SYNTHESIS OF POTENTIALLY ACTIVE QUINOLINE DERIVATIVES AGAINST PROSTATE CANCER

by

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To My Beloved Parents,
Siblings and Girlfriend

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ABSTRACT

SYNTHESIS OF POTENTIALLY ACTIVE QUINOLINE DERIVATIVES AGAINST PROSTATE CANCER

Prostate cancer is the major cause of death among elderly men all around the world. According to the recent reports, 15% of the US men are faced with prostate cancer and 3% of them lose their lives. Researches on prostate cancer have shown that increased levels of androgens are the primary reason for being prostate cancer. Testosterone and dihydrotestosterone are the two important male hormones which stimulate the androgen biosynthesis. Since those two hormones contribute to the progression of prostatic tumors, suppression of these hormones may be a good solution for the treatment of prostate cancer. In this respect, hormone therapy is generally preferred to treat prostate cancer, because inhibition of the target enzyme might be resulting in the total blockage of androgen biosynthesis in adrenal glands and testes. Many studies have indicated that CYP-17 enzyme catalyzes the last step of the androgen production; therefore, CYP-17 enzyme was selected as the primary target enzyme for the treatment of prostate carcinoma. With the help of computational software, steroidal and non steroidal inhibitors of CYP-17 enzyme were determined in Koc University. Due to the drawbacks of steroidal inhibitors, a non-steroidal lead compound was then chosen. Necessary modifications were done on the lead compound and molecular docking studies were performed for the derivatives of the lead molecule by using Autodock program. In this project, synthesis of quinoline derivatives as part of larger drug molecules potentially active against prostate cancer was targeted. Quinoline derivatives containing an amino group at the 8th position and an alkyl substitution at varying positions were synthesized using different approaches. Three derivatives were synthesized; 3-butylquinolin-8-amine, 4-butylquinolin-8-amine and 6-butylquinolin-8-amine. After the synthesis of those quinoline derivatives, *in-situ* coupling reactions were done with benzoic acid and naphthoic acid derivatives. All transformations of quinoline derivatives and coupling products were verified with 1D NMR and 2D NMR data.18 drug candidates were successfully synthesized and sent to Koc University for the biological testing.

ÖZET

PROSTAT KANSERİNE KARŞI POTENSİYEL AKTİVİTELİ KİNOLİN TÜREVLERİNİN SENTEZİ

Prostat kanseri yaşlı erkekler arasında ölümle sonuçlanan dünya çapında bir kanser türüdür. Son bulgulara göre Amerikalı erkeklerin %15'lik kısmı prostat kanserine yakalanmış ve bunların %3'u hayatlarını kaybetmişlerdir. Prostat kanseri üzerindeki araştırmalar hastalığın birincil sebebi olarak artan androjen seviyesini göstermektedir. Testosteron ve dihidrotestosteron androjen biyosentezinde görev alan en önemli iki erkek hormonudur. Bu iki hormon prostat kanserinin oluşum sürecine katkıda bulunduklarından, testosterone ve dihidrotestosteron hormonlarının salgılanmasını önlemek iyi bir tedavi yöntemi olabilir. Bu sebeple hormon terapisi prostat kanseri tedavisinde sıklıkla tercih edilir çünkü hedef enzimin inhibe edilmesi böbreküstü bezlerindeki ve testislerdeki androjen biyosentezini tamamen durdurabilir. Yapılan çalışmaların çoğu CYP-17 enziminin androjen üretiminin son basamağını katalizlediğini gösterdi. Bu yüzden CYP-17 enzimi prostat kanseri tedavisinde başlıca hedef enzim olarak seçildi. Koç Üniversitesi'nde bilgisayar destekli yazılımlar aracılığıyla CYP-17 enziminin steroid bazlı ve steroid olmayan inhibitörleri belirlendi. Steroid bazlı inhibitörlerin bazı dezavantajlarından ötürü öncü bileşik olarak steroid bazlı olmayan bir inhibitör daha sonra belirlendi. Öncü bileşik üzerinde gerekli düzenlemeler yapıldı ve Autodock programı kullanılarak öncü molekülün türevlerinin yaklaşma ve bağlanma enerjilerinin hesaplamaları yapıldı. Bu projede prostat kanserine karşı potansiyel olarak aktif özellikteki birçok ilaç moleküllerinin büyük bir kısmını oluşturan kinolin türevlerinin sentezlenmesi amaçlanmıştır. Çeşitli yöntemler kullanılarak sekizinci pozisyonunda amin grubu ve farklı pozisyonlarda alkil grubu içeren kinolin türevleri sentezlenmiştir. Üç tane kinolin türevi sentezlendi; 3-bütil-kinolin-8-amin, 4-bütil-kinolin-8-amin ve 6-bütil-kinolin-8-amin. Sentezlenen bu kinolin türevi bileşiklerinin daha sonra benzoik asit ve çeşitli naftoik asit türevleriyle bağlama reaksiyonları yapıldı. Tüm kinolin bileşiklerinin dönüşümleri ve son ürünlerin yapıları 1D NMR ve 2D NMR verileriyle aydınlatıldı. 18 tane aday ilaç molekül başarıyla sentezlendi ve biyolojik testler için Koç Üniversitesi'ne gönderildi.

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LIST OF ACRONYMS/ABBREVIATIONS

1D	One Dimensional
2D	Two Dimensional
3D	Three Dimensional
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
COSY	COrrelation SpectroscopY
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
LDA	Lithium Diisopropylamide
LH-RH	Luteinizing Hormone-Releasing Hormone
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Enhancement SpectroscopY
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. Defining Cancer

Cancer is a worldwide affliction resulting in death. It is not contagious, though; deaths due to cancer have a very high percentage. As reported by World Health Organization (WHO), in every year over 11 million people are diagnosed with cancer and in 2008 approximately 7.6 million people passed away because of cancer. Moreover, it is estimated that deaths stemming from cancer will continue to increase all around the world and about 12 million people may die in 2030 [1].

Surveillance Epidemiology and End Results (SEER) statics from 2004 to 2008 indicates that the average age of the subjects with cancer of all types was 66. 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. Plus, it is predicted that 1.529.560 men and women (51.6% of men and 48.4% of women) might be faced with cancer disease and 569.490 men and women are assumed to lose their lives due to cancer [2].

Cancer is a common term used for a group of over 100 separate diseases in which anomalous cells grow without control and order and are able to invade other tissues [3]. Malignant tumors and neoplasms are the other terms used instead of cancer [1]. Normal body cells grow, divide and die in a controlled way in order to keep the body normally functioning [3]. Unlike normal cells, cancerous cells do not die and they generate new malignant cells, as well [3]. These cancerous cells can infect to the other parts of the body via bloodstream and lymph systems, where they slowly grow and replace normal tissue [3]. This kind of spreading process is known as metastasis [3].

In fact, doctors have some difficulties in explaining why some people have tumor cells. However, it has been scientifically affirmed that there are many risk factors increasing the possibility of bearing cancer cells. Those risk factors are:

- Genetic predisposition
- Growing older
- Tobacco usage
- Alcohol consumption
- Exposure to radiation
- Various viruses and bacteria
- Cancerogenic chemicals and other substances [4]

Symptoms of the cancer incidents are various and they vary according to the type of the disease, its locus and where the malignant cells have spread. Although there are no apparent symptoms of cancer, fever, over fatigue, loss of weight, change in the functioning of bowel or bladder, unexpected bleeding, stubborn cough, epidermal changes and lumps or tissue masses usually occur in many cancer patients [5].

There are many types of cancer and they are mostly named after the organ or type of the cell in which they grew, as the prostate cancer initializes in the prostate area. Different kinds of cancer incidents might act differently so each treatment will also be different. As it is concluded, prostate cancer and lung cancer are totally two different diseases. Therefore, they grow at different rates and respond to different treatments. Even though the treatment procedures can be extended, the patients are often treated with a combination of therapies. Chemotherapy, immunotherapy, hormone therapy, gene therapy, radiation and surgery techniques are the ways to cure cancer [6].

1.2. What is Prostate Cancer?

The most common cancer type among elderly men all around the world is the prostate cancer [7]. As it is stated by American Cancer Society (ACS), prostate cancer (PC) is the most prevalent carcinoma among male population in the States causing death apart from skin cancer in 2010 [8]. It is predicted that about 17% of US men will be faced with PC during their lifespan and approximately 3% of them will lose their lives [8].

According to Prostate Cancer Foundation (PCF), the risk of developing PC increases after the age of 65 [9, 10]. In addition to the age group; heredity, ethnicity, living environment and certain changes in genome and prostate glands are the other major risk factors [9].

Human prostatic cancer develops in prostate gland which is a part of men reproductive organ locating under bladder and in front of the rectum [10]. In a younger man, it weighs about 20 grams and is about 3 centimeters long like a walnut [10, 11]. One of the most important functions of prostate gland is to store and help to produce seminal fluid [10].

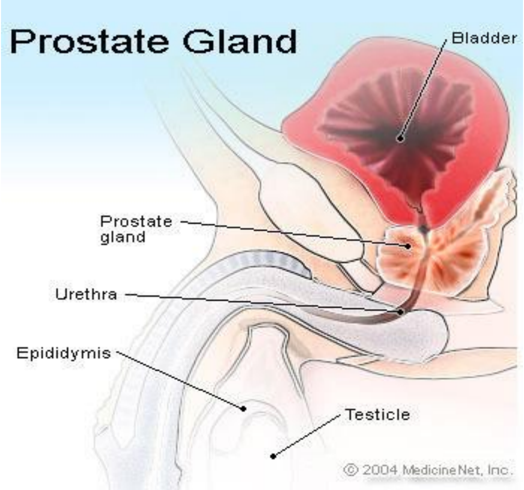


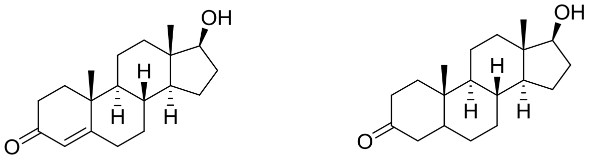
Figure 1.1. The prostate glands [10].

The prostate glands enlarge with aging leading to urination problems [10]. This is known as benign prostatic hyperplasia (BPH), which is not related to PC directly [10, 12]. Therefore, having urinary problems linked to the age may not mean that prostate is developing malignant tumors.

It is difficult to see the symptoms of PC in the early stages because the tumor develops very slowly and it does not show any clues. In order to diagnose PC, several screening methods such as Prostate-Specific Antigen (PSA) and Digital Rectal Exam (DRE) may apply. According to ACS; PSA gives more reliable results for the early diagnosis of prostatic cancer [8]. Common symptoms of PC can be stated as follows:

- Problems with urination
    (i) Frequent urination, usually at night time
    (ii) Weak or intermittently urination
    (iii) Difficulty in starting or finishing urination
- Unexpected blood in the urine
- Frequent low back pain and having pain in the hips
- Erection problems [13].

It has been reported that mutation in the DNA of the prostatic cells and increased levels of certain hormones directly contribute to the development of PC [14, 15]. The 80% of human prostatic tumors are assumed to be based on androgens which have a significant role in the enlargement of the prostate cancer cells [7, 16]. Androgens are the steroid hormones mediating the development of male sex characteristics [14]. Therefore, it can be concluded that higher levels of androgens increase the risk of getting cancer in some men. Testosterone and 5α-dihydrotestosterone (DHT) are the masculine hormones being produced mostly in testes [16]. Many studies have shown that these hormones stimulate androgen biosynthesis; therefore, 5α-dihydrotestosterone (DHT) and higher serum testosterone levels of free testosterone raise the PC risk [15].



Testosteron **5α-dihydrotestosterone**

Figure 1.2. Molecule structures of male characteristic hormones.

It seems that it is not hundred percent possible for men to get rid of PC. However, it might be possible to impede PC by having a nutritious diet, doing exercise, quitting smoking, avoiding stress and having regular check-ups [18].

1.3. Diagnosis of Prostate Cancer

As mentioned before, PSA level and DRE tests are applied to diagnose PC earlier. In addition to those methods, doctors may suggest other procedures, namely transrectal ultrasound (TRUS) and transrectal biopsy [19]. If the PSA level is very high and DRE is unsteady, PC could be confirmed by performing a prostate biopsy and determining the Gleason score which is a grade that shows the stage of PC [20]. There are mainly four stages in the progress of PC:

- Stage I: The Gleason level is low and DRE is normal; then it is accidentally found out during false surgeries, such as BPH.
- Stage II: Observable; cancerous tumor spreads over only in the prostate, detectable during DRE.
- Stage III: Carcinoma has evolved outside of the gland and started to invade seminal vesicles.
- Stage IV: More advanced stage; metastasis occurs and the tumor continually invades other parts of the body [21].

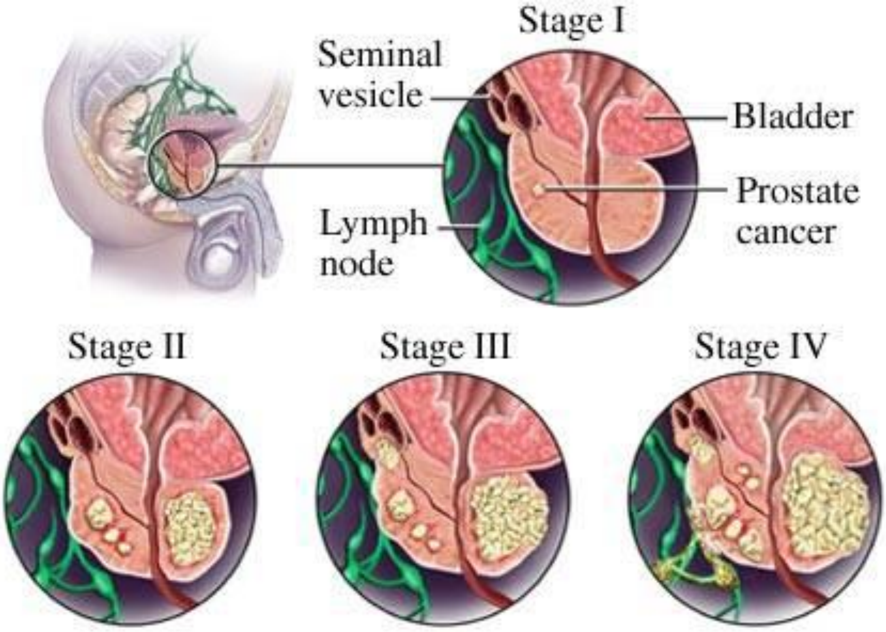


Figure 1.3. Progression of prostate cancer from stage I to IV [40].

1.4. Treatment of Prostate Cancer

Treatment methods for PC have been improved in the last decade but it is still difficult to choose the best treatment convenient to the patient. Age problems, average lifetime, adverse effects and personal preferences are the main factors affecting such decisions [22]. Treatments can be varied according to the actual stage of PC. The main treatment methods for PC as follows:

- Active Surveillance (Watchful Waiting)
- Medical Surgery (Prostatectomy or Orchiectomy)
- Radiation Therapy
- Chemotherapy
- Hormone Therapy [22]

Furthermore; Cryosurgery, Biologic Therapy, High-Intensity Focused Ultrasound and Proton Beamed Radiation Therapy are the other alternative treatment techniques for PC [22].

Active surveillance is to monitor the progress of PC with regular PSA level checking in every 3 to 6 months or sometimes additional biopsy may be deemed [22]. Surgical procedures can be classified in two: Radical prostatectomy and orchiectomy. Former is ablating entire or a part of the prostate gland to take malignant tumor out [11]. And the latter is the removal of testes since the androgens are produced mostly in testicles [11]. However, those therapies may not be preferred by many patients since there have remarkable side effects such as urination problems and infertility [11, 22].

Chemotherapy and radiation therapy are other techniques which employ the use of cytotoxic drugs and high energy x-rays to kill the cancerous cells. However, those therapies have many side effects [22].

Hormone therapy – known as Androgen Deprivation Therapy (ADT) – is one of the most preferable therapeutic strategies to treat PC. As the high levels of androgens stimulate the PC, removal of androgens may hinder malignant cells from developing [7].

1.5. Why Hormonal Therapy?

As it is mentioned before, the majority of the human prostatic cancer cells are androgen based; therefore, androgen levels are proportional to the increased risk of carcinogenic cells [23]. Testosterone and 5α-dihydrotestosterone (DHT) are the well-known steroid hormones which are responsible for developing masculine characteristics [14]. About 90% of the testosterone is produced by testicles and the rest is in adrenal glands [24]. Testosterone hormone is reduced to DHT by the 5R-reductase enzyme staying in the prostate [24]. Since those two fundamental hormones contribute to the progression of malignancy, suppression of these androgens may be a good solution to deal with prostatic cells.

It has been observed that removing of androgens cause to a decrease in the PSA level in the bloodstream [25]. Also, suppressing the androgen biosynthesis makes cancerous cells shrink or stop growing [26]. Hormonal therapy is often preferred for the advanced PC in order to defuse (known as apoptosis) or slow down the spread of tumors [27]. However, some prostatic tumors may not depend on the androgens so; receiving only hormonal therapy may be insufficient for the treatment of PC [28].

Hormonal treatment, named Androgen Deprivation Therapy (ADT), can be achieved by surgery or medicine support [29]. The surgical treatment, known as orchiectomy, is removing the main source of androgens – namely testes. Medicinal hormone therapy can be classified in two:

(i) LH-RH (Luteinizing Hormone – Releasing Hormone) agonists, blocking the delivery of LH-RH from the brain.
(ii) Anti-androgenic (Androgenic receptor antagonist) drugs, working against testosterone in order to block its effects on the prostate [29].

Many prostate patients mostly prefer hormonal therapy to surgical treatment due to its destructive effects on the body [29]. However, hormonal therapy has also the same efficiency and side effects compared to surgical therapies [29]. For instance, ketoconazole is a synthetic antifungal agent which prevents the androgen biosynthesis in testes and glands [16, 30]. Due to its non-selectivity, it also inhibits the other cytochrome P-450 enzymes; thus it causes further problems on different organs [16]. Moreover, antiandrogen agents may lead nausea, anemia, and liver problems.

Thus, due to the many adverse effects of the existing treatments, it is required to develop new treatment techniques which have minimum side effects and maximum therapeutic efficiency.

1.6. New Methods for the Treatment of PC

Due to the many side effects of standard treatment techniques, PC researches have focused on developing newer treatment methods over the past 15 years. Hence, many studies have indicated that androgen deprivation therapy (ADT) is a promising therapy which gives the most beneficial responses for the prostate patients [16].

As stated before, androgens stimulate the growth of PC; therefore, hormonal therapy might be convenient for both early and metastatic prostate cancer. Androgen ablation therapy [16] targets the suppression of androgen level by using anti-androgens or LH-RH blockers in order to lessen and control the biological androgen synthesis in both testes and prostate gland [29]. In this respect, since some effective inhibitors of the enzymes take action in androgen biosynthesis, it is required to examine the mechanisms of testosterone and DHT biosynthesis in detail.

1.6.1. Biological Synthesis of Androgens in Testes and Adrenal Glands

As mentioned before, the well-known male sex hormones, namely testosterone and DHT, are mostly (about 90%) produced in testicles and the rest in adrenal glands. Therefore, it can be concluded that drugs inhibiting androgen biosynthesis may be a promising tool to deal with prostate carcinoma and BPH [31]. Studies have shown that cytochrome P-450 enzyme family plays a catalysis role in the steroid hormone biosynthesis.

The cytochrome P-450 enzyme family is a large and ubiquitous enzyme system belonging to the hemoproteins [32]. It has a single iron heme group with cystein residue and the role of the cytochrome P-450 monooxygenase enzyme is to synthesize and/or disrupt many endogenous substances [33]. Moreover, it also plays a significant role in drug metabolism and the biological transformation of some xenobiotics [33].

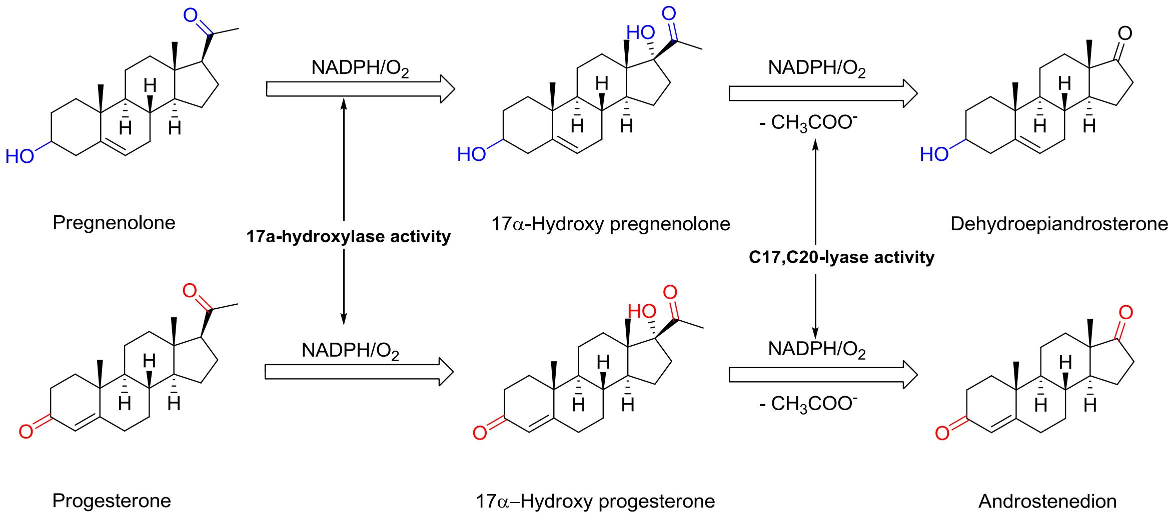


Figure 1.4. Biosynthesis of androgens catalyzed by P-450 [33].

The biosynthesis of testicular and adrenal androgens is initialized with the cholesterol as the starting compound [23]. The cytochrome P-450 monooxygenase enzyme catalyzes a series of reactions to end up with steroidal androgens [34]. The CYP17 enzyme, called as 17α-hydroxylase-C17, C20 lyase enzyme, catalyzes the last step of androgen formation [23, 34]. As it is seen in the Figure 1.4, firstly pregnenolone and progesterone are hydroxylated by CYP17 to 17α- hydroxyl pregnenolone and 17α-hydroxyl progesterone [23]. Soon after the cleavage of acetyl group, dehydroepiandrosterone and androstenedion are formed [23]. Those compounds are further catalytically converted to testosterone and DHT [23].

1.6.2. Specifying Target Enzyme: CYP 17

In order to abort the testicular and adrenal androgen biosynthesis, specifying a target enzyme is required. As mentioned earlier, CYP17 enzyme catalyzes the production of both testosterone and DHT. Therefore, the development of strong inhibitors of CYP17 ($P450_{17\alpha}$), which in result means the total blockage of androgen biosynthesis, can be a novel promising treatment option.

Specific identification of the target enzyme is vital because it might help to prevent the undesirable side effects of the treatment [23]. It is known that CYP17 and 5α-steroid reductase enzymes are the target enzymes of the PC treatment [31]. However, 5α-reductase enzyme is initially responsible for BPH together with its small contribution in PC treatment. Thus, cytochrome CYP17 ($P450_{17\alpha}$) enzyme is the main target of prostatic tumor treatment [31].

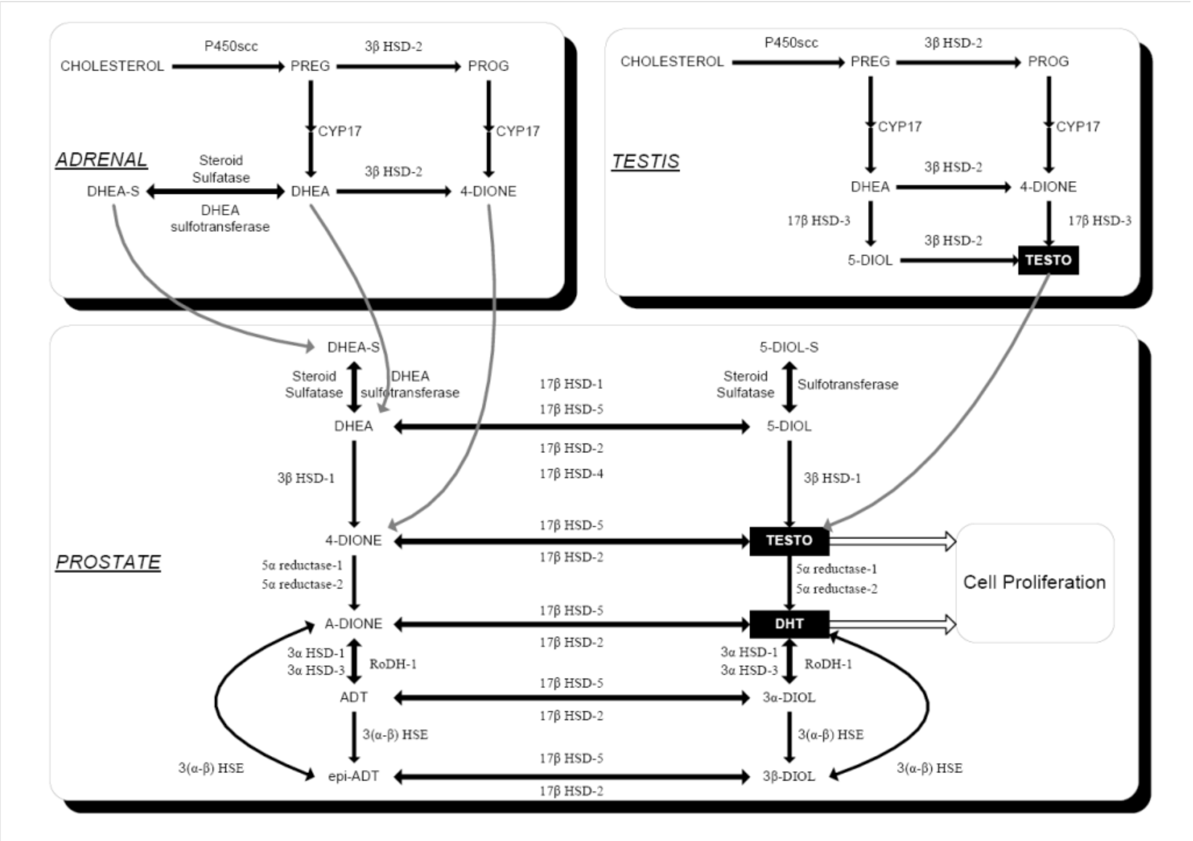


Figure 1.5. Catalytic pathway of androgen biosynthesis [11].

CYP17 enzyme is a microsomal enzyme which is found mostly in the mammalian testicles, adrenal and ovarian theca tissue [11]. Many studies have shown inhibiting CYP17 enzyme results in a decrease in the androgen level [23]. Figure 1.5 shows the enzymatic pathway of androgen biosynthesis. Since CYP17 enzyme plays a catalytic role in the biosynthesis of androgens, it can be concluded that CYP17 is the primary target enzyme for the treatment of PC.

1.7. Structure Based Approach for Drug Design and Discovery

1.7.1. Drug Discovery

Drugs are the small organic molecules having therapeutic effects on human body. Many brand new drugs have been discovered by screening of natural products randomly or examining mechanisms of macromolecular receptors in detail [35].

In the first step, drug discovery starts with defining a disease and continues with the identification of suitable protein target as the second step. Target selectivity and specificity are important factors because if the drug is at the most selectivity for its target, it will not interact with the other targets, so unwanted side effects can be eliminated. After the identification of target structure, it is crucial to find a lead compound. A lead compound is a chemical substance which shows desired biological and pharmacological activity, and the structure of lead compound is accepted as the starting point for the drug design [37].

1.7.2. Drug Design and Optimization

Drug design, known as rational drug design, is the iterative process of discovering new drugs based on the knowledge of biological receptors and target molecules [36]. It is crucial for a drug molecule to be complementary to its biomolecular target in terms of shape and charge in order to bear a good selectivity, level of activity and less adverse effects are desired [37].

Once a lead compound is found, it may be required to optimize the structure of the lead compound in order to increase its efficiency. Actually, a lead molecule should fit very tightly into the enzyme pocket. With this purpose, medicinal chemists work on structure-activity relationships (SAR) [37]. Examining the functional groups and the type of the intermolecular bonds that they form are crucial to understand the drug-enzyme interactions.

Studies have proved that many functional groups such as amines, alcohols, ketones, aldehydes, amides, alkyl chains present in the structure can either contribute to the binding of drug to its target tightly or help and protect it during its travel in the body [37]. As it is seen in the Figure 1.6, variation of the alkyl chain ably fills the hydrophobic pocket of the enzyme (van der Waals interactions) and increases the enzyme-drug interaction [37].

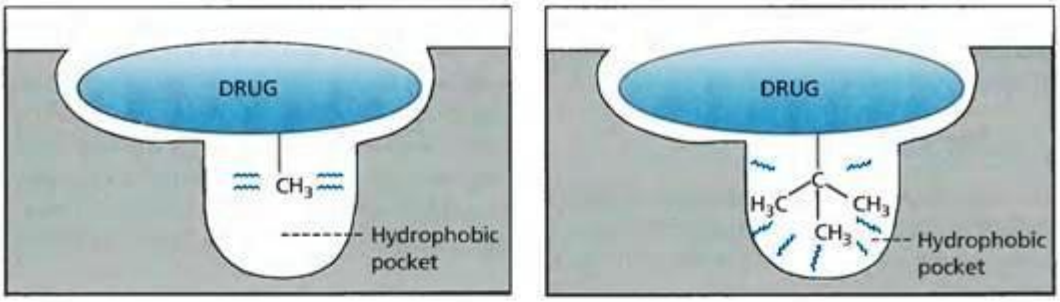


Figure 1.6. Addition of alkyl chain to fill a hydrophobic pocket [37].

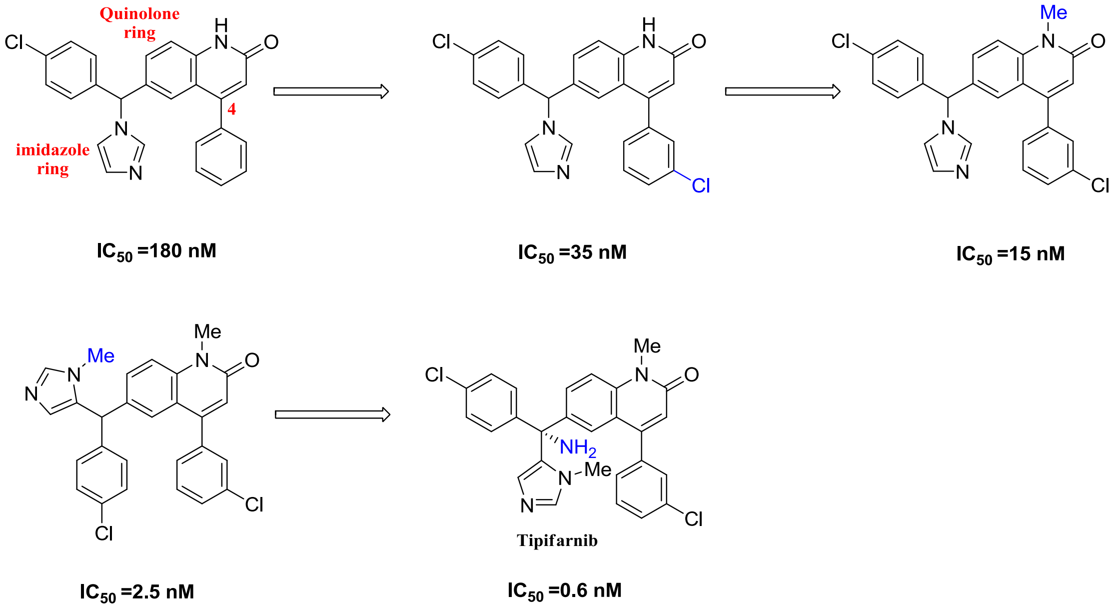


Figure 1.7. Development of tipifarnib [37].

Moreover, changes in the lead compound may increase not only binding affinity of a drug to an enzyme but also the efficacy and potency of drug molecule. For example, as it can be seen in the Figure 1.7 after the SAR studies have been done, the IC_{50} value of lead compound, called as tipifarnib, is enhanced by attaching chlor, methyl and amine functional groups respectively [37].

There are mainly two approaches in the drug design. The first is the ligand based drug design (indirect drug design) and the second is the structure based drug design which is also the method employed in this project [36].

1.7.3. Structure Based Drug Design

Structure based drug design is a novel iterative approach which involves identifying the best protein target and the three-dimensional structure of the target protein by using X-Ray crystallography, NMR techniques and computer assisted software programs [38]. Moreover, structure guided drug design process requires implementing accurate and high-throughput screening assay, determination of a lead compound, using the latest software programs predicting the affinity of new compounds and synthetic strategies to synthesize the desired compounds [38].

In this approach, it is crucial to isolate and crystallize the target molecule in order to determine the structure with the help of X-ray crystallography. However, this is insufficient to reveal the active site of the protein; therefore, it is better to bind the defined inhibitor to the active site of the protein in order to determine the complex structure of the protein. Then, by using molecular modeling program, locus of the ligand and the binding site can be easily identified. Thereafter, ligand is removed from the binding site *in silico* (the virtualization process) and the lead compound is inserted instead so in this way, how the lead molecule complements to the protein can be monitored [37].

It is important that the drug molecule fits perfectly to the active site of the protein in terms of the charges, shape and intermolecular interactions [37]. In order to understand the relationship of a potential drug molecule with an enzyme, one should evaluate the docking and binding energy parameters [39]. Those two parameters give significant information about the candidate molecules. For instance, potential drug molecules having lower docking and binding energies (higher negative values) are generally preferred for *in vivo* and *in vitro* tests.

Consequently, modifications on the lead compound can be performed to optimize and enhance the potency of the drug.

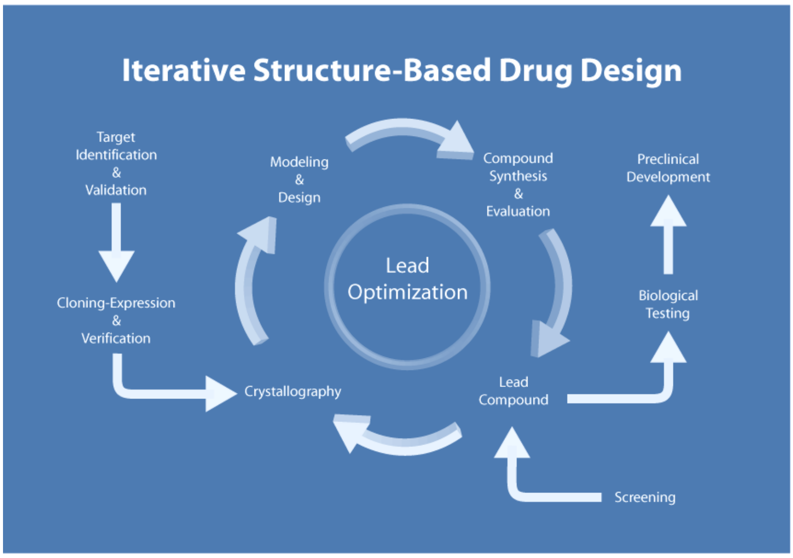


Figure 1.8. Iterative structure based drug design [43].

1.8. Computational Strategies

Computer assisted drug design (CADD) is a powerful technique in order to discover and develop new drugs [36]. With the help of advanced computer softwares, it is possible to see how well drug candidates bind to the target enzymes and to determine the potential structure of a lead compound [37]. Plus, thanks to the computers, new lead compounds can be found out by doing computerized searching of structural databases [37]. There are mainly three steps in CADD approach:

(i) Hit identification by carrying out virtual screening (Structure or ligand based design).

(ii) Hit-to-lead optimization of selectivity and affinity (Quantitative structure-activity relationship (QSAR), Structure based drug design (SBDD)).

(iii) Optimization of the lead molecule and other pharmaceutical properties such as the maintenance of the affinity [36].

1.8.1. Computer Modeling of the CYP 17 Enzyme

Computer assisted modeling software allows chemists to examine the three-dimensional (3D) structure of the target enzyme [37]. When the 3D model of an enzyme is constructed, various properties of it such as all of its bond lengths, bond angles and torsion angels, steric energy, charge density, partial charges and polarizability can be analyzed [37]. Since all of those data give important information about the enzyme; it may be possible to determine the significant binding interactions between the ligand and the active site of the enzyme.

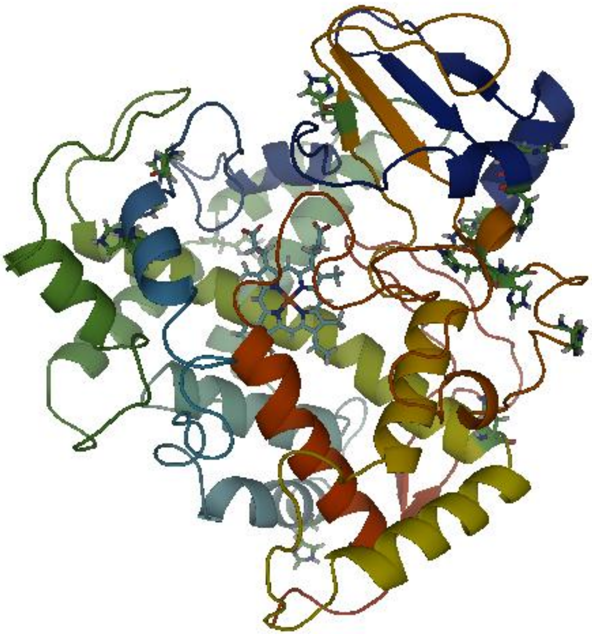


Figure 1.9. Computer generated model of CYP17 enzyme.

Construction of 3D structure of the CYP17 enzyme assists to understand catalytic activities, substrate and reaction selectivity [24]. Therefore, it is necessary to have the knowledge of 3D structure of CYP17 in order to design new drug candidates which can inhibit the catalytic activities of the enzyme. The crystal structure of CYP17 enzyme is still unknown in the literature due to the membrane-bound property of all related mammalian P450 enzymes and practical problems with crystallization [17]. However, there are many studies on computer generated models of CYP17 or active site and one example of the computer generated model for CYP17 can be seen in Figure 1.9 with the PDB access code 2c17 [24].

The computational part of this study was done in Koc University by Prof. Metin Türkay and Assoc. Prof. Halil Kavaklı. The most up-to-date 3D modeling of CYP17 was generated based on class II (microsomal) P450 crystal structure, namely P450BMP [24].

According to the three dimensional structure of the CYP17 enzyme, active site of the enzyme has a hydrophobic environment and a prosthetic heme group (i.e. a porphyrin ring with a central iron ion) which is a common feature of the P450 enzyme family [17]. After a detailed examination of CYP17 enzyme, molecular interactions between enzyme and inhibitors for CYP17 were determined.

1.8.2. Inhibitory Studies of the CYP 17 Enzyme

It is crucial to consider the features of the binding site of the enzyme during the determination of potential inhibitors. Many chemical compounds may interact with the target protein. Inhibitors may show various interactions with the active site of the enzyme. These interactions can be blocking, accelerating, decelerating, reversing or initiating reactions [24].

Figure 1.10 shows the inhibition of CYP17 enzyme by an original substrate or a competitive inhibitor. As it can be seen, the active site of the enzyme is a prosthetic heme group. It is known that heme group is primarily responsible for the catalytic reactions because heme iron is a good anchor point.

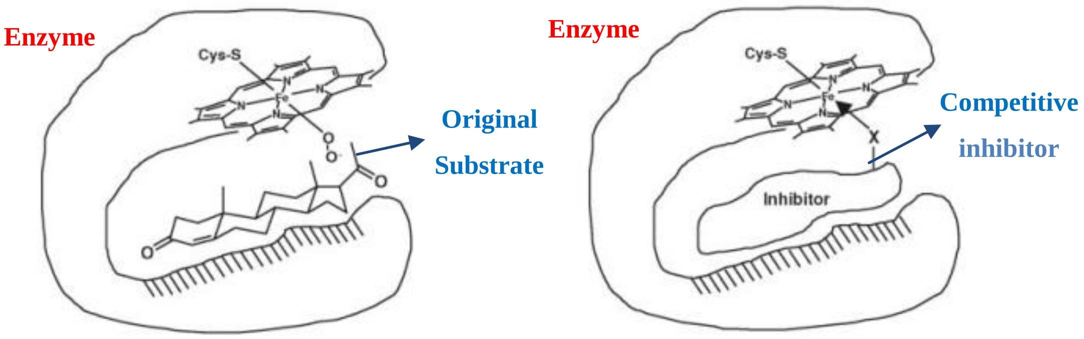
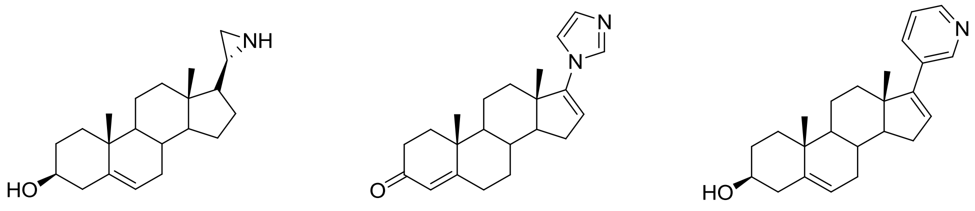


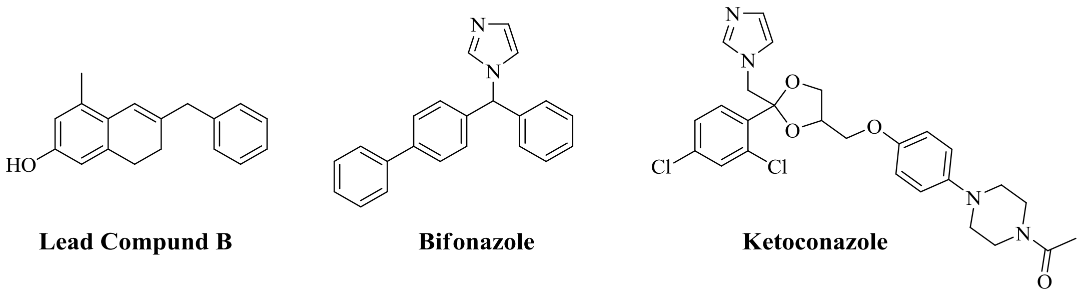
Figure 1.10. Binding of an original substrate (progesterone) and a competitive inhibitor [23].

Steroidal Inhibitors



Lead Compund A **VN/108-1** **Abiraterone**

Non-steroidal Inhibitors

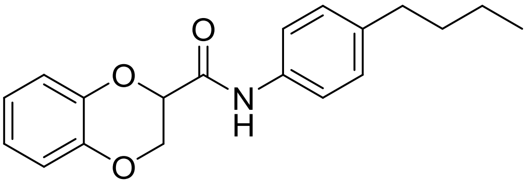


Lead Compund B **Bifonazole** **Ketoconazole**

Figure 1.11. Literature examples of steroidal and non-steroidal inhibitors of CYP17 enzyme [11].

As it is mentioned before, the CYP17 enzyme is a well known target for the treatment of prostate cancer, because selective inhibition of this enzyme is crucial for eliminating androgen biosynthesis. In order to find a selective inhibitor of CYP17, many computational and experimental studies have been performed [11]. Initially, by modifying pregnenolone and progesterone substrates, which have high affinity to the CYP17 enzyme, steroid based potential CYP 17 inhibitors were found [11]. Although steroidal molecules have inhibitory effects on CYP17 enzyme, they are not preferred for PC treatment due to its reported drawbacks, such as; poor selectivity, high affinity to steroid receptors, relative short half-life, poor bioavailability, poor acid stability and first pass effects when orally administered [23]. Because of that, it is beneficial to replace steroidal inhibitors with steroidomimetics (non-steroidal) in order to increase the efficacy of the drug molecule.

As stated above, steroidal inhibitors have shown weak results compared to steroidomimetic ones due to their drawbacks. In this respect, since non-steroidal inhibitors of CYP17 enzyme are more potent to inhibit CYP17 enzyme in terms of docking and binding energies, 23 non-steroidal candidates were found by computer screening of about 50000 drug candidates. Among those 23 compounds, a lead molecule giving the best docking and binding energy results was determined. Apart from the docking and binding energy calculations, also ADMET (adsorption, distribution, metabolism, elimination and toxicity) studies, Quantitative Structure Activity Relationship (QSAR) studies and IC_{50} measurements were performed and finally lead compound in Figure 1.12 was determined.



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

Figure 1.12. Structure of the lead compound.

1.8.3. Substitutents on the Lead Molecule and Their Role

Optimization of the lead compound is very crucial to find the best molecule which has the best binding interactions with the target enzyme. In this respect, Structure Activity Relationships (SAR), the relationship between the three dimensional structure of a compound and its biological activity, should be analyzed [37]. The aim is to recognize the functional groups on the lead compound and understand their possible functions. Therefore, by modifying the lead molecule, the therapeutic effect of the drug molecule may be enhanced. In Figure 1.12, functional groups on the lead molecule and their possible functions are summarized.

