41.96 mL of 20% H_2SO_4 was added drop by drop to the reaction flask and refluxed at 70^0C for 6 hours. The reaction was monitored by using TLC silica gel plates and CH_2CI_2 as the eluent phase. At the end of the 6 hours 5% Na_2SO_4 added until the medium become basic. Then extraction was made three times with 70 mL CH_2CI_2 solutions. Then the organic phase was dried over Na_2SO_4 by leaving overnight. The product was pure so no purification process was done. After concentrating and drying processes 1.59g brown liquid product was obtained in 89% yield. **^{1}H-NMR** ($CDCl_3$), δ: 0.83 (t, 6H, CH_2CH_3), 1.17 (m, 8H, $CH_2CH_2CH_3$), 1.51 (m, 4H, $CH_2CH_2CH_2$), 2.35 (m, 1H, ArCH), 3.2 (b, 1H, OH), 6.40 (d, 2H, ArH), 6.92 (d, 2H, ArH), 7.26 (s, 1H, NH) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 14.04 (CH_3), 22.81 (2C, CH_2), 29.86 (2C, CH_2), 36.84 (2C, CH_2), 45.01 (CH), 115.24 (2C, ArC), 128.35 (2C, ArC), 136.75 (ArC), 143.76 (ArC) ppm.



4 **5**

Figure 4.4. Synthesis of 4-(nonan-5-yl)aniline.

4.3.5. Synthesis of N-(4-(nonan-5-yl)phenyl)benzamide (7)

The coupling reaction was done according to the literature procedure [55]. The experiment was done under nitrogen by using dry CH_2Cl_2. Benzoic acid (**6**) (67.1 mg, 0.55 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.11 mL, 1.11 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.22 mL, 1.65 mmol) was added at that time

fume occurred because of neutralizing of HBr. 4-(nonan-5-yl)aniline (5) (80 mg, 0.36 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed over-night. To this mixture, 10 mL CH_2Cl_2 was added and it was extracted with H_2O. When the water was added, yellow solid and fume occurred. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was impure and a column was prepared by using silica gel and hexane/ CH_2Cl_2 (3:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.82 (t, 6H, CH_2CH_3), 1.18 (m, 8H, $CH_2CH_2CH_3$), 1.57 (m, 4H, $CH_2CH_2CH_2$), 2.46 (m, 1H,ArC*H*), 7.48 (d, 2H, Ar*H*), 7.54 (d, 2H, Ar*H*), 7.28 (s, 1H, Ar*H*), 7.85 (d, 2H, Ar*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.99 (2C, CH_3), 22.74 (2C, CH_2), 29.79 (2C, CH_2), 36.70 (2C, CH_2), 45.49 (*CH*), 120.15 (3C, Ar*C*), 126.93 (2C, Ar*C*), 128.19 (2C, Ar*C*), 131.66 (Ar*C*), 135.13 (Ar*C*), 135.49 (Ar*C*), 165.64(*C*=O) ppm.

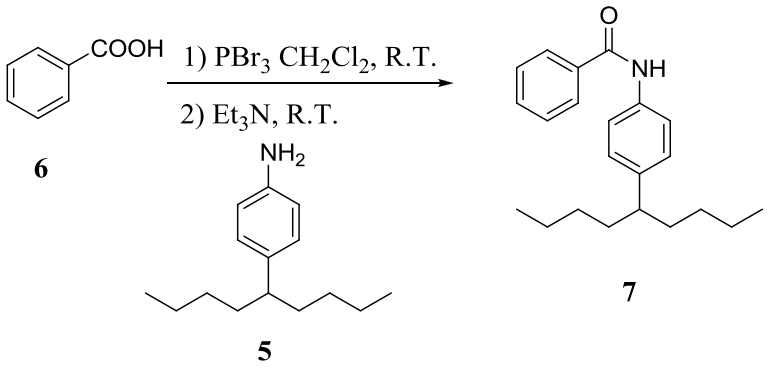


Figure 4.5. Synthesis of N-(4-(nonan-5-yl)phenyl)benzamide.

4.3.6. Synthesis of N-(4-(nonan-5-yl)phenyl)-1-naphthamide (9)

The coupling reaction was done according to the literature procedure [55]. The experiment was done under nitrogen by using dry CH_2Cl_2. 1-naphtoic acid (**8**) (129.14 mg, 0.75 mmol) was dissolved in 5 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.14 mL, 1.5 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.31 mL, 2.25 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-(nonan-5-yl)aniline (**5**) (110 mg, 0.50 mmol) was dissolved in 3 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed over-night. To this mixture, 10 mL CH_2Cl_2 was added and it

was extracted with H_2O. When the water was added, yellow solid and fume occurred. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was impure and a column was prepared by using silica gel and hexane/ CH_2Cl_2 (3:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.88 (t, 6H, CH_2CH_3), 1.21 (m, 8H, $CH_2CH_2CH_3$), 1.60 (m, 4H, $CH_2CH_2CH_2$), 2.49 (b, 1H,ArCH), 7.12 (d, 2H, ArH), 7.35 (t, H, ArH), 7.49 (m, 2H, ArH), 7.57 (m, 3H, ArH), 7.85 (t, 2H, ArH), 8.05 (s, H, NH), 8.28 (d, H, ArH), ppm. **^{13}C-NMR** ($CDCl_3$), δ: 14.11 (2C, CH_3), 22.84 (2C, CH_2), 29.88 (2C, CH_2), 36.79 (2C, CH_2), 45.55 (CH), 119.38 (2C, ArC), 124.65 (ArC), 125.06 (ArC), 125.33 (ArC), 126.45 (ArC), 127.17 (ArC), 128.16 (2C, CH_2), 128.32 (ArC), 130.05 (ArC), 130.78 (ArC), 133.65 (ArC), 134.51 (ArC), 135.79 (ArC), 142.82 (C=O), 167.57 (C=O) ppm.

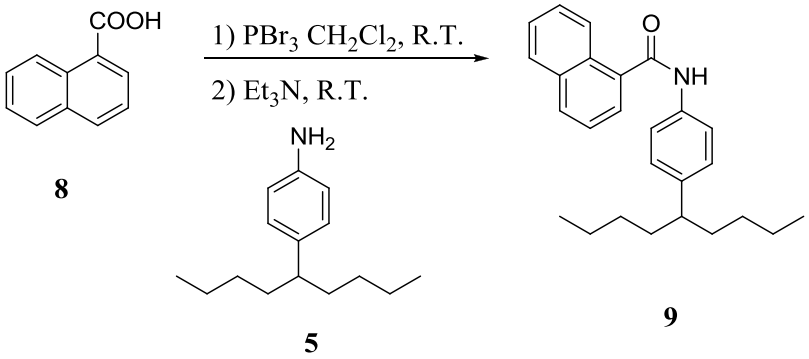
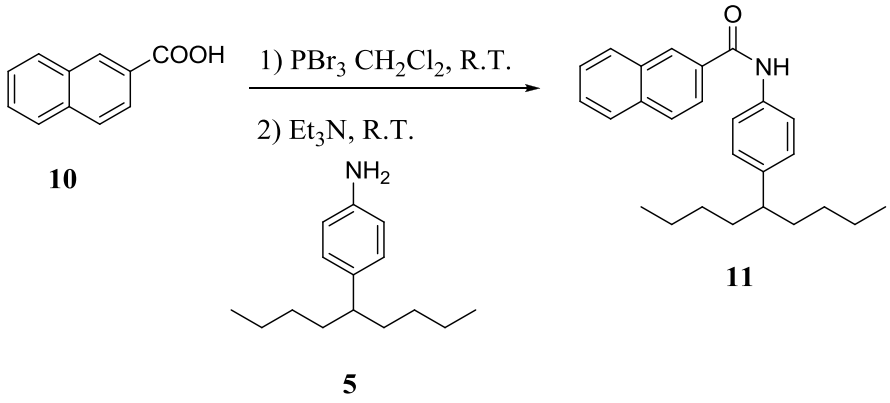


Figure 4.6. Synthesis of N-(4-(nonan-5-yl)phenyl)-1-naphthamide.

4.3.7. Synthesis of N-(4-(nonan-5-yl)phenyl)-2-naphthamide (11)

The coupling reaction was done according to the literature procedure [55]. The experiment was done under nitrogen by using dry CH_2Cl_2. 2-naphtoic acid (**10**) (63.22 mg, 0.37 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.74 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.152 mL, 1.1 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-(nonan-5-yl)aniline (**5**) (58 mg, 0.25 mmol) was dissolved in 1 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed over-night. To this mixture, 10 mL CH_2Cl_2 was added and it was extracted with H_2O. When the water was added, yellow solid and fume occurred. The

organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was impure and a column was prepared by using silica gel and hexane/ CH_2Cl_2 (3:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.85 (t, 6H, CH_2CH_3), 1.21 (m, 8H, $CH_2CH_2CH_3$), 1.58 (m, 4H, $CH_2CH_2CH_2$), 2.48 (m, 1H,ArC*H*), 7.14 (d, 2H, Ar*H*), 7.53 (m, 2H, Ar*H*), 7.62 (d, 2H, Ar*H*), 7.85 (m, 4H, Ar*H*), 7.85 (t, 2H, Ar*H*), 8.22 (s, H, Ar*H*), 8.31 (s, H, N*H*), ppm.



10 **5** **11**

Figure 4.7. Synthesis of N-(4-(nonan-5-yl)phenyl)-2-naphthamide.

4.3.8. Synthesis of 3-methoxy-N-(4-(nonan-5-yl)phenyl)-2-naphthamide (13)

The coupling reaction was done according to the literature procedure [55]. The experiment was done under nitrogen by using dry CH_2Cl_2. 3-methoxy-2-naphthoic acid (**12**) (124.4 mg, 0.62 mmol) was dissolved in 5 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.1 mL, 1.12 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.26 mL, 1.86 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-(nonan-5-yl)aniline (**5**) (90 mg, 0.41 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed over-night. To this mixture, 15 mL CH_2Cl_2 was added and it was extracted with H_2O. When the water was added, yellow solid and fume occurred. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was impure and a column was prepared by using silica gel and hexane/CH_2Cl_2 (3:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ : 0.76 (t, 6H, CH_2CH_3), 1.12 (m, 8H, $CH_2CH_2CH_3$), 1.50 (m, 4H, $CH_2CH_2CH_2$), 2.40 (m, 1H,ArC*H*), 4.06 (s, 3H, CH_3), 7.08 (d, 2H, Ar*H*), 7.19 (d, 1H, Ar*H*), 7.34 (t, 1H, Ar*H*), 7.46 (t, 1H,

Ar*H*), 7.55 (d, 2H, Ar*H*), 7.69 (d, 1H, Ar*H*), 7.85 (d, 1H, Ar*H*), 8.77 (s, 1H, Ar*H*), 9.78 (s, 1H, Ar*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 14.04 (2C, *C*H_3), 22.79 (2C, *C*H_2), 29.84 (2C,*C*H_2), 36.76 (2C, *C*H_2), 45.53 (*CH*), 56.18 (C, *C*H_3),106.68 (2C, ArC), 120.49 (2C, ArC), 124.73 (Ar*C*), 126.23 (2C, Ar*C*), 128.12 (2C, Ar*C*), 128.41 (2C, Ar*C*), 129.22 (2C, Ar*C*), 134.20 (Ar*C*), 135.74 (Ar*C*), 135.95 (Ar*C*), 154.39 (Ar*C*), 162.92 (*C*=O) ppm

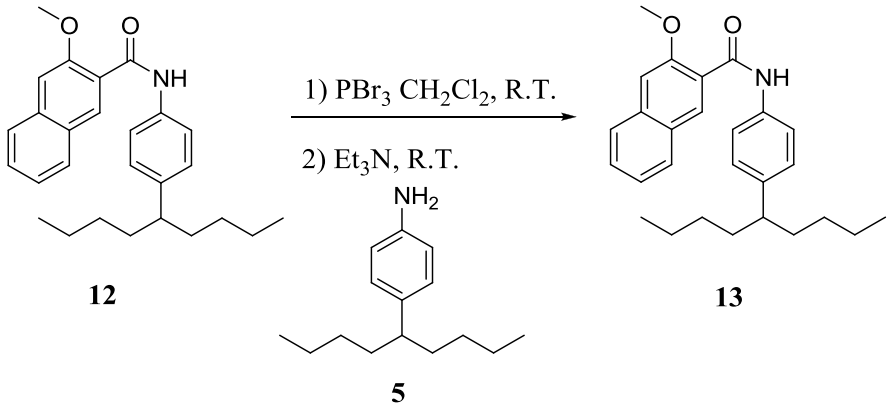
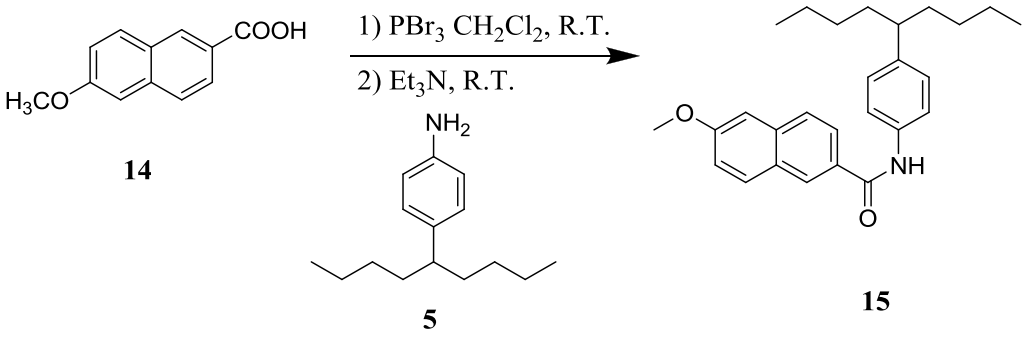


Figure 4.8. Synthesis of 3-methoxy-N-(4-(nonan-5-yl)phenyl)-2-naphthamide.