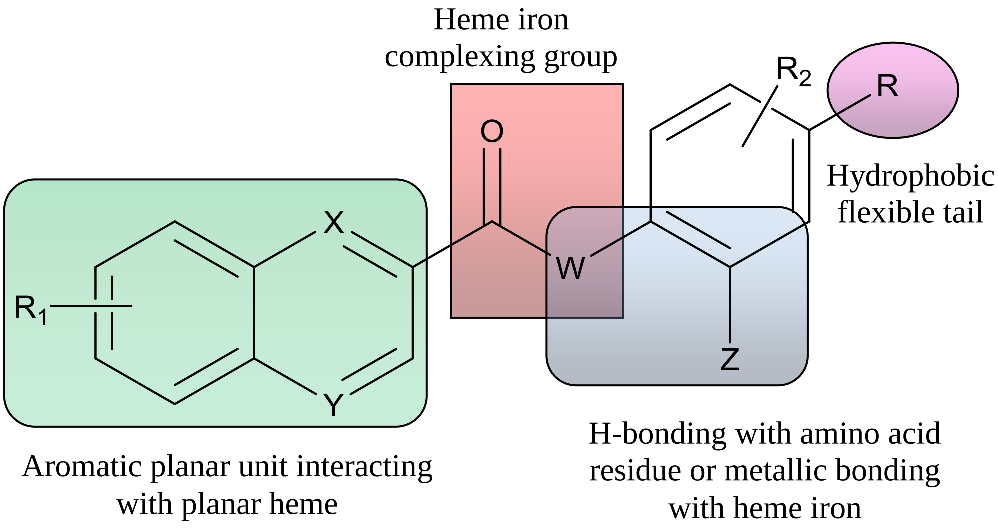


Figure 1.13. Functional groups on the lead compound and their possible functions.

Table 1.1. Possible changes on substituent parts of 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$_1$	-MeO, -H, -F (at different positions)

1.8.4. Molecular Docking Studies

Once the structure of the target binding site is known, molecular docking studies are performed to identify the potential role of a given functional group in a lead molecule [37]. Docking and binding energies are the two most important parameters involved in molecular docking studies.

Docking energy is related to the energy that describes the approach of a candidate drug molecule to the enzyme [41]. Also, docking energy is known as the sum of van der Waals and electrostatic energies among all the atoms present in the complex. It is generally used to estimate the binding orientation of a candidate drug to its protein target to predict the affinity and activity of the drug molecule, respectively [41]. On the other hand, binding energy is the related energy to the interaction of a potential drug molecule with the enzyme. Compounds that have lower docking and binding energy values are often desired to determine a lead compound.

1.8.5. Docking and Binding Energy Calculations

Molecular docking calculations were performed with the help of Autodock 3.05. software program at Koc University. Autodock and the other docking programs have a major drawback due to the quality of the results which is often based on how the initial structure is placed in the binding site. However, many scientists have used a combination of docking programs to address this problem [37].

Firstly, the original substrates of CYP17 enzyme and current drug molecules' relative docking and binding energy calculations were done in order to have an idea about their docking and binding energies. After derivatization of the lead compound, relative docking and binding calculations of some derivatives were calculated in order to find out how they could be enhanced.

Table 1.4 shows docking and binding energy calculations of the derivatives of lead compound. It can be concluded that some derivatives of the lead molecule show also good docking and binding energy results when compared to the original substrates. As stated above, since Autodock is a semi-empirical program, those results are not conclusive to determine the structure of the best drug candidate for the enzyme. However, they may be helpful to have an idea about the interactions between the active sites of the enzyme and the drug candidate.

Table 1.2. Docking and binding energies of some natural substrates and current drugs.

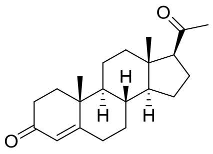
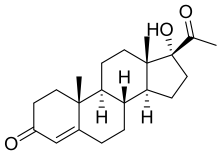
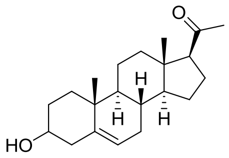
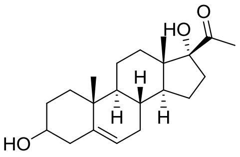
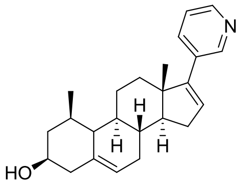
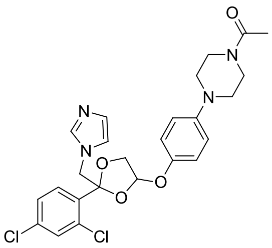
Compounds	**Docking (kcal/mol)**	**Binding (kcal/mol)**	**Compounds**	**Docking (kcal/mol)**	**Binding (kcal/mol)**
 Progesterone	-10.04	-9.73	 17hydroxyprogesterone	-9.61	-9.68
 Pregnenolone	-9.71	-9.44	 17hydroxypregnenolne	-10.15	-10.10
 Abiraterone	-9.30	-9.33	 Ketoconazole	-11.13	-9.33

Table 1.3. Docking and binding energies of the lead molecule.

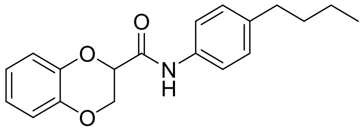
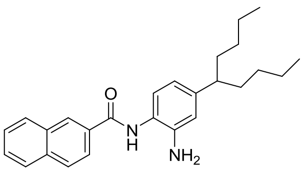
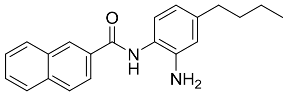
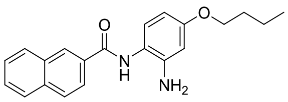
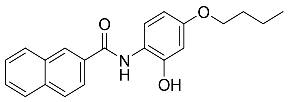
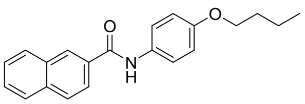
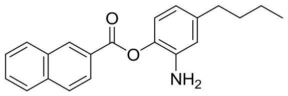
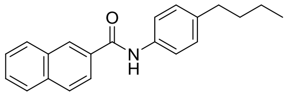
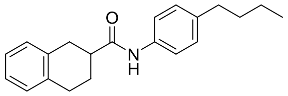
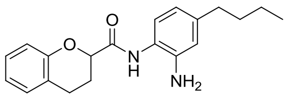
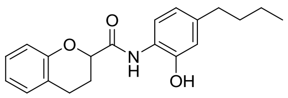
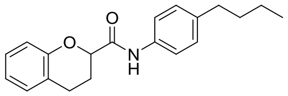
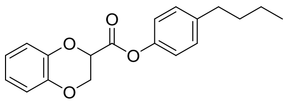
Lead Compound	**Docking Energy (D.E.) (kcal/mol**	**Binding Energy (B.E.) (kcal/mol)**
	**-9.38**	**-7.45**

Table 1.4. Docking and binding energies of some derivatives of the lead compound.

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

2. AIM OF THE STUDY

As it is seen in Figure 2.1, a potential derivative of the lead compound consists of two parts. The first part, left hand sight, is the naphthoic unit and the second part, right hand sight, is the phenyl unit. In this respect, it is important to examine both parts in detail in order to modify the lead molecule.

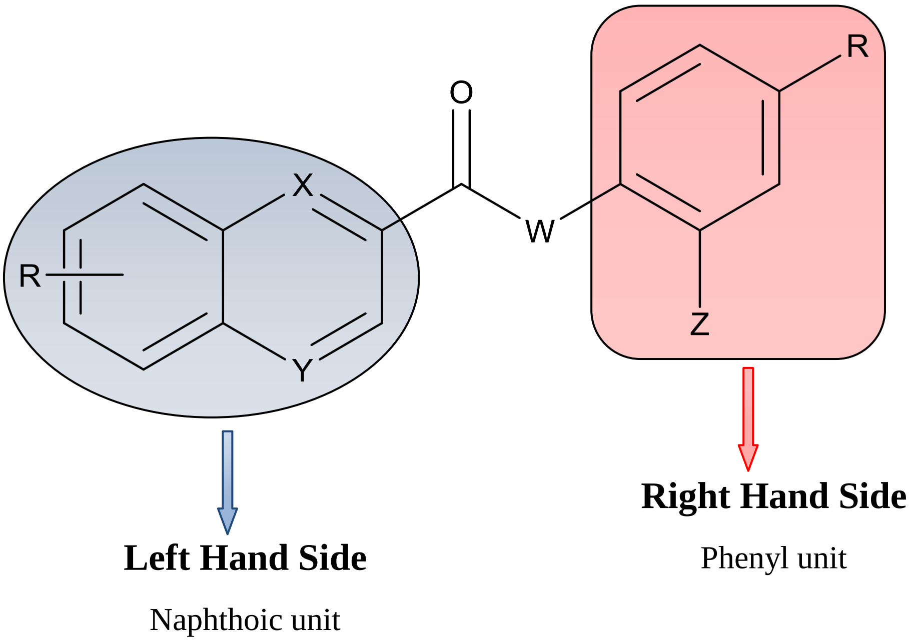


Figure 2.1. Parts of the lead molecule.

At the left hand side of the lead compound, since aromatic rings are planar and they may interact with the planar heme via Pi-Pi stacking interactions, X and Y atoms were determined as carbon atoms. Therefore, the left hand side is consisted of naphthoic acid derivatives which have -H or -OCH_3 substitutents at different positions.

As it is seen from Table 1.1, W atom can be C, N or O atom. It is known that amides are likely to interact with the active site through hydrogen bonding. Carbonyl group may act as hydrogen bond acceptor and –NH group may act as hydrogen bond donor. Moreover, heme iron of the enzyme can complex with nitrogen atom; therefore, W atom was chosen as nitrogen atom.

It is thought for the right hand side of the lead molecule to replace the phenyl unit with N containing heterocycles such as quinoline compound. It is known that nitrogen-containing heterocycles can be involved in complicated H bonding networks within the active site. Moreover, heterocycles might have potential van der Waals interactions and hydrophobic interactions with the binding site [37]. As stated in the Table 1.1, Z may be a pendent NH_2 group on phenyl. It is important for the mode of action of non-steroidal drug candidates to be nitrogen bearing heterocycles which are capable of complexing the heme iron of the enzyme; therefore, replacing this pendent NH_2 functional group with nitrogen bearing heterocycles might increase the efficacy of the drug molecules.

Furthermore, as the phenyl unit has a hydrophobic flexible tail interacting with binding site through hydrophobic interactions, it is thought that quinoline compound should also have four-carbon alkyl chain, namely n-butyl group, on it. The Figure 2.2 summarizes the modifications on the lead compound.

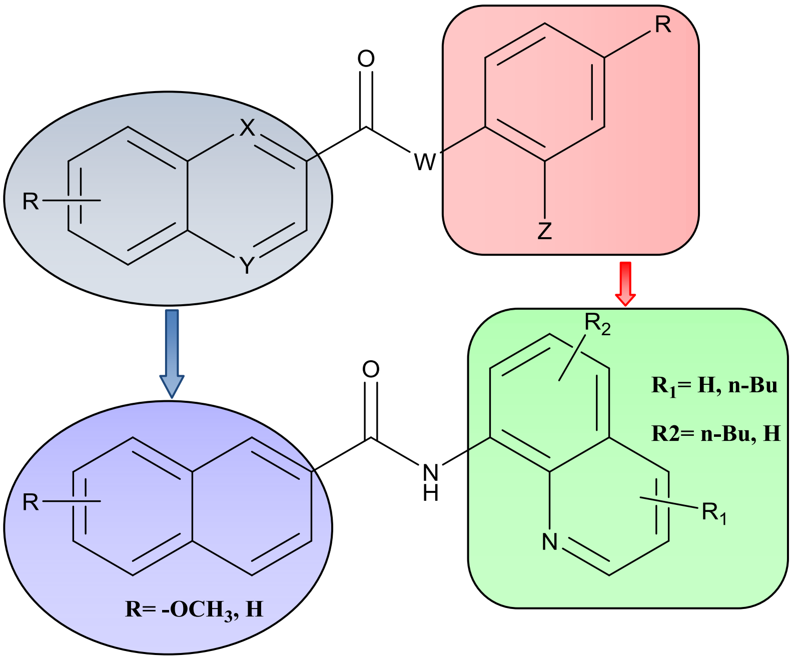


Figure 2.2. Modifications on the lead compound.

Those modified quinoline compounds have good interactions with the active site of the enzyme. A computer generated 3D structure of N-(3-butylquinolin-8-yl)-1-

naphthamide has shown that this derivative has better interactions with the active site of the enzyme. (Figure 2.3)

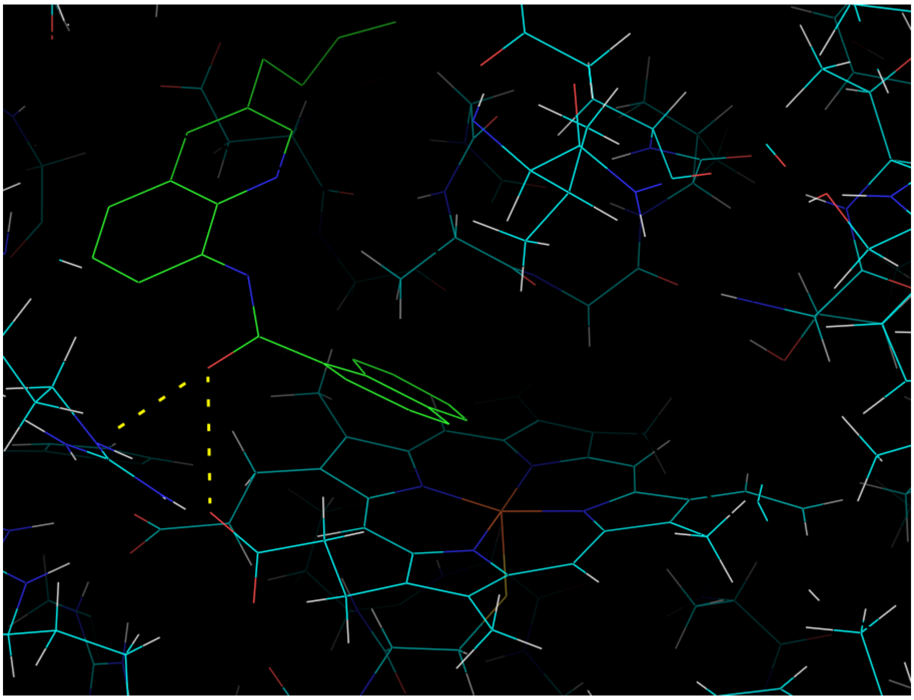


Figure 2.3. Interactions between N-(3-butylquinolin-8-yl)-1-naphthamide and the active site of the CYP 17.

In order to compare docking and binding energy results of the previous derivatives and lead compound with butyl substituted quinoline derivatives, docking calculations for quinoline derivatives were also performed by using Autodock 4.0 software. Docking and binding calculations indicate that quinoline derivatives have better results than the lead compound.

Table 2.1. Docking and binding energy of the lead molecule.

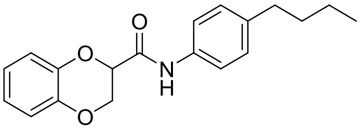
Lead Compound	**Docking Energy (D.E.) (kcal/mol**	**Binding Energy (B.E.) (kcal/mol)**
	**-9.38**	**-7.45**

Table 2.2. Docking and binding energies of quinoline derivatives.

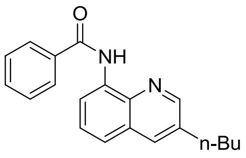
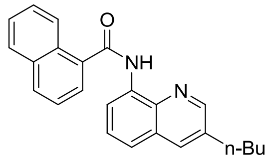
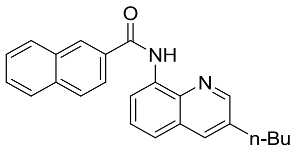
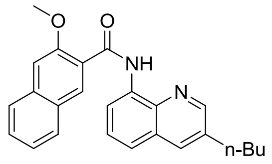
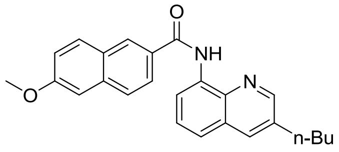
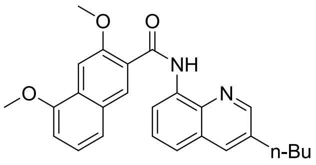
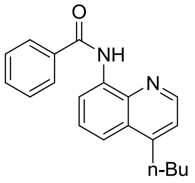
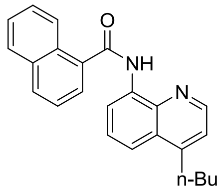
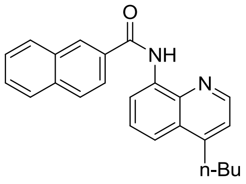
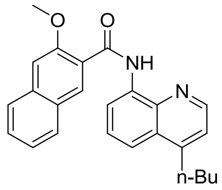
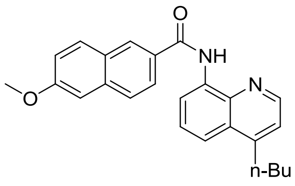
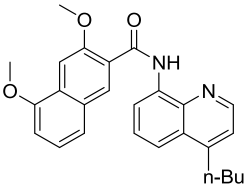
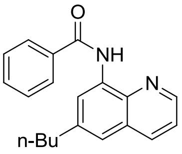
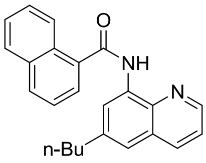
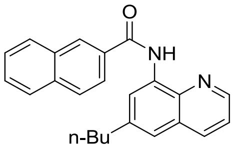
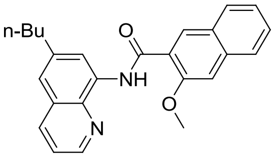
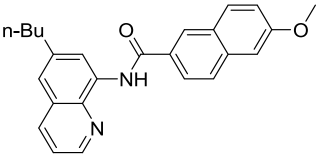
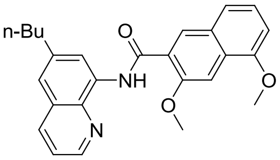
Final Product	**D.E**	**B.E**	**Final Product**	**D.E**	**B.E**
	-9.78	-7.95		-11.01	-9.07
	-10.12	-8.09		-10.70	-8.53
	-10.51	-8.38		-10.54	-7.85
	-9.69	-7.48		-10.60	-8.31
	-9.47	-7.27		-9.84	-7.72
	-9.61	-7.43		-10.53	-7.99

Table 2.2. Docking and binding energies of quinoline derivatives. (contd.)

Final Product	**D.E.**	**B.E**	**Final Product**	**D.E**	**B.E**
	-9.93	-7.51		-10.59	-8.52
	-11.37	-9.21		-11.19	-8.40
	-9.98	-7.73		-10.25	-8.08

The aim of the present study is to synthesize 8-amino quinolines which have n- butyl group at different positions and then couple them with naphthoic acid derivatives. After the syntheses of the final products, it is also aimed to test the biological activity of those drug candidates.

3. RESULTS AND DISCUSSIONS

In this project, synthesis of potentially active quinoline derivatives against prostate cancer was targeted. Molecular docking studies have shown that a nitrogen bearing heterocycle has better docking results than the lead compound. (Table 2.2) In this respect, the right hand side of the lead compound was replaced with an alkyl and amine substituted quinoline compounds. As it is stated before, the left hand side of the lead molecule is exchanged with naphthoic acid derivatives. Moreover, quinoline derivatives were coupled with benzoic acid in order to understand whether or not the naphthoyl group can be replaced with the benzoyl group.

Quinoline derivatives containing an amino on the 8th position and an alkyl chain at various positions were targeted. The synthetic strategy used mainly involved, first the synthesis of an alkyl substituted quinoline where different positions of the quinoline ring were alkylated either pre- or post-cyclisation. Then, a nitro group was introduced preferably to the 8th position of the quinoline which was then reduced to an amine and coupled with the naphthoic or benzoic acid derivatives. A slightly different approach was used in the synthesis of 3-butylquinolin-8-amine (5) where the nitro group and the alkyl group were introduced together via a single step cyclisation process. (Section 3.1)

The same strategy was followed in the synthesis of 18 potential drug candidates. Initially, benzoic acid and naphthoic acid derivatives were converted *in-situ* to the acid bromides and then, amine derivatives of quinolines were coupled with those acid bromides to obtain the final products.

In order to verify those transformations, 1D NMR spectroscopy (^{1}H-NMR and 13C-NMR) and 2D- NMR spectroscopy (COSY (Correlation Spectroscopy) and NOESY (Nuclear Overhauser Enhancement Spectroscopy) experiment data have been used. Moreover, LC-MS (Liquid Chromatography-Mass Spectroscopy) and Elemental Analysis methods will be done.

3.1. Synthetic Strategies Used in the Synthesis of 3-Butylquinolin-8-Amine

The synthetic pathway for the synthesis of 3-butylquinolin-8-amine (5) is shown in Figure 3.1.

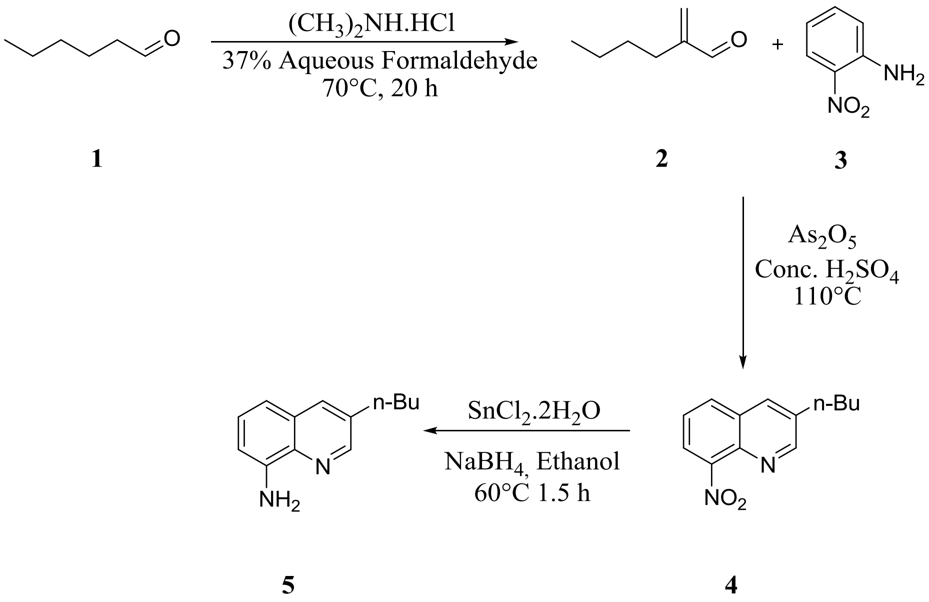


Figure 3.1. Synthetic approach used in the synthesis of 3-butylquinolin-8-amine.

For the synthesis of 3-butylquinolin-8-amine, firstly hexanal (1) was transformed to 2-methylenehexanal (2) by using dimethylamine hydrochloride and 37% aqueous formaldehyde. In order to purify the compound 2, a vacuum distillation setup was set and pure colorless oil was collected at 70°C, 40 mmHg in a high yield (79%). In order to directly obtain 3-butyl-8-nitroquinoline (4), Skraup method was used by employing As_2O_5 as the catalyst and concentrated sulfuric acid. Due to the difficulties in the work up and purification of the compound 4, was obtained in 35% yield. At the last step of the synthesis, the nitro compound (4) was reduced to 3-butylquinolin-8-amine (5) by using $SnCl_2.2H_2O$ and $NaBH_4$ as the reducing agents and ethanol as the solvent. This reaction again was performed in a high yield (85 %).

3.2. Synthetic Strategies Used for Coupling of 3-Butylquinolin-8-Amine with Naphthoic Acid Derivatives

After obtaining 3-butylquinolin-8-amine (5), the next step is *in-situ* coupling of this amine compound with benzoic acid and naphthoic acid derivatives. Figure 3.2 indicates the benzoic acid and all naphthoic acid derivatives involved in the coupling reaction.

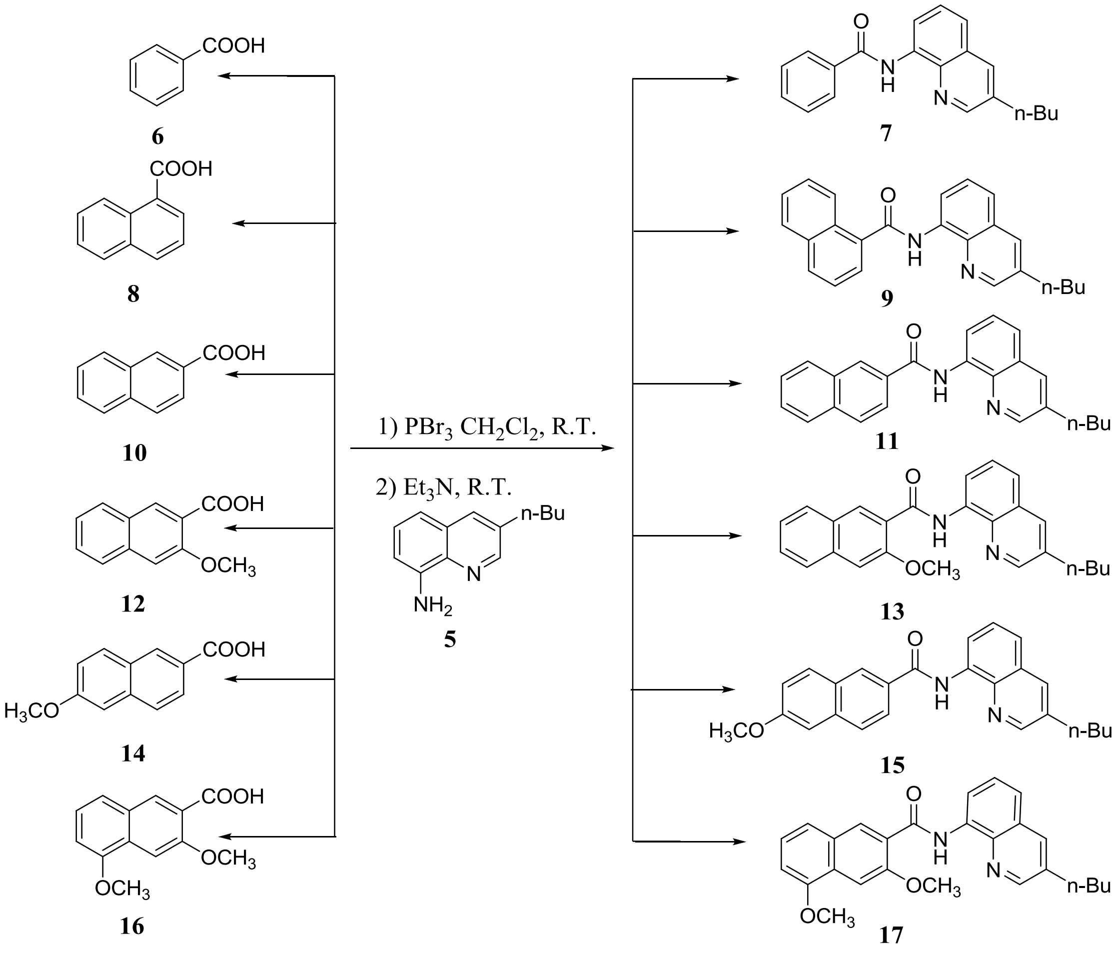


Figure 3.2. *In-situ* coupling of 3-butylquinolin-8-amine with benzoic acid and naphthoic acid derivatives.

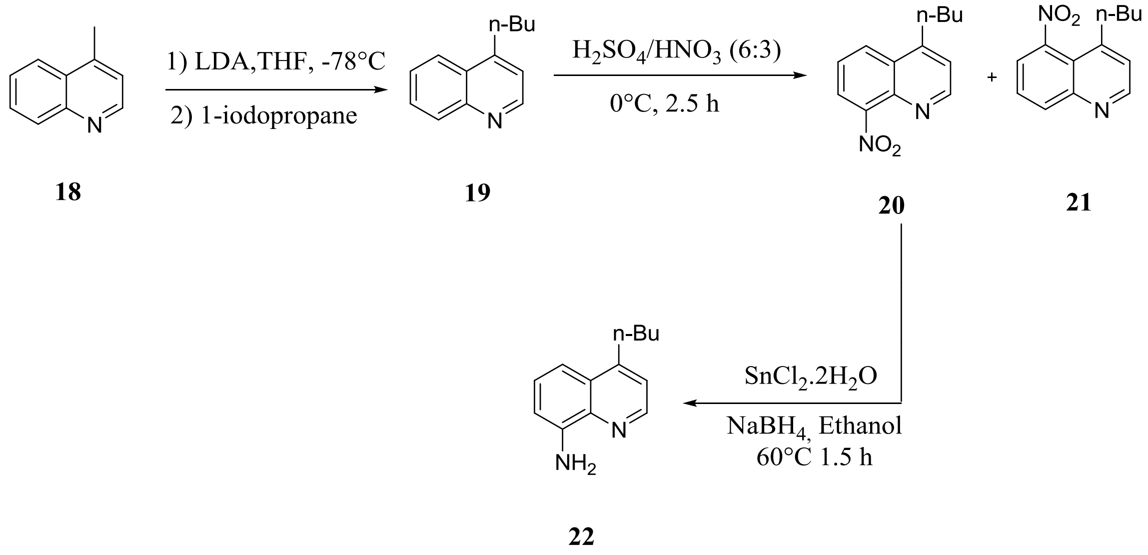
During the coupling reaction; firstly, the benzoic acid and naphthoic acid derivatives were converted to the acid bromides by using PBr_3 as the brominating reagent in dry dichloromethane (CH_2Cl_2) under the nitrogen blanket. Since this reaction is an *in-situ* coupling reaction, acid bromides were not isolated. After 3 hours, triethylamine (TEA) was added as the neutralizing reagent to neutralize the HBr and then 3-butylquinolin-8-amine was added. The reaction mixture was stirred for an additional 3 hours to give the final product. After concentration and purification, final product was obtained in a very low yield (20-30 %). This *in-situ* coupling reaction has several advantages, such as short reaction time and being one-pot reaction at room temperature; however, yields are so low. In fact, in order to obtain the final product in high yields, the reaction time was prolonged to 24 hours. But the prolonged reaction times were not successful to increase the reaction yield. The reason for low yields might be stemming from the short lifetime of the acid bromides. All those transformations were verified by using ^{1}H-NMR and ^{13}C-NMR.

3.3. Synthetic Strategies Used in the Synthesis of 4-Butylquinolin-8-Amine

The synthetic approach used in the synthesis of 4- butylquinolin-8-amine is shown in Figure 3.3. The synthesis of 4-butylquinolin-8-amine (22) was done in 3 steps. In the first step, 4-methylquinoline (lepidine) (18) was used as the starting material. Methyl group of 4-methyquinoline (18) is fairly acidic; therefore, lithium diisopropylamide (LDA) was used as a base to take one of the hydrogens of the methyl group. This reaction was carried out in dry tetrahydrofuran (THF) at -78 °C under inert atmosphere by using N_2. LDA is a very sensitive material; therefore, lithium diisopropylamine was mixed with n-BuLi in 2.5M hexane solution at -78 °C under N_2. The stock LDA adduct was then added to lepidine (18) to form the corresponding carbonanion. After that, iodopropane was added to the reaction flask and the mixture was stirred 3 hours at -78 °C. 4-Butylquinoline (19) was obtained in 77% yield after purifying with column chromatography.

In the second step, 4-butylquinoline (19) was nitrated by using concentrated sulfuric acid and H_2SO_4/HNO_3 mixture (6:2). According to the examples in the literature, the 5th and 8th positions of quinoline are most likely to be nitrated. Therefore, as expected, after the nitration, both 4-butyl-8-nitro-quinoline (20) and 4-butyl-5-nitroquinoline (21) were obtained. Among these, only the 4-butyl-8-nitroquinoline (20) was purified in 66% yield by using column chromatography.

At the last step, the compound 20 was reduced to 4-butylquinolin-8-amine by using $SnCl_2.2H_2O$ and $NaBH_4$ in ethanol in a very high yield 93%.



18 **19** **20** **21** **22**

Figure 3.3. Synthetic approach to the synthesis of 4-butylquinolin-8-amine.

Here it was important to determine the exact structure of the compound 22. The position of the amine had to be confirmed since the nitration was known to give both the 5 and 8 isomers. The exact position of the nitration was unknown up to this point and assumptions were made only. In order to understand which compound is 8-nitro, ^{1}H-NMR was insufficient. Therefore, 2D NOESY NMR experiments were carried out. 2D NOESY (Nuclear Overhauser Enhancement Spectroscopy) experiments are often used to determine the protein structures. NOESY experiment can only be applied when the distance between two protons are smaller than 5 Å and there is no scalar coupling between them. NOESY experiments can in principle correlate all protons which are close enough [42].

As it can be seen in the 3D structure of 4-butyl-nitroquinolin-5-amine (21), one of the amine's hydrogen is very close to the hydrogen of CH_2 (Figure 3.4). Therefore; if the 5-amino compound was isolated, there could be a correlation between those 2 hydrogen atoms. However, NOESY experiment (Figure 3.6) has shown that there was no correlation between amine hydrogen and butyl hydrogen. On the other hand, 3D structure of 4-butylquinolin-8amine has shown that amine hydrogen atoms which are close to each other have correlation with aromatic hydrogen atoms and this was verified by examining the 2D NOESY NMR spectrum.

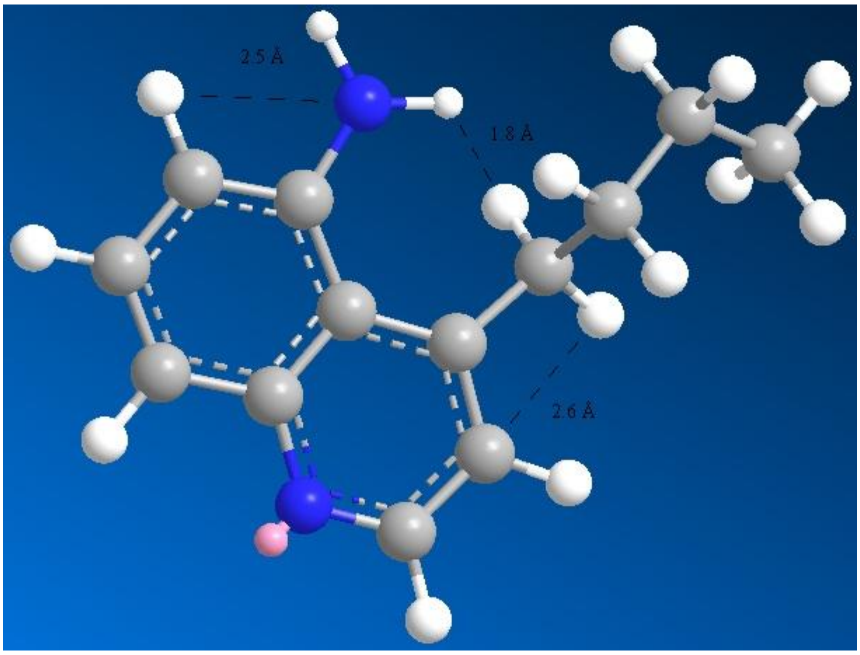


Figure 3.4. 3D structure of 4-butylquinolin-5-amine.

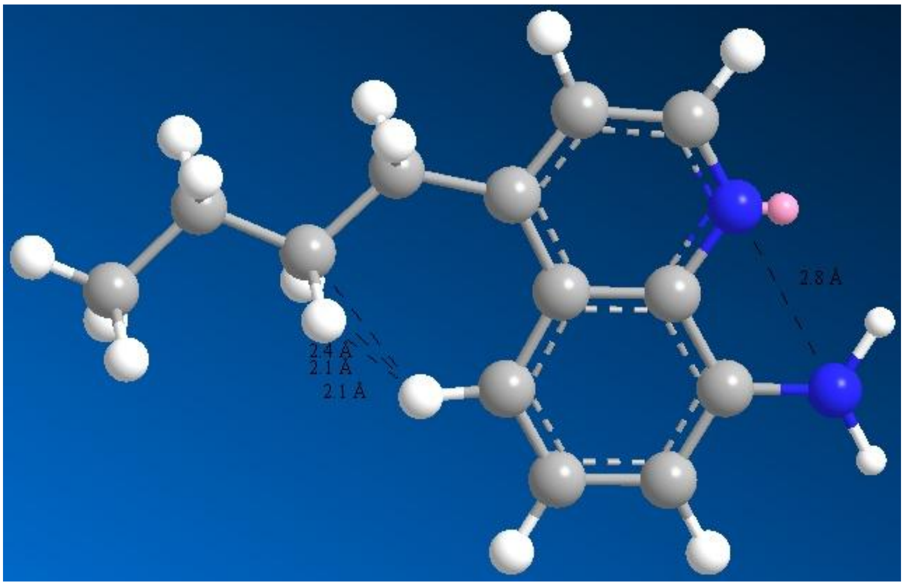
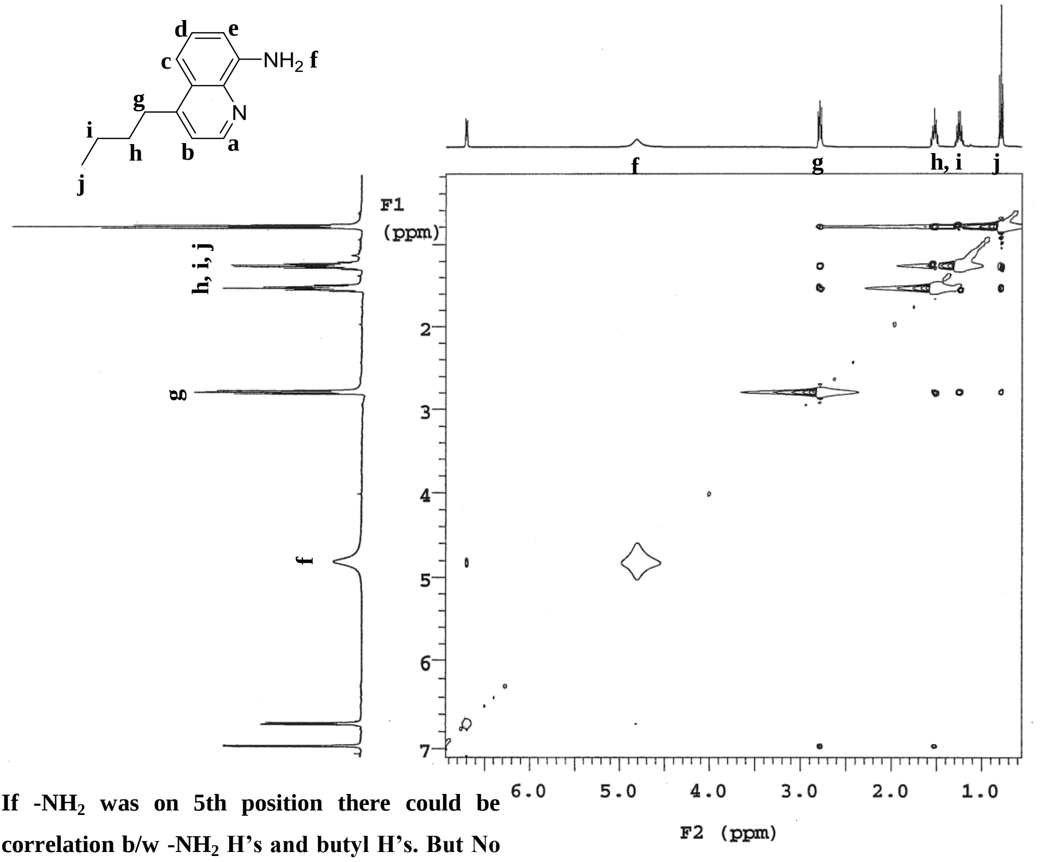


Figure 3.5. 3D structure of 4-butylquinolin-8-amine.



If -NH$_2$ was on 5th position there could be correlation b/w -NH$_2$ H's and butyl H's. But No Correlation, so -NH$_2$ is on the 8th position.

Figure 3.6. 2D NOESY NMR of 4-butylquinolin-8-amine.

3.4. Synthetic Strategies Used for Coupling of 4-Butylquinolin-8-Amine with Naphthoic Acid Derivatives

4-butylquinolin-8-amine (22) was again coupled *in-situ* with benzoic acid and naphthoic acid derivatives. The same coupling procedure was followed as done in the 3-butyl-quinolin-8-amine (5). Figure 3.7 shows the benzoic acid and all naphthoic acid derivatives involved in the coupling reaction. The structures of those final products were verified with ^{1}H-NMR and ^{13}C-NMR.

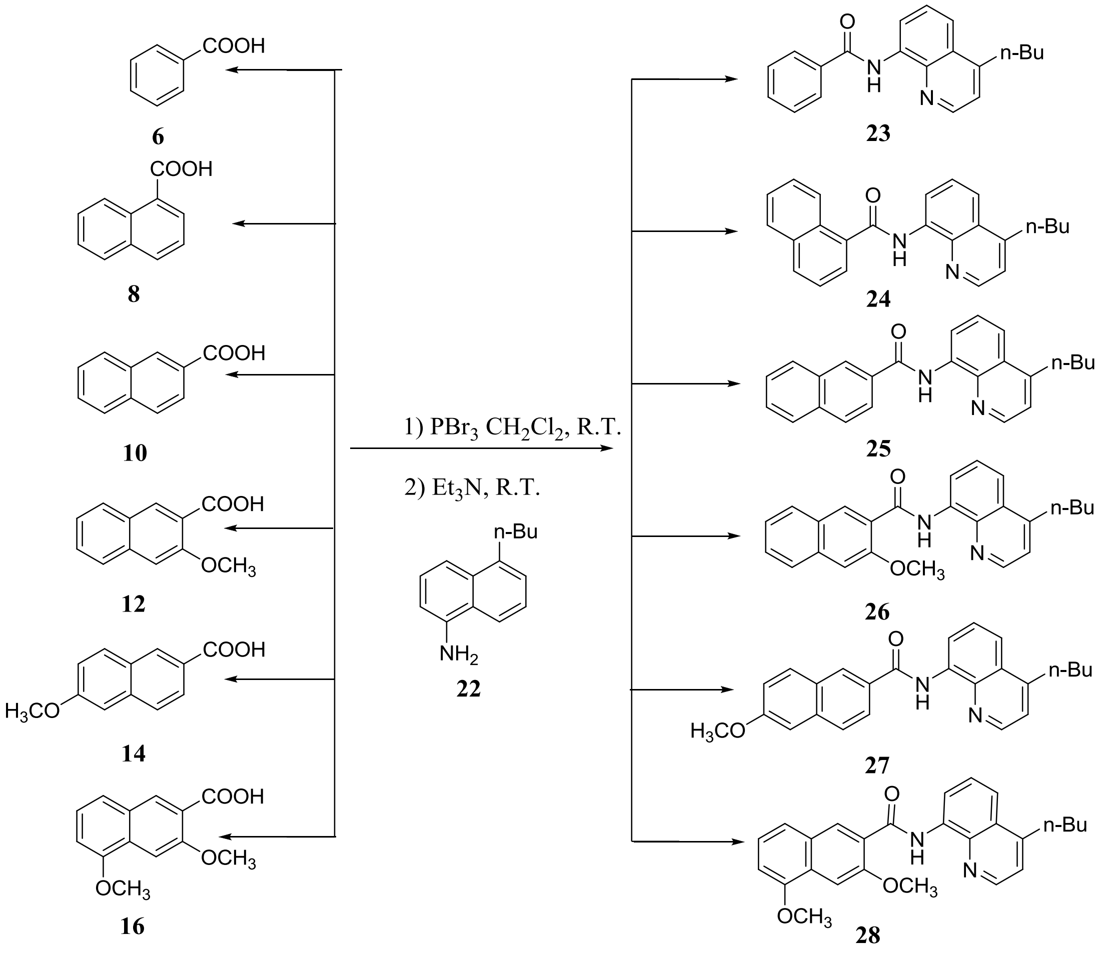


Figure 3.7. *In-situ* coupling of 4-butylquinolin-8-amine with benzoic acid and naphthoic acid derivatives.

3.5. Synthetic Strategies Used in the Synthesis of 6-Butylquinolin-8-Amine

Several synthetic pathways were followed to synthesize 6-butylquinolin-8-amine. Initially by following the Skraup procedure, 4-butylaniline (29) was reacted with glycerol and concentrated sulfuric acid to give 6-butylquinoline (31). Then, it was nitrated in order to obtain 6-butyl-5-nitroquinoline (32) and 6-butyl-8-nitroquinoline (32a) compounds; however, there was only one spot on TLC plate which then was found to be belonged 6-butyl-5-nitroquinoline (32). In other words, the nitration of the 8th position was unsuccessful.

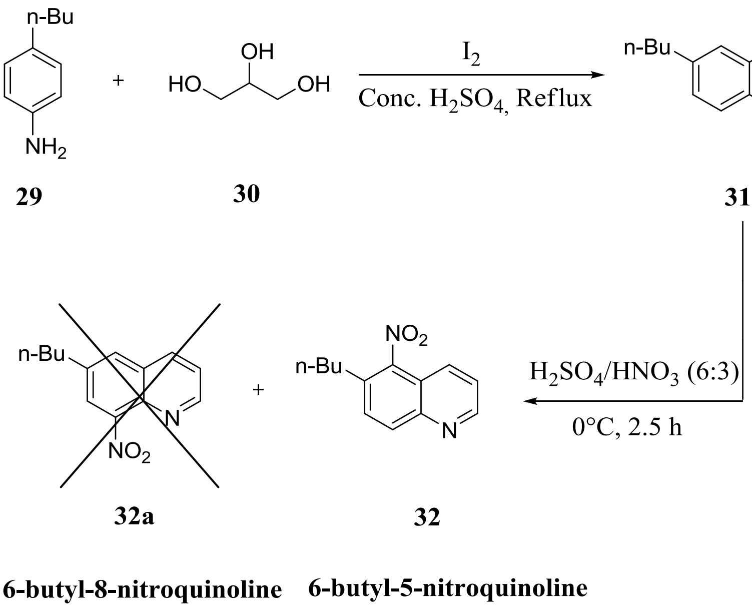


Figure 3.8. The first synthetic strategy for the synthesis of 6-butylquinolin-8-amine.

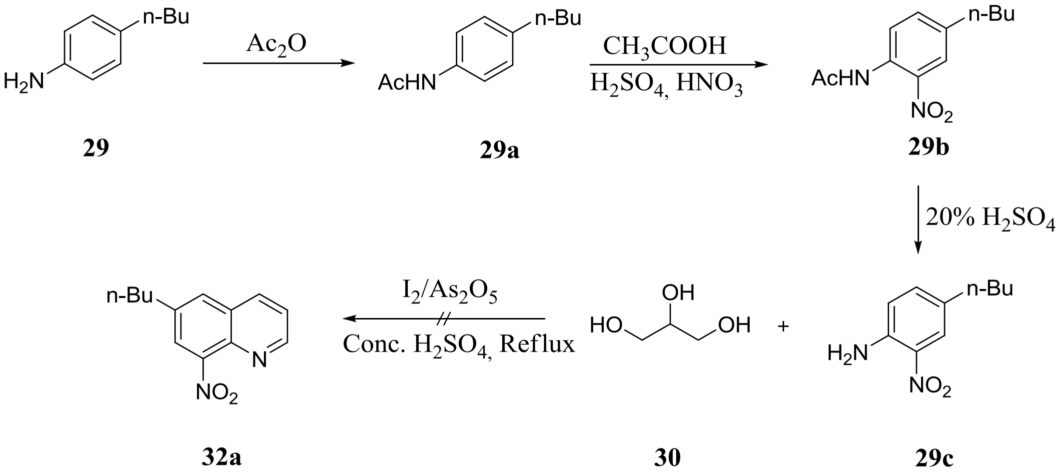


Figure 3.9. The second synthetic strategy for the synthesis of 6-butylquinolin-8-amine.

Then, an alternative synthetic strategy was followed to obtain 6-butyl-8-nitroquinoline (Figure 3.9). In this method, firstly 4-butylaniline was protected with acetic anhydride (Ac_2O) and then nitration with glacial acetic acid, concentrated sulfuric acid and the nitrating mixture (H_2SO_4/HNO_3) was done to obtain 4-butyl-2-nitroacetanilide (29b). After deprotection of the 4-butyl-2-nitroacetanilide, 4-butyl-2-nitroaniline (29c) was synthesized. Then finally, using the Skraup method, 4-butyl-2-nitroaniline (29c) was reacted with glycerol and I_2 or As_2O_5 to directly obtain 6-butyl-8-nitroquinoline. Although many trials were done, this reaction was not achieved.

Since the ^{1}H-NMR was insufficient to determine the position of the nitro substituent, 2D COSY (Correlation Spectroscopy) NMR was used. 2D COSY NMR spectra have shown that isolated compound was 6-butyl-5-nitroquinoline (32).

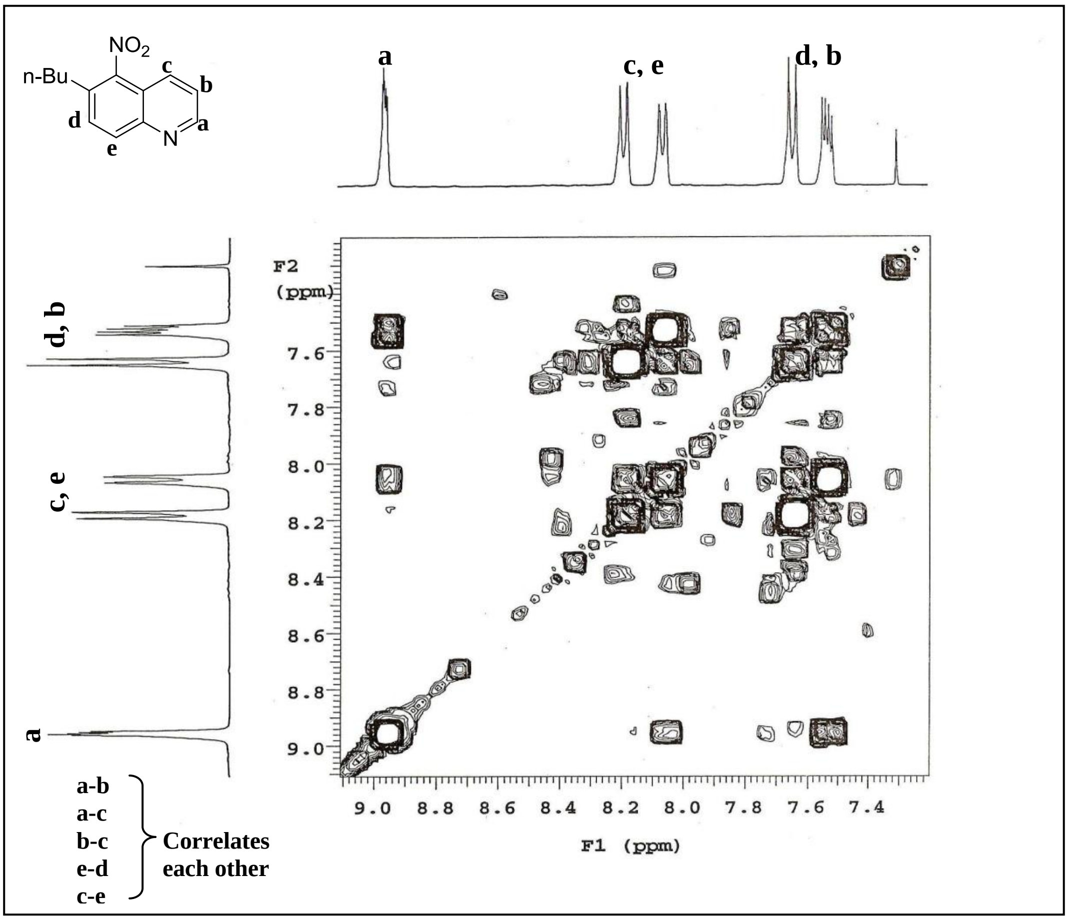
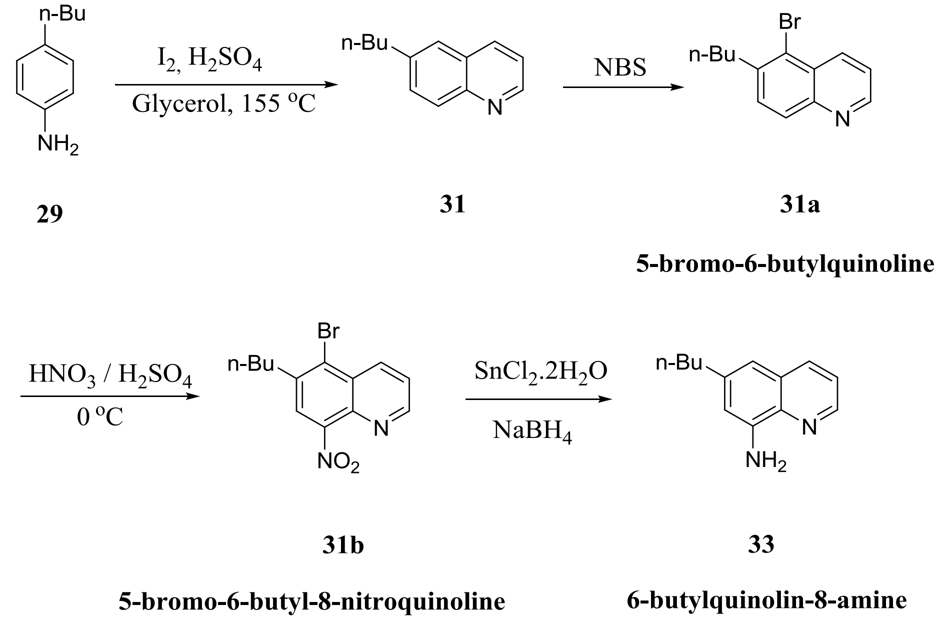


Figure 3.10. 2D COSY NMR spectrum of 6-butylquinolin-5-amine.

As it was stated, many experiments were performed in order to obtain 6-butyl-8-nitroquinoline. If these reactions were achieved, the next step would be the reduction of the nitro compound to the corresponding amine. By this way 6-butylquinolin-8-amine might be synthesized but since it was not successful, a new synthetic approach was followed by Ahmet Köseoğlu [Cited therein Ahmet Köseoğlu Ph.D. proposal seminar] (Figure 3.11).



29

31

31a

5-bromo-6-butylquinoline

31b

5-bromo-6-butyl-8-nitroquinoline

33

6-butylquinolin-8-amine

Figure 3.11. The third synthetic strategy for the synthesis of 6-butylquinolin-8-amine.

In this approach, firstly 6-butylquinoline (31) was synthesized and this compound was brominated with NBS (N-Bromosuccinimide) below 0 °C. During the bromination reaction, 5-bromo-6-butylquinoline and 5,8-dibromo-6-butylquinoline compounds were obtained. 5-bromo-6-butylquinoline was nitrated with H_2SO_4/HNO_3 to end up with 5-bromo-6-butyl-8-nitroquinoline. By using $SnCl_2.2H_2O$ and $NaBH_4$ reagents, while the nitro group was reduced to amine, the bromine was removed from the compound through hydrogenolysis and 6-butylquinolin-8-amine (33) was synthesized.

In order to verify the structure of 6-butylquinolin-8-amine (33), 2D COSY experiment was performed. Thus, 2D COSY proved that synthesized compound was the desired compound. Figure 3.12 shows the 2D COSY NMR data.

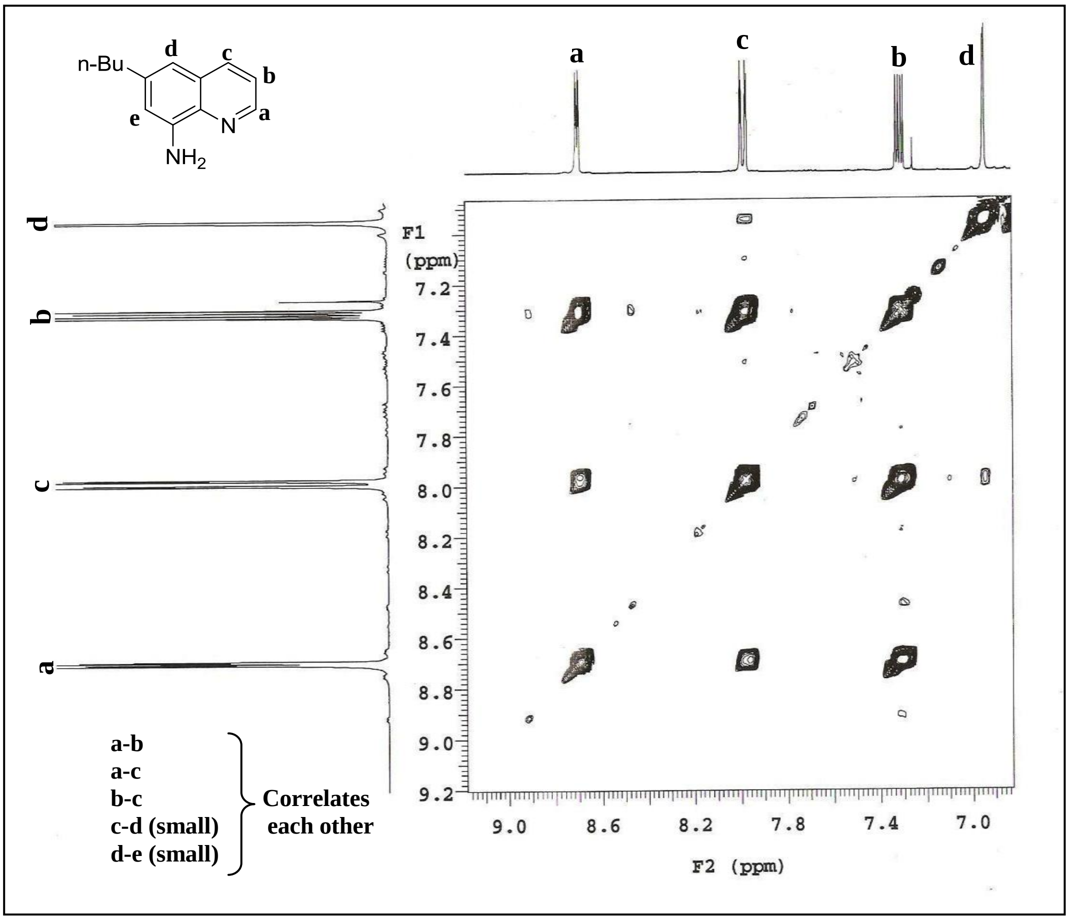


Figure 3.12. 2D COSY NMR of 6-butylquinolin-8-amine.

3.6. Synthetic Strategies Used for the Coupling of 6-Butylquinolin-8-Amine with Naphthoic Acid Derivatives

The coupling of 6-butylquinolin-8-amine with benzoic acid and naphthoic acid derivatives were done as described earlier using the *in-situ* generated acid bromides. Again, the yields for the coupling reactions were low. All the coupling products are shown in the Figure 3.12. The structures of those final products were determined with ^{1}H-NMR and ^{13}C-NMR.

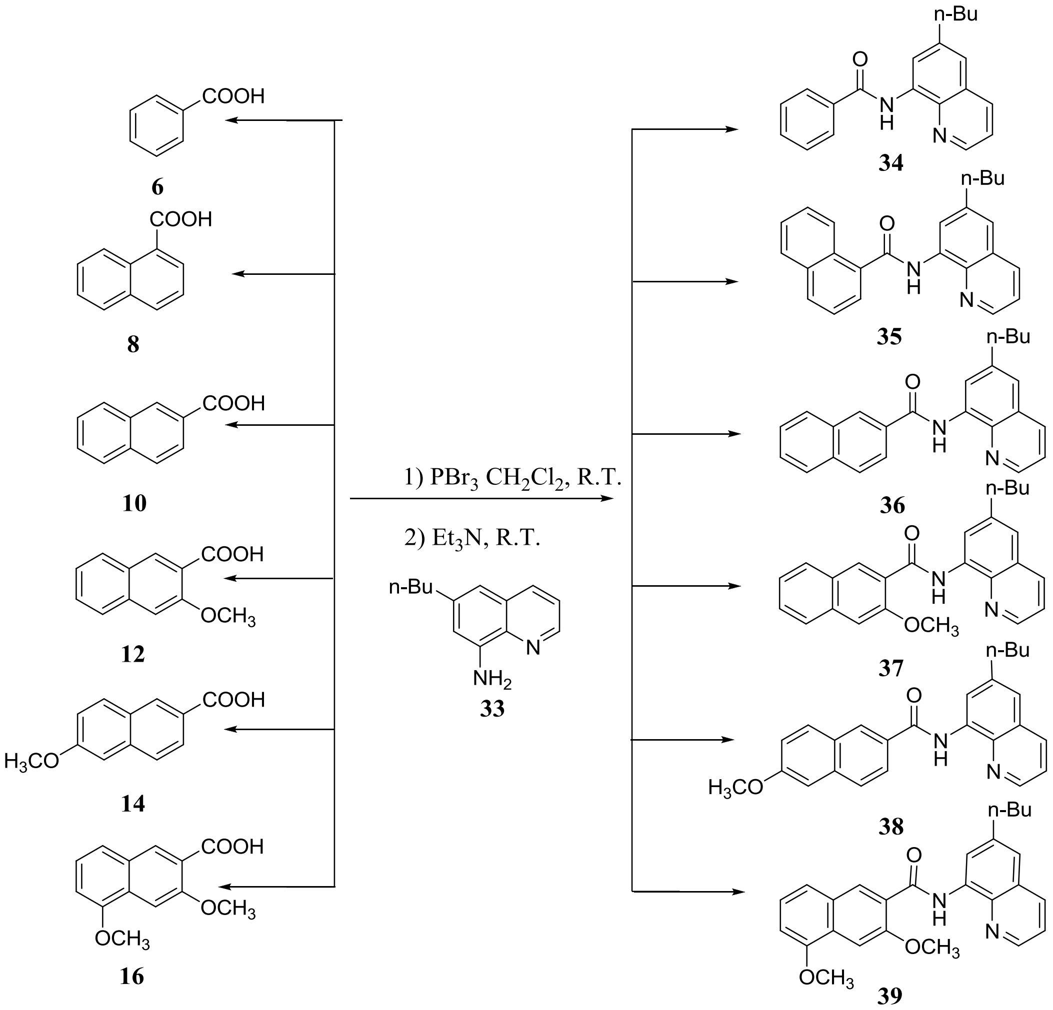


Figure 3.13. *In-situ* coupling of 6-butylquinolin-8-amine with benzoic acid and naphthoic acid derivatives.

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 of molecular sieves. Cooling to -78°C was carried out at 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, 2D COSY (Correlation Spectroscopy) and 2D NOESY (Nuclear Overhauser Enhancement Spectroscopy) 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.

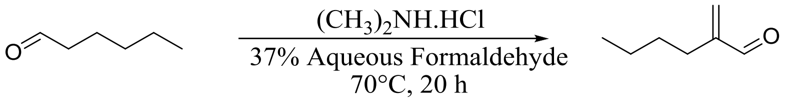
4.3. Synthesis of the Lead Compound Derivatives

In this study, firstly; 3-butylquinolin-8-amine, 4-butylquinolin-8-amine and 6-butylquinolin-8-amine derivatives of quinolines were synthesized. Then these quinoline derivatives were *in-situ* coupled with benzoic and naphthoic acid derivatives.

4.3.1. Synthesis of 3-Butylquinoline Derivatives

During the synthesis of 3-butylquinolin-8-amine, 3 steps of synthetic strategy were followed. After synthesis of 3-butylquinolin-8-amine, *in-situ* coupling reactions were done.

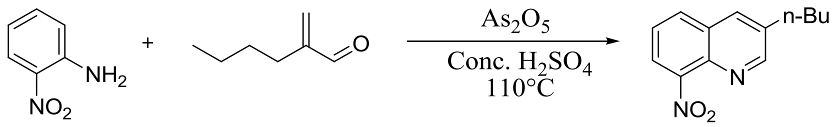
4.3.1.1. 2-Methylenehexanal (2). The synthesis was done according to the literature procedure [44]. A mixture of hexanal (1) (12 mL, 0.10 mol), dimethylamine hydrochloride (9.85 g, 0.12 mol) and 37% aqueous formaldehyde (9 mL, 0.12 mol) were stirred at 70°C for 20 hours. The aqueous phase was separated and extracted with 3x60 mL diethyl ether. The combined organic phases were dried over $CaCl_2$ and solvent was evaporated under reduced pressure. The product was purified by distillation to afford pure colorless oil (70°C, 40 mmHg). Compound (2) was obtained in 79% yield. **^{1}H-NMR** ($CDCl_3$), δ: 0.97 (t, 3H, $CH_2C\mathit{H}_3$), 1.23 (m, 2H, $CH_2C\mathit{H}_2CH_3$), 1.37 (m, 2H, $CH_2C\mathit{H}_2CH_2$), 2.18 (t, 2H, $CH_2CH_2C{=}CH_2$), 5.91 (s, 1H, $C\mathit{H}_2{=}C$), 6.17 (s, 1H, $C\mathit{H}_2{=}C$), 9.45 (s, 1H, $CO\mathit{H}$) ppm.



1 **2**

Figure 4.1. Synthesis of 2-methylenehexanal.

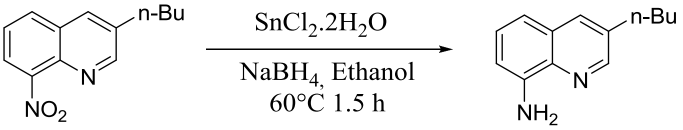
4.3.1.2. 3-Butyl-8-Nitroquinoline (4). The synthesis was done according to the literature procedure [45]. 2-nitroaniline (3) (4.213g, 30.5 mmol) and As_2O_5 (3.448g, 15 mmole) were added to a mixture of H_2SO_4 (1.5 mL H_2SO_4, 0.4 mL H_2O). The mixture was stirred mechanically and heated to 100°C. 2-methylenehexanal (2) (4.162mL, 30.5 mmol) was then added slowly without exceeding 120°C. The reaction mixture was refluxed overnight at 110°C. The color of the solution turned to black and was very viscous. After cooling, the solution was neutralized with aqueous NaOH. A fraction of the resulting viscous black solid was filtered under vacuum. Both the solid and the aqueous phase were extracted with 3x60 mL CH_2Cl_2. The combined organic phases were dried with anhydrous Na_2SO_4. The orange solid obtained after evaporation was chromatographed on silica, eluting with dichloromethane/hexane (2:1), gradient to pure dichloromethane. The resulting solid was recrystallized from ethanol to give pure orange crystals of 3-butyl-8-nitroquinoline (4) in 35% yield. **^{1}H-NMR** ($CDCl_3$), δ: 0.83 (t, 3H, $CH_2C\mathit{H}_3$), 129 (m, 2H, $CH_2C\mathit{H}_2CH_3$), 1.57 (m, 2H, $CH_2C\mathit{H}_2CH_2$), 2.71 (t, 2H, $ArC\mathit{H}_2$), 7.44 (t, 1H, Ar*H*), 7.84 (m, 1H, Ar*H*), 7.86 (m, 1H, Ar*H*), 7.89 (d, 1H, Ar*H*), 8.76 (d, 1H, Ar*H*) ppm.



3 **2** **4**

Figure 4.2. Synthesis of 3-butyl-8-nitroquinoline.

4.3.1.3. 3-Butylquinolin-8-Amine (5). The reduction of nitro to amine was done according to the literature procedure [46]. This experiment was carried out under inert atmosphere using nitrogen. 3-butyl-8-nitroquinoline (4) (0.640 g, 2.78 mmol) was dissolved in 10 mL ethanol. Stannous chloride dihydrate (3.14 g, 13.92 mmol) was added to this solution. The color of the solution turned to yellow-orange. This mixture was refluxed at 60°C for 1.5 hours. $NaBH_4$ (52.6 mg, 1.39 mmol) was dissolved in 2 mL ethanol and then injected to the reaction mixture. Resulting mixture was refluxed for another 1 hour. The reaction mixture was made alkaline with 5-6 mL 40 % NaOH. The color of the mixture changed to gray. Reaction mixture was extracted with 3x50 mL ethyl acetate, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. No need to column (85% yields). **^{1}H-NMR** ($CDCl_3$), δ: 0.89 (t, 3H, CH_2CH_3), 1.33 (m, 2H, $CH_2CH_2CH_3$), 1.62 (m, 2H, $CH_2CH_2CH_2$), 2.71 (t, 2H, $ArCH_2$), 4.90 (s, 2H, NH_2), 6.80 (dd, 1H, Ar*H*), 7.01 (dd, 1H, Ar*H*), 7.23 (t, 1H, Ar*H*), 7.75 (d, 1H, Ar*H*), 8.54 (d, 1H, Ar*H*) ppm.

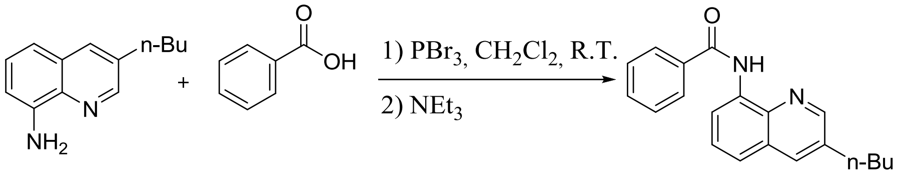


4 **5**

Figure 4.3. Synthesis of 3-butylquinolin-8-amine.

4.3.1.4. N-(3-Butylquinolin-8-yl)benzamide (7). The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. Benzoic acid (6) (56.1 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5

mmol) was added at that time fume occurred because of neutralizing of HBr. 3-butylquinolin-8-amine (5) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (2:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.97 (t, 3H, CH_2CH_3), 1.34 (m, 2H, $CH_2CH_2CH_3$), 1.63 (m, 2H, $CH_2CH_2CH_2$), 2.73 (t, 2H, ArCH_2), 7.39 (s, 1H, Ar*H*), 7.47 (m, 4H, Ar*H*), 7.82 (d, 1H, Ar*H*), 7.98 (d, 1H, Ar*H*), 8.00 (d, 1H, Ar*H*), 8.60 (d, 1H, Ar*H*), 8.78 (d, 1H, Ar*H*), 10.65 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.90 (CH_3), 22.23 (CH_2), 32.82 (CH_2), 32.25 (CH_2), 115.64 (2C, Ar*C*), 121.31 (2C, Ar*C*), 127.28 (Ar*C*), 127.41 (Ar*C*), 127.90 (Ar*C*), 128.78 (Ar*C*), 131.79 (Ar*C*), 134.46 (Ar*C*), 134.51 (Ar*C*), 135.21 (Ar*C*), 136.07 (Ar*C*), 137.32 (Ar*C*), 149.92 (Ar*C*), 165.24 (*C*=O) ppm.

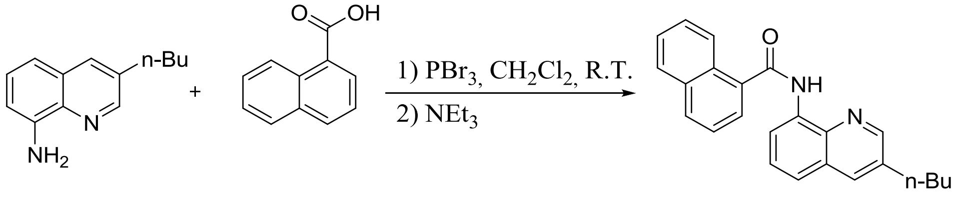


5 **6** **7**

Figure 4.4. Synthesis of N-(3-butylquinolin-8-yl)benzamide.

<u>4.3.1.5. N-(3-Butylquinolin-8-yl)-1-Naphthamide (9).</u> The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 1-naphthoic acid (8) (86.1 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 3-butylquinolin-8-amine (5) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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

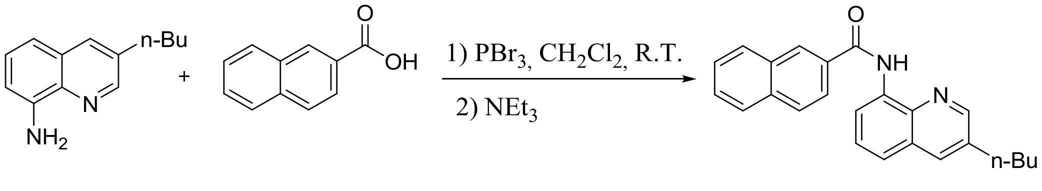
and concentrated under reduced pressure. The crude product was impure and a column was prepared by using silica gel and CH_2Cl_2 and Hexane (2:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.97 (t, 3H, CH_2CH_3), 1.42 (m, 2H, $CH_2CH_2CH_3$), 1.70 (m, 2H, $CH_2CH_2CH_2$), 2.80 (t, 2H, ArCH_2), 7.55 (m, 5H, Ar*H*), 7.92 (m, 3H, Ar*H*), 8.01 (d, 1H, Ar*H*), 8.56 (d, 1H, Ar*H*), 8.60 (d, 1H, Ar*H*), 9.01 (d, 1H, Ar*H*), 10.45 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.88 (CH_3), 22.23 (CH_2), 32.80 (CH_2), 33.23 (CH_2), 115.85 (Ar*C*), 121.55 (Ar*C*), 124.87 (Ar*C*), 125.50 (Ar*C*), 125.61 (Ar*C*), 126.50 (Ar*C*), 127.28 (Ar*C*), 127.41 (Ar*C*), 127.95 (Ar*C*), 128.37 (Ar*C*), 130.36 (Ar*C*), 131.07 (Ar*C*), 133.89 (Ar*C*), 134.48 (Ar*C*), 134.72 (Ar*C*), 134.76 (Ar*C*), 136.10 (Ar*C*), 137.19 (Ar*C*), 149.93 (Ar*C*), 167.71 (*C*=O) ppm.



5 **8** **9**

Figure 4.5. Synthesis of N-(3-butylquinolin-8-yl)-1-naphthamide.

4.3.1.6. N-(3-Butylquinolin-8-yl)-2-Naphthamide (11). The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 2-naphthoic acid (10) (86.1 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 3-butylquinolin-8-amine (5) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (2:1) as the eluent phase. **^{1}H NMR** ($CDCl_3$), δ: 0.92 (t, 3H, CH_2CH_3), 1.38 (m, 2H, $CH_2CH_2CH_3$), 1.69 (m, 2H, $CH_2CH_2CH_2$), 2.78 (t, 2H, ArCH_2), 7.42 (d, 1H, Ar*H*), 7.53 (m, 3H, Ar*H*), 7.88 (m, 2H, Ar*H*), 7.94 (d, 1H, Ar*H*), 7.98 (d, 1H, Ar*H*), 8.07 (d, 1H, Ar*H*), 8.53 (s, 1H, Ar*H*), 8.67 (s, 1H, Ar*H*), 8.85 (s, 1H, Ar*H*), 10.90 (s, 1H, N*H*) ppm. **^{13}C NMR** ($CDCl_3$), δ: 13.92 (*C*H_3), 22.25 (*C*H_2), 32.86 (*C*H_2), 33.30 (*C*H_2), 115.72 (Ar*C*), 121.34 (Ar*C*), 123.78 (Ar*C*), 126.80 (Ar*C*), 127.47 (Ar*C*), 127.80 (Ar*C*), 127.84 (Ar*C*), 127.92 (Ar*C*), 127.94 (Ar*C*), 128.69 (Ar*C*), 129.21 (Ar*C*), 132.45 (Ar*C*), 132.75 (Ar*C*), 134.53 (Ar*C*), 134.58 (Ar*C*), 134.92 (Ar*C*), 136.11 (Ar*C*), 137.36 (Ar*C*), 149.99 (Ar*C*), 165.51 (*C*=O) ppm.

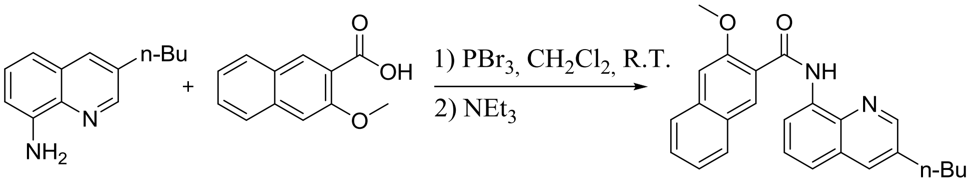


5 **10** **11**

Figure 4.6. Synthesis of N-(3-butylquinolin-8-yl)-2-naphthamide.

<u>4.3.1.7. N-(3-Butylquinolin-8-yl)-3-Methoxy-2-Naphthamide (13).</u> The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 3-methoxy-2-naphthoic acid (12) (100 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 3-butylquinolin-8-amine (5) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (2:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.90 (t, 3H, CH_2C*H_3*), 1.36 (m, 2H, CH_2C*H_2*CH_3), 1.66 (m, 2H, CH_2C*H_2*CH_2), 2.75 (t, 2H, ArC*H_2*), 4.24 (s, 3H, OC*H_3*), 7.24 (s, 1H, Ar*H*), 7.34 (m, 1H, Ar*H*), 7.42 (dd, 1H, Ar*H*), 7.46 (m, 1H, ArH), 7.50 (m, 1H, Ar*H*), 7.72 (d, 1H, Ar*H*), 7.85, 1H, Ar*H*), 7.89 (dd, 1H, Ar*H*), 8.69 (dd, 1H, Ar*H*), 8.83 (s, 1H, Ar*H*), 8.94 (dd, 1H, Ar*H*), 12.30 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.89 (*C*H_3), 22.26 (*C*H_2), 32.85 (*C*H_2), 33.31 (*C*H_2), 56.13 (O*C*H_3), 106.65 (Ar*C*), 116.65 (Ar*C*), 121.23 (Ar*C*), 123.36

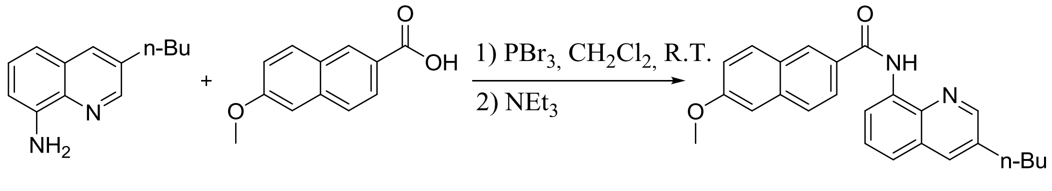
(Ar*C*), 124.52 (Ar*C*), 126.21 (Ar*C*), 127.57 (Ar*C*), 128.02 (Ar*C*), 128.34 (Ar*C*), 129.30 (Ar*C*), 134.12 (Ar*C*), 134.41 (Ar*C*), 135.58 (Ar*C*), 135.78 (Ar*C*), 135.93 (Ar*C*), 137.87 (Ar*C*), 149.95 (2C, Ar*C*), 154.97 (Ar*C*), 163.40 (*C*=O) ppm.



5 **12** **13**

Figure 4.7. Synthesis of N-(3-butylquinolin-8-yl)-3-methoxy-2-naphthamide.

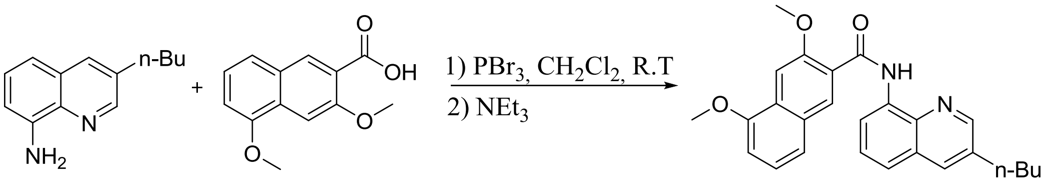
4.3.1.8. N-(3-Butylquinolin-8-yl)-6-Methoxy-2-Naphthamide (15). The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 6-methoxy-2-naphthoic acid (14) (100 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 3-butylquinolin-8- amine (5) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (2:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.91 (t, 3H, CH_2CH_3), 1.37 (m, 2H, $CH_2CH_2CH_3$), 1.68 (m, 2H, $CH_2CH_2CH_2$), 2.80 (t, 2H, $ArCH_2$), 3,88 (s, 3H, OCH_3), 7.16 (s, 1H, Ar*H*), 7.19 (s, 1H, Ar*H*), 7.44 (d, 1H, Ar*H*), 7.52 (t, 1H, Ar*H*), 7.81 (s, 1H, Ar*H*),7.84 (d, 1H, Ar*H*), 7.89 (s, 1H, Ar*H*), 8.06 (d, 1H, Ar*H*), 8.47 (s, 1H, Ar*H*), 8.68 (s, 1H, Ar*H*), 8.85 (d, 1H, Ar*H*), 10.80 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 12.88 (CH_3), 21.20 (CH_2), 31.79 (CH_2), 32.22 (CH_2), 54.35 (OCH_3), 104.58 (Ar*C*), 114.57 (Ar*C*), 118.73 (Ar*C*), 120.12 (Ar*C*), 123.33 (Ar*C*), 126.29 (Ar*C*), 126.41 (Ar*C*), 126.73 (Ar*C*), 126.87 (Ar*C*), 127.08 (Ar*C*), 129.11 (Ar*C*), 129.68 (Ar*C*), 133.48 (Ar*C*), 133.56 (Ar*C*), 135.00 (Ar*C*), 135.416 (Ar*C*), 136.29 (Ar*C*), 148.87 (Ar*C*), 158.14 (Ar*C*), 164.46 (*C*=O)



5 **14** **15**

Figure 4.8. Synthesis of N-(3-butylquinolin-8-yl)-6-methoxy-2-naphthamide.

4.3.1.9. N-(3-Butylquinolin-8-yl)-3,5-Dimethoxy-2-Naphthamide (17). The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 3,5-dimethoxy-2-naphthoic acid (16) (116 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 3-butylquinolin-8-amine (5) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (2:1) as the eluent phase. **^{1}H NMR** ($CDCl_3$), δ: 0.88 (t, 3H, CH_2CH_3), 1.37 (m, 2H, $CH_2CH_2CH_3$), 1.66 (m, 2H, $CH_2CH_2CH_2$), 2.80 (t, 2H, ArCH_2), 3.97 (s, 3H, OCH_3), 4.26 (s, 3H, OCH_3), 6.83 (d, 1H, Ar*H*), 7.25 (t, 1H, Ar*H*), 7.42 (m, 1H, Ar*H*), 7.49 (m, 2H, Ar*H*), 7.64 (s, 1H, Ar*H*), 7.86 (d, 1H, Ar*H*), 8.70 (d, 1H, Ar*H*), 8.80 (s, 1H, Ar*H*), 8.94 (dd, 1H, Ar*H*), 12.45 (s, 1H, N*H*) ppm. **^{13}C NMR** ($CDCl_3$), δ: 12.90 (CH_3), 21.26 (CH_2), 28.69 (CH_2), 32.33 (CH_2), 54.54 (OCH_3), 55.21 (OCH_3), 100.42 (Ar*C*), 104.86 (Ar*C*), 115.63 (Ar*C*), 120.21 (Ar*C*), 120.44 (Ar*C*), 122.42 (Ar*C*), 123.35 (Ar*C*), 126.57 (Ar*C*), 126.88 (Ar*C*), 126.98 (Ar*C*), 128.22 (Ar*C*), 132.66 (Ar*C*), 133.42 (Ar*C*), 134.57 (Ar*C*), 134.77 (Ar*C*), 136.85 (Ar*C*), 148.97 (Ar*C*), 153.06 (Ar*C*), 153.71 (Ar*C*), 162.45 (*C*=O) ppm.



5 **16** **17**

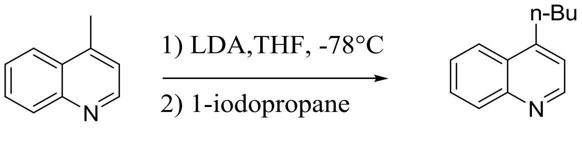
Figure 4.9. Synthesis of N-(3-butylquinolin-8-yl)-3,5-dimethoxy-2-naphthamide.

4.3.2. Synthesis of 4-Butylquinoline Derivatives

4-butylquinolin-8-amine compound was synthesized by following 3 steps of synthetic strategy. After synthesis of 4-butylquinolin-8-amine, *in-situ* coupling reactions were done.

4.3.2.1. 4-Butylquinoline (18). The synthesis was done according to the literature procedure [48]. This experiment was carried out under inert atmosphere using nitrogen at -78°C. In order to prepare LDA (Lithium diisopropylamine) solution, firstly in a 100 mL of flask equipped with a magnetic stirrer, diisopropylamine (6.48 mL, 46.2 mmol) was dissolved in 65 mL dry THF under N_2 at -78°C. To this solution, n-BuLi in 2.5M Hexane (16.8 mL, 42 mmol) was added and the mixture was warmed to 0°C for 30 minutes. Then the mixture was again cooled to -78°C for 2.5 hours. For enolate formation, 65 mL dry THF was put in to a 250 mL round bottom flask with a magnetic stirrer. To this solution, 4-methylquinoline (Lepidine) (18) (4.72 mL, 34.9 mmol) was added under N_2 at -78°C. LDA solution was successfully added to this solution at -78°C.The color of the solution turned to dark orange. This mixture was kept at -78°C for 2.5 hours. Iodopropane (4.10 mL, 42 mmol) was added dropwise to this mixture at -78°C under N_2 and this mixture was kept at -78°C for 3 hours. The resulting mixture was allowed to warm up to room temperature overnight. The color of the solution turned to light orange. The reaction was then quenched with saturated 50 mL NH_4Cl and extracted with 3x100 mL EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was further purified with column chromatography using silica gel as the packing material and CH_2Cl_2 as the mobile phase. 4-butylquinoline

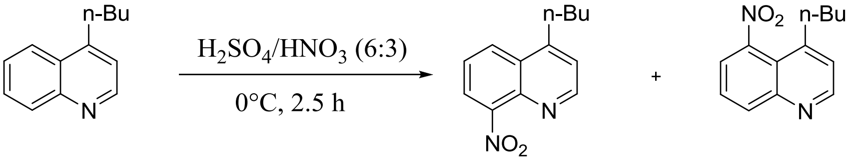
(19) was obtained in 77% yield. ^{1}**H-NMR** ($CDCl_3$), δ : 0.94 (t, 3H, CH_2CH3), 1.45 (m, 2H, $CH_2CH_2CH_3$), 1.71 (m, 2H, $CH_2CH_2CH_2$), 3.10 (t, 2H, $ArCH_{2,}$), 7,19 (dd, 1H, Ar*H*), 7.53 (dd, 1H, Ar*H*), 7.68 (dd, 1H, Ar*H*), 8.01 (d, 1H, Ar*H*), 8.10 (dd, 1H, Ar*H*), 8.77 (dd, 1H, Ar*H*) ppm.



18 **19**

Figure 4.10. Synthesis of 4-butylquinoline.

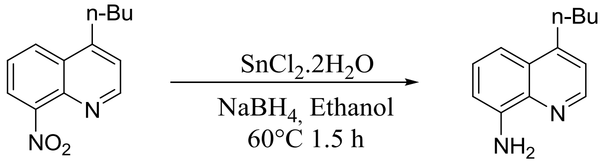
4.3.2.2. 4-Butyl-8-Nitroquinoline (20). The nitration of compound (19) was done according to the literature procedure [49]. To a solution of 4-butylquinoline (19) (1.11 g, 6 mmol) in concentrated 2.5 mL H_2SO_4, cooled in an iced bath was added dropwise 2 mL of concentrated H_2SO_4/HNO_3 mixture (6:2). Reaction was maintained at lower temperature, stirred rapidly and monitored by TLC until all the quinoline had been consumed for about 2.5 hours. Mixture was diluted with 10 mL water and NaOH was added until the solution reached pH 10-11. Solution was extracted with 3x50 mL CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and evaporated. Nitration of 4-butylquinoline resulted with 4-butyl-8-nitroquinoline (20) and 4-butyl-5-nitroquinoline (21).In order to separate 4-butyl-8-nitroquinoline a column was prepared by using silica gel and CH_2Cl_2 as the eluent phase. 4-butyl-8-nitroquinoline (20) was obtained in 66% yield. ^{1}**H-NMR** ($CDCl_3$), δ : 0.95 (t, 3H, CH_2CH_3), 1.45 (m, 2H, $CH_2CH_2CH_3$), 1.74 (m, 2H, $CH_2CH_2CH_2$), 3,12 (t, 2H, $ArCH_2$), 7.37 (d, 1H, Ar*H*), 7.61 (m, 1H, Ar*H*), 7.97 (dd, 1H, Ar*H*), 8.25 (dd, 1H, Ar*H*), 8.93 (d, 1H, Ar*H*) ppm.



19 **20** **21**

Figure 4.11. Synthesis of 4-butyl-8-nitroquinoline.

<u>4.3.2.3. 4-Butylquinolin-8-Amine (22).</u> The reduction of nitro to amine was done according to the literature procedure [46]. This experiment was carried out under inert atmosphere using nitrogen. 4-butyl-8-nitroquinoline (20) (0.495 g, 2.15 mmol) was dissolved in 10 mL ethanol. Stannous chloride dihydrate (2.73 g, 10.77 mmol) was added to this solution. The color of the solution turned to yellow-orange. This mixture was refluxed at 60°C for 1.5 hours. $NaBH_4$ (5.5 mg, 1.075 mmol) was dissolved in 2 mL ethanol and then injected to the reaction mixture. Resulting mixture was refluxed for another 1 hour. The reaction mixture was made alkaline with 5-6 mL 40 % NaOH. The color of the mixture changed to gray. Reaction mixture was extracted with 3x50 mL ethyl acetate, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. No need to column and reduced compound was obtained in 93% yield. **^{1}H-NMR** ($CDCl_3$), δ: 0.90 (t, 3H, CH_2CH_3), 1.36 (m, 2H, $CH_2CH_2CH_3$), 1.66 (m, 2H, $CH_2CH_2CH_2$), 2.93 (t, 2H, $ArCH_2$), 4.90 (s, 2H, NH_2), 6.84 (dd, 1H, Ar*H*), 7.13 (d, 1H, Ar*H*), 7.25 (d, 1H, Ar*H*), 7.37 (d, 1H, Ar*H*), 8.57 (d, 1H, Ar*H*) ppm.

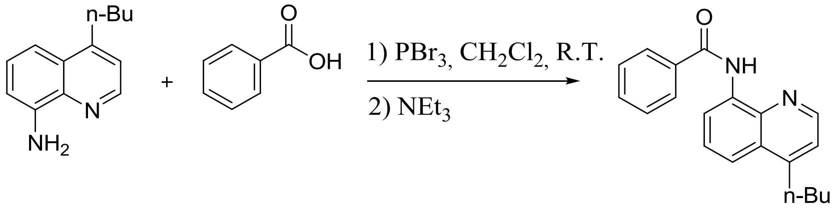


20 **22**

Figure 4.12. Synthesis of 4-butylquinolin-8-amine.