4.3.9. Synthesis of 6-methoxy-N-(4-(nonan-5-yl)phenyl)-2-naphthamide (15)

The coupling reaction was done according to the literature procedure [55]. The experiment was done under nitrogen by using dry CH_2Cl_2. 6-methoxy-2-naphthoic acid (**14**) (125.4 mg, 0.61 mmol) was dissolved in 5 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.1 mL, 1.12 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.26 mL, 1.86 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-(nonan-5-yl)aniline (**5**) (90 mg, 0.41 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed over-night. To this mixture, 15 mL CH_2Cl_2 was added and it was extracted with H_2O. When the water was added, yellow solid and fume occurred. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was impure and a column was prepared by using silica gel and Hexane and CH_2Cl_2 (3:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.76 (t, 6H, CH_2CH_3), 1.11 (m, 8H, $CH_2CH_2CH_3$), 1.50 (m, 4H, $CH_2CH_2CH_2$), 2.40 (m, 1H,ArC*H*), 3.88 (s, 3H, CH_3), 7.09 (d, 3H, Ar*H*), 7.14 (dd, 1H, Ar*H*), 7.52 (d, 2H, Ar*H*),

7.75 (t, 2H, Ar*H*), 7.81 (dd, 1H, Ar*H*), 7.86 (s, 1H, Ar*H*), 7.82 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 14.02 (2C, *C*H_3), 22.76 (2C, *C*H_2), 29.81 (2C,*C*H_2), 36.72 (2C, *C*H_2), 45.51 (*CH*), 55.34 (C, *C*H_3),105.67 (ArC), 120.13 (ArC), 124.15 (Ar*C*), 127.26 (Ar*C*), 127.38 (Ar*C*), 128.22 (2C, Ar*C*), 130.46 (2C, Ar*C*), 135.69 (2C, Ar*C*), 136.35 (2C,Ar*C*), 142.74 (Ar*C*), 159.18 (Ar*C*), 165.70 (Ar*C*), 198.50 (*C*=O) ppm



14 **5** **15**

Figure 4.9. Synthesis of 6-methoxy-N-(4-(nonan-5-yl)phenyl)-2-naphthamide.

4.3.10. Synthesis of 5-fluoro-N-(4-(nonan-5-yl)phenyl)-2-naphthamide (17)

The coupling reaction was done according to the literature procedure [55]. The experiment was done under nitrogen by using dry CH_2Cl_2. 6-fluoro-2-naphthoic acid (**16**) (104.6 mg, 0.55 mmol) was dissolved in 5 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.11 mL, 1.11 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.23 mL, 1.65 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-(nonan-5-yl)aniline (**5**) (80 mg, 0.36 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed over-night. To this mixture, 15 mL CH_2Cl_2 was added and it was extracted with H_2O. When the water was added, yellow solid and fume occurred. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was impure and a column was prepared by using silica gel and hexane/CH_2Cl_2 (3:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.83 (t, 6H, CH_2CH_3), 1.19 (m, 8H, $CH_2CH_2CH_3$), 1.62 (m, 4H, $CH_2CH_2CH_2$), 2.47 (m, 1H,ArC*H*), 7.14 (d, 2H, Ar*H*), 7.29 (t, 1H, Ar*H*), 7.45 (d, H, Ar*H*), 7.60 (d, 2H, Ar*H*), 7.80 (d, 1H, Ar*H*), 7.87 (m, 2H, Ar*H*), 8.14 (s, 1H, Ar*H*), 8.31 (s, 1H, N*H*) ppm.

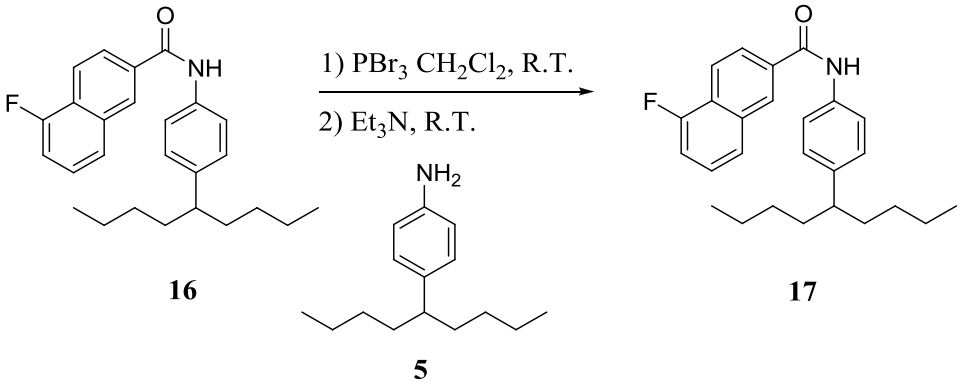


Figure 4.10. Synthesis of 5-fluoro-N-(4-(nonan-5-yl)phenyl)-2-naphthamide.

4.3.11. Synthesis of N-(4-propylphenyl)-2-naphthamide (19)

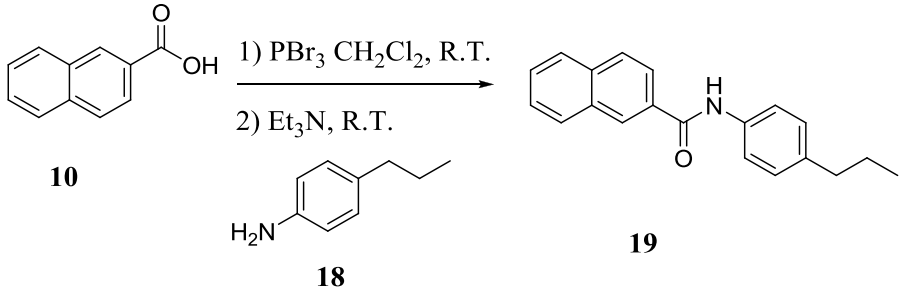


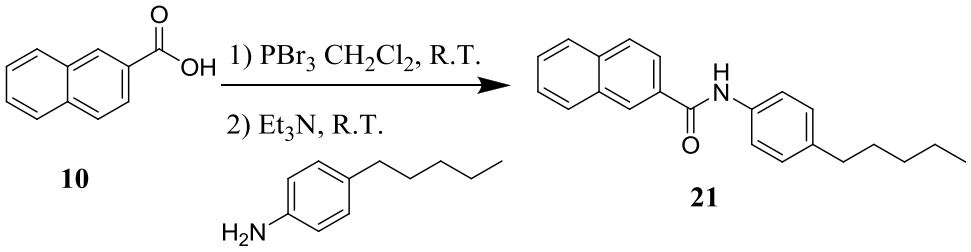
Figure 4.11. Synthesis of N-(4-propylphenyl)-2-naphthamide.

The coupling reaction was done according to the literature procedure [55]. The experiment was done under nitrogen by using dry CH_2Cl_2. 2-naphthoic acid (**10**) (77.48 mg, 0.45 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.9 mL, 0.90 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.19 mL, 1.35 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-propylaniline (**18**) (40.56 mg, 0.30 mmol) was added to the reaction mixture. Reaction mixture was mixed over-night. To this mixture, 10 mL CH_2Cl_2 was added and it was extracted with H_2O. When the water was added, yellow solid and fume occurred. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was impure to purify the product recrystallization was made with CH_3OH. **^{1}H-NMR** ($CDCl_3$), δ: 0.86 (t, 3H, CH_2CH_3), 1.54 (m, 2H, $CH_2CH_2CH_3$), 2.28 (m, 2H, $CH_2CH_2CH_2$), 7.06 (d, 2H, Ar*H*), 7.43 (m, 2H, Ar*H*), 7.50 (d, 2H, Ar*H*), 7.76 (m, 4H, Ar*H*), 8.09 (s, 1H, N*H*), 8.22 (s, H, Ar*H*),

ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.73 (*C*H_3), 24.53 (*C*H_2), 37.48 (*C*H_2), 120.32 (2C,ArC), 123.56 (ArC), 126.84 (Ar*C*), 127.44 (Ar*C*), 127.78 (2C,Ar*C*), 128.64 (Ar*C*), 128.91 (Ar*C*), 129.01 (2C, Ar*C*), 132.32 (Ar*C*), 132.62 (Ar*C*), 134.79 (Ar*C*), 135.64 (Ar*C*), 139.10 (Ar*C*), 165.70 (*C*=O) ppm.

4.3.12. Synthesis of N-(4-pentylphenyl)-2-naphthamide (21)

The coupling reaction was done according to the literature procedure [55]. The experiment was done under nitrogen by using dry CH_2Cl_2. 2-naphthoic acid (**10**) (77.48 mg, 0.45 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.9 mL, 0.90 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.19 mL, 1.35 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-pentylaniline (**20**) (48.98 mg, 0.30 mmol) was added to the reaction mixture. Reaction mixture was mixed over-night. To this mixture, 10 mL CH_2Cl_2 was added and it was extracted with H_2O. When the water was added, yellow solid and fume occurred. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was impure to purify the product recrystallization was made with CH_3OH. **^{1}H-NMR** ($CDCl_3$), δ: 0.82 (t, 3H, CH_2CH_3), 1.26 (m, 4H, $CH_2CH_2CH_3$), 1.54 (m, 2H, $CH_2CH_2CH_2$), 2.51 (t, ArCH_2), 7.09 (d, 2H, Ar*H*), 7.49 (m, 4H, Ar*H*), 7.81 (m, 4H, Ar*H*), 7.99 (s, 1H, N*H*), 8.26 (s, H, Ar*H*), ppm. **^{13}C-NMR** ($CDCl_3$), δ: 14.00 (*C*H_3), 22.52 (*C*H_2), 31.14 (CH_2), 31.42 (*C*H_2), 35.36 (CH_2), 120.27 (2C,ArC), 123.53 (ArC), 127.41 (Ar*C*), 127.77 (Ar*C*), 127.80 (2C,Ar*C*), 128.69 (Ar*C*), 128.91 (Ar*C*), 128.97 (2C, Ar*C*), 132.34 (Ar*C*), 132.64 (Ar*C*), 134.82 (Ar*C*), 135.58 (Ar*C*), 139.39 (Ar*C*), 165.61 (*C*=O) ppm.



10 **20** **21**

Figure 4.12. Synthesis of N-(4-pentylphenyl)-2-naphthamide.

4.3.13. Synthesis of N-(4-heptylphenyl)-2-naphthamide (23)

The coupling reaction was done according to the literature procedure [55]. The experiment was done under nitrogen by using dry CH_2Cl_2. 2-naphthoic acid (**10**) (77.48 mg, 0.45 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.9 mL, 0.90 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.19 mL, 1.35 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-heptylaniline (**22**) (57.40 mg, 0.30 mmol) was added to the reaction mixture. Reaction mixture was mixed over-night. To this mixture, 10 mL CH_2Cl_2 was added and it was extracted with H_2O. When the water was added, yellow solid and fume occurred. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was impure to purify the product recrystallization was made with CH_3OH. **^{1}H-NMR** ($CDCl_3$), δ: 0.81 (t, 3H, CH_2CH_3), 1.24 (m, 8H, $CH_2CH_2CH_2CH_2CH_3$), 1.53 (m, 2H, $ArCH_2CH_2$), 2.52 (t, $ArCH_2$), 7.11 (d, 2H, Ar*H*), 7.50 (m, 4H, Ar*H*), 7.83 (m, 4H, Ar*H*), 7.92 (s, 1H, N*H*), 8.28 (s, H, Ar*H*), ppm. **^{13}C-NMR** ($CDCl_3$), δ: 14.00 (CH_3), 22.64 (CH_2), 29.19 (2C, CH_2), 31.48 (CH_2), 31.81 (CH_2), 35.40 (*C*H2),120.25 (2C,ArC), 123.52 (ArC), 126.90 (Ar*C*), 127.42 (Ar*C*), 127.81 (2C,Ar*C*), 128.70 (Ar*C*), 128.92 (Ar*C*), 128.97 (2C, Ar*C*), 132.34 (Ar*C*), 132.64 (Ar*C*), 134.82 (Ar*C*), 135.55 (Ar*C*), 139.40 (Ar*C*), 165.59 (*C*=O) ppm.

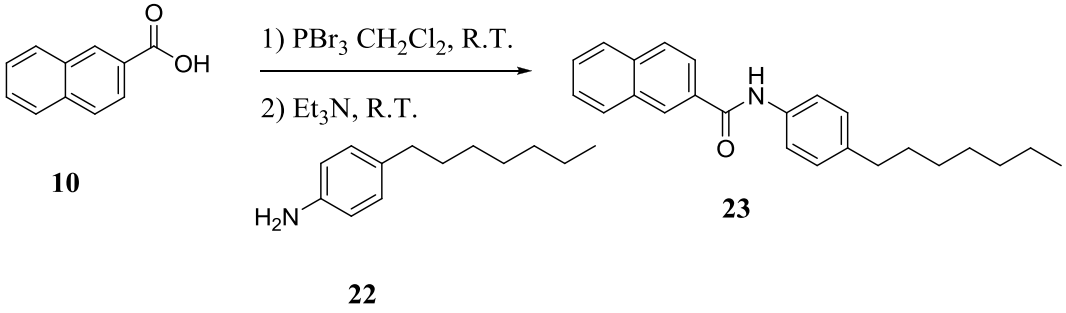


Figure 4.13. Synthesis of N-(4-heptylphenyl)-2-naphthamide.

5. FUTURE WORK

For future work synthesized drug candidates will be tested on mammalian cells (percent inhibition test at 5μM). Test results will indicate the effect of alkyl chain length and alkyl branching on the activity. Based on these results new drug candidates will be synthesized.

Moreover, in some of the synthesized final products the amide groups will be converted to the thioketones by the Lawesson's Reagent (Figure 5.1) which is a mild thionating reagent for amides (Figure 5.1) and thionated products will be sent for biological testing (Figure 5.2).

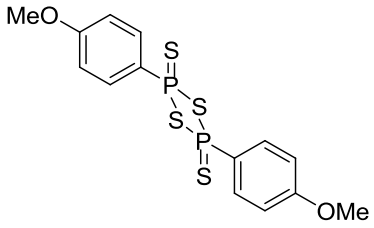


Figure 5.1. Structure of the Lawesson' Reagent.

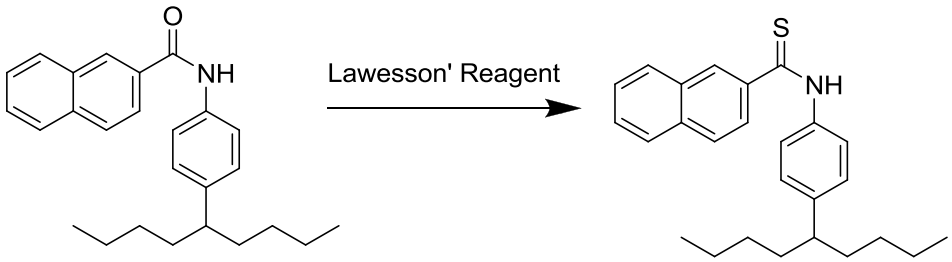


Figure 5.2. Lawesson' Reaction for N-(4-(nonan-5-yl)phenyl)-2-naphthamide.

6. CONCLUSION

The aim of this study was to synthesize derivatives of SE6 which contained linear alkyl chain and had an IC_{50} value of 2.3μM . The modifications included variation of the chain length and branching of the alkyl substitituent on the phenylene ring. The effect of both chain length and branching on the activity of the drug was targeted. For this purpose compounds in the Table 2.3 were synthesized successfully and sent for biological testings.

APPENDIX A: SPECTROSCOPY DATA

^{1}H and ^{13}C NMR and spectroscopy of the synthesized products are included. Necessary expansions were made on the NMR data.