<u>4.3.2.4. N-(4-Butylquinolin-8-yl)benzamide (23).</u> The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. Benzoic acid (6) (56.1 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-butylquinolin-8-amine (22) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (2:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.88 (t, 3H, CH_2CH_3), 1.35 (m, 2H, $CH_2CH_2CH_3$), 1.64 (m, 2H, $CH_2CH_2CH_2$), 2.94 (t, 2H, $ArCH_2$), 7.18 (s, 1H, Ar*H*), 7.45 (m, 4H, Ar*H*), 7.62 (d, 1H, Ar*H*), 7.97 (d, 1H, Ar*H*), 8.00(d, 1H, Ar*H*), 8.60 (d, 1H, Ar*H*), 8.82 (d, 1H, Ar*H*), 10.80 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.91 (*C*H_3), 22.75 (*C*H_2), 32.00 (*C*H_2), 32.18 (*C*H_2), 116.09 (2C, Ar*C*), 117.65 (2C, Ar*C*), 121.34 (Ar*C*), 126.93 (Ar*C*), 127.30 (Ar*C*), 127.33 (Ar*C*), 128.76 (Ar*C*), 131.76 (Ar*C*), 135.09 (Ar*C*), 135.27 (Ar*C*), 138.81 (Ar*C*), 147.86 (Ar*C*), 149.42 (Ar*C*), 165.40(*C*=O) ppm.

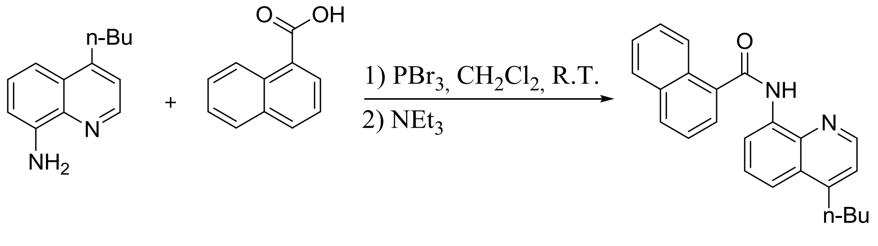


22 **6** **23**

Figure 4.13. Synthesis of N-(4-butylquinolin-8-yl)benzamide.

<u>4.3.2.5. N-(4-Butylquinolin-8-yl)-1-Naphthamide (24).</u> The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 1-naphthoic acid (8) (86.1 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-butylquinolin-8-amine (22) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (2:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.99 (t, 3H, CH_2CH_3), 1.46 (m, 2H, $CH_2CH_2CH_3$), 1.75 (m, 2H, $CH_2CH_2CH_2$), 3.07 (t, 2H, $ArCH_2$), 7.25 (s, 1H, Ar*H*), 7.51 (m, 4H, Ar*H*), 7.78 (d, 1H, Ar*H*), 7.91 (d, 1H, Ar*H*), 7.92 (s, 1H, Ar*H*), 8.01 (d, 1H, Ar*H*), 8.55 (d, 1H, Ar*H*), 8.61 (s,

1H, Ar*H*), 9.05 1H, Ar*H*), 10.58 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.92 (CH_3), 22.75 (CH_2), 32.02 (CH_2), 32.21 (CH_2), 116.30 (Ar*C*), 117.92 (Ar*C*), 121.38 (Ar*C*), 124.88 (Ar*C*), 125.52 (Ar*C*), 125.62 (Ar*C*), 126.48 (Ar*C*), 126.93 (Ar*C*), 127.26 (Ar*C*), 127.38 (Ar*C*), 128.37 (Ar*C*), 130.37 (Ar*C*), 131.06 (Ar*C*), 133.89 (Ar*C*), 134.80 (Ar*C*), 135.34 (Ar*C*), 138.67 (Ar*C*), 147.88 (Ar*C*), 149.39 (Ar*C*), 167.72 (*C*=O) ppm.

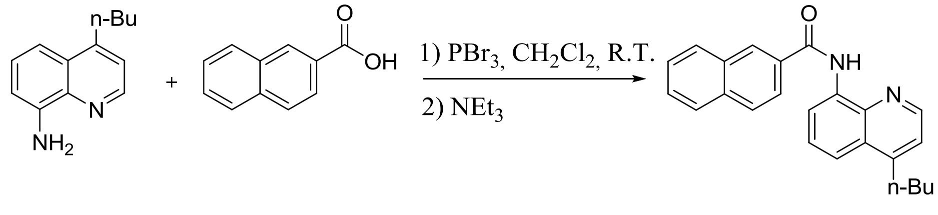


22 **8** **24**

Figure 4.14. Synthesis of N-(4-butylquinolin-8-yl)-1-naphthamide.

4.3.2.6. N-(4-Butylquinolin-8-yl)-2-Naphthamide (25). The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 2-naphthoic acid (10) (86.1 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-butylquinolin-8-amine (22) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (2:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.90 (t, 3H, CH_2CH_3), 1.39 (m, 2H, $CH_2CH_2CH_3$), 1.66 (m, 2H, $CH_2CH_2CH_2$), 2.98 (t, 2H, $ArCH_2$), 7.22 (d, 1H, Ar*H*), 7.50 (m, 3H, Ar*H*), 7.66 (dd, 1H, Ar*H*), 7.82 (dd, 1H, Ar*H*), 7.89 (d, 1H, Ar*H*), 7.95 (dd, 1H, Ar*H*), 8.04 (dd, 1H, Ar*H*), 8.51 (s, 1H, Ar*H*), 8.66 (d, 1H, Ar*H*), 8.88 (dd, 1H, Ar*H*), 10.95 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 12.88 (CH_3), 21.72 (CH_2), 30.99 (CH_2), 31.14 (CH_2), 115.22 (Ar*C*), 116.68 (Ar*C*), 120.32 (Ar*C*), 122.74 (Ar*C*), 125.73 (Ar*C*), 125.95 (Ar*C*), 126.34 (Ar*C*), 126.74 (Ar*C*), 126.76 (Ar*C*), 126.92 (Ar*C*), 127.61 (Ar*C*), 128.17 (Ar*C*), 131.43 (Ar*C*), 131.73

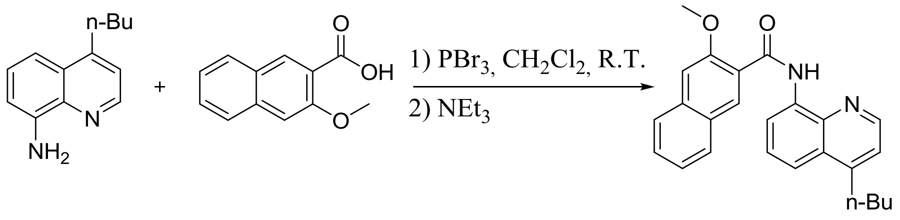
(Ar*C*), 133.88 (Ar*C*), 134.09 (Ar*C*), 137.76 (Ar*C*), 146.83 (Ar*C*), 148.49 (Ar*C*), 164.43 (*C*=O) ppm.



22 **10** **25**

Figure 4.15. Synthesis of N-(4-butylquinolin-8-yl)-2-naphthamide.

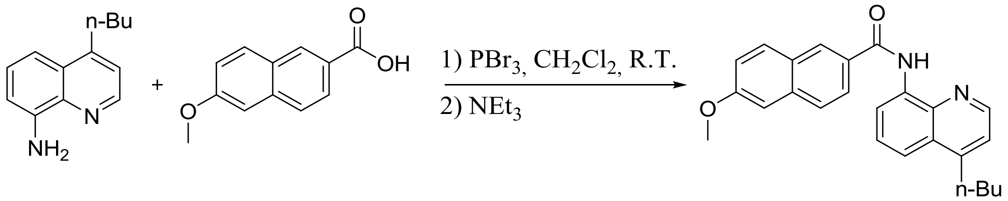
<u>4.3.2.7. N-(4-Butylquinolin-8-yl)-3-Methoxy-2-Naphthamide (26).</u> The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 3-methoxy-2-naphthoic acid (12) (100 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-butylquinolin-8-amine (22) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (2:1) as the eluent phase. . **^{1}H-NMR** ($CDCl_3$), δ: 0.98 (t, 3H, CH_2CH_3), 1.45 (m, 2H, $CH_2CH_2CH_3$), 1.74 (m, 2H, $CH_2CH_2CH_2$), 3.05 (t, 2H, ArCH_2), 4.25 (s, 3H, OCH_3), 7.26 (s, 1H, Ar*H*), 7.27 (s, 1H, Ar*H*), 7.39 (m, 1H, Ar*H*), 7.54 (m, 1H, Ar*H*), 7.60 (dd, 1H, ArH), 7.73, (dd,1H, Ar*H*), 7.75 (dd, 1H, Ar*H*), 7.93 (d, 1H, Ar*H*), 8.74 (d, 1H, Ar*H*), 8.90 (s, 1H, Ar*H*), 9.06 (dd, 1H, Ar*H*), 12.30 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.92 (CH_3), 22.76 (CH_2), 32.03 (CH_2), 32.16 (CH_2), 56.04 (OCH_3), 106.59 (Ar*C*), 117.05 (Ar*C*), 117.54 (Ar*C*), 121.12 (Ar*C*), 123.40 (Ar*C*), 124.46 (Ar*C*), 126.21 (Ar*C*), 127.06 (Ar*C*), 127.41 (Ar*C*), 128.28 (Ar*C*), 129.24 (Ar*C*), 134.05 (Ar*C*), 135.91 (Ar*C*), 136.22 (Ar*C*), 139.31 (Ar*C*), 147.86 (Ar*C*), 149.11 (2C, Ar*C*), 154.94 (Ar*C*), 163.37 (*C*=O) ppm.



22 **12** **26**

Figure 4.16. Synthesis of N-(4-butylquinolin-8-yl)-3-methoxy-2-naphthamide.

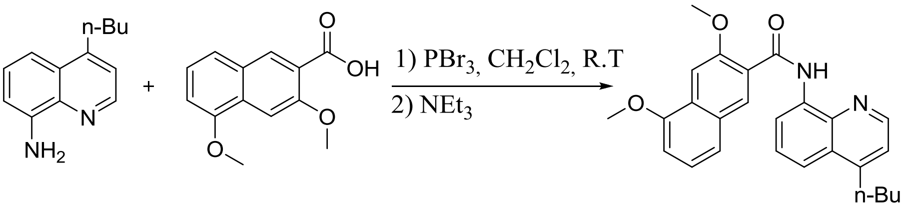
4.3.2.8. N-(4-Butylquinolin-8-yl)-6-Methoxy-2-Naphthamide (27). The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 6-methoxy-2-naphthoic acid (14) (100 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-butylquinolin-8-amine (22) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (2:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.91 (t, 3H, CH_2CH_3), 1.41 (m, 2H, $CH_2CH_2CH_3$), 1.68 (m, 2H, $CH_2CH_2CH_2$), 3.00 (t, 2H, $ArCH_2$), 3,88 (s, 3H, OCH_3), 7.10 (d, 1H, Ar*H*), 7.15 (dd, 1H, Ar*H*), 7.23 (d, 1H, Ar*H*), 7.53 (t, 1H, Ar*H*), 7.67 (dd, 1H, Ar*H*),7.80 (d, 1H, Ar*H*), 7.85 (s, 1H, Ar*H*), 8.03 (dd, 1H, Ar*H*), 8.45 (d, 1H, Ar*H*), 8.68 (d, 1H, Ar*H*), 8.89 (d, 1H, Ar*H*), 12.57 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.92 (CH_3), 22.76 (CH_2), 32.04 (CH_2), 32.19 (CH_2), 55.40 (OCH_3), 105.68 (Ar*C*), 116.14 (Ar*C*), 117.54 (Ar*C*), 119.74 (Ar*C*), 121.34 (Ar*C*), 124.40 (Ar*C*), 127.00 (Ar*C*), 127.32 (Ar*C*), 127.37 (Ar*C*), 127.81 (Ar*C*), 128.17 (Ar*C*), 130.25 (Ar*C*), 130.75 (Ar*C*), 135.24 (Ar*C*), 136.48 (Ar*C*), 138.84 (Ar*C*), 147.85 (Ar*C*), 149.46 (Ar*C*), 159.21 (Ar*C*), 165.53 (*C*=O) ppm.



22 **14** **27**

Figure 4.17. Synthesis of N-(4-butylquinolin-8-yl)-6-methoxy-2-naphthamide.

<u>4.3.2.9. N-(4-Butylquinolin-8-yl)-3,5-Dimethoxy-2-Naphthamide (28).</u> The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 3,5-dimethoxy-2-naphthoic acid (16) (116 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 4-butylquinolin-8-amine (22) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (2:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.97 (t, 3H, CH_2CH_3), 1.44 (m, 2H, $CH_2CH_2CH_3$), 1.72 (m, 2H, $CH_2CH_2CH_2$), 3.02 (t, 2H, $ArCH_2$), 3.99 (s, 3H, OCH_3), 4.25 (s, 3H, OCH_3), 6.84 (d, 1H, Ar*H*), 7.24 (d, 1H, Ar*H*), 7.29 (t, 1H, Ar*H*), 7.52 (d, 1H, Ar*H*), 7.59 (t, 1H, Ar*H*), 7.64 (s, 1H, Ar*H*), 7.69 (d, 1H, Ar*H*), 8.73 (d, 1H, Ar*H*), 8.85 (s, 1H, Ar*H*), 9.06 (d, 1H, Ar*H*), 12.45 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.92 (CH_3), 22.76 (CH_2), 32.02 (CH_2), 32.14 (CH_2), 55.52 (OCH_3), 56.11 (OCH_3), 101.42 (Ar*C*), 105.83 (Ar*C*), 117.05 (Ar*C*), 117.51 (Ar*C*), 121.10 (Ar*C*), 121.38 (Ar*C*), 123.53 (Ar*C*), 124.31 (Ar*C*), 127.05 (Ar*C*), 127.41 (Ar*C*), 127.91 (Ar*C*), 129.23 (Ar*C*), 133.57 (Ar*C*), 136.26 (Ar*C*), 139.32 (Ar*C*), 147.87 (Ar*C*), 149.08 (Ar*C*), 154.09 (Ar*C*), 154.69 (Ar*C*), 163.43 (*C*=O) ppm.



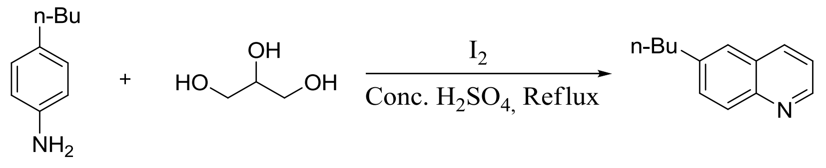
22 **16** **28**

Figure 4.18. Synthesis of N-(4-butylquinolin-8-yl)-3,5- dimethoxy-2-naphthamide.

4.3.3. Synthesis of 6-Butylquinoline Derivatives

In order to synthesize 6-butylquinolin-8-amine, 3 different synthetic approaches were followed. However one of them was successful and this quinoline derivative was again coupled with benzoic and naphthoic acid derivatives.

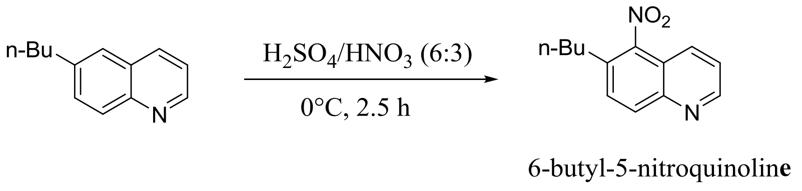
4.3.3.1. 6-Butylquinoline (31). Reaction was done according to the literature procedure [50]. In a 250 mL round-bottom flask was added 4-butylaniline (29) (9.58 g, 64.2 mmol), glycerol (30) (9.00 g, 97.8 mmol) and iodine (0.3 g, 1.18 mmol). The reaction mixture was stirred and 9.84 mL concentrated sulfuric acid was added down the condenser from a dropping funnel. Reaction soon commenced, the temperature raised to 100- 105°C. Flask was heated gradually, with stirring, in a silicone bath to 140°C; the reaction proceeded with the evolution of sulphurdioxide and a little iodine vapor and the liquid refluxed. Heating at 170°C was continued for 1.5- 2.5 hours. Reaction was monitored by TLC. When the reaction completed, mixture was cooled and 51 mL 5M sodium hydroxide was added to render the mixture alkaline. Mixture was extracted dichloromethane (3x50 mL), dried over anhydrous sodium Na_2SO_4 and filtered. Solvent was removed on a rotary evaporator. The crude material was purified via column chromatography on silica gel using 10% hexanes in dichloromethane as eluent to give 7.3 g (59.3% yields) of the title compound. **^{1}H-NMR** ($CDCl_3$), δ: 0.86 (t, 3H, $CH_2C\mathit{H}_3$), 1.30 (m, 2H, $CH_2C\mathit{H}_2CH_3$), 1.60 (m, 2H, $CH_2C\mathit{H}_2CH_2$), 2.70 (t, 2H, ArCH_2), 7.26 (dd, 1H, Ar*H*), 7.48 (m, 2H, Ar*H*), 7.94 (d, 1H, Ar*H*), 7.99 (d, 1H, Ar*H*), 8.75 (dd, 1H, Ar*H*), ppm.



29 **30** **31**

Figure 4.19. Synthesis of 6-butylquinoline.

4.3.3.2. 6-Butyl-5-Nitroquinoline (32). Reaction was done according to the literature procedure [49]. To a solution of 6-butylquinoline (31) (2.2 g, 12 mmol) in concentrated sulfuric acid (10 mL) cooled in an ice bath was added drop wise 8 mL of conc. H_2SO_4 / HNO_3 mixture (6:2). Reaction mixture maintained at low temperature, stirred rapidly and monitored by TLC until all the quinoline had been consumed (2 hours). Reaction mixture was diluted with 10 mL distilled water. Sodium hydroxide was added to the solution until the mixture reached pH 10-11. The solution was extracted with diethyl ether (3x50 mL). Organic phase was dried over anhydrous Na_2SO_4 and then filtered. Solvent was removed under reduced pressure to give 0,427 g 6-butyl-5-nitroquinoline (32). **^{1}H-NMR** ($CDCl_3$), δ: 0.83 (t, 3H, CH_2CH_3), 1.30 (m, 2H, $CH_2CH_2CH_3$), 1.59 (m, 2H, $CH_2CH_2CH_2$), 2.67 (t, 2H, $ArCH_2$), 7,42 (m, 1H, Ar*H*), 7.52 (d, 1H, Ar*H*), 7.94 (d, 1H, Ar*H*), 8.75 (d, 1H, Ar*H*), 8.84 (dd, 1H, Ar*H*) ppm.

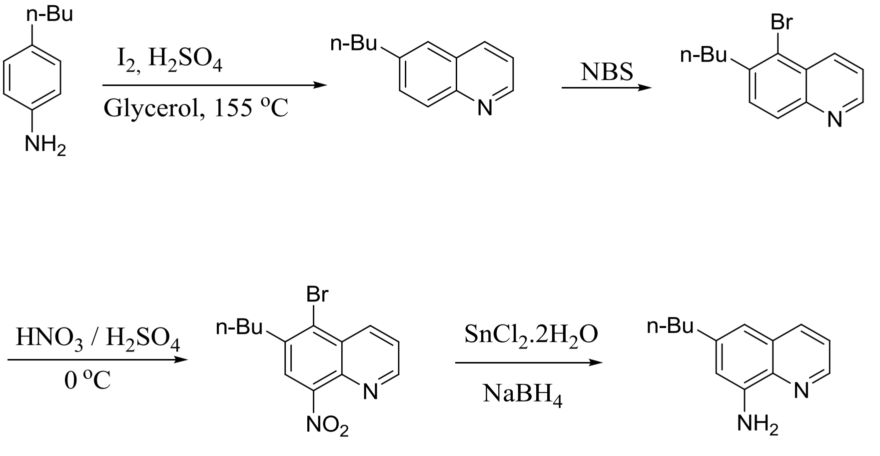


31 **32**

Figure 4.20. Synthesis of 6-butyl-5-nitroquinoline.

4.3.3.3. 6-Butylquinolin-8-Amine (33). As it is stated before, it was aimed to synthesize 6-butylquinolin-8-amine (33) by firstly nitrating 6-butylquinoline and then reducing 6-butyl-8-nitroquinoline. However, after nitration reaction, there was just only one compound which is 6-butylquinolin-8-amine (32). Therefore; in order to synthesize 6-butylquinolin-8-

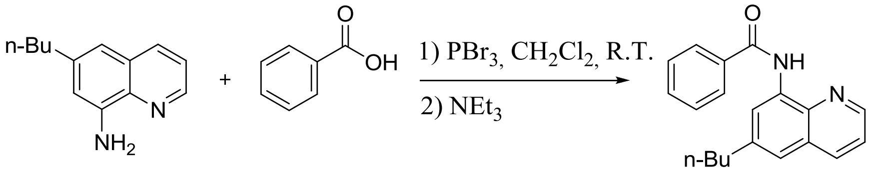
amine (33), a new synthetic pathway was done by Ahmet Köseoğlu –one of our group members [Cited therein Ahmet Köseoğlu Ph.D. proposal seminar]. **^{1}H-NMR** ($CDCl_3$), δ: 0.96 (t, 3H, CH_2CH_3), 1.39 (m, 2H, $CH_2CH_2CH_3$), 1.68 (m, 2H, $CH_2CH_2CH_2$), 2.68 (t, 2H, ArCH_2), 4.49 (s, 2H, NH_2), 6.80 (d, 1H, Ar*H*), 6.95 (s, 1H, Ar*H*), 7.32 (dd, 1H, Ar*H*), 7.98 (dd, 1H, Ar*H*), 8.69 (dd, 1H, Ar*H*) ppm.



33

Figure 4.21. Synthesis of 6-butylquinolin-8-amine.

4.3.3.4. N-(6-Butylquinolin-8-yl)benzamide (34). The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. Benzoic acid (6) (56.1 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 6-butylquinolin-8-amine (33) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (1:2) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.89 (t, 3H, CH_2CH_3), 1.35 (m, 2H, $CH_2CH_2CH_3$), 1.65 (m, 2H, $CH_2CH_2CH_2$), 2.76 (t, 2H, ArCH_2), 7.25 (d, 1H, Ar*H*), 7.36 (dd, 1H, Ar*H*), 7.50 (m, 3H, Ar*H*), 8.01 (d, 1H, Ar*H*), 8.02 (dd, 1H, Ar*H*), 8.04 (d, 1H, Ar*H*), 8.70 (dd, 1H, Ar*H*), 8.78 (d, 1H, Ar*H*), 10.65 (s, 1H, N*H*) ppm. ^{13}**C-NMR** ($CDCl_3$), δ: 13.97 (*C*H_3), 22.48 (*C*H_2), 33.42 (*C*H_2), 36.38 (*C*H_2), 118.03 (Ar*C*), 120.05 (Ar*C*), 121.67 (Ar*C*), 127.28 (2C, Ar*C*), 128.02 (Ar*C*), 128.79 (2C, Ar*C*), 131.80 (Ar*C*), 134.24 (Ar*C*), 135.19 (Ar*C*), 135.79 (Ar*C*), 137.72 (Ar*C*), 142.59 (Ar*C*), 147.39 (Ar*C*), 165.45 (*C*=O) ppm.

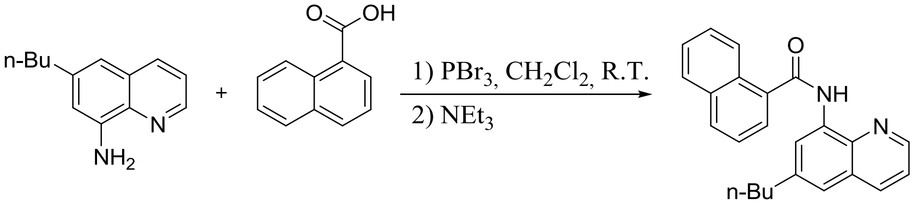


33 **6** **34**

Figure 4.22. Synthesis of N-(6-butylquinolin-8-yl)benzamide.

<u>4.3.3.5. N-(6-Butylquinolin-8-yl)-1-Naphthamide (35).</u> The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 1-naphthoic acid (8) (86.1 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 6-butylquinolin-8-amine (33) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (1:2) as the eluent phase. ^{1}**H-NMR** ($CDCl_3$), δ: 0.92 (t, 3H, CH_2CH_3), 1.39 (m, 2H, $CH_2CH_2CH_3$), 1.73 (m, 2H, $CH_2CH_2CH_2$), 2.81 (t, 2H, $ArCH_2$), 7.29 (d, 1H, Ar*H*), 7.34 (dd, 1H, Ar*H*), 7.51 (m, 3H, Ar*H*), 7.87 (dd, 1H, Ar*H*), 7.85 (t, 1H, Ar*H*), 7.94 (d, 1H, Ar*H*), 8.04 (dd, 1H, Ar*H*), 8.48 (dd, 1H, Ar*H*), 8.60 (dd, 1H, Ar*H*), 8.88 (s, 1H, Ar*H*), 10.32 (s, 1H, N*H*) ppm. ^{13}**C-NMR** ($CDCl_3$), δ: 13.99 (*C*H_3), 22.53 (*C*H_2), 33.46 (*C*H_2), 36.41 (*C*H_2), 118.20 (Ar*C*), 120.25 (Ar*C*), 121.67 (Ar*C*), 124.88 (Ar*C*), 125.51 (Ar*C*), 125.63 (Ar*C*), 126.49 (Ar*C*), 127.25 (Ar*C*), 128.04 (Ar*C*), 128.37 (Ar*C*), 130.35 (Ar*C*), 131.08 (Ar*C*), 133.88 (Ar*C*), 134.51

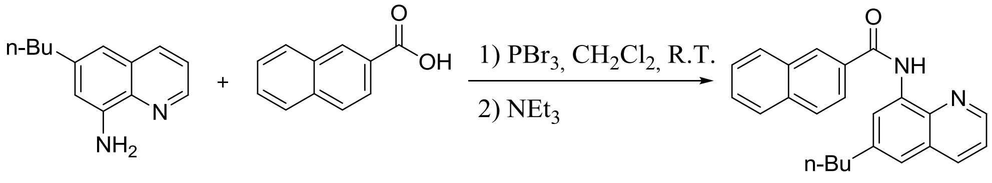
(Ar*C*), 135.74 (Ar*C*), 135.76 (Ar*C*), 137.55 (Ar*C*), 142.60 (Ar*C*), 147.40 (Ar*C*), 167.72 (*C*=O) ppm.



33 **8** **35**

Figure 4.23. Synthesis of N-(6-butylquinolin-8-yl)-1-naphthamide.

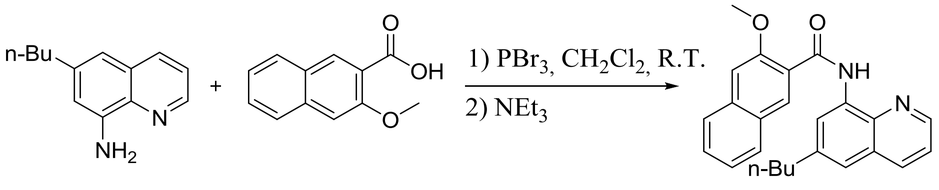
<u>4.3.3.6. N-(6-Butylquinolin-8-yl)-2-Naphthamide (36).</u> The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 2-naphthoic acid (10) (86.1 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 6-butylquinolin-8-amine (33) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (1:2) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.97 (t, 3H, CH_2CH_3), 1.45 (m, 2H, $CH_2CH_2CH_3$), 1.77 (m, 2H, $CH_2CH_2CH_2$), 2.86 (t, 2H, $ArCH_2$), 3,88 (s, 3H, OCH_3), 7.34 (d, 1H, Ar*H*), 7.46 (dd, 1H, Ar*H*), 7.60 (m, 2H, Ar*H*), 7.94 (d, 1H, Ar*H*), 8.00 (d, 1H, Ar*H*), 8.06 (dd, 1H, Ar*H*), 8.14 (m, 2H, Ar*H*), 8.61 (s, 1H, Ar*H*), 8.82 (dd, 1H, Ar*H*), 8.91 (d, 1H, Ar*H*), 10.87 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.98 (CH_3), 22.49 (CH_2), 33.43 (CH_2), 36.41 (CH_2), 118.11 (Ar*C*), 120.09 (Ar*C*), 121.70 (Ar*C*), 123.75 (Ar*C*), 126.80 (Ar*C*), 127.79 (Ar*C*), 127.84 (Ar*C*), 127.92 (Ar*C*), 128.06 (Ar*C*), 128.69 (Ar*C*), 129.23 (Ar*C*), 132.42 (Ar*C*), 132.77 (Ar*C*), 134.32 (Ar*C*), 134.94 (Ar*C*), 135.83 (Ar*C*), 137.77 (Ar*C*), 142.63 (Ar*C*), 147.44 (Ar*C*), 165.52 (*C*=O) ppm.



33 **10** **36**

Figure 4.24. Synthesis of N-(6-butylquinolin-8-yl)-2-naphthamide.

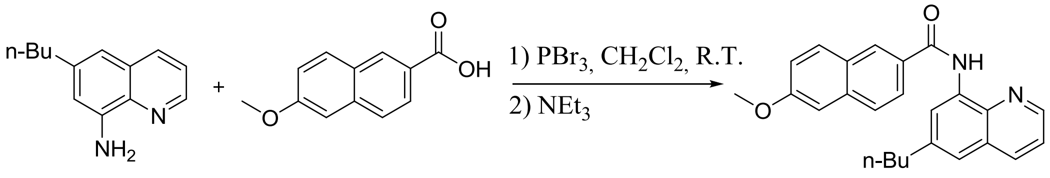
4.3.3.7 N-(6-Butylquinolin-8-yl)-3-Methoxy-2-Naphthamide (37). The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 3-methoxy-2-naphthoic acid (12) (100 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 6-butylquinolin-8-amine (33) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (1:2) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.90 (t, 3H, CH_2CH_3), 1.37 (m, 2H, $CH_2CH_2CH_3$), 1.70 (m, 2H, $CH_2CH_2CH_2$), 2.78 (t, 2H, ArCH_2), 3.90 (s, 3H, OCH_3), 7.13 (d, 1H, Ar*H*), 7.16 (dd, 1H, Ar*H*), 7.26 (d, 1H, Ar*H*), 7.38 (dd, 1H, Ar*H*), 7.80 (d, 1H, Ar*H*), 7.87(d, 1H, Ar*H*), 8.03 (d, 1H, Ar*H*), 8.05 (d, 1H, Ar*H*), 8.46 (d, 1H, Ar*H*), 8.75 (dd, 1H, Ar*H*), 8.83 (d, 1H, Ar*H*), 10.76 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.98 (CH_3), 22.51 (CH_2), 33.43 (CH_2), 36.42 (CH_2), 56.11 (OCH_3), 106.66 (Ar*C*), 119.04 (Ar*C*), 120.04 (Ar*C*), 121.45 (Ar*C*), 123.34 (Ar*C*), 124.52 (Ar*C*), 126.22 (Ar*C*), 128.12 (Ar*C*), 128.37 (2C, Ar*C*), 129.31 (Ar*C*), 134.11 (Ar*C*), 135.34 (Ar*C*), 135.69 (Ar*C*), 135.94 (Ar*C*), 138.28 (Ar*C*), 142.66 (Ar*C*), 147.42 (Ar*C*), 154.98 (Ar*C*), 163.47 (*C*=O) ppm.



33 **12** **37**

Figure 4.25. Synthesis of N-(6-butylquinolin-8-yl)-3-methoxy-2-naphthamide.

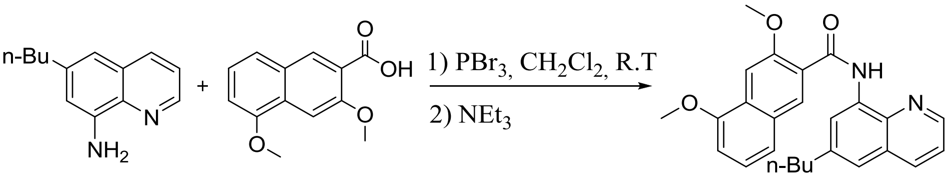
4.3.3.8. N-(6-Butylquinolin-8-yl)-6-Methoxy-2-Naphthamide (38). The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 6-methoxy-2-naphthoic acid (14) (100 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 6-butylquinolin-8-amine (33) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (1:2) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.91 (t, 3H, CH_2CH_3), 1.37 (m, 2H, $CH_2CH_2CH_3$), 1.68 (m, 2H, $CH_2CH_2CH_2$), 2.80 (t, 2H, ArCH_2), 3,88 (s, 3H, OCH_3), 7.16 (s, 1H, Ar*H*), 7.19 (s, 1H, Ar*H*), 7.44 (d, 1H, Ar*H*), 7.52 (t, 1H, Ar*H*), 7.81 (s, 1H, Ar*H*), 7.84 (d, 1H, Ar*H*), 7.89 (s, 1H, Ar*H*), 8.06 (d, 1H, Ar*H*), 8.47 (s, 1H, Ar*H*), 8.68 (s, 1H, Ar*H*), 8.85 (d, 1H, Ar*H*), 10.80 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.98 (CH_3), 22.49 (CH_2), 33.43 (CH_2), 36.41 (CH_2), 55.41 (OCH_3), 105.69 (Ar*C*), 118.03 (Ar*C*), 119.77 (Ar*C*), 119.94 (Ar*C*), 121.66 (Ar*C*), 124.38 (Ar*C*), 127.36 (Ar*C*), 127.78 (Ar*C*), 128.05 (Ar*C*), 128.17 (Ar*C*), 130.18 (Ar*C*), 130.77 (Ar*C*), 134.40 (Ar*C*), 135.82 (Ar*C*), 136.50 (Ar*C*), 137.74 (Ar*C*), 142.64 (Ar*C*), 147.39 (Ar*C*), 159.24 (Ar*C*), 165.56 (*C*=O) ppm.



33 **14** **38**

Figure 4.26. Synthesis of N-(6-butylquinolin-8-yl)-6-methoxy-2-naphthamide.

4.3.3.9. N-(6-Butylquinolin-8-yl)-3-5-Dimethoxy-2-Naphthamide (39). The coupling reaction was done according to the literature procedure [47]. The experiment was done under nitrogen by using dry CH_2Cl_2. 3-5-dimethoxy-2-naphthoic acid (16) (116 mg, 0.5 mmol) was dissolved in 3 mL dry CH_2Cl_2 under N_2. To this solution, PBr_3 (0.07 mL, 0.75 mmol) was added at 0°C and the reaction mixture was mixed for 3 hours at room temperature. After 3 hours, triethyl amine (0.21 mL, 1.5 mmol) was added at that time fume occurred because of neutralizing of HBr. 6-butylquinolin-8-amine (33) (100 mg, 0.5 mmol) was dissolved in 2 mL dry CH_2Cl_2 and it was added to the reaction mixture. Reaction mixture was mixed for 1 hour. 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 CH_2Cl_2 and Hexane (2:1) as the eluent phase. **^{1}H-NMR** ($CDCl_3$), δ: 0.97 (t, 3H, CH_2CH_3), 1.44 (m, 2H, $CH_2CH_2CH_3$), 1.77 (m, 2H, $CH_2CH_2CH_2$), 2.85 (t, 2H, ArCH_2), 4.04 (s, 3H, OCH_3), 4.32 (s, 3H, OCH_3), 6.88 (d, 1H, Ar*H*), 7.31 (d, 1H, Ar*H*), 7.33 (d, 1H, Ar*H*), 7.43 (dd, 1H, Ar*H*), 7.55 (d, 1H, Ar*H*), 7.72 (s, 1H, Ar*H*), 8.11 (dd, 1H, Ar*H*), 8.83 (dd, 1H, Ar*H*), 8.87 (s, 1H, Ar*H*), 9.00 (d, 1H, Ar*H*), 12.48 (s, 1H, N*H*) ppm. **^{13}C-NMR** ($CDCl_3$), δ: 13.99 (CH_3), 20.51 (CH_2), 33.42 (CH_2), 36.42 (CH_2), 55.56 (OCH_3), 56.18 (OCH_3), 101.48 (Ar*C*), 105.90 (Ar*C*), 119.04 (Ar*C*), 120.02 (Ar*C*), 121.44 (2C, Ar*C*), 123.49 (Ar*C*), 124.36 (Ar*C*), 127.95 (Ar*C*), 128.11 (Ar*C*), 129.27 (Ar*C*), 133.63 (Ar*C*), 135.37 (Ar*C*), 135.66 (Ar*C*), 138.28 (Ar*C*), 142.65 (Ar*C*), 147.42 (Ar*C*), 154.11 (Ar*C*), 154.75 (Ar*C*), 163.52 (*C*=O) ppm.



33 **16** **39**

Figure 4.27. Synthesis of N-(6-butylquinolin-8-yl)-3,5- dimethoxy-2-naphthamide.

5. FUTURE WORK

As a future work, it is aimed to perform *in vitro* tests (percent inhibition test at 2μM) of the synthesized drug candidates on mammalian cells to check whether they are biologically active or not. According to these results, new derivatives of quinoline compounds may be generated. The potential drug molecules will be tested to find their IC_{50} value (half maximal inhibitory concentration). The IC_{50} value of the lead molecule is 35μM; therefore, it is aimed to decrease the value to nM level. Moreover, the elemental and LC-MS (Liquid chromatography–Mass spectrometry) analyses of the synthesized drug candidates will be performed.

6. CONCLUSION

In this study; in order to increase the efficacy of the lead molecule, necessary modifications were performed. Left hand side was determined as naphthalene derivatives and right hand side of the molecule was thought as a nitrogen bearing heterocycle which has good interactions with the active site of the enzyme, namely quinolines.

Docking and binding energies were calculated by using Autodock software and the results have shown that quinoline derivatives have better docking and binding energies than the lead molecule. In this respect, initially 3-butylquinolin-8-amine (5), 4-butylquinolin-8-amine (22) and 6-butylquinolin-8-amine (33) were successfully synthesized. In order to verify those compounds, 2D NMR (COSY and NOESY) experiments were performed. Afterwards, those quinoline derivatives were coupled with benzoic acid (6), 1-naphthoic acid (8), 2-naphthoic acid (10), 3-methoxy-2-naphthoic acid (12), 6-methoxy-2-naphthoic acid (14) and 3,5-dimethoxy-2-naphthoic acid (16), respectively. The characterization of those synthesized potential drug candidates were again proved by performing ^{1}H-NMR, ^{13}C-NMR experiments.

During the synthesis, some results were very remarkable. For example, in order to synthesize 6-butylquinolin-8-amine (33), it was firstly aimed to nitrate 6-butylquinoline (31) to obtain both 6-butyl-8-nitroquinoline and 6-butyl-5-nitroquinoline (32). Secondly, by reducing the 6-butyl-8-nitroquinoline, it was expected to synthesize compound 33; however, ^{1}H-NMR and COSY NMR results indicated that only 6-butyl-5-nitroquinoline (32) was synthesized. In order to synthesize 6-butylquinolin-8-amine, many experiments were done but then a new synthetic pathway [Cited therein Ahmet Koseoglu Ph.D. proposal seminar] was performed to synthesize 6-butylquinolin-8-amine (33).

All in all, those 3-butyl, 4-butyl and 6-butylquinoline derivatives were successfully synthesized and purified. In order to test the biological activity of potential drug candidates, those compounds were sent to Koc University.

APPENDIX A: SPECTROSCOPY DATA

1D NMR (^{1}H, ^{13}C NMR) and 2D NMR (COSY, NOESY) spectroscopy of the synthesized products are included. Necessary expansions were made on the NMR data.

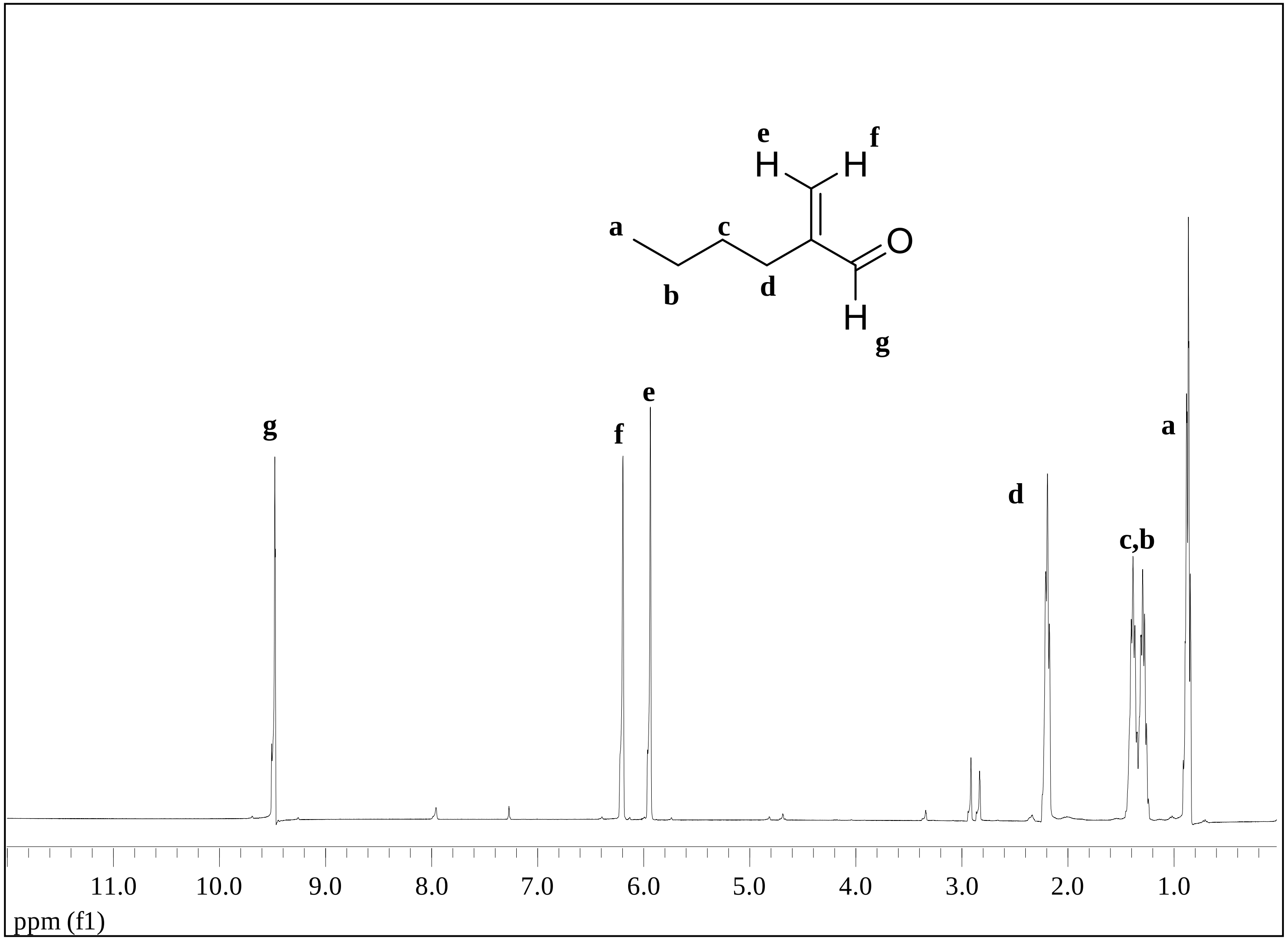


Figure A.1. ^{1}H-NMR Spectrum of 2-methylenehexanal.

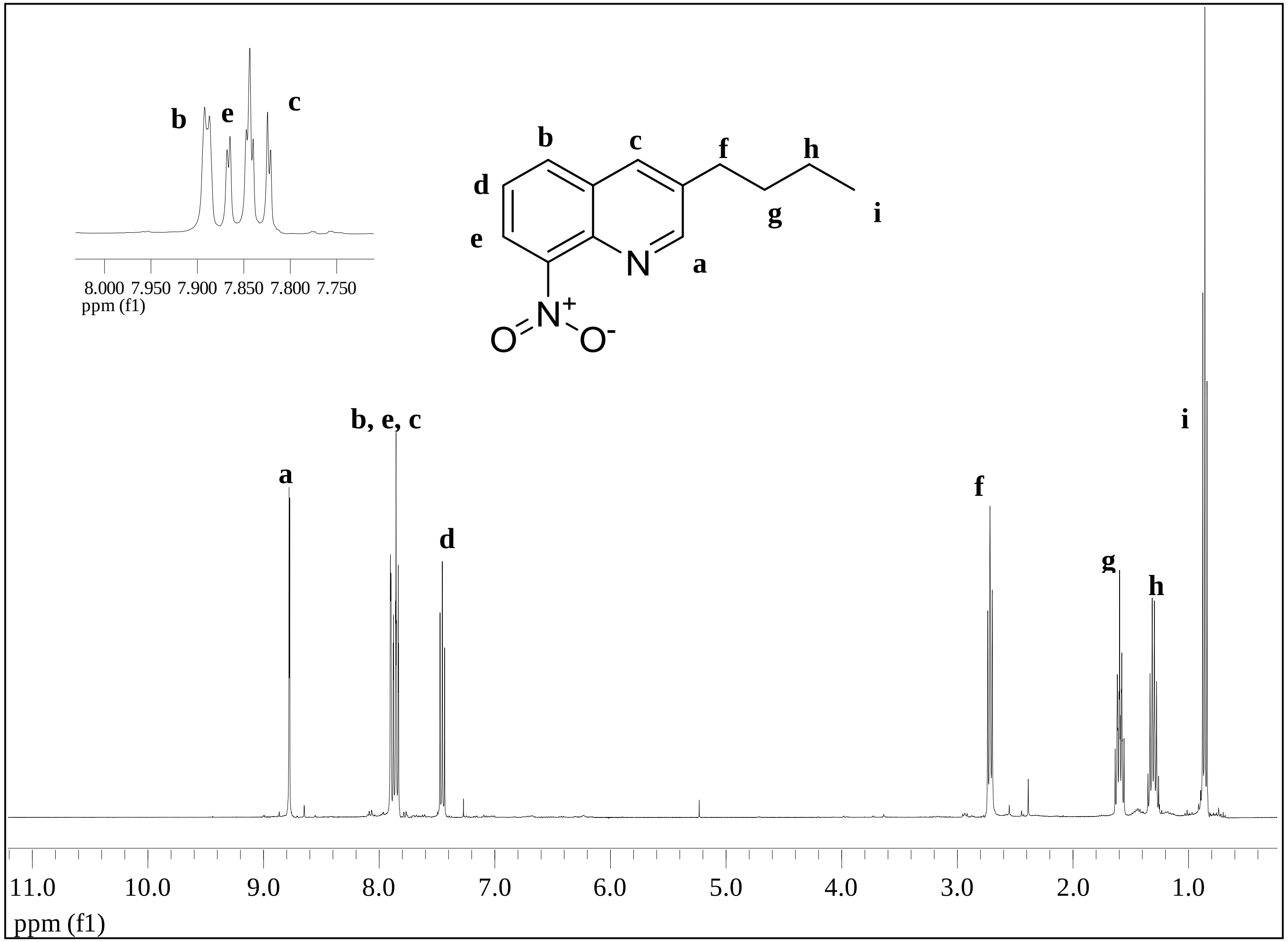


Figure A.2. ^{1}H-NMR Spectrum of 3-butyl-8-nitroquinoline.

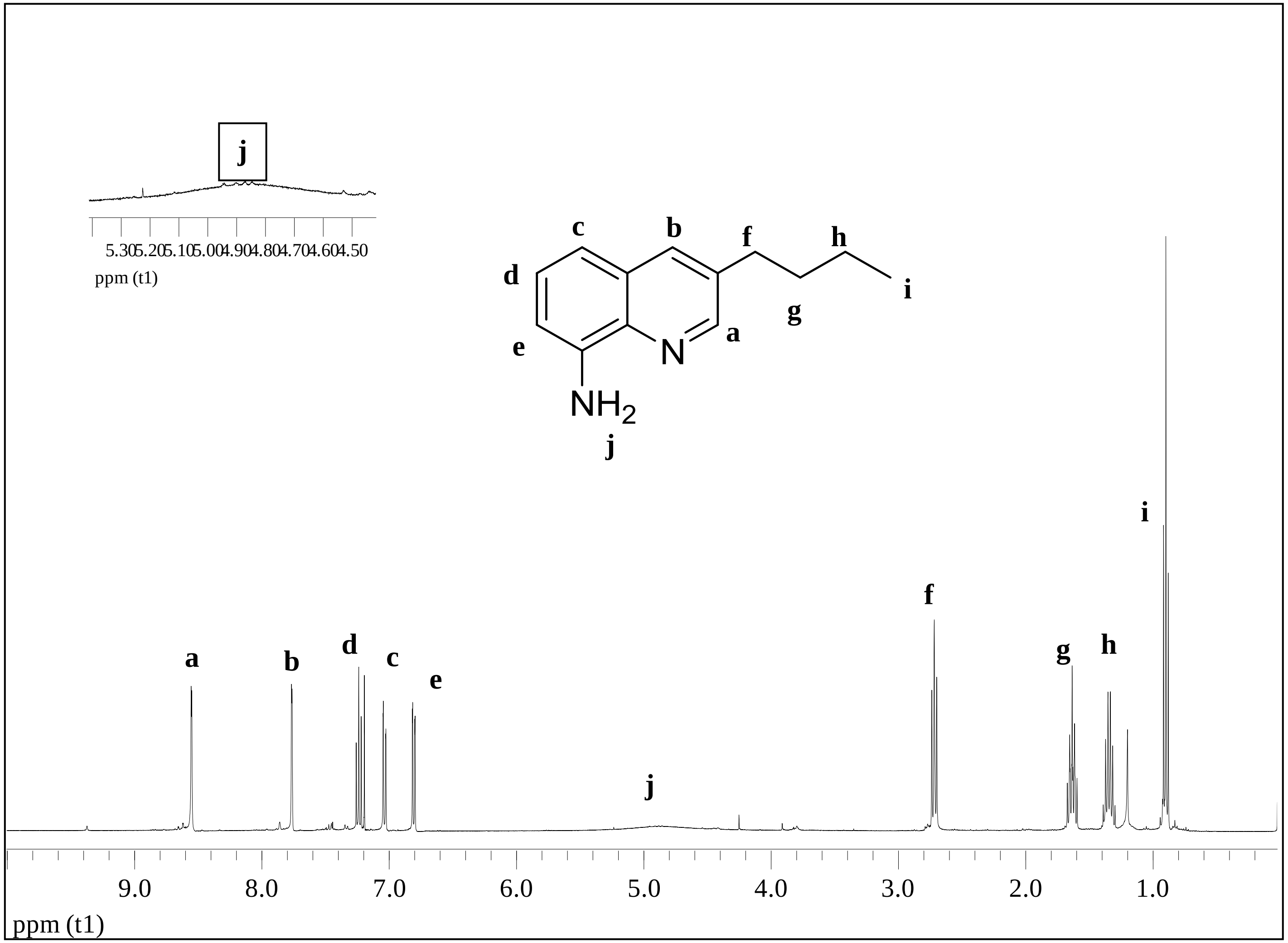


Figure A.3. ^{1}H-NMR Spectrum of 3-butylquinolin-8-amine.

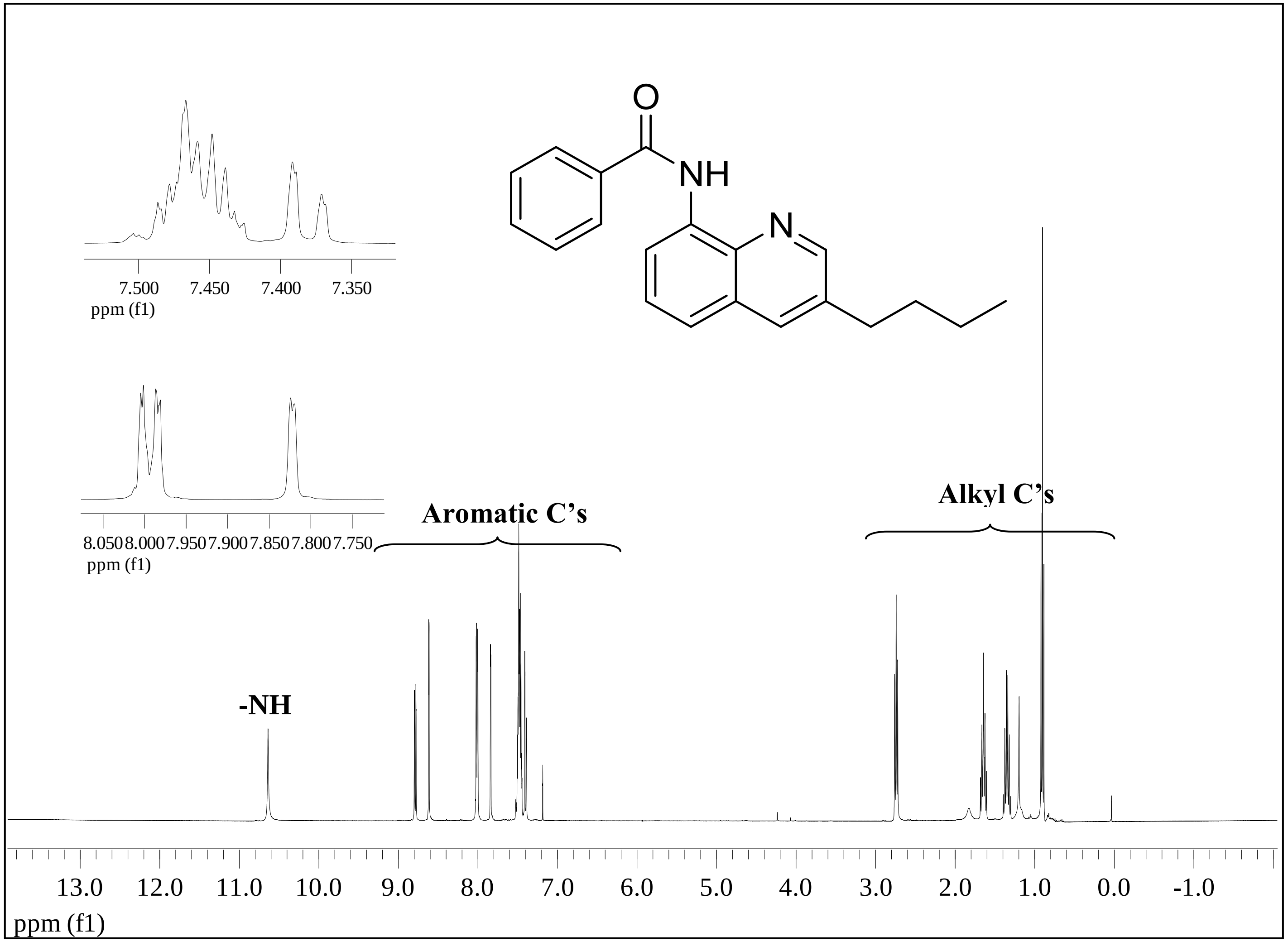


Figure A.4. ^{1}H-NMR Spectrum of N-(3-butylquinolin-8-yl)benzamide.

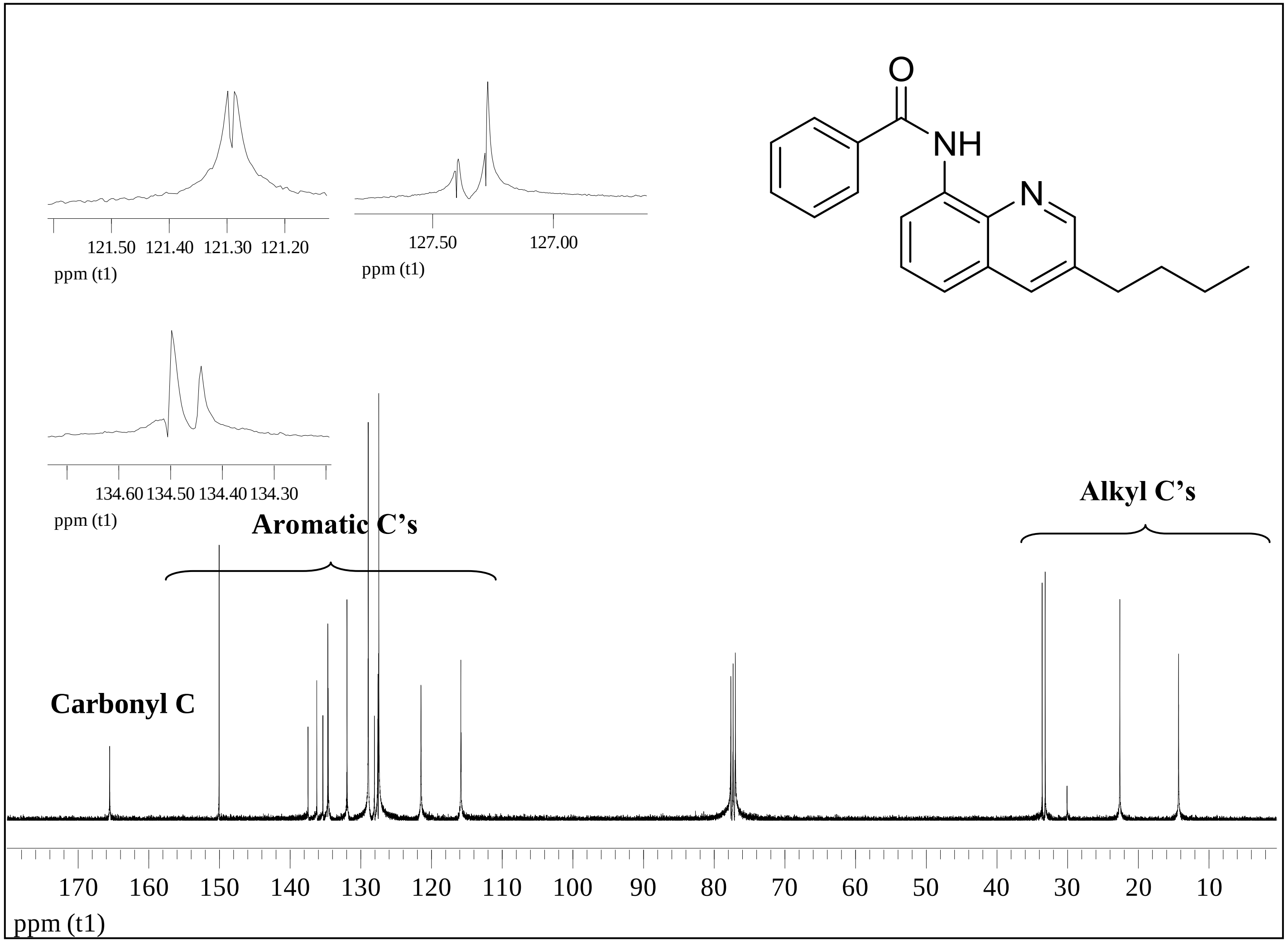


Figure A.5. ^{13}C-NMR Spectrum of N-(3-butylquinolin-8-yl)benzamide.

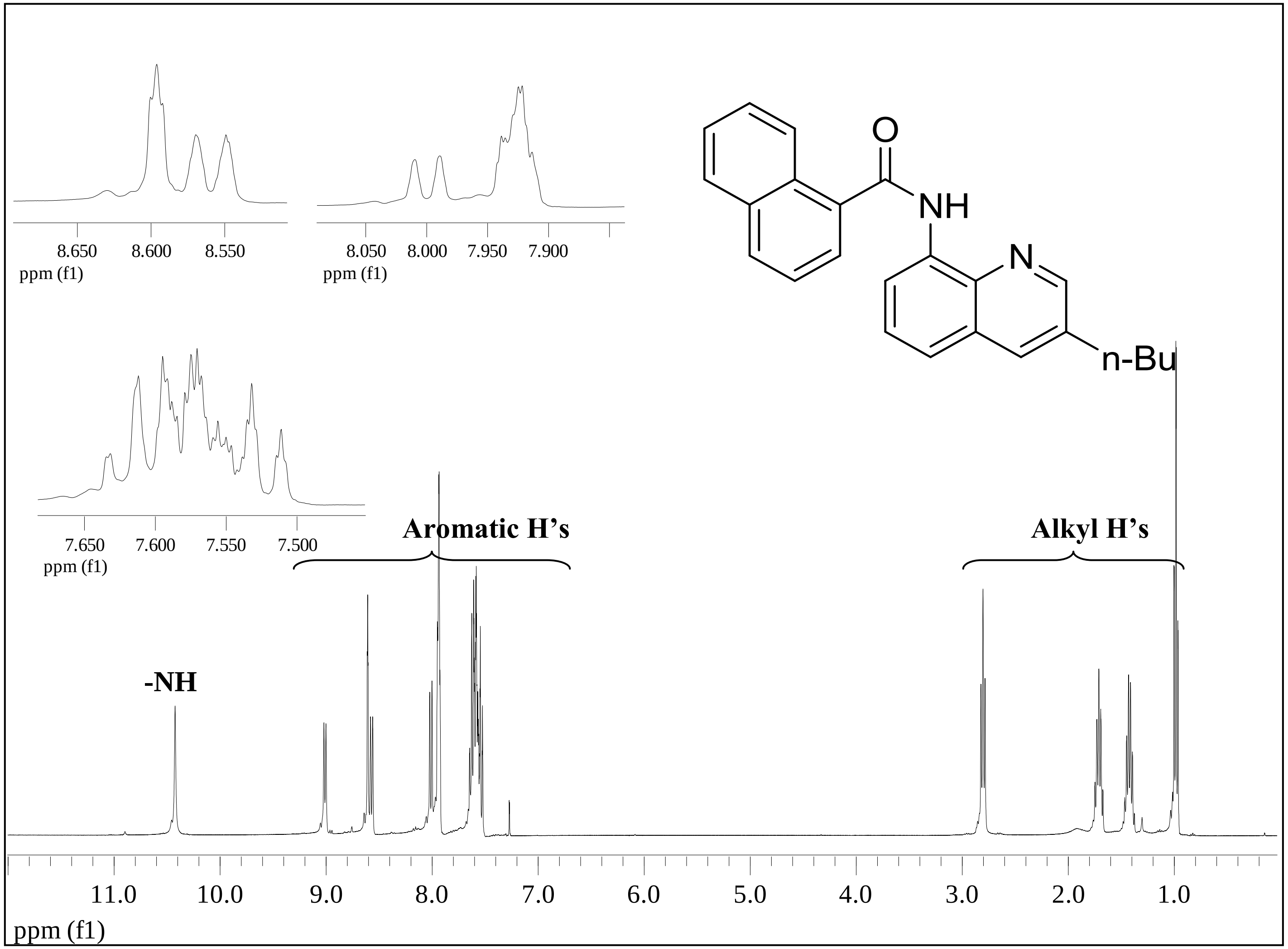


Figure A.6. ^{1}H-NMR Spectrum of N-(3-butylquinolin-8-yl)-1-naphthamide.

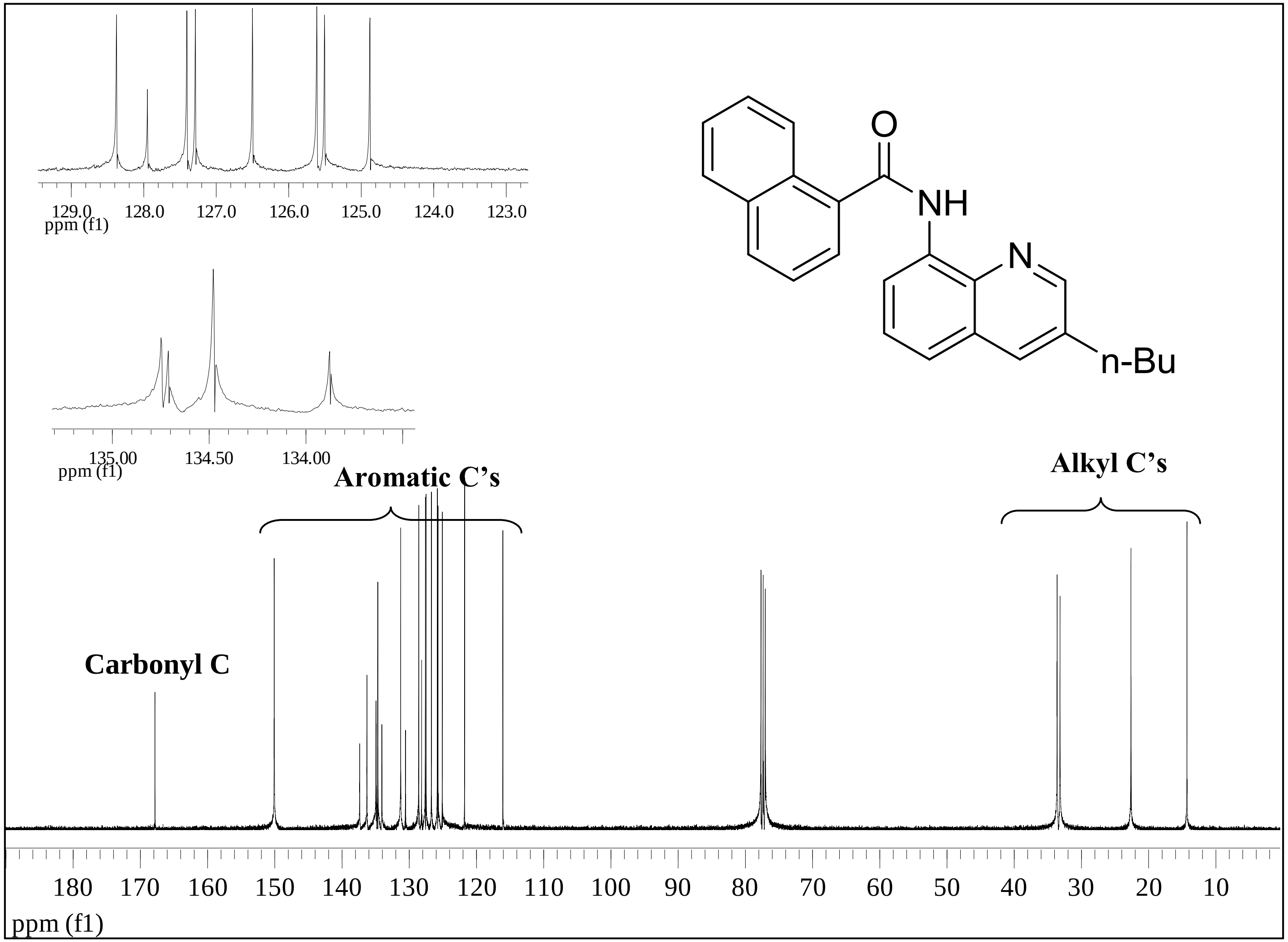


Figure A.7. ^{13}C-NMR Spectrum of N-(3-butylquinolin-8-yl)-1-naphthamide.

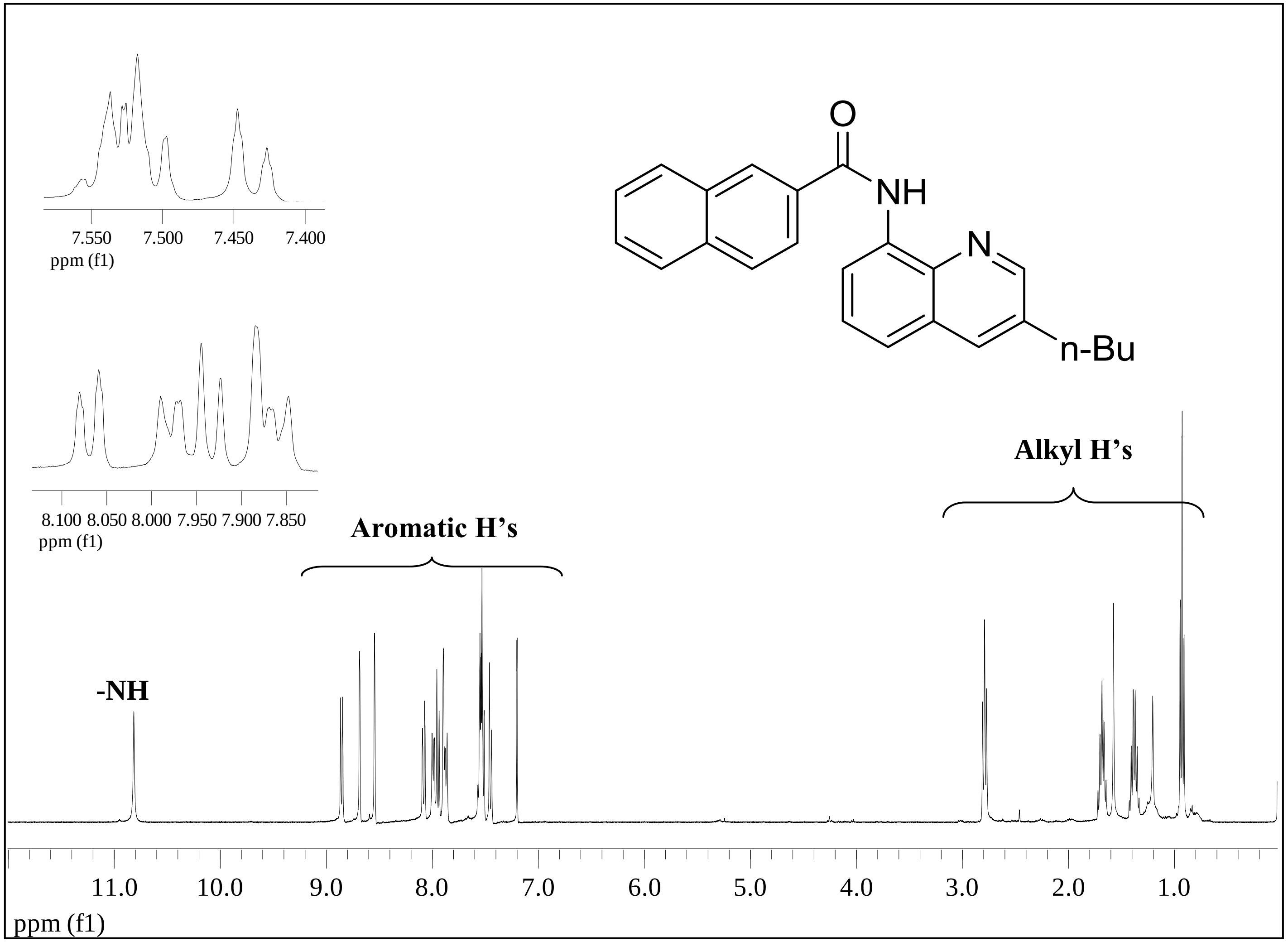


Figure A.8. ^{1}H-NMR Spectrum of N-(3-butylquinolin-8-yl)-2-naphthamide.

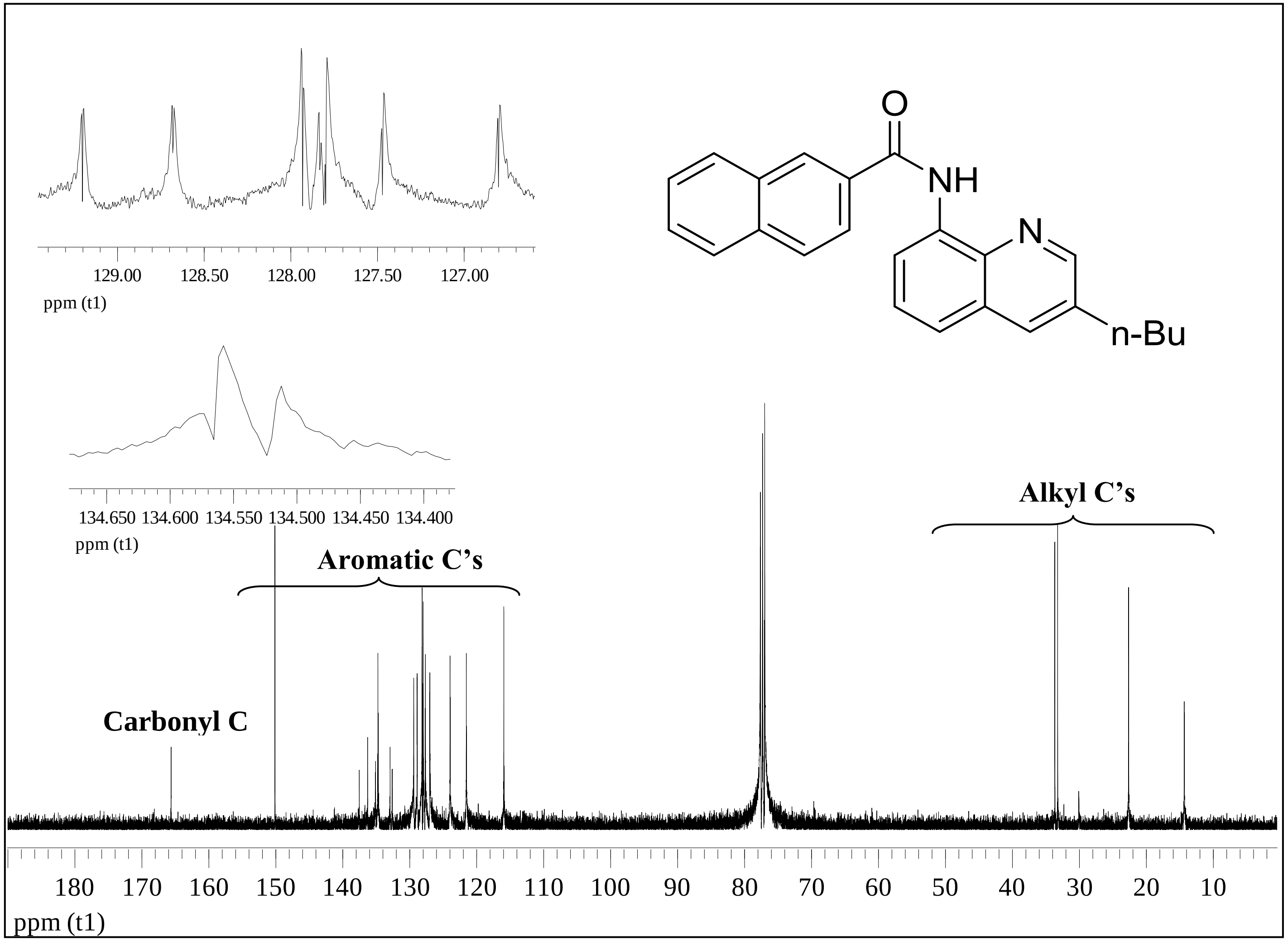


Figure A.9. ^{13}C-NMR Spectrum of N-(3-butylquinolin-8-yl)-2-naphthamide.

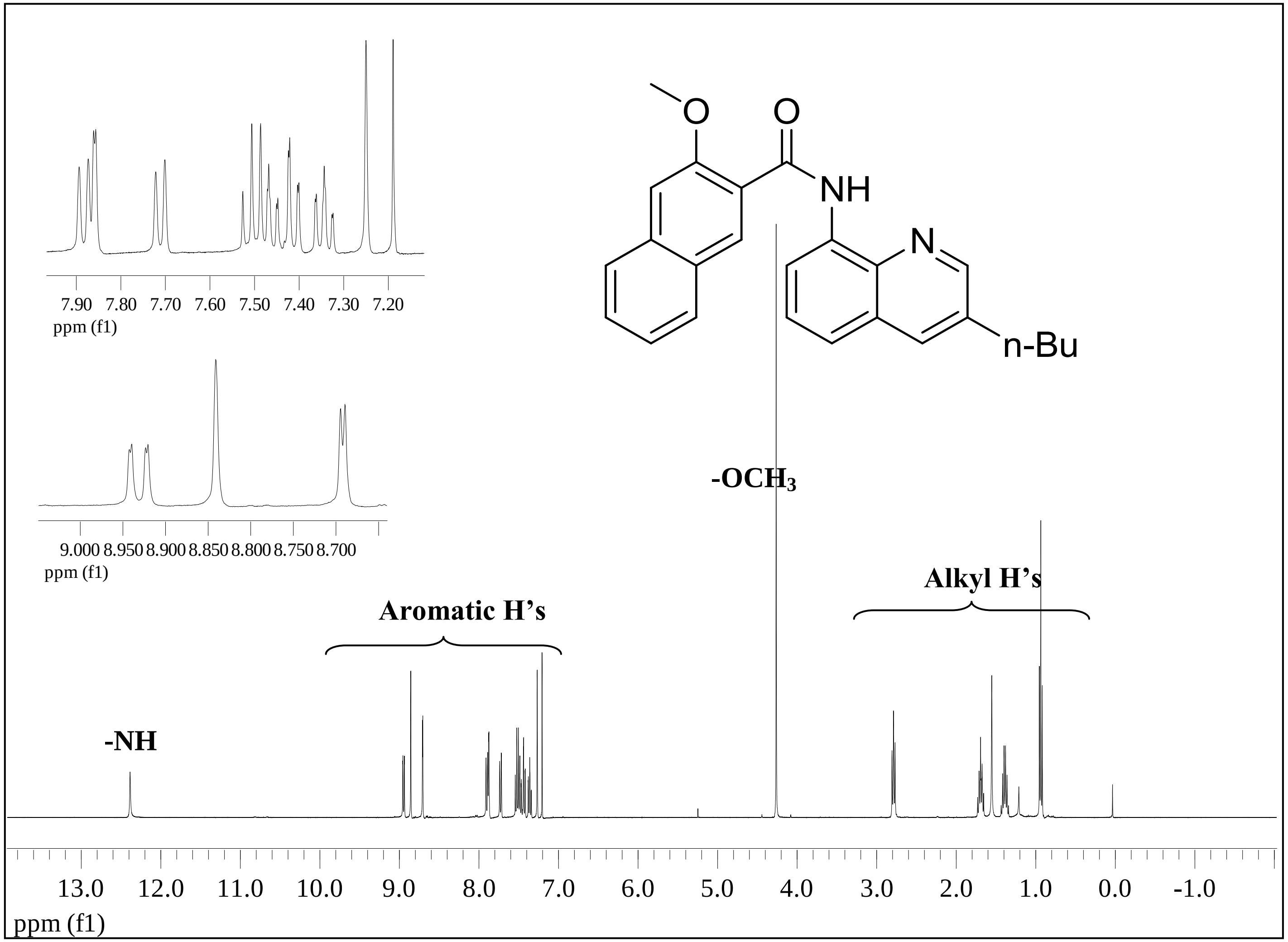


Figure A.10. ^{1}H-NMR Spectrum of N-(3-butylquinolin-8-yl)-3-methoxy-2-naphthamide.

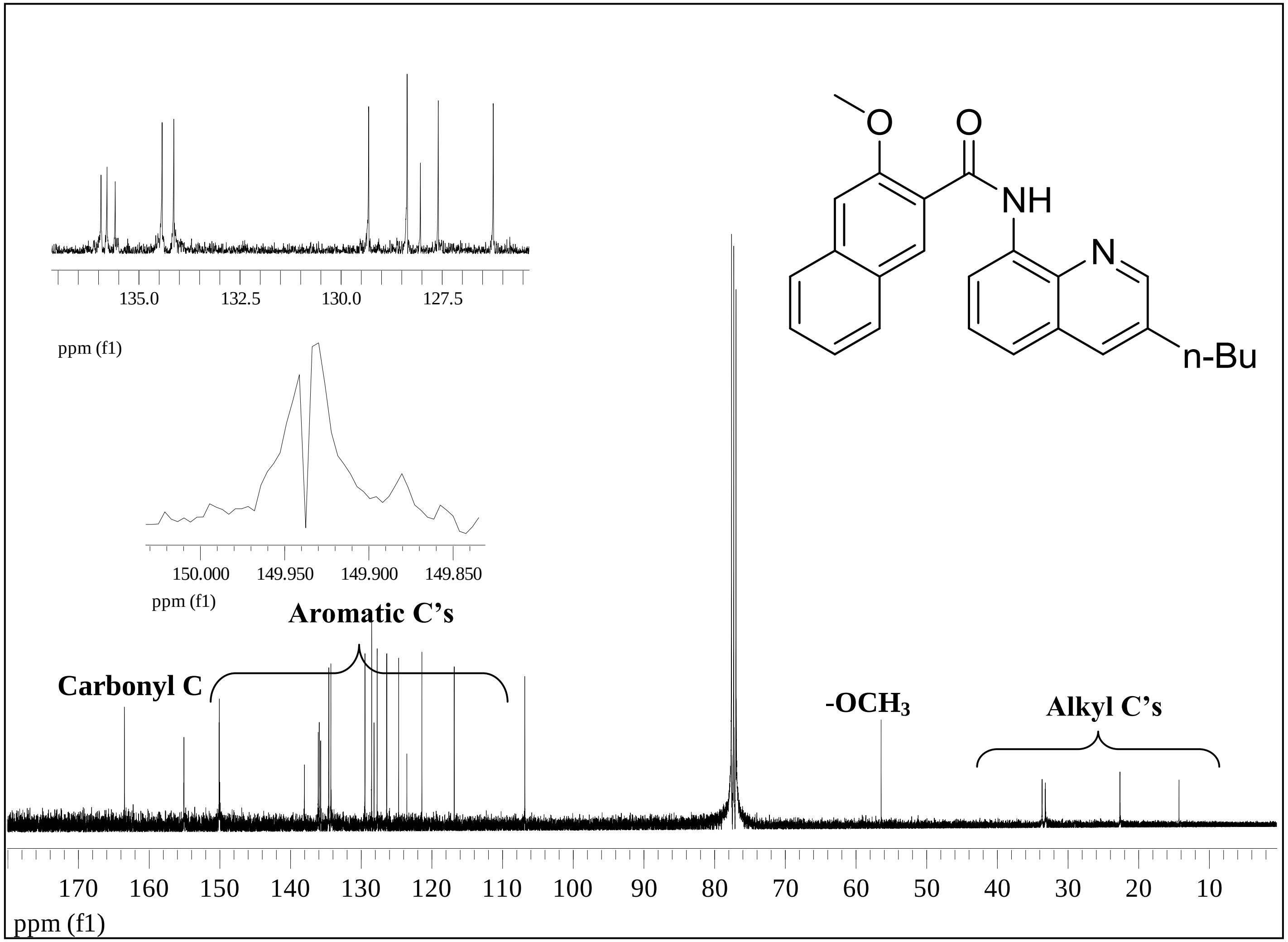


Figure A.11. ^{13}C-NMR Spectrum of N-(3-butylquinolin-8-yl)-3-methoxy-2-naphthamide.

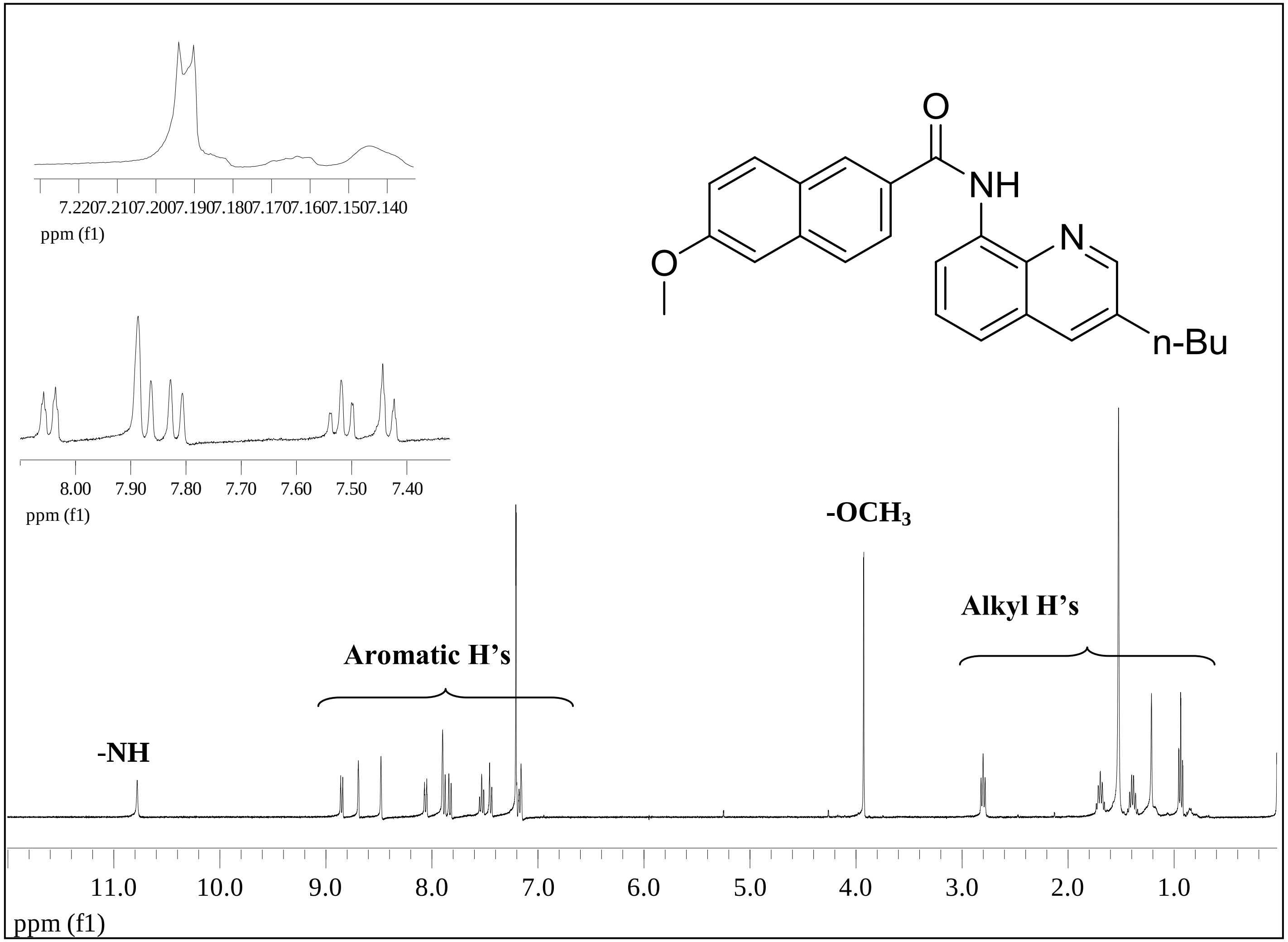


Figure A.12. ^{1}H-NMR Spectrum of N-(3-butylquinolin-8-yl)-6-methoxy-2-naphthamide.

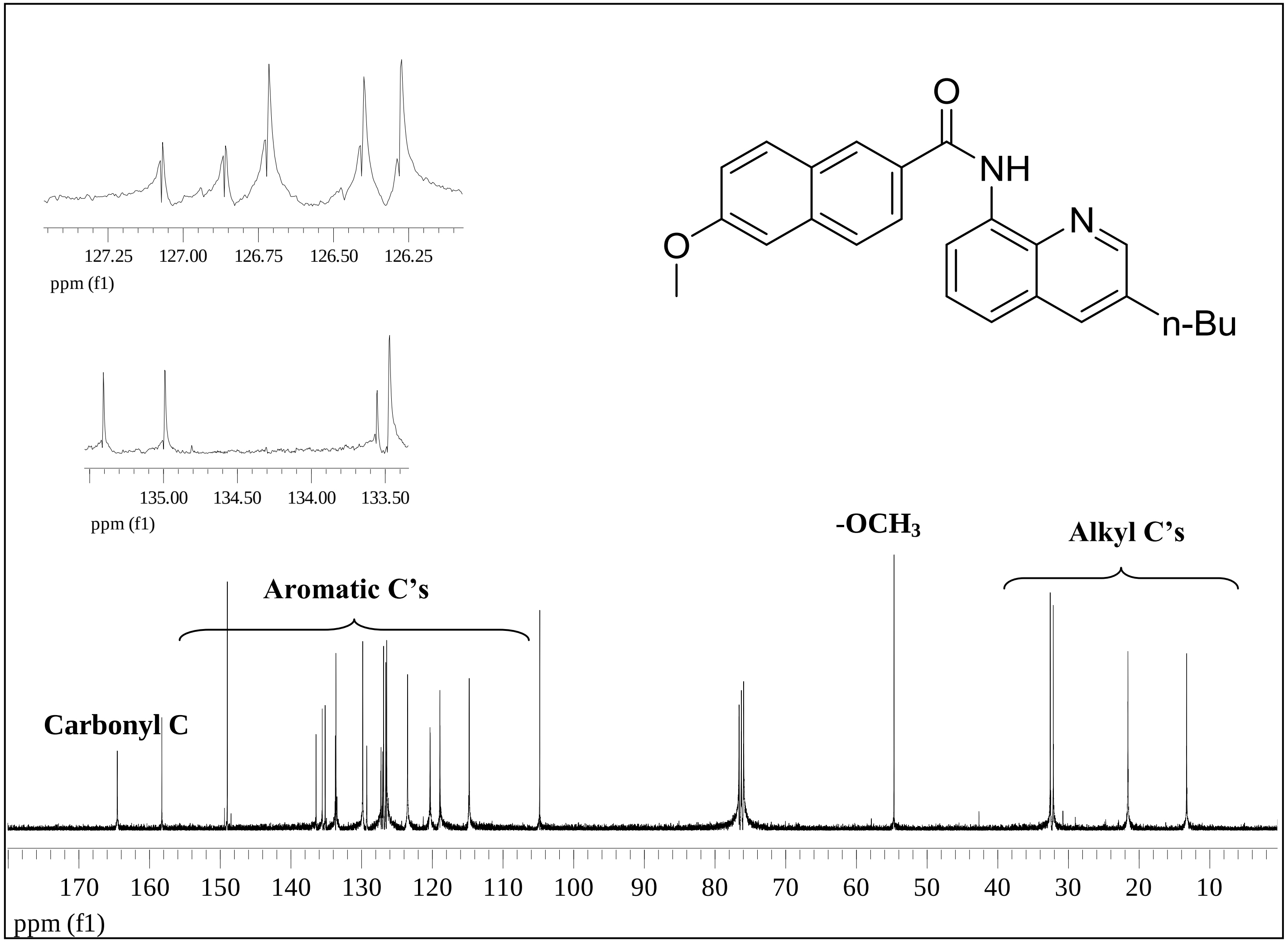


Figure A.13. ^{13}C-NMR Spectrum of N-(3-butylquinolin-8-yl)-6-methoxy-2-naphthamide.