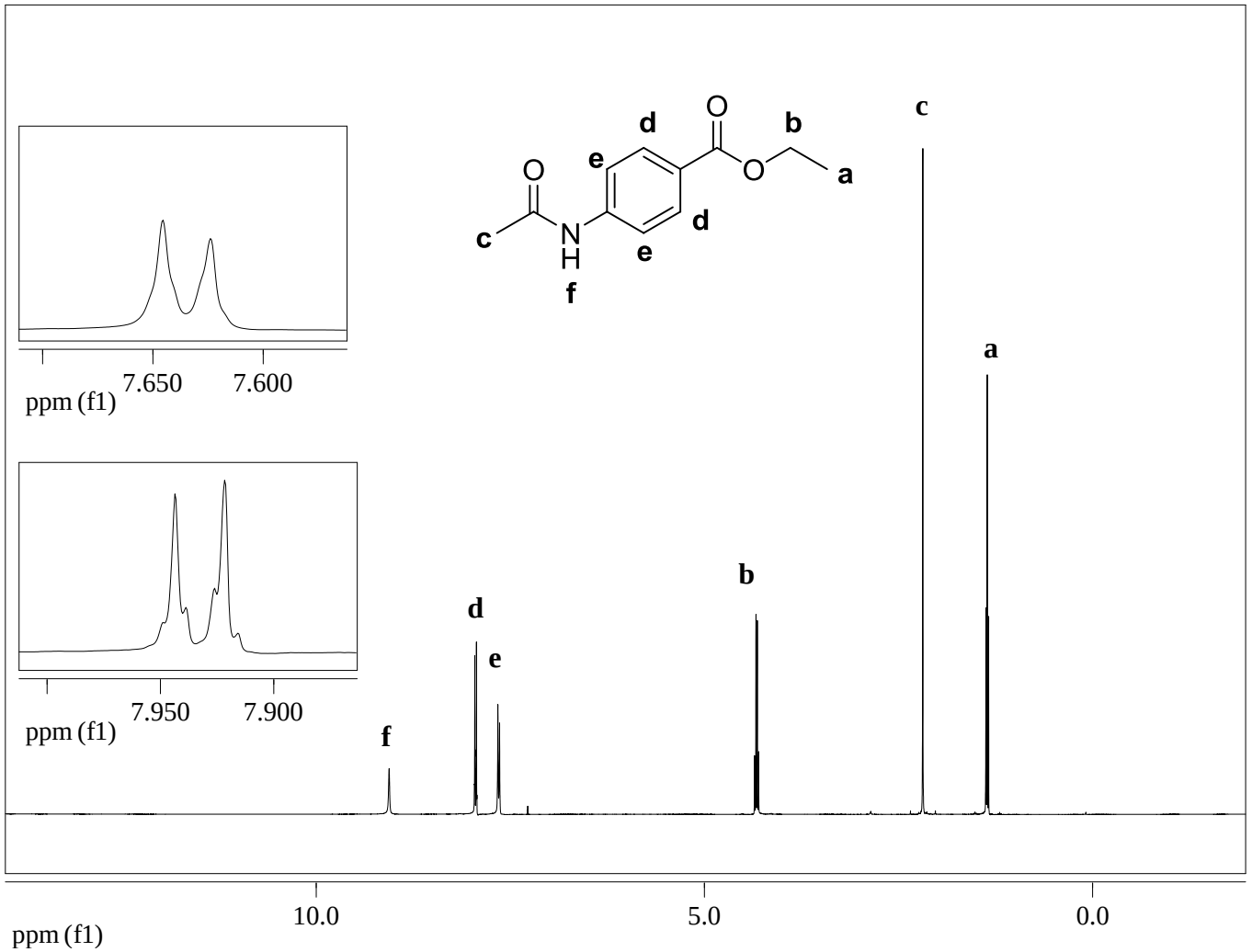


Figure A. 1. ^{1}H-NMR Spectrum of ethyl 4-acetamidobenzoate.

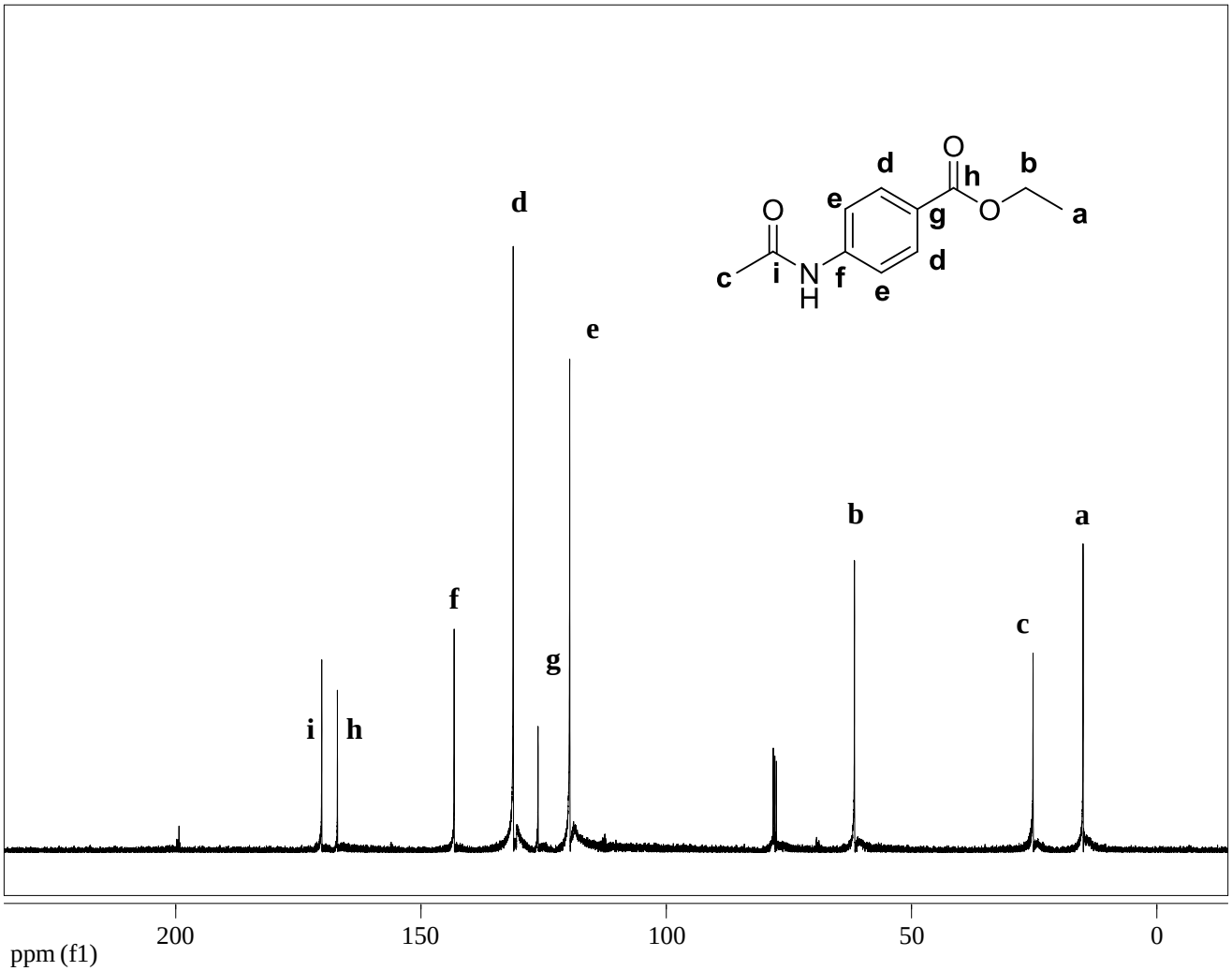


Figure A. 2. ^{13}C-NMR Spectrum of ethyl 4-acetamidobenzoate.

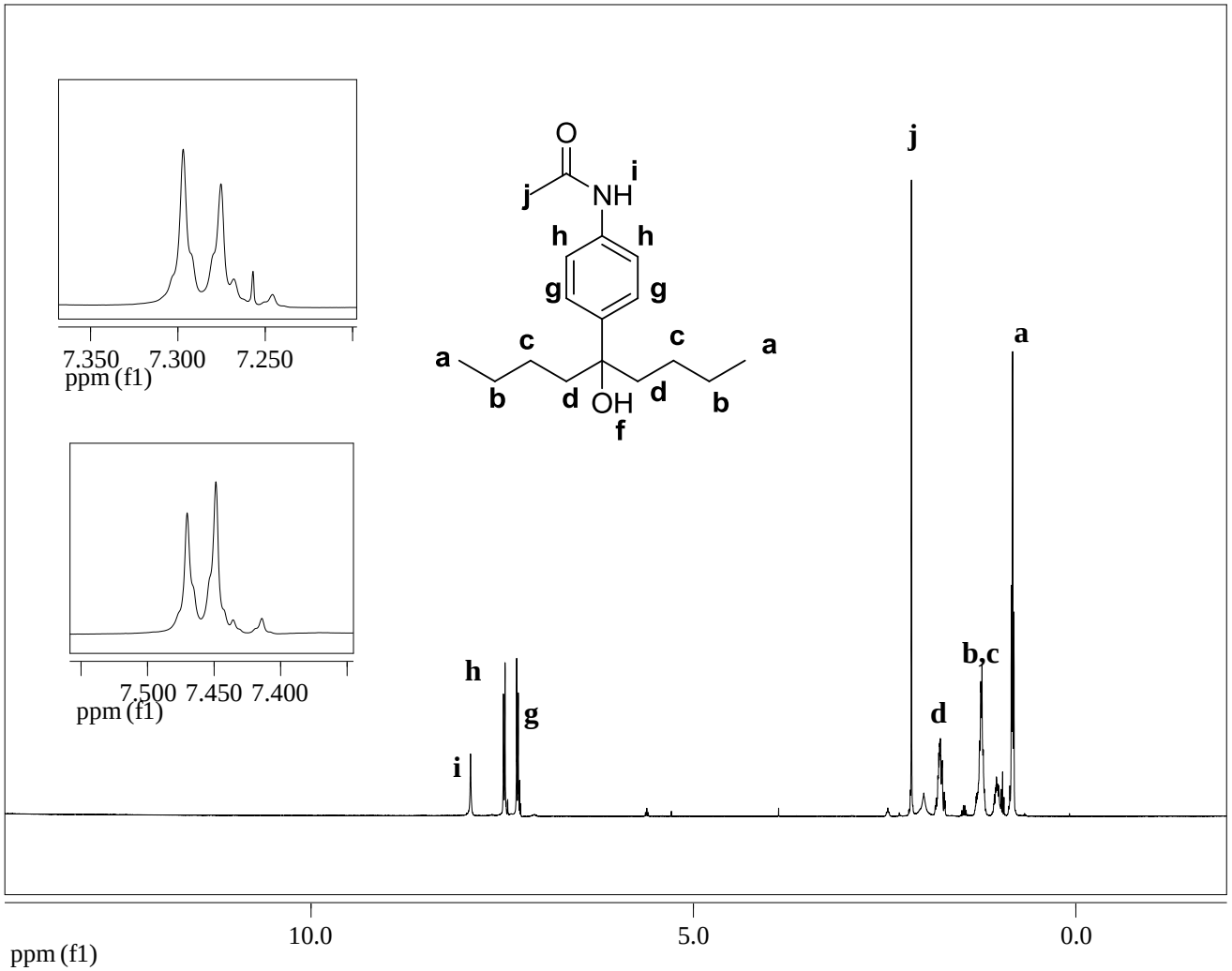


Figure A. 3. ^{1}H-NMR Spectrum of N-(4-(5-hydroxynonan-5-yl)phenyl)acetamide.

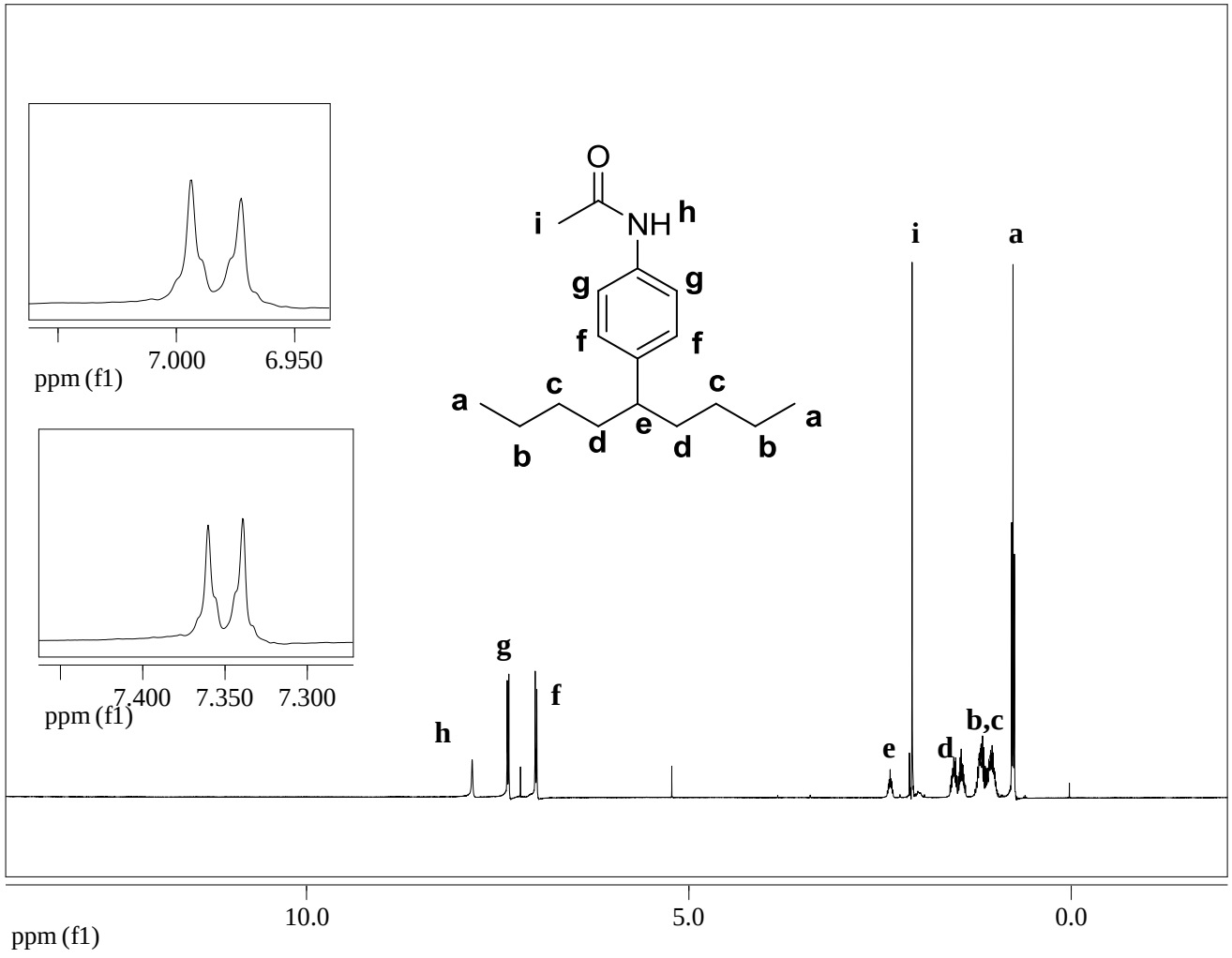


Figure A. 4. ^{1}H-NMR S pectrum of N-(4-(nonan-5-yl)phenyl).