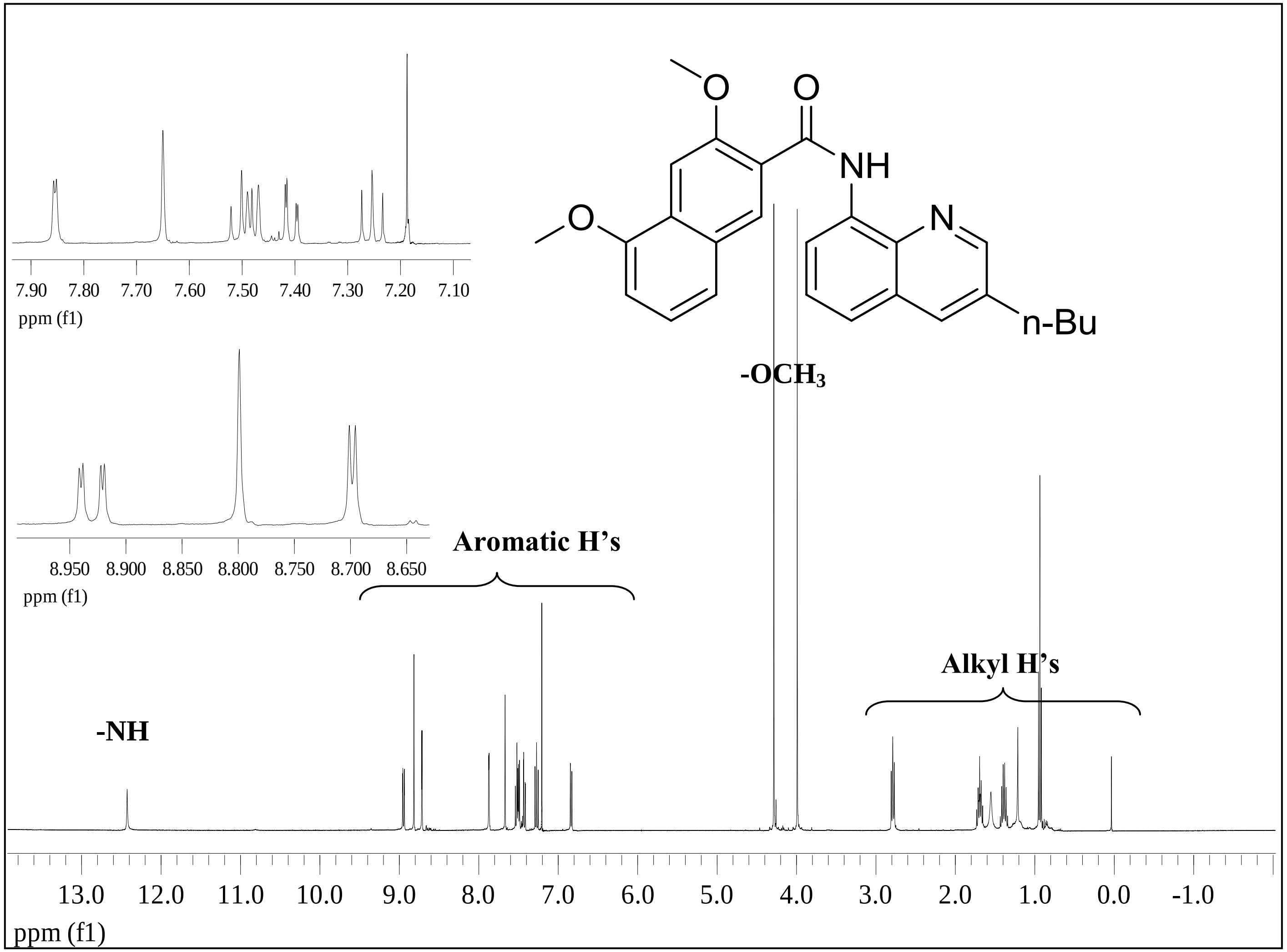


Figure A.14. ^{1}H-NMR Spectrum of N-(3-butylquinolin-8-yl)-3,5-dimethoxy-2-naphthamide.

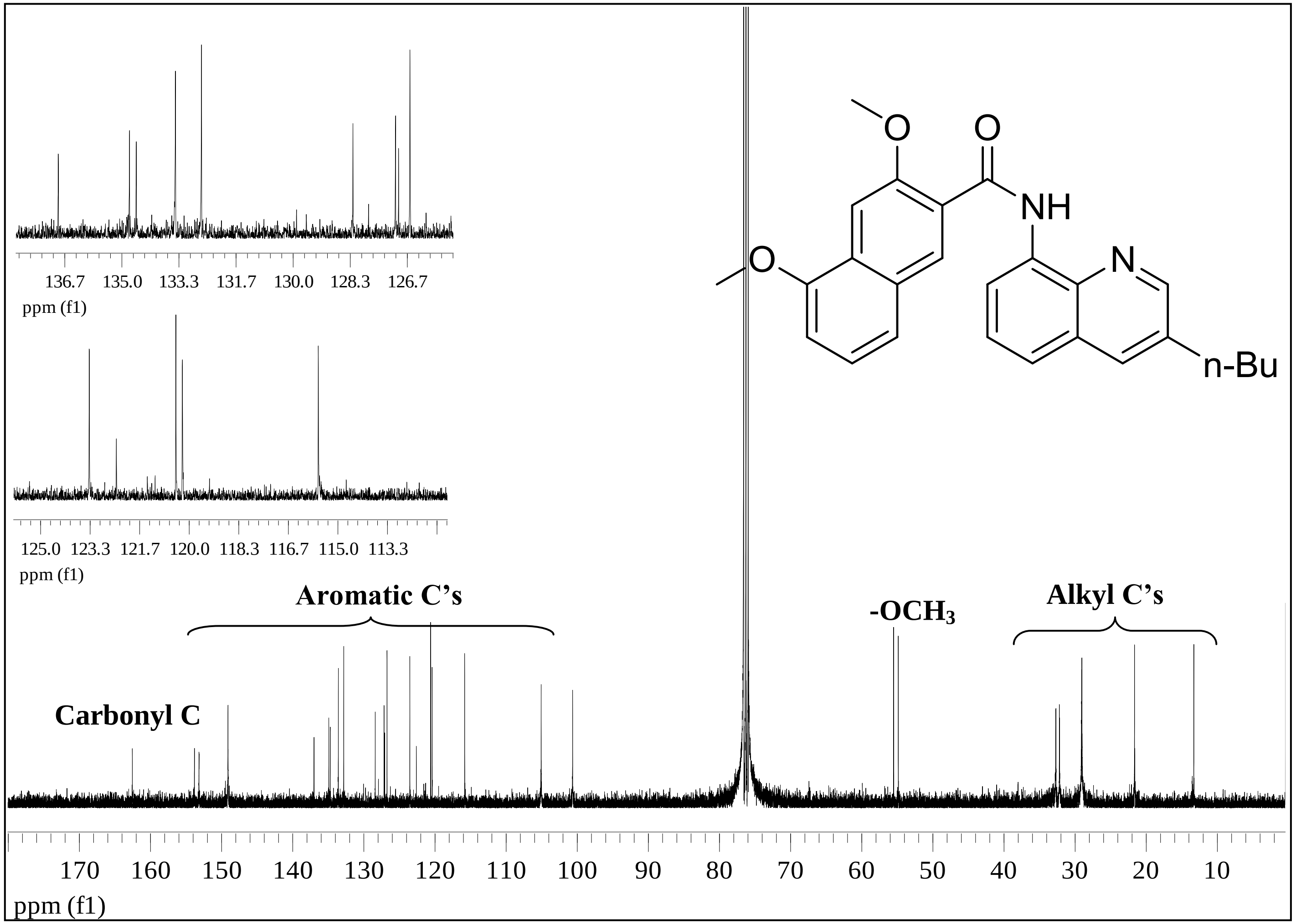


Figure A.15. ^{13}C-NMR Spectrum of N-(3-butylquinolin-8-yl)-3,5-dimethoxy-2-naphthamide.

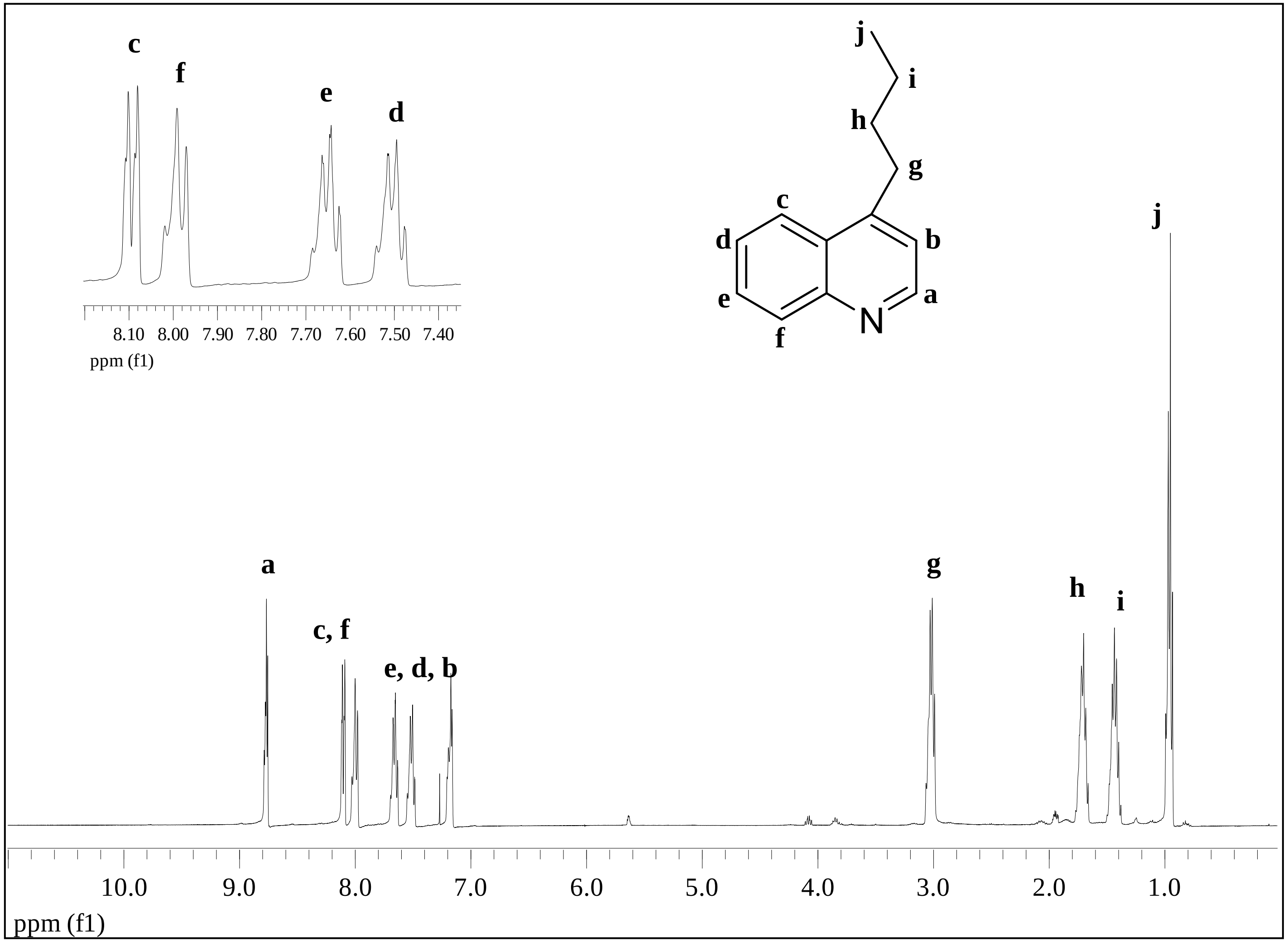


Figure A.16. ^{1}H-NMR Spectrum of 4-butylquinoline.

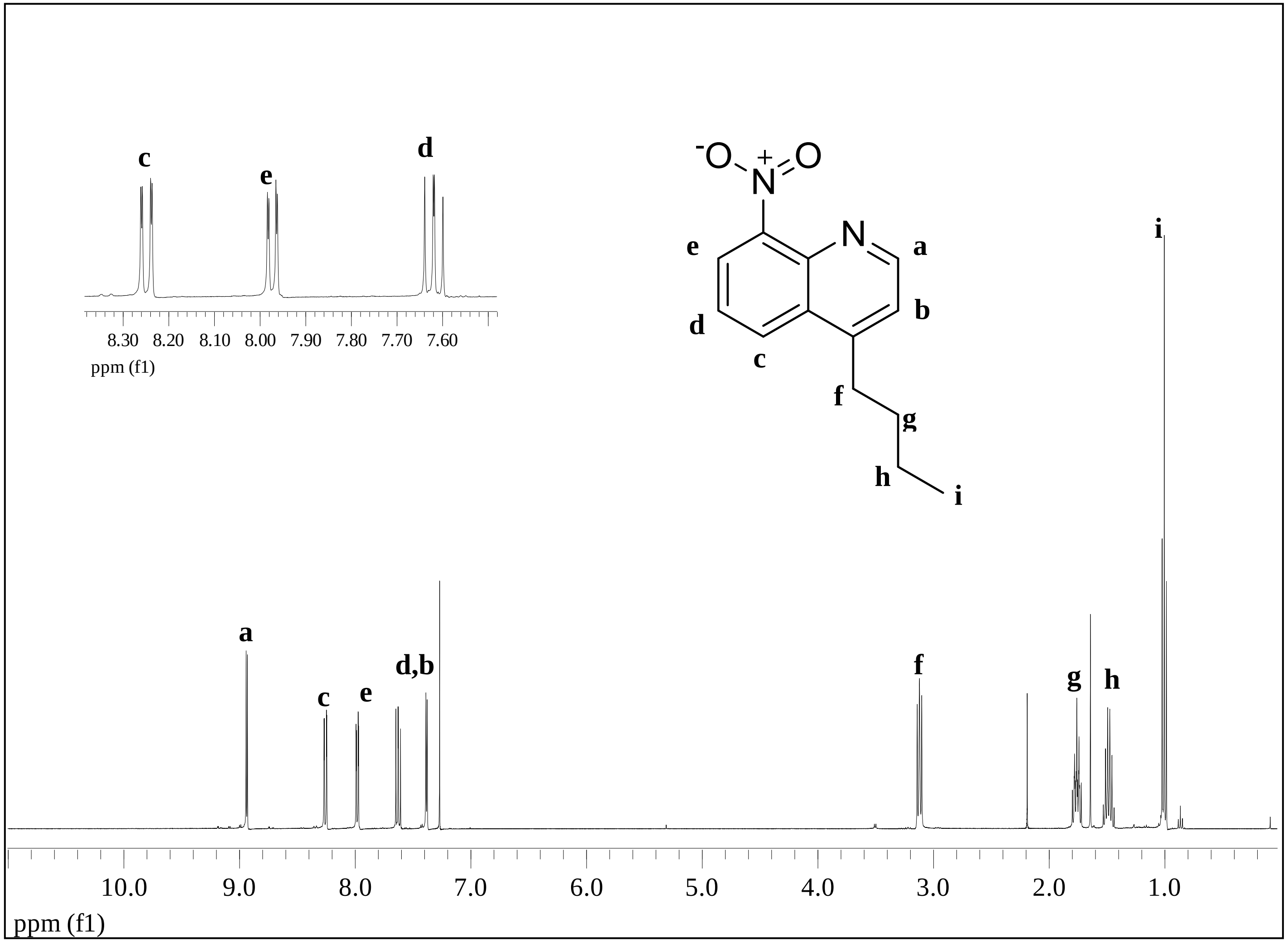


Figure A.17. ^{1}H-NMR Spectrum of 4-butyl-8-nitroquinoline.

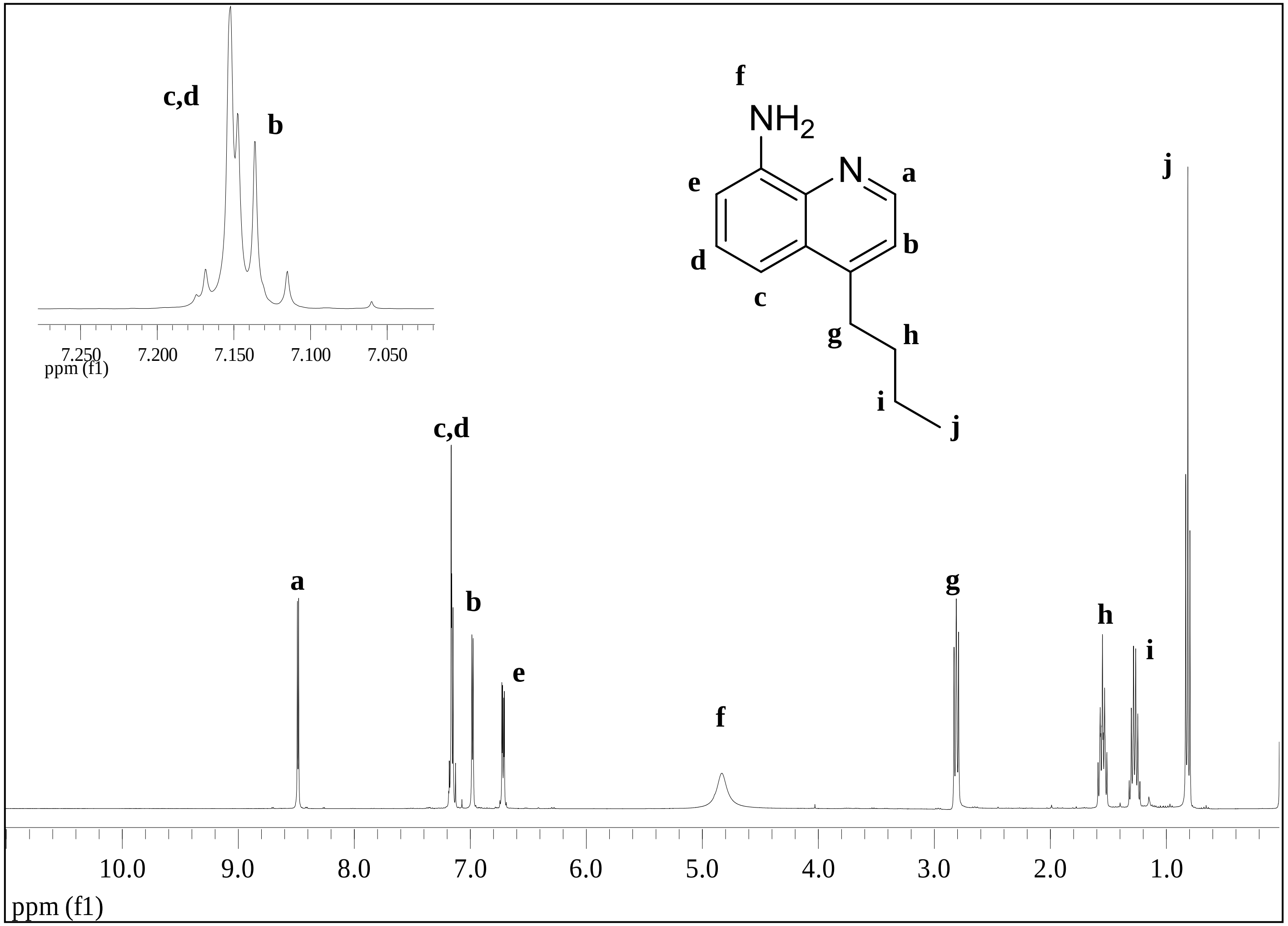
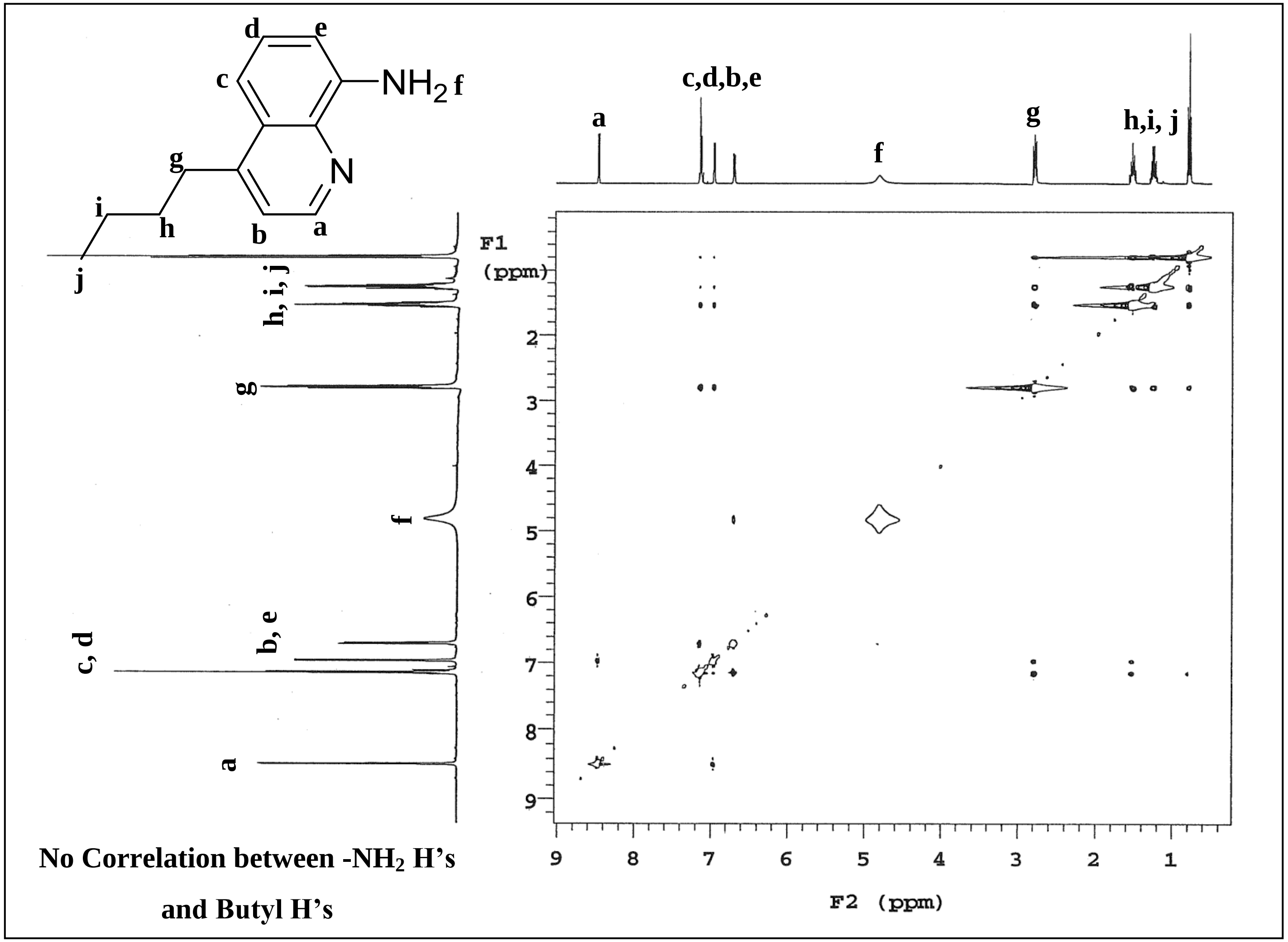


Figure A.18. ^{1}H-NMR Spectrum of 4-butylquinolin-8-amine.



No Correlation between $-NH_2$ H's and Butyl H's

Figure A.19. 2D-NMR Spectrum (NOESY) of 4-butylquinolin-8-amine.

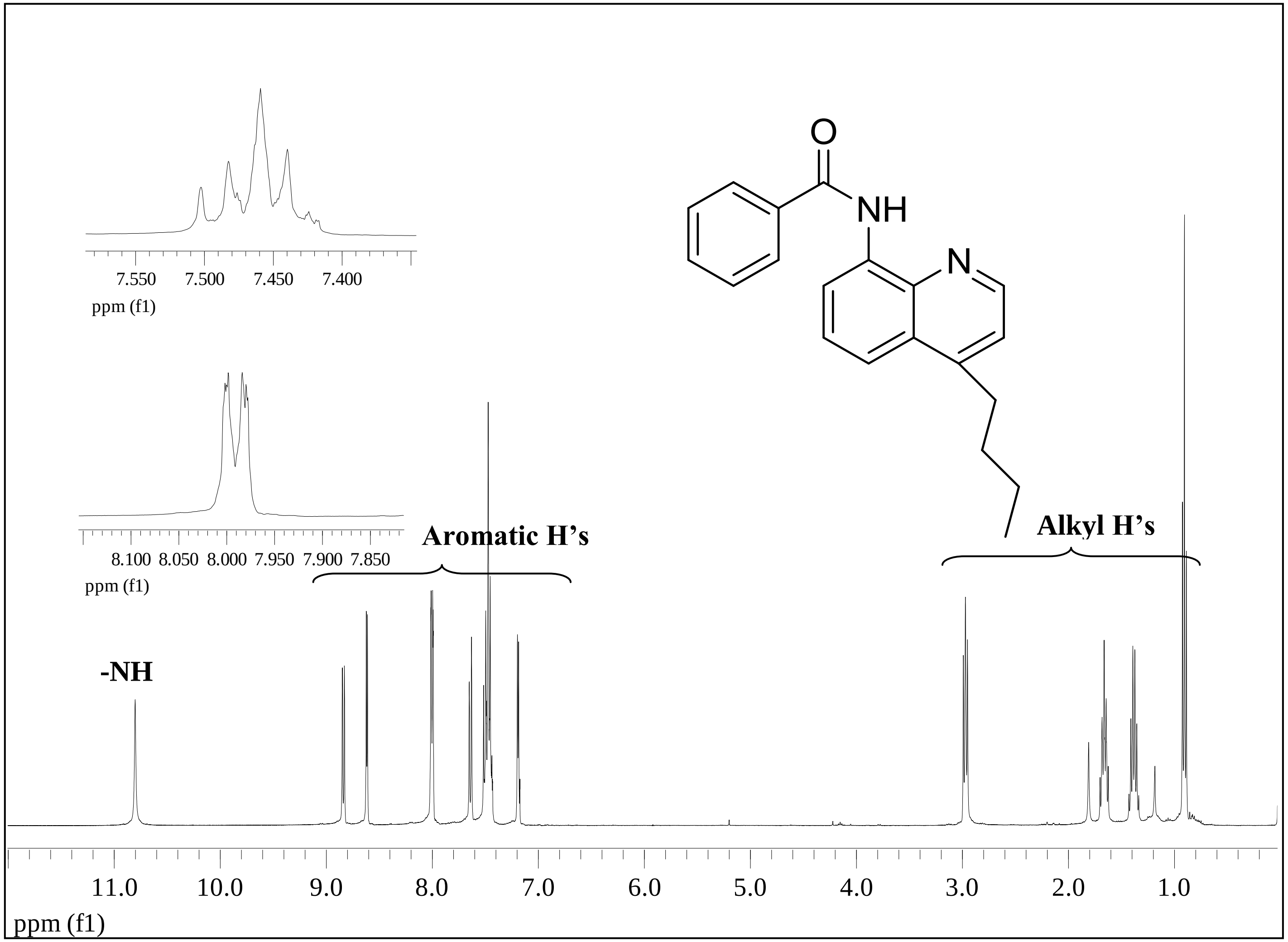


Figure A.20. ^{1}H-NMR Spectrum of N-(4-butylquinolin-8-yl)benzamide.

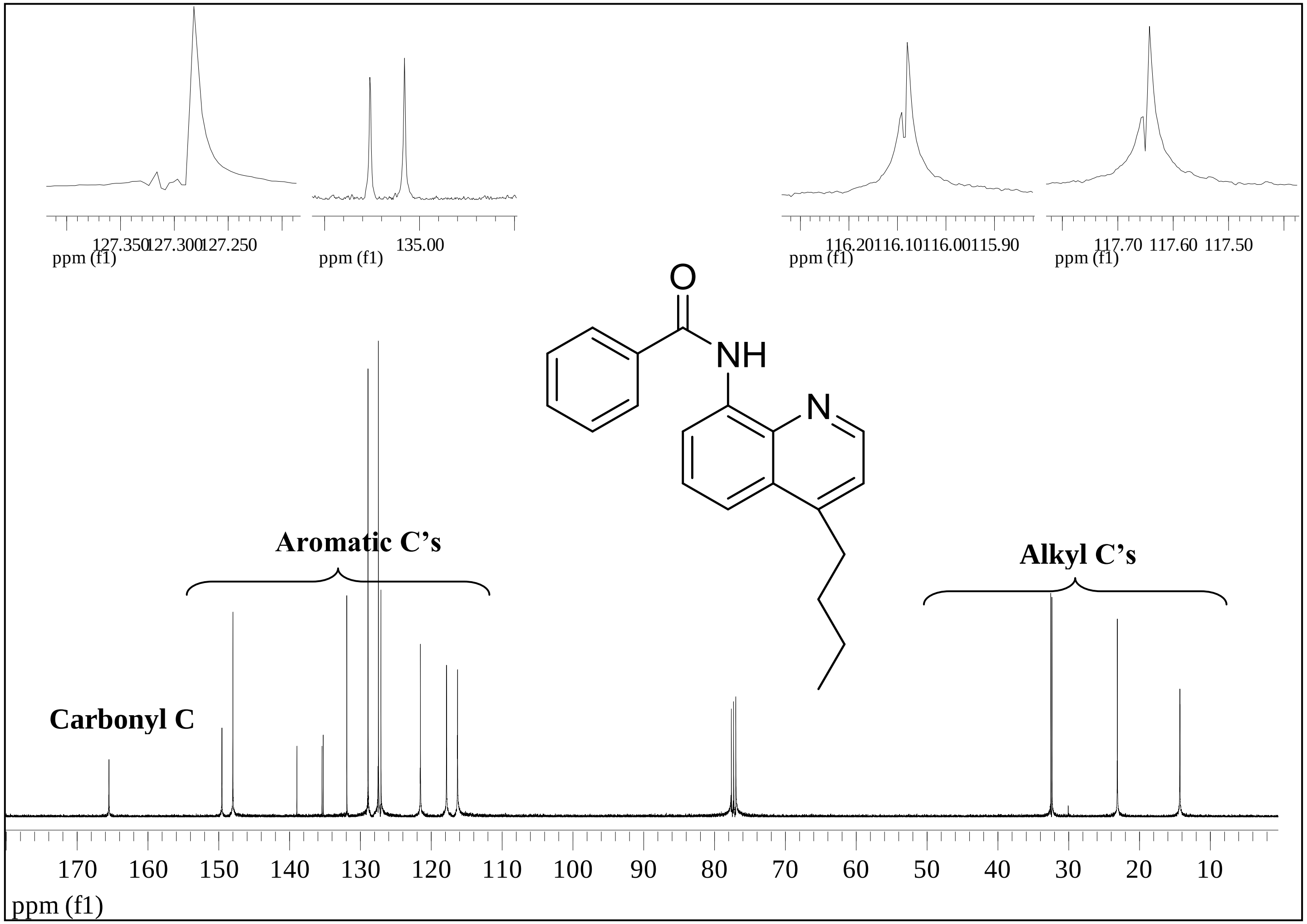


Figure A.21. ^{13}C-NMR Spectrum of N-(4-butylquinolin-8-yl)benzamide.

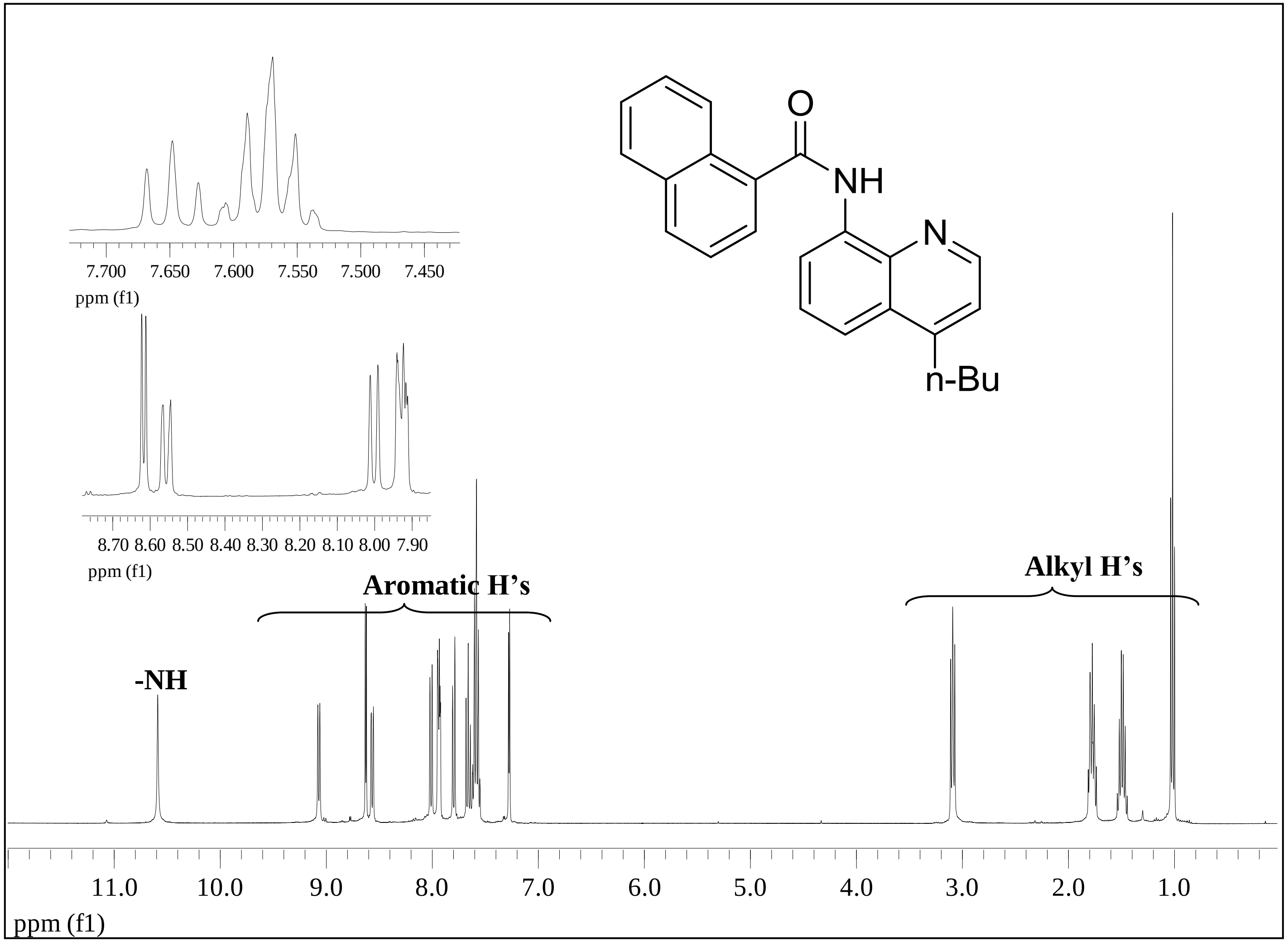


Figure A.22. ^{1}H-NMR Spectrum of N-(4-butylquinolin-8-yl)-1-naphthamide.

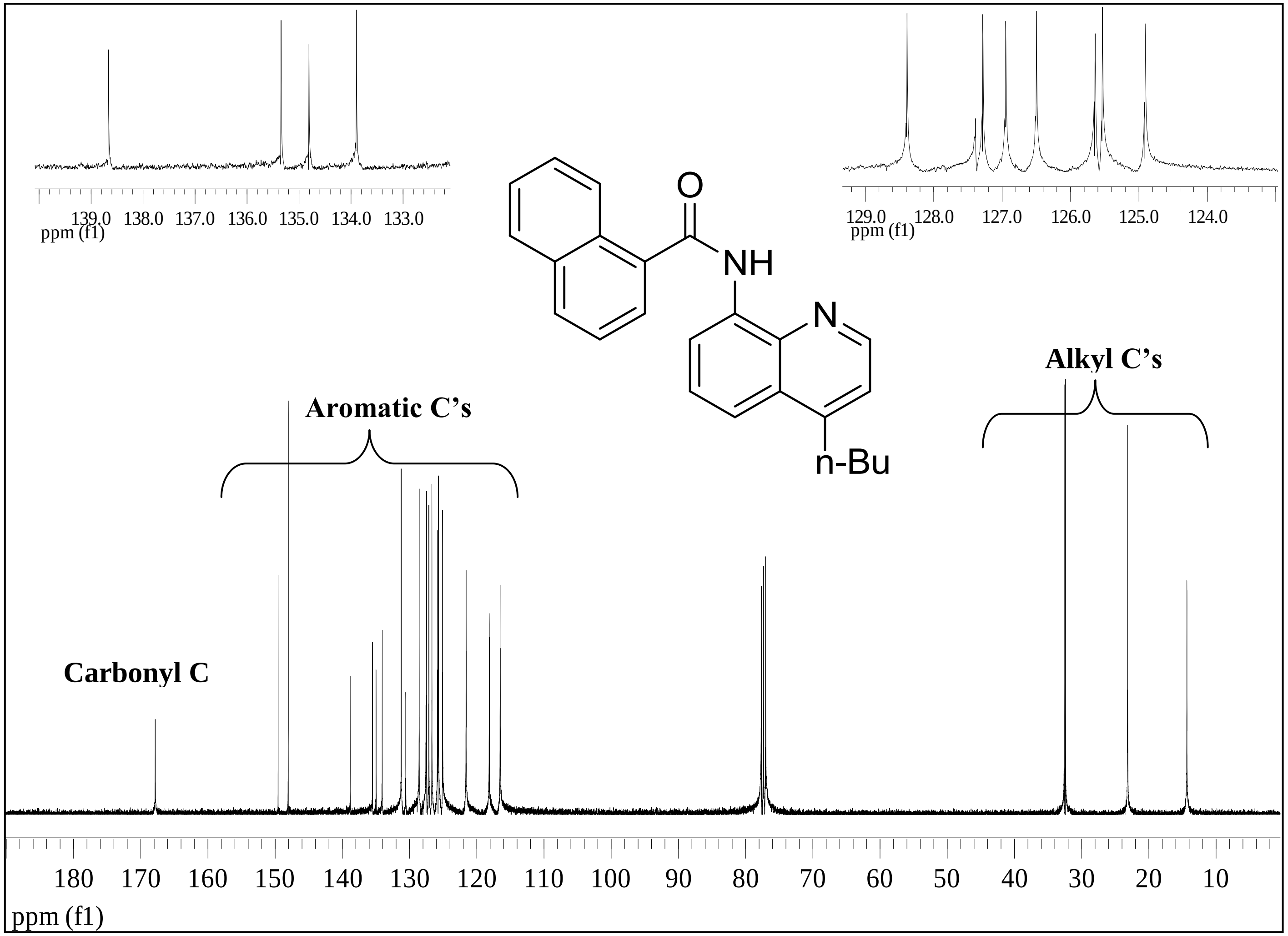


Figure A.23. ^{13}C-NMR Spectrum of N-(4-butylquinolin-8-yl)-1-naphthamide.

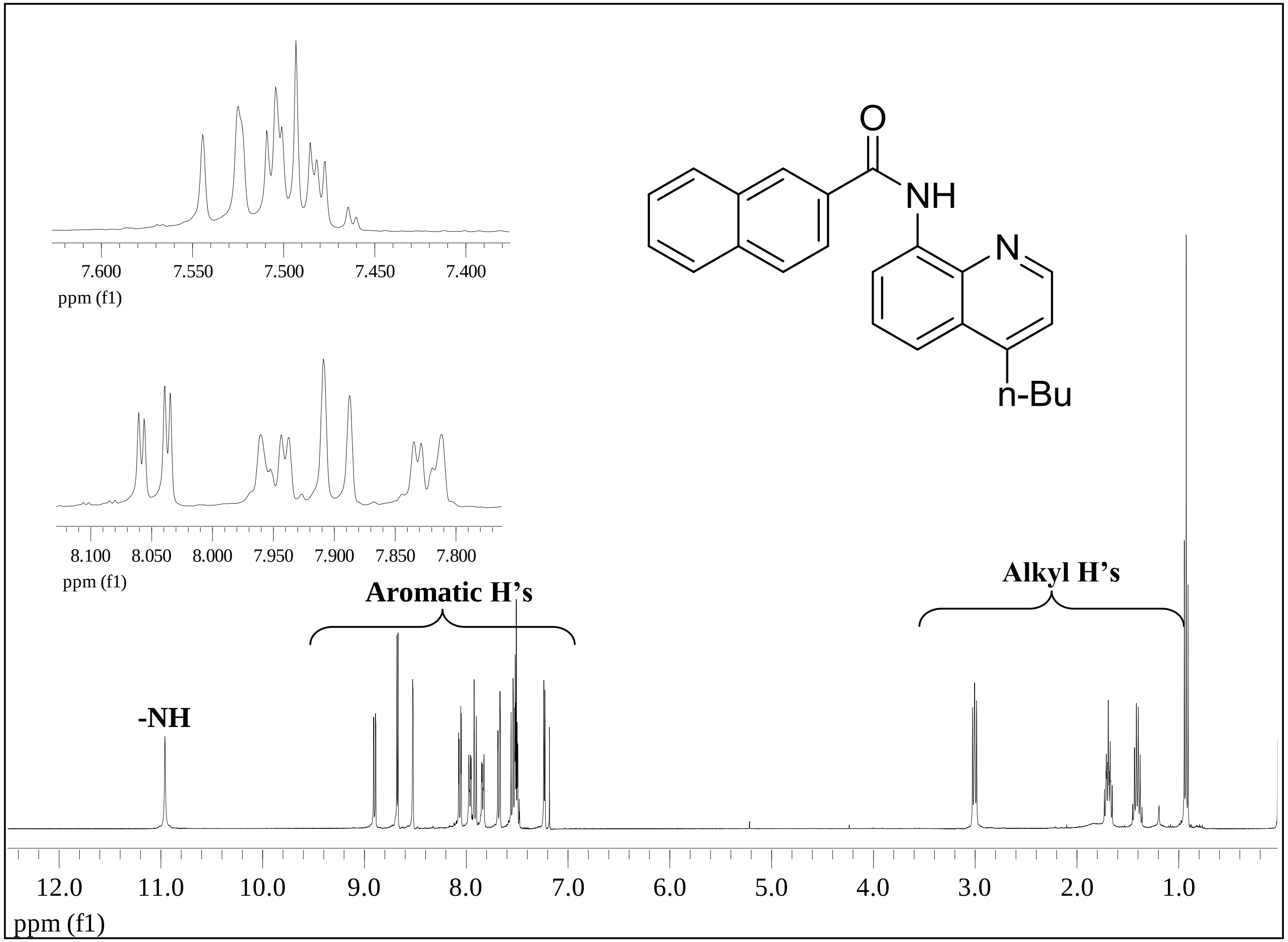


Figure A.24. ^{1}H-NMR Spectrum of N-(4-butylquinolin-8-yl)-2-naphthamide.

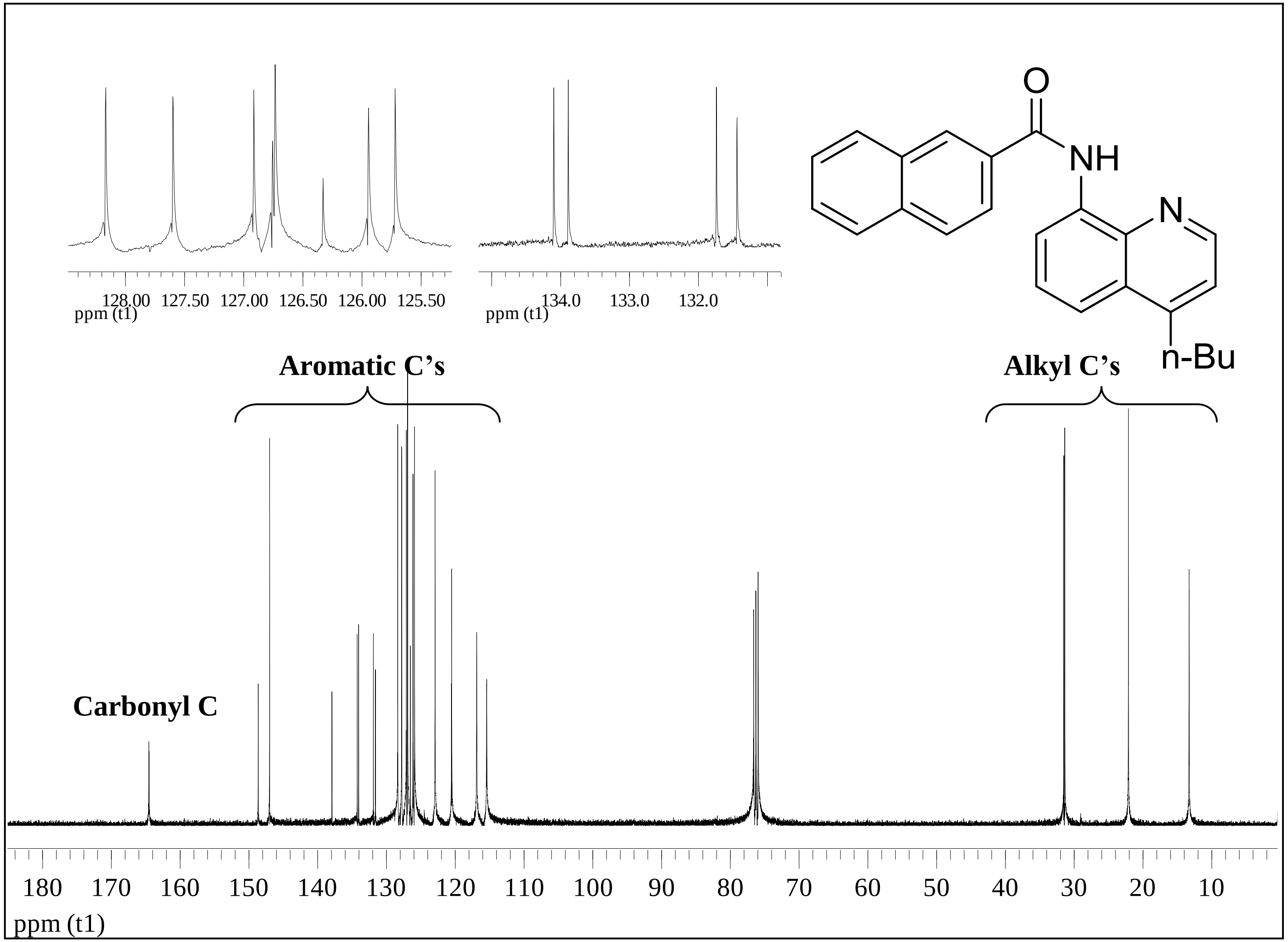


Figure A.25. ^{13}C-NMR Spectrum of N-(4-butylquinolin-8-yl)-2-naphthamide.

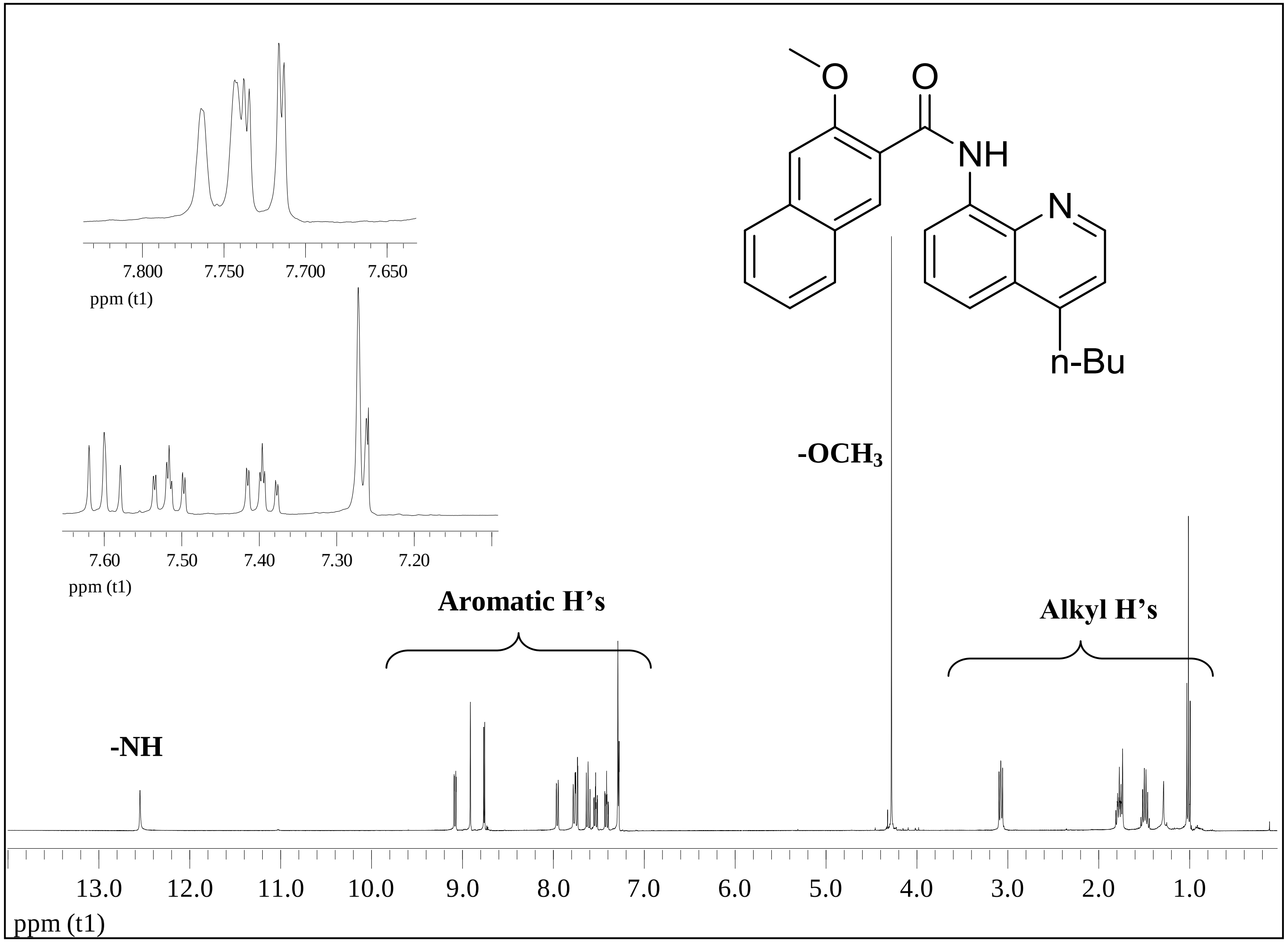


Figure A.26. ^{1}H-NMR Spectrum of N-(4-butylquinolin-8-yl)-3-methoxy-2-naphthamide.

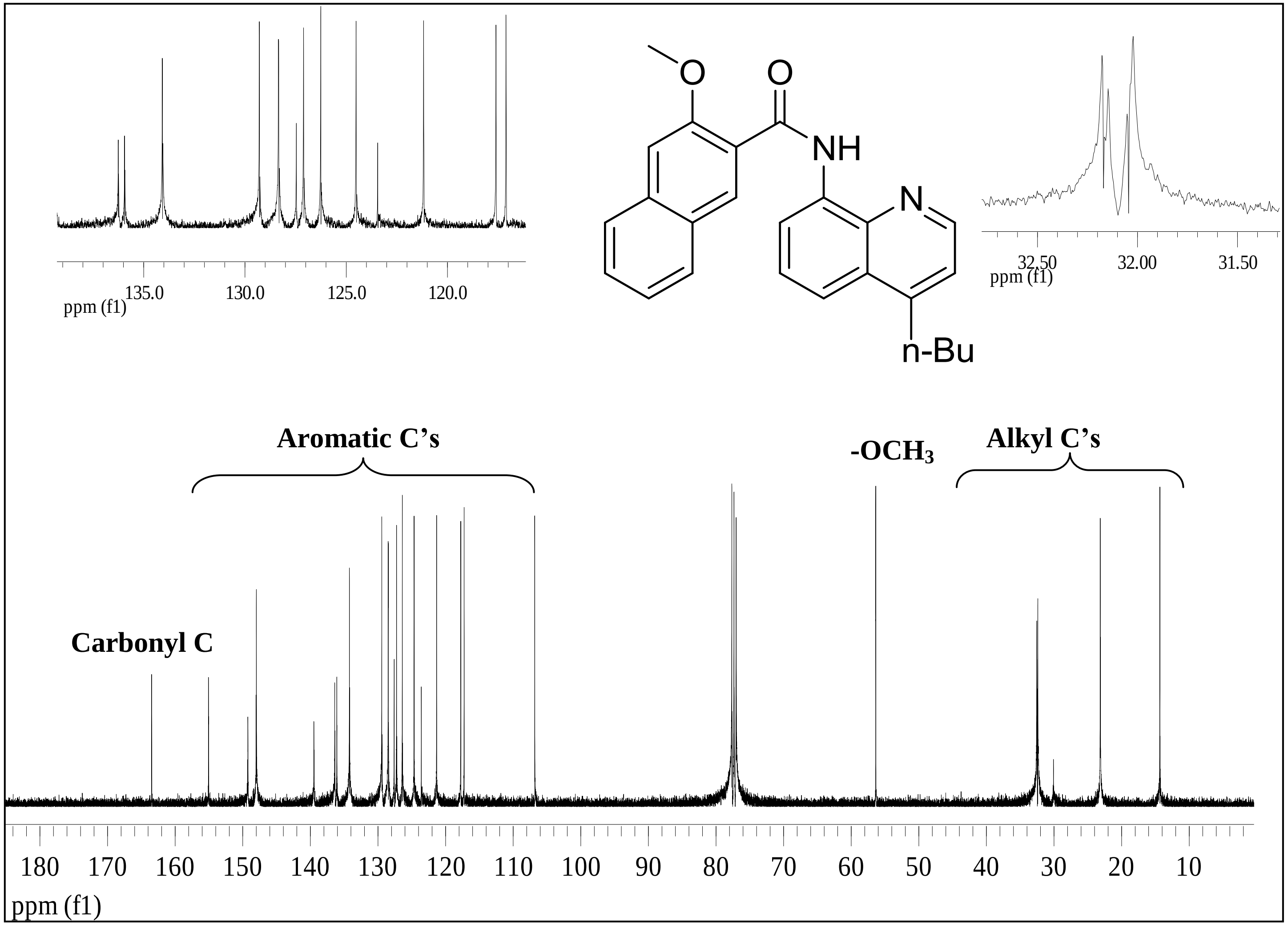


Figure A.27. ^{13}C-NMR Spectrum of N-(4-butylquinolin-8-yl)-3-methoxy-2-naphthamide.

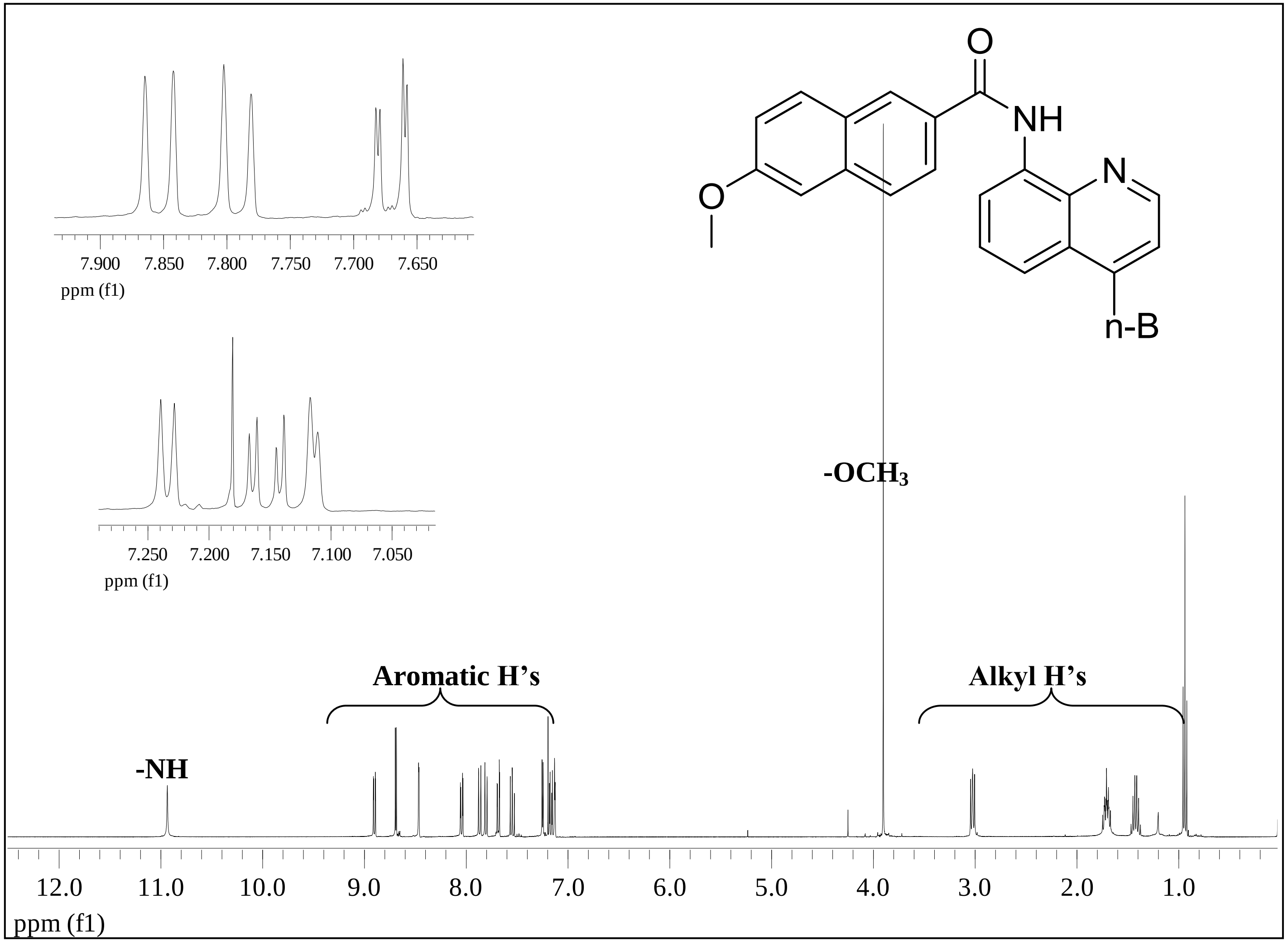


Figure A.28. ^{1}H-NMR Spectrum of N-(4-butylquinolin-8-yl)-6-methoxy-2-naphthamide.

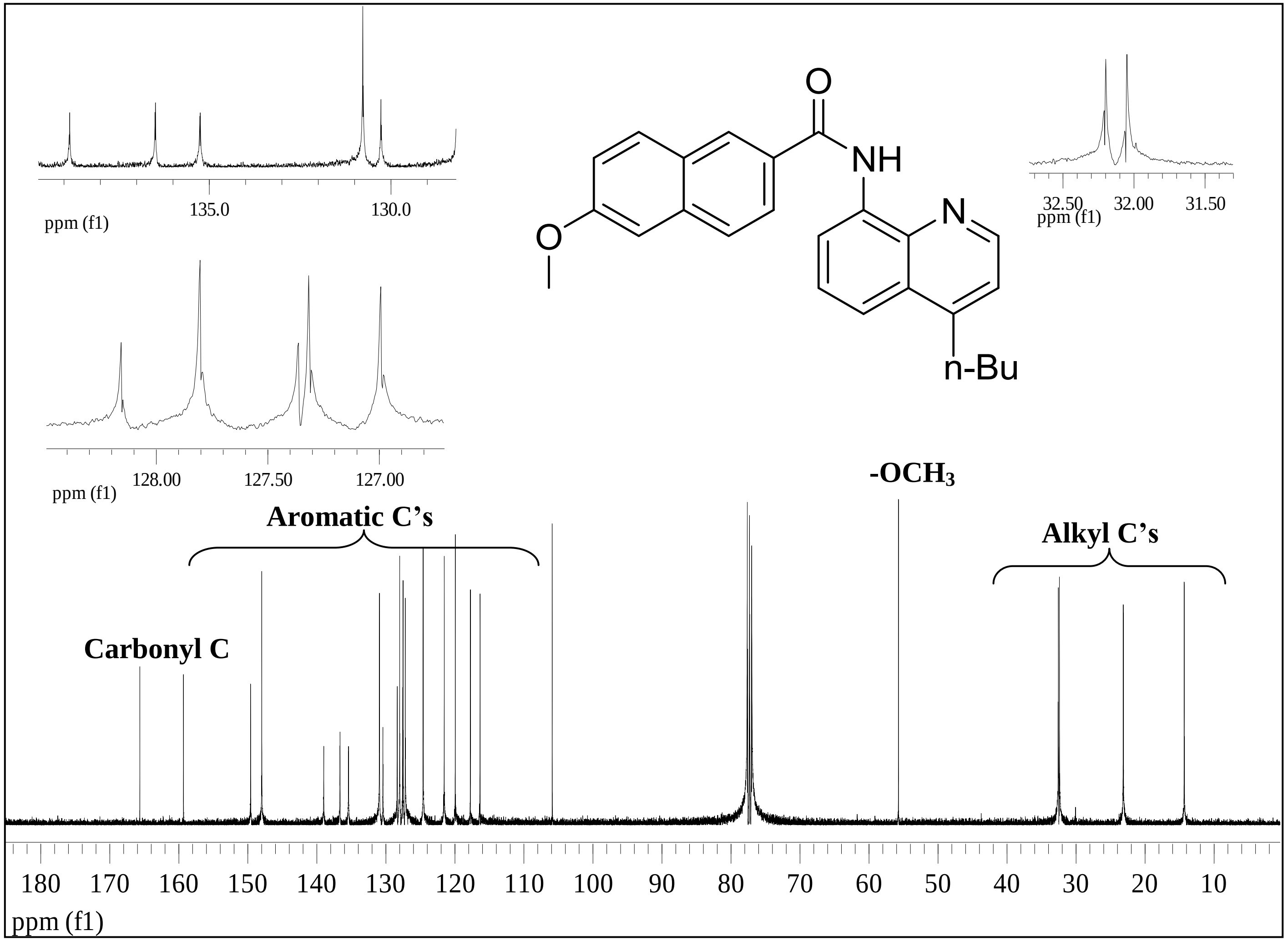


Figure A.29. ^{13}C-NMR Spectrum of N-(4-butylquinolin-8-yl)-6-methoxy-2-naphthamide.

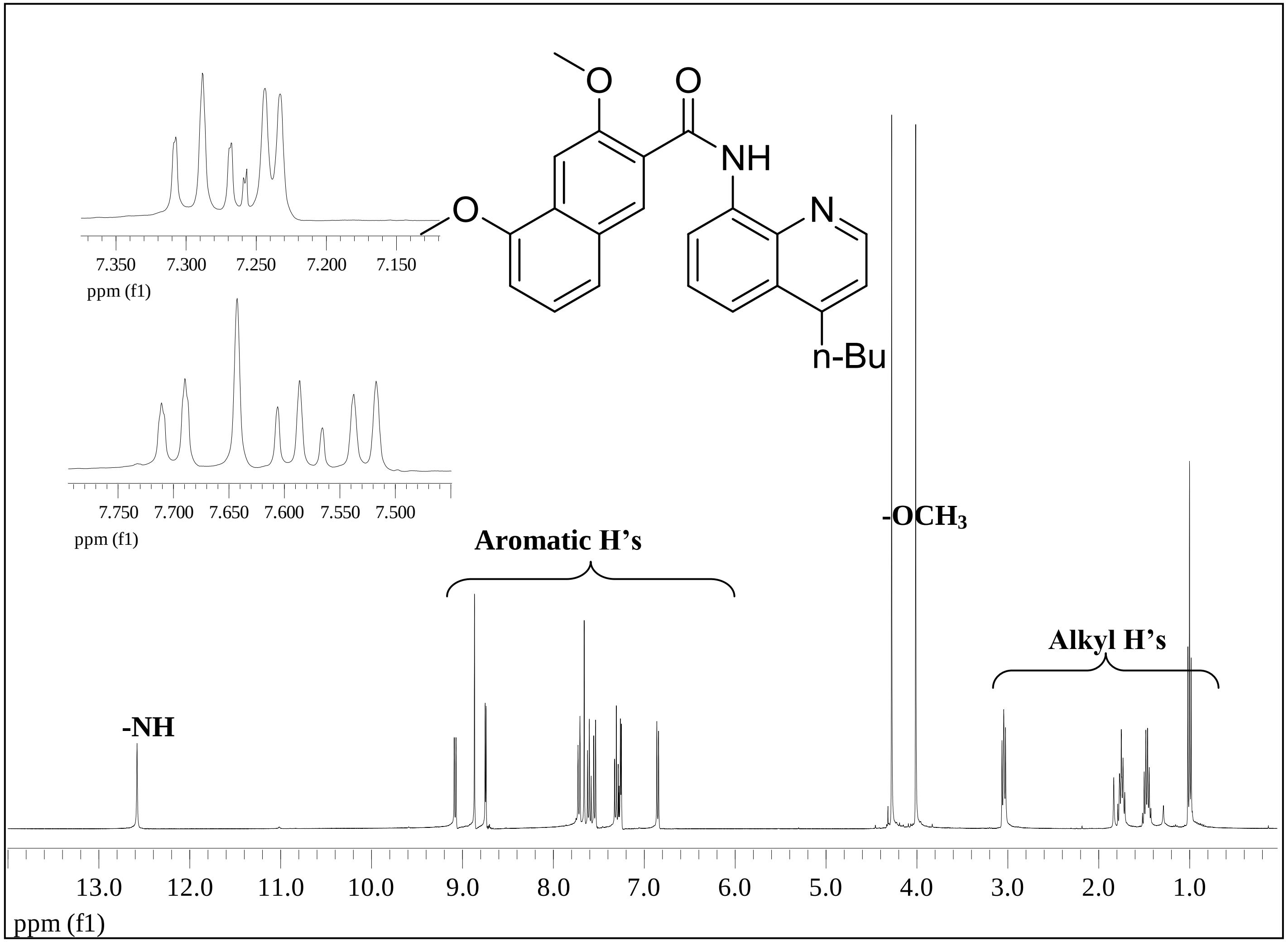


Figure A.30. ^{1}H-NMR Spectrum of N-(4-butylquinolin-8-yl)-3,5-dimethoxy-2-naphthamide.

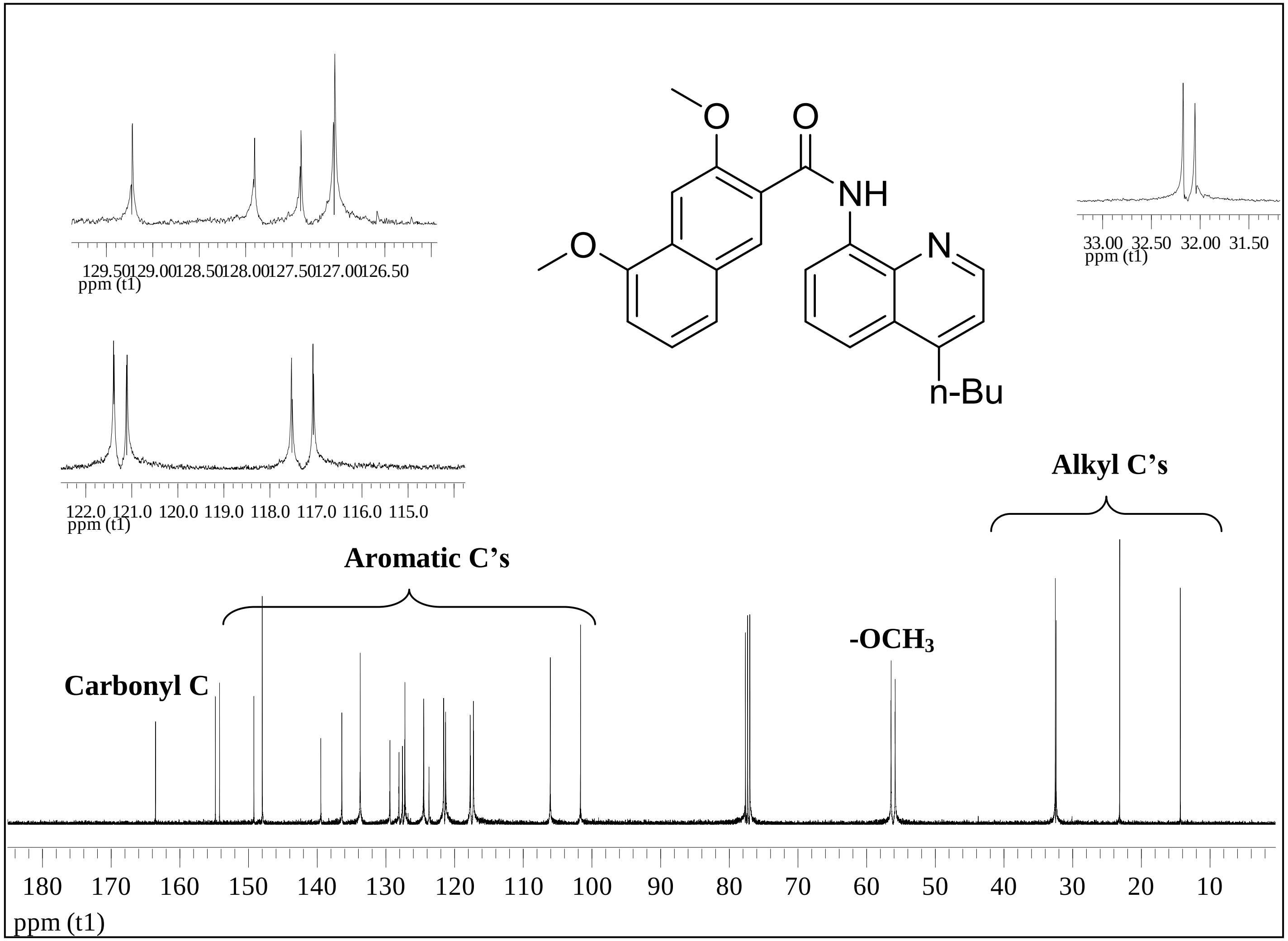


Figure A.31. ^{13}C-NMR Spectrum of N-(4-butylquinolin-8-yl)-3,5-dimethoxy-2-naphthamide.

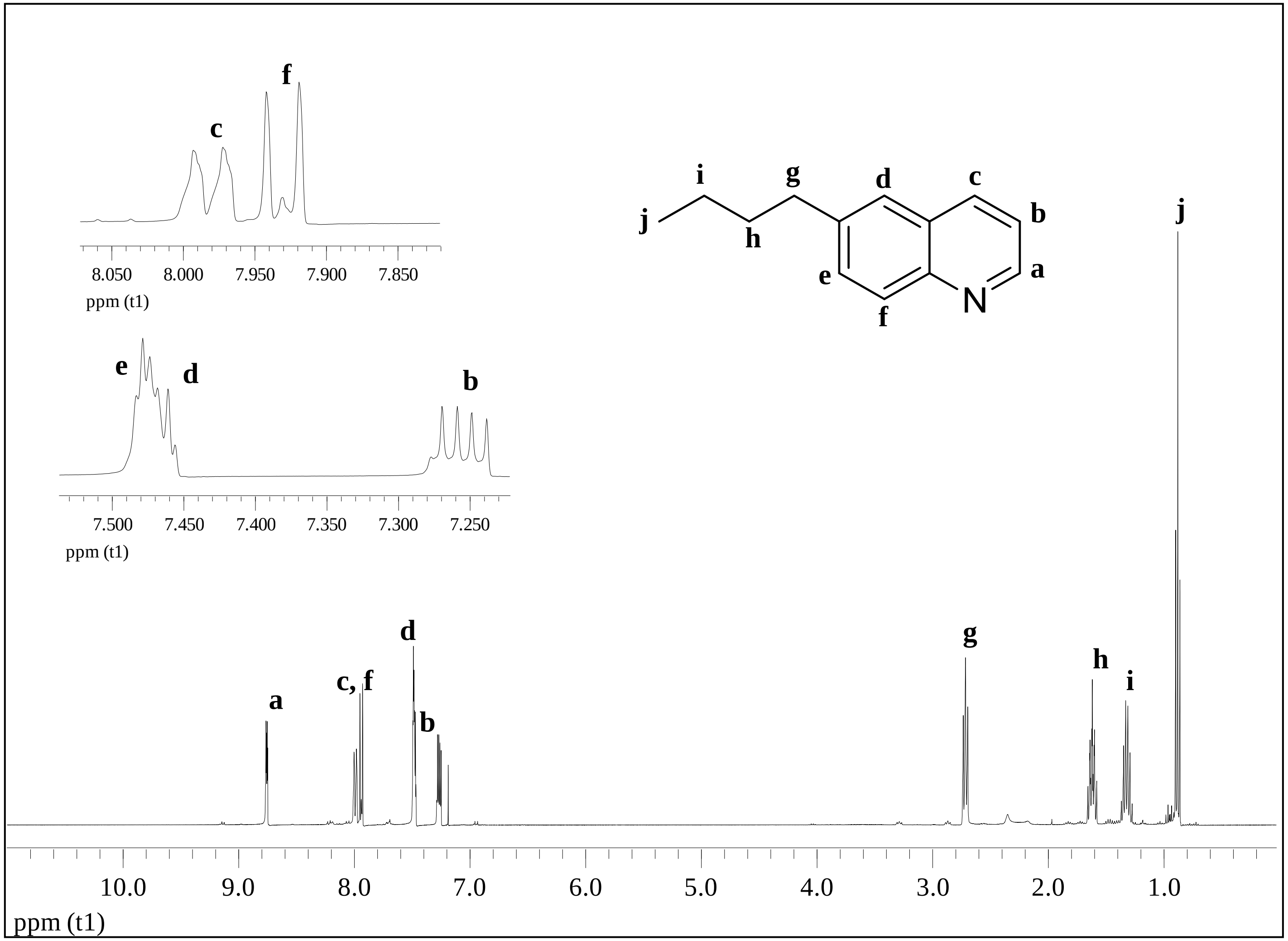


Figure A.32. ^{1}H-NMR Spectrum of 6-butylquinoline.

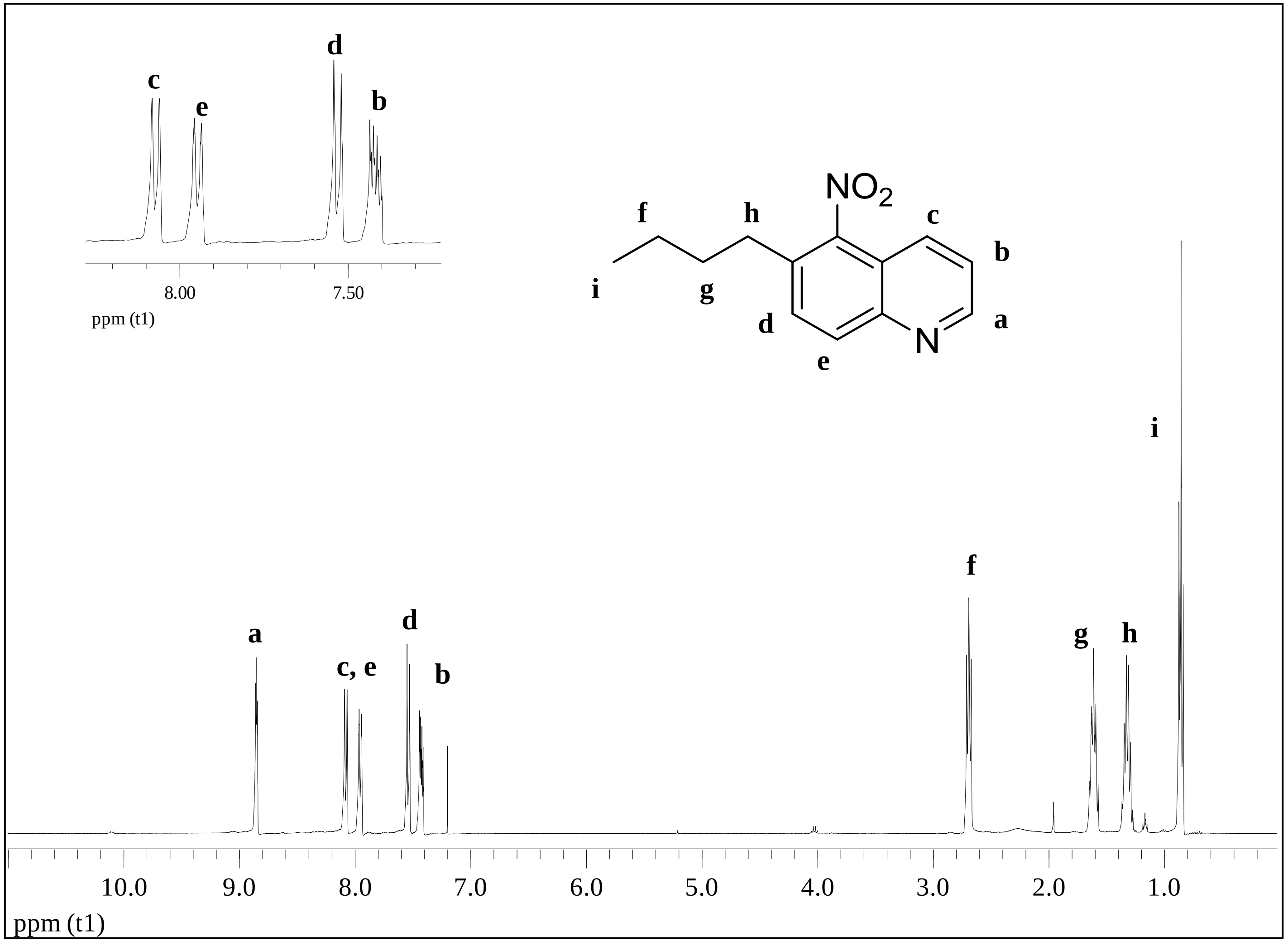


Figure A.33. ^{1}H-NMR Spectrum of 6-butyl-5-nitroquinoline.

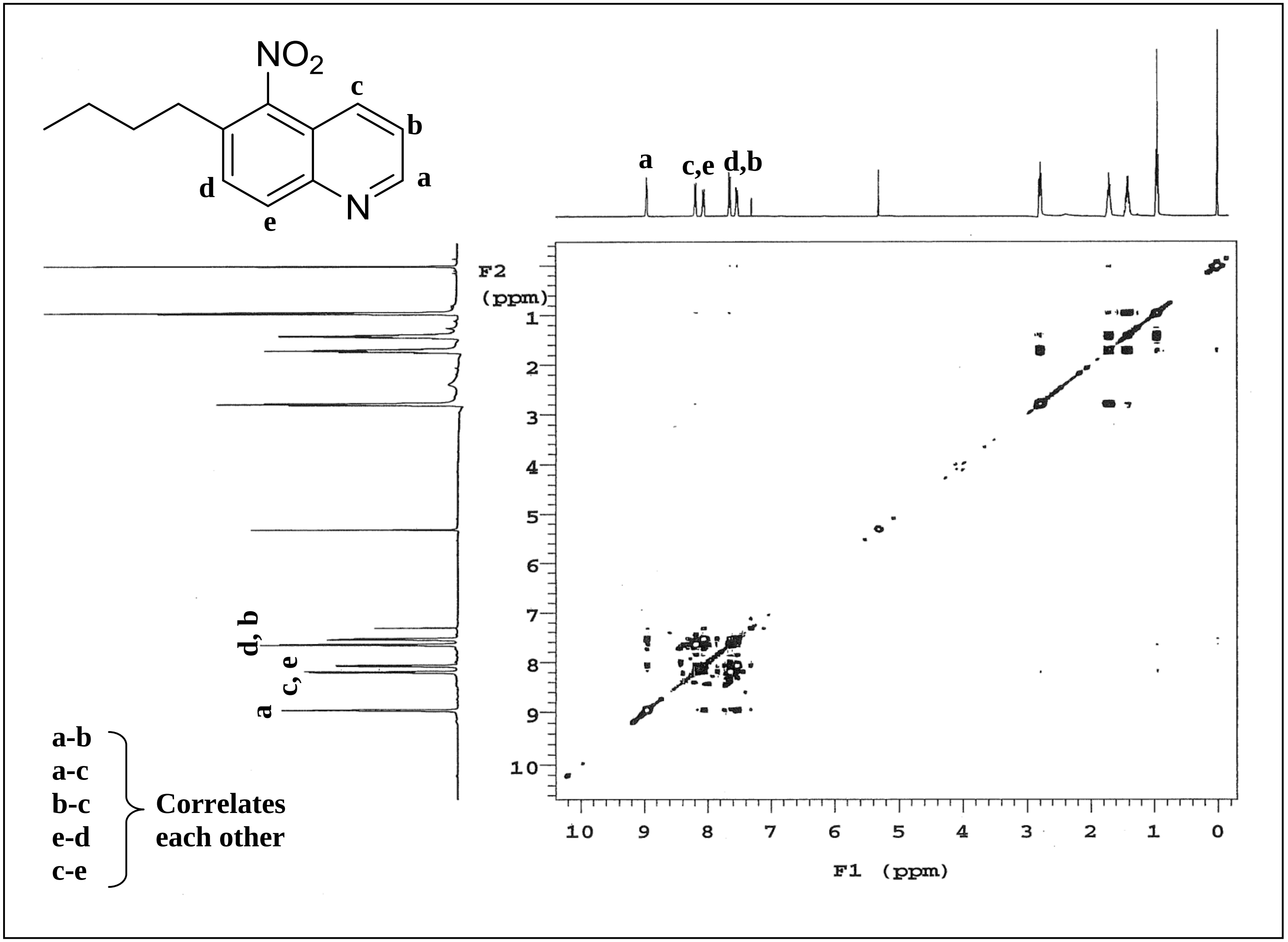


Figure A.34. 2D-NMR Spectrum (COSY) of 6-butyl-5-nitroquinoline.

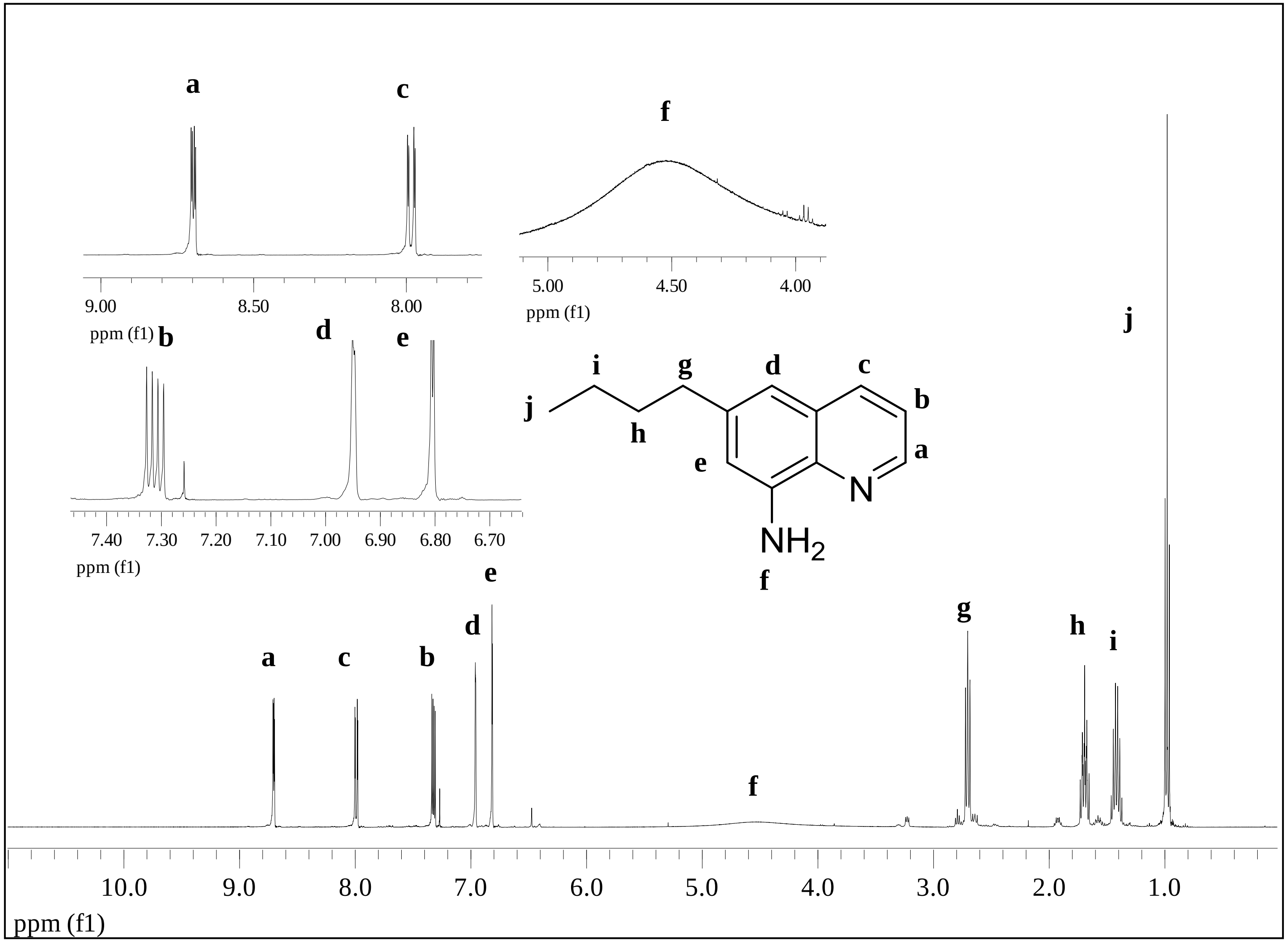


Figure A.35. ^{1}H-NMR Spectrum of 6-butylquinolin-8-amine.

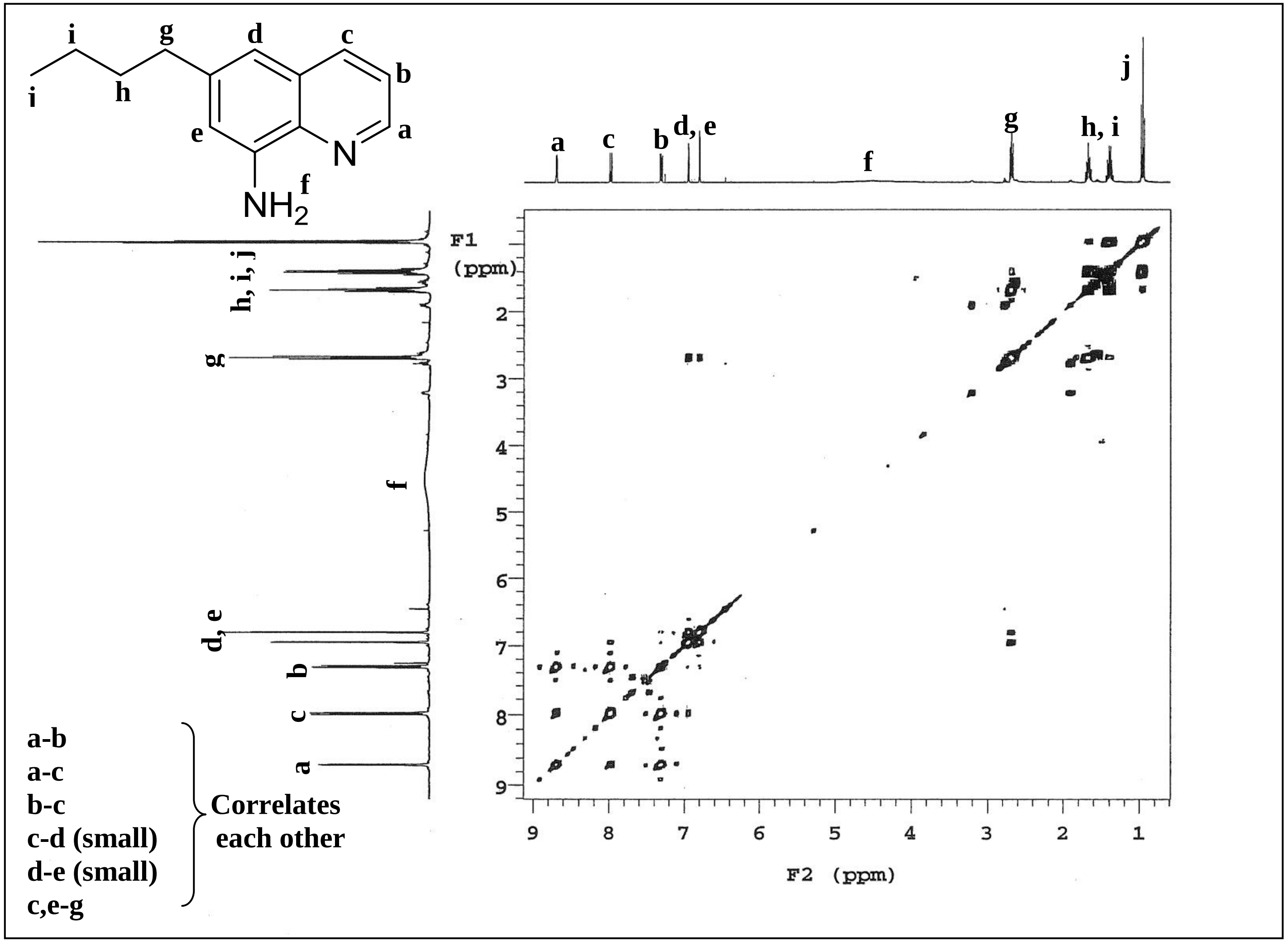


Figure A.36. 2D-NMR Spectrum (COSY) of 6-butylquinolin-8-amine.