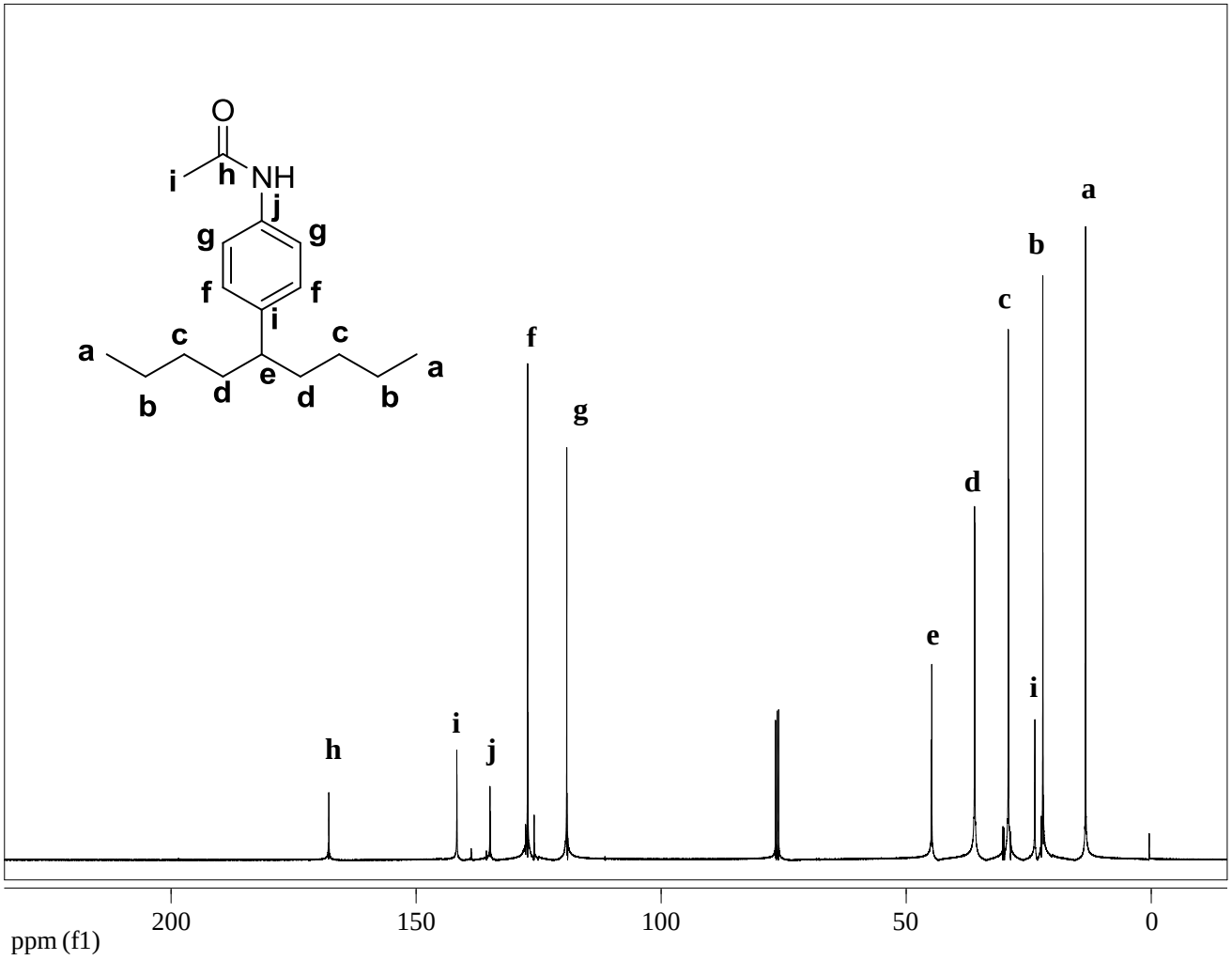


Figure A. 5. ^{13}C-NMR Spectrum of N-(4-(nonan-5-yl)phenyl).

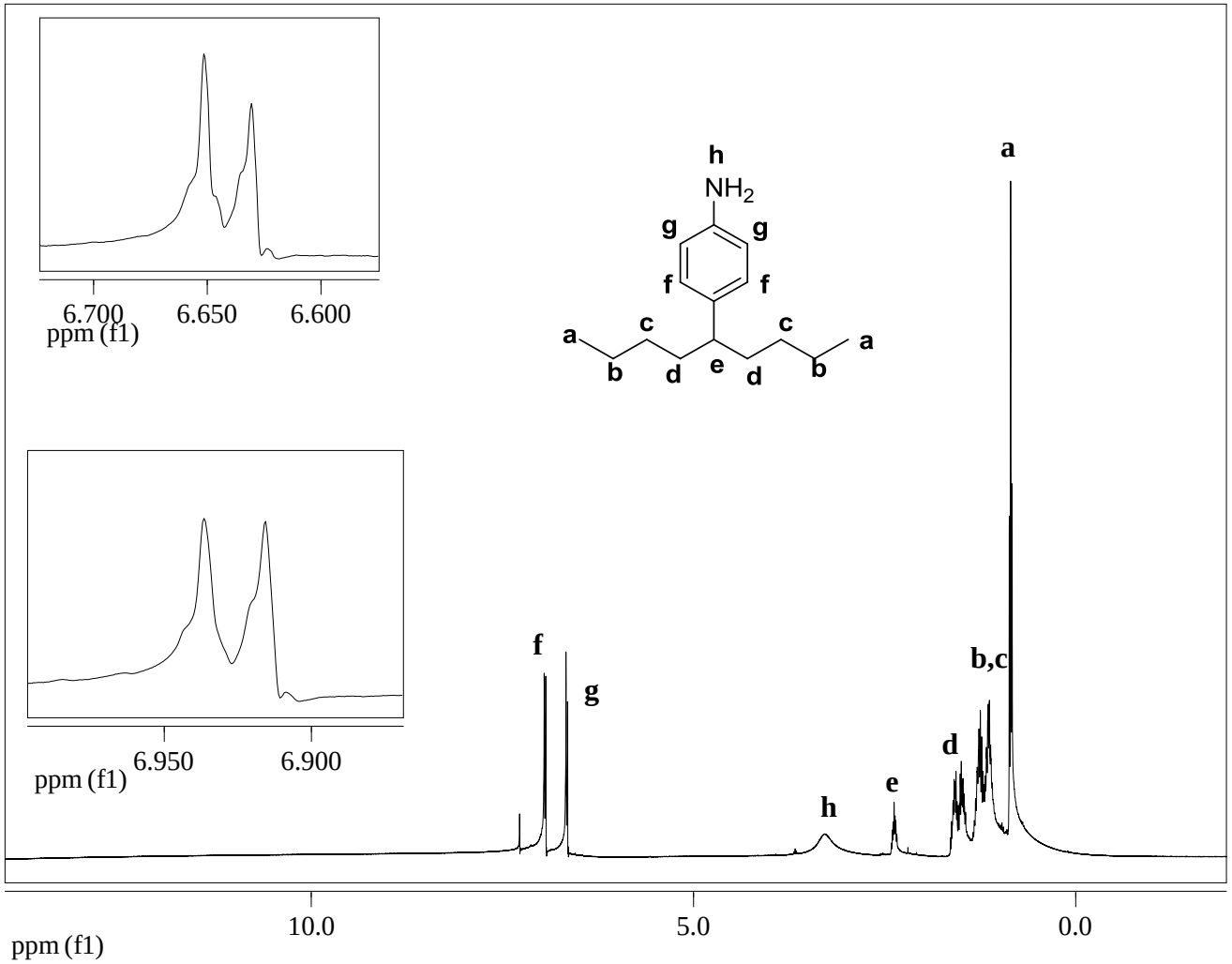


Figure A. 6. ^{1}H-NMR Spectrum of 4-(nonan-5-yl)aniline.

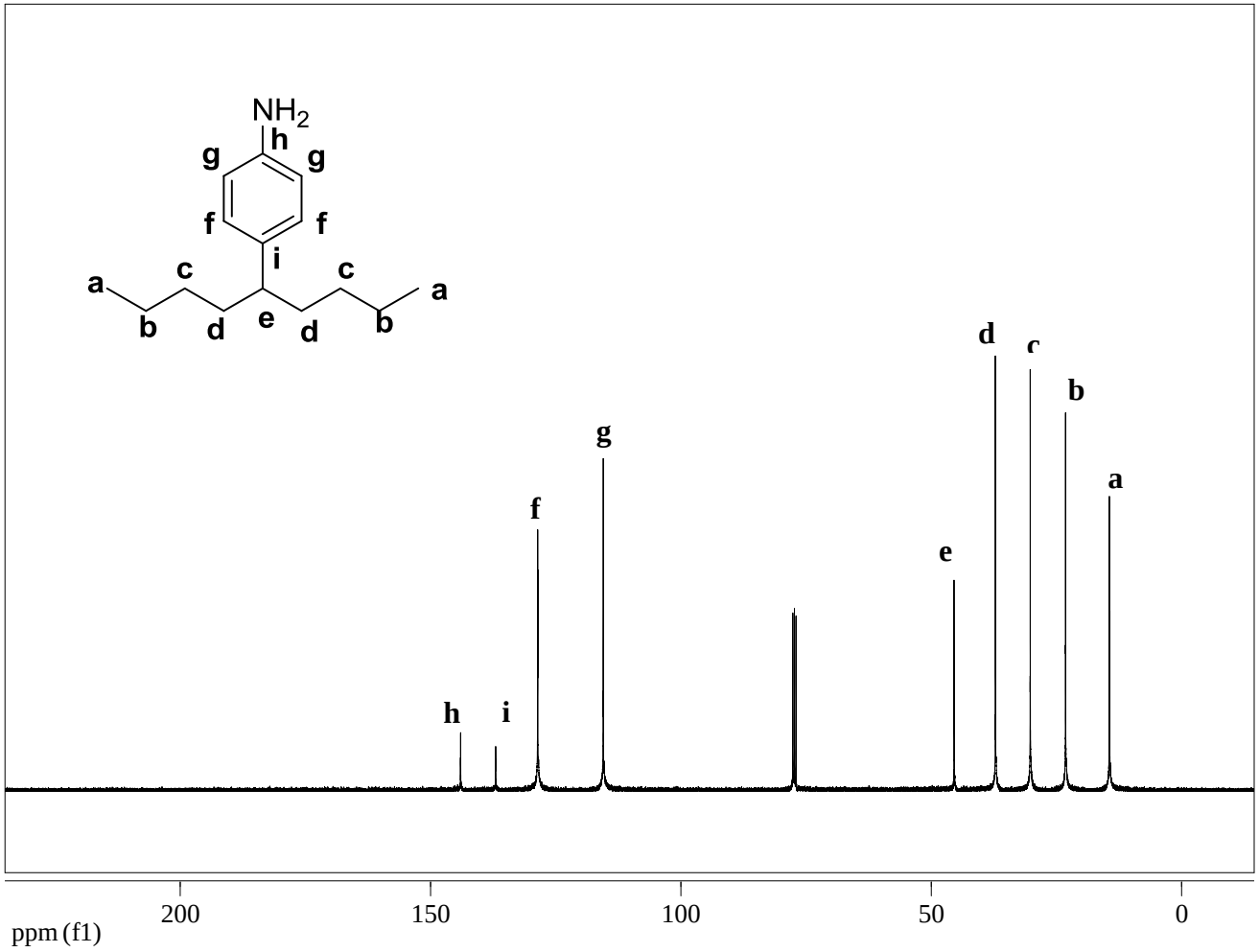


Figure A. 7. ^{13}C-NMR Spectrum of 4-(nonan-5-yl)aniline.

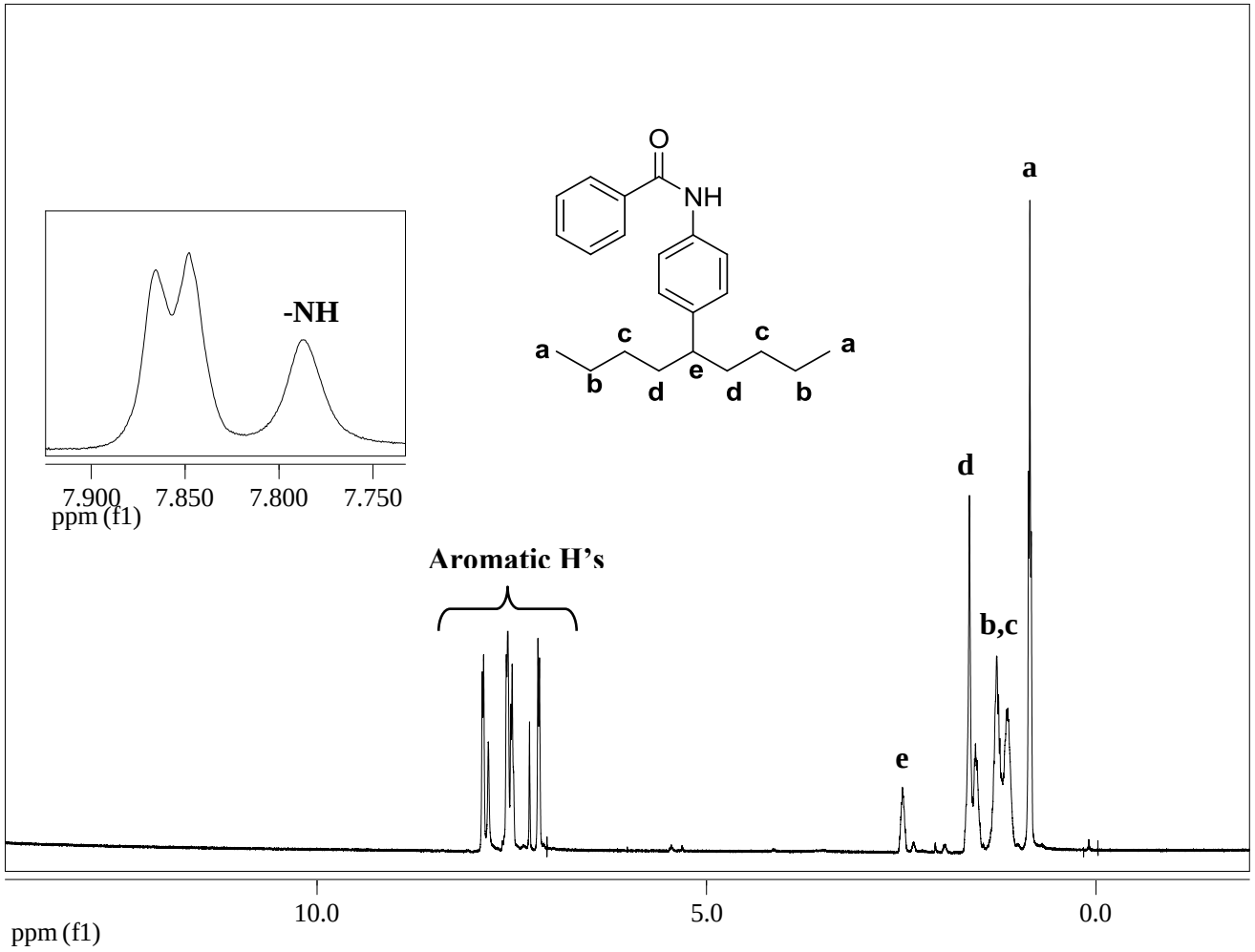


Figure A. 8. ^{1}H-NMR Spectrum of N-(4-(nonan-5-yl)phenyl)benzamide.

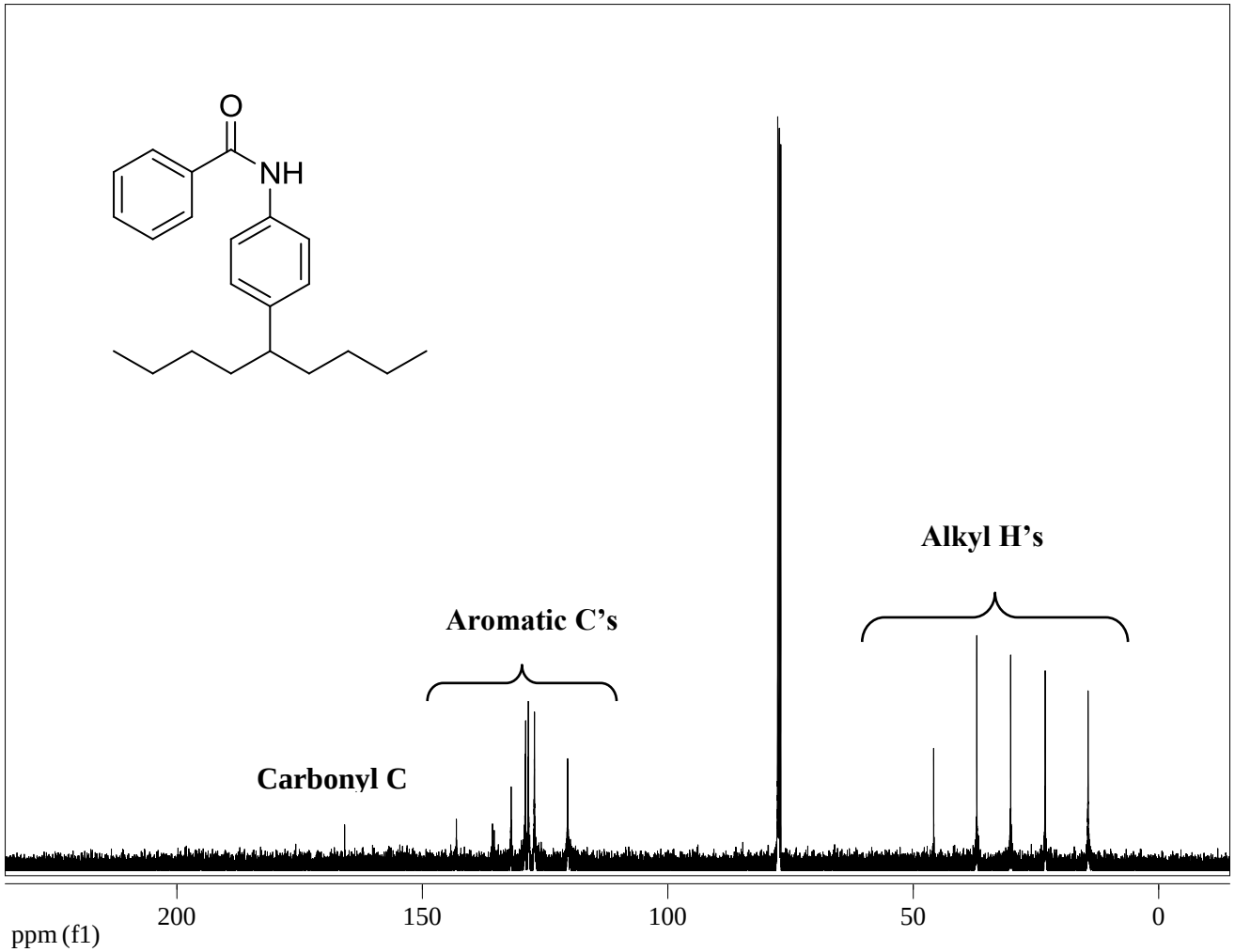


Figure A. 9. ^{13}C-NMR Spectrum of N-(4-(nonan-5-yl)phenyl)benzamide.

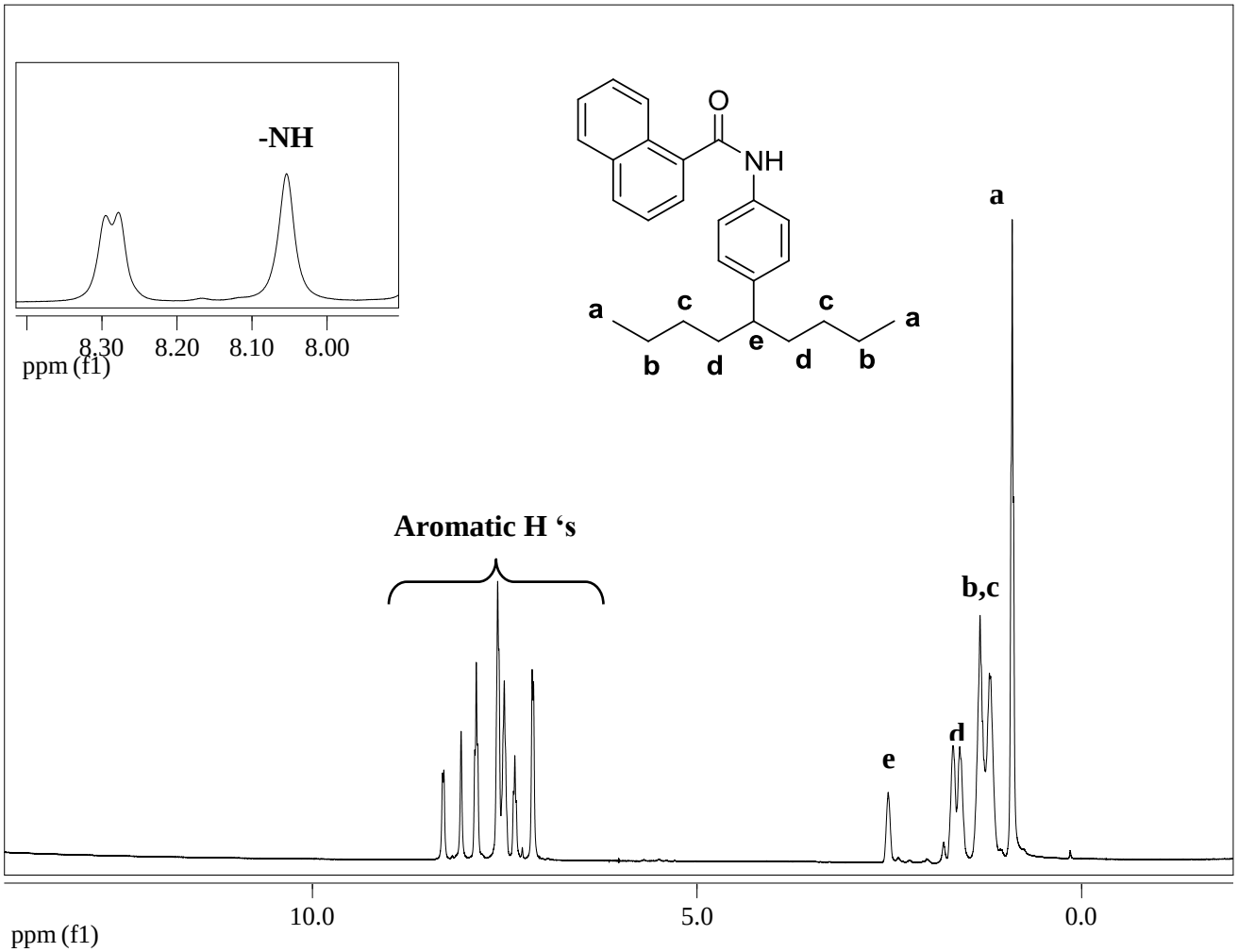


Figure A. 10. ^{1}H-NMR Spectrum of N-(4-(nonan-5-yl)phenyl)-1-naphthamide.

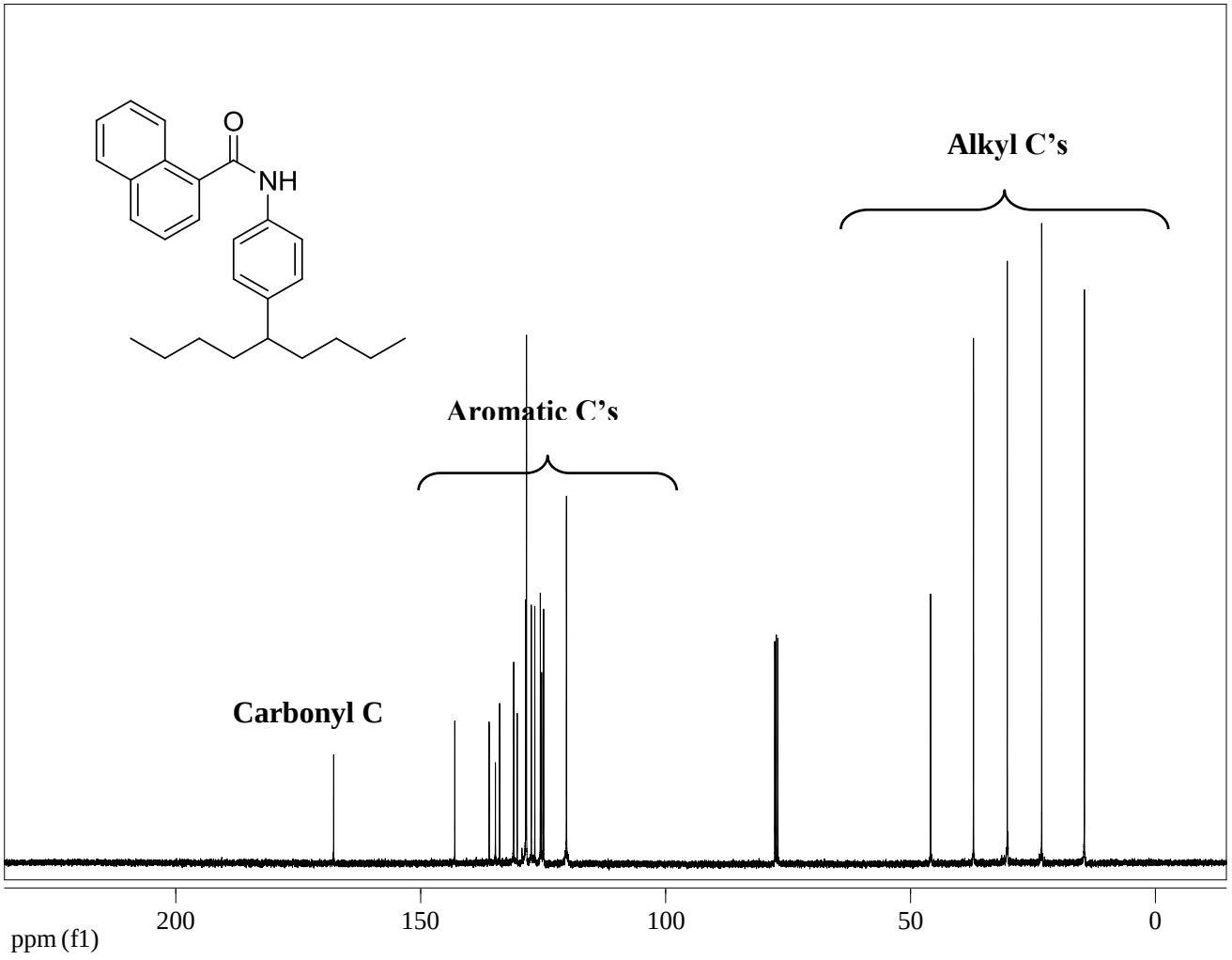


Figure A. 11. ^{13}C-NMR Spectrum of N-(4-(nonan-5-yl)phenyl)-1-naphthamide.

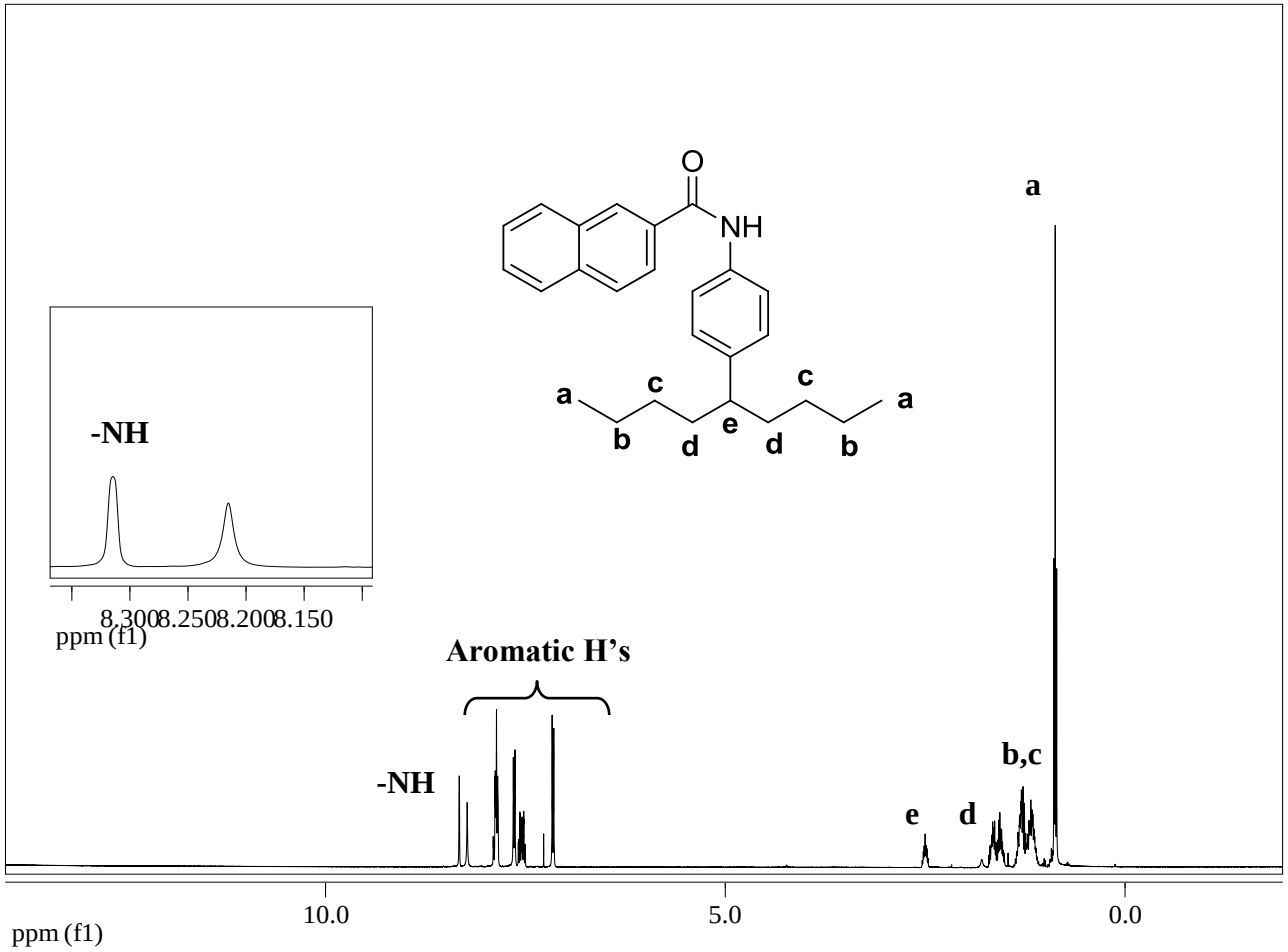


Figure A. 12. ^{1}H-NMR Spectrum of N-(4-(nonan-5-yl)phenyl)-2-naphthamide.