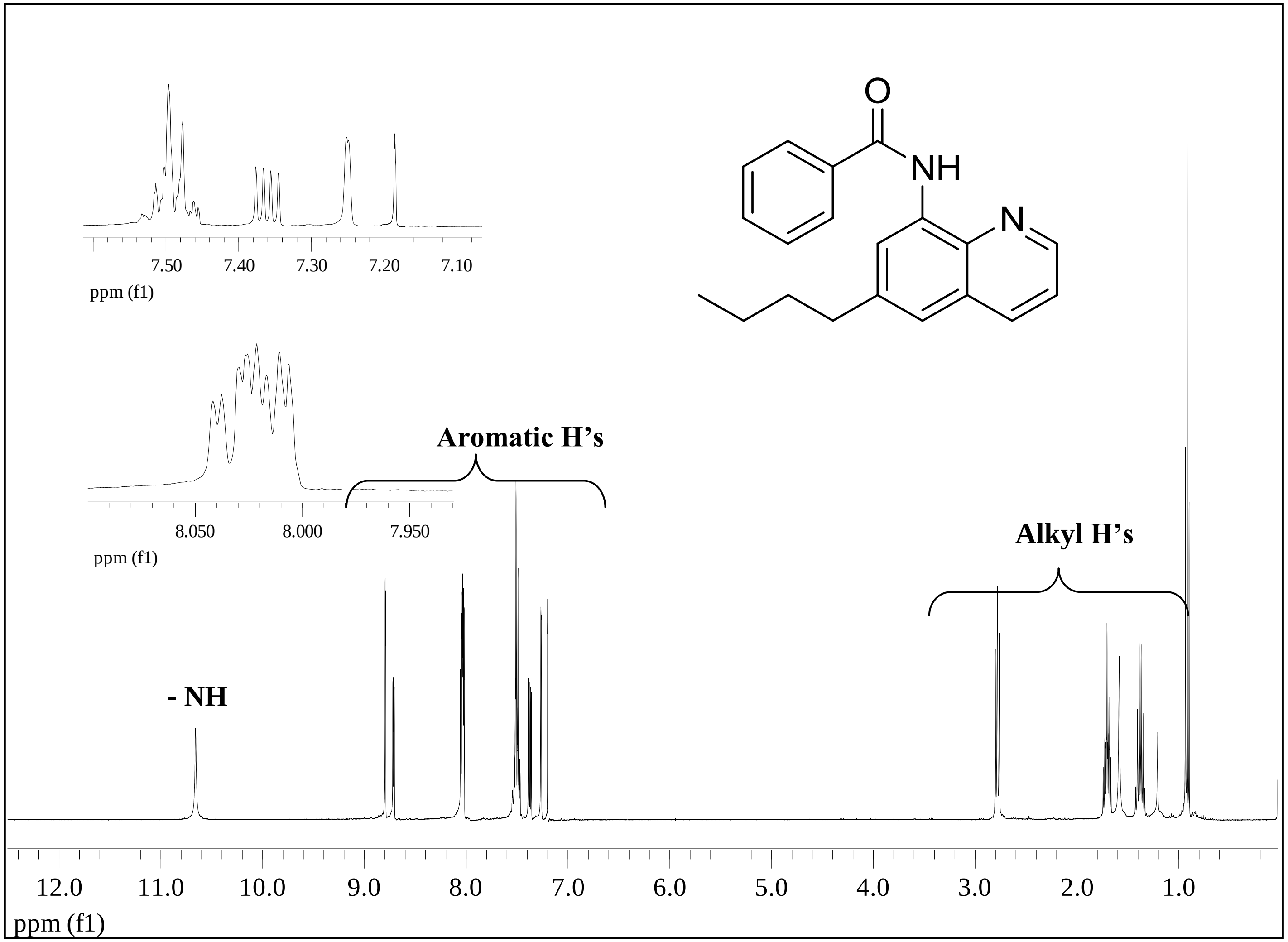


Figure A.37. ^{1}H-NMR Spectrum of N-(6-butylquinolin-8-yl)benzamide.

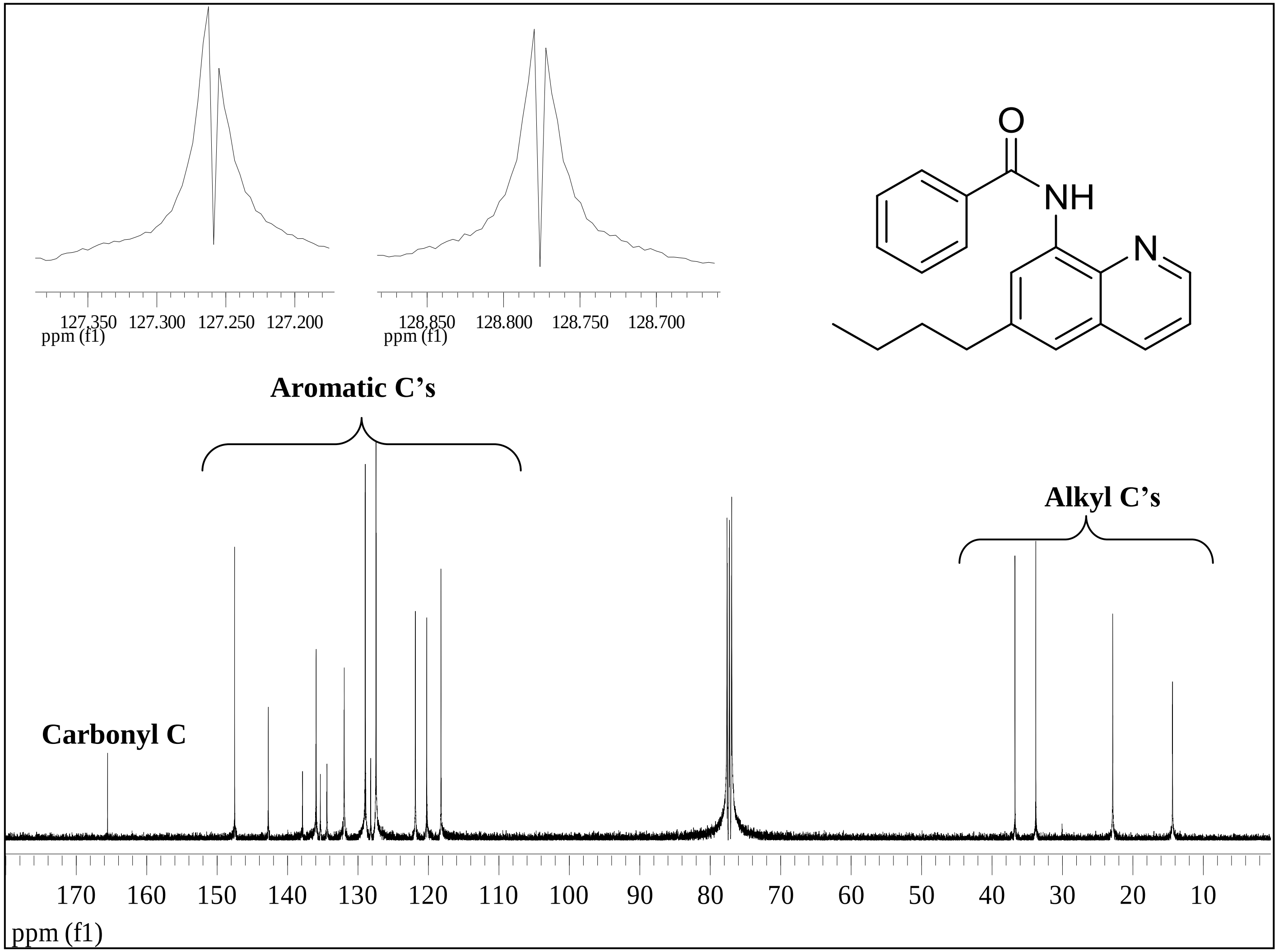


Figure A.38. ^{13}C-NMR Spectrum of N-(6-butylquinolin-8-yl)benzamide.

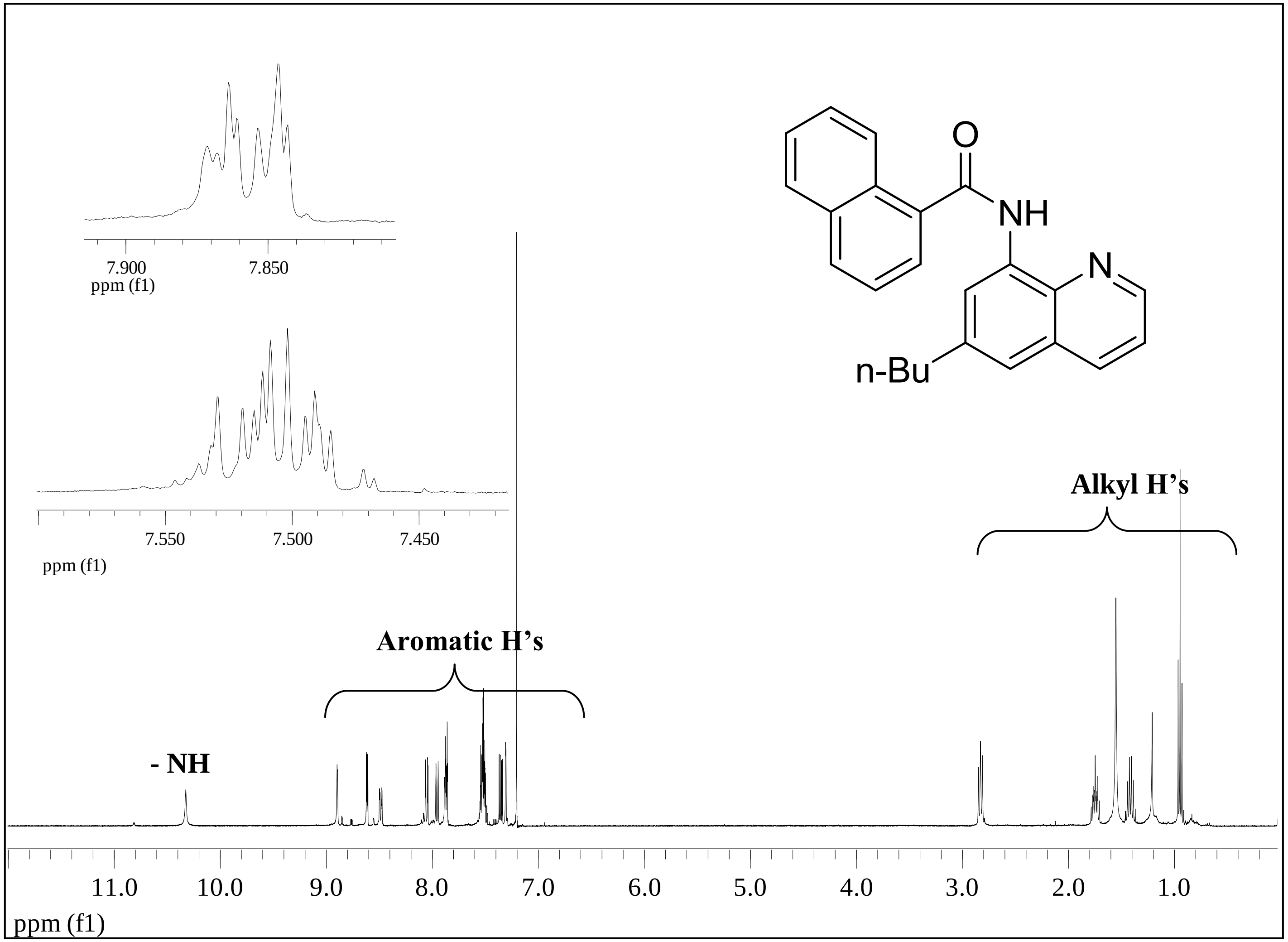


Figure A.39. ^{1}H-NMR Spectrum of N-(6-butylquinolin-8-yl)-1-naphthamide.

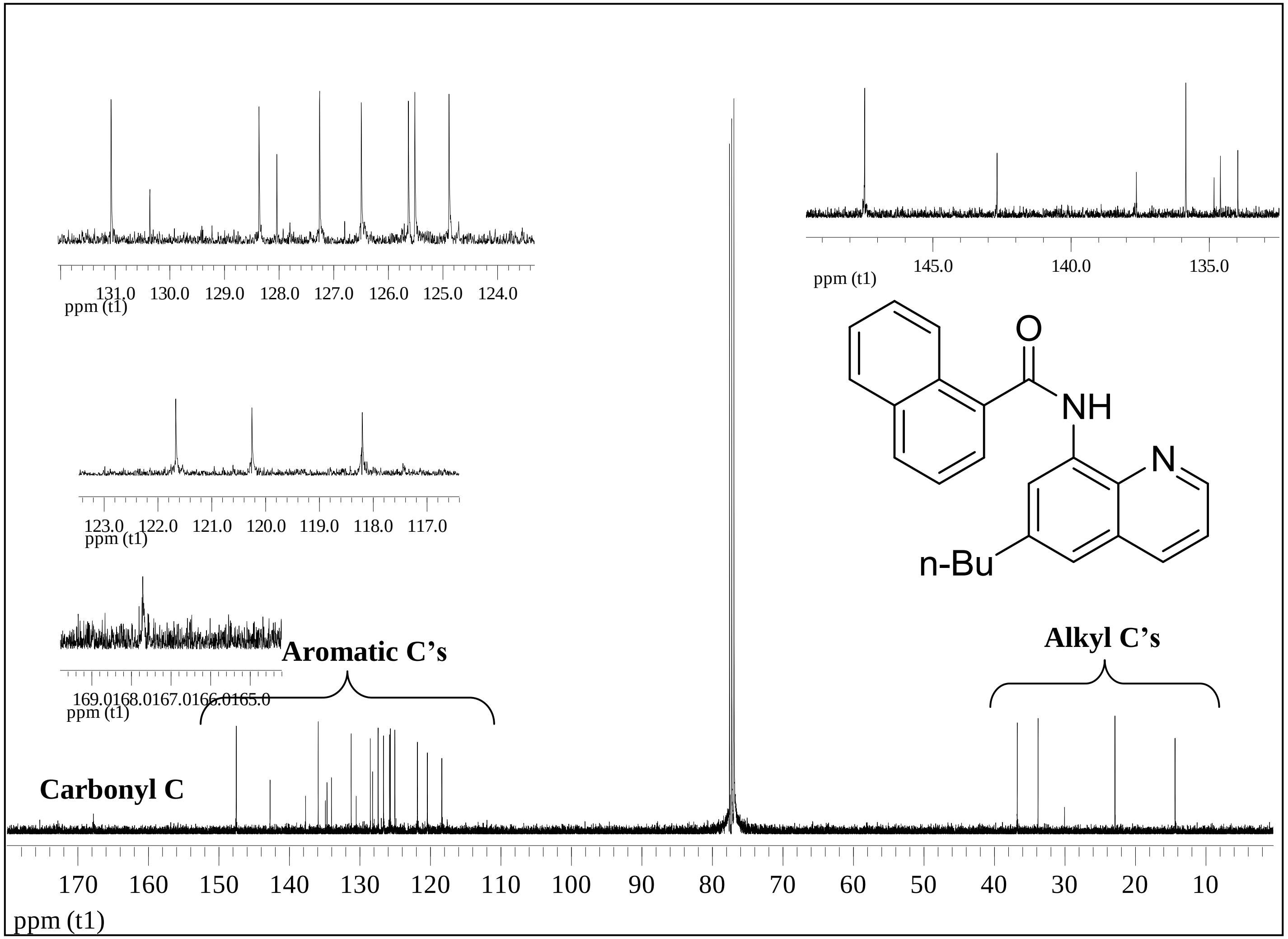


Figure A.40. ^{13}C-NMR Spectrum of N-(6-butylquinolin-8-yl)-1-naphthamide.

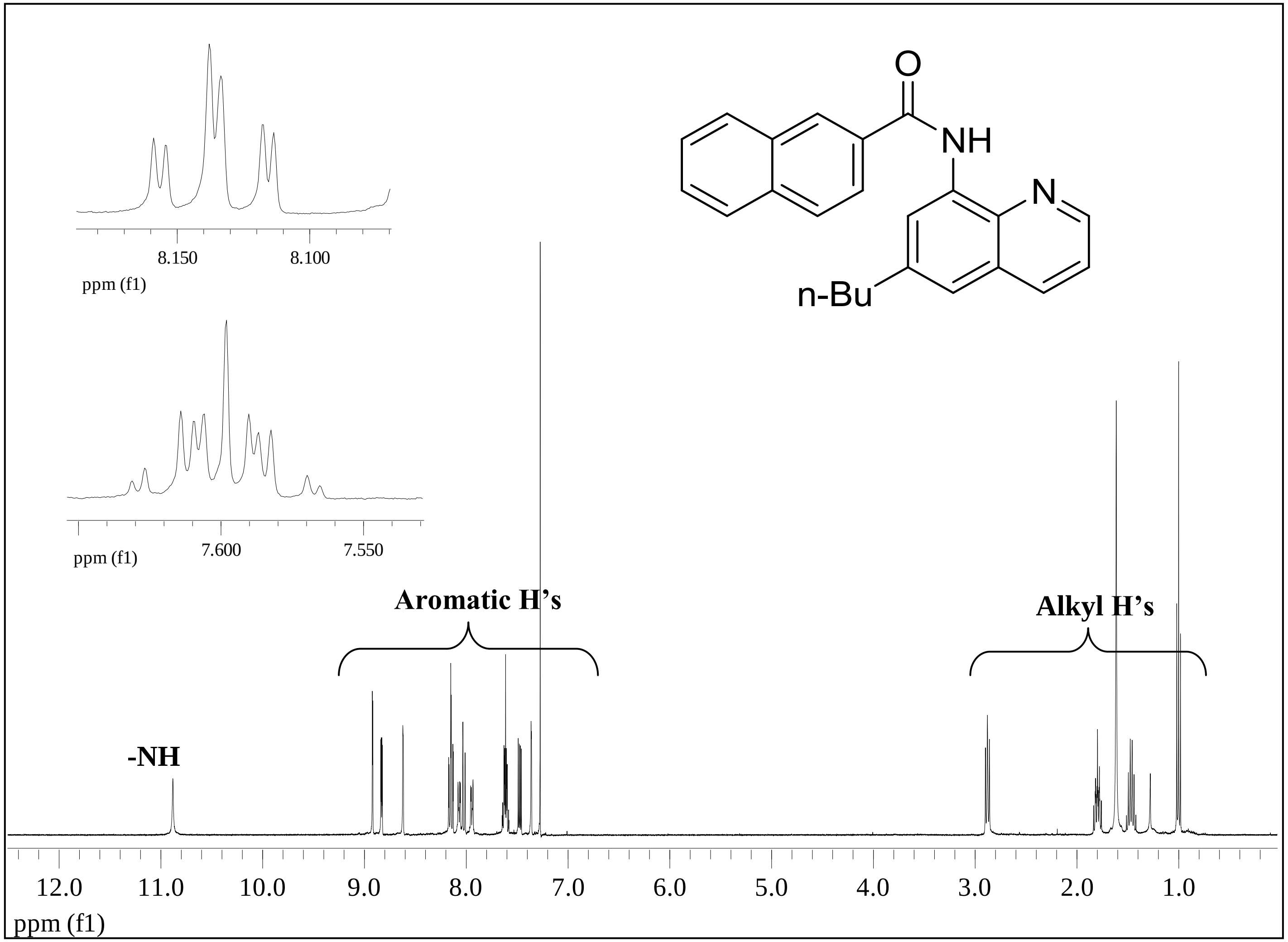


Figure A.41. ^{1}H-NMR Spectrum of N-(6-butylquinolin-8-yl)-2-naphthamide.

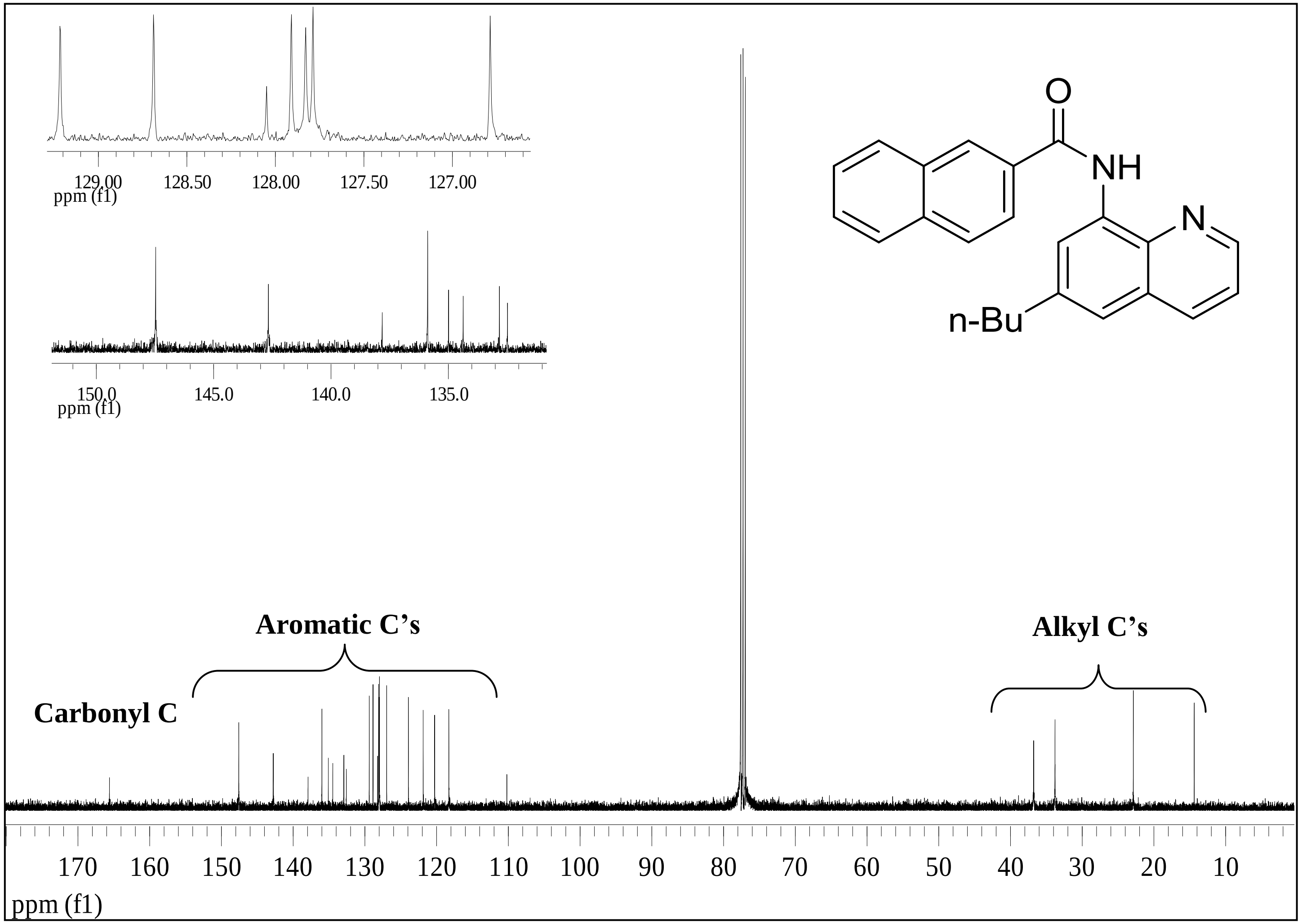


Figure A.42. ^{13}C-NMR Spectrum of N-(6-butylquinolin-8-yl)-2-naphthamide.

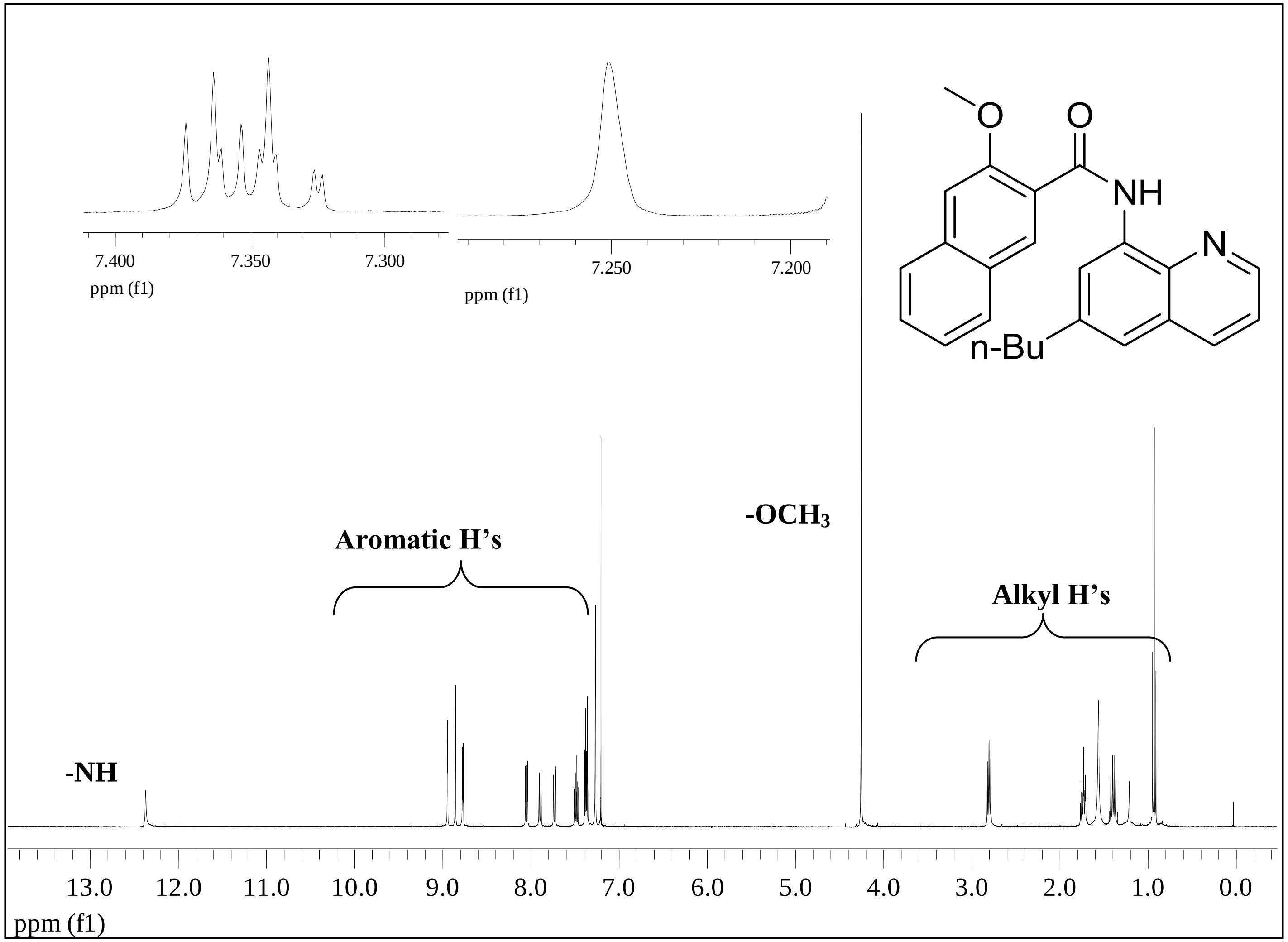


Figure A.43. ^{1}H-NMR Spectrum of N-(6-butylquinolin-8-yl)-3-methoxy-2-naphthamide.

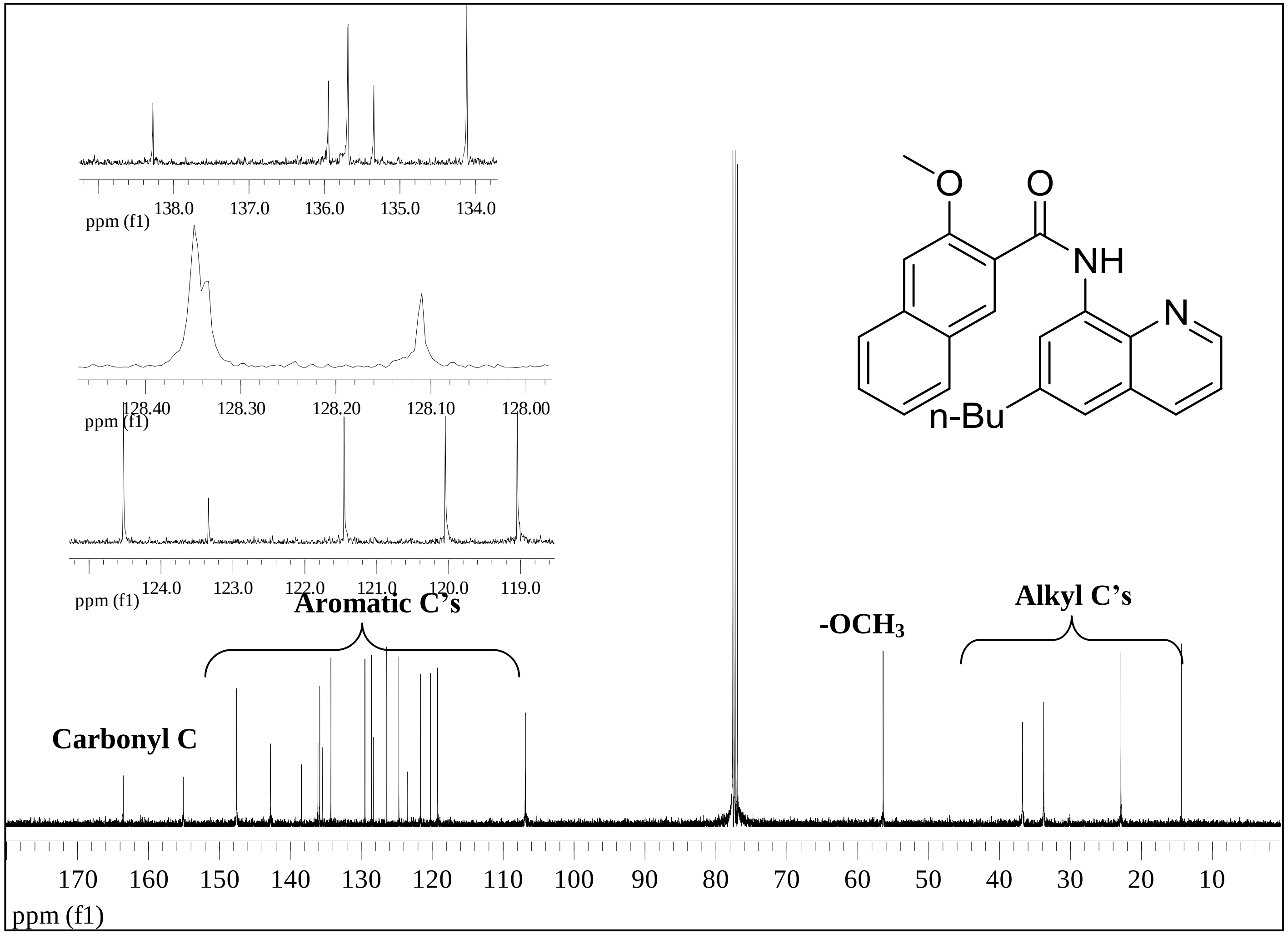


Figure A.44. ^{13}C-NMR Spectrum of N-(6-butylquinolin-8-yl)-3-methoxy-2-naphthamide.

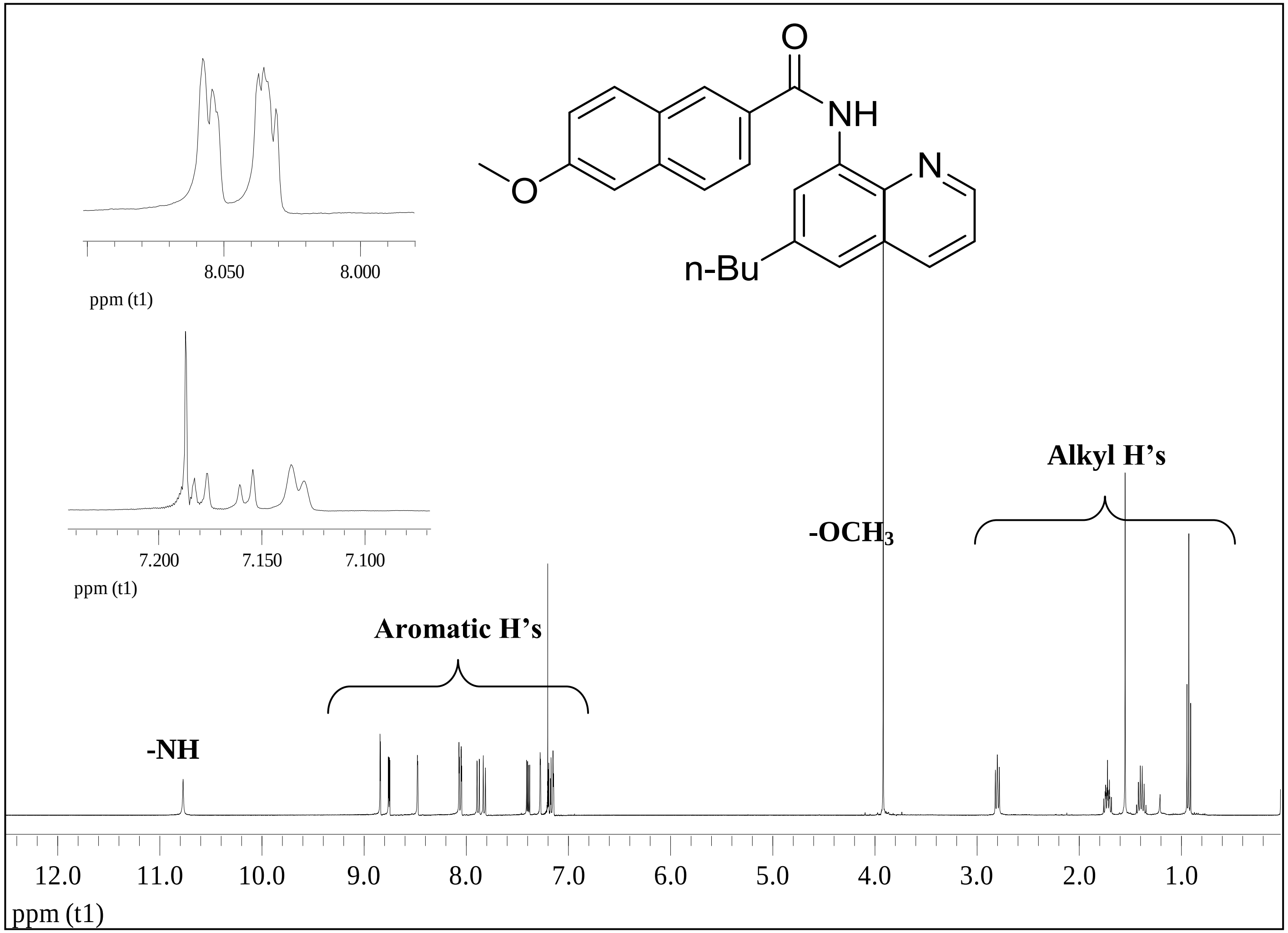


Figure A.45. ^{1}H-NMR Spectrum of N-(6-butylquinolin-8-yl)-6-methoxy-2-naphthamide.

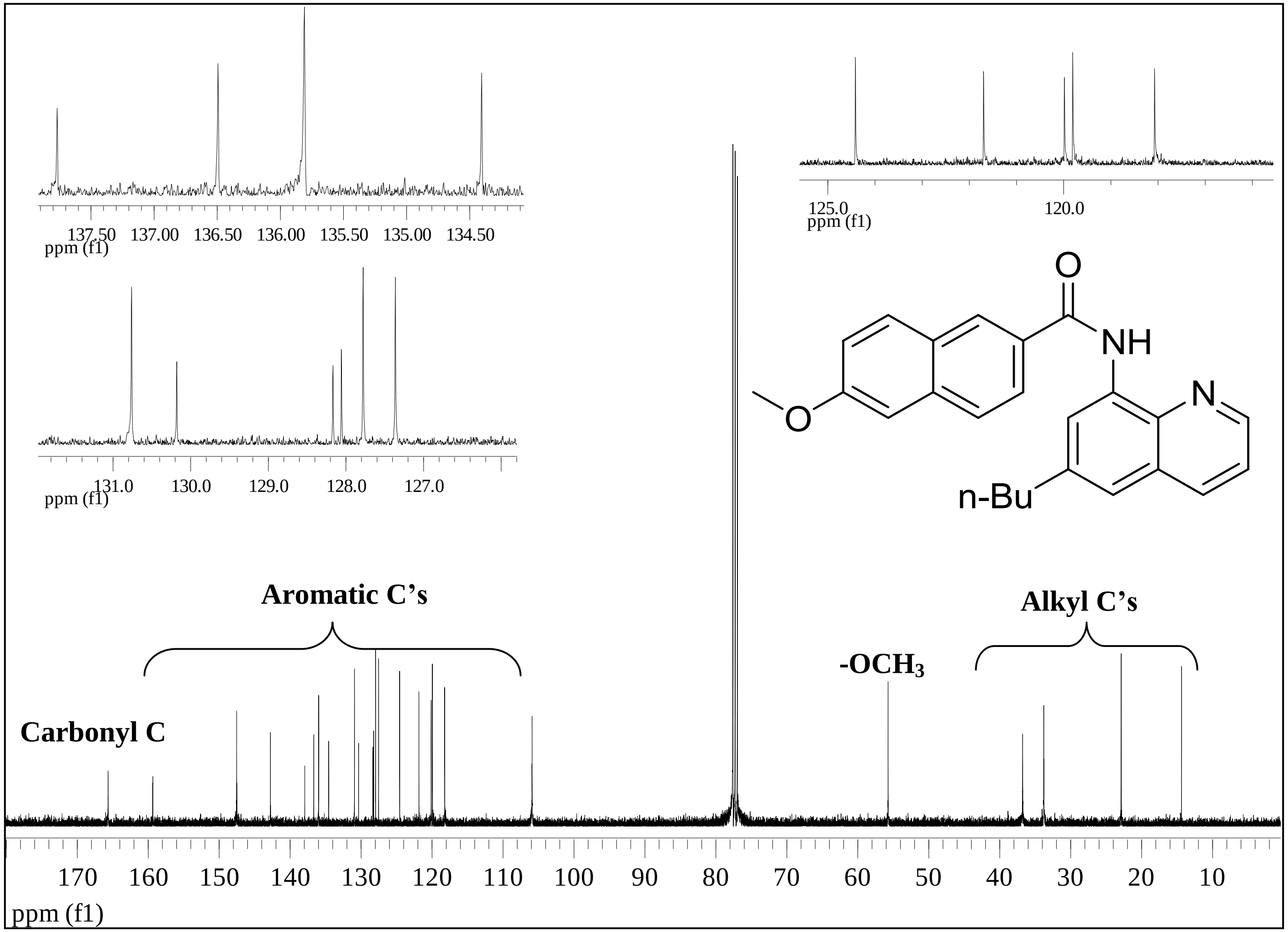


Figure A.46. ^{13}C-NMR Spectrum of N-(6-butylquinolin-8-yl)-6-methoxy-2-naphthamide.

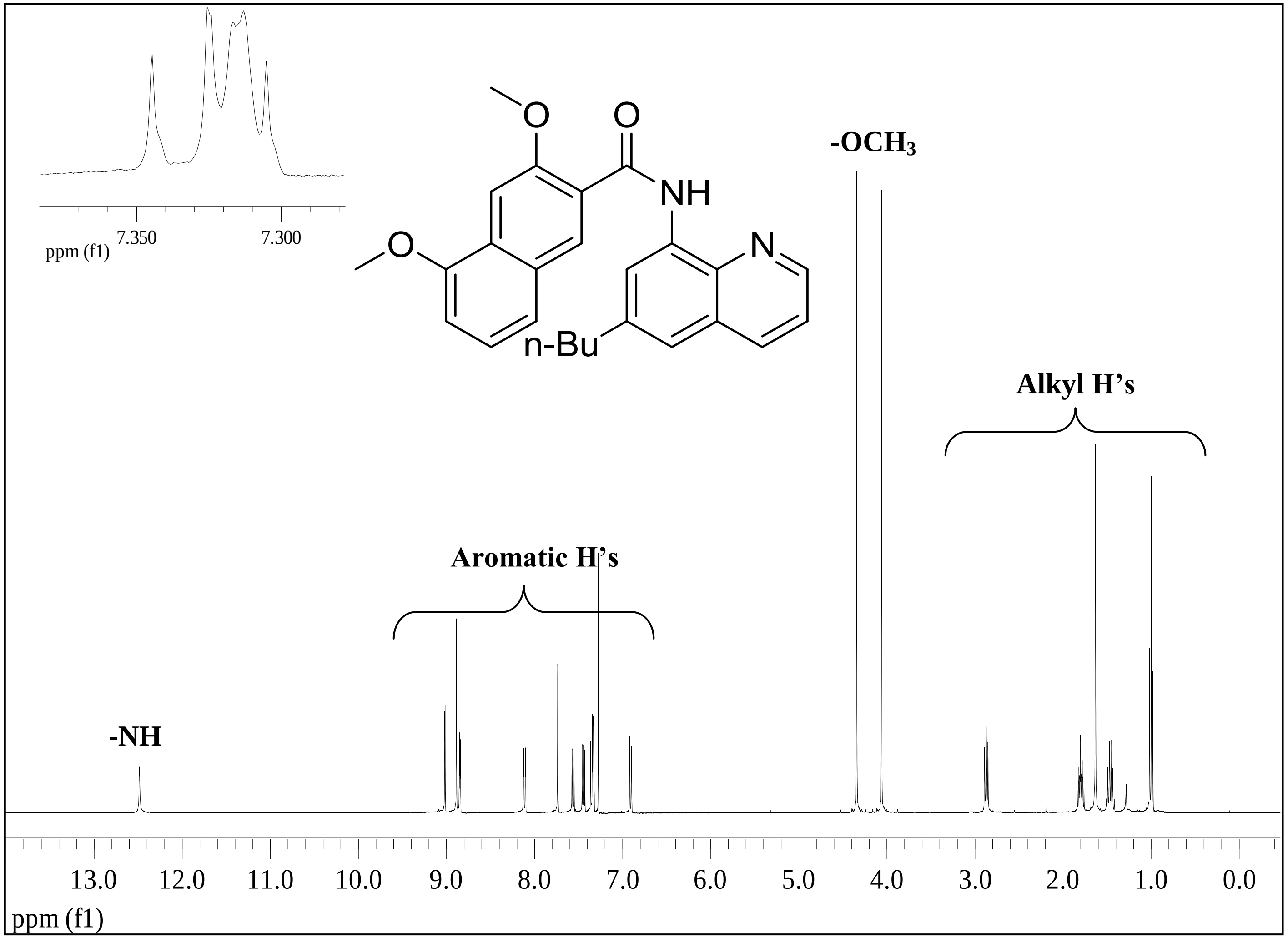


Figure A.47. ^{1}H-NMR Spectrum of N-(6-butylquinolin-8-yl)-3,5-dimethoxy-2-naphthamide.

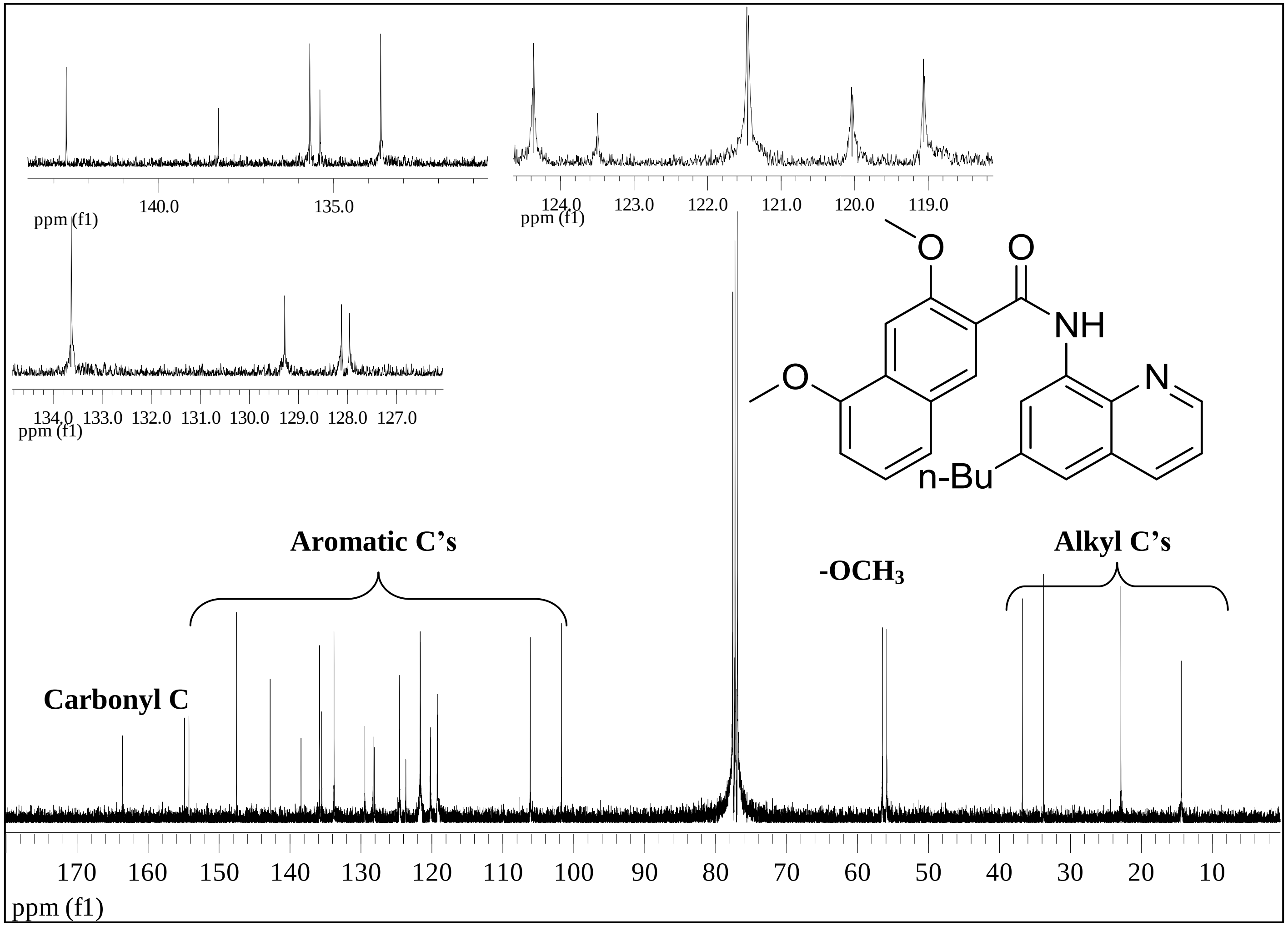


Figure A.48. ^{13}C-NMR Spectrum of N-(6-butylquinolin-8-yl)-3,5-dimethoxy-2-naphthamide.

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