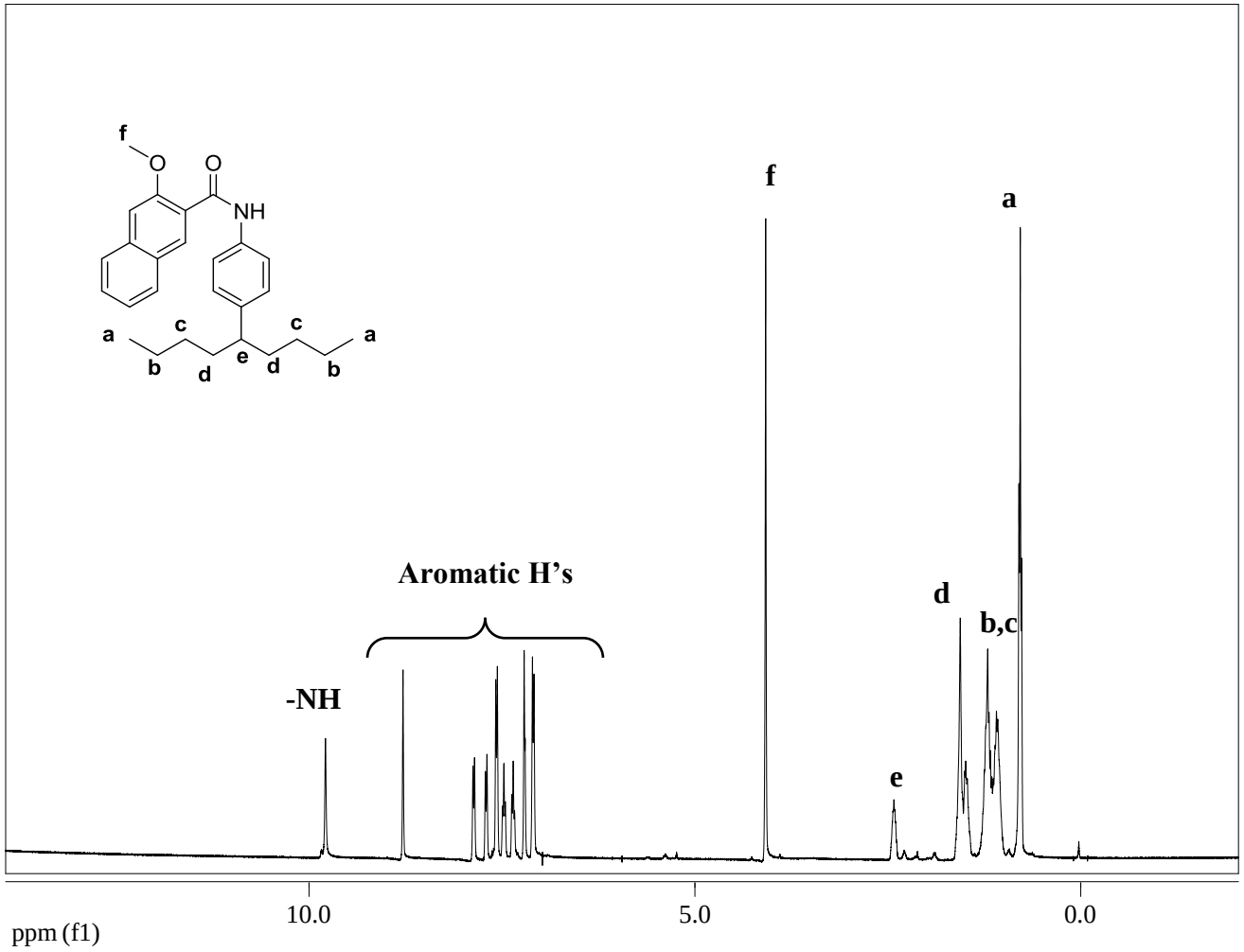


Figure A. 13. ^{1}H-1 NMR Spectrum of 3-methoxy-N-(4-(nonan-5-yl)phenyl)-2-naphthamide.

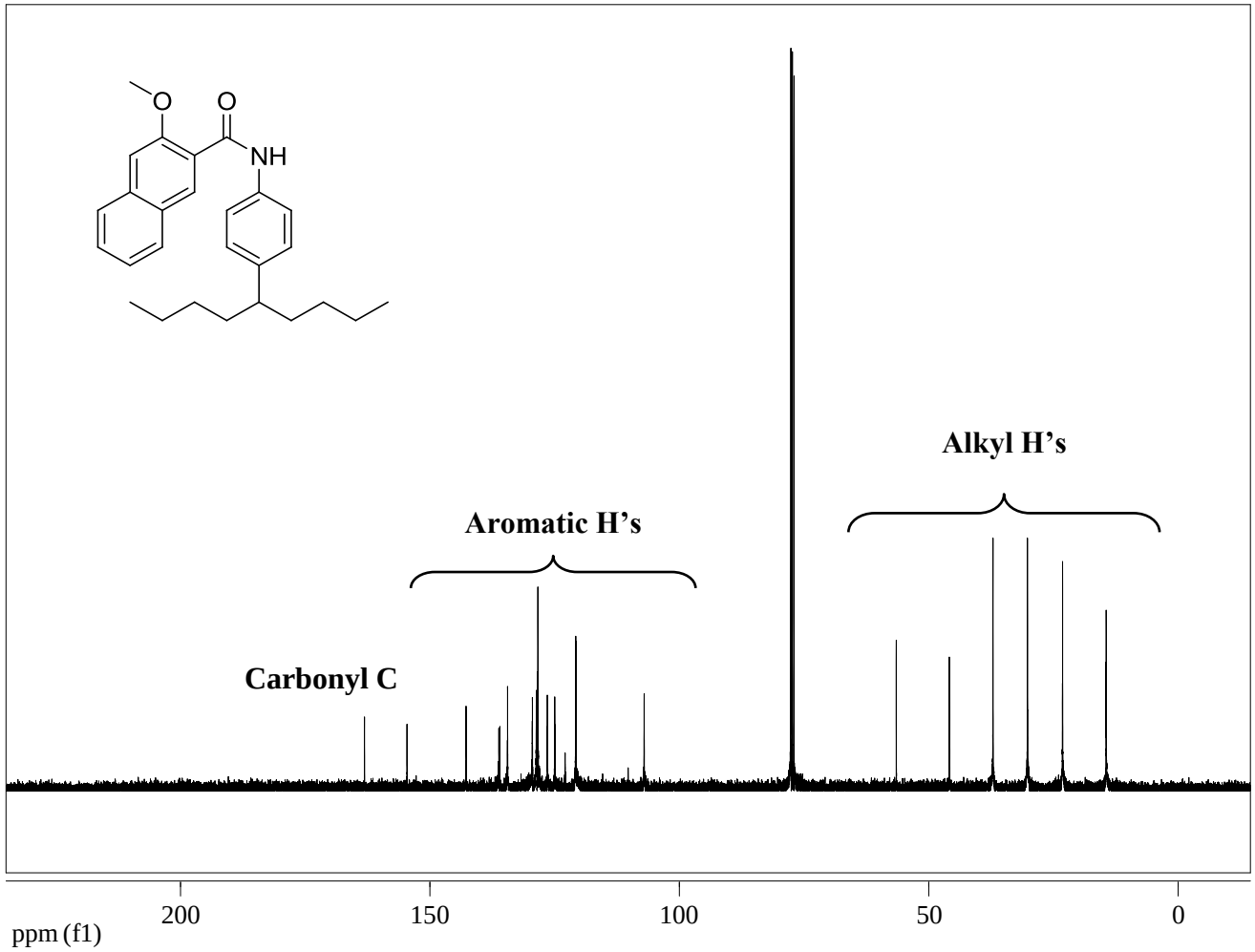


Figure A. 14. ^{13}C-NMR Spectrum of 3-methoxy-N-(4-(nonan-5-yl)phenyl)-2-naphthamide.

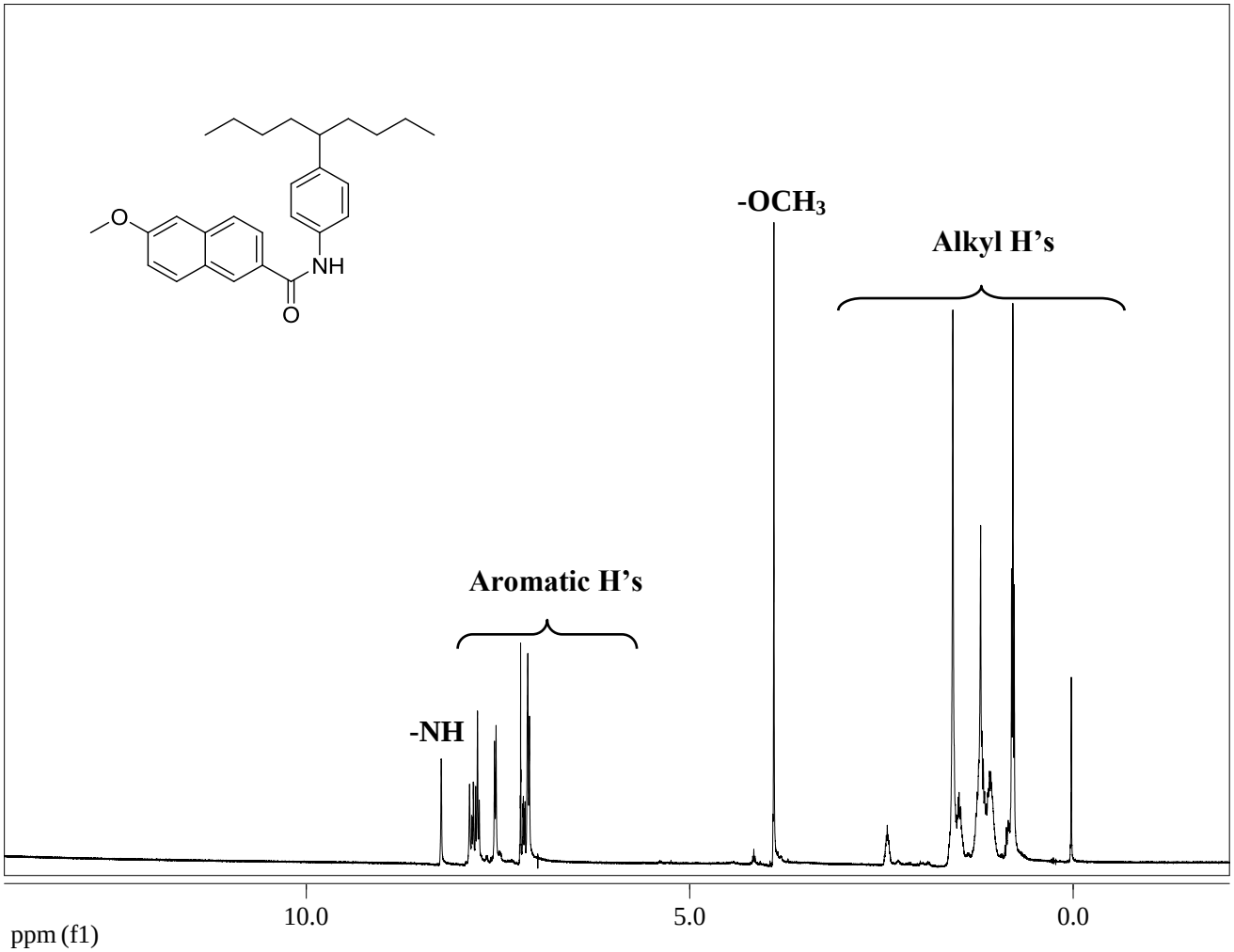


Figure A. 15. ^{1}H-NMR Spectrum of 6-methoxy-N-(4-(nonan-5-yl)phenyl)-2-naphthamide.

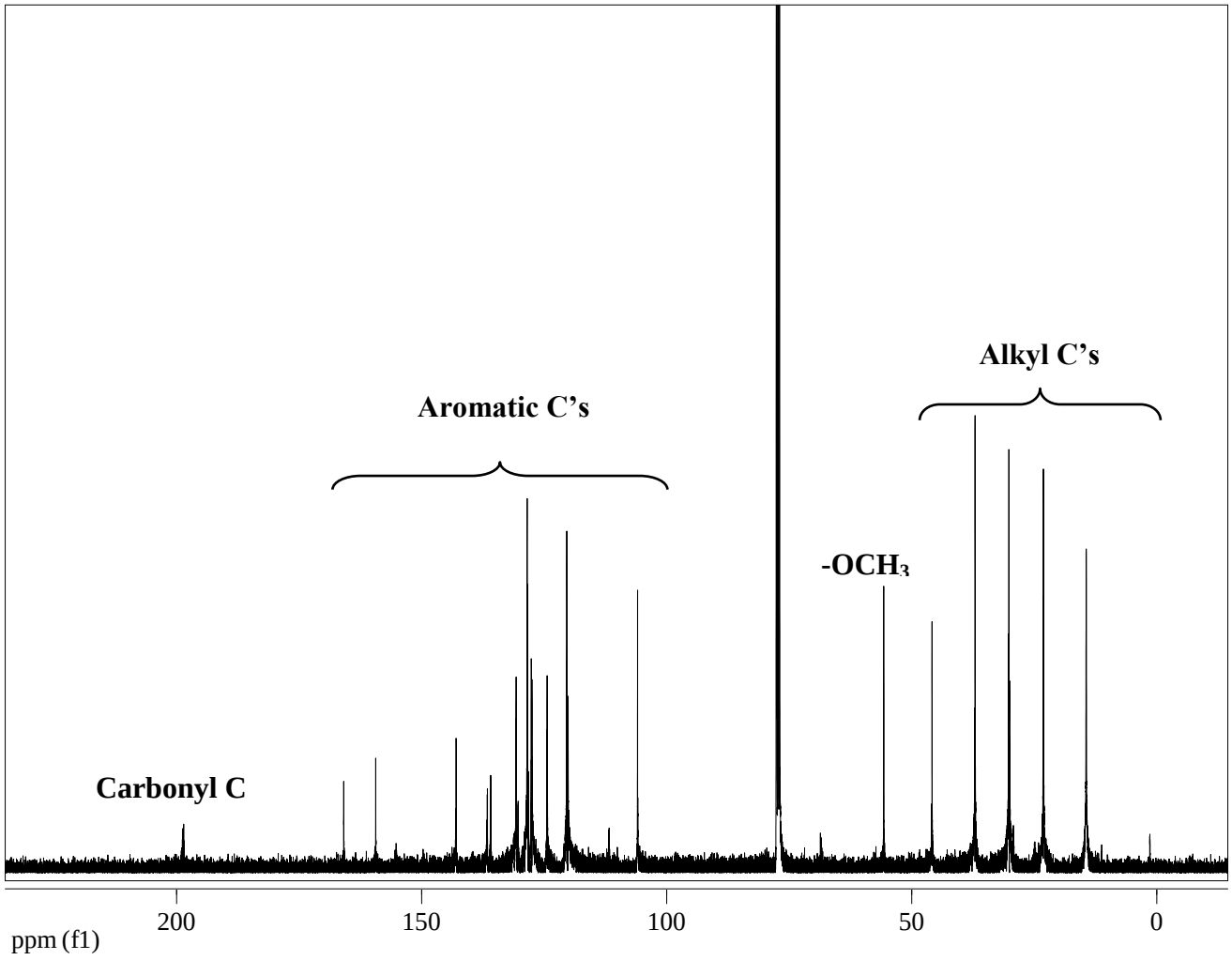


Figure A. 16. ^{13}C-NMR Spectrum of 6-methoxy-N-(4-(nonan-5-yl)phenyl)-2-naphthamide.

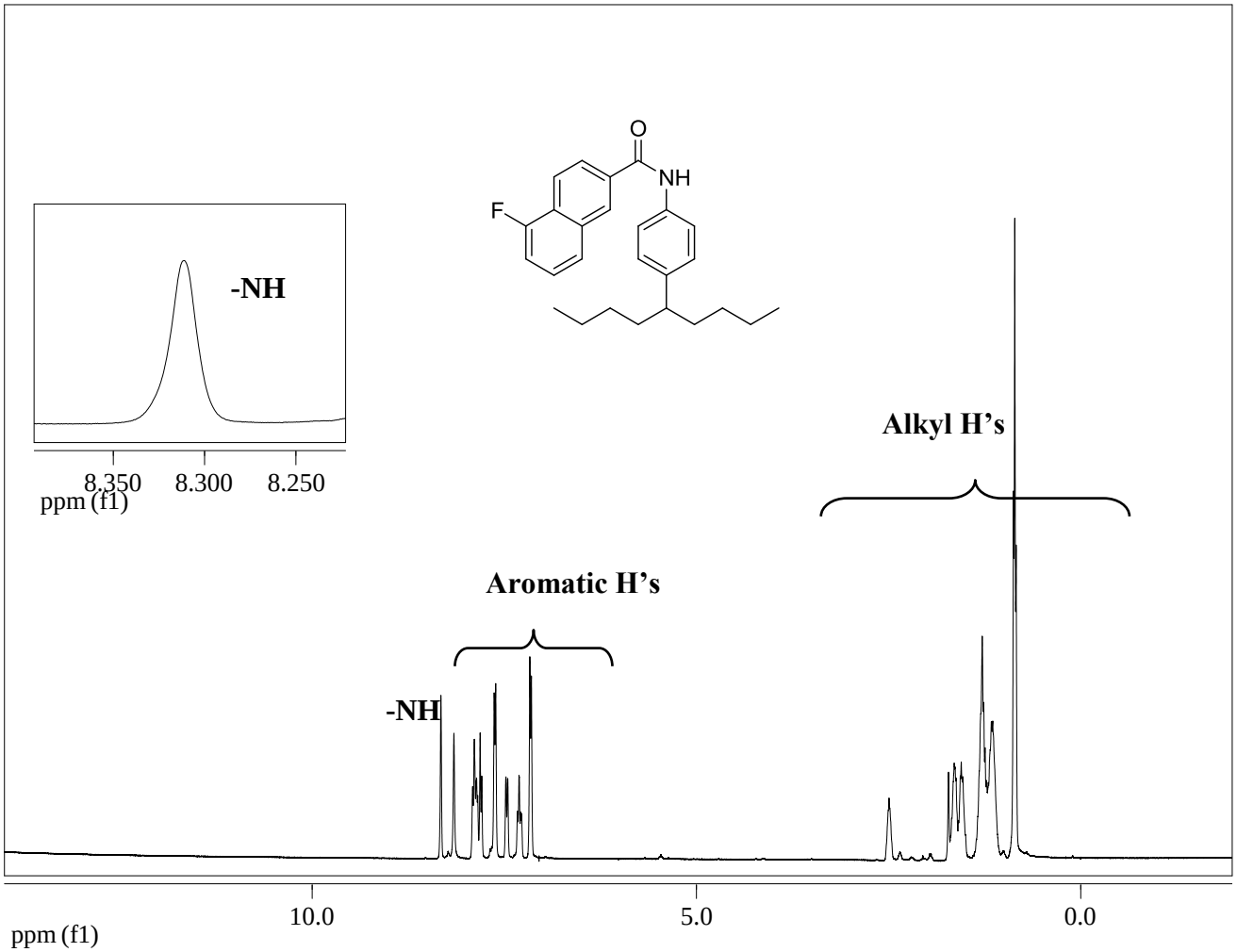


Figure A. 17. ^{1}H-NMR Spectrum of 5-fluoro-N-(4-(nonan-5-yl)phenyl)-2-naphthamide.

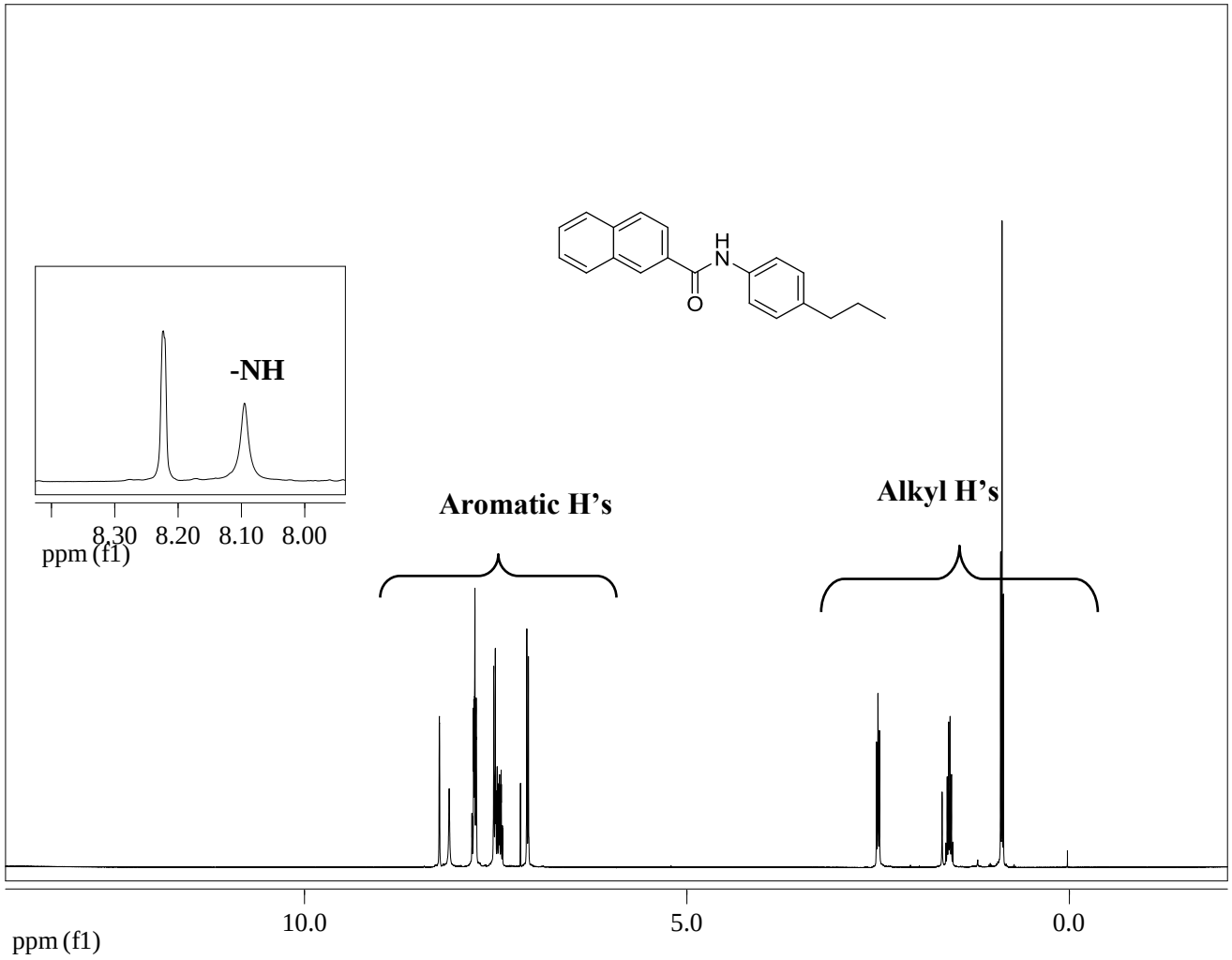


Figure A. 18. ^{1}H-NMR Spectroscopy of N-(4-propylphenyl)-2-naphthamide.

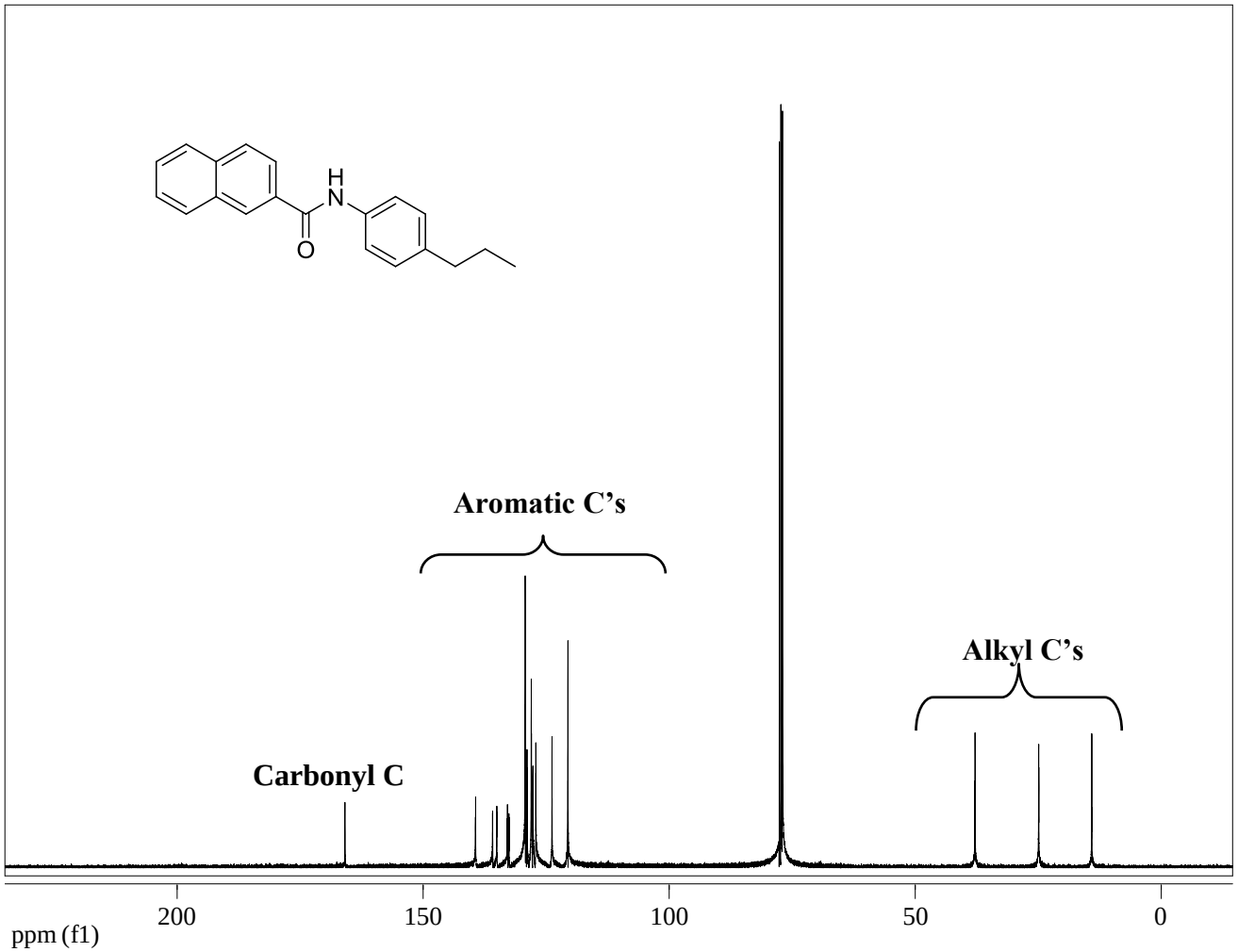


Figure A. 19. ^{13}C-NMR Spectroscopy of N-(4-propylphenyl)-2-naphthamide.

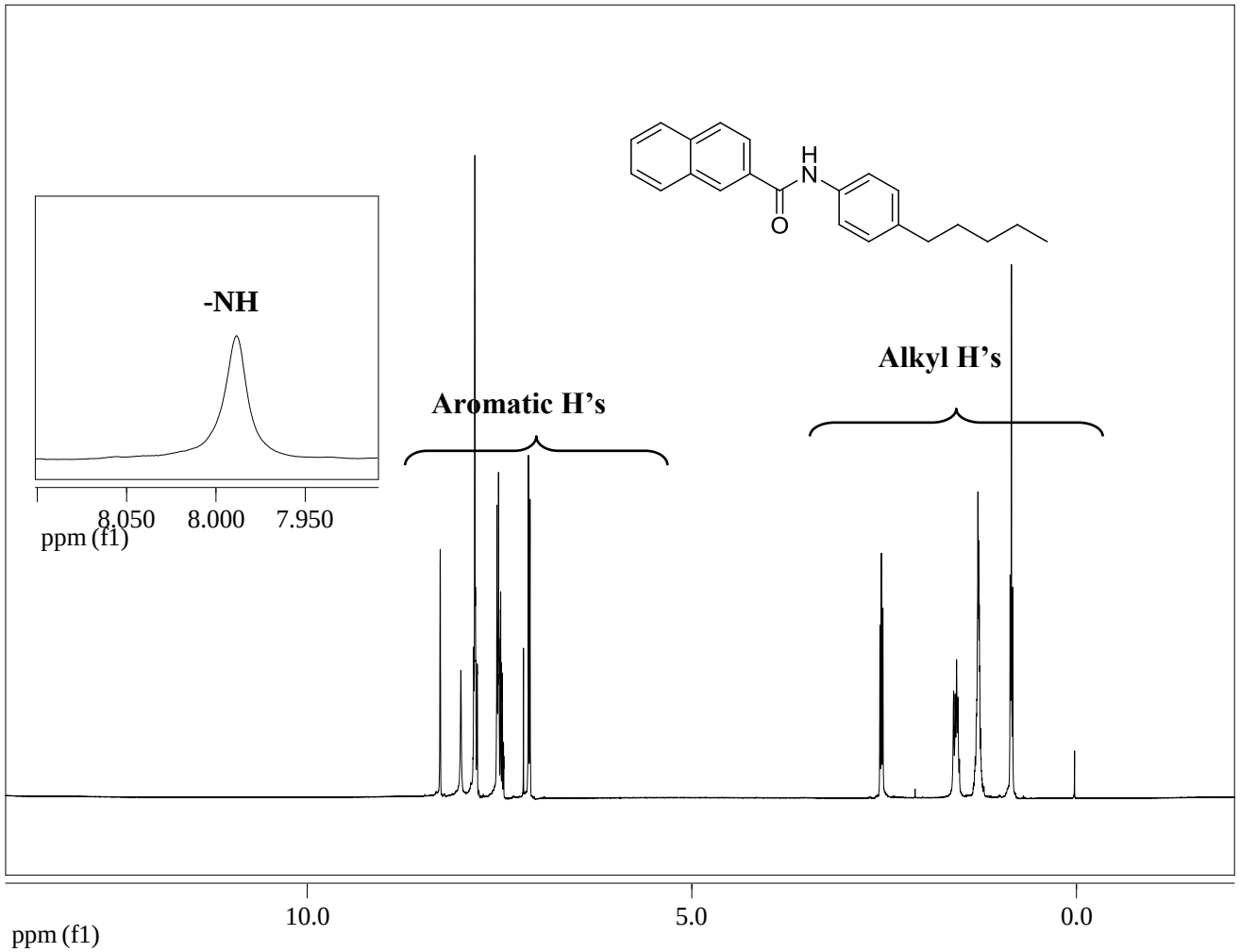


Figure A. 20. ^{1}H-NMR Spectrum of N-(4-pentylphenyl)-2-naphthamide.

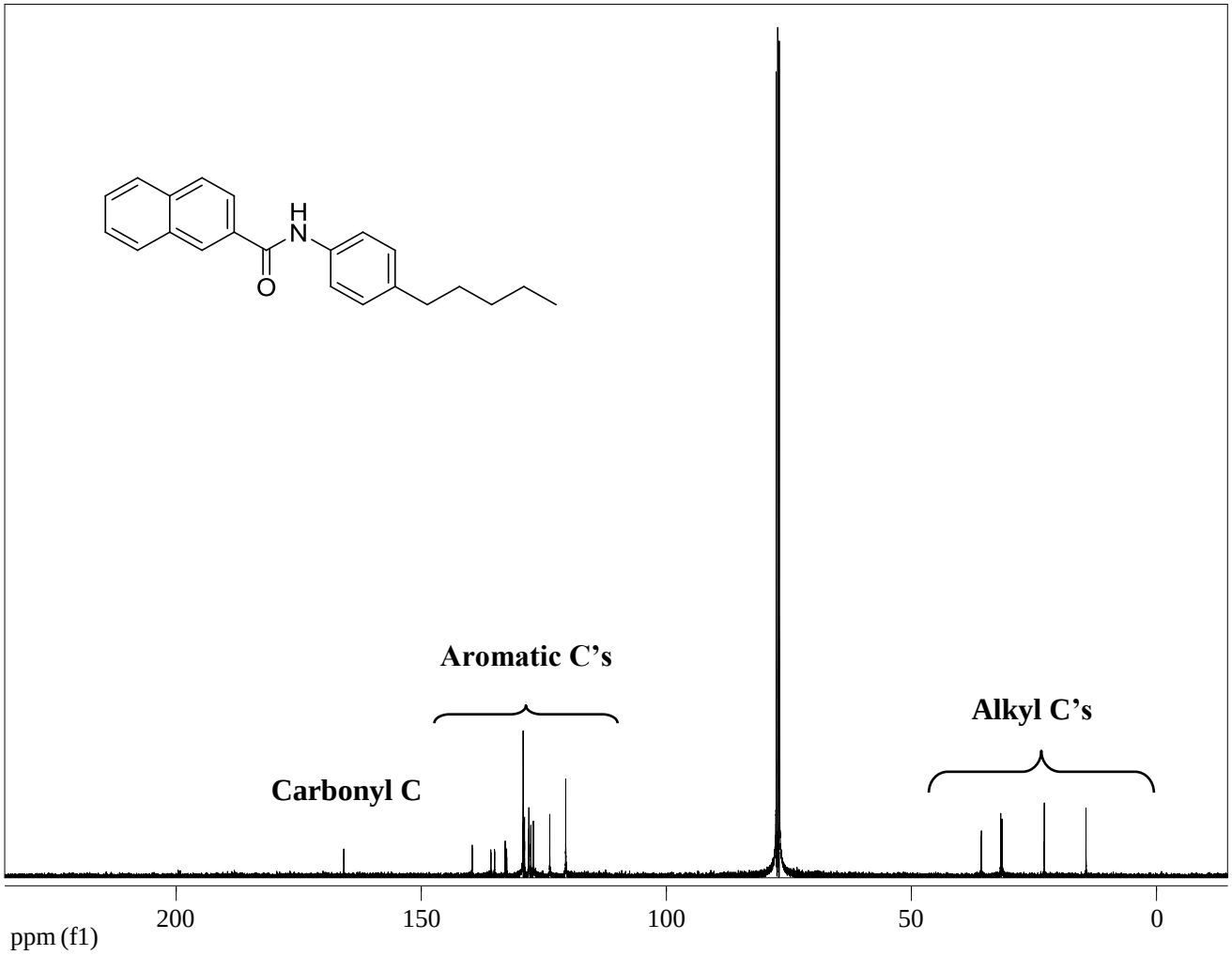


Figure A. 21. ^{13}C-NMR Spectroscopy of N-(4-pentylphenyl)-2-naphthamide.

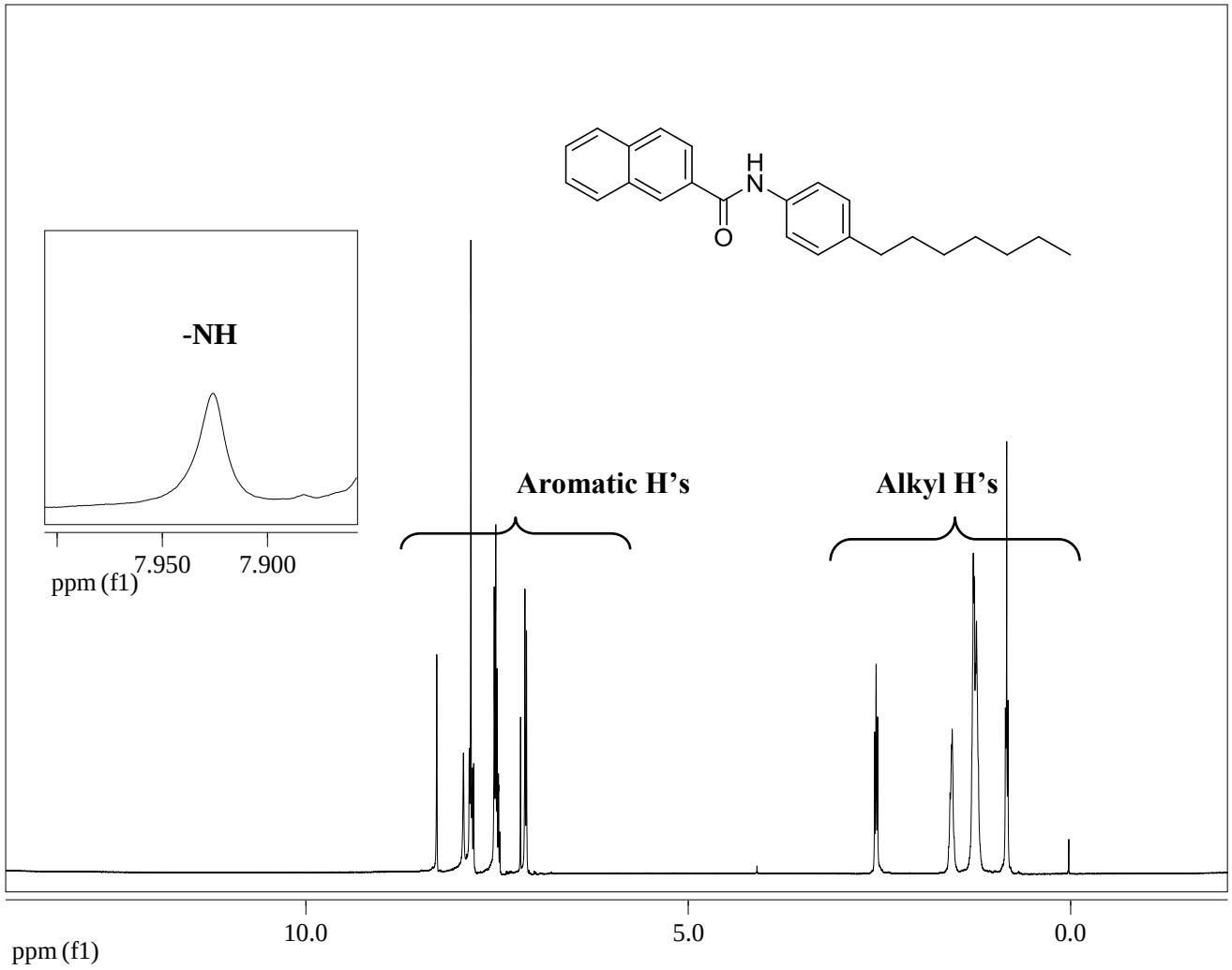


Figure A. 22. ^{1}H-NMR Spectroscopy of N-(4-heptylphenyl)-2-naphthamide.

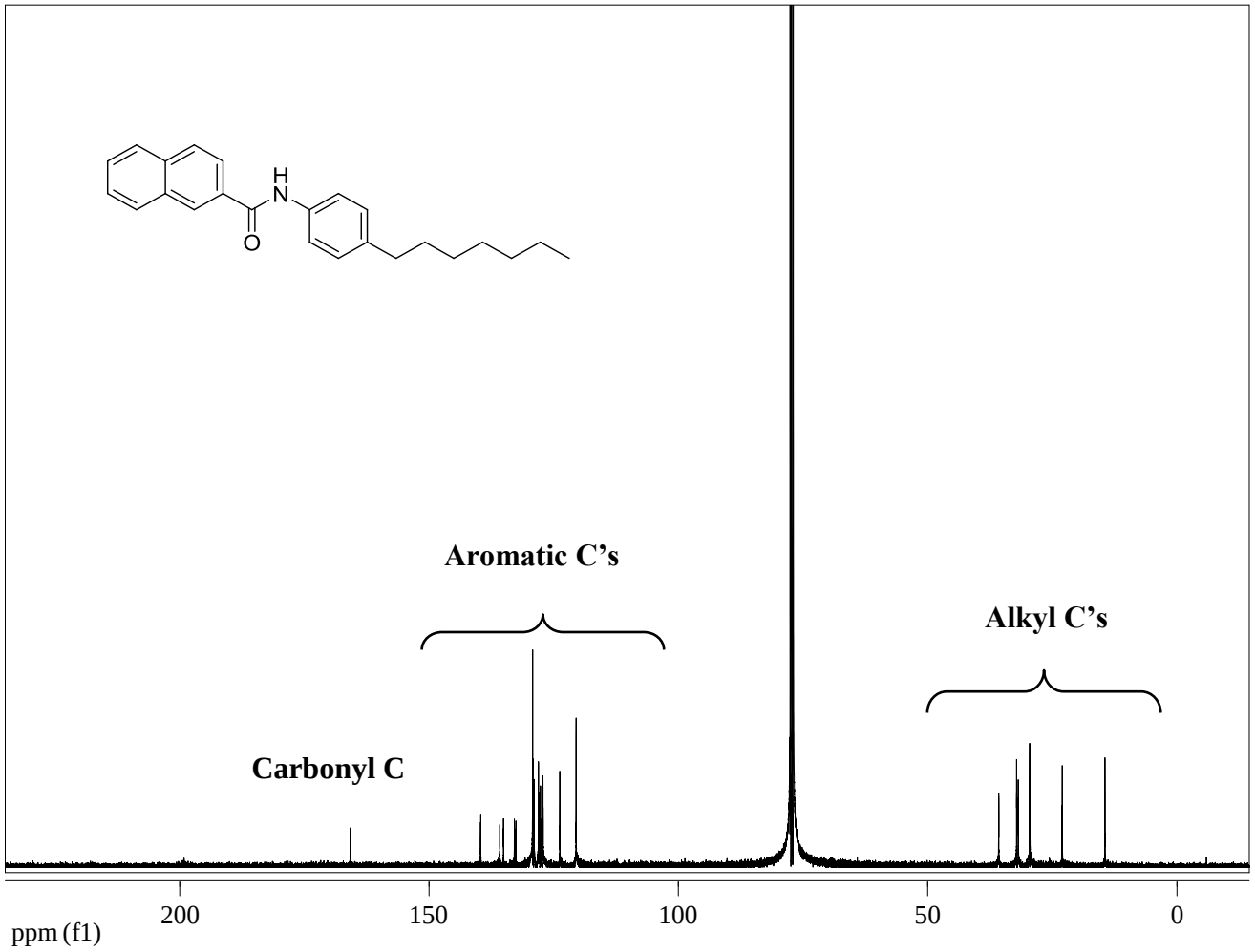


Figure A. 23. ^{13}C-NMR Spectroscopy of N-(4-heptylphenyl)-2-naphthamide.

